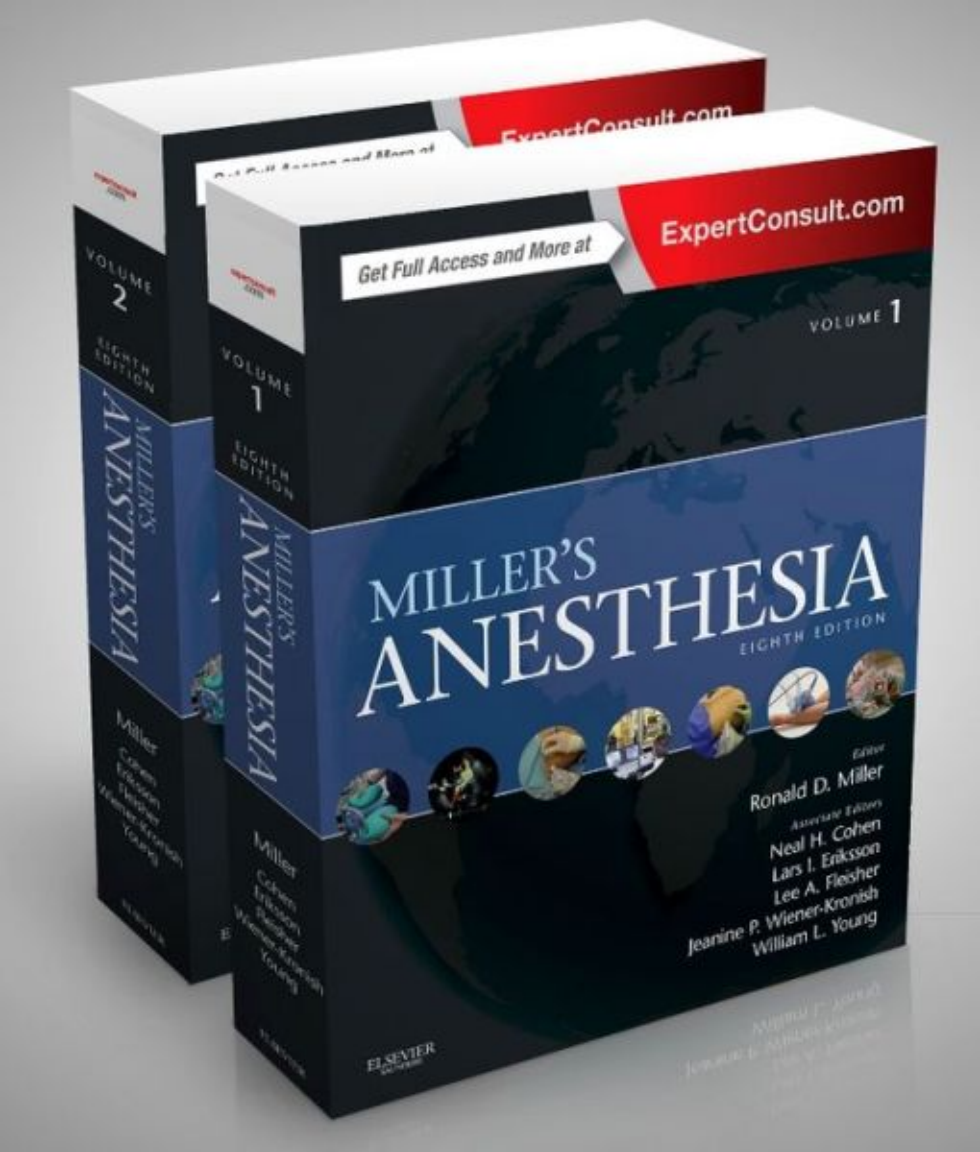

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To all of the residents, faculty, and colleagues who have helped advance the practice of anesthesiology and who serve as the foundation upon which the eighth edition has been completed

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Preface

For more than 30 years *Miller's Anesthesia* has been recognized as the most complete and thorough resource on the global scope and practice of contemporary anesthesiology. It is used worldwide and has been translated into several languages. Since the publication of the seventh edition in 2010, the associate editors, the Elsevier publishing staff, and I have had many conversations regarding the eighth edition and how we could ensure that *Miller's Anesthesia* continued to rank as the most influential and comprehensive text on our specialty in the world. Together we gathered information from various sources and solicited comments from colleagues worldwide to evaluate the seventh edition's content. We carefully updated each chapter and introduced new chapters with topics that represent the changes and current information in anesthesiology as it evolved over the past 5 years. The results of these deliberations are presented in the pages that follow.

The eighth edition of *Miller's Anesthesia* has several new chapters that have been created in one of two ways—either by introducing topics that have grown in importance since the publication of the previous edition or by dividing a very large chapter into two smaller ones. Ten of the chapters cover topics new to this edition, such as "Perioperative and Anesthesia Neurotoxicity" (Chapter 15), "Gastrointenstinal Physiology and Pathophysiology" (Chapter 21), and "Palliative Medicine" (Chapter 65).

Historically, anesthesia has been dominated by intraoperative care. Over many years, the preoperative and postoperative periods of perioperative care have become more prominent. This development is evident in the names of our institutions as more and more anesthesia departments have changed their titles to better reflect both anesthesia and perioperative care. Accordingly, the chapters "Perioperative Management" (Chapter 3) and "Anesthesia Business Models" (Chapter 12) were included. Developments in pharmacology have necessitated a new chapter, "Nonopioid Pain Medications" (Chapter 32). Because transplantation of various organs continues to expand, "Anesthesia for Organ Procurement" (Chapter 75) has been added. The associate editors and I thought that we should look to the future by adding "Anesthesia for Fetal Surgery" (Chapter 78) and "Administration of Anesthesia by Robots" (Chapter 86). Lastly, the expansion of anesthesia administration into non–operating room settings has been occurring for many years; thus the chapter "Non–Operating Room Anesthesia" (Chapter 90) was needed.

The splitting of four large chapters has resulted in eight chapters that are of greater focus. This has allowed us to more thoroughly present material that reflects current knowledge in these subjects. The following shows how these new chapters were created:

Seventh Edition Chapter	*Eighth Edition Chapters*
11. Sleep, Memory, and Consciousness	13. Consciousness and Memory 14. Sleep Medicine
29. The Pharmacology of Muscle Relaxants and Their Antagonists	34. Pharmacology of Neuromuscular Blocking Drugs 35. Reversal (Antagonism of Neuromuscular Blockade)
37. Neuromuscular Disorders and Malignant Hyperthermia	42. Neuromuscular Disorders and Other Genetic Disorders 43. Malignant Hyperthermia and Muscle-Related Disorders
75. Anesthesia for Eye, Ear, Nose, and Throat Surgery	84. Anesthesia for Eye Surgery 85. Anesthesia for Ear, Nose, and Throat Surgery

The separation of these topics into two chapters has another noteworthy benefit; we have added to our list of experts new authors who are recognized authorities in their specialties. Also, three chapters devoted to transfusions and coagulation have been placed in the overall category of "Patient Blood Management" (Chapters 61, 62, and 63).

As we proceeded with this book, a unique opportunity was presented to us and resulted in Chapter 112, "Evaluation and Classification of Evidence for the ASA Clinical Practice Guidelines." For many years, the American Society of Anesthesiologists (ASA) has developed practice guidelines on a broad spectrum of clinical and anesthetic specialty activities. These guidelines have been developed based on a well-defined process that incorporates input from many sources, including extensive examination of the literature and clinical insights from anesthesia practitioners. We think that the ASA guidelines have had considerable positive influence on our clinical practices and that it is important to document and understand their history and the course by which these guidelines were developed. We are grateful to Richard T. Connis, David G. Nickinovich, Robert A. Caplan, and Jeffrey L. Apfelbaum for organizing these guidelines for the current edition of this book.

The revision of the table of contents and the selection of authors was a very intense process. Initially, the associate editors, the publishing staff, and I discussed the new table of contents and potential authors online. We then met as a group to carefully review and select subject matter experts. Often the authors who wrote a chapter for the seventh edition were asked to do so for the eighth edition. To ensure that submitted chapters were updated and met our quality standards, we initiated a very thorough review process that included the associate editors, editorial analyst Tula Gourdin, and myself. After our reviews were completed, the manuscript for each chapter was then sent to the publisher for further review and creation of the page proofs. From there, all chapters were sent through a final review cycle by the editorial staff and the authors. We tenaciously adhered to this rigorous and comprehensive editorial process so that we could present an international text like no other in our field. This edition is a collection of the knowledge and experience of some of the world's most renowned anesthesiologists. It thoroughly covers anesthesiology, its subspecialties, and related subjects, and its content is brought to our readers with our upmost attention to quality and veracity.

We are especially proud of Chapter 2, "International Scope, Practice, and Legal Aspects of Anesthesia." This chapter was introduced in the previous edition and continues in this edition with new and updated content. In this edition, we elicited individual contributions from leaders in anesthesiology all over the world. Each contributor describes the development and current status of anesthesiology in his or her region or country. The following have been added for this edition:

1. Discussions of anesthesiology in Brazil by Maria J.C. Carmona
2. New coauthors for Japan (Naoyuki Hirata), Europe (Jannicke Mellin-Olsen), and Russia (Yury S. Polushin)
3. A section on safety and medicolegal initiatives in various regions of the world

A significant number of the chapter authors are from countries other than the United States. All of our decisions regarding this edition were made with the strong motivation to make this text truly international. Fortunately, the increasing prominence of information technology has facilitated the transfer of clinical concepts globally; so with just a handful of exceptions, most countries are no longer intellectually isolated.

Miller's Anesthesia, eighth edition, includes access to the Expert Consult website, allowing users to view the complete text online from any computer and to download the electronic book to a smartphone or tablet. Fully searchable and containing references linked to PubMed abstracts and full-text articles, the website is a powerful tool that gives the reader access to interactive content and a seamless integration between devices. In addition, Expert Consult offers the reader regular content updates and an extensive video library that features video presentations of anesthesia procedures, including airway and ultrasound-guided regional anesthesia techniques.

In addition to our authors, the associate editors of *Miller's Anesthesia* are recognized internationally for their contributions to anesthesiology. One of our associate editors, William L. Young, MD, passed away at the beginning of the review process for this edition. The Remembrance section summarizes Bill's enormous contributions to anesthesiology and his passion for jazz music. During our concerted efforts with writing, editing, and developing the eighth edition, Dr. Young's influence and dedication to excellence were always present.

We wish to express our appreciation to the individual contributors of this 112-chapter book, including those authors from previous editions whose contributions laid the foundation for this edition. *Miller's Anesthesia* would not have been possible without their hard work and dedication. We also acknowledge the contribution of time and expertise by the associate editors, Neal H. Cohen, Lars I. Eriksson, Lee A. Fleisher, and Jeanine P. Wiener-Kronish, and William L. Young. We are grateful for the ongoing efforts of editorial analyst Tula Gourdin, who managed communication with the contributors and the publisher, facilitated the flow of manuscript and page proofs, and checked every detail to ensure that the chapters are as accurate and consistent as possible. We also wish to acknowledge our publisher, Elsevier, and the help and dedication of their staff, in particular executive content strategist, William R. Schmitt; senior content development specialist, Ann Ruzycka Anderson; and senior project manager, Doug Turner.

RONALD D. MILLER, MD, MS

Remembrance



William L. Young, MD
August 6, 1954–August 1, 2013
(Pictured at the UCSF Department of Anesthesia's Fiftieth Anniversary Gala on November 15, 2008)
Professor and Vice Chair
Department of Anesthesia and Perioperative Care
Professor of Neurological Surgery and Neurology
Director, Center for Cerebrovascular Research
University of California, San Francisco, School of Medicine
Associate Editor, *Miller's Anesthesia,* editions six through eight
(Courtesy Christine Jegan.)

William L. Young, MD, the James P. Livingston Endowed Chair in the Department of Anesthesia and Perioperative Care at the University of California, San Francisco (UCSF), was an accomplished anesthesiologist and prolific investigator. His work has had an impact on the scholarly development of neuroanesthesia and on our ability to understand the mechanisms, pathophysiology, and care of patients with neurovascular disease.

In 2009 he was awarded the American Society of Anesthesiologists (ASA) Excellence in Research Award, the highest honor that the ASA can bestow on an investigator, and it is hard to imagine a more deserving colleague. He was instrumental in establishing the multidisciplinary UCSF Center for Cerebrovascular Research, which has been the vehicle for extending the boundaries of our specialty's influence to include neurosurgery, radiology, neurology, and other various neuroscience fields. When interviewed for our department's fiftieth anniversary, Bill said, "Ultimately, the current status of our specialty should be an effect—not a cause—of the questions we ask, and our reach should exceed our grasp." It is this approach that distinguished his career and points the way for anesthesiology to continue to thrive.

Bill grew up in Munster, Indiana, and coincidentally we both attended medical school at Indiana University. In 1985, after clinical anesthesia training at New York University Medical Center, he joined the faculty at the Columbia University College of Physicians and Surgeons, where he had completed clinical and research fellowships. He quickly grew into a productive and successful National Institutes of Health (NIH)–funded investigator in the specialty of anesthesiology. In 2000 he relocated to UCSF where he became the James P. Livingston Professor and Vice Chair of Anesthesia and Perioperative Care. His unwavering dedication to excellence had an enormous impact on faculty members in our department and across the entire UCSF campus. His productivity in research and NIH grant funding was incredibly consistent. He had continuous NIH funding since 1990, two concurrent NIH grants since 1994, and at least three—and up to five—NIH grants concurrently since l999. He was one of the most prolific recipients of NIH grants in the history of anesthesiology.

He was the principal director of a program project grant, "Integrative Study of Brain Vascular Malformations," which was renewed in 2009 for a second 5 years. Bill's remarkable run began when he was an early recipient of the Foundation for Anesthesia Education and Research (FAER) award system; his success supported the direction that FAER and the ASA pursued in those days. Bill's focus and calm dedication to excellence were inspiring to me personally, and he served as a role model for the entire UCSF faculty.

The substance of his research was even more impressive. From his early studies on the cerebral effects of anesthetics, he gradually moved to more unexplored pathophysiologic areas in anesthesia, neurocritical care, and intraoperative neurosurgery. This led to the understanding of reperfusion hyperemia, or perfusion pressure breakthrough, which is associated with arteriovenous malformation treatment. This work also led to epidemiologic, clinical risk prediction, and imaging studies. When he arrived at UCSF from Columbia University, Bill

approached cerebrovascular biology of vascular remodeling and angiogenesis using molecular and genetic techniques. Studying patients with giant cerebral aneurysms, he used network models, including innovative collaborations with bioengineers and imaging scientists.

Bill was someone the NIH would turn to when it needed leaders. From 1997 until his death, he served on various NIH review committees. In 2005 he became a member of the Clinical Neuroscience and Disease Study Section. In 2008 he was selected to co-chair the first-ever National Institute of Neurological Disorders and Stroke (NINDS) workshop on vascular malformations of the brain. The workshop, which took place in Madrid, involved a gathering of some 50 international clinical and basic science experts. In addition, Bill was instrumental in expanding the number of anesthesiologists conducting high-level basic and clinical research—filling a critical need that was well recognized by ASA leadership and several Rovenstine Lecturers.

He had remarkable success in helping junior faculty obtain career development awards and served as primary mentor on seven NIH-funded K awards (K08, K23, and K25) and three American Heart Association development awards. He was one of the first to be recognized by the NIH for mentoring efforts by receipt of a K24 award in 1999. Several of his trainees are faculty in institutions that include Columbia, Cornell, and UCSF.

His editorial responsibilities were also extensive, having served on the editorial boards of the *Journal of the American Heart Association, Stroke,* and *Neurosurgical Anesthesia*, as well as on the associate editorial board of *Anesthesiology* earlier in his career. He was also the coeditor of a major text, *Cerebrovascular Disease*, and an associate editor for the sixth, seventh, and eighth editions of *Miller's Anesthesia*.

Perhaps the most intriguing evidence of Bill's multifaceted approach to his work and his world was that he was a passionate and professional-level jazz pianist. Being a pianist myself, I was stunned by the complexity and innovation of the many chord progressions he used in his jazz music. When he moved to San Francisco, he gravitated toward the jazz scene and easily worked his way into jam sessions with some of our city's superb professional jazz musicians. And for our department's fiftieth anniversary party with more than 300 attendees, he provided our after-dinner music. Why hire someone else when Bill could do the job as well as anyone?

By using the unique skillsets gained from his training in anesthesia, Bill Young made major contributions to understanding both the biology and the management of neurovascular disorders that many anesthesiologists must manage. He would say, "If anesthesiologists take care of vascular disease patients, then we should strive to understand the totality of the disease process and not accept any *a priori* limitations to the nature of the questions we ask nor investigations we pursue." Indeed, his search for answers began at the bedside, thus instigating the most innovative and productive physiologic approach to understanding these disorders to date, and he continued to conduct this search at the level of program director of an NIH program project grant at the time of his death. Reaching the limits of current physiologic technology, Bill recognized real progress would only occur through a thoughtful laboratory and bedside approach.

For all of these reasons and more, my colleagues and I remember Bill Young and the life he led, which was one of dedication to excellence in all he did.

Ronald D. Miller, MD, MS

Chapter 1

Scope of Modern Anesthetic Practice

LARS I. ERIKSSON • JEANINE P. WIENER-KRONISH • NEAL H. COHEN • LEE A. FLEISHER • RONALD D. MILLER

Acknowledgment: The editors and the publisher recognize the contributions of Dr. William L. Young, who was a contributing author to this topic in prior editions of this work. It has served as the foundation for the current chapter.

Key Points

- Advances in anesthesia care and the scope of anesthesia practice have impressively facilitated the overall care of increasingly complex patient populations. This is especially important for the care of patients who are at the extremes of the age spectrum (i.e., younger and older). One indication of the expanded scope of anesthesiology is the increase in the number of chapters in this book, from 46 in the first edition (1981) to 112 in the eighth edition (2014).
- The scope of anesthesia services has expanded, in part due to the increase in the number of minimally invasive or noninvasive procedures being offered to patients. These changes in practice create both opportunities and challenges for anesthesiologists. The settings in which anesthesia is required continue to expand outside of the operating room and into ambulatory and other settings. These changes in practice require new providers with varying backgrounds and skills. These changes also provide the opportunity to identify new models of care, including telemedicine, to support the diverse patient and provider needs. A major challenge will be to continue the emphasis on safety as these new approaches to anesthesia care become less invasive but in non–operating room locations.
- Overall, national and international mandates for quality, competency, and uniform processes will change the manner in which anesthesia is delivered. More standardization and protocols will be used. These mandates will allow and require more evaluation of clinical practices and research to define the optimal approach to anesthesia and the clinical competence of the providers caring for each patient.
- The anesthesia workforce is changing as a result of subspecialization and expanded use of advanced practice nurses, anesthesia assistants, and other provider groups. The increase in nurses with advanced degrees will have added effects on the practice of anesthesiology. Team management will become more commonplace and, as a result, relationships between physicians and nurses will become a critical determinant of patient outcomes.
- Advances in anesthesia practice based on the underlying science and quality initiatives have been impressive. Although these advances have contributed greatly to the quality of patient care and to patient safety, current trends suggest that there is insufficient breadth and scope of research in anesthesiology to ensure its continued success. Anesthesiologists must be encouraged to engage in research to maintain and even enhance our academic foothold in medicine overall. There are increasing opportunities for multidisciplinary research; these approaches need to be embraced to increase the number of research-trained anesthesiologists. It is also necessary to identify alternative funding sources to support the specialty.



Figure 1-1. Changing scope and settings of anesthesia and perioperative medicine. **A,** *The Cure of Folly,* by Hieronymus Bosch (c 1450-1516), depicting the removal of stones in the head, thought to be a cure for madness. **B,** Friedrich Esmarch amputating with the use of anesthesia and antisepsis. **C,** Harvey Cushing performing an operation. The Harvey Cushing Society is observing (1932). **D,** Placement of a deep brain stimulator for the treatment of Parkinson disease using a real-time magnetic resonance (MR) imaging technology (MR fluoroscopy). The procedure occurs in the MR suite of the radiology department. The patient is anesthetized (**D**) and moved into the bore of the magnet (**E**). A sterile field is created for intracranial instrumentation (**F**), and electrodes are placed using real-time guidance (**G**). *(**A,** Museo Nacional del Prado, Madrid. **B,** Woodcut from Esmarch's* Handbuch Der Kriegschirurgischen Technik *[1877]; Jeremy Norman & Co. **C,** Photograph by Richard Upjohn Light (Boston Medical Library). **D to G,** Courtesy Paul Larson, University of California–San Francisco, San Francisco Veterans Administration Medical Center.)*

SCOPE OF ANESTHESIA AND PERIOPERATIVE CARE IN HEALTH CARE AND FORCES THAT WILL CHANGE PRACTICES (Fig. 1-1)

Since 1940, the specialty of anesthesiology has contributed greatly to major advances in health care. The contributions by anesthesiologists to the care of surgical patients have been well described in the literature. With the use of new approaches to general and regional anesthesia, new technologies to facilitate the handling of patients with complex physiologic and anatomic (e.g., airway) management and improved monitoring, anesthesiologists and surgeons have been able to provide care to an increasingly complex patient population safely and with few complications. At the same time, anesthesiologists have been instrumental in a number of other ways to improve patient care, including but not limited to new approaches to cardiopulmonary resuscitation, technical developments such as arterial blood gas machines, pulse oximetry for monitoring adequacy of gas exchange, the creation of critical care medicine as a subspecialty, and for advances in pain medicine and transfusion medicine. Each of these advances has benefited patients greatly, but they have also resulted in marked expansion of the scope of anesthesiology. Many of these advances are outlined in detail throughout the 112 chapters in this edition of the text. Each chapter also reflects the advances in the topics covered in these chapters. The book also reflects the commitment of anesthesiologists to addressing the medical needs of society in addition to providing outstanding care to individual patients. Anesthesiologists both in the operating room environment and throughout the health care system currently provide care to a considerable portion of the population in industrialized countries. Approximately 7% to 8% of the total worldwide population requires anesthetic management in association with surgical or diagnostic procedures annually. Perioperative care and anesthetic management have thus had a considerable effect on global public health and have a vital role in health care systems throughout the world. In addition, the specialty of anesthesia has extended beyond the boundaries of perioperative care to include critical care, pain management, sleep medicine, and palliative care.

Advances in diagnostic, pharmacologic, and technical resources have made it possible to provide anesthesia and perioperative care to patients at the extremes of age (i.e., both very young and very old) and to those with complex comorbidities. These systematic developments and enhancements in perioperative care have paralleled and

perhaps facilitated an equally rapid introduction of novel surgical techniques and resources for less invasive surgical approaches. Surgical outcomes have improved considerably, allowing anesthesiology to care for patients with more advanced and complex disorders. At the same time, anesthesiology is recognized as a cornerstone within the modern hospital, extending beyond the operating room.

While most patients understand how important anesthesiology has been to their care, the Institute of Medicine (IOM) of the National Academy of Sciences has publicly praised the commitment of anesthesiology to patient safety and the successful initiatives to ensure it in the book *To Err is Human*.[1] These improvements in the quality and safety of perioperative care are the result of the combined dedication of the entire profession, including both community practices and academic anesthesia departments and their training programs. The combined efforts to obtain a fundamental understanding of the mechanisms behind anesthesia and regulation of vital organ functions and the biologic processes that drive organ failure and complications in the perioperative setting have been crucial. Novel therapies and advanced monitoring equipment have improved patient safety and outcomes in the perioperative setting, pain management, and intensive care medicine.

Although the role of anesthesiology services within the health care system has expanded and the effect of anesthesia on overall quality and safety has been remarkable, health care continues to undergo radical changes that will affect the roles, responsibilities, and scope of anesthesia services in the future, within the United States and throughout the world. The involvement and role of anesthesia providers is gradually increasing within modern perioperative care processes. A more extended scope for preoperative and postoperative care includes more specialized preoperative evaluations and risk assessments with potential biomarkers of adverse outcomes. As the importance of extended and intensive postoperative care for at-risk patient populations increases, the role of anesthesiologists will expand and the practice of anesthesia and perioperative care will become more diversified. In addition, because an increasing percentage of the general population within industrialized countries is older, many with comorbidities will require diagnostic and surgical procedures, with the participation of anesthesiologists in their perioperative care becoming even more critical. In addition, as more of these patients receive complex clinical services, the financial burdens associated with care will escalate throughout the world. The increased cost will be counterbalanced with more scrutiny on the need for surgical care, the expectation that providers must document quality of care, and the requirement to use care pathways and protocols to standardize care. In a changing health care system, anesthesia and perioperative care need to have well designed quality assurance systems and outcome measures that document that the services provided are of the highest quality and safety. Relevant measures of patient outcomes, costs, and cost-benefit analysis will be required for payers, government agencies, and the general public.

Technology is also having a major effect on clinical care. In the surgical setting, technical advancement has led to less invasive and traumatic procedures with fewer negative side effects (e.g., tissue trauma, pain, risk of complications). These advancements can potentially shorten the duration of the perioperative period and subsequent need for in-hospital care. New devices are becoming available to allow remote monitoring of patients not only during and immediately after procedures, but also in the extended care and home environments. Alternative delivery systems for anesthesia will allow it to be provided in nontraditional settings beyond the operating room or procedure rooms, to the intensive care unit, other hospital units, and perhaps other clinical settings. Changes in the anesthesia workforce are also occurring, and additional will be created to facilitate the care of a larger group of patients by a collaborative group of providers working in physical proximity to the patient and, at the same time, with remote monitoring and medical direction from anesthesiologists. The involvement of advance practice nurses and other medical personnel in anesthetic practice has also allowed anesthesiologists to assume greater roles in perioperative management, rapid response teams, triage, and resuscitation outside of the operating room environment.

Electronic health records are being used worldwide, allowing for improved documentation of individual patient care and providing important data for millions of patients. Eventually, minimal to no human interaction will be required for complete data capture and integration for an automatic vigilant system. Complete integration of surgical equipment, anesthesia, and monitors of infusion pumps will enable an analysis of all patient data and clinical responses to facilitate patient care. Assessments regarding the quality of anesthesia can be made by analyzing information from large numbers of patients to evaluate outcomes of care and to facilitate the development of evidence-based clinical practices. One example is the comparative effectiveness and data-mining studies in orthopedic surgery patients; these studies have concluded that neuraxial techniques lead to superior outcomes.[2,3] Furthermore, data can be collected prospectively in consecutive patients from different environments and countries so that perioperative outcomes can be compared and best practices can be identified.[4] Of approximately 46,000 patients in this investigation, 4% died before hospital discharge and the majority of patients who died (73%) were not admitted to a critical care unit after surgery. Conclusions from this investigation suggested that planned critical care after surgery improved outcomes as compared with unplanned admissions to critical care, which were associated with poorer outcomes. Given the more frequent incidence of perioperative mortality than expected, future investigations are planned, including similar investigations in the United States. These investigations will lead to an understanding of the factors that are important behind perioperative mortality and investigations into the treatments that lead to better outcomes.

The IOM described and evaluated the effectiveness and cost of American health care systems (Report Brief, January 2013).[5] They have compared health care outcomes in the United States with those in the rest of the world. The United States spends more money per person than any

other country, yet ranks seventeenth in the world for life expectancy at birth. The IOM concluded that Americans fare worse in several health areas, including infant mortality, injuries, adolescent pregnancy, HIV, drug-related deaths, disability, and especially obesity and diabetes. They also noted that the United States has a larger uninsured population with lapses in the quality and safety of care outside the hospital and more frequent rates of drug abuse, violence, and use of weapons. Americans benefit less from safety net programs than in other countries. In another report (Report Brief, July 2013),[6] the IOM concludes that Medicare payment (i.e., a major source of funding for American medicine) needs to "reorient competition in the health care system around the value of services provided rather than the volume of services provided." These brief conclusions serve as the basis upon which major changes are occurring in health care delivery and financing, particularly regarding the need to demonstrate value. Anesthesia must understand all these changes and priorities in health care delivery and finance to define how to participate and benefit as a specialty and to retain its leadership role in quality and safety.

This summary emphasizes the implications for anesthesiology, but there are also ramifications for medicine overall, particularly in but not limited to the United States. Worldwide, the quality and expense of health care is a challenge. The changes occurring in health care obviously have implications for the role of anesthesiology in both the practice and delivery of medicine overall. Some of the guidelines developed by the American Society of Anesthesiologists (ASA) document the leadership role the specialty has assumed in addressing the needs of our patients (see Chapter 112.).

As mentioned previously, the availability of large clinical databases will also prove to be a valuable tool for refining and improving clinical care. These databases will enable data mining to evaluate the process of care and approaches to identify best practices. Anesthesiology, with its expanding roles in the health care delivery system must be an integral participant in these changes. Clearly, the outcomes after major surgery need far more attention globally with sufficiently large clinical studies focusing on patient-centered outcome measures related to survival and relevant quality-of-life end points. We can only speculate as to what the practice of anesthesia will be like in the future, but these forces will likely have a major effect on the overall scope of anesthesia and perioperative care, thus creating new opportunities that anesthesiology should embrace. Analysis of current national and global priorities can provide some basis for anticipating the future of anesthesiology.[7]

AGING OF SOCIETY

The aging of the world's population combined with improvements in anesthetic and surgical methods are resulting in older patients undergoing increasingly complex surgical procedures. This patient population commonly has decreased general health and organ function, and an increased incidence of chronic medical illness (see Chapter 80). In the United States, the national social insurance program, Medicare, covers more than 47 million Americans, with 39 million being older than 65 years and 8 million having disabilities (data from IOM). The use of surgical services by older patients is not unexpectedly more frequent than with younger patients. For example, in a report by the Centers for Disease Control and Prevention studying inpatient hospitalizations in the United States for 2005, there were 45 million procedures performed on inpatients with a similar number of outpatient procedures. From 1995 through 2004, the rate of hip replacements for patients 65 years and older increased 38%, and the rate of knee replacements increased 70%.

CHANGES IN LOCATION OF CARE

Because of the high costs associated with hospital care, the funding agencies (governmental and private insurance companies) are pressuring providers to perform more procedures in nontraditional settings, both within the hospital and in ambulatory and other less costly sites.[8] Technology and the shift to minimally invasive procedures associated with advances in anesthesia care are facilitating this transition. Providing anesthesia in ambulatory surgical settings and out-of-hospital offices has dramatically increased over the past several decades. With this transition, it is becoming critically important to determine when an anesthesiologist or other anesthesia provider is required to provide care, when alternative providers with or without supervision might be appropriate, and the role for the anesthesiologist in defining standards of care. There are many situations when an anesthesiologist may not be required, for example in administration of conscious sedation to an otherwise healthy patient, but an anesthesiologist is the most appropriate provider in many situations. Not only are there situations in which the risks associated with airway compromise are great (e.g., deep sedation), but there are many clinical situations in which care by an anesthesiologist has been demonstrated to improve clinical outcome and often reduce overall costs of care. Anesthesiologists need to participate actively in discussions within their respective institutions or health systems to define the standards of care, implement best practices, and document clinical value.

In many cases, in part because of costs and changing capabilities, extended postoperative care has shifted from the medical setting to the home. For some families, this transition has created significant clinical and social problems. As care is moved from inpatient settings to other nonhospital settings, anesthesiologists must be involved in determining the most appropriate setting for a procedure and how to manage the transitions of care. Advances in technology can facilitate some of these changes by allowing remote monitoring, and they can create opportunities for anesthesiologists to assume a role in managing patients in these new settings.[9]

COST OF MEDICAL CARE

As the cost of health care in the United States approaches 18% of the gross domestic product,[10] there has been an intensified interest in determining the factors that are

increasing the costs, attempting to find methods to decrease the cost, and obtaining more value for money spent. The primary cost driver in the United States appears to be technical progress, because to some extent the increases in health care costs are occurring throughout the world, regardless of the payment system.[11-13] The increases in the elderly population and patients with chronic disease within that sector are also adding to health care costs.[12]

The escalating costs have led to pressure to get more value for the money spent. There have been pay-for-performance programs—that is, rewarding medical care that is consistent with published evidence and not paying for care that is inconsistent with evidence.[15-17] For the most part, the performance measures, at least in the United States, are process measures rather than measures of outcome (e.g., for anesthesia services, administering antibiotics within 1 hour of incision rather than rates of infection). The concept of pay-for-performance and its implementation have also migrated to other countries, particularly the United Kingdom.[18]

In the nonsurgical arena, the concept of pay-for-performance has been studied for several years.[19,20] In addition to paying for performance, in the United States there is increasing emphasis on not paying for "never" events, such as decubitus ulcers or urinary tract infections, unless they are present on admission to the hospital. The translation of this approach is lack of payment for complications, especially if they could have been prevented with better care (i.e., never events). Because of anesthesia's role in the entire continuum of perioperative care, including postoperative intensive care and pain management, we have an opportunity to influence many of these practices, which can be associated with poor outcomes and increased cost, but which have traditionally not been considered under our domain of care. For example, appropriate and timely administration of antibiotics has a significant effect on surgical site infection, but prior to the initiation of the Surgical Care Improvement Project (SCIP), many anesthesiologists were arguing that control of antibiotics was not within their domain.[21] Anesthesiologists and intensivists can also have a significant effect on the rate of ventilator-associated pneumonia or outcomes that are dependent on strategies for intravenous fluid therapy in the critically ill patients.[22] However, some of these proposed measures, particularly the use of ventilator-associated pneumonia as a quality measure, have become controversial.[23] Pain is considered the fifth vital sign, and the management of postoperative pain is another area in which we can have a significant effect on cost and potential interactions with other members of the hospital team.

PROCESS ASSESSMENT AND QUALITY METRICS

Anesthesiology was among the first professions to focus on reducing the risk of complications partly by developing evidence-based guidelines and standards. The American Society of Anesthesiologists standards and practice parameters are prime examples of this important direction in medicine.[24] Anesthesiology should continue to be involved in these initiatives and should do so collaboratively with other disciplines, including but not limited to surgical specialties. Examples from the perspective of the United States are the involvement of anesthesiologists in the Society of Thoracic Surgeons database and the National Surgical Quality Improvement Project (NSQIP).[25,26] More recently, the Society of Cardiovascular Anesthesiologists has begun discussions with the Society of Thoracic Surgeons. On the other hand, anesthesiologists have been involved from an early stage in quality initiatives with the Institute for Healthcare Improvement and the Surgical Care Improvement Project.[27] Moreover, in many countries, anesthesiology has a key role in the development of quality assurance systems within prehospital care, multidisciplinary critical care, and pain medicine.

Another quality measure that will have global impact on anesthesiologists and all physicians is the new demand for documentation of competency for each clinical privilege assessed not just at the time of recredentialing, but also assessed on an ongoing basis. Defining competency will demand that medicine in general and anesthesiologists specifically adhere to more protocols; the concept of safe anesthesia includes standardization of clinical management overall, including the development and use of standardized protocols. Rather than stifling medical innovation, standardization should be viewed as a mechanism for evaluating process and outcomes; such comparisons cannot be made without standardization. Anesthesiologists will need to be leaders in creating quality and competency metrics. This opportunity can be used to formulate meaningful metrics for practicing anesthesiologists and training physicians. Such metrics will also be required for certified nurse anesthetists and other health care professionals as well. In some cases, documentation of competencies will require the use of simulation or other models to emulate the clinical environment, particularly for rarely performed procedures.

"Change process" has become a cottage industry in medical care, with courses being offered on how to change behaviors and processes in medical care. These mandates can be imposing and possibly frustrating, but they offer the opportunity for more research on identifying the processes that actually improve patient outcomes. These mandates also allow anesthesiologists to assume a leadership role in team management. To accomplish this mandate, new skills need to be taught, including leadership training, improved communication skills, and improved relationship training in the overall atmosphere of pursuing excellence in clinical care and education.

Anesthesiologists already have a long tradition with and training in system approaches to care. These approaches date back to the original checklists created over 50 years ago for the anesthesia machine. It is critical that this skill set be disseminated beyond the intraoperative setting to medicine overall. The understanding of these principles has created many leadership responsibilities for anesthesiologists in a variety of venues including surgical facilities, ambulatory surgery centers, and medical centers.

CHANGES IN PERSONNEL

Within the United States, there are approximately 250,000 active physicians, one third of whom are older than 55 years and are likely to retire by 2020.[28] Although the enrollment in U.S. medical schools in the 1960s doubled, there has been no such increase from 1980 to 2005. Thus, there has been zero growth in U.S. medical school graduates. Yet, the U.S. population has increased by more than 70 million, creating a discrepancy between the supply of medical school graduates and the demand for physician-associated care. Similar developments are seen elsewhere (for more detailed description of workforce changes in Europe, see Chapter 2).

From a global perspective, the number of women in medical schools has increased, so that approximately 50% of the medical students are now women.[29,30] Furthermore, independent of gender, physicians work hours have decreased over the past 40 years.[28,31] To decrease the incidence of fatigue and long durations of "being on call," the reduction in work hours is probably accounting for improved quality of care in addition to lifestyle, but it has consequences. The workforce requirements will have to increase in response to the reduced duty hours and to address the implications of the aging anesthesiologists.

A number of methods have been used within the United States to expand the work force. There has been a steady increase in the recruitment of international medical graduates; approximately 60,000 international medical graduates are residents and constitute 25% of all residents in training.[32] In the United States, the number of osteopathic schools and schools offering advanced degrees in nursing, including training of nurses to become nurse anesthetists, has increased.[28] Given the growing demand for medical care partly owing to the increase in the geriatric population, this need will most likely be met by a combination of physician and nonphysician personnel.

RESEARCH

In terms of creative new investigations, most benchmarks suggest that the specialty of anesthesiology fares poorly in funding when compared with other disciplines, especially clinical disciplines. Using data gleaned from publicly available National Institutes of Health (NIH) sources, Reves[33] compared the specialty with a number of other medical disciplines and produced a troubling figure showing that anesthesiology ranked second to last in funding. Disturbingly, this low ranking has existed for many years preceding Reves's publication in 2007 and has not improved in the years since. However, the fact that anesthesiology in the United States is in the lowest quartile of NIH funding continues to be a concern, particularly because the external forces on the practice components are generally applicable to all specialties. The NIH is not the only source of funding that might influence the specialty; in fact, it is not even the largest source of total research funding in the United States (Fig. 1-2).[34] For all sources, there has been a doubling over the past decade in research expenditures for health and biomedical science research, although compared with biologically based disciplines, health services research is considerably less well funded. In fact, much of the clinical and some basic research are funded from other sources other than the NIH or other federal programs. These sources include foundations (e.g., Foundation for Anesthesia Education and Research) and industry and local institutional sources. Some departments have traditionally supported research by devoting some of their clinically derived incomes for research, especially for young faculty members.

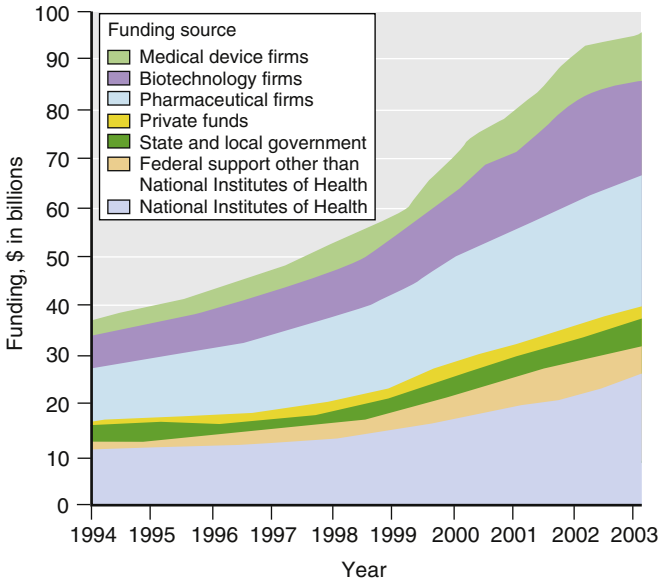


Figure 1-2. U.S. Research expenditures, 1994 to 2003, by funding source. *(From National Center for Health Statistics: Health, United States, 2007, with Chartbook on Trends in the Health of Americans. <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?indexed=google&rid=healthus07.chapter.trend-tables>; National Center for Health Statistics: Health, United States, 2007 With Chartbook on Trends in the Health of Americans Hyattsville, MD: 2007. <http://www.cdc.gov/nchs/hus/previous.htm.>(Accessed 19.05.14.))*

The financial challenges of funding research and the increasing clinical demands of faculty in the United States are evident when reviewing the publications in peer-reviewed journals. In anesthesiology journals, the fraction of original peer-reviewed articles from non-U.S. authors has increased dramatically. The reasons for this change are probably multifactorial, but warrant evaluation. Some have suggested that European and Asian investigators are better funded than in the United States. Yet, adjusted per capita, research support in Europe is only 10% of that in the United States, even though the proportion of scientists in the population is similar.[35] Perhaps, U.S. Food and Drug Administration (FDA) policies bear some responsibility. In the 1980s and 1990s, much "new anesthetics and drug" research started in the United States. Now, most of the new drugs are initially approved in countries other than the United States. Historically, the clinical studies with new drugs are started in the countries of initial approval, which is often not the United States. Finally, many young anesthesiologists have started their research based on opportunities driven by industry-funded novel drugs, a situation that is not as readily available currently as in the past.

Participating in research projects that advance clinical care and translate basic science to the bedside requires the

involvement of a diverse group of investigators. Practically all new frontiers lie at the boundaries of established departmental or specialty divisions, which are largely a historical relic of nineteenth-century or early twentieth-century conceptualizations. A look at any large institution's roster of academic divisions yields a growing number of "centers," "programs," and "institutes," reflecting the ever-increasing interdependency of branches in biomedical knowledge.[36,37] In basic science departments, with conjugate names like Physiology and Cellular Biophysics, Anatomy and Cell Biology, Biochemistry and Biophysics, and Cellular and Molecular Pharmacology, it is becoming increasingly difficult to differentiate one faculty research program from another, solely on the basis of the topics and methods of study. Although this is clearly less complicated for those domains that do not involve patient care, the trend is evident. One might cite the example of endovascular surgery as but one example in the collision of technology and historical boundaries of medical specialties.[38] With this change in approach to advances in the specialty, anesthesiology must actively seek collaborative research environments or organizational structures that allow the development of anesthesiology research in close collaborations to relevant basic science groups and departments such as epidemiology and health policy.

Medical research is at one level original creative work that involves systemic investigation of medical phenomena with the direct or indirect consequence of improving health care. However, anesthesiology is in a position to address research questions in new and creative ways, and it has done so taking advantage of the large clinical databases to assess clinical practices, outcomes of care, and evaluate personalized medicine in defining the best way to manage an individual patient. The Anesthesia Quality Institute (sponsored by the ASA) has implemented a robust database of anesthesia care that will improve the current understanding of clinical practices and outcomes and provide valuable insights to guide future advances in care.

More than ever, anesthesiologists are involved in measuring perioperative outcomes and evaluating the comparative effectiveness of medications and techniques, as documented by an increase in the number of NIH training grants in anesthesia.

To have an influence and impact on the clinical and policy research domain, anesthesia must continue to be involved in all aspects of perioperative care. Building on these experiences, an area of potential focus for anesthesia research is in the perioperative outcomes associated with a variety of new or controversial clinical programs that involve a variety of specialties. It is reasonable to assume that in the future reimbursement for delivery of clinical care will be tied to documentation of quality outcomes that are based on demonstrated efficacy of a procedure, such as randomized clinical trials that involve anesthesiologists and surgeons who assess efficacy and define the right patient populations to undergo a procedure. One such example is the randomized clinical trial of lung reduction surgery for patients with bullous emphysema.[39] Similar approaches can be used to evaluate controversial or costly procedures in high-risk patients, as in the case of minimally symptomatic cerebrovascular diseases.[38,40] By participating in the multidisciplinary teams, anesthesiologists can continue to exert influence in other aspects of patient care besides anesthesia and remain key contributors to defining best surgical practices.

In addition to helping define best practices and advance perioperative care, it is critical for anesthesiology as a physician specialty to remain at the forefront of basic science and clinical research. Other disciplines are becoming more actively involved in health care and health policy research, offering advanced degrees, including doctorates in their own disciplines. While their contributions are important to the overall health care needs of patients, it is critical for physicians to pursue and take leadership roles in investigative research. The various governmental and institutional bodies that regulate health care delivery and patients demand that we do so and require that we document our commitment to high-quality, safe, and efficient care—the mainstay of our specialty for the past 50 years.

Complete references available online at expertconsult.com

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Chapter 2

International Scope, Practice, and Legal Aspects of Anesthesia

RONALD D. MILLER, EDITOR

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Use of Spongia Somnifera
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Russia (Yury S. Polushin and Olga N. Afonin)
Southeast Asia (Forian R. Nuevo)

†Deceased.

Chapter Outline—cont'd

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Conclusion

At an international anesthesia conference several years ago, the value of using modern electronic monitoring devices in the operating room was emphasized. Because appropriate monitoring (see Chapter 50) improves patient safety, the speaker hoped that hospitals worldwide would adopt and use these devices. During the question and answer session, however, a physician from another country—one whose hospital resources were limited—expressed his frustration and disagreement with this argument. In his country, he believed, there were other priorities and the sheer cost of monitoring equipment prohibited its widespread adoption. Another physician, also from a country whose hospitals had limited resources, disagreed; he argued that by understanding what monitoring devices were available, he would pick the most effective equipment in accordance with his hospital's limited resources. A spirited exchange ensued. Of course, there is no single correct way for hospitals to spend their limited resources. There was, however, enormous value in this exchange among physicians from different countries with distinct cultures, resources, and perspectives. With these types of discussions, the profession can create fully informed baseline standards that foster more successful levels of patient safety and improved outcomes worldwide.

Such discussions also inspired this chapter on the international or global scope and practice of anesthesia. Throughout the career of this book's editor, Ronald D. Miller, he has had the privilege and pleasure of speaking and working with leading anesthesiologists from all over the world. His work and discussions with international colleagues spurred a desire to recognize and honor the growth and practice of anesthesia outside North America. He wanted to describe the different ways that anesthesia began from place to place and to follow the regions through time so that we can better understand how the various regions influence each other today.

This chapter is the first step in realizing Dr. Miller's hope. Work on this chapter began in earnest when the editor invited a number of colleagues whom he had met over the years—prominent anesthesiologists in their parts of the world—to contribute a short summary describing the growth and practice of anesthesia in their country or region. When the contributions arrived, they proved to be a fascinating read: creative, informative, and inspirational. Yet for all their rich content, they also posed an editorial challenge in that the unique geographic features, cultures, politics, economics, and developments in various regions prompted the contributors to emphasize different ideas, discoveries, or time periods. These differences in emphasis and coverage reflect the freedom that the contributors were given to describe their country or region. In the future, we hope to expand on this topic by covering other areas of practice and including world regions not featured in this chapter.

It was in the face of this challenge that Dr. Schwartz was asked to integrate the short individual contributions into a single chapter without compromising their integrity in the seventh edition of *Miller's Anesthesia*. Dr. Miller and Dr. Schwartz chose to create a chronologic narrative that progresses through three distinct periods. Each period is discussed by region; each regional narrative draws directly from the work of the international contributors. Our intent was to always acknowledge and document the sources and wherever possible maintain each contributor's individual voice, and we hope that we have achieved that goal. Because this chapter was so successful, the associate editors and Dr. Miller decided to retain and update it.

Dr. Miller is deeply grateful to all the colleagues who contributed to this chapter, for their insightful writing and the time that they devoted to their tasks, with the only regret that more contributions of this kind could not be included in this edition because of time and space constraints. This chapter represents a preliminary endeavor and by no means a comprehensive look at the development of anesthesia around the world. Future editions will deepen and broaden the international focus.

The first section of this chapter is a sprint through a vast stretch of history, from ancient times through the early twentieth century. Over these 2000 or so years, with a few notable exceptions, the practice of anesthesia grew independently by region in response to the need for pain relief during medical procedures.

The second section covers the period from the 1920s through the early 1980s. Modern communications and international travel expanded dramatically during this period, leading to increased cross-pollination of anesthesia techniques. Physicians and researchers began to travel regularly to foreign countries, receive training and education abroad, and hear others speak at conferences. As the number of international journals increased, knowledge about emerging practices in anesthesia spread further.

The third section covers the time from the late 1980s through the present. This period has been exciting because today nearly all anesthesiologists, no matter where they practice in the world, can gain access to the information necessary to deliver safe anesthesia at the most basic level. Although there are still significant differences in resource levels, some of which undermine the practice of safe anesthesia, at least all anesthesiologists worldwide today know how to avoid the common complications of anesthesia that can endanger patients' lives. This section details the state of anesthesia in the regions covered—from education, accreditation, professional exchanges, and actual practice to available facilities and equipment. No matter how remote a clinician may be, access to a computer will enable the use of the most current principles of perioperative care. Knowledge should no longer be a limiting factor. Unfortunately, limited financial resources can constrain the availability of modern technology.

A fourth section has been added to cover safety and medicolegal aspects. To accommodate the contribution of one of our authors, a future considerations section has also been included.

The chapter concludes by raising questions about what is next in terms of the way various countries and regions practice anesthesia. How integrated should the practice of anesthesia become? What can be done to increase the quality of care worldwide? Certainly many international organizations have tried to enhance the quality of patient care worldwide, which this author recognizes. Leading authors from around the world have been asked to describe the evolution and status of anesthesia in their respective countries. Although there are no simple answers, learning from each other will enhance the transfer of information and knowledge worldwide.

EARLY HISTORY OF INTERNATIONAL ANESTHESIA

Before the early twentieth century, transfer of information internationally was obviously limited. This editor thought that a comparison of the evolution of anesthesia in different countries would not only be interesting, but also educationally instructional regarding the effects of societal pressures and clinical needs on its development. In response to patient needs, physicians from various regions came to different but often similar conclusions about pain relief and surgical anesthesia. In many places, herbs, opium, and alcohol were the mainstays of pain relief medication.

Regions were not completely isolated, however. As the narratives herein describe, the traditional ways of spreading culture and information, such as war, trade, and immigration, enabled at least some sharing of anesthesia techniques. In particular, the first published account of ether used as an anesthetic in 1846 seems to have been a watershed for the field of anesthesia.

BRAZIL (Maria Carmona)

The first ether anesthesia in Brazil was administered in the Military Hospital of Rio de Janeiro by Dr. Roberto Jorge Haddock Lobo on May 25, 1847. Ether was soon replaced by chloroform, which became widespread until other new anesthetic drugs were discovered and introduced into medical practice. Until the early twentieth century, anesthesia was delivered primarily by nurses and surgeons.

INDIA (Deepak K. Tempe)

The history of anesthesia in India dates back to the era of Susruta, the great surgeon of ancient India. During his time, around 600 BC, operations were performed with the use of opium, wine, and Indian hemp (an herb). Surgical science was called *salya-tantra* (*salya*: broken parts of an arrow and other sharp weapons; *tantra*: maneuver).[1]

Much later, in AD 980, Pandit Ballala mentioned in *Bhoj Prabandh* that Raja (King) Bhoj underwent a cranial operation under the anesthetic influence of a plant called *sammohini*. The same plant was applied as a healing balm to surgical wounds. A drug called *sanjivan* was administered to revive the Raja and help him regain consciousness.[2]

Nearly 900 years later, after the first widely publicized demonstration of ether anesthesia in the United States in 1846, India quickly followed suit by administering ether anesthesia on March 22, 1847, in Calcutta under the supervision of a surgeon named Dr. O'Shaughnessy.[3] Later, chloroform was also used but fell into disrepute because of the frequent morbidity associated with it. Despite this morbidity—and the fact that the world began to discard chloroform in preference for ether by 1890—India continued to use chloroform until 1928.

Among the several interesting case reports related to anesthetic practice is the emergency appendectomy performed on Mahatma Gandhi on January 12, 1925, at Sassoon Hospital, Pune (Fig. 2-1). During an electricity failure, the mahatma was administered open-drop chloroform anesthesia, with the surgery being completed by the light of a kerosene lamp and battery-operated torch.[4]

JAPAN (Naoyuki Hirata and Michiaki Yamakage)

In Japan, it is believed that Seishu Hanaoka (Fig. 2-2, *A*) probably first introduced general anesthesia for surgery on October 13, 1804, which was 42 years before W. Morton introduced ether anesthesia to the world.[5] Hanaoka achieved general anesthesia using an herbal concoction



Figure 2-1. Mahatma Gandhi after surgery with the surgeon Col. C. Maddock. *(Courtesy Professor Kalpana Kelkar, Head of Anesthesiology, Sasoon Hospital, Pune, India.)*



Figure 2-2. A, Seishu Hanaoka (1760-1835), the Japanese pioneer of anesthesia and surgery. **B,** Seishu's disciple recorded his first operation (mastectomy, *bottom*) using general anesthesia performed on Kan Aiya (*top*). *(With permission from Wakayama prefecture and Naito Museum of Pharmaceutical Science and Industry.)*



Figure 2-3. A, *Datura alba* was the primary ingredient of mafutsusan, which was the first general anesthetic produced by Seishu. **B,** *Datura alba* is now a symbol of the Japanese Society of Anesthesiologists (JSA).

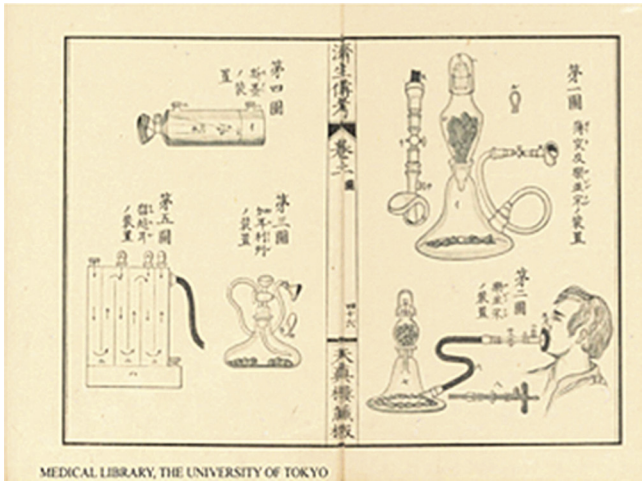


Figure 2-4. Seikei Sugita introduced materials and methods of ether anesthesia to Japan in 1850 by translating Dutch text. *(With permission from Medical Library of Tokyo University.)*

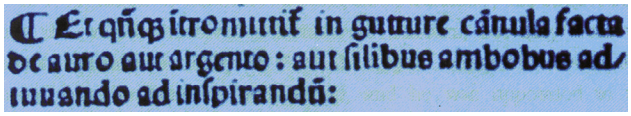
called *mafutsusan*, which mainly contained *Datura alba*, for Kan Aiya, a female patient with breast cancer (see Fig. 2-2, *B*). Hanaoka's colleagues recorded the anesthetic and surgical courses. According to these records, after mafutsusan was administered orally, the patient became drowsy and lost consciousness; Hanaoka then performed a mastectomy without any patient movement. After several hours, the patient recovered from anesthesia. However, the patient died 4.5 months after the surgery. After this first general anesthesia for performing a mastectomy, Hanaoka improved his surgical and anesthetic skills and performed over 200 surgeries using general anesthesia. He accepted many medical students to his school and instructed them privately. At that time, Japan closed its doors to most of the outside world. Therefore, Hanaoka's method had little effect on Western medicine. Nevertheless, Hanaoka's surgical and medical treatments spread widely throughout Japan and prepared the way for the rapid and smooth acceptance of modern Western surgery. *D. alba*, the main component of mafutsusan, is now a symbol of the Japanese Society of Anesthesiologists (JSA; Fig. 2-3).

Forty-six years after Hanaoka's first use of general anesthesia, Seikei Sugita introduced ether anesthesia to Japan in 1850. He translated the Dutch text by J. Sarluis that described the methods and materials of ether anesthesia (Fig. 2-4). The Dutch text was not original but was translated from the German text by J. Schlesinger in 1847.[5a] As mentioned previously, Japan limited its contact with the outside world in those days. Japan was conducting trade with only China and the Netherlands. Therefore, Japan obtained information and knowledge about Western medicine from the Netherlands in the 1800s.

THE MIDDLE EAST (Anis Baraka and Fouad Salim Haddad)

With the decline of the Greco-Roman Empire in the fifth century AD, the Middle East witnessed the rise of an Arab/Islamic civilization that within 100 years (AD 632-732) expanded over a 3000-mile stretch extending from the

A



B

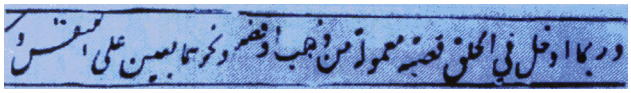


Figure 2-5. A, The Latin version of oral intubation: *Et quandoque intromittiture in gutture canula facta de auro aut argento: aut silibus ambobus, adjuvando ad inspirandu.* **B,** The Arabic version of oral intubation; it translates as, "When necessary, a cannula made of gold, silver, or another suitable material is advanced down the throat to support inspiration." *(From Haddad FS: Ibn Sina [Avicenna] advocated orotracheal intubation 1000 years ago: documentation of Arabic and Latin originals.* Middle East J Anesthesiol *17:155-162, 2000.)*

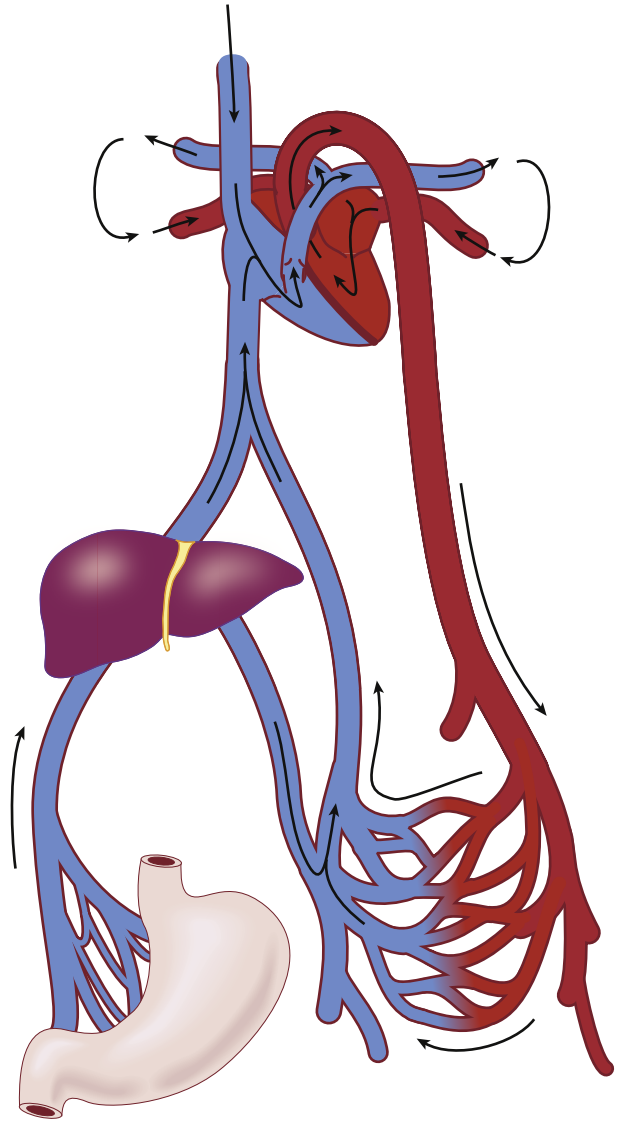
western borders of India, through northern Africa and Sicily, to Andalusia on the Atlantic coast of Spain. This civilization interacted with the ancient Egyptian, Hellenistic, Byzantine, Syrian, Persian, and Indian cultures. Many Arab/Islamic, Christian, and Jewish scholars translated, refined, and augmented the knowledge contained in these cultures. The new civilization that evolved lasted for approximately 1000 years, carried the torch of knowledge in the Middle Ages, and through its transmission via Spain and Sicily, contributed to the European Renaissance.

In this epoch, some prominent Arab/Islamic, Christian, and Jewish scholars made important contributions in the fields of medicine, philosophy, astronomy, mathematics, and chemistry. A wealth of knowledge was thus inherited by several succeeding ages. Of special interest, the following scholars made contributions to the field of anesthesia. First, Al-Rhazi (AD 865-925), born in Ray, Persia, described the pupillary reaction to light and the laryngeal branch of the recurrent laryngeal nerve.[6] Second, Avicenna (AD 980-1037), born near Bukhara, Persia, enumerated drugs that alleviate pain: opium, henbane, and mandrake; in his *Canon of Medicine*, he advocated oral endotracheal intubation: "When necessary, a cannula of gold, silver, or another suitable material is advanced down the throat to support inspiration" (Fig. 2-5).[7,8] Third, Ibn al-Nafis (AD 1208-1288), born in Quresh, near Damascus, Syria, criticized in his *Sharh Tashrih Al Qanou* Galen's theory of blood movement, which said that blood from the right ventricle passes into the left ventricle through small invisible pores in the septum (Fig. 2-6, *A*). Ibn al-Nafis asserted that there is no direct pathway between the chambers and the thick septum of the heart is not perforated, and he described the pulmonary circulation as we know it today (see Fig. 2-6, *B*).[9,10] And fourth, Al-Khawarizmi (died AD 840), born in Balkh, Persia, was a famed mathematician; the word *algorithm,* a mathematical tool, is attributed to him. Algorithm is defined as "a step-by-step problem-solving procedure."[11]

Use of Spongia Somnifera

In the Middle Ages, the concept of inhalation to induce sedation before surgery with use of the sleeping sponge, or *spongia somnifera*, is attributed to Arab origins.[12,13]

A



B



Figure 2-6. A, Galen's theory of blood movement. According to Galen, blood reached the periphery through the veins (most of it departing from the liver), as well as through the arteries (departing from the heart). Little blood went to the lungs from the right ventricle of the heart. He thought that most of the blood passed from the right to the left ventricle through pores in the intraventricular septum. **B,** Photographic reproduction of the original manuscript of Ibn al-Nafis, denying the presence of intraventricular pores and describing the pulmonary circulation.

With the Arab conquest of Sicily in the ninth century and the Latin translations of Arabic medical books that followed, Arabic medicine, including the soporific sponge, took hold in southern Italy (Salerno, Monte Cassino). From there it spread to other parts of Europe and was used in the Middle Ages.[13] A probability also exists that it was carried from the Andalus of Spain by Michael Scot, who in the thirteenth century transmitted scientific culture from Toledo to Bologna via the Court of Frederick II Hohenstaufen in Sicily.[14,15]

After the Middle Ages, major political events in the nineteenth century affected the development of medicine throughout the countries of the Middle East. First, with Napoleon's invasion of Egypt in 1798, the medical awakening of Middle Eastern countries to Western medicine can be said to have started. To win the cooperation of the Egyptian people, Napoleon brought with him men of all specialties.[16] After Napoleon's departure from Egypt and the assumption of power by Mohammad Ali in 1805, efforts to propagate knowledge and education continued. Mohammad Ali brought doctors from Europe and France to take care of the health of his army. Of those, the most remarkable was Dr. Antoine Berthelemy Clot (later Clot Bey) (1793-1868), who was brought to Egypt in 1825. In 1835, Bey established a medical school in Kasr Al Aini Hospital in Cairo, the only Arab medical school in the Middle East at the time.[16]

The developing renovation of Egypt then influenced other regions of the Middle East, either through students flocking to study medicine in Kasr Al Aini Hospital or through the influence of the Egyptian military campaign (Ibrahim Pasha, son of Mohammad Ali) against the then known Syria (1831-1840). Graduates from the medical school in Cairo practiced in all big cities of the Middle East: Beirut, Damascus, Allepo, Jerusalem, Safad, Nablus, Haifa, and Nazareth. It is assumed that the analgesia practiced in major cities of the Middle East was the same technique used in Cairo. Relief of surgical pain in Cairo then consisted of herbal medications and antispasmodics.[16] No kind of inhaled anesthesia was known.

After the invasion of Syria by Ibrahim Pasha from 1831 to 1840, the Egyptians, with the influence of Western missionaries, built two military hospitals—one in Allepo and one in Damascus—and established free medical clinics.[16,17] The presence of Clot Bey in the campaign was instrumental in sending the first five Lebanese students to study medicine at Kasr Al Aini Hospital.[16]

Finally, after massacres in 1860, Western powers (American, French, and British) intervened in Lebanon, and with the inflow of missionaries, more medical schools and hospitals were established. In 1866, the Americans founded the Syrian Protestant College, which in 1920 became the American University of Beirut. In 1883, the French founded their medical school (Faculté Française de Médecine).[16]

Introduction of Modern Anesthesia to the Middle East

In 1846, the first published account of the use of ether anesthesia for a surgical operation appeared, and the innovation spread rapidly,[18,19] including to London in December 1846 and Paris in January 1847. Twenty-seven years later, in 1873, anesthesia arrived in Beirut[16] with the help of an American surgeon, Dr. George Post (Fig. 2-7, *A*).

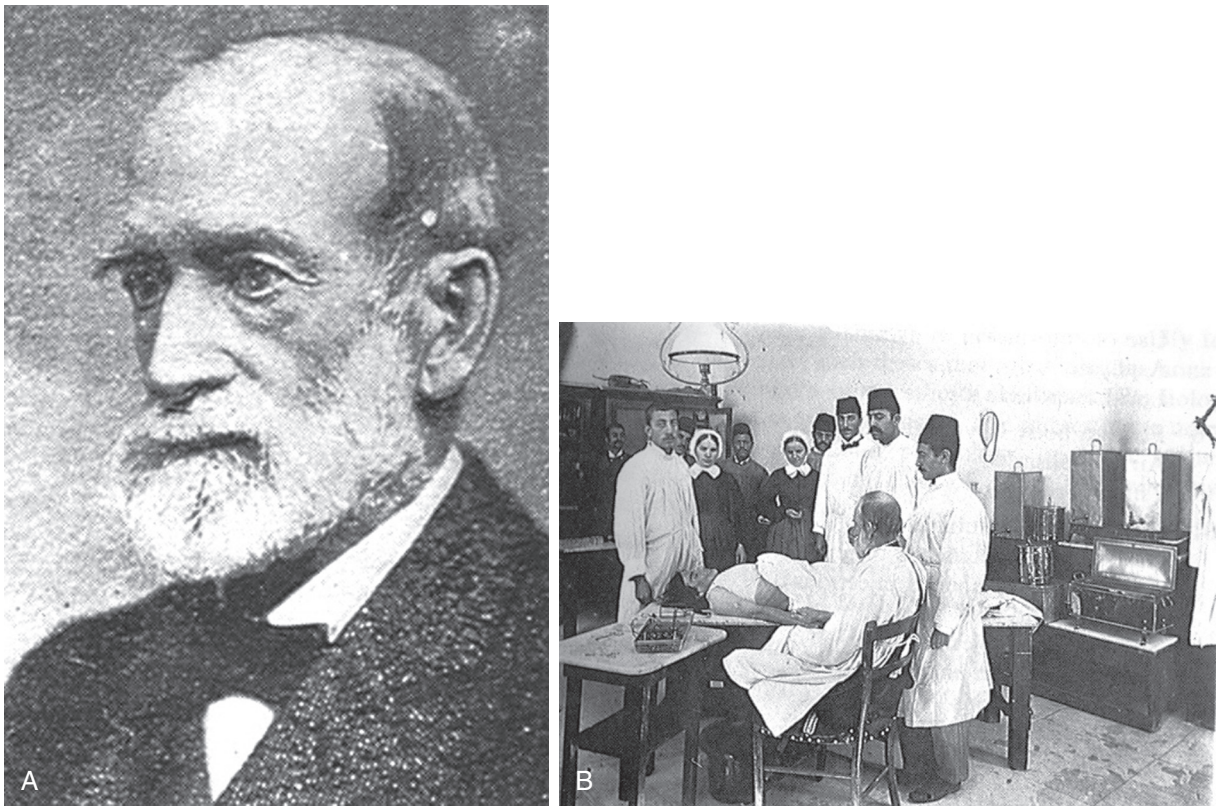


Figure 2-7. A, Dr. George Post (1838-1909). **B,** Dr. George Post in the operating room with a female patient on the operating table.

Dr. Post arrived in Lebanon in 1863 to assist with missionary work. In 1867, he and others established the medical school of the then Syrian Protestant College, and in 1873, Dr. Post wrote a book on surgery in the Arabic language, which included a chapter on general anesthesia, the first of its kind in the Middle East. This chapter described the administration of chloroform. This anesthetic facilitated the ability to reduce a dislocated shoulder of a patient, which was performed at the Syrian Protestant College's Johanniter Hospital in Beirut. To describe this action, Dr. Post coined the word *kulfera,* an Arabization of the word *chloroform*. Dr. Post rightly deserves the title of the First Pioneer of Modern Anesthesia in Lebanon and the Middle East (Fig. 2-7, *B*).[16]

Graduates of the Syrian Protestant College in Lebanon and other graduates of medical schools in the Middle East probably administered open-drop ether or chloroform along with local and spinal anesthesia through the rest of the nineteenth century and middle of the twentieth century. Physicians, students, nurses, nuns, and technicians were most likely also involved.

RUSSIA (Yury S. Polushin)

The history of Russian medicine has its roots in the history of medieval European medicine. Right through the eighteenth and nineteenth centuries, much of the information about anesthetic techniques—applying "snow" 15 minutes before surgical procedures and analgesics for the cardiovascular and respiratory systems and wound healing, as well as the use of bellows for lung ventilation—came from various leaders in European medicine. In addition, like their colleagues in the Middle East and India, Russian physicians heard of the first use of ether on October 16, 1846; that day is still a professional holiday for anesthesiologists in Russia. A brief 4 months later, Dr. F. I. Inozemtzev of Moscow became the first in Russia to use ether for anesthesia during surgery.

Around the same time, the art of local anesthesia was developing rapidly after the publication of an article by the Russian doctor Vassili von Anrep. He described the effects of cocaine as a topical and subcutaneous local anesthetic in 1879. Isolated by the German chemist Friedrich Gaedcke in 1855 and purified by University of Gottingen student Albert Niemann in 1859, cocaine was first given to a patient in 1884. It was the only local anesthetic until 1904, when procaine was synthesized.

Von Anrep's ideas of local anesthesia were highly popular. Famous physicians of Europe and Russia (Shleich, Lukashevich, Vishnevskiy, Bier) were developing the knowledge of local anesthesia, which gave rise to new methods of preventing pain: local field anesthesia, local infiltration anesthesia, nerve blocks, plexus anesthesia, intravenous anesthesia, and neuraxial anesthesia.

In general anesthesia, Nikolay Pirogov (1810-1881) was a prominent Russian physician and surgeon, well known in Europe. He was the first to describe the negative effects of general anesthesia and the possibility of severe complications. He postulated the necessity of acquiring detailed knowledge of the physiologic and clinical effects of anesthetics and requiring a separate course on anesthesia during medical education. He also described many of the modern methods of anesthesia, including inhaled endotracheal anesthesia, intravenous anesthetics, rectal use of anesthetics, and spinal anesthesia. In 1847, he was the first to use ether narcosis on wounded soldiers, and he performed approximately 100 operations on the battlefield during the war in the Caucasus. This had a major effect on the analgesia provided to wounded soldiers in terms of increasing surgical success and rates of survival. (R.D. Miller: Although wars cause an enormous harm to humanity, they have facilitated development of anesthetic techniques for patients undergoing trauma and other major surgical procedures, including Russia in the late 1800s.)

In 1904, the Russian physicians S.P. Feodorov and N.P. Kravkov described and demonstrated total intravascular anesthesia with the intravenous anesthetic gedonal. They were also the first to use combined narcosis through induction with gedonal and maintenance with inhaled chloroform.

Another area in which Russian physicians made advances was in the field of blood transfusions (see Chapter 61). In 1901, Karl Landsteiner reported his discovery of the possible existence of blood types. In 1909, he expanded his initial discovery by establishing the A, B, AB, and O blood types. He demonstrated that transfusions between individuals with the same blood group do not result in the destruction of new blood cells and that this catastrophe occurs only when a person is transfused with the blood of a person belonging to a different group. In 1930, Landsteiner received the Nobel Prize for his work. In 1907, Russian physician Yanskiy had also described four blood types and created the basics of blood transfusion. His work, however, went unnoticed.

Just a few short years later, World War I began, followed by the October Revolution in 1917, which destroyed the monarchy in Russia. Civil war, general poverty, and empowerment of the Communist Party in the early 1920s led to dramatic changes in Russia's political philosophy, economics, and technical and scientific progress, all of which affected the development of medicine. With Joseph Stalin coming to power in the 1920s, communication with other countries in Europe was terminated, exchange of information stopped, and Russian physicians had to continue treating their patients while developing the art of medicine separate from the knowledge and advances in the rest of the world. Likewise, Russian medical advances were not known to the rest of the world and were often reinvented elsewhere.

THE CROSS-POLLINATION PERIOD: 1920-1980

In the late 1970s, the editor (R.D. Miller) took a sabbatical in Holland, during which time he lectured at a local university hospital. Also in residence at the time was a young anesthesiologist from Ecuador. The two physicians became friends as they shared ideas about the practice of anesthesiology and its future. This rich exchange about their profession continues to this day. This was the beginning of this editor's understanding of the interesting

and varied approaches in different parts of the world to achieve the status of anesthesiology as it now stands.

This cross-cultural exchange, however, is no aberration. Over the approximately 60 years from the end of World War I through the early 1980s, anesthesiologists from around the world began to meet in a variety of forums facilitated by air travel and modern communications.

Physicians received training and education abroad. Lecturers from diverse nations spoke frequently outside their home country and brought in new ideas and techniques. Academic and research journals proliferated, as did international congresses and access to textbooks, thereby laying the groundwork for a common understanding of how to practice anesthesia.

BRAZIL (Maria Carmona)

The participation of some Brazilian physicians in World War II was an excellent opportunity to practice and learn more about this emerging specialty (another example of the advance of anesthesia in a military conflict). In 1948, the Brazilian Society of Anesthesiology (SBA) was founded, and since then the SBA and the Federal Council of Medicine have played important roles in defining anesthesia policy and guidelines in Brazil.

CHILE/SOUTH AMERICA (Guillermo Lema)

General Concepts

Geographic and economic diversity have characterized the development of South America. The continent is the site of the Andes (the longest continental mountain range in the world), five desert regions, and rain forests—all of which have given rise to countries with distinct features. This geographic diversity has isolated most of the countries and created huge natural frontiers.

The immigrant populations and the heritage of the native peoples have added their own characteristics. Development has been unique for most countries, resulting in enormous disparity. This disparity is present in numerous aspects of people's lives.

South America's economic growth has been influenced by foreign countries, their economic resources, and investment policies. Some have assumed that most countries would have developed at almost the same speed; however, this has not been the case.

Immigration has also played an important role. The European influence may have been one of the factors for better and faster development in some countries, possibly because of a higher standard of education, a strong will to overcome hard times in their own native countries, and good integration into the South American society. This has certainly been the case in medicine.

South American countries have had to overcome local structural and economic difficulties over the last 50 years, and this has had an obvious effect on daily life.

It is obvious that, because of an economic liberalism in several countries in South America, economic development and disparity throughout the countries has increased enormously, with a discernible effect on medicine, including anesthesia.

In general, economic growth leads to the availability of better and more expedient medical care; however, this is not the case in many South American countries. Although personal incomes have increased, access to medicine of good quality has not been achieved as expected, probably because of the increasing complexity and rising costs of medical care. Indeed, more patients claim that they are receiving good medical care, but according to government authorities at the National Health Services, most countries have not been able to reach the desired goals.

These general concepts should be borne in mind when consideration is given to anesthesia in this region.

Medicine

The main influences on the South American practice of medicine in general, and anesthesia and surgery in particular, come from Europe. For many years, and particularly during the first six decades of the twentieth century, many doctors were trained in different parts of Europe, including France, Germany, and Scandinavian countries. The European influence was as strong in medicine as it was in other aspects of daily life.

One example of Europe's influence was the widespread use of the Ombrédanne in South America (Fig. 2-8). This device, used to deliver ether anesthesia, was invented in France in 1908 by a surgeon named Dr. Louis Ombrédanne (1871-1956). It is believed that South America is likely the only continent where this equipment was clinically acceptable and used widely.

Of course, ether was not the only anesthetic used during this time. Cyclopropane was also used, although Chile had a dramatic experience with this gas that eventually caused it to be banned. In 1963 at the Manuel Arriarán Hospital in Santiago, a cyclopropane tank exploded in a pediatric operating room. Two small boys and four physicians—two of them anesthesiologists—died. This remains one of the worst anesthesia-related accidents



Figure 2-8. The Ombrédanne anesthesia delivery device.

ever to happen in the world. New standards, including the banning of cyclopropane, were imposed to avoid further accidents.

The European influence remained strong for many years. In the 1970s, the influence of North America started to grow and continues through today. The North American influence is evident in many countries such as Argentina, Brazil, Colombia, Chile, and Uruguay, which have advanced technology, monitoring devices, drugs, and associations with various institutions in North America. In other South American countries where cultural and economic growth are deficient, contact with more developed countries is still lacking.

Because Spanish is the predominant language on the continent, with the exception of Brazil, a language barrier affects the relationship between doctors and foreign institutions. English is considered a second language in only a few countries. As a result, doctors can communicate fluently in English in relatively few places, such as in their sharing of medical experiences, attendance of meetings, and access to medical and anesthesia journals.

English as a second language is essential to obtain access to full information and to stay updated. If one is not able to do this, then there is the likelihood of being left behind. Unfortunately, this is the current situation in many countries.

Even with the availability of medical information online, a foreign language such as English is needed and should be part of undergraduate or postgraduate medical education. There are many medical journals in Spanish, but anesthesiologists must understand that English is by far the most common language used in the medical field.

CHINA (Yuguang Huang)

In the early twentieth century, with the introduction of Western medicine into China, modern anesthesia began to be applied in clinics. At that time, anesthesia was implemented mainly by nurses or surgeons. Only a few Western professional anesthesiologists, such as Yueqing Ma from the Peking Union Medical College, could undertake clinical anesthesia in China.

After the foundation of the People's Republic of China in 1949, some early pioneers—such as Jue Wu and Xingfang Li from Shanghai and Rong Xie, Deyan Shang, and Huiying Tan from Beijing—returned from the United States and Europe to help modern anesthesia take shape in China.

In the 1950s, only simple anesthesia was available in China, such as the ether open-drop method, inhaled tracheal intubation anesthesia, and single procaine spinal anesthesia. Peripheral nerve block and continuous epidural anesthesia were introduced on a gradual basis. From the 1950s to the 1980s, intravenous procaine combined anesthesia and continuous epidural anesthesia were the most common methods in China. When anesthetic drugs and monitoring tools became scarce in the 1960s, Chinese anesthesiologists tried to develop acupuncture anesthesia based on the pain-relieving mechanisms of traditional Chinese acupuncture. In the 1970s, Chinese anesthesiologists investigated the anesthetic effect of Chinese herbal medicine. However, beginning in the late 1970s, because of the success of reform and the government's more open foreign policy, many new anesthetic drugs and instruments were introduced into China. At that time, acupuncture anesthesia and herbal anesthesia stepped down from the clinical stage because of their unsatisfying anesthetic efficacy and adverse effects.

Raising the Professional Profile of Anesthesia

Chinese anesthesiologists also began raising their profile as early as the 1950s, when they took part in the rescue of critically ill patients via cardiopulmonary resuscitation. For example, in 1959, Professor Yuanchang Wang from Tianjin Medical College shared his experience in the *Chinese Journal of Surgery* by reporting that a woman whose life was in danger during cesarean section was saved by chest compressions. Partly because of the influence of anesthesiologists, since the 1970s intensive care units (ICUs) and postanesthesia care units (PACUs) have gradually been established in many domestic hospitals.

China has also participated in numerous international conferences and professional groups (Fig. 2-9). The First National Conference on Anesthesia was held in Nanjing in 1964, during which the development and achievements of Chinese anesthesiology were systematically reviewed. In 1979, the Chinese Society of Anesthesiology (CSA) was founded during the Second National Conference on Anesthesiology held in Harbin. Professor Deyan Shang was elected as president of the first CSA committee. Since then, national CSA conferences have been held every 3 or 4 years.

During this period, there was also a foray into professional publications, most notably by Professor Jue Wu, the leader of Chinese anesthesia, who was the lead editor of *Clinical Anesthesiology* in 1954 and *Practical Anesthesiology* in 1976.

Western medicine introduced by the United States also helped to promote the development of modern medicine in China. A good example is Peking Union Medical College Hospital, which was founded by the Rockefeller Foundation in 1917. Even today, Peking Union Medical College Hospital is still regarded as an "ivory tower" of Chinese medicine. Some professors from Peking Union Medical College Hospital moved to Taiwan in 1949, and some of them changed their specialization from surgery to anesthesiology and became the early practitioners of anesthesiology there. They made important contributions to the foundation and development of modern anesthesiology in Taiwan.

INDIA (Deepak K. Tempe)

Until approximately 30 years ago, anesthetic equipment in Indian operating rooms often consisted solely of a simple anesthesia machine, a suction unit, and perhaps an electrocardiographic monitor. Even the oxygen supply was mainly via cylinders, with few hospitals having a centralized medical gas supply. The first medical pipeline system was installed in Vellore in 1954.

Today it is widely accepted that postoperative care is crucial for the success of surgery, but in previous days,

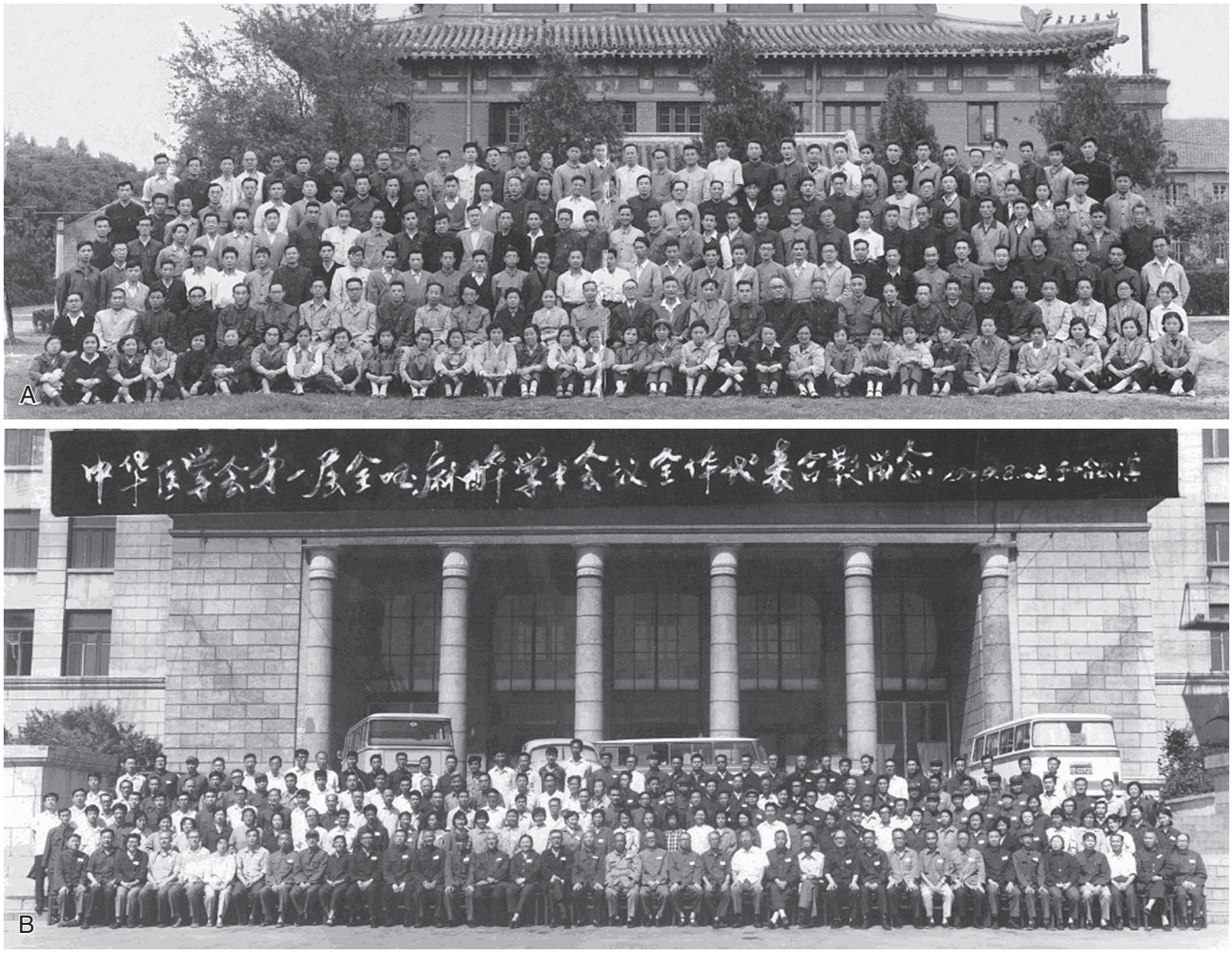


Figure 2-9. A, Participants of the First National Conference on Anesthesia, Nanjing, 1964. **B,** Participants of the Second National Conference on Anesthesia, Harbin, 1979, during which the Chinese Society of Anesthesiology was founded.

many patients were sent back to the ward directly after surgery and only a few would go to the recovery room. In recognition of the fact that surgical patients often need to be observed in a specialized area, India commissioned its first ICU in 1963 in an Army hospital in Delhi. Notably, that was the same year that an ICU was first established by an anesthesiologist at the University of California, San Francisco.

During this period of the twentieth century, Indian anesthesiologists also recognized the need for professional societies. The idea of the Indian Society of Anaesthesiologists (ISA) was conceived in 1946, and the group was formally established in 1947. The first ISA meeting was held in 1949 during a surgeons' conference in Mumbai, and the first independent ISA conference was held in Hyderabad in 1965. Professors Macintosh and Gray were the distinguished guests during the conference. The ISA published its first official journal in July 1953 and joined the World Federation of Societies of Anesthesiologists (WFSA) in 1956. The group has grown from 19 members when it began to nearly 18,500 members in 2012. The Diploma in Anesthesia (DA) was first started in 1946 in Mumbai University, and the postgraduate degree course (Master of Science in Anesthesia) was started in 1955 at Darbhanga Medical College, Bihar.

JAPAN (Naoyuki Hirata and Michiaki Yamakage)

In the early 1900s, the Japanese government began using primarily Western medicine rather than Eastern medicine, which had been used for a long time. The Japanese government invited many medical instructors from Germany (Prussia at that time) to teach in Japan, and medical students from Japan studied in Germany. In those days, German physicians promoted local anesthesia rather than general anesthesia. Therefore, surgeons in Japan focused on local anesthesia, whereas general anesthesia dramatically developed in the United States and the United Kingdom.

In 1950, Dr. Meyer Saklad came to Japan to participate in the Joint Meeting of American and Japanese Medical Educators. He presented novel information on anesthesiology, including general anesthesia, to Japanese surgeons. His lectures created shock waves among Japanese

surgery professors. Since his lecture, anesthesiology in Japan has become much more developed; a Department of Anesthesiology was established at Tokyo University in 1952, and the JSA was established in 1954.

THE MIDDLE EAST (Anis Baraka and Fouad Salim Haddad)

At the end of World War I, the Middle East was divided by Western powers into small countries that were placed under British and French mandate. The major pattern in the practice of anesthesia was complete dependence on foreign surgeons, who could administer anesthetics, and on local and foreign nurses or nonanesthesiologists and technicians, who administered ether or chloroform. This period also witnessed the foundation of faculties of medicine in some countries of the Middle East (Syria, Sudan, and Iraq).[17]

By the end of World War II, the beginning of oil production contributed to an improving economy, which meant more funds available for anesthesia machines, endotracheal tubes, and thiopental, all of which began to appear in many countries of the Middle East. An influx of newly trained surgeons increased the demand for qualified anesthesiologists, thus prompting anesthesia residencies. In addition, in response to a manpower shortage in many countries in the Middle East, nurse and technician training began as well, although this was gradually phased out as locally and internationally trained and certified anesthesiologists began arriving in many countries of the Middle East.

During the second half of the twentieth century, all countries of the Middle East were striving to attain state-of-the-art anesthesia. The World Health Organization (WHO) played a significant role in encouraging and sponsoring graduate physicians for training in anesthesia at the World Anesthesiology Training Center in Copenhagen.

Raising the Professional Profile of Anesthesia

As in many other places in the world, the status of anesthesia in the Middle East depends partly on the establishment of fully independent departments of anesthesia that have their own structure, staff, residency training, research, and certification by international academic institutions and that offer fellowships in cardiovascular, obstetric, and pediatric anesthesia, as well as pain management. To that end, certain landmark strides were taken during this period.

In 1966, the *Middle East Journal of Anesthesiology* was founded. Its main objectives are to act as a forum for education and exchange of opinions and to promote research and publication of Middle Eastern medicine and anesthesia. The journal is accepted for inclusion in the Index Medicus and MEDLARS system.

In addition, in the 1960s and 1970s, many Middle Eastern countries founded their own national societies of anesthesia, which promoted the practice and image of the specialty. In 1990, The Pan Arab Society of Anesthesia and Intensive Care was founded and became a member of the WFSA. Every 2 years, the Pan Arab Society holds The Pan Arab Congress of Anesthesia and Intensive Care in one of the member countries.

RUSSIA (Yury S. Polushin and Olga N. Afonin)

In the midst of the economic difficulties and political upheaval after the Russian civil war, medical services underwent dramatic reorganization and expansion, and some positive developments ensued, including campaigns against diseases and poor hygiene. Thousands of unpaid men and women underwent short courses in nursing. They then went all over the country to educate people and treat deadly diseases, often risking their own lives. This remarkable effort was rewarded in just a few years. Epidemics were stopped, and control of many diseases was established. This experience emphasized the importance of preventive measures, including vaccinations, and Soviet physicians began working on preventive medicine.

Meanwhile in Moscow, Dr. Vadim Yurevich was the first in the world to begin using citrate for blood conservation. His colleague Dr. Vladimir Shamov was the first to use cadaveric blood for transfusion in 1928, thus giving birth to a new field of medicine—transplantation.

The first Institute of Blood Transfusion, a scientific center for study and development of the science of blood and blood component use and storage, was formed in 1926 in Moscow by Professor A. A. Bogdanov. Physicians of the institute developed and published the first systematic approach to the treatment of shock, including traumatic, hypovolemic, and "burn related." Another dramatically important innovation by Russian physicians was the introduction of methods of diagnosis and treatment of electrolyte and acid-base imbalances with complex salt solutions, blood substitutes, and total parenteral nutrition solutions.

In 1924, S. S. Bryuchonenko and S. I. Chechulin constructed and used the first artificial heart machine in the world, the forerunner of what is now known as a cardiopulmonary bypass machine. Surgical procedures were becoming more complex and required more advanced methods of exposure of the abdominal and thoracic organs. The bellows of Dr. Henry Hickman was transformed into many different machines to provide artificial ventilation, including the famous iron lung at Harvard, used first in Boston in 1928.

In Moscow in 1936, the Laboratory of Resuscitation of the Academy of Medical Sciences of the U.S.S.R. began investigations on the dynamics of vital functions during the terminal period and methods for the resuscitation of the dying organism.[20] As the head of the laboratory, V.A. Negovsky was instrumental in the integration of resuscitation in practical health care.

In 1939, N.L. Gurvich and G.S. Yun'ev developed the physiologic basis and methods of indirect heart massage and electrical defibrillation. These methods were used successfully on patients requiring complicated cardiothoracic surgeries in Russia.

In the U.S.S.R., the first endotracheal anesthesia with muscle relaxants was given by M. Anichkov in 1947 at the Military Medical Academy in Leningrad. The book *Intratracheal Anesthesia in Thoracic Surgery,* by S. M. Grigoriev and M. N. Anichkov, chronicles this event. After its publication, doctors from different regions of the country started to apply this method clinically.

As all these developments grew into complex surgical procedures and as the use of neuromuscular blocking drugs spread, it became necessary in Russia to develop a new kind of subspecialty in medicine: anesthesiology. This would require extensive and detailed knowledge of many disciplines, including physiology, biochemistry, surgery, medicine, neurology, pharmacology, traditional anesthesia, and critical care.

The first Department of Anesthesiology in Russia was formed in 1958 at the Military Medical Academy in Leningrad. Within a year, a second Department of Anesthesiology was formed in the Department of Cardiothoracic Surgery in Moscow (now the Russian Medical Academy of Physicians Postgraduate Education); this is the same year that the current Department of Anesthesia was formed at the University of California–San Francisco. The first postgraduate courses for physicians to become anesthesiologists lasted 4 months. Later, more courses of anesthesiology were incorporated, requiring additional months of training and including the basics of intensive care.

The broad variety of topics covered and the complexity of the potential patient care issues meant that the new specialists needed more time to prepare properly for their careers. These careers were in demand as newly formed anesthesiology and intensive care departments required more anesthesiologists to teach and take care of patients.

In 1966, the Ministry of Health of the Soviet Union released the "Order of improvement of anesthesiologic and reanimatologic (intensive care) services in the country." This governmental act legalized anesthesiology and gave it the financial and administrative support required at that time for any significant changes to take place. Along with the legalization of anesthesiology came the definition of functions and organizational structure. Most hospitals deployed units of anesthesiology, whereas institutions and universities formed departments of anesthesiology. Since 1969, anesthesiology and intensive care have been merging into a single specialty called anesthesiology-reanimatology.

THE MODERN PERIOD: THE ESSENTIALS OF MODERN ANESTHESIA AROUND THE WORLD

The last 30 years has been an exciting period for anesthesia, largely because the ability to share clinical and research experience has made the practice safer and better than it ever has been.

Today, all anesthesiologists, no matter where they practice in the world, can gain access to the information necessary to deliver safe anesthesia. However, there are still places in the world that do not have access to the equipment or supplies needed to implement that knowledge. This section details the essentials: the roles and responsibilities, the facilities and equipment available, the education and accreditation, the professional societies, the research conducted by anesthesiologists around the world, and the safety and medicolegal initiatives that have developed in these countries.

ROLES AND RESPONSIBILITIES OF ANESTHESIA PROVIDERS

Brazil (Maria Carmona)

Currently, only physicians are allowed to administer anesthesia, and the care of simultaneous procedures is prohibited. In other words, anesthesia was given to only one patient at a time. The Resolution from the Federal Council of Medicine (CFM 1802/06) related to the use of anesthesia recommends routine preoperative evaluation, and it defines the minimal structures and required equipment to perform anesthesia safely and for adequate postoperative care.

An electrocardiogram, noninvasive blood pressure meter, and a pulse oximeter are the minimal monitors for any kind of anesthesia. End-tidal carbon dioxide ($ETCO_2$) monitoring should also be available for any patients undergoing assisted or mechanical ventilation.

Chile/South America (Guillermo Lema)

For the past 50 years, anesthesiologists have been involved in PACUs and more recently have been responsible for them, including determination of the standards of care for these areas. Pediatric and cardiovascular anesthesia is generally performed by physicians with subspecialty training in these areas. Pain management and critical care reflect important areas in which the influence of the anesthesiologist has been important. Anesthesia-trained personnel run most of these units.

Another area of interest is the choice that many physicians, including anesthesiologists, must make between public and private hospitals. Historically, anesthesiologists have worked in public hospitals. The development of private practices in small clinics and in other institutions attracted many practitioners, who then reduced their work in public hospitals to part-time in the mornings. Currently, anesthesiologists work solely in one hospital, either public or private, with strict professional duties and cost containment as a major responsibility.

Most of the private clinics are run by private economic groups that operate under stringent financial criteria. In these institutions, the activities of anesthesiologists and other specialists are restricted, and only a few colleagues dedicate their time to administrative duties.

Although the resources to public hospitals are increasing, the benefit of these resources is less than one might have expected, probably because of their centralized administration, which is not run by practitioners. Thus, economic restraints and inadequate conditions for anesthesiologists make positions in public practice unlikely to be filled completely, because private work is a more attractive option.

China (Yuguang Huang)

In the last decade, the overall professional level and social status of Chinese anesthesiologists have gained prominence, as has medical education in the field. Each year, large numbers of outstanding medical graduates enter the anesthesiology resident training program, adding greatly to the activities of existing teams. Accompanying the country's economic prosperity are developments in the medical field that put China on par with developed

countries in terms of routinely prescribed drugs and commonly used sophisticated monitoring equipment. The development of anesthesiology has also encouraged the continuing growth of other surgical departments.

The specialty of anesthesiology in China is mainly composed of clinical anesthesia, pain management, emergency resuscitation, and extracorporeal circulation. The scope and versatility of clinical anesthesia have greatly expanded. For example, Chinese anesthesiologists can now receive training for transesophageal echocardiography (TEE) examinations through continuing medical education lectures at large hospitals, with the more outstanding ones having obtained the senior certification for TEE from the United States and Hong Kong. These clinicians are capable of performing intraoperative ultrasound examinations independent of assistance from ultrasound physicians. Therefore, the nation's objective is to train Chinese anesthesiologists so that they have multidisciplinary talents within the near future. Aside from clinical practice in the operating theaters, anesthesiologists are also becoming involved in such clinical diagnostic and therapeutic procedures as endoscopy, fetus reduction at the fertility center, and provision of comfortable alternative solutions to patients undergoing mini-invasive procedures outside the operating theater. Anesthesiologists are earning more respect and recognition from physicians of other specialties and patients in China.

Anesthesiology has also evolved to be the perioperative medicine in multiple aspects. Patient blood management and perioperative blood conservation techniques are an internationally acknowledged issue. Over the years, the Chinese Ministry of Health (MOH), which in 2013 was integrated into a new agency called the National Health and Family Planning Commission, has invested tens of millions of dollars to support the study and improvement of clinical rational blood use, in which anesthesiologists have played a crucial role in education and team leadership. MOH is the leading unit and pilot center for this project, and the Anesthesiology Department of the Peking Union Medical College Hospital has made great contributions to the project through collaborations with other medical centers in Wuhan, Shanghai, Chengdu, and Zhejiang.

Currently, national guideline and blood management standards have been adopted in a majority of provinces, greatly alleviating the pressures exerted by limited blood supply and avoiding transfusion-related complications to a large extent. In addition, a number of hospitals have pain clinics providing good pain management for in-hospital patients. Anesthesiology has evolved as a crucial medical specialty that enjoys rising status in general hospitals, with department chiefs being involved in the leadership of hospital management.

In addition, anesthesiologists have become integral to multidisciplinary collaborations, reflecting the growing status and recognition of anesthesiologists by their peers. Primary trauma care, a program promoted globally by the WHO, focuses on increasing awareness, and enabling and promoting training of medical practitioners in trauma management. MOH has designated the project as a high priority and assigned the Chinese Association of Anesthesiologists and Chinese Association of Emergency Physicians to oversee its responsible implementation. In the past 2.5 years, 4847 doctors and nurses in 1927 hospitals from 15 provinces have been trained with primary trauma care throughout China, resulting in an improvement in the level of primary trauma care in China. This project has received great acclaim and recognition from physicians and local hospital leaders, reflecting the execution skills, unified collaboration, and leadership capabilities of Chinese anesthesiologists.

Europe (Lars I. Eriksson and Jannicke Mellin-Olsen)

The main activities in European anesthesia departments are to provide operating room anesthesia, postoperative care, critical care medicine, pain medicine, and critical emergency medicine.

The concept of anesthesiologists as perioperative physicians is a hallmark and well developed in many European countries. A considerable proportion of health care leaders are anesthesiologists who have a good overview of hospitals in general. In addition, in recent years anesthesiologists have taken more responsibility in leading patient safety initiatives.

In some countries, such as the Czech Republic, Germany, Italy, Moldova, Norway, and the United Kingdom, more than 30% of the activity of anesthesiologists is devoted to critical care medicine. Even in those countries where critical care is recognized as a separate primary specialty, as in Spain and Switzerland, anesthesiologists are involved in the care of the critically ill. Some physician groups want to introduce more specialties on a European level, such as in critical care medicine. Thus far, anesthesiologists have opposed such initiatives as counterproductive and assert that it is more desirable to define and develop competencies and particular qualifications to develop critical care medicine further. Emergency medicine is currently a separate specialty in Europe, but anesthesiologists regard critical emergency medicine a part of the professional domain. Anesthesiologists are involved, not least in the prehospital phase. In some countries, a large proportion of anesthesiologists are also active in acute and chronic pain medicine.[19]

In most of Europe, unlike in the United States, anesthesia can be delivered only by an anesthesiologist. In most European countries, nurses are involved, but with varying tasks and responsibilities. In general, there are two models of anesthesia nurses who participate in care. One model is the nurse anesthetist who is allowed to provide anesthesia without the presence of the in-charge physician in the room. Nurse anesthetists generally have a nursing degree with an additional 1 to 4 years of training, resulting in a diploma that entitles the nurse to administer anesthesia according to a plan defined by the anesthesiologist, including medication administration, tracheal intubation, and monitoring, depending on local protocol and terms and conditions of service. Countries where anesthesiologists work with nurse anesthetists are Scandinavia, the Netherlands, France, the Slovak Republic, and Bulgaria. The other model is the circulation nurse or anesthesia nurse, who can assist anesthesiologists during procedures but are not allowed to perform any direct patient-related roles beyond basic nursing tasks, such as preparing medication and administering intravenous fluid. In Ireland and Malta, even this model is not

allowed, in contrast to Finland, Germany, Italy, Romania, United Kingdom, and other countries.[21]

India (Deepak K. Tempe)

The current Indian government expenditure on health is 1% of gross domestic product (GDP). This amount will increase to 1.5% during the next 5-year plan (2012-2017).[22] This public spending on health as a proportion of GDP is far too small as compared with the expenditure in the United States and Europe (6% to 7%). In India, anesthesia can be administered by a qualified anesthesiologist or by a trainee anesthesiologist under the supervision of a qualified anesthesiologist. In some states, such as Delhi, a directive from the government has been issued that states, "Anesthesia must be administered by a qualified anesthesiologist, that is, an anesthesiologist with a postgraduate qualification and who has been actively working."

The duties and responsibilities of anesthesiologists have been evolving, but they have not yet been clearly defined by the ISA or Ministry of Health officials. Nevertheless, it is now well recognized that an anesthesiologist's work is not limited to the operating room. Typically, anesthesiologists in India are involved in the following types of care: (1) preoperative assessment and preparation of patients; (2) perioperative care of patients; (3) pain relief during the perioperative period; (4) management of critically ill patients; (5) management of acute, chronic, and cancer-related pain; (6) management and teaching of resuscitation skills; (7) provision of outpatient anesthesia services; (8) administrative involvement in establishing and managing health care organizations; (9) disaster management coordinator in the hospital; and (10) teaching and training of the medical and paramedical staff.

In addition to the duties just listed, both natural and manmade disasters have provided an extra challenge for anesthesiologists. By virtue of their ability to administer emergency life support measures, as well as their perioperative management skills, anesthesiologists were at the forefront during the 2001 Gujrat earthquake and tsunami disasters, and they actively participated in establishing operating theaters on site and providing care to victims. Likewise, during the 2011 Mumbai and Delhi bomb blasts, anesthesiologists played a leading role in performing emergency surgery and perioperative management.

Preoperative Evaluation. Preoperative evaluation and preparation of the patient are integral components of safe surgery; however, no dedicated preoperative anesthesia clinics (PACs) existed in India until the early 1980s, and currently almost all hospitals have a dedicated PAC that screens patients before surgery (including outpatient day surgery). In some government hospitals, the PAC is located in the main outpatient department block, signifying that it is an integral part of this department. PACs have become increasingly important because of the growing incidence of cardiovascular and other systemic diseases in patients undergoing surgery. In PACs, anesthesiologists review and optimize the treatment of other systemic diseases and detect new diseases and health concerns. PACs have improved patient outcomes, and they are credited with facilitating the patient-physician relationship and discussions on patient awareness of anesthesia. A few hospitals have started awareness programs wherein a lecture is delivered (with illustrations) on a monthly basis to patients and their relatives to familiarize them with the anesthetic techniques and procedures that they will undergo.

Operating Room. The operating room continues to be the mainstay of anesthetic practice, where the anesthesiologist fulfills his primary responsibility of providing safe anesthesia to patients undergoing surgery. Operating rooms are major consumers of hospital resources and major sources of income for private hospitals; therefore, it is imperative that they be managed in the most efficient manner. However, there is no consensus on an ideal system to ensure efficiency in this area. The anesthesiologist is actively involved in trying to improve efficiency, especially with triage and the scheduling of urgent and emergency cases. In addition, the anesthesiologist is responsible for designing and equipping the operating rooms.[23] Safety is another concern. The professional risks (especially those related to needlestick injuries) of anesthesiologists, as well as other operating room staff, are well recognized, and preventing such health care hazards has become an important consideration.

Recovery Room and Postoperative Intensive Care Units. Appropriate postoperative care is crucial for the success of surgery. Today in India, depending on the nature of the surgery and the patient's condition, the patient is transferred to a recovery room or an ICU. Some version of an ICU or recovery room exists in almost all major hospitals in India today. The nomenclature used to describe these areas is not uniform. As a result, terms such as *postoperative ward, recovery room, high-dependence unit, critical care unit,* and *PACU* are often used to describe the same facility. At some hospitals, especially those in which major and complex surgery requiring postoperative ICU management is not performed regularly, there is no demarcation between an ICU and the recovery room. A single area designated as a recovery room is used for both purposes.

Where there is a distinction, the decision about where a postsurgical patient belongs is governed by the degree of morbidity. If a patient is very sick and requires ventilation and careful hemodynamic monitoring, the patient is transferred to an ICU. If mechanical ventilation and continuous hemodynamic monitoring are not required, the patient is transferred to a recovery room, which is perhaps the equivalent of the PACU. Patients undergoing day surgery (if practiced in a given hospital) are also transferred to the recovery room before discharge.

Most recovery rooms are under the charge of an anesthesiologist; in the case of ICUs, sometimes the anesthesiologist is in charge. Practice varies by location, and it is generally governed more by the logistics involved in a particular hospital than by any definite norms.

Ambulatory Care and Other Areas. Although it is recognized and appreciated that ambulatory care is a distinct possibility in a substantial number of patients, it

is not practiced as much as it should be. It is difficult to provide exact figures in this matter, but in general, the private (corporate) hospitals provide ambulatory care. The number of government hospitals practicing ambulatory care is relatively small, mainly because of logistic reasons. However, that is likely to change with the increasing availability of short-duration anesthetic drugs and modern surgical facilities (tools for minimally invasive surgery). Saving costs to the patient and the hospital and increasing patient turnover have been the major factors influencing interest in ambulatory care. The safety issues related to ambulatory care are well recognized, but there are no guidelines or recommendations from the ISA or any other regulatory body on this matter.

Anesthesia services are also frequently required in several other areas within the hospital but outside the operating room. These areas tend to be less familiar to most anesthesiologists and provide less access to the facilities typically available in an operating room. Their proliferation, however, has increased the demands on the field of anesthesiology. Areas where anesthesia is playing an increasingly prominent role include radiology suites (computed tomography, magnetic resonance imaging [MRI], and interventional radiology), the cardiac catheterization laboratory, electrophysiologic laboratories, the endoscopy room, and the electroconvulsive therapy room. In most of these areas, patients require sedation, but with some lengthy procedures—such as MRI, electrophysiologic studies, and some interventional procedures—patients tend to get restless and may require general anesthesia. In addition, special considerations such as long breathing circuits or MRI-compatible equipment may be necessary. The anesthesiologist should be familiar with these requirements to maintain safety standards. There is a tendency to consider these procedures as minor (by our clinical counterparts), thus undermining the safety requirements. However, the anesthesiologist must ensure that adequate safety standards are maintained in all these areas.

Critical Care Medicine. In the beginning, the anesthesiologist's focus on critically ill patients was ventilatory care because anesthesiologists are well versed in cardiorespiratory physiology and ventilatory management. Furthermore, managing a critically ill patient was considered an extension of the job that anesthesiologists performed in the operating room. Therefore, the anesthesiologist managed patients receiving controlled ventilation via a ventilator and, ultimately, weaned patients from mechanical ventilation.

Subsequently, however, it became obvious that respiratory function was only one aspect (albeit a crucial one) of the care of the critically ill. Anesthesiologists then became well informed about cardiovascular support, nutrition, infection, and various other diagnostic procedures. However, the interest of anesthesiologists in critical care medicine has vacillated, and other specialists have entered this field. Currently, management of critical care units in India tends to be split: some are managed by physicians not trained in anesthesia, others by anesthesiologists.

There is widespread agreement that a critical care specialist who is devoted full-time to the care of critically ill patients should manage a critical care unit. The consensus includes three key items: (1) a dedicated expert irrespective of the specialty (if not holding a critical care qualification) should be in charge of the critical care unit; (2) each hospital can follow practices according to the availability of trained or experienced personnel with the primary aim of giving the best possible care; and (3) care of critically ill patients is always a team-based process, and the practice of taking the advice of different experts in managing a particular case is encouraged to achieve better outcomes.

Critical care training has long been part of the anesthesia residency program in India, but in 2001 the National Board of Examinations initiated a full-fledged 2-year training program in critical care medicine with six seats throughout India; the number has now increased to 40. Anesthesiologists, chest physicians, and general physicians are eligible to seek admission to this program. Clearly, the number of these specialized intensivists is not sufficient to cater to the critical care units that have mushroomed all over India. In an attempt to increase the number of critical care specialists in the country, the Indian Society of Critical Care Medicine has initiated a 1-year diploma course (335 total seats), and 1-year fellowship course after obtaining the diploma (66 total seats).[24] Although these courses are not recognized, they have helped to increase the number of critical care specialists in the country. Anesthesiologists account for approximately half of the training seats, followed by general physicians (30%) and chest physicians (20%). The fact that all the seats in this program are filled suggests the growing interest in this specialty area. The Medical Council of India has recognized critical care medicine as a separate subject vide by way of amendment notification dated December 8, 2010. Thus, it will not be long before medical colleges start postdoctoral courses (DM and others) in critical care medicine.

In summary, critical care medicine has emerged as a new specialty that is still evolving in India. Because the number of people with a qualification in the critical care area is not sufficient to fill current needs, anesthesiologists and physicians with an interest in the specialty continue to practice critical care medicine. Such an arrangement is likely to continue until a sufficient number of qualified critical care specialists are available in the country. Going by the current number of seats available in critical care training programs, this transition period is likely to be rather prolonged. The author believes that once the transition period is over, critical care units will be manned full time only by qualified critical care personnel so that the anesthesiologist–turned–critical care expert will not practice anesthesia and a physician–turned–critical care expert will not practice medicine. Anesthesiologists will be more focused on postoperative care, which will include pain relief and short-term ventilation.

One problem that has emerged in India is the indiscriminate use of antibiotics, leading to the emergence of resistant bacterial strains.[25] The emergence of New Delhi metallo-B-lactamase-1 (NDM-1) and its prevalence in India was highlighted recently.[26] There is thus

a potential for wider international spread of plasmids encoding NDM-1. A coordinated, concentrated, and collective effort from clinicians worldwide is needed to prevent the emergence of resistant strains and their spread.[27]

Pain Management. Over the last 30 years, there has been a growing interest in managing acute and chronic pain. Yet the specialty is in its infancy in India, the number of pain clinics is limited, and there is no formal training program. According to one estimate, only about 10% of medical colleges in the country have pain clinics, so aspiring pain management professionals will almost always have to train abroad.[28] Some private corporate hospitals have now incorporated this facility. The focus has largely been on the treatment of chronic pain, including cancer pain. Most anesthesiology departments perform nerve blocks, with a few even practicing acupuncture. There are, however, few departments that have the facilities to conduct procedures such as radiofrequency ablation, implantation of intrathecal pumps, or spinal cord stimulation. The thrust now is toward treating pain as a disease, especially in patients suffering from nervous disorders or in terminal cancer patients, for whom the only possible form of management is alleviation of pain.

There is also growing awareness of the management of acute pain, including the possibility of providing the patient with a totally pain-free surgical experience. After all, the WHO now recognizes pain as the fifth vital sign, and alleviation of pain is regarded as a basic human right. Various forms of medicine and equipment (patient-controlled analgesia pumps, intrathecal, epidural, and intrapleural techniques) can now offer the possibility of a relatively pain-free course of surgical treatment. Indeed, management of acute pain during the entire perioperative period is a leading concern of all anesthesia departments, and it is actively practiced in recovery rooms or PACUs. Still, much remains needs to be done regarding pain management in India.

The Indian Society for the Study of Pain was formed in 1984 and currently has more than 1300 members from almost 25 different specialties.[29] The society is working toward improving pain management, but it is facing tough challenges, mainly because of lack of awareness. Most medical professionals tell most patients to live with pain, and patients tend to believe that pain is simply an expected part of the suffering caused by their disease. In addition, many doctors believe that referring a patient to a pain management expert would essentially be a statement of their medical shortcomings—and if the pain is relieved, the patient may never come back.[28] This author looks forward to improving pain relief facilities in the country.

Japan (Naoyuki Hirata and Michiaki Yamakage)

Anesthesiologists in Japan work in operating rooms, emergency departments, ICUs, pain clinics, and palliative units. The JSA recommends that perioperative management be provided by experienced anesthesiologists or residents supervised by certified anesthesiologists. Based on a survey of the JSA membership in 2005, over 90% of surgical anesthesia was provided by anesthesiologists or supervised residents at university hospitals. On the other hand, about 10% of surgical anesthesia was still performed by surgeons at nonuniversity hospitals. In Japan, there is no educational program for nurse anesthetists. The JSA survey also showed that the ratio of daily time spent by anesthesiologists on perioperative management was 60% to 70%, with 10% in ICUs, 13% in emergency departments, 30% in education and research work at university hospitals, and 12% in education and research work at nonuniversity hospitals.

Middle East (Anis Baraka and Fouad Salim Haddad)

In the Middle East, anesthesia is routinely administered by a qualified anesthesiologist. Trainee anesthesiologist or anesthesia nurses can administer anesthesia under the supervision of a qualified anesthesiologist. In addition, the departments and societies of anesthesiology in the different countries of the Middle East are responsible for setting the guidelines for sedation and analgesia by doctors who are not anesthesiologists.

The responsibilities of the anesthesiologist have evolved to include preoperative assessment, premedication, and preparation of patients, as well as postoperative anesthesia care in the PACU, which functions for 24 hours, as well as in the ICU. A preoperative informed consent for anesthesia must be completed by the anesthesiologist and signed by the patient, the guardian, or his or her legal representative.

Anesthesia administration is not limited to the operating room, but includes other areas such as the radiology department, ambulatory anesthesia, and obstetric anesthesia in the delivery suite. In addition, pain management, whether acute postoperative pain management or chronic pain management, is becoming routinely practiced and is evolving as a subspecialty of anesthesia. Subspecialization by a fellowship program is expanding to cover many areas such as obstetric, cardiopulmonary, and pediatric anesthesia, as well as critical care and pain management.

Russia (Yury S. Polushin and Olga N. Afonin)

Until the 1980s, Russia's anesthesia educational system was unified and structured into courses for nurse anesthetists and postgraduate education for physicians that included either a 1-year anesthesiology internship or a 2-year "Orditatura" (analogue of residency). All the programs included intensive care (reanimatology) as an obligatory part of the education. Participants were working in operating rooms and ICUs under the supervision of attending physicians and had a required course of lectures. Self-education was encouraged as well. After completion of training, graduates had to pass an oral qualification examination and were granted a Diploma of a Physician Anesthesiologist-Reanimatologist.

The quality of the education and the amount of experience varied significantly from program to program, and there were no universally accepted standardized examinations. Many conscientious anesthesiologists took additional courses on "qualification improvements" from the

Academy of Physicians Postgraduate Education. However, there were also "specialists" whose education was finalized on completion of the courses.

By the end of the 1980s, it became clear that the quality of education had to be monitored; debate led to the acceptance of standardized examinations. Meanwhile, the Iron Curtain had become partially permeable to some of the information about accepted standards of education and care in the other countries. The future promised improvements, but not for long. The "era of stagnation" of the 1980s led to economic imbalance and a gradual decline in political structures. By the end of the 1980s, Communist leaders embarked on major reforms in an effort to revive the country's economics, which led to the collapse of the Soviet Union.

Consequently, government financial support for the entire medical structure was reduced and eventually disappeared. All financially unsound programs, such as research, education, and the development of new technologies or educational methods, were frozen. The government-funded health care system no longer existed. Many professionals had to quit their careers for their families to survive. The private sector was in the very beginning of its development, and the majority of the population could not afford private health care. It was not uncommon for patients to be asked to bring supplies for the medical care that they required, even for surgeries, and it was not uncommon for people to die because of the lack of proper medications or proper medical care. This continued until the mid-1990s, when things began to turn around. The damage, however, has not been completely overcome, even now.

Southeast Asia (Florian R. Nuevo)

The political, geographic Association of Southeast Asian Nations (also known as ASEAN) includes Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Vietnam. During the past 5 years, the role of physician anesthesiologists in this region has changed remarkably. Physician anesthesiologists have gained recognition by peers and the populace, undeniably maintaining a strong respectable presence in the operating suites and ambulatory centers. Apart from this role, the physician anesthesiologists who have undergone subspecialization are now recognized as coequals by their colleagues in the realm of pain management and intensive care.

Tangible evidence of the fortified role of ASEAN physician anesthesiologists in pain management is the Association of Southeast Asian Pain Societies (ASEAPS), formed in 2004 with the goal of further advancing the study of pain in the region. As a result, there are more academic pain management fellowships in the region. This specialized body has inspired anesthesiologists and other pain specialists to work together and develop practical, cost-effective, and rational approaches in addressing the continuing concerns of acute surgical pain, cancer pain, and chronic nonmalignant pain problems, particularly in resource-challenged work environments. Their unified objectives paved the way for governments to join in the advocacy of adequate pain control, particularly among cancer patients. Hospice care and palliative medicine are also areas in which anesthesiologists are now team leaders.

Another recent development is the increased interest among newly qualified physician anesthesiologists to become intensivists with special focus in areas such as pediatric intensive care, cardiothoracic intensive care, neurosurgical intensive care, and surgical intensive care. This development has broadened leadership in ICUs to include anesthesiologists, which had been dominated by specialists such as cardiologists, pulmonologists, and surgeons.

Specific mention must also go to the increased presence of the Asian Society of Cardiothoracic Anesthesia (ASCA). The ASCA serves as the unifying body for Asian cardiac anesthesiologists and envisions itself as the focal organization to address the evolving responsibilities of cardiac anesthesiologists on the utility of intraoperative TEE monitoring. This is now at a critical phase that is challenging the ASEAN cardiac anesthesiologists who must, for the moment, continue to share the stage with cardiologists inside the operating rooms.

Through ASCA, efforts to develop proficiency on TEE as an essential monitoring tool have instigated collaborations and strengthened cooperation between cardiologists, surgeons, and cardiac anesthesiologists. The Japanese Society of Cardiovascular Anesthesiologists has pioneered the proficiency on TEE and its Japanese Board of Perioperative Transesophageal Echocardiography has gained recognition by accreditation commissions in the United States and Europe. In the last 5 years, ASCA has offered basic TEE workshops for noncardiac anesthesiologists in many anesthesia conferences. Today, ASCA plans to offer more intermediate TEE workshops and introduce master TEE workshops for cardiac anesthesiologists in the region. It is hoped that in the next 5 years, ASEAN cardiac anesthesiologists will be duly given an independent role, similar to the current situation of cardiac anesthesiologists in Japan, China, Korea, and Taiwan.

With the introduction of ultrasound machines into the region, the application of regional blocks in orthopedic surgery has soared because of the increased demand from surgeons. This evolvement has contributed to better pain management in orthopedic surgery patients.

Among ASEAN anesthesiologists, the overall mood is optimistic and forward thinking. As ASEAN anesthesiologists succeed in their new roles that are outside the traditional anesthetist role in delivery rooms and operating suites, they must remember their primary responsibilities as anesthesia care providers while also recognizing the need to continue to evolve in order to become truly competent perioperative physicians.

Nurse anesthesia practitioners in the region do not yet have full autonomy. They are part of the perioperative anesthesia care team and are supervised as appropriate by physician anesthesiologists (Table 2-1). Nurse anesthesia practitioners are legally allowed only in Thailand, Indonesia, and Taiwan. In these countries, physicians design and conduct their respective nurse anesthesia training programs. However, in the Philippines, Singapore, and Malaysia, these societies maintain that anesthesia is a practice of medicine by qualified medical doctors.

TABLE 2-1 **WORKFORCE, SCOPE, AND TYPE OF PRACTICE IN SOUTHEAST ASIAN COUNTRIES**

	Indonesia	Malaysia	Philippines	Singapore	Thailand
Workforce					
Physician anesthesiologists	Yes	Yes	Yes	Yes	Yes
Nurse anesthetists	Yes	No	No	No	Yes
Anesthesia Scope of Practice					
Anesthetizing locations	Yes	Yes	Yes	Yes	Yes
Pain management	Yes	Yes	Yes	Yes	Yes
Intensive care	Yes	Yes	Yes	Yes	Yes
Type of Practice					
Physician and nurse anesthetists	Nurse anesthetists trained and supervised by physician anesthetists		Group practice slowly gaining support		Nurse anesthetists trained and supervised by physician anesthetists

With professional pride, ASEAN anesthesiologists have emerged as capable leaders in their respective national medical organizations, and they are driven with passionate social advocacies to help society and to partner with their government agencies to improve the delivery of medical and surgical care. It is no longer unusual for physician anesthesiologists to be designated as quality management officers or as medical directors.

FACILITIES AND EQUIPMENT

Brazil (Maria Carmona)

Brazil is the fifth largest country in the world in terms of area and the fifth most populous with approximately 200 million inhabitants. Although the Brazilian constitution declares health care to be the right of every citizen and its provision to be a duty of the state, there is a substantial gap between the aspirations of Brazil's Unified System of Health and reality. Total expenditure on health in Brazil is only 8.4% of gross national product, which is half the amount invested by the United States. In addition, almost half of all health care costs in Brazil are met by private health care. Consequently, both the provision of anesthesia and the entire health care system itself present a great heterogeneity in quality and service throughout the country, and this is closely related to the economic development of different regions. Apart from the excellent anesthesia care available in some government and private hospitals in a few cities, the majority of the poor population in urban and rural areas do not receive good quality care, regardless of whether the financing is public or private. On the other hand, the dynamics between private and public health sectors is constantly changing with continuous pressure on both to expand delivery. However, the bureaucracy of the public system and the apparently superior performance of private health care sometimes involve the transfer of public funds to the private sector, followed by reductions in public sector service budgets and staff availability. These public–private partnerships and the increasing number of people buying into private services are moving the Brazilian health care system through a slow, passive privatization.

Brazil's aging population is increasing faster than ever before, and it has the sixth largest population of older adults in the world. Although longevity is a significant measure of social well-being, it is a challenge for public health care and increases the complexity of anesthesia care.

Considering obstetrics care, although the WHO guidelines state that the proportion of cesarean births should range between 5% and 15%, the incidence of cesarean sections in Brazil is approximately 50%—one of the highest worldwide. The higher rates of cesarean section are observed both in private and public hospitals, and spinal anesthesia is the most frequent technique for this surgery.

Regional anesthesia is popular in Brazil because of its many advantages, such as a smooth recovery, maintenance of the patient's own airway, low risk of aspiration of gastric contents, and less need for skilled nursing care than with general anesthesia. Brazilian anesthesiologists are highly skilled in different regional anesthesia techniques.

Most of the equipment and drugs used in anesthesia are produced in Brazil. The country has several equipment manufacturers who are trying to develop products that match the best in the world. They provide products to the domestic market and export to a number of Latin American and African countries. Moreover, the world's most important manufacturers of equipment and pharmaceutical companies also manufacture or market their products in Brazil. To improve the population's access to health care, incentives have been offered for marketing generic drugs at a lower cost than brand name products.

Chile/South America (Guillermo Lema)

The huge disparity in economic growth among countries in the region has produced an enormous difference in public resources allocated to health care and created different conditions for public health management. Governments view anesthesiology as a low priority because, in their view, it has not had a significant effect on the improvement of health care, and the technology involved is costly.

The current status of the practice of anesthesia is being replicated by all countries in South America with most

at different stages of the process. Some countries have standards of care comparable to American or European countries, whereas others are only beginning to have anesthesia as a mature specialty. Countries such as Argentina, Brazil, Colombia, Chile, and Uruguay are in the mature phase and have modern equipment, advanced monitoring technology, and access to a variety of anesthetics and ancillary drugs.

Anesthesia techniques vary, and many different types are being practiced. Anesthesia with halogenated drugs has been used widely, for many years, and in all countries. Total intravenous anesthesia is now common, especially with younger colleagues. The use of regional anesthesia has been widespread in all countries, and each country has its own training programs and congresses.

Although some countries have modern equipment, monitors, and drugs comparable to the United States or Europe, others have very basic systems to perform anesthesia appropriately; therefore, cost containment has been a critical aspect in clinical practice. Indeed, this situation is common globally. This disparity in medical resources among countries has been reduced because of trade with different countries, such as China, India, Brazil, and some European countries. Prices of products from these countries are much lower than from North American companies.

China (Yuguang Huang)

China's rapid economic growth has been accompanied by the acquisition of updated anesthetic equipment and apparatus. Except for a few distant rural areas and smaller provincial hospitals, the ratio of anesthetic machines, multifunction monitors, and expirium gas monitors in the operating theaters has reached a 1-to-1 capacity. National-level hospitals in more developed areas are equipped with international-class modern anesthetic machines and a variety of monitors, including neuromuscular monitors, anesthesia depth-monitoring devices, coagulation function test equipment, three-dimensional TEE or portable ultrasound equipment, neurostimulation devices, and pulse index continuous cardiac output hemodynamic monitors. Even MRI-compatible anesthesia machines are available in some large hospitals. By using current equipment and devices, medical practitioners and their facilities are providing better patient care and safety. Upgraded utensils on difficult airway carts and workshops on various airway techniques (e.g., visual digital laryngoscope, laryngeal mask) have helped China to realize great improvements in airway management.

However, an imbalance in economic development across massive mainland China has resulted in a corresponding imbalance in the sophistication and quantity of anesthesia devices. Currently, primary-level hospitals lack sufficient modern anesthesia equipment. Local investigations indicate that in second-level hospitals, the ratio of anesthetic machines to operating theaters is 0.7-0.8 to 1, whereas the ratio in national-level hospitals is 0.5 to 1. Thus, safety in clinical anesthesia faces major challenges. To resolve the existing problems, MOH approved the *Anaesthesiology Standard Regulatory Protocol* in 2012, which established national standards for all hospitals. These standards address facility and personnel qualifications and determine the minimum standards and facility requirements for clinical anesthesiology safety. The expectation is that the protocol will bring about changes to the current status in remote and rural areas.

Europe (Lars I. Eriksson and Jannicke Mellin-Olsen)

The WHO lists 53 countries in their Regional Section of Europe, reflecting diversity from Scandinavia and Germany to Georgia and Uzbekistan. The European Union (EU) has 28 member countries, and an additional nine have applied to become members, most of them from Eastern Europe.

Despite their political and economic partnership in the EU, the countries of Europe remain heterogeneous, which is reflected in the prevailing diversity of medical systems, research, and education, as well as in language and culture.

India (Deepak K. Tempe)

In India, the journey from open-drop chloroform and ether anesthesia to the present day high-tech operating rooms with anesthesia workstations and monitors, ICUs, PACUs, pain clinics, and preanesthetic checkup clinics is nearly complete. In fact, the operating rooms in India have undergone significant change during the last 20 to 30 years. The present-day operating room is modular in structure with high-tech anesthesia workstations, monitoring systems, and on-line networking. Such a change has been largely due to the arrival of private investment and management in the health care business. These corporate hospitals have built state-of-the-art operating rooms that match the best operating rooms in the rest of the world.

However, it is necessary to keep in mind that like many other things in India, diversity is also a hallmark of the health care system—that is, the assortment of medical facilities and level of available services vary considerably. Although corporate and other private hospitals have state-of-the-art operating rooms, government hospitals—other than those in cities such as Delhi and Mumbai—may not. In general, government hospitals cater to the general population, are overcrowded, and have long waiting lists. The situation in rural areas in particular is not up to the benchmark because these places typically have only primary health centers with basic facilities, and the operating rooms are equipped to deal with minor surgical procedures. However, it is possible to perform extraordinary procedures successfully in some of these rural hospitals. For example, on June 20, 2012, six doctors from the 1982 graduating class of Christian Medical College in Vellore, Tamil Nadu, and their former professors successfully operated on conjoined twins in a village in Betul district of Madhya Pradesh. This was the first successful separation of conjoined twins in a rural setting in India. The equipment necessary for this operation was borrowed from private industry. The case demonstrates that if the government and the doctors care enough, such complex surgeries can be performed even in remote settings. Thus, operating rooms of several

varieties can still be seen in India, and one hopes that this diversity gradually changes to uniformity in times to come.

Accreditation for Quality Health Services. In 2006, the Quality Council of India established the National Accreditation Board for Hospitals and Healthcare Providers (NABH) to address the needs of consumers and to set benchmarks for the progress of the health industry. The accreditation by the NABH ensures high-quality care and patient safety in a given hospital. More hospitals in India are striving to obtain NABH accreditation, and to do so they have to achieve standards set by the NABH. Thus, the establishment of NABH is a welcome step toward ensuring quality health care in the country. Two hundred nineteen hospitals have received NABH accreditation so far. Although, this includes mostly private hospitals, some public hospitals have also been accredited by the NABH.[30]

The evolutionary development of anesthesiology in India has been a challenging and turbulent journey from the days when Mahatma Gandhi was operated on with the open-drop chloroform technique to today. However, it is satisfying to see that developments in anesthesia have kept pace with time in India. Even the heads of government such as governors, cabinet ministers, and the prime minister no longer travel to foreign countries for their complex surgeries. Anesthesiologists have access to most modern medicines and equipment to provide the care of the highest order to these officials. The use of balanced general anesthesia with drugs such as fentanyl, midazolam, sevoflurane, and atracurium, full-fledged monitoring, and pain relief by patient-controlled analgesia pumps is now readily available in larger hospitals.

Indian College of Anaesthesiologists. The idea of forming an Indian College of Anaesthesiologists (ICA) was conceived in 2001. The objective was to form an academic wing of the ISA that could subserve the function of supervision and guidance of anesthesia education all over the country so that uniformity in medical education is maintained. Thus, it is expected to function as a leading advisory body to the Medical Council of India. In addition, it has undertaken a major challenge of formulating practice guidelines and protocols for anesthesiologists in the country. The existing Western guidelines are often difficult to apply in the Indian scenario. The college also awards fellowships in anesthesia. The ICA was officially registered November 2008 and currently has 450 members.[31]

Japan (Naoyuki Hirata and Michiaki Yamakage)

The following summary of the facilities and equipment of anesthesia in Japan was excerpted, with permission, from the *Journal of Anesthesia*.[32]

In the 1980s, general anesthesia was mainly conducted using halothane or enflurane with nitrous oxide. Fentanyl, an opioid analgesic, was also available, but was rarely used because it was believed to cause delay in awakening. Epidural anesthesia was used more frequently than it is now. For example, cervical epidural anesthesia was generally used in surgery on upper limbs or for breast cancer. The only intravenous anesthetics available at that time were thiamylal and ketamine, which was administered to asthma patients despite its known secretion-promoting effects. The depolarizing neuromuscular blocking drug (NMBA) succinylcholine was used for induction of anesthesia, and the nondepolarizing NMBA pancuronium was the only NMBA available for maintenance of anesthesia. During the 1980s, there was no awareness of the progression of acute renal failure during emergency surgery, and some patients did not awaken from anesthesia for a long time after surgery because of the prolonged effect of pancuronium.

Since the 1980s, various anesthetic drugs have become available in Japan. The availability of a wide range of anesthetics and the development of anesthetic monitors have made anesthesia a much safer and more comfortable procedure for patients. However, Japan (possibly because of its unique medical system) lags behind the United States and Europe in the use of anesthetic drugs other than sevoflurane. Remifentanil, rocuronium, and desflurane have finally been launched in Japan. In 2010, sugammadex was approved for clinical use in Japan, 2 years later than in Europe. As of this writing, it has been reported that sugammadex shares 70% of the relaxant antagonists [market] in Japan, which may be the highest share in the world.

General anesthesia with airway management using a laryngeal mask is increasing in Japan because of the promotion of this device and the widespread use of ProSeal (Laryngeal Mask, Jersey, UK) with high sealability, which makes it easy to eliminate leaks around the mask. The indication for this method of anesthesia depends on the anesthesiologist, although it is generally not used for laparotomy, thoracotomy, or prolonged general anesthesia. If the device has high sealability and can withstand positive-pressure ventilation, anesthetic management is sometimes performed using artificial ventilation with the use of NMBAs. The use of the laryngeal mask is expected to continue to increase.

Because of the high costs of hospitalization in the United States and Europe, day surgery has become popular. Day surgery in Japan, however, is rare because most patients have national and private medical insurance. However, the duration of hospitalization is expected to become shorter with the introduction of a comprehensive medical system, although it is impossible to predict whether this will have an effect on the methods of anesthesia used.

Methods used for postoperative analgesia differ greatly between countries and between institutions in Japan. In the United States and Europe, patient-controlled analgesia is popular, and intravenous opioids alone are used in approximately two thirds of patients. The combination of intravenous opioids with epidural analgesia appears to be used only for patients who have undergone upper abdominal surgery or thoracotomy. In Japan, epidural analgesia with or without intravenous opioids is used for postoperative pain control in approximately 50% of patients.

Finally, the number of surgical cases in specialized hospitals, including university hospitals, is expected to continue to rise in Japan. This increase is related to the



Figure 2-10. The operating room at the American University of Beirut Medical Center, which shows the updated anesthesia equipment and monitoring of a patient undergoing coronary artery bypass grafting.

growing population of older patients and the increase in incompatibility complication; the number of cases anesthetically managed by neural block or general anesthesia alone is also expanding.

The Middle East (Anis Baraka and Fouad Salim Haddad)

The anesthetic machinery, monitoring equipment, and anesthetics used match the international standards that are approved by international societies, such as the American Society of Anesthesiologists (ASA). Every patient undergoing surgery under general or regional anesthesia is routinely monitored with electrocardiography, pulse oximetry, noninvasive arterial blood pressure monitoring, and end-tidal capnography. In critical care patients or in patients undergoing cardiac surgery, monitoring includes pulmonary artery catheterization, mixed venous oximetry, cerebral oximetry, intraarterial blood pressure monitoring, and blood gas analysis. Figure 2-10 shows the operating room and illustrates monitoring of a patient undergoing coronary artery bypass grafting at the American University of Beirut Medical Center, which has updated anesthesia equipment.

Preoperative checking of anesthesia equipment and gases and the labeling of drug syringes are routine practices. In addition, the "time out" policy confirming the identity of the patient, the type, and site of surgery are practiced before surgery by the anesthesiologist, the surgeon, and the operating room nurses involved in the surgical procedure.

Russia (Yury S. Polushin and Olga N. Afonin)

By the end of the twentieth century, the country faced a severe political crisis resulting from former President Mikhail Gorbachev's program of economic, political, and social restructuring called *perestroika*. The Soviet Union collapsed into separate and independent states, causing the destruction of the national economy and leading to violations of the links between the regions that had evolved over the years. In the field of medicine, the manufacture of medical equipment almost ceased while the pharmaceutical companies either stopped production or moved outside the country. The results were drastic in the lives of the Russian people. There was a change of economic structure, which led to the need to reform the system of medical aid to the population. This was a difficult period in the history of Russian medicine, with the breakdown of existing health care mechanisms and a void in establishing new systems of medical care. In anesthesiology and intensive therapy, which rely on sound economic factors, the situation was particularly difficult. In many small hospitals, units of anesthesiology were closed because it was not possible to update equipment and medications. The salary of doctors and nurses was extremely low, and the prestige of the specialty declined, leading to a considerable shortage of personnel. The All-Union Scientific Society of Anesthesiologists and Intensive Care of the U.S.S.R. ceased to exist, and it was replaced with a variety of regional organizations that did not have legal status or proper authority with the institutional health managers.

Just over 20 years after the end of perestroika, the economy has revived and the state can distribute considerable resources for the development of medicine. A new health care system has been developed, multifunctional medical centers have been built in several regions of the country, and funds have been allocated for the modernization of hospitals, including the anesthesiology and intensive care units. In 2011 a new order of the Ministry of Health of the Russian Federation was activated that defines the procedure for the provision of anesthesia and intensive care in hospitals. As a result of these changes, the field of anesthesiology is again recruiting young and active professionals. In addition, the Federation of Anesthesiologists and Reanimatologists of Russia has strengthened its position and is uniting its ranks with members of affiliated organizations in the Russian Federation, and communications between Russian anesthesiologists with colleagues from other countries has improved.

Of course, the reform of medicine is still far from complete, and some institutions still have not made noticeable changes. Although modern, influential, and well-equipped hospitals exist, there remains a need for medical services, particularly in remote regions that lack facilities and access to medical care. There is a great shortage of personnel, which limits the needed radical reform of the medical education system, including anesthesiology, to meet international requirements. However, progress is evident and is continuing at a gradual pace and with the support of the Russian Federation.

Southeast Asia (Florian R. Nuevo)

The biggest change in the region in the last 2 years is the mandatory use of pulse oximetry as a basic monitoring standard on any patient who is given an anesthetic that leads to changes on sedation levels. The requirement for pulse oximetry monitoring is part of the WHO Surgical Safety Checklist, which has become part of the requirements prescribed by most accreditation organizations in the region. Credit must be given to the WFSA, which has

worked closely with the WHO to make pulse oximeter monitoring a part of the surgical safety checklist. The WFSA has also made pulse oximetry a mandatory requirement at all levels of care in the 2010 WFSA International Standards for Safe Anesthesia Practice.

Although there is no robust database available to measure the reduced incidence of intraoperative deaths in the last 5 years because of pulse oximeter monitoring, no ASEAN anesthesiologist would readily agree to administer a general anesthetic without this monitoring device. Nevertheless, surveys among anesthesia care providers confirm that the change is palpable. The audit reviews also report this observation.

The safety of remote anesthesia continues to be a great challenge. Safe delivery of anesthesia is frequently compromised because of the limited availability of proper equipment and manpower. A typical example is the lack of MRI-compatible devices and equipment. Quite often anesthesiologists have to rely on visual assessment of breathing patterns in sedated patients during MRI procedures because MRI-compatible oximeters are not available.

The use of capnography in the operating room is still infrequent and usually limited to laparoscopic procedures. This situation is typical in low-to-middle income countries in the region. There is still much work to be done to make capnography a part of the safety standards for every patient who undergoes mechanical ventilation, not only in the operating theaters but also in ICUs.

Another persistent challenge in the region is the inadequate availability of anesthesia machines that have passed the safety standards prescribed by the American Society for Testing Materials. Because of this, the practice of mixing anesthetic gases, such as oxygen-air or oxygen-nitrous oxide, and applications of closed-circuit or low-flow anesthesia techniques are limited. The administration of 100% inspired oxygen is often the norm in places without modern anesthesia machines. In developing countries, there is a need for oxygen concentrators in clinical practice, because their use can reduce costs and make oxygen more readily available in difficult and remote work environments.

The advent of laryngeal mask airway devices has greatly improved the management of difficult airways in the region. Until recently, fiberoptic bronchoscopy was rarely available for use by anesthesiologists. Use of the LMA has curtailed the loss of lives of those who succumbed to failed intubations or difficult mask ventilation scenarios. A related and integral contributor to improved airway management in the region has been the addition of difficult airway workshops that are conducted in collaboration with industry in almost all anesthesia meetings throughout Southeast Asia.

Uganda and Sub-Saharan Africa (Ronald D. Miller and D.G. Bogod)

A recent editorial stated that the United States spent an average of $8233 per person per year for health care.[33] In contrast, in countries with either "low" or "intermediate" budgets, this expenditure rarely reaches $30 per person per year.[34] From a quality-of-care point of view, in a 2007 survey of more than a quarter of Uganda's anesthetic practitioners, only 23% thought that their facilities met all the widely accepted minimal standards for the practice of safe, adult anesthesia. Categories surveyed included access to updated information, basic operating room equipment, and the most basic supply of anesthetic drugs. For safe pediatric anesthesia, only 13% thought that their facility met the basic requirements.[35]

For spinal anesthesia techniques, more than half of the anesthesiologists surveyed did not have regular access to the necessary local anesthetics, and others did not have a ready supply of spinal needles. Only 23% could guarantee being able to find a brush to clean their tracheal tube between procedures.[35]

For cesarean sections in women during childbirth, nearly all the respondents (94%) said that they did not have the facilities to perform this procedure safely. More than three fourths did not have reliable access to magnesium sulfate, and half of them said that they could never get it.[35]As D.G. Bogod, editor-in-chief of *Anaesthesia*, wrote in the editorial of the issue in which these numbers were published:

The figures revealed by this survey show that despite the best efforts of all involved, 27 million Ugandans essentially enter a lottery every time they undergo anesthesia—a lottery with poor odds of a happy outcome. What the authors cannot tell us is whether this problem is confined to Uganda alone . . . it would be foolish to try to extrapolate from one country to another, but it is unlikely that Uganda data differ wildly from most of Sub-Saharan Africa. . . . If the situation in Uganda is bad, it is likely to be far worse in Ethiopia, Somalia, Tanzania and many other neighbouring countries.[35]

The above description was published in the seventh edition of *Miller's Anesthesia*. Have conditions improved in the last 5 to 6 years? Current literature is available regarding the status of personnel in anesthesia (described later). The status of facilities and equipment is less clear. A direct quote[36] is not encouraging:

The most common technique is general anesthesia (with spontaneous or manually assisted ventilation). Nonmedical anesthetists with limited training and supervision and lacking the most common drugs and anesthetic equipment administer anesthesia usually for emergency surgery . . . the morbidity and mortality rate is high.

This description strongly suggests a lack of facilities and equipment.

EDUCATION, ACCREDITATION, AND AVAILABILITY OF PRACTITIONERS

Brazil (Maria Carmona)

Currently, more than 10,000 Brazilian anesthesiologists are affiliated with the SBA, the second largest anesthesiology society in the world. In addition, a significant number of physicians not affiliated with the SBA or without a specialization also work as anesthesiologists, primarily in smaller towns and poor areas of the country. Yet, over the last decade, it has become evident that

there is a lack of anesthesia providers in most Brazilian cities because of the increasing elderly population, the diversity of surgical and diagnostic procedures, and the extension from 2 to 3 years for specialization in anesthesiology. Partly because of this shortage, clinical anesthesia is the main activity of Brazilian anesthesiologists with only a minority involved with intensive care, pain care, and research. This deficiency has led to an expansion in the number of training centers and positions for specialization in anesthesiology in most residency programs in the country.

In Brazil, residency in anesthesiology is regulated by both the Ministry of Education and the SBA, and approximately 650 physicians are admitted annually to a 3-year specialization program. Although the best residency programs are related to university hospitals, the majority of the 93 training centers are isolated programs in medium-sized hospitals. The residents have intensive training in the different areas that qualify them to administer anesthesia safely. All the centers are accredited, and they should offer good training in preoperative evaluation, the main anesthesia specialties, intensive care, and pain treatment. A practical and theoretical program is followed, and the residents are evaluated annually with a test conducted by the SBA, which publishes a ranking of the training centers based on specific criteria. The majority of candidates in residency programs are Brazilian, but a few candidates from other Latin American and African Portuguese-speaking countries have also participated. The official instructors on these residency programs are certified by the SBA, and few of these have PhDs. For PhD certification, which is the top title in anesthesiology, specialists undergo a multiple-choice test followed by an oral examination administered by a board assigned by the SBA.

The high quality of teaching and clinical care contrasts with the poor focus on research, which is the greatest weakness in the field of anesthesia in Brazil. There are few universities with well-structured anesthesia departments, and the effect of the few publications in existence is limited. Although the rules for the training centers also recommend that residents be involved in research projects, few universities are able to offer such opportunities. This situation is changing, and many training centers are realizing the importance of research as a way to improve education and assistance. Each year, a greater number of anesthesiologists are enrolled in the few postgraduate programs available in Brazil, and some PhD students are enrolled in postdoctoral programs in Brazil or abroad. The large number of attended cases is a robust base for observational and randomized clinical trials, and these are gradually increasing. The peer-reviewed *Brazilian Journal of Anesthesiology* is the official journal of the SBA, and it publishes most of the country's anesthesia research, together with other high-impact international journals in anesthesia or related areas.

Chile/South America (Guillermo Lema)

The training of anesthesiologists is a contentious issue in South America. There is a large discrepancy between the views of governments and those of anesthesia societies, and this relates to the number of anesthesiologists needed and the quality and duration of training required. All countries on the continent have anesthesia training programs of varying quality. The governments run a few, but universities conduct most of the programs.

There is agreement among all about the basic length of time needed for training; regardless of whether the government or the anesthesia society runs the program, 3 years is required to complete training. Some countries have added a fourth year with emphasis on research or a specific specialty; however, there is lack of financial support from governments, and this has stymied acceptance of this additional year. In addition, some countries have specific scientific organizations run by universities and scientific societies to certify the various places where anesthesia is taught. However, some facilities without proper certification contine to teach residents. Gradually, these places are being restricted from teaching.

Governments and scientific societies also view the requirements for anesthesiologists differently. Governments are pushing for more practitioners, whereas universities prefer better training. Despite such difficulties, anesthesiologists and their scientific societies have campaigned for greater influence in the process of accreditation.

Although advances in medical training by the universities, anesthesia societies, or both, continue, there remains the issue of an inadequate number of practitioners. Public hospitals do not have enough anesthesiologists, and universities are teaching at full capacity. In an effort to create more practitioners, governments are driving the universities to enroll more students, while the universities are concurrently striving to accommodate the growing number of students and provide quality education. Both institutions are diligently working to meet their respective needs. The results will be seen in the near future.

Anesthesia meetings achieve the goal of educating residents and older generations of anesthesiologists. Anesthesia journals are in existence, and although none are comparable to the Institute for Scientific Information, efforts are being made to become part of international medical databases.

China (Yuguang Huang)

Currently in China, medical students are educated for 5 to 8 years in medical colleges (5 years for undergraduate education and an additional 3 to 5 years for a master's or doctoral degree), followed by a resident training program of 5 years.

Differences in education quality still exist among medical colleges across the country because of imbalances in local economies. Despite the improved overall standard of anesthesiologists in the country, it is obvious that in primary-level hospitals, both the clinical performance of the resident and the level of resident training are still relatively low. As a result, anesthesia providers in larger medical centers usually excel beyond their counterparts at primary-level hospitals by a large magnitude.

To address the imbalanced human resource distribution in different areas, the government has been promoting standardized resident training nationwide since 2000. The act was first implemented in pilot centers in Sichuan, Beijing, Shanghai, and other large cities and

has extended to all the other cities throughout China. Medical graduates are required to start their training at an accredited institution upon graduation, and only those who have passed national examinations receive their license. The *Anesthesiology Standard Regulatory Protocol* released in 2012 clearly states the requirements for anesthesiologists in different hospitals; these requirements will help to improve the basic knowledge and clinical practice of young anesthesiologists in primary-level institutions. Meanwhile, the Chinese Medical Association and Chinese Society of Anesthesiologists have also been providing various continuing medical education programs to local hospitals. The overall professional level of Chinese anesthesiologists is expected to be elevated through such efforts.

In summary, the Chinese anesthesiologist team is continuing to evolve. As anesthesiologists have gained prominence in China, more medical graduates are selecting anesthesia as their career after graduation. Graduates with higher education levels are primary contributors to the medical team. In some well-known medical centers, personnel with master's and doctoral degrees hold over 75% of the positions in the department. However, there is a significant gap between the country's urgent clinical needs and the number of competent anesthesiologists. This situation requires additional recruitment efforts.

Europe (Lars I. Eriksson and Jannicke Mellin-Olsen)

Shortly after the European Economic Community (EEC) was established in 1958, representatives from professional organizations representing the Inner Six founding member countries (Belgium, France, West Germany, Italy, Luxembourg, and the Netherlands) created the European Union of Medical Specialists (UEMS). The UEMS soon established contacts with the EEC to define basic principles for medical specialist training in Europe. The aim was to define a high level of training with common general criteria for future European medical specialists, which would lead to harmonized and coordinated specialist training throughout Europe. It would also facilitate the free movement of European specialists from one member country to another. As a tool to achieve this objective, the UEMS created Specialist Sections for the main specialties in 1962. One of these sections is the European Section and Board of Anaesthesiology (EBA), which includes reanimation and intensive care medicine. The role of the EBA is political, working as the anesthesiology branch of UEMS and the EU. EBA is also the interface with other medical specialties including multidisciplinary fields such as critical care and pain medicine, education, and patient safety.

Migration and Work Force Shifts. The EU has defined the duration of training needed to become a specialist in anesthetics to be 3 years; however, in most EU countries, it currently takes 4 to 7 years to fulfill the requirements of a certified anesthesiologist. The content of the training programs varies largely by country with the specialist certificate awarded by each individual country. Yet, being on the specialist register in one EU country entitles the person to be accepted as a specialist in any other EU country, in line with the principle of free movement of specialists within Europe. Although in accordance with the EU spirit, this can create problems. Sometimes, the hired anesthesiologist is not qualified to work in the local setting of another EU country because of insufficient or inappropriate training and lack of language skills.

As in other parts of the world, the quality of care in hospitals and the opportunities for professional and economic development are in general better in the cities. Similarly, the less affluent EU member states that invest in the training of anesthesiologists often do so only to see their practitioners move to other countries within the EU, typically from Eastern to Western Europe. Of course, the main driving forces behind this migration are better economic and professional development opportunities. Recently, financial issues have led to new routes of work migration with practitioners moving from southern European countries to the north.

The supply and demand of anesthesiologists varies considerably between parts of Europe for many reasons. All countries are experiencing an increased aging population who require more health interventions, thereby increasing the demand for workers. Another contributing factor is the European Working Time Directive, a mandatory regulation that limits the number of hours any person is allowed to work per week. In addition, there is an increasing tendency by younger anesthesiologists of both genders who want to spend more time with their families and less time in the hospital. All these issues underlie the current labor shortage that exists in a majority of EU member states.

The shortage of specialists is not made easier when governments fail to foresee the consequences of shortsighted planning and then have to seek ad hoc solutions when avoidable problems arise. This seems true for all countries, but it manifests in various ways depending on a country's historical and cultural factors. When financial restrictions are added to these factors, even traditionally rich countries have to face the probability of compromising their standards by reducing training requirements and recruiting less educated anesthesia providers.

However, statistics on workforce availability and migration in Europe are ambiguous and often associated with error. Unfortunately, the data do not reflect whether individuals are working full time or whether an anesthesiologist is registered in more than one country. Some medical students go abroad to study and return to their home countries but are then counted as a migrated doctor. These issues all add to the complexity of workforce planning. Despite the statistical shortcomings, there is no doubt that the average number of anesthesiologists in Europe has increased over the last few decades.[19,37] The increase is larger in older EU member countries than in the newer ones because of demand, training, availability, migration, and other factors. The average number of anesthesiologists is unscientifically estimated as 14.5 per 100,000 population in Western Europe, but in the East it is only 6.1 per 100,000 population.[19]

In most European countries, health care is funded by the government, although there are local exceptions. Whereas more than 50% of anesthesiologists in some Western European countries (Luxembourg, the

Netherlands) are involved in private practice, anesthesiologists within Scandinavia and the United Kingdom rarely (less than 5%) work in private practice, although the number is increasing.

European Society of Anaesthesiology. The European Society of Anaesthesiology (ESA) is Europe's counterpart to the ASA; however, there are differences. Whereas the ASA is the national society of one country, the ESA Council consists of representatives from 30 nations (data from 2013). European countries with 25 individual members or more (or more than 10% of practicing anesthesiologists in smaller countries) are entitled to council representation. The council members serve to facilitate and harmonize the activities of national and international societies of anesthesiologists in European countries. In addition, all national societies in Europe have formed a separate body within the ESA, known as the National Anaesthesia Societies Committee.

The objectives of the ESA are to promote the exchange of information among European countries; to disseminate information on anesthesiology; to raise the standards of the specialty by fostering and encouraging education, research, scientific progress, and the exchange of information; to promote and protect the interest of its members; and to promote improvements in safety and quality of care of patients undergoing anesthesia by facilitating and harmonizing the activities of national and international societies of anesthesiologists in European countries.

The Euroanaesthesia Annual Congress is the main scientific event of the ESA, but other scientific meetings are arranged, such as the autumn meeting. Education, research, and providing specialty resources are also major activities of the ESA.

European Postgraduate Training Program in Anesthesiology, Pain, and Intensive Care Medicine. In 2011, the EBA published a completely revised postgraduate training program in the specialty[38] based on consultations with national societies, the ESA, and other stakeholders. The new program is considered a paradigm shift from structure- and process-based to competence-based training.

Some years ago, an EU directive mandated a 3-year training program to become a specialist in anesthesia; however, that decision was made at a time when the complexity of anesthesia was much less. This directive is still valid, but the current duration in most EU countries varies from 4 to 7 years, and it is described as a traditional process-based education model. Several governments have recently tried to reduce the duration of training in an effort to train more anesthesiologists in less time and more inexpensively, but this has been fiercely opposed by the EBA.

Since 2001, the EBA has stated that the minimum duration of training should be 5 years, of which at least 6 months should be spent in critical care, 3 months in emergency medicine, and 3 months in pain therapy. Simulation-based training, logbooks, and portfolios were recommended. These guidelines were streamlined and developed further in 2008. The resulting 2011 program requires training of at least 5 years, but with at least 1 year specifically directed to intensive care medicine training. The guideline now states the minimum estimated time required to achieve the defined competences to fill the roles of an anesthesiologist, rather than just a description of length of time.

The training program builds on the competency initiative—the Canadian Medical Education Directives for Specialists definition of the seven roles of a medical specialist. In turn, a list of 10 domains of general core competencies (e.g., disease management, patient assessment and preparation, anesthesia nontechnical skills, and quality-safety-management-health economics) and seven domains of specific core competencies (e.g., obstetric anesthesiology, multidisciplinary pain management) were described. For all competencies in each domain, learning objectives are defined in the form of knowledge, technical skills, clinical and case-management skills, drills, and specific attitudes. This has resulted in a completely new syllabus.

The new curriculum requires new assessment tools, in addition to the old summative examinations.[39] Examples are self-assessment, evaluation of clinical performance, and patient management problems. New online assessment systems are being launched in all-in-one formats. The new curriculum has been introduced in Moldova and Romania, and several other European countries are changing their education systems.

European Diploma in Anesthesiology and Intensive Care. Introduced in 1984, the European Diploma in Anesthesiology and Intensive Care (EDAIC) remains the recommended theoretical examination tool. It is a multilingual, end-of-training, two-part examination covering the relevant basic sciences and clinical subjects for a specialist anesthesiologist. It provides an international European standard that allows harmonization of training and assessment of knowledge across Europe. The EDAIC has been adopted as the national examination in Austria, Switzerland, Hungary, Poland, Malta, Romania Slovenia, Turkey, the Czech Republic, Moldova, Finland, and in 2014, the Netherlands. In 2007, non-Europeans were also allowed to sit for the EDAIC, as stated by the Glasgow Declaration by the Council of European Specialist Medical Assessments. Although the EDAIC does not represent a ticket to work in Europe, the examination has become increasingly popular worldwide.

EDAIC Part 1 consists of multilingual, multiple-choice questions, one part on basic physiology, pharmacology, physics, clinical measurement, and statistics, and a second part on clinical practice associated with anesthesia and its subspecialty areas. It is to be taken after approximately 2 years of anesthesiology training. Part 2 consists of four oral examinations, each with two examiners moderating each other. Candidates may choose the language in which they wish to be examined within the constraints available at the examination center. Part 2 is an end-of-training examination, and successful completion qualifies the candidate to receive the EDAIC. Because the EDAIC is an assessment of theoretical anesthesia knowledge, it must be supplemented by the local assessment of skills and professional attitudes or behavior that takes place in each country according to local systems and is

a requirement before an individual can be placed on the specialist register in that country.

The Committee for European Education in Anaesthesiology (CEEA) was formed as a foundation, Foundation for European Education in Anaesthesiology (FEEA) in 1986. The program consists of a cycle of six courses, covering all the fields of anesthesia, intensive care, emergency medicine, and acute pain management. The program is to be completed in sequences of 3 years and is conducted in the national language of each country. The initial aim was to provide continuing medical education in anesthesiology within the European Community. With the expansion of the EU, the FEEA was introduced to the new member countries and to other European countries. Since 1995, new centers have been established in cooperation with the WFSA in other parts of the world, such as Latin America, Africa, and in Asia. In 2009, the FEEA activities were transferred to the ESA, and the CEEA was created as a joint committee of the ESA and WFSA. Currently, there are more than 100 regional CEEA centers.

ESA/EBA Joint Hospital Visiting and Training Accreditation Program. The ESA/EBA Joint Hospital Visiting and Training Accreditation Program (HVTAP) has been in place since January 1996 as a joint permanent committee of the ESA and the EBA. The goal is to encourage and enhance training standards across Europe and to ensure that an academic institution meets the prerequisites of training in anesthesiology specified in the EBA training guidelines. Together with the EDAIC, the HVTAP serves to improve the overall quality of the specialty of anesthesiology and to harmonize its activities throughout Europe. The visit consists of a detailed presentation of the staffing and organization of the hospital, the department (or the institute), and the structure of training. This forms the basis for discussion and evaluation of all aspects of the teaching and training process with the staff members involved for the purpose of complementing and building on strengths and encouraging development and change to address areas of weakness. A subsequent comprehensive report of the visit, together with recommendations for improvement or accreditation (or both), is presented by the program committee.

India (Deepak K. Tempe)

In India, there are mainly two types of postgraduate qualifications that can be obtained in the field of anesthesiology. The first, provided by medical colleges (MD in anesthesiology, a 3-year degree program), is governed by the Medical Council of India, which oversees the syllabus and other teaching and training standards. The second one is provided by the National Board of Examinations, which awards a Diplomate of National Board (DNB). In addition, the Medical Council of India regulates the diploma in anesthesiology (DA), which is a 2-year training program that is available at medical colleges.

In 1992, it was determined that no new medical college or postgraduate course could be started without the prior approval of the Medical Council of India, and its recommendation became mandatory for all medical colleges. Thus, it was only after the addition of this section, known as *10a,* that teaching and training in the medical field in India were standardized and minimum standards were enforced. In 1998, a Supreme Court judgment reinforced the statutory body's position in establishing and maintaining high standards of medical education and recognition of medical qualifications in India. The recognition awarded by the Medical Council of India for all courses must be reviewed every 5 years by a Medical Council of India inspection team. Thus, teaching and training in anesthesiology in India are standardized through the setting of minimum standards throughout the country in terms of the facilities (space, equipment, manpower, and infrastructure) and the syllabus.

Growth of the Specialty. The interest of Indian medical students in the specialty of anesthesiology has shown a dramatic increase during the last decade. Previously, candidates for a postgraduate course in anesthesiology were admitted based on scores obtained on the MBBS examination. The practice now is to conduct a common entrance examination, with admission into a given subject area based on the rank attained by the student. In a few states such as Delhi, this has been the practice for approximately 25 years.

Table 2-2 shows the top and bottom ranks that were admitted into an MD anesthesiology program between 2002 and 2007 in the states of Maharashtra and Delhi. The table indicates that interest among students to learn and practice anesthesia is increasing. Over the years, the situation has remained more or less similar, except that the total number of MD seats has more than doubled. Reasons for the growing interest in anesthesia among students could be related to the increasing scope of anesthesia (as discussed earlier) and better job prospects. In addition, other fields such as general surgery and general medicine require further subspecialty training, and this could be motivating students to pursue anesthesia. In Delhi, anesthesiology is among the top six specialties preferred by medical students, along with radiology, dermatology, pediatrics, orthopedics, and gynecology. This development is in sharp contrast to the situation 15 to

TABLE 2-2 **OVERALL RANKINGS OF POSTGRADUATE STUDENTS ENROLLED IN ANESTHESIOLOGY PROGRAMS IN MAHARASHTRA AND DELHI (2002-2007)**

	Maharashtra		Delhi	
Year	Top Rank	Bottom Rank	Top Rank	Bottom Rank
2002	228	854	65	98
2004	No exam		53	96
2005	405	642	32	96
2006	160	606	33	99
2007	106	504	61	85

The total number of postgraduate seats in all subjects is 140 in Delhi and 450 in Maharashtra. The students often sit for entrance examinations in several states, which probably explains why the last rank exceeds the number of seats in Maharashtra.

20 years ago, when anesthesiology was among the bottom five choices.

There are a total of 381 medical colleges in India with 50,078 seats.[40] Of these, there are 1386 seats in MD anesthesia and 644 in DA anesthesia. In addition, the Ministry of Health and Family Welfare of India recognizes the DNB as a qualification in the given field and equates it with the postgraduate degrees awarded by other Indian universities. There are approximately 200 DNB seats in anesthesiology.

Assigning seats is especially challenging because it remains unclear just how many anesthesiologists India needs. According to one estimate, there are approximately 35,000 to 40,000 anesthetists in India for a population of 1.27 billion (personal communication, Dr. Anjan Dutta, President of ISA). The majority of these anesthesiologists are in cities. This number is far too few as compared with the United Kingdom, which has 12,000 anesthetists for a population of 64 million.[41] This fact has been recognized by health officials and, as a result, the number of postgraduate seats in anesthesia has more than doubled during the last 5 years. Major factors that limit any additional increase in the quantity of seats are the inadequate supply of recognized medical teachers and the limited number of medical colleges. Consequently, although the situation has improved, the shortage of anesthetists continues. It is generally believed that in the interest of safety, short-term courses in anesthesia should be discouraged to fill this deficiency.[42] The ISA has also suggested that during the teaching course of MD, the final-year student can have a rural posting for 3 to 6 months with one qualified anesthetist.[43] However, the government is actively considering a short-term training course in obstetrics anesthesia (3 to 6 months) for MBBS doctors to provide much needed anesthesia services to improve maternal health. Some states, such as Andhra Pradesh, already have this in place while other states are considering it. The Delhi High Court has proclaimed that training for life-saving anesthesia skills and emergency obstetric care will continue until the requirement of anesthesiologists is fulfilled[32]; however, these doctors will be allowed to administer anesthesia only in government rural health centers.

Japan (Naoyuki Hirata and Michiaki Yamakage)

In Japan, the specialty of an anesthesiologist is certified differently by the government and by the JSA. To be certified by the government, a trainee anesthesiologist must perform general anesthesia in more than 300 cases over a 2-year period under the supervision of certified anesthesiologists. On the other hand, the JSA certifies anesthetic specialists by clinical training over a 5-year period in various types of anesthesia that include academic activities and success in oral, written, and skill examinations. The present examination pass rate is approximately 60%. To update the certification of the JSA (the government does not require updates), anesthetic specialists must report on their anesthetic case experience, teaching career, and academic activities every fifth year. When the first renewal is accepted by the JSA, the anesthetic specialist is also qualified as a supervisory anesthesiologist. Thus, 10 years of substantial experience in the field of anesthesiology is required to be certified as a supervisory anesthesiologist in Japan.

The Middle East (Anis Baraka and Fouad Salim Haddad)

The departments of anesthesia in the different countries of the Middle East are staffed by highly qualified academic faculty certified either by the Arab Board or by foreign academic bodies, such as the American Board of Anesthesiology of the United States and the Faculty of the Royal College of Anaesthetists of the United Kingdom.

Anesthesiology training following MD graduation consists of 4 years of residency in a recognized medical center. This may be followed by 1 to 2 years of a subspecialization fellowship in areas such as pain management, critical care, obstetric anesthesia, cardiopulmonary anesthesia and more. Anesthesia specialization and Board certification by the training hospitals must be recognized by the anesthesia societies within the respective countries, which also track medical training, as well as continued medical education.

In addition to the annual regional anesthesia society conferences such as Egyptian Anesthesia (Fig. 2-11, *A*), and the Pan Arab Congress of Anaesthesia (see Fig. 2-11, *B*), the Anesthesiologists of the Middle East participate actively in the activities of other national society meetings such as the Pan African meetings, and the annual meetings of the ESA and the ASA. In addition, they actively participate in the administrative and academic activities of the World Congress of Anaesthesiologists (WCA) and the WFSA.

Russia (Yury S. Polushin and Olga N. Afonin)

As of today, anesthesiology education in Russia still requires revision and improvements. There is need for structured residency programs that teach the standards accepted around the world, which are based on decades of experience in the safe practice of anesthesiology. The Academy of Postgraduate Education recently introduced new standardized tests, comparable to internationally accepted graduation examinations that permit objective measurement of the knowledge of newly graduated anesthesiologists.

Southeast Asia (Forian R. Nuevo)

The required number of years of training in anesthesiology varies among the member countries of the ASEAN region between 2 to 3 years (Table 2-3). Some countries follow the European model, and some adopt the American model (see Chapter 9), whereas others develop a hybrid model that is a combination of training programs from across the world. Of course, selection of an appropriate model is heavily influenced by the country's prevailing education system, which has been in place from the time it was colonized through the time it gained sovereignty. Currently, the lack of anesthesia care providers continues to be a persistent problem, and most countries are reviewing their respective curricula to address their particular needs.

An education abroad, such as in the United States or Europe, can be cost prohibitive for many young physicians,

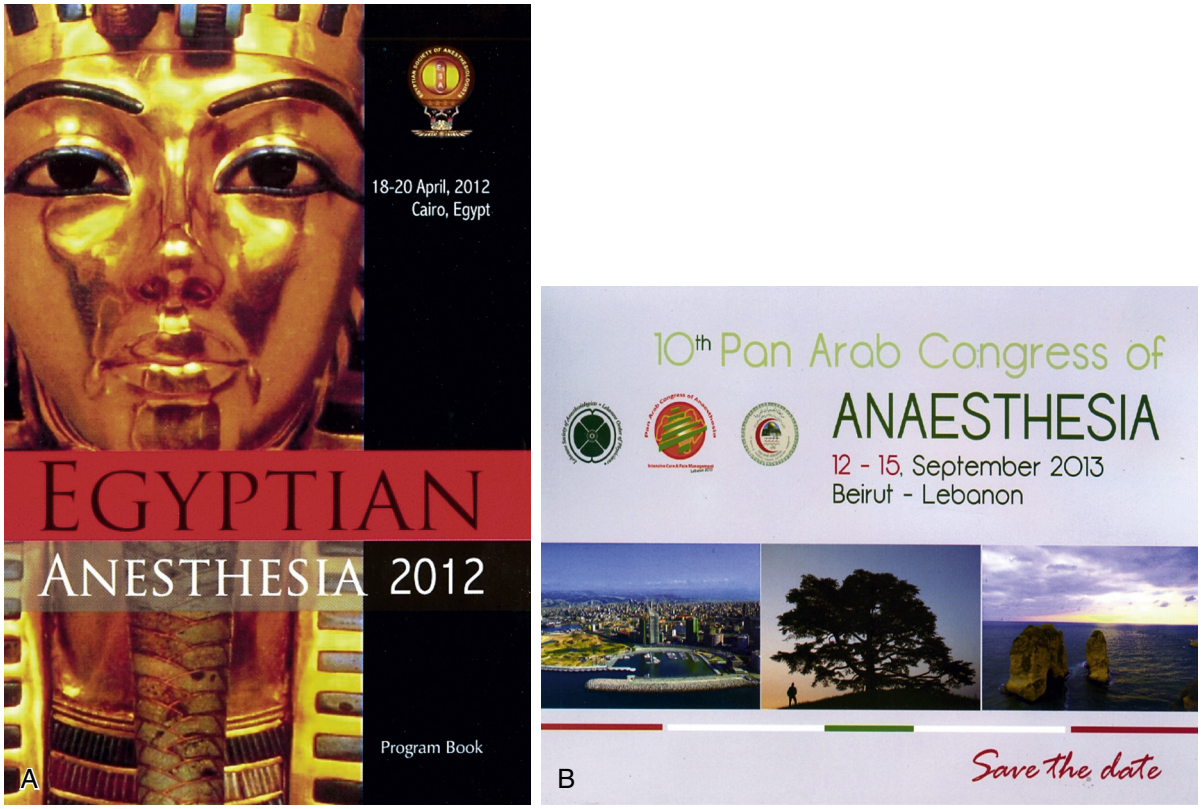


Figure 2-11. A, The Annual Conference of the Egyptian Society of Anesthesiologists, 2012. **B,** The Pan Arab Congress of Anaesthesia, 2013.

TABLE 2-3 **ORGANIZATIONS, CERTIFICATION REQUIREMENTS, AND RECOGNITION OF ANESTHESIOLOGISTS IN SOUTHEAST ASIAN COUNTRIES**

	Indonesia	Malaysia	Philippines	Singapore	Thailand
Influence on medical education	Britain	Britain	United States	Combination Britain + United States	Britain
Anesthesia					
Residency	3.5 years		3 years		3 years
Subspecialty fellowship	Variable number of training years, depending on subspecialty				
Pain			Yes	Yes	Yes
Obstetrics			Yes	Yes	
Cardiovascular/ thoracic	Yes	Yes	Yes	Yes	Yes
Pediatric			Yes	Yes	
Intensive care		Yes		Yes	Yes
Neuroanesthesia	Yes	Yes		Yes	Yes
Certifying body	Collegium of Indonesian Anesthesiologist	Malaysian Society of Anesthesiologists	Philippine Board of Anesthesiology	Singapore Society of Anesthesiologists	Royal College of Anesthesiologists in Thailand

particularly those coming from low- to middle-income countries. Thus, many young anesthesiologists select Singapore, Malaysia, or Thailand for anesthesia subspecialty fellowships because of the country's proximity and affordability. Furthermore, these training destinations are equally excellent centers of learning. However, in Indonesia, there are only 10 accredited training institutions, and being admitted into a program on the anesthesia fundamentals can be nearly impossible for many Christian Indonesians. As a result, many come to the Philippines for their 3-year anesthesia residency training, which is facilitated by institutional memorandum of agreements. The Philippines has accepted anesthesia trainees from many countries, including Nepal.

Anesthesiology Center for the Western Pacific. In January 1970, the Philippines established the Anesthesiology Center for the Western Pacific (ACWP) in Manila. It had an 11-month course on the basic fundamentals of anesthesia. This was a joint activity of

the WHO Regional Office for the Western Pacific, the University of the Philippines, the China Medical Board, and the WFSA.

The rationale for the creation of the ACWP was to help alleviate the shortage of reliable anesthesiologists in the region and to underscore the importance of administering safe anesthesia. The center did not seek to provide a complete training program; rather its purpose was to emphasize the basic sciences in anesthesiology. It created a foundation for students to build on so that they could eventually qualify, through further training, as specialist anesthesiologists.

Students at ACWP were from the Pacific Islands, Southeast Asia, southern Asia, Hong Kong, Taiwan, Korea, Japan, Iraq, Russia, and Sudan. The program served the region for 16 consecutive years, and many of its graduates have become respected leaders in anesthesia and have contributed to the development of anesthesia programs and safe anesthesia care in their respective countries. Unfortunately, in 1986, the ACWP ceased its operations.

Bangkok Anesthesia Regional Training Center. After the closure of the ACWP, a very timely project arose in Thailand. The Bangkok Anesthesia Regional Training Center (BART) was created with modest financial assistance from the WFSA Education Committee. The impetus behind the formation of the BART was the need to train anesthesiologists from the neighboring countries of Laos, Cambodia, Vietnam, and Mongolia. This program is still operational and is a source of pride, because BART graduates have all gone back to their countries of origin and helped to advance the field of anesthesia in their respective workplaces.

Uganda and Sub-Saharan Africa (Ronald D. Miller and D.G. Bogod)

In a survey by Hodges and colleagues,[44] there was only one medical anesthesiologist among the 91 anesthesia practitioners who participated in the survey, which means that, as is often the case, many trained physicians in Uganda probably traveled to the West to obtain a better life for their families. In addition, based on the survey, access to up-to-date textbooks seems iffy at best—fewer than half of those surveyed have access to such texts.[35]

The preceding paragraph, published in the seventh edition of this text, pointed to an inadequacy of trained anesthesia personnel and equipment that is being increasingly recognized. As stated in 2007, "the absolute numbers of anesthesiologists decreased during the nineties. Most anesthesia was delivered by nurse-anesthetists, either certified or trained on the job."[34] Because of age, a shortage will occur in 15 years. Experienced anesthesiologists are now so few that, in most countries, the critical mass of knowledgeable specialists no longer exists to train new anesthesia providers.

These conditions and inadequacies have been recognized by international anesthesia groups and organizations for years. Many improvements have been made (e.g., increased use of pulse oximetry). A few years ago, a "parallel anesthesia and surgical provider training program was started in Sub-Africa in a rural hospital." Basically, this program was designed to provide integrated care to a certain geographic area. Although the specific outcome of this organizational approach was not described, there is evidence of creativity in trying to solve basic inadequacies in health care delivery.

Encouragingly, communications in *The Lancet* are appearing regarding anesthesia-related mortality in Sub-Saharan Africa. With the advancing sophistication of information technology, comparison of outcome data among countries and/or areas of the world are possible. Bainbridge and associates[45] compared anesthesia related mortality between developing and developed countries. The anesthesia-related mortality rate was at least twofold to threefold more frequent than in developed countries. Cesarean section was the most common procedure with a mortality rate of near 1%.[46] Further, in several low-income countries, anesthesia is administered almost exclusively by nonphysicians, regardless of the patient's physical status and often without supervision.

The attention that developing and poor countries are receiving regarding anesthesia care will likely improve that care. The evolution of information technology will probably become more important and direct our attention to where it is most needed. While emphasis has appropriately been on mortality rates, more sophisticated and detailed outcome data are required so that resources can be directed in a productive direction.

SUBSPECIALIZATION

Brazil (Maria Carmona)

As part of its focus on improving the progress of anesthesiology in Brazil and stimulating educational and regulatory activities, the SBA has created specific member committees, such as those for ambulatory anesthesia, cardiovascular and thoracic anesthesia, obstetric anesthesia, pediatric anesthesia, regional anesthesia, venous anesthesia, perioperative medicine, palliative care, organ transplants, sleeping disturbances, malignant hyperthermia, resuscitation, trauma care, difficult airway, and more recently, committees related to occupational health and quality and safety. The resuscitation and the difficult airway committees develop specific workshops related to continuous education and training on these topics. The SBA also offers both a physical and virtual library that deliver scientific publications on demand, as well as video lessons previously delivered in society meetings or specifically prepared for attendees of the residency program.

Chile/South America (Guillermo Lema)

In South America, only Colombia and Chile have specialty laws. In all other countries, physicians can perform professional actions without a law to certify the proficiency and quality of care and protect patients. In fact, physicians with a low level of training have practiced anesthesia for many years; in most of these countries, paramedical personnel have performed anesthesia because of the lack of sufficient medical personnel or interest in the specialty. In some countries, surgeons conduct both anesthesia and surgery with the help of technical personnel. This practice

has been abandoned in most countries, but in countries such as Bolivia, Ecuador, Paraguay, Peru, and Venezuela, this situation persists and with government authorization.

Currently, the law in most countries specifies that only physicians can provide anesthesia; however, the shortage of trained physicians has left some countries with inadequately trained ones. Nevertheless, the process of certification of specialties, including anesthesia, is present in several countries. Most countries have medical organizations and anesthesia societies demanding proper certification methods. In Chile, Colombia, and other countries, the government has definitively reached agreement on minimum standards for certification in all medical specialties. It includes the recognition that only certain universities with full accreditation can teach medical specialties. So, as of the end the end of 2013, only colleagues who complete their studies in accredited institutions will be considered anesthesiologists, and only they will be allowed to work in public hospitals and private clinics.

India (Deepak K. Tempe)

For more than two decades, anesthesiologists have recognized the need for dedicated practice in the field of cardiac anesthesia and neuroanesthesia. There are anesthesiologists who are working exclusively in these specialties, but very few separate departments of cardiac anesthesia and neuroanesthesia exist. The All India Institute of Medical Sciences (AIIMS), a group of autonomous public medical colleges of higher education, is an exception in this respect because it created two such departments in 1986. Postdoctoral courses in these specialties have been started in the country. AIIMS has conducted the courses in both specialties since 2002, whereas the Sri Chitra Tirunal Institute of Medical Sciences, Thiruvananthpuram, has offered a course in cardiac anesthesia since 2003. The number of seats, however, is grossly inadequate, with four seats in cardiac anesthesia and two in neuroanesthesia. The National Board of Examinations started a DNB fellowship program (2 years) in cardiac anesthesia in 2002; it began with 4 seats, and the number has increased to 18. The Medical Council of India has now recognized the separate subjects of cardiac anesthesia (based on a Gazette of India notification dated July 24, 2009) and neuroanesthesia (based on an amendment notification dated December 8, 2010). This recognition allows all medical colleges to start the postdoctoral courses in these specialties, and the number is likely to increase.

Japan (Naoyuki Hirata and Michiaki Yamakage)

Although most anesthesiologists in Japan have performed various methods of surgical anesthesia, it has been well recognized that cardiovascular anesthetic management requires specialized experience. Recently, TEE has been recognized as essential for diagnosis and intervention during cardiovascular anesthesia. The Japanese Society of Cardiovascular Anesthesiologists has established a qualification system that certifies specialists of cardiovascular anesthesia. To be a specialist, significant clinical experience with cardiovascular anesthesia and passing of the TEE examination, created in 2004 by the Japanese Board of Perioperative Transesophageal Echocardiography, are required. These specialized anesthesiologists may further improve cardiovascular anesthetic management.

PROFESSIONAL AND RESEARCH ACTIVITY

Brazil (Maria Carmona)

The SBA is a highly structured association that is also in charge of the monitoring and engagement with federal and state legislative and regulatory activities affecting the practice of medicine by anesthesiologists. The SBA website (http://www.sba.com.br) also has a specific area for communication with the lay public. The SBA promotes an annual congress of anesthesiology, and the state and regional societies promote their own congresses. Besides presenting scientific and educational topics, the congresses provide a venue for meetings of the educational and political committees. Every 4 years, the Brazilian Congress of Anesthesiology occurs in conjunction with the Portuguese Society of Anesthesiologists. The SBA's association with other South American societies of anesthesiology, all of them Spanish speaking, is less expressive, but the Latin American Society of Regional Anesthesia is in charge of the development of this area of anesthesia in South America and promotes its own annual congress and other activities.

In conclusion, the well-established teaching programs, along with the emerging economic situation in Brazil, are major contributors to the growth of good anesthesia care throughout the country.

Chile/South America (Guillermo Lema)

Time, funding, and expertise are the basic requirements for research of sufficient quality to support publications or communications internationally. These requirements are not found widely in South America. Only a few university anesthesia departments have the capability of producing clinical research of sufficient quality to be published in esteemed journals such as the Institute for Scientific Information, notably in Chile, Brazil, and Argentina. The government and some colleagues have argued that research is not important in a continent that has more pressing priorities. This author does not agree.

Research is a tool for learning, and it should be encouraged, at least at university-based anesthesia residencies. Unfortunately, research does not generate income, and most of the clinical groups are not willing to dedicate time or money to this particular activity. Funding is lacking, and although some countries have national research grants to support clinical research, most do not. Basic research in anesthesia virtually does not exist in South America.

Financial support from pharmaceutical companies is weak, usually depending on the effects of their drugs in a clinical setting. Because of economic constraints, a large number of generic drugs are used; therefore, major pharmaceutical companies are not willing to support activities of this nature.

Conflict of interest has become a major issue; yet its regulation is weak. Many anesthesia departments in

private and public hospitals face financial limitations, and in this author's opinion, it is obvious that the tendency is to ask for support from companies in the medical industry. Although anesthesia is not a large recipient of medical industry funds, other specialties (e.g., cardiology, ophthalmology) are supported by the industry without restraint.

China (Yuguang Huang)

There are now two large anesthesia academic organizations in China: the CSA and the Chinese Association of Anesthesiologists. The CSA seeks to improve the national academic level in anesthesiology and to offer patients higher standards of clinical service. The Chinese Association of Anesthesiologists was established in 2005 and is focused on team construction and humanistic concern for anesthesiologists. Annual meetings are held in September for the CSA and in April for the Chinese Association of Anesthesiologists, with attendance in the thousands for each. As general anesthesiology has advanced, its subspecialties have also flourished with the start of several subspecialty academic groups. More than 30 clinical guides and expert consensus materials have also been published.

In 1986, the Beijing International Conference on Anesthesia was held successfully. Many experts from abroad, including Professor Ronald D. Miller (this textbook's editor), were invited to join as keynote speakers. From that point on, Chinese anesthesiologists began to communicate more with international professionals. At the first Sino-Japanese Clinic Anesthesia Symposium held in 1986, the CSA and Japan Society for clinical Anesthesia agreed to hold a symposium every 2 years.

The rapid development of the discipline has led to increasing opportunities for Chinese anesthesiologists to communicate and exchange information with their international colleagues. Some of them have obtained recognition from international organizations. Several renowned Chinese anesthesiologists have been admitted into well-known international anesthesiology societies. Professors Rong Xie, Ailun Luo, and Xinmin Wu were named Honorary Academician by the Royal British College of Anaethetists. Professor Yuguang Huang was nominated President Elect for the International Society for Anaesthetic Pharmacology in 2012 and Board Member of the worldwide Primary Trauma Care Foundation. Professor Lize Xiong was elected as a standing committee member of the WFSA in 2012. Professor Yunxia Zuo was elected as President for the Asian Society of Paediatric Anaesthesiologists in 2012.

Anesthesiology publications in China include *Chinese Journal of Anaesthesiology, Journal of Clinical Anaesthesiology, Journal of Pain Medicine,* and the Chinese edition of *Anaesthesia and Analgesia*. More than 100 research programs in anesthesiology are supported by the National Natural Science Foundation of China each year, and large scientific grants have been invested in anesthesiology research in the past years. Authors from mainland China publish more than 500 Science Citation Index manuscripts per year on average, and more presentations and publications have been released at international meetings year by year.

Europe (Lars I. Eriksson and Jannicke Mellin-Olsen)

European Academy of Anaesthesiology. Before the formation of the European Academy of Anaesthesiology (EAA) in 1978, there was no formal representative structure except the EBA for the specialty within Europe. The five statutory aims of the EAA were (1) to raise the scientific level of the discipline; (2) to improve the training of anesthetists, their clinical and theoretical education, and their competence at the completion of the training period by holding examinations; (3) to hold scientific meetings, conferences, and seminars; (4) to facilitate research in anesthesia and its associated disciplines; and (5) to promote exchange among anesthetists and discussion of all matters concerning their profession.

The EAA had a limited number of members and academicians and, as European anesthesiology grew, was perceived by many to be an exclusive and elitist organization. In 1992, the ESA was formed and was open to everyone. Its chief aims were to conduct an annual Euroanaesthesia meeting to replace the European Congress, which had formerly run on a 4-year cycle alternating with the World Congress, and to support educational and research activities by awarding grants and fellowships. Whereas the ESA was concerned with the practice of clinical anesthesia and supporting its membership, the EAA had developed formal initiatives such as the EDAIC, the *European Journal of Anaesthesiology (EJA)*, and a system of hospital visiting and accreditation training in conjunction with the EBA.

The fourth organization that existed at that time was the Confederation of European National Societies of Anaesthesiology (CENSA), which was effectively the European section of the WFSA.

For some years, the roles of all the various organizations made it increasingly necessary for an individual anesthesiologist to be a member of more than one body to participate in and benefit from all the variety of activities. As a result, in 1998 a decision was made to amalgamate the former ESA, EAA, and CENSA into one organization. A temporary organization, the European Federation of Anaesthesiologists, was established in 2001, under which amalgamation was successfully achieved. Subsequently, the new European Society of Anaesthesiology, which now represents every anesthesiologist in Europe, was launched in January 2005 in its interim form before becoming fully established in January 2006. Moreover, because the formal, declared responsibilities of the parent organizations were essentially different with little overlap between them, a strong and comprehensive organization was established right from the start. Under this new organizational structure, CENSA became the ESA National Anaesthesiology Societies Committee, now ESA National. Each country has a number of delegates to ESA National, depending on the number of members in its national society. This body constitutes the European Regional Section of the WFSA.

The ESA National provides a comprehensive range of activities to support European anesthesiology, primarily aimed at sustaining and enhancing the safety, efficacy, and quality of care of patients through publication of the EJA and the Euroanaesthesia organization and other

meetings; it supports the interests of its members and facilitates the exchange and dissemination of information related to anesthesiology, critical care, pain, and emergency medicine. It encourages research and scientific progress by conducting academic meetings and clinical studies, by awarding grants and fellowships, and by raising and harmonizing the standards of anesthesiology. This is achieved by delivering education, training, continuous medical education, developing guidelines and accreditation of anesthesiologists through educational programs, the EDAIC, and in-service training examinations, as well as through the HVTAP run jointly with EBA. The whole structure of the new ESA is currently undergoing a major revision, including changes in the by-laws.

European Journal of Anesthesiology. The EJA is the official journal of the ESA and is distributed to all ESA members. It is published monthly and is owned by the ESA. It is also the official journal of EBA. A group of editors is responsible for the content of the journal. The EJA publishes original work of high scientific quality. Preference is given to experimental work or clinical observation in humans and to laboratory work of clinical relevance. The journal also publishes commissioned reviews by an authority in a field of interest to those working in anesthesiology, pain, or critical care. Editorials, commentaries, book reviews, news, and notices are also included. In addition, the ESA publishes a newsletter four times per year, separately from the EJA. This newsletter contains items of interest to ESA members as well as information and formal announcements.

India (Deepak K. Tempe)

Since its inception in 1947, the ISA has grown from 19 to nearly 21,000 members in 2014. The South Asian Confederation of Anaesthesiologists with member countries India, Bangladesh, Sri Lanka, Pakistan, Nepal, and Maldives was formed in November 1991. Currently, there are also separate Indian associations of cardiothoracic anesthesia and neuroanesthesia. The Indian Association of Cardiovascular and Thoracic Anesthesiologists (IACTA) is 16 years old and holds an annual meeting. The IACTA awards fellowships in cardiac anesthesia after holding an exit examination of eligible candidates. Furthermore, a fellowship program in TEE has been initiated in collaboration with the Indian Academy of Echocardiography. Since 2007, a national workshop on perioperative TEE has been organized for cardiac anesthetists to learn this technique, which is now readily available in most cardiac centers. The IACTA also publishes the journal *Annals of Cardiac Anaesthesia,* which is now in its fifteenth year of publication. It has the distinction of being included in MEDLINE and being the first Indian journal in anesthesia to be indexed in the National Library of Medicine and has been followed by the *Indian Journal of Anaesthesia* and the *Journal of Anaesthesiology and Clinical Pharmacology*. In addition, a number of societies have been formed, including ones for the study of pain (founded in 1984), for critical care medicine (founded in 1992), and for obstetrics anesthesia (founded in 2005). Asian societies in cardiac anesthesia, neuroanesthesia, and pediatric anesthesia have also been formed.

Professional and research activities in India have increased with the formation of subspecialty groups in the country. Among them, cardiac anesthesia has made a particular mark. An article published in the *Journal of Cardiothoracic and Vascular Anesthesia* has highlighted that India is second to the United States and leads the rest of the world in number of related publications during the last decade. Although there were fewer original articles published in India, the authors concluded that the research activities from India cannot be ignored.[47]

Japan (Naoyuki Hirata and Michiaki Yamakage)

As mentioned before, the JSA was established in 1954, and it has held annual meetings every year since then. Subcommittees on anesthesiology, focusing on cardiovascular anesthesia, pediatrics, obstetrics, geriatrics, monitoring and equipment, nerve blocks, research, and education have been established. As of 2012, the JSA has 5450 certified anesthesiologists and 3341 supervisors. Most Japanese anesthesiologists regularly interact with colleagues internationally and in Japan to maintain their own expertise, and more than 250 Japanese anesthesiologists attend the annual meeting of the ASA every year.

In addition, the JSA has published the *Journal of Anesthesia* since 1987, and it has been indexed in the National Library of Medicine, including the MEDLINE database. Numerous manuscripts have been submitted from many countries. The number of articles published annually has increased to nearly 180.

The Middle East (Anis Baraka and Fouad Salim Haddad)

Most anesthesiologists in the Middle East keep in close contact with developments in anesthesia throughout the world by attending national and international congresses, subscribing to various international anesthesia journals, and maintaining worldwide friendships. Some anesthesiologists in the Middle East, including those who have emigrated abroad, have become leaders in the specialty and have made original contributions in the fields of muscle relaxants,[48-50] semi-open systems, obstetrics,[51] pediatric anesthesia,[52,53] and the pathophysiology of open heart surgery.[54] In addition, the Middle East actively contributes to publications. The *Middle East Journal of Anesthesiology,* which is published by the Department of Anesthesiology at the American University of Beirut, is widely distributed all over the world and is recognized by Index Medicus (Fig. 2-12).

Russia (Yury S. Polushin and Olga N. Afonin)

With the exception of a few medical centers, most anesthesiologists have to practice their art of extremely invasive and possibly dangerous science without sufficient monitoring. Pulse oximeters, gas analyzers, and capnographs are still a luxury in many medical centers. Medical science is again government financed, but it is often still dependent on the good will of the physicians who carve out time for research from their private lives. Russian anesthesiologists, as well as medics in other specialties, have been raising their concerns to the government. The Ministry of Health has accepted a new national program



Figure 2-12. Cover of the *Middle East Journal of Anesthesiology*.

for improvement in medical services, but it will take dramatic measures and significant investments in the health of Russian citizens for the country to achieve the goal of a safe and effective health care system in compliance with international standards. Statistics and the experience of multiple countries prove that the huge initial investments are returned as improvements in population health as medical and illness-related costs decrease. It would be gratifying to see Russia, the country that contributed so much to the growth and development of medicine and anesthesiology, return to the international scene as a partner in health promotion in all forms of medical science and art.

Southeast Asia (Florian R. Nuevo)

Two pioneering anesthesiologists, Professor Quintin J. Gomez of the Philippines and Dr. Saywan Lim of Malaysia, conceived the Confederation of ASEAN Societies of Anesthesiologists (CASA) in Kuala Lumpur in September 1974 during a meeting after the Fourth Asian Australasian Congress of Anaesthesiologists, a regional congress of the WFSA. The first ASEAN Congress of Anaesthesiologists was held in December 1979 in Manila, Philippines, under the leadership of Professor Gomez, who was then the incumbent president of the WFSA (1976-1980).

The main objective of CASA is to enhance and promote the specialty of anesthesiology in the region by hosting biennial congresses of anesthesia called the ASEAN Congress of Anaesthesiologists. These congresses serve as a venue for ASEAN anesthesiologists to meet experts from the United States and Europe, as well as other international anesthesia leaders, and to learn current practices in anesthesia from them. The congresses also inspire trainees and younger anesthesiologists in Southeast Asia to present their clinical trials and modest research activity and to participate in scientific activities as resource speakers or workshop facilitators.

Currently, CASA member societies conduct clinical research activities in anesthesia, but there is much room for improvement. Most research studies involve clinical drug trials funded by pharmaceutical companies. There is a paucity of published papers in peer-reviewed anesthesiology. What is also lacking is translating the research activities into well-written research papers. The *ASEAN Journal of Anesthesiology* serves as a venue to publish all of these research endeavors in the region.

Over time, the objectives of CASA have grown. The group has strived to promote closer ties among member societies, to enhance the image of the specialty in the region, and to upgrade the specialty through the exchange of information between local and international experts in anesthesia. CASA also supports interacting with other anesthesia regional sections such as the South Asian Association for Regional Cooperation, which represents Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka.

Many anesthesia subspecialty organizations have been created. To date, these include the Obstetric Anesthesia Society for Asian and Oceania (OASAO), Asian Society for Pediatric Anesthesiologists, ASCA, Asian Oceanic Society for Regional Anesthesia (AOSRA), Asian Society for Neuroanesthesia and Critical Care (ASNACC), and ASEAPS. Indeed, through CASA and these subspecialty groups, a wealth of information is paving the way to upgrade and develop the practice of anesthesia and the anesthesiologists themselves.

Despite threats of terrorism and the risks of epidemics such as avian flu and severe acute respiratory syndrome (SARS), the ASEAN confederation has persisted in hosting its biennial congress. Their leaders have been inspired to step up these academic activities, and CASA members take turns, with much enthusiasm and camaraderie, in hosting these meetings. Attendance has grown from 400 to almost 1000 anesthesiologists coming from ASEAN and non-ASEAN countries, such as Japan, Korea, China, Saudi Arabia, Mongolia, Canada, and the Middle East. The faculty of speakers includes local ASEAN and international anesthesia experts from the United States, Europe, Canada, Australia, and New Zealand, some of whom were supported by the WFSA, by industry, by respective anesthesia societies, and by the faculty themselves.

SAFETY AND MEDICOLEGAL INITIATIVES IN THE REGION

Chile/South America (Guillermo Lema)

Medicolegal issues and increased concern from patients have been behind the adoption of accreditation requirements. It is encouraging that most anesthesiologists are willing to obtain certification; clinics and hospitals are

also requiring certification for physicians to work in these institutions.

Furthermore, the medical community recognizes and has adopted certification of specialties, accreditation of both national and international public and private hospitals, the need for full and proper communication with patients and relatives, the creation of rules for different procedures, and the requirement for written consent. Disclosure of morbidity and mortality has also helped patients to be aware of the medical care to be received.

China (Yuguang Huang)

Anesthesia is undoubtedly a high-risk profession. The uneven development across the country in the economy and in clinical medicine in different areas has resulted in even larger differences in anesthesia safety. Therefore, well-established quality assurance systems and a culture that cultivates safety are keys to achieving higher safety coefficients. The National Anaesthesiology Quality Assurance Centre, which was established by the MOH in 2011, performed a series of measures for safety control, including designing standardized sheets for the intraoperative anesthesia record, encouraging surgical time out procedures, and constructing an incident report system. The National Anaesthesiology Quality Assurance and Assessment Standards were also established by the MOH in June 2012. Branches of the Quality Assurance Centre have also been established in each province throughout China, composing a nationwide network for quality and safety.

Europe (Lars I. Eriksson and Jannicke Mellin-Olsen)

Helsinki Declaration on Patient Safety in Anaesthesiology. Anesthesiologists are in a unique position to safeguard patients' best interests whenever they are at their most vulnerable, be it in the operating room, the critical care unit, in need of critical emergency care, or when suffering great pain. It is estimated that 200,000 patients in Europe die every year from complications due to surgical procedures. The EBA worked closely with the ESA and other bodies to develop the Helsinki Declaration on Patient Safety in Anaesthesiology (Declaration), which was launched in 2010.[55] The text emphasizes the roles of anesthesiologists, patients, clinical partners, funders of health care, and partners in drug and technical industries. It highlights the role of education, training, and human factors. The principal requirements to obtain the goals are listed, and anyone involved in health care was invited to sign. Representatives from the EBA, ESA, health politicians, patients' organizations, the WHO, WFSA, UEMS, and others participated in the launch. The declaration was immediately signed by most European anesthesiology societies. It has since been translated to several languages and is used actively to promote patient safety in a majority of European countries. EBA and ESA have installed a Patient Safety Task Force that is working on the follow-up and the implementation of the declaration.

An unexpected consequence of the declaration was the attention it has received across the world. It has been signed by the countries in CASA and the by those in Latin America. The South Asian Societies signed a similar Bangalore Declaration in 2011, and the Australian, New Zealand, and Canadian Societies also support the intention of the declaration. This support implies movement toward a global effort to improve patient safety.

Another program that is linked to patient safety is the Lifebox project, initiated by the WFSA, the Association of Anaesthetists of Great Britain and Ireland, and the Harvard School of Public Health to provide pulse oximeters to every operating room in the world, including education, training, and peer support. The goal is to close the pulse oximetry gap. The ESA and other European anesthesiology bodies endorse the program.

India (Deepak K. Tempe)

Medicolegal Aspects of Anesthesia Practice in India. As in most other countries, it is unlawful to practice medicine in India without proper registration with the State Medical Council or Medical Council of India.[56] The medical profession is regarded as noble in India, and at one time doctors were considered as having an integrity beyond doubt (next to God). This situation existed before 1980 when patients and the public accepted without question the outcome of their illness. However, this perspective has gradually changed as a result of the increased awareness brought about by consumer and social organizations and the media.[57] The gross commercialization of the medical profession coupled with the abject failure to self-regulate has also been responsible.

The Consumer Protection Act (CPA) of 1986 addresses the consumer grievances arising from the service providers. Section 2(1)(0) of the CPA defines the word *service,* and Section 2(1)(d) defines *consumer* (i.e., persons availing such services). Initially, it was controversial whether the medical practitioner could be regarded as rendering a service.[58,59] However in 1995, the Supreme Court judgment in the Indian Medical Association (IMA) *v* V. Shantha case clarified that service rendered to a patient by a medical practitioner (except where the doctor renders service free of charge to every patient or under a contract of personal service), by way of consultation, diagnosis and treatment, both medicinal and surgical, would fall within the ambit of "service" as defined in section 2(1)(0) of the act. Furthermore, any hospital, whether government or private, that collects charges from all or some of its patients is covered by the CPA. In these hospitals, even patients treated free of charge are entitled to go to the consumer courts for compensation for deficiency of service.[60] Likewise, anesthesiologists, even if not hired by the patient directly (i.e., hired by surgeon, private clinic, or hospital), are liable to pay compensation under CPA.[61]

Consequently, most of the cases relating to medical negligence go to the consumer courts, because these courts are inexpensive and provide a speedy disposal of cases. Depending on the value of services and compensation claimed, complaints can be filed with the district, state, or national commission.

The CPA created significant discomfort within the medical fraternity in India with initial protests from medical professionals and the IMA, as well as several heated and emotional debates among the senior doctors. Eventually, they came to the realization that the act covers the medical profession and is here to stay.[57]

As in many other countries, insurance companies in India consider anesthesiology a high-risk specialty. In addition, the public is still relatively unfamiliar and unaware about anesthetic risks. As a result, anesthetic complications are not as readily acceptable as surgical complications are. Many times the complaint is lodged against the treating doctor (generally the surgeon) or the hospital, and the anesthesiologist is subsequently made the party. Indian society is more aware of patient's rights as seen from the recent spurt in litigations concerning medical professionals or establishment liability, claiming redress for the suffering caused by medical negligence, vitiated consent, or breach of confidentiality arising out of doctor-patient relationships.[62] Slowly, people are also realizing that it is not easy to obtain compensation through the court unless there is strong evidence of negligence.[63]

Establishing medical negligence and successful litigation requires that four criteria be satisfied. First, the claimant must be owed a duty of care. Second, a breach of that duty of care by failure to provide reasonable standard of care should be established. Third, the claimant should have suffered damages resulting from the actions of the anesthesiologist. Fourth, a reasonably close causal relationship must exist between the anesthesiologist's actions and the resultant injury.[64] These criteria are similar to the ones followed in the Western world.[65] Therefore, it can be considered that following the Bolam principle can be the defense for the anesthesiologist. According to the Bolam principle, the doctor is not liable for his diagnosis, treatment, or refusal to give information to the patient, if he follows a responsible body of medical opinion.[66] This principle poses a significant problem in India, because the guidelines in most of the anesthetic areas are nonexistent. Barring the minimal monitoring standards, the health authorities or the ISA have no recommendations or practice guidelines for dealing with different clinical problems. In this respect, the ICA is expected to play a big role. It has the responsibility of formulating guidelines for the various anesthetic practice issues. However, this task is challenging and daunting because of the broad variations in the facilities and services that exist in this country.

Currently, most anesthesiologists in the country tend to follow the British or American guidelines. Unfortunately, these guidelines may not be applicable in a large number of clinical circumstances in India, and following them as a benchmark of standard of care is not without problems. First, it is important to ensure that clinicians are not following outdated ideas or principles. Second, acceptable clinical practice continues to evolve rapidly, necessitating frequent updates. Furthermore, the professional standards given in the guidelines might be insufficiently comprehensive or too vague, allowing for subjective interpretation of management strategies in a given clinical scenario. Because of the absence of guidelines as well as the equivocation of the guidelines (even if they were present), the processing of a negligence claim is predominantly opinion-based in India. Opinion on negligence claims is generally sought from the regional medical councils, which have a panel of experts to investigate a particular case. This is not to say that the ICA should not strive to prepare the guidelines; on the contrary, the need for guidelines is clear, at least in cases of common clinical scenarios, such as cesarean section, laparoscopic surgery, or cardiac patient undergoing noncardiac surgery.

The state medical councils have taken a lead in such matters. They have the responsibility of ensuring that no unqualified person practices modern medicine and of providing the expert opinion in complaints of negligence against doctors. For example, the 1997 Delhi Medical Council (DMC) act empowers this body to initiate disciplinary action or award compensation and to take action against frivolous complaints.[67] Currently, it has become a custom for the police and the criminal courts to send all complaints to the DMC for an expert opinion in the matter. The consumer courts, on the other hand, may or may not send all the matters for expert opinion; however, barring obvious cases in which the principle of *res ipsa loquitur,* meaning "the thing itself speaks," applies (e.g., artery forceps left in the abdomen during an operation), the expert opinion is generally sought. The matter may be referred to DMC or any other medical college for this purpose. In addition, the DMC receives complaints directly.

The DMC has an executive committee (consisting of executive members of the DMC and one or two experts in the field) that acts as a screening committee, and in case it finds any prima facie evidence, the matter is referred to the disciplinary committee. The disciplinary committee includes a member of the legislative assembly (nominated by the speaker), a legal expert, an eminent public person nominated by the government, an eminent medical specialist in the relevant specialty to which the complaint pertains, and a member nominated by the Delhi Medical Association with a minimum 10 years' standing.[67] The disciplinary committee is empowered to pass an order that can initiate disciplinary action. However, all decisions of the executive committee and the disciplinary committee need approval from the council, which consists of 20 council members. Table 2-4 shows the number of cases against doctors and anesthesiologists during the last 5 years in the state of Delhi.[68] It was observed that most of the complaints were related to relatively trivial matters against the hospital, such as overcharging, performing unnecessary investigations, practitioners practicing without valid registration, a laboratory submitting a wrong report, issuing of false medical certificates, and negligence in medical care leading to nonfatal harm to patients. A few cases were brought directly against

TABLE 2-4 NUMBER OF LITIGATIONS AGAINST HOSPITALS AND DOCTORS IN DELHI, 2007-2011

Year	Total complaints	Against anesthesiologists	Against hospital or treating doctor where anesthesiologist was made party subsequently
2007	105	0	7
2008	79	1	7
2009	98	0	8
2010	199	1	6
2011	107	0	10

anesthesiologists, but usually, anesthesiologists are made a party to a complaint against the hospital or the treating doctor (generally surgeons).

One unusual situation in which the anesthesiologist may be held liable is the use of local anesthetics by the surgeon for some minor surgical procedure, such as debridement or suturing. Often local anesthetics are used by surgeons and other practitioners for this purpose in the absence of an anesthesiologist. At times, a reaction to the local anesthetic can lead to serious consequences and because the anesthetist is often called for resuscitation and further management, he or she is also made a party if a complaint is filed by the patient's relatives. Thus, the anesthesiologist can be named in a legal suit even if he or she did not administer the local anesthetic. Likewise, use of ketamine and sometimes propofol is practiced by some practitioners in the absence of an anesthesiologist. Although such a practice is endorsed by some,[69] it is believed that the presence of an anesthetist is mandatory.[70] This may be hard to implement in India because of a shortage of anesthetists. This is just one of the many challenging issues the ICA has to address and resolve.

In India, it is accepted that there can be more than one way of dealing with a problem, and an anesthesiologist has the discretion of choosing the treatment, with broader discretion in emergency cases. The National Commission and the Supreme Court have held that the doctor should have a reasonable degree of skill and knowledge and exercise a reasonable degree of care. However, the doctor is not liable for negligence simply because someone else of better skill or knowledge would have prescribed a different treatment.[71] Thus, mere allegation of negligence is not enough; it is for the complainant to prove the negligence or deficiency in service by adducing expert evidence or opinion, and this fact is to be proved beyond all reasonable doubt.[72,73]

Frivolous complaints against doctors have increased in India, especially after the CPA was enacted. The courts recognize this.[74,75] The court has no sympathy for doctors who are negligent, but to avoid unnecessary harassment of doctors, the court has directed that whenever a complaint is received against a doctor or hospital by the consumer forum (district, state, or national) or by the criminal court, before issuing notice to the doctor or hospital against whom the complaint was made, the consumer forum or criminal court should first refer the matter to a competent doctor or committee of doctors specialized in the field to which the medical negligence is attributed. Only after that doctor or the committee reports that there is a prima facie case of medical negligence should a notice be issued to the concerned doctor or hospital, or both. The court has further directed that police cannot routinely arrest a doctor simply because a charge has been brought against him or her. Instead, the investigating officer should, before proceeding against the accused doctor, obtain an independent and competent medical opinion. Such an approach by the judiciary has come as a significant relief for doctors.

The effect of the CPA is evident on anesthesia practice in India. It is imperative that anesthesiologists have informed consent, be vigilant, keep up to date on the guidelines and their knowledge in the discipline, and maintain proper record keeping. Accurate and adequate record keeping can be their defense in cases of litigation. Under Indian law, a case can be filed with the consumer courts up to 2 years after the occurrence of an incident. Thus, there may be a considerable time lapse between the occurrence of an incident and the hearing of a court case. Therefore, the anesthetic record should be as accurate, complete, and neat as possible. In addition, developing good patient relationships is considered another important factor to avoid litigation.

It is imperative that ISA and ICA issue guidelines, recommendations, and protocols be followed in different clinical situations to help the judiciary apply the Bolam's principle to the facts collected in the investigation of a particular case.

Southeast Asia (Florian R. Nuevo)

As in the United States, medical malpractice lawsuits are increasing in the ASEAN region. The threat of malpractice has pressed the need for high standards of monitoring as a mandatory requirement, because some hospitals in low- to middle-income countries cannot afford to procure the necessary equipment and complete array of anesthetics and related medications.

The region's maldistribution of anesthesiologists, the poverty of some societies, the unavailability of essential drugs, and the lack of the necessary infrastructure or resources further aggravate the problem of patient safety.

Although remarkable improvements have occurred in anesthesia education and the development of life-saving skills, perioperative anesthesia-related morbidities still occur. There is growing awareness of the influence human factors and anesthesia nontechnical skills have on patient outcomes. All these factors should be subjects of discussion in anesthesia training programs and postgraduate medical education. Cultural sensitivities must also be underscored to find effective solutions to our problems.

Fortunately, the tides of change are continual, and almost all national anesthesia societies have adopted guidelines or standards for safe anesthesia practice. Credit must be given to Malaysia for its pioneering efforts establishing a national medical audit system. This model is currently used in Singapore and Thailand, as well. Thailand has developed its own national anesthesia incident reporting program and, through ASEAN anesthesia leadership, other ASEAN anesthesia societies are encouraged to duplicate this program.

The WHO Safe Surgery Saves Lives initiatives have helped to arouse interest in the promotion of patient safety. Anesthesia patient safety is now recognized as a public health concern because of the morbidities and mortalities related to surgery and anesthesia.

The Helsinki Declaration on Patient Safety in Anesthesiology further awakened the region with more practical guidelines. These have gained the full support of members of CASA. Many safety initiatives are now underway.

Thus, the current challenge is the earnest and sincere implementation and sustainability of all these safety initiatives. Steadfast leadership is necessary to sustain these patient safety programs. Collaboration among all

stakeholders is essential to bridge the existing gaps in patient safety.

CONCLUSION

As demonstrated in this chapter, anesthesiology as a discipline and a profession has grown dramatically around the world. Differences in the rate of growth and scope of practice exist for a variety of reasons, largely because of disparities in resources and socioeconomic and political factors. Nevertheless, regardless of country of residence, patients receiving anesthesia can feel much safer today than even 20 or 30 years ago in most countries (exception exist, as indicated in this chapter). Providing safe anesthesia requires knowledge, resources, and adequate numbers of trained anesthesia personnel. Over the previous decades, adequate resources for health care including anesthesia are increasingly available. However, some areas of the world still do not have adequate training or resources; Sub-Saharan Africa is an example. Fortunately, international organizations are attempting to address these deficiencies.

On the positive side, some of the most powerful advances are the spread of knowledge, professional integrity, curiosity, and the utmost desire to practice anesthesiology at the highest possible level. Especially with the widespread expansion of information technology anesthesiologists can quickly learn of the advances of their colleagues worldwide and better understand and respond to the needs of their patients.

So where do we go from here? Some authorities suggest taking advantage of the latest advances to further the interconnectedness of the profession, such as conducting more in-depth comparisons of the effectiveness of various techniques from country to country and engaging in more joint research. Others believe that such comparisons would serve no useful purpose, given the evident disparities in resources and different approaches to care. The editor has dreamed of the day that anesthesiologists worldwide would form global think tanks to ask and answer the most important questions to advance our intellectual foundations and benefit society. As noted in the opening paragraph, the purpose of this chapter is not to invite comparisons or highlight differences in the practice of anesthesiology around the world, but rather to encourage and invite anesthesiologists globally to keep talking to each other. The editor was thrilled and honored that his invitation to contribute to this chapter has resulted in so many interesting contributions from leaders of anesthesia worldwide. When viewed together, the journey of anesthesiology has been an amazing story worldwide.

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Chapter 3

Perioperative Management

NEAL H. COHEN

Key Points

- The practice of anesthesia has expanded beyond the traditional operating room environment to other sites throughout the hospital and ambulatory facilities. Concurrently, anesthesia has evolved to include acute and chronic pain management, critical care medicine, palliative care, and sleep medicine.
- The expanded scope of anesthesiology creates opportunities for anesthesiologists to take on a broader role in perioperative care, providing management of patients through the continuum of the perioperative period and transition to outpatient care.
- Unfortunately, the costs of hospital care and perioperative care continue to escalate. In response to the increasing costs and emphasis on quality and patient safety, payers are modifying payment methodologies to better align goals of care. Both government (e.g., Medicare) and private payers (e.g., insurance companies) are implementing bundled payment and other payment methods designed to transfer the risk associated with management of complications and preventable harm to providers (e.g., hospitals and physicians).
- To provide optimal perioperative care under these circumstances requires more collaborative interactions among providers and new models of care. Many delivery models have been implemented with varying outcomes. Clarifying roles and responsibilities of the surgeon, anesthesiologist, and other providers is critical to delivering high-quality cost-effective care. Although nonanesthesiologists, including hospitalists, can be very helpful in addressing some clinical needs for the surgical patients, anesthesiologists are well positioned to take a more prominent role in overall perioperative management, benefiting patients, optimizing quality and outcomes of care, and improving efficiency during and after surgical procedures.
- Accomplishing these goals requires reevaluation of overall perioperative management strategies, including preoperative evaluation, intraoperative care, and postoperative management. These goals also depend on accessibility to clinical and financial data and personnel with the skills to analyze the information for delivery of optimal care while improving efficiencies.
- Many models of perioperative management have been implemented with varying success. The perioperative surgical home (PSH) is an example of a new model that might have great benefit for selected patient populations, aligning patient's, provider's, hospital's, and payer's goals, and significantly improving perioperative care.

Fifty years ago, anesthesia care was dominated by intraoperative management, and most clinical income came from services related to surgical care. Gradually, the scope of anesthesia broadened beyond the intraoperative period to include preoperative evaluation, intraoperative management, and postoperative assessment to determine whether the patient suffered any consequences of anesthesia care. Although this model of care—and the associated payment methodology—was an appropriate model of anesthesia care in the past, today the changing needs of the patient, complexity of care, and the role of the various health care providers mandate that we define alternative models for perioperative management to optimize clinical outcomes.

This chapter reviews the changing and expanding focus of the anesthesia practice. Management of clinical care throughout the perioperative period includes preoperative assessment and management to optimize outcomes after procedures, intraoperative care, and postoperative strategies. Thus, the anesthesiologist has an expanded scope of practice and participates more broadly in all aspects of care, with the overall result of improving outcomes and reducing costs.

The impetus for expansion of the scope of anesthesia practice comes from multiple perspectives. First and foremost is the commitment to provide patients with high-quality and safe care that fulfills their goals. To do so requires a broader focus on the overall perioperative course rather than a scope of care that is limited to the intraoperative and immediate postoperative care periods.

A second and equally important goal toward which the anesthesiologist plays an integral role is the increasing emphasis on evidence-based practice, limiting unnecessary or redundant services, and providing more efficient care, particularly in the immediate perioperative period. There is no question that the high costs of inpatient services, particularly for patients with underlying comorbidities who undergo complex surgical procedures, contribute to escalating overall health care expenditures.[1] Although many of these services are important to ensure that the patient is adequately prepared for anesthesia and surgery, some aspects of care may be based on tradition rather than demonstrated benefit. At the same time, the evolution and expansion of anesthesia practice have created many new opportunities for anesthesiologists to participate in perioperative care beyond the immediate postoperative period—and to define standards of care for selected patient populations. Some anesthesiologists are integral members of teams of providers who care for selected surgical patient populations, and they collaborate with surgeons to develop clinical pathways and identify ways to improve preoperative care as well as intraoperative and postoperative management strategies that enhance outcomes. For example, transplant anesthesiologists (also see Chapter 74) are often involved in discussions about patient selection, preoperative management, and transitions of care from the operating room to postoperative period. As a result of these efforts, many transplant patients who previously required postoperative care in the intensive care unit (ICU) can now bypass the ICU and have reduced hospital lengths of stay.[2] Similar outcomes have been documented for patients who have anesthesiologists participate in their perioperative management for cardiac surgery (also see Chapter 67), pediatric surgery (also see Chapter 93), neurosurgery (also see Chapter 70), and other subspecialties. In each of these examples, collaboration among the surgeons, anesthesiologists, and the overall team of providers both within and beyond the operating room environment is critical to realizing improved outcomes and reduced costs of care.

The role of the anesthesiologist in perioperative management also includes the subspecialties of pain medicine and critical care. Pain management strategies have significant positive impact on the care of patients with both acute and chronic pain (also see Chapters 64, 96, and 98). More rational approaches to perioperative pain management, particularly for patients with longstanding chronic pain, have had positive impact on perioperative outcomes and, in many cases, reduced lengths of stay in hospitals and improved patient satisfaction.[3-5] Similarly, critical care anesthesiologists play a large role in improving perioperative management of patients requiring ICU care. The critical care physician's value in improving ICU utilization, reducing complications of mechanical ventilation, providing early diagnosis and treatment of sepsis, and improving management strategies for patients with renal dysfunction is well documented[6-9] (see Chapters 96, 101-103, and 105). Although not frequently addressed by anesthesiologists, postdischarge care needs are often related to perioperative management; anesthesiologists can have a meaningful role in addressing some of these significant costs of care and the related issues that lead to dissatisfied patients and providers.

A third area of concern that has taken on greater importance over the past decade is the rising cost of health care in general and perioperative care in particular. Advances in technology for both anesthesiologists and surgeons have made it possible for patients who previously were denied surgery because of underlying chronic medical conditions, anesthesia risk, or limited surgical options to undergo often complex and costly procedures that may require prolonged postoperative and rehabilitative care. In addition to surgery costs, additional costs (often significant) are associated with complications of care, postdischarge care, and readmissions.[10] The acknowledgment of these frequently underestimated costs is having a major impact on models of perioperative care delivery and payment methodologies. For example, in the United States, both government and private payers have raised concerns about the costs associated with managing complications of care, some of which are relevant to anesthetic management. These payers have been reducing payment for costs associated with complications and denying payment for costs associated with readmissions.[11,12] Anesthetic management has implications for the occurrence of some of these complications, as well as for the need for prolonged ICU stays and other clinical outcomes. For example, central line infections, ventilator-associated pneumonia, decubitus ulcers, and renal failure may be either directly or indirectly related to perioperative (anesthetic) management. Implementing strategies to reduce these complications has been very successful; a more coordinated approach to perioperative management by the anesthesiologists can have significant positive impact on both clinical care and costs.

Another change that is having considerable impact on surgeon, anesthesiologist, and other provider relationships is the transition from fee-for-service (FFS) payment for clinical care to alternative bundled payment methodologies, such as providing a single payment for hospital care, physician services, and in some cases rehabilitation that is related to an episode of care or specific surgical procedure.[10] In the United States, FFS is still the most common payment methodology. Under this payment methodology, each provider receives compensation for the specific services provided to the patient. Payment is encounter based and does not encourage collaboration or coordination of care. Although the implications of FFS

payment on quality of care and resource utilization are widely debated, it is a methodology that has been demonstrated to result in overuse of some services and poor coordination of care.[13] In response to the perceived and documented problems with FFS payment, a number of alternative payment methodologies have been implemented with variable outcomes. Many of these payment methodologies have significant impact on anesthesiologists and the roles they play in perioperative management. For example, to the extent that anesthesiologists can help reduce costs during the course of care for a surgical patient, they can benefit financially under bundled payment methodologies, shared savings plans, and accountable care organizations (ACOs). Although issues related to payment methodologies differ greatly from one country to another and are beyond the scope of this chapter, the goals and implications of these newer payment methodologies have major effects on the practice of anesthesia. Also, these various models provide potential opportunities for expanding the role of the anesthesiologist or other providers in perioperative management.

Finally, although the expanded roles of anesthesiologists in perioperative management have had a positive impact and, in some cases, resulted in more cost-effective and efficient care, the subspecialization of anesthesia care has, in some ways, fragmented care and detracted from a coordinated approach to perioperative management. Under current models of care delivery, perioperative care is rarely provided by a single anesthesia provider. More often, the care is provided by multiple providers, each with a specific role and responsibility. Preoperative care is now often provided in a dedicated preoperative evaluation clinic, which is physically separate from the operating room or other clinical sites. The evaluation is performed at some time before the surgical procedure; communication about the patient's status and clinical plans is most often done electronically with no face-to-face communication with the anesthesiologist who will deliver care during the procedure. Operating room care is provided by an anesthesiologist either individually or as part of the anesthesia care team model. Postoperative management—including care in the postanesthesia care unit (PACU), pain management, and ICU care—is often provided by another set of caregivers. Although each of these providers is critical to the overall care of the patient, the coordination of care among the anesthesiologists as a group becomes a critical element in optimizing care, understanding and fulfilling the patient's goals for care, and improving efficiencies. New models of care that more effectively integrate the diverse roles of anesthesiologists are required to effectively fulfill the goals outlined here.

PERIOPERATIVE MANAGEMENT

Throughout this text, the role of the anesthesiologist in various aspects of perioperative management is discussed. For example, Chapter 38 emphasizes the changing role of the anesthesiologist in preoperative assessment and management. Formal preoperative assessment of an otherwise healthy patient may not be needed in all cases[14,15]; however, advances in surgery and anesthesia have made it possible to identify patients who require more comprehensive evaluation that includes extensive testing and management of underlying conditions in order to prepare them for surgery and the postoperative course.[16] Some patients require assessment and management by other specialists, such as cardiologists, nephrologists, or pulmonary medicine physicians. However, in many cases, the management strategies required to optimize the patient before surgery are best determined by the anesthesiologist, who is most knowledgeable about the impact of chronic conditions on perioperative care needs and the implications of anesthesia on underlying physiology. The anesthesiologist is the provider who can most appropriately coordinate the preoperative assessment and management of the patient to confirm that the evaluation and interventions are necessary to optimize the patient for surgery and anesthesia and to minimize unnecessary assessment and care that will not affect the perioperative course. Similarly, the anesthesiologist, whether individually or as part of the care team model, provides intraoperative care (although in some cases nurse anesthetists have obtained independent practice). In situations in which the anesthesiologist is personally providing or medically directing care, the anesthesiologist can and should ensure a coordinated approach to the transitions from preoperative to intraoperative care, as well as the collaboration required for optimal postoperative management. As important, the anesthesiologist—in conjunction with the surgeon, operating room nurses, and other staff—must communicate effectively to ensure that the correct procedure is being performed on the correct patient, to ensure that all supplies and equipment are available, to facilitate the timely turnover of operating rooms, and to optimize coordination of care from the preoperative to the postoperative period.

A number of initiatives have been implemented in hospitals throughout the world to improve intraoperative management, minimize complications, and reduce costs. The implementation of checklists has been demonstrated to improve patient safety in the operating room[17-19] (also see Chapters 4 and 6). Similarly, the routine briefing (i.e., time out) before beginning a surgical procedure reduces the incidence of wrong-site surgery, facilitates communication among providers, and permits optimal patient care.[20] Some hospitals and surgical services also conduct debriefings at the end of each surgical procedure to define what procedure has been completed, clarify the postoperative expectations for the patient, and ensure that all supplies and materials have been appropriately retrieved from the surgical field.[21] These initiatives have not only been very successful in reducing complications during surgery but, in some cases, reduced costs of care and waste in the operating room. For example, the British National Health Service instituted The Productive Operating Theatre (TPOT) to improve productivity and patient outcomes during surgical procedures.[22,23] The program includes both briefings and debriefings to identify critical issues during and after a surgical procedure. This process has reduced errors and facilitated the transition from the operating room after a surgical procedure. Efficient operating room utilization has increased, turnaround times have shortened, and waste has been reduced. Significant

financial savings have also resulted from this effort. The National Health Service is implementing similar initiatives in other hospital settings, such as "The Productive Ward" to build on the success achieved in the operating room environment.[24] Similar initiatives are required to ensure an integrated approach to management during the entire continuum of perioperative care in order to demonstrate a significant and sustained impact on outcomes.

Traditionally, anesthesiologists have focused on the intraoperative care setting to improve patient care. The transition out of the operating room represents another important opportunity for anesthesiologists to build on the quality and safety advances achieved in the operating room and to improve perioperative patient outcomes. Advances in anesthesia safety have been acknowledged by the Institute of Medicine of the National Academy of Sciences and other groups[25] as a result of better anesthetic drugs, new anesthetic techniques, and improved monitoring techniques (also see Chapter 44), such as pulse oximetry, capnography, and echocardiography. However, the implications of anesthetic management on postoperative outcomes—beyond the immediate postoperative period—have received increasing attention and importance for both patients who remain hospitalized and those who experience unintended and often unrecognized sequelae of anesthesia and surgery after discharge. For example, after a surgical procedure requiring tracheal intubation, a significant number of patients experience postextubation stridor or dysphagia that may last for days, thus compromising the ability to protect the airway, particularly during sleep.[26] Does the dysphagia contribute to postoperative pneumonia that may not become clinically apparent until after discharge? Similarly, the most common health care–associated infections are pneumonia and surgical site infection, which confirms that intraoperative management is an important determinant of postoperative outcome.[27] Many other intraoperative strategies also affect long-term outcomes beyond the immediate postoperative period. Three examples support this conclusion. First is the influence of intraoperative fluid and vasopressor management on postoperative metabolic status and renal function.[28,29] Second, intraoperative glucose control can have a major impact on wound healing.[30] Finally, and more recently, anesthetic management can influence postoperative cognitive dysfunction for both adults and children.[31-33] As a result of these findings, anesthesiologists have a responsibility and an opportunity to understand the causes for these and other complications. We need to understand how anesthetic management can be used more effectively to reduce these adverse outcomes and, if necessary, to manage them effectively in the postoperative period.

PERIOPERATIVE MANAGEMENT STRATEGIES

With this background, perioperative management strategies must be defined more broadly than in the past. Many patients require a limited preoperative assessment or postoperative follow-up, and some require significantly more perioperative support, particularly preoperative management and postoperative care. In addition, many surgical procedures and perioperative management strategies are neither efficient nor cost-effective—for patients or providers. Anesthesiologists, with their particular background, understanding of the environment, and clinical expertise, are equipped to address these issues and to ensure optimal perioperative care. To achieve these goals, anesthesiologists will need to reevaluate current models of care. In most clinical situations, it is no longer possible, or appropriate, for a single anesthesia provider to participate in all aspects of the perioperative course. Care—perioperative, intraoperative, and postoperative—is often provided by different anesthesiologists, in some cases including those who administer pain medicine and critical care needs. Optimizing perioperative management under this model requires improved communication and collaboration among the anesthesia providers, as well as others who participate in a patient's care. The electronic health record is a valuable source of clinical information, but it cannot substitute for more direct communication among providers, particularly in the management of complex clinical problems (also see Chapters 4 and 6).

This collaborative approach to care may not seem necessary for healthy patients undergoing straightforward procedures. However, the value and opportunities for anesthesiologists to play a larger role in perioperative care is clearly evident for most patients. For example, patients undergoing "simple" procedures often have postoperative clinical issues that are underrecognized and require assessment and management. Anesthesiologists, surgeons, and nurses provide patients with instructions and information to help them manage their postoperative course, often at a time when they are not able to understand or process the information. As a result, even in these simple cases, the anesthesiologist can be instrumental in addressing postoperative problems and coordinating the transition of the patient's care back to the primary care provider. The surgeon can provide information about the surgical procedure by forwarding the operative note to the primary care provider, but it rarely addresses any issues related to anesthetic management, concerns about the airway or potential for airway obstruction, or response to anesthetic drugs, narcotics, and muscle relaxants. A postoperative evaluation after discharge can be very helpful in determining whether complications of anesthetic care occurred and in addressing any questions or concerns the patient or family might have about postoperative needs. In many cases, a phone consultation or teleconference is sufficient to address clinical needs. In other cases, a formal postoperative office visit may be required. Some anesthesia departments provide these postoperative options to patients, most often using the preoperative evaluation site. Expansion of the postoperative assessment and management can be very helpful to patients, surgeons, and primary care physicians in providing a level of support to the patients that is often unavailable. The adoption of information technology resources and continued evolution of medical informatics (also see Chapter 5) can enhance communication between patients and physicians during the entire perioperative period.

Besides the desire for a more coordinated approach to the entire perioperative course for every patient, a more formal and robust perioperative management strategy

must be available for those patients with underlying medical conditions, those undergoing complex surgical procedures, and those needing prolonged hospitalization. In addition, for patients who require skilled nursing or rehabilitation services after discharge and for those needing home health services, the transitions of care create challenges for ensuring that postoperative management strategies are maintained, responses are assessed, and therapy is modified as needed. By its very nature, perioperative care for these patients is collaborative, requiring input and expertise from a number of different disciplines, including, but not limited to, anesthesia subspecialty expertise, surgeons, and medical subspecialists. Diverse perspectives and clinical expertise are essential, particularly for the more complex procedures in patients with multiple comorbidities. At the same time, the coordination of care must be assumed by a provider who is able to integrate the diverse perspectives into a comprehensive plan of care consistent with each patient's needs and goals. In the distant past, this coordination was provided by the patient's primary care provider, who maintained a role throughout the perioperative period. With the increasing complexity of perioperative care, changing demographics, and the need to provide more efficient and coordinated care to reduce overall costs, the anesthesiologist has the opportunity to assume a more involved role in the management of some of these patients. To do so will require the commitment of the anesthesia practice to this new model of care and, in many cases, the acquisition of new clinical and management skills to deliver optimized care that it is efficient and consistent with patient expectations.

Often, the most challenging barriers for a department that seeks more involvement in perioperative care come from its own members. It is imperative that there be consensus among all members of the discipline that this strategy is important and consistent with their expectations. To achieve department support, it is critical to clarify that perioperative management is a comprehensive approach to care that involves a diverse group of providers. Every member of the group must participate in the overall commitment to perioperative care. The care will be provided by a number of different anesthesiologists, each with different clinical expertise. One example of this coordinated approach to perioperative care is the management of a patient with a history of chronic severe pain who undergoes a complex surgical procedure. The patient will undergo extensive evaluation and optimization of care in the preoperative evaluation programs. Intraoperative care will be provided by another anesthesiologist, one who has communicated with the patient and understands all of the clinical issues identified and addressed preoperatively. When the patient is transferred to the ICU for postoperative care, which includes ventilator support, intensive respiratory care, hemodynamic monitoring, and fluid management, the transition from the anesthesiologist who provided intraoperative care to the critical care anesthesiologist is seamless. Pain management is provided by the pain service in collaboration with the critical care anesthesiologist (also see Chapters 64 and 98). The remainder of the patient's course of care will be managed by a member of the anesthesia department to facilitate transition to another care facility or home and to ensure effective communication with the primary care provider or other caregivers. Although this model is foreign to many practices, it represents one of many approaches to optimizing perioperative management and takes advantage of the expertise of anesthesiologists in the overall care of the patients they anesthetize.

Although clinical expertise is essential to provide optimal perioperative care for the individual patient, new approaches to perioperative management require that each practice have the necessary clinical and financial data, as well as the analytical capability to interpret it. Larger regional and national organizations tend to have the broad expertise available to analyze the practice and determine where improvements in processes can benefit patients and enhance the efficiency of the practice. For smaller practices, it can be a challenge to have this broad level of expertise and access to information. As a consequence, in the United States considerable consolidation of anesthesia practices has been adopted, with large regional and national organizations acquiring anesthesia practices.[34] In doing so, the larger group is able to ensure that the practice has the resources needed to optimize perioperative management and document the value of the anesthesia services from both a clinical and financial perspective. Some groups have recruited hospitalists or other providers that supplement the clinical skills of the anesthesiologists to ensure that the department has the diverse clinical expertise needed to optimize perioperative care. This multidisciplinary approach to perioperative care enables the group to expand its scope of practice and to develop clinical and administrative databases that allow them to document the value of their services to both patients and the institution. From an administrative perspective, this strategy allows the practice to negotiate from a position of strength with representatives from the hospital or health system, particularly when advocating for the share of bundled payments. Because the administrative and analytical capabilities are essential to optimize delivery of perioperative care, each practice will need to identify the most effective ways to develop this needed expertise and acquire the data needed to successfully address the many challenges facing anesthesia practices.

MODELS OF PERIOPERATIVE CARE

Most health systems and providers are challenged to identify ways to become more efficient and reduce costs while maintaining or improving the quality of care. Accomplishing these diverse goals is difficult. No single model of care works for every patient population or health care setting. As a result, many approaches to delivery of perioperative care have been implemented, some of these successful and some for which the outcome remains unknown. Although models of perioperative management include the anesthesiologist, other providers have participated in the preoperative and postoperative management of complex patient populations, each with variable success. Based on these experiences, the key aspects for any model for perioperative management include (1) an understanding of the specific patient population included in the model (e.g., specific surgical procedure), (2) sufficient clinical and financial information

to allow evaluation of the management strategies, and (3) coordination and collaboration among all providers participating in the model.[35] As models for perioperative management have evolved, they have taken advantage of the experiences from the hospitalist model for inpatient care and the medical home model for chronic disease management.

Patient-Centered Medical Home

The medical home model, also referred to as the patient-centered medical home (PCMH), is a model of care in which a primary care physician provides comprehensive care to improve health outcomes for a population of patients.[36] The critical element of the PCMH is the coordination of care to reduce emergency department visits and hospitalizations. In managing the patient population, a number of strategies have been used to reduce costs and improve outcomes. These models often utilize additional providers, including advance practice nurses, respiratory therapists, physical therapists, and patient advocates, to manage chronic diseases such as asthma, chronic obstructive pulmonary disease (COPD), heart failure, and diabetes mellitus. Payment for the PCMH includes FFS payments for episodes of care and payment to coordinate care. This model has been successful in improving care, particularly for some chronic diseases, although the financial success has not been as consistent.[36-38] In some cases, the PCMH actually resulted in increased hospital admissions.[36] Despite the variable success of the PCMH, some lessons can be learned in defining how to manage the perioperative period most effectively. First, preoperative assessment must be comprehensive enough to identify underlying clinical problems and effectively manage them, both preoperatively and postoperatively (also see Chapter 38). For the anesthesiologist managing the perioperative period, chronic conditions must be addressed; they cannot be deferred to other providers. Second, the underlying medical conditions must be addressed as part of the overall postoperative management in coordination with the issues specific to anesthesia and surgery. For example, a patient with peripheral neuropathy associated with diabetes mellitus may be unable to participate in traditional approaches to rehabilitation; care must be tailored to the specific needs of each patient. Third, many aspects of perioperative care can be managed by other providers, including other physicians and advance practice nurses. The keys to successful perioperative management, however, are the identification of a single physician to coordinate care among the team of providers, consistent and ongoing communication about patient care needs, and availability of data that can be used to analyze clinical and business practices, costs of care, and outcome measures.

Surgical Hospitalist

Another model that has been implemented in many hospitals in the United States and other parts of the world is the surgical hospitalist model, which builds on the hospitalist model of care for inpatient medical patients. Many studies have documented the clinical value and other advantages associated with implementation of a robust hospitalist program[39,40]; yet most hospitalist programs emphasize the care of patients with acute (and perhaps underlying chronic) medical problems. However, the increasing percentage of surgical patients in many hospitals, the changing role of surgeons in overall clinical management, and the complexity of inpatient care have brought attention to expanding hospitalist programs to support the care of surgical patients.[41,42] Many institutions have recruited surgical hospitalists to work collaboratively with specific surgical services (or individual surgeons) to manage overall care and transitions of care into and out of the hospital environment. The models for surgical hospitalist programs vary—in some cases incorporating hospitalists with primary training in internal medicine or pediatrics, in other cases having a surgeon with interest in perioperative care take on the hospitalist role. In each model, the clinical management issues are similar.

Many of these surgical hospitalist models have been successful, particularly in improving the management of underlying chronic diseases. Although the ability to document the effect on hospital lengths of stay and readmission rates has been limited, the models have been effective at improving timeliness of interventions and patient and staff satisfaction.[41] At the same time, medical care can be fragmented, with the hospitalist effectively managing the underlying chronic diseases (such as diabetes mellitus or hypertension) without having a significant role in the management of other aspects of perioperative care. For this model to be most effective, the surgical hospitalist must be educated in the idiosyncrasies of perioperative management of patients undergoing complex surgical procedures. The effectiveness of surgical hospitalist models is most evident when the care of underlying medical conditions is carefully coordinated with the other perioperative needs of the patient. For example, the neurosurgical hospitalist must understand concepts such as cerebral autoregulation and the impact of clinical interventions on cerebral hemodynamics. Similar considerations must be addressed for hospitalists working collaboratively with other surgical services.

The surgical hospitalist model has expanded considerably, allowing surgeons to concentrate their efforts in the operating room. However, the optimal relationship between the surgical hospitalist (either a surgeon who has assumed this nonoperative responsibility or a medical hospitalist) and anesthesiologist has not been defined. In some cases, perioperative care is transferred from the anesthesiologist to the hospitalist in the immediate postoperative period; in other cases, care may be transferred from the anesthesiologist to an intensivist (either a critical care anesthesiologist or another intensive care physician) while the hospitalist maintains responsibility for managing some of the underlying clinical conditions. In the latter case, the roles and responsibilities of the anesthesiologist, critical care provider, and hospitalist need to be clearly defined to ensure appropriate coordination and transitions. Either model can be effective when coordination of responsibilities is clearly delineated. Equally important, the transition from inpatient to outpatient care must be coordinated among the inpatient providers to ensure that the outpatient physician understands the intraoperative course and its implications, including any

issues that arise as part of the anesthetic management, and can facilitate management in the ambulatory setting.

Enhanced Recovery After Surgery

Enhanced recovery after surgery (ERAS) is another example of a creative approach to the perioperative management of patients who undergo major surgical procedures.[43,44] ERAS is designed to enhance recovery by managing the entire course of care by using evidence-based practices to optimize outcomes. ERAS emphasizes a multidisciplinary approach to perioperative care with particular emphasis on preoperative education, pain management, and early rehabilitation, particularly for patients who undergo laparoscopic surgery and colorectal procedures. This approach has been successful, with documented reductions in hospital length of stay and postoperative complications of 30% and 50%, respectively.[45-47]

The key features of the ERAS program, as with other pathways designed to improve perioperative care, are its multidisciplinary nature and the emphasis on collaboration of care and seamless coordination among the preoperative, intraoperative, and postoperative periods. The ERAS protocols emphasize the value of the anesthesiologist in providing optimal perioperative care, which facilitates early ambulation, returns bowel function to normal, and initiates nutritional support. Although the program has concentrated on optimizing care during and after elective and minimally invasive gastrointestinal surgical procedures, the same approaches should also be successful for other types of surgical procedures.

Perioperative Surgical Home

Although ERAS has identified strategies to provide an optimal continuum of care for patients undergoing minimally invasive procedures, most of the models of care described earlier in this chapter address individual components of care for the surgical patient. Some address improved preoperative screening and evaluation, others minimize complications and costs within the operating room environment, and a number of initiatives improve postoperative care. Many of these models have a positive impact on care, quality, and costs; however, in many cases, the overall costs of care have not been affected. More important, the coordination and transitions of care from the immediate perioperative period have generally not been optimal.

The expanding role of anesthesiologists, both within and outside the operating room, presents an opportunity for them to serve as perioperative physicians.[48-50] The increasing complexity of patient care related to surgical services has also created a demand for improved coordination of care from preoperative management through outpatient follow-up. Recently, the American Society of Anesthesiologists (ASA) proposed development of the perioperative surgical home (PSH), built in part on the PCMH model of care.[51-53] The PSH emphasizes clinical management of the patient through the perioperative period, with coordination of care specifically designed to optimize outcomes after surgery and facilitate the transition of the patient back to the primary care provider. Within the PSH, care is coordinated by the anesthesiologist, who works collaboratively with a team of providers to identify evidence-based clinical pathways, improve outcomes, and reduce overall costs of care across the continuum, including postoperative costs such as home care and skilled nursing facilities. As is true for the PCMH, the PSH is designed to be patient focused. This approach requires a reassessment of the entire perioperative experience to ensure that the patient's needs are an integral part of each element of the perioperative course. Although the PSH concept is currently being implemented for selected patient populations and the outcomes are still being defined, other initiatives that address some of the components of the PSH suggest that this more integrated approach to care (at least for some patient populations) should improve outcomes and patient (and provider) satisfaction while reducing costs.[53,54]

As envisioned by the ASA, the PSH has five major goals:

1. Identifying the patient and proposed plans and facilitating communication among the surgeons, anesthesiologists, and others as needed to coordinate care
2. Providing optimal preoperative assessment and plans, including management of underlying chronic diseases
3. Developing and implementing evidence-based protocols for clinical care throughout the perioperative period
4. Managing clinical care across the continuum
5. Measuring and publicly reporting outcomes and performance

The implementation of the PSH model could be a very effective way to optimize perioperative care for selected patient populations. The model may also define some generic strategies that can be implemented for all patients undergoing surgical procedures and new approaches to clinical care and assessment that will benefit patients, providers, and payers.

CONCLUSION

The changing demographics of hospitalized patients have created significant challenges for hospitals, health systems, and providers. For many hospitals, the percentage of surgical patients continues to grow. Many surgical procedures are performed on patients with underlying comorbidities that not only complicate surgical management and anesthesia care but also require coordinated care of primary care providers, surgeons, anesthesiologists, and other medical specialists. This chapter has defined some of the challenges of coordinating and optimizing perioperative management. Although no single strategy is appropriate for all clinical settings and patient needs, the one critical element in perioperative care is the need to implement a model of care that ensures coordination and transition across the continuum from preoperative assessment and management to postoperative rehabilitation. A number of alternative approaches can be used, and multiple strategies may be required to address the idiosyncrasies of each patient population, surgical procedure, and institutional capabilities. The expanded role for the anesthesiologist in many of these models requires the

commitment and skills to acquire and analyze data on outcomes and costs, while also defining ways to optimize clinical care. The PSH is an example of a new creative model that might have significant benefit for selected patient populations, thus aligning patient's, provider's, hospital's and payer's goals and significantly improving perioperative care by building on the experience and successes of other approaches, including ERAS, the surgical hospitalist model, and the PCMH.

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Chapter 4

Operating Room Management

JAMES D. KINDSCHER

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Key Points

- Organizing the governance structure of the operating rooms (ORs) to consolidate control and authority into one position, such as the OR medical director, has many advantages in making the OR function at an optimal level.
- Improvement in the OR scheduling process may lead to the biggest gains in OR efficiency. Block time scheduling allows better predictability and satisfaction for OR personnel.
- On-time OR starts, surgical case performance benchmarks, and room turnover are all critical elements in making an OR run efficiently.
- Traditional OR use assessments may not reflect how well an OR is working. Newer methods that focus on OR productivity are increasingly being used to determine allocation of OR resources.
- Managing the daily surgical schedule requires careful planning, as well as frequent reevaluation, to deal with the variability in case times, add-ons, and cancellations.
- The OR director must create a professional environment in the OR and not allow disruptive behavior patterns to exist.
- OR management is often coupled with increasing numbers of non–operating room anesthesia settings (see Chapter 90).
- A detailed OR information system is essential in tracking OR activity and creating reports for assessment and improvement projects. OR cost accounting is essential to the OR director in guiding decisions for resource application.

The operating room (OR) is a major source of both revenues and expenses for hospitals.[1] Hospital chief executive officers must now focus on the profitability of the OR service, and this emphasis has led to the rapid growth and development of OR management. The goal of OR management is to replace the previously ill-defined structures for OR decision-making and administration with more formal and efficient structures. In the past 10 years, there has been an explosion of research and publications concerning OR management (see reference list).

HISTORY

The roles of the OR and non–operating room anesthesia within the hospital have evolved. The organized structure and daily management of the OR are markedly different than they were 20 to 30 years ago.[2] In the past, ORs generated large profits; their priorities were to maximize convenience for surgeons and attract a greater market share for the hospital, with little emphasis on controlling costs. Because most surgical patients required inpatient hospital beds, the surgery schedule was primarily limited by the number of beds allocated to each surgical service. Hospital administrators assumed that any new investment in the OR would lead to increased revenue. This mentality thrived in a period when revenues were plentiful, which allowed hospitals to provide new equipment or OR expansions upon request. Surgeons could schedule procedures as they desired, usually on a first-come, first-served basis. The authority for OR management was dispersed between hospital administrators, with little direct OR experience, and the OR nurse managers, who oversaw all of the complex activities in the OR. Because the hospital administrators had responsibilities for several areas of the hospital, they left daily control to the OR head nurse, who became the de facto leader of the unit. Many of the supporting services (housekeeping, admitting, materials management, and laundry) had separate administrative reporting structures. The low procedure complexity of ORs allowed for these simplified support services. Physicians often had a limited role in directing OR function.

As surgical procedures became more complex and competition for OR time increased, surgeons and anesthesiologists often became dissatisfied with the control structure of OR management. Physicians formed OR committees to voice their thoughts to hospital leadership. The hospital and OR committees created rules and policies governing OR function. Dedicated rooms for complex procedures and increased scheduling demands led to

the development of guaranteed reserved OR times called *blocks*. These blocks allowed better predictability for surgeons to schedule and perform their procedures and allowed the hospital to provide the necessary support for these cases, but the authority for daily OR management still resided primarily with nursing leaders.

As diagnosis-related group (DRG) reimbursement and capitated payment for care became more common, OR revenue declined. Hospital administrators noted that ORs were very expensive to furnish and staff with skilled nursing personnel. The overall hospital operating margin (profit) declined from 6.3% in 1997 to 2.7% in 1999.[3] By 1999, 43% of not-for-profit hospitals actually lost money. Such losses forced hospital leaders to rethink how ORs should be run. If the ORs consumed 9% to 10% of the institution's annual budget, the hospital needed to analyze and control these costs. With the advent of general medical restructuring and primary care "gatekeepers," it was predicted there would be reduced demand for specialists and surgical services. Therefore, hospitals reduced inpatient beds and limited OR growth. The net effect of these changes was increased frustration with OR function and management.

Predictions of reduced surgical caseload volume proved untrue. Surgical demand began to increase faster than the number of ORs that were available and staffed. Shortages of hospital beds, intensive care unit (ICU) beds, and personnel led to increased pressure to manage ORs with maximum efficiency while controlling costs. The hospitals expected all of these OR changes to occur simultaneously while maintaining high surgeon and patient satisfaction. Hospital administrators realized that they needed more direct physician leadership in handling complex OR matters. As a result, they appointed medical directors to give more voice and authority to physicians in OR leadership roles. This physician leadership structure began in academic departments but has now expanded to many public and private organizations throughout the world.

As more cost-efficient care became the focus of health care, a tremendous expansion of outpatient facilities took place. Ambulatory surgery centers and office suites began to overtake the traditional hospital as sites for the majority of surgical procedures in the United States (also see Chapter 89). Even in large community hospitals and academic centers, fewer than one third of patients came from inpatient wards to the OR. Challenges in running efficient outpatient surgical practices and large tertiary care facilities made the need for expert and dedicated OR management even more essential. The focus on leadership structure and management techniques to improve OR function has led to the organized approach to OR management described in this chapter.

STRUCTURE FOR OPERATING ROOM MANAGEMENT

Operating rooms are complex and expensive facilities that require a structure for management that allows rapid adaptability and integration of many different groups. As medical needs and regulatory requirements evolve, an OR governance structure must rapidly adapt to accommodate these changes. Traditionally, ORs followed a "top-down" management style. Hospital administrators were distant and unfamiliar with the daily workflow of the OR. They would often appoint the OR nursing director to serve as the unit manager, but this nursing director may have been unfamiliar with the specific needs of surgeons and anesthesiologists, leading to frustration in how the OR was managed. This created roadblocks to rapidly addressing the evolving needs of the OR. In response to this problem, the OR director position was created. Initially this concept involved creating an "OR czar," someone imbued with complete authority and decision-making power; but this approach was flawed because it implied an authoritarian ruling style that disenfranchised other physicians. This type of management style is rarely successful in actual practice.

Proper OR governance must include participation of the key stakeholders and offer transparent management practices to achieve improved performance of this unit. Surgeons, anesthesiologists, OR nursing staff members, and hospital leaders all need to participate together in the governance of this complex unit. The purview of the governance group includes creation of an OR Charter, setting performance metrics, development of policies, and participation in future planning decisions.

The position of OR director arose in response to the competing priorities of the diverse groups working within the OR (surgeons, anesthesiologists, nurses, and hospital administrators). For the OR to function effectively, the OR director must balance the priorities of each group while working cooperatively to achieve success for the overall unit. Surgeons want maximum convenience and service, easy OR access, and state-of-the-art equipment. Nurses want predictable hours and standardization of cases. Anesthesiologists want high demand during peak scheduled hours and adequate support for starting procedures and turnovers. Hospital administrators want high utilization and low cost for personnel and equipment. These competing priorities can create conflict and inhibit productivity. The purpose of the OR director is to align the forces working in the OR to work in an efficient and productive manner. The most important advantage to this structure is that providing control and authority to one knowledgeable individual allows the OR to adapt to changes and make critical improvements. Creating an organizational structure with an OR director improves OR performance; increases physician, nursing, and patient satisfaction; permits rapid adaptability to changing market forces; improves communications throughout the system; and strengthens accountability and enforcement of OR rules and regulations. Figure 4-1 shows an organizational structure that describes how the OR director may fit into the hierarchy of OR governance.

Anesthesiologists are good candidates for the position of OR director for several reasons. They often have a global view of the OR and understand each component of the OR process. They share with the hospital administrators a desire for a smooth-running and cost-effective OR. Because anesthesiologists are familiar with preoperative, intraoperative, and postanesthesia care unit (PACU) processes, they appreciate how to make the OR flow as a unit. They are also familiar with the different surgical specialties and can balance the needs of these different groups. Anesthesiologists

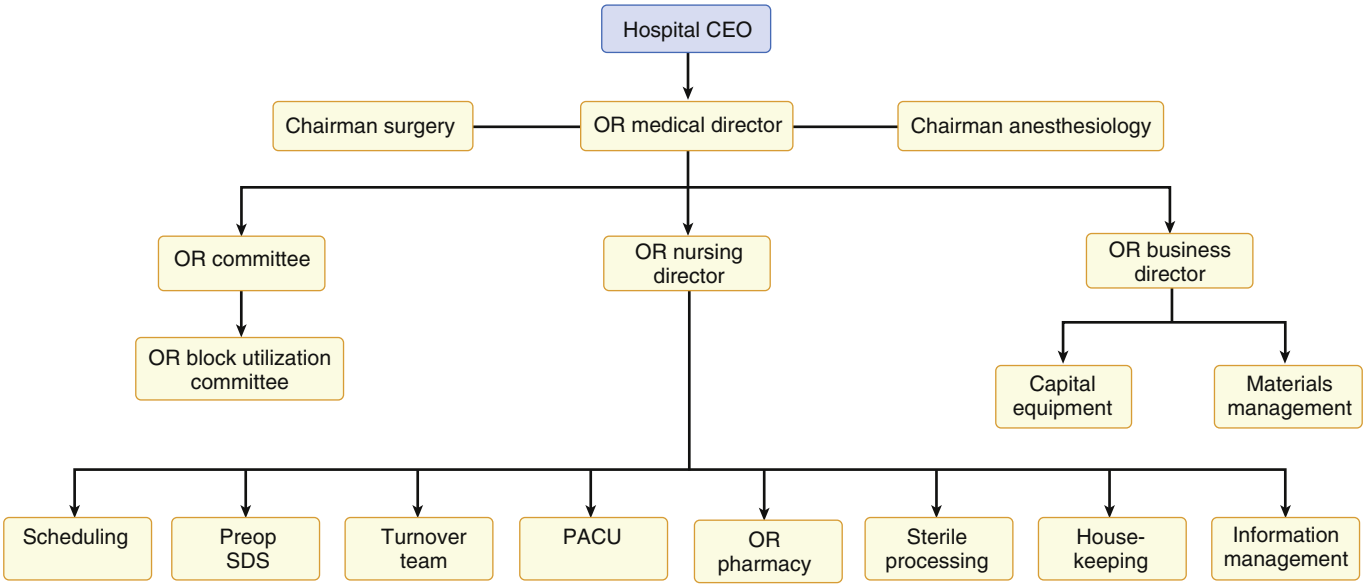


Figure 4-1. Organizational structure that describes how the medical director may fit into the OR system. *CEO*, chief executive officer; *OR*, operating room; *PACU*, postanesthesia care unit; *SDS*, same-day surgery.

BOX 4-1 ***Characteristics of the Medical Director of an Operating Room***

- Experienced individuals, usually in the middle of their careers
- Respected for clinical skills
- Strong interpersonal skills
- Integrity and trust by all groups
- Perceived neutrality and balanced views on issues
- Leadership style by consensus development
- Strong analytical and problem-solving skills
- Detailed data management traits
- Ability to commit significant time and focus to operating room
- Appreciation of hospital's goals
- Good long-range planning development
- Ability to address regulatory and oversight controls

are present in the OR daily and can intervene in urgent situations. Box 4-1 identifies personal characteristics that are beneficial for an OR director to possess.

Another position that may complement the role of OR director is that of the hospital director of perioperative services. Responsibilities of this individual include managing the workflow of the hospital personnel in the preanesthesia testing clinic, ORs, and PACU (also see Chapter 96). This person works closely with the OR director managing preoperative and postoperative problems that have a direct impact on the flow of the OR. Bottleneck stoppages in throughput, which occur before or after the surgical procedure, will neutralize efficiencies developed within the OR.

OR directors face many challenges. The position requires time away from clinical practice to attend meetings, plan projects, and coordinate OR activities. The OR director must have buy-in from his or her group or department to accommodate these scheduling demands and accomplish the OR's mission. The hospital should view the OR directorship as an investment and provide the appropriate financial support. Likewise, the chairs of surgery and anesthesiology must cede some of their departmental control and authority involving OR matters. Time and energy demands may limit OR directors from advancing within their departments, organizations, or academic institutions. The OR director must make difficult decisions and be able to withstand criticism and challenges to his or her role. In addition, OR directors may require additional business training or data processing support.

Dealing with OR conflicts is another difficult aspect of management for OR directors, perhaps one of the least desirable roles of the position. With increased awareness of "culture" in the OR, it is imperative to maintain a professional environment in which staff members exhibit mutual respect for all parties.[4,5] The OR should develop performance policies including scheduling rules, surgeon presence in the OR, charting requirements, and behavioral expectations. The OR is one of the most common sites for disruptive physician behavior owing to the high intensity and stress of the environment. The OR director should have a leading role in developing clear policies for addressing disruptive behavior. Box 4-2 lists steps for dealing with disruptive behavior.[6] Disruptive individuals or those who attempt to circumvent the established OR policies and rules create a dysfunctional system and dissatisfaction among the OR staff.[6] The OR director should set the tone for teamwork in the OR.

In 2002, the Association of Anesthesia Clinical Directors (AACD) conducted a survey of its membership (Box 4-3).[7] The survey noted that the concept of a medical director, which began in academic organizations, has now spread to university-affiliated and private practice hospitals. Seventy-nine percent of OR directors served in hospitals with more than 200 beds. The survey disclosed that financial support varies, but most OR directors receive salary supplementation of less than $10,000 per year. Appendix 4-1 provides the AACD guidelines for the role of medical director. Information is also available on the AACD website (www.AACDhq.org).

BOX 4-2 *Dealing With Disruptive Behavior*

- Educate the OR staff on hospital policies and definitions of disruptive behavior.
- Set a low threshold for identification and reporting.
- Respond immediately to an incident.
- Make the behavior the issue, not the individual.
- Focus on the acute behavior and not past frustrations.
- Do not accept excuses or explanations of justification.
- Set clear target goals for behavior modification and then follow up directly with the individual.
- Be sympathetic to the perspective of public humiliation of the individual. Deal with the individual in a quiet, private setting with one or two witnesses.
- Seek out other issues in the physician's practice that may be the source of stress. Often, factors outside the OR lead to the disruptive behavior that is manifested in the OR.
- Be prepared to enforce your Disruptive Behavior Policy completely. If the physician does not reform or persists in the disruptive behavior, removal from the hospital staff may be the best solution.
- Enforce your policy evenly. Do not allow exceptions for behavior of high-profile individuals. Frequently, action against one physician will demonstrate the seriousness of your commitment to physician behavior standards and serve to deter others from acting out.

OR, Operating room.

BOX 4-3 *American Association of Clinical Directors 2002 Survey of Operating Room Medical Directors*

Hospital Type	
University teaching	44%
Community hospital	33%
University affiliated	33%
No. Hospital Beds	**Size**
<50	5%
50-100	4%
100-200	13%
200-500	54%
>500	25%
Hospital Compensation for Medical Director (per Year)	
None	40%
0-$10,000	25%
$10,000-$25,000	18%
$25,000-$50,000	13%
>$50,000	4%

If an organization adopts the position for an OR director, the responsibilities, expectations, and support should be clear. As stated earlier, the motivation for creating an OR director is often a result of frustration and low satisfaction among OR staff. Newly appointed OR directors can gain early success and acceptance by initially identifying issues that they can easily remedy. Coordination with the OR head nurse and OR business manager will unite the resources necessary for change. Regular communication with hospital superiors and OR staff will help define progress and identify future plans. OR directors need to involve other physicians in setting goals and priorities. Success will require hospital administration and physicians to bring about change through compromise. The OR committee, with hospital administration, should create reasonable rules and standards with equitable enforcement. Although individual contributions should be rewarded, a team approach is essential. Alan Marco's "game theory" is a useful analogy for various situations a director may encounter in running an OR.[8]

Operating room management may be improved by subdividing groups into functioning committees with discrete tasks and areas of control. Often a separate group that addresses OR use and awarding of surgical time or blocks is necessary. Resource or capital equipment needs may be best addressed by a committee with this solitary focus. Facility planning, regulatory compliance, and quality committees may also be used to support OR governance. These committees should report to the OR governance committee and OR director.

OPERATING ROOM FUNCTION GOALS

The OR is a complex environment that relies on distinct and separate working groups to pull together to achieve results. Some have equated the OR to a three-legged stool, with surgeons, anesthesiologists, and nursing personnel representing each leg. If any one leg does not perform to its best ability, the whole "stool" becomes dysfunctional and tips over. One of the goals for OR management is to integrate these different groups into a coordinated unit. The function of the OR depends on several important aspects. Scheduling, preanesthesia testing clinic, first case on-time starts, predictability of to-follow cases, turnovers, management of add-on cases and cancellations, measuring OR use, and employment of the necessary staff to run the ORs are all essential for maximizing OR function.

SCHEDULING

Accurate scheduling in the OR is crucial to running an efficient surgical service. Poor and inaccurate scheduling results in delays and confusion on the day of surgery. It also engenders dissatisfaction for patients, surgeons, and anesthesiologists. The scheduling process involves estimating, organizing, and assembling the necessary personnel, equipment, space, and time to perform a procedure.

Most ORs use a computerized scheduling system, with data integrity being of paramount importance. Errors or omissions in documentation, including the patient's name, age, disposition (inpatient versus outpatient), procedure description, or surgical case duration, can have a major impact on how efficiently the OR will function. The personnel who input these data should take precautions to reduce errors. Many computerized systems track posted cases to verify that available equipment matches resource needs. This prevents overbooking items with high demand, including C-arm radiography machines, microscopes, or robotic devices.

Accurate prediction of surgical case times is also essential to scheduling.[9] Errors in estimated times will affect

the predicted start of every subsequent case.[10,11] Gathering surgeon-specific data is important because operating times may differ significantly among surgeons and hospitals.[12] Strum et al. described how this uncertainty for case durations affects the schedule.[13,14] More recently, Dexter et al. identified the value of historical case durations and Bayesian methods to more effectively predict case durations.[15,16] Because there are wide differences among surgeons, as well as multiple variations of a particular procedure, the potential surgical times for a case may be difficult to predict. If the hospital has computerized historical data, it can base the surgical case time on a set number of similar performed cases. The scheduling system may give the expected time for the procedure at the time it is posted. The surgeon may then increase or subtract time from this estimate based on his or her knowledge of the patient or predicted difficulty of the case.[17] In our institution, based on this system, 50% of all cases were completed within 30 minutes of the scheduled time. Fifteen per cent of cases ran 30 minutes longer than the scheduled time, whereas 35% of cases finished more than 30 minutes ahead of schedule.

In reality, predicting a point value for case duration is not logical. As described by Dexter and Macario,[11,16] surgical cases are a probability estimate for time, with upper and lower bounds for duration. For example, a surgeon posts time for a Whipple procedure on a patient with a pancreatic mass, and the historical times for all cases posted by this surgeon average at 4 hours. Sixty percent of the time, it is determined the tumor is not resectable, and the case time is then 3 hours. The other 40% of the time, the Whipple procedure is performed with a case duration of 6 hours. Although the average duration used for scheduling is slightly more than 4 hours, in practice none of these cases uses exactly 4 hours. The case times are also not distributed as a Bell curve but are frequently right-shifted. Dexter has suggested that Bayesian analysis be used to predict case duration probabilities.[9] Other challenges to case duration scheduling is that more than one third of specific posted procedures by a single surgeon do not have enough historical data to make accurate predictions. Using a combination of historical data, specific patient predictors, and then allowing the surgeons to revise the duration up or down by 10%, may yield the best estimate for case duration.

Historically, ORs were scheduled under an "open block" system. Surgeons scheduled cases in available rooms on a first-come, first-served basis. This system worked if there was little demand for OR time and each room was suited for all types of procedures. However, open block scheduling has many undesirable consequences. Surgeons with a short lead time in deciding to operate are unable to predict the availability of rooms. Personnel have to move complex equipment from room to room to accommodate demand from multiple types of surgeries. There is also marked variability between busy and light days, resulting in poor overall OR efficiency and difficulty anticipating demand and allocating resources.

Because of the limitations of the open block system, ORs moved toward a system of "block" scheduling. Block scheduling guarantees a certain degree of OR availability to a specific service or surgeon. Under this system, the institution assigns a specific room on a specific day to a surgeon or surgical group. The surgeon or group may then schedule its cases for that room on that day. This arrangement permitted the development of specialized ORs (i.e., rooms with heart-lung machines for cardiothoracic surgery, rooms with ophthalmologic fixed ceiling–mounted microscopes, and rooms with dedicated laparoscopic equipment).

TABLE 4-1 SUGGESTED BLOCK RELEASE TIMES

Service	Release Time
Cardiothoracic	1 day
Vascular surgery	2 days
Orthopedics	3 days
Neurosurgery	4 days
Pediatric surgery	1 week
General surgery	1 week
Gynecology	1 week
Ophthalmology	1 week
Otolaryngology	1 week
Plastic surgery	2 weeks

The use of block scheduling follows several best practice standards. For example, block time may work most effectively when it is granted to a surgical service (e.g., orthopedics or gynecology) rather than to an individual surgeon. In addition, full-day blocks (8 hours of OR availability) work better than half-day blocks because patient flow and case start times are more predictable. The reduced movement of personnel and equipment improves room setup and shortens turnover times.

For block scheduling to succeed, the institution should develop rules governing its use. For example, ORs may use measures of surgical demand, such as historical surgical hours per week, to grant blocks to a surgical group. Key topics the rules should address include advance scheduling, turnover time,[18,19] and hold time or release time.[19,20] The release time, which varies among surgical specialties and institutions,[21] is the time when the block is no longer reserved for a particular service. Surgical procedures that are somewhat urgent or have a short lead time, such as heart or vascular surgery, have shorter times from release to the surgery date than services with a more elective practice, such as cosmetic plastic surgery or orthopedic joint replacement. Services with a high referral practice (cancer procedures or trauma) will also need shorter release periods for their blocks (Table 4-1). Once a release time is reached, the remaining time (unused block time) is available to any surgeon on a first-come, first-served basis.

An institution should closely monitor block time use and adjust it as surgical practice changes within the hospital. For example, if a surgical service is filling more than 90% of its block time, it becomes difficult to perform additional cases or manage variability in the surgical referral base. On the other hand, if block use is low (60% to 70%), predictable OR time is not available to other surgeons who may need several days of advance planning to schedule cases. Each institution should set a threshold for block use to determine how services will gain or lose OR blocks.[22,23] A block committee with representatives from hospital administration, surgery, anesthesiology, and nursing should develop these thresholds.

The institution should ensure it applies them equitably to avoid potential games to change OR availability.[8] The group should then monitor and enforce compliance with the rules.

Today, hospitals often schedule most of their ORs under a block system, reserving some ORs in open blocks to accommodate surgeons with small numbers of patients and urgent add-on operations. The number and availability of open rooms will depend on the volume of urgent, emergency, and add-on cases. If the hospital has a significant number of elective cases, it may be appropriate to block schedule up to 80% of the ORs and leave the remaining 20% as open rooms. If a hospital is large with a number of surgeons who do not have block time, then 25% to 30% of OR time should be open and not blocked. Several authors have described strategies to maximize surgical blocks and reduce variability to improve OR use.[24,25]

Decisions to expand OR capacity and provide more block time are complex. Because ORs are expensive, costing up to $1 million per room to build, the hospital should carefully plan growth in surgical services. Wachtel described the important factors that should be considered in adding OR capacity, including giving OR blocks to subspecialties with the greatest contribution margin per hour, those that have the greatest potential for growth, and those that have a limited need for additional system resources such as ICU beds.

A review by Sulecki et al. studying the influence of moving cases within a large health system with 12 separate operating facilities showed that it was not possible to shift cases between facilities to improve efficiency.[26] Surgeons' total case hours, travel between facilities, and proximity to clinic and other office support limited the utility of moving cases from busy sites to sites with more unused OR time.

A final important aspect of scheduling is how to manage non-OR anesthesia cases such as endoscopy, radiology, computed tomography, and magnetic resonance imaging. These patients often require perioperative resources, although they do not actually enter the OR. They often require a dedicated anesthesia team, spend recovery time in the PACU, and are processed through the preoperative unit. Institutions should include these patients and procedures in the OR scheduling system to assist the perioperative units and anesthesia schedule runner, assign appropriate resources, and track progress of the daily schedule.

PREOPERATIVE CLINIC

With 75% to 80% of surgical patients coming into the surgery suite from home, the ability to optimize their medical conditions is challenging. This has led to the development of the preoperative clinic, where an evaluation and testing algorithm are used to ensure best outcomes. This subject is covered in Chapter 38, but its value to OR management cannot be overlooked. Attending to patients who need additional time for evaluation or laboratory analysis may lead to delays in the surgical schedule. A well-organized preoperative clinic can also help reduce the number of cancellations and prevent delays for surgical procedures. The clinic also aids the hospital by reducing the risk for complications, which will result in added costs and application of resources to the surgical population. Patients who have been seen in the preoperative clinic in our institution have a lower incidence of cancellations and a higher rate of on-time starts than patients who have not been seen in this clinic.

On-Time Starts and Tardiness

Perhaps some of the most frequently discussed issues by OR committees are on-time starts and turnovers. Delays in getting the surgical list started and prolonged time between cases lead to inefficiency and frustration by everyone working in this environment. From an atmosphere standpoint, it is crucial to start the first procedure of the day on time. An on-time start provides tangible (scheduling) and intangible (mood and tone) benefits. If there is a delay in starting the first case, it can negatively affect the satisfaction of patients and surgeons, possibly leading to complaints relayed to the hospital's administration. One reason on-time start success is measured so commonly is that it is an easy data point to track and is less affected by issues like delays in a previous case. Often, institutions with a high on-time start success rate will also have brief turnover times. Therefore, on-time starts are one way to benchmark an OR facility's performance. It is important for everyone to agree on the definition of start time. Surgeons often define start time as when the first incision is made. Anesthesiologists define start time based on when they complete induction. Nurses associate start time with the completion of room preparation. Disagreements in what constitutes start time will result in misunderstandings and dissatisfaction with OR start times.

In 1997, a group in the AACD published a "procedure times" glossary that created standards for OR events and time periods.[25] This glossary is accepted by the American Society of Anesthesiologists, Association of Operating Room Nurses, and the American College of Surgeons and serves as the standard for descriptive terms in the OR. Appendix 4-2 contains an excerpt of the glossary; it describes *start time* as the time at which the patient enters the OR. This time has not proved to be useful in identifying cause for delay on a case-by-case basis. Furthermore, surgeons indicate that the time the patient enters the room has little bearing on when the patient will be ready for the surgical incision. The newer concepts of "anesthesia ready" (AR) or "anesthesia release time" (ART)[27] may be more helpful in determining surgical preparation and incision times. The AACD glossary describes *anesthesia ready* as the time at which the patient has a sufficient level of anesthesia established to begin their surgical preparation, and remaining anesthetic procedures do not preclude positioning and prepping the patient. At our institution, we reviewed times from the patient entering the OR to completion of preparation. In uncomplicated cases (patient supine with no invasive monitoring lines), staff completed preparation in 15 minutes in 78% of cases. If the case was complicated (position other than supine, invasive monitors), the duration from start time to completion of preparation averaged 30 minutes. These data are useful for surgeons to anticipate the time from room start (patient in room) until completion of preparation.

On-time starts depend on the completion of many factors. Patients must arrive on time and complete preoperative preparations including compliance with all preoperative instructions ("nothing by mouth," medications, laboratory tests). Preoperative testing clinics and assessment protocols have helped reduce delays on the day of surgery, as well as reduce costs.[28,29] The preoperative/admitting process should have sufficient personnel, organization, and space to process patients and make them available to surgeons and anesthesiologists. Operating room nurses must prepare the OR and equipment. Anesthesia personnel must check the equipment in the room, prepare drugs, complete paperwork, place intravenous lines, and address special patient or surgical needs. Surgeons must be available to complete the patient's consent, history, and physical examination and to address any patient questions or needs.

A common misconception is that anesthesia factors result in the majority of room start delays. Many anecdotal reports by OR clinical directors do not support this concept. We recently studied reasons for all delayed room starts and grouped those delays into factors controlled by patients, surgeons, anesthesiologists, and nursing/hospital. The results (Box 4-4) demonstrate that surgeons controlled the largest number of delays in first starts. Box 4-5 lists some of the most common reasons for delays.

Starting first cases on time is a complex and challenging process. When defining an on-time start as having the patient in the room by the start time, delays occur in 40% to 90% of first starts.[30,31] When defining an on-time start as having the patient in the room within 10 minutes of the scheduled start time, delays still occur in 5% to 50% of cases. Identifying causes of delays; removing barriers to smooth patient flow; improving communications among preoperative personnel, patients, surgeons, nurses, and anesthesiologists; and creating an atmosphere (culture) of shared ownership in starting on time will improve on-time starts. Box 4-6 lists other key factors for increasing the percentage of on-time starts.

The direct economic benefit for reducing first-case delays depends on the size and volume of cases performed in an institution.[32,33] In a study by Dexter and Epstein, only 1.1 minute was saved at the end of the day for each 1-minute reduction of delays.[34] If the OR suite has a small number of rooms and the cases finish within the scheduled time, then no economic benefit was achieved by reducing delays. As an example, if an eight-room surgical suite has an average of two rooms that start 10 minutes late, but all of the cases in the 8-hour nursing shift are completed, then no savings will occur if the cases start on time. However, in a facility with a large number of ORs and with some rooms running for more than 8 hours, reducing these delays may result in less overused time and expense.

The term *tardiness* may be used to describe the difference between scheduled start time and actual start time for all cases on the surgical schedule. This measures both first-case starts as well as the to-follow cases. Wachtel and Dexter have identified several factors that relate to tardiness of the surgery schedule.[35,36] As might be expected, the first case of the day had fewer instances of tardiness than cases later in the day. Because case duration is unpredictable, if the first case runs long, then the second case will be tardy in starting at the scheduled time. Although surgeons believed the most common time for tardiness was late in the afternoon during nursing shift change, the peak time for tardiness was between 11:00 AM and 1:00 PM, when most rooms were still running and multiple turnovers were occurring. Later in the day, tardiness decreased, likely balanced by some cases finishing earlier than predicted or when cases were moved to an available unoccupied OR. The best strategy to reduce tardiness was to recalculate the OR schedule and account for potential late-starting cases or case durations that may be longer than planned; then cases could be moved or adjusted to improve starting times.

BOX 4-4 *Delays in Start of First Case of the Day*

Surgeon controlled: 60%
Patient controlled: 20%
Anesthesia controlled: 6 %
Nursing/hospital controlled: 14%

BOX 4-5 *Reasons for Surgeon-Controlled Delays*

- No history and physical examination in chart
- No consent obtained
- Ordered new laboratory test; results not available
- Changed schedule order or procedure
- Surgeon not available

BOX 4-6 *Key Factors to Increasing On-Time Starts and Decreasing Turnover Times*

Keys to Increasing On-Time Starts

- Do not require the surgeon to be present before the patient enters the OR.
- Use guaranteed block time to allow for predictable OR times and locations for surgeons.
- Have specialty teams dedicated to complex cases.
- Standardize preoperative orders and testing.
- Review the patient's chart the day before surgery to identify potential delays in getting the patient ready.
- Call patients the day before surgery to clarify instructions and answer questions.
- Triage personnel in the preoperative area to effectively manage patient needs before start of the procedure.

Keys to Decreasing Turnover Times

- Organize a turnover team to clean and prepare the room.
- Have the same surgeon follow in the same room with all of their cases.
- Use specialty-specific nurses and anesthesiologists.
- Maintain an accurate surgery schedule and reduce changes in the surgical list (i.e., order changes, cancellations, add-ons).
- Streamline the preoperative process.
- Ensure that the communication process informs all personnel involved with case turnover in a timely manner.

OR, Operating room.

Turnovers

The definition of *turnover* varies among OR personnel, often leading to confusion.[37,38] A surgeon may view surgical "down time" (the time between closing the incision on one patient and beginning the incision on the next patient) as turnover. Academic surgeons consider turnover to be the period between leaving the OR (before the incision is closed by a junior resident or medical student) and returning for the beginning of the next case. Thus surgeons frequently complain that slow turnovers between cases cause significant delays in completing the surgery schedule. The OR nurse may treat turnover as the time from removing the used equipment from the first case until the equipment is in place for the next patient. Anesthesia personnel believe that turnover is the time between leaving the previous patient in the PACU and bringing the next patient into the room. With varying definitions of turnover, it can be difficult to measure and create improvements in this area of OR function.[39] The AACD glossary (see Appendix 4-2) defines *turnover* as the time from when one patient exits the OR until the succeeding patient enters. This turnover time applies only when the second case is scheduled to immediately follow the first case.

The period between patients occupying the OR is busy. The nurses must return used instruments for decontamination processing. A housekeeping service must clean the floors and sterilize all surfaces, including the OR table. Nurses must assemble and organize equipment for the next case. They must also check on the next patient and verify that the paperwork is complete and the procedure is listed correctly. Anesthesiologists must transport the previous patient to the PACU, assess vital signs, give a report to the PACU nurse, and submit the required paperwork. They must return unused drugs and prepare new drugs for the next case. They must also ensure that anesthesia equipment is replaced and prepared for the next patient. Finally, they must see the next patient, complete their preoperative paperwork, obtain consent forms, discuss anesthesia plans with the patient, and answer any questions.

Multiple system factors can affect turnover time, and several units must function efficiently together to be successful. Attention should be given to the preoperative process (see Chapter 38) to efficiently prepare patients for surgery and readily locate the required paperwork and preoperative test results. Hospital transportation services should allow patients to be reliably available when called for the OR.[40] The drug management system must permit access to medications and manage controlled substances. A turnover team must organize, clean, and prepare the OR for the next case. The PACU must function well to allow efficient OR throughput.[41,42] Limited hospital floor bed and ICU bed availability may result in delays in patients being discharged from the PACU, limiting PACU space for OR patients. Chapter 96 further discusses ways to improve PACU function. Each of these individual factors contributes to the overall ability of the team to facilitate turnover.

There is no national standard for acceptable turnover time. In most facilities, turnover represents only 10% to 20% of the total case time. When performing turnover between simple procedures, such as cataract extractions, it is reasonable to expect a turnover time of 10 minutes or less. However, when changing between heart bypass procedures or complex orthopedic cases, the turnover may require 45 minutes or longer. The complexity of room set-up and the need for specialized patient preparation contribute to the length of turnover. Box 4-7 illustrates average turnover times reported for various types of surgical procedures.[43] Some benchmarking data are available on turnover for specific procedures.[43,44] A review at four academic institutions indicated that turnover times ranged from 34 to 66 minutes.[45]An institution should consider this information when it looks at its specific turnover data to determine realistic goals for OR improvement.

BOX 4-7 *Average Turnover Times*

Total-hip replacement	44 minutes
Total-knee replacement	46 minutes
Knee arthroscopy	38 minutes
Coronary artery bypass	52 minutes
Laparoscopic cholecystectomy	30 minutes
Cataract extraction	21 minutes

Although reductions in turnover times may save 5 to 10 minutes per case, these time savings do not usually translate into large time reductions in a single OR's schedule. Reducing turnover time does improve efficiency and focus, which may translate to improvement in surgical preparation and case completion times. The intangible benefits of reducing turnover may be the most important. Reducing turnover can build teamwork and encourage the institution's focus on achieving maximum OR efficiency. However, excessive focus on turnover time is counterproductive. Staff risk losing more time strategizing than can realistically be gained from the resulting changes.[44] Turnover time is also a favorite topic of consultants because it tends to strike an emotional chord with surgeons and hospital administrators. In reality, most efforts to reduce turnover times result in modest reductions in completion of the surgical schedule.[45] As an example, if a single OR performs four cases in a day and can reduce turnovers by 10 minutes, the total time that can be saved is 30 minutes (3 turnovers × 10 minutes × 30 minutes). This small time savings may result in reduced overtime expenses if more than 8 hours of surgery are regularly performed, and improved satisfaction measures, but it will not provide sufficient time to perform additional cases.

Operating Room Utilization

Operating room utilization is an important concept that guides the direction of OR management.[46] It is also a significant part of the OR director's job. To understand the concept of OR utilization, it is important to understand several definitions from the AACD glossary (see also Appendix 4-2):

- *Case time* is the time from the start of room setup to the end of room clean-up. It accounts for the entire

TABLE 4-2 UTILIZATION COMFORT ZONES

Utilization	Hospital Administration	Anesthesiology	OR Nursing	Surgeons
>100%	++	--	---	----
85%-100%	++++	++	-	--
70%-85%	+++	++++	+	±
55%-70%	+	+++	+++	++
<55%	--	-	++	++++

From Mazzei W: AACD Workshop on Operating Room Management, 2003.
Ranges of greater negativity (-,--,---,----) and ranges of greater positivity (± ,+, ++, ++++, ++++). As an example, + is a mildly positive aspect, but +++++ is strongly positive. Likewise, - is a mildly negative aspect, but ---- is strongly negative.

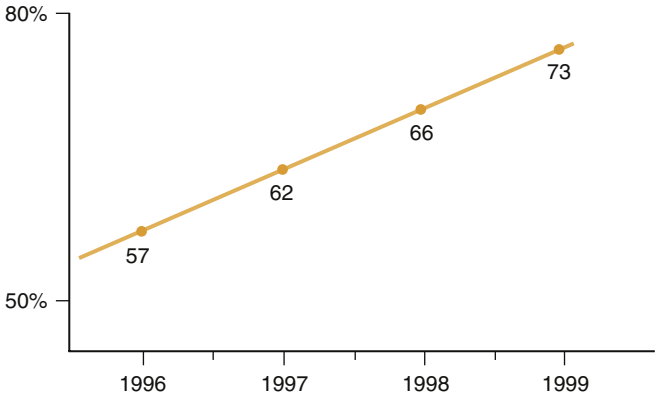


Figure 4-2. Raw utilization for operating rooms.

time that the OR is dedicated to the performance of a procedure and cannot be used for any other purpose.

- *Resource hours* are the total number of hours that a room is staffed and available for the performance of procedures. Many ORs are staffed for 8 hours of regular resource hours (e.g., 7:00 AM to 3:00 PM). Resource hours do not include overtime or periods when on-call personnel are staffing the OR. Resource hours serve as the denominator in calculating use of the available blocked or open scheduled elective OR times.
- *Raw utilization* is the ratio of the time that patients are in the OR to the available resource hours. It does not include time spent preparing the OR or turnover time; therefore, it understates the actual time that the OR is committed to a case.
- *Adjusted percent utilization* is similar to raw utilization, but it includes case setup time and turnover time. This figure more accurately reflects the time that the OR is used for case performance and is unavailable for any other activity.

Utilization is most commonly determined for a service or group of surgeons based on their set amount of block time. For example, if a group of orthopedic surgeons has block time in two rooms on Monday through Friday, their resource hours per week are 80 (2 rooms × 5 days per week × 8 hours per day). If their total case time (in-room time plus turnover) is 72 hours per week, the adjusted percent utilization is 90% (72 hours per week □ 80 hours per week).

Regularly tracking utilization is important. To achieve an efficient balance of available times for surgical divisions, hospitals should reassess block times based on utilization on a 3- to 6-month basis. For hospitals using utilization to track surgery performance and allocate block time, it is better to assign block time to a group of surgeons or a surgical division. Granting block time to individual surgeons produces more variability in use and may result in lower utilization.

There is no defined target for optimal utilization. Opinions of optimal utilization vary among entities involved in the OR (Table 4-2). As utilization increases to above 80%, surgeons may have difficulty scheduling patients, and the increased wait time may create patient dissatisfaction. Studies have shown that for elective procedures in the United States, most patients are willing to wait 1 week.[24] Waiting longer than this because of unavailable block time will lead to patient and surgeon dissatisfaction and possibly loss of the case to another institution. Utilization percentages that are very low represent lost opportunities to generate revenue. Anesthesiologists prefer to be busy during regular resource hours yet have some flexibility for covering urgent and emergent cases.

The exact break-even point for utilization is dependent on the OR's fixed versus variable costs and reimbursement mix. Consultants often quote 80% to 85% utilization as a target. This figure was used as a benchmark in the 1970s because hospitals were required to demonstrate a certificate of need before expansion of OR facilities. Most ORs seek a utilization of 70% to 85% to maximize benefits and reduce stress on the system. Trends have shown that, with increasing surgical volume and reduction in OR availability, the overall raw utilization has been steadily increasing in hospitals (Fig. 4-2). Data from 1999 revealed that hospital-based ORs have higher utilization than ambulatory ORs (73% versus 55%).[47] Tracking overall OR utilization may be beneficial in demonstrating the need to expand OR capacity.

There are costs associated with both underutilization and overutilization. There are fixed costs for ORs regardless of utilization. Underutilization results in lower revenue generation to offset the fixed costs. Overutilization (cases running late) may require overtime pay for nurses or hiring temporary nurse services, which results in higher costs per minute of OR use. In addition, personnel who frequently must stay late may become dissatisfied and quit, increasing the costs associated with recruitment. Many recent studies have identified ways to maximize utilization or to assist with scheduling to improve percent utilization.[47,48] Because many ORs have frequent last-minute changes, cancellations, add-ons, and emergency cases, the ability to apply these simulations to actual OR practice may be limited.

Utilization should not be used to assess how efficiently an OR is working. Utilization is only a measure of resource consumption. For example, if surgeon A takes 2.5 hours to perform a laparoscopic cholecystectomy and conducts three procedures in an eight-hour block, this results in a raw utilization of 94% (2.5 hours per case × 3 cases = 7.5 hours; 7.5 hours per 8-hour block = 94%). However, surgeon B, who completes laparoscopic cholecystectomies in 1 hour and is able to do 6 procedures during an 8-hour block, has

a raw utilization of 75% (1.0 hour per case × 6 = 6 hours; 6 hours per 8-hour block = 75%). Even though surgeon A has a more frequent utilization, surgeon B's financial margin is better. Table 4-3 illustrates these calculations.

Hospitals are becoming more refined at analyzing OR production. By looking at revenue generation and associated costs for each surgeon, they can determine the profit margin for each individual. Although studies have shown that nearly all surgeons contribute a positive profit margin for their OR cases, the range of profit margin is wide.[49] Table 4-4 shows an example of a report generated with this approach. OR managers and hospitals are increasingly using this type of information to make decisions concerning OR resources. Box 4-8 contains a list of key issues to improve OR utilization, throughput, and efficiency.

Another important way to approach OR function is to consider the OR workload (demand) and the fixed nursing shifts (typically 8 hours) that are scheduled. Some useful definitions in considering performance of each OR are:

OR Workload: The total hours of OR case time plus turnover on that day.
Allocated Time: Time reserved for a surgeon or service on a particular day (block time)
Underutilized Time: Allocated Time – OR Workload (if this value is <1 then default to 0)
Overutilized Time: OR Workload – Allocated Time (if this value is <1 then default to 0)
OR Labor Costs: 1.0 × Allocated Time + 1.5 × Overutilized Time
Inefficiency Measure of OR Time: Underutilized Time + 1.5 × Overutilized Time

As described in these definitions, nursing shifts are paid for their 8-hour shift, even if only 7 hours of OR workload occur. The underutilized time may be insufficient to perform another case, so no additional revenue can be generated in this OR, but neither can costs be reduced by finishing early. If an OR has 10 hours of OR workload, then there are 2 hours of overutilized time, which must be paid at overtime rates (1.5 times normal pay). Overutilized time may be even more expensive if this leads to staff dissatisfaction and added costs for retention and recruitment of nurses. Therefore, overutilized time is much more important to control than underutilized time. Wachtel and Dexter described this concept in a review article on OR management.[50,51] A goal for the OR directors might be to limit overutilized time so that it occurs in fewer than one third of the ORs and accept two thirds of the ORs being underutilized, finishing before the end of the nursing shift. This would limit expense and yet allow for higher economic performance.

DAILY SCHEDULE MANAGEMENT

The "running" of the daily schedule is a complex job.[52] An accurate and realistic schedule is one of the most important factors in completing the surgical list. Frequently, an anesthesiologist partners with an OR nursing leader to run the daily surgery schedule. This team must be able to make fair decisions regarding moving cases, managing add-on and cancelled cases, and using the nursing and anesthesia workforce to complete the surgical list efficiently. The OR nursing director's willingness to accept risk in running the schedule may create significantly less unused OR capacity and also improve the anesthesia group's productivity.[53] It is interesting that a recent paper by Masursky et al. showed that OR nursing directors may

BOX 4-8 *Keys to Increasing Operating Room Throughput*

- Schedule full-day blocks rather than half-day blocks.
- Surgeons should follow themselves in the same operating room.
- Verify schedule accuracy to decrease delays in case completion.
- Streamline preoperative processes and standardize testing.
- Use specialty teams of nurses and anesthesiologists.
- Organize supply and equipment needs for easy room setup.
- Focus attention on room starts and turnover to create a culture of timeliness and efficiency.
- If you have a significant number of add-on cases, plan for an open room or be able to move cases to available time slots.
- Ensure that the communication pattern throughout the perioperative area informs all necessary individuals of case progression.

TABLE 4-3 **RAW UTILIZATION CALCULATIONS**

	Case Time (hr)	No. Cases Performed	Total In-Room Time (hr)
Surgeon A	2.5	3	7.5
Surgeon B	1.0	6	6.0
Surgeon A	7.5 hr in room time 8.0-hr block available = 94% raw utilization		
Surgeon B	6.0 hr in room time 8.0-hr block available = 75% raw utilization		

TABLE 4-4 **OPERATING ROOM ASSESSMENT REPORT**

Surgeon	Cases	Collection	Avg Collection/Case	OR Minutes	Avg Minutes/Case	Collection/OR Minute
Green	53	$43,116	$813	1150	22	$37.49
Jones	17	$16,802	$988	989	58	$16.99
Smith	10	$17,179	$1718	588	59	$29.22
Rogers	19	$11,947	$629	800	42	$14.93
Wilson	12	$13,341	$1112	1052	88	$12.69
Lynch	13	$7,398	$569	883	68	$8.38

OR, Operating room.

have priorities that run counter to increased productivity.[54] The OR nursing director may prioritize nursing relations and budgets that lead to more underutilized time and therefore lower productivity. For these reasons, it is essential that the physician and nursing OR directors develop a management style that benefits the function of this unit.

Making the cases flow smoothly takes several steps (Box 4-9). The initial step is to review the schedule of cases the evening before and again the morning of surgery. These reviews should focus on identifying potential obstacles to patient flow such as delayed starts, surgeon preferences, and opportunities to deal with add-ons or changes. During the course of the day, the scheduler should frequently walk the "floor" in the OR to check on the status of room starts, case progression, and turnovers. Because surgical procedures have a high degree of variability, plans on how cases should proceed change frequently, and adaptation is paramount. The OR should create a tracking system to monitor the day's progress and should be available for people working in the OR so they can see schedule adjustments including starts, completed cases, cancellations, and add-ons.

Every OR has add-ons and case cancellations. As the number of add-ons and cancellations increases, so does the complexity of scheduling.[55-57] There are no national benchmarks for schedule changes, but planning measures to keep add-on rates less than 12% and cancellation rates less than 4% will help to effectively and efficiently manage the schedule. Cancellation rates vary, based on patient population and surgical procedures, but are generally in the range of 6% to 9%.[28] If an OR has a higher cancellation rate, staff should assess why this is taking place. One strategy to reduce cancellations is to evaluate patients in an organized and efficient preoperative clinic with standardized algorithms for further testing and evaluation. These clinics reduce delays and cancellations on the day of surgery.[28] Box 4-10 shows some of the common issues in case cancellations.

Cancelled cases can significantly affect OR productivity and access to elective scheduling for cases. Recent reviews by Dexter et al. and Tung et al. have identified issues related to cancelled cases.[58,59] Because the surgical schedule has so many changes with add-ons and cancellations, it is unproductive to actively manage the surgical list before 2 days leading up to the day of surgery. Beginning 2 days before surgery, the OR director should begin to look for opportunities to move cases and adjust the schedule to maximize filling rooms and decrease overutilized time. One predictor of the net added hours of surgery within the 2 days leading up to the day of surgery is the availability of open or underutilized time. The day before surgery the OR director should "sculpt" the schedule to balance overutilized and underutilized rooms. If flexible staffing is an option for nursing staff, decisions on the number of nurses needed to limit overutilized time can be made. Some patient predictors for cancellations are number of missed clinic appointments, insurance status, and patients not seen in the preoperative anesthesia clinic. Other factors identified that increase cancellations are surgical service (general surgery > gynecologic surgery) and size of the hospital (large or academic facility > medium or small hospitals). In a German study, the most common causes for cancellations were organization/resource based (overutilized time, emergency cases lack of ICU beds) followed by new medical issues discovered in patients.[60]

There should be a well-defined system for triage to improve the efficiency of performing add-on cases. Generally, the scheduled elective cases take precedence over add-on cases, but there are exceptions. Situations will arise in which an urgent or emergent case will delay or "bump" a planned elective case from the schedule. As a result, managing and scheduling urgent or emergent cases must also follow a well-understood system. Table 4-5 shows one algorithm used to handle emergency cases.

BOX 4-9 ***Ten Steps to Completing the Daily Schedule***

1. Recheck the schedule the afternoon before surgery to look for potential difficulties and to identify opportunities.
2. Review the schedule early in the morning on the day of surgery and note cancellations and add-ons.
3. Ensure that rooms have accurate start times by walking through the OR suites.
4. Set expectations for surgical case progress by using benchmark case times if available.
5. Organize the turnover process to manage peak room changes from midmorning until early afternoon.
6. Develop a well-understood policy for working add-on cases into the schedule.
7. Look for open room time to move cases from late-running rooms or to move add-on cases into them.
8. Identify cancellations early and redeploy the room and personnel resources to complete other cases.
9. Set realistic staffing patterns to meet the surgical caseload demand. Use nonstandard shifts so that rooms do not have to be closed in the early afternoon.
10. Use a case-tracking system so that others can see where resources are needed to complete the caseload.

BOX 4-10 ***Common Case Cancellation Issues***

PATIENT

Self-cancellation or no-show
Desired second opinion
Patient not NPO
Preferred transfer to another institution

SURGEON

Not available; busy with an emergency or another case
Decided surgery was not indicated
Patient needed further workup

ANESTHESIOLOGIST

Patient needed further workup

HOSPITAL

Nursing staff not available
Lack required equipment or implants for case
Scheduling error; wrong date for surgery
Lack beds; ICU at capacity

ICU, intensive care unit; *NPO*, nothing by mouth.

Surgeons often help control add-on placement by scheduling OR availability during specific days. If a group or division of surgeons is busy, they may have set OR days when they are available for surgical procedures and other days when they are committed to clinic visits and are unavailable. Often, the surgeons' add-on cases are self-channeled into days on which they are already using the OR. In this situation, the add-ons should be scheduled into that surgeon's preexisting room. If a hospital system has a large number of add-ons that surgeons must perform at the end of the elective schedule late in the day, the OR should be scheduled to properly staff and support these times. Nursing shifts using the traditional 8-hour (7:00 AM to 3:00 PM) shift may need to be modified to cover late rooms by creating either 12-hour shifts (7:00 AM to 7:00 PM) or staggered shifts (10:00 AM to 6:00 PM). Anesthesiology departments must also address coverage of this off-peak OR time. If a hospital had a large number of add-ons that are urgent, such as is frequently seen with trauma centers, consideration for keeping one or more rooms unblocked but staffed for urgent add-ons may be successful.

Despite the best planning, the daily schedule is often challenging because cases are unpredictable. A good rapport among schedulers and surgeons is helpful in diffusing potential scheduling conflicts. Macario's[11] article on game theory creates an interesting analogy of these interactions as they apply to the OR. This perspective can be helpful in scheduling efficiently and seeking support for organizational success. Routine reviews of utilization reports and the daily schedule are important to identify opportunities for improvement, including decreasing underutilized OR time (Figs. 4-3 and 4-4). Regardless of the desire to run the schedule efficiently, the quality of a patient's care should always remain the top priority.

TABLE 4-5 ADD-ON CASE MANAGEMENT

Emergency	Urgent	Elective
Come to the OR within 30 min *Example:* gunshot to the abdomen	Come to the OR within 2 hr *Example:* appendectomy or ectopic pregnancy	No time constraints *Example:* revision dialysis shunt
Place in any open room	Place in available staffed open block room or in room with cancellations.	Follow elective cases in first available room.
If no room is open, bump any room that is turned over and ready	If no room is open, bump the posting surgeon's elective cases.	
	If posting surgeon has no room available, bump same surgical division.	
	If no cases within same surgical division, bump room with the shortest surgical list.	

OR, Operating room.

ANESTHESIA SERVICE

It is important for OR directors to include anesthesia service management in their scope of OR management. If an OR director succeeds in streamlining and maximizing the efficiency of the OR, productivity within the anesthesia service will also increase. Better OR scheduling, on-time starts, efficient turnovers, and proper management

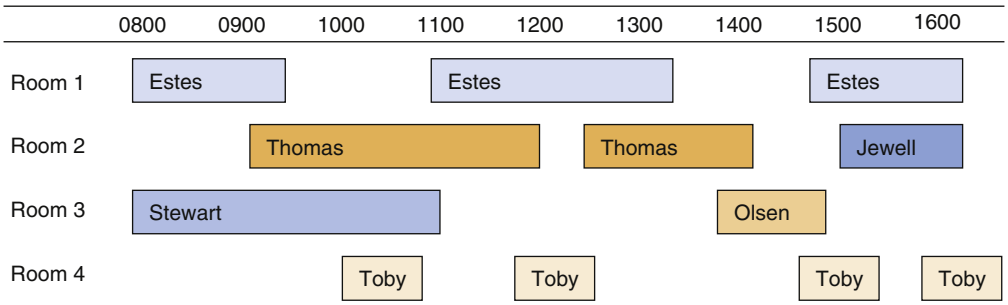


Figure 4-3. An example of schedule utilization.

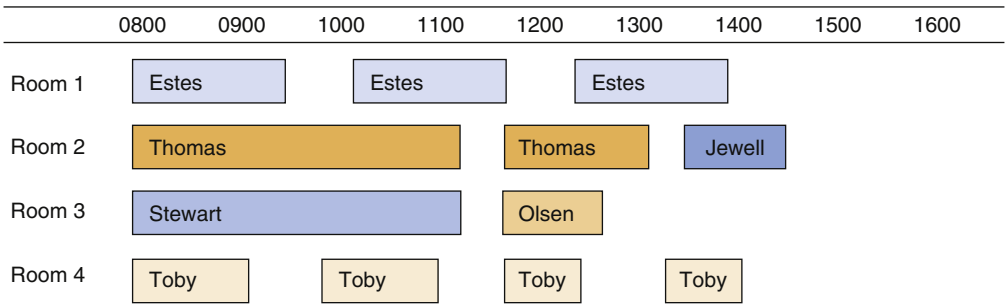


Figure 4-4. Improved schedule utilization.

of add-ons and cancellations will result in concomitant improvement in anesthesia service utilization.

The two main components of anesthesia service management involve personnel issues and pharmaceutical costs. Anesthesia-related costs represent 3% to 5% of the total health care expenditures in the United States.[61] Although most of these costs involve personnel,[62] anesthesia-related drugs comprise the majority of the 20 most costly drugs used in the hospital.

Optimal staffing patterns for providing anesthesia coverage for the surgical schedule[63] are a frequent point of discussion. Staffing coverage depends on provider availability and local conditions. The benefits of physician-only versus concurrent supervision of multiple providers are not clear cut.[64] ORs must also consider the requirements for specialty teams to cover areas such as cardiac, organ transplant, obstetric, trauma, and pediatric cases, which may limit the ability to maximize staff utilization. Supervision ratios may affect first-case starts and quality.[65] Today, more anesthesia groups are negotiating financial support from hospitals for added call coverage for these specialty teams. There are several models for calculating this support, with the intent of benefitting both the anesthesia group and the hospital. Within the anesthesia group, there are also models described that focus on mission-based compensation that can lead to increased productivity.[66,67]

As a result of growing pressure to quantify anesthesia output, ORs have refined the measurement of anesthesia productivity.[68,69] Methods to track anesthesia output have evolved from simple availability to more sophisticated measurements of production and call coverage.[70,71] Clear differences exist between academic and private settings. Abouleish et al.[69] and colleagues showed that an anesthesiologist in an academic setting needed to work 30% longer than one in private practice to generate the same level of billable services (7.8 hours versus 6.0 hours). Development of incentive plans can be useful to improve productivity and retain physicians.[72,73] Anesthesia drugs are expensive and are a frequent focus for reducing hospital expenses.[74] Overall, pharmaceutical costs approximate 5.6% of a hospital's total operating costs. Anesthesia drugs represent 22% of the total pharmacy costs.[75] Newly developed anesthesia drugs often have significantly higher costs (muscle relaxants, narcotics, antiemetics). Although these drugs may appear to be cost effective by improving patient throughput (decrease OR or PACU times) or increasing patient satisfaction (faster discharge, less postoperative nausea and vomiting), studies have been inconsistent in demonstrating those benefits.[76] Because there are many variables that contribute to change in resource utilization and drug cost, true assessment of the resulting changes from drug choices is difficult. It is also difficult to assess the fixed versus variable costs of those changes. If anesthesia-controlled costs represent 6% of the total cost for a surgical patient, it is likely that half of these costs are fixed. ORs can modify the remaining 3% of costs (drugs and supplies); however, experience has shown that intensive restructuring of anesthesia drug use only results in small reductions in overall pharmacy costs. In many cases, the savings are difficult to sustain and ORs return to previous drug choices.[75]

OPERATING ROOM QUALITY AND PATIENT SAFETY (Also See Chapters 6 and 7)

QUALITY MEASURES

Hospital care is particularly expensive in the United States, but the increased expense does not lead to uniform or improved outcomes. Federal and private groups have suggested ways to improve quality with standardized care and reporting of measure outcomes. The Surgical Care Improvement Project (SCIP) identifies several measures designed to reduce surgical site infections. Tracking these measures and achieving their benchmarks is increasingly being tied to payment, as well as being used to gain market share. Government programs such as Pay-for-Performance are also used to drive standardized care, with the goal of leading to improved outcomes at lower costs. The Affordable Care Act that overhauled the approach to health care in the United States has numerous provisions that deal with reporting and following best practices. Because many of these regulations involve surgical patients and activities in the OR, the OR director must ensure that compliance and strategies lead to success in meeting these expectations. The Centers for Medicare and Medicaid Services (CMS) and The Joint Commission use these regulations in evaluating a hospital for accreditation purposes. The OR director must be familiar with these regulations and facilitate data collection and compliance. Because the OR director is knowledgeable of OR function and policies, they occupy a lead role in site visits by these outside agencies.

Operating room activities are complex and critical to the delivery of health care. A large number of agencies and regulations oversee how an OR functions. The OR director must be familiar with these various agencies and regulations to ensure compliance within the OR. Box 4-11 lists these entities.

The OR director must focus on meeting the regulatory requirements for hospital accreditation. Patient and employee safety (infective agents, fire safety, laser safety, electrical safety) and proper use and tracking of drugs and medical devices are also important areas of focus. State and local regulations, as well as hospital policies, have

BOX 4-11 ***Operating Room Agencies and Regulators***

- The Joint Commission
- Accreditation Association for Ambulatory Healthcare (AAAH)
- Drug Enforcement Administration (DEA)
- Food and Drug Administration (FDA)
- Centers for Disease Control and Prevention (CDC)
- Department of Health and Human Services (DHHS)
- Centers for Medicare and Medicaid Services (CMS)
- Occupational Safety and Health Administration (OSHA)
- American National Standards Institute (ANSI)
- National Fire Protection Association (NFPA)
- National Committee for Quality Assurance (NCQA)
- National Academy of Sciences/Institute of Medicine
- Safe Medical Devices Act
- Health Insurance Portability and Accountability Act (HIPAA)

specific requirements for the OR. Privileging and monitoring the quality of outcomes for physicians in the OR are paramount. Internal data collection and quality measures should be designed to demonstrate the performance of individual physicians and the OR.

CHECKLISTS

The focus on improving quality in the OR has led to the concept of using checklists to ensure best practices are followed.[77] Atul Gawande popularized this in the book *The Checklist Manifesto*. The use of checklists has been proven to improve safety in the airline and space industries. The World Health Organization has also adopted the plan to increase the use of checklists to reduce errors. Because the OR involves interactions among nursing, surgery, and anesthesia personnel working in a complex environment under production pressures, errors occur too frequently. Checklists are used to prevent things such as wrong-site surgery or identification of drug allergies. The OR director should balance the number of items on checklists with maintaining efficiency and quality in this unit.

ELECTRONIC MEDICAL RECORDS

With new federal regulations concerning medical information, the use of electronic record keeping has accelerated. Requirements that all patient information be readily available have caused hospitals to spend considerable amounts of their budgets for this support. The OR generates a large amount of data that presents challenges to electronic systems to organize and capture.[78] These anesthesia information management systems (AIMS) can be an effective way to increase compliance, demonstrate quality, and improve outcomes.[79,80] They can be designed to provide prompts when important points of care arise, such as antibiotic administration. The accuracy of these systems to capture data and potential errors in recording care have led to concerns about how these new systems will benefit anesthesia groups. But as AIMS become more refined and automated, they offer the OR director a tremendous source of data to track compliance and outcomes.

COST ACCOUNTING IN THE OPERATING ROOM

Financially managing the OR is a difficult task. Most physicians have not had a formal business education and are unfamiliar with OR financial management concepts. Health care in the United States is a complicated financial industry, with 17.6% of the gross domestic product devoted to it.

The concept of management control in nonprofit organizations is becoming more sophisticated.[81] Financial management of the OR is analogous to running a business.[82,83] A hospital can classify an OR as an expense center or a profit center. If it is an expense center, attempts to improve the financial position of the hospital would focus on minimizing costs. If, however, the OR is a profit center, the OR director must pay attention to the margin between costs and revenues and attempt to maximize profit. It is essential for hospitals to focus on the financial performance of the OR. The OR averages 40% of the total costs of a hospital, but it is responsible for as much as 70% of the revenue.[1] As ambulatory health care activity has moved out of the hospital, many hospitals have become primarily tertiary care surgical facilities. Managing costs and increasing revenue in the OR will result in a hospital with strong profitability and the ability to expand its health care delivery services.

The OR director needs a basic understanding of cost accounting to ensure effective OR decision making. Cost accounting focuses on understanding the costs of running the OR to determine an optimal price for services. Hospital management should use the information that cost accounting provides to plan and control activities, to make strategic decisions, and to improve the quality and efficiency of services in the OR. Box 4-12 contains a list of accounting terms.

It is important to recognize the difference between costs and charges. Costs include all of the fixed and variable expenses associated with a specific procedure. Charges are the sum of all the costs plus the amount of profit over the costs that the hospital bills to insurers. In the 1970s and 1980s, most hospitals used the theory of cost-plus billing. In cost-plus billing, the hospital added an amount of money (profit) to the costs for a procedure. It submitted the resulting charge to insurers. However, as reimbursements declined, insurers began to contract services for a specific price, regardless of the hospital's costs for that service. The ratio of costs to charges varied widely for different services throughout the hospital.[1] For example, the cost-to-charge ratios at Stanford Hospital were 0.29 for anesthesia, 0.50 for laboratory, and 0.92 for the surgery admission unit.[1]

Because of the arbitrary nature of assigning charges to a service, as well as the variable reimbursement, decisions concerning OR management should use costs and not charges. Costs are either fixed or variable. Fixed costs (overhead) are costs that do not change in the short term regardless of the number of completed procedures. In the OR, these costs include rent or depreciation of the surgical suite, capital equipment in the OR, salaried employees, and administrative overhead (OR directors, medical records, admitting personnel). Fixed costs may change over longer periods if the hospital changes the number

BOX 4-12 ***Operating Room Accounting Terminology***

Charges: The fee listed for an item or procedure based on assumptions of resource consumption
Costs: The actual expenses incurred in delivery of a service
Fixed costs: Overhead; costs that do not change up or down over a finite period, regardless of the volume of activity
Variable costs: Costs that change directly up or down with changes in volume of activity
Profit: Revenue–costs (both fixed and variable)
Contribution margin: Revenue–variable costs
Capacity: Maximum amount of activity that a facility can deliver without increasing fixed costs

of OR suites or the budgeted number of OR staff. Variable costs will increase or decrease directly with the level of surgical activity. In the OR, variable costs include disposable supplies, sutures, linens, implants, and contracted labor. Fifty-six percent to 84% of OR costs are fixed.[84] Short- and intermediate-term cost reductions will apply only to the variable portion of OR costs, representing a smaller part of the total OR costs as fixed costs remain unchanged.

The two methods to account for costs in the OR are either top-down or bottom-up. Top-down accounting uses cost-to-charge ratios to average and estimate the costs for a particular procedure. This is an easy and simplified calculation but has critical disadvantages. Top-down accounting is imprecise, and the ratio will vary because of changes in either costs or charges. This makes period-to-period comparisons difficult because it is difficult to isolate whether the cost-to-charge ratio trend is a result of changes in costs, charges, or a combination of both. Bottom-up accounting (microcosting) is more precise, requiring a detailed measurement of all the expenses for a procedure. Bottom-up accounting also requires classifying costs as fixed or variable, which makes decision-making easier in OR planning.

Profit for the OR is equal to the total revenues minus the total costs. The OR must produce profit to pay for other areas within the hospital (e.g., emergency department) that operate at a loss. However, in assessing changes in surgical activity, the "contribution margin" is more important. Contribution margin is equal to the total revenues minus the variable costs. A larger contribution margin indicates that more money is available to pay the overall fixed costs of the institution.

A specific example of OR cost analysis is provided in the 1999 review of costs by Macario.[84] In the review, he found that the majority of costs for care of a patient undergoing laparoscopic cholecystectomy occurred in the OR.[84] The OR (37%), anesthesia (7%), PACU (6%), and OR-related laboratory and pharmacy costs accounted for more than 50% of the total hospital costs. For any OR procedure, most of the costs occur in the first hour of the case. These costs include room preparation, opening basic supplies, linens, and use of instruments or implants for the procedure. Subsequent time in the OR is less expensive and consists primarily of labor costs. Using a detailed analysis, Macario[84] established that the basic costs of an OR, exclusive of procedure-specific needs (e.g., trocars or implants), was $13.54 per minute. Of this amount, 62% of the costs were fixed and 38% were variable. Cost-savings measures (i.e., changing physician practice) will affect only the variable costs of this expense. OR costs vary by institution, depending on labor and overhead costs.[85,86] Ambulatory surgical facilities, with reduced overhead, may have overall OR costs that are 20% less than traditional hospital facilities.

The potential benefit of cost analysis is illustrated by considering the amount of costs that can be reasonably reduced. For example, anesthesia costs, such as machine depreciation, supplies, and drugs, average 6% of the total hospital costs for a procedure.[1] Of these costs, approximately 50% are fixed and 50% are variable. To reduce overall anesthesia costs in the OR, a hospital can only modify the variable part of the anesthesia costs. Therefore, it is only possible to manage 3% of the total hospital costs when reviewing the anesthesia practice for cost savings. The PACU is also an area with high fixed costs—up to 67% of the total PACU costs.[1] For this reason, opportunities for large cost reductions in the PACU by changing practice are difficult.

The largest variable costs associated with health care and the OR are personnel costs.[87] The unpredictable nature of the surgical volume, as well as late-running cases, may lead to increased labor costs. The Fair Labor Standards Act requires overtime wages of 150% of regular wages for hours worked over 40 per week. As a result, personnel costs increase significantly with poorly planned labor use in the OR. Strategies to minimize overtime including using 12-hour shifts, staggering nurse work times, and creating greater scheduling control will help reduce these labor costs. Careful analysis of nursing requirements and the creation of optimal staffing patterns can have a significant impact on OR costs.[88,89]

Studies on the contribution margin of individual surgeons to the hospital have shown that nearly all surgeons have a positive contribution margin.[49,90] However, the difference in the contribution margin between surgeons varies greatly, in some cases by as much as 1000%.[91] To improve profitability for the OR, efforts to increase the volume of highly profitable surgeons will have the greatest impact. However, before assigning more OR time to these surgeons, several questions must be addressed. Will the surgeon's utilization decrease if volume or OR time is increased? Do the surgeon's cases require hospital resources (ICU beds, specialty nursing) that have limited capacity? Does the system have enough overall capacity (OR rooms, nurses, anesthesia coverage) to increase volumes of services and hold fixed costs neutral? If an additional volume of cases requires building more infrastructure (new rooms or more OR nurses), the fixed costs will increase and negate profit. Clear, accurate information is necessary for the OR director to track costs and make rational decisions to improve OR performance.

SUMMARY

Operating rooms are complex environments that are vital to the success of hospitals. Hospitals have reevaluated OR management structures to improve efficiency while emphasizing quality and cost. Redesigning OR governance has been essential in addressing the changes required to make ORs run more effectively. Such redesign has resulted in an increasing trend to place overall responsibility in the hands of a single person, the OR director.

The OR director must understand OR economics and use sound strategies for cost control and revenue enhancement. A comprehensive OR information system that can capture and organize OR data is essential for the OR director. Hospitals set targets for performance, and regulatory organizations set quality measures for the OR. Information systems help monitor whether the OR is meeting these targets and standards. Detailed data are required for instituting a successful business plan for the OR and implementing changes in how the OR functions.

The OR director's position has evolved into a broad and encompassing role as a manager of the perioperative process. The director must focus efforts on ensuring smooth, efficient throughput of patients in the perioperative area. Accurate scheduling, on-time OR starts, efficient turnover, and proper surgical case management are critical to the success of running the surgical schedule. OR directors must develop strategies to manage surgical schedule variability as a result of add-ons, emergency cases, and cancellations. They must also construct systems to control surgical and anesthesia costs. Although the challenges in making an OR function optimally are great, the benefits of an efficient and successful OR are critical to the hospital, to anesthesiologists, and to surgeons who work in this environment.

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APPENDIX 4-1 *Guidelines for the Role of the Clinical Director of Anesthesiology and Director of the Operating Rooms*

I. Responsibilities to the Department of Anesthesiology
  A. Personnel management
    1. Long-term faculty scheduling
    2. Daily faculty/resident/certified registered nurse anesthetist assignments; assurance of comprehensive resident case exposure/coordination with program director
    3. Staffing calculations and planning; recommendations to chairman
    4. Creation of management team representing all clinical aspects of the department
  B. Subspecialty coverage
    1. Develop appropriate faculty daily and on-call coverage
    2. Participate in resident subspecialty rotation development
  C. Daily operations
    1. Early morning review of schedule
    2. Morning clinical/staffing conference
    3. Assignment changes during the day
    4. Chief arbiter of clinical and interstaff disputes
  D. Participative roles (with significant institutional variations)
    1. Preoperative evaluation clinic/preadmission testing procedure
    2. Anesthesia equipment/monitoring
    3. Quality assurance/quality management process
    4. Disaster planning
  E. Evaluation and promotion of the clinical director
    1. Clinical management–oriented job may require special criteria
    2. Clinical tract appointment most appropriate
    3. Teaching time may be limited
    4. Research areas may exist in management and statistical and clinical studies

II. Responsibilities to the OR/Hospital/Medical Staff
  A. Scheduling and data collection
    1. Daily review/final arbiter of OR scheduling
    2. Supervisor of scheduling/data processing personnel
    3. Enforce scheduling policy
    4. Management of OR utilization data and submission of reports to appropriate governing body
  B. Communications center (OR desk)
    1. Establish practices that provide expeditious service
    2. Supervise OR desk personnel
  C. Clinical director's role with OR nurses, PACU nurses, and support staff (with significant institutional variation)
    1. Leadership and supervisory role for OR personnel
    2. Strong working relationship with nursing hierarchy and hospital administration
    3. May function as OR manager with budgetary, materials management, and quality assurance functions
  D. Chief liaison to:
    1. Hospital administration (formal position)
    2. Nursing administration
    3. OR committee (may serve as chairman of the committee); authority must be delegated from surgical and anesthesiology departments and hospital administration
  E. Basic support from hospital administration
    1. Office, secretary, scheduler, and other personnel as necessary
    2. Financial subsidy may be appropriate
    3. Administrative authority

III. General Qualifications
  A. Seniority, appropriate academic rank—associate or professor level may facilitate the role
  B. Clinical proficiency/commitment—being respected for clinical abilities is a significant attribute
  C. Educational qualifications—formal training or experience in negotiation and interpersonal relationships and business administration may be desirable

OR, Operating room; *PACU,* postanesthesia care unit.

APPENDIX 4-2 *Selected Items From the Procedural Times Glossary of the American Association of Clinical Directors*

Room ready: Time when the room is cleaned and supplies and equipment necessary for beginning of next case are present.

Start time: Patient in room time.

Preparation completed: Time at which prepping and draping have been completed and patient is ready for the procedure or surgery to start.

Case time: Time from room setup start to room cleanup finished. This definition includes all the time for which a given procedure requires an OR. It allows for the different duration of room setup and room cleanup times that occur because of the varying supply and equipment needs for a particular procedure.

Turnover time: Time from prior patient out of room to succeeding patient in room for sequentially scheduled cases.

Resource hours: Total number of hours scheduled to be available for performance of procedures (i.e., the sum of all available block time and open time).

Block time: Hours of OR time reserved for a given service or surgeon. Within a defined cutoff period (e.g., 72 hours before day of surgery), this is time into which only the given service may schedule.

Open time: Hours of OR time not reserved for any particular service, into which any service or surgeon may schedule according to the rules established by the given institution.

Raw utilization: For the system as a whole, this is the percent of time that patients are in the room during resource hours. For an individual service, this is the percent of its block time during which it has a patient in the OR.

Adjusted percentage: (In-own block hours + Outside-own block hours × 100 per block time)

Service utilization: This measures the percentage of time a service uses its block time during resource hours. It is adjusted compared with raw utilization, in that it gives a service "credit" for the time necessary to set up and clean up a room, during which time a patient cannot be in the room. It may exceed 100% because of the inclusion of cases performed during resource hours that are outside-own block hours.

OR, Operating room.

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Chapter 5

Medical Informatics

C. WILLIAM HANSON

Key Points

- A computer's hardware serves many of the same functions as those of the human nervous system, with a processor acting as the brain and buses acting as conducting pathways, as well as memory and communication devices. Clinical information systems and most medical devices have computers as a core component of the instrumentation.
- The computer's operating system serves as the interface or translator between its hardware and the software programs that run on it, such as the browser, word processor, and e-mail programs. The software used to support medical informatics allows the computers to manage information for clinical uses, including manipulating the data to optimize patient care and communication among providers.
- The hospital information system includes a network of interfaced subsystems, both hardware and software, that are integrated to serve the multiple computing requirements of a hospital or health system, including business services (scheduling, admissions, discharge, and financial transactions) and clinical services (electronic health record [EHR], order entry systems, laboratory and radiology studies, and other clinical information).
- An EHR is a computerized record of patient care that gives a comprehensive overview of all clinical problems and their management and medical reconciliation, and it replaces the traditional paper record.
- Computerized provider order entry (CPOE) systems are designed to minimize errors in ordering, increase patient care efficiency, and provide decision support at the point of entry. CPOE systems ensure that the care provided to the patient is safe and takes into account underlying medical conditions, minimizes the likelihood of duplicate ordering, addresses incompatibilities of medications, and reduces redundancies.
- Decision support systems (DSSs) can give health care providers descriptions of current clinical practices, disseminate best-practice protocols, and provide up-to-date information on diseases and their management. DSSs also can be used to act or to automatically intervene in patient care when appropriate and assist patients in managing their clinical problems.
- The *Health Insurance Portability and Accountability Act* is a comprehensive piece of legislation designed in part to enhance the privacy and security of computerized patient information. The *Health Information Technology for Economic and Clinical Health Act* enacted as part of the *American Recovery and Reinvestment Act* of 2009 is designed to promote the adoption and meaningful use of health information technology. It also addresses the privacy and security concerns associated with the electronic transmission of health information. Because this legislation addresses important issues in the management of clinical information, all clinicians must understand it to minimize risks associated with electronic communication between health care providers and patients.
- Using electronic health records and telecommunication technologies, health care providers are increasingly able to communicate with and care for patients remotely via the Internet. Telehealth strategies are being implemented to improve access to specialty care and optimize clinical care to underserved populations. Advances in technology, improved patient access, and new payment methodologies will be required to take full advantage of telehealth capabilities, and telemedicine will continue to grow as technology improves, reimbursement becomes available, and legislation evolves.

COMPUTER HARDWARE

CENTRAL PROCESSING UNIT

The central processing unit (CPU) represents the "brain" of a modern computer. It sits on the motherboard, which is the computer's skeleton and nervous system, and communicates with the rest of the computer and the surrounding world through a variety of "peripherals." Information travels through the computer on "buses," which are the computer's information highways or "nerves," in the form of "bits." Bits are aggregated into meaningful information in exactly the same way that dots and dashes are used in Morse code. Bits are the building blocks for both the instructions, or programs, and the data, or files, with which the computer works.

Today's CPU is a remarkable piece of engineering, totally comparable in scope and scale to our great bridges and buildings but so ubiquitous and hidden that most of us are unaware of its miniature magnificence. Chip designers essentially create what can be thought of as a city, complete with transportation, utilities, housing, and a government, every time they create a new CPU. With each new generation of chips, the "cities" grow substantially, yet their size remains miniaturized.

For the purposes of this text, the CPU can be treated as a black box into which flow two highways: one for data and the other for instructions. Inside that black box, the CPU (Fig. 5-1) uses the instructions to determine what to do with data—for example, how to create this sentence from interaction with the computer's keyboard. The CPU's internal clock is like a metronome, pacing the speed with which the instructions are executed.

The speed with which a computer processes information is critically important, particularly when used in the clinical setting. Clinicians expect an "immediate" response to every interaction with the computer, keyboard, or instrumentation. Most people think that the clock speed of the CPU, which is measured in megahertz (MHz) and gigahertz (GHz), or millions and billions of instructions per second, determines the performance speed of the unit. In reality, the performance of a CPU is a function of several factors that should be familiar to the anesthesia provider when an operating room analogy is used. Let us first compare the clock speed of the computer to surgical speed, with a fast clock comparable to a fast surgeon and vice versa. Second, similar to operating rooms, CPUs have what are called caches, which are holding areas for data and instructions, quite comparable to preoperative holding areas. Information is moved around in the CPU on buses, which can be likened to the number of operating rooms. In other words, it is possible to have a CPU that is limited because it has a slow or small cache, in the same way that operating room turnover is limited by the lack of preoperative preparation beds or too few operating rooms for the desired caseload.

The speed of a processor is a function of the width of its internal buses, clock speed, the size and speed of internal caches, and the effectiveness with which it anticipates the future. Although this last concept may seem obscure, an operating room analogy would be an algorithm that predicts a procedure's length based on previous operations of the same type by the same surgeon. Without going into detail, modern processors use techniques termed *speculation, prediction,* and *explicit parallelism* to maximize efficiency of the CPU.

True general-purpose computers are distinct from their predecessor calculating machines in that, regardless of whether they are relatively slow and small, as in dedicated devices such as smart phones, or highly streamlined and fast, as in supercomputers, they can perform the same tasks given enough sufficient time. This definition was actually formalized by Alan Turing, who is one of the fathers of computing.

Each type of CPU has its own instruction set, which is essentially its language. Families of CPUs, such as Intel's processors, tend to use one common language, albeit with several dialects, depending on the specific chip. Other CPU families use a very different language. A complex instruction–set computer has a much more lush vocabulary than a reduced instruction–set computer, but the latter may have certain efficiencies relative to the former. It is the fact that both types of computer architecture can run exactly the same program (i.e., any windowed operating system) that makes them general-purpose computers.

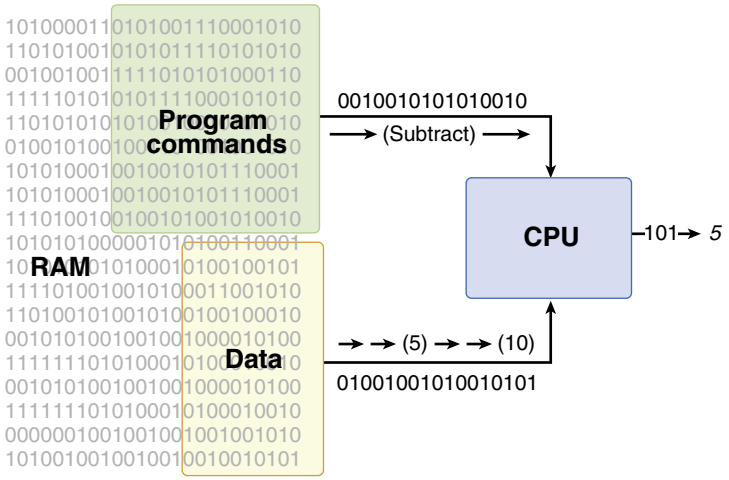


Figure 5-1. Programs and data are stored side by side in memory in the form of single data bits. The program tells the central processing unit (*CPU*) what to do with the data. *RAM,* Random-access memory.

MEMORY

Memory is the method by which the computer stores information and allows the user to retrieve the data needed to perform a task or complete an interaction. Computers have a variety of different kinds of memory, ranging from very small, very fast memory in the CPU to much slower, typically much larger memory storage sites that may be fixed (hard disk) or removable (compact disk, flash drive).

For clinical purposes, we would like to have an infinite amount of extremely fast memory immediately available to the CPU, just as we would like to have all of the operating room patients for a given day waiting in the holding area ready to roll into the operating room as soon as the previous case is completed. Unfortunately, this would be infinitely too costly and probably would never completely achieve the desired goals. The issue of ready data availability is particularly important now—as opposed to a decade ago—because improvements in central processing speed have outpaced gains in memory speed such that the CPU can sit idle for extended periods while it waits for a desired chunk of data from memory.

Computer designers have come up with an approach that ensures a high likelihood that the desired data can be easily retrieved. This necessitates the storage of redundant copies of the same data in multiple locations at the same time. For example, the sentence I am currently editing in a document might be stored in very fast memory next to the CPU, whereas a version of the complete document, including an older copy of the same sentence, could be stored in slower, larger capacity memory (Fig. 5-2). At the conclusion of an editing session, the two versions are reconciled and the newer sentence is inserted into the document.

The very fast memory adjacent to the CPU is referred to as cache memory, and it comes in different sizes and speeds. Cache memory is analogous to the preoperative and postoperative holding areas in an operating suite in that both represent rapidly accessible buffer space. Modern computer architectures have primary and secondary caches that can either be built into the CPU chip or be situated adjacent to it on the motherboard. Cache memory is typically implemented in static random-access memory (SRAM), whereas the larger and slower "main memory" consists of dynamic random-access memory (DRAM) modules. RAM has several characteristics, including the fact that it can be read or written (in contrast with read-only memory), it disappears when the electricity is turned off, and it is much faster than the memory on a disk drive.

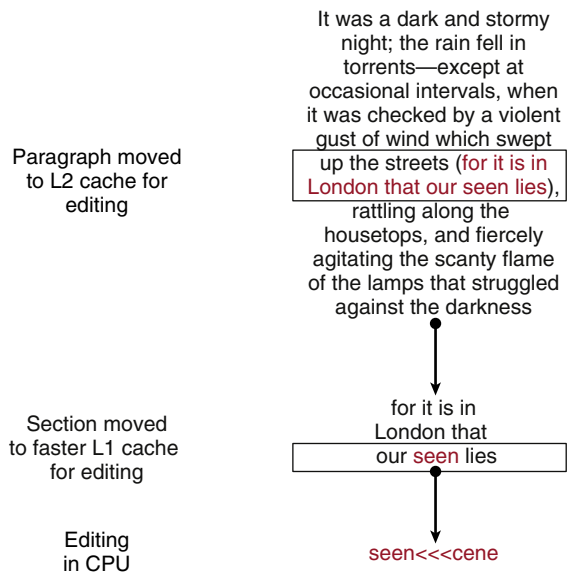


Figure 5-2. Processing of text editing using several "memory" caches in which duplicate copies of the same text may be kept nearby for ready access. *CPU,* Central processing unit.

To understand the impact of the mismatch in memory access times and CPU speed, consider the following. Today's fastest hard disks have access times measuring about 10 msec (to get a random chunk of information). If a 200-mHz CPU had to wait for 10 msec between each action requiring new data from a hard disk, it would sit idle for 2 *million* clock cycles between each clock cycle used for actual work. Furthermore, it takes 10 times longer for the computer to get data from a compact disk or digital video disk than it does for data from a hard disk.

COMMUNICATIONS

The many functionally independent parts of a computer need to communicate seamlessly and rapidly. The keyboard and mouse have to be able to signal their actions, the monitor must be refreshed continuously, and the memory stores have to be read and written correctly. The CPU orchestrates all of this by using various system *buses* as communication and data pathways. Some of the buses are dedicated to specific tasks on newer computers, such as communication with the video processor over a dedicated video bus, and others are general-purpose buses.

Buses are analogous to highways traveling between locations in the computer (Fig. 5-3). In most computers, the buses vary in width, with the main bus typically being the widest and other buses narrower and therefore of lower capacity. Data (bits) travel along a bus in parallel, like a rank of soldiers, and at regular intervals determined by the clock speed of the computer. Older computers had main buses 4 or 8 bits wide, whereas newer Pentium-class computers use buses as wide as 64 or 128 bits. Many current-generation computers actually have multicore processors, in which multiple CPUs collaborate, operating on complex problems in parallel.

Input-output buses link peripheral devices such as the mouse, keyboard, removable disk drives, and game controllers to the rest of the computer. These buses have become faster and increasingly standardized. The universal serial bus (USB) is a widely accepted standard, as is Apple's proprietary FireWire bus. These buses allow "on-the-fly" attachment and removal of peripherals by a standardized plug, and a user can expect that a device plugged into one of these ports will identify itself to the operating system and function without the need for specific configuration. This is a distinct improvement over the previous paradigm, in which a user typically needed to open the housing of the computer to attach a new peripheral and then configure a specific software driver to permit communication between the device and the computer.

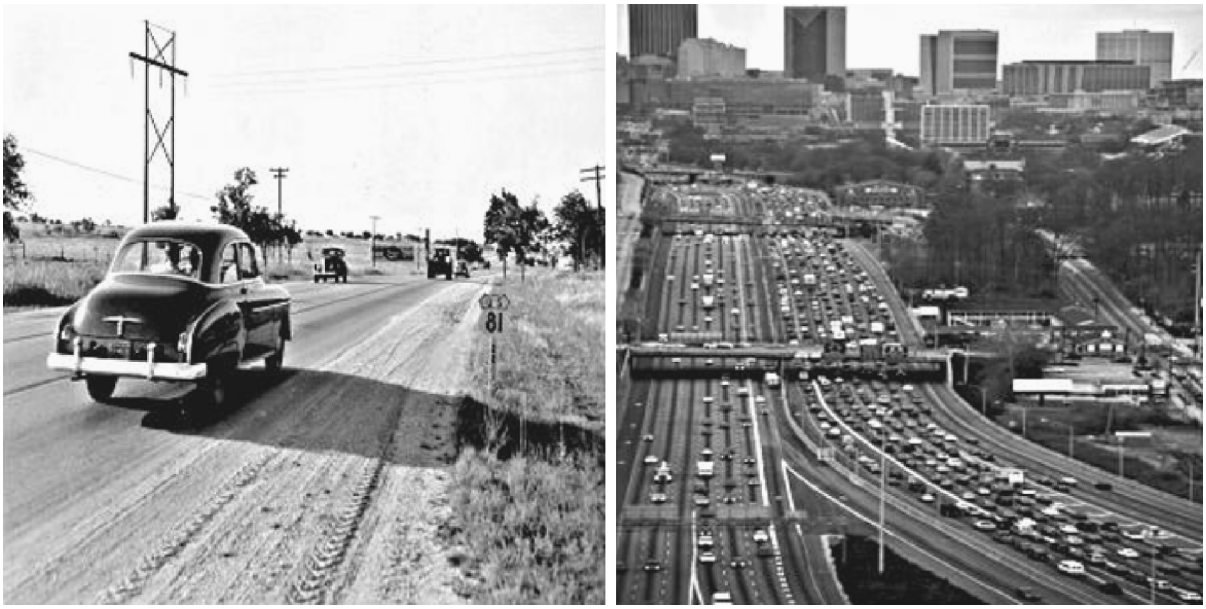


Figure 5-3. Buses are like highways, where the number of available "lanes" relates to bus capacity.

In addition to their local computing function, modern personal computers have become our conduits to networks and must therefore act as terminal points on the Internet. As with houses or phones, each computer must have an individual identifier (address, phone number) to receive communications uniquely intended for it. Examples of these kinds of specific addresses are the Internet protocol (IP) address and the media access control (MAC) address. The IP address is temporarily or permanently assigned to a device on the Internet (typically a computer) to uniquely identify it among all of the other devices on the Internet. The MAC address is used to specifically identify the network interface card for the computers that assign IP addresses.

The computer must also have the right kind of hardware to receive and interpret Internet-based communications. Wired and wireless network interface cards are built into all new computers and have largely replaced modems as the hardware typically used for network communications. Whereas a modem communicates over existing phone lines also used for voice communication, network cards communicate over channels specifically intended for computer-to-computer communications and are almost invariably faster than modems.

Although we commonly think of the Internet as being one big network, it is instructive to understand a little bit about the history of computer networking. In the beginning there were two independent types of networks: the office networks and the progenitor Internet. The first office network was designed at the Palo Alto Research Center, which is the Xerox research laboratory where some of the major computer innovations were developed. That office network was called Ethernet and was designed as part of the "office of the future," where word-processing devices and printers were cabled together. Separately, the ARPAnet was the Defense Advanced Research Project Agency's creation and linked mainframe computers at major universities. Over time, the two networks grew toward one another almost organically, and today we have what seems to be a seamless network that links computers all over—and above—the world.

Networking technology has evolved almost as rapidly as computer technology. As with buses in a computer, the networks that serve the world can be likened to highways. Backbone networks (Fig. 5-4) are strung across the world and have tremendous capacity, like interstate highways. Lower-capacity systems feed into the backbones, and traffic is directed by router computers. Before transmission, to facilitate traffic management, messages are cut into discrete packets, which travel autonomously to their destination and are there reassembled. Internet packets may travel over hard-wired, optical, or wireless networks en route to their destination.

COMPUTER SOFTWARE

OPERATING SYSTEM AND PROGRAMMING

The operating system (OS) is the "government" of the computer. As with a municipal government, the OS is responsible for coordinating the actions of disparate components of a computer, including its hardware and various software programs, to ensure the computer runs smoothly. Specifically, it controls the CPU, memory, interface devices, and all the programs running on the machine at any given time. The OS also needs to provide a consistent set of rules and regulations that new programs must adhere to if they are to participate.

Although most of us think of Apple and Windows synonymously with OSs, other OSs deserve mention. Linux is an open-source, meaning nonproprietary, OS for personal computers that is distributed by several vendors and is continuously maintained by a huge community of passionate programmer devotees who contribute updates and new programs. In addition, every cell phone, tablet, and smart device has its own OS that performs exactly the same role as a personal computer OS.

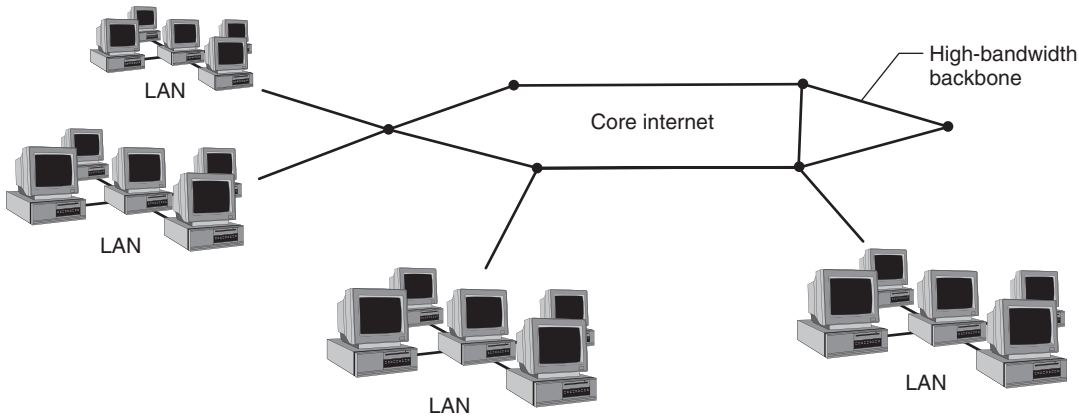


Figure 5-4. Lower-speed networks are attached to high-speed "core" networks that span the globe. *LAN,* Local area network.

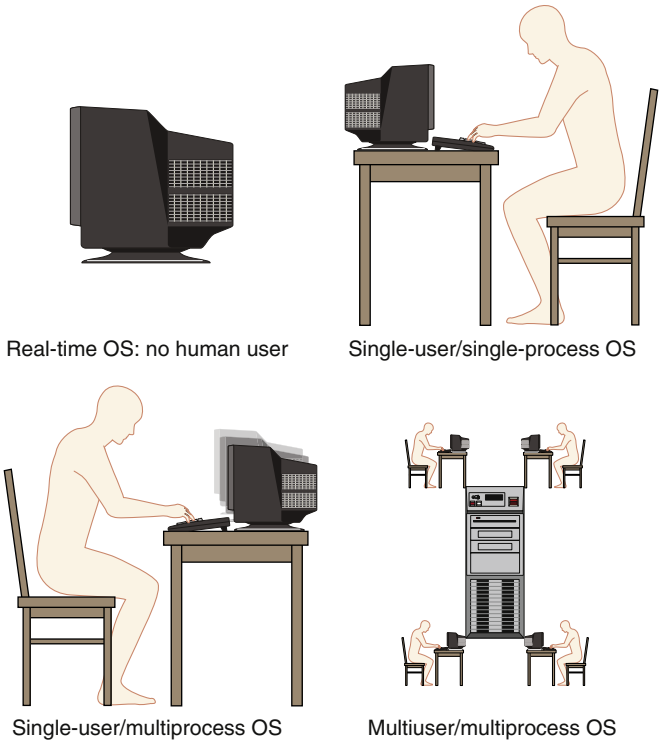


Figure 5-5. Several operating system (*OS*) configurations.

OSs can be categorized into four broad categories (Fig. 5-5). A real-time OS is typically used to run a specific piece of machinery, such as a scientific instrument, and is dedicated solely to that task. A single-user, single-task OS is like that found on a cell phone, where a single user does one job at a time, such as dialing, browsing, or e-mail. Most of today's laptop, desktop, and tablet computers are equipped with single-user, multitasking OSs, whereby a single user can run several "jobs" simultaneously, such as word processing, e-mail, and a browser. Finally, multiuser, multitasking OSs are usually found on mainframe computers and run many jobs for many users concurrently.

All OSs have a similar core set of job tasks—CPU management, memory management, storage management, device management, application interfacing, and user interfacing. Without getting into detail beyond the scope of this chapter, the OS breaks a given software job down into manageable chunks and orders them for sequential assignment to the CPU. The OS also coordinates the flow of data among the various internal memory stores, determines where that data will be stored for the long term, and keeps track of it from session to session. The OS provides a consistent interface for applications so that the third-party program purchased at a store will work properly on a given OS.

Finally, and of most importance for many of us, the OS manages its interface to you, the user. Typically, today that takes the form of a graphic user interface (GUI).

E-MAIL

E-mail communication over the Internet antedated the browser-based World Wide Web by decades. In fact, the earliest e-mail was designed for communication among multiple users in a "time-sharing," multiuser environment on a mainframe computer. E-mail was used for informal and academic communications among the largely university-based user community. Without going into great detail, an e-mail communication protocol was designed so that each message included information about the sender, the addressee, and the body of the message. The protocol is called the Simple Mail Transfer Protocol (SMTP), and the process of message transmission proceeds as follows. The sender composes a message using a software-based messaging program (such as Outlook, Gmail). The sender then applies the recipient's address and dispatches the message. The message travels through a series of mailboxes, much as a regular letter does, and eventually arrives at the addressee's mailbox, where it sits awaiting "pickup."

Although e-mail has had dramatic and largely positive implications for the connectedness of organizations and people, it also has created previously unimagined problems, including spam, privacy issues, and the need for new forms of etiquette.

The term *spam* is said to have come from a Monty Python skit. Spam is such a ubiquitous problem that most e-mail crossing the Internet is spam at this point. Spam is essentially bulk e-mail and was never envisioned by the creators of SMTP. Spam is a generic problem with e-mail communications, but the issues of privacy and etiquette are of much greater relevance for medically oriented e-mail.

The American Medical Informatics Association has taken a lead role in defining the issues associated with e-mail in the medical setting. The organization defined patient–provider e-mail as "computer based communication between clinicians and patients within a contractual relationship in which the health care provider has taken on an explicit measure of responsibility for the client's care."[1] A parallel set of issues relates to medically oriented communications between providers.[2-5] Another category of medically oriented communications is that in which a provider offers medical advice in the absence of a "contractual relationship." An egregious example of the latter is the prescription of erectile dysfunction remedies by physicians who review a web-based form submitted by the "patient" and then prescribe a treatment for a fee.

In theory, e-mail is a perfect way to communicate with patients.[6-9] Because of its asynchronous nature, it allows two parties who may not be available at the same time to communicate efficiently (Fig. 5-6), and it represents the middle road between two other types of asynchronous communication: voice mail and traditional mail. E-mail also can be tailored to brief exchanges, more structured communications, and information broadcasts (such as announcements). Thus, a patient could send interval updates (blood pressure, blood sugar) to the physician. Alternatively, the physician could follow up on an office visit by providing educational material about a newly diagnosed condition or planned procedure.

Even though e-mail has many advantages in medicine, a variety of risks are associated with its use.[10] Some of the problems are generic to any e-mail exchange. Specifically, it is a more informal and often unfiltered form of communication than a letter and often has the immediacy of a conversation but lacks its visual and verbal cues. Emoticons (such as the use of ":)" to indicate that a comment was sent with a "smile") evolved as a remedy for this problem.

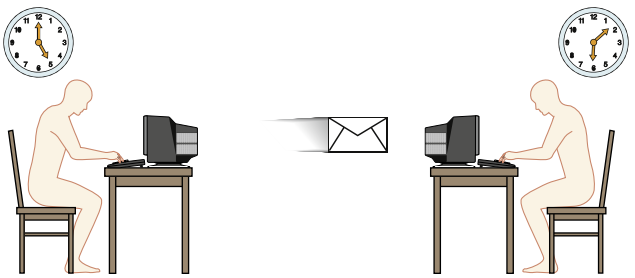


Figure 5-6. E-mail is an effective form of communication between a patient and a physician because it does not require both parties to be present at the same time.

E-mail is also permanent in the sense that copies of it remain in mailbox backups even after deletion from local files (Fig. 5-7). Every e-mail should therefore be thought of as discoverable from both a liability and recoverability standpoint. Before dispatching, e-mail should be scrutinized for information or content that might be regretted at a later date.

Perhaps of greatest significance for communication between patients and health care providers is the lack of security of personal health information. E-mail is vulnerable to inadvertent or malicious breaches in privacy or disclosure through improper handling of data at any point along the "chain of custody" between the sender and the recipient. Alternatively, a hacker could potentially acquire sensitive medical information from unsecured e-mail or possibly even alter medical advice and test results in an e-mail from physician to patient.

The HIPAA legislation mandates secure electronic communication in correspondence regarding patient care. Three prerequisites for secure communication include authentication (that the message sender and recipient are who they say they are), encryption (that the message arrived unread and has not been tampered with), and time-date stamping (that the message was sent at a verifiable time and date), although these techniques are not yet widely deployed in the medical community.

It is beyond the scope of this chapter to go into great detail about the methods used to authenticate, encrypt, and time-date stamp e-mail. However, these elements can be ensured by using mathematically linked pairs of numbers (keys), in which an individual's public key is published and freely available through a central registry (like a phone book) whereas a linked private key is kept secret (Fig. 5-8). Public key encryption combined with traditional encryption is used to transmit messages securely across public networks, ensure that messages can be read only by a specific individual, and digitally sign the message.

Although the use of e-mail for medical patient–provider and provider–provider communications is growing, it is not yet universally adopted for several reasons, including physician distrust of the medium, unfamiliarity with software, lack of standards, and lack of clear methods for reimbursement for time spent in e-mail communications. Nevertheless, several professional societies have published

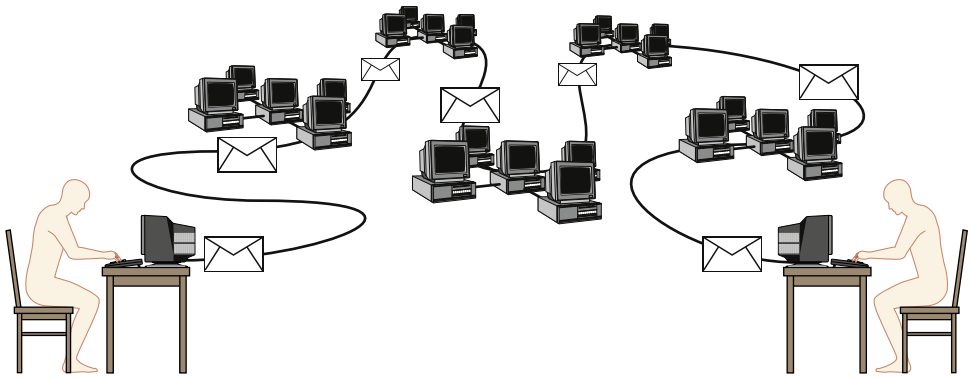


Figure 5-7. E-mail leaves copies of itself as it travels across the Internet.

consensus recommendations about the management of e-mail in medical practice. Common consensus-based elements are enumerated in Box 5-1. Even when these security measures are adopted, e-mail is probably not the best way to communicate with patients. Most importantly, if e-mail is used, the e-mail system must be encrypted to minimize the risk for inappropriate access by others. It is difficult for an individual provider to be sure a patient's e-mail is encrypted. In addition, although the information in e-mail accounts is "saved," it does not become a part of the permanent medical record. As a result, communication through e-mail creates risks related to documentation of the communication, assurance that information has been received, and, to the extent needed, confirmation that appropriate follow-up actions have been taken. Most electronic health records (EHRs) now allow the option of communicating directly through the EHR—providing documentation of the communication, allowing access to laboratory and other test results, and fostering follow-up communication between patients and their providers. This type of secure communication can be very effective in facilitating patient care and follow-up, although electronic communication may not always adequately address high-risk patient needs.[11]

BROWSER

Many people think of the Internet and the World Wide Web as one and the same. The Internet is the worldwide network, whereas the Web is one of its applications characterized by the browsers with which its users interact. The browser was invented in 1990 by Tim Berners-Lee at the European Organization for Nuclear Research, commonly known as CERN. Marc Andreessen wrote the Mosaic browser and subsequently the Netscape browser, which, like all subsequent browsers, has a GUI and uses a specific "language" called hypertext markup language (HTML). Microsoft eventually developed its own version of the browser, Internet Explorer, after recognizing the critical value of the Web.

The browser is a computer program, just like a word-processing or e-mail program, with a GUI. It can be thought of as a radio or television insofar as it serves as an interface to media that do not originate within it. The address of a webpage is analogous to the channel or frequency of a television or radio, and the browser "tunes in" to that address. In actuality, the local browser on your computer communicates with a server somewhere on the Internet (at the address specified in the address line) and uses the communication protocol HTML as its language. The webpage displayed on your local browser was first constructed on the server and then sent to you.

The original HTML was extremely spare and had significant limitations, such as the construction of only very simple webpages. A variety of new "languages" and protocols have subsequently come into existence, such as Java, JavaScript, ActiveX, Flash, and others, that allow enhancements to HTML. New browsers support interactivity, security, display of audio and video content, and other functions. Even though the scope of topics that could be covered in discussing browser communications far exceeds that of this chapter, certain issues deserve mention.

Cookies is the term used for short lines of text that an Internet server (such as Google or Yahoo) can store on a user's hard disk. Cookies allow a website to store information about the client computers with which it interacts. Cookies allow the server to keep track, for example, of the items that you have put in your virtual shopping cart as you shop (Fig. 5-9). Although cookies are not inherently risky, other risks exist to the use of a browser.

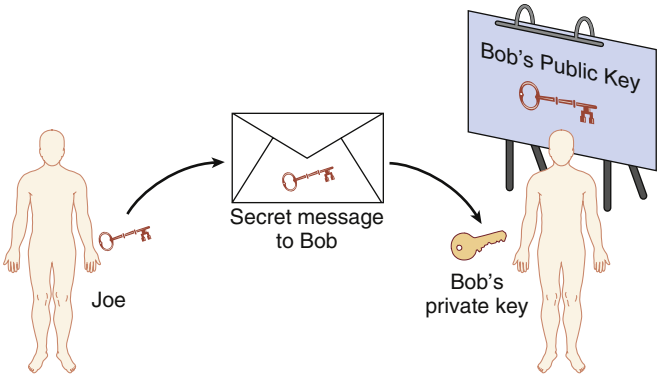


Figure 5-8. Public and private key encryption in which Joe sends a message intended only for Bob by using Bob's public key—the message remains encrypted until Bob decrypts it with his private key.

BOX 5-1 ***Suggested Rules for E-mail Correspondence in a Medical Setting***

All patient–provider e-mail should be encrypted.
Correspondents should be authenticated (guarantee you are who you say you are).
Patient confidentiality should be protected.
Unauthorized access to e-mail (electronic or paper) should be prevented.
The patient should provide informed consent regarding the scope and nature of electronic communications.
Electronic communications should (ideally) occur in the context of a preexisting physician–patient relationship.
Online communications are to be considered a part of the patient's medical record and should be included with the same.

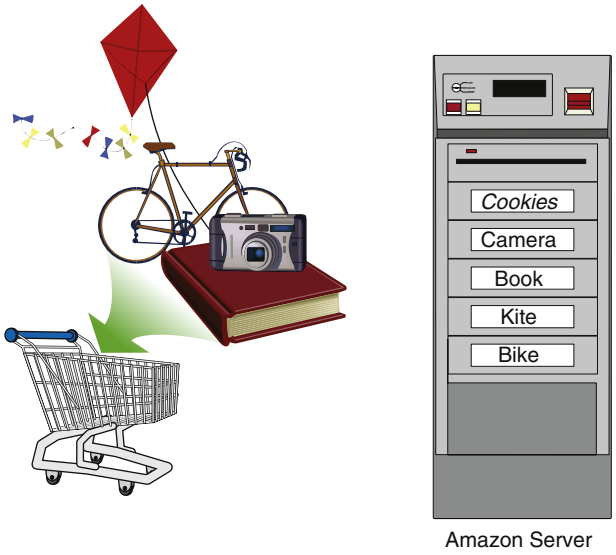


Figure 5-9. Cookies are used by a website, for example, to keep track of the items that a user has put in the "shopping cart."

Like a television, the browser acts like a window on the Internet, and for a long time it was safe to think of that window as being made of one-way glass. Unfortunately, many of the new innovations that allow us to function interactively with websites also have built-in flaws that permit malicious programmers to gain access to your computer or to track movements from website to website. Companies such as Google and Facebook can now develop highly detailed profiles of individuals and populations from their interactions with the network. The best way to protect a computer involves timely application of all updates and patches issued by software manufacturers and the use of antivirus software with up-to-date definitions. The best way to preserve privacy is to minimize the amount of personal information stored on the Internet and use independent passwords for each site that are not easy to hack.

COMPUTERS AND COMPUTING IN MEDICINE

HOSPITAL INFORMATION SYSTEMS

Modern hospital information systems invariably fall somewhere on the spectrum between a monolithic single comprehensive system design, in which a single vendor provides all of the components of the system, and a "best-in-breed" model consisting of multiple vendor-specific systems interacting through interfaces or, more typically, an interface "engine."[12-15] The monolithic system has the advantage of smooth interoperability, but some of the component elements may be substantially inferior to those offered by best-in-breed vendors.

Component elements of a hospital information system include administrative, clinical, documentation, billing, and business systems.[16-18] Medical information technology is increasingly subject to governmental regulation, security concerns, and standards. Standards are essential for interoperability among systems and to ensure that systems use uniform terminology.[19]

Health Level 7 (HL7) is an accepted set of rules and protocols for communication among medical devices. Clinical Context Management Specification (also known as CCOW) is a method to enable end users to seamlessly view results from disparate "back-end" clinical systems as though they were integrated. Some of the common medical terminologies or vocabularies include the Systematized Nomenclature of Medicine (SNOMED) and the International Classification of Diseases (the ICD family of classifications).[20] Modern complicated medical information systems often weave a host of disparate systems at geographically dispersed locations into an extended "intranet." A core hospital, for example, may share an intranet with a geographically remote outpatient practice, or several hospitals in the same health system may coexist within the same intranet. Some of the elements may be physically connected (Fig. 5-10) along a network "backbone," whereas others may use virtual private network (VPN) connections that allow the user to appear to be part of the network while at a remote location.[17]

ELECTRONIC HEALTH RECORD

The electronic record (see also Chapter 4) has been described variously as a computerized medical record, computerized patient record, electronic medical record, and EHR.[21-24] Various settings clearly require radically different EHRs, and EHRs need to interface seamlessly.[25,26]

Historically, patient records have been controlled or "owned" by hospitals and doctor's practices, and their electronic manifestation in the form of the EHR creates a series of issues pertaining to privacy, security, and economic interests of the involved parties. For example, patients have an interest in the privacy and security of the information contained in their records and claim some ownership and control over what is recorded in the medical record. In contrast, doctors have traditionally "owned" their patients' records and transferred patient records to another provider in the course of the sale of a medical practice (albeit with appropriate notice to the involved patients). Most importantly, hospitals and health systems

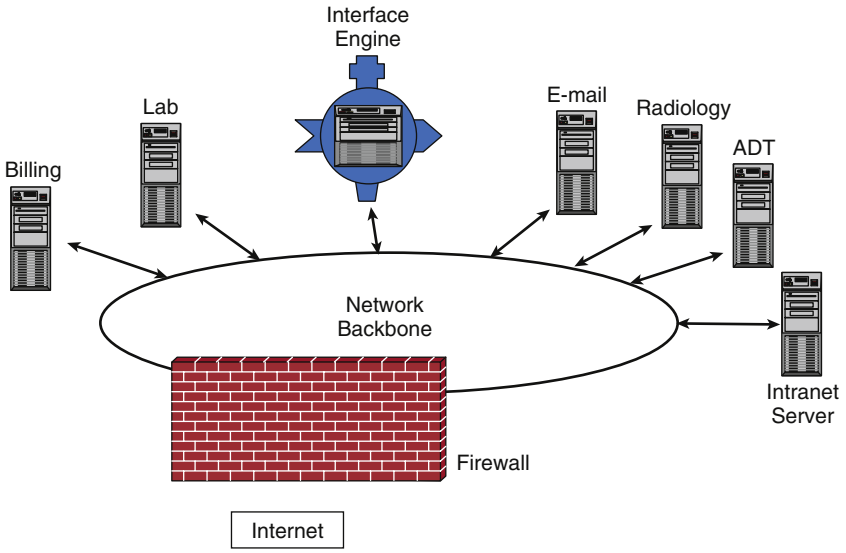


Figure 5-10. Modern health care information systems consist of elements attached to a backbone. *ADT,* Admission, discharge, and transfer; *Lab,* laboratory.

have historically exercised significant controls over the records and access rights to medical records. The transition to the electronic record, interoperability between health systems and physician practices, and improved communication with patients has significantly changed the concept of medical record ownership. The Centers for Medicare & Medicaid Services (CMS) meaningful use regulations have also focused attention on the issue of ownership of health information and are designed to enhance the patient's access to discharge summaries. The patient has the right to challenge information in the medical record, and the health care provider is obligated to respond to the request, either by modifying incomplete or inaccurate information or by including the patient's statement of disagreement in the record. After each visit the provider is required to give each patient access to the discharge summary, including information about the evaluation, care provided, and reconciliation of all medications. This increased access puts greater responsibility on the patient to "manage" their health information, ensure its accuracy, and exert control on accessibility by others.

The current evolution of software-based EHRs is recapitulating the evolution of hospital information systems as it occurred over the 1980s and 1990s—in both cases, specialized individual systems have contended with integrated packages of modules. Best-in-breed commercial systems or "home-grown" site-specific systems are evolving, such as automated anesthesia EHRs[27,28] and intensive care unit (ICU) EHRs (Fig. 5-11). At the same time, large vendors have developed generic inpatient and outpatient EHRs. Health systems face the same choices about whether to go with monolithic or best-in-breed EHR software that they have with clinical systems.

The Institute of Medicine issued a report characterizing key aspects of an EHR, including an integrated, longitudinal view of patient data; concurrent access to the body of knowledge pertaining both to the patient's condition and to the rules and regulations associated with reimbursement in this age of managed care; order and data entry; and decision support tools that provide current knowledge about diseases, treatments, drug interactions, and risk profiles.

Ideally, the electronic record provides tools for communication among providers. The EHR also should provide immediate access to population-level information for administrative and research applications.

The U.S. Veterans Health Administration is an example of a very successful EHR implementation; however, in most hospitals, orders, notes, and reports are still maintained on paper. Additionally, very few small-practice environments have undergone any degree of computerization, because the barriers to computerization are formidable.

Technical obstacles to computerization of the medical record are relatively obvious, but organizational, financial, and policy obstacles also exist.[29-31] Adoption of an EHR implies a fundamental reorganization of the way medicine is practiced in a clinical environment.[32,33] For example, many older physicians have had little occasion to use a computer and are likely to be slowed in their performance of formerly routine tasks, which is a major barrier at a time when demands for efficiency are increasing substantially (Fig. 5-12).

Despite the barriers, governmental and private stakeholders are developing incentives, bonuses, and low-cost capital to encourage use of the EHR. Providers may eventually mandate EHR systems as a condition of participation in certain U.S. insurance plans, such as Medicare. *American Recovery and Reinvestment Act* of 2009 provided 19 billion dollars for health information technology (HIT), and specifically supported a plan of incentives for the adoption of certified EHRs by hospitals and providers. Specifically, to receive an EHR incentive payment, the hospital or provider must show that they are "meaningfully using" EHRs by meeting thresholds for discrete objectives as defined by the CMS. The meaningful use EHR incentive program has been designed with progressively more rigorous stages. Stage 1 concluded in 2012 with 50% of providers and 82% of hospitals adopting EHRs—a substantial improvement over the preceding era. Stages 2 and 3 are scheduled for 2014 and 2016, respectively. These stages put increasing emphasis on the use of the information included in the integrated health record to improve patient quality and safety.

The EHR was originally designed to digitize the information in the medical record and improve access to it. In addition the EHR was meant to improve patient care by reducing redundancies and errors in management that resulted from a lack of coordination of care. Although these values are significant, the transition to a comprehensive health record that includes documentation of ambulatory and inpatient care provides other important enhancements to both individual patient care and the care of patient populations. The shift to electronic records has led to follow-on opportunities, such as enhanced patient care delivery, improved efficiency,

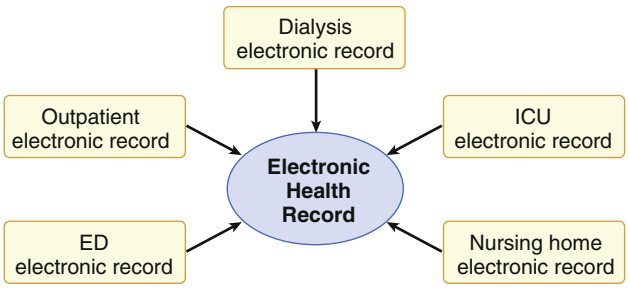


Figure 5-11. Vendors have developed specialty electronic health records. *ED,* Emergency department; *ICU,* intensive care unit.

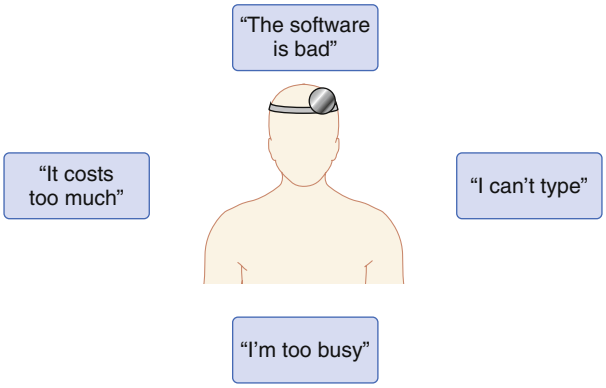


Figure 5-12. Various barriers to adoption of electronic health records.

reduced redundancy in the processing of ancillary support services (e.g., laboratory, radiology, housekeeping, transport), and automation of many administrative functions (e.g., billing and reimbursement). The EHR also has been used as a vehicle to improve communication among providers and patients and foster education, provider regulation, clinical and translational research, public health, and health policy support (Fig. 5-13).

The core functions of EHRs fall into eight general categories: (1) Management of patient health information and data; (2) presentation of results acquired from patient testing; (3) computerized order entry (CPOE); (4) decision support, whereby automatically generated reminders and prompts are used to guide clinicians and support evidence-based practice; (5) communication tools for provider to provider or provider to patient messaging that automatically generate patient support materials such as pamphlets that describe a disease or give discharge directions; (6) integrated administrative processes, including scheduling systems, billing management, and insurance validation; and (7) and (8) internal and external reporting requirements are simplified by using the systems built into the EHRs.

Although stand-alone anesthesia information management systems (AIMS) have been in existence for well over a decade, these products have historically functioned in isolation—that is, unintegrated with electronic inpatient or outpatient records. However, with the increased adoption of both inpatient and outpatient EHRs, spurred by federal incentives, desire is growing in the anesthesia community to deploy AIMS that can interface with or be integrated with clinical and billing software (e.g., KLAS report).

The selection of an AIMS involves trade-offs between a best-of-breed versus an enterprise model and the accompanying differences in functionality and integration, also taking into consideration the needs of the anesthesia department versus those of the hospital. Some of the factors that must be considered include the ease of access to preoperative information, which is often entered electronically into another system or module, the ease of intraoperative use, and the integration with devices in the operating room and with other systems such as the laboratory, and the facility with which information can be transferred to the receiving team at the conclusion of the procedure. As electronic records have matured, the needs of the hospital and the anesthesia community relative to interoperability (KLAS) and quality of care are increasingly convergent.[33a] Hospitals and practitioners are increasingly at risk financially and in the eyes of the public and must have access to published quality data for measures such as those targeted by the Surgical Care Improvement Project (SCIP), a national consortium of quality organizations. Anesthesiologists play a critical role in compliance with these measures, and AIMS are a tool by which compliance can be recorded and tracked.

AIMS are increasingly embedded into the more general hospital EHR, permitting information transparency as patients move through an operative encounter. As with the ICU, which is a similarly high-tech, data-rich environment, automated data capture from physiologic monitors and devices such as infusion pumps is highly desirable—freeing the hands and time of providers from transcription, but data entering the record requires validation to prevent the inclusion of inaccurate information in the chart. Inaccurate information may be recorded or transmitted during the course of normal care, such as artifactually elevated blood pressure during the process of flushing a transducer or moving a patient from one position to another. Most ICU systems mandate validation of vital signs, for instance, before they become official entries, whereas most AIMS allow the clinician to edit (albeit with an audit trail) individual data elements but do not require validation.

The concept of a universal medical record also deserves specific attention. It has always been desirable for providers in one location to have access to data from a medical record generated at another location. Although many potential models exist of a universal medical record, such as a record owned and kept by the patient on a piece of hardware such as a flash drive, this approach has a variety of problems; patients may not be able to or wish to maintain such a record, it is unclear how information would be securely ported from a provider to the patient's medical repository, and hardware devices such as a USB are susceptible to loss. Google and Microsoft both attempted in recent years to provide a personal health record controlled by the patient, but neither initiative has met with widespread public adoption. A more practical approach is currently being deployed by large vendors, which now offer patient medical "vaults" that are maintained online and over which the patient has read and write and access control.

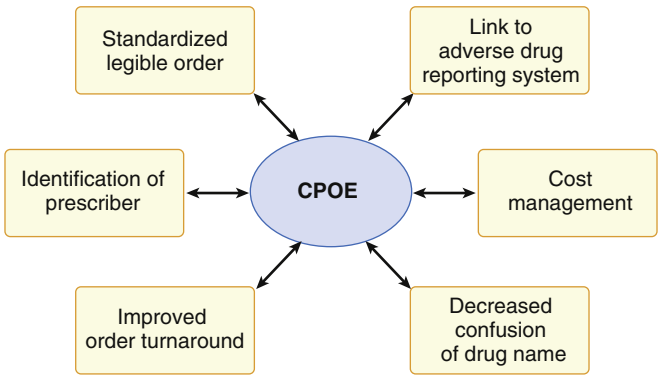


Figure 5-13. Various benefits of a computerized order entry (CPOE).

COMPUTERIZED ORDER ENTRY

CPOE systems have gained prevalence in the provision of care at many hospitals, spurred in part by the meaningful use incentive program of the CMS, yet 50% of American hospitals still lack one. Prescribing errors are the most common source of adverse drug events, and CPOEs—with or without decision support tools—are widely viewed as being integral to a reduction in errors and improved formulary control. CPOEs came into the spotlight after the Institute of Medicine's 1999 report "To Err Is Human: Building a Safer Health System," in which 44,000 to 98,000 deaths per year were attributable to medical errors; however, although CPOE has great

potential, poorly designed or deployed systems will either not be adopted or potentially cause errors.

Broadly, the term CPOE is used to refer to computer-based ordering systems designed to automate the ordering process, be it for drugs or for requesting pathologic or radiologic tests. Benefits include the output of standardized, complete, legible orders consistent with the hospital's formulary and automatically sent to the pharmacy (see Fig. 5-13). CPOE is also almost invariably associated with a decision support system (DSS), which will be discussed in more detail in the next section.

Successful deployment of CPOE will occur only when the system is deployed as part of a fundamental redesign in the delivery of patient care. The organizational aspects of CPOE deployment have been described by a recent consensus panel from the American Medical Informatics Association in which the following nine elements of successful systems were highlighted:

1. Development of a clear understanding of the institution-specific drivers for implementation of a CPOE system, be they regulatory, regional competition for patients, or internal
2. Sustained internal leadership-level support during implementation of the CPOE system
3. A CPOE system adequately funded in all respects, including training of personnel
4. Prospective understanding of the way in which CPOE will affect workflow at all sites in the organization (Fig. 5-14)
5. A positive cost-to-benefit ratio for each of the providers who use the system, ensured by the creation of time-savers such as order sets
6. Selection of an appropriate deployment strategy, whether it be an all-at-once or a staged approach
7. Attention paid to the technical details of CPOE implementation, such as the replacement of legacy systems
8. Comprehensive training and support
9. A plan designed for continuous quality improvement after implementation of the system

Medication safety is critical to safe patient care because medication errors are a key cause of adverse events; according to the Institute of Medicine, medication errors injure 1.5 million people and cost $3.5 billion each year. Computerized medication management systems have been designed to cover the entire medication process from prescription to administration, including the following discrete elements:

- Computerized provider order entry (CPOE)
- Electronic medication administration record (eMAR)
- Electronic prescription (ePrescribing)
- Integrated pharmacy administration systems (which may include pharmacy-based robotic medication dispensing and labeling)
- Electronic medication reconciliation at each point of patient transition from one environment or provider to another
- Bar code medication administration matching the right medication to the right patient at the right time

As with many of today's electronically based medical functions, a variety of vendors operate in the medication management space and providers are inevitably faced with issues relating to integration among systems, varying and changing formularies, and drug lexicons. Some vendors market end-to-end integration, whereas others specialize in one step of the process.

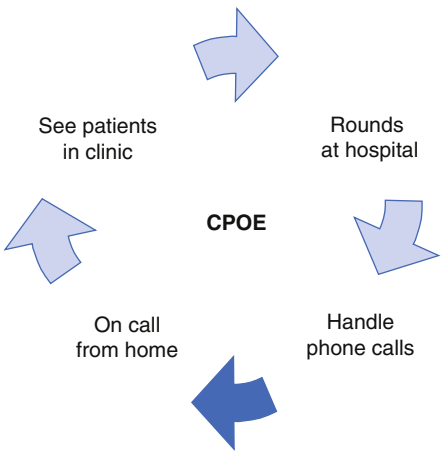


Figure 5-14. Integration of computerized order entry (CPOE) into the workflow of an organization.

DATA REGISTRIES

Electronic records, order entry systems, and automated device interfaces are several mechanisms by which the data associated with anesthesia care can be captured and subsequently used to populate data repositories. These data may then be stored in a local, vendor-specific data store (i.e., in an AIMS-specific database), ported to a hospital or system data "store" and integrated with other data sources, or extracted to a multiinstitutional registry such as the Multicenter Perioperative Outcomes Group (MPOG)* hosted at the University of Michigan. MPOG is an academic consortium "aggregating large volumes of observational inpatient electronic health record data, patient reported outcomes and long term administrative outcomes." Data repositories may be used to analyze and track individual patients, groups of patients, or pathologic conditions. Much as the availability of large, comprehensive data sets has transformed other industries by enabling, for example, sophisticated pattern recognition algorithms that can detect fraud, analyzing purchasing patterns, or projecting election outcomes, perioperative data registries have been used to evaluate perioperative practices.[34]

The Anesthesia Quality Institute created a nationwide system to collect data about adverse events relating to anesthesia, pain management, and perioperative care in 2011. The system is called the Anesthesia Incident Reporting System (AIRS) and represents a data registry designed to collect information about anaphylactic reactions, device malfunctions, medication side effects, unusual vascular or neurologic injuries, and complications relating to the use of EHRs in anesthesia settings. Data are submitted anonymously or confidentially over a secure, encrypted Internet link and used for educational purposes or for monitoring emerging trends in anesthesia patient safety

*Multicenter Perioperative Outcomes Group: <http://mpog.med.umich.edu/>

relating to new medications and techniques, data records, or patient risk factors.

DECISION SUPPORT SYSTEMS AND ARTIFICIAL INTELLIGENCE

Decision support tools integrated into the EHR and CPOE can provide immediate access to current medical knowledge, institutional best practices, billing compliance information, and administrative functions and can facilitate cost control. Although a wide range of architectures are used, DSSs fall somewhere on the spectrum between expert systems, in which rules developed by domain experts are used to drive decision support, and autonomous systems that have the ability to "learn" and make observations about large data sets. An example of the latter might be a system that automatically culls through a physician's orders to develop a profile of prescribing patterns.

A DSS can "act" in one of three ways. It may be a passive system that responds with information when asked. Alternatively, it may be semiactive and provide alerts or alarms only when certain conditions are met. Finally, a system may be active and autonomous and generate an order set or manage a medical process automatically, such as automated weaning of mechanical ventilation according to built-in rules.

Clinicians want certain functions from a DSS, such as access to national consensus guidelines when available, concurrent presentation of relevant patient information when ordering, intelligent alerts, reminders to engage in patient-specific activities (such as immunizations), and the ability to measure their performance versus that of peers in a way that results in continuous improvement in performance.

THE HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT AND DATA SECURITY

Enacted in 1996, the *Health Insurance Portability and Accountability Act* (HIPAA) was initially designed to protect workers from losing their health insurance (portability) during job transition and to protect the integrity, confidentiality, and availability of their medical information (accountability). HIPAA covers three critical aspects of automated health care information: privacy, universal coding formats, and security.[35-40]

The target of the privacy element is what is known as protected health information, and the bill ensures a patient's right to control the use of that information as it relates to health care, the business of health care, and research. HIPAA mandates the creation of universal code sets that cover, for example, the classification of diseases and describes both a national provider and national patient identification number. The many concerns about the latter have prevented its adoption to date. The security aspect of the legislation relates to the physical and electronic aspects of ensuring the protection of patient health information (Fig. 5-15).

The *Health Information Technology for Economic and Clinical Health Act* (HITECH) was enacted as part of the *American Recovery and Reinvestment Act* of 2009, and its final regulations represent "the most sweeping changes to the HIPAA Privacy and Security Rules since they were first implemented"[†] and went into effect in September of 2013. The rules extended the responsibility of physicians and other health care providers regarding patients' protected health information (PHI), expanded those responsibilities to cover parties that do business with providers (business associates) and thereby gain access to PHI, and enhance penalties for violations of these obligations.

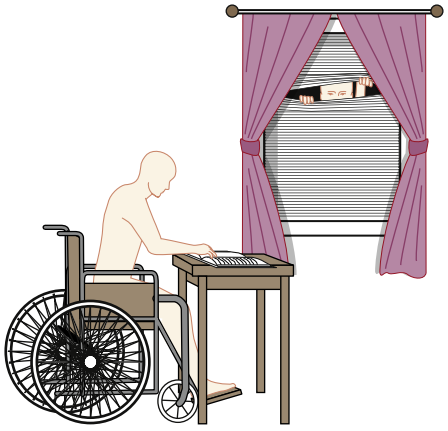


Figure 5-15. Security aspects of the Health Insurance Portability and Accountability Act legislation relate to the physical aspects protecting unauthorized access to protected health information.

TELEMEDICINE

Telemedicine and telehealth are the application of health care services across space, time, and social and cultural barriers. Telemedicine has been demonstrated in a variety of disciplines, including surgery, emergency medicine, cardiology, dermatology, ophthalmology, neurology, gastroenterology, rehabilitation, and critical care medicine.[27,41-52] However, although telemedicine has already had an enormous impact on the ability of patients to access medical information, a variety of barriers exist to widespread implementation of clinical care at a distance, including licensure, credentialing, malpractice, and reimbursement. Although advances in the use of telehealth are progressing at a rapid pace and the technologic improvements will create new applications, these issues, including credentialing of providers across state lines and determining how to compensate providers for telehealth, must be overcome.

Telemedicine holds great promise as a means of making medical care available to underserved areas, providing access to specialists at remote locations, and allowing patients to receive medical attention in their home when physical contact is not a critical element of an encounter. In addition, new technologies are currently under development, including teleimmersion and telepresence. Teleimmersion permits geographically dispersed people to collaborate in a shared virtual space, and telepresence refers to a system in which the human practitioner may

[†]See The Health Insurance Portability and Accountability Act (HIPAA) Omnibus Final Rule Summary <http://www.ama-assn.org/resources/doc/washington/hipaa-omnibus-final-rule-summary.pdf>

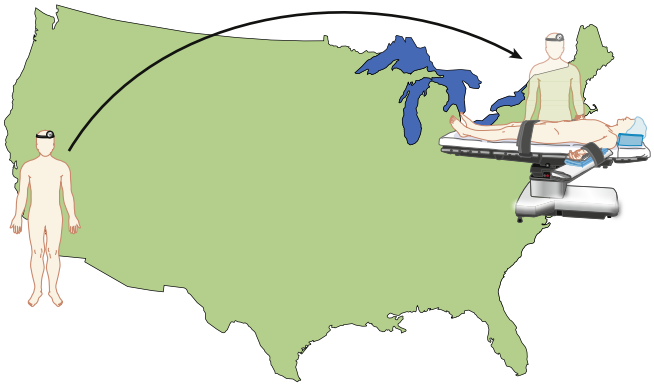


Figure 5-16. Telepresence relates to the ability to be virtually present at a patient's bedside.

have visual and mechanical actuators and sensors permitting them to "see," "feel," and "move" objects in a remote environment (Fig. 5-16).

Telesurgery demonstration projects have been done, for example, with both laparoscopic and robotic instruments to operate at a distance. Other demonstration projects are under way in various fields of medicine, and reimbursement agencies are beginning to develop methods of reimbursement for telemedicine-based activities. In addition, a few commercially available models for delivery of telemedicine exist, including remote radiographic interpretation, in some cases from appropriately credentialed radiologist interpretation from international locations, and critical care coverage from remote, virtual ICUs.

Telemedicine has specific application in the provision of anesthesia care as well. Anesthesiologists may participate in preoperative evaluation, anesthesia monitoring, and perioperative consultation via telemedical links, as well as in simulation and training. In sparsely populated areas, for example, anesthesiologists can evaluate remotely located patients to optimize preoperative preparation and limit the possibility of day-of-procedure cancellation when a patient has travelled a great distance to the hospital or surgery center. Many products have been developed to permit remote monitoring of physiologic data and audio and video links by which an anesthesia provider can remotely support a health care provider in the field, such as during a military or mass-casualty situation. Similarly, the same equipment and linkages can be used for remote consultation during a complicated procedure. Although remote preoperative evaluation is common, a variety of licensing, credentialing, professional liability, and billing barriers must be hurdled before remote provision of care becomes commonplace. Finally, sophisticated simulation suites have been developed that permit training students remotely.

Telemedicine will eventually change the way that medicine is practiced in many fundamental ways. It is equally certain that the speed of technologic change will outstrip that of regulatory, reimbursement, and legislative change.[53]

MOBILE

Another area in which health information technology is evolving rapidly has to do with the deployment of medical software on mobile devices such as cell phones and tablets or on small form-factor, Wi-Fi–enabled devices such as notebooks or netbooks.

Although the deployment of mobile technology is a critical enhancement to the workflow of providers, associated risks are the transmission of HIPAA-protected information over wireless networks and the security of such information once it arrives on the device. Although an extensive discussion of these issues is beyond the scope of this chapter, the benefits of mobile health care information technology clearly outweigh the risks, and ways to mitigate risks include encryption, password protection, and the use of techniques that allow interaction with protected data without storing it on a device.

New devices allowing remote monitoring of patients are in use or under evaluation. For example, remote telemetric transmission of pulse oximeter, blood pressure, glucose, and other data are now being used to manage patients after surgery or to help guide management of patients with chronic illnesses. Other devices are capable of determining that patients are taking medications as prescribed or following other clinical recommendations. The implications of advances in mobile technologies can be significant for any patient and for the anesthesia practitioner. The use of these technologies for managing patients in the perioperative period has not been extensively evaluated and remain largely untested. Smartphone applications such as Airstrip permit remote monitoring, event review, trend assessment, and alert delivery. These capabilities are not suited to primary provision of anesthesia care, but they can be used to support an anesthesia provider supervising care in multiple rooms or locations, by providing vital sign and event alerts. Continued advances in the use of these devices could have significant impact on perioperative care and the role of the anesthesiologist in managing patients before and after surgical procedures.

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Chapter 6

Quality Improvement and Patient Safety

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Key Points

- Quality is an integral characteristic of the system in which care is delivered, and ideally, every system is perfectly designed to realize the results that it achieves. Improving the quality of care probably requires reorganization of the way we work. A challenge to the anesthesia provider is to combine efficiency in perioperative care (especially the operating room) with safety and the best quality possible (see Chapters 3, 4, and 7).
- The growing demand from patients, providers, insurers, regulators, accreditors, and purchasers for improved quality and safety in health care requires that anesthesiologists and other anesthesia providers persistently evaluate the quality of care they provide.
- Improving quality of care requires measuring performance. Clinicians have an enhanced ability to obtain feedback regarding performance in their daily work, in part because of the increasing use of information systems. Unfortunately, consensus has not been reached on how to measure quality of care.
- The goal of measurement is to learn and improve. The measurement system must fit into an improvement system; caregivers must have the will to work cooperatively to improve, and they must have ideas or hypotheses about changes to the current system of care. Also, the clinical team must have a model for testing changes and implementing those that result in improvements.
- Outcome measures, including in-hospital mortality rates, have been the basis for evaluating performance and quality. However, hospital mortality alone provides an incomplete picture of quality and does not include all domains of quality. A balanced set of structures (how care is organized), processes (what we do), and outcome measures (results we achieve) is needed to evaluate the quality of care overall.
- Future efforts to improve quality of care require development of valid, reliable, and practical measures of quality. Identification of clinical care that truly achieves excellence would be helpful not only to anesthesia, but also to health care overall. Examples of excellence in clinical care could serve as models to other anesthesia providers.
- Developing a quality measure requires several steps: prioritizing the clinical area to evaluate; selecting the type of measure; writing definitions and designing specifications; developing data collection tools; pilot-testing data collection tools and evaluating the validity, reliability, and feasibility of measures; developing scoring and analytic specifications; and collecting baseline data.
- The best opportunities to improve quality of care and patient outcomes will most likely come not only from discovering new therapies, but also from discovering how to better deliver therapies that are already known to be effective.

†Dr. Elizabeth Martinez, a wonderful friend, a delightful and energetic colleague, a role model physician who loved taking care of patients, and a passionate and productive researcher in quality improvement, died on September 19, 2013. She will be remembered with much love by all who knew her.

Key Points—cont'd

- A system that has been used by the airline industry, reducing complexity and creating redundancies, can ensure that critical processes occur. The practice of anesthesia may also benefit by reducing complexity and redundancies.
- Health care providers can organize their patient safety and quality improvement (QI) efforts around three key areas: (1) translating evidence into practice, (2) identifying and mitigating hazards, and (3) improving culture and communication. Although each of these areas requires different tools, they all help health care organizations evaluate progress in patient safety and quality.

The need for improving the quality and reducing the cost of health care has been highlighted repeatedly in the scientific literature and lay press. Improving care, minimizing variation, and reducing costs have increasingly become national priorities in many countries. Quality improvement (QI) programs that address these issues not only improve delivery of care but also have a positive effect on practitioner job satisfaction and organizational commitment.[1]

The goal of this chapter is to present a practical framework for developing and implementing QI programs in anesthesiology and critical care medicine that are both scientifically sound and feasible. To accomplish this goal, we review the science of QI, present measures that help evaluate whether QI programs have resulted in improvements, and describe examples of successful QI efforts.

WHAT IS QUALITY?

DEFINITION OF QUALITY

W. Edwards Deming, scholar, professor, author, lecturer, and consultant to business leaders, corporations, and governments defined quality as "a predictable degree of uniformity and dependability with a quality standard suited to the customer."[2] This early definition of quality, in the context of QI, stems from its application to industrial production. However, when the term *quality* is applied to health care, the subtleties and implications of treating a human being are of prime importance, as opposed to the concerns involved in producing consumer goods. Use of the term *quality* in the context of health care can sometimes lead to defensive attitudes, economic concerns, and even ethical debates.

In the health care sector, quality can have various meanings to different people. For example, a daughter may evaluate quality by the level of dignity and respect with which her elderly mother is treated by a nurse. A cardiac surgeon may see quality as a percentage of improvement in the function of a heart on which he or she has just operated. A business may judge quality by the timeliness and cost effectiveness of the care delivered to its employees and its effect on the bottom line. Finally, society may evaluate quality by the ability to deliver care to those who need it, regardless of their cultural or socioeconomic backgrounds.

Despite the numerous definitions of quality in both business and medicine, a unified definition of quality in the context of QI should exist in health care. This definition of quality may have implications for both its measurement and its improvement. In order to help standardize the definition of quality in health care, the Institute of Medicine (IOM) published its own definition in a 1990 report titled *Medicare: A Strategy for Quality Assurance*. The IOM defined *quality* as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[3] Inherent in this definition are the elements of measurement, goal orientation, process and outcomes, individual and society preferences, and a dynamic state of professional knowledge. This IOM definition of quality in health care has gained the most widespread acceptance.

SIX AIMS OF QUALITY IN HEALTH CARE

The IOM subsequently outlined six dimensions or aims of quality in its 2001 report, *Crossing the Quality Chasm*.[4] These dimensions include and go beyond the issues of patient safety described in their earlier report *To Err Is Human*.[5] The aims have been adopted by many organizations, including the Institute for Healthcare Improvement (IHI), as a basis on which quality is evaluated and improved. The six aims of the IOM are safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity.

1. Safety. No patient or health care worker should be harmed by the health care system at any time, including during transitions of care and "off hours," such as nights or weekends. Errors may be categorized as either failure of an action to occur as planned, such as the administration of a wrong medication to a patient, or having the wrong plan altogether, such as misdiagnosing and subsequently mistreating a patient.[4] As much as possible, patients should be informed about the risks and benefits of medical care in advance. If a complication does occur, medical staff should make full disclosure, provide assistance to the patient and family, and exercise due diligence in preventing any recurrences of the error.
2. Effectiveness. Effective medicine necessitates evidence-based decisions about treatment for individual patients, when such evidence exists. The best available evidence should be combined with clinical expertise and patient values in forming a treatment plan. With effective care, medical practitioners avoid underuse by

providing a treatment to all who will benefit and avoid overuse by refraining from giving treatment to those unlikely to benefit.

3. Patient-centeredness. Patient-centered care is respectful of individual patient preferences, needs, and values and uses these factors to guide clinical decisions.[4] More specifically, according to Gerteis and colleagues,[6] patient-centered care encompasses respect for patients' values; coordination and integration of care; information, communication, and education; physical comfort; emotional support that relieves fear and anxiety; and involvement of family and friends. The dramatic increase in access to health information on the Internet has resulted in more patients who are well informed and proactive in their care. Patient-centered care embraces this trend and shifts more of the power and control to patients and their families. Examples of patient-centered care include shared decision making, patient and family participation in rounds, patient ownership of medical records, schedules that minimize patient inconvenience, and unrestricted visitation hours.[7]
4. Timeliness. Reduced wait time is important to both patients and health care practitioners. Long waits signal a lack of respect for a patient's time. Furthermore, delays may not only affect patient satisfaction, but may impair timely diagnosis and treatment. For health care workers, delays in availability of equipment or information may decrease job satisfaction and the ability to perform their jobs adequately.
5. Efficiency. Rising costs have increased scrutiny of waste in health care; this includes waste in labor, capital, equipment, supplies, ideas, and energy.[8] Improved efficiency reduces waste and results in an increased output for a given cost. Examples of efficiency measures include mean length of hospital stay, readmission rate, and mean cost of treatment for a diagnosis. In many circumstances, efficiency can be improved by eliminating waste, which often results in better quality of care for patients.
6. Equity. Equitable care does not vary in quality based on personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status. The IOM defines equitable care at two levels. At the population level, equitable care means reducing or eliminating disparities between subgroups. At the individual level, it means absence of discrimination based on factors such as gender, race, age, ethnicity, education, sexual orientation, disability, or geographic location.[4]

METHODS OF QUALITY ASSESSMENT

QUALITY ASSURANCE VERSUS CONTINUOUS QUALITY IMPROVEMENT

Although the terms *continuous quality improvement (CQI)* and *quality assurance (QA)* are often used interchangeably, substantial differences exist between the two. Most medical CQI systems have been built on the foundation of a traditional QA system that uses *standards* to define quality.[9] Standards can be defined as an "acceptable" level of performance. For example, a standard for overall mortality after cardiac surgery is less than 3%; however, is 3% (versus 4% or 2%) mortality after cardiac surgery acceptable? Similarly, a standard for head injury evaluation is a computerized tomography (CT) brain scan within 4 hours of admission, but in certain circumstances, patients with head injury may warrant a CT scan sooner than that.

Most standards are inherently arbitrary and often lack consensus among medical professionals.[9] Additionally, QA systems typically react only when a standard is not met. Examples of traditional standard-based QA systems are peer review systems and morbidity and mortality reviews. These systems often exist to flag certain cases or practitioners for intense review. Practitioners may regard this intense review as a punishment because only "failures" or "bad apples" are identified, and process failures are not connected with the outcome on every case. Thus, QA systems are inherently judgmental and, if not carefully administered, can hold practitioners responsible for random causes over which they have no control. CQI systems, on the other hand, are gaining popularity because they recognize that errors occur and require different responses. Often excellence in health care is not identified by analysis of QA systems. Excellence is sometimes defined by the lack of failure. Is there a difference between good (acceptable) and excellent health care?

Systems within health care are a series of interlinked processes, each of which results in one or more outputs. CQI systems, as opposed to QA systems, include an explicit approach to process and the use of specifications to improve a process or outcome. A specification is an explicit, measurable statement regarding an important attribute of a process or the outcome it produces.[9] Specifications identify variables that need to be measured but typically do not set acceptable limits or standards. Once specifications have been defined in a CQI system, all outputs or cases, not just failures, are evaluated against these specifications. The system then attempts to correct errors by fixing the process rather than the people. Thus, CQI aims to change the process and prevent quality failures before they happen by building improvements into the process. To quote Philip Crosby, "The system for causing quality is prevention, not appraisal."[10]

FRAMEWORKS FOR IMPROVEMENT

Model for Improvement

The journey toward improvement can be made more efficient and more effective with a systematic approach. The Model for Improvement, developed by the training and management consulting company Associates in Process Improvement, is one such approach adopted by organizations across varied disciplines and is currently the approach used by IHI. It is a structured, dynamic model that applies the scientific method to testing and implementing a change.[11] In 1939, Walter A. Shewhart, a physicist, engineer, and statistician, introduced the science of modern QI.[12] He introduced a three-step scientific process of specification, production, and inspection, stating that "these three steps must go in a circle instead of in a straight line."[13] In the 1940s, his protégé, W. Edwards

TABLE 6-1 STEPS OF A PLAN, DO, STUDY, ACT (PDSA) CYCLE

Step	Description
Plan	Make a plan for the test of change. Include predictions of results and how data will be collected.
Do	Test change on a small scale. Document data, observations, and problems that occur.
Study	Use data gathered from previous stages to build new knowledge and make predictions. Knowledge is gained from both successful and unsuccessful changes.
Act	Adopt the change, or use knowledge gained to plan or modify the next test of action.

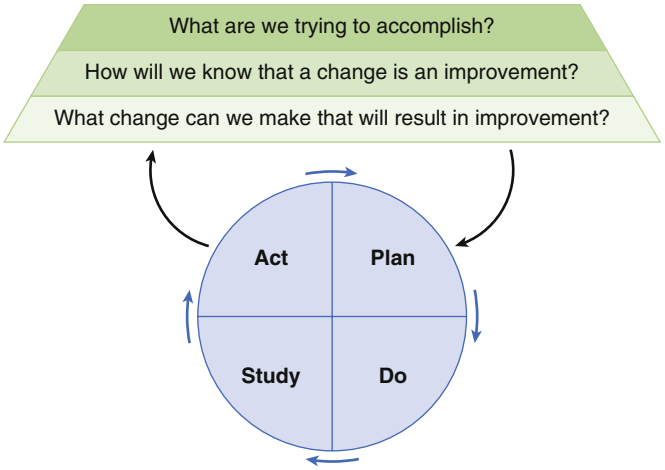


Figure 6-1. Diagram of Model for Improvement. *(From Langley GJ, Moen RD, Nolan KM, et al.* The improvement guide: a practical approach to enhancing organizational performance. *San Francisco, 2009, Jossey-Bass. With permission from John Wiley & Sons.)*

Deming, applied these concepts to government and industry and developed the Plan, Do, Study, Act (PDSA) cycle (Table 6-1).[14] A modification of the PDSA by the addition of three fundamental questions resulted in the Model for Improvement (Fig. 6-1).[13]

Beginning an improvement project with the three fundamental questions for improvement helps set a clear direction for the project, define what success will look like, and hypothesize successful interventions. The three fundamental questions for improvement are:

1. What are we trying to accomplish? (Aim) The aim (or objective) for improvement should be specific, measurable, actionable, relevant, and time-specific (also referred to as a SMART aim). Ideas for improvements may come from interviewing those involved or affected by the process, such as staff or patients. Ideas may also come from examining previous data on operational, clinical, or financial processes.
2. How will we know if change is an improvement? (Measures) Ideally, measures should be linked directly to the aim or goal of the project and should ensure that the interests of the stakeholders of the process are represented.[11] Quantitative measures should be used when possible to measure change over time. These measures provide the feedback that enables one to know whether or not the change is an improvement. However, not all projects have an easily quantifiable outcome and the outcome may be more qualitative. It is worth the time and effort to identify opportunities to translate goals into quantifiable outcomes if possible. These can be easier to use to communicate success.
3. What changes can we make that will result in improvement? (Changes) Ideas for changes that result in improvement often start with observations, modeling the success of others, and brainstorming. The more intimate the understanding of a process and its key drivers, the higher the likelihood of generating successful changes.

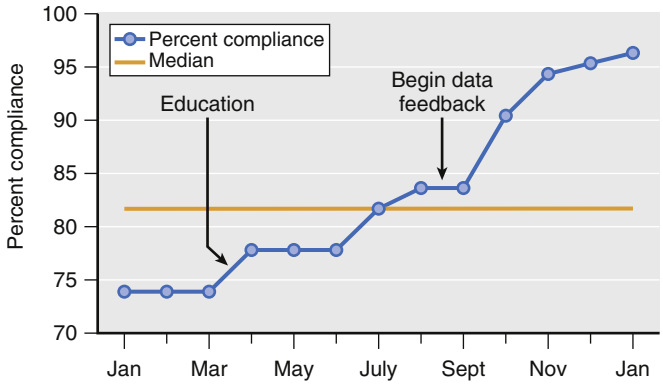


Figure 6-2. Example of a run chart. This chart shows the plot of a performance measure over time. The horizontal (*x*) axis represents time in months, and the vertical (*y*) axis represents the performance measure—the percentage of compliance with the timing of preoperative antibiotics.

The three fundamental questions are followed by a PDSA cycle, which is the framework for testing and implementing previously generated ideas for change. Improvement may require multiple cycles of preferably small tests of change over time. By testing changes on a small scale before implementation, risk is mitigated. Small tests of change may also help overcome individuals' resistance to change. Through repeated cycles, increased knowledge is acquired, and actions are continuously modified or changed. Measures defined in the first part of the model help determine whether or not a change is a success. These measures are often plotted over time on run charts or control charts (Figs. 6-2 and 6-3). Knowledge can be gained from both successful and unsuccessful tests! Finally, PDSA cycles both test a change and implement a successful change on a larger scale or in diverse clinical areas.

Lean Methodology and Six Sigma

In addition to the Model for Improvement, CQI initiatives have many other frameworks. Two of these frameworks, Lean Production and Six Sigma, are briefly discussed here. These frameworks are sometimes combined, such as in Lean-Six Sigma. Regardless of which framework is employed, benefits are gained by retaining a structured and consistent approach to CQI.

Lean methodology has its roots in Japanese manufacturing, particularly in the Toyota Production System.[15] More recently, Lean has found success in the health

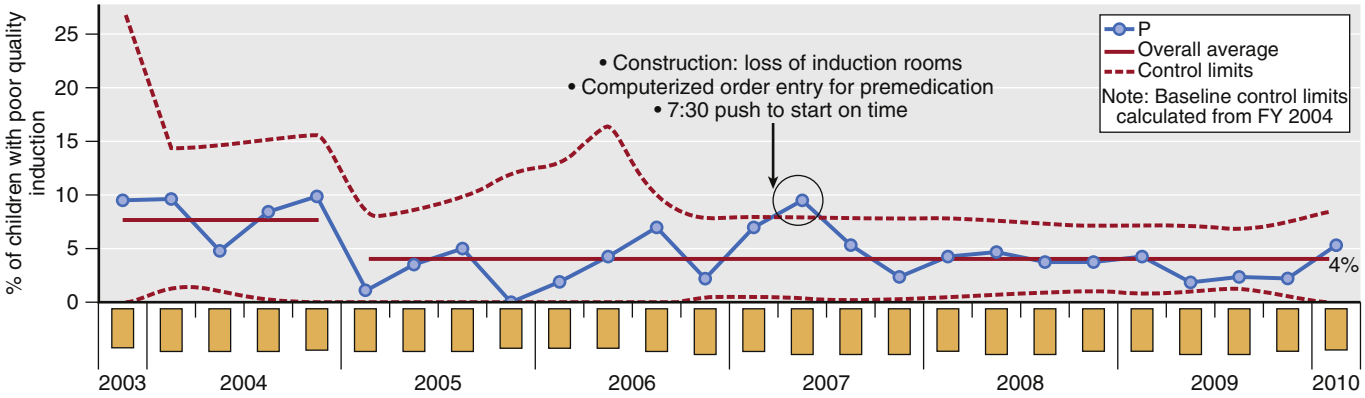


Figure 6-3. Example of a control chart that monitors the quality of the anesthesia induction process, as measured by an induction compliance checklist. The *solid red line* marks the mean, and the *dashed lines* indicate the upper control limit (UCL) and lower control limit (LCL), which are ±3 standard deviations from the mean. The *circled point* represents a single special cause variation in quality of induction. *ICC,* Induction Compliance Checklist score. *(From Varughese AM: Quality in pediatric anesthesia,* Paediatr Anaesth *20:684-696, 2010.)*

care industry. Two notable examples of its use are Virginia Mason Medical Center and ThedaCare, Inc., both of which have transformed their organizations through the application of Lean principles. In fact, ThedaCare reported $3.3 million in savings in 2004 with reduced accounts receivable, redeployed staff, reduced phone triage times, reduced time spent on paperwork, and decreased medication distribution time.[15]

Lean methodology is focused on creating more value for the customer (i.e., the patient) with fewer resources. Every step in a process is evaluated to differentiate those steps that add value from those that do not. The ultimate goal is to eliminate all waste so that every step adds value to a process. Other key components of Lean include reducing unevenness of workflow—for instance, what we might find in intensive care unit (ICU) admissions or emergency cases—and eliminating the overburdening of people and equipment. Five principles govern Lean improvement:[11]

1. Define the value that the customer is seeking.
   Virginia Mason Medical Center has a "Patient First" focus for all its processes.[15]
2. Identify and map the value stream.
   If evaluating preoperative assessment (also see Chapter 38), map the physical flow of a patient from the scheduling of a procedure through the day of surgery (history and physical, preoperative counseling, lab tests, imaging, consultations, etc.). In this process, all of the steps are accounted for, including the back-and-forth flow of the patient to the front desk, to the laboratory, and so on. Time spent during each step of the process should be documented.
3. Smooth the flow between value-added steps.
   Eliminate steps that do not add value to the overall process and are likely a poor use of time or effort on the part of the caregivers or the patient. An example of this process might be eliminating unnecessary tests or consultations in a patient's preoperative evaluation and reducing excess wait times that are the result of correctable inefficiencies.
4. Create pull between steps.
   Customer demand should trigger the start of a downstream process. Examples include opening operating rooms or increasing staffing based on surgical demand, as opposed to having a fixed amount of time for each surgeon or surgical division.
5. Pursue perfection by continuing the process until you have achieved ultimate value with no waste.

The transformation of Motorola in the 1980s from a struggling company to a high-quality, high-profit organization helped give rise to the Six Sigma methodology. Two key fundamental objectives of Six Sigma are a virtually error-free process and a large focus on reducing variation.[16] In fact, a Six Sigma process, or a process six deviations from the mean, corresponds to just 3.4 errors per million.

Health care often falls far short of this standard. In a 1998 report, Chassin[17] reported that hospitalized patients harmed by negligence were at a four sigma level (10,000 per million), patients inadequately treated for depression were at a two sigma level (580,000 per million), and eligible heart attack survivors who failed to receive β-adrenergic blockers were at a one sigma level (790,000 per million). In contrast, Chassin found that anesthesiology was the one health care specialty that approached the six sigma level, with deaths caused by anesthesia as low as 5.4 per million.[17] In comparison with health care, airline fatalities were a two sigma process (230 per million) and a traditional company operated around four sigma, the equivalent of 6200 errors per million.[17] Considering that errors are often tied directly to cost, this error rate has significant financial implications.

Six Sigma is similar to the Model for Improvement in that it makes use of a simple framework to guide improvement, in this case using Define, Measure, Analyze, Improve, Control (DMAIC).[16] The DMAIC steps are described in Table 6-2. As mentioned earlier, many organizations have found the greatest benefit by combining elements of different methodologies in their CQI work. One popular example of this is Lean-Six Sigma, which combines improvements in flow and value with reduction in error and variation. Furthermore, individual tools from these strategies, such as PDSA cycles or DMAIC processes, can be applied where appropriate.

TABLE 6-2 STEPS IN THE LEAN OR SIX SIGMA PROCESS

Step	Description
Define	Define the goals of the improvement project. Obtain necessary support and resources and put together a project team.
Measure	Establish appropriate metrics. Measure baseline performance of the current system.
Analyze	Examine the system for possible areas of improvement.
Improve	Improve the system through implementation of ideas. Statistically validate improvements.
Control	Institutionalize the new system and monitor its stability over time.

QUALITY IMPROVEMENT MEASURES AND TOOLS

The concept of using measurement to drive improvement has its origins in both medicine and industry. The use of data to improve the health of patients originated in the mid-1800s with two pioneers, Florence Nightingale and John Snow. Nightingale used data on mortality among British soldiers to drive improvements in sanitation in field hospitals. Similarly, Snow used data on the incidence and geographic location of cholera to make the connection between the incidence of the disease and water obtained from the Broad Street water pump. In the early 20th century, Ernest Codman, a surgeon at Massachusetts General Hospital, was the first to advocate tracking of patient outcomes so that adverse events could be identified and improvements in care made for future patients. In the 1970s, Avedis Donabedian emphasized the importance of measurement and described a model for evaluating quality of health care based on structure, process, and outcomes—*structure* being the environment in which health care is provided, *process* being the method by which it is provided, and *outcomes* being the result of the care provided. More recently, in 1991, Paul Baltaden and Don Berwick developed the IHI, one of the leaders in the application of improvement science to health care.[18]

In QI, measurement can serve many purposes. It can be used to identify problems and establish baseline performance, inform and guide QI projects, select and test changes for improvement, and assess and align progress with organizational goals. Selecting and developing measures that are useful can be challenging. Optimal measures must be comprehensive, carefully defined, tailored to the target audience, and involve minimal measurement burden. Target audiences usually include clinical staff, so measures should address and align with clinical targets for specific patient populations with whom the staff work. Measures should pass the face validity test with clinical practitioners delivering care. National or organizational measures, if applicable, can also be used, but they may not always be relevant or credible to the local target audience. Within an organization, target audiences should include system leaders, so measures should also align with organizational priorities and strategic goals.

PROCESS AND OUTCOME MEASURES

Measures should include the following:

1. Process measures that address the processes of health care delivery (e.g., perioperative β-adrenergic blocker administration for patients, antibiotic administration for prevention of surgical site infection)
2. Outcome measures that address patient outcomes from delivery of these services, such as clinical and functional outcomes or satisfaction with services (e.g., morbidity, mortality, length of stay, quality of life, or perceptions of care)
3. Balancing measures that address the possible consequences of changes in the process (e.g., when process improvements are made to improve efficiency, other outcomes, such as patient satisfaction, should not be adversely affected)

Each of these measures has advantages and limitations.[19] A comprehensive set of measures should include at least one process, outcome, and balancing measure. In addition, structural measures, such as ICU nurse-to-physician staffing ratios, can be important to include when appropriate.[20,21]

Health care providers readily accept process measures because they demonstrate the degree to which caregivers can influence a process with the intention to improve patient outcomes. Practitioners generally feel more accountable for the process of care than its outcomes, because outcomes may be affected by many other variables.[19] An obstacle to using process as a measure of quality is sustainability; frequent updating is required as the science of medicine advances.

Process measures, which evaluate how care is delivered, may be easier to measure and implement than outcome measures and can provide important insight into care.[22] Process measures can provide immediate feedback regarding performance, allowing for rapid improvements in care. Process measures have two other important advantages: first, they generally have face validity for providers, meaning that providers believe they can use the data to improve care; and second, because risk adjustment is less important, broad implementation is feasible. Moreover, joint efforts among providers, professional societies, and external government or payer agencies have made process measures more feasible.[22]

To be valid, process measures should have causal links to important outcomes; a change in the process should produce a desired change in outcome. One of the best opportunities to improve patient outcomes may well come from discovering how to deliver therapies (processes) that are known to be effective in producing a desired outcome.[23] For example, hand hygiene and application of chlorhexidine to sterilize the skin site before insertion of a central venous catheter (CVC) are two of five processes known to reduce catheter-related bloodstream infections (CRBSI).[24] Process measures such as these are indicators of whether patients reliably receive evidence-based interventions known to prevent complications.

When measuring processes, patient factors, measurement bias, and interventions already in place as part

of standard practice all play a role in outcomes. The linkage of process to outcomes must be demonstrated scientifically or widely accepted by peers, although the latter risks the linkage being accepted but wrong. In general, a balanced set of process and outcome measures helps inform improvement efforts and provides evidence that efforts have made a difference in the lives of patients.

The need for risk adjustment and long-term follow-up is complex. If an outcome occurs infrequently, providers will obtain meaningful feedback on a timely basis. For example, evidence of improved rates of CRBSI (an outcome measure) may require 3 months of data (because few patients develop infections), whereas improved adherence to evidence-based practices to reduce infections (process measures) may be observed within a week (because all patients can be evaluated to determine whether they received the intervention). Nevertheless, consumers and employers are increasingly requesting outcome measures both to improve care and decrease cost. The relative focus on outcome and process measures will depend on balancing the collection of data between that which is scientifically sound and that which is feasible.

For measurement to be effective, the following principles are important. First, measures should focus on something that the improvement team has the power to change and should initially be simple, small-scale measures that focus on the process itself and not on people. Second, measures should be practical, seek usefulness—not perfection—and fit the work environment and cost constraints. Third, data for measurement should be easy to obtain; finding ways to capture data while the work is getting done allows measures to be built into daily work. Fourth, qualitative data (e.g., reasons for patient dissatisfaction) are often highly informative and easy to obtain and should complement quantitative data (e.g., percentage of patients satisfied with care). Finally, when using measures, balance is key; a balanced set of measures can help answer the question, Are we improving parts of our system at the expense of others?

Measurement should not overwhelm the change process. Improvement teams should minimize the burden of measurement whenever possible. Measurement can have both direct and indirect consequences on resource use, provider behaviors, and patients.[25] Measurement of performance and outcomes of care can be costly, especially if the data collection process is manual and involves chart reviews. The burden of measurement is reduced with an electronic medical record system and computerized order entry, although these information technology systems are costly to implement and maintain. Additionally, these resources may not be equally available throughout a system or organization, leading to disparities in the care provided.

Measurement fixation is an unintended consequence on health care staff behavior that may occur with the use of process measures. For example, when a process measure such as "the percentage of diabetic patients who received an action plan" is used rather than an outcome measure such as "improved patient understanding about diabetic management," the measure is perceived by the clinician as defining what is important. Thus, measurement of the process becomes the priority, rather than the intended outcome.[25] Alternatively, the clinician may become so focused on what is being measured that different aspects of care are not equally prioritized. In addition, a predominance of process rather than outcome measures can stifle innovation by scripting a process, thus inhibiting process-level innovation. Practice variation does have some utility because medical practice is dynamic, and it is through the trial of new methods of care that innovation occurs. Finally, QI performance measures may not match patient preferences for clinical care. Performance measures that do not take patient preference into account can lead to decreased patient satisfaction, trust, and confidence in their health care practitioners and system.[25] Thus, selection of a set of appropriate measures with the attributes described previously can be a balancing act that includes weighing the tradeoffs involved.

ANALYSIS AND DISPLAY OF QUALITY IMPROVEMENT DATA

Interpretation of data and understanding of process variation are fundamental to QI work. Data elements central to improvement are first and foremost—those data are collected as a basis for action. Second, interpretation of data is made within the context of the process. Last, the analysis technique should filter out noise in the process. Aggregate data or summary statistics typically do not filter out noise in the system and do not present a broad enough context to point practitioners in the direction of proper action or process improvement.

Shewhart postulated that data contain both signal and noise; to be able to learn, one must separate the signal from the noise.[26] CQI science defines two types of variation within a process: random variation and specific variation. Random variation, also known as common-cause variation, results from differences in the inputs that a process receives or inherent factors in the process itself. Random variation is the random background noise within a system and occurs in the process all the time. Specific variation, also known as special-cause or attributable variation, is not present all of the time as background noise, but rather arises from one or more specific causes that are not part of the system. A process is considered to be unstable when specific variation exists, and efforts should be made to learn about the special causes for this variation. A stable process exists when specific variation no longer occurs, leaving only random or common variation.[9] CQI aims to eliminate specific variation for every process so that only random variation remains. A standards-based QA system fails to distinguish random cause from special cause and attempts to correct all variation. Attempts to correct random variation will necessarily fail—a process CQI defines as "tampering." When a process exhibits only random variation, the process should be evaluated to determine whether it is functioning at an acceptable level. If it is not, the process will need to be changed so that the average is moving in the desired direction. Standardization of a process is often the key to reducing random variation and improving a process.

Run Charts and Control Charts

Run charts and control charts are graphic displays of data that enable observation of trends and patterns over time. They are the best tools for determining whether improvement strategies have had an effect. A run chart (see Fig. 6-2), also called a time series chart, plots the variable or measure being studied on the vertical axis and plots the time on the horizontal axis. The average, or centerline, is the median. At least 12 data points are required to establish a baseline, and at least 20 to 25 data points are required to detect trends and patterns. Run charts should be annotated with tests of change to provide the context within which data can be interpreted. Four rules can be used with run charts to determine whether nonrandom patterns exist or to detect whether the change has led to an improvement:

1. A shift is indicated by six or more consecutive points above or below the median.
2. A trend is indicated by five or more points all increasing or all decreasing.
3. A run is defined as a series of consecutive points on the same side of the median line.
4. An astronomical data point is an unusual point that is obviously different in value (an outlier).[11]

Because change is by nature temporal, run charts in which data are presented over time are powerful tools for interpreting data within the context of the process.

A control chart (see Fig. 6-3),[27] also known as a Shewhart chart,[11,12] is an extension of a run chart and is used to distinguish between specific and random variation. As on a run chart, the variable is plotted on the vertical axis and time on the horizontal axis. However, with a control chart the centerline or average is the mean, rather than the median, and the upper control limit (UCL) and lower control limit (LCL) are calculated. The UCL and LCL correspond to ± 3 sigma from the mean. A process is considered to be "in control," or stable, when data points are within these control limits.[11] Random variation, or variation that is the result of the regular rhythm of the process, produces a stable process. However, in an unstable process that contains variation from special causes, data points exceed the UCL or LCL.[28]

Dashboards and Scorecards

A dashboard of measures functions like an instrument panel for an aircraft or automobile and provides real-time feedback on what is happening. Balanced *scorecards,* or "whole system measures," are similar to dashboards and are used to provide a complete picture of quality. Developed by Kaplan and Norton, the balanced scorecard is defined as a "multidimensional framework for describing, implementing, and managing strategy at all levels of an enterprise by linking objectives, initiatives, and measures to an organization's strategy."[29] A set of measures should reflect the culture and mission of an organization. Viewed collectively, this set of measures provides a gauge of current performance and can also guide the direction for future organizational improvement efforts. A balanced set of measures is critical to ensure that improvement efforts in one area do not adversely affect outcomes in other areas.

Additional QI Evaluation and Communication Tools

In most situations, QI frameworks such as the Model for Improvement or Lean Sigma are sufficient to help guide the development, testing, implementation, and spread of improvement. However, to better understand problems within a system or process, QI professionals have developed or adapted a number of methods and tools. Some of these methods and tools help with viewing systems and processes and organizing and communicating information. These are described in the following section.

Understanding how a process or system works is fundamental to improving it. Process mapping is a method to gain this understanding. A flow diagram, or flow chart, is an improvement tool used during process mapping; it provides a visual picture of the process being studied, wherein the series of activities that define a process is graphically represented. Flow charts identify and clarify all steps in the process. They also help the team understand the complexity of the process and identify opportunities for improvement.

Failure mode and effects analysis is a systematic, proactive method of identifying and addressing problems associated with a process. It uses a standardized approach to analysis that includes identifying the various steps in a process and addressing their failure modes, effects, and possible interventions.

Key Driver Diagram (KDD) (Fig. 6-4)[30] is another approach to organizing the theories and ideas for improvement that a team has developed. The KDD presents the aim or outcome of the project with both the theories (key drivers) behind the improvement and ideas for test of change.[11] Initially, the driver diagram helps lay out the descriptive theory behind the improved outcomes. As these theories are tested, the driver diagram is updated and enhanced to develop a predictive theory. KDDs are extremely useful because they provide a shared mental model for the team during its improvement efforts.

IMPROVEMENT INTERVENTION TOOLS

Efforts in QI and patient safety have produced tools with which to reorganize the way care is delivered. QI intervention tools are used to improve communication and teamwork. Examples of these tools include daily goals sheets, briefings/debriefings, and checklists.

Daily Goals Sheet

Since July 2001, the daily goals sheet has been used to improve communication during multidisciplinary rounds in the ICU at Johns Hopkins Hospital.[31] A one-page checklist, this tool is completed every morning to establish the care plan, set goals, and review potential safety risks for each patient (Fig. 6-5). The goals sheet stays with the patient, is updated as needed, and is used as an information sheet for all staff involved in the patient's care. It can be modified for use on other nursing units or during operating room (OR) sign-out or emergency department rounds (also see Chapters 101 and 102).

Before implementation of the daily goals sheet, an initial survey showed that ICU team members were unable

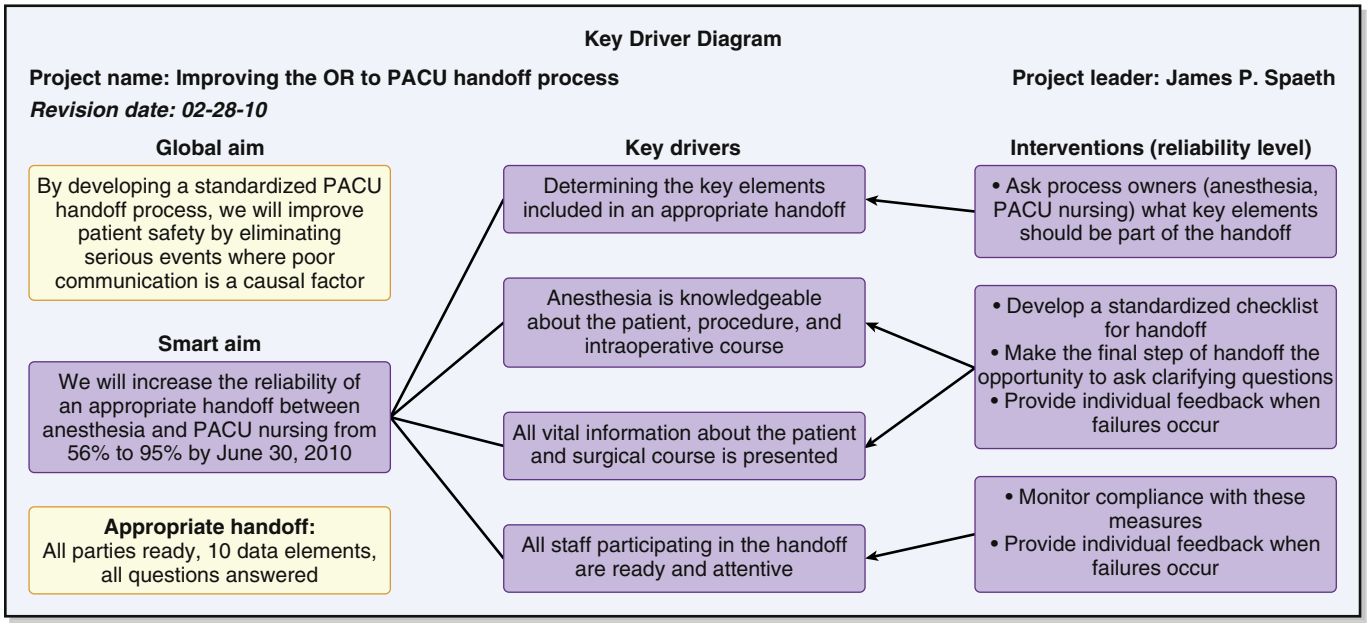


Figure 6-4. Example of a key driver diagram (KDD) developed to improve the operating room (OR) to postanesthesia care unit (PACU) handoff process. This diagram incorporates the global and smart aim of the project, the key drivers inherent to the process, and specific interventions targeting each of the key drivers. *(From Spaeth J, Varughese A:* Improving the OR to postanesthesia care unit handoff process: a quality improvement initiative. *Society for Pediatric Anesthesia Meeting Abstract, San Diego, CA, 2011.)*

to answer two simple questions after rounding at each patient's bedside: "Do you understand the patient's goals for the day?" and "Do you understand what work needs to be accomplished on this patient today?" Fewer than 10% of the residents and nurses knew the care plan for the day—a finding that was not surprising because traditional bedside rounds tended to focus on teaching the staff about disease processes rather than focusing on the work that was necessary to treat the patient. Approximately 4 weeks after the daily goals sheet was implemented, 95% of residents and nurses understood the goals for each patient. Moreover, after the daily goals sheet was implemented, length of stay in a surgical ICU at Johns Hopkins decreased from a mean of 2.2 days to only 1.1 days.[31]

Briefings and Debriefings

Similar to the daily goals sheet, briefing and debriefing tools are designed to promote effective interdisciplinary communication and teamwork. Both have been used in the OR, during sign-out from the ICU nursing staff to the intensivist, and between OR nursing and anesthesia coordinators.[32-34] A briefing is a structured review of the case at hand that takes place among all team members before the start of an operative procedure. A debriefing occurs after the procedure; the team reviews what worked well, what failed, and what could be accomplished better in the future (Fig. 6-6).

An example of an OR briefing includes introduction by name (first and last) and role of each team member, confirmation of the correct patient, confirmation of the site/side and procedure (time-out), and a verbal assurance that all team members agree that they understand the procedure and what is required to ensure its success. A check of all necessary equipment, medications (e.g., appropriate antibiotic), and blood availability is performed. The question, "If something were to go wrong, what would it be?" is asked, and plans to mitigate or respond to the potential hazard are discussed (also see Chapter 3).

Checklists

Checklists have been used in health care and other industries to ensure that important steps in a process are not forgotten. The Food and Drug Administration recommends that a checklist be used when checking out and inspecting an anesthesia machine before use to ensure that the equipment and monitors are functioning properly.[33,35] As part of a QI project to reduce CRBSI at Johns Hopkins, care providers implemented a checklist as one of several interventions to reduce complexity and to introduce a redundant safety check. The checklist, typically completed by a nurse, was attached to the CVC insertion cart to ensure compliance with the best practices for CVC placement. The nurse was empowered to stop the procedure if the checklist was not followed or if sterile technique was compromised. This intervention resulted in a 66% reduction in the overall CRBSI rate; the median rate was reduced from 2.7 per 1000 catheter days before the intervention to 0 by month 3 and through month 18 of the postintervention.[36] In general, these QI tools seek to standardize both communication and technical work.

Haynes and colleagues[37] described the use of a checklist to guide the perioperative time-out, briefing, and debriefing process. They showed that implementing the World Health Organization (WHO) Surgical Safety Checklist (Fig. 6-7)[38] reduced mortality and inpatient complications.[37]

	Room Number _____	Shift: ❒ AM / ❒ PM
Safety	What needs to be done to d/c patient from the ICU?	
	Patient's greatest safety risk? How can we ↓ risk?	
	What events or deviations need to be reported? ICUSRS issues?	
Patient Care	Pain & Sedation Management	Pain goal ____ /10
	Cardiac Review ECGs	HR goal ____ ❒ at goal ❒ ↑ ❒ ↓ β-blockade
	Volume status Net goal for midnight	Even ❒ Pos ❒ Neg ___ Net ___ (cc) ❒ Patient determined
	Pulmonary: Ventilator, ventilator bundle, HOB ↑, wean	❒ OOB/pulmonary toilet/ambulation
	SIRS/Infection/Sepsis evaluation Temp >38°C or <36°C; HR >90 RR >20 or $Paco_2$ <32 WBC >12000 < 4000 or >10% bands	❒ No current SIRS/sepsis issues ❒ Known/suspected infection ❒ Culture blood ×2/urine/sputum ❒ Antibiotic changes ❒ Discontinue sepsis bundle
	Can catheters/tubes be removed?	Y/N
	GI/Nutrition/Bowel regimen: TPN catheter, ND tube PEG needed?	❒ TPN ❒ NPO/Advance diet
	Is patient receiving DVT/PUD prophylaxis?	Y/N
	Can meds be discontinued, changed to PO, adjusted?	
To Do	Tests/Procedures today	
	Scheduled labs	
	AM labs needed/CXR?	
	Consultations	
Description	Has primary service been updated?	
	Has family been updated? Social issues addressed? Long-term/Palliative care	

Figure 6-5. Example of an intensive care unit (ICU) daily goals sheet. *CXR*, Chest radiograph; *d/c*, discharge; *DVT*, deep vein thrombosis; *EKG*, electrocardiogram; *GI*, gastrointestinal; *HOB*, head of bed; *HR*, heart rate; *ICUSRS*, ICU self-reporting system; *ND*, naso-duodenal; *NPO*, nothing by mouth; *OOB*, out of bed; *PEG*, percutaneous endoscopic gastrostomy; *PUD*, peptic ulcer disease; *RR*, respiratory rate; *SIRS*, severe infectious respiratory syndrome; temp, temperature; *TPN*, total parenteral nutrition; vent, ventilator; *WBC*, white blood cell count.

SOURCES OF QUALITY IMPROVEMENT INFORMATION

Development of a QI program first requires that an issue be identified; then baseline data are collected and an improvement intervention instituted. Data are re-collected after the intervention. If the intervention is found to be effective, ongoing monitoring or audits are instituted to ensure that the change is sustained. As part of the audits, feedback must be given to the providers. Health care providers traditionally have had limited ability to obtain feedback regarding performance in their daily work, in part because of a lack of information systems and a lack of agreement on how to measure quality of care.[39]

Ideas for QI programs can be identified from a multitude of sources, but they typically start with surveys and input from local medical staff and reviews of reported incidents. Additional information is gathered from the literature, review of national guidelines and quality metrics, and information obtained from external or internal reviews.

Sources of QI data that span both the clinical and administrative arenas include evidence-based medicine (EBM) and evidence-based clinical practice guidelines, alerts from accrediting agencies and nonprofit safety organizations, standards and guidelines put forth by medical specialty associations, closed claims databases, and government agency administrative databases. United States governmental agencies, including the Agency for Healthcare Research and Quality (AHRQ), Centers for Medicare and Medicaid (CMS), and the National Quality Forum (NQF), promote the development and reporting of health care quality measures.[40]

INCIDENT REPORTING

Voluntary incident reporting that captures hazardous systems has been successfully used to improve patient care and foster QI programs.[41] As the potential of voluntary incident reporting is being realized in health care, this reporting has become less punitive and more focused on systems rather than on individuals. Voluntary incident reporting, when appropriately applied, helps identify hazards to patients that can then become the focus of QI efforts that seek to mitigate those hazards.[42] Unlike other methods that evaluate harmed patients, voluntary incident reporting provides the potential to also learn from near misses—incidents that did not lead to harm

	Briefing: Before Every Procedure
	Team introductions: First and last names, including roles; write names on board
	Verify: Patient ID band, Informed Consent (read out loud), site marking, OR posting, patient's verbalization of procedure (if patient awake), H&P or clinic note
	Are there any safety, equipment, instrument, implant, or other concerns?
	Have antibiotics been given, if indicated?
	What are the anticipated times of antibiotic redosing?
	Is glucose control or β-blockade indicated?
	Is the patient positioned to minimize injury?
	Has the prep solution been applied properly, without pooling, and allowed to dry?
	Have the goals and critical steps of the procedure been discussed?
	Is the appropriate amount of blood available?
	Is DVT prophylaxis indicated? If yes, describe.
	Are warmers on the patient?
	Is the time allotted for this procedure an accurate estimate?
	Have the attendings reviewed the latest laboratory and radiology results?
	Debriefing: After Every Procedure
	Could anything have been done to make this case safer or more efficient?
	Has the Surgical Site Infection data collection form been completed?
	Are the patient's name, history number, surgical specimen name, and laterality on the paper work? (must be independently verified by the surgeon)
	Did we have problems with instruments? Were they reported?
	Plan for transition of care to postop unit discussed? ❒ Fluid management? ❒ Blood transfusion paperwork in chart? ❒ Antibiotic dose and interval to be continued postop? ❒ Pain management/PCA plan? ❒ New medications needed immediately postop? ❒ β-blockers needed? ❒ Glucose control? ❒ DVT prophylaxis?

Figure 6-6. Example of an operating room briefing and debriefing tool. *DVT,* Deep vein thrombosis; *H&P,* history and physical; *ID,* identification.

but were potentially hazardous. A rich source for QI projects should be these near misses and potential hazards, so that prevention of events is highlighted.

All anesthesiology departments should have a process in place for capturing adverse events and near misses. Although most departments have a process for reporting, many incidents go unreported for a variety of reasons. Departments should encourage voluntary reporting without threat of punishment. Electronic capture of adverse events, near misses, and complaints can provide data that can subsequently be analyzed to identify trends and assess the degree of harm that a hazard poses to patients.

Events that occur frequently with low harm can be just as important as an event that occurs rarely with high harm. At the local level, it is more effective to focus on a more frequently occurring adverse event (e.g., perioperative skin abrasions, mislabeling of laboratory specimens) or on a process that can be measured with high frequency (e.g., hand hygiene, administration of antibiotic prophylaxis). For rarely occurring harmful events, a QI initiative may encompass a more expansive analysis of a national adverse-event database with multicenter participation.

With multiinstitutional event reporting systems, events that would rarely be seen in a single institution can be collected in larger numbers. Such systems allow analysis for common causes that increase our knowledge base for prevention initiatives. Larger multiinstitutional data gathering systems include the University HealthSystem Consortium (www.uhc.edu), which supports event reporting and databases that can be used to develop QI programs, benchmarking, and evidence-based practice. Reporting systems that have been developed specifically to investigate rarely occurring anesthesia-related events include the Anesthesia Incident Reporting System (AIRS) created by AQI (www.aqihq.org/airs/airsIntro.aspx) and Wake Up Safe (www.wakeupsafe.org), a QI initiative of the Society for Pediatric Anesthesia. The AIRS program publishes a learning case each month in the *ASA Newsletter,* including a summary of a reported case with learning points.

More expansive international incident-reporting systems that are anonymous and voluntary have also been analyzed in the literature and have provided important information. Examples are the United Kingdom's Serious Incident Reporting and Learning Framework[43] (www.nrls.npsa.nhs.uk/report-a-patient-safety-incident/serious-incident-reporting-and-learning-framework-sirl/) and the Australian Incident Monitoring Study.[44] These incident registries do not require that the events be considered human error or preventable to merit reporting and are a source of ideas for QI projects.

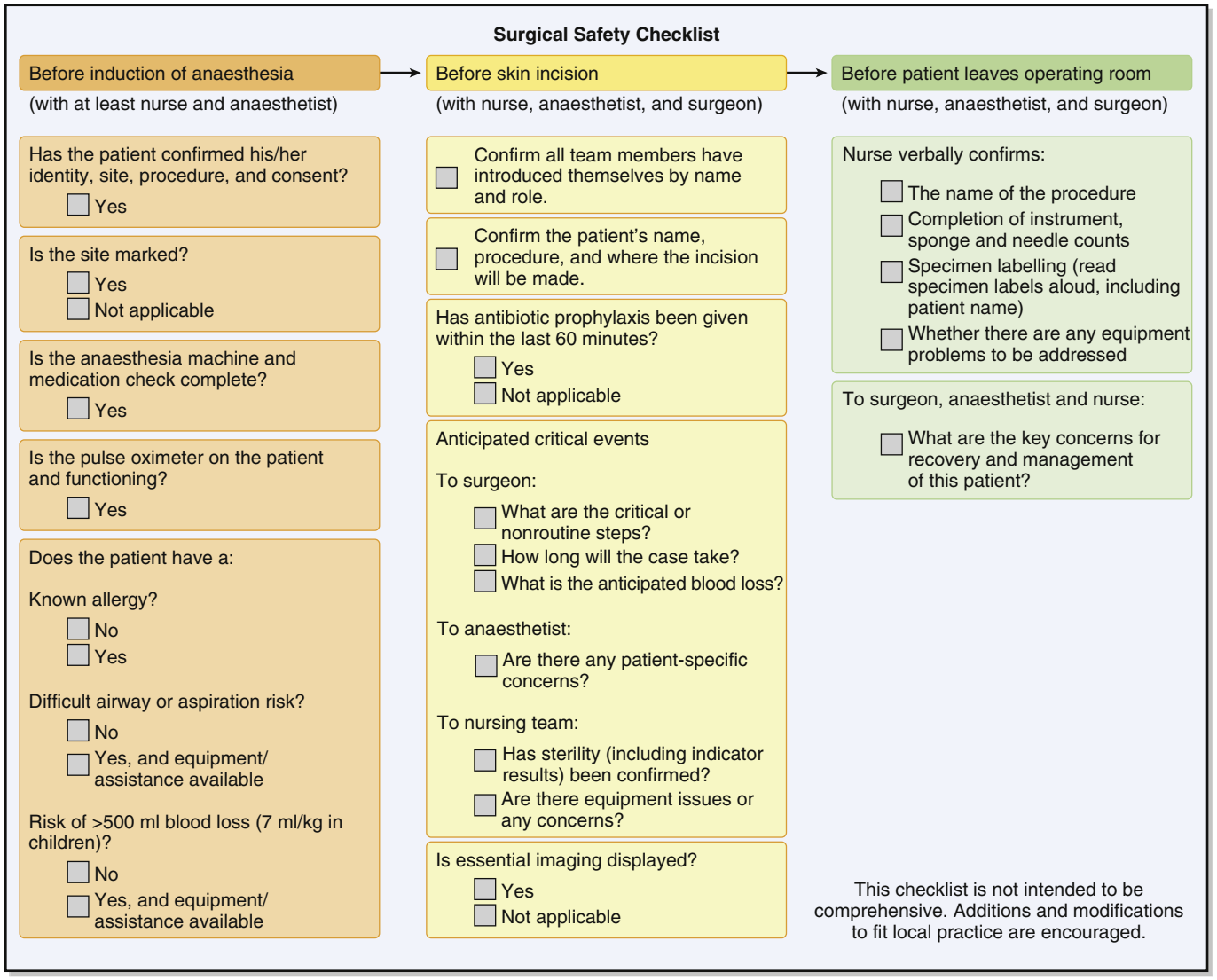


Figure 6-7. WHO Safe Surgery Checklist. *(Reproduced with permission from World Health Organization. WHO Surgical Safety Checklist.* www.safesurg.org/uploads/1/0/9/0/1090835/surgical_safety_checklist_production.pdf.*)*

Although voluntary systems often prove fruitful, many events and near misses still frequently go unreported. One way to capture these incidents is to survey local medical staff members to obtain their thoughts on how the last patient was harmed or how the next patient might be harmed. This process of performing a staff safety assessment survey is described in two later sections of this chapter (see "Collaborative Programs" and "Comprehensive Unit-Based Safety Program"). Staff safety assessment surveys can be particularly helpful for identifying issues for QI projects. Additionally, if staff members identify the issue, the likelihood is greater that they will have a vested interest in participating in the QI efforts.

PUBLISHED LITERATURE

Literature reviews offer ideas for QI topics in specific areas and information to guide interventions. For example, if the QI project plan is to reduce hazards in cardiac anesthesia, a literature review will provide reports of various cardiac anesthesia risks. Once a topic within a clinical area is selected, a literature search should be performed again to determine whether similar QI projects have been performed and whether they were successful. Such information will help with the design of a future initiative. The literature also provides published reports that identify guidelines and/or evidence-based practices that can be the basis for future programs.[45,46]

NATIONAL INITIATIVES AND QUALITY METRICS

The AHRQ is the source for both the National Quality Measures Clearinghouse and the National Guideline Clearinghouse. National professional organizations, such as the American Society of Anesthesiologists (ASA) and the Society for Critical Care Medicine (SCCM), offer guidelines specific to the field. The ASA has supported the review and development of many important guidelines that can serve as a rich source of QI initiatives. These

BOX 6-1 *Surgical Care Improvement Project (SCIP) Process and Outcome Measures*

Surgical Site Infection

- Prophylactic antibiotics
  - Received within 1 hour before surgical incision
  - Appropriately selected for surgical patients
  - Discontinued within 24 hours after surgery end time (48 hours for cardiac surgery)
- Cardiac surgery patients with controlled 6 AM postoperative serum glucose
- Postoperative wound infection diagnosed during index hospitalization (**OUTCOME**)
- Surgery patients with appropriate hair removal
- Colorectal surgery patients with immediate postoperative normothermia

Cardiac Surgery

- Noncardiac vascular surgery patient with evidence of coronary artery disease who received β-blockers during the perioperative period
- Surgery patients on a β-blocker before arrival who received a β-blocker during the perioperative period
- Intraoperative or postoperative acute myocardial infarction diagnosed during index hospitalization and within 30 days of surgery (**OUTCOME**)

Venous Thromboembolism (VTE)

- Surgery patients with recommended VTE prophylaxis ordered
- Surgery patients who received appropriate VTE prophylaxis within 24 hours before surgery to 24 hours after surgery
- Intraoperative or postoperative pulmonary embolism diagnosed during index hospitalization and within 30 days of surgery (**OUTCOME**)
- Intraoperative or postoperative deep vein thrombosis diagnosed during index hospitalization and within 30 days of surgery (**OUTCOME**)

Respiratory

- Number of days ventilated surgery patients had documentation of HOB being elevated from recovery end date (day 0) through postoperative day 7
- Patients diagnosed with postoperative VAP during index hospitalization (**OUTCOME**)
- Number of days ventilated surgery patients had documentation of stress ulcer disease prophylaxis from recovery end date (day 0) through postoperative day 7
- Surgery patients whose medical record contained an order for a ventilator weaning program (protocol or clinical path)

Global

- Mortality within 30 days of surgery
- Readmission within 30 days of surgery

Vascular Access

- Proportion of permanent hospital end-stage renal disease vascular access procedures that are autogenous arterial venous fistulas

HOB, Head of bed; *VAP,* ventilator-associated pneumonia; *VTE,* venous thromboembolism.

guidelines cover a range of practices and include guidelines for the placement of central venous access,[47] management of patients with obstructive sleep apnea,[48] and management of preoperative fasting.[49] For those who are also involved in critical care medicine, guidelines and protocols do improve performance with specific care processes such as sedation and ventilator weaning protocols in ICUs. Such protocols decrease the duration of mechanical ventilation and ICU length of stay[50,51] (also see Chapters 101 and 102).

Review of national quality metrics is another source of ideas for QI topics. National initiatives from CMS, such as the Physician Quality Reporting System (PQRS) and Surgical Care Improvement Project (SCIP), provide quality metrics and are associated with pay for performance. The Joint Commission (TJC) website (www.jointcommission.org) lists national patient safety goals and national quality core measures that are surveyed during site visits for accreditation. In 2004, TJC partnered with CMS to align measures common to both organizations in an initiative called Hospital Quality Measures. These measures are also endorsed by the NQF, a private, nonprofit membership organization created to develop and implement a national strategy for health care quality measurement and reporting (www.qualityforum.org). One of NQF's functions is to endorse certain quality and safety measures (consensus standards), which are then incorporated into other national quality initiatives. The goal for NQF-endorsed standards is that they become the primary standards used to measure the quality of health care in the United States. Increasingly, anesthesia programs are focusing on the standards that are relevant to the specialty because facilities are being evaluated on compliance with regulations and are required to report their performance regarding these standards to the governing bodies.

SCIP, a national collaborative of public and private entities that has outlined perioperative QI goals, is in partnership with TJC and CMS in a national initiative (www.qualitynet.org). This initiative uses both process and outcome measures (Box 6-1) to focus on key clinical areas, including surgical site infection, perioperative myocardial infarctions, venous thromboembolism, mortality, and readmission.

An increasing number of regional and national organizations are developing initiatives that are stimulating the reporting of specific evidence-based practices and outcomes. These initiatives are also determining the local selection of areas for QI (Table 6-3). Reporting of these measures to CMS is being incentivized by pay for performance and performance-based payment. National professional organizations such as the ASA are developing metrics specific to the field.

OUTCOMES RESEARCH

The comparison of outcomes associated with different process decisions, or variations in care delivery, is the basis for outcomes research. Outcomes research[52] offers a potential to identify these variations in care and to determine whether they improve outcomes for patients undergoing anesthesia. One of the key issues in outcomes research is risk adjustment, a challenging goal

TABLE 6-3 **NONPROFIT AND GOVERNMENTAL QUALITY IMPROVEMENT ORGANIZATIONS PERTINENT TO ANESTHESIA**

Quality Improvement Organization	Website	Description
Agency for Healthcare Research and Quality (AHRQ)	www.ahrq.gov	Lead federal agency charged with improving the quality, safety, efficiency, and effectiveness of health care
American Health Quality Association (AHQA)	www.ahqa.org	Represents quality improvement organizations and professionals working to improve the quality of health care
Anesthesia Patient Safety Foundation (APSF)	www.apsf.org	Promotes investigations and programs that will provide a better understanding of anesthetic injuries
Centers for Disease Control (CDC)	www.cdc.gov	One of the major operating components of the U.S. Department of Health and Human Services
Emergency Care Research Institute (ECRI)	www.ecri.org	Uses applied scientific research to discover which medical procedures, devices, drugs, and processes are best
Institute for Healthcare Improvement (IHI)	www.ihi.org	Health care improvement organization based in Cambridge, Massachusetts
Institute for Safe Medication Practices (ISMP)	www.ismp.org	The nation's only 501(c)(3) organization devoted entirely to medication error prevention and safe medication use
Medicare Quality Improvement Community (MedQIC)	www.medquic.org	A national knowledge forum for health care and quality improvement professionals
National Quality Forum	www.qualityforum.org	Created to develop and implement a national strategy for health care quality and reporting
National Patient Safety Foundation (NPSF)	www.npsf.org	An independent 501(c)(3) organization with a mission to improve the safety of patients

that requires a robust dataset. Using administrative data to identify patient risk factors has many limitations. Registries designed specifically for research, benchmarking, and QI are good sources for this purpose.

The Society of Thoracic Surgeons (STS) and the National Surgical Quality Improvement Programs (NSQIP) are examples of outcomes research registries. Established in the early 1990s, the STS database now includes participation by nearly all U.S. cardiac surgery centers and has developed robust risk-stratification models. Findings from this database have led to initiatives associated with significant reductions in mortality; examples include the use of β-adrenergic blockers and aspirin perioperatively (also see Chapter 3) and the use of internal mammary arteries for coronary artery bypass grafting. NSQIP is a newer registry that was developed by the U.S. Department of Veterans Affairs (VA). Findings from this risk-adjusted outcomes database were used to identify variations in care. The changes that were instituted based on these findings resulted in improved outcomes throughout the VA network. NSQIP has been adopted by the American College of Surgeons (ACS) to provide comparisons among hospitals. Currently, more than 350 general surgery centers participate.[53] Hospitals that participate submit detailed data on a sample of general surgical patients for a number of common surgical procedures. They then receive a graphic display that compares their outcomes with those of the entire cohort. Surgery centers then use these data to identify areas in which they might be able to make improvements and initiate QI projects with that focus. As an example, the Kaiser Permanente group used this information to develop a QI program focused on reducing the percentage of patients with prolonged perioperative intubation.[53]

The ASA created the Anesthesia Quality Institute (AQI) and the National Anesthesia Clinical Outcomes Registry (NACOR) with the goal of improving anesthesia outcomes through capture of case-specific data directly from electronic anesthesia data systems. These resources are still evolving and moving forward to improve outcomes in anesthesia. Another important effort in anesthesia is the Multicenter Perioperative Outcomes Group (MPOG), which is led by researchers at the University of Michigan. MPOG has established a national network of anesthesia practice groups that contribute data to a unified database. The goals of MPOG are to develop a structure for multiinstitutional collaboration and data sharing, to develop the information technology infrastructure to pool a wide variety of perioperative data for patient-centered research, to develop the statistical infrastructure to analyze the data, and to provide an academic venue in which faculty from multiple institutions will be able to collaborate in outcomes research (http://mpog.med.umich.edu).[52]

INTERNAL OR EXTERNAL INSTITUTIONAL REVIEWS

Internal or external institutional reviews of health care processes can provide important insights and ideas for QI initiatives. In addition to the external regulatory reviews, institutions are expected to perform internal reviews of quality and identify areas for improvement. These reviews are often used for QI projects at the institutional level.

PRIVATE INSURERS

Many private insurers now collect data on certain quality elements. The Leapfrog group is one such entity. The Leapfrog Hospital Quality and Safety Survey assesses hospital performance based on three evidence-based safety practices: (1) use of computerized physician order entry, (2) evidence-based hospital referral, and (3) ICU physician staffing. In 2010, the NQF Safe Practices were added as a Leapfrog Safe Practices score (a fourth leap), which is based on the level of performance of other NQF-endorsed practices (www.leapfroggroup.org). Leapfrog reports the results and rankings of its survey, allowing employers to

use the results to guide their choices in selecting health care coverage for their employees.

Public and private insurers are demanding increased accountability secondary to rising health care costs and threatened budgets. In response, performance-based payments, such as those used successfully in business, are being introduced as a means of improving quality. Pay for performance (P4P) refers to financial incentives that reward practitioners for the achievement of a range of payer objectives, including efficiency (quality care at a smaller cost), submission of data and measures to payers, and improved quality and patient safety (www.ahrq.gov/qual/pay4per.htm#1). Measures that are incorporated into P4P and performance-based measures must be evidence-based, consistent with national goals, or based on consensus in the absence of evidence. Furthermore, it is important that measures be reliable, valid, and feasible and that the programs be voluntary. Although the strategy of P4P is to align quality of care and payment, the impact of P4P on quality of care has thus far been modest. Currently, some Medicare programs also withhold payment for certain hospital-acquired conditions.

The PQRS is a reporting program that uses a combination of incentive payments and payment adjustments to promote reporting of quality information to CMS by eligible professionals. Physicians (anesthesiologists) and practitioners (certified registered nurse anesthetists and anesthesia assistants) can earn a 2% bonus from CMS by reporting their compliance with measures. Most anesthesia groups report through their billing software on the following measures: appropriate timing of prophylactic antibiotics to prevent surgical site infection, normothermia at the time of postanesthesia care unit admission (or documentation of active warming efforts), and observation of a bundle of sterile precautions when inserting a central line (use of the central line checklist). An additional 0.5% is awarded to those who participate in the maintenance of a certification program for their specific specialty board. An initial step in this program was payment for participation; ultimately, successful compliance with the clinical measures will be the basis for bonus payments. One question is whether payments may be decreased to those with less-than-desirable outcomes or nonparticipation in the reporting programs listed earlier. Additional measures are being evaluated, and the methods by which they will be incorporated into national initiatives and/or P4P will continue to evolve.[54, 55]

EXAMPLES OF QUALITY IMPROVEMENT PROGRAMS

Examples of QI frameworks and tools have been discussed. This section addresses broad initiatives for quality and safety improvement that have used some of the methodologies and tools detailed earlier in this chapter.

COLLABORATIVE PROGRAMS

Use of a collaborative is one approach to improving broad areas of care. A quality improvement collaborative involves the participation of two or more health care teams working toward a shared goal. In health care, a set of multidisciplinary representatives (from all of the clinical and administrative areas that are linked to the area of focus) should participate in the collaborative. A collaborative can be developed within a single organization and/or across multiple health care organizations. Collaborative programs are typically led by a team that is responsible for the following:

1. Determining the evidence-based interventions to be used and presenting these to the participants (if evidence-based interventions are not available, the team will generate interventions based on local and broad expert consensus)
2. Establishing the data collection approach (defining measures, collection methods, and feedback mechanism)

A key element to the success of collaboratives is an established process for educating members and for sharing interventions and obstacles. Through group discussions (meetings and/or conference calls), teams can learn about best practices and innovative methods used by other teams to approach a problem. In addition, collaboratives bring a shared momentum and enthusiasm that can increase sustainability.[21,56,57]

IHI has used collaboratives for more than a decade to improve patient care. In 2003 they introduced their Breakthrough Series Collaboratives in 2003,[58] which are characterized by these key standard steps: topic selection, expert faculty recruitment, enrollment of participating teams, learning sessions, action periods, the model for improvement, summative congresses and publications, and measurement and evaluation (Fig. 6-8).

Sawyer and associates[59] reported the success of a collaborative that incorporates a "mechanism to move evidence to the bedside and foster a culture where the focus is the patient."[59] The collaborative includes an emphasis on translating evidence into practice (TRIP) and the Comprehensive Unit-Based Safety Program (CUSP). This methodology has been reproduced and validated in several large collaborative efforts (Fig. 6-9).[59-61]

The TRIP model incorporates the following key steps and emphasizes the importance of measurement and feedback of data to teams.

1. Identify evidence-based interventions associated with an improved outcome through review of peer-reviewed publications.
2. Select goal-oriented interventions that have the most impact on outcomes and transform them into behaviors. In selecting behaviors, focus on interventions with the strongest treatment effect (smallest number needed to treat) and the lowest barrier to use.
3. Develop and implement measures that evaluate either the interventions (processes) or the outcomes.
4. Measure baseline performance and establish databases to facilitate accurate data management and timely feedback to teams.
5. Ensure that patients receive evidence-based interventions through four basic steps: engagement, education, execution, and evaluation (Table 6-4).

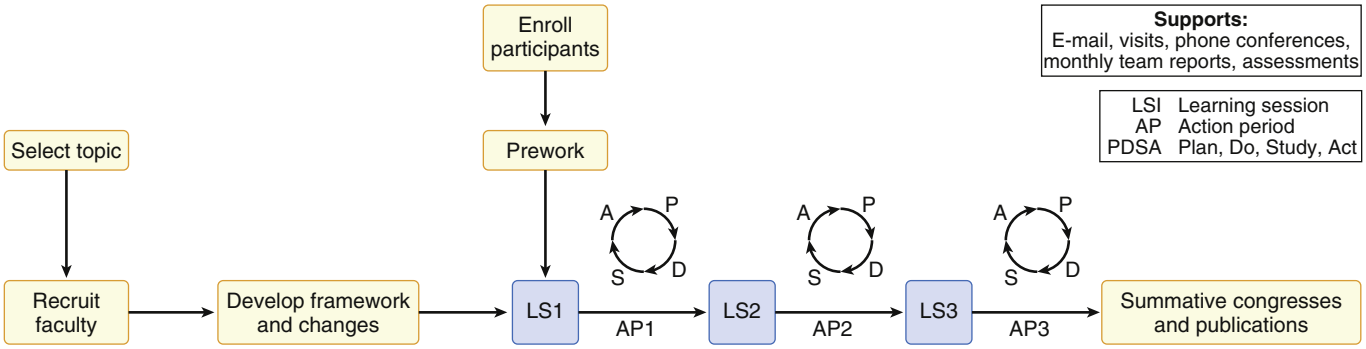


Figure 6-8. Breakthrough Series Collaborative Model. *(Reproduced with permission from Institute for Healthcare Improvement: The Breakthrough Series: IHI's Collaborative Model for Achieving Breakthrough Improvement. IHI Innovation Series white paper, Boston, 2003.* http://www.ihi.org/knowledge/Pages/IHIWhitePapers/TheBreakthroughSeriesIHIsCollaborativeModelforAchievingBreakthroughImprovement.aspx.*)*

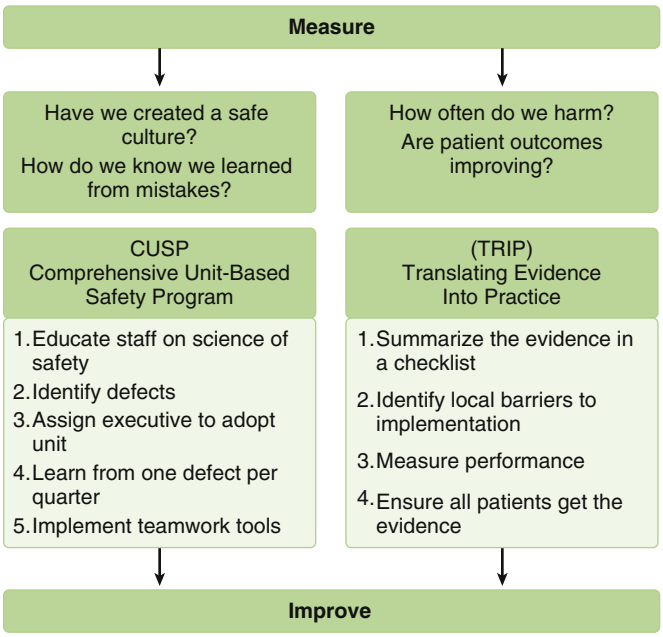


Figure 6-9. Translating evidence into practice (TRIP): four basic steps to ensure patients receive evidence-based care. *(Reproduced with permission from Sawyer M: Using evidence, rigorous measurement, and collaboration to eliminate central catheter-associated bloodstream infections,* Crit Care Med *38:S292-298, 2010.)*

The format for the collaborative also includes annual face-to-face meetings with the participating teams and periodic conference calls, which focus on education about the actual processes being implemented, the evidence base to support these processes, and the sharing of experiences. First, weekly immersion calls provide an initial overview of the program, describe the roles and responsibilities of each of the individuals, and introduce the tools that are to be used. Once the collaborative is introduced, monthly content calls are held throughout the program and are typified by a slide presentation of the evidence base for the intervention or of other components of the program to be implemented. The monthly coaching calls offer an opportunity for teams to share how well or how poorly they are implementing the interventions and share ideas for overcoming barriers.

TABLE 6-4 FOUR STEPS THAT ENSURE PATIENTS RECEIVE EVIDENCE-BASED INTERVENTIONS THROUGH A COLLABORATIVE USING THE EXAMPLE OF CATHETER-RELATED BLOODSTREAM INFECTIONS

Step	Action	Example
Engage	Make the problem real	Share information of local CRBSI rate vs. national rate
Educate	Develop an educational plan to reach ALL members of the caregiver team	Present evidence-based practices at grand rounds and multidisciplinary team meetings Present plans to improve care and measure outcome
Execute	Develop a safety culture Reduce complexity of the processes Introduce redundancy in processes Hold regular team meetings	Develop a culture of intolerance for CRBSI Ensure that all equipment and supplies for sterile CVC insertion are in one place and easily available Use checklists that identify key steps to reduce CRBSI Focus on 1 to 2 tasks per week and identify team member responsible for task
Evaluate	Measure and provide feedback	Develop data collection plan and database to track progress Give staff real-time feedback; post progress in highly visible location Identify causes of defects

CRBSI, Catheter-related bloodstream infections; *CVC,* central venous catheter.

Inclusion of the CUSP program in the collaborative provides a structured approach to improve safety culture and identify and mitigate hazards (i.e., learn from mistakes).[31,34] CUSP is a five-step program that has been tested and used successfully to improve quality and safety in ICUs (Table 6-5).[62,63]

Safety culture is assessed before the implementation of CUSP and reassessed after 1 year to evaluate the impact of the program. Multiple culture assessment tools are available.[64,65] The AHRQ offers a free survey online (www.ahrq.gov). The initial measure provides a baseline

TABLE 6-5 FIVE-STEP COMPREHENSIVE UNIT-BASED SAFETY PROGRAM

	Step	Description
1	Present educational material	Educate staff on science of safety though lectures and other educational materials
2	Complete forms that identify patient safety issues	Ask the following questions: • How will the next patient be harmed? • How can this harm be prevented? • Establish voluntary incident reporting
3	Assign senior executive responsible for specific area	Senior executive meets with all staff of the clinical area to: • Help prioritize safety efforts • Remove barriers for system changes • Provide resources • Demonstrate hospital commitment to patient safety • Foster relationship between senior leadership and staff
4	Learn from defects	Implement projects focused on two to three safety issues Keep goals simple: • Reduce complexity in the process • Create independent redundancies to ensure critical steps are accomplished
5	Implement teamwork tools	Implement programs such as checklists, training, and daily goals targeted at improving teamwork and communication

assessment of staff perceptions of safety culture in their clinical areas and their perceptions of the organization's commitment to patient safety.

Education is a crucial aspect of CUSP; it provides staff with a new set of lenses through which to identify hazards and recommend system changes to improve care. The objectives of these educational efforts are to ensure that staff: (1) understand that safety is a system property, (2) learn concepts for reliable health care design, and (3) understand the basics of change management. After an educational lecture on the science of safety, staff members are requested to identify patient safety hazards in their clinical areas and suggest improvement interventions. For this process, staff members review incident reports, liability claims, and sentinel events from their unit. In addition, two questions are asked: "How do you think the next patient will be harmed?" and "How can we prevent it from happening?"

After the completion of the survey and educational component, a senior leader of the institution (e.g., hospital president, vice president, director) is partnered with a unit or clinical area. This leader attends rounds on the unit monthly to help staff members prioritize safety efforts, to ensure that they have the resources to implement improvements, and to hold them accountable for evaluating whether safety has improved. Staff members are asked to learn from one defect per month and to implement one tool per quarter designed to improve care delivery.[31,34]

CUSP was pilot-tested in ICUs and subsequently implemented throughout Johns Hopkins Hospital and in the Michigan Keystone project.[60] In the pilot, a patient-safety team that consisted of staff from the clinical area was responsible for oversight of the program. To be most effective, this team included the ICU director as the ICU physician safety champion, the nurse manager, another ICU physician and nurse, a risk manager or patient-safety officer, and a senior executive from the institution. The program worked best if the physician and nurse who led the program dedicated at least 20% of their time to improving quality and patient safety. The first unit was the beta site; subsequent teams from other clinical areas would learn from its successes and failures. The ultimate goal was to have every area in the hospital organizing and managing safety through CUSP.

CUSP has been associated with significant improvements in safety culture. The percentage of staff reporting a positive safety climate increased from 35% before CUSP to 60% after CUSP.[63,66] In addition, teams identified and mitigated several specific hazards through CUSP. As a result of asking staff members to speculate on how the next patient might be harmed, the ICU created a dedicated ICU transport team, implemented point-of-care pharmacists, implemented the daily goals sheet, clearly labeled epidural catheters to prevent inadvertent intravenous connection, and standardized the equipment in transvenous pacing kits.[67] Moreover, the use of CUSP decreased the length of stay and nurse turnover.

In summary, CUSP provides several benefits for improving safety culture and is a primer for staff compliance in implementing any safety or QI intervention or project. It provides enough structure to convert the often-vague goals of improving safety into a focused strategy; yet it is flexible enough to allow units to work on issues most important to them. CUSP provides a venue to introduce rigorous research methods, acts as a learning laboratory to identify and mitigate hazards, and has the potential to improve patient outcomes.

CHALLENGES AND BARRIERS TO QUALITY IMPROVEMENT PROJECTS

Multicentered and/or single-hospital projects can fail because of inadequate resources, lack of leadership support, vague expectations and objectives for team members, poor communication, complex study plans, inadequate management of data collection, and wasted efforts to "reinvent the wheel" rather than adopting practices proven to be effective. Successful collaboratives require a local culture (the set of values, attitudes, and beliefs of the group) that is ready for change and participants who have a shared view of safety and who understand the science of patient quality and safety (i.e., the technical components of how care is organized and delivered).

THE FUTURE: RESEARCH, EDUCATION AND ETHICS

Much remains to be accomplished in QI research and practice. The opportunity to improve patient care is substantial, and the pressure to improve the quality of perioperative care continues to increase. Improving quality of care requires the ability to measure and improve

performance. Research is needed to develop measures of quality that clinicians believe are valid and to learn how to ensure that all patients reliably receive recommended interventions. Innovation is needed to develop information systems that can be used by multiple disciplines. Anesthesiologists and professional societies may need to partner with experts in quality measurement to develop and implement quality measures. Future efforts should balance the feasibility and validity of quality measures and develop integrated approaches to improving quality, including strategies to develop care bundles, decrease complexity, and create independent redundancies.

Clinicians now need the skills necessary to improve quality. Health care will cross the quality chasm only when all view quality and safety as their primary job, rather than as an added activity, and health care organizations provide the infrastructure to monitor and improve performance. Frontline health care providers must understand the science of quality and safety and evaluate safety risks as hazardous systems, not incompetent people. Integral to this is the education of our trainees. CQI in anesthesia residency training programs has been touted for well over a decade.[68] In recent years, residents in training were presented with six core competencies to master, mandated by the Accreditation Council of Graduate Medical Education,[69] and the IOM put forth their six Aims for Improvement[4] (Table 6-6). In an effort to link these two sets of goals and apply them to the clinical setting for training purposes, Bingham and colleagues[70] developed a framework called the Healthcare Matrix that can be used as both an educational tool and a research tool for improvement.

With the increasing amount of intellectual focus and health care resources being directed toward QI programs, the ethics of QI have come to light. QI projects have generally been exempt from the rigorous review of human-subjects research. However, a Hastings Center Report on the ethics of using QI methods to improve health quality and safety suggests that some QI projects may involve risk to patients and should undergo a formal review.[71] This report lists QI initiatives that may trigger the need for a review as those that have a randomized design, use novel treatments, involve researchers, have delayed feedback of monitoring, or are funded by external sources. The reporting of QI activities should be encouraged, as should requiring approval by an internal review board and following a standardized format for reporting the results. All of these practices support the premise that delivery of quality care is a science as well as an art.

TABLE 6-6 ACCREDITATION COUNCIL OF GRADUATE MEDICAL EDUCATION (ACGME) SIX CORE COMPETENCIES AND INSTITUTE OF MEDICINE (IOM) SIX AIMS FOR IMPROVEMENT

	ACGME Core Competencies	IOM Aims for Improvement
1	Patient care	Safe
2	Medical knowledge	Timely
3	Interpersonal and communication skills	Effective
4	Professionalism	Efficient
5	System-based practice	Equitable
6	Practice-based learning and improvement	Patient-centered

SUMMARY

Health care organizations need a systematic approach to three areas of patient safety: (1) translating evidence into practice, (2) identifying and mitigating hazards, and (3) improving culture and communication. The underlying principle for all of the approaches discussed in this chapter is that improvement of the quality of care dictates that practitioners must be able to measure their performance. Health care practitioners traditionally have had limited ability to obtain feedback regarding performance in their daily work, in part because of the absence of information systems and a lack of agreement on how to measure quality of care.[39] As a result, many in health care do not have access to performance data and consequently do not know what results they achieve (or fail to achieve). As consumers, payors, regulators, and accreditors increasingly require evidence regarding quality of care, the demand for quality measures will grow. To meet these demands, anesthesiologists must be prepared to use valid measures to evaluate the quality of care that they provide and to implement evidence-based best practices in the perioperative care of patients.

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Chapter 7

Human Performance and Patient Safety

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Key Points

- Clinical excellence is not achieved by the use of sound medical knowledge alone. Human factors and the interaction of team members, as well as organizational conditions in the system of care, also play major roles. Therefore, the study of human performance and related organizational matters is very important.
- The health care system in general and clinical institutions in particular must provide appropriate organizational characteristics to allow and foster safe patient care practices (e.g., improve safety culture, integrate effective incident reporting and analysis systems).
- High-reliability organization theory describes the key features of systems that conduct complex and hazardous work with very low failure rates. Errors do occur in such organizations, but their systems make them more impervious to errors and their sequelae (resilience).
- In dynamic domains such as anesthesia, continuous decision making, as described in the cognitive process model, is critical to achieving safe patient care.
- Several error mechanisms have been demonstrated through human factors research. Understanding these psychological "traps" (e.g., "fixation errors") can help anesthesia professionals to avoid or mitigate them.
- The introduction and spread of crisis resource management (CRM) training, including the application of realistic simulation exercises, are starting to improve patient safety in anesthesia and other acute care domains.
- As for all human beings, the performance of individual anesthesia professionals can be adversely influenced by "performance-shaping factors," including noise, illness, aging, and especially sleep deprivation and fatigue.
- A particular technique of human factors research called task analysis has been useful in understanding the work of anesthesia professionals.
- Observation of anesthesia professionals during routine operations or in the handling of adverse events (by using realistic patient simulators) has improved our knowledge of critical decision making, team interactions, and the impact of using cognitive aids such as checklists or emergency manuals.
- Future progress on patient safety in anesthesia will require interdisciplinary research and training, improvements in systems safety and organizational learning, and the involvement of all levels of the health care industry.

IMPACT OF HUMAN PERFORMANCE ON PATIENT SAFETY

The most important component of every anesthetic regimen is the human performance of the anesthesia professional and its relation to patient safety. More than 70% of accidents are caused by "human factors." Because the performance of the anesthesia professional—embedded in a larger system of care—is such a critical and most determining aspect of patient safety, education and training of health care professionals in this area need improvement. This chapter aims to provide an overview of the importance of human performance and systems safety in anesthesia and to provide start-up knowledge of key safety factors and methods.

Anesthesia is an intrinsically hazardous undertaking, but as hazardous activities go, its track record is indeed a model of patient safety for the rest of health care.[1,2] The Institute of Medicine (IOM) asserts: "Anesthesia is an area in which very impressive improvements in safety have

been made."[3,4] However, the theory of organizational safety teaches us that safety is a never-ending process; any patient harmed by an anesthetic is one patient too many (in concert with the "zero vision" statement of the U.S. Anesthesia Patient Safety Foundation [APSF]: "That no patient shall be harmed by anesthesia"). Cooper and Gaba wrote:

Anesthesiologists should remain aware of the hazards they still face, take pride in having been the leaders in patient safety efforts, and stay motivated to continue the pursuit of "no harm from anesthesia" with the passion it still demands.[1]

Because most of the work on human performance (and also on simulation) has been started and has focused on anesthesiology in the operating room (OR), this chapter deals primarily with aspects of performance and safety in the OR setting. Nevertheless, most of the same principles and issues are relevant to the postanesthesia care unit (PACU), the intensive care unit (ICU), emergency medicine, and to a lesser degree, pain therapy and other domains of importance to anesthesiologists. For readers with a special interest in the ICU, a selection of references is given as a starting point.[5-22]

Safe conduct of anesthesia depends on the appropriate application by skilled anesthesia professionals of knowledge concerning surgical procedures, the physiology of patients during and after anesthesia, the characteristics of anesthetic and adjuvant drugs, and the means of monitoring the patient and the life-support equipment throughout the perioperative period. In this chapter, we use "anesthesia professional" to refer to any anesthesia clinician taking care of a patient, whether a physician, certified registered nurse anesthetist (CRNA), or anesthesia assistant (or to similar positions in other countries).

Traditionally, an adequately trained anesthesia professional automatically was assumed to perform appropriately. Deviations from optimal outcomes were understood to result from imperfections in the art and science of anesthesia, which led to heavy emphasis on the scientific and technical aspect of anesthesia training and care. More rarely, adverse outcomes were ascribed to negligence or incompetence on the part of the anesthesia professional. Today, a more complete understanding exists that anesthesia professionals themselves, both as a profession and as individuals, have strengths and vulnerabilities pertaining to their work environment. The performance of human beings is incredibly flexible and powerful in some aspects but very limited in others. Humans are vulnerable to distractions, biases, and errors. This chapter surveys some of the human characteristics that define the performance of anesthesia professionals. These characteristics (also termed human factors) are by no means constant; for example, a person may communicate very effectively in one instance and fail to close the loop in the next challenging communication role.

The domain of the anesthesia professional is very challenging; it is at least as difficult as other domains that more readily capture the public's imagination, such as aviation. Since the 1980s, research has been conducted on the nature and limitations of professional judgment and decision making in this dynamic and complex world. Chapter 8 explores developments in the methods of using simulations and simulation technologies that have contributed to this research and that may open new opportunities to prepare anesthesia professionals to handle the challenges they face in their work.

The literature related to human performance and patient safety is vast. Standard reference works are available[23-34] (Appendix 7-1), and this chapter samples only a portion of this literature as it most closely relates to the work of anesthesia professionals. Moreover, this chapter does not address human-machine interactions and the physical design of the work environment in depth. These aspects of human factors, or ergonomics, in anesthesia have considerable importance in their own right. The reader is referred to several publications that review these issues in detail.[35-46]

NATURE OF THE OPERATIONAL DOMAIN OF ANESTHESIOLOGY

The operational domain of anesthesia is a complex, dynamic world with a cognitive profile common to many real-world task domains. Analysis of complex dynamic worlds since 2000 has departed sharply from previous conceptions of decision making.[47] Classic decision-making approaches, such as decision theory and multiattribute utility theory, are mathematic techniques that were traditionally used as the dominant framework for understanding human performance. They worked well in simplified laboratory experiments on decision making and action, yet some investigators had significant difficulty in applying these approaches to real-world decision and action settings.[47] Orasanu and colleagues identified eight factors that characterize such naturally occurring complex dynamic worlds.[47] These factors apply to anesthesia as follows:

1. **Ill-structured problems.** Unlike traditional decision experiments, there is not just a single decision to be made. Rather, a variety of interrelated decisions must be made by the anesthesia professional and surgeon. The patient's physiologic behavior is not an independent random variable but is causally linked to previous decisions and actions.
2. **Uncertain dynamic environment.** Dynamism stems from the frequency of routine and anomalous changes or events, the rapidity with which they evolve, and the unpredictability of the patient's physiology and response to interventions. An anesthetized patient is in a constant state of change during surgery, with many events outside the anesthesia professional's control. Although preventive measures can reduce the likelihood of some events, other events cannot be avoided because they are inevitable side effects of medically necessary procedures (e.g., surgical blood loss). Unpredictable and dynamic occurrences compete with the preplanned aspects of the case and drive the anesthesia professional's actions. The true state

of the patient cannot usually be measured directly. It must be inferred from ambiguous patterns of clinical observations and data from electronic monitors. These data are imperfect because, unlike industrial systems that are designed and built with sensors in key areas to measure the most important variables, patients are typically instrumented to measure the variables that are easiest to monitor, predominantly with the use of noninvasive methods. Most physiologic functions are observed indirectly through weak signals available at the body surface and thus are prone to various types of electrical and mechanical interference. Invasive measurements are also vulnerable to artifacts and uncertainties of interpretation. Even if the anesthesia professional knew the exact state of the patient, the patient's response to interventions would be unpredictable.

3. **Time stress.** Because the OR is a scarce resource, an incessant overall time pressure exists to use the OR efficiently. An even more intense immediate time stress occurs within each case and is generated by dynamic situations that evolve rapidly and must be dealt with in timely fashion.
4. **Shifting, ill-defined, or competing goals.** Multiple goals of case management (e.g., hemodynamic stability, good operating conditions for the surgeon, rapid emergence from anesthesia) may compete with each other. The surgeon's goals may sometimes compete with those of the anesthesia professional. All these goals shift as the patient's situation changes dynamically throughout the procedure.
5. **Action-feedback loops.** The time constants of actions and their effects are very short, on the order of seconds to minutes. Complete intermixing of decision making and action occurs; these functions are not performed in separate cycles. Most decisions and actions are implemented and evaluated incrementally, with the effect of one cycle assessed before deciding on further possible actions.
6. **High stakes.** The stakes are high because even for elective surgery in healthy patients, there is an ever-present and very real risk of injury, brain damage, or even death. A catastrophe is often the end result of many pathways that begin with seemingly innocuous triggering events. Each intervention, even if appropriate, is associated with side effects, some of which are themselves serious. Some risks cannot be avoided. Unlike an event such as a commercial flight, which can be delayed or aborted if a problem occurs, during an event in the OR this is not usually possible, and immediate surgery may be necessary to treat a medical problem that is itself life-threatening. Analogous to military aviation, balancing the risks of action (anesthesia and surgery) against those of inaction is often extremely difficult.
7. **Multiple players.** Anesthesia domains involve multiple players from different professional backgrounds. Each individual has a set of goals, abilities, and limitations. In some situations, interpersonal interactions, among anesthesia personnel and between them and other OR team members, dominate the work environment.
8. **Organizational goals and norms.** The anesthesia professional works within the stated and unstated norms of the OR suite, the anesthesia department, the institution, and the profession as a whole. Decisions are sometimes made to conform to these norms even though they are not wholly subscribed to by the anesthesia professional.

Although many of these features apply to other domains of medicine, anesthesiology is unique in that all eight factors are prominent. In particular, what sets anesthesia apart from clinic- or ward-based medicine is the intensity of the dynamism, time pressure, and uncertainty, with danger lurking just below the surface.

SAFETY CULTURE OF THE OPERATING ROOM AND INTENSIVE CARE ENVIRONMENT

ANALYZING THE ANESTHESIA PROFESSIONAL'S DOMAIN: THE OPERATIONAL WORLD VERSUS THE ORGANIZATIONAL WORLD

Psychologists and cognitive engineers who study real work environments describe each field as a domain. Each domain has specific characteristics that set it apart from others, including the nature of the tasks to be performed, the relationships among the tasks, the time scale over which they must be executed, and the criteria for their successful performance. This chapter deals mainly with the operational domains in which anesthesia care is delivered, primarily the OR, the PACU, and the ICU (see also Chapters 4, 109, and 110). However, as pointed out by Reason,[48-51] as well as by Cook, Woods, and McDonald,[52] what goes on in the operational domain is extensively shaped by the organizational and managerial environment in which it is located, even to the point that operational personnel believe themselves to be the "victims" of problematic decisions further back in the system.

In everyday practice, these distinctions are hidden or blurred. The positive and negative contributions of the organizational and management elements are often so embedded in the normal routine that they are difficult to isolate. Interesting information about the system often comes from considering abnormal situations, accidents, or near misses instead of normal events. For example, investigation of the loss of the space shuttle Columbia revealed a variety of latent errors within the procedures and safety culture at the National Aeronautics and Space Administration (NASA): "The accident was probably not an anomalous, random event, but rather likely rooted in NASA's history and the space flight program's culture."[53]

The report placed as much weight on these factors as on the direct technical causes of the accident. Traditionally, one speaks of errors arising in decisions and actions that lead to a mishap. However, the term "error" is increasingly considered an inappropriate way to categorize behavior (being a judgment of attribution and blame) and should be thought of merely as a way to identify behavior at the locus of a critical situation. In

this context it must be understood that "errors are not the cause of an accident." Rather, errors are usually the consequence of a combination of several underlying factors. Beyond that, errors must combine with other circumstances to result in an accident or adverse outcome.[54] This concept is illustrated in Figure 7-1. Some errors are actively produced in the operational domain, whereas others are introduced by the organizational environment. James Reason, a psychologist at the University of Manchester, England, described the latter by using the concept of "latent errors":

... errors whose adverse consequences may lie dormant within the system for a long time, only becoming evident when they combine with other factors to breach the system's defenses. [They are] most likely to be spawned by those whose activities are removed in both time and space from the direct control interface: designers, high-level decision makers, construction workers, managers and maintenance personnel.[54]

Latent errors probably exist in all complex systems, and Reason adopted a medical metaphor to describe them as "resident pathogens." Like microorganisms in the body, the resident pathogens remain under control until sets of local circumstances "combine with these resident pathogens in subtle and often unlikely ways to thwart the system's defenses and bring about its catastrophic breakdown" (Fig. 7-2). This "threat and error model" was also articulated by the noted aviation-oriented psychologist Robert Helmreich at the University of Texas (Fig. 7-3).[55]

A variety of latent failures can exist in the anesthesia environment. They may include such issues as how surgical cases are booked, how cases are assigned to specific anesthesia professionals, what provisions are made for preoperative evaluation of outpatients, and what relative priority is given to rapid turnover between cases or avoiding cancellation of cases as opposed to avoiding risk. Latent errors can also result from the design of anesthesia equipment and its user interfaces, which in some cases lead clinicians to err or are unforgiving of errors. Manufacturing defects and routine maintenance failures are also types of latent failure.

Investigation of untoward events must address both latent and active failures and both the organizational and managerial environment and the operational domain. One risk of focusing solely on active failures is that operational personnel may be "victims of the system" in a "catch-22"–type situation and be pushed to maximize production while admonished to "be safe." Addressing only their actions—and not the latent pressures under which they must work—can make them defensive and uncooperative. Cook, Woods, and McDonald pointed out that if one looks at the chain of events in an accident sequence, one can always find a failure on the part of an operator.[52] If the analysis stops at this point, the operator (i.e., the anesthesia professional) may be wrongly blamed for a failure, the real roots of which go back to latent failures in the organization. If the underlying latent errors are never identified or never fixed, they will remain in the system and will probably induce another accident chain in the future. This situation is visualized in Reason's accident trajectory, shown in Figure 7-2.

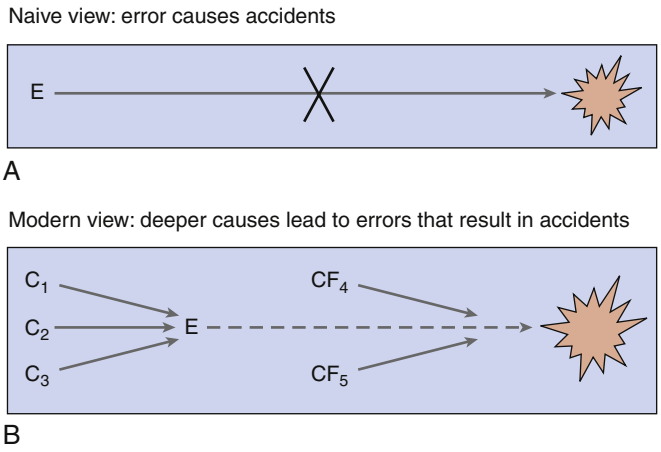


Figure 7-1. Relationship between errors (E) and adverse events. **A,** Errors are not the cause of accidents but in rare cases they lead directly to the adverse event. Multiple root causes (C_1, C_2, C_3) lead to the error (**B**). For the most part, additional contributing factors (CF_4, CF_5) are necessary to allow the error to evolve into an adverse event. Incident reporting systems should try to identify as many of the root causes and contributing factors before an accident happens and try to influence these factors in such a way that no accident will happen. *(Modified from Rall M, Manser T, Guggenberger H, et al: Patient safety and errors in medicine: development, prevention and analyses of incidents [in German],* Anasthesiol Intensivmed Notfallmed Schmerzther *36:321-330, 2001 with permission.)*

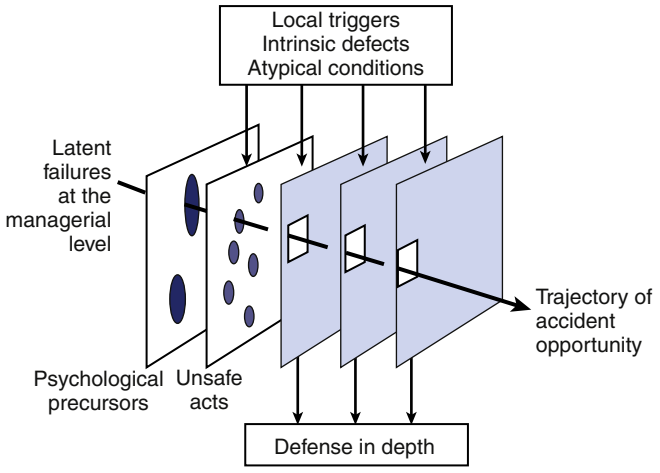


Figure 7-2. James Reason's model of the causation of accidents. Latent failures at the managerial level may combine with psychological precursors and event triggers at the operational level to initiate an accident sequence. Most accident sequences are trapped at one or more layers of the system's defenses. The unforeseen combination of organizational or performance failures with latent errors and triggers may lead to breach of the system's defenses and allow the accident to take place. The diagram should be envisioned as being three-dimensional and dynamic — with " shields " moving around and holes in the defenses opening and closing. *(Redrawn from Reason JT:* Human error, *Cambridge, 1990, Cambridge University Press.)*

ASYMMETRY BETWEEN SAFETY AND PRODUCTION

An additional difficulty in achieving optimal safety is an inherent asymmetry of information and concern about safety versus production (Table 7-1).[54] Investments for

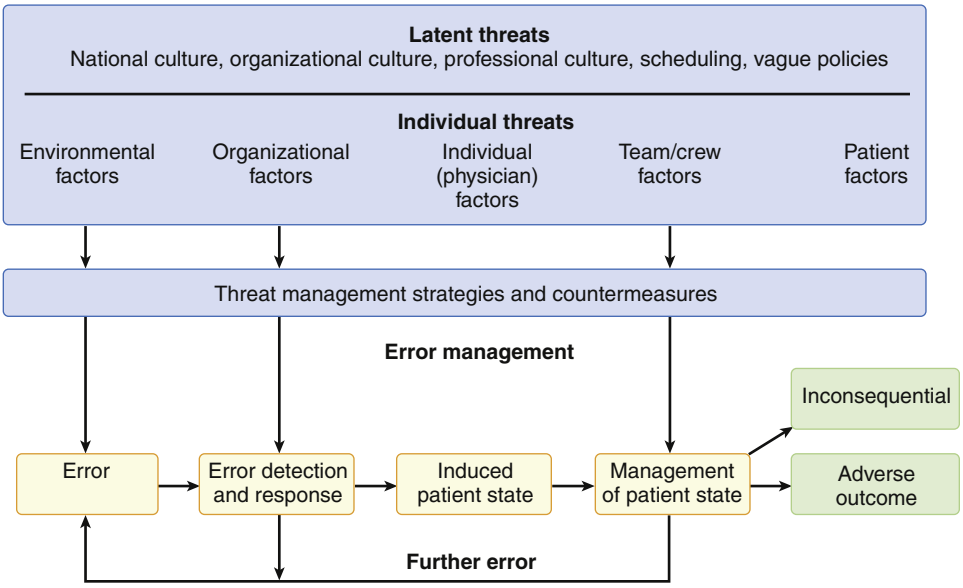


Figure 7-3. University of Texas threat and error model.[55] This model, which illustrates the evolution of errors, is used in the analysis of incidents and accidents.

TABLE 7-1 ASYMMETRY OF SIGNALS OF SAFETY VERSUS SIGNALS OF PRODUCTION

Production	Safety
Feedback about production is easy to measure reliably and nearly continuously ("revenue," "earnings," "expenses") and indicates success in a positive fashion	Traditional measures of "safety" are indirect and discontinuous, thus making them noisy and difficult to interpret or even deceptive
Success is indicated "positively" (e.g., increasing earnings), is obviously reinforcing, and has high salience (the bottom line is the "bottom line" for a firm)	Feedback is provided "negatively" (fewer accidents or incidents) and has little reinforcement value in itself. High salience is achieved only after an accident or a scary near miss
The relationship between the application of resources (money, effort, time) and production goals is relatively certain, thus making it easy to use feedback	Even when interpreted correctly, the relationship between application of resources and safety goals is relatively uncertain, thus making it difficult to use the feedback

Modified from Reason JT: Human error, *Cambridge, 1990, Cambridge University Press.*

BOX 7-1 ***Recommendations of the Institute of Medicine Report*** **To Err Is Human**

- Make patient safety a declared and serious aim.
- Provide strong, clear, and visible attention to safety.
- Implement nonpunitive systems for reporting and analyzing errors.
- Incorporate well-understood safety principles, such as standardizing and simplifying equipment, supplies, and processes.
- Establish interdisciplinary programs to improve teamwork and communication by using modalities proven in other industries, including simulation.

From Kohn LT, Corrigan JM, Donaldson MS: To err is human: building a safer health system, *Washington, DC, 1999, National Academy Press.*

production are easy to plan for and measure; feedback about production is easy to obtain and to interpret. Investments for safety are more difficult to plan for, and the costs are more difficult to measure. Most importantly, feedback about safety is inherently weak and ambiguous. How can one measure the accidents that could have occurred but did not? Only after a catastrophe takes place do the costs of a safety failure become apparent.

ORGANIZATIONAL SAFETY

Since the 1990s, many landmark publications and activities have addressed patient safety and the organizational aspects of reducing errors.[3,30,50,56-62] The report of the IOM in 1999, *To Err Is Human,*[3] was a highly publicized awakening in the United States about the problems of patient safety. Summarizing the primary literature, the report stated that "tens of thousands die each year from errors in their care and hundreds of thousands suffer or barely escape from nonfatal injuries that a truly high-quality care system would largely prevent." The most important recommendations of this report, which led to nationwide activities to promote patient safety, are shown in Box 7-1.

The subsequent report of the IOM Committee on Quality of Health Care in America, entitled *Crossing the Quality Chasm: A New Health System for the 21st Century,*[56] took a systematic approach to improvement of the entire health care system. It stated that "between the healthcare we have and the care we could have, lies not just a gap, but a chasm" because the health care system today harms too frequently yet routinely fails to deliver its potential benefits. The report concluded: "The current care system cannot do the job. Trying harder will not work. Changing the systems of care will." In the following text we consider the organizational and systems aspects of anesthesia care and patient safety.

Several schools of thought about organizational safety in highly hazardous activities exist. Two theories, normal accident theory (NAT) and high-reliability organization

TABLE 7-2 **COMPLEMENTARY VIEWS OF HIGH-RELIABILITY ORGANIZATION THEORY VERSUS NORMAL ACCIDENT THEORY**

HROT	NAT
Accidents can be prevented through good organizational design and management	Accidents are inevitable in complex and tightly coupled systems
Safety is the priority organizational objective	Safety is one of a number of competing objectives
Redundancy enhances safety; duplication and overlap can make a reliable system out of unreliable parts	Redundancy often causes accidents because it increases interactive complexity and opaqueness and encourages risk taking by social shirking and cue-taking behavior
Decentralized decision making is needed to permit prompt and flexible field-level responses to surprises	Organizational contradiction: decentralization is needed to handle the distributed complexity, but centralization is needed to manage tightly coupled systems
A "culture of reliability" will enhance safety by encouraging uniform and appropriate responses by field-level operators	A military model of intense discipline, socialization, and isolation is incompatible with democratic values
Continuous operations, training, and simulations can create and maintain high-reliability operations	Organizations cannot train for unimagined, highly dangerous, or politically unpalatable operations
Trial-and-error learning from incidents (through effective incident reporting) can be effective and supplemented by anticipation and simulations	Denial of responsibility, faulty reporting, and biased reconstruction of history frequently cripple learning efforts

Modified from Sagan SD: The limits of safety, *Princeton, NJ, 1993, Princeton University Press.*
HROT, High-reliability organization theory; *NAT,* normal accident theory.

theory (HROT), have dominated the discussion of safety in many domains and have been applied individually to health care with increasing frequency since the 1980s.[51-60,63] NAT was originally promulgated by the sociologist Charles Perrow in the wake of the Three Mile Island (Pennsylvania) nuclear accident,[64] and the theory has been applied by him and others to such diverse fields as commercial aviation, maritime transport, and the handling of nuclear weapons. HROT was put forth initially by a group of researchers at the University of California at Berkeley. It has also been applied to diverse domains, including aircraft carrier flight decks, offshore oil platforms, air traffic control, nuclear power production, and the financial transaction industry (Karlene Roberts, personal communication). These workers' complementary views of organizational safety are summarized briefly here and in Table 7-2.

NORMAL ACCIDENT THEORY

NAT focuses primarily on two features of a system: (1) the complexity of interactions among the system's elements and (2) the presence of tight coupling among the system's elements. A system is tightly coupled when a change in one part of the system rapidly alters other parts of the system. For example, some physiologic systems are buffered from changes in others, whereas certain core components, such as oxygen delivery and blood flow, are tightly coupled and interact strongly. The patient's physiology may become tightly coupled to external systems such as ventilators and infusions of hemodynamically active drugs. When complexity and tight coupling coexist, abnormal sequences of events can sometimes be hidden and have complex or unpredictable consequences. Typically, active errors in the system do not result in an accident because they are trapped at some point by the system's multiple layers of checks and defenses (see Fig. 7-2). Even a minor perturbation can cause normal system behavior to be out of control when complex interactions and tight coupling are present. Perrow called this a "normal accident" because the perturbations are common and arise out of otherwise normal system operations.[64] He suggested that attention should be directed at strengthening the recovery pathways by which small events can be properly handled before they evolve into a serious accident.

COMPLEXITY AND TIGHT COUPLING: LATENT ERRORS IN ANESTHESIA

Clearly, the anesthesia domain involves complex interactions with tight coupling.[65] The complexity stems to some degree from the variety of devices in use and their interconnections, but these are, in truth, vastly simpler than those found in an oil refinery, a 747 aircraft, or a space shuttle. A more important source of complexity is the "uncertainty complexity" of the patient.[65] The human body is an incredibly complex system containing numerous components, the interactions of which are only vaguely understood. Because many body systems affect each other, the patient is a major site of tight couplings. Furthermore, the anesthetic state tends to ablate the buffers between some of these interconnected systems, thereby strengthening the coupling between them and between the patient and external mechanical supports. Galletly and Mushet studied anesthesia "system errors" and observed tight coupling associated with "the use of neuromuscular blocking drugs, the presence of cardiorespiratory disease, certain types of surgical procedures, and the effect of general anesthetic agents.[66] Looser coupling was observed with the use of high concentrations of oxygen and air mixtures, preoxygenation, and spontaneous breathing techniques."

According to the NAT view, we delude ourselves by believing that we can control our hazardous technologies and forestall disaster; in reality, many of the efforts we make at management and design tend only to increase the opacity and complexity of the system (making more holes in the barriers), thereby increasing the likelihood of accidents. The combination of these factors provides fertile ground for the occurrence of accidents—indeed, according to NAT it makes it inevitable that some of the

"normal" everyday faults, slips, and incidents will evolve into tragic accidents. NAT is often considered a "pessimistic" view of the ability of organizations to conduct highly hazardous operations without harmful errors.

The very concept of risk is constructed and negotiated. This was perhaps expressed most clearly by Dianne Vaughan in her powerful analysis of the explosion of the Challenger space shuttle:

Risk is not a fixed attribute of some object, but constructed by individuals from past experience and present circumstance and conferred upon the object or situation. Individuals assess risk as they assess everything else—through the filtering lens of individual worldview.

Vaughan's main thesis is that the Challenger exploded not because "risk-taking" managers "broke the rules" but because the system evolved to make excessive risk a part of "following the rules." This happened in response to the system's "culture of production" with ingrained production pressure; it was a regular occurrence that aberrant findings be explained away ("normalization of deviance"), and "structural secrecy" was enforced between departments, between manufacturers and NASA, and between engineers and managers. Sadly, many of these same phenomena occurred yet again and led to the Columbia accident.[53] Unfortunately, each of these system characteristics is also present in perioperative settings.

HIGH-RELIABILITY ORGANIZATION THEORY

In contrast to these rather pessimistic views of the organizational challenges to safety is the HROT view that although it is not easy, proper organization of people, technology, and processes can handle complex and hazardous activities at acceptable levels of performance.[61,67] Even though accidents can never be totally eliminated, high-reliability organizations (HROs) (Fig. 7-4) must be judged by the benefits that we derive from their activities and their small absolute risk of failure. This view seems particularly appropriate in anesthesiology because forgoing surgical treatment is not a viable option for many patients, and challenges to safety must often be met head-on. Although the concepts of HROT have varied over the years, the core characteristics of HROs are shown in Boxes 7-2 and 7-3.[68-70]

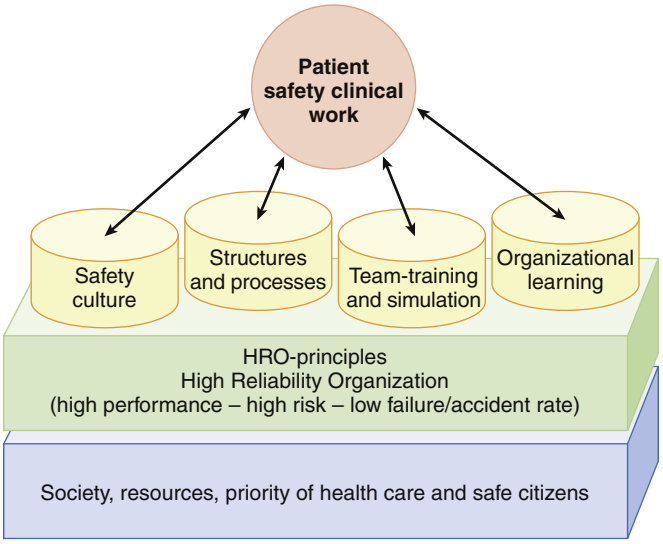


Figure 7-4. High-reliability organization.

A key aspect of HROT is that of a culture of safety (or "safety culture"). Since publication of the reports from the IOM, health care has begun paying attention to certain elements of "culture." However, most of the attention has been devoted to the "culture of blame" in a system whereby problems are addressed largely in terms of who is to blame rather than what can be done to prevent these problems. Safety culture goes beyond the issue of blame by dealing with a host of aspects related to how individuals and groups conduct their work. Culture is made up of values (what is important), beliefs (how things should work), and norms (the way things work). These elements are shown in Box 7-2. It is equally important that the culture be highly uniform throughout the organization and be continually reinforced by peers, more so than by enforcement of rules.

High-Reliability Organization Theory in the Specialty of Anesthesiology

Anesthesiology has traditionally been strong at some elements of an HRO, particularly in redundancy and technical safety measures. A movement is growing in anesthesia to implement HRO philosophies and techniques more fully.[63] In fact, anesthesiologists not only have been promoters of the patient safety movement in general but also have been leaders at applying HROT principles to health care. In 2003, the APSF began initiatives in high-reliability perioperative health care (see the special issue of the *APSF Newsletter,* summer 2003, at www.apsf.org).

BOX 7-2 ***Elements of a Culture of Safety****

VALUES

- Safety is the most important goal, overriding production or efficiency.
- The preoccupation is with possible "failures," rather than past "successes."
- Necessary resources, incentives, and rewards are provided for optimal safety, not only for optimal production.

BELIEFS

- Safety must be actively managed.
- Processes and routines of care are as (or more) important to safety as individual dedication, skill, or effort.
- Openness about safety and errors is essential; learning from normal and adverse events should be thorough.

NORMS

- Low-ranking personnel raise safety issues and challenge ambiguity regardless of hierarchy or rank.
- Calling for help is encouraged and occurs frequently, even (or especially) by experienced personnel.
- Explicit communication is frequent.
- The hierarchy is flat—leaders listen to juniors; juniors speak up; and calling for help is routine regardless of rank.
- People are rewarded for rationally erring on the side of safety, even when their credible concerns turn out to be wrong.

Modified from Weick KE: Organizational culture as a source of high reliability, Calif Manage Rev *29:112-127, 1987.*

*Part of high-reliability organization theory as described in Box 7-3.

Box 7-3 summarizes key elements of an HRO adapted to health care.

TEAMS AND COMMUNICATION

Unlike teams in aviation, the military, and police and fire services, the OR team is unusual in that the command structure is ambiguous. Physicians (surgeon and anesthesiologist) are nominally superior to nursing and technical staff, but physicians are coequally responsible for the patient during the immediate perioperative period. Surgeons were historically considered the "captain of the ship," with even a legal doctrine giving them responsibility for the actions of all other OR team members. Although this legal doctrine has formally fallen by the wayside, remnants of it remain in aspects of the organizational structure and culture of OR environments. Nonetheless, when both an anesthesiologist and a surgeon are caring for a patient, they are coequally responsible, and this situation can lead to complex issues of command authority, hierarchy, and control.

Each physician, as well as the nurses and technicians, has a primary territory of knowledge, skill, and responsibility, but considerable overlap exists among them.

Strictly speaking, a team is defined as "a distinguishable set of two or more people who interact, dynamically, interdependently, and adaptively toward a common and valued goal/objective/mission, who have each been assigned specific roles or functions to perform, and who have a limited life-span of membership." A team is distinct from a group in that a group is an ad hoc collection of individuals without a specific mission and without specific roles. In the OR, all team members have the common goal of a good outcome for the patient. However, considerable disagreement can exist on how to achieve this goal and which elements of patient care have the highest priority. These differences are probably traceable to the fact that the OR team is itself made up of several "crews" (i.e., surgery, anesthesiology, nursing, perfusionist, radiology), each of which has its own command hierarchy, its own global properties (professional standing, culture, traditions, and history), and its own set of local goals and objectives for management of the patient. The differences among the crews can be so striking that we sometimes refer to them as separate tribes (transcript of the Conference on Human Error in Anesthesia, Asilomar, Calif., 1991).

Each "crew" has one or more members who must work effectively together, and crews combine to form a team. A critical component of the success of this process comprises the establishment and maintenance of a shared mental model of the situation. To the degree that these objectives can be accomplished, the different individuals will be able to tailor their efforts toward a common goal. Experience working together as a crew or team will improve the likelihood of generating a shared mental model.

Cooke and Salas and their associates made some interesting statements on teams and team knowledge (Box 7-4).[71,72] In their view, "team knowledge" is more than the sum of individual team members' knowledge, and these investigators demonstrated the need for new methods to elicit team knowledge (e.g., a collective holistic approach). In team knowledge, Cooke and Salas distinguished between "team mental model" and "team situation model." To judge team knowledge, information is also needed on the broader aspect of "team cognition," which involves team knowledge itself, team decision making, team situation awareness, and team perception. Figure 7-5 reflects these components of team cognition and team knowledge.[71]

BOX 7-3 *Key Elements of a High-Reliability Organization in Medicine*

Established Culture of Safety (See Box 7-2)

Optimal Structures and Procedures

- Decision making rests with those with greatest knowledge or experience about specific issues regardless of rank or job type.
- The unit integrates crews from different departments (e.g., cardiac surgery, cardiac anesthesia, OR nursing, perfusion, ICU) into a coherent clinical team. Teamwork and resiliency are emphasized.
- Formal procedures are in place to maximize transfer of information to all team members before a case (e.g., briefings or time-out procedures).
- Schedules are designed to keep work hours and duty periods at reasonable levels to avoid undue fatigue. Personnel under excessive stress are supported or replaced as needed.
- Standardized procedures, techniques, and equipment are adopted whenever possible so that similar tasks or operations are performed similarly regardless of the personnel involved; conversely, when necessary (in an emergency or adverse event), the team is resilient and responds as needed to the situation without slavish dependence on standard routines.
- The use of preplanned algorithms, checklists, and cognitive aids is actively encouraged.
- Easy access to current information systems is available at all times and all locations.

Training and Practice in Routine Procedures and Simulations

- Debriefings are conducted after each case.
- Nonpunitive assessment instruments are used on a regular basis to provide current feedback and identify elements requiring special training.
- Initial and recurrent simulation-based single-discipline and multidisciplinary training in crew resource management occurs (see Chapter 8).
- Actual clinical crews and teams conduct periodic drills or simulations of critical situations in the real OR, PACU, and ICU.
- Resident training uses a guided curriculum; training goals and the level of responsibility assigned to a resident match the current proficiency level of the trainee with the complexity of the procedure.

Organizational Learning

- Robust mechanisms are in regular use for organizational learning, both prospectively (considering in advance how to optimize protocols and procedures, such as failure mode and analysis of effects) and retrospectively (from analyzing reports of adverse events, near misses, or problems such as root cause analysis).
- Problems are analyzed primarily to determine what can be improved, rather than whom to blame. Altered procedures are assessed and adopted as appropriate. Process changes reflect appropriate analysis.

ICU, Intensive care unit; *OR,* operating room; *PACU,* postanesthesia care unit.

Status and Hierarchy Effects

Status and hierarchy effects are important in team performance. Especially in crisis situations, the lower-status crew member tends to defer to the higher-status individual, even if that individual is performing poorly. In aviation, some airplane crashes have occurred in which overbearing captains were combined with unassertive subordinates (first officer copilot and flight engineers). The team was not able to respond effectively, even when the subordinates knew that something was wrong.

In aviation, as in academic anesthesia practice, training is an ongoing activity in the domain. Although the captain is in charge of the flight, the captain and the first officer (who is essentially in training to become a captain) traditionally alternate the roles of "pilot flying" and "pilot not flying" on each leg of a flight. Each of these roles is carefully defined and involves separate but interrelated tasks (the pilot flying handles the flight controls, whereas the pilot not flying handles radio communications and other tasks). In anesthesiology, the roles of the trainee and the faculty member during patient care are rarely made explicit. The trainee is often expected to do all tasks with only occasional assistance from the supervisor (part of a training method known as cognitive scaffolding). The exact responsibility for different tasks in a crisis is not predefined. It is interesting that two factors frequently found to be associated with critical incidents in anesthesia have been "teaching in progress" and "inadequate supervision."[73]

A particular issue of hierarchy is known as *cue giving and cue taking,* in which people give off cues (often without even knowing it) that are taken up by others.[74] Those people not at the top are very sensitive to cues emitted by their superiors. The cues sent by high-status personnel can inhibit action or even questions from lower-status people. One effect of this phenomenon is that dyads and teams that expect to have redundancy from "multiple sets of eyes" on a patient may not achieve this goal because the views of a single person dominate the thinking of the group.

BOX 7-4 *Teamwork Principles*

- Team leadership matters.
- Team members must have clear roles and responsibilities.
- Shared understanding of the task, teammates, and objectives goes a long way.
- Take time to develop a discipline of prebriefing, performance, and postbriefing.
- Teamwork effects matter.
- Clinical expertise is necessary but insufficient for patient safety; cooperation, communication, and coordination skills matter.
- Teams must have clear and valued visions.
- Learning from mistakes, self-correction, and adaptability are the hallmarks of high-performance teams.

From Salas E, Rosen MA, King H: Managing teams managing crises: principles of teamwork to improve patient safety in the emergency room and beyond, Theoret Issues Ergonomics Sci *8:381-394, 2007.*

PRODUCTION PRESSURE

The social and organizational environment may also act as a source of production pressure on anesthesia professionals (see also Chapters 3, 4, and 6). *Production pressure* encompasses the economic and social pressures placed on workers to consider production, not safety, their primary priority.[64] In anesthesiology, this typically means keeping the OR schedule moving speedily, with few cancellations and minimum time between cases. In principle, safety and efficiency can go hand in hand. Many aspects of high reliability, such as standard operating procedures, preprocedure briefings, and flattening the hierarchy, may smooth operation of the system, as well as make it safer. Frequently, however, the pressure for throughput can erode safety.

For example, when anesthesia professionals succumb to these pressures, they may skip appropriate preoperative evaluation and planning, or they may fail to perform adequate pre-use checkout of equipment. Even when preoperative evaluation does take place, overt or covert pressure from surgeons (or others) can cause anesthesia professionals to proceed with elective cases despite the existence of serious or uncontrolled medical problems. Production pressure can cause anesthesia professionals to choose techniques that they would otherwise believe to be inadvisable.

<table>
<tr><td rowspan="4">Team cognition</td><td>Team decision-making</td><td colspan="2" rowspan="3">Model and structure of embedded team knowledge in the broader concept of team cognition</td></tr>
<tr><td>Team situation awareness/ vigilance</td></tr>
<tr><td>Team perception</td></tr>
<tr><td>Team knowledge</td><td>Team mental model</td><td>Team situation model</td></tr>
<tr><td colspan="2">• Long lasting, prior to task
• Through training, experience
• Collective knowledge base, common expectations</td><td>• Fleeting, dynamic
• Through task, situation specific
• Interpret situation</td></tr>
</table>

Figure 7-5. Components of team cognition and team knowledge.

Gaba and associates reported on a randomized survey of California anesthesiologists concerning their experience with production pressure.[75] These investigators found that 49% of respondents had witnessed a situation in which patient safety was compromised by pressure on the anesthesiologist. Thirty percent reported strong to intense pressure from surgeons to proceed with a case that they wished to cancel. Notably, 20% agreed with the statement that "If I cancel a case, I might jeopardize working with that surgeon at a later date."

Production pressure also leads to haste by the anesthesia professional, a psychological precursor to the commission of unsafe acts. In the survey, 20% of respondents answered "sometimes" to the statement that "I have altered my normal practices in order to speed the start of surgery," whereas 5% answered "often" to this statement. Twenty percent of respondents rated pressure by surgeons to hasten anesthetic preparation or induction as strong or intense. Repeated exposure to these conflicts can cause the anesthesia professional to internalize pressures; 38% of survey respondents felt strong to intense internal pressure to "get along" with surgeons, and 48% reported strong internal pressure to avoid delaying cases. Anesthesia professionals may then feel impelled to go ahead with cases against their better judgment, even in the absence of overt pressure.

Investigating these aspects of the work environment is difficult because such relationships are driven by economic considerations, as well as by the complex organizational and interpersonal networks linking the different medical cultures. Changing the environment will be equally challenging.

ASSESSING RISK FACTORS IN ANESTHESIA

An innovative attempt was made by a team of engineers and anesthesiologists to apply a technique called *probabilistic risk analysis* (PRA) to model cascading risks and the effects of different types of organizational interventions.[76,77] PRA has been used extensively in nuclear power and other highly hazardous industries (e.g., it was used for analysis of the risks to the space shuttle from thermal tile failure). Complete PRA models are very complex and extensive. In the anesthesiology study, a highly simplified PRA model was used to assess the feasibility of applying this technique to health care. The PRA analysis of organizational changes in anesthesia suggested that patient risk could be reduced best by closer supervision of residents, the use of patient simulators for training and periodic recertification, and regular medical examination of anesthesia professionals for fitness for duty. As yet it has not been possible to develop comprehensive PRA models of anesthesia risk because the number of decision and action elements is very large, and knowledge of the probability of success or failure for each of the decisions or actions is very limited. The PRA approach may be a useful heuristic to help clinicians lay out critical decision-making and therapy issues, but it may never make any meaningful contribution as a quantitative safety management technique.

Interest has been growing in applying process-oriented systems analysis to patient care flows and processes. For example, a group in Tübingen, Germany, performed a process-oriented systems analysis at a medical university hospital to assess the anesthesia work system's ability to regulate variances and disturbances in the work process.[78] These investigators showed that the internal work process can be regulated well but that the high interdependence of the anesthesia work system with other systems requires extensive coordination activities.

CHARACTERISTICS OF SUCCESSFUL INCIDENT REPORTING SYSTEMS

INCIDENT REPORTING SYSTEMS FOR LEARNING FROM PROBLEMS

An important strategy for improving patient safety (and a core tenet of HROT) is *organizational learning*. Such learning can be both prospective (deliberating in advance of process changes how they could affect safety) and retrospective (learning from events that have already transpired). Most high-hazard and high-reliability industries have made special efforts to create systems for retrospective organizational learning, often by concentrating on the reporting, investigation, and analysis of both frank accidents or errors and near-miss events with no negative outcome.[30,54,55,79-82] The details of successful incident reporting systems (IRSs) are covered in a number of publications (see also Chapter 6).[5,7,22,50,60,83-102]

Historically, investigation of errors in the health care system has been hindered by a "culture of blame,"[100-104] in which naming, blaming, and shaming are the main features of event reporting and review, rather than analysis by experts and focus on the development of systematic countermeasures. A culture of blame in which it is posited that errors, accidents, and near misses primarily result from a lack of knowledge, a bad attitude, or a lack of commitment to patients leads to a heavy burden on those involved in adverse events. It may also compound internalized negative feelings over having contributed to harming a patient.[104,105]

Anesthesiology as a specialty has played a leading role in the attempt to turn this culture of blame into a safety culture—putting safety first[1,2] and trying to understand how errors, incidents, and adverse events evolve.*

Errors Per Se Are Not the Cause of Accidents

Only a minor fraction of errors will lead to a negative patient outcome. However, the "harmless" error may well point to a systematic weakness (latent problem) in the system that, if investigated further, can lead to a systematic change. Unfortunately, the reverse is often true. The lack of a negative outcome is interpreted as "success" of the system, and the underlying vulnerabilities are ignored. In most cases, errors in complex systems are not the sole causes of accidents and rarely lead inevitably to an adverse event (see Fig. 7-1, *A*). In actuality, there are probably underlying reasons (C_1 to C_3 in Fig. 7-1, *B*) as to why someone commits an error initially, and then

*References 5, 30, 50, 63, 82, 83, 85, 106-115.

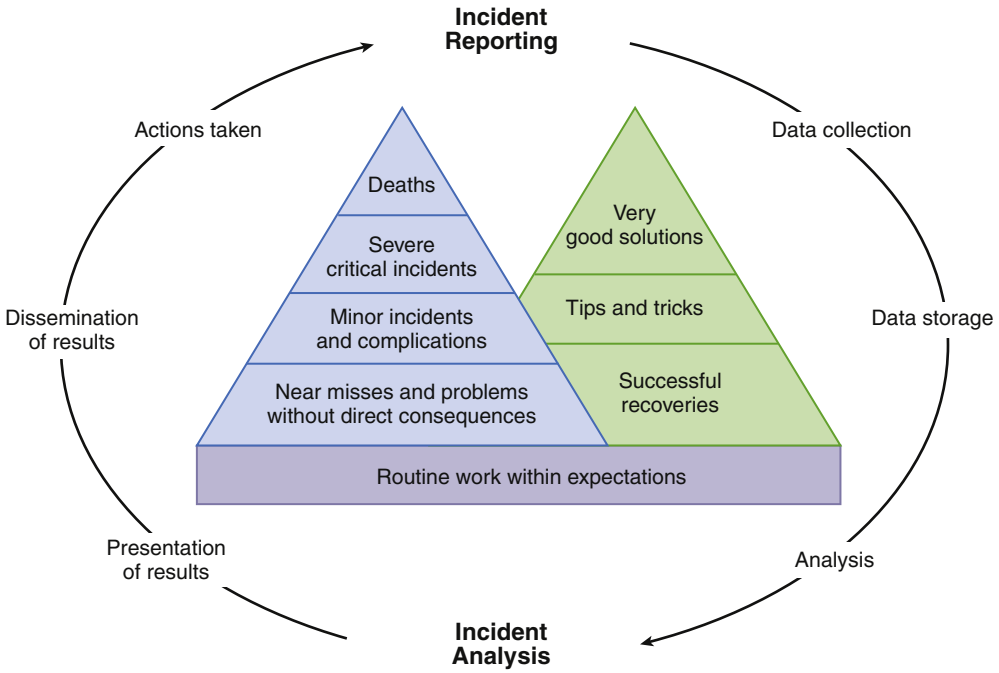


Figure 7-6. Process model of an incident reporting system that is constructed as a complete system. The data must be collected, saved securely, and analyzed independently, and the results must be visualized in a relevant way, distributed to stakeholders in an applicable way, and produce concrete action by the reporting organization. It should be possible to report all incidents and errors, independent of the outcome. Innovative systems should even include positive reports. *(Figure by P. Dieckmann.)*

additional contributing factors (CF_4, CF_5) are "needed" to allow an accident to develop. The main idea of modern IRSs is to identify the factors that make errors more likely to occur, as well as additional factors that allow a negative outcome to ensue. By reporting and analyzing factors C_1 to C_3 and CF_4 and CF_5 in Figure 7-1 regardless of the outcome, it may be possible to eliminate or reduce the probability or the harm potential of the accident long before it ever happens.

If reporting is safe and provides useful information from expert analysis, it can measurably improve safety.[90]

IRSs, if well-structured and operated, can make a substantial difference in system safety (Fig. 7-6). The knowledge about weaknesses and strengths of the health care system that is "out there" already can finally be extracted and made available for others. IRSs are often referred to as "learning systems," similar to the National Reporting and Learning System of the National Patient Safety Agency in the National Health Service (NHS) of the United Kingdom.

Effective IRSs allow insights into the health care system that are otherwise very difficult to acquire. In this sense IRSs can open "windows to the system."[106]

Merely having a reporting form or a database of information does not constitute an effective reporting system. These forms or databases can be effective only when they are constructed, established, and maintained as an entire system (Fig. 7-7; see also Fig. 7-6) and are successfully embedded in the organization or industry. Omission of or faults in any of the requirements in Box 7-5 will limit the success of the system.[98]

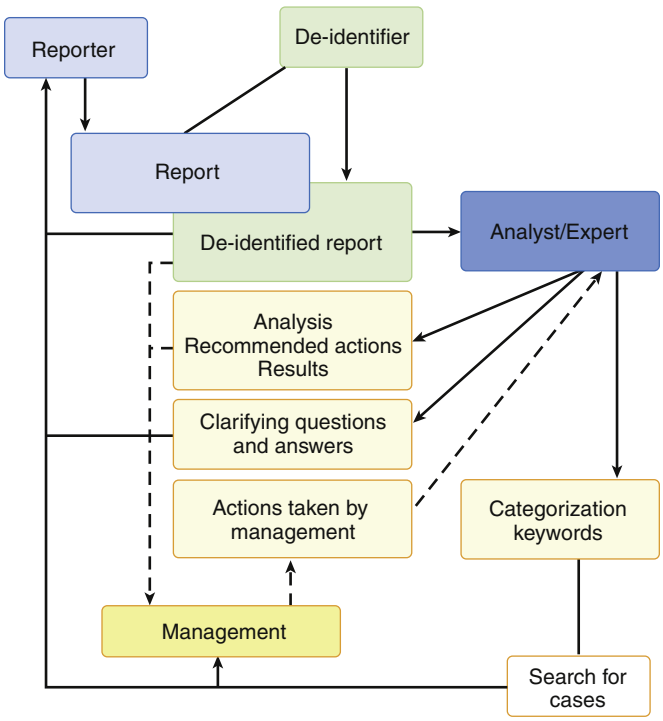


Figure 7-7. Data handling in a modern incident reporting system with de-identification. The incoming reports are first completely de-identified by a trained de-identifier. Only after this step is the report ready to be analyzed. It is important that the reports are analyzed by a multiprofessional team and that recommendations be fed back to the management of the organization from which the report came. The analysis and feedback should be transparent for all stakeholders.

BOX 7-5 ***Important Characteristics of Effective Incident Reporting Systems***

- Integration of the incident reporting system into the organization and full support by management
- The absence of negative sanctions for reporters and people involved
- Confidential or anonymous reporting option, with active de-identification (domain expertise required)
- Legal protection and state-of-the-art data security
- Independence of the organizational hierarchy: reports are sent to a trusted subunit outside the hierarchy of the organization or outside the organization (external trust center, e.g., NASA for the ASRS)
- Orientation to a system that enables all stakeholders of patient safety, including physicians, nurses, and technicians, to file reports easily
- Easy and fast reporting
- Training of stakeholders to file valuable reports (e.g., focusing on human factors issues, as well as medical-technical aspects)
- Timely feedback about reception of the report, its analysis, and proposed measures to be taken from it
- Analysis of each report by experts (a multiprofessional team that has a background not only in the medical domain but also in issues of human performance and analysis methods)
- Deep analysis of selected cases by using root cause analyses or failure modes and effect analyses with the aim of improving systems safety in the future
- Timely implementation of improvements to confirm the "reactivity" of the system and to *make a difference*
- Evaluation of improvements and special care to avoid "improvements for the worse" (quick fixes without improving the underlying latent dangers)
- Organizational support of reporting and analysis of cases, as well as the implementation of improvements
- Supports continuous improvement of the positive proactive safety culture in the department (systems perspective!)

Data from references 30, 87, 90, 116.
ASRS, Aviation Safety Reporting System; *NASA,* National Aeronautics and Space Administration.

What Should Be Reported?

Uncertainty about *what* should be reported is one of the barriers for an IRS.[117] In aviation, it has been necessary to create a reporting system for "incidents" (without negative outcome) that is distinct from systems for reporting or analyzing accidents. Of course, in aviation the occurrence of an accident is usually known immediately, and such events are never "supposed to happen." Yet in health care every human being will get sick and will die; in fact, most people will die in proximity to medical care. Thus, negative outcomes are inherent to the progression of disease, so determining which outcomes are the result of "errors" or "accidents" is much more difficult in health care settings. For this reason many experts believe that for health care event reporting systems, it should be possible to report all critical incidents, with or without a negative outcome. In fact, the system may also solicit reports of "positive events" in which the outcome was good despite challenging clinical circumstances. In general, the invitation to report should be very broad and cast a "wide net" to find all interesting occurrences.

What Should Report Forms Look Like?

Reporting systems that rely primarily on an array of checkboxes for the reporter to choose from regarding the "causes" of the incident have not proved to be useful. In fact, it is thought in the Aviation Safety Reporting System (ASRS), for example, that "counting incidents is a waste of time" (quote from Charles Billings, a founder of the ASRS). In a voluntary reporting system, one has no way to estimate the true number of specific problems. Similarly, trend analysis is not feasible because the frequency of events and the frequency of reporting are confounded. A free-text description of the reported incident has been more helpful in identifying what can be learned from the report. This view is also supported by the World Health Organization's guidelines for incident reporting[87]:

However, much of what promotes learning in patient safety lacks crisply defined data elements, so most authorities believe it is important for reports to include narrative to convey meaning. Narrative reports provide the opportunity to capture the rich context and storyline that allow the conditions that contributed to the error to be explored and understood.

Indeed, some believe that only narrative reports are capable of providing information that provides meaningful insight into the nature of the underlying systems defects that caused the incident (Richard Cook, personal communication).

Clearly, no reporting system can detect all the problems in a clinical institution, even ones that create a severe vulnerability. For one thing, it is known that between 50% and 96% of critical incidents are not reported with current systems,[118,119] although newer thrusts in incident reporting hope to increase the percentage of events reported.

Legal Issues of Reporting Systems

Especially in jurisdictions for which medical liability litigation is common, certain legal issues affect reporting systems. First, for some kinds of events in some settings, legal requirements to report the event to a governmental body are in place. This is true in the United States for certain kinds of adverse drug events or for certain failures of medical devices. Moreover, some states have started mandatory reporting programs about so-called never events that are thought should never occur in the absence of systems failure. In general, voluntary IRSs operate completely in parallel with any other types of reporting systems.

An important question for most reporters is whether the report will be confidential or anonymous and whether the report will confer any immunity to the reporter. Anonymous reporting provides maximum protection for reporters but limits the amount of information that can be acquired about any given event and the cogency of that information. Confidential reporting can allow confidential interaction between analysts and the reporter to acquire all the information and context needed concerning the event, but the linkage between the report and the identity of the reporter exposes a risk even if confidentiality is formally provided. The ASRS—on which many reporting systems have been modeled—operates as a confidential system but with subsequent de-identification of the reports to make them anonymous. Furthermore, the ASRS was able to offer

BOX 7-6 ***Characteristics of the German National Anesthesia and Intensive Care Incident Reporting System PaSOS (www.pasos-ains.de)***

- The system is provided by the two German anesthesia societies and run by a professional interdisciplinary group.
- Every anesthesia department and ambulatory anesthesia unit in Germany is entitled to take part. The basic functionality, software, server storage, and updates are free of charge (a service by the societies).
- The system is Web-based with an anonymous secure login (SSL). No data are stored locally in the hospitals, but users work directly on the central secure server with php technology.
- The reports are primarily sent outside one's own institution for de-identification by the system's own independent and interdisciplinary patient safety group (TuPASS), which increases trust of employees in the safety of the system.
- All reports undergo a professional four-eye active anonymization and de-identification process by domain experts trained in incident reporting and using checklist protocols to prevent any lapses in de-identification.
- After de-identification, most reports can be read in full text by all employees. This is meant to sensitize all by reading all the cases and to stimulate discussion about patient safety in the department and to report your own cases. It also provides very powerful feedback to the reporter, who can read "his" or "her" report in the Web.
- Every department has a unique department login that is provided to all employees (e.g., physicians, nurses, technicians).
- This login allows you to separate "your" reports from the national reports. So every department has its own "local" incident reporting system inside the big national system. No personal logins are provided because the system is anonymous.
- Most reports are readable in the national IRS, open to all anesthesiologists. This should contribute to the national spread of important critical safety information. Of course, on this level, nobody can see where the reports came from. (You can select "your" reports with your department login, but you cannot identify the origin of reports once they are in the national database).
- All reports are manually tagged with key words for meaningful search results; they are classified according to the U.K. NHS NPSA contributory factors framework,[52,94,95] and they are also categorized with the CRM key points (see text).[63,122]
- A local de-identifier does not exist and can therefore not be interviewed by any legal authorities.
- An optional module, "feedback and analysis suggestions," is available on request; it provides expert feedback about every report from the IRS provider team back to the organization's risk management, including systems safety analysis and suggestions for countermeasures.
- Several organizational prerequisites must be fulfilled by departments to take part (organizational embedding before starting to report). For example, all departments must send their PaSOS representatives to an initial workshop for briefing about the do's and don'ts of IRS. They also receive a set of slides and information material to spread the messages in their local departments (snowball effect).
- Departments that do not comply with the minimal requirements, especially prerequisites such as the written "no-blame assurance" to their employees, are not allowed to take part or may even be excluded from the system.

Data from references 63, 116, 120, 299.
CRM, Crisis resource management; *IRS,* incident reporting system; *NHS NPSA,* National Health Service National Patient Safety Agency.

limited immunity from administrative actions for those who filed a report. This was a major incentive for reporting events. In health care, physicians largely fear malpractice litigation, and it is not possible to offer immunity from litigation to reporters, although offering immunity from administrative action (e.g., an official reprimand) within the hospital itself could be an incentive to report.

Statutory Protection. The United States now provides both federal and state statutory protection (shield) from discovery of any voluntary event reports that may be available (depending on the locale and many other circumstances). The U.S. Congress passed the Patient Safety and Quality Improvement Act of 2005 (Public Law 109-41). This authorized the Department of Health and Human Services to certify patient safety organizations (PSOs) to collect confidential reports about events and to analyze the information. The act provides strong legal protection (privilege) from any compelled release of the information, as in the process of discovery in a lawsuit.

Internal reporting systems within hospitals may be protected as quality improvement activities in states that provide privilege from discovery of such reports and deliberations. State laws vary widely on this matter. In addition, the quality improvement protections are often questioned during litigation, and whether the privilege will be applied depends on the ruling of a judge in each individual case.

Reporting systems in other countries have used other strategies. For example, in Germany, national IRSs have constituted themselves as a "press office" (informing the anesthesia public as a journal would); this then brings them under the protection of the "free press act and rights" and makes it almost impossible to use its data in litigation.

De-identification Before Information

A common strategy of confidential reporting systems is to convert the data quickly to anonymous status by "de-identification." To do this, it is necessary to edit the reports and delete all information that could be used to identify persons or organizations. Systems vary by what stage of analysis they conduct de-identification and where they set the balance between acquiring needed information and deleting possibly identifying data. One issue in all reporting systems, especially in health care, is that the key facts of many events may be unique and may thereby lead to a high risk of "intrinsic identification" even when all objective identifiers are stripped.

Many countries have IRSs with various designs and operational processes (see Appendix 7-1).[5,7,50,60,83-100] Many systems are installed locally, but more and more national systems, or at least systems with a national common data set, are being installed.[120] Box 7-6 shows some of the features of and lessons learned from different German national IRSs.

The Anesthesia Incident Reporting System in the United States. In 2011 the Anesthesia Quality Institute, affiliated with the American Society of Anesthesiologists (ASA), initiated the Anesthesia IRS (AIRS) to collect reports of critical events in anesthesia (see also Chapter 6). Incidents can be reported by secure Web-based data collection, either confidentially or anonymously. Confidential reporting allows the AIRS analyst to contact the individual for clarification or follow-up. Legal protection is provided by 2005 US federal legislation that makes reports to, and analysis work products of, approved PSOs free from "discovery" in legal proceedings. The law also imposes strict guidelines on how confidentiality of the work must be preserved. The AIRS publishes a monthly column in the *ASA Newsletter,* in which it describes—in de-identified form—an interesting case report and its analysis by the AIRS Committee. As of January, 2013, 713 total reports had been received (95% "confidential"), with 16 published cases in the *ASA Newsletter.*

AN INDEPENDENT ORGANIZATION FOR ACCIDENT INVESTIGATION IN HEALTH CARE (MEDICAL NATIONAL TRANSPORTATION SAFETY BOARD)?

In the United States, transportation accidents are investigated by the National Transportation Safety Board (NTSB; http://www.ntsb.gov/), an independent federal government organization. Similar agencies exist in most countries. Suggestions have been made for several decades for N NTSB-like body to investigate accidents in health care. In the Past few years, new calls have been made to establish such an organization. The complexities and pitfalls of such a system (including the fact that adverse outcomes are several orders of magnitude more common in health care than in commercial aviation) have so far obstructed any progress toward creating such a program. Nevertheless, the results of such professional interdisciplinary investigations, directed toward how such accidents can be prevented in the future, could be very beneficial. The debate about the feasibility and advisability of such high-level investigating organizations will probably continue for a long time.

PERSONNEL SELECTION TO IMPROVE SAFETY

Each profession has special requirements of personnel so that they are able perform tasks optimally. Selection of the right people to do the job is among a few core human factors issues. In most countries personnel selection in health care puts a high premium on education and knowledge-based test scores, but very little emphasis on measuring underlying cognitive abilities. Unlike the situation in military aviation, there are few formal selection criteria for entry into anesthesia practice. Instead, the criteria are decided on by each department's trainee selection committee. Nearly every student who chooses anesthesia as a specialty will be accepted by some training institution. Moreover, few trainees are terminated from their anesthesia training—and then usually only because of normative failures (e.g., drug abuse; ill-treatment of patients or co-workers; failure to show up) rather than lack of performance in doing anesthetic work.

Some work has attempted to define the underlying ability characteristics of a successful anesthesia professional. Greaves and Grant presented an inventory of 16 characteristics of "good" anesthetic practice—knowledge, skill, perception, confidence, prudence, vigilance, fluency, decisiveness, anticipation, organization, flexibility, responsiveness, good manner, assertiveness, good management, and good communication.[26] This inventory can serve as a basis for discussion of anesthesia professionals' education and training. The authors of the inventory recommended its use for formalized consultant feedback to trainees while noting the inventory's unproven validity and reliability. An interdisciplinary group in Germany conducted an evaluation of another list of critical abilities for anesthesia professionals that was published in German.[121]

HUMAN FACTORS

This section of the chapter deals with human factors in the broadest sense of the meaning. In contrast to the previous section, which covered aspects of the health care system and organizational matters, the human factors portion is related to the performance of individuals and teams and to factors influencing their performance and promoting or preventing active or passive errors. Because more than 70% of all errors in medicine can be attributed to problems with human factors rather than problems with knowledge or practical skills, the impact of human factors cannot be overestimated. On this basis, perhaps human factors should take 70% of the whole book. Given that this chapter cannot deal with human factors in a comprehensive way, many topics can be touched on only briefly, and the reader is directed to the available literature. We focus on the most important aspects of human factors that are directly relevant to practicing anesthesia professionals.

NONTECHNICAL SKILLS IN ANESTHESIA

Since the 1980s, the health care professions have become more aware of the importance of "nontechnical" skills in the delivery of safe, high-quality medical care. This recognition has brought an increased need for assessment, evaluation, and training of these skills. Patient simulators were perhaps the first opportunity to show and train these skills under realistic stressful conditions.[122-125] The introduction of simulators and the associated training concepts accelerated understanding of these human factors by the medical community.[2] Some of the needed "crisis management skills"[25,126] can be trained for without the use of simulators, as shown in other domains (aviation, oil platforms, military).[81,127-129] The baseline level of crisis resource management (CRM) performance is somewhat low.[130] Helmreich stated that as a first step in establishing error management programs, it is necessary to provide formal training in teamwork, the nature of error, and the limitations of human performance.[55]

Different ways exist to group the nontechnical skills that are at the heart of CRM training. One approach is to distinguish between two categories of nontechnical

TABLE 7-3 NONTECHNICAL SKILLS IN ANESTHESIA: CLASSIFICATION, MARKERS, AND TEACHING POINTS

	Anesthesia Nontechnical Skills (Fletcher et al[164])		Performance Markers (Gaba et al[142])	Key Teaching Points in Anesthesia Crisis Resource Management (Howard et al[165], Gaba et al[166])
Concepts	**Elements**	**Categories**	**Markers**	**Reminders**
Cognitive and mental skills	Planning and preparing Prioritizing Providing and maintaining standards Identifying and using resources Gathering information Recognizing and understanding Anticipating Identifying options Balancing risks and selecting options Reevaluating	Task management Situation awareness Decision making	Orientation to case Leadership (also a social and interpersonal skill) Planning Workload distribution Anticipation Vigilance Preparation Reevaluation	Anticipate and plan Know your environment Exercise leadership Set priorities dynamically Use cognitive aids Distribute the workload Mobilize all available resources Use all available information Allocate attention Anticipate and plan Prevent and manage fixation errors Reevaluate repeatedly
Social and interpersonal skills	Coordinating activities with team Exchanging information Using authority and assertiveness Assessing capabilities Supporting others	Team working	Inquiry and assertion Communication feedback Group climate Followership	Communicate effectively Teamwork Communicate effectively Exercise leadership and followership Exercise followership
Overall assessment	Not applicable Assessments are made only at the element and category level		Overall nontechnical performance of the primary anesthetist Overall nontechnical performance, not who is right of the whole team	Teamwork! Concentrate on what is right, not who is right

skills: (1) cognitive and mental skills, including decision making, planning, and situation awareness (Table 7-3); and (2) social and interpersonal skills, including aspects of teamwork, communication, and leadership. Another approach is to split nontechnical skills into five major groups, as shown in Figure 7-8.

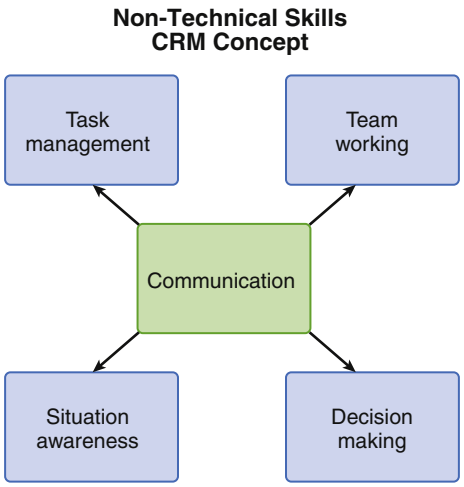


Figure 7-8. Five main groups of nontechnical skills. In this approach, effective communication is like the glue that holds all the other components together. *CRM,* Crisis resource management.

CRISIS RESOURCE MANAGEMENT

What Exactly Is Crisis Resource Management?

Cockpit (later "crew") resource management was introduced in aviation in the mid-1980s and is considered to be successful in that industry and other industrial and military settings (although admittedly, there is not what evidence-based medicine would call "level 1 evidence" for this success).[29,30,49,131-134] Crew resource management is now taught systematically to crew members of all major U.S. airlines and at many airlines around the world.[135] A similar program in anesthesiology was first developed by Gaba, Howard, and associates at the Veterans Affairs (VA) Palo Alto Health Care System and Stanford School of Medicine in Palo Alto, California,[4,117,122,125,136] originally as Anesthesia Crisis Resource Management (ACRM). The ACRM curriculum and its variants have since been adopted by training centers worldwide. A detailed description of the ACRM course is provided.

In overview, CRM means to coordinate, use, and apply all available resources to protect and help the patient as best as possible. Resources include all the personnel involved, along with all their skills, abilities and attitudes—albeit also with their human limitations. Machines, devices, and information sources, including cognitive aids, are also critical resources.

BOX 7-7 ***Crisis Resource Management—Key Points in Health Care***

1. Know the environment.
2. Anticipate and plan.
3. Call for help early.
4. Exercise leadership and followership with assertiveness.
5. Distribute the workload (use the 10-seconds-for-10-minutes principle).
6. Mobilize all available resources.
7. Communicate effectively—speak up.
8. Use all available information.
9. Prevent and manage fixation errors.
10. Cross check and double check (never assume anything).
11. Use cognitive aids.
12. Reevaluate repeatedly (apply the 10-seconds-for-10-minutes principle).
13. Use good teamwork—coordinate with and support others.
14. Allocate attention wisely.
15. Set priorities dynamically.

Modified from Rall M, Gaba DM: Human performance and patient safety. In Miller RD, editor: Miller's anesthesia, *ed 6. Philadelphia, 2005, Churchill Livingstone.*



Figure 7-9. Crisis resource management (CRM) cards for training. The cards are given to each participant during simulation training sessions. One side shows the 15 CRM key points of Rall and Gaba; the other side shows a tool for formalizing decision making to reach better decisions and avoiding fixation errors. It also shows a short graphic version of the "10-seconds-for-10-minutes" concept, reminding participants to take the necessary time to organize into a team, whenever appropriate. *(Photograph by M. Rall.)*

Although it is termed crisis management, CRM principles actually also apply before a crisis ensues. CRM includes preventing and intercepting threats and errors and minimizing their negative consequences to the patient.

The key points of CRM as they apply to anesthesia care have been steadily updated and expanded over time (Box 7-7). During simulation training sessions, little cards with CRM key points are usually given to the participants to keep the memory of these points alive when the participants are back in the real world (Fig. 7-9). Some of the principles may seem obvious or self-evident. However, from our experience in simulation training, it is in fact *not* trivial to apply these principles whether during routine work or during crises. More theoretic background on the principles can be found in the textbook on ACRM by Gaba, Fish, and Howard,[137] as well as in related safety literature.[†]

As with nearly all principles of sound human factors, application of CRM key points to patient care must be supported by top leadership and reinforced in the actual work environment. It is of no worth to study these principles (or even practice them in simulations) only to find that the pressures and culture of the "real OR" make them impossible to implement for real patients. Fully integrating these key points into the structures and processes of clinical practice has proved to be a significant challenge.

Know the Environment! (CRM Key Point 1). CRM begins before the crisis starts. One of the prerequisites for CRM is to *know the available resources and the details of the specific working environment.* Resources are *personnel, equipment* (software, hardware, or cognitive aids), and *supplies*. It is important to know who can be asked for help, who is available at different times of the day, how to call those helpers quickly, and how long it will take them to arrive. Regarding equipment, it is necessary to not only know *what* is available and *where to find it* but also *how* to operate it. The anesthesiologist is responsible for being well versed in the operation of all relevant equipment and should also use manuals and other cognitive aids to learn to use the gear and as a backup source of information during patient care.

Anticipate and Plan (CRM Key Point 2). Anticipation is key for goal-oriented behavior. Anesthesia professionals must consider the requirements of a case in advance and plan for the key milestone. They must imagine what could go wrong and plan ahead for each possible difficulty. Savvy anesthesia professionals expect the unexpected, and when it does strike, they then anticipate what could happen next and prepare for the worst. People often talk about "staying ahead of the game" or, conversely, "falling behind" or "being behind the eight ball."

Call for Help Early (CRM Key Point 3). Knowing one's own limitations and calling for help are signs of a strong character and a competent person. Trying to handle everything alone or toughing out a critical situation is dangerous and unfair for the patient, who should not suffer to protect the anesthesia professional's pride or ego. In case of an emergency or even a suspected emergency, help should be called early rather than late. Some typical triggers for calling for help that apply to any anesthesia professional at any level are (1) when there are too many tasks to do, (2) when the situation is already catastrophic (e.g., cardiac arrest, difficulty securing the airway), (3) when serious problems are becoming worse or are not responding to the usual maneuvers (or both), and (4) when you do not know what is going on. It is important to know in advance who is available and how to call for help and to plan for how best to use the help when it arrives.

Exercise Leadership and Followership With Assertiveness (CRM Key Point 4). A team needs a leader. Someone has to take command, distribute tasks, collect

[†]References 30, 49, 51, 54, 55, 80-82, 138-142.

information, and make key decisions. Leadership rarely means knowing more than everybody else, doing everything alone, or putting other people down. Leadership is about planning, deciding, and distributing tasks by clear communication. Followership is also an important skill. Followers are key members of the team who listen to what the team leader says and do what is needed. However, it does not mean shutting off their own brains. Followers should be assertive if they think that the team leader is making wrong decisions. It is their responsibility to make sure that the leader is aware of their concerns. Whenever people work together, conflict can ensue; anyone on the team may need to diffuse conflicts to focus the team on care of the patient. Get everyone to concentrate on *what* is right, not on *who* is right.

Distribute the Workload—10-Seconds-for-10-Minutes Principle (CRM Key Point 5). One of the main tasks of a team leader is distribution of the workload. Someone is needed to define the necessary tasks and ensure that they are fulfilled properly and that everything fits together. If possible, the team leader should remain free of manual tasks to observe, gather information, and delegate tasks. Team members should also look actively for things that need to be done. It is not a good team if the team leader has to express every idea and nothing is done before it is explicitly ordered.

A corollary is known as the "10-seconds-for-10-minutes principle,"[143] which posits that if a team can slow its activities down just a little, it can gain more than enough benefit in rational decision making and planning to offset the delay. The need to slow down appears to be greatest in critical situations such as the beginning of the diagnosis and treatment planning or when the team "feels stuck" because the usual treatment is not working (Fig. 7-10).

A prehospital emergency service in Germany, after being trained by Rall and having more than 2 years of ongoing simulation team training, reported that they frequently used the "10-for-10" principle in the field with a high subjective improvement of team decisions and team work (Sascha Langewand, EMS Cooperation, Schleswig-Holstein Ltd, www.rkish.de, personal communication).

Mobilize All Available Resources (CRM Key Point 6). Everyone and everything that could help deal with the problem at hand should be mobilized, including humans and technology embedded in organizational processes. On the human side, the anesthesia professional's knowledge and skills (mitigated by knowledge of one's human deficiencies) are the most important resources, complemented by the human helpers who can be brought to bear. Equipment and supplies are the means by which knowledge is translated into action. Some equipment will be readily available, but other equipment will need time to be mobilized.

Communicate Effectively—Speak Up (CRM Key Point 7). Communication is key in crisis situations. Good team work depends on everybody's being on the same page and coordinating their efforts; communication is the glue that holds the disparate members together (see Fig. 7-8). Effective communication is challenging to accomplish. Several aspects

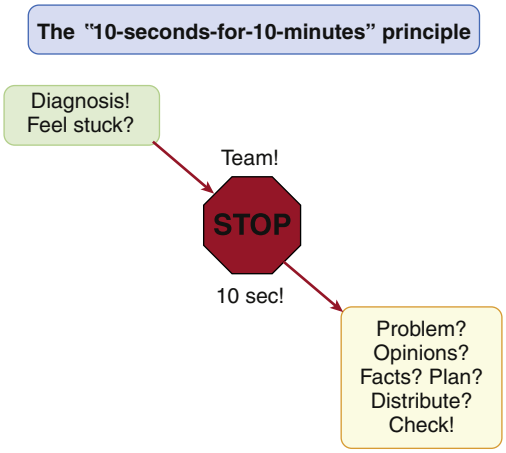


Figure 7-10. The "10-seconds-for-10-minutes principle." When making a *diagnosis* or *feeling stuck*, perform the 10-second team time-out and check to see "what the biggest problem is (the most dangerous aspect right now)" (*Problem*). Clarify this with all available team members (*Opinions*). Gather the information available (*Facts*). Plan the treatment, including the desired sequence of actions. Distribute the workload by assigning tasks and responsibilities. *Check* with all team members about any further concerns or suggestions.

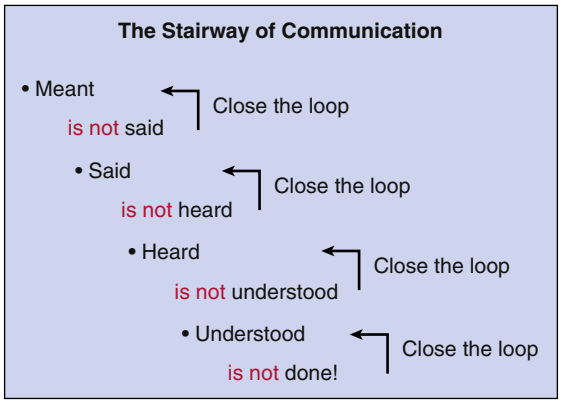


Figure 7-11. Model showing the importance of proper communication. When dealing with complex situations under time pressure, people tend to "mean" a lot but "say" little. It is important to let other team members know what you think (mental model). Not everything that is said is necessarily heard by those who should hear. This is often not the "fault" of the receiving end; acoustic hearing and mental understanding are not the same. It is important for the sender and receiver of a message to close the communication loop. Some tasks need time to be completed and may fail. Let the team know.

make communication difficult sometimes; for example, saying something is meaningful communication only if the messages are received and understood (Fig. 7-11).

Use All Available Information (CRM Key Point 8). Anesthesiology is particularly complex because information must be integrated from many different sources. Every bit of information can assist in understanding a patient's status better and in arriving at the correct diagnosis. Information sources include those immediately at hand (the patient, monitors, the anesthesia record), secondary sources such as the patient's chart, and external sources such as cognitive aids (see later) or even the Internet.

Prevent and Manage Fixation Errors (CRM Key Point 9). Human actions are based on an instantaneous mental model of the current situation. If the model of the situation is erroneous, the actions will probably be wrong.

The term *fixation error* describes a model that is persistently faulty despite sufficient evidence to correct it. A fixation error is the persistent failure to revise a diagnosis or plan in the presence of readily available evidence suggesting that a revision is necessary. This type of error is extremely common in dynamic situations. Three main types of fixation errors are recognized.[144,145]

One type of fixation error is called *this and only this*—sometimes also called *cognitive tunnel vision.* In this type of error, attention is focused on only one possibility, and other (possibly or actually correct) alternatives are not taken into account. Another fixation error is *everything but this,* which is the persistent search for irrelevant information and failure to treat a probable cause, with serious consequences.

Perhaps the most insidious fixation error is the persistent claim that *everything is OK,* in which all information is attributed to artifact, and possible signs of a catastrophic situation are otherwise dismissed. Another form of "everything is OK" is the failure to transition from routine mode to emergency mode when the situation demands it.

One principle of managing fixation errors is to obtain a new view—a second opinion—on the situation from someone unaware of the faulty previous assumptions. Although it is appropriate to brief the new person on the situation, it is best to avoid biasing the person with the conclusions already drawn. Even when working alone, the anesthesia professional can deliberately change perspectives (physically or mentally) and look for information not fitting the picture of the situation, as though entering the room for the first time.

The aforementioned 10-for-10 principle (CRM key point 5) may also be helpful in managing fixation errors. More information on fixation error is provided later in the section on core process.

Cross Check and Double Check—Never Assume Anything (CRM Key Point 10). Cross checking means to correlate information from different sources. There are often three independent sources of information on the patient's heart rate (electrocardiogram [ECG], pulse oximetry, and blood pressure monitor), for example, and two on the rhythm (ECG and pulse oximetry).

Another aspect of cross checking involves reviewing the status of actions that have been done or are under way. Human memory of actions performed is vulnerable, especially when interruptions have occurred. Moreover, although we often attempt to check things "at a glance," such fleeting observations are prone to error. Checking numbers and settings on equipment by actually touching them and looking carefully may be worth the effort. In general it is best to "never *assume* anything"; make sure and double check important information.

Use Cognitive Aids (CRM Key Point 11). Cognitive aids—such as checklists, handbooks, calculators, and advice hotlines—come in different forms but serve similar functions. They make knowledge "explicit" and "in the world" rather than only being implicit, in someone's brain. Memory and cognitive functioning are vulnerable to error or complete failure, especially in stressful situations. Cognitive aids offload memory and safeguard the recall of critical items. They also help ensure the use of current best practices because during a crisis, people sometimes revert to what they originally learned as the best, not what is the latest recommendation. The use of cognitive aids rather than memory alone is another sign of strength. Cognitive aids are discussed in more detail later in this chapter.

BOX 7-8 ***Reevaluation Questions—Maintaining Situation Awareness***

- Was the initial assessment of the situation or diagnosis correct?
- Did the actions have any effect? (e.g., Did the drug reach the patient?)
- Is the problem getting better, or is it getting worse?
- Does the patient have any side effects resulting from previous actions?
- Are there any new problems or other problems that were missed before?
- What further developments can be expected in the (near) future?

Reevaluate Repeatedly—Apply the 10-Seconds-for-10-Minutes Principle (CRM Key Point 12). Acute medicine is dynamic. What is correct now may be wrong in the next minute. Some parameters may change slowly over time, and subtle changes can be difficult to perceive. Trend monitoring can be helpful to detect slow, but insidious changes.

Furthermore, the dynamic nature of critical events makes it necessary to repeatedly reevaluate the situation. Box 7-8 shows a set of questions that should be raised repeatedly to check whether one is still treating the most serious problem most effectively.

Implement Principles of Good Teamwork—Coordinate With and Support Others (CRM Key Point 13). Teamwork in multidisciplinary teams is at the heart of much patient management in the OR and ICU. Key principles of teamwork in dynamic situations have been delineated, especially in the work of Eduardo Salas and colleagues at University of Central Florida (see Fig. 7-5). Coordination within a team ideally begins before a team gathers. If all members know about the tasks to be done and their roles during these tasks, coordination is easier. Short briefings at the beginning of a task are common in aviation and are worth the time spent. During the acute phase of a crisis situation, it is valuable to spend a small amount of time to coordinate the team's activities (see 10-for-10 earlier in CRM key point 5). "Dream teams" support each other continuously, with everybody looking after each other.

Allocate Attention Wisely (CRM Key Point 14). Human attention is very limited, and multitasking is very difficult. Attention must be dynamically allocated where it is needed. One can develop rhythms and scan

patterns to do this. The "ABC equals airway, breathing, circulation" mnemonic is based on this principle. Other strategies are to alternate between focusing on details and focusing on the big picture and to offload certain responsibilities, tasks, or information streams to other qualified team members, provided these teams members periodically update the team leader about the situation.

Set Priorities Dynamically (CRM Key Point 15). Dynamic situations demand dynamic measures with decisive, purposeful preliminary decisions and actions that are constantly reevaluated and modified as new information becomes available or the results of treatment are apparent. What was not a right move at one time may become the right move at another. In addition, having one solution to an obvious problem does not guarantee that it is the best solution to the one problem or that only one problem exists. However, one priority is always paramount—ensuring adequate oxygenation and perfusion of critical organs.

HOW CAN CRISIS RESOURCE MANAGEMENT SKILLS BE LEARNED AND TRAINED?

CRM is taught in many different ways. Seminar-based training on human factors and CRM principles has become popular in health care (e.g., programs called TeamSTEPPS, MedTeams, Medical Team Training, LifeWings),[146-153] although the role of such activities versus simulation-based CRM approaches has not yet been fully delineated. Seminars use didactic sessions, group exercises, and sometimes discussion and analysis of "trigger videos."

Such training seems useful for learning about CRM principles and articulating how they could apply to anesthesia professionals' work environments. Newer studies even show an improvement in patient outcomes.[154-156] Given the experience in the airline industry, it is likely that to address CRM skills for both trainees and experienced personnel completely, a combination of seminars and simulation-based exercises will be needed. We believe that practicing the execution of CRM skills requires exposure to challenging clinical situations in realistic simulation scenarios, followed by detailed group debriefings (often using video of the simulations) to analyze what transpired. As detailed in Chapter 8, such CRM-oriented simulation training may be available in dedicated simulation centers or as in situ simulation training in actual work environments. Many simulation centers also offer mobile training, which means that they can bring the simulator and everything else needed (e.g., audio/video equipment) to any facility to train the staff in institutions that do not have a simulator or staff capable of conducting the training.

HOW CAN CRISIS RESOURCE MANAGEMENT SKILLS CONTRIBUTE TO PATIENT SAFETY?

Although 70% of all errors in anesthesia may be attributable to human factors, interventions to improve this picture have only partially penetrated the fabric of the industry. CRM-oriented training is one component of a comprehensive approach to addressing human factors issues in anesthesia safety, but it is not yet a standard part of clinical training. Meanwhile, some definitive evidence indicates that CRM training improves patient outcomes,[154,156-158] even though it is often functionally very difficult to acquire such evidence. Nevertheless, CRM training is an integral and accepted part of training in aviation, nuclear power, and other industries in which human errors can lead to catastrophic events. There is no reason to assume that anesthesia professionals would be less error prone or would benefit less from human factors–based CRM training than the professionals in other high-hazard industries.

ASSESSING NONTECHNICAL SKILLS IS MORE SUBJECTIVE THAN ASSESSING TECHNICAL SKILLS

A study by Morgan and Cleave-Hogg concluded that "the simulator environment is somehow unique and allows different behaviors to be assessed."[159] As Glavin and Maran stated, "Any scoring system that attempts to address the assessment of clinical competence clearly has to address both technical and non-technical skills."[160] Consequently, there is still a long road ahead in measuring performance.

Two research groups (VA-Stanford and the University of Basel in Switzerland) studied adaptations of the anchored subjective rating scales developed by the NASA/University of Texas Aerospace Crew Performance Project. The VA-Stanford group published preliminary data reviewing the interrater reliability of subjective ratings of behavior on five-point anchored scales.[142,161] Using a fairly stringent test of interrater reliability (the topic is quite complex in the statistical literature), these investigators found only moderate reliability when 5 trained raters used a 5-point scale to score 14 anesthesia teams, each managing 2 different complex critical events in the simulator (malignant hyperthermia and cardiac arrest). Despite some difficulty in agreement on the operational definitions of each type of behavior, the investigators stated that the largest problem in achieving agreement was the high variability of each behavior over the course of a simulation. For example, an anesthesia crew could show evidence of good communication at a particular instant, only to be shouting ambiguous orders into thin air at the next instant. Aggregating such behavior into a single rating was extremely difficult, even for the bounded time segments of the scenario. These data demonstrate the importance of evaluating performance by more than one rater, who, no matter how well trained, may produce scores that differ significantly from another single rater. The investigators suggested combining scores from a minimum of a pair of raters inasmuch as it was shown that the mean of scores from two raters had a very low probability of differing from the mean of five raters by more than a single rating point. The behavioral markers of their score are shown in Table 7-3 and are compared with Fletcher's anesthesia nontechnical skills (ANTS) score and the ACRM key teaching points (see Box 7-7).

The Anesthesia Nontechnical Skills System

Fletcher, from the Industrial Psychology Group of Aberdeen, Scotland (a group headed by Rhona Flin) and working with clinicians from the Scottish Clinical Simulation Centre (Glavin and Maran), performed an in-depth review of the role of nontechnical skills in anesthesia. Fletcher stated that nontechnical skills had not been explicitly addressed in the traditional education and training of anesthesiologists, even though they have always been demonstrated and used during clinical work. The group analyzed incident reports and observations of real cases, as well as attitude questionnaires and theoretic models.[162] Like others, these investigators recognized that simulation offers the opportunity to identify, develop, measure, and train nontechnical skills in a safe learning environment, so they also included significant observations during realistic simulations.[163]

Incident reports proved very limited because they did "not provide the finer-grained level of information necessary to understand where the skills broke down."[164] These workers defined nontechnical skills as "attitudes and behaviours not directly related to the use of medical expertise, drugs or equipment." Although nontechnical skills can be seen under the heading of "human factors," it is preferred that they be addressed as "nontechnical skills," which is more specific.

As in the ACRM instructional paradigm,[122,165,166] Fletcher and colleagues identified two categories of nontechnical skills:

- Cognitive and mental skills, including decision making, planning, and situation awareness
- Social and interpersonal skills, including aspects of team working, communication, and leadership

Fletcher's ANTS scheme is shown in Table 7-4, along with the behavioral markers of Gaba's team and the ACRM key teaching points. A description of the ANTS categories and elements, including examples of good practice and poor practice, is presented in Table 7-4.

The structure of the new ANTS scheme was derived from a system of behavioral markers that had been developed for aviation in a European project called "NOTECHS," which itself was an evolution of the UT-Markers of the University of Texas (Helmreich). A summarized comparison of the aviation systems and explanations about using nontechnical markers for training and evaluation can be found in the book, "Group Interaction in High Risk Environments," written by an international group of human factors specialists.[166a] Several comments about the ANTS approach are appropriate.

ANTS' intent is to score only those skills that can be identified unambiguously through observable behavior. Such restriction may enhance the reliability of the scoring but could exclude relevant personal factors such as self-presentation, stress management, and maintaining perspective. ANTS assumes that "communication" is included or "even pervades" all other categories and does not score communication as a separate skill. This

TABLE 7-4 EXAMPLE OF A DESCRIPTION OF THE ANESTHESIA NONTECHNICAL SKILLS SYSTEM (ANTS SYSTEM V1.0)

Task Management—skills for organizing resources and required activities to achieve goals, be they individual case plans or longer-term scheduling issues; four skill elements: planning and preparing, prioritizing, providing and maintaining standards, and identifying and using resources

Planning and preparing—developing primary and contingency strategies in advance for managing tasks, reviewing these tasks, and updating them if required to ensure that goals will be met; making necessary arrangements to ensure that plans can be achieved

Behavioral Markers for Good Practice	*Behavioral Markers for Poor Practice*
Communicates plan for case to relevant staff	Does not adapt plan in light of new information
Reviews case plan in light of changes	Does not ask for drugs or equipment until the last minute
Lays out drugs and equipment needed before starting case that are suitable for the patient	Does not have emergency or alternative drugs available
Makes postoperative arrangements for patient	Fails to prepare postoperative management plan

Prioritizing—scheduling tasks, activities, issues, information channels, and so on, according to importance (e.g., because of time, seriousness, plans); being able to identify key issues and allocate attention to them accordingly; and avoiding being distracted by less important or irrelevant matters

Behavioral Markers for Good Practice	*Behavioral Markers for Poor Practice*
Discusses priority issues in case	Becomes distracted by teaching trainees
Negotiates sequence of cases on list with surgeon	Fails to allocate attention to critical areas
Conveys order of actions in critical situations	Fails to adapt list to changing clinical conditions

Providing and maintaining standards—supporting safety and quality by adhering to accepted principles of anesthesia; following, when possible, codes of good practice, treatment protocols or guidelines, and mental checklists

Behavioral Markers for Good Practice	*Behavioral Markers for Poor Practice*
Follows published protocols and guidelines	Does not adhere to emergency protocols or guidelines
Cross-checks drug labels	Does not check blood with patient and notes
Checks machine at beginning of each session	Breaches guidelines such as minimum monitoring standards
Maintains accurate anesthetic records	Fails to confirm patient's identity and consent details

From Fletcher GCL, Flin R, Glavin RJ, Maran NJ: Framework for observing and rating anaesthetists' non-technical skills: anaesthetists'non-technical skills (ANTS) system V1.0, *version 22, Aberdeen, Scotland, 2003, University of Aberdeen.*

approach is in contrast to that of others who believe that communication is a specific skill that should be rated separately.[127,167] The category "task management" of the ANTS includes the element "providing and maintaining standards," which may be a point of discussion if it can be an observable behavior "not directly related to medical expertise" as stated in the definition. In addition, a problem may arise because there are not so many well-accepted standards in medicine (in strong contrast to, e.g., aviation).

Flin's group, meanwhile, adapted nontechnical skills scoring systems for several other medical fields, such as for surgeons and ICU care.[30,82,135,140-142,168-175] These investigators have not yet made adaptations that fully describe multidisciplinary crews and teams.

Not all nontechnical skills will be expected to be observed during every scenario or clinical situation. It is important to delineate between "required behaviors" in a given scenario and the generic set of behaviors. If a required behavior is not observed, the rating system advises that one rate that behavior as poor nontechnical skills, whereas the absence of a given nontechnical skill behavior otherwise has no particular meaning and should be rated as "not observed." As in all subjective nontechnical performance systems, training plus calibration of raters is necessary.

Fletcher and co-workers evaluated ANTS by using scripted videotapes taken in a realistic simulator.[164] Fifty consultant anesthesia professionals were given 4 hours of training as raters and then rated 8 test scenarios ranging from 4 to 21 minutes each. They rated performance at the level of specific elements and also at the broader level of category (see Table 7-3) by using a 4-point scale (they could also enter "not observed"). Three investigator anesthesia professionals also rated the scenarios and agreed on a "reference rating" to be used as the benchmark for the study. In questionnaires, the ANTS system was evaluated by raters as relatively complete, possibly with superfluous elements. Raters found that nontechnical skills were usually observable, and most thought that it was not difficult to relate observed behavior to ANTS elements. The interrater reliability, accuracy, and internal consistency of the ratings were good to acceptable and are presented in Table 7-5.

Although well performed, some caveats about these data are in order. Because scripted videos were used as the basis for ratings, it is possible that the observability or scorability of the desired sets of behavior was greater than in actual simulation scenarios. The scripted scenarios were rather short (4 to 21 minutes), which perhaps made it relatively easy to remember certain aspects of the performance and reduced the likelihood that the raters would encounter the problem of aggregating a score from fluctuating behavior over time. The window of "accuracy" as "±1 point" on a 4-point scale seems to be rather wide.

On the whole, the ANTS system appears to be a useful tool to enhance assessment of nontechnical skills in anesthesia and other medical fields further, and its careful derivation from a current system of nontechnical assessment in aviation (NOTECHS) may even allow some inter-domain comparisons.[21,171]

PERFORMANCE-SHAPING FACTORS

With a few exceptions, the foregoing discussion of the performance of skilled anesthesia professionals has assumed that they are normally fit, rested, and acting in a standard working environment. Experience in human performance in the laboratory and other domains suggests that internal and external performance-shaping factors exert profound effects on the ability of even highly trained personnel. The degree to which performance-shaping factors affect the overall performance of anesthesia professionals and the outcome of patients is highly uncertain. In extreme cases, such as profound fatigue, no question exists that these factors can result in severe degradation of the anesthesia professional's performance or even complete incapacitation. However, these extreme conditions are quite unusual, and it is unclear whether the levels of performance decrement likely to be induced in typical work situations have any significant effect. Although the practice of anesthesia does require an attentive and skilled individual, it does not require peak human performance. It would be unrealistic to expect peak performance for every anesthetic regimen because on the order of 60,000 anesthetics are administered each day in the United States by a total of approximately 40,000 to 60,000 anesthesia professionals. Although it is unrealistic to expect peak performance for every case, society expects anesthesia professionals to come to work prepared—not impaired. As stated in the ASA guidelines for the ethical

TABLE 7-5 **RESULTS OF AN EVALUATION STUDY OF ANESTHESIA NONTECHNICAL SKILLS BY FLETCHER AND COLLEAGUES**

Measure	Score	Range	Maximum/Minimum	Element/Category
Interrater agreement	Element level	0.55-0.67	Highest element	Identifying/using resources
	Category level	0.56-0.65	Lowest element	Recognizing/understanding
			Highest category	Task management
			Lowest category	Team working
				Situation awareness
Accuracy relative to the reference rater's score	% within ±1 point	88%-97%	Highest element	Identifying options
	Mean absolute deviation	0.49-0.84, depending on elements	Lowest element	Assessing capabilities
			Highest element	Authority/assertiveness
			Lowest element	Providing standards

From Fletcher R, Flin P, McGeorge R, et al: Anaesthetists' non-technical skills (ANTS): evaluation of a behavioural marker system, Br J Anaesth *90:580-588, 2003.*

practice of anesthesiology, anesthesiologists have ethical responsibilities to themselves. The guideline goes further by stating the following:

the practice of quality anesthesia care requires that anesthesiologists maintain their physical and mental health and special sensory capabilities. If in doubt about their health, then anesthesiologists should seek medical evaluation and care. During this period of evaluation or treatment, anesthesiologists should modify or cease their practice.

With these caveats in mind, however, several performance-shaping factors are potentially of sufficient magnitude to be of concern. Ambient noise, music, fatigue and sleep deprivation, aging, illness, drug use, and attitudes are discussed later. Several other issues that are not discussed include the level of illumination and environmental temperature. These factors can be shown to have a performance-shaping effect in the laboratory, but it is uncertain how much they affect performance in the OR. Currently, the responsibility for ensuring fitness for duty rests solely with the individual clinician. In HROs, the institution implements measures to mitigate performance-shaping factors.

Ambient Noise and Music in the Operating Room

The OR is a relatively noisy work environment (see also Chapter 6).[176-180] Mean sound levels are considerably higher than in most offices or control rooms (continuous movement of air through an open surgical suction tip is a common source of continuous noise), and peak sound levels can be quite high. Some sources of noise are uncontrollable, such as surgical drills, monitor alarms, and inadvertently dropped instrument pans; other sources are controllable, such as conversation and music (see later). Evidence in the general literature indicates that noise can adversely affect human performance.[176] Furthermore, studies by Murthy and colleagues demonstrated that volume-accurate replay of recordings of OR noise significantly interfered with the speech discrimination ability of anesthesia residents during laboratory testing.[181,182] The OR noise also caused a significant reduction in residents' performance on psychometric tests of mental efficiency and short-term memory.[181] The potential interference of noise with communication and situation awareness among personnel in the OR is particularly worrisome to those concerned with optimizing teamwork in this complex work environment.

The use of music in the OR is now widespread. Many health care professionals believe that music enlivens the workday and can build team cohesiveness when all team members enjoy the music. A controversial study by two social psychologists, Allen and Blascovich, suggested that surgeon-selected music improved surgeons' performance on a serial subtraction task and reduced their autonomic reactivity (i.e., "relaxed" them) when compared with control conditions consisting of experimenter-selected music or no music at all.[183] The methodology of this study has been criticized.[184]

In response to Allen and Blascovich, several anesthesiologists challenged the notion that the surgeon's preference for the type or volume of music can or should override the needs of other members of the team.[184,185] This issue generated considerable controversy among surgeons and anesthesiologists. In a reply to some of the letters to the editor commenting on their study, Allen and Blascovich stated the following:

The letters here suggest that not everyone on the surgical team always appreciates the type of music chosen by the surgeon, and anesthesiologists in particular appear to prefer silence in surgery. When we asked the surgeons in our study about this issue, we were told that the environment of surgery does not lend itself to the democratic process, and music was part of the environment in which they felt most comfortable.[186]

Murthy and colleagues[181] studied the effect of OR noise (80 to 85 dB) and music on knot-tying ability in a laparoscopic skill simulator. They found no difference in time or knot quality in the conditions tested and concluded that surgeons can effectively block out noise and music. Invited commentary that accompanied the article brings up important issues: what impact does noise have on other members of the surgical team, how does noise affect communication between team members, does noise affect judgment, and other unanswered questions.

The question of the proper role of music in the OR has no simple answer. Clearly, optimal patient care is the primary goal. Some surgical and anesthesia personnel explicitly forbid any type of music in the OR. A more common approach of many OR teams is to allow any team member to veto the choice or volume of music if they believe that it interferes with their work.

Reading in the Operating Room and Other Distractions

The observation that some anesthesia professionals were observed to read journals or books casually during patient care led to a vigorous debate of the appropriateness of such activity.[187] Although it is indisputable that reading could distract attention from patient care, a study by Slagle and Weinger in 2009 suggested that when the practice of reading is confined to low-workload portions of a case, it has no effect on vigilance[188] (see later). In their opinion, blanket policies against reading nonessential materials are both doomed to failure and possibly detrimental because reading could counteract boredom in some situations. Furthermore, reading as a distraction is not necessarily any different from many other kinds of activities not related to patient care that are routinely accepted, such as idle conversation among personnel. Many comments about the issue were related not to the actual decrement in vigilance induced by reading but rather to the impact of the negative perception of the practice (and of those who do it) by surgeons and by patients (if they were aware of it). Slagle and Weinger also wondered about the impact of Internet use during anesthesia care, a growing phenomenon. Wax and colleagues looked at electronic anesthesia records from more than 1000 cases by 171 anesthesia professionals, all of whom used a record-keeping computer system that also allowed, and tracked, access to the Internet.[189] These investigators correlated

hemodynamic variability and adverse hemodynamic outcomes versus the extent of Internet use both within and between cases. They found no significant impact of Internet use on these variables. However, this methodology does not assess the vigilance of the anesthesia professional directly. As Domino and Sessler point out in an accompanying editorial, it is well established that cell phone use and texting reduce vigilance while driving automobiles (or trains) and increases the risk of accidents.[190]

As pointed out by nearly all authors on these topics, the bottom line is as follows, to quote Slagle and Weinger: "(1) the patient must be the foremost priority and (2) being distracted or performing noncritical tasks during critical or unstable situations is inappropriate and dangerous." In our training course on ACRM, we teach that the anesthesia professional is responsible for modulating all controllable distractions—for example, allowing music during routine work (if all agree), reading, or Internet use, but eliminating it when the workload increases or a situation becomes more complex or urgent. Similarly, although our own institutions do not have a fixed policy against reading in the OR (or against casual conversation, for that matter), everyone expects the anesthesia professional to have a very low threshold for abandoning any potential distractions to provide maximum attention to patient care.

The issue of potential distractions in general, which include "all the various stimuli that could prevent someone from concentrating," was studied by Campbell and associates.[191,192] These investigators also looked at interruptions—"a stimulus that briefly requires the attention of the anesthesia professional." With such broad definitions, the distractions and interruptions in this study varied widely: from work-related or unrelated conversations; maneuvering within the OR suite or OR; music, pagers, phone calls, and noise; and even conversation with a patient to reassure him or her. Distractions occurred, on average, between once every 2 minutes to once every 7 minutes, depending on the phase of the anesthetic case. Slightly more than 20% of distractions—particularly interruptions—were associated with an observable negative impact. Such events are particularly problematic when they disrupt prospective memory, which is the memory to do something in the future. Disruptions in prospective memory are known to be an issue in aviation safety and health care safety,[193-200] and this study reinforced the special risk of interruptions in anesthesia safety.

Sleep Deprivation and Fatigue*

General Principles. Scientists are discovering the importance of adequate sleep to allow normal human performance. A consensus report by leaders in the field of sleep medicine stated the following:

[we] evaluated scientific and technical reports on the distribution throughout the 24-h day of medical incidents (such as heart attack and stroke) and performance failures (such as vehicular accidents and human errors in industrial and technical operations that can affect public safety). We found that these events occur most often at times of day coincident with the temporal pattern of brain processes associated with sleep. It thus appears that the occurrence of a wide range of catastrophic phenomena are influenced by sleep-related processes in ways heretofore not fully appreciated.[201]

This report goes on to give many examples of catastrophes that have occurred at least in part because of the effects of sleep deprivation and fatigue.

Investigations in other complex industries (aviation, nuclear power, maritime, long-haul trucking) have identified fatigue as the probable cause of or a contributing factor in many accidents. Unlike health care, the transportation industries have a body—the NTSB—that actively evaluates accident causation, including performance-shaping factors such as fatigue and sleep deprivation. By formal analysis, fatigue has been implicated in many famous accidents. For example, fatigue was a contributing factor in the Exxon Valdez grounding (in Alaska), the nuclear disasters at Three Mile Island (in Pennsylvania) and Chernobyl (in the Ukraine), and the decision-making process that led to explosion of the space shuttle Challenger. We have no such mechanism for evaluating fatigue causation in medical error, so what is not looked for will not be found.

Based on these findings, however, it is likely that chronic sleep deprivation, circadian rhythm abnormalities, and fatigue can be blamed for some iatrogenic adverse patient outcomes. As previously mentioned, the IOM report published in 1999 revealed that thousands of patients are harmed each year by preventable error. Some of these errors may have fatigue as a causative factor, and this should be an area of active study. However, it is difficult to determine the degree to which this is true because no blood test equivalent exists for level of impairment secondary to fatigue. Although these factors have long been minimized or ignored by health care professionals, an understanding of them is critical to maximize patient safety, as reflected in these reviews.[202,203]

The process of ignoring this issue may be coming to an end. In December 2011, The Joint Commission published a "Sentinel Event Alert" documenting the impact of fatigue on patient safety.[204] The Joint Commission suggested actions for organizations aimed to mitigate fatigue-related safety breaches (Appendix 7-2; www.jointcommission.org/assets/1/18/sea_48.pdf).

Normal Sleep. Carskadon and co-workers referred to sleep as a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment that is usually accompanied by postural recumbency, quiescence, closed eyes, and other indicators commonly associated with sleeping.[205] Sleep can be thought of as a physiologic drive state similar to hunger or thirst and is necessary for maintenance of alertness, performance, and overall well-being (see also Chapter 14). The intensity of this drive can be inferred by noting how quickly an individual falls asleep. Just as eating and drinking satiate hunger and thirst states, sleeping reverses the desire to sleep.

The amount of sleep required by any individual is genetically determined and is the amount that allows

*This section was edited by Steve Howard, Veterans Affairs Palo Alto Health Care System and Stanford University.

that individual to be awake and alert throughout the day. The average sleep time for young adults is 7 to 8 hours per 24-hour period, with an approximately 15% interindividual variation. These sleep requirements do not change with age, and humans can do little to train their physiology to function optimally on less sleep than required.

Sleep Debt. If adequate sleep is not obtained for whatever reason, daytime sleepiness and impaired performance ensue. Sleep loss is cumulative and results in what is referred to as sleep debt. An individual who has obtained an optimal amount of sleep is better prepared to perform long periods of sustained work than one who is operating from a sleep debt.

Because of the additive effects of chronic partial sleep loss, even minor sleep restriction on a nightly basis can insidiously accumulate into a substantial sleep debt.[206] The only way to pay back a sleep debt is with sleep.

Sleep debts are commonplace in our culture. The National Sleep Foundation's annual survey continues to reveal that Americans chronically undersleep by 60 to 90 minutes each day (http://www.sleepfoundation.org/article/sleep-america-polls/national-sleep-foundation-bedroom-poll). Shift work, long and irregular work hours, and the demands of family and recreation lead to irregular sleep patterns and prevent restful sleep. This is particularly true for physicians, who often work in shifts, have long duty periods, and must frequently care for patients for long periods.

Circadian Rhythms. Rhythms that fluctuate on a 24-hour time scale are known as circadian rhythms. The biologic clock that is responsible for these rhythms is located in the suprachiasmatic nucleus in the human brain. The best-known circadian rhythms are those of body temperature, hormone secretion, metabolism, and the sleep-wake cycle. The circadian system is synchronized to the 24-hour day by external stimuli referred to as "zeitgebers," the most influential of which is the light-dark cycle of day and night.

The circadian system is biphasic in that it produces a state of increased sleep tendency and decreased performance capacity during two periods throughout the 24-hour day—from 2 AM to 6 AM and from 2 PM to 6 PM. These periods are sometimes referred to as circadian lulls or low points. These are periods when we are more vulnerable to incidents and accidents because our body clock is "turned off." The circadian clock is very resistant to alterations, and it does not adjust rapidly to changes such as those produced by jet lag or shift work. Disruption of the normal circadian rhythm or incomplete circadian adaptation leads to acute and chronic sleep deprivation, decreased alertness, increased subjective fatigue, and decreased physical and mental performance.[207]

Sleepiness and Alertness. Sleepiness and alertness are at opposite ends of a continuum. Daytime sleepiness is the most obvious effect of failing to obtain adequate sleep. Healthy adults are maximally alert by midmorning. This is sequentially followed by a circadian lull in the early afternoon (causing some cultures to incorporate an afternoon "siesta"), increased alertness in the early evening, and finally increased sleepiness that normally results in falling asleep at night.

The most extreme periods of sleepiness become manifest when one is out of sync with the circadian clock (either staying awake and working when our clock is pressuring sleep or attempting to sleep when our clock is pressuring wakefulness). Data from the U.S. Department of Transportation reveal that the greatest number of single-vehicle accidents takes place during the early morning hours when people are at a circadian lull of alertness. These accidents are thought to result from inadvertent lapses in driver attention brought about by extremes of sleepiness.[208]

Determinants of Sleepiness. The major factors causing sleepiness are decreased quantity of sleep, poor quality of sleep (sleep fragmentation resulting from multiple awakenings or abnormal progression of sleep states and stages), disrupted circadian rhythms, and the use of certain medications. The amount of sleep obtained is directly related to daytime sleepiness. If sleep is restricted in healthy adults, daytime sleepiness can be demonstrated the following day.[206] If one is allowed to extend sleep beyond the usual sleep time, increased alertness can be demonstrated in the laboratory.[4] Sleep quality is affected by many factors. Sleep fragmentation affects older adults and patients with sleep disorders such as sleep apnea and periodic limb movements. Sleep fragmentation commonly occurs in physicians who are awakened from sleep to care for patients while in the hospital.

Caffeine and other stronger stimulants are known to reduce nocturnal sleep if ingested close to bedtime, hence decreasing sleep quantity and quality.[209] Potent stimulants such as amphetamines do produce increased alertness and performance, but they have significant side effects and are not an option for health care personnel (e.g., the individual must undergo a substantial amount of recovery sleep ["crash"] after their effect is gone). Newer, nonamphetamine alertness-enhancing drugs (e.g., modafinil) are currently under study and are being used in shift workers, including health care workers (see the later section on fatigue countermeasures).

Mood. Long work hours, fatigue, and sleep deprivation have also been shown to bring about consistent and dramatic changes in mood and emotions.[210,211] Depression, anxiety, irritability, anger, and depersonalization have all been shown to increase during testing of chronically fatigued house staff. These emotions are an obvious source of stress between anesthesia professionals and their coworkers, patients, and families. The relationship of mood, performance, and patient safety has yet to be determined.

Vigilance. Vigilance, the centerpiece of the ASA logo, is defined as "alert watchfulness." Vigilance is critical, although studies of the performance of anesthesiologists make it clear that vigilance is not the only key characteristic of careful anesthesiologists. Vigilance is a necessary but not sufficient condition to permit the safe passage of a patient through the perioperative period. If vigilance and other aspects of decision making are impaired by performance-shaping factors such as sleep deprivation and fatigue, the likelihood of an adverse patient outcome is greater.

Monitoring of slowly changing stimuli is a classic vigilance task that makes up a significant proportion of the anesthesia professional's work. This type of task is most sensitive to the degrading effects of sleepiness and fatigue. During the performance of lengthy vigilance tasks, the most common types of decrements include increased reaction time, lapses (transient periods of unawareness), and a reduction in the probability of detecting an alarm. This type of performance impairment has been documented after as little as 30 minutes of time on a task, and the decrement is even more pronounced if the individual is physiologically sleepy at the beginning of the task.

Microsleep Events. The most extreme cause of impaired vigilance is the occurrence of actual sleep episodes (microsleeps) encroaching into periods of wakefulness. Microsleep events typically last a few seconds to a few minutes. They are intermittent in onset, and their impending occurrence is difficult for the individual to predict. Most individuals underestimate their level of sleepiness when they can be objectively shown to be extremely sleepy, thus making this problem even more insidious. In other words, one can fall asleep and not be perceptually aware of it. This has significant meaning in the workplace and when driving home after long work periods. Microsleep episodes are the probable cause of many single-vehicle crashes.

Microsleeps are a sign of extreme sleepiness and are harbingers of the onset of longer sleep periods. Typically, they occur during periods of low workload or stimulation and when an individual is maximally sleepy. In addition, an individual's performance between microsleep episodes is impaired. Frequent and longer microsleeps increase the number of errors of omission.

Driving while drowsy may be less forgiving than practicing medicine while drowsy. It is easy to imagine that if a driver has a microsleep for only seconds while traveling at 60 miles per hour, the likelihood of an accident will be high. Although the anesthesia professional's work environment does not (usually) evolve as fast as that of the driver, the safety implications of falling asleep while providing care are similarly obvious.[212]

Scientists at the NASA Ames Research Center in Mountain View, California studied the occurrence of microsleep episodes in pilots during transmeridian flights.[213] These flights involve multiple time zone changes with long, irregular work schedules and resultant disruption of circadian rhythms. This situation causes fatigue, sleepiness, and decreased performance, which are believed to have an impact on flight safety. This particular protocol compared two pilot groups flying equivalent flights: a control (non-nap) group and a nap group. Electroencephalographic monitoring of the pilots was performed to determine the extent of microsleep episodes and also to document whether pilots were actually able to nap if given the opportunity. In brief, the study revealed that (1) crew members were able to nap seated in the cockpit if given the opportunity, (2) the non-nap crew had significantly more microsleep episodes during critical phases of flight than did the crew that had napped, and (3) performance on a standardized test of visual reaction time was worse in the non-nap group than in the group that had napped. This study demonstrated that microsleeps do occur even in a work environment in which sleep is strictly forbidden and in which work hours are tightly regulated. Napping appears to be a reasonable countermeasure to decrease the likelihood of microsleeps and improve performance. Other work on napping supports these conclusions.

Do anesthesia professionals suffer microsleep events? The answer almost certainly is yes. Anecdotal evidence, as well as unpublished reports from our own surveys, suggests that these events do occur from time to time. Microsleeps occurred in a study of anesthesiologists performing work in a simulated environment.[214] Studies from the Harvard Work Hours and Safety group revealed that interns working traditional shifts in the ICU were more prone to microsleeps during their work shifts (they used the term "attentional failures") than individuals who worked shortened shifts.

Shift Work. From a practical standpoint, shift work will remain a common method to provide 24-hour care in the hospital setting.[215-217] Workers and managers should learn how circadian factors, sleep-related factors, and social factors affect the lives of workers and their families. Hospital organizations should make it a priority to establish that workers are appropriately rested, just as they try to ensure that workers are not impaired by drugs or alcohol on the job. Given current knowledge concerning shift work and the many factors that affect an individual's ability to cope, no single "best" schedule for shift work exists. Some workers tolerate systems that others find excessively onerous. If given a choice, many workers choose suboptimal shift work rotations when doing so gives them increased pay or more time off work.

Methodologies for Assessing Sleepiness. Various methods are used for assessing an individual's level of sleepiness, including behavioral indicators, subjective measures, and physiologic measures (see also Chapter 14). Behavioral indicators of sleepiness include yawning, ptosis, decreased social interaction, and microsleep events. Many of these behaviors are difficult to quantify.

Subjective measures include various types of numeric or visual analog scales that attempt to measure how sleepy the individual *feels*. These methods are used frequently in studies of sleepiness because they are very easy to implement; however, subjective feelings of fatigue and sleepiness are often underestimated by individuals in comparison to their level of physiologic sleepiness. Both behavioral and subjective sleepiness can be masked by a stimulating environment, even though the individual remains physiologically sleepy. When environmental stimuli wane, physiologic sleepiness manifests itself as an overwhelming propensity to fall asleep. A person who is physiologically alert does not experience sleepiness as environmental stimuli decrease. For example, without physiologic sleepiness, an individual may become bored during a lecture but does not fall asleep.

Physiologic (objective) measures of sleepiness have been used extensively in sleep research and sleep medicine. Richardson, Carskadon, Dement, and colleagues developed the Multiple Sleep Latency Test (MSLT), which is the standard method for quantifying daytime

sleepiness.[218,219] The MSLT tests the propensity of an individual to fall asleep in a sleep-inducing environment during the daytime. A short sleep latency (i.e., falling asleep quickly) is a sign of increased sleepiness, whereas a long sleep latency is a sign of decreased sleepiness. A normal MSLT score is greater than 10 minutes, whereas pathologic daytime sleepiness is defined as 5 minutes or less. Pathologic levels correspond to the daytime sleepiness typically seen in patients with narcolepsy or sleep apnea or in healthy individuals deprived of sleep for 24 hours.

Evaluation of Physiologic Sleepiness in Anesthesia Residents. Using the MSLT, Howard and colleagues evaluated the physiologic daytime sleepiness of anesthesia residents under three different conditions: (1) "baseline" (daytime shift, no on-call duty period in the previous 48 hours), (2) "post-call" (immediately after a 24-hour work and in-house on-call period), and (3) "sleep extended."[203,220] In the sleep-extended condition, residents were told to maximize sleep and were allowed to arrive for work at 10 AM (3 to 4 hours later than normal) for 4 consecutive days before testing. They were not on call during this time. The sleep-extended condition was included to provide a true control state of maximal rest and optimum alertness.

In this study, anesthesia residents had an MSLT score of 6.7 ± 5.3 minutes in the "baseline" condition and 4.9 ± 4.7 minutes in the "post-call" condition; both scores revealed the nearly pathologic levels of daytime sleepiness seen in patients with narcolepsy or sleep apnea. The "baseline" group slept an average of 7.1 ± 1.5 hours per night, whereas the "post-call" group reported an average of 6.3 ± 1.9 hours of sleep during their night on call. Ironically, although the on-call periods occurred during rotations that often have very busy call nights, only a few subjects were, in fact, awake most of the night. In the "sleep-extended" condition, the subjects extended their sleep to an average of more than 9 hours per night, and MSLT scores were in the normal range (12.0 ± 6.4 minutes). These results clearly demonstrate that medical personnel who have not been on call cannot be assumed to be "rested" when compared with "fatigued" post-call residents. These data also indicate that under "normal" working conditions, the resident physicians studied were physiologically sleepy to nearly pathologic levels. This finding documents a previously unknown level of chronic sleep deprivation in this population. Notably, these data cast substantial doubt on previous studies of the performance of medical personnel that have relied on the assumption that individuals working under "normal" conditions are truly rested (see also Chapter 9).

Evaluation of Subjective Sleepiness. In the previously discussed study, Howard and colleagues also investigated the degree of discrepancy between the residents' subjective sleepiness (how sleepy they felt) and their physiologic sleepiness (how easily they fell asleep). Subjective sleepiness was measured with a validated numeric scale (Stanford Sleepiness Scale); physiologic sleepiness was measured with the MSLT, as described earlier. Subjects' self-reported sleepiness immediately before each sleep opportunity during the MSLT did not, in general, correlate with their MSLT score. As in previous studies, subjective sleepiness correlated better with physiologic sleepiness when subjects were extremely alert or extremely sleepy.

The authors also found that subjects demonstrated little ability to determine whether they had actually fallen asleep during the MSLT sleep opportunities. For example, in 51% of trials in which the electroencephalographic and electro-oculographic measurements showed that the subject had fallen asleep, the subjects thought they had remained awake throughout the test. These results support the contention that medical personnel are physiologically vulnerable to degraded alertness yet are unable to perceive this decrement. Thus, an anesthesia professional could, in fact, fall asleep during a case, awaken, and be totally unaware of the lapse in vigilance.

Sleep Deprivation and Fatigue in Medical Personnel. Human error represents a significant risk to hospitalized patients,[3] and it has been estimated to play a role in more than 70% of anesthesia mishaps.[221] This is similar to the error rate seen in cognitively similar work environments such as aviation.[222] Clearly, the physiologic capabilities and limitations of the human operator in complex work environments remain central to safe and productive performance. The 24-hour demands of medical care parallel the physiologic challenges present in other operational domains; nevertheless, minimal data are available to quantify the fatigue-related risk to performance and alertness in medical personnel.

Providing quality health care requires physicians to attend to details critical for life, such as monitoring of changing vital signs, administering the correct type and dose of medications, and in general, making crucial decisions to achieve optimal patient care. Physicians, like other workers, are affected by all the physiologic, psychological, and behavioral demands that characterize work environments requiring continuous, around-the-clock operation. However, whereas much of the health care system (e.g., nursing) relies on multiple work shifts to cover the 24-hour day (which is also not a perfect system), physicians more typically work long duty periods and frequently experience sleep loss, circadian disruption, and fatigue. Even minimal levels of sleep loss (e.g., obtaining as little as 2 hours less sleep than an individual requires) can lead to lapses in performance, increased physiologic sleepiness during the daytime (including microsleeps), and altered moods.[223] This level of degraded performance and alertness almost certainly contributes to medical error and health care mishaps.[202]

Work Hour Regulations. In July 2003, The Accreditation Council for Graduate Medical Education (ACGME) in the United States instituted the first set of common duty hour requirements for all accredited residency training programs. In 2011, the ACGME published a revised set of guidelines in response to the 2008 IOM report entitled *Resident Duty Hours: Enhancing Sleep, Supervision, and Safety*.

The current ACGME requirements can be found at www.acgme.org and are as follows:

- Eighty hours per week are averaged over a period of 4 weeks (including all in-hospital call).

- One day (continuous 24-hour period) in 7 is free of all duties (clinical and educational) averaged over a 4-week period.
- Postgraduate year 2 (PGY-2) residents and above must be scheduled for in-house call no more frequently than every third night (when averaged over a 4-week period).
- Maximum duty periods:
  - Duty periods of PGY-1 residents must not exceed 16 hours in duration.
  - Duty periods of PGY-2 residents and above may be scheduled to a maximum of 24 hours of continuous duty in the hospital. Programs must encourage residents to use alertness management strategies in the context of patient care responsibilities. Strategic napping, especially after 16 hours of continuous duty and between the hours of 10:00 PM and 8:00 AM, is strongly suggested.
  - Residents must not be assigned additional clinical responsibilities after 24 hours of continuous in-house duty.
- In-hospital call is not to exceed 24 hours; residents may remain on duty for 6 additional hours to participate in educational activities, transfer care of patients to another team, conduct outpatient clinics, and maintain continuity of care.
- No new patients are accepted after 24 hours of continuous duty.
- Residents must not be scheduled for more than 6 consecutive nights of night float.
- Residents should have a 10-hour period between all daily duty periods and must have 8 hours free of duty. They must have at least 14 hours free of duty after 24 hours of in-house duty.
- Moonlighting hours are to be included as part of the 80-hour limit and must not interfere with the ability of the resident to achieve the goals and objectives of the educational program.
- Exceptions: a residency review committee may grant exceptions for up to a 10% increase in the 80-hour limit to individual programs on a case-by-case basis (maximum increase to 88 hours per week).

The most significant change with the revised requirements affect interns, so anesthesia training programs that have categorical positions (interns as well as anesthesia trainees) will be required to maintain these work hour requirements. Training programs were never given direction on how to accomplish the work hour restrictions, but most anesthesiology training programs have been able to adopt them successfully. Interestingly, no work hour restrictions are given for practitioners or any other care providers beyond residency training. There is no proof that the change has had a positive or negative impact on patient or provider safety, although pundits continue to debate both sides of the issue.[224,225] Studies showed that the number of hospitalwide adverse drug events remained constant after the limitations,[226] and postoperative outcomes were not affected in the programs studied.[227]

Compliance rates for the common program requirements have been tracked by Landrigan and co-workers.[228] In a survey of interns, these investigators found that more than 80% reported some kind of work hour violation during 1 or more months of the study. Average work duration decreased and sleep time increased when compared with an equivalent time before duty hour limits. Reporting of compliance by individual residents is complicated by many factors, so the true amount of work being performed is not known. Many surgical programs have requested and been given a 10% work hour extension, but it is not known how many of these requests have been turned down.

European and Australian Regulations. Work hour regulations in the European Union and in Australia or New Zealand are much more stringent than they are for trainees in the United States. In 2009, the maximum hours that junior medical staff in the NHS in the United Kingdom work was reduced from 58 to 48 under European law. This is a major challenge for the health service and will require new ways of working to be adopted. The NHS National Workforce Projects has been appointed as the lead organization to help support the NHS in finding and implementing solutions to the changes in the work environment (http://www.healthcareworkforce.nhs.uk/). The results of these restrictions on patient and provider safety are still being evaluated, and these findings may have an impact on any further restrictions that may occur in the U.S. system. Empiric studies documenting the effect of the European Union changes are lacking, although several arguments for and against the directive have been presented.[229,230]

Harvard Work Hours, Health, and Safety Group Studies. A series of interesting studies was published by a group from the Brigham and Women's Hospital in Boston.[231,232] The investigators conducted a randomized study comparing interns working in an ICU on a traditional schedule (every third night on call with shifts longer than 24 hours in duration) and an intervention schedule that reduced work shift duration (to less than 17 hours) and the number of hours worked per week. Interns made 35.9% more serious medical errors and had twice as many attentional failures (microsleeps) during the traditional schedule. Those on the traditional schedule worked more hours per week (85 versus 65 hours) and slept less (5.8 hours), which led the investigators to conclude that elimination of long work shifts reduced errors and decreased manifest sleepiness.

This group also conducted a monthly prospective nationwide survey of interns' first postgraduate year to evaluate the risk for motor vehicle accidents with extended work shifts.[233] They found an increased likelihood of motor vehicle accidents and near-miss accidents after extended work shifts and an increased monthly risk with increasing number of shifts.

The Harvard group also conducted a survey of house staff on percutaneous injuries during work.[234] They found that from a total of 17,003 monthly surveys with interns, 498 percutaneous injuries were reported (0.029/intern-month). Among other factors, lapses in concentration and fatigue were the most commonly reported contributing factors (64% and 31% of injuries, respectively). Percutaneous injuries were more frequent during extended work compared with nonextended work (1.31 in 1000 opportunities versus 0.76 in 1000 opportunities, respectively. Injuries were more frequent during the nighttime than during

the daytime (1.48 in 1000 opportunities versus 0.70 in 1000 opportunities, respectively). It is easy to conclude from the science that fatigue can harm both the patient and the practitioner.

Sleep and Performance. Previous studies addressed the effects of sleep deprivation and fatigue on physician performance and well-being (see also Chapter 14). Major reviews of this literature identified little consensus.[235,236] Several methodologic flaws are present in the existing literature:

1. The degree of acute sleep deprivation of subjects was poorly defined, and no assessment of chronic fatigue was made. Typically, studies relied on only the previous night's sleep as a level of "fatigue," and subjects could well have been chronically fatigued during baseline (control) trials, which could mask the degree of impairment resulting from the acute fatigue of being on call. This continues to be the greatest weakness in studies of fatigued health care providers.
2. Measuring actual clinical performance is difficult and was not attempted. Most studies had to rely on simple cognitive tasks that probed only short-term memory, immediate recall, and simple reaction time; the validity of using such simple tests to probe complex performance has been challenged because these simple tests do not assess the higher-level cognitive functions most critical to skilled medical care.
3. Most of the performance tests were of very short duration (3 to 5 minutes). Studies have shown that if sufficiently motivated, even fatigued subjects can perform well on short-duration tasks.
4. Practice effects were not adequately accounted for. If subjects have not learned a particular performance test sufficiently to achieve maximum performance, subsequent trials will almost certainly show improvement in performance because of further learning of the task.

Some studies requiring subjects to perform sustained vigilance tasks of long duration have, in fact, shown impairment in the performance of fatigued physicians. Tasks of this type, which require sustained attention to detail, are highly relevant to the anesthesia professional's tasks, and they are the most sensitive to the effects of sleep loss and fatigue.

Do Anesthesiologists Perceive Fatigue As a Problem? The survey by Gaba and associates revealed that more than 50% of respondents believed that they had made an error in clinical management that they thought was related to fatigue.[237] In another survey of anesthesiologists and CRNAs, the majority (61%) of respondents recalled having made an error in the administration of anesthesia that they attributed to fatigue.[238] Data from these surveys and others reveal that issues of sleepiness and fatigue are perceived by anesthesia practitioners as being important causative factors in reducing anesthesia-related patient safety.[239]

Howard and colleagues conducted a study of rested versus sleep-deprived anesthesiology residents by using a realistic patient simulator.[214] Multiple measures of performance were collected during this 4-hour experiment (e.g., psychomotor tests, reaction to secondary task probes, response to clinical events). In the rested condition, subjects had 4 consecutive days of sleep extension (showing up at work at 10:00 AM), whereas in the sleep-deprived condition they had remained awake for 25 hours (during a "pseudo"–on-call period) before performing the simulated anesthetic. Subjects in the rested condition were able to increase their total sleep time more than 2 hours from baseline. Psychomotor tests revealed progressive impairment of alertness, mood, and performance over the course of the pseudo–on-call period, as well as on the experimental day, when compared with the well-rested condition. Secondary task probe response times were slower after sleep deprivation, although this reached statistical significance in just one of three probe types. No statistical difference in case management between conditions was reported—in fact, subjects in both conditions made significant errors. The behavioral alertness scores in the sleep-deprived condition were different from those of subjects who had increased their sleep time. Even when well rested, the subjects in this experiment did not perform perfectly; however, they did not show any of the behavior indicative of being sleepy (e.g., head nodding, eyes closing). Sleep-deprived subjects cycled (often rapidly) in and out of sleepy behavior, and the most impaired individuals showed such behavior for more than 25% of the experiment (60 minutes).

Fatigue Countermeasures. Studies such as the ones described previously are establishing the true picture of sleepiness and fatigue in medical personnel. From studies of the performance of fatigued individuals in other domains, we know that professionals become increasingly vulnerable to the degrading effects of sleepiness as the sleep debt accumulates. It may be difficult to determine a causal relationship between anesthesia professional fatigue and patient outcome. However, it is clear that if anesthesia professionals are not awake, they cannot possibly be aware. Such a lapse in vigilance is unacceptable. Furthermore, anesthesia professionals cannot prevent sleep by willpower alone because it is a fundamental physiologic drive. Demands for clinical services must be balanced against the potential for reduced vigilance and error by seriously fatigued practitioners, anesthesia professionals, and surgeons alike.

Because fatigue is such a widespread and insidious problem, it is important to determine ways to counteract its effects. Strategies that institutions or practitioners can use to minimize the negative effects of sleepiness and fatigue on performance include the following:

- Education
- Improved sleep habits
- Rest breaks at work
- Strategic napping
- Medications
- Light therapy

Education. The first step in addressing sleepiness and fatigue of medical personnel is to educate practitioners and the administrators of health care institutions about the impact of sleep issues on work performance, mood,

job satisfaction, and health (see Chapter 9). Education is a relatively simple and inexpensive countermeasure that can be implemented immediately. Educational programs covering sleep deprivation, circadian disruption and fatigue, and countermeasures have been enthusiastically adopted by an increasing fraction of the aviation community.[240,241] Similar programs should be developed for the health care community. Education alone is sufficient for some individuals and institutions to change their work and sleep habits or their organizational and scheduling procedures. However, it is clear at both the individual and organization level that education will not be sufficient to address this issue fully. Other competing forces (e.g., measures of production versus safety) are very powerful and difficult for practitioners to manage.

Improved Sleep Habits. The most important factor is to obtain adequate sleep—most adults need at least 8 hours. Good sleep habits include the following: regularity of bedtime and wake-up time; sufficient time for sustained and individually adequate sleep; restriction of alcohol, caffeine, and nicotine before bedtime; and use of exercise, nutrition, and environmental factors so that they enhance rather than disturb sleep. A regular sleep schedule is an important part of optimal sleep hygiene, but it is often not possible for medical personnel, given the requirement to cover clinical needs on a 24-hour basis. Medical personnel should make greater effort to maintain as constant a sleep schedule as possible and to maximize sleep opportunities before and after periods of reduced sleep.

Social drug use can have profound effects on sleep. Physicians frequently use caffeine to stay awake during on-call periods, but often its use could be more strategic. Strategic use (i.e., use when its alerting effects are needed) of caffeine requires knowledge about its onset and duration of action. Besides its alerting effects, caffeine produces an increase in awakenings and decreases the total nocturnal sleep time if ingested close to sleep opportunities. Individuals who ingest large amounts of caffeine and who have nocturnal sleep disturbances should limit or cease their intake of caffeine. Long-term use of caffeine, common in our culture, produces tolerance to the alerting effect of the drug and hence should be avoided when using caffeine strategically. Nicotine is a stimulant that produces effects similar to those of caffeine. Alcohol is often used successfully to initiate sleep, but its effect on sleep architecture after sleep onset can be devastating. After ingestion of alcohol, frequent awakenings from sleep occur that can be associated with increased sympathetic nervous system activity, often manifested as headache, sweating, and tachycardia. Clearly, use of these substances should be restricted near bedtime.

Physicians often lack good nutritional habits, especially during long duty periods. Meals may be skipped or ingested quickly whenever there is adequate time. If one is hungry before bedtime, it is best to avoid eating or drinking heavily because this, too, can disturb sleep.

The effects of age can make optimum sleep habits difficult to achieve because sleep requirements do not change once reaching adulthood. The number of awakenings per night rises after the age of 45 years and results in decreased sleep efficiency (time in bed versus total sleep time). The ability to initiate sleep at any time during a 24-hour day is diminished after the age of 25 years, and "sleeping in" to make up for lost sleep is more difficult as individuals grow older. Sleep-related disorders such as breathing disruptions (obstructive sleep apnea) and periodic limb movements also become more common with age.

Ideally, the sleep setting should be a dark, quiet room devoid of sources of interruption such as pets, telephones, pagers, and children. The sleeping surface and environmental temperature should be comfortable. Psychological stressors increase baseline physiologic arousal and can impair the quality and quantity of sleep. For example, reviewing the previous day's events or attempting to plan tomorrow's activities while trying to fall asleep is not conducive to sleep. Effort should be made to separate the work of the day with a period of relaxation before attempting to initiate sleep.

Rest Breaks at Work. Although other industries have openly recognized the reality of decrements in vigilance resulting from fatigue and sleepiness, the health care system has not. Rest breaks and rotation of task duties are mandatory for air traffic controllers and are part of naval ship command procedures in an attempt to prevent potential lapses in vigilance. Short breaks have been shown to increase productivity and job satisfaction, and they probably also help alleviate boredom. In anesthesia training programs, residents are frequently given rest breaks during the daytime, but this is often not the case with private practitioners. Private practice anesthesia typically does not provide the mechanisms for rest breaks or task duty rotation, in part because of fiscal issues. An "extra" anesthesia professional would be necessary to provide these opportunities on a regular basis.

The optimal timing and length of breaks are unknown, but periodic relief from duty should be taken when possible. Cooper and co-workers studied the effects of intraoperative exchange of anesthesia personnel.[242,243] Although in some cases the process of relieving OR personnel caused a problem, it more frequently was associated with the discovery of a preexisting problem. The positive effect of relief of personnel probably depends on the quality of the handover briefing conducted by anesthesia professionals. Studies are currently being performed to address standardized handover of intraoperative care of patients.

If anesthesia professionals are unable to obtain a break during long work periods, they can take other measures to remain alert. They can engage other OR personnel in conversation (although this, too, can be distracting), thereby increasing the level of stimulation in the environment. Walking around and standing up are also techniques that decrease subjective (but not physiologic) sleepiness. If anesthesia professionals are having microsleep events, which may be noticed by other personnel rather than by the anesthesia professionals themselves, fatigue is already very severe, and complete sleep is imminent. In such a situation, the practitioner must secure additional assistance in surveillance of the patient and, if necessary, obtain relief to allow time for sleep.

Strategic Napping. If adequate sleep during the night cannot be obtained, naps can be used to decrease sleepiness and improve performance. The optimal nap length for most individuals is about 45 minutes; this duration

acutely improves alertness, allows improved performance, and minimizes the possibility of sleep inertia on awakening. Naps as short as 10 minutes have beneficial effects on alertness. A nap of 90 to 120 minutes allows a full sleep cycle and can additionally boost alertness and performance over that of shorter nap periods. Data from NASA studies of flight crews demonstrate that on the whole, napping is a useful countermeasure to fatigue and sleep deprivation.[213]

Smith-Coggins and associates studied the effect of naps during the night shift on health care providers working in a busy suburban university emergency department.[241] Workers were randomized to work a night shift without rest (as was the norm in this facility) or to receive a 40-minute nap opportunity at 3 AM. The investigators found that a nap taken at this time improved performance on some (but not all) measures. The most important result of this study may be the fact that the subjects were able to (1) use this strategy successfully in the real workplace and (2) improve alertness and performance.

Investigators at the VA Hospital at Palo Alto, California, have developed a Strategic Nap Program that has been successfully piloted at two sites within the Veterans' Affairs system. This program has been implemented in ICU settings but is equally applicable to other high-risk, dynamic domains such as the OR. Components of the program include a formal educational program, program guidelines for the individual practitioner and the facility, and other guidance for implementation.

Certain issues complicate the appropriate use of naps by medical professionals. Physicians have an individual and cultural tendency to ignore or to minimize the effect of fatigue and sleep deprivation. The culture of medicine views work breaks and naps as signs of weakness. The military has addressed similar attitudes with the concept of "power napping." Troops are strongly encouraged to take naps of 10 minutes to 1 hour when the situation permits to increase their strength and performance. This approach appropriately presents the idea of napping in a positive light as a sign of wisdom and strength rather than one of cowardice and frailty.

Sleep Inertia. Sleep inertia corresponds to the period of reduced ability to function optimally immediately on awakening.[226,244] This phenomenon usually occurs when individuals are awakened out of slow-wave sleep and is manifested as grogginess and impaired performance lasting as long as 15 to 30 minutes after awakening. Sleep inertia can also occur after being awakened from normal sleep and is most common during the early morning circadian trough (2 to 6 AM). Depending on the preexisting level of sleepiness, individuals who take naps longer than 40 minutes are at greater risk for sleep inertia on awakening. Sleep inertia can be important to health care professionals who may be awakened out of deep sleep to provide emergency care to patients (e.g., emergency cesarean section or emergency intubation). If urgent work can be anticipated, the sleeping individual should be awakened with sufficient time (at least 15 minutes) to minimize the fogginess and decrement in performance associated with sleep inertia. If sleep inertia is unavoidable, it would be wise for the affected person to ask for help until the grogginess dissipates.

Medications. A few studies have evaluated the use of sedative-hypnotics for promotion of sleep during nonduty hours by nonmedical personnel (e.g., to assist in daytime sleep after a night shift). Many questions remain unanswered regarding the quality of sleep obtained after using hypnotics, the severity of hangover effects, and the potential risk of abuse. Melatonin, which is a hormone secreted by the pineal gland, may have promise as a nonaddictive daytime sleep-inducing agent, but the results of existing studies are controversial.

Stimulants may have a role in the maintenance of alertness during periods of extreme sleepiness. Modafinil is a nonamphetamine alertness-enhancing drug that has been approved for use in narcolepsy and shift work sleep disorder.[245] The side effect profile of this drug is so promising that it has been studied extensively by the military and shift workers as a nonaddicting adjunct for alertness management. Its use in health care is also being studied but cannot be sanctioned at this point.[246] The use of sedatives and potent stimulants to manipulate sleep is not considered an appropriate option for anesthesia professionals. Caffeine is used frequently to increase alertness temporarily, but caveats about its use exist, as discussed earlier. Caffeine should be used strategically to maximize its effect when needed. Strategic use of caffeine includes (1) knowledge of its onset (15 to 30 minutes) and duration of action (3 to 4 hours) and (2) use when alertness is required and the opportunity to sleep is minimal.

Countermeasures should be studied and implemented in health care. Major financial incentives support maintaining the status quo.[202] If anesthesiologists know that they are impaired (from fatigue or for any other reason), the assistance of a colleague should be enlisted so that patient safety is not negatively affected.

Light Therapy. Timed cycles of bright light and darkness have been used in certain circumstances to facilitate adaptation to shift work. Exposure to bright light (>7000 to 12,000 lux) and darkness at the appropriate points in the circadian cycle has been shown to reset the circadian pacemaker by 12 hours over a period of 2 to 3 days.[247] This important finding demonstrates the ability to make significant changes in the circadian system relatively quickly. However, resetting the circadian timekeeper is critically dependent on the timing, intensity, and duration of exposure to light and to "total" darkness. Being off by only an hour can prevent the desired effect. Adhering to such time-critical schedules for this treatment is probably impractical for anesthesia professionals, given the many work-related and social factors that affect their activities. Research on light treatment continues and may eventually result in more practical treatment regimens.

Aging

All individuals understand that their abilities cannot be maintained indefinitely as they age (see also Chapter 80). On average, performance on laboratory tests of discrete sensory-motor and cognitive skills can be shown to decrease with increasing age.[248] However, large differences are noted among individuals. Again, except at extreme points of performance failure (e.g., severe impairment of vision or hearing), the contribution of isolated

changes in physiologic or cognitive performance is difficult to relate to real work situations.[249] For one thing, the work environment is often rich with redundant cues involving multiple sensory modalities. For another, technologic compensation may be possible, as with the use of hearing aids or glasses. Finally, along with possible physiologic changes of age typically comes greater experience with a variety of situations. For many individuals, the lessons learned from experience more than offset the modest degree of physiologic impairment that they face as they grow older. This compensation has, in fact, been documented for skilled typists, chess players, and bridge players. Middle-aged individuals can use their experience to solve everyday problems better than young individuals can; however, for older adults (on average), compensation by experience is no longer sufficient to offset cognitive slowing.[249] Age takes a toll on short-term (or "working") memory,[250] and evidence indicates that aged workers are more sensitive to the interruptions in attention that are so prevalent in dynamic environments. Nevertheless, few of these deficits have been documented in complex work settings, largely because it is so difficult to measure performance in these domains. The issue of the aging anesthesiologist has raised considerable controversy among anesthesiologists.

What do other industries do about this issue? From 1959 until the end of 2007, U.S. and aviation regulations forced airline pilots to retire at 60 years of age regardless of their health or competence. When the "Age 60 Rule" was put in force, the rationale was that the "increased speeds and passenger loads of commercial airliners placed greater demands on pilots with respect to their physical fitness and piloting skills." Some experts may argue that the increasingly challenging nature of anesthesia practice also places greater demands on anesthesia professionals than ever before.

After intense debate and many studies since the 1980s,[251,252] with partially contradictory studies and few data suggesting that pilots between the ages of 60 and 65 years are at greater risk, the Age 60 Rule was modified by law (HR 4343) at the end of 2007. The new rule allows airline pilots to continue flying until age 65 years, although for captains in international operations, a pilot younger than 60 years must be the copilot.

Federal Aviation Administration (FAA) regulations do require air transport pilots to pass "class I" medical examinations every 6 months. However, the medical examination process appears to be largely aimed at identifying individuals with chronic medical conditions that place them at risk for sudden incapacitation (e.g., significant coronary heart disease). Pilot incapacitation during high-workload phases of flight has been shown in simulator testing to lead to a significant rate of crashes, even when a second pilot is at the controls. These physical examinations may weed out pilots with severe cognitive or sensory-motor deficiencies, but they are not designed to assess subtle aspects of changes in performance resulting from age. Of course, no requirements whatsoever exist for medical examination or certification of anesthesia professionals, nor is there any limitation on the practice of anesthesia at any age.

It is likely that age alone does not independently cause a significant decrement in performance, but age correlates with other factors that are likely to affect performance. The concern about aging professionals revolves more around the loss of knowledge and skill as one becomes farther removed from initial training than around the loss of fundamental mental capacity. Thus, the originally well-trained practitioner who keeps abreast of the changing standard of care and who exercises emergency skills frequently is less likely to be affected by advancing age than is a marginal practitioner whose knowledge and skills were frozen immediately after completion of training and who practices in a low-complexity environment. The FAA regulations deal with this issue for air transport pilots by requiring frequent (every 6 months) evaluation of performance by FAA-certified check pilots. These evaluations are performed during actual flights and in realistic simulators, and they, in essence, check fitness for duty regardless of age. Currently, no similar program exists in anesthesia to assess the competency of practitioners at any age, except for initial board certification, which is voluntary. Periodic maintenance of certification in anesthesiology is required by the American Board of Anesthesiology for diplomates attaining certification after the year 2000, but it is not mandatory to be board certified to practice anesthesia, and the recertification examinations are not as intense, as thorough, or as frequent as those required for air transport pilots. Thus, the issue of age-related effects on anesthesia professional performance is likely to continue to be raised periodically for the foreseeable future.

Illness and Drug Use

Every anesthesia professional is vulnerable to transient illnesses, which in some cases probably reduce performance ability (see Chapter 110). All personnel are vulnerable to chronic medical conditions that could directly or indirectly affect their fitness and performance capability. The culture of the caring professions often leads individuals to continue to work with illnesses that would cause other professionals to stay at home or to seek medical advice. The performance-shaping effects of the illness can be exacerbated by the use of either over-the-counter or prescribed medications. The degree to which illnesses and medications affect professional performance in anesthesia is unknown.

A serious problem for anesthesia professionals is that of drug abuse (see Chapter 110).[253-258] It is estimated that up to 8% of physicians could be classified as having alcoholism. In an anonymous survey of anesthesia personnel from one institution, 75% of respondents reported drinking alcohol on a regular basis. They reported drinking an average of 1.6 drinks per day 2.7 days per week. Just less than 10% of subjects reported having been "hung over" while conducting anesthesia, and 40% reported having given anesthesia within 12 hours of alcohol consumption; 84% stated that alcohol use never adversely affected their clinical performance.

The degree to which small doses of alcohol or hangovers affect the performance of complex, real-world tasks is uncertain. Some studies of general aviation and navy pilots suggested that hangover effects can degrade performance even when more than 8 hours has elapsed since alcohol consumption and no blood alcohol level

is detectable.[251,259-261] Nonetheless, although statistically significant, the changes in performance seen in these studies may not have been functionally significant. These studies also suggested interactions among age, workload, and hangover in causing decrements in performance.[251,259-261] However, the "aged" cohort was defined as 31 years or older and was compared with a cohort of pilots in their early 20s. Extrapolating these results to the anesthesia domain is difficult.

Nevertheless, the natural history of serious abuse of alcohol, cocaine, sedatives, or narcotics by anesthesia professionals is such that cognitive performance will at some point be seriously compromised. However, addiction specialists frequently report that job performance is one of the last areas of life to become impaired.[262,263] For this reason, the period of time in which an addicted anesthesia professional's performance in the OR is significantly impaired is a relatively small fraction of the total time during which drugs are abused. Although this in no way excuses the practice of conducting anesthesia while under the influence of drugs, it may account for the fact that reports of addicted anesthesiologists are, unfortunately, common, whereas reports of overt patient risk or harm resulting from an addicted physician's errors are unusual.

Anesthesiology has been at the forefront in dealing with impaired medical personnel. Management of personnel discovered with a drug impairment is fairly standardized,[256,264] but the question whether to return these individuals to anesthesia practice is increasingly controversial, even when they return under carefully monitored reentry protocols.[256] The main risk appears to be to the addict's own safety, although questions about patient safety can never be eliminated.

Ultimately, in the current medical system the responsibility rests with anesthesia professionals to ensure that their own performance level is sufficient for the work at hand. Pilots use a mnemonic checklist to review the effects of potential performance-shaping factors and are instructed not to fly if they are impaired for any reason. The difficulty in anesthesiology (and to some degree in aviation) is that the real-world organization and incentives of many practice settings do not provide mechanisms for personnel to excuse themselves if they are temporarily impaired. Ironically, better means may be available to identify and support a practitioner with a serious addiction than for the more common occurrences of profound sleep deprivation or impairment by a transient or chronic illness.

THE STUDY OF HUMAN PERFORMANCE

Study of human performance involves research paradigms different from those typically used in the science of anesthesia. Many obstacles exist to obtaining hard, statistically valid data on human performance. There are no animal models for expert human performance and no "Sprague-Dawley anesthesiologists" to be studied in detail, nor can studies of professional performance be conducted with the psychologist's typical experimental subject, the university undergraduate student. Recruiting expert anesthesia professionals to be the subjects of study is difficult and raises issues of selection bias concerning those who do volunteer. Especially if conducted during actual patient care, investigations of human performance are strongly influenced by concerns about litigation, credentialing, and confidentiality, thus making it difficult to execute optimal studies.

Furthermore, variability among individual anesthesia professionals is quite striking because different anesthesia professionals respond to the same situation in different ways, and each individual may act differently on different days or at different times of the same day. The magnitude of this intraindividual variability is often nearly the same as the interindividual variability.

"Performance" itself is an intuitively meaningful concept that is difficult to define precisely. No universal standards are available for the clinical decisions and actions of anesthesia professionals. They depend heavily on the context of specific situations. In addition, determining how anesthesia professionals perform their jobs, whether successfully or unsuccessfully, means delving into their mental processes. This cannot be measured easily. Experimental designs can involve artificial laboratory tasks for which performance can be objectively measured, but these tasks will then be far removed from the real world of administering anesthesia. Conversely, investigating the actual performance of trained practitioners in the real world yields primarily subjective and indirect data. Understanding the anesthesia professional's performance must be seen as analogous to solving a jigsaw puzzle. Pieces of the puzzle probably come from a variety of sources, none of which by itself captures the entire picture. These pieces include objective data from artificial laboratory tasks, prospective observation of routine patient care, analysis of retrospective reports of near misses or anesthetic mishaps, and prospective observation of the response to simulated events. To achieve the best possible understanding of the situation, it is necessary to accept many data that seem uncomfortably subjective to the physical or biologic scientist. Because the research methodologies may be unfamiliar to anesthesia professionals, some pioneering studies of anesthesia professional performance are described in detail in this chapter.

WHY STUDY HUMAN PERFORMANCE IN ANESTHESIA?

How can improved understanding of the human performance of anesthesia professionals help them provide patient care more safely, in a wider variety of clinical situations, with greater efficiency, and with increased satisfaction to both patients and practitioners? The possibilities include the following:

1. Improved operational protocols and enhanced training of anesthesia professionals. The way in which individuals conduct anesthesia is based, in part, on knowing the limits of their performance envelope. Anesthetic techniques and OR practices should draw on anesthesia professionals' abilities and should mitigate their weaknesses. Anesthesia professionals' abilities are strongly affected by training. Understanding the required performance

characteristics and inherent human limitations will lead to improved training, which will most fully develop the strengths and counter the existing vulnerabilities of the anesthesia professional. This process should make patient care safer, less stressful, and more efficient.
2. A more rational view of professional work and legal responsibility (see Chapters 10 and 11). Modern medicine, especially in the United States, is strongly influenced by medicolegal concerns. The litigation system has a major selection bias in that every case that comes before it involves an adverse outcome for a patient. The duty of the practitioner is to render care as a "reasonable and prudent" specialist in the area of anesthesia. What is reasonable and prudent? What type of performance is to be expected from appropriately trained human beings in a complex and dynamic environment? By understanding human performance, it may be possible to generate a more rational view of what is and is not within the standard of care.
3. A more effective work environment. Anesthesia professionals now perform their tasks by using an array of technologies, most of which have not been designed to support the anesthesia professional's work optimally. By understanding the anesthesia professional's tasks and performance requirements, the workspace and tools could be improved for better support of the most difficult tasks. This, too, can lead to greater safety and to greater efficiency and work satisfaction.
4. A more efficient organizational system (see Chapter 4). Anesthesia is embedded within a larger system of organized medical care that involves interactions among numerous institutions, organizations, and professional domains. Understanding how the anesthesia professional's work relates to the larger system may enable the development of more rational and efficient flow of information and organizational control.

Although anesthesiologists have been basing analysis of human performance on individual actions, decisions, and mental models and the influence of organizational factors and safety culture for some time (see survey articles[1,2,265]), their importance to health care in general has only relatively recently been appreciated.[3,56]

COGNITIVE PROCESS MODEL OF THE ANESTHESIA PROFESSIONAL

The empiric data can best be interpreted in accordance with an explicit model of the cognition involved in an anesthesia professional's performance. Several investigators have written about the cognitive elements in anesthesiology.[52,65,125,162,266-275] The model developed here is explicit, comprehensive, and specific to anesthesia. It is described in detail as a framework for understanding the empiric data and provides a vocabulary for discussing the elements of both successful and unsuccessful performance by anesthesia professionals. This model draws heavily on the work of a number of other investigators who studied human performance in a variety of complex, dynamic worlds.[138,275-278]

DECISION MAKING INVOLVES MULTIPLE LEVELS OF MENTAL ACTIVITY

The entire model, which is shown in Figure 7-12, depicts the anesthesia professional as working at five different interacting cognitive levels to implement and control a core process of observation, decision making, action, and reevaluation (Box 7-9). The core process must then be integrated with the behavior of other team members and with the constraints of the work environment.

The division of mental activities into levels follows the work of Rasmussen and Reason.[277,279,280] Having multiple levels supports parallel processing (performing more than one task at a time) and multitasking (performing only one task at a time but switching very rapidly from one task to another). The anesthesia task analyses,[281-285] as well as the direct observations of anesthesia professionals in Toronto[266] and Tübingen,[286-289] have provided clear evidence for the occurrence of parallel processing and multitasking. Table 7-6 gives an overview of the mental activity levels.

At the sensorimotor level, activities involving sensory perception or motor actions take place with minimal conscious control; they are smooth, practiced, and highly integrated patterns of behavior. At the procedural level, the anesthesia professional performs regular routines in a familiar work situation. These routines have been derived and internalized from training and from previous work episodes. A level of abstract reasoning is used during preoperative planning, and intraoperatively it is used in unfamiliar situations for which no well-practiced expertise or routine is available from previous encounters.

Dynamic Adaptation of the Anesthesia Professional's Thought Processes

Rasmussen's model[277] was extended by the explicit addition of two additional levels of mental activity that provide for dynamic adaptation of the anesthesia professional's own thought processes. This ability to "think about thinking" to control one's own mental activities strategically is called metacognition by psychologists, and it is thought to be an important component of working in complex, dynamic domains. Supervisory control is concerned with dynamically allocating finite attention between routine and nonroutine actions, among multiple problems or themes, and among the five cognitive levels. Resource management deals with the command and control of available resources, including teamwork and communication.

CORE PROCESS

An overview of the core process and its elements is given in Box 7-9. The elements are explained in detail in the following sections.

Observation

Management of rapidly changing situations requires the anesthesia professional to assess a wide variety of information sources, including visual observation of the patient and the surgical field, visual inspection of a multitude of displays from electronic monitors, visual observation of

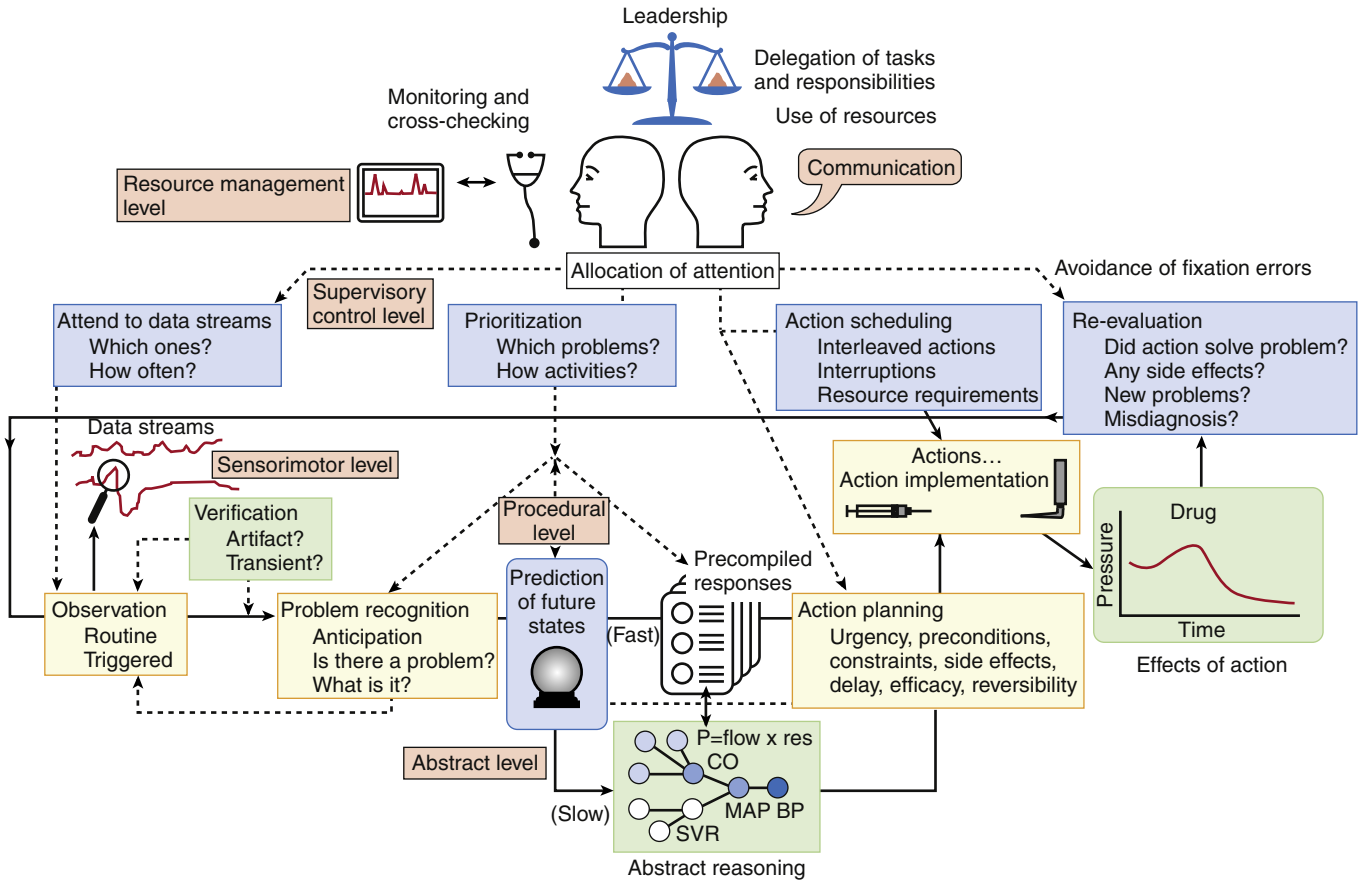


Figure 7-12. Cognitive process model of the anesthetist's real-time problem-solving behavior (see text for a detailed description). Five levels of cognition operate in parallel. The core process involves a main loop (*solid arrows*) of observation, decision, action, and reevaluation. The core process is managed by two levels of metacognition that involve supervisory control, allocation of attention, and resource management (above the core process). Each component of the model requires different cognitive skills, and each component is vulnerable to a different set of performance failures or "errors." *BP,* Blood pressure; *CO, cardiac* output; *MAP,* mean arterial pressure; *SVR,* systemic vascular resistance. *(From Gaba DM, Fish KJ, Howard SK:* Crisis management in anesthesiology. *New York, 1994, Churchill Livingstone.)*

the activities of nurses and the contents of suction canisters and sponges, listening for normal and abnormal sounds from the patient and equipment, interpretation of radiographs, and reading of reports of laboratory test results. Because the human mind can attend closely to only one or two items at a time, the anesthesia professional's supervisory control level must decide what information to attend to and how frequently to observe it.

The multitasking involved in observing multiple data streams was probed by experiments measuring secondary task performance and vigilance. The realistic simulation studies demonstrated the large number of information sources actually used during the response to a critical event. Routine parts of the core process operate primarily at the sensory, motor, and procedural levels and are executed repetitively throughout the course of an anesthetic regimen. Results from the University of California, San Diego (UCSD), and from the Department of Veterans Affairs and Stanford University (UCSD/VA-Stanford group) concerning the vigilance of experienced anesthesia professionals versus novices suggested that novices had not fully developed their core process as a highly automated function and thus were required to devote more mental resources to routine activities.

BOX 7-9 ***Elements of the Core Mental Process***

1. Observation
2. Verification
3. Problem recognition
4. Prediction of future states
5. Decision making
   a. Application of precompiled responses (recognition-primed decision making)
   b. Decision making using heuristics and probability
   c. Decision making including abstract reasoning
6. Action implementation
7. Reevaluation (avoiding fixation errors)
8. Start again with 1 (loop continues)

Verification

In the OR environment, the available information is not always reliable. Most monitoring is noninvasive and indirect and is susceptible to artifacts (false data). Even direct clinical observations such as vision or auscultation can be ambiguous. Brief transients (true data of short duration) can occur that quickly correct themselves. To prevent them from triggering precipitous actions that may have

TABLE 7-6 **LEVELS OF MENTAL ACTIVITY**

Level of Control	Explanation	Comments
Resource management level	Command and control of all resources, including teamwork and communication	Incident analysis shows a huge contribution of lack of resource management and communication skills to the development of incidents and accidents; the importance of these factors is reflected in the ACRM principles and simulation training courses (see Chapter 8)
Supervisory control level	Metacognition: thinking about thinking	Dynamic adaptation of the thought process, decision making (e.g., avoiding fixation errors), scheduling, and remembering actions (e.g., prospective memory tasks)
Abstract reasoning level	Use of fundamental medical knowledge, search for high-level analogies, deductive reasoning	Often in parallel with other levels; in emergency situations often too slow and too sensitive to distractions in high-workload situations
Procedural level	Precompiled responses, following algorithms, heuristics, "reflexes"	Recognition-primed decision making—experts are more often on this level; special errors may occur as a result of not checking for the appropriateness of the "procedure"; less experienced personnel may misuse this level for ill-considered, unadapted "cookbook medicine"
Sensorimotor level	Use of all senses and manual actions; "feeling, doing, hearing"; sometimes subconscious control of actions	Experts perform smooth action sequences and control their actions by direct feedback from their senses (e.g., action sequences of placing an intravenous line or endotracheal intubation; skill-based errors such as slips and lapses may occur)

ACRM, Anesthesia crisis resource management.

significant side effects, critical observations must be verified before the clinician acts on them. Verification uses a variety of methods, shown in Table 7-7.

If in doubt, it should always be assumed that the patient is at risk and that the parameter in question is real ("rule out the worst case"). The assumption of a technical artifact should be the last step.

Knowing when and how to verify data is a good illustration of strategic knowledge (metacognition). For example, the anesthesia professional must decide under what conditions it is useful to invest time, attention, and energy in establishing a new information source (e.g., a pulmonary artery catheter) in the middle of a case rather than relying on more indirect information sources that are already in place.

Problem Recognition

Anesthesia professionals are taught the importance of scanning their instruments and environment, but they must use these observations to decide whether the patient's course is "on track" or whether a problem is occurring. If a problem is found, a decision must be made regarding its identity and its importance. This process of problem recognition (also known as situation assessment) is a central feature of several theories of cognition in complex, dynamic worlds.[162,290-292]

Problem recognition involves matching sets of environmental cues to patterns that are known to represent specific types of problems. Given the high uncertainty seen in anesthesia, the available information sources cannot always disclose the existence of a problem, and even if they do, they may not specify its identity or origin. The experiment by Westenskow and colleagues with the intelligent alarm system mainly probed these parts of problem recognition.[293] In this experiment, subjects were already alerted to the existence of a problem by an alarm, so they could immediately focus their attention specifically on information sources concerning ventilation. In 11 cases, the fault could not be identified, but compensation for the fault was successful, as described in the next paragraphs.

The supervisory control level mediates the decision when a clear-cut match or "diagnosis" cannot be made. Anesthesia professionals and other dynamic decision makers use approximation strategies to handle these ambiguous situations; psychologists term such strategies *heuristics*.[294] One heuristic is to categorize what is happening as one of several "generic" problems, each of which encompasses many different underlying conditions. Another is to gamble on a single diagnosis (frequency gambling[279]) by initially choosing the single most frequent candidate event. During preoperative planning, the anesthesia professional may adjust a mental "index of suspicion" for recognizing certain specific problems anticipated for that particular patient or surgical procedure. The anesthesia professional must also decide whether a single underlying diagnosis explains all the data or whether these data could have multiple causes. This decision is important because excessive attempts to refine the diagnosis can be very costly in terms of allocation of attention. By contrast, a premature diagnosis can lead to inadequate or erroneous treatment.

The use of heuristics is typical of expert anesthesia professionals and often results in considerable time savings in dealing with problems. However, it is a double-edged sword. Both frequency gambling and inappropriate allocation of attention solely to expected problems can seriously undermine problem solving when these gambles

TABLE 7-7 **METHODS FOR VERIFICATION OF CRITICAL OBSERVATIONS**

Method	Explanation and Example
Repeating	The observation or measurement is repeated to rule out a temporary wrong value (e.g., motion artifacts during noninvasive blood pressure measurement)
Checking trend information	The short-term trend is observed for plausibility of the actual value. Trends of physiologic parameters almost always follow curves, not steps
Observing a redundant channel	An existing redundant channel is checked (e.g., invasive arterial pressure and cuff pressure are redundant, or heart rate from an ECG and pulse oximeter)
Correlating	Multiple related (but not redundant) variables are correlated to determine the plausibility of the parameter in question (e.g., if the ECG monitor shows a flat line and "asystole" but the invasive blood pressure curve shows waves)
Activating a new monitoring device	A new monitoring modality is installed (e.g., placing a pulmonary artery catheter). This also adds another parameter for the method of "correlating"
Recalibrating an instrument or testing its function	The quality and reliability of a measurement are checked, and its function is tested (e.g., if the CO_2 detector shows no values, the anesthetist can exhale through it to see whether the device works). Observation of redundant channels can also help verify a value (see above)
Replacing an instrument	If doubt exists about the function of a device, an entirely new instrument or an alternative backup device may be installed
Asking for help	If the decision on the values remains unclear, help should be sought early to obtain a second opinion from other trained personnel

ECG, Electrocardiogram.

do not pay off if the reevaluation component of the core process does not correct the situation.

Prediction of Future States

Problems must be assessed in terms of their significance for the future states of the patient.[162,290] Problems that are already critical or that can be predicted to evolve into critical incidents receive the highest priority. Prediction of future states also influences action planning by defining the timeframe available for required actions. Cook and colleagues described "going sour" incidents in which the future state of the patient was not adequately taken into account when early manifestations of problems were apparent.[295] It is also known from research in psychology that the human mind is not very well suited to predict future states, especially if things are changing in a nonlinear fashion. Under such circumstances, which are not uncommon for natural systems such as the human body, the rate of change is almost invariably underestimated, and people are surprised at the outcome.[51] Slow but steady and sustained blood loss in a child during surgery may result in few or subtle changes in hemodynamics for some time until rapid decompensation occurs. If the weak signs of the developing problem were not detected, the ensuing catastrophe may seem to have occurred "suddenly."

Decision Making

Having recognized a problem, how does an expert anesthesia professional respond? The classic paradigm of decision making posits a careful comparison of the evidence with various causal hypotheses that can explain them.[47] This is then followed by a careful analysis of all possible actions and solutions to the problem. This approach, although powerful, is relatively slow and does not work well with ambiguous or scant evidence. In complex, dynamic domains such as anesthesia, many problems require "decisions under uncertainty,"[273,296] with quick action to prevent a rapid cascade to a catastrophic adverse outcome. For these problems, deriving a solution through formal deductive reasoning from "first principles" is too slow.

Precompiled Responses and Abstract Reasoning

In complex, dynamic domains, the initial responses of experts to the majority of events stem from precompiled rules or response plans for dealing with a recognized event.[279] This method is referred to as recognition-primed decision making,[276,297] because once the event is identified, the response is well known. In the anesthesia domain, these responses are usually acquired through personal experience alone, although there is a growing realization that critical response protocols must be codified explicitly and taught systematically. Experienced anesthesia professionals have been observed to rearrange, recompile, and rehearse these responses mentally based on the patient's condition, the surgical procedure, and the problems to be expected.[298] Ideally, precompiled responses to common problems are retrieved appropriately and executed rapidly. When the exact nature of the problem is not apparent, a set of generic responses appropriate to the overall situation may be invoked. For example, if a problem with ventilation is detected, the anesthesia professional may switch to manual ventilation at a higher fraction of inspired oxygen (FiO_2) while considering further diagnostic actions.

However, experiments involving screen-only[298] and realistic[161,299-301] simulations have demonstrated that even experienced anesthesia professionals show great variability in their use of response procedures to critical situations. This finding led these investigators to target simulator-based training in the systematic training of responses to critical events.[122,266,302-304]

Even the ideal use of precompiled responses is destined to fail when the problem does not have the suspected cause or when it does not respond to the usual actions. Anesthesia cannot be administered purely by precompiled

"cookbook" procedures. Abstract reasoning about the problem through the use of fundamental medical knowledge still takes place in parallel with precompiled responses, even when quick action must be taken. This seems to involve a search for high-level analogies[279] or true deductive reasoning using deep medical and technical knowledge and a thorough analysis of all possible solutions. Anesthesia professionals managing simulated crises have linked their precompiled actions to abstract medical concepts.[298] It is unclear whether this represents merely self-justification as opposed to true abstract reasoning, in part because the particular simulated crises they faced did not require novel abstract solutions. At this time, the degree to which abstract reasoning is necessary for optimal intraoperative crisis management is unknown.[125,266,296]

Taking Action

A hallmark of anesthesia practice is that anesthesia professionals do not just write orders in a patient's chart; they are directly involved in implementing the desired actions.

Although such direct involvement has many benefits in timeliness and flexibility of action, it also poses risks. Implementation of action can usurp a large amount of the anesthesia professional's attention and can be distracting. This is particularly an issue when other tasks have been interrupted or temporarily suspended. The "prospective memory" to complete these tasks can be erased. (For a more detailed explanation of prospective memory, see later.) In addition, anesthesia professionals engaged in a manual procedure are strongly constrained from performing other manual tasks, as demonstrated in several of the mental workload and vigilance studies described earlier.

Errors in executing a task are termed *slips*, as distinguished from errors in deciding what to do, which are termed *mistakes*.[278] Slips are actions that do not occur as planned, such as turning the wrong switch or making a syringe swap. Thus, when critical incident[221,305] and quality assurance studies described "technical errors" in using equipment, they were referring to slips, whereas "judgment errors" referred to mistakes. One particular type of execution error, termed a *mode error*,[278] is becoming more frequent in all domains with the increased use of microprocessor-based instrumentation and devices.[267] In a mode error, actions appropriate for one mode of a device's operation are incorrect for another mode. An example in anesthesiology is the "bag/ventilator" selector valve in the anesthesia breathing circuit, which selects between two modes of ventilation. Failing to activate the ventilator when in the "ventilator mode" can be catastrophic. Mode errors can also occur with monitoring or drug delivery devices if they assign different functions to the same displays or switches depending on the mode of operation selected.

Particularly dangerous slips of execution can be addressed through the use of engineered safety devices that physically prevent incorrect actions.[54] For example, newer anesthesia machines have interlocks that physically prevent the simultaneous administration of more than one volatile anesthetic drug. Other interlocks physically prevent the selection of a gas mixture containing less than 21% oxygen.

Certain very complex issues concerning human-machine interactions and the ways in which technology affects behavior in complex patient care environments are beyond the scope of this chapter. Other publications address these issues.[‡]

Reevaluation and Situation Awareness

To cope with the rapid changes and profound diagnostic and therapeutic uncertainties seen during anesthesia, the core process must include repetitive reevaluation of the situation. Thus, the reevaluation step returns the anesthesia professional to the observation phase of the core process, but with specific assessments in mind (as shown in Box 7-7 at CRM key point 12, "Reevaluate repeatedly").

The process of continually updating assessment of the situation and monitoring the efficacy of chosen actions is termed *situation awareness*.[290-292,307,308] Situation awareness is a very interesting and important topic in analyzing performance and reasons for errors.[162,309,310] A review of situation awareness issues in anesthesiology has been published.[162]

MANAGEMENT AND COORDINATION OF THE CORE PROCESS

Empiric studies have clearly demonstrated that attention sharing is needed among cognitive levels, among tasks, and often among problems. The intensive demands on the anesthesia professional's attention could easily swamp the available mental resources. Therefore, the anesthesia professional must strike a balance between acting quickly on every small perturbation (which requires a lot of attention) and adopting a more conservative "wait-and-see" attitude. This balance must be constantly shifted between these extremes as the situation changes. However, during simulated crisis situations, some practitioners showed great reluctance to switch from business as usual to emergency mode even when serious problems were detected. Erring too far in the direction of wait and see is an error that can be particularly catastrophic.

In addition to the attentional demands of the anesthesia professional's core tasks, the OR environment is full of distractions. Routine events, such as turning the OR table or repositioning the patient, distract attention from the main process of conducting the anesthesia. Noise is prevalent, with peak levels exceeding that of a freeway. Practitioners find false auditory alarms from monitors or other equipment extremely distracting.[311-313] Other distractions include teaching in progress,[314] incoming telephone calls, background music, and conversation with OR personnel. Expert anesthesia professionals modulate the distractions by eliminating them when the workload is high and allowing them to occur when the workload is low (to improve morale and team building).

Active Management of Workload

One major aspect of strategic control of attention is the active management of workload. Rather than passively dealing with rising or falling workload, the anesthesia professional actively manages it. Schneider and Detweiler[187] and Gopher (position paper, Conference on Human Error in Anesthesia, Asilomar, Calif., 1991) described the

[‡]References 35, 37, 39-43, 45, 46, 267, 306.

theoretic basis for a variety of strategies of workload management. These strategies were addressed specifically for anesthesiology by several investigators.[266,268] The anesthesia professional actively manages workload by the following techniques.

Avoiding High-Workload Situations. Experts may choose techniques and plans that reduce the workload (especially when their individual and team resources are limited), even when those plans are marginally inferior from a technical standpoint. For example, a single anesthesia professional may choose not to use a high-tech, high-workload monitor such as transesophageal echocardiography (TEE) because of the high workload required to use it properly.

Distributing Workload over Time. The anesthesia professional can prepare for future tasks when the current load is low (preloading) and can delay or shed low-priority tasks when the workload is high (offloading). Resources that require a significant amount of workload to prepare, such as intravenous infusions, are often made ready before the case starts. Multitasking is also a way to distribute work over time. Every task is made up of several subtasks, each of which has a finite duration. Because close attention may not be required during each of these subtasks, they can be interleaved with a fixed amount of attention (multiplexing). Multiplexed tasks must be scheduled and coordinated in real time at the supervisory control level.

Distributing Workload Over Personnel. When workload cannot be distributed over time and when additional resources are available, tasks can be distributed to them. Some resources are internal to the individual anesthesia professional, whereas others require additional personnel. For example, a single anesthesia professional can simultaneously ventilate the patient by hand, assess cardiac rhythm, and discuss patient care with the surgeon. A single anesthesia professional cannot simultaneously insert a pulmonary artery catheter and ventilate the patient's lungs by hand. If these tasks are to be performed at the same time, they must be assigned to different individuals.

Changing the Nature of the Task. The nature of a task is not fixed. Surgery and anesthesia can sometimes be postponed or aborted. Tasks can be executed to different standards of performance; as standards are loosened, the workload required to perform them is reduced. For example, during periods of massive blood loss, the anesthesia professional focuses primarily on administering blood and fluids and on monitoring blood pressure. In such cases, less critical tasks such as writing on the anesthesia record are offloaded to lessen the workload. The acceptable limits of blood pressure will also be widened.

Action Selection and Scheduling

At any time during an anesthetic regimen there may be multiple things to do, each of which is intrinsically appropriate, yet they cannot all be done at once. Simulator experiments have shown that anesthesia professionals sometimes have difficulty selecting, planning, and scheduling actions optimally. The anesthesia professional must consider the following factors:

1. Preconditions are necessary for carrying out the actions (e.g., it is impossible to measure a thermodilution cardiac output if no pulmonary artery catheter is in place).
2. Constraints are placed on the proposed actions (some actions are incompatible with other aspects of the situation; e.g., it is impossible to check the diameter of the pupils when the head is fully draped in the surgical field).
3. Side effects of the proposed actions often play a controlling role in choosing among possible drug therapies.
4. The rapidity and ease of implementation of proposed actions are factors; those that are easily and rapidly performed are preferred over those that require more time, attention, and skill.
5. Certainty of success of the actions is often traded off against rapidity and ease of implementation (under some circumstances, the higher certainty of success of a set of actions justifies the investment of time, attention, and resources needed to implement them).
6. The reversibility of the action and the cost of being wrong are considered, with rapidly reversible actions preferred over those that cannot be reversed, especially when potential side effects are significant.
7. The cost of the action in terms of attention, resources, and money is taken into account.

Experts in other complex, dynamic domains (specifically tank commanders and fire chiefs) have been observed to conduct a mental simulation of the actions that they are contemplating to determine whether their plans have hidden flaws.[315] Anesthesia professionals have been observed to rehearse a plan mentally in advance of a case,[268] but the degree to which this is done in real time is not known. Because most actions can be executed incrementally, as in titrating a drug in small aliquots, adverse consequences can often be discovered through repetitive reevaluation.

Resource Management

The ability of the anesthesia professional to command and control all the resources at hand to execute the anesthetic regimen as planned and to respond to problems that arise is termed *resource management* (another concept first described in aviation that applies equally well to anesthesiology; see the earlier section on CRM key points). Resource management involves translating the knowledge of what needs to be done into effective team activity by taking into account the limitations of the complex and ill-structured OR, PACU, or ICU domain. Resource management explicitly requires teamwork and crew coordination. It is not enough for the anesthesia professional to know what to do or even to be able to do each task alone. The anesthesia professional can accomplish only so much in a given time, and some tasks can be performed only by other skilled personnel (e.g., laboratory tests, taking radiographs). When the task load exceeds the resources available, the anesthesia professional must mobilize help and distribute the tasks among those present. Many issues concerning optimum resource management and crew coordination are not yet well understood and are the focus of active research by cognitive scientists and experts

in many complex and dynamic domains.[29,127-129,316-318] Research in aviation has already demonstrated that many aircraft accidents are linked to failures on the part of crews with appropriate technical skills to manage the flight deck effectively.[222] The hallmarks of resource management derived from these studies are discussed in detail in the earlier section on CRM key points.

Dynamic Prioritization of Tasks. Complex multiple-personnel simulations of anesthetic crises have been used to address the issue of resource management. Although the data from these simulations are still preliminary, it appears that poor supervisory control and resource management were substantial components of suboptimal management of the simulated crises.[301] In other words, like the pilots, anesthesia professionals had the knowledge and technical skill to manage the patient, but they failed to manage their environment properly to achieve success (hence termed CRM skills or nontechnical skills). (In aviation, such situations have often resulted in what is called "controlled flight into terrain.")

Prospective Memory

Prospective memory describes one's ability to remember in the future to perform an action.[319] It is particularly prone to disruption by concurrent tasks or interruptions. Disruption of intentions or ongoing tasks is common in everyday life and has also been described in pilots and air traffic controllers.[320-324] In anesthesia, for example, if the anesthesia professional suspends ventilation temporarily (say to allow a radiograph to be taken), the intention to restart the ventilator depends on prospective memory and can be easily forgotten. Chisholm and associates performed a study in an emergency department and looked for "interruptions" and "breaks in task." They found that during a 3-hour period, the emergency physician was faced with more than 30 interruptions and more than 20 breaks in task. It is likely that similar results would be found in the ICU.[325]

A variety of methods may preserve prospective memory of intentions. Visual or auditory reminders can be used (physiologic monitor alarms often serve this purpose whether intended or not), although the effectiveness of such methods seems to be less than one would expect. Special actions—such as leaving one's finger on the ventilator switch—can be used to indicate that an important intention is pending.

FIXATION ERRORS

Faulty reevaluation, inadequate adaptation of the plan, or loss of situation awareness can result in a type of human error termed a *fixation error*.[144,145] Fixation errors have been described by all the investigators conducting experimental studies of responses of anesthesia professionals to abnormal situations.[300,301,326] Avoiding fixation errors in the field of anesthesia is CRM key point 9 and is covered in the section on CRM key points.

HAZARDOUS ATTITUDES

Attitudes are important components of ability that can affect performance as strongly as can physiologic performance-shaping factors. Psychologists studying judgment in aviators have identified five types of attitude as being particularly hazardous, and they have developed specific antidote thoughts for each hazardous attitude.[231] These attitudes as related to anesthesia are shown in Table 7-8. Aviation psychologists instruct pilots to verbalize the antidote thought whenever they find themselves thinking in a hazardous way.

TABLE 7-8 **EXAMPLES OF HAZARDOUS ATTITUDES AND THEIR ANTIDOTE THOUGHTS**

Hazardous Attitude	Antidote Thoughts
Antiauthority: "Don't tell me what to do. The policies are for someone else."	"Follow the rules. They are usually right."
Impulsivity: "Do something quickly—anything!"	"Not so fast. Think first."
Invulnerability: "It won't happen to me. It's just a routine case."	"It *could* happen to me. Serious problems can develop even in routine cases."
Macho: "I'll show you I can do it. I can intubate the trachea of anyone."	"Taking chances is foolish. Plan for failure."
Resignation: "What's the use? It's out of my hands. It's up to the surgeon."	"I'm not helpless. I can make a difference. There is always something else to try that might help."

The *invulnerable* and *macho* attitudes are particularly hazardous for anesthesia professionals. They are compounded by production pressures to handle more cases in less time with fewer cancellations and less opportunity for preoperative evaluation. The feeling that a catastrophe "cannot happen to me" and that perfect performance can always be called on to avert a disaster can lead to cavalier behavior and poor planning. It can alter thresholds for believing that abnormal data represent a problem, thereby leading to the fixation error of "everything's OK." In 1984, Cooper wrote the following about studies of critical incidents in anesthesia:

Perhaps the most insidious hazard of anesthesia is its relative safety. The individual anesthesia professional rarely, on average, will be responsible for a serious iatrogenic complication. It is our impression from the process of collecting incidents, that most seemingly minor errors are not taken seriously and that risk management depends almost solely on the anesthesia professional's ability to react instinctively and flawlessly every time a problem arises.[314]

Expert human performance is the anesthesia professional's most powerful tool to safeguard the patient. However, planning to avoid catastrophe is likely to be more successful than battling to avert it.

THE ANESTHESIA PROFESSIONAL'S TASKS

Investigation of a complex work environment typically starts with task analysis (reviews of this technique were published in the journal *Human Factors*[327]). One can perform an abstract analysis of the work goals

and constraints and then derive the tasks required to achieve the goals. Alternatively, one can observe what skilled practitioners actually do in their work and classify these actions into task elements. Often the techniques are combined. In this section the anesthesia professional's tasks are examined in the abstract, and then the empiric task analysis approach is reviewed. The two distinct phases of anesthetic care are as follows: (1) preoperative evaluation, planning, and preparation; and (2) conduct of the anesthetic regimen and immediate postoperative care.

PREOPERATIVE EVALUATION AND PLANNING

Few data are available on how well anesthesia professionals identify important patient conditions through history taking and physical examination (see also Chapter 38). A frequent organizational obstacle to the anesthesia professional's evaluation task is difficulty obtaining the patient's previous medical records. The performance of anesthesia professionals in selecting appropriate laboratory tests has been found to be relatively poor. Roizen and associates stated the following:

Even when physicians agree to reduce testing by using specific, agreed upon criteria for selectively ordering tests based on history and physical examination, they still make a surprising number of mistakes when ordering tests. Approximately 30% to 40% of patients who should have certain tests … do not get them, and 20% to 40% of patients who should not have tests are subjected to them.[328]

Roizen has argued for automation of routine patient questioning and selection of laboratory tests and has participated in the development of commercial devices to do so. Whether these devices, in combination with human follow-up for patients with medical problems, will improve the efficiency and accuracy of preoperative evaluation remains to be determined. The performance of anesthesia professionals in interpreting ECGs and chest radiographs also appears to be poor relative to specialists in these fields. The extent to which this factor influences the design of anesthetic plans or patient outcomes is unknown.

ANESTHETIC PLAN

In constructing the plan, the anesthesia professional uses the preoperative evaluation of the patient to match the technical requirements of the surgical procedure and the physiologic characteristics of the patient to the mental, physical, and technologic resources available. A typical anesthetic plan contains several elements. For example, the plan for general anesthesia includes choices for the means of inducing anesthesia, securing the airway and ensuring proper ventilation, maintaining anesthesia, conducting emergence from anesthesia, and controlling postoperative pain. Skilled planning is as critical as skilled execution in safe patient care. If a significant feature of the situation is missed in formulating the plan, it can leave the patient vulnerable, regardless of how adeptly the plan is implemented.

The technical requirements of most surgical procedures are well known. Most patients do not have medical problems that could significantly alter the anesthetic plan, although Gibby and associates found that 20% of outpatients, most of them with ASA physical status 1 or 2, had conditions identifiable through an anesthesia professional's history and examination that required changes from a "standard" anesthetic plan.[329] When a procedure is new or challenging, when the patient has significant underlying disease, or when needed resources are not available, creative planning may be needed to identify a set of physiologic goals for the anesthetic regimen. Routine anesthetic plans can be modified or combined to produce a compromise plan that best fits the goals and constraints of the situation.

The process of constructing anesthetic plans has been studied very little. Most of the existing literature on preoperative planning concentrates only on narrow medical and physiologic aspects of underlying diseases and their anesthetic ramifications. No systematic research has been conducted on how various tradeoffs are made or on how normal anesthetic processes are adapted to suit the needs of specific situations.

PRE-USE PREPARATION AND CHECKOUT OF EQUIPMENT

After the plan is established, the anesthesia professional must prepare the work environment. This involves obtaining the necessary equipment and supplies, assembling infusions, preparing syringes of needed drugs, and conducting pre-use checkouts of life-support equipment (see Chapter 44). The performance of anesthesia professionals at these tasks is not optimal. Buffington and co-workers demonstrated that only 3% of anesthesia professionals examining an anesthesia machine could identify all five faults with which it had been rigged; most practitioners found only two of the five.[330] Nearly 30% missed such major faults as complete absence of both unidirectional valve disks in a circle anesthesia breathing system and swap of the nitrous oxide and oxygen cylinders (made possible by a fault in the pin-indexing system).

The Food and Drug Administration (FDA), in cooperation with the ASA, the APSF, and experts from academics and industry, developed a set of recommendations for checkout of the anesthesia apparatus.[331] This checklist was widely disseminated by the ASA and the APSF. However, it was found that use of the checkout procedure was minimal and that the extent of pre-use checkout by practitioners was extremely variable. A newer study was conducted to compare the checkout of anesthesia machines by practitioners with and without use of the FDA checkout procedure.[332] Most of the faults were detected by 50% or fewer participants, regardless of the checkout procedure used. Only for one fault, failure of the oxygen–nitrous oxide ratio protection system, did the FDA checklist offer significant advantages; when using it, the detection rate increased to 65%. Interestingly, 34% of the faults that were not detected were missed by practitioners who had in fact correctly answered three out of three written test questions concerning that fault.

This finding suggests that although some of the performance deficit may be related to lack of knowledge, a substantial proportion of it results from the inability to apply abstract knowledge to the practical performance of equipment checkout.

The original checklist was widely criticized, particularly for its complexity.[333] A streamlined version of the original checklist was published by the FDA in 1994.[334] A study of the new checklist, however, showed no significant benefit from its use and a disturbingly low rate of detection of machine faults (≈50%).[335] In another study, anesthesia professionals using a highly interactive electronic checklist (developed by Blike and Biddle) improved their detection of "easy faults" but still missed a high proportion of difficult faults.[336] A study performed more recently to measure the influence of fatigue on performance in a simulator showed that subjects in both the rested and fatigued conditions left out significant portions of the machine checkout.[214]

In early 2013 the APSF issued a request for proposals to study the large-scale implementation of a more general preinduction checklist for anesthesia professionals that is aimed to catch a variety of preventable problems before the anesthetic is begun. The intention of the APSF is to make such preinduction checks adopted by the anesthesia community as a universal practice.

EMERGENCY CHECKLISTS OR EMERGENCY MANUALS

One aspect of preparedness to handle possible emergencies is to rehearse their management mentally in advance (see also Chapters 33 and 102). Another approach consists of the readiness and ability to use emergency cognitive aids, particularly emergency checklists or emergency manuals (also known by similar terms, including emergency response protocols, critical event algorithms, and so on). Despite many advances, the use of such cognitive aids is still not a regular part of the culture of medical work in many locales.

In 2003 the U.S. Department of Veterans Affairs National Center for Patient Safety developed a set of emergency checklists, in concert with the VA Palo Alto-Stanford group, and derived from the catalog of critical incidents in the book *Crisis Management in Anesthesiology*. The VA Health Administration had placed a set of these checklists on plastic laminated sheets in every OR of 105 hospitals. Other emergency checklists have been made available electronically.[337,338] A study of the use of the VA cognitive aids suggested that they were beneficial to VA anesthesia professionals.[339] Other research has demonstrated that (1) medical and technical performance is better during simulated crisis malignant hyperthermia when a cognitive aid is used[340] and (2) it can be very helpful to the anesthesia professional leading the team if a "reader" is present whose job is to read the relevant aid to the team and keep track of whether the relevant tasks have been performed.[341] A group from Boston has published two articles about simulation testing of 12 "crisis checklists" that demonstrated a substantial reduction in failure to adhere to well-recognized critical steps in patient management when the checklists were used.[342,343]

The Stanford Anesthesia Cognitive Aid Group (SACAG) has conducted many years of simulation testing of cognitive aids meant for real-time intraoperative use,[340,341] with increasing levels of optimization through graphic design. SACAG has produced the *Emergency Manual: Cognitive Aids for Perioperative Critical Events* comprising 23 optimized emergency checklists (Fig. 7-13). (Much of the work in the *Emergency Manual* was adapted from cognitive aids originally published in "Appendix of Crisis Management Algorithms in Anesthesia" in the *Manual of Clinical Anesthesiology*, edited by Stanford anesthesiologists Larry Chu and Andrea Fuller and published by Lippincott Williams & Wilkins in 2011). In 2013 these cognitive aids were placed in all anesthetizing locations

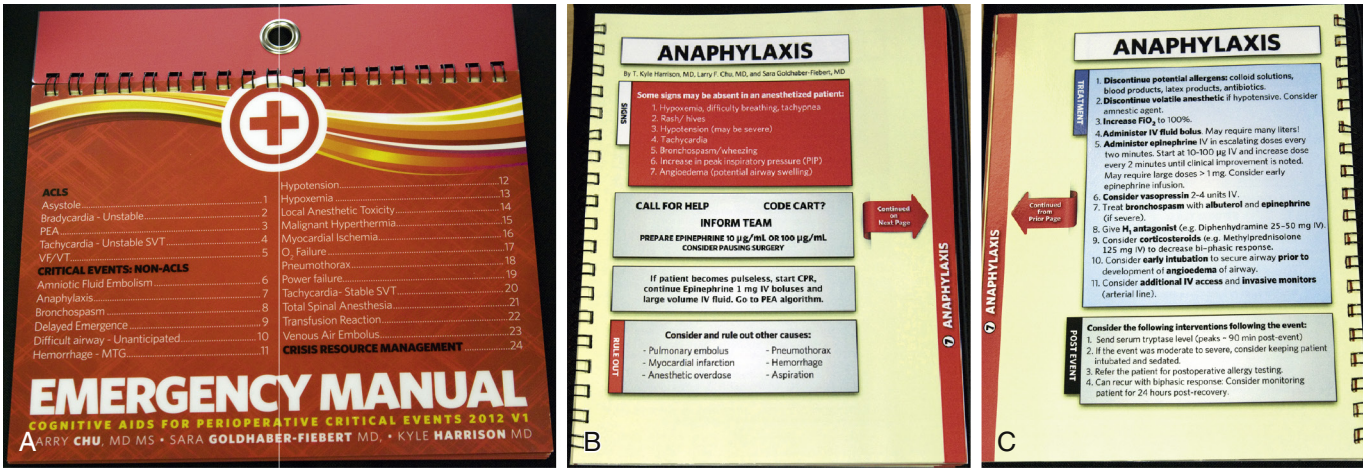


Figure 7-13. A, Front cover of the Stanford Anesthesia Cognitive Aid Group (SACAG) *Emergency Manual.* To reduce cost, the manual is printed on sealed paper; only the front and back pages are laminated. It can be hung by its strong metal grommet. On the front page, it shows the emergency events, thus making it easy to jump to the right page. Experience shows that clinicians must be familiarized with the manual in advance for optimal use. **B** and **C,** Two pages of the *Emergency Manual* checklist for "Anaphylaxis": The content and the layout have been optimized through graphic layout and careful choice of words for easy and ergonomic use in actual operating room emergencies. *(Photographs by D. Gaba.)*

in the Stanford family of teaching hospitals. The *Emergency Manual* is now available free electronically throughout the world as a downloadable portable document format (PDF) file under a Creative Commons Attribution; Non-Commercial; No-Derivatives License. Users are able to choose to print out the *Emergency Manual* locally, and instructions are given on choices of printing paper (e.g., nonflammable and able to be wiped with disinfectant), binding, and placement in perioperative patient care settings. The movement for the dissemination and use of such cognitive aids is growing. An *Emergency Manual* Implementation Collaborative has been started bringing together several leading centers in this arena to facilitate the development, testing, dissemination, adoption, and use of these resources.

EXECUTION AND ADAPTATION OF PLANS

Anesthetic plans are dynamic. The anesthesia professional must monitor the plan as it is executed and must adapt it in response to dynamically changing events. The key features of this task are (1) checking for the achievement of milestones and (2) reactive plan adaptation. These features are shown schematically in Figure 7-14. At various points of a procedure, critical milestones must be achieved to keep the original plan unaltered. If a milestone is not achieved, the anesthesia professional must decide whether to delay the next action in the sequence, modify the plan, or suspend or abort the procedure. On some occasions, the milestones are explicitly identified in advance, whereas in others the milestones are implicit.

The anesthesia professional must also react to a large number of other contingencies, some of which can be predicted in advance based on the patient's history and the type of surgery, whereas others cannot be anticipated. Incoming data streams must be constantly scrutinized (see the "police cars" in Fig. 7-14) to determine whether an expected or unexpected contingency is occurring. If so, the existing plan may have to be modified. As plans are changed, actions may be taken that invalidate other aspects of the previous plan, thereby

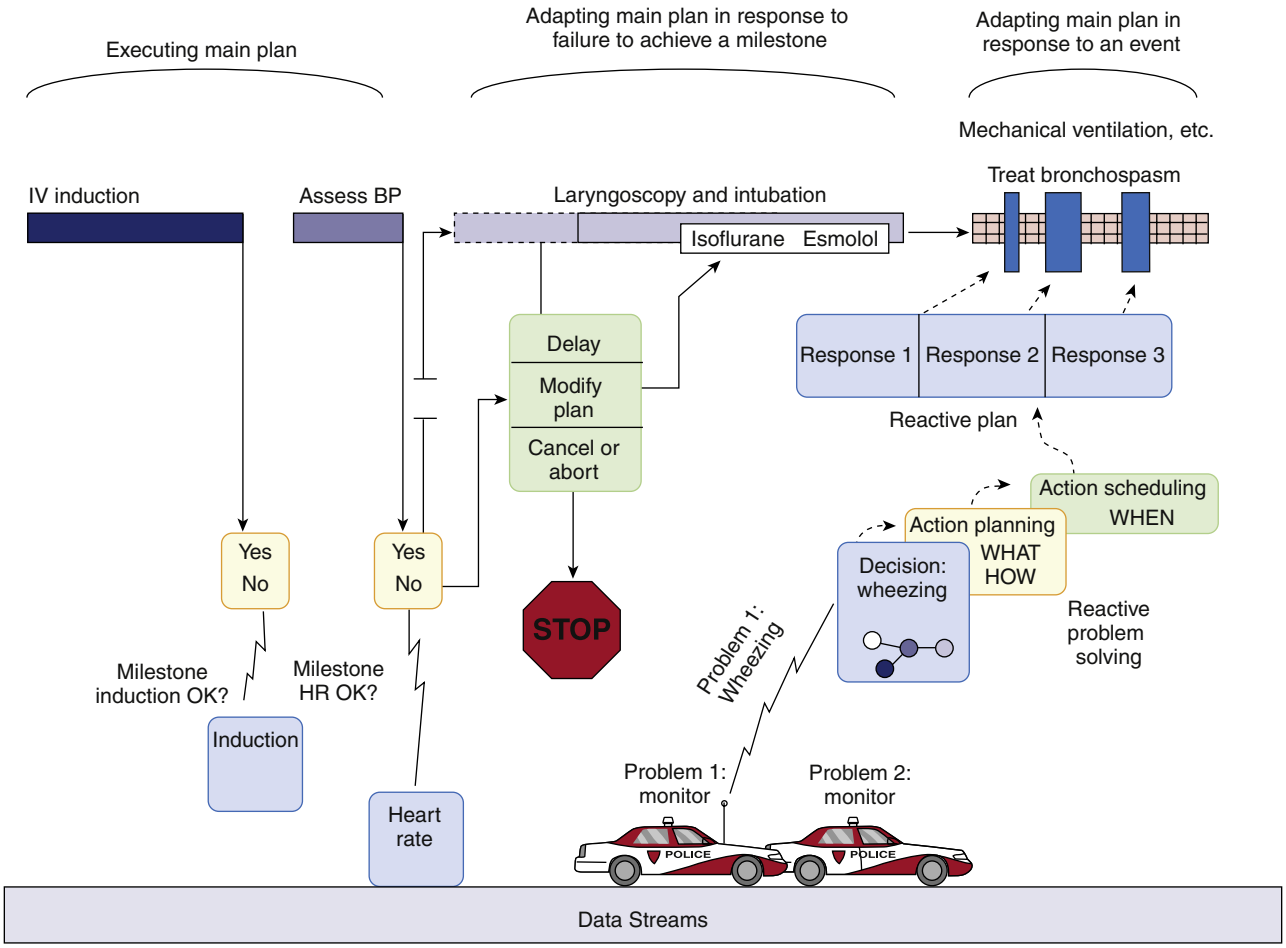


Figure 7-14. Schematic diagram of the dynamic adaptation of preoperative plans. The anesthetist begins with intravenous (IV) induction of anesthesia as planned *(top left)*. On achieving the milestone of successful induction of anesthesia, blood pressure (BP) is checked before proceeding with laryngoscopy and intubation *(center)*. If BP is not satisfactory, the next step may be delayed and the plan amended to optimize BP. If necessary, the procedure may even be aborted at this stage. Throughout the procedure, the anesthetist is vigilant for the occurrence of new problems ("police cars"). If a problem is detected, a process of reactive problem solving takes place that may result in new adaptations to the plan (in this case, treatment of bronchospasm). *HR,* Heart rate. *(From Gaba DM:* Human error in dynamic medical environments. *Hillsdale, NJ, 1994, Lawrence Erlbaum, pp 197-224.)*

requiring further adaptation of the plan. In some cases, even the original goals of the anesthetic plan may need to be adapted.

FREQUENCY OF EVENTS REQUIRING ACTIVE INTERVENTION BY THE ANESTHESIA PROFESSIONAL

The preceding analysis of Figure 7-14 suggests that anesthesia professionals must be prepared to react dynamically to changing events. How frequent is this requirement? In the Multicenter Study of General Anesthesia,[344] 86% of patients had at least one undesirable outcome. Although most events were minor and caused no injury to the patient, more than 5% of patients had one or more severe events requiring "significant therapy, with or without full recovery." This incidence is probably a lower limit for severe events because the entry criteria of the study precluded the enrollment of critically ill patients or emergency surgical procedures, for which the likelihood of severe problems requiring intervention would be expected to be high.

In another study by Cooper and associates,[345] impact events, defined as "undesirable, unexpected, and which could cause at least moderate morbidity," occurred in 18% of patients either in the OR or in the PACU, and 3% of all cases involved a "serious" event. These figures are also probably lower limits because for technical reasons the study excluded patients going directly from surgery to an ICU.

Moller and coauthors reported 4439 "impact events" in 10,312 patients either in the OR (2441) or in the PACU (1998).[346] Here again, some patients had several events, whereas others had none. The investigators did not compute the frequency of severe events, but overall, these data appear to be consistent with those from earlier studies.

MODEL OF EVENT EVOLUTION

The findings just discussed, as well as the larger system issues raised by Reason and Perrow, can be summarized in a model of event evolution (Fig. 7-15).[65,125,266]

Similar models incorporating some of the same features have also been described.[66,347] Underlying aspects of the system can generate latent failures. Either by random chance or because of interactions between the latent failures, an event may be triggered by one of four components of the operational system in the OR: the anesthesia professional, the surgeon, the patient, or the equipment. Anesthesia professionals have traditionally been most interested in events that they trigger

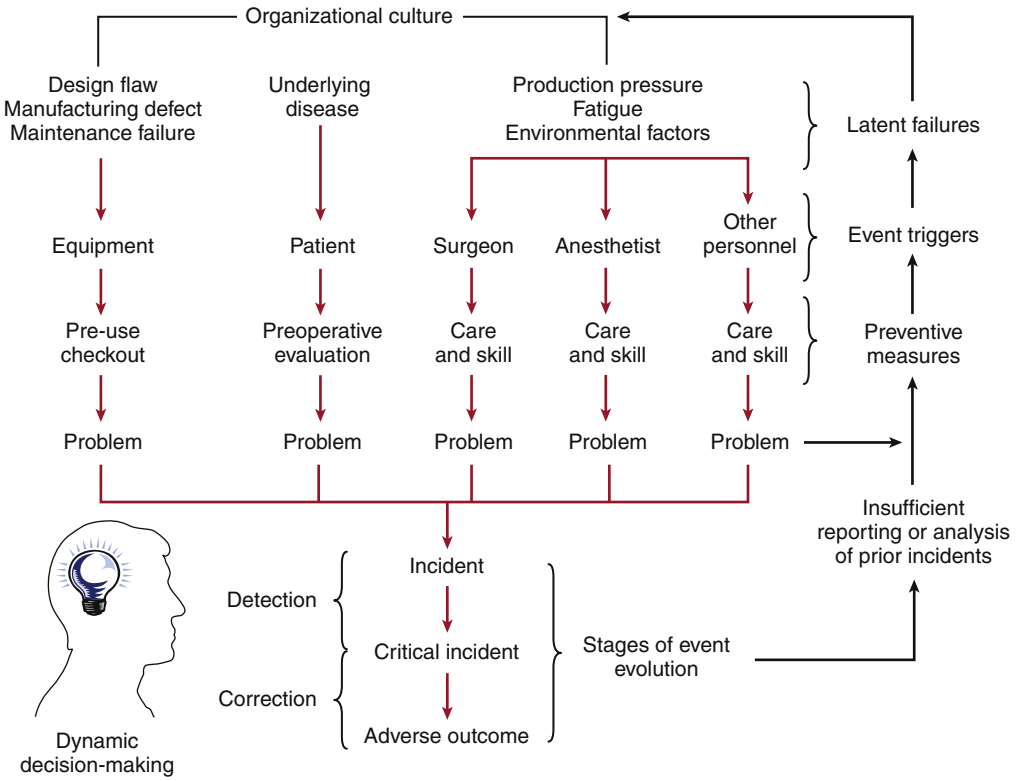


Figure 7-15. Chain of accident evolution in anesthesia. As in Reason's model, underlying latent failures (and the organizational culture) predispose to triggering of an accident sequence by equipment, the patient, the surgeon, the anesthesiologist, and other personnel. This sequence can be prevented by prophylactic measures such as preoperative evaluation and treatment of patient diseases or pre-use checkout of life-support equipment. Once a problem occurs, it may remain self-limited or evolve further down the accident chain. Using dynamic decision making, the anesthetist must detect and correct the problems that do occur at the earliest possible point in the chain of evolution. Interruption of the accident chain is made more difficult when tight coupling exists within the system, when multiple interacting problems are present, or when problems disrupt recovery processes. Efficient use of incident analysis may make it easier in the future to prevent or interrupt problem evolution. *(Redrawn with modification from Gaba DM, Fish KJ, Howard SK:* Crisis management in anesthesiology. *New York, 1994, Churchill Livingstone.)*

themselves (e.g., esophageal intubation), but in fact, most events are initiated by a combination of underlying patient disease and another of the triggering factors. Most problems are not directly harmful to the patient unless they evolve further. Possibilities for evolution of the problem include the following:

1. A single problem worsens and by itself evolves into an adverse outcome.
2. The problem begins to evolve but remains self-limited without any intervention.
3. Multiple small problems combine to trigger a problem that can evolve into an adverse outcome; the original problems by themselves would not have evolved further.
4. A single problem triggers another problem that evolves into an adverse outcome.
5. An evolving problem should be able to be stopped, but the recovery pathway is faulty.
6. Two problems are triggered. Attention focused on one (minor) problem distracts attention from the (serious) evolution of another.

The system has a variety of interruption points at which the occurrence of problems can be prevented (preoperative evaluation of patients and pre-use checkout of equipment). Moreover, although anesthesiology is far more dynamic than many medical domains, it is relatively slow in comparison with many human activities such as sports, driving, and combat flying. Thus, events often evolve slowly enough that the process of accident evolution can be thwarted before an adverse patient outcome actually occurs. The interruption of accident evolution corresponds to the "defense-in-depth" in Reason's "Swiss cheese" model[80] and to recovery from a normal accident in Perrow's paradigm (see Figs. 7-2 and 7-3 and the overview on NAT in Table 7-2).

In the prospective studies of intraoperative events cited earlier, the incidence of undesirable situations was surprisingly high, whereas the rate of actual patient harm was quite low. The patient's safety was frequently protected only by the skilled intervention of a trained anesthesia professional. This is a markedly different picture from that in commercial aviation, although the accident rate in aviation is very low. Approximately 30,000 airline flights take place each day in the United States, and very few serious incidents or accidents occur, although the exact number is unknown. The *total* accident rate from *all causes* (not including terrorist acts) for scheduled airline flights from 2002 through 2011 was 0.29 per 100,000 departures. Air carrier accidents with one or more fatalities occurred at a rate of 0.009 per 100,000 departures. In fact, according to the National Transportation Safety Board, in the years 2007 to 2011 there was only a single fatal airline accident (http://www.ntsb.gov/data/table6_2012.html).

The actual number of events in aviation matching the "impact event" criteria given earlier is not known, but it is probably at least 100 times greater than the number of accidents. Even so, this still makes aviation incidents far less frequent than the 3% to 5% rate of "significant" impact events in anesthesia. Based on these data, it is clear that the intraoperative management of abnormal, dynamically changing events remains the critical locus of anesthesia skill.

EMPIRIC STUDIES OF ANESTHESIA PROFESSIONALS' TASKS

Since the 1970s, numerous studies of anesthesia professionals' intraoperative activities have been conducted.[§] In addition, an increasing number of studies have been performed in realistic simulation environments.[2,21,24,220,352-368]

The earliest studies used time-lapse photography of a handful of anesthetic cases with a frame-by-frame analysis of tasks. One major finding of the first task analysis, by Drui and associates in 1973, was that "the anesthesiologist's attention was often directed away from the patient-surgical field."[369] In subsequent studies, it was found that approximately 40% to 50% of the time the anesthesia professional's gaze was directed away from the patient or surgical field.[281-283] McDonald and Dzwonczyk, studying cases from 1981, classified direct patient activity as "one during which the anesthesia professional had contact with the patient and a view of the surgical field."[282] These investigators explicitly noted "observation of skin color," "palpation of pulse," and "auscultation of heart and breath sounds" as direct patient activities. Observing arterial pressure or the ECG and observing or adjusting the anesthesia machine or intravenous infusions were classified as indirect patient activities. In this study, 83% of the anesthesia professional's time was spent on activities that were not direct patient activities. The same group repeated its study for cases from 1985 and demonstrated a much higher rate of direct patient monitoring than obtained in 1981 (44.8% versus 16.8%).[283] This group attributed the difference to the change from manual ventilation in 1981, which took up much of the anesthesia professional's visual attention, to the use of mechanical ventilators in 1985, which freed the anesthesia professional to watch the patient.

It is true that looking at the patient and at the surgical field is a hallmark of an excellent clinician. Opponents of technology decry the degree to which monitors and therapeutic devices distract the anesthesia professional's gaze from the patient. However, an important distinction must be made between the anesthesia professional's attention, which surely must be directed to the patient's needs, and the anesthesia professional's gaze, which in fact may best serve the patient by being directed elsewhere. Many of the tasks cited in the study by McDonald and Dzwonczyk and their co-workers were highly related to management of the patient,[283] even though they did not involve direct visualization of or contact with the patient. The critical question, which task analysis by itself cannot answer, is when anesthesia professionals gaze at the surgical field, how often are they gathering information, and how often are they just "watching the scenery"? Put more generally, what is the information content of the various observations being made, and what is their relation to action tasks and to the goals of conducting a safe anesthetic regimen?

[§]References 39, 43-46, 48, 214, 235, 275, 348-351.

Intriguingly, Drui and associates had asked physicians who were helping code their films, "What information, if any, do you gain from the direct performance of this activity?"[369] However, these investigators never described what information was available from each activity, although they seem to have assumed that turning the anesthesiologist's gaze away from the patient and surgical field was bad. Boquet and co-workers not only studied the gaze of anesthesia professionals (by using a sophisticated eye-tracking system) but also asked consultant anesthesia professionals to grade the importance of different visual targets and manual tasks.[281] "The patient" was assigned the maximal importance on the scale. However, "the surgical field," which occupied 25% of the anesthesia professional's time, was apparently not listed by the consultants. Perhaps, in their minds, the surgical field was lumped together with the patient.

Another key finding of the study by Drui and co-workers was that 40% of the anesthesia professional's time was coded as "idle," meaning that no obvious task was seen on that frame of film.[369] In 1988, McDonald and Dzwonczyk stated that this and other "studies showed that the anaesthetist spends most time performing tasks that are either secondary or unrelated to patient care."[282] However, in their original article, Drui and associates correctly recognized that the absence of visually apparent activity did not mean that the anesthesia professional was truly idle; in fact, these investigators hypothesized that this time was used by anesthesia professionals to make the decisions on which the observable tasks were based.[369]

The most detailed task analyses took place in a series of studies carried out by the UCSD/VA-Stanford group.[235,275,284,285,350,370] These analyses used progressively more task categories (11 to 28 to 32) to analyze the activities of novice and experienced anesthesia professionals in day surgery cases and the activities of senior residents during cardiac surgery. The studies showed that a small number of tasks, repeated frequently, occupied the majority of case time. Four tasks (observing monitors, recording, conversing with attending staff [for novice residents], and adjusting monitors) accounted for 50.1% of the total case time in one study. Specific activities such as airway management (e.g., bag ventilation, laryngoscopy) occurred in brief, but intense clusters (Fig. 7-16). Given the larger number of task categories, the anesthesia professional was rarely seen to be idle.

Studies by this group have attempted to determine whether a difference exists in task patterns between novice and experienced anesthesia professionals. Confirming a priori expectations, the investigators found that novices perform many of the same tasks as do experienced personnel at specific phases of an anesthetic regimen; however, the novices had a longer dwell time, on average, for each task. These studies also showed that experienced providers had lower heterogeneity of tasks and greater efficiency of tasks per unit time.[371]

Of note (but also not unexpected), novice residents spent more time speaking to their attending staff (11% of preintubation time) than did experienced residents or CRNAs. Experienced personnel observed the surgical field more than did the novices. The implications of this finding are not clear. Novices did take longer to complete patient preparation and induction of anesthesia, but it appeared that some of the extra time taken by novices working under supervision was offset by the efficiency of offloading other concurrent tasks to the attending anesthesiologist such that preintubation time was increased by only 6 minutes for novices.[371] This group also reported that as the density of tasks per unit time increased, the dwell time on each task decreased, and vice versa. This finding has important implications for how anesthesia professionals allocate their attention (see the earlier section on management and coordination of the core process).

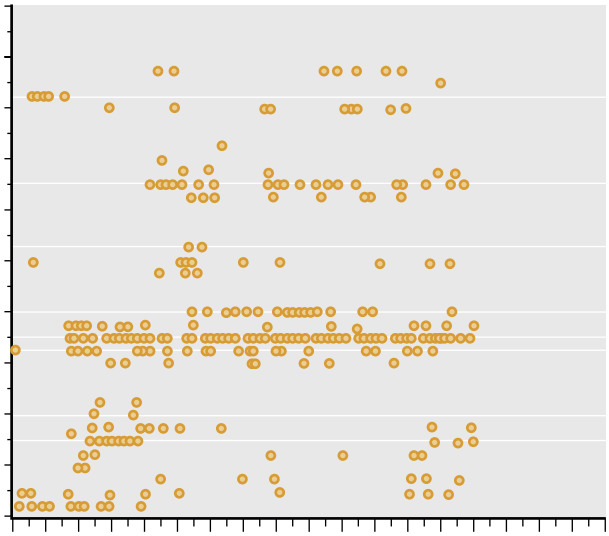


Figure 7-16. Distribution of the anesthetist's tasks during an actual ambulatory surgery procedure. The anesthetist was directly observed by an investigator who recorded a code number for each task as it was performed (there were 28 task codes). Certain tasks, such as bag ventilation, were clustered in specific phases of the case, whereas others, such as observing monitors, were repeated frequently throughout the procedure.

Task Analysis and Action Density

An interdisciplinary research group consisting of the Work and Organisational Psychology Department of the Swiss Federal Institute of Technology in Zurich and the Center for Patient Safety and Simulation of the Department of Anaesthesiology of the University of Tübingen performed several task analysis studies using the Flexible Interface Technique (FIT) system[372] (Fig. 7-17), which facilitates analysis of multiple parallel and overlapping actions.[286] The group produced a set of 41 observation codes—representing a single action (Table 7-9). Because the method allowed true capture of overlapping actions, it was possible to describe a valid task density in the analysis of anesthesia professionals' action sequences.

Figures 7-18 and 7-19 show examples of observations of 24 real OR studies. The observation data contain many short-term fluctuations (*dots*); the moving average of action density of the previous 5 minutes was charted as well (*line*). Figure 7-18 shows a complete anesthesia procedure with obvious increases in action density during induction and emergence from anesthesia. Figure 7-19 shows 2 final phases of cardiac cases involving cardiopulmonary bypass. The described task analysis technique

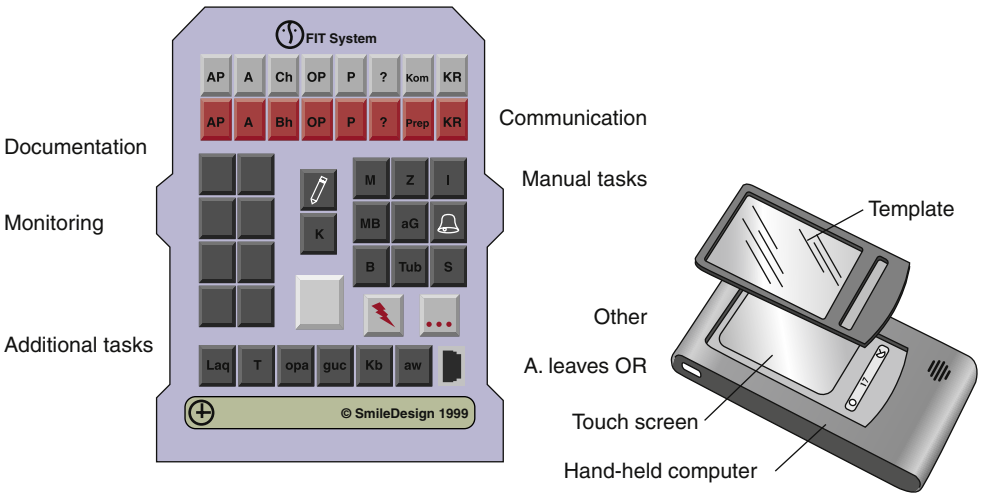


Figure 7-17. Flexible Interface Technique system. The system allows easy reorganization of task analysis items and categories and can properly resolve overlapping actions. *OR,* operating room.

TABLE 7-9 OBSERVATION CODES USED TO CLASSIFY TASKS AND ACTIONS

Task Group	Actions
Monitoring	Reading of patient record, observation of patient, observation of patient monitors, observation of anesthesia machine, observation of intravenous drip, observation of syringe pumps, measurement, scanning of area
Measures	Placement of IV, drug administration, adjustment of IV, mask ventilation, intubation or extubation, adjustment of anesthesia machine, use of other equipment, quitting alarms, suctioning
Communication	(1) Active conversation with nurse anesthetist, attending anesthetist, surgeon, OR nurse, patient, others; (2) responsive conversation with nurse anesthetist, attending anesthetist, surgeon, OR nurse, patient, others; and (3) response to pager
Documentation	Patient chart labeling (drugs, drips, laboratory results)
Additional operations	Positioning of patient, patient transfer, tasks of others (circulating nurse, orderly), arrangement of workplace, conversation with observer ("just looking"), miscellaneous, leaving OR (with possible audiovisual contact with OR)

IV, Intravenous line; *OR,* operating room.

was also used successfully by the Tübingen group to study action sequences in a simulator and compare them with findings in the real OR to demonstrate and evaluate the ecologic validity of simulators (see Chapter 8).

Automation

Early task analyses identified repetitive tasks that did not appear to offer substantial information content or therapeutic benefit as candidates for automation. Drui and associates identified filling out anesthesia records, measuring blood pressure, and adjusting intravenous infusions.[369] Kennedy and colleagues identified data display and trend plotting.[373] Many of these tasks have in fact been automated since the 1990s. Loeb, from the University of California, Davis (UCD), showed that anesthesiologists typically observed monitors for approximately 1 to 2 seconds every 10 to 20 seconds and that it usually took several observing cycles before they detected a subtle cue on the monitor.[374] Gurushanthaiah and co-workers studied the effect of more sophisticated display modalities on detection of signals by anesthesiologists and found that histogram and polygon formats improved response latency in the laboratory setting over formats using raw numbers only.[375] However, the applicability of these laboratory finding to the more complex signal detection that must occur during patient care is uncertain. Incidentally, the experience in the field of aviation suggests that automation of both monitoring and therapeutic devices produces its own problems in human-machine interactions and may well be a causative or contributing factor in some adverse anesthetic events. Some of the same types of automation-related adverse events seen in aviation are now observed in anesthesiology.[267]

The impact of automation on task distribution is uncertain. The change to mechanical ventilation did affect the analyses of McDonald and Dzwonczyk,[282] as detailed earlier. A study by Allard and co-workers showed no reduction in time spent recording when automated record-keeping devices were used.[376] However, the UCSD/VA-Stanford collaboration published data demonstrating a 20% reduction in the time spent record keeping when automated record keeping was in use during cardiac anesthesia.[371] The investigators noted a slight, but not significant increase in time spent on direct patient care activities when electronic record keeping was in use. No clear evidence indicates that electronic record keeping will yield a marked enhancement of the anesthesia professional's ability to perform other patient care tasks, although automated record keeping may yield other benefits. The UCD and UCSD/VA-Stanford groups demonstrated that electronic automated record keeping does not significantly reduce the vigilance of anesthesia professionals.[377,378]

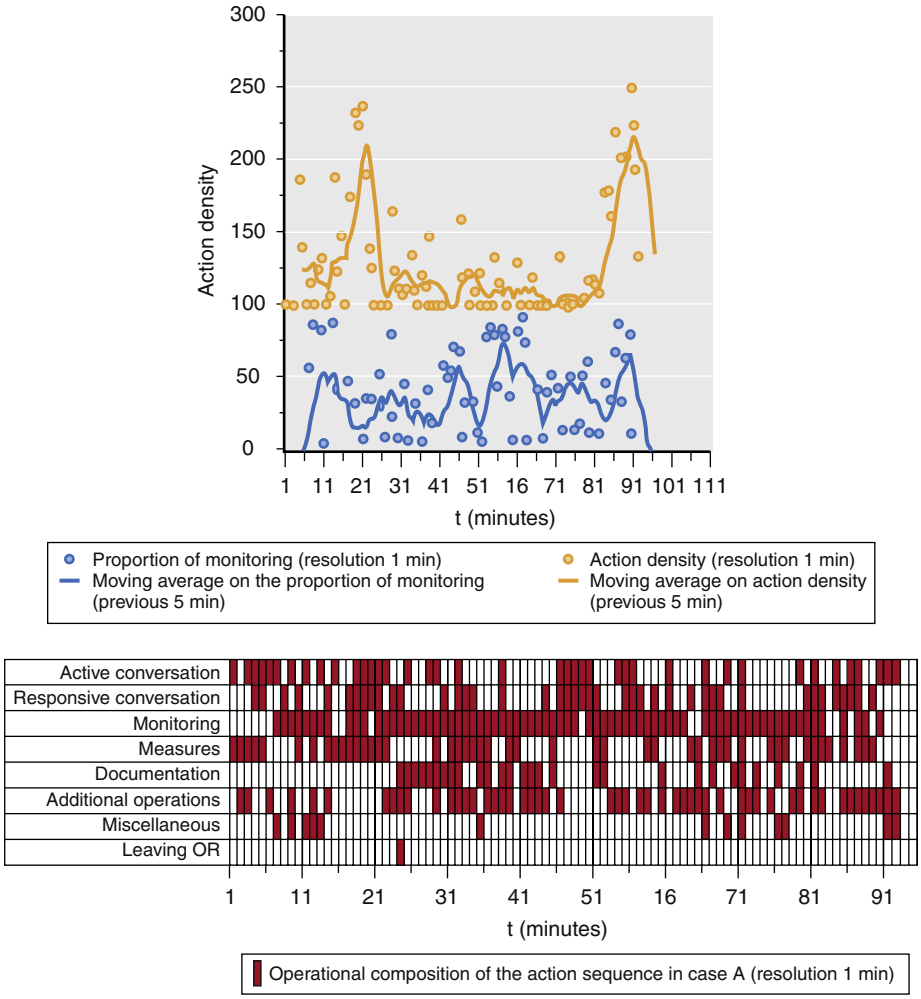


Figure 7-18. Action density diagram illustrating the derived parameter "action density" from induction of anesthesia to emergence in a real anesthetic case. The *yellow line* in the graph shows the overall action density and the *dots* show the moving average of the density. The *blue line* shows the contribution of one task group, "monitoring," as an example. The table in the lower graph shows the composition of the data for all eight task groups from the same case. *OR,* Operating room.

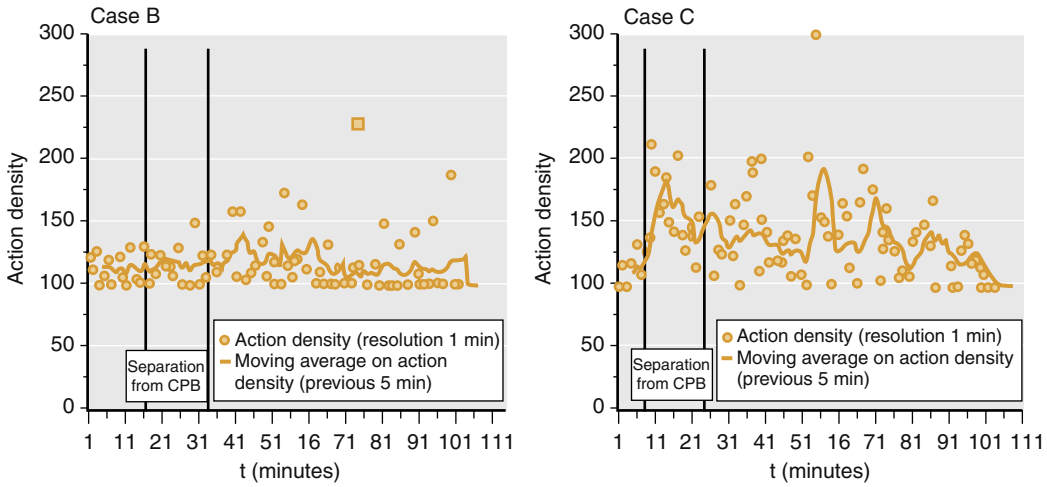


Figure 7-19. Action density during separation from cardiopulmonary bypass (CPB) without and with complications. The graph on the *left* is the density diagram of an uncomplicated case (case B) with a "flat" action density diagram during (between the two *vertical lines)* and after separation from CPB. In contrast, case C, shown in the graph on the *right,* had a complicated weaning from CPB; a very high action density is followed by an elevated density with further peaks after separation.

MENTAL WORKLOAD OF ADMINISTERING ANESTHESIA

The observable tasks do not tell the whole story of what the anesthesia professional is doing. As Drui and co-workers suggested, mental activity is going on even when the anesthesia professional appears idle.[369] What, then, is the mental workload of administering anesthesia? Mental workload is another concept that is readily understood but difficult to define precisely. Various ways exist to measure mental workload, none of which are ideal.

Primary Task Performance Measure

The primary task performance measure assesses the subject's performance on standard work tasks as they are made progressively more difficult by increasing the number of tasks, task density, or task complexity. At first the subject is able to keep up with the increasing task load, but at some point the workload exceeds the ability to manage it, and performance on the standard tasks decreases. The disadvantage of the primary task performance measure is that in many complex task domains no accepted way exists to measure the subject's performance on the primary work tasks objectively except by loading to the point of catastrophic performance failure, which is easily detected. In actual high-risk domains, one cannot allow primary task performance to degrade, and one certainly cannot allow it to fail catastrophically. Although experiments of this type are in principle feasible with anesthesia simulators, they have not yet been attempted.

Secondary Task Probing

A more useful technique, secondary task probing, tests the subject with a minimally intrusive secondary task that is added to the primary work tasks. The secondary task is a simple one for which performance can be objectively measured, and the subject is instructed that the primary tasks of patient care take absolute precedence over the secondary task. Therefore, assuming that the secondary task requires some of the same mental resources as the primary task, the performance of the subject on the secondary task is an indirect reflection of the spare capacity available to deal with it; thus, it is an inverse measure of primary task workload (the greater the spare capacity, the lower the primary workload). Secondary tasks such as reaction time (with or without choice), finger tapping, and mental arithmetic have been used for this technique in the psychology laboratory, in high-fidelity simulators, and in some field studies of actual work situations.

Gaba and Lee presented two-digit addition problems on a computer screen placed in the anesthesia workspace at random approximately every 45 seconds.[379] The delay in responding to problems and the number of problems skipped were logged over time and correlated with a concurrent six-category task analysis. The dynamic ebb and flow of mental workload during cases of varying complexity was documented. For example, cardiopulmonary bypass was confirmed as a time of very low workload for the anesthesia professional, whereas induction of anesthesia was confirmed as a period of high workload. Manual tasks and conversing with the attending physician were correlated with a delayed or absent response to the secondary task.

Subsequent studies by the UCSD/VA-Stanford group[284,285] and the UCD group[374,378,380] used the reaction time to a changing display in or around the clinical monitors as a secondary task to assess mental workload, vigilance, or both. For the UCSD/VA-Stanford group, the display was a red light placed next to the main physiologic monitor. This secondary task was analogous to but totally separate from the standard tasks of clinical work. When the secondary task was embedded in the regular work tasks, it was called an embedded task. The UCD group used a secondary task involving recognition of changes in the alphanumeric display of an unused channel of an actual clinical monitor (a parameter labeled "Vig" on the monitor changed values from "5" to "10"). This task was only partially embedded because although it did involve an actual clinical monitor, it displayed on an otherwise unused channel and was not of clinical significance. The VA-Stanford group has experimented with fully embedded secondary tasks during simulator anesthetic cases in which the values of actual clinical variables can be manipulated at will to evaluate the subject's response time to the excursion of data values beyond predefined reporting thresholds.

The mean response time to the red light used by the UCSD/VA-Stanford group was markedly less than 60 seconds for experienced subjects in both the induction and postinduction (maintenance) phases, but it was much higher for novice residents during the induction phase (Fig. 7-20). The probe was not given frequently enough to track the ebb and flow of workload. The response to the UCD task typically (56%) occurred within 60 seconds, but 16% of stimuli overall (27% during the induction period) were not responded to within 5 minutes. The conclusion was that spare capacity may be limited by the workload of the case during certain periods of anesthesia care.

These workload studies have several problems. One is interference with the "response channel." If responding

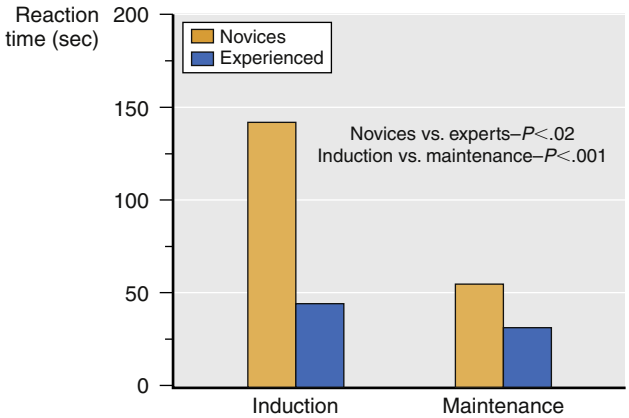


Figure 7-20. A test of the anesthetist's vigilance. Shown is the mean reaction time of novice residents and experienced anesthetists in response to the illumination of a red light placed next to the electrocardiogram monitor display during actual ambulatory surgery procedures. In both groups the reaction was faster in the maintenance phase than during induction of anesthesia. Novices reacted significantly more slowly than did experienced anesthetists. Because the distribution of reaction times was skewed and nongaussian, error bars are not shown, and nonparametric statistics were used for hypothesis testing.

to the probe requires manual activity with a mouse or keyboard (as in the studies of Gaba and Lee and the UCD group), it cannot be performed whenever the subject is occupied with a manual task. This is especially true during a sterile procedure. Therefore, it may be impossible to distinguish between a high primary task load (i.e., no spare capacity to address the secondary task) and a low primary task load that happens to usurp the manual response channel. However, in the study by Gaba and Lee, 37% of the problems that were skipped for lack of spare capacity did not occur during a manual task.[379] All the UCSD/VA-Stanford studies have allowed multiple response channels (manual, voice, and gesture), so there was no response channel interference; however, the potential for interference remains in the UCD studies.

An additional problem with these studies is that even these simple secondary tasks were intrusive when repeated frequently. Thus, a tradeoff was seen between temporal resolution of the measurement and its intrusiveness. Controversy also exists about whether these probes measure "vigilance" or "workload," although the same techniques probably measure both aspects of performance. When probes occur infrequently, are subtle, have multiple response channels, and are performed with a low level of existing workload, they are more likely to measure vigilance; when they are frequent, readily detectable, require a manual response, and are performed during a high-workload period, they probably are more indicative of spare capacity and workload.

Slagle and colleagues carried out an assessment of an established clinical task analysis methodology regarding intrarater and interrater reliability.[349] These investigators had a trained observer rating 20 routine anesthesia cases, by first rating cases in the OR and then rating the same cases from a videotape, with another observer rating the same videotapes twice. A computerized task analysis program with 38 task categories was used. The results showed good intrarater reliability and also high concordance between real-time and video analyses. This finding is important because real-time observation is unfeasible in many circumstances. This study had problems in analyzing parallel tasks because the technique of "toggling between the task categories at a rate proportional to the time spent on each task" resulted in large differences in "task duration" and "task occurrences" between the two raters. This problem of recording parallel tasks (two or more) was solved by Manser and colleagues in Tübingen.[286,287,381]

Subjective Measures

A third modality of workload assessment consists of subjective measures in which individuals are asked, either in retrospect or in real time, how much load they were or are under during actual work situations. Subjective measures complement objective measurements because the subjective perceptions of the anesthesia professional may be an important source of stress and anxiety; conversely, an anesthesia professional may subjectively underestimate the workload in settings in which objective measurements demonstrate a marked reduction in spare capacity.

Various scales have been proposed to measure dimensions of mental workload that are, in theory, different. However, Gaba and Lee adapted a set of workload scales from those used at NASA and showed that workload ratings on each of the scales were highly correlated.[379] In subsequent studies by the UCSD/VA-Stanford group, a single dimension of overall load was assessed by using an asymmetric numeric scale that minimized biases caused by a tendency to group responses at the middle and extremes of symmetric scales. This group demonstrated that a neutral observer can estimate the subjective workload of the anesthesia professional in real time with high correlation to the self-rated workload of the subject.[284] Again, as could be expected, subjective workload was highest during induction and emergence from anesthesia, especially for novices.

Physiologic Measures

The final set of techniques for assessing workload consists of physiologic measures. Visual or auditory evoked potentials have been used successfully to assess mental workload, but this technique can be used only in a static laboratory environment. Heart rate is a relatively easily measured variable that may be altered by mental workload. Toung and associates showed that the anesthesia professional's heart rate increases at the time of intubation, and the amount of increase is inversely related to the amount of overall medical training.[382] Azar and co-workers found that anesthesia faculty members' heart rate and blood pressure increased during induction of anesthesia, and significant ST-segment depression developed in one individual.[383] Bitetti and colleagues confirmed that heart rate changes occurred during anesthesia but did not always correlate with contemporaneous self-recordings of "stress."[384]

Because of the many factors that affect heart rate, the beat-to-beat variability of the heart rate is thought to be a better indicator of mental workload. The frequency components of heart rate variability can be separated by spectral analysis; a component at 0.1 Hz has been linked to mental workload. Although several groups have acquired heart rate data on anesthesiologists, none has reported an analysis of the workload-related frequency components.

APPLICATIONS OF TASK ANALYSIS AND WORKLOAD METHODOLOGIES

The results of task analyses and workload measurements have primarily provided objective confirmation of several intuitive beliefs about anesthesia practice. The real importance of these studies is that a coherent methodology has been developed that may be useful for studying a variety of interesting questions.[287,385] The question of the impact of electronic automated record-keeping systems was addressed earlier. Another question concerns TEE. This monitoring modality has become commonplace during cardiac anesthesia and anesthesia for other patients with cardiovascular disease who undergo complex operations. It is widely recognized that evaluating TEE images and manipulating the TEE probe require substantial visual and mental attention.

The UCSD/VA-Stanford group has published data suggesting that vigilance (as measured by response latency to illumination of a red light) was substantially lower when the anesthesiologist was involved in manipulating,

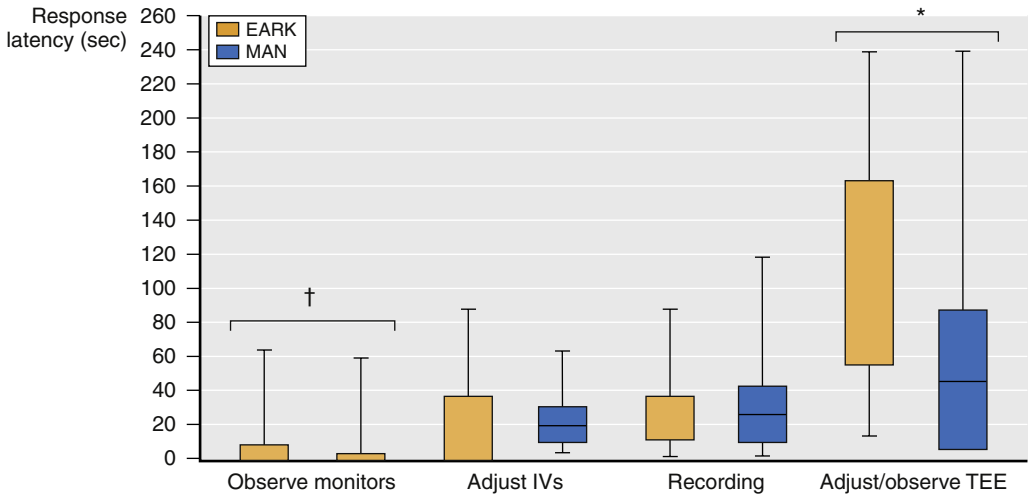


Figure 7-21. Vigilance test data during anesthetic tasks with and without automated record keeping. The range of data is shown for each of four task categories in electronic automated record keeping (EARK) and manual record keeping (MAN). Each box contains 50% of the data for that subgroup (the upper limit of the box is the 75th percentile; the lower limit is the 25th percentile), whereas the maximum and minimum are shown by the upper and lower *horizontal bars.* The response latency during record keeping was not significantly different between EARK and MAN. In both record-keeping groups, subjects had significantly slower responses when observing or adjusting the transesophageal echocardiogram (TEE) than when recording, observing monitors, or adjusting intravenous lines (IVs). Subjects in both groups had faster response latency when observing the monitoring array, which contained a red light, than when performing the other three tasks. $^{*}P < .05$; $^{\dagger}P < .05$. *(From Weinger MB, Herdon OW, Gaba DM: The effect of electronic record keeping and transesophageal echocardiography on task distribution, workload, and vigilance during cardiac anesthesia,* Anesthesiology *87:144-145, 1997.)*

adjusting, or examining the TEE images than when other patient care tasks were being performed (Fig. 7-21).[377] This finding may reflect, in part, the layout of the workspace. The TEE machine is large and is often placed near the left side of the head of the OR table, whereas the anesthesia machine and attendant monitors, by convention, are typically placed near the right side of the head of the table. Remote displays slaved to the primary monitor are also more likely to be on the patient's right side. This arrangement makes it physically difficult to glance from one modality to another. The degree to which the mental concentration required to use TEE itself detracts from vigilance for other signals remains to be determined explicitly.

It is important to differentiate the various uses of TEE. When TEE is used to answer specific clinical questions triggered by events or milestones during the procedure, the value of the information may be worth an investment of effort despite the reduction in overall vigilance. When TEE is used as a continuous monitor for myocardial ischemia or during a detailed routine examination, the reduction in vigilance must be considered when evaluating the potential benefits of the technology. Some practitioners describe special ways to handle the attention required for TEE, including tightening alarm thresholds (to provide audio warnings of changed values) and assigning specific patient monitoring functions to another individual while conducting the initial TEE placement and examination.

Many other interesting questions on the performance of anesthesia professionals are still unanswered and can be addressed with the techniques of task analysis and workload and vigilance assessment, including the following:

1. How do task load and task density differ between private practice settings and academic settings?
2. Do characteristic "patterns" for experts and novices (or should we say for "good" and "bad" anesthesiologists?) exist in the analysis of tasks and their densities? And if yes,
   a. How do the work patterns of novices change to become those of "experts"? How can the training of novices be focused to support these changes best? Is suboptimal performance of novices detectable through analysis of task distributions and mental workload?
   b. Can work patterns be linked to safe anesthetic practice, or can special patterns be linked to unsafe behavior? Perhaps this could be done by assessing high-workload simulator scenarios. In a proactive safety culture, this would allow us to identify such colleagues and train them individually.
3. How much task load can the average anesthesia professional handle? How are tasks distributed among personnel (e.g., between resident and faculty, between CRNA and supervisor, and among staff anesthesia professionals) during the high-workload periods of patient care? This question is just beginning to be addressed by applying the task analysis techniques described earlier to videotapes of actual anesthetic cases. With use of these tapes, the task sequences of multiple anesthesia personnel can be elicited separately, as can the communications used to coordinate their activities.

OTHER STUDIES OF "VIGILANCE" AND DECISION MAKING BY ANESTHESIA PROFESSIONALS

STUDIES OF "VIGILANCE"

The dominant metaphor for the mental activity of the anesthesia professional has been that of a vigilance task.

"Vigilance" is the motto on the seal of the ASA. What is vigilance, and to what degree does it capture the complex nature of the anesthesia professional's work? "Vigilance, or sustained attention, refers to the ability of observers to maintain their focus of attention and to remain alert to stimuli for prolonged periods of time" (J. Warm, presentation at the Panel on Vigilance, ASA annual meeting, 1992). The literature concerning vigilance is abundant. Many laboratory studies have demonstrated decrements in vigilance during prolonged vigilance tasks that are exacerbated or ameliorated by a variety of factors. These studies have generated considerable controversy. Some psychologists believe that the results of laboratory studies of vigilance have little application to complex real-world task domains.[386,387] Certainly, the anesthesia professional's work involves vigilance as a necessary component because no meaningful work can be accomplished if new stimuli are not perceived. However, the anesthesia professional's task is much more complex than just vigilant alertness to stimuli. Therefore, vigilance is a necessary but not sufficient condition for appropriate performance.[65]

Several studies have attempted to quantitate the vigilance of anesthesia professionals to changes in clinically important variables by using low-fidelity simulation. Beatty and associates had anesthesia professionals watch for changes in displays of six vital signs on a video monitor.[388] Denisco and colleagues used videotapes containing abnormal changes in anesthesia flow meter settings and physiologic monitor displays.[389] The raw reaction times were not reported—only the "vigilance scores." Such studies purported to demonstrate a degradation in performance for sleep-deprived and fatigued residents, but these studies had methodologic flaws. For example, in the study of Denisco and colleagues, the subjects were never told the threshold of change for them to report.[389]

In addition, the work environment of the anesthesia professional is much more complex than that presented in these low-fidelity simulations. Although it can be argued that complexity will worsen vigilance, such is not necessarily the case. Complexity can combat boredom, which is a distinct possibility in vigilance experiments. In addition, the real work environment often provides redundant data cues on changes that offer multiple possibilities for their detection.

A study of rested anesthesia professionals using realistic anesthesia simulation measured detection times (first awareness of a problem) for a variety of intraoperative events embedded within a realistic case situation.[214] An event that caused alarms to sound immediately, such as ventricular tachycardia or fibrillation, was detected in 10 seconds or less (thus confirming its veracity, but acting on it took longer in many instances). Another event, occlusion of the intravenous line, was detectable only by visual observation in the direction opposite the anesthesia machine and monitors. This event took several minutes (on average) to detect, but it was corrected quickly after detection. The redundancy of cues in the task domain was confirmed in that 6 different observational modalities were used by at least 1 of the 19 residents studied to detect endobronchial intubation initially.

Other vigilance studies have focused on detecting the loss of an existing monitoring modality during actual patient care. In one study,[390] the esophageal stethoscope was occluded with a clamp after a staged distraction (conversation or a loud noise). Subjects most commonly detected the occlusion by observing the clamp, rather than by noting a loss of sound. Although this study purported to show a difference in vigilance related to the use of automatic blood pressure measurement devices, the artificial distraction could have biased the results; the subjects typically failed to hear the loss of sounds, and a significant result was reported for only one group of residents, arbitrarily stratified by length of training. Another study,[391] which evaluated reaction time to loss of esophageal stethoscopy more carefully, showed that 13% of occlusions were detected after 1 minute. However, this study required a manual response, and the investigators noted that in some instances of delay, the subject was involved in a manual clinical activity such as administering blood or drugs.

Apparent reductions in vigilance could result either from a reduction in "spare capacity" to attend to the stimuli immediately or from a reduction in the overall alertness of the anesthesia professional. Enhancements in the display and annunciation of relevant information would be a useful ameliorative strategy in the first case, whereas this strategy would not be useful if the anesthesia professional's overall alertness were impaired, such as by sleep deprivation or illness. The influence and impact of fatigue and possible countermeasures are covered in the earlier section on performance-shaping factors.

EMPIRIC STUDIES OF COMPLEX DECISION MAKING AND ACTION BY ANESTHESIA PROFESSIONALS

Traditional concepts of decision making in medicine have concentrated on relatively static, well-structured decisions. For example, should patient A with an elevated blood pressure be treated for hypertension with drug X, or should no treatment be started? Other investigators have looked only at "diagnosis" as an isolated task (specifically, "diagnostic explanation") both in internal medicine[392-394] and in radiology. These approaches to decision making have not captured the unique aspects of dynamism, time pressure, and uncertainty seen in anesthesiology. Since the 1980s, a paradigm has emerged regarding decision making and action in complex real-world situations.[47,276,290] The cognitive model of dynamic decision making was described previously. Several teams from inside the anesthesiology profession and from the human performance community have been striving to develop a more comprehensive understanding of the complex performance of anesthesia professionals. Their work has been based on a small number of new experiments (often involving medium- or high-fidelity anesthesia simulators), reinterpretation of previous experiments, direct and indirect observation of the conduct of anesthesia, and extrapolations from other industries to anesthesiology. Each experiment has probed several aspects of decision making and action, which are described in the following section.

Responding to Simulated Critical Incidents

Many studies using simulations have been performed and published. Because the results of later studies are largely in accord with those of the original studies, we describe

the original studies as examples that also represent some of the more recent literature.[20,21,395-404]

Using a realistic hands-on anesthesia simulator, Gaba and DeAnda studied the response of anesthesia trainees and experienced anesthesia faculty and private practitioners to six preplanned critical incidents of differing type and severity[123,300,405]:

1. Breathing hoses too short to turn the table 180 degrees, as requested by the surgeon
2. Endobronchial intubation (EI) resulting from surgical manipulation of the tube
3. Occlusion of intravenous tubing
4. Atrial fibrillation (AF) with a rapid ventricular response and hypotension
5. Disconnection between the endotracheal tube and the breathing circuit
6. Ventricular tachycardia or fibrillation

These investigators measured the detection time (as described in the section on vigilance) and the correction time (the time from the event's onset until any one of a predefined set of corrective actions was first taken). They assessed the information sources by which subjects detected the incidents and then confirmed and diagnosed the problem. They asked subjects to "think aloud" to permit subjective analysis of their decision-making strategies. A summary of the data is shown in Figure 7-22. Major findings from this set of studies included the following:

1. Events differed from each other in their inherent ease of solution. Some events (e.g., airway disconnection) were detected rapidly and corrected. Some problems (e.g., intravenous occlusion) were difficult to detect, but once they were detected, diagnosis and therapy were achieved rapidly. Other problems (EI, AF) were easy to detect by using one of several redundant information sources as

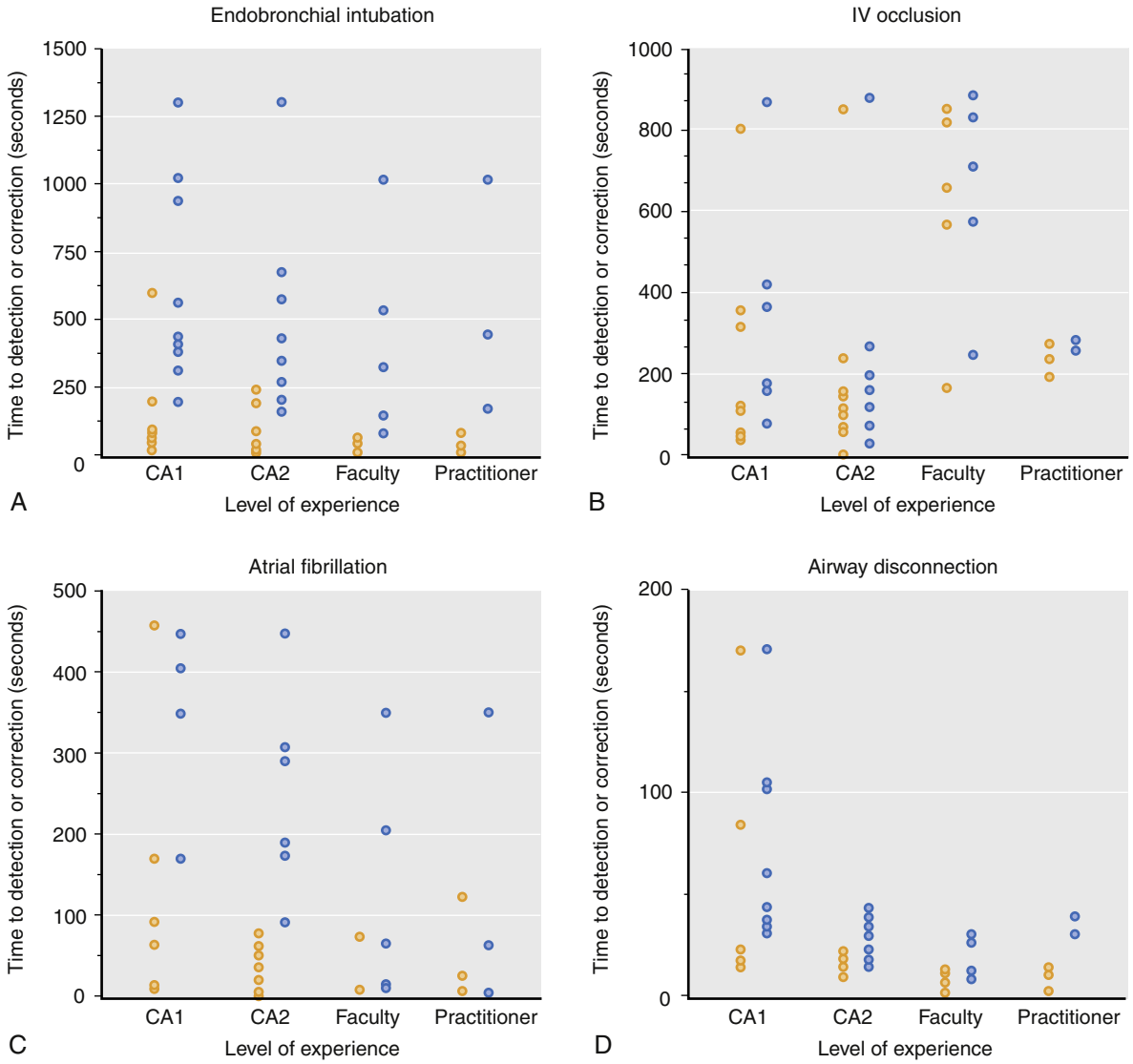


Figure 7-22. Response times of anesthesiologists with different levels of experience to four simulated critical incidents: **A,** endobronchial intubation; **B,** intravenous (IV) occlusion; **C,** atrial fibrillation; and **D,** airway disconnection. Detection time is represented by *yellow circles* and correction time by *blue circles* (see text for definitions of these times). Unless an overlap exists between response times, each circle represents a single individual. The scale of response times is different for each event. Variability among incidents and among individuals is substantial. Despite a trend to better performance with increased experience, major errors were made by individuals in all groups. *CA1,* First-year clinical anesthesia residents; *CA2,* second-year clinical anesthesia residents. *(From DeAnda A, Gaba DM: Role of experience in the response to simulated critical incidents,* Anesth Analg *72:308-315, 1991.)*

the first clue (6 for EI; 4 for AF), but they required additional time (7 to 8 minutes for EI; 1.5 to 4.5 minutes for AF) to confirm the abnormality, establish a diagnosis, and initiate appropriate therapy. Diagnosis and planning and monitoring of therapy used a large number of information sources (11 for EI; 9 for AF).
2. For each incident, considerable interindividual variability was found in detection and correction times, in information sources used, and in actions taken. Each experience group contained some who required excessive time to solve the problem or who never solved it. In addition, in each experience group at least one individual made major errors that could have had a substantial negative impact on a patient's clinical outcome. For example, one faculty member never used electrical countershock to treat ventricular fibrillation. One private practitioner treated the EI as though it were "bronchospasm" and never assessed the symmetry of ventilation. One resident never found the airway disconnection.
3. The average performance of the anesthesia professionals tended to improve with experience, although this varied by incident. The performance of the experienced groups was not definitively better than that of the second-year residents (who were in their final year of training at that time). Many (but not all) novice residents performed indistinguishably from more experienced subjects.
4. The elements of suboptimal performance were both technical and cognitive. Technical problems included choosing defibrillation energies appropriate for internal paddles when using external paddles, ampule swap, and failure to inflate the endotracheal tube cuff that resulted in a leak. Cognitive problems included failure to allocate attention to the most critical problems and fixation errors.

Schwid and O'Donnell, from the University of Washington, used the Anesthesia Simulator Consultant (ASC) screen-only simulator (Anesoft Corp., Issaquah, Wash.) (Table 7-10) to perform an experiment similar to those of Gaba and DeAnda with a realistic simulator.[298] This method enabled them to evaluate some elements of anesthesia professional behavior more carefully, albeit with the limitations imposed by presenting the OR "on the screen." After working on several practice cases without critical incidents, each subject was asked to manage 3 or 4 cases involving a total of 4 serious critical events (esophageal intubation, myocardial ischemia, anaphylaxis, and cardiac arrest). The progression of each event was mediated by the interaction of physiologic and pharmacologic models with the actions taken by the subject. The anesthesiologists studied had varying experience levels. One group was made up of 10 anesthesia residents with at least 1 year of anesthesia training, whereas the other 2 groups contained 10 anesthesia faculty members and 10 private practitioners, respectively.

Major findings of the study included the following:

1. Significant errors in diagnosis or treatment were made in every experience group. The errors occurred in both diagnosis of problems and in deciding on and implementing appropriate treatment. For example, 60% of subjects did not make the diagnosis of anaphylaxis despite available information on heart rate, blood pressure, wheezing, increased peak inspiratory pressure, and the presence of a rash. In managing myocardial ischemia, multiple failures occurred (Table 7-11).
2. Thirty percent of subjects did not compensate for severe abnormalities while considering diagnostic maneuvers.
3. Fixation errors in which initial diagnoses and plans were never revised were frequent, even when they were clearly wrong.

Westenskow and colleagues used a test lung and remotely activated faults in the breathing circuit to test the anesthesia professional's ability to identify faults related to ventilation and the anesthesia breathing circuit after hearing an alarm.[293] One group of subjects used standard alarms, set to factory defaults, on an anesthesia machine, which included a capnograph. The other group used the same anesthesia machine with the alarms disabled along

TABLE 7-10 INCIDENCE OF TOTALLY CORRECT DIAGNOSIS OR TREATMENT OF SIMULATED CRITICAL INCIDENTS WITH USE OF THE ANESTHESIA SIMULATOR CONSULTANT

Incident	Anesthesia Residents (%)	Anesthesia Attendings (%)	Anesthesiologists in Practice (%)
Diagnosis of esophageal intubation	80	100	100
Treatment of myocardial ischemia	20	40	20
Diagnosis of anaphylaxis	20	60	40
Treatment of cardiac arrest	40	30	20

From Schwid HA, O'Donnell D: Anesthesiologists' management of simulated critical incidents, Anesthesiology *76:495-501, 1992.*

TABLE 7-11 FAILURE RATE IN THE MANAGEMENT OF SIMULATED MYOCARDIAL ISCHEMIA WITH THE ANESTHESIA SIMULATOR CONSULTANT

Incident	Anesthesia Residents (%)	Anesthesia Attendings (%)	Anesthesiologists in Practice (%)
Untreated tachycardia	30	50	70
Untreated hypotension	40	60	20
Inappropriate drug	20	10	0
Inability to recall infusion dose	50	20	10
Inability to calculate infusion rate	70	40	40

From Schwid HA, O'Donnell D: Anesthesiologists' management of simulated critical incidents, Anesthesiology *76:495-501, 1992.*

with a neural network–based intelligent alarm and fault identification system. The mean "human response time," which was the time between sounding of the first alarm and identification of the event, ranged from approximately 15 seconds for airway disconnection to approximately 90 seconds for an endotracheal tube cuff leak. The 10 anesthesiologists tested with the standard alarm setup were unable to identify the fault within 2 minutes on 11 occasions—5 cuff leaks, 3 airway obstructions, and 3 stuck-open expiratory valves. However, in such circumstances they did take appropriate compensatory actions while continuing to search for the cause (e.g., increasing fresh gas flow to compensate for a cuff leak).

The intelligent alarm apparatus used data from three sensors (in-line capnograph, spirometer, and airway pressure). A neural network determined whether any of seven faults was present and, if so, displayed a text message specifying the fault, as well as an animated diagram of the lung, airway, and anesthesia breathing circuit with the faulty component highlighted in red. The smart alarm system took slightly longer on average to detect a fault than did the conventional alarm system (25 versus 21 seconds), but the human response time was markedly reduced for three of the seven faults. No statistically significant differences were noted between anesthesia residents and faculty members with either alarm system.

The investigators suggested that the more specific alarm messages in their intelligent alarm system could direct the attention of the anesthesia professional to the occurrence of specific problems and in so doing would decrease workload and reduce the likelihood of fixating on inappropriate information. They stated that such a system's advantages would be even greater in a more realistic clinical environment in which the anesthesia professional has multiple complex tasks and not just detection and identification of ventilation-related events.

Loeb and Fitch developed and tested an auditory display of six physiologic variables.[406] Encouraged by the popularity of the pulse oximeter's pulse tone,[407-409] these workers investigated whether the addition of auditory cues would enhance the rate and speed of detection of predefined events. The results showed that the combined display (visual and auditory) lead to faster detection of events, even though the rate for correct identification of the event was slightly higher in the "visual only" display (80% versus 88%). It seems a potential exists to improve the rate of detection of changes in physiologic variables with more sophisticated display modalities, thereby enhancing the "effective vigilance" of anesthesia professionals.

Complex, Multiple-Personnel Simulations of Anesthetic Crises

Once again, the literature now contains numerous studies of more complex simulations of intraoperative events with multiple anesthesia professionals interacting either with "confederate" actors in the roles of other clinicians (e.g. surgeons, nurses), or in some cases with actual clinicians in those roles. Again, because much of the more recent literature recapitulates findings of the pioneering studies, we describe those studies but refer the reader to newer studies.[339,343,400,401,410-413]

In the process of evaluating a new type of training for anesthesia professionals involving crisis management, Howard and colleagues collected anecdotal data on the responses of teams of anesthesia professionals, surgeons, and nurses to planned (and unplanned) critical events.[122] These experiments largely confirmed the results of the studies described earlier and extended them to include more complex management issues and team interactions. Howard and colleagues found a substantial incidence of difficulties managing multiple problems simultaneously, applying attention to the most critical needs, acting as team leader, communicating with personnel, and using all available OR resources to best advantage.

Botney and associates analyzed similar videotapes from 18 different simulator training sessions on crisis management.[414] In a single event, a volatile anesthetic vaporizer had been left on at 4% and was hidden beneath a printout from the noninvasive blood pressure monitor. Simultaneously, a mechanical failure of the capnograph occurred and made it impossible to confirm endotracheal intubation with carbon dioxide measurements. This event purposefully presented an invitation to become fixated on the endotracheal tube while ignoring other relevant information. Five of 18 subjects never discovered the volatile anesthetic overdose despite catastrophic effects on blood pressure and heart rate and clear evidence that the endotracheal tube was correctly placed. Of those who did detect the vaporizer setting, the average time to detection was nearly 4 minutes, with some subjects taking longer than 12 minutes.

In the second event studied, a loss of pipeline oxygen supply occurred while an anesthesia professional was assuming the care of a critically ill patient who required an FiO_2 of 100% to achieve satisfactory blood oxygenation. The oxygen cylinder on the machine was empty (i.e., it had not been checked by the initial anesthesia professional, who had left the case after becoming ill). The pipeline failure was quickly detected (19 seconds), but the responses to it were extremely variable and showed a variety of problems. Five of 18 anesthesia professionals closed the anesthesia circuit (which preserves the existing oxygen in the circuit), but all 5 subsequently switched to ventilation with a self-inflating bag using room air or to mouth-to-tube ventilation. Five of 18 could not open the reserve oxygen cylinder because they could not locate the tank wrench attached to the machine (it tended to rest between two gas cylinders). Several teams had trouble mounting a new oxygen tank on the anesthesia machine; problems with the gasket disk were frequent. The individuals did not appear to have a well-formulated plan for managing this event, and they did not optimally coordinate their actions with their assistants or with the other OR personnel.

A study by Byrne and Jones looked at differences in the performance of experienced and less experienced anesthesia professionals.[356] Using a self-developed patient simulator system, these investigators measured time to treatment and deficiencies in patient care in 180 simulations. The results showed significant differences only between the first and second year. As seen in other studies,[365] significant errors occurred at all levels of experience, and most of the anesthesia professionals deviated

from established guidelines. These studies underscore the importance of recurrent training for experienced anesthesia professionals and the truism that experience is not a substitute for excellence.

The reader is referred to Chapter 8 for discussion of newer studies with the use of patient simulators and performance assessment as such.[¶]

Indirect Observation of Anesthesia Professionals Involved in Difficult Cases

An unusual approach involving indirect observation of actual cases was used by Cook and colleagues at the Ohio State University in Columbus.[295] Rather than collecting data on the case itself, these investigators transcribed the discussions of interesting cases occurring at a weekly quality assurance conference. These investigators argued that this approach allowed them to apply a "neutral observer criterion" to the behavior of the anesthesia professional. The investigators acknowledged the risks of hindsight bias and selection bias with this methodology, but they suggested that their technique provided a unique window on human performance issues.

Fifty-seven cases were analyzed, 21 of which had a full cognitive analysis in the final report. From the presentation and discussion of a case, the investigators classified evolution of the events into 1 of 5 categories: acute incident, going-sour incident, inevitable outcome incident, difficult-airway incident, and no-incident incident. For each case, the cognitive analysis was "based on using knowledge about the cognitive demands of the task domain and data about practitioner activities to analyze the practitioner's information-processing strategies and goals, given the resources and constraints of the situation." The investigators postulated a cognitive cycle as a component of data-driven activation of knowledge and knowledge-driven observation and action.

Cook and colleagues called attention to several issues that surfaced in their cognitive analysis of these cases, including the following[295]:

1. Multiple themes. Many cases involved several lines of concern simultaneously, each of which could have interacted with another (e.g., tight coupling). Each theme had multiple means available to deal with it. Maintaining "situation awareness" was important. The multiple themes sometimes generated competing or conflicting goals. Adaptive planning (as described in the section on abstract task analysis) was sometimes required.
2. Unusual situations. The greatest expertise was seen with infrequent or unusual situations rather than with typical situations.
3. Allocation of attention. Allocation of attention to relevant stimuli or to the most important "theme" was an important issue. The attentional shifts were not always well supported by existing alarm and display technologies.
4. Cognitive workload. Anesthesia professionals attempted to reduce their cognitive workload whenever possible.
5. Team interaction. Cooperative work, team interaction, and communications issues were problems in several cases. These stemmed from both individual and organizational failures to coordinate information and efforts from different organizational components (e.g., ICU and OR, surgeons and anesthesiologists).

[¶]References 17, 25, 160, 166, 358, 365, 415-419.

Direct Observation of Anesthesia Professionals

A team of cognitive scientists and anesthesiologists at the University of Toronto conducted direct observations of anesthesiologists and obtained verbal "think aloud" protocols during actual case management.[266] The group in Tübingen also performed direct observations for their task analysis studies.[287,377] Devitt and co-workers performed a study to assess the validity of performance assessment during simulated scenarios.[24]

Video Analysis of Actual Trauma Resuscitation and Anesthesia

Mackenzie and Xiao and their colleagues pioneered in the analysis of actual clinical care of anesthesia professionals captured on videotape, with a focus on trauma resuscitation and anesthesia for trauma patients at the Maryland Shock Trauma Unit in Baltimore.[420-424] Their sophisticated recording system captures audio, video, and vital signs data and requires only that the clinicians insert a videotape to start the whole system.[425] Analysis of these cases has revealed inadequacies in the availability and arrangement of monitoring equipment, as well as nonexistent or ambiguous communication. Meanwhile, a few groups around the world have started to use video for task analysis and assessment of performance for research and training, which are not detailed here.[168,214,311,349,381,426-432]

Problems faced by all investigators are the lack of an accepted standard for objective or subjective evaluation of anesthesia professional performance and the absence of an agreed-on methodology for analyzing and describing anesthesia professional performance. Several of the previously mentioned groups are working on methodologies for evaluating technical and behavioral aspects of performance.[#] Measurement of complex performance is a difficult problem, and it is likely to be some time until a metric for assessment of performance is well established.

[#]References 25, 89, 91, 160, 161, 235, 275, 286, 349, 360, 371, 377.

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APPENDIX 7-1 *Links and Useful Resources*

Links

- Links to patient safety and crisis resource management resources
  - National Patient Safety Foundation: http://www.npsf.org/
  - Veterans Affairs patient safety information: www.patientsafety.va.gov
  - The Joint Commission: http://www.jointcommission.org/
  - United Kingdom National Health Service National Patient Safety Agency: www.npsa.nhs.uk
  - Veterans Affairs Palo Alto Health Care System–Stanford School of Medicine simulator: http://anesthesia.stanford.edu/VASimulator
  - World Health Organization (WHO) Patient Safety Curriculum: http://www.who.int/patientsafety/education/curriculum/en/
  - Patient Safety Education Programme: http://www.patient-safetyeducationproject.org/index.php
  - Australian patient safety site: http://www.safetyandquality.gov.au/our-work/national-perspectives/australian-safety-and-quality-framework-for-health-care/
- Links to different incident reporting systems
  - The American Society of Anesthesiologists reporting system: https://www.aqihq.org/airs/airsIntro.aspx
  - United Kingdom National Health Service National Patient Safety Agency reporting system: http://www.nrls.npsa.nhs.uk/report-a-patient-safety-incident/
  - Patient Safety Reporting System: http://psrs.arc.nasa.gov/
  - Pronovost's intensive care unit safety reporting system[85]

Valuable Sources

- WHO "World Alliance for Patient Safety"
  - *WHO Draft Guidelines for Adverse Event Reporting and Learning Systems—From Information to Action*
  - www.who.int/patientsafety/events/05/Reporting_Guidelines.pdf
- U.S. Department of Veterans Affairs Patient Safety Reporting System
  - http://www.psrs.arc.nasa.gov
- U.S. Patient Safety and Quality Improvement Act
  - Agency for Healthcare Research and Quality patient safety organization information: http://www.pso.ahrq.gov/psos/overview.htm
- Root-cause analysis tools
  - http://www.patientsafety.va.gov/professionals/onthejob/rca.asp
  - http://www.nrls.npsa.nhs.uk/resources/collections/root-cause-analysis/
- Failure modes and effects analysis tools
  - http://www.patientsafety.va.gov/professionals/onthejob/HFMEA.asp

APPENDIX 7-2 *The Joint Commission Sentinel Event Alert*[*]
HEALTH CARE WORKER FATIGUE AND PATIENT SAFETY

The link between health care worker fatigue and adverse events is well documented, with a substantial number of studies indicating that the practice of extended work hours contributes to high levels of worker fatigue and reduced productivity. These studies and others show that fatigue increases the risk of adverse events, compromises patient safety, and increases risk to personal safety and well-being.[1-5] While it is acknowledged that many factors contribute to fatigue, including but not limited to insufficient staffing and excessive workloads, the purpose of this Sentinel Event Alert is to address the effects and risks of an extended work day and of cumulative days of extended work hours.

The Impact of Fatigue

Fatigue resulting from an inadequate amount of sleep or insufficient quality of sleep over an extended period can lead to a number of problems, including:

- Lapses in attention and inability to stay focused
- Reduced motivation
- Compromised problem solving
- Confusion
- Irritability
- Memory lapses
- Impaired communication
- Slowed or faulty information processing and judgment
- Diminished reaction time
- Indifference and loss of empathy[6]

Contributing Factors to Fatigue and Risks to Patients

Shift length and work schedules have a significant effect on health care providers' quantity and quality of sleep and, consequently, on their job performance, as well as on the safety of their patients and their individual safety. This fact has been borne out in numerous studies. Findings from a groundbreaking 2004 study of 393 nurses over more than 5300 shifts—the first in a series of studies of nurse fatigue and patient safety—showed that nurses who work shifts of 12.5 hours or longer are 3 times more likely to make an error in patient care.[7] Additional studies showed that longer shift length increases the risk of errors and close calls and is associated with decreased vigilance,[7] and that nurses suffer higher rates of occupational injury when working shifts in excess of 12 hours.[8] Still, while the dangers of extended work hours (more than 12 hours) are well known, the health care industry has been slow to adopt changes, particularly with regard to nursing.

"An overwhelming number of studies keep saying the same thing—once you pass a certain point, the risk of mistakes increases significantly," says Ann Rogers, PhD, RN, FAAN, a nationally renowned sleep medicine expert with Emory University's Nell Hodgson Woodruff School of Nursing. "We have been slow to accept that we have physical limits and biologically we are not built to do the things we are trying to do."

Resident physician duty hours have also been the focus of many studies. While the Accreditation Council for Graduate Medical Education (ACGME) implemented duty hour restrictions in July 2003 that limited work shifts to a maximum of 30 hours and no more than 80 hours of work per week, numerous subsequent studies indicated that risks to patient safety and personal injury remain high for resident physicians working recurrent 24-hour shifts.[9,10] In September 2010, the ACGME published the final version of new standards, which became effective in July 2011 (www.acgme-2010standards.org).

An article in the November 2007 *Joint Commission Journal on Quality and Patient Safety* concluded that evidence strongly suggests that extended-duration work shifts significantly increase fatigue and impair performance and safety.[11] The article reported that residents who work traditional schedules with recurrent 24-hour shifts:

- Make 36% more serious preventable adverse events than individuals who work no more than 16 consecutive hours.[12]
- Make five times as many serious diagnostic errors.[12]
- Have twice as many on-the-job attentional failures at night.[13]
- Experience 61% more needlestick and other sharp injuries after their twentieth consecutive hour of work.[14]
- Experience a 1.5- to 2-standard deviation deterioration in performance relative to baseline rested performance on both clinical and nonclinical tasks.[15]
- Report making 300% more fatigue-related preventable adverse events that led to a patient's death.[16]

A subsequent 2009 study also revealed an increased rate of complications among post-nighttime surgical procedures performed by attending physicians who had slept less than 6 hours.[17]

"We have a culture of working long hours, and the impact of fatigue has not been a part of our consciousness," says Christopher P. Landrigan, MD, MPH, director of the Sleep and Patient Safety Program, Brigham and Women's Hospital. The author of several research studies exploring the effects of provider sleep deprivation on patient and provider safety, Dr. Landrigan stresses the importance of reduced work hours for all health care workers and the need for widespread education of health care providers to recognize their limits. "Most are unaware of sleep and circadian biology and the degree that it affects performance. And, most do not realize how much research supports the need to make changes."[18,19]

Actions Suggested by The Joint Commission

There are some evidence-based actions that health care organizations can take to help mitigate the risks of fatigue that result from extended work hours—and, therefore, protect patients from preventable adverse outcomes.

For all organizations:

1. Assess your organization for fatigue-related risks. This includes an assessment of off-shift hours and consecutive shift work and a review of staffing and other relevant policies to ensure they address extended work shifts and hours.
2. Since patient hand-offs are a time of high-risk—especially for fatigued staff—assess your organization's hand-off processes and procedures to ensure that they adequately protect patients.[20]
3. Invite staff input into designing work schedules to minimize the potential for fatigue.

* From The Joint Commission: *Sentinel Event Alert,* Issue 48, December 14, 2011.

Published for Joint Commission accredited organizations and interested health care professionals, *Sentinel Event Alert* identifies specific types of sentinel events, describes their common underlying causes, and suggests steps to prevent occurrences in the future.

Accredited organizations should consider information in an Alert when designing or redesigning relevant processes and consider implementing relevant suggestions contained in the Alert or reasonable alternatives.

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The Patient Safety Advisory Group informs The Joint Commission on patient safety issues and, with other sources, advises on topics and content for Sentinel Event Alert. Members: James P. Bagian, MD, PE (chair); Michael Cohen, RPh, MS, ScD (vice chair); Jane H. Barnsteiner, RN, PhD, FAAN; Jim B. Battles, PhD; William H. Beeson, MD; Patrick J. Brennan, MD; Martin H. Diamond, FACHE; Cindy Dougherty, RN, CPHQ; Frank Federico, B.S., RPh; Steven S. Fountain, MD; Suzanne Graham, RN, PhD; Jerril W. Green, MD; Peter Gross, MD; Carol Haraden, PhD; Martin J. Hatlie, Esq; Jennifer Jackson, BSN, JD; Paul Kelley, CBET; Henri R. Manasse, Jr, PhD, ScD; Jane McCaffrey, MHSA, DFASHRM; Mark W. Milner, RN, MBA, CPHQ, FACHE; Jeanine Arden Ornt, JD; Grena Porto, RN, MS, ARM, CPHRM; Matthew Scanlon, MD; Carl A. Sirio, MD; Ronni P. Solomon, JD; Dana Swenson, PE, MBA; Susan M. West, RN.

APPENDIX 7-2 ***The Joint Commission Sentinel Event Alert*** *(Continued)*
HEALTH CARE WORKER FATIGUE AND PATIENT SAFETY

4. Create and implement a fatigue management plan that includes scientific strategies for fighting fatigue. These strategies can include: engaging in conversations with others (not just listening and nodding); doing something that involves physical action (even if it is just stretching); strategic caffeine consumption (don't use caffeine when you're already alert, and avoid caffeine near bedtime); taking short naps (less than 45 minutes).[21,22] These strategies are derived from studies conducted by the National Aeronautics and Space Administration (NASA) that state that people can maximize their success by trying different combinations of countermeasures to find what works for them. The NASA studies stress that the only way to counteract the severe consequences of sleepiness is to sleep.[21] Strategies for determining shift durations and using caffeine to combat fatigue can be found in Chapter 40 of *Patient Safety and Quality: An Evidence-Based Handbook for Nurses.*[23]
5. Educate staff about sleep hygiene and the effects of fatigue on patient safety. Sleep hygiene includes getting enough sleep and taking naps, practicing good sleep habits (for example, engaging in a relaxing presleep routine, such as yoga or reading), and avoiding food, alcohol, or stimulants (such as caffeine) that can impact sleep.[21,22]

Safety culture (for all organizations):

6. Provide opportunities for staff to express concerns about fatigue. Support staff when appropriate concerns about fatigue are raised, and take action to address those concerns.
7. Encourage teamwork as a strategy to support staff members who work extended work shifts or hours and to protect patients from potential harm.[20] For example, use a system of independent second checks for critical tasks or complex patients.
8. Consider fatigue as a potentially contributing factor when reviewing all adverse events.

For organizations with a current policy that allows for sleep breaks for staff defined as essential by the organization:

9. Assess the environment provided for sleep breaks to ensure that it fully protects sleep. Fully protecting sleep requires the provision of basic measures to ensure good quality sleep, including providing uninterrupted coverage of all responsibilities (including carrying pagers and phones, and coverage of both admissions and all continuing care by another provider) and providing a cool, dark, quiet, comfortable room and, if necessary, use of eye mask and ear plugs.

See relevant Joint Commission requirements: LD.01.03.01 element of performance 5, LD.03.06.01 EP 3, LD.04.01.01 EP 2, LD.04.04.05 EP 13, PI.02.01.01 EPs 12-14, (hospital and long-term care); NR.02.01.01 EP 1-6, NR.02.02.01 EP 1-4, (hospital).

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Chapter 8

Patient Simulation

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Key Points

- Simulators and the use of simulation have become integral parts of medical education, training, and research. The pace of developments and applications is fast, and the results are promising.
- The different types of simulators are either primarily computer screen–based simulators (microsimulators) or mannequin-based simulators. Mannequin-based simulators can be divided into script-based and model-based simulators.
- The development of mobile and less expensive simulator models allowed for substantial expansion of simulator training to areas and locales where this training could not be afforded previously. The greatest obstacles to providing simulation training are not the simulator hardware but rather are (1) obtaining access to the learner population for the requisite time and (2) providing appropriately trained and skilled instructors to prepare, conduct, and evaluate the simulation sessions.
- The anesthesia crisis resource management (ACRM) course model with its ACRM key points (see also Chapter 7) is popular worldwide for human factor–based simulation training in anesthesia. Curricula should use scenarios that are tailored to the stated teaching goals, rather than focusing solely on achieving maximum "realism."
- Simulation training has been adapted by many other fields outside anesthesia (e.g., emergency medicine, neonatal care, and intensive care, as well as for medical and nursing students).
- Simulation has proved valuable in research to study human factors and failure modes during anesthesia care, in the development of new treatment concepts (e.g., checklist use and telemedicine), and in the support of bioengineering system development (e.g., device beta-testing, educating the manufacturers' workforce).
- Research continues on the use of simulation for performance assessment.
- Assessment of nontechnical skills (or behavioral markers) has evolved considerably and can be accomplished with a reliability that matches that of many other subjective judgments in patient care. Systems for rating nontechnical skills have been introduced and tested in anesthesia and other fields
- The most important component of high-fidelity simulation training is the self-reflective (often video-assisted) debriefing session after the clinical scenario. The quality of debriefing strongly depends on the skills and experience of the instructor. Most methods of debriefing stress open-ended questions and inquiry to trigger insightful analysis by the learner group
- A simulator is just a tool to accomplish learning objectives that are difficult to achieve during real patient care. The design of curricula and scenarios and the ability of instructors to create appropriate learning situations are the factors that determine whether the simulation tool is effective in achieving the relevant goals.

How can clinicians experience the difficulties of patient care without putting patients at undue risk? How can we assess the abilities of clinicians as individuals and teams when each patient is unique? These questions have challenged medicine for years. These and related questions have begun to be answered in health care by the application of approaches relatively new to medicine but borrowed from years of successful service in other industries facing similar problems. These approaches focus on *simulation,* a technique well known in the military, aviation, space flight, and nuclear power industries.

Simulation refers to the artificial replication of sufficient elements of a real-world domain to achieve a stated goal. The goals can include understanding the domain better, training personnel to deal with the domain, or testing the capacity of personnel to work in the domain.

The *fidelity* of a simulation refers to how closely it replicates the domain and is determined by the number of elements that are replicated and the discrepancy between each element and the real world. The fidelity required depends on the stated goals. Some goals can be achieved with minimal fidelity, whereas others require very high fidelity.

Simulation has probably been a part of human activity since prehistoric times. Rehearsal for hunting activities and warfare was most likely an occasion for simulating the behavior of prey or enemy warriors. Technologic simulation probably dates back to the dawn of technology itself. Good and Gravenstein pointed to the medieval quintain as a technologic device that crudely simulated the behavior of an opponent during sword fighting.[1] If the swordsman did not duck at the appropriate time after striking a blow, he would be hit by a component of the quintain. In modern times, preparation for warfare has been an equally powerful spur to the development of simulation technologies, especially for aviation, shipping, and the operation of armored vehicles. These technologies have been adopted by their civilian counterparts, but they have attained their most extensive use in commercial aviation.

SIMULATION IN AVIATION

Although some aircraft simulators were built between 1910 and 1927, none of them could provide the proper feel of the aircraft because they could not dynamically reproduce its behavior. In 1930, Link filed a patent for a pneumatically driven aircraft simulator. The Link Trainer was a standard for flight training before World War II, but the war accelerated its use and the further development of flight simulators. In the 1950s, electronic controls replaced pneumatic ones through analog, digital, and hybrid computers. The aircraft simulator achieved its modern form in the late 1960s, but it has been continuously refined. Aviation simulators are so realistic now that pilots with experience flying one aircraft are routinely certified to fly totally new or different aircraft, even if they have never flown the actual aircraft without passengers on board. Similar stories of the development of simulators can be told for numerous other industries.

USES OF SIMULATORS

Although simulators originally were used to provide basic instruction on the operation of aircraft controls, the variety of uses of simulators in general has expanded greatly. Box 8-1 lists possible uses of simulators in all types of complex work situations. Simulation is a powerful generic tool for dealing with human performance issues (e.g., training, testing, and research) (see Chapter 7), for investigating human-machine interactions, and for the design and validation of equipment. As described later in this chapter, each of these uses is potentially relevant to anesthesiology. A few books are devoted solely to the topic of simulation and its use in and outside of anesthesia.[2-4]

BOX 8-1 ***Use of Simulators in Complex Work Environments***

- Team training, as human factor or crisis resource management training
- Training in dynamic plant control
- Training in diagnostic skills
- Dynamic mockup for design evaluation
- Test bed for checking operating instructions
- Environment in which task analysis can be conducted (e.g., on diagnostic strategies)
- Test bed for new applications (e.g., telemedicine tools such as the Guardian Angel System)
- Source of data on human errors relevant to risk and reliability assessment
- Vehicle for (compulsory) testing/assessment and recertification of operators

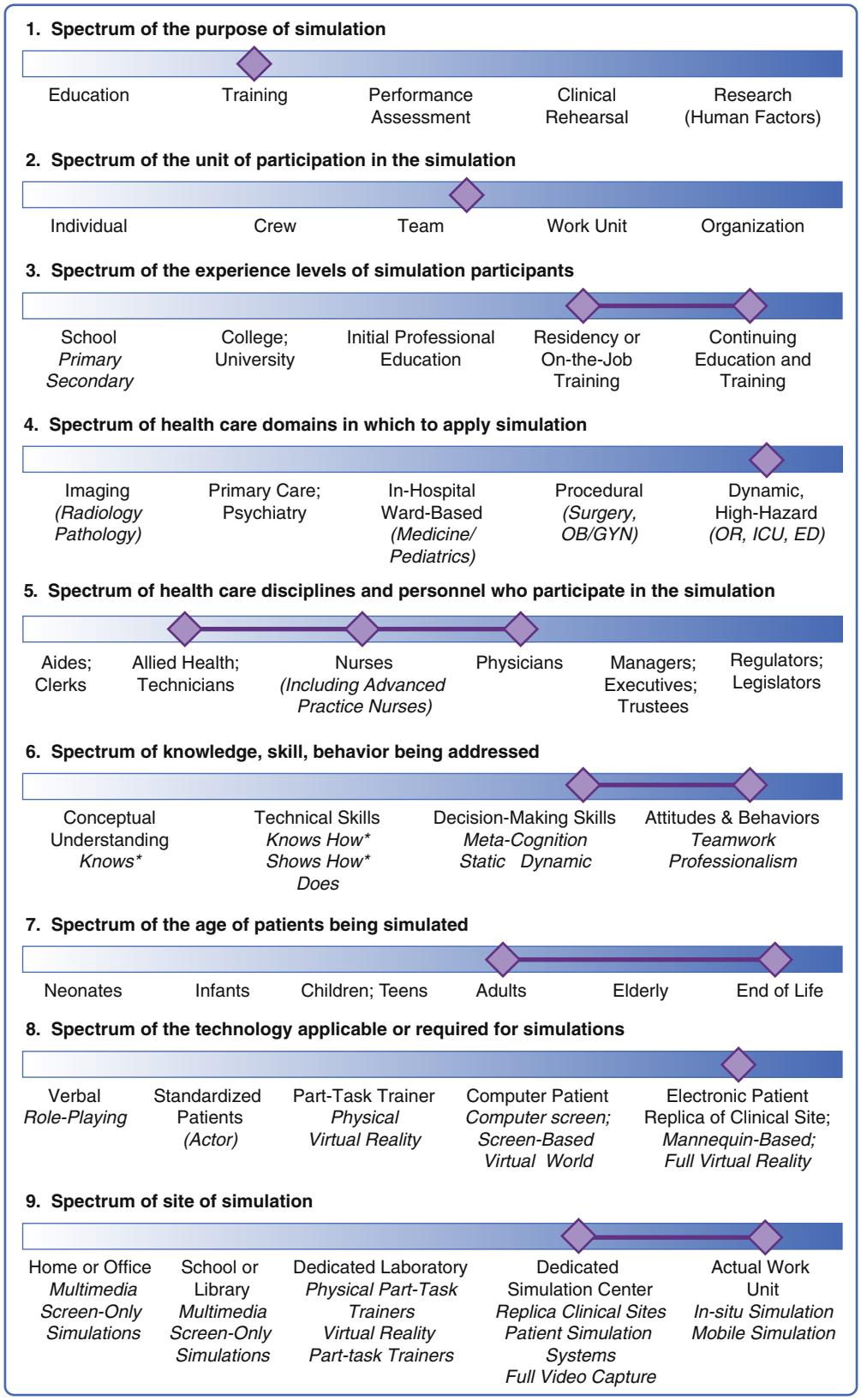
Modified from Singleton WT: *The mind at work.* Cambridge, 1989, Cambridge University Press.

TWELVE DIMENSIONS OF SIMULATION

Current and future applications of simulation can be categorized by 12 dimensions, each of which represents a different attribute of simulation (Fig. 8-1).[5] Some dimensions have a clear gradient and direction, whereas others have only categoric differences. The total number of unique combinations across all the dimensions is very large (on the order of 4^{12} to 5^{12}—4 million to 48 million). Some combinations overlap strongly with others, and some are inappropriate or irrelevant, so the actual number of meaningful combinations is much lower. Nonetheless, although the demonstrated applications of simulation in health care have been quite diverse, the range of possible applications (a large number, although quite a bit smaller than millions) has by no means been fully examined.

DIMENSION 1: PURPOSE AND AIMS OF THE SIMULATION ACTIVITY

The most obvious application of simulation is to improve the education and training of clinicians, but other purposes also are important. As used in this chapter, *education* emphasizes conceptual knowledge, basic skills, and an introduction to work practices. *Training* emphasizes the actual tasks and work to be performed. Simulation can be used to *assess performance* and competence of individual clinicians and teams, both for low-stakes or formative testing and (to a lesser degree) for high-stakes certification testing.[6,7] Simulation *rehearsals* are now being explored as adjuncts to actual clinical practice; for example, surgeons or an entire operative team can rehearse an unusually complex operation in advance by using a simulation of the specific patient.[8-10] Simulators can be powerful tools for research and evaluation with regard to *organizational practices* (patient care protocols) and for the *investigation of human factors* (e.g., of performance-shaping factors, such as fatigue,[11] or of the user interface and operation of medical equipment in high-hazard clinical settings[12]). Simulation-based empiric tests of the usability of clinical equipment already have been used in designing equipment that is currently for



A

Figure 8-1. The 12 dimensions of simulation applications. **A,** Dimensions 1 to 9. *These terms are used according to Miller's pyramid of learning.

Continued

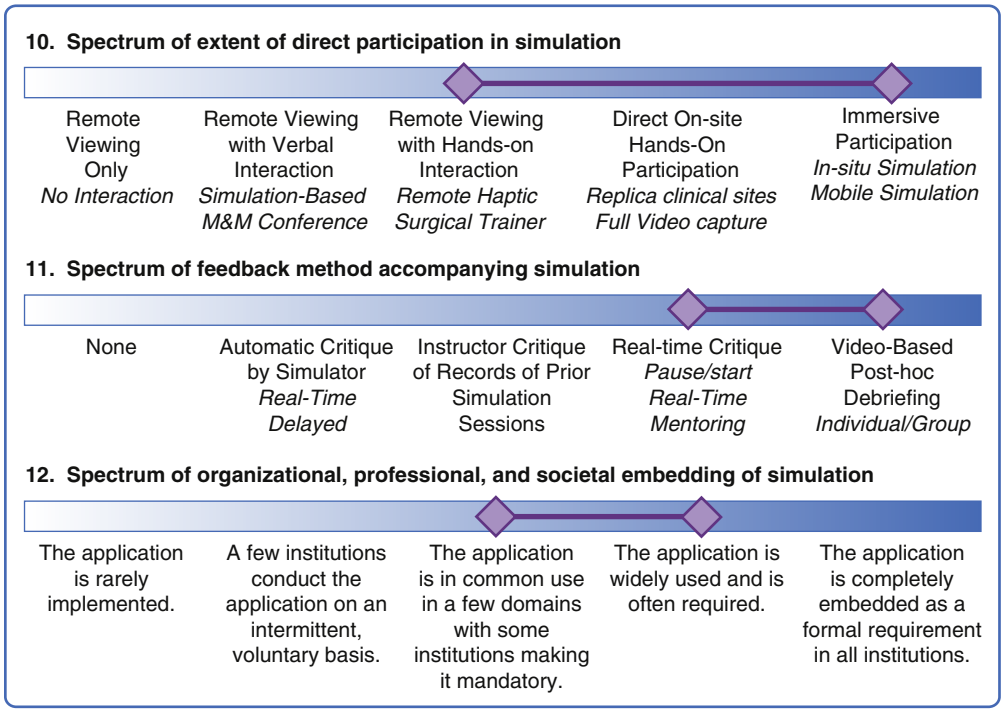


Figure 8-1, cont'd B, Dimensions 10 to 12. Any particular application can be represented as a point or range on each spectrum (shown by *diamonds*). This figure illustrates a specific application—multidisciplinary crisis resource management (CRM)–oriented decision making and teamwork training for adult intensive care unit (ICU) personnel. *ED,* Emergency department; *M&M,* morbidity and mortality; *OB/GYN,* obstetrics and gynecology; *OR,* operating room.

sale; ultimately, such practices may be required by regulatory agencies before approval of new devices.

Simulation can be a bottom-up tool for changing the culture of health care concerning patient safety. First, it allows hands-on training of junior and senior clinicians in practices that enact the desired culture of safety.[13] Simulation also can be a rallying point about culture change and patient safety that can bring together experienced clinicians from various disciplines and domains (who may be captured because the simulations are clinically challenging), along with health care administrators, risk managers, and experts on human factors, organizational behavior, or institutional change.

DIMENSION 2: UNIT OF PARTICIPATION IN THE SIMULATION

Many simulation applications are targeted at individuals. These may be especially useful for teaching knowledge and basic skills or for practice on specific psychomotor tasks. As in other high-hazard industries, individual skill is a fundamental building block, but a considerable emphasis is applied at higher organizational levels, in various forms of teamwork and interpersonal relations (often summarized under the rubric of *crisis resource management* (CRM) adapted from aviation cockpit resource management.) (For more on human factors and CRM concepts, see Chapter 7.)[14,15] CRM is based on empiric findings that individual performance is not sufficient to achieve optimal safety.[16] Team training may be addressed first to crews (also known as *single-discipline teams*), consisting of multiple individuals from a single discipline, and then to teams (or *multidisciplinary teams*).[17] Addressing teamwork in the single-discipline approach that trains crews to work in teams, in contrast to the combined team training of multiple disciplines together, has advantages and disadvantages.[18] For maximal benefit, these approaches are used in a complementary fashion.

Teams exist in actual work units in an organization (e.g., a specific intensive care unit [ICU]), each of which is its own target for training. Growing interest and experience have also been shown in applying simulation to nonclinical personnel and work units in health care organizations (e.g., to managers or executives)[19] and to organizations as a whole (e.g., entire hospitals or networks).

DIMENSION 3: EXPERIENCE LEVEL OF SIMULATION PARTICIPANTS

Simulation can be applied along the entire continuum of education of clinical personnel and the public at large. It can be used with early learners, such as schoolchildren, or with lay adults to facilitate bioscience instruction, to interest individuals in biomedical careers, or to explain health care issues and practices. The major roles of simulation have been, and will continue to be, to educate, train, and provide rehearsal for individuals actually involved in the delivery of health care. Simulation is relevant from the earliest level of vocational or professional education (students) and during apprenticeship training (interns and residents), and it is increasingly

used for experienced personnel undergoing periodic refresher training. Simulation can be applied regularly to practicing clinicians (as individuals, teams, or organizations) regardless of their seniority,[20,21] thus providing an integrated accumulation of experiences that should have long-term synergism.

DIMENSION 4: HEALTH CARE DOMAIN IN WHICH THE SIMULATION IS APPLIED

Simulation techniques can be applied across nearly all health care domains. Although much of the attention on simulation has focused on technical and procedural skills applicable in surgery,[11,18,19,21] obstetrics,[22,23] invasive cardiology,[24,25] and other related fields, another bastion of simulation has been recreating whole patients for dynamic domains involving high-hazard and invasive intervention, such as anesthesia,[26,27] critical care,[28,29] and emergency medicine.[30-33] Immersive techniques can be used in imaging-intensive domains, such as radiology and pathology, and interactive simulations are relevant in the interventional sides of such arenas.[34] In many domains, simulation techniques have been useful for addressing nontechnical skills and professionalism issues, such as communicating with patients and co-workers, or addressing issues such as ethics or end-of-life care.

DIMENSION 5: HEALTH CARE DISCIPLINES OF PERSONNEL PARTICIPATING IN THE SIMULATION

Simulation is applicable to all disciplines of health care, not only to physicians. In anesthesiology, simulation has been applied to anesthesiologists, certified registered nurse anesthetists, and anesthesia technicians. Simulation is not limited to clinical personnel. It also may be directed at managers, executives, hospital trustees, regulators, and legislators. For these groups, simulation can convey the complexities of clinical work, and it can be used to exercise and probe the organizational practices of clinical institutions at multiple levels.

DIMENSION 6: TYPE OF KNOWLEDGE, SKILL, ATTITUDES, OR BEHAVIOR ADDRESSED IN SIMULATION

Simulations can be used to help learners acquire new knowledge and to understand conceptual relations and dynamics better. Physiologic simulations allow students to watch cardiovascular and respiratory functions unfold over time and respond to interventions—in essence bringing life textbooks, diagrams, and graphs. The next step on the spectrum is acquisition of skills to accompany knowledge. Some skills follow immediately from conceptual knowledge (e.g., cardiac auscultation), whereas others involve intricate and complex psychomotor activities (e.g., catheter placement or basic surgical skills). Isolated skills must be assembled into a new layer of clinical practices. An understanding of the concepts of general surgery cannot be combined only with basic techniques of dissecting and suturing or manipulation of instruments to create a capable laparoscopic surgeon. Basic skills must be integrated into actual clinical techniques. Simulation may have considerable power in this process, especially because it can readily provide experience with even uncommon anatomic or clinical presentations. In the current health care system, for most invasive procedures, *novices at a task typically first perform the task on a real patient,* albeit under some degree of supervision. These novices climb the learning curve and work on patients while under varying levels of guidance. Simulation offers the possibility of having novices practice extensively before they begin supervised work on real patients in apprenticeship-like situations.

In this way and others, simulation is applicable to clinicians throughout their careers to support lifelong learning. It can be used to refresh skills for procedures that are not performed often. Knowledge, skills, and practices honed as individuals must be linked into effective teamwork in diverse clinical teams, which must operate safely in work units and larger organizations.[35-37] Perpetual rehearsal of responses to challenging events is needed because the team or organization must be practiced in handling these responses as a coherent unit.

DIMENSION 7: AGE OF THE PATIENT BEING SIMULATED

Simulation is applicable to nearly every type and age of patient, literally from cradle to grave. Simulation may be particularly useful for pediatric patients and clinical activities because neonates and infants have smaller physiologic reserves than do most adults.[38,39] Fully interactive neonatal and pediatric patient simulators are now available. Simulation also addresses issues of older adults and end-of-life issues for every age.

DIMENSION 8: TECHNOLOGY APPLICABLE OR REQUIRED FOR SIMULATIONS

To accomplish these goals, various technologies (including no technology) are relevant for simulation. Verbal simulations ("what if" discussions), paper and pencil exercises, and experiences with actors playing standardized patients[39-41] require no technology, but they can effectively evoke or recreate challenging clinical situations. Similarly, very low technology—even pieces of fruit or simple dolls—can be used for training in some manual tasks. Certain aspects of complex tasks and experiences can be recreated successfully with little technology. Some education and training on teamwork can be accomplished with role playing, analysis of videos, or drills with simple mannequins.[42]

Ultimately, learning and practicing complex manual skills (e.g., surgery, cardiac catheterization) or practicing the dynamic management of life-threatening clinical situations that include risky or noxious interventions (e.g., intubation or defibrillation) can be fully accomplished only using either animals—for reasons of cost and issues of animal rights, this approach is becoming very difficult—or technology to recreate the patient and the clinical environment. The different types of simulation technologies relevant to anesthesiology are discussed later in this chapter.

DIMENSION 9: SITE OF SIMULATION PARTICIPATION

Some types of simulation—those that use videos, computer programs, or the Web—can be conducted in the privacy of the learner's home or office using his or her own equipment. More advanced screen-based simulators may need more powerful computer facilities available in a medical library or learning center. Part-task trainers and virtual reality simulators are usually fielded in a dedicated skills laboratory. Mannequin-based simulation also can be used in a skills laboratory, although the more complex recreations of actual clinical tasks require either a dedicated patient simulation center with fully equipped replicas of clinical spaces or the ability to bring the simulator into an actual work setting (in situ simulation). Performing clinical simulations in situ, as opposed to in a dedicated center, has advantages and disadvantages. Using the actual site allows training of the entire unit with all its personnel, procedures, and equipment. The availability of actual clinical sites is limited, and the simulation activity may distract from real patient care. The dedicated simulation center is a more controlled and available environment, which allows more comprehensive recording of sessions and imposes no distraction from real activities. For large-scale simulations (e.g., disaster drills), the entire organization becomes the site of training.

Video conferencing and advanced networking may allow even advanced types of simulation to be conducted remotely (see dimension 10). The collaborative use of virtual reality surgical simulators in real time already has occurred, even in locations separated by thousands of miles (see later for more on the site of the simulator).

DIMENSION 10: EXTENT OF DIRECT PARTICIPATION IN SIMULATION

Most simulations—even screen-based simulators or part-task trainers—were initially envisioned as highly interactive activities with significant direct hands-on participation virtual on-site setting. Not all learning requires direct participation, however. Some learning can occur merely by viewing a simulation involving others because the viewer can readily imagine being in the shoes of the participants. A further step is to involve remote viewers either in the simulation itself or in debriefings about what transpired. Several centers have been using videoconferencing to conduct simulation-based exercises, including morbidity and mortality conferences.[43] Because the simulator can be paused, restarted, or otherwise controlled, the remote audience can readily obtain more information from the on-site participants, debate the proper course of action, and discuss with those in the simulator how best to proceed.

DIMENSION 11: FEEDBACK METHOD ACCOMPANYING SIMULATION

One can learn a great deal just from simulation experiences themselves, without any additional feedback. For many simulations, specific feedback is provided to maximize learning. On screen-based simulators or virtual reality systems, the simulator itself can provide feedback about the participant's actions or decisions,[44] particularly for manual tasks for which clear metrics of performance are readily delineated.[45,46] More commonly, human instructors provide feedback. This can be as simple as having the instructor review records of previous sessions that the learner has completed alone. For many target populations and applications, an instructor provides real-time guidance and feedback to participants while the simulation is ongoing. The ability to start, pause, and restart the simulation can be valuable. For the most complex uses of simulation, especially when training experienced personnel, the typical form of feedback is a detailed postsimulation debriefing session, often using audio-video recordings of the scenario. Waiting until after the scenario is finished allows experienced personnel to apply their collective skills without interruption and then allows them to see and discuss the advantages and disadvantages of their behaviors, decisions, and actions.

DIMENSION 12: ORGANIZATIONAL, PROFESSIONAL, AND SOCIETAL EMBEDDING OF SIMULATION

The final important dimension is the degree to which the simulation application is embedded into an organization or industry.[47] Being highly embedded may mean that the simulation is a formal requirement of the institution or is mandated by the governmental regulator. Another aspect of embedding may be that—for early learners—the initial (steep) part of the learning curve is required to occur in a simulation setting before the learners are allowed to work on real patients under supervision. In addition, complete embedding of simulation into the workplace means that simulation training is a normal part of the work schedule, rather than being an add-on activity attended in the spare time of clinicians.

CONCEPTUAL ISSUES ABOUT PATIENT SIMULATION

"The key is the program, not the hardware," was a truth about simulation learned early in aviation. Using simulators in a goal-oriented way is at least as much about the conceptual aspects of the technique as it is about the technology of the simulation devices. An understanding of the conceptual and theoretical aspects of the use of simulation techniques can be helpful for determining the right applications of the technique and the important matchups that must be made in the design and conduct of simulation exercises to obtain the best results. When used most effectively, simulation can be—to borrow a line from the band U2—"even better than the real thing."[21] The concepts discussed in this section concern the nature of realism and reality as they apply to simulation and the way that these issues relate to the goals of simulation endeavors to generate a complex social undertaking. The ideas and concepts presented here are largely contributed by Peter Dieckmann and his adaptation of broader psychological concepts to simulation in medicine.

REALITY AND REALISM OF SIMULATION

Unless we are dreaming about it or we are an unrepentant solipsist, a simulation exercise is always real (it is actually happening), but it may or may not be a realistic replication of the reality that is the target of the exercise. Realism addresses the question of how closely a replication of a situation resembles the target. A key distinction is between a *simulator* (a device) and a *simulation* (the exercise in which the device is used). A simulator could be indistinguishable from a real human being (e.g., an actor playing a standardized patient) and yet be used in an implausible and useless fashion. Conversely, certain kinds of realism (see later) can be evoked by simulation exercises that use very simple simulators or even no simulator at all (as in role playing, when the participants in a sense become the simulator). Merely creating a realistic simulation does not guarantee meaning or utility (e.g., learning).[18,19] A closely related aspect concerns the questions of relevance and the social character of simulation.

THREE DISTINCT DIMENSIONS FOR SIMULATION REALISM

Simulator realism and simulation realism, using a variety of terms and concepts, are subtly different and often overlapping. These include *physical fidelity* (the device replicates physical aspects of the human body), *environmental fidelity* (the simulation room looks like an operating room), *equipment fidelity* (the clinical equipment works like or is the real thing), and *psychological fidelity*[22] (the simulation evokes behaviors similar to the real situation), as well as a variety of forms of validity, such as *face validity* (looks and feels real to participants), *content validity* (the exercise covers content relevant to the target situation), *construct validity* (the simulation can replicate performance or behavior according to predefined constructs about work in real situations), and *predictive validity* (performance during a simulation exercise predicts performance in an analogous real situation).[23,24]

The results of studies trying to investigate roots and effects of simulation realism are not conclusive partly because each study may concentrate on a different aspect of this complex whole. It is simply not true that maximum "realism" is either needed or desired for every type of simulation endeavor. For some applications with some target populations, it can be highly advantageous to reduce the realism to heighten the learning experience.[25]

In 2007, we published an article attempting to clarify some issues about realism, reality, relevance, and the purposes of conducting simulations.[18] We applied the model of thinking about reality by the German psychologist Laucken to the realism of simulation.[18] Laucken described three modes of thinking—physical, semantic, and phenomenal, which were renamed physical, conceptual, and emotional and experiential modes by colleagues in Boston.[26]

Physical Mode

The *physical mode* concerns aspects of the simulation that can be measured in fundamental physical and chemical terms and dimensions (e.g., centimeters, grams, and seconds). The weight of the mannequin, the force generated during chest compressions, and the duration of a scenario all are physical aspects of the simulation reality. Existing simulator mannequins have many unrealistic physical elements despite their roughly human shape: they are made of plastic, not flesh and bone; they may have unusual mechanical noises detectable during auscultation of the chest; the "skin" does not change color. Some physical properties are not readily detectable and can be manipulated. Some clinical equipment used in mannequin-based simulation is fully functional and physically identical to the real thing, although in some cases, functional physical limitations may have been introduced for convenience or for safety.[23] Labeled syringes may contain only water instead of opioids, or a real defibrillator may have been modified so that it does not actually deliver a shock (one manufacturer sells a "Hollywood defibrillator"). That certain physical properties and functions have been altered is not usually apparent to participants, at least without special briefings or labels.

Semantic Mode

The *semantic mode* of thinking concerns concepts and their relationships. Within the semantic mode, a simulation of hemorrhage could be described in conceptual terms as "bleeding" of flow rate x beginning at time y occurring at site z and associated with a blood pressure of b that is a decrease from the prior value of a. In this mode of thinking, it is irrelevant how the information is transmitted or represented. The same pieces of *information* could be represented using a vital signs monitor, a verbal description, or the tactile perception of decreasingly palpable pulses. The semantic *recoding* of physical objects is the cornerstone of simulation. It allows the simulation exercise to represent a real situation, and it allows water-filled syringes to be treated as if they contain a drug.

Phenomenal Mode

The *phenomenal mode* deals with the experience, including emotions and beliefs triggered by the situation. For many purposes, providing high phenomenal realism is the key goal, and the physical realism and semantic realism are merely means to this end.

RELEVANCE VERSUS REALITY

A naïve view of simulation would suggest that greater realism in all modes would lead to better achievement of the goals of simulation; this view has been criticized repeatedly.[22,27,28] Simulation is a complex social endeavor, conducted with different target populations for different purposes. The relevance of a simulation exercise concerns the match between the characteristics of the exercise and the reasons for which the exercise is conducted. Different elements of realism are emphasized or sacrificed to maximize the relevance of a simulation exercise. When training on invasive procedures, it is typical to forgo phenomenal realism and emphasize physical and semantic realism so that psychomotor skills can be the focus.

Semantic realism may be sacrificed, especially to help early learners. Situations that could become lethal (e.g., trigger cardiac arrest) very quickly may be slowed

down so that inexperienced clinicians can try to think their way out of the problem. If such a situation were allowed to evolve at its normal speed, it would transition to management of cardiac arrest before the participants could deal with the original problem. Other realism-sacrificing strategies for early learners include cognitive scaffolding, which provides various forms of assistance or cues to help these learners as they struggle with decision making and therapy selection. It is important to select which aspects of the simulation are the most relevant to reach the training goal and should be focused on in terms of optimizing their realism in the different modes.

SETTING OF THE SIMULATION EXERCISE

Simulation exercises have a purpose and are generally integrated into a larger training context (often a course or a series of exercises) that influences how these exercises are conducted, how they are perceived by participants, and what kind of effects they may have. This context has been called the *simulation setting*. The typical elements of the simulation setting are discussed next and are shown graphically in Figure 8-2.

Setting introduction (SI): The introduction delivers general information on how the exercise will be conducted, logistical information, and some of the known pitfalls of the course. Through this introduction and other components of the course, group norms are established explicitly and implicitly.

Simulator briefing (SB) or familiarization: Participants need to be familiar with the simulator and the simulated environment through explanations, demonstrations, and hands-on time. They learn how to use the simulator, what it can and cannot do, what is normal (e.g., normal breath sounds), and how they can interact with the environment (e.g., how to call for help, how to request information about the patient that is not directly available in the simulation environment). The familiarization session also is an opportunity for participants to practice the information gathering they must conduct when first entering a new work environment (e.g., for locum tenens practice).

Theory input (T): Most exercises have didactic and theory components on relevant content information. Sometimes this material is made available in advance through readings or online exercises. It may be presented before or after a simulation session. Sometimes didactic or group-work modules are put in place at different junctures of the course or series.

Breaks (B): For complex courses (e.g., anesthesia CRM [ACRM]), breaks are important for socialization among participants and with instructors. Breaks also provide a venue for informal sharing and storytelling.

Case briefing (C): In many simulation scenarios, participants receive a briefing about the upcoming case. Sometimes this is done explicitly before entering the scenario; sometimes it is embedded into a natural hand-off of the case from one clinician to another.

Simulation scenario (S): Most simulation exercises involve a scenario that posits a given clinical situation and challenges to be posed to participants. Commonly, the possible evolutions of the scenario are delineated in advance by instructors, although occasionally an intrinsically challenging situation is started and then allowed to play out naturally, depending on how the participants react.

Debriefing (D): Most scenarios are followed by some form of debriefing or feedback. In some courses, feedback is only minimal, whereas other courses have a dedicated debriefing session (as long as or longer than the scenario itself) after each scenario (see the later section on debriefing for more detail).

Ending (E): Especially for multiple-scenario courses, a separate final session may be included to end the course. This is an opportunity to summarize issues that were covered, to address questions, and to consider how best to apply the principles covered to real patient care.

Components of a course are expected to have a cumulative effect. Similarly, problems in early portions of a course (e.g., an inability to create an open learning atmosphere during the introduction) can carry over into later

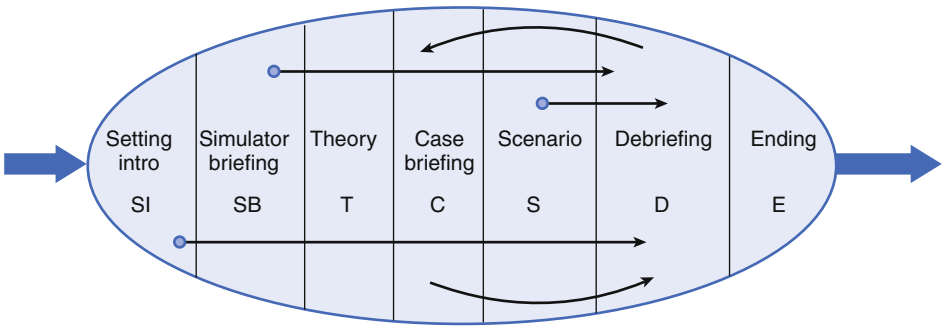


Figure 8-2. The simulator setting. A simulation course consists of different modules or different phases (e.g., setting introduction [SI], simulator familiarization, scenarios [S], debriefings [D]). This figure shows a typical flow for a course with repeated loops back from debriefing to case briefing (C) for each scenario. The different modules are interrelated, and problems arising in one module can affect other modules (*thin arrows*). For example, it could be difficult to conduct an open, constructive debriefing if the scenario were irrelevant, or the simulator briefing insufficient, and or the instructor did not succeed in creating an open atmosphere in the beginning of the course. *E,* Ending; *SB,* simulator briefing; *T,* theory. *(Courtesy P. Dieckmann.)*

phases. Inadequate familiarization briefings leave participants confused as they try to perform "clinical work" with the patient replaced by a mannequin.

SITE OF SIMULATION

Over decades of experience, many different variants of simulation have evolved. One particularly rich set of variations involves the site of simulation. The types of sites currently in use are described; the advantages and disadvantages of each are summarized in Table 8-1. Many of these variants are not mutually exclusive and can be combined in different hybrids. They are often administratively linked—a simulation group that operates a dedicated center often also conducts in situ, mobile, and moving patient simulation exercises at various times for different target populations and applications.

DEDICATED SIMULATION CENTER

One or more simulators may be used in a dedicated simulation facility, typically in rooms that can partially or fully replicate, in a relatively generic fashion, various clinical environments (e.g., operating room, ICU, labor and delivery, emergency department). (For more details see the later section on characteristics of simulation centers.)

IN SITU SIMULATION

In situ simulation is conducted in an actual clinical workplace; the simulator replaces a patient. In situ simulation is a necessity in the absence of a dedicated center, and it can be used in any clinical environment. It is especially useful for unusual workplaces that are difficult to recreate realistically in a simulation center, such as a catheterization laboratory, computed tomography scanner, ambulance, or air rescue aircraft (Figs. 8-3 to 8-9). Most in situ simulation is performed mobile as a temporary setup, but increasingly in situ simulation is established as residential simulation, in which a simulator is permanently installed in a clinical workplace (e.g., creating a simulation-specific room in the actual ICU).

MOVING THE SIMULATED PATIENT FROM ONE SITE OR CARE TO ANOTHER

The advent of completely portable and wireless simulators supports exercises in which the simulated patient can be moved from one clinical site to another (see also

TABLE 8-1 **SITE OF SIMULATION**

Site of Simulation	Explanation	Advantages	Disadvantages
Dedicated center	Fixed facility not part of an actual clinical work unit	Equipment permanently installed	Inability to recreate exact work unit, equipment, supplies of diverse target populations
		Facilitation of complex audiovisual systems	Possible difficulties for clinicians to be free to attend training
		Ease of scheduling	
		Personnel not readily available for clinical work	
		No interference with actual clinical work	
		Multipurpose use	
Temporary in situ	Actual work unit; temporary setup and takedown	Real clinical site	Difficulties in scheduling—may need site for clinical use
		Probing or training of personnel in their actual work unit and using real equipment and supplies	Interference with actual clinical work; personnel readily drafted to return to clinical work
		Ready ability for clinicians to attend in proximity to their work	Great effort of setup and takedown; minimal audiovisual system
Residential in situ	Actual work unit; permanent facility	Same as temporary in situ	High cost of creating a permanent simulation bed in a clinical work unit
			Possible distraction from real clinical work; personnel possibly drafted
Patient movement simulations	Simulated transport from site to site	The challenging clinical work of transport itself	Requirement for multiple simulation sites
		Replication of natural flow of patients and handoffs between teams	Technologic limitations of portable wireless simulators
Mobile simulation	Travel of simulation systems and instructor crew to client (or neutral) sites	Simulation expertise brought to those who cannot or wish not to invest in it themselves	Possibly high transport costs (driver, fuel, vehicle)
		For in situ use, all advantages thereof	For in situ use, all disadvantages thereof plus even greater effort for setup and takedown



Figure 8-3. In situ mobile simulation in a catheterization laboratory. The simulator is placed on the catheterization laboratory tables, surrounded by the x-ray machines, thus complicating treatment of the patient by limiting space. The vital signs monitor is connected to the real monitors, providing relevant data to the catheterization laboratory team. The simulator is controlled from the catheterization laboratory control room. Multiple mobile cameras and a scan converter for vital signs provide a live video transmission to a temporary debriefing area for the nonactive part of the training group and allow for crisis resource management–based debriefings. *(Photograph by M. Rall.)*



Figure 8-4. In situ mobile simulation in a dentist chair. The simulator was equipped with artificial teeth gum and a chalk tooth preparation to drill, thereby simulating the dentist's procedures (administering anesthetic or drilling). Then emergencies developed, and the team response was trained, focusing on crisis resource management key points and important medical aspects, including automated external defibrillator use. *(Photograph by M. Rall.)*

Chapter 90). The patient could be brought into the emergency department by ambulance; taken to a computed tomography scanner, interventional radiology, or operating room; and finally transferred to an ICU. Under what circumstances such movements are worth the effort remains to be determined.

MOBILE SIMULATION: "HAVE SIMULATOR—WILL TRAVEL"

Mobile simulation means that the simulator and the audiovisual gear are moved (made mobile) outside the originating institution for purposes of the simulation event.



Figure 8-5. In situ mobile simulation team training in an ambulance. The limitations regarding space to work and move around inside an ambulance are very important. This situation represents a classic need for in situ training of prehospital teams (in Germany consisting of three paramedics and a prehospital emergency physician). In addition, takeover scenarios (e.g., the helicopter team is taking over a patient from the ground-based team) are a challenge for crisis resource management expertise (e.g., information transfer and continuous patient treatment). *(Photograph taken by M. Rall at an air rescue center in Germany.)*



Figure 8-6. In situ mobile simulation team training in a helicopter. The mobile simulation control room with several cameras and microphones is set up outside the helicopter and also provides a multiperspective view inside to monitor the scenario and react to activities performed. *(Photograph taken by M. Rall at Airmed 2008 with the German Air Rescue (DRF) team.)*



Figure 8-7. A, In situ mobile simulation training in a simulated apartment for prehospital teams. Apartment (living space) scenarios are very common for prehospital teams and require adaptation to local space availability and other circumstances (e.g., bystanders, dogs). **B,** Emergency department simulation with the prehospital team handing over a patient to the hospital staff—always a phase of high-demand and goal-oriented interactions. From a crisis resource management (CRM) training perspective, this scenario is a very good opportunity to highlight problems and unsafe practices (in the sense of high reliability) and to show good team performances using video clips of a scenario. *(**A,** Photograph taken by M. Rall at a CRM training session with the South Tyrolean White Cross in Bolzano, Italy. **B,** Photograph taken by M. Rall during an instructor training course.)*



Figure 8-8. In situ mobile simulation in an intensive care unit (ICU)/intermediate medical care unit location. The training in actual clinical areas also is especially useful for ICU-like surroundings. Crisis resource management–based trainings are very important to showcase these highly complex problems and the interactions needed to coordinate high-performing ICU teams. The training also allows for checking the local arrangement of equipment and possibilities to react to certain emergencies. There are already a few examples of residential in situ simulation in ICUs (see text). *(Photograph by M. Rall.)*



Figure 8-9. In situ mobile crisis resource management (CRM)–focused simulation team training inside an actual operating room. This debriefing room is temporarily set up in an induction room. The use of videos for debriefing (here on a 42-inch flat panel placed over the basin) is highly recommended. Training inside a hospital often includes training actual teams and training a large proportion of employees with the same setup. These mass training sessions seem to have a much greater impact and longer-lasting effects of the lessons learned, including CRM behaviors (see text on subthreshold training). *(Photograph by team TuPASS [Center for Patient Safety and Simulation, University Hospital, Tübingen, Germany], who performed at a full team training of the anesthesia department at Steinenberg Medical Center, Reutlingen, Germany.)*

In other words, the simulator comes to the participants. Mobile simulation can be conducted as in situ simulation in an actual site of a remote client institution, by setting up for simulation in conference rooms or hotel meeting rooms, or by having a simulation facility built into a truck or bus. The built-in mobile facility saves time in setup and takedown. It also is possible to conduct simulated field exercises by setting up the simulator outside (e.g., in a parking lot or athletic field).

ADVANTAGES AND DISADVANTAGES OF DIFFERENT APPROACHES

The advantages and disadvantages of different approaches are summarized in Table 8-1. Sites that lack a dedicated simulation center have no practical alternative either to perform in situ simulation or to be a client for mobile simulation. Simulation in the dedicated center facilitates scheduled training and the use of complex audiovisual gear. Simulators can be preset, tested, and ready to go. Briefing and debriefing facilities are immediately at hand. In a dedicated center, it is common to use inexpensive discarded, flawed, or outdated clinical equipment and supplies. The major disadvantage to a dedicated center is that regardless of how well equipped it is, it can never replicate the equipment, layout, and clinical processes of actual clinical workplaces. In addition, participants know that

they are in a simulation center, and this knowledge may alter their demeanor and reduce the impact of training.

In situ simulation seems ideal in that it probes and challenges personnel and systems as they actually exist, thus unmasking real issues of patient care. It is available, in principle, to all sites, even those without a dedicated center, and it is conducive to short courses and unannounced mock event drills. In situ simulation has disadvantages, however. It is difficult to organize, schedule, and control. The clinical area planned for simulation may not be vacant or may be needed on short notice. The simulations can be distracting to real patient care surrounding them, staff members engaged in the simulation are prone to being pulled into clinical duty, and training sessions may be constantly interrupted. Most clinical supplies must be taken from the stocks of the work unit to prevent mixups with outdated simulation supplies, thereby adding expense. The audiovisual gear that can be deployed in a real clinical site has major limitations. A permanent in situ facility may provide the best of both worlds. Such an arrangement offers unique opportunities, such as the ability to replay immediately difficult cases in the simulator next door, the possibility to use low workload times for spur-of-the-moment simulation sessions, and the ability to conduct long-term simulations (team members responsible for a simulated ICU patient over days or weeks). The major drawback to this approach is that addressing diverse clinical domains requires such a site in every domain, and this could be extremely costly.

TEAM TRAINING, SINGLE DISCIPLINE, AND CREWS

Each discipline in health care can be considered a crew containing one or more individuals. Several crews may work together closely as a team. The operating room team consists of an anesthesia crew, a surgery crew, and a nursing crew (and crews of technicians and support personnel).

Further complementarity exists regarding the homogeneity of the target population in simulations. When the simulation is intended to go beyond specific medical and technical skills for individuals (as in CRM-oriented simulations) and to involve nontechnical skills and teamwork, we distinguish between single-discipline approaches (training crews to work in teams) and true combined team (multidisciplinary) training.

The importance of teamwork and team training is widely accepted,[29-34] although team training is still not widely implemented. The prerequisites for effective teamwork (e.g., team leadership, mutual performance monitoring, backup behavior, adaptability and team orientation,[34] and the concept of team cognition) are discussed in Chapter 7.

SINGLE DISCIPLINE

Training for single-discipline crews (e.g., anesthesiologists) involves curricula in which all participants are from a single discipline, and other crew members' roles are played either by instructors and confederates or by other simulation participants. This approach allows tailoring simulations to challenge skills, knowledge, and situations specific to the discipline, including material that may be of little relevance to other crews and in the context of a wide variety of clinical situations (e.g., cardiac, orthopedic, or general surgery; labor and delivery; intensive care). Single-discipline training can emphasize generic skills of dynamic decision making, resource management, leadership, and teamwork applicable to any challenging clinical situation. In the single-discipline approach, scenarios can be designed that present specific types of personalities and behaviors by other crew or team members, rather than relying on the ad hoc behavior of real personnel from those disciplines. Even without actual personnel from other disciplines, training crews to work in teams also provides a degree of cross-discipline understanding by allowing participants to discuss other team members' views of the same situation.

For dedicated center simulations, single-discipline sessions are simpler logistically because only one discipline needs to be present, rather than scheduling someone from each of the disciplines. In addition, simulations can be applied to some disciplines even in domains where credible simulators for the work of each team member are not yet available. The single-discipline approach may be of particular relevance for trainees who, when finished with their training, will go on to work in many different settings and with many different kinds of personnel. It also may be of greatest value for individuals who do not work in fixed crews or teams and who must acquire generic teamwork skills that can be used with all co-workers.

COMBINED TEAM TRAINING

The complementary approach is to conduct *combined team training,* in which all participants of the team, from crews of several different disciplines (e.g., surgeons, nurses, anesthesiologists), undergo training together. Combined team training allows for more natural team interactions and reinforces understanding across disciplines. Successful examples of such undertakings have been reported in many fields, including obstetrics (combining obstetrics, anesthesia, nursing, and neonatology and pediatrics) and intensive care (combining physicians from multiple disciplines with nursing, respiratory therapy, and pharmacy).[31,35-48]

Combined team training may be most effective when a specific group of individuals is to work together clinically as a dedicated team. In dedicated simulation centers, combined team training can be difficult to schedule, and it may require instructors from several of the disciplines to conduct the debriefings. Combined team simulations may be easiest to organize when they are conducted as unannounced mock events that activate the actual bedside team (e.g., ward or unit team, rapid response team, or code team). In such situations, the real combined team is mobilized as they would be in real life.

DEBRIEFING FOR SIMULATION TRAINING

Debriefing refers to a special time and format for talking about an episode of action in the past; it is the counterpoint to a briefing, which occurs before an action or task.

The term originally came from the military, for after-action reviews of real missions and simulations. In medicine, the debriefing concept was introduced to simulation training by Gaba and colleagues as part of the whole concept of CRM-based simulation training for anesthesia teams.[17,49] This section focuses on debriefings in the context of simulation team training.

DEBRIEFING—HEART AND SOUL OF SIMULATION TRAININGS

In aviation and health care simulations, debriefing after a simulation team training session is a key element—perhaps the most important element—of simulation training.[45] Debriefing offers an unparalleled opportunity to reflect and discuss openly and understand other team member's intentions, thoughts, and problems. Much of the learning occurs in this self-reflective episode. Eventually, these routines will be applied to clinical medicine (e.g., surgical team timeout).

NEW WAY OF TEACHING

Debriefing, as described in aviation and introduced and refined for medicine by Gaba and others,[46,50] requires a complete understanding by instructors of their role in promoting learning (see Chapter 9).[51] The philosophy of teaching and learning in a debriefing of a CRM-based simulation course differs from the traditional clinical teaching style (Table 8-2). The instructor's role is to *facilitate* the learning process, by *directing the participants* to the most interesting and important areas for consideration and *stimulating discussion* among participants to *find the underlying issues* and to seek solutions for future events of similar type. *Facilitation* is a new way of teaching and often must be learned by instructors, even though they have many years of traditional teaching experience. The use of video for debriefing can advance the self-reflective component of debriefings, but it requires additional expertise to integrate it successfully with self-reflection.[52-57] Generally, faculty members intending to be primary debriefers need special training and practice in this teaching method (see the later section on instructor qualification).[52,56-64] Several simulation centers conduct instructor training that emphasizes debriefing skills, and debriefing is a frequent topic of workshops at large simulation conferences.

TECHNIQUE OF DEBRIEFING

Although debriefing styles and philosophies differ at centers around the world, a common ground is shared by most centers: debriefing should *stimulate self-reflection,* and it should analyze *how* something happened and what the *underlying concepts* for doing so were, rather than merely finding out *what* happened. Usually the debriefing session lasts at least as long as the scenario itself.

Detailed discussions about the different techniques appear in the literature.[45,46,51,65-68] To prepare a good debriefing, the instructor is challenged during the scenario with performing several tasks in the control room, such as listening to trainees, talking to the instructor team, controlling the simulator, and making notes for the debriefing. Figure 8-10 illustrates the different levels of attendance.

Debriefings by nature have different phases, as shown in Table 8-3. The phases are not meant to be followed in this time sequence and order. Often two or more phases are covered for one problem of the scenario—especially clinical problems are covered while discussing how and

TABLE 8-2 **TRADITIONAL TEACHING VERSUS FACILITATION IN SIMULATION TRAINING COURSES**

Traditional Teaching: "Teacher"	Debriefing Facilitation: "Instructor/Facilitator"
Focus on theoretical knowledge	Focus on human factors and CRM aspects
Focus on what	Focus on why and deeper analysis of why it did (not) work
Teacher is the best (expert)	Instructor just moderates, uses knowledge of participants
Teacher tells participants what to do	Instructor helps participants to find what they could have done and what would be the best way
Teacher knows what is important for participants	Instructor helps to self-reflect and gain realistic self-awareness and consciousness
	Instructor guides toward interesting areas
Talks most	Stimulates discussion among participants
Domain expert	CRM expert
No teaching training	Extensive instructor training
No video	Use of video of own and others' scenarios
Teacher knows what has been learned (or not)	Instructor may not be aware of all aspects that participants take home

CRM, Crisis resource management.



Figure 8-10. The multiple levels of work for crisis resource management (CRM)–based instructors in the control room. The reflections in the one-way mirror of the control room make the multiple levels of activity transparent. The team of instructors has to control the simulation as such, but team members also make notes for the CRM-based debriefing. The scenario inside and the audio streams (telephone call) must be monitored. In addition, the instructors must deal with simulation team role players and instructor trainees inside the control room. These complex tasks need some training and good team organization on the part of the simulation center team. *(Photograph by B. Schaedle, at a PaedSim training at University Hospital, Tübingen, Germany.)*

TABLE 8-3 **PHASES OF DEBRIEFINGS: ISSUES RELEVANT TO CRISIS RESOURCE MANAGEMENT–BASED SIMULATION DEBRIEFING**

Phase of Debriefing	Explanation
Ending the scenario	When possible, the scenario should not be stopped too early. Participants should be allowed to realize the natural end of the scenario. Ideally, it should not be terminated when participants are in the thick of it.
Scenario-to-debriefing transition	Most sites use "hot" debriefing, in which participants enter the debriefing room immediately from the simulation room. This allows the instructor to hear and see participants' direct reactions. Another option is to give the participants a few minutes to discuss the scenario itself while the instructor is planning the debriefing.
Emotional venting	All participants who were actively involved are given the opportunity to say how they *felt* during the scenario. This vents pent-up feelings and may be a time to deal with anomalies in the scenario (e.g., simulator malfunction).
Descriptive phase	Participants describe what happened (or portions of the video are replayed). Different points of view (e.g., "hot seat" versus first responder versus surgeon confederate) are shared.
Self-identification of issues	It can be useful, before anyone else, including the instructor, is allowed to critique the scenario, to allow active participants to say whether they themselves detected any errors or actions that they would do differently. It can be painful and rude to critique participants about something they are aware of themselves.
Discussion of clinical content	Any major issues of clinical treatment and related crisis resource management points should be covered. A debriefing should not end without discussing and clarifying any significant clinical errors and ensuring that participants understand the correct management.
Analysis	Debriefings should provide considerable analysis of *why* things happened vis-à-vis the intentions of all parties, as well as alternatives and their pros and cons.
Opportunities for systems improvement	Based on the analyses, participants can be asked to suggest how the system can be changed to improve handling of similar situations in the future.
Transfer to the "real world"	Participants can discuss how lessons from the scenario or debriefing can be applied in the real clinical world. They should discuss barriers to improvement and ways to overcome them.
Providing a "take-home message" from the scenario and debriefing	A summary of the key points of the debriefing, either by the instructor or the participants themselves, can be useful.
Terminating the debriefing	Debriefings are rich in content and could extend beyond the time available. Marking the end of the debriefing can be a useful transition to preparing for the next scenario or to the end-of-day activities.

when they happened (analysis). Then another problem is analyzed and discussed in terms of different phases. Nevertheless, at the end of a good debriefing, all phases should have been covered according to their respective importance. No debriefing style is associated with a proven better learning outcome, and there may never be definitive data on the techniques because of the nature of the topic—reflective practice of high-level cognition.

USE OF VIDEO FOR DEBRIEFINGS

Although the value is not proved, segments of video recordings to support and deepen debriefing as a learning and self-awareness experience are frequently used.[57,69] Anesthesia does not allow for much self-reflection and feedback during routine clinical work. Experienced colleagues typically work alone, and there is often little feedback from other anesthesiologists or from other operating room personnel. This situation is changing, however, with the use of automatic anesthetic records and information technology (see Chapters 1, 4, 5, and 6).

The lack of feedback leaves a large theoretical gap between the way individuals think they perform and how they act in reality. Video sequences can correct this gap and provide an awareness of how participants have really acted. In addition, one's own video recordings can be compared with the recordings of other participants (either their own course coparticipants or trigger videos meant to stimulate discussion). "Live transmission" of scenarios to participants not actively involved in the scenario also is useful. When this technique is used, the observers can be given special tasks (e.g., look for CRM key points 10 and 11 in Box 8-4). A study in Tübingen, Germany evaluated the use of so-called collaboration scripts in the passive phase of watching others perform.

The video should be used in the service of the debriefing, rather than the other way around. We believe that if the discussion is active and on target, it is useless to interrupt it just to show a video. Video may have a greater impact during participants' first simulation experiences. Here they are sometimes struck by what can be revealed on seeing themselves and others work. As they gain more experience with simulation, and when debriefers are experienced, participants may not need exposure to the video to hone in on key issues to discuss.

CLINICAL APPLICATION OF DEBRIEFING METHOD

The application of the previously described debriefing techniques to the discussion of real-world clinical critical

incidents seems very promising. Applying the debriefing technique learned in the simulator after a critical incident in short debriefing circles of the involved clinical team has proved quite valuable.[41,50,70,71-73]

SCENARIO DESIGN

The design of scenarios for interactive simulation team trainings is demanding and typically differs from preparing training exercises for traditional curricula, such as megacode trainings in advanced life support. Full simulation scenarios are complex enough that their design is usually an iterative process by which the scenarios are continually improved through experience.

This section can give only an overview of the important aspects of scenario design for realistic simulation team training. The reader is referred to detailed published examples of scenarios in *Simulation in Healthcare,*[74] as well to more detailed literature about the principles of scenario design.[3,75] The topic also is covered extensively in most of the instructor training curricula that are offered at sites around the world. International and regional simulation meetings (International Meeting on Simulation in Healthcare [IMSH] of the Society for Simulation in Healthcare [SSH], Society in Europe for Simulation Applied to Medicine [SESAM]) often provide workshops on scenario design, and the user groups of the major simulator manufacturers also have workshops on the topic (see the later section on simulation societies).

GOAL ORIENTED

Scenarios usually are designed to achieve learning objectives or other goals, such as a formal needs analysis of the relevant target group for training concerning clinical and technical skills or nontechnical CRM skills, or both (see Chapter 7). Alternatively, simulation-savvy clinician educators may intuitively know what kinds of scenarios are likely to be valuable for their participant populations, or they may have learned about good examples in their instructor training or in the literature. The cases are not as important as the nature of the underlying challenges that they pose to participants. *Train the causes, not the cases.*

Scenarios should be relevant to the trainees. This relevance is more important than realism and depends on many factors, including the trainees' backgrounds and experience and the method of conducting the scenario and related parts of the simulation course (e.g., familiarization, case briefing, role players).

CONSTRAINTS AND LIMITATIONS

It is easy to suggest a scenario on paper but more difficult to translate it into an effective scenario for actual use. Limitations and constraints must be considered, including features and limitations of the simulators available, personnel resources at hand, the props or external systems that would be needed to engage participants, and the time available for the proposed scenario. In our experience, most scenarios are first generated with an idea that may be small or undeveloped. The idea is fleshed out by discussion and on paper in an iterative fashion, with limitations addressed either by creative redesign of the proposed situation or by minor technical modifications using the simulator software or simulation environment. The new scenario usually is tested out first by instructors and simulationists (the technical staff members who operate the simulators and prepare the environment). It can be pilot tested with a volunteer group of participants from the target population. The first one or two sessions typically will reveal many problems and flaws in the original scenario layout. After a scenario has been designed and tested, it is advisable to add comments and suggestions for improvement continuously after each training session.

SCENARIO TEMPLATES

Many centers have developed templates for the design of their scenarios. Figure 8-11 is an example of a summary sheet of the template used by M. Rall and P. Dieckmann and taught during their instructor courses. The full version of it is available online (www.inpass.de/download/scenarioscript.html). Other scenario templates are popular, including the Duke University template (simcenter.duke.edu/SimTemplate1203.doc). The peer-reviewed journal *Simulation in Healthcare* publishes "Simulation Case Reports," which contain detailed scenario descriptions. Some professional societies have created scenario repositories for members; the American Society of Anesthesiologists (ASA) Simulation Committee has a repository for scenarios to be shared among its ASA-endorsed simulation programs.

INSTRUCTOR QUALIFICATION

Teaching with simulation covers a diverse spectrum of applications. In some cases, it is similar to teaching at the bedside, only the patient is a simulator, in which case the skills needed are nearly identical to those used in ordinary clinical supervision and teaching. Special implications exist for instructing in courses that involve complex realistic scenarios, with multiple personnel in crews and teams, using video-facilitated debriefings in small groups, and with a focus on human factors and CRM principles and countermeasures. In such courses, the skills needed to be a successful instructor go considerably beyond those typically used by teaching clinicians. Quality of the instructors is *the* essential element for any simulation course: "The key is the program, not the hardware."[10] Ensuring instructor competence in using simulation and in debriefing facilitation skills is very important.

Advanced simulation course formats generally closely reflect Kolb's circle of adult experiential learning: (1) self-experience (participate in the scenario) or vicarious experience (observe scenario live), (2) reflect on experience (debriefing), (3) abstract conceptualization (debriefing, relate to theoretical material), and (4) active experimentation (future scenarios and use of skills in real cases)[76] (Fig. 8-12).

Scenario Script Developed by P. Dieckmann & M. Rall, Germany		
Quick reference: Scenario name		
Major problem	Medicine	CRM
Learning goal	Medicine	CRM
Narrative description		
Staffing	Simulator team	Participants
Case briefing	All participants	"Hot seats" only
Simulator setup Mannequin preparation		
Room setup		
Simulator operation		
Scenario lifesavers		
Props needed		

Figure 8-11. A scenario design template. The figure shows the summary page of a scenario design template, which has more space and details in the full version. The template also includes a script to explain the different fields and their best use. The template is a regular part of the instructor training courses. It can be obtained in a more detailed version from www.inpass.de/download/scenarioscript.html. *(scenario script template by P. Dieckmann and M. Rall.)*

TASKS OF INSTRUCTORS

The tasks of a simulation instructor differ from the tasks of a classic medical educator or a trainer for part-task or skills training. The most prominent differences are the following:

- Need to brief the course participants about an unfamiliar environment
- Creation of relevant, plausible scenarios to reach the intended learning goals
- Theatrical aspects of enacting complex realistic scenarios
- Need for simultaneous control of the simulator, the simulation personnel (instructors, actors, and confederates), and learning objectives during multiperson complex scenarios with built-in problems and challenges and an uncertain flow pathway of action by participants
- Need to provide debriefing and feedback after the scenario, often assisted by replay of video recordings, primarily using a facilitation style in small groups and handling group dynamics and individual sensitivities
- Concentration largely on CRM nontechnical skills of decision making, team management, interpersonal relationships, communication, and professionalism

INSTRUCTOR TRAINING

For such complex instructor skills, formal training seems warranted. David Gaba pioneered instructor training for CRM-oriented simulation courses in a consortium of the Veterans Affairs (VA)–Stanford Simulation Center (Palo Alto, CA) with the Boston Center for Medical Simulation and the University of Toronto Sunnybrooke Simulation Center. This consortium spread the ideas and format of CRM simulation instructor training around the world. Marcus Rall has been running instructor courses in cooperation with Peter Dieckmann for more than 1000 international participants. Many institutions offer different instructor courses nationally and internationally (ranging

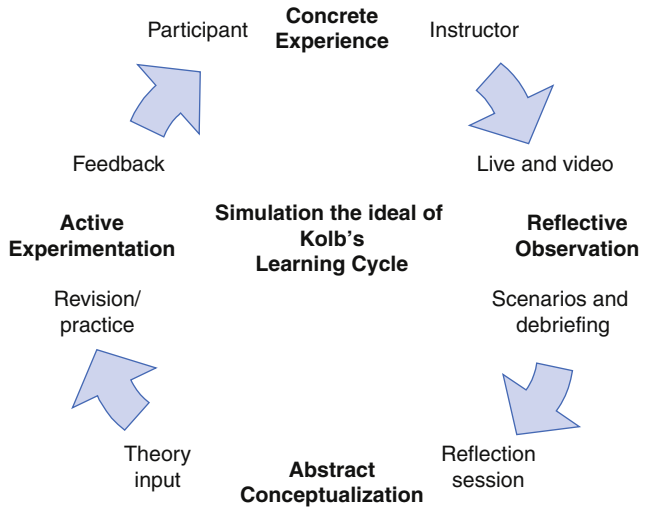


Figure 8-12. Simulation team training with live video transmission as an ideal representation of Kolb's learning circle. During the scenario, trainees have a hands-on experience. This is actively reflected in the debriefing. The live video to the nonactive group in the current scenario allows useful reflective observation. During the debriefing, all trainees have a phase of conceptualization, in which the instructor uses generalizations of factors and root causes to show how behavior developed as it did in the scenario (deep learning). During the feedback in the debriefing, but also in the next active scenarios, participants have opportunities to apply and experiment with the newly learned input. (*Modified from Kolb DA:* Experiential learning: experience as the source of learning and development. *Englewood Cliffs, NJ, 1984, Prentice-Hall.*)

BOX 8-2 ***Learning Objectives for Crisis Resource Management–Oriented Simulation Instructor Courses***

Understand how it feels to be a participant in a simulation scenario and to be debriefed in a group while seeing oneself on video.

Understand the interdependent influence of the different course phases (see Fig. 8-2), and apply this knowledge to a simulation course.

Reflect on the changing instructional styles that can be applicable to simulation courses (instruction—facilitation).

Understand basic concepts of human factors, systems theory, and organizational safety.

Be able to detect, explain, and discuss crisis resource management key points in the debriefing of scenarios.

Use recorded video of scenarios well, and select the most relevant portions for replay and discussion.

Be able to facilitate a debriefing in a nonjudgmental atmosphere with appropriate boundaries.

Understand how to manage the individual sensitivities and group dynamics of participants during debriefing.

Be able to focus debriefing on the analysis of what happened, why things happened the way they did, and how to apply these lessons to real patient care.

Modified from the learning objectives of former instructor courses by Gaba, Rall, and Dieckmann.

from 2 to 6 days in length, depending on the course and its scope); the reader is referred to the simulation societies for information about such courses (SSH, SESAM). The process and impact of instructor training are being evaluated, much as the process of simulation training itself is being assessed. Some early evidence is emerging that such courses have value. In addition, shorter introductory courses on instructor skills are offered every year at the international health care simulation meetings (e.g., SSH's IMSH conference or the SESAM annual meeting), and many workshops at the meetings cover topics such as debriefing, instructor training, and CRM training.

Box 8-2 presents an example of learning objectives for an instructor training course. For experiences and effects of the instructor course by Dieckmann and Rall, a poster presented at the IMSH 2006 with a short description of the InFacT course and results from a response-shift bias analysis can be downloaded from the following website: www.inpass.de/download/infactposter.html. The most difficult task for traditional medical teachers is to learn to stop instructing and start facilitating—guiding participants toward a deep learning experience.

CERTIFICATION OF INSTRUCTORS

The original simulation instructors were self-taught in these skills, and the programs or centers that they founded were pioneers in this field (see also the later sections on pitfalls of performance assessment and the use of simulation for high-stakes evaluation). Now, simulation has become widespread. How can programs of different levels of maturity, experience, and quality be differentiated? Several systems of program approval have emerged, some of them of particular interest to anesthesia professionals. The ASA in 2008 began a process to endorse anesthesia simulation programs (the ASA chose not to use the term accredit) (see also Chapter 1). Centers were originally endorsed for their ability to deliver high-quality continuing medical education (CME) to ASA members. After reaching agreement with the American Board of Anesthesiology (ABA) in 2010, this ASA Simulation Education Network (SEN) rapidly transformed into a group of programs capable of conducting the semistandardized Maintenance of Certification in Anesthesia (MOCA) Simulation Course, a component of Part IV of the ABA MOCA process. As of May, 2013, the ASA had endorsed 36 programs, each of which was reviewed and approved by the ASA Committee on Simulation Education (now considered a Simulation Education Editorial Board) after completion of a detailed application documenting the capability and experience of their simulation instructors, leadership, facilities, and procedures (for ASA members, see http://www.asahq.org/For-Members/Education-and-Events/Simulation-Education.aspx). The American College of Surgeons (ACS) has an accreditation program for Surgical Education Institutes, of which simulation in various forms is an important component. Many anesthesia simulation programs are partners in their institution's ACS accreditation package. The SSH offers a more comprehensive set of accreditations. Most anesthesia simulation programs, even those in the ASA SEN, have chosen not to obtain SSH accreditation and have relied instead on the anesthesia-focused endorsement.

Should instructors receive documented formal training and certification? The SSH offers a Certification for

Healthcare Simulation Educator (CHSE). It is largely oriented to those relatively new to simulation, to document their experience, skills, and knowledge (a written test is given). However, most anesthesia simulation personnel have not and are not planning to obtain SSH CHSE certification. The ASA SEN endorsement process examines the simulation background of instructors, as well as the process by which each site trains and approves new instructors for their program.

It is likely that the skills and certification needed (if any) for an instructor will vary greatly with the particular course or curriculum being taught. Competence in conducting a video-based CRM debriefing would not be needed, and would not help, to teach specific manual procedures (e.g., airway management or central venous cannulation) using part-task trainers. Instructor certification, whether internal to a program or external, could ultimately be connected to the specific types of courses each individual is capable of conducting. A tiered instructor certification system also would likely provide for advancement from novice instructor to grand master as experience and special training are acquired.

CLASSIFICATION OF PATIENT SIMULATORS

No accepted classification scheme has been devised for the use of patient simulators in anesthesia. Any classification involves some overlapping and gray areas.[47] Cumin and Merry published a review about available simulators.[77] The following classification and definitions are used in this chapter. In addition to simulators, computer-assisted instruction programs and computer-based training devices are available. Although training devices may replicate certain portions of the clinical domain, they do not attempt to replicate the bulk of the work environment. Some individuals consider the screen-only microsimulator (also known as a screen-based simulator) to be a training device and not a simulator. Computer-assisted instruction programs and training devices are not reviewed in this chapter. This chapter addresses patient simulators in anesthesia that present the overall patient as would be seen by anesthesiologists, intensivists, or others. Devices related purely to emergency medicine, surgical or procedural simulators that present only the technical work of surgery or invasive manipulations (e.g., bronchoscopy, intravenous access), and partial-task screen-based simulators (e.g., Gas Man, Med Man Simulations, Inc, Boston) are not discussed here.

In this chapter, a *patient simulator* is a system that presents a patient and a clinical work environment of immediate relevance to anesthesiologists (e.g., operating room, postanesthesia care unit, ICU) in one of the following ways:

1. In actual physical reality, defined as a mannequin-based simulator (former and still commonly used synonyms are full-scale simulator, hands-on simulator, realistic simulator, high-fidelity simulator). These simulators can be subdivided in terms of the way that vital signs monitoring is accomplished (interfacing to real clinical monitoring devices or using its own virtual replica of a monitor screen) and in terms of the primary control logic of the simulator (by individual controls and scripts or by using physiologic and pharmacologic modeling).
2. On a computer screen only, defined as a screen-only or screen-based simulator (some anesthesiologists prefer the term microsimulator).
3. Using virtual reality, defined as a virtual reality simulator. In such a device, parts or all of the patient and environment are presented to the user by three-dimensional representations with or without "touch" to create a more immersive experience. A screen-only simulator could be viewed as a very limited virtual reality simulator.

COMPONENTS OF A PATIENT SIMULATOR

A patient simulator system contains several components (Fig. 8-13).[47] A set of outputs makes up a representation of the patient, the clinical environment, and diagnostic and therapeutic equipment. For screen-only simulators, this representation is generated graphically on the computer screen. For mannequin-based simulators, the representation is generated by using a patient mannequin, in addition to either actual clinical equipment or virtual replicas of monitor screens, placed (typically) in a recreated actual clinical setting. The mannequin and, where appropriate, the clinical equipment are stimulated or actuated by interface hardware. Mannequin-based simulators often use physical stimulation of clinical equipment in addition to electronic stimulation. The mannequin can actually be ventilated with any desired mixture of inspired gases. Carbon dioxide and other gases can be introduced physically by the simulator into the mannequin's lungs to provide the desired elements of gas exchange. A real respiratory gas analyzer can be used to measure the inspired and expired gases. The currently available features of full-scale, mannequin-based patient simulators are presented in Table 8-4.

Any simulator must have control logic by which changes in the simulated patient's condition can be generated, controlled, and sent to the appropriate output of the representation. Originally, the control logic was embedded in the software as a fixed sequence of events, or it consisted largely of continuous input from the instructor working from a script. Some current simulators use upgraded types of manual control logic that allow scripting of combinations of changes in control input. Other current simulators incorporate a more sophisticated technique using mathematic difference equations that model a patient's physiology and pharmacology to provide the bulk of the control logic. These models can be tailored to represent different patients with different pathophysiologic abnormalities.

Not all states or changes in a patient can be modeled by differential equations. Ventricular fibrillation is a totally different state of heart rhythm that does not evolve continuously from normal rhythms. No model can predict exactly when a patient will have a myocardial infarction or when an ischemic heart will begin to fibrillate. A model can predict only factors that increase the likelihood of such events. Most simulators incorporate

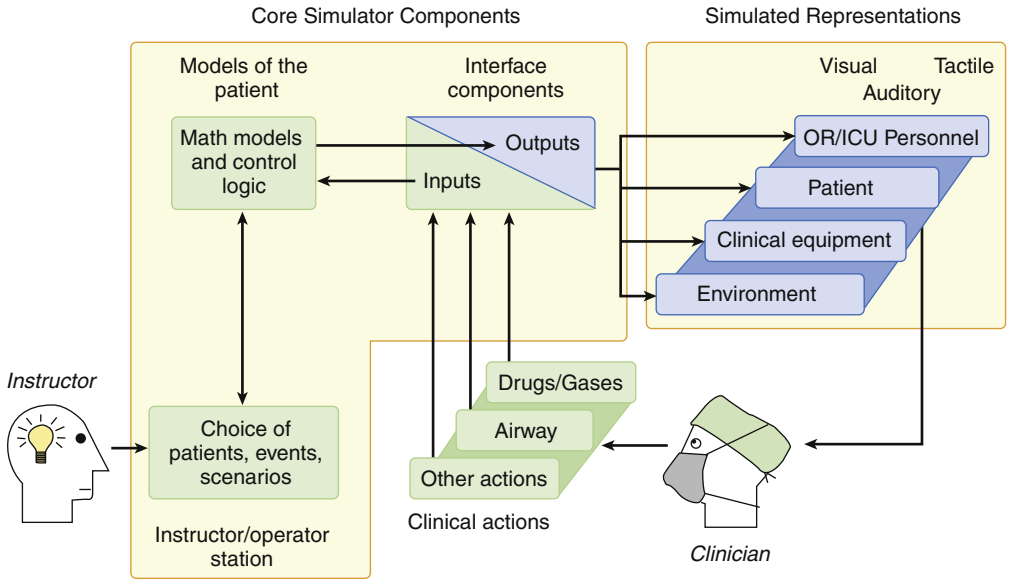


Figure 8-13. Schematic diagram of the generic architecture of patient simulator systems. The simulator generates a representation of the patient and the work environment with appropriate interface hardware, display technologies, or both. The representation is perceived by the anesthesiologist, whose actions are input to the simulator through physical actions or input devices. The behavior of the simulated scenario is manipulated by the instructor or operator through a workstation that allows selection of different patients, abnormal events, and other features of the simulated patient. The control may be manual, script based, or model based with manual adaptation to reach optimal learning outcomes. ICU, intensive care unit; OR, operating room. *(Diagram by D.M. Gaba.)*

TABLE 8-4 **FUNCTIONALITY OF CURRENT MANNEQUIN-BASED SIMULATOR SYSTEMS***

Clinical Area	Features and Functions	Remarks
Airway	Appropriate pharyngeal and glottic anatomy	The airway often provides an acceptable seal for ETT; the seal for supraglottic airway devices can be variable, but it generally does allow positive pressure ventilation.
	Placement of facemask, ETT, LMA, LT, Combitube	
	Laryngospasm, tongue and airway swelling, cervical immobility, jaw closure, breakable teeth	
	Cricothyrotomy	The facemask seal is often difficult, as is placement of the ETT.
	Transtracheal jet ventilation	
	Bronchial anatomy (to the lobar bronchus level)	Cricotomy of modest anatomic realism; the tissue does not feel like real skin and lacks a subcutaneous fat layer; no bleeding occurs; however, the simulation does allow going through the physical steps of inserting a subglottic surgical airway.
Head	Eyelid movement, pupil dilation, and reaction to light or medications	
	Patient voice and sounds such as coughing and vomiting (through built-in loudspeaker)	The live voice is preferred to the prerecorded audio clips because of higher flexibility in scenarios.
	Palpable carotid pulses	
	Cyanosis represented by blue light at the edge of the mouth	The blue light is a cue that the patient is cyanotic, but it does not physically replicate the appearance of cyanosis.
	Tearing, sweating	
Chest	Physiologic and pathophysiologic heart and breath sounds	Breath and heart sounds through loudspeakers; sounds contain artifacts and mechanical noise. Often sound level depends on position of stethoscope relative to loudspeaker.
	Spontaneous breathing with chest wall movement	
	Bronchospasm	
	Adjustable pulmonary compliance	
	Adjustable airway resistance	
	Pneumothorax	
	Needle thoracotomy and chest tube placement	As for cricothyrotomy the anatomy is not very realistic, but the mannequin may allow performance of these procedures.
	Defibrillation, transthoracic pacing ECG	
	Chest compressions	

Continued on following page

TABLE 8-4 **FUNCTIONALITY OF CURRENT MANNEQUIN-BASED SIMULATOR SYSTEMS (Continued)**

Clinical Area	Features and Functions	Remarks
Extremities	Palpable pulses (dependent on arterial pressure)	
	Cuff blood pressure by auscultation, palpation, or oscillometry	
	Modules for fractures and wound modules	
	Intravenous line placement	
	Thumb twitch in response to peripheral nerve stimulation	
	Arm movement	Most current simulators do not provide even limited robotic movement of limbs.
	Representations of tonic-clonic seizure activity	These representations are cues that lack anatomic reality.
Monitoring (waveforms or numeric readouts)	ECG (including abnormalities in morphology and rhythm)	Most simulators provide a simulated virtual vital signs display; some can interface to actual clinical monitors.
	SpO_2	
	Invasive blood pressure	
	CVP, PAP, PCWP	
	Cardiac output	
	Temperature	
	CO_2 (may be actual CO_2 exhalation)	
	Anesthetic gases (may have actual uptake and distribution of agents)	
	Cardiopulmonary bypass	Some simulators include(d) a virtual cardiopulmonary bypass machine.
Automation and sensors	Chest compressions	
	Ventilation rate and volume	
	Defibrillation and pacing (including energy measurement)	
	Gas analyzer (inspired O_2, anesthetics)	
	Drug recognition (drug identification and amount)	

CVP, Central venous pressure; *ECG,* electrocardiogram; *ETT,* endotracheal tube; *LMA,* laryngeal mask airway; *LT,* larynx tube; *PAP,* positive airway pressure; *PCWP,* pulmonary capillary wedge pressure; *SpO_2,* saturation of peripheral oxygen.
*The features listed are each present in some existing simulators, but not all features are present on any single device. Sets of features depend on the device and model.

other modeling techniques in addition to the basic physiologic and pharmacologic mathematic equations, including finite-state models, instructor initiation of abnormal events, and manual modulation of modeled parameters. In finite-state models, different underlying clinical states are defined, each of which has appropriate entry conditions and transition conditions to other states. When an entry or transition condition is met, a new state becomes active and may directly trigger new observable phenomena (e.g., ventricular fibrillation) or may alter constants in the mathematic models that then evolve in time.[78-80]

The control logic of most simulators is manipulated through an instructor or operator's station that allows the instructor to create specific patients, select and implement abnormal events and faults, and monitor the progress of the simulation session. The system may have a remote-controlled, handheld instructor or operator's station in addition to the main instructor or operator's station. The instructor or operator's station typically provides logs of physiologic changes and the anesthesiologist's response, and it may provide graphics to support the analysis of a simulation run. Some screen-based simulators provide advice and tutorials linked to the management of simulated events. With mannequin-based simulators, especially for applications in which complete work environments are recreated, it is common to obtain detailed records of the simulation and the actions taken from video and audio recordings of the personnel working in the replicated clinical environment.

Modern simulators still do not provide many of the desired features listed in Box 8-3. Many different simulator systems are available. No single system is the best choice for all uses, so the decision about the type of simulator required must be based on the objectives and needs of the application. In our experience, the success of a simulator program is not determined primarily by the type of the simulator used, but mostly by the enthusiasm, skill, and creativity of instructors, as well as the time and effort devoted to preparing and performing credible simulation scenarios.[27]

Audio Announcements Are Very Powerful Simulation Tools

In general, a good way to feed information to participants about various phenomena that cannot be simulated physically is to announce the missing signs and symptoms by loudspeaker from the control room to the scenario room. Such information is transmitted at the semantic level of reality and is usually incorporated by participants into their mental model of the simulation (although occasional misunderstandings or mismatches occur between what is observed physically and the information announced by loudspeaker).

BOX 8-3 ***Desirable Features of Future Mannequin-Based Simulator Systems****

Advanced skin signs such as
- Change in skin color to cyanotic or pale
- Improved diaphoresis
- Change in skin temperature (e.g., as a result of shock or fever)
- Rash, hives, or generalized edema

Regurgitation, vomiting, airway bleeding or secretions
Physical coughing (currently only sounds are simulated)
Realistic convulsions
Purposeful movements of extremities
Improved or possible support for spinal, epidural, or other regional anesthesia procedures
Improved EEG signals (e.g., for BIS, AEP, PSI)
Improved intracranial pressure
Support for physical central venous and arterial cannulation
Improved fetal and maternal cardiotocogram

AEP, Auditory evoked potential; *BIS,* bispectral index; *EEG,* electroencephalographic; *PSI,* patient state index.

* This list contains features that are not currently incorporated. Some features may be under development and could be available after publication of this book. In addition, some features are currently available as third-party or homemade add-ons.

VIRTUAL REALITY SIMULATORS

Virtual reality refers to a set of techniques in which one interacts with a synthetic (virtual) environment that exists solely in the computer.[81] In the typical conception of virtual reality, representation of the synthetic environment is fed directly to the eyes (three-dimensional head-mounted displays), the ears, and possibly the hands and limbs (special instrumented gloves and sensors). The actions of the user in the environment are translated directly from typical physical activities, not through manipulating a special pointing device. Realization of this ideal is a continuum involving compromises in these input-output modalities. At one end of the continuum, which we call a *complete virtual reality simulation,* the participant is immersed in a virtual world that fully replicates at least three sensory inputs—full three-dimensional vision, hearing, and touch (the last is more technically known as a haptic-kinesthetic system)[81]—and allows complete physical interaction with the world. The "holodeck" of *Star Trek* would be an example.

At the other extreme of the continuum is a screen-based simulator that generates a limited virtual setting, with its output restricted to a screen display, and provides interaction with the virtual world only through a pointing device. Screen-based simulators provide an interface to the human sensory system that is very far from physical reality, whereas a complete virtual reality simulation may be, in its most advanced form, nearly indistinguishable from the real world. A partial virtual reality simulator would replicate fewer senses (or less complete replication, such as a three-dimensional visual representation on a two-dimensional screen) or could restrict physical interaction with the world, or both. Finally, one can imagine hybrids of realistic simulators and virtual reality simulators (sometimes called mixed reality) in which the virtual reality representation is overlaid onto a real physical environment.

Some surgical and procedural part-task trainers and simulators, such as those used for laparoscopic, endoscopic, or endovascular procedures, could be considered virtual reality because the real procedure is performed only using a video display that can be recreated by the simulator. A comprehensive virtual reality patient simulator would be very complicated, however, because it requires the following:

Complete computer model of the patient, the environment, and the function of every object in the environment that could be used (e.g., monitoring devices, carts)
Means of tracking visual, audio, and touch fields of the user to determine what is to be displayed and to identify what physical actions are being performed
Appropriate display hardware for every sensory modality and appropriate input hardware for each action pathway (e.g., touch, speech)
Hardware to compute all the models, to conduct the tracking, and to produce all the output to the display hardware in real time

Immersive virtual reality is a rapidly developing field. It has stimulated intense interest in numerous domains, particularly space flight, the military, and entertainment. Although the potential of this approach is very exciting, virtual reality is still under development. Prototype virtual reality patient simulators in anesthesia or intensive care have been discussed informally, but as of this writing, no published experience with any meaningful immersive virtual reality patient simulation system exists.

A related type of simulation is the virtual environment or virtual world. According to Wikipedia, a virtual world is a computer-based simulated environment intended for its users to inhabit and interact through avatars (users' graphic [often perspective three-dimensional] representation of their selves). Such systems typically allow multiple participants to control their own avatars (including speech) simultaneously over a network and to interact verbally and by virtual physical actions within a commonly perceived virtual environment. This technology currently portrays the virtual world as perspective three-dimensional images on a computer screen with sound. Virtual worlds have been commonly used for games (the popular World of Warcraft game has 9 million monthly subscribers), whereas other virtual worlds encompass online communities (e.g., Second Life, in which the primary activity is socializing, although commerce and education take place).

In a medical virtual world, the patient may be an automated avatar controlled by the computer, or the patient may be an avatar inhabited by a human participant (an unusual case of an actor playing a standardized patient). Virtual worlds are starting to be used in health care, especially for acute care settings such as the ICU, the emergency department, or field resuscitation.

Although virtual reality simulators have many theoretical advantages over screen-based and mannequin-based simulators (e.g., more overall realism in some cases, instantaneous reset of the environment), these advantages are currently offset by the immaturity of the field. Despite considerable hype about virtual reality, such systems are now either very limited in

capability or very expensive, and in most cases, they are both limited and expensive. A true virtual reality *immersion* experience in a patient care setting comparable to that obtainable with a mannequin-based simulator is not yet on the horizon. Nonetheless, it is likely that virtual reality techniques eventually will eclipse other types of simulators. In the 1990s, Gaba predicted that this would occur by 2020, but the rate of development of immersive virtual reality has been slower than expected.[82,83]

DEVELOPMENT OF PATIENT SIMULATORS

The descriptions given in the following sections are very brief, and the introduction of new or upgraded features in all the simulation systems continues steadily. For up-to-date information about any of the current systems, the reader is advised to contact the manufacturers or developers directly.

The history of the development of patient simulators—particularly the mannequin-based simulators that are in wide use—has been well covered in several review articles and book chapters.[5,84-86] The history is of some relevance to anesthesiology because of the dominant role played by anesthesiologists in the early development of mannequin-based simulation. Anesthesiologists continue to play a major role in this field today, far out of proportion to their numbers relative to other medical domains.

In the late 1960s, a mannequin-based simulator—Sim One—was produced by an aerospace company working with anesthesiologists at the University of Southern California. For that era, it was a technologic marvel and was years ahead of its time.[87] The Sim One project drifted into oblivion, however, largely because the medical professions were not ready to understand the applicability of simulation to key issues of training, research, and assessment, especially regarding the importance of human factors.

Several patient simulators were developed and introduced in the middle to late 1980s. Each was an independent development, and none had any direct connection with the Sim One project. Several factors led to these advances. Most prominent was the new availability of powerful (comparable to advanced minicomputers of a decade earlier) personal computers (PCs) at a relatively cheap price. The popularity of various simulators for PCs (e.g., flight simulators, driving simulators) showed that simulation of complex systems was possible with a PC, and a screen-based simulator could give users some degree of feel that they had been in the environment. On the applications side, the public and the anesthesia profession had become more aware of the utility of simulation-based training for military and commercial aviation, space flight, automobile driving, shipping, military command and control, and the operation of nuclear power plants. Media coverage of the space program and corrective responses to the 1979 Three Mile Island nuclear power plant accident in Pennsylvania highlighted the role of simulators. Another pivotal factor was growing interest in anesthesiology in studying the anesthesiologist's performance and the human factors and ergonomics of the anesthesia work environment (see Chapter 7).[88-91]

SCREEN-BASED SIMULATORS (MICROSIMULATORS)

Beginning in the mid-1980s, several screen-based simulators were developed by anesthesiologists. These included part-task trainers that simulated isolated aspects of anesthesia, such as the uptake and distribution of anesthetic gases in the body given different physiologic and physical chemistry situations (the well-known Gas Man simulator has excelled in this role). Other overall-task screen-based simulators represented nearly all aspects of the patient and clinical environment. Originally, the control logic was based heavily on mathematic models of physiology and pharmacology; some of the screen-based simulators have converted to control largely from scripts and finite-state models. Originally, the patient was represented by drawings or animations, but increasingly in these systems the representation of the patient is by photographs or videos. Vital signs appear on virtual monitors that may mimic real clinical devices. Actions are selected typically using a graphic user interface, pointing and clicking on menus and buttons, and using sliders and numeric entry boxes to allow control of most kinds of interventions that clinicians use on a regular basis.

EXPERIENCE WITH PATIENT SIMULATORS IN ANESTHESIA

Several companies now offer mannequin-based patient simulators with a wide range of capabilities (the term *fidelity* is reserved for the apparent veracity of the simulation; the simulator device has a set of features or capabilities) and with different user interfaces and control logics. Most simulators in use today (coming from several vendors) are considered medium-capability devices. They do approximately 70% as much as a top-of-the-line simulator, but at approximately 15% of the cost of the most expensive simulators. This value proposition has been persuasive to most customers, although for certain applications the high-end simulators still may be required.

The new patient simulators have been in use in anesthesia since the 1990s, and considerable collective experience with the devices already has been achieved. This section and subsequent sections cover the use of simulators for education, training, evaluation, and research (the last especially in decision making and human factors). The results of simulator studies with regard to human performance and patient safety are discussed primarily in Chapter 7.

SIMULATION FOR EDUCATION AND TRAINING OF HEALTH CARE PERSONNEL

The various available patient simulators offer an unparalleled opportunity for students to experience physiologic and pathophysiologic reactions in a realistic manner. Different objectives are possible for teaching sessions. A study by Morgan and Cleave-Hogg concluded that "the simulator environment is somehow unique and allows different behaviors to be assessed."[92] The objectives of *education* are to provide conceptual understanding and an introduction to skills, whereas the objective of *training* is to

implement specific skills and behaviors applicable directly to real-world surroundings. Consistency in objectives is important for evaluating education and training; if we are teaching conceptual understanding, but assessing specific skills, we may obtain misleading results.[93]

A Best Evidence Medical Education (BEME, www.bemecollaboration.org) review by Issenberg and colleagues concluded that high-fidelity medical simulations are educationally effective, but only if the right conditions are met, as follows[24]:

- Educational feedback is provided.
- Repetitive practice is used or is allowed.
- Simulation is integrated sensibly into the standard curriculum.
- The range of task difficulty can be adapted to the level of the learner.

SIMULATION FOR EDUCATION AND TRAINING OF MEDICAL AND OTHER HEALTH PROFESSION STUDENTS

The structured review about simulation effects on simulation-based medical education by Issenberg and colleagues showed the following: (1) the methodologic quality of educational research is often weak; and (2) in the high-quality studies that were evaluated, the effect between hours of simulator practice and learning outcomes equaled a dose-response relationship.[24] Studies by Coates and associates[94] and Gordon and co-workers[95] showed that simulator education for medical students on patient management skills related to dyspnea was superior to problem-based learning.

Various curricula exist,[68,93,96-106] including the following:

- Educational sessions and demonstrations on basic cardiopulmonary physiology or pharmacology; in some institutions, these sessions replace animal laboratory exercises.[107]
- Introduction to integrated management (i.e., interweaving of diagnosis and treatment) of critically ill patients; this training is offered to immediate preclinical medical students as part of their preparation for clinical medicine courses.
- Anesthesia practicum for clinical students during anesthesia or intensive care clerkships.
- Problem-solving skills training; simulation has been tested as a means of educating and training students in the appropriate response to specific critical events. Morgan and Cleave-Hogg tested simulation versus instructor-facilitated viewing of a videotape for this purpose and found no difference between the two.[108] The generalizability of this finding has been questioned, however.[93]
- Adaptation of curricula originally aimed at experienced trainees or practicing clinicians to students; interest is increasing in providing early exposure to medical students, and possibly students of nursing or allied health professions, to interdisciplinary team aspects of medical practice. The aim is to inculcate concepts of teamwork and communication at the earliest stages of education and training as a vehicle to implement long-term culture change in the health care system.

A stimulating critical overview of medical education in general was written by Hodges and was provocatively titled "Medical Education and the maintenance of *Incompetence*" (emphasis added).[109] The article points out that any type of education runs a risk of creating or maintaining *incompetence* in certain areas, especially areas that are ignored by the actual educational program. Objective structured clinical examination–style methods in particular are criticized because students may learn to pass the objective structured clinical examination but still have even gross incompetence in important aspects of real patient care that are not covered by the objective structured clinical examination rating scale. Simulation offers the promise of targeting more thorough integration of different kinds of skills into a better representation of the realities of clinical care. Nonetheless, we recommend that all simulation instructors be especially cognizant of the risks that Hodges articulates.

ANESTHESIA CRISIS RESOURCE MANAGEMENT

In 1989, based on the cognitive process model presented in Chapter 7 and the research results of Cooper and coworkers,[88,110] Howard and associates[111] and Gaba[89,90] of the VA-Stanford group identified gaps in the training of anesthesiologists regarding several critical aspects of decision making and crisis management that were not systematically taught during standard residency or postgraduate education. These gaps were (1) inadequate learning of precompiled plans for dealing with perioperative events; (2) inadequate skills of metacognition and allocation of attention; and (3) inadequate skill in resource management behavior, including leadership, communication, workload management, monitoring, and cross checking of all available information. Historically, it had been assumed that anesthesiologists would acquire these plans and skills by osmosis, solely by experience and by observing role models who had these qualities. As indicated in a previous section, the aviation field had learned that such skills were not acquired unless specifically taught, and CRM training was created to address these issues for flight crews. The VA-Stanford group modeled their ACRM training after CRM,[111] and this approach has been highly influential. ACRM-like curricula are taught at simulation centers around the world, not only in anesthesia, but also in many other domains of health care, including ICU, emergency medicine, labor and delivery, trauma, and field responders.* Figure 8-14 shows a typical ACRM team training scenario.

To target the identified gaps in training, approximately 40% of the emphasis of ACRM is on the medical and technical management of specific high-risk perioperative situations, but at least 60% of the emphasis is on generic principles of crisis management that apply to nearly every complex patient care situation. The key teaching points of ACRM are shown in Box 8-4. These points are emphasized during the ACRM simulation course, and their occurrence or omission is highlighted during the video-assisted debriefing sessions (see more on CRM in Chapter 7).

*References 17, 34, 37, 39, 41, 42, 68, 84, 112-129.



Figure 8-14. Anesthesia crisis resource management team training scenario. A full operating room team (enacted surgeons and nurses) is performing a complicated endoscopic surgical procedure (replayed on screen). The anesthesia team consisting of the trainee ("hot seat") and the nurse must solve complex problems. Video cameras (ceiling), microphones, and loudspeakers provide the necessary connectivity and debriefing tools. *(Photogtaph taken by M. Rall at the Center for Patient Safety and Simulation, University Hospital, Tübingen, Germany.)*

BOX 8-4 ***Key Points in Anesthesia Crisis Resource Management****

1. Know the environment.
2. Anticipate and plan.
3. Call for help early.
4. Exercise leadership and followership with assertiveness.
5. Distribute the workload (10 seconds for 10 minutes).
6. Mobilize all available resources.
7. Communicate effectively.
8. Use all available information.
9. Prevent and manage fixation errors.
10. Cross check and double check (never assume anything).
11. Use cognitive aids.
12. Reevaluate repeatedly (apply the 10 seconds for 10 minutes concept).
13. Use good teamwork.
14. Allocate attention wisely.
15. Set priorities dynamically.

* Detailed explanation of crisis resource management key points is given in Chapter 7.

A working group of the original ACRM centers (VA-Stanford, Boston CMS, Toronto Sunnybrooke) promulgated a set of criteria to be met by a curriculum to be called either "ACRM" or "ACRM-like." Box 8-5 presents an excerpt of the criteria. The full set of criteria is available at http://med.stanford.edu/VAsimulator/acrm/.

These criteria delineate that special training is needed for instructors in ACRM-like curricula. Experience suggests that the most difficult aspect of ACRM instructing is debriefing, and new instructors require a significant period of experience, preferably under supervision by more senior instructors, before being ready to be fully independent instructors. Several groups working separately or collectively have developed comprehensive training programs on simulation instruction, including substantial modules on debriefing and scenario design.

BOX 8-5 ***Characteristics of Anesthesia Crisis Resource Management–Like Simulator Training***

Objectives

Learn generic principles of complex problem solving, decision making, resource management, and teamwork behavior.

Improve participants' medical and technical, cognitive, and social skills in the recognition and treatment of realistic, complex medical situations.

Enhance capacity for reflection, self-discovery, and teamwork and for building a personalized tool kit of attitudes, behaviors, and skills.

Aim

Prevent, ameliorate, and resolve critical incidents.

Setting Characteristics

A realistic simulation environment replicates a relevant work setting (or an actual patient care setting with in situ simulation).

Personnel will represent those persons found in the typical work environment of the participant, including nurses, surgeons, and technicians.

The bulk of the training course consists of realistic simulations followed by detailed debriefings.

Primary participants can request and receive help from other participants.

Participants may rotate among various roles during different scenarios to gain fresh perspectives.

Simulation scenarios may be supplemented by additional modalities, including activities such as assigned readings, didactic presentations, analysis of videotapes, role playing, or group discussions.

Training involves significant time (>4 hours, typically ≥8 hours) and is conducted with a small group of participants.

Content Characteristics

Scenarios require participants to engage in appropriate professional interactions.

At least 50% of the emphasis of the course is on crisis resource management behavior (nontechnical skills), rather than medical or technical issues (nontechnical skills are discussed in Chapter 7).

Observation only is not equivalent to actual participation in the course.

Faculty Characteristics

Training is intense and entails a high level of involvement of faculty with the participants and a low participant-to-faculty ratio.

Faculty members, especially those leading debriefing, have special training or experience in conducting crisis resource management–oriented training.

Debriefing Characteristics

Debriefings are performed with the whole group of participants together and use (as appropriate) audio-video recordings of the simulation sessions.

Debriefings emphasize constructive critique and analysis in which the participants are given the greatest opportunity possible to speak and to critique and to learn from each other (debriefing facilitation).

ACRM-like curricula use several teaching modalities to achieve these goals, including the following:

- A comprehensive textbook on anesthesia crisis management: *Crisis Management in Anesthesiology*. This book includes didactic material on ACRM principles and a comprehensive catalog of critical incidents in

TABLE 8-5 **EVALUATION OF ANESTHESIA CRISIS RESOURCE MANAGEMENT COURSE IN HARVARD ANESTHESIA SIMULATION TRAINING**

		Attending Staff (n = 30)		Residents and Fellows (n = 34)	
Rating	Scale	Evaluation of Simulator Environment (%)	Value of ACRM Course (%)	Evaluation of Simulator Environment (%)	Value of ACRM Course (%)
Less favorable	1	13	3	9	1
	2	10	3	6	2
	3	15	15	11	4
	4	10	25	28	28
More favorable	5	33	54	46	75

Modified from Holzman RS, Cooper JB, Gaba DM, et al: Anesthesia crisis resource management: real-life simulation training in operating room crises, J Clin Anesth *7:675-687, 1995.*
ACRM, Anesthesia crisis resource management.

anesthesia that provides guidelines for preventing, recognizing, and managing 83 perioperative situations in a uniform format. The catalog section of the text is intended to provide study material to increase anesthesiologists' stock of precompiled response plans to common and uncommon situations. This textbook has been translated into Japanese and German.

- A brief presentation reviewing the principles of CRM and patient safety.
- Analysis of a videotape of an aviation accident.
- Small group exercises analyzing a videotape of an actual patient care mishap or analyzing written or video presentations about difficult cases.
- Several hours of complex multifaceted realistic simulations in which training participants rotate through different roles, including primary anesthesiologist, first responder (called cold, with no knowledge of the situation), and scrub nurse. Other personnel play the roles of surgeons, nurses, and technicians as in a real operating room. Each situation is followed by a detailed debriefing with video feedback (see the earlier discussion of debriefing).

Several publications have detailed the response of participants with varying levels of experience to ACRM training.[111,125] Participants have been extremely positive about their experience in the ACRM course, and most believe that it contributes to their safe practice of anesthesia. Table 8-5 shows the results of one of the earliest studies on that topic. At VA-Stanford, ACRM has been extended to a multilevel course conducted over several years (i.e., ACRM 1, 2, 3). As the course levels progress, the scenarios become more complex and involve subspecialties of anesthesia. In addition, additional teaching modules cover other important aspects of organizational safety, such as systems thinking in morbidity and mortality conference settings or peer review settings, follow-up response to severe adverse perioperative events, and disclosure to the patient or family of bad news after an adverse event.

ACRM courses and ACRM-like variants are now offered worldwide and are often mandatory for trainees (and in some cases for experienced personnel). In Denmark, ACRM-like training courses are a legal requirement for nurse anesthetists (3-day course) and for first-year (2-day course) and third-year residents (4-day course), in addition to some other simulator training courses (e.g., difficult airway). Further plans are being made to require simulation training for ICU and recovery room nurses and ICU residents.[130-132] Salas and colleagues published an excellent critical overview about prerequisites for effective CRM training.[32]

SIMULATION FOR TRAINING OF ANESTHESIA RESIDENTS

Simulation is now a widely used technique in the training of anesthesia residents (see also Chapter 9). It is used in various ways—for technical training on particular procedures or patient care protocols (especially for airway management), for supplementing didactic instruction about anesthesia equipment, and for training on issues of decision making and nontechnical skills as outlined earlier concerning ACRM. Nearly every anesthesia residency program in the United States offers some cogent simulation training experiences, although the scope, frequency, and target content vary.

Other disciplines and other countries may not have adequate simulation training coverage during residency, as evidenced by a study by Hayes and colleagues.[133] This study examined the perception of Canadian internal medicine residents to be qualified for their service on the cardiac arrest team: 49% felt inadequately trained, 50% believed that the provided advanced life support course did not prepare them enough to lead the arrest team, and almost none received postevent debriefing or feedback.[133]

SPECIAL CONSIDERATIONS IN PEDIATRIC SIMULATION

A sizable body of international experience with simulation in pediatric settings now exists (see Chapter 93).[41,59,127,134,135-140] A study by Overly and co-workers that assessed airway management skills in pediatric residents identified many areas of concern about residents' abilities.[141] The authors concluded that high-fidelity simulation can be used to assess residents' airway management, and that the training program was effective to teach these skills.

Many centers use pediatric simulators predominantly for training of the management of critical incidents and medical emergencies. These simulations target trainees and specialists in anesthesia and pediatric critical care medicine. Because of the frequent organizational and



Figure 8-15. Pediatric full team simulation training. The primary trainees (anesthesia) must solve problems with the infant simulator while urologic surgical team members perform the procedure. *(Photograph provided by C. Eich.)*



Figure 8-16. Neonatal crisis resource management and resuscitation training at a neonatal emergency workplace. All treatment steps must be performed in the simulation to show the need to coordinate and delegate. The experienced instructor (on the right side of the infant) is taking part as a team member, whereas another instructor team is in the control room, to preside over simulation control and debriefing videos. *(Photograph taken at Stanford Simulation Center, Stanford University, Palo Alto, Calif.)*

BOX 8-6 ***Unique Aspects of Simulation in Pediatric Anesthesia***

- Huge discrepancy between high degree of required clinical proficiency and an often limited level of expertise
- Strong demand for training on medical-technical aspects of management—recommendation to participate in a pediatric advanced life support course before simulation team training course
- Need to familiarize with parental presence during pediatric anesthetic care by combination of simulation and role play
- Requirement by the small patient of an even better organization of the work environment and task responsibilities (in situ training)
- High-impact multidisciplinary team training, including crisis resource management
- High level of interest in assessment and certification of trainees and subspecialists for work in pediatric anesthesia

clinical overlap among personnel engaged in pediatric anesthesia, critical care, and emergency medicine, multispecialty personnel (physician crews from different specialties), and multidisciplinary personnel (crews from different professional disciplines), team training can be particularly helpful to prevent failures of cooperation at treatment interfaces (Figs. 8-15 and 8-16). A review by Eppich and colleagues on team training in pediatric acute care settings underlined the impact and effectiveness of team training for pediatric teams.[34] The American Academy of Pediatrics specifically recommends teamwork and communication training for all health care professionals in pediatric emergency settings, and the American Heart Association has included a team concept video and eight elements of team dynamics in its training programs.[142-144]

In contrast to adult medicine, the demand in pediatrics for simulation has been largely to address particular points of medical knowledge and technical skill, perhaps because many medical staff have little experience with pediatric care, especially for cases involving neonates and infants (Box 8-6).[145] Many simulation courses in pediatric anesthesia or intensive care need extensive involvement by experienced pediatric clinicians. More senior clinical personnel who work regularly in pediatric settings may be comfortable with their pediatric clinical skills, but they may be more interested in the generic nontechnical skills that are equally applicable to pediatric and adult care.[142]

A positive correlation exists between the difficulty of pediatric scenarios and the participants' own perception of the learning effect.[145] Scenarios that participants rarely encounter in their clinical practice (e.g., an infant in circulatory shock secondary to extensive thermal injury) on the one hand are thought to be threatening, but on the other hand are considered to be particularly beneficial in terms of training effect. A commonplace but interesting aspect inherent in pediatric simulation is the incorporation of role play by family members. Although family members may be present in adult medicine, their presence in pediatrics is nearly ubiquitous.[146] This presence can put further strain and stress on the provider, thus making it particularly useful to add family role players (either trained actors or instructors or even the participants themselves) to pediatric simulation scenarios.[134]

CONTINUING MEDICAL EDUCATION

Most simulation centers offer CME for experienced practitioners, and nearly all aspects of simulation training for residents (except novice training) can be expanded for this purpose. Several studies have shown that experienced anesthesiologists also have deficiencies in the management of critical patient situations and make severe errors comparable to those of anesthesia residents.[80,132,147-151] A study by Jacobsen and associates in Denmark,[152] involving 42 specialist anesthesiologists, showed major deficiencies in the diagnosis and treatment of anaphylactic shock and in application of the ACRM principles when a score adopted from Gaba and Howard was used.[85,153] Because crisis situations are rare during routine clinical work, these results are not unexpected. In addition, experience in terms of years on the job and hierarchy probably do not correspond to expertise and excellence. Crisis management training with simulators should be started early in education and training and applied on a recurring basis during practice.

An aspect of CME training in the United States is that it is regulated separately by each state, and it is nearly uniformly based only on the number of hours spent in the activity. Reading a short article and answering a handful of questions can generate 1 hour of credit, as can sitting through a lecture. Simulation training is generally much more interactive and much more intensive than other activities. In Australia and Germany, CME requirements are expressed in terms of points to be accrued. Simulation training counts for a large number of points per hour spent, commensurate with its intensity, which may make simulation-based CME financially competitive relative to simpler methods.

The ASA has established a standing Simulation Editorial Board. The ASA offers an endorsement (analogous to but different from an accreditation) of simulation programs that can show their capability to offer excellent CME curricula to ASA members. The Committee began reviewing applicants for endorsement in 2008.

At the Harvard University hospitals, the captive insurer, Harvard Risk Management Foundation, has taken unprecedented steps to link simulation-based CME training to discounts for medical malpractice premium rates for experienced clinicians in anesthesia and in obstetrics (J. Cooper, personal communication, 2005). This forward-thinking program is now being adopted by other malpractice carriers. In some jurisdictions, risk managers have chosen to invest directly in simulation activities at their institution, rather than to use the premium discount approach.

USE OF PATIENT SIMULATION FOR TRAINING HEALTH CARE PERSONNEL OUTSIDE ANESTHESIA

Anesthesiology remains a driving force in the use of simulation in health care, but simulation has spread to nearly every discipline and domain. It has proved particularly applicable to other areas that share the cognitive profile of anesthesiology—dynamic decision making (played out over seconds, minutes, and hours), with complex teams, wielding highly lethal interventions. ACRM-like training has been performed in settings that include, but are not limited to, intensive care,[129,154] emergency medicine and emergency field responders,[155-160] trauma medicine and surgery, neonatology (neonatal resuscitation and neonatal ICU), labor and delivery (see Fig. 8-16),[161,162] cardiac arrest and rapid response teams,[163-165] and radiology. Simulation is such a diverse technique that it is equally applicable—using different modalities of simulation—to nearly all domains. Knudson and colleagues found a significant improvement in overall and teamwork scores in surgical residents taking care of critically injured simulated trauma patients if the residents had undergone CRM-like simulation training.[35]



Figure 8-17. Simulation-based training center for military medics. The room is equipped with 10 SimMan training stations. During training sessions, one instructor team is sitting at each foot of each mannequin. Teaching is provided on scene during the sessions.

The military and the U.S. Department of Homeland Security also have been heavy users of simulation in health care; simulation has been applied to the initial training of new field medics and to the recurrent training of experienced clinicians and clinical teams.[166] Figure 8-17 shows a room with 10 simulators in a training center for military medics that has more than 100 simulator mannequins altogether. In 2013, a first instructor course for North Atlantic Treaty Organization (NATO) Special Operations Forces (SOF) was held at NATO headquarters in Brussels to bring together medical experts from the U.S. SOF, the NATO SOF, and some civilian instructor experts (including M. Rall). By now several such instructor courses have followed.

Simulation is now used more frequently in training for the management of chemical, biologic, or nuclear threats from accidents, weapons of mass destruction, or terrorism. One group in Tübingen, Germany, used their simulator to test the constraints of treating patients in full chemical protection gear (publication of the results is in preparation) to optimize the strategies of the German Ministry of Internal Affairs for dealing with terror attacks or chemical plant disasters (Figs. 8-18 and 8-19) (see Chapter 83). Several investigators have performed multidisciplinary studies with combined simulation modalities (script-based simulators, model-based mannequin simulators, and simulated acted patients) to teach the management of victims of an attack with weapons of mass destruction and terrorism.[74,75] The demand for such training is substantial in nations engaged in active



Figure 8-18. Realistic patient simulation as a test bed for studying the performance of medical rescue teams in full chemical protection gear. Teams wore normal uniforms or full protection suits while performing basic resuscitation actions (e.g., placement of intravenous lines, drawing up drugs, intubation). *(Photograph taken by M. Rall at the Center for Patient Safety and Simulation, Tübingen, Germany.)*



Figure 8-19. In rescue situations with full protective gear, communication within the team and with the patient is difficult. *(Photograph taken by M. Rall from a video screen at the Center for Patient Safety and Simulation, Tübingen, Germany.)*

military conflicts or with an ongoing need to prepare for war or terrorist attacks (e.g., the United States and Israel).

USE OF PATIENT SIMULATION FOR RESEARCH

Research in simulation falls into two categories: (1) research *about* simulation—testing or improving the techniques, technologies, and pedagogy of simulation; and (2) research that uses simulation as a tool to study other things, such as human performance, clinical cognition, or clinical care processes (see Chapter 7). Box 8-7 provides a sampling of these second types of questions. As a research tool, simulation offers some unique features, and it can be thought of as a complementary window on the clinical world relative to other modalities. One can study clinical work by using prospective observation of real cases. This has the benefit of being prospective, but by nature, more cases in most domains would be unremarkable, and one would mostly observe the routine and banal. For

BOX 8-7 *Research Issues That Can Be Addressed by Using Simulation*

Cognitive Science of Dynamic Decision Making (See Chapter 7)

What is the interaction of precompiled procedural knowledge versus deep medical knowledge and abstract reasoning?

How does supervisory control of observation relate to vigilance, data overload, and visual scanning patterns?

What is the information content of watching the surgical field?

How are optimal action planning and scheduling implemented?

How does reevaluation fail and result in fixation errors?

Human-Machine Interactions

What is the distraction penalty for false alarms?

Do integrated monitors and displays have an advantage over multiple stand-alone devices and displays?

How easy to use are the controls and displays of existing anesthesia equipment in standard case situations and in crisis situations?

Teaching Anesthesia in the Operating Room (See also Chapters 4 and 9)

How much teaching can be accomplished in the operating room without sacrificing the anesthesia crew's vigilance?

How well can faculty members detect and categorize the performance of anesthesia trainees?

What teaching styles are best integrated with case management in the operating room?

Issues of Teamwork

How does an anesthesia crew (attending anesthesiologist plus resident or certified registered nurse anesthetist) interact during case and crisis management?

How is workload distributed among individuals?

How do crew members communicate with each other, and how do they communicate with other members of the operating room team?

Effects of Performance-Shaping Factors on Anesthesiologist Performance

How do sleep deprivation, fatigue, aging, and the carryover effects of over-the-counter medications, coffee, or alcohol affect the performance of anesthesiologists?

Intelligent Decision Support

Can smart alarm systems or artificial intelligence provide correct and clinically meaningful decision support in the operating room or intensive care unit?

Development of New Devices and Applications: Research Regarding Techniques of Simulation

How well do simulators resemble the operating room and provoke the same actions as used in the operating room (ecologic validity of simulators)?

How much does debriefing add to learning from simulation? Are specific techniques of debriefing (e.g., use of video, participant-centered discussion) of significant utility?

How does the setting of simulation scenarios influence aspects of perceived reality, and how does it influence transfer into the real world?

Does simulation training lead to better clinical practice and improved clinical outcomes?

TABLE 8-6 **TRANSLATIONAL RESEARCH LEVELS OF SIMULATION-BASED TRAINING**

Level	Description of Study Methodology (Typically in a With/Without Simulation Training Intervention Study Design)	Comments or Examples
0	No measurement of learner performance	Questionnaire of reaction to simulation or change in knowledge
1	Performance measured during simulation only	Can they do better in a simulation?
2	Performance measured during actual clinical care	Can they do better in clinical practice
3	Measurement of improvement in patient outcome	Do patients actually fare better?
3′ (cost effectiveness)	Measurement of the cost of the intervention and the outcome and monetary benefit	Does the intervention yield a net saving of money (with/without also improving outcome)?
4	Measurement of dissemination of the intervention to sites beyond trial sites	Can the intervention be spread elsewhere successfully?
5	Measurement of the adoption of the intervention in regular practice	Can the intervention be widely adopted?
6	Measurement of population health outcome	Will it make an impact on the patient population as a whole?

some purposes, this study would be more than sufficient. Another source of information is in case reports of challenging cases, whether the challenges were expected or unexpected. These also are real cases, and they are out of the ordinary, but the data obtained from such retrospective reports are usually scant and biased.

Simulation provides an alternative view of clinical work that can be prospective and about challenging cases, albeit simulated cases. The simulation centers around the world probably have the largest experience by far of observing anesthesiologists managing (simulated) malignant hyperthermia. It is difficult to imagine how else one could gather systematic data about how clinicians work while managing this uncommon, life-threatening situation.

An important milestone for simulation-based research of both types was the initial publication by the Society for Simulation in Healthcare in 2007 of their peer-reviewed journal, *Simulation in Healthcare* (David Gaba is the founding editor-in-chief of the journal). In addition, for research that is linked tightly to a specific clinical domain, the traditional medical specialty journals have become more welcoming to articles about simulation or that use simulation as an experimental technique.

Cooperation between simulation directors or instructors and psychologists, human factors engineers, or educators has proved useful in research and training. Such collaborations have helped delineate the theoretical foundations of simulation-based experiential learning, improve the understanding of debriefing, and research on work psychology and human performance in health care.[†] Many institutions have integrated psychologists or educators, or both, into their simulation center staff.[120] Ways to make such collaborations fruitful and rewarding also have been described.

APPLYING THE TRANSLATIONAL RESEARCH PARADIGM TO SIMULATION

The concepts of a continuum of research from fundamental science through clinical trials to widespread use in patient care and of potential translational blocks were articulated by Sung and colleagues in 2003.[169] From this publication emerged various nomenclatures for the different levels of the research continuum in terms of increasing level of translation. William McGaghie, PhD, then at Northwestern University, first adapted the T levels of translational research to the arenas of medical education and simulation in health care, comprising T1, T2, T3, and T3′ (Table 8-6).[170-172]

Gaba then adapted additional levels mentioned in other sources,[173] including the website of the U.S. National Cancer Institute (http://www.cancer.gov/researchandfunding/trwg/TRWG-definition-and-TR-continuum), and added levels of T0, T4, T5, and T6 (see Table 8-6). Researchers in simulation are now encouraged to use this terminology in describing and comparing their research protocols and results. At this point, most studies of simulation-based learning are at level T0 or T1. A few studies have been at T2 and only a handful at T3 or T3′. Levels T4 and T5 can be considered implementation science, but few studies of implementation have been performed. The field is encouraged to move toward higher levels of translational research whenever possible. However, doing so will be very difficult, especially in going to the T3 level. Many applications of simulation in anesthesiology especially focus on preparing anesthesia professionals to prevent and manage uncommon but serious adverse events more effectively. The rarity of such events and the many confounding variables that affect patient outcome will make intervention studies very difficult to perform.[174] These studies would perforce need to be large, long, and complicated. To date, almost all studies have been too short and too unsystematic, with weak interventions and without adequate control of confounding variables. Unlike many types of clinical trials, which are funded by the pharmaceutical industry, which is willing to invest heavily even in complex trials because of the high direct payoff when a blockbuster drug is found, simulation interventions have no equivalent funding sources. Obtaining level 1A evidence (multiple randomized controlled trials) of simulation's impact on patient outcome may well take studies of thousands to hundreds of thousands of patients, cared for by hundreds or thousands of clinicians, with simulation

[†]References 18, 19, 25, 26, 47, 167, 168.

interventions that are powerful, comprehensive, sustained, and also linked to performance assessment (and remediation) of individual clinicians. As yet, no agency or commercial firm is willing to fund these kinds of large, long, and complex studies.[174]

USE OF PATIENT SIMULATION IN SUPPORT OF BIOMEDICAL INDUSTRIES

Various simulation activities have been undertaken by the pharmaceutical or medical equipment industries. Numerous centers (perhaps the University of Florida at Gainesville was the first) offer training to executives and sales representatives of equipment and pharmaceutical manufacturers. The simulator allows these individuals to gain some understanding of the clinician's task demands during patient care and the situations in which their company's drugs or devices could be useful. At the Boston Center for Medical Simulation, this course is dubbed "Anesthesia for Amateurs." Other industrial uses include training personnel in the use of novel pharmaceuticals. Simulators have been featured in a multifaceted approach to launch the opioid remifentanil. Simulators were used to train the manufacturer's representatives and clinicians in safe use of the drug, and it was possible to train anesthesiologists in the application of remifentanil with the simulator before remifentanil was approved by the U.S. Food and Drug Administration (W.B. Murray, personal communication, 1998.) Besides offering important educational benefits, industrial activities are an important source of income for simulation centers to help defray the costs of training students and residents.

Simulators have been used to conduct research on human factors issues in the development of new monitoring and therapeutic devices. The simulator also provides a unique test bed and demonstration modality for preprocurement evaluation of the usability of medical devices from different manufacturers. In our own hospitals (Stanford University, Palo Alto, Calif., and Tübingen, Germany), simulators enabled us to conduct evaluations of prototype monitoring systems that were not yet approved for clinical use and could not be evaluated in a preprocurement clinical trial.

OTHER USES OF SIMULATORS

Other unique applications of simulators have surfaced. Some centers use simulators for conducting outreach programs with high school or college students interested in health care. Simulators have been used to help produce educational videos on various patient safety issues. Holding a "legislator day" in a simulator center to familiarize legislators with the demands of dynamic patient care has been suggested.

Simulators have been used as adjuncts in medicolegal proceedings.[175] Current patient simulators cannot predict the exact physiologic behavior of a specific patient, but they can be used to illustrate typical perioperative situations and the role of different monitors and therapeutic actions and to provide context for the patient management questions of the litigation.

EFFECTIVENESS OF SIMULATION TRAINING

Flanagan and associates provided a thorough review of the literature to date on the efficacy of simulation-based training for learning and assessment.[176] The investigators identified more than 3500 articles, of which 458 were included in the review. The conclusion was that "simulation makes a valuable contribution to learning for students, trainees and clinicians. It enables learning of both routine and non-routine procedures and management of patients."[176] They further concluded that simulation is widely used in teaching and learning, is increasingly used for formative and low-stakes assessments, and is rarely used (but under growing consideration for) high-stakes summative assessment. These investigators also observed that the range of simulation modalities used for these activities varies widely.[176] Similar to the BEME review by Issenberg and colleagues,[24] Flanagan and associates found that many studies lacked a robust design, and that the level of outcome effectiveness as measured with a modified Kirkpatrick scale rarely exceeded 3 out of 6, with most at the level of 2 or lower.

The most important question concerning simulator-based training in anesthesia is its cost effectiveness. This complicated question has two independent components. The first component pertains to the impact and benefit of the training on the performance abilities of participants, and the second is the cost to achieve that impact. In principle, simulation has many advantages as a training tool, as follows[177]:

- No risk is posed to a patient.
- Exercises in routine procedures can be repeated intensively, whereas situations and events involving uncommon but serious problems can be presented at will.
- Participants can learn to use actual complex devices (with a hands-on simulator).
- The same situation can be presented independently to multiple subjects for evaluating individual or group performance.
- Errors can be allowed to occur that in a clinical setting would require immediate intervention by a supervisor.
- The simulation can be frozen to allow discussion of the situation and its management, and it can be restarted or begun anew to show alternative strategies or techniques.
- Recording, replay, and critique of performance are facilitated because patient safety or confidentiality is not an issue.

The fidelity required of the simulator and the choice between screen-only and realistic simulators depend on the intended goals of the training and the relevant target population. A spectrum of computer-based training is possible. Computer-assisted instruction programs and part-task trainers can be used to teach basic concepts and technical material, such as the uptake and distribution

of inhaled anesthetics or the pharmacokinetics of intravenous drugs. These uses are appropriate for students, novices, advanced residents, and experienced practitioners. Screen-only simulators are inexpensive and easy to use. They allow the presentation of and practice with the concepts and procedures involved in managing normal and abnormal case situations. They also are useful for numerous user populations. Realistic simulators can be used to capture the full complexity of the real task domain, including human-machine interactions and the complications of working with multiple personnel. They are most appropriately used for residents and experienced practitioners. Regardless of the device used, the simulator is only a teaching tool that must be coupled with an effective curriculum for its use.[24]

The evaluations conducted suggest that simulator-based training is a powerful technique that novice and experienced anesthesiologists believe to be highly beneficial and that participants and instructors alike believe may improve clinical performance. As the developers of Sim One 7 pointed out, when simulation provides an opportunity to teach material that cannot be taught in another way, as for the systematic instruction of anesthesiologists in handling severe critical events such as cardiac arrest, anaphylaxis, or malignant hyperthermia, there is nothing with which to compare the simulator. Assessing whether the actual outcome of patients can be affected by this or any other training modality would be extremely difficult and expensive. Individuals investigating simulator-based training do not believe that definitive outcome studies of this type are logistically feasible.[178] Determining the impact of a given type of simulator training on the intermediate variables of performance and ability is feasible, but it would not be easy. The Leiden group provided data supporting the contention that simulation training improves performance in handling a malignant hyperthermia situation. The potential exists, however, for substantial bias when attempting to measure the impact of simulator training by using performance in the simulator as a criterion. The control procedures used by the Leiden group alleviate this bias, but they cannot eliminate it.[179]

Perhaps of even greater importance, no methodology is currently accepted for measuring the clinical performance of anesthesiologists either in the simulator or in actual practice.[180] Ironically, the simulator itself provides a tool for presenting the same calibrated situation to multiple anesthesiologists and may be a crucial tool in developing such performance measures. Many groups around the world are trying to refine performance measurement tools,[123,162,181-200] but no gold standard measurement is yet available to assess a simulation's effectiveness (see the later section on evaluation of performance).[180]

HOW SIMULATION CAN BE MORE EFFECTIVE

Health care has not yet scratched the surface of assessing the impact of simulation-based training. Most simulation is currently targeted at students and trainees (i.e., residents), although programs targeting experienced personnel are growing. The assessment of the impact of simulation to date can be seen using the following analogy to drug development and testing. Suppose we wished to test whether a purported antihypertensive drug actually succeeded in reducing blood pressure in patients and, more importantly, whether it reduced the occurrence of adverse cardiovascular events, such as myocardial infarction and stroke. Imagine then that we proceeded as follows: Administer a relatively small dose of this drug only a few times per year. Acknowledge variable compliance in taking even these few doses of drug. Immerse all subjects in an environment full of stress and other factors predisposing to cardiovascular events. Use only a few patients, and follow them for a very short time.

Using this methodology, would anyone wonder if no significant effect was found even for a drug otherwise known to be effective? Simulation in health care has so far been tested in this way: very small, short-term studies of infrequent (often short) simulation sessions, whose lessons are not fully reinforced in real clinical environments full of production pressure and stress. In truth, the question is not, Does one run through a simulation course make a practitioner better? To follow the lead of other industries of intrinsic hazard, such as commercial aviation or nuclear power production, the real question is, What is the impact on health care as an industry adopting a comprehensive integrated strategy of intensive simulation-based training and continued performance assessment of clinical personnel, over a long period of time? This is the approach in aviation, in which no matter how senior and how experienced pilots are, they still undergo training and assessment in simulation every year, for the entirety of their careers.

Even so, industries such as aviation do not have anything resembling level 1A evidence for the benefits of simulation, even though such studies could be grafted onto the existing structure of yearly training and testing. It is unlikely that aviation would ever attempt randomized trials. For one thing, as the saying goes, pilots are the first ones at the scene of the accident. It seems unlikely that pilots would forgo simulation training and assessment when their own lives are on the line. For another thing, the public has come to expect a regulatory safety floor imposed by the government to ensure the competence of pilots. The regulator is unlikely to forgo its requirement for mandatory training and testing of pilots. If such requirements continue, there may be only two options: conduct these exercises in real airplanes, with the attendant costs (e.g., fuel) and risks; or conduct them using simulation. With health care heading in that direction,[36,37,41,44,201-205] we may be able to assess the impact of more effective simulation programs, although we may lose a control group that has never experienced simulation.

AVOIDING SUBTHRESHOLD TRAINING EFFECTS

To date, simulation training has largely been employed in small doses given intermittently, not sustained over the long term, and ignoring many personnel who are crucial in the chain of patient care. When conducted this way, simulation training may not achieve a critical mass and may produce a subthreshold effect. It seems likely that a long-term cumulative effect would be achieved only

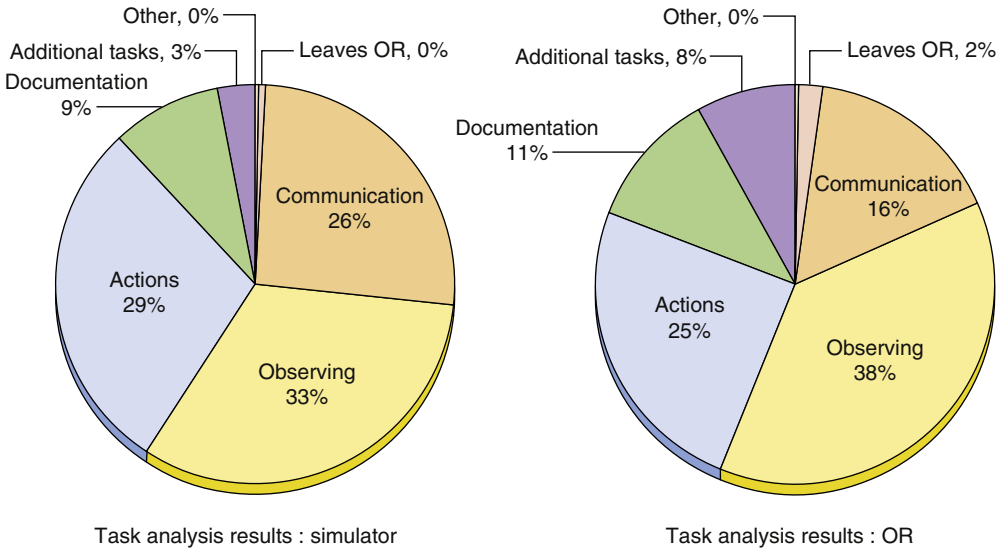


Figure 8-20. Validity of simulator systems versus the operating room (OR). The same anesthesiologists were observed in the OR and in the simulator environment with full enactment of the OR personnel, surgical team, and anesthesia nurse. Even though the two settings have some interesting differences, the overall ecologic validity of the simulator is good. *(Courtesy of T. Manser, ETH Zurich, and University Hospital, Tübingen, Germany.)*

with a long-term comprehensive program of training and performance assessment.

Perhaps it is worth the inherent logistical difficulties and costs to undertake bulk training (>75% of personnel trained in a short time, rather than starting a program of training a few individuals a month and achieving a high penetration rate only in months or years). Where the training is about teamwork and behavioral issues (CRM focused), this may be especially important, so that the lessons taught in the simulator are continuously reinforced by experiences in real patient care. The hope is that creating a critical mass of adherents to CRM principles through simulation would create self-sustaining reinforcement of safety-oriented behaviors that continues with only occasional refresher sessions of simulation.

An analogy for that effect would be the starting of a fire with wood logs: If you take away the match too early, you do not light the fire, and all you get is a black mark on the wood, but if you keep the match on the wood long enough (similar to activation energy), the fire starts to burn and spread to all logs without any more input—similar to what we would like to see with CRM team behaviors.

ECOLOGIC VALIDITY OF SIMULATORS COMPARED WITH THE OPERATING ROOM

The question whether full-scale simulators are an ecologically valid representation of the operating room (i.e., to what extent "the environment experienced by the subjects in a scientific investigation has the properties it is supposed or assumed to have by the experimenter"[206]) was investigated by an interdisciplinary research group in Tübingen, Germany and Zurich[167] (see also Chapter 4). If the actions in the simulator resemble the actions in real operating room environments (*behavioral validity*), it is much more likely that the results of research conducted in a simulator setting or lessons learned in the simulator environment will be transferable to the context of actual patient care. The group developed an improved task analysis method that allows the recording of overlapping activities (41 actions from 5 categories—monitoring, actions, communication, documentation, and other) to analyze and describe the performance of anesthesia.[207]

This method is described in more detail in Chapter 7. Each of the six anesthesiologists participating in the study was observed during two clinical cases and during three comparable simulator cases (one routine and two involving critical incidents). Analysis of the study showed good comparability of the different action categories (Fig. 8-20). The interpretation of the group was that overall comparability between the operating room and the simulator setting is good, thereby indicating high ecologic validity for simulators in anesthesia. The results of the study also showed few, but distinct variations in the task structure of operating room and simulator cases. These variations were mostly the result of organizational factors (e.g., fewer additional tasks required in the simulator). These studies provide objective confirmation of the favorable subjective impressions of realistic simulation scenarios by anesthesiologists of varying levels of experience.[148,149,187,189,208-210]

Some differences between simulation and real patient care are inherent to simulation. Subjects realize that they are in a simulator and are likely to be hypervigilant (e.g., many participants neglect documentation in the simulator while waiting for a disaster to happen). In addition, some organizational factors are usually different in the simulator from the real operating room (e.g., reflected in fewer additional tasks in the simulator compared with the real operating room in the study of Manser and Rall). Careful and creative scenario design and introductory briefings may mitigate the hypervigilance and organizational effects.[45,211]

EVALUATION OF CLINICAL PERFORMANCE DURING SIMULATION SCENARIOS

The introduction of patient simulators allowed the study of human performance when responding to critical events (see Chapter 7). Techniques are needed to assess anesthesiologists' performance.[212] Performance can be divided

into two components: medical or technical performance, which is the appropriateness and thoroughness of the medical and technical response to the critical event; and behavioural or nontechnical[213] performance, which is the appropriate use of sound crisis management behaviors (e.g., leadership, communication, distribution of workload).[214,215] (See Chapter 7 on CRM.) Assessment of medical and technical responses has resulted in technical scores suggested by different authors.[179,180,188,189,216-219]

Simulation offers some benefits in assessing medical or technical performance. Because the nature and cause of the critical incident are known, one can construct in advance a list of appropriate technical activities. Relative weighting of the importance of the different activities can be applied to reflect the fact that different activities, even if appropriate, differ in their importance. This weighting can be done either in advance of data collection, or post hoc (but in an appropriately blinded fashion). For example, when assessing medical or technical performance in managing malignant hyperthermia, termination of the trigger agent and administration of intravenous dantrolene would be highly important, indeed essential, items. Cooling measures, hyperventilation, and bicarbonate therapy would be among many appropriate (but less critical) responses. One also can predict in advance specific technical errors. For example, for malignant hyperthermia management, these could include diluting dantrolene with the wrong diluent or an insufficient quantity of diluent. These errors are known to plague clinicians unfamiliar with therapy for malignant hyperthermia.

Can the clinical outcome of the simulator's mathematic physiology model (if present) predict how a real patient would have fared under the clinician's care? Even when mathematic models are used, they are insufficient to predict what would happen to any actual patient after complex sequences of therapy and more subtle patient care judgments. The models have not proven to be robust enough for such purposes and have shown a lack of reproducible outcomes even when the same patient in the simulation is given identical perturbations and treatments at exactly the same times.

In situations of extremely poor (or good) performance, the model's predicted outcome may properly indicate failure or success of performance. For example, a subject who shows totally erroneous decision making (e.g., failure to defibrillate a simulated patient with ventricular fibrillation) unmistakably allows a patient's state to deteriorate quickly. However, the converse may not be true. Perfect decision making in resuscitation of a real patient cannot guarantee that electric countershock would successfully restore a normal cardiac rhythm. We suggest that even with model-driven simulators, the clinical outcome of the simulated patient is at best one datum that can be used to assess the performance of the anesthesia professional on a simulation scenario. For the foreseeable future, any credible performance measurement technique must involve many subjective and semiobjective judgments by clinical experts. Many empiric studies have attempted to use simulation for different forms of performance assessment in various domains and disciplines.‡

‡References 11, 31, 35, 38, 42, 75, 141, 149, 190, 201, 204, 220-246.

PITFALLS OF PERFORMANCE ASSESSMENT

Previous trials, experience in other industries, and theoretical analysis suggest that simulation offers substantial opportunities to facilitate performance assessment. The following issues must be resolved, however, to make performance assessment a robust capacity:

Technical versus nontechnical (CRM) skills. As indicated in previous sections, it is feasible (if difficult) to assess a technical response to specific events and generic nontechnical behaviors (CRM). For which kinds of assessments is it appropriate to measure only technical performance, only nontechnical performance, or some combination of the two?

Number of scenarios. How many different scenarios are needed to achieve robust performance assessment of individuals in all relevant aspects (technical and nontechnical) of patient care? The literature suggests that having a larger number of scenarios is more effective in improving the reliability of ratings than is having a larger number of raters.[247-249]

Rating individuals versus rating crews or teams. Anesthesiologists work as individuals and in crews and teams with other anesthesiologists and with surgeons, nurses, technicians, and others. Should the performance of individuals working alone be assessed? Should anesthesiologists be able to call for and use help in solving problems? If so, can one still rate the individual when working with a team?

Performance fluctuation. How can performance that fluctuates substantially over time be aggregated into a single rating? This issue was recognized by Gaba and colleagues as a major apparent source of interrater disagreement.[215] It is not addressed by the Anaesthetists' Non-Technical Skills (ANTS) system.[190,250] Which techniques would best address this issue, especially as applied to scenarios that represent the actual complexity of clinical practice?

Criterion thresholds. What level of performance should be set as criterion thresholds for different purposes? Can benchmarks of performance be established by truly expert clinicians (recognizing that years of experience and hierarchic rank are not surrogates for expertise or skill)? Similarly, how does the rating system deal with single actions or behaviors that were lethal or harmful in the presence of otherwise good performance? If used for formative assessment, a rating system should indicate the successes of the examinee and the failures. If used for summative or high-stakes assessment, however, it may be critical to ensure that the examinee who risks harming a simulated patient cannot outscore another examinee whose overall performance is less strong but who at least did not endanger the patient. Not performing chest compressions in a cardiac arrest situation would be such criterion for exclusion.

Appropriate statistical analysis of validity, interrater reliability, and reproducibility of these assessments. Various statistical tests and approaches have been used to evaluate these characteristics. The data on performance show various levels of interrater variance and high interindividual (and interteam) variability.[149,179,187-189,208,215,251] As detailed by Gaba and colleagues,[215] some interrater reliability statistics are more stringent than others, especially in terms of the nature of the "by chance" benchmark. No

firm consensus has been reached regarding which tests are most appropriate to answer key questions about simulation-based performance assessment. Some of the rating systems (including ANTS) have used less stringent tests of interrater reliability. Generalizability theory offers a set of statistical techniques to sort out the impact of scenario, subject, rater, number of scenarios, and other facets on such assessments.[252,253] This technique also specifies how comparisons can be made against reference performance levels or as relative comparisons between subjects without a fixed benchmark.

Although simulation should enable performance assessment, a robust set of performance measures of anesthesiologists' skill would be difficult to develop,[254] even if the simulator is used as a tool to present standardized patient scenarios.[255]

Klemola and Norros published a newer way of looking at performance that involves anesthesiologists' habit of actions.[256] These authors distinguished between "reactive habits" (conservative, self-contained, reluctant to construct subjective evaluations) and "interpretative habits" (creative, interactive, continuous integrative reasoning). This article showed that many issues must be considered when discussing the best method of education and evaluation. Additional issues include defining and assessing professional competence. A more consultant-based method was introduced by Greaves and Grant,[257] who compiled an inventory of characteristics of the anesthesiologist's practice. Epstein and Hundert provided a review.[258]

USE OF SIMULATORS FOR THE EVALUATION AND TESTING OF ANESTHESIA PROFESSIONALS

The use of simulation as a tool for performance assessment has presumed advantages: scenarios are known, errors can be allowed to occur and play out, and intensive recording and archiving of performance is possible; all these features provide a window on performance that is otherwise unattainable.[259] Scoring or certifying competence by using the simulator is more problematic than using the simulator as a teaching tool, however. Anesthesiologists have long discussed the possibility of using the simulator as a tool for examinations, either for graduation from a residency or for ABA certification. In Israel, a simulation examination has become part of the board certification process.[260]

Despite these difficulties, the use of anesthesia simulators to assist in evaluating performance is likely to increase in the future.[§]

Even though simulation is currently used for some high-stakes examinations, the challenges remain the same:

It requires independent evaluation of the simulation scenarios and assessment of the predictive power of the subjective judgments made by experts scoring the examinee.

One obstacle is the lack of any well-accepted standard for performance evaluation.

Another difficulty with using simulation for board certification testing is that the operating room equipment would rarely be the same as that used by the candidate, and the operating room staff's operational protocols could differ from the protocols familiar to the candidate. In the training situation, these difficulties can be overlooked as part of the global suspension of disbelief needed to maximize the benefits of simulator training. In the test situation, these differences potentially could skew the results. This issue could be addressed by allowing candidates preparing to take their examination to undergo sufficient practice sessions to familiarize themselves fully with the standard simulation environment used for the test.

Another situation of simulation-based performance assessment would be for the evaluation of trainees or experienced clinicians who have been placed on probation or for whom dismissal from their position is already a distinct possibility. For these clinicians, the burden of proof is on them to show their skills. Simulation could offer a more controlled environment for these clinicians to do so. The same could be true for practitioners who wish to return to clinical work after a hiatus.

The existing systems of performance evaluation, which use a haphazard composite of subjective judgment of clinical competency in clinical work along with written and oral examinations, has itself never been validated. Many experts believe that the written examination does not correlate well with clinical ability, and the degree to which the oral examination process tests actual clinical skill is unknown. Simulation could offer candidates the opportunity to show their clinical abilities in a controlled clinical domain; appropriate scenarios can also probe language skills and the ability to act as an effective consultant to other clinicians.[263-265]

In the United States, the ABA has been monitoring the progress of simulation for training and performance assessment. The ABA now requires attendance at a simulation training course at an ASA-endorsed simulation program in the 10-year cycle of MOCA for ABA diplomates[266] (Box 8-8). The course must be at least 6 hours in length, must provide every attendee a chance to be the primary anesthesiologist for a scenario, and must cover cases of hemodynamic instability, hypoxemia, and issues of teamwork and communication, and include postscenario debriefing. However, except for the formative assessment intrinsic to debriefing, the MOCA simulation course does not involve any performance assessment of participants and is specifically not an examination. The ABA announced in late 2012 that it will transition by 2017 to a new format for the Part 2 Examination, named the APPLIED Examination, to include an Objective Standardized Clinical Examination (OSCE) component along with the traditional structured oral examination component. An eight-member OSCE Development Advisory Panel has been selected, and it contains many individuals with extensive experience in simulation. The OSCEs may use part-task trainers, actors playing standardized patients or other role players, and other elements within the broad scope of simulation. It appears that the OSCEs will not use full-blown mannequin-based simulations.

[§] References 36, 37, 112, 201, 203, 227, 261-264.

BOX 8-8 ***Simulation as a Required Element of Part IV of the U.S. Maintenance of Certification in Anesthesia Program by the American Board of Anesthesiology (See Also Chapter 1)***

The simulation course must be held at a site endorsed by the American Society of Anesthesiologists (ASA), with a curriculum meeting minimum standards set by the ASA. Although not specifying anesthesia crisis resource management (ACRM) directly, the standards for the U.S. Maintenance of Certification in Anesthesia (MOCA) simulation are clearly derived from the ACRM simulation courses that have become common around the world:

- A minimum of 6 hours of total course instruction
- Active participation in realistic (mannequin-based) simulation scenarios
- Postscenario instructor-facilitated peer debriefing
- Management of difficult patient-care scenarios, including at least scenarios involving the following: (1) hemodynamic instability; and (2) hypoxemia of any cause, including management of the difficult airway
- An emphasis on teamwork and communication
- All participants have at least one opportunity to be the primary anesthesiologist in charge (i.e., the "hot seat")
- The instructor–to–student ratio must be no greater than 1:5 (i.e., at least one instructor per five participants)

The first 2 years' experience with the MOCA simulation course showed that participants consistently found the experience to be realistic, relevant, and likely to result in practice change.[266,274] During or after the course, participants must declare what changes they intend to make to their practice. They are queried electronically by the ASA 30 to 90 days after the course to determine whether they made those changes and/or what barriers they encountered in trying to do so. These data are analyzed by the ASA Simulation Editorial Board to attempt to determine the likely impact of MOCA simulation on clinical care by American Board of Anesthesiology diplomates.

Thus, reasonable arguments can be made that the field of performance assessment has advanced sufficiently to allow consideration of simulation-based examinations, including full mannequin-based simulations, even for high-stakes purposes, especially considering the limitations of the current systems of written and oral examination.[263] Nonetheless, simulation-based performance assessment remains a controversial topic for discussion in the simulation and clinical anesthesiology communities. The anesthesia professions should be careful about how they may introduce simulation-based performance evaluation.[267] The controversy should not divert attention from the most common application of simulation, which is to improve clinical performance through training individuals and team to prevent and manage adverse clinical events.

CHARACTERISTICS OF SIMULATION CENTERS

Although one can install a simulator in a laboratory or conference room, or conduct only in situ simulation, many institutions have chosen to construct complete simulation centers. Figures 8-21 and 8-22 show floor plans of medium-sized centers (two to four simulation rooms) for mannequin-based simulation. Typically, these centers provide a separate control room to allow complex simulations to be presented without an instructor intruding on the simulated case. The center also provides a debriefing room where videotapes of the simulation session can be reviewed. Some centers have elaborate computer-controlled audio-video systems allowing the recording of multiple views with real-time annotation rapid search to annotated portions of the recording. Figure 8-23 shows the simulator control room with advanced audio-video equipment at Rall's Center for Patient Safety and Simulation (TuPASS) in Tübingen, Germany.

Universities and hospitals or hospital networks are increasingly constructing very large multidisciplinary and multimodal simulation facilities. Often, these facilities combine all the types of simulation and immersive learning in one large unit, including actors playing standardized patients (usually in clinic settings), mannequin-based simulation, part-task and surgical and procedural trainers, wet and dry work (e.g., plaster casting or procedures on food products), and different forms of virtual reality. Sometimes these also incorporate facilities for dissection of cadavers or the use of anesthetized animals. Having all forms of simulation together also fosters hybrid techniques, as when an actor playing a standardized patient is combined with a part-task trainer, or when a surgical simulator is combined with a mannequin-based patient simulator. Large multidisciplinary facilities may have anesthesiologists in leadership positions. Figure 8-24 shows the floor plan of the center for immersive learning at Stanford University.

The cost structure of a simulation center is a complex issue (see the next section). The cost varies greatly depending on the scope of the facility and its programs, the nature of the target populations, and the extent of use by the different possible stakeholder groups. How the costs are allocated to different elements of an institution or consortium is equally complicated and depends highly on local conditions. No one formula for success exists. In some models, the center is wholly responsible for its own costs but is completely free to generate and retain revenue. At the other extreme is a model whereby the host institution bears all costs of operating a central core facility, but it also collects any and all revenues and may even tax components of the institution (e.g., departments) to offset the costs. Perhaps most common are mixed models in which the central authority bears the costs of initial construction and outfitting (often funded by philanthropy) and some portion of the ongoing infrastructure (simulation operations personnel, capital refurbishment, utilities), and each user (e.g., department) is responsible for providing instructors and paying for the marginal costs of any specific course or application. To date, few, if any, centers truly generate a profit, but many sites have successfully garnered external funds to offset some of the costs of training their own key target populations.



Figure 8-21. Multiroom simulation center at the Veterans Affairs–Palo Alto Health Care System and Stanford University (Palo Alto, Calif.). Two control rooms and two audiovisually interconnected lecture rooms provide the opportunity to run three patient simulators at the same time. *ER,* Emergency room; *ICU,* intensive care unit; *OR,* operating room.

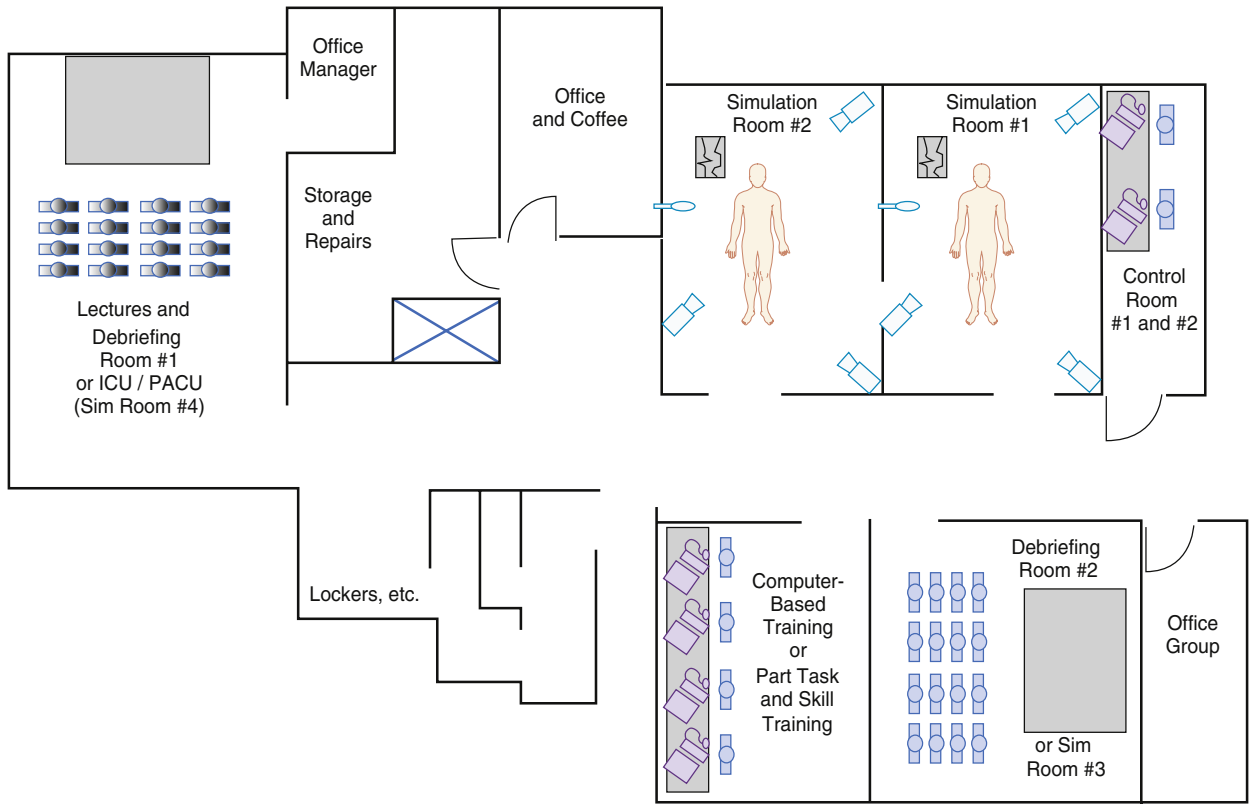


Figure 8-22. An intermediate-sized simulation center with four simulation rooms (Sim Room), a computer-based training room, and several multipurpose rooms, equipped with audio-video patch panels to adjust the room use flexibly to the needs of different training activities (e.g., the large seminar room also can be used as a large intensive care unit [ICU] or postanesthesia care unit [PACG]). *(Photograph by E. Stricker from the Center for Patient Safety and Simulation [TuPASS], Tübingen, Germany.)*



Figure 8-23. Simulator control room. On the left side is the simulator workstation for control of the simulator system itself. In the middle is the audio control desk with integrated control of the simulated patient voice and several wireless headset channels and the remote mixer. On the right are flat screens for selection and control of the multiple views of the video cameras. For anesthesia crisis resource management courses, a multiquad-split view, including the vital sign monitor, is digitally recorded on a hard disk and used for playback. Marks allow jumping to interesting scenes without fast forward or rewind delay. *(Photograph taken by M. Rall in the control room of the Center for Patient Safety and Simulation [TuPASS], Tübingen, Germany.)*

COSTS

What are the costs of simulator-based training? These costs depend on many of the same factors that determine the curriculum, as follows:

Types of training involved, ranging from technology in-service to training in basic anesthesia skills, critical incident management, or CRM
Target populations for the training, whether equipment technicians, medical students, novice residents, experienced residents, nurse anesthetists, teaching faculty, or private practitioners
Organizational and financial characteristics of the institution

The hardware and software costs of the screen-only simulators are quite low (a few hundred dollars), whereas the equivalent cost of a complete hands-on simulator is higher. The prices of commercial simulators range from approximately $25,000 for intermediate-capability simulators to more than $150,000, depending on features; one should contact the manufacturers for detailed information. Cumin and Merry reported on available simulators.[77] This cost does not include the necessary clinical equipment (which might run as high as $150,000) and space.[268] Even these large expenditures do not dominate in the cost equation, however, because the capital equipment can be amortized over a relatively long useful life, with appropriate provisions for service and upgrades.

The dominant cost is likely to be the salaries of expert instructors and trainees. An expert must oversee the curriculum, but the type of training and the target population determine the amount of expert instruction required. A single faculty member can review the summaries of exercises performed by residents on a screen-based simulator in a few hours per resident per year. Nonphysician instructors may be suitable for some task training or for drill and practice sessions. A single instructor can use the simulator to show pulmonary or cardiovascular physiology to a whole class of medical students. For training novice residents in basic anesthesia skills, it may be possible to have senior residents or fellows conduct the sessions at a low marginal cost. For training experienced residents and practitioners in complex material, such as the handling of critical events, no substitute for expert instructors is likely to exist. The cost of expert instruction depends on the organizational arrangements of the institution. In a teaching institution where faculty members all have at least some time allocated for teaching or scholarly activities, some faculty may choose to fulfill this requirement in simulation-based teaching or scholarship. When further staffing is needed, payment for clinical release time may be needed.

Another organizational factor that affects cost has to do with making trainees available for what can be complex, exhausting, and lengthy training sessions. Removing residents from revenue-producing work for training purposes is expensive. If simulator training could allow residents or other anesthesiologists to work more safely and efficiently, the benefit would outweigh the cost. Some residency programs provide protected time for education of residents (e.g., one half day per week). In such cases, residents should be available for educational activities, but faculty time may be even more scarce. Many anesthesia programs have used simulation training as a recruiting tool for residency candidates, although some experts believe that with the high proportion of programs that already have simulation activities (the scope and quality of which are difficult for applicants to judge), the competitive value of simulation has disappeared. Programs that lack such facilities and activities would be the exception and would likely be seen negatively by applicants.

Signs indicate that simulation team training may also improve job satisfaction and effectiveness of routine care, as well as contributing to reduced illness leave and job fluctuations.[269]

Without question, simulation-based training is more costly than exhorting learners to read or putting them in a room with a lecturer. Simulation-based training allows a host of issues to be addressed that cannot be easily tackled in other ways. It is our belief—one that has been borne out by programs "voting with their feet" since the 1990s—that if simulator-based training is deemed to be desirable, innovative changes in organization will evolve to allow it to occur.

PROLIFERATION OF SIMULATION CENTERS

Currently, despite the lack of definitive cost-effectiveness data, training with realistic simulators is under way in many sites around the world,[270] and many of these sites choose to conduct high-end crisis management and

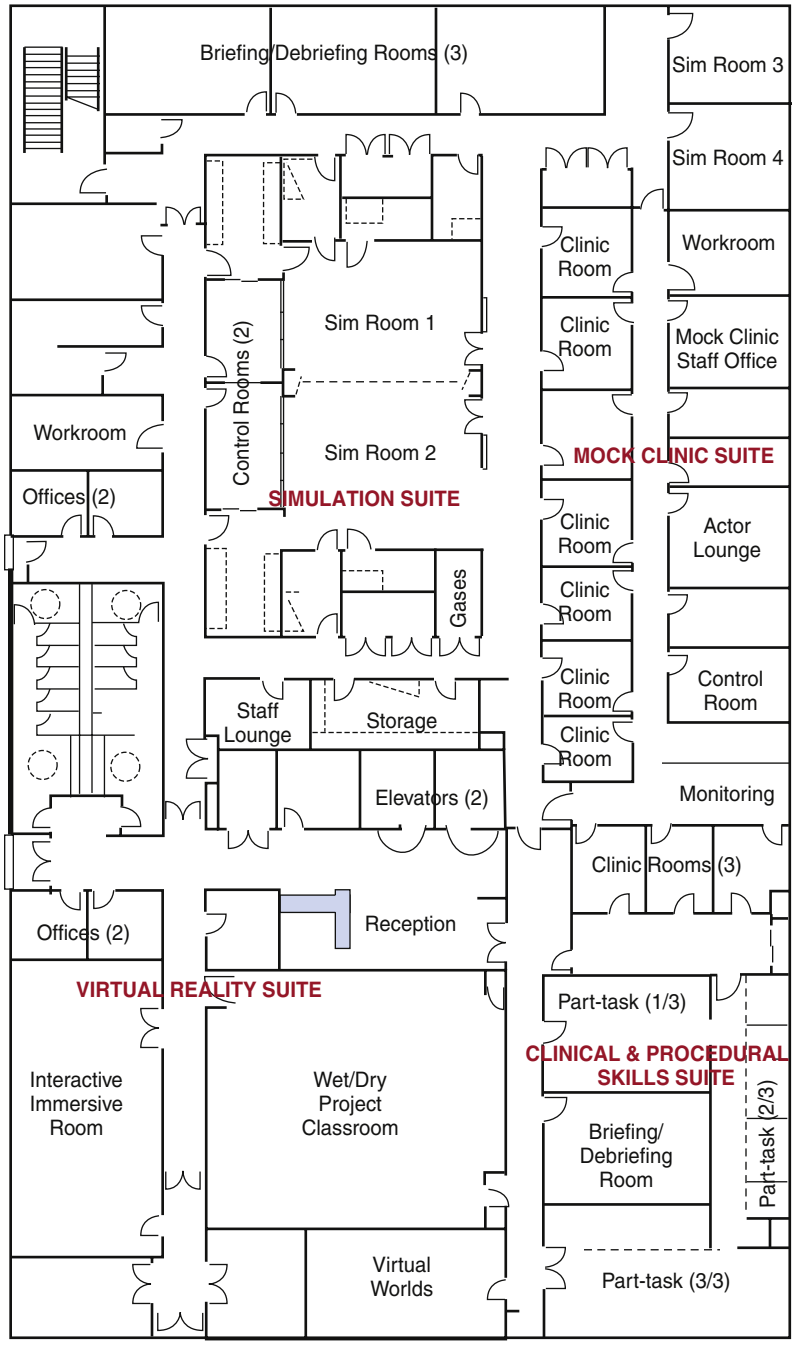


Figure 8-24. Floor plan of a large interdisciplinary simulation center for multiple domains (anesthesia, surgery, students) with several multipurpose simulation rooms (Sim Room) and skills laboratories. *(Photograph taken by D. M. Gaba at the Center for Immersive and Simulation-based Learning at Stanford Medical School, Palo Alto, Calif.)*

critical incident training sessions. Some useful websites of simulation centers and other resources are listed at the end of the chapter (Appendix 8-1). These programs have already voted with their feet on the issue of cost versus benefit. With so many centers exploring the realities of simulation training, we can expect to see additional data on efficacy and cost within the next few years. A definitive study is in principle possible, but it would require a very large number of subjects evaluated by multiple raters and would be complex and costly.

Still other factors complicate assessment of the effectiveness of simulator-based training. Studying the impact of a single session of a course that uses a new technology and a new approach to training may underestimate the course's impact when it is used on a regular and repetitive basis. It is widely believed in commercial aviation that CRM training must begin with the initial training of pilots and must be continued throughout their career. Social psychologists Helmreich and Foushee, two of the main architects of CRM training, wrote: "Data indicate that even intensive initial CRM training constitutes only

an awareness phase and introduction to the concepts, and that continuing reinforcement is essential to produce long-term changes in human factors practice." Similarly, United Airlines states in its CRM manual: "Command/Leadership/Resource management [United's terminology for CRM] cannot be a one-shot approach. It has to be a coordinated long range program. It must therefore be an integral part of the entire training effort: new hire training, transition and upgrade programs, and recurrent training."[271]

Finally, the principles and procedures taught in training must be reinforced within the operational environment. Simulator-based safety training can be totally negated if production pressures or latent failures in the workplace make it impossible to implement its teachings effectively.

It is still too early to make definitive statements about either the benefits or the costs of simulator-based training in anesthesia. To some extent, a catch-22 is involved. One cannot attempt to determine the true cost effectiveness until simulation is widespread enough for complex and expensive studies to be undertaken and until more experience has been gained on the different organizational aspects of providing the training. Many institutions are likely to shy away from taking the risk until the cost effectiveness is proven.

SIMULATION SOCIETIES: SOCIETY FOR SIMULATION IN HEALTH CARE AND SOCIETY IN EUROPE FOR SIMULATION APPLIED TO MEDICINE

One measure of the evolving maturity of simulation in health care consists of the formation and growth of professional societies focused on this topic. Although anesthesiology was the medical field that initiated work on the fully interactive mannequin-based simulator and that dominated the early developments in the field, simulation is a broad strategy that has now been widely adopted by many different disciplines and domains in health care. For the most part, simulation professional societies have sprung up as explicitly multidisciplinary organizations. Major leadership roles in these societies have been played by anesthesiologists and engineers associated with anesthesiology, however.

The largest simulation organization is the Society for Simulation in Healthcare (SSH; www.ssih.org), which was founded in 2004 as the outgrowth of the group that had operated the International Meeting on Medical Simulation for several years as a satellite to the annual meeting of the Society for Technology in Anesthesia. Under the new auspices of SSH, the meeting was transformed into the International Meeting on Simulation in Healthcare (IMSH), encompassing all health care disciplines and domains, not just medicine. Regular scientific congresses on simulation had been under way since the mid-1990s (the Rochester Conferences on Simulation in Anesthesia). Although they originally had approximately 100 attendees, Society in Europe for Simulation Applied to Medicine (SESAM) meetings have now approximately 400 attendees. The IMSH meeting in 2014 had nearly 3000 attendees. This number places it in the category of a medium-sized scientific meeting; to put this in the context of anesthesiology, it would rank as the third largest scientific meeting in the United States, falling below only the ASA meeting and the New York Postgraduate Assembly in Anesthesiology (PGA) conference, but ranking ahead of the International Anesthesia Research Society (IARS) annual meeting.

Another sign of the mainstream nature of simulation is that the SSH has published a quarterly peer-reviewed journal, *Simulation in Healthcare,* since 2006. This journal was approved for indexing by PubMed in 2008. It is an official publication of many international professional societies of simulation in health care, including SESAM (www.sesam.ws), the Australian Society for Simulation in Healthcare, and the Association of Standardized Patient Educators. The organizations have become affiliates of the SSH.

Another sign of maturity is the emergence of a trade organization for simulation in health care dedicated to educating and influencing policy makers, primarily concerning federal legislation and health policy. The Advanced Initiatives in Medical Simulation (AIMS) is a 501c6 organization that is allowed to lobby the U.S. government. What was previously seemingly the province of a few technologically minded anesthesiologists has blossomed into a substantial industry and profession with all the trappings of organizations, meetings, journals, and even lobbyists.

FUTURE OF PATIENT SIMULATION IN ANESTHESIA

The future is now—we are it.[272]

Although nearly 3 decades of consistent development have passed, the field of simulation in health care is still relatively new.[5,17,273] Thousands of simulators are in use around the world, many targeting anesthesiology and critical care, but the fraction of clinicians in these fields who have undergone a meaningful simulation experience is still small.

Simulators have become more sophisticated, and users now can choose from many different models offered by multiple manufacturers. Improvements in simulators depend on the demand for the devices and on the tradeoff between fidelity and cost. Many otherwise desirable improvements may be too costly for their expected impact. Technologic advances are likely to be targeted at portability and reliability, rather than at supporting increasingly esoteric feature sets. Many users have opted for simpler and cheaper simulators that use direct control, modest scripts, and finite state machines to control the changing state of the simulated patient, rather than complex mathematic models. This is partly because the production and use of robust mathematic models have been more difficult than anticipated.

In contrast to aeronautical engineers, physicians do not design and build the systems that they wish to model.

The fundamental differential equations of fluid mechanics and aerodynamics are firmly established, allowing supercomputers to provide technically meaningful simulations as replacements for many wind tunnel tests. There are still wind tunnel tests, however, and test flights of actual prototype aircraft. Sophisticated instrumentation can be built into test structures to define their behavior accurately. Physicians will never have this type of knowledge about the human body. The advantages and disadvantages of the various types of control logic for different applications are still being sorted out.

Interest has been growing in purely virtual reality simulations, often of a type similar to massive online games or to the popular Second Life system. Participating with others in the same virtual world, linked by the Internet, is appealing for many purposes. Such simulations are only as good as the "engines" that drive the underlying patients that may be found there, and the quality of the data provided and interventions and choices supported for implementation in these settings. Virtual reality proponents imagine a virtual reality so realistic that it rivals, or is indistinguishable from, the real world. This would approach the *Star Trek* holodeck. Although we once predicted that such systems could be in place by 2020, the development of such high-veracity virtual reality has not proceeded as quickly as previously imagined, and it is unclear whether full virtual reality of this nature will be available in the next decade.

Patient simulation has now become a regular part of initial and recurrent training of most anesthesia professionals and many other clinicians in the United States, Australia, and the United Kingdom and some other European countries. With patient simulation, the human error–based CRM concept was introduced to medicine as ACRM training, which revolutionized traditional methods and content of teaching and learning. The anesthesia community can be proud of its pioneering role in developing patient simulation technology and simulation-based training curricula, and anesthesiologists and others working with them continue to play dominant leadership roles in many settings of simulation, even those devoted to fields outside anesthesia.

If it can be shown that fully integrated simulation team training with a significant focus on human factors and CRM improves patient safety and acute care quality, and if this type of training is also shown to increase employee satisfaction and effectiveness of routine work, then we may expect a substantial increase in simulation team training as a de facto mandatory feature of clinical work because no one could afford not to use simulation in this way. Whether unequivocal data to this effect can be acquired or not remains to be seen.

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APPENDIX 8-1 *Links and Useful Resources*

- ASA Simulation Education Network
  - Many resources on simulation and links to ASA-endorsed simulation centers
  - http://www.asahq.org/For-Members/Education-and-Events/Simulation-Education/Endorsed-Simulation-Centers.aspx
- Society for Simulation in Healthcare (SSH; largest simulation annual meeting IMSH; see website of SSH)
  - www.ssih.org
  - Journal *Simulation in Healthcare,* Elsevier
  - Website of the Instructor Certification programme of SSH
  - Detailed list of Standards & Elements
  - http://ssih.org/uploads/static_pages/PDFs/Certification/CHSE%20Standards.pdf
  - https://ssih.org/certification
  - Criteria for Accredition of Simulation Centers by SSH
    - http://ssih.org/uploads/static_pages/PDFs/Accred/2013_AccreditationStandards.pdf
    - http://ssih.org/accreditation/how-to-apply
- Society in Europe for Simulation in Medicine SESAM
  - www.sesam-web.org
- Stanford Simulation Site
  - http://cisl.stanford.edu
  - Neonatal Sim Center at Stanford
- Center for Advanced Pediatric and Perinatal Education
  - http://cape.lpch.org/
- Penn State Medical Center (lists of available simulator systems and links to manufacturers)
  - http://www.hmc.psu.edu/simulation/

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Chapter 9

Teaching Anesthesia

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Key Points

- Clinician educators are challenged with having to provide meaningful educational experiences for residents and students in an increasingly complex health care environment, under pressure to be clinically efficient and yet to ensure high quality and safe patient care.
- Additional challenges in anesthesia education include the need to integrate increasingly complex knowledge, to provide adequate clinical experiences (in the face of reduced trainee hours), to ensure acquisition of broad skills, to assess learners in a fair and comprehensive manner, and to ensure patient safety.
- To develop competence in any aspect of clinical care, learners must have a deep foundation of factual knowledge, understand facts and ideas in the context of a conceptual framework, and organize their knowledge to facilitate retrieval and application.
- Competency-based medical education is an approach that incorporates trainee outcomes in the design, implementation, assessment, and evaluation of medical education.
- Competency-based education principles can be combined with a model of skill acquisition to develop a framework for performance assessment. The Dreyfus model describes five stages of development ranging from novice to master.
- The educator in anesthesiology may encounter a wide variety of learners, including anesthesia residents and fellows, medical students, student registered nurse anesthetists, anesthesiologist assistants, and anesthesiologists in continuing medical education courses. In addition to training anesthesia providers, the educator in anesthesiology must also be able to provide appropriate experiences for other trainees in specialties such as otolaryngology, head and neck surgery, plastic and reconstructive surgery, orthopedic surgery, oral-maxillofacial surgery, and emergency medicine.
- Residency programs in the United States are accredited by the Accreditation Council for Graduate Medical Education (ACGME). In addition, the ACGME offers accreditation for anesthesia fellowships in critical care medicine, pain medicine, pediatric anesthesiology, adult cardiothoracic anesthesiology, and obstetric anesthesiology.
- The ACGME established a framework for "milestones" of competency development and advocated for implementation of common evaluation tools in each discipline to document resident achievement of the milestones.
- Resident duty hours have been the focus of much discussion and considerable debate in graduate medical education for several decades. The ACGME recently added additional restrictions on duty hours.
- The ACGME requirements also address new standards for supervision, teamwork, transitions of care, fitness for duty, alertness management, and fatigue mitigation that affect the educational environment.
- Good clinical teaching is multifactorial with emphasis on the noncognitive aspects of teaching (e.g., developing positive relationships with students, creating a supportive learning environment, communication skills, and enthusiasm) more so than the cognitive aspects (e.g., clinical knowledge and reasoning).
- Experienced clinical teachers make use of "teaching scripts" to guide many of their teaching interactions. A teaching script includes three to five teaching points with supporting material, an overview of common errors made by learners, and effective ways to create a framework for understanding.

Key Points—cont'd

- The amount of self-study by residents correlates with scores on anesthesia resident in-training examinations (ITEs). ITE scores predict subsequent performance on certifying examinations.
- Advances in education technology provide new models to deliver content (e-Learning, podcasts), teach and assess (simulations), provide collaborative learning environments (wikis), and increase classroom interactivity (audience response systems).
- Although delivery of anesthesia is the primary responsibility of anesthesiologists, education, responsibility, and leadership in the entire perioperative environment is important. In addition, anesthesiologists frequently have the responsibility for critical care medicine and both inpatient and outpatient pain medicine.
- Advances in the education of anesthesia providers are occurring all over the world (see Chapter 2). While this chapter emphasizes American educational principles, anesthesia educational approaches and systems are extensively being improved in accordance with the increasing complexity of anesthesiology and its responsibilities.

BACKGROUND AND HISTORY OF ANESTHESIA EDUCATION (ALSO SEE CHAPTER 1)

Education in the medical specialty of anesthesiology began after the initial public demonstration of ether as a method to reduce pain during a surgical procedure. Based on that introduction to the use of volatile anesthetics, in 1850, John Collins Warren, a general surgeon at the Massachusetts General Hospital, delivered an address to the American Medical Association on the progress of surgery, including practical advice on how to administer ether safely.[1] He outlined nine steps, many of which remain critical elements in the safe administration of anesthesia today. His steps included recommendations regarding the need for the patient to be fasting, supine positioning, monitoring of pulse and respirations, evaluating the level of muscle relaxation as a sign of anesthetic depth, and avoiding cautery when administering ether anesthesia because of the risk of fire. These principles provided the foundation upon which to begin to train physicians in the practice of anesthesiology. Despite the acknowledgement of the need for training regarding anesthesia administration and safety, formal training programs in anesthesiology did not become the norm until the twentieth century. Initially, implementation of anesthesia care was provided by medical students, interns, and ward nurses, none of whom had any formal or informal training or experience in anesthesia. Although some of the steps described by Warren were addressed, the "art and science" of anesthesia practice were undervalued. In fact, at institutions such as the Mayo Clinic in Rochester, Minnesota, surgeons William and Charles Mayo believed that nurses were better suited to provide anesthesia since "the intern was naturally more interested in what the surgeon was doing."[2]

The first formal anesthesia training program was developed by Ralph Waters at the University of Wisconsin in the late 1920s.[3] The program included didactic elements such as case conferences, Grand Rounds, and literature reviews, for the most part based on models from other specialties. Anesthesia residents, who spent 3 years in training, were responsible for patient care, research, and teaching of medical students and interns. Many of the graduates of the training program at the University of Wisconsin went on to become chairs of other academic departments, disseminating Water's model for academic anesthesiology in the United States, Canada, and the United Kingdom.[4] Although anesthesiology was recognized as a critical skill in caring for surgical patients, anesthesiology was considered a subordinate medical specialty to surgery. Few departments of anesthesiology existed in any U.S. medical schools, and the majority of anesthesia training programs were apprenticeships managed as a division of the Department of Surgery.

Certification in anesthesiology followed a similar course to the formal educational programs. The American Board of Anesthesiology (ABA) was established in 1938, initially as a subordinate board to the American Board of Surgery. The transition to a separately recognized medical specialty followed shortly thereafter with the ABA becoming an independent board in 1939. The ABA helped define the training and clinical experience required to practice anesthesiology by specifying that anesthesiologists had to complete at least 3 years of postgraduate training, have some experience in clinical practice, and pass a series of examinations (written, oral, and practical) to achieve diplomate status.[5] Despite the ABA definition of a curriculum and continuum to achieve board certification, for many of the early years, most residencies were more apprenticeships than formal educational programs.

Medical education and health care delivery have been transformed since the days of the first training program and the founding of the ABA. This chapter addresses the principles of education in anesthesiology during formal residency and fellowship programs and throughout one's career, with an emphasis on both learning and teaching

the principles and practices of anesthesia. Although these principles and practices are relevant to almost any anesthesia practice, the chapter uses specific examples that for the most part reflect the approach to training in the United States. See Chapter 2 for international perspectives on anesthesia training.

CHALLENGES IN MEDICAL EDUCATION

Education and training in anesthesiology and all other medical specialties has evolved considerably since the administration of the first ether anesthetic. Because of the many changes in patient population, surgical and other approaches to managing clinical problems and the major advances in anesthesia care, the concept that clinical experience alone is adequate to prepare the anesthesia provider, is not sufficient. The concept of an apprenticeship in anesthesiology—or the notion that one can isolate oneself behind the "ether screen" disinterested in what a surgeon or other physician is doing—is not an acceptable model of care or training. Anesthesiology has a sound scientific foundation and as a result has fostered development of new technologies and approaches to clinical care within and beyond the operating room that allow patients with complex underlying comorbidities to safely undergo procedures that were previously not possible. While our understanding of the principles and practice of anesthesia evolved with exponential increases in medical knowledge, these other advances in medical technology and changes in health care delivery have created opportunities and challenges related to anesthesia training. For example, whereas medical education continues to be focused on hospitalized patients, particularly those undergoing procedures in an operating room, an increasing amount of patient care has shifted to settings less familiar to the anesthesiologist, including the outpatient setting. Anesthesia practice is no longer restricted to the surgical suite. At the same time, the clinical instructors are under pressure to generate additional income from patient care activities and to improve efficiency of care. Health care systems focus on financial viability and must respond to external pressures to demonstrate quality of care. Accrediting agencies such as The Joint Commission and Centers for Medicare & Medicaid Services provide increasing scrutiny of many aspects of clinical care. Against this backdrop, the Carnegie Foundation for the Advancement of Teaching issued a report calling for reform of medical school and residency, 100 years after their influential Flexner Report of 1910.[6] They identified four goals for medical education:

1. Standardization and individualization: standardizing learning outcomes through assessment of competencies, while also individualizing the learning process
2. Integration: connecting formal knowledge to clinical experience; integrating basic, clinical, and social sciences; incorporating interprofessional and teamwork education into the curriculum
3. Habits of inquiry and improvement: preparing learners to develop expertise, engaging learners in challenging problems including quality improvement and patient safety
4. Formation of professional identity: offering feedback and assessment of professionalism, promoting relationships with supportive faculty who encourage high standards, creating collaborative learning environments committed to excellence and improvement

The challenges in anesthesia education reflect these larger issues (Box 9-1).[7]

LEARNING PRINCIPLES AND LEARNING STYLES

A basic understanding of the science of learning can provide context for teachers as they try to meet these challenges. Over the last 40 years, research on learning, cognitive psychology, social psychology, and anthropology has resulted in an evolving understanding of the scientific basis of learning. The National Academy of Sciences prepared a monograph synthesizing this literature.[8] The key findings, which are relevant to learners of all levels in all disciplines, include the following learning principles:

1. Learners bring preconceptions about how the world works. If their initial understanding is not engaged, they might fail to understand the material that is presented.
2. To develop competence in a topic, learners must have a deep foundation of factual knowledge, understand facts and ideas in the context of a conceptual framework, and organize their knowledge to facilitate retrieval and application.
3. Metacognition refers to the learner's ability to monitor the state of their knowledge of a particular topic. A metacognitive approach to instruction can help learners take control of their learning by defining goals and monitoring progress toward achieving them.

BOX 9-1 *Challenges in Anesthesia Education*

Quantity of Knowledge

- Exponential growth in knowledge—impossible to master the anesthesia literature

Adequate Patient Care Experiences

- Duty hour restrictions affect amount and continuity of patient care
- Health system emphasis on efficiency can exert pressure to minimize trainee involvement
- Appropriate use of education technology (e.g., computer, Internet, simulation) or other means to supplement direct patient care experiences

Learner Assessment

- Competency-based education expected by accreditation bodies
- New assessment methods (e.g., milestones) require faculty training to obtain meaningful measurements

Patient Safety in Era of Cost Containment

- Providing adequate supervision of trainees
- Promoting learner autonomy and preparedness for independent practice

Adapted from Bould MD, Naik VN, Hamstra SJ: Review article: new directions in medical education related to anesthesiology and perioperative medicine, Can J Anaesth *59:136-150, 2012.*

Key aspects of the learning environment are displayed in Figure 9-1. Examples of strategies in the application of these learning principles in anesthesia teaching are shown in Table 9-1.

A *learning style* refers to the complex way that an individual prefers to acquire and process information. The VARK learning style uses the learner's preferred sensory mode of receiving information.[9] The *visual learner* is said to process new information best when it is visually presented, such as with tables, graphs, and diagrams. The *auditory learner* processes new information best by listening, explaining ideas to others, or engaging in group discussions. The *read/write learner* prefers to use textbooks, handouts, and note taking when receiving new information. The *kinesthetic learner* processes new information best when it can be touched or manipulated, such as with concrete, multisensory experiences. This learner responds well to laboratory demonstrations and experiments, and they will likely enjoy participating in simulation activities.

There is no evidence that matching teaching style to the learning style of an individual improves learning outcomes in medical education. The rationale for teachers to understand learning styles is to be cognizant of instructional methods that correspond to the varied learning styles in a group of learners. In addition, knowledge of a particular student's preferred learning style can help a teacher explain a difficult or challenging topic.

ANESTHESIA LEARNERS

Although anesthesia education is generally defined in terms of the training of anesthesiologists through formal residency programs, the learner may be at any of a number of levels of experience and training. In some cases, the learners are from other specialties or professions for which anesthesia training and care are critical elements. With the continuing advances in the science and practice of anesthesiology, the need for continuing education by practicing anesthesiologists, as well as the need for retraining, has taken on greater importance. As a result, the anesthesia educator will encounter a wide variety of learners, including anesthesia residents and fellows, medical students, student registered nurse anesthetists, and anesthesiologist assistants (AAs). In addition, the training programs of specialties such as otolaryngology, head and neck surgery, plastic and reconstructive surgery, orthopedic surgery, and oral-maxillofacial surgery require anesthesia rotation experiences. Practicing anesthesiologists also require continuing medical education and ongoing documentation of clinical competence. As a result, the educator must understand the background, experience, and goals of each learner and develop a curriculum to address their needs.

It is a challenge to address the educational needs of such a diverse group of trainees. One approach is to consider the learner's professional practice after formal training is concluded, and the specific anesthesiology knowledge that will be most relevant. In addition, the educator should determine the current state of the learner's knowledge about anesthesiology in order to design the appropriate learning experience. For example,

TABLE 9-1 APPLYING LEARNING PRINCIPLES IN ANESTHESIA TEACHING: EXAMPLES

Learning Principle	Teaching Strategies
Teachers must determine learners' preexisting understanding	Use open-ended questions In lecture setting, use pretest or audience response system as first step In case discussion, allow learners to share prior experience after case stem is first introduced
Teachers must know common conceptual barriers (misconceptions) and effective strategies for teaching	Use a variety of teaching materials (e.g., textbooks, web pages, simulations, videos, podcasts) Use a variety of teaching methods (e.g., demonstrations, discussions) rather than just one (e.g., lecture)
Learning environment should be knowledge centered	Emphasize practical application of knowledge (e.g., if studying basic science topic, find clinical application) Draw links from what is being learned to examples in practice that learner wants to become competent at.
Learning environment should be assessment centered	To review a topic, use practice questions instead of simply restudying topic For residents who will take American Board of Anesthesiology board examinations, show how topic being discussed was covered on previous examinations (e.g., examinations keywords)

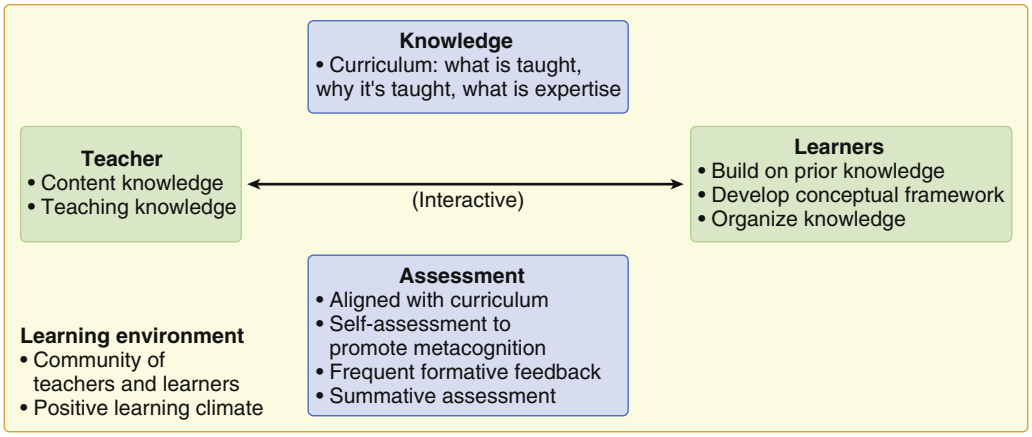


Figure 9-1. Key aspects of the learning environment.

an otolaryngology–head and neck surgery resident may participate in a 1-month anesthesiology rotation as an intern. Appropriate goals of the experience may include preoperative evaluation, airway assessment, and prediction of difficult mask ventilation and tracheal intubation. Topics such as regional anesthesia or epidural anesthesia are likely to be less relevant to this group of learners.

Continuing education and the training of nonanesthesiologists in some aspects of anesthesia care are important, but the primary focus of this chapter is on the training of medical students and anesthesia residents and fellows in the United States. For these trainees, the elements of an anesthesia curriculum include formal and informal didactics, appropriate clinical assignments, and other learning activities. The curriculum is generally conducted over a defined time span, which can vary from 1 to 2 weeks for a medical student rotation to 3 to 5 years for anesthesia residents and fellows. The specific educational goals, clinical exposure, and didactic sessions vary considerably for each level of training.

MEDICAL STUDENTS

The foundation of an anesthesiologist's medical knowledge and clinical skills is established during medical school. Therefore, anesthesia educators must be aware of the medical student curriculum and how clinical skills are being taught. Table 9-2 displays the number of medical students, full-time faculty members, and anesthesiology faculty members in the United States. Anesthesiologists represent a small percentage of medical school faculty members, but should be involved in medical school curriculum committees to understand the school's curriculum management process and potentially influence the curriculum to incorporate anesthesia experiences. Although many medical schools do not mandate an anesthesia clerkship for its students, there are several advantages to a required ("core") clerkship in anesthesia.[10] While providing exposure to the practice of anesthesia may seem the most obvious, a focus on topics of relevance to all medical students may be more appealing to medical school curriculum planners. Topics within the expertise of the anesthesiologist include applied cardiovascular and pulmonary physiology, clinical pharmacology, pain management, preoperative evaluation, care of the critically ill patient, and basic and advanced cardiac life support. In addition, anesthesiologists are capable of teaching basic procedural skills such as airway management and vascular access placement. Besides providing teaching content, anesthesiologists can influence medical student attitudes toward anesthesia. Finally, although many factors affect specialty choice, students who choose anesthesiology careers are more likely to have taken an anesthesiology clerkship.[11]

The traditional clerkship model is a one-discipline experience, typically inpatient-focused during the latter half of the undergraduate medical curriculum. A traditional anesthesia clerkship would include clinical assignments focusing on intraoperative patient care plus didactic sessions covering predetermined topics. An example of the structure of a 2-week anesthesia clerkship is shown in Table 9-3. A new model for the structure of the core clinical clerkship year is the longitudinal, integrated clerkship.[12] The term *longitudinal* refers to the 6- to 12-month period that students spend in a multidisciplinary setting. The organizing principle of this model is continuity. The integration of disciplines takes place via an integrated schedule of discipline-based experiences or by having the student see the variety of patients seen by a primary care physician.[12] This approach allows a student to appreciate a patient's perspective of the health care system, and it provides the opportunity to care for the patient through an entire illness episode even if different

TABLE 9-2 NUMBER OF MEDICAL STUDENTS AND FULL-TIME FACULTY (TOTAL AND ANESTHESIOLOGY-SPECIFIC) IN U.S. MEDICAL SCHOOLS

Academic Year	Number of Medical Students	Total Number of Full-Time Faculty	Number (% of Total Faculty) of Full-Time Anesthesiology Faculty
1990	65,081	72,320	3393 (4.7)
1995	67,030	90,016	4535 (5)
2000	66,500	102,446	4979 (4.9)
2005	68,280	119,025	5471 (4.6)
2010	75,394	133,452	6469 (4.8%)

Data from Rowley B, et al: Graduate medical education in the United States, JAMA *264:822-832, 1990; Graduate medical education,* JAMA *274: 755-762, 1995; Graduate medical education,* JAMA *284:1159-1172, 2000; Graduate medical education,* JAMA *294:1129-1143, 2005; Brotherton SE, Etzel SI: Graduate medical education 2006-2007,* JAMA *298:1081-1096, 2007; Brotherton SE, Etzel SI: Graduate medical education 2010-2011,* JAMA *306:1015-1030, 2011; and The Association of American Medical Colleges. Available at <http://www.aamc.org>. (Accessed 28.02.13.)*

TABLE 9-3 SAMPLE SCHEDULE FOR 2-WEEK MEDICAL STUDENT ANESTHESIA CLERKSHIP

	Monday	Tuesday	Wednesday	Thursday	Friday
Week 1	Orientation Airway workshop Sedation lecture	Clinical assignment	Preoperative assessment lecture Clinical assignment	Clinical assignment	Clinical assignment
Week 2	Simulation/crisis management session Clinical assignment	Case conference Clinical assignment	Grand rounds conference Clinical assignment Acute pain lecture Mechanical ventilation lecture	Clinical assignment	Clinical assignment Reflections session

Learning activities:

- Clinical assignment—clinical teaching by faculty and residents
- Interactive workshops—airway management, simulation/crisis management, reflections
- Lectures—sedation, preoperative assessment, acute pain, mechanical ventilation
- Case-based conferences—case conference, grand rounds

specialty care is needed. An example of how to integrate the discipline of anesthesia into a longitudinal integrated clerkship is shown in Box 9-2. One obvious disadvantage is the time lag between anesthesia clinical experiences, but the continuity of the faculty preceptor allows a focus on the learning goals not yet achieved by the student. Many factors influence the rate of adoption of longitudinal clerkship models, including financial implications and the need for faculty time and training.

GENERATIONAL DIFFERENCES IN LEARNERS

The focus on learner-centered educational environments has implications for teachers and learners. Teachers should be aware that the new generation of learners has been taught with different approaches to meeting learning objectives using more interactive teaching approaches and technology. Teachers are undoubtedly aware that there are generational differences in today's learners. In medical schools, most students are members of one of two generational cohorts: Generation X (born between 1965 and 1980) and Millennial (born between 1981 and 1999). One medical school surveyed more than 800 graduates who matriculated between 1989 to 1994 and 2001 to 2004.[13] The survey tool was the 16 Personality Factor Questionnaire, which measures 16 independent dimensions of personality. Millennial students scored significantly higher than Generation X students on factors such as rule-consciousness, emotional stability, sensitivity, and perfectionism. Generation X students scored higher than Millennial students on self-reliance. It is unclear how (or whether) medical schools, residency, and fellowship programs should adapt to the new generation of learners. Educators have questioned whether changing personalities should lead to changes in the teaching of medical professionalism, advising and mentoring programs, and faculty development.[13]

Teachers should be aware of generational changes in their learners, but learners should be aware of the expectations for excellence of their teachers. At the resident level, there are several features that have characterized excellence (Box 9-3).[14] Another framework is to consider the seven core tasks that may be required of a teacher (Table 9-4), and to determine the corresponding task required of the learner (Table 9-5).[15]

BOX 9-2 *Example of Longitudinal Anesthesia Clerkship Experience*

- Time period of clerkship: 1 year
- Time assigned to anesthesiology: 6 days
- Didactic sessions: six lectures, simulation workshop
- Continuity of anesthesia preceptor: one preceptor for all 6 days
- Required patient care experiences and learning goals
  - Orthopedic surgery patient: exposure to regional anesthesia, laryngeal mask placement
  - General surgery patient: basic anesthesia drug pharmacology, airway management, approach to postoperative pain
  - Major spine surgery patient: monitoring, approach to transfusion
  - Gastric bypass patient: approach to difficult airway management, postoperative pain, and patient safety

Adapted from Sullivan KR, Rollins MD: Innovations in anaesthesia medical student clerkships, Best Pract Res Clin Anaesthesiol *26:23-32, 2012.*

RESIDENT AND FELLOW EDUCATION

ROLE OF THE ABA, ACGME, SCHOOL, AND DEPARTMENT

The educational curriculum and core competencies in anesthesia residencies are defined by the Accreditation Council for Graduate Medical Education (ACGME) and the ABA. The residency programs in the United States

BOX 9-3 *Select Features That Characterize Excellence Among Resident Learners*

1. Great fund of knowledge and the ability to apply that knowledge to patient care
2. Skill in performing essential tasks of daily practice
3. Curiosity and love of learning; seeking to understand "how" and "why"
4. Approach to errors: making the most of their own mistakes and those of others, and use to improve their practice
5. Conscientiousness: effective and efficient use of time; enjoy doing a good job for patients and colleagues
6. High degree of personal initiative; doing what is required and then going beyond
7. Reliability: when asked to do something, they can be relied upon to see that it gets done
8. Affable: tend to be liked by most because they treat people fairly and respectfully and have a genuine interest in the well-being of others
9. Character: honest, unselfish, understanding of others, trustworthy

Adapted from Gunderman R: Achieving excellence in medical education. *ed 2, London, 2011, Springer.*

TABLE 9-4 **REQUIRED TEACHING TASKS AND DESCRIPTIONS**

Task	Description
Teach in clinical setting	Teach appropriate knowledge, skills, attitudes
Teach large and small groups	Prepare and deliver lecture; choose and manage appropriate small group format
Facilitate and manage learning	Assist trainee in achieving learning goals; advise and mentor for career goals
Plan learning	Manage the curriculum development process, from needs assessment to implementation
Develop and work with learning resources	Create instructional materials, including handouts and multimedia resources; use appropriate technology including Internet-based and clinical simulation
Assess trainees	Use appropriate assessment tools for learning setting and assessment goal
Evaluate courses and undertake research in education	Use appropriate methods to evaluate courses, teachers, and resource materials; encourage research in medical education

Adapted from Hesketh EA, Bagnall G, Buckley EG, et al: A framework for developing excellence as a clinical educator, Med Educ *35:555-564, 2001.*

are accredited by the ACGME. In addition, the ACGME offers accreditation for the following anesthesia fellowships: critical care medicine, pain medicine, pediatric anesthesiology, adult cardiothoracic anesthesiology, and obstetric anesthesiology. The number of anesthesiology core residency and ACGME subspecialty trainees is shown in Tables 9-6 and 9-7. The ACGME sets forth common program requirements that address issues relevant to all graduate medical education training programs, including institutional responsibilities, program personnel and resources, resident appointments, educational program, evaluation, resident duty hours in the learning and working environment, and program innovations.[16]

While the ACGME accredits residency programs, the ABA provides certification to individual anesthesiologists. Anesthesia residents are offered an annual in-training examination (ITE). After conclusion of residency training, an eligible resident takes the ABA Part 1 (written) and Part 2 (oral) examination. In 2012, the ABA divided the Part 1 examination into two parts. The Basic Examination (written, multiple choice), focusing on basic science and basic clinical aspects of anesthetic practice, is taken at the start of CA-2 year, and an Advanced Examination (written, multiple choice), focusing on clinical aspects of anesthetic practice and emphasizing subspecialty-based practice and advanced clinical issues, is taken after completion of residency.[17] The Applied (oral) Examination is currently scheduled to begin in 2016. It will be taken after successful completion of the Basic and Advanced Examinations, and it will include an objective structured clinical examination (OSCE) component. The ABA publishes a content outline that is used to determine subject matter for the ITE, as well as for the Basic and Advanced Examinations that are part of the certification process (Appendix 9-1). It is a common practice for training programs to address many of these topics in the didactic elements of the curriculum. The ABA also grants certification in anesthesiology subspecialties including critical care medicine,

TABLE 9-5 TEACHING TASKS AND LEARNER ROLES

Teaching Task	Learner Role	Learner Description
Teach in clinical setting	Clinical learner	Be a "cognitive apprentice." Observe and apply thinking processes used by clinicians. Apply skills learned; discover and reflect on new concepts.
Teach large and small groups	Information receiver	Ensure understanding, relate to prior knowledge (e.g., use textbooks or other resources). Teaching peers may help solidify understanding. Ask questions: "Why is this subject being presented?" and "What do I know about this subject?" Note problems of understanding and ask questions.
Facilitate and manage learning	Teaching facilitator, mentee	Should not be an "empty box" passively receiving information. Should act as teacher's facilitator, listening but ready to react. Intention to learn should be clear. Help lead teacher to the point most important for progress. As mentee, learner should give teacher urge and motivation to continue working with interest and enthusiasm. Do this by being present, curious, and involved.
Plan learning	Curriculum co-planner, active participator	Learner should understand demanding nature of medical curriculum, should make effort to keep up with pace of instruction, and alert teacher if pace is too rapid or slow. Learner should participate actively in curriculum.
Develop and work with learning resources	Resource consumer	Use ("consume") learning resources, including those offered by teacher and external resources. Main challenge is often what not to consume, given proliferation of information available on the Internet.
Assess trainees	Teacher's assessor	Should strive for valid, reliable, fair, and congruent way to assess whether teacher delivers course or instruction effectively. Also need to assess teacher's professional interactions.
Evaluate courses and undertake research in education	Curriculum evaluator	Provide feedback on courses and curriculum to enable teacher to adapt or modify curriculum to meet learner needs.

Adapted from Karakitsiou DE, Markou A, Kyriakou P, et al: The good student is more than a listener—The 12+1 roles of the medical student, Med Teach *34:e1-8, 2012.*

TABLE 9-6 NUMBER OF ANESTHESIOLOGY SPECIALTY AND SUBSPECIALTY GRADUATE MEDICAL EDUCATION PROGRAMS, RESIDENTS, AND FELLOWS: CORE ANESTHESIOLOGY RESIDENCIES AND RESIDENTS IN GME PROGRAMS IN THE UNITED STATES ACCREDITED BY THE ACGME

Academic Year	Number of Accredited Core Anesthesiology Residency Programs	Total Number of Core Anesthesiology Residents on Duty	Number (%) of Core Anesthesiology Residents on Duty Who Are U.S. Medical Graduates	Number of Residencies/ Residents on Duty in All ACGME-Accredited and Combined Specialty GME Programs
1990	157	4362	3871 (88.7)	4144/69,798
1995	149	5490	4395 (81.1)	4245/85,732
2000	134	3837	1627 (42.4)	4268/85,460
2005	132	4785	3450 (72.1)	4151/86,975
2010	132	5322	4212 (79.1)	4128/91,963

ACGME, Accreditation Council for Graduate Medical Education; *GME,* Graduate Medical Education.

pain medicine, hospice and palliative medicine, sleep medicine, and pediatric anesthesiology. The number of certificates issued is published by the American Board of Medical Specialties (ABMS), of which the ABA is 1 of 24 medical specialty member boards[18] (Table 9-8).

Although the ABA and ACGME provide content and program requirements, this alone does not ensure that anesthesiologists are trained to meet the current and future needs of our specialty. Both organizations have approved innovative approaches to training residents, including integrating core residency and fellowship programs and combining core residency and research training to foster academic careers.

The roles of the department and school involve providing a variety of resources for training programs. Department faculty members are the primary teachers and evaluators for residents. Department chairs must ensure that an appropriate amount of nonclinical time is allocated to meet the administrative and teaching needs of faculty. Resident (and ACGME fellow) salaries are largely funded by Medicare, although there is a cap on the total number of positions funded. If Medicare funding decreases and hospitals do not provide financial support, then departments have to fund positions or decrease the number of residents. The institution (department, school, or teaching hospital) must also provide adequate space and equipment for the education program, including classrooms, study areas, office space, and on-call facilities.

RESIDENT EDUCATION

Over the past few years, medical education has been refocused on documentation of specific competencies as a measure of proficiency and a guide to advancing from one level of training to another. This concept of deconstructing the abilities of a professional into parts, called *competencies*, was first described over 60 years ago as a way to focus on the outcome of an education program. In medical education, competency-based approaches gained prominence

TABLE 9-7 NUMBER OF ANESTHESIOLOGY SPECIALTY AND SUBSPECIALTY GRADUATE MEDICAL EDUCATION PROGRAMS, RESIDENTS, AND FELLOWS: SUBSPECIALTY ANESTHESIOLOGY FELLOWSHIPS AND FELLOWS IN ACGME-ACCREDITED GME PROGRAMS IN THE UNITED STATES

Academic Year	Number of Accredited Subspecialty Anesthesiology Fellowship Programs	Total Number of Subspecialty Anesthesiology Fellows on Duty	Subspecialty Anesthesiology Fellows on Duty Who Are U.S. Medical Graduates	Number of Subspecialty Programs/Fellows on Duty in All ACGME-Accredited GME Programs
1990	Critical care medicine, 27	7	4 (57.1)	2447/8,006
1995	Critical care medicine, 46	70	52 (74.3)	3264/12,100
	Pain medicine, 55	112	83 (74.1)	
2000	Critical care medicine, 53	59	29 (49.2)	3678/12,529
	Pain medicine, 98	215	100 (46.5)	
	Pediatric anesthesiology, 37	63	33 (52.4)	
2005	Critical care medicine, 47	43	20 (46.5)	4095/14,316
	Pain medicine, 95	190	88 (46.3)	
	Pediatric anesthesiology, 43	91	43 (47.3)	
2010	Adult cardiothoracic anesthesiology, 47	69	42 (60.9)	4747/17,877
	Critical care medicine, 46	80	41 (51.3)	
	Pain medicine, 92	244	172 (70.5)	
	Pediatric anesthesiology, 46	143	104 (72.7)	

United States, JAMA *264:822-832, 1990; Graduate medical education,* JAMA *274:755-762, 1995; Graduate medical education,* JAMA *284:1159-1172, 2000; Graduate medical education,* JAMA *294:1129-1143, 2005; Brotherton SE, Etzel SI: Graduate medical education 2006-2007,* JAMA *298:1081-1096, 2007; Brotherton SE, Etzel SI: Graduate medical education 2009-2010,* JAMA *304:1255-1270, 2010.*

ACGME, Accreditation Council for Graduate Medical Education; *GME,* graduate medical education.

TABLE 9-8 AMERICAN BOARD OF MEDICAL SPECIALTIES CERTIFICATES ISSUED

Discipline	Before 1997	1997-2006	2000-2006	2007-2011
Anesthesiology*	28,515	12,012	7,592	7,832
Critical care medicine†	—	480	267	301
Pain medicine‡	—	1941	1233	1032
Hospice and palliative medicine§	—	—	—	59
Sleep medicine¶	—	—	—	4
Pediatric anesthesiology#	—	—	—	—
All specialties	602,578	242,684	167,656	127,009
All subspecialties	—	76,782	51,057	54,454

Data from 2012 Reference handbook and certificate statistics, *Evanston, IL, 2012, American Board of Medical Specialties.*

*First American Board of Medical Specialties (ABMS) certificate issued in 1938; first time-limited (10 years) certificate issued in 2000

†First ABMS certificate issued in 1986; first time-limited (10 years) certificate issued in 2000.

‡First ABMS certificate issued in 1993; first time-limited (10 years) certificate issued in 1993.

§First ABMS certificate issued in 2008; first time-limited (10 years) certificate issued in 2008.

¶First ABMS certificate issued in 2011; first time-limited (10 years) certificate issued in 2011.

#First ABMS certificate issued in 2013; first time-limited (10 years) certificate to be issued in 2013.

when they were adopted as a framework for evaluation in the United States, Canada, and Scotland—and now in many other countries. *Competency-based medical education* refers to an "outcomes-based approach to the design, implementation, assessment, and evaluation of medical education programs, using an organizing framework of competencies."[19] A *competency* refers to an observable ability of a health professional (e.g., knowledge, skills, attitudes) that can be measured and assessed. The term *competent* refers to "possessing the required abilities in all domains in a certain context at a defined stage of medical education or practice."[19] To have value as a tool for documenting capabilities, a competency must be able to be observed, measured, and assessed, rather than simply described.

The main principles of competency-based medical education (CBME) include the following[19]:

1. Focus on outcomes: This includes ensuring that every graduate is prepared for practice and that they are competent in all domains of their intended practice.
2. Emphasis on abilities: Curriculum is organized around competencies or abilities rather than long lists of knowledge objectives.
3. De-emphasis on time-based training: CBME can shift focus to the abilities actually acquired during training rather than time spent in training.
4. Promotion of greater learner centeredness: CBME encourages learners to take responsibility for their progress through training by mapping out a transparent pathway from predefined milestone to milestone on the path to becoming competent, and beyond.

The terms *competence* and *competency* can be confusing when one considers the spectrum of performance of a given practitioner.[20] To simplify the terminology, a *competency* can be considered a skill, and *competence* can be considered a point on the spectrum of performance. For example, nasogastric tube insertion is a patient care competency. An intern may be competent (has the ability) to insert the nasogastric tube (the competency), but may not be an expert at the procedure. Thus, although ensuring that practitioners are competent may be a goal of CBME, teachers (and learners) should also be concerned with developing higher (i.e., more skillful) levels of performance. In addition, one may be competent at one point in time, but not maintain competence, or can be competent to perform a task in one setting but not another. One might also be competent under ideal circumstances without pressure or stress, but not maintain the same level of competence in urgent or emergent situations.

ACGME CORE COMPETENCIES

In 1999, the ACGME began its Outcome Project to change the focus of residency accreditation from the structure and process of training to the outcomes of training—that is, competency-based medical education.[21] In the first phase of the Outcome Project, programs defined objectives to demonstrate learning in the competencies. In phase 2, programs integrated competencies into their curriculum and assessment. In phase 3, programs were to use resident performance data as a means for program improvement. In phase 4, the ACGME intends to focus on identifying benchmark programs. The deconstruction of the work of a physician to six core competencies (patient care, medical knowledge, professionalism, interpersonal and communication skills, systems-based practice, and practice-based learning and improvement) occurred after considering 84 potential physician competencies in 13 categories.[22] Since then, the six core competencies have also been adopted by medical schools, certifying boards (including the American Board of Anesthesiology), continuing medical education programs, the American Osteopathic Association, and The Joint Commission. The ACGME competencies are incorporated in the common program requirements for all specialties. The specific language used is contained in Appendix 9-2. Two of the competencies (Systems-Based Practice and Practice-Based Learning and Improvement) can be difficult to understand based on their name alone, especially for individuals who have not used those terms in other settings. Examples of how the work of an anesthesiologist can be described by competencies are provided in Table 9-9. Specialty-specific Residency Review Committees (RRCs) determine the program requirements for both residencies and fellowships. The specialty program requirements must incorporate all aspects of the ACGME core program requirements. Key structural elements of the Anesthesiology Program Requirements are listed in Box 9-4.

The widespread adoption of the competency model was accompanied by a proliferation of assessment tools to assess resident achievement of the competencies. In 2000, the ACGME, in conjunction with the ABMS, published a Toolbox of Assessment Methods that listed 13 assessment tools: 360-degree evaluation, chart stimulated recall oral examination, checklist evaluation, global rating, objective structured clinical examination, case/procedure logs, patient surveys, portfolios, medical record review, simulations, standardized oral examinations, standardized patient examination, and written examination.[16] A review of four evaluation tools (global ratings, 360-degree evaluations, direct observation, and portfolios) sought to determine

TABLE 9-9 ACGME COMPETENCIES AND ANESTHESIA CARE—EXAMPLES

Anesthesia Event	Relevant ACGME Competencies
Evaluate patient in preoperative clinic	Patient Care, Interpersonal and Communication Skills
Determine dose of intravenous anesthetic	Medical Knowledge
Place internal jugular central venous line	Patient Care
Interact with operating room and PACU nurses	Professionalism, Interpersonal, and Communication Skills
Patient with nerve injury—refer to quality improvement/patient safety committee	Systems-Based Practice
Patient with central line infection—compare prevention strategy with medical literature	Practice-Based Learning and Improvement

ACGME, Accreditation Council for Graduate Medical Education; *PACU,* postanesthetic care unit.

whether the six general competencies can be measured independently of one another in a reliable and valid manner.[23] The studies did not find a method to assess the competencies as independent constructs, with the exception of medical knowledge. Instead, the available assessment tools related to several different competencies. For example, one large study examined global evaluations from more than 1300 residents in 92 specialties.[24] Whereas the global evaluations asked faculty to rate residents on items in all six competencies, analysis of the ratings found that two independent factors could explain most of the variance in the evaluations. The two factors were described as "medical knowledge, patient care and systems-based care" and "interpersonal communication skills and professionalism." Although it is not clear that current evaluation tools can discriminate between individual competencies, it is possible that they can discriminate among different levels of performance within a single competency or a subset of one.[25]

ASSESSMENT AND MILESTONES

The principles of competency-based education can be combined with a model of skill acquisition to develop a richer framework for performance assessment. One such framework, the Dreyfus model, arose from a U.S. Air Force–sponsored research study examining the skill acquisition of pilots.[26] It described five stages of development ranging from novice to master. In health care, the model has been adapted to describe both physician and nursing skills acquisition.[20,27] The principles of the Dreyfus model are highlighted in Table 9-10. For individuals to progress to the expert stage, they need supervision, training, and opportunities for deliberate professional practice.[20,28]

Another framework of clinical skills assessment is known as Miller's Pyramid. Miller, a widely respected medical education researcher, acknowledged that "no single assessment method can provide all the data required for judgment of anything so complex as the delivery of professional services by a successful physician."[29] He suggested a framework within which assessment could occur (Table 9-11) and noted "the inescapable truth that examinations drive the educational system." Miller's Pyramid has served as a useful tool for considering the progression of learners and the types of assessment needed to judge performance. There are several criticisms of the model.[20,28] First, the original description of "knows how" was labeled "competence" and "shows how" was labeled "performance." These terms are misleading when viewed in the context of competency-based medical education and the Dreyfus model of performance assessment. Second, the behavior of a learner in a workplace-based assessment, such as direct observation, may be influenced by their knowledge of being observed and may not necessarily reflect their actual behavior. Third, the model implies that a learner's inability to "show how" (e.g., intubate a mannequin airway) should translate to an inability to "do" in an actual patient; however, this might reflect a lack of fidelity in the mannequin rather than a

BOX 9-4 ***Key Structural Elements in Anesthesiology Program Requirements***

- Duration of training: 12 months of clinical base year, 36 months of clinical anesthesia (CA-1, CA-2, and CA-3 years)
- Required rotation experiences:
  - Two months of obstetric anesthesia
  - Two months of pediatric anesthesia
  - Two months of neuroanesthesia
  - Two months of cardiothoracic anesthesia
  - Four months of critical care medicine
  - Three months of pain medicine (may include 1 month of acute perioperative pain, 1 month of chronic pain, and 1 month of regional analgesia)
  - One month preoperative evaluation clinic
  - Two weeks postanesthesia care unit

From ACGME Program Requirements for Graduate Medical Education in Anesthesiology. <http://www.acgme.org/acgmeweb/Portals/0/PFAssets/ProgramRequirements/040_anesthesiology_f07012011.pdf>. (Accessed 14.03.13.)

TABLE 9-10 PRINCIPLES OF DREYFUS MODEL OF SKILL DEVELOPMENT IN PHYSICIANS

Level of Performance	Description and Attributes of Performance
Novice	Rules and protocols guide performance Uses analytical reasoning to solve problems Minimal ability to filter and prioritize information Unable to manage complexity
Advanced Beginner	Is able to sort through rules and information to determine relevance based on past experience Uses both analytic reasoning and pattern recognition to solve problems Able to achieve partial resolution of complex tasks
Competent	More expansive experience leads to more frequent use of pattern recognition to solve problems May need analytic reasoning for complex or uncommon problems Task seen as one construct (i.e., able to see big picture) Seeks out and applies advice from experts and uses it effectively Reliesy on deliberate planning and experience and less on intuition
Proficient	Breadth of experience allows extensive use of pattern recognition; clinical problem solving seems intuitive Routinely meets acceptable clinical standards Comfortable with evolving situations, can extrapolate from known to unknown situation May need to fall back on analytic reasoning for certain problems
Expert	Performance based on experience and intuition Achieves excellent performance Is open to notice the unexpected Can discriminate features not fitting recognizable patterns In complex situations, moves easily between analytic and intuitive solutions

Adapted from Carraccio CL, Benson BJ, Nixon LJ, Derstine PL: From the educational bench to the clinical bedside: translating the Dreyfus developmental model to the learning of clinical skills, Acad Med *83:761-767, 2008; and Khan K, Ramachandran S: Conceptual framework for performance assessment: competency, competence and performance in the context of assessments in healthcare—deciphering the terminology,* Med Teach *34:920-928, 2012.*

lack of learner skill. Finally, another implication is that if a learner does a skill appropriately and successfully, that level of skill has been attained and can be applied to all practice settings. However, it is clear that performance is highly dependent on context.[28] For example, the ability to place a central venous catheter before elective surgery might not translate to successful performance of the same procedure on a semiconscious injured patient in the emergency department.

TABLE 9-11 MILLER'S PYRAMID FRAMEWORK FOR CLINICAL ASSESSMENT

Level of Pyramid (Highest to Lowest)	Description	Possible Assessment Approach
Does	What learner does in clinical practice	Direct observation, workplace evaluations
Shows how	Learner shows how (i.e., performs)	Simulations, objective structured clinical examination, standardized patient
Knows how	Learner must know how to use knowledge accumulated	Case presentations, essays
Knows	Learner knows what is required to carry out professional function	Cognitive examination

Adapted from van der Vleuten CP, Schuwirth LW, Scheele F, et al: The assessment of professional competence: building blocks for theory development, Best Pract Res Clin Obstet Gynaecol *24:703-719, 2010; and Miller GE: The assessment of clinical skills/competence/performance,* Acad Med *65:S63-67, 1990.*

To advance the core competencies approach, the ACGME adopted the Dreyfus model of skill acquisition to create a framework for milestones of competency development and advocated for implementation of common evaluation tools in each discipline to document resident achievement of the milestones.[30] Programs will use milestones in the resident evaluation and feedback process, and the ACGME will use milestones as part of the accreditation of the residency program. An example of a patient care milestone for various levels of anesthesia residents is shown in Table 9-12.

CURRICULUM DEVELOPMENT

The curriculum for anesthesia residency training is composed of clinical assignments (clinical rotations) that include general and subspecialty rotations. Each rotation should have specific goals and learning objectives, as well as teaching and assessment methods and educational resources. A sample set of goals and objectives for a rotation is provided in Appendix 9-3. As a resident advances through training, the rotations should become progressively more challenging. The resident should also assume progressive responsibility for patient care and be appropriately supervised during the entire training period.

To ensure that the anesthesia resident has a satisfactory breadth of clinical experiences, the program requirements provide a list of minimum numbers of key patient care encounters that should be achieved by the end of training (Box 9-5). Throughout the training period, the resident should gain experience caring for patients with complex comorbid illnesses undergoing complicated surgical procedures. By the end of training, it is expected that the resident will exhibit sound clinical judgment in a variety of clinical circumstances and can function in a leadership role on the

TABLE 9-12 EXAMPLE OF ANESTHESIA RESIDENT MILESTONES: PATIENT CARE COMPETENCY—ANESTHETIC CHOICE AND CONDUCT

Level 1 (end CBY)	Level 2 (Before Subspecialty Rotations)	Level 3 (Completed Subspecialty Rotations)	Level 4 (Ready to Graduate)	Level 5 (After Beginning Independent Practice)
Formulates patient care plans that include consideration of underlying clinical conditions, past medical history, and patient, medical, or surgical risk factors	Formulates anesthetic plans for patients undergoing routine procedures that include consideration of underlying clinical conditions; past medical history; patient, anesthetic, and surgical risk factors; and patient choice	Formulates anesthetic plans for patients undergoing common subspecialty procedures that include consideration of medical, anesthetic, and surgical risk factors and that take into consideration a patient's anesthetic preference	Formulates and tailors anesthetic plans that include consideration of medical, anesthetic, and surgical risk factors and patient preference for patients with complex medical issues undergoing complex procedures with conditional independence	Independently formulates anesthetic plans that include consideration of medical, anesthetic, and surgical risk factors, as well as patient preference, for complex patients and procedures
Adapts to new settings for delivery of patient care	Conducts routine anesthetics, including management of commonly encountered physiologic alterations associated with anesthetic care, with indirect supervision Adapts to new settings for delivery of anesthetic care	Conducts subspecialty anesthetics with indirect supervision, but may require direct supervision for more complex procedures and patients	Conducts complex anesthetics with conditional independence; may supervise others in the management of complex clinical problems	Conducts complex anesthetic management independently

From Anesthesiology Residency Review Committee: The Anesthesiology Milestone Project. *December 2013. <http://www.acgme.org/acgmeweb/Portals/0/PDFs/Milestones/AnesthesiologyMilestones.pdf>. (Accessed 19.04.14.)*
CBY, Clinical Base Year.

care team. The didactic and clinical teaching in a residency program is designed to address subject matter listed in the ABA content outline. In addition, the ACGME program requirements stipulate a few topics that must be in the residency curriculum, including recognizing fatigue and sleep deprivation, alertness management and fatigue mitigation processes, practice management, geriatric patient care, and management of the ambulatory surgery patient.

Anesthesia residents in the United States are offered an annual in-training examination (ITE) by the ABA. Independent study, including assigned reading, has traditionally been used as the main method of preparation. One study assessed the relationship between the amount of independent reading by residents in one program, and their ITE scores.[31] The average weekly self-study time was 8 ± 3.6 hours (range, 1 to 20 hours). Linear regression revealed a positive correlation between hours of self-study and ITE-scaled score (correlation coefficient 0.64; $p < 0.0001$). The correlation seems intuitively obvious, but this relationship had not been confirmed in anesthesiology training. Another expectation is that ITE performance will predict performance on the ABA Part 1 (written, multiple choice) examination. This expectation was confirmed in a 2010 study revealing that the ITE score in clinical anesthesia year 1 (CA-1) was a significant predictor of both Part 1 and Part 2 (oral) examination performance.[32] There are multiple other factors involved in ITE performance, including prior performance on national examinations, program didactics, and study habits of trainees.

WORK HOURS AND IMPLICATIONS FOR ANESTHESIA TRAINING

The duty hours of residents have been a subject of considerable debate in graduate medical education for several decades. For many years, a resident might remain on duty in the hospital overnight ("take call") every other night. On the day after call, the resident could remain in the hospital until the evening to provide patient care. In a given week, a resident might spend over 120 hours on duty. This culture of dedication to patient care had advantages, but there was no doubt that limitations of performance accompanied sleep deprivation. A 1971 study showed that sleep-deprived interns (mean of 1.8 hours sleep) were twice as likely to fail to recognize cardiac arrhythmias on an electrocardiogram than a rested intern with 7 hours of sleep.[33] The 1984 death of college student Libby Zion brought resident duty hours to the national spotlight.[34] Zion was admitted to New York Hospital with fever, tremors, and disorientation. She was given intravenous hydration and meperidine, which likely caused a drug reaction with an antidepressant drug she was taking, phenelzine. She developed extreme fever and died of cardiac arrest. A Manhattan grand jury investigation criticized the 36-hour duty periods worked by the residents, and inadequate supervision by attending physicians.[35] The New York Health Commissioner formed a committee that became known as the Bell Commission, which recommended an 80-hour per week limit on resident duty hours, a maximum of 24 consecutive hours on duty, and the requirement for senior physicians to be present in the hospital. These recommendations were incorporated into the New York State Health Code in 1989.

The ACGME also formed task forces and provided position statements on duty hours. In 1992, the ACGME mandated that all programs require one 24-hour period per week without patient care responsibilities, with assignment to call duty limited to every third night. While the 1992 ACGME rules did not specify hourly limits on resident duty hours, many individual specialty RRCs imposed such limits, including internal medicine, dermatology, ophthalmology, and emergency medicine. Most of these RRCs chose 80 hours as the weekly limit, with emergency medicine setting a limit of 72 hours. There was additional pressure for change. In 2001, a petition requested that the Occupational Safety and Health Administration (OSHA) regulate duty hours of residents because of its potential role as a workplace health hazard. Also in 2001, the U.S. Congress considered legislation to limit resident work hours. In 2003, the ACGME set a maximum limit of 80 hours per week on the duty hours of all residents in all specialties. They also set a maximum of 24 hours of continuous duty, plus 6 hours for continuity and transfer of care. While one intent of duty-hour regulations was to improve patient safety, it was not clear that overall patient safety had improved. This was not unexpected given the many factors that affect patient outcomes and the complexity of the modern health care system. The U.S. Congress requested that the Institute of Medicine, the health arm of the National Academy of Sciences, study the relationship between resident duty hours and patient safety. In 2008, the Institute of Medicine released a report titled "Resident Duty Hours: Enhancing Sleep, Supervision, and Safety." The report "asserts that revisions to medical residents' workloads and duty hours are necessary to better protect patients against fatigue-related errors and to enhance the learning environment for doctors in training. The report recommends that residency programs provide regular opportunities for sleep each day and each week during resident training."[36] In 2011, the ACGME revised its common program requirements to include additional restrictions on duty hours, the most notable being a reduction of continuous duty for interns to a maximum of 16

BOX 9-5 ***Minimum Clinical Experience for Anesthesia Resident***

1. 40 patients undergoing vaginal delivery
2. 20 patients undergoing cesarean section
3. 20 patients undergoing cardiac surgery
4. 20 patients undergoing open or endovascular procedures on major blood vessels
5. 20 patients undergoing noncardiac intrathoracic surgery
6. 20 patients undergoing intracerebral procedures
7. 20 patients undergoing procedures for complex, life-threatening injuries
8. 40 patients undergoing surgical procedures in whom epidural anesthetics are used
9. 40 patients undergoing surgical procedures with spinal anesthetics
10. 40 patients undergoing surgical procedures in whom peripheral nerve blocks are used

From ACGME Program Requirements for Graduate Medical Education in Anesthesiology. <http://www.acgme.org/acgmeweb/Portals/0/PFAssets/ProgramRequirements/040_anesthesiology_f07012011.pdf>. (Accessed 14-03-2013.)

BOX 9-6 *ACGME Duty Hour Regulations*

Maximum Hours of Work per Week

- Duty hours must be limited to 80 hours per week, inclusive of all in-house call activities and all moonlighting.*

Duty Periods

- Residents must be scheduled for a minimum of 1 day free of duty every week.*
- Duty periods of PGY-1 residents must not exceed 16 hours.
- Duty periods of PGY-2 residents and above may be scheduled to a maximum of 24 hours of continuous duty in the hospital.
- It is essential for patient safety and resident education that effective transitions in care occur. Residents may be allowed to remain on-site to accomplish these tasks; however, this period must be no longer than an additional 4 hours.
- In unusual circumstances, residents, on their own initiative, can remain beyond their scheduled period of duty to continue to provide care to a single patient.
- PGY-1 residents should have 10 hours, and must have 8 hours, free of duty between scheduled duty periods. PGY-1 residents are not permitted to moonlight.
- Intermediate-level residents should have 10 hours free of duty, and must have 8 hours between scheduled duty periods. They must have at least 14 hours free of duty after 24 hours of in-house duty.
- PGY-2 residents and above must be scheduled for in-house call no more frequently than every third night.*
- Residents must not be scheduled for more than 6 consecutive nights of night float.

From ACGME Common Program Requirements. Effective July 1, 2011. <http://www.acgme.org/acgmeweb/Portals/0/dh_dutyhoursCommonPR07012007.pdf>. (Accessed 14-03-2013.)

* When averaged over a 4-week period. PGY=Postgraduate year

TABLE 9-13 **RESIDENT AND PROGRAM DIRECTOR PERCEPTIONS OF 2011 DUTY HOUR REQUIREMENTS**

Variable	Resident Perception*	Program Director Perception†
Patient safety	Worse: 27% Unchanged: 53% Improved: 20%	Worse: 36% Unchanged: 57% Improved: 7%
Resident education	Worse: 41% Unchanged: 43% Improved: 16%	Worse: 65% Unchanged: 27% Improved: 8%
Preparation for senior resident role	Worse: 52% Unchanged: 38% Improved: 11%	Worse: 73% Unchanged: 25% Improved: 2%
Quality of life for senior resident (or intern)	Worse: 50% (18%) Unchanged: 37% (20%) Improved: 14% (62%)	Worse: 18% Unchanged: 33% Improved: 50%
Supervision	Worse: 8% Unchanged: 74% Improved: 18%	Worse: 5% Unchanged: 62% Improved: 33%
Frequency of handoffs	Decrease: 3% Unchanged: 26% Increased: 72%	Decrease: 3% Unchanged: 10% Increased: 88%

Data abstracted from Drolet BC, Christopher DA, Fischer SA: Residents' response to duty-hour regulations–a follow-up national survey, N Engl J Med *366:e35, 2012; and Drolet BC, Khokhar MT, Fischer SA: The 2011 duty-hour requirements–a survey of residency program directors,* N Engl J Med *368:694-697, 2013.*

*Resident responses: 6202 (23% response rate).

†Program director responses: 549 (75% response rate).

hours. A summary of current duty hour regulations is listed in Box 9-6. The ACGME also addressed other aspects of patient safety, including new standards for supervision, teamwork, transitions of care, fitness for duty, alertness management, and fatigue mitigation.[37]

In 2011, the ACGME defined three different levels of supervision that apply during training: direct, indirect, and oversight.[16] With direct supervision, the supervising physician is physically present with both resident and patient. There are two types of indirect supervision. Under "indirect with direct supervision immediately available," the supervising physician is physically present at the patient care site and can immediately provide direct supervision. Under "indirect with direct supervision available," the supervising physician is not physically present at the patient care site, but is immediately available by telephone, and is available to provide direct supervision. With oversight supervision, the supervising physician is available to provide review and feedback after patient care has been delivered.

Since the implementation of the ACGME 2011 duty hour regulations, residents and residency program directors have been surveyed to determine their perceptions of the changes. (Table 9-13).[38,39] Of note, the majority of residents and program directors surveyed believed that patient safety and availability of supervision were unchanged. Perceived quality of life for interns was improved, though quality of life for senior residents was believed to be worse. In addition, preparation for more senior resident roles was perceived to be worse. Other notable survey results included a marked increase in the frequency of handoffs in care, increased assumption of junior resident work by senior residents, and a marked increase in the use of physician extender (nurse practitioner or physician assistant) coverage.[38,39] While these perceptions relate to the initial experience with the new regulations, it is clear that additional work will be needed to determine their effect on the achievement of milestones and readiness for independent practice, which is the ultimate goal of a residency program.

ANESTHESIA FELLOWSHIP TRAINING

As the specialty of anesthesiology has advanced, a number of subspecialties have developed over the past 25 to 30 years that focus on the care of selected patient populations and on the scientific underpinnings of these subsets of the medical specialty of anesthesiology. Many of the subspecialty fellowships are accredited by ACGME, including critical care medicine, pain medicine, pediatric anesthesiology, adult cardiothoracic anesthesiology, and obstetric anesthesiology. The accreditation process requires formal educational curriculum and compliance with the many rules and regulations expected of the core residency program (competencies, milestones, duty hour restrictions). Subspecialties for which the ABA has developed special qualifications with formal examination have a content outline describing the educational requirements. For accredited subspecialties for which there is no formal qualifying examination, the curriculum is defined by each subspecialty, although there is no formal oversight of each educational program. As a result, the teachers have a great deal of flexibility in

defining the content outline. More importantly, many subspecialties are not accredited by ACGME and have no oversight of the trainees by the ABA. For example, neuroanesthesia training programs are not accredited by ACGME, nor do they have formalized didactic or clinical curricula to guide each program and the faculty. As a result, the faculty has a great deal of leeway in defining the clinical experiences and didactic and other educational initiatives, as well as a great deal of responsibility to ensure that the training is evidence-based and comprehensive.

The implication for teaching anesthesia fellows in non-ACGME–accredited programs such as neuroanesthesia is that each individual program must define their own curriculum, clinical experiences, mentorship, and scholarly activity requirements. The lack of accepted standards and an oversight system can lead to significant variability in experiences among fellows in one program and among fellows in different programs. Another important issue for unaccredited fellowships is the service-versus-education balance. A fellow could spend a significant amount of time in junior attending roles that are not in their designated subspecialty area, thereby diluting their educational experience.

ANESTHESIA TEACHING METHODS

Although physicians are expected to mentor colleagues and educate trainees and their patients, few have formal training in teaching methodologies. At the same time, there is an implicit expectation that each physician is a teacher. In fact, the word *doctor* derives from the Latin word *docere,* which means "to teach." For formal educational programs, the lack of education for physicians in teaching and evaluation methodologies is now recognized as a deficiency. In academic health systems in particular, there is increasing acknowledgment of the need for faculty development in anesthesia education.[40] In the last decade, many medical schools have transformed their curriculum, incorporating new approaches such as problem-based learning, computer-based instruction, standardized patients, and simulation training.[41] Similarly, residency and fellowship programs have adapted to new ACGME accreditation requirements. In order to describe the skills needed for excellence as a teacher, one must first define the types of teaching roles encountered in contemporary medical education. One framework describes seven core tasks that may be required of a teacher (Table 9-4).[42] The following section addresses two of the most common anesthesia teaching situations: clinical teaching and classroom teaching of large and small groups.

CLINICAL TEACHING

Learning from the clinical care of patients is the essence of medical education. There are many challenges to teaching in the clinical environment, including other demands for faculty time and attention, the potentially rapid pace of clinical care with associated production pressure, and teaching different levels of learners at the same time. The clinical teacher must provide supervision of clinical care while serving as a professional role model and creating opportunities for the trainee to learn.[43] The question "What makes a good clinical teacher in medicine?" was the subject of a systematic literature review.[44] Good clinical teaching is clearly multifactorial, but analysis of the most commonly reported themes revealed that noncognitive aspects of teaching such as developing positive relationships with students, creating a supportive learning environment, communication skills, and enthusiasm were emphasized more than cognitive aspects such as medical or clinical knowledge, clinical or technical skills, and clinical reasoning.

One model for clinical teaching that has been disseminated and validated is the Stanford Faculty Development Program.[45,46] This model uses seven categories to describe important aspects of clinical teaching.

1. Establish a positive learning climate; this involves the tone of the teaching setting, including learner comfort, enthusiasm of teacher, and mutual respect.
2. Control the teaching session; this includes the teacher's ability to focus and pace the encounter.
3. Communicate goals; this refers to establishment of expectations, which can include knowledge, skills, and attitudes of the learner.
4. Promote understanding and retention; this refers to teaching methods used to enhance the learner's initial understanding and remember it.
5. Establish evaluation techniques to assess a learner's achievement of goals; this can be used to assess ongoing progress or for a final assessment.
6. Provide feedback; this describes how the teacher provides learners with information about their performance for them to improve.
7. Promote self-directed learning; this stresses the importance of acquiring skills to continue learning beyond the teaching session itself.

These skills can be developed in workshop settings and in collaboration with faculty development "peer-coaching" programs.

Another model of clinical teaching that was initially developed in the ambulatory medicine setting is the One-Minute Preceptor.[47] This model describes five sequential steps that can be used to structure clinical encounters that last several minutes.

1. Get a commitment. Ask the learner to articulate their opinion on the patient's diagnosis or an aspect of management. At this point, teachers should not share their opinion.
2. Probe for supporting evidence. Encourage the learner to share their rationale for the commitment they made.
3. Teach general rules. Teachers can help learners understand how the learning from this patient can be applied to other patients.
4. Reinforce what was done well. Positive feedback should be as specific as possible, based on behaviors observed.
5. Correct mistakes. While some teachers avoid giving corrective feedback, this is essential for competent care of patients.

This model can be adapted to many anesthesia clinical settings. Two examples of One-Minute Preceptor teaching sessions are shown in Table 9-14.

TABLE 9-14 EXAMPLES OF ONE-MINUTE PRECEPTOR TEACHING MODEL IN THE ANESTHESIA CLINICAL SETTING

Scenario	Step	Actions	Dialogue With Learner
You are working with a medical student on an anesthesia rotation. A healthy patient is receiving general anesthesia for ventral hernia repair. After skin incision, the heart rate increases.	1	Get a commitment	Why do you think the heart rate is increasing?
	2	Probe for supporting evidence	Why do you think the elevated heart rate is from inadequate anesthesia?
	3	Teach general rules	Discuss how to approach acute elevations in heart rate during general anesthesia.
	4	Reinforce what was done well	You nicely incorporated other vital signs such as blood pressure and respirations into your assessment.
	5	Correct mistakes	In the future, you should not give β-blocker without first ensuring adequate depth of anesthesia.
You are working with a new resident in the ICU. A patient with hypotension requires arterial line placement for monitoring.	1	Get a commitment	Where and how would you place an arterial line in in this patient?
	2	Probe for supporting evidence	Why do you think a guide wire would facilitate line placement in this patient?
	3	Teach general rules	Discuss clinical pearls for arterial line placement.
	4	Reinforce what was done well	The needle angle into the skin was optimal for use of a guide wire.
	5	Correct mistakes	If the guide wire becomes bent, a new one should be used.

ICU, Intensive care unit.

BOX 9-7 ***Strategies for Effective Questions and Explanations in Teaching***

Asking Questions

- Consider whether to use closed, open or clarifying questions. Closed questions can evoke simple recall but can be useful to establish basic facts. Open questions are more likely to promote deeper thinking unless question is overly broad.
- Allow adequate time for learner to respond. Avoid the temptation to speak too soon.
- Resist the urge to answer the learner's question right away. Use a counter question instead.
- Follow a poor answer with another question.
- Consider statements to reduce confrontation, such as "This is sometimes difficult to understand."

Giving Explanations

- Check understanding before, during, and after your explanation. Pay attention to nonverbal cues as well.
- Provide information in easily understood units ("bite-sized chunks").
- Put an explanation in a broader context if appropriate.
- Summarize periodically, or ask the learner to summarize to gauge understanding.
- Reiterate the take-home messages, or ask the learner to do so.

Adapted from Spencer J: Learning and teaching in the clinical environment, BMJ *326:591-594, 2003.*

Experienced clinical teachers make use of "teaching scripts" to guide many of their teaching interactions.[43,48] A teaching script includes three to five teaching points with supporting material, an appreciation of common errors made by learners on that particular topic, and effective ways to create a framework for learners to build on. The use of the One-Minute Preceptor Model can be considered as a way to develop a teaching script. A teacher's communication skills are crucially important, including active listening, sensitivity to verbal and nonverbal cues, asking questions, and giving explanations. Practical tips for asking questions and giving effective explanations are provided in Box 9-7.[49]

Another aspect of clinical teaching is procedural skills teaching. For many generations of physicians, the primary teaching method was captured by the phrase "see one, do one, teach one." This is no longer appropriate in a health care system focused on maximizing patient safety and improving efficiency. In the motor skills and surgical literature, a three-stage theory of motor skill acquisition is widely accepted.[50,51]

In the *cognitive stage*, the learner must understand the task from an intellectual perspective, and then plan distinct steps to accomplish it. The teacher must be able to break down the steps, explain, and demonstrate them.

In the *integrative stage*, the learner's goal is to comprehend and perform the appropriate motor activities. At this stage, the learner still thinks about each step, but the execution is more fluid, with fewer interruptions. Practice with formative feedback is critically important at this stage so that the learner knows whether the steps are correctly performed, and if not, how to adjust accordingly.

In the *autonomous stage*, the learner performs the task smoothly, with speed, efficiency, and precision. At this stage, routine execution of the task is accomplished with little cognitive input, allowing the learner to focus on other aspects of the procedure. An approach to procedural skills learning is depicted in Figure 9-2.[52,53] The first step is to ensure that the learner has the appropriate motivation and background knowledge for performing the task, and that the environment is conducive to learning. For example, it might not be appropriate for a new anesthesia resident to insert their first internal jugular central line in an obese patient who is coagulopathic and receiving mechanical ventilation. Second, the teacher "shows the learner how" to appropriately perform the task. The learner should view a demonstration or video of the entire procedure on a real patient performed by an expert. The teacher then describes the steps of the procedure while explaining each step carefully; this can involve simulations or low-fidelity models. In the next step, which can be considered "guided discovery," the teacher provides appropriate guidance as the learner performs the task

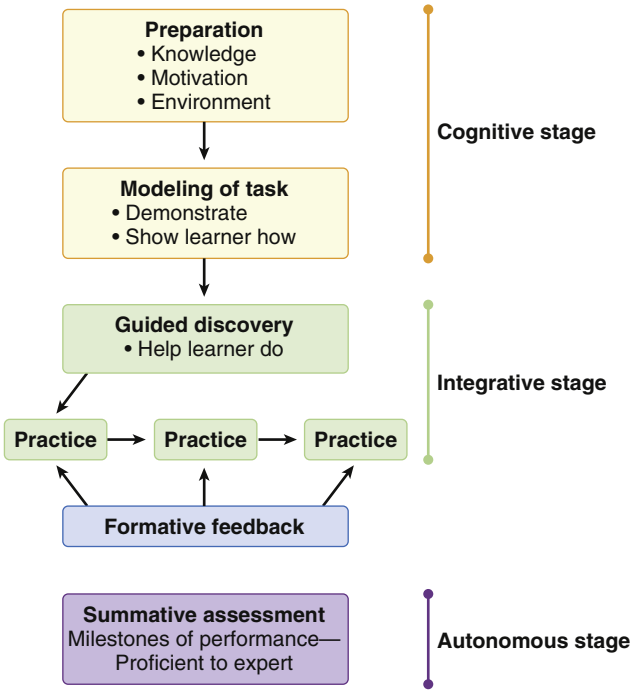


Figure 9-2. Approach to teaching procedural skills.

("helps learner do"). The learner is then allowed supervised opportunities to practice the skill while being provided timely and frequent feedback. Summative assessment of performance occurs after adequate opportunities for practice. Depending on the summative assessment, the level of supervision for subsequent procedures of the same type may be reduced. As part of the spectrum of expertise development, the learner may eventually be expected to teach the procedure to others. If a skill or task is considered complex, one should consider dividing it up into simpler component parts, practicing in isolation, and then progressively combining the parts of the total skill until the learner is able to perform the entire complex task. For example, when teaching a resident to perform a basic transesophageal echocardiography (TEE) examination, one might divide the task as follows: (1) learning to place the TEE probe in a simulator or patient, (2) manipulating the probe in a TEE task trainer, (3) studying the basic TEE views to understand the expected anatomic features of each view, (4) obtaining the TEE views in a task trainer, and finally (5) performing the entire basic TEE examination in a patient under direct supervision.

Medical schools and residency programs (and hopefully individual teachers) desire excellence in clinical teaching. The same learning principles apply to teachers who seek improvement in their teaching skills, including the important role of assessment.[8] One large study in an academic anesthesia department examined 5 years of resident teaching evaluations, and addressed whether evaluation and feedback to anesthesiology faculty teachers from anesthesiology resident learners improved clinical teaching scores. Anesthesia residents' numerical evaluation scores (quantitative summary report) and all narrative comments were provided to each clinical teacher. The average teaching score for the entire faculty rose over time and the increase in teaching scores was attributed to improved teaching. This study suggested that clinical teachers are able to improve their clinical teaching by using feedback from resident learners.[54]

CLASSROOM TEACHING

Classroom teaching of large and small groups is another important teaching skill. Many of the clinical teaching principles of the Stanford Faculty Development model can be applied to this settings as well. However, the lecture format is less conducive to the evaluation of a learner's achievement of goals, and it is not likely to elicit many opportunities for feedback to learners. Some relevant principles for teaching in this setting include:

1. Learn and use the information as soon as possible. For example, a lecture on the management of sepsis should occur during a rotation in critical care as opposed to an ambulatory surgery rotation
2. Activate prior knowledge. Use analogies and examples that connect to students' existing knowledge. Make sure that new information can be situated meaningfully in the context of what learners already know.
3. Make it relevant. Describe how the information presented is relevant to their future performance. Tailor instruction to the type of learner (e.g., medical student, anesthesia resident). Case presentations can be a particularly powerful method.
4. Use multiple modes of explanation. Be prepared to use different approaches to present information, such as words, images, figures, pictures, cases, or problems.
5. Less may be more. The length of a teaching session does not necessarily correlate with the quantity of learning. For example, the *segmenting principle* of multimedia learning states that people learn better when a continuous or large lesson is broken down into smaller, learner-paced segments.[55]

The traditional approach to large classroom teaching consists of a teacher-provided lecture followed by assigned homework that builds on the lecture. An approach called the *inverted* or *flipped classroom model* shifts this dynamic. The foundational learning is done by the student before class. Preparation can consist of required readings or online videos followed by a brief test to reinforce the expectation of preparedness. Classroom time is used for interactive exercises such as audience response system questions and feedback, small group activities, or case discussions. This approach has been studied in a large college physics class, in which the flipped classroom students had higher attendance, more engagement in class, and higher scores on a knowledge examination.[56] In the health sciences, two pharmacy schools have reported positive results in transforming large group courses using the flipped classroom model, including improved grades and favorable student perceptions of the new teaching approach.[57,58]

FACULTY DEVELOPMENT FOR TEACHING

At many institutions, faculty development programs have been designed to improve the teaching abilities of

faculty. One review examined the outcomes of more than 50 different faculty development programs using the Kirkpatrick evaluation model, which describes four levels of impact: learner reaction, learning (change in attitude, knowledge, or skill), behavior change, and results (at the learner level or the organization itself).[59] The program types included seminar series, workshops, and longitudinal programs. The instructional methods used included lectures, small group discussions, role playing, simulations, and video reviews of performance. The following beneficial effects were observed: improvements in teaching behavior, gains in teaching knowledge and skill, and a positive change in attitudes towards teaching and faculty development itself.[60] According to Kirkpatrick, there are four conditions needed to promote behavior change in an individual: desire for change, knowledge of what to do, a supportive work environment, and rewards for changing.[59] While faculty development efforts can help address the first two conditions, the latter two conditions will need support from the community of teachers and learners.

NEW MODELS OF TEACHING

Changes in clinical practice have affected resident education and resulted in the need for new teaching models. The use of technology in patient care (e.g., ultrasound-guided regional anesthesia and vascular access, echocardiography) required instructors to incorporate these tools in their clinical and classroom teaching efforts. Other educational needs are more difficult to address. For example, residents care for many patients undergoing endovascular approaches to vascular surgery. In many programs, however, residents have limited experience with complex procedures such as open aortic vascular surgery. Improvements in patient safety in anesthesia have led to a decrease in crises that are managed by residents. To ensure that anesthesiologists are skilled in the management of rare events and less commonly encountered procedures, residency programs must incorporate alternative methods to prepare residents for practice. Simulation is one such method. Teachers should also be aware of other advances in education technology that present new ways to deliver content, teach and assess, provide collaborative learning environments, and increase classroom interactivity. These methods, which include e-Learning, wikis, podcasts, and audience response systems, have been used increasingly in the teaching of elementary school, high school, college, and medical students. In the future, teachers will be faced with learners who have considerable experience with these approaches. The use of new education technology does not guarantee that the learning process will be more effective. However, teachers and learners should understand how these new teaching models work because there are some features that can facilitate the principles of learning discussed here.

SIMULATION (SEE ALSO CHAPTER 8)

Simulation is a technique to recreate reality in an interactive manner for training or other purposes. There are numerous dimensions to the use of simulation in medical education, including the purpose of the simulation (e.g., training, assessment, research), spectrum of technology (e.g., verbal role play, standardized patient actor, part-task trainer, virtual reality trainer, computer screen-based simulator, mannequin-based patient simulator), site of simulation (e.g., home office, skills laboratory, dedicated simulation center, actual work place—aka in situ), and spectrum of feedback accompanying simulation (e.g., none, automatic critique by simulator, real-time instructor critique, video-based post hoc debriefing).[61] For medical student anesthesia learners, simulation (in the form of part-task trainers) can be used for teaching procedures such as peripheral intravenous catheter placement, mask ventilation, direct laryngoscopy, and tracheal intubation. A mannequin patient simulator can be used to teach intraoperative critical event management (e.g., hypoxemia, hypotension) in novice anesthesia residents.[62] A preliminary evaluation of a virtual reality–based spinal anesthesia simulator described its use as part of an integrated training program, including a cognitive examination, as well as simulator and clinical testing.[63] Simulation can also be used for teaching crisis resource management and teamwork training in anesthesia and other health care settings.[64] Several types of assessment can be performed using simulation, including procedural skills,[65] acute care skills,[66] and nontechnical skills such as communication, teamwork, and situational awareness.[67]

In 2011, the Anesthesiology Residency Review Committee added a new requirement that all U.S. residents. must participate in at least one simulated clinical experience per year. A 2010-2011 survey of U.S. academic anesthesiologists showed that residents in their departments participated in approximately two to three simulation sessions per year (R. Schell, M. Pardo, R. Gaiser, unpublished data). A 2008 survey of all Canadian anesthesia residents revealed that they participated in an average (median) of two simulation training sessions per year.[68] Many residents (81%) experienced anxiety during the simulation exercises; reasons included not knowing the scenario they were about to manage, performing in front of fellow residents and faculty, and limited prior experience with simulation. Despite their anxiety, the Canadian residents expressed desire for more simulation sessions per year and increased participation in multidisciplinary scenarios.

In comparison with no intervention, technology-enhanced simulation training in health professions education is consistently associated with large effects for outcomes of knowledge, skills, and behaviors.[69] However, there is little evidence that simulation improves patient care outcomes. A question that needs answering is: What is the validity and reliability of simulation for procedural clinical and behavioral competency evaluation? In other words, will performance on a given assessment predict future performance in actual practice?

Simulation can provide the opportunity for deliberate practice (i.e., practice undertaken over an extended period to attain excellence), but most anesthesia training programs are not currently structured to provide extensive and frequent simulation training. The use of simulation for team training is also underutilized, in spite of the widespread acceptance of the importance of teamwork (see Chapter 7).

E-LEARNING

e-Learning is also called web-based learning, online learning, distributive learning, computer-assisted instruction, or Internet-based learning. Advantages include widespread access, ability to self-pace learning, and delivery of a consistent curriculum. However, an e-learning module must adhere to proper instructional design principles.[70,71] When properly designed, e-learning is an approach that is flexible, engaging, learner-centered, and interactive. A meta-analysis suggested that e-learning has equivalent time and learning efficiency compared with traditional instruction.[72]

WIKIS

Wikis are collaborative websites that can be edited by groups of individuals (e.g., Wikipedia). A wiki can serve as a central repository for educational content such as slideshow presentations, lecture handouts, lecture podcasts, and journal articles. Wikis can become a tool for collaboration, actively involving learners in their own construction of knowledge, and can provide an opportunity for learners to function as teachers as they provide educational content for others. Potential drawbacks include the open access nature of wikis, which can result in inaccurate information being added by a user. OpenAnesthesia.org, a wiki sponsored by the International Anesthesia Research Society, is an online toolkit intended for anesthesia resident learners.[73]

PODCASTS

Podcasts are repositories of audio or video materials that can be downloaded to portable media players, adding the potential for mobile learning. Podcasts are widely used in medical schools to allow learners to review lectures presented in the classroom. Although lectures are recorded in real time, they can be played back at twice the normal speed to allow for more efficient review of the material.

AUDIENCE RESPONSE SYSTEMS

An audience-response system (ARS) is a classroom technology that allows learners to respond to questions in a slide presentation via small, hand-held remote keypads ("clickers"). Educational uses for the ARS include the following: (1) assess student preparation, (2) provide formative feedback to teacher about the state of learners' understanding, (3) enhance interaction and student attention, (4) use quizzes or tests, and (5) make the lecture more fun for the presenter.[74] Students generally have positive reactions to use of ARS in the classroom, for reasons that include the anonymity of responses, reinforcement of learning, and an ability to compare one's answers to others. A recent systematic review of audience response systems on learning outcomes in health professionals provides some evidence to suggest the effectiveness of ARS in improving learning outcomes, especially when interactive learning sessions with ARS are compared with noninteractive sessions.[75]

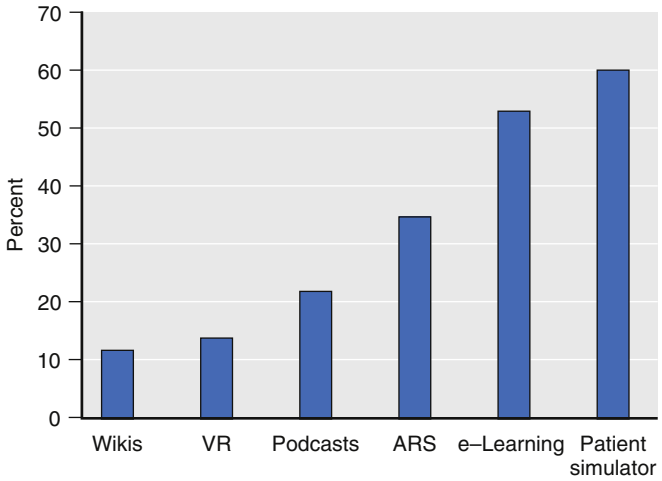


Figure 9-3. Use of technology in anesthesiology education. Responses of the members of the Association of University Anesthesiologists (n = 346) in 2011 to the question, "Which of the following does your department currently utilize?" (R. Schell, M. Pardo, R. Gaiser; unpublished data). *ARS,* Audience-response system; *VR,* virtual reality.

USE AND ACCEPTANCE OF TECHNOLOGY IN ANESTHESIA EDUCATION

In 2011, members of the Association of University Anesthesiologists (AUA) responded to a survey about technology and the self-reported use of technology in anesthesia resident education. (R. Schell, M. Pardo, R. Gaiser, unpublished data) When respondents were asked to rate their feelings about the use of technology in general, most reported that they enjoyed using and learning about new technologies. The data demonstrating which of the technologies their departments used is shown in Figure 9-3. Patient simulation and e-learning modules were used by the majority of respondents, whereas wikis and virtual reality were used the least. The AUA respondents to the survey almost unanimously believed that technology in education will increase in the future. However, perceived reasons for the increased use of technology included "newer generation of learners expect it" and "competition for applicants to programs." Few believed that technology was increasing because it "could replace aspects of clinical training" or "improve outcomes."

THE FUTURE OF ANESTHESIA EDUCATION

Over the past decade, the number of anesthesiology residency positions has increased, and the medical student applicant pool has become stronger academically. However, several factors have the potential to change the desirability of an anesthesiology career, including the changing health care environment, different career expectations, and the ongoing debate about the role of nonphysician providers in health care. Training programs will have to prepare graduates for their roles in clinical practice. Clinical experiences should be broadly based, yet may need to be supplemented using simulation or other teaching methods. Already, a significant proportion of residency training occurs outside the operating room setting. It is likely

that other out-of-operating-room clinical activities will be more important to the anesthesiologist of the future. Evaluation tools such as milestones will be useful to guide residents during training, and perhaps throughout an entire career. Residents will need continued exposure to the quality improvement process, including the use of root-cause analysis and other approaches to evaluate patient care quality and outcomes critically. As health care systems become more complex, residents will need knowledge of how patient care outcomes can be influenced by using and applying evidence-based practices. The challenges of meeting the health care needs of the future must be done in the face of increased public accountability—for patient safety, health care quality, oversight of training programs, and individual practitioners.

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APPENDIX 9-1 *Abridged List of Subjects in American Board of Anesthesiology Content Outline*

Basic Sciences

- Anatomy
- Physics, monitoring, and anesthesia delivery devices
- Mathematics
- Pharmacology

Clinical Sciences: Anesthesia Procedures, Methods, and Techniques

- Evaluation of the patient and preoperative preparation
- Regional anesthesia
- General anesthesia
- Monitored anesthesia care and sedation
- Intravenous fluid therapy during anesthesia: water, electrolyte, glucose requirements and disposition, crystalloid versus colloid
- Complications (etiology, prevention, treatment)
- Postoperative period
- Special techniques

Organ-Based Basic and Clinical Sciences

- Central and peripheral nervous systems
- Respiratory system
- Cardiovascular system
- Gastrointestinal and hepatic systems
- Renal and urinary systems
- Electrolyte balance
- Hematologic system
- Endocrine and metabolic systems
- Neuromuscular diseases and disorders

Clinical Subspecialties

- Painful disease states
- Pediatric anesthesia
- Obstetric anesthesia
- Otorhinolaryngology (ear, nose, and throat) anesthesia: airway endoscopy, microlaryngeal surgery, laser surgery, hazards, complications (e.g., airway fires)
- Anesthesia for plastic surgery and liposuction
- Anesthesia for laparoscopic surgery, cholecystectomy, gynecologic surgery, gastric stapling, hiatal hernia repair, anesthetic management, complications
- Ophthalmologic anesthesia, retrobulbar and peribulbar blocks, open eye injuries
- Orthopedic anesthesia, tourniquet management, complications, regional versus general anesthesia
- Trauma anesthesia
- Anesthesia for ambulatory surgery
- Geriatric anesthesia/aging
- Critical care

Special Problems or Issues in Anesthesiology

- Electroconvulsive therapy
- Organ donors: pathophysiology and clinical management
- Radiologic procedures, computed tomography, magnetic resonance imaging and anesthetic implications and management, anesthesia in locations outside the operating room
- Physician impairment or disability: substance abuse, fatigue, aging, visual and auditory impairment, Americans with Disabilities Act
- Ethics, practice management, and medicolegal issues

From American Board of Anesthesiology: Content Outline, Basic/Advanced. Revised January 2014. <http://www.theaba.org/pdf/Basic-and-Advanced-Content Outline.pdf>. (Accessed 19.04.4.)

APPENDIX 9-2 *ACGME Competencies in Residency Program Requirements*

The program must integrate the following Accreditation Council for Graduate Medical Education (ACGME) competencies into the curriculum

Patient Care

Residents must be able to provide patient care that is compassionate, appropriate, and effective for the treatment of health problems and the promotion of health.

Medical Knowledge

Residents must demonstrate knowledge of established and evolving biomedical, clinical, epidemiologic, and social-behavioral sciences, as well as the application of this knowledge to patient care.

Practice-Based Learning and Improvement

Residents must demonstrate the ability to investigate and evaluate their care of patients, to appraise and assimilate scientific evidence, and to improve patient care continuously based on constant self-evaluation and life-long learning. Residents are expected to develop skills and habits to be able to meet the following goals:

- Identify strengths, deficiencies, and limits in one's knowledge and expertise
- Set learning and improvement goals
- Identify and perform appropriate learning activities
- Systematically analyze practice using quality improvement methods, and implement changes with the goal of practice improvement
- Incorporate formative evaluation feedback into daily practice
- Locate, appraise, and assimilate evidence from scientific studies related to their patients' health problems
- Use information technology to optimize learning
- Participate in the education of patients, families, students, residents, and other health care professionals.

Interpersonal and Communication Skills

Residents must demonstrate interpersonal and communication skills that result in the effective exchange of information and collaboration with patients, their families, and health professionals. Residents are expected to:

- Communicate effectively with patients, families, and the public, as appropriate, across a broad range of socioeconomic and cultural backgrounds
- Communicate effectively with physicians, other health care professionals, and health-related agencies
- Work effectively as a member or leader of a health care team or other professional group
- Act in a consultative role to other physicians and health professionals
- Maintain comprehensive, timely, and legible medical records, if applicable

Professionalism

Residents must demonstrate a commitment to performing professional responsibilities and adhering to ethical principles. Residents are expected to demonstrate:

- Compassion, integrity, and respect for others
- Responsiveness to patient needs that supersedes self-interest
- Respect for patient privacy and autonomy
- Accountability to patients, society, and the profession

APPENDIX 9-2 *ACGME Competencies in Residency Program Requirements*—cont'd

- Sensitivity and responsiveness to a diverse patient population, including but not limited to diversity in gender, age, culture, race, religion, disabilities, and sexual orientation

Systems-Based Practice

Residents must demonstrate an awareness of and responsiveness to the larger context and system of health care, as well as the ability to call effectively on other resources in the system to provide optimal health care. Residents are expected to:

- Work effectively in various health care delivery settings and systems relevant to their clinical specialty
- Coordinate patient care within the health care system relevant to their clinical specialty
- Incorporate considerations of cost awareness, risk-benefit analysis in patient and population-based care as appropriate
- Advocate for quality patient care and optimal patient care systems
- Work in interdisciplinary teams to enhance patient safety and improve patient care quality
- Participate in identifying system errors and implementing potential systems solutions

From ACGME Common Program Requirements. Effective July 1, 2011. <http://www.acgme.org/acgmeweb/Portals/0/dh_dutyhoursCommonPR07012007.pdf>. (Accessed 14.03.13.)

APPENDIX 9-3 *Sample Rotation Goals and Objectives (Abridged)*

Description of Rotation

The first month rotation is the introduction to clinical anesthesia. It provides an overview exposure to the delivery of operative anesthesia. Through the arc of providing comprehensive anesthetic care, residents are exposed to preoperative patients on the wards and in the preoperative holding area, intraoperative patients in the procedure suites, and immediate postoperative patients in the postanesthetic care unit (PACU). This comprehensive exposure, coupled with daily lectures and educational conferences, allows the residents to achieve the following competency-based goals and objectives.

Patient Care

Goal

Residents must be able to provide patient care that is compassionate, appropriate, and effective for the treatment of health problems and the promotion of health.

Objectives

For each patient preoperatively:

- Demonstrate comprehensive exam of the airway.
- Assign an American Society of Anesthesiologists (ASA) risk class.
- Formulate an anesthetic plan (including appropriate premedication).
- Prepare, start, and secure an intravenous (IV) catheter.

For each patient intraoperatively:

- Prepare the operating room for anesthetic care, including a machine check, suction, preparation of appropriate drugs, and preparation of appropriate airway management tools.
- Demonstrate preoxygenation and mask ventilation.
- Demonstrate endotracheal intubation, including endotracheal intubation for the patient with a "full stomach."
- Formulate changes in anesthetic management, based on interpretation of data from monitors.
- Maintain amnesia and analgesia through selection of appropriate anesthetic options.
- Plan and demonstrate a plan for safe emergence, including reversal of neuromuscular blockade and extubation.

For each patient postoperatively:

- Transport the patient to the recovery room (PACU) or intensive care unit (ICU)

Medical Knowledge

Goal

Residents must demonstrate knowledge of established and evolving biomedical, clinical, epidemiologic, and social-behavioral sciences, as well as the application of this knowledge to patient care. In this first month of clinical anesthesia year 1 (CA-1), the following objectives are designed to be covered at the introductory level, and will be followed in more detail in subsequent rotations throughout the residency.

Objectives

- Describe basic structure of an anesthesia machine, including vaporizers.
- Describe anesthetic preoperative evaluation.
- Review basic airway anatomy and pulmonary physiology.
- Review basic cardiovascular physiology.
- Review basics of monitors encountered in the operating room: pulse oximetry, capnography, circuit pressure, flow monitors, gas mixture monitors, oscillometric blood pressure cuffs, electrocardiograph, temperature, arterial line, central venous pressure.
- Formulate a plan for IV fluid administration and electrolyte maintenance.
- Review the basic pharmacology of inhaled anesthetics, induction agents, narcotics, local anesthetics, ephedrine, phenylephrine, neuromuscular blockers, and reversal agents.
- Explain how to use a twitch monitor for muscle relaxation.
- Review the ASA difficult airway algorithm and use of the airway management devices included in it.

Practice-Based Learning and Improvement

Goal

Residents must demonstrate the ability to investigate and evaluate their care of patients, to appraise and assimilate scientific evidence, and to improve patient care continuously based on constant self-evaluation and life-long learning. Residents are expected to develop skills and habits to be able to incorporate formative evaluation feedback into daily practice.

Objectives

Discuss positive and negative outcomes of anesthetic care choices by following selected patients (chosen by discussion with one-on-one attending supervisor) postoperatively until discharge.

Systems-Based Practice

Goal

Residents must demonstrate an awareness of and responsiveness to the larger context and system of health care, as well as the ability to call effectively on other resources in the system to provide optimal health care. Residents are expected to work in interdisciplinary teams to enhance patient safety and improve patient care quality.

Objectives

- Coordinate patient care with other health care professionals and trainees from surgical teams and perioperative nursing teams

Continued

APPENDIX 9-3 *Sample Rotation Goals and Objectives (Abridged)*—cont'd

- Participate in the performance of the procedural "time out" before every procedure undertaken
- Keep dirty and clean equipment and medications separate.

Professionalism

Goal

Residents must demonstrate a commitment to performing professional responsibilities and adhering to ethical principles. Residents are expected to demonstrate compassion, integrity, and respect for others.

Objectives

- Complete all anesthetic records, with all required information, for care delivered.
- Demonstrate signing out and accounting for controlled substances.
- Be punctual in care delivery.

Interpersonal and Communication Skills

Goal

Residents must demonstrate interpersonal and communication skills that result in the effective exchange of information and teaming with patients, their families, and professional associates. Residents are expected to communicate effectively with patients and families across a broad range of socioeconomic and cultural backgrounds.

Objectives

- Present comprehensively the findings of preoperative history and physical examination for each patient to be anesthetized.
- Coordinate operating room readiness with surgical, nursing, and technical support staff members.
- Perform appropriate sign-out of care to other residents at end of shift or at breaks.
- Summarize information appropriately to be able to give report to recovery room nurse or ICU care team at end of anesthetic care.

Teaching Methods

Teaching methods will include the following:

- Clinical teaching: one-on-one attending supervision (direct supervision) for entire rotation
- Departmental conferences: daily resident lectures broadly covering the scope of anesthetic care, including drugs, monitors, fluids, and physiology; weekly morbidity and mortality conferences; weekly patient-care conferences; and weekly educational seminars on care-related topics
- Patient simulator: realistic scenarios allowing residents to apply the skills they are learning by working through challenging scenarios independently and as part of resident teams
- Anatomic models: residents practicing airway device use and vascular cannulation
- Role modeling: working daily one-on-one with attending physicians to portray the professional skills and behaviors that residents attain over time

Assessment Method

Assessment methods will include the following:

- Global assessment at end of rotation by faculty preceptors
- Case log review
- Cognitive examinations: Anesthesia Knowledge Tests (AKT-0, AKT-1)

Educational Resources

Educational resources the residents should use on this rotation include the following:

- *Basics of Anesthesia*, ed 6. Philadelphia, 2011, Churchill Livingstone
- Multiple handouts provided over the month during the lecture series

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Chapter 10

Ethical Aspects of Anesthesia Care

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Key Points

Ethical Theory

- Deontologic ("rules-based") ethical theory and utilitarian (outcome-based) theory clash in clinical scenarios in which the interests of individual patients are pitted against the interests of larger populations.
- In the United States, the predominant medical ethical principle is that of respect for the patient's autonomy.

Informed Consent

- Informed consent is legally mandated and based on the principle that competent and autonomous individuals can both make choices about their medical care and refuse medical treatments including lifesaving care.
- Physicians have ethical obligations to promote the patient's autonomy.
- Competence to make medical decisions is present if the patient can understand information relevant to the decision, understand consequences of the decision, and express a decision regarding the medical advice being given to them.
- Physicians are obligated to disclose alternatives to medical therapies and the common and serious risks of the proposed therapy.
- In general, competent adult patients can refuse blood transfusions, but rights of children and pregnant women to refuse therapy are less clear.
- Minor patients have varying degrees of decision-making capacity, and they may have legal rights to make certain decisions. Pediatric patients should be involved to the degree that they can be in medical decision making, particularly with regard to elective therapy.

Ethics of Preoperative Testing

- Medical testing should follow the ethical principles of beneficence and nonmaleficence and should be based on sound algorithms whenever possible.
- Medical tests with special social significance, such as pregnancy and human immunodeficiency virus testing, should be undertaken only with the patient's informed consent and should not be undertaken without sound evidence that they are necessary and beneficial.

Ethics of Anesthesia Involving Pregnant Women

- In general, the rights of pregnant women are weighed against the rights of fetuses in a decremental fashion as the fetus approaches and surpasses viable age.
- Women do not lose their rights to bodily integrity and informed consent when they become pregnant, and neither fetal "rights" nor state interests supersede a pregnant woman's right as medical decision maker. A mother's refusal of care can rarely be overridden and generally only when (1) the fetus *will* suffer irrevocable harm without the treatment, (2) the treatment is *clearly indicated* and likely to be effective, and (3) the risk to the woman is low.
- Laboring women are capable of giving informed consent, and the validity of "Ulysses directives" at the time of labor is ethically arguable.

Coercion and Restraint

- Use of restraints is antithetical to promotion of autonomy, and anesthesiologists have both ethical and legal obligations to determine whether such extreme intervention is warranted.

Key Points—cont'd

- Coercing or using physical or chemical means to force competent patients to undergo treatment they are refusing is both unethical and illegal.
- Use of restraints in children is questionable in elective medical care; when treatment must proceed, ethical care should prioritize the patient's safety and dignity.

Truth Telling

- A medical mistake is "a commission or omission with potentially negative consequences for the patient that would have been judged wrong by skilled and knowledgeable peers at the time it occurred, independent of whether there are any negative consequences."
- Respect for patients' autonomy requires that we disclose mistakes that harm patients because in so doing we release patients from misconceptions about their medical past and enhance their ability to share decision making about their medical care.

Advance Directives and Surrogate Decision Making

- An advance directive is a document executed by the patient before incapacity to provide the patient's physicians with guidance in medical decision making when the patient cannot communicate for himself or herself: these directives include, but are not limited to, durable powers of attorney, living wills, transfusion decisions, do-not-attempt-resuscitation (DNAR) directives, and decisions regarding organ donation.
- Surrogate decision makers explicitly act in "substituted judgment" to provide what the patient would have wanted and are not being asked merely for their own preferences. Surrogate decision makers at best only approximate the patient's decisions.
- Some medical decisions may not legally be made by a surrogate decision maker; laws are variable, but such decisions often include those involving electroconvulsive therapy and sterilization.

Do-Not-Attempt-Resuscitation Orders in the Operating Room

- Patients have moral and legal rights to refuse even life-sustaining therapy, and those rights extend to the operating room. DNAR orders should not be automatically suspended in the operating room, but rather they require discussion of risks and benefits, and the goals and decisions of competent patients should generally be honored.
- DNAR orders must never be construed as an excuse to not "care" for the patient. A patient's decision to forgo resuscitation does not imply a wish to avoid other beneficial interventions.

End-of-Life Decision Making

- Arguments that withdrawing or withholding life-sustaining therapy does not violate rules against killing patients are based on ethical differences between killing and letting die and between acts of commission (e.g., lethal injection) and acts of omission (e.g., withdrawal or withholding of ventilator therapy).
- Terminal care requires special knowledge and experience on the part of the physician. It requires expertise in medically supportive therapy, management of problematic symptoms, knowledge about physiologic changes in the dying patient, support and counseling of patients and families, understanding and respect for the patient's autonomy and religious and cultural practices and beliefs, the ability to work within complex health care teams, the ability to communicate well, and empathy.
- Several interventions have special ethical implications—fluid and nutritional management; the administration of sedatives and/or narcotics that have the potential to hasten death; the administration of neuromuscular blocking agents; and deactivating pacemakers, ventricular assist devices, and implanted cardioverter-defibrillators.
- Medical, legal, and religious authorities have all clearly accepted the principle of "double effect," in which an action intended to produce a benefit for the patient produces not only the expected benefit but also potentially significant harm.

Key Points—cont'd

- Neuromuscular blocking agents have no anesthetic, analgesic, or sedative properties, and they have no role in palliative care.
- The use of deactivating cardiac devices at the end of life in response to a competent patient's wishes is ethical, but it should occur only after careful consideration, and with attention to management of distressing symptoms and administration of appropriate comfort measures.

Physician-Assisted Suicide and Euthanasia

- Physician-assisted suicide (PAS) is the provision of medication and/or prescriptions to patients by specific request for the purpose of ending their life.
- Euthanasia involves the administration of medication by someone other than the patient for the express purpose of causing death.
- PAS and euthanasia are legal only in specific parts of the world, but they are generally supported by public opinion polls.
- Concerns about PAS and euthanasia center around the risk that vulnerable populations will be preferentially and disproportionately directed to PAS or euthanasia as an end-of-life management strategy. However, data from regions where PAS or euthanasia is legal suggest that this is not happening.

Organ Transplantation

- Brain death is legally and medically defined as the point at which all cardiorespiratory function irreversibly ceases *or* all function of the whole brain irreversibly stops.
- In donation after cardiac death (DCD), withdrawal of life support occurs with provisions for immediate organ donation after cardiac arrest.
- Controversies around DCD include concerns about when cardiopulmonary death can be declared and whether medications that preserve organ function but may hasten the donor's death can be administered.

Research Ethics—Human Subjects

- Research in human subjects must balance many conflicting interests such as the needs and rights of the research subject; the hypothetic interests of future patients; and the physician's financial, professional, and personal goals.
- The ethical conduct of research in human subjects follows three principles: (1) respect for autonomy, and the obligation to protect subjects with limited autonomy; (2) beneficence, with obligations to minimize risks, maximize benefits, and ensure that the research design is scientifically sound; and (3) justice, the obligation to treat each person with regard to what is morally right and to ensure fair distribution of benefits and burdens.
- Anesthesiologic research often involves the treatment or prevention of unpleasant symptoms, such as pain and nausea, for which effective treatments are well established. Such studies should be restricted to comparison of treatments with known efficacy, not placebo-controlled trials, and "escape" analgesics or antiemetics must be provided on the patient's request.
- If a minor child is "able" to assent, then assent must usually be obtained in addition to the consent of any legal surrogate decision makers. In the United States, federal law requires assent of any minor 7 years old and older to participate in medical research.

Research Ethics—Animal Subjects

- Advances in understanding animal cognition have led most biologists to believe that many, if not all, animals are capable of feeling pleasure, pain, anticipation, and fear, and thus they experience both enjoyment and suffering.
- Allowing animal suffering because of pain, fear, sickness, or poor standards of care is a moral harm that must be avoided, mitigated, and weighed heavily against the benefits it produces.
- Researchers should mind the "Three Rs"—replacement, reduction, and refinement—that is, use animal subjects only when necessary, minimize any suffering incurred in the study, and seek nonanimate replacements for animal subjects.

KEY POINTS—cont'd

Physician Participation in Executions

- U.S. professional organizations for physicians have consistently stated that participation in executions by physicians is unethical.
- Arguments for participation generally cite "beneficence" issues of providing a humane death for prisoners, whereas those against participation cite harms to the profession and erosion of trust in physicians by their agreement to be agents of the state.
- The American Board of Anesthesiologists stated that participation in executions would constitute unprofessional behavior that would result in investigation and possible decertification of anesthesiologists.

Conscientious Objection

- Acceptance of moral objections to certain hotly contended issues such as abortion or PAS may be reasonable, but objections to well-established standards, such as informed consent, are not.
- Moral objections of physicians are also likely to carry more weight if they involve concepts that the physician believes supports him or her as an ethical doctor and not just as an ethical person.

Medicine is a respected profession with codes of behavior and definite rules of conduct. Modern medical practitioners have tremendous power, recognized social import, and powerful financial interactions that touch nearly everyone's lives. In the context of long-held and highly developed rules and practices, this chapter examines the ethical bases of the practices of medicine and the implications for anesthesiologists.

ETHICAL THEORY

VIRTUE ETHICS, UTILITARIANISM, AND DUTY-DRIVEN ETHICS

The classic style of medical practice, called paternalism, is derived from *virtue-based ethics*. In this view, the physician is a genuinely virtuous person, with inherent qualities of competence, sincerity, confidentiality, and altruism, who naturally knows and does what is correct for the patient. The patient, who is not knowledgeable in the art of medicine, should trust the physician to decide what is best. Our society and legal system have changed substantially since paternalism flourished, but some patients and physicians still see this as a desirable component of medicine.

In *utilitarian ethics*, actions are judged right or wrong on the balance of their good and bad consequences. A "right" action produces the most good, based on a perspective that gives equal weight to the interests of all affected parties. Although utilitarian theory is compelling (who would not want to do the most good and minimize evil?), it falls short in defining which benefits are most important. Is it the "good" that all reasonable people want or the "good" defined by the individual patient? What if the only way to maximize "good" is to commit an entirely immoral act? Suppose, for example, the only way to win a war is to torture children systematically? Determinations of "right" or "wrong" based on the outcomes of actions presents other challenges as well. Outcomes of actions often continue to accumulate over time—when on that continuum is it appropriate to determine that an action was right or wrong? The "good" act of saving an individual's life today may be viewed through a different lens when, 20 years from now, that same individual becomes a mass murderer.

Utilitarian theory may be best when applied to analyzing broad-based policies, in decisions regarding rationing of resources, and when attempting to resolve conflicting ethical obligations.

The premise of Kantian-based ethics (also called deontologic—or *duty-based*—theory) is that certain features of actions other than their consequences make those actions right or wrong. Intention is more important than outcome. Furthermore, no person should use another exclusively as a means to an end, because each person *is* the end for which we should act. No person should be used to further the purposes of another person without that other person's autonomous consent. Kantian philosophy would forbid killing one innocent person to save another innocent person, for example.

Deontologic and utilitarian theories are applied to varying degrees in modern medical ethics. Individualism and autonomy are valued highly in Western society, and people tend to turn to Kantian philosophy when ethical questions arise that balance the authority of the physician against the goals and values of individual patients. When broad-based social issues are at stake, such as allocation of scarce medical resources, utilitarian arguments are often used. Some of the toughest ethical questions in medical practice occur when the rights and desires of individual patients are in conflict with social policies. Clashes between deontologic and utilitarian principles are common in the intensive care unit (ICU) (see also Chapters 101 and 102), in managed

care settings, and in the care of poor and older patients whose medical management is funded by the government. In each of these settings, the will of the individual patient may be in conflict with broader principles of minimizing expense, fairly allocating scarce resources, and determining where and how society's health care dollars are best spent.

The political tradition of the United States provides a clear underpinning to individual freedom, hence the translation of the Jeffersonian "life, liberty, and the pursuit of happiness" into the contemporary interest in the physician's beneficence and the patient's autonomy. With the background of this political tradition, contemporary bioethics shifted away from paternalism. At the beginning of the twentieth century, the concept of the autonomy of patients began to emerge.

CLINICAL ETHICS

INFORMED CONSENT AND INFORMED REFUSAL

Legal and moral imperatives for informed consent are based on the ethical principle of respect for patient autonomy. *Autonomy* refers to the ability to choose without controlling interferences by others and without personal limitations that prevent meaningful choices, such as inadequate information or understanding.[1] Individuals have the right to determine what happens to them to the degree that they are capable of doing so. In the United States, this right is rooted in constitutional guarantees of privacy and noninterference. In 1914, the case of *Schloendorff v Society of New York Hospital* established that it was the right of "every human being of adult years and sound mind to determine what shall happen to his own body."[2] In 1957, the term *informed consent* was first used in the case of *Salgo v Trustees of Leland Stanford Hospital*, which established that it is not sufficient for physicians simply to secure consent; physicians have a duty to inform patients about the risks and alternatives to treatment, in addition to the procedures themselves and their consequences.[3]

Respect for the patient's autonomy requires physicians to respect decisions made by competent patients and to *promote* autonomy by removing barriers to competent participation in decisions. Such obstacles range from incomplete or inaccurate information to reversible medical conditions that interfere with a patient's ability to understand the information given to him or her.

Competence or Capacity

Autonomy to make medical decisions cannot exist in the absence of competence. Because *competence* is a legal term, most medical experts prefer the term *capacity* to describe the necessary skills to participate in medical decisions.

Impairments of capacity can be temporary or permanent. Examples include some mental illnesses, dementia, immaturity, anxiety, pain, and medication effects. Older patients, patients suffering from mental impairment, and children are particularly vulnerable to having their participation in medical decisions inappropriately curtailed or even denied because their capacity to participate is frequently underestimated. Hearing loss and expressive aphasia can create the false impression that capacity is impaired. Many children make medical decisions in ways similar to those of adults but may be mistakenly excluded from the decision-making process solely because of their age. Language barriers can present significant challenges to communication.

Capacity is both relative and task specific. Patients may be able to understand and make decisions about medical issues while being unable to care for themselves in other ways.

Both prejudice and paternalism permeate physicians' behavior in the informed consent process. Challenges to a patient's competence rarely occur unless the patient and the physician have a difference of opinion or values. Patients are often referred for competency evaluations because they refuse medical advice, although refusal of treatment is not itself evidence of incompetence.[4] Physicians often disagree with a patient's decisions because they regularly ascribe a lower quality of life to impaired and handicapped patients than do patients themselves. Doctors are mistaken about patients' preferences regarding life-extending therapies in the majority of cases, and they underestimate older patients' desires for life-extending therapies in up to 30% of cases.[5] Moreover, surveys indicate that physicians and other health care workers are likely to *act* on personal prejudices regarding handicapped or impaired patients.[6]

Functional capacity for decision making must be judged separately from the perceived quality of the decision itself. Patients have the right to make "bad" decisions if they are competent and have appropriate information. Otherwise, the physician could merely substitute his or her own judgment for that of the patient, and autonomy in medical decision making would be nonexistent.

How do we recognize competence? When assessing a patient for anesthesia care, the anesthesiologist should focus on the following concerns: (1) Can the patient receive and understand the information relevant to the decision? (2) Can the patient understand potential consequences of the decision, including potential risks and benefits, even if in a very simplified way? (3) Can the patient express a decision and communicate his or her values regarding the medical advice being given?

The anesthesiologist has an ethical duty to treat reversible conditions that interfere with medical decision making. Elective surgery may have to be postponed until expert consultation for a determination of mental capacity or treatment of reversible conditions can occur. When surgery is urgent or a patient is impaired by an irreversible condition, the anesthesiologist may have to rely on a surrogate decision maker or proceed with the best determination of the patient's interests in mind.

Disclosure

The informed consent process requires honest disclosure of medical information to the patient. U.S. courts currently rely on two standards of disclosure: the reasonable person standard and the subjective standard. A third, professional standard, in which the physician is obligated to disclose only what other physicians of the same specialty

would disclose, was subject to abuse and manipulation and is essentially no longer recognized. In the *reasonable person standard,* the physician must disclose any information that a theoretically reasonable person would want to know. This standard does not require an exhaustive recitation of facts, and it acknowledges that not all information related to the procedure is integral to making a decision about whether to undergo that procedure. The *subjective standard* recognizes that some patients may have special needs for specific information, and when that need is obvious or has been brought to the attention of the physician, the information must be disclosed. A concert violinist may have a specific need to know about the potential for nerve damage from an axillary block, for example. In general, legal and ethical standards now require that the physician (1) accurately discuss the therapy and its potential alternative—including no therapy—and (2) disclose the common risks (because they are more likely to happen) and the serious risks (because the consequences are severe).

The doctrine of *therapeutic privilege* is sometimes cited to avoid discussing risks, the reasoning being that the stress of discussing risks can psychologically or physically harm the patient. Studies of patients' stress during the informed consent process *do not* support this concept.[7] Therapeutic privilege is probably invoked in many cases because the physician is uncomfortable with disclosure or wants to curtail discussion. Although it is ethical to forgo or curtail risk discussions at the patient's request, it is generally not ethical for the physician to decide to do so unilaterally.

The physician-patient relationship is inherently unequal because of the physician's knowledge and authority and the patient's dependence on the physician for care. Physicians have ethical obligations to avoid exploiting their influence for the purpose of accomplishing their own ends. Although offering a rational basis for a medical choice is acceptable, it is generally unethical to coerce or manipulate patients into decisions by presenting real or implied threats or by omitting or misrepresenting key information.

Legal Implications of Informed Consent

The informed consent process does not prevent legal liability when adverse events occur. Flawed informed consent processes have been cited, however, as evidence of a lack of quality of care by the physician. The American Society of Anesthesiologists (ASA) closed-claims database reveals that informed consent is cited in approximately 1% of cases, and cases with inadequate informed consent documentation are associated with larger monetary awards.[8] Studies repeatedly show that the risk of filing a malpractice claim is directly related to the patient's perception of his or her relationship with the physician.[9] The informed consent process provides one of the few opportunities anesthesiologists have to establish that relationship, however brief, and the medicolegal importance of that process should not be underestimated.

Informed Refusal

Informed consent is meaningless if the patient cannot also refuse medical therapy because the consent process is then merely an exercise in the patient's acquiescence to the physician's will. Examples of informed refusals in anesthesiology include the following: requests to withdraw or withhold life-supporting care in the ICU; do-not-attempt-resuscitation (DNAR) orders in the operating room; cases in which the patient has objections to certain forms of therapy, such as the Jehovah's Witness who refuses blood transfusions; and cases in which a patient refuses preoperative testing, such as human immunodeficiency virus (HIV) or pregnancy testing.

Informed refusal has concerns and requirements similar to those of informed consent. When patients refuse medical care or insist on what the physician believes is suboptimal care, disclosure of the risks and benefits becomes even more important because these decisions may veer from options that are already widely accepted and for which the risks are believed to be lowest. It is easier to justify agreeing to unusual preferences of a well-informed patient than to subject a poorly informed patient to unorthodox care.

Despite full information, patients may sometimes request or demand care that is unreasonable, either because it will adversely affect the performance of a surgical procedure or because it would be associated with unreasonably high risks. When a patient demands a technique that is inappropriate or outside of the realm of reasonable practice, the anesthesiologist is under no ethical obligation to provide that care. No physician can be compelled by a patient to practice negligently.

Special Issues in Informed Consent and Informed Refusal

The Jehovah's Witness Patient. The classic example of a patient who refuses therapy in anesthesia practice is that of Jehovah's Witnesses, many of whom believe that accepting a blood transfusion violates a Biblical injunction. The Jehovah's Witness doctrine has been subject to change over time, with resulting inconsistencies in religious practice with regard to which, if any, blood components may be acceptable. Individuals interpret religious doctrines in light of their own spiritual contexts, and not all believers hold to the same tenets with identical fervor. Church doctrines, like medical practices, evolve over time, and practices that are acceptable at one time may not be years later. Anesthesiologists and surgeons have cited individual and doctrinal inconsistencies as justification for ignoring the wishes of Jehovah's Witness patients, but to do so is no more logical than assuming that every hypertensive patient needs or will respond well to identical treatment or that optimal treatments will not evolve over time.[10] Moreover, *any* patient has the right to refuse blood transfusion therapy, regardless of whether this desire is founded in religious preference. Such refusals have become more common in patients who are not Jehovah's Witnesses because blood transfusion therapy was connected to cases of acquired immunodeficiency syndrome (AIDS) in the 1980s, and patients began questioning the value and necessity of transfusion therapy in light of its risks (see also Chapter 61).

Because of the differing beliefs regarding which, if any, blood replacement therapies are acceptable, the anesthesiologist must have a thorough and detailed preoperative

discussion of possible therapies with the Jehovah's Witness patient, and the conclusions should be documented in the patient's chart. An anesthesiologist who cannot comply with an adult patient's desire to forgo transfusion has an ethical obligation to find an alternative caregiver whenever possible.[11]

The courts strongly support the rights of adult patients to refuse blood products for themselves but have been inconsistent and have interfered in cases of some pregnant patients. Transfusion of pediatric Jehovah's Witness patients by court order is common. However, this may become ethically and legally less acceptable as alternative bloodless therapies to maintain oxygen-carrying capacity evolve, as the Jehovah's Witness church further defines its doctrines with regard to children, and as the capacity of children to consent to or to refuse therapy is better understood.

The Pediatric Patient and Other Patients With Impaired Competence. The ethical practice of medicine weighs heavily toward adherence to the respect for autonomy in patients who are competent to make medical decisions (see Chapter 93) or who have executed advance directives when they were competent to do so. Medical care of individuals who have never been autonomous relies on principles such as respect for human dignity, beneficence, avoidance of harm, and adherence to the principle of justice.

Children are examples of persons who may or may not yet be autonomous (see also Chapter 92). Laws in each state define the age at which children become *legally* competent to make medical decisions (usually 18 years of age), but many younger children have the mental and emotional capacity to make medical decisions. Forcing such individuals to undergo treatments they do not want is unethical and could be illegal as well.

Decision-making capacity in children is variable. Most 2-year-old children are clearly not able to make medical decisions. However, the range of capability in children as young as 7 or 8 years old is wide, and studies suggest that the average 14-year-old adolescent makes medical decisions in ways similar to adults. In one study, children 6 through 9 years of age who were invited to participate in influenza vaccine research asked pertinent questions about individual risks and benefits and whether their community and other children would benefit.[12]

Most states recognize "emancipated minor" status, in which a court determines that a minor can legally make medical decisions for himself or herself. Legal exceptions to the age of consent are recognized in most states when treatment is believed to be in the minor's best interest and when a requirement for parental consent would interfere with the child's ability to receive medical help. The law recognizes that, tragically, some conditions for which a minor seeks therapy may even be the result of parental abuse, and seeking parental permission for treatment may actually further endanger the minor. Thus, minors are allowed in many states to consent for treatment for substance abuse, sexually transmitted disease, mental illness, and medical care affecting pregnancy, including abortion. When a minor has decision-making capacity but is not "emancipated," a judge may declare the child to be a "mature minor," with decision-making rights.

Ideally, individuals of any age should be involved in medical decisions to the degree that their capacity allows. A minor who possesses capacity to make decisions should not be coerced or restrained under most circumstances.[13] Determining whether a minor has such capacity may require formal consultation and assessment. The term *assent* rather than consent is used to refer to agreement with treatment from children who do not fall into legal categories awarding them adult rights. The American Academy of Pediatrics has stated that physicians who care for children "should give serious consideration to each patient's developing capacities for participating in decision-making, including rationality and autonomy."[14]

When children dissent from medical care, persistent refusals may be ethically binding, particularly in the case of participation in research. Medical personnel should respect the wishes of a patient who withholds assent and should try to gain a better understanding of the patient's situation or deal with his or her fears. "A patient's reluctance or refusal to assent should also carry considerable weight when the proposed intervention is not essential to his or her welfare and/or can be deferred without substantial risk."[14]

Ethical Challenges of Preoperative Testing

The ethical implications of medical tests, such as genetic testing, have been widely discussed in the literature, but the ethical implications of more routine testing have been largely overlooked by professional societies (see also Chapter 38). The performance of diagnostic tests does have ethical dimensions, however. We generally undertake such tests precisely because we intend to help the patient (beneficence) or to use the information to minimize other risks (nonmaleficence). However, medical tests may also carry implications for the patient's autonomy, privacy, and even social justice.

Routine Preoperative Testing Protocols. Preoperative testing may help identify unrecognized or disguised conditions that could adversely affect anesthetic risk. All medical tests carry risks, however. False-positive and false-negative results may either label patients as having a condition they do not have or inappropriately assure patients that they do not have a condition that they in fact do. Erroneous results may lead either to further testing or to inappropriate and unnecessary therapy associated with further complications. Errors can also cause patients to be deprived of important therapy they would otherwise receive. Tests sometimes have accompanying physical complications, and they are certainly always associated with economic costs. Systematic overtesting increases the costs of health care for entire populations, thus unnecessarily burdening an already costly system and diverting badly needed funds to unnecessary enterprise. Medical tests may involve problems of conflicts of interest, if the physician determining the need for testing has an economic relationship with the entity that will carry out the tests. In addition, not all medical tests are ethically equivalent. Certain tests, such as pregnancy testing and HIV testing, may have complex social consequences and may lead to specific, avoidable harms.

Modern medicine is a science that incorporates theories that are expected to be consistent and generalizable. Although all data are deeply theory laden, the practice of evidence-based medicine (EBM) is founded in the concept that conscientious, judicious, and explicit use of the best available medical evidence should be integrated with clinical experience derived from systematic research in making decisions about the medical care of individual patients. In general, nonsystematic clinical experience, anecdote, and untested theory are not sufficient grounds for clinical decision making.

The practice of EBM also focuses on patients' autonomy through informed consent and recognitions of patients' values and goals. EBM and medical ethics share common principles and goals: both are aimed at maximizing benefits and minimizing risks, as well as at involving the patient in shared decision making.[15]

The use of EBM to guide clinical testing and therapy is supported by analysis of traditional therapies that were never subjected to rigorous testing but that, on examination, were shown to be not only unhelpful to patients but also possibly harmful. A Cochrane review, for example, suggested that administration of human albumin, a mainstay of therapy for treatment of shock, may be associated with increased mortality.[16] Another Cochrane review demonstrated that although mammography screening will prolong the life of 1 in 2000 women over a 10-year period, it will lead to the false diagnosis of cancer and the institution of cancer treatment in 10 women during that same period; these findings raise serious questions about the benefits and risks of routine mammography.[17] With regard to hydroxethyl starch administration, the decision to administer this colloid was complicated by a leader in the field (Boldt) who provided "fake" data (see Chapter 61). Using systematic evaluation of medical diagnostic testing to develop principles of preoperative testing not only serves the ethical principles of beneficence and nonmaleficence but also permits us to provide patients with accurate and up-to-date information on the potential benefits of tests to aid their understanding and input in their medical care—thus honoring the principle of respect for the patient's autonomy.

Conversely, EBM presents potentially significant ethical concerns. In relying on traditional medical experimentation, EBM may not sufficiently take into account the role of social and cultural factors (e.g., poverty, ethnicity, spirituality, and gender) that may have considerable influence on health and instead may rely too heavily on a narrowly drawn biomedical model of the patient's experience of health and disease. In the words of Rogers, "those with the greatest burden of ill health are disenfranchised, as there is little research that is relevant to them, there is poor access to treatments, and attention is diverted from activities that might have a much greater impact on their health."[18]

Despite the potential limitations of EBM, it nevertheless seems reasonable to believe that in trying to maximize beneficence and minimize nonmaleficence, EBM provides at least an improvement in the search for a rational, cost-effective approach to medical testing over simply adopting "traditional" therapies or protocols without evidence that they will contribute to accomplishing those goals. Applying medical tests inappropriately can cause very real harm to patients. Simply stated, if medical care is not valid, then it is not ethical.

Evidence that routine tests or traditional patterns of preoperative testing enhance perioperative outcomes is often scant. Large population studies of many routine preoperative tests, such as coagulation screening,[19] chest radiography,[20] and electrocardiography,[21] have, on the contrary, suggested that these tests increase costs without necessarily positively affecting outcomes and can even lead to detrimental outcomes (see also Chapter 38). The ASA Task Force for Preanesthesia Evaluation acknowledged that most routine testing is not necessary.[22] When evidence-based algorithms for preoperative testing are available, they should be used to guide clinical decision making.

Routine Preoperative Pregnancy and HIV Testing. Social risks of preoperative testing may not be as obvious to the physician as medical risks, but they can be the source of significant harm (see also Chapter 77). Examples of tests that can produce social harm and are of limited preoperative utility are HIV and pregnancy tests. Both tests have serious ethical consideration; have limited, if any, beneficial impact in the setting of surgery; may have serious social and economic consequences for the patient beyond the operating room; and require the patient's informed consent.

HIV tests are usually ordered for the purpose of singling out patients for whom extra universal precautions could be taken to reduce transmission in the operating room. Most surgeons and anesthesiologists believe that compulsory HIV testing would reduce their risk of exposure, and many believe that this testing is the physician's prerogative and can be done without the patient's consent.[23]

However, HIV testing does not necessarily yield safer anesthetic management and is more costly than diligent application of universal precautions.[24] In low-prevalence populations, testing is more likely to give false-positive results that wrongly reassure operating room workers that a patient is not infected. This may paradoxically increase the risk of HIV transmission if relaxation in vigilance is the result.

HIV tests can result in loss of employment or insurance coverage, or both. Seropositive women often experience marital breakup, abandonment, verbal abuse, and physical violence if their status is disclosed.[25,26] The threat of compulsory HIV testing almost certainly would prevent some patients from seeking needed surgical care.[23]

Routine preoperative pregnancy testing has ethical ramifications analogous to those of HIV testing. Despite pervasive beliefs to the contrary, large, well-designed population studies did not demonstrate that anesthetic agents lead to early fetal loss or increased fetal malformation.[27-30] Studies have also shown that even adolescent girls generally accurately report the possibility of pregnancy when asked privately.[31] Legal ramifications of not routinely testing for pregnancy preoperatively have been virtually nonexistent, and fewer than one third of practices in the United States require this testing.[32] A positive pregnancy test may have extremely negative consequences if a vulnerable patient is in a social situation in

which pregnancy is not accepted. Abandonment, negative family interactions, and violence to the patient or her fetus, or both, may all occur. Adolescent pregnancies are sometimes the result of child abuse or rape, and referral of adolescents who are pregnant to child protective services should be considered.[32] In many states, it is illegal to disclose or even insinuate a child's pregnancy status to her parents regardless of her age. Therefore, the anesthesiologist who discovers an adolescent patient's pregnancy has few comfortable or legal options.

Many patients may choose not to undergo an elective surgical procedure if they know they are pregnant. However, *coercing* a female patient to have a test against her wishes and that she may find insulting explicitly violates the principle of the patient's autonomy. The physician's self-interest is not a sufficient justification for disregarding a patient's autonomy or violating a patient's privacy. The ASA Task Force on Preoperative Testing and the ASA Committee on Ethics jointly recommended that anesthesiologists offer the *choice* of preoperative pregnancy testing to any female patient who may desire it, explain the potential risks and benefits, and obtain informed consent for the test.[22]

Ethics of Anesthesia Involving Pregnant Women

Maternal-Fetal Conflicts. In general, the rights of pregnant women to refuse therapy, even if it will be detrimental to their fetuses, are protected under right-to-privacy provisions in the U.S. Constitution (see also Chapter 77). Those rights are weighed against potential harms to the fetus in a decremental fashion as the fetus approaches and surpasses viable age. When the fetus is of nonviable age, the mother's rights prevail. Court decisions have consistently upheld the rights of pregnant women to have abortions, to not be subjected to drug testing, and to forgo transfusions early in pregnancy. Attempts to charge women with child abuse, child endangerment, drug trafficking, murder, and attempted murder for activities deemed dangerous to their fetuses have almost uniformly failed.[33] In general, women do not lose their rights to bodily integrity and informed consent when they become pregnant, and neither fetal "rights" nor state interests supersede a pregnant woman's right as medical decision maker.

The American Academy of Pediatrics Committee on Ethics outlined conditions that in their view are necessary to override a mother's refusal of care: (1) the fetus *will* suffer irrevocable harm without the treatment, (2) the treatment is *clearly indicated* and likely to be effective, and (3) the risk to the woman is low.[34] The American College of Obstetricians and Gynecologists condemned the use of coercion in pregnant women and advocated counseling the patient carefully about risks, as well as consultation with an ethics committee.[35]

Informed Consent in Laboring Women. The validity of informed consent for epidural anesthesia in laboring women is a topic of concern to anesthesiologists, who periodically raise the question whether laboring women are able to consider and weigh the risks of labor analgesia sufficiently while they are in pain. Although ideal conditions for informed consent are often lacking during labor, it is important to realize that the ideal is seldom achieved even in surgical patients; therefore, it is crucial to distinguish between conditions that are not *ideal* from conditions that are not *adequate*.

Competence to give consent requires the ability to assimilate information, debate the risks and benefits, and communicate a decision. Despite frequently voiced concerns by anesthesiologists about informed consent during labor, most studies show that laboring women have the same capacity to give informed consent as the general surgical population,[36,37] are able to recall details of the consent process long after labor is finished, and indicate that labor did not alter their decision making.[38] Some investigators even argue that it is only after the patient can assess the severity of pain and consequences of proceeding without analgesia that she can be fully informed.[37]

An ethical conflict can arise in the case of so-called Ulysses directives in which, before labor, a woman executes an advance directive that refuses epidural analgesia and instructs doctors to ignore her pleas for epidural anesthesia at the time of labor should she change her mind. Although some experts suggest that ignoring the Ulysses directive disrespects a woman's long-term preferences, others argue that "information and valid experience are critical prerequisites for autonomous decision making" and that only the current wish (to receive an epidural) is ethically relevant.[36] Such cases appear to have no clear and unequivocal ethical ground on which to proceed, and circumstances must guide the physician. However, if an anesthesia practice decides to disregard Ulysses directives routinely, this should obviously be disclosed to patients in advance of labor whenever possible.

The Uncooperative Patient—Coercion and Restraint

The use of physical restraint to control medical research subjects was first directly addressed in the Nuremberg Code following the Doctors' Trial in 1947 to 1949 and is a continuing subject of intense scrutiny.[39] For anesthesiologists, chemical restraints often replace physical ones, but the ethical issues are the same. Anesthesiologists are often asked by medical colleagues to chemically restrain uncooperative patients. Use of restraints is antithetical to promotion of autonomy, and anesthesiologists have both ethical and legal obligations to determine whether such extreme intervention is warranted. Coercing or using physical or chemical means to force a competent patient to undergo treatment that he or she is refusing is both unethical and illegal. Refusal of medical care and angry behavior are not proof of incompetence, intoxication, or inability to make medical decisions.[40]

When faced with the uncooperative adult patient, questions to ask include the following: (1) Is the patient clearly incompetent or merely angry and uncooperative? Does the patient show evidence of neurologic impairment, acute intoxication, or severe mental disability? (2) Is the patient in immediate danger? (3) Does the patient pose a direct threat to staff or other patients? (4) Does a compelling need to treat life-threatening injuries exist? In the absence of any of the foregoing, the use of coercion or physical or chemical restraints is neither ethical nor legal.

Physicians may be forced in some situations to act within a time frame that does not permit lengthy evaluation of a patient's competence or a protracted search for a surrogate decision maker. In such cases, the physician must rely on professional judgment in deciding how to care for the uncooperative patient who either cannot speak for himself or herself or who appears incompetent to refuse care at a time when a decision must be made. The standard applied in such cases would be to do what a "reasonable" person would wish. Coercion or restraint (or both) in such situations is not ideal, but it may be necessary and ethically permissible.

The uncooperative child presents special ethical concerns. When a patient who does not have the capacity to make health care decisions dissents from medical care, the anesthesiologist is ethically required to provide care that is most likely to benefit the patient and prevent harm while preserving the dignity and safety of the patient. Although violation of respect for autonomy is technically not possible in a patient who does not have autonomy, violations of principles of beneficence, nonmaleficence, and respect for dignity certainly are. Indiscriminate use of physical or chemical restraints is not without physical risk, and the fear and anger provoked by such tactics can lead to future aversion of medical care and mistrust of health care providers. The American Academy of Pediatrics Committee on Child Abuse and Neglect stated that restraint should not be used in pediatric care "unless it is necessary for proper diagnosis and treatment in a sick child, as in the case of a child with a high fever and potential ear infection, or in emergency situations."[41]

Behavioral control in the uncooperative child or incompetent adult should focus on alternatives to physical restraint, such as offering choices on how to go to sleep and use of fantasy or hypnotic suggestion. Despite many possible social, economic, and scheduling pressures to the contrary, delaying or rescheduling a surgical procedure in a hysterical patient is better than using coercion or force. Delaying elective surgery may reduce stress, allow adequate premedication, and promote safer induction conditions. If medical care is urgent, or if delay is unlikely to result in better conditions for the patient, then the anesthesiologist should proceed in a manner designed to preserve the patient's dignity and safety.

TRUTH TELLING—DISCLOSURE OF ERRORS AND APOLOGY

Nonmaleficence has been a foundational principle for the medical profession since the time of Hippocrates, and this principle draws no distinction between deliberate and unintended harms (see also Chapter 11). Medical care is fraught with uncertainty, risk, and error. Harms resulting from unexpected complications, accidents, systems issues, and medical mistakes are to be gently avoided with equal diligence whenever possible.

Wu and colleagues defined a medical mistake as "a commission or omission with potentially negative consequences for the patient that would have been judged wrong by skilled and knowledgeable peers at the time it occurred, independent of whether there are any negative consequences."[42] Medical errors occur in 3% to 5% of all hospitalizations.[43] More than 40% appear to be preventable, and more than 15% result in patients' deaths.[44] In 1999, the release of the Institute of Medicine's report *To Err Is Human* focused public and political attention on the terrible fallout of medical errors in the United States.[45]

Studies showed that 76% of physicians admitted to a medical error that they did not disclose to the patient,[46] and 22% of physicians indicated that they would not disclose an error that caused a patient's death.[47] Reasons cited for a physician's reluctance to disclose errors included personal shame, fear of loss of prestige in the physician's cohort, fear of direct reprisal, lack of experience in disclosing uncomfortable information, fear of causing further harm (emotional or psychological) to the patient and family, and fear of litigation.[48] In many cases, legal advice to physicians has discouraged disclosure and apology in the belief that these tactics decrease medicolegal liability.

Obfuscating the root cause of a patient's complication when it is caused by a medical error is not difficult in the physician-patient relationship because the physician has unique expertise and is the recipient of unique trust. Furthermore, a minimum standard of disclosure simply does not exist. The Code of Ethics of the American Medical Association (AMA) states that patients have a right to be free of misconceptions about their medical condition and that physicians have ethical obligations to "inform the patient of all the facts necessary to ensure understanding of what has occurred."[49] However, the AMA Code of Ethics addresses only "harms" and not "errors," thus implying no duty to disclose medical errors that do not lead to harm. Although some experts state that physicians may have a lesser obligation to disclose harmless errors and/or "near misses," it is nevertheless arguable that they should consider doing so. The physician has little to lose, and such disclosures may enhance discussion of medical care with the patient and result in a strengthened doctor-patient relationship. Legalistically, some experts consider full disclosure of medical errors to be an extension of the legal principle underlying informed consent: "Clearly, if the patient is entitled to know the risks of a procedure and what could go wrong prior to giving their consent, it follows that they would be entitled to know if something has in fact gone wrong, regardless of whether it was unanticipated."[50]

Respect for patients' autonomy requires that we disclose mistakes that harm patients because in so doing we release patients from misconceptions about their medical past and enhance their ability to share decision making about their medical care.

Both deontologic ethics and consequentialist (utilitarian) ethics support ethical obligations of beneficence and nonmaleficence and require physicians to report errors to patients. The patient can then seek and receive timely treatment of adverse effects of the error. Disclosure prevents mistaken attribution by the patient of adverse consequences to noncontributory causes. Disclosure is usually necessary for informed consent for treatments to address complications of the error. Disclosure may enhance patients' trust in physicians. Moreover, disclosure may facilitate a patient's obtaining just and fair

compensation for economic consequences of the injury, such as lost work and pay.

The concern that disclosure of errors to patients will increase litigation or decrease patients' trust, either in the doctor involved or in doctors in general, has not been borne out. Studies have suggested that full disclosure of a medical error reduces the likelihood that patients will change doctors, improves patients' satisfaction, increases trust in the physician, and leads to a more positive emotional response.[51] Studies also have demonstrated that patients take legal action because they want more honesty from their physicians and assurances that the physician has learned from the mistake and that future patients therefore are less likely to suffer.[52]

Physicians may benefit from a sense of relief after disclosure and, in many cases, the forgiveness of the patient. Disclosure helps physicians learn and improve their practice. Failures to report errors, learn from errors, and communicate errors and their potential solutions within a health care system are major causes of medical errors themselves. One could argue that a physician who does not disclose a preventable error, such that it is repeated, bears responsibility for harm not only to his or her own patient but also to all future patients in whom the error could have been prevented had it been disclosed.

Harms that can arise from disclosure are generally visited on the physician: disclosure is stressful, litigation may result, malpractice premiums may rise, and future employment may be adversely affected. However, in the doctor-patient relationship, ethical frameworks hold that benefits and harms to the patient should hold greater weight than benefits and harms to the physician.

Do we have an ethical duty to disclose the errors of others? Legally, some North American courts have held that we do not,[50] and social norms about "tattling" on others are powerful deterrents to such disclosures. The reporting physician may hesitate because of a lack of definitive information, potential accusations of interfering in the doctor-patient relationship of another, worry that professional interactions such as patient referrals and performance evaluations may be affected, and fear of libel suits. When a physician observes a medical error committed by another physician, the options include nondisclosure, recommendations to the involved physician to disclose the error, disclosure of the error to a third party such as a risk-management group, or direct disclosure to the patient. Although no strict legal guidelines are in place, ethical principles favor actions that lead the patient to have a full understanding of what has occurred during the course of his or her medical care.

Apology (as opposed to disclosure) remains a controversial aspect of communication following medical errors, largely because of a well-founded fear, at least in the past, that it could be used as an admission of negligence in subsequent litigation. Yet apology appears in many cases to decrease the risk of subsequent litigation, and lack of apology is a commonly cited reason among malpractice plaintiffs for their legal action.[53] Spurred on by a desire to reduce litigation, many states have enacted "apology laws" that prohibit use of various types of apologies in court against physician defendants in malpractice cases. The impact of these laws and the impact of apologies on the incidence and outcomes of malpractice litigation remain unclear, although significant numbers of patients who have sued physicians have indicated that an apology would have prevented them from doing so.

ADVANCE DIRECTIVES AND SURROGATE DECISION MAKERS

Critical decisions regarding medical care often arise when patients are too ill to formulate or express decisions regarding medical interventions (see also Chapter 11). *Advance directives* were developed after several legal decisions affirmed that patients can refuse even lifesaving medical care and that clear and convincing evidence of the patient's wishes is needed to allow surrogate decision makers to request withdrawal of life-sustaining therapies.[54] An advance directive is a document executed by the patient before incapacity to provide the patient's physicians with guidance in medical decision making when the patient cannot communicate for himself or herself. Such directives include the following: living wills, which detail the therapies a patient would accept or refuse in the case of terminal incapacity; DNAR orders; and any other information regarding medical care decisions.

A surrogate decision maker may be someone whom the patient has appointed to make health care decisions for him or her (a durable power of attorney [durable POA]) or an individual with other legally recognized authority by virtue of his or her relationship with the patient.

A durable POA for health care decisions may be given by the patient to a specific person he or she designates to make health care decisions for the patient if he or she becomes incapacitated. The authority vested in a POA supersedes most other decision makers, including family members, except a court-appointed guardian.

When the patient has not designated a durable POA, doctors rely on family members to make decisions for the patient. Many states have a legally defined hierarchy of decision makers. Usually, the spouse or legally recognized domestic partner is considered the first-line surrogate decision maker. Commonly, the surrogate hierarchy after the spouse is children, if all are in agreement, then parents, if both are in agreement, and then siblings, if all are in agreement. When a patient has no advance directives and either a surrogate decision maker is not available or family members cannot agree, the courts may appoint a guardian ad litem to represent the patient in medical decision making.

Surrogate decision makers explicitly act in "substituted judgment" to provide what the patient would have wanted and theoretically are not asked merely for their own preferences. However, surrogate decision makers at best only approximate the patient's decisions because their interpretation is subject to their own biases, values, and psychological agendas. Incompetent patients can be emotionally and financially burdensome, and decision makers may have conflicts of interest that distort their beliefs and testimony about what the patient would have wanted.

Studies demonstrate that patients and their proxies only infrequently discuss issues and values involving life-sustaining technologies. Discrepancies between

patients and proxies are often significant in the assessment of patients' emotional health and satisfaction. Neither physicians nor proxies can always accurately predict the patient's preferences for life-sustaining therapies.[55-57] Nevertheless, with all the imperfections, proxy decision making may be the only option if a patient has not left specific directives.

Medical Decisions That Cannot Be Made by a Surrogate Decision Maker

Some medical treatments have intense cultural connotations, may involve limitation on private freedoms such as reproduction, or may have historically been subject to abuse. Decisions regarding these interventions *cannot* be made by a surrogate decision maker (even if one is available) and require a court review. Examples of such treatments in many states include sterilization and electroshock therapy.

The anesthesiologist should review the patient's record before taking the patient to the operating room and ascertain (1) whether the patient has advance directives, (2) who the patient's surrogate decision makers are, (3) whether the procedure is legally allowed with consent from a surrogate decision maker, and (4) in special cases, whether an appropriate court order has been obtained.

Special Issues With Advance Directives—Do-Not-Attempt-Resuscitation Orders in the Operating Room

Up to 60% of anesthesiologists wrongfully believe that DNAR orders are automatically suspended during anesthesia and surgery. The ASA,[11] the American College of Surgeons,[58] the Association of Operating Room Nurses,[59] and The Joint Commission[60] all published practice guidelines requiring reconsideration, not abandonment, of the DNAR orders in the perioperative period.

The DNAR order is, in essence, documentation of the patient's wishes to avoid the medical interventions associated with resuscitation. Because the causes and outcomes expected with a cardiac arrest in the operating room are different from what may happen elsewhere and prognosis is more favorable, it is very important to reassess the patient's desires when surgery is anticipated.

The ASA issued guidelines for management of the patient with DNAR orders and other directives limiting medical care.[11] Although the patient's primary care physician may have introduced the idea of DNAR orders to the patient or the surrogate decision maker, it is specifically the anesthesiologist's duty to discuss the risks and benefits of resuscitation in the setting of anesthesia and surgery before undertaking the patient's care. The anesthesiologist should include in this discussion the following steps: (1) determine the patient's goals regarding surgery and resuscitation; (2) establish exactly what is meant by "resuscitation," in contrast to routine anesthetic care; (3) educate the patient about the risks and benefits of resuscitation in the operating room setting; and (4) document the agreements reached with the patient about which interventions commonly associated with resuscitation are acceptable to him or her. Such interventions could include, but are not limited to, intubation, administration of vasoactive drugs, administration of direct current (DC) countershock, and institution of chest compressions. Many patients who express reluctance about resuscitation during surgery are fearful of burdensome outcomes, such as permanent neurologic impairment. Education and discussion may reassure these patients about the favorable outcomes of resuscitation in the operating room and can establish ground rules for discontinuing interventions postoperatively if they do not lead to a chance of meaningful recovery.

Surgery depends on the cooperation of many caregivers with differing expertise, each of whom has independent ethical obligations to the patient. Therefore, resuscitation agreements must be discussed with other members of the operating room team. This communication prevents crucial disagreements from occurring during a critical event when treatment decisions must be made quickly. It also allows "conscientious objectors" to withdraw from the health care team.

Advance directives are legally and ethically binding. Despite clear, consistent, and forceful legal decisions, many physicians still resist imperatives to respect patients' wishes regarding resuscitative care, life-sustaining therapies, or both. Anesthesiologists have ignored DNAR directives under the false assumption that the legal authority of advance directives and living wills is not binding in the operating room or that the physician has discretion in deciding when to follow or ignore such directives. In response, courts have awarded significant monetary damages for the costs of continued health care and punitive damages for the pain, suffering, and mental anguish of the patients' survivors when DNAR instructions are ignored.[61]

Finally, DNAR orders must never be construed as an excuse to not "care" for the patient. A patient's decision to forgo resuscitation does not imply a wish to avoid other beneficial interventions. Placement of a pulmonary artery catheter, for example, may help ensure optimal management of a frail patient who has a DNAR order by enabling the anesthesiologist to avoid situations in which the patient's DNAR status becomes pivotal.

END-OF-LIFE DECISION MAKING

A 1996 review by the AMA showed that the following end-of-life issues were of foremost importance to patients: control over the timing and location of death; management of symptoms such as pain, dyspnea, anxiety, and depression; financial management of medical care; and maintenance of therapeutic options, including physician-assisted suicide (PAS).[62]

Withdrawal or Withholding of Medical Therapies—*Curing* versus *Caring*

More than 80% of deaths in the United States occur in health care facilities, and most deaths in ICUs occur after an explicit decision to withdraw or withhold treatments.[63] Patients and doctors alike recognize that aggressive medical therapy may not be desired or even appropriate in the presence of advancing disease. Continued therapy may not be warranted or desired when quality of life is extremely poor, even if the patient is not suffering from terminal disease.

Before the midtwentieth century, the concept of beneficence in the eyes of physicians was strongly tied to preventing death. Ethical distinctions between acts of omission ("letting die") and acts of commission ("killing") were and remain confusing at best. Worse, physicians faced threats of criminal punishment if a patient's death resulted from withdrawal of medical treatments. In 1976, the case of Karen Ann Quinlan established that patients have a right to forgo invasive treatments, even if lifesaving, and that surrogate decision makers could ask for withdrawal of lifesaving therapies if the surrogates could show that the patient would not have wanted them.[64] The right to forgo lifesaving treatments was later extended in the cases of Claire Convoy and Nancy Cruzan to include *any* treatment if the patient refused it or if clear and convincing evidence indicated that the patient would have refused therapy if he or she could not speak for himself or herself.[54] These decisions were revisited and reconfirmed in the tragic case of Theresa Schiavo in 2005.[65]

Arguments that withdrawing or withholding life-sustaining therapy does not violate rules against killing patients are based on ethical differences between killing and letting die and between acts of commission (e.g., lethal injection) and acts of omission (e.g., withdrawal or withholding of ventilator therapy).[66] Because such distinctions are confusing to both physicians and patients, a *principle of proportionality* is often applied when withholding or withdrawing treatments.[67] In this principle, treatment is indicated to the extent that it is likely to present more benefits than burdens to the patient based on the patient's perception of such medical, social, and psychological benefits and burdens. Of course, competent patients still always have the right to refuse therapy, even if lifesaving and otherwise indicated.

Two common settings in which anesthesiologists may be involved in withdrawing or withholding life-sustaining interventions are the ICU and the operating room before organ donation after cardiac death (DCD). In both cases, the issues and principles of withdrawing or withholding treatments are the same.

Withdrawal of life-sustaining interventions heralds the final phase of end-of-life care, and it is a socially critical phase in the life of the patient and family. Terminal care requires special knowledge and experience on the part of the physician. It requires expertise in medically supportive therapy, management of problematic symptoms, knowledge about physiologic changes in the dying patient, support and counseling of patients and families, understanding and respect for the patient's autonomy and religious and cultural practices and beliefs, the ability to work within complex health care teams, the ability to communicate well, and empathy.[68] Anyone intimately involved in care of the dying patient should also be intimately familiar with ethical and legal standards.

Withdrawal of life-sustaining care begins with an assessment of the individual patient's physiology, level of dependence on therapy, degree of consciousness, preferences regarding sedation and analgesia, and preferences regarding privacy and level of involvement of family and other loved ones. All the patient's treatment orders should be reviewed to meet the new treatment goals. Treatments promoting the patient's comfort should generally be continued, whereas those directed only at physiologic maintenance may all be withdrawn. Family members and others attending the patient at the end of life should be educated about physical and mental changes they can expect to see as treatments are scaled back, including the possibility that death will not occur imminently once support is withdrawn.[69]

Several interventions have ethical implications and deserve special consideration—fluid and nutritional management; the administration of sedatives and narcotics that have the potential to hasten death; the administration of neuromuscular blocking drugs; and deactivation of pacemakers, ventricular assist devices, and implantable cardioverter-defibrillators.

The issue of fluid and nutritional support is controversial. Burdens associated with continuation of fluid and nutritional support include prolongation of the dying process and complications and suffering from placement and maintenance of intravenous or enteral access (or both). However, feeding and hydration may have important connotations for family members and members of the health care team by allowing a sense of nurturing and mitigating feelings that they are "abandoning" the patient.[70]

Pain, dyspnea, and depression are all common symptoms that cause suffering in the dying patient. Alleviating pain and dyspnea carries the risk of hastening death. Medical, legal, and religious authorities have all clearly accepted the principle of "double effect," in which an action intended to produce a benefit for the patient produces not only the expected benefit but also the potential for significant harm. It is entirely ethical and legal to administer high doses of pain medication and sedatives for the intended effect of relieving suffering, even if the treatment has the side effect of hastening death. However, to administer any medication with the explicit intention of hastening death is euthanasia and not medical therapy.[70]

Neuromuscular blocking drugs have no anesthetic, analgesic, or sedative properties and have no role in palliative care. Such drugs should not be initiated if withdrawal of ventilatory support is anticipated. When withdrawal of ventilator support is anticipated in a patient already receiving such drugs, they should be withheld in all but extraordinary cases. Paralyzing the patient to comfort *the family* so that they see no disturbing movements or respirations as the patient dies is not justifiable. Even worse, it can mask symptoms and signs of distress and can thus prevent relief of suffering during the dying process[69] (see also Chapter 101).

Pacemakers, implantable cardioverter-defibrillators, and ventricular assist devices are increasingly used in both long-term medical therapy and intensive care (see also Chapters 48 and 101). When a patient who has a cardiac device requests withdrawal of life-sustaining interventions, questions sometimes arise about whether it is ethical to deactivate such devices.

Some experts have said that that these devices must be treated differently from other medical interventions because by virtue of implantation they have become a "biofixture," or literally a part of the patients

themselves.[71] Such arguments are difficult to sustain when we consider that many people undergo implantation of medical devices and subsequent explantation of them when the devices are no longer working or do not serve the patient's purpose. Common examples include artificial joints, intraocular lenses, medication delivery devices, and orthopedic hardware. Furthermore, these devices are never uniquely a part of the patient in the same sense as DNA or their native organs. In fact, the ethical distinction between disabling a pacemaker in a pacer-dependent patient and turning off a ventilator for a ventilator-dependent patient is minimal, if the request comes from a competent patient or the surrogate decision maker. Both actions involve discontinuance of artificial therapies that the patient no longer desires, and both may be followed by rapid death.

As with other end-of-life therapies, discontinuance of such devices should include due consideration of whether the decision is made by a competent patient and with full informed consent. Management of discontinuance of device therapy should always include planning for treatment of distressing symptoms and administration of appropriate comfort measures.

Physician-Assisted Suicide and Euthanasia

PAS involves the provision of medication or prescriptions to patients by specific request for the purpose of ending their life. PAS requires a patient who is both competent and capable of communicating the request. Euthanasia involves the administration of medication by someone other than the patient for the express purpose of causing death, in the belief that this would be best for the patient (but not necessarily at the specific request of the patient). Both practices differ ethically from withdrawing or withholding life-supporting medical treatments. In PAS and euthanasia, the primary intention is to cause death, which secondarily ends suffering. In withdrawal of withholding of life-supporting treatment, the primary intention is to discontinue treatments that are causing suffering with an understanding that death may or probably will result.

Currently, euthanasia is legal only in the Netherlands, Belgium, and Luxembourg. In the United States, euthanasia remains illegal regardless of circumstance, but PAS is legal in the states of Oregon, Washington, Montana, and Vermont and is being considered in other states. Internationally, PAS is legal in the Netherlands, Belgium, Luxembourg, Germany, and Switzerland.[72]

Supporters of PAS argue that the right to privacy and respect for autonomy support a patient's right to determine the time, location, and circumstance of his or her own death. The public consistently rates loss of autonomy and control, inability to pursue previously valued activities, and loss of dignity as the major concerns at the end of life.[73] Adequate control of pain, anxiety, dyspnea and other symptoms at the end of life remain a challenge to the medical profession, thereby fueling the desire for a means to end life when suffering cannot be controlled. Opponents argue that PAS "medicalizes" death, overly idealizes the physician-patient relationship, ignores possible personal and professional conflicts of interest, and leads to erosion of trust between dying patients and their doctors. Although many ethicists acknowledge that individual circumstances may make assisted suicide an ethically permissible action, most express concerns about potential abuse. Vulnerable members of society, such as the poor, old, and handicapped, could be pressed by financial and social factors into a suicide option in preference to palliative care.

An additional argument against PAS or legalized euthanasia is that these approaches could provide solutions to the medical, social, and economic problems common to older and poor patients that are simpler and less expensive than seeking and requiring more difficult, but definitive remedies.

More than 10 years have passed since Oregon legalized PAS and the Netherlands legalized both PAS and euthanasia, and significant data now provide some insights into whether these concerns about PAS and euthanasia are materializing.

More than two thirds of the U.S. population polled favored legalizing PAS, and approximately 58% favored legalization of euthanasia.[74] The percentage of U.S. oncology patients favoring a PAS or euthanasia option in end-of-life care rises to approximately 65%,[75] whereas physicians frequently involved in end-of-life care, such as intensive care specialists, oncologists, and palliative care specialists, are the most uniformly opposed specialists.[76] This finding represents a significant discordance between physicians and their patients.

In Oregon, where PAS has been legalized for the longest period of time in the United States, data show that patients who requested PAS had generally higher economic status and education, more than 96.7% were insured, and 92.5% were enrolled in hospice care. Most were more than 65 years old (65%), and 82% were suffering from cancer. Approximately 20% of patients receiving prescriptions for PAS never used them and ultimately died of their underlying disease—with many surviving significantly longer than predicted. More than 93% of patients enrolled in the Oregon program cited loss of autonomy as a primary reason for pursuing the option.[77,78] Some authors have suggested that the possession of a means to end their lives legally and humanely prevented "preemptive" suicides that could have occurred earlier and thus may have prolonged lives.[79]

Concerns regarding abuses of PAS and euthanasia will undoubtedly continue, but thus far, evidence of systematic abuse is lacking in places where PAS is legalized and regulated. As the population ages and patients desire greater control over end-of-life care and circumstances, debate over PAS and euthanasia in the United States can be expected to grow.

ETHICAL ISSUES IN ORGAN TRANSPLANTATION

Two issues critical to vital organ transplantation that confront anesthesiologists are the concept of brain death and the linkage of withdrawal of life-sustaining therapies with organ retrieval and transplantation after cardiac death (DCD) (see also Chapters 74 to 76).

Brain Death

Before the 1960s, death was defined as the moment when the heartbeat stopped and respirations ceased. Advances in cardiopulmonary resuscitation and mechanical ventilation then made it possible to postpone death, seemingly indefinitely. In 1968, the Ad Hoc Committee of the Harvard Medical School proposed redefining death as the point at which all cardiorespiratory function had irreversibly ceased, *or* all function of the whole brain had irreversibly stopped (brain death).[80] The committee gave two explicit reasons for redefining death. The first was to allow patients to be declared dead and not maintained on machines—thus limiting expense; reallocating medical resources to other, salvageable patients; and allowing the social rituals surrounding death to occur. The second was to allow the donation of vital organs before circulation stopped.

The public has been slow to accept brain death, in part because it requires complete trust in physicians and ignores indicators of death that the public already understands. To nonphysicians, brain-dead donors are superficially indistinguishable in many ways from living persons, and nonphysicians must therefore rely completely on the physician for both accurate and honest information of a loved one's death.

Diagnosing brain death is relatively straightforward. In the United States, it requires demonstration that, in the absence of drugs, paralytic agents, hypothermia, and other reversible conditions that mimic loss of brain function, no cortical or brainstem function is present. The diagnosis is usually made either clinically, by demonstrating that cortical activity and brainstem reflexes are absent, or by radiographic studies demonstrating the complete absence of cerebral blood flow.

Although brain death is a *social* and not a *biologic* definition of death, medical, ethical, theologic, and legal experts generally agree that brain death adequately defines a condition in which a person with ethical and legal rights and moral standing ceases to exist and should no longer be treated as though alive. Expensive medical interventions can be discontinued without legal ramifications, and vital organs can be donated for transplantation if the patient or the surrogate decision maker agrees.

Before assuming care of a brain-dead organ donor, the anesthesiologist is obligated to review the chart for documentation of the declaration of brain death and the criteria on which it was based. If any questions exist about the diagnosis, organ donation should be postponed until the anesthesiologist is satisfied that these concerns are addressed.

Donation After Cardiac Death

DCD occurs when a patient wishes to have life-sustaining medical therapies withdrawn and also wishes to proceed with vital organ donation after death. Controlling the time and place of death so that timing of organ donation can be optimized has obvious medical and ethical advantages. The decision to donate organs is made before death, thereby allowing time for discussion and informed consent. Ischemia time can be minimized. The dual decision to withdraw life-sustaining interventions and donate vital organs after death can create ethical conflicts, however. When a dying patient becomes an imminent organ donor, the risk is that the patient's interests will be minimized or ignored in favor of the organ recipient.

The Institute of Medicine reviewed DCD in 1997[81] and 2000[82] and found serious ethical questions, such as determining how quickly after asystole organ donation can begin and whether medications can ethically be administered to the donor before death that are solely for the purpose of organ preservation.

Ethical, theologic, and legal principles prohibit us from killing one person to benefit another, but the point at which actual death has occurred in DCD donors is unclear. Although expedient donation is the very purpose of DCD, doctors must never sacrifice any living patient in the process or even take significant risks of doing so; the mistrust this would engender among the public could place the entire concept of DCD donation at risk by reducing potential donors and ultimately harming future potential organ recipients.[83-85] Loss of consciousness occurs quickly after asystole, but brain function can continue for some time, and irreversible brain injury may not occur for many minutes. Yet many protocols call for organ retrieval to begin only 2 minutes after circulation has stopped, and in at least one institution, organ donation is allowed to begin within seconds of cardiac arrest.[86] Scientific and philosophic uncertainty exists about when death is complete—this could even lead to accusations that physicians deliberately kill patients to obtain organs for transplantation. Mistakes have occurred in some cases of brain-dead organ donors for which clear clinical criteria exist; DCD organ donation is potentially even more prone to error because no such clinical guidelines are universally accepted.[87]

Donation of vital organs after brain death and DCD are both ethical and legal, but the interests of the dying patient must be absolutely protected until after death has occurred. Anesthesiologists can play a vital role in the organ donation process by helping hospitals develop reasonable and ethical policies for the management of brain-dead donors and DCD donors. Every anesthesiologist should be thoroughly familiar with brain death criteria and should review the process of brain death determination before accepting care of a brain-dead donor. It is inappropriate for anesthesiologists to be involved in organ DCD unless they have expertise in the relevant ethical, legal, and medical issues and are experienced in end-of-life care.

RESEARCH ETHICS

HUMAN SUBJECT RESEARCH

The premise that the physician always puts the best interests of the patient first can be jeopardized when research objectives enter the doctor-patient relationship. Human subjects are asked to put aside their own interests to benefit some future, hypothetic group of patients. In extreme cases, the patient becomes a research "object" who will not benefit personally from the experiment at all. Two examples include experiments in healthy subjects and phase I cancer trials in terminally ill patients in which

the goal is to determine the toxicity of treatment—not remission, palliation, or cure.

Human subject research must balance many conflicting interests, such as the needs and rights of the research subject, the hypothetic interests of future patients, and the physician's financial, professional, and personal goals. Academic or corporate advancement, personal prestige, and financial incentives may be disincentives to researchers who diligently protect patients' interests or who remain objective in designing protocols and analyzing and reporting their findings. Thus, human subject research is more closely regulated, supervised, and controlled than any other medical endeavor.

Regulation of research began after World War II, with the Nuremburg Code and the Helsinki Declaration outlining the ethical obligations of physicians engaged in human research. The United States was slow to awaken to the parallels between the concentration camp experiments and the sometimes gruesome treatment to which they subjected their own subjects in similar trials.[88] In the years that followed the Doctors' Trial at Nuremburg, Fox[89] and Beecher[90] found that researchers were aware of the standards set at Nuremberg but regularly did not comply with them. In 1974, the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, out of which the modern institutional review board was born.[54]

The ethical conduct of human subject research follows three principles: (1) respect for autonomy and the obligation to protect subjects with limited autonomy; (2) beneficence, with obligations to minimize risks, maximize benefits, and ensure that the research design is scientifically sound; and (3) justice, the obligation to treat each person with regard to what is morally right and to ensure fair distribution of benefits and burdens.

In addition to the comprehensive presentation to research subjects of the risks and benefits of procedures or medications to which they will be subjected, disclosure must include the possibility of commercialization of the results, financial interests of the researchers, and any other actual or perceived conflicts of interest on the part of researchers and their institutions and sponsors. Subjects must be free to refuse or end participation at any time without penalty. *Situational coercion,* in which subjects feel that they are not truly free to refuse, should be avoided or mitigated. Examples of situational coercion include prisoners whose terms and experiences of incarceration may be affected by their decision to participate or refuse and hospitalized patients who may believe that their care could be compromised if they do not cooperate with researchers.[88]

Monetary or other inducements to participate in research are probably permissible if they do not undermine the freedom of the subject to refuse under reasonable circumstances. Significant monetary awards may have adverse effects on the autonomy of subjects and may negatively affect the scientific quality of the research. If remuneration is high, for example, subjects could conceal factors that would otherwise disqualify them from participating, thus compromising the research results and exposing themselves to greater risks.

Researchers are obligated to maximize benefits and minimize potential harms, including physical, psychological, social, legal, and financial harms. The research must address a question of sufficient value to justify the level of risk and must follow the approved protocol. Findings must be promptly and accurately reported. The research must be terminated immediately if it is suspected to be harmful to the participants.

Anesthesiology research often involves the treatment or prevention of unpleasant symptoms, such as pain and nausea, for which effective treatments are well established. Such studies should be restricted to comparison of treatments with known efficacy, not placebo-controlled trials, and "escape" analgesics or antiemetics must be provided on the patient's request.[70]

No population group should be unfairly subjected to research without having equal access to its benefits. Finally, the interests of the individual must always prevail over the interests of society.

Children as Research Subjects

Children are particularly vulnerable as research subjects because they may lack the ability to make mature decisions, are subject to the authority of others, may defer to their parents and others in ways that mask underlying dissent, and may have conditions requiring immediate decisions not consistent with informed consent (see also Chapters 92 and 93).[91] Children's rights are frequently undervalued, whereas parental authority may be overvalued. Studies show that even children with decision-making capacity are often excluded from the consent process by both parents and physicians.[92]

If a minor child is "able" to assent, then assent must usually be obtained in addition to the consent of any legal surrogate decision makers. In the United States, federal law requires assent of any minor 7 years old and older to participate in medical research. Particularly for research in which no substantive individual benefit is expected, many ethicists believe that a child's dissent *must always be honored*.[92,93]

ETHICS OF ANIMAL RESEARCH

The animal rights movement in the United States has gained significant momentum since the 1980s, following in the wake of the U.S. civil rights movement and paralleling increasing awareness and concerns about the human impact on the environment and other animal species. In 1959, William Russell and Rex Burch published their sentinel book regarding the ethics of animal research, *The Principles of Humane Experimental Technique*, introducing the concept that humane treatment of animals was not merely an ethical imperative, but absolutely necessary to high-quality research.[94] Federal legislation protecting animal welfare began with the Laboratory Animal Welfare Act of 1966. In 1985, the Health Extension Act and amendments to the Animal Welfare Act required the establishment of Institutional Animal Care and Use Committees (IACUCs), which oversee conditions of laboratory animals; review and approve animal research protocols; educate and train investigators in ethical issues and aspects of animal handling such as

anesthesia, analgesia, and euthanasia; and act as community liaisons.[95]

Some researchers deny that animal experimentation could be subject to any moral reservations and assert that medical advances have been and continue to be completely dependent on continued animal research. Many animal welfare activists insist on the moral equivalence of animal experimentation to that of human experimentation and accuse researchers of being blind to or, even worse, actually unmoved by the suffering of animal subjects. The simplicity of these polarized views does not do justice to the complexity of the issues.

Advances in the understanding of animal cognition led most biologists to believe that many, if not all, animals are capable of feeling pleasure, pain, anticipation, and fear and thus experience both enjoyment and suffering. Many bioethicists accept that the higher animals therefore have sufficient awareness to possess moral standing, although how much moral standing is intensely debated.[96,97] Allowing animal suffering as a result of pain, fear, sickness, or poor standards of care is a moral harm that must be avoided, mitigated, and weighed heavily against the benefits it produces. Ethicists maintain that cruelty to animals is immoral and that animals should be protected from it, not merely because they have moral standing, but because he who is cruel to animals is more likely to be cruel to humans.[98]

Researchers have obligations to provide clean and humane conditions and appropriate veterinary care for animal subjects. Researchers should mind the "Three Rs"—replacement, reduction, and refinement—that is, use animal subjects only when necessary, minimize any suffering incurred in the study, and seek nonanimate replacements for animal subjects.[99] Mediocre or repetitive research using animal subjects should not be allowed. It is the responsibility of the medical and scientific community to continue aggressively to seek and promote alternatives to the use of animal subjects.[98]

PHYSICIAN PARTICIPATION IN EXECUTIONS

U.S. professional organizations for physicians have consistently stated that physicians' participation in executions is unethical, yet many physicians admit that they would agree to be involved. The role of physicians in euthanasia and executions is of particular concern to anesthesiologists, who have been identified as ideal candidates for duties that involve killing because of their particular professional skills. Arguments in favor of physicians' involvement in executions usually cite the principle of beneficence in allowing a humane death.

Historically, however, beneficence arguments have led to "slippery slope" justifications for physicians to be involved in the killing of persons who have never faced an accuser or had a fair hearing—such killings have included persons with physical or mental handicaps and other "social flaws" for the "benefit" of the individual and of society as a whole. Once physicians accept a beneficence argument for participating in executions, it is difficult ethically to draw the line at participating in other state-sponsored activities, such as torture, coercion, and "medical incarceration," because these activities are also usually defended as being beneficial to society.[100]

When physicians agree to participate in an execution, they act as agents of the state while appearing to act on behalf of the "patient." This situation can lead to eventual erosion of public trust and respect. It also at times undoubtedly leads to physicians' participation in the killing of innocent persons.[101]

To avoid intolerable self-condemnation, virtually all executioners undergo "moral disengagement" in which they dehumanize the convicts and devalue their lives, thereby deflecting moral responsibility for the execution away from themselves by blaming juries, judges, governors, and "the law," rather than accept the responsibility they share in ending the prisoner's life.[102] It is difficult to reconcile the medical profession's overt ethical imperatives of valuing human life, respecting individuals, and accepting personal moral responsibility with participation in a process that requires a rejection of these very values.

In 1980, the AMA issued an opinion that physicians' involvement in capital punishment is unethical and defined "participation" broadly as including not only actions that themselves would lead to the death of the condemned but also any activity that assisted, supervised, or contributed to another's being able to do so.[103] However, no direct sanctions of any participating physician were addressed. In 2010, the American Board of Anesthesiology (ABA) became the first organization of physicians not only to condemn participation in capital punishment as unethical but also to state that physicians who were certified by their board and who participated in lethal injection would be subject to disciplinary action that could include revocation of their diplomate status.[104]

MORAL INTEGRITY—CAN THE PHYSICIAN BE A CONSCIENTIOUS OBJECTOR IN MEDICINE?

Anesthesia care of patients can involve ethical controversy, legitimate disagreement, and moral ambiguity. When a physician's personal values run counter to acceptable ethical standards of care, how should the physician resolve such conflicts? Medical professional societies recognize the right to conscientious objection in medical practice. The ASA, the British Medical Association, and the Hastings Center all have issued statements recognizing the physician's right to withdraw from situations in which ethical standards of patient care are in serious conflict with his or her personal values.[105] The ASA specifically recognizes conscientious withdrawal from patient care in the case of patients with DNAR orders or other directives that limit treatment.[11] These rights have limitations, however. Acceptance of moral objections to certain hotly contended issues such as abortion or PAS may be reasonable, but objections to well-established standards, such as informed consent, are not. Moral objections of physicians are also likely to carry more weight if they involve concepts that the physician believes supports him or her as an ethical doctor, and not just as an

ethical person, because these concepts are more likely to be founded in professionally established standards than in personal beliefs.[105]

SUMMARY

Anesthesiologists face many ethical challenges, including promotion of the patient's autonomy, resolution of patient-physician conflicts in medical decision making, ethical obligations in human subject and animal research, and ethical conflicts during end-of-life care in the ICU and during organ donation. Knowledge of the ethical and professional standards in patient care and research is essential in the specialty of anesthesiology, which is more than the mere provision of a technical service on demand. Anesthesiologists may find that accepted values in ethical practice sometimes conflict with personal values and goals. This is a common challenge to all physicians, but ethical decisions cannot be left to the individual physician's values, and adherence to the ethical principles of the medical profession should prevail.

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Chapter 11

Legal Aspects of Anesthesia Care in America

DAVID B. WAISEL

Key Points

- The medical malpractice tort system is intended to improve patient care.
- Medical negligence occurs when a physician's failure to meet the standard of care directly leads to a patient's injury.
- A fully informed attorney is the physician's best advocate.
- Physicians having their medical competence publicly questioned may feel guilt, failure, anger, shame, isolation, depression, fatigue, denial, and physical symptoms.
- A detailed, legible anesthesia record strengthens the defense against a malpractice suit.
- More than half the states have laws prohibiting the admission of apology or sympathy as evidence of wrongdoing.
- The goal of informed consent is to maximize the ability of the patient to make substantially autonomous informed decisions.
- Evidence of decision-making capacity (the ability to make a particular decision at a specific time) includes the ability to understand medical problems, proposed treatments, alternatives, options to refuse treatment, and foreseeable consequences of accepting or refusing proposed treatments and the ability to express a preference based on rational, internally consistent reasoning.
- The reasonable person standard of disclosure requires that the extent of the disclosure be based on what a reasonable person would consider material for choosing whether to undergo the proposed intervention.
- Anesthesiologists may refuse to provide care when they ethically or morally disagree with the procedure or if they believe the patient's choice is too inappropriate or likely to result in harm.
- Competent patients have a virtually unlimited right to refuse life-sustaining medical treatment.
- Anesthesiologists are responsible for negligent acts made within the scope of defined duties by trainees and certified registered nurse anesthetists (CRNAs).
- Physicians have been held liable for inadequate pain control.
- In the end, case law does not provide clear guidance. If the information is possibly relevant to decision making, it is prudent to disclose, even if not absolutely legally required.

Statute law, case law, and regulations affect anesthesiologists (Table 11-1).[1-7] Statute law is the body of prescriptive law created by a legislature to achieve a specific purpose. For example, the National Organ Transplant Act is the law that established the Organ Procurement and Transplantation Network and authorized it to maintain a national registry for organ matching. State legislatures subsequently establish state laws governing organ procurement (see also Chapters 74 and 75).

When statute laws need interpretation, when they clash, or when no definitive statute law exists, disagreements may be adjudicated by the judicial system. The aggregate of reported cases, known as case law or common law, is used as the basis for future court decisions. The results of these cases are rarely prescriptive and may lead to a collection of confusing, ambiguous, and even contradictory cases that rest on diverse rulings in different jurisdictions. For example, a widow donated the kidney of her deceased husband to a long-time friend. The transplant surgeon, upon receiving and examining the kidney, declared it unsuitable because of a renal artery aneurysm. The transplant surgeon then asked for the donor's second kidney. By then, the donor's second kidney had been allocated to another patient. The plaintiff

TABLE 11-1 LAWS AND REGULATIONS THAT AFFECT MEDICAL PRACTICE

Law or Regulation	Comments
Patient Protection and Affordable Care Act (PPACA; commonly known as ACA or Obamacare)[1]	The PPACA is a wide-ranging act that will be phased in over several years. It mandates that an individual carry health insurance, establishes standards and requirements for health insurance, launches health insurance exchanges to market policies, increases clinical preventive services, and restructures Medicare reimbursement. It establishes the National Prevention, Health Promotion and Public Health Council to develop a national preventive health strategy and the Patient Centered Outcome Research Institute to perform comparative effectiveness research. The PPACA specifically authorizes funding to advance research and treatment of pain management.
Health Insurance Portability and Accountability Act (HIPAA)[3]	HIPAA's privacy rules protect individually identifiable health information held or transmitted in any form, whether electronic, paper, or oral. This includes a patient's past, present, or future health or condition, provision of health care or payment for the provision of health care, and information that either identifies the individual or for which there is a basis to believe the individual can be identified through common identifiers. Privacy rules apply to health plans, to health care clearinghouses, and to any health provider who transmits health information. HIPPA is a complex law that includes many other provisions, including making insurance portable from one employer to another. The PPACA added requirements and increased the penalties for noncompliance.
Health Information Technology for Economic and Clinical Health Act (HITECH)[2]	The 2009 HITECH was instituted to develop a nationwide health information technology infrastructure that would improve health care quality and care coordination. HITECH established economic incentives tied to "meaningful use" of electronic health records.[104] HITECH also established requirements for federal notification in the event of a breach of privacy for health care information, the effects of which have been seen in high-profile cases over the last few years, usually involving stolen laptop computers. The act also provided for patients to obtain an audit of all disclosures and uses of their electronic records, and it prohibited selling patients' health information. Since 2010, more than 500 breaches have occurred. More than 60% involved theft or loss of information, typically on electronic devices such as laptop computers.[2]
Emergency in Medical Treatment and Active Labor Act (EMTALA)[4,5]	EMTALA governs when a patient may be refused treatment and when an unstable patient may be transferred from one hospital to another. More commonly stated, the purpose of EMTALA is to prohibit "dumping" of emergency patients onto other hospitals. Hospitals must perform a screening medical examination to determine whether an emergency condition exists, must provide stabilizing treatment if an emergency condition does exist, and may transfer the patient to another hospital only under certain conditions, such as the patient requests transfer, the patient is stable and transfer will not worsen the patient's condition, and the receiving hospital has treatment capabilities unavailable at presenting hospital. The receiving hospital must accept the transfer, and physicians must certify that the patient can be safely transferred. EMTALA also requires assigned on-call physicians to respond to emergency situations.
Employment Retirement Income Security Act (ERISA; several amendments to ERISA are relevant to health benefits, including HIPAA)[7]	ERISA established uniform federal standards to protect private employee benefit plans. The U.S. Department of Labor administers and enforces ERISA, and federal courts interpret it. The relevance in medicine is that it regulates health benefit plans. Case law interpretation of ERISA affects how, where, and for what members may sue health maintenance organizations.
Controlled Substance Act (CSA)[6]	This act permits the federal government to regulate manufacture, importation, possession, and distribution of certain drugs to control traffic of controlled substances. This act permits the federal government to determine whether a drug should be a controlled substance and into what drug schedule it should be placed. This act does not control the medical use of these drugs.

sued, claiming that the organ procurement organization misappropriated the donor's second kidney and alleging in part that, under conversion tort, the organ procurement organization interfered with the plaintiff's right of possession of personal property, in this case, the kidney (see also Chapters 74 and 75). On appeal, the court ruled for the defendant, the organ procurement organization, because the plaintiff had no common law right to the second kidney, given that a person cannot have property rights to a dead body.[8]

This chapter uses descriptions of legal cases. Readers should be aware that the medical facts of these cases are based on information presented in possibly incomplete or erroneous court documents.

Regulations arise from administrative authorities tasked with applying the law. For example, the U.S. Department of Health and Human Services develops the regulations that implement the health care insurance requirements stipulated by the Patient Protection and Affordable Care Act (PPACA).[1]

PROFESSIONAL LIABILITY

THE MEDICAL MALPRACTICE TORT SYSTEM

The medical malpractice system is intended to improve patients' safety and compensate patients injured by negligence (see also Chapter 10). To do so, malpractice cases would have to influence the behaviors of individual clinicians and organizations appropriately but not encourage "defensive medicine." Systems would have to encourage the communication needed to improve patient care systems.

The malpractice system does not achieve these goals. Jury trials of medical malpractice suits do not reliably inform physicians, in part because of the inconsistencies in case law and in part because juries tend to correlate liability with severity of harm and not with physicians' negligence. Cases are often appellate decisions that are decided on legal rather than medical grounds. Indeed, malpractice cases increase liability concerns and lead to more expensive and possibly riskier interventions. Nearly all physicians have made clinical decisions to avoid liability, and these "defensive" decisions may contribute up to 25% of health care costs.[9,10] Data regarding the effects of defensive medicine are primarily self-reported, however, and are open to memory and response bias.

Physicians fear a mercurial malpractice system.[11] Fear thwarts honest discussion of clinical events. More than 60% of physicians feel the threat of malpractice litigation in their day-to-day practice, and more than 60% are concerned that they will be involved in a malpractice case over the next 10 years.[10] Although these concerns are significantly out of proportion to the actual risk, heightened sensitivity to malpractice is likely attributable to the tendency to overestimate the likelihood of rare events and to magnify the risks of unfamiliar, devastating, or arbitrary events.[10]

Juries may not be as pro plaintiff as physicians seem to think. Medical experts and juries overwhelmingly agree in assigning liability in cases with weak evidence of negligence.[12] In cases with strong evidence of negligence, experts are far more likely than juries to assign liability to the defendants.[13]

Reform efforts have focused on reducing the costs of the medical liability system (Box 11-1).[14] Caps on noneconomic damages have reduced claim payouts by 20% to 30%.[14,15] For the most part, other reforms have had limited effects on costs. In other health care systems, administrative medical injury compensation systems seem to decrease cost but may increase claims.[11] The Congressional Budget Office has suggested five reforms that will reduce the cost of malpractice insurance by 10% (Box 11-2).[16]

Whether financially centered reforms will minimize some of the harms of the medical malpractice system depends on whether defensive medicine is rooted in financial concerns or more complex motivations.[17,18] Some experts argue that successful reform requires fundamental change, such as safe-harbor legal protection for following clinical guidelines.[15,17] Another possible fundamental change is judicial branch reform, whereby judges are supported by neutral medical experts, are trained in adjudicating medical malpractice, and will "own" the case from beginning to end. This reform is expected to promote speedier resolution through earlier, more frequent, and private meetings.[15] The 2010 PPACA authorized grants for seeking new ways to resolve medical injury disputes.[1]

DISCLOSURE, APOLOGY, AND OFFER

The disclosure, apology, and offer approach may increase frank discussion about medical error, provide fair compensation to patients, decrease costs, and reduce the stress and the harms of the current system (Table 11-2).[19]

BOX 11-1 *Traditional Malpractice Reforms*

Malpractice reforms are designed to encourage parties to settle legitimate claims and deter questionable suits.

Caps on noneconomic damages: They limit the amount of money that can be awarded for noneconomic ("pain and suffering") losses.

Pretrial screening panels: They provide an opinion on whether a claim has sufficient merit to proceed to trial. This opinion may be advisory or binding and is a possible source of evidence.

Certificate of merit: This requires a plaintiff to present an affidavit certifying that a medical expert believes there is a reasonable and meritorious cause for the suit.

Attorney fee limit: This limits the amount of a malpractice award a plaintiff's attorney may take in a contingent-fee arrangement.

Joint-and-several liability reform: This reform limits the financial liability of each defendant to the percentage fault that the jury allocates to that defendant. If the jury determines that a specific party is 20% responsible for the outcome, then that specific party is liable for only 20% of the award, even if other parties cannot pay their share.

Collateral-source offset: This requires that other reimbursements related to the injury must be deducted from the award the defendant must pay.

Periodic payment: Awards may be paid over time rather than in one sum.

Schedule of noneconomic damages: This reform guides financial awards by categorizing the extent of "pain and suffering" by the severity of injury. This compensation schedule may be advisory or binding.

Administrative compensation systems or "health courts": These alternative processes for resolution of malpractice claims often involve specialized judges, decision and damages guidelines, and neutral experts.

From Mello MM, Kachalia A, Goodell S: Medical malpractice: April 2011 update, Synth Proj Res Synth Rep *21(Suppl 1), 2011.*

BOX 11-2 *Congressional Budget Office Recommendations to Reduce the Cost of Malpractice Insurance by 10%*

1. A cap of $250,000 on awards for noneconomic damages
2. A cap on awards for punitive damages of $500,000 or two times the award for economic damages, whichever is greater
3. Modification of the "collateral source" rule to allow evidence of income from such sources as health and life insurance, workers' compensation, and automobile insurance to be introduced at trials or to require that such income be subtracted from awards decided by juries
4. A statute of limitations—1 year for adults and 3 years for children—from the date of discovery of an injury
5. Replacement of joint-and-several liability with a fair-share rule, under which a defendant in a lawsuit would be liable only for the percentage of the final award that was equal to his or her share of responsibility for the injury

From Elmendorf DW: Letter to Hon. Bruce L. Braley, Dec 29, 2009. <http://www.cbo.gov/ftpdocs/108xx/doc10872/12-29-Tort_Reform-Braley.pdf/> (Accessed 27.09.13.)

This approach rejects the traditional "deny and defend" response of physicians and hospitals that generates an adversarial relationship. It embraces disclosing freely, offering compensation for questionable care, and vigorously defending reasonable care. The University of Michigan

TABLE 11-2 DISCLOSURE, APOLOGY, AND OFFER

Objective	Action of Hospital or Insurer
Increase transparency, reduce adversarial relationships	1. Disclose adverse outcomes of care 2. Build a system to support disclosure 3. Apologize 4. Explain results of investigation and changes to be implemented
Improve patients' safety	1. Implement systems to encourage sufficient clinician candor to address patients' safety 2. Implement systems in a timely manner to avoid recurrence
Avoid lawsuits, reduce liability costs, and improve access to compensation of families and patients	1. Distinguish between injuries from medical negligence and those from disease or as a result of high-risk medical care 2. Offer financial compensation when care was unreasonable without the patient's needing to initiate a lawsuit 3. Defend "vigorously" when care was reasonable

Data from Bell SK, Smulowitz PB, Woodward AC, et al: Disclosure, apology, and offer programs: stakeholders' views of barriers to and strategies for broad implementation. Milbank Q *90:682-705, 2012; and Boothman RC, Imhoff SJ, Campbell DA Jr: Nurturing a culture of patient safety and achieving lower malpractice risk through disclosure: lessons learned and future directions.* Front Health Serv Manage *28:13-28, 2012.*

TABLE 11-3 CAUSES OF ACTION MOST RELEVANT TO ANESTHESIOLOGISTS

Type	Description
Medical negligence	Breach of a duty of a standard of care with resulting harm
Wrongful death	A wrongful death is one that occurs earlier than it would have otherwise; if negligence causes death, survivors may sue for damages
Lack of informed consent	Obligation to provide information material to a reasonable person
Abandonment	Obligation to provide continuity of care once physician assumes responsibility for the patient
Vicarious liability	Obligation for reasonable oversight of those persons working for the physician
Loss of chance of recovery or survival	The patient must show that the chance of recovery was likely but for the action of the physician
Battery	Touching a person without their express or implied consent; no need for the plaintiff to prove harm in battery cases
Assault	The attempt to touch another person; no need to prove actual harm

From White C, Rosoff AJ, LeBlang TR: Informed consent to medical and surgical treatment. In Sanbar AA, Firestone MH, Fiscina S, et al, editors: Legal medicine, *ed 7. Philadelphia, 2007, Mosby, pp 337-343.*

Health System, an early adopter of this approach, reported a resultant reduction in number of claims, settlement amounts, and defense costs.[20]

The disclosure, apology, and offer approach has legal, cultural, and logistic barriers. It likely fails in systems of asymmetric risk. For example, in some states, charitable corporations such as hospitals have limited tort liability, which means that in the short run, the practice of offering compensation may increase their costs.[19] To be successful, the disclosure, apology, and offer approach must be practiced by all the hospitals and physicians within a health care system. Otherwise, ill-aligned values and strategies will bring chaos, followed by the death knell.

The current system endorses name-based reporting to various state and national authorities. Because most systems require settlements to be reported, physicians may be tainted even if the injury was unrelated to their actions. To be sure, this concern in part reflects an extremely out-of-proportion view of how malpractice reports affect credentialing or licensing. Addressing these concerns will require both a change in reporting requirements and a willingness of institutions to accept responsibility for system-level events.

Attorneys may impede adoption of the disclosure, apology, and offer approach. Plaintiff attorneys may believe that the tort system best protects the patient's interest. Defense attorneys may be concerned that this approach is not in the individual client's interest.

MEDICAL MALPRACTICE

The most common cause of medical malpractice is medical negligence (Table 11-3). *Negligence* is a breach of a duty that is the proximate cause of a harm.[21] *Medical negligence* occurs when a physician's failure (breach) to meet the standard of care (duty) directly leads (proximate cause) to a patient's injury (harm). Proximate cause should be tightly coupled and requires proof of cause-in-fact and foreseeability. *Cause-in-fact,* often known as the "but for" test, means that without the negligent act, the harm would not have occurred. The classic definition is that the act was indispensable in causing harm. Some jurisdictions have expanded the "but for" rule to include actions that substantially contribute to the harm. Foreseeability suggests that injuries must be of the type that would be anticipated by a reasonable practitioner. For example, an unrecognized esophageal intubation would have been prevented "but for" the anesthesiologist's forgoing end-tidal carbon dioxide monitoring because the reasonable anesthesiologist would foresee that this breach of standard of care could lead to an unrecognized esophageal intubation. A harm must have occurred for which the individual needs to be compensated. Awards may be given for noneconomic losses, for the economic costs of repairing the damage, and for loss of income. *Statute of limitations* defines the amount of time in which a plaintiff can bring an action; it is governed by state law and typically begins upon the occurrence or discovery of the allegedly negligent act or of the harm.

Medical negligence may be adjudged as *criminal medical negligence* if it deviates greatly from the standard of care, whether unknowingly (criminal negligence) or knowingly (criminal recklessness).[22] Criminal medical negligence is rarely prosecuted, but characteristics of these cases include failing to modify care based on past similar experiences, hiding errors, and practicing in a way that appears

to favor financial and personal gains over patient care. For example, an anesthesiologist was prosecuted (but eventually acquitted) for reckless manslaughter when, after more than five documented episodes of falling asleep during anesthesia, he fell asleep during a case in which the child died. He was convicted of criminal medical negligence, although that conviction was eventually overturned because the prosecutors had not brought the criminal medical negligence charge within legal time limits.[23]

THE PROCESS OF BEING SUED

Some lawsuits may begin "informally" by a request from a potential plaintiff's attorney to review records or to discuss a case. An attorney should be consulted before engaging in these actions to ensure that proper procedure is followed. Lawsuits officially begin with a document called a Summons and Complaint, which is a notification to respond to allegations by the plaintiff.

Following initiation of the suit, the process of discovery begins through an exchange of documents and a deposition. The purpose of the deposition is for the other side of a legal action to obtain information or clarification otherwise unavailable, particularly about the reasoning underlying actions.[24] At the deposition, oral testimony is taken under oath, is transcribed, and may be used as evidence in trial. Experts, consultants, clinicians, witnesses to the event, or defendants may be deposed. Some conversations are privileged and may not be discovered by the plaintiff. These include discussions with attorneys, risk management personnel, insurance company representatives, a spouse, personal clinicians (including psychotherapists), and clergy. Conversations with close friends are discoverable.

Before the deposition, the physician should inform the attorney about his or her relationship with the plaintiffs and any problems that may have occurred. The physician should educate the attorney about complex medical components of the case and expected weaknesses. A fully informed attorney is the best advocate.

In addition to the defendant, the defendant's attorney, the plaintiff's attorney, and the court reporter, the plaintiff may also be present at the deposition. After the court reporter administers the oath, the plaintiff's attorney will ask standard questions, including education, licensing, and certification. The defendant's attorney will intercede as appropriate. The same questions may be asked several times over. One goal of a plaintiff's attorney is to develop a casual atmosphere to lower the guard of the defendant before asking the more relevant questions. A defendant is best served by not speculating about factual matters that may be found on the medical records, answering only the questions asked, and asking for clarification if unclear about the meaning of a question.

MALPRACTICE DEFENSE

Physicians having their medical competence publicly questioned may feel guilt, failure, anger, shame, isolation, depression, fatigue, denial, and physical symptoms.[25] If the suit is based on what the physician believes was a medical error, these feelings are intensified. After a medical error or a "near-miss," many physicians demonstrate symptoms similar to posttraumatic stress disorder.[26] Perhaps most damning to future practice is self-doubt to the extent that practice is affected.[27] Lawsuits recrudesce quiescent insecure feelings related to the event. It is important to be forthright about these feelings and to manage them, if for no other reason than to be able to participate fully and positively in the legal defense.

Defendants often rebut the claims that the standard of care was not met and that the alleged failure to meet the standard of care was a proximate cause to harm. To help support these arguments, expert witnesses, medical texts, journal articles, practice guidelines, and anesthesia records are often used.

Expert witnesses explain the relevant science and offer professional opinions about the standard of care and causation.[28] Although courts commonly accept the expertise of most expert witnesses, courts and juries do use qualifications to modulate the weight they give the testimony. An expert witness can support the idea that a different explanation or approach, especially one that other physicians would support, may meet a sufficient standard of care. The obligations of expert witnesses include that "…expert testimony by anesthesiologists should be readily available, objective and unbiased. To limit uninformed and possibly misleading testimony, experts should be qualified for their role and should follow a clear and consistent set of ethical guidelines" (Box 11-3).[29] The American Society of Anesthesiologists (ASA) has an Expert Witness

BOX 11-3 ***Guidelines for Expert Witness Qualifications and Testimony***

Expert Witness Qualifications

1. The physician (expert witness) should have a current, valid, and unrestricted license to practice medicine.
2. The physician should be board certified in anesthesiology or hold an equivalent specialist qualification.
3. The physician should have been actively involved in the clinical practice of anesthesiology at the time of the event and should have relevant clinical experience and knowledge in the clinical practice areas that are the subject of the proceeding.

Expert Witness Ethical Guidelines

1. The physician's review of the medical facts should be truthful, thorough, and impartial. The physician should not exclude any relevant information to create a view favoring either the plaintiff or the defendant.
2. The physician's testimony should reflect scientific evidence and accepted practice standards prevalent at the time of the event in question.
3. The physician should make a clear distinction between medical malpractice and adverse outcomes not necessarily related to negligent practice.
4. The physician should make every effort to assess whether the alleged substandard practice was causally related to the adverse outcome.
5. The physician's fee for expert testimony should relate to the time spent and in no circumstances should be contingent upon outcome of the claim.
6. The physician should be willing to submit such testimony for review.

From American Society of Anesthesiologists: Guidelines for expert witness qualifications and testimony. <https://www.asahq.org/For-Members/Standards-Guidelines-and-Statements.aspx>. *Amended 16.10.13.*

Testimony Review Program,[30,31] through which an ASA member may file a complaint about the expert testimony of another member. The ASA reserves the right to censure, suspend, or expel members who violate these ethical guidelines, with concomitant reporting to the National Practitioner Data Bank.

Practice guidelines are increasingly used as evidence of a standard of care.[32] Although authors of practice guidelines routinely state that guidelines are not intended to set a standard of care, it is highly likely that juries will be strongly influenced by them. Some authors have even proposed that practice guidelines should replace expert opinion.[32]

A detailed anesthesia record often strengthens the defense against a malpractice suit. A goal of documentation should be that uninvolved anesthesiologists should be able to understand interventions, the reasons for interventions, and the outcomes of interventions. Precise documentation and written explanations of thought processes lead to better understanding, which is important because malpractice claims often result from a failure or delay in diagnosing problems. For example, when using a nerve stimulator to administer regional anesthesia, an anesthesiologist may want to document the length and type of needle used, the nerve stimulator type and settings, the number of attempts, the strength and location of muscle contractions, whether paresthesia occurred, and how the paresthesia was managed.[33] Alternatively, consider the effect of documentation on the fairly routine event of decreased urine output. Assume that a patient had no urine output over a certain period in a previously functioning bladder catheter. The anesthesiologist treated the decreased urine output by the intravenous administration of crystalloid. The record would ideally indicate "zero" under urine output and indicate a bolus of fluid under fluid administration. Assume, then, that 30 minutes after the crystalloid administration, the patient still had no urine output. At this point, it would be reasonable for the anesthesiologist to write a note on the anesthesia record that discussed the decreased urine output, the initial interpretation and treatment of the decreased urine output, the results of that treatment, and the current interpretation (including differential diagnoses) and planned treatment of the decreased urine output. The anesthesia record should contain certain information (Box 11-4).[30,31]

Countersuits such as abuse of process, malicious prosecution, and defamation have been consistently rejected by the courts.[34] From a public policy perspective, the courts may be concerned that abuse of process countersuits that may limit the ability for plaintiffs to seek redress.

BOX 11-4 ***Guidelines for Documentation***

I. Preanesthesia evaluation
  a. Patient interview
    i. Patient and procedure identification
    ii. Medical history (medication, allergies, family history of anesthesia problems, pertinent review of systems)
    iii. Anesthetic history
    iv. Nil per os status
  b. Appropriate physical examination (including vital signs, documentation of airway status, and pertinent negatives)
  c. Review of objective diagnostic data (e.g., laboratory, electrocardiogram, radiographs) and medical records.
  d. Assignment of ASA physical status
  e. Medical consultations
  f. Formulation of the anesthetic plan, and discussion of the risks, benefits, and indications
  g. If appropriate, explanations of what may be considered atypical choices of the anesthesiologist or the patient
  h. Documentation of appropriate informed consent
  i. Appropriate premedication and prophylactic antibiotic administrations

II. Intraoperative or procedural anesthesia (time-based record of events)
  a. Immediate review before initiation of anesthetic procedures
    i. Patient reevaluation
    ii. Check of equipment, drugs, and gas supply
  b. Monitoring of the patient vital signs, oxygenation, and ventilation data and the use of any nonroutine monitors
  c. Doses of drugs and agents used, times and routes of administration, and any adverse reactions.
  d. The type and amounts of intravenous fluids used, including blood and blood products, and times of administration
  e. Estimated blood loss and urine output
  f. The technique(s) used and patient position(s).
  g. Intravenous/intravascular lines and airway devices that are inserted including technique for insertion, and location
  h. Unusual or unexpected events during the administration of anesthesia, including explanations of the recognition, treatment, and outcome of the event
  i. The status of the patient at the conclusion of anesthesia

III. Postanesthesia evaluation
  a. Evaluation and documentation by a practitioner who is qualified to administer anesthesia consistent with hospital policies and state licensure
  b. Patient evaluation on admission and discharge from the postanesthesia care unit
  c. A time-based record of vital signs and level of consciousness
  d. A time-based record of drugs administered, their dosage, and route of administration
  e. Type and amounts of intravenous fluids administered, including blood and blood products
  f. Any unusual events including postanesthesia or postprocedural complications
  g. Medical interventions
  h. Postanesthesia visit
    i. Must be completed within 48 hours from when the patient is moved from the designated recovery area
    ii. Must occur for surgery involving general anesthesia, regional anesthesia, or monitored anesthesia care
    iii. Elements of a postanesthesia evaluation
      (1) Respiratory function
      (2) Cardiovascular function
      (3) Mental status
      (4) Temperature
      (5) Pain
      (6) Nausea and vomiting
      (7) Postoperative hydration

Data from American Society of Anesthesiologists: Documentation of anesthesia care. *Amended 16.10.13 and Merchant R, Chartrand D, Dain S, et al: Guidelines to the practice of anesthesia, revised edition 2013.* Can J Anaesth *60:60-84, 2013.*
ASA, American Society of Anesthesiologists.

APOLOGY AND DISCLOSURE BY THE INDIVIDUAL

Although often inappropriately conflated, an apology, an expression of regret or sorrow, is distinct from a disclosure, which is a revelation about what happened. Apologies and disclosures may occur at the same time.

More than half the states have laws prohibiting the admission of apology or sympathy as evidence of wrongdoing.[25,35] Most apology laws permit the sympathetic statement "I am sorry this happened," but they do not protect sympathetic statements that include explanations ("I am sorry I made a mistake."). Fewer states have disclosure laws, which typically require notification of untoward events. Laws that require disclosure and protect sympathetic statements but do not protect explanations can lead to odd discussions, which may be perceived by patients as insincere.[35]

Some recommendations suggest apologizing for the effect on the patient but without admitting fault. Sometimes this approach may make sense, for example, if a previously acceptable antibiotic caused a rash. Not to take responsibility may seem stilted, however, such as when an anesthesiologist errantly administers an antibiotic to a patient who has a clearly documented allergy to that medication. In the name of good relationships with patients, apologies should not be limited to events that may result in a suit. For example, consider a 6-year-old girl who is wildly screaming and thrashing upon entering the operating room. Following a discussion with the father, who is present, a decision is made to hold her down and apply the mask. A follow-up discussion with the family may include not only an apology for the induction ("I am sorry that was so unpleasant for Becky and you.") but also an acknowledgment that the induction did not produce the desired reaction ("That is not our goal for induction. We would like it to be smoother." and "Going without sedation turned out to be a mistake."), as well as a recommendation for the future ("In the future, I would give oral sedation before going to the operating room."). Although this approach technically seems to admit wrongdoing, it is simply acknowledging what happened and educating the family for the future.

Although I believe that it is better to apologize, concerns exist about apologizing. The action for the physician, particularly if the apology is not readily accepted, may be painful. An apology may also embolden an otherwise unsure plaintiff,[36] and it may be construed as admission of error in court.

Whether one should admit fault for something that more likely may be medically negligent is more complicated. Consider, for example, repeated attempts to place an epidural needle in a patient who is anesthetized and has previously undergone back surgery. The anesthesiologist tries repeatedly without success and without incorporating other methods such as fluoroscopy. The patient awakens with a nerve injury consistent with wayward insertion of an epidural needle. Some experts would suggest that although it is acceptable to express sympathy for the pain and discomfort ("I am sorry for your discomfort."), it would be legally harmful to acknowledge fault and a desire to do it differently ("I am sorry about your injury. In retrospect, although I am not sure what happened, I suspect that it was the result of the needle placement. I should have used direct imaging of the back such as fluoroscopy.") Another opinion suggests that the second apology with the disclosure is better because it explains what happened, why it happened, and how it may be prevented in the future. Although this disclosure and apology approach admits culpability, it discloses only information that would be eventually discovered. I would suggest that the potential advantages gained by a genuine apology, delivered properly and under the appropriate circumstances, outweigh the potential harms of admitting culpability.

Full disclosure makes sense. From a wholly practical point of view, the patient will eventually learn what was withheld and will wonder, probably with animosity, why such information was not disclosed. Apology and disclosure for a potentially negligent event should be performed with thoughtful planning and support, and it is best practice to include in the discussion an expert in apology and disclosure. Disclosure may have three components. Upon realization of the problem, the goal is to give as much information as known, but not to speculate about what is not known, particularly about fault. Physicians should clarify the medical implications of the event, any necessary treatment or follow-up, and who will function as a contact for the patient regarding the event. The hospital's apology and disclosure expert often coordinates communication and follow-up. The next step should be to conduct a thorough investigation, with an eye toward minimizing problems in the future. Finally, the patient should be informed about what the investigation found, including the cause of the event and how such events will be prevented in the future.

LEGAL ASPECTS OF INFORMED CONSENT

Until the 1950s, physicians routinely obtained assent, the general agreement of the patient to have a procedure. The 1957 legal case *Salgo v Trustees of Leland Stanford Hospital* codified the modern concept of informed consent.[37] The judge clarified the difference between informed consent and assent by declaring, "A physician violates his duty to his patient and subjects himself to liability if he withholds any facts which are necessary to form [the] basis of an intelligent consent by the patient to a proposed treatment…."[37]

The goal of informed consent is to maximize the ability of the patient to make substantially autonomous informed decisions. The modifier "substantially" is used because it is unreasonable to expect a patient to be fully informed. The more appropriate goal of substantially informed consent acknowledges that consent may be sufficiently autonomous even if not completely informed. Modern informed consent has seven components.

COMPONENTS OF INFORMED CONSENT

Decision-Making Capacity

Decision-making capacity is defined as the ability to make a particular decision at a specific time. Evidence of

decision-making capacity includes the ability to understand medical problems, proposed treatments, alternatives, options to refuse treatment, foreseeable consequences of accepting or refusing proposed treatments and the ability to express a preference based on rational, internally consistent reasoning. Decision-making capacity is distinct from the legal concept of competency. Courts determine competency and often make a global determination of competency, thus declaring that a person is either competent or incompetent for all matters. Adults are presumed to be legally competent unless declared otherwise by a court. In contrast, anesthesiologists are responsible for assessing decision-making capacity and can make this determination only in specific situations.

Anesthesiologists should permit patients to make decisions to the extent of their abilities. For most patients, decision-making capacity is not in question. However, anesthesiologists must actively evaluate the decision-making capacity for patients whose decision-making capacity has been temporarily altered, who do not have legal decision-making authority, or who have preexisting limitations in decision-making capacity. Consider the patient who has received pain medication before giving informed consent. The level of impairment varies depending on the medication, the tolerance of the patient to the medication, and the decision to be made. Indeed, some patients, such as parturients, may have improved decision-making capacity when pain is decreased. To determine whether a patient has decision-making capacity for a specific decision, anesthesiologists need to balance the medication given and its expected effects with the ability of the patient to show evidence of rational reasoning and understanding. When a patient has temporarily lost decision-making capacity, such as when the patient is anesthetized, anesthesiologists should not implement nonemergency care until after the patient regains decision-making capacity and gives consent. However, in emergencies, anesthesiologists should proceed without obtaining informed consent, based on the presumption that patients want life-sustaining treatment unless they have declared otherwise.[38]

Voluntariness

Physicians should perform procedures only on competent patients who participate willingly. Anesthesiologists compromise voluntariness through manipulation and coercion. *Manipulation* involves the deliberate distortion or omission of information in an attempt to induce the patient to accept a treatment, such as downplaying or omitting information to influence a patient to make a specific decision. *Coercion* involves the use of a credible threat to ensure complicity.

Anesthesiologists also hinder voluntariness when they physically restrain or sedate patients who have sufficient decision-making capacity. Competent patients have the legal and moral right to refuse treatment even in life-threatening emergency situations. It is often difficult for physicians to accept that a patient wishes to make what a physician perceives to be a foolish decision. *Shine v Vega* illustrates the complexity of these situations.[39] In 1990, Shine, a competent adult, went to the hospital and received oxygen and an unspecified medication for an asthma attack. Vega, the emergency department attending physician, thought that the patient was very ill and recommended endotracheal intubation. Shine stated her long-standing refusal of endotracheal intubation (confirmed contemporaneously by her sister and father) and continued to receive oxygen by mask. Later, Shine's sister came into her room in the emergency department and noted that Shine was breathing more easily but was arguing with the staff. Shortly thereafter, Shine and her sister attempted to leave but were forcibly detained by a physician and security. Shine was placed in four-point restraints, and Vega, choosing to disregard Shine's objection, intubated the patient's trachea. On appeal, the Massachusetts Supreme Court stated that the competent patient has a right to refuse potentially life-sustaining treatment, even if her decision is considered unwise.

Another issue of voluntariness is when the interests of a woman and her fetus differ (see also Chapter 77). When a woman refuses a recommended diagnostic or therapeutic procedure, such as cesarean delivery for fetal indications, physicians may choose to respect the patient's autonomy and not proceed, to encourage the woman to seek health care elsewhere, or to seek judicial involvement. Before seeking judicial involvement, physicians should consider the social, physical, and psychological harms of violating individual liberty and the fallibility and limitations of medical knowledge. Physicians may want to seek judicial involvement only when they are highly confident that the recommended treatment will substantially reduce harm to the fetus, that the risks to the woman are relatively small, and that no comparably effective less-intrusive option exists.[40] Particularly relevant to anesthesiologists is the American College of Obstetricians and Gynecologists position on forced interventions: "Even the strongest evidence for fetal benefit would not be sufficient ethically to ever override a pregnant woman's decision to forgo fetal treatment."[40]

Disclosure

The goal of disclosure is to provide information relevant to the decision maker and the decision to be made. Skilled disclosure builds trust, helps patients make good decisions, and is a fundamental component of the obligation to respect a patient's autonomy.

Established in 1972, the *reasonable person standard* requires that the extent of the disclosure be based on what a reasonable person would consider material for choosing whether to undergo the proposed intervention.[41,42] Informed consent discussions should routinely include the specific risks and benefits of reasonable anesthetic options and monitoring techniques, as well as the presence and use of a fallback plan.[38] Anesthesiologists may want to inform patients of common but less severe risks, such as postoperative nausea and vomiting, and uncommon risks of more long-term significance, such as brain injury and death. If appropriate, the patient should be informed of the quality of the data, such as whether the information has questionable certainty. Anesthesiologists should also inform the patient whether an individual or an anesthesia care team will be providing anesthesia

services, and, if a team, the names and specific roles of the team members. To maintain good relations, patients should be told about other practical matters, such as the likely sequence of events upon arrival to the surgical unit, who will be with them at the various stages, what to expect for postoperative pain management, and realistic time estimates.

In general, courts have not actively required disclosure of professional experience, personal health matters, and disciplinary history, except when relevant to a patient's decision making.[43]

Lack of disclosure about experience is often not admitted into evidence in part because the experience of a physician is not a risk inherit to the procedure.[44] In case law, however, these matters are decided on the specific merits of the case. Therefore, it may be prudent to inform patients if the individual clinician or "system" is inexperienced in a particular situation. A dentist was found liable when she failed to disclose that she was using equipment novel to her.[45] The court ruled that a reasonable person would desire this information and could expect it to be offered unsolicited. In another case, the court interpreted the hospital environment (decreased staffing on the weekend) and other available opportunities (a nearby hospital with greater experience in a complex surgery) as relevant within the legal definition of disclosure and informed consent.[46]

Courts have at times expanded the duty of disclosure to include personal issues, such as alcohol abuse, prior license suspension, and a directly relevant medical problem.[47] Other courts have considered such data to be in the domain of hospital credentialing and not a relevant part of disclosures.[48] Courts have ruled that doctors do not need to disclose the chance of negligence.[49] Whether a clinician's history of success with a procedure must be disclosed depends on the particular situation.[50]

Exceptions to the obligation to disclose material information include patients who choose not to be informed,[51] emergencies in which a valid informed consent cannot be obtained, and situations of therapeutic privilege. Physicians employ therapeutic privilege when they choose to withhold information because they believe disclosure would cause the patient to become "so ill or emotionally distraught on disclosure as to foreclose a rational decision, or complicate or hinder treatment, or perhaps even pose psychological damage to the patient."[52] Therapeutic privilege has a narrow scope and should be used prudently. Simply because information is undesirable or upsetting to the patient does not mean that such information should be withheld. For example, it may be reasonable to invoke therapeutic privilege when discussing the risk of death with a patient who is acutely having a myocardial infarction; it would not be reasonable to do the same when discussing the risk of death with the parents of an infant.

Recommendation

Anesthesiologists should offer an opinion about which options are preferable and the advantages and disadvantages of each option. By explaining the value judgments and the quality of data supporting their opinions, anesthesiologists allow the patient not only to receive the benefit of their expertise but also to understand the reasons for the recommendations. Patients can then decide for themselves which choices best fit their priorities.

Understanding

Patients need to understand the risks and benefits of the proposed procedures, the recommendations made, and the reasons those recommendations were made. It is difficult to determine whether a patient fully understands the informed consent discussion, and, indeed, many patients may not. Pain and distress do not seem to compromise the ability to recall risks and do not preclude obtaining a legally sufficient informed consent.

Decision

After considering the information and the anesthesiologist's recommendation, the patient chooses an anesthetic technique. Patients vary in their preferences for participation in decision making, and anesthesiologists should be sensitive to these preferences. The desire to participate in the decision-making process may be a function of the individual, extent of illness, gender, age, and level of education. Anesthesiologists should attempt to tailor the extent of the patient's and the physician's decision making to the patient and the situation.[51]

When a patient refuses an anesthesiologist's recommendation or requests a technique that the anesthesiologist believes is inappropriate, the focus of the conversation moves from informed consent to informed refusal. Informed refusal requirements are similar to informed consent requirements in that the patient should be substantially well versed about the risks, benefits, and alternatives before declining. However, although it may be reasonable to permit a patient who agrees with a recommended or acceptable procedure to refuse extensive information (especially if the likelihood of harm is low), it is more difficult to honor a patient's preference to receive limited information when that patient desires a suboptimal approach.[53] The anesthesiologist may wish to provide additional information about the choice to be sure that the patient has all possible information. If, in fact, the patient chooses without sufficient information, the anesthesiologist has not fulfilled the obligation of informed refusal. Of course, a patient still may refuse to hear information. In either case, when a patient chooses a technique that the anesthesiologist believes is inappropriate, anesthesiologists are not obligated to provide care in nonemergency situations.

Autonomous Authorization

The informed consent process concludes with the patient's intentionally authorizing the anesthesiologist to perform a specific procedure. This authorization is the expression of the patient's self-determination and is the basis of informed consent.

DOCUMENTATION OF INFORMED CONSENT

Informed consent for anesthesia may be documented on the surgical consent form, by a handwritten note, or by a separate anesthesia consent form (see also Chapter 38).

The use of a surgical consent form is suboptimal because surgeons cannot capably discuss the risks of anesthesia, and therefore it is unclear what is being documented. Both handwritten notes and anesthesia consent forms may be acceptable. Handwritten notes detail specific discussions with patients. Writing a note for each patient, however, may be impractical and time consuming, and it may miss key aspects of informed consent. Anesthesia consent forms may act as a prompt for anesthesiologists to discuss key aspects of informed consent. Space for handwritten notes on the consent form will permit additional details to be documented. Having the patient sign the handwritten consent or the consent form gives an indication that some form of communication took place. However, because consent forms by themselves do not fulfill the legal requirement of informed consent, an informed consent discussion must still occur.

THEORIES OF SUIT IN INFORMED CONSENT

Negligence relating to the informed consent process may occur if the anesthesiologist provides a disclosure that is insufficient to allow a patient to make an informed decision and an injury subsequently occurs, even if the injury was foreseeable and took place in the absence of a treatment error.[38] To determine whether sufficient information was given, the courts look for materiality and causation. *Materiality* assesses whether the information given met the standard of care. If the disclosure did not meet the standard of care, then it may be considered a breach of duty. *Causation* then assesses whether sharing the omitted information would have caused the patient to choose a different option.[38] Most jurisdictions use the *objective standard,* which bases causation on whether a hypothetic reasonable person would have used the additional information to make a different decision. Some jurisdictions use the *subjective standard,* which is contingent on whether the specific patient involved would have made a different decision. A few jurisdictions combine the two standards by heeding the objective standard while considering factors specific to the patient and situation. Courts also consider how the information was given. The informed consent discussion should occur in a setting conducive to decision making, and it should give the patient a chance to ask questions and consider answers.

The disclosure process is not intended to be armor against medical malpractice liability if an adverse event happens. Informing a patient about a risk does not eliminate liability for its occurrence. *Liability* is based on negligence theory and depends mainly on whether the standard of care was met and whether the failure to meet the standard of care was a proximate cause of injury.

REFUSING TO PROVIDE CARE

Anesthesiologists may refuse to provide care when they ethically or morally disagree with the procedure or situation, such as elective termination of pregnancy. Although physicians have an obligation to provide care altruistically, this requisite does not always oblige physicians to subjugate their morals. Furthermore, society and medicine have a fundamental interest in preserving the moral fabric of individual physicians. Anesthesiologists should perform care that violates their conscience and possibly weakens their moral constitution only in critical, presumably life-or-death, circumstances. More practically, an anesthesiologist who ethically or morally disagrees with a patient's choice will have difficulty in providing the care requested. In a nonemergency situation, such an anesthesiologist should withdraw from patient care. The anesthesiologist may then be obligated to make a reasonable effort to find a competent and willing replacement.

Physicians may also ethically refuse to provide care if they believe the patient's choice is too inappropriate or is likely to result in harm. Determining that an anesthetic choice is inappropriate is difficult and should not be invoked lightly or out of convenience. The patient's choice and the resultant risks must be sufficiently extreme that they, say, elicit a similar response from at least several other anesthesiologists. In addition, anesthesiologists may refuse to provide care if they do not feel qualified to provide the needed care.

LEGAL ASPECTS OF END-OF-LIFE CARE

Acknowledgment of patients' rights to refuse life-sustaining treatment began in the midtwentieth century with the rise of civil liberties, individual rights, and respect for the importance of self-determination (see Chapters 75 and 101). In 1974, the American Medical Association asserted the following: "The purpose of cardiopulmonary resuscitation is the prevention of sudden unexpected death. Cardiopulmonary resuscitation is not indicated in cases of terminal irreversible illness where death is not unexpected."[54] Policies acknowledging the need to permit patients to limit resuscitation during terminal illness were prominently published several years later.

Progression of the rights of the individual to refuse potentially life-sustaining care may be seen through case law. The 1976 case of Karen Ann Quinlan first established the right to refuse potentially life-sustaining care. In *Quinlan,*[55] the courts upheld the legality of disconnecting the ventilator from a patient thought to be ventilator dependent and in a permanent vegetative state.[55] The court based this decision on the general constitutional right to privacy. In addition, the court determined that a surrogate had the right to decline medical treatment for an incompetent patient if the surrogate concluded that the patient would have preferred limited care. Quinlan's father thus discontinued his daughter's mechanical ventilation. Quinlan lived for nearly a decade, sustained by nasogastric feeding.

The right of a competent person to refuse potentially life-sustaining care was established in the 1984 case of *Bartling v Superior Court*.[56] Bartling was a competent adult patient with an incurable disease who for 6 months received medical therapy against his clear wishes. After a pneumothorax from a needle biopsy, Bartling became ventilator dependent. He subsequently received a tracheotomy to facilitate weaning attempts. During this ordeal, Bartling made clear his desire not to receive continued therapy, and at one point he declared: "While I have no wish to die, I find intolerable the living conditions forced

upon me by...."[56] Although Bartling died before his case could be adjudicated, the appellate court issued an opinion based on the constitutional right of privacy that supported the right of a competent patient to refuse medical treatment.

The 1990 case of *Cruzan v Director, Missouri Department of Health* concerned a young woman involved in an automobile accident that left her incapable of expressing a preference.[57] Several years before the accident, Cruzan had expressed to a friend in a somewhat serious conversation a desire not to live in a state of diminished capacity. In seeking to withdraw potentially life-sustaining treatment, the Cruzan family used this conversation as evidence that Cruzan would have wanted therapy stopped. The Supreme Court of Missouri held that Cruzan's informal statements did not meet Missouri's evidentiary standard of "clear and convincing evidence" of a patient's wish to terminate potentially life-sustaining care and thus mandated continuation of treatment. The case was appealed to the U.S. Supreme Court.[58] Unlike *Quinlan* and *Bartling*, the Supreme Court grounded the right of a competent patient to refuse treatment in the liberty interest of the Fourteenth Amendment, which states, "No State shall make or enforce any law which shall abridge the privileges or immunities of citizens of the United States; nor shall any State deprive any person of life, liberty or property...." The decision also upheld the rights of states to determine the standards for the level of certainty required, thus permitting Missouri to use the "clear and convincing evidence" standard.

Competent patients have a virtually unlimited right to refuse potentially life-sustaining medical treatment.[59] For the incompetent patient, three hierarchical levels of judgment direct the decision-making process for end-of-life care. The once-competent patient's previously expressed preferences for end-of-life care should be followed as best as possible. When the patient's declared preferences are not known, *substituted judgment,* which is the use of the surrogate's intimate knowledge of the patient's attitudes and beliefs to determine what the patient would have chosen, may be used to direct care. Although these are two distinct categories, both levels require the surrogate to know the patient sufficiently to choose or interpret the patient's preferences appropriately. These standards put significant burdens on decision makers who may have legitimate doubts about the appropriateness of their decisions. When a surrogate has to make decisions for a patient who has never been competent, such as a young child or a mentally disabled adult, substituted judgment is impossible, and the surrogate must rely on the best interest standard. The *best interest standard* requires the surrogate to make decisions based on the surrogate's view of what is best for the patient.

ADVANCE CARE PLANNING

Advance care planning permits a patient to declare preferences for medical treatment if he or she becomes incapacitated. Advance directives are designed to minimize the likelihood of undesired overtreatment and undertreatment. Partially as a result of *Cruzan*, the Patient Self-Determination Act (PSDA) was introduced in 1991 to increase the use of advance directives.[60] The PSDA requires health care institutions, such as hospitals, nursing homes, and hospice programs, to notify individuals about their rights regarding advance directives. Three types of advance directives are living wills, health care proxies (also known as durable power of attorney for health care decisions), and physician orders for life-sustaining treatment (POLST). Living wills allow patients to declare the extent of desirable interventions, but they may not be able directly to address the subtle differences that characterize clinical situations. The difficulty of applying living wills to clinical situations led some patients to prefer the greater flexibility provided by the health care proxy, in which the surrogate decision maker can consider the specific details when making clinical decisions. Health care proxies permit patients to designate surrogate decision makers (including those who are not family members) to make decisions for them should they become unable to make such decisions for themselves. If the patient does not assign surrogacy, most jurisdictions have a hierarchy for assigning surrogacy, but this approach often excludes domestic partners and other individuals the patient would prefer to be the decision makers.[61]

Surrogacy is not always effective, particularly for patients who do not make their preferences clearly known to the surrogate before losing their decision-making capacity.[62] Given the strengths and weaknesses of each approach, the best option may be preparation of a designated proxy with some written form of preferences, which can then be followed by a POLST when appropriate.

POLST (sometimes known as MOLST or COLST with "medical" or "clinical" replacing "physician" or sometimes with the name of the state as the first word) supplements advance directives by focusing on advance planning for the seriously ill. Similar to other advance directives, POLST forms present options regarding cardiopulmonary resuscitation, medical interventions, and artificial nutrition. Traditional advance directives require frequent reinterpretation and must be reestablished in every treatment venue. In contrast, POLST is a medical order signed by a physician, and it remains in force whether the patient is at home, in the hospital, or at a long-term care facility. POLST is designed to increase the likelihood of compliance with the patient's wishes for life-sustaining treatment. This may be particularly important in areas that require specific authorization to refuse artificial nutrition.[63]

Advance care planning is an ongoing process. Competent patients may obviously modify their previously declared preferences. Demented patients, who previously made an informed choice to limit certain therapy, may express an interest in receiving that therapy.[64] If patients have evidence of decision-making capacity, such as being able to provide internally coherent reasoning, their wishes to receive therapy should be honored. However, the process of resolving this situation in a patient without decision-making capacity and with almost no likelihood of regaining decision-making capacity is more complex. In this situation, it is better to base judgment on therapy from multiple sources, including significant others, the type of documentation, and the best interests standard.

REFUSAL OF CARDIOPULMONARY RESUSCITATION

The right of a patient to reject unwanted therapy in the operating room is well accepted (see also Chapter 108). Before the patient proceeds to the operating room, perioperative do-not-resuscitate orders should be reevaluated in light of the surgical procedures, the anesthetic options, and the patient's overall goals. Anesthesiologists are then prepared to clarify and document the desired resuscitation status in the operating room, often by using the goal-directed approach.[65] The process of obtaining and documenting perioperative refusal of resuscitation should comply with hospital policy and jurisdictional law. Written documentation may include the patient's diagnosis and prognosis, the characteristics of perioperative resuscitation, likely outcomes, and the patient's reasoning. If a surrogate is making the decision, the record should note the surrogate's relationship with the patient and the basis of the surrogate's decision.

Refusal of resuscitation in an emergency situation without time to clarify a patient's wishes is inherently different. The traditional bias of providing treatment in the absence of a clear decision not to treat still holds for the anesthesiologist in the emergency situation. The situation can always be clarified later, and the patient can be withdrawn from the ventilator if it is determined that the patient would have preferred not to receive the interventions. In short, the "inconvenience" of a short period of mechanical ventilation is worth the opportunity to ascertain the patient's desires correctly.

THE DEMAND FOR LIFE-SUSTAINING THERAPIES

Patients or families may demand therapies that clinicians believe are inadvisable because of burden to the patient, cost, or uncertain benefit. When these cases become irreconcilable, the cases may go to court, often not to determine what therapy should be given but to determine who should be the decision maker for a noncompetent person. For example, Helga Wanglie was an 86-year-old patient in a persistent vegetative state who was receiving mechanical ventilation. The medical center believed that further therapy was inadvisable for Mrs. Wanglie and wanted to withdraw mechanical ventilation. When Mr. Wanglie refused the medical center's request to stop mechanical ventilation, the medical center sought appointment of an independent guardian to supplant Mr. Wanglie as her guardian. The Court declared that Mr. Wanglie was best able to be Mrs. Wanglie's surrogate.[66,67]

In the 1995 case of Gilgunn,[68] a jury supported a unilateral refusal of potentially life-sustaining care. Catherine Gilgunn had multiple medical problems and severe brain damage, and she was in a coma. Her daughter Joan, representing the family, requested that everything be done. The Optimum Care Committee of the hospital agreed with the physicians that providing cardiopulmonary resuscitation was not a genuine therapeutic option. The legal division approved the do-not-resuscitate order because they believed that the physicians were acting in the patient's best interest. Gilgunn was disconnected from ventilator support and died a few days later. The jury supported the actions of the physician and hospital to impose a unilateral do-not-resuscitate order. There was no appeal.

Physicians and hospitals have been very successful in defending lawsuits about unilateral refusal of potentially life-sustaining care.[69,70] Nonetheless, unilateral physicians' declarations are insufficiently respectful of patients' autonomy. Evidence indicates that negotiation nearly always resolves these problems without the need to resort to unilateral action. However, being able to resolve differences of opinions about applying treatments with low likelihoods of success is important. Policies for resolution based on a procedural approach, in which the process for resolving conflict is described, are more practical. Good policies are public, reflect the moral values of the community, and include processes for identifying stake holders, for initiating and conducting the policy, for commencing appellate mechanisms, and for determining relevant information.[71]

In a different approach, the Texas Advance Directives Act permits physicians to unilaterally withhold or withdraw treatments they regard as "futile," provided the physicians follow certain guidelines, including obtaining the agreement of the hospital ethics committee.[72] Other states are considering this approach.[73] On the other end of the spectrum, some jurisdictions have passed laws requiring treatment against the clinician's wishes until the patient can be transferred to a willing clinician or hospital or until judicial review.[74,75] Another approach is seen in the Consent and Capacity Board in Ontario, Canada. This is an independent, government-based tribunal for resolution of consent and capacity issues. Although most cases involve involuntary commitment to a psychiatric facility, this board has been involved in cases regarding end-of-life care. Other areas are exploring this approach.

PHYSICIAN-ASSISTED SUICIDE

Physician-assisted suicide is the act by a physician of prescribing lethal quantities of medication for self-administration by the patient (see also Chapter 10). In the United States, courts have held that no constitutional right to physician-assisted suicide exists.[76,77] The courts have followed common ethical opinion in drawing a distinction between the positive right to demand an action (e.g., physician-assisted suicide) and the more powerful negative right to be free of bodily invasion. Although no constitutional right to assisted suicide exists, individual states may choose to legalize or prohibit this act.[78] In 1997, the State of Oregon legalized the Oregon Death With Dignity Act, which permitted terminally ill patients to receive prescriptions in lethal quantities for the purpose of self-administration. This law does not permit any other forms of physician-related aid-in-dying, such as having another person administer the medication. From 1998 through 2011, prescriptions were written for 935 patients, and 596 patients used them. The most common diseases in patients who chose to ingest a lethal dose of medication were malignant neoplasms (81% of patients), amyotrophic lateral sclerosis (7% of patients), and chronic lower respiratory tract diseases (4% of patients).[79] The number of prescriptions written and used annually has

slowly and steadily increased since 1998.[79] The financial and educational status of patients does not seem to play a role in the request for physician-assisted suicide.

OTHER LEGAL ASPECTS OF ANESTHESIOLOGY

CARE OF THE JEHOVAH'S WITNESS

Jehovah's Witnesses interpret Biblical scripture to prohibit taking in blood because it holds the "life force," and anyone who partakes of it shall be "cut off" from eternal life after death.[80] Jehovah's Witnesses have different interpretations about the prohibition of blood transfusions, and anesthesiologists must actively clarify what the patient considers acceptable (see also Chapter 63). Documenting acceptable interventions crystallizes the patient's desires and provides legal documentation for the anesthesiologist. Anesthesiologists must be certain that they are capable of fulfilling the patient's requests; otherwise, they should not agree to provide anesthesia. Indeed, the anesthesiologist and surgeon should provide nonemergency care to the patient only if all parties can agree on the approach to blood management.

Case law strongly supports the right of the adult patient to refuse blood products. One case illustrates a different consideration in the care of Jehovah's Witnesses. Mary Stinemetz, a practicing Jehovah's Witness, refused to have a liver transplant in Kansas because she wanted to go to Nebraska to receive a "bloodless transplant." An appeals court ruled that the state had violated her constitutional right when they denied Medicaid coverage for the out-of-state transplant.[81]

LAW REGARDING PEDIATRIC PATIENTS

For the most part, parents or other surrogate decision makers of children make health care decisions for minors (in general, children <18 years of age) (see also Chapters 92 and 93). However, the participation of children should increase as they grow older, and it depends on both the patient's maturity and the consequences of the decision. Informed assent acknowledges that although most pediatric patients cannot legally consent to medical care, they should share in decision making to the extent that their development permits.

Some minors are permitted to consent for themselves.[82] *Emancipated minors* are patients less than 18 years old who have been given the global right to make their own health care decisions. This status varies by state but is generally awarded to patients who are married, parents, in the military, and economically independent, and it may include patients who are pregnant. The *mature minor doctrine* holds that minors who have decision-making capacity are legally and ethically capable of giving informed consent in specific situations as determined by a court. Although particulars vary, the mature minor doctrine in general requires patients to be at least 14 years old, and it tends to permit decisions of lesser risk. The courts will balance the maturity and decision-making capacity of the minor with the risks associated with honoring the minor's wish. As minors near the age of majority, the likelihood increases that the court will support the right of minors to determine therapy. For example, in a case in 2007 that seemed be on the margin, a judge ruled that a 14-year-old practicing Jehovah's Witness would be permitted to refuse transfusion therapy during treatment for a type of cancer that had a 70% 5-year survival rate. The patient subsequently died.[83]

Even though pediatric patients who are pregnant may be considered emancipated, many states require some form of parental involvement such as parental consent or notification before an elective abortion in an adolescent (see also Chapter 77). If a state requires parental involvement, the ability of the minor to circumvent this regulation by seeking relief from a judge, known as judicial bypass, must be available. Requirements and enforcement of statutes vary from state to state. The need for parental involvement in minors who have abortions is not always legally straightforward, and it may be best to consult with hospital counsel in determining such issues.[84,85]

Parents and medical personnel may disagree about what is in the best interest of the child. Based on the legal doctrine of *parens patriae,* which is the government's obligation to protect the interests of incompetent patients, parents are not permitted to make decisions that represent grossly inappropriate overtreatment or undertreatment.[86,87] One way to decide what is in the best interest of the child is to define what choices fall outside of the range of acceptable decision making. The extent to which one intervenes between a patient and the surrogate's decision depends primarily on how harmful the decision is to the patient. Criteria to make this determination include the amount of harm to the child by the intervention or its absence, the likelihood of success, and the overall risk-to-benefit ratio.[87] Charging a parent with not acting in the child's best interests has significant social, fiscal, and familial ramifications. If, however, after exhausting other options the anesthesiologist believes the parent has chosen unacceptable treatment, the anesthesiologist should report the situation to proper child welfare authorities for possible legal action.

Anesthesiologists caring for a child of a Jehovah's Witness should inform the patient and family that attempts will be made to limit the need for transfusion therapy and to abide by their transfusion preferences, but that in a life-threatening situation the anesthesiologist will seek a court order authorizing the administration of potentially life-sustaining blood. When the likelihood of requiring blood is high or the local judiciary is not that familiar with case law for Jehovah's Witnesses, the anesthesiologist may choose to obtain the court order before the operation. In crisis situations in which no court order exists, anesthesiologists should initiate emergency transfusion therapy before obtaining a court order. As a child becomes older, the courts become less likely to intervene, and they often grant the emerging adolescent more decision-making latitude. In elective procedures that may be safely delayed, the patient and family may also consider postponing the procedure until the child is of sufficient age and maturity to decide about transfusion therapy (see also Chapter 61).

SUPERVISION AND PROFESSIONAL ASSOCIATIONS

Attending physicians may be sued because of residents' actions. The question of what is considered acceptable resident supervision is affected by local policies and national guidelines, but again, in any individual case, a jury often determines the standard of care. Specific guidelines about what trainees are permitted and not permitted to do may provide some protection for the attending physician if the trainee deviates from these guidelines (see also Chapter 9). In addition, residents are being named in lawsuits with increasing frequency. As a general rule, a resident is held to the same standard of care as a practicing attending physician in that specialty.[88]

Under the doctrine of *respondeat superior* and the theory of *vicarious liability,* anesthesiologists are responsible for negligent acts made within the scope of defined duties by certified registered nurse anesthetists (CRNAs).[89] The fundamental issue of vicarious liability is whether the anesthesiologist is controlling the activities of the CRNA. Although the question of vicarious liability may depend on who remunerates the CRNA, this tends to be an ineffective defense because in these situations anesthesiologists tend to have full authority to direct CRNAs medically. The scope of defined duties and the determination whether adequate supervision occurred are affected by societal expectations, medical customs, history, practice, manuals, agreements, actions, expert analysis, and written documentation, but they are ultimately determined by a jury in any individual case. For example, in one case, a CRNA did not promptly summon the anesthesiologist for help in managing fatal postoperative laryngospasm and bronchospasm.[90] The anesthesiologist was found vicariously liable for negligence, in part because of the lack of clear understanding between the professional group and the CRNA about when the anesthesiologist should be called.

Many controlling authorities (e.g., state statutes or hospital bylaws) require physicians to participate in certain aspects of anesthesia care when they supervise CRNAs. It is also the responsibility of the professional association to set forth the expectations in a manner that is consistent with law and regulations. Accepting a standard below the medical community's published standards (e.g., ASA guidelines) risks liability.

Federal regulations for accreditation of hospital and ambulatory surgery facilities require that a CRNA must be supervised by the physician performing the procedure or by an immediately available anesthesiologist.[91,92] State governors may opt out of this supervision requirement if they deem doing so to be in the best interests of their citizens. For the opt-out approach to have practical consequences, however, state laws must also not require supervision. Pending appeals, 17 states have opted out of the federal rule requiring physician supervision. Health care facilities within states that have opted out may still require supervision.

Anesthesiology professional associations may be held libel if they do not ensure that members are competent and that appropriate policies are followed.[93] Many agreements between professional associations and hospitals require service that complies with governmental and professional standards.[93] Obligations of professional associations may extend to letters of reference. For instance, an anesthesiologist was terminated with cause secondary to abuse of meperidine (Demerol).[94] When the anesthesiologist went to a locum tenens company, letters of reference from shareholders of the previous professional association did not mention the abuse or that the anesthesiologist was fired with cause. Subsequent negligent care by this anesthesiologist caused severe brain damage to a patient. The court held the previous professional association liable for part of the financial award.

Professional associations are responsible for addressing impairment of physicians. An *impaired physician* is one who is unable to perform professional or personal responsibilities. Physicians impaired through alcohol and other addictive disorders are considered to have chronic medical illnesses. The Americans with Disability Act, written in 1990 and amended significantly in 2008, forbids discrimination against individuals who are in recovery.[95] Treatment records of impaired physicians are confidential.

LEGAL ISSUES IN PAIN MANAGEMENT

Inadequate pain management is a health problem (see also Chapters 64 and 98). Part of the problem may stem from the tension inherent in unclear regulations, regulatory scrutiny, and criminal investigation and prosecution by state medical boards and drug enforcement agencies.[96,97] For example, the Drug Enforcement Administration's ability to monitor prescriptions for controlled substances electronically gives this agency access to physicians' prescription histories. Physicians are concerned that knowledge of prescribing practices, divorced from patient-specific context, will lead to misunderstandings and possible investigations. Physicians' concern about being investigated may affect the doses, quantities, number of refills, or even type of drug used in the care of patients with chronic pain.[97] The Drug Enforcement Agency suggested that this issue should have no effect and emphasized that only 0.06% of all physicians had investigations initiated, 0.05% of all physicians had actions taken against them, and 0.01% of all physicians were arrested.[98,99] However, 0.06% may be fallaciously low because that percentage is out of all practicing physicians. A more relevant percentage would be based on a population comprising only physicians who prescribe narcotics for pain control and thus are at risk for investigation. Many of the physicians investigated did have actions taken against them.

The *Gonzales v Oregon* decision should comfort physicians because it limits the effects of the Drug Enforcement Agency on physicians.[100] *Gonzales v Oregon* prohibited the U.S. Attorney General from forbidding physicians in Oregon to prescribe schedule 2 drugs for terminally ill patients to use to commit suicide. The point of the case

TABLE 11-4 **DATA BANKS**

Data Bank	Purpose	Information	Who Can Query
National Practitioner Data Bank (NDPB)[105]	"To restrict the ability of incompetent physicians to move from State to State without disclosure or discovery of the physician's previous damaging or incompetent performance"[105]	Medical malpractice payments Adverse actions: licensing, clinical privileges, professional society, Medicare and Medicaid exclusions and U.S. Drug Enforcement Administration actions	Hospitals Health care entities with review process Professional societies State licensing boards Plaintiffs and their attorneys Self-query
Healthcare Integrity and Protection Data Bank (HIPDB)[106]	To stop fraud and abuse in health insurance and health care delivery and to promote quality care	Licensing and certification Civil judgments Criminal convictions Exclusions from federal or state health programs	Government agencies Health plans Self-query Researchers
Federation of State Medical Boards (FSMB)[107]	"[P]romoting excellence in medical practice, licensure, and regulation as the national resource and voice on behalf of state medical boards in their protection of the public"	Recording of actions by state medical boards against physicians	Medical boards Public

is that the U.S. Congress can set national drug prescribing rules through the Controlled Substances Act (CSA), but Congress cannot affect the ability of states to set medical practice standards. Although several reasons existed, the primary reason was that the CSA does not regulate the practice of medicine. The practice of medicine is regulated by the state.

Physicians have been held liable for inadequate pain control. For example, an 85-year-old man was admitted to a medical center for 5 days in 1998 before his death several days later.[101] He received inadequate pain control during his hospital stay. Although a medical malpractice suit was dismissed and the state medical board did not pursue any action against the physician, the family won a civil suit against the physician under the California's Elder Abuse and Adult Civil Protection Act.

ELECTRONIC MEDIA

Physicians may violate privacy while "blogging" or otherwise discussing clinical practice on various forms of social media. Using electronic media while providing patient care is a distraction and increases liability because the times and extent of electronic media use can be precisely defined. Even if no event occurs during that time, it sets the tone for the quality of care that increases the likelihood of a successful lawsuit. It was reported that in one settled case, a surgeon made numerous personal cell phone calls during an operation that resulted in permanent harm to the patient.[102]

Heightened societal awareness of poorly timed electronic media use (e.g., while driving) has increased patients' concerns about use during patient care. A 2010 survey of perfusionists found that more than 50% had texted or used a cell phone during cardiopulmonary bypass, and more than 20% had accessed email.[103] One of the problems is the routine and unthinking nature with which we consult electronic media. Many institutions are implementing policies defining appropriate use of electronic media, to increase awareness of the problem, clarify expectations, and provide legal protection.

ELECTRONIC RECORDS

The 2009 Health Information Technology for Economic and Clinical Health Act (HITECH)[2] authorized a nationwide technology infrastructure to improve health care quality and care coordination. It established economic incentives tied to "meaningful use" of electronic health records.[104] HITECH also required federal notification for breaches of privacy of health care information. Since 2010, more than 500 breaches have occurred. More than 60% involved theft or loss of information, typically on electronic devices such as laptop computer.[2] To improve transparency, patients may obtain an audit of the use of their electronic records.

DATA BANKS

Federal data banks are designed to improve health care by tracking performance and by flagging suspect health care practitioners and entities (Table 11-4).[105-107] By way of context, from 2001 to 2011, the National Practitioner Data Bank recorded 134,862 malpractice payments and 58,285 adverse actions. Reports of malpractice payments have steadily decreased from nearly 16,000 in 2001 to approximately 8500 in 2011. Adverse actions have remained consistent during this period. Adverse actions include clinical privilege actions and society membership actions.[99] Concerns about adverse actions prompted proposal of a bill "to prohibit health care entities from reporting certain professional review actions against health care professionals before adequate notice and hearing procedures are afforded to such professionals…."[108]

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Chapter 12

Anesthesia Business Models

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Key Points

- Anesthesia practices have evolved over the past decade, in part due to changes in the roles anesthesiologists play in the management of both inpatients and outpatients and in part due to dramatic changes in the relationship between anesthesia practices, other providers, and health care systems.
- At the same time, models of health care and the clinical scope of practice for anesthesiologists have expanded dramatically. As a result, anesthesia practices have had to respond to the changing health care environment, gain new skills, and tailor their practices to ensure continued success.
- To retain a meaningful role in perioperative care, pain management, and critical care medicine, anesthesia practices must expand their clinical perspective and in doing so document clinical and economic value to patients, health systems, and payers.
- To ensure the long-term future of the practice, anesthesiologists must deliver care that is safe, of high quality, and efficient and provide metrics to document outcomes of care. Public reporting of outcomes associated with all aspects of care is now expected, particularly in the United States.
- Anesthesia business practices also have to be revised to address the changing needs of patients, other providers, and health care systems to maintain a meaningful role in health care delivery.
- Anesthesia practices have adopted a variety of business models to address the needs of the local environment, the relationship between the anesthesiologists and the community, and the roles played by anesthesiologists in perioperative management.
- At the same time, particularly in the United States, consolidation of anesthesia practices through acquisition and other business relationships has created large national and regional practices that contract with health care systems to provide clinical care and practice management services. In some cases, these large groups include other specialists, such as hospitalists, emergency department physicians, and interdisciplinary critical care providers. This multispecialty model allows the groups to coordinate care and offer broad services to hospitals and health systems.
- While there is no single business model that is appropriate for every anesthesia practice, the key components of any model must ensure a collaborative business relationship and financial support from the health systems.
- For academic programs, the traditional business model that relies on clinical income to support the other missions, including education and research is no longer viable. Alternative sources of revenue are required to ensure the scientific underpinnings of the specialty while partnering with the clinical enterprise to optimize patient care.

This chapter provides an overview of the essential business, management, and staffing models utilized in anesthesia practices in a variety of settings, including urban and rural practices and community-based and academic programs. While no single model is appropriate for every practice setting, whatever approach is used must not only address the financial viability of the practice but must also ensure that the anesthesiologists are valued and collaborative partners with other providers and the health system and that they ensure the delivery of safe, high-quality, and efficient care. At the same time, while this discussion identifies some of the current approaches to practice management, it is important to acknowledge the dynamic health care environment, both internationally and in the United States. Anesthesiologists have been leaders in patient safety and quality and have expanded their roles to include preoperative management, extended postoperative care, intensive care medicine, pain medicine, and in some countries sleep medicine and palliative care. In addition, a number of new opportunities have presented themselves as a result of changes in the delivery systems and the role of other providers in perioperative care. Implementing some of these new practice opportunities in perioperative management, such as the perioperative surgical home and other initiatives, will require considerable creativity and flexibility. The traditional business models no longer apply. New approaches to clinical care, staffing, and compensation must be implemented to achieve the goals of both patients and health systems. While some of these new opportunities are briefly discussed in this chapter, they are more comprehensively described in Chapter 3. This discussion will identify some of the critical business practices and ways to optimize the financial performance of anesthesia departments in the changing health care environment. Although the financial support for education and research is beyond the scope of this chapter, the discussion here will identify some ways in which the business models may need to be modified to address the needs of the academic departments and ensure the future scientific foundation for the specialty.

It is essential that each practice build a business model that is financially viable and supports clinical needs within the health care system. At the same time, however, business practices and staffing models must be designed to optimize delivery of high-quality, safe care to the patient populations being served. Each practice must determine the model that most effectively and efficiently ensures the availability of well-trained anesthesia providers to its population. In addition, anesthesia providers across the spectrum of subspecialties, critical care anesthesiologists, and pain medicine physicians are required to support the needs of the health system or facility in which the practice works. The expanding role for anesthesiologists in preoperative management, pain medicine, critical care medicine, and ambulatory care provides new opportunities and requires different approaches to practice management (see Chapter 1).

Some of the business practices described in this chapter apply to every practice setting whereas others are appropriate for select practices, such as in large urban or academic settings, or both. In addition, although this chapter defines some of the current business models, the dynamic health care environment mandates flexibility and entrepreneurship to take advantage of new technologies, such as telemedicine, and to manage the evolving needs of an increasingly complex patient population. Some new opportunities related to the perioperative surgical home (PSH) and other initiatives beyond traditional perioperative management by anesthesiologists will also have an effect on the business models for anesthesia practices. Although these opportunities are discussed briefly in this chapter, they are more comprehensively described in Chapter 3.

PRACTICE MODELS

GENERAL MODELS OF ANESTHESIA PRACTICE

The models of anesthesia practice vary considerably within the United States and throughout the world. This variability is true for practices in all settings, including private practice, military medicine, and government-supported hospitals (e.g., Veterans Administration and city-county hospitals). In those countries with primarily publicly supported health care systems, physicians are often employed by the government directly or through a government-supported health authority, and care is provided within public hospitals, including military institutions. In some countries, there is a parallel private health care system and physicians may work outside the government system, providing care in the private sector, often while also spending the majority of the clinical time in the public sector, "moonlighting" in the private institutions to supplement income. In these parallel structures, the anesthesiologists and other physician practices are salaried within the government system and bill personally for care provided to patients in the private system. For many of these practice options, the business models are relatively straightforward. The government or health authority compensates the anesthesia providers based either on an annual budget or contract or on the basis of some assessment of work units. Compensation for care delivered outside of the public sector is often self-paid on a fee-for-service basis because in many cases there are limited health insurance options for patients receiving care in the private sector. Recently, in many countries, private insurance options have become more common, though the payment for services varies considerably based on the insurance options, costs, and other considerations.

In the rapidly changing health care environment throughout the world, anesthesia practices are evolving and identifying new ways of caring for patients in the operating room and other inpatient and ambulatory settings. While many of these changes are now being implemented within the United States, many of the models of care being evaluated in the United States are based on delivery and financing models used in other countries. The changes in the financing of health care, payment models for anesthesia services, and the expanding role of anesthesia services outside of the traditional operating room environment require new models of practice and

new skills to ensure that the practice is financially viable and that patient care is optimized.

EUROPEAN BUSINESS MODELS

The business models for anesthesia practices in Europe provide interesting examples of the differences in health systems and their impact on anesthesiologists throughout the world. There are various models of practice throughout the continent. These models are largely dependent on the distribution of governmental health care systems or private practices within each country. For example, in France more than 60% of anesthesia services are provided by private practice, whereas in Scandinavia and the United Kingdom more than 90% is provided within governmental health care systems.

In Germany and Sweden, payment for perioperative care is typically based on disease-related groups, that is, a single payment for all in-hospital care costs related to a specific disorder or surgical or diagnostic procedure. This payment includes costs for anesthesia and postoperative care. The disease-related group payment is made to the primary care provider (e.g., gastric surgery department for a bariatric surgery procedure) and is followed by internal cost allocation, which can be made in several ways. As a result, the business models used for internal cost allocation to anesthesia departments varies between countries and can vary within a country.

In Germany, one third of anesthesia departments receive internal cost allocation payments based on a median national anesthesia cost estimation that is related to each specific disease-related group. The remaining two thirds of anesthesia departments in Germany generate their internal reimbursement based on a combined flat rate payment that includes payment for case load and time—that is, a combined formula with a flat rate for preanesthesia and postanesthesia visits, staffing, and maintenance, with additional payment for cases that are complex and that require intraoperative and postoperative time. While each of these payment distribution models is unique to the environment in which they have been implemented, they provide some important lessons, particularly to practices in the United States which are likely to have an increasing proportion of payments for clinical services be bundled.

In the United Kingdom, more than 90% of anesthesia departments are primarily funded through the National Health Service. Each department is provided an annual budget for staffing and maintenance of the department's infrastructure, whereas surgery departments receive additional funds to cover surgical services, including drugs, operating room equipment, and postoperative care. To the extent that the anesthesiologists broaden their clinical role to optimize perioperative management, they may (or may not) be successful in generating additional payment for these expanded services. Similar models are used in other countries that have national health programs, though some countries have a parallel private system with a different, usually a fee-for-service model of payment.

In France, government-based anesthesia services are reimbursed based on cost estimates made jointly by the Ministry of Health and associations of physicians. These estimates are based on a flat rate that pays for basic anesthesia services, with provisions for additional payment for more complex procedures and patients with comorbidities of certain risk factors (e.g., at the extremes of age).

UNITED STATES BUSINESS MODELS

In the rapidly changing health care environment of the United States, anesthesia practices are evolving and identifying new ways of caring for patients in the operating room and other inpatient and ambulatory settings. While many of the changes are being implemented in practices within the United States, many of these models have accounted for lessons learned from business and clinical models in other countries. At the same time, particularly in the United States, changes in the financing of health care and payment models for anesthesia services and the expanding role of anesthesia services outside of the traditional operating room environment require new models of practice and new skills to ensure that the practice is financially viable and that patient care is optimized.

The United States has a wide variety of business models for the practice of anesthesia in both community and academic practices, each developed in large part based on the source(s) of funding, how the funding is distributed, and the requirements that must be met to receive these funds. Academic practices have generally been more integrated with the health system, either through a faculty practice plan (in many cases an independent corporation) or through an employment model. In these models, income from patient care is often the largest source of funding, though many departments also receive funds from research grants and contracts and, in rare cases some financial support for the educational initiatives (payment for residency program direction, course directors, etc.). While these other sources of revenue are critically important to academic departments, much of the funding to support the academic missions has traditionally come from patient care. As clinical demands have increased, academic faculty have less time to pursue research and educational activities, limiting the ability to generate other sources of support. At the same time, the clinical income has not kept pace with the increasing financial pressures on the academic departments, requiring academic practices to identify new business models and new relationships with the health systems to fulfill their academic potential.

Similarly, the business models required to support community practices are also undergoing dramatic changes. The historical practice model for anesthesiology was often a loosely affiliated group of anesthesiologists who shared clinical coverage for patients undergoing anesthesia in a hospital setting, including providing call coverage. The primary roles fulfilled by the anesthesia practice in this "informal" model included scheduling of anesthesia providers. In most other respects, each anesthesiologist was relatively autonomous, although in some cases billing was centralized for all providers either within the group structure or outsourced to a billing company familiar with anesthesia billing requirements. In some of these models of practice, anesthesiologists worked with individual surgeons, rather than as a

coordinated group of providers. Although this approach worked well for the individual anesthesia provider and the surgeon, scheduling and coordination became increasingly complex, particularly when care was provided in more than one facility.

Over the past 2-3 decades, the relationship with hospitals and health systems and the changing health care environment has necessitated that practices become more integrated group practices. While in some cases there remain individual or small group practices providing care in physician offices or ambulatory surgery centers, most practices have evolved and become more sophisticated in the business aspects of anesthesiology in order to compete successfully and to ensure the financial viability of the practice. A number of "group" models of practice have been created; with the current challenges in health care financing and the mandate to document and publicly report clinical outcomes, the practices have had to develop or acquire additional skills to remain successful both clinically and financially. As a result, while in some select situations the "independent" anesthesiologist model is still viable, for the most part group practices that share both clinical responsibilities and business practices now dominate the specialty. The model has evolved to include formally incorporated partnerships and corporations to coordinate anesthesia care, manage the business practices and optimize contractual relationships with payors.

Many other factors have contributed to the changes in and coordination of business practices for anesthesia groups. First, the clinical capabilities and skill sets have expanded considerably, requiring each group to ensure that among the members of the group, the clinical needs of a diverse population can be met. As a result, recruitment and retention of anesthesia providers has taken on greater significance. Second, most health systems prefer to either employ physicians or contract with a single anesthesia group (i.e., rather than individuals) to provide the needed services. In order to be competitive under this model, the group must have sound business capabilities and negotiating skills. Most groups have also expanded the scope of services beyond scheduling, billing and collection to include benefit management (e.g., retirement plans), and malpractice insurance and increasingly other services to support members of the group. At the same time, the consolidation of hospitals into health systems and the need for sophisticated clinical and business systems to support the anesthesia practice have led either to the acquisition of many "hospital-based" anesthesia practices by regional or national anesthesia groups or to their integration into multispecialty practices within a community or region. The pace of acquisition of anesthesia practices into these systems has accelerated over the past 3 to 5 years. According to some estimates, as many as 31 anesthesia and pain practices were acquired mostly by national or regional anesthesia provider groups in the United States in 2013.[1]

While the consolidation is changing the landscape of anesthesia practices, there are other pressures that are having major implications on the future of anesthesiology practices, both within the United States and internationally. Most significant have been the dramatic changes in the clinical practice of anesthesiology and the scope of anesthesia services (see Chapter 1). Because of these changes—a focus on evidence-based clinical practice and the development of clinical guidelines, protocols and practice parameters[2,3] (also see Chapter 6), new drugs, improved monitoring capabilities, and better preoperative assessment and management—a more diverse and in many cases complex patient population is now receiving anesthesia services. The practice of anesthesiology has expanded to include preoperative assessment and preparation of patients with chronic medical problems, acute and chronic pain management, critical care medicine, perioperative care and management services, and other clinical and administrative roles (see Chapter 1). These changes have had a major effect on the business models for anesthesia practices and the scope of services provided by anesthesiologists. The business models and scope of activities required of each practice is determined in large part on the relationship between the practice and the environment within which it provides care. In most cases, however, to maintain a consistent standard of care, to provide ongoing documentation of clinical competence, and to monitor outcomes of care, a group must have a strong management structure and analytic skills to document its value to the health system.

STAFFING MODELS

PHYSICIAN ONLY PRACTICES

In most parts of the world, anesthesiology is provided by physicians with specialty training in anesthesiology and, in some cases subspecialty training. In some locations in the United States, physician anesthesia practices predominate, particularly on the West coast. In this model of care, anesthesiologists provide care in the operating room and, now, commonly in other settings including, but not limited to, ambulatory surgery centers and ever expanding non–operating room environments. In this model, anesthesia is personally provided by the anesthesiologist; preoperative and postoperative care may be provided by the same individual or another member of the same anesthesia group.

As the roles and clinical scope of practice have expanded, anesthesia departments have recruited anesthesiologists with diverse subspecialty skills, not only to improve care within the operating room, but also to provide care in other settings. Many departments now include physicians with subspecialty training in critical care medicine, pain management as well as the other subspecialties of anesthesiology (pediatrics, cardiothoracic anesthesia, obstetric anesthesiology). This expansion in the scope of practice has been successful for the departments, health systems and, most importantly patient care, but it has also complicated scheduling and coordination of services across the continuum of patient care. For example, staffing all subspecialty surgical services can present operating room management challenges (see Chapter 4).

Some anesthesia practices have also incorporated physicians from other specialties to expand the clinical

capabilities and improve coordination of care. For example, some groups include hospitalists with a special interest in perioperative care, internal medicine physicians to improve preoperative management of complex patients, and critical care and pain medicine physicians whose primary training is in a specialty other than anesthesiology.

ANESTHESIA CARE TEAM MODELS OF PRACTICE

In most countries and selected areas of the United States, anesthesia is provided by physicians practicing independently; however, the anesthesia care team model predominates in some parts of the United States, with the practice employing anesthesiologists, CRNAs, and AAs in some states.[3,4]

For groups that use the anesthesia care team model, the relationship between the anesthesiologist and the nonphysician providers varies, although in most cases the CRNAs and AAs are employed by the anesthesia group. All business practices are managed by the group, and the providers are employed by the group. In some cases, the nonphysician providers are employed by the health system, though no matter who employs the nonphysician providers, in all cases the anesthesiology department has responsibility for oversight of all anesthesia services. In states that require supervision of all nonphysician anesthesia providers, when CRNAs and AAs are employed, the anesthesiologist is responsible for the care provided during the entire perioperative or periprocedural period, including the preoperative evaluation, presence for critical portions of each case, and postoperative management. In most cases, based on requirements outlined by the U.S. Centers for Medicare and Medicaid Services, the anesthesiologist may supervise up to four CRNAs at a time.

Nurse Anesthetists

A nurse anesthetist is a nurse who has specialized in the administration of anesthesia. Nurse anesthetists typically complete a 4-year undergraduate degree, have 2 years of clinical work experience (often in an ICU setting) and then a 2-year master's level anesthesia training program. Nurse anesthetists have a certification examination and, after successful completion of the examination become certified nurse anesthetists (CRNAs). Recently, some nurse anesthetist programs have begun to offer a doctorate of nursing practice (DNP) or doctorate of nurse anesthesia practice (DNAP). In many parts of the United States, nurse anesthetists work in the anesthesia care team model under medical direction or medical supervision. As part of the anesthesia care team, a nurse anesthetist may evaluate patients preoperatively and administer anesthesia under the supervision of an anesthesiologist as noted above. In some states, nurses may work independent from physician supervision, in accordance with each state's nurse practice act.[6]

Anesthesia Assistants

Anesthesia assistants (AA) work under the direction of an anesthesiologist as a physician extender in the anesthesia care team model. AAs complete a 4-year bachelor's degree, with a 2-year master's level program, followed by a certification examination. AAs can take preanesthetic health history, perform preoperative physical examinations, establish noninvasive and invasive monitors, administer medications, evaluate and treat life-threatening situations, and execute general and regional anesthetic techniques, as delegated by the anesthesiologist. Currently, AAs are not able to practice independently in any state in which they are licensed.

HEALTH SYSTEM–EMPLOYED PHYSICIAN MODELS

With the increasing consolidation of health systems, hospitals are now more commonly employing physicians directly. In these models, the practices are managed by the health system rather than an independent group or practice plan. Some states do not allow these employment models,[7] but a number of alternative models have developed that effectively result in the physicians becoming employees either directly or through a foundation or other approach that is essentially controlled by the health system. These models are becoming more common in selected parts of the United States, often initially developing on employment relationships for hospital-based physicians, such as anesthesiologists. In these employed or foundation models, the anesthesia providers are salaried. All business aspects of the practice are managed by the health system or foundation, including, but not limited to contracting, billing, coding, and collections.

Employment relationships with physicians are being expanded in a variety of not-for-profit as well as for-profit hospital systems, in an attempt to more effectively create coordinated approaches to clinical management, cost containment, and alignment of incentives. Currently, a majority of hospitals and health systems provide some level of financial support for physician practices in both academic and community environments. More than 80% employ primary care physicians, and more than 60% employ some office-based specialists. Almost one third of the hospitals are pursuing some form of joint venture with segments of their medical staffs, and a number of others are considering this possibility. Initiatives include cardiac services, magnetic resonance imaging, positron emission tomography scans, mammography, sleep laboratory, wound care, women's health, oncology services, and medical office buildings. Surprisingly, only one third of those involved in a joint venture gave it a high rating related to hospital-physician alignment. Hospital chief executive officers admit that negotiating and managing these initiatives is difficult and time consuming.

Despite the challenges associated with these changes in the hospital-physician relationship, the trends are clear. As more physicians become employees of health systems or foundation models, the ability of independent physician practices to compete will diminish. As a result of these pressures to align more closely with the health systems, many anesthesia practices are finding it difficult to address some of the pressures put on them by the health system, payers, and other providers. In response, there has been increasing consolidation of anesthesia practices into regional and national groups with the size

and sophistication to not only manage the clinical practices, but also provide the data needed to effectively negotiate with the health systems and payers and to provide metrics to document clinical outcomes. If this consolidation continues, the survival of individual hospital-based or independent anesthesia practices is in jeopardy.

Company Model

While most employed models compensate anesthesia providers based on either clinical productivity (e.g., work relative value units) or fees collected on behalf of the anesthesia group minus administrative costs, one employment model for anesthesia practice raises considerable concern. The "company model" has gained some support from other physician specialties such as gastroenterologists and other proceduralists.[8] Under the company model, referring physicians, who typically also own the facility where procedures are performed, form a separate "anesthesia company" to share in anesthesia revenue. The intermediary company employs anesthesiologists, collects the professional fees on their behalf, and shares the difference between the collected fees and salary with the corporate shareholders. The fees are generally not based on the costs of managing the anesthesia billing and collections, but rather are described as management fees retained by the corporation. Many questions have been raised by this model of practice, since the arrangements between the physicians who own the facility and the anesthesiologists might violate the federal anti-kickback statutes.

In June 2012, the Office of Inspector General (OIG) for the U.S. Department of Health and Human Services issued Advisory Opinion 12-06 citing the "company model" and "management fee" both posed more than a minimal risk of fraud and abuse.[9] Anesthesiologists being approached with such offers should review the documents with their attorneys to avoid violating anti-kickback laws that could lead to civil penalties and criminal fines.

Academic Practices

In most academic practices, anesthesiologists work within the academic structure, as employees of the school of medicine or the faculty practice plan. With an academic structure, medical centers (i.e., hospitals) may provide funding to the faculty practice plan. In many but not all academic practices, the anesthesia group is a member of the faculty practice, sharing business practices with the other departments represented by the faculty practice plan. The specific business models vary considerably, although in most cases the faculty anesthesiologists are employed by the university, the health system, or the faculty practice. In selected cases, the anesthesia department is an independent corporation or partnership functioning autonomously from other physician groups or the health system. Because of the increasing support required from the health system to ensure availability of anesthesia services across the spectrum of clinical services, these autonomous models are rapidly being replaced by the integrated practice plan. In most academic models, contracting and other business services are provided by the practice plan. Because of the diverse roles and responsibilities of the faculty in academic departments, the financing of the department and compensation of the staff is complex, with various approaches to determining total compensation based on clinical effort as well as other roles and responsibilities (teaching, research, administration). Over the past few years, most academic departments have transitioned to providing base salary with an increasing proportion of overall compensation based on incentives.

The academic practices have multiple missions, which complicates the business models and creates potential and real conflicts between clinical and academic needs. The "triple threat" academic physician who is the outstanding clinician, educator, and researcher is often perceived (particularly by the hospital leadership) to be less efficient and less committed to patient care. In response, many academic departments have recruited faculty with a primary (sole) commitment to clinical care. This change has created a two-tiered system and, in some cases undervalued the teaching and research roles. At the same time, research funding has decreased and many departments are finding it difficult to maintain scholarship while also addressing the increasing clinical demands of the health care system.[10]

Another challenge facing academic departments is the changing role for residents (see Chapter 9). In addition to providing high-quality, efficient, and safe care, the academic departments are responsible for training the next generation of anesthesiologists and for providing broad-based clinical experiences and didactic educational programs. The anesthesia residencies are accredited by the Accreditation Council for Graduate Medical Education. The oversight and accreditation process has become more rigorous and challenging for the academic departments to meet. Residents have restricted work hours to reduce the effects of fatigue on performance. Supervisory expectations have increased, requiring more one-on-one oversight of the resident in the clinical environment. In addition, the implementation of simulation and other models of education have replaced some of the clinical experiences. Because of these changes, the residents are no longer the primary providers of clinical care under faculty supervision; faculty members are providing personal care or supervising other nonphysician providers more commonly in academic environments. The financial and business implications of these changes are significant. Anesthesia departments in the United States now receive significant support from the academic health system in order to remain financially viable.[11,12] Although clinical income has always provided the resources to support the academic programs in the past, the importance of clinically generated income has increased as extramural research funding has decreased. The business practices required to support academic practices are now highly similar to those required to support other large group practices. As a result of these significant challenges for academic departments, the "value" of the academic program to the health system has been questioned. In some cases, entire academic departments have been replaced by large national anesthesia groups to manage the department and deliver care,[13] putting into question how we can ensure the ongoing training of anesthesiologists.

ESSENTIAL BUSINESS PRACTICES

In order to concentrate on delivering anesthesia services, each anesthesia practice has to ensure that the business functions of the practice are being provided appropriately and responsibly. Although each model of practice may have a different business structure to support the practice, the anesthesia providers retain the responsibility for ensuring that the business practices are ethical, fulfill legal and regulatory requirements, and that the quality of care is continuously assessed and refined to remain evidence-based and within the standard for the community. These responsibilities can be delegated, but cannot be abrogated. As a result, whether the anesthesia providers are employed or are members of a professional corporation, they must understand the business practices, provide oversight, and continuously ensure that the practice is well managed. To fulfill these critical responsibilities, the basic business functions of the anesthesia practice should focus on the most effective ways to facilitate high-quality, safe patient care in whatever clinical settings the practice works, optimize the clinical environment, and identify new opportunities to expand or enhance the practice while also ensuring the financial underpinnings of the practice. Achieving these goals requires that the business practices be built on a foundation of collaboration and cooperation with other providers from other specialties, hospitals, health systems, and payers. The business functions should support each of the following requirements of practice.

FOSTER CLINICAL CARE

The business models should be designed to allow anesthesia providers to concentrate their attention on patient care. Most anesthesiologists have little interest in managing their practices, although some members have both the interest and skills to do so. The practice should be designed to take advantage of the skills of each member, allowing those interested in participating in the business functions to do so, while the majority of the group concentrates on delivering high-quality care, assessing outcomes of care, and modifying practices to improve quality and safety.

One of the major challenges facing every practice is the transition from payment for clinical care, primarily the fee-for-service model, to pay for performance. In some cases, rather than paying for documented performance on specific process or outcome measures, payers are not paying if there is evidence of poor outcome (e.g., central line infection, ventilator-associated pneumonia).[14] At the same time, not only are third-party payers reducing payment when complications occur, but hospital subsidies can also be based on specific quality metrics. For the practice to ensure that clinical care is optimal as is often required for payment of clinical services, reliable information about all aspects of the clinical practice must be available. Good data about the practice will allow an organization to identify and promote best practices and improve both the quality and efficiency of care. Data will also facilitate the sharing of information among all the providers, precisely defining opportunities to improve care. To provide the data on outcomes and costs of care, coordination and integration of information is required from the anesthesia record, operating room, and the overall hospital information system. Now, these goals are increasingly dependent on implementation of an integrated electronic medical record (see Chapter 5). Most independent anesthesia practices cannot afford to implement the electronic anesthesia record on their own and, more importantly, cannot easily integrate their data with that of the hospital system without considerable support. As a result, only larger organizations that are working collaboratively with health systems will be in a position to acquire, analyze, and disseminate data to support the quality and efficiency of care provided by the group.

MANAGE THE PRACTICE

Although patient care is the primary purpose for which the anesthesia practice exists, the anesthesia providers will only be successful in providing high-quality, safe care if the business model supports the needs of the practice and its patients. The business model must provide the infrastructure to ensure that systems are in place to foster clinical care in every environment in which the providers practice. The usual business practices, including billing, coding, and collections, must be managed either internally or through contracts with other companies that have the experience to do so cost-effectively.

The group that provides billing and coding services must understand that it is handling sensitive patient information and under The Health Insurance Portability and Accountability Act of 1996 (HIPAA) privacy, security and breach notification rules, it is responsible for protecting the security and confidentiality of health data on the patient's behalf. If an outside vendor is providing these services, the group must have a business associates' agreement documenting the responsibilities of each party, particularly related to HIPAA requirements.

Coding of claims is a challenging task. Specific documentation of all aspects of care provided to the patient is critical; the documentation is the basis on which to code a claim. If the documentation is inadequate, the payment will not reflect the physician's work. In all cases, the claim should be easily determined from the clinical documentation. The claims should be standardized and "clean." There should be no ambiguities in the reason a service was provided (ICD-9/ICD-10 diagnosis code) and what service was provided (Common Procedural Terminology [CPT] code). For most services, clinical face-to-face time is required in the submittal, so the actual time spent with the patient must be clearly reported in the clinical documentation and on the claim.

Whoever provides the coding and billing functions must be aware of the regulatory requirements and the guidelines established by the practice related to ethical billing practices. An outside contractor can do the coding or bill for clinical services, but the ultimate responsibility for correct coding and billing remains with the anesthesiologist who provides the clinical care. The providers must ensure that documentation supports all clinical care and that charges reflect the actual service provided to the patient. For operative anesthesia services billed in the United States, the American Society of Anesthesiologists' *Relative Value Guide* is generally used to determine

the anesthesia unit value; the conversion factor for each payer determines the payment for anesthesia services. For nonprocedure billing, such as critical care and some pain medicine services, most charges are based on evaluation and management codes, which are billed using the resource-based relative value system (RBRVS). For evaluation and management services, the level of service is determined by the care provided to the patient as documented in the medical record. If documentation is inadequate, the charges and collections might not reflect the level of service actually provided to the patient. Each practice should routinely monitor the documentation to ensure that the coding is correct.

The real value of a billing service is not the timely filing of the claim (billing) for service, but in the tenacity of follow-up. While payers seem to be reluctant to pay claims and may even deny them on administrative technicalities, a "clean" claim with persistent follow-up will be paid. The same is true for the patient's contribution or copayment. The patient copayment is often the most difficult to collect and is a differentiator between billing companies.

While correct coding, billing, and collections are critical for the ongoing financial viability of the practice, the business office also facilitates contracting and negotiation with payers and the health systems to ensure that the practice is compensated at a level consistent with the services provided. To do so requires strong financial expertise and an understanding of the current and rapidly changing health care environment, as well as the ability to gather key measures of outcome and performance (e.g., patient satisfaction) to market the practice and to justify contractual negotiations. Without objective data to support the practice claims about quality, safety, and patient satisfaction, the practice is vulnerable and its future relationships with the health system could be compromised by competing practices.

CONTRACTING

One of the critical roles for the practice is to contract with payers independently or jointly with other providers and the health system to provide services to select (covered) groups of patients. Traditionally, fee-for-service contracting models were most common; however, other models of payment have been developed to reduce overall costs of care and, more importantly, to align incentives to optimize care and quality and reduce costs and needless services. In the United States, each state has laws regarding who can contract with providers to deliver health care. Contracting entities typically have direct contact with the providers and provide for the selling or the assigning of physicians or physician panels to other health care entities. The providers are then termed *participating*. Contracting entities can only grant access to a participating physician by a health care contract. Contracting entities offer contracts to providers that are generally either risk-sharing or non–risk-sharing agreements. A non-risk contract to a provider means that the contracting entity bears all the financial risk and pays the provider for the services requested and rendered. A shared-risk contract pays providers for services rendered, but withholds some of the payment depending upon the use of services.

A number of different contracting vehicles are used in health care, including managed care contracts (e.g., health maintenance organizations [HMOs]), physician health organizations (PHOs), preferred provider organizations (PPOs), and other models. Although the various approaches differ and have important implications for anesthesia practices, some general principles differentiate the approaches. The managed care model, which was common about 20 years ago, gave responsibility for managing the care of a population of patients to a primary care provider. Referrals to specialists were determined by the primary care provider, who in most cases was compensated based on a capitated payment methodology. The primary care provider received a monthly payment for managing the care of each patient; specialists were paid using a fee-for-service (or reduced fee for service) payment methodology. The HMO model did not significantly reduce the cost of care nor improve quality. As a result, a number of alternative models have been used to better align the physicians, patients, payers, and health systems. Newer models of care incorporate both risks and incentives into the payment methodology and potentially improve the ability for physicians and hospitals to collaborate on initiatives to improve outcomes, reduce costs, and optimize patient care during hospitalization and through the continuum of care needs.

One area that has the potential to benefit both parties is gainsharing, which has typically referred to an arrangement in which a hospital provides the physicians with a share of any reduction in the hospital's costs attributable in part to the physician's efforts. Gainsharing programs are designed to align the economic incentives of hospitals and physicians to provide cost-effective care and to maintain or improve quality of care and patient satisfaction. In addition, gainsharing programs allow physicians to share in the cost savings through some combination of a percentage payment, hourly or fixed fee, and to play a significant role in the planning process to achieve those savings. From the hospital perspective, gainsharing programs reduce costs through standardization and economic efficiencies of scale. From the physician's perspective, gainsharing programs provide a financial incentive to cooperate with hospitals in the development and planning of programs designed to reduce hospital operating costs without compromising quality of care to patients. Gainsharing programs work to gain physician acceptance and change practices to control costs and increase margins on hospital business.

Recent actions by both the OIG and the Medicare Payment Advisory Commission (MedPAC) seem likely to increase hospital–physician gainsharing agreements. In March 2005, the OIG issued six favorable advisory opinions involving hospital–physician gainsharing programs.[15] MedPAC recommended to the U.S. Congress that the Secretary of Health and Human Services be granted the authority to permit and regulate gainsharing arrangements between hospitals and physicians.

AUDITS

The practice should have documentation of billing policies and procedures and a well-defined compliance plan to support all clinical and business functions. As a routine part of management, the practice should regularly

review the claims management processes, cash flow, and compliance with applicable regulations. Billing audits identify when claims are appropriately coded according to CPT codes, have sufficient documentation to support the claim, and when they adhere to payer payment policies. Claims need to be reviewed regularly for underpayment, overpayment, and billing errors. If irregularities are identified, these require immediate resolution, including notification to the payer and refunds as appropriate. Audit findings are discoverable, and thus all reviews and audits should be managed under the direction of the practice attorney. In general, the findings are privileged communications between the attorney and the practice, although each practice should be aware of all regulatory and legal issues related to billing and compliance reviews and audits.

For government payers, the OIG Compliance Guidance for Individual and Small Group Physician Practices outlines the requirements.[16] It describes a variety of business practices physicians can adopt that, in the agency's view, will help them avoid submitting erroneous claims or engaging in unlawful conduct. The physician guidelines describe seven basic compliance plan elements:

1. Conducting internal monitoring and auditing with periodic audits and implementing compliance and practice standards with written standards and procedures
2. Designating a compliance officer or contact to monitor compliance efforts and enforce practice standards
3. Conducting appropriate training and education on practice standards and procedures
4. Responding appropriately to detected violations with an investigation
5. Developing corrective action and disclosure to appropriate government entities as necessary
6. Developing open lines of communication including staff meetings, bulletins
7. Enforcing disciplinary standards through well-publicized guidelines

Anesthesia practices have some specific guidelines and requirements that must be fulfilled.

LEGAL SERVICES

Anesthesia groups should utilize the expertise of attorneys knowledgeable about each aspect of clinical practice as well as the relationship between the group and other health care entities (see Chapter 11). The legal counsel should be familiar with issues specific to anesthesiology and should understand the specific practice model and relationships. Some of the common issues that benefit from legal assistance include employment agreements; regulatory and compliance issues; physician licensure issues, including reporting to the National Practitioner Data Bank; antitrust issues; restrictive practice covenants; and interactions with industry, particularly related to Physician Financial Transparency Reports (Sunshine Act).[17]

INSURANCE

Anesthesiologists must protect themselves from legal action, whether related to clinical care or other aspects of practice. The anesthesia practice should ensure that both the practice and each provider have appropriate levels of insurance, including, but not limited to professional and general liability insurance. For officers of a practice, the group should provide directors and officers with insurance to cover claims related to wrongful acts of a director or officer. Other insurance coverage, such as disability, worker's compensation, and property and auto insurance are provided by the practice in some circumstances. The practice should seek counsel from insurance professionals to determine the specific needs of the practice.

Each anesthesiologist must have professional liability insurance to cover the full cost of legal defense related to a malpractice suit. In most cases, professional liability coverage is provided by the practice, although in some cases individual providers must purchase their own insurance. There are two types of professional liability (i.e., malpractice) insurance policies in the United States: occurrence-based and claims-made. Occurrence-based policies provide protection against incidents that occur during the *term* of the policy, regardless of when the claim is made. Claims-made policies provide coverage for incidents that occur during the *policy period*.

When terminating a claims-made policy, "tail insurance" can be purchased to provide coverage from incidents that occurred when a claims-made policy was active. Tail insurance is typically a single payment and often costs a multiple (1.5 to 2.5 times) of the annual claims-made policy. On occasion, a physician will change malpractice carriers. When this occurs, "nose insurance" (i.e., for prior acts) can be purchased to function similarly to tail insurance.

The cost of professional liability coverage includes the cost of claims made for pain and suffering and other losses. Some states have adopted tort reform, limiting the payment for pain and suffering. The cost of professional liability insurance in the states that have adopted tort reform is considerably lower than it is in states without any limits for malpractice claims.

RECRUITMENT

One of the key roles for the practice is the recruitment and retention of an appropriately diverse group of providers to meet the clinical needs of the patient population being served by the practice. Practices must have a formal process for recruiting new members. In each case, it should define the goals for the recruitment and the relationship that the new member of the group will have. The group should clarify the business relationship with every new recruit, in addition to whether the new member will be an employee, whether a partnership track is possible, and the terms and conditions for becoming a partner. The recruit should be provided with a contract that defines the relationship, compensation package, and all other terms and conditions. The American Medical Association provides a useful resource describing the basics of a physician employment agreement.[18]

One of the other important aspects of recruitment relates to the clinical needs of the department and the skills and clinical expertise expected of the recruit. Because the practice generally works within one or more health

systems, the recruitment of new surgeons or other physicians may necessitate hiring new anesthesia providers with specialized skills, such as pediatric anesthesiologists, cardiothoracic anesthesiologists, neuroanesthesiologists. Every anesthesiologist certified by the American Board of Anesthesiologists is trained to care for the wide spectrum of patients requiring anesthesia services, but there are selected groups of patients for whom subspecialty training and certification may be required. For example, the needs of pediatric patients are currently undergoing evaluation to define children for whom pediatric certified anesthesiologists should be available and those who can receive care from a board-certified anesthesiologist who has not completed pediatric anesthesia subspecialty training (see Chapter 93). Recently, the American College of Surgeons published recommendations for pediatric surgical care based on the model used to support trauma care (see Chapter 81).[19] The recommendations provide a framework for considering the most appropriate way to provide care to pediatric patients requiring surgery, although they have also raised some concerns about access to anesthesia care for all pediatric surgery patients. The practice leaders and practitioners must be aware of their diverse clinical needs in order to recruit, credential, and retain the appropriate balance of anesthesia providers.

In most cases, the practice should be working collaboratively with the health systems, hospitals, and freestanding facilities to identify opportunities to expand their scope of services. Many anesthesia groups provide critical care, pain management, and other specialty care services to support the needs of the patients served by the health systems in which the group works. The expansion of anesthesia services outside the operating room has also created new opportunities for anesthesiologists to participate in care for a much broader range of patients (see Chapter 90). For example, the care of patients undergoing some diagnostic and therapeutic procedures is improved when an anesthesia provider is caring for and monitoring the patient during the procedure. Some payers have suggested that anesthesia services are not required for some of these procedures and that they simply add unnecessary costs to care; therefore, the practice should be able to document improved outcomes and reduced costs. To do so requires that the practice understand the overall cost structure of the services provided to the patient and that it work collaboratively with the hospital or other facility to document the costs of care and clinical outcomes.

Additional opportunities that should have support from practice leaders include development of new models of care, such as the preoperative management of patients with underlying chronic diseases (e.g., diabetes, chronic obstructive pulmonary disease), PSH, and the provision of postoperative monitoring after discharge using technology to foster communication and coordination of care with the primary care provider. To take advantage of these opportunities, the practice must define the staffing needs and in some cases try to identify new models of care that include anesthesiologists working collaboratively with nonanesthesiologists (e.g., surgical hospitalists) in relationships that can be both clinically and financially successful models.

PARTICIPATION IN HEALTH SYSTEM GOVERNANCE

Anesthesiologists should be active participants in governance of the health system in which they work. The medical staff members provide the professional oversight for medical care in facilities in many states based on legal statute. The most important component of the medical staff is medical peer review, the promotion of the highest quality of medical care, and patient safety. Its secondary function is to determine whether a practitioner's clinical privileges or membership in a professional society will be adversely affected by a physician's competence or professional conduct.

In most cases, the chief of the anesthesia service will serve as member of the medical staff executive committee, unless anesthesia services are not structured as a separate clinical department. Each practice should identify opportunities to participate in both the medical staff structure and the governance and operations committees of the health system. Anesthesiologists can have numerous opportunities to take leadership roles in the oversight of perioperative services, critical care medicine, pharmacy and therapeutics committees, patient safety initiatives, code blue committees, rapid response teams, and other patient safety programs. The more engaged in medical staff and system roles, the greater the likelihood that the anesthesia practice will be highly valued by the organization and will maintain its role in providing the staffing and oversight of all anesthesia care.

NEW FINANCIAL MODELS

Traditional fee-for-service payment has been the most common method of payment for physician services for some time. The fee-for-service methodology provides payment based on the level of service provided to the patient. Unfortunately, this model of payment has been criticized for contributing to the increasing costs of health care, encouraging overuse of clinical services, and fostering the implementation of expensive technologies that do not necessarily improve outcomes. As a result, a number of other payment methodologies have been developed to reduce costs of care and overuse of clinical services and to align the goals for the patient, health system, and providers. Each practice should understand the various payment methodologies and ensure that it has the information about the practice to understand the risks, benefits, and financial implications of each model.

A number of alternative models have been proposed, including a shared savings model of payment, episode of care payments, and bundled payment models for physicians alone or combined physician and health system payments. In some cases, these models are proposed for all levels of service and in some cases to coordinate clinical care for specific patient populations, such as solid organ transplants, selected surgical procedures. Under a shared savings program, the provider receives a share of savings associated with reduced health care spending. This model is essentially a pay-for-performance system. Unfortunately, shared savings rewards the high spenders rather than the high performers and is not sustainable.

Comprehensive care payment is intended to reduce the number of unnecessary episodes of care. It is proposed as a methodology to reduce the cost associated with management of chronic conditions. This model encourages preventive care, and it is intended to reduce the number of procedures, which could have implications for anesthesia services.

Recently, a number of new models of care have been implemented to optimize comprehensive care and overall health outcomes. The Patient-Centered Medical Home model is designed to improve management and coordination of patient care across the continuum with management by a primary care provider in conjunction with other clinical providers (e.g., advance practice nurses, physical therapists, social workers). The outcomes of care associated with the medical home are still unknown, although early data provide interesting information about where this model might be most successful and some of the challenges associated with its implementation.[20,21]

A recently proposed model of care that is gaining momentum is the accountable care organization (ACO). It was first described by Dr. Elliot Fischer and incorporates three core principles: (1) a provider-led organization with a strong primary care base, (2) payments that are linked to quality improvements that lower overall cost, and (3) reliable performance measures that support the quality improvements for a population of patients.[22] In this case, *accountable* refers to the role of both patients and payers to ensure delivery of appropriate, high-quality, and cost-effective care. The ACO model has been promoted as a way to improve care and outcomes under the Affordable Care Act adopted by the U.S. Congress in 2010.[23,24] The proposed goal is to promote clinical excellence and control costs by coordinating the care provided by facilities, physicians, and other providers and providing financial incentives to limit unnecessary expenditures. For anesthesiologists, the ACO model can create some opportunities to extend care through the entire perioperative period both within the hospital and after discharge. In the role as a perioperative physician, the anesthesiologist (or group of anesthesia providers working collaboratively) can direct the entire surgical process—that is, evaluate and optimize the condition of the patient preoperatively, manage the intraoperative course, provide appropriate postsurgical care (including critical care and pain management), and facilitate the transition of care to the primary care physician. In the current health care system, many of these services are either not provided by the anesthesiologist or are provided informally and are often not documented, measured, or directly compensated. If the anesthesia practice is to assume this new role, it will have to document the services provided, their value, and negotiate with the health system for appropriate compensation for the services provided.

Whether the ACO model will succeed remains unknown. Many health care systems are participating in ACOs with variable outcomes. The primary reticence of health care systems and providers to participate in this model is probably related to concerns about whether the organizations are prepared to accept the risks.[25]

More important to anesthesia practices than participation in the ACO model is the current interest in developing the PSH model of care, which provides the opportunity for the anesthesia practice to expand its role in the care of selected patient populations and to assume a greater role in the overall management of the surgical patient. In many respects, it builds on the medical home model of care. In this model, anesthesiologists should be able to improve outcomes and reduce costs. Compensation to the anesthesia group will be based on these achieved goals. This model of care and payment can also serve as the model for distribution of payment for other bundled clinical services. The concept of the PSH and its implications for anesthesia practices is described in more detail in Chapter 3.

Anesthesia business practices continue to evolve in response to changes in the health care environment and advances in clinical practice resulting from improved technology. The dramatic changes in the financing and delivery of clinical care will continue to challenge anesthesia practices, but also create new opportunities to expand the scope of anesthesiology. For example, new practice initiatives such as the PSH will allow anesthesiologists to assume a broader and exciting new role in health care. The challenge is to ensure that business practices advance at the same pace as these new clinical initiatives so that the desired outcomes of improving quality, maintaining safety, and reducing costs are achieved.

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Chapter 13

Consciousness, Memory, and Anesthesia

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Key Points

- Mechanisms of consciousness and memory, and their interruption by general anesthetics, are important scientific problems that have clinical relevance for the practice of anesthesiology.
- Consciousness is characterized by wakefulness (i.e., state of being arousable) and awareness (i.e., subjective experience).
- Anesthetics act at structures in the brainstem, hypothalamus, and basal forebrain that regulate sleep-wake states, which may account for loss of wakefulness.
- Anesthetics disrupt connectivity and communication across cortical and thalamocortical networks, which may account for loss of awareness.
- Memory can be subdivided into explicit (conscious) and implicit (unconscious) recall; an example of explicit episodic recall is remembering a surgical event.
- Suppression of explicit episodic recall is one of the most potent effects of most general anesthetics.
- Effects on the hippocampus, amygdala and prefrontal cortex—as well as the connectivity of these structures—may account for anesthetic-induced amnesia, even before loss of consciousness.

SCIENTIFIC AND CLINICAL IMPORTANCE

Consciousness and memory are among the most fascinating and complex subjects in all of science. The richness of human consciousness and memory—and the ability to express this richness in language—is a defining characteristic of homo sapiens. These cognitive processes, however, are also notoriously difficult to study. As Thomas Huxley famously noted, "How it is that anything so remarkable as a state of consciousness comes about as a result of irritating nervous tissue, is just as unaccountable as the appearance of the Djin when Aladdin rubbed his lamp."[1] The medical specialty of anesthesiology is in a unique position to shed light on the problems of both consciousness and memory because the drugs used in common anesthetic practice infallibly place the genie of consciousness back in the lamp—and bring it out again almost just as uniformly. Furthermore, at doses significantly smaller than those required for unconsciousness, general anesthetics also cause amnesia. As such, anesthetics are being recognized increasingly as tools to study consciousness and cognition,[2,3] a trend that fulfills the vision of anesthesiologist Henry K. Beecher in the 1940s.[4]

Consciousness and memory also have clinical relevance for the anesthesiologist; together, the experience and explicit episodic recall of surgical events is known as the problem of "intraoperative awareness." This complication occurs in approximately 1 to 2 cases per 1000[5-7] and is associated with a frequent incidence of posttraumatic stress disorder.[8] As such, there is a strong motivation to prevent consciousness and explicit recall, but current technology may not be a significant advance over traditional methods of assessing anesthetic depth such as minimum alveolar concentration[9,10] (see Chapter 50). To advance the field of perioperative brain monitoring, a detailed understanding of the neurobiology of consciousness, memory, and anesthesia is required.[11]

CONSCIOUSNESS

HISTORY AND TERMINOLOGY

For the greater part of the twentieth century, the study of consciousness was not considered a serious scientific pursuit. Yet, the past two decades have seen a dramatic increase in the number of rigorous investigations into consciousness. This was stimulated, in part, by public attention in the 1990s from a number of high-profile scientists such as Nobel Laureates Francis Crick and Gerald Edelman, as well as renowned physicist Roger Penrose. At approximately the same time, the first multidisciplinary conference on consciousness studies was hosted in 1994 at the University of Arizona, and several journals on the

subject were founded (*Journal of Consciousness Studies*, *Consciousness and Cognition*). Although some seminal papers on consciousness and anesthesia were published more than a decade ago,[12] the specialty of anesthesiology has now turned its attention to the science of consciousness. Indeed, it was only in the seventh edition of *Miller's Anesthesia* that consciousness made its formal appearance[13] in the chapter titled, "Sleep, Memory, and Consciousness." Since then there has been an explosion of exciting data on the neurobiology of consciousness and anesthesia.

The field of consciousness studies is complicated by the indiscriminate use of the term *consciousness*. In this discussion of consciousness, *subjective experience* is meant. As has been suggested, consciousness is what we lose when we have dreamless sleep and what we regain again in the morning upon awakening.[3] There are several important definitions and distinctions that should be considered.

1. **Awareness**: Cognitive neuroscientists and philosophers use the term *awareness* to mean only subjective experience. In clinical anesthesiology, the term *awareness* is used (inaccurately) to include both consciousness and explicit episodic memory (the taxonomy of memory will be discussed in the next major section of this chapter).[11]
2. **Wakefulness versus Awareness**: *Wakefulness* refers to the state of being arousable, which can be manifest by sleep-wake cycles and can occur even in pathologic conditions of unconsciousness such as vegetative states. Thus, being awake is dissociable from being aware.[14]
3. **Phenomenal versus Access Consciousness**: Phenomenal consciousness is a subjective experience itself, whereas access consciousness is that which is available to other cognitive processes, such as working memory or verbal report.[15]
4. **External versus Internal Consciousness**: External consciousness is the experience of environmental stimuli (e.g., the sound of an orchestra), whereas internal consciousness is an endogenous experience (e.g., a dream state).[16]
5. **Consciousness versus Responsiveness**: An individual may fully experience a stimulus (e.g., the command "Open your eyes!") but not be able to respond (as when a patient is paralyzed but conscious during surgery).[17,18]
6. **Levels of Consciousness versus Contents of Consciousness**: Levels of consciousness can include alert versus drowsy versus anesthetized, whereas the contents of consciousness refers to the particular phenomenal aspects such as a red rose versus a blue ball.

SYSTEMS-BASED APPROACH

There have been a number of theories proposed to explain the mechanisms of consciousness and general anesthesia. Advances in neuroscience, however, have now enabled us to move beyond speculative frameworks and focus on a systems-based approach to both subjects.[19] The remainder of this section on consciousness will adopt such an approach by discussing (1) brainstem and hypothalamic nuclei regulating the sleep-wake cycle (and therefore arousal states), (2) the role of the thalamus in consciousness and anesthesia, (3) cortical-subcortical connectivity, with a focus on the thalamocortical system, (4) corticocortical communication, and (5) network-level organization.

SUBCORTICAL NUCLEI REGULATING AROUSAL

It was hypothesized in the mid-1990s that anesthetics suppress consciousness by actions at the subcortical nuclei that evolved to control sleep-wake cycles.[20] The past decades have supported the hypothesis that anesthetics interact with a number of these sleep-wake centers,[21] although precise interactions and contributions to the state of general anesthesia have yet to be elucidated. The following is a description of select subcortical nuclei in the brainstem and hypothalamus that mediate sleep-wake cycles and, potentially, some traits of anesthesia. The basic neurochemistry of the sleep-wake cycle is shown in Figure 13-1.

Brainstem

Locus Ceruleus. Norepinephrine is synthesized in the locus ceruleus (LC), which is located in the pons and projects widely throughout the cortex.[22] Like other monoaminergic neuronal populations, LC activity is highest during waking consciousness, decreased during non–rapid eye movement (NREM) sleep, and at its nadir during rapid eye movement (REM) sleep.[23,24] Thus, the LC is associated with cortical arousal only during wakefulness and not with the cortical activation during REM sleep. LC neurons are hyperpolarized by halothane.[25] The role of norepinephrine (generated by the LC) in anesthesia is likely important because barbiturate anesthesia time is increased by antagonizing norepinephrine and reduced by agonizing it.[26,27] Norepinephrine transmission in the basal forebrain may be of particular relevance to anesthetic depth.[28] The LC and the role of norepinephrine in hypnosis are of particular interest because of the alpha-2 agonist dexmedetomidine in clinical care. Microinjection of dexmedetomidine in the LC results in reduced levels of consciousness that can be prevented by coadministration of the alpha-2 antagonist atipamezole.[29] Expression of c-fos, a marker of antecedent cellular metabolism, after exposure to dexmedetomidine mimics NREM sleep in that the LC and tuberomammillary nucleus (TMN) are deactivated, whereas the ventrolateral preoptic nucleus (VLPO) is activated.[30] However, recent data in dopamine-β-hydroxylase knockout mice (which lack the ability to synthesize norepinephrine) demonstrate a hypersensitivity to dexmedetomidine, suggesting alternative mechanisms of action.[31] In addition, administration of ketamine increases c-fos expression in the LC,[32] which appears to contribute to its anesthetic effects.[33]

Laterodorsal/pedunculopontine tegmentum (LDT/PPT). Along with the basal forebrain, the laterodorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT) in the pons are the brain's source of acetylcholine and project throughout the cortex.[34] There are also direct projections to the thalamus with a known role in the generation of slow oscillations and sleep spindles,[35] which together represent a neurophysiologic sign that information transfer to the cortex is likely blocked.[36] As with the noradrenergic LC, activity of the LDT/PPT is high during waking consciousness and decreases during

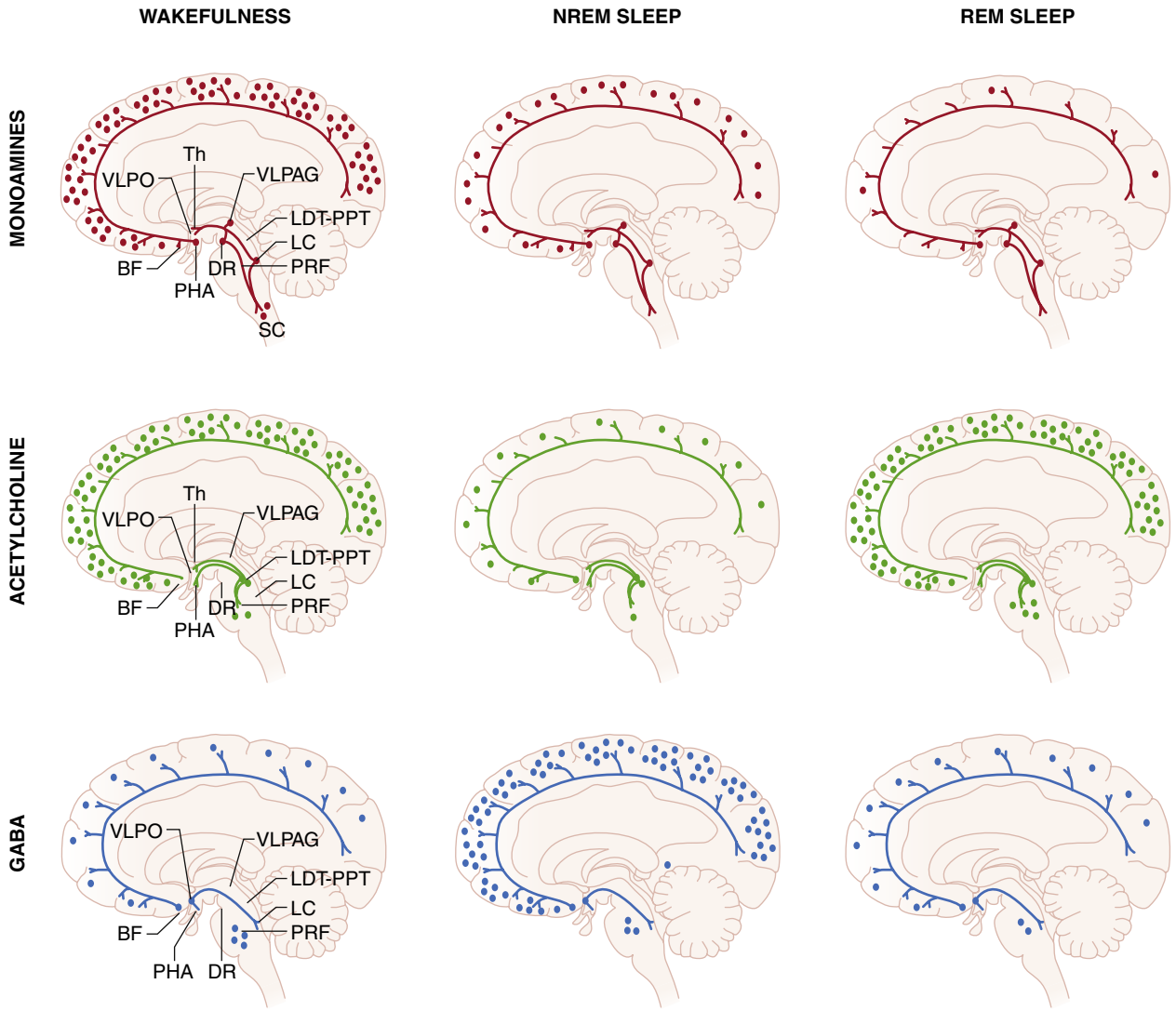


Figure 13-1. Neurochemistry of sleep and wakefulness. State-dependent changes in monoaminergic (*red*), cholinergic (*green*), and γ-aminobutyric acid (GABA)ergic (*blue*) neurotransmitter systems across the sleep-wake cycle. The density of the dots at the schematized nerve terminal reflects the state-dependent increases or decreases of release of the particular neurotransmitter. Monoamines (e.g., norepinephrine) have peak release during wakefulness, with decreases during non–rapid eye movement sleep and a nadir during rapid eye movement (REM) sleep. Cholinergic transmission is associated with cortical activation during waking or REM sleep. Acetylcholine and GABA have an inverse relationship across the sleep-wake cycle. The "shared circuits" of sleep and anesthesia suggests that general anesthetics have their effects through, in part, the sleep and arousal centers identified in the figure. *BF,* Basal forebrain; *DR,* dorsal raphe; *LC,* locus ceruleus; *LDT-PPT,* laterodorsal and pedunculopontine tegmentum; *PHA,* posterior hypothalamic area; *PRF,* pontine reticular formation; *SC,* spinal cord; *Th,* thalamus; *VLPAG,* ventral periaqueductal gray; *VLPO,* ventrolateral preoptic nucleus. *(Reproduced from Baghdoyan H, Lydic R: The neurochemistry of sleep and wakefulness. In Brady S, et al, editors:* Basic neurochemistry, Oxford, UK, *2012, Elsevier.)*

NREM sleep.[22] However, in contrast to the LC and other monoaminergic neurons, the cholinergic LDT/PPT is also active during REM sleep, during which the cortex is aroused. Thus, both states of cortical activation across the sleep-wake cycle are associated with high cholinergic tone. General anesthetics modulate cholinergic projections from the LDT/PPT. Sleep spindles occur during halothane anesthesia and are associated with decreased cholinergic transmission to the medial pontine reticular formation (PRF).[37,38] In addition, synaptic and extrasynaptic γ-aminobutyric acid (GABA) receptors play a role in modulating LDT neurons,[39] which could provide a direct link to molecular mechanisms of numerous general anesthetics.

Pontine Reticular Formation. The PRF is part of the reticular activating system, which plays an important role in cortical arousal. Although GABA is the primary inhibitory neurotransmitter in the brain, the actions of GABA in the PRF are associated with cortical arousal.[40] For example, there is increased time spent in the waking state when the $GABA_A$ receptor agonist muscimol is microinjected in the PRF.[41] When the $GABA_A$ antagonist bicuculline is microinjected, wakefulness is suppressed, but REM sleep (another state of cortical arousal) is triggered. Vanini and colleagues[42] found that decreased levels of GABA in the PRF correlated with isoflurane-induced unconsciousness, muscular hypotonia, and decreased respiratory rate. Since the effects of anesthetics are normally associated with a

potentiation of GABA activity, these findings highlight that a specific neuroanatomic and neurochemical milieu can play a unique and unexpected role in the mechanisms of consciousness and anesthesia. In addition, the mesopontine tegmental anesthesia area is located in the PRF. When pentobarbital is microinjected in this area, a reversible state with anesthetic traits is induced.[43]

Ventral Tegmental Area. Dopaminergic neurons of the ventral tegmental area (VTA) in the midbrain have not classically been considered key mediators of sleep-wake cycles because of relatively less evidence of state-dependent changes compared with other brainstem nuclei. This view has been challenged in sleep neurobiology,[44] and there is a renewed interest in the ability of dopaminergic activity in the reversal of general anesthesia. Studies of the dopamine agonist methylphenidate have revealed an ability to reverse the effects of both isoflurane and propofol[45,46]; preliminary evidence suggests that the VTA is the source of the dopaminergic transmission mediating arousal during exposure to anesthesia and that electrical stimulation of the VTA itself can reverse the state of general anesthesia.[47] Of note, a dopaminergic pathway regulating sleep-wake states has been identified in drosophila.[48]

Hypothalamus

Ventrolateral Preoptic Nucleus. The anterior hypothalamus plays an important role in sleep-wake regulation.[49] The VLPO is a structure in this region that transmits GABA and galanin.[50] Neurons in the VLPO are maximally active during NREM and REM sleep[51,52]; the median preoptic nucleus is also active during sleep. Of note, the activity profile of GABAergic neurons in the VLPO correlates with sleep amount, whereas the activity of GABAergic neurons in median preoptic nucleus correlates with homeostatic sleep pressure or propensity.[53] Importantly, the activity of the VLPO during sleep is correlated with inhibition of other arousal centers in the brainstem and hypothalamus.[51,54] Given its potentially central role as a mediator of sleep, the VLPO is an attractive candidate as a mediator of anesthetic-induced unconsciousness. Nelson and colleagues[55] demonstrated an increase in c-fos expression (a marker of neuronal activity) in the VLPO after systemic administration of propofol or thiopental. Eikermann and associates[56] conducted studies of rats with chronic lesions of the VLPO and found that ablation of VLPO resulted in sleep deprivation (as expected) but increased sensitivity to the effects of isoflurane.[56] This finding would argue against a critical role of the VLPO in the mechanism of anesthesia; however, acute lesions of the VLPO confer resistance to the effects of isoflurane, an effect that appeared to be mediated specifically through the sleep-active neurons in the VLPO.[57] Taken together, these data suggest that the VLPO plays a role in anesthetic-induced unconsciousness (as evidenced by acute lesion data), but the effects of sleep deprivation associated with chronic VLPO lesions could overwhelm this role. Indeed, the effects of both intravenous and inhaled anesthetics are potentiated by sleep deprivation[58,59] and by mechanisms that are likely independent of the VLPO (e.g., adenosine signaling in basal forebrain).

Orexinergic Neurons. Orexinergic neurons are found in the perifornical region of the lateral hypothalamus and provide an important arousal stimulus for the cortex. There are two types of orexin (A and B), which are also referred to as *hypocretins*. These neurons innervate other arousal centers in the brainstem and basal forebrain. Orexinergic neurons fire maximally in the waking state, are suppressed during NREM sleep, and show occasional bursts during phasic REM sleep.[60,61] Dysfunction of the orexinergic system is associated with narcolepsy in both humans and animal models.[62,63] The often dramatic delay of anesthetic emergence in narcoleptic patients[64] has motivated the study of orexin in anesthetic mechanisms. Orexins attenuate the effects of isoflurane,[65] propofol,[66] ketamine,[67] and barbiturates[68] using various measures. Local infusion of orexin in the basal forebrain is associated with electroencephalographic arousal and decreased emergence time in animals anesthetized with sevoflurane[69] and isoflurane.[70] Microinjection of propofol in the perifornical region of the hypothalamus (the locus of orexinergic neurons) is associated with a decrease in cortical acetylcholine, an important mediator of arousal.[71] Importantly, both genetic and pharmacologic studies have demonstrated that orexins do not influence induction, but play an important role in the emergence from sevoflurane and isoflurane anesthesia.[72] This seminal study suggested that there is a distinct neurobiology of induction and emergence, and formed the basis for a theory of "neural inertia" across state transitions.[73] Yet, halothane did not influence orexinergic neurons, and emergence time was not altered in orexin knockout mice.[74] Data from sevoflurane and isoflurane have recently been confirmed for propofol, which reduces c-fos expression in orexinergic neurons in rats. Infusion of orexin in the basal forebrain affects emergence but not induction time.[75]

Tuberomammillary nucleus. The TMN is located in the caudal hypothalamus and is the brain's source of histamine, an arousal-promoting transmitter. TMN activity and histamine levels are highest during wakefulness and lowest during sleep[76]; the TMN is thought to have a relationship of reciprocal inhibition with the sleep-promoting GABAergic neurons of the VLPO.[51,54,77] Histamine release in the anterior hypothalamus is depressed during sleep[78] and halothane anesthesia.[79] Systemic administration of propofol, pentothal, and the GABA agonist muscimol all result in decreased c-fos expression in the TMN, suggesting depressed activity.[55] Microinjection of histamine in the nucleus basalis magnocellularis of the basal forebrain reverses the depressant effects of isoflurane on the electroencephalogram (EEG), an effect likely mediated by H1 histamine receptors.[80] A recent study in which $GABA_A$ receptors were genetically removed demonstrated that histaminergic neurons are resistant to the effects of propofol.[81] However, at the behavioral level, there was no effect of the genetic alteration on loss of righting reflex, a surrogate for anesthetic-induced unconsciousness. Thus, the role of TMN and histaminergic transmission in the mechanism of anesthesia is still unclear.

ROLE OF THE THALAMUS

The thalamus is composed of approximately 50 nuclei and subnuclei that serve either as relays for sensory

input from the periphery ("specific" nuclei) or as multimodal, integrative regions that receive input from the cortex ("nonspecific" nuclei). The thalamus has been of continued and intense interest to those investigating mechanisms of general anesthesia. There are at least three possible roles for the thalamus in the suppression of consciousness by general anesthetics.

Thalamus as Switch

The thalamus has been proposed as an ON/OFF switch for anesthetic state transitions.[12] This theory was generated based on the consistent metabolic depression of the thalamus by a number of inhaled and intravenous anesthetics[82-84] (with the exception of ketamine[85]). The hyperpolarization of the thalamus would shift tonic firing to burst firing that—as with sleep—would prevent afferent sensory stimuli from arousing the cortex. Evidence for the thalamus as an ON switch has been derived primarily from animal experiments, in which stimulation of the centromedian thalamus by either nicotine or antibodies blocking voltage-gated potassium channels could reverse the effects of inhaled anesthetics.[86,87] Although microinjection of large doses of nicotine into the thalamus could precipitate anesthetic emergence, antagonism of nicotinic acetylcholine receptors in the same location did not appear to contribute to anesthetically induced unconsciousness. Central thalamic activation results in behavioral improvement in humans with traumatic brain injury.[88] In addition, activation of the thalamus (along with other subcortical structures) in humans is correlated with recovery from anesthesia, suggesting the involvement of the thalamus in the primitive or "core" consciousness observed at emergence.[89]

Thalamus as Cortical Readout

The studies identifying the depression of the thalamus were derived from neuroimaging modalities such as positron emission tomography (PET) or magnetic resonance imaging, which are both associated with poor temporal resolution. These studies could not distinguish definitively whether deactivation of the thalamus was a cause of anesthetic-induced unconsciousness or the consequence of a deactivated cortex. Nonspecific nuclei of the thalamus have been proposed as a computational blackboard for the cortex.[90] Thus, if the mechanism of anesthetic-induced unconsciousness was achieved primarily by a suppression of cortical computation, a depressed thalamus should be the result. To address this question, Velly and colleagues[91] conducted a neurophysiologic study using scalp electroencephalography (reflecting cortical signals) and subthalamic nuclei electrodes (which were argued to reflect thalamic activity). Induction of anesthesia with either propofol or sevoflurane was associated with cortical rather than subcortical changes, suggesting that the depression of the thalamus identified through neuroimaging studies reflected an effect rather than a cause of anesthetically induced unconsciousness.

Thalamus as Participant

The prior two possibilities treat the thalamus as a passive player in general anesthesia; however, recent theories suggest that it might play an active role. A study using human electroencephalographic data and computational modeling argued that the action of propofol on GABA receptors in the nucleus reticularis generates a hypersynchronous alpha rhythm (8-13 Hz) with the frontal cortex that potentially blocks sensory input.[92] Hypersynchrony of alpha may block the flexible corticocortical communication required for normal consciousness.[93] The potential role of thalamocortical interactions in anesthetic-induced unconsciousness stimulates additional consideration of the thalamus and its connectivity to the cortex.

CORTICAL-SUBCORTICAL CONNECTIVITY

The closely integrated function of the cortex and thalamus (which has been referred to as the *seventh layer* of the cortex) suggests that the two can be treated as a single thalamocortical system. The thalamocortical system undergoes state-dependent changes across the sleep-wake cycle, and it is thought to play a critical role in consciousness. This role is defined by its ability to integrate the activities of functionally diverse cognitive modules, a property that is central to the integrated information theory of consciousness.[94] This theory argues that consciousness is informative (in that it reduces uncertainty by discriminating among multiple possible states) and unified (in that a number of distinct modalities are fused into one experience). Based on neuroimaging data, the connectivity of the thalamocortical system has been investigated during the state of general anesthesia. A reanalysis of early PET studies demonstrating the metabolic depression of the thalamus by halothane and isoflurane revealed a disruption of thalamocortical connectivity during general anesthesia.[95] Recent studies using functional magnetic resonance imaging have refined the role of thalamocortical connectivity in anesthesia. One study identified a propofol-induced disruption of connectivity between the thalamus and lateral frontal-parietal networks, which are thought to be important for external consciousness.[96] Similarly, a study of the specific nuclei (linked to particular sensory modalities) and nonspecific nuclei (linked to integrative functions) found that disrupted connectivity between the nonspecific nuclei and the cortex best accounted for a reduction in the level of consciousness by propofol.[97] Disrupted thalamocortical connectivity has also been identified in animals anesthetized with propofol[98]; impaired functional connectivity of the thalamus and posterior parietal cortex has been found in humans exposed to 1% sevoflurane.[99] However, the finding of impaired thalamocortical connectivity in association with anesthetic-induced unconsciousness has not been universal. A functional magnetic resonance imaging (fMRI) study of propofol revealed more profound functional disconnections between the cortex and putamen, a subcortical structure in the basal ganglia.[100] In contrast, thalamic connectivity was relatively well preserved. The potential role of the striatum (composed of the putamen and caudate) in anesthetic-induced unconsciousness has been demonstrated in a study of rats undergoing isoflurane anesthesia.[101] This study was conducted with fMRI and found that the functional connection between the frontal cortex and the basal ganglia was disrupted during general anesthesia. A functional disconnection of association cortex and subcortical structures has also been shown by fMRI in a study of propofol-induced unconsciousness in humans.[102]

CORTICOCORTICAL CONNECTIVITY AND COMMUNICATION

The last three sections were organized according to a bottom-up approach to consciousness and anesthesia, starting with the brainstem and then moving to the diencephalon and thalamocortical system. Sleep is clearly generated through such bottom-up mechanisms[103]; however, it is not yet clear whether anesthetic-induced unconsciousness is accomplished through a bottom-up or top-down mechanism. If it were the latter, the effects of general anesthetics on the cortex would be of paramount importance. Early studies using PET demonstrated regional depression in cortical areas, including lateral and medial frontal-parietal networks.[104] These networks can mediate external consciousness of the environment (lateral system) and internal consciousness of, for example, dream states (medial system). Disruption of functional connectivity across the cortex during general anesthesia has been demonstrated in a number of different imaging studies using fMRI.[96,99,105-107] However, the cortex is amenable not only to fMRI but also neurophysiological techniques of assessing connectivity, enabling data on anesthetic-induced unconsciousness with improved temporal resolution. EEG can be used to measure functional connectivity (the statistical covariation of the activities of brain regions) and effective connectivity (the presumed causal influence of one brain region on another).[108] There are several key studies to consider that assess corticocortical communication (i.e., exchange of information) after anesthetic-induced unconsciousness.

As with fMRI, there is neurophysiologic evidence of disrupted functional connectivity during a variety of anesthetics. Quantitative EEG analysis of 176 surgical patients anesthetized with volatile anesthetics, propofol, and nitrous oxide suggested that there is a functional uncoupling of interhemispheric and anterior and posterior brain regions.[109] The anesthetic-mediated inhibition of anterior-posterior phase synchrony has also been shown in a rodent model.[110] However, communication between anterior and posterior brain regions may not be completely disrupted by general anesthetics. In rats, Imas and colleagues[111] measured transfer entropy in the γ bandwidth of EEG in response to visual flash stimuli and found that during isoflurane-induced unconsciousness, the anterior-to-posterior communication ("feedback" connectivity) was disrupted, whereas posterior-to-anterior communication ("feedforward" connectivity) was preserved. It was only at levels of surgical anesthesia that communication in both directions was suppressed. Lee and associates[112] studied directed connectivity in human volunteers and found that feedback connectivity from frontal to parietal regions was selectively inhibited by an intravenous bolus dose of propofol. In surgical patients undergoing induction of anesthesia with either propofol or sevoflurane, Ku and coworkers[113] used symbolic transfer entropy to identify a preferential inhibition of frontoparietal feedback connectivity in association with anesthetic-induced unconsciousness (Figure 13-2). Both directions of connectivity were suppressed at the level of surgical anesthesia, and frontoparietal connectivity returned to baseline at recovery. The unique importance of frontoparietal connectivity was demonstrated in a study of recovery from propofol-induced and dexmedetomidine-induced unconsciousness using PET scanning.[89] An investigation of human volunteers using high-density EEG has confirmed the loss of frontal-to-parietal feedback connectivity, and dynamic causal modeling has supported the hypothesis that this is indeed a corticocortical (as opposed to thalamocortical) interaction.[114] Hypersynchronized thalamocortical α rhythms[92] may be a neurophysiological mechanism for the interruption of corticocortical communication.[93] The selective loss of feedback connectivity is of particular interest to the field of consciousness research because feedforward communication can mediate subliminal (i.e., unconscious) sensory processing, whereas feedback connectivity (both within and across modalities) mediates conscious perception.[115] The findings of inhibited feedback connectivity and preserved feedforward connectivity (which is thought to mediate sensory representation) during anesthesia are consistent with results of the previously discussed fMRI studies in which sensory networks are maintained during anesthetic-induced unconsciousness. Preserved feedforward, but inhibited frontal-to-temporal connectivity, occurs in patients in vegetative states, but not in minimally conscious states or normal controls.[116] Other methods of measuring corticocortical communication, such as Granger causality, have yielded different results in terms of the directionality of information transfer.[117]

The inhibition of frontal-parietal communication is likely representative of a more global disruption of cortical communication. A study using high-density EEG and transcranial magnetic stimulation revealed an inhibition of cortical effective connectivity after midazolam-induced unconsciousness.[118] After administration of the benzodiazepine, local cortical activation could be observed at the site of magnetic stimulation, but robust evoked potentials were terminated at less than 100 ms, and cortical communication was limited (Figure 13-3). Of note, this finding is consistent with findings in NREM sleep.[119] The concordant findings could reflect a common neurophysiologic mechanism of disrupted cortical connectivity through slow oscillations, which share a number of characteristics in NREM sleep and general anesthesia.[120] A study of three epilepsy patients who received implants of both cortical grids (for clinical purposes) and a 96-channel microarray (for research purposes) sheds light on this potential mechanism.[121,122] Within 5 seconds of propofol-induced unconsciousness, there was a dramatic increase in the power of slow oscillations. Although single-unit neuronal activity was initially suppressed, it returned to baseline (or above baseline) but was fragmented into highly active and quiescent periods. Neural firing became coupled with the slow oscillation. However, the slow oscillations themselves demonstrated decay in phase coupling with increased distance across the cortex. Thus, neuronal spike activity became fragmented into "on" and "off" periods, which became temporally uncoordinated across the cortex. These neurophysiologic conditions dramatically reduce the probability of meaningful corticocortical communication. Whether the slow oscillation is a cortical or thalamocortical phenomenon is still unclear. Understanding the origin and regulation of the slow oscillation could help clarify whether anesthetic-induced unconsciousness has a top-down or bottom-up mechanism.

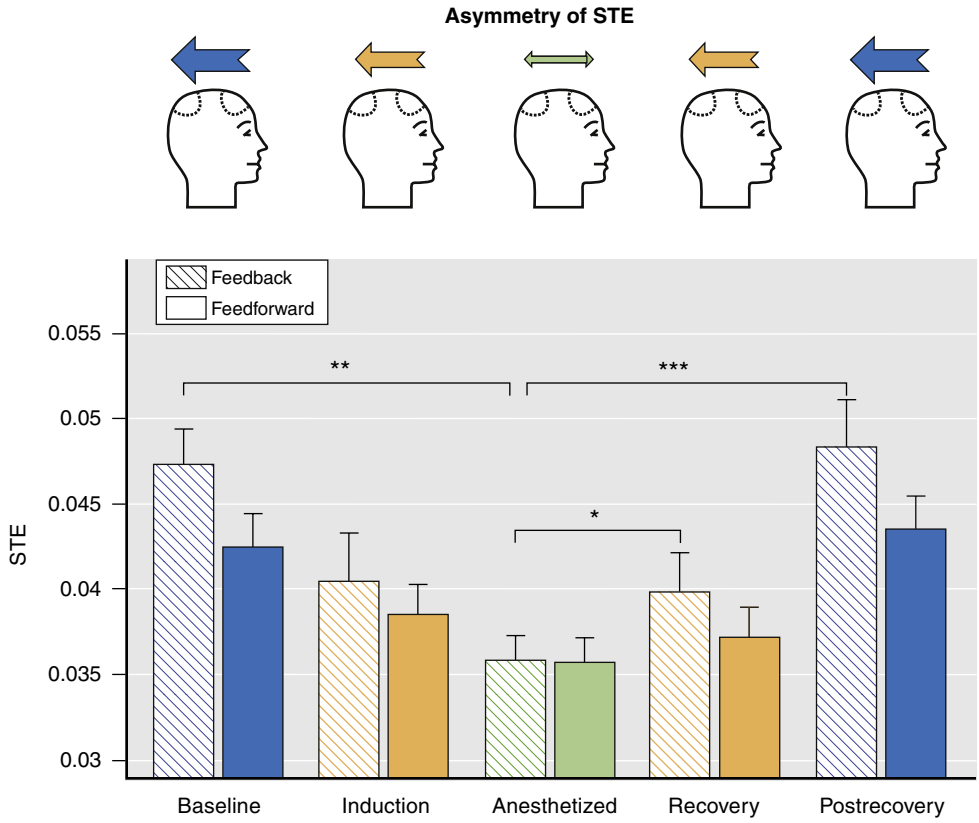


Figure 13-2. Frontoparietal communication during consciousness, anesthesia, and recovery. The lateral frontoparietal system is thought to be important for consciousness and is inhibited during general anesthesia, sleep, and vegetative states. This study of 18 surgical patients induced with propofol or sevoflurane shows state-dependent changes in communication across frontal and parietal regions, as assessed with electroencephalography and a method of measuring directed functional connectivity termed *symbolic transfer entropy* (STE). Feedback connectivity is thought to be particularly important for conscious processing and appears to be preferentially susceptible to the effects of general anesthetics. Of note, feedback connectivity also appears to be selectively suppressed (compared with feedforward connectivity) in vegetative states. *(Reproduced from Ku, et al: Preferential inhibition of frontal-to-parietal feedback connectivity is a neurophysiologic correlate of general anesthesia in surgical patients,* PLoS One *6:e25155, 2011.)*

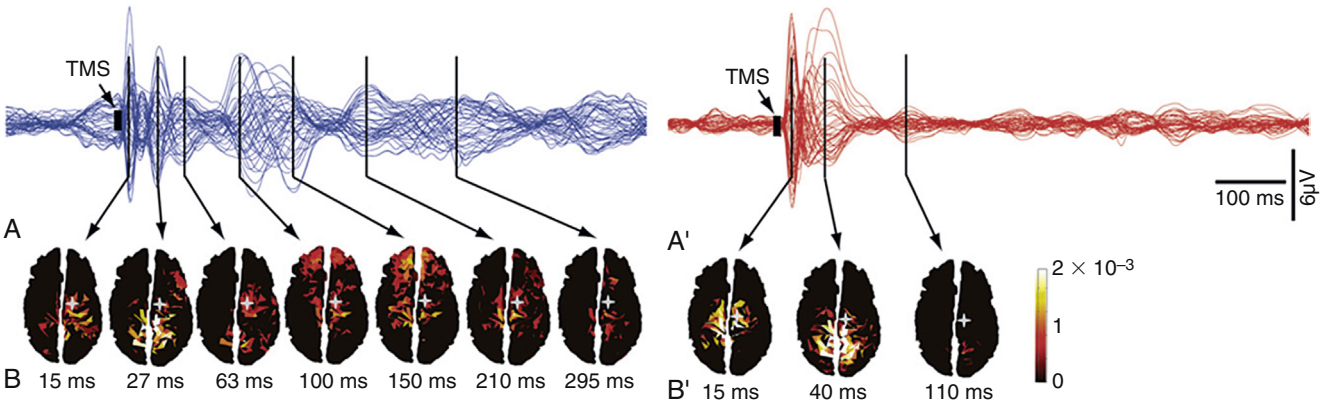


Figure 13-3. Effective connectivity and anesthetic-induced unconsciousness. Effective connectivity is the measure of causal influence among distinct brain regions. In this study, six human volunteers underwent high-density electroencephalography and transcranial magnetic stimulation (TMS) during wakefulness or midazolam-induced unconsciousness. **A** and **A′** show the potentials evoked by TMS during wakefulness **(A)** and after loss of consciousness **(A′). B** and **B′** show the cortical currents (dark red, minimal; white, maximal) in response to TMS during wakefulness **(B)** and after loss of consciousness **(B′).** Note the midazolam-induced reduction in cortical potentials and currents, which terminate at less than 120 ms. Similar findings were obtained in humans during non–rapid eye movement sleep. Importantly, cortical activation can occur during anesthesia (or sleep), but communication and causal influence (i.e., effective connectivity) across the cortex are suppressed. *(Figure reproduced from Ferrarelli, et al: Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness,* Proc Natl Acad Sci U S A *107:2681-2686, 2010.)*

NETWORK-LEVEL ORGANIZATION

It would be reasonable to assume that the widespread effects of general anesthetics on corticocortical and cortical-subcortical connectivity would lead to a complete breakdown of functional network organization in the brain. Surprisingly, this is not the case. The functional architecture associated with the performance of human sensory, motor and cognitive tasks is still present in anesthetized nonhuman primates.[123] Using electrocorticography in humans receiving propofol, Breshears and coworkers[124] demonstrated a number of dynamic neurophysiologic changes that occur against the backdrop of such preserved functional architecture. The brain can reconfigure network structure as a method of adapting to the anesthetized condition while maintaining global organization. Using EEG, Lee and associates[125] demonstrated that humans undergoing induction of anesthesia with propofol maintain scale-free features in dynamic networks despite marked changes in connectivity. The hypothesis of "adaptive reconfiguration" during anesthesia has been supported by a study of humans using fMRI, in which key organizational network properties such as "small worldness" (an organization similar to that of an airport system with large hubs) were maintained despite propofol-induced unconsciousness.[102] In rats, isoflurane is also associated with an organizational shift of networks in which the "community structures" of interacting brain regions are reconfigured, whereas small-world and other network features are maintained.[101] Thus, although critical information processing hubs (e.g., the posterior parietal cortex)[126] can be particularly susceptible to the effects of general anesthetics, it appears that important network features are maintained.

This line of investigation is important for several reasons. First, these studies suggest that key principles of network efficiency and organization are not specific to the conscious state because they persist during general anesthesia. Second, the adaptive reconfiguration of networks to maintain global organizational features may be relevant to the reversibility of the anesthetized state, in contrast to more chronic brain disorders (e.g., Alzheimer dementia, schizophrenia) in which these features are lost. Finally, these types of studies demonstrate the power of general anesthetics to probe the mechanisms of consciousness and the functional organization of the human brain. The next section discusses memory, the thread that links conscious experiences together to form the narrative of "self."

MEMORY

HISTORY AND TERMINOLOGY

Modern understanding of the structure and organization of human memory is deeply informed by the study of amnesia. As early as the seminal writings of Théodule Ribot[127] and Hermann Ebbinghaus[128] in the late nineteenth century, it was appreciated that the meticulous description of memory failure could yield valuable insights into the underlying architecture and mechanism of normal memory function. The culmination of this tradition occurred in 1957, when Brenda Milner of the Montreal Neurological Institute reported the remarkable case of Henry Gustav Molaison (1926-2008),[129] an amnesiac who would be known famously as H.M. and who would represent the single most influential case study in the history of neuroscience. In an experimental procedure intended to treat a refractory seizure disorder, neurosurgeon William Beecher Scoville removed significant portions of the medial temporal lobe (MTL) bilaterally—including the hippocampus, amygdala, and adjacent parahippocampal gyrus. Postoperatively, H.M. developed profound and enduring anterograde amnesia, and he was unable to establish any new memory, irrespective of the sensory modality. He also developed a window of retrograde amnesia and was unable to recall events occurring within the 3 years preceding his surgery. Remarkably, though, most of his associated functions—perceptual processing, language, attention, access to semantic knowledge, and capacity to retain small packages of information in constant rehearsal—remained largely or entirely intact. Before H.M., the prevailing theory—articulated by eminent neuropsychologist Donald Hebb[130]—was that there was no brain region dedicated to memory function. Instead, memory processes were thought to be distributed and integrated into region-specific perceptual and cognitive functions. As a result, for example, the visual attribute of a memory would be wholly served within the striate and extrastriate cortical regions responsible for visual perception. The description of H.M. immediately disproved this model. It became clear that the MTL was a specialized and obligatory structure for the establishment and early preservation of all modalities of conscious memory. The trajectory of memory research was powerfully transformed. Initially, largely independent branches evolved to focus on the structural-functional organization of the MTL (Figure 13-4) and the nature of cellular-level neuroplastic processes—the latter notably marked by the discovery of long-term potentiation (LTP) by Terje Lømo and Timothy Bliss in 1973.[131] Subsequently, systems-level constructs were developed emphasizing the pivotal role of oscillatory phase synchronization in neuronal assemblies and networks subserving memory.[132]

Amnesia is also the term used to describe one of the cardinal properties of general anesthesia. As understood by most anesthesiologists and the layperson, this description is phenomenological; it states that patients do not recall the events that occur to them while under anesthesia. However, this usage confuses a critical mechanistic and semantic distinction. Unlike H.M., who had intact perception and conscious experience of himself and the external environment but could not establish memories, patients in a true state of general anesthesia are unable to process and bind perceptual elements into an integrated conscious experience. From the perspective of cognitive neuroscience, the "amnesia" of general anesthesia does not constitute a problem of memory. It is a problem of consciousness. It simply reflects that a conscious experience cannot be represented and reconstructed by memory processes when it does not exist in the first place. Further confusion is added by the frequent use of the term *awareness*—a synonym for conscious perception—to describe the (usually undesirable) case in which a patient is able to

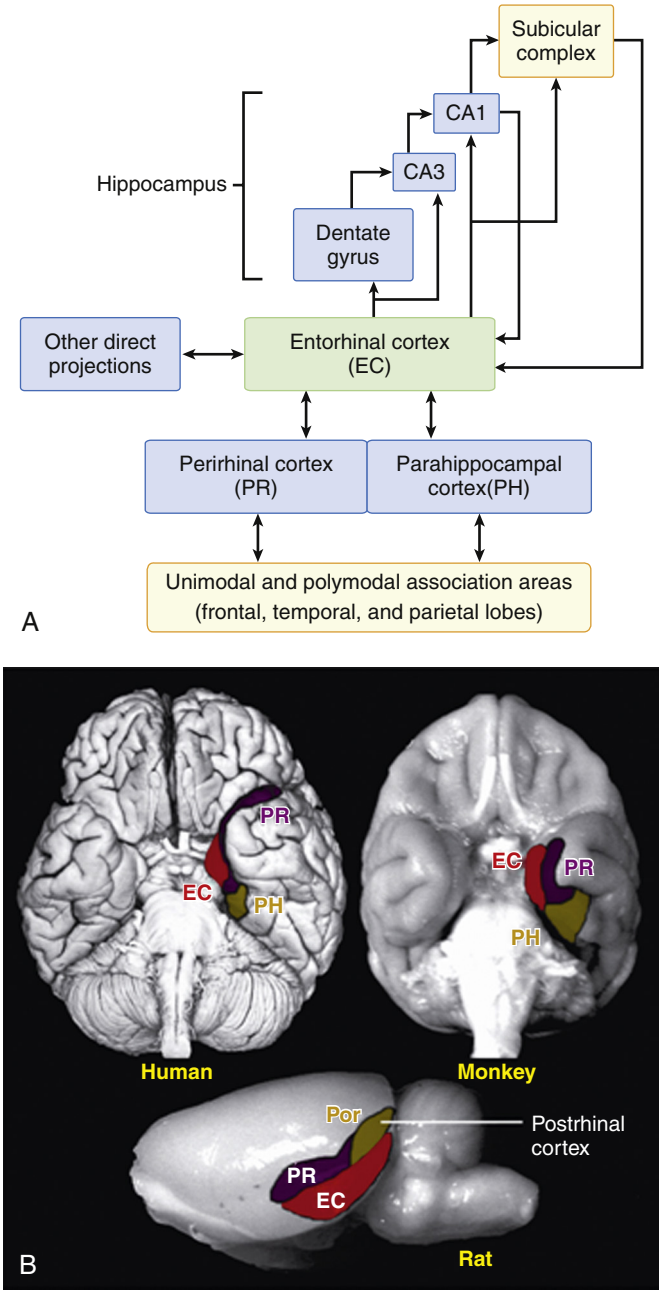


Figure 13-4. Medial temporal lobe memory system. **(A)** Schematic view of the medial temporal lobe memory system for declarative memory, which is composed of the hippocampus and the perirhinal, entorhinal, and parahippocampal cortices. In addition to the connections shown here, there are also weak projections from the perirhinal and parahippocampal cortices to the CA1-subiculum border. **(B)** Ventral view of a human brain (*upper left*), monkey brain (*upper right*), and a lateral view of a rat brain (*lower center*). The major cortical components of the medial temporal lobe are highlighted and outlined. The hippocampus is not visible from the surface, and in the human, lies beneath the cortex of the medial temporal lobe. Its anterior extent lies below the posterior entorhinal (*red*) and perirhinal (*purple*) cortices, and the main body of the hippocampus lies beneath the parahippocampal cortex. In the rat, the parahippocampal cortex is termed *postrhinal cortex*. *EC,* Entorhinal cortex; *PH,* parahippocampal cortex (*dark yellow*); *Por,* postrhinal cortex; *PR,* perirhinal cortex. *(From Squire LR, Wixted JT: The cognitive neuroscience of human memory since H.M.,* Annu Rev Neurosci *34:259-288, 2011.)*

consciously recall events occurring during the administration of an anesthetic. This ignores the fundamental lesson from H.M. that memory is functionally dissociable from consciousness. Awareness is *necessary* for the establishment of memory under anesthesia, but it is not *sufficient*. Conscious recall can occur only if awareness is accompanied by memory processes in the MTL that establish and preserve a representation that can be reconstructed later.

These statements of causality construct a framework for the scientific study of how anesthetic drugs affect memory. First, they establish an axiom: Patients who form memories while under anesthesia must possess a conscious substrate and therefore cannot be truly unconscious. Second, they pose a question: Do anesthetic drugs have direct effects on memory processes dissociable from those on consciousness? That is, are anesthetics true amnestic agents? The affirmative answer to this second question is unambiguous and is encountered in everyday anesthetic practice—in the patient receiving a small dose of propofol or midazolam who engages in a normal conversation that they are later unable to recall, or in the postanesthetic patient who has no memory of a lucid discussion with their surgeon in the recovery room.

Hidden in this everyday clinical experience is an observation of tremendous significance to cognitive neuroscience: anesthetics possess a remarkable ability to create a state of anterograde amnesia that bears a striking resemblance to that experienced by H.M. Although the study of anesthetics on memory is in infancy, its scientific foundation is the profound legacy of H.M.—more than a half century of vigorous multidisciplinary investigation into the MTL and other memory processes and systems. The promise of the research is not only to understand the mechanisms underlying the clinically relevant amnestic effects of anesthetic drugs. The selective memory effects of the drugs provide inducible, reversible, and reproducible pseudo-knockout behavioral models that can be evaluated safely in animals and humans and that are complemented by parallel knowledge of the pharmacology. Therefore, the promise of the research is also to make an important contribution to neuroscience through building on the tradition of understanding memory through the study of amnesia.

ORGANIZATION AND FUNCTION OF NORMAL MEMORY

Multiple Memory Systems

When the term *memory* is used in everyday language, it almost always refers to declarative memory. Declarative memory is the representation of prior events and knowledge that is accessible to consciousness and is manipulable by attention and executive function. It is the form of memory that H.M. was unable to establish and is the form of memory referred to in the context of anesthetic amnesia.

Further important organizational structure exists within declarative memory. The first is the distinction between episodic and semantic memory. *Episodic memory* is the recollection of events with a clear spatiotemporal context (as when recalling autobiographical events with

a distinct sense of personal experience, time, and place), whereas *semantic memory* is the capacity to recall facts and knowledge about the world without spatiotemporal context (as when recalling that Mount Everest is the tallest mountain in the world without any sense of time and place for the acquisition of that knowledge). Episodic and semantic memory are dependent on the MTL and medial diencephalon,[133] but episodic memory is additionally dependent on frontal and parietal structures.[134,135] A second organizational structure is the dual-process distinction between recollection and familiarity. *Recollection* involves remembering specific contextual details about a prior event, whereas *familiarity* represents recognition devoid of associated contextual details (as when one recognizes a face, but cannot remember a context of person, place, or time). Whether this distinction reflects the functional organization of the MTL is not clear. One model proposes that the hippocampus selectively supports recollection, whereas the adjacent perirhinal cortex supports familiarity.[136] An alternate view holds that the functional organization is not based on these psychological constructs, but on the processing of stimulus attributes[137,138]; perirhinal cortex neurons are often constrained to an attribute-specific response, and are sufficient to support familiarity judgments, but hippocampal neurons, which combine multiple attributes of a stimulus, are required for the association of an item and its context.

Early findings from H.M. suggested that other forms of memory are dissociable from declarative memory. H.M. was capable of learning a hand-eye coordination skill over several days, even while possessing no memory of having practiced the task.[139] Similar findings led to an initial distinction between declarative and *procedural* memory, with the latter being dependent on the caudate nucleus. Subsequently, memory-impaired patients were also found to have intact *priming*,[140] which is a nonconscious or *implicit* memory process in which exposure to a stimulus influences the response to a later stimulus—for example, amnesiacs can name pictures 100 ms faster if they have seen them previously, despite having no declarative memory of the exposure.[141] The neuroanatomic correlates of most priming behaviors remain poorly understood but must not rely on the MTL. In the last two decades, a large body of work, principally in rodents, has extensively elucidated the *emotional learning* system, which is experimentally studied using classical (Pavlovian) and variant fear conditioning paradigms: an emotionally neutral conditioned stimulus is paired with an aversive unconditioned stimulus, leading to an involuntary associative response to the conditioned stimulus. This is dependent on convergence in the lateral nucleus of the amygdala[142] and can occur in the absence of conscious perception.[143] With these progressive developments, the initial distinction between declarative and procedural memory eventually shifted to a framework that accommodated multiple memory systems in the brain.[144] Although these systems are distinct, the term *nondeclarative memory* is often used as an umbrella to collectively distinguish them from MTL-dependent declarative memory.

Usually considered separately, *working memory* refers to the capacity to maintain limited amounts of information in mind, which can be manipulated to perform complex cognitive tasks such as reasoning, comprehension, and learning.[145] The concept of working memory evolved from, and has largely replaced, earlier ideas about *short-term memory*, but the terms should not be used interchangeably. Working memory implies both a short-term memory store and the capacity for manipulation. The most influential current model, first proposed by Baddeley and Hitch in 1974,[146] divides working memory into capacity-limited component subsystems: a *phonological loop* that maintains information through vocal or subvocal rehearsal, such as when one holds a telephone number in mind; a *visuospatial sketchpad*, which holds and manipulates spatial, visual, and kinesthetic information; and a *central executive*, which is responsible for regulating selective attention and inhibition. A fourth subsystem, the *episodic buffer*, was recently added to the model[147] and is responsible for temporarily storing multidimensional representations and integration with declarative memory.

H.M. possessed intact working memory, and subsequent investigations continue to reinforce the view that working memory is not supported by the MTL.[148] Rather, working memory appears to be served by a distributed cortical network with a critical executive hub that is situated in the dorsolateral prefrontal cortex and is interconnected with the parietal cortex, thalamus, caudate, and globus pallidus.[149] This functional and structural distinction between working memory and the MTL does not mean that working memory and declarative memory systems do not interact. Working memory depends on declarative memory representations to provide semantic meaning and context. During working memory tasks, cortical perceptual areas associated with representations of declarative memory become activated and show increased synchrony with prefrontal regions.[150] Reciprocally, the establishment of declarative memory is strongly influenced by the nature of processing occurring in working memory, with deeper levels of executive processing resulting in better learning.[151]

Intuitively, one might suspect that the relationship between working memory and declarative memory was sequential—that is, information that is established in declarative (long-term) memory is longitudinally transferred from working (short-term) memory. However, this conclusion may be incorrect based on rare case examples of patients who have a selective short-term memory deficit but intact declarative memory function.[152] The presence of information in working memory and then in declarative memory retain "appears to occur". Understanding is not so definitive to go beyond this. via parallel (albeit interacting) processes and not through sequential transfer.

Long-Term Potentiation, Synaptic Tagging, and the Consolidation Model of Memory

The consolidation hypothesis of memory was first proposed by Müller and Pilzecker in 1900.[153] They noted that memory for new information could be disrupted by learning other information shortly after the initial training. This effect, called *retroactive interference*, is temporally graded such that the susceptibility of the memory is greatest immediately after learning and decreases with time. Müller and Pilzecker proposed that the memory trace must initially exist in a fragile state, but subsequently becomes stable through the process of *consolidation*.

The consolidation hypothesis remains the framework for understanding the temporal course of memory processes and behavior.[154] Consolidation was what H.M. was unable to perform and, as discussed later, consolidation appears to be the critical functional target of amnestic anesthetics.

For a memory trace to be consolidated, it must of course be created. The term used to describe this process is *encoding*. Encoding implies that the networks serving the neural representation of an event do not immediately return to their previous state, and are modified in such a way that potentiates reactivation of that representation. Within the framework of the *synaptic plasticity* and *memory hypothesis,* which states that activity-induced synaptic plasticity is both necessary and sufficient for the information storage underlying memory,[155] encoding therefore implies that some form of synaptic plasticity has been initiated. However, to be viewed correctly as a separate process from consolidation, encoding cannot in itself assure the propagation of a memory trace. Encoding creates the potential for the formation of a long-term memory.

The minimal events that constitute initial synaptic potentiation as it relates to memory, that is, the neural correlates of encoding, are incompletely understood. An immediate functional expression of change in synaptic strength seen in cellular models can occur in the absence of any structural change in dendritic spines.[156] Therefore, the most nascent form of potentiation can be mediated by purely functional changes: a presynaptic increase in glutamate neurotransmitter release, and increased postsynaptic incorporation of α-amino-3-hydroxyl-5-methyl-isoxazole-propionate receptors (AMPARs).

The perpetuation of these initial changes in synaptic strength through structural and functional remodeling represents the neural correlate of memory consolidation. The prevailing cellular model for this is LTP, which describes a durable increase in synaptic transmission efficiency following a stimulation protocol. The initial description reported that high-frequency stimulation of the perforant path (connecting entorhinal cortex to hippocampus) caused a sustained increase in synaptic transmission in the dentate gyrus.[131] It is now recognized that LTP occurs richly throughout the hippocampus (although the synapses between the Schaffer collateral and commissural axons and the apical dendrites of CA1 pyramidal cells are most frequently investigated), as well as in other afferent pathways.[157] In addition, in addition to high-frequency stimulation, which is nonphysiologic, LTP can be induced by stimulation protocols that resemble physiologic activity, the most important of which are bursts in the hippocampal theta (θ) range (4 to 8 Hz).[158] This is of particular relevance to memory, because synchronized hippocampal θ oscillations appear critical to successful memory behaviors.[132]

The breadth and depth of literature on the mechanisms of LTP are far too voluminous to summarize here. Nonetheless, certain principles are essential and relevant to anesthesia studies and can be stated succinctly. The induction of most forms of LTP requires activation of postsynaptic *N*-methyl-D-aspartate (NMDA) receptors, and specific NMDA receptor antagonists block the induction of LTP.[159] On depolarization, Mg^{2+} dissociates from its binding site in the receptor, allowing influx of Ca^{2+}. This rise in intracellular Ca^{2+} is the critical trigger for LTP. Next, downstream activation of calcium-calmodulin-dependent kinase II (CaMKII) is required,[160] which is maintained by autophosphorylation.[161] CaMKII and integrin-driven actin polymerization are necessary for the initial cytoskeletal reconfiguration.[156,162] Activation of several other cell-signaling cascades also contribute to LTP: cyclic adenosine 3′,5′-monophosphate (cAMP)-dependent protein kinase, protein kinase C, tyrosine kinase, phosphatidylinositol 3-kinase (PI 3-K), and mitogen-activated protein kinase (MAPK/ERK). The downstream effects of MAPK/ERK activation are diverse and include as substrates the nuclear proteins *c*-Myc, *c-fos*, and *c-jun*, cytoskeletal proteins Tau and MAP-2, Elk-1, and cAMP response-element binding protein.[163] The terminal expression of LTP is protein synthesis, occurring in both the soma and local dendrites, and resulting in enduring structural changes at the synapse.[164,165] A large number of experiments have demonstrated protein synthesis inhibitors to prevent sustained LTP in vitro and learning in vivo.[166]

LTP thus proceeds in two phases, corresponding to memory phases observed across multiple species. Early LTP (E-LTP) is the phase independent of protein synthesis and can be sustained across an interval of minutes to a short number of hours. Late LTP (L-LTP) is dependent on intracellular signaling and protein synthesis and can be sustained across many days. The MAPK/ERK cascade likely represents the critical transition between the two phases.[157,164] However, LTP in simple systems is incomplete in explaining the time course of human memory, which can endure over years or decades.

A contemporary theory that explains several characteristics of LTP, and conceptually bridges encoding to long-term memory, is the *synaptic tagging* and *capture hypothesis*.[167] In this model, encoding sets a synaptic tag—a temporary change in the structural state of the synapse—that is dependent on CaMKII. This tag establishes the potential for long-term structural changes, but for the cascade to continue the tags must capture plasticity-related proteins (PRPs) synthesized in the soma or dendrites. The tag exists for a limited time window, and in the absence of arrival and capture of PRPs, it will decay and the potential for the transition to long-term structural changes will expire. In contrast, if PRPs are captured a cascade of presynaptic and postsynaptic changes are triggered[168] and lead to the induction of L-LTP. What makes the synaptic tagging model so attractive to systems-based models of memory is that it allows the thousands of dendrites of a single neuron to support memory stabilization processes at various states of evolution because the tagging and PRP capture need not occur as a singular event. In other words, past and future PRP release modulates the fate of the tag. This nondeterminism is consistent with true memory behavior, which in multiple contexts is influenced by events preceding and following encoding.

Reconsolidation

For decades, the understanding of memory consolidation was that it was a unitary process; that is, once protein

transcription occurred and a memory trace was stabilized, it was no longer dynamic and underwent gradual decay. In 2000, Nader and colleagues[169] reported that an old memory for auditory fear conditioning, which would normally not be sensitive to protein inhibitors, can be made newly sensitive if it is retrieved. The implication was that retrieval of a memory renders it transiently plastic, after which it restabilizes. This process is termed *reconsolidation* and has been subsequently demonstrated in multiple settings and species, including in human behavioral paradigms.[170,171] Reconsolidation can be viewed as a modulatory process that mediates strengthening of an existing memory, but it is clear that it also provides a window in which the existing memory is malleable and can be updated with the addition of novel information.[172,173] Both explicit recall and implicit internal reactivations—as likely occur during sleep—elicit reconsolidation events. Reconsolidation shares many of the cellular mechanisms of LTP that are associated with initial consolidation. However, the temporal dynamics differ, and consolidation appears to require several areas that are not required for reconsolidation.[174] Reconsolidation may represent a modulatory phase of an extended consolidation process. Certainly, most pharmacologic agents—including anesthetic drugs—that inhibit consolidation would be rational candidates for similar effects on reconsolidation.

Phase Synchronization

The neurons in assemblies and networks do not function in isolation but undergo oscillatory activation and inhibition. Phase synchronization of these oscillations, which coordinates the excitability of related neurons, is a fundamental neural mechanism. It supports neural communication by creating transient and dynamic associations between different functional brain regions. For example, a significant body of evidence supports the hypothesis that γ-phase (~40 Hz) synchronization binds the regions serving the various attributes of a conscious perception.[175]

Phase synchronization appears to be fundamental to neural plasticity and memory,[132,176] and studies have shown that increased synchrony during encoding is predictive of improved learning and memory.[177-179] γ-Phase synchronization is believed to support Hebbian plasticity in the hippocampus; that is, plasticity that involves the coordinated firing of presynaptic and postsynaptic neurons. The frequency of γ oscillations is optimal to coordinate presynaptic and postsynaptic inputs inside a window of 10 to 30 ms, which is key to the induction of LTP in so-called spike-timing-dependent plasticity.[180] However, γ synchrony cannot fully explain declarative memory, in part because the phase is not time-locked to a stimulus; that is, γ synchrony supports the induction of plasticity in a network serving a memory, but is agnostic to specific content. Here, significant interest has focused on θ-phase (4 to 8 Hz) synchronization, which in contrast to γ undergoes phase reset in response to a stimulus. Many studies have connected θ reset and phase synchrony with LTP and successful declarative learning.[181-184] Furthermore, amygdalo-hippocampal θ synchronization has been identified as critical in fear-based memory.[185-187] θ-Dependent plasticity is non-Hebbian, in that it is determined only by the incoming (presynaptic) conditions. LTP is induced only during the peak of a θ oscillation,[182] and so θ phase reset and synchronization may therefore function to coordinate input from broadly distributed brain regions. A cooperative relationship between θ and γ synchrony exists such that the phase of γ oscillations are coupled to the amplitude (phase-amplitude coupling) or phase (phase-phase coupling) of the slower θ oscillation.

EFFECTS OF ANESTHETIC DRUGS ON DECLARATIVE MEMORY FUNCTION IN HUMAN SUBJECTS

The theoretical number of mechanistic pathways through which an anesthetic drug could cause amnesia is enormous, most of which cannot be directly assessed in human subjects. However, the putative candidates can be dramatically narrowed by appreciating that memory-related processes are constrained to operating within a specific time domain and in a specific neuroanatomic location. A significant emphasis of current research in humans is therefore the drive to define the temporal and neuroanatomic characteristics of anesthetic amnesia precisely, because these characteristics richly inform and dismiss hypotheses regarding underlying mechanisms.

Behavioral Studies of Retrograde Amnesia and Retrograde Facilitation

Although some anecdotal accounts and isolated case reports have led to occasional confusion, in systematic investigations there is no evidence that anesthetic drugs cause retrograde amnesia in humans. Studies in the early 1970s found no retrograde amnesia with the administration of thiopental (6 mg/kg) and methohexital (4 mg/kg).[188] Adult patients have normal memory for visual stimuli presented 4 minutes before administering midazolam (2, 5, and 10 mg[189]). Similarly, memory is normal for word lists learned in the preoperative holding area or operating room immediately before induction,[190] and for pictures viewed immediately before propofol induction.[191] Studies of pediatric patients have shown normal memory for pictures presented immediately before sedation with both midazolam[192] and propofol[193] (see Chapter 93). In controlled laboratory settings using human volunteer subjects, there is no impairment of memory for pictures[194] or words[195,196] presented before target-controlled sedative infusions of propofol (brain concentration [C_{es}], 0.3 to 2.5 μg/mL), midazolam (20 to 35 ng/mL), thiopental (2 to 7 μg/mL), or dexmedetomidine (0.25 to 0.8 ng/mL).

A recent study[197] described an experiment in which volunteer subjects learned a word list and were then immediately administered a steady-state infusion of either propofol (0.9 μg/mL) or placebo for 90 minutes. Memory for the words was tested at several intervals across a time domain spanning from 20 minutes to 24 hours after encoding. In contrast to finding retrograde amnesia, propofol subjects paradoxically retained more material than did placebo subjects. A similar effect is described for midazolam in the psychology literature.[198] This phenomenon is called *retrograde facilitation*. The basis is best appreciated by considering the opposite effect, called *retrograde interference*—the observation that mental exertion, especially that engaging memory processes, inhibits the consolidation of recently formed memories, with the

newest memories being most vulnerable.[199] In mechanistic analogues, it is clear that the induction of new LTP interferes with recently formed LTP and memory performance, even when the tasks are unrelated.[200,201] When the induction of new LTP is blocked by a selective NMDA antagonist such as AP5 or CPP, interference with recently formed LTP does not occur, and memory performance improves[202-204]—that is, the analogue of retrograde facilitation occurs. The most parsimonious explanation for the retrograde facilitation seen with propofol and midazolam is that it similarly blocks the induction of new LTP—albeit likely via a GABAergic pathway—freeing consolidation resources that enhance the survival of recently formed LTP.

The finding of retrograde facilitation and failure to identify retrograde amnesia strongly suggest that the mechanism of anesthetic amnesia is restricted to induction processes in the consolidation cascade. Induction failure will have effects on downstream processes, but it is more difficult to rationalize that downstream elements represent independent targets. To illustrate: if a drug had a direct effect on a process occurring t_c minutes after encoding, the effect would be to block consolidation for an event that occurred t_c minutes in the past, creating a clear retrograde amnesia window. Although current studies do not have the temporal resolution to dismiss the possibility of drugs targeting processes commencing only seconds after the initiation of E-LTP, later stages of the E-LTP time domain, and the time domain covering the transition from E-LTP to L-LTP have certainly been tested. The strongest counterargument to the induction hypothesis has suggested a direct role for downstream protein transcription processes,[205] but the temporal window in which this might occur remains undefined.

Clinically, there is no basis for the use of any anesthetic drug as a retroactive treatment for the prevention of intraoperative awareness with recall. Acute stress and anxiety have complex noradrenergic-mediated effects on memory that can cause anterograde and retrograde amnesia surrounding emotional events,[206,207] and this constitutes a credible explanation for the small percentage of patients who do not recall the immediate preanesthetic period.

Mathematical Modeling of Anesthetic Amnesia

Attempts to model mathematically what happens to memory over time date back to the late nineteenth century, when Ebbinghaus[128] demonstrated that memory decay is characterized by a rapid initial decline, followed by a more gradual loss. Nearly a century later, Wickelgren[208] developed a complex predictive model that is neuroscientifically attractive because its component elements—the coefficients—are hypothesized to index specific memory processes. The most complete version of the *Wickelgren Power Law* is as follows:

$$m_t = \phi\,(1 + \beta t)^{-\psi} e^{-\pi t}$$

where m_t is memory at time t, ϕ reflects the degree of initial learning (and is thus a measure of encoding strength), β is a scaling constant derived from differential equations describing memory trace fragility, ψ describes the core decay characteristics (and thus reflects consolidation processes), and the exponential term $e^{-\pi t}$ expresses decay caused by interference from interpolated material that is similar to the learned items.

A simplified version of the Wickelgren Power Law was applied in a large human volunteer study to characterize the amnestic effects of several intravenous anesthetic drugs.[195] Using reasonable assumptions, the complete equation was reduced to a two-parameter power decay function:

$$m_t = \lambda t^{-\psi}$$

where λ reflects the initial memory strength (the encoding index), and ψ expresses the rate of decay (the consolidation index). A given memory state m_t is thus a function of two variables that can theoretically be modulated independently. The power of the mathematical modeling technique is that it enables characterization in terms of both encoding failure (decreased λ) and consolidation failure (increased ψ). In contrast, measurement of m_t at a single point in time—that is, simply sampling how much has been forgotten after t minutes—captures no such information.

The two-parameter power decay function accurately describes the temporal course of amnesia for subjects receiving propofol (0.45/0.90 μg/mL), midazolam (20/35 ng/mL), dexmedetomidine (0.20/0.40 ng/mL), and thiopental (1.5/3.0 μg/mL); it also characterizes the drugs by demonstrating marked differences in the way they modulate the component elements. Propofol, a moderately selective $GABA_A$ receptor agonist, is an archetypal amnestic drug: it permits robust encoding of material, but the information undergoes accelerated decay because of a failure of consolidation. In contrast, dexmedetomidine—a highly selective α_{2A}-adrenoceptor agonist that causes a widespread decrease in noradrenergic tone throughout cortical and subcortical structures—archetypally conserves consolidation, but leads to memory impairment because of a failure of information to be strongly encoded. Thiopental—less selective than propofol, but which nonetheless shares the $GABA_A$ receptor as its primary target—interestingly behaves similarly to dexmedetomidine, causing marked encoding failure but demonstrating minimal effect on consolidation. The benzodiazepine midazolam, another $GABA_A$ receptor agonist long used clinically for its amnestic potency, behaves like propofol at lower doses—selectively causing consolidation failure while leaving encoding intact—but with increasing dose a significant encoding impairment emerges. The discrepant patterns observed in the three GABAergic drugs demonstrate that nonspecific $GABA_A$ agonism per se is not sufficient to explain the ability of a drug to cause consolidation failure.

Neuroimaging Studies of Cortical Encoding Processes

A small number of functional neuroimaging studies have evaluated the effect of anesthetics on cortical regional activation during memory encoding. An early PET study investigated propofol (0.52/0.83 μg/mL) using a word memory task.[209] In this study, the regions of interest were the left inferior prefrontal cortex (LIPC), associated with successful encoding,[210] and the dorsolateral prefrontal cortex (DLPFC), a region most associated with executive

functioning. LIPC activation was conserved, suggesting that propofol did not block the processes required to support successful encoding. DLPFC activation was decreased. In a subsequent investigation using an auditory depth of processing task, LIPC function was again found to be preserved with propofol (0.9 μg/mL), but was decreased with thiopental (3.0 μg/mL).[211] Although thiopental subjects had inferior LIPC activation at the time of encoding, propofol subjects had a significantly poorer memory performance at 200 minutes. The characterization of the drugs based on functional neuroimaging is thus congruent with that derived from mathematical modeling: thiopental impairs memory because information fails to be encoded, whereas propofol exhibits a clear amnestic potency that is unrelated to its effect on encoding processes.

An earlier PET study of midazolam (74/129 ng/mL) using an oddball detection paradigm reported a dose-dependent decrease in activation in Brodmann areas 9, 10, and 46, which overlap regions of both DLPFC and LIPC. Interpretation of this study in context of memory function is difficult, because the experimental task was not memory-related. A recent fMRI study of dexmedetomidine (0.15 ng/mL) reported a generalized effect of bilateral prefrontal suppression in Brodmann areas 9 and 10 during an emotional picture memory task, but no detailed analysis of cortical encoding activation was conducted.[212]

Studies of the Relationship Between Encoding and Attention or Arousal

A convergence of evidence suggests that the effect of anesthetic drugs on encoding processes is related to the modulation of attention. Attention is necessary for the successful establishment of declarative memory,[213] with distinct networks required for maintaining an alert state, orienting to targets, and for exerting executive control of thought.[214] Attention is thus a prime modulator of the assembly of an integrated conscious percept and the depth of its processing, although the degree to which attention and consciousness are dissociable remains a topic of current debate. The dominant effect on attention for most anesthetic drugs is that of decreasing arousal, which of course progresses to profound sedation and unconsciousness as dose is increased. The NMDA antagonist ketamine is a notable exception, with dominant effects on orienting and selection.[215] A complete understanding of anesthetic amnesia cannot be achieved unless the effect of modulating arousal and attention is dissociated from effects on memory-specific processes, a principle articulated by Veselis and colleagues[216] and followed in a series of studies.

In PET neuroimaging, the effect of thiopental on LIPC mimicked that of adding an attentional challenge task to the memory paradigm in placebo subjects.[211] A study of propofol (0.3 to 2.5 μg/mL), thiopental (2 to 7 μg/mL), and dexmedetomidine (0.25 to 0.8 ng/mL) demonstrated that memory retention at 33 seconds—an interval sufficiently short so as to be dominated by encoding strength rather than consolidation—was related to the level of arousal.[196] Arousal was also predictive of memory at 225 minutes for thiopental and dexmedetomidine, whereas propofol caused a significantly greater loss of memory than would be predicted by modulation of arousal alone. Thus, arousal was found to be predictive of subsequent memory only for drugs that cause memory impairment through encoding failure.

Further evidence for the relationships among arousal, attention, and encoding come from the mathematical modeling study described earlier.[195] In that study, arousal predicted the coefficient of encoding strength (λ) with remarkable precision for dexmedetomidine, thiopental, midazolam, and the propofol 0.45 μg/mL. The one exception was subjects receiving propofol 0.90 μg/mL; they had better encoding strength than would be predicted for their level of sedation. Notably, this paradoxic effect was observed at the same concentration at which excitatory phenomena emerge in neuronal network models, wherein an interaction between $GABA_A$ current and an intrinsic membrane slow potassium current (M-current) lead to interneuron asynchrony.[217] Paradoxic improvements in cognitive function following the administration of low concentrations of GABAergic drugs are also reported in patients in pathologic, minimally conscious states, probably because of the release of inhibitory control signals.[218]

Studies of Hippocampal Function

Despite its critical role in memory, few neuroimaging or electrophysiologic studies have been directed toward evaluating hippocampal function during anesthetic amnesia in humans. The deep location of the hippocampus makes it inaccessible to surface EEG, and in standard fMRI acquisition protocols it is susceptible to signal artifact from the pharyngeal air-tissue interface (although contemporary acquisition techniques have reduced this limitation). PET studies require signal to be acquired as a block of multiple stimuli that cannot be individually separated and analyzed based on subsequent memory behavior. Only event-related fMRI, which is technically challenging, permits individual hippocampal activations to be grouped and analyzed according to the ultimate fate of the memory—something that cannot be known at the time the image is captured.

Two recent studies have used event-related fMRI to evaluate hippocampal activation during amnestic infusions of propofol (0.90 μg/mL)[219] and dexmedetomidine (0.15 ng/mL).[212] Although earlier reports found that propofol does not significantly attenuate hippocampal and peri-hippocampal activity at rest,[84,220] the event-related fMRI study demonstrated that propofol causes a generalized attenuation of hippocampal activation in response to all stimuli, and the degree of this attenuation correlates with the degree of amnesia. The study design provided solid behavioral confirmation that encoding had occurred; therefore, the hippocampal attenuation likely corresponded to a failure of consolidation processes. Dexmedetomidine attenuates the subsequent-memory effect—that is, dynamics of hippocampal activation become less predictive of subsequent memory, but the overall level of hippocampal activity appears preserved. In contrast to propofol, the explanation offered here is that upstream cortical actions of dexmedetomidine weaken encoding, with attenuated hippocampal dynamics reflecting a downstream effect. Hippocampal attenuation during encoding has also been correlated with amnesia for face-name pairs for the benzodiazepine lorazepam and the cholinergic antagonist scopolamine.[221]

Attenuation was also found in DLFPC and fusiform cortex, more suggestive of an effect on distributed encoding processes than a restricted consolidation effect.[222] In a largely exploratory investigation, 0.25% sevoflurane was found to reduce hippocampal activation in response to auditory and visual stimuli, but no memory performance was assessed.[223]

A single electrophysiologic study used implanted intracranial depth electrodes in epileptic patients to evaluate the effects of propofol on hippocampal spectral coherence and power characteristics at rest.[224] At amnestic serum concentrations (0.5 to 1.0 μg/mL), there is a minimal and quite possibly nonsignificant increase in spectral power across frequency bands ranging from δ (1 to 4 Hz) through γ (32 to 48 Hz). There is a significant increase in hippocampus-rhinal spontaneous coherence in the δ band, but minimal changes in other bands: the trend is toward a slight loss of spontaneous coherence in the θ (4 to 8 Hz), α (8 to 12 Hz), β_1 (12 to 20 Hz), and β_2 (20 to 32 Hz) bands, and a slight increase in the γ band. Cortico-hippocampal coherence was not assessed. Hippocampal coherence dynamics, especially in the θ and γ bands, are of critical importance to memory function, but interpretation of rest data must be limited. This is especially true for θ coherence, for which the role in memory appears to involve phase reset in response to a stimulus. Although electrophysiologic studies of the human hippocampus are of tremendous interest, they are currently restricted to epileptic patients and introduce the possibility that data are being acquired from regions of abnormal brain.

Studies of Cortical Event-Related Potentials

The event-related potential (ERP) is a stereotypic signal fluctuation in the EEG that is time-locked to a stimulus. For any individual event, the ERP signal is overwhelmed by non–stimulus-locked EEG activity. However, by repeating the stimulus task over multiple trials (usually at least 50) and then averaging, the non–stimulus-locked EEG behaves as random noise and subtracts to zero, revealing the ERP signal. The ERP itself is a series of positive and negative fluctuations. For decades, the origin of these fluctuations was believed to be stimulus-induced activation of dormant neuronal clusters. More recently, however, consensus has favored the theory that ERPs emerge not because new oscillations are induced, but because of a stimulus-induced phase resetting of ongoing oscillations.[225] Modulations of the ERP have been associated with a significant number of cognitive processes, including many related to memory.

Curran and colleagues[226] used ERPs to demonstrate that drug-induced effects on arousal and memory may be electrophysiologically dissociable. The GABAergic benzodiazepine lorazepam (2 mg orally) and cholinergic antagonist scopolamine (0.6 mg subcutaneously) were compared with diphenhydramine (25/50 mg orally), which provided a nonamnestic, equally sedative control. Changes in the P1N1 and N1P2 early complexes, associated with arousal, were seen for all three drugs. However, changes in later complexes associated with memory, notably the P3 and N2P3, were seen only with the amnestic drugs. No ERP distinction could be made between lorazepam and scopolamine, despite their different receptor mechanisms. Interpretation of the study was limited because the paradigm used to elicit the ERPs (oddball detection) did not directly assess memory behavior.

The work of Curran and colleagues[226] was extended in a series of studies by Veselis[216,227] evaluating intravenous anesthetics. An early investigation demonstrated that propofol amnesia was associated with decreased P3 amplitude.[227] In a more sophisticated auditory memory task, with drugs dosed to cause equal levels of sedation, propofol and midazolam possessed markedly greater amnestic potency than thiopental.[216] Indeed, the relative amnestic potency of thiopental was not substantially greater than that of fentanyl. This finding provided key evidence that GABAergic agonism per se does not explain the amnestic potential of a drug: propofol and midazolam clearly possess selective memory actions that are not shared by thiopental. In a subsequent analysis, it was shown that central frontoparietal N2P3 amplitude was the best predictor of memory. N2 latency was related to the reaction time, which was interpreted to measure arousal, although some exceptions suggested that the relationship does not hold true for all drugs.

The mathematical modeling study described earlier examined early-latency and mid-latency ERPs originating from the midline parietal precuneal region (Pz).[195] The decay coefficient ψ, which indexed modulation of consolidation, was tightly correlated with the P2 amplitude and N2 latency observed at the time of encoding. As the correlation between P2N2 changes and ψ was remarkably consistent across drugs from multiple classes and at multiple doses, it suggests that while substantial variation exists in the potency of anesthetic drugs in causing consolidation failure, a common mechanistic pathway may be involved. Furthermore, the observation supports the assertion that the underlying mechanism involves induction events in the consolidation cascade; consolidation failure evolving over several hours could be predicted by electrophysiologic events occurring within several hundred milliseconds of exposure to the stimulus. An alternate analysis[228] of the study examined the "old/new effect," a robust phenomenon observed in the parietal ERP that distinguishes the response to initial item exposure from subsequent exposures. At a presentation interval of 27 seconds, no degradation in memory performance was evident, but significant attenuation of the old/new effect was observed with propofol and midazolam. In contrast, no change was observed with thiopental and dexmedetomidine. Again, the analysis distinguished the dominantly amnestic drugs from the dominantly sedative drugs and constrained the mechanism to early in the consolidation cascade.

An intriguing possibility raised by the relationship between modulation of P2N2 and consolidation failure lies in the origin of the complex. P2N2 is known to derive largely from synchronous θ oscillations,[229] which as discussed earlier are critical to non-Hebbian plasticity and strongly correlated with memory behavior. As such, one interpretation is that a common mechanism underlying the selective effect of anesthetic drugs on the induction of consolidation involves changes in θ oscillations across a distributed cortico-hippocampal network. Unfortunately, no direct measures of θ synchrony in an

appropriate memory paradigm have yet been performed, and the location of the hippocampus confers enormous methodologic barriers.

Another intriguing finding from the study was a pristine correlation between reaction time, P2N2, and the consolidation coefficient ψ, which was preserved across all drugs and dosages. In nonpharmacologic studies, reaction time has long been interpreted as an index of sedation, but in the anesthetic study, no relationship with sedation was identified; this suggests caution in interpreting it as a behavioral marker of sedation in future drug studies. Reaction time has been related to interregional synchrony.[230] Therefore, what functionally connects the effect of amnestic drugs on θ-dependent elements of the ERP and reaction time is that they may both represent a loss of synchronous activity across distributed networks.

NONHUMAN STUDIES OF ANESTHETIC EFFECTS ON HIPPOCAMPAL MEMORY PROCESSES AND BEHAVIOR

Anesthetic Effects on Hippocampal Memory Processes In Vivo

GABAergic interneurons project within and across subregions of the hippocampus,[231] providing an abundant density of rational targets for anesthetic drugs. In a study using tetanic stimulation of the Schaffer collateral-commissural pathway,[232] isoflurane (0.2 to 0.3 mM) blocked the induction of LTP. Isoflurane similarly blocked the induction of long-term depression (LTD) by low-frequency stimulation. The effect of isoflurane on both LTP and LTD was blocked by the addition of the $GABA_A$ receptor antagonist picrotoxin (50 μM), providing strong evidence that the effect of isoflurane on LTP is GABAergically mediated. In a similar protocol, amnestic concentrations of sevoflurane (0.04 mM) allow posttetanic potentiation but cause a failure of LTP, which is prevented by the addition of the $GABA_A$ antagonist bicuculline (10 μM).[233]

An early study of propofol conducted in live rats with electrodes implanted in CA1 neurons yielded unexpected results. It was suggested that propofol had little effect on the induction of LTP, but significant effects on maintenance, and that LTD was enhanced.[234] Subsequent investigations do not support these findings and have instead demonstrated that propofol inhibits the induction, but not the maintenance of LTP. Furthermore, the effect is blocked by the addition of picrotoxin, implicating a $GABA_A$ receptor-mediated mechanism.[235-237] Notably, one study found that propofol inhibited LTP only at anesthetic concentrations (50 μM), and not at amnestic concentrations (5 to 20 μM).[236] Other notable observations from this cluster of work are that propofol also inhibits NMDA-receptor–independent LTP, and the LTP-associated downregulation of the K^+/Cl^- cotransporter 2. Propofol (1 to 10 μM) has also been demonstrated to inhibit NMDA receptor-dependent activation of extracellular signal-regulated protein kinase 1/2,[238,239] an important subclass of MAPKs, which as previously discussed are a critical component of the LTP cascade. Finally, propofol reduces expression of activity-related cytoskeleton-associated protein (Arc) in the hippocampus in response to inhibitory avoidance training but does not appear to reduce Arc mRNA.[240] This finding is notable because it suggests a posttranscriptional mechanism. This effect is blocked by infusion of the GABAergic antagonist bicuculline into the basolateral amygdala (BLA), implicating an amygdalo-hippocampal network.

The hippocampal $GABA_A$ergic interneuron population is notable for a high density of the α_5-subunit subtype, which is far less common in other regions.[241] This observation has driven a series of studies by Orser[242-246] using α_5-$GABA_A$-knockout mice. The α_5 –/– mutants are resistant to the amnestic effects of etomidate, but not to its general anesthetic effects. Furthermore, etomidate blocks LTP measured in CA1 neurons in wild type mice, but not in α_5 –/– mutants.[242] In wild type mice, the effects of etomidate on LTP and memory behaviors are reversed by the addition of L-655,708, which selectively reduces the activity of α_5-$GABA_A$ receptors.[243] A later study evaluated the enduring memory effects of 1 minimum alveolar concentration isoflurane and sevoflurane by examining performance 24 hours after anesthetic administration. Memory deficits were observed in wild type mice, but not in α_5 –/– mutants or in wild types receiving L-655,708.[244,245] The amnestic effect of etomidate and volatile anesthetics thus appears to critically involve the α_5-$GABA_A$ receptor. Significantly, the α_5-$GABA_A$ receptor has recently been shown to regulate the threshold for LTP, but only in response to stimulus frequencies in the θ range,[246] thus converging with other lines of investigation suggesting that θ is a key mechanistic target.

The association of amnesia with the α_5-$GABA_A$ receptor is not exclusive. α_4-$GABA_A$ receptors are concentrated in the dentate gyrus and dorsal thalamus, and α_4 knockouts are resistant to the amnestic effects of isoflurane but not to its general anesthetic effects.[247] Likewise, β_3-$GABA_A$ receptor knockout mice are resistant to the amnestic effects of isoflurane,[248] although in an earlier study using β_3-$GABA_A$ receptor knock-in mutants, it appeared that the β_3 subtype was not a significant mediator of isoflurane amnesia.[249] Other studies have demonstrated that the α_2 subunit is not a mediator of isoflurane amnesia. A study of α_1-$GABA_A$ receptor knock-in mice suggested that the α_1 subunit was not involved in the amnestic actions of isoflurane,[250] in contrast to an earlier study using α_1 knockouts in a fear-conditioning paradigm suggesting that the α_1 subtype was a mediator of isoflurane amnesia.[251]

The effect of anesthetics have been studied on hippocampal θ oscillations in vivo. Perouansky and colleagues[252] used a fear conditioning paradigm to study isoflurane 0.32%, nitrous oxide 60%, and halothane 0.24%, and reported that suppression of hippocampal-dependent contextual conditioning was proportionate to slowing of θ peak frequency. An earlier study also demonstrated that isoflurane caused slowing of θ oscillations in the CA1 neuronal bundle without changing absolute power. In some contrast, the nonimmobilizer F6, which causes amnesia without sedation or a loss of motor activity, caused a loss of θ oscillatory power without θ slowing.[253] This finding suggests that the disruption of hippocampal θ oscillations required to cause amnesia might not be specific. In fact, although isoflurane and F6 amnesia are both associated with changes in θ, isoflurane

appears to antagonize the amnestic potential of F6, suggesting that they do not share a common mechanism.[254] Scopolamine causes amnesia at doses associated with acceleration of θ oscillations, which might otherwise be expected to improve learning.[255] However, a significant loss of absolute power is also observed.

ANESTHETIC EFFECTS ON AMYGDALA-DEPENDENT MEMORY PROCESSES

The amygdala sits immediately anterior to the hippocampus and is a cluster of interconnected nuclei with afferent and efferent projections to a wide distribution of cortical and subcortical structures. The amygdala is recognized as critical to fear learning and memory, and the systematic study of amygdala-dependent classical (Pavlovian) fear conditioning has produced much information regarding the mechanisms of associative learning.[142,256,257] The basolateral nucleus of the amygdala (i.e., the BLA) also functions to modulate the encoding and consolidation of memory in the hippocampus and elsewhere in response to emotion, arousal, and stress.[258,259] This modulatory function largely explains why emotionally significant experiences are better remembered. The mechanism is dependent on noradrenergic projections terminating on both α and β receptors within the BLA,[260] but can also be triggered by systemic epinephrine binding to β-adrenoreceptors in the vagus nerve and projecting to the nucleus of the solitary tract,[261] with downstream modulation of norepinephrine release in the BLA either directly or via the locus ceruleus. Amygdalo-hippocampal connectivity occurs via direct and indirect projections, and it is dependent on θ oscillatory synchrony.[185-187,262] Local α_1 and α_2-rich GABAergic circuits situated in the BLA and intercalated bundles gate the noradrenergic processes, providing rational targets for anesthetic drugs.[263]

Lesions of the BLA block anterograde amnesia for an inhibitory avoidance task in rats receiving diazepam,[264] propofol,[265] and sevoflurane.[266] Conversely, when the BLA is injected with the selective GABA antagonist bicuculline, the amnesia for inhibitory avoidance caused by propofol is blocked.[240] Further, this intra-amygdalar injection reverses the propofol-induced suppression of Arc protein expression in the hippocampus via a $GABA_A$ receptor mechanism. Thus, the amygdala is a key mechanistic site for anesthetic amnesia in certain experimental contexts. However, inhibitory avoidance, like many associative learning experimental paradigms performed in animals, is selectively amygdala dependent. Finding that the amygdala is critical to anesthetic amnesia in an amygdala-dependent paradigm does not necessarily extrapolate to its importance in the sort of contextually rich, non–fear-based memory that is fundamental to the human experience, which is difficult to model in animals.

The effects of anesthetic drugs on amygdala-dependent memory modulation in human subjects have been studied (Figure 13-5). The experimental paradigms all involve the presentation of emotionally negative and arousing images. Such items are established to activate the amygdalo-hippocampal modulatory axis[267,268] and should be better remembered than emotionally neutral items. An early behavioral study demonstrated that negative-arousing items were more resistant to the amnestic effect of thiopental than were neutral items, suggesting that amygdala-dependent modulatory processes remained intact.[194] At the same level of overall memory performance (50% retention), no significant mnemonic advantage for negative-arousing items was retained in subjects receiving propofol or dexmedetomidine, suggesting that in contrast to thiopental, these anesthetics could attenuate amygdala-dependent modulatory processes. However, the small numbers of subjects in the dexmedetomidine cohort limit interpretation of the negative finding.

Two recent, event-related fMRI studies developing these concepts have provided significant mechanistic insight. Pryor and colleagues[219] reported that activation of the amygdala in response to negative-arousing items remains robust in the presence of propofol (0.90 μg/mL), but activation of the hippocampus is markedly attenuated, with corresponding amnesia and loss of mnemonic advantage. This finding suggests that the afferent processes serving higher-order interpretative functions and amygdala activation are unaffected by amnestic levels of propofol, whereas efferent processes underlying amygdala-dependent modulation of hippocampal plasticity are disrupted. Hayama and colleagues[212] studied dexmedetomidine (0.15 ng/mL) and similarly reported that activation of the amygdala in response to negative-arousing items is preserved. However, unlike propofol, a mnemonic advantage for those items is seen, and subsequent memory is correlated with activation in the amygdala and hippocampus on the left side. Taken together, these studies suggest that propofol is more effective at attenuating the amygdalo-hippocampal modulatory axis. One suggested explanation is that amygdalo-hippocampal connectivity is markedly disrupted by the loss of θ oscillatory synchrony caused by propofol, whereas α_{2A} antagonism at the locus ceruleus causes only limited downstream attenuation of noradrenergic signaling in the BLA.

An earlier PET study by Alkire and colleagues[269] demonstrated that the mnemonic advantage for negative-arousing items was preserved at 0.1% and 0.2% sevoflurane, but lost at 0.25%. Structural equation modeling of the PET data demonstrated that this was associated suppression of amygdalo-hippocampal effective connectivity.

Amygdala hyperreactivity is of importance in a number of fear-based psychopathologies, including anxiety, phobia, panic disorder, and posttraumatic stress disorder.[270,271] The neurohumoral stress response to surgery provides a number of potential substrates for amygdala activation, and as such there is basis for concern that this activation might induce plastic changes that could prime the development of long-term changes in neuropsychological functioning. Thus, anesthetics might not be potent attenuators of amygdala activation, even if they are highly effective at preventing downstream modulation of the hippocampus and memory. This is particularly relevant to the frequent incidence of posttraumatic stress disorder following intraoperative awareness[272] and intensive care therapy,[273,274] but further investigation is required before any clinical strategies can be offered.

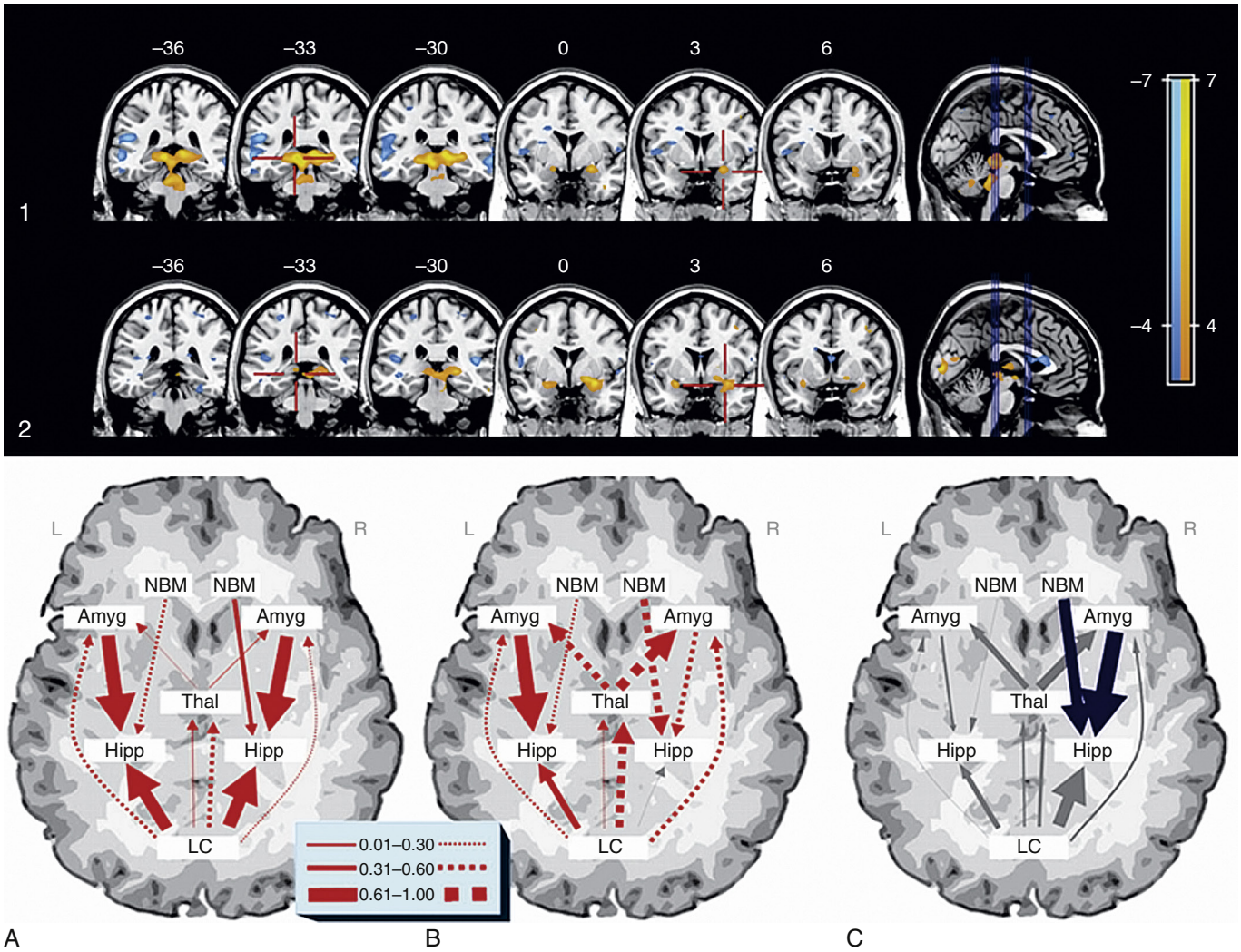


Figure 13-5. The effects of GABAergic anesthetics on the amygdalo-hippocampal axis in humans. *(Top)* Shown is the contrast between exposure to negative-arousing items and exposure to neutral items in human subjects receiving either placebo *(row 1)* or propofol 0.90 μg/mL *(row 2)*. Six coronal slices through the hippocampus (three leftmost slices, marked above by *y* coordinates –36, –33, –30) and amygdala (coordinates 0, 3, 6) are selected, with the coronal planes shown on the sagittal slice on right. In the placebo group, significant activations (negative-arousing > neutral) are seen in both right and left amygdala, and in both right and left hippocampus. In the propofol group, similar significant activations are seen in the right and left amygdala, but no significant activations are observed in the hippocampi. The scale shows color rendering of the group-wise *t* values obtained from Statistical Parametric Mapping. The threshold for color rendering is $|t| \geq 3.37$. *(Bottom)* Shown is a positron emission tomography study applying structural equation modeling (connectivity) analysis in human subjects at rest, receiving either no anesthetic **(A)** or sevoflurane 0.25% **(B).** Positive influences of one region onto another are shown as solid lines, and negative influences are shown as dotted lines. Line width represents the magnitude of the effective influence, with larger widths indicating a larger influence, according to the scale shown. The numerical difference in path weights between conditions is shown in **C.** Paths that significantly contribute to the network model more in the placebo state versus the anesthesia state are highlighted; all other paths are shown grayed out. A large change in path weights is noted for the effective influence of the amygdala and the nucleus basalis of Meynert on the hippocampus during sevoflurane. *Amyg,* Amygdala; *Hipp,* hippocampus; *LC,* locus ceruleus; *NBM,* nucleus basalis of Meynert; *Thal,* thalamus. *(*Top *from Pryor KO, Root JC, Mehta M, et al. Propofol amnesia is predicted by a loss of hippocampal and amygdala activation: fMRI evidence.* Anesthesiology *2010; 113:A369;* Bottom *from Alkire MT et al: Neuroimaging analysis of an anesthetic gas that blocks human emotional memory,* Proc Natl Acad Sci U S A *105:1722-1727, 2008.)*

ANESTHETIC EFFECTS ON IMPLICIT MEMORY FUNCTION

In contrast to declarative memory, implicit memory processes do not axiomatically require a conscious substrate, nor are they dependent on hippocampal plasticity. Therefore, there is no a priori basis to assume that the effect of anesthetic drugs on implicit memory function will parallel those on declarative memory. A number of investigations have sought evidence for implicit processing in unconscious subjects. More rigorous studies have used variants of a word stem completion task: subjects are exposed to a word item during anesthesia, and implicit memory is evidenced by an increased propensity to think of that word when later presented with the first few letters. A more rigorous variant—termed the *process dissociation procedure*—enables the separation of explicit from implicit processes.

Two early studies in patients undergoing coronary artery[275] and gynecologic[276] procedures showed evidence of implicit learning using word completion tests. Another early study demonstrating implicit recall in cardiac surgery patients correlated performance with preservation of the midlatency auditory evoked potential, and in particular with the early cortical Pa and Na complexes[277]. Lubke and colleagues[278] later demonstrated implicit memory in both trauma patients (see Chapter 81) and patients undergoing an emergency cesarean section[279] (see Chapter 77) using the process dissociation procedure, and further demonstrated that the degree of processing is related to depth of hypnosis as measured by the bispectral index (see Chapter 50). However, other studies using similar procedures either have failed to show significant implicit priming effects or have been equivocal.[280-283] Synthesis of these disparate results is difficult, and although differences in patient populations and anesthetic regimens may be of relevance, most concern has been raised about the validity of the experimental techniques; errors in the assumptions of the process dissociation procedure might explain false-positive results.[283] Recent investigations evaluating implicit memory processes in children under anesthesia have also offered conflicting results. Phelan and colleagues[284] reported an increased ability to distinguish a primed animal sound from white noise, but other investigations found no evidence of priming.[285,286]

CONCLUSION

Consciousness and memory are among the most fascinating and complex functions of the brain. Further scientific investigation in the twenty-first century is likely to deepen the connections between the fields of anesthesiology and neuroscience. Hopefully, a more precise understanding of anesthetic effects on consciousness and cognition will enrich both fields and, ultimately, improve patient care.

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Chapter 14

Sleep Medicine

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Key Points

- Sleep is a dynamic neuronal and behavioral state that can be characterized using specific electroencephalographic, electrophysiologic, and behavioral findings.
- Associations with sleep are sometimes investigated using questionnaires, actigraphy, or respiratory polygraphy. However, polysomnography, including electroencephalogram, electrooculogram, submental electromyogram, and analysis of breathing, is required to identify and characterize sleep and its disorders.
- Activation of hypothalamic sleep promoting pathways including the ventrolateral preoptic nucleus and the median preoptic nucleus produce the physiological switch from wakefulness to sleep.
- Sleep and anesthesia can look similar from a distance. Although small doses of anesthetics can induce sleep by activating sleep-promoting pathways, immobilization cannot be induced by these circuits.
- Control of breathing is altered during sleep and anesthesia, typically leading to a decreased drive to upper airway dilator and respiratory pump muscles.
- Persistent respiratory depressant effects of anesthetics and neuromuscular blocking drugs increase the risk of postoperative respiratory complications, particularly in patients with obstructive sleep apnea.
- Anesthesia and surgery, as well as treatment in the intensive care unit, alter sleep duration and sleep architecture, which leads to impaired outcome.

Probably the earliest mention of "overpowering sleep" as a metaphor describing what possibly characterizes anesthesia can be found in Genesis 2:21, "And the Eternal God caused an overpowering sleep to fall upon the man and he slept. He took one of his ribs and shut in flesh instead thereof." Although this "overpowering sleep" allegedly occurred by divine intervention and did not represent drug-induced unconsciousness and immobility that characterizes the definition of anesthesia, the basic narrative is an example of antiquarian history that implicates the concept that deep sleep may be a viable condition that allows a surgical procedure to be completed successfully.[1]

In the twenty-first century, an increasing body of knowledge has revealed the common ground between sleep and anesthesia, as well as their fundamental differences in clinical picture and underlying mechanisms.

Sleep is required for survival. Rats deprived of sleep will die within 2 to 3 weeks, a time frame similar to death due to starvation.[2] In humans, sleepiness can be deadly. Approximately 100,000 motor vehicle crashes each year result from drivers who are "asleep at the wheel." In a survey of drivers in New York State, approximately 25% reported they had fallen asleep at the wheel at some time.[3] Perioperative sleep deprivation occurs frequently, particularly in critically ill patients and translates to harmful pathophysiologic conditions and morbidity. Primary sleep disorders result in chronic sleep deficiency, a state of inadequate or mistimed sleep of any mechanism, an underappreciated determinant of disease. Among sleep disorders, sleep apnea has probably the most meaningful consequences for perioperative treatment.[4]

Therefore, high-quality physiologic sleep is a key domain of public health that needs to be considered as we are in the process of evaluating how to translate bench-research discoveries effectively into high-quality perioperative medicine.

DEFINITION OF SLEEP

Sleep is the natural periodic suspension of consciousness during which the powers of the body are restored. A behavioral definition of sleep includes a species-specific posture and behavioral quiescence, as well as elevated

arousal thresholds. However, sleep is much more than an absence of activity. The brain is highly active during sleep, especially during rapid eye movement (REM) sleep, during which atonia, phasic muscle movements (driven by different activation levels in distinct areas of the brain), and vivid dreaming occur. Sleep is not a single phenomenon. At different stages of sleep, brain activities can be as distinct from each other as they are from wakefulness.[5] In humans and other vertebrates (see Evolution) sleep has two major stages: REM sleep and non-REM (NREM) sleep, with each of these further divided into sub-states. Most of sleep time is spent in NREM sleep, which is characterized by relatively low electroencephalogram (EEG) frequencies with higher amplitudes compared with waking EEG frequencies (Figure 14-1). In the transition from wake to NREM sleep, the fast activity of waking disappears (α-θ transition) and then in the deeper stages of NREM large, slow waves (i.e., Δ waves) emerge. Thus, deep NREM sleep is also referred to as *slow-wave sleep*. NREM sleep is associated with waxing and waning muscle tone, as well as decreased body temperature, and heart rate. By contrast, REM sleep is characterized by muscle atonia, loss of slow waves in the EEG (see Figure 14-1), and bursts of rapid eye movements that give this state its name.[6] Other prominent features of REM include marked irregularities of respiration and heart rate, as well as penile and clitoral erection. REM sleep is associated with the high likelihood of vivid dreaming. A distinct property of REM sleep is the operation of a system that suppresses motor activity, which is responsible for baseline atonia and suppression of motor commands that would otherwise result in acting out of dreams, a phenomenon known as *REM sleep behavior disorder*. This REM atonia system is not absolute, as it periodically allows breakthrough muscle activity that comprises REM sleep and twitching of the extremities. Therefore, REM sleep is not homogeneous but can be subdivided into *tonic REM sleep* (i.e., a period with muscle atonia and without eye movements) and *phasic REM sleep*, which is interrupted by short phasic events of eye and other movements.[7] The patterning and amounts of NREM sleep, REM sleep, and wakefulness throughout the night is referred to as *sleep architecture*, and there are many physiologic and pathophysiologic processes that can affect sleep architecture. For example, many antidepressant medications selectively suppress REM sleep. A disease example is narcolepsy, in which individuals often transition directly from wake to REM, whereas normally REM is nearly always entered from an NREM state. To investigate both physiologic and pathologic sleep in humans, different methods for assessments in clinical and research settings have been developed.

HOW TO ASSESS SLEEP

The complexity of signs and symptoms of sleep suggests that different instruments need to be applied to capture all the important elements of sleep.

QUESTIONNAIRES

Several questionnaires are used for the assessment of sleep duration, sleep quality, and the related physiologic and pathophysiologic consequences. Quality of sleep is a frequent target of generic health surveys for measuring patient-reported outcomes, using instruments such as the World Health Organization Quality of Life questionnaire, the Beck Depression Inventory, and Patient Health Questionnaire-9-item. Other questionnaires quantify the consequences of sleep deprivation, specific sleep disorders, or both (Table 14-1). The most commonly used instrument in sleep medicine is probably the Epworth Sleepiness Scale, a short questionnaire to assess symptoms of daytime sleepiness, expressed as intolerance to monotony. The questionnaire asks the subject to rate the probability of falling asleep on a scale of increasing probability from 0 to 3 for eight different situations such as such as watching TV, reading, lying down in the afternoon, and so on.[10] Despite the fact that the Epworth Sleepiness Scale is reliable for detection of daytime sleepiness[8,9,13] in multiple sleep centers, the instrument does not help determine the mechanism of daytime sleepiness.[14,15]

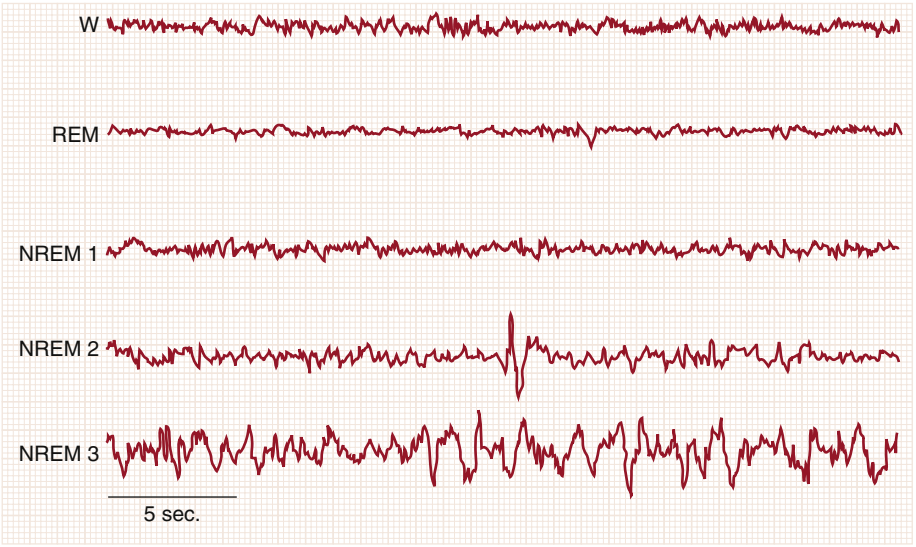


Figure 14-1. Representative electroencephalogram activity seen during different behavioral states. Electroencephalogram recordings of one patient during wakefulness (eyes closed; [W]), rapid eye movement sleep [REM] (B), and non-REM [NREM] sleep stages 1 to 3.

Other clinically useful questionnaires are focused on the detection of signs and symptoms of sleep disorders (e.g., Pittsburgh Sleep Quality Index[8,9,13]; the STOP-Bang). Questionnaires for specific subpopulations are available (e.g., patients with gastroesophageal reflux, Parkinson disease[16]), which is important because the prevalence of sleep pathologies typically varies in a wide range across populations.

An effective process for clinical assessment of sleep-related diseases might be a stepwise assessment using a screening tool first (e.g., Epworth Sleepiness Scale), followed by a more specific questionnaire that helps to identify individual mechanisms or consequences of sleepiness.

A special form of sleep questionnaires are sleep diaries, or sleep logs, and "morningness-eveningness" questionnaires. In these questionnaires, daily sleep habits are documented by the patient before going to sleep in the evening and after waking in the morning. This documentation includes factors such as sleep time, sleep duration, number of nocturnal awakenings, and subjective sleep quality, with the advantage of being less prone to recall bias.[17]

Although questionnaires allow a quick and easy screening for daytime symptoms of sleep disturbances, they cannot be used to quantify sleep architecture. Furthermore, subjective and objective measurements of sleep time, such as actigraphy, do not agree consistently well with the results of subjective measurements,[18] for which the patient is the major source of measurement variability. Subjective methods of assessing sleep are influenced by the spectrum of disease within a tested group, actual clinical change over time, the testing conditions, and recall bias.[17] Although a questionnaire cannot replace a medical history or objective assessment for sleep disorders, sleep questionnaires are important tools for measuring health improvement or decline, predicting medical expenses, assessing treatment effects, or comparing disease burden across populations.

TABLE 14-1 SLEEP QUESTIONNAIRES: QUESTIONNAIRES COMMONLY USED FOR CLINICAL AND RESEARCH PURPOSES AND THEIR FOCUS

Questionnaire	Focus	References
*Pittsburgh Sleep Quality Index (PSQI)**	Sleep and sleep disorders	8, 9, 10
Sleep Quality Scale (SQS)	Sleep quality	11
Functional Outcome of Sleep Questionnaire (FOSQ)	Impact of daytime sleepiness on daily living	12
Pediatric Sleep Questionnaire	Sleep and SDB in children	13
Child Sleep Habits Questionnaire (CSHQ)	Sleep	14
Epworth Sleepiness Scale (ESS)	Daytime sleepiness	8, 9, 15
Sleep Diaries / Sleep Logs	Sleeping times, sleep duration	16
Morningness-Eveningness Questionnaire	Sleeping times, sleep duration, circadian rhythm	17
Loughborough Occupational Impact of Sleep Scale (LOISS)	Sleep quality	18
Insomnia Sleep Questionnaire (ISQ)	Insomnia	19
Berlin Questionnaire	SDB in surgical patients	20
STOP/STOP-Bang Questionnaire	Obstructive sleep apnea	21, 22
Brief Insomnia Questionnaire (BIQ),	Insomnia	23
International Restless Legs Syndrome Study Group Rating Scale (IRLS)	Restless legs syndrome	24, 25
Clinical Global Impression (CGI) Scale	Restless legs syndrome	25

*Recommended questionnaires are italicized.
SDB, Sleep-disordered breathing; *STOP,* snoring, tiredness, observed apneas, and high blood pressure.

ACTIGRAPHY

Actigraphy has been used to study sleep-wake patterns for more than 20 years. This method detects motion of the wrist with linear accelerometers in single or multiple axes. Based on movement-derived data combined with calibration data on file, predictions of the time spent during sleep and wakefulness can be made, and even assumptions on sleep staging are made. Actigraphy can be used conveniently in a patient's home for several nights, weeks, or longer. Actigraphy has a high reliability and validity for detecting transitions from wakefulness to sleep,[19] but some studies have shown a low specificity for the diagnosis of wakefulness when compared with the golden standard polysomnography,[20-22] especially in patients with high levels of sleep fragmentation.[19,23] In the clinical setting, actigraphy is reliable for evaluating sleep patterns in patients with insomnia, for diagnosis of circadian rhythm disorders (including shift work), and in evaluating sleep in individuals who are less likely to tolerate polysomnography, such as infants and demented elderly. In addition, actigraphy allows for convenient follow-up measurements to evaluate the effects of treatments designed to improve sleep.[24]

RESPIRATORY POLYGRAPHY

Home respiratory polygraphy can be a cost-effective alternative to polysomnography (PSG) for the diagnosis of sleep apnea-hypopnea syndrome. Respiratory polygraphy (RP) usually calculates airflow through nasal pressure changes taken via nasal cannula. Thoracic and abdominal movements are measured by piezoelectric bands, which also measure body position and blood oxygen saturation by pulse oximetry. Using these parameters, RP can identify respiratory events (i.e., apnea and hypopnea), and categorize their mechanisms into obstructive versus central. Furthermore, similar to actigraphy, RP provides some analysis of sleep duration and time spent awake, using its body position sensor. However, the quality of the latter can be more precisely evaluated by a combination of sleep diary and actigraphy with an EEG required to make final determinations as to whether a subject was awake or sleeping (Table 14-2).

TABLE 14-2 **PROS AND CONS OF DIFFERENT METHODS OF SLEEP EVALUATION**

Method	Pros	Cons	Recommendation
Sleep questionnaire	Low costs Good compliance Easy to use	Recall bias Limited reliability in some populations Limited validity	Should be combined with interview
Sleep diary	Less recall bias Easy to administer Low costs Documentation of daily variability	Lower compliance compared with other questionnaires Biased by daily mood and expectations on sleep	Should be combined with other measurement of sleet duration (e.g., actigraphy)
Actigraphy	Provides objective information about daily variability and sleep duration Provide information on sleep habits at home Not influenced by patient expectations, recall bias, or memory impairments Lower costs than laboratory polysomnography	Limited assessment of sleep stages and sleep onset latency Higher cost than questionnaires	Should be combined with other measurement of sleep duration (e.g., sleep diary)
Polygraphy	Lower costs than laboratory polysomnography Objective assessment of respiratory events Provide information on sleep habits at home	Limited assessment of sleep Higher cost than questionnaires Limited assessment of sleep disorders other than sleep-disordered breathing	Should be accompanied by questionnaires and clinical interview
Laboratory polysomnography	Objective assessment of sleep, sleep stages and sleep disorders	High costs First-night effect Limited capacity High costs No information about sleep habits at home	Should be last step in sleep evaluation with previous questionnaires and ambulatory screening (e.g., polygraphy)
Out-of-center polysomnography	Objective assessment of sleep, sleep stages and sleep disorders Less first-night effect Lower costs than laboratory polysomnography Can provide information about sleep habits at home	Limited observation may lead to decreased recoding quality	Good patient education mandatory If possible, surveillance recording preferred

Adapted in part from Martin JL, Hakim AD: Wrist actigraphy, Chest *139:1514-1527, 2011.*

POLYSOMNOGRAPHY

Polysomnography is the only method that can precisely determine the actual sleep stage and is a diagnostic reference tool (i.e., gold standard) that is required for the diagnosis of several sleep disorders.[25] PSG measurements include EEG, electrooculography for the measurement of eye movements, and at least electromyographic measurement of muscle activity of the chin.[26] These three measurements are typically supplemented by further channels for the detection of sleep disordered breathing such as a nasal sensor to detect apneas and hypopneas, oximetry, inductance plethysmography for respiratory effort of the chest and abdomen, and a body position sensor and leg electromyogram[27] to identify periodic limb movement syndrome or REM sleep behavior disorder, respectively.[28] A sample of such a typical PSG recording is shown in Figure 14-2. More than 40 years ago, Rechtschaffen and Kales[26] standardized the method of scoring polysomnographic recordings—the R&K criteria. Since then, major innovations in technology have transformed the science and clinical practice of sleep medicine. The new criteria of the American Academy of Sleep Medicine (AASM)[27] capture the full potential of innovations resulting from computerization of data, including automation of sleep scoring, recognition of disorders that occur during sleep, and integration with other procedures, such as positive airway pressure titration. Nevertheless, the R&K criteria are still sufficient for clinical and research purposes and consequently are used in sleep centers around the world.

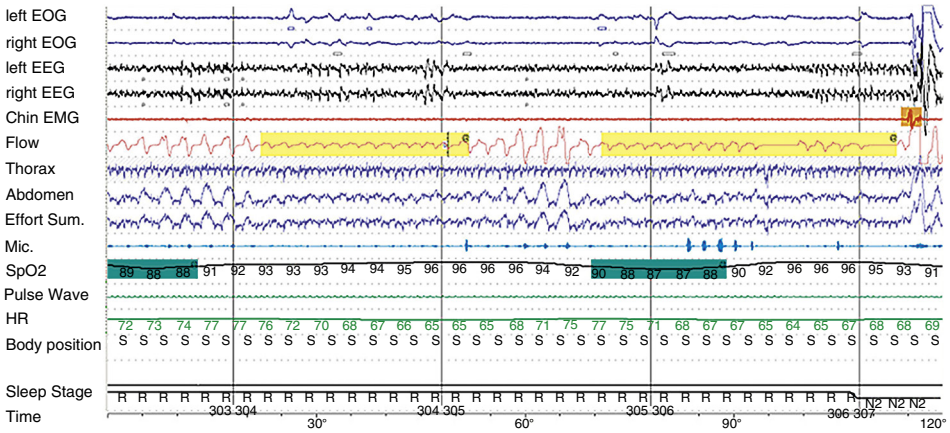


Figure 14-2. Polysomnographic recording. Left and right electrooculogram (EOG), two electroencephalogram (EEG) channels, and mental electromyogram (Chin EMG) allow scoring of sleep stage (REM sleep [R] with typical eye movements in the electrooculogram channels). Additional channels (e.g., respiratory flow [Flow], respiratory effort of thorax [Thorax] and abdomen [Abdomen], microphone [Mic.] oxygen saturation [SpO_2]) allow diagnosis of sleep disordered breathing. In this patient, apneas *(yellow boxes)* led to oxygen desaturation *(blue boxes)* and finally to arousal *(far right, brown box).*

Sleep Laboratory Testing

For several decades, PSG was performed only within a sleep laboratory, but an increasing number of devices are now available offering the possibility of recording PSG in almost every environment, such as the patient's home, within the patient's hospital or nursing home room, and even within the recovery room. A current standard for the measurement of sleep is the attended sleep laboratory PSG with a trained technician.[27,29-32] The study is analyzed by a clinician trained in sleep medicine following the published guidelines by Rechtschaffen and Kales[33] or the newer guidelines published by the AASM.[27] Nevertheless, it is evident that there are many more patients potentially suffering from obstructive sleep apnea (OSA) than are being seen at sleep centers. A contributing factor could be that the waiting time for an in-laboratory PSG is several weeks for patients in the United States[34] and illustrates the need for other diagnostic procedures that are comparably sensitive and specific to laboratory PSG testing. Other limitations, such as the high cost and requirement of an overnight stay, can present socioeconomic challenges that affect the accessibility of this method. In addition, the in-center PSG provides only a momentary view of the patient's sleep, and the measurements themselves can impair the patient's sleep (the so-called first-night effect). Thus, in-center PSG does not provide information about the patient's sleep at home, and multiple repeated measurements to tailor treatment over time are challenging or even impossible from a logistic and healthcare economics perspective.

Out-of-Center Testing

Given the disadvantages of laboratory PSG, portable out-of-center PSG devices are a reasonable, reliable, and effective method for diagnosing OSA[35] that are not inferior to PSG recording performed within a sleep laboratory.[36-39] Guidelines published in 2007 by Collop and associates[35] for the Portable Monitoring Task Force of the AASM, as well as a recent review providing a score for the classification of portable devices for outpatient PSG,[40] support the reliability of such devices in subjects for clinical and research purposes and indicates a comparable quality of PSG data.

Scoring of Sleep and Sleep Disordered Breathing

Currently two different guidelines for the staging of sleep and sleep-related events are used.

Rechtschaffen and Kales Criteria. One of the first characterizations and scoring guidelines for the different sleep stages was published in 1968 by Rechtschaffen and Kales[26] and is still being used for clinical and research purposes in sleep medicine (Table 14-3). NREM sleep stage 1 (S1) is characterized by a low-voltage EEG of mixed frequencies (2 to 7 Hz) without REM sleep (see Figure 14-1, *C*). In humans, S1 usually occupies 1 to 7 minutes of sleep time, mostly during transition from wakefulness to sleep or after movements. Vertex sharp waves (amplitudes up to 200 μV) occasionally appear, predominantly during the late phase of S1 sleep. Additional sleep spindles (rhythmic discharges with a frequency of 12 to 14 Hz) or K-complexes, as well as slow waves with high amplitudes, characterize NREM sleep stage 2 (S2). S2 is the sleep stage in which a healthy person spends the most time of physiologic nighttime sleep. K-complexes are defined as a characteristic electric activity of more than 0.5 seconds duration comprised of a negative sharp wave immediately followed by a positive wave. K-complexes can occur spontaneously or as the result of external stimuli, and the characteristic EEG finding can be followed by slow-rolling eye movements. NREM sleep stages 3 and 4 are characterized by slow waves (≤2 Hz) with high amplitudes (>75 μV). During NREM sleep stage 3 (S3), slow waves occupy 20% to 50% of time. Amounts of more than 50% of slow waves are seen during NREM sleep stage 4.[41]

AASM Criteria. New guidelines of the AASM for sleep-stage scoring were published in 2007.[27] In contrast to the

TABLE 14-3 POLYSOMNOGRAPHIC CHARACTERISTIC OF THE DIFFERENT BEHAVIORAL STATES

	EEG and EOG Characteristics	R & K	AASM
Wakefulness	Alpha rhythm (8-13 Hz) present in more than 50% of an epoch	W	W
Non-REM sleep stage 1	Lower amplitudes and activity in range of 4–7 Hz (vertex sharp waves,* slow eye movements*)	S1	N1
Non-REM sleep stage 2	EEG of sleep stage 1 with additional a sleep spindles and K-complexes; slow waves not fulfilling the criteria for sleep stage 3	S2	N2
Non-REM slow wave sleep	20% to 50% of slow wave activity (0.5-2 Hz)	S3	N3
	>50 % of slow wave activity	S4	
REM sleep	EEG of low amplitude and mixed frequencies, low chin electromyogram activity, rapid eye movements	R	R
Movement time	High amplitude activity in electromyogram channels	MT	NS

AASM, American Academy of Sleep Medicine criteria; *EEG,* electroencephalography; *EOG,* electrooculogram; *MT,* movement; *N1,* stage 1 AASM; *N2,* stage 2 AASM; *N3,* Stage 3 AASM; *NS,* not scored; *R&K,* Rechtschaffen and Kales criteria; *REM,* rapid eye movement; *S1,* stage 1 R&K; *S2,* stage 2 R&K; *S3,* stage 3 R&K; *S4,* stage 4 R&K; *W,* awake.
*Not necessary but may be present
Electrophysiologic criteria used for sleep stage scoring according to R&K criteria,[26] and the AASM criteria.[27]

R&K criteria, EEG recording following the AASM guidelines is taken from three instead of two different EEG channels[42] to account for possible topographic differences in most sleep scoring features in the EEG.[42-44]

The main differences between R&K and AASM scoring criteria are summarized in Table 14-3. Importantly, the two NREM slow-wave sleep stages 3 and 4 are lumped and defined as slow-wave sleep stage N3. Furthermore, new AASM guidelines also include new standardized scoring rules for respiratory events during sleep,[27] as follows:

1. Apnea with drop in respiratory flow of 90% or more from baseline for at least 10 seconds, whereas a minimum of 90% of the event duration has to meet the criteria of respiratory flow reduction, and
2. Hypopneas—the signal of respiratory flow measurement drops at least 30%, whereas oxygen saturation (SpO_2) decreases by 4% or more compared to preevent baseline for at least 90% of the duration (minimum of 10 seconds).

Alternatively, hypoxia can also be defined as a decrease in respiratory flow measurement of at least 40% with a decrease in SpO_2 of only 3%.

3. *Respiratory event-related arousal* is defined as a sequence of breaths not meeting the criteria for apnea or hypopnea lasting at least 10 seconds characterized by increasing respiratory effort or flattering of the nasal pressure waveform leading to an arousal from sleep.[27]
4. *Hypoventilations* are defined as an increase of 10% or more in CO_2 pressure ($PaCO_2$).

Although these criteria published in 2007[27] are commonly used in many sleep centers for clinical and research purposes all over the world, questions about whether the new criteria should be used in children[45] and the scoring of some respiratory events are still unanswered.

PHYSIOLOGY

EVOLUTION

In a rhythmic world, organisms must adapt to alternating changes in the environment, such as daily and seasonal rhythms in light intensity, ambient temperature, and humidity. It is unknown why we sleep; however, one can imagine that evolutionary pressure would favor systems that are optimized for nature's rhythms.[46-48]

Species-dependent temporal behavior can be adapted depending on the environmental conditions: behaviorally, anatomically, and physiologically. Circadian rhythms affect almost every aspect of the body, including activity and rest patterns, cognitive function (e.g., learning and memory), physiology (e.g., heart rate, metabolism, and hormone secretion), and gene expression; 15% of the genes in the human body show daily rhythms.

CIRCADIAN RHYTHMS

Virtually all species show circadian rhythms that regulate periodic changes in behavioral and physiologic parameters within a period of approximately 24 hours.[49] These rhythms can be characterized as a synchronization of activity to the external light-dark cycle in the majority of living creatures. Bacteria, plants, animals, and humans exhibit such a behavior that helps them stay in tune with the environmental light-dark cycles.[50] Clock genes generate endogenous clock pulses in most (if not all) cells of the body, synchronized by regulatory pathways across the body to a superior rhythm generator (a so-called master clock). Desynchronization of these rhythms seems to be involved in the pathogenesis of metabolic, psychiatric, and other disorders.[50] The superior rhythm generator in humans is located in the suprachiasmatic nucleus that receives external inputs about light and darkness from the retinal cells and synchronizes inputs of melatonin levels. While this master clock synchronizes the behavioral and biological rhythms of the human body to the changing demands of the environment during the solar day, sleep itself entrains circadian rhythms,[50-52] and the temporal organization of circadian rhythms and nocturnal sleep must be preserved to accomplish a restful and refreshing experience that fulfills the sleep needs produced by the second major regulatory factor, sleep homeostasis. During waking, "sleep pressure" continuously increases, leading to a consecutive decrease in the threshold preventing a transition from wakefulness to sleep.[53] Increasing homeostatic sleep pressure can be partly offset by a sufficient circadian wakening stimulus during the circadian wake phase, but

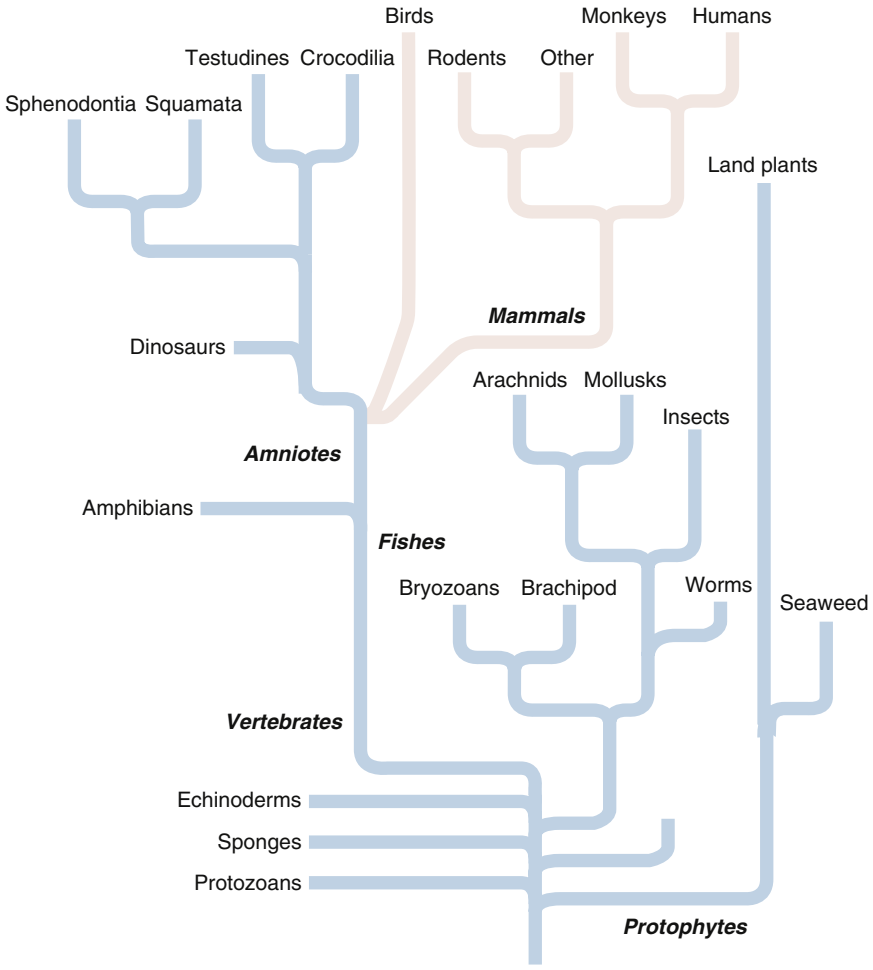


Figure 14-3. Evolutionary tree. Circadian rhythms are common among all living beings. However, only mammals and birds *(red)* have integrated sleep with different stages. Fish, reptiles, insects, and plants *(blue)* manifest circadian rhythms as periods of activity and rest.

the circadian wake stimulus disappears in the presence of an overwhelming sleep pressure.[54,55] In this situation, sleep sufficient in quantity and quality is needed to reestablish proper functioning.

Although circadian and homeostatic regulation of sleep can be observed in almost all living organisms,[56] differentiation of sleep into NREM and REM sleep ("integrated sleep") probably has developed during the last 300 to 350 million years because it appears only in birds and the majority of terrestrial mammals (Figure 14-3).[57,58]

Sleep Stages and Sleep Cycles

Sleep architecture, which is a structured temporal order of different sleep stages, are important determinants of sleep quality. If tired individuals rest in their individual sleeping postures, the increasing level of drowsiness is paralleled by continuous EEG slowing from EEG activity seen during attention and cortical activation (16 to 30 Hz, "beta activity") to slower frequencies, predominantly between (7.5 and 11 Hz, "alpha activity," typically observed in subjects at reduced attention and closed eyes). During this state of vigilance the individuals do not sleep, and a full level of cognitive function can be established easily even without a strong sensory stimulus. The transition from the alpha state to sleep is paralleled by a decrease in alpha and beta activity and an increase of EEG activity in the theta band (4.5 to 7.5 Hz; Figure 14-4).

This transition from alpha to theta activity is widely accepted as the electroencephalographic correlate of sleep onset.[59] At this transition from wakefulness to NREM sleep stage 1, heart rate and heat production decrease resulting in a slight decrease in body temperature. Furthermore, respiration is regular and deep. As sleep deepens, EEG activity shows low amplitudes and theta activity with intermittent sleep spindles and K-complexes. The latter can represent an activation of brainstem and subcortical brain areas during sleep,[60,61] potentially representing selective processing of unexpected sensory inputs (e.g., sounds) that require complete arousal and restoration of consciousness to address a potential threat.[62] In accordance with that hypothesis, in comatose patients with brain injury, the presence of K-complexes in response to an acoustic stimulus during coma seems to be a marker of a better outcome compared to comatose patients with no evoked K-complexes.[63]

With increasing depth of sleep, during NREM sleep, electrical activity of the cortex measured by EEG is dominated by slower frequencies and high amplitudes (stage 3 and 4 R&K[26] and NREM sleep 3 AASM[40]), also referred to as *slow-wave sleep*.

REM sleep, or paradoxic sleep, is associated with an alteration of homeostatic regulation, increased heart rate variability, irregular respiration, and impaired body temperature control. Brain metabolism increases while



Figure 14-4. Electroencephalogram recording during sleep onset *(arrow)*. The *two top rows* show bipolar electroencephalogram (EEG) signals from left (C3-A1) and right (C2-A1) frontal leads. Rows 3 to 5 show the relative amount (EEG power) of beta, alpha, and theta activity calculated using fast fourier transformation.

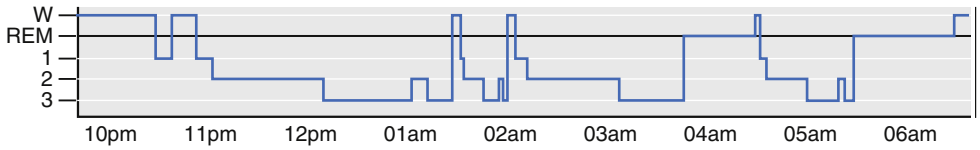


Figure 14-5. Hypnogram of a night of physiologic sleep. During one night (time on *x* axis) of sleep, humans transition repetitively from one sleep stage to another with short episodes of occasional wakefulness (indicated on *y* axis). *REM,* Rapid eye movement sleep; *W,* awake; *1,* non-REM sleep stage 1; *2,* non-REM sleep stage 2; 3, non-REM sleep stage 3 (slow wave seep).

EEG recordings show similarities to wakefulness with low voltage and mixed-frequency power spectra. There are also prominent theta waves generated by the hippocampus. These waves are not apparent in the scalp EEG recording from humans, but in rodents, in which the hippocampus is larger and closer to the brain surface, the EEG is dominated by theta during REM. This sleep state is associated with a decreased tone in skeletal muscles (except for extraocular muscles that control eye movement). Dreaming is a typical experience during REM sleep,[77] but can happen also during NREM sleep.[65] During physiologic sleep, an individual typically switches back and forth across sleep stages, interrupted by occasional arousals from sleep (Figure 14-5).

NEUROANATOMY OF SLEEP

Sleep Promoting and Arousal Pathways

Several neuronal pathways have evolved to maintain cortical activation and behavioral arousal during normal waking, and others have evolved to promote and maintain sleep (Figure 14-6). It is the balance between these two systems that determines whether one is awake or asleep.

Ascending Arousal System. The ascending arousal system (AAS) is the main wakefulness-mediating network in the brain. Main pathways within the network receive cholinergic, monoaminergic, dopaminergic, and glutamatergic inputs. Cholinergic inputs originate from pedunculopontine and laterodorsal tegmental nuclei, and they mainly innervate the lateral hypothalamus, prefrontal cortex, basal forebrain, and thalamic relay nuclei (i.e., medial and lateral geniculate nuclei; mediodorsal nucleus; pulvinar; anterior, ventral and lateral thalamic cell groups).[66,67] Glutamatergic neurons that provide inputs to the AAS are mainly located within a small area just ventral of the locus coeruleus (LC), the precoeruleus area (PC), as well as in the parabrachial nuclei that mainly project to the basal forebrain and the lateral hypothalamus.[68-73] Monoaminergic inputs mainly come from noradrenergic neurons within the locus coeruleus, histaminergic neurons of the tuberomammillary nuclei (TMN), serotoninergic neurons of the median and dorsal raphe nuclei,[74-76] as well as dopaminergic neurons adjacent to dorsal raphe nuclei.[76,77] Beside

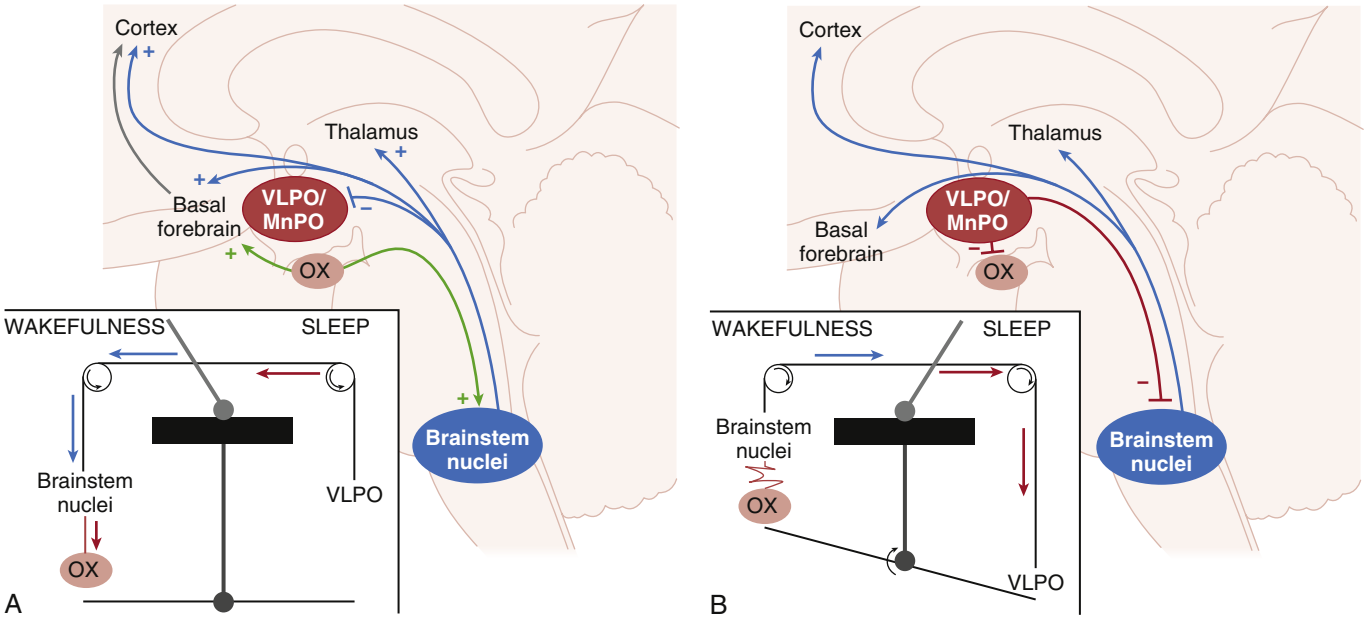


Figure 14-6. Flip-Flop switch ensuring rapid transitions between wakefulness and sleep. During wakefulness *(top)*, brainstem nuclei of the ascending arousal system (AAS) directly and indirectly provide excitatory input to the thalamus, basal forebrain (BF), and the cerebral cortex, while they inhibit the ventrolateral (VLPO) and median (MnPO) preoptic nuclei (switch flips to wakefulness). The excitatory, wake-promoting stimulus is enforced by additional excitatory input of orexinergic neurons (OX) to the BF and the AAS. During sleep *(bottom)*, neurons of VPLO and MnPO inhibit the brainstem and orexinergic neurons of the AAS (switch flops to sleep) *(Modified from Saper CB et al: Hypothalamic regulation of sleep and circadian rhythms,* Nature *437:1257–1263, 2005; and Saper CB et al: Sleep state switching,* Neuron *68:1023–1042, 2010.)*

projections to the basal forebrain, multiple inputs are sent to the thalamus, mainly the inter-laminar and reticular nuclei, as well as the amygdala and cerebral cortex. Furthermore, noradrenergic neurons of the LC project mainly to the posterior part of the lateral hypothalamus. In return, the latter area of the lateral hypothalamus projects to the LC and to the TMN.

Some neurons of the posterior hypothalamus produce orexin A and B (also known as hypocretin 1 and 2). These neurons project to the basal forebrain and the amygdala and cerebral cortex and other important arousal areas, and they are essential for stabilizing the waking state.[78] Orexin deficiency causes narcolepsy (severe daytime sleepiness) with cataplexy (abrupt loss of muscle tone),[79] a disorder showing some characteristics of REM sleep (i.e., REM sleep atonia during wakefulness [discussed later]).

NREM Sleep-Promoting Pathways. About 100 years ago during the epidemic of encephalitis lethargica, it was observed that lesions in the preoptic region around the rostral end of the third ventricle were associated with profound insomnia,[80] which was confirmed in neuroanatomic experiments (lesion studies) in rats and cats.[81,82] Recent data show that neurons in the preoptic area are active during sleep.[83-87] Two key nuclei within this area are the ventrolateral preoptic nucleus (VLPO) as well as the median preoptic nucleus. VLPO neurons fire at a higher frequency during sleep compared with wakefulness.[85,88] Anatomically, the VLPO consists of a dense core of sleep-active, galanin-positive neurons innervating the TMN (which is part of the AAS) while being surrounded dorsally and medially by a more diffuse population of sleep-active, galanin-positive neurons that project to the dorsal raphe and LC.[89,90] Physiologically, the VLPO neurons constitute a sleep-promoting pathway that inhibits many components of the arousal system during sleep. Likewise, parts of the arousal system such as the laterodorsal tegmental nucleus and the pedunculopontine tegmental nucleus, as well as the locus coeruleus, the parabrachial nucleus, the dorsal raphe nucleus, the precoeruleus area, the ventral periaqueductal gray, and the TMN are capable of inhibiting the VLPO. The mutually inhibitory relationship of the arousal and sleep-promoting pathways produces the conditions for a flip-flop switch, which can generate rapid and complete transitions between waking and sleeping states[91,92] (see Figure 14-3). It also makes simultaneous activation of arousal and sleep circuits highly improbable.

Because animal experiments showed that even large lesions of the VLPO substantially reduce but do not completely erase sleep, other brain areas beside this nucleus are likely involved in promoting sleep.[93] Several basal forebrain areas,[84,87,94] as well as some γ-aminobutyric acid (GABA)-ergic interneurons across the cerebral cortex[95] have been implicated to function as sleep-active neurons. Nevertheless, the role of these brain regions in the promotion or regulation of sleep remains unclear.

REM Sleep-Promoting Pathways and NREM-REM Transition. During normal sleep that presents at onset as a sharp alpha-theta EEG activity transition, a similar sharp transition from NREM to REM sleep can be observed. Two groups of mutually inhibitory neurons located in the pons are involved in mediating the switch between NREM and REM sleep.[71] The first group consists of REM active inhibitory neurons of the sublaterodorsal nucleus and the precoeruleus region.[73,92,96] These neurons inhibit and are

inhibited by a second group of neurons that are located in ventrolateral periaqueductal gray and adjacent lateral pontine tegmentum. This mutually inhibitory relationship produces a REM-NREM flip-flop switch, promoting rapid and complete transitions between sleep states.[92]

Within the sublaterodorsal nucleus and PC, glutamatergic neurons are mixed within the population of REM-on GABAergic neurons. The glutamatergic sublaterodorsal nucleus neurons project to the spinal cord and are important for REM sleep atonia; the glutamatergic PC neurons activate forebrain pathways driving EEG desynchronization and hippocampal theta rhythms—that is, the characteristic EEG signs of REM-sleep.[97]

BIOLOGIC EFFECTS OF SLEEP AND SLEEP DEPRIVATION

Sleep conserves energy and suppresses energy-consuming behaviors, similar to the effect of hibernation.[57,98] Recent findings indicate that sleep can protect against aging-related neurodegeneration by decreasing effects of oxidative stress. More specifically, sleep deprivation increases oxidative stress in the hippocampus and subcortical brain regions and impairs the generation of new neurons in the dentate gyrus of the hippocampus.[99] Together, these data suggest that NREM sleep has a general role in allowing or facilitating neurogenesis, preventing neurodegeneration, and neuronal energy consumption.[57]

In addition, compelling evidence links sleep to the metabolic, endocrine, immune, and inflammatory systems.[100-104] For example, sleep deprivation during influenza vaccination delays the increase of antibody titers.[105] Furthermore, even short sleep deprivation in otherwise healthy young subjects has been shown to be associated with impaired glucose tolerance, glucose effectiveness, and early insulin response, to levels usually seen in patients in the early course of diabetes mellitus, as well as changes in the activity of the hypothalamo-pituitary-adrenal axis with altered plasma levels of cortisol and thyrotropin.[106] These findings have been hypothesized to affect the outcome of critically ill patients[107] (see also Sleep in the Intensive Care Unit).

SLEEP AND BREATHING

RESPIRATORY REGULATION DURING SLEEP

Sleep puts breathing at risk. The upper airway dilator muscle activity is decreased during sleep compared with wakefulness, particularly at sleep onset and during REM sleep. Furthermore, the ventilatory response to hypoxia can be impaired, such that critical hypoxia levels can occur during sleep that can be offset only by arousal from sleep.

The major determinant of minute ventilation during wakefulness and sleep is the arterial partial pressure of carbon dioxide ($PaCO_2$). In contrast to wakefulness where $PaCO_2$ is maintained close to 40 mm Hg, the chemosensitivity to CO_2 decreases during sleep, as does the chemosensitivity for oxygen. This leads to $PaCO_2$ values of 45 mm Hg commonly occurring during stable sleep, while ventilatory demand is decreased and the arousal threshold varies with sleep stages.

Accordingly, the changes in respiratory muscle activity, ventilatory demand, and arousal threshold observed from wakefulness to sleep and across sleep stages challenge ventilatory control and can lead to instability in breathing. A structured approach to evaluating breathing instabilities is the loop gain. This engineering term is used to describe the stability of a feedback-controlled system (in this case, the chemical feedback loop controlling an individual's ventilation). In the setting of ventilatory control, loop gain reflects the propensity of an individual to develop periodic (unstable) breathing. Patients with a high loop gain caused by a more sensitive respiratory controller (i.e., high controller gain), more effective CO_2 excretion (i.e., high plant gain), or an increased delay because of slowed CO_2 distribution from peripheral tissues to the central chemoreceptors based on, for example, reduced blood circulation (i.e., mixing gain), may be more vulnerable to disturbances of the feedback system, such as slight hypoventilation that occurs as a consequence of decreased upper airway dilator muscle activity during the transition from wakefulness to sleep (Figure 14-7).

If airway obstruction causes arousal, there will be an abrupt decrease in the CO_2 set-point. Excessive hyperventilation as a consequence of high loop gain will lead to relative hypocapnia as the system overcompensates. It is believed that this lower CO_2 level will suppress upper airway dilator muscle activity and make the individual more susceptible to subsequent airway occlusion when he or she returns to sleep. Thus, high loop gain may contribute to severity of obstructive sleep apnea. Moreover, subjects with a high loop gain have been shown to be more likely to develop breathing instabilities such as Cheyne-Stokes respiration (CSR; see *Central Sleep Apnea*).

SLEEP-DISORDERED BREATHING

Sleep-associated respiratory signs and symptoms of dysfunction are referred to as *sleep-disordered breathing* (SDB) and are defined by the occurrence of respiratory events, which are cessations in breathing rhythm (apneas) or momentary or sustained reduction in the breathing amplitude (hypopnea) during the sleeping state, leading to arterial hypoxemia.[108] They are usually caused either by increases in upper-airway resistance because of a reduction in the airway intraluminal diameter (the obstructive event), marked reduction or cessation of brain stem respiratory motor output (the central event), or both. A specification of SDB into predominantly obstructive or central sleep apneas is being developed based on the type of respiratory events.

Obstructive Sleep Apnea

Definition. The most common type of SDB is OSA, usually quantified by the number of respiratory events per hour of sleep. A quantification of nocturnal respiratory events is necessary because a low number of short apneas and hypopneas can occur up to about five times

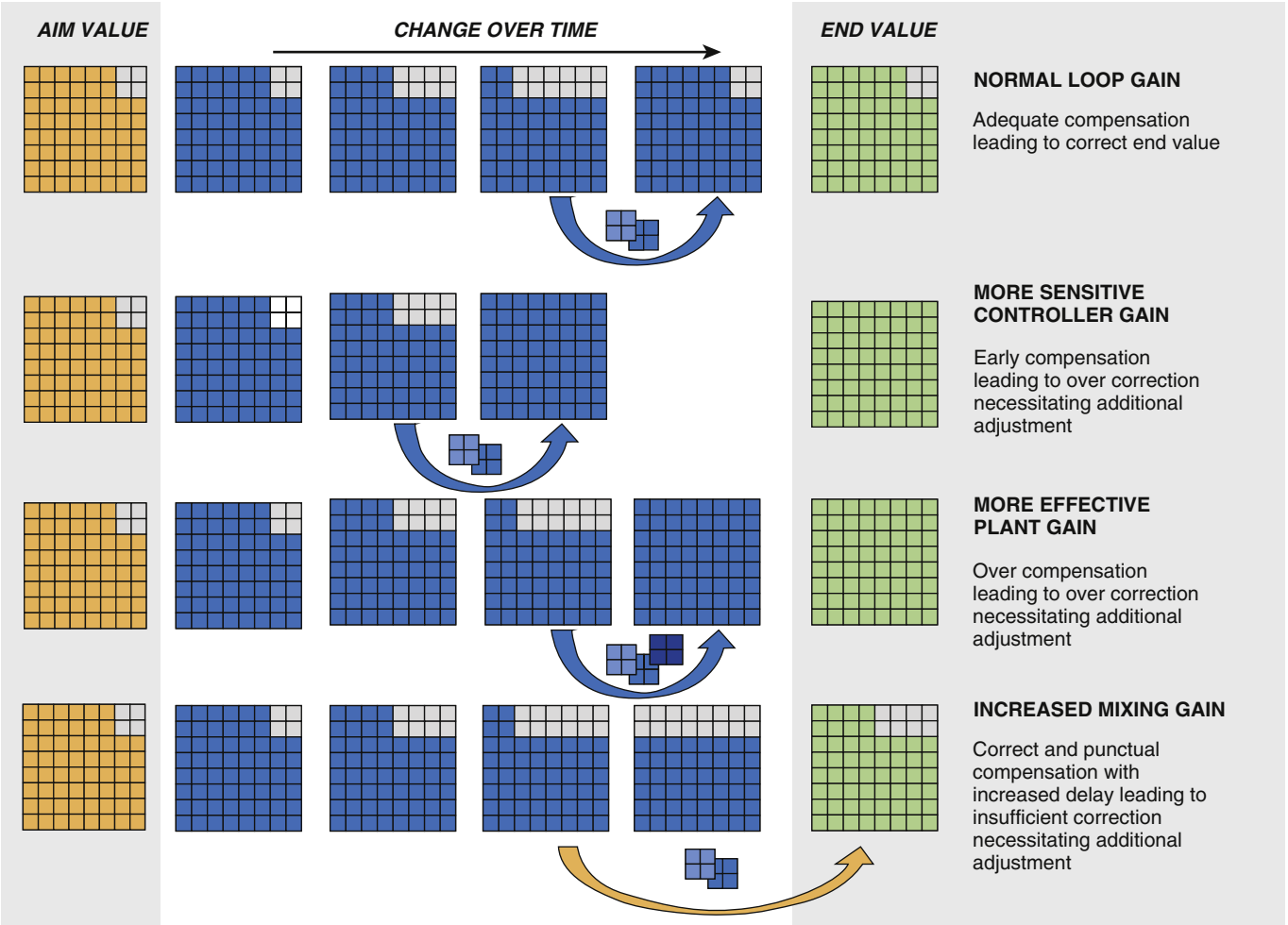


Figure 14-7. Model of changes in loop gain and its effect on the stability of a feedback controlled system. Low or normal loop gain provides adequate compensation of external disturbing stimulus *(top),* while increased controller gain *(second from top),* increased plant gain *(third from top),* or mixed gain *(bottom)* result in an inadequate duration of compensatory mechanisms *(red arrow),* thus leading to an instability in the feedback controlled system.

$$\text{AHI} = \frac{\text{Apneas (10 sec without flow)} + \text{Hypopneas (reduced flow with desaturation)}}{\text{Total sleep time (h)}}$$

$$\text{RDI} = \frac{\text{Apneas} + \text{Hypopneas} + \text{Arousals (in EEG) associated respiratory event}}{\text{Total sleep time (h)}}$$

Figure 14-8. Definition of apnea hypopnea index (AHI) and respiratory disturbance index (RDI).

per hour in healthy subjects. Two measures can be used for this purpose: the apnea hypopnea index (AHI) and the respiratory disturbance index (RDI). Typically, the AHI (number of hypopneas and apneas per hour of sleep; Figure 14-8, *top*) and RDI (number of hypopneas, apneas, and arousals related to respiratory events per hour of sleep; see Figure 14-8) are used to quantify the severity of SDB.

RDI values of five or more predominantly obstructive events per hour of sleep are commonly referred to as OSA; this cut-off value has been used as an indication for treatment by clinicians based on the current clinical guidelines of the AASM,[27,28] in which the severity of sleep apnea is further characterized as mild with 5 to 15 or less events per hour of sleep, as moderate with 15 to 30 or less events per hour of sleep, and as severe sleep apnea with 30 or more events per hour of sleep (Table 14-4).[27,31,109]

Epidemiology. OSA with daytime symptoms affects 0.3% to 5% of the general population.[110-112] As obesity is one of the major risk factors for OSA, the prevalence might continue to increase with higher rates of obesity in the general population.[113-115] The prevalence of SDB without daytime symptoms is even higher, with rates of up to 9% in women and 24% in men between the ages of 30 and 60 years and is often unrecognized.[116,117]

TABLE 14-4 SEVERITY OF SLEEP APNEA BASED ON RDI OR AHI

	RDI (per hour)	AHI (per hour)
No sleep apnea	<5	<5
Mild sleep apnea	≥5 to <15	≥5 to <15
Moderate sleep apnea	≥15 to <30	≥15 to <30
Severe sleep apnea	≥30	≥30

A respiratory disturbance index (RDI) less than 5 per hour is physiologic and found in healthy humans. Sleep apnea is mild with RDI between 5 and 15 per hour, moderate with RDI between 15 and 30 events per hour, and considered severe with an RDI of 30 and greater per hour of sleep. Equal cutoff values are similar for severity based on the apnea hypopnea index (AHI).

BOX 14-1 ***Symptoms of Obstructive Sleep Apnea***

Nighttime Symptoms

- Frequent awakening during the night (e.g., pseudo nocturia)
- Awaking from own snoring with choking sensation
- Tachycardia
- Sleep that is not restorative

Daytime Symptoms

- Awaking with dry mouth
- Dull headache in the morning
- Daytime sleepiness
- Falling asleep during monotonic situations (e.g., watching television)
- Subjective impairment of cognitive function

Symptoms Reported by Bed Partner

- Snoring, especially when loud and arrhythmic
- Observed pauses in breathing during sleep

Furthermore, the prevalence of OSA varies widely between different populations. Individuals with a high susceptibility to OSA include the obese (see Chapter 71), the elderly (see Chapter 80), and those with specific comorbidities (e.g., stroke, myocardial infarction), as well as surgical patients. Depending on methodology, the rates of OSA in surgical patients is between 45%[118] and 75%.[119] A recent study in patients undergoing bariatric surgery revealed an incidence of OSA of as high as 77.5% (618 of 797 patients) in this population.[120]

Clinical Symptoms. Approximately one third of patients with OSA complain of typical signs and symptoms occurring during wakefulness. Awaking with dry mouth, headache in the morning, daytime sleepiness, falling asleep during monotonous situations (e.g., watching television), as well as subjective impairment of cognitive function are frequently reported. This combination of OSA with daytime symptoms is usually referred to as OSA syndrome (OSAS).[121,122]

Sleep-associated signs and symptoms of OSAS include witnessed pauses in breathing or snoring, and a high number of nocturnal awakenings, mostly reported as pseudonocturia with patients occasionally complaining of tachycardia or respiratory distress upon awakening (choking sensation) and other symptoms (Box 14-1).

During clinical examination, craniofacial abnormalities affecting the airway, or other facial anatomic structures limiting the upper airway diameter might, indicate a patient at risk for OSA. A neck circumference of 43.2 cm (17 inches) in men or 40.6 cm (16 inches) in women has been shown to be associated with an increased risk for OSA. Although OSA is more frequent in obese patients, it might also occur in patients with normal or even low body mass indices. Given the variety of pathophysiologic mechanisms of OSA, it is not a surprise that even slim patients have OSA or OSAS.

Consequences and Comorbidities. Obstructive sleep apnea is associated with meaningful medical consequences, such as hypertension, myocardial infarction, stroke,[121,123-129] impaired glucose tolerance, diabetic neuropathy, as well as cognitive dysfunction resulting in occupational difficulties and motor vehicle crashes.[130-134] The development of cognitive impairment in patients with OSA[135] is paralleled by an atrophy of brain structures relevant for cognition and memory (hippocampal areas)[136] that can at least be partially reversed by adequate treatment.[137] Whether the negative effects of OSA are due to impaired sleep architecture or effects of intermittent hypoxia remain unclear,[138] because data investigating the effect of intermittent hypoxia without other symptoms in OSA patients are limited. Nevertheless, recent findings suggest that even asymptomatic OSA might be associated with cardiovascular effects, such as altered daytime autonomic regulation (i.e., heart rate variability).[139]

Given the frequent rate of complications associated with OSA, it is not a surprise that OSA leads to increased socioeconomic costs because of significantly more frequent rates of health-related contacts and medication use, and even higher rates of unemployment.[140]

Risk Factors. Predisposing factors for obstructive sleep apnea are obesity,[141] age,[141,142] male sex,[141] factors leading to swelling of the superficial tissue of the upper airway (smoking),[143] allergic rhinitis,[144] and decreased muscle tone of upper airway dilator muscles (e.g., central nervous system) caused by depressants.[145-147]

Pathophysiology. Respiratory events during OSA are characterized by decreased respiratory flow with persisting respiratory effort due to reduced intraluminal diameter of the upper airway up to complete pharyngeal airway collapse (see Figure 14-2). The muscles involved in respiration are morphologically and functionally skeletal muscles and can be classified by their anatomic function into two groups: upper airway dilator muscles and respiratory pump muscles.

Upper airway dilator muscles counterbalance the negative inspiratory pressure generated by the pump muscle to permit airflow during inspiration. Respiratory pump muscles are the collection of muscles responsible for generating inspiratory and expiratory forces in the thorax across the breathing cycle (Figure 14-9). The patency of the upper airway is maintained by balancing dilating forces (generated by the upper airway dilator muscles) and collapsing forces (i.e., negative intraluminal pressure generated by the respiratory pump during inspiration and compressive extraluminal forces from the surrounding tissues).[148]

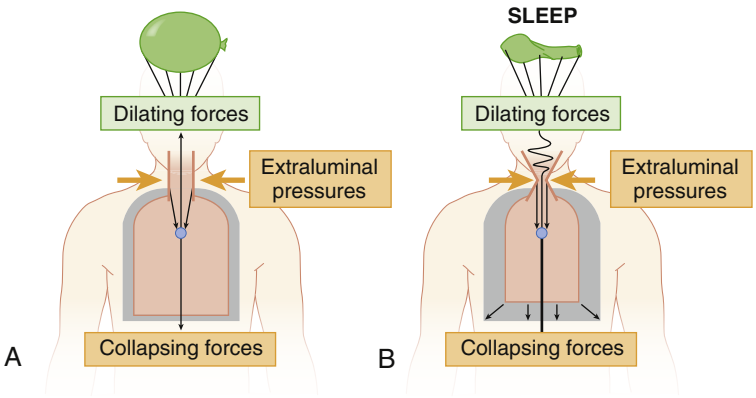


Figure 14-9. Relationship of upper airway patency and respiratory pump activation. During wakefulness, the force of the upper airway dilator muscles (*green balloon,* dilating forces) counterbalance the collapsing forces imposed on the upper airway by extraluminal pressures and negative inspiratory pressure generated by the respiratory pump muscles (represented by the *orange counterweight* [collapsing forces]). In obstructive sleep apnea, sleep onset *(blue needle)* leads to decreased upper airway patency by reducing the dilating forces. *(Modified from Sasaki N et al: Postoperative respiratory muscle dysfunction: pathophysiology and preventive strategies,* Anesthiology *118:961-978, 2013.)*

TABLE 14-5 SOME MUSCLES OF THE UPPER AIRWAY RELEVANT FOR UPPER AIRWAY STABILITY

	Activity (Tonic* and Phasic†)		
Muscle		**Insp.**	**Exp.**
Tensor palatini[153]	+	+	–
Levator palatine[153]	+	+	–
Genioglossus[154]	+	+	–
Geniohyoid[155]	+	–	+
Thyrohyoid	X	X	X

+, present; –, absent; *X,* insufficient data.
Major muscles of the upper airway and their activity during breathing. Tonic activity, as well as inspiratory [Insp.] and expiratory [Exp.] muscle activity.
*Tonic activity is noted in columns 2 through 4.
†Phasic activity is noted in columns 3 and 4.

Upper Airway Dilator Muscles. The most extensively studied of the upper airway dilating muscles are the genioglossus and the tensor palatini (Table 14-5). The genioglossus receives a variety of inputs, including phasic (inspiratory) and tonic (noninspiratory) drive, which are distributed differentially across the hypoglossal motoneuron pool.[149] In response to negative pharyngeal pressure created by the respiratory pump during inspiration, the genioglossus reflexively stabilizes the upper airway in animals and humans.[150,151] This reflex is likely a product of signaling from inspiratory modulated motor units. Whereas the genioglossus responds to phasic input on top of its tonic (nonrespiratory) activation, the tensor palatini is considered a tonic muscle with consistent tone throughout the respiratory cycle.[152]

Anatomic Vulnerability to Collapsing Forces. The soft tissues of the pharynx are enclosed and stabilized by bony structures, such as the mandible and the spine, and complete collapse of the pharyngeal airway ordinarily requires extraluminal forces, such as hematoma, edema, or peripharyngeal masses. Pharyngeal manifestation of obesity compresses the airway.[153] Craniofacial abnormalities can further increase the collapsing effects of excessive pharyngeal extraluminal soft tissue in obese patients and lead to pharyngeal collapse and OSA.[154] The extraluminal soft tissue, as well as size and shape of the bony enclosure, are determinants of the extraluminal pressure that need to be antagonized by the upper airway dilator muscle contraction during inspiration, to avoid an upper airway obstruction related apnea.[154] In addition, the upper airway is more vulnerable to collapse in the supine position than in the lateral or sitting positions.[155-157] These improvements in airway patency caused by the lateral and sitting positions as compared with the supine position are due to gravitational effects.

Excessive intravenous fluid administration can affect upper airway patency. In awake, healthy volunteers, the inflation of antishock trousers displaced so much fluid from the lower extremities that neck circumference increased, the pharynx narrowed,[158] and the upper airway had a lower threshold for collapse.[159] This concept is reinforced in studies of subjects with lower extremity venous insufficiency[160] and congestive heart failure.[161] These studies have shown nocturnal redistribution of fluid from the lower extremities into the neck increases upper airway collapsibility[160] and the severity of central apnea and OSA.[161]

Another important component of airway patency is the interplay between lung volume and upper airway collapsibility. Higher end-expiratory lung volumes are associated with a decrease in upper airway resistance to airflow in awake healthy humans,[162] and an increase in upper airway lumen dimensions in subjects with and without OSA.[163] The mechanism for the interaction between upper airway patency and lung volume is thought to lie in the generation of longitudinal traction forces in the trachea.[164,165] Upon inspiration, the lung inflates and effectively forces the carina into a more caudal position, creating stretching forces on the fixed trachea.[164] These forces are transferred to the upper airway walls through assorted soft tissue connections, resulting in improved upper airway dilatation.[165] Effectively, tracheal traction allows the respiratory pump muscles to contribute to upper airway patency.

Collapsing Intraluminal Pressure. The respiratory pump is the motorized action driving inspiration and expiration. It is the force that broadens the thoracic cavity and creates negative intrathoracic pressure to draw a breath in, and, when needed, positive intrathoracic pressure to exhale rapidly. Inspiratory pump muscles are an anatomically diverse group with the most studied being the muscles of the thoracic wall and the diaphragm, which accounts for 60% to 70% of lung volume change

during simple respiration.[166] During inspiration, the volume of the thoracic cavity increases as a result of contraction of the diaphragm and the external intercostal muscles. The lungs expand secondarily to the increased negative intrathoracic pressure generated by these phasic actions of the inspiratory pump muscles. The negative intrathoracic pressure translates into a negative intraluminal pressure in the upper airway, forcing the airway to collapse as soon as this pressure drops below a critical value.[167,168]

Although this critical airway pressure is typically negative (approximately –5 cm H_2O) in paralyzed healthy controls, the upper airway in patients with OSA has been shown to collapse when paralyzed, and positive intraluminal pressure is required for reopening the airway in patients with OSA.[169] Thus, the two compressing factors, negative intraluminal pressure and positive extraluminal pressure, need to be actively compensated by muscular activity of the upper airway dilator muscles to maintain airway patency.[108]

Wakefulness Stimulus and Sleep. Excitatory inputs to the upper airway motoneurons (e.g., hypoglossal motoneurons) include those from serotoninergic and noradrenergic neurons that fire predominantly during wakefulness,[170-173] resulting in a "wakefulness stimulus" that increases the activity of upper airway dilator muscles during this arousal state. On sleep onset, this arousal-dependent neuronal input (active awake, less active, or inactive asleep) disappears, leading to a decrease in upper airway muscle activity and causing increased upper airway resistance in healthy controls and airway collapse in patients with OSA.[174-177]

Respiratory Arousal. Respiratory arousal is arousal from sleep owing to cumulative and progressive increases in stimuli related to breathing (hypoxia, hypercapnia, and respiratory effort).[178]

Three primary inputs contribute to arousal-related restoration of breathing following an apnea (Figure 14-10):

1. Peripheral and central chemoreceptors sensitive to partial pressures of oxygen and carbon dioxide[179]
2. Sensors in the upper airway responsive to negative pressure generated by the respiratory pump[150,151]
3. Cortical inputs directly related to state of consciousness or wakefulness[177]

Any of these inputs can restore respiratory muscle tone if the magnitude is sufficient. Cortical awakening from sleep, identified by EEG signs of wakefulness, is an adequate stimulus for ventilation. Importantly, obstructive apneas, such as upper airway collapse in OSA, can be terminated by increased drive to the respiratory muscles not involving cortical arousal.[180] For example, hypercarbia resulting from sustained hypopnea[179] and elevated upper airway negative pressure[150,151] can independently restore tone to the respiratory muscles. The level of drive provided to the respiratory muscles depends on the summation of stimuli in the central respiratory pattern generator output, including peripheral and central chemo-responsiveness, reflex responsiveness to the negative airway pressure, and strength of the wakefulness drive.

Treatment. Adequate treatment of OSA improves nocturnal oxygen saturation as well as duration and quality of sleep, which translates to reduced daytime sleepiness and associated functional daytime impairments, and improved quality of life. Successful treatment of OSA reduces cardiovascular risk, improves insulin sensitivity, and increases neurobehavioral performance.[181-184] Therefore all patients with a diagnosis of OSA should be offered a sufficient treatment of the disorder as soon as the diagnosis of OSA has been established and its severity has been

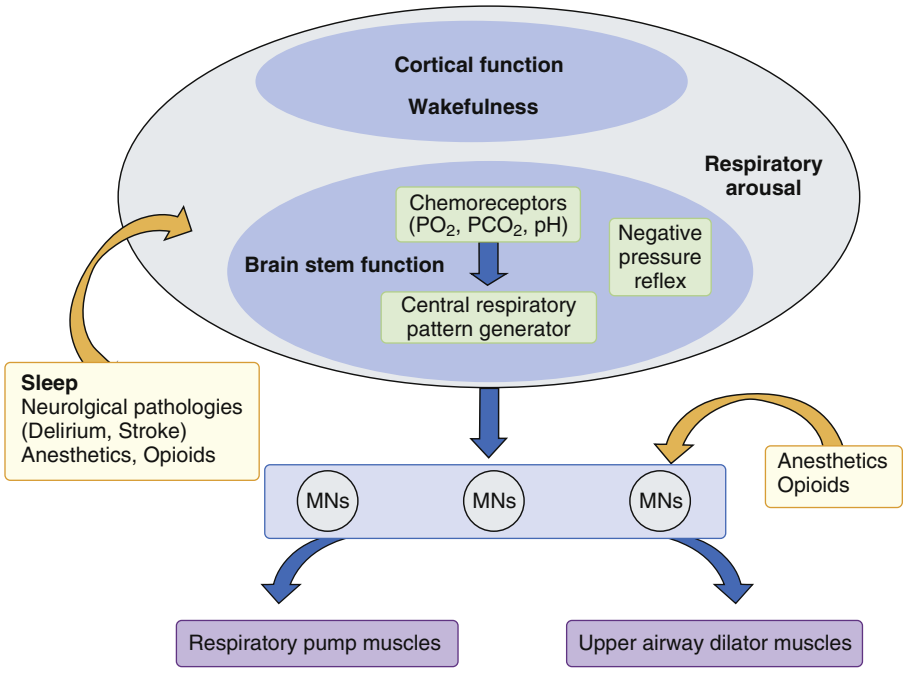


Figure 14-10. Effects of respiratory arousal on upper airway dilator and respiratory pump muscles. Respiratory arousal is composed of three primary inputs: central respiratory pattern generator processing peripheral and central chemoreceptor afferents, reflex responsiveness to the magnitude of negative pressure in the airway generated by the respiratory pump muscles, and strength of the wakefulness stimulus. Different factors can impair respiratory arousal, such as sleep and neurologic pathologies, anesthetics, and opioids. *Blue arrows* indicate excitatory effect; *yellow arrows* indicate inhibitory effect. *MN,* motor neuron. *(Modified from Sasaki N et al: Postoperative respiratory muscle dysfunction: pathophysiology and preventive strategies,* Anesthiology *118:961-978, 2013.)*

determined by objective testing (i.e., PSG).[28,31] Although different treatment options for OSA have been developed during the last decades (Table 14-6), noninvasive ventilation with positive airway pressure (PAP) is still the most effective treatment for OSA of all severities.[189,190]

Positive Airway Pressure Treatment. Noninvasive ventilation as a treatment for sleep disordered breathing is typically applied continuously (i.e., continuous positive airway pressure [CPAP]), which dose dependently reverses any sleep-associated upper airway obstruction, as outlined in Figure 14-11. The CPAP level needed for treatment of OSA varies between 5 and 20 cm H_2O and is different for every patient. An overnight study is necessary to titrate the airway pressure to a level sufficient to abolish airway obstruction in each patient. After titration, the prescribed treatment pressure is applied continuously throughout the night. Although this treatment is efficient in abolishing the underlying pathology and daytime functions, as well as the long-term consequences, the effect of PAP impact on outcome is limited by patient adherence,[42,129] mostly because of local side-effects at the nose or face, or discomfort caused by the mask.[186] When applied with high pressure, the amount of airflow can prevent the patient from falling asleep while using the treatment device. Some treatment devices offer a ramp or delay function that gradually increases treatment pressure from a low starting pressure to the prescribed pressure over a period of 5 to 45 minutes, allowing the patient to fall asleep more easily. Some patients report difficulties exhaling against high CPAP. To avoid this problem, bilevel treatment with reduced expiratory positive airway pressure (EPAP) and a sufficiently high inspiratory positive airway pressure (IPAP) can be combined.

In some cases, one CPAP pressure level is not sufficient to treat sleep apnea. PAP devices with dynamic pressure levels can improve treatment success, particularly in patients with a variable severity of sleep disordered breathing during different sleep stages. These automatic positive airway pressure or autotitrating devices measure different variables associated with hypopnea, such as oropharyngeal wall vibration, snoring, and inspiratory flow limitation and increase the airway pressure until these signs and symptoms of hypopnea disappear.

PAP treatment is recommended in patients with moderate to severe OSA, and it is the favored treatment for mild OSA. PAP is superior to all other OSA treatment options currently available, and it is recommended as the primary treatment of OSA by all major pulmonary and sleep medicine societies of Northern America and Europe, including the AASM,[27] the American Thoracic Society (ATS),[29] the American College of Chest Physicians, the European Respiratory Society,[29,186] the Canadian Thoracic Society,[31] the American Heart Association, and the American College of Cardiology.[32]

Although CPAP is sufficient in the treatment of patients with OSA, patients may need different treatment methods. For example, patients with mixed apneas (obstructive and central) or predominantly central apneas need a more controlled (frequency or time controlled),

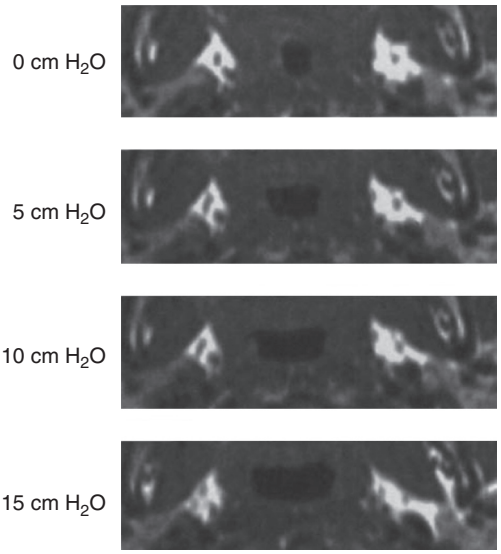


Figure 14-11. Magnetic resonance imaging of the human upper airway during different levels of continuous positive airway pressure. Magnetic resonance imaging of the upper airway during continuous positive airway pressure of 0, 5, 10 and 15 cm H_2O shows a dose-dependent increase in upper airway diameter. *(Obtained from Schwab RJ et al: Upper airway and soft tissue structural changes induced by CPAP in normal subjects,* Am J Respir Crit Care Med *154:1106-1116, 1996.)*

TABLE 14-6 **TREATMENT POSSIBILITIES FOR OBSTRUCTIVE SLEEP APNEA**

Treatment	Procedure/Device	Recommendation	References
Weight reduction	Reduction of body weight	Medium to high, SU	181, 198
	Weight-loss surgery (improves success of weight loss)		
Medication	Drug-based treatment (e.g., tricyclic antidepressants, serotonin reuptake inhibitors, cholinergic agonists, carbonic anhydrase inhibitors)	NR, ID	199, 200
Surgical	Nasal surgery	Low, SU	8, 26, 199, 201, 202
	Palatal surgery and implants	Low, MC	
	Tongue base surgery	Low, MC	
Increase of muscle activity	Muscle training	ID	8, 203, 204
	Hypoglossal nerve stimulation	ID	
Nonsurgical	Oral appliance	High, AT	41, 205
	Positive airway pressure	High, GS	41

AT, Alternative treatment if positive airway pressure is not tolerated; *GS,* gold standard; *ID,* data not sufficient for recommendation; *MC,* may be concerned in carefully selected patients if conservative treatment fails; *NR,* not recommended; *SU,* supportive treatment.

noninvasive ventilation with predefined minimal respiratory frequency or respiratory timing that automatically induces the next inspiration (ventilation) if the patient does not induce the next breath within preset parameters.

Alternative Treatment Options. Oral appliances (OAs) are possible treatment options in patients with mild to moderate OSA who do not tolerate CPAP therapy. Two major designs are currently used in clinical practice: (1) mandibular repositioning appliance, which holds the mandible in an advanced position (a protrusion of at least 50% of the maximal possible extension is recommended for effective treatment),[186] and (2) tongue retaining devices leading to repositioning of the tongue into a forward position without any protrusion of the mandible. A multidisciplinary approach including a sleep physician and a dental technician experienced in oral appliances have been recommended for this purpose, because both factors are crucial for patient adherence and outcome from OA treatment.[121] OAs are recommended in patients with mild to moderate OSA who do not tolerate,[186] not respond to, fail, or are not appropriate candidates for PAP treatment.[28]

Historically, surgical treatment methods were the only approach to treatment of OSA, but the evidence of effectiveness of most of the nasopharyngeal surgical approaches to treatment of severe OSA is poor. However, tonsillectomy is beneficial in adult patients with OSA from tonsillar hypertrophy, and adenotonsillectomy is recommended in children with OSA and adenotonsillar hypertrophy[41] (see Chapter 93). Repeated sleep testing following surgery is recommended to assure sufficient long-lasting therapeutic effects.[28,186,191]

Electrical stimulation of the upper airway muscles has recently been postulated as a new approach to treatment of OSA. Hypoglossal nerve stimulation induces dose-related increases in airflow of sufficient magnitude to eliminate inspiratory flow limitation due to airway collapse during obstructive sleep apnea,[188] but this new therapeutic approach cannot be recommended as a first-line treatment of OSA.[172]

While pharyngeal fat deposits led to a decrease in pharyngeal patency, underlining the risk factor of obesity,[192,193] weight loss leads to a reduction in Pcrit and the severity of OSA[168,185,194] and is recommended as adjunctive treatment in all overweight patients with OSA.[195] Because long-term weight reduction is more effective when accompanied by weight loss surgery, bariatric surgery may be considered as an adjunctive therapy in very obese patients (body mass index [BMI] ≥ 40 k/m^2), as well as in those with important comorbidities and BMI of 35 kg/m^2 or greater and in whom dietary attempts at weight control have been ineffective.[28]

Oxygen is currently not recommended as primary treatment of OSA, but can be used as an adjunctive treatment in some patients.[28,187]

Although OSA is more common in the older population, it occurs in children with a peak in the incidence between 2 and 5 years of age (see Chapter 93). Obesity predicts snoring and other signs of obstructive respiratory events in children.[121] Tonsillar and adenoidal hypertrophy is another important cause of OSA in children and can be treated surgically.[196]

Central Sleep Apnea

Definition. Central sleep apnea (CSA) is defined as cessation of air flow without respiratory effort,[197] which separates it from OSA where respiratory effort is maintained during an apnea. In clinical sleep apnea, considerable overlap between OSA and CSA occur that need to be identified and subsequently treated.[198]

Epidemiology. Central sleep apnea can be found in older patients and in patients with severe comorbidities such as stroke and congestive heart failure (CHF). Two studies investigated the occurrence of CSA in the general population. In a southern Pennsylvania cohort, CSA (AHI ≥ 20/h) was found in 5% of men aged 65 years and older, but it was not found in younger men or in women of any age. For an AHI of 2.5 per hour and greater, the prevalence estimates in men younger than 45 years remains negligible, while CSA was found in 1.7% of men between 45 and 64 years, and 12% in men older than 65 years,[199,200] or 9% in individuals between 40 and 97 years, respectively.[201]

CSA mechanisms can be categorized into those with high loop gain and low loop gain. The most common subtype of CSA with an increased loop gain is CSR commonly seen in patients with CHF and left-ventricular systolic dysfunction. CSR is defined as a crescendo-decrescendo pattern of hyperventilation between 20 and 30 seconds in duration, followed by 10 to 40 seconds of hypopneas or apneas (Figure 14-12) usually occurring during NREM sleep stage 1 and 2.[202] Nevertheless, CSR can also occur

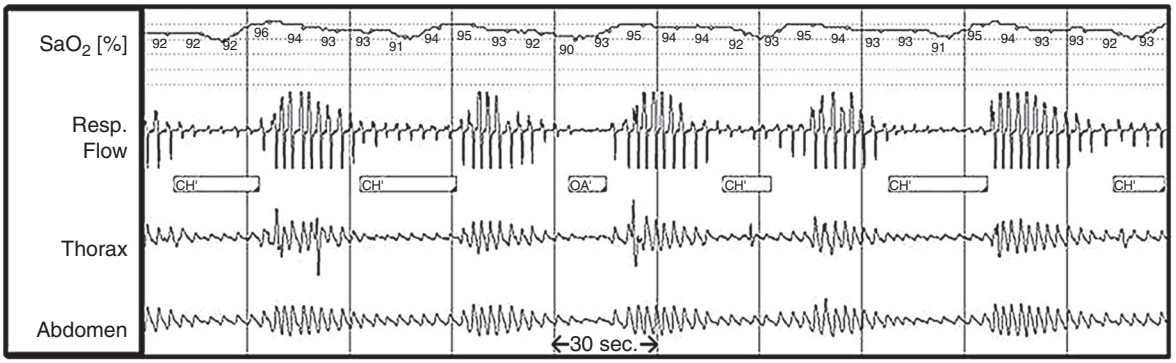


Figure 14-12. Polysomnographic recording of an episode of Cheyne-Stokes respiration. *CH,* Central hypopnea; *OA,* obstructive apnea.

during exercise or wakefulness. Almost one out of two patients with CHF shows Cheyne-Stokes respiration.[203] CSR is more common in men and worse in the supine body position.[204]

Consequences and Comorbidities. Central sleep apnea impairs quality of life[205] and is associated with adverse outcome in CHF patients,[206,207] but CSR by itself might not be just a marker of a "sicker" patient but an independent risk factor.[197,208]

Treatment. Potential respiratory therapies of CSR include oxygen, respiratory stimulants (e.g., CO_2, theophylline, and acetazolamide) and CPAP. It is difficult to quantify whether the hemodynamic or the respiratory effects of CPAP are the main mechanism of treatment success. A pilot study in 66 patients with CHF published by Sin and colleagues[209] showed a potential beneficial effect of CPAP treatment in patients with CHF with CSR on transplant-free survival. In these patients, cardiac function was improved after CPAP; however, this study is limited by the small number of subjects, lack of β-adrenergic blocker treatment in the majority of the subjects, as well as the absence of usage of intention-to-treat analytical technique. The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP) failed to corroborate these findings[210] and did not show improvement in outcome. In contrast, the data suggest a harmful effect of CPAP treatment in the short-term followed by a later improvement leading to an overall survival in this group equivalent to the survival in the control group. The improvements in morbidity also found in this study included left ventricular ejection fraction. The mechanism underlying the short-term worsening is unclear. It may relate to hypovolemia among CPAP-treated patients, which theoretically can decrease in cardiac output with nasal CPAP therapy (hypovolemic patients are pre-load dependent); whereas improved cardiac output with CPAP may be experienced in hypervolemic patients (more after-load dependent). A follow-up study of the CANPAP study population examined various subgroups, not prespecified in the initial study showing an improved outcome among the CPAP patients.[211] Follow-up trials investigating the effect of newer noninvasive ventilation devices in CHF are underway.[212,213] Because long-term data on the effect on mortality and morbidity of CPAP treatment are still missing, it is still not completely clear how CSR should be treated with noninvasive ventilation. Optimization of medical therapy is the optimal treatment, because CSR will often resolve with adequate treatment of CHF (cardiac resynchronization therapy and surgical treatment, such as heart transplant).[202,214]

Other Forms of Central Breathing Disorders. The term *periodic breathing* refers to altitude-induced breathing instability that can occur in most subjects transferred to a high altitude, whereas ambient hypoxia caused by low barometric pressure leads to an increased controller gain[108,215] or idiopathic central sleep apnea, which is a relatively uncommon disorder at sea level. This type of CSA occurs in individuals with an elevated hypercapnic ventilatory response (high controller gain) that leads to hypocapnia and respiratory control instability during sleep. Patients with idiopathic central sleep apnea tend to have low $PaCO_2$ levels, even during wakefulness.[216,217]

Obesity Hypoventilation Syndrome

Alveolar hypoventilation is defined as insufficient ventilation leading to hypercapnia (increased $PaCO_2$). Mechanisms of alveolar hypoventilation include central hypoventilation, chest wall deformities, neuromuscular disorders, chronic obstructive pulmonary disease, as well as severe obesity (obesity hypoventilation syndrome [OHS]). OHS is defined as the combination of nocturnal and daytime hypoventilation, usually leading to hypercapnia, in obese subjects (BMI ≥ 30 kg/m^2) in the absence of other causes of hypoventilation.

The prevalence of OHS is estimated to be up to 50% in obese patients with OSA (see Chapter 71). It is estimated to occur in up to 50% of patients with a BMI of 50 kg/m^2 and greater,[218] compared with 0.15% to 0.3% in the general adult population. Ninety percent of patients with OHS also suffer from OSA.[219,220] OHS often remains undiagnosed, and the true prevalence is unclear.

Severe obesity is associated with an increase in respiratory drive that helps to maintain eucapnia in the presence of the abnormal chest wall mechanics and high work of breathing.[221-223] In OHS, this compensatory mechanism is abolished,[223,224] which in part might be explained by leptin resistance.[225-228] Typically, OHS manifests as a reduced lung capacity, vital and functional residual capacity, expiratory reserve volume, respiratory system compliance, and inspiratory muscle strength, whereas response to CO_2 might be reduced or normal. In addition, there is an increase in serum bicarbonate and alveolar PCO_2, as well as in the work of breathing and leptin-levels.[228,229]

Impairment of the effectiveness of respiratory pump muscle function in patients with OHS can be explained by the effects of low lung volume because of central fat distribution, leading to a cranial displacement of the diaphragm during supine position.[229-234] In addition, diaphragmatic myopathy might be a contributing factor of OHS.[228] Treatment options include weight loss and noninvasive ventilation.[234,235]

SLEEP AND ANESTHESIA: TWO UNEQUAL TWINS INFLUENCING PERIOPERATIVE MEDICINE

CLINICAL PICTURE OF SLEEP AND ANESTHESIA

Although physiologic sleep and anesthesia share some clinical features (loss of consciousness and a modulation of brainstem autonomic function), major differences can be found when closer observations of both behavioral states are undertaken. In contrast to anesthesia, sleep shows spontaneous generation and termination, ready reversibility by noxious stimuli, and homeostatic regulation. Anesthesia does not share the stage-wise structure seen during physiologic sleep. Even the ether anesthesia derived stages of anesthesia, which do not apply to

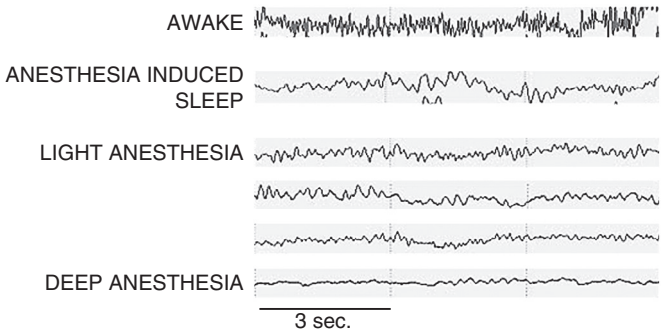


Figure 14-13. Electroencephalographic recording during sedation and loss of consciousness induced by anesthetics (i.e., propofol). Compared with physiologic sleep (see Figure 14-1), sedation shows electroencephalographic (EEG) traces comparable to slow wave sleep, indicating the sleep-inducing effect of anesthetics. Anesthesia-induced loss of consciousness *(lower four traces),* shows different EEG activity with reduced amplitudes and burst suppression. (Burst suppression is not shown in these traces.)

modern anesthesia, do not correspond to sleep stages (see Sleep Stages and Sleep Cycle). In addition, functional imaging studies underline the fundamental differences during onset of anesthesia and wakefulness-sleep transition.

Although there are similarities in the EEG patterns between slow-wave sleep and anesthesia-induced unconsciousness, the EEG patterns during sleep and anesthesia are different,[235] with different frequencies and types of activation in EEG recorded during physiologic sleep and the uniform EEG picture observed during anesthesia-induced unconsciousness (Figure 14-13).[41,237]

During anesthesia induction, the level of consciousness continuously decreases from fully awake through states of reduced response to external stimuli up to a completely unresponsive patient.[238] This is in contrast to the sharp alpha-theta EEG transitions seen while an individual proceeds from wakefulness to sleep without any transient stages. Individuals in a steady state of physiologic sleep can be aroused with sufficient stimulation, whereas drug-induced unconsciousness needs at least some drug elimination to occur before individuals can be aroused from this state.[239]

ACTIVATION OF SLEEP PROMOTING PATHWAYS DURING ANESTHESIA

The role of the endogenous sleep-promoting system in the mechanism of action of general anesthetics has recently received much attention. This hypothesis is attractive because of the similarities of sleep and anesthesia and some evidence that anesthetically induced sleep could meet some of the homeostatic need for sleep.[240a] (Tung 2004). It is even more attractive because, despite the large database of the molecular effects of anesthetics, how loss of consciousness occurs is still not explained. An important discovery was that some of the neurons that are active during sleep in the VLPO are also activated by certain anesthetics.[240-242] A second key observation was that inhibition of the arousal nuclei, the TMN, contributes to anesthesia.[241] This effect also implicates VPLO because it provides the major source of inhibition of the TMN. The idea has emerged that anesthesia-induced loss of consciousness is mediated by effects of the anesthetics on the flip-flop switch centered in the VLPO that is responsible for the sharp transition from wakefulness to sleep and back (see Sleep Promoting and Arousal Pathways).[239,243,244] There are a number of problems with this theory including, that rats and mice with complete lesions of the VLPO can still be anesthetized.[242,245]

Although lesions of VLPO lead to a transient resistance to volatile anesthetics,[242] if some time elapses following a VLPO lesion, the animals show increased sensitivity to isoflurane anesthesia attributable to increased homeostatic sleep drive.[242,245-247] Another problem with the VLPO-TMN circuit hypothesis of anesthesia is that direct inhibition of the TMN produces sedation but not produce anesthesia.[241]

Animals that have lost VLPO neurons have profound insomnia; however, they still sleep, indicating the existence of other sleep-promoting pathways.[93] Therefore, anesthesia might be the result of simultaneously driving all the endogenous sleep circuitry. This theoretical possibility is unlikely based on the key difference between anesthesia and sleep arousability. Sleep, but not anesthesia, is easily reversed or prevented by real or perceived environmental threats. This is the difference between the AAS being shut down by natural neural processes versus being shut off pharmacologically. Sleep promoting neurons work by inhibiting arousal pathways, but this inhibition does not and cannot prevent arousal to sufficient external stimuli. The unique property of anesthesia to do so has to be mediated by an additional mechanism. Nonetheless, the finding that GABAergic anesthetics engage sleep pathways is still important and meaningful; this is undoubtedly an important mechanism by which this class of anesthetics promotes sleep.

POSSIBLE MECHANISMS OF UNCONSCIOUSNESS

Defining the mechanism of anesthesia-induced loss of consciousness is a bold endeavor considering that the neurological substrate for consciousness is still unknown. However, the clinical characteristics of anesthesia as well as findings from basic science indicate that anesthetic drugs can induce unconsciousness mainly by altering neurotransmission in the cerebral cortex and possibly the thalamus.[248,249] Whether these effects are direct or occur via inhibition of brainstem ascending arousal pathways, or both, remains to be determined.[236,250] The GABA and NMDA receptors that are major targets of hypnotic drugs are found throughout the neuraxis.[251,252]

In anesthetized rodents, cortical neural activity is reduced.[253] These findings are in line with positron-emission tomographic studies in humans, which revealed a decrease in cortical metabolic activity under general anesthesia.[248,254]

Hypnotics have also been shown to inhibit brainstem arousal pathways.[236] Direct injection of a barbiturate into the mesopontine tegmental area has been shown to induce unconsciousness in rodents.[250] Such observations

are in line with brain-injury studies showing that brain stem unconsciousness typically involves the midbrain paramedian region and the lateral dorsal tegmental areas of the pons.[255]

PERIOPERATIVE INTERACTIONS BETWEEN ANESTHESIA AND SLEEP

Anesthesia and painful surgical procedures affect sleep and circadian rhythms[256-259] for as long as 6 months, depending on the complexity of the procedure performed.[260] A substantial decrease in REM sleep occurs on the first night after surgery and anesthesia, followed by a profound REM rebound phenomenon on the second to fourth postoperative night, when REM sleep increases in both intensity and amount.[256,258,259] Although most anesthetics can lead to an impairment of sleep architecture, such as REM depression and reduced sleep quality during postsurgical period, the extent of this impairment probably depends on the pharmacokinetics and pharmacodynamics of the anesthetic drug used, as well as the duration of administration. Opioids impair sleep quality[261,262] and the duration of REM sleep when given during anesthesia or for pain treatment.[263-266] These effects of opioids can be mediated in part by decreasing GABAergic transmission in the oral part of the pontine reticular nucleus.[267] GABAergic anesthetics, such as sevoflurane, also suppress REM sleep during the postanesthesia period.[268,269]

The effect of propofol on sleep architecture and REM sleep is complex and may be dose dependent. In long-term ventilated, critically ill patients, propofol sedation completely abolishes REM sleep and diminishes sleep quality,[270] whereas its lingering effects seem to have less intense effects on REM sleep.[247] The effects of ketamine sedation on sleep architecture have not been studied in detail yet, it may have rather mild effects on REM duration.[271]

Anesthetics can affect circadian rhythms. A recent trial in honeybees suggested an anesthetically induced circadian shift. Inside the laboratory with no outdoor cues, daytime anesthesia threw off the usual activity patterns in the hive for the next several days. In addition, cycles of clock gene activity showed a delay.[272,273] The mechanisms of these effects are unclear. More specifically, although circadian variation in drug metabolism may be linked to anesthetic drug efficacy, it is unknown whether anesthetics themselves can directly influence the regulation of the circadian clock. The psychotropic effects of anesthetics at subanesthetic doses cannot be isolated easily from anesthetic effects.[274] Of note, different psychotropic nonanesthetics, such as opioids, have been shown to affect melatonin secretion indirectly, independent of the behavioral state anesthesia.[275] Previous work in humans has shown that even 3 hours of anesthetic exposure in humans does not affect the circadian phase of the body temperature rhythm.[276]

In summary, the ability to distinguish between effects occurring directly on the circadian pacemaker and those occurring downstream from the pacemaker on other physiologic control systems requires extremely rigorous experimental conditions.

Surgical treatment itself impairs sleep, expressed as reduced REM sleep duration even in the absence of general anesthesia.[261,262] Pain, inflammation, stress immobility, and anxiety seem to be contributing factors.[277] After surgery, patients show a significant impairment of sleep quality and duration. Eventually, it will be known whether specific anesthetics are preferable to avoid the adverse effects of sleep deprivation.

SLEEP AND SEDATION IN THE INTENSIVE CARE UNIT

Sedation is frequently required in the intensive care unit (ICU) to treat excessive agitation or to fulfill specific therapeutic needs; however, heavy sedation is associated with prolonged ICU and hospital stays.[278] Pain is a common experience for most patients in the ICU,[279] and failure to recognize that pain can result in excessive administration of sedatives.[278] Accordingly, an aggressive approach to managing pain has been strongly recommended by published consensus opinions regarding sedation in the ICU.[280]

Impaired sleep is common in ICU patients,[11,281] and the mechanisms are intuitive: exposure to pain and anxiety, inflammation, noise, light, fluid, and nutrition without accounting for circadian considerations that induce a scenario comparable to an experimental "constant routine," in which effects produced by rhythmicity of habits and environmental stimuli are artificially abolished.

Sleep duration in the ICU shows a wide inter-individual variability among ICU patients depending on environmental conditions and the severity of the patient's disease.[282] Sleep fragmentation is seen in most ICU patients, especially during sedation and mechanical ventilation.[283,284] Deep NREM and REM sleep are severely reduced in ICU patients,[285-290] and variables reflecting circadian rhythm may be abolished.[291] Sedatives and pain medication, commonly applied during ICU treatment, can increase the severity of signs and symptoms of pathologic sleep.[270] Both noninvasive ventilation and ventilation via breathing tube impair sleep architecture and quality.[283,292] It is unclear how the issue of ICU-associated circadian disruption can be prevented or treated. Data suggest that some ventilator settings are less harmful than others; weaning procedures during daytime combined with a less activating ventilation mode during nighttime seem to improve sleep expressed as reduced numbers of arousal in patients requiring long-term ventilation.[288,289]

Studies on the use of melatonin for the treatment of sleep disturbances and delirium in ICU patients are too heterogeneous to recommend this treatment.[293] Nonpharmacologic treatments, such as earplugs and eye masks, have been shown consistently to improve sleep quality in ICU patients and possibly reduce the risk of delirium.[294-296] Additional research is needed to describe the biological consequences of ICU treatment-related impairment of circadian rhythms, and to develop protocols that successfully prevent severe disruption of the physiologic rhythmicity in critically ill patients.

SLEEP-DISORDERED BREATHING AND AIRWAY PATENCY DURING ANESTHESIA

Perioperative complications occur more often in patients with OSA than in healthy controls,[296,297] but the reasons

for this observation are unclear. It is challenging to isolate the effect of OSA from the known adverse effects on perioperative outcome of typical OSA comorbidities, such as hypertension, diabetes, coronary artery disease, neurovascular vulnerability, and obesity. Fortunately, severe postoperative complications are rare. As a consequence, large sample size trials (30,000 to 50,000 patients) need to be designed to isolate a cause-and-effect relationship between sleep-disordered breathing and meaningful perioperative complications, such as severe respiratory failure, thromboembolic complications, increased hospital length of stay, and mortality.

OSA is not (independently of obesity) associated with difficult tracheal intubation or mask ventilation.[298-302] However, a recent metaanalysis reported a significantly higher risk of postoperative cardiac events and acute postoperative respiratory failure, compared with control subjects.[303,304] These findings need to be confirmed in future trials with a larger sample size and a more homogenous population such that confounder control can be established. OSA is associated with postoperative delirium,[297,305] which is a meaningful perioperative complication associated with increased costs, morbidity, and mortality. However, it is currently unclear if this is due to repetitive hypoxia or sleep fragmentation. In contrast, a recent study using the Nationwide Inpatient Sample (NIS) database analyzed data from 1,058,710 patients undergoing elective surgeries. These authors showed that patients previously diagnosed with SDB had significantly higher rates of emergent mechanical ventilation, use of noninvasive ventilation, and CPAP, as well as increased rates of respiratory failure. Nevertheless, the study also showed that patients with SDB had better outcomes after emergent intubation and had lower care associated costs compared with their non-SDB counterparts.[306] Similar findings were reported by the same group for data from 91,028 patients undergoing bariatric surgery.[307] In this study patients with a previous diagnosis of SDB had shorter hospital length of stay and lower total costs compared with non-SDB patients. The reasons for the differences are unclear. Patients with a known history of sleep apnea may receive more sophisticated perioperative monitoring and more aggressive treatment of their respiratory disease, which might also explain the higher rate of postoperative reintubation in SDB patients reported by in the same group.[306] Another possible explanation relates to the consequences of chronic nocturnal desaturation, which can have preventive effects in terms of the consequences of perioperative acute hypoxia. Most importantly, these findings indicate that the association of SDB and perioperative outcome is likely to be more than a unidirectional relationship. More likely is that SDB could have a dual effect, leading to increased rates of perioperative respiratory complications in patients with SDB, but additionally protecting the same population from the fatal consequences of these complications. The mechanism of the potential link between OSA and postoperative respiratory failure, as well as postoperative delirium, is probably multifactorial. Frequent episodes of airway collapse in OSA lead to hypoxia, disrupted sleep, sleep inertia, daytime sleepiness, and increased arousal threshold from sleep, all of which can be considered as potential precipitating or augmenting factors of postoperative complications. It is intriguing to note that patients with OSA appear to be most vulnerable to hypoxia on postoperative night 2 or 3, the time interval during which postoperative delirium most typically manifests.

One population that might deserve additional attention in perioperative care is patients with OHS who, compared with obese patients, are more likely to be admitted to a hospital and require more healthcare resources.[306,308] In addition, higher rates of intensive care admission, lengthier long-term care requirements at discharge, and higher mechanical ventilation rates have been reported in patients with OHS compared to severe obese patients without OHS.[307-310]

In summary, patients with SDB are more vulnerable to developing severe perioperative complications. Nevertheless, it is currently unclear whether these complications translate to a poorer overall postoperative outcome for these patients.

PERIOPERATIVE MANAGEMENT IN PATIENTS WITH SLEEP DISORDERED BREATHING

The standard of care for perioperative management of patients with SDB depends on the severity of the disease, comorbidities, and the threat associated with the planned surgical procedure. It is probably neither feasible nor required to conduct a sleep study in all obese patients at risk for sleep apnea who are scheduled for surgery; however, high-risk patients need to be identified and treated perioperatively. Figure 14-14 shows an algorithm that is being developed at the Massachusetts General Hospital (MGH) in Boston. The algorithm is driven by the idea that patients who have been prescribed CPAP preoperatively should use CPAP perioperatively. In addition, the MGH algorithm indicates that patients characterized as double high-risk, in terms of surgical procedure and highly likelihood of meaningful sleep apnea, may need perioperative CPAP.

Preoperative Screening

Several strategies need to be considered to identify patients with SDB adequately.[39,309,310] Although clinical examination is the easiest and most cost-effective method of assessment using predisposing physical characteristics, it has a poor sensitivity and specificity of only 50% to 60% to diagnose OSA accurately.[311,312] However, the clinical value of using questionnaires relates to the fact that they help to identify a high-risk perioperative population, independently of the question of whether an individual patient has OSA. For example, the STOP-BANG questionnaire basically screens for comorbidities of OSA that we know increase the risk of perioperative complications (hypertension, obesity, male sex, older age) rather than direct breathing disorder–associated characteristics.

PSG is required to identify SDB specifically, but it cannot be used for preoperative screening of surgical patients. PSG is expensive, can delay surgery, and is inconvenient for the patient. A multistep approach of preoperative screening is required. Preoperative assessment should

include a screening for SDB and for the current use of noninvasive ventilation (NIV). OSA might not represent a meaningful risk in patients scheduled for low-risk procedures from a surgery and anesthesia point of view (e.g., hardware removal, ankle block). The authors believe that patients with no previously diagnosed SDB undergoing a low-risk surgical procedure should receive standard perioperative monitoring and treatment.

Patients undergoing high-risk surgical procedures should receive further work-up using a clinical examination combined with standardized and validated questionnaires (e.g., Berlin).[310,313] Although this diagnostic regimen might be a sufficient screening for OSA, it might be insufficient to detect OHS.[307,309] A blood gas analysis should be considered as a method to detect hypercapnia as a major symptom of OHS (criterion: awake daytime hypercapnia [$PaCO_2 \geq 45$ mm Hg]). Alternatively, a venous bicarbonate concentration of 27 mmol/L or greater is highly sensitive (92%) for an increased $PaCO_2$, which combined with hypoxemia (peripheral oxygen saturation [SpO_2] of 94%) indicates a high risk of OHS in these patients.[307,309,312,314] Of note, OHS is a diagnosis by exclusion. Severe obstructive airways disease, severe interstitial lung disease, severe chest wall disorders (e.g., kyphoscoliosis), severe hypothyroidism, neuromuscular disease, and congenital central hypoventilation syndrome need to be excluded, and further evaluation of sleep by a sleep medicine specialist before anesthesia should be considered. In these cases, the sleep specialist should determine the optimal diagnostic instruments in cooperation with the perioperative team, prescribe the perioperative autotitrating PAP device, and offer in collaboration with respiratory therapy specialists to improve tolerability of perioperative PAP therapy.

Perioperative Management of Patients With Possible Sleep-Disordered Breathing

Although the data on optimal intraoperative and perioperative management are still limited, the techniques and procedures summarized in Box 14-2 might be considered during the perioperative management of patients with SDB. Patients with a history of SDB who are undergoing surgery and anesthesia with high risk of morbidity should receive an "OSA anesthesia bundle," (see Box 14-2) that includes special procedures and preparations during intubation, extubation, pain therapy, and perioperative PAP and NIV treatment.

Endotracheal Intubation. Patients with OSA are frequently obese, and obesity is a risk factor for difficult intubation.[301,313-317] Patients should be preoxygenated efficiently before injection of the anesthetic drug. Sniffing and reverse Trendelenburg position are preferred before intubation, which improves maintenance of the passive (i.e., paralyzed) pharyngeal airway in patients with OSA[316,318] and increases functional residual capacity. To reduce the duration of paralysis, nondepolarizing NMDAs should be used with caution supported by quantitative neuromuscular transmission monitoring. Immediately after successful intubation, a lung recruitment maneuver and the application of postexpiratory positive airway pressure for maintaining lung volume during surgery might be considered.[317,319]

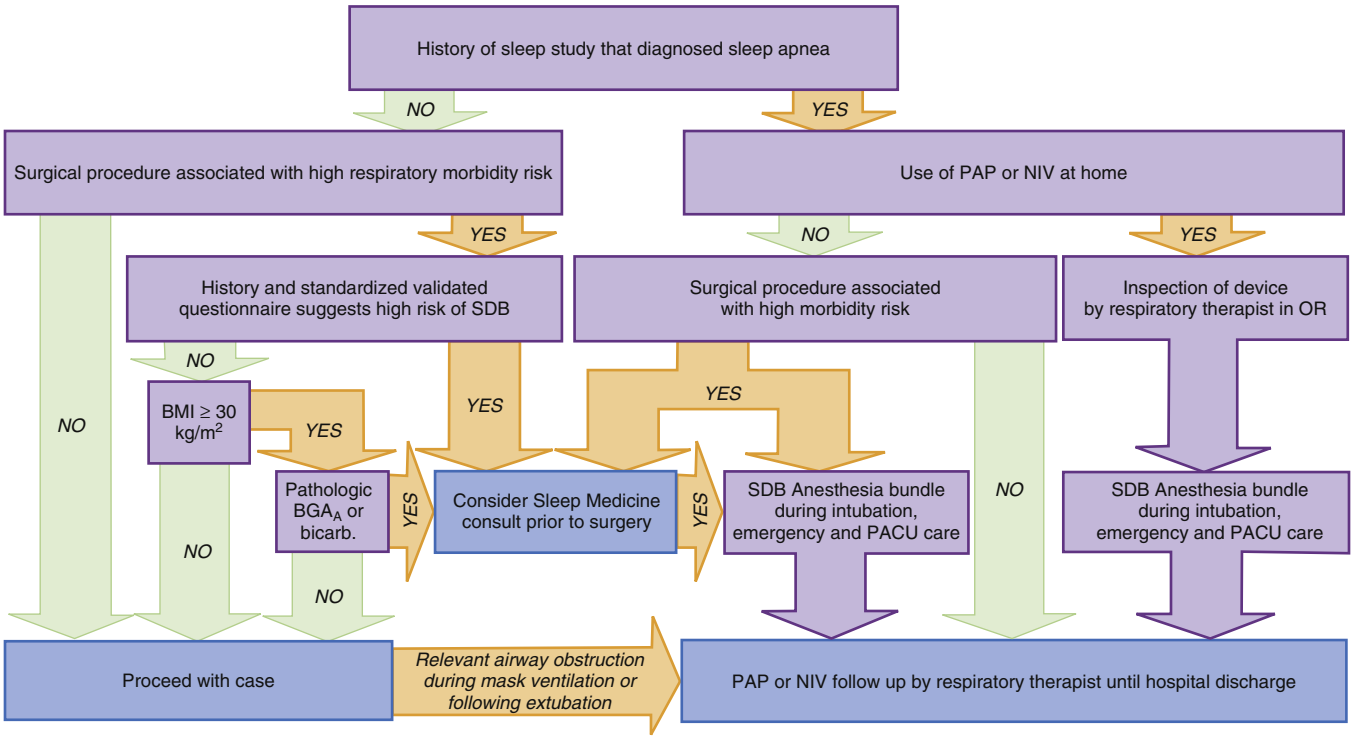


Figure 14-14. Clinical pathway for perioperative management of patients with sleep disordered breathing. *BGA_A,* Arterial blood gas analysis; *bicarb,* venous bicarbonate level; *BMI,* body mass index; *NIV,* non-invasive ventilation; *PACU,* post-anesthesia care unit; *PAP,* positive airway pressure.

BOX 14-2 ***Special Sleep-Disordered Breathing Anesthesia Bundle: Special Procedures Performed During Anesthesia in Patients With Diagnosed Sleep-Disordered Breathing and Positive Airway Pressure or Noninvasive Ventilation Treatment***

Preanesthesia Period

- Consider regional anesthetic techniques techniques that minimize the chance of postoperative sedation

Induction Strategy

- Monitoring: capnogram, tidal volume measurement
- Sniffing position
- Reverse Trendelenburg position
- Consider intubation without nondepolarizing NMBA, consider succinylcholine
- Triple airway maneuver with two hands
- Lung recruitment maneuvers immediately after intubation and apply PEEP for maintaining lung volume during surgery.
- PCV with PEEP
- Short-acting anesthetics and narcotics preferred
- Avoid high-dose steroidal NMBA
- Use neuromuscular transmission monitoring

Intraoperative Management

- Whenever possible, use of sedatives and narcotics should be reduced.
- Agents with reduced impairing effect on upper airway patency might be considered (e.g., ketamine, pentobarbital).
- Neuromuscular blockade should be monitored.
- Residual neuromuscular blockade should be reversed.

Extubation and Postanesthesia Care Unit

- Patient should be able to cooperate before extubation. Consider positioning of patients in PACU bed: upper body should be elevated by 45 degrees, lateral position preferred to minimize gravitational effects on the upper airway.
- In case of impaired respiratory function, a plan needs to be defined and documented for monitoring and treatment, including the consideration of noninvasive ventilation.
- Patients will be discharged to an unmonitored environment or home when they meet discharge criteria:
  - Vital signs within 20% from baseline
  - Adequate treatment of nausea
  - Pain score ≤ 40%
  - Aldrete-score ≥ 8
  - Passed room air challenge test

Pain Therapy

- Consider nonsteroidal antiinflammatory drugs to reduce opioid use whenever possible, if not contraindicated.
- Use caution when combining opioids with sedatives or hypnotics.

NMBA, Neuromuscular blocking agents; *PACU,* postanesthesia care unit; *PCV,* patient controlled ventilation; *PEEP,* postexpiratory positive airway pressure.

Intraoperative Treatment. Sedatives and anesthetic opioids,[318-321] as well as all GABAergic hypnotics and sedatives impair upper airway patency.[320-330] Recent preclinical data suggest that certain GABAergic anesthetics, including barbiturates[328-331] and isoflurane,[330,332] may be less harmful than others, such as propofol.[329-332] Ketamine abolishes the impairment of upper airway patency during loss of consciousness and sleep.[331,333] Short-acting anesthetics and narcotics are preferred in patients with OSA to reduce the risk of residual impairment of the upper airway after the end of anesthesia.

Nondepolarizing neuromuscular blocking drugs should be titrated optimally by quantitative neuromuscular transmission monitoring to avoid residual neuromuscular blockade, which increases the risk of postoperative respiratory complications.[332-337] The effects of neuromuscular blockade should be reversed only when present, because inappropriate reversal by cholinesterase inhibitors (e.g., neostigmine) can impair upper airway function in animals and humans[336-339] (see Chapters 34 and 35.)

Postoperative Care. Obstructive sleep apnea occurs during sleep and sedation[338,340]; therefore, extubation should be delayed until recovery of consciousness, expressed as a patient's ability to follow commands after emergence from anesthesia.

Patients should be positioned with the upper body elevated by 45 degrees, which improves airway patency[317,318] and functional residual capacity. The lateral body position is an alternative for patients who do not tolerate an elevated upper body position. Noninvasive ventilation is a viable treatment of postoperative respiratory failure and helps to prevent deoxygenation and the development of postoperative negative pressure pulmonary edema; it can also prevent the respiratory depressant effects of opioids.[339,341]

Before discharge from the postanesthesia care unit, vital signs should recover to values within 20% from preanesthesia baseline, and a room air-challenge test should be conducted. Adequate treatment of nausea and pain should be accomplished (pain score ≤ 40% max; Aldrete-score ≥ 8).

Pain Therapy. Pain treatment is of special concern during the postoperative period. Opioids can reduce respiratory function, and special caution is recommended when opioids are combined with sedatives or hypnotics. If not contraindicated, regional anesthesia and nonopioid analgesics should be considered to reduce opioid use for pain therapy whenever possible. The most important goal is maintenance of adequate respiratory drive, which can be accomplished under opioid therapy as long as the effects of pain stimulus and opioids on respiratory drive are in optimal balance. Pain intensity typically decreases over time following surgery. Decreasing opioid doses are typically required to maintain the balance of decreasing and increasing effects on respiratory drive.

Patients with SDB being treated with PAP or NIV at home should proceed with these treatments throughout the perioperative period. Sufficient functioning of the treatment device needs to be assured preoperatively by the respiratory technician or another clinician familiar with PAP and NIV devices and the treatment of SDB. These patients should receive the same care as patients with SDB who are not undergoing PAP or NIV treatment (see Box 14-2).

EFFECT OF OTHER SLEEP DISORDERS ON PERIOPERATIVE MANAGEMENT

Narcolepsy

Narcolepsy is a neurologic sleep disorder with a prevalence of 0.05% to 0.8% in most ethnic groups,[340-343] and it is characterized by excessive daytime sleepiness, involuntary daytime sleep episodes, and disturbed nocturnal sleep. It is accompanied by sleep-associated muscular hypotension. Narcolepsy is divided into narcolepsy with or without cataplexy (sudden loss of muscle tone without loss of consciousness).[342,344]

It has been suggested that an autoimmune pathology against hypothalamic hypocretin (orexin) (hcrt) neurons is involved in the pathogenesis of narcolepsy.[343,345] A mutation of the hcrt receptor 2 or loss of hcrt neurons have been shown to cause a narcolepsy-like state in dogs and mice,[344-347] and the deficiency of hcrt has been shown to be associated with narcolepsy in humans.[346-350] Hcrt is involved in control of several biological functions such as feeding, cardiovascular regulation, upper airway stability, pain, locomotion, stress, and addiction.[92,172,349,351] Environmental factors play a key role in the pathogenesis of the disorder, as the disease concordance rate between monozygotic twins is only 20% to 35%.[350-353]

Treatment of narcolepsy consists of (1) behavioral treatment, as well as pharmacologic treatment for (2) daytime sleepiness, and (3) cataplexies. Periodic and regular sleep times and scheduled daytime naps are recommended. Pharmaceutical treatments of daytime sleepiness include amphetamines, methylphenidate, modafinil, or selegiline (also effective for treatment of cataplexy), and cataplexies can be treated using tricyclic antidepressants, selective serotonin reuptake inhibitors, or γ-hydroxybutyrate/sodium oxybate. Medical treatment should always be accompanied by behavioral therapy.

Delayed emergence from anesthesia, postsurgical hypersomnia, and apneic episodes are in part related to an increased sensitivity to anesthetic drugs.[352-354] Medical treatment of narcolepsy should be maintained during the preoperative period.[354-357] The most commonly used treatment of daytime sleepiness is modafinil, which acts via dopaminergic pathways and accelerates emergence from anesthesia.[356-359] Some authors recommend not using sedative premedication[354-357] and to consider regional anesthesia.[358-361] Of note, narcoleptic or cataplectic events can also occur during regional anesthesia.[360-363]

Restless Legs Syndrome and Periodic Limb Movement Disorder

Restless legs syndrome, or Ekbom syndrome, is a neurologic disorder with a prevalence of 2% to 5% as defined by four cardinal features including: (1) the urge to move the limbs, usually associated with paresthesias or dysesthesias, (2) aggravating effects of rest, (3) ameliorating effects of physical activity, and (4) symptoms that worsen during the course of day, with a peak during the evening or at night. Patients with restless leg syndrome usually also complain about sensory symptoms in the legs.

Isolated periodic limb movements during sleep are a rare symptom, commonly referred to as *periodic limb movement disorder*. The characteristic periodic episodes of repetitive limb movements during sleep occur most often in the lower extremities, including the toes, ankles, knees, and hips, and occasionally in the upper extremities. These movements can be associated with frequent arousals leading to sleep disruption, causing excessive daytime sleepiness, which often is the only symptom reported by the patients themselves in the most cases.[12]

Symptomatic restless leg syndrome can occur in patients with iron deficiency and uremia, during pregnancy,[362,364] or during the use of neurotropic medications (dopamine antagonists, neuroleptics, selective serotonin reuptake inhibitors, tricyclic antidepressants, antihistamines, caffeine, alcohol, nicotine). Although daytime symptoms of restless leg syndrome can be sufficiently diagnosed clinically (clinical examination in combination with standardized questionnaires), a PSG is recommended to rule out SDB, especially in patients complaining of daytime sleepiness or sleep fragmentation.

According to the most recent guidelines of the AASM, the first-line treatment of restless leg syndrome should consist of dopamine agonists (i.e., ropinirole and pramipexole) in the evening (two or three times per day in some patients, at least 30 minutes before the usual time of symptom onset). Furthermore, gabapentin enacarbil, levodopa with dopa decarboxylase inhibitor, or opioids can be used. Medication impairing the dopaminergic system (dopamine antagonists, neuroleptics, selective serotonin reuptake inhibitor, and tricyclic antidepressants, antihistamines, caffeine, alcohol, and nicotine) should be avoided, if possible.

Exacerbation of restless leg syndrome symptoms can follow general anesthesia,[363,365] and the urge to move the limbs may be misinterpreted as agitation or delirium.[364,366] The first manifestation of restless leg syndrome can occur after spinal anesthesia[365,367] or general anesthesia,[366,368] and the prevalence of restless leg syndrome after surgery seems to be higher than expected in this population.[362,365]

To prevent perioperative exacerbation of symptoms, patients with restless leg syndrome should be scheduled for surgery early in the day, given the circadian character of the disorder. Restless leg syndrome medication should be continued until the day of surgery, whenever appropriate. Drugs that block the central dopamine transmission, such as neuroleptics, should be avoided. In contrast, ketamine might be the superior anesthetic drug for patients with restless leg syndrome.[367,369] In addition, intravenous or subcutaneous opioids and benzodiazepines during and after the surgery procedure might be beneficial in patients with restless leg syndrome. The best way to provide symptom release in patients restless leg syndrome might be early mobilization after surgery. In patients who are not eligible for mobilization, compression treatment[368,370] or intravenous administration of magnesium[369,371] and physiostigmine[370,372] have been shown to lead to relief of restless leg syndrome symptoms. Iron and ferritin blood levels should be monitored closely before, during, and after surgery, especially in surgical cases with iron loss (i.e., bleeding), to prevent symptomatic restless leg syndrome symptoms.

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Chapter 15

Perioperative and Anesthesia Neurotoxicity

RODERIC ECKENHOFF • VESNA JEVTOVIC-TODOROVIC

Key Points

- General anesthetic exposure in both young and elderly patients can influence neuronal processes, which have the potential to influence later cognitive and behavioral states.
- Clinical studies at both extremes of life are, until now, largely retrospective and confounded, but consistently suggest an association between surgery and long-term cognitive outcomes.
- Potential mechanisms for anesthetic neurotoxicity are numerous, including calcium dysregulation, mitochondrial dysfunction, free-radical damage, amyloidopathy, and tauopathy. Important mechanisms in the developing brain are likely different from those in the aged brain (see also Chapter 80).
- The inflammatory response to surgery is important, especially with preexisting vulnerabilities such as aging or neurodegeneration. This conclusion implies that surgery and its response have a larger role in the elderly than in the young.
- Cognition and behavior are late manifestations of underlying toxicity and neurodegeneration; biochemical and imaging biomarkers enhance the ability of interventions to influence brain pathology and function.

Perioperative management decisions likely have consequences far beyond the perioperative period. Although cardiovascular and cerebrovascular abnormalities increase risk, a more subtle and delayed effect may occur from uncomplicated surgery on cognitive processes. First identified more than 50 years ago,[1] and anecdotally since, cognitive and behavioral disturbance after anesthesia and surgery at both extremes of age has now been largely validated (see also Chapters 80 and 93). This chapter recognizes the increased interest in the potential mechanisms of durable cognitive disturbances and how they relate to other better understood and defined entities, such as Alzheimer disease (AD) in the elderly and learning disabilities and attention deficit disorder in young patients. The authors make no assumptions regarding a relationship between these disorders and reversible postoperative cognitive decline (POCD), which is extensively discussed in Chapter 99, and caution the lumping together of these cognitive disorders. The underlying mechanisms of durable cognitive decline in the elderly and the young are likely fundamentally different. For example, perhaps neither fit neatly into the term *anesthetic toxicity,* but rather the observed disorders are the result of a series of off-pathway effects of perioperative management in general considering the extreme complexity of the perioperative period. Yet few evidence-based changes in practice can be offered at this point, and certainly more investigation is warranted.

DEVELOPMENTAL NEUROTOXICITY

As a result of skillful and sophisticated pediatric anesthesia management (see also Chapter 93), the exposure of very young children, including premature babies as young as 20 weeks postconception to general anesthesia is becoming common, resulting in the annual administration of more than 3 million anesthetics to children.[2] The frequency of surgery and anesthesia has increased exponentially, as has the length of stays in intensive care units (ICUs). Heroic attempts to save premature and very ill infants have resulted in prolonged, deep sedation, and repeated anesthesia during an extremely complex and delicate period of human development. We must question the safety of this practice.

In addition to many unique physiologic characteristics of young children, the human central nervous system (CNS) is not fully developed at birth; it continues to grow and develop for several years postnatally.[3,4] In utero, the CNS goes through extensive *neurogenesis,* which is almost completed by the end of the second trimester (see also Chapter 77). During the last trimester and the first 2 years or so of postnatal life, CNS development is marked by massive growth.[4] The human brain doubles in size during the first 6 months after birth and triples in size by 12 months of age, largely as a result of extensive dendritic branching, myelination, and glia proliferation. This is also the period of *synaptogenesis,* a process requiring several

key events to occur in a highly synchronized fashion. These events include neuronal migration, differentiation, and dendritic branching. The formation of synapses then leads to neuronal maturation and creation of circuitries via processes that are tightly controlled by the glial cells. Glia actively communicate with neurons while providing a nurturing milieu for neuron-neuron interactions.[5]

DEVELOPMENTAL APOPTOSIS

The transmitter glutamate promotes all key aspects of neuronal development.[6] The fine balance between γ-aminobutyric acid (GABA)-mediated versus glutamate-mediated neurotransmission is important for proper and timely formation of synapses and neuronal circuitries. Neurons that are not successful in making meaningful connections are somehow marked as redundant and undergo programmed cell death, or *apoptosis,* which is a normal occurrence during development of the CNS. Although normal, apoptosis during development is tightly controlled, resulting in the removal of only a small percentage of neurons.[7] However, a disturbance in the glutamatergic and GABAergic balance during this crucial stage of brain development may excessively signal developing neurons to self-destruct. The question becomes whether general anesthetics, at doses that almost certainly disrupt the glutamate and GABA signaling balance, could be promoting excessive activation of neuroapoptosis and the death of large populations of developing neurons.

General anesthetics do cause significant and widespread neuroapoptotic degeneration of developing neurons in various mammalian species, including mice,[8,9] rats,[7] guinea pigs,[10] piglets[11] and nonhuman primates[12-14] (Fig. 15-1). The peak of vulnerability to anesthesia-induced neuroapoptosis in each species coincides with its peak of synaptogenesis, with much less vulnerability observed during late stages of synaptogenesis.[10,15] The mechanisms of anesthesia-induced developmental neuroapoptosis are presently being intensely studied.

Mitochondria-Dependent Apoptotic Cascade

The mitochondria-dependent pathway of apoptotic activation, also termed the intrinsic pathway, involves down-regulation of antiapoptotic proteins from the bcl-2 family (e.g., Bcl-xL), increased mitochondrial membrane permeability, and increased release of cytochrome c into the cytoplasm. This, in turn, activates caspase-9 and caspase-3, resulting in apoptosis. Accordingly, general anesthesia administered at the peak of synaptogenesis activates the mitochondria-dependent cascade within 2 hours and is characterized by a decrease in Bcl-xL, a rise in cytochrome c, and activation of caspase-9.[15] Melatonin, a sleep hormone known to up-regulate Bcl-xL, offers some protection by partially inhibiting anesthesia-induced cytochrome c leakage and caspase-9 activation.[16]

Death Receptor–Dependent Apoptotic Cascade

Apoptosis can proceed via the extrinsic pathway, triggered by the activation of death receptors. This involves the formation of a death-inducing signaling complex (DISC), which results in the activation of caspase-8 and caspase-3, resulting in cell death. General anesthesia promotes DISC formation[15] and thereby apoptosis. Studies suggest that anesthesia-induced activation of the intrinsic pathway occurs before activation of the extrinsic pathway.[15]

Neurotrophic Factor–Dependent Apoptotic Cascade

The neurotrophins, a family of neuronal growth factors, support neuronal survival and differentiation and synaptic plasticity. Thus, they are important in synaptogenesis of the mammalian brain. Neurotrophins are synthesized and released by neurons; both their biosynthesis and secretion depend on neuronal activity. Extensive depression of neuronal activity can impair neurotrophin-regulated survival-promoting signals and consequently promote apoptosis. When clinically used general anesthetics were administered at the peak of synaptogenesis, the observed neuroapoptotic damage was mediated, at least in part, by a brain-derived neurotrophic factor (BDNF)-modulated apoptotic cascade.[17,18] Anesthesia-induced disturbances in BDNF-mediated neuronal survival pathways were rapid, and the underlying mechanisms may show region specificity. A sex hormone, β-estradiol, offers some protection against the anesthetic-induced neuroapoptosis by partially inhibiting anesthesia-induced caspase-3 activation.[17]

Anesthetic-Induced Neuroapoptosis Leads to Neuronal Depletion

An important question with potential functional implication is whether the observed anesthesia-induced apoptosis of developing neurons results in permanent neuronal deletion. Careful quantification of neuronal densities in the most vulnerable cortical and subcortical regions revealed that animals treated with general anesthesia had as much as a 50% decrease in neuronal densities in these brain regions in contrast to untreated animals.[10,19] Although physiologic "pruning" of redundant neurons commonly is observed in the developing mammalian brain, only approximately 1% to 2% do not survive normal synaptogenesis. Perhaps clinical doses of anesthetic jeopardizes the survival of such an excess of developing neurons.[10]

Neuroapoptosis: Anesthetic Versus Changes in Cardiovascular and Respiratory Homeostasis

Of prime importance in clinical anesthesia is the maintenance of adequate oxygenation and ventilation; tissue perfusion; and, ultimately, the stability of vital signs. Because of the technical limitations imposed by the small size of rodent pups, these important parameters cannot be monitored and controlled continuously in many of the preclinical studies that generated the previously mentioned data. Thus, some of the preclinical findings may be a result of inadequate maintenance of physiologic homeostasis. To address this concern, researchers have used guinea pigs[10] and primates,[12-14] species in which it is technically possible to more tightly control and monitor

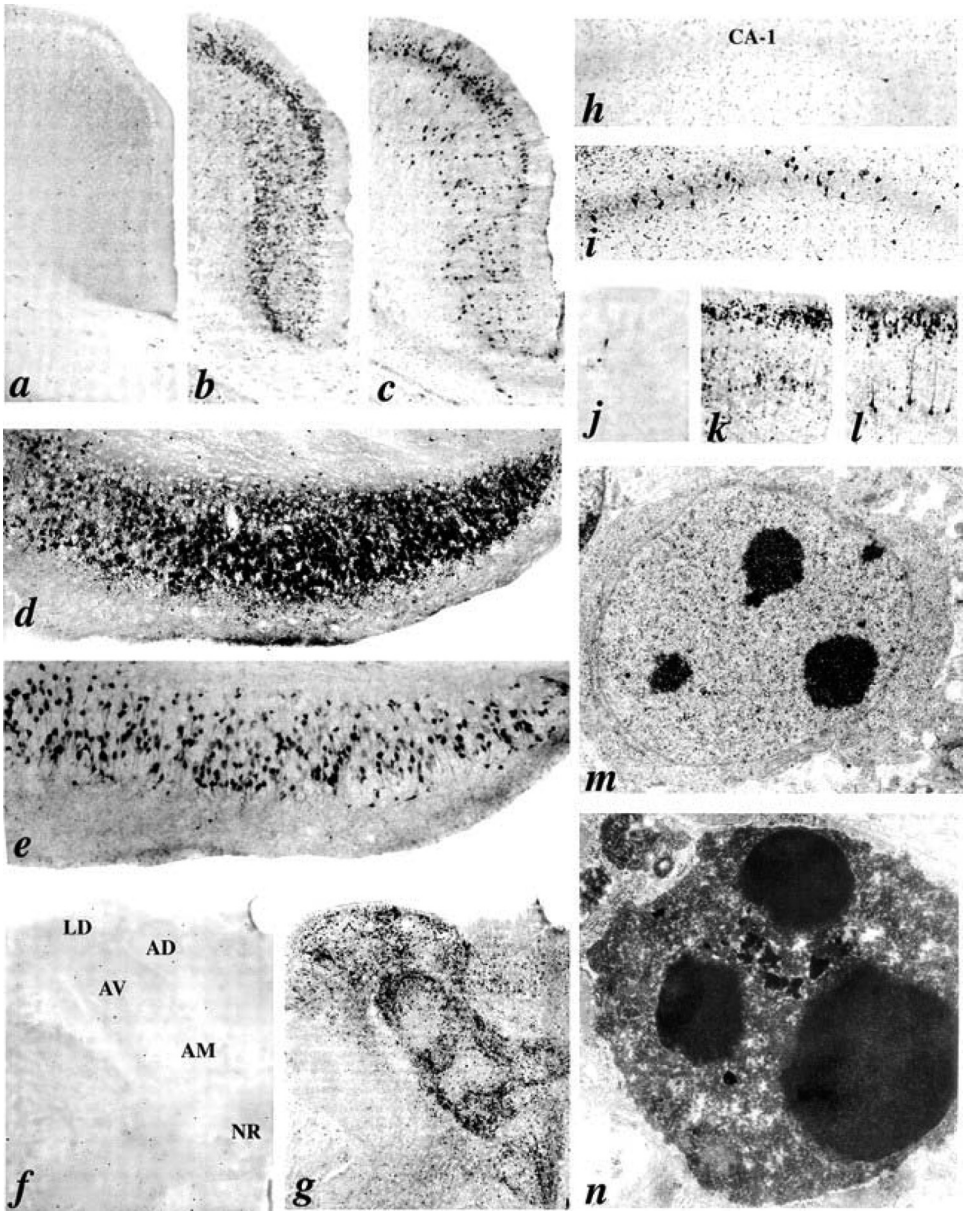


Figure 15-1. Anesthesia induces apoptotic neurodegeneration. Panels *a* to *l* are light micrographs of various brain regions of a control rat *(a, f, h, j)* and a rat exposed to isoflurane (0.75 vol%), midazolam 9 mg/kg subcutaneously, and nitrous oxide 75 vol% for 6 hours *(b* to *e, g, i, k, l).* Some sections were stained by the de Olmos silver method *(a, b, d, f, g, k);* the others were immunocytochemically stained to reveal caspase-3 activation *(c, e, h* to *j, l).* Regions are the posterior cingulate and retrosplenial cortex *(a* to *c),* subiculum *(d, e),* anterior thalamus *(f, g),* rostral CA1 hippocampus *(h, i),* and parietal cortex *(j* to *l).* The individual nuclei shown in the anterior thalamus *(f, g)* are laterodorsal *(LD),* anterodorsal *(AD),* anteroventral *(AV),* anteromedial *(AM),* and nucleus reuniens *(NR).* Panels *m* and *n* are electron micrographs of neurons undergoing apoptosis. The cell in *m* displays an early stage of apoptosis in which dense chromatin balls form in the nucleus while the nuclear membrane remains intact. The cell in *n* exhibits a much later stage of apoptosis in which the entire cell is condensed, the nuclear membrane is absent, and intermixing of nuclear and cytoplasmic constituents is seen. *(From Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al: Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits,* J Neurosci *23:876-882, 2003.)*

the adequacy of ventilation, oxygenation, and tissue perfusion. These studies confirm the smaller animal studies, suggesting that the histomorphologic changes observed are caused by general anesthesia per se and not by hypoxia, hypercarbia, or metabolic imbalance. Moreover, neither hypoglycemia[9] nor hypercarbia[20] significantly worsens anesthesia-induced developmental neuroapoptosis, again implicating the anesthetic as opposed to the physiologic state.

MITOCHONDRIAL MECHANISMS FOR ANESTHESIA-RELATED DEVELOPMENTAL NEUROTOXICITY

In addition to jeopardizing the integrity of the mitochondrial membrane and activating the intrinsic apoptotic cascade, general anesthetics cause a significant and long-lasting disturbance in mitochondrial morphogenesis. Early exposure to general anesthesia causes mitochondrial

enlargement and disruption of the cristae and inner mitochondrial membrane.[21] Mitochondrial regeneration in neurons depends on a fine dynamic balance between mitochondrial fusion and fission.[22] Deranged fusion leads to mitochondrial fragmentation, whereas deranged fission leads to enlargement. Thus, general anesthetics may disturb this fine dynamic balance, favoring mitochondrial fusion. Such dysfunction may be the cause of anesthesia-induced developmental neurodegeneration,[21] especially because an imbalance that favors fusion may contribute to several adult neurodegenerative diseases.[23,24]

Anesthetic-induced mitochondrial enlargement may slow migration, delaying their delivery to highly arborized dendritic branches at a time when their presence is necessary for normal synapse formation and development.[25,26] Anesthesia reduces the number of mitochondria in these distal sites[21] and impairs plasticity of dendritic spines and the formation,[27,28] stability,[18] and function of developing synapses.[29]

The morphologic distortion and impairment of regional distribution is also accompanied by production of excessive reactive oxygen species (ROS) and peroxidation of lipids and proteins. ROS clearly contribute to the development and progression of several neuronal diseases associated with cognitive decline, including Parkinson disease,[30] AD,[31,32] and Huntington[33] disease. Neurons produce ROS as by-products of their high metabolic activity and yet are relatively deficient in oxidative defenses. This vulnerability, combined with a high polyunsaturated fatty acid content, makes them susceptible to excessive lipid peroxidation and cellular damage.[34] A functional link between anesthetic-induced mitochondrial dysfunction, ROS up-regulation, and cognitive decline may exist. Administration of either radical scavengers or mitochondrial permeability transition pore blockers with anesthetics at postnatal day 7 (the peak of synaptogenesis) prevented the development of learning and memory impairment as adolescents. Moreover, melatonin, a naturally occurring sleep hormone,[16] and carnitine, a nutritional supplement that protects mitochondrial integrity,[35] cause significant protection against neuronal apoptosis. Thus, preventing excessive lipid peroxidation and protecting mitochondria may be the key to safe use of general anesthesia during early stages of brain development.

ENDOPLASMIC RETICULUM MECHANISMS FOR ANESTHESIA-RELATED DEVELOPMENTAL NEUROTOXICITY

An upstream trigger for the mitochondrial and apoptotic observations discussed earlier could be the excessive release of calcium from the endoplasmic reticulum resulting in cytosolic and mitochondrial calcium overload. In turn, this causes cytochrome c leak,[36] further compromising mitochondrial function. Thus, the endoplasmic reticulum could be an important initial target organelle of anesthesia-induced developmental neurotoxicity. Indeed, isoflurane directly activates inositol 1,4,5-trisphosphate receptors ($InsP_3R$), producing an exaggerated and prolonged calcium release, and increases cytosolic calcium.[37] This increases mitochondrial permeability transition pore activity[38] and modulates mitochondrial Bcl-xL protein, events that promote apoptotic neuronal death in the immature rat brain. Desflurane and sevoflurane, but less so propofol, activate the $InsP_3R$ and with similar consequences.

Calcium dysregulation is not an all-or-none phenomenon. Moderate increases in endoplasmic reticulum calcium release may provide neuroprotection,[39] whereas excessive release may push calcium into the toxic range. As a second messenger, intracellular calcium regulates many aspects of neuronal development, including synapse formation and function, membrane excitability, protein synthesis, neuronal apoptosis, and autophagy—all important elements of neuronal survival.[36,40,41] Disturbances in calcium homeostasis underlie some forms of learning and memory deficits[42,43] and may play an important role in anesthetic-induced developmental dysfunction.

LYSOSOME AND AUTOPHAGY MECHANISMS IN ANESTHESIA-RELATED DEVELOPMENTAL NEUROTOXICITY

Anesthesia may produce an excess of defective organelles, often referred to as biologic "garbage" that must be degraded to ensure neuronal survival. The process for clearing this debris without causing damage to the neuron is the multistep process, autophagy (i.e., autophagocytosis). Autophagy is initiated by the formation of autophagosomes, double-membrane–bound cellular structures that enter lysosomes, the acidic vacuolar compartment that contains various lytic enzymes.[44-46] Defective organelles are autophagocytosed at a slow rate, resulting in lysosomal accumulation of an undegradable, polymeric, autofluorescent material termed lipofuscin. General anesthetics heighten the formation of autophagic bodies,[21] raising the possibility that anesthesia kills developing neurons in part by inducing autophagic stress, a form of self-cannibalism. Accordingly, a relationship between autophagy and neuroapoptosis may occur in other models of cell injury. However, whether autophagy is important for the initiation of apoptosis[47] or whether autophagy and apoptosis are independent of each other is not known.[48] Regardless, the neurotoxic effect of general anesthetics during early stages of development may involve the growth and demise of neuronal organelles (Fig. 15-2).

ANESTHESIA-RELATED IMPAIRMENT OF SYNAPTOGENESIS

Exposure of rodents to general anesthetics at the peak of synaptogenesis results in severe, long-lasting functional and ultrastructural abnormalities of synapses of the developing hippocampal complex[29] (Fig. 15-3). This observation agrees with a study showing that exposure of mice to general anesthesia during synaptogenesis results in significant reductions in dendritic filopodial spines and synapse formation both in vivo and in vitro.[18]

General anesthetics are powerful modulators of synaptogenesis not only in terms of causing significant deletion of neuronal synapses and neurons but also in causing

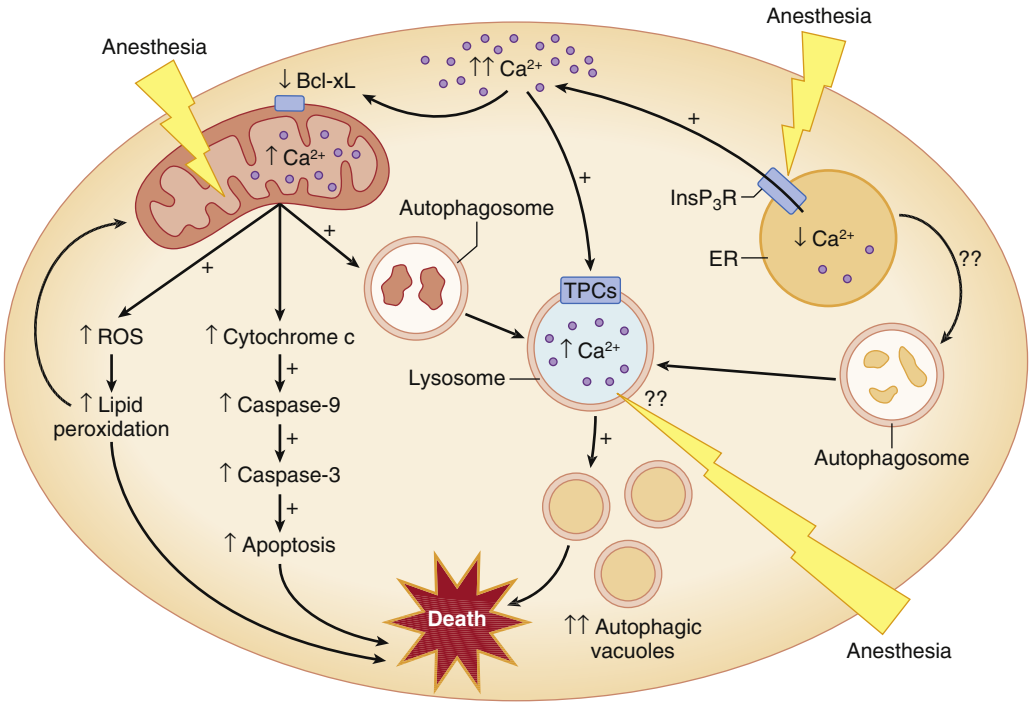


Figure 15-2. Anesthesia-induced pathways of developmental neurodegeneration. Three pathways are proposed: (1) The endothelial reticulum–dependent pathway involves anesthesia-induced activation of inositol 1,4,5-trisphosphate receptors *($InsP_3R$)* causing excessive calcium *(Ca^{2+})* release and acute elevation of cytosolic Ca^{2+}. This causes down-regulation of mitochondrial antiapoptotic protein, *Bcl-xL*, producing cytochrome c leak into the cytoplasm, which in turn activates apoptosis by activating caspase-9 and caspase-3. (2) The mitochondria-dependent pathway relies on anesthetic-induced up-regulation of reactive oxygen species *(ROS),* leading to the excessive lipid peroxidation of mitochondrial and endoplasmic reticulum *(ER)* membranes. Damaged mitochondrial and ER are sources of more ROS, cytochrome c, and calcium, so these cells have to be removed by apoptosis or autophagy. (3) The lysosome-dependent pathway involves lysosome activation by nicotinic acid adenine dinucleotide phosphate–gated two-pore channels *(TPCs),* which control Ca^{2+} uptake into the lysosomes. An increase in lysosomal calcium increases proteolytic activity, which in turn promotes the formation of autophagic vacuoles and autophagy. It is unclear whether anesthesia causes lysosomal activation indirectly by an increase in cytosolic Ca^{2+} from the ER or directly via lysosomal activation. *(From Jevtovic-Todorovic V, Boscolo A, Sanchez V, Lundari N: Anesthesia-induced developmental neurodegeneration: the role of neuronal organelles,* Front Neurol *3:141, 2012.)*

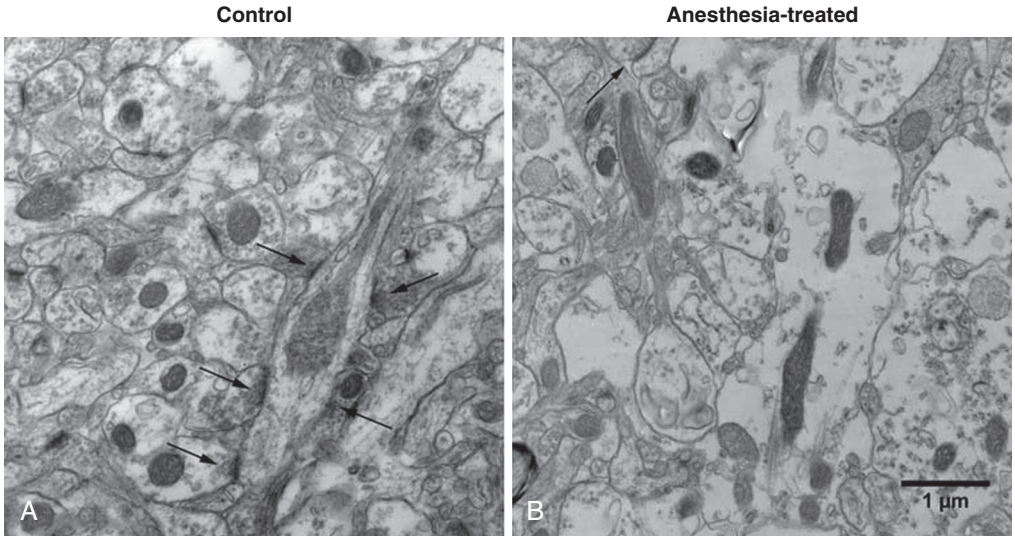


Figure 15-3. Anesthesia-treated animals had scarce multiple synaptic boutons (MSBs). **A,** The abundance of MSBs *(arrows)* on the neuronal profile of a control subiculum. In contrast, anesthesia (**B**) produces a reduction of synaptic contacts (magnification 12,000×). *(From Lunardi N, Ori C, Erisir A, et al: General anesthesia causes long-lasting disturbances in the ultrastructural properties of developing synapses in young rats,* Neurotox Res *17:179-188, 2010.)*

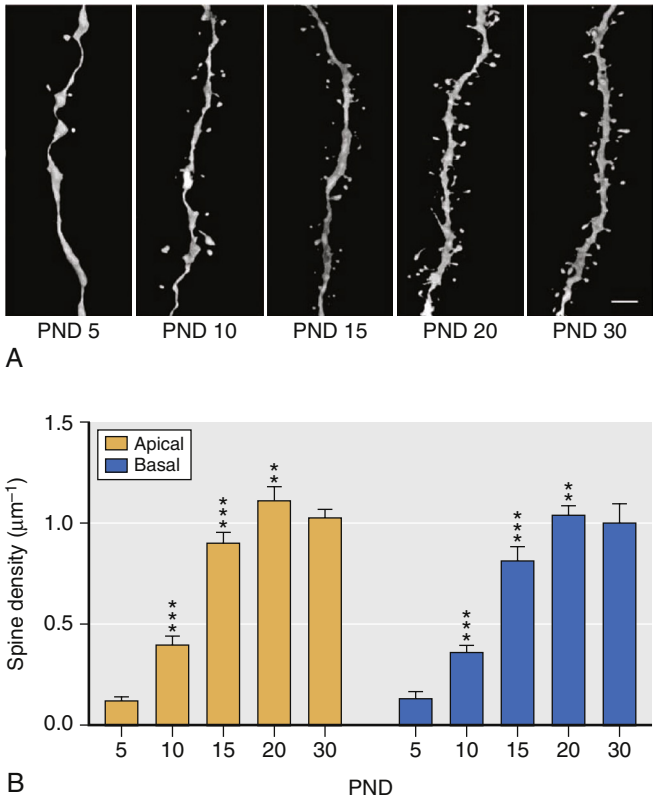


Figure 15-4. Dendritic spine development in pyramidal neurons during the first month of postnatal life. **A,** Confocal microscope images show the temporal evolution of dendritic spine density on apical dendritic shafts of layer 5 pyramidal neurons between postnatal days 5 and 30. ***B,*** Quantitative analysis of the temporal evolution of dendritic spine density on apical *(red columns)* and basal *(blue columns)* dendritic shafts during this period (mean ± SD). *PND,* Postnatal day. ** = $P < 0.01$, *** = $P < 0.001$), scale bar = 6 μm. *(Briner A, Nikonenko I, De Roo M, et al: Developmental stage-dependent persistent impact of propofol anesthesia on dendritic spines in the rat medial prefrontal cortex,* Anesthesiology *115:282-293, 2011.)*

undue up-regulation of synaptic contacts when the exposure occurs at the later stages of synaptogenesis[27,28] (Fig. 15-4). Of course, the functional outcomes of either morphologic phenomenon remain to be deciphered.

LONG-TERM COGNITIVE OUTCOME IN ANIMALS AFTER EARLY ANESTHETIC EXPOSURE

The pathomorphologic findings discussed earlier make it clear that anesthesia exposure results in neuronal deletion[10,19] and long-lasting impairment of synapses in vulnerable brain regions.[18,29] The question now is whether these observations translate to lasting effects on behavior.

The answer, at least in animals, is yes. The development of cognitive abilities of animals exposed to general anesthetics at the peak of synaptogenesis lagged behind those of controls, with the gap widening into adulthood (Fig. 15-5). Even intravenously administrated general anesthetics such as propofol or thiopental in combination with ketamine (but not singly) at postnatal day 10 alter mouse behavior later in young adulthood.[49] Similar adult behavioral deficits were noted when mice were exposed at postnatal day 10 to a cocktail containing ketamine and diazepam.[50]

Although anesthesia cocktails seem to be most detrimental, ketamine given alone during early stages of brain development in rats also caused later deficits in habituation, learning, and memory.[50] When anesthetic drugs with GABAergic and *N*-methyl-D-aspartate antagonist properties are combined, which is done frequently in the clinical setting (e.g., nitrous oxide [N_2O] and volatile anesthetics or propofol and ketamine), cognitive deficits are more profound.[7,49,50] Although causality is difficult to establish, anesthesia-induced neuroapoptosis (discussed previously) is at least in part responsible for the observed cognitive deficits. Whether multiple, longer-lasting exposures to anesthesia cocktails during vulnerable periods have more effects than predicted on neurocognitive development is not known.

General anesthesia is rarely administered in the absence of surgery and its associated pain and tissue injury. Thus, the reported neurotoxic potential of general anesthesia during brain development needs to be confirmed in the setting of surgical stimulation. Using clinically relevant concentrations of N_2O and isoflurane, Shu and colleagues[51] found that nociception enhanced neuroapoptosis and worsened long-term cognitive impairments in contrast to anesthesia alone (Fig. 15-6). On the other hand, Liu and colleagues[52] found that noxious stimulation attenuated the apoptotic effect of ketamine anesthesia. Resolution is needed in these conflicting results in the combined effects of surgery and anesthesia in the neonate.

Results from rodent studies usually translate poorly to humans, but newly emerging behavioral studies with nonhuman primates suggest that translation is likely. Paule and colleagues[53] examined the effects of continuous neonatal (age 5 or 6 days) ketamine infusion (24 hours) sufficient to maintain a light surgical plane of anesthesia on behavioral development in primates. They observed that ketamine-treated primates exhibit long-term disturbances in all important aspects of cognitive development, such as learning, psychomotor speed, concept formation, and motivation. These effects occurred despite an absence of physiologic or metabolic trespass. Although 24 hours of anesthetic exposure would be considered unusual, it certainly occurs, especially in critically ill patients of all ages.

LONG-TERM COGNITIVE AND BEHAVIORAL DEFICITS IN HUMANS AFTER CHILDHOOD SURGERY

The effects of perioperative events on the psychological and emotional development of children have been known for decades. In 1945, Levy's retrospective study[54] was the first to make an association between relatively short surgical procedures, such as tonsillectomy, adenoidectomy, or appendectomy, in otherwise healthy children and the development of new behavioral problems such as terrors, dependency, destructiveness, and disobedience within the first 6 postoperative months. Most of the sensitive children were in the youngest age group; 33% to 58% of them were between 0 and 2 years of age. We now know

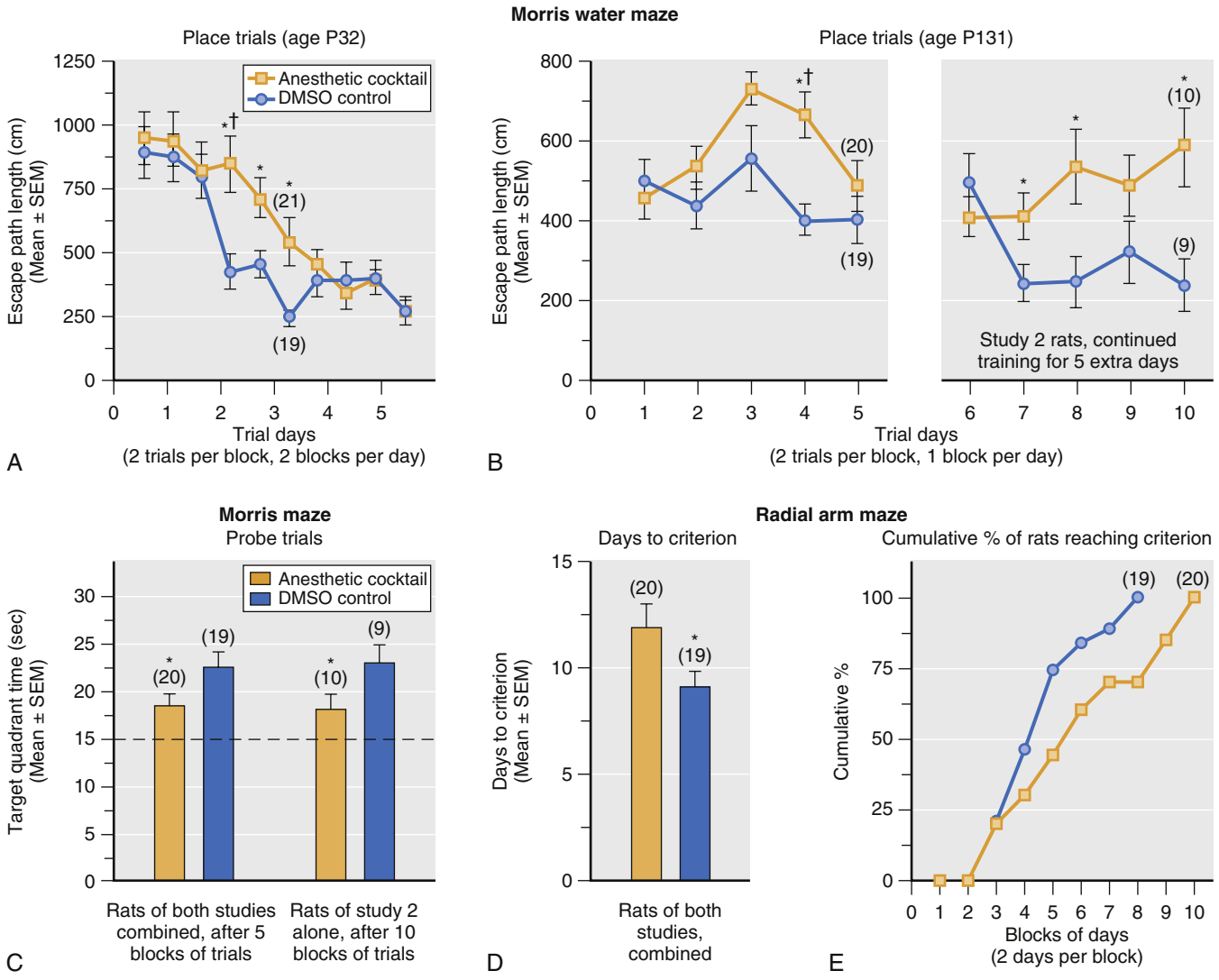


Figure 15-5. Effects of neonatal anesthetic cocktail treatment on spatial learning. Typical cognitive studies demonstrate durable anesthetic-induced defects. **A,** Rats were tested at P32 for their ability to learn the location of a submerged (not visible) platform. ANOVA analysis of data on the length of escape paths yielded a significant main effect of treatment ($P = 0.032$) and a significant treatment by blocks of trials interaction ($P = 0.024$). These results indicated that the place-training performance of rats given an anesthetic cocktail (0.75-vol% isoflurane with midazolam at 9 mg/kg, s.c., and nitrous oxide at 75-vol% for 6 hrs) was significantly inferior to that of control rats. Subsequent pairwise comparisons indicated that differences were greatest during blocks 4, 5, and 6 ($P = 0.003$, 0.012, and 0.019, respectively). However, rats given the anesthetic cocktail improved their performance to control-like levels during the last four blocks of trials. **B,** Rats were retested as adults (P131) for their ability to learn a different location of the submerged platform. The graph *on the left* shows the path-length data from the first five place trials when all rats were tested. ANOVA analysis of these data yielded a significant main effect of treatment ($P = 0.013$), indicating that the control rats, in general, used significantly shorter paths in swimming to the platform than did rats treated with the anesthetic cocktail. Subsequent pairwise comparisons showed that differences were greatest during block 4 ($P = 0.001$). The graph *on the right* shows the data from rats given 5 additional training days as adults. During these trials, rats in the control group improved their performance and appeared to reach asymptotic levels, whereas the rats given the anesthetic cocktail showed no improvement. ANOVA analysis of these data yielded a significant main effect of treatment ($P = 0.045$), as well as a significant treatment by blocks of trials interaction ($P = 0.001$). Additional pairwise comparisons showed that group differences were greatest during blocks 7, 8, and 10 (P = 0.032, 0.013, and 0.017, respectively). **C,** Probe trial performance of rats given the anesthetic cocktail and control rats during adult testing. Search behavior of the rats was quantified when the submerged platform was removed from the pool after the last place trials in blocks 5 and 10. The histogram *on the left* presents data for rats in both studies 1 and 2 combined after five blocks of place trials were completed. The histogram *on the right* presents data for rats in study 2 alone, after 10 blocks of place trials were completed. The *dotted line* represents the amount of time that animals would be expected to spend in the target quadrant based on chance alone. Both histograms show that the control rats spent significantly more time in the target quadrant than did the anesthesia-exposed rats, regardless of whether the probe tests were done on both study groups after five blocks or only on the study 2 rats after 10 trials. **D** and **E,** Data are shown from the radial arm maze test done on P53 to evaluate spatial working memory capabilities. The histogram in **D** shows that rats given the anesthetic cocktail rats required significantly more days to reach a criterion demonstrating learning (8 correct responses out of the first 9 responses for 4 consecutive days) compared with controls. The plot in **E** shows the days to criterion data as the cumulative percentage of rats reaching criterion in each group as a function of blocks of training days. The acquisition rate of rats given the anesthetic cocktail began to slow around the fourth block of trials and remained slower throughout the rest of the experiment. Numbers in parentheses in each graph indicate sample sizes. *$P < 0.05$; Bonferroni corrected level: $P < 0.005$ in a; $P < 0.01$ in b. *(From Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al: Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits,* J Neurosci *23:876-882, 2003.)*

that the incidence of surgery-associated psychological disturbances ranged from 9% to 20% and that children younger than 2 years of age were at most risk. Furthermore, the risk was independent of the anesthetic drug used,[55-58] and in some cases the behavioral disturbances persisted for months and even years. In a prospective multicenter survey of 551 children, Campbell and associates[59] found a 47% overall incidence of new behavioral problems, including anxiety, nightmares, and attention seeking, and again noted a relatively more frequent risk in those having procedures in the first 2 years of life.

Because the behavioral changes were independent of drug or technique, the emotional shocks of hospitalization, separation from family, and the physical traumas of surgical intervention, including pain, fluid imbalance, nutritional changes, and blood loss, were thought to cause the regressive behavioral changes. However, the relationship between anesthesia and acute personality changes was suggested in 1953, when Eckenhoff[56] published a retrospective study of 612 patients younger than 12 years of age who had either a tonsillectomy or appendectomy while anesthetized with a variety of anesthetics (cyclopropane, N_2O, morphine, and pentobarbital). Behavioral changes and new-onset bedwetting occurred on average 2 months after surgery, with the most frequent incidence (57%) in those younger than 3 years and lowest incidence (8%) in those older than 8 years.

Backman and Kopf[58] were the first to suggest a relationship between anesthesia and long-term cognitive delay. In this report, children were anesthetized with ketamine and halothane for removal of congenital nevocytic nevi, a fairly minor procedure. Nevertheless, the authors reported an increased incidence of cognitive impairment, described as regressive behavioral changes, lasting up to 18 months after the procedure. Again, children younger than 3 years of age were the most sensitive. These authors clearly voiced concern that general anesthetics may cause long-term cognitive effects.

Clinical investigations are still at an early stage, but the evidence that has emerged over the last few years consistently points to detrimental effects of anesthetic exposure in young children on subsequent behavioral and cognitive development.

In a population-based retrospective birth-cohort study of 5357 children, Wilder and associates[60] found that children who received two or more general anesthetics before the age of 4 years were at increased risk for learning disability as adolescents (Fig. 15-7). Moreover, the

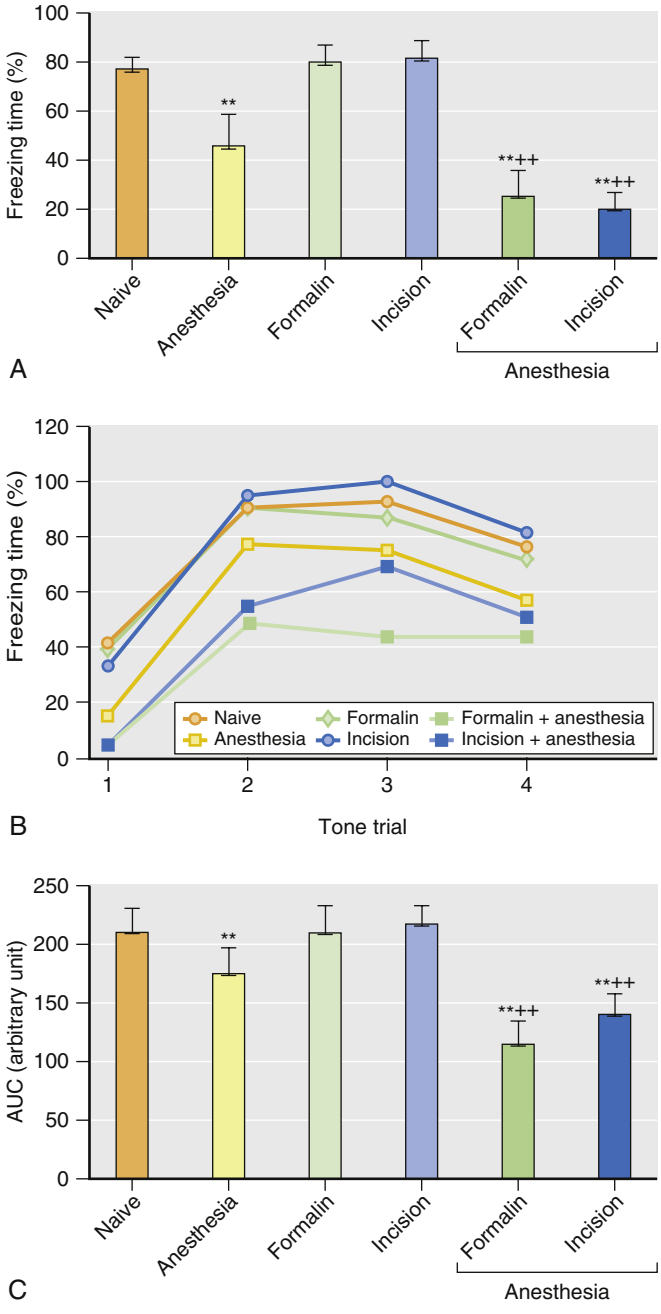


Figure 15-6. Cognitive function assessed with trace fear conditioning. To test the combined effect of noxious stimulation and anesthesia, P7 rats received 70% nitrous oxide plus 0.75% isoflurane with or without noxious stimulation (formalin paw injection or skin incision). At 40 days of age, the rats were tested with a fear-conditioning assay, in which longer freezing times reflect better memory. **A-C** show that the addition of noxious stimulation to the anesthetic at P7 actually further reduces cognitive performance as young adults. *(From Shu Y, Zhou Z, Wan Y, et al: Nociceptive stimuli enhance anesthetic-induced neuroapoptosis in the rat developing brain,* Neurobiol Dis *45:743-750, 2012.)*

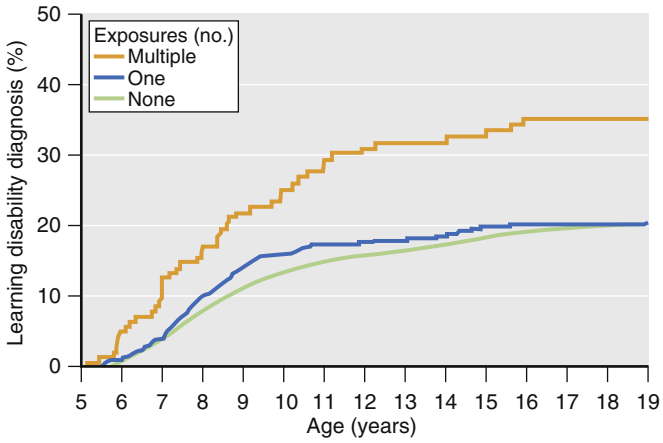


Figure 15-7. Learning disabilities in children having surgery before 4 years of age. Only multiple surgical procedures before age 4 had a significant effect on the cumulative incidence of learning disability. *(From Wilder RT, Flick RP, Sprung J, et al: Early exposure to anesthesia and learning disabilities in a population-based birth cohort,* Anesthesiology *2009;110:796-804.)*

risk increased with longer cumulative exposure duration (>2 hours). Of particular concern is their finding that the cohort exposed to anesthesia before 4 years of age had cognitive scores that were 2 standard deviations below predicted. This implies that early exposure to general anesthesia may have prevented achievement of full cognitive potential. In an even larger population study, Sun and co-workers[61] assessed learning disabilities in 228,961 individuals. Children who had procedures requiring anesthesia before 3 years of age required more Medicaid services for learning disability than did children not having these procedures. Kalkman and associates[62] also found more learning deficits in a similarly exposed but smaller population of children in the Netherlands. Procedures in premature infants have also been associated with an excess of behavioral disabilities later in life. For example, surgically treated premature infants with patent ductus arteriosus[63] or necrotizing enterocolitis[64] had worse neurologic outcomes than did premature infants who were treated medically.

A recent retrospective clinical study examined the association between procedures requiring general anesthesia before the age of 2 years and the occurrence of attention deficit/hyperactivity disorder (ADHD) up to the age of 19 years.[65] As found in the prior Wilder study,[60] only the cohort having two or more exposures before 2 years of age was associated with ADHD; the lack of association in single exposures was not explained by anesthetic type or comorbidities (Fig. 15-8).

Despite the limitations inherent in retrospective clinical studies, such as lack of randomization, unmatched controls, and numerous uncontrolled (and unknown) variables, this study points to yet another behavioral impairment that could be associated with early exposure to anesthesia. But association does not imply causality. A measure of caution is advisable because the effects of surgery or the illness requiring surgery cannot be clearly separated from the effects of anesthesia in retrospective clinical studies. However, the complex issues associated with the design of randomized, double-blinded prospective clinical studies of very young patients cannot be underestimated. These issues include, but are not limited to, ethical considerations; the lack of biomarkers of apoptosis that can be used safely in a living organism; the complexity and significance of various clinical outcomes, especially neurocognitive ones; and the lack of appropriate controls.

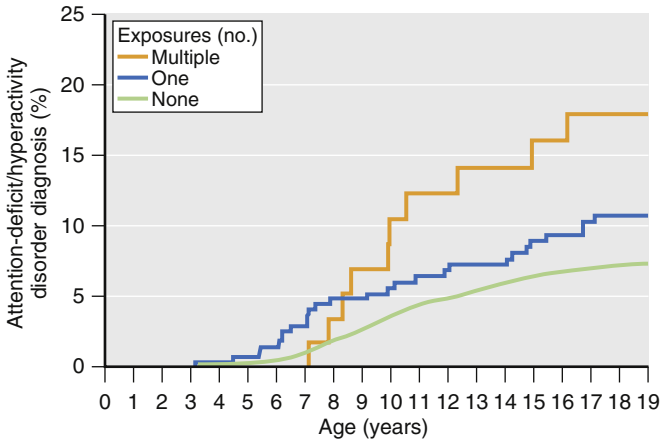


Figure 15-8. Attention-deficit/hyperactivity disorder (ADHD) in children having surgery before 2 years of age. Similar to the data on learning disability (see Fig. 15-7), the largest effect on ADHD incidence of prior surgery occurred in the cohort having multiple procedures before 2 years of age. *(From Sprung J, Flick RP, Katusic SK, et al: Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia,* Mayo Clin Proc *87:120-129, 2012.)*

PRACTICE GUIDELINES AND RECOMMENDATIONS

Although appreciation of anesthesia-induced developmental neurotoxicity is rapidly emerging, it is premature to draw definite conclusions regarding the human risk in anesthesia in the developing brain. However, if developmental events (e.g., synaptogenesis) present distinct vulnerabilities, the timing and duration of anesthesia exposure might be considered in the decision whether to operate. The most vulnerable age group is younger than 4 years, but whether a specific anesthetic technique, surgical procedure, comorbidity, or genotype presents additional vulnerability is unknown and requires further study. A reasonable recommendation is to avoid anesthesia until most of the synaptogenesis has been completed and/or to limit the duration of exposure to less than 2 hours whenever possible. Ultimately, however, general anesthesia cannot be avoided in cases in which life-threatening conditions make frequent surgical interventions and prolonged stays in ICUs a necessity.

NEUROTOXICITY IN THE ELDERLY

See also Chapter 80.

ANESTHETICS

While they are in the central nervous system (CNS), general anesthetics alter cognitive states. Depending on the drug and the duration and magnitude of exposure, the altered cognitive state can outlast the surgery itself for a considerable period, but rarely for more than a day or two. Thus, anesthetic drugs should be considered as candidates for more durable cognitive influences. Clinical studies of POCD, however, have not been able to find differences attributable to the anesthetic or the anesthetic approach, except for the initial International Study on Postoperative Cognitive Dysfunction, which detected anesthetic duration as a significant risk factor. Because anesthesia and surgery are inextricably linked in human studies, the possibility that the anesthetic per se is causing the cognitive deficits has been studied in cell culture and in animal models. Culley and associates first established a model of POCD in elderly rats after anesthesia alone by showing that isoflurane and N_2O exposure caused memory and learning deficits that lasted at least 3 weeks,[66] but not in younger rats.[67] A later study implicated isoflurane as the probable cause[68] rather than N_2O. This was confirmed by work in elderly mice in which Bianchi and colleagues[69] also provided evidence for an isoflurane-induced cognitive decline in a wild-type strain in the absence of surgery. Few studies have rigorously compared different

anesthetics, but desflurane may be less provocative than isoflurane and the injectable anesthetics, such as propofol, even less. In general, however, all of the preclinical investigations of anesthetic exposure alone have revealed only a modest and transient cognitive disturbance. This is consistent with the multitude of small human trials (see later discussion) that have not detected an association of POCD risk with any particular feature of anesthetic management. Yet, perhaps small vulnerable populations exist that have ongoing neuropathology and in which the anesthetic alone might have a deleterious effect.

Amyloid-β and Anesthesia

Strongly implicated in the pathogenesis of AD is amyloid-β, a small proteolytic fragment of a larger membrane protein (amyloid precursor protein [APP]) of synaptic origin but still unknown function. All known familial forms of AD involve mutations directly in the *APP* gene or its interactors, and the only mutation found to protect against AD is also in this gene.[70] Excessive amyloid-β accumulates extracellularly and, through poorly understood mechanisms, begins to form oligomers and ultimately plaques (Fig. 15-9). Currently, the amyloid plaques are considered to be a form of inert material that has been sequestered, and the smaller oligomers are capable of causing both direct neuronal toxicity and an inflammatory response by interacting with the brain's primary immune surveillance cell, the microglia. The smoldering neurotoxic and inflammatory insult gradually depletes both synapses and neurons, which at some point, cross a threshold after which cognitive consequences emerge. Most mouse models of AD involve alterations in the *APP* gene. For example, the Tg2576 model incorporates the human *APP* gene containing the "Swedish" mutation, which results in excessive proteolysis and release of the amyloid-β peptide. The mice develop an age-related decline in cognition and demonstrate amyloid-β plaque in similar areas of the brain, as seen in humans (subiculum, hippocampus, and cortex) (Fig. 15-10). Interestingly, exposure of elderly, symptomatic Tg2576 mice to anesthetics *did not* result in a further decline in their cognition.[69] The investigators attributed these counterintuitive results to a "floor-effect"; in other words, the mice were already so compromised that an incremental effect from the anesthetic was undetectable. In support of this notion, it is known that cognitive decline in humans, once detectable, proceeds along a relatively relentless trajectory that might not respond to perturbants in either direction[71] (Fig. 15-11). This may be the primary reason for the multitude of failed therapeutic trials in AD, because improvement in already symptomatic individuals has been the most common end point. Thus, cognitive measures alone might be relatively insensitive to these incremental effects, but biomarkers of the actual pathologic process have been more revealing.

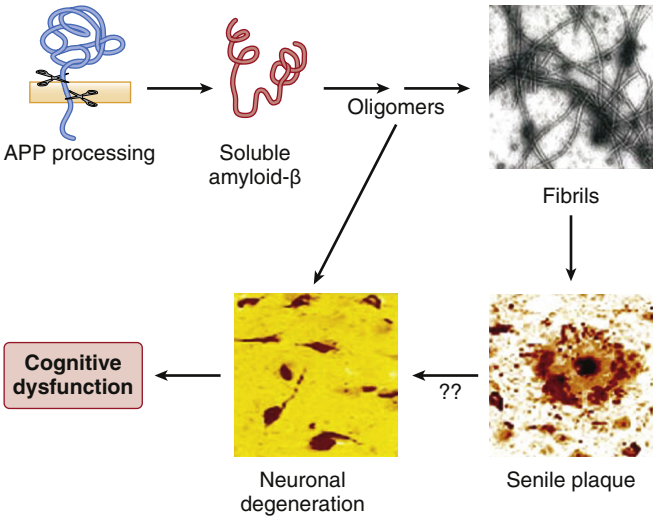


Figure 15-9. Amyloid-β cascade hypothesis. Amyloid precursor protein *(APP)* is cleaved by secretase and other enzymes to produce a variety of fragments, among which is soluble amyloid-β peptide. Once a critical but variable concentration threshold is reached, these monomers begin to aggregate into oligomers of 2 to 20 monomers. These oligomers, through poorly understood mechanisms cause direct cellular toxicity or inflammation, which ultimately leads to cell death and cognitive dysfunction. In addition to causing direct toxicity, these oligomers also reorganize into fibrils, which in turn attract other extracellular components to form the hallmark lesion of Alzheimer disease, the senile plaque. Whether these plaques actually contribute to neurodegeneration, or simply serve as a bystander marker of it, is not yet clear.

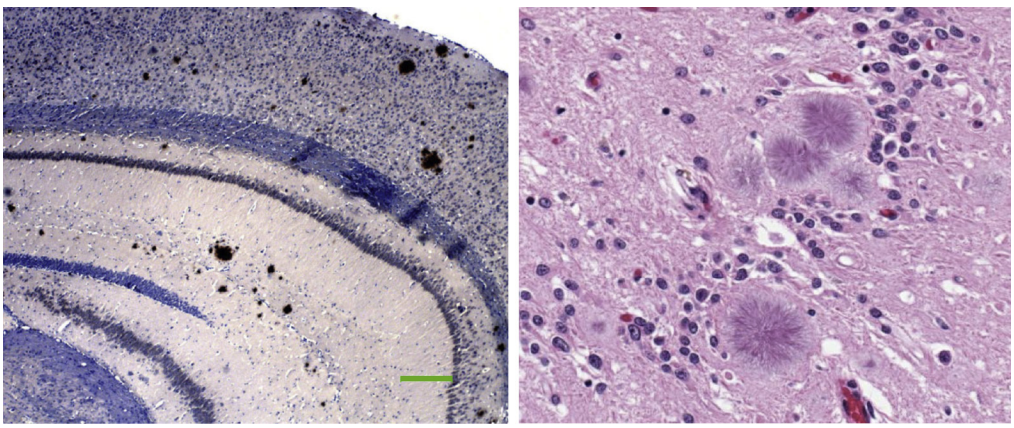


Figure 15-10. Brain amyloidopathy. Both sections show extracellular amyloid plaque. The left section (magnification 30×) is from an Alzheimer mouse model stained with an anti–amyloid antibody, and the right (magnification 150×) is from human brain stained with hematoxylin and eosin only.

Halothane exposure in the Tg2576 mouse caused significant increases in amyloid plaque, a hallmark biomarker of AD pathologic findings.[69] This was the first study to link anesthetic exposure to AD pathologic findings in vivo, and a host of other studies have now appeared. For example, in vitro and in cell culture, the inhaled anesthetics promote amyloid-β production[72] and aggregation[73] (see Fig. 15-9), events that accelerate the onset of AD.[74] If and how these provocative in vitro effects translate to humans is not known, but it is clear that other factors are necessary. For example, the equivalent anesthetic exposures in *young* transgenic mice failed to produce a change in amyloid burden and in fact produced an *improvement* in learning and memory.[75] Perhaps, then, multiple susceptibility factors may be necessary to transduce anesthetic exposure to a change in pathologic factors and cognition.

Tau and Anesthesia

The other hallmark lesion of dementia of the AD-type is the neurofibrillary tangle (NFT), composed largely of phosphorylated and aggregated (fibrillar) τ protein. The τ protein is microtubule associated and regulates microtubule stability and dynamics. When phosphorylated, it detaches from microtubules, and, if excessive, can stay unattached and form aggregates that eventually become fibrillar and cytotoxic (Fig. 15-12). This is in addition to leaving microtubules, essential for many cellular functions, destabilized and perhaps dysfunctional. Thus, small molecules that stabilize microtubules have been shown to improve pathogenesis and behavior in animals and are currently in clinical trials in patients. Anesthetics have not been directly implicated in the τ aggregation process as they have for amyloid-β, but features of the anesthetic *state* have been implicated in τ phosphorylation and detachment. For example, the enzymes responsible for dephosphorylating τ (phosphatases) are very temperature-sensitive, and thus even the temperature decline of 2° to 3°C that is common in modern anesthetic practice can increase populations of phospho-τ, at least transiently. The clinical implication of transient changes in τ populations is unclear, but it appears that populations also can be shifted on a more permanent basis by repeated exposures. Le Freche and colleagues[76] found that repeated sevoflurane exposures increased phospho-τ, whereas single exposures did not. Similarly, Tang and colleagues[75] found that multiple midlife isoflurane and halothane exposures also increased phospho-τ durably. In addition to the inhaled anesthetics, propofol may modulate τ populations.[77] The mechanistic basis for these less transient effects may be changes in the activity of the underlying kinases as opposed to phosphatases.[78] Thus, the second hallmark lesion of AD, tauopathy, is also influenced by general anesthetics or physiologic states that commonly accompany general anesthesia, providing

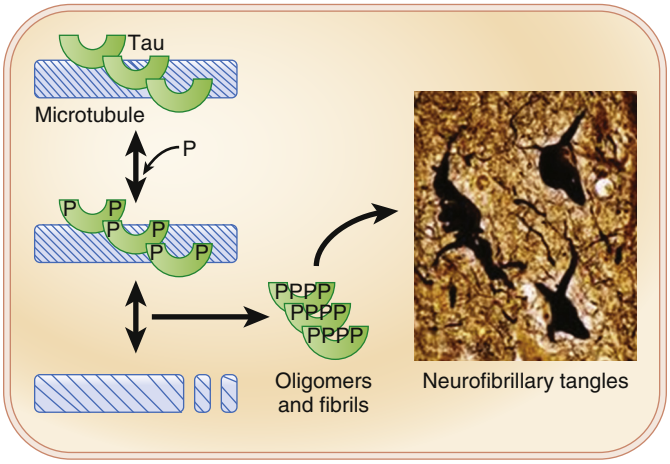


Figure 15-12. Tauopathy pathways. The τ protein is attached reversibly to microtubules, an interaction thought to stabilize the microtubule polymer. It has multiple phosphorylation sites, which modulate microtubule binding affinity. Hyperphosphorylation not only releases τ from microtubules but also facilitates τ aggregation into oligomers; fibrils; and ultimately, large intracellular deposits termed neurofibrillary tangles (NFTs). Depletion of functional τ is thought to leave microtubules destabilized. It is not clear whether cellular dysfunction associated with tauopathy is caused by a loss of function (microtubules) or gain of toxic function (NFTs). *P,* Phosphorylation site.

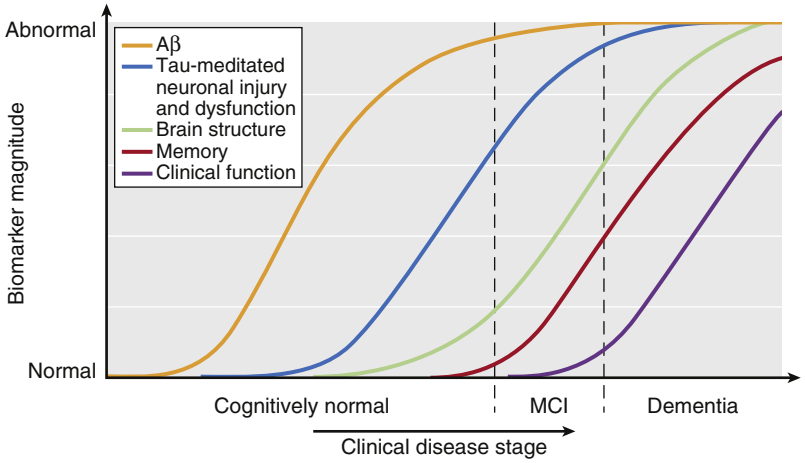


Figure 15-11. Correlation of pathologic processes and disease stage. This figure emphasizes that amyloidopathy, tauopathy, and structural loss are well advanced before the ability to detect significant cognitive consequences. In addition, it is not clear to what degree pathologic processes and degeneration are reversible once cognitive decline is detected. This recent understanding makes cognitive markers of neurodegeneration of questionable value in judging the effect of interventions, both positive and negative. *MCI,* Mild cognitive impairment.

additional rationale that an interaction between anesthesia and AD pathogenesis might underlie postoperative cognitive decline.

Calcium and Anesthesia

A third major mechanism thought to underlie dementia of the AD type is calcium dysregulation and is one mechanism that might be shared with neurotoxicity of the young (see earlier discussion). That anesthetics cause changes in calcium regulation is widely known, and this is likely to occur through interactions with several types of channels[79] (Fig. 15-13). Implicated in AD is one group of receptor channels that control calcium release from the endoplasmic reticulum, specifically the ryanodine and the IP_3 receptors. The neuronal endoplasmic reticulum is a normal cellular store of calcium that is released in a highly regulated fashion through these channels. It is now thought that mutations in either of these channels, or exposure to drugs that interact with either, may lead to an exaggerated release of calcium that could trigger apoptosis.[80] General volatile anesthetics such as halothane and isoflurane are known to trigger a syndrome termed malignant hyperpyrexia in susceptible individuals by actions on the muscle-type ryanodine receptor (see also Chapter 43); thus, it is feasible that similar but less dramatic effects may happen in the neuronal subtypes. Recent in vitro and cell culture work have also implicated the IP_3 receptor as a direct target for the general volatile anesthetics, which results in an excessive dumping of calcium into the cytosol.[81] In vivo, calcium dysregulation induced by anesthetics may require other susceptibility factors (phospho-τ, amyloid-β) that prime the $InsP_3R$ for excessive calcium release. Propofol appears to be much less provocative.

If endoplasmic reticulum calcium release contributes to AD pathogenesis or anesthetic-induced apoptosis, drugs that inhibit these channels may be useful not only during surgery but also as a delaying tactic for AD itself. Initial studies of this premise in animals using the ryanodine receptor inhibitor dantrolene are inconsistent, perhaps because of difficulty in getting this drug across the blood-brain barrier. Further work with this and related drugs seems warranted.

Mitochondria and Anesthesia

These small organelles are the powerhouses of cells, and their function is tightly integrated with most cellular functions. Not surprisingly, mitochondrial dysfunction has been implicated in aging, in AD,[82] and as a target for the general anesthetics. For example, anesthetics decrease activity of the respiratory chain,[83] influence K_{ATP} channels, and directly bind to a wide variety of mitochondrial proteins, including those responsible for initiating apoptosis.[84,85] Mitochondrial mechanisms for initiating apoptosis are covered in the earlier discussion on developmental neurotoxicity, so discussion will not be repeated here, because the underlying mechanisms are likely to be similar.

Neuroinflammation and Anesthesia

That inflammation contributes to cognitive decline is well known. This may be transduced through the release of peripheral proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor–α (TNF-α), or through vagal afferents. That inflammatory pathways contribute to the dementing diseases such as AD was first recognized by the robust protection afforded by years of nonsteroidal antiinflammatory drug (NSAID) use by patients with arthritis.[86] The literature on inflammation in dementia, especially in AD, has subsequently increased. Inflammatory cascades clearly play at least a

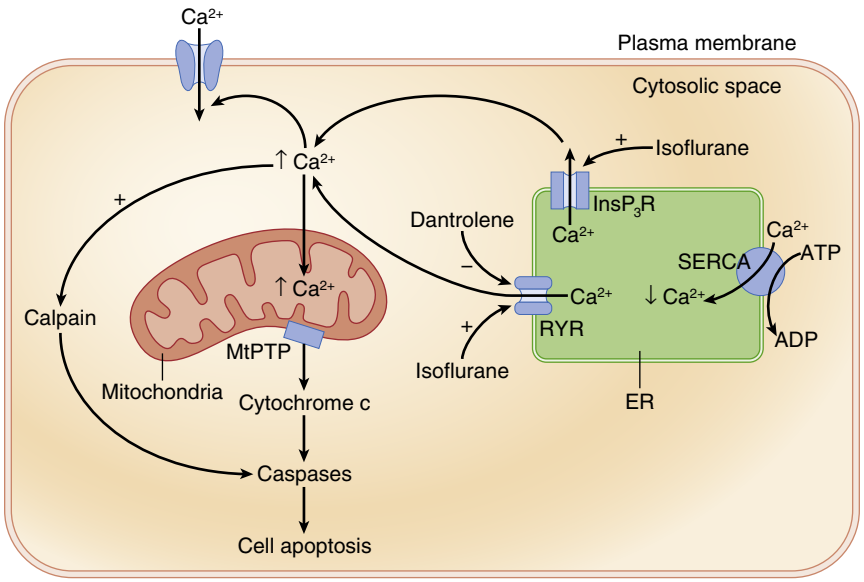


Figure 15-13. Cellular calcium dynamics. In this much simplified scheme, anesthetics (isoflurane shown) activate both the $InsP_3R$ and RyR calcium release channels on the endoplasmic reticulum (ER), elevating cytosolic calcium level. This initiates several processes. First, it activates calcium channels on the plasma membrane to allow further calcium entry. Second, it activates proteases (e.g., calpain) to activate caspase enzymes that initiate cell apoptosis. Third, excess cytosolic calcium is buffered by mitochondrial uptake, although when excessive the mitochondrial permeability transition pore (MtPTP) is activated. The MtPTP then releases cytochrome C, causing further activation of caspase activity and amplifying apoptosis. A role for dantrolene mitigation is suggested via its known actions on the ER RyR.

modulatory role; microglia are activated by amyloid-β, proinflammatory cytokines are up-regulated, and peripheral monocytes are recruited.[87] Although the role for neuroinflammation is clear, prospective trials of NSAIDs have not duplicated these results, perhaps because of timing. Perioperative management frequently includes drugs capable of modulating inflammatory cascades (e.g., lidocaine, dexamethasone, ketorolac), but whether this is being done by anesthetics is not clear. Inhaled anesthetics such as isoflurane and sevoflurane are not likely antiinflammatory, but literature in favor of propofol being antiinflammatory has increased. Certainly, propofol is a radical scavenger, but whether this is responsible for any salutary effects is not yet clear. Studies examining POCD have not yet exonerated propofol.

Summary

The durable effects of anesthetics alone on cognition and on the pathologic factors that underlie some of the known cognitive disorders such as AD suggests an unfavorable contribution, the magnitude of which is not clear. In general, however, it appears from anesthetic-only studies, especially those that examined long-term effects, that anesthetics produce few to no cognitive effects and only small and often reversible pathologic effects.

SURGERY

Animal Studies

Anesthesia is indicated for the ablation of consciousness and pain during surgery, endoscopy, and percutaneous catheter procedures and is rarely used by itself. Given that many of these procedures elicit inflammation, they may contribute to cognitive problems, especially in vulnerable populations. That surgery itself can contribute to short-term cognitive loss was first shown in mice exposed to either an injectable anesthetic alone or combined with an orthopedic operation.[88,89] Substantial cognitive decline was detected, but only in the surgery group. Further, they were able to attribute this to neuroinflammation provoked by the peripheral inflammatory response, most notably the cytokine TNF-α.[90] However, the surgery-induced cognitive effects were, like the anesthetic effects mentioned earlier, fully reversible in less than a week. Moreover, these animals were healthy and young, a group at infrequent risk for cognitive complications and hardly representative of most of our patients. The question of whether the cognitive consequences of surgery are more pronounced in vulnerable populations has been recently tested in a somewhat different transgenic model of AD, but it is still one that acquires an AD phenotype and pathologic findings at 10 to 12 months of age. In this case, desflurane anesthesia alone produced only a transient cognitive consequence whereas the addition of surgery caused a much larger decrement that lasted—essentially unchanged—for at least 3 months.[91] Again, the evidence supported that surgery-induced peripheral inflammation provoked a neuroinflammatory response that interacted with the AD pathologic factors to produce an irreversible acceleration in damage (Fig. 15-14). Such a mechanism may explain why everyone does not suffer cognitive decline after surgery. First, patients arrive for surgery with vastly different vulnerabilities, most of which are unknown. Second, the inflammatory response to an intervention such as surgery is known to be enormously variable. Understanding both of these features may, in the future, allow us to predict and prevent cognitive decline.

Patient Studies

As mentioned earlier, patient studies invariably combine both anesthesia and surgery, but serve as the ultimate test of whether the notions described dictate a change in perioperative management. With respect to long-term cognitive problems, several small retrospective studies addressed the question of whether anesthesia and surgery alter the incidence, age of onset, or trajectory of AD. In one study of approximately 250 subjects, the authors found that anesthesia and surgery significantly reduced the age of diagnosis but that the overall odds ratio for an ultimate diagnosis of AD of 1.5 was not statistically significant.[92] A similar pattern was seen in two other studies, suggesting that perhaps the negative results were the result of a lack of power.[93,94] In an examination of cardiac surgery patients, two studies had conflicting results. One compared coronary artery bypass graft (CABG) surgery under general anesthesia with percutaneous transluminal coronary angioplasty under sedation and found a significantly higher rate of AD in the CABG group.[94] Looking at this question somewhat differently, Knopman and colleagues[95] found that the rate of having had CABG surgery was no more frequent in patients

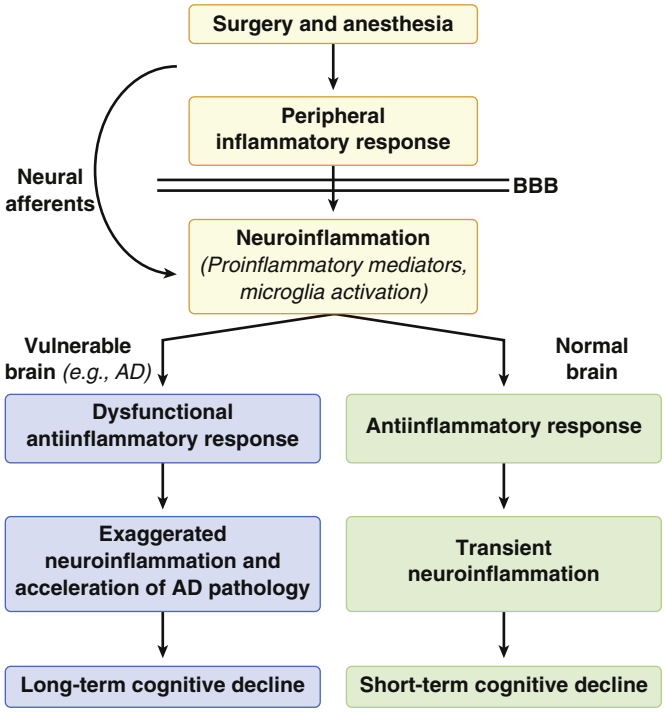


Figure 15-14. The "vulnerable" brain. Because cognitive dysfunction does not occur in everyone, we propose in this model that the combination of surgery-induced neuroinflammation and a preexisting dysfunctional immune response resulting from ongoing neuropathology (such as aging or Alzheimer disease [AD]) conspire to produce exaggerated neuroinflammation (analogous to autoimmunity) and a persistent cognitive consequence. *BBB,* Blood-brain barrier; *FDG,* fluorodeoxyglucose; *PIB,* Pittsburg compound B.

TABLE 15-1 CEREBROSPINAL FLUID BIOMARKERS OF NEURODEGENERATION

				T-τ	*P*-τ
ADNI Cohort	$A\beta_{42}$ Mean (SD)	*T*-τ Mean (SD)	*P*-τ Mean (SD)	$A\beta_{42}$ Mean (SD)	$A\beta_{42}$ Mean (SD)
AD	143	122	42	0.9	0.3
N = 102	(41)	(58)	(20)	(0.5)	(0.2)
MCI	164	103	35	0.8	0.3
N =200	(55)	(61)	(18)	(0.6)	(0.2)
Normal	206	70	25	0.4	0.1
N = 114	(55)	(30)	(15)	(0.3)	(0.1)

From Shaw LM, Vanderstichele H, Knapik-Czajka M, et al: Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann Neurol* 65:403-413, 2009.

Through the Alzheimer Disease NeuroImaging (ADNI) study (Shaw and colleagues), it has been found that levels of both amyloid-$\beta_{(1-42)}$ and τ (both phosphorylated and total) are associated with progressive cognitive decline characteristic of AD. These biomarkers, especially the ratio of τ to amyloid-β, are now being used to both establish a diagnosis of AD and to stratify patients for interventional trials.

AD, Alzheimer disease; *MCI,* mild cognitive impairment; *SD,* standard deviation.

with already diagnosed AD than in age-matched controls. More recently, a meta-analysis of 15 case-control studies was conducted, concluding that an association between prior anesthesia and surgery and the risk for AD could not be detected.[96] These authors also concluded "there are few high quality studies in this area" and "Prospective cohort studies with long-term follow-up or randomized controlled trials are required to further understand the association between general anesthesia and Alzheimer's disease."

Investigators have begun to leverage the work taking place in Alzheimer disease centers across the world to study the impact of surgery and anesthesia, despite the fact that few of these centers have been systematically collecting data on surgery or anesthesia. In these centers, elderly patients with and without cognitive symptoms are recruited and studied extensively with a variety of tests, including cognition, imaging, and biomarker assays. They are then followed longitudinally for many years to seek associations between cognitive decline and the various biomarkers. In a recently published study, the patients from the centers were retrospectively examined for associations between their cognitive trajectory and the occurrence of either a surgical procedure or a serious illness (requiring hospitalization). The small number of surgical procedures in these patients limited power, but the authors were able to conclude an absence of any relationship between cognitive trajectory and either surgery or serious illness.[97] In a similar but larger study that examined primarily hospitalization for serious illness, a significant association with subsequent cognitive trajectory was detected.[98] In a subsequent study again using patients from Alzheimer disease centers, surgery and anesthesia were associated with cognitive decline approximately 6 months later in contrast to a control group of matched patients. Most interestingly, larger losses of hippocampal and cortical gray matter volume were detected in the surgical group, suggesting a brain structural correlate to the cognitive defect. This work is one of the first to use biomarkers in establishing an effect of surgery and anesthesia on the brain.

Biomarkers

Especially in disorders with a very long presymptomatic phase, biomarkers are important to understand the linkage between interventions and outcomes. Neurodegeneration begins decades before the first memory complaints, and yet it is likely that this presymptomatic phase is a period of vulnerability, both to therapy and to acceleration by interventions such as surgery. Thus, biomarkers can have a two-pronged benefit. First, to establish this vulnerability preoperatively to tailor perioperative management (when we know how) and, second, to understand the impact of perioperative management on the trajectory of the pathology. In addition to the retrospective imaging study mentioned previously, several perioperative cerebrospinal fluid (CSF) biomarker studies have begun to appear. Specific CSF biomarkers are currently a cornerstone of AD diagnosis. These are amyloid-β_{42}, total τ, and phosphorylated τ (Table 15-1). In AD, the CSF amyloid-β_{42} is low and both forms of τ are high. The ratio of total τ to amyloid-β_{42} is a very sensitive and specific predictor of AD. In a study of patients who have undergone CABG, Palotas and coworkers[99] found only small changes in the early postoperative period but significant and striking changes in an AD-like direction at 6 months postoperatively. In another study, CSF assayed before and at 24 hours after CABG surgery revealed large increases in proinflammatory cytokines but only small changes in amyloid-β_{42} (99). In the authors' work, CSF proinflammatory cytokines and total and phospho-τ were significantly elevated in patients 24 to 48 hours after endoscopic nasal surgery, with no change in amyloid-β_{42}.[100] Although one of these studies suggested that total intravenous anesthesia evoked a smaller CSF IL-6 response than sevoflurane,[100] rigorous, prospective comparisons of perioperative management on CSF biomarker outcomes have not yet been reported. The unique skills and opportunity that the anesthesiologist has with respect to lumbar puncture should greatly facilitate generation of the necessary data.

Other biomarker modalities that might reflect perioperative neurotoxicity include plasma (e.g., S100β) and imaging. Plasma biomarkers of neuronal injury are in their infancy and not yet rigorously validated,[101] but significant advances in imaging have occurred. In particular, positron emission tomography (PET) imaging for either glucose usage or one of the characteristic lesions of AD, the amyloid plaque, has dramatically enhanced the ability to diagnose AD, stratify patients for therapeutic trials, and follow the course of disease after interventions[102,103] (Fig. 15-15). No perioperative

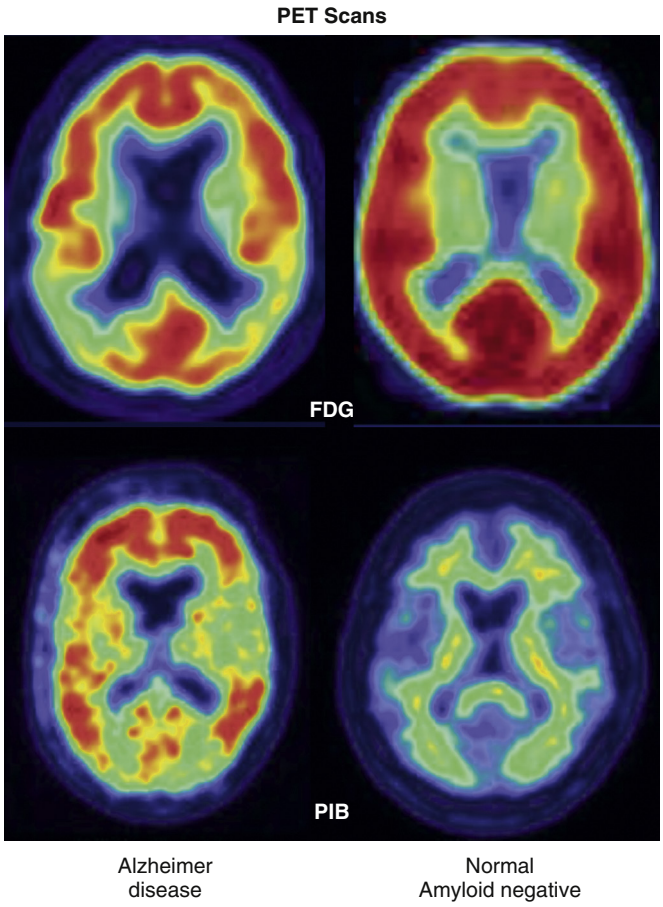


Figure 15-15. Positron emission tomography (PET) imaging. This form of "biomarker" has proved useful for evaluating brain vulnerability. Fluorodeoxyglucose (FDG) imaging reports brain areas undergoing active glucose uptake and usage. Thus, the Alzheimer brain (*left*) shows a much lower global signal than the normal brain (*right*), presumably as a result of both neuron loss and neuronal dysfunction. The Pittsburgh compound B (PIB) is a small carbon-13–containing radioligand with high affinity for fibrillar amyloid deposits (mostly plaque); thus, the signal is much higher in the Alzheimer brain than in the normal brain. These imaging biomarkers hold promise for determining vulnerability and the response to therapy (or surgery). *AD-BSL,* Alzheimer disease—baseline; *CI,* confidence interval; *MCI-BSL,* mild cognitive impairment—baseline; *NL-BSL,* normal—baseline.

studies using PET imaging have appeared, and this represents an opportunity for perioperative practitioners. Similarly, magnetic resonance imaging (MRI), either functional or structural, is being increasingly used to document neurodegenerative changes.[104,105] The functional MRI (e.g., blood-O_2 level–dependent [BOLD], or arterial spin labeling [ASL]) is thought to reflect early events in neurodegenerative diseases, whereas the structural imaging would reflect very late events, such as neuronal and glial depletion. Only a single study has retrospectively examined structural MRI in patients after surgery.[106] These investigators found a small but significant decline in hippocampal and cortical gray matter volume an average of 6 months after surgery in contrast to a matched control group that did not have surgery (Fig. 15-16).

A final "biomarker" used to establish vulnerability is genetic testing. Specific genetic mutations (e.g., *APPswe, PS1,* trisomy-21) that lead to very-high-penetrance "familial" neurodegeneration are rare and are responsible for a small minority of disease, but no information on optimal perioperative management of these patients is available. Two susceptibility genes for late-onset, or sporadic, AD have been identified: *TOMM40* and *apoEε4*.[107] Similarly, whether perioperative management should be altered when faced with these patients (some patients are acquiring their own genetic data from private companies) is not known. Until such time that this information is available, the cost of routine genetic testing cannot be justified, unless these patients are enrolled in studies.

SUMMARY OF ADULT NEUROTOXICITY

In contrast to the case in the neonate, general anesthetics may be neurotoxic in the adult or elderly brain at conventional clinical concentrations. On the other hand, the potential impact of surgery itself, via inflammatory pathways, is more compelling and supported by both preclinical and clinical data. The neuropathologic and behavioral outcome of surgery in the elderly is likely to be strongly modulated by many patient vulnerability factors, in addition to perioperative management decisions.

PRACTICE GUIDELINES AND RECOMMENDATIONS

As stated at the outset, few evidence-based changes in practice can be recommended except for the most obvious—not to have surgery. This will require, of course, careful balancing of the risks for cognitive decline against the risk for not receiving needed surgery. In most cases, the latter risk would be higher; thus, elements of perioperative management contributing to cognitive decline need to be identified and managed. The evidence at this point implicates inflammatory pathways and also suggests that anesthetic choice matters. Nothing has been confirmed in prospective clinical trials that strongly emphasizes this need. Finally, reliable biomarkers are needed to stratify patients and follow the effects of interventions.

SUMMARY AND CONCLUSIONS

The complexity of our patients and their disorders combined with the complexity and perceived chaos of the perioperative period make it extremely difficult to prove what feature, if any, of the perioperative period is responsible for long-term cognitive decline in the young or in the old. However, significant progress in the laboratory has made a compelling case that anesthesia and surgery may indeed be the cause of durable cognitive problems—at both extremes of age. These preclinical studies have allowed more focused clinical studies, many of which are under way. It is too early to make recommendations for detailed changes in perioperative management, but it is not too early to call for more investigation into the causes and prevention of perioperative neurotoxicity.

Complete references available online at expertconsult.com

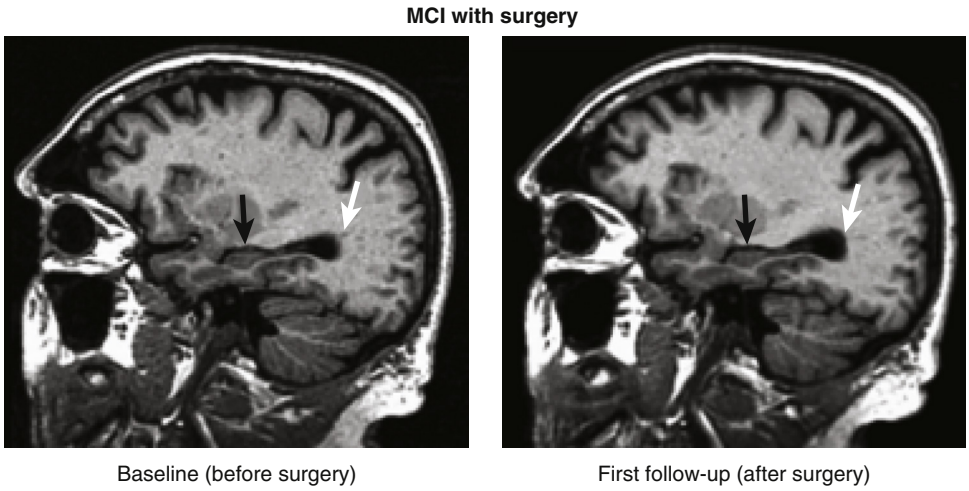


Figure 15-16. Magnetic resonance imaging. Similar to positron emission tomography, this imaging biomarker has helped establish a link between prior surgery and structural defects in the brain. These data from reference 106 show gray matter loss in both the hippocampus and cortex in a cohort of patients that underwent surgery in contrast to age-matched controls. Shown in the bar graph for comparison are the gray matter changes that occur in patients with mild cognitive impairment and with Alzheimer disease. *Black arrow,* hippocampus; *white arrow,* lateral ventricle. *AD-BSL,* Alzheimer disease—baseline; *MCI-BSL,* mild cognitive impairment—baseline; *NL-BSL,* normal—baseline.

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Chapter 16

The Autonomic Nervous System

DAVID B. GLICK

Key Points

- The autonomic nervous system works in concert with renin, cortisone, and other hormones to respond to internal and external stresses.
- The hallmark of the sympathetic nervous system is amplification; the hallmark of the parasympathetic nervous system is a limited targeted response.
- Inhaled and intravenous anesthetics can alter hemodynamics by influencing autonomic function.
- β-Adrenergic blockade has emerged as important prophylaxis for ischemia and as therapy for hypertension, myocardial infarction, and congestive heart failure.
- The sympathetic nervous system demonstrates acute and chronic adaptation to stress presynaptically and postsynaptically (e.g., biosynthesis, receptor regulation).
- Presynaptic α receptors play an important role in regulating sympathetic release.
- Many therapies for the treatment of hypertension are based on direct or indirect effects on sympathetic function.
- The vagus nerve is the superhighway of parasympathetic function; it accommodates 75% of parasympathetic traffic.
- Aging and many disease states (e.g., diabetes, spinal cord injury) are accompanied by important changes in autonomic function.

The autonomic nervous system (ANS) controls involuntary activities of the body outside consciousness. It is at once the most primitive and among the most essential of control systems—primitive in that its characteristics are largely preserved across all mammalian species and essential in that it oversees responses to immediate life-threatening challenges and the body's vital maintenance needs (including cardiovascular, gastrointestinal, and thermal homeostasis). The ANS is divided into two subsystems, the sympathetic nervous system and the parasympathetic nervous system. A third subsystem, the enteric nervous system, has been added to the original characterization of the ANS. Activation of the sympathetic nervous system elicits what is traditionally called the fight-or-flight response, typically including redistribution of blood flow from the viscera to skeletal muscle, increased cardiac function, sweating, and pupillary dilation. The parasympathetic system governs activities of the body more closely associated with maintenance needs, such as digestive and genitourinary function. A major goal of administration of anesthetics is maintaining optimum homeostasis in patients despite powerful challenges to the contrary. Safe administration of anesthetic care to patients requires knowledge of ANS pharmacology to achieve desirable interactions of anesthetics with the involuntary control system and to avoid responses or interactions that produce deleterious effects. Furthermore, disease states may impair ANS function and thereby alter the expected responses to surgery and anesthesia. In addition, the human stress response may be harmful. Modification or ablation of the stress response may actually improve perioperative outcome.

HISTORY AND DEFINITIONS

Initially, nerves were thought to be connected in a giant syncytium. Claude Bernard, a student of Magendie, postulated the theory of transmission by synapses through the release of chemical mediators. Later, Sherrington initiated a systematic study of reflexes and described some characteristics of reflex function. A chemist, J.J. Abel, first synthesized epinephrine in 1899, and his student Langley demonstrated that it caused effects similar to those produced by stimulating postganglionic sympathetic neurons. Furthermore, Langley found that when the nerve was cut and epinephrine was injected, a more profound effect was produced, thus demonstrating denervation supersensitivity. From these observations, the concept of chemical transmission in the ANS developed. Sir Henry Dale isolated choline and subsequently studied acetylcholine in animals, in which he demonstrated that acetylcholine causes vasodilation and hypotension.

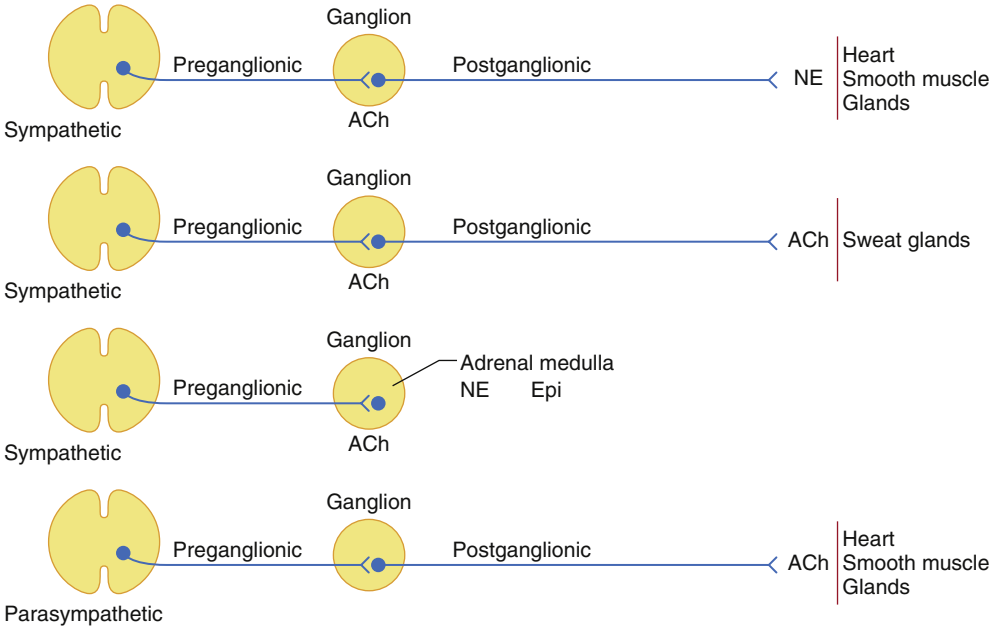


Figure 16-1. Autonomic nervous system neurotransmission. *ACh,* Acetylcholine; *Epi,* epinephrine; *NE,* norepinephrine.

Nerves that operate by acetylcholine are called *cholinergic*, whereas those using norepinephrine are called *adrenergic*. In addition to classifying nerves, the term cholinergic refers to other structures or functions that relate in some way to acetylcholine. For instance, cholinergic receptors (i.e., cholinoceptors) are proteins in cell membranes that interact with acetylcholine and cause the cell to respond in a characteristic way (e.g., muscles contract, glands secrete). Cholinergic agonists are drugs that act like acetylcholine on cholinoceptors to cause the cell to react in its characteristic way. They are sometimes referred to as cholinomimetic drugs. Cholinergic antagonists are drugs that react with cholinoceptors to block access by acetylcholine and thereby prevent its action. These drugs may also be referred to as cholinolytic, cholinergic-blocking, or anticholinergic drugs.

Because muscarine, a chemical isolated from a mushroom, causes effects similar to those produced by activation of the parasympathetic nervous system, it was thought to be the endogenous parasympathetic transmitter. Thus, drugs that mimic the effects of muscarine on parasympathetically innervated structures, including the heart, smooth muscles, and glands, have been called *muscarinic* drugs.

In the early 1900s, nicotine was found to interact with ganglionic and skeletal muscle synapses and on nerve membranes and sensory endings. Accordingly, drugs that act on these parts of the cholinergic system are called *nicotinic* drugs. Nicotinic drugs that are more specific in their action have been discovered and are referred to by the name of the system that they affect, such as ganglionic drugs, neuromuscular drugs, and drugs affecting nicotinic transmission with the central nervous system (CNS). For the purposes of this chapter, cholinergic nerves include the following (Fig. 16-1):

1. All the motor nerves that innervate skeletal muscle
2. All postganglionic parasympathetic neurons
3. All preganglionic parasympathetic and sympathetic neurons
4. Some postganglionic sympathetic neurons, such as those that innervate the sweat glands and certain blood vessels
5. Preganglionic sympathetic neurons that arise from the greater splanchnic nerve and innervate the adrenal medulla
6. Central cholinergic neurons

Drugs mimicking the action of norepinephrine are referred to as *sympathomimetic*, whereas drugs inhibiting the effects of norepinephrine are called *sympatholytic*. Adrenergic nerves release norepinephrine at the neuroeffector junction, whereas epinephrine and norepinephrine are released by the adrenal medulla.

Adrenergic receptors have been identified and subdivided into α and β receptors and further subdivided into α_1, α_2, β_1, β_2, and other types. α_2-Adrenergic receptors are primarily located on the presynaptic membrane and modulate release of norepinephrine, whereas postsynaptic α_1-adrenergic receptors mediate smooth muscle vasoconstriction (Fig. 16-2). β_1-Adrenergic receptors are found primarily on cardiac tissue, and β_2-adrenergic receptors mediate smooth muscle relaxation in some organs. Adrenergic neurons include the following (see Fig. 16-1):

1. Postganglionic sympathetic neurons
2. Some interneurons
3. Certain central neurons

FUNCTIONAL ANATOMY

Each branch of the ANS exhibits a different anatomic motif that is recapitulated on a cellular and molecular level. The underlying theme of the sympathetic nervous system is an amplification response, whereas that of the parasympathetic nervous system is a discrete and narrowly targeted response. The enteric nervous system is arranged nontopographically and relies on the mechanism of chemical coding to differentiate among nerves serving different functions.

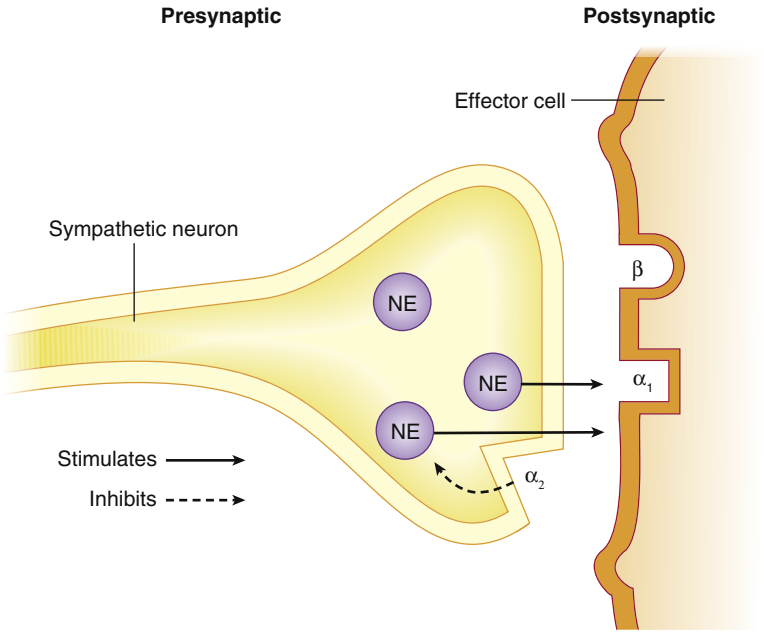


Figure 16-2. Preganglionic and postganglionic α receptors of the sympathetic nervous system. α_1 Receptors and β receptors are located postsynaptically on the membrane of the effector cell, whereas α_2 receptors are located presynaptically on the cell membrane of the sympathetic nerve innervating the effector cell. *NE,* Norepinephrine.

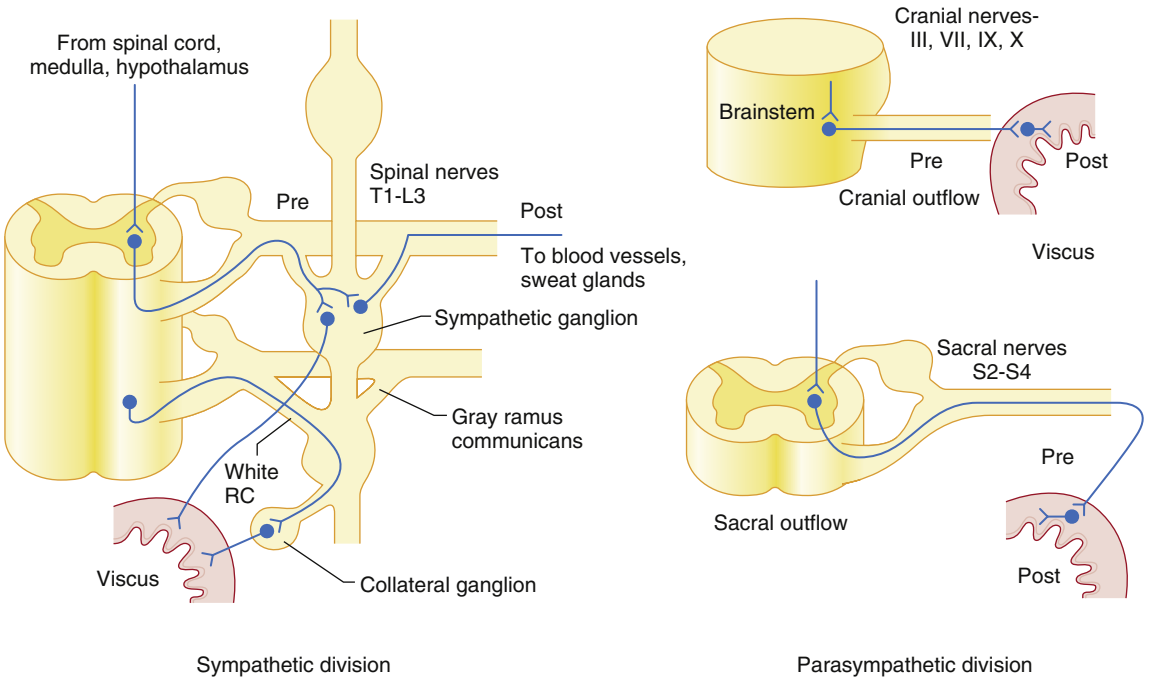


Figure 16-3. Autonomic nervous system. *Pre,* Preganglionic neuron; *Post,* postganglionic neuron; *RC,* ramus communicans. *(From Ganong W: The autonomic nervous system. In Ganong W, editor:* Review of medical physiology, *ed 15. Norwalk, Conn, 1991, Appleton & Lange, p 210.)*

SYMPATHETIC NERVOUS SYSTEM

The sympathetic nervous system originates from the spinal cord in the thoracolumbar region, from the first thoracic through the second or third lumbar segment. The preganglionic sympathetic neurons have cell bodies within the horns of the spinal gray matter (i.e., the intermediolateral columns). Nerve fibers from these cell bodies extend to three types of ganglia grouped as paired sympathetic chains, various unpaired distal plexuses, or terminal or collateral ganglia near the target organ.

The 22 paired ganglia lie along either side of the vertebral column. Nerve trunks connect these ganglia to each other, and gray rami communicantes connect the ganglia to the spinal nerves. The preganglionic fibers leave the spinal cord in the anterior nerve roots, join the spinal nerve trunks, and enter the ganglia at their respective level through the white (myelinated) ramus. Leaving the ganglion, postsynaptic fibers reenter the spinal nerve through the gray (unmyelinated) ramus and then innervate the pilomotor and sudomotor (sweat gland) effectors and blood vessels of the skeletal muscle and skin (Fig. 16-3). Sympathetic postganglionic fibers innervate the trunk and limbs through the spinal nerves.

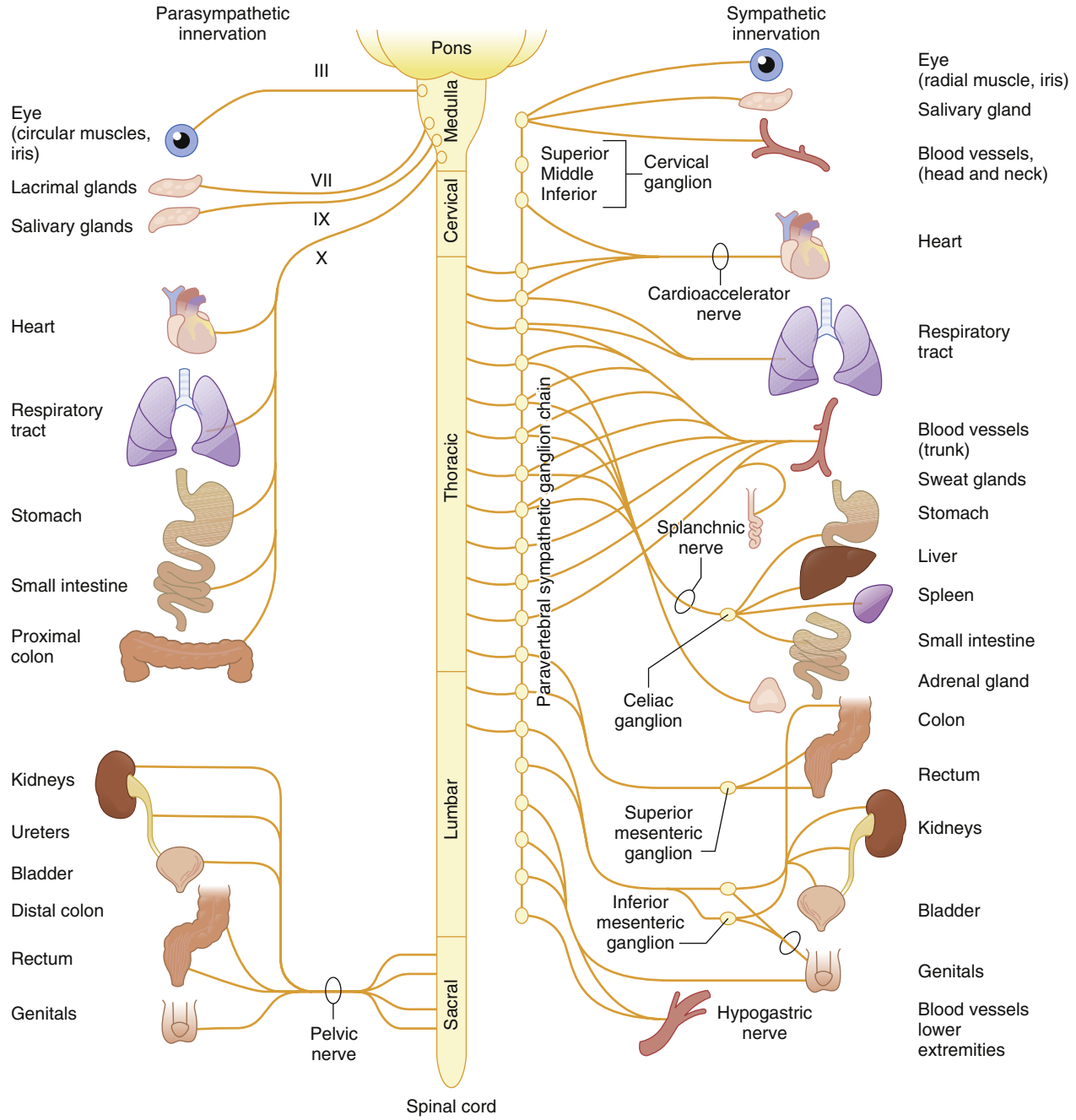


Figure 16-4. Schema of the autonomic nervous system depicting the functional innervation of peripheral effector organs and the anatomic origin of peripheral autonomic nerves from the spinal cord. The Roman numerals on nerves originating in the tectal region of the brainstem refer to the cranial nerves that provide parasympathetic outflow to the effector organs of the head, neck, and trunk. *(From Bylund, DB: Introduction to the autonomic nervous system. In Wecker L, Crespo L, Dunaway G, et al, editors:* Brody's human pharmacology: molecular to clinical, *ed 5. Philadelphia, 2010, Mosby, p 95.)*

The sympathetic distribution to the head and neck that enables and mediates vasomotor, pupillodilator, secretory, and pilomotor function comes from the three ganglia of the cervical sympathetic chain. Preganglionic fibers of these cervical structures originate in the upper thoracic segments. In 80% of people, the stellate ganglion is formed by fusion of the inferior cervical ganglion with the first thoracic ganglion on each side.

The unpaired prevertebral ganglia reside in the abdomen and pelvis anterior to the vertebral column and are the celiac, superior mesenteric, aorticorenal, and inferior mesenteric ganglia. Postganglionic fibers arising from synaptic links of the upper thoracic sympathetic fibers in the paravertebral ganglia form the terminal cardiac, esophageal, and pulmonary plexuses. The postganglionic fibers from the celiac, superior, and inferior mesenteric plexuses innervate the viscera of the abdomen and pelvis (Fig. 16-4).

Ganglia of the third type, the terminal or collateral ganglia, are small, few in number, and near their target

organs (e.g., the adrenal medulla). The adrenal medulla and other chromaffin tissues are homologous to the sympathetic ganglia, and all are derived embryonically from neural crest cells. Unlike sympathetic postganglionic fibers, however, the adrenal medulla releases epinephrine and norepinephrine.

Sympathetic preganglionic fibers are relatively short because sympathetic ganglia are generally close to the CNS, but they are distant from the effector organs; therefore, postganglionic fibers run a long course before innervating effector organs. Preganglionic sympathetic fibers may pass through multiple ganglia before synapsing, and their terminal fibers may contact large numbers of postganglionic neurons. Thus, preganglionic sympathetic fibers not only synapse at the ganglion of the level of their origin in the spinal cord but also can course up and down the paired ganglia. Because sympathetic response is not confined to the segment from which the stimulus originates, an amplified, diffuse discharge is allowed.

PARASYMPATHETIC NERVOUS SYSTEM

The parasympathetic nervous system arises from cranial nerves III, VII, IX, and X, as well as from sacral segments. Unlike in the sympathetic nervous system, ganglia of the parasympathetic nervous system are in close proximity to or within the innervated organ. This location of ganglia makes the parasympathetic nervous system more targeted and less robust than the sympathetic nervous system.

Preganglionic fibers of the parasympathetic nervous system originate in three areas of the CNS: the midbrain, the medulla oblongata, and the sacral part of the spinal cord. Fibers arising in the Edinger-Westphal nucleus of the oculomotor nerve course in the midbrain to synapse in the ciliary ganglion. This pathway innervates the smooth muscle of the iris and the ciliary muscle. In the medulla oblongata lie parasympathetic components of the facial (lacrimatory nucleus), glossopharyngeal, and vagus (dorsal nucleus) nerves. The facial nerve gives off parasympathetic fibers to the chorda tympani, which subsequently synapses in ganglia of the submaxillary or sublingual glands, and to the greater superficial petrosal nerve, which synapses in the sphenopalatine ganglion. The glossopharyngeal nerve synapses in the otic ganglion. The postganglionic fibers innervate the mucous, salivary, and lacrimal glands; they also carry vasodilator fibers.

The vagus is the most important of the parasympathetic nerves and transmits fully 75% of the traffic of the parasympathetic nervous system. It supplies the heart, tracheobronchial tree, liver, spleen, kidney, and entire gastrointestinal tract except for the distal part of the colon. The preganglionic fibers of the vagus are long, whereas the postganglionic fibers are short. Most vagal fibers do not synapse until they arrive at small ganglia on and about the thoracic and abdominal viscera. Although the parasympathetic nerves may synapse with a 1:1 ratio of nerve to effector cell, the vagal innervation of the Auerbach plexus may connect 1 nerve fiber to 8000 cells.

The second through fourth sacral segments contribute the nervi erigentes, or the pelvic splanchnic nerves. They synapse in terminal ganglia associated with the rectum and genitourinary organs.

ENTERIC NERVOUS SYSTEM

Given the importance of clinical phenomena such as nausea, vomiting, and alterations in bowel function associated with anesthesia, the third branch of the ANS is not well understood. The enteric nervous system is the network of neurons and their supporting cells found within the walls of the gastrointestinal tract, including neurons within the pancreas and gallbladder. It is derived from neuroblasts of the neural crest that migrate to the gastrointestinal tract along the vagus nerve. Notably, the enteric nervous system contains as many nerve cells as the spinal cord.

One major difference between the enteric nervous system and the sympathetic and parasympathetic branches of the ANS is its extraordinary degree of local autonomy. Digestion and peristalsis occur even after spinal cord transection or during spinal anesthesia, although sphincter function may be impaired.

Although functionally discrete, the gut is influenced by sympathetic and parasympathetic activity. The sympathetic preganglionic fibers from T8 through L3 inhibit gut action through the celiac, superior, and inferior mesenteric ganglia; a spinal or epidural anesthetic covering the midthoracic levels removes this inhibition and yields a contracted, small intestine that may afford superior surgical conditions in combination with the profound muscle relaxation of a spinal anesthetic. The sphincters are relaxed, and peristalsis is normally active.

Norepinephrine within the gut is the transmitter of postganglionic sympathetic neurons to the gut. For example, if the contents of the upper intestine become overly acidic or hypertonic, an adrenergically mediated enterogastric reflex reduces the rate of gastric emptying. The adrenergic neurons, which run to the myenteric ganglia of the gastrointestinal tract from the thoracic and lumbar spinal segments, are usually inactive in resting individuals. Reflex pathways within and external to the alimentary tract cause discharge of these neurons. When the viscera are handled during abdominal surgery, reflex firing of the adrenergic nerves inhibits motor activity of the intestine for an extended period. This adrenergic inhibition is thought to be the basis of the common condition known as postoperative ileus. Loss of parasympathetic nervous control usually decreases bowel tone and peristalsis, but over time, the increased activity of the enteric plexus compensates for the loss. Spinal cord lesions may remove sacral parasympathetic input, but cranial parasympathetic signals may still be carried by branches of the vagus nerve down to the end-organ ganglia. Thus, colonic dilation and fecal impaction (which may precipitate hypertension in patients with autonomic dysreflexia) occur more often than small intestinal dysfunction.

Enteric neurons can be sensory and monitor tension in the wall of the intestine or its chemical contents; associative and act like interneurons; or motor and contract intestinal muscles, dilate vessels, or transport water and electrolytes. Motor neurons in the enteric nervous system may be excitatory or inhibitory.

Certain plexuses play important roles in the enteric nervous system. The myenteric plexus, also called the Auerbach plexus, is a network of nerve strands and small ganglia lying in the plane between the external

longitudinal and circular muscle layers of the intestine. The submucous plexus (Meissner plexus) consists of nerve cell bodies, glial cells, and glial and neuronal processes, but it does not contain connective tissue or blood vessels. Within the ganglia, many neuronal processes contain vesicles that store neurotransmitters.

Unlike the sympathetic and parasympathetic nervous systems, in which geographic location can confer selective action, this is anatomically impossible in the gut, and an alternative pattern of chemical coding for function assumes an important organizational role. The combination of amines and peptides and their relative concentrations within the enteric neuron determine its function.

Acetylcholine, the principal excitatory trigger of the nonsphincteric portion of the enteric nervous system, causes muscle contraction. Cholinergic neurons have several roles in the enteric nervous system, including excitation of external muscle, activation of motor neurons augmenting secretion of water and electrolytes, and stimulation of gastric cells. Neural control of gastrointestinal motility is mediated through two types of motor neurons: excitatory and inhibitory. These neurons act in concert on the circular smooth muscle layer in sphincteric and nonsphincteric regions throughout the digestive tract and supply muscles of the biliary tree and the muscularis mucosae. Enteric motor neurons to the circular muscle of the small and large intestine are activated by local reflex pathways contained within the wall of the intestine. Distention evokes polarized reflexes, including contraction proximally and relaxation distally, which in synchrony constitute peristalsis. Nicotinic antagonists abolish enteric reflexes, thus suggesting that the sensory neurons or interneurons in the pathway are cholinergic. In cases of cholinergic overload, such as insecticide poisoning or an excess of neostigmine when reversing a nondepolarizing muscle relaxant (see Chapter 35), the gut (in which cholinesterase is inhibited) has a tendency to become hyperactive.

Many neuroactive compounds other than norepinephrine and acetylcholine participate in the autonomic control of intestinal function. Predominant among these nonadrenergic noncholinergic (NANC) neurotransmitters appears to be nitric oxide (NO), a primary intrinsic inhibitor, but other NANC neurotransmitters such as substance P, a variety of opiate peptides, vasoactive intestinal polypeptide (VIP), and a growing population of peptide hormones are also present (Table 16-1) (see Chapter 104).

TABLE 16-1 NEUROPEPTIDES AND THEIR ACTIONS IN THE GASTROINTESTINAL TRACT

Peptide	Action(s)
Bombesin	Multiple stimulatory effects (including gastrin release)
Calcitonin gene–related peptide	Gastric acid secretion, muscle constriction
Cholecystokinin	Unknown
Dynorphin	Opiate effects
Endothelin-1	Vasoconstriction
Galanin	Muscle constriction
Leu-enkephalin	Opiate effects
Met-enkephalin	Opiate effects
Neuromedin U	Muscle constriction, vasoconstriction
Neuropeptide Y	Vasoconstriction
Pituitary adenylate cyclase	Adenylate cyclase activation
Peptide histidine methionine	Muscle relaxation, secretion
Somatostatin	Multiple inhibitory effects (including gastrin inhibition)
Substance P	Vasodilation, muscle constriction
Vasoactive intestinal polypeptide	Vasodilation, muscle relaxation, secretion

Modified from Bishop A, Polak J: The gut and the autonomic nervous system. In Mathias C, Bannister R, editors: Autonomic failure: a textbook of clinical disorders of the autonomic nervous system, *ed 4. Oxford, 1999, Oxford University Press, p 120.*

FUNCTION

ORGANIZATION AND INTEGRATION

The sympathetic system, in response to internal or external challenges, acts to increase the heart rate, arterial pressure, and cardiac output; dilate the bronchial tree; and shunt blood away from the intestines and other viscera to voluntary muscles. Parasympathetic nervous input acts primarily to conserve energy and maintain organ function and to support vegetative processes.

Most organs of the body exhibit dual innervation, with input from the sympathetic and parasympathetic systems frequently mediating opposing effects (Table 16-2).[1] Stimulation of one system may have an excitatory effect on the end organ, whereas stimulation of the other system may have an inhibitory effect. For example, sympathetic stimulation acts on the heart to increase the rate and vigor of contraction and enhance conduction through the atrioventricular (AV) node, whereas parasympathetic stimulation acts to decrease the heart rate, atrial contractility, and conduction through the AV node. One of the two systems normally dominates a particular organ function, thus providing its "resting tone." In a few organs, the sympathetic system alone provides innervation; most blood vessels, the spleen, and piloerector muscles are examples.

To predict the effects of drugs, the interaction of the sympathetic and parasympathetic system in different organs must be understood. Blockade of sympathetic function unmasks preexisting parasympathetic activity, and the converse relationship is also true. For example, administration of atropine blocks the resting muscarinic tone of the parasympathetically dominated heart, and the unopposed sympathetic tone then causes tachycardia. Clinically, cardiac autonomic denervation occurs with cardiac transplantation; it may also occur with neuraxial anesthesia, diabetes, and myocardial infarction (MI); and it can be assessed by changes in the time interval between successive heartbeats (i.e., beat-to-beat or heart rate variability) as a measure of sympathovagal balance.[2]

ADRENERGIC FUNCTION

Overview of the Effects of Sympathetic Mediators

Adrenergic neurons influence and adjust body functions, and their effects on circulation and respiration are among the most important (Table 16-3).

The endogenous catecholamines norepinephrine and epinephrine possess α- and β-receptor agonist activity. Norepinephrine has minimal β_2-receptor activity, whereas epinephrine stimulates β_1 and β_2 receptors (Table 16-4). α-Receptor–mediated activity is responsible for most of the sympathetically induced smooth muscle contraction throughout the body, including the ciliary muscle of the eye and vascular, bronchial, and ureteral smooth muscle. The gastrointestinal and genitourinary sphincter mechanisms are stimulated by α-adrenergic receptors. α-Receptor agonism also mediates sympathetic nervous system control of pancreatic insulin secretion, with stimulation of α_2 receptors leading to decreased release of insulin from pancreatic

TABLE 16-2 RESPONSES ELICITED IN EFFECTOR ORGANS BY STIMULATION OF SYMPATHETIC AND PARASYMPATHETIC NERVES

Effector Organ	Adrenergic Response	Receptor Involved	Cholinergic Response	Receptor Involved	Dominant Response (A or C)
Heart					
Rate of contraction	Increase	β_1	Decrease	M_2	C
Force of contraction	Increase	β_1	Decrease	M_2	C
Blood vessels					
Arteries (most)	Vasoconstriction	α_1			A
Skeletal muscle	Vasodilation	β_2			A
Veins	Vasoconstriction	α_2			A
Bronchial tree	Bronchodilation	β_2	Bronchoconstriction	M_3	C
Splenic capsule	Contraction	α_1			A
Uterus	Contraction	α_1	Variable		A
Vas deferens	Contraction	α_1			A
Gastrointestinal tract	Relaxation	α_2	Contraction	M_3	C
Eye					
Radial muscle, iris	Contraction (mydriasis)	α_1			A
Circular muscle, iris			Contraction (miosis)	M_3	C
Ciliary muscle	Relaxation	β_2	Contraction (accommodation)	M_3	C
Kidney	Renin secretion	β_1			A
Urinary bladder					
Detrusor	Relaxation	β_2	Contraction	M_3	C
Trigone and sphincter	Contraction	α_1	Relaxation	M_3	A, C
Ureter	Contraction	α_1	Relaxation		A
Insulin release from pancreas	Decrease	α_2			A
Fat cells	Lipolysis	β_1 (β_3)			A
Liver glycogenolysis	Increase	α_1 (β_3)			A
Hair follicles, smooth muscle	Contraction (piloerection)	α_1			A
Nasal secretion	Decrease	α_1	Increase		C
Salivary glands	Increase secretion	α_1	Increase secretion		C
Sweat glands	Increase secretion	α_1	Increase secretion		C

From Bylund, DB: Introduction to the autonomic nervous system. In Wecker L, Crespo L, Dunaway G, et al, editors: Brody's human pharmacology: molecular to clinical, *ed 5. Philadelphia, 2010, Mosby, p 102.*
A, Adrenergic; *C,* cholinergic; *M,* muscarinic.

TABLE 16-3 EFFECTS OF ACTIVATION OF THE SYMPATHETIC NERVOUS SYSTEM

Site of Action	Stimulation	Inhibition
Heart	Rate, conduction, contractility	
Blood vessels	Vasoconstriction (skin, gut, liver, heart, kidney)	Vasodilation (skeletal muscle, heart, brain)
Respiration	Respiratory center (increased drive to breath) Bronchodilation	
Gastrointestinal tract	Sphincters (increased tone)	Smooth muscle peristalsis
Genitourinary tract	Sphincters (increased tone)	Ureteral and uterine muscle contraction
Metabolic and endocrine effects	Glycogenolysis (muscle, liver) Gluconeogenesis Insulin release Renin release ADH release	Insulin release (α stimulation or β_1 antagonism) Lipolysis

ADH, Antidiuretic hormone or arginine vasopressin.

β cells. In the peripheral vasculature, α_1 and α_2 receptors modulate vascular tone in response to humorally borne neurotransmitters and exogenously administered drugs.

β-Receptor agonism is primarily responsible for sympathetic stimulation of the heart, relaxation of vascular and bronchial smooth muscle, stimulation of renin secretion by the kidney, and several metabolic consequences, including lipolysis and glycogenolysis. The β_1 receptor is thought to primarily be involved in cardiac effects[3] and release of fatty acids and renin, whereas β_2 receptors are primarily responsible for smooth muscle relaxation and hyperglycemia. In specialized circumstances, however, β_2 receptors may also mediate cardiac activity. Although acute changes in arterial pressure and heart rate can be caused by norepinephrine or epinephrine, chronic hypertension does not appear to be related to circulating levels of these hormones.[4] Notably, 85% of resting arterial pressure is determined by the level of renin activity (Fig. 16-5**)**. An additional important effect of epinephrine is to increase gap junctions in bone and thereby cause an increase in circulating blood elements.[5]

Psychological and physical stimuli may evoke different sympathetic compensatory responses. Public speaking activates the adrenal gland with a disproportionate rise in serum epinephrine, whereas physical exercise elicits primarily a marked rise in serum norepinephrine.[6] Thus, the stress response should not be thought of as a uniform response; it can vary in mechanism, intensity, and manifestations.

TABLE 16-4 ADRENERGIC RECEPTOR DIFFERENTIATION

Receptor	Stimulation	Inhibition
α		
Blood vessels	Vasoconstriction (skin, gut, kidney, liver, heart)	
Gastrointestinal tract	Sphincters	
Genitourinary tract	Sphincters	
Metabolic and endocrine effects		Insulin release
β		
Heart	(1) Rate, conduction, contractility	
Blood vessels		(2) Vasodilation (skeletal muscle, heart, brain)
Respiration	(?) Respiratory center (2) Bronchodilation	
Gastrointestinal tract		(2) Smooth muscle
Genitourinary tract		(2) Ureteral and uterine muscle
Metabolic and endocrine effects	(2) Glycogenolysis (muscle, liver) (1) Lipolysis (2) Gluconeogenesis (1) Insulin release (?) Renin release (?) Antidiuretic hormone release	

(1), Mediated by β_1 receptors; *(2),* mediated by β_2 receptors; *(?),* controversial.

Blood Glucose

Sympathetic nervous stimulation of β receptors increases glycogenolysis in liver and muscle and liberates free fatty acids from adipose tissue, thereby ultimately increasing blood glucose levels. In neonates, epinephrine plays an additional role in the exothermic breakdown of brown fat to maintain body temperature (i.e., nonshivering thermogenesis).

Also present in the pancreas are α_2 and β_2 receptors. α_2-Receptor activation suppresses insulin secretion by pancreatic islet cells; blockade of these receptors may increase release of insulin and thus could be associated with significant lowering of blood glucose levels. β_2-Receptor stimulation increases glucagon and insulin secretion and decreases peripheral sensitivity to insulin.[7]

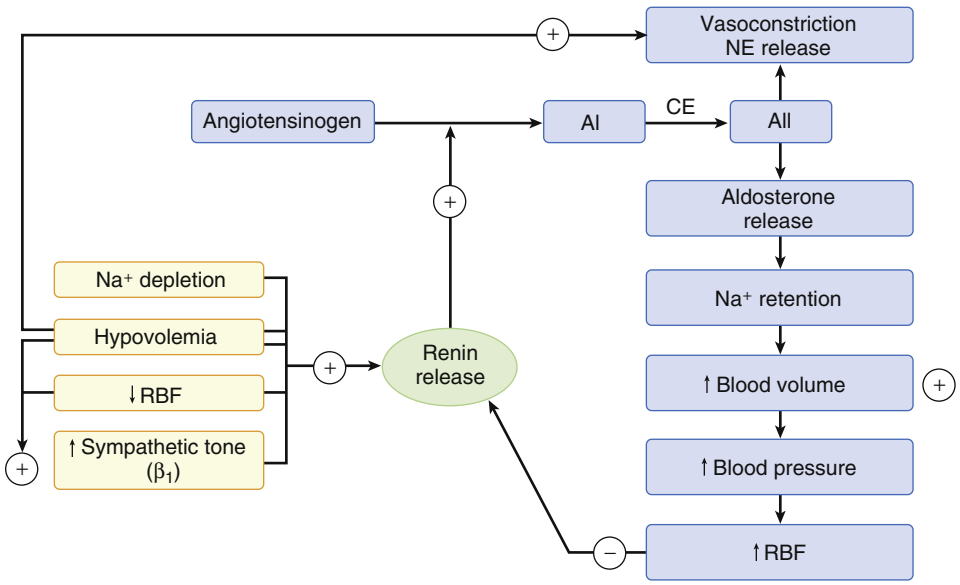


Figure 16-5. Interactions of the renin-angiotensin-aldosterone and sympathetic nervous systems in maintaining blood pressure and volume. *AI,* Angiotensin I; *AII,* angiotensin II; *CE,* converting enzyme; *Na^+,* sodium; *NE,* norepinephrine; *RBF,* renal blood flow; +, stimulating effects; –, inhibiting effects.

Potassium Shift

Plasma epinephrine also takes part in regulation of the serum potassium concentration. β-Adrenergic activity can initiate transient hyperkalemia as potassium shifts out of hepatic cells with the glucose efflux produced by β_2-adrenergic stimulation. This effect is followed by a more prolonged hypokalemia as β_2-adrenergic stimulation drives potassium into red blood cells and muscle cells. Stimulation of the β_2 receptors of red blood cells by exogenously administered or endogenously released epinephrine activates adenylate cyclase and sodium-potassium adenosine triphosphatase (ATPase) and drives potassium into cells. Serum potassium concentrations are then reduced and may contribute to the cardiac arrhythmias accompanying MI and other stresses. Selective β_2-adrenergic blockade has the theoretic advantage of inhibiting this potassium shift. However, selective and nonselective β-blockers are equivalent in protecting the postinfarcted heart against arrhythmias.[8-12]

CHOLINERGIC FUNCTION

Overview of the Effects of Acetylcholine

In contrast to the diffuse discharge of the sympathetic nervous system that constitutes the fight-or-flight response, the parasympathetic system is anatomically and functionally more localized in its effects. Parasympathetic activation conserves energy and maintains organ function. A massive parasympathetic response would prostrate the organism and leave it helplessly salivating, weeping, wheezing, vomiting, urinating, defecating, and seizing. Although the sympathetic system is needed for the emergency response to stressful situations, it is not necessary for day-to-day survival; the parasympathetic system is, however, essential for maintenance of life.

Release of acetylcholine is the hallmark of parasympathetic activation. The actions of acetylcholine are almost diametrically opposed to those of norepinephrine and epinephrine. In general, the muscarinic effects of acetylcholine are qualitatively the same as the effects of vagal stimulation.

Acetylcholine decreases the heart rate, the velocity of conduction in the sinoatrial and AV nodes, and atrial contractility (although this decrease is not as marked as the increase in contractility produced by sympathetic stimulation). In the sinoatrial node, acetylcholine causes membrane hyperpolarization, which delays attainment of the threshold potential and the ability to generate another action potential, thereby slowing the heart rate. In the AV node, acetylcholine decreases conduction velocity and increases the effective refractory period. This decrease in AV nodal conduction accounts for the complete heart block seen when large amounts of cholinergic agonists are given. In the ventricle, acetylcholine decreases automaticity in the Purkinje system and thus increases the fibrillation threshold (see also Chapters 20 and 47). Cardiac presynaptic and postsynaptic muscarinic receptors are involved in these effects. Acetylcholine inhibits adrenergic stimulation of the heart presynaptically by inhibiting the release of norepinephrine from sympathetic nerve endings and postsynaptically by opposing the effects of catecholamines on the myocardium.

Parasympathetic activation has many effects outside the cardiovascular system. Cholinergic stimulation causes smooth muscle constriction, including that of the bronchial walls. In the gastrointestinal and genitourinary tracts, smooth muscle in the walls constricts, but the sphincter muscles relax, which results in incontinence. Topically administered acetylcholine constricts the smooth muscle of the iris and causes miosis.

The signs and symptoms of cholinergic overload reflect all these effects, as well as nausea and vomiting, intestinal cramps, belching, urination, and urgent defecation. All glands innervated by the parasympathetic nervous system are stimulated to produce secretions, including the lacrimal, tracheobronchial, salivary, digestive, and exocrine glands.

Local Control of Vascular Tone

In addition to the pharmacologic effects of acetylcholine that are mediated by the parasympathetic nervous system, bloodborne acetylcholine has a significant effect on blood vessels in that it dilates virtually all vessels in vivo. Endothelial cells respond to acetylcholine stimulation by producing one or more endothelium-derived relaxing factors (EDRFs).[13] It now appears that endothelial cells have receptors for numerous agonists, including serotonin, adenosine, histamine, and catecholamines (Fig. 16-6).

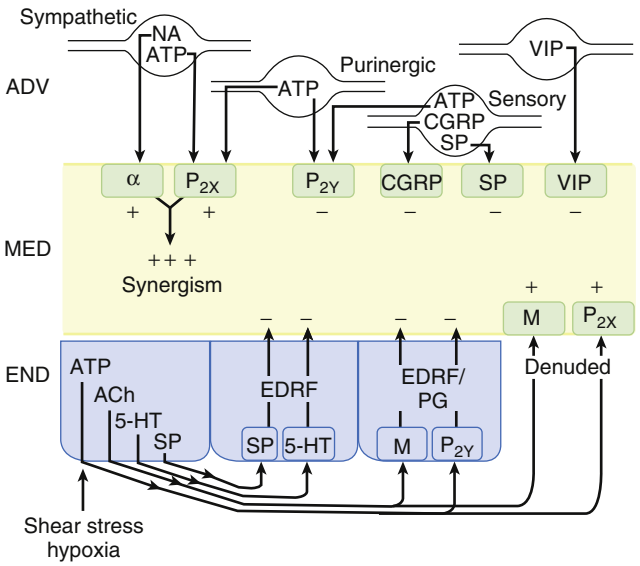


Figure 16-6. Schematic representation of potential modes of regulation of vascular tone by endothelial cell–related mechanisms. Norepinephrine (NA), adenosine triphosphate (ATP), calcitonin gene–related peptide (CGRP), substance P (SP), and vasoactive intestinal polypeptide (VIP) can be released from nerves in the adventitia (ADV) to act on their respective receptors in the media (MED) and cause vasoconstriction or vasodilation. ATP, acetylcholine (ACh), 5-hydroxytryptamine (5-HT), and SP released from endothelial cells (END) by shear stress or hypoxia act on their receptors on endothelial cells to cause release of endothelium-derived relaxing factors (EDRF) or prostaglandins (PG), which act on smooth muscle to cause relaxation. In areas denuded of endothelial cells, opposite effects may be produced by receptors on smooth muscle. *α,* Norepinephrine receptor; *M,* muscarinic receptor; P_{2X}, P2X purinoceptor; P_{2Y}, P2Y purinoceptor. *(From Lincoln J, Burnstock G: Neural-endothelial interactions in control of local blood flow. In Warren J, editor:* The endothelium: an introduction to current research. *New York, 1990, Wiley-Liss, p 21.)*

The radical NO was the first identified EDRF (see Chapter 104 for details). When the endothelium is damaged, as in atherosclerosis, production of EDRF diminishes and constriction increases. This change explains why patients with damaged or diseased vessels react differently.

An understanding of the biology of NO is fundamental to an appreciation of many vital body functions (see Chapter 104).[14] Endothelial cells play a role in control of the circulation in addition to the production of NO. Endothelial cells metabolize many vasoactive amines, convert angiotensin I to angiotensin II, and secrete prostacyclin and the vasoconstrictive peptide endothelin-1 (ET-1). NO, ET-1, and prostacyclin are local hormones released by endothelial cells to influence their immediate microenvironment. Prostacyclin and NO relax vascular smooth muscle, whereas in the lumen, they act separately or in concert to prevent platelets from clumping onto the endothelium.

NO, prostacyclin, and ET-1 appear to be operative in local control of the circulation. The prostacyclin system may be a redundant mechanism that reinforces the NO system in the presence of endothelial damage. Acting together, these two dilators are also a strong defense mechanism against intravascular thrombosis. ET-1 can be produced locally in response to trauma, such as wounds to the vessel wall, and it perhaps decreases blood loss. The long-term functions of these local hormones are of considerable interest in the pathophysiology of many disease states, including septic shock, pulmonary hypertension, and renal failure.[15,16] For more information on NO biology, see Chapter 104.

PHARMACOLOGY

ADRENERGIC PHARMACOLOGY

Synthesis of Norepinephrine

Norepinephrine is synthesized from tyrosine, which is actively transported into the varicosity of the postganglionic sympathetic nerve ending (Fig. 16-7). Tyrosine is synthesized from phenylalanine. Precursors are taken up in greater amounts in shock and may have beneficial effects on the effort of the sympathetic nervous system to maintain perfusion pressure.

A series of steps results in conversion of tyrosine to norepinephrine and epinephrine (in the adrenal medulla). The first of these steps involves the rate-limiting

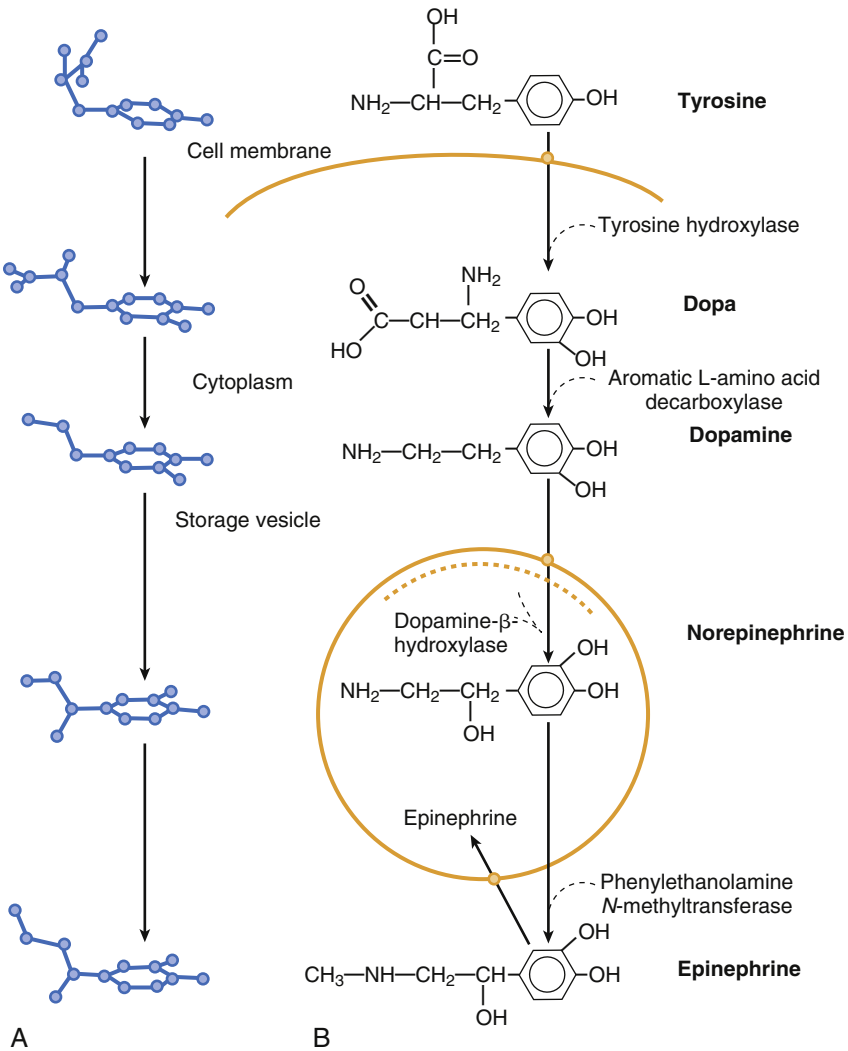


Figure 16-7. Biosynthesis of norepinephrine and epinephrine in sympathetic nerve terminal (and the adrenal medulla). **A,** Perspective view of molecules. **B,** Enzymatic processes. *(From Tollenaeré JP:* Atlas of the three-dimensional structure of drugs. *Amsterdam, 1979, Elsevier North-Holland, as modified by Vanhoutte PM: Adrenergic neuroeffector interaction in the blood vessel wall,* Fed Proc *37:181, 1978.)*

cytoplasmic enzyme tyrosine hydroxylase (TH). High levels of norepinephrine inhibit TH, and low levels stimulate the enzyme. During stimulation of the sympathetic nervous system, an increased supply of tyrosine also increases the synthesis of norepinephrine. TH activity is modified by phosphorylation. TH depends on a pteridine cofactor and the presence of molecular oxygen. When the quantity of molecular oxygen is reduced, synthesis of norepinephrine may be decreased significantly, a condition that could account for changes in wakefulness. Whereas acute control of TH occurs by altering enzyme activity, chronic stress can elevate TH levels by stimulating the synthesis of new enzyme. Under the influence of TH, tyrosine is converted to dihydroxyphenylalanine (DOPA), which is decarboxylated to dopamine by an aromatic amino acid decarboxylase (DOPA decarboxylase), a relatively promiscuous enzyme in its substrate specificity.

Dopamine acts as a neurotransmitter in some cells, but most of the dopamine produced is β-hydroxylated within the vesicles to norepinephrine by the enzyme dopamine β-hydroxylase (DβH). In the adrenal medulla and to a limited extent in discrete regions of the brain, another enzyme, phenylethanolamine *N*-methyltransferase (PNMT), methylates approximately 85% of the norepinephrine to epinephrine. Glucocorticoids from the adrenal cortex pass through the adrenal medulla and can activate the system, and stress-induced steroid release can increase the production of epinephrine. This local circulation amplifies the effects of glucocorticoid release.[17]

Storage of Norepinephrine

Norepinephrine is stored within large, dense-core vesicles where dense cores in these vesicles are filled not only with norepinephrine but also with binding proteins. In addition, the vesicles contain calcium, a variety of peptides, and adenosine 5′-triphosphate (ATP). Depending on the nature and frequency of physiologic stimuli, the ATP can be released selectively for an immediate postsynaptic effect through purinoreceptors, yet norepinephrine is the predominant neurotransmitter at sympathetic nerve endings.

Synaptic vesicles are heterogeneous and exist within functionally defined compartments. An actively recycling population of synaptic vesicles has been defined, together with a reserve population of vesicles that are mobilized only upon extensive stimulation. Functionally, norepinephrine is stored in compartments, and 10% of it is readily releasable. In general, 1% of the stored norepinephrine is released with each depolarization, thus implying a significant functional reserve.

Release of Norepinephrine

The contents of the vesicle enter the synaptic cleft by several different processes. The dominant physiologic mechanism of release is exocytosis, during which the vesicle responds to the entry of calcium by initiating vesicular docking, fusion, release of vesicular contents, and ultimately, endocytosis (the process by which the vesicular membrane and proteins are recaptured) (Fig. 16-8). The entire contents of the vesicle are liberated by stimulation of the nerve. The biology of vesicular release is not a random event, but a highly differentiated process. The finding that exocytosis is so highly conserved from species to species indicates its biologic importance. Angiotensin II, prostacyclin, and histamine potentiate release, whereas acetylcholine and prostaglandin E inhibit release. Further details on neurotransmitter release are discussed in Chapter 28.

Although chromaffin cells in the adrenal medulla synthesize epinephrine and norepinephrine, the two compounds are stored in and secreted from distinct

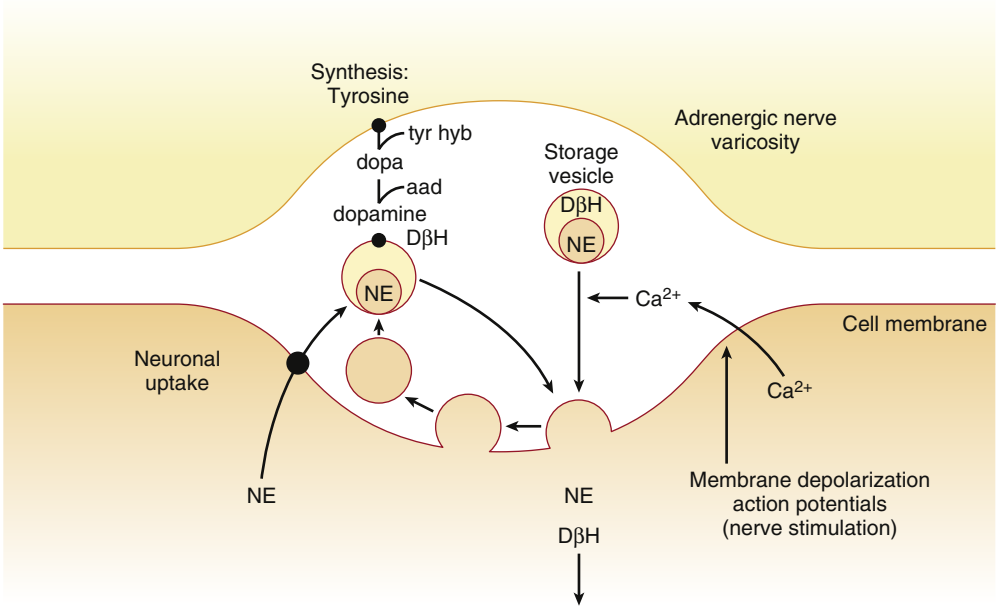


Figure 16-8. Release and reuptake of norepinephrine at sympathetic nerve terminals. *aad,* Aromatic L-amino decarboxylase; *DβH,* dopamine β-hydroxylase; *dopa,* L-dihydroxyphenylalanine; *NE,* norepinephrine; *tyr hyd,* tyrosine hydroxylase; *solid circle*, active carrier. *(From Vanhoutte PM: Adrenergic neuroeffector interaction in the blood vessel wall,* Fed Proc *37:181, 1978, as modified by Shepherd J, Vanhoutte P: Neurohumoral regulation. In Shepherd S, Vanhoutte P, editors:* The human cardiovascular system: facts and concepts. *New York, 1979, Raven, p 107.)*

chromaffin cell subtypes. Pharmacologic differences between cells containing norepinephrine and those containing epinephrine have been described, and data suggest possible preferential release from one or another form of chromaffin cell contingent on the nature of the stimulus. Nicotinic agonists or depolarizing agents cause the preferential release of norepinephrine, whereas histamine elicits predominantly epinephrine release.[18-20] Protein kinase C plays an important role in regulating the secretion of catecholamines from norepinephrine-containing chromaffin cells.[21]

Inactivation

Most of the norepinephrine released is rapidly removed from the synaptic cleft by an amine mechanism (i.e., uptake-1 mechanism) or by nonneuronal tissue (i.e., uptake-2 mechanism). The uptake-1 mechanism represents the first and most important step in the inactivation of released norepinephrine. Most of the norepinephrine released is transported into storage vesicles for reuse. This uptake of neurotransmitter into synaptic vesicles is driven by an electrochemical proton gradient across the synaptic vesicle membrane. The vacuolar proton pump is a large, hetero-oligomeric complex that contains eight to nine different subunits. After reuptake, the small amounts of norepinephrine not taken up into the vesicle are deaminated by cytoplasmic monoamine oxidase (MAO). Several organ-specific forms of this enzyme exist.

Since the isolation and cloning in 1991 of the human norepinephrine transporter, considerable information has accumulated.[22,23] The pharmacologic characteristics of this binding protein identify it as the cocaine binding site, although tricyclic antidepressants (i.e., desipramine and nortriptyline) are also potent antagonists.

Uptake of norepinephrine into the nerve varicosity and its return to the storage vesicle, albeit efficient, are not specific for the neurotransmitter. Some compounds structurally similar to norepinephrine may enter the nerve by the same mechanism and result in depletion of the neurotransmitter. These false transmitters can be of great clinical importance. Moreover, some drugs that block reuptake into the vesicle or into the synaptic ending itself may enhance the response to catecholamines (i.e., more norepinephrine is available to receptors). Such drugs include cocaine and tricyclic antidepressants (Table 16-5).

Activity of the uptake-1 system varies greatly among different tissues. Because of anatomic barriers, peripheral blood vessels exhibit almost no reuptake of norepinephrine; consequently, rapid rates of norepinephrine synthesis are needed in peripheral blood vessels to modulate vascular tone. The highest rate of reuptake is found in the heart. Drugs or disease states that alter biosynthesis or storage (e.g., methyldopa decreases storage) have a more profound effect on blood pressure; those that affect reuptake would be expected to affect cardiac rate and rhythm.

Typically, the lungs remove 25% of the norepinephrine that passes through the pulmonary circulation, whereas epinephrine and dopamine pass through unchanged. Pulmonary uptake of norepinephrine appears to be a sodium-dependent, facilitated transport process in the endothelial cells of precapillary and postcapillary vessels and pulmonary veins. Significant uptake by nerve endings occurs. Primary or secondary pulmonary hypertension diminishes uptake of norepinephrine, presumably because of concomitant thickening of the pulmonary vasculature. Although the functional significance of the endothelial uptake mechanism of the pulmonary vascular wall is unknown, uptake of other powerful vasoactive compounds suggests that the pulmonary endothelium functions to protect the left side of the heart.

Defects in the ANS are common in patients with congestive heart failure (CHF). Acute stress-induced (takotsubo) cardiomyopathy has been linked to abnormal cardiac sympathetic activity.[24] In chronic heart failure, the heart is depleted of catecholamines, and reuptake of norepinephrine is decreased.[25] Sustained sympathoexcitation results in increased neuronal release of norepinephrine.[26] Cardiac norepinephrine spillover rates differ widely, even among patients with end-stage heart failure who are awaiting cardiac transplantation, but some studies suggest that elevated plasma catecholamine levels portend a poorer prognosis than can be anticipated with traditional cardiovascular indices.[27,28] Because augmentation of catecholamine release is markedly impaired in patients with CHF, compensation for further decreases in systemic vascular resistance requires activation of the renin-angiotensin system. Together, these events result in increased adrenergic drive, desensitization of β receptors, and depletion of norepinephrine stores, all of which contribute to insufficient inotropic function.[29,30]

Metabolism

During storage and reuptake, a small amount of norepinephrine escapes uptake into the nerve ending and enters the circulation, where it is metabolized by MAO,

TABLE 16-5 COMPARISON OF DIRECT- AND INDIRECT-ACTING SYMPATHOMIMETICS

	Response of Effector Organ to	
Pretreatment	**Direct Sympathomimetics (e.g., Epinephrine): Acts at the Receptor**	**Indirect Sympathomimetics (e.g., Tyramine): Causes Release of NE After Its Uptake by Uptake-1**
Denervation Loss of uptake-1 sites Receptor up-regulation	Increased	Reduced
Reserpine Blocks vesicular uptake Depletes NE May cause up-regulation	Slightly increased	Reduced
Cocaine Blocks uptake-1 Depletes NE	Increased	Reduced

Adapted from Minneman KP: Drugs affecting the sympathetic nervous system. In Minneman K, Wecker L, editors: Brody's human pharmacology: molecular to clinical, *ed 4. Philadelphia, 2005, Mosby, p 125.*

NE, Norepinephrine.

catechol-*O*-methyltransferase (COMT), or both in the blood, liver, and kidney.

Epinephrine, which is released by the adrenal medulla, is inactivated by the same enzymes. The final metabolic product of inactivation is vanillylmandelic acid (VMA). Because of its rapid clearance, the half-life of norepinephrine (and most biogenic amines) in plasma is short, less than 1 minute. This short half-life necessitates administration of these drugs by infusion. Another consequence of their short half-life is that a more ideal measure of catecholamine production may be metabolic products rather than the catecholamines themselves. For example, screening for a norepinephrine-producing pheochromocytoma is best performed by measuring the level of plasma free metanephrines.[31]

Inhibition of MAO has a large impact on the sympathetic function of a patient. MAO inhibitors (MAOIs) are generally well tolerated, but the stability of the patient belies the fact that amine handling is fundamentally changed. Clinically important, life-threatening drug interactions are discussed later in the section on drugs and the ANS.

Other compounds can be metabolized by catabolic enzymes to produce false transmitters. Although not used therapeutically, tyramine is the prototypical drug studied. Tyramine is present in many foods, particularly aged cheese and wine, and it can be synthesized from tyrosine. Tyramine enters the sympathetic nerve terminal through the uptake-1 mechanism and displaces norepinephrine from the vesicles into the cytoplasm. The released norepinephrine leaks out of the cytoplasm and is responsible for the hypertensive effect of tyramine. However, a secondary effect can occur. In the vesicle, tyramine is converted by DβH to octopamine, which is eventually released as a false transmitter in place of norepinephrine, but without the hypertensive effect because it has only 10% of the potency of norepinephrine.

Adrenergic Receptors

Initially, α-adrenergic receptors were distinguished from β-adrenergic receptors by their greater response to epinephrine and norepinephrine than to isoproterenol. The development of α- and β-antagonists further supported the existence of separate α receptors. Traditionally, adrenergic receptors have been classified as α or β and more recently as α_1, α_2, β_1, or β_2 based on responses to specific drugs. With technologic advances in molecular biology, classification evolved to three major subtypes and nine sub-subtypes (Fig. 16-9).[32] Table 16-6 describes the distribution, response, typical agonists, and antagonists of the α_1, α_2, β_1, and β_2 receptors.

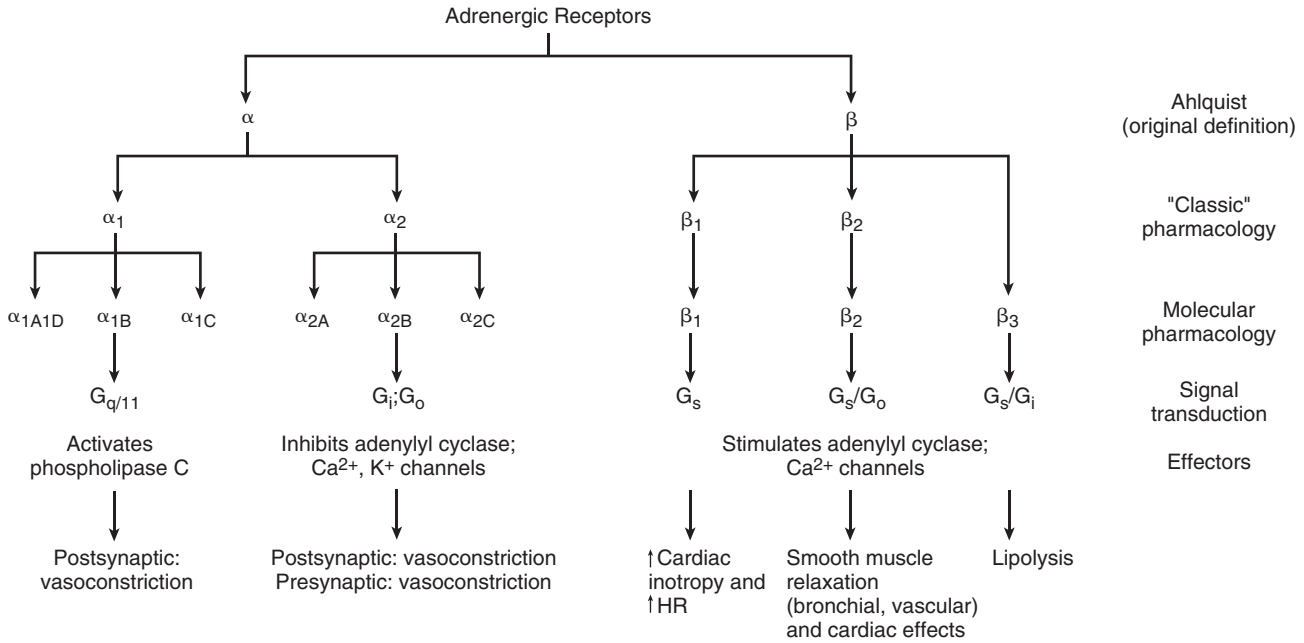


Figure 16-9. Classification of adrenergic receptors. *Ca^{2+}, Calcium; HR,* heart rate; *K^+*, potassium.

TABLE 16-6 **DISTRIBUTION OF α AND β RECEPTORS**

Receptor	Distribution	Response	Agonist	Antagonist
α_1	Smooth muscle	Constriction	Phenylephrine	Prazosin
α_2	Presynaptic	Inhibits norepinephrine release	Clonidine Dexmedetomidine	Yohimbine
β_1	Heart	Inotropy Chronotropy	Dobutamine	Metoprolol
β_2	Smooth muscle	Dilation Relaxation	Terbutaline	

α-Adrenergic Receptors. Functional and binding assays and molecular biologic methods have unequivocally confirmed the classification of α adrenoceptors into subtypes.[33] Within α_1-adrenergic receptors, $\alpha_{1a/d}$, α_{1b}, and α_{1c} receptors have been characterized. Several α_2 isoreceptors (α_{2a}, α_{2b}, and α_{2c}) have also been described. α_2 Receptors are usually expressed presynaptically or even in nonneuronal tissue. α_2 Receptors are found in the peripheral nervous system, in the CNS, and in a variety of organs, including platelets, liver, pancreas, kidney, and eyes, where specific physiologic functions have been identified.[34] The predominant α_2 receptor of the human spinal cord is the α_{2a} subtype.[32,35] Mammalian genomes probably contain two sets of at least three unique genes encoding the α adrenoceptors. Genes encoding α_2 receptors have been localized to chromosomes 2, 4, and 10. There is more than theoretic relevance in the subclassification of receptors,[36] in that mutations that decrease α_{2c} presynaptic function and enhance β_1-receptor linkage cause adrenergic hyperactivity and predispose to CHF.[37]

Amino acid sequence comparisons indicate that α receptors are members of the 7–transmembrane segment gene superfamily, which uses G protein for signal transduction. A core of 175 amino acids constitutes the 7 transmembrane regions and is highly conserved among different family members. The plethora of receptor subtypes remains incompletely explained, although the observation that different signal transduction mechanisms are used suggests finer control and physiologic significance. Considerable variability in α-adrenergic receptor subtypes exists among species.[38]

Receptors can be presynaptic as well as postsynaptic. Presynaptic receptors may act as heteroreceptors or autoreceptors. An *autoreceptor* is a presynaptic receptor that reacts with the neurotransmitter released from its own nerve terminal to provide feedback regulation. A *heteroreceptor* is a presynaptic receptor that responds to substances other than the neurotransmitter released from that specific nerve terminal. This regulatory scheme is present throughout the nervous system but is particularly important in the sympathetic nervous system.[39]

Although several presynaptic receptors have been identified, the α_2 receptor may have the greatest clinical import. Presynaptic α_2 receptors regulate the release of norepinephrine and ATP through a negative-feedback mechanism.[40] Activation of presynaptic α_2 receptors by norepinephrine inhibits subsequent release of norepinephrine in response to nerve stimulation. A similar inhibitory response is produced by attachment of acetylcholine to presynaptic cholinergic receptors within the ANS. In the human brain, ligand studies reveal a high density of α_2 receptors, particularly in the cerebral cortex and medulla.[41] This latter distribution may account for the bradycardic and hypotensive responses to α_2-agonist drugs.

β-Adrenergic Receptors. Like the α receptor, the β receptor is one of the superfamily of proteins that have seven helices passing through the cell membrane. These transmembrane domains are labeled M_1 through M_7; antagonists have specific binding sites, whereas agonists are more diffusely attached to hydrophobic membrane-spanning domains (Fig. 16-10). The extracellular portion of the receptor ends in an amino group. A carboxyl group occupies the intracellular terminal, where phosphorylation occurs. At the cytoplasmic domains, G proteins and kinases, including β-adrenergic receptor kinase, interact. The β receptor has mechanistic and structural similarities with muscarinic but not nicotinic receptors, primarily in the transmembrane sections.

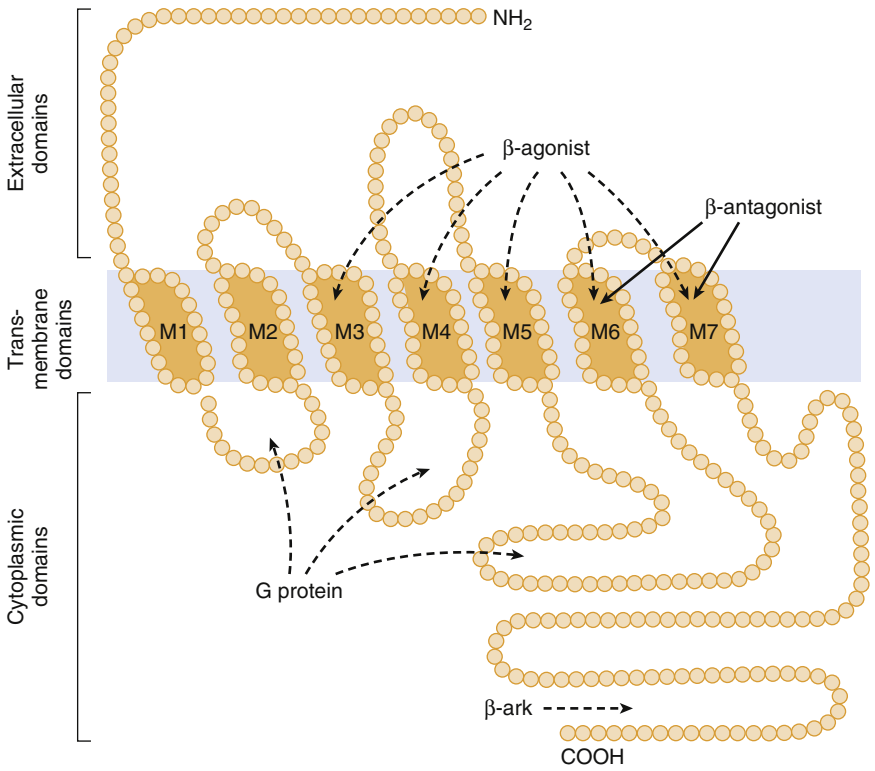


Figure 16-10. Molecular structure of the classic G-protein–coupled β-adrenergic receptor. Notice the three domains. The transmembrane domains act as a ligand-binding pocket. Cytoplasmic domains can interact with G proteins and kinases such as β-adrenergic receptor kinase (β-ark). The latter can phosphorylate and desensitize the receptor. *COOH,* Carboxyl; *NH_2,* amine. *(From Opie L: Receptors and signal transduction. In Opie LH, editor:* Heart physiology: from cell to circulation, *ed 4. Philadelphia, 2004, Lippincott Williams & Wilkins, 2004, p 194.)*

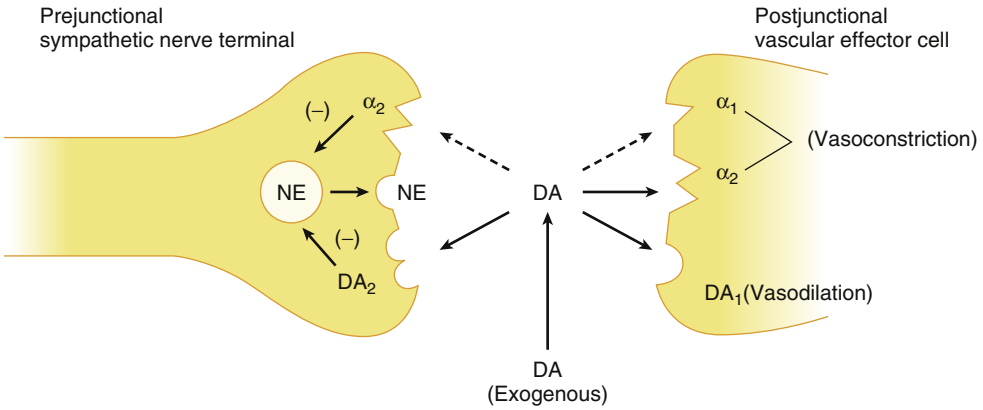


Figure 16-11. Location of dopamine type 1 (DA_1) receptors and α_1 and α_2 adrenoceptors on postganglionic vascular effector cells and DA_2 receptors and α_2 adrenoceptors on the prejunctional sympathetic nerve terminal. When dopamine is administered, activation of DA_1 receptors causes vasodilation, whereas activation of DA_2 receptors causes inhibition (–) of release of norepinephrine (NE) from storage granules. A larger dose of dopamine activates α_1 and α_2 adrenoceptors on the postjunctional effector cells to cause vasoconstriction and α_2 adrenoceptors on the prejunctional sympathetic terminal to inhibit release of NE. NE released from the prejunctional sympathetic terminal also acts on α_1 and α_2 adrenoceptors. *(From Goldberg LI, Rajfer SI: Dopamine receptors: applications in clinical cardiology,* Circulation *72:245, 1985.)*

β Receptors have been further divided into β_1, β_2, and β_3 subtypes, all of which increase cyclic adenosine monophosphate (cAMP) through adenylate cyclase and the mediation of G proteins.[42] Although β_1 receptors were traditionally thought to be isolated to cardiac tissue and β_2 receptors were believed to be restricted to vascular and bronchial smooth muscle, we now know that the β_2-receptor population in human cardiac tissue is substantial and accounts for 15% of β receptors in the ventricles and 30% to 40% in the atria.[43] β_2 Receptors may help compensate for disease by maintaining response to catecholamine stimulation when β_1 receptors are down-regulated during chronic catecholamine stimulation and in CHF.[44] The β_2-receptor population is almost unaffected in end-stage congestive cardiomyopathy.[45] In addition to positive inotropic effects, β_2 receptors in the human atria participate in regulation of the heart rate. Generation of cAMP in the human heart appears to be mediated primarily by β_2 receptors, although this may be an artifact related to the lability of β_1 receptors.[45] Localization of β_3 receptors to fat cells suggests a new therapy for obesity.[46] Polymorphism of this β-receptor subtype is associated with obesity and the potential for the development of diabetes.[47-49] Similarly, point mutations in genes encoding β_2 receptors are correlated with decreased down-regulation of β receptors and nocturnal asthma.[50,51]

Dopamine Receptors

Dopamine exists as an intermediate in the biosynthesis of norepinephrine, and in addition, exogenous dopamine exerts α- or β-adrenergic effects (depending on the dose administered). Goldberg and Rajfer demonstrated physiologically distinct dopamine type 1 (DA_1) and dopamine type 2 (DA_2) receptors,[52] and these remain the most important of the five dopamine receptors cloned (Fig. 16-11). DA_1 receptors are postsynaptic and act on renal, mesenteric, splenic, and coronary vascular smooth muscle to mediate vasodilation through stimulation of adenylate cyclase and increased production of cAMP. The vasodilatory effect tends to be strongest in the renal arteries. It is for this action, particularly the redistribution of blood flow to the kidneys, that dopamine is most frequently used. Additional renal DA_1 receptors located in the tubules modulate natriuresis through the sodium-potassium ATPase pump and the sodium-hydrogen exchanger.[52-55] DA_2 receptors are presynaptic; they may inhibit release of norepinephrine and perhaps acetylcholine. In addition, central DA_2 receptors may mediate nausea and vomiting, a finding that may explain why the antiemetic activity of droperidol is thought to be related to its DA_2 activity.

Guanosine Triphosphate–Binding Regulatory Proteins (G Proteins)

After adrenergic receptor stimulation, the extracellular signal is transformed into an intracellular signal by a process known as signal transduction in which α_1 and β receptors are coupled to G proteins. When activated, G proteins can modulate the synthesis or availability of intracellular second messengers (Fig. 16-12). The activated second messenger diffuses through the cytoplasm and stimulates an enzymatic cascade. The sequence of first messenger → receptor → G protein → effector → second messenger → enzymatic cascade is found in a wide variety of cells; the specific entities that fulfill the separate roles vary from cell to cell.[56] G proteins located on the inner surface of the cell membrane can also directly modify the activity of transmembrane ion channels.

G proteins are heterotrimeric compounds composed of three subunits labeled α, β, and γ. The β and γ subunits form a stable complex, and the α subunit associates with them in a reversible fashion. The β and γ subunits show little variation in their structure. In contrast, 20 different α subunits have been identified. The structure of the attached α subunit defines the function of the G protein. Four classes of α subunits have been defined: α_s, α_i, α_q, and α_{12}. The corresponding G-protein complexes formed when these α subunits bind to the βγ structure are called G_s, G_i, G_q, and G_o.[57]

Each class of adrenergic receptor couples to a different major subfamily of G proteins, which are linked to different effectors. The major subtypes of α_1, α_2, and β receptors are linked to G_q, G_i, and G_s, respectively, which

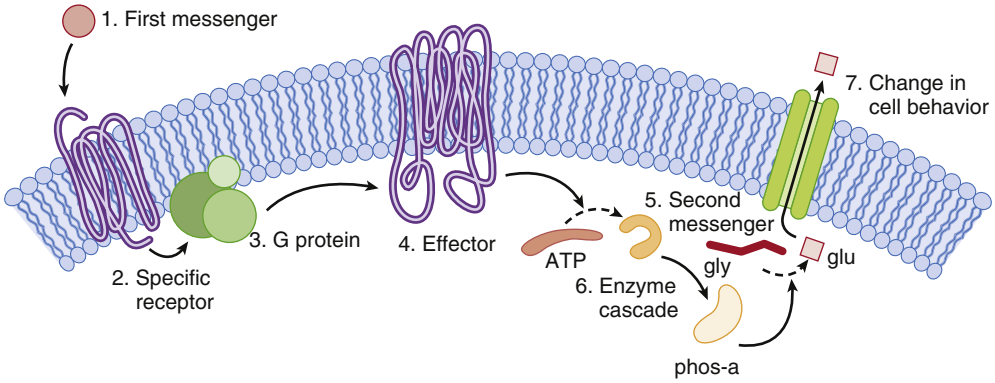


Figure 16-12. Epinephrine-stimulated glycogenolysis in a liver cell demonstrates the role of G proteins in cellular function. The first messenger (epinephrine) binds to its specific receptor and stimulates the G protein (in this case, G_s) to activate the effector adenylyl cyclase. This enzyme converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate, the second messenger, which then triggers a cascade of enzymatic reactions that stimulates the enzyme phosphorylase (phos-a) to convert glycogen (gly) into glucose (glu), which the cell extrudes. *(From Linder ME, Gilman AG: G Proteins,* Sci Am *267:56, 1992.)*

are linked to activation of phospholipase C (α_1), inhibition of adenylyl cyclase (α_2), or stimulation of adenylyl cyclase (β) (see Fig. 16-9). In its resting state, the G protein is bound to guanosine diphosphate (GDP) and is not in contact with the receptor. When the receptor is activated by the first messenger, it stimulates the G protein to release GDP and bind guanosine triphosphate (GTP) to its α subunit, thereby activating itself. The bound GTP signals the G protein to split into two parts consisting of the α-GTP structure and the βγ subunit. The released α subunit binds to the effector, activates it, and then converts its attached GTP to GDP, thereby returning itself to the resting state. The α subunit joins with the βγ unit, and the reconstructed G protein again waits at the inner membrane.

β-Receptor stimulation of G proteins enhances the activity of adenylate cyclase and the formation of cAMP. The briefest encounter of plasma membrane β-adrenergic receptors with epinephrine or norepinephrine results in profound increases (≤400-fold higher than the basal level within minutes) in intracellular levels of cAMP. Increased cAMP synthesis activates protein kinases, which phosphorylate target proteins to elicit various cellular responses that complete the path between receptor and effect. Stimulation of α_2 receptors results in G_i inhibition of adenylate cyclase. The relative abundance of G proteins results in amplification of receptor agonism at the signal transduction step. The number of G-protein molecules greatly exceeds the number of β-adrenergic receptors and adenylate cyclase molecules. The receptor concentration and ultimately adenylate cyclase activity limit the response to catecholamines, and this perhaps explains the efficacy of phosphodiesterase inhibitors.[58,59]

Myocardial cells respond to receptor stimulation differently, depending on the identity of the first messenger. Two opposing effects, inhibition and stimulation of contractility, are both produced by the sequence of receptor → G protein → effector → enzymatic cascade. However, the identity of the chemicals in the sequence differs.[60] Norepinephrine causes myocardial cells to contract with more vigor when the α subunit of the stimulatory protein (G_s) activates adenylate cyclase. The α subunits of this protein cause potassium channels to open and permit efflux of potassium ion. The force of contraction is diminished when acetylcholine acts as a first messenger and stimulates its receptor to activate the inhibitory protein G_i or G_o. Clinically important, second-to-second changes in heart rate can be explained by the simultaneous activation of G_s and G_o. The current caused by G_o is larger than that caused by G_s, and this finding explains the clinical impression that vagal inhibition of heart rate predominates in the presence of sympathetic stimulation, such as may occur in unpremedicated patients.[60]

Up-regulation and Down-regulation

β-Adrenergic receptors are not fixed; they change significantly in dynamic response to the amount of norepinephrine present in the synaptic cleft or in plasma. For β-adrenergic receptors, this response is fast; within 30 minutes of denervation or adrenergic blockade, the number of receptors increases. Such up-regulation may explain why sudden discontinuation of β-adrenergic receptor blocking drugs causes rebound tachycardia and increases the incidence of MI and ischemia. Many chronic phenomena, such as varicose veins[61] or aging, can decrease adrenergic receptor number or responsiveness systemically.

Clinically and at the cellular level, responses to many hormones and neurotransmitters wane rapidly despite continuous exposure to adrenergic agonists.[62] This phenomenon, called desensitization, has been particularly well studied for the stimulation of cAMP levels by plasma membrane β-adrenergic receptors. Mechanisms postulated for desensitization include receptor uncoupling (e.g., phosphorylation), sequestration, and down-regulation. The molecular mechanisms underlying rapid β-adrenergic receptor desensitization do not appear to require internalization of the receptors, but rather an alteration in the functioning of β receptors themselves that uncouples the receptors from the stimulatory G_s protein. Agonist-induced desensitization involves phosphorylation of G-protein–coupled receptors by two classes of serine-threonine kinases. One of these classes initiates receptor-specific or homologous desensitization. The other works through second messenger–dependent kinases and mediates a general cellular hyporesponsiveness called

heterologous desensitization. Ultimately, an inhibitory arrestin protein binds to the phosphorylated receptor and causes desensitization by blocking signal transduction. Because enzymatic phosphorylation occurs only in the activated state, transient β blockade has been used in states of receptor desensitization such as CHF or cardiopulmonary bypass to achieve a "receptor holiday."[63] Regeneration of a functional β-adrenergic receptor is contingent on sequestration of the receptor, with dephosphorylation and presumed recycling. Some evidence indicates that the arrestins contribute to desensitization by uncoupling signal transduction and by contributing to the process of receptor internalization.[64,65] Receptor populations can change rapidly with such sequestration, which does not require protein synthesis.

Down-regulation may be distinguished from these rapid mechanisms in that it occurs after hours of exposure to an agonist (as in chronic stress or CHF), and receptors are destroyed. New receptors must be synthesized before return to a baseline state is possible.

Chronic CHF is one of the most important and best-studied pathophysiologic situations in which tolerance or down-regulation occurs (see Chapter 20). It was initially observed that the density of cardiac β receptors decreases markedly in patients with terminal heart failure in response to the elevated plasma catecholamine levels. This finding explained why administration of exogenous β-agonists was relatively ineffectual in this syndrome. With the demonstration that β_1 and β_2 receptors coexist in human ventricles,[66] Bristow and co-workers, using radioligand techniques, documented that β_1-receptor density decreases without change in the density of β_2 receptors in human ventricles affected by CHF. Consequently, β_2 agonism accounted for 60% of the total inotropic response stimulated by isoproterenol in the failing heart as compared with 40% in a nonfailing heart.[67]

The activity of the thyroid gland influences receptor density; hyperthyroidism increases density, and hypothyroidism decreases density. Clinically, β-receptor blockade is important in the acute treatment of hyperthyroidism. Some evidence indicates that corticosteroids decrease receptor density. Consequently, the reaction of the body to well-characterized sympathetic agonists may be considerably different, depending on the pathologic and environmental circumstances. However, the structural similarity of thyroid hormone and tyrosine suggests that false transmitters may play a role (see Chapters 84 and 85).[68]

CHOLINERGIC PHARMACOLOGY

Acetylcholine Synthesis

Many of our assumptions about cholinergic pharmacology are drawn from our understanding of the prototypical nicotinic cholinergic receptor at the neuromuscular junction. The chemistry of cholinergic synthesis and metabolism is covered in detail in Chapter 18.

Cholinergic Receptors

Traditionally, cholinergic receptors have been organized into two major subdivisions, nicotinic and muscarinic. Muscarinic receptors belong to the G-protein–coupled superfamily and are present mostly in peripheral visceral organs. Nicotinic receptors are ligand-gated ion channels typically found on parasympathetic and sympathetic ganglia (neuronal subtypes) and on the neuromuscular junctions of skeletal muscle (neuronal and muscle subtypes).

Although these two structurally and functionally distinct classes of receptors have significantly different responses to acetylcholine, the chemical itself exhibits no specificity. However, specific antagonists can exploit the difference between muscarinic and nicotinic receptors. As a result, structure-activity relationships have emerged. All cholinergic agonists need a quaternary ammonium group, as well as an atom capable of forming a hydrogen bond through an unshared pair of electrons. The distance between the two sites may determine whether the agonism is nicotinic or muscarinic. With muscarinic agonists, the distance appears to be approximately 4.4Å, whereas for nicotinic agonists, the distance is 5.9Å.

The neuronal and muscle subtypes of nicotinic receptors on ganglia and motor end plates, respectively, differ. Nondepolarizing neuromuscular blocking drugs block neuronal nicotinic acetylcholine receptors present in ganglia, in the carotid body,[69] and at the neuromuscular junction (see Chapter 18),[70] whereas hexamethonium blocks the ganglionic receptors.

Ganglionic nicotinic receptors are likely more sensitive to anesthetics than receptors at the neuromuscular junction.[71]

The nicotinic receptors on ganglia and motor end plates are discussed in detail in Chapter 18. In brief, they are pentameric membrane proteins that form nonselective cation channels. There are two α units (each 40 kDa) and one each of the β, ε, and δ units. These five subunits surround each ion channel through which sodium or calcium enters the cell or potassium exits. Each ion has its own separate channel. For the channel to open, acetylcholine must occupy a receptor site on each of the two α subunits.

In contrast to ligand-gated ion channel nicotinic receptors, muscarinic receptors have greater homology to α- and β-adrenergic receptors than to nicotinic receptors. Like the other members of the family of receptors with seven helices (i.e., α_2, β_1, β_2, serotonin, rhodopsin, and opsin), muscarinic receptors use G proteins for signal transduction. Five muscarinic receptors (i.e., M_1 through M_5) exist, with the primary structural variability residing in a huge cytoplasmic loop between the fifth and sixth membrane-spanning domains. Although molecular studies have described five forms, four of which are defined pharmacologically (i.e., M_1, M_2, M_3, and M_4), selective muscarinic drugs are not available. The M_2 cholinergic postjunctional receptor predominates in visceral organs. M_2 and M_3 receptors have been identified in the airway smooth muscle of many species. In vitro studies reveal that the M_3 receptor mediates the contractile and secretory response. However, the excess of M_2 receptors could explain the relative ineffectiveness of β-adrenergic agonists in reversing cholinergic bronchoconstriction.[72]

The muscarinic receptors have diverse signal transduction mechanisms. The odd-numbered receptors (i.e., M_1, M_3, and M_5) work predominantly through hydrolysis of polyphosphoinositide, whereas the even-numbered receptors work primarily to regulate adenylate cyclase.[73]

When the M_3 muscarinic receptor is activated, G_q activates phospholipase C, which catalyzes the hydrolysis of phosphatidylinositol bisphosphate into diacylglycerol and inositol triphosphate. Receptors in the muscarinic series are coupled to second messenger systems, such as cyclic nucleotides or phosphoinositides. These are coupled to ion channels. In other cases, influx of a cation is the trigger for cellular response. For example, the influx of calcium ions can act as a messenger that reacts with and opens other ion channels. In addition to affecting ion channels, the messenger calcium can stimulate various intracellular proteins to alter cell activity. In cardiac atria, activation of muscarinic receptors leads to the efflux of potassium and hyperpolarization of the cell membrane. This hyperpolarization slows conduction and slows or stops atrial pacemakers. In glands, an influx of calcium or sodium, or both, activates intracellular events and causes the cells to secrete. Similarly, influx of these ions into smooth muscle cells causes them to contract.

Muscarinic receptors are found on central and peripheral neurons; a single neuron may have muscarinic receptors with excitatory as well as inhibitory effects. Prejunctional autoreceptors are not as well studied in the parasympathetic nervous system as in the sympathetic nervous system. Presynaptic muscarinic receptors may inhibit the release of acetylcholine from postganglionic parasympathetic neurons; prejunctional nicotinic receptors may increase its release.

Because of the complex coupling, the response of the muscarinic system is sluggish; no response is seen for seconds to minutes after the application of acetylcholine. Similarly, the effect long outlives the presence of the agonist. Even though the transmitter is destroyed rapidly, the train of events that it initiates causes the cellular response to continue for many minutes. Muscarinic receptors are desensitized through agonist-dependent phosphorylation in a mechanism similar to that described earlier for β-adrenergic receptors.

NONADRENERGIC NONCHOLINERGIC NEUROTRANSMISSION IN THE AUTONOMIC NERVOUS SYSTEM

NANC components such as monoamines, purines, amino acids, and polypeptides are part of the ANS. Other transmitter candidates demonstrated in perivascular nerves by histochemical and immunohistochemical techniques include ATP, adenosine, VIP, substance P, 5-hydroxytryptamine (5-HT), neuropeptide Y (NPY), and calcitonin gene–related peptide (CGRP). Immunocytochemical studies show that more than one transmitter or putative transmitter may be colocalized in the same nerve. The most common combinations of transmitters in perivascular nerves are norepinephrine, ATP, and NPY in sympathetic nerves (Fig. 16-13); acetylcholine and VIP in parasympathetic nerves (Fig. 16-14); and substance P, CGRP, and ATP in sensorimotor nerves. Many of these putative transmitters act through cotransmission, which comprises the synthesis, storage, and release of more than one transmitter by a nerve. Initially, the multiplicity of transmitters released in various combinations appeared random and bewildering, but a pattern is emerging that clarifies the situation. Autonomic nerves exhibit chemical coding—individual neurons serving a specific physiologic function contain distinct combinations of transmitter substances.[74]

The concepts of cotransmission and neuromodulation are accepted mechanisms in autonomic nervous control. To establish that transmitters coexisting in the same nerves act as cotransmitters, each substance must act postjunctionally on its own specific receptor to produce a response.

For many perivascular sympathetic nerves, norepinephrine and ATP act as cotransmitters and are released from the same nerves but act on α_1 adrenoceptors and P_2 purinoceptors, respectively, to produce vasoconstriction (see Fig. 16-13).[75,76] ATP probably mediates contraction

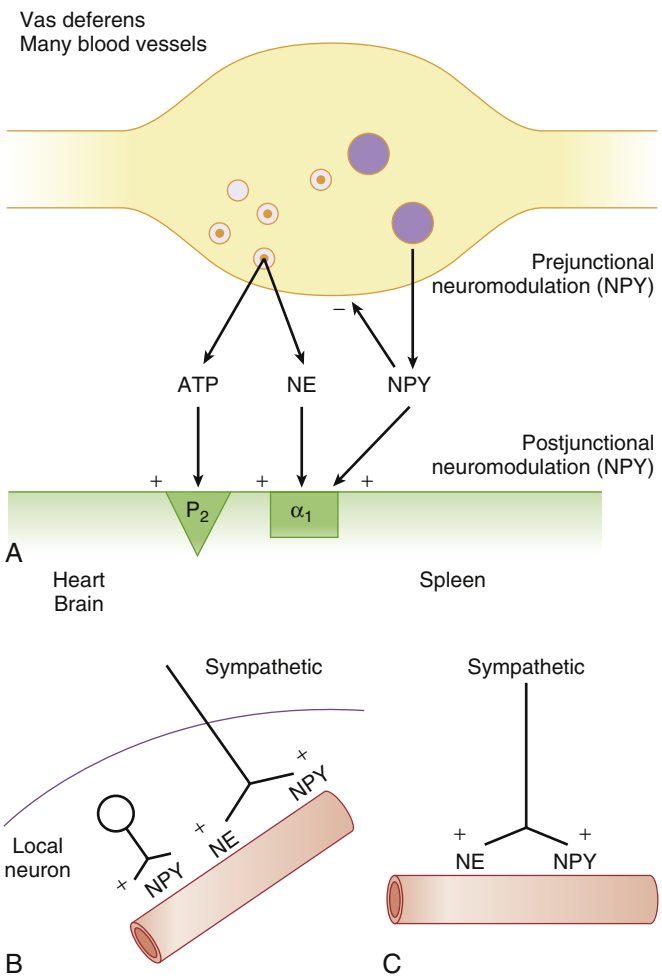


Figure 16-13. Schematic representation of different interactions that occur between neuropeptide Y (NPY) and adenosine triphosphate (ATP) and the norepinephrine (NE) released from single sympathetic nerve varicosities. **A,** Diagram showing what occurs in the vas deferens and many blood vessels, where NE and ATP, probably released from small granular vesicles, act synergistically to contract (+) the smooth muscle through α_1 adrenoceptors and P_2 purinoceptors, respectively. **B** and **C,** Sympathetic neurotransmission in the heart and brain (**B**) and the spleen (**C**). *(From Lincoln J, Burnstock G: Neural-endothelial interactions in control of local blood flow. In Warren J, editor:* The endothelium: an introduction to current research. *New York, 1990, Wiley-Liss, p 21.)*

through P_2 receptors by voltage-dependent calcium channels.[77] The fast component of contraction is mediated by these purinoceptors, whereas norepinephrine sustains contraction of muscle by acting on the α_1 adrenoreceptor through receptor-operated calcium channels. ATP is stored in vesicles along nerve varicosities. It is released into the synaptic cleft by exocytosis and then binds to postsynaptic purinergic receptors. ATP is then degraded to adenosine by membrane-bound ATPases and 5′-nucleotidases. Adenosine is subsequently taken up into the presynaptic neuron, where ATP is resynthesized and incorporated into vesicles for later release.[78]

Purinergic receptors are categorized as P_1 or P_2 receptors. P_1 receptors bind adenosine, whereas P_2 receptors bind ATP. Four subtypes of P_1 receptors have been identified (A_1, A_{2A}, A_{2B}, and A_3). All the P_1 receptors are coupled to membrane-bound G proteins. The two subclasses of P_2 receptors are P2X and P2Y. P2X receptors bind ATP and open ligand-gated ion channels. In contrast, P2Y receptors are coupled to G proteins and their associated secondary messenger systems. Seven P2X subtypes ($P2X_{1\text{-}7}$) and eight P2Y subtypes ($P2Y_{1,2,4,6,11,12,13,14}$) have been identified. Some P2Y receptors are preferentially activated by adenosine diphosphate rather than ATP, and some can be activated by pyrimidine nucleosides (uridine triphosphate), as well as by purinergic agonists.

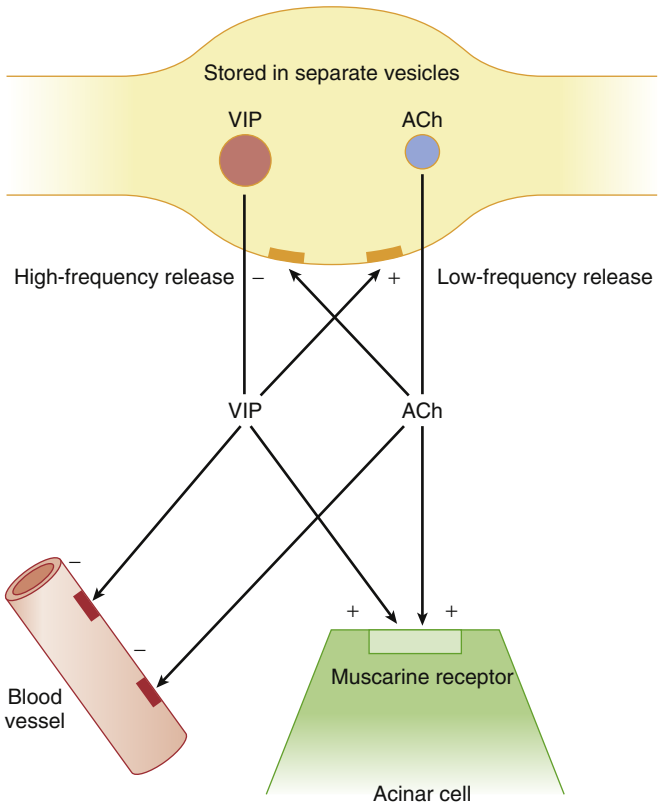


Figure 16-14. The classic transmitter acetylcholine (ACh) coexists with vasoactive intestinal polypeptide (VIP) in parasympathetic nerves supplying the cat salivary gland. ACh and VIP are stored in separate vesicles; they can be released differentially at different stimulation frequencies to act on acinar cells and glandular blood vessels. Cooperation is achieved by the selected release of ACh at low impulse frequencies and VIP at high frequencies. Prejunctional and postjunctional modulation is indicated. *(From Burnstock G: Local mechanisms of blood flow control by perivascular nerves and endothelium,* J Hypertens Suppl *8:S95, 1990.)*

ATP released at nerve endings in the setting of hypertension leads to marked decreases in arterial pressure. ATP bound to magnesium chloride ($MgCl_2$) is a potent pulmonary vasodilator used to treat patients with pulmonary hypertension secondary to congenital heart disease. In addition, it is used to treat postischemic renal injury. Purinergic cotransmission is also seen in the gastrointestinal tract, where ATP (and NO) receptor stimulation inhibits peristalsis.

Neuromodulators modify the process of neurotransmission. They may be circulating neurohormones, local agents, or neurotransmitter substances released from the same nerves or from others nearby. Neuromodulation can occur prejunctionally by decreasing or increasing the amount of transmitter released during transmission or postjunctionally by altering the extent or time course of the neurotransmitter's effect. In all known examples in which prejunctional and postjunctional neuromodulation occurs, these substances act in concert to attenuate or augment effective transmission. The rationale for such effects may reflect the variable geometry of the autonomic neuroeffector junction.[79,80] Unlike the neuromuscular junction, the autonomic neuroeffector junction exists in a dynamic state and manifests only modest postjunctional specialization. Biogenic amines often must traverse wide distances. Given the short half-lives of these chemicals, neuromodulation provides a biologic mechanism for augmentation and prolongation of their action.[81]

NPY is also colocalized with norepinephrine and ATP. However, in some vessels, NPY has little or no direct action; instead, it acts as a neuromodulator prejunctionally to inhibit the release of norepinephrine from the nerve or postjunctionally to enhance the action of norepinephrine (see Fig. 16-13, *A*).[82,83] In other vessels, notably those of the spleen, skeletal muscle, and cerebral and coronary vasculature, NPY has direct vasoconstrictor actions. In the heart and brain, local intrinsic (nonsympathetic) neurons use NPY as the principal transmitter (see Fig. 16-13, *B*). In the spleen, NPY appears to act as a genuine cotransmitter with norepinephrine in perivascular sympathetic nerves (see Fig. 16-13, *C*).[84] The frequency of stimulation determines which vesicles are mobilized to release their transmitters.

A classic transmitter such as acetylcholine coexists with VIP in the parasympathetic nerves of many organs, but in this instance, the two transmitters are stored in separate vesicles. They can be released differentially at different stimulation frequencies, depending on where they are located.[85,86] For example, in the salivary gland, they can act independently on acinar cells and glandular blood vessels (see Fig. 16-14).[76] Cooperation is achieved by the selective release of acetylcholine at low frequencies and VIP at high frequencies of stimulation. Elements of prejunctional and postjunctional modulation have also been described. In many biologic states, including pregnancy[87] (see Chapter 77), hypertension, and aging (see Chapter 80), the relationships among cotransmitters may be an important determinant of a compensatory response to allow finer control of important physiologic function. Additionally, the large number of different receptors may provide targets for potential pharmacologic interventions.

GANGLIONIC PHARMACOLOGY

Ganglia serve far more complex functions than simply being a link between the nerve process of one cell and the cell body of its next connection. Integrative and processing functions contribute to the subtlety of response and organization of the ANS. The electrophysiology of ganglionic stimulation is complex, with at least four different types of responses to electrical stimulation, based on their characteristic excitatory postsynaptic potential (EPSP) or inhibitory postsynaptic potential (IPSP).[88]

The central event at the ganglion is the EPSP when acetylcholine interacts with a neuronal-type nicotinic receptor to depolarize the postsynaptic membrane. Depolarization results primarily from the influx of sodium ions through the nicotinic receptor channel, and it is sensitive to nondepolarizing nicotinic blocking drugs such as hexamethonium. The other changes in electrical potential are related to secondary or subsidiary pathways that augment or suppress; these pathways are insensitive to classic nicotinic antagonists.

Secondary pathways are indicated by the following changes in potential elicited by electrical stimulation of the ganglia: (1) slow EPSP, (2) late slow EPSP, and (3) IPSP.

Autonomic ganglia may be stimulated by two groups of drugs: nicotinic and muscarinic agonists. Nicotinic agonists cause a rapid onset of excitatory effects, mimic the initial EPSP, and are blocked by classic nondepolarizing ganglionic blocking drugs. Muscarinic agonists delay onset of the excitatory effects and are blocked by atropine.

Blockade of ganglionic transmission results primarily from action at the nicotinic receptor to stop or inhibit transmission. Two groups of drugs block ganglionic transmission. The first group is classically represented by nicotine and initially stimulates the receptor but then blocks it. This action is similar to the action of persistent depolarization. The second group does not cause initial stimulation or a change in ganglionic potentials. This group includes the drugs hexamethonium, trimethaphan, and mecamylamine. Trimethaphan acts by competing with acetylcholine at cholinergic receptor sites on the ganglia; hexamethonium blocks the channel when it is open. Either mechanism blocks the initial EPSP and ganglionic transmission.

Muscarinic antagonists and α-agonists are incapable of completely blocking transmission, but they may inhibit normal modulation of the nerve impulse. β-Adrenergic stimulation facilitates nicotinic and muscarinic transmission, whereas α-adrenergic stimulation inhibits it. 5-HT is mostly facilitative, but it can be inhibitory in certain areas. Dopamine may also be inhibitory through stimulation of the IPSP. The adrenal medulla is a specialized ganglionic synapse and is therefore under influences similar to those arising on the autonomic ganglia.

DRUGS AND THE AUTONOMIC NERVOUS SYSTEM

The structure and function of the sympathetic and parasympathetic systems are discussed in the preceding sections. Pharmacologic manipulation of autonomic function is the basis of therapy for many acute and chronic illnesses. The complex physiology allows many points for intervention, including enhancement or inhibition of synthesis, storage, or receptor-mediated activity. In the following sections, specific autonomic drugs of interest to anesthesiologists and the mechanisms by which they work are discussed.

DRUGS AFFECTING ADRENERGIC TRANSMISSION

Endogenous Catecholamines

The endogenous sympathetic transmitters norepinephrine, epinephrine, and dopamine are catecholamines, an important subclass of the sympathomimetic drugs (Fig. 16-15). The parent compound of this sympathomimetic group is β-phenylethylamine, the structure of which includes a benzene ring and an ethylamine side chain. Substitution of hydroxyl groups at the 3 and 4 positions of the benzene ring converts benzene to catechol, and these compounds are known as catecholamines. Although synthetic, isoproterenol and dobutamine are also catecholamines. In addition, noncatecholamine drugs may act as sympathomimetics and have a similar structure.

The catecholamines are primarily metabolized by COMT. The loss of either hydroxyl group enhances oral

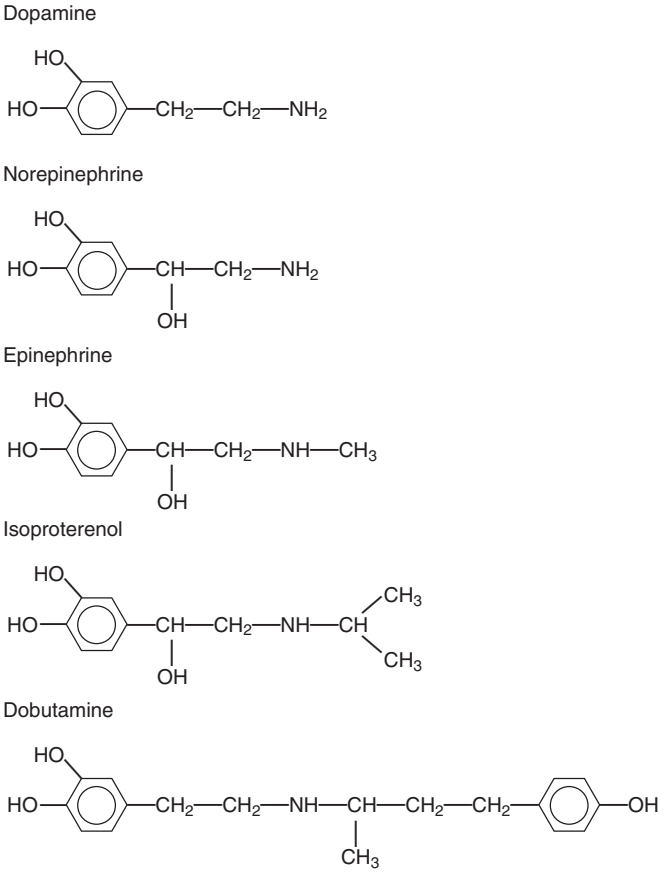


Figure 16-15. Catecholamine structures. A benzene ring with two adjacent hydroxyl groups forms the catechol nucleus.

effectiveness and duration of action because the drug is no longer metabolized by COMT. Noncatecholamine sympathomimetics are primarily metabolized by MAO. The noncatecholamines that have a substituted α-carbon have a longer duration of action because they are not metabolized by COMT or MAO.

Epinephrine. Epinephrine is used intravenously in life-threatening circumstances, including the treatment of cardiac arrest, circulatory collapse, and anaphylaxis, but it is also commonly used locally to limit the spread of local anesthetics or to reduce blood loss. The systemic effects of epinephrine are variable and are related to blood levels. The choice of dosing and the route of administration are determined by the indication for use and its urgency.

Epinephrine activates all adrenergic receptors: α_1, α_2, β_1, β_2, and β_3. Potential therapeutic effects of epinephrine include the following: positive inotropy, chronotropy, and enhanced conduction in the heart (β_1); smooth muscle relaxation in the vasculature and bronchial tree (β_2); and vasoconstriction (α_1). With vasoconstriction, aortic diastolic pressure is increased, thereby promoting coronary flow during cardiac arrest, which may be the single most important determinant of survival.[89] Endocrine and metabolic effects of epinephrine include increased levels of glucose, lactate, and free fatty acids.

Epinephrine may be given intravenously as a bolus or by infusion. The usual bolus doses for pressure support begin at 2 to 8 μg given intravenously; 0.02 mg/kg or approximately 1.0 mg is given for cardiovascular collapse, asystole, ventricular fibrillation, electromechanical dissociation, or anaphylactic shock[90] (see also Chapter 108). The larger dose range is recommended in these critical situations to maintain myocardial and cerebral perfusion through peripheral vasoconstriction. High-dose epinephrine (0.1 to 0.2 mg/kg) has been studied in resuscitation from cardiac arrest; rates of survival in adults are not improved. In pediatric patients, outcome after asystole and pulseless cardiac arrest is abysmal, and the current recommendation is an initial dose of 0.01 mg/kg repeated every 3 to 5 minutes throughout resuscitative attempts[42,91] (see Chapter 95). In unusual circumstances, larger doses may be given, and doses as large as 0.2 mg/kg may be effective.[92] Patients vary tremendously in their response to epinephrine, and given rates of infusion cannot guarantee the expected serum levels in all patients; the "pressors" should therefore be carefully titrated, and measures to monitor renal, cerebral, and myocardial perfusion are more critical than adherence to a rigid dosing scheme (Table 16-7). A rate of 1 to 2 μg/minute, although rarely used, should predominantly activate β_2 receptors, with resulting vascular and bronchial smooth muscle relaxation. A rate of 2 to 10 μg/minute (25 to 120 ng/kg/minute) increases heart rate, contractility, and conduction through the AV node and decreases the refractory period. Doses in excess of 10 μg/minute (100 ng/kg/minute) cause marked α-adrenergic stimulation with resultant generalized vasoconstriction. Epinephrine is a potent renal vasoconstrictor that acts directly by α-receptor stimulation and indirectly by stimulation of renin release. Although low-dose epinephrine increases the heart rate by direct β_1-adrenergic stimulation, reflex bradycardia is seen with higher doses because of the marked elevation in blood pressure resulting from peripheral vasoconstriction.

TABLE 16-7 DOSE-DEPENDENT ACTIONS OF INOTROPES AND CHRONOTROPES

Drug*	Receptors	Usual Infusion Rate
Epinephrine	β_2	1-2 μg/min
	$\beta_1 + \beta_2$	2-10 μg/min
	α_1	≥10 μg/min† (bolus: 2-10 μg; 0.5-1.0 mg‡)
Norepinephrine	α_1, $\beta_1 >> \beta_2$	4-12 μg/min†
Dopamine	Dopaminergic	0-3 μg/kg/min
	β	3-10 μg/kg/min
	α	>10 μg/kg/min†
Dobutamine	$\beta_1 >> \beta_2$, α	2.5-10 μg/kg/min†
Isoproterenol	$\beta_1 > \beta_2$	0.5-10 g/min

Data from Hoffman BB, Lefkowitz RJ: Catecholamines and sympathetic drugs. In Goodman A, Rall T, Nies A, et al, editors: Goodman and Gilman's the pharmacological basis of therapeutics, *ed 8. New York, 1990, Pergamon Press, p 187.*

*All drugs have elimination half-lives of a few minutes except amrinone (half-life, 3.6 hours; 5.8 hours in congestive heart failure).

†Much larger doses have been used in clinical practice.

‡With anaphylaxis or cardiac arrest.

Racemic epinephrine (i.e., mixture of the levorotary and dextrorotary isomers) constricts edematous mucosa and is used for the treatment of severe croup,[93] as well as for postextubation and traumatic airway edema. A 2.25% solution is diluted with water or saline in a 1:8 ratio and is nebulized. Treatments may be given as frequently as every 2 hours, with effects lasting 30 to 60 minutes; the patient should remain under observation for at least 2 hours because initial improvement may be followed by rebound swelling up to 2 hours after administration. Although it is common clinical practice to use the racemic form of epinephrine for these clinical applications, data show that L-epinephrine is 15 to 30 times more potent than the mixture,[94] and it is equally effective and less expensive for treating these clinical complications.[95]

Bronchospasm may also be treated by subcutaneous administration of epinephrine in doses of 300 μg every 20 minutes with a maximum of three doses. In addition to its direct bronchodilatory effects, epinephrine may decrease antigen-induced release of endogenous bronchospastic substances from mast cells and is particularly useful in anaphylactic reactions.[96] Relative contraindications include advanced age, significant tachycardia, hypertension, and coronary occlusive disease. Absorption of subcutaneous epinephrine is extremely slow because of intense local vasoconstriction, and the effect of a very large subcutaneous dose of 0.5 to 1.5 mg is roughly equivalent to an intravenous infusion of 10 to 30 μg/minute. Intravenous injection of epinephrine in a dose appropriate for subcutaneous administration can result in life-threatening ventricular arrhythmias, hypertension, and cerebral hemorrhage. Epinephrine is often applied locally to mucosal surfaces to decrease bleeding at an operative site. It is mixed with local anesthetics for infiltration into tissues or intrathecal injection. The α-mediated

vasoconstriction decreases bleeding in the area and slows vascular uptake of local anesthetic, thereby prolonging the duration of effect and decreasing the peak serum level of the local anesthetic. Although clinicians express concern about the possible systemic effects of such injections, the increases in plasma levels from vascular uptake are relatively modest and are substantially less than levels seen during psychological stress.[97] This conclusion assumes the absence of overt intravenous injection.

Drug interactions with epinephrine are often predictable. Cocaine and other uptake inhibitors enhance the effect and duration of exogenous epinephrine. Preexisting α_1 blockade can cause the paradoxical phenomenon of epinephrine reversal (a hypotensive and tachycardic response) as the β_2-vasodilating effects are unmasked. Patients receiving nonselective β-blockers may demonstrate unopposed α responses. Cardioselective (β_1) blockade does not have this effect.[98]

Halothane (which is still used in some countries) sensitizes the heart to catecholamines and can cause arrhythmias during light levels of anesthesia. Epinephrine decreases the refractory period and thus renders the heart more susceptible to arrhythmias. In adults, the epinephrine dose required to produce three premature ventricular contractions in 50% of patients (ED_{50}) at 1.25 minimum alveolar concentration (MAC) was 2.1 μg/kg for halothane, 6.7 μg/kg for isoflurane, and 10.9 μg/kg for enflurane.[99] Children tolerate larger doses than do adults (see Chapter 93). In addition, children undergoing halothane anesthesia may receive a maximum of 10 to 15 μg/kg of epinephrine subcutaneously every 10 minutes.[92] Hypocapnia potentiates this drug interaction.

Norepinephrine. Norepinephrine differs structurally from epinephrine only in its lack of a methyl group. Like epinephrine, norepinephrine acts at α and β receptors, but it is typically used for its potent α agonism. It is frequently the pressor of last resort in supporting systemic vascular resistance. Because of its short half-life of 2.5 minutes, continuous infusion is preferred. Whereas less than 2 μg/minute (30 ng/kg/minute) may uncover the effects of β_1-adrenergic stimulation, the usual infusion rates of greater than 3 μg/minute (50 ng/kg/minute) elicit peripheral vasoconstriction from α-adrenergic stimulation.

Peripheral vasoconstriction increases arterial blood pressure and may cause reflex bradycardia. Venous return is increased by the powerful venoconstriction. Cardiac output is frequently unchanged or decreased; oxygen consumption is markedly increased. Because pulmonary vascular resistance may be increased, norepinephrine should be used with caution in patients with pulmonary hypertension.[100]

Like epinephrine, norepinephrine is a potent constrictor of the renal and mesenteric vascular beds and can cause renal failure, mesenteric infarction, and peripheral hypoperfusion. The decrease in hepatic flow is of clinical relevance because plasma levels of hepatically metabolized drugs (e.g., lidocaine) are markedly increased. To ameliorate the renal effects, a low-dose dopamine infusion may be added to norepinephrine.[101] Extravasation of norepinephrine can cause tissue necrosis and may be treated by local infiltration of phentolamine. Prolonged infusion has caused gangrene of the digits. The potential for profound vasoconstriction makes careful patient selection and close monitoring mandatory.

Dopamine. Dopamine acts at α-adrenergic, β-adrenergic, and dopaminergic receptors; it also acts to release norepinephrine and therefore has mixed direct and indirect effects. Although dopamine is a precursor of norepinephrine, its most important ANS effect in the periphery may be to cause peripheral vasodilation. Improvement of blood flow through the renal and mesenteric beds in shocklike states is expected through its action at dopamine receptors on the postjunctional membrane. It is rapidly metabolized by MAO and COMT and has a half-life of approximately 1 minute. Like other endogenous catecholamines, dopamine is given as a continuous intravenous infusion without a loading dose. At low doses (0.5 to 2.0 μg/kg/minute), DA_1 receptors are stimulated, and renal and mesenteric vascular beds dilate.[102] In addition to an improvement in renal blood flow, the glomerular filtration rate and sodium excretion increase. With an infusion rate of 2 to 10 μg/kg/minute, β_1 receptors are stimulated, and cardiac contractility and output are increased. Rates higher than 5 μg/kg/minute stimulate the release of endogenous norepinephrine, which contributes to cardiac stimulation. In larger doses (10 to 20 μg/kg/minute), α and β_1 receptors are stimulated, the α-adrenergic vasoconstrictive effect predominates, and the benefit to renal perfusion may be lost.[103]

In the past, dopamine was frequently used for the treatment of shock (especially in vasodilated states such as sepsis). Infusions of dopamine, by increasing renal blood flow, may protect the kidney and aid in diuresis.[104] However, dopamine may not have a beneficial effect on renal function in shock states, and its routine use in these patients is questionable (see Chapters 102 and 107).[105,106]

Dopexamine hydrochloride, an inotropic vasodilator, is a synthetic parenteral dopamine analogue that may be of use in CHF. Dopexamine is approximately 60 times more potent at β_2-adrenergic receptors than dopamine is, one third as potent at DA_1 receptors, and one seventh as potent at DA_2 receptors.[107,108] Unlike dopamine, it shows no α-adrenergic effects and negligible β_1-adrenergic effects and is consequently devoid of vasoconstrictive activity.[107,109] Dopexamine has a reported half-life of 3 to 7 minutes in healthy patients and approximately 11 minutes in patients with low cardiac output.[110] β_2 Agonism produces systemic vasodilation and indirect inotropic activity (through inhibition of neuronal uptake of norepinephrine).[107-109,111,112] Stimulation of dopaminergic receptors produces selective vasodilation of renal and splanchnic vessels and increases the glomerular filtration rate, diuresis, and natriuresis.[108,113-116]

The use of dopexamine is preferable when vascular resistance is high. Within the dose range of 1 to 6 μg/kg/minute, the combined inotropic, vasodilative, diuretic, and natriuretic effects have shown benefit in the management of CHF,[117-120] but an indeterminate outcome in the treatment of septic shock.[119,121-125] Use of this agent has been limited by dose-dependent tachycardia, mainly at doses higher than 4 μg/kg/minute.[126,127] The effects of dopexamine on intestinal mucosal and hepatic perfusion

remain controversial.[128-133] In general, systemic vasodilation is more pronounced with dopexamine, and positive inotropic effects appear more marked with dopamine[134] and dobutamine.[135]

Fenoldopam is a selective DA_1 agonist and potent vasodilator (i.e., six to nine times as potent as dopamine) that enhances natriuresis, diuresis, and renal blood flow.[136-140] Because of its poor bioavailability and varied results in clinical trials, fenoldopam is no longer being investigated as a candidate for the treatment of chronic hypertension or CHF. Instead, intravenous fenoldopam, given by infusion at rates of 0.1 to 0.8 μg/kg/minute with incremental titration at 0.1 μg/kg/minute, has been approved to treat severe hypertension. It is an alternative to sodium nitroprusside, with potentially fewer side effects (i.e., no thiocyanate toxicity, rebound effect, or coronary steal) and improved renal function. The peak effects of fenoldopam occur within 15 minutes.[141,142]

Noncatecholamine Sympathomimetic Amines

The β-agonist isoproterenol and the α-agonists phenylephrine and methoxamine act predominantly at only one type of receptor, but most noncatecholamine sympathomimetic amines act at α and β receptors because they have two mechanisms of action: directly at a receptor and indirectly by releasing endogenous norepinephrine.

Mephentermine, ephedrine, and metaraminol are mixed-acting drugs. Ephedrine increases arterial blood pressure and has a positive inotropic effect. Because uterine blood flow is not decreased, ephedrine is widely used as a pressor in hypotensive parturient patients (see Chapter 77), although more recent evidence suggests that phenylephrine may be as safe or safer in this setting.[143] As a result of its β_1-adrenergic–stimulating effects, ephedrine is helpful in treating moderate hypotension, particularly if accompanied by bradycardia. It also has some direct β_2-adrenergic–stimulating effects and has been used orally as a bronchodilator. The usual dose is 2.5 to 25 mg given intravenously or 25 to 50 mg administered intramuscularly. Mephentermine is similar to ephedrine in its effects, whereas metaraminol has relatively stronger direct α_1-adrenergic–stimulating effects and may be associated with reflex bradycardia.

Tachyphylaxis to the indirect effect may develop through depletion of norepinephrine stores. Although all sympathomimetic amines are capable of producing tolerance or tachyphylaxis, the mechanism has been studied best with metaraminol. Metaraminol is taken up into the sympathetic nerve ending, where it displaces norepinephrine and produces its sympathomimetic effect. However, after some time, the drug acts as a false transmitter, and subsequent sympathetic nerve stimulation results in much less effect. Consequently, metaraminol probably should not be used when other, more effective drugs are available. Its indirect action is attenuated in the presence of long-term reserpine or cocaine use, but it may still be efficacious at larger doses. Although indirect-acting drugs are widely used as a first-line therapy for intraoperative hypotension, epidemiologic studies of adverse reactions under anesthesia suggest that dependence on these agents in life-threatening events may contribute to morbidity if they delay the administration of epinephrine.[144]

α-Receptor Agonists

Phenylephrine and methoxamine are selective α_1-agonists. These drugs are commonly used when peripheral vasoconstriction is needed and cardiac output is adequate, as in the hypotension that may accompany spinal anesthesia, as well as in patients with coronary artery disease or aortic stenosis to increase coronary perfusion pressure without chronotropic side effects. Phenylephrine has a rapid onset and relatively short duration of action (5 to 10 minutes) when given intravenously. It may be given in bolus doses of 40 to 100 μg or by infusion at a starting rate of 10 to 20 μg/minute. Larger doses of up to 1 mg are used to slow supraventricular tachycardia through reflex action. Phenylephrine is also used as a mydriatic and nasal decongestant. In anesthetic practice, it is applied topically, alone or mixed with local anesthetic gel, to prepare the nostril for nasotracheal intubation. It is also added to local anesthetic to prolong subarachnoid blockade. In contrast, methoxamine is a much longer-acting drug (30 to 60 minutes).[145] In larger doses, methoxamine possesses some membrane-stabilizing and β-blocking properties.

α_2-Agonists are assuming greater importance as anesthetic adjuvants and analgesics. Their primary effect is sympatholytic. They reduce peripheral norepinephrine release by stimulation of prejunctional inhibitory α_2 adrenoreceptors. They inhibit central neural transmission in the dorsal horn by presynaptic and postsynaptic mechanisms and also have direct sympatholytic effects on spinal preganglionic sympathetic neurons. Traditionally, they have been used as antihypertensive drugs, but applications based on their sedative, anxiolytic, and analgesic properties are being developed.

Clonidine, the prototypic drug of this class, is a selective partial agonist for α_2 adrenoreceptors, with a ratio of approximately 200:1 (α_2 to α_1). Its antihypertensive effects are caused by central and peripheral attenuation of sympathetic outflow and central activation of nonadrenergic imidazoline-preferring receptors.[146-148] The decrease in central sympathetic outflow reduces activity in peripheral sympathetic neurons without affecting baroreceptor reflexes.[149] Arterial blood pressure is thereby decreased without the accompanying orthostatic hypotension produced by many antihypertensive drugs.[150] Because clonidine is lipid soluble, it penetrates the blood-brain barrier to reach the hypothalamus and medulla, and unlike methyldopa, it does not require transformation into another substance.[151] Clonidine withdrawal may precipitate hypertensive crises, so the drug should be continued throughout the perioperative period or at the least be replaced by close monitoring of arterial blood pressure and ready ability to treat hypertension. The administration of nonselective β-blockers during clonidine withdrawal can worsen hypertension by leaving α_1-receptor–mediated vasoconstriction unopposed. Labetalol can be used to treat this withdrawal syndrome.

Although experience with α_2-agonists as sole anesthetics is limited,[152] these drugs reduce anesthetic requirement and provide a more stable cardiovascular course, presumably because of their sympatholytic effect

and the need for lower doses of cardioactive anesthetics.[153,154] Oral, intravenous, epidural, or intrathecal administration of clonidine potentiates the anesthetic action of other volatile or intravenous anesthetics and reduces general and regional anesthetic requirements with correspondingly fewer side effects.[153,155-162] Additionally, a meta-analysis of the perioperative use of clonidine and the other α_2-agonists dexmedetomidine and mivazerol indicated a decrease in MI and perioperative mortality in patients undergoing vascular surgery (see Chapter 69).[163]

Dexmedetomidine has a 1600:1 preference for α_2 receptors relative to α_1 receptors.[164] This drug was introduced into clinical practice as an adjunct to regional, local, and general anesthetics.[165] Dexmedetomidine has a half-life of 2.3 hours, although its context-specific half-life is less than 5 minutes,[166] thus making its clinical effect short.

In healthy volunteers, dexmedetomidine increases sedation, analgesia, and amnesia and decreases heart rate, cardiac output, and circulating catecholamines in a dose-dependent fashion.[164] The purported MAC-reducing sedative and analgesic effects demonstrated in preclinical and volunteer studies have largely been borne out in clinical practice. Although dexmedetomidine infusions attenuate the hemodynamic lability of induction, maintenance, and emergence, the dose of other anesthetics must be carefully reduced[167,168] because requirements for other anesthetics may decrease. Another use for this drug is to provide sedation for mechanically ventilated patients during weaning from the ventilator (see Chapter 103).[169]

In addition to their use in the operative setting, α_2-agonists provide effective analgesia for acute and chronic pain, particularly as adjuncts to local anesthetics and opioids. The addition of clonidine increases the duration of analgesia and reduces dose requirements for local and narcotic pain medications.[159,170-184] Epidural clonidine is indicated for the treatment of intractable pain; that is, patients unresponsive to maximum doses of oral or epidural opioids may benefit from oral, patch, intramuscular, or neuraxial administration of clonidine,[185-188] as do patients with reflex sympathetic dystrophy[189] and neuropathic pain.[190] The intrinsic analgesic effects of α_2-agonists have been demonstrated with large doses of clonidine alone administered intrathecally (as much as 450 μg) or epidurally (1 to 2 μg/kg/hour) to control intraoperative and postoperative pain. Clonidine decreases postoperative oxygen consumption and the adrenergic stress response.[191,192] Although dose-dependent adverse effects such as hypotension and sedation and idiosyncratic adverse effects such as bradycardia do occur, clonidine seems to have limited effects on respiratory control and only mildly potentiates opiate-induced respiratory depression.[193,194] The impact of α_2-induced sedation on respiratory function combined with the short duration of action of dexmedetomidine led to several reports of the use of dexmedetomidine for awake fiberoptic intubation.[195,196] The authors of these reports emphasize the ability to maintain spontaneous ventilation in the context of adequate sedation for the procedure as the reason for selecting the short-acting α_2-agonist for sedation in patients with difficult or at-risk airways. For similar reasons, dexmedetomidine infusions have been used for the perioperative management of obese patients with obstructive sleep apnea to minimize their narcotic needs while providing adequate analgesia.[197]

Aside from its role as an anesthetic adjuvant and antihypertensive agent, clonidine has been used to treat the following: panic disorder[198]; symptoms of opiate, benzodiazepine, and ethanol withdrawal[199]; cigarette craving after smoking cessation[200]; emesis in cancer chemotherapeutic regimens; and diabetic diarrhea. Experimental data also suggest that α_2-agonists have protective effects against anesthetic neurotoxicity in the developing brain.[201]

Clonidine may increase blood glucose concentrations by inhibiting release of insulin.[202] Unlike spinal opioids, clonidine does not cause urinary retention and may hasten the time to first micturition after spinal anesthesia.[203,204] The breadth of experience with dexmedetomidine is much less than with clonidine. Nevertheless, infusions of the short-acting intravenous α_2-agonist have been used for sedation after extubation at the intensive care unit (ICU),[205] during neurosurgical cases (to facilitate intraoperative wake-ups and to improve signal quality during neuromonitoring)[206] (see Chapters 49 and 70), and as part of a postoperative pain management regimen.[207] Patients in the ICU who are sedated with dexmedetomidine appear to have a lower incidence of delirium and/or coma.[208,209] An important characteristic of dexmedetomidine that makes it an attractive choice in these settings is the "rousable" sedation that it creates (see also Chapter 102). Specifically, patients awaken from apparently deep states of sedation to verbal commands or light tactile stimulation.

β-Receptor Agonists

Nonselective β-Receptor Agonists

Dobutamine. Although at clinical doses it can act at β_2 and α_1 receptors, dobutamine, a synthetic analogue of dopamine, has predominantly β_1-adrenergic effects. When compared with isoproterenol, it is reported to affect inotropy more than chronotropy, but it increases conduction velocity through nodal tissue to the same extent. Dobutamine exerts less of a β_2-type effect than does isoproterenol and less of an α_1-type effect than does norepinephrine. Unlike dopamine, dobutamine does not directly release endogenous norepinephrine, nor does it act at dopaminergic receptors.

Dobutamine may be useful in CHF and MI complicated by a low cardiac output state, although in cases of severe hypotension, it may not be effective because it lacks a significant α_1-pressor effect. It is relatively safe to use in patients with myocardial ischemia without increasing the size of the infarct or causing arrhythmias. Doses lower than 20 μg/kg/minute do not produce tachycardia, but in especially severe CHF, significant tachycardia is the primary adverse effect. Because dobutamine directly stimulates β_1 receptors, it does not rely on norepinephrine stores and may still be effective in catecholamine-depleted states such as chronic CHF. However, in severe chronic CHF, the down-regulation of β-adrenergic receptors may hamper the drug's effectiveness.

The β_2-vasodilating effects of dobutamine are almost exactly offset by its α_1-constricting effects, which can be revealed experimentally by administering a nonselective β-blocking drug. Its modest ability to dilate the

peripheral vasculature is probably more closely connected with its ability to relieve the high-adrenergic state of decompensated CHF than with specific β_2-mediated vasodilation.[210] Clinical situations that call for distinct afterload reduction may be better served by an agent such as nitroprusside.

Prolonged treatment with dobutamine causes downregulation of β receptors; tolerance to its hemodynamic effects is significant after 3 days and may be temporarily offset by increasing the rate of infusion. [211] Intermittent infusions of dobutamine have been used in the long-term treatment of heart failure and have improved exercise tolerance,[212] although not survival.[213]

Isoproterenol. Isoproterenol provides relatively pure nonselective β-adrenergic stimulation with no significant effect at α receptors. Its β_1-adrenergic stimulation is significantly stronger than its β_2 stimulation, but it still causes more β_2-adrenergic activity than does dobutamine. Since the development of other inotropes, the popularity of isoproterenol has declined because of its adverse effects of tachycardia and arrhythmias. Isoproterenol was historically used for bradycardia or heart block resistant to atropine (see Chapter 108). Its primary use at this time is as a chronotropic agent in patients after heart transplantation. These patients are unable to generate an endogenous sympathetic response to challenges because the sympathetic fibers are divided when the native heart is removed. The availability of superior pharmacologic options for most clinical indications has led to removal of isoproterenol from many hospital formularies. Infusion rates start at 0.5 to 5 μg/minute for adults. Because isoproterenol is not taken up into adrenergic nerve endings, its duration of action is slightly longer than that of the natural catecholamines.

Selective β_2-Receptor Agonists. In the past, isoproterenol was used in the treatment of bronchospasm for its β_2-adrenergic–stimulating properties, but unpleasant and dangerous β_1-mediated adverse effects limited its use. The development of β_2-selective agents made β stimulants a cornerstone of the treatment of bronchospasm. However, this β_2 selectivity is only relative, and it may be lost at higher doses; in addition, β_2 receptors in the sinoatrial node may cause tachycardia when stimulated. The structures of these drugs have been modified to slow their metabolism, thereby prolonging their therapeutic benefit and enabling oral administration. In particular, the addition of bulky structures on the catecholamine amino group increases β_2 selectivity, decreases affinity for α receptors, and protects against metabolism by COMT. These drugs are aerosolized and given by inhaler for rapid onset and to minimize systemic drug levels and adverse effects.

An increase in the annual number of deaths from asthma has been well documented, and investigators have suggested that this increase may be related to β_2-agonist use.[214-216] Susceptibility to arrhythmia by direct cardiac stimulation or by β_2-induced hypokalemia is a suggested mechanism of these effects. It has also been hypothesized that long-term use of these drugs may increase airway hyperreactivity. Nonetheless, their safe use in many thousands of patients is well documented.

Commonly used drugs include metaproterenol, terbutaline, and albuterol. Metaproterenol is probably less β_2 selective than albuterol or terbutaline. Terbutaline is the only β_2-selective agent that can be given subcutaneously and may therefore have particular use in status asthmaticus. The normal subcutaneous dose is 0.25 mg, which may be repeated after 15 to 30 minutes.

β_2-Agonists are also used to treat premature labor (see Chapter 77). β_1-Adrenergic adverse effects are common, particularly when the drugs are administered intravenously. As a consequence, their use for the purpose of tocolysis has been questioned.[217]

α-Receptor Antagonists

α_1-Antagonists have long been used clinically as antihypertensives, but they have become less popular over the years. α_1 Blockade vasodilates by blocking the arterial and venous constriction caused by endogenous catecholamines. The effects are potentiated when standing or in the presence of hypovolemia. Reflex tachycardia and fluid retention can ensue.

Phenoxybenzamine is the prototypic α_1-antagonist, although it irreversibly binds to α_1 and α_2 receptors. New receptors must be synthesized before complete offset of its effects occurs. Its half-life after oral administration is unknown, but after an intravenous dose its half-life is approximately 24 hours. Phenoxybenzamine decreases peripheral resistance and increases cardiac output, and blood flow to the skin and viscera is increased. As expected, the primary adverse effect of phenoxybenzamine is orthostatic hypotension; nasal stuffiness may also occur. In addition to receptor blockade, phenoxybenzamine inhibits neuronal and extraneuronal uptake of catecholamines. Phenoxybenzamine is used for the treatment of pheochromocytoma; with extended use, it establishes a "chemical sympathectomy" preoperatively that aids in blood pressure control, permits correction of the contracted plasma volume, and protects against catecholamine-induced cardiac damage. Thus, phenoxybenzamine treatment allows a smoother perioperative course for patients undergoing removal of a pheochromocytoma. When exogenous sympathomimetics are administered after α_1-receptor blockade, their vasoconstrictive effects are inhibited. The effect of phenylephrine is completely blocked, whereas that of norepinephrine is limited to its β_1-adrenergic effect of cardiac stimulation. Epinephrine reversal caused by unopposed β_2 agonism when exogenous epinephrine is given is manifested as severe hypotension and tachycardia. Despite phenoxybenzamine's irreversible binding to the receptor, the recommended treatment of phenoxybenzamine overdosage is norepinephrine infusion because some receptors remain free of the drug.[218]

Phentolamine is a shorter-acting drug that blocks α_1 and α_2 receptors. Historically used to treat pulmonary hypertension, it has largely been supplanted by epoprostenol (prostaglandin I_2). It is also used to treat the hypertension associated with clonidine withdrawal or with tyramine ingestion during MAOI therapy, but few data have been collected on its efficacy and safety for these indications. Phentolamine has also been infiltrated

into affected tissues after extravasation of agents such as norepinephrine in an attempt to relax vasoconstriction; for this purpose, 5 to 10 mg is diluted in 10 mL of saline. Adverse effects of phentolamine include hypotension and gastrointestinal distress; reflex tachycardia and arrhythmias may result from action at α_2 receptors. Coronary artery disease and peptic ulcer disease are relative contraindications to its use. As in phenoxybenzamine overdosage, severe hypotension may require treatment with norepinephrine rather than epinephrine.

Prazosin is a potent selective α_1-adrenergic blocker often used as a prototypic antagonist in pharmacologic experiments. It antagonizes the vasoconstrictor effects of norepinephrine and epinephrine, thereby causing a decline in peripheral vascular resistance and venous return to the heart. Although the heart rate does not normally increase, orthostatic hypotension is a major problem. Unlike other antihypertensive drugs, prazosin improves lipid profiles by lowering low-density lipid levels while raising the level of high-density lipids. It is primarily used to treat hypertension. It has also been used in patients with CHF, but unlike the angiotensin-converting enzyme inhibitors (ACEIs), prazosin does not prolong life. It is metabolized by the liver. Supplied as 1-, 2-, and 5-mg tablets, its starting dose is usually 0.5 to 1 mg given at bedtime because of the orthostatic hypotension. Eventually, it can be taken twice daily.

α_2-Antagonists such as yohimbine increase sympathetic outflow by enhancing release of norepinephrine. These drugs have proved to be of little clinical utility in anesthesia, although they are used in urology.

β-Receptor Antagonists

Pharmacology. β-Adrenergic receptor antagonists (i.e., β-blockers) are among the most commonly prescribed drugs and are frequently taken by patients about to undergo surgery. Current indications for the use of β blockade include ischemic heart disease, postinfarction management, arrhythmias, hypertrophic cardiomyopathy, hypertension, heart failure, and prophylaxis for migraine headache. Concern that patients treated with β-blockers would be hemodynamically unstable under anesthesia has proved to be largely unjustified. These drugs are an important part of the armamentarium of the anesthesiologist in the ongoing attempt to limit stress responses perioperatively and to protect the cardiovascular system. A comprehensive analysis found that the use of β-blockers perioperatively reduces morbidity and mortality in noncardiac surgery for patients at risk.[219] Several well-known clinical trials,[220-224] as well as the widespread use and safety of these drugs in heart failure,[225] have made β blockade an evolving standard (see Chapter 38).

A wide spectrum of β-adrenergic blockers is available to the clinician. The most important properties to consider when choosing a β-blocker for long-term use are cardioselectivity, intrinsic sympathomimetic activity (ISA), and lipid solubility. In anesthetic practice, cardioselectivity, duration of action, and a formulation suitable for intravenous use are crucial factors (Table 16-8). β-Antagonists resemble isoproterenol in structure and bind competitively to the β receptor, thereby blocking access by more potent β-agonists (Fig. 16-16). Competitive inhibition at the β receptor can be overcome by increasing the available concentration of β-agonist. The potency of a β-blocker is often determined by its ability to inhibit induction of tachycardia by isoproterenol. Propranolol is assigned a potency of 1, and the other drugs are evaluated in relation to it.

Nonselective β-adrenergic blockers act at the β_1 and β_2 receptors and include propranolol, nadolol, pindolol, sotalol, oxprenolol, penbutolol, and timolol. Cardioselective β-blockers have stronger affinity for β_1-adrenergic receptors than for β_2-adrenergic receptors, and the predominant effects are therefore cardiac. With β_1-selective blockade, AV conduction velocity, heart rate, and cardiac contractility are decreased, as are release of renin by the juxtaglomerular apparatus and lipolysis at adipocytes. At larger doses, the relative selectivity for β_1-adrenergic receptors is lost and β_2 receptors are also blocked, with

TABLE 16-8 PHARMACOKINETICS AND PHARMACOLOGY OF SELECTED β-ADRENOCEPTOR BLOCKERS

Characteristic	Atenolol	Metoprolol	Propranolol HCl	Labetalol	Esmolol	Carvedilol
Relative β sensitivity	+	+	0	0	+	0
Intrinsic sympathetic activity	0	0	0	+	0	0
Membrane-stabilizing activity	0	0	++	0	0	*
Lipophilicity†	Low	Moderate	High	Low	Low	High
Predominant route of elimination	RE (mostly unchanged)	HM	HM	HM	Hydrolysis by RBC esterase	HM
Drug accumulation in renal disease	Yes	No	No	No	No	No
Elimination half-life (hr)	6-9	3-4	3-4	≈6	9 min	2-8
Usual oral maintenance dose	50-100 mg daily	50-100 mg qid	60 mg qid	100-600 mg bid	N/A	25 mg bid
Usual intravenous dose (caution)		5 mg q5min × 3	0.1 mg/kg (maximum)	1-2 mg/kg	50-300 μg/kg/min infusion	15 mg

HM, Hepatic metabolism; *N/A,* not applicable; *RBC,* red blood cell; *RE,* renal excretion; *0,* no effect; +, mild effect; ++ moderate effect.
*Data not available.
†Determined by the distribution ratio between octanol and water.

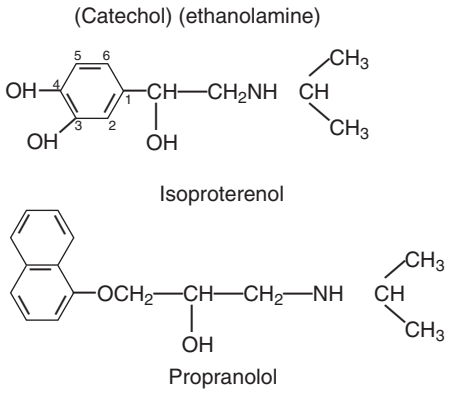


Figure 16-16. Structure of isoproterenol and propranolol. *(From Tollenaeré JP:* Atlas of the three-dimensional structure of drugs. *Amsterdam, 1979, Elsevier North-Holland.)*

the potential for bronchoconstriction, peripheral vasoconstriction, and decreased glycogenolysis.

Cardioselective drugs include atenolol, betaxolol, bevantolol, esmolol, and metoprolol. These drugs may be preferable for patients with obstructive pulmonary disease, peripheral vascular disease, Raynaud phenomenon, and diabetes mellitus. Although previously a matter of controversy, a meta-analysis concluded that cardioselective β-blockers can be given safely to patients with chronic obstructive pulmonary disease.[226] Nevertheless, because the selectivity is only relative and may be lost at conventional clinical doses, extreme care should be taken when administering a β-blocker in the presence of pulmonary disease. Some β-antagonists also have vasodilatory effects, thus making them particularly useful in the treatment of hypertension and CHF.[227,228] Labetalol vasodilates by blocking α_1 receptors and by direct β_2-receptor agonism.

β-Blockers exerting a partial agonist effect at the receptor while blocking access by more potent agonists possess ISA. Drugs with ISA include acebutolol, carteolol, celiprolol, dilevalol, oxprenolol, penbutolol, and pindolol. These drugs primarily decrease arterial blood pressure and, to a lesser extent, heart rate and left ventricular function. When sympathetic activity is high, such as during exercise, these drugs behave more like conventional β-blockers. The partial β_2 agonism of pindolol induces bronchodilation. ISA may therefore be useful if β blockade is required in a patient with bradycardia, peripheral vascular disease, or very mild hyperreactive airway disease. Drugs with ISA may not be as effective in controlling symptoms in severe angina or in reducing mortality after MI.[229] ISA may protect against β-blocker withdrawal syndrome.[230]

Propranolol and acebutolol possess membrane-stabilizing activity (MSA), also referred to as the quinidine-like or local anesthetic effect. This effect reduces the rate of rise in cardiac action potential. The MSA of propranolol may explain the decrease in the oxygen affinity of hemoglobin when the drug is administered. However, MSA is seen only at concentrations 10 times those required for blockade of β receptors and is probably of little clinical consequence. Overdose with drugs that exhibit MSA is associated with a higher incidence of fatality.[231]

Indications for Use

Perioperative β Blockade. In the late 1990s, two important studies established the value of perioperative β blockade in patients at risk for coronary ischemia who were undergoing noncardiac operations (see Chapters 38 and 39). Patients were labeled as "at risk" if they fit into one of two categories: they were undergoing high-risk vascular surgery and had no evidence of inducible coronary ischemia, or they were undergoing a nonvascular procedure but had traditional risk factors for coronary artery disease (older age, high cholesterol, hypertension, cigarette smoking, family history of coronary disease, or diabetes).[232] The Multicenter Study of Perioperative Ischemia Research Group enrolled 200 patients about to undergo surgery who had risk factors for coronary artery disease and randomized these patients to receive placebo or atenolol before and after surgery.[221] The results of the study demonstrated that although no improvement occurred in in-hospital outcomes (cardiac death or MI) in the atenolol-treated group, the treated group did have a lower incidence of cardiac events at the 6- to 8-month follow-up and a marked decrease in all-cause mortality that persisted at 2-year follow-up (survival rate at 2 years: 68% in the placebo group and 83% in the atenolol-treated group). The second study enrolled patients with known ischemic disease demonstrated on preoperative stress echocardiography.[222] The treatment group in this study was given bisoprolol, and the dose was titrated to achieve a heart rate less than the patients' ischemic threshold. The results of this study, whose participants were at much higher risk for ischemic events than were the patients in the previous study, demonstrated a 10-fold decrease in perioperative cardiac death and MI (3.4% versus 34%). These powerful demonstrations that β blockade could decrease perioperative cardiac risk and improve survival out to 2 years led to tremendous political and administrative pressure to increase the use of β-blockers perioperatively.[233] Unfortunately, the value of routine perioperative β blockade is now questionable.

The Perioperative Beta-Blockade (POBBLE) study results showed no reduction in 30-day cardiovascular morbidity in patients undergoing vascular surgery (one of the "at-risk" groups from previous studies).[234] Similarly, the Diabetic Postoperative Mortality and Morbidity (DIPOM) study showed no benefit of β blockade in diabetic patients (another "at-risk" group) undergoing major noncardiac operations.[235] Finally, a large retrospective study looking at in-hospital mortality in more than 780,000 patients demonstrated a neutral or even negative effect of perioperative β blockade in patients without clear-cut coronary artery disease. β Blockade was associated with a reduced mortality rate in only the 3% of patients who had three or more risk factors (based on the revised Cardiac Risk Index) for coronary ischemia.[236] Thus, until larger studies are completed, the only strong indications for initiating β blockade preoperatively are for patients undergoing vascular or intermediate-risk surgical procedures who are at high cardiac risk as a result of multiple risk factors or the finding of ischemia on preoperative testing.[233] These more stringent standards for initiating preoperative β blockade have led to a decrease in the perioperative use of these drugs.[237]

When perioperative β-blocker therapy is initiated, it should be titrated to a non–ischemia-inducing heart rate (usually 60 to 70 beats/minute) and not given as a standard fixed dose to all patients. β-blockers should be continued in patients who are already taking them as treatment for their angina, symptomatic arrhythmia, or hypertension.

The safety of continuing long-term β blockade perioperatively is well established, and initial concerns regarding interaction with general anesthesia have not been confirmed. Attempts to discontinue β-blockers increase the risk for rebound tachycardia (with or without atrial fibrillation) and myocardial ischemia in patients with coronary disease. These drugs should be given up to the time of surgery, and intravenous forms in appropriate dosages should be used whenever gastrointestinal absorption may be in question. If β-blockers have been omitted from the preoperative regimen, esmolol or labetalol may be used acutely to blunt tachycardia and hypertension. Cardioselective and nonselective β-blockers are effective in blocking the chronotropic effects of endotracheal intubation and surgical stress.[238]

Myocardial Ischemia. Propranolol was initially introduced for the treatment of myocardial ischemia in the 1960s, and β-adrenergic blocking drugs remain an important part of drug therapy for myocardial ischemia (see Chapter 39). This class of drugs reduces oxygen demand by decreasing the heart rate and cardiac contractility. Although initially there was concern that β_2-receptor blockade could worsen ischemia through unopposed α-mediated vasoconstriction, this phenomenon is rarely seen, even in patients with variant (Prinzmetal) angina. β-Antagonists are used to treat acute MI and on a long-term basis to reduce reinfarction and mortality in patients after infarction.[239-242] Early administration of intravenous β-blocking agents to patients receiving thrombolytic therapy appears to lower the incidence of ischemia and reinfarction,[243] and it may reduce the incidence of serious ventricular arrhythmias.[244] Long-term use of β-blockers (i.e., timolol, propranolol, metoprolol, and atenolol) has been shown to decrease mortality after MI. In usual clinical practice, the dose is increased until the heart rate is 60 to 80 beats/minute at rest and no tachycardia occurs with exercise.

Congestive Heart Failure. Since the 1990s, β-blockers have become first-line agents for the treatment of CHF of ischemic and nonischemic origin. Clinicians had been disinclined to use β-blockers for heart failure patients because of the drugs' negative inotropic effects. These effects have not turned out to be a significant concern in clinical practice. Early studies demonstrated a significant decrease in all-cause mortality for patients with heart failure who were treated with metoprolol or bisoprolol. Several large studies were stopped because the decrease in mortality in treated patients with moderate to severe heart failure was so pronounced.[245,246] The benefits of β-blockers in patients with heart failure have been attributed to the following: normalization and remodeling of the ventricle, which begin after 1 month of β blockade[247]; reduced norepinephrine-related cardiomyocyte apoptosis in the presence of β_1 blockade[248]; decreased sudden cardiac death because of the β-blockers' antiarrhythmic activity; and, most recently, altered expression of genes in the myocardium that regulate contractility and pathologic hypertrophy.[249] To avoid worsening a patient's heart failure symptoms and to minimize negative inotropic effects, β-blockers are started at very low doses and are titrated to the target dose.[250] If decompensation occurs with the β-blocker, phosphodiesterase inhibitors are the inotropes of choice because their effects are not antagonized by β blockade.[251]

Hypertension. The mechanisms by which β-antagonists treat hypertension are incompletely understood. Arterial blood pressure is specifically decreased in hypertensive patients because long-term treatment of normotensive individuals does not decrease blood pressure. Reduced cardiac output and renin release have been suggested as mechanisms. In hypertensive patients, β-antagonists without ISA may cause a 15% to 20% reduction in cardiac output and a 60% reduction in renin release. However, pindolol, which has ISA and minimal effect on renin, is also successful in treating hypertension.[252] Maximum renin suppression precedes significant changes in arterial blood pressure.[253] Initially, β blockade increases peripheral vascular resistance and then over time lowers it.[254] The decrease in cardiac output and eventual lowering of peripheral resistance may account for much of the antihypertensive efficacy of these drugs. However, this too is an incomplete explanation because labetalol is an effective antihypertensive despite its lack of effect on cardiac output. A primary CNS effect is not likely to be a major mechanism because the antihypertensive efficacy of lipophilic and hydrophilic compounds is similar. Generally, β blockade is ineffective as monotherapy in hypertensive African American patients who are older than 60 years.

Cardiac Arrhythmias. β-Blockers are widely used in the treatment of tachyarrhythmias as class II agents (see Chapters 38, 67, and 68). Two possible mechanisms of action are blockade of catecholamine effects and MSA, although MSA is most likely not clinically significant because antiarrhythmic effects are present in agents without MSA.[255] β-Antagonists slow the rate of depolarization of the sinus node and any ectopic pacemakers, slow conduction through atrial tissue and the AV node, and increase the refractory period of the AV node. These drugs can convert atrial arrhythmias to sinus rhythm,[256] but β blockade is primarily used to slow the ventricular response. Reentrant tachyarrhythmias and those associated with Wolff-Parkinson-White syndrome, mitral valve prolapse, and a prolonged QT interval may also respond to these drugs. Care should be exercised if AV block is present, as in digitalis toxicity, although these drugs are useful in the treatment of digitalis-associated tachyarrhythmias. Sotalol, a β-blocker with added class III activity, is effective against ventricular tachyarrhythmias; however, in a trial comparing racemic sotalol with D-sotalol in post-MI patients, mortality increased with D-sotalol.[257] The trial was terminated when patients at lowest risk for arrhythmic events after MI had an increased mortality rate with this drug.[258]

Tachycardia. β-Antagonists are frequently used as adjuvants to moderate the reflex tachycardia associated with vasodilators (see Chapter 68). In addition to potentiating a reduction in blood pressure, β blockade also reduces the velocity of left ventricular ejection (dP/dt) and attenuates the shearing force associated with the increased velocity

of ventricular contraction when afterload is reduced with nitroprusside without concomitant β blockade.[259] This is important in the management of aortic dissections, in which increased dP/dt can extend the tear. Labetalol has been particularly useful in this situation.[260]

Thyrotoxicosis. Cardiac complications are a primary cause of morbidity in thyrotoxicosis (see Chapter 85). β Blockade can suppress the tachycardia and rhythm disturbances, although very large doses may be required. β-Antagonists also may be combined with digitalis for their synergistic effect on AV node conduction. Propranolol inhibits conversion of thyroxine to the active form triiodothyronine in the periphery.[261]

Miscellaneous Conditions. Timolol and betaxolol are β-blocking drugs used topically in the eye to treat glaucoma. They reduce the production of aqueous humor. Even topical use of these agents has been associated with significant systemic effects of β blockade. β-Blockers are used in patients with idiopathic hypertrophic subaortic stenosis to reduce the dynamic obstruction to left ventricular outflow. These drugs are also effective in the prophylaxis, but not the treatment, of migraine headaches and in controlling acute panic symptoms and essential tremor.

Adverse Effects. The adverse effects of most concern are those involving cardiopulmonary function. Severe noncardiopulmonary reactions such as cutaneous reactions or anaphylaxis are rare. Life-threatening bradycardia, even asystole, may occur, and decreased contractility may precipitate CHF in vulnerable individuals. In patients with bronchospastic lung disease, β_2 blockade may be fatal. CNS effects, although an appropriate consideration with long-term therapy, are not a concern with the usual anesthetic use of β-receptor antagonists. Diabetes mellitus is a relative contraindication to the long-term use of β-antagonists because hypoglycemia in the presence of sympathetic blockade is not accompanied by warning signs such as tachycardia and tremor and because compensatory glycogenolysis is blunted. However, most non–insulin-dependent diabetic patients can tolerate these drugs, although β blockade may cause insulin resistance in rare cases. In addition to the potential worsening of peripheral perfusion by β_2 blockade in patients with peripheral vascular disease, Raynaud phenomenon may be triggered in susceptible patients. Sudden withdrawal of β-blockers may cause myocardial ischemia and possibly infarction, but this is less of a problem with β-blockers that have ISA, such as pindolol.[262] Even though β-antagonists may reduce renal blood flow and the glomerular filtration rate, these agents can be used in renal failure. For such patients, the doses of lipid-insoluble drugs should be reduced. To avoid worsening of hypertension, use in pheochromocytoma should be avoided unless α receptors have previously been blocked. Nonselective agents may elicit hypertensive responses in cases of high sympathetic stimulation.[263]

Undesirable drug interactions are possible with β-blockers. The rate and contractility effects of verapamil are additive to those of β-blockers.[264,265] When combining these drugs, caution should be taken in acute situations such as supraventricular tachycardia. The combination of digoxin and β-blockers can have powerful effects on heart rate and conduction. Pharmacokinetic interactions are predictable from the degree of lipid solubility of the drug. Cimetidine and hydralazine may reduce hepatic perfusion, thereby increasing plasma levels and half-lives of the lipid-soluble β-antagonists. Barbiturates, phenytoin, rifampin, and smoking may induce hepatic enzymes and enhance metabolism. Propranolol may reduce hepatic clearance of lidocaine and increase the risk for toxicity.

Overdose of β-blocking drugs may be treated with atropine, but isoproterenol, dobutamine, or glucagon infusions (or some combination) may be required along with cardiac pacing to ensure an adequate rate of contraction.

Specific Drugs. The drugs propranolol, metoprolol, labetalol, and esmolol are particularly useful in anesthetic practice because they are widely available in intravenous formulations and have well-characterized effects. If the drug that the patient has taken on a long-term basis is propranolol, metoprolol, or labetalol, it may be continued in intravenous form. In deciding which intravenous β-blocker to substitute in a patient taking a β-blocker on a long-term basis, the need for cardioselectivity is a primary consideration. Cardioselectivity is provided by metoprolol or esmolol. If the long-term agent has ISA, oxprenolol and acebutolol have intravenous forms, but they are not readily available. In many situations, esmolol may be substituted and titrated to effect, with the expectation that its effects will fade relatively rapidly if it is not well tolerated.

Propranolol. Propranolol (Inderal, Ipran), the prototypic β-blocker, is a nonselective β-blocking drug with MSA but no ISA. It readily penetrates the CNS. Because of its high lipid solubility, it is extensively metabolized in the liver, but metabolism varies greatly from patient to patient. Its effective dose is extremely variable: 10 mg to as much as 320 mg may be given orally each day. Clearance of the drug can be affected by liver disease or altered hepatic blood flow, which may result in markedly increased plasma concentrations during continuous intravenous administration if the dose regimen is not adjusted. Renal impairment does not require adjustment of dosing. Despite its half-life of 4 hours, its antihypertensive effect persists long enough to permit dosing once or twice daily. Propranolol is available in an intravenous form and was initially given as either a bolus or an infusion. Infusions of propranolol have largely been supplanted by esmolol. For bolus administration, doses of 0.1 mg/kg may be given, although most practitioners initiate therapy with much smaller doses, typically 0.25 to 0.5 mg, and titrate to effect. Propranolol shifts the oxyhemoglobin dissociation curve to the right, an effect that perhaps accounts for its efficacy in vasospastic disorders.[266]

Metoprolol. Metoprolol (Lopressor) is approved for the treatment of angina pectoris and acute MI. It is cardioselective and lacks ISA and MSA. Because it is metabolized in the liver by the monooxygenase system, doses need not be adjusted in the presence of liver failure. The usual oral dose is 100 to 200 mg/day given once or twice daily for hypertension and twice daily for angina pectoris. It may be administered intravenously in doses of 2.5 to 5 mg every 2 to 5 minutes up to 15 mg, with titration to heart rate and blood pressure.

Labetalol. Labetalol is representative of a class of drugs that act as competitive antagonists at the α_1- and

β-adrenergic receptors. Labetalol consists of four isomers that block the α_1, β_1, and β_2 receptors, inhibit neuronal uptake of norepinephrine (uptake-1), act as a partial agonist at β_2 receptors, and possibly have some direct dilating ability. The potency of the mixture for β blockade is 5- to 10-fold that for α blockade. The usual oral dose of labetalol is 200 to 400 mg twice daily, although much larger doses have been used. It is metabolized by the liver, and clearance is affected by hepatic perfusion. The dose need not be adjusted for renal dysfunction. Labetalol may be given intravenously every 5 minutes in 5- to 10-mg doses or up to a 2 mg/minute infusion. It significantly blunts cardiovascular responses to tracheal intubation.[267] This drug can be effective in the treatment of aortic dissection,[259] hypertensive emergencies,[268,269] and postoperative cardiac surgical patients,[270] particularly because vasodilation is not accompanied by tachycardia. It may be used in pregnancy to treat hypertension on a long-term basis and in more urgent situations.[271] Uterine blood flow is not affected, even with a significant reduction in blood pressure (see Chapter 77).[272]

Carvedilol. Carvedilol, a mixed α- and β-antagonist, has been introduced as therapy for mild or moderate hypertension,[273-281] for the management of stable or unstable angina, and after acute MI.[282-286] Clinical trials of carvedilol for the treatment of controlled CHF (New York Heart Association class II to IV) suggest a significant reduction in mortality,[244,245,287,288] especially for patients with diabetes.[289]

Esmolol. Because of its hydrolysis by esterases, esmolol has a uniquely short half-life of 9 to 10 minutes that makes it particularly useful in anesthetic practice. It is administered when β blockade of short duration is desired or in critically ill patients for whom the adverse effects of bradycardia, heart failure, or hypotension may necessitate rapid withdrawal of the drug. The peak effects of a loading dose are seen within 5 to 10 minutes and diminish rapidly (within 20 to 30 minutes). Esmolol is cardioselective and may be given as a bolus of 0.5 mg/kg to blunt cardiovascular responses to tracheal intubation. If it is used as an infusion for the treatment of supraventricular tachycardia, 500 μg/kg is given over a 1-minute period, followed by an infusion of 50 μg/kg/minute for 4 minutes. If the rate is not controlled, a repeat loading dose followed by a 4-minute infusion of 100 μg/kg/minute is given, and this sequence is repeated with the infusion increased in 50 μg/kg/minute increments up to 200 or 300 μg/kg/minute if needed. The effect may persist for 20 to 30 minutes after discontinuation of the infusion. When compared with verapamil, esmolol is more likely to convert atrial fibrillation to sinus rhythm.[255] Esmolol is safe and effective for the treatment of intraoperative and postoperative hypertension and tachycardia.[290-292] If continuous use is required, esmolol may reasonably be replaced by a longer-lasting cardioselective drug such as intravenous metoprolol. Esmolol has been used safely even in patients with compromised left ventricular function.[293,294]

Drugs that Inhibit Synthesis, Storage, or Release of Norepinephrine

Some early antihypertensive drugs acted by replacing norepinephrine in the nerve ending with a much less potent false transmitter. Methyldopa is such a drug and was the most popular nondiuretic antihypertensive used before the development of β-blockers.[219] Like DOPA, methyldopa enters the biosynthetic pathway for norepinephrine (see Fig. 16-7). It is then decarboxylated to α-methylnorepinephrine. Initially, this chemical was thought to act as a false transmitter, but it was found to be almost as potent as norepinephrine. In the CNS, methyldopa may be further metabolized to α-methylepinephrine, and it acts at α_2 receptors to decrease sympathetic outflow, which reduces blood pressure. Because of its sedating qualities, fluid retention, postural hypotension, and occasional reports of hepatic necrosis, methyldopa is now used much less often.

Methylparatyrosine is a potent inhibitor of TH, which catalyzes the formation of DOPA from tyrosine (see Fig. 16-7). Because this is the rate-limiting step in the biosynthesis of norepinephrine, the drug significantly decreases levels of endogenous catecholamines and is useful in treating inoperable or malignant pheochromocytomas.

Reserpine affects the uptake of norepinephrine, not at the neuronal membrane but at the vesicular membrane, thereby inhibiting transport and storage of norepinephrine and dopamine. However, this drug is rarely used in modern medicine.

Guanethidine acts initially by blocking the release of norepinephrine, and then it is taken up into adrenergic nerve endings by the uptake-1 mechanism and depletes norepinephrine stores. This drug is used to treat hypertension, usually after many other drugs have been tried. Its inability to cross the blood-brain barrier accounts for its lack of sedative effects. Guanadrel is similar to guanethidine, but it has a faster onset and shorter duration of action.

Bretylium, a class III antiarrhythmic used parenterally to treat life-threatening ventricular tachyarrhythmias, is now largely of historical interest. Like guanethidine, it is taken up into adrenergic nerve terminals, but its mechanism of action is otherwise quite different. Bretylium initially causes release of norepinephrine and subsequently blocks that release by decreasing sympathetic nerve excitability. Unlike guanethidine, bretylium does not deplete norepinephrine stores. The initial catecholamine release may cause marked hypertension and worsen some arrhythmias, such as those associated with digitalis toxicity and myocardial ischemia.[241] As a consequence, bretylium, which had been part of the advanced cardiac life support protocols for treating ventricular arrhythmias, has been dropped from the algorithms.

MAO and COMT are enzymes important in degradation of the catecholamines. MAOIs bind irreversibly to the enzyme and increase the amine concentration within the presynaptic terminal. Long-term MAOI use is associated with antihypertensive, antidepressant, and antinarcoleptic effects. MAOIs are thought to exert their antihypertensive effect through a false transmitter mechanism. Tyramine is usually oxidatively deaminated in the gut by MAO. With administration of an MAOI, tyramine levels rise. When tyramine is taken up into the sympathetic nerve terminal by the uptake-1 mechanism, it enters the varicosities and is transformed by DβH into octopamine. On its subsequent release in place of norepinephrine, octopamine is only weakly reactive at sympathetic

receptors, thereby resulting in lowering of blood pressure. The MAOIs are no longer used as antihypertensives because many other drugs with better risk-to-benefit profiles have been developed.

MAOIs are primarily used in psychiatric practice. The use of MAOIs as antidepressants is based on the theory that depression is caused by decreased amine in the synapses of the CNS. Inhibition of MAO makes more amine available for release. MAOIs available for the treatment of depression include isocarboxazid, phenelzine sulfate, and tranylcypromine sulfate.

Based on substrate specificity, at least two forms of MAO exist. MAO-A acts on 5-HT, epinephrine, norepinephrine, tyramine, and dopamine, whereas MAO-B is specific for tyramine and dopamine. A specific MAO-B inhibitor, selegiline hydrochloride, has been developed for the treatment of Parkinson disease in the hope that by blocking central dopamine breakdown, more dopamine will be preserved in the affected areas.[295]

Drug and food reactions have been of great concern in patients taking MAOIs. Tyramine-containing foods such as red wine and aged cheese must be avoided by patients taking these drugs. Consumption delivers a huge amount of tyramine to the adrenergic nerve terminal, with subsequent massive release of norepinephrine. This release is manifested clinically as a hypertensive crisis with the potential for MI, cerebral hemorrhage, and death. Any intake of biogenic amine precursors can be expected to increase catecholamine levels greatly, as seen with the concurrent administration of levodopa with MAOIs. The effects of sympathomimetic amines, particularly the indirectly acting drugs, are enhanced. Narcotics, most notably meperidine, have been associated with hyperpyrexic coma and death in patients treated with MAOIs. The depressant effects of agents such as sedatives, alcohol, and general anesthetics are enhanced in these patients. Anesthetic interactions with deprenyl have not been reported, but experience with this drug is limited. Great concern has been expressed that patients receiving long-term therapy with an MAOI risk life-threatening drug interactions during anesthesia. Emergency surgery in patients given an MAOI can be punctuated by marked hemodynamic instability. Severe reactions to narcotics and indirect-acting sympathomimetics, as well as altered metabolism of endogenous and exogenous catecholamines, make these patients potentially difficult to manage. Because of the possibly dangerous interactions of many drugs with MAOIs, controversy exists about the best way to anesthetize these patients.[296,297] The level of concern expressed over the years may be excessive. Although prudence and custom dictate discontinuation of MAOIs at least 2 weeks in advance of elective procedures, there appear to be rational anesthetic choices based on pharmacology and risk-to-benefit considerations for patients to continue their MAOIs when surgery cannot be delayed or no effective alternative psychiatric medications are available.

DRUGS AFFECTING THE RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system maintains blood pressure and fluid balance. The major end product of the system, angiotensin II, is a potent vasoconstrictor that also stimulates release of aldosterone from the adrenal cortex, which causes salt and water retention by the kidney. The juxtaglomerular cells of the renal cortex secrete the proteolytic enzyme renin, which cleaves angiotensinogen, a protein synthesized in the liver, and produces the decapeptide angiotensin I. Angiotensin I is converted almost immediately to angiotensin II by angiotensin-converting enzyme (ACE). This converting enzyme is located predominantly in the endothelial tissue of the lung. In addition to its direct vasoconstrictive activity, angiotensin II enhances the prejunctional release of norepinephrine from adrenergic nerve endings and increases efferent sympathetic nerve activity. Angiotensin II also affects sodium and water homeostasis by directly decreasing tubular reabsorption of sodium, increasing antidiuretic and adrenocorticotropic hormone secretion, and stimulating the secretion of aldosterone. ACE is also a kinase that degrades the vasodilator bradykinin. ACE inhibition blocks angiotensin II formation and delays the breakdown of bradykinin, along with effects on associated prostaglandins.[298]

Although only a few hypertensive patients have high circulating plasma renin levels, 70% of patients will respond to the antihypertensive effects of ACEIs. In patients who have elevated plasma renin levels (e.g., patients with CHF or salt depletion states), ACEI therapy must be initiated at lower doses because these patients are extremely sensitive to the effects of ACEIs, and significant hypotension can follow the administration of a standard starting dose of these drugs.[219]

ACEIs have proved useful in the treatment of hypertension and CHF and have decreased mortality after MI.[299] Captopril was the first active oral agent available, followed by enalapril and lisinopril. ACEIs affect the renin-angiotensin-aldosterone system by inhibiting ACE activity.[300,301] Enalapril is the only ACEI available as an intravenous preparation at this time. Lisinopril offers once-daily dosing, which is convenient for long-term use, but the drug can lead to troublesome hypotension if it is not held on the day of surgery and significant intraoperative blood loss occurs.

All the ACEIs are approved for the treatment of hypertension. Captopril, enalapril, ramipril, and trandolapril all decrease morbidity and mortality in patients with CHF. Captopril is associated with more frequent adverse effects than the other agents, may have a few more drug interactions, and has a dosing regimen of two or three times daily, in contrast to the other ACEIs, which have a dosing regimen of once or twice daily.

Some adverse effects observed with ACEIs are common to the entire class, such as cough, angioedema, acute renal failure, and hyperkalemia. Angioedema, especially after the first dose, affects the face, extremities, lips, mucous membranes, tongue, glottis, or larynx.[302,303] Some occurrences may be fatal.[298,304] Rash and taste disturbances are more frequent with captopril than with the other ACEIs. Because impairment of renal function with an ACEI is usually reversible after withdrawal of the drug, renal function must be monitored, and because hyperkalemia may result from inhibition of aldosterone secretion, serum potassium levels should be monitored. ACEIs can cause fetal morbidity and mortality in humans.

These agents should not be used at all during the second or third trimester of pregnancy.[300] The adverse effect profile of the ACEIs led to the development of angiotensin II receptor blockers (ARBs). Losartan was the first of this newer class of antihypertensive agents, which now includes six other ARBs. Initial trials did not demonstrate ARBs to be superior to ACEIs; however, the addition of these agents during long-term ACEI therapy reduced all-cause mortality and hospitalization in patients with heart failure.[305]

CHOLINERGIC DRUGS

Overview of Mechanisms of Action

Cholinergic drugs act by mimicking, amplifying, or inhibiting the effects of acetylcholine. Cholinergic drugs do not behave exactly like acetylcholine. Their drug action is more specific, with fewer sites affected than with acetylcholine, and their duration of action is generally longer than that of acetylcholine.

Unlike adrenergic pharmacology, in which the clinician can select from a wide choice of drugs, relatively few drugs influence parasympathetic function. In general, drugs that affect the parasympathetic system act in one of four ways:

1. As an agonist by stimulating cholinergic receptors
2. As an antagonist by blocking or inhibiting the actions mediated by the cholinergic receptor
3. By blocking or stimulating receptors on autonomic ganglia
4. By inhibiting the enzymatic breakdown of acetylcholine and thereby causing an increased and prolonged effect

No effective clinically used drugs act through mechanisms affecting the synthesis of acetylcholine (by inhibiting choline acetyltransferase) or by causing indirect release of acetylcholine. Hemicholinium, which interferes with choline uptake and could deplete acetylcholine stores, is not used clinically. Adenosine may inhibit the release of acetylcholine by decreasing the affinity of binding sites for calcium ions; aminoglycoside antibiotics compete with calcium for membrane calcium channels, as does magnesium. Exocytotic release of acetylcholine is inhibited by botulinum toxin. This toxin is sometimes given by local injection to treat strabismus and blepharospasm and has also been used for trigger point injections in pain clinics and to treat age lines. The popularity of off-label uses of this toxin increases the chance of botulism poisoning. In a full-blown botulism poisoning syndrome, fatalities may result from muscle weakness and respiratory failure.

Cholinergic Agonists

Cholinergic agonists have limited therapeutic use because of their detrimental effects. As a result of its diffuse, nonselective actions and rapid hydrolysis by acetylcholinesterase and butyrylcholinesterase, acetylcholine has had almost no therapeutic use other than as an intraocular medication for transient constriction of the pupil during ophthalmic surgery.

Cholinergic agonists in clinical use have been derived from acetylcholine, but they resist hydrolysis by cholinesterase, which permits a useful duration of action. The different systemic effects of the cholinergic agonists are more quantitative than qualitative, although some limited organ selectivity is useful therapeutically, as seen with the synthetic choline esters bethanechol and carbachol. Methacholine and bethanechol are primarily muscarinic agonists; carbachol has significant nicotinic and muscarinic effects. Adding a methyl group to the β position of the choline in acetylcholine produces methacholine, which is almost purely muscarinic and nearly totally resistant to hydrolysis by either of the cholinesterases. An intravenous infusion of methacholine causes hypotension and bradycardia; a small subcutaneous dose causes transient hypotension with a reflex increase in heart rate. The sole current use of methacholine is as a provocative agent in diagnosing hyperreactive airways, thereby making positive use of the deleterious bronchoconstrictive effect of muscarinic agonists. It is administered only by inhalation; serious adverse effects include gastrointestinal symptoms, chest pain, hypotension, loss of consciousness, and complete heart block when the drug is given orally or parenterally. An excessive bronchoconstrictive response should be treated by an inhaled β-agonist; coexisting β blockade is considered a contraindication to the use of methacholine.

The carbamate derivative of methacholine, bethanechol, is occasionally used postoperatively to reinstitute peristaltic activity in the gut or to force the extrusion of urine from an atonic bladder. Bethanechol shows preferential activity at intestinal and urinary receptors relative to cardiac sites, so stimulation of the gastrointestinal tract and bladder is achieved with minimal cardiovascular effects. Bethanechol is usually given orally, but if gastrointestinal function is not adequate to permit absorption of an oral dose, the drug can be given subcutaneously as well.

Carbachol is used topically or intraocularly to constrict the pupil for the long-term treatment of wide-angle glaucoma. When used topically, this drug is often better tolerated than the ophthalmic anticholinesterase agents, and it may be effective in patients resistant to pilocarpine and physostigmine. The rapid pupillary constriction is caused by the combination of ganglionic blockade and muscarinic effects. Another natural alkaloid, pilocarpine, was used to treat glaucoma until the advent of more modern drugs.

Muscarinic Antagonists

Muscarinic antagonists are the active ingredients in some common plants used since antiquity for medicinal and poisonous effects. Despite their age, muscarinic antagonists still represent important drugs in anesthesia and critical care.

Muscarinic antagonists compete with neurally released acetylcholine for access to muscarinic cholinoceptors and block its effects. They also antagonize the actions of muscarinic agonists at noninnervated, muscarinic cholinoceptors. Presynaptic muscarinic receptors on the adrenergic nerve terminal may inhibit release of norepinephrine, and muscarinic antagonists may enhance sympathetic activity. With the exception of quaternary ammonium compounds that do not readily cross the blood-brain barrier and have few CNS actions, no significant specificity of

TABLE 16-9 MUSCARINIC ANTICHOLINERGIC DRUGS

Drug	Duration	Central Nervous System*	Antisialagogue	Heart Rate
Atropine	Short	Stimulation	+	++
Glycopyrrolate	Long	0	++	+
Scopolamine	Short	Sedation	++	0/+

0, No effect; +, mild effect; ++, moderate effect.
* The effects of atropine are limited with the usual clinical doses, but they can be significant in older patients.

action exists among these drugs; they block all muscarinic effects with equal efficacy, although some quantitative differences in effect may be seen (Table 16-9). Research has revealed several subtypes of muscarinic receptors, and agonists and antagonists have been synthesized that bind preferentially to one or another of these subtypes. Pirenzepine preferentially blocks the M_1 receptor, tripitramine shows highest affinity for the M_2 receptor, and darifenacin binds preferentially to the M_3 receptor. The distinctive pharmacology of the various antimuscarinic agents has played a major role in the development of new treatments of overactive bladder disorders. Oxybutynin, tolterodine, darifenacin, solifenacin, and trospium have all been developed to optimize the relief of bladder symptoms while minimizing effects on muscarinic receptors outside the bladder.

Historically, muscarinic antagonists were used to treat peptic ulcer disease, various forms of spastic bowel syndrome, upper respiratory illness, and asthma. However, with the availability of specific histamine (H_2)–blocking drugs and proton pump inhibitors to treat peptic ulcer disease, these uses have markedly decreased. Atropine, once used to treat bronchospasm, was displaced with the introduction of β_2-agonist drugs that did not dry secretions or diminish ciliary motility. Topical use of atropine analogues in ophthalmologic practice to dilate the pupil is still common.

The addition of a muscarinic anticholinergic drug to anesthetic premedication for decreasing secretions and preventing harmful vagal reflexes was mandatory in the era of ether anesthesia, but it is less important with modern inhaled agents. Routine preoperative use of these drugs as antisialagogues continues in some pediatric and otorhinolaryngologic cases or when fiberoptic intubation is planned.

Atropine has a tertiary structure that easily crosses the blood-brain barrier (Fig. 16-17). CNS effects have been seen with the relatively large doses (1 to 2 mg) given to block the adverse muscarinic effects of the anticholinesterase drugs that reverse neuromuscular blockade (see Chapter 35). In contrast, one of the synthetic antimuscarinic drugs, glycopyrrolate, does not cross the blood-brain barrier because of its quaternary structure and has gained popularity for this use. Glycopyrrolate has a longer duration of action than does atropine.

Scopolamine, which resembles the others of this class in peripheral actions, has pronounced CNS effects. It is the active ingredient in most over-the-counter preparations sold as soporifics, and it is effective in preventing motion

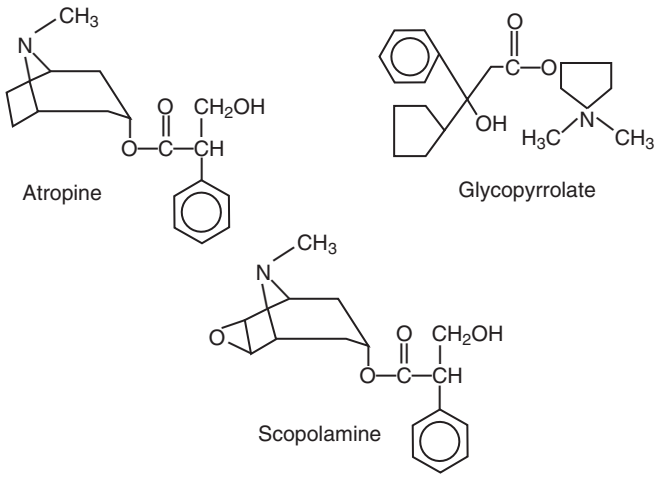


Figure 16-17. Structural formulas of clinically useful antimuscarinic drugs.

sickness. The patch preparation of scopolamine can be used prophylactically for motion sickness and for postoperative nausea and vomiting, but like the oral and parenteral forms, it may be associated with adverse eye, bladder, skin, and cognitive and psychological effects.[306,307]

The development of ipratropium reestablished antimuscarinic drugs for the treatment of asthma and bronchospastic disorders.[308] Although ipratropium is structurally similar to atropine and has essentially the same effects when administered parenterally, an important difference is that ipratropium is a quaternary ammonium compound. It is very poorly absorbed when inhaled and has few extrapulmonary effects, even in extremely large doses by this route. Ninety percent of the inhaled drug is swallowed, but only 1% of the total dose is absorbed systemically.

When administered to normal volunteers, ipratropium provides almost complete protection against bronchospasm induced by a variety of provocative agents. However, in asthmatic patients, results vary. The bronchospastic effects of some agents, such as methacholine or sulfur dioxide, are completely blocked, whereas ipratropium has little effect on leukotriene-induced bronchoconstriction. The onset of bronchodilation is slow, and the maximum effect is less than that seen with β-agonists. Unlike atropine, ipratropium has no negative effect on ciliary clearance. In general, the therapeutic effect of antimuscarinics, including ipratropium, is greater in patients with chronic obstructive pulmonary disease than in asthmatic patients.[305] Ipratropium is supplied as a metered-dose inhaler that dispenses 18 μg per puff. Two puffs are taken orally four times each day. Maximum bronchodilation occurs in 30 to 90 minutes and may last 4 hours.

The toxic effects of muscarinic antagonists come from the blockade of muscarinic cholinoceptors in the periphery and the CNS. The peripheral effects (e.g., dry mouth) may be irritating but are not life-threatening in healthy adults. However, children depend more than adults on sweating for thermoregulation and can become dangerously hyperthermic when they are given these agents. Moreover, older individuals may not be able to

tolerate the cardiac, ocular, or urinary effects of muscarinic blockade.

Increasing doses of atropine or scopolamine cause greater distortions of mentation that progress from thought disorders to hallucinations, delusions, delirium, and severe psychoses. These effects are reversible, but the mental dysfunction can persist for weeks. Small doses of atropine (0.05 mg) can evoke bradycardia, a finding that has led some clinicians to increase the dose in children. It was thought that a CNS effect of atropine could be responsible, but the time course and the fact that bradycardia occurred in animals without vagal function cast doubt on this explanation. Whether this paradoxical bradycardia is a central or peripheral effect, or both, and the role of muscarinic subtypes are still subjects of debate.[309]

Atropine or scopolamine toxicity (the central anticholinergic syndrome) has been treated for decades with the naturally occurring alkaloid physostigmine, which is an anticholinesterase that penetrates the blood-brain barrier. Use of this drug in doses of 1 to 2 mg given intravenously to treat the postoperative CNS effects of intravenous atropine or scopolamine has been successful. Physostigmine may also reverse the CNS effects of other compounds with anticholinergic activity, including the tricyclic antidepressants, several major tranquilizers, and antihistamine drugs. Physostigmine may also antagonize the sedative effects of the benzodiazepines, but a specific benzodiazepine antagonist, flumazenil, has supplanted physostigmine for this use.[310] Physostigmine must be administered with care because of its potentially lethal nicotinic effects, which are not prevented by the muscarinic antagonists, and because its half-life rarely matches that of the intoxicant.

Cholinesterase Inhibitors

Anticholinesterase drugs are a common means of producing sustained, systemic cholinergic agonism. These drugs are used to reverse neuromuscular blockade and to treat myasthenia gravis and certain tachyarrhythmias.

Three chemical classes of compounds are used as cholinesterase inhibitors: carbamates, organophosphates, and quaternary ammonium alcohols. Physostigmine, neostigmine, and pyridostigmine are carbamates, whereas edrophonium is a quaternary ammonium alcohol. The cholinesterase enzyme is inhibited as long as the esteratic site is bound to an acetate, carbamate, or phosphate. Carbamate and phosphate bonds are much more resistant to attack by hydroxyl groups than are acetate bonds. The acetylated form lasts for only microseconds, whereas the carbamylated form lasts for 15 to 20 minutes. Organophosphates include diisopropyl fluorophosphate, parathion, malathion, soman, sarin, VX, and a variety of other compounds used as insecticides. Although the toxicity of the organophosphate insecticides is primarily related to their anticholinesterase activity, the mechanism of this effect is different from the clinically used anticholinesterase drugs (see Chapter 83). The organophosphates produce irreversible enzyme inhibition and have CNS effects. Consequently, treatment of organophosphate insecticide poisoning relies on chemical compounds capable of displacing the insecticides from the enzyme to reactivate the cholinesterase activity. The best documented of these chemicals is pralidoxime (2-PAM). Physostigmine and most of the organophosphates are not quaternary ammonium compounds and have major effects on cholinergic functions in the CNS (see Chapter 83).

Because these compounds can increase the effect and duration of neurally released acetylcholine, they are useful in situations in which such release is deficient, such as myasthenia gravis. Anticholinesterase drugs are occasionally used to stimulate intestinal function and are applied topically in the eye as a miotic. An irreversible organophosphate anticholinesterase that is used clinically is echothiophate iodide, which is available as topical drops for the treatment of glaucoma. Its major advantage over other topical agents is its prolonged duration of action. Because this chemical also inactivates plasma cholinesterase, it may prolong the action of succinylcholine. Although prudence dictates discontinuation of echothiophate for 1 week before surgery, numerous case reports exist of successful anesthesia performed under emergency conditions and without discontinuation of echothiophate.

GANGLIONIC DRUGS

Ganglionic Agonists

Ganglionic agonists are essential for analyzing the mechanism of ganglionic function, but they have no therapeutic use. Nicotine is the classic ganglionic agonist, and its effects have been well described.

Parasympathetic drugs stimulate ganglia, but this action is usually masked by the other parasympathomimetic effects of these drugs. Experimentally, relatively large doses of acetylcholine administered intravenously after blockade of muscarinic receptors by atropine cause ganglionic stimulation and release of epinephrine by the adrenal medulla.

Ganglionic Antagonists

Ganglionic antagonists were the first effective therapy for the management of hypertension and were used extensively during the 1950s and 1960s. However, because of interference with transmission through sympathetic and parasympathetic ganglia, their antihypertensive action was accompanied by numerous undesirable effects. Hexamethonium, the prototypic drug of this class, has minimal neuromuscular and muscarinic activity. The systemic effects of ganglionic blockade are determined by the resting tone of a specific body system before the initiation of ganglionic blockade (see Table 16-2). With the disappearance of trimethaphan from clinical use, these drugs are largely of historical interest.

AUTONOMIC DYSFUNCTION

ASSESSMENT OF AUTONOMIC FUNCTION

The increased operative risk for patients with autonomic dysfunction that may occur with aging and diabetes[311] makes the diagnosis of autonomic neuropathy extremely important. A panel of five tests of cardiovascular function was developed to evaluate autonomic function in

diabetic patients (see Chapter 39).[312] The tests include heart rate responses to the Valsalva maneuver, standing up, and deep breathing and blood pressure responses to standing up and sustained handgrip. The tests involving changes in heart rate measure injury to the parasympathetic system, which precedes changes in the measures of blood pressure that reflect sympathetic injury. *Early autonomic dysfunction* is defined as a single abnormal or two borderline-abnormal results on the tests involving changes in heart rate. *Definite involvement* is diagnosed when the results are abnormal on two of the tests of changes in heart rate. *Severe dysfunction* is defined as abnormality in blood pressure assessments. Application of these standards requires that the investigator understand the proper techniques for performing the five tests and the expected results in patients without autonomic neuropathy (Table 16-10). The simplicity and effectiveness of this clinical assessment led to its use in the evaluation of patients with nondiabetic causes of autonomic dysfunction as well. The validity of the tests in the "nonstandardized" setting of a preoperative clinic was also demonstrated, a finding suggesting that the tests can be used in preoperative screening for surgical patients at risk for autonomic dysfunction.[313]

TABLE 16-10 **NONINVASIVE TESTS FOR ASSESSING THE AUTONOMIC NERVOUS SYSTEM**

Clinical Examination	Technique	Normal Value
Parasympathetic		
HR response to a Valsalva maneuver	The seated subject blows into a mouthpiece (while maintaining a pressure of 40 mm Hg) for 15 sec; the Valsalva ratio is the ratio of the longest R-R interval (which comes shortly after release) to the shortest R-R interval (which occurs during the maneuver)	Ratio of >1.21
HR response to standing	HR is measured as the subject moves from a resting supine position to standing; a normal tachycardic response is maximal around the fifteenth beat after rising; a relative bradycardia follows that is most marked around the thirtieth beat after standing; the response to standing is expressed as a 30:15 ratio and is the ratio of the longest R-R interval around the thirtieth beat to the shortest R-R interval around the fifteenth beat	Ratio of >1.04
HR response to deep breathing	The subject takes six deep breaths in 1 min; the maximum and minimum heart rates during each cycle are measured, and the mean of the differences (maximum HR – minimum HR) during three successive breathing cycles is taken as the maximum-minimum HR	Mean difference >15 beats/min
Sympathetic		
BP response to standing	The subject moves from resting supine to standing, and standing SBP is subtracted from supine SBP	Difference <10 mm Hg
BP response to sustained handgrip	The subject maintains a handgrip of 30% of the maximum handgrip squeeze for up to 5 min; BP is measured every minute, and the initial DBP is subtracted from the DBP just before release	Difference >16 mm Hg

BP, Blood pressure; *DBP,* diastolic blood pressure; *HR,* heart rate; *SBP,* systolic blood pressure.

PLASMA CATECHOLAMINES

Accurate and sensitive techniques for measuring plasma catecholamines have existed since the 1970s, but interpretation of the data that they yield has been controversial. Normal plasma epinephrine and norepinephrine levels are typically in the range of 100 to 400 pg/mL, and they can increase sixfold or more with stress.

Plasma concentrations of epinephrine, which reflect adrenal medullary activity if not overall sympathetic activity, are labile. Significant isolated adrenal medullary secretion results from certain stressful situations, such as public speaking.[5] Moreover, venous samples may reflect epinephrine kinetics in the organ being sampled rather than in the whole body, so arterial samples may be more reliable.

The significance of the norepinephrine concentration in plasma is even more controversial. Even though the adrenal medulla secretes some norepinephrine, levels in plasma generally reflect spillover from sympathetic stimulation that was not taken up again by the nerve terminal. Although reuptake may be tissue specific and markedly influenced by alterations in physiology or diseases, spillover in humans is 10% to 20% of the synthesis rate of norepinephrine at baseline and may be greatly enhanced in periods of sympathetic activation.[314] The most compelling argument for the use of plasma norepinephrine as a marker of sympathetic activity comes from animal studies in which plasma norepinephrine levels directly mirrored nerve stimulation. Many important studies correlated increases in plasma catecholamines with acute and chronic stress, which led to the concept of stress-free anesthesia. A striking relationship between mortality rates for patients with CHF and elevated plasma norepinephrine levels resulted in the use of β-adrenergic antagonists to treat ventricular dysfunction.[315,316]

The development of experimental radiotracer techniques to assess the in vivo kinetics of catecholamines provided additional information that is of clinical importance, particularly in relation to regional kinetics. For example, studies relying only on arterial and venous catecholamines suggested that the hepatomesenteric bed contributes significantly to total-body clearance of catecholamines but only minimally (<8%) to spillover. However, later studies of regional norepinephrine kinetics demonstrated that release of norepinephrine from the gut (≤25% of the total body) was largely obscured by efficient

extraction (>80%) in the liver. Similarly, selective elevations in release of norepinephrine from the heart, which may be associated with ischemia, early onset of CHF, and tachyarrhythmias, may not be apparent in measured arterial or venous levels.[317] Observations involving regional spillover led to the realization that although stress may activate a generalized sympathetic response, there may be different patterns contingent on the stimulus. It is possible that the lack of consistency of plasma norepinephrine levels in the presence of clinically significant sympathetic activation may be a function of the measurement technique or the particular stressor.

On balance, given the effects of age, posture, and hydration, small changes in plasma catecholamine levels correlate poorly with hemodynamic changes and merit cautious interpretation, whereas significant increases (>1000 pg/mL) in levels are good markers of activation of the sympathetic nervous system.

CLINICAL SYNDROMES

Surgical Stress Response

Surgical stress, particularly that associated with major operations, results in profound metabolic and endocrine responses. The combination of autonomic, hormonal, and catabolic changes that accompany surgery has been called the surgical stress response.[318] Despite widespread clinical intuition that attenuation of the stress response is beneficial, there has been long-standing debate about whether such a strategy affects outcome. Three separate lines of evidence suggest that attenuation of the surgical stress response can lead to improved outcomes. In a series of studies, interruption of the sympathetic response to surgery markedly reduced surgical stress intraoperatively and postoperatively. The use of continuous thoracic epidural infusions of local anesthetics minimized the rise in plasma catecholamines, cortisol, and glucagon and improved outcomes. Improved outcome was independent of the patient's level of pain because metabolic and endocrine responses to surgery were not similarly reduced in patients receiving other methods of pain relief, including nonsteroidal anti inflammatory drugs and opioids.[319] Continuation of epidural infusions well into the postoperative period was regarded as essential to improving outcome. Inflammatory and immunologic responses, which are necessary for infection control and wound healing, appear to be unaffected. With the use of similar techniques and other stress-reducing maneuvers, faster and more complete recovery was achieved in older patients undergoing colon resection.[320]

A separate line of evidence supporting the hypothesis that long-term attenuation of the stress response alters surgical outcomes comes from the pediatric literature. When neonates with complex congenital heart disease underwent cardiac surgery, those who received high-dose sufentanil infusions intraoperatively and for the first 24 hours postoperatively to reduce the stress response had lower β-endorphin, norepinephrine, epinephrine, glucagon, aldosterone, and cortisol levels than did controls.[318] The mortality rate in the high-dose opiate group was significantly lower than in the study or historical controls, a finding suggesting that anesthetic techniques can have profound effects on the metabolic and endocrine responses to surgery and that effective management of these reflexes can alter outcomes.

A third line of evidence involves results from the multicenter study of the Perioperative Ischemia Research Group (see the earlier discussion of perioperative β blockade).[221] The ability to alter overall survival at 2 years with a perioperative regimen of β blockade provided compelling evidence of the benefit of attenuating the stress response,[222,223,225] and it changed clinical practice in patients at risk for cardiac morbidity. Similar results were achieved when perioperative α_2-agonists were given to "at-risk" patients as well.[321] Presumably, the decrease in sympathetic tone that accompanied administration of the β-blocker or the α_2-agonist suppressed the stress response and improved outcomes.

Diabetes Mellitus

Diabetic autonomic neuropathy is the most common form of autonomic neuropathy and the most extensively investigated (see Chapter 39). It occurs in 20% to 40% of all insulin-dependent diabetic patients. The symptoms associated with diabetic autonomic neuropathy confer an increased risk during anesthesia and surgery by direct and secondary mechanisms. Common manifestations of diabetic autonomic neuropathy include impotence, postural hypotension, gastroparesis, diarrhea, and sweating abnormalities. Early small-fiber damage is revealed by loss or impairment of vagally controlled normal heart rate variability, decreased peripheral sympathetic tone with a subsequent increase in blood flow, and diminished sweating. In a diabetic neuropathic foot, the senses of pain and temperature are lost before touch or vibration is affected. With sympathetic denervation, the sympathetic nerves normally found supplying small arterioles are entirely absent or are abnormally distant from their effector sites. When impotence or diarrhea is the sole manifestation, little effect is seen on survival; however, with postural hypotension or gastroparesis, 5-year mortality rates are greater than 50%.

Most clinicians recognize that diabetic patients with autonomic neuropathy may be at additional risk during general anesthesia.[322] Gastroparesis is probably caused by vagal degeneration and is of clinical relevance because awake or rapid-sequence intubation may be required. Systemic injury to the vasa vasorum in patients with postural hypotension increases the risk for hemodynamic instability and cardiovascular collapse in the perioperative period. Mechanisms that maintain normal standing blood pressure are altered, and normal precapillary vasoconstriction in the foot on standing may be diminished. Baroreceptors in the carotid sinus and aortic arch are compromised by diabetic neuropathy. Diabetic patients with orthostatic hypotension usually have lower norepinephrine levels.

Even in seemingly minor surgery, diabetic autonomic neuropathy can lead to significant complications.

Diabetic patients with autonomic neuropathy may have a significantly greater decline in blood pressure with induction and a greater need for vasopressors than do diabetic patients without autonomic dysfunction.[322] Page

and Watkins reported five cases of unexpected cardiorespiratory arrest in young diabetic patients, all of whom had symptoms of autonomic neuropathy.[323] In a large, prospective study of diabetic autonomic neuropathy involving use of the five evocative clinical tests discussed earlier, parasympathetic dysfunction preceded sympathetic failure in 96% of the patients.[324] This battery of autonomic tests identifies patients with autonomic neuropathy and is highly predictive of mortality and perioperative risk.[311]

AUTONOMIC CHANGES WITH AGING

Aging is associated with alterations in vascular reactivity manifested clinically as exaggerated changes in blood pressure—hypertension and orthostatic hypotension (see Chapter 80). Orthostatic hypotension is quite common (≈20%) in older persons and may result largely from diminished baroreceptor responsiveness. Heart rate responses to changes in blood pressure, the Valsalva maneuver, and the respiratory cycle are blunted with aging.[325]

Resting and exercise-induced norepinephrine levels increase with age in healthy subjects (by ≈13% per decade), in part because of decreased clearance.[326] Previously a matter of controversy, it now appears that besides the well-documented reduction in vagal function associated with aging,[327] the primary autonomic defect in aging is an impairment in reuptake of norepinephrine, perhaps as a function of decreased nerve density. Although no apparent age-dependent decrement in nerve firing rates from sympathetic efferents in skeletal muscle occurs,[328] kinetic studies reveal selective and dramatic increases in cardiac norepinephrine spillover attributable to the decreased reuptake in older patients subjected to mental stress or exercise. [314] This situation can precipitate clinical complications (i.e., arrhythmogenesis and sudden cardiac death) in patients with cardiac disease. However, end-organ responsiveness is blunted by compensatory down-regulation of β_1 adrenoreceptors (i.e., decreased receptor density and affinity) and uncoupling of β_2 adrenoreceptors through decreased G_s activity.[329] Despite increased cardiac spillover, cardiac oxygen consumption is not altered.[330]

Attenuation of presynaptic α_2-adrenoreceptor–mediated inhibition of neuronal norepinephrine release also accounts for the increased norepinephrine levels observed with age.[331-333] Reduced postsynaptic α-adrenoreceptor activity decreases contractile responses and further attenuates vasoconstrictor tone. In a seemingly vicious cycle, the increase in circulating norepinephrine levels is associated with down-regulation of platelet α_2-adrenoreceptor density and responsiveness. The loss of adrenergic control through the reduction of α_2- and β-receptor–mediated responses with age causes a decrease in the sympathetic nervous system's ability to maintain cardiovascular homeostasis, thus implying a relationship with or an explanation for the increased incidence of cardiovascular disorders such as CHF in older adults.

AUTONOMIC CHANGES IN SPINAL CORD TRANSECTION

The most drastic alteration in the ANS that an anesthesiologist may encounter is in patients with complete spinal cord transection (see Chapters 52, 70, and 81). Spinal cord transection affects motor and sensory function, and it may also result in profound changes in autonomic activity that can alter anesthetic care. Spinal cord injuries or transection can cause various degrees of autonomic dysfunction, depending on the site, extent, and timing of the lesion. Many autonomic reflexes are inhibited by the supraspinal feedback that is lost after spinal cord transection. Thus, in paraplegic patients, small stimuli can evoke exaggerated sympathetic discharges.

In patients with cervical spinal cord transection, sympathetic and parasympathetic outflow is detached from central control mechanisms. In addition to the expected motor and sensory changes, profound abnormalities alter the cardiovascular, thermoregulatory, gastrointestinal, and urinary systems. The autonomic consequences of transection are not always apparent because the distal portion of the spinal cord may retain some function and thereby result in unanticipated autonomic abnormalities.

Fundamental differences exist between the acute and chronic effects of spinal cord transection. Initially, a transient state of decreased excitability occurs. This phenomenon, known as spinal shock, usually takes place immediately after the lesion and may last for days to weeks. In these patients, the periphery is generally atonic, and the peripheral vascular bed is dilated. In patients with high thoracic lesions who have sustained recent injury, basal supine blood pressure is usually low and is accompanied by plasma catecholamine levels that are approximately 35% of normal.[334] Patients with recent low spinal injuries may exhibit compensatory tachycardia from intact parts of the ANS.

Patients with chronic high spinal lesions may fail to respond to hypovolemia with an increased heart rate and may exhibit bradycardia. The only intact efferent component of the baroreflex pathways in quadriplegic patients is the vagus. Bradycardia occurs with changes in position and with Valsalva maneuvers or increased intrathoracic pressure.[335]

One aspect of care that is frequently overlooked is the effect of tracheal suctioning on patients with high spinal transection. Given that many of these patients depend on artificial respiration because of their respiratory muscle paralysis, unopposed vagal stimuli may contribute to profound bradycardia. This vagal response is accentuated by hypoxemia.

Because the sympathetic nervous system may be dysfunctional in these patients, the renin-angiotensin-aldosterone system compensates for the maintenance of blood pressure. Patients with spinal cord transection may be exquisitely sensitive to ACEIs, even with modest changes in intravascular volume or posture. The release of renin may be independent of sympathetic stimulation and may be caused by the renal baroreceptor stimulation that accompanies the decline in renal perfusion pressure.

Although pressure stimuli above the lesion do not usually change arterial blood pressure, the phenomenon of autonomic dysreflexia can occur with stimulation below the lesion. Bladder or bowel distention can elicit the so-called mass reflex. This autonomic reflex includes a dramatic rise in blood pressure, a marked reduction in flow to the periphery, and flushing and sweating in areas

above the lesion. In addition, contraction of the bladder and rectum, skeletal muscle spasms, and penile erection often occur.

The heart rate may decline as a reflex. Surprisingly, evidence from microneurography studies indicates only a modest rise in sympathetic nerve activity during activation of the mass reflex,[336] as well as a modest increase in plasma norepinephrine levels. Speculation has arisen that the exaggerated blood pressure response may be caused by supersensitivity of adrenoreceptors. As anticipated, quadriplegic patients exhibit an increase in sensitivity to exogenously administered pressors.[334] Blood pressure in quadriplegic patients may increase dramatically in response to the exogenous administration of angiotensin and to catecholamines. Impairment of the descending inhibitory reflex pathways that are activated during hypertension may contribute to the supersensitivity. This hypothesis is supported by the finding that sensitivity is rarely increased when the lesion is below T5. These patients with lower spinal lesions, even those patients with long-standing quadriplegia, apparently have a normal level of adrenoceptors.

Management of autonomic dysreflexia is of clinical importance. Although the anesthesiologist may be tempted to opt for minimal anesthesia in a patient without sensory or motor function, significant visceral reflexes can be evoked. The anesthesiologist may use spinal anesthesia, general anesthesia, or a vasodilator such as nitroprusside or nitroglycerin to attenuate this reflex, even if pain is not appreciated. There has been some enthusiasm for using clonidine prophylactically to diminish this response.

An additional problem arising from the autonomic denervation of spinal cord transection is thermogenesis. In these patients, hypothermia may result from cutaneous vasodilation and the inability to shiver. Similarly, hyperthermia can occur because the normal sweating mechanism is impaired. It is therefore important to monitor temperature assiduously in these patients during the course of anesthesia.

NEW CONCEPTS IN AUTONOMIC ACTIVITY

GENETIC CONTRIBUTORS TO AUTONOMIC FUNCTION AND DRUG RESPONSIVENESS

As this chapter is being written, an explosion of scientific research is taking place to identify single nucleotide polymorphisms (SNPs) in β-adrenergic receptor genes and to relate them to autonomic pathophysiology.[337] In general, these studies are statistical, associating the incidence of SNPs with disease entities, including hypertension, asthma, CHF, and arrhythmias. However, in some instances, the underlying biologic links have been more intensively explored, and therapeutic implications are beginning to emerge. A U.S. Food and Drug Administration conference on genomics summarized the first recommendations for genetic testing before initiating drug therapies. At this time, the recommendations are limited to chemotherapeutic agents, and work with drugs affecting the ANS is labeled as purely informational.

Although the association between asthma susceptibility and β-adrenergic polymorphisms in the general population has not been confirmed, asthma phenotypes, including severity of asthma and bronchial hyperresponsiveness, have been associated with β_2-receptor polymorphisms. Most notably, changes in the coding region may alter response to short-acting and long-acting agonists, a finding suggesting the possibility of a different therapeutic response contingent upon the underlying genetic makeup. Similarly, increasing interest has been shown in the extent to which adrenergic receptor polymorphisms play a role in hypertension, heart failure,[338] sudden death, and response to β-adrenergic antagonists. Whereas intensive studies of β-receptor polymorphisms have led to a greater understanding of important clinical syndromes such as postural tachycardia syndrome[339] and sudden death, specific changes in clinical management have lagged considerably. Nowhere has this been more evident than in heart failure, in which receptor function has been studied for decades[340] but for which investigators remain unable to translate pharmacogenetic insights into therapeutic recommendations.[341]

More recently, however, emerging data have suggested that differences in the underlying signaling and recovery mechanism beyond receptors may play a role in autonomic pathophysiology.[342] It has been proposed that variability in the genetics of the arrestin system, which not only participates in the regeneration of adrenergic function but also can act as a second messenger, could account for differences in therapeutic efficacy of various cardiac drugs.

Therefore, although the ANS could fairly be called primitive (it is largely preserved across all mammalian species), its incredible complexity leaves it incompletely understood. As the understanding of the genetic determinants of autonomic activity and of the functional and cellular interactions of the ANS grows, the ability to interrupt or augment various autonomic effects with greater and greater precision will increase. This, in turn, will allow for improvements in both the long-term health and the acute perioperative safety of our patients.

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Chapter 17

Cerebral Physiology and the Effects of Anesthetic Drugs

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Key Points

- The brain has a high metabolic rate and receives approximately 15% of cardiac output. Under normal circumstances, cerebral blood flow (CBF) is approximately 50 mL/100 g/min. Gray matter receives 80% and white matter receives 20% of this blood flow.
- Approximately 60% of the brain's energy consumption supports electrophysiologic function. The remainder of the energy consumed by the brain is involved in cellular homeostatic activities.
- CBF is tightly coupled to local cerebral metabolism. When cerebral activity in a particular region of the brain increases, a corresponding increase in blood flow to that region takes place. Conversely, suppression of cerebral metabolism leads to a reduction in blood flow.
- CBF is autoregulated and remains constant over a mean arterial pressure (MAP) range estimated at 65 to 150 mm Hg, given normal venous pressure. Appreciable intersubject variability exists. CBF becomes pressure passive when MAP is either less than the lower limit or more than the upper limit of autoregulation.
- CBF is also under chemical regulation. CBF varies directly with arterial carbon dioxide tension in the arterial partial pressure of carbon dioxide ($Paco_2$) range of 25 to 70 mm Hg. When arterial partial pressure of oxygen (Pao_2) decreases to less than 60 mm Hg, CBF dramatically increases. Reductions in body temperature influence CBF primarily by suppression of cerebral metabolism.
- Systemic vasodilators (e.g., nitroglycerin, nitroprusside, hydralazine, calcium channel blockers) vasodilate the cerebral circulation and can, depending on the MAP, increase CBF. Vasopressors such as phenylephrine, norepinephrine, ephedrine, and dopamine do not have direct effects on the cerebral circulation. Their effect on CBF is via their effect on arterial blood pressure. When the MAP is less than the lower limit of autoregulation, vasopressors increase the MAP and thereby increase CBF. If the MAP is within the limits of autoregulation, then vasopressor-induced increases in systemic pressure have little effect on CBF.
- All volatile anesthetics suppress the cerebral metabolic rate (CMR) and, with the exception of halothane, can produce burst suppression of the electroencephalogram. At that level, the CMR is reduced by approximately 60%. Volatile anesthetics have dose-dependent effects on CBF. In doses less than the minimal alveolar concentration (MAC), CBF is modestly decreased. In doses larger than 1 MAC, direct cerebral vasodilation results in an increase in CBF and cerebral blood volume.
- Barbiturates, etomidate, and propofol decrease the CMR and can produce burst suppression of the electroencephalogram. At that level, the CMR is reduced by approximately 60%. Because blood flow and metabolism coupling are preserved, CBF is decreased. Opiates and benzodiazepines effect minor decreases in CBF and CMR. In contrast, ketamine can significantly increase the CMR with a corresponding increase in blood flow.
- Brain stores of oxygen and substrates are limited, and the brain is extremely sensitive to decreases in CBF. Severe decreases in CBF (less than 6 to 10 mL/100 g/min) lead to rapid neuronal death. Ischemic injury is characterized by early excitotoxicity and delayed apoptosis.

KEY POINTS—cont'd

- Barbiturates, propofol, ketamine, volatile anesthetics, and xenon have neuroprotective efficacy and can reduce ischemic cerebral injury in experimental models. This anesthetic neuroprotection is sustained only when the severity of the ischemic insult is mild; with moderate-to-severe injury, long-term neuroprotection is not achieved. The neuroprotective efficacy of anesthetics in humans is limited. Administration of etomidate can decrease regional blood flow, which can exacerbate ischemic brain injury.

This chapter reviews the effects of anesthetic drugs and techniques on cerebral physiology, in particular, their effects on cerebral blood flow (CBF) and metabolism. The final section presents a brief discussion of pathophysiologic states, including cerebral ischemia and cerebral protection. Prime attention is directed to the immediate relevance of the rationale for use of the anesthetic and the intensive care management of patients with intracranial pathologic conditions. Chapter 70 presents the clinical management of these patients in detail. Neurologic monitoring, including the effects of anesthetics on the electroencephalogram (EEG) and evoked responses, is reviewed in Chapter 49.

ANATOMY OF THE CEREBRAL CIRCULATION

The arterial blood supply to the brain is composed of paired right and left internal carotid arteries, which give rise to the anterior circulation, and paired right and left vertebral arteries, which give rise to the posterior circulation. The connection of the two vertebral arteries forms the basilar artery. The internal carotid arteries and the basilar artery connect to form a vascular loop called the circle of Willis that permits collateral circulation between both the right and left and the anterior and posterior perfusing arteries. Three paired arteries that originate from the circle of Willis perfuse the brain: anterior, middle, and posterior cerebral arteries. The posterior communicating arteries and the anterior communicating artery complete the loop. The anterior and the posterior circulations contribute equally to the circle of Willis.

Under normal circumstances, blood from the anterior and posterior circulations does not admix because the pressures in the two systems are equal. Similarly, side-to-side admixing of blood across the circle is limited. The vessels that originate from the circle provide blood flow to well-delineated regions of the brain. However, in pathologic circumstances during which occlusion of one of the arterial branches occurs, the circle of Willis can act as an anteroposterior or side-to-side shunt to increase collateral blood flow to the region of the brain with reduced perfusion.

A complete circle of Willis is shown in Figure 17-1, *A*. However, substantial variability exists in the anatomy of the circle of Willis, and a significant proportion of individuals may have an incomplete circular loop.[1] The variations in the circle and their prevalence are shown in Figure 17-1, *B*.

Three sets of veins drain blood from the brain. The superficial cortical veins are within the pia mater on the brain surface. Deep cortical veins drain the deeper structures of the brain. These veins drain into dural sinuses, of which the superior and inferior sagittal sinuses and the straight, transverse and sigmoid sinuses are the major dural sinuses. These ultimately drain into the right and left internal jugular veins. A schematic representation of the cerebral venous circulation is shown in Figure 17-1, *C*.

REGULATION OF CEREBRAL BLOOD FLOW

Anesthetic drugs cause dose-related and reversible alterations in many aspects of cerebral physiology, including CBF, cerebral metabolic rate (CMR), and electrophysiologic function (EEG, evoked responses). The effects of anesthetic drugs and techniques have the potential to adversely affect the diseased brain and are thus of clinical importance in patients with neurosurgical disease. Conversely, the effects of general anesthesia on CBF and CMR can be altered to improve both the surgical course and the clinical outcome of patients with neurologic disorders.

The adult human brain weighs approximately 1350 g and therefore represents approximately 2% of total body weight. However, it receives 12% to 15% of cardiac output. This high flow rate is a reflection of the brain's high metabolic rate. At rest, the brain consumes oxygen at an average rate of approximately 3.5 mL of oxygen per 100 g of brain tissue per minute. Whole-brain oxygen consumption (50 mL/min) represents approximately 20% of total body oxygen utilization. Normal values for CBF, CMR, and other physiologic variables are provided in Box 17-1.

Approximately 60% of the brain's energy consumption supports electrophysiologic function. The depolarization-repolarization activity that occurs, reflected in the EEG, requires expenditure of energy for the maintenance and restoration of ionic gradients and for the synthesis, transport, and reuptake of neurotransmitters. The remainder of the energy consumed by the brain is involved in cellular homeostatic activities. Local CBF and CMR within the brain are very heterogeneous, and both are approximately four times greater in gray matter than in white matter. The cell population of the brain is also heterogeneous in its oxygen requirements. Glial cells make up approximately one half of the brain's volume and require less energy than neurons. Besides providing a physically supportive latticework for the brain, glial cells are important in the reuptake of neurotransmitters, in the delivery

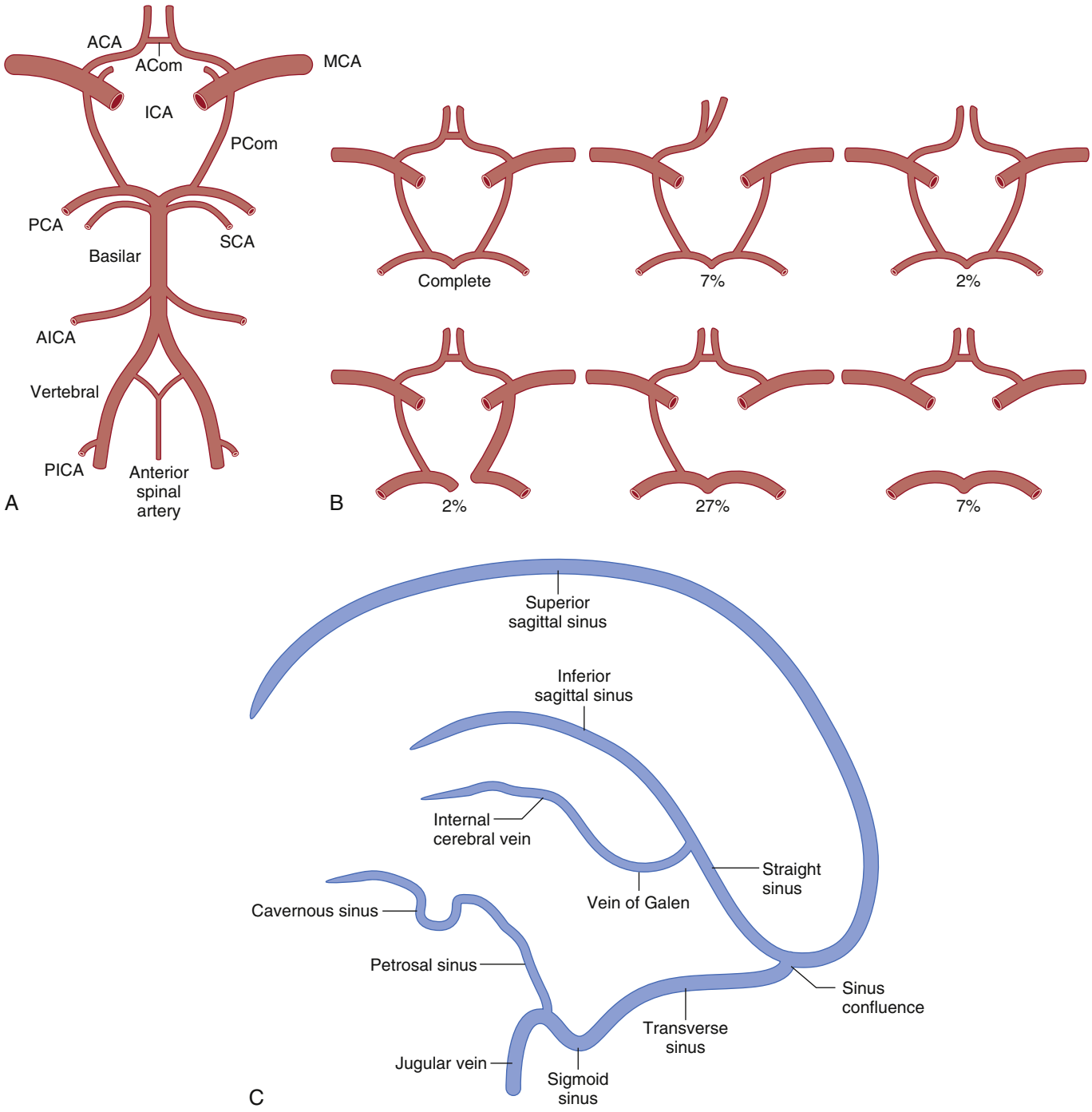


Figure 17-1. Vascular anatomy of the blood supply to and drainage from the brain. **A,** Arterial input into a complete circle of Willis. *ACA,* anterior cerebral artery; *ACom,* anterior communicating artery; *AICA,* anterior inferior cerebellar artery; *ICA,* internal carotid artery; *MCA,* middle cerebral artery; *PCA,* posterior cerebral artery; *PCom,* posterior communicating artery; *PICA,* posterior inferior cerebellar artery; *SCA,* superior cerebellar artery. **B,** Variations in the anatomy of the circle of Willis. The prevalence of each of the variations is shown in the figure. **C,** Venous drainage of the brain.

and removal of metabolic substrates and wastes, and in blood-brain barrier (BBB) function.

The brain's substantial demand for substrate must be met by adequate delivery of oxygen and glucose. However, the space constraints imposed by the noncompliant cranium and meninges require that blood flow not be excessive. Not surprisingly, elaborate mechanisms regulate CBF. These mechanisms, which include chemical, myogenic, and neurogenic factors, are listed in Table 17-1.

CHEMICAL REGULATION OF CEREBRAL BLOOD FLOW

Several factors, including changes in CMR, arterial partial pressure of carbon dioxide ($Paco_2$), and arterial partial

BOX 17-1 *Normal Cerebral Physiologic Values*

CBF	
Global	45-55 mL/100 g/min
Cortical (mostly gray matter)	75-80 mL/100 g/min
Subcortical (mostly white matter)	≈20 mL/100 g/min
$CMRO_2$	3-3.5 mL/100 g/min
CVR	1.5-2.1 mm Hg/100 g/min/mL
Cerebral venous Po_2	32-44 mm Hg
Cerebral venous So_2	55%-70%
$SjVo_2$	≈65%
ICP (supine)	8-12 mm Hg

CBF, Cerebral blood flow; *$CMRO_2$,* cerebral metabolic rate of oxygen; *CVR,* cerebral vascular resistance; *ICP,* intracranial pressure; *Po_2,* partial pressure of oxygen; *$SjVo_2$,* jugular venous oxygen saturation; *So_2,* oxygen saturation.

TABLE 17-1 **FACTORS INFLUENCING CEREBRAL BLOOD FLOW***

Factor	Comment
Chemical, Metabolic, Humoral	
CMR	CMR influence assumes intact flow-metabolism coupling, the mechanism of which is not fully understood.
Anesthetics	
Temperature	
Arousal; seizures	
$Paco_2$	
Pao_2	
Vasoactive drugs	
Anesthetics	
Vasodilators	
Vasopressors	
Myogenic	
Autoregulation; MAP	The autoregulation mechanism is fragile; in many pathologic states, CBF is regionally pressure passive.
Rheologic	
Blood viscosity	
Neurogenic	
Extracranial sympathetic and parasympathetic pathways	Contribution and clinical significance are poorly defined.
Intraaxial pathways	

*See text for discussion.
CBF, Cerebral blood flow; *CMR,* cerebral metabolic rate; *MAP,* mean arterial pressure; *$Paco_2$,* arterial partial pressure of carbon dioxide; *Pao_2,* arterial partial pressure of oxygen.

pressure of oxygen (Pao_2), cause alterations in the cerebral biochemical environment that result in adjustments in CBF.

Cerebral Metabolic Rate

Increased neuronal activity results in increased local brain metabolism, and this increase in the CMR is associated with a proportional change in CBF that is referred to as *flow-metabolism coupling*. The traditional view of this coupling is that it is a positive feedback mechanism wherein increased neuronal activity results in a demand for energy; this demand is met by an increase in CBF. More recent data indicate that coupling is based on a feed-forward mechanism wherein neuronal activity directly increases CBF, thereby increasing energy supply.[2] Although the precise mechanisms that mediate flow-metabolism coupling have not been defined, the data available implicate local by-products of metabolism (potassium ion [K^+], hydrogen ion [H^+], lactate, adenosine, and adenosine triphosphate [ATP]). Increased synaptic activity with the attendant release of glutamate leads to the downstream generation of a variety of mediators that affect vascular tone (Fig. 17-2). Glutamate, released with increased neuronal activity, results in the synthesis and release of nitric oxide (NO), a potent cerebral vasodilator that plays an important role in coupling of flow and metabolism. Glia play an important role in flow-metabolism coupling, and their processes make contact with neurons. These processes may serve as conduits for the coupling of increased neuronal activity to increases in blood flow. Glutamate activation of metabotropic glutamate receptors (mGluR) in astrocytes leads to arachidonic acid (AA) metabolism and the subsequent generation of prostaglandins and epoxyeicosatrienoic acids (EETs). Local by-products of metabolism (K^+, H^+, lactate, adenosine, and ATP) can also directly modulate vascular tone. Oxygen modulates the relative contribution of these pathways, and in the setting of reduced oxygen tension at the tissue level, the release of adenosine can contribute to vascular dilation. The net result therefore on vascular tone is determined by the relative contribution of multiple signaling pathways. In addition, nerves that innervate cerebral vessels release peptide neurotransmitters such as vasoactive intestinal peptide (VIP), substance P, cholecystokinin, somatostatin, and calcitonin gene–related peptide. These neurotransmitters may also potentially be involved in neurovascular coupling. Flow-metabolism coupling within the brain is a complex physiologic process that is regulated, not by a single mechanism, but by a combination of metabolic, glial, neural, and vascular factors.

CMR is influenced by several phenomena in the neurosurgical environment, including the functional state of the nervous system, anesthetic drugs, and temperature.

Functional State. CMR decreases during sleep and increases during sensory stimulation, mental tasks, or arousal of any cause. During epileptic activity, increases in the CMR may be extreme, whereas regionally after brain injury and globally with coma, the CMR may be substantially reduced.

Anesthetic Drugs. The effect of individual anesthetic drugs on the CMR is presented in greater detail in the second section of this chapter. In general, anesthetic drugs suppress the CMR, with the exception of ketamine and nitrous oxide (N_2O). The component of the CMR on which they act is electrophysiologic function. With several anesthetics, including barbiturates, isoflurane, sevoflurane, desflurane, propofol, and etomidate, increasing plasma concentrations cause progressive suppression of EEG activity and a concomitant reduction in the CMR. However, increasing the plasma level beyond what is required to first achieve suppression of the EEG results in no further depression of the CMR. The component of the CMR required for the maintenance of cellular integrity, the "housekeeping" component, is unaltered by anesthetic drugs (Fig. 17-3).

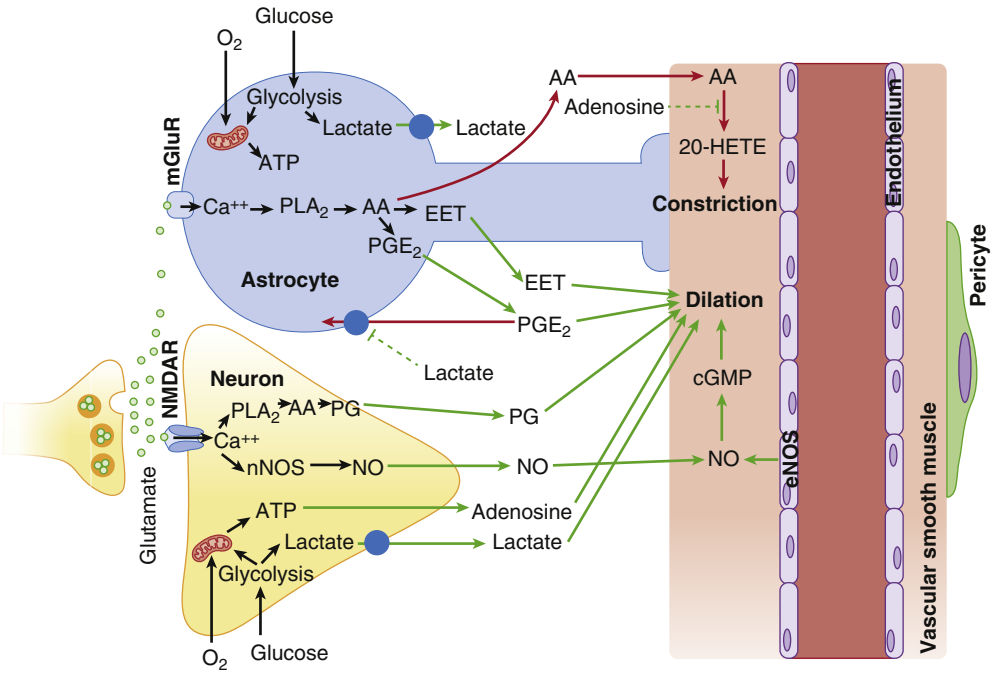


Figure 17-2. Cerebral flow-metabolism coupling. Synaptic activity leads to glutamate release, activation of glutamatergic receptors, and calcium entry in neurons. This results in a release of arachidonic acid (AA), prostaglandins (PGs), and nitric oxide (NO). Adenosine and lactate are generated from metabolic activity. These factors all lead to vascular dilation. Glutamate also activates metabotropic glutamate receptors (mGluR) in astrocytes, causing intracellular calcium entry, phospholipase A_2 (PLA_2) activation, release of AA and epoxyeicosatrienoic (EET) acid and prostaglandin E_2 (PGE_2). The latter two AA metabolites contribute to dilation. By contrast, AA can also be metabolized to 20-hydroxyl-eicosatetraenoic acid (20-HETE) in vascular smooth muscle. 20-HETE is a potent vascular constrictor. *cGMP,* Cyclic guanosine monophosphate; *eNOS,* endothelial nitric oxide synthase; *NMDAR, N*-methyl D-aspartate glutamate receptor; *nNOS,* neuronal nitric oxide synthase. *(Modified from Attwell D, Buchan AM, Charpak S, et al: Glial and neuronal control of brain blood flow,* Nature *468(7321):232-243, 2010.)*

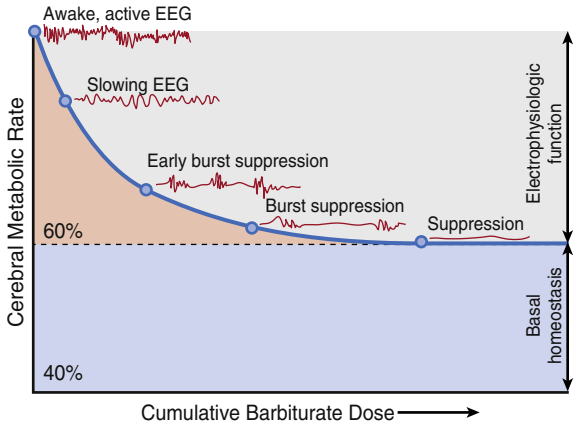


Figure 17-3. Interdependency of cerebral electrophysiologic function and cerebral metabolic rate (CMR). Administration of various anesthetics, including barbiturates, results in a dose-related reduction in the CMR of oxygen ($CMRO_2$) and cerebral blood flow (CBF). The maximum reduction occurs with the dose that results in electrophysiologic silence. At this point, the energy utilization associated with electrophysiologic activity has been reduced to zero, but the energy utilization for cellular homeostasis persists unchanged. Additional barbiturates cause no further decrease in CBF or $CMRO_2$. *EEG,* Electroencephalogram.

When complete suppression of EEG is achieved, the cerebral metabolic rate of oxygen ($CMRO_2$) is similar irrespective of the anesthetic agent used to achieve EEG suppression. Yet, anesthetic-induced EEG suppression is not a single physiologic state and is influenced by the drug that is used to produce suppression. When barbiturates are administered to the point of EEG suppression, a uniform depression in the CBF and CMR occurs throughout the brain. When suppression occurs during the administration of isoflurane and sevoflurane, the relative reductions in the CMR and CBF are more intense in the neocortex than in other portions of the cerebrum. Electrophysiologic responsiveness also varies. Cortical somatosensory-evoked responses to median nerve stimulation can be readily recorded at doses of thiopental far in excess of those required to cause complete suppression of the EEG but are difficult to elicit at concentrations of isoflurane associated with a burst-suppression pattern (~1.5 MAC) (Fig. 17-4[3,4]). In addition, the EEG characteristics of the burst-suppression states that occur just before complete suppression differ among anesthetic drugs. These differences may be of some relevance to discussions of differences in the neuroprotective potential of drugs that can produce EEG suppression.

Temperature. The effects of hypothermia on the brain have been reviewed in detail[5] (also see Chapter 54). The CMR decreases by 6% to 7% per degree Celsius of temperature reduction. In addition to anesthetic drugs, hypothermia can also cause complete suppression of the EEG (at approximately 18° C to 20° C). However, in contrast to anesthetic drugs, temperature reduction beyond that at which EEG suppression first occurs *does* produce a further decrease in the CMR (Fig. 17-5). This decrease occurs because anesthetic drugs reduce only the component

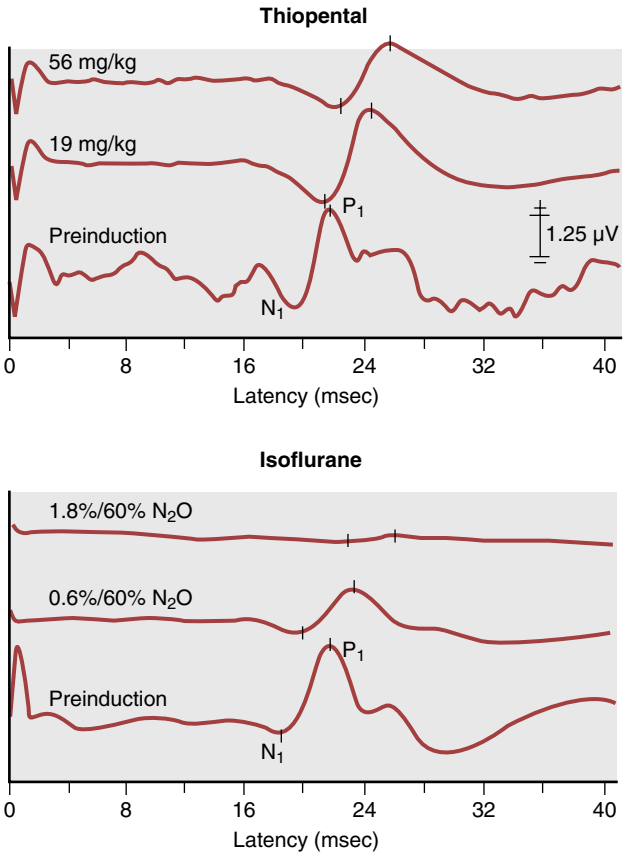


Figure 17-4. Cortical somatosensory-evoked responses to median nerve stimulation in humans before induction and during anesthesia with thiopental–nitrous oxide (N_2O) and isoflurane-N_2O. Despite an equivalent or greater degree of reduction in the cerebral metabolic rate with thiopental, cortical evoked responses are better preserved[3] than during anesthesia with isoflurane,[4] which suggests that the electroencephalographic suppression achieved with different anesthetic drugs should not be assumed to be equivalent electrophysiologic states. The cumulative thiopental doses and expired concentrations of isoflurane and N_2O are indicated in this figure.

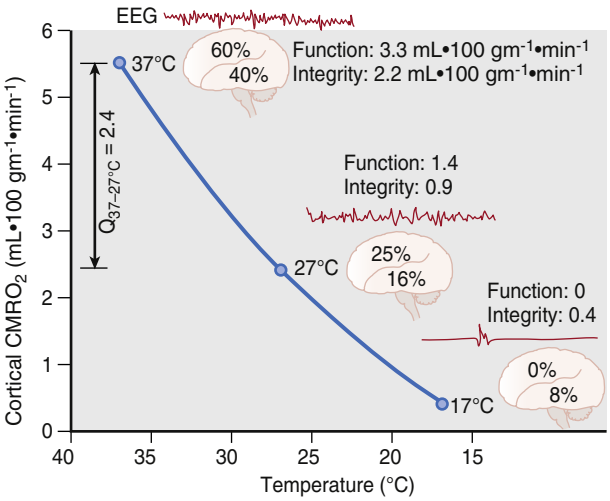


Figure 17-5. Effect of temperature reduction on the cerebral metabolic rate of oxygen ($CMRO_2$) in the cortex. Hypothermia reduces both of the components of cerebral metabolic activity identified in Figure 17-3—that associated with neuronal electrophysiologic activity (Function) and that associated with the maintenance of cellular homeostasis (Integrity). This is in contrast to anesthetics that alter only the functional component. The ratio of cerebral metabolic rate (CMR) at 37° C to that at 27° C, the Q10 ratio, is shown in the graph. Note that the $CMRO_2$ in the cortex (grey matter) is greater than global $CMRO_2$, considering the lower metabolic rate in white matter. *(Modified from Michenfelder JD:* Anesthesia and the brain: clinical, functional, metabolic, and vascular correlates. *New York, 1988, Churchill Livingstone.)*

of the CMR associated with neuronal function, whereas hypothermia decreases the rate of energy utilization associated with both electrophysiologic function and the basal component associated with the maintenance of cellular integrity. Mild hypothermia preferentially suppresses the basal component of the CMR. The $CMRO_2$ at 18° C is less than 10% of normothermic control values, which may explain the brain's tolerance for moderate periods of circulatory arrest at these and cooler temperatures.

Hyperthermia has an opposite influence on cerebral physiologic function. Between 37° C and 42° C, CBF and CMR increase. However, above 42° C, a dramatic reduction in cerebral oxygen consumption occurs, an indication of a threshold for a toxic effect of hyperthermia that may occur as a result of protein (enzyme) denaturation.

$Paco_2$. CBF varies directly with $Paco_2$ (Fig. 17-6), especially within the range of physiologic variation of $Paco_2$. CBF changes 1 to 2 mL/100 g/min for each 1 mm Hg change in $Paco_2$ around normal $Paco_2$ values. This response is attenuated at a $Paco_2$ less than 25 mm Hg. Under normal circumstances, the sensitivity of CBF to changes in $Paco_2$ ($\Delta CBF/\Delta Paco_2$) is positively correlated with resting levels of CBF. Accordingly, anesthetic drugs that alter resting CBF cause changes in the response of the cerebral circulation to carbon dioxide (CO_2). The magnitude of the reduction in CBF caused by hypocapnia is more intense when resting CBF is rapid (as might occur during anesthesia with volatile agents). Conversely, when resting CBF is slow, the magnitude of the hypocapnia-induced reduction in CBF is decreased. However, CO_2 responsiveness has been observed in normal brain during anesthesia with all of the anesthetic drugs that have been studied.

The changes in CBF caused by $Paco_2$ are dependent on pH alterations in the extracellular fluid of the brain. NO, in particular NO of neuronal origin, is an important although not exclusive mediator of CO_2-induced vasodilation.[6] The vasodilatory response to hypercapnia is also mediated in part by prostaglandins. The changes in extracellular pH and CBF rapidly occur after $Paco_2$ adjustments because CO_2 freely diffuses across the cerebrovascular endothelium. In contrast with *respiratory* acidosis, acute systemic *metabolic* acidosis has little immediate effect on CBF because the BBB excludes H^+ from the perivascular space. The CBF changes in response to alterations in $Paco_2$ rapidly occur, but they are not sustained. Despite the maintenance of an increased arterial pH, CBF returns toward normal over a period of 6 to 8 hours because the pH of cerebrospinal fluid (CSF) gradually returns to normal levels as a result of extrusion of bicarbonate (see Fig. 70-6). Consequently, a patient who has had a sustained period of hyperventilation or hypoventilation deserves special consideration. Acute restoration of a

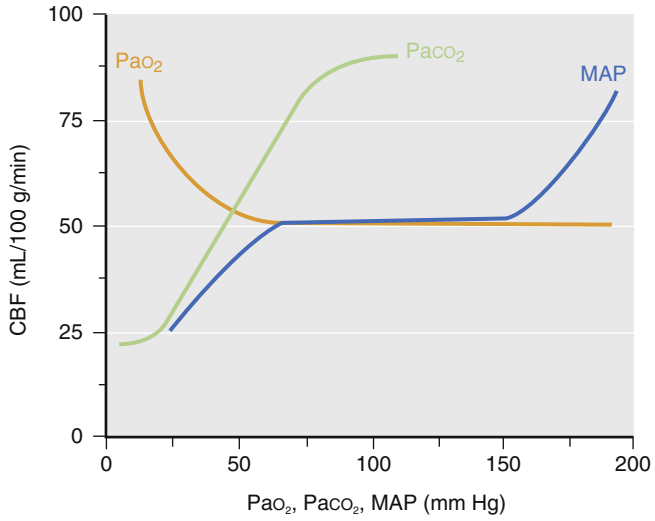


Figure 17-6. Changes in cerebral blood flow (CBF) caused by independent alterations in arterial partial pressure of carbon dioxide ($Paco_2$), partial pressure of oxygen (Pao_2), and mean arterial pressure (MAP).

normal $Paco_2$ value will result in a significant CSF acidosis (after hypocapnia) or alkalosis (after hypercapnia). The former results in increased CBF with a concomitant increase in intracranial pressure (ICP) that depends on the prevailing intracranial compliance. The latter conveys a theoretic risk for ischemia.

Pao_2. Changes in Pao_2 from 60 to more than 300 mm Hg have little influence on CBF. Less than a Pao_2 of 60 mm Hg rapidly increases CBF (see Fig. 17-6). The mechanisms mediating cerebral vasodilation during hypoxia may include neurogenic effects initiated by peripheral and neuraxial chemoreceptors, as well as local humoral influences. At least part of the hyperemic response to hypoxia is mediated by NO of neuronal origin. Hypoxia-induced opening of ATP-dependent K^+ channels in vascular smooth muscle also leads to hyperpolarization and vasodilation. The rostral ventrolateral medulla (RVM) serves as an oxygen sensor within the brain. Stimulation of the RVM by hypoxia results in an increase in CBF (but not the CMR), and lesions of the RVM suppress the magnitude of the CBF response to hypoxia. The response to hypoxia is synergistic with the hyperemia produced by hypercapnia and acidosis. At high Pao_2 values, CBF modestly decreases. At 1 atmosphere of oxygen, CBF is reduced by 12%.

MYOGENIC REGULATION (AUTOREGULATION) OF CEREBRAL BLOOD FLOW

Autoregulation refers to the capacity of the cerebral circulation to adjust its resistance to maintain CBF constant over a wide range of mean arterial pressure (MAP) values. In normal *human* subjects, the limits of autoregulation likely occur at MAP values of approximately 70 and 150 mm Hg (see Fig. 17-6). The lower limit of autoregulation (LLA) may be a MAP value of 50 mm Hg. Although this number was derived from animal studies, the LLA is likely higher in humans.[7] The units used on the *x* axis of autoregulation curves will influence the correct inflection points of the curve. When the *x* axis is the MAP, the normal average LLA is not less than 70 mm Hg (with considerable interindividual variation). Because ICP is not usually measured in normal subjects, cerebral perfusion pressure (CPP) (MAP – ICP) is rarely available. Assuming a normal ICP of 5 to 10 mm Hg in a supine subject, an LLA of 65 mm Hg expressed as MAP corresponds to an LLA of 55 to 60 mm Hg expressed as CPP.

Above and below the autoregulatory plateau, CBF is pressure dependent (pressure passive) and linearly varies with CPP. Autoregulation is influenced by various pathologic processes, as well as the time course over which the changes in CPP occur. Even within the range over which autoregulation normally occurs, a rapid change in arterial pressure will result in a transient (i.e., 3 to 4 minutes) alteration in CBF.

The *limits of autoregulation* are conceptual constructs for the purpose of analysis. They do not represent physiologic "all-or-none" responses. A continuum of vascular responsiveness in both the lower and upper limits probably exists as the ability of the arteriolar bed to dilate or constrict is exhausted. Furthermore, the morphologic form of the autoregulation is strongly influenced by the background level of vasodilation or vasoconstriction (e.g., $Paco_2$ or anesthetic conditions).

The precise mechanisms, by which autoregulation is accomplished and its overlap with flow-metabolism coupling are not known. According to the myogenic hypothesis, changes in CPP lead to direct changes in the tone of vascular smooth muscle; this process appears to be passive. NO may participate in the vasodilation associated with hypotension (also see Chapter 104). Autonomic innervation of cerebral blood vessels may also contribute to the autoregulation of blood flow (discussed in the next section).

NEUROGENIC REGULATION OF CEREBRAL BLOOD FLOW

The cerebral vasculature is extensively innervated.[8] The density of innervation declines with vessel size, and the greatest neurogenic influence appears to be exerted on larger cerebral arteries. This innervation includes cholinergic (parasympathetic and nonparasympathetic), adrenergic (sympathetic and nonsympathetic), serotoninergic, and VIPergic systems of extraaxial and intraaxial origin. An extracranial sympathetic influence via the superior cervical ganglion, as well as parasympathetic innervation via the sphenopalatine ganglion, certainly exists in animals. The intraaxial pathways likely result from innervation arising from several nuclei in animals, including the locus coeruleus, the fastigial nucleus, the dorsal raphe nucleus, and the basal magnocellular nucleus of Meynert. Evidence of the functional significance of neurogenic influences has been derived from studies of CBF autoregulation and ischemic injury. Hemorrhagic shock, a state of high sympathetic tone, results in less CBF at a given MAP than occurs when hypotension is produced with sympatholytic drugs. During shock, a sympathetically mediated vasoconstrictive effect shifts the lower end of

the *autoregulatory* plateau to the right. It is not clear what the relative contributions of humoral and neural mechanisms are to this phenomenon; however, a neurogenic component certainly exists because sympathetic denervation increases CBF during hemorrhagic shock. Moreover, sympathetic denervation produced by a blockade of the stellate ganglion can increase CBF in humans.[9] Activation of cerebral sympathetic innervation also shifts the upper limit of autoregulation to the right and offers some protection against hypertensive breakthrough of the BBB. Experimental interventions that alter these neurogenic control pathways influence outcome after standardized ischemic insults, presumably by influences on vascular tone and therefore CBF. The nature and influence of such pathways in humans are not known, and their manipulation for the purposes of clinical management remains to be systematically investigated.

EFFECTS OF BLOOD VISCOSITY ON CEREBRAL BLOOD FLOW

Blood viscosity can influence CBF. Hematocrit is the single most important determinant of blood viscosity.[10] In healthy humans, variation of the hematocrit within the normal range (33% to 45%) probably results in only modest alterations in CBF. Beyond this range, changes are more substantial. In anemia, cerebral vascular resistance is reduced and CBF increases. However, this may result not only from a reduction in viscosity but also as a compensatory response to reduced oxygen delivery.[11] The effect of a reduction in viscosity on CBF is more important with focal cerebral ischemia, a condition in which vasodilation in response to impaired oxygen delivery is probably already maximal. In this situation, reducing viscosity by hemodilution increases CBF in the ischemic territory. In patients with focal cerebral ischemia, a hematocrit of 30% to 34% will result in optimal delivery of oxygen. However, manipulation of viscosity in patients with acute ischemic stroke is not of benefit in reducing the extent of cerebral injury.[12] Therefore viscosity is not a target of manipulation in patients at risk as a result of cerebral ischemia, with the possible exception of those with hematocrit values higher than 55%.

VASOACTIVE DRUGS

Many drugs with intrinsic vascular effects are used in contemporary anesthetic practice, including both anesthetic drugs and numerous vasoactive drugs specifically used for hemodynamic manipulation. This section deals with the latter. The actions of anesthetics are discussed in the section, "Effects of Anesthetics on Cerebral Blood Flow and Cerebral Metabolic Rate."

Systemic Vasodilators

Most drugs used to induce hypotension, including sodium nitroprusside, nitroglycerin, hydralazine, adenosine, and calcium channel blockers, also cause cerebral vasodilation. As a result, CBF either increases or is maintained at prehypotensive levels. In addition, when hypotension is induced with a cerebral vasodilator, CBF is maintained at lower MAP values than when induced by either hemorrhage or a noncerebral vasodilator. In contrast to direct vasodilators, the angiotensin-converting enzyme (ACE) inhibitor enalapril does not have any significant impact on CBF.[13] Anesthetics that simultaneously vasodilate the cerebral circulation cause increases in cerebral blood volume (CBV) with the potential to increase ICP. The effects of these anesthetics on ICP are less dramatic when hypotension is slowly induced, which probably reflects the more effective interplay of compensatory mechanisms (i.e., shifts in CSF and venous blood) when changes occur more slowly.

Catecholamine Agonists and Antagonists

Numerous drugs with agonist and antagonist activity at catecholamine receptors (α_1, α_2, β_1, β_2, and dopamine) are in common use. The effects of these vasoactive drugs on cerebral physiology are dependent on basal arterial blood pressure, the magnitude of the drug-induced arterial blood pressure changes, the status of the autoregulation mechanism, and the status of the BBB. A drug may have direct effects on cerebral vascular smooth muscle or indirect effects mediated by the cerebral autoregulatory response to changes in systemic blood pressure (or both types of effects). When autoregulation is preserved, increases in systemic pressure should increase CBF if basal blood pressure is outside the limits of autoregulation. When basal pressure is within the normal autoregulation range, an increase in systemic pressure does not significantly affect CBF because the normal autoregulatory response to a rising MAP entails cerebral vasoconstriction (i.e., an increase in cerebral vascular resistance) to maintain a constant CBF. When autoregulation is defective, CBF will vary in direct relation to arterial pressure. The information in the following paragraphs and in Table 17-2 emphasizes data obtained from investigations of vasopressors in intact preparations and gives priority to the results obtained in humans and higher primates.

TABLE 17-2 BEST ESTIMATES OF THE INFLUENCE OF PURE CATECHOLAMINE RECEPTOR AGONISTS AND SPECIFIC PRESSOR SUBSTANCES ON CEREBRAL BLOOD FLOW AND CEREBRAL METABOLIC RATE*

Agonist	Cerebral Blood Flow	Cerebral Metabolic Rate
Pure		
α_1	0/–	0
α_2	–	–
β	+	+
β (BBB open)	+++	+++
Dopamine	++	0
Dopamine (high dose)	–	?0
Fenoldopam	–	?0
Mixed		
Norepinephrine	0/–	0/+
Norepinephrine (BBB open)	+	+
Epinephrine	+	+
Epinephrine (BBB open)	+++	+++

BBB, Blood-brain barrier; +, increase; –, decrease; 0, no effect.
*Where species differences occurred, data from primates were given preference. See text for complete discussion.
The number of symbols indicates the magnitude of the effect.

α_1-Agonists. Will the administration of α_1-agonists (phenylephrine, norepinephrine) reduce CBF?

Studies in humans and nonhuman primates do not confirm this concern. Intracarotid infusions of norepinephrine in doses that significantly increase the MAP result in no change in CBF. Administration of phenylephrine to patients undergoing cardiopulmonary bypass does not decrease CBF.[14] There are, however, some species differences with regard to the CBF response to α-agonists. α_1-Agonists also do not cause cerebral vasoconstriction in rats but do produce modest decreases in CBF in dogs and goats; this decrease in CBF can be blocked by α_1-antagonists (also see Chapter 16).

Norepinephrine can increase CBF. Such increases might occur if autoregulation were defective or its limit exceeded. In some instances the increases may be the result of abnormalities in the BBB. β-Mimetic drugs (norepinephrine has β_1 activity) may cause activation of cerebral metabolism[15] with a coupled increase in CBF. This effect is more apparent when these drugs can gain greater access to the brain parenchyma via a defective BBB (see Table 17-2).

The traditional view that CBF can be maintained by the administration of α_1-agonists without any adverse effect on cerebral oxygenation has been challenged. In anesthetized patients,[16-18] phenylephrine administration by bolus modestly reduced cerebral oxygen saturation (S_{CO_2}), measured by near-infrared oximetry. Ephedrine, although increasing arterial blood pressure to a similar extent as phenylephrine, did not reduce S_{CO_2}, presumably because of its ability to maintain cardiac output. In human volunteers, a norepinephrine-induced increase in arterial blood pressure slightly reduced middle cerebral artery (MCA) flow velocity and S_{CO_2} and jugular venous oxygen saturation (SjV_{O_2}).[19] By contrast, although phenylephrine decreased S_{CO_2}, MCA flow velocity was increased and SjV_{O_2} was unchanged.[20] Do phenylephrine and norepinephrine administration negatively impact cerebral oxygenation? Several factors argue against this possibility. The first concern is methodology. Near-infrared spectroscopy (NIRS) measures oxygenated and deoxygenated blood in a defined region of brain and is a composite of arterial, capillary, and venous blood. Vasopressors affect both arterial and venous tone. Even a minor change in the volume of arterial and venous volumes within the region of the brain can affect the S_{CO_2} measurement. Moreover, extracranial contamination is a significant component of the S_{CO_2} values reported by the currently available NIRS monitors.[21] This contamination is more important than the slight reduction in S_{CO_2} observed in these investigations. In the absence of direct measurement of brain tissue oxygenation, a modest reduction in S_{CO_2} in the face of increasing arterial blood pressure cannot be taken as evidence of impairment of cerebral oxygenation. In addition, phenylephrine did not decrease SjV_{O_2}, a more global measurement of cerebral oxygenation. Although norepinephrine decreased SjV_{O_2} by approximately 3% (a mild reduction at best), its administration has been previously shown to increase the $CMRO_2$. Finally, the minor reduction in S_{CO_2} effected by phenylephrine is no longer apparent when an increase in the $CMRO_2$ is concurrent. Phenylephrine apparently does not prevent an increase in CBF when such an increase is warranted by increased brain metabolism.

These studies were conducted in patients with a normal central nervous system (CNS). Although unlikely, the concern is that α_1-agonists might reduce cerebral perfusion in the injured brain. For example, in patients with a head injury, the administration of phenylephrine increased CPP and did not reduce regional CBF.[22] Transient changes may occur in CBF and S_{CO_2} (on the order of 2 to 5 minutes) in response to bolus doses of phenylephrine; however, with a continuous infusion, α_1-agonists have little direct influence on CBF and cerebral oxygenation in humans.[23] Thus maintenance of CPP with these vasopressors does not have an adverse effect on the brain.

α_2-Agonists. α_2-Agonists have both analgesic and sedative effects. This class of drugs includes dexmedetomidine and clonidine, with the latter being a significantly less specific and less potent α_2-agonist. Two investigations in human volunteers have confirmed the ability of dexmedetomidine to decrease CBF. Dexmedetomidine dose-dependently decreased MCA flow velocity, with the maximum reduction being approximately 25%.[24] Dexmedetomidine (1-μg/kg loading dose and infusion at either 0.2 or 0.6 μg/kg/hr) decreased CBF by approximately 30%[25] in healthy human volunteers. In both these investigations, the CMR was not measured; whether the reduction in CBF was due to a direct vasoconstrictor activity of dexmedetomidine or to suppression of the CMR with a corresponding reduction in CBF is not clear. In a more recent study of dexmedetomidine during which both MCA flow velocity and the CMR were measured in healthy humans, dexmedetomidine decreased MCA flow velocity in parallel with a reduction in the CMR.[26] The effects of dexmedetomidine on CBF were primarily mediated by its ability to suppress the CMR. The well-known effect of dexmedetomidine to decrease arterial blood pressure merits careful consideration if used in patients who are critically dependent on collateral perfusion pressure, especially in the recovery phase of an anesthetic.

β-Agonists. β-Receptor agonists, in small doses, have little direct effect on the cerebral vasculature. In larger doses and in association with physiologic stress, they can cause an increase in the CMR with an accompanying increase in CBF.[27] The β_1-receptor is probably the mediator of these effects. In doses that do not result in substantial changes in the MAP, intracarotid epinephrine does not change CBF in unanesthetized humans. However, with larger doses that lead to an increase in the MAP, both CBF and $CMRO_2$ can increase by approximately 20%.

Evidence suggests that a defect in the BBB enhances the effect of β-agonists.[28] Intracarotid norepinephrine, which does not normally affect CBF and CMR, increases CBF and CMR when BBB permeability is increased with hypertonic drugs. Epinephrine caused an elevation in the $CMRO_2$, but only when the BBB was made permeable.[28] These observations beg the interpretation that β-agonists will increase CBF and CMR *only* when the BBB is injured. However, when epinephrine was given in doses that did not significantly increase the MAP, increases in CBF and CMR occurred.[29] Accordingly, BBB injury may exaggerate

but not be a necessary condition in humans for the occurrence of β-mediated increases in CBF and CMR.

β-Blockers. β-Adrenergic blockers either reduce or have no effect on CBF and CMR. In two investigations in humans, propranolol, 5 mg intravenously,[30] and labetalol, 0.75 mg/kg intravenously,[31] had no effect on CBF and cerebral blood flow velocity (CBFV), respectively. Modest reductions in CBF occur after the administration of labetalol to patients undergoing craniotomy who become hypertensive during emergence from anesthesia. Esmolol shortens seizures induced by electroconvulsive therapy (ECT), which suggests that esmolol does cross the normal BBB. Catecholamine levels at the time of β-blocker administration or the status of the BBB (or both) may influence the effect of these drugs. β-Adrenergic blockers are unlikely to have adverse effects on patients with intracranial pathologic abnormalities, other than effects secondary to changes in perfusion pressure.

Dopamine. Dopamine can treat hemodynamic dysfunction. It also augments the function of the normal cardiovascular system when an increase in the MAP is desired as an adjunct to the treatment of focal cerebral ischemia, especially in the setting of vasospasm. Nonetheless, its effects on CBF and CMR have not been defined with certainty. The likely predominant effect of dopamine in the normal cerebral vasculature, when administered in small doses, is probably slight vasodilation with a minimal change in the CMR.[32] Increased CMR in discrete regions of the brain, such as the choroid plexus and basal ganglia, can occur. However, overall cortical blood flow is not influenced.[33] Vasoconstriction of the cerebral circulation is not observed even when dopamine is administered in doses of up to 100 μg/kg/min. In that same investigation, dobutamine increased CBF and CMR by 20% and 30%, respectively.[32] Fenoldopam is a dopamine agonist with activity at the DA_1-receptor and α_2-receptor. The administration of fenoldopam leads to systemic vasodilation and a decrease in arterial blood pressure. In humans, fenoldopam decreased systemic blood pressure to a level that was above the LLA; however, a modest (≈15%) reduction was observed in CBF that did not increase to normal levels when systemic blood pressure was supported.[34] This reduction in CBF was attributed to the α_2 activity of fenoldopam; its effect on the injured brain is not known.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Antagonists. Both ACE inhibitors and angiotensin-receptor antagonists (ARAs) are commonly used to treat hypertension. In the surgical setting and in the neurocritical care unit, these drugs are administered to control arterial blood pressure acutely. ACE inhibitors and ARAs reduce arterial blood pressure when hypertension is present. However, they do not affect resting CBF, and autoregulation is maintained.[35] In patients with acute stroke, ACE inhibitors and ARAs reduce arterial blood pressure but do not acutely affect CBF.[36-38] Apparently, these drugs did not reduce CBF when arterial blood pressure modestly decreased (also see Chapter 16).

AGE

The loss of neurons is progressive in the normally aging brain from young adulthood to advanced age. Initial studies showed a reduction in neuronal density of as much as 60%.[39] More recent investigations reveal neuronal loss of approximately 10%.[40] The loss of myelinated fibers results in reduced white matter volume.[41] By contrast, the loss of synapses in the aged brain is considerably greater. The majority of excitatory synapses in the brain are on dendritic spines. Dendrite branching and volume progressively decrease, and the number of dendritic spines is reduced by approximately 25% to 35%.[41] Attendant with the loss of neuropil, both CBF and $CMRO_2$ decrease by 15% to 20% at the age of 80 years[42] (also see Chapters 80 and 93).

EFFECTS OF ANESTHETICS ON CEREBRAL BLOOD FLOW AND CEREBRAL METABOLIC RATE

This section discusses the effects of anesthetic drugs on CBF and CMR. It includes limited mentions of the influences on autoregulation, CO_2 responsiveness, and CBV. Effects on CSF dynamics, the BBB, and epileptogenesis are discussed in the section, "Epileptogenesis."

In neuroanesthesia, the manner in which anesthetic drugs and techniques influence CBF receives prime attention. The rationale is twofold. First, the delivery of energy substrates is dependent on CBF, and modest alterations in CBF can substantially influence neuronal outcome in the setting of ischemia. Second, control and manipulation of CBF are central to the management of ICP because as CBF varies in response to vasoconstrictor-vasodilator influences, CBV varies with it.[43] With respect to ICP, CBV is the more critical variable. In the normal brain, CBV is approximately 5 mL/100 g of brain,[44] and over a $Paco_2$ range of approximately 25 to 70 mm Hg, CBV changes by approximately 0.049 mL/100 g for each 1 mm Hg change in $Paco_2$. In an adult brain weighing approximately 1400 g, this change can amount to 20 mL in total CBV for a $Paco_2$ range of 25 to 55 mm Hg. Because CBV is more difficult to measure than CBF few data exist, especially in humans.

Although CBV and CBF usually vary in parallel, the magnitude of change in CBV is less than the magnitude of change in CBF (Fig. 17-7). In addition, CBV and CBF independently vary under some circumstances. During cerebral ischemia, for example, CBV increases, whereas CBF is significantly reduced.[45] Autoregulation normally serves to prevent MAP-related increases in CBV. In fact, as the cerebral circulation constricts to maintain a constant CBF in the face of an increasing MAP, CBV actually decreases.[46] When autoregulation is impaired or its upper limit (≈150 mm Hg) is exceeded, CBF and CBV then increase in parallel as arterial blood pressure increases (see Fig. 17-6). A declining MAP results in a progressive increase in CBV as the cerebral circulation dilates to maintain constant flow, and exaggerated increases in CBV occur as the MAP decreases to less than the LLA.[46] In normal subjects, the initial increases in CBV do not increase ICP because there

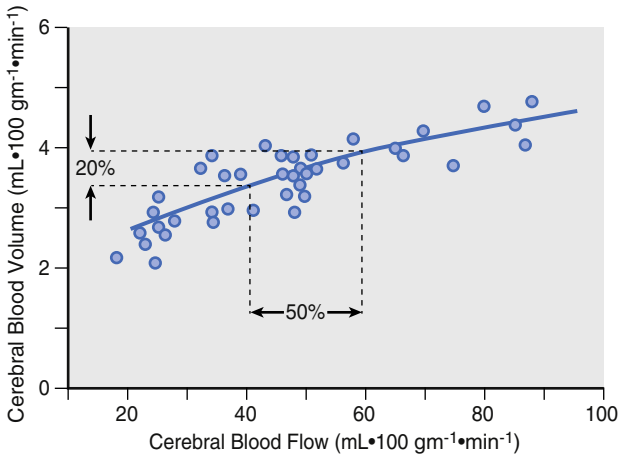


Figure 17-7. Relationship between cerebral blood flow (CBF) and cerebral blood volume (CBV). Although a linear relationship exists between CBF and CBV, the magnitude of the change in CBV for a given change in CBF is considerably less. An increase in CBF of 50% results in a change in CBV of only 20%.

is latitude for compensatory adjustments by other intracranial compartments (e.g., translocation of venous blood and CSF to extracerebral vessels and the spinal CSF space, respectively). When intracranial compliance* is reduced, an increase in CBV can cause herniation or sufficiently reduce CPP to cause ischemia.

INTRAVENOUS ANESTHETIC DRUGS

The action of most intravenous anesthetics leads to parallel reductions in CMR and CBF. Ketamine, which causes an increase in the CMR and CBF, is the exception. The effects of selected intravenous anesthetic drugs on human CBF are compared in Figure 17-8[25,47-59] (also see Chapter 30).

Changes in CBF induced by intravenous anesthetics are largely the result of the effects on the CMR with parallel (coupled) changes in CBF. If this were the entire explanation, then the CBF/CMR ratio would be the same for all anesthetics. Unfortunately, it is not. In addition, direct effects on cerebral vascular smooth muscle (e.g., vasoconstriction, vasodilation, alteration of autoregulatory function) contribute to the net effect. For instance, barbiturates are cerebral vasoconstrictors, yet some barbiturates actually cause relaxation of cerebral vascular smooth muscle in isolated vessel preparations.[60] However, a substantial reduction in the CMR occurs in vivo, and the net effect at the point of EEG suppression is vasoconstriction and a substantial decrease in CBF.[61] In general, autoregulation and CO_2 responsiveness are preserved during the administration of intravenous anesthetic drugs.

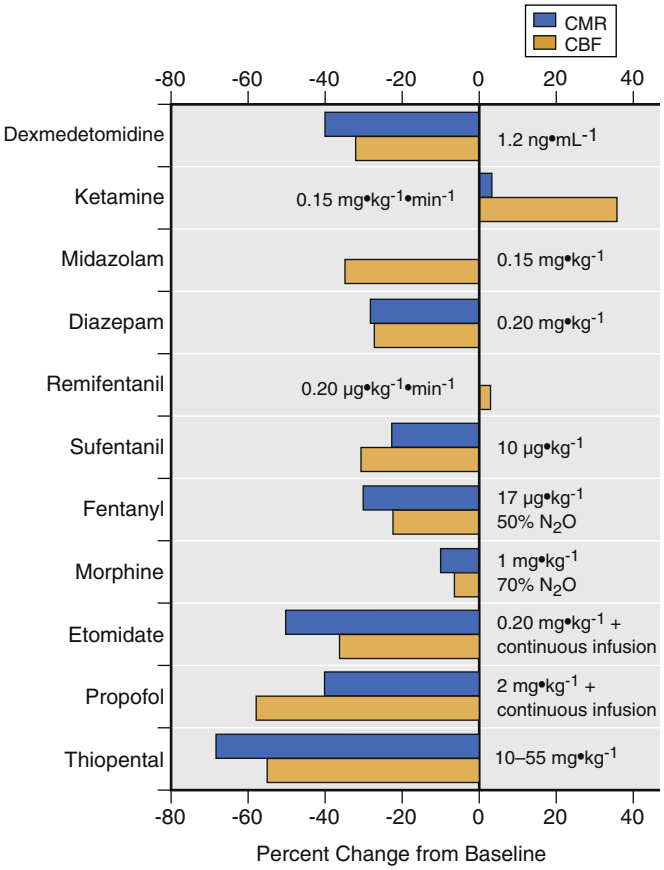


Figure 17-8. Changes in cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen ($CMRO_2$) caused by intravenous anesthetic drugs. The data are derived from human investigations and are presented as percent change from unanesthetized control values. Dexmedetomidine CMR values were determined on a background of 0.5% isoflurane anesthesia (see the text for details). No data for the $CMRO_2$ effects of midazolam in humans are available. *(Data from references 25, 47-59.)*

Barbiturates

A dose-dependent reduction in CBF and CMR occurs with barbiturates. With the onset of anesthesia, both CBF and $CMRO_2$ are reduced by approximately 30%.[62] When large doses of thiopental cause complete EEG suppression, CBF and CMR are reduced by approximately 50%.[61,63] Further increases in the barbiturate dose have no additional effect on the CMR.[61] These observations suggest that the major effect of nontoxic doses of depressant anesthetics is a reduction in the component of cerebral metabolism that is linked to electrical brain function (e.g., neurophysiologic activity) with only minimal effects on the second component, which is related to cellular homeostasis (see Fig. 17-3).

Tolerance to the CBF and CMR effects of barbiturates may quickly develop.[64] In patients with severe head injury in whom *barbiturate coma* was maintained for 72 hours, the blood concentration of thiamylal required to maintain EEG burst suppression was observed to be increased by the end of the first 24 hours and continued to increase over the next 48 hours.[65] During deep pentobarbital anesthesia, autoregulation is maintained at mean arterial pressures as low as 60 mm Hg. CO_2 responsiveness also persists.

*Note a well-entrenched misuse of terminology.[206] The "compliance" curve that is commonly drawn to describe the ICP-volume relationship (see Fig. 70-3) actually depicts the relationship $\Delta P/\Delta V$ (elastance) and not $\Delta V/\Delta P$ (compliance). The reference to "reduced compliance" in this text is more correctly described as "increased elastance." However, because the existing literature most commonly uses the "compliance" terminology, the authors have left the misuse uncorrected herein.

Propofol

The effects of propofol (2,6-diisopropylphenol) on CBF and CMR are similar to those of barbiturates. Both CBF and CMR decrease after the administration of propofol in humans.[66] In healthy volunteers, surgical levels of propofol reduced regional CBF by 53% to 79% in co-mparison with the awake state.[67,68] Alkire and co-workers[69] assessed cerebral glucose metabolism in volunteers by positron-emission tomography (PET) before and during infusion of propofol to the point of unresponsiveness. The whole-brain metabolic rate decreased by 48% to 58%, with limited regional heterogeneity observed. When compared with isoflurane-fentanyl or sevoflurane-fentanyl anesthesia, a combination of propofol and fentanyl decreased subdural pressure in patients with intracranial tumors and decreased the arteriovenous oxygen content difference ($AVDO_2$).[70] Collectively, these investigations in human subjects indicate that propofol effects reductions in the CMR and secondarily decreases CBF, CBV, and ICP.

Both CO_2 responsiveness and autoregulation are preserved in humans during the administration of propofol,[71,72] even when administered in doses that produce burst suppression of the EEG.[73] The magnitude of the reduction in CBF during hypocapnia is decreased during propofol administration. This effect is probably due to the cerebral vasoconstriction induced by suppression of CMR, which further limits hypocapnia-mediated vasoconstriction.

Etomidate

The effects of etomidate on CBF and CMR are also similar to those of barbiturates. Roughly parallel reductions in CBF and CMR occur in humans,[47,74] and, in general, they are accompanied by progressive suppression of the EEG. Induction of anesthesia with either thiopental or etomidate resulted in a similar reduction in MCA flow velocity of approximately 27%.[75] The changes in CBF and CMR are substantial. Renou and colleagues[47] administered approximately 0.2 mg/kg of etomidate to adults and observed mean reductions in CBF and CMR of 34% and 45%, respectively. As is the case with barbiturates, no further reduction in the CMR occurs when additional drug is administered beyond a dose sufficient to produce EEG suppression. This latter phenomenon has not been demonstrated in humans. However, Bingham and associates[76] observed that etomidate lowered ICP when administered to patients with severe head injuries in whom EEG activity was well preserved but was ineffective when substantial antecedent EEG suppression existed. The global CMR suppression attainable with etomidate is slightly less profound than that achieved with isoflurane and barbiturates. This finding is consistent with the observation that unlike barbiturates, which cause CMR suppression throughout the brain, the CMR suppression caused by etomidate is regionally variable and predominantly occurs in forebrain structures.

Etomidate is effective in reducing ICP without causing a reduction in CPP in patients with intracranial tumors[77] and patients with head injuries.[78] However, the administration of etomidate resulted in an exacerbation of brain tissue hypoxia and acidosis in patients in whom the MCA was temporarily occluded during surgery.[79] Additional concerns regarding the occurrence of adrenocortical suppression caused by enzyme inhibition and renal injury caused by the propylene glycol vehicle[80] will probably preclude more than episodic use.

Reactivity to CO_2 is preserved in humans during the administration of etomidate.[47,74] Autoregulation has not been evaluated. Myoclonus and epileptogenesis are discussed in the section, "Epileptogenesis."

Narcotics

Inconsistencies can be found in the available information, but narcotics likely have relatively little effect on CBF and CMR in the normal, unstimulated nervous system. When changes do occur, the general pattern is one of modest reductions in both CBF and CMR. The inconsistencies in the literature probably largely arise because the *control* states entailed paralysis and nominal sedation in many studies, often with N_2O alone. In these studies, in which substantial reductions in CBF and CMR were frequently observed, the effect of the narcotic was probably a combination of the inherent effect of the drug plus a substantial component attributable to reduction of arousal. Comparable effects related to reduction of arousal may occur and can be clinically important. However, they should be viewed as nonspecific effects of sedation or pain control, or both, rather than specific properties of narcotics. The following discussion emphasizes investigations in which control measurements were unlikely to have been significantly influenced by arousal phenomena.

Morphine. When morphine (~1 mg/kg) was administered as the sole drug to humans, Moyer and associates[81] observed no effect on global CBF and a 41% decrease in the $CMRO_2$. The latter is a substantial reduction, and the absence of a simultaneous adjustment in CBF is surprising. No other investigations of morphine have been conducted in humans alone. Jobes and co-workers[48] gave morphine (1 and 3 mg/kg) with 70% N_2O to patients and observed no significant change in CBF or CMR. The N_2O that was used might be expected to have caused a tendency toward increases in CBF and CMR. The relative absence of *net* changes in these variables from awake control measurements suggests a small-to-moderate depressive effect of morphine on CBF and CMR at this large dose. However, morphine can cause a substantial release of histamine in individual patients. Histamine is a cerebral vasodilator that will cause an increase in CBV and a CBF effect that will vary, depending on the systemic blood pressure response.

Autoregulation was observed to be intact between MAP values of 60 and 120 mm Hg in human volunteers anesthetized with morphine, 2 mg/kg, and 70% N_2O.[82]

Fentanyl. Limited human data are available. Vernhiet and colleagues[49] measured CBF and $CMRO_2$ before and during anesthesia with 12 to 30 (mean, 16) μg/kg of fentanyl and 50% N_2O in patients about to undergo cerebral angiography. Atropine and pancuronium were the only other agents administered. Neither CBF nor $CMRO_2$ significantly changed from awake control values in their group of six subjects. However, one of the patients (with epilepsy and with normal results on computed tomography

[CT]) had dramatic and unexplained increases in both CBF and $CMRO_2$. For the remaining five patients, CBF and $CMRO_2$ decreased by 21% and 26%, respectively ($P < .05$). The data for fentanyl-N_2O presented in Figure 17-8 are derived from these patients, who received an average of 17 μg/kg of fentanyl. Murkin and associates[83] measured CBF before and after induction of anesthesia with high-dose fentanyl, 100 μg/kg, and diazepam, 0.4 mg/kg. CBF fell by 25%, although part of this effect may well have been a result of benzodiazepine (see later discussion in the section, "Benzodiazepine") rather than fentanyl. Firestone and co-workers,[84] using PET, observed a heterogeneous CBF response to 1.5 μg/kg of fentanyl in healthy volunteers. Increases occurred in the frontal, temporal, and cerebellar areas simultaneous with decreases in discrete areas associated with pain-related processing. CO_2 responsiveness and autoregulation are unaffected, and the hyperemic CBF response to hypoxia remains intact.

In conclusion, fentanyl will cause a moderate global reduction in CBF and CMR in the normal quiescent brain and will, similar to morphine, cause larger reductions when administered during arousal.

Alfentanil. McPherson and associates[85] administered alfentanil, 320 μg/kg, to pentobarbital-anesthetized dogs. They observed no changes in CBF, CMR, CO_2 responsiveness, autoregulation, or CBF response to hypoxia. No studies of the effects of alfentanil on the CMR in humans have been conducted. Schregel and colleagues[86] administered 25 to 50 μg/kg of alfentanil to patients receiving 60% N_2O after induction of anesthesia with thiopental. CBFV transiently decreased. A Doppler measure of MCA diameter was simultaneously unchanged, thus suggesting that the reduction in CBFV was indicative of a decrease in CBF. Mayberg and co-workers[87] also observed no change in CBFV in response to 25 to 50 μg/kg of alfentanil given to patients during maintenance of anesthesia with isoflurane-N_2O.

Although data are few, the general pattern is similar and the conclusions should be the same as for sufentanil (see the next paragraph).[88-92] Alfentanil was included with fentanyl and sufentanil in two of the investigations of conditions in the surgical field mentioned in connection with sufentanil.[93,94] No adverse effects were noted.

Sufentanil. Studies in animals[95,96] and humans indicate that sufentanil causes, depending on the dose, either no change or a reduction in CBF and CMR. Stephan and colleagues[50] measured CBF and $CMRO_2$ in patients before and after induction of anesthesia with 10 μg/kg of sufentanil. They observed a 29% reduction in CBF and a 22% reduction in $CMRO_2$. Murkin and co-workers,[97] in a study involving the same dose of sufentanil and a similar design, made essentially identical observations. Mayer and associates[98] gave 0.5 μg/kg of sufentanil to volunteers and observed no change in CBF. Weinstabl and co-workers[99] observed reductions in CBFV when 1.0 and 2.0 μg/kg of sufentanil were given to patients with increased ICP who were in the intensive care unit (ICU).[99] Neither Weinstabl and colleagues[99] nor Mayer and associates,[98] who administered sufentanil to healthy volunteers, observed changes in CBFV after 0.5 μg/kg of sufentanil.

A logical conclusion is that no change and no reduction in ICP occurs as a result of the administration of either sufentanil or alfentanil.[99-104] However, in some investigations in humans, sufentanil was associated with modest increases in ICP. The increases in ICP associated with sufentanil are likely the consequence, in part, of a normal autoregulatory response to the sudden reduction in the MAP that can occur as a consequence of sufentanil administration.[105] Therefore sufentanil and fentanyl[102] should be administered in a manner that does not produce a sudden reduction of MAP. Such a decrease will reduce CPP and may increase ICP, each of which, in sufficient extreme, may be deleterious. However, ICP increases attributed to sufentanil are small. Furthermore, four investigations[93,94,106,107] that compared conditions in the surgical field, including pressure under brain retractors,[93] identified no adverse influences attributable to sufentanil. Accordingly, sufentanil need not be viewed as contraindicated in any way, although its effect on the MAP should be closely followed.

Remifentanil. Investigations of moderate doses of remifentanil in patients have revealed similar effects to that of other synthetic narcotics (with the exception of its substantially shorter duration of action). In patients undergoing craniotomy for supratentorial space-occupying lesions, 1 μg/kg of remifentanil caused no change in ICP.[108] In a second investigation in patients undergoing craniotomies, approximately 0.35 μg/kg/min of remifentanil resulted in CBF values comparable to those observed with moderately deep anesthesia with either isoflurane-N_2O or fentanyl-N_2O,[109] and CO_2 responsiveness was preserved. Greater doses of remifentanil may have more substantial effects. CBFV in the MCA decreased 30% in response to 5 μg/kg, followed by 3 μg/kg/min of remifentanil at a constant MAP in patients being anesthetized for bypass surgery.[51] A lower dose of 2 μg/kg, followed by an infusion of 3 μg/kg/min, however, did not affect CBFV. Quantitatively similar observations were made after a large dose of sufentanil in patients undergoing cardiac anesthesia (see earlier discussion in the section, "Sufentanil").[50]

Remifentanil was administered with other drugs that might influence cerebral hemodynamics. More recent studies in human volunteers have demonstrated that the infusion of *small* (*sedative*) doses of remifentanil can increase CBF. A PET study in human subjects to whom remifentanil, 0.05 and 0.15 μg/kg/min, was administered revealed increases in CBF in the prefrontal, inferior parietal, and supplementary motor cortices; reductions in CBF were observed in the cerebellum, superior temporal lobe, and midbrain gray matter.[108] The relative increase in CBF was greater with the administration of the larger dose of remifentanil. Similar data were obtained by Lorenz and colleagues,[110] who used magnetic resonance imaging (MRI) to determine CBF.[110] In a PET investigation in human volunteers, Kofke and co-workers[111] observed remifentanil-induced increases in regional CBF within the limbic system. Although the underlying mechanisms of the increases in CBF are not clear, disinhibition produced by the small-dose remifentanil infusion, or perhaps the sensation of side effects (e.g., warmth, comfort, pruritus),[110] may have contributed. When combined with

N_2O, CBF and CO_2 reactivity is similar in patients given remifentanil or fentanyl.[109] In conclusion, sedative doses of remifentanil alone can cause minor increases in CBF. With larger doses or with the concomitant administration of anesthetic adjuvants, CBF is either unaltered or modestly reduced.

Benzodiazepines

Benzodiazepines cause parallel reductions in CBF and CMR in humans. CBF and $CMRO_2$ decreased by 25% when 15 mg of diazepam was given to patients with head injuries.[52] The effects of midazolam on CBF (but not on CMR) have also been studied in humans. Forster and associates[53,112] observed a 30% to 34% reduction in CBF after the administration of 0.15 mg/kg of midazolam to awake healthy human volunteers. Veselis and coworkers,[113] using PET, observed a global 12% reduction in CBF after a similar dose and noted that the decreases preferentially occurred in the brain regions associated with arousal, attention, and memory. CO_2 responsiveness was preserved.[114]

In conclusion, benzodiazepines cause a moderate reduction in CBF in humans, which may be metabolically coupled. The extent of the maximal reductions of CBF and CMR produced by benzodiazepines is probably intermediate between the decreases caused by narcotics (modest) and barbiturates (substantial). It appears that benzodiazepines should be safe to administer to patients with intracranial hypertension, provided that respiratory depression and an associated increase in $Paco_2$ do not occur.

Flumazenil

Flumazenil is a highly specific, competitive benzodiazepine receptor antagonist. It had no effect on CBF when administered to unanesthetized human volunteers.[112,115] However, flumazenil reverses the CBF-, CMR-, and ICP-lowering effects of midazolam. Whereas Knudsen and colleagues[116] observed no change in either CBF or CMR when patients were aroused from midazolam anesthesia with flumazenil at the conclusion of craniotomy for brain tumor resection, Chiolero and coauthors[117] reported severe increases in ICP when flumazenil was given to patients with head injuries who were sedated with midazolam and in whom ICP was poorly controlled before the administration of flumazenil. These latter observations are consistent with animal investigations during which flumazenil not only reversed the CBF and CMR effects of midazolam, but it also caused a substantial, although short-lived, overshoot above premidazolam levels in both CBF and ICP by 44% to 56% and 180% to 217%, respectively. The CMR did not rise above control levels, thus indicating that the increase in CBF was not metabolically coupled. The CBF overshoot effect is unexplained, but it may be a neurogenically mediated arousal phenomenon. Flumazenil should be very cautiously used to reverse benzodiazepine sedation in patients with impaired intracranial compliance.

Droperidol

No human investigations of the CBF and CMR effects of droperidol have been conducted in isolation. However, the information available from animal investigations and combination drug administration in humans,[118,119] taken together, suggests that droperidol is not a cerebral vasodilator and probably has little effect on CBF and CMR in humans. The occasional increases in ICP that have been observed[118] probably reflect normal autoregulation-mediated vasodilation in response to an abrupt decrease in the MAP.

Ketamine

Among the intravenous anesthetics, ketamine is unique in its ability to cause increases in both CBF and CMR.[120] Animal studies indicate that the changes in the CMR are regionally variable. In rats, substantial increases occur in limbic system structures with modest changes or small decreases in cortical structures.[121] PET studies in humans have demonstrated that subanesthetic doses of ketamine (0.2 to 0.3 mg/kg) can increase global CMR by approximately 25%.[122] The greatest increase in the CMR occurred in the frontal and anterior cingulate cortex. A relative reduction in the CMR in the cerebellum was also observed. Commercially available formulations of ketamine contain both the (*S*)- and (*R*)-ketamine enantiomers. The (*S*)-ketamine enantiomer substantially increases CMR, whereas the (*R*) enantiomer tends to decrease the CMR, particularly in the temporomedial cortex and in the cerebellum.[123] These changes in the CMR are accompanied by corresponding changes in CBF.[124] Global, as well as regional, increases in CBF in humans that were not accompanied by similar increases in the $CMRO_2$ after the administration of (*S*)-ketamine enantiomer have been observed. Both subanesthetic and anesthetic doses of ketamine increased global CBF by approximately 14% and 36%, respectively, without altering global $CMRO_2$. As expected, the oxygen extraction ratio was reduced, considering the unchanged CMR and increased CBF. CBV increased by approximately 50%.[59] The majority of investigations indicate that autoregulation is maintained during ketamine anesthesia,[125] and CO_2 responsiveness is preserved.

The anticipated ICP correlate of the increase in CBF and CBV has been confirmed to occur in humans. However, anesthetic drugs (e.g., diazepam, midazolam, isoflurane-N_2O, propofol) blunt or eliminate the increases in ICP or CBF associated with ketamine.[120,126,127] In fact, decreases in ICP occur when relatively large doses of ketamine (1.5 to 5 mg/kg) are administered to patients with head injuries who are sedated with propofol.[128] Accordingly, although ketamine is probably best avoided as the sole anesthetic drug in patients with impaired intracranial compliance, it may be cautiously given to patients who are simultaneously receiving the drugs mentioned earlier (e.g., propofol, opioids).

Lidocaine

Lidocaine produces a dose-related reduction in the $CMRO_2$ in experimental animals.[129] In dogs, 3 mg/kg decreased the $CMRO_2$ by 10%, and 15 mg/kg decreased it by 27%. When very large doses (160 mg/kg) were given to dogs maintained on cardiopulmonary bypass, the reduction in the $CMRO_2$ was apparently more than that observed with large-dose barbiturates.[130] In addition, the membrane-stabilizing effect of lidocaine likely reduces

the energy required for the maintenance of membrane integrity. In unanesthetized human volunteers, Lam and colleagues[131] observed reductions in CBF and CMR of 24% and 20%, respectively, after the administration of 5 mg/kg of lidocaine over a 30-minute period, followed by an infusion of 45 μg/kg/min.

Bedford and co-workers[132] compared the effectiveness of bolus doses of thiopental, 3 mg/kg, and lidocaine, 1.5 mg/kg, in controlling the acute increase in ICP that occurred after the application of a pin head holder or skin incision in patients undergoing craniotomies. The two regimens were equally effective in causing a reduction in ICP. However, the decrease in the MAP was greater with thiopental. Accordingly, a bolus dose of lidocaine is a reasonable adjunct to the prevention or treatment of acute increases in ICP and can prevent increases in ICP associated with endotracheal suctioning. Although large doses of lidocaine can produce seizures in humans and in some experimental animals, lidocaine-induced seizures have not been reported in anesthetized humans. Nonetheless, lidocaine doses should be adjusted to those that achieve serum levels less than the seizure threshold (>5 to 10 μg/mL) in awake humans. After a 2-mg/kg bolus, peak serum concentrations of 6.6 to 8.5 μg/mL are below the seizure threshold. Bolus doses of 1.5 to 2.0 mg/kg therefore seem appropriate.

INHALED ANESTHETICS

Volatile Anesthetics

The pattern of volatile anesthetic effects on cerebral physiology is quite different than the pattern from intravenous anesthetics, which generally cause parallel reductions in CMR and CBF. All volatile anesthetics, similar to intravenous sedative-hypnotic drugs, suppress cerebral metabolism in a dose-related manner.[133-136] Volatile anesthetics also possess intrinsic cerebral vasodilatory activity as a result of direct effects on vascular smooth muscle. The net effect of volatile anesthetics on CBF is therefore a balance between a reduction in CBF caused by CMR suppression and an augmentation of CBF caused by the direct cerebral vasodilation. When administered at a dose of 0.5 MAC, CMR suppression–induced reduction in CBF predominates, and net CBF decreases in comparison with the awake state. At 1 MAC, CBF remains unchanged; at this dose, CMR suppression and vasodilatory effects are in balance. Beyond 1 MAC, the vasodilatory activity predominates, and CBF significantly increases, even though the CMR is substantially reduced (Fig. 17-9[137]). Vasodilation with increasing doses of volatile agents leads to an attenuation of cerebral autoregulation. With large doses, autoregulation is abolished and cerebral perfusion becomes pressure passive (Fig. 17-10).

The increase in CBF produced by volatile anesthetics at doses larger than 1 MAC could reflect uncoupling of flow and metabolism. However, coupling (CBF adjustments paralleling changes in the CMR) persists during anesthesia with volatile anesthetics.[138-141] Accordingly, the conclusion should be that the CBF/CMR ratio is altered (increased) by volatile anesthetics. This alteration is dose related, and, under steady-state conditions,

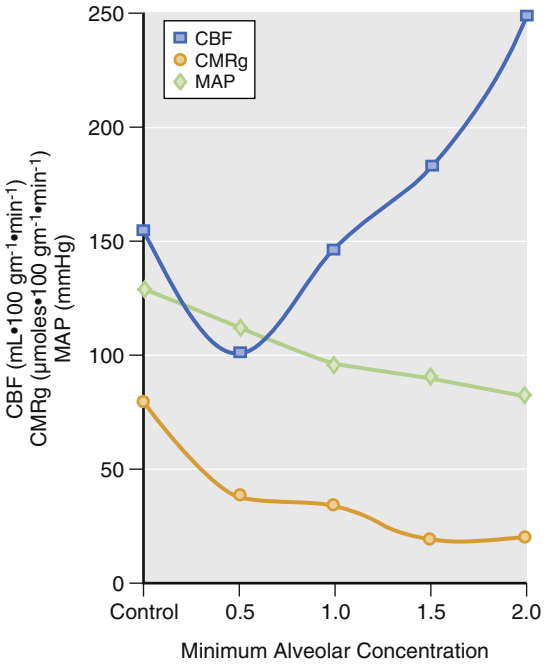


Figure 17-9. Relationship between changes in the cerebral metabolic rate of glucose (CMRg) and cerebral blood flow (CBF) in the motor-sensory cortex in rats during isoflurane anesthesia. The majority of the suppression in the CMR caused by isoflurane has occurred by 1 minimum alveolar concentration (MAC); CBF is not increased in this concentration range. Thereafter, additional isoflurane causes little further reduction in the CMR, and cerebral vasodilation occurs. These data (± standard deviation [SD]) from Maekawa and colleagues[137] suggest the importance of metabolic coupling in determining the effects of isoflurane on CBF. *MAP,* Mean arterial pressure.

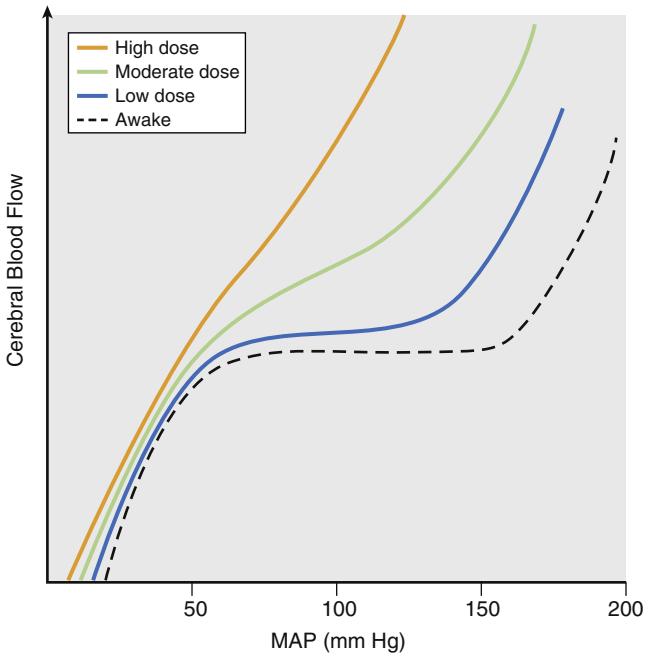


Figure 17-10. Schematic representation of the effect of increasing concentrations of a typical volatile anesthetic drug on autoregulation of cerebral blood flow. Dose-dependent cerebral vasodilation results in attenuation of autoregulatory capacity. Both the upper and lower thresholds are shifted to the left. *MAP,* Mean arterial pressure.

increasing doses of volatile agents lead to greater CBF/$CMRO_2$ ratios[134,142]; that is, higher MAC levels cause more *luxury* perfusion.

The important clinical consequences of the administration of volatile anesthetics are derived from the increases in CBF and CBV—and consequently ICP—that can occur. Of the commonly used volatile anesthetics, the order of vasodilating potency is approximately halothane ≫ enflurane > desflurane ≈ isoflurane > sevoflurane.

Effects on Cerebral Blood Flow. Volatile anesthetics possess intrinsic vasodilatory activity, and they not only modify cerebral autoregulation, but they also produce a dose-dependent decrease in arterial blood pressure. Hence, their effects on CBF and CMR are best evaluated when arterial blood pressure is maintained at the same level. In addition, the cerebrovascular effects of volatile anesthetics are modulated by the simultaneous administration of other CNS-active drugs. The control state, awake, sedated, or anesthetized, against which the CBF and CMR effects of volatile anesthetics are compared, is important to recognize. The best information concerning the cerebrovascular effects of volatile anesthetics is obtained in studies during which a nonanesthetized awake control state is used.

Data on the cerebrovascular effects of halothane and enflurane are limited. Initial studies in humans demonstrated that the administration of 1 MAC halothane significantly increases CBF, even when systemic blood pressure is substantially reduced, in comparison with preanesthetic CBF.[143] The same investigators subsequently showed that in humans, when the MAP is maintained at 80 mm Hg, 1.1 MAC levels of halothane increase CBF by as much as 191% and decrease the CMR by approximately 10% (Fig. 17-11).[143,144,146,148] When compared with awake values, 1.2 MAC enflurane also increased CBF and decreased CMR by 45% and 15%, respectively.[145] The dramatic increases in CBF with a simultaneous modest reduction in the CMR attest to the cerebral vasodilatory properties of halothane and enflurane. Isoflurane, by contrast, does not increase CBF as much as halothane or enflurane. At doses of 1.1 MAC, isoflurane increases CBF by approximately 19% when arterial blood pressure is maintained within the normal range. The CMR is reduced by approximately 45%.[141]

Both sevoflurane and desflurane can significantly reduce CBF in humans when compared with CBF in awake, nonanesthetized patients. At 1 MAC concentrations, sevoflurane[147] and desflurane[145] decreased CBF by 38% and 22% and CMR by 39% and 35%, respectively. These results, which suggest that the cerebral vasodilation produced by isoflurane is greater than that produced by sevoflurane and desflurane, were obtained with CBF measured by the inert gas technique. This technique primarily measures CBF within the cortex and therefore may have substantially underestimated global CBF. PET studies in healthy humans have shown that sevoflurane dose-dependently suppresses the $CMRO_2$ and CBF; at 1 MAC levels, the reduction in CBF and $CMRO_2$ is approximately 50% and 50% to 60%, respectively.[67,68] Even with a significant reduction in CBF, the administration of sevoflurane does not cause a decrease in CBV. In addition, other

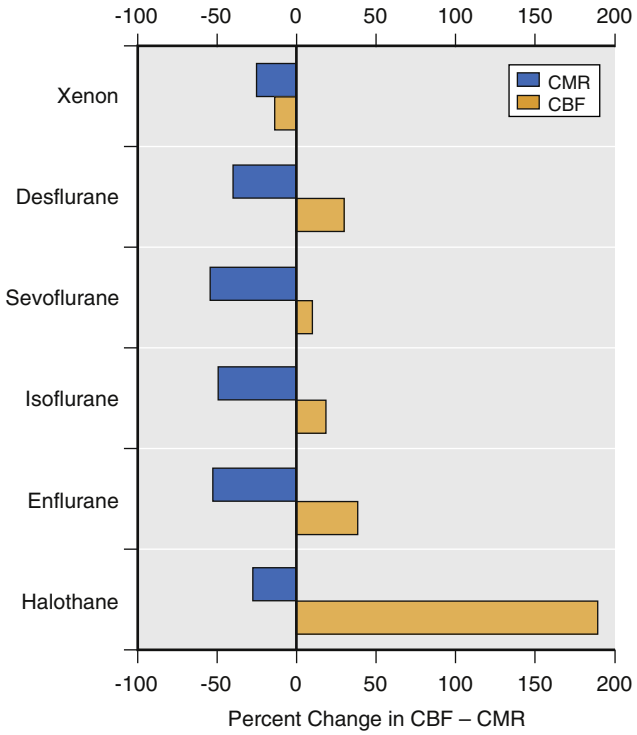


Figure 17-11. Estimated changes in cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen ($CMRO_2$) caused by volatile anesthetics. The CBF data for halothane, enflurane, and isoflurane were obtained during anesthesia (with blood pressure support) at 1.1 minimum alveolar concentration (MAC) in humans[144] and are expressed as percent change from awake control values. The $CMRO_2$ data for halothane, enflurane, and isoflurane were obtained in cats[134,146] and are expressed as percent change from N_2O-sedated control values. The data for sevoflurane were obtained during 1.1 MAC anesthesia in rabbits and are expressed as percent change from a morphine-N_2O–anesthetized control state.[136] CBF values were obtained in patients who received 1 MAC sevoflurane anesthesia.[147] Desflurane data were obtained in patients to whom 1 MAC desflurane was administered.[148]

investigations in humans, most using the measurement of MCA flow velocity by transcranial Doppler, indicate that differences in the effects of isoflurane, desflurane (Fig. 17-12, *A*), and sevoflurane are, at best, modest.[149-151] Unfortunately, a strictly quantitative comparison among these volatile anesthetics is not possible, considering the variations in arterial blood pressure among study group patients. In addition, some discrepancy exists among studies in the literature regarding the magnitude of the effects of volatile anesthetics on CBF. Much of this inconsistency may occur as a result of the interaction of regionally selective CBF methods with the heterogeneity within the cerebrum of the CBF effects of volatile anesthetics. (See the later section, "Distribution of Changes in Cerebral Blood Flow/Cerebral Metabolic Rate.")

The anesthetic properties of xenon were recognized several decades ago, but this anesthetic is only now being evaluated for possible use in patients. The MAC of xenon has been estimated to be 63% to 71%, with female patients having significantly lower MAC values (51%).[152] Xenon primarily exerts its anesthetic effect via noncompetitive antagonism of the *N*-methyl-D-aspartate receptor (NMDAR),[153] although activation of the TREK two-pore

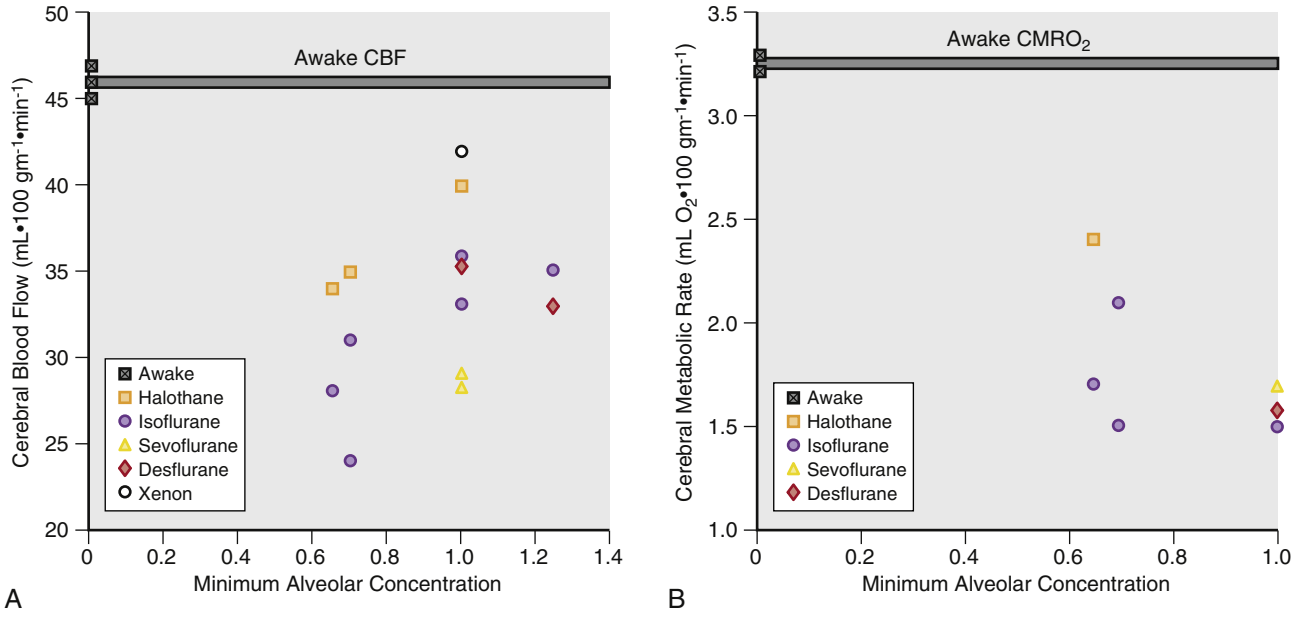


Figure 17-12. Effect of volatile anesthetics on cerebral blood flow (CBF) (**A**) and the cerebral metabolic rate of oxygen ($CMRO_2$) (**B**) in awake humans. The results are a composite of CBF and $CMRO_2$ values obtained from a number of separate investigations.[54,96,134,135,139-151] In these studies, arterial partial pressure of carbon dioxide ($Paco_2$) was maintained in the normocapnic range (~35 to 40 mm Hg), and mean arterial pressure was supported. In most of the investigations, CBF was measured by the inert gas technique. This technique primarily measures cortical CBF and, as such, may underestimate global CBF.

K^+ channel might also play a role.[154] In healthy humans, the administration of 1 MAC xenon resulted in a reduction in CBF by approximately 15% in the cortex and by 35% in the cerebellum; interestingly, CBF in white matter increased by 22%.[155] This reduction in CBF is accompanied by a parallel reduction of the cerebral metabolic rate of glucose (CMRg) by 26%.[156] Cerebral autoregulation and CO_2 reactivity are preserved during xenon anesthesia in animals.[157] Under background pentobarbital anesthesia in an experimental model of increased ICP, the administration of xenon did not increase ICP, and the response to both hypocapnia and hypercapnia was preserved.[158] Diffusion of xenon into air-containing spaces such as the bowel does occur, although the magnitude of air expansion is considerably less than that with N_2O.[159] Accordingly, caution will have to be exercised with the use of xenon in patients with intracranial air. These data indicate that it has a favorable profile for neuroanesthesia.

Effects on Cerebral Metabolic Rate. All of the volatile anesthetics cause reductions in the CMR. The degree of reduction in the $CMRO_2$ that occurs at a given MAC is less with halothane than with the other four anesthetics. Sevoflurane's effect on the $CMRO_2$ is very similar to that of isoflurane. The available information, derived in separate investigations, suggests that desflurane causes slightly less suppression of the $CMRO_2$ than isoflurane, especially at concentrations above 1 MAC.[135] Although a direct comparison of the $CMRO_2$ effects of all of the volatile anesthetics has not been performed in humans, doses of 1 MAC isoflurane, sevoflurane, and desflurane clearly reduce the $CMRO_2$ ($AVDO_2$ in arterial and jugular bulb blood samples) by 25%,[160] 38%,[148] and 22%,[161] respectively. Halothane (0.9 MAC) and isoflurane (0.5 MAC) can decrease the CMRg by 40% and 46%, respectively, in PET studies.[69,162] The decrease in the $CMRO_2$ is dose related. With isoflurane (and almost certainly desflurane and sevoflurane as well), the maximal reduction is simultaneously attained with the occurrence of EEG suppression,[135] which occurs at clinically relevant concentrations, such as 1.5 to 2 MAC in humans. Additional isoflurane up to 6% end-tidal volume results in no further reduction in the CMR and no indication of metabolic toxicity. Halothane presents a contrast to this pattern. Halothane concentrations in excess of 4 MAC are required to achieve EEG suppression in animals, and additional halothane causes a further reduction in the $CMRO_2$ in concert with alterations in energy charge. The latter changes, which are reversible, suggest interference with oxidative phosphorylation. These data indicate that, unlike isoflurane, halothane can produce reversible toxicity when administered in very high concentrations.

Some nonlinearity exists in the CBF and CMR dose-response relationships for volatile anesthetics. The initial appearance of an EEG pattern associated with the onset of anesthesia with halothane, enflurane, and isoflurane is accompanied by a precipitous decline in the $CMRO_2$.[135] Thereafter, the $CMRO_2$ declines in a slower dose-dependent manner. Such an effect has also been demonstrated for sevoflurane. In a dose escalation study in humans, the greatest reduction in entropy (i.e., a measure of anesthetic depth) was observed with 1 MAC sevoflurane anesthesia, with lesser reductions occurring at increasing concentrations.[163] Other studies during anesthetic induction with halothane found significant increases in CBF before any alteration in the CMR. This finding suggests that the direct effect of a volatile agent on smooth muscle may develop more rapidly than influences related to the depression of the CMR.

Distribution of Changes in Cerebral Blood Flow and Cerebral Metabolic Rate. The regional distribution of anesthetic-induced changes in CBF and CMR significantly differs with halothane and isoflurane. Halothane produces relatively homogeneous changes throughout the brain. CBF is globally increased, and CMR is globally depressed. The changes caused by isoflurane are more heterogeneous. Increases in CBF are greater in subcortical areas and hindbrain structures than in the neocortex.[140,164,165] The converse is true for the CMR, with a larger reduction in the neocortex than in the subcortex.[137] In humans, 1 MAC sevoflurane (Fig. 17-13) results in a reduction in CBF within the cortex and the cerebellum. With an increase in sevoflurane dose, CBF within the cortex decreases further. By contrast, flow increases in the cerebellum with doses greater than 1.5 MAC.[67] These effects of sevoflurane are similar to those produced by isoflurane.[67,165] Desflurane has not been evaluated by local CBF studies. However, considering the similarity of its effects on the EEG (suggesting similar cortical CMR and CBF effects), the interim assumption of similar heterogeneity in CBF distribution seems reasonable. These distribution differences may explain certain apparent contradictions in reported CBF effects in the existing literature for isoflurane. Methods that assess global hemodynamic effects reveal greater changes than those that emphasize the cortical compartment. For instance, Eintrei and co-workers[166] found no increase in CBF by surface xenon washout when isoflurane was administered to patients undergoing craniotomy, yet others[167-169] have reported that the administration of isoflurane to normocapnic subjects with intracranial pathologic conditions can result in increases in CSF pressure.

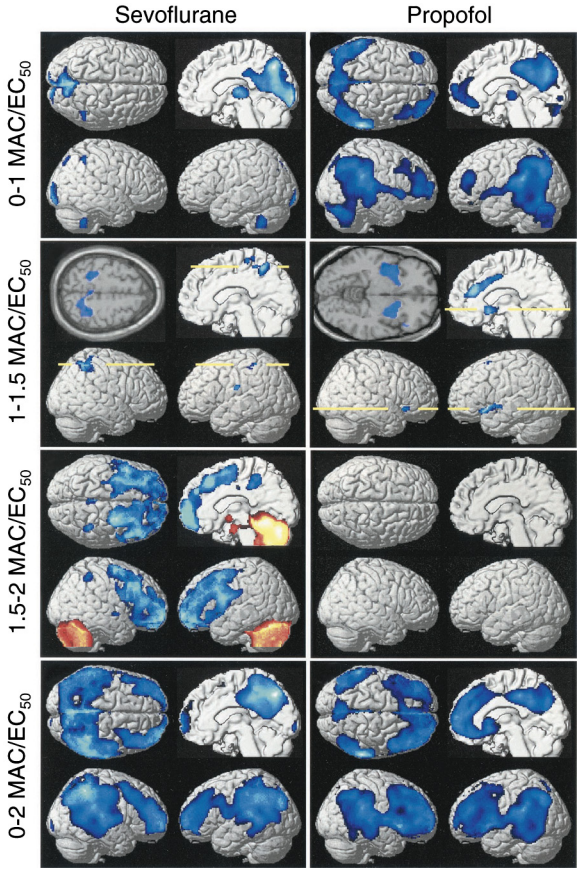


Figure 17-13. Dose-dependent redistribution of cerebral blood flow (CBF) in humans. Positron-emission tomography (PET) scans demonstrate a dose-dependent reduction in CBF in both sevoflurane-anesthetized (*left*) and propofol-anesthetized (*right*) subjects. During sevoflurane anesthesia, an increase in concentration from 1.5 to 2 minimum alveolar concentration (MAC) leads to an increase in CBF within the subcortex, particularly in the cerebellum. A gradual reduction in the mean arterial pressure (MAP) occurred with increasing concentrations of sevoflurane, and the MAP was not supported. The CBF values would be expected to be considerably greater had blood pressure been maintained within the normal range. Therefore the CBF values represented in this figure probably *underestimate* true CBF during sevoflurane anesthesia. In propofol-anesthetized subjects, CBF was uniformly decreased and redistribution of CBF was not observed. EC_{50}, Half-maximal effective concentration. *(From Kaisti K, Metsähonkala L, Teräs M, et al: Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography,* Anesthesiology *96:1358-1370, 2002.)*

Time Dependence of Cerebral Blood Flow Effects. The effects of volatile anesthetics on CBF are time dependent in animal investigations. After an initial increase, CBF substantially decreases and reaches a steady state near pre–volatile agent levels between 2.5 and 5 hours after exposure.[164,170,171] The mechanism of this effect is not understood, and the phenomenon was not evident in humans studied during a 3- or 6-hour exposure to halothane, isoflurane, desflurane, or sevoflurane.[151,172]

Cerebral Blood Volume. The extensive investigation of the influence of volatile anesthetics on CBF has been primarily based on the concern that the cerebral vasodilation produced by volatile anesthetics might increase ICP. However, it is CBV and not CBF, per se, that influences ICP. Most of the intracranial blood is within the cerebral venous circulation; although a reasonable correlation exists between vasodilation-induced increases in CBF and CBV, the magnitude of changes in CBF is considerably greater than that in CBV (see Fig. 17-7). Hence, changes in CBF do not reliably predict changes in CBV and, by extension, in ICP. Nonetheless, CBV is considerably greater during isoflurane anesthesia than during propofol or pentobarbital anesthesia.[43] In human volunteers, 1 MAC sevoflurane reduced regional CBF but not regional CBV; by contrast, propofol reduced both regional CBF and regional CBV (Fig. 17-14).[68] In addition, CBV responds to changes in $Paco_2$ by a reduction in CBV with hypocapnia and an increase in CBV with hypercapnia. The magnitude of the change in CBV is, however, less than the change in CBF. In aggregate, although the effect of anesthetics and interventions on CBF may parallel the effect on CBV, substantial qualitative and quantitative differences may well be observed.

Carbon Dioxide Responsiveness and Autoregulation. CO_2 responsiveness is well maintained during anesthesia with all volatile anesthetics.[173-175] As with all vasodilators, CBF is preserved up to lower MAP values during the administration of volatile anesthetics with no evidence of differences among the various anesthetics. Direct comparisons of CBF with isoflurane, desflurane, and sevoflurane anesthesia

during hypotension are not available. By contrast, autoregulation of CBF in response to increasing arterial blood pressure is impaired, which is most apparent with the anesthetics that cause the most cerebral vasodilation and are dose related. Sevoflurane may cause less impairment of autoregulation than other volatile anesthetics. Recent studies surprisingly report no change in CBFV in response to phenylephrine-induced increases in the MAP during anesthesia with 1.2 to 1.5 MAC sevoflurane[176,177] or in CBF during hemorrhagic hypotension.[178] The autoregulatory response to increasing blood pressure may be pertinent during acute episodes of hypertension, such as during laryngoscopy or mismatch of surgical stimulation to anesthetic depth. Some relevance to hyperemic states after carotid endarterectomy (CEA) or resection of arteriovenous malformations might exist (also see Chapter 70).

Cerebral Vasodilation by Anesthetics—Clinical Implications. Isoflurane, desflurane, and sevoflurane may have a modest cerebral vasodilating effect in the human cortex when administered at doses of 1 MAC or less. In fact, the administration of volatile anesthetics can effect net decreases in CBF (see Fig. 17-12, *A*). These data, however, should be interpreted with considerable caution because the critical variable that is of interest in the clinical setting is CBV. Although a direct correlation exists between CBF and CBV, as noted earlier, the relationship is not strictly 1:1. The magnitude of the changes in CBV is significantly less than the magnitude of the changes in CBF, and modest reductions in CBF may not necessarily be accompanied by reductions in CBV. This finding is exemplified by clinical investigations in which a significant increase in ICP (and by extension, CBV) was observed in patients to whom isoflurane was administered at doses that should reduce CBF.[167,169] Although induction of hypocapnia mitigated the increase in ICP, hyperventilation may not be effective in blunting isoflurane-induced increases in ICP in patients with intracranial tumors.[168] In experimental investigations of cerebral injury, volatile anesthetics significantly increased ICP, which was not ameliorated by hypocapnia.[179] Collectively, these data suggest that volatile anesthetics have minimal effects on cerebral hemodynamics in patients with normal intracranial compliance. However, in patients with abnormal intracranial compliance, the potential for volatile anesthetic–induced increases in CBV and ICP exist. Accordingly, volatile anesthetics should be used with caution in the setting of large or rapidly expanding mass lesions, unstable ICP, or other significant cerebral physiologic derangements in which CO_2 responsiveness and flow-metabolism coupling may be impaired. When they occur (e.g., a somnolent, vomiting patient with papilledema; a large mass; compressed basal cisterns), the clinician may well be advised to use a predominantly intravenous technique until such time when the cranium and dura are open and the effect of the anesthetic technique can be directly assessed. Such circumstances will be relatively rare in elective neurosurgery.

Situations in which the CMR has been decreased by drug administration or disease processes should also justify caution in the use of volatile anesthetics. If a volatile anesthetic has a substantial direct vasodilating effect on the cerebral vasculature that is normally offset by an opposing metabolically mediated vasoconstricting influence, then a near-maximal reduction of the CMR may have occurred; a volatile anesthetic will have a predominantly vasodilating effect.[73,139] These data suggest that isoflurane is a significant cerebral vasodilator when administered in situations during which the component of the CMR that is associated with electrophysiologic function is already suppressed by other drugs[73,139] or pathologic processes, such as traumatic brain injury.

The net vasodilating effects of equi-MAC concentrations of isoflurane, desflurane, and sevoflurane are less in

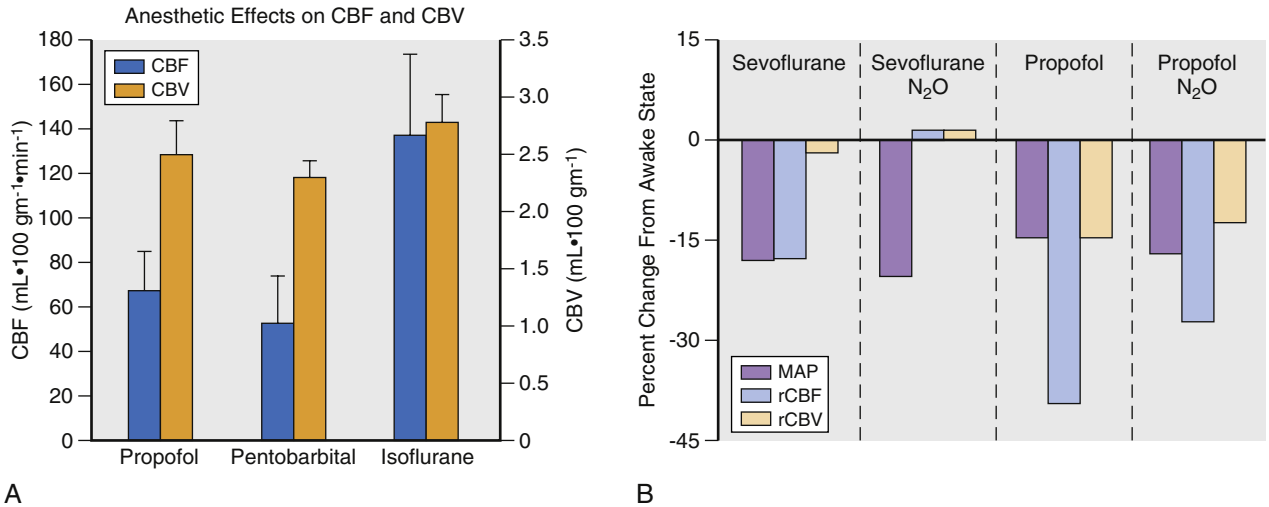


Figure 17-14. Effect of anesthetic drugs on cerebral blood flow (CBF) and cerebral blood volume (CBV). **A,** When compared with isoflurane, propofol and pentobarbital effected substantial reductions in CBF. However, reductions in CBV were more modest.[156] **B,** Although sevoflurane effected a significant reduction in regional CBF (rCBF), regional CBV (rCBV) was unchanged; had blood pressure been supported to normal levels, rCBV may have been greater than the awake state. By contrast, propofol effected a significant reduction in both rCBF and rCBV. These data indicate that the magnitude of the effect of anesthetics on rCBF is substantially greater than on rCBV. Hence, decreases in rCBF may not lead to equivalent reductions in rCBV. *MAP,* Mean arterial pressure; *N_2O,* nitrous oxide.

humans than that of halothane, and the former are probably therefore preferable if a volatile anesthetic is to be used in the setting of impaired intracranial compliance. When hypocapnia is established before the introduction of halothane, the increases in ICP that might otherwise occur in a normocapnic patient with poor intracranial compliance can be prevented or greatly attenuated. Nonetheless, isoflurane, desflurane, or sevoflurane are preferred because the margin for error is probably wider than with halothane.

Nitrous Oxide

N_2O can cause increases in CBF, CMR, and ICP. At least a portion of the increases in CBF and CMR may be the result of a sympathoadrenal-stimulating effect of N_2O. The magnitude of the effect considerably varies according to the presence or absence of other anesthetic drugs (Fig. 17-15[180-182]). When N_2O is administered alone, very substantial increases in CBF and ICP can occur. In sharp contrast, when N_2O is administered in combination with intravenous drugs, including barbiturates, benzodiazepines, narcotics, and propofol, its cerebral-vasodilating effect is attenuated or even completely inhibited. The addition of N_2O to anesthesia established with a volatile anesthetic will result in moderate increases in CBF.

Nitrous Oxide Administered Alone. The most dramatic reported increases in ICP or CBF in humans[183] and experimental animals[184] have occurred when N_2O was administered alone or with minimal background anesthesia. For instance, Henriksen and Jorgensen[183] recorded ICP before and during spontaneous breathing of 66% N_2O by patients with intracranial tumors. Mean ICP increased from 13 to 40 mm Hg. The increases in CBF observed in humans are more modest than those observed in animals but are still substantial.[180] Whether these substantial increases represent the effects of N_2O, per se, or whether they reflect the nonspecific effects of a *second-stage* arousal phenomenon is not known.

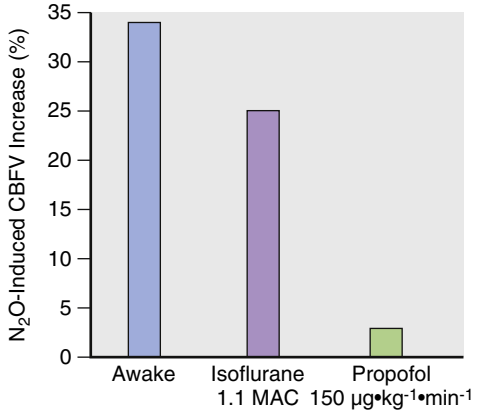


Figure 17-15. Mean percent increases in cerebral blood flow velocity (CBFV) in the middle cerebral artery of normocapnic subjects exposed to 60% nitrous oxide (N_2O) after control recording in three conditions: awake[180]; 1.1 minimum alveolar concentration (MAC) of isoflurane[181]; and propofol, 150 μg•kg^{-1}•min^{-1}.[182]

Nitrous Oxide Administered With Intravenous Anesthetics. When N_2O is administered in conjunction with certain intravenous anesthetics, its CBF effect may be considerably attenuated. Phirman and Shapiro[185] observed that a reproducible increase in ICP that occurred in response to the administration of 70% N_2O to a comatose patient was prevented by the previous administration of a combination of thiopental and diazepam, despite no change in baseline ICP. In an investigation of patients with intracranial tumors and poor intracranial compliance (mean preinduction ICP, 27 mm Hg),[186] 50% N_2O introduced during barbiturate anesthesia and after the induction of hypocapnia had a negligible effect on ICP. Jung and associates[187] compared lumbar CSF pressure in patients with brain tumors during the administration of 0.7% isoflurane or 70% N_2O after the induction of anesthesia with a barbiturate. Lumbar CSF pressure was modestly but significantly greater with N_2O. The fact that the increase was less dramatic than those cited earlier for N_2O alone may reflect the presence of residual barbiturate. Benzodiazepines administered alone have been shown to blunt the CBF response to N_2O in both animals and humans.[110] Narcotics appear to have a similar effect. Jobes and coauthors[48] reported that anesthesia with 1 mg/kg morphine plus 70% N_2O resulted in no change in CBF from awake control values. Because of the very minor effect of morphine on CBF, these data suggest that N_2O did not cause substantial cerebral vasodilation. Although the addition of N_2O to propofol anesthesia in children increased MCA flow velocity,[188] such increases have not been demonstrated by other investigators[182] (also see Chapter 93).

Nitrous Oxide Administered With Volatile Anesthetics. In most investigations, including several in humans, during which N_2O has been added to an anesthetic of 1 MAC or greater, substantial increases in CBF have been recorded.[181,189-192] Algotsson and associates[193] examined the effect of an approximately equi-MAC substitution of N_2O for isoflurane. They compared CBF in patients anesthetized with 1.5 MAC isoflurane and 0.75 MAC isoflurane with 65% N_2O. They observed 43% greater CBF with the latter, again consistent with a substantial vasodilating effect of N_2O in the presence of a volatile agent. Similar observations were made by Lam and coauthors[181] and Strebel and colleagues.[192] Several investigations have confirmed that CBF will be less with 1 MAC isoflurane than with a 1 MAC combination achieved with 50% to 65% N_2O and isoflurane.[181,193,194]

This vasodilating effect of N_2O may be positively correlated with the concentration of inhaled drug[192] and suggests that, in general, the increase in CBF caused by N_2O is exaggerated at higher concentrations of both halothane and isoflurane. Of importance, however, is the observation of Reinstrup and co-workers,[195] who demonstrated that the administration of 50% N_2O to healthy volunteers did not significantly alter CBV. In support of this observation, Kaisti and colleagues[68] did not observe any effect of N_2O on CBV when added to a background of 1 MAC sevoflurane anesthesia. Although N_2O can increase CBF, these data indicate that its effect on CBV is modest at best.

Effects of Nitrous Oxide on Cerebral Metabolic Rate. No uniform agreement has been reached concerning the effect of N_2O on the CMR. Parallel changes in CBF and CMR,[184] increases in CBF without alteration of the CMR,[196] and CMR alteration occurring without changes in CBF[143] have all been reported. These findings are, doubtless, the product of differences in species, methods, depth of background anesthesia, and interactions with simultaneously administered anesthetics. In a recent investigation in humans, the administration of 70% N_2O on a background of either sevoflurane or propofol anesthesia resulted in modest increases in the $CMRO_2$, thus indicating that N_2O does indeed increase cerebral metabolism.[68]

The CBF response to CO_2 is preserved during the administration of N_2O.[197]

Clinical Implications. Despite the inconsistencies that are evident, the vasodilatory action of N_2O can be clinically significant in neurosurgical patients with reduced intracranial compliance. However, N_2O-induced cerebral vasodilation can be considerably blunted by the simultaneous administration of intravenous anesthetics. By contrast, the addition of N_2O to a volatile drug–based anesthetic can modestly increase cerebral metabolism and blood flow. N_2O has been widely used in neurosurgery, and banishing it is inconsistent with the accumulated experience. Nonetheless, in circumstances wherein ICP is persistently elevated or the surgical field is persistently *tight*, N_2O should be viewed as a potential contributing factor. Because N_2O rapidly enters a closed gas space, it should be avoided or omitted when a closed intracranial gas space may exist or intravascular air is a concern.

MUSCLE RELAXANTS

Nondepolarizing Relaxants

The only recognized effect of nondepolarizing muscle relaxants on the cerebral vasculature occurs via the release of histamine (also see Chapters 34 and 53). Histamine can result in a reduction in CPP because of the simultaneous increase in ICP (caused by cerebral vasodilation) and a decrease in the MAP.[198] When the BBB is intact, it is not entirely clear whether histamine directly causes cerebral vasodilation or whether it is a secondary (autoregulatory) response to a reduction in the MAP. *d*-Tubocurarine is the most potent histamine releaser among available muscle relaxants. Metocurine, atracurium, and mivacurium also release histamine in lesser quantities. This effect is likely to be clinically inconsequential unless these muscle relaxants are administered in the large doses necessary to achieve endotracheal intubating conditions rapidly. Of this group of drugs, cisatracurium has the least histamine-releasing effect. No evidence of histamine release was observed after the administration of 0.15 mg/kg (three times the 95% effective dose [ED_{95}] for twitch depression) of cisatracurium to neurosurgical patients in the ICU.[199] Yet, cisatracurium's slow onset of action makes it not useful for a rapid-sequence induction of anesthesia.

Vecuronium, in relatively large doses of 0.1 to 0.14 mg/kg, had no significant effect on cerebral physiology in patients with brain tumors.[200] The other aminosteroids, pipecuronium and rocuronium, should be similarly without direct effect, and no adverse events have been reported.

The indirect actions of relaxants may also have effects on cerebral physiology. Pancuronium given as a large bolus dose can cause an abrupt increase in arterial pressure, which might increase ICP in patients with impaired intracranial compliance and defective autoregulation; however, no significant clinical event has ever been reported. Muscle relaxation may reduce ICP because coughing and straining are prevented, which decreases central venous pressure with a concomitant reduction in cerebral venous outflow impedance.

A metabolite of atracurium, laudanosine, may be epileptogenic. However, although large doses of atracurium caused an EEG arousal pattern in dogs, CBF, CMR, and ICP were unaltered.[201] In rabbits, the administration of laudanosine did not increase the severity of the epileptoid activity caused by the direct application of a cephalosporin to the cortical surface.[202] It appears highly unlikely that epileptogenesis will occur in humans with atracurium.[203]

In summary, vecuronium, pipecuronium, rocuronium, atracurium, mivacurium, cisatracurium, metocurine, and pancuronium (if acute MAP increases are prevented with the latter) are all reasonable muscle relaxants for use in patients with or at risk for intracranial hypertension. Doses of metocurine, atracurium, and mivacurium should be limited to ranges not associated with hypotension.

Rocuronium will probably be increasingly used for the induction of anesthesia, as well as for intraoperative relaxation. It has the most rapid onset time of any nondepolarizing muscle relaxant. With sugammadex, even a profound neuromuscular blockade can be rapidly reversed (see Chapters 34 and 35).

Succinylcholine

Succinylcholine can produce modest increases (~5 mm Hg) in ICP in lightly anesthetized humans. This effect appears to be the result of cerebral activation (as evidenced by EEG changes and increases in CBF) caused by afferent activity from the muscle spindle apparatus.[204] However, a poor correlation between the occurrence of visible muscle fasciculations and an increase in ICP have been noted. As might be expected with what appears to be an arousal phenomenon, deep anesthesia has been observed to prevent succinylcholine-induced increases in ICP in the dog. In humans, the increase in ICP is also blocked by paralysis with vecuronium and by *defasciculation* with metocurine, 0.03 mg/kg.[200] The efficacy of other defasciculating anesthetics has not been examined in humans.

Although succinylcholine *can* produce increases in ICP, it can still be used for a rapid-sequence induction of anesthesia. Kovarik and coauthors[205] observed no change in ICP after the administration of succinylcholine, 1 mg/kg, to 10 nonparalyzed, ventilated neurosurgical patients in the ICU, 6 of whom had sustained a head injury. Their observations are very relevant because it is in precisely this population of patients that the issue of the use of succinylcholine arises most frequently. Considering that the ICP effects of succinylcholine may be an arousal

phenomenon caused by increased afferent traffic from muscle spindles,[204] it is not unreasonable to assume that disease processes that substantially blunt the level of consciousness might similarly blunt this response. As with many anesthetics, the concern should not be whether it is used but how it is used. If administered with proper attention to the control of CO_2 tension, arterial blood pressure, and depth of anesthesia and after defasciculation, then little hazard should attend its use.

OTHER EFFECTS OF ANESTHETICS ON CEREBRAL PHYSIOLOGY

CEREBROSPINAL FLUID DYNAMICS

Approximately 150 mL of CSF is in the adult human, one-half within the cranium and one-half in the spinal CSF space. CSF, which is formed in the choroid plexuses and, to a lesser extent, in the brain's interstitium with transependymal diffusion into the ventricular system, is replaced approximately three to four times per day. It functions both as a cushion for the CNS and as an excretory pathway. Anesthetics have been shown to influence both the rate of formation and the rate of reabsorption of CSF. Table 17-3 provides nonquantitative information about the direction of the influences of common anesthetic drugs. All the information has been derived from animals,[207-213] and these processes have not been examined in humans. Of the volatile anesthetics, halothane decreases secretion of CSF, isoflurane has no effect, and enflurane and desflurane increase secretion. Absorption of CSF is reduced by halothane and enflurane, unchanged by desflurane, and increased by isoflurane. Although probably of minimal relevance to clinical practice, a theoretic concern might be in the setting of a prolonged closed-cranium procedure in a patient with poor intracranial compliance. The most deleterious potential combination of effects in a patient with poor intracranial compliance is increased CSF production and decreased reabsorption. This pattern occurs with enflurane in the dog, which is perhaps another reason (in addition to the potential for epileptogenesis in the presence of cerebral injury and hypocapnia) for omission of enflurane in this circumstance.

BLOOD-BRAIN BARRIER

In the majority of the body's capillary beds, fenestrations between endothelial cells are approximately 65 Å in diameter. In the brain, with the exception of the choroid plexus, in the pituitary, and in the area postrema, tight junctions reduce this pore size to approximately 8 Å. As a result, large molecules and most ions are prevented from entering the brain's interstitium (BBB). A limited number of studies of anesthetic effects on the BBB have been conducted. In experimental animals, 1% isoflurane leads to extravasation of albumin into the thalamus, indicating some compromise of the BBB integrity. At higher doses, isoflurane (3%) significantly increases protein extravasation, not only in the thalamus but also in the cortex.[214] This disruption of the BBB is quantitatively similar to what is achieved by mannitol. In experimental models of brain injury, isoflurane has been reported to both exacerbate[215] and ameliorate[216] edema formation in the injured brain. Whether these effects are the result of isoflurane action at the BBB, per se, or to hemodynamic perturbations attendant with anesthesia is not known. The clinical relevance of the potential BBB modulation by anesthetics is not clear. To the authors' knowledge, no peer-reviewed investigation has attempted a comparison of anesthetic effects on BBB function during anesthesia in normotensive humans.

EPILEPTOGENESIS

An extensive review of the convulsant and anticonvulsant effects of anesthetics and adjuvants is available.[217,218] Several commonly used anesthetics have some epileptogenic potential, particularly in predisposed individuals. A concern is that seizure activity may go unrecognized in an anesthetized and paralyzed patient and may result in neuronal injury if substrate demand (CMR) exceeds supply for a prolonged period.[219] A second concern is that the epileptogenic effect will persist in the postanesthesia period when seizures may occur in less well-controlled circumstances than those that exist in the surgical unit. In practice, it appears that spontaneous seizures during or after anesthesia have been extremely rare events. Nonetheless, in patients with processes that might predispose them to seizures, the use of potentially epileptogenic drugs should be avoided in situations during which reasonable alternatives are available.

Volatile Anesthetics

Enflurane is potentially epileptogenic in the clinical setting. Of particular relevance to neuroanesthesia is the observation that hypocapnia potentiates seizure-type discharges during enflurane anesthesia.[220] A 50% decrease in the $CMRO_2$ was noted in human volunteers anesthetized with 3% enflurane; however, with the onset of seizure activity, the $CMRO_2$ returned to normal,[221] thus indicating preservation of flow-metabolism coupling. No evidence suggests that this type of EEG activity is deleterious when oxygen delivery is maintained during the event. However, because seizure activity can elevate brain metabolism by as much as 400%, the use of enflurane,

TABLE 17-3 EFFECTS OF ANESTHETIC AGENTS ON THE RATE OF CSF SECRETION AND ABSORPTION

	Halothane	Enflurane	Isoflurane	Desflurane	Fentanyl	Etomidate
Secretion	↓	↑	---	↑	---	↓
Absorption	↓	↓	↑	---	↑	↑

Upward arrows indicate an increase in the rate of cerebrospinal fluid (CSF) absorption or secretion, and downward arrows indicate a decrease. The information is presented nonquantitatively, and effects may vary with dose.

especially at high doses and with hypocapnia, should probably be avoided in patients predisposed to seizures or those with occlusive cerebrovascular disease.

The EEG-activating property of enflurane has been intraoperatively used to activate and identify seizure foci that are to be surgically resected; and, in this situation, spike activity not preoperatively present has been observed to persist after surgery.[222] In addition, two reports of seizures in the immediate postoperative period after enflurane anesthesia in both predisposed[223] and nonpredisposed[224] individuals have been recounted. No permanent sequelae appeared to occur as a result of these events, and, in fact, this association is not a rigorously proven one. At worst, such occurrences are extremely uncommon.

Isoflurane can cause EEG spiking and myoclonus, but it has not been associated in the experimental setting with the frank epileptoid activity induced by enflurane. The clinical experience with isoflurane is extremely large, and unexplained seizurelike activity has been reported in only two patients. One occurrence was intraoperative,[225] and the other incidence was immediately postoperative.[226] Therefore epileptogenesis does not appear to be a clinical concern with isoflurane. In fact, isoflurane has been successfully used to control EEG seizure activity in refractory status epilepticus.[227]

Seizures occur during the induction of anesthesia with high concentrations of sevoflurane in children, including those without a recognized seizure diathesis.[228] In two healthy humans, EEG burst suppression with 2 MAC sevoflurane was accompanied by epileptiform discharges that were observed during EEG monitoring.[229] These discharges were associated with a significant increase in CBF, thus demonstrating that flow-metabolism coupling was preserved. In patients with temporal lobe epilepsy, the administration of 1.5 MAC sevoflurane elicited widespread paroxysmal EEG activity. Of note was the observation that paroxysmal activity was not restricted to the ictal focus and that the administration of sevoflurane did not provide any assistance in localizing the epileptogenic region of the brain.[230] The development of tonic-clonic movements indicative of seizure activity has also been reported in otherwise healthy patients on emergence from sevoflurane anesthesia.[231,232] In all of the reported cases of seizure activity attributable to sevoflurane anesthesia, untoward sequelae have not been documented. These reports highlight sevoflurane's ability, albeit small, to evoke epileptiform activity; accordingly, the use of sevoflurane in patients with epilepsy should be undertaken with appropriate caution.

Methohexital

Myoclonic activity is sometimes observed with methohexital. Accordingly, this anesthetic has been used to activate seizure foci during cortical mapping.[229,233] In neurosurgical patients to whom larger doses of methohexital were administered to produce burst suppression of the EEG, refractory seizures have occurred.[234] Accordingly, it appears that patients with seizures of temporal lobe origin, typically of the psychomotor variety or those to whom large doses are administered, are at risk for seizure activation by methohexital. However, prolonged seizure activity after single-dose methohexital administration has not been reported in patients who undergo ECT.

Ketamine

Ketamine can elicit seizures in patients with an epileptic diathesis.[235] Depth electrode recordings in epileptic patients have revealed the occurrence of isolated subcortical seizure activity originating in the limbic and thalamic areas during ketamine anesthesia and demonstrated that this subcortical activation may not be reflected in surface EEG recordings.[236] Seizures have also been reported to occur after ketamine anesthesia in subjects who are neurologically normal on only two occasions[237,238]; seizure thresholds may have been lowered by aminophylline in one of these instances.

Etomidate

Etomidate frequently produces myoclonus that is not associated with epileptiform activity on the EEG.[239] A single instance of severe, sustained myoclonus immediately after anesthesia with etomidate by infusion has been reported.[240] Etomidate has also been shown to precipitate generalized epileptic EEG activity in epileptic patients,[241] and its use in this population should probably be avoided. However, it has been electively used in low doses to activate seizure foci for the purposes of intraoperative EEG localization.[242] In the experience of the authors (unpublished), selective activation of a quiescent focus can be achieved with 0.1 mg/kg etomidate. Larger doses are more likely to lead to generalized activation.

Etomidate is also associated with longer seizures in response to ECT than seizures that occur after the administration of methohexital or propofol. Remarkably, etomidate, in the dose range of 0.15 to 0.3 mg/kg, does not cause dose-related seizure inhibition during ECT as is readily demonstrated with methohexital or propofol.

The preceding information notwithstanding, no convincing reports indicate epileptogenesis in subjects who are neurologically normal, and the use of etomidate need not be restricted on this basis. In fact, etomidate has been used to control refractory status epilepticus.

Propofol

Seizures and opisthotonos can occur after propofol anesthesia. However, systematic studies in both humans[243] and animals,[244] although identifying the occurrence of occasional dystonic and choreiform movements, have failed to confirm propofol as a proconvulsant. In fact, propofol appears to be anticonvulsant in mice.[244] Furthermore, ECT seizures were shorter after induction with propofol than after induction with methohexital,[245] which is more consistent with an *anticonvulsant* effect. In addition, propofol sedation has been widely used during *awake* resection of seizure foci and other intracranial lesions. Although pronounced high-amplitude beta-frequency activity in the EEG has been observed,[246] unexpected incidences of seizures have not been reported.

Narcotics

Seizures or limbic system hypermetabolism (or both) can be readily elicited in some animal species with narcotics. Although an increase in CBF in deep brain

structures associated with pain processing has been observed in human volunteers,[84] humans do not have a clinically apparent correlate of the hypermetabolism effect observed in animals. Several anecdotal accounts, unaccompanied by EEG recordings, have reported the occurrence of grand mal convulsions in patients who received both high and low doses of fentanyl. However, systematic investigations of EEG changes during the administration of relatively large doses of fentanyl, sufentanil, and alfentanil in humans have *not* documented neuroexcitatory activity,[247-249] and the seizures may have been an exaggerated rigidity phenomenon. There are exceptions. Tempelhoff and coauthors[250] reported partial complex seizures on the induction of anesthesia with fentanyl in patients undergoing anterior temporal lobectomy. Eight of the nine patients displayed electrical seizure activity at a range of clinically relevant fentanyl doses (mean, 26 μg/kg).[250] Another study found that alfentanil, 50 μg/kg, augmented temporal lobe spike activity in patients with temporal lobe epilepsy.[251] Untreated rigidity may, itself, also have important CNS consequences. ICP elevation can occur during narcotic-induced rigidity, probably as a consequence of cerebral venous congestion.

NEONATAL ANESTHETIC NEUROTOXICITY

This subject is discussed in detail in Chapter 93.

CEREBRAL PHYSIOLOGY IN PATHOLOGIC STATES

CEREBRAL ISCHEMIA—PATHOPHYSIOLOGIC CONSIDERATIONS

Critical Cerebral Blood Flow Thresholds

The brain has a high rate of energy utilization and very limited energy storage capacity. The brain is therefore extremely vulnerable in the event of interruption of substrate (e.g., oxygen, glucose) supply. Under normal circumstances, global CBF is maintained at approximately 50 mL/100 g/min. In the face of a declining CBF and therefore oxygen supply, neuronal function deteriorates in a progressive manner rather than in an all-or-none fashion (Fig. 17-16[256,257]). There is substantial reserve below normal CBF levels, and not until EEG evidence of ischemia begins to appear is CBF decreased to approximately 20 mL/100 g/min. At a CBF level of approximately 15 mL/100 g/min, the cortical EEG is isoelectric. However, only when CBF is reduced to approximately 6 to 10 mL/100 g/min are indications of potentially irreversible membrane failure, such as increased extracellular potassium[252] and a loss of the direct cortical response, rapidly evident. As CBF decreases in the flow range between 15 and 10 mL/100 g/min, a progressive deterioration in energy supply occurs and eventually leads to membrane failure and neuronal death at a time course that may last hours rather than minutes. The brain regions falling within this CBF range (6 to 15 mL/100 g/min) encompass brain tissue in which neuronal dysfunction is temporarily reversible but within which neuronal death will occur if flow is not restored; such regions are referred to as the *ischemic penumbra*.[252,253] Studies defining progression to cerebral infarction within the penumbra have been principally performed in the cerebral cortex of primates, and the actual CBF levels at which the various decrements in function occur may vary with both anesthetic[254] and species. However, in humans anesthetized with halothane and N_2O, the CBF threshold for the initial EEG change[255] is similar to that observed in the animal investigations.

Models of Cerebral Ischemia

How different is complete cerebral ischemia, as occurs during cardiac arrest, and incomplete cerebral ischemia, as may occur during occlusion of a major cerebral vessel or severe hypotension? From the clinician's vantage, the important difference is that the residual (i.e., collateral) blood flow during incomplete ischemia may result in enough delivery of oxygen to allow some generation of ATP and thereby stave off the catastrophic irreversible membrane failure that occurs within minutes during normothermic complete cerebral ischemia. This difference in the rate of failure of the energy supply[258,259] (Fig. 17-17) can result in significantly more apparent tolerance for focal or incomplete ischemia than for complete global ischemia (e.g., cardiac arrest).

Energy Failure and Excitotoxicity

Energy failure is the central event that occurs during cerebral ischemia.[260] ATP is required for the maintenance of the normal membrane ionic gradient, and energy failure is rapidly attended by membrane depolarization and influx of sodium (Na^+) and calcium (Ca^{2+}) into the neuron. Voltage-dependent Ca^{2+} channels are then activated, and Ca^{2+} gains entry into the cytosol. Depolarization of presynaptic terminals also results in the release of massive quantities of excitatory neurotransmitters, particularly

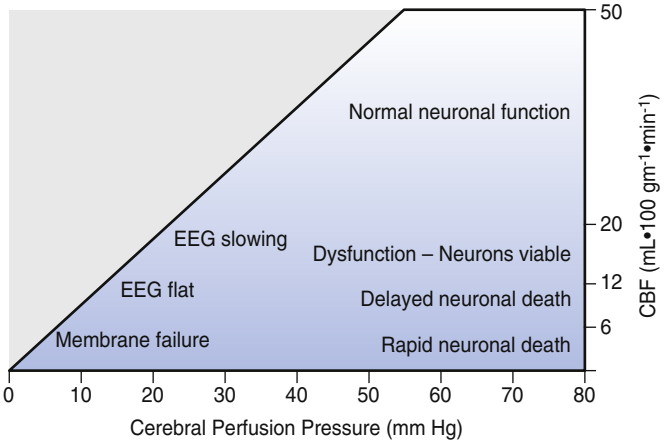


Figure 17-16. Relationships between cerebral perfusion, cerebral blood flow (CBF), the electroencephalogram (EEG), and the functional status and viability of neurons. Note that in the approximate CBF range of 6 to 12 mL/100 g/min, the energy supply is insufficient to support electrophysiologic activity (i.e., flat EEG) but can prevent complete membrane failure and neuronal death for extended periods. These areas are referred to as the *ischemic penumbra*.[252] The data are derived from studies on the cerebral cortex of barbiturate-anesthetized baboons[252,256] and unanesthetized monkeys.[257] The CBF and mean arterial pressure thresholds may vary with anesthetic and species.[254]

glutamate, into the synaptic cleft. Activation of glutamatergic receptors, the NMDAR and the α-amino-3-hydroxy-5-methyl-4-isoxazopropionic acid receptors (AMPAR), adds to the influx of Na^+ and Ca^{2+} (Fig. 17-18). Initiation of cellular signaling by the activation of mGluR leads to the release of stored Ca^{2+} from the endoplasmic reticulum (ER) via inositol 1,4,5-triphosphate (IP_3) receptors. Ionic influx is accompanied by an influx of water, and neuronal swelling rapidly occurs after membrane depolarization. The injury that is initiated by excessive mGluR activity is referred to as *excitotoxicity*.

Ca^{2+} is a ubiquitous second messenger in cells and is a cofactor required for the activation of a number of enzyme systems. The rapid, uncontrolled increase in cytosolic Ca^{2+} levels initiates the activation of a number of cellular processes that contribute to injury. Cytoskeletal proteins such as actin are cleaved by activated proteases. These enzymes also degrade a number of the protein constituents of the neuron. Lipases attack cellular lipids and produce membrane damage. An important lipase, phospholipase A_2, releases fatty acids such as AA from membranes. Metabolism of AA to prostaglandins and leukotrienes by cyclooxygenase and lipoxygenase is accompanied by the generation of superoxide free radicals. The latter, in combination with other free radicals generated in response to mitochondrial injury, can lead to lipid peroxidation and membrane injury. Prostaglandins and leukotrienes also evoke an inflammatory response and are powerful chemotactic drugs. Activation of platelets within cerebral microvessels, as well as an influx of white blood cells into damaged areas, aggravates the ischemic injury by occluding the vasculature.

DNA damage is also an important event during ischemic neuronal injury. Generation of free radicals from AA metabolism, from injured mitochondria, and from the production of peroxynitrite from NO leads to oxidative injury to DNA. Activation of endonucleases also produces DNA strand breaks. Under normal circumstances, DNA injury results in the activation of poly–adenosine diphosphate [ADP]–ribose polymerase (PARP), an enzyme that participates in DNA repair. With excessive DNA injury,

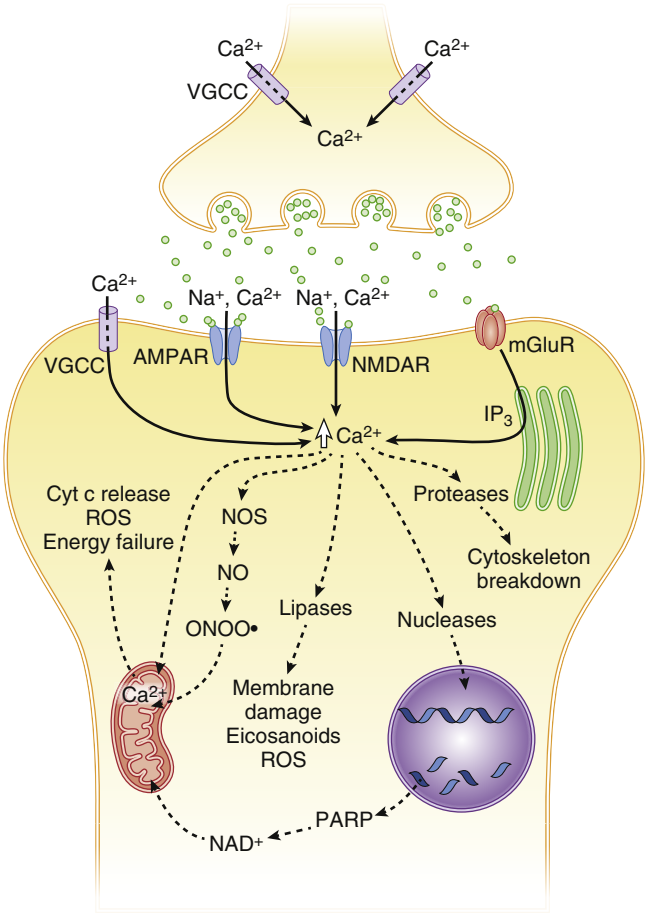


Figure 17-18. During ischemia, depletion of adenosine triphosphate (ATP) leads to neuronal depolarization and the subsequent release of supranormal quantities of neurotransmitters, especially glutamate. Excessive stimulation of ligand-gated channels and the simultaneous opening of voltage-dependent calcium (Ca^{2+}) channels permit rapid entry of Ca^{2+} into neurons. Stimulation of metabotropic glutamate receptors (mGluR) generates inositol 1,4,5-triphosphate (IP_3), which causes the release of Ca^{2+} from the endoplasmic reticulum (ER) and mitochondria. Activation of the α-amino-3-hydroxy-5-methyl-4-isoxazopropionic acid receptors (AMPAR)–gated subset of glutamate receptors also permits excessive entry of sodium (Na^+). Excessive free Ca^{2+} results in the activation of numerous enzymes: protease activation causes the breakdown of the cytoskeleton of the neuron; lipases damage plasma membrane lipids and release arachidonic acid (AA), which is metabolized by cyclooxygenases and lipoxygenases to yield free radicals and other mediators of cell injury; activation of nitric oxide synthase (NOS) leads to the release of nitric oxide (NO) and, in turn, the generation of peroxynitrite (ONOO), a highly reactive free radical; and activated endonucleases damage DNA, thereby rendering the neuron susceptible to apoptosis. Injury to the mitochondria leads to energy failure, generation of free radicals, and the release of cytochrome *c* (cyt c) from the mitochondria; the latter is one of the means by which neuronal apoptosis is initiated. *mGluR,* Metabotropic glutamate receptor; *NAD^+,* oxidized form of nicotinamide adenine dinucleotide; *NMDAR, N*-methyl-D-aspartate receptor; *PARP,* poly-ADP-ribose polymerase; *ROS,* reactive oxygen species; *VGCC,* voltage-gated calcium channel.

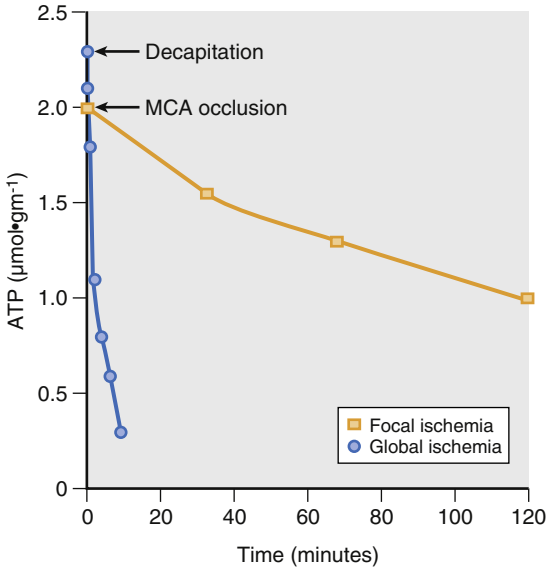


Figure 17-17. Comparison of rates of failure of energy supply (adenosine triphosphate [ATP]) in complete global ischemia in dogs (produced by decapitation[259]) and in incomplete focal ischemia in monkeys (middle cerebral artery [MCA] occlusion[258]). In the presence of residual CBF, energy supply failure is substantially delayed.

PARP activity dramatically increases, which can lead to the depletion of nicotinamide adenine dinucleotide (NAD^+), a substrate of PARP. NAD^+ is also an important coenzyme in energy metabolism, and its depletion further exacerbates energy failure.

Lactate formation is an additional element of the pathophysiologic process. Lactic acid is formed as a result of the anaerobic glycolysis that takes place after failure of the supply of oxygen. The associated decline in pH contributes to the deterioration of the intracellular environment. An increased preischemic serum glucose level may accelerate this process by providing additional substrate for anaerobic glycolysis.

NO, which has emerged as a probable mediator of CBF changes in many normal physiologic states (see the preceding section, "Cerebral Metabolic Rate"), is also of relevance to pathophysiologic ischemia. NO is, in fact, a weak free radical that in turn leads to the generation of a more reactive species (peroxynitrite), and it is the *killer substance* used by macrophages. In cerebral ischemia, NO is probably both friend and foe. During a period of focal ischemia, the vasodilating effect of NO (probably constitutively elaborated NO of endothelial origin) likely serves to augment collateral CBF. However, in the postischemic phase, NO (probably derived from neurons or macrophages) contributes to neuronal injury.

Collectively, the simultaneous and unregulated activation of a number of cellular pathways overwhelms the reparative and restorative processes within the neuron and ultimately leads to neuronal death.

Nature of Neuronal Death

Neuronal death that occurs in response to these processes has been categorized as necrotic or apoptotic in nature. Necrotic death of neurons, mediated by excitotoxic injury, is characterized by rapid cellular swelling, condensation and pyknosis of the nucleus, and swelling of the mitochondria and ER. A characteristic of these necrotic neurons is the presence of acidophilic cytoplasm.[261] Necrotic neuronal death results in local infiltration of the brain by inflammatory cells. A consequence of this inflammation is a considerable amount of collateral damage.

Neuronal apoptosis, a form of *cellular suicide*, has also been demonstrated in a variety of models of cerebral ischemia. Apoptosis is characterized by chromatin condensation, involution of the cell membrane, swelling of mitochondria, and cellular shrinkage. In the later stages of apoptosis, neurons fragment into several apoptotic bodies, which are then cleared from the brain.[261] The lack of a substantial inflammatory response to apoptotic death limits injury to surrounding neurons that have survived the initial ischemic insult.

A number of biochemical pathways that lead to apoptosis have been described. Initiation of apoptosis by the release of cytochrome *c* from injured mitochondria has been studied the most (Fig. 17-19). Cytochrome *c* is restricted from the cytoplasm by the outer mitochondrial membrane.[262] When mitochondria are injured, pores within the outer membrane allow cytochrome *c* to be released into the cytoplasm, where it interacts with procaspase-9 and apoptosis-activating factor (APAF) to produce an apoptosome. Procaspase-9 undergoes activation

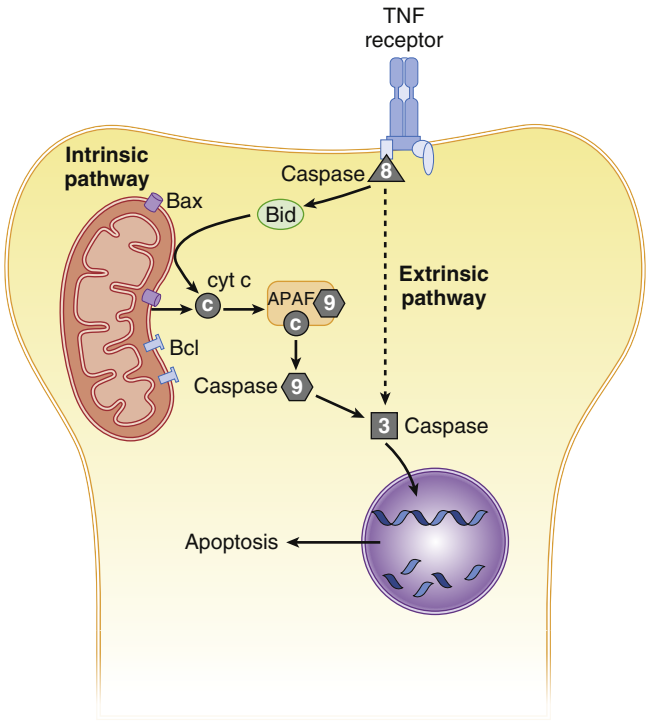


Figure 17-19. Cellular processes that lead to neuronal apoptosis. Cytochrome *c* (cyt c), which is normally restricted to the space between the inner and outer mitochondrial membranes, is released in response to mitochondrial injury. Cyt c, in combination with apoptosis-activating factor (APAF), activates caspase-9 by proteolytic cleavage. Activated caspase-9 then leads to the activation of caspase-3. This enzyme cleaves a number of substrates, including those necessary for DNA repair. Within the mitochondria, Bax augments and Bcl prevents the release of cyt c. The release of cyt c can also be initiated by Bid, a substance that is activated by caspase-8 via tumor necrosis factor (TNF) signaling. In addition, caspase-8 can directly activate caspase-3. Excessive activation of poly-ADP-ribose polymerase (PARP), an enzyme integral to DNA repair, depletes cellular stores of oxidized nicotinamide adenine dinucleotide (NAD^+). Depletion of NAD^+ further exacerbates the energy failure because of its critical role in energy metabolism.

by proteolytic cleavage. Activated caspase-9 then activates caspase-3. The latter serves as an executor of apoptosis by cleaving a number of protein substrates that are essential in DNA repair (such as PARP). Activation of caspase-3 can also occur by inflammatory signaling via tumor necrosis factor alpha (TNF-α) and the activation of caspase-8.[263] It should be noted that the neuronal injury that occurs in response to ischemia cannot be easily divided into necrosis or apoptosis. The nature of neuronal death probably encompasses a spectrum in which some neurons undergo necrosis or apoptosis whereas others undergo cell death that has features of both necrosis and apoptosis.

Timing of Neuronal Death

The traditional concept of ischemic injury was that neuronal death was restricted to the time of ischemia and during the early reperfusion period. However, more recent data indicate that postischemic neuronal injury is a dynamic process during which neurons continue to die for a long period after the initiating ischemic insult (Fig. 17-20).[264] This delayed neuronal death, which was

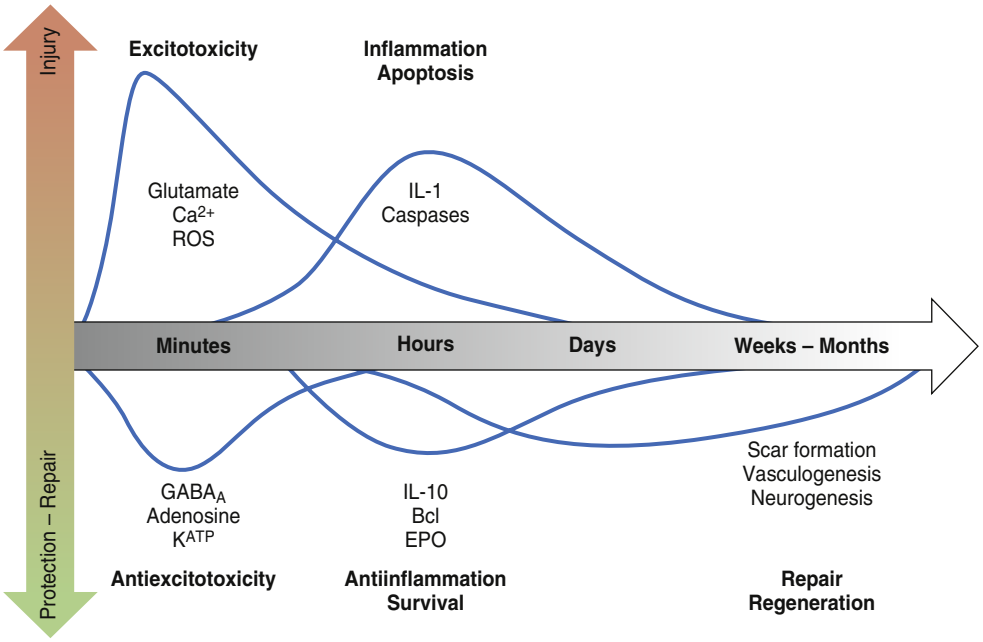


Figure 17-20. Time course of neuronal death. Excitotoxic (glutamate-mediated) injury results in neuronal death within the first few hours after the onset of ischemia. Brain tissue injury elicits an inflammatory response—an important process in the removal of injured tissue and in healing—that leads to a substantial amount of collateral damage. Inflammation-mediated neuronal death can continue for several days. Neuronal apoptosis can occur in injured neurons that survived the initial insult. Apoptotic neuronal death has been demonstrated to occur for many days after the initiating ischemic insult. It is now apparent that ischemic neuronal death is a dynamic process during which neurons continue to die for a long period. *Ca^{2+},* Calcium; *EPO,* erythropoietin; *$GABA_A$,* gamma-aminobutyric acid A; *K^{ATP},* adenosine triphosphate–regulated potassium; *IL-1,* interleukin 1; *IL-10,* interleukin 10; *ROS,* reactive oxygen species. *(Adapted from Dirnagl U, Iadecola C, Moskowitz M: Pathobiology of ischaemic stroke: an integrated view,* Trends Neurosci *22:391-397, 1999.)*

first demonstrated in models of global cerebral ischemia, has been demonstrated during focal ischemia as well. The extent of delayed neuronal death depends on the severity of the ischemic insult. With severe ischemia, most neurons undergo rapid death. With more moderate insults, neurons that survive the initial insult undergo delayed death. This ongoing neuronal loss contributes to the gradual expansion of cerebral infarction after focal ischemia. In experimental studies, evidence of cerebral inflammation, which can theoretically contribute to further injury, has been demonstrated even 6 to 8 months after the primary ischemia.

The occurrence of delayed neuronal death has important implications for the evaluation of studies in which neuroprotective strategies are being investigated. A wide variety of interventions have shown neuroprotective efficacy in studies in which the extent of injury is evaluated within 3 to 4 days after ischemia. However, this neuroprotective efficacy may not be sustained. Recent data indicate that cerebral infarction undergoes gradual expansion and that a reduction in injury attributed to a particular therapeutic intervention is no longer apparent when the injury is evaluated after a long postischemic recovery period.[264] Long-term (>1 month) evaluation of the efficacy of a particular intervention is therefore important.

Much of the literature on the pathophysiologic process of cerebral ischemia has primarily been focused on neuronal injury. However, recent work has highlighted the importance of the contribution of astrocytes, microglia, vascular cells (e.g., endothelium, smooth muscle cells, pericytes), basement membranes, and extracellular matrix to stroke. These individual components in aggregate form the neurovascular unit. A detailed understanding of the contribution of each component of the neurovascular unit is a prerequisite, not only for the protection of the brain against ischemic and traumatic injury, but also for therapeutic approaches for the regeneration of the CNS.

BRAIN PROTECTION

The literature on cerebral ischemia and brain protection is vast, and a detailed discourse on this topic is beyond the scope of the present discussion. A number of excellent recent reviews on the subject are available.[265-273]

Considerations Relevant to Complete Global Ischemia (Cardiac Arrest)

Maintaining adequate perfusion pressure after cardiac arrest is of considerable importance. Hypotension developing after resuscitation from cardiac arrest may aggravate the microcirculatory and vasospastic processes occurring at this time and may increase brain damage. A late phase of intracranial hypertension may occur and is due to the development of extensive cerebral edema (probably both vasogenic and cytotoxic edema) associated with brain necrosis. Attempts to control this type of intracranial hypertension with osmotherapy usually fail. ICP monitoring is not generally used because the patients in whom these delayed increases in ICP develop have sustained massive tissue damage.

Both barbiturates and calcium channel blockers have been administered after cardiac arrest. The former are

ineffective.[274] In a small cohort (51 patients) of patients after cardiac arrest, nimodipine was shown to improve CBF but not neurologic outcome.[275] In a second trial with approximately 150 patients after cardiac arrest, no overall benefit in neurologic outcome was observed.[276] However, a subset of patients in whom the initiation of advanced life support was delayed for longer than 10 minutes demonstrated improved survival. This single study cannot serve as justification for the administration of nimodipine after cardiac arrest, especially in the face of the unequivocally negative results of the multicenter lidoflazine cardiac arrest study.[277] Once again, the important therapeutic objectives are the maintenance of normocapnia and normotension, normalization of systemic pH, avoidance of hyperthermia, and prevention and treatment of seizures.

Induced mild hypothermia is effective in reducing mortality and morbidity in patients who sustain a cardiac arrest that is followed by altered mental status with a Glasgow coma scale of 7 or less.[278] Induction of mild hypothermia in the range of 32° C to 34° C for a period of approximately 24 hours improved neurologic outcome and survival 6 months after cardiac arrest in comparison with a normothermic group. Mild hypothermia was induced without difficulty. Passive rewarming of patients was slowly accomplished over a period of 8 hours. The incidence of complications was similar to that in the control normothermic group. This important study is one of the first to demonstrate the feasibility and efficacy of induced hypothermia as a treatment to prevent injury from global ischemia. In neonates who sustained hypoxic-ischemic encephalopathy, induction of whole body hypothermia (33.5° C) for 72 hours resulted in a reduced incidence of mortality.[279] Long-term follow-up of patients enrolled in the study confirmed the potentially beneficial effects of mild hypothermia.[280] In many institutions, induced hypothermia has been added to the armamentarium for the treatment of cerebral complications of cardiac arrest or global neonatal hypoxic-ischemic encephalopathy.

Considerations Relevant to Focal (Incomplete) Ischemia

Before discussing individual anesthetics, it should be noted that anesthesia, per se, is protective. For undefined reasons, reducing the level of systemic stress associated with a standardized experimental insult results in an improved outcome.[281,282] In reviewing the protection-by-anesthetics literature, readers should be conscious of the possibility that the protective benefit ascribed to an intervention with an anesthetic drug may, in fact, be the product of exaggeration of the injury in a high-stress control state, such as N_2O sedation.

Barbiturates. Numerous demonstrations have revealed the protective efficacy of barbiturates in focal cerebral ischemia in animals,[283-285] and a single demonstration confirmed the effectiveness in a human.[286] The effect has been principally attributed to suppression of the CMR. However, the effects of CBF redistribution and free radical scavenging[287] have been suggested to contribute, and evidence indicates that CMR suppression is not the sole mechanism.[288] Suppression of the CMR might logically be expected to be of benefit to brain regions in which oxygen delivery is inadequate to meet normal demands but is sufficient to allow energy consumption by some ongoing electrophysiologic activity (i.e., in which the EEG was abnormal but not flat). Such regions are likely to be limited in size in the setting of focal ischemia, yet several of the animal investigations suggest a very substantial protective effect.[283,284] Review of these experiments reveals that the methods used to monitor and maintain temperature, although accepted at the time, were below the standards that have evolved from a more recent understanding of the effects of both deliberate[289,290] and inadvertent hypothermia. Unrecognized cerebral hypothermia may well have been a factor in some of the cited investigations, and it is therefore possible that the protective efficacy of barbiturates may have been overestimated. Although more recent publications involving suitable temperature control methods do, in fact, indicate a protective effect of barbiturates,[288,291,292] the magnitude of that effect was modest when compared with the results of earlier studies. Barbiturate-induced EEG suppression in an already anesthetized patient may still be logical therapy when it can be applied before or early in the course of a period of temporary focal ischemia (e.g., temporary occlusion during aneurysm surgery). However, the decision to institute such therapy should be made only after considering the risk of the occlusive event, the patient's cardiovascular status, and the physician's willingness to accept the possibility of delayed emergence, together with an objective view of the probable magnitude of the protective effect.

Numerous investigations in animals and humans have failed to demonstrate any protective effect of barbiturates in the setting of global cerebral ischemia (e.g., cardiac arrest).[274]

Because CMR suppression has been the presumed mechanism of effect, barbiturates have traditionally been administered to produce maximal reduction of the CMR (which is nearly complete when EEG burst suppression has been achieved). However, data presented by Warner and colleagues[288] demonstrated that the same protective benefit (expressed as a reduction of infarct volume) could be achieved with a third of the burst-suppression dose, which raises a clinically important issue. The various barbiturates (e.g., thiopental, thiamylal, methohexital, pentobarbital) have similar effects on the CMR and have generally been assumed to have equal protective efficacy. However, if the mechanism of protection is a pharmacologic effect other than a reduction in the CMR, then is it reasonable to assume equivalence among the barbiturates? Recent data suggest that the neuroprotective efficacy of barbiturates is not similar. In a direct comparison of three clinically used barbiturates, methohexital and thiopental, but not pentobarbital, reduced injury in an animal model of focal ischemia.[293] These data suggest that mechanisms other than or at least in addition to metabolic suppression may contribute to the protective effect of barbiturates.

Volatile Anesthetics. Isoflurane is also a potent suppressant of the CMR in the cerebral cortex, and EEG evidence suggestive of a protective effect in humans has been reported.[254] In comparison with the awake

or N_2O-fentanyl–anesthetized state, isoflurane is neuroprotective in models of hemispheric,[294] focal,[295] and nearly complete ischemia.[296,297] Of interest is the recent observation that isoflurane's neuroprotective efficacy is not sustained.[298] When injury is evaluated 2 days after ischemia, a robust reduction in injury is observed with isoflurane anesthesia. However, by 14 days this reduction in injury was not apparent. These data indicate that neuronal injury continues well into the postischemic recovery period and that the neuroprotective benefit that is evident shortly after ischemia may not persist for the long term. More recent data have shown that isoflurane treatment can improve neuronal survival when the severity of ischemia is limited and the restoration of blood flow after ischemia is complete.[299] The neuroprotective effect of isoflurane is not substantially different from that of other volatile anesthetics. Sevoflurane reduces ischemic injury in animal models of focal[300] and hemispheric ischemia[301]; its efficacy is not different from that of halothane. Desflurane also reduces neuronal injury to the same extent that isoflurane does.[302] The available data therefore suggest that adequate anesthesia, per se, may have a protective effect[281,282] versus the awake state, but there does not appear to be any difference in neuroprotective efficacy among the volatile anesthetics.

Xenon. The inert gas xenon exerts its anesthetic action by noncompetitive blockade of NMDAR. As such, it is logical to suspect that it might provide neuroprotection against excitotoxic injury. The neuroprotective efficacy of xenon has been demonstrated against oxygen-glucose deprivation in vitro,[303] focal ischemia in vivo in mice,[304] and cardiopulmonary bypass–induced cognitive dysfunction in rats.[305] Of interest are observations that simultaneous administration of *subanesthetic* doses of xenon in combination with either hypothermia or isoflurane[306] significantly reduces neuronal injury and improves neurologic function in a neonatal rodent model of hypoxia-ischemia; this protective effect was apparent as late as 30 days after injury. Moreover, the administration of xenon has been shown to have a preconditioning effect on the brain[307]; previous exposure reduces the vulnerability of the brain to ischemic injury. Anesthetic drugs that have activity at NMDAR (ketamine) and γ-aminobutyric acid A ($GABA_A$) receptors (e.g., volatile anesthetics, barbiturates, benzodiazepines, propofol) have been shown to cause neuronal injury in rodent neonatal pups during the critical period of synaptogenesis.[308] Although xenon has antagonist activity at NMDAR, the evidence to date suggests that it does not lead to apoptosis in the developing brain.[309] Note should be made, however, that long-term neuroprotection with xenon has not yet been demonstrated in experimental adult subjects. The specific use of xenon for the purpose of neuroprotection awaits results from outcome studies in humans.

Propofol. EEG suppression can also be achieved with clinically feasible doses of propofol. Anecdotal information suggests that it is being used to provide *protection* during both aneurysm surgery[310] and CEA. In experimental models of cerebral ischemia, the extent of neurologic injury in propofol-anesthetized animals was similar to that in halothane-anesthetized animals.[311] Given the previous demonstration that halothane can reduce injury, these data provide indirect evidence of propofol's neuroprotective efficacy. In a more recent investigation, cerebral infarction was significantly reduced in propofol-anesthetized animals in comparison with awake animals.[312] Direct comparison of propofol to pentobarbital has also demonstrated that cerebral injury after focal ischemia is similar in animals anesthetized with the two drugs.[313] Similar to the situation with volatile anesthetics, initial investigations revealed that propofol protection is not sustained.[314] Durable protection with propofol is achievable if the severity of the ischemic insult is mild.[302] Collectively, these data are consistent with the premise that propofol can reduce ischemic cerebral injury.

Etomidate. Etomidate was proposed as a potential protective anesthetic in the setting of aneurysm surgery.[315] It, too, produces CMR suppression to an extent equivalent to barbiturates, and, similar to the barbiturates, etomidate is an agonist at the (inhibitory) $GABA_A$ receptor. To the contrary, in an experimental model of focal ischemia, the volume of injury was not reduced by etomidate relative to a 1.2 MAC halothane-anesthetized control group. In fact, the volume of injury with etomidate was significantly larger than that in the control group. In patients subjected to temporary intracranial vessel occlusion, the administration of etomidate results in greater tissue hypoxia and acidosis than does equivalent desflurane anesthesia. The aggravation of injury produced by etomidate (an imidazole) may be related to direct binding of NO as a consequence of etomidate-induced hemolysis[316] combined with direct inhibition of the NO synthase enzyme by etomidate. Therefore no scientific studies support the current use of etomidate for cerebral protection.

Calcium Channel Antagonists. Orally administering nimodipine (the intravenous preparation is not approved for clinical use in North America) for 21 days beginning as soon as possible after subarachnoid hemorrhage (SAH) is now established clinical practice.[317] Other calcium channel blockers have reduced vasospasm after SAH but have not improved patient outcome, suggesting that nimodipine's benefit is a cellular rather than a vascular effect. However, routinely administering nimodipine or any other calcium channel blocker after neurologic stroke that has occurred in the surgical unit or in any other environment has not yet become standard practice. Despite favorable results in small trials, not all investigations of those who sustain stroke have confirmed the benefits of nimodipine.[318]

Other Anesthetics. A remarkable number of anesthetics have shown neuroprotective efficacy in animal studies. However, to date, large-scale randomized trials of a variety of anesthetics in patients with stroke have not demonstrated neuroprotection for any drug. With the exception of tissue plasminogen activator (tPA) for thrombolysis and the calcium channel blockers nimodipine and nicardipine for the management of SAH, pharmacologic neuroprotective anesthetics are not available for the treatment

of patients with cerebral ischemia. Details about drugs that have undergone clinical trials and those that are currently being investigated in humans can be found at the Stroke Trials Registry (www.strokecenter.org/trials/TrialDetail.aspx?tid=338) of Washington University in St. Louis.

Cerebral Ischemia: Influence of Physiologic Variables

Cerebral Perfusion Pressure. Measures designed to augment CBF (an important determinant of energy supply) are also important. In the *ischemic penumbra* (described in the section, "Critical Cerebral Blood Flow Thresholds"), small improvements in CBF have the potential to prolong neuronal survival substantially. Maintenance of high-normal CPP can augment collateral perfusion pressure and maintain CBF[319] and has been shown to result in improvement in various neurophysiologic parameters, including neurologic function.[320,321] By contrast, hypotension can reduce CBF and exacerbate injury. In trials of nimodipine in patients with acute stroke, a reduction in blood pressure of 10% to 20% increased the probability of an adverse outcome (either death or dependency) fourfold,[322] thus emphasizing the adverse impact of blood pressure reduction on an injured brain. Therefore in patients with cerebral ischemia, hypotension should be promptly treated and normotension restored. Although the target MAP should obviously be based on knowledge of a patient's preexisting blood pressure, data to provide specific guidelines are insufficient in humans. In the majority of patients, maintenance of the MAP in the 70 to 80 mm Hg range should be adequate. The available data provide support for reducing blood pressure to less than 180/105 mm Hg in patients with stroke who have been treated with tPA in the hope of reducing the incidence of hemorrhage into the ischemic brain.[323,324] In addition, blood pressure augmentation to a systolic pressure of 180 to 220 mm Hg in patients with SAH-induced vasospasm and to a CPP greater than 60 mm Hg in patients with traumatic brain injury is reasonable.[323] Note, however, that augmentation of CPP in the high-normal range carries the inadequately explored risks of increased edema and hemorrhagic infarction if used as support during more than brief periods of ischemia, particularly when several hours has elapsed since the onset of ischemia.

Carbon Dioxide Tension. Hypercapnia has the potential to cause intracerebral steal and may worsen intracellular pH. Despite some support for the occurrence of a favorable so-called Robin Hood or inverse steal,[325] hypocapnia has not generally proved effective in either laboratory or clinical settings.[326-328] Pending further information and in the absence of a means of verifying the perfusion response to the manipulation of $Paco_2$, normocapnia remains standard practice.

Temperature. Hypothermia is *the* principal cerebral protective technique for circulatory arrest procedures (also see Chapter 54). It unequivocally enhances cerebral tolerance for episodes of ischemia. For deep hypothermia, this effect is largely a function of the reduction in the CMR. Although barbiturates reduce only the component of the CMR associated with electrophysiologic *work* (approximately 60% of the $CMRO_2$ in the awake state), hypothermia causes a reduction in both electrophysiologic energy consumption and energy utilization related to the maintenance of cellular integrity; mild hypothermia may preferentially suppress the latter.[329,330] A substantial number of laboratory studies have demonstrated that mild degrees of hypothermia (2° C to 4° C) during an episode of ischemia can confer substantial protection as histologically measured.[289,290] In addition, evidence from animal studies suggests that hypothermia initiated in the immediate postischemic period confers a protective benefit.[331,332]

In light of this dramatic protective effect of mild hypothermia in the laboratory, its use in the surgical setting may be advocated. Proponents of its use argue that hypothermia is readily achieved and not accompanied by significant myocardial depression or arrhythmias. In addition, the patient can be easily rewarmed in the surgical unit after the risk of ischemia has subsided. Results of a pilot study clearly demonstrated a trend toward improved neurologic outcome in hypothermic patients undergoing intracranial aneurysm clipping.[333] Unfortunately, the subsequent definitive trial did not demonstrate any improvement in outcome that could be attributable to hypothermia.[334] However, it should be noted that the majority of the patients in that study had SAH of grades I, II, and III. In addition, the number of patients who had temporary clips applied in excess of 20 minutes was quite small (five to six patients). Consequently, an argument has been made that mild hypothermia may well be of benefit in patients with high-grade aneurysms or in those in whom the complexity of the aneurysm clipping is such that prolonged temporary clipping may be required. Considering that temperature reduction takes time, the decision to induce hypothermia must be made in advance. Therefore the therapeutic use of hypothermia may be considered in such high-risk patients.

The application of mild hypothermia after head injury reduced ICP[335] and improved neurologic outcome[336] in pilot trials. Of note is the finding that complications attributable to hypothermia were not observed. A subsequent multicenter trial of hypothermia in patients with head injuries, however, failed to confirm the findings of the pilot studies.[337] Induction of mild hypothermia did not improve long-term neurologic outcome. Note should be made, however, of the post hoc finding that the outcomes in patients younger than 45 years of age who were initially hypothermic were worse if these patients were rewarmed; these data suggest that such patients should be rewarmed over a prolonged period.

A number of clinical trials of induced hypothermia in a limited number of patients with stroke have been conducted. To date, these trials have demonstrated the feasibility of inducing hypothermia in the range of 33° C to 35° C, even in patients who are not subjected to endotracheal intubation and mechanical ventilation.[338] Hypothermia was associated with improved ICP and CPP. However, complications, particularly thrombocytopenia, bradycardia, ventricular ectopy, hypotension, and infection, are frequent. In addition, an intractable increase in ICP can occur during rewarming, even if the elevation in temperature is gradual and accomplished over a period of

several hours. These side effects attest to the need to conduct randomized trials to evaluate properly the efficacy of mild hypothermia in patients with stroke. Such trials are currently under way.

Data regarding the application of mild hypothermia in survivors of cardiac arrest are more positive. Two recent trials have demonstrated that the induction of hypothermia (32° C to 34° C) after successful resuscitation from cardiac arrest resulted in a significantly better neurologic outcome 6 months after the arrest.[278,339] These studies demonstrate the clinical efficacy of hypothermia for the purposes of reducing ischemic cerebral injury and to provide support for the use of intraoperative hypothermia in patients who are considered to be at high risk.

By contrast, increases in brain temperature during and after ischemia aggravate injury.[340] An increase of as little as 1° C can dramatically increase injury. Ischemia that normally results in scattered neuronal necrosis produces cerebral infarction when body temperature is elevated. Therefore avoiding hyperthermia in patients who have suffered an ischemic insult or in those who are at risk for cerebral ischemia seems prudent. In the surgical setting, hyperthermia is seldom a problem (witness the authors' efforts to prevent hypothermia). One situation in which body temperature is often allowed to increase is during rewarming after hypothermic cardiopulmonary bypass. In this situation, hyperthermia (core body temperature in excess of 38° C) is not uncommon. The suggestion that increases in temperature in excess of 37° C to 38° C are detrimental has some merit, considering the recent information regarding the deleterious effect of hyperthermia.

Glucose. Withholding glucose-containing solutions in situations during which cerebral ischemia may occur is now an established practice. The practice is based on numerous demonstrations in animal models of brain and spinal cord ischemia that elevation of plasma glucose before episodes of either complete or incomplete ischemia results in aggravation of neurologic injury. However, it should be noted that the majority of investigations involved adult animals and that certainty concerning the adverse effects of hyperglycemia in immature subjects, such as neonates, is less.[341] Furthermore, it should be noted that only some[342,343] and not all[344] of the investigations in humans have provided confirmation of an independent effect of serum glucose on neurologic outcome. Nonetheless, in long-term outcome studies, diabetic and nondiabetic hyperglycemia has been shown to be an independent predictor of poor outcome.[343] In the National Institutes of Health–sponsored recombinant tPA stroke trial, hyperglycemia was associated with significantly lower odds for desirable clinical outcomes and a higher incidence of intracranial hemorrhage.[345] These data prompted a randomized clinical trial of the efficacy of insulin administration to patients with acute stroke. Although the trial was underpowered, the results showed that the administration of insulin to control blood glucose levels in patients with stroke did not improve outcome 3 months after stroke.[346] A recurrent theme in the discussion of these studies is that glucose elevation may be the *result* of the stress associated with a severe insult, either ischemic or traumatic, rather than its *cause*. In addition, the inevitable questions of whether and how quickly immediate prerisk treatment of an elevated plasma glucose level with insulin reduces risk to normoglycemic levels have not been thoroughly examined. It is the opinion of the authors that, at this juncture, acute insulin administration (with its attendant risk of hypoglycemia) in patients with modest glucose elevation (~150 mg/dL) in the surgical setting is not yet justified.

By contrast, hypoglycemia is also associated with cerebral injury. With a gradual reduction in blood glucose values to approximately 40 mg/dL, a shift in EEG frequencies occurs from alpha and beta toward delta and theta.[347] Below a blood glucose level of 20 mg/dL, suppression of the EEG (flat) is observed. Persistence of this level of hypoglycemia results in seizure activity and neuronal injury, particularly to the hippocampus.

Seizures. Normalization of systemic pH, prevention and treatment of seizures, which dramatically increase the CMR, and control of the ICP and CPP are all important elements of brain protection and resuscitation, although mundane and lacking in appeal of the pharmacologic silver bullet.

Intravascular Volume and Hematocrit Manipulation. Although hemodilution has not proved effective in studies of human stroke, both laboratory and human data support the practice; hemodilution is an established part of the management of ischemia associated with vasospasm. However, the data do not currently justify routine hemodilution (a hematocrit of 30% to 35% is the theoretic optimum) in patients in whom focal ischemia *might* occur in the surgical unit.[348] On the other hand, the potentially deleterious effects of hemoconcentration should help further suppress the out-of-date notion that neurosurgical patients should be run dry. An increased hematocrit, because of viscosity effects, reduces CBF.[10] In anticipation of a procedure wherein incomplete ischemia might occur, such as CEA, a hematocrit in excess of 55% should be considered for decrease by preoperative phlebotomy.

Summary of Anesthetics and Neuroprotection

In comparison to the awake or lightly sedated state, the vulnerability of the brain to ischemic injury is reduced under anesthesia. Volatile anesthetics, barbiturates, propofol, xenon, and ketamine reduce injury in experimental models and may reduce injury in comparison with a pure N_2O-narcotic anesthetic. However, direct comparison has not demonstrated the superiority of any one anesthetic (or combination of anesthetics) over another. Therefore, based on the available data, the use of a specific anesthetic or anesthetic regimen for the purpose of brain protection in the clinical setting cannot be recommended.

There is a paucity of information about anesthetic neuroprotection in humans and the lack of clinical trials is understandable, considering the low frequency of stroke and ischemic injury in the perioperative setting. There are, however, a few clinical investigations from which inferences about anesthetic neuroprotection can be made. In the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST), a subset of patients received

supplemental doses of thiopental, etomidate, or propofol for the purposes of neuroprotection. The neurologic outcome in these patients was no different than those who did not receive these anesthetics.[349] In the general anesthesia versus local anesthesia trial,[350] patients undergoing CEA were randomized to receive either general anesthesia or local anesthesia (also see Chapter 70); in the latter group, patients were lightly sedated but were arousable during surgery. The outcome between the two groups was not different, indicating that the general anesthetic state did not provide any protective benefit.[350] Finally, in a recent retrospective trial of thrombolysis for acute stroke, patients who were anesthetized had a worse outcome than those who were only mildly sedated. Although the worse outcome with general anesthesia was attributed to a lower CPP in that group,[351] the results do not provide evidence of anesthetic neuroprotection. In aggregate, these data suggest that supplemental drugs that produce burst suppression of the EEG do not provide protection in anesthetized patients and that the state of general anesthesia does not improve neurologic outcome.

The neuroprotective efficacy of anesthetic drugs in experimental studies is achieved only by strict attention to the maintenance of physiologic homeostasis; in fact, the potential for exacerbation of cerebral injury, either traumatic or ischemic, with physiologic mismanagement is significantly more likely than the modest protection afforded by pharmacologic drugs—these are important observations. Accordingly, with respect to brain protection, efforts should be focused on the maintenance of physiologic parameters (e.g., perfusion pressure, oxygenation, normocapnia, temperature management, control of hyperglycemia, seizure prophylaxis) within the appropriate ranges and less on pharmacologic or anesthetic drugs to reduce cerebral injury.

Deferring Elective Procedures After Stroke

The risk of extension of cerebral infarction in the event of subsequent anesthesia and surgery has not been systematically studied. In patients who have suffered a stroke, CBF undergoes significant changes. Areas of both high and low CBF occur, and stabilization of regional CBF and CMR is apparent after approximately 2 weeks.[352] Loss of normal vasomotor responses (e.g., CO_2 responsiveness, autoregulation) in the early postinsult period is very common,[353-355] and these changes persist beyond 2 weeks in a small percentage of patients with stroke.[354,355] BBB abnormalities, as reflected by the accumulation of CT contrast material or brain scan isotopes, are still present 4 weeks after the insult,[356] and the histologic resolution of large infarcts is not complete for several months. Early CEA after stroke in patients with large strokes and neurologic disability was accompanied by an increased risk of intracerebral hemorrhage.[357] Based on early CEA experience, deferring CEA for 4 to 6 weeks after stroke is recommended.[357] A 6-week delay should give some assurance of the probable recovery of autoregulation, CO_2 responsiveness, and BBB integrity.

A delay in CEA after stroke, however, poses risks. In patients who have sustained a stroke, the incidence of a second stroke is approximately 12%.[358] The risk of a complete carotid occlusion is considerable with delayed surgery. In addition, early CEA can restore cerebral perfusion to the ischemic penumbra, possibly improving long-term functional recovery. [359] However, the size and location of the infarction should be weighed. A small infarction in silent cortex may offer wider latitudes than a large lesion that has resulted in a paresis that is still resolving. A small prospective study suggests that in patients with nondisabling stroke, early CEA can be safely performed within 2 weeks of the stroke.[360] Candidates for early CEA after stroke may include patients with relatively small cerebral infarctions, resolution (either complete or near complete) of neurologic symptoms, and ipsilateral carotid artery stenosis.[361] Delaying CEA in patients who have had large strokes with significant neurologic disability, reduced level of consciousness, and displaying a midline shift on the CT scan is generally preferable.

Outcome data to inform the decision about surgery for the patient after stroke, other than CEA, is lacking. With the extrapolation of the information from the CEA studies, pending other information, deferring elective surgery for at least 4 weeks after a cerebral vascular accident and preferably for 6 weeks from the point at which a stable postinsult neurologic state has been achieved seems reasonable.

CHRONIC ARTERIAL HYPERTENSION

A recurrent concern is that of acceptable levels of arterial blood pressure reduction in patients who are chronically hypertensive. Firm guidelines have not been established. However, from the vantage of cerebral well-being, limiting elective MAP reduction to 30% to 35% of resting mean levels seems appropriate for both hypertensive and normotensive patients. The same guidelines might apply in both populations because in chronic hypertension, both the lower and upper limits of autoregulation are shifted to the right with apparently little distortion.[362]

The rationale for a limit of 30% to 35% is as follows. MAP reductions of 50% in nonanesthetized patients, both normotensive and hypertensive, will commonly produce reversible symptoms of cerebral hypoperfusion.[362-364] Although even greater reductions will probably be tolerated provided that exposures are brief, the hematocrit is reasonable, and the cerebral vasculature is patent, the authors counsel against it. A reduction in the MAP of this magnitude will significantly increase the probability of CPP being close to or below the LLA, thereby reducing cerebrovascular reserve. It has been demonstrated that a 25% reduction in the MAP will bring both normotensive and hypertensive patients to the LLA.[362] As the reduction in the MAP exceeds 25% of baseline, CBF values will be below normal, albeit in patients free of occlusive vascular disease, above the threshold for neurophysiologic dysfunction or injury (see Fig. 17-6). However, physiologic reserve is being encroached upon, thereby leaving little margin for error or for other causes of impaired cerebral oxygen delivery such as low hematocrit or unrecognized cerebrovascular disease.

In animals, treatment of chronic hypertension can restore the LLA to normal.[365,366] A similar phenomenon has been observed in humans by Strandgaard, although restoration was incomplete and had failed to occur after

as long as 12 months of treatment in some patients.[362] It is an unexplored possibility that the extent of restoration of the LLA with antihypertensive therapy is agent dependent. Some may restore the LLA more effectively than others. In particular, ACE inhibitors have been shown to decrease the LLA acutely in both normotensive and hypertensive subjects.[367,368]

Intracranial Hypertension

Control of intracranial hypertension is discussed in detail in Chapter 70.

BRAIN TUMORS

There are few data regarding the physiologic function of intracranial tumors. Arbit and colleagues[369] measured CBF in cerebral tumors with laser Doppler technology. In general, they found that tumors had lower CBF than the normal brain. Autoregulation was occasionally apparent. Vascular responsiveness to changes in Pa_{O_2}[370] and Pa_{CO_2}[371] are generally preserved in patients with gliomas. However, in some circumstances, hyperventilation can at times be associated with paradoxical increases in MCA flow velocity ipsilateral to the tumor.[372] Measurement of regional CBF in the area of the tumor might also be a useful predictor of the grade of intracranial gliomas; both regional CBF and regional CBV are greater with high-grade gliomas.[373] Considerable edema is often associated with intracranial tumors, and the radiologic extent of the edema, which presumably represents the extent of abnormal vessel leakiness, correlates with the severity of the elevation in ICP that occurs in association with intubation-related hypertension.[374] Edema formation in the peritumoral region can be characterized as vasogenic with leakage of plasma proteins from the vascular space, hydrocephalic secondary to obstruction of CSF flow, or static as a result of venous obstruction by tumor.[375] Although the precise mechanisms by which edema formation occurs are not clear, the loss of integrity of the tight junctions of components of the BBB, an increased permeability induced by vascular endothelial growth factor expressed by tumors, and an increased expression of leukotriene C4 in peritumoral fluid probably play a role.[376] Osmotherapy with mannitol will affect a reduction in edema; however, with a permeable BBB, mannitol can diffuse into the peritumoral space and lead to rebound edema formation.[375] For acute reduction of ICP in the surgical unit, this concern is not significant. Dexamethasone remains the mainstay of treatment of tumor edema; it causes a reduction in edema formation with little effect on edema reabsorption, a reduction in permeability of the BBB that can be recognized as rapidly as 1 hour after administration,[377] and a modest reduction in tumor size. See Chapter 70 for a complete discussion.

COMA AND EPILEPSY

Regardless of its cause, coma reduces brain metabolism. In the case of lesions occurring in the reticular activating system, the reduction in the CMR probably represents a normal physiologic adjustment to reduced functional activity. During generalized seizure activity, CMR and CBF may dramatically increase.[202] The intensive motor and brain activity associated with generalized seizures leads to the development of systemic and cerebral acidosis, often accompanied by a reduction in arterial oxygenation, an increase in Pa_{CO_2}, and peripheral lactic acidosis. If generalized seizure activity continues unabated, then arterial hypotension ensues. With muscular relaxation and measures ensuring adequate oxygenation and ventilation, the systemic acidosis and hypotension can be avoided and the severity of the cerebral acidosis diminished. During relatively brief episodes of continuous seizures, the brain seems able to meet the high metabolic demands.[219] However, even with effective ventilation and maintenance of perfusion pressure, when seizures continue for a prolonged period, they can lead to the development of irreversible neuronal damage.[378] Therapy aimed at interrupting the seizure and restoring a normal balance between cerebral metabolic demand and blood flow is indicated. Barbiturates, benzodiazepines, or other potent anticonvulsants are appropriate. Adequate ventilation, oxygenation, and maintenance of arterial blood pressure are important adjunctive measures. Muscle relaxants must be viewed as purely symptomatic therapy because they do not alter the abnormal cerebral electrical activity.

The potentially injurious nature of seizures justifies attention to prevention. Practices vary. However, patients who have sustained a severe head injury or SAH and any patient on whom a substantial cortical incision is planned are at risk, and prophylactic anticonvulsants should be considered.

Complete references available online at expertconsult.com

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Chapter 18

Neuromuscular Physiology and Pharmacology

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Key Points

- The neuromuscular junction contains the distal nerve terminal, synaptic cleft, and muscle end plate and provides an array of receptors and substrates for drug action. Neuromuscular transmission is predominately dependent on acetylcholine as the natural transmitter. Acetylcholine, when released from the prejunctional nerve terminal, binds to typical acetylcholine receptors (AChRs) that are present either prejunctionally or postjunctionally within the neuromuscular junction and, depending on their structural composition, are classified into the usual muscle subtype AChRs or a variety of neuronal subtype AChRs.
- Muscle relaxants have multiple sites of action. Although the major actions occur by mechanisms and at sites described as agonistic and antagonistic actions at postjunctional receptors for depolarizing and nondepolarizing muscle relaxants (NDMRs), this description of neuromuscular drug action is a simplistic one. Neuromuscular transmission is impeded by NDMRs because they prevent access of acetylcholine to its preferred recognition site on the postjunctional nicotinic AChR.
- If the concentration of NDMR is increased, another, noncompetitive action—block of the ion channel—is superimposed. The postjunctional paralytic effects of muscle relaxants can be enhanced by the actions of the relaxant on prejunctional AChRs, which modulate the release of acetylcholine. The latter can be documented as *fade* that occurs with increased frequency of stimulation. Fade can also be seen when the postjunctional AChRs alone are functionally blocked (e.g., by bungarotoxin) or when the number of AChRs (e.g., myasthenia gravis) is decreased. Hence, the neuromuscular junction is a complex and dynamic system in which the phenomena produced by drugs are composites of actions that vary with the drug, dose, activity at the nerve terminal and muscle, time after administration, presence of anesthetics or other drugs, and age and condition of the patient.
- Inhibition of muscle acetylcholinesterase enzyme by anticholinesterases (e.g. neostigmine) increases the concentration of acetylcholine, which can compete with and displace the NDMRS and thus reverse the paralysis. These anticholinesterase drugs (e.g., neostigmine) also have other effects, including those on nerve terminals and on the receptor, by an allosteric mechanism. Acute bolus or prolonged administration of anticholinesterases can have deleterious effects on neuromuscular function in otherwise healthy patients. A modified cyclodextrin such as sugammadex is a novel and innovative class of compound that reverses paralysis of only steroidal muscle relaxants by encapsulation of this series of compounds.
- Depolarizing compounds (e.g., succinylcholine) initially react with the acetylcholine recognition site and, like the transmitter, open AChR ion channels during depolarization of the end-plate membrane. Unlike the transmitter, they are not subject to hydrolysis by acetylcholinesterase and therefore remain in the junction. Soon after the administration of succinylcholine, some receptors are desensitized, and, although occupied by the agonist, they do not open to allow current to flow to depolarize the muscle membrane area.
- If the depolarizing relaxant is applied in higher-than-usual concentrations or is allowed to remain at the junction for a long time, then other neuromuscular effects occur. Depolarizing relaxants have effects on prejunctional structures, and

KEY POINTS—cont'd

the combination of prejunctional and postjunctional effects plus secondary ones on muscle and nerve homeostasis results in the complicated phenomenon known as *phase II blockade.*

- Intense research in the area of neuromuscular transmission continues at a rapid pace. Newer observations on muscle and neuronal types of AChRs, ion channels, membranes, and prejunctional function reveal a much broader range of sites and mechanisms of action for agonists and antagonists.
- Some of the other drugs used clinically (e.g., Botox) have effects on the nerve and therefore indirectly on muscle. Systemic infection with clostridial toxins (*Clostridium botulinum*, gas gangrene) can lead to systemic paralysis as a result of decreased release of acetylcholine from the nerve terminal. NDMRs administered even for 12 hours or for prolonged periods can have effects on the postsynaptic receptor and simulate denervation (chemical denervation). Magnesium given to preeclamptic mothers decreases the release of acetylcholine with a potential for muscle weakness in the mother or newborn. In recognizing these sites and mechanisms, we begin to bring our theoretical knowledge closer to explaining the phenomena observed when these drugs are exposed to living humans.
- Contemporary research work has focused on the control of AChR expression on the postjunctional membrane in normal and diseased states. The presence or absence of mature and immature isoforms seems to complicate matters further. In certain pathologic states (e.g., denervation, stroke, sepsis, burns, immobilization, chronic use of NMDRs), AChRs are upregulated, with increased expression of the immature isoform. More recently, another isoform of the nicotinic AChR, previously described in neuronal tissues only, the $\alpha 7$ neuronal AChR, has been identified in muscle. These receptors have different functional and pharmacologic properties than conventional muscle postsynaptic receptors. The altered functional and pharmacologic characteristics of the immature (γ-subunit) and neuronal ($\alpha 7$-subunit) receptors result in increased sensitivity to succinylcholine with hyperkalemia and resistance to NDMRs.
- An area of increasing attention is control of the expression of mature versus the other two receptor isoforms (immature γ- and $\alpha 7$-subunits). Re-expression of the immature γ- and $\alpha 7$-subunit receptors is probably related to aberrant growth factor signaling. Genetic mutations in the AChR that result in prolonged or fast open-channel time, can lead to a myasthenia-like state, even in the presence of normal receptor numbers. The weakness is usually related to ineffective depolarization or to the altered open-channel time, or to both.

Despite the fact that cholinergic neurotransmission in the neuromuscular junction is the most widely studied synapse within the nervous system, complete knowledge of its workings has not yet been achieved. This is an area of continuing interest for many researchers worldwide.

The physiology of neuromuscular transmission could be analyzed and understood at the most simple level by using the classic model of nerve signaling to muscle through the acetylcholine receptor (AChR). The mammalian neuromuscular junction is the prototypical and most extensively studied synapse. Research has provided more detailed information on processes that, within the classic scheme, can modify neurotransmission and response to drugs. One example is the role of qualitative or quantitative changes in AChRs that modify neurotransmission and the response to drugs.[1-3] In myasthenia gravis, for example, the decrease in AChRs results in decreased efficiency of neurotransmission (and therefore muscle weakness)[4] and altered sensitivity to neuromuscular relaxants.[3] Another example is the importance of nerve-related (prejunctional) changes that alter neurotransmission and the response to anesthetic drugs.[5-7] Yet, muscle relaxants act in ways that are not encompassed by the classic scheme of a unitary site of action. The observation that muscle relaxants can have prejunctional effects[5] or that some nondepolarizing muscle relaxants (NDMRs) can also have agonist-like stimulatory actions on the receptor,[8] whereas others have effects not explainable by purely postsynaptic actions on muscle,[9-11] has provided new insight into some previously unexplained observations. Although muscle relaxants are known to have effects on the presynaptic and postsynaptic receptors of the neuromuscular junction, recent evidence indicates that they can react with nicotinic and muscarinic AChRs other than those in muscle, including receptors on the carotid sinus, on the vagus to the heart, and on bronchial smooth muscle.[9-13] Although this multifaceted action-response scheme makes the physiologic and

pharmacologic neurotransmission more complex, these added insights also bring experimentally derived knowledge much closer to clinical observations.

Crucial to the seminal concepts that have developed, relative to the neurotransmitter acetylcholine and its receptor systems, is the introduction of powerful and contemporary techniques in molecular biology, immunology, electrophysiology, and genetic manipulation, as well as more elegant techniques for the observation of the neuromuscular junction in vivo.[14] These techniques have augmented the more traditional pharmacologic, protein chemical, morphologic, and cytologic approaches.[15-17] Research has elucidated the manner in which the nerve ending regulates the synthesis and release of transmitter and trophic factors, both of which control muscle function, as well as explained how exogenous and endogenous substances influence these processes.[15-17] Research continues to reveal how receptors are synthesized and anchored at the end plate, the role of the nerve terminal in the maturation processes, and the synthesis and control of acetylcholinesterase, the enzyme that breaks down acetylcholine. Several reviews that provide detailed insight into these areas are available.[16-19]

NEUROMUSCULAR TRANSMISSION

Neuromuscular transmission occurs by a fairly simple and straightforward mechanism. The nerve synthesizes acetylcholine and stores it in small, uniformly sized packages called *vesicles*. Stimulation of the nerve causes these vesicles to migrate to the surface of the nerve, rupture, and discharge acetylcholine into the cleft separating the nerve from muscle. AChRs in the end plate of the muscle respond by opening their channels for influx of sodium ions into the muscle to depolarize the muscle. The endplate potential created is continued along the muscle membrane by the opening of sodium channels present throughout the muscle membrane to initiate a contraction.[16,17] The acetylcholine immediately detaches from the receptor and is destroyed by the enzyme, acetylcholinesterase, which is also present in the cleft. Drugs, notably depolarizing muscle relaxants or nicotine and carbachol (a synthetic analog of acetylcholine not destroyed by acetylcholinesterase), can also act on these receptors to mimic the effect of acetylcholine and cause depolarization of the end plate. These drugs are therefore called *agonists* of the receptor because they turn the receptor into an active state, at least initially. NDMRs also act on the receptors, but they prevent acetylcholine from binding to the receptor and thus prevent depolarization by agonists. Because these NDMRs prevent the action of agonists (e.g., acetylcholine, carbachol, succinylcholine), they belong to the class of compounds known as *antagonists* at the muscle AChRs. Other compounds, frequently called *reversal drugs* or antagonists of neuromuscular paralysis (e.g., neostigmine, prostigmine), inhibit acetylcholinesterase and therefore impair the hydrolysis of acetylcholine. The increased accumulation of undegraded acetylcholine can effectively compete with NDMRs and thereby displace the latter from the receptor (i.e., law of mass action) and antagonize the effects of NDMRs.

MORPHOLOGY

The neuromuscular junction is specialized on both the nerve side and on the muscle side to transmit and receive chemical messages.[15-19] Each motor neuron runs without interruption from the ventral horn of the spinal cord or medulla to the neuromuscular junction as a large, myelinated axon (Fig. 18-1, *A*). As the motor neuron approaches the muscle, the neuron repeatedly branches to contact many muscle cells and gather them into a functional group known as a *motor unit* (see Fig. 18-1, *B*). The architecture of the nerve terminal is quite different from that of the rest of the axon. As the terminal reaches the muscle fiber, it loses its myelin, forms a spray of terminal branches against the muscle surface, and is covered by Schwann cells. This arrangement conforms to the architecture on the synaptic area of the muscle membrane (see Fig. 18-1, *C*). The nerve is separated from the surface of the muscle by a gap of approximately 20 nm, called the *junctional cleft* or *synaptic cleft*. The nerve and muscle are held in tight alignment by protein filaments called *basal lamina* that span the cleft between the nerve and end plate. The muscle surface is heavily corrugated, with deep invaginations of the junctional cleft—the primary and secondary clefts—between the folds in the muscle membrane; thus the end plate's total surface area is very large. The depths of the folds also vary between muscle types and species. Human neuromuscular junctions, relative to muscle size, are smaller than those of the mouse, although the junctions are located on muscle fibers that are much larger. Human junctions have longer junctional foldings and deeper gutters.[14,17] The sodium channels, which propagate the wave of depolarization, are located in the depths of the folds (see Fig. 18-1, *D*). The shoulders of the folds are densely populated with AChRs, approximately 5 million of them in each junction. AChRs are sparse in the depths between the folds.

The trophic function of the nerve is vital for the development and maintenance of adequate neuromuscular function. Before birth, each muscle cell commonly has contacts with several nerves and has several neuromuscular junctions.[14,19] At birth, all but one of the nerves retract, and a single end plate remains (see "Neuromuscular Junction at Extremes of Age" later in this chapter). Once formed, the nerve-muscle contact, especially the end plate, is durable. Even if the original nerve dies, the one replacing it innervates exactly the same region of the muscle. The nerve endings on fast muscles are larger and more complicated than those on slow muscles. The reason for this is unclear. These differences in the nerve endings on muscle surfaces may play a role in the difference in response of fast- and slow-twitch muscle fibers to muscle relaxants.

Because all the muscle cells in a unit are excited by a single neuron, stimulation of the nerve electrically or by an action potential originating from the ventral horn or by any agonist, including depolarizing relaxants (e.g., succinylcholine), causes all muscle cells in the motor unit to contract synchronously. Synchronous contraction of the cells in a motor unit is called *fasciculation* and is often vigorous enough to be observed through the skin. Although most adult human muscles have only one neuromuscular junction per cell, an important exception is some of

the cells in extraocular muscles. The extraocular muscles are *tonic* muscles, and, unlike other mammalian striated muscles, they are multiply innervated with several neuromuscular junctions strung along the surface of each muscle fiber.[20-23] Quite in contrast to other muscles, even the adult ocular muscle contains mature and immature fetal receptors (see "Biology of Prejunctional and Postjunctional Nicotinic Acetylcholine Receptors" later in this chapter) segregated into distinct synapses on different fibers.[20,22] The ocular muscles slowly contract and relax rather than quickly as do other striated muscles; they can maintain a steady contraction, or contracture, the strength of which is proportional to the stimulus received. Physiologically, this specialization apparently holds the eye steadily in position. Ocular muscles are important to an anesthesiologist because depolarizing muscle relaxants (e.g., succinylcholine) affect them differently than they do most skeletal muscles. Instead of causing a brief contraction, followed by paralysis, the drug causes a long-lasting contracture response that pulls the eye against the orbit and could contribute to an increase in intraocular fluid pressure.[22,23] The clinical significance of the succinylcholine-induced increase in intraocular pressure has been questioned. Although many textbooks invoke the reported extrusion of intraocular content with succinylcholine, the basis for this effect seems to be anecdotal.[24] Clinical studies,

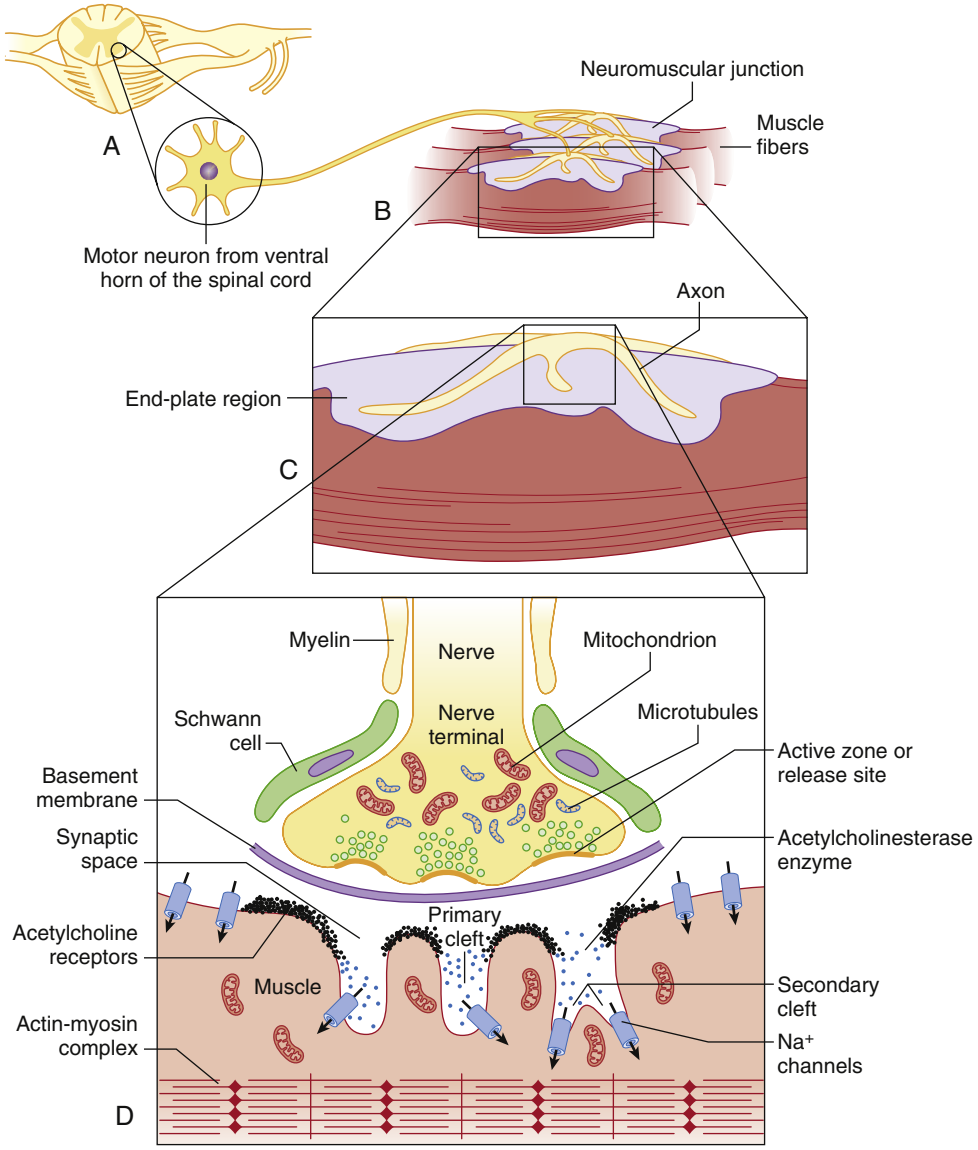


Figure 18-1. Structure of the adult neuromuscular junction shows the three cells that constitute the synapse: the motor neuron (i.e., nerve terminal), muscle fiber, and Schwann cell. **A,** The motor nerve originates in the ventral horn of the spinal cord or brainstem. **B,** As the nerve approaches its muscle fibers and before attaching itself to the surface of the muscle fiber, the nerve divides into branches that innervate many individual muscle fibers. **C,** Each muscle receives only one synapse. The motor nerve loses its myelin and further subdivides into many presynaptic boutons to terminate on the surface of the muscle fiber. **D,** The nerve terminal, covered by Schwann cells, has vesicles clustered about the membrane thickenings, which are the active zones, toward its synaptic side and mitochondria and microtubules toward its other side. A synaptic gutter or cleft made up of a primary and many secondary clefts separates the nerve from the muscle. The muscle surface is corrugated, and dense areas on the shoulders of each fold contain acetylcholine receptors. Sodium (Na^+) channels are present at the bottom of the clefts and throughout the muscle membrane. The acetylcholinesterase and proteins and proteoglycans that stabilize the neuromuscular junction are present in the synaptic clefts.

however, have indicated that succinylcholine-induced contractions of the extraocular muscles can last as long as 1 to 2 minutes and isometric tensions larger than 12 g can develop for each extraocular muscle.[23] Thus succinylcholine probably should not be given to patients with open eye injuries (also see Chapters 34 and 84).

The perijunctional zone is the area of muscle immediately beyond the junctional area and is critical to the function of the neuromuscular junction. The perijunctional zone contains a mixture of receptors, including a smaller density of AChRs and a high density of sodium channels (see Fig. 18-1, *D*). The admixture enhances the capacity of the perijunctional zone to respond to the depolarization (i.e., end-plate potential) produced by the AChRs and to transduce it into the wave of depolarization that travels along the muscle to initiate muscle contraction. The density of sodium channels in the perijunctional area is richer than in more distal parts of the muscle membrane.[25,26] The perijunctional zone is close enough to the nerve ending to be influenced by transmitter released from it. Moreover, special variants (i.e., isoforms) of receptors and sodium channels can appear in this area at different stages of life and in response to abnormal decreases in nerve activity (see "Biology of Prejunctional and Postjunctional Nicotinic Acetylcholine Receptors" later in this chapter). Congenital abnormalities in the AChRs or in the sodium and calcium channels (i.e., mutations) are also known.[25-27] These variabilities seem to contribute to the differences in response to relaxants that are observed in patients with different pathologic conditions and ages.[17,27]

QUANTAL THEORY

The contents of a nerve ending are not homogeneous. As illustrated in Figures 18-1 and 18-2, vesicles are congregated in the portion toward the junctional surface, whereas microtubules, mitochondria, and other support structures are located toward the opposite side. The vesicles containing transmitter are ordered in repeating clusters alongside small, thickened, electron-dense patches of membrane referred to as *active zones* or *release sites*. This thickened area is a cross section of a band running across the width of the synaptic surface of the nerve ending that is believed to be the structure to which vesicles attach (active zones) before they rupture into the junctional cleft (see "Process of Exocytosis" later in this chapter). High-resolution

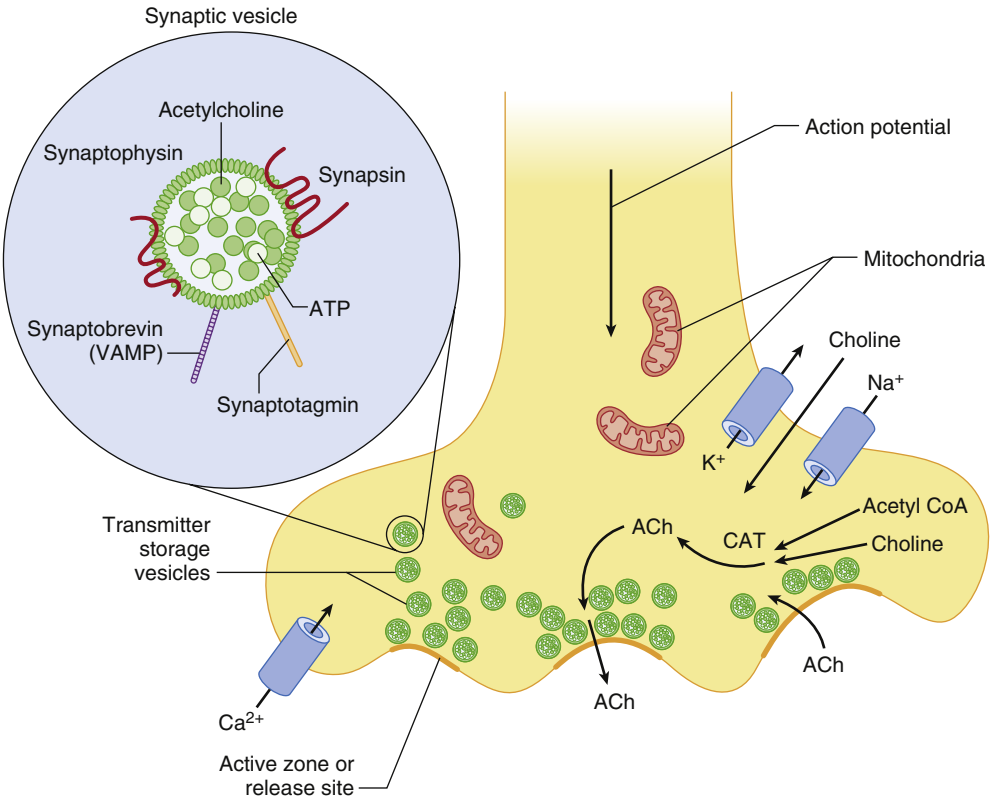


Figure 18-2. The working of a chemical synapse, the motor nerve ending, including some of the apparatus for synthesis of transmitter, is illustrated. The large intracellular structures are mitochondria. Acetylcholine (ACh), synthesized from choline and acetate by acetyl coenzyme A (CoA), is transported into coated vesicles, which are moved to release sites. A presynaptic action potential that triggers the influx of calcium (Ca^{2+}) through specialized proteins (i.e, Ca^{2+} channels) causes the vesicles to fuse with the membrane and discharge transmitter. Membrane from the vesicle is retracted from the nerve membrane and recycled. Each vesicle can undergo various degrees of release of contents—from incomplete to complete. The transmitter is inactivated by diffusion, catabolism, or reuptake. The inset provides a magnified view of a synaptic vesicle. Quanta of ACh, together with adenosine triphosphate (ATP), are stored in the vesicle and covered by vesicle membrane proteins. Synaptophysin is a glycoprotein component of the vesicle membrane. Synaptotagmin is the vesicle's calcium sensor. Phosphorylation of another membrane protein, synapsin, facilitates vesicular trafficking to the release site. Synaptobrevin (vesicle-associated membrane protein [VAMP]) is a SNARE protein involved in attaching the vesicle to the release-site proteins at the nerve terminal (see also Fig. 18-3). *CAT,* Choline acetyltransferase; *K^+*, potassium; *Na^+*, sodium.

scanning electron micrographs reveal small protein particles arranged alongside the active zone between vesicles. These particles are believed to be special channels—voltage-gated calcium channels—that allow calcium to enter the nerve and cause the release of vesicles.[28,29] The rapidity with which the neurotransmitter is released (200 μsec) suggests that voltage-gated calcium channels are close to the release sites. Proteomic studies suggest that at least 26 genes encode presynaptic proteins, and mutations in 12 of them cause defects in presynaptic structure that can lead to decreased acetylcholine release and muscle weakness.[30] These defects can be related to exocytosis, endocytosis, formation of active and periactive zones, vesicle transport, and neuropeptide modulation.[30]

When observing the electrophysiologic activity of a skeletal muscle, small, spontaneous depolarizing potentials at neuromuscular junctions can be seen. These potentials have only one hundredth the amplitude of the evoked end-plate potential produced when the motor nerve is stimulated. Except for amplitude, these potentials resemble the end-plate potential in the time course and manner in which they are affected by drugs. These small-amplitude potentials are called *miniature end-plate potentials* (MEPPs). Statistical analysis led to the conclusion that they are unitary responses; that is, there is a minimum size for the MEPP, and the sizes of all MEPPs are equal to or multiples of this minimum size. Because MEPPs are too large to be produced by a single molecule of acetylcholine, it was deduced that they are produced by uniformly sized packages, or quanta, of transmitter released from the nerve (in the absence of stimulation). The stimulus-evoked end-plate potential is the additive depolarization produced by the synchronous discharge of quanta from several hundred vesicles. The action potential that is propagated to the nerve ending allows the entry of calcium into the nerve through voltage-gated calcium channels, which causes vesicles to migrate to the active zone, fuse with the neural membrane, and discharge their acetylcholine into the junctional cleft.[28,29] Because the release sites are located immediately opposite the receptors on the postjunctional surface, little transmitter is wasted, and the response of the muscle is coupled directly with the signal from the nerve.[17,28]

Alignment of the presynaptic receptor site is achieved by adhesion molecules or specific cell-surface proteins located on both sides of the synapse that grip each other across the synaptic cleft and hold together the prejunctional and postjunctional synaptic apparatuses.[14,19,31] One such protein implicated in synapse adhesion is neurexin, which binds to neuroligins on the postsynaptic membrane. The amount of acetylcholine released by each nerve impulse is large, at least 200 quanta of approximately 5000 molecules each, and the number of AChRs activated by transmitter released by a nerve impulse is also large, approximately 500,000 molecules. The ions (mostly sodium and some calcium) that flow through the channels of activated (open) AChRs cause maximum depolarization of the end plate, which results in an end-plate potential that is greater than the threshold for stimulation of the muscle. This system is extremely vigorous. The signal is carried by more molecules of transmitter than are needed, and they evoke a response that is larger than needed. At the same time, only a small fraction of the available vesicles and receptors or channels are used to send each signal. Consequently, transmission has a substantial margin of safety, and, at the same time, the system has substantial capacity in reserve.[16-18,32]

NEUROMUSCULAR JUNCTION

FORMATION OF NEUROTRANSMITTER AT MOTOR NERVE ENDINGS

The axon of the motor nerve carries electrical signals from the spinal cord to muscles and has all of the biochemical apparatus needed to transform the electrical signal into a chemical one. All the ion channels, enzymes, other proteins, macromolecules, and membrane components needed by the nerve ending to synthesize, store, and release acetylcholine and other trophic factors are made in the cell body and transmitted to the nerve ending by axonal transport (see Fig. 18-2).[15,28,29] The simple molecules, choline and acetate, are obtained from the environment of the nerve ending, where choline is transported by a special system from extracellular fluid to the cytoplasm and acetate in the form of acetyl coenzyme A from mitochondria. The enzyme choline acetyltransferase brings about the reaction of choline and acetate to form acetylcholine. After synthesis, acetylcholine is stored in cytoplasm until it is transported and incorporated into vesicles, which are better positioned for release when an action potential reaches the nerve terminal.

NERVE ACTION POTENTIAL

During a nerve action potential, sodium from outside flows across the membrane, and the resulting depolarizing voltage opens the calcium channels, which allows entry of calcium ions into the nerve and causes acetylcholine to be released. A nerve action potential is the normal activator that releases the transmitter acetylcholine. The number of quanta released by a stimulated nerve is greatly influenced by the concentration of ionized calcium in extracellular fluid. If calcium is not present, then depolarization of the nerve, even by electrical stimulation, will not produce the release of transmitter. Doubling the extracellular calcium results in a 16-fold increase in the quantal content of an end-plate potential.[33] The calcium current persists until the membrane potential is returned to normal by outward fluxes of potassium from inside the nerve cell. Along with calcium channels on the nerve terminal are potassium channels, including the voltage-gated and calcium-activated potassium channels, whose function is to limit entry of calcium into the nerve and therefore depolarization.[26,32] The calcium current can be prolonged by potassium channel blockers (e.g., 4-aminopyridine, tetraethylammonium), which slow or prevent the efflux of potassium out of the nerve. The increase in quantal content produced in this way can reach astounding proportions.[17,34] An effect of increasing calcium in the nerve ending is also clinically observed as the so-called *posttetanic potentiation*, which occurs after a nerve of a patient paralyzed with an NDMR is stimulated at high, tetanic frequencies. Calcium enters

the nerve with every stimulus, but it accumulates during the tetanic period because it cannot be excreted as quickly as the nerve is stimulated. Because the nerve ending contains more than the normal amount of calcium for some time after the tetanus, a stimulus applied to the nerve during this time causes the release of more than the normal amount of acetylcholine. The abnormally large amount of acetylcholine antagonizes the relaxant and causes the characteristic increase in the size of the twitch.

Calcium enters the nerve through specialized proteins called *calcium channels*.[15,35] Of the several types of calcium channels, two seem to be important for the release of transmitter: P channels and the slower L channels. P channels, probably the type responsible for the normal release of transmitter, are found only in nerve terminals.[13,35] In motor nerve endings, they are located immediately adjacent to the active zones (see Fig. 18-2). They are voltage dependent and are opened and closed by changes in membrane voltage caused by the nerve action potential. In addition to calcium channels, several forms of potassium channels are present in the nerve terminal, including voltage-gated and calcium-activated potassium channels. Potassium channels limit the duration of nerve terminal depolarization and hence the entry of calcium and the release of transmitter.[26] Alterations in entry of calcium into the nerve ending can also alter the release of transmitter. The Eaton-Lambert myasthenic syndrome, which should not be confused with myasthenia gravis, is an acquired autoimmune disease in which antibodies are directed against voltage-gated calcium channels at nerve endings.[36] In this syndrome, decreased function of the calcium channel causes decreased release of transmitter, which results in inadequate depolarization and muscle weakness. Patients with the Eaton-Lambert syndrome exhibit increased sensitivity to depolarizing and nondepolarizing relaxants.[37]

Higher-than-normal concentrations of bivalent inorganic cations (e.g., magnesium, cadmium, manganese) can also block the entry of calcium through P channels and profoundly impair neuromuscular transmission. This mechanism is behind the typical muscle weakness and potentiation of the effect of muscle relaxants in a mother and fetus when magnesium sulfate is administered to treat preeclampsia. P channels, however, are not affected by calcium entry–blocking drugs such as verapamil, diltiazem, and nifedipine. These drugs have profound effects on the slower L channels present in the cardiovascular system. As a result, the L-type calcium channel blockers have no significant effect at therapeutic doses on the normal release of acetylcholine or on the strength of normal neuromuscular transmission. However, calcium entry–blocking drugs may increase the block in neuromuscular transmission induced by NDMRs. The effect is small, and not all investigators have been able to observe it. The explanation may lie in the fact that nerve endings also contain L-type calcium channels.

SYNAPTIC VESICLES AND RECYCLING

Two pools of vesicles seem to release acetylcholine, a readily releasable pool and a reserve pool, sometimes called VP2 and VP1, respectively.[38,39] Vesicles in the former are a bit smaller and limited to an area very close to the nerve membrane, where they are bound to the active zones. These vesicles are the ones that ordinarily release transmitter. Electron microscopic studies have demonstrated that the majority of synaptic vesicles (VP1) are sequestered in the reserve pool and tethered to the cytoskeleton in a filamentous network made up of primarily actin, synapsin (an actin-binding protein), synaptotagmin, and spectrin.[38,39]

Release occurs when calcium ions enter the nerve through the P channels lined up on the sides of the active zones by soluble *N*-ethylmaleimide–sensitive attachment protein receptor (SNARE) proteins.[38,39] The SNARE proteins are involved in fusion, docking, and release of acetylcholine at the active zone. Calcium needs to move only a very short distance (i.e., a few atomic radii) to encounter a vesicle and activate the proteins in the vesicle wall involved in a process known as *docking* (see "Process of Exocytosis" later in this chapter).[39] The reactivated proteins seem to react with the nerve membrane to form a pore through which the vesicle discharges its acetylcholine into the junctional cleft. Studies using fluorescent proteins have visualized how synaptic vesicles fuse with release sites and release their contents, which are then retrieved. Some vesicles stay open briefly before retrieval and do not completely collapse into the surface membrane ("kiss and run"). Others stay open longer and probably do not completely collapse ("compensatory"). Still others completely collapse and are not retrieved until another stimulus is delivered ("stranded").[38,39]

The larger reserve (VP1) vesicles, from their position deep from the nerve ending and firmly tethered to the cytoskeleton by many proteins, including actin, synapsin (an actin-binding protein), synaptotagmin, and spectrin,[37,38] may be moved to the readily releasable store to replace worn-out vesicles or to participate in transmission when the nerve is called on to work especially hard (e.g., when it is stimulated at very high frequencies or for a very long time). Under such strenuous circumstances, calcium may penetrate more deeply than normal into the nerve or may enter through L channels to activate calcium-dependent enzymes that break the synapsin links holding the vesicles to the cytoskeleton, thereby allowing the vesicles to be moved to the release sites. Repeated stimulation requires the nerve ending to replenish its store of vesicles filled with transmitter, a process known as *mobilization*. The term is commonly applied to the aggregate of all steps involved in maintaining the nerve ending's capacity to release transmitter—everything from the acquisition of choline and the synthesis of acetate to the movement of filled vesicles to release sites. Uptake of choline and the activity of choline acetyltransferase, the enzyme that synthesizes acetylcholine, are probably the rate-limiting steps.[15,29]

PROCESS OF EXOCYTOSIS

The readily releasable pool of synaptic vesicles constitutes the vesicles directly available for release. During an action potential and calcium influx, neurotransmitter is released. Studies have shed some light on the inner workings by which the vesicle releases its contents. The whole process is called *exocytosis*. The SNARE proteins include the synaptic-vesicle protein, synaptobrevin; the plasmalemma-associated

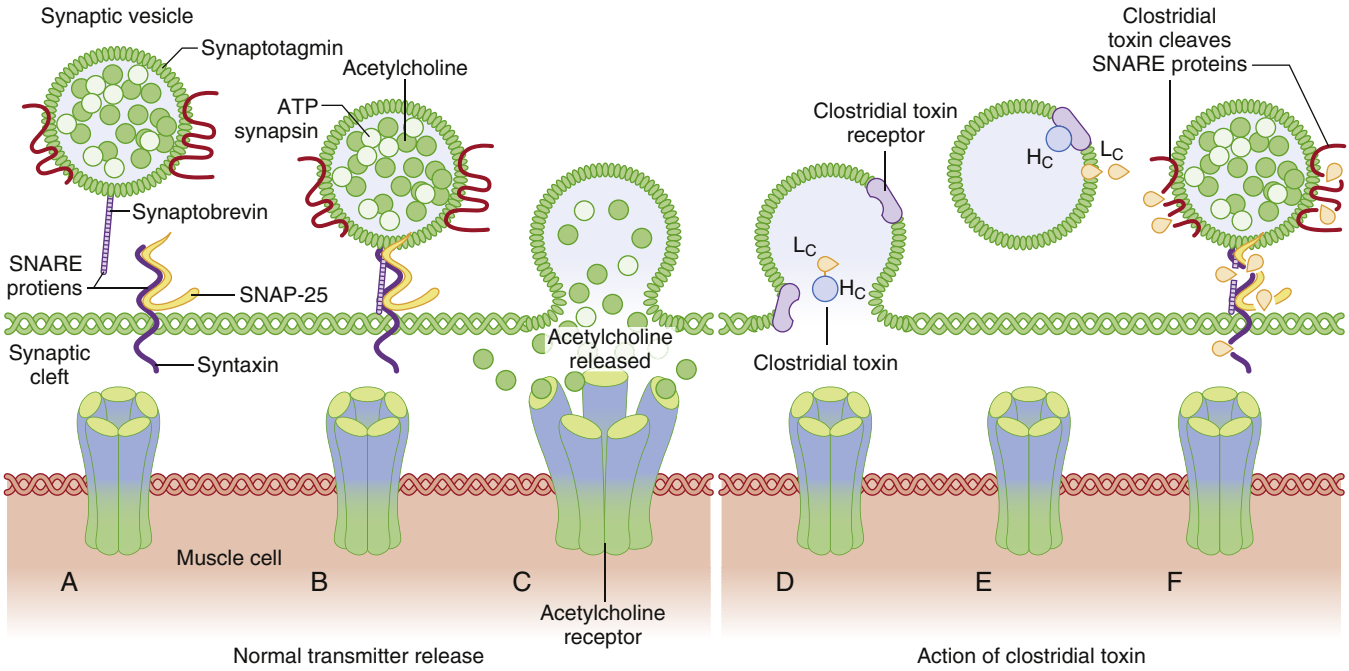


Figure 18-3. Model of protein-mediated membrane fusion and exocytosis. **A,** Release of acetylcholine from vesicles is mediated by a series of proteins collectively called SNARE proteins. Synaptotagmin is the neuronal calcium receptor that detects entry of calcium. Synaptobrevin (i.e., vesicle-associated membrane protein [VAMP]) is a filament-like protein on the vesicle. **B,** During depolarization and entry of calcium, synapsin is also present on the vesicle membrane. Synaptobrevin on the vesicle unfolds and forms a ternary complex with syntaxin/SNAP-25 on the nerve terminal membrane. **C,** Assembly of the ternary complex forces the vesicle in close apposition to the nerve membrane at the active zone with release of its contents, acetylcholine. The fusion is disassembled, and the vesicle is recycled. **D,** Clostridial toxin, botulinum, inhibits the release of acetylcholine and causes paralysis of muscles. The toxin consists of a light chain (L_c) and a heavy chain (H_c). The first stage in intoxication is the interaction of the toxin with a thus far unidentified receptor. **E,** This interaction is followed by internalization of the toxin within the vesicle and the release of the L_c of toxin from the vesicle. **F,** The liberated L_c cleaves a variety of SNARE proteins, depending on the type of toxin released, thereby preventing assembly of the fusion complex and thus blocking the release of acetylcholine. *ATP*, Adenosine triphosphate; *SNAP-25*, synaptosome-associated protein of 25-kd.

protein, syntaxin; and the synaptosome-associated protein of 25-kd (SNAP-25).[38,39] The current model of protein-mediated membrane fusion in exocytosis is as follows. When there is an action potential and calcium ions enter, synapsin becomes phosphorylated, which frees the vesicle from its attachment to the cytoskeleton. Syntaxin and SNAP-25 are complexes attached to the plasma membrane. After the initial contact, the synaptobrevin on the vesicle forms a ternary complex with syntaxin and SNAP-25. Synaptotagmin is the protein on the vesicular membrane that acts as a calcium sensor, localizes the synaptic vesicles to synaptic zones rich in calcium channels, and stabilizes the vesicles in the docked state.[38] Assembly of the ternary complex forces the vesicle to move close to the underlying nerve terminal membrane (i.e., the active zone), and the vesicle is then ready for release (see Fig. 18-3). The close proximity of release sites, calcium channels, and synaptic vesicles and the use of the calcium sensor lead to a burst of release of new transmitter synchronous with the stimulus.[37-40] The vesicle can release part or all of its contents, some of which can be recycled to form new vesicles as previously described ("kiss and run," "compensatory," "stranded").[37-40]

Botulinum neurotoxin selectively digests one or all of these SNARE proteins and blocks exocytosis of the vesicles,[41-42] which ultimately results in muscle weakness or more profound muscle paralysis. This toxin may produce a partial or complete chemical denervation. Botulinum toxin is therapeutically used to treat spasticity or spasm in several neurologic and surgical diseases, to prevent hyperhidrosis in patients with excessive sweating, and cosmetically to correct wrinkles.[43,44] Botulinum toxin consists of two protein segments known as heavy and light chains. The heavy chain interacts with lipid molecules called *polysialogangliosides* in the cell membrane and synaptotagmin on the vesicle to enter the vesicle. Once in the vesicle, the light chain inactivates neuromuscular transmission by breakdown and thereby inhibits the function of SNARE proteins (Fig. 18-4). Some reports indicate an increased incidence of clostridial infections in both Canada and the United States, with *Clostridium botulinum* infection being particularly common after traumatic injuries, in drug abusers, and after musculoskeletal allografts.[6,7] Thus systemic paralysis can occur after clostridial infection. Local injection for therapeutic purposes will usually result in localized paresis, although systemic effects have been reported.[7,45]

ACETYLCHOLINESTERASE

The acetylcholine released from the nerve diffuses across the junctional cleft and reacts with specialized receptor proteins in the end plate to initiate muscle contraction. Transmitter molecules that do not immediately react with a receptor or those released after binding to the

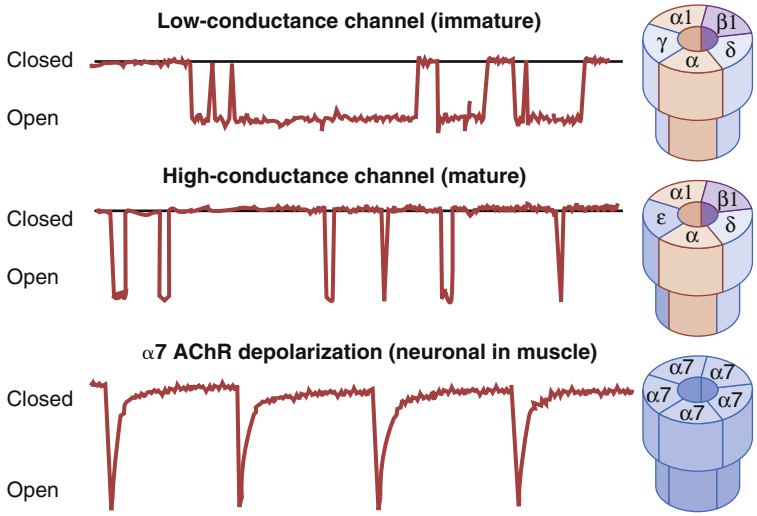


Figure 18-4. Schematic illustration depicts acetylcholine receptor (AChR) channels *(right)* and tracings of cell-patch records of receptor channel openings *(left)*. The mature or junctional receptor consists of two α1-subunits and one each of β1-, δ-, and ε-subunits. The immature, extrajunctional, or fetal form consists of two α1-subunits and one each of β1-, δ-, and γ-subunits. The latter is thus called the γ-subunit receptor. Recently, a neuronal receptor consisting of five α7-subunits has been described in muscle. All of the subunits are arranged around the central cation channel. The immature isoform containing the γ-subunit has long open times and low-amplitude channel currents. The mature isoform containing the ε-subunit has shorter open times and high-amplitude channel currents during depolarization. Substitution of the ε-subunit for the γ-subunit gives rise to the fast-gated, high-conductance channel type. As expected, application of acetylcholine to the α7 AChR also results in a fast, rapidly decaying inward current. All of these depolarizing events are insensitive to treatment with atropine but sensitive to treatment with α-bungarotoxin or muscle relaxants, which block the flow of current. The affinity of the muscle relaxants to each of the three isoforms may be different, α7 AChR being the least sensitive to block.

receptor are almost instantly destroyed by acetylcholinesterase in the junctional cleft. Acetylcholinesterase at the junction is the asymmetric or A12-form protein made in the muscle under the end plate. Acetylcholinesterase (enzyme classification 3.1.1.7) is a type B carboxylesterase enzyme. A smaller concentration of the enzyme is found in the extrajunctional area. The enzyme is secreted from the muscle but remains attached to it by thin stalks of collagen fastened to the basement membrane.[15,37] Most of the molecules of acetylcholine released from the nerve initially pass between the enzymes to reach the postjunctional receptors; however, as they are released from the receptors, they invariably encounter acetylcholinesterase and are destroyed. Under normal circumstances, a molecule of acetylcholine reacts with only one receptor before it is hydrolyzed. Acetylcholine is a potent messenger, but its actions are very short lived because it is destroyed in less than 1 millisecond after it is released.

Some congenital and acquired diseases are caused by altered activity of acetylcholinesterase. The congenital absence of the secreted enzyme (in knock-out mice) leads to impaired maintenance of the motor neuronal system and organization of nerve terminal branches.[46] Many syndromes caused by congenital abnormalities in cholinesterase function have been described and result in neuromuscular disorders whose symptoms and signs usually resemble those of myasthenia gravis or myasthenic syndromes.[27,47] Denervation decreases acetylcholinesterase at the junctional and extrajunctional areas.[37] Other acquired diseases involving cholinesterases are related to chronic inhibition of acetylcholinesterase by organophosphate pesticides or nerve gas (e.g., sarin) or to chronic pyridostigmine therapy given as prophylaxis against nerve gas poisoning.[48,49] Symptoms ranging from chronic fatigue to muscle weakness have been attributed to chronic cholinesterase inhibition, thus underscoring the importance of acetylcholinesterase in normal and abnormal neuromuscular function. A recent rodent study confirms that the muscle weakness associated with chronic pyridostigmine therapy is related to both AChRs downregulation and to receptor-independent factors.[50]

POSTJUNCTIONAL ACETYLCHOLINE RECEPTORS

The similarity of AChRs among many species and the abundance of AChRs from *Torpedo electric fish* have greatly facilitated research in this area. The availability of messenger RNA from humans and other species and DNA has allowed the study of the receptor in artificial systems such as oocytes from frogs and in mammalian cells that do not express the receptor, such as COS or fibroblast cells. Receptors can also be mutated by molecular techniques to simulate pathologic states; the study receptor function in these artificial systems can then be studied. By using these and related techniques, much has been learned about the synthesis, composition, and biologic function and mechanisms that underlie the physiologic and pharmacologic responses in AChRs.[51-53] Three isoforms of postjunctional nicotinic AChRs exist: a junctional or mature receptor, an extrajunctional or immature (fetal) receptor, and the more recently described neuronal α7 receptor[2,16,18] (see "Biology of Prejunctional and Postjunctional Nicotinic Receptors" later in this chapter). The differences between receptor subtypes, however, can be neglected in a general discussion of the role of receptors in neuromuscular transmission.

AChRs are synthesized in muscle cells and are anchored to the end-plate membrane by a special 43-kd protein known as *rapsyn*. This cytoplasmic protein is associated with the AChR in a 1:1 ratio.[16-19] The receptors, formed of five subunit proteins, are arranged like the staves of a barrel into a cylindrical receptor with a central pore for ion channeling (the key features are illustrated in Fig. 18-4). The receptor protein has a molecular mass of approximately 250,000 daltons. Each receptor has five subunits. The mature receptor consists of α1-, β1-, δ-, and ε-subunits, and the fetal (immature, extrajunctional) receptor consists of α1-, β1-, δ-, and γ-subunits; there are two subunits of α and one each of the others. The neuronal α7 AChR consists of five α7-subunits.[16,18] Each of all receptor subunits consists of approximately 400 to 500 amino acids. The receptor-protein complex passes entirely through the membrane and protrudes beyond the extracellular surface of the membrane and into the cytoplasm. The binding site for acetylcholine is on each of the α1-subunits, which is located on the extracellular component and α1-subunit, and these are the sites of competition between receptor agonists and antagonists. Agonists and antagonists are attracted to the binding site, and either may occupy the site, which is located near cysteine residues (unique to the α-chain) at amino acid positions 192-193 of the α-subunit.[16-18] Radiolabeled α-bungarotoxin from the cobra, used to quantitate or fluorescent stain the receptor, binds to heptapeptide region 185-199 of the α-subunit.[54] Motor neuron–derived neuregulin-1β (NRβ-1), originally described as AChR-inducing activity (ARIA), induces AChR gene transcription in subsynaptic myonuclei by activating ErbB receptors.[16-19]

SYNTHESIS AND STABILIZATION OF POSTJUNCTIONAL RECEPTORS

Muscle tissue is formed from the mesoderm and initially appears as myoblasts. Myoblasts fuse to produce myotubes, which therefore have multiple nuclei. As the myotubes mature, the sarcomere, which is the contractile element of the muscle consisting of actin and myosin, develops.[55] The protein β-integrin seems to be essential for myoblast fusion and sarcomere assembly.[55] Shortly afterward, motor nerve axons grow into the developing muscle, and these axons bring in nerve-derived signals (i.e., growth factors), including agrin and neuregulins (NRβ-1 and NRβ-2), which are key to the maturation of myotubes to muscle.[19] Agrin is a protein from the nerve that stimulates postsynaptic differentiation by activating muscle-specific tyrosine kinase (MuSK), a tyrosine kinase expressed selectively in muscle. With signaling from agrin, the AChRs, which have been scattered throughout the muscle membrane, cluster at the area immediately beneath the nerve. Agrin, together with neuregulins and other growth factors, induce the clustering of other critical muscle-derived proteins, including MuSK, rapsyn, and ErbB proteins, all of which are necessary for maturation and stabilization of AChRs at the junction. In addition to the effects on postsynaptic differentiation, agrin and MuSK display effects on presynaptic differentiation as well. Agrin and MuSK induce retrograde signals that instruct axons to undergo neuron outgrowth and terminal differentiation.[19] Current understanding of presynaptic development of the neuromuscular junction, however, is significantly less advanced than the understanding of postsynaptic development. Just before and shortly after birth, the immature, γ-subunit–containing AChRs are replaced by the mature, ε-subunit–containing receptors. Although the mechanism of this change is unclear, a neuregulin, NRβ-1, also called *ARIA*, that binds to one of the ErbB receptors seems to play a role.[19,56]

BASIC ELECTROPHYSIOLOGY OF NEUROTRANSMISSION

Progress in electrophysiologic techniques has moved at a pace equal with the advances in molecular approaches for studying prejunctional and postjunctional receptors. Patch-clamping is a technique during which a glass micropipette is used to probe the membrane surface until a single functional receptor is encompassed. The tip of the pipette is pressed into the lipid of the membrane, and the electronic apparatus is arranged to keep the membrane potential clamped (i.e., fixed), and the current that flows through the channel of the receptor is measured. The solution in the pipette can contain acetylcholine, muscle relaxant, another drug, or a mixture of drugs. By applying these drugs to the receptor through the micropipette, electrical changes can be monitored.

Figure 18-5 illustrates the results of the classic depolarizing action of acetylcholine on end-plate receptors. Normally, the pore of the channel is closed by approximation of the cylinders (i.e., subunits). When an agonist occupies both α-subunit sites, the protein molecule undergoes a conformational change with a twisting movement along the central axis of the receptor that results in the opening of the central channel through which ions can flow along a concentration gradient. When the central channel is open, sodium and calcium flow from the outside of the cell to the inside and potassium flows from the inside to the outside. The channel in the tube is large enough to accommodate many cations and electrically neutral molecules, but it excludes anions (e.g., chloride). The current transported by the ions depolarizes the adjacent membrane. The net current is depolarizing and creates the end-plate potential that stimulates the muscle to contract. In this instance, downward-going (i.e., depolarizing) current can be recorded by the patch-clamp electrophysiologic technique previously described (see Fig. 18-4).

The pulse stops when the channel closes by a reversed mechanical conformation (see earlier discussion), which is typically initiated when one or both agonist molecules detach from the receptor. In the activated, open state, the current that passes through each open channel is minuscule, only a few picoamperes (approximately 10^4 ions/msec). However, each burst of acetylcholine from the nerve normally opens approximately 500,000 channels simultaneously, and the total current is more than adequate to produce depolarization of the end plate and contraction of muscle. Opening of a channel causes conversion of chemical signals from a nerve to the flow of current on the muscle disease to

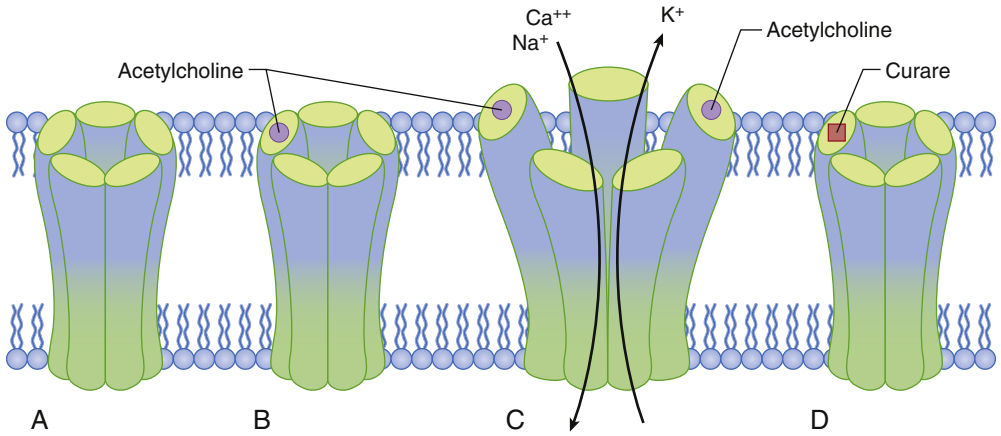


Figure 18-5. Actions of acetylcholine or curare on end-plate receptors. **A,** The ion channel is inactive and does not open in the absence of acetylcholine. **B,** Although one acetylcholine molecule *(filled circle)* is binding to one of two binding sites, the central channel does not open. **C,** When acetylcholine simultaneously binds to the recognition sites of both α-subunits *(filled circles)*, a conformation change is triggered that opens the channel and allows the cations to flow across the membrane. **D,** Action of antagonists such as curare *(filled square)*. Acetylcholine is in competition with tubocurarine for the receptor's recognition site but may also react with acetylcholinesterase. Tubocurarine is a prototypical nondepolarizing muscle relaxant. Inhibiting the acetylcholinesterase enzyme increases the lifetime of acetylcholine and the probability that it will react with a receptor. When one of the two binding (recognition) sites is occupied by curare, the receptor will not open, even if the other binding site is occupied by acetylcholine. Ca^{2++}, Calcium ion; K^{+}, potassium ion; Na^{+}, sodium ion.

cause end-plate potentials, thereby leading to muscle contraction. The end-plate potential has been viewed as a graded event that may be reduced in magnitude or extended in time by drugs, but, in reality, the end-plate potential is the summation of many all-or-nothing events simultaneously occurring at myriad ion channels. It is these tiny events that are affected by drugs.

Receptors that do not have two molecules of agonist (e.g., acetylcholine) bound remain closed. Both α-subunits must be simultaneously occupied by agonist; if only one of them is occupied, then the channel remains closed (see Fig. 18-5). This is the basis for preventing depolarization by antagonists. NDMRs act by binding to either or both α-subunits and thus preventing acetylcholine from binding and opening the channel. This interaction between agonists and antagonists is competitive, and the outcome—transmission or block—depends on the relative concentrations and binding characteristics of the drugs involved (see "Drug Effects on Postjunctional Receptors").

Individual channels are also capable of a wide variety of conformational states.[17,57] They may stay open or remain closed and thereby affect total current flow across the membrane, but they can do more. They may open for a longer or shorter time than normal, open or close more gradually than usual, open briefly and repeatedly (i.e., chatter), or pass fewer or more ions per opening than they usually do. Their function is also influenced by drugs, changes in fluidity of the membrane, temperature, electrolyte balance in the milieu, and other physical and chemical factors.[38,39] Receptor channels are dynamic structures that are capable of a wide variety of interactions with drugs and of entering a wide variety of current-passing states. All these influences on channel activity are ultimately reflected in the strength or weakness of neuromuscular transmission and the contraction of a muscle.

DRUG EFFECTS ON POSTJUNCTIONAL RECEPTORS

CLASSIC ACTIONS OF NONDEPOLARIZING MUSCLE RELAXANTS

Neurotransmission occurs when acetylcholine released by the nerve action potential binds to nicotinic AChRs. All NDMRs impair or block neurotransmission by competitively preventing the binding of acetylcholine to the muscle AChR. The final outcome—block or transmission—depends on the relative concentrations of the chemicals and their comparative affinities for the receptor. Figure 18-5 shows a system exposed to acetylcholine and the nondepolarizing neuromuscular blocking compound, tubocurarine. All other muscle relaxants (e.g., pancuronium, vecuronium) (also see Chapter 34) have similar actions as that of tubocurarine. One receptor has attracted two acetylcholine molecules and has opened its channel, where current will flow to depolarize that segment of membrane. Another has attracted one tubocurarine molecule; its channel will not open, and no current will flow, even if one acetylcholine molecule binds to the other site. The third receptor has acetylcholine on one α-subunit and nothing on the other. What will happen depends on which of the molecules binds. If acetylcholine binds, then the channel will open and the membrane will be depolarized; if tubocurarine binds, then the channel will remain closed and the membrane will not be depolarized. At other times, one or two tubocurarine molecules may attach to the receptor, in which case the receptor is not available to agonists; no current flow is recorded. In the presence of moderate concentrations of tubocurarine, the amount of current flowing through the entire end plate at any instant is reduced from normal, which results in a smaller end-plate potential and, if carried far enough, a block in neurotransmission or the production of neuromuscular paralysis.

Normally, acetylcholinesterase destroys acetylcholine and removes it from competition for a receptor; therefore tubocurarine has a better chance of inhibiting transmission. If, however, an inhibitor of acetylcholinesterase such as neostigmine is added, then the cholinesterase cannot destroy acetylcholine. The concentration of agonist in the cleft remains high, and this high concentration shifts the competition between acetylcholine and tubocurarine in favor of the former, thereby improving the chance of two acetylcholine molecules binding to a receptor even though tubocurarine is still in the environment. This mechanism causes the cholinesterase inhibitors to overcome the neuromuscular paralysis produced by NDMRs. The channel opens only when acetylcholine attaches to both recognition sites. A single molecule of antagonist, however, is adequate to prevent depolarization of that receptor. This modifies the competition by strongly biasing it in favor of the antagonist (relaxant). Mathematically, if the concentration of tubocurarine is doubled, then the concentration of acetylcholine must be increased fourfold if acetylcholine is to remain competitive. Paralysis produced by high concentrations of muscle relaxants (antagonist) is more difficult to reverse with cholinesterase inhibitors than that produced by low concentrations. After large doses of NDMRs, cholinesterase inhibitors may be ineffective until the concentration of relaxant in the perijunctional area decreases to a lower level by the redistribution or elimination of the drug. In contrast to reversal with a cholinesterase inhibitor, cyclodextrin encapsulation takes place at any concentration of a steroid-based compound, such as vecuronium or rocuronium, and reversal by this novel mechanism can therefore be achieved at any level of neuromuscular block provided the amount of cyclodextrin (sugammadex) is large enough (for further details, see also Chapter 35).

CLASSIC ACTIONS OF DEPOLARIZING MUSCLE RELAXANTS

Depolarizing relaxants (e.g., succinylcholine, decamethonium) initially simulate the effect of acetylcholine and can therefore be considered agonists, despite the fact that they block neurotransmission after the initial stimulation. Structurally, succinylcholine is very similar to the natural ligand acetylcholine and consists of two molecules of acetylcholine bound together through their backbones. It is thus not surprising that succinylcholine can mimic the effects of acetylcholine.

Succinylcholine or decamethonium can bind to the receptor, open the channel, pass current, and depolarize the end plate. These agonists, similar to acetylcholine, attach only briefly; each opening of a channel is very short in duration—1 millisecond or less. The response to acetylcholine, however, is over in milliseconds because of its rapid degradation by acetylcholinesterase, and the end plate resets to its resting state long before another nerve impulse arrives. In contrast, the depolarizing relaxants characteristically have a biphasic action on muscle—an initial contraction, followed by relaxation lasting from minutes to hours. Because they are not susceptible to hydrolysis by acetylcholinesterase, the depolarizing relaxants are not eliminated from the junctional cleft until after they are eliminated from plasma. The time required to clear the drug from the body is the principal determinant of how long the drug effect lasts. Whole-body clearance of the relaxant is very slow in comparison to acetylcholine, particularly when plasma (pseudo) cholinesterase is abnormal. Because the relaxant molecules are not quickly cleared from the cleft, compared with acetylcholine, they repeatedly react with receptors even with normal levels of plasma cholinesterase, almost immediately attaching to a receptor after separating from another, thereby repeatedly depolarizing the end plate and opening channels. For details on the effect of succinylcholine in patients with cholinesterase deficiency, also see Chapter 34.

The quick shift from excitation of muscle contraction to block of transmission by depolarizing relaxants occurs because the end plate is continuously depolarized. This comes about as a result of the juxtaposition of the edge of the end plate with a different kind of ion channel, the sodium channel that does not respond to chemicals but opens when exposed to a transmembrane voltage change. The sodium channel is also a cylindrical transmembrane protein through which sodium ions can flow. Two parts of its structure act as gates that allow or stop the flow of sodium ions.[58] Both gates must be open if sodium is to flow through the channel; closing of either cuts off the flow. Because these two gates act sequentially, a sodium channel has three functional conformational states and can progressively move from one state to another (Fig. 18-6).

When the sodium channel is in its resting state, the lower gate (i.e., the time-dependent or inactivation gate) is open, but the upper gate (i.e., the voltage-dependent gate) is closed, and sodium ions cannot pass. When the molecule is subjected to a sudden change in voltage by the depolarization of the adjacent membrane, the top gate opens; because the bottom (time-dependent) gate is still open, sodium flows through the channel. The voltage-dependent gate stays open as long as the molecule is experiencing a depolarizing influence from the membrane around it; it will not close until the depolarization disappears. However, shortly after the voltage-dependent gate opens, the bottom gate closes and again cuts off the flow of ions. It cannot open again until the

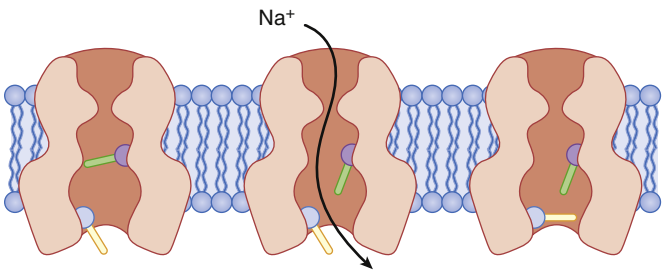


Figure 18-6. Illustration of a sodium (Na^+) channel. The bars represent parts of the molecule that act as gates. The upper bar is voltage dependent; the lower bar is time dependent. The left side of the drawing represents the resting state. Once activated by a change in voltage, the molecule and its gates progress as illustrated *(left to right)*. See text for details.

voltage-dependent gate closes. When depolarization of the end plate stops, the voltage-dependent gate closes, the time-dependent gate opens, and the sodium channel returns to its resting state. This whole process is short lived when depolarization occurs with acetylcholine.[58] The initial response of a depolarizing muscle relaxant resembles that of acetylcholine, but because the muscle relaxant is not rapidly hydrolyzed, depolarization of the end plate is not brief.

Depolarization of the end plate by the depolarizing relaxant initially causes the voltage gate in adjacent sodium channels to open, thereby producing a wave of depolarization that sweeps along the muscle and generates a muscle contraction. Shortly after the voltage-dependent gate opens, the time-dependent inactivation gate closes. Because the relaxant is not removed from the cleft, the end plate continues to be depolarized. Because the sodium channels immediately adjacent to the end plate are influenced by depolarization of the end plate, their voltage-dependent gates stay open and their inactivation gates stay closed. Since sodium cannot flow through a channel that has a closed inactivation gate, the perijunctional muscle membrane does not depolarize. When the flow of ions through sodium channels in the perijunctional zone stops because of a closure of the inactivation gates, the channels downstream (beyond the perijunctional zone) are freed of depolarizing influence. In effect, the perijunctional zone becomes a buffer that shields the rest of the muscle from events at the end plate. Consequently, the muscle membrane is separated into three zones: (1) the end plate, which is depolarized by succinylcholine; (2) the perijunctional muscle membrane, in which the sodium channels are frozen in an inactivated state; and (3) the rest of the muscle membrane, in which the sodium channels are in the resting state. Because a burst of acetylcholine from the nerve cannot overcome the inactivated sodium channels in the perijunctional zone, neuromuscular transmission is blocked. This phenomenon is also called *accommodation*. During accommodation, when the synapse is inexcitable through the nerve (transmitter), direct electrical stimulation of muscle causes muscle contraction because the sodium channels beyond the junctional area are in the resting excitable state.

The extraocular muscles are tonic muscles, which are multiply innervated and chemically excitable along most of its surface.[20-23] Despite its innervated state, the ocular muscles express both mature and immature receptors.[20,22] Accommodation does not occur, and these muscles can undergo a sustained contracture in the presence of succinylcholine. The tension thus developed forces the eye against the orbit and accounts for part of the increase in intraocular pressure produced by depolarizing relaxants (also see Chapter 34). The extraocular muscles contain a special type of receptor that does not become desensitized (see later discussion) during the continued presence of acetylcholine or other agonists.[21,23] A single dose of succinylcholine can cause contracture lasting several minutes.[23] Whether it is the immature γ-subunit AChR or the α7 AChR subunit that plays a role in this resistance to desensitization in the ocular muscles is unknown.

NONCLASSIC AND NONCOMPETITIVE ACTIONS OF NEUROMUSCULAR DRUGS

Several drugs can interfere with the receptor, directly or through its lipid environment, and can change transmission. These drugs react with the neuromuscular receptor to change its function and impair transmission, but they do not act through the acetylcholine binding site. These reactions cause drug-induced changes in the dynamics of the receptor; instead of sharply opening and closing, the modified channels are sluggish. They open more slowly and stay open longer, or they close slowly and in several steps, or both. These effects on channels cause corresponding changes in the flow of ions and distortions of the end-plate potential. The clinical effect depends on the molecular events. For example, procaine, ketamine, inhaled anesthetics, or other drugs that dissolve in the membrane lipid may change the opening or closing characteristics of the channel.[57,59] If the channel is prevented from opening, then transmission is weakened. If, however, the channel is prevented from or slowed in closing, then transmission may be enhanced. These drugs do not fit the classic model, and the impaired neuromuscular function is not antagonized by increasing perijunctional acetylcholine concentrations with cholinesterase inhibitors. Such drugs can be involved in two clinically important reactions: receptor desensitization and channel blockade. The former occurs in the receptor molecule, whereas the latter occurs in the ion channel.

DESENSITIZATION BLOCK

The AChR, as a result of its flexibility and the fluidity of the lipid around it, is capable of existing in a number of conformational states.[57-61] Because the resting receptor is free of agonist, its channel is closed. The second state exists when two molecules of agonist are bound to the α-subunit of the receptor and the receptor has undergone the conformational change that opens the channel and allows ions to flow. These reactions are the bases of normal neuromuscular transmission. Some receptors that bind to agonists, however, do not undergo the conformational change to open the channel. Receptors in these states are called desensitized (i.e., they are not sensitive to the channel-opening actions of agonists). They bind agonists with exceptional avidity, but the binding does not result in the opening of the channel. The mechanisms by which desensitization occurs are not known. The receptor macromolecule, 1000 times larger by weight than most drugs or gases, provides many places at which the smaller molecules may act. The interface between lipid and receptor protein provides additional potential sites of reaction. Several different conformations of the protein are known, and because acetylcholine cannot cause the ion channel to open in any of them, they all are included in the functional term *desensitization*. Desensitization is accompanied by phosphorylation of a tyrosine unit in the receptor protein.[61,62]

Although agonists (e.g., succinylcholine) induce desensitization, the receptors are in a constant state of transition between resting and desensitized states, regardless of whether agonists are present. Agonists do

promote transition to a desensitized state or, because they bind very tightly to desensitized receptors, trap a receptor in a desensitized state. Antagonists also tightly bind to desensitized receptors and can trap molecules in these states. This action of antagonists is not competitive with that of acetylcholine; it may be augmented by acetylcholine if the latter promotes the change to a desensitized state. Desensitization can lead to significant misinterpretation of data. Superficially, the preparation seems to be normal, but its responsiveness to agonists or antagonists is altered. One variety occurs very rapidly, within a few milliseconds after application of an agonist, which may explain the increased sensitivity to nondepolarizing relaxant after the prior administration of succinylcholine. Desensitization may also be a part of the phenomenon known as *phase II block* (see "Phase II Block," later in this chapter), which is caused by a prolonged administration of depolarizing relaxants. Phase II block is frequently referred to as a desensitization block, but it should not be because desensitization of receptors is only one of many phenomena that contribute to the process.

Many other drugs used by anesthetists also promote the shift of receptors from a normal state to a desensitized state.[58-60] These drugs, some of which are listed in Box 18-1, can weaken neuromuscular transmission by reducing the margin of safety that normally exists at the neuromuscular junction, or they can cause an apparent increase in the capacity of nondepolarizing agents to block transmission. These actions are independent of the classic effects, based on competitive inhibition of acetylcholine. The presence of desensitized receptors means that fewer receptor channels than usual are available to carry transmembrane current. The production of desensitized receptors decreases the efficacy of neuromuscular transmission. If many receptors are desensitized, then insufficient normal ones are left to depolarize the motor end plate, and neuromuscular transmission will not occur. Even if only some receptors are desensitized, neuromuscular transmission will be impaired, and the system will be more susceptible to block by conventional antagonists such as atracurium or rocuronium.

BOX 18-1 ***Drugs That Can Cause or Promote Desensitization of Nicotinic Cholinergic Receptors***

- Volatile anesthetics
  - Halothane
  - Sevoflurane
  - Isoflurane
- Antibiotics
  - Polymyxin B
- Cocaine
- Alcohols
  - Ethanol
  - Butanol
  - Propanol
  - Octanol
- Barbiturates
  - Thiopental
  - Pentobarbital
- Agonists
  - Acetylcholine
  - Decamethonium
  - Carbachol
  - Succinylcholine
- Acetylcholinesterase inhibitors
  - Neostigmine
  - Pyridostigmine
  - Difluorophosphate
  - Edrophonium
- Local anesthetics
  - Dibucaine
  - Lidocaine
  - Prilocaine
  - Etidocaine
- Phenothiazines
  - Chlorpromazine
  - Trifluoperazine
  - Prochlorperazine
- Phencyclidine
- Calcium channel blockers
  - Verapamil

CHANNEL BLOCK

Local anesthetics and calcium entry blockers prevent the flow of sodium or calcium through their respective channels, thus explaining the term *channel-blocking drugs*. Similarly, block of the flow of ions can occur at the AChR with concentrations of drugs used clinically and may contribute to some of the phenomena and drug interactions observed at the receptor. Two major types, closed-channel and open-channel block, can occur.[60,63,64] In a closed-channel block, certain drugs can occupy the mouth of the channel and prevent ions from passing through the channel to depolarize the end plate. The process can take place even when the channel is not open. In an open-channel block, a drug molecule enters a channel that has been opened by reaction with acetylcholine but does not necessarily penetrate all the way through. Open-channel blockade is a use-dependent block, which means that molecules can enter the channel only when it is open. In open- and closed-channel blocks, the normal flow of ions through the receptor is impaired, thereby resulting in the prevention of depolarization of the end plate and a weakened or blocked neuromuscular transmission. However, because the action is not at the acetylcholine recognition site, it is not a competitive antagonism of acetylcholine and is not relieved by anticholinesterases that increase concentrations of acetylcholine. Increasing the concentration of acetylcholine may cause the channels to open more often and, consequently, become more susceptible to blockade by use-dependent compounds. Evidence suggests that neostigmine and related cholinesterase inhibitors can act as channel-blocking drugs.[17,63]

Channel block may account for the antibiotic-, cocaine, quinidine-, piperocaine-, tricyclic antidepressant–, naltrexone-, naloxone-, and histrionicotoxin-induced alterations in neuromuscular function. Muscle relaxants, in contrast, can bind to the acetylcholine recognition site of the receptor and occupy the channel. Pancuronium

preferentially binds to the recognition site. Gallamine seems to act equally at the two sites (channel-blocking and acetylcholine-blocking sites). Tubocurarine is in between; at small doses that clinically produce minimal blockage of transmission, the drug is essentially a pure antagonist at the recognition site; at larger doses, it also enters and blocks channels. Decamethonium and succinylcholine, as agonists, can open channels and, as slender molecules, also enter and block them. Decamethonium and some other long, thin molecules can penetrate all the way through the open channel and enter the cytoplasm of muscle cells. Whether prolonged administration of NDMRs, as used in an intensive care unit, can result in the NDMR occupation of the channel, and even entry of drug into the cytosol is unknown.

PHASE II BLOCK

A phase II block is a complex phenomenon associated with a typical fade in muscle during continuous exposure to depolarizing drugs. This fade phenomenon is likely due to the interaction of depolarizing action of succinylcholine on distinct neuronal (prejunctional) AChRs; these prejunctional receptors are blocked by higher than usual concentrations of succinylcholine. This fade after succinylcholine is at least partly dependent on a presynaptic interaction with cholinergic transmission of importance for neurotransmitter mobilization and release. However, fade in muscle during repetitive nerve stimulation can also be attributable to postjunctional AChR block.[65]

Other factors may also be involved. The repeated opening of channels allows a continuous efflux of potassium and influx of sodium, and the resulting abnormal electrolyte balance distorts the function of the junctional membrane. Calcium entering the muscle through the opened channels can cause disruption of receptors and the sub–end-plate elements themselves. The activity of the sodium-potassium adenosine triphosphatase pump in the membrane increases with increasing intracellular sodium and, by pumping sodium out of the cell and potassium into it, works to restore the ionic balance and membrane potential toward normal. As long as the depolarizing drug is present, the receptor channels remain open and ion flux through them remains frequent.[66]

Factors influencing the development of a phase II block include the duration of exposure to the drug, the particular drug used and its concentration, and even the type of muscle (i.e., fast or slow twitch). Interactions with anesthetics and other agents also affect the process. All of these drugs may also have prejunctional effects on the rate and amount of transmitter released and mobilized. With so many variables involved in the interference with neuromuscular transmission, a phase II block is a complex and ever-changing phenomenon. The reversal response of a phase II block produced by a depolarizing muscle relaxant to the administration of cholinesterase inhibitors is difficult to predict. It is therefore best that reversal by cholinesterase inhibitors not be attempted, although the response to tetanus or train-of-four stimulation resembles that produced by NDMRs.

BIOLOGY OF PREJUNCTIONAL AND POSTJUNCTIONAL NICOTINIC ACETYLCHOLINE RECEPTORS

POSTJUNCTIONAL CONVENTIONAL ACETYLCHOLINE RECEPTORS IN MUSCLE VERSUS NEURONAL ACETYLCHOLINE RECEPTORS IN MUSCLE

Currently, three variants of postjunctional AChRs have been identified. The AChR isoform present in the innervated, adult neuromuscular junction is referred to as the adult, mature, or junctional receptor. Another AChR isoform, also described more than 4 decades ago, is expressed when activity in muscle is decreased, as observed in the fetus before innervation or after chemically or physically induced immobilization; after lower or upper motor neuron injury, burns, or sepsis; or after other events that cause increased muscle protein catabolism, including sepsis or generalized inflammation.[1-3] In contrast with the mature or junctional receptors, the other isoform is referred to as the immature, extrajunctional, or fetal form of AChR. Some evidence suggests that the immature isoform is not observed in the muscle protein catabolism and wasting that occur with malnutrition.[67] Qualitative differences in the mature isoform can occur as a result of gene mutations, which therefore alters the subunit protein structure. These qualitative changes in AChR can also cause abnormalities in neurotransmission (e.g., slow- or fast-channel syndrome)[27,47] and therefore the response to muscle relaxants.

At the molecular level, the mature and immature receptors consists of five subunits (see Fig. 18-4).[1-3] The mature junctional receptor is a pentamer of two α1-subunits and one each of the β1-, δ7-, and ε-subunits. The immature receptor consists of two α-subunits and one each of the β7-, δ7-, and γ-subunits; that is, in the immature receptor, the γ-subunit is present instead of the ε-subunit. The γ- and ε-subunits differ very little from each other in amino acid homology, but the differences are great enough to affect the physiologic function and pharmacologic characteristics of the receptor and its ion channel. Junctional receptors are always confined to the end-plate region of the muscle membrane. The immature, or extrajunctional, receptor may be expressed anywhere on the muscle membrane, although their junctional expression seems minimal.[16] During development and in certain pathologic states, junctional and extrajunctional receptors can coexist in the perijunctional area of the muscle membrane (Fig. 18-7).

Quite in contrast to the conventional muscle AChRs consisting of α1-, β1-, δ-, and ε/γ-subunits described earlier, receptors formed of α7 AChR subunits have recently been found in skeletal muscle during immobilization, sepsis, and denervation.[68,69] Two recent studies have evidenced the increased expression of α7 AChR subunits in muscle by Western blotting, ligand binding or genetic techniques after sepsis, and burn injury or immobilization, during which no overt denervation occurs.[16,70] These α7 AChR subunits are homomeric (i.e., formed of the same subunits) channels arranged as pentameres (see Fig. 18-4). Ligand (drug)–binding pockets are thought to be formed

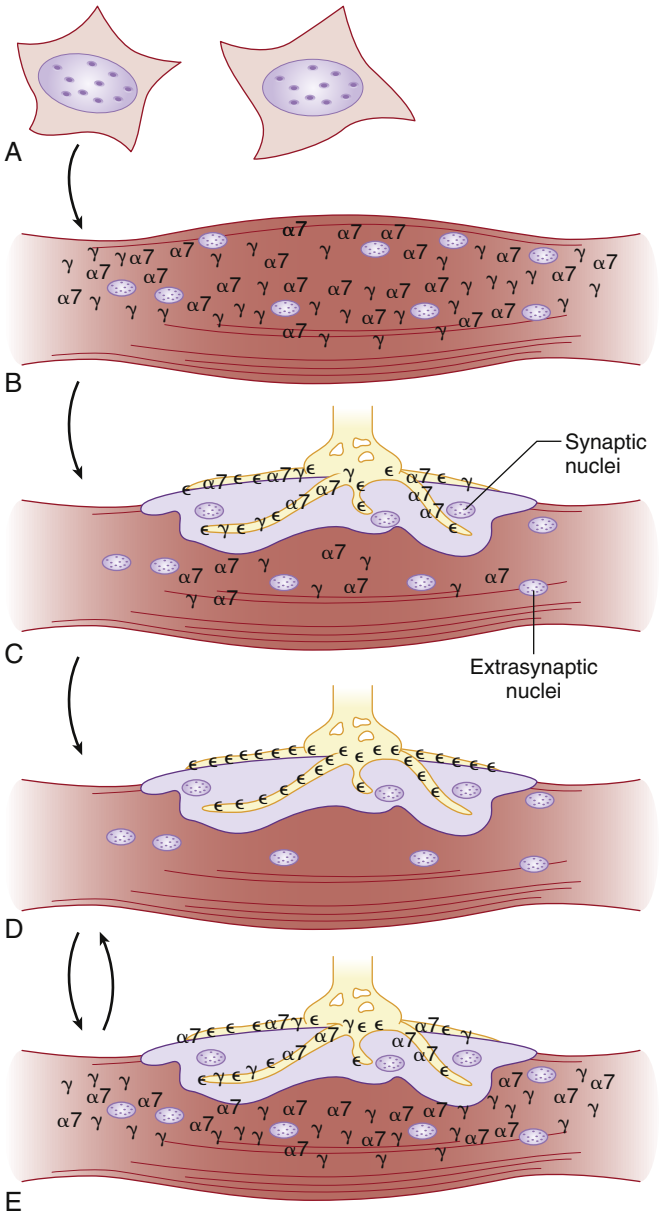


Figure 18-7. Distribution of acetylcholine receptors in developing adult, mature, denervated muscle or in immobilized or inflammation-induced catabolic muscle. **A** and **B**, In the early fetal stage, mononucleated myoblasts, derived from the mesoderm, fuse with each other to form multinucleated myotubes. The γ-subunit–containing immature acetylcholine receptors (AChRs) and the neuronal α7-subunit AChRs are scattered throughout the muscle membrane before innervation. **C,** As the nerve makes contact with muscle, clustering of the receptors occurs at the synapse and is associated with some loss of extrasynaptic receptors. **D,** Maturation of the junction is said to occur when ε-subunit–containing receptors replace γ-subunit– and α7-subunit–containing AChRs at the neuromuscular junction. Even mature muscle is multinucleated, but it is devoid of extrasynaptic AChRs. **E,** Denervation and some other pathologic states, even without anatomic denervation (e.g., burns, immobilization, chronic muscle relaxant therapy, stroke, sepsis), lead to the re-expression of the γ-subunit–containing AChRs mostly at the extrajunctional areas. The α7-subunit AChRs are expressed in the junctional areas and are also most likely in the extrajunctional areas. These receptor changes are potentially reversible if muscle immobilization, catabolism, and inflammation are restored to normal.

at negative and positive faces of the α7-subunit assembly interphases. As expected, the endogenous agonist, acetylcholine, binds to α7 AChR subunits, and each of the five subunits has the potential to bind acetylcholine or succinylcholine molecules.[18,69] Other agonists, including nicotine and choline, and antagonists, including muscle relaxants, cobra toxin, and α-bungarotoxin, also bind to the α7 AChR.[18,69-72]

The α7 AChRs in muscle display unusual functional and pharmacologic characteristics when compared with conventional muscle (α1, β1, δ, ε/γ) AChRs or neuronal α7 AChRs in the brain. Choline, a precursor and metabolite of acetylcholine (and succinylcholine), is a weak agonist of conventional muscle AChRs but is a full agonist of muscle α7 AChRs; that is, concentrations of choline that do not open conventional AChR channels will open α7 AChR channels.[69] Furthermore, no desensitization of the α7 AChRs occurs even during the continued presence of choline,[69] thus allowing a greater chance for potassium to efflux (approximately 145 mEq/L) from within the cell to the extracellular space, including plasma (approximately 4.5 mEq/L), down its concentration gradient. The chemical α-conotoxin GI from the snail specifically inhibits the conventional (mature and immature) AChRs in muscle but does not inhibit α7 AChRs. The important role of α7 AChRs in resistance to NDMRs is evidenced by the presence of immobilization-induced resistance in wild-type mice and the absence of resistance in α7 AChRs knockout mice.[73] The α7 AChRs expressed in neuronal tissue are also readily desensitized with choline, a feature that contrasts with muscle α7 AChRs, which do not desensitize with choline.[69] The α7 AChRs in muscle also have lower affinity for its antagonists, including pancuronium, rocuronium, atracurium, or α-bungarotoxin; higher concentrations of these drugs are therefore required to block agonist-induced depolarization in α7 AChRs *in vitro* or cause neuromuscular paralysis *in vivo* or *ex vivo* when α7 AChRs are upregulated.[69-72] In the conventional muscle AChRs, binding of even one of the α1-subunits by an antagonist results in inactivation of that receptor because acetylcholine needs both α1-subunits of the AChR for its activation. In α7 AChRs, however, even when three subunits are bound by an antagonist (e.g., muscle relaxant), two other subunits are still available for binding by agonist and cause depolarization. This feature may account for some of the resistance to muscle relaxants when α7 AChRs are expressed in muscle and other tissues in pathologic states.[69-73]

The clinical pharmacologic characteristics of the muscle α7 AChR have not yet been completely studied, but its basic composition also provides some insight into succinylcholine-related hyperkalemia. Chemical or physical denervation of muscle results in not only upregulation and qualitative (ε-subunit → γ-subunit) changes in AChRs, but it also results in upregulation of α7 AChRs in muscle. Succinylcholine, a synthetic analog of acetylcholine that consists of two molecules of acetylcholine joined together, is capable of depolarizing not only conventional AChRs but also α7 AChRs in muscle.[72] In addition, the metabolite of succinylcholine, choline, can depolarize α7 AChRs with little desensitization. The depolarizing effects of succinylcholine and choline on upregulated α7 AChRs can

result in continued leakage of intracellular potassium and flooding of extracellular fluid, including plasma, thereby leading to hyperkalemia. Thus differences in the subunit composition and number of the three isoforms junctionally and extrajunctionally expressed may account for aberrant responses to muscle relaxants clinically observed as resistant only to NDMRs and hyperkalemic response to succinylcholine.[2,72,73]

MAINTENANCE OF MATURE NEUROMUSCULAR JUNCTIONS

Quite unlike other cells, muscle cells are unusual in that they have many, usually hundreds, of nuclei per cell. Each nucleus has the genes to make all three isoform receptors. Multiple factors, including electrical activity, growth factor signaling (e.g., insulin, agrin, neuregulins), and the presence or absence of innervation, control the expression of the three types of receptor isoforms.[19,37] This control is most clearly observed in the developing embryo as the neuromuscular junction is formed. Before they are innervated, the muscle cells of a fetus synthesize only immature and α7 AChRs—hence the term *fetal isoform* for the former receptor. Synthesis is directed by nearly all of the nuclei in the cell, and the receptors are expressed throughout the membrane of the muscle cell (Fig. 18-8). As the fetus develops and the muscles become innervated, muscle cells begin to synthesize the mature isoform of receptors, which are exclusively inserted into the developing (future) end-plate area.[14-19] The nerve releases several growth factors that influence the synthetic apparatus of the nearby nuclei. First, nerve-supplied factors induce the subsynaptic nuclei to increase synthesis of AChRs. Next, the nerve-induced electrical activity results in the repression of receptors in the extrajunctional area. Nerve-derived growth factors, including agrin and ARIA/neuregulin, cause the receptors to cluster in the subsynaptic area and prompt the expression of the mature isoform (see Fig. 18-8).[19,37] Several lines of evidence indicate that clustering, expression, and stabilization of mature receptors are triggered by at least two growth factors: agrin, neuregulin/ARIA, and possibly calcitonin gene–related peptide.[56,74,75] Neuregulin and agrin are also released from muscle, but muscle-derived agrin is not as important in clustering and maturation of the receptor. ARIA is made in the nerve and plays a role in the maturation of vesicular arrangement and conversion of the γ-to-ε switch.[75] All of these growth factors interact with distinct membrane and cytosolic receptor proteins to cause phosphorylation and activation of nuclear (gene) transcriptional systems. Agrin signals through MuSK and neuregulins through ErbB receptors (see Fig. 18-8). These receptors control qualitative and quantitative changes at the junction. Once begun, the process is very stable, and nuclei in the junctional area continue to express mature receptors. In certain pathologic state–induced insulin resistance, a concomitant proliferation of AChRs seems to occur beyond the junctional area. Conditions in which this form of insulin resistance (i.e., decreased growth factor signaling) has been observed include immobilization, burns, and denervation[75-78]; in these conditions, not only does upregulation of total AChRs occur, but *de novo*

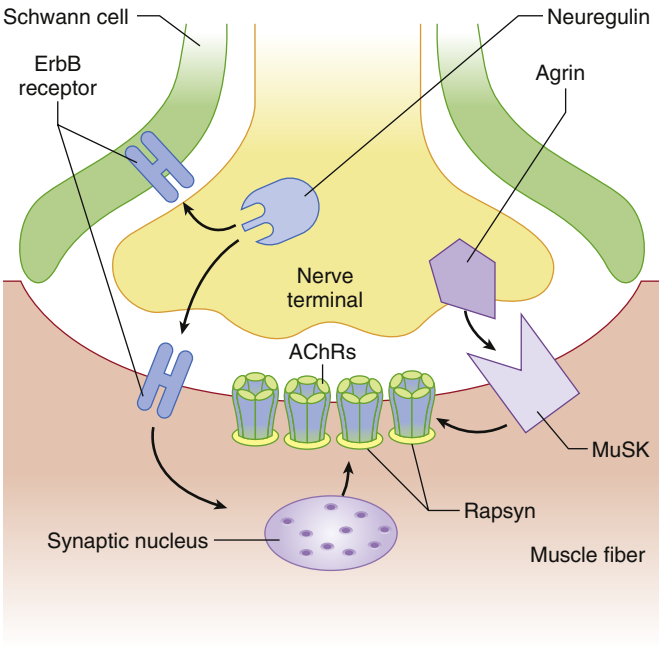


Figure 18-8. Diagram of agrin- and acetylcholine receptor–inducing activity (ARIA)/neuregulin-dependent events during maturation of the neuromuscular junction. After the establishment of a nerve on the muscle, growth factors, including agrin and neuregulins, are released. Neuregulin signaling is essential for Schwann cell survival, and Schwann cells are essential for axonal maintenance. Agrin interacting with its receptor muscle-specific tyrosine kinase (MuSK) enhances the clustering of synaptic proteins, including acetylcholine receptors (AChRs), rapsyn, and ErbB receptors. ARIA/neuregulin is the best candidate for the involvement in the conversion of γ-subunit–containing immature receptor to ε-subunit–containing mature (innervated) receptor, which is synapse specific and therefore not inserted in the extrajunctional area.

upregulation of the immature and α7 AChR isoforms are also observed.[1-3] This upregulation may be related to the fact that agrin and possibly neuregulin signal via some of the same downstream signaling proteins as insulin (e.g., phosphoinositide 3-kinase [PI3K]).[56,76-79] Therefore agrin and neuregulin signaling may be important for the suppression of α7 AChRs and immature AChRs in the normal neuromuscular junction.

Before innervation, as in the fetus, AChRs are present throughout the muscle membrane. After innervation, AChRs become more and more concentrated at the postsynaptic membrane and are virtually absent in the extrasynaptic area at birth. The innervation process progresses somewhat slowly during fetal life and matures during infancy and early childhood.[14-19] With time, the immature receptors diminish in concentration and disappear from the peripheral part of the muscle. In the active, adult, and normal innervated muscle, just the nuclei under and very near the end plate direct the synthesis of the receptor; only the genes for expressing mature receptors are active. Nuclei beyond the junctional area are not active, and therefore no receptors are expressed anywhere in the muscle cells beyond the perijunctional area. Conversion of all of the γ-subunit– to ε-subunit–containing AChRs in the perijunctional area continues to take place after birth. In the rodent, conversion takes approximately

2 weeks.[14-19] In humans, this process takes longer. The timeframe for the disappearance of α7 AChRs in the fetus or newborn is also unknown. Proteins implicated in the linking of mature receptors to the cytoskeleton include integrin, syntrophin, utrophin, α- and β-dystroglycan, and rapsyn, just to name a few.[14-19]

RE-EXPRESSION OF IMMATURE (FETAL) γ-SUBUNIT AND α7-SUBUNIT AChRs IN ADULT LIFE

The extrajunctional immature receptors can reappear soon after upper and lower motor denervation and in certain pathologic states (e.g., burns, sepsis, immobilization, chronic muscle relaxant therapy or botulism, loss of muscle electrical activity). Stimulation of a denervated muscle with an external electrical stimulus can prevent the appearance of immature receptors. It has been suggested that the calcium that enters the muscle during activity is important in the suppression process.[16,17] In the pathologic states previously enumerated, if the process is severe and prolonged, then extrajunctional receptors are inserted all over the surface of the muscle, including the perijunctional area (see Fig. 18-7). The junctional nuclei also continue to make mature receptors. The synthesis of immature receptors is initiated within hours of inactivity, but it takes several days for the whole muscle membrane to be fully covered with receptors. This upregulation of receptors has implications for the use of depolarizing and possibly NDMRs. The changes in α7 AChRs parallel the expression of immature receptors, although this has not been well studied.

The changes in subunit composition (γ versus ε) in the receptor confer certain changes in electrophysiologic (functional), pharmacologic, and metabolic characteristics.[16-18] Mature receptors are metabolically stable, with a half-life approximating 2 weeks, whereas immature receptors have a metabolic half-life of less than 24 hours. Immature receptors have a smaller single-channel conductance and a twofold to tenfold longer mean channel open time than do mature receptors (see Fig. 18-4). The changes in subunit composition may also alter the sensitivity or affinity, or both, of the receptor for specific ligands. Depolarizing or agonist drugs such as succinylcholine and acetylcholine more easily depolarize immature receptors, thereby resulting in cation fluxes; doses one tenth to one hundredth of those needed for mature receptors can effect depolarization.[2] The potency of nondepolarizers is also reduced, as demonstrated by the resistance to nondepolarizers documented in patients with burns, denervation, and immobilization.[1,3] In light of recent research, however, it seems that the resistance to nondepolarizers is more likely due to the junctional area expression of the α7 AChRs, which has a decreased affinity NDMRs.[16,69-73] Some NDMRs may also cause a partial agonist response in immature receptors, thus explaining the decreased potency in conditions in which upregulation of AChRs occurs.[8] The upregulation of immature AChRs in the perijunctional and extrajunctional areas may have a buffering effect for diffusion of relaxants, contributing to resistance to NDMRs.[80]

The altered sensitivity to muscle relaxants may occur in only certain parts of the body or certain muscles if only some muscles are affected by the diminution in nerve activity (e.g., after a stroke). Sensitivity to relaxants can begin to change between 48 and 72 hours after an injury or hospitalization. The most serious side effect with the use of succinylcholine in the presence of upregulated AChRs in one or more muscles is hyperkalemia.[1-3] In these subjects, the receptors can be scattered over a large surface of the muscle. The AChR channels opened by the agonist (succinylcholine) allow potassium to escape from the muscle and enter the blood (Fig. 18-9).[2,3] If a large part of the muscle surface consists of upregulated (immature) receptor channels, each of which stays open for a longer time, then the amount of potassium that moves from muscle to blood can be considerable. The resulting hyperkalemia can cause dangerous disturbances in cardiac rhythm, including ventricular fibrillation. Moreover, hyperkalemia probably cannot be prevented by prior administration of NDMRs because large doses required to block the AChRs, in and of itself, will cause paralysis, obviating the need for succinylcholine.[3] Larger-than-normal doses of NDMRs may attenuate the increase in blood potassium concentrations but cannot completely prevent it. However, hyperkalemia and cardiac arrest can occur after the administration of succinylcholine, even in the absence of denervation states. These effects are observed in certain congenital muscle dystrophies in which the muscle membrane is prone to damage by the depolarization produced by succinylcholine, resulting in potassium release via the membrane damage.[81]

PREJUNCTIONAL ACETYLCHOLINE RECEPTORS

Nicotinic AChRs exist in a variety of forms apart from that observed in muscle.[16,18] The classic muscle-type nicotinic AChR is postsynaptically present, whereas neuronal subtype receptors may be presynaptically and postsynaptically present. The neuronal subtype nicotinic AChRs expressed prejunctionally are usually heteromeric and built up by *only* α- and β-subunits. This family of nicotinic AChRs is widely expressed in the peripheral and central nervous systems, on autonomous nerves and ganglia on oxygen-sensing cells within the carotid bodies. There are also α7 AChRs in immune-competent cells, such as macrophages, lymphocytes and granulocytes, and fibroblasts and chondrocytes.[16,18] Diverse genes encode the heterogeneous AChRs, and the ion channel is formed of multiple subunits (multimers). Seventeen AChR genes have been cloned from vertebrates. They include various combinations of α-subunits (α1 through α10) and β-subunits (β1 through β4) and one each of γ-, δ-, and ε-subunits. The γ-, δ-, and ε-subunits are found only in muscle.[16-18]

Prejunctional- or nerve terminal–associated cholinergic receptors have been demonstrated by morphologic pharmacologic and by molecular biologic techniques, but their form and functions are not as completely understood as those in the postjunctional area. Many drugs with an abundance of potential targets for drug action can affect the capacity of the nerve terminal to carry out

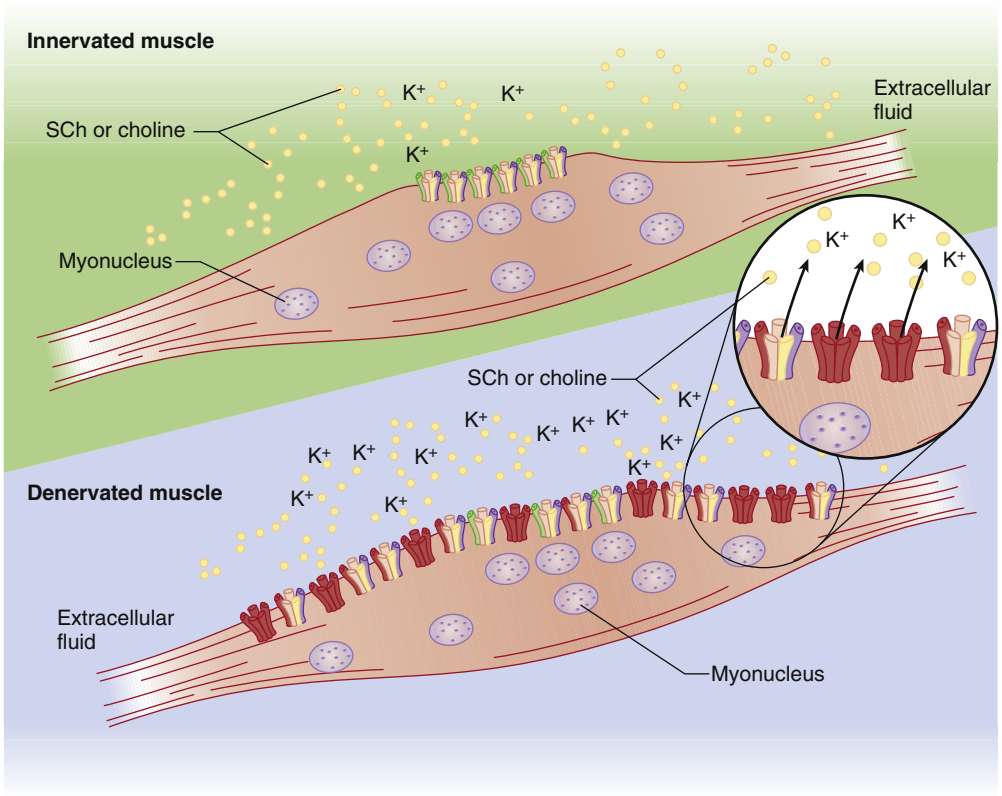


Figure 18-9. Schematic of the succinylcholine (SCh)–induced potassium (K^+) release in an innervated *(top)* and denervated muscle *(bottom)*. In the innervated muscle, the systemically administered SCh reaches all of the muscle membrane but depolarizes only the junctional (α1, β1, δ/ε) receptors because acetylcholine receptors (AChRs) are located only in this area. With denervation, the muscle nuclei express not only extrajunctional (α1, β1, δ/γ) AChRs but also α7-nicotinic AChRs throughout the muscle membrane. Systemic SCh, in contrast to acetylcholine released locally, can depolarize all of the up-regulated AChRs, which leads to massive efflux of intracellular K^+ into the circulation, resulting in hyperkalemia. The metabolite of SCh, choline, and possibly succinylmonocholine can maintain this depolarization via α7-nicotinic AChRs, enhancing the K^+ release and maintaining the hyperkalemia. *(From Martyn JAJ, Richtsfeld M: Succinylcholine-induced hyperkalemia in acquired pathologic states: etiologic factors and molecular mechanisms,* Anesthesiology *104: 158-169, 2006.)*

its functions. The trophic function to maintain nerve-muscle contact involves the release and replenishment of acetylcholine together with other trophic factors that require signaling through many receptors, of which the prejunctional nicotinic AChR is just one. Succinylcholine produces fasciculations that can be prevented by NDMRs. Because a fasciculation is, by definition, the simultaneous contraction of the multitude of muscle cells in a single motor unit and because only the nerve can synchronize all the muscles in its motor unit, it became apparent that succinylcholine must also act on nerve endings. Because NDMRs prevent fasciculation, it was concluded that they acted on the same prejunctional receptor. Very small doses of cholinergic agonists (e.g., succinylcholine) and antagonists (e.g., NDMRs) affect nicotinic receptors on the nerve ending, the former by depolarizing the ending and sometimes inducing repetitive firing of the nerve and the latter by preventing the action of agonists.[5]

By the use of specific monoclonal antibodies, the presence of nicotinic α3-subunits has been demonstrated in the nerve terminal.[82] Another clue to the differences between prejunctional and postjunctional AChRs was the finding that some drugs (e.g., dihydro-β-erythroidine) bind only to prejunctional AChRs, whereas other drugs (e.g., α-bungarotoxin) bind only to postjunctional receptors.[65] Additional clues were found in the many demonstrations of quantitative differences in the reaction of prejunctional and postjunctional nicotinic receptors to other cholinergic agonists and antagonists.[65,82-84] For instance, it was known that tubocurarine binds with lower affinity to the recognition sites of ganglionic nicotinic cholinoceptors and is not a competitive antagonist of acetylcholine at this site. Decamethonium (i.e., a depolarizing muscle relaxant no longer clinically used) is a selective inhibitor of the muscle receptor, and hexamethonium is a selective inhibitor of nicotinic receptors in the autonomic ganglia.[80-85] Instead, D-tubocurarine and hexamethonium can block the opened channels of these receptors and owe their ability to block ganglionic transmission to this property. The functional characteristics of prejunctional receptor channels may also be different. For example, the depolarization of motor nerve endings initiated by the administration of acetylcholine can be prevented by tetrodotoxin, a specific blocker of sodium flux with no effect on the end plate.

Specific information on the molecular organization of neuronal nicotinic receptors on the motor neuron terminal is still lacking. Some of the subunit composition is similar, but other subunits do not resemble those of the postjunctional receptor. Of the 16 different nicotinic AChR gene

products identified, only 12 (α2 to α10 and β2 to β4) are thought to contribute nicotinic receptors expressed on neurons. Most strikingly, nervous tissue does not express γ-, δ-, or ε-receptor subunits; it contains genes only for the α- and β-subunits. The α- and β-subunit genes in nerve and muscle are not exactly the same; they are variants. To emphasize the distinction between neural and muscle nicotinic receptors, the former are sometimes designated *Nn* and the latter *Nm*. With so many different subunits available, possible combinations are many, and it is not known which combinations are found in motor nerves. Their physiologic roles have also not been completely characterized. Expression of neuronal nicotinic AChRs in *in vitro* systems has confirmed that muscle relaxants and their metabolites can bind to some of these neuronal AChRs.[53,83-85]

The nicotinic receptor on the junctional surface of the nerve (nerve terminal) senses transmitter in the cleft and, by means of a positive-feedback system, causes the release of more transmitter. In other parts of the nervous system, this positive feedback is complemented by a negative-feedback system that senses when the concentration of transmitter in the synaptic cleft has appropriately increased and shuts down the release system. It is believed that tetanic fade and train-of-four fade during neuromuscular blockade with NDMRs arise from presynaptic cholinergic autoreceptors at the motor nerved ending.[5,52]

The neuronal AChR subtype that is critically involved in acetylcholine release and subsequent fade phenomenon (as observed in tetanic or train-of-four stimulus patterns) has been identified as the α3β2-subtype nicotinic AChR.[10,84] When this prejunctional receptor is specifically blocked by a nondepolarizing relaxant such as tubocurarine, a reduction in neurotransmitter release occurs upon repeated stimulation with subsequent fade phenomenon. It should be noted, however, block of the prejunctional AChRs alone is not necessary and sufficient to induce fade; concomitant reduction in the safety of neurotransmission prejunctionally or postjunctionally must be present for it to be noticeable.[65] Although all clinically used nondepolarizing neuromuscular blocking drugs inhibit this prejunctional nicotinic AChR, as well as several other neuronal nicotinic AChRs, in the clinically relevant concentration range, succinylcholine neither activates nor inhibits the presynaptic α3β2 autoreceptor at clinically relevant concentrations.[53,85] This observation may be the reason for the typical lack of fade during succinylcholine-induced neuromuscular block. Succinylcholine, however, does not interact with α3β4 AChR found in autonomic ganglia.[53] It has also been shown that NDMRs reduce the hypoxic ventilatory response in partially paralyzed humans,[86] and the mechanism behind the depression might be related to inhibition of nicotine receptors on the carotid body.[11] Nicotinic α3, 7, and β2 AChRs have recently been documented in the human carotid body.[87] Whether the inhibition of these receptors plays a role in attenuated response to hypoxia drive needs further investigation. The motor nerve terminal is also known to bear several other receptors, such as opioid, adrenergic, dopamine, purine, and adenosine receptors, as well as receptors for endogenous hormones, neuropeptides, and a variety of proteins.[88,89] The physiologic roles of these receptors and the effects of anesthetics on them are unknown.

NEUROMUSCULAR JUNCTION AT EXTREMES OF AGE

NEWBORN

Just before birth, the AChRs are all clustered around the nerve in the junctional area, and minimal extrajunctional AChRs are present. The newborn postsynaptic membrane, itself, is not specialized, having almost no synaptic folds, a widened synaptic space, and a reduced number of AChRs.[14,19] The early postnatal AChR cluster appears as an oval plaque (Fig. 18-10). Within a few days,

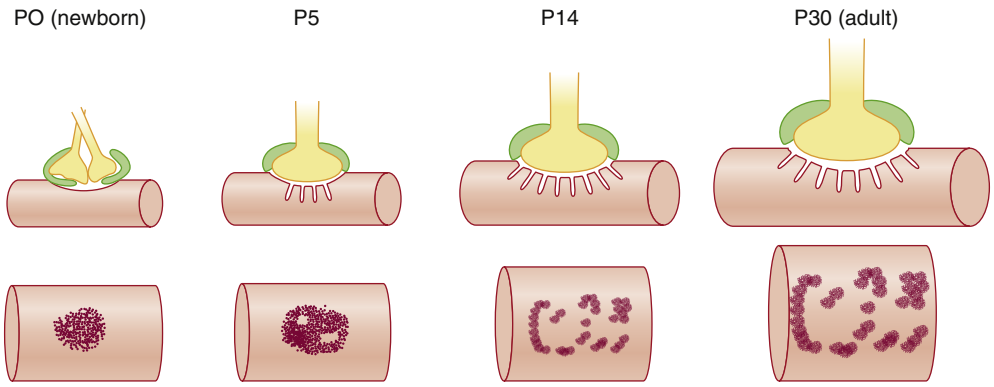


Figure 18-10. Maturation of the postsynaptic apparatus. *Postnatal day 0 (PO)*: At the time of birth, the aggregates of AChRs have consolidated to form an oval-like plaque with irregular borders. At this point, each junction may have more than one nerve terminal innervating it. *Postnatal day 5 (P5)*: Approximately 5 days after birth, the postsynaptic membrane invaginates to form a gutter and small perforations develop on the plaque. *Postnatal day 14 (P14)*: At approximately 14 days after birth, the immature γ-subunit–containing acetylcholine receptors (AChRs) are completely replaced by mature AChRs containing α-subunit. The invaginations or clefts increase in numbers, resulting in more perforations in the pretzel-shaped junction. The perforations correspond to the synaptic clefts or folds. *Postnatal day 30 (P30)*: The neuromuscular junction is completely developed at 30 days after birth. The AChRs have maximal density. A distinct set of postsynaptic proteins and signaling molecules are selectively transcribed in the subsynaptic area, providing integrity to the neuromuscular junction and efficient neurotransmission. *(Modified from Shi L, Fu AK, Ip NY: Molecular mechanisms underlying maturation and maintenance of the vertebrate neuromuscular junction,* Trends Neurosci *35:441-453, 2012; and Sanes JR, Lichtman JW: Induction, assembly, maturation and maintenance of a postsynaptic apparatus,* Nat Rev Neurosci *2:791-805, 2001.)*

simplified folds appear. With continued maturation, the plaque is transformed to a multiperforated pretzel-like structure. The polyinnervated end plate is converted to a singly innervated junction because of a retraction of all but one terminal. In the adult, the terminals perfectly align with the AChR clusters. Morphologically, the postsynaptic membrane of the newborn and that from the patient with myasthenia gravis is not too different; the AChR number is decreased, and the postsynaptic folds are decreased. It is not surprising therefore that neurotransmission is not as efficient in the newborn and in patients with myasthenia gravis. For this reason, neonates and infants behave similar to patients with myasthenia gravis when NDMRs are administered to them.[90] In humans, maturation of the neuromuscular junction probably occurs at approximately 2 years of age[90] (see also Chapter 93).

OLD AGE

Old age–associated functional denervation, muscle wasting, and weakness is now well established.[91,92] Anatomic changes involve increased preterminal and axonal branching within the individual neuromuscular junction, either with or without an increase in the junctional size. The points of contacts between the prejunctional and postjunctional membrane decrease, resulting in a decline in trophic interactions between nerve and muscle and stimulus transmission. Muscle weakness associated with aging is not entirely peripheral in origin.[93] The ability to communicate neural activity from brain to skeletal muscle is impaired with age. Despite these structural and functional changes associated with aging, the overall margin of safety is better in the older individual than in the neonate.[94] (Also see Chapter 80.)

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Chapter 19

Respiratory Physiology and Pathophysiology

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KEY POINTS

- Removal of CO_2 is determined by alveolar ventilation, not by total (minute) ventilation.
- Dead space ventilation can be dramatically increased in patients with chronic obstructive pulmonary disease and pulmonary embolism to more than 80% of minute ventilation.
- Breathing at small lung volumes increases airway resistance and promotes closure of airways.
- Hypoxemia can be caused by alveolar hypoventilation, diffusion impairment, ventilation-perfusion mismatch, and right-to-left shunt.
- Almost all anesthetics reduce skeletal muscle tone, which decreases functional residual capacity (FRC) to levels close to the awake residual volume (RV).
- Atelectasis during anesthesia is caused by decreased FRC and the use of high inspired oxygen concentrations (Fio_2), including breathing oxygen before induction of anesthesia.
- General anesthesia causes ventilation-perfusion mismatch (airway closure) and shunts (atelectasis).
- Venous admixture is due to $\dot{V}_A/\dot{Q}$ mismatch (response to increased Fio_2) and shunts (unresponsive to increased Fio_2).
- Hypoxic pulmonary vasoconstriction is blunted by most anesthetics, and this results in increased ventilation-perfusion mismatching.
- Respiratory work is increased during anesthesia as a consequence of reduced respiratory compliance and increased airway resistance.

RESPIRATORY PHYSIOLOGY IS CENTRAL TO THE PRACTICE OF ANESTHESIA

Respiratory function is inextricably linked to the practice of anesthesia. Adverse respiratory effects can occur during anesthesia,[1] and the most serious cases of adverse events involve hypoxemia. These events range from intractable hypoxemia caused by loss of airway patency to postoperative respiratory depression from opioids or regional anesthesia (see Chapter 96).[2,3] In the absence of adverse outcomes, general anesthesia has significant effects on respiratory function and lung physiology by observations made in the operating room. Improved appreciation of anesthesia-induced physiologic alterations (e.g., mechanisms of bronchospasm,[4] impact of mechanical ventilation),[5] as well as pioneering developments in monitoring (e.g., pulse oximetry and capnography; see Chapter 44),[6] together are associated with the specialty of anesthesiology's emergence as a leader in patient safety (see Chapter 6).[7] Finally, integrative measures of respiratory function, ranging from exercise capacity,[8] spirometry to tissue oxygenation,[9] or global O_2 consumption,[8] are likely predictors of outcome following anesthesia and surgery.

PULMONARY PHYSIOLOGY IN HEALTH

The mechanisms by which anesthesia-associated respiratory dysfunction are caused can be determined with an examination of the normal functions and mechanisms of respiration in health. We briefly review cellular respiration whereby O_2 is consumed and CO_2 is produced, the transport of O_2 and CO_2 in the blood, and the principles by which the lung oxygenates blood and eliminates CO_2.

RESPIRATION IN THE CELL

The partial pressure of oxygen (PaO_2) in normal arterial blood is approximately 100 mm Hg, and decreases to 4 to 22 mm Hg in the mitochondrion where it is consumed. Glucose ($C_6H_{12}O_6$) is converted into pyruvate (CH_3COCOO^-) and H^+ by glycolysis in the cytoplasm, and the pyruvate diffuses into the mitochondria and forms the initial substrate for Krebs cycle, which in turn produces nicotinamide adenine dinucleotide (NADH), as well as adenosine triphosphate (ATP), CO_2, and H_2O. The NADH is a key electron (and H^+) donor in the process of oxidative phosphorylation, wherein O_2 and adenosine diphosphate (ADP) are consumed and ATP and H_2O are produced. Thus, the net effect is oxidation of glucose to produce energy (ultimately as ATP), H_2O, and CO_2.[10]

TRANSPORT OF O_2 IN THE BLOOD

O_2 reaches the cells following transport by arterial blood, and the overall delivery of O_2 ($\dot{D}O_2$) is the product of the arterial blood O_2 content (CaO_2) and blood flow (cardiac output, $\dot{Q}$) as:

$$\dot{D}O_2 = CaO_2 \times \dot{Q}$$

The carriage in the blood is in two forms: O_2 bound to hemoglobin (the vast bulk), and O_2 dissolved in the plasma, and is expressed as the sum of these components as follows:

$$CaO_2 = \left[\begin{array}{l} (SaO_2 \times Hb \times O_2 \textit{ combining capacity of Hb}) \\ + (O_2 \textit{ solubility} \times Pao_2) \end{array} \right]$$

where CaO_2 (O_2 content) is the milliliters of O_2 per 100 mL of blood, SaO_2 is the fraction of hemoglobin (Hb) that is saturated with O_2, O_2-combining capacity of Hb is 1.34 mL of O_2 per gram of Hb, *Hb* is grams of Hb per 100 mL of blood, Pao_2 is the O_2 tension (i.e., dissolved O_2), and solubility of O_2 in plasma is 0.003 mL of O_2 per 100 mL plasma for each mm Hg Pao_2

The binding of O_2 to hemoglobin is a complex, allosteric mechanism. Important insights can be gained by understanding how characteristic abnormalities of blood O_2 carriage (e.g., carbon monoxide [CO] poisoning, methemoglobinemia) affect on O_2 tension, content, and delivery.

Methemoglobin (MetHb), formed by the oxidation to Fe^{3+} (ferric) instead of the usual Fe_2^+ (ferrous), is less able to bind O_2, resulting in diminished O_2 content and less O_2 delivery. Here, the Pao_2 (in the absence of lung disease) will be normal: if the O_2 content is calculated from the Pao_2, it will appear normal, but if measured it will be low. In contrast, MetHb level will be elevated. In severe cases, lactic acidosis develops because of impaired O_2 delivery. In addition, because MetHb has a blue-brown color, the patient will appear blue, even if the fraction of MetHb is modest and specialized oximetry can separately measure MetHb levels.[11,12] The apparent cyanosis is not responsive to supplemental O_2, and therapy involves converting (i.e., reducing) the MetHb to Hb (e.g., by using methylene blue). Important medical causes of MetHb include benzocaine; dapsone; or in susceptible patients, inhaled nitric oxide (NO).

In CO poisoning, the CO binds to Hb, with far greater (over ×200-fold) avidity than molecular O_2, tightly forming CO-Hb and resulting in two main effects.[13] First, formation of CO-Hb results in fewer sites available for O_2 binding, and this reduces the blood O_2 content. Second, the formation of CO-Hb causes conformational changes in the Hb molecule such that the tendency to release bound O_2 is reduced. This effect corresponds to a leftward shift of the Hb-O_2 dissociation curve, and although this aspect of CO binding does not reduce the O_2 content or "global" delivery of O_2, it does reduce the release of O_2 and its delivery to the cells. Because the color of CO-Hb closely resembles that of O_2-Hb, the color of the blood (and the patient) is bright red; however, as with Met-Hb, the PaO_2 will be normal (assuming no pulmonary disease) as will the calculated CaO_2; however, the measured CaO_2 will be low and if severe, a lactic acidosis will be present. Modern can distinguish between Hb-O_2 and CO-Hb.[13]

Finally, the *Bohr effect* refers to a shift of the Hb-O_2 dissociation curve caused by changes in CO_2 or pH.[14] In the systemic capillaries, the Pco_2 is higher than in the arterial blood (and the pH correspondingly lower) because of local CO_2 production. These circumstances shift the Hb-O_2 dissociation curve to the right, which increases the offloading of O_2 to the tissues. The opposite occurs in the pulmonary capillaries; the $Paco_2$ is lower (and the pH correspondingly higher) because of CO_2 elimination, and the dissociation curve is shifted to the left to facilitate O_2 binding to Hb.

TRANSPORT OF CO_2 IN THE BLOOD

CO_2 is produced by metabolism in the mitochondria, where the CO_2 levels are highest. The transport path (involving progressively decreasing pressure gradients) is from mitochondria through cytoplasm, into venules and finally, in mixed venous blood from where it is eliminated through the alveoli. In the blood, CO_2 is transported in three main forms: dissolved (reflected as $Paco_2$, partial pressure; accounts for approximately 5% of transported CO_2), bicarbonate ion (HCO_3^-; almost 90%), and carbamino CO_2 (CO_2 bound to terminal amino groups in Hb molecules; approximately 5%).[10] The usual quantities of CO_2 in the arterial and (mixed) venous blood are approximately 21.5 and 23.3 mmol of CO_2 per liter of blood, respectively.

Breathing O_2 can sometimes induce hypercapnia, as occurs in patients with severe chronic lung disease who are breathing supplemental O_2. Although traditionally thought to occur because increased Pao_2 reduces ventilatory drive, this is now known not to be the case[15]; it results from the Haldane effect, as well as from impairment of hypoxic pulmonary vasoconstriction (HPV). The Haldane effect[16] is the difference in the amount of CO_2 carried in oxygenated versus deoxygenated blood, and two mechanisms explain this. First, increased Pao_2 decreases the ability to form carbamino compounds—reducing the amount of CO_2 bound to Hb—thereby raising the amount of dissolved CO_2 (i.e., elevated Pco_2). Second, the amino acid histidine, which has an imidazole group that is an effective H^+ buffer at physiologic pH, is an important linking molecule between heme groups

and the Hb chains. Increasing the partial pressure of oxygen (PO_2) increases the amount of O_2 bound to Hb; this changes the conformation of the Hb molecule, which in turn alters the heme-linked histidine and reduces its H^+ buffering capacity. Therefore, more H^+ is free (not buffered) and binds to HCO_3^-, releasing stored CO_2. Impairment of HPV by elevated O_2 allows increased perfusion to poorly ventilated regions; this has the effect of decreasing perfusion (and delivery of CO_2) to better ventilated regions, diminishing the efficiency of CO_2 elimination. Patients with impaired ability to increase alveolar ventilation ($\dot{V}_A$) cannot compensate for the increased CO_2 availability, and therefore, in these patients, adding supplemental O_2 can result in elevated Pa_{CO_2}.

OXYGENATION IN THE LUNG

Systemic venous blood (central venous blood) enters the right ventricle via the right atrium. The O_2 saturation (SO_2) differs among the major veins: higher venous SO_2 reflects greater blood flow, less tissue oxygen uptake, or both.[17] SO_2 is usually higher in the inferior vena cava (IVC) than in the superior vena cava (SVC), possibly because of the high renal and hepatic flow relative to O_2 consumption. In the right ventricle, the central venous blood ($S_{cv}O_2$) from the SVC and IVC, is joined by additional venous blood from the coronary circulation (via the coronary sinuses). In the right ventricle, an additional small amount of venous drainage from the myocardium enters through the Thebesian veins, and as all this venous blood enters the pulmonary artery it is well mixed and is termed *mixed-venous blood* ($S_{\bar{v}}O_2$); thus, $S_{\bar{v}}O_2 < S_{cv}O_2$, although the trends of each usually run in parallel.[18]

VENTILATION

Ventilation refers to the movement of inspired gas into and exhaled gas out of the lungs.

ALVEOLAR VENTILATION

Fresh gas enters the lung by cyclic breathing at a rate and depth (tidal volume, V_T) determined by metabolic demand, usually 7 to 8 L/min.[19] While most inspired gas reaches the alveoli, some (100 to 150 mL) of each V_T remains in the airways and cannot participate in gas exchange. Such dead space (V_D) constitutes approximately one third of each V_T.[20] Anatomic V_D is the fraction of the V_T that remains in the "conducting" airways, and physiologic V_D is any part of a V_T that does not participate in gas exchange (Fig. 19-1).

For a single tidal volume (V_T, mL), the following is true:

$$V_T = V_A + V_D$$

The product of V_T (mL) times the respiratory rate (per minute) is the minute ventilation ($\dot{V}_E$). Aggregated over time, minute ventilation ($\dot{V}_E$, mL/min) is:

$$\dot{V}_E = \dot{V}_A + f \times V_D$$

The portion of the $\dot{V}_E$ that reaches the alveoli and respiratory bronchioles each minute and participates in gas exchange is called the *alveolar ventilation* ($\dot{V}_A$), and it is approximately 5 L/min. Because this is similar to the blood flow through the lungs (i.e., the cardiac output, also 5 L/min), the overall alveolar ventilation-perfusion ratio is approximately 1.

DEAD SPACE VENTILATION

Maintenance of Pa_{CO_2} is a balance between CO_2 production ($\dot{V}CO_2$, reflecting metabolic activity) and alveolar ventilation ($\dot{V}_A$. If $\dot{V}_E$ is constant but V_D is increased, $\dot{V}_A$ will naturally be reduced, and the Pa_{CO_2} will therefore rise. Therefore, if V_D is increased, $\dot{V}_E$ must also increase to prevent a rise in Pa_{CO_2}. Such elevations in V_D occur when a mouthpiece or facemask is used, and in such cases, the additional V_D is termed "apparatus deadspace" (which can be up to 300 mL; anatomic V_D of the airways is 100 to 150 mL).[21]

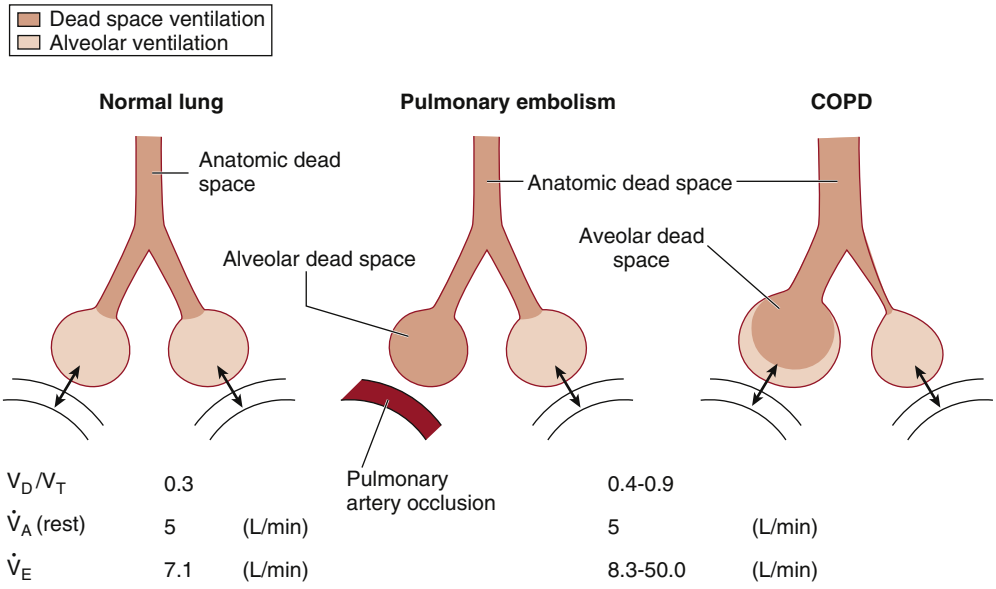


Figure 19-1. Dead space and alveolar ventilation in normal and diseased lungs. Either cessation of blood flow or excessive alveolar ventilation relative to perfusion will cause an increase in dead space. If V_D is increased, a large compensatory increase in minute ventilation is required to preserve $\dot{V}_A$. V_D/V_T, dead space to tidal volume ratio; $\dot{V}_A$, alveolar ventilation; $\dot{V}_E$, minute ventilation. $\dot{V}_E = \dot{V}_A + f \times V_D$. *Double arrows* indicate normal CO_2 exchange. *COPD*, Chronic obstructive pulmonary disease. *(From Hedenstierna G: Respiratory measurement. London, 1998, BMJ Books, 1998, p. 184; see also book review of* Respiratory Measurement in Thorax *53:1096, 1998.)*

Increases in the volume of the conducting airways (e.g., bronchiectasis) increase the overall V_D only slightly. Far more significant increases in V_D occur when perfusion to a large number of ventilated alveoli is interrupted, as occurs in a pulmonary embolus (see Fig. 19-1). Indeed, with multiple pulmonary emboli, V_D/V_T can exceed 0.8 (2.7-fold normal). In such a case, to maintain a normal $\dot{V}_A$ (5 L/min), the $\dot{V}_E$ would have to increase (also 2.7-fold) to almost 20 L/min. This effort would cause considerable dyspnea, in addition to the dyspnea induced by the lowered PaO_2.

Obstructive lung disease can result in diversion of inspired air into (nonobstructed) ventilated, but poorly perfused, regions of the lung. This results in local excesses of ventilation versus perfusion (high $\dot{V}_A/\dot{Q}$ ratio) in such regions,[22] which is equivalent to an increase in V_D/V_T (see Fig. 19-1). Patients with severe chronic obstructive pulmonary disease (COPD) may have a V_D/V_T ratio of up to 0.9, and would have to hyperventilate massively (30 to 50 L/min) to maintain normal $Paco_2$, which is not possible where ventilator reserve is diminished. Such patients demonstrate reduced $\dot{V}_A$ but often have an elevated $\dot{V}_E$. An important compensatory mechanism is that a lower level of $\dot{V}_A$ will maintain stable CO_2 excretion where the $Paco_2$ is increased (Box 19-1).

STATIC LUNG VOLUMES—FUNCTIONAL RESIDUAL CAPACITY

The amount of air in the lungs after an ordinary expiration is called *functional residual capacity* (Fig. 19-2); it is usually 3 to 4 L and occurs because of the balance of inward (lung) forces and outward (chest wall) forces. The inward force is the "elastic recoil" of the lung and emanates from the elastic lung tissue fibers, contractile airway smooth muscle, and alveolar surface tension. The outward force is developed by passive recoil from the ribs, joints, and muscles of the chest wall. FRC is greater with increased height and age (loss of elastic lung tissue), and smaller in women and in obesity (see Chapter 71).[19,23]

There are two reasons why maintenance of gas in the lung at end-expiration (i.e., FRC) is important. First, inflating an already opened (inflated) lung is easier than when the lung is already deflated. This is because complete collapse results in liquid-only surfaces interfacing in alveoli (high surface tension), whereas alveoli in partially inflated lung have air-liquid interfaces (lower surface tension). Second, although perfusion in the lung is phasic, the frequency is rapid and the oscillations in flow are low, resulting in nearly continuous flow. Ventilation is different: the frequency is far slower and the size of the oscillations far larger. If the lung (or large parts of it) completely deflate between breaths, the blood flowing from closed alveoli (that contain zero O_2) would have very low SO_2 (the same as mixed venous blood); this would mix into the overall blood flow from the lungs and cause a major O_2 desaturation after every exhalation.

RESPIRATORY MECHANICS

The study of respiratory mechanics tells us how inspired air is distributed within the lung and permits quantitation of the severity of lung disease. The components of overall impedance to breathing results from elastance (the reciprocal of compliance), resistance, and inertia.

COMPLIANCE OF THE RESPIRATORY SYSTEM

The lung is like a rubber balloon that can be distended by positive pressure (inside) or negative pressure (outside). Under normal circumstances, inflation of the lung is maintained because although the pressure inside (alveolar pressure) is zero, the outside pressure (i.e., the pleural pressure) is sufficiently negative. The net distending pressure, which is the difference of the (positive) airway pressure (P_{AW}) and the (negative) pleural pressure (P_{PL}) is termed the *transpulmonary pressure* (P_{TP}). Thus:

$$P_{TP} = P_{AW} - P_{PL}$$

Clearly, increasing the P_{AW} increases the P_{TP}. In addition, lowering the P_{PL} (which is usually negative and making it more negative) making it more negative) also increases the P_{TP}.

Compliance—the reciprocal of elastance—is the term that expresses how much distention (volume in liters) occurs for a given level of P_{TP} (pressure, cm H_2O); it is usually 0.2 to 0.3

BOX 19-1 *Alveolar Gas Equations*

Alveolar Oxygen Tension (PAO_2)

$$PAO_2 = PIO_2 - \frac{PACO_2}{R} + \left[PACO_2 \times FiO_2 \times \frac{1-R}{R}\right]$$

where PIO_2 is inspired oxygen tension, $PACO_2$ is alveolar CO_2 tension (assumed to equal arterial Pco_2), R is the respiratory exchange ratio (normally in the range of 0.8 to 1.0), and FiO_2 is the inspired oxygen fraction. The term within brackets compensates for the larger O_2 uptake than CO_2 elimination over the alveolar capillary membranes.

A simplified equation can be written without the compensation term:

$$PAO_2 = PIO_2 - \frac{PACO_2}{R}$$

Alveolar Ventilation

Alveolar ventilation ($\dot{V}A$) can be expressed as

$$\dot{V}A = f \times (VT - VDS)$$

where f is breaths/min, VT is tidal volume, and VDS is physiologic dead space.

Alveolar ventilation can also be derived from:

$$\dot{V}CO_2 = c \times \dot{V}A \times FACO_2$$

where $\dot{V}CO_2$ is CO_2 elimination, c is a conversion constant, and $FACO_2$ is the alveolar CO_2 concentration.

If $\dot{V}A$ is expressed in L/min, $\dot{V}CO_2$ in mL/min, and $FACO_2$ is replaced by $PACO_2$ in mm Hg, $c = 0.863$. By rearranging:

$$\dot{V}A = \frac{\dot{V}CO_2 \times 0.863}{PACO_2}$$

L/cmH_2O.[24] However, although higher values of P_{TP} maintain greater levels of lung opening, the relationship—as with most elastic structures—between applied pressure and resultant volume is curvilinear (Fig. 19-3).[24] Lung compliance depends on the lung volume; it is lowest at an extremely low or high FRC (see Fig. 19-3). In lung diseases characterized by reduced compliance (e.g., ARDS, pulmonary fibrosis or edema), the pressure-volume curve is flatter and shifted to the right (Fig. 19-4).[24] In contrast, although emphysema involves the loss of elastic tissue, the overall loss of lung tissue (as seen on computed tomography [CT] scanning)[25] means that the compliance is increased; the pressure-volume curve is therefore shifted to the left and is steeper (see Fig. 19-4).[24]

The chest wall impedance is not noticed during spontaneous breathing because the respiratory "pump" includes the chest wall. Chest wall mechanics can be measured only if complete relaxation of the respiratory muscles can be achieved[26]; however, during mechanical ventilation the respiratory muscles can be completely relaxed. As the lung is inflated by P_{AW}, the properties of the chest wall will determine the resulting change in P_{PL}. Under these circumstances, the increase in lung volume per unit increase in P_{PL} is the chest wall compliance. Values of chest wall compliance are about the same as that of the lung and are reduced with obesity, chest wall edema, pleural effusions, and diseases of the costovertebral joints.[26]

RESISTANCE OF THE RESPIRATORY SYSTEM

Airways

Resistance impedes airflow into (and out of) the lung. The major component of resistance is the resistance exerted by the airways (large and small), and a minor component is the sliding of lung and the chest wall tissue elements during inspiration (and expiration).[27] Resistance is overcome by (driving) pressure. In spontaneous breathing, driving pressure will be the P_{PL}; in positive pressure ventilation, the

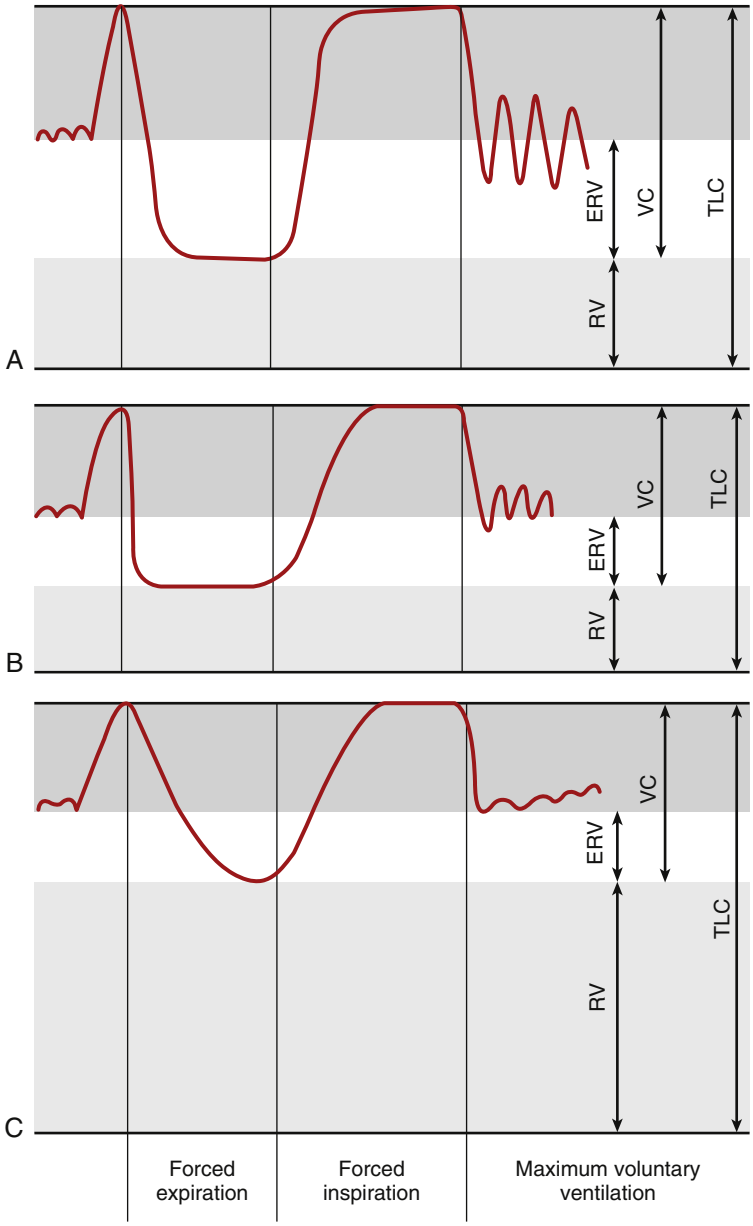


Figure 19-2. A, Ventilation and lung volumes in a healthy subject with normal lungs. **B,** A patient with restrictive lung disease. **C,** A patient with chronic obstructive pulmonary disease (COPD). In restrictive disease, the vital capacity (VC) is decreased and expiratory flow rate is increased (i.e., steeper than the normal slope of the forced expiratory curve). In COPD, the residual volume (RV) is increased, the VC is reduced, and forced expiration is slowed. *ERV,* Expiratory reserve volume; *TLC,* total lung capacity. *(From Hedenstierna G: Respiratory measurement. London, 1998, BMJ Books, 1998, p. 184; see also book review of* Respiratory Measurement in Thorax *53:1096, 1998.)*

driving pressure will be difference between the pressures applied to the endotracheal tube (P_{AW}; "source") and the alveolus (P_{ALV}; "destination"). Resistance (R) is calculated as driving pressure (ΔP) divided by the resultant gas flow (F):

$$R = {}^{\Delta P}/_{F}$$

The value of airway resistance is approximately 1 cm H_2O/L/sec, and is higher in obstructive lung disease (e.g., COPD, asthma); in severe asthma, it is elevated approximately tenfold.[28] The presence of an endotracheal tube adds a resistance of 5 (or 8) cm H_2O/L/min for a tube with internal diameter of size 8 (or 7) cm.[29] For any tube for which the airflow is laminar (smooth, streamlined), the resistance increases in direct proportion to the tube length and increases dramatically (to the fourth power) as the diameter of the tube is reduced.

Two factors explain why most (approximately 80%) of the impedance to gas flow occurs in the large airways.[27] First, as bronchi progressively branch, the resistances are arranged in parallel and the total cross-sectional area at the level of the terminal bronchioles adds up to almost tenfold that at the trachea. Second, in tubes that are large, irregular or branched, the flow is often turbulent, not laminar. When flow is laminar:

$$F_{(lam)} = {}^{\Delta P}/_{R}$$

In contrast, when flow is turbulent:

$$F_{(turb)} = {}^{\Delta P}/_{R^2}$$

Therefore, for a given radius, far more pressure is required to achieve comparable flow where flow is turbulent; thus, the effort required is greater and if prolonged or severe, respiratory failure is more likely.

Several factors can alter airflow resistance. First, resistance lessens as lung volume increases; this is intuitive as increasing volume (positive pressure or spontaneous breathing) stretches the diameter of the airways; because this is the key determinant of resistance, the resistance falls to a small extent. The opposite occurs with exhalation (Fig. 19-5). However, as lung volume approaches RV—as can happen during anesthesia—the airways are narrowed in parallel with the compressing lung tissue and the resistance rises

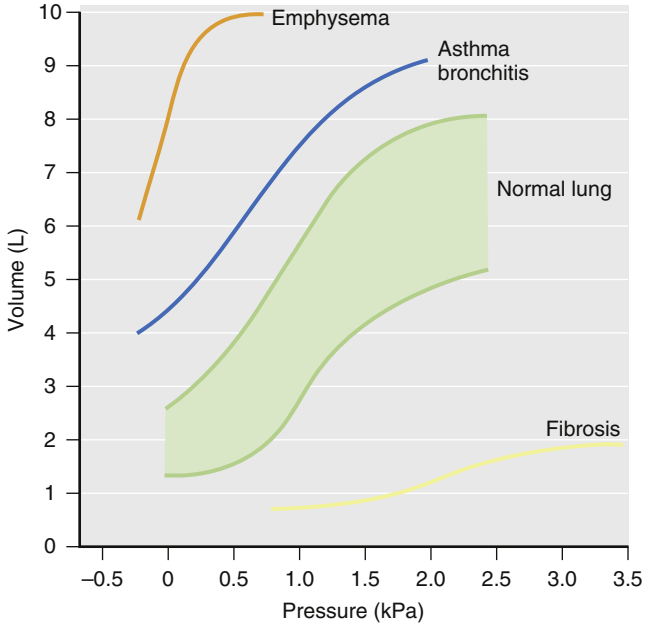


Figure 19-4. Pressure-volume curves of the lung in health and lung disease. In fibrosis, the slope of the curve is flatter, reflecting considerable increases in pressure variation and in respiratory work. In asthma or bronchitis, there is a parallel (upward) shift of the pressure-volume curve, indicating an increase in lung volume but no change in compliance. In emphysema, the slope of the curve is steeper, reflecting tissue loss and possible increased compliance. However, in emphysema, asthma, or bronchitis, the airway resistance is increased; this increases work of breathing and overrides any benefit from increased compliance. *(From Hedenstierna G: Respiratory measurement. London, 1998, BMJ Books, 1998, p. 184; see also book review of* Respiratory Measurement in Thorax *53:1096, 1998.)*

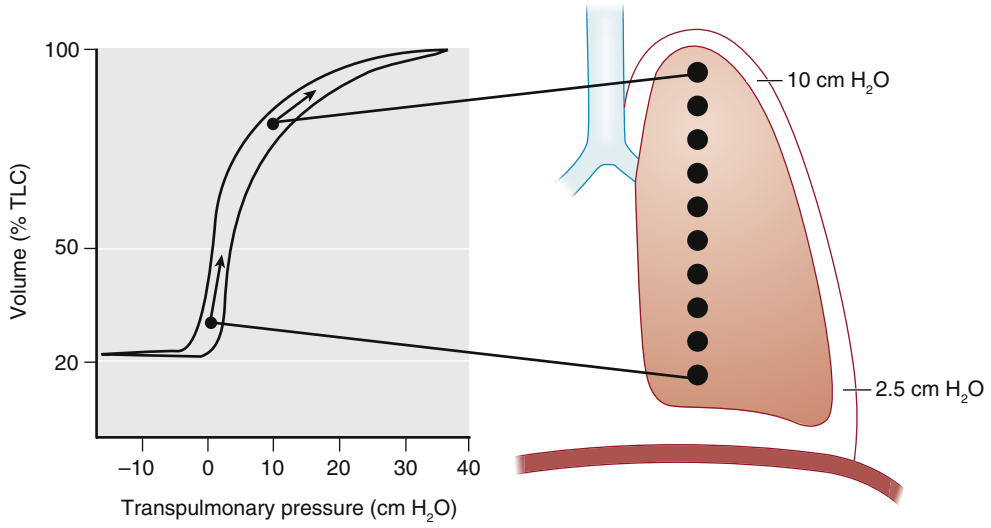


Figure 19-3. The pressure-volume relationships of the lung. The relationship is curvilinear (typical for an elastic structure). The pleural pressure is lower (more subatmospheric) in the upper regions. In the upright subject, the transpulmonary pressure ($P_{TP} = P_{AW} - P_{PL}$) is higher in apical than in basal regions. This results in different positions on the pressure volume curve of the upper (flatter, less compliant) versus lower (steeper, more compliant) lung regions. Thus, lower lung regions expand more (i.e., receive more ventilation) for a given increase in transpulmonary pressure than upper units. *TLC,* Total lung capacity.

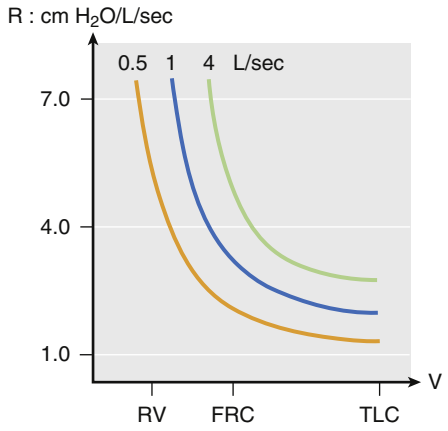


Figure 19-5. Schematic drawing of airflow resistance against lung volume at different flow rates. As lung volume falls, the resistance to flow increases; the steepness of this increase is far greater at lung volumes below functional residual capacity (FRC). In addition, higher airflow rates are associated with greater resistance. At extremely low lung volume, the resistance is comparable to values seen in moderate to severe asthma (6 to 8 cm $H_2O \times l^{-1} \times$ sec). *RV,* residual volume; *TLC,* total lung capacity.

exponentially. These effects are apparent with active or passive ventilation. Second, active ventilation has additional effects. Forced expiration can compress small airways (i.e., that do not contain cartilage).[27] In addition, forced expiration can cause turbulent flow in small airways in patients with COPD, precipitously dropping pressure in the lumen and thereby narrowing the bronchioles[30] and resulting in expiratory flow limitation and, after multiple breaths, eventual "dynamic hyperinflation."[31] Expiring against resistance (or pursed-lips breathing) is sometimes used by those with COPD to make breathing easier. This works by increasing expiratory resistance and slowing expiration. The slowed expiration reduces the pressure gradient driving expiration (i.e., pressure highest in the alveolus, lower toward the mouth). Therefore, the point along the airway tree at which pressure inside the airway has decreased to less than that outside the airway (equal to pleural pressure) is moved from smaller collapsible airways toward the mouth to noncollapsible, cartilaginous airways (Fig. 19-6); this prevents collapse of the smaller airways, which are vital for proper gas exchange.[32]

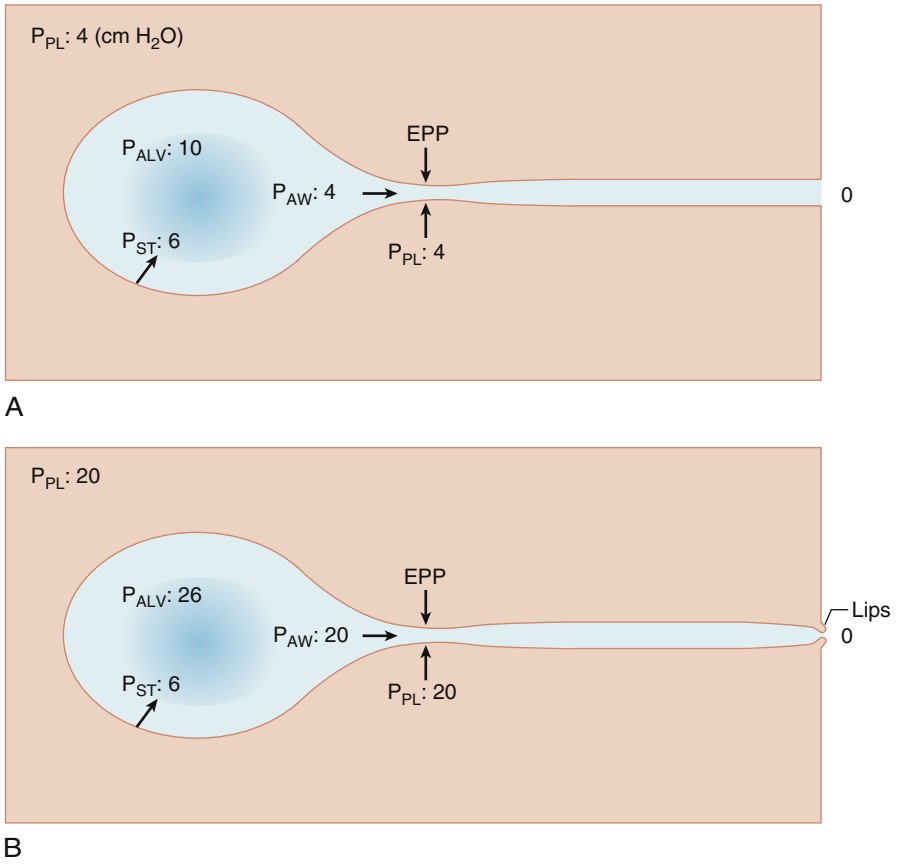


Figure 19-6. Schematic drawings of the equal pressure point (EPP) concept and dynamic compression of airways. **A,** Slightly forced expiration during otherwise normal conditions. With the application of some expiratory muscle effort, pleural pressure (P_pl) is positive, 4 cm H_2O (0.4 kPa). The elastic recoil pressure (Pst) of the alveoli (6 cm H_2O) and the pleural pressure add together to yield intraalveolar pressure (Palv) (10 cm H_2O). This causes expiratory flow. At some point downstream toward the airway opening, airway pressure (Paw) has dropped by 6 cm H_2O, so intraluminal pressure and pleural, extraluminal pressure are the same. This is the EPP. From this point to the mouth, intraluminal airway pressure is lower than the surrounding, extraluminal pressure and the airway may be compressed. **B,** An attempt to stabilize the airway by so-called "pursed-lip" breathing. The increased resistance to expiratory flow requires increased expiratory effort to maintain gas flow. Thus, pleural pressure is increased in comparison to the normal conditions (Ppl = 20 cm H_2O). Alveolar elastic recoil pressure (Pst) is the same as in the earlier condition, provided that lung volume is the same. If expiratory flow is of the same magnitude as during normal breathing, pressure along the airway falls to the same extent as during normal breathing. Thus the EPP will have the same location as during normal breathing, and no stabilization of the airway has been achieved. The two ways of moving the EPP toward the mouth and to less collapsible airways is by raising alveolar recoil pressure (Pst) by an increase in lung volume or by lowering the expiratory flow rate so that the pressure drop along the airway tree is slowed down.

The large airways (i.e., pharynx, larynx, and trachea) are outside the chest wall. During inspiration, the intrathoracic airways are exposed to extraluminal pressure (i.e., P_{PL}) that is less than the lumen pressure; in contrast, the extrathoracic airways are exposed to lumen pressure that is less than the extraluminal (i.e., atmospheric) pressure.[27] This feature, coupled with downward stretch induced by inspiration, narrows the large extrathoracic airways; in the presence of preexisting narrowing (e.g., thyroid enlargement or tumor, paralyzed vocal cord, epiglottitis), it can critically reduce the cross-sectional area.

Tissue

Although not intuitively obvious, resistance of the lung tissue is the applied pressure on tissue divided by the resulting velocity of tissue movement. There are various approaches to determining this in humans, including separately considering the pressure-volume (PV) characteristics using plethysmography (where the area of the PV curve corresponds to work against total pulmonary resistance) and esophageal pressure (where the area of the PV curve corresponds to work against "tissue" resistance).[33] Alternative approaches mathematically model the lung responses to varying respiratory frequencies.[34] Lung tissue resistance amounts to 20% of the total resistance to breathing; it can be increased threefold or fourfold in chronic lung disease[35] and is reduced by panting respirations.[36] Finally, in ARDS the chest wall resistance is increased (see Chapter 103).[37]

INERTIA OR ACCELERATION OF GAS AND TISSUE

A final component of the total impedance to breathing is inertance, or the pressure required to accelerate air and tissue during inspiration and expiration. This component is minor, however, and can hardly be measured under normal breathing, regardless of whether the lungs are healthy. Nonetheless, tissue inertia is large during rapid ventilation,[38] and it could be important during the rapid, shallow breathing characteristic of weaning failure or during high-frequency oscillation.

DISTRIBUTION OF INSPIRED GAS

Inspired gas is not evenly distributed throughout the lung; naturally, more gas enters those lung units that expand most during inspiration. In the resting lung, the basal (dependent) regions are less aerated than the apical (nondependent) regions; therefore, they have the capacity to undergo greater expansion. During inspiration, most gas goes to the basal units (dorsal, when supine; lower right lung when in the right lateral position).[39] This distribution is because of the compliance properties of the lung and the effects of position on the distribution of the distending pleural pressure (i.e., the P_{PL} gradient). These changes are not related to the properties of the inspired gas.

In the upright position, the P_{PL} is less negative at the base of the lung than at the apex. Because the P_A is uniform throughout the lung, the distending P_{TP} is greater at the apex; therefore, before inspiration commences, the apical lung is more open (and is less compliant) than the basal lung (Figs. 19-3 and 19-7). With inspiration, the contracting diaphragm lowers the P_{PL} by a comparable amount in all areas of the pleural surface (because of the fluid-like behavior of normal lung[39]) and distends the basal more than the apical regions (see Figs. 19-3 and 19-7). Because the pleural pressure gradient is oriented according to gravity, the distribution of ventilation changes with body position.

The P_{PL} gradient exists because lung density, gravity, and conformation of the lung to the shape of the thorax[40] result in crowding the basal lung tissue, making the local P_{PL} less negative in the basal regions. Because the density of normal lung is approximately 0.3, P_{PL} will become more positive by 0.3 cm H_2O for each downward vertical centimeter, and more so with injured or edematous lungs. Indeed, experimentally induced weightlessness decreases inhomogeneity in the distribution of ventilation[41], but does not eliminate it; therefore, nongravitational (e.g., tissue, airway) factors also play a role.[42]

Although the vertical height of the lung is the same in the prone and supine positions, the vertical gradient P_{PL} is less when prone,[43] perhaps because the mediastinum compresses the dependent lung when supine but rests on the sternum when prone.[44] A more even distribution of inspired gas—with improved oxygenation—in the prone position was predicted by Bryan in 1974[44]; this has been confirmed experimentally.[45,46]

During low-flow states (e.g., at rest) distribution is determined by differences in compliance and not by airway resistance. Because compliance at the start of inflation is less in the (already more aerated) apex, ventilation is preferentially directed to the base. In contrast, at high airflow, resistance (not compliance) is the key determinant of distribution; because the resistance is lower in upper, more expanded lung regions, increasing flow rate equalizes the distribution of ventilation, as shown by distribution of ^{133}Xe gas in humans[47,48] (Fig. 19-8). This is important during exercise or stress because greater amounts of the alveolar-capillary surface area will be used.

AIRWAY CLOSURE

Expiration causes the airways to narrow, and deep expiration can cause them to close. The volume remaining above RV where expiration below FRC closes some airways is termed *closing volume* (CV), and this volume added to the RV is termed the *closing capacity* (CC; i.e., the total capacity of the lung at which closing can occur).[49] Closure of airways during expiration is normal and is potentiated by increasing P_{PL}, especially with active expiration. When P_{PL} exceeds the P_{AW}, the airway—if collapsible—will tend to close, and this usually commences at the bases because the basal P_{PL} is greatest (see Fig. 19-7).

Three applications of this important principle are of key relevance to anesthesia. First, airway closure depends on age: in youth, the closure does not occur until expiration is at or near RV, whereas with older age, it occurs earlier in expiration (i.e., at higher lung volumes). This occurs because P_{PL} is on average more "positive"

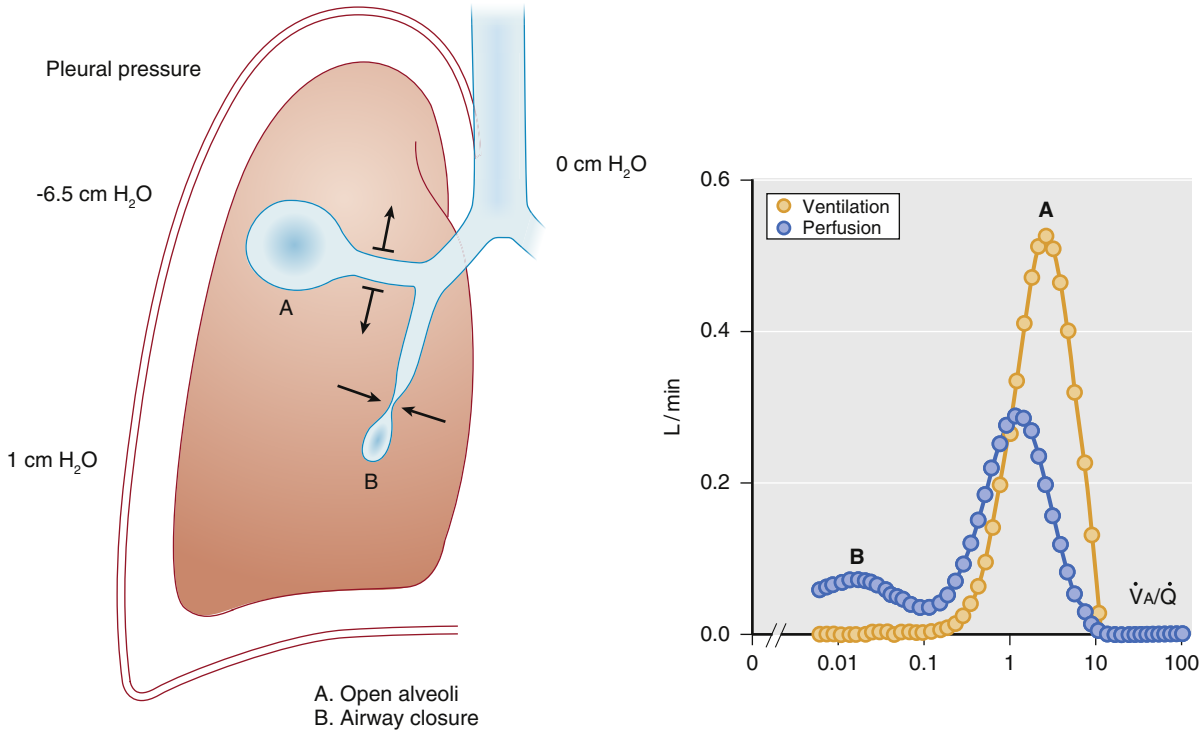


Figure 19-7. Schematic of regional alveolar and airway volume at an upper (*A*) and a lower (*B*) lung level (*left panel*). There is a vertical pleural pressure (P_{PL}) gradient between the uppermost and lowermost regions (–6.5 to 1 = –7.5 cm H_2O). Airway pressure (P_{AW}) is athmospheric, or 0 cm H_2O throughout; thus, in the upper regions, $P_{AW} > P_{PL}$ maintains airways open. In contrast, in the lower regions, $P_L > P_{AW}$ causes airway closure—potentially exacerbated by subsequent alveolar gas absorption behind the occluded airway. The *right panel* shows the distribution of ventilation and perfusion ratios from the multiple inert gas elimination technique. A "normal" mode of ventilation and blood flow (*A*) can be seen corresponding to the open and ventilated alveoli in the upper parts of the lung. In addition there is a range of low $\dot{V}_A/\dot{Q}$ ratios with more perfusion than ventilation (*B*). This pattern is compatible with intermittent airway closure during breathing.

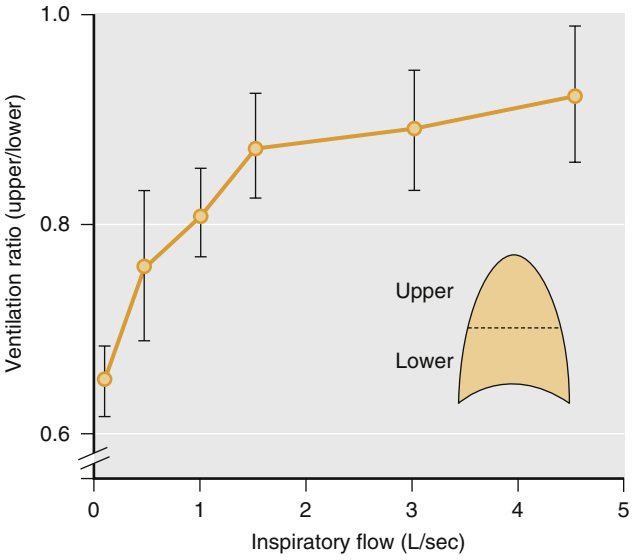


Figure 19-8. Distribution of ventilation to upper versus lower lung regions as inspiratory flow is altered. At low flow, the bulk of the airflow goes to the lower regions. At higher flow rates (e.g., during exercise) the distribution is more even, ensuring more efficient use of all alveolar-capillary membranes for gas transfer (provided that pulmonary blood flow shows a similar distribution pattern).

(i.e., atmospheric, equal to P_{AW}) as age increases. Closing can occur at or above FRC in individuals aged 65 to 70 years[50] such that dependent regions will undergo closure during normal expiration. This may be the major reason why oxygenation decreases with age (see Chapter 80). Second, in the supine position FRC is less than when upright, but CC is unchanged; therefore, exhalation of a usual V_T (from FRC) encroaches on CC in a supine 45 year old, and closure may be continuous in a supine 70 year old (Fig. 19-9). Finally, COPD increases the lung volume at which closure occurs, possibly exacerbated by airway edema and increased bronchial tone.[49]

DIFFUSION OF GAS

Gas moves in the large and medium-sized airways by bulk flow (i.e., convection) meaning that the gas molecules travel together at a given mean velocity according to a driving pressure gradient. Flow is through multiple generations of bronchi, and the net resistance falls with each division. After the fourteenth generation, airways merge with alveoli and participate in gas exchange (respiratory bronchioles). The cross-sectional area expands massively (trachea, 2.5 cm^2; twenty-third generation bronchi, 0.8 m^2; alveolar surface, 140 m^2),[51] resulting in a sharp drop in overall resistance. Because the number of gas molecules is constant, the velocity falls rapidly, which by the time the gas enters the alveoli is miniscule (0.001 mm/sec) and is

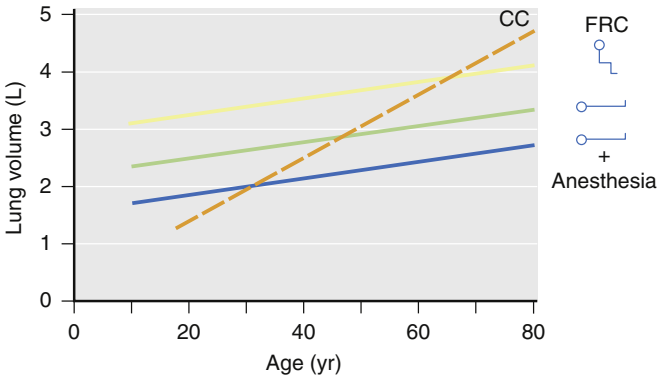


Figure 19-9. Resting functional residual capacity (FRC) and closing capacity (CC). FRC increases with age (because of loss of elastic tissue), and superimposed upon this is a step decrease in FRC with supine position (because of diaphragm elevation by abdominal contents), and a further decrease with anesthesia in the supine position. The CC is also increased with age, but far more steeply, causing airway closure above FRC in upright subjects (>65 yr) and in supine subjects (>45 yr). This relationship between CC and FRC explains decreasing oxygenation with age.

zero when it reaches the alveolar membrane. The velocity of the gas entering the alveolus is slower than the diffusion rates of O_2 and CO_2; therefore, diffusion—not convection—is necessary for transport in the distal airways and alveoli. Indeed, CO_2 is detectable at the mouth after just seconds of breath holding, because of rapid diffusion and because of cardiac oscillations (i.e., mixing).

Gas mixing is complete in the alveoli of a normal lung during normal breathing. However, if the alveolus expands (e.g., emphysema), the diffusion distance may be too great to allow complete mixing, potentially leaving a layer of CO_2-rich gas lining the alveolar membrane and a core of O_2-rich gas in the alveolus. This represents a "micro" version of inhomogeneous distribution of ventilation.[52]

PERFUSION

The pulmonary circulation differs from the systemic circulation: it operates at a five fold to tenfold lower pressure, and the vessels are shorter and wider. There are two important consequences of the particularly low vascular resistance. First, the downstream blood flow in the pulmonary capillaries is pulsatile, in contrast to the more constant systemic capillary flow.[53] Second, the capillary and alveolar walls are protected from exposure to high hydrostatic pressures; therefore, they can be sufficiently thin to optimize diffusion (i.e., exchange) of gas but not permit leakage of plasma or blood into the airspace. Whereas an abrupt increase in the pulmonary arterial (or venous) pressure can cause breaks in the capillaries,[54] slower increases (i.e., months to years) stimulate vascular remodeling.[55] This remodeling might protect against pulmonary edema[56] (and possibly against lung injury[57]), but diffusion will be impaired.

DISTRIBUTION OF LUNG BLOOD FLOW

Pulmonary blood flow depends on driving pressure and vascular resistance; these factors (and flow) are not homogenous

$$\text{Pulmonary vascular resistance (PVR)} = \frac{\bar{P}_{PA} - P_{LA}}{\dot{Q}_T}$$

(true only if lung is in zone III)

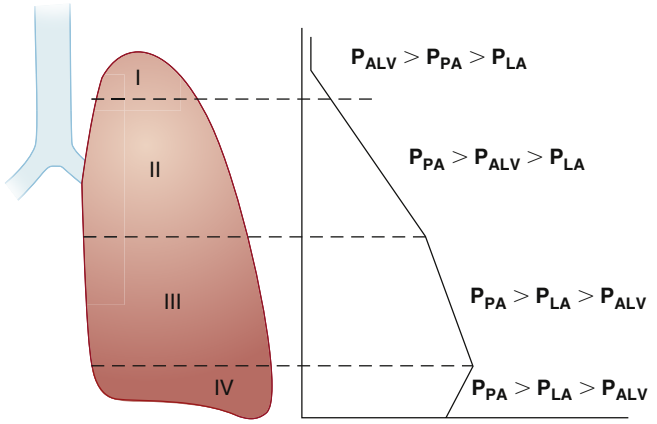


Figure 19-10. Vertical distribution of lung blood flow. The so-called zones I, II, III, and IV are indicated. In zone I there is no perfusion, only ventilation. In zone II, pulmonary artery pressure exceeds alveolar pressure which in turn exceeds venous pressure; the driving pressure is P_{PA}-P_A. In zone III, arterial and venous pressures both exceed alveolar pressure, and here the driving pressure is P_{PA}-P_{LA}. In the lung base, blood flow is decreased possibly because of increased interstitial pressure that compresses extra alveolar vessels. P_A, Alveolus pressure; P_{ALV}, positive intraalveolar pressure; P_{LA}, positive artery pressure; P_{PA}, pulmonary artery pressure; Q_T, cardiac output.

throughout the lung. The traditional thinking about lung perfusion emphasized the importance of gravity[58]; however, factors other than gravity are also important.

DISTRIBUTION OF BLOOD FLOW IN THE LUNG: THE EFFECT OF GRAVITY

Blood has weight and therefore blood pressure is affected by gravity. The height (base to apex) of an adult lung is approximately 25 cm; therefore, when a person is standing, the hydrostatic pressure at the base is 25 cm H_2O (i.e., approximately 18 mm Hg) higher than at the apex. The mean pulmonary arterial pressure is approximately 12 mm Hg at the level of the heart, and the pulmonary artery pressure at the lung apex can therefore approach zero. Thus, less blood flow will occur at the apex (versus the base), and in the setting of positive pressure ventilation, the apical alveoli can compress the surrounding capillaries and prevent any local blood flow.

Based on such gravitational distribution of pulmonary artery pressure, as well as the effect of alveolar expansion, West and colleagues[59] divided the lung into zones I to III (Fig. 19-10). This system is based on the principle that perfusion to an alveolus depends on the pressures in the pulmonary artery (P_{PA}), pulmonary vein (P_{PV}), and alveolus (P_{ALV}). In the apex (zone I), the key issue is that pulmonary arterial pressure is less than alveolar pressure; therefore, no perfusion occurs. Zone I conditions can exist during mechanical ventilation and be exacerbated by low P_{PA}. Whenever zone I conditions exist, the nonperfused alveoli constitute additional dead space (V_D).

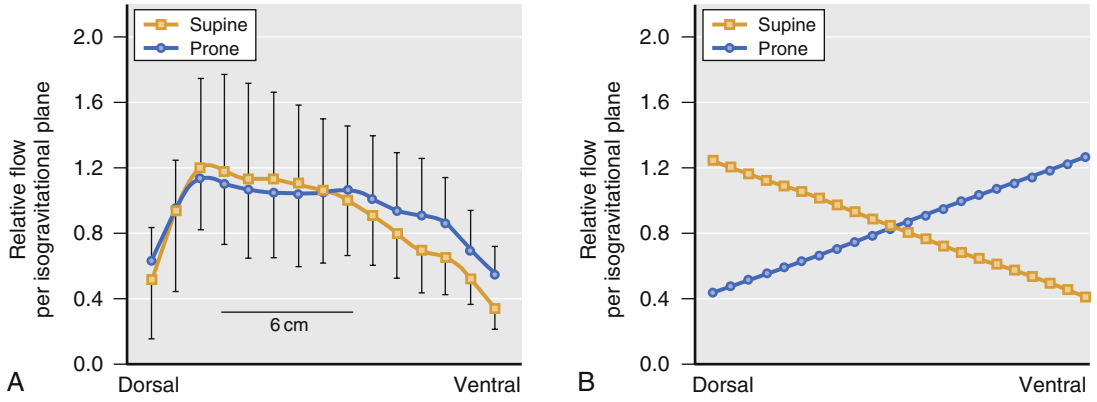


Figure 19-11. Distribution of blood flow (ventral, dorsal) in supine versus prone position. The distributions from ventral to dorsal are similar, irrespective of position, suggesting that that anatomic features (and not simply gravity) determine the distribution of flow. The magnitude of the variability in either the prone (or in the supine) position (i.e., nongravitational inhomogeneity) is far greater than the differences in distribution between the prone and the supine positions (i.e., gravitational inhomogeneity). *(From Glenny RW et al: Gravity is a minor determinant of pulmonary blood flow distribution,* J Appl Physiol *71:620-629, 1991.)*

Below the apex in zone II, P_{PV} is less than alveolar pressure, and the veins are collapsed except during flow, as in a "vascular waterfall." Although P_{ALV} is always greater than P_{PV}, perfusion occurs when P_{PA} exceeds P_{ALV} (i.e., intermittently, during systole). Below this zone is zone III, in which there are two important differences: P_{PA} and P_{PV} both always exceed P_{ALV}. As a result, there is perfusion throughout systole and diastole (and inspiration and expiration). Gravity results in equal increases in both P_{PA} and P_{PV} toward the lung base; therefore, gravity cannot affect flow throughout zone III by increasing the P_{PA} to P_{PV} pressure gradient alone. Nonetheless, it is possible that the greater weight of the blood nearer the base results in vessel dilatation, thereby lowering vascular resistance and increasing flow.[58] It was subsequently recognized that there is also a decrease in perfusion in the lung base, or zone IV, that is thought to occur because of the effects of gravity compressing the lung at the bases—and the blood vessels therein—and thereby increasing vascular resistance.[60]

Finally, additional evidence for the effect of gravity comes from volunteer experiments in which gravity was increased or abolished by altering the flight pattern of a jet aircraft.[61] In these experiments, zero gravity decreased cardiac oscillations of O_2 and CO_2 during a breath hold, indicating development of more homogeneous perfusion. In contrast, more recent experiments of exhaled gas analysis (on the Mir space station) reported that the heterogeneity of lung perfusion was reduced, but not eliminated, in the presence of microgravity, indicating that gravity contributes to the heterogeneity of blood flow distribution but does not explain it entirely.[62] While the precise role of gravity is disputed, it is likely to play a smaller role when supine versus when upright.

DISTRIBUTION OF BLOOD FLOW IN THE LUNG: INFLUENCE OF FACTORS NOT RELATED TO GRAVITY

Key experiments have reconsidered the effects of gravity. Blood flow measured in the same gravitational plane was less per unit of lung tissue at the apex than at the base.[63] In addition, microsphere assessment demonstrated significant variability within iso-gravitational planes, and lung height appeared to account for less than 10% of the distribution of flow in either the prone or supine positions.[64] In addition, inhomogeneity in the horizontal planes can exceed that in the vertical direction (Fig. 19-11).[65] Other studies have reported a preponderance of perfusion to the central lung (versus peripheral) tissue,[66] which can be reversed by the application of positive end-expiratory pressure (PEEP).[67] Although greater length of radial blood vessels was considered to explain this central-peripheral difference, others have suggested that it is not significant.[64] Finally, differences have been reported among lung regions in local vascular resistance.[68]

Fractal distribution of blood flow may be more important than the influence of gravity.[69] A fractal pattern of perfusion means that in any given region, there will be "spatial correlation" (similarity) of the blood flow between neighboring regions.

Although the methods to study lung perfusion are complex—and there is a spectrum of opinion[71,72], the aggregate data suggest that factors other than gravity contribute to the heterogeneity of the distribution of perfusion.

HYPOXIC PULMONARY VASOCONSTRICTION

Hypoxic pulmonary vasoconstriction is a compensatory mechanism that diverts blood flow away from hypoxic lung regions toward better oxygenated regions.[73] The major stimulus for HPV is low alveolar oxygen tension (P_AO_2), whether caused by hypoventilation or by breathing gas with a low PO_2, and is more potent when affecting a smaller lung region. The stimulus of hypoxic mixed venous blood is weaker.[74,75] Whereas in humans older volatile anesthetics were thought to inhibit HPV more than intravenously based anesthesia (in humans), modern volatile anesthetics, including sevoflurane[76] and desflurane,[77] have little effect. During intravenously based anesthesia, exposure of one lung to an Fio_2 of 1.0 and the contralateral to a hypoxic gas mixture (Fio_2, 0.12 to 0.05) reduced perfusion to the hypoxic lung to 30% of

the cardiac output.[78] Pulmonary hypertension, because of vascular remodeling owing to ongoing HPV, can develop in humans at high altitude[79] or in the presence of chronic hypoxemic lung disease.

CLINICAL ASSESSMENT OF LUNG FUNCTION

SPIROMETRY—TOTAL LUNG CAPACITY AND SUBDIVISIONS

The gas volume in the lung after a maximum inspiration is called the *total lung capacity* (TLC; usually 6 to 8 L). TLC can be increased in COPD either by overexpansion of alveoli or by destruction of the alveolar wall, resulting in loss of elastic tissue, as in emphysema (see Fig. 19-4).[80] In extreme cases, TLC can be increased to 10 to 12 L. In restrictive lung disease, TLC is reduced, reflecting the degree of fibrosis, and can be as low as 3 to 4 L (see Fig. 19-4).[80]

Following maximum expiratory effort, some air is left in the lung and constitutes the RV (about 2 L). However, usually no region develops collapse because distal airways (<2 mm) close before alveoli collapse,[81] trapping gas and preventing further alveolar emptying. In addition, there is a limit to how much the chest wall, rib cage, and diaphragm can be compressed. The importance of preventing collapse of lung tissue was presented earlier (see Fig. 19-6).

The maximum volume that can be inhaled and then exhaled is the vital capacity (VC; 4 to 6 L), and this is the difference between TLC and RV. VC is reduced in both restrictive and obstructive lung disease. In restriction, VC reduction reflects the loss of lung volume, such as from the constricting (i.e., shrinking) effects of fibrosis. In obstructive lung disease, long-term trapping of air increases the RV and can occur either by encroaching on (and reducing) the VC or in association with a (proportionally smaller) increase in FVC.[80]

Tidal volume (V_T, usually 0.5 L) is inspired from the resting lung volume reached at end-expiration (FRC, 2.0 L). With increased ventilation, as in exercise, V_T is increased and FRC may be reduced by approximately 0.5 L. However, in airway obstruction, exhalation is impeded such that inspiration commences before the usual resting lung volume is reached; thus end-expiratory volume is increased.[80] Such air trapping reduces the resistance to gas flow in the narrowed airways, but because the lung tissue is hyperinflated and mechanically disadvantaged, the work of breathing overall is increased (also see Chapter 103).

FRC increases with age as elastic lung tissue is lost; this reduces the lung recoil force countering the outward chest wall force, and lung assumes a higher volume (see Chapter 80). The rate of this aging process is accelerated in COPD because of the contributions of chronic air trapping and marked loss of elastic tissue.[19] FRC is reduced in fibrotic lung diseases,[80] sometimes to 1.5 L (see Fig. 19-4). Lung resection also reduces FRC, but the remaining lung will expand to fill the lung tissue void partially; this is called *compensatory emphysema* (see Chapter 66).

DIFFUSING CAPACITY (DL_{CO})—DIFFUSION ACROSS ALVEOLAR-CAPILLARY MEMBRANES

The diffusing capacity test integrates many phenomena that are central to respiratory physiology. The test and the factors affecting its interpretation are described here. In the lungs, O_2 and CO_2 diffuse passively: O_2 from alveolar gas into plasma and red cells, where it binds to hemoglobin, and CO_2 in the opposite direction, from plasma to the alveoli. The amount that can diffuse across a membrane in a given period is the diffusing capacity, and it is determined with the following equation:

$$Diffusing\ capacity = \frac{(SA \times \Delta P \times Sol)}{\left(h \times \sqrt{MW}\right)}$$

where SA is the surface area of the membrane exposed to gas, ΔP is the gradient of partial pressure between administered gas vs. blood tension, Sol is the solubility of the gas in the membrane, h is the thickness of the membrane, and MW is the molecular weight of the gas.

Assessment of diffusing capacity (sometimes called *transfer factor*) uses CO as the test gas; it is inhaled at a small concentration (0.3%) to TLC just after a maximal expiration, filling the lung as much as possible with the dilute CO. The breath is held and then deeply exhaled to RV. The difference between the quantity of CO exhaled versus inhaled will therefore either be taken up by the perfusing blood (i.e., Hb) or remain in the lung (RV). The latter can be determined if the CO is coadministered with an insoluble gas (e.g., He) that remains in the lung.

Surface Area

The surface area is taken as the area that is capable of exchanging gas on the alveolar and the capillary sides; thus, it assumes a ventilated and perfused lung (i.e., not dead space). It will be lower in small lungs, lung fibrosis (restriction), after lung resection, or in cases of lung tissue destruction, such as emphysema.

Membrane Thickness

Thicker membranes reduce the CO transfer because the longer diffusion distance lowers the diffusion capacity, and the solubility of O_2 (and CO_2) is lower in fibrotic tissue than in plasma. Differentiating between effects of the volume of capillary blood and the membrane thickness can be difficult, but because oxygen and CO compete for binding to hemoglobin, distinguishing between these issues may be possible by measuring CO transfer with altered Fio_2 (see review by Hughes and colleagues[82,83]).

Pressure Gradient

The larger the O_2 or CO_2 tension difference (ΔP) between the gas phase (alveolus) and the plasma (capillary), the greater the rate of diffusion. The mixed venous blood entering the pulmonary capillary has a PO_2 of 40 mm Hg (5.3 kPa), and alveolar PO_2 is approximately 100 mm Hg (13.3 kPa); therefore, the driving pressure (ΔP) is 60 mm Hg (8 kPa).

When blood flows through the capillary, it takes up oxygen and delivers CO_2, but because oxygen pressure

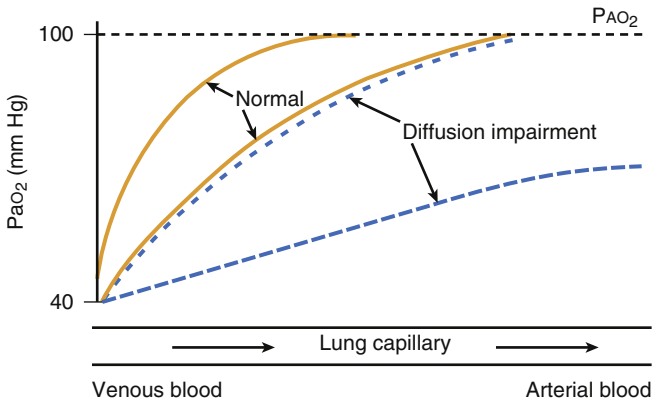


Figure 19-12. Schematic of oxygenation of pulmonary capillary blood. In a healthy subject, there is a rapid equilibration (<30% capillary length) of the oxygen tension in capillary blood with that in alveolar gas; however, during exercise, the flow rate is greater (i.e., transit time shorter) and most of the capillary distance is used before equilibration is reached. This effect can be offset by distention and recruitment of pulmonary capillaries. If diffusion is impaired, equilibration takes longer, and it might not occur with exercise.

builds up in capillary blood, the diffusion rate slows down and becomes zero when pressure is equilibrated across the alveolar-capillary wall. At rest, equilibrium is usually reached within 25% to 30% of the capillary length, and almost no gas transfer occurs in the remaining capillary (Fig. 19-12). However, during exercise or stress (i.e., high cardiac output), blood flow through the capillary is faster, and a longer capillary distance is required before equilibrium is reached. Thickened alveolar-capillary membranes will also prolong the equilibration process and, if severe, can prevent equilibration occurring and increasing the propensity to hypoxemia. If the mixed venous PO_2 ($P_{mv}O_2$) is lower than normal, the driving pressure increases and partially compensates towards achieving equilibrium with alveolar O_2. The driving pressure is expressed:

$$\Delta P = (PaO_2 - P_{mv}O_2)\ mm\ Hg$$

Most of the oxygen that dissolves in plasma diffuses into the red cell and binds to hemoglobin; therefore, 1 L of blood (Hb 150 g/L) with a saturation of 98%—normal in arterial blood—carries 200 mL of Hb-bound O_2, compared with 3 mL that is dissolved (PaO_2 100 mm Hg). The Hb-bound oxygen creates no pressure in plasma, which is important because it allows much more oxygen to diffuse over the membranes before a pressure equilibration is reached. Anemia (or prior CO exposure) reduces—and polycythemia increases—diffusion capacity.

Molecular Weight and Solubility

The rate of diffusion of a gas is inversely related to the square root of its molecular weight (MW); the larger the molecule, the slower the diffusion. O_2 is a light gas (MW 32) and CO_2 is heavier (MW 44). However, diffusion is also directly proportional to solubility in tissue, and CO_2 is almost thirtyfold times more soluble than O_2. The aggregate effect is that CO_2 diffuses about twentyfold faster than O_2[84]; therefore, there is no lung disease compatible with life that measurably impairs CO_2 diffusion.

INTRAOPERATIVE RESPIRATORY EVENTS

RESPIRATORY FUNCTION DURING ANESTHESIA

Anesthesia impairs pulmonary function, whether the patient is breathing spontaneously or is receiving mechanical ventilation. Impaired oxygenation of blood occurs in most subjects who are anesthetized,[85] and this is why supplemental O_2 (Fio_2 usually 0.3 to 0.5) is almost invariably used. Mild to moderate hypoxemia (SaO_2, 85% to 90%) is common and lasts from seconds to minutes; sometimes it is severe, and approximately 20% of patients may suffer from SaO_2 less than 81% for up to 5 minutes.[86] Indeed, greater than 50% of claims in anesthesia-related deaths relate to hypoxemia during anesthesia.[2] Beyond the operating room, the alterations in lung function acquired during anesthesia persist: clinically significant pulmonary complications can be seen in 1% to 2% patients after minor surgery, and in up to 20% of patients after more major upper abdominal or thoracic surgery.[87] Such consequences of anesthesia place prime importance on ascertaining the causes of perioperative respiratory dysfunction and the clinical approaches to treatment.

In this section, w describe the effects of anesthesia and mechanical ventilation on lung function. The arrangement of this section parallels the sequence of events involved in oxygenating the blood and removing CO_2. Thus, the first phenomenon that might be seen with anesthesia is loss of muscle tone with a subsequent change in the balance between outward forces (i.e., respiratory muscles) and inward forces (i.e., elastic tissue in the lung) leading to a fall in FRC. This causes or is paralleled by an increase in the elastic behavior of the lung (reduced compliance) and an increase in respiratory resistance. The decrease in FRC affects the patency of lung tissue with the formation of atelectasis (made worse with the use of high concentrations of inspired oxygen) and airway closure. This alters the distribution of ventilation and matching of ventilation and blood flow and impedes oxygenation of blood and removal of carbon dioxide.

LUNG VOLUME AND RESPIRATORY MECHANICS DURING ANESTHESIA

Lung Volume

Resting lung volume (i.e., FRC), is reduced by almost 1 L by moving from upright to supine position; induction of anesthesia further decreases the FRC by approximately 0.5 L.[88] This reduces the FRC from approximately 3.5 to 2 L, a value close to RV. General anesthesia causes a fall in FRC (approximately 20%), whether breathing is controlled or spontaneous[89,90] and whether the anesthetic is inhalational or intravenous[91]; this is a major contributor to lowered oxygenation (discussed later). Muscle paralysis in the context of general anesthesia does not cause additional reduction in FRC.

The anatomic basis of the FRC reduction is not well understood. A landmark experiment on three volunteers using two-dimensional tomography suggested that a cephalad shift of the diaphragm, induced by anesthesia

and paralysis, was responsible.[92] Recent studies using CT scanning also suggest cephalad diaphragm shift, as well as a decrease in the transverse chest area.[91,93] However, other data suggest little role for the diaphragm, with possible caudal (not cephalad) shift of its anterior aspect.[94] Simple CT suggests a cranial displacement except in severe obstructive lung disease. Although the anatomic components of reduced FRC are debatable, the mechanism appears to be related to loss of respiratory muscle tone. FRC is maintained by a balance of the forces inward (lung recoil) versus forces outward (chest wall recoil, chest wall muscles, diaphragm). For example, maintenance of muscle tone using ketamine as the anesthetic does not reduce FRC.[91] Because patients are usually supine, the FRC will already have been reduced, and in elderly patients, this is particularly the case; in this context, the effects of anesthesia are more marked (see Fig. 19-9). As can be seen in the figure, FRC decreases with age assuming that weight does not change.

Compliance and Resistance of the Respiratory System

Static compliance of the total respiratory system (lungs and chest wall) is reduced on average from 95 to 60 mL/cm H_2O during anesthesia.[95] Most studies of lung compliance during anesthesia indicate a decrease compared with the awake state, and pooled data from several studies suggest that anesthesia is associated with a reduction in mean static compliance from almost 190 to approximately 150 mL/cm H_2O.[95] Data on changes in respiratory resistance are less clear. Although most studies suggest that anesthesia increases respiratory resistance, especially during mechanical ventilation,[95] no studies have corrected for lung volume and flow rates (both affect resistance considerably), and it is possible that changes in resistance occur merely because of volume (i.e., FRC) loss (Fig. 19-13).

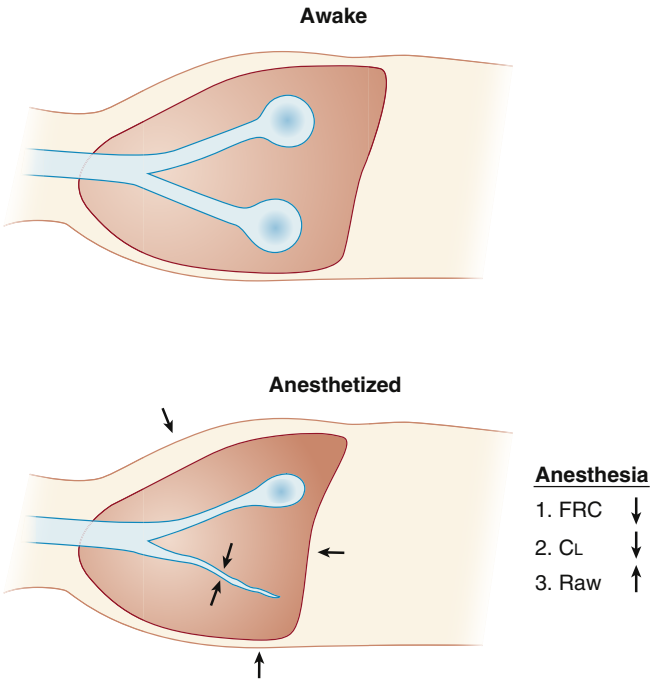


Figure 19-13. Anesthesia induces cranial shift of the diaphragm and a decrease of transverse diameter of the thorax. These effects contribute to a lowered functional residual capacity (FRC). The decreased ventilated volume (atelectasis and airway closure) can contribute to reduced compliance (C_L). Decreased airway dimensions by the lowered FRC can contribute to increased airway resistance (Raw).

ATELECTASIS AND AIRWAY CLOSURE DURING ANESTHESIA

The classic article by Bendixen and colleagues[96] proposed "a concept of atelectasis" as a cause of impaired oxygenation and reduced respiratory compliance during anesthesia.[96] That study described a progressive decrease in compliance that paralleled decreases in oxygenation in both anesthetized humans and experimental animals, which was interpreted as progressive of atelectasis. However, others noticed an abrupt decrease in compliance and PaO_2 during induction of anesthesia, and yet atelectasis could not be shown on conventional chest radiography.

Since then, CT scanning has improved our knowledge of the nature of anesthesia-induced atelectasis, and the technique reveals prompt development of densities in the dependent regions of both lungs during anesthesia (data up to 1990 reviewed by Moller and associates[86,97]). Morphologic studies of these densities in various animals supported the diagnosis of atelectasis. An example of atelectasis as seen on a CT scan is shown in Figure 19-14.

Atelectasis develops in approximately 90% of patients who are anesthetized, but it is unrelated to the choice of

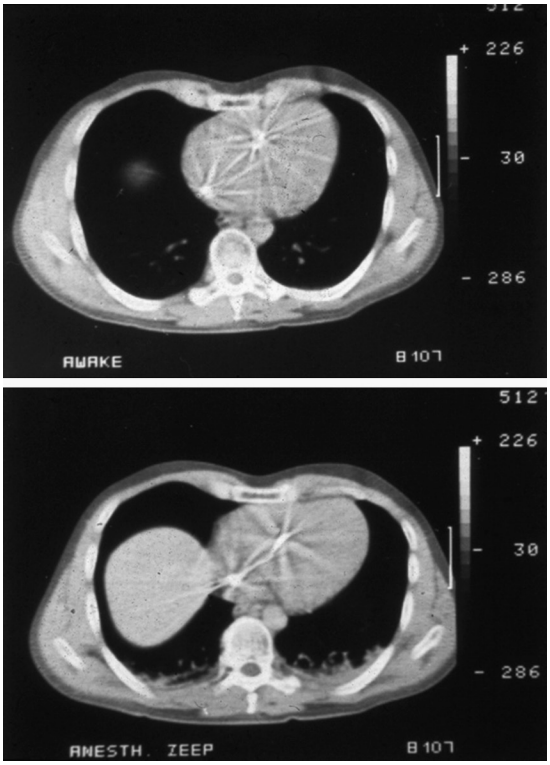


Figure 19-14. Computed tomography with transverse exposures of the chest when the subject is awake (upper panel) and anesthetized (lower panel). In the awake condition, the lung is well aerated (radiations from a pulmonary artery catheter are seen in the heart). During anesthesia, atelectasis has developed in the dependent regions (grey/white irregular areas). The large grey/white area in the middle of the right lung field is caused by a cranial shift of the diaphragm and the underlying liver.

anesthesia.[98] It is seen during spontaneous breathing and after muscle paralysis and when intravenous or inhaled anesthetics are used.[91] The atelectatic area near the diaphragm is 5% to 6% of the total lung area, but can easily exceed 20%. The amount of lung tissue that is collapsed is larger, because the atelectatic area consists mostly of lung tissue, whereas normal aerated lung consists of 20% to 40% tissue (the rest being air). Thus, 15% to 20% of the lung is atelectatic during uneventful anesthesia, before surgery has commenced; it decreases toward the apex, which usually remains aerated (Fig. 19-15). However, this degree of atelectasis is larger (upwards of 50% of lung volume) after thoracic surgery or cardiopulmonary bypass, and can last for several hours.[99] Abdominal surgery adds little to the atelectasis, but after such surgery it can persist for several days.[100]

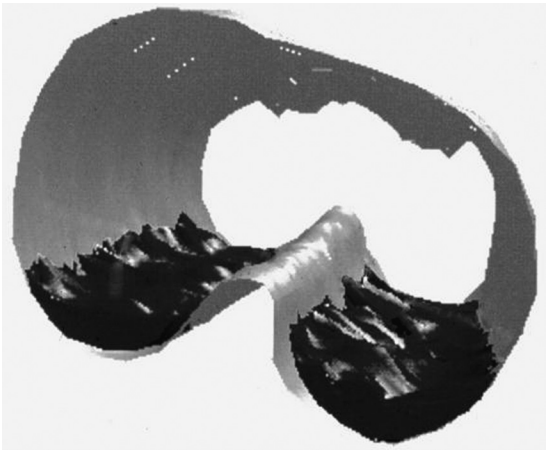


Figure 19-15. A three-dimensional reconstruction of the thorax of an anesthetized patient with atelectasis in the dependent regions of both lungs. There is a slight decrease in the degree of atelectasis toward the apex (distal in this image). *(Data from Reber A, Nylund U, Hedenstierna G: Position and shape of the diaphragm: implications for atelectasis formation.* Anaesthesia *53:1054-1061, 1998.)*

Atelectasis is an important cause of hypoxemia: there is a strong and significant correlation between the degree of atelectasis and the size of the pulmonary shunt ($R = 0.81$), where atelectasis is expressed as the percentage of lung area just above the diaphragm on CT scan and shunt is expressed as the percentage of cardiac output using the multiple inert gas elimination technique (MIGET).[98] The site of the increased shunt has been colocalized to the areas of atelectasis, using a technique that combines CT scanning and single photon emission computed tomography (SPECT; Fig. 19-16).[101] In addition to shunt, atelectasis may form a focus of infection and can certainly contribute to pulmonary complications.[102]

Aside from anesthesia (and the type of surgery), it is difficult to predict the development of atelectasis. Although obesity is associated with greater degrees of atelectasis, there is only poor correlation between the magnitude of the body weight (or body mass index [BMI]) and the extent of atelectasis.[89,91] Moreover, neither age[98] nor the presence of COPD[103] predicts the development or extent of atelectasis. In COPD, it may be that airway closure precedes (and therefore prevents) alveolar closure. Alternatively, the greater loss of lung (elastic recoil) versus chest wall tissue may serve to protect against atelectasis.

PREVENTION OF ATELECTASIS DURING ANESTHESIA

Several interventions can help prevent atelectasis[97] or even reopen collapsed tissue, as discussed in the following paragraphs.

Positive End-Expiratory Pressure

The application of PEEP (10 cm H_2O) has been repeatedly demonstrated to reexpand atelectasis partially

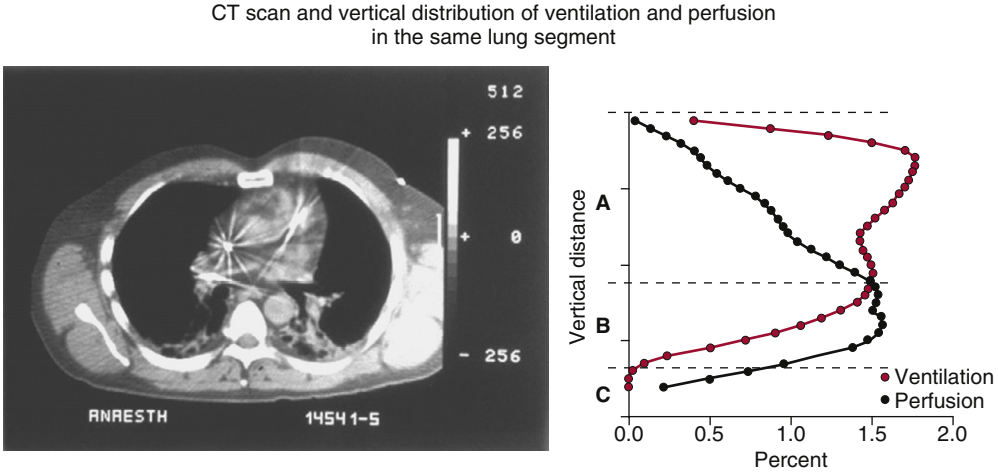


Figure 19-16. Atelectasis and distribution of ventilation and blood flow. The *left panel* is a cross-sectional slice of a computed tomographic image of the chest of an anesthetized patient, illustrating atelectasis in the basal (dorsal) regions. The *right panel* illustrates the distribution of ventilation and perfusion throughout that slice. The bulk of the ventilation is to the upper lung region (zone *A*), in contrast to the awake subject without atelectasis, and it exceeds the level of local perfusion; this results in wasted ventilation (i.e., deadspace) in the upper regions. In the lower region (zone *B*), the ventilation is less (probably because of intermittent airway closure) and is exceeded by the local perfusion, resulting in areas of low $\dot{V}_A/\dot{Q}$, causing hypoxemia. In the next lowest region (zone *C*), there is complete cessation of ventilation because of atelectasis, but some perfusion exists and causes a shunt. The farther from the top of the lung, the higher the perfusion; however, in the lowermost regions perfusion decreases (see text). *(Data from Hedenstierna G: Alveolar collapse and closure of airways: regular effects of anaesthesia,* Clin Physiol Funct Imaging *23:123-129, 2003.)*

(Fig. 19-17). Some atelectasis may persist and might require higher PEEP and inspiratory airway pressure.[91] The application of larger levels of PEEP can have complex effects. Reversal of hypoxemia is not proportionally associated with applied PEEP, and a threshold exists in many cases. In addition, SaO_2 may decrease during the application of increased PEEP for two reasons. First, the increased P_{PL} owing to the PEEP can impair venous return, especially in the presence of hypovolemia, lowering the cardiac output and DO_2 and thereby reducing mixed venous O_2 content ($C_{\bar{v}}O_2$). In the presence of an intrapulmonary shunt, such as with atelectasis, the mixed venous blood is shunted directly into pulmonary venous blood causing arterial desaturation. Second, increased PEEP can cause redistribution of blood flow away from the aerated, expanded regions (distended by PEEP) toward atelectatic areas (not distended by PEEP; Fig. 19-18).[104] In this context, persisting atelectasis in dependent lung receives a larger proportion of the total pulmonary blood flow than without PEEP.[59] Finally, anesthesia-induced atelectasis rapidly reemerges after discontinuation of PEEP.[91] Indeed, Hewlett and coworkers[105] in 1974 cautioned against "indiscriminate use of PEEP in routine anesthesia."

Recruitment Maneuvers

A sigh maneuver, or a large V_T, has been suggested for reversing atelectasis[10]; however, atelectasis is not uniformly reduced by a V_T increase or sigh up to P_{AW} of 20 cm H_2O.[106] Instead, a P_{AW} of 30 cm H_2O is required for initial opening, and 40 cm H_2O for more complete reversal (Fig. 19-19). In the presence of normal lungs, such inflation is equivalent to a VC and can therefore be called a *VC maneuver* (albeit achieved with positive P_{AW}). In addition, a significant hemodynamic effect is likely if the VC maneuver is sustained; in fact, inflation with a P_{AW} of 40 cm H_2O for 7 to 8 seconds appears to successfully open almost all anesthesia-induced atelectasis.[107]

Minimizing Gas Resorption

Although recruitment of anesthesia-induced atelectasis is completely possible with either PEEP or a VC maneuver, continuous application of some level of PEEP is required to prevent rapid recurrence of the atelectasis.[108] However, N_2—an insoluble gas that is not absorbed into the blood—can "splint" the alveolus if the alveolus is already opened. As a result, in anesthetized patients, a VC maneuver followed by ventilation with a gas mixture containing 60%

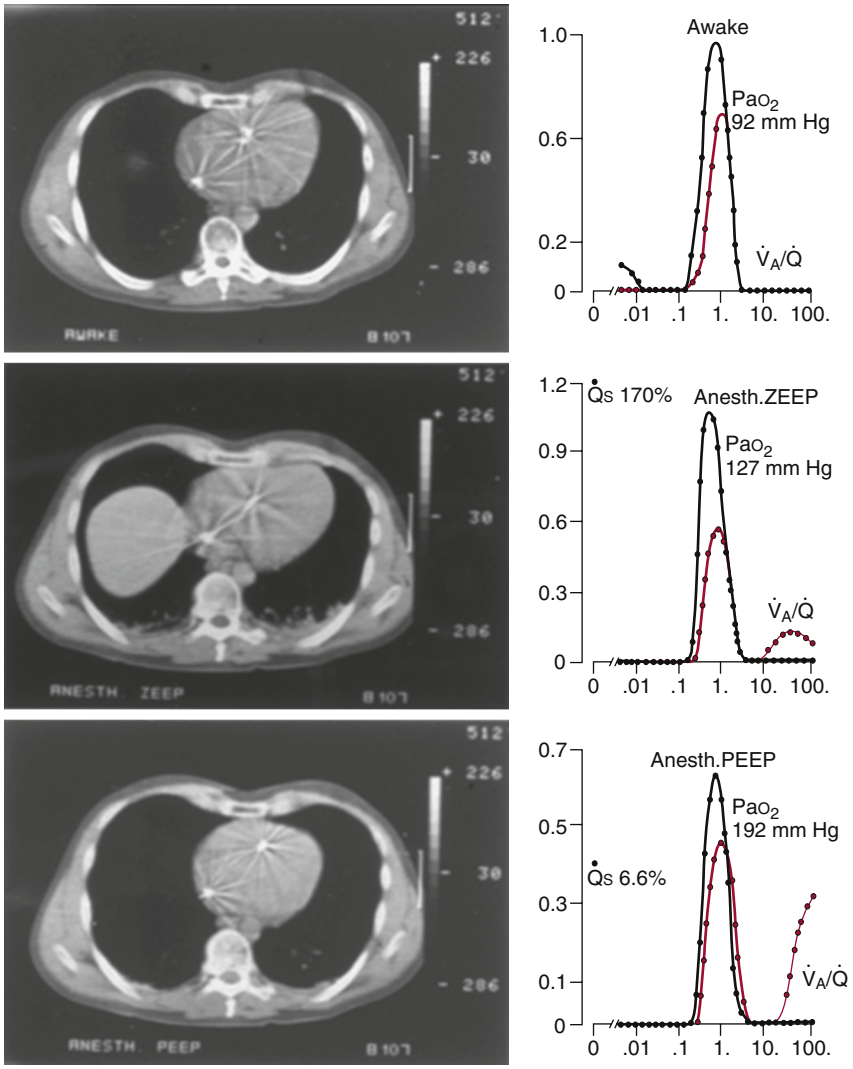


Figure 19-17. Computed tomographic scans and $\dot{V}_A/\dot{Q}$ distributions in the lung of a healthy, awake subject during anesthesia (zero positive end-expiratory pressure [ZEEP]) and during anesthesia (10 cm H_2O positive end-expiratory pressure [PEEP]). In the awake state, there is no atelectasis and the corresponding minor low $\dot{V}_A/\dot{Q}$ distribution (*left side* of plot) may reflect intermittent airway closure. During anesthesia with ZEEP, atelectasis is apparent in the lung bases (and the diaphragm has been pushed cranially). The low $\dot{V}_A/\dot{Q}$ has been replaced by atelectasis and large shunt; in addition, a small "high" $\dot{V}_A/\dot{Q}$ mode (right side of plot) may reflect alveolar dead space in upper lung regions. With the addition of PEEP during anesthesia, the collapsed lung tissue has been recruited and the shunt has been reduced considerably. Moreover, the "high" $\dot{V}_A/\dot{Q}$ mode (*right side* of plot) has significantly increased; this may reflect additional inflation of nonperfused upper lung.

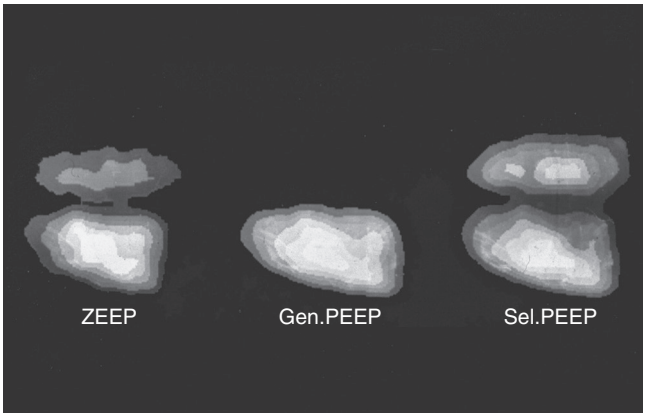


Figure 19-18. Gamma camera images of lung blood flow in an anesthetized subject in the lateral position. During mechanical ventilation with zero end-expiratory pressure (ZEEP), perfusion is predominantly (60% to 70% of cardiac output) to the lower lung. Applying PEEP (10 cm H_2O) to both lungs forces more perfusion to the lower lung, leaving almost no perfusion to the upper lung (i.e., major increase in V_D). In contrast, selective application of PEEP to the lower lung causes redistribution of perfusion to the upper lung. Of course, the image presented is perfused tissue (not total anatomic lung tissue; in the right lateral position the upper-right lung would be larger). *(From Hedenstierna G et al: Ventilation and perfusion of each lung during differential ventilation with selective PEEP,* Anesthesiology *61:369-376, 1984.)*

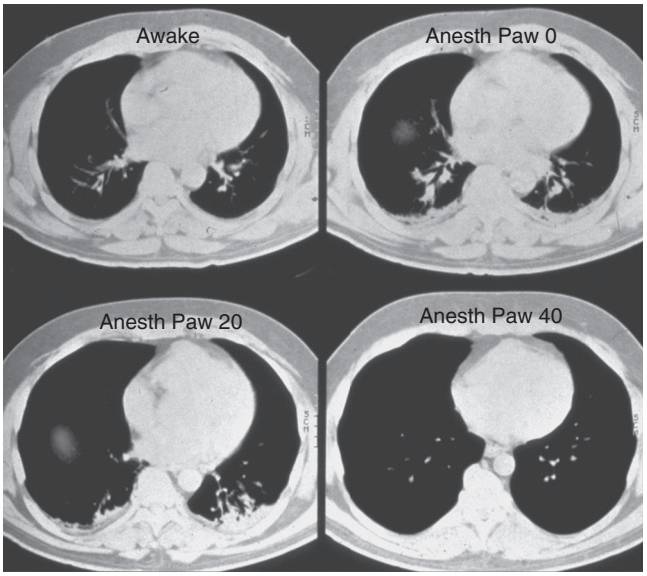


Figure 19-19. Computed tomographic (CT) scans during awake and anesthetized states with altered airway pressure (P_{AW}). The CT scan in the awake subject (*upper left panel*) shows normal vasculature and no atelectasis. During anesthesia (P_{AW}, 0 cm H_2O; *upper right panel*), bilateral basal atelectasis is seen; the PAW is increased in increments (20 cm H_2O shown), but the atelectasis is not reversed until a P_{AW} of 40 cm H_2O is applied (*lower right panel*). Thus, a vital capacity maneuver was required to open the lung. *(From Rothen HU et al: Re-expansion of atelectasis during general anaesthesia: a computed tomography study,* Br J Anaesth *71:788-795, 1993.)*

N_2 (40% O_2) reduced the propensity for reaccumulation of atelectasis with only 20% reappearing 40 minutes after recruitment.[108]

The same principles apply in the practice of preoxygenation of patients during induction of anesthesia.

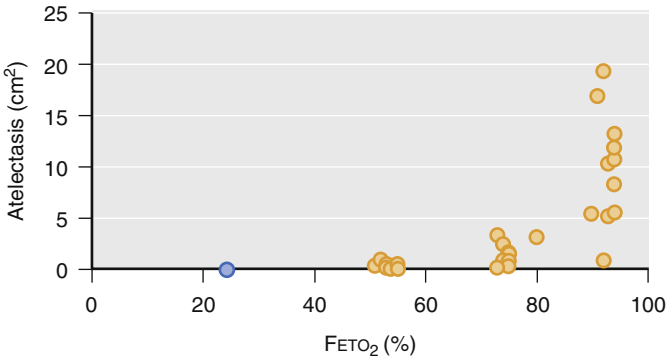


Figure 19-20. Atelectasis formation in anesthetized subjects following preoxygenation with different inspired oxygen concentrations. Increasing the Fio_2 during preoxygenation increases the propensity to subsequent atelectasis (closed symbols), although there is much variability. The open circle at around an expired oxygen concentration (FeO_2) of 25% represents data from anesthesia being induced while breathing 30% O_2. *(From Rothen HU et al: Prevention of atelectasis during general anaesthesia,* Lancet *345:1387-1391, 1995.)*

Here, the aim is to prevent O_2 desaturation (i.e., gain an O_2 safety margin) during induction before the airway has been secured when the anesthesiologist can better manage ventilation and oxygenation. Traditionally, the application of Fio_2 1.0 has been used. Although the SaO_2 is usually well maintained with this approach, atelectasis inevitably forms. The use of 30% versus 100% O_2 during induction was demonstrated in a clinical study to eliminate the formation of atelectasis.[109] Later, a comparison of breathing 100%, 80%, and 60% O_2 during induction demonstrated ubiquitous atelectasis with 100%, less with 80%, and even less with 60% O_2 (Fig. 19-20); however, the trade-off for less atelectasis was a shorter safety margin before occurrence of O_2 desaturation.[110]

An alternative approach may be continuous positive airway pressure (CPAP). Application of CPAP 10 cm H_2O permitted the use of 100% inspired O_2 without formation of significant degrees of atelectasis.[111] This might provide an ideal combination of minimal risk of either O_2 desaturation or atelectasis, but it has not been repeatedly verified.

Maintenance of Muscle Tone

Because loss of muscle tone in the diaphragm or chest wall appears to increase the risk of atelectasis, techniques that preserve muscle tone may have advantages. Intravenous ketamine does not impair muscle tone and is the only individual anesthetic that does not cause atelectasis. If neuromuscular blockade is added, atelectasis occurs as with other anesthetics.[91] Ketamine is an extremely useful agent in special circumstances, but it has significant challenges in routine cases.

An experimental approach is restoration of respiratory muscle tone by diaphragm pacing. This approach is achieved with phrenic nerve stimulation, and it can modestly reduce the degree of atelectasis; however, the effect is minor and the approach complicated.[112]

Atelectasis Following Surgery

Hypoxemia is common after anesthesia and surgery. It is enhanced by breathing oxygen before induction of

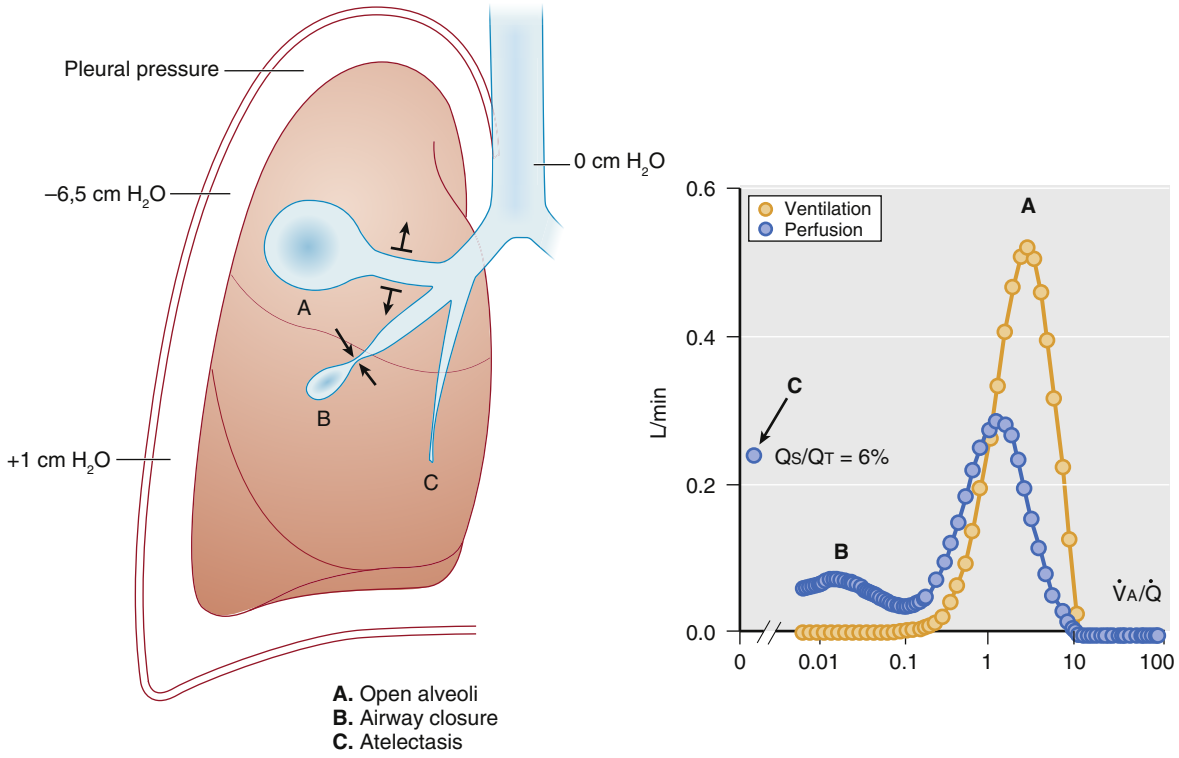


Figure 19-21. A three-compartment model of ventilation and perfusion during anesthesia. In the upper regions, the alveoli and airways are open (*left panel, A*). In the middle region, the airways are intermittently closed (*B*), and atelectasis is present in the lower region (*C*). The corresponding ventilation-perfusion distribution (multiple inert gas elimination technique) is illustrated in the *right panel*. Mode *A* reflects good ventilation and perfusion, whereas mode *B* reflects intermittent airway closure. In addition, there is a shunt in the atelectatic region (mode *C*).

anesthesia and suctioning of the airway (negative pressure) before extubation of the trachea. In addition, splinting and inhibition of coughing associated with pain can cause atelectasis postoperatively. Several approaches have been tried to address such atelectasis-associated hypoxemia following surgery. Administration of 100% O_2 coupled with a VC maneuver is not effective; this is probably because while the VC maneuver recruits lung, alveolar opening is not maintained (in fact closure is encouraged by the N_2-free O_2).[113] However, a VC maneuver followed by a lower O_2 concentration (40% O_2 in N_2) can maintain an open lung until the end of anesthesia.[107] Oxygenation is sustained for a longer period following ventilation with 50% O_2 in air (i.e., N_2) compared with 100%, following cardiopulmonary bypass.[114] Finally, treatment of postoperative hypoxemia, considered to be due to atelectasis, is associated with better outcomes when CPAP is used instead of 100% O_2.[115]

AIRWAY CLOSURE

Intermittent airway closure reduces ventilation of the affected alveoli. Such lung regions can become regions of low $\dot{V}_A/\dot{Q}$ if perfusion is maintained or is not reduced to the same degree as ventilation. The propensity to airway closure increases with age[49] (see Fig. 19-9), as does perfusion to low $\dot{V}_A/\dot{Q}$ regions.[116] Anesthesia reduces FRC by about 0.5 L,[88] which increases airway closure during tidal ventilation.[117,118] In fact, the reduction in ventilation in the nonatelectatic lung (Fig. 19-21) is caused by airway closure. In addition, ventilation in these regions is less than perfusion (i.e., regions of low $\dot{V}_A/\dot{Q}$) and contributes to impaired oxygenation during anesthesia. Taken together, the combination of atelectasis and airway closure explain about 75% of the overall impairment in oxygenation.[89] In addition, where (CV – ERV) indicates the amount of airway closure occurring above FRC (and ERV is expiratory reserve volume), this value increased with induction of anesthesia, and there is good correlation between low $\dot{V}_A/\dot{Q}$ and the extent of airway closure.[89] In summary, a simple three-compartment lung model (normal $\dot{V}_A/\dot{Q}$ matching regions, region of airway closure, and atelectatic lung) describes well the components contributing to impairment of oxygenation during anesthesia (see Fig. 19-21).

DISTRIBUTION OF VENTILATION AND BLOOD FLOW DURING ANESTHESIA

Distribution of Ventilation

Redistribution of inspired gas away from dependent to nondependent lung regions has been demonstrated, using isotope techniques in anesthetized supine humans. Radiolabeled aerosol and SPECT demonstrate that ventilation is distributed mainly to the upper lung regions, with a successive decrease toward the lower lung regions, and an absence of ventilation in the lowermost regions, a finding consistent with the atelectasis demonstrable using CT (see Fig. 19-16).[101]

Recruitment maneuvers increase dependent lung ventilation in anesthetized subjects in the lateral[119] and supine[120] positions, restoring the distribution of ventilation to that in the awake state. Thus, restoration of overall FRC toward the awake level returns gas distribution toward the awake pattern. The explanations are recruitment of atelectatic lung, reopening of closed airways, and further expansion of already expanded (upper) lung regions, decreasing regional compliance and lessening incremental ventilation.

Distribution of Lung Blood Flow

The distribution of lung blood flow has been studied by injection of radioactively labeled macroaggregated albumin and SPECT.[101] During anesthesia, a successive increase in perfusion occurs from upper towards lower regions, with a slight drop in perfusion in the lowermost portion of the lung, which was atelectatic on simultaneous CT (see Fig. 19-16). PEEP will impede venous return to the right heart and reduce cardiac output. It can also affect pulmonary vascular resistance, although this would have little effect on cardiac output. In addition, PEEP redistributes blood flow toward dependent lung regions,[59,120] reducing flow (and increasing deadspace) in the upper lung; the increased dependent flow may increase shunt through atelectatic lung.[104]

HYPOXIC PULMONARY VASOCONSTRICTION

Several inhaled—but not intravenous—anesthetics inhibit HPV in isolated lung preparations.[121] Human studies of HPV are complex with multiple parameters changing simultaneously, thereby confounding the HPV response with changes in cardiac output, myocardial contractility, vascular tone, blood volume distribution, pH, P_{CO_2}, and lung mechanics. However, studies with no obvious changes in cardiac output, isoflurane and halothane depress the HPV response by 50% at a minimum alveolar concentration (MAC) of 2 (Fig. 19-22).[122]

VENTILATION-PERFUSION MATCHING DURING ANESTHESIA

DEAD SPACE, SHUNT, AND VENTILATION-PERFUSION RELATIONSHIPS

CO_2 Elimination

Anesthesia impairs CO_2 elimination and oxygenation of blood. The explanation for reduced CO_2 elimination is reduced minute ventilation ($\dot{V}_E$) because of respiratory depression, or where this is preserved, because of an increase in the V_D/V_T. Single-breath washout recordings demonstrate that "anatomic" dead space is unchanged, indicating that increased V_D/V_T is alveolar and confirmed by MIGET scan (Fig. 19-23).[10] Such high $\dot{V}_A/\dot{Q}$ can be explained by the tiny perfusion of corner vessels in interalveolar septa in the upper lung regions, where alveolar pressure can exceed pulmonary vascular pressure (zone I).[85] The impaired CO_2 elimination is most easily corrected by increasing the ventilation and is seldom a problem in routine anesthesia with mechanical ventilation.

Oxygenation

The impairment in arterial oxygenation during anesthesia is more marked with increased age, obesity, and smoking (see Chapter 80).[123,124] Venous admixture, as calculated by the standard oxygen shunt equation, is also increased during anesthesia to approximately 10% of cardiac output. However, this is an averaged calculation that considers hypoxia caused by pure shunt only, when actually it is due to a combination of "true" shunt (i.e., perfusion of nonventilated lung), poor ventilation of some regions, and regions that are ventilated but are perfused in excess of their ventilation (low $\dot{V}_A/\dot{Q}$ regions). The combination of these effects is called *venous admixture*. The shunt equation (derived in Box 19-2) assumes that all blood flow through the lung goes to either of two compartments: in one (the non–shunt fraction), all the blood is oxygenated; and in the other (the shunt fraction), all blood is shunted.

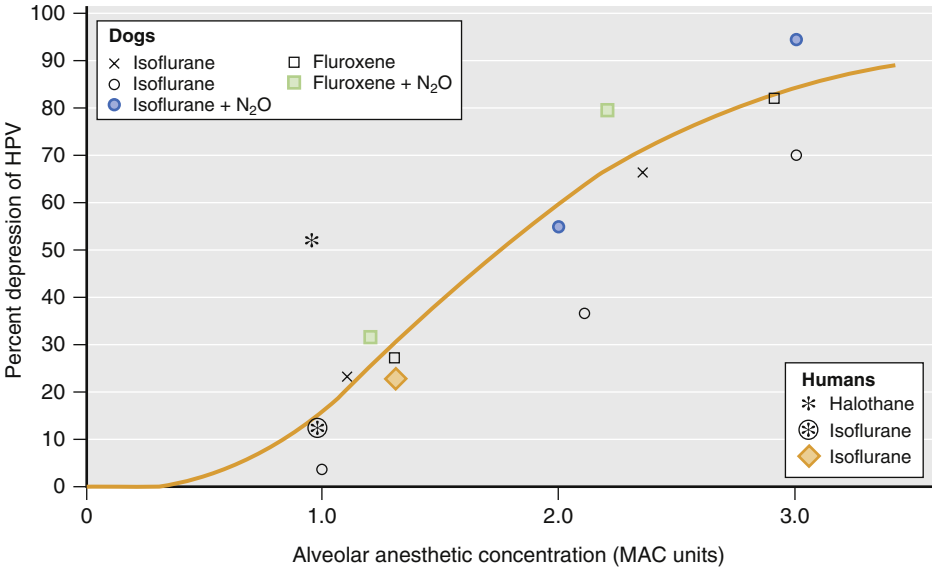


Figure 19-22. Effect of inhaled anesthetics on hypoxic pulmonary vasoconstriction (HPV). A concentration of 1 MAC causes a 20% to 30% depression of HPV, and the HPV depression decreases sharply with higher concentrations. The effect is that the shunt (i.e., perfusion through nonventilated regions) will be less reduced during inhalational anesthesia. *(From Marshall BE: Hypoxic pulmonary vasoconstriction,* Acta Anaesthesiol Scand Suppl *94:37-41, 1990.)*

The shunt equation (or venous admixture) can be written[125]:

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{(C_cO_2 - C_aO_2)}{(C_cO_2 - C_{\bar{v}}O_2)}$$

Because pulmonary end-capillary blood is assumed to be maximally saturated (therefore, $S_cO_2 = 1$), the quantity of dissolved O_2 can be ignored, and it can be the difference between $C_{\bar{v}}O_2$ and $C_{\bar{v}}O_2$ can be assumed to be small ($C_vO_2 = C_{\dot{v}}O_2$):

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{(1 - S_aO_2)}{(1 - S_vO_2)}$$

Thus, the effect of interventions on estimated shunt can be calculated easily from the changes in SaO_2 and SvO_2.

The extent of venous admixture depends on the inspired oxygen fraction (Fio_2). The higher the inspired oxygen fraction, the less there are of the low $\dot{V}_A/\dot{Q}$ regions. However, with high Fio_2, regions with low $\dot{V}_A/\dot{Q}$ may collapse because of gas adsorption and be transformed to shunt regions.[126] A good correlation between venous admixture vs. the sum of "true" shunt and perfusion of low $\dot{V}_A/\dot{Q}$ regions was seen in a study involving 45 anesthetized subjects (Fig. 19-24).[98] Derivation of the "oxygen shunt" or venous admixture is shown in Box 19-2.

In young healthy volunteers during anesthesia with thiopental and methoxyflurane, both ventilation and perfusion were distributed to wider ranges of $\dot{V}_A/\dot{Q}$ ratios,

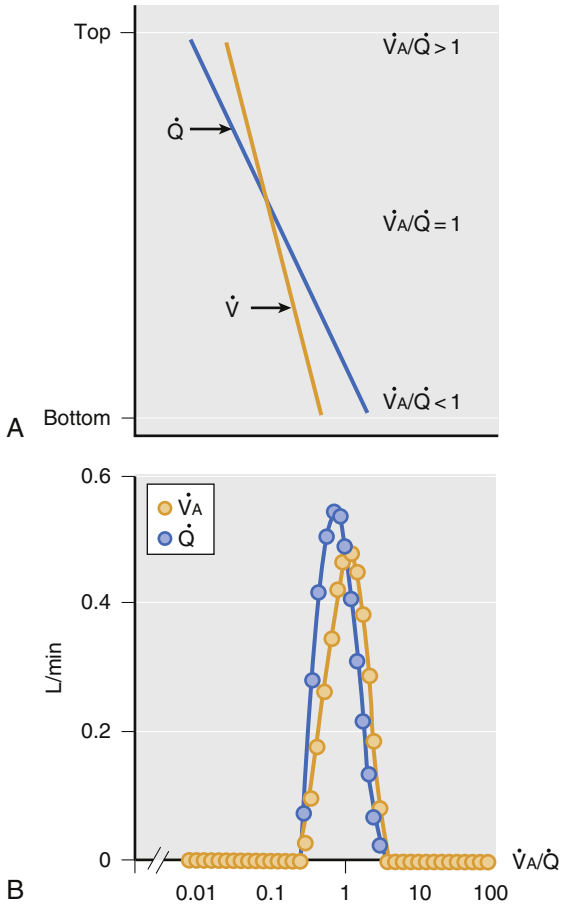


Figure 19-23. A schematic drawing of **(A)** the vertical distributions of ventilation ($\dot{V}_A$) and blood flow through the lung ($\dot{Q}$) and **(B)** the resulting ventilation-perfusion distribution ($\dot{V}_A/\dot{Q}$). The $\dot{V}_A/\dot{Q}$ distribution is centred at a ratio of 1, corresponding to the intersection of the ventilation and perfusion distribution curves. The slightly larger ventilation than perfusion in upper lung regions contribute to the high $\dot{V}_A/\dot{Q}$ ratios greater than 1, whereas the larger perfusion than ventilation in the lower part of the lung is the cause of the lower $\dot{V}_A/\dot{Q}$ ratios, less than 1. Although there is a moderate increase in ventilation down the lung, the increase in perfusion is greater.

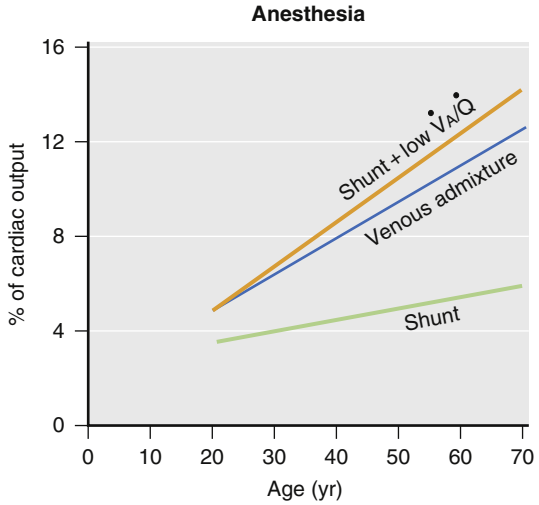


Figure 19-24. The effect of age on oxygenation during anesthesia. The combination of shunt with low $\dot{V}_A/\dot{Q}$ increases sharply with age (as does the degree of venous admixture). The increase in shunt with age, while significant, is less striking. *(From Gunnarsson L et al: Influence of age on atelectasis formation and gas exchange impairment during general anaesthesia,* Br J Anaesth *66:423-432, 1991.)*

BOX 19-2 *Derivation of the Venous Admixture (Shunt) Equation*

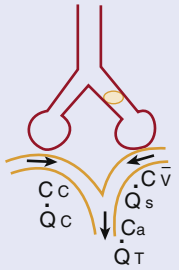
$$Ca \times \dot{Q}_T = \left(Cc' \times \dot{Q}_C\right) + \left(C\bar{v} \times \dot{Q}_S\right) \quad (1)$$

$$\dot{Q}_C = \dot{Q}_T - \dot{Q}_S \quad (2)$$

By inserting Equation 2 (accounts for all blood flow through the lungs) into Equation 1 (accounts for all oxygen carriage through the lungs),

$$Ca \times \dot{Q}_T = \left(Cc \times \left[\dot{Q}_T - \dot{Q}_S\right]\right) + (C\bar{v} \times \dot{Q}_S)$$

Rearranging,



$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{Cc' - Ca}{Cc' - C\bar{v}}$$

where Cc', Ca, and Cv are oxygen content in pulmonary end-capillary, arterial, and mixed venous blood, respectively; $\dot{Q}_T$ is cardiac output; $\dot{Q}_C$ is capillary flow; and $\dot{Q}_S$ is shunt.

which can be expressed as an increase in the logarithmic standard deviation of the perfusion distribution (log SD$\dot{Q}$). In a similar group of patients studied during halothane anesthesia and muscle paralysis, log SD$\dot{Q}$ was almost doubled (0.43 awake, 0.80 during anesthesia). In addition, true shunt was increased to a mean of 8%. A similar increase in shunt from 1% awake to a mean of 9% during anesthesia was recorded in a study on middle-aged (37 to 64 years) surgical patients, and there was a widening of the distribution (log SD$\dot{Q}$: 0.47 awake, 1.01 during anesthesia). In older patients with more severe impairment of lung function, halothane anesthesia with muscle paralysis, with or without nitrous oxide, caused considerable widening of the $\dot{V}_A/\dot{Q}$ distribution (log SD$\dot{Q}$ 0.87 awake, 1.73 during anesthesia). In addition, shunt increased to a mean of 15%, with large variation among patients (0% to 30%). Thus, the most consistent findings during anesthesia are an increased $\dot{V}_A/\dot{Q}$ mismatch, expressed as an increased log SDQ, and an increase in shunt. For review, see the article by Hedenstierna.[85]

Spontaneous ventilation is frequently reduced during anesthesia; therefore, inhaled anesthetics[127] or barbiturates[128] reduce sensitivity to CO_2. The response is dose-dependent; ventilation decreases with deepening anesthesia. Anesthesia also reduces the response to hypoxia, possibly because of effects on the carotid body chemoreceptors.[129]

The effects of anesthesia on respiratory muscle function are becoming better understood.[130] The effects are not uniform. Rib cage excursions diminish with deepening anesthesia.[131] The normal ventilatory response to CO_2 is produced by the intercostal muscles,[132,133] but with no clear increase in rib cage motion with CO_2 rebreathing during halothane anesthesia. Thus, the reduced ventilatory response to CO_2 during anesthesia is due to impeded function of the intercostal muscles.

FACTORS THAT INFLUENCE RESPIRATORY FUNCTION DURING ANESTHESIA

SPONTANEOUS BREATHING

Most studies of lung function have been performed on anesthetized, mechanically ventilated subjects or animals. Spontaneous breathing has been studied rarely. FRC decreases to the same extent during anesthesia, regardless of whether a muscle relaxant is used,[90,91] and atelectasis occurs to almost the same extent in anesthetized, spontaneously breathing subjects as during muscle paralysis.[134] Furthermore, the cranial shift of the diaphragm, as reported by Froese and Bryan,[92] was of the same magnitude both during general anesthesia with spontaneous breathing and with muscle paralysis, even though a difference in movement of the diaphragm from the resting position was noted. Thus, during spontaneous breathing, the lower, dependent portion of the diaphragm moved the most, whereas with muscle paralysis, the upper, nondependent part showed the largest displacement.

All these findings have raised the question of whether regional ventilation is different between spontaneous breathing and mechanical ventilation and whether mechanical ventilation worsens $\dot{V}_A/\dot{Q}$ as a consequence of poor ventilation of well-perfused, dependent lung regions. However, there is not much support for worsening of gas exchange by muscle paralysis in the literature. There is also no support from the few studies of $\dot{V}_A/\dot{Q}$ distribution that have been performed. Dueck and colleagues[135] found the same increase in $\dot{V}_A/\dot{Q}$ mismatch in anesthetized sheep during anesthesia, regardless of whether they were spontaneously breathing or ventilated mechanically. The log SDQ, indicating the degree of mismatch, increased (0.66 [awake], 0.83 [inhaled anesthesia with spontaneous breathing], 0.89 [mechanical ventilation]). Shunt is also increased during anesthesia from 1% (awake) to 11% (anesthetized, spontaneous breathing) or 14% (anesthetized, mechanical ventilation). In a study of anesthetized human subjects, shunt and log SDQ increased from 1% and 0.47 while awake to 6% and 1.03 during anesthesia with spontaneous breathing and 8% and to 1.01 during mechanical ventilation.[85] Thus, most of the gas exchange effects of anesthesia occurs during spontaneous breathing, with little or no further derangement added by muscle paralysis and mechanical ventilation.

INCREASED OXYGEN FRACTION

In the studies cited thus far, an inspired oxygen fraction (Fio_2) of approximately 0.4 was used. Anjou-Lindskog and colleagues[136] induced anesthesia in subjects breathing air (Fio_2, 0.21) in middle-aged to older patients during intravenous anesthesia before elective lung surgery and found only small shunts of 1% to 2%, although log SDQ increased from 0.77 to 1.13. When Fio_2 was increased to 0.5, the shunt increased (by 3% to 4%). In another study of older patients during halothane anesthesia,[85] an increase in Fio_2 from 0.53 to 0.85 caused an increase in shunt from 7% to 10% of cardiac output. Thus, increasing Fio_2 increases shunt, possibly because of attenuation of HPV by increasing Fio_2[122] or further development of atelectasis and shunt in lung units with low $\dot{V}_A/\dot{Q}$ ratios.[126]

BODY POSITION

Functional residual capacity is reduced dramatically by the combined effect of the supine position and anesthesia (see Chapter 41). The effects on the FRC of inducing anesthesia in the upright position were tested by Heneghan and associates,[137] and there was no difference in oxygenation in the semirecumbent versus supine position. Decreased cardiac output and enhanced inhomogeneity of blood flow distribution can outweigh any effects of posture. Fractional perfusion of the most dependent lung regions—likely poorly or not ventilated—may actually have been increased in the semirecumbent position. In the lateral position, differences in lung mechanics, resting lung volumes, and atelectasis formation between the dependent and nondependent portions of the lung have been demonstrated[138] and shown to result in further disturbance of the ventilation-perfusion match, with severe impairment in oxygenation. However, there are large and unpredictable inter-individual variations.[139] Using isotope techniques, an increase in $\dot{V}_A/\dot{Q}$ mismatch was also demonstrated in anesthetized, paralyzed patients in the lateral position,[140] and an improvement was noticed in the prone position.[141]

In addition, the vertical inhomogeneity of perfusion distribution is less marked in the prone position,[69] possibly reflecting regional differences in vascular configuration that promote perfusion of dorsal lung regions, regardless of whether they are in a dependent or nondependent position. Finally, distribution of ventilation may be uniform in anesthetized subjects when prone.[142]

AGE

Oxygenation is less efficient in older patients (see Chapter 80).[10] However, the formation of atelectasis does not increase with age in adults, and the few CT studies of infants during anesthesia suggest greater degrees of atelectasis.[98] In addition, shunt is independent of age between 23 and 69 years. However, $\dot{V}_A/\dot{Q}$ mismatch increases with age, with enhanced perfusion of low $\dot{V}_A/\dot{Q}$ regions when awake and when anesthetized. The major cause of impaired gas exchange during anesthesia in those younger than 50 years is shunt, whereas beyond 50 years $\dot{V}_A/\dot{Q}$ mismatch (i.e., increased log SDQ) becomes increasingly important (see Fig. 19-24). Because the correlation between log SDQ and age during anesthesia is almost parallel with that during the awake state, it can be said that anesthesia worsens $\dot{V}_A/\dot{Q}$ matching to the same extent as 20 years of aging.

OBESITY

Obesity worsens oxygenation (see Chapter 71)[143,144] predominantly because of reduced FRC resulting in a greater propensity to airway closure.[145] In addition, the use of high inspired oxygen concentrations promotes rapid atelectasis formation in alveoli distal to closed airways,[89,110] and there are good correlations between BMI and the extent of atelectasis (both during and after anesthesia)[101,146] and between BMI and pulmonary shunt (Fig. 19-25).[145]

Preventing a decrease in FRC by applying CPAP during induction of anesthesia probably reduces atelectasis formation, and thereby maintains oxygenation.[124,147,148] Indeed, the reduced "safety window" (the time taken to develop desaturation following breathing oxygen before induction of anesthesia) is much reduced in obese patients, and this may be prolonged by PEEP or CPAP[149] increasing lung volume and increasing the reservoir of O_2 available for diffusion into the capillary blood.

The use of high levels of inspired oxygen concentration, often almost 100%, to keep an acceptable level of oxygenation during anesthesia and surgery may be the simplest but not necessarily the best approach. It will promote further atelectasis formation,[109] and if the shunt is larger than 30%, which may well be the case in these patients, additional oxygen will add little to arterial oxygenation.[150] The application of PEEP has been advocated, and it may reduce the atelectasis[123,145,147] but will also have adverse effects, such as reduced cardiac output and redistribution of blood flow toward residual collapsed lung regions. Ventilation with inflations close to VC to reopen collapsed tissue, followed by ventilation with added PEEP, is another option. Recruitment of the lung with an inflation to 55 cm H_2O opened essentially all collapsed lung tissue in patients with a BMI of 40 kg/m^2 or more.[151] However, a recruitment alone did not keep the lung open for more than a few minutes. To keep the lung open, a PEEP of 10 cm H_2O after the recruitment was needed. PEEP of 10 was not enough to open up the lung.[151] Body position can have a substantial effect on lung volume and should be considered to the extent that surgery allows.[152]

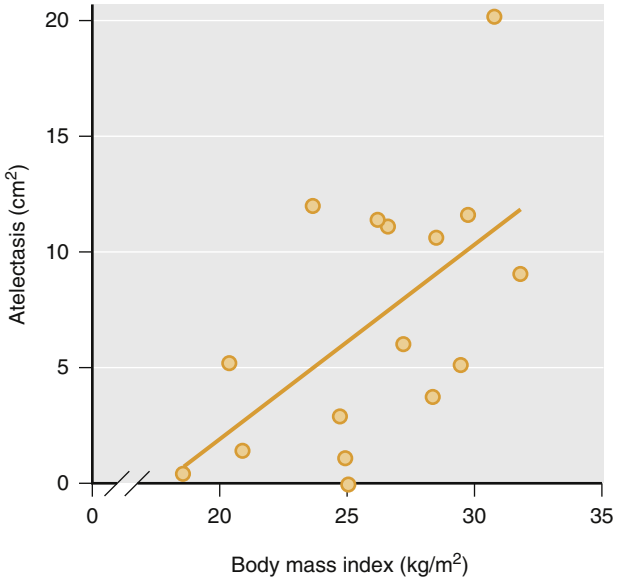


Figure 19-25. Relationship between body mass index (BMI) and extent of atelectasis during general anesthesia. As BMI increases, so does the extent of atelectasis (although there is considerable variability). *(From Rothen HU et al: Re-expansion of atelectasis during general anaesthesia: a computed tomography study,* Br J Anaesth *71:788-795, 1993.)*

PREEXISTING LUNG DISEASE

Smokers and patients with chronic lung disease have impaired gas exchange in the awake state, and anesthesia-associated deterioration in oxygenation is greater than in healthy individuals.[10] Interestingly, smokers with moderate airflow limitation may have less shunt as measured by MIGET than in subjects with healthy lungs. Thus, in patients with mild to moderate bronchitis who were to undergo lung surgery or vascular reconstructive surgery in the leg, only a small shunt was noticed, but log SDQ was increased.[85] In patients with chronic bronchitis studied by MIGET and CT, no or limited atelectasis developed during anesthesia and no or only minor shunt[103]; however, a considerable mismatch was seen with a large perfusion fraction to low $\dot{V}_A/\dot{Q}$ regions. Consequently, arterial oxygenation was more impaired than in lung-healthy subjects, but the cause was different from that in healthy subjects. A possible reason for the absence of atelectasis and shunt in these patients is chronic hyperinflation, which changes the mechanical behavior of the lungs and their interaction with the chest wall such that the tendency to collapse is reduced. It should be kept in mind that a patient with obstructive lung disease may have large regions with low $\dot{V}_A/\dot{Q}$ ratios that can be converted over time to resorption atelectasis. Thus, the protection against atelectasis formation during anesthesia by

TABLE 19-1 CAUSES OF HYPOXEMIA

Disturbance	Pao_2 (Breathing Air) at Rest	Pao_2 (Breathing Oxygen) at Rest	Pao_2 (Breathing air) With Exercise (Versus Rest)	$Paco_2$
Hypoventilation	Reduced	Normal	No change or further decrease	Increased
$\dot{V}_A/\dot{Q}$ mismatch	Reduced	Normal	No change or minor increase or decrease	Normal
Shunt	Reduced	Reduced	No change or further decrease	Normal
Diffusion impairment	Reduced	Normal	Small to large decrease	Normal

the obstructive lung disease might not last long. Regions with low $\dot{V}_A/\dot{Q}$ can be replaced by atelectasis as a result of slow absorption of gas behind occluded airways later during surgery and in the postoperative period.

REGIONAL ANESTHESIA

The ventilatory effects of regional anesthesia depend on the type and extension of motor blockade (see Chapters 56 and 57). With extensive blocks that include all the thoracic and lumbar segments, inspiratory capacity is reduced by 20% and expiratory reserve volume approaches zero.[153,154] Diaphragmatic function, however, is often spared, even in cases of inadvertent extension of subarachnoid or epidural sensory block up to the cervical segments.[153] Skillfully handled regional anesthesia affects pulmonary gas exchange only minimally. Arterial oxygenation and carbon dioxide elimination are well maintained during spinal and epidural anesthesia. This is in line with the findings of an unchanged relationship of CC and FRC[155] and unaltered distributions of ventilation-perfusion ratios assessed by MIGET during epidural anesthesia.[85]

CAUSES OF HYPOXEMIA AND HYPERCAPNIA

In the previous sections, we discussed ventilation, gas distribution, and the respiratory mechanics that govern distribution, diffusion, and pulmonary perfusion. All these components of lung function can affect the oxygenation of blood, and all except diffusion can also measurably affect CO_2 elimination. The different mechanisms behind hypoxemia and CO_2 retention, or hypercapnia or hypercarbia, have been mentioned previously but will be analyzed in more detail here.

Causes of hypoxemia include hypoventilation, $\dot{V}_A/\dot{Q}$ mismatch, impaired diffusion, and right-to-left shunt (Table 19-1). Hypercapnia is usually caused by hypoventilation although it can be caused by, $\dot{V}_A/\dot{Q}$ mismatch and shunt (Table 19-2). Increased $\dot{V}CO_2$ occurs in hypermetabolic conditions (e.g., fever, malignant hyperthermia, thyroid crisis) or with the use of CO_2-generating buffers such as $NaHCO_3$.

HYPOVENTILATION

If ventilation is low in proportion to metabolic demand, elimination of CO_2 will be inadequate, and CO_2 will accumulate in the alveoli, blood, and other body tissues. Hypoventilation is often defined as ventilation that results in a Pa_{CO_2} greater than 45 mm Hg (6 kPa). Thus, hypoventilation could be present even when minute ventilation is high, provided the metabolic demand or dead space ventilation is increased to a greater extent.

TABLE 19-2 MECHANISMS OF HYPOXEMIA IN DIFFERENT LUNG DISORDERS

Disorder	Hypoventilation	Diffusion Impairment	$\dot{V}_A/\dot{Q}$ Mismatch	Shunt
Chronic bronchitis	(+)	–	++	–
Emphysema	+	++	+++	–
Asthma	–	–	++	–
Fibrosis	–	++	+	+
Pneumonia	–	–	+	++
Atelectasis	–	–	–	++
Pulmonary edema	–	+	+	++
Pulmonary emboli	–	–	++	+
Acute respiratory distress syndrome	–	–	+	+++

The increased alveolar P_{CO_2} reduces the alveolar space available for oxygen. Alveolar PO_2 (PAO_2) can be estimated by the alveolar gas equation (see Box 19-1). The simplified equation is expressed:

$$PaO_2 = P_IO_2 - \left(Pa_{CO_2}/R\right)$$

Assuming that the respiratory exchange ratio (R) is 0.8 (more or less true at rest), PAO_2 can be estimated. In the ideal lung, PaO_2 equals PAO_2. For example, if PiO_2 is 149 mm Hg (19.9 kPa) and Pa_{CO_2} is 40 mm Hg (5.3 kPa), then PaO_2 is 99 mm Hg (13.2 kPa). If hypoventilation develops and the Pa_{CO_2} rises to 60 mm Hg (8 kPa) and there is no other gas exchange impairment, the PaO_2 will fall to 74 mm Hg (9.9 kPa). Clearly, a decrease in PaO_2 caused by hypoventilation is easily overcome by increasing PiO_2 (i.e., by increasing Fio_2). If there is a gap between the PAO_2 (estimated from this equation) and the measured (actual) PaO_2, then a cause of hypoxemia in addition to hypoventilation is present. These causes are discussed in the following paragraphs.

VENTILATION-PERFUSION MISMATCH

For optimal gas exchange, ventilation and perfusion must match each other in all lung regions. At rest, both ventilation and perfusion increase downward through the lung. However, perfusion increases more than ventilation, the

TABLE 19-3 **MEAN (SD) VENTILATION-PERFUSION RELATIONSHIPS WITH NO CARDIOPULMONARY DISEASE (NORMAL, *N* = 45), AWAKE AND DURING GENERAL ANESTHESIA AND MUSCLE PARALYSIS**

	$\dot{Q}$ mean	log SD$\dot{Q}$	$\dot{V}$ Mean	Log SD$\dot{V}$	Shunt (% Q_T)	Dead Space (% V_T)	Pao_2/Fio_2 (kPa)*
Awake	0.76 (0-33)	0.68 (0.28)	1.11 (0.52)	0.52 (0.15)	0.5 (1.0)	34.8 (14.2)	59.5 (8.1)
Anesthetized	0.65 (0.34)	1.04 (0.36)	1.38 (0.76)	0.76 (0.31)	4.8 (4.1)	35.0 (9.9)	50.9 (15.2)

log SD$\dot{Q}$, standard deviations of the logarithmic distribution of perfusion; log SD$\dot{V}$, standard deviations of the logarithmic distribution of ventilation; $\dot{Q}$ mean, mean $\dot{V}_A/\dot{Q}$ of the perfusion distribution; $\dot{V}$ mean, mean $\dot{V}_A/\dot{Q}$ of ventilation distribution.

difference between the uppermost and lowermost 5-cm segments being threefold for ventilation and tenfold for perfusion. This change results in a mean $\dot{V}_A/\dot{Q}$ ratio of approximately 1 somewhere in the middle of the lung and a range of $\dot{V}_A/\dot{Q}$ ratios (0.5 at the bottom, 5.0 in the apex; see Fig. 19-23, upper panel, the perfusion distribution being a simplified drawing of Fig. 19-11).

Another way of showing the matching between ventilation and blood flow is by illustrating a multicompartmental analysis of ventilation and distribution of blood flow against $\dot{V}_A/\dot{Q}$ ratios. This can be achieved with MIGET.[156] In short, MIGET is based on the constant intravenous infusion of a number of inert gases (usually six) with differing solubilities in blood. When passing through the lung capillaries, the different gases are eliminated via the alveoli and expired in indirect proportion to their solubility. A poorly soluble gas will rapidly leave the bloodstream and be more or less completely eliminated and exhaled (e.g., sulfur hexafluoride); a gas with a high solubility in blood will be almost completely retained in the blood and will not be exhaled (e.g., acetone); and a gas of intermediate solubility will be retained (and expired) to an intermediate extent (e.g., halothane).

As a result, the concentration of the different gases in arterial blood will differ, with higher concentrations of gases with high solubility. Retention can be calculated as the ratio between arterial and mixed venous blood concentrations. Similarly, the ratio of the concentrations (i.e., expired:mixed venous) can be calculated and gives the excretion for each gas. With knowledge of the retention, excretion, and solubility of each gas, an essentially continuous distribution of blood flow against $\dot{V}_A/\dot{Q}$ ratios can be constructed. The lower panel in Figure 19-23 shows an example from a healthy subject. Note that ventilation and blood flow are well matched, being distributed to a limited number of compartments centered on a $\dot{V}_A/\dot{Q}$ ratio of 1. MIGET has a high discriminatory capacity of detecting different $\dot{V}_A/\dot{Q}$ disturbances, but does not provide topographic information. Several variables that reflect the degree of mismatch can be calculated and are shown in Table 19-3. In the following paragraphs, examples of $\dot{V}_A/\dot{Q}$ mismatch are discussed.

If ventilation and perfusion are not matched, gas exchange will be affected. The most common cause of impaired oxygenation is $\dot{V}_A/\dot{Q}$ mismatch. Low $\dot{V}_A/\dot{Q}$ will impede oxygenation because ventilation is insufficient to fully oxygenate the blood, and the degree of impairment is dependent on the degree of $\dot{V}_A/\dot{Q}$ mismatch; in fact, even normal lung regions $\dot{V}_A/\dot{Q}$ (0.5 to 1) cannot completely saturate the blood. Thus, PaO_2 cannot equal alveolar PO_2, and a difference ($PAO_2 - PaO_2$) of 3 to 5 mm Hg (0.4 to 0.7 kPa) is normal. With more $\dot{V}_A/\dot{Q}$ mismatch, the PAO_2–PaO_2 difference is further increased. The $\dot{V}_A/\dot{Q}$ mismatch can account for all the hypoxemia seen in a patient with severe obstruction.[116] Shunt ($\dot{Q}$, but no $\dot{V}_A$), which is often claimed to exist in patients with COPD, is mostly absent when analyzed with a more sophisticated technique such as MIGET. Indeed, shunt in a patient with obstruction likely represents a complicating factor in the disease (Fig. 19-26).

In severe asthma, a distinct bimodal pattern of low ratios occurs when using MIGET[157] (see Fig. 19-26). The reason may be that alveoli behind airways obstructed by edema (or a mucous plug or spasm) can still be ventilated by collateral ventilation (i.e., alveolar pores, interbronchial communications); these regions would otherwise be shunt (no $\dot{V}_A$, some $\dot{Q}$), resulting in the additional peak in $\dot{V}_A/\dot{Q}$ explaining the bimodal distribution. Such collateral ventilation might be part of the reason that true shunt is not normally seen in COPD. Of course, if the standard shunt equation is used to explain hypoxemia, there is no capacity to distinguish between the contributions of low $\dot{V}_A/\dot{Q}$ vs. shunt to hypoxemia (the net effect is best called *venous admixture*).

Airway obstruction is distributed unevenly, and a large variation in $\dot{V}_A/\dot{Q}$ ratios results. Indeed, ventilation is redistributed from regions with high airway resistance to other regions that can then become overventilated in proportion to their perfusion; this causes high $\dot{V}_A/\dot{Q}$ ratios. There are normally regions in the apex that have $\dot{V}_A/\dot{Q}$ ratios of up to 5, but ratios of 100 or more exist in patients with obstruction, making the regions practically indistinguishable from true dead space; this is what causes the increase in physiologic dead space in obstructive lung disease. The effect of high $\dot{V}_A/\dot{Q}$ is also the same as for airway dead space—that is, ventilation that seems not to participate in gas exchange ("wasted ventilation"). Consequently, a patient with COPD has low $\dot{V}_A/\dot{Q}$ (impedes oxygenation) and high $\dot{V}_A/\dot{Q}$ (mimics dead space, impedes CO_2 elimination). However, MIGET is a complex, research-orientated tool, and the calculation of dead space for clinical purposes relies instead on expired CO_2. Derivation of the CO_2 dead space is shown in Box 19-3.

$\dot{V}_A/\dot{Q}$ mismatch exists to varying degrees in all patients with COPD, and it fully explains hypoxemia in most of them. Hypoventilation can also contribute, whereas impaired diffusion or shunt rarely contributes to hypoxemia. Diffusion capacity, or transfer test, can be reduced markedly in severe COPD, in particular in emphysema; in this case the decrease is not caused by thickened alveolar-capillary membranes but rather by reduced capillary blood volume and reduced area for diffusion.

Pulmonary vessels can be affected by lung disease and can cause $\dot{V}_A/\dot{Q}$ mismatch by impeding regional blood flow. Systemic diseases with vascular involvement can cause severe pulmonary dysfunction because of $\dot{V}_A/\dot{Q}$

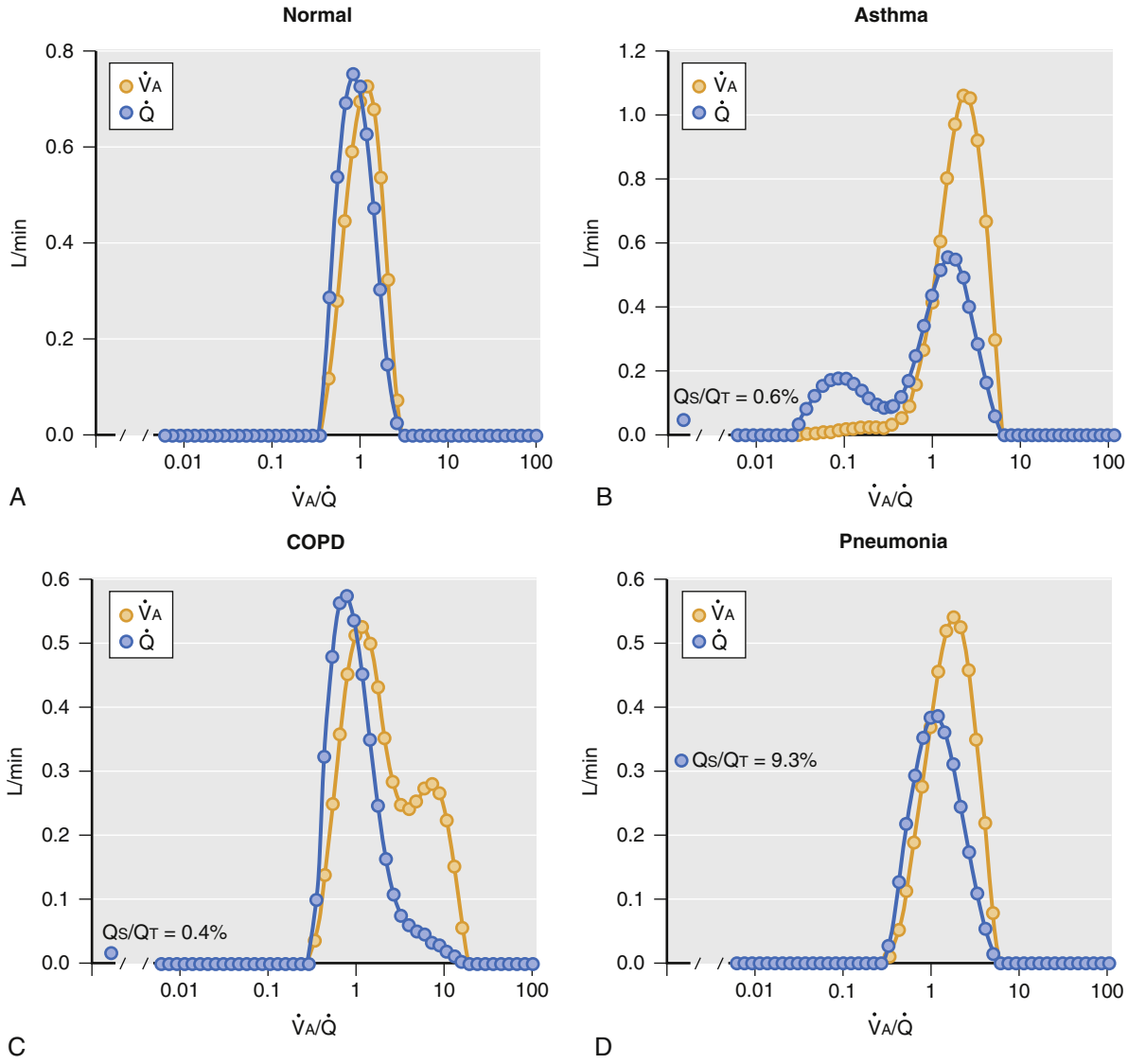


Figure 19-26. Distribution of ventilation and perfusion in normal lungs, asthma, chronic obstructive pulmonary disease (COPD), and pneumonia. **A,** In normal lungs **(A)** there is good matching between ventilation (o) and perfusion (•) with a mode centerd around a $\dot{V}_A/\dot{Q}$ ratio of 1. This results in near optimal oxygenation of blood and CO_2 removal. **B,** In asthma **(B)** there is broader distribution of $\dot{V}_A/\dot{Q}$ with some regions being ventilated well in excess of perfusion ($\dot{V}_A/\dot{Q}$ = 10 and greater), with another mode of low $\dot{V}_A/\dot{Q}$ centred around a ratio of 0.1. This mode can be explained by collateral ventilation maintaining gas exchange in alveoli behind occluded airways. There is no shunt seen in asthma. **C,** In COPD **(C)** the pattern is similar to asthma, but with an additional "high" $\dot{V}_A/\dot{Q}$ mode that adds to dead space such as ventilation. Shunt is not present, and the pattern of $\dot{V}_A/\dot{Q}$ distribution is not associated with significant hypoxemia. **D,** In lobar pneumonia **(D)** the major finding is pure shunt (consolidated, perfused, and poorly ventilated lobe); there is only minor widening of the $\dot{V}_A/\dot{Q}$ distribution.

mismatch, impaired diffusion, and shunt. $\dot{V}_A/\dot{Q}$ mismatch causes most of the hypoxemia in pulmonary fibrosis.[158] In addition, hypoxemia can be caused by impaired diffusion (in particular, during exercise, when it can dominate) and a varying degree of shunt (discussed later).

Pulmonary emboli cause $\dot{V}_A/\dot{Q}$ mismatch in three ways. First, vascular beds are occluded, causing extremely high $\dot{V}_A/\dot{Q}$ locally; this is manifest as increased dead space. Second, the occluded vascular bed diverts blood flow to other, already ventilated regions, thus converting these into low $\dot{V}_A/\dot{Q}$ regions. Finally, if P_{PA} (pulmonary artery pressure) is markedly increased, then any propensity to shunt will be increased.[159] In patients with acute pulmonary embolism,[160] hypoxemia appears to be principally caused by increased variability of $\dot{V}_A/\dot{Q}$, and this has been confirmed experimentally.[161]

Pneumonia involving large areas of consolidated, edematous, or atelectatic (i.e., all non-aerated) lung involves significant shunt, and areas of partial aeration contribute to $\dot{V}_A/\dot{Q}$ mismatch (see Fig. 19-26).[150] In bacterial pneumonia, HPV appears to be inhibited, which is an important mechanism that worsens hypoxemia.[162,163]

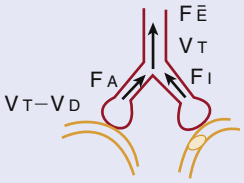
EFFECT OF $\dot{V}_A/\dot{Q}$ ON CO_2 ELIMINATION

A common perception is that although $\dot{V}_A/\dot{Q}$ impedes oxygenation, it has little effect on CO_2 clearance. Actually, elimination of CO_2 is even more limited by $\dot{V}_A/\dot{Q}$ mismatch than is oxygenation of blood[84]; however this seldom results in hypercapnia because minimal increases in $\dot{V}_A$ rapidly correct Pa_{CO_2}. If alveolar ventilation is

BOX 19-3 ***Derivation of the Physiologic Dead Space Equation***

The quantity of CO_2 expired in an exhaled tidal volume = $F_ECO_2 \times V_T$

This comes from perfused lung and from nonperfused lung.



CO_2 exhaled from perfused lung = $F_ACO_2 \times V_A = F_ACO_2 \times (V_T - V_D)$

CO_2 from nonperfused (dead space) lung is derived from inspired gas = $F_ICO_2 \times V_D$

Thus, $F_ECO_2 \times V_T = F_ACO_2(V_T V_D) + (F_ICO_2 \times V_D)$

By rearranging,

$$\frac{V_{DS}}{V_T} = \frac{F_A - F_E}{F_A - F_I}$$

If $F_I = 0$, F is replaced by P, and P_A is replaced by Pa, for CO_2,

$$\frac{V_{DS}}{V_T} = \frac{Paco_2 - P_Eco_2}{Paco_2}$$

where F_E, F_A, and F_I are mixed expired, alveolar, and inspired gas concentration, respectively, and V_T, V_{DS}, and V_A are tidal volume, dead space, and part of the tidal volume to perfused alveoli, respectively.

already impaired and cannot be increased, the addition of $\dot{V}_A/\dot{Q}$ mismatch will increase $Paco_2$.

IMPAIRED DIFFUSION

Hypoxemia can occur because of impaired diffusion in fibrosis or vascular diseases because of severely thickened of the alveolar-capillary membranes. Diffusion is slowed down and the entire length of capillary may be required before the capillary blood has been fully oxygenated, even in resting conditions. On the other hand, this means that a diffusion barrier is unlikely to cause hypoxemia provided the perfusion time and distance permits O_2 equilibration (see Fig. 19-12); however, when these reserves are spent, PaO_2 begins to fall. This decrease is particularly noticeable in patients with pulmonary fibrosis, who might have normal PaO_2 at rest but show dramatic decreases during exercise.[84,116] Development of, or increase in right-to-left shunting in the heart, such as atrial septal defect, can also cause this exercise-induced hypoxemia because the left-to-right shunt at rest becomes right-to-left (or a small right-to-left shunt increases) because of increased P_{PA}.

RIGHT-TO-LEFT SHUNT

If blood passes through the lung without contacting ventilated alveoli, then the blood will not oxygenate or release CO_2. This condition is called a *shunt*, and it lowers PaO_2 and can increase $Paco_2$. Healthy people have a small shunt (2% to 3% of cardiac output) that is caused by venous drainage of the heart muscle into the left atrium by the Thebesian veins. In pathologic states, the shunt ranges from 2% to 50% of cardiac output.

Shunt is often confused with $\dot{V}_A/\dot{Q}$ mismatch. While a $\dot{V}_A/\dot{Q}$ of zero (some perfusion, no ventilation) constitutes a shunt, there are two clear and important differences between low $\dot{V}_A/\dot{Q}$ and shunt. First, the anatomy of a shunt differs from an area of low $\dot{V}_A/\dot{Q}$. Regions with low $\dot{V}_A/\dot{Q}$ are characterized by narrowing of the airways and vasculature, which reduces ventilation and blood flow in some regions and increases them in others. Examples are obstructive lung disease and vascular disorders. Shunt is caused by the complete cessation of ventilation in a region, usually as a result of collapse (atelectasis) or consolidation (e.g., pneumonia). Asthma or COPD does not involve the formation of a shunt[116]; if a shunt is present, it indicates a complication. Second, supplemental O_2 improves the hypoxemia caused by low $\dot{V}_A/\dot{Q}$, but it has less effect on hypoxemia caused by shunt. Although aeration may be poor in regions of low $\dot{V}_A/\dot{Q}$, aeration does exist in these regions, and the concentration of O_2 in these alveoli can be enriched by increasing Fio_2. In contrast, supplemental O_2 cannot access the alveoli in a true (anatomic) shunt.

Anatomic shunt and low $\dot{V}_A/\dot{Q}$ usually coexist, and the net effect is sometimes referred to as *percent shunt* (per the standard shunt equation). In this situation, the low $\dot{V}_A/\dot{Q}$ component will contribute to the response from increasing Fio_2, and the regions of anatomic (true) shunt will not; therefore, shunt will always lower PaO_2 (at any Fio_2). When the calculated fraction increases to 25%, the response to increased Fio_2 will be small; when it increases to 30% or greater, the response will be negligible.[150] This varying response is the net effect of mixing blood with normal pulmonary end-capillary PO_2 and shunt blood, which has the same PO_2 as mixed venous blood. If shunt is a large enough fraction of total lung blood flow, the additional O_2 that can be physically dissolved by the raised Fio_2 is so small that it is almost immeasurable; such a shunt is said to be refractory.

RESPIRATORY FUNCTION DURING ONE-LUNG VENTILATION

Oxygenation can be a challenge during one-lung surgery. One lung is not ventilated but is still perfused, and in the postoperative period, restoration of lung integrity and ventilation–perfusion matching can take time (see Chapter 66).[164]

The technique of one-lung anesthesia and ventilation means that only one lung is ventilated and that the lung provides oxygenation of—and elimination of carbon dioxide from—the blood. Persisting perfusion through the nonventilated lung causes a shunt and decreases PaO_2 (Fig. 19-27); measures can be taken to reduce this blood flow.[165,166]

During one-lung anesthesia, there are two main contributors to impaired oxygenation: (1) the persisting blood flow through nonventilated lung and (2) development of atelectasis in the dependent lung, resulting in local shunt and low $\dot{V}_A/\dot{Q}$.[139] A recruitment maneuver can dissect the influence of the dependent atelectasis[167]; serial increases in peak airway pressure and PEEP directed to the dependent, ventilated lung increased significantly the PaO_2, indicating that dependent atelectasis was an important cause of hypoxemia. In this situation, diversion of perfusion from the dependent (ventilated) to the

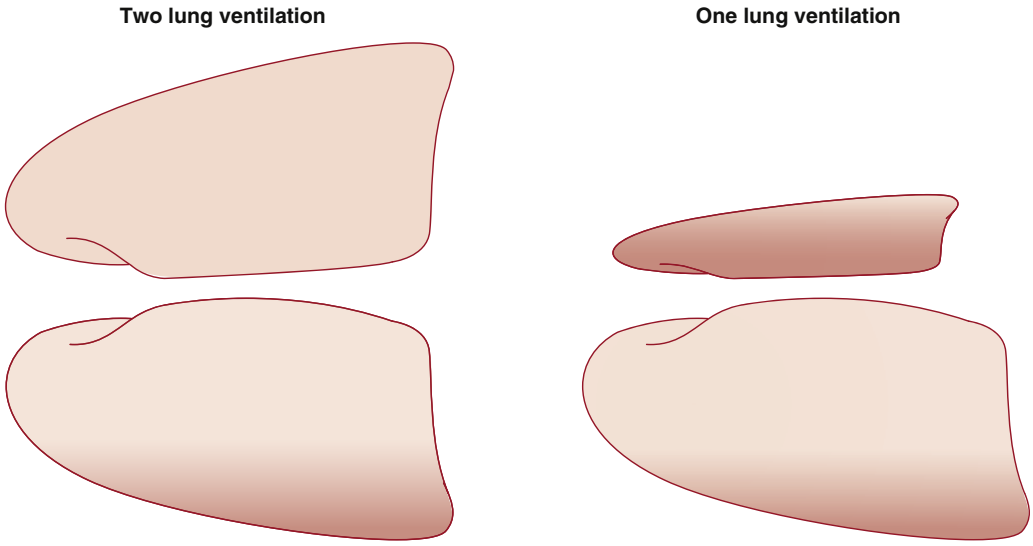


Figure 19-27. Schematic drawing of the distribution of shunt during two-lung ventilation and one-lung ventilation during anesthesia. Shunt region is indicated by dark area in the lower lung during two-lung ventilation and in the lower lung—plus the entire upper lung—during one-lung ventilation.

nondependent (i.e., nonventilated) lung would have worsened oxygenation and not improved it.

Recruitment can also affect V_D. Recruitment during one-lung anesthesia improved oxygenation, but also decreased V_D.[168] The slope of the CO_2 curve during a tidal expiration (phase III) was flatter, indicating a more even distribution of inspired gas throughout the lung and more synchronous alveolar emptying. Thus, a secondary effect of recruiting collapsed lung tissue can be (presumably not when recruitment causes overinflation) more even distribution of ventilation and a decrease in the dead space fraction. This effect should facilitate the use of a smaller V_T. In contrast to an individual recruitment, the application of continuous elevated P_{AW} (PEEP titrated to optimal compliance in the ventilated lung) increased compliance by 10% but slightly worsened oxygenation, probably because of redistribution of blood from the ventilated to the nonventilated (nondependent) lung.[169] The rationale for identifying and using optimal PEEP has also been reviewed.[170]

Maneuvers can also be applied to the nondependent lung. The effects of compressing the nondependent lung on oxygenation were examined using an intra-arterial O_2 sensor, which provides instantaneous and continuous PaO_2.[171] Compression resulted in increased PaO_2, suggesting a shift of blood flow from the nondependent (nonventilated) to the dependent (ventilated) lung; development of complete absorption atelectasis in the nondependent lung may have similar effects.[172]

Inhaled nitric oxide (NO; pulmonary vasodilator) and intravenous almitrine (pulmonary vasoconstrictor) have been studied alone and in combination (see Chapter 104). NO alone has little effect,[173] but oxygenation is improved when NO is combined with almitrine.[174,175] Almitrine alone also improves oxygenation[176] at a dose that does not alter P_{PA} or cardiac output. Although inhaled NO increases perfusion to already ventilated regions (increasing $\dot{V}_A/\dot{Q}$), almitrine potentiates HPV, decreasing perfusion to nonventilated (i.e., shunt) areas (reducing shunt) and potentially diverting blood flow to ventilated regions of the lung. Selective pulmonary vasodilation is reviewed.[177,178]

Careful analysis of the mechanical obstruction caused by kinking of pulmonary vessels and by HPV has shown that HPV is the important determinant of diversion of blood flow away from nonventilated lung (though not complete).[179] Moreover, positioning of the patient can affect the degree of shunting.[180]

PNEUMOPERITONEUM

Laparoscopic operations are usually performed by insufflation of CO_2 into the abdominal cavity The effects are twofold. First, the consequences of hypercapnic acidosis[181,182] include depressed cardiac contractility, sensitization of the myocardium to the arrhythmogenic effects of catecholamines, and systemic vasodilation.[183] There can also be long-lasting postoperative effects on breathing control.[184] In addition, the physical effects of pneumoperitoneum are important. These include decreased FRC and VC,[185] formation of atelectasis,[186] reduced respiratory compliance,[187] and increased peak airway pressure.[188] Nonetheless, shunt is reduced and arterial oxygenation is mostly improved during CO_2 pneumoperitoneum.[189] This paradox—more atelectasis and less shunt—suggests that efficient redistribution of blood flow away from collapsed lung regions is attributable to hypercapnic acidosis CO_2. Indeed, a recent experimental study showed that if the abdomen was inflated with air, a much larger shunt developed than if CO_2 had been used for inflation.[190]

LUNG FUNCTION AFTER CARDIAC SURGERY

Cardiac surgery produces the greatest degree of atelectasis in the postoperative period (see Chapter 67),[191] perhaps because both lungs are often collapsed. Spontaneous resolution of the atelectasis is gradual, leaving a residual shunt of up to 30% by day 1 or 2[99,192]; however, recruitment at the end of the case is possible. In some cases, 30 cm H_2O for 20 seconds is sufficient,[99] facilitated by the chest being open. A recruitment maneuver

(with zero PEEP) causes transient increase in PaO_2 and EELV, and with PEEP alone EELV was increased but PaO_2 unchanged; however, a recruitment maneuver followed by PEEP resulted in a large and sustained increase in both Pa_{O_2} and EELV.[193] The separation of effect whereby PEEP alone increases EELV to a greater extent than it increases oxygenation suggests further opening of already opened lung rather than opening of atelectatic lung.

Head-to-head comparison of intermittent CPAP versus constant noninvasive pressure support ventilation reported intriguing findings. There was less radiographic evidence of atelectasis following pressure support, without differences in oxygenation of bedside pulmonary function testing.[194] Although the authors' conclusion was no clinical benefit with noninvasive pressure support ventilation, differences in Fio_2 could cause differences in propensity to atelectasis. Recruitment maneuvers up to moderately high levels of airway pressure (46 cm H_2O) do not appear to affect the pulmonary vascular resistance or right ventricular afterload,[195] which is an issue of considerable importance following cardiac surgery. Nonetheless, it is prudent to consider RV loading and ejection in such circumstances, especially in the setting of diminished RV reserve or tricuspid regurgitation. Finally, many cardiac surgeries are now being performed "off pump," and the postoperative pulmonary effect is reduced, with less postoperative intrapulmonary shunt and correspondingly shorter hospital stays.[196]

POSTOPERATIVE PHYSIOTHERAPY

Physiotherapy, much debated after surgery (including cardiac surgery; see Chapter 103)[197] is associated with more effective lung recruitment (seen on thoracic CT) when involving deliberate approaches, such as flow bottles following exercise.[198] In effect, large and early inspiration following surgery may be key to preventing postoperative lung complications. Whether the deep inspiration needs to be accomplished with a specific forced breathing device is uncertain.

EFFECT OF SLEEP ON RESPIRATION

Sleep has a major effect on many aspects of respiration, perhaps the most obvious being ventilation.[199] Sleep reduces V_T and inspiratory drive, and $\dot{V}_E$ falls by approximately 10%, depending on the sleep stage, with the most marked fall occurring during rapid-eye-movement (REM) sleep. Lung volume (i.e., FRC) is also reduced[200]; this commences almost immediately after the onset of sleep, and the lowest levels of FRC (down to 10% of resting levels) occur in REM sleep.[201] CT studies in healthy volunteers demonstrate that the sleep-induced decrease in FRD is accompanied by reduced aeration in the dependent lung. Such loss in aeration was demonstrated in anesthetized patients when their Fio_2 was increased from 0.3 to 1.0; atelectasis developed rapidly. It is possible that during normal sleep, breathing with high levels of O_2 would also cause atelectasis.

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Chapter 20

Cardiac Physiology

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KEY POINTS

- The cardiac cycle is the sequence of electrical and mechanical events during the course of a single heartbeat.
- Cardiac output is determined by the heart rate, myocardial contractility, and preload and afterload.
- The majority of cardiomyocytes consist of myofibrils, which are rodlike bundles that form the contractile elements within the cardiomyocyte.
- The basic working unit of contraction is the sarcomere.
- Gap junctions are responsible for the electrical coupling of small molecules between cells.
- Action potentials have four phases in the heart.
- The key player in cardiac excitation-contraction coupling is the ubiquitous second messenger calcium.
- Calcium-induced sparks are spatially and temporally patterned activations of localized calcium release that are important for excitation-contraction coupling and regulation of automaticity and contractility.
- β-Adrenoreceptors stimulate chronotropy, inotropy, lusitropy, and dromotropy.
- Hormones with cardiac action can be synthesized and secreted by cardiomyocytes or produced by other tissues and delivered to the heart.
- Cardiac reflexes are fast-acting reflex loops between the heart and central nervous system that contribute to the regulation of cardiac function and the maintenance of physiologic homeostasis.

In 1628, English physician, William Harvey, first advanced the modern concept of circulation with the heart as the generator for the circulation. Modern cardiac physiology includes not only physiology of the heart as a pump but also concepts of cellular and molecular biology of the cardiomyocyte and regulation of cardiac function by neural and humoral factors. Cardiac physiology is a component of the interrelated and integrated cardiovascular and circulatory physiology. This chapter discusses only the physiology of the heart. It begins with the physiology of the intact heart. The second part of the chapter focuses on cellular cardiac physiology. Finally, the various factors that regulate cardiac function are briefly discussed.

The basic anatomy of the heart consists of two atria and two ventricles that provide two separate circulations in series. The pulmonary circulation, a low-resistance and high-capacitance vascular bed, receives output from the right side of the heart, and its chief function is bidirectional gas exchange. The left side of the heart provides output for the systemic circulation. It functions to deliver oxygen (O_2) and nutrients and to remove carbon dioxide (CO_2) and metabolites from various tissue beds.

PHYSIOLOGY OF THE INTACT HEART

Understanding of mechanical performance of the intact heart begins with the knowledge of the phases of the cardiac cycle and the determinants of ventricular function.

CARDIAC CYCLE

The cardiac cycle is the sequence of electrical and mechanical events during the course of a single heartbeat. Figure 20-1 illustrates (1) the electrical events of a single cardiac cycle represented by the electrocardiogram (ECG) and (2) the mechanical events of a single cardiac cycle represented by left atrial and left ventricular pressure pulses correlated in time with aortic flow and ventricular volume.[1]

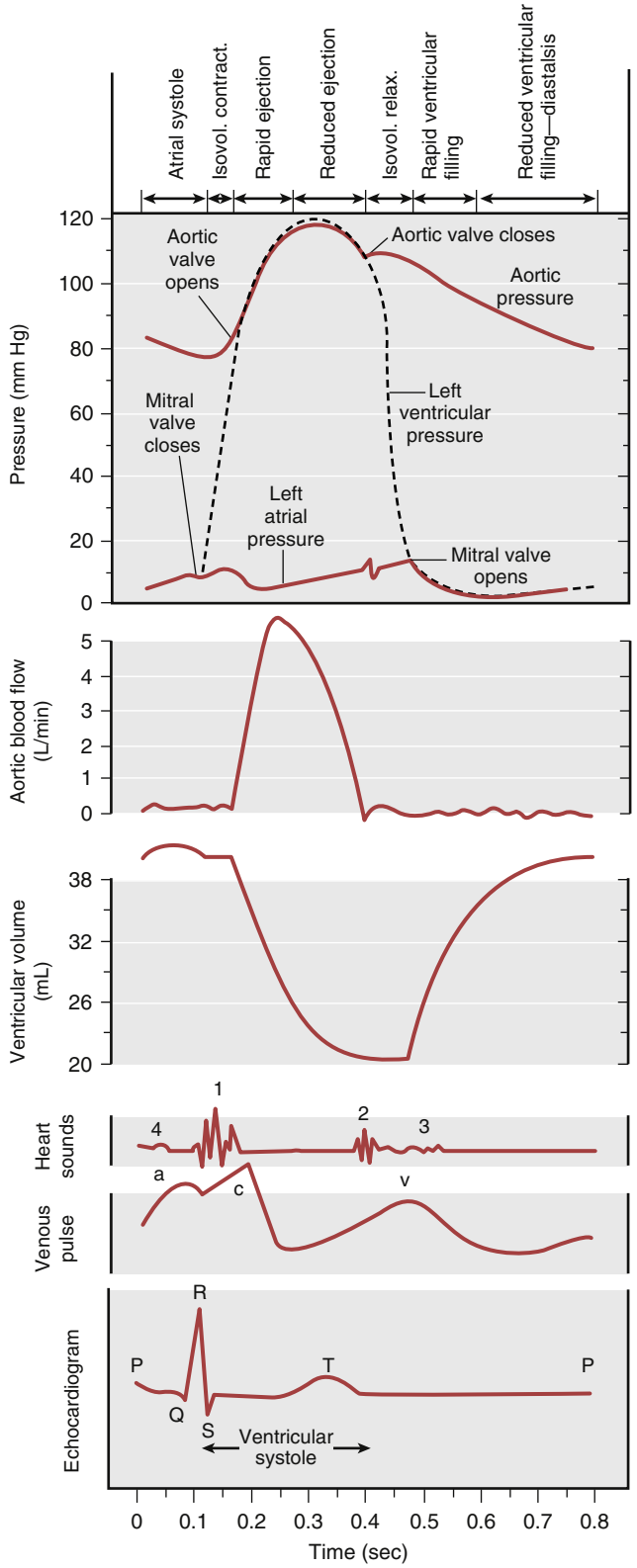


Figure 20-1. Electrical and mechanical events during a single cardiac cycle. The pressure curves of aortic blood flow, ventricular volume, venous pulse, and electrocardiogram are shown. *(From Berne RM, Levy MN: The cardiac pump. In* Cardiovascular physiology, *ed 8. St. Louis, 2001, Mosby, pp 55-82.)*

The cardiac cycle begins with the initiation of the heartbeat. Intrinsic to the specialized cardiac pacemaker tissues is automaticity and rhythmicity. The sinoatrial (SA) node is usually the pacemaker; it can generate impulses at the greatest frequency and is the natural pacemaker.

Electrical Events and the Electrocardiogram

Electrical events of the pacemaker and the specialized conduction system are represented by the ECG at the body surface (also see Chapters 45 and 47). The ECG is the result of differences in electrical potential generated by the heart at sites of the surface recording. The action potential initiated at the SA node is propagated to both atria by specialized conduction tissue that leads to atrial systole (contraction) and the P wave of the ECG. At the junction of the interatrial and interventricular septa, specialized atrial conduction tissue converges at the atrioventricular (AV) node, which is distally connected to the His bundle. The AV node is an area of relatively slow conduction, and a delay between atrial and ventricular contraction normally occurs at this locus. The PR interval represents the delay between atrial and ventricular contraction at the level of the AV node. From the distal His bundle, an electrical impulse is propagated through large left and right bundle branches and finally to the Purkinje system fibers, which are the smallest branches of the specialized conduction system. Finally, electrical signals are transmitted from the Purkinje system to individual ventricular cardiomyocytes. The spread of depolarization to the ventricular myocardium is exhibited as the QRS complex on the ECG. Depolarization is followed by ventricular repolarization and the appearance of the T wave on the ECG.[2]

Mechanical Events

The mechanical events of a cardiac cycle begin with the return of blood to the right and left atria from the systemic and pulmonary circulation, respectively. As blood accumulates in the atria, atrial pressure increases until it exceeds the pressure within the ventricle, and the AV valve opens. Blood passively flows first into the ventricular chambers, and such flow accounts for approximately 75% of the total ventricular filling.[3] The remainder of the blood flow is mediated by active atrial contraction or systole, known as the atrial *kick*. The onset of atrial systole is coincident with depolarization of the sinus node and the P wave. While the ventricles fill, the AV valves are displaced upward and ventricular contraction (systole) begins with closure of the tricuspid and mitral valves, which corresponds to the end of the R wave on the ECG. The first part of ventricular systole is known as *isovolumic* or *isometric contraction*. The electrical impulse traverses the AV region and passes through the right and left bundle branches into the Purkinje fibers, which leads to contraction of the ventricular myocardium and a progressive increase in intraventricular pressure. When intraventricular pressure exceeds pulmonary artery and aortic pressure, the pulmonic and aortic valves open and ventricular ejection occurs, which is the second part of ventricular systole.

Ventricular ejection is divided into the rapid ejection phase and the reduced ejection phase. During the rapid

ejection phase, forward flow is maximal, and pulmonary artery and aortic pressure is maximally developed. In the reduced ejection phase, flow and great artery pressure taper with progression of systole. Pressure in both ventricular chambers decreases as blood is ejected from the heart, and ventricular diastole begins with closure of the pulmonic and aortic valves. The initial period of ventricular diastole consists of the isovolumic (isometric) relaxation phase. This phase is concomitant with repolarization of the ventricular myocardium and corresponds to the end of the T wave on the ECG. The final portion of ventricular diastole involves a rapid decrease in intraventricular pressure until it decreases to less than that of the right and left atria, at which point the AV valve reopens, ventricular filling occurs, and the cycle repeats itself.

VENTRICULAR STRUCTURE AND FUNCTION

Ventricular Structure

The specific architectural order of the cardiac muscles provides the basis for the heart to function as a pump. The ellipsoid shape of the left ventricle (LV) is a result of the laminar layering of spiraling bundles of cardiac muscles (Fig. 20-2). The orientation of the muscle bundle is longitudinal in the subepicardial myocardium and circumferential in the middle segment and again becomes longitudinal in the subendocardial myocardium. Because of the ellipsoid shape of the LV, regional differences in wall thickness result in corresponding variations in the cross-sectional radius of the left ventricular chamber. These regional differences may serve to accommodate the variable loading conditions of the LV.[4] In addition, such anatomy allows the LV to eject blood in a corkscrew-type motion beginning from the base and ending at the apex. The architecturally complex structure of the LV thus allows maximal shortening of myocytes, which results in increased wall thickness and the generation of force during systole. Moreover, release of the twisted LV may provide a suction mechanism for filling of the LV during diastole. The left ventricular free wall and the septum have similar muscle bundle architecture. As a result, the septum moves inward during systole in a normal heart. Regional wall thickness is a commonly used index of myocardial performance that can be clinically assessed, such as by perioperative echocardiography or magnetic resonance imaging.

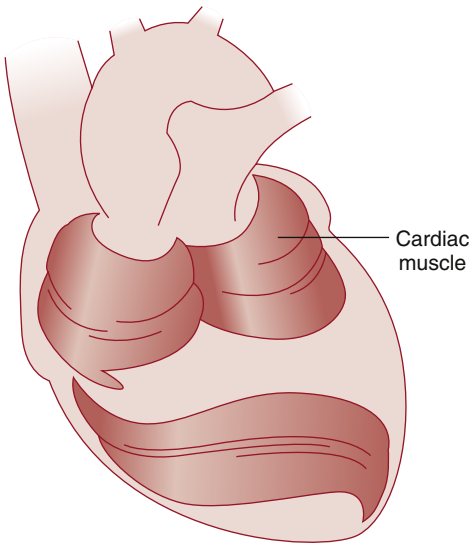


Figure 20-2. Muscle bundles. *(From Marieb EN:* Human anatomy & physiology, *ed 5. San Francisco, 2001, Pearson Benjamin Cummings, p 684.)*

Unlike the LV, which needs to pump against the higher-pressure systemic circulation, the right ventricle (RV) pumps against a much lower pressure circuit in the pulmonary circulation. Consequently, wall thickness is considerably less in the RV. In contrast to the ellipsoidal form of the LV, the RV is crescent shaped; as a result, the mechanics of right ventricular contraction are more complex. Inflow and outflow contraction is not simultaneous, and much of the contractile force seems to be recruited from interventricular forces of the LV-based septum.

An intricate matrix of collagen fibers forms a scaffold of support for the heart and adjacent vessels. This matrix provides enough strength to resist tensile stretch. The collagen fibers are made up of mostly the thick collagen type I fiber, which cross-links with the thin collagen type III fiber, the other major type of collagen.[5] Elastic fibers that contain elastin are in close proximity to the collagen fibers. They account for the elasticity of the myocardium.[6]

Ventricular Function

Systolic Function. The heart provides the driving force for delivering blood throughout the cardiovascular system to supply nutrients and to remove metabolic waste. Because of the anatomic complexity of the RV, the traditional description of systolic function is usually limited to the LV. Systolic performance of the heart is dependent on loading conditions and contractility. Preload and afterload are two interdependent factors extrinsic to the heart that govern cardiac performance.

Diastolic Function. Diastole is ventricular relaxation, and it occurs in four distinct phases: (1) isovolumic relaxation; (2) the rapid filling phase (i.e., the LV chamber filling at variable left ventricular pressure); (3) slow filling, or diastasis; and (4) final filling during atrial systole. The isovolumic relaxation phase is energy dependent. During the auxotonic relaxation (phases 2 through 4), ventricular filling occurs against pressure. It encompasses a period during which the myocardium is unable to generate force, and filling of the ventricular chambers takes place. The isovolumic relaxation phase does not contribute to ventricular filling. The greatest amount of ventricular filling occurs in the second phase, whereas the third phase adds only approximately 5% of total diastolic volume and the final phase provides 15% of ventricular volume from atrial systole.

To assess diastolic function, several indices have been developed. The most widely used index for examining the isovolumic relaxation phase of diastole is to calculate the peak instantaneous rate of decline in left ventricular pressure ($-dP/dt$) or the time constant of isovolumic decline in left ventricular pressure (τ). The aortic closing–mitral opening interval and the isovolumic relaxation time and peak rate of left ventricular wall thinning, as determined by echocardiography, have both been used to estimate

diastolic function during auxotonic relaxation. Ventricular compliance can be evaluated by pressure-volume relationships to determine function during the auxotonic phases of diastole.[7,8]

Many different factors influence diastolic function: magnitude of systolic volume, passive chamber stiffness, elastic recoil of the ventricle, diastolic interaction between the two ventricular chambers, atrial properties, and catecholamines. Whereas systolic dysfunction is a reduced ability of the heart to eject, diastolic dysfunction is a decreased ability of the heart to fill. Abnormal diastolic function is now being recognized as the predominant cause of the pathophysiologic condition of congestive heart failure.[9]

Ventricular interactions during systole and diastole are internal mechanisms that function as internal feedback to modulate stroke volume. Systolic ventricular interaction involves the effect of the interventricular septum on the function of both ventricles. Because the interventricular septum is anatomically linked to both ventricles, it is part of the load against which each ventricle has to work. Therefore, any changes in one ventricle will also be present in the other. In diastolic ventricular interaction, dilatation of either the LV or RV will have an impact on effective filling of the contralateral ventricle and thereby modify function.

Preload and Afterload. *Preload* is defined as the ventricular load at the end of diastole, before contraction has started. First described by Starling, a linear relationship exists between sarcomere length and myocardial force (Fig. 20-3). In clinical practice, surrogate representatives of left ventricular volume such as pulmonary wedge pressure or central venous pressure are used to estimate preload.[3] With the development of transesophageal echocardiography, a more direct measure of ventricular volume is available.

Afterload is defined as systolic load on the LV after contraction has begun. Aortic compliance is an additional determinant of afterload.[1] Aortic compliance is the ability of the aorta to give way to systolic forces from the ventricle. Changes in the aortic wall (dilation or stiffness) can alter aortic compliance and thus afterload. Examples of pathologic conditions that alter afterload are aortic stenosis and chronic hypertension. Both impede ventricular ejection, thereby increasing afterload. Aortic impedance, or aortic pressure divided by aortic flow at that instant, is an accurate means of gauging afterload. However, clinical measurement of aortic impedance is invasive. Echocardiography can noninvasively estimate aortic impedance by determining aortic blood flow at the time of its maximal increase. In clinical practice, the measurement of systolic blood pressure is adequate to approximate afterload, provided that aortic stenosis is not present.

Preload and afterload can be thought of as the wall stress that is present at the end of diastole and during left ventricular ejection, respectively. Wall stress is a useful concept because it includes preload, afterload, and the energy required to generate contraction. Wall stress and heart rate are probably the two most relevant indices that account for changes in myocardial O_2 demand. Laplace's law states that wall stress (σ) is the product of pressure (P) and radius (R) divided by wall thickness (h)[3]:

$$\sigma = P \times R/2h$$

The ellipsoid shape of the LV allows the least amount of wall stress such that as the ventricle changes its shape from ellipsoid to spherical, wall stress is increased. By using the ratio of the long axis to the short axis as a measure of the ellipsoid shape, a decrease in this ratio would signify a transition from ellipsoid to spherical.

Thickness of the left ventricular muscle is an important modifier of wall stress. For example, in aortic stenosis, afterload is increased. The ventricle must generate a much higher pressure to overcome the increased load opposing systolic ejection of blood. To generate such high performance, the ventricle increases its wall thickness (left ventricular hypertrophy). By applying Laplace's law, increased left ventricular wall thickness will decrease wall stress, despite the necessary increase in left ventricular pressure to overcome the aortic stenosis (Fig. 20-4).[10] In a failing heart, the radius of the LV increases, thus increasing wall stress.

Frank-Starling Relationship. The Frank-Starling relationship is an intrinsic property of myocardium by

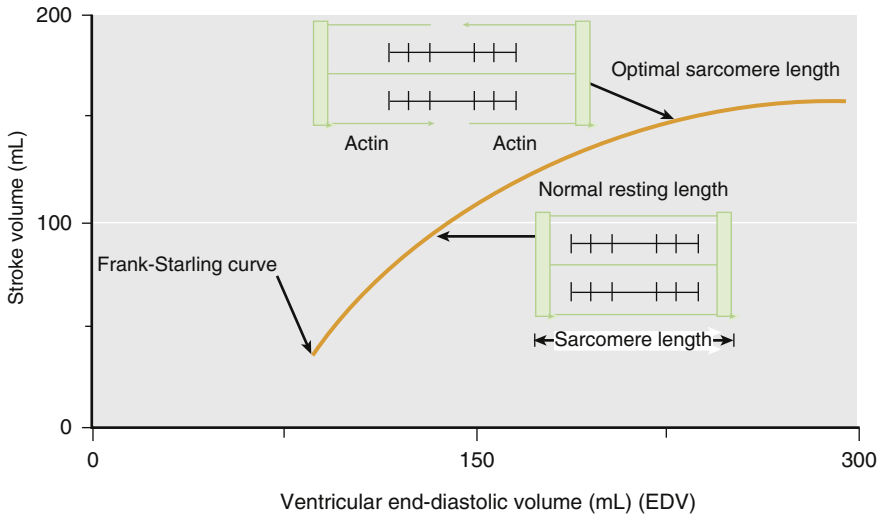


Figure 20-3. Frank-Starling relationship. The relationship between sarcomere length and tension developed in cardiac muscles is shown. In the heart, an increase in end-diastolic volume is the equivalent of an increase in myocardial stretch; therefore, according to the Frank-Starling law, increased stroke volume is generated.

which stretching of the myocardial sarcomere results in enhanced myocardial performance for subsequent contractions (see Fig. 20-3). In 1895, Otto Frank first noted that in skeletal muscle, the change in tension was directly related to its length, and as pressure changed in the heart, a corresponding change in volume occurred.[11] In 1914, E. H. Starling, using an isolated heart-lung preparation as a model, observed that "the mechanical energy set free on passage from the resting to the contracted state is a function of the length of the muscle fiber."[12] If a strip of cardiac muscle is mounted in a muscle chamber under isometric conditions and stimulated at a fixed frequency, then an increase in sarcomere length results in an increase in twitch force. Starling concluded that the increased twitch force was the result of a greater interaction of muscle bundles.

Electron microscopy has demonstrated that sarcomere length (2 to 2.2 μm) is positively related to the amount of actin and myosin cross-bridging and that there is an optimal sarcomere length at which the interaction is maximal. This concept is based on the assumption that the increase in cross-bridging is equivalent to an increase in muscle performance. Although this theory continues to hold true for skeletal muscle, the force-length relationship in cardiac muscle is more complex. When comparing force-strength relationships between skeletal and cardiac muscle, it is noteworthy that the reduction in force is only 10%, even if cardiac muscle is at 80% sarcomere length.[11] The cellular basis of the Frank-Starling mechanism is still being investigated and is briefly discussed later in this chapter. A common clinical application of Starling's law is the relationship of left ventricular end-diastolic volume (LVEDV) and stroke volume. The Frank-Starling mechanism may remain intact even in a failing heart.[13] However, ventricular remodeling after injury or in heart failure may modify the Frank-Starling relationship.

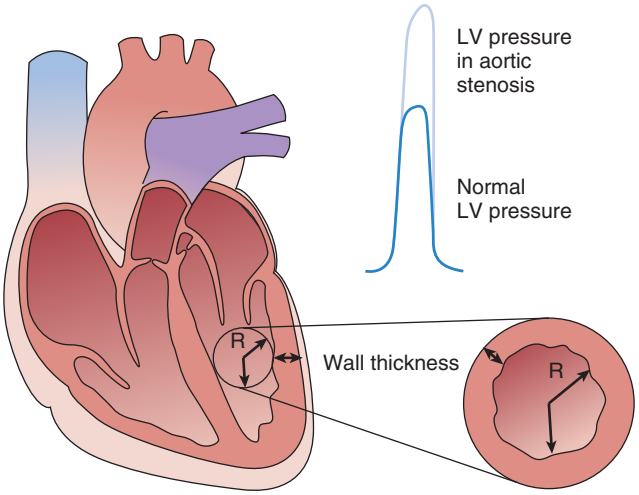


Figure 20-4. In response to aortic stenosis, left ventricular (LV) pressure increases. To maintain wall stress at control levels, compensatory LV hypertrophy develops. According to Laplace's law, wall stress = pressure · radius (R) ÷ (2 × wall thickness). Therefore the increase in wall thickness offsets the increased pressure, and wall stress is maintained at control levels. *(From Opie LH: Ventricular function. In* The heart. Physiology from cell to circulation, *ed 4. Philadelphia, 2004, Lippincott-Raven, pp 355-401.)*

Contractility. Each Frank-Starling curve specifies a level of contractility, or the inotropic state of the heart, which is defined as the work performed by cardiac muscle at any given end-diastolic fiber. Factors that modify contractility will create a family of Frank-Starling curves with different contractility (Fig. 20-5).[10] Factors that modify contractility are exercise, adrenergic stimulation, changes in pH, temperature, and drugs such as digitalis. The ability of the LV to develop, generate, and sustain the necessary pressure for the ejection of blood is the intrinsic inotropic state of the heart.

In isolated muscle, the maximal velocity of contraction (Vmax) is defined as the maximal velocity of ejection at zero load. Vmax is obtained by plotting the velocity of muscle shortening in isolated papillary muscle at varying degrees of force. Although this relationship can be replicated in isolated myocytes, Vmax cannot be measured in an intact heart because complete unloading is impossible. To measure the intrinsic contractile activity of an intact heart, several strategies have been attempted with varying success. Pressure-volume loops, albeit requiring catheterization of the left side of the heart, are currently the best way to determine contractility in an intact heart (Fig. 20-6).[10] The pressure-volume loop represents an indirect measure of the Frank-Starling relationship between force (pressure) and muscle length (volume). Clinically, the most commonly used noninvasive index of ventricular contractile function is the ejection fraction, which is assessed by echocardiography, angiography, or radionuclide ventriculography.

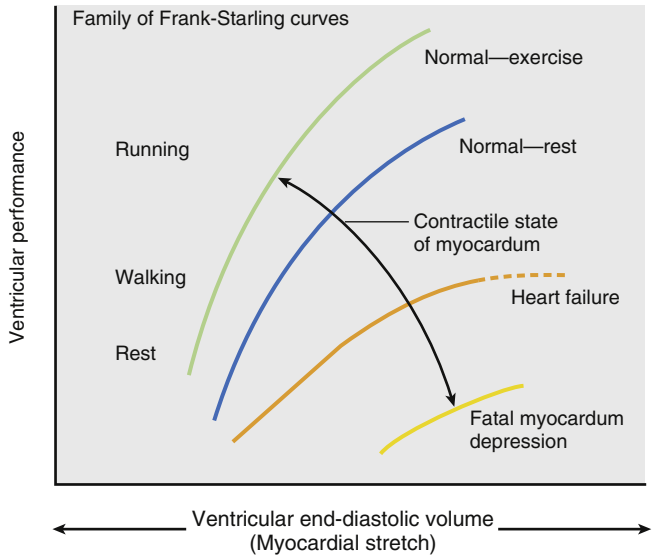


Figure 20-5. A family of Frank-Starling curves is shown. A leftward shift of the curve denotes enhancement of the inotropic state, whereas a rightward shift denotes decreased inotropy. *(From Opie LH: Ventricular function. In* The heart. Physiology from cell to circulation, *ed 4. Philadelphia, 2004, Lippincott-Raven, pp 355-401.)*

$$\text{Ejection fraction} = (\text{LVEDV} - \text{LVESV})/\text{LVEDV}$$

where LVESV is left ventricular end-systolic volume.

Cardiac Work. The work of the heart can be divided into external and internal work. External work is expended to eject blood under pressure, whereas internal work is expended within the ventricle to change the shape of the heart and to prepare it for ejection. Internal work contributes to inefficiency in the performance of the heart. Wall stress is directly proportional to the internal work of the heart.[14]

External work, or stroke work, is a product of the stroke volume (SV) and pressure (P) developed during ejection of the SV.

$$\text{Stroke work} = \text{SV} \times \text{P} \text{ or } (\text{LVEDV} - \text{LVESV}) \times \text{P}$$

The external work and internal work of the ventricle both consume O_2. The clinical significance of internal work is illustrated in the case of a poorly drained LV during cardiopulmonary bypass. Although external work is provided by the roller pump during bypass, myocardial ischemia can still occur because poor drainage of the LV creates tension on the left ventricular wall and increases internal work.

The efficiency of cardiac contraction is estimated by the following formula[8]:

$$\text{Cardiac efficiency} = \text{External work}/\text{Energy equivalent of } O_2 \text{ consumption}$$

The corkscrew motion of the heart for the ejection of blood is the most favorable in terms of work efficiency, based on the architecture in a normal LV (with the cardiac muscle bundles arranged so that a circumferentially oriented middle layer is sandwiched by longitudinally oriented outer layers). In heart failure, ventricular dilation reduces cardiac efficiency because it increases wall stress, which in turn increases O_2 consumption.[11]

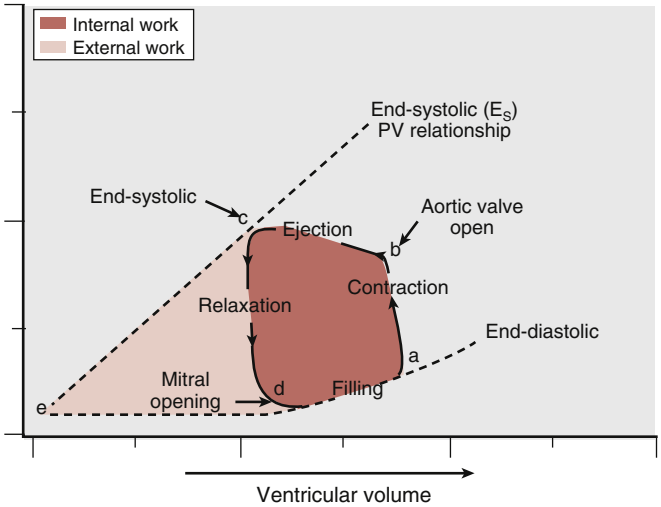


Figure 20-6. Pressure-volume (PV) loop. Point *a* depicts the start of isovolumetric contraction. The aortic valve opens at point *b,* and ejection of blood follows *(points b→c).* The mitral valve opens at point *d,* and ventricular filling ensues. External work is defined by points *a, b, c,* and *d,* and internal work is defined by points *e, d,* and *c.* The PV area is the sum of external and internal work. *(From Opie LH: Ventricular function. In* The heart. Physiology from cell to circulation, *ed 4. Philadelphia, 2004, Lippincott-Raven, pp 355-401.)*

Heart Rate and Force-Frequency Relationship. In isolated cardiac muscle, an increase in the frequency of stimulation induces an increase in the force of contraction. This relationship is termed the *treppe*, which means *staircase* in German, and is the phenomenon or the force-frequency relationship.[8,15] At between 150 and 180 stimuli per minute, maximal contractile force is reached in an isolated heart muscle at a fixed muscle length. Thus an increased frequency incrementally increases inotropy, whereas stimulation at a lower frequency decreases contractile force. However, when the stimulation becomes extremely rapid, the force of contraction decreases. In the clinical context, pacing-induced positive inotropic effects may be effective only up to a certain heart rate, based on the force-frequency relationship. In a failing heart, the force-frequency relationship may be less effective in producing a positive inotropic effect.[8]

CARDIAC OUTPUT

Cardiac output is the amount of blood pumped by the heart per unit of time ($\dot{Q}$) and is determined by four factors: two factors that are intrinsic to the heart—heart rate and myocardial contractility—and two factors that are extrinsic to the heart but functionally couple the heart and the vasculature—preload and afterload.

Heart rate is defined as the number of beats per minute and is mainly influenced by the autonomic nervous system. Increases in heart rate escalate cardiac output as long as ventricular filling is adequate during diastole. *Contractility* can be defined as the intrinsic level of contractile performance that is independent of loading conditions. Contractility is difficult to define in an intact heart because it cannot be separated from loading conditions.[8,15] For example, the *Frank-Starling relationship* is defined as the change in intrinsic contractile performance, based on changes in preload. Cardiac output in a living organism can be measured with the Fick principle (a schematic depiction is illustrated in Fig. 20-7).[1]

The Fick principle is based on the concept of conservation of mass such that the O_2 delivered from pulmonary venous blood (q_3) is equal to the total O_2 delivered to pulmonary capillaries through the pulmonary artery (q_1) and the alveoli (q_2).

The amount of O_2 delivered to the pulmonary capillaries by way of the pulmonary arteries (q_1) equals total pulmonary arterial blood flow ($\dot{Q}$) times the O_2 concentration in pulmonary arterial blood ($CpaO_2$):

$$q_1 = \dot{Q} \times CpaO_2$$

The amount of O_2 carried away from pulmonary venous blood (q_3) is equal to total pulmonary venous blood flow ($\dot{Q}$) times the O_2 concentration in pulmonary venous blood ($Cpvo_2$):

$$q_3 = \dot{Q} \times CpvO_2$$

The pulmonary arterial O_2 concentration is the mixed systemic venous O_2, and the pulmonary venous O_2 concentration is the peripheral arterial O_2. O_2 consumption

is the amount of O_2 delivered to the pulmonary capillaries from the alveoli (q_2). Because $q_1 + q_2 = q_3$,

$$\dot{Q}\,(CpaO_2) + q_2 = \dot{Q}\,(CpvO_2)$$

$$q_2 = \dot{Q}\,(CpvO_2) - \dot{Q}\,(CpaO_2)$$

$$q_2 = \dot{Q}\,(Cpvo_2) - CpaO_2$$

$$\dot{Q} = q_2 / (CpvO_2 - CpaO_2)$$

Thus if the $CpaO_2$, $CpvO_2$, and O_2 consumption (q_2) are known, then the cardiac output can be determined.

The indicator dilution technique is another method for determining cardiac output also based on the law of conservation of mass. The two most commonly used indicator dilution techniques are the dye dilution and the thermodilution methods. Figure 20-8 illustrates the principles of the dye dilution method.[1]

CELLULAR CARDIAC PHYSIOLOGY

CELLULAR ANATOMY

At the cellular level, the heart consists of three major components: (1) cardiac muscle tissue (contracting cardiomyocytes), (2) conduction tissue (conducting cells), and (3) extracellular connective tissue. A group of cardiomyocytes with its connective tissue support network or extracellular matrix make up a myofiber (Fig. 20-9). Adjacent myofibers are connected by strands of collagen. The extracellular matrix is the synthetic product of fibroblasts and is made up of collagen, which is the main determinant of myocardial stiffness, and other major matrix proteins. One of the matrix proteins, elastin, is the chief constituent of elastic fibers. The elastic fibers account for, in part, the elastic properties of the myocardium.[6] Other matrix proteins include the glycoproteins or proteoglycans and matrix metalloproteinases. Proteoglycans are proteins with short sugar chains, and they include heparan sulfate, chondroitin, fibronectin, and laminin. Matrix metalloproteins are enzymes that degrade collagen and other extracellular proteins. The balance between the accumulation of extracellular matrix proteins by synthesis and

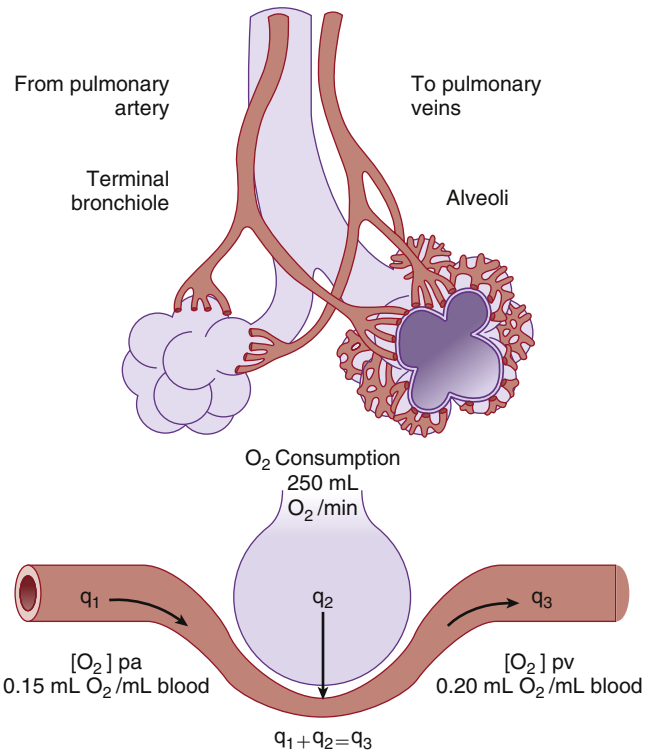


Figure 20-7. Illustration demonstrates the principle of determination of cardiac output according to the Fick formula. If the oxygen (O_2) concentration in pulmonary arterial blood ($CpaO_2$), the O_2 concentration of the pulmonary vein ($CpvO_2$), and the O_2 consumption are known, then cardiac output can be calculated. *pa,* Pulmonary artery; *pv,* pulmonary vein. *(From Berne RM, Levy MN: The cardiac pump. In* Cardiovascular physiology, *ed 8. St. Louis, 2001, Mosby, pp 55-82.)*

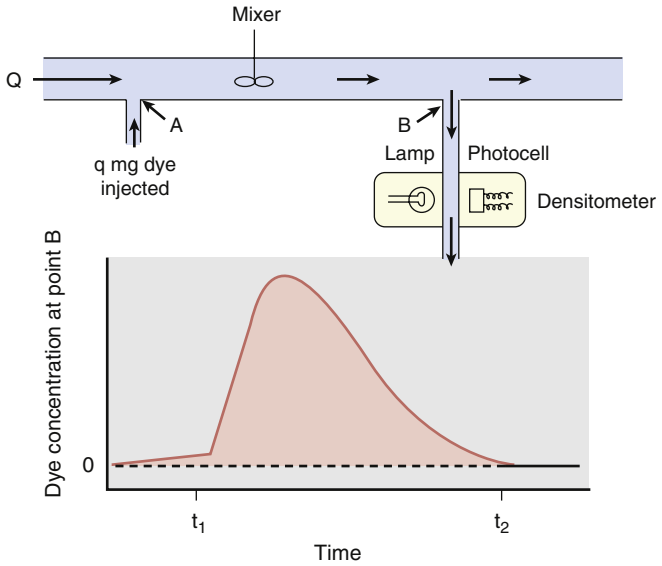


Figure 20-8. Illustration demonstrates the principle of determining cardiac output with the indicator dilution technique. This model assumes that there is no recirculation. A known amount of dye *(q)* is injected at point *A* into a stream flowing at $\dot{Q}$ (mL/min). A mixed sample of the fluid flowing past point *B* is withdrawn at a constant rate through a densitometer. The change in dye concentration over time is depicted in a curve. Flow may be measured by dividing the amount of indicator injected upstream by the area under the downstream concentration curve. *(From Berne RM, Levy MN: The cardiac pump. In* Cardiovascular physiology, *ed 8. St. Louis, 2001, Mosby, pp 55-82.)*

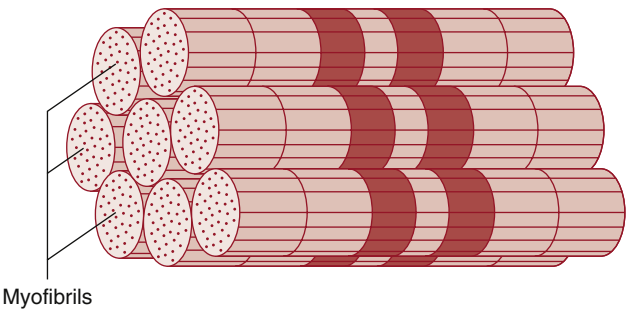


Figure 20-9. Organization of cardiomyocytes. Fifty percent of cardiomyocyte volume is made up of myofibrils; the remainder consists of mitochondria, nucleus, sarcoplasmic reticulum, and cytosol.

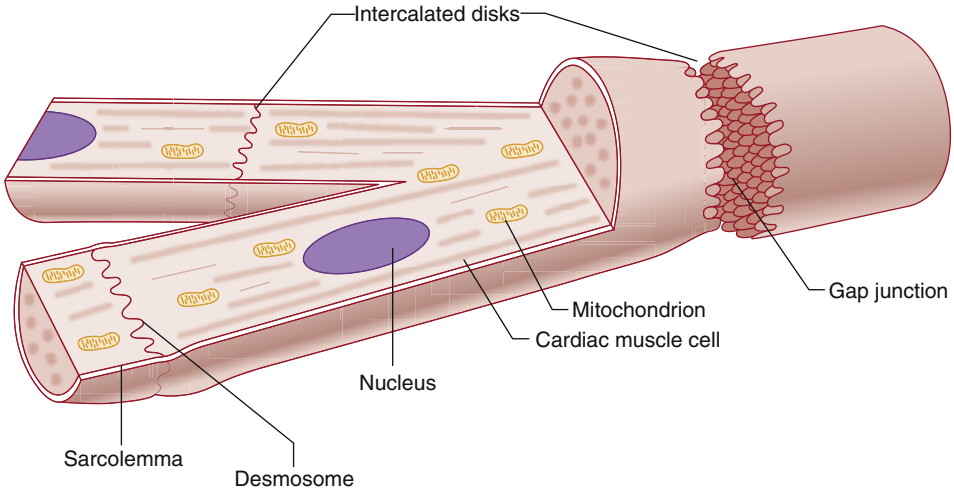


Figure 20-10. The sarcolemma that envelops cardiomyocytes becomes highly specialized to form the intercalated disks where ends of neighboring cells are in contact. The intercalated disks consist of gap junctions and *spot* and *sheet* desmosomes.

their breakdown by matrix metalloproteins contributes to the mechanical properties and function of the heart.[6]

CARDIOMYOCYTE STRUCTURE AND FUNCTION

Individual contracting cardiomyocytes are large cells between 20 μm (atrial cardiomyocytes) and 140 μm (ventricular cardiomyocytes) in length. Approximately 50% of the cell volume in a contracting cardiomyocyte is made up of myofibrils, and the remainder consists of mitochondria, nucleus, sarcoplasmic reticulum (SR), and cytosol. The myofibril is the rodlike bundle that forms the contractile elements within cardiomyocytes. Within each contractile element are contractile proteins, regulatory proteins, and structural proteins. Contractile proteins make up approximately 80% of the myofibrillar protein, with the remainder being regulatory and structural proteins.[16,17] The basic unit of contraction is the sarcomere (see discussion under "Contractile Elements" later in this chapter).

The sarcolemma, or the outer plasma membrane, separates the intracellular and extracellular space. It surrounds the cardiomyocyte and invaginates into the myofibrils through an extensive tubular network known as *transverse tubules* or *T tubules*, and it also forms specialized intercellular junctions between cells.[18,19]

Transverse or T tubules are in close proximity to an intramembranous system and the SR, which plays an important role in the calcium (Ca^{2+}) metabolism that is critical in the excitation-contraction coupling (ECC) of the cardiomyocyte. The SR can be further divided into the longitudinal (or network) SR and the junctional SR. The longitudinal SR is involved in the uptake of Ca^{2+} for the initiation of relaxation. The junctional SR contains large Ca^{2+}-release channels (ryanodine receptors [RyRs]) that release SR Ca^{2+} stores in response to depolarization-stimulated Ca^{2+} influx through the sarcolemmal Ca^{2+} channels. The RyRs are not only Ca^{2+}-release channels, but they also form the scaffolding proteins that anchor many of the key regulatory proteins.[20]

Mitochondria are immediately found beneath the sarcolemma, wedged between myofibrils within the cell. They contain enzymes that promote the generation of adenosine triphosphate (ATP), and they are the energy powerhouse for the cardiomyocyte. In addition, mitochondria can also accumulate Ca^{2+} and thereby contribute to the regulation of the cytosolic Ca^{2+} concentration. Nearly all of the genetic information is found within the centrally located nucleus. The cytosol is the fluid-filled microenvironment within the sarcolemma, exclusive of the organelles and the contractile apparatus and proteins.

Cardiac muscle cells contain three different types of intercellular junctions: gap junctions, *spot* desmosomes, and *sheet* desmosomes (or fasciae adherens) (Fig. 20-10).[18,21] Gap junctions are responsible for electrical coupling and the transfer of small molecules between cells, whereas desmosome-like junctions provide mechanical linkage. The adhesion sites formed by spot desmosomes anchor the intermediate filament cytoskeleton of the cell; those formed by the fasciae adherens anchor the contractile apparatus. Gap junctions consist of clusters of plasma membrane channels directly linking the cytoplasmic compartments of neighboring cells. Gap junction channels are constructed from connexins, a multigene family of conserved proteins. The principal connexin isoform of the mammalian heart is connexin 43; other connexins, notably connexins 40, 45, and 37, are also expressed but in smaller quantities.[20,21]

The conducting cardiomyocytes, or Purkinje cells, are cells specialized for conducting propagated action potentials. These cells have a low content of myofibrils and a prominent nucleus, and they contain an abundance of gap junctions. Cardiomyocytes can be functionally separated into (1) the excitation system, (2) the ECC system, and (3) the contractile system.

Excitation System

The cellular action potential originating in the specialized conduction tissue is propagated to individual cells where it initiates the intracellular event that leads to the contraction of the cell through the sarcolemmal excitation system.

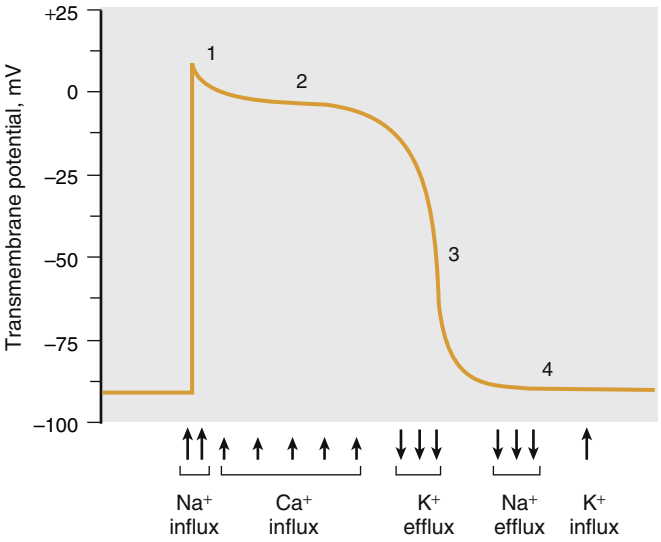


Figure 20-11. Phases of cellular action potentials and major associated currents in ventricular myocytes. The initial phase (0) spike and overshoot (1) are caused by a rapid inward sodium (Na^+) current, the plateau phase (2) by a slow calcium (Ca^{2+}) current through L-type Ca channels, and repolarization (phase 3) by outward potassium (K^+) currents. Phase 4, the resting potential (Na^+ efflux, K^+ influx), is maintained by Na^+-K^+-adenosine triphosphatase (ATPase). The Na^+-Ca^{2+} exchanger is mainly responsible for extrusion of Ca^{2+}. In specialized conduction system tissue, spontaneous depolarization takes place during phase 4 until the voltage resulting in opening of the Na channel is reached. *(From LeWinter MM, Osol G: Normal physiology of the cardiovascular system. In Fuster V, Alexander RW, O'Rourke RA, editors:* Hurst's the heart, *ed 10. New York, 2001, McGraw-Hill, pp 63-94.)*

Action Potential. Ion fluxes across plasma membranes result in depolarization (attaining a less negative membrane potential) and repolarization (attaining a more negative membrane potential). They are mediated by membrane proteins with ion-selective pores. Because these ion channel proteins open and close the pores in response to changes in membrane potential, the channels are voltage gated. In the heart, sodium (Na^+), potassium (K^+), Ca^{2+}, and chloride (Cl^-) channels contribute to the action potential.

The types of action potential in the heart can be separated into two categories: (1) fast-response action potentials, which are found in the His-Purkinje system and atrial or ventricular cardiomyocytes; and (2) slow-response action potentials, which are found in the pacemaker cells in the SA and AV nodes. A typical tracing of an action potential in the His-Purkinje system is depicted in Figure 20-11.[8] The electrochemical gradient for K^+ across the plasma membrane is the determinant for the resting membrane potential. Mostly as a result of the influx of Na^+, the membrane potential becomes depolarized, which leads to an extremely rapid upstroke (phase 0). As the membrane potential reaches a critical level (or threshold) during depolarization, the action potential is propagated. The rapid upstroke is followed by a transient repolarization (phase 1). Phase 1 is a period of brief and limited repolarization that is largely attributable to the activation of a transient outward K^+ current, i_{to}. The plateau phase (phase 2) occurs with a net influx of Ca^{2+} through L-type Ca^{2+} channels and the efflux of K^+ through several K^+ channels—the inwardly rectifying i_k, the delayed rectifier i_{k1}, and i_{to}. Repolarization (phase 3) is brought about when an efflux of K^+ from the three outward K^+ currents exceeds the influx of Ca^{2+}, thus returning the membrane to the resting potential. Very little ionic flux occurs during diastole (phase 4) in a fast-response action potential.

In contrast, during diastole (phase 4), pacemaker cells that show slow-response action potentials have the capability of spontaneous diastolic depolarization and generate the automatic cardiac rhythm. Pacemaker currents during phase 4 are the result of an increase in the three inward currents and a decrease in the two outward currents. The three inward currents that contribute to spontaneous pacemaker activity include two carried by Ca^{2+}, i_{CaL} and i_{CaT}, and one that is a mixed cation current, I_f.[22] The two outward currents are the delayed rectifier K^+ current, i_k, and the inward rectifying K^+ current, i_{k1}. When compared with the fast-response action potential, phase 0 is much less steep, phase 1 is absent, and phase 2 is indistinct from phase 3 in the slow-response action potential.[23] In SA node cells, the pacemaker I_f current is the principal determinant of duration diastolic depolarization, and it is encoded by four members of the hyperpolarization-activated cyclic nucleotide-gated gene (HCN1-4) family.[24]

During the cardiac action potential, movement of Ca^{2+} into the cell and Na^+ out of the cell creates an ionic imbalance. The Na^+-Ca^{2+} exchanger restores cellular ionic balance by actively transporting Ca^{2+} out of the cell against a concentration gradient while moving Na^+ into the cell in an energy-dependent manner.

Excitation-Contraction Coupling

Structures that participate in cardiac ECC include the sarcolemma, transverse tubules, SR, and myofilaments (Fig. 20-12, *A*).[25] The process of ECC begins with depolarization of the plasma membrane and spread of electrical excitation along the sarcolemma of cardiomyocytes.

The ubiquitous second messenger Ca^{2+} is the key player in cardiac ECC (see Fig. 20-12, *B*).[23] Cycling of Ca^{2+} within the structures that participate in ECC initiates and terminates contraction. Activation of the contractile system depends on an increase in free cytosolic Ca^{2+} and its subsequent binding to contractile proteins.

Ca^{2+} enters through plasma membrane channels concentrated at the T tubules, and such entry through L-type Ca^{2+} channels (dihydropyridine receptors) triggers the release of Ca^{2+} from the SR.[26] This evokes a *Ca^{2+} spark*. Ca^{2+} sparks are considered to be the elementary Ca^{2+} signaling event of ECC in heart muscle. A Ca^{2+} spark occurs with the opening of a cluster of SR RyRs to release Ca^{2+} in a locally regenerative manner. It, in turn, activates the Ca^{2+}-release channels and induces further release of Ca^{2+} from subsarcolemmal cisternae in the SR and thus leads to a large increase in intracellular Ca^{2+} (iCa^{2+}). These spatially and temporally patterned activations of localized Ca^{2+} release, in turn, stimulate myofibrillar contraction. The increase in iCa^{2+}, however, is transient inasmuch as Ca^{2+} is removed by (1) active uptake by the SR Ca^{2+} pump adenosine triphosphatase (ATPase), (2) extrusion of Ca^{2+} from the cytosol by the Na^+-Ca^{2+} exchanger, and (3) binding of Ca^{2+} to proteins.[27] Ca^{2+} sparks have also been implicated

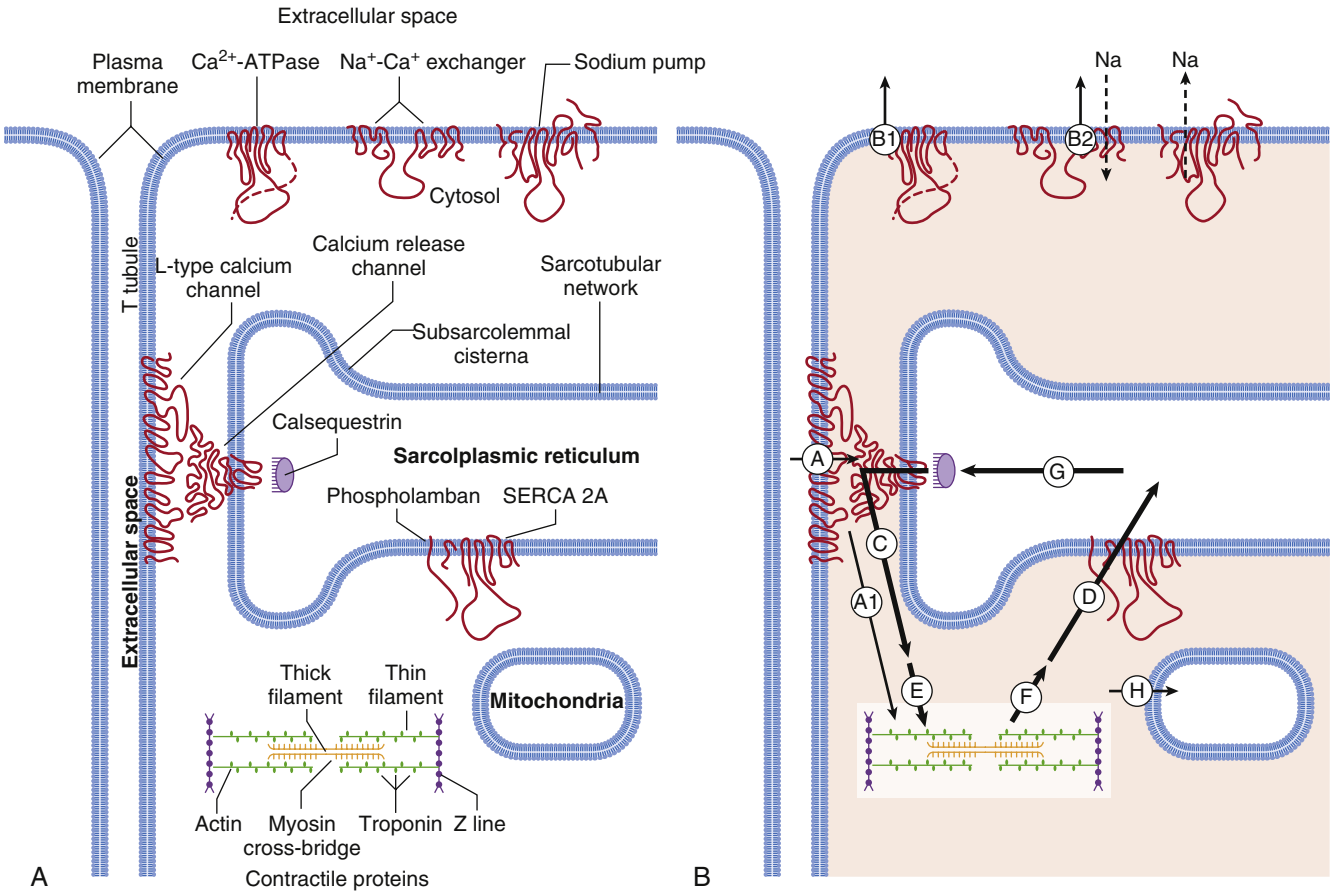


Figure 20-12. A, Diagram depicts the components of cardiac excitation-contraction coupling. Calcium pools are noted in **bold** letters. **B,** Extracellular (*arrows A, B1, B2*) and intracellular calcium flux (*arrows C, D, E, F,* and *G*) are shown. The thickness of the *arrows* indicates the magnitude of the calcium flux, and the vertical orientations describe their energetics: *downward-pointing arrows* represent passive calcium flux, whereas *upward-pointing arrows* represent energy-dependent calcium transport. Calcium entering the cell from extracellular fluid through L-type calcium channels triggers the release of calcium from the sarcoplasmic reticulum. Only a small portion directly activates the contractile proteins (*arrow A1*). *Arrow B1* depicts active transport of calcium into extracellular fluid by means of the plasma membrane calcium adenosine triphosphatase (Ca^{2+}-ATPase) pump and the sodium-calcium (Na^{+}-Ca^{2+}) exchanger. Sodium that enters the cell in exchange for calcium (*dashed line*) is pumped out of the cytosol by the sodium pump. SR regulates calcium efflux from the subsarcolemmal cisternae (*arrow C*) and calcium uptake into the sarcotubular network (*arrow D*). *Arrow G* represents calcium that diffuses within the SR. Calcium binding to (*arrow E*) and dissociation from (*arrow F*) high-affinity calcium-binding sites of troponin C activate and inhibit interactions of the contractile proteins. *Arrow H* depicts movement of calcium into and out of mitochondria to buffer the cytosolic calcium concentration. *SERCA 2A,* Sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase. *(From Katz AM: Calcium fluxes. In* Physiology of the heart, *ed 3. Philadelphia, 2001, Lippincott-Raven, pp 232-233.)*

in pathophysiologic diseases such as hypertension, cardiac arrhythmias, heart failure, and muscular dystrophy.[28-30]

The SR provides the anatomic framework and is the major organelle for the cycling of Ca^{2+}. It is the depot for iCa^{2+} stores. The cyclic release plus reuptake of Ca^{2+} by the SR regulates the cytosolic Ca^{2+} concentration and couples excitation to contraction. The physical proximity between L-type Ca^{2+} channels and RyRs at the SR membrane makes Ca^{2+}-induced Ca^{2+} release to occur easily. The *foot* region of the RyR is the part that extends from the SR membrane to the T tubules, where the L-type Ca^{2+} channels are located.[17,27,31]

The SR is also concerned with the reuptake of Ca^{2+} that initiates relaxation or terminates contraction. The sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pump is the ATP-dependent pump that actively pumps the majority of the Ca^{2+} back into the SR after its release. SERCA makes up close to 90% of all of the SR proteins and is inhibited by the phosphoprotein, phospholamban, at rest. Phospholamban is an SR membrane protein that is active in the dephosphorylated form. Phosphorylation by a variety of kinases as a result of β-adrenergic stimulation or other stimuli inactivates phospholamban and releases its inhibitory action on SERCA. Positive feedback ensues and leads to further phospholamban phosphorylation and greater SERCA activity. Active reuptake of Ca^{2+} by SERCA then promotes relaxation.[17,27,31]

Once taken up into the SR, Ca^{2+} is stored until it is released during the next cycle. Calsequestrin and calreticulin are two storage proteins in the SR. Calsequestrin is a highly charged protein located in the cisternal component of the SR near the T tubules. Because it lies close to the Ca^{2+}-release channels, the stored Ca^{2+} can be quickly discharged for release once the Ca^{2+}-release channels are stimulated. Cytosolic Ca^{2+} can also be removed by extrusion through the sarcolemmal Ca^{2+} pump and the activity of the Na^{+}-Ca^{2+} exchanger. The protein, calmodulin, is an important *sensor* and regulator of iCa^{2+}.[19]

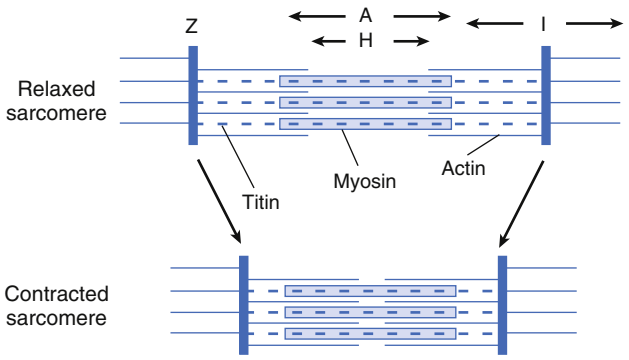


Figure 20-13. The basic unit of contraction is the sarcomere. A contracted and relaxed sarcomere is depicted. Z lines are located at the ends of the sarcomere. The A band is the site of overlap between myosin and actin filaments. The I band is located on either side of the A band and contains only actin filament. The H zone is located in the center of the A band, and only myosin is present.

Contractile System

Contractile Elements. The basic working unit of contraction is the sarcomere. A *sarcomere* is defined as the distance between Z lines (*Z* is an abbreviation for the German word, *Zuckung*, meaning *contraction*), which join the sarcomeres in series. Each sarcomere consists of a central A band that is separated by one half of an I band from the Z lines on each side because the Z line bisects the I band. A schematic representation is depicted in Figure 20-13.[8] Within each sarcomere are two principal contractile proteins (see the next section, "Contractile Proteins") and one noncontractile protein, titin.[27] The two contractile proteins are actin, the thin filament, and myosin, the thick filament. Actin filaments and titin are both tethered to the Z line, but the thick myosin filaments do not actually reach the Z lines. Titin, the third filament protein, tethers the thick-filament myosin to the Z line. The Z lines at the two ends of the sarcomere are brought closer together during contraction as the thick-filament myosin heads interact with the thin actin filaments and slide over each other.[32,33]

Familial hypertrophic cardiomyopathy is an inherited autosomal dominant sarcomeric disease[34] that is the most common cause of sudden death in otherwise healthy individuals. Its clinical features are left ventricular hypertrophy and myocyte and myofibrillar disarray. Mutations in at least eight different genes encoding sarcomere proteins have been identified to be the molecular basis for the disorder. These genes are β-cardiac myosin heavy chain, cardiac troponin T (TnT), α-tropomyosin, cardiac myosin-binding protein C, essential or regulatory myosin light chain, cardiac troponin I (TnI), α-cardiac actin, and titin.[34]

Contractile Proteins. The contractile apparatus within the cardiomyocyte consists of contractile and regulatory proteins.[19,35,36] The thin-filament actin and the thick-filament myosin are the two principal contractile proteins. Actin contains two helical chains. Tropomyosin, a double-stranded α-helical regulatory protein, winds around the actin array and forms the backbone for the thin-filament actin. The thick-filament myosin is made up of 300 myosin molecules. Each myosin molecule has two functional domains: the body or filament and the bilobar myosin head. The myosin head is made up of one heavy chain and two light chains. The heavy head chain has two domains: the larger one interacts with actin at the actin cleft and has an ATP-binding pocket where myosin ATPase is located, and the other smaller one is flexible and attached to the two light chains. The regulatory troponin heterotrimer complex is found at regular intervals along tropomyosin. The heterotrimer troponins are made up of troponin C (TnC), the Ca^{2+} receptor; TnI, an inhibitor of actin-myosin interaction; and TnT, which links the troponin complex to tropomyosin. Tropomodulin is another regulatory protein. It is located at the end of the thin-filament actin and caps the end to prevent any excessive elongation of the thin filament.[32,33]

Myocyte Contraction and Relaxation. At rest, cross-bridge cycling and generation of force do not occur because either the myosin heads are blocked from physically reacting with the thin filament or they are only weakly bound to actin (Fig. 20-14).[16] Cross-bridge cycling is initiated on binding of Ca^{2+} to TnC, which increases TnC-TnI interaction and decreases the inhibitory TnI-actin interaction. These events, which ensue from the binding of Ca^{2+} to TnC, lead to conformational changes in tropomyosin and permit attachment of the myosin head to actin. Cross-bridging involves the detachment of the myosin head from actin and a reattachment of myosin to another actin on hydrolysis of ATP by myosin ATPase. Binding of ATP to the nucleotide pocket of the myosin head leads to the activation of myosin ATPase,[31-33] ATP hydrolysis, and changes in the configuration of the myosin head, all of which facilitate binding of the myosin head to actin and the generation of the power stroke of the myosin head. Based on this model, the rate of cross-bridge cycling is dependent on the activity of myosin ATPase.[36] Turnoff of cross-bridge cycling is largely initiated by the decrease in cytosolic Ca^{2+}.

Myocyte relaxation is an energy-dependent process because restoration of cytosolic Ca^{2+} to resting levels requires the expenditure of ATP. The decrease in cytosolic Ca^{2+} occurs through active reuptake of Ca^{2+} into the SR by SERCA and extrusion of Ca^{2+} by the Na^{+}-Ca^{2+} exchanger. This activity results in the release of Ca^{2+} binding to TnC and the separation of the myosin-actin cross-bridge. Myocyte relaxation is dependent on the kinetics of cross-bridge cycling, the affinity of Ca^{2+} for TnC, and the activity of the Ca^{2+}-reuptake mechanisms. Relaxation is enhanced by the increased kinetics of cross-bridge cycling, decreased Ca^{2+} affinity for TnC, and increased activity of Ca^{2+}-reuptake mechanisms.[27]

Titin is a giant stringlike protein that acts as the third filament within the sarcomere. A single titin molecule spans one half of the sarcomere. Structurally, titin consists of an inextensible anchoring segment and an extensible elastic segment. Its two main functions involve muscle assembly and elasticity. Titin is the principal determinant of the passive properties of the myocardium at small ventricular volumes.[37]

The Frank-Starling relationship states that an increase in end-diastolic volume results in enhanced systolic function.[38,39] At the cellular level, the key component for the Frank-Starling relationship is a length-dependent shift

in Ca^{2+} sensitivity.[40-42] Several possible mechanisms for this change in Ca^{2+} sensitivity have been implicated, including Ca^{2+} sensitivity: (1) as a function of myofilament lattice spacing, (2) involving positive cooperativity in cross-bridge binding to actin, and (3) dependence on a strain of the elastic protein titin.[36,40]

Cytoskeleton Proteins. The cytoskeleton is the protein framework within the cytoplasm that links, anchors, or tethers structural components inside the cell.[16,19] Microfilaments (actin filaments), microtubules, and intermediate filaments are three classes of cytoskeleton proteins found in the cytoplasm. Microfilament proteins are actin filaments, either sarcomeric or cortical, depending on their location. Sarcomeric actin filaments are the thin filaments in the contractile machinery that have been previously described. Cortical actin filaments are found below the plasma membrane at the cell surface and are linked to several other microfilament proteins, including dystrophin, vinculin, and ankyrin. Microtubules assemble by polymerization of the α- and β-dimers of tubulin. They play a major role in intracellular transport and cell division.[43] Attachment of the ends of microtubules to cellular structures causes the microtubules to expand and contract, thereby pulling and pushing these structures around the cell. The intermediate filaments are relatively insoluble. They have been demonstrated to be important in normal mitochondrial function and behavior. The desmin intermediate filament in cardiomyocytes connects the nucleus to the plasma membrane and is important in the transmission of the stress and strain of contractile force between cells.[44] The cytoskeleton provides the organization of microenvironments within the cell for enzyme and protein activity and interaction.

Whereas familial hypertrophic cardiomyopathy is a genetic sarcomeric disease, familial dilated cardiomyopathy

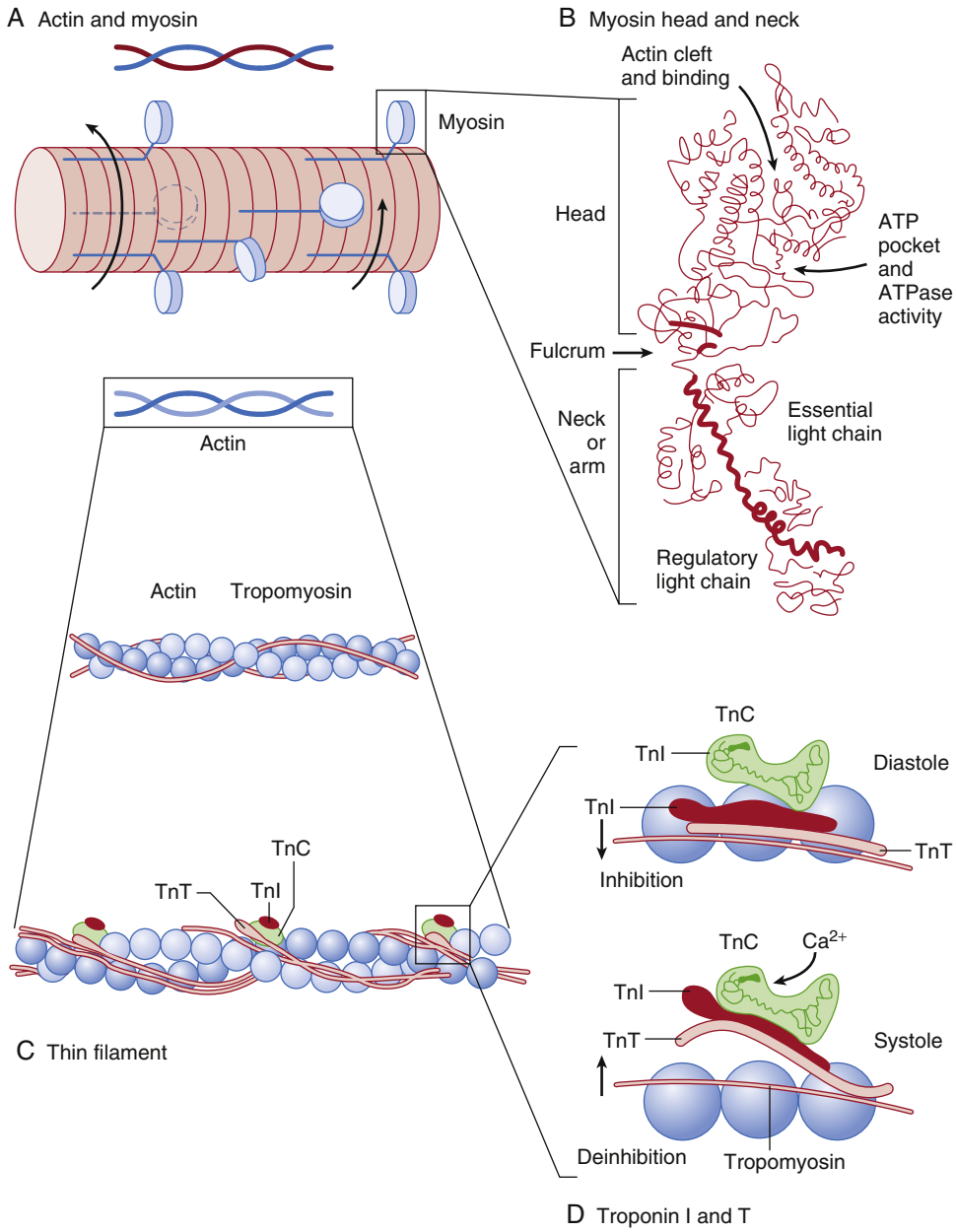


Figure 20-14. Molecules of the contractile system, troponins C, I, and T (TnC, TnI, and TnT). *ATP*, Adenosine triphosphate; *ATPase*, adenosine triphosphatase. *(From Opie LH: Ventricular function. In* The heart. Physiology from cell to circulation, *ed 4. Philadelphia, 2004, Lippincott-Raven, pp 209-231.)*

(FDCM) is a disease of cytoskeleton proteins. The genetic basis of FDCM includes two genes for X-linked FDCM (dystrophin, G4.5) and four genes for the autosomal dominant form (actin, desmin, lamin A/C, and δ-sarcoglycan).[16]

CONTROL OF CARDIAC FUNCTION

NEURAL REGULATION OF CARDIAC FUNCTION

The two limbs of the autonomic nervous system provide opposing input to regulate cardiac function.[45] The neurotransmitter of the sympathetic nervous system is norepinephrine, which provides positive chronotropic (heart rate), inotropic (contractility), and lusitropic (relaxation) effects. The parasympathetic nervous system has a more direct inhibitory effect in the atria and has a negative modulatory effect in the ventricles. The neurotransmitter of the parasympathetic nervous system is acetylcholine. Both norepinephrine and acetylcholine bind to seven-transmembrane–spanning G protein–coupled receptors to transduce their intracellular signals and affect their functional responses (Fig. 20-15).[46] At rest, the heart has a tonic level of parasympathetic cardiac nerve firing and little, if any, sympathetic activity. Therefore, the major influence on the heart at rest is parasympathetic. During exercise or stress, however, the sympathetic neural influence becomes more prominent.

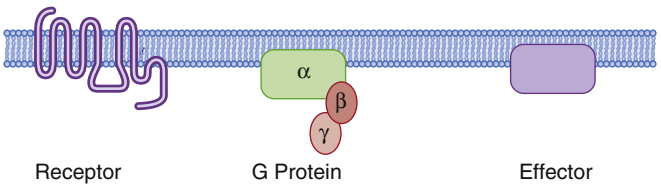


Figure 20-15. General scheme for a G protein–coupled receptor consisting of receptor, the heterotrimeric G protein, and the effector unit. *(Reprinted with permission from Bers DM: Cardiac excitation-contraction coupling,* Nature *415:198-205, 2002. Copyright MacMillan Magazines Ltd.)*

Parasympathetic innervation of the heart is through the vagal nerve. Supraventricular tissue receives significantly more intense vagal innervation than do the ventricles. The principal parasympathetic target neuroeffectors are the muscarinic receptors in the heart.[47,48] Activation of muscarinic receptors reduces pacemaker activity, slows AV conduction, directly decreases atrial contractile force, and exerts inhibitory modulation of ventricular contractile force. A total of five muscarinic receptors have been cloned.[49] M_2 receptors are the predominant subtype found in the mammalian heart. In the coronary circulation, M_3 receptors have been identified. Moreover, non–M_2 receptors have also been reported to exist in the heart. In general, for intracellular signaling, M_1, M_3, and M_5 receptors couple to $G_{q/11}$ protein and activate the phospholipase C–diacylglycerol–inositol phosphate system. On the other hand, the M_2 and M_4 receptors couple to the pertussis toxin–sensitive G protein, $G_{i/o}$, to inhibit adenylyl cyclase. M_2 receptors can couple to certain K^+ channels and influence the activity of Ca^{2+} channels, I_f current, phospholipase A_2, phospholipase D, and tyrosine kinases.

In contrast to vagal innervation, sympathetic innervation of the heart is more predominant in the ventricle than in the atrium. Norepinephrine released from sympathetic nerve terminals stimulates adrenergic receptors (adrenoreceptors [AdRs]) located in the heart. The two major classes of ARs are α and β, both of which are G protein–coupled receptors that transduce their intracellular signals by means of specific signaling cascades (Fig. 20-16).

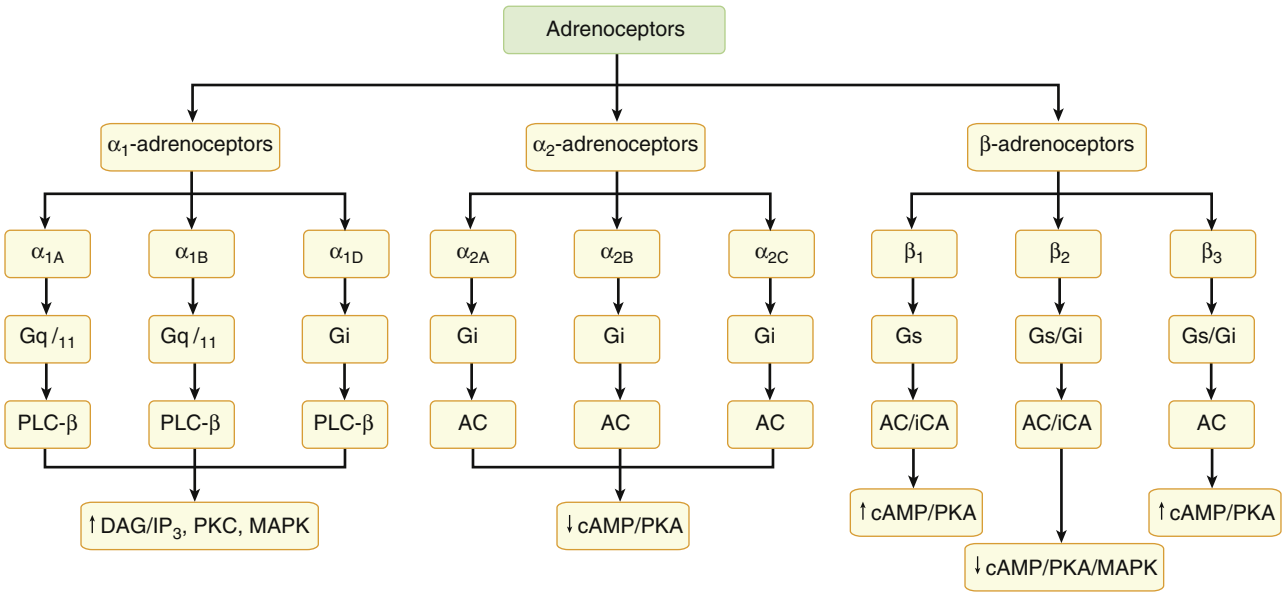


Figure 20-16. Adrenoceptor signaling cascades involving G proteins and effectors are adenylyl cyclase (AC), L-type calcium current (iCA), and phospholipase β (PLC-β) in the heart. The intracellular signals are diacylglycerol (DAG), inositol 1,4,5-triphosphate (IP_3), protein kinase C (PKC), cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), and mitogen-activated protein kinase (MAPK). *$Gq/_{11}$*, Heterotrimeric G protein; *Gi*, inhibitory G protein; *Gs*, stimulatory G protein.

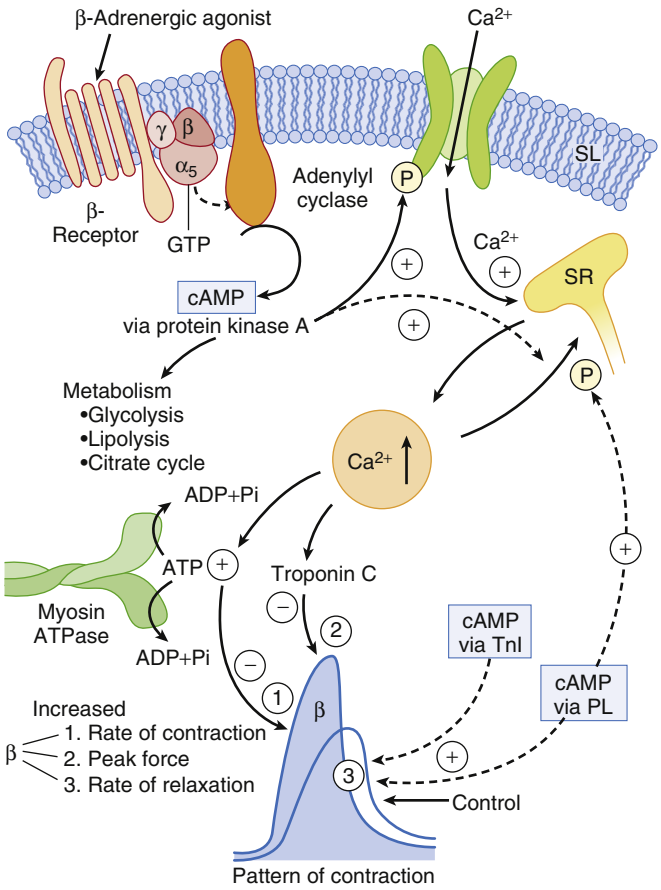


Figure 20-17. The β-adrenoceptor signaling system leads to an increased rate and force of contraction and increased relaxation. *ADP,* adenosine diphosphate; *ATP,* adenosine triphosphate; *ATPase,* adenosine triphosphatase; *cAMP,* cyclic adenosine monophosphate; *GTP,* guanosine triphosphate; *Pi,* phosphatidylinositol; *PL,* phospholipase; *SL,* sarcolemma; *SR,* sarcoplasmic reticulum; *TnI,* troponin I. *(From Opie LH: Receptors and signal transduction. In* The heart. Physiology from cell to circulation, *ed 3. Philadelphia, 1998, Lippincott-Raven, p 195.)*

β-ARs can be further divided into subpopulations of β_1, β_2, and β_3.[50] Although most mammalian hearts contain β1-ARs and β_2-ARs, β_3-ARs also exist in many mammalian ventricular tissues. The relative contribution of each β-AR subtype to modulation of cardiac function varies among species. In humans, β_1-ARs are the predominant subtype in both the atria and ventricles, but a substantial proportion of β_2-ARs are located in the atria, and approximately 20% of β_2-ARs are found in the LV. Much less is known about β_3-ARs, but they do exist in the human ventricle. Despite the fact that the β_1-AR population is more intense than the β_2-AR population, the cardiostimulant effect is not proportional to the relative densities of these two subpopulations, which is largely attributable to the tighter coupling of β_2-ARs than β_1-ARs to the cyclic adenosine monophosphate (cAMP) signaling pathway. Both β_1-ARs and β_2-ARs activate a pathway that involves the stimulatory G protein (Gs), activation of adenylyl cyclase, accumulation of cAMP, stimulation of cAMP-dependent protein kinase A, and phosphorylation of key target proteins, including L-type Ca^{2+} channels, phospholamban, and TnI.

Although traditional teaching is that both β_1-ARs and β_2-ARs are coupled to the G_s-cAMP pathway, more recent experimental evidence indicates that β_2-ARs also couple to the inhibitory G protein (Gi) to activate non–cAMP-dependent signaling pathways. Additionally, β_2-ARs can couple to G protein–independent pathways to modulate cardiac function. β-AR stimulation increases both contraction and relaxation, as summarized in Figure 20-17.

The two major subpopulations of α-ARs are α_1 and α_2. α_1-ARs and α_2-ARs can be further subdivided into different subtypes. α_1-ARs are G protein–coupled receptors and include the α_{1A}, α_{1B}, and α_{1D} subtypes. The α_1-AR subtypes are products of separate genes and differ in structure, G protein coupling, tissue distribution, signaling, regulation, and function. Both α_{1A}-ARs and α_{1B}-ARs mediate positive inotropic responses. However, the positive inotropic effect mediated by α_1-ARs is believed to be of minor importance in the heart. α_1-ARs are coupled to phospholipase C, phospholipase D, and phospholipase A_2; they increase iCa^{2+} and myofibrillar sensitivity to Ca^{2+}.

Cardiac hypertrophy is primarily mediated by α_{1A}-ARs.[51,52] Cardiac hypertrophic responses to α_1-AR agonists involve activation of protein kinase C and mitogen-activated protein kinase through G_q-signaling mechanisms. Three subtypes of α_2-ARs are recognized: α_{2A}, α_{2B}, and α_{2C}. In the mammalian heart, α_2-ARs in the atrium play a role in the presynaptic inhibition of norepinephrine release. These prejunctional α_2-ARs are believed to belong to the α_{2C} subtype.

Neural regulation of cardiac function involves a complex interaction between the different classes and subpopulations of adrenoceptors and their signaling pathways. Targeted therapeutics in cardiovascular medicine involve the clinical application and manipulation of a basic understanding of adrenoceptor pharmacology.

HORMONES AFFECTING CARDIAC FUNCTION

Many hormones have direct and indirect actions on the heart (Table 20-1). Hormones with cardiac actions can be synthesized and secreted by cardiomyocytes or produced by other tissues and delivered to the heart. They act on specific receptors expressed in cardiomyocytes. Most of these hormone receptors are plasma membrane G protein–coupled receptors (GPCRs). Non-GPCRs include the natriuretic peptide receptors, which are guanylyl cyclase–coupled receptors, and the glucocorticoid and mineralocorticoid receptors, which bind androgens and aldosterone and are nuclear zinc finger transcription factors. Hormones can have activity in normal cardiac physiologic function or are active only in pathophysiologic conditions, or both situations can apply. Most of the new information regarding the action of hormones in the heart has been derived from the endocrine changes associated with chronic heart failure.[53]

Cardiac hormones are polypeptides secreted by cardiac tissues into the circulation in the normal heart. Natriuretic peptides,[54,55] aldosterone,[56] and adrenomedullin[57] are hormones secreted by cardiomyocytes. Angiotensin II, the effector hormone in the renin-angiotensin system, is also produced by cardiomyocytes.[58,59] The

TABLE 20-1 **ACTIONS OF HORMONES ON CARDIAC FUNCTION**

Hormone	Receptor	Cardiac Action	Increase (+) or Decrease (–) With CHF
Adrenomedullin	GPCR	+Inotropy/+chronotropy	+
Aldosterone	Cytosolic or nuclear MR	?	+
Angiotensin	GPCR	+ Inotropy/+ chronotropy	+
Endothelin	GPCR	?	+
Natriuretic peptides	GCCR		
ANP (ANF)			+
BNP			+
Neuropeptide Y*	GPCR	– Inotropy	+
Vasopressin	GPCR	+ Inotropy/+ chronotropy	+
Vasoactive intestinal peptide†	GPCR	+ Inotropy	No
Estrogen	ERα/ERß	Indirect	No
Testosterone	AR	Indirect	No
Progesterone	PR	Indirect	No
Thyroid hormones	NR	+ Inotropy/+ chronotropy	—
Growth hormones	IGF-1	+ Inotropy/+ chronotropy	—

ANF, Atrial natriuretic factor; *ANP,* atrial natriuretic peptide; *AR,* androgen receptor; *BNP,* B-type natriuretic peptide; *CHF,* congestive heart failure; *ER,* estrogen receptor; *GCCR,* guanylyl cyclase–coupled receptor; *GPCR,* G protein–coupled receptor; *IGF-1,* insulin growth factor 1; *MR,* mineralocorticoid receptor; *NR,* nuclear receptor; *PR,* progesterone receptor.

*Data from Grundemar L, Hakanson R: Multiple neuropeptide Y receptors are involved in cardiovascular regulation. Peripheral and central mechanisms, *Gen Pharmacol* 24:785-796, 1993; and Maisel AS, Scott NA, Motulsky HJ, et al: Elevation of plasma neuropeptide Y levels in congestive heart failure, *Am J Med* 86:43-48, 1989

†Data from Henning RJ, Sawmiller DR: Vasoactive intestinal peptide: cardiovascular effects, *Cardiovasc Res* 49:27-37, 2001.

renin-angiotensin system is one of the most important regulators of cardiovascular physiology. It is a key modulator of cardiac growth and function. Angiotensin II stimulates two separate receptor subtypes, AT_1 and AT_2, both of which are present in the heart. AT_1 receptors are the predominant subtype expressed in the normal adult human heart. Stimulation of AT_1 receptors induces a positive chronotropic and inotropic effect. Angiotensin II also mediates cell growth and proliferation in cardiomyocytes and fibroblasts and induces the release of the growth factors aldosterone and catecholamines through the stimulation of AT_1 receptors. Activation of AT_1 receptors is directly involved in the development of cardiac hypertrophy and heart failure, as well as adverse remodeling of the myocardium. In contrast, AT_2 receptor activation is counterregulatory and generally antiproliferative. Expression of AT_2 receptors, however, is relatively scant in the adult heart because they are most abundant in the fetal heart and decline with development. In response to injury and ischemia, AT_2 receptors become upregulated. The precise role of AT_2 receptors in the heart remains to be defined.

The beneficial effects of blockade of the renin-angiotensin system with angiotensin-converting enzyme inhibitors in the treatment of heart failure have been attributed to an inhibition of AT_1-receptor activity. In addition to the renin-angiotensin system, other cardiac hormones that have been shown to play pathogenic roles in the promotion of cardiomyocyte growth and cardiac fibrosis, development of cardiac hypertrophy, and progression of congestive heart failure include aldosterone,[56] adrenomedullin,[60-62] natriuretic peptides,[54,55] angiotensin,[63-65] endothelin,[66] and vasopressin.[67,68]

Increased stretch of the myocardium stimulates the release of atrial natriuretic protein (ANP) and B-type natriuretic protein (BNP) from the atria and ventricles, respectively. Both ANP and BNP bind to natriuretic peptide receptors to generate the second messenger cyclic guanosine monophosphate and represent part of the cardiac endocrine response to hemodynamic changes caused by pressure or volume overload. They also participate in organogenesis of the embryonic heart and cardiovascular system.[54,55] In patients with chronic heart failure, increases of serum ANP and BNP levels are a predictor of mortality.[69]

Adrenomedullin is a recently discovered cardiac hormone that was originally isolated from pheochromocytoma tissue. It increases the accumulation of cAMP and has direct positive chronotropic and inotropic effects.[57,60,61] Adrenomedullin, with interspecies and regional variations, has also been shown to increase nitric oxide production, and it functions as a potent vasodilator.

Aldosterone is one of the cardiac-generated steroids, although its physiologic significance remains to be defined. It binds to mineralocorticoid receptors and can increase the expression or activity (or both) of cardiac proteins involved in ionic homeostasis or the regulation of pH, such as cardiac Na^+/K^+-ATPase, the Na^+-K^+ cotransporter, Cl^--bicarbonate (HCO_3^{2+}), and the Na^+-hydrogen (H^+) antiporter.[56] Aldosterone modifies cardiac structure by inducing cardiac fibrosis in both ventricular chambers and thereby leads to impairment of cardiac contractile function.

Other hormones such as the growth hormone,[70] thyroid hormones,[71] and sex steroid hormones (see the following text) can also have cardiac effects through direct actions of nuclear receptors or indirect effects.

Sex Steroid Hormones and the Heart

Cardiac contractility is more intense in premenopausal women than in age-matched men, and withdrawal of hormone replacement therapy in postmenopausal women leads to a reduction in cardiac contractile function. The gender dimorphism in heart function and its adaptive responses to injury and disease states are partly mediated by sex steroid hormones.

The most extensively studied sex steroid hormones are estradiol-17β (E2) and its bioactive metabolites. They bind and act on the two subtypes of estrogen receptors (ERs) in the heart: ERα and ERβ. Progesterone and testosterone (two other sex steroid hormones) and the enzyme aromatase, which converts testosterone to estrogen, are much less well investigated. Progesterone and testosterone bind and act on their respective progesterone receptors and androgen receptors in the heart. Sex steroid hormones interact with their receptors to affect postsynaptic target cell responses and to influence presynaptic sympathoadrenergic function. Cardiomyocytes are not only targets for the action of sex steroid hormones, but they are also the source of synthesis and the site of metabolism of these hormones.[72]

E2 is derived from testosterone and is primarily metabolized in the liver to form hydroxyestradiols, catecholestradiols, and methoxyestradiols. Estradiol metabolism also takes place in vascular smooth muscle cells, cardiac fibroblasts, endothelial cells, and cardiomyocytes. Cardiomyocytes express nuclear steroid hormone receptors that modulate gene expression and nonnuclear receptors for the nongenomic effects of sex steroid hormones. They interact with many different coregulators to confer tissue and temporal specificity in their transcriptional actions. These cell-specific coactivator and corepressor proteins are known as estrogen-related receptors.[73] Sex steroid hormones can activate rapid signaling pathways without changing gene expression (Fig. 20-18). One such example is stimulation of vascular endothelial nitric oxide synthase to mediate vascular dilatation. Estrogen's vasodilatory effect might explain the lower systolic blood pressures of premenopausal women when compared with age-matched men. In men, aromatase-mediated conversion of testosterone to estrogen maintains normal vascular tone. In addition to sex steroid hormone stimulation of nuclear or nonnuclear receptors, sex steroid hormone receptors could also induce rapid signaling of growth factor pathways in the absence of ligands.

Gender differences exist in cardiac electrophysiologic function. The modulatory actions of estrogen on Ca^{2+} channels might be responsible for sex-based differences in repolarization of the heart, such as the faster resting heart rate of women, as well as the increased propensity of women to have prolonged QT syndrome.[74] Estrogen, through the activation of ERβ, confers protection after ischemia and reperfusion in murine models of myocardial infarction. In contrast, testosterone, in the same model, has the opposite effect. Aromatase also has protective effects, probably through its action to increase estrogen and to decrease testosterone.

Gender differences in cardiac physiology should include consideration of the cellular physiology of sex steroid hormones in males and females; intrinsic differences in the physiology of cardiomyocytes, vascular smooth muscle cells, and endothelial cells between males and females; and gender-based differences in the autonomic modulation of cardiac physiology.

CARDIAC REFLEXES

Cardiac reflexes are fast-acting reflex loops between the heart and the central nervous system (CNS) that contribute to regulation of cardiac function and the maintenance of physiologic homeostasis. Specific cardiac receptors elicit their physiologic responses by various pathways. Cardiac receptors are linked to the CNS by myelinated or unmyelinated afferent fibers that travel along the vagus nerve. Cardiac receptors are in the atria, ventricles, pericardium, and coronary arteries. Extracardiac receptors

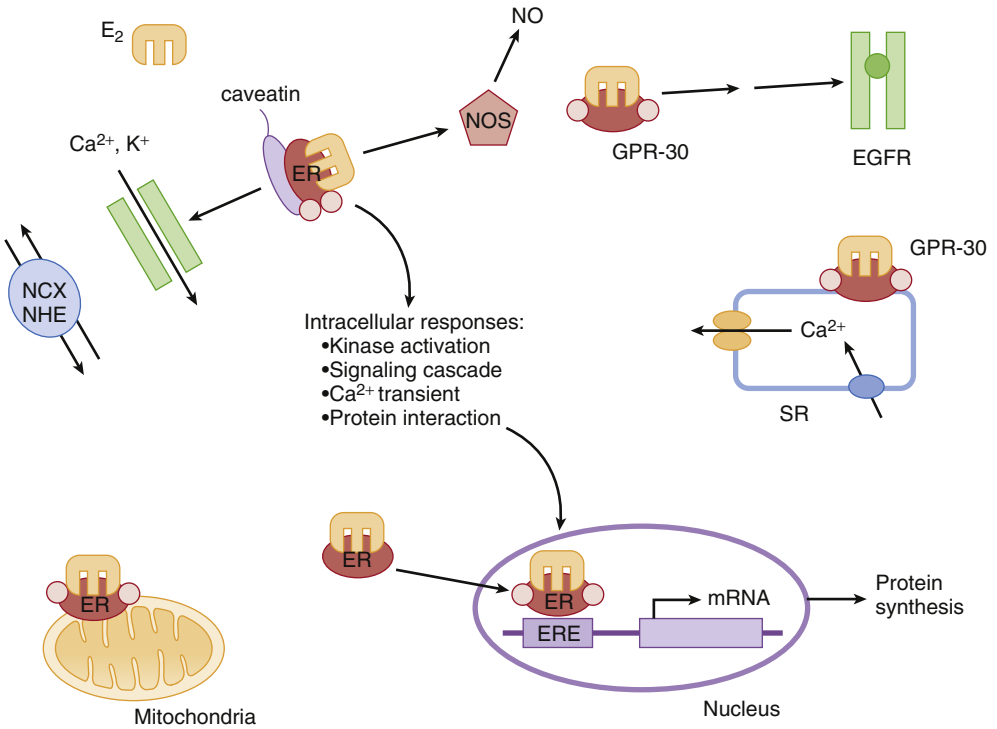


Figure 20-18. Signaling mechanism of nuclear and nonnuclear localized estrogen receptor (ER) and the estrogen-binding receptor, GPR-30. Nuclear ER influences the transcription of target genes by binding to an ER-response element (ERE) within the promotor region of target genes. *E_2*, Estrogen; *EGFR*, epidermal growth factor receptor; *NCX*, Na^+-Ca^{2+} exchanger; *NHE*, Na^+-H^+ exchanger; *NO*, nitric oxide; *NOS*, nitric oxide synthase, *SR*, sarcoplasmic reticulum. *(From Du XJ, Fang L, Kiriazis H: Sex dimorphism in cardiac pathophysiology: experimental findings, hormonal mechanisms, and molecular mechanisms,* Pharmacol Ther *111:434-475, 2006.)*

are located in the great vessels and carotid artery. Sympathetic and parasympathetic nerve input is processed in the CNS. After central processing, efferent fibers to the heart or the systemic circulation will provoke a particular reaction. The response of the cardiovascular system to efferent stimulation varies with age and duration of the underlying condition that elicited the reflex in the first instance.

Baroreceptor Reflex (Carotid Sinus Reflex)

The baroreceptor reflex is responsible for the maintenance of arterial blood pressure. This reflex is capable of regulating arterial pressure around a preset value through a negative-feedback loop (Fig. 20-19).[75,76] In addition, the baroreceptor reflex is capable of establishing a prevailing set point for arterial blood pressure when the preset value has been reset because of chronic hypertension. Changes in arterial blood pressure are monitored by circumferential and longitudinal stretch receptors located in the carotid sinus and aortic arch. The nucleus solitarius, located in the cardiovascular center of the medulla, receives impulses from these stretch receptors through afferents of the glossopharyngeal and vagus nerves. The cardiovascular center in the medulla consists of two functionally different areas; the area responsible for increasing blood pressure is laterally and rostrally located, whereas the area responsible for lowering arterial blood pressure is centrally and caudally located. The latter area also integrates impulses from the hypothalamus and the limbic system. Typically, stretch receptors are activated if systemic blood pressure is greater than 170 mm Hg. The response of the depressor system includes decreased sympathetic activity, leading to a decrease in cardiac contractility, heart rate, and vascular tone. In addition, activation of the parasympathetic system further decreases the heart rate and myocardial contractility. Reverse effects are elicited with the onset of hypotension.

The baroreceptor reflex plays an important beneficial role during acute blood loss and shock. However, the reflex arch loses its functional capacity when arterial blood pressure is less than 50 mm Hg. Hormonal status and therefore sex differences may alter baroreceptor responses.[77] Furthermore, volatile anesthetics (particularly halothane) inhibit the heart rate component of this reflex.[78] Concomitant use of Ca^{2+}-channel blockers, angiotensin-converting enzyme inhibitors, or phosphodiesterase inhibitors will lessen the cardiovascular response of raising blood pressure through the baroreceptor reflex. This lessened response is achieved by either their direct effects on the peripheral vasculature or, more importantly, their interference with CNS signaling pathways (Ca^{2+}, angiotensin).[79] Patients with chronic hypertension often exhibit perioperative circulatory instability as a result of a decrease in their baroreceptor reflex response.

Chemoreceptor Reflex

Chemosensitive cells are located in the carotid bodies and the aortic body. These cells respond to changes in pH status and blood O_2 tension. At an arterial partial O_2 pressure (PaO_2) of less than 50 mm Hg or in conditions of acidosis, the chemoreceptors send their impulses along the sinus nerve of Hering (a branch of the glossopharyngeal nerve) and the tenth cranial nerve to the chemosensitive area of the medulla. This area responds by stimulating the respiratory centers and thereby increasing ventilatory drive.

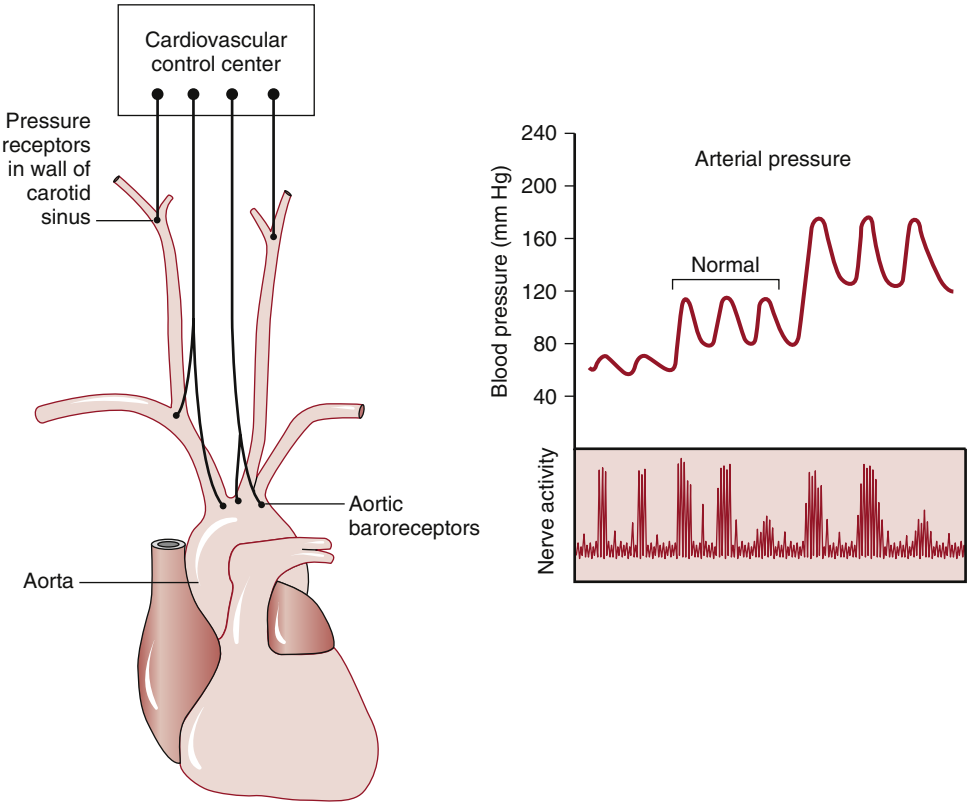


Figure 20-19. Anatomic configuration of the baroreceptor reflex. Pressure receptors in the wall of the carotid sinuses and aorta detect changes in arterial pressure in the circulation. These signals are conveyed to afferent receptive regions of the medulla through the Hering and vagus nerves. Output from effector portions of the medulla modulates peripheral tone and heart rate. The increase in blood pressure results in increased activation of the reflex (*right*), which affects a decrease in blood pressure. *(From Campagna JA, Carter C: Clinical relevance of the Bezold-Jarisch reflex,* Anesthesiology *98:1250-1260, 2003.)*

In addition, activation of the parasympathetic system ensues and leads to a reduction in heart rate and myocardial contractility. In the case of persistent hypoxia, the CNS will be directly stimulated, with a resultant increase in sympathetic activity.

Bainbridge Reflex

The Bainbridge reflex[80-82] is elicited by stretch receptors located in the right atrial wall and the cavoatrial junction. An increase in right-sided filling pressure sends vagal afferent signals to the cardiovascular center in the medulla. These afferent signals inhibit parasympathetic activity, thereby increasing the heart rate. Acceleration of the heart rate also results from a direct effect on the SA node by stretching the atrium. The changes in heart rate are dependent on the underlying heart rate before stimulation.

Bezold-Jarisch Reflex

The Bezold-Jarisch reflex responds to noxious ventricular stimuli sensed by chemoreceptors and mechanoreceptors within the left ventricular wall by inducing the triad of hypotension, bradycardia, and coronary artery dilatation.[75] The activated receptors communicate along unmyelinated vagal afferent type C fibers. These fibers reflexively increase parasympathetic tone. Because it invokes bradycardia, the Bezold-Jarisch reflex is thought of as a cardioprotective reflex. This reflex has been implicated in the physiologic response to a range of cardiovascular conditions such as myocardial ischemia or infarction, thrombolysis, or revascularization and syncope. Natriuretic peptide receptors stimulated by endogenous ANP or BNP may modulate the Bezold-Jarisch reflex. Thus the Bezold-Jarisch reflex may be less pronounced in patients with cardiac hypertrophy or atrial fibrillation.[83]

Valsalva Maneuver

Forced expiration against a closed glottis produces increased intrathoracic pressure, increased central venous pressure, and decreased venous return. Cardiac output and blood pressure will be decreased after the Valsalva maneuver. This decrease will be sensed by baroreceptors and will reflexively result in an increase in heart rate and myocardial contractility through sympathetic stimulation. When the glottis opens, venous return increases and causes the heart to respond by vigorous contraction and an increase in blood pressure. This increase in arterial blood pressure will, in turn, be sensed by baroreceptors, thereby stimulating the parasympathetic efferent pathways to the heart.

Cushing Reflex

The Cushing reflex is a result of cerebral ischemia caused by increased intracranial pressure. Cerebral ischemia at the medullary vasomotor center induces initial activation of the sympathetic nervous system. Such activation will lead to an increase in heart rate, arterial blood pressure, and myocardial contractility in an effort to improve cerebral perfusion. As a result of the high vascular tone, reflex bradycardia mediated by baroreceptors will ensue.

Oculocardiac Reflex

The oculocardiac reflex is provoked by pressure applied to the globe of the eye or traction on the surrounding structures. Stretch receptors are located in the extraocular muscles. Once activated, stretch receptors will send afferent signals through the short- and long-ciliary nerves. The ciliary nerves will merge with the ophthalmic division of the trigeminal nerve at the ciliary ganglion. The trigeminal nerve will carry these impulses to the gasserian ganglion, thereby resulting in increased parasympathetic tone and subsequent bradycardia. The incidence of this reflex during ophthalmic surgery ranges from 30% to 90%. Administration of an antimuscarinic drug such as glycopyrrolate or atropine reduces the incidence of bradycardia during eye surgery (also see Chapter 84).

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Chapter 21

Gastrointestinal Physiology and Pathophysiology

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Key Points

- The functional role of the gastrointestinal (GI) tract is the digestion and absorption of nutrients. These processes are facilitated by the integrated movement of luminal contents (food, digestive enzymes, secretions) along the gastroenteral tube from the mouth to the anus.
- The wall structure of the GI tract consists of a few layers. Main layers of the GI tract are the serosa, muscularis (longitudinal and circular muscle layers), submucosa, and mucosa. The mucosa has three components: a single layer of epithelial cells (epithelium), the lamina propria, and the muscularis mucosae.
- The regulation of digestion and absorption is principally the result of the in-depth networking between the enteric mucosal membrane, the enteric nervous system, and the autonomic nervous system. The enteric nervous system contains two main plexuses: the submucosal plexus, which controls mainly absorption, secretion, and mucosal blood flow; and the myenteric plexus, which regulates tone and tonic contractions of the intestinal wall.
- Motility plays a vital role in regulating speed and intensity of absorption through regulation of transit time and exposure of nutrients to the mucosal brush border.
- Achlorhydria, such as chronic proton pump inhibitor or histamine antagonist use or the removal of much of the oxyntic region of the stomach (gastrectomy, bariatric surgery), results in a profound offset of the balance between digestive and protective secretion and can result in severe depletion of nutrients and vitamins over time.
- Manipulation of the intestines leads to a cascade of neural and inflammatory responses that propagate through the entire gut. The main pathophysiologic event in postoperative ileus is the neuroimmune interaction, which is the bidirectional communication between the immune system within the GI tract as well as the entire body and the autonomic nervous system, including the enteric nervous system.
- The main purpose of the GI blood flow is to deliver nutrients and hormones to the gut, to remove metabolic waste from the gut, and to maintain the mucosal barrier to prevent transepithelial migration of antigens, toxic chemicals, and pathogenic microbiota.
- Approximately 70% of the total blood volume is in the veins. The splanchnic system receives 25% of cardiac output and contains approximately one third of the total blood volume. Approximately 1 L of blood can be recruited from the splanchnic vasculature into the systemic circulation when needed.
- Hemodynamic changes observed during capnoperitoneum are the result of the complex interaction between anesthesia, surgical insult, the patient's position, carbon dioxide, and an increase (followed by a reduction at the end of surgery) in intra-abdominal pressure and oxidative stress, which plays an important role in the overall response to this procedure. It is not surprising that some authors are replacing the term *minimally invasive surgery* with the more precise term *minimal-access surgery.*

The gastrointestinal (GI) tract constitutes approximately 5% of the total human body mass but receives 25% of the cardiac output. The main functions of the GI tract include motility, digestion, absorption, excretion, and circulation (blood flow and blood volume regulation). Other important functions have been studied extensively only for the past few decades. These functions include local and general immunity and the overall role of the GI tract in inflammatory responses, including the resolution of inflammation. These multiple functions require sophisticated integration and regulation; information from the body and the environment must be sensed and processed into appropriate command centers, and then necessary activities are initiated. The structure and regulatory mechanisms of the GI tract fulfill these requirements.

The walls of the GI tract are multilayered (Fig. 21-1). The main layers are (from outermost to inmost) the serosa, muscularis (longitudinal and circular muscle layers), submucosa, and the mucosa. The mucosa has three components (from innermost to outermost): a single layer of epithelial cells (epithelium), the lamina propria, and the muscularis mucosae. Every organ along the GI tube has a generally similar structure; however, the specifics are remarkably different and mainly have to do with the mucosa. GI epithelial cells turn over every 3 days, undergoing divisions and differentiation, followed by programmed death (apoptosis). The contents of the GI tract are sensed by the epithelium, where the enteric reflexes originate. Secretion of enzymes, absorption of nutrients, and excretion of waste products occur through the epithelium.

Beneath the epithelium is a membrane called the *lamina propria*. It contains blood vessels and nerve endings as well as immune and inflammatory cells that are part of the host defense mechanisms. Beneath the lamina propria, there is a thin layer of smooth muscle called the *muscularis mucosa,* which is responsible for movement of the villi. Beneath the mucosa is a tangled network of nerve cell bodies called the *submucosal plexus*, which transmits information from the epithelial cells to the enteric and central nervous systems. Beneath the mucosa, two layers of smooth muscle provide gut motility. The one closer to the mucosa is a layer of circular muscle with contractions that decrease the diameter of the intestinal lumen. The outer layer of smooth muscle is longitudinal, and its contractions shorten the length of the intestinal segment. Between these two smooth muscle layers is the myenteric plexus, consisting of nerves regulating the function of the gut smooth muscle.

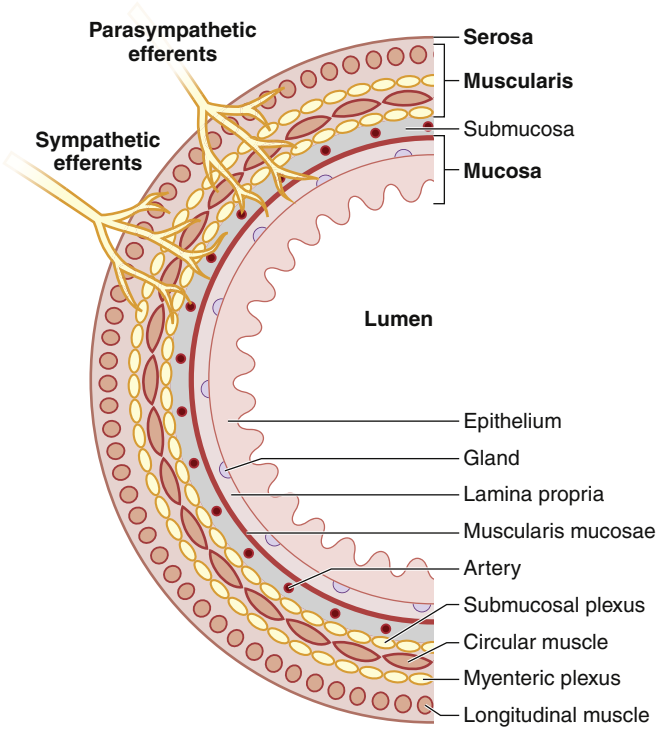


Figure 21-1. The gut wall.

REGULATION OF GASTROINTESTINAL FUNCTION

Four modes of communication control the GI system: endocrine, neurocrine, paracrine, and juxtacrine (immune) regulation. Endocrine regulation is important in integrating the function of the GI organs in their response to a meal. Barrett compares endocrine regulation to a radio broadcast.[1] When a hormone is released, it affects many receptors throughout the GI system and beyond. On the other hand, neurocrine regulation transmits information over long distances, but the communication is narrow and precise, traveling from the end of the nerve fiber to release neurotransmitters that activate the appropriate receptor and then affects the effector. For its specificity, neurocrine communication has been compared with the telephone rather than the radio.[1] Paracrine and juxtacrine (immune) regulation are usually effective in the immediate vicinity of the mediator release. These modes are analogous to live conversations among a few individuals,[1] such as a conference call, to extend Barrett's metaphor**.** In paracrine communication, certain substances are released from cells other than nerves. Such substances provide additional (sometimes redundant) regulation of GI functions, including motility. Juxtacrine or immune communications are achieved with the release of substances from the mucosal immune system. These immune cells are activated by pathogenic microorganisms during invasion of the mucosa by pathogens or antigenic substances and release chemical mediators that include histamines, prostaglandins, and cytokines. Mast cells are particularly important in these processes, and their density is high in the lamina propria. Paracrine and immune regulation involve the release of different mediators.

INTESTINAL MUCOSAL IMMUNOLOGY

The inner surface of the GI tract is really a continuation of the exterior of the body and provides an entrance to the body for microbes and toxic compounds. To protect the body, the intestine has developed a highly effective immune defense system, in effect making the GI tract the largest lymphoid organ in the body.[1] The intestinal immune system can distinguish between harmful and

benign antigens within food. The mucosal immune system is composed of mucosa-associated lymphoid tissues and is one of the most powerful barriers to invasion by pathogens. The system includes nonimmunologic barriers such as acid in the stomach and other digestive secretions and enzymes. The immune host defense barriers include innate and adaptive or acquired immune systems. The innate mucosal immune system responds quickly to pathogens by expressing pattern recognition receptors that detect molecules in pathogenic microbes. For example, lipopolysaccharide and peptidoglycan are often present within pathogenic microbes. The innate system senses these chemicals, activating and releasing chemotactic molecules that stimulate the influx of other inflammatory cells, including microphages and neutrophils. These activated cells facilitate microbial killing by releasing a variety of toxic products such as oxygen free radicals. These inflammatory mediators are important in host-defense mechanisms against microbes, but they also may traumatize nearby uninfected tissues. The innate immune system generates cytokines that facilitate the response and activation of the adaptive immune system, which recognizes components of microorganisms, antigens within microorganisms, as well as abnormal host cells. Such recognition is mediated by specific receptors expressed on lymphoid cells and T and B cells. The B cells secrete antibodies specific for a given antigen; this process is facilitated by T cells, which release cytokines (transforming growth factor β) and interleukins (IL-4, IL-5, and IL-6). Antibodies produced by B cells activate other classes of cells, such as natural killer (NK) cells, which link the adaptive and innate branches of the intestinal immune system. NK cells destroy particles and microbes that have been opsonized or coated with antibodies specific for the NK cell surface components

NK cells also release cytotoxic compounds that are independent of adaptive responses. Transport of antigens and microbes through epithelial cells to lymphoid cells for destruction by the immune system is accomplished by epithelial M cells; they provide an opening in the epithelial barrier through vesicular transport.[2]

Glycocalyx is a general term describing the glycoproteins, mucosaccharides, and other compounds located at the apical part of epithelial cells. The functions of the glycocalyx include protection of the cellular membrane from chemical injury. The glycocalyx also enables the immune system to recognize and selectively attack foreign organisms. It coats the endothelial cells within blood vessels and prevents leukocytes from rolling. When the glycocalyx is damaged by inflammation, its permeability increases, leading to loss of water, electrolytes, and proteins during many inflammatory conditions, including the perioperative period. The amount of water lost from the circulation in this way can reach 1 L.[3]

NEUROCRINE REGULATION OF MOTILITY

Motility refers to the contractions of the muscles of the GI tract that move ingested material from the mouth to the anus. During this long trip, the particles of the ingested mass are reduced in size and mixed with GI secretions. The GI tract is innervated by the autonomic nervous system, which includes the extrinsic nervous system with its sympathetic and parasympathetic branches and the enteric nervous system.

EXTRINSIC SYMPATHETIC INNERVATION

Preganglionic sympathetic fibers that innervate the GI tract originate in the spinal cord at the T5-L2 segments. The ganglionic presynaptic fibers leave the spinal cord, enter the sympathetic chain of ganglia (celiac ganglion and a few mesenteric ganglia), synapse with postganglionic neurons, and travel to the gut, terminating at the neurons of the enteric nervous system. The main neurotransmitter in the sympathetic innervation of the GI tract is norepinephrine. Vasoactive intestinal polypeptide (VIP) also plays a role in transmission of sympathetic signals. The main physiologic action of the sympathetic nervous system is inhibitory; strong sympathetic stimulation can stop the movement of food through the GI tract.

EXTRINSIC PARASYMPATHETIC INNERVATION

Preganglionic parasympathetic nerves arise from cell bodies in the medulla and in the sacral region of the spinal cord. They synapse mainly in the cells of the enteric nervous system. The multiple afferent nerves that travel within the vagus and pelvic nerves provide information to the brain and spinal cord for integration. Vagus fibers provide innervation to the esophagus, stomach, pancreas, small intestine, and the first half of the large intestine. The sacral parasympathetic nerves originate in the sacral segments of the spinal cord and within the pelvic nerves, innervating the lower part of the large intestine, sigmoid, rectal, and anal regions. The main physiologic effect of the parasympathetic influence is activation of the GI functions. The main parasympathetic neurotransmitter is acetylcholine (ACh).

INTRINSIC INNERVATION (ENTERIC NERVOUS SYSTEM)

The GI tract has its own independent nervous system—the enteric nervous system; it is often called the *little brain* because it functions independently from the central nervous system to control GI tract functions such as motility, secretion, and blood flow.[1] The motor apparatus consists of enteric neurons, interstitial cells of Cajal (ICCs), and smooth muscle cells.[4] The enteric nervous system receives information concerning the physiologic status of the intestine instantly, integrating it and effecting necessary changes in the function of the smooth muscle and other structures within the GI tract. This information is also transmitted to the central nervous system, which modulates it with the adaptive plasticity of mostly vagal brainstem circuits and sends signals back to the enteric nervous system, modifying the functional result. This process ensures that extrinsic factors such as stress or the time of day are incorporated as well.

The enteric nervous system contains two main plexuses (see Fig. 21-1). The outer plexus is located between

the longitudinal and circular muscular layers and is called the *myenteric plexus*, or *Auerbach plexus*. The inner plexus is located within submucosa and is called the *submucosal plexus*, or *Meissner plexus*. The motility of the GI tract is mainly controlled by the myenteric plexus. ICCs are pacemaker cells that generate intrinsic electrical activity. ICCs reside within the myenteric plexus and are functionally connected with smooth muscle cells via gap junctions. ICCs are densely associated with enteric nerve terminals and are interposed between them and the smooth muscle syncytium. The submucosal plexus controls mainly absorption, secretion, and mucosal blood flow.[5] Sympathetic and parasympathetic fibers are connected with the myenteric and submucosal plexuses. Stimulation of the myenteric plexus mainly increases the tone or tonic contraction of the intestinal wall, mediated by neurotransmitters within the enteric nervous system. ACh and tachykinins such as substance P are excitatory, whereas VIP and nitric oxide (NO) are inhibitory.

There are reflexes that occur within the enteric nervous system. Many are bidirectional, connecting the spinal cord or brainstem with the GI tract. Activation of sympathetic neurons and norepinephrine do not directly affect the basic myogenic tone of the GI tract, but instead reduce the amount of ACh released from intrinsic cholinergic neurons.[6] The sympathetic neurons also constrict the sphincters. Both mechanisms (reducing ACh release and constricting sphincters) retard the transit of intestinal content along the digestive tract. There are many sympathetic enteric reflexes. Distention of the distal ileum or the colon leads to inhibition of motility within the proximal ileum, slowing down gastric emptying to protect the duodenum from excessive exposure to the highly acid gastric contents.[6] The main neurotransmitter within the excitatory nerves is ACh, which activates muscarinergic receptors. Inhibitory nerves release predominantly NO, although other inhibitory neurotransmitters include VIP and adenosine triphosphate (ATP). Sympathetic inhibitory effects within the enteric nervous system are achieved by norepinephrine.

Decreases in motility are mediated partially by the inhibition of ACh release from enteric cholinergic neurons, secondary to α_2 adrenoceptor activation.[6] This effect is supplemented by direct relaxation of the intestinal muscles by activation of β-adrenergic receptors. Sphincter muscles (unlike nonsphincter muscles) have excitatory α and inhibitory β-adrenergic receptors. Development of dystrophic and degenerative processes in sympathetic efferent fibers innervating the GI tract have been observed in diabetic sympathetic neuropathy,[6] leading to more rapid transit of food through the distal small intestine.

Nervous control of GI motility is complex and includes communication from the central nervous system to the periphery; it also messages from the GI tract to the central nervous system. The role of the enteric nervous system within the GI tract cannot be overestimated.

TRAVEL AND MIXING OF FOOD IN THE GASTROINTESTINAL TRACT

There are two main types of movement within the GI tract: mixing movements (which keep the intestinal contents well mixed at all times) and propulsive movements (which move the GI contents along the tract, allowing necessary time for digestion and absorption). The propulsive movements result from periodic contractions of certain segments of the GI tract (peristalsis). The distention of intestinal segments is the most important stimulus of peristalsis.

SWALLOWING AND THE MOTILITY OF THE ESOPHAGUS

The pharynx is divided into three regions: nasopharynx, oropharynx, and hypopharynx. Muscles in the nasopharynx prevent food from moving into the nasal passages during swallowing. The oropharynx pushes the food bolus backwards and down into the esophagus. The hypopharynx is located between the base of the tongue and the cricoid cartilage; it contains the upper esophageal sphincter. The functional coordination between muscles during swallowing is regulated by the swallowing center in the brain.

There are two phases of swallowing, the first of which is the initiatory voluntary stage. When the food is ready to be swallowed, it is voluntarily squeezed and rolled posterior into the pharynx by the pressure of the tongue upwards and backwards against the palate. Next, the process becomes automatic and cannot stop. During the second phase, the food is passed through the pharynx into the esophagus. At the beginning, the soft palate moves upwards to close the posterior nares, preventing the reflux of food into the nasal cavities. Next, the combined action of muscles within the larynx and the neck prevents the movement of the epiglottis upwards, protecting the opening of the larynx and trachea. This stage of swallowing takes approximately 1 or 2 seconds, during which the swallowing center specifically inhibits the respiratory center of the medulla.

The function of the esophagus is not dependent on gravity; food can be moved from the mouth to the stomach even if a person is standing on his or her head.[1] Food enters the esophagus and enters the stomach with two waves of peristalsis. The first wave moves the main part of the food; the second wave takes the remaining part of the food to the stomach. There is an upper esophageal sphincter, which is also called the *pharyngoesophageal sphincter*. This sphincter constricts after food moves to the esophagus, preventing it from moving back into the pharynx. The upper esophageal sphincter produces pressure of approximately 60 mm Hg. At the distal end of the esophagus, approximately 2 to 5 cm above the junction with the stomach, the esophageal circular muscle thickens and functions as the gastroesophageal or lower esophageal sphincter; this sphincter can produce pressure between 20 and 40 mm Hg.

The many enteric neurons within the esophagus sense the presence of food and coordinate local reflexes, supplementing central control of swallowing and esophageal peristalsis. Sensory afferents transmit the signals to the dorsal vagal complex, which activates the somatic and vagal efferents terminating on the striated muscle in the upper third of the esophagus or on the nerves of the enteric nervous system. The enteric nervous system

releases ACh (which contracts the muscle) or NO or VIP (which induce relaxation).

The lower esophageal sphincter contracts in response to distention; the response is mainly myogenic. However, neurohumoral substances (ACh and gastrin) are also released in concert with the ingestion of the meal. Relaxation of this sphincter allows food to enter the stomach and it is mediated mainly by VIP. The lower esophageal sphincter is controlled by myogenic mechanisms, neurohumoral factors, and neural regulation from both the central nervous system as well as the enteric plexus.

Difficulty swallowing is called *dysphagia*. Dysphagia is a frequent problem, especially among the elderly, and increases the risk of aspiration, choking, and malnutrition. Approximately 13% of patients in hospitals and 60% of patients in nursing homes have some degree of dysphagia.[1] Anatomic reasons for dysphagia include diverticula, hiatal hernia, the formation of fibrosis, and scarring of the esophagus as a consequence of reflux disease. Causes of functional dysphagia include stroke and other neurologic diseases.

One of the most common dysfunctions of the lower esophagus is heartburn, which is caused by the reflux of gastric acid and can result in injury to the esophageal mucosa. The acid in the esophagus is partially neutralized by bicarbonate contained in the swallowed saliva; however, with progression of reflux, the stomach contents (including acid) stay in the esophagus longer than under normal conditions, and gastroesophageal reflux disease develops. The activity of the gastroesophageal sphincter and the pressure of the esophageal sphincter are both reduced in critically ill patients.[7,8] Gastroesophageal sphincter tone decreases reflexively when cricoid pressure is applied to awake patients.[9] Remifentanil infusion, with or without a propofol bolus, reduces the decrease in gastroesophageal barrier pressure caused by cricoid pressure.[10]

MOTILITY OF THE STOMACH

The stomach functions as a homogenizer, mechanically breaking down ingested food into an emulsion of small particles. The proximal stomach (i.e., the cardia, fundus, and corpus**)** functions primarily as a reservoir. The distal stomach consists of the distal portion of the body of the stomach, the antrum, and the pylorus that controls the amount and size of food particles entering the duodenum. The stomach is shaped like a sac rather than a tube. The muscle layers are thick and contract in different directions. There are three main motor functions of the stomach. The first function is the storage of large quantities of food. The stomach can easily accommodate about 1500 mL of contents without a significant increase in intragastric pressure. This process is called *receptive relaxation* and is mediated by a vagovagal reflex; vagotomy abolishes this reflex. The second function of the stomach is mixing food with gastric secretions until it forms a semifluid mixture called *chyme*. The third function is slow emptying of the stomach into the small intestine. Solid food tends to be retained in the proximal stomach, while liquids are distributed throughout the stomach. Liquids are emptied faster than solids. Gastric emptying of solids is a two-stage process: an initial retention period during which solids are broken down to approximately 2 mm diameter followed by a generally linear emptying phase.[5] It takes approximately 3 to 4 hours to empty solids from the stomach into the duodenum. Characteristics of the food within the stomach affect the pace of stomach emptying; for example, isotonic saline leaves the stomach the fastest, while lipids empty slowly.

Vagal afferents provide information from mechanosensitive and chemosensitive receptors to the nucleus tractus solitarius of the dorsal motor nucleus in the brain. Gastric motility is controlled by intrinsic (myenteric plexus) and extrinsic neural regulation. Extrinsic control regulates motility via parasympathetic nerves carried by the vagus. Stimulation of the vagus increases the number and force of contractions, while sympathetic nerves usually inhibit contractions. The hormones gastrin and motilin increase frequency and strength of contractions, while gastric inhibitory polypeptide inhibits them.

Sympathetic innervation reaches the stomach through the splanchnic nerve. The main neurotransmitter there is norepinephrine, which functions as an inhibitor at the postganglionic level within the enteric ganglia. Myenteric neurons provide coordination for gastric motility.

The effectiveness of such complex innervation and interconnectedness is illustrated by the fact that distention of the duodenum leads to a decrease in the tone of the gastric fundus. Such reflexes and actions depend on the characteristics of the contents of the duodenum. For example, an increase in fat or protein within the duodenal lumen slows gastric emptying until the duodenum is able to process additional nutrients. Colon distention also leads to relaxation of the stomach. Cholecystokinin (CCK) is considered one of the main neurotransmitters mediating retrograde signaling from the intestines to the stomach. CCK is released from the mucosa of the jejunum in response to fatty substances in the intestinal contents. CCK constricts the gallbladder, expelling bile into the small intestine and inhibiting stomach motility. The combination of these two functions leads to slower movement and longer exposure of the intestinal contents to digestive enzymes.

The motility of the stomach is organized to accomplish the orderly emptying of the contents into the duodenum. When the stomach is filled with a meal, the pylorus is closed for a prolonged period and opens for short periods to let only small amounts of food enter the duodenum. The specific chemical composition of a meal can also prolong constriction of the pylorus to prevent food from entering the duodenum prematurely. This feature is used in the formulation of medications; pills can be coated with a substance that is sensed by the gastric chemoreceptors and through enteric reflexes prevents the pylorus from relaxing for a relatively long period (referred to as *slow-release pills*).

The emptying of the stomach is regulated by neural mechanisms (the reflex is a reaction to the distention of the stomach) and hormonal mechanisms (release of gastrin from the mucosa of the stomach). The pyloric tone is regulated by inhibitory and excitatory vagal pathways and also by myenteric ascending and descending reflexes. The main mediator of pyloric relaxation is NO, which is formed through both extrinsic and intrinsic pathways.

Suppressed gastric motility and slow gastric emptying aggravate and increase the risk of gastroesophageal reflux. This condition often develops in critically ill patients. Delayed transit has been observed following administration of opioids and during the postoperative period.[7,11] Retrograde flow of gastric contents is observed frequently.[11,12] Gastroparesis can result from abnormalities in the intrinsic and extrinsic innervation of the GI tract. Vagal neuropathy is an important cause of gastroparesis in patients with diabetes.[13] Gastric emptying can be slowed to 1 kcal/min from the 2 to 3 kcal/min seen in healthy humans.[7]

Slow gastric emptying was observed in approximately half of critically ill patients receiving mechanical ventilation.[14] Hyperglycemia and increased intracranial pressure are associated with delayed gastric emptying. Administration of dopamine and other catecholamines stimulates β-adrenergic receptors, reduces intestinal motility, and slows gastric emptying. Erythromycin and metoclopramide accelerate gastric emptying in critically ill patients and can be effective as prokinetic drugs in this population.[15]

MOTILITY OF THE SMALL INTESTINE

The proximal part of the small intestine is called the *jejunum* and the distal part is called the *ileum*, with total length approximately 6 m. There are two layers of smooth muscle within the intestinal wall (see Fig. 21-1). Slow intestinal motility serves several purposes: mixing of the contents with digestive enzymes; further reduction of particle size, increasing their solubility; circulation of the contents to ensure optimal exposure to the intestinal cell membrane; and finally, propulsion of the contents through the small intestine into the colon. A number of reflexes are involved in these activities; they occur within the intrinsic or extrinsic neurons or both. For example, the peristaltic reflex depends on the enteric nervous system. The intestinal reflex depends on the extrinsic neural connection; when one of the areas of intestines is distended, contractile activity in the rest of the intestines is inhibited. The section of the extrinsic nerves abolishes this reflex.

Two types of contractions occur within the small intestines to serve particular purposes: mixing contractions and propulsive contractions. Periodic contractions of the same segment of intestine help to blend the chyme with the intestinal secretions. Peristaltic contractions occur in segments of the intestine in a well-regulated order that pushes the chyme along the GI tract. The constriction of the ileocecal valve keeps the chyme in the ileum to facilitate absorption and to prevent the contents of the large intestine from entering. The ileocecal valve contracts when the colon is distended; this reflex is mediated by sympathetic input from the splanchnic nerve.

The smooth muscles of the intestine provide for "two steps forward, one step back"—that is, retaining the intestinal contents long enough to assure the extraction of useful substances.[1] One of the mechanisms involved is segmentation. When two nearby areas contract, a segment of the small intestine becomes isolated. Next, a contraction in the middle of this segment occurs, further dividing it. Each of the two smaller segments is then divided by other contractions. Both circular and longitudinal muscles shorten and relax in concert to achieve this effect. Segmentation is controlled by the enteric nervous system; specifically, the myenteric plexus receives input from other neurons within the plexus, from receptors located in the mucosa and muscle layers, and from the central nervous system by way of the parasympathetic and sympathetic nerves. Plexus neurons in turn provide integrated output to the smooth muscle cells as well as to epithelial cells and probably to endocrine and immune cells.

Extrinsic innervation is provided by the vagus and by nerve fibers from the superior mesenteric ganglia. The main contracting neurotransmitters of this system are ACh and substance P; VIP and NO are inhibitory. However, intestinal motility is mainly regulated by intrinsic innervation. The main function of extrinsic innervation is to modulate the motility pattern established by the "little brain" of the enteric nervous system. In addition, many circulating compounds are involved in regulation of intestinal motility, including epinephrine (released from adrenal glands), secretin, and glucagon, which inhibit contractions, whereas serotonin (contained in the wall of the small intestine), gastrin, motilin, and insulin stimulate them.

Vomiting is the forceful expulsion of intestinal and gastric contents through the mouth. An increase in tone of the autonomic nervous system usually precedes and accompanies vomiting. The symptoms are nausea, salivation, sweating, rapid breathing, and sometimes an irregular heartbeat. During vomiting, the pressure gradient between different areas of the intestines and stomach can reach 200 mm Hg, and often the stomach partially slides through the hiatus in the diaphragm into the thorax. Vomiting is usually a protective mechanism to eliminate toxic compounds; however, prolonged vomiting can lead to fluid and electrolyte imbalance. Transit of contents through the small intestine can be substantially faster in critically ill patients than in healthy individuals.[16] Faster transit decreases absorption and contributes to malnutrition.[7]

MOTILITY OF LARGE INTESTINE

The colon (large intestine) is a reservoir for waste and indigestible material prior to elimination through defecation. The colon (the GI tract distal to the ileocecal junction) is anatomically divided into the cecum; ascending, transverse, and descending colon; sigmoid; the rectum; and the anal canal. Unlike the small intestines, the main function of the colon is to extract electrolytes and remaining water from the intestinal contents, to transfer the contents to the rectum, and then promote the urge to defecate. Distention of the colon contracts the ileocecal sphincter, whereas distention of the ileum relaxes it; both actions are mediated by enteric nerves. Relaxation of the ileocecal sphincter and increase in contractile activity of the ileum occur shortly after eating. This gastroileal reflex is mediated by GI hormones, mainly gastrin and CCK; both hormones increase contractions of the ileum and relax the ileocecal sphincter.

Most movements within the colon are segmental; they move the contents back and forth, exposing them to absorptive surfaces. The contractions generate intraluminal pressure between 10 and 50 mm Hg and are of either short or long duration. Short-duration contractions occur mainly within the circular muscle and create waves of contraction approximately 8 seconds long, effecting local mixing. Long-duration contractions last 20 to 60 seconds and can propagate the contents for a short distance.

The motility of the large intestine is controlled almost entirely by the enteric nervous system; the major effect of regulation is inhibitory. Cells of the myenteric plexus receive the input from receptors within the intestines as well as from extrinsic nerves. Both parasympathetic and sympathetic branches of the autonomic nervous system are involved in the regulation of colon motility. Pelvic nerves enter the colon near the rectosigmoid junction and then travel along the colon proximally and distally. The distal rectum and anal canal are innervated by sympathetic fibers from the hypogastric plexus. The external anal sphincter striated muscle is innervated by somatic pudendal nerves. The main neurotransmitters involved in the innervation of the large intestine include ACh, substance P, NO, VIP, and ATP. Transmission between pudendal nerves and the external anal sphincter is mediated by ACh.

Movement of the colon mass into the rectum leads to the beginning of defecation. Filling and distention of the rectum causes relaxation of the internal anal sphincter, mediated by release of VIP and NO from intrinsic nerves. This effect is offset by the simultaneous increase of the tone of the external anal sphincter. This action not only allows postponement of defecation until an appropriate time; it also prevents leakage.

Defecation is controlled by extrinsic and intrinsic nerves. The sensation of distention and voluntary control of the external anal sphincter are mediated by nerves within the spinal cord and the cerebral cortex.

GASTROINTESTINAL TRACT AND EMOTIONS

Experiments using magnetic resonance imaging (MRI) and other methods have demonstrated the relationships amongst eating, overall quality of food, and emotions. The design of one such experiment included ratings of hunger, mood, and feeling of fullness; then the subjects were exposed to musical and visual cues intended to induce sadness. At the same time nutrients were infused into the stomach. It was found that induced sadness was attenuated by fatty acid infusion; increased neural activity in the part of the brain processing emotions was also observed.[17]

Gut-brain communications are also influenced by enteric microflora. Ingestion of probiotic bacteria influences emotional state by modulating subunits of receptors of the neurotransmitter γ-aminobutyric acid. Probiotic bacteria are beneficial in stress-related disorders, such as anxiety and depression, and during the course of common comorbidities and some bowel disorders.[18] It seems that the connections between GI function and emotional state have been discussed for centuries: expressions such as "butterflies in the stomach" or "I do not have the stomach for this" were probably not created by chance.

POSTOPERATIVE ILEUS

The following description of postoperative ileus (POI) and its pathophysiology includes only the uncomplicated course of changes in motility of the GI tract after laparotomy or surgery, or both, on GI organs. Not included are descriptions of any unexpected complications (e.g., perforations, peritonitis, bleeding) during the postoperative period. Such complications would have additional pathophysiologic features necessitating different additional treatments.

The main pathophysiologic event in POI is neuroimmune interaction, which is based on bidirectional communication between the immune system within and outside the GI tract (including mast cells, macrophages, and other leukocytes) on one hand and the autonomic nervous system (which includes afferents, efferents, and the enteric nervous system) on the other.[19] The course of uncomplicated POI lasts approximately 3 to 4 days and consists of two phases: the early neurogenic phase and the second inflammatory phase.[19] Manipulation of the intestines is the main factor initiating POI. However, many additional factors contribute to its development, including anesthesia, postoperative pain, and opioids.

The early, neurogenic phase of POI begins with the manipulation of the intestine, which leads to almost complete cessation of GI motility. This effect is mediated via adrenergic innervation. Afferent splanchnic nerves convey the information from the manipulated intestine to the spinal cord. After synapsing within the spinal cord, the efferent fibers convey the information back to the GI organs. These signals also travel through the afferents to the hypothalamus, specifically to the nucleus tractus solitarii and the paraventricular and supraoptic nuclei**.** This pathway activates secretion of corticotropin-releasing factor (CRF). CRF activates neurons in the supraoptic nucleus of the hypothalamus, from which the information travels distal to the spinal cord to the synaptic preganglionic neurons. Activation of the postganglionic neurons inhibits motility of the GI tract. This early phase of POI usually lasts approximately 3 to 4 hours after surgery. The late, inflammatory phase of POI also starts with the manipulation of the intestines, which leads to influx of leukocytes into the traumatized segments of the intestine. This increases the overall sympathetic tone, including the activation of sympathetic efferents. Sympathetic activation within the myenteric plexus contributes to the increased influx of leukocytes into the manipulated segment of the intestine (Fig. 21-2).

Trauma of serosa and activation of sympathetic neurons within the myenteric plexus lead to activation of phagocytosis[20] and an increase in the release of cytokines and chemokines, which further increases the influx of leukocytes first into the manipulated segment of the intestine and later into the entire GI tract.

Degranulation of mast cells and release of their mediators within the traumatized segment increases permeability and facilitates translocation of intraluminal

bacteria, exacerbating the inflammatory process. Mast cells are highly effective in recruiting neutrophils and eliminating bacteria within the peritoneal cavity. Some data suggest that substance P and calcitonin gene–related peptide (CGRP) released from activated afferent nerves are involved in the triggering of mast cell degranulation. During the process, released histamines and proteases have been found in the peritoneal fluid after intestinal manipulation.[21,22] Thus, mast cells and macrophages play central roles in the inflammatory process leading to POI.

The neural response to surgical manipulation of the intestines is important in initiating POI, but becomes less important during the inflammatory phase. POI still develops after small intestine transplantation despite the transplanted intestine being completely denervated.[23]

Under normal conditions, macrophages are located at the level of the myenteric plexus (between the longitudinal and circular muscle layers) and the intestinal serosa.[20] The products released from cells damaged during manipulation of the intestine (which includes ATP and others), and particularly the products of mast cell degranulation, activate muscularis phagocytes.[24] Cytokines and chemokines released thereafter activate resident macrophages.[25]

Pharmacologic or genetic manipulation leading to depletion of resident macrophages leads to a decrease in release of inflammatory mediators and decreases the recruitment of leukocytes into the muscularis. Thus, resident macrophages are activated by direct manipulation of the intestines, which activate muscular phagocytes. Released cytokines reinforce the inflammatory process. Preoperative treatment with antibiotics

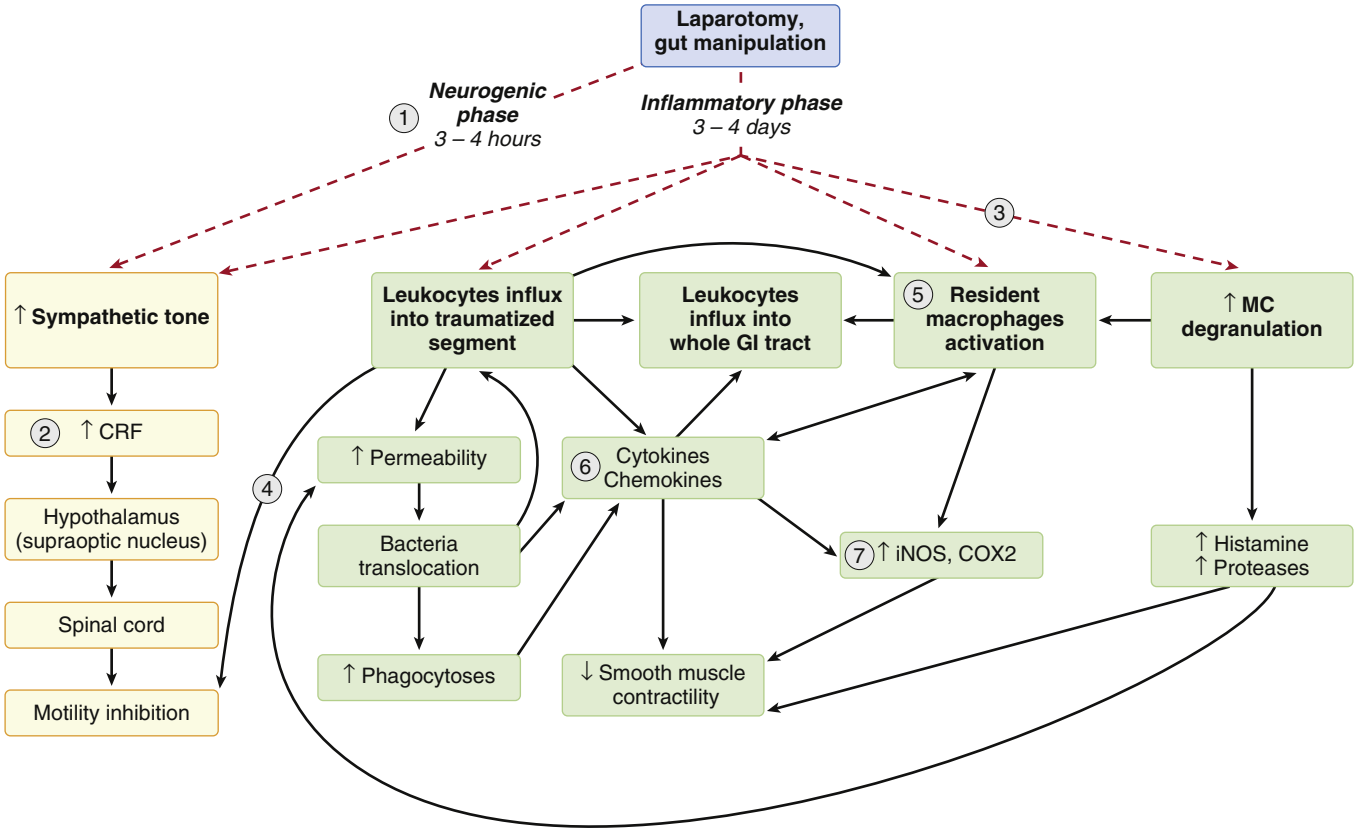


Figure 21-2. Pathophysiology of postoperative ileus (POI). The key feature in the development of POI is the crosstalk between the immune system (mast cells, macrophages, and other leukocytes) and the autonomic nervous system (afferents, efferents, and myenteric plexus). The diagram incorporates main events. The majority of important afferents and efferents are not depicted; see text for explanation. (1) The manipulation of the intestines leads to activation of sympathetic nervous system. Neural pathways involve afferents from the gut, synapses in the spinal cord, and efferents traveling back to the gut directly or through the enteric nervous system. (2 and 3) Released CRF together with substance P initiate MC degradation; the following effects are depicted in the diagram. (4) Manipulation of the intestines triggers the influx of leukocytes in the manipulated segment immediately impairing the smooth muscle function within the segment. (5) Resident macrophages located in serosa and between circular and longitudinal muscle layers close to myenteric plexus are activated directly by manipulation of the intestinal segment leading to an increase in iNOS and COX-2 and directly inhibiting function of the smooth muscles by production of nitric oxide and prostaglandins, particularly PGE-2. (6) Released cytokines tumor necrosis factor α, IL-1β, and IL-6, chemokines MCP-1 and macrophage inflammatory protein-1α (MIP-1α) upregulate adhesion molecules (ICAM-1) in the endothelium and increase further the influx of leukocytes. Neuroinput into this process is illustrated by the decrease in inflammation and POI symptoms during sympatholytic influences, including thoracic epidural anesthesia. (7) Influx of leukocytes triggers neural pathways and inhibits motility illustrating the importance of the crosstalk between neural and immunity or inflammatory systems during the development of POI. *CRF*, corticotropin-releasing factor; *MC*, mast cells.

modifies the overall inflammatory process within the intestines.

The influx of leukocytes into the muscularis starts approximately 3 hours after manipulation of the intestines; during the next 24 hours, the influx increases in the manipulated segment of the intestine and the entire GI tract. These events in turn induce iNOS and cyclooxygenase-2 (COX-2) in the resident macrophages. Thus, the inflammatory process that includes influx of leukocytes into the muscularis of the intestinal wall is one of the main mechanisms responsible for the late inflammatory phase of POI. The up-regulation of iNOS and COX-2 in the resident macrophages inhibits motility in the inflamed intestines[26,27]; therefore, the prevention and treatment of POI can include the blockade of iNOS and COX-2. Preoperative administration of antibiotics decreases the overall inflammatory process and can reduce POI.

Pharmacologic or electrical stimulation of the vagus reduces macrophage activation and attenuates POI.[28] Stabilizing mast cells, administering antibodies to IL-12, or inhibiting Th_1 cell migration were also effective in reducing POI symptoms.[29] Ganglion antagonists such as hexamethonium significantly ameliorate the inhibition of intestinal motility during POI.[30] Thoracic epidural anesthesia placed below T12 does not affect the course of POI; however, if it is administered above T12, attenuation of POI has been observed.[31] Thoracic epidural anesthesia promotes GI motility by blockade of afferent nerves, blockade of thoracolumbar sympathetic efferent nerves, unopposed parasympathetic efferent nerves, reduced need for postoperative opioids, increased GI blood flow, and systemic absorption of local anesthetics.[31] These observations show clearly that both neural and inflammatory mechanisms (and interactions between them) play an important role in the pathogenesis of POI.

Manipulation of the intestines leads to a cascade of neural and inflammatory responses. Leukocyte influx into manipulated segments is associated with release of cytokines and chemokines that initiate and potentiate the recruitment of leukocytes into the intestinal segment and then into the entire GI tract. Motility is decreased in the inflamed intestine by increased production of NO and COX-2. These events and the activation of inhibitory adrenergic neural signals are responsible for the course of POI (see Fig. 21-2).

SECRETION

OVERVIEW

Initially, the secretory function of the GI tract supports the digestion of a swallowed bolus of food to promote the absorption of nutrients, electrolytes, and vitamins contained in food. It also protects the GI tract from ingested bacteria. Next, the secretion of hormones, peptides, and mediators not only regulates the intake of food through intensive crosstalk with the central nervous system; it also ensures the optimal digestion and absorption of luminal content by modulating digestive secretion and its rate of delivery throughout the intestinal tract. It regulates mucosal proliferation, maturation and regeneration, and modulates immune function. The integral secretory activity of the GI tract controls food ingestion, its digestion, absorption, and the advancement through the intestine to optimize extraction of vital nutrients, vitamins, and electrolytes while ensuring the maintenance of homeostasis of the complex ecosystem of the GI tract, the integrity of its own structure by adapting to the ever changing needs of quiescence during night and fasting, and the dynamics of food processing during digestion.

DIGESTIVE SECRETION

Hydrochloric Acid Secretion

Hydrochloric acid is secreted in the stomach by parietal cells found in the oxyntic region (Fig. 21-3) and facilitates digestion and absorption of proteins, iron, electrolytes, and certain medications such as thyroxin.[32] Hydrochloric acid also controls ingested bacteria and sterilizes food. Hydrochloric acid production and secretion must be tightly regulated, because too much gastric acid is detrimental to the stomach itself or the adjacent esophagus and duodenum and it might overwhelm self-protective measures causing significant pathology (gastric ulcers, duodenal ulcers, esophagitis, intestinal metaplasia [Barrett esophagus], and ultimately gastric or esophageal cancer). Too little gastric acid can lead to malabsorption of essential vitamins and electrolytes or increase the risk for intestinal infections and modification of the enteral ecosystem by bacterial overgrowth. The chronic use of acid-suppressing drugs, such as histamine-2 receptor antagonists or proton pump inhibitors (PPIs), can also increase the risk for community-acquired pneumonia.[33] Electrolyte abnormalities, such as hypomagnesemia and low vitamin B_{12} levels, should be anticipated with long-term use of such medications. An increased risk of fractures has been noted as well when gastric hydrochloric acid is reduced chronically by means of a PPI.[34] Lastly, when administered with clopidogrel, a GP2b/3a receptor inhibitor frequently used as an antiplatelet agent after stent placement, PPIs are thought to reduce the efficacy of clopidogrel in various but clinically significant degrees.[35]

Acid secretion is a complex and highly integrated process involving hormonal, paracrine, and enteric as well as central neuronal pathways that are modulated by both local and central feedback loops (Fig. 21-4). The cephalic phase of acid secretion is initiated by sensory inputs such as the thought, sight, smell, taste, or sound of food. The cephalic phase contributes about 50% of the overall acid response to a meal.[5] GI peptides such as ghrelin and leptin can act directly in the brain or indirectly by acting on the abundant afferent neurons that terminate in the spinal cord or the brain stem. The mechanical and chemical milieu is monitored continuously by as many as 16,000 afferent vagal neurons that convey information to the nucleus tractus solitarius in the medulla and the paraventricular nucleus in the hypothalamus. Only 6000 efferent preganglionic neurons originating from

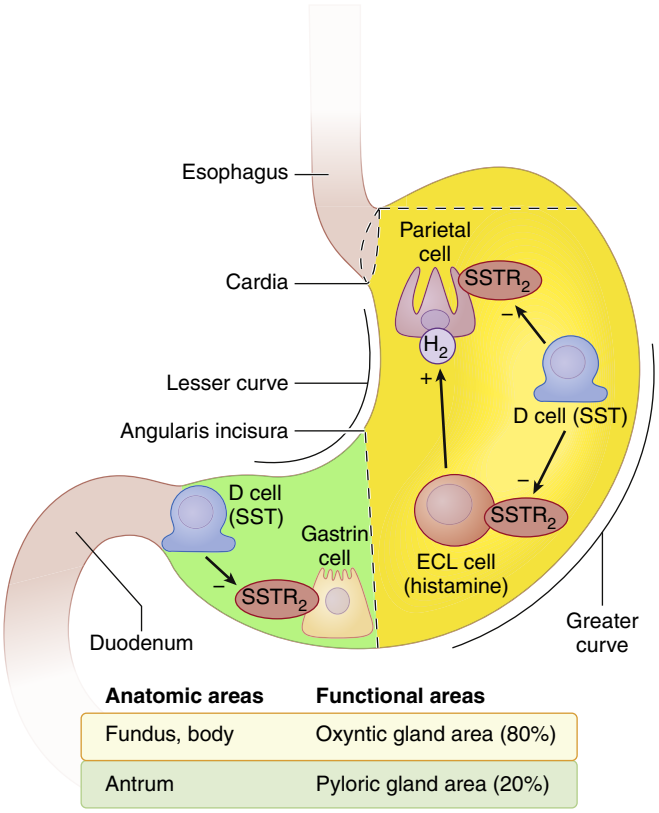


Figure 21-3. Functional gastric anatomy. The stomach consists of three anatomic (fundus, corpus or body, and antrum) and two functional (oxyntic and pyloric gland) areas. The hallmark of the oxyntic gland area is the parietal cell. The hallmark of the pyloric gland area is the gastric (G) cell. Somatostatin (SST)-containing D cells are structurally and functionally coupled to their target cells: parietal, enterochromaffin-like (ECL), and gastric cells. SST, acting via $SSTR_2$ receptors, tonically restrains acid secretion. This restraint is exerted directly on the parietal cell and indirectly by inhibiting histamine secretion from ECL cells and gastrin secretion from G cells. H_2, histamine H_2 receptor. *(Redrawn from Functional Gastric Anatomy from Schubert ML: Regulation of gastric acid secretion. In Johnson LR, Ghishan FK, Kavnitz JD, et al, editors:* Physiology of the gastrointestinal tract, *vol 2, ed 5. Boston, 2012, Academic Press.)*

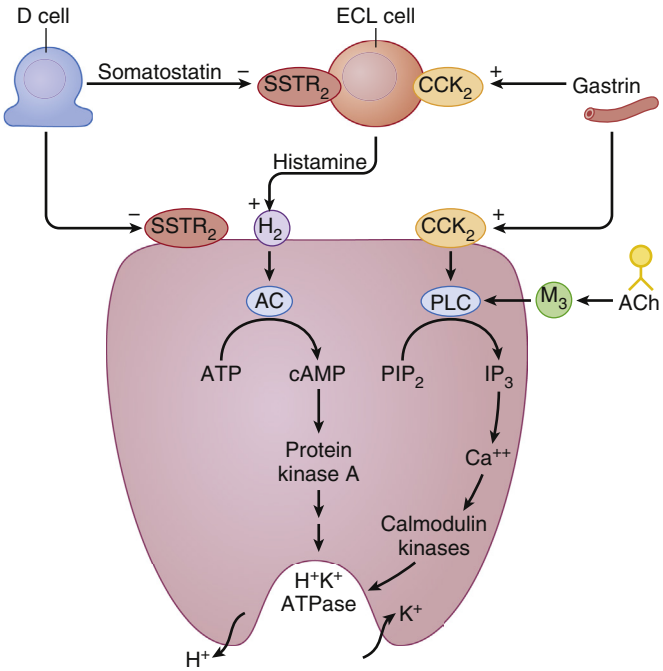


Figure 21-4. Model illustrating parietal cell receptors and signaling pathways. The principal stimulants of acid secretion at the level of the parietal cell are histamine (paracrine), gastrin (hormonal), and acetylcholine (ACh; neurocrine). Histamine, released from enterochromaffin-like (ECL) cells, binds to H_2 receptors coupled to activation of adenylate cyclase, which converts cytosolic adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Increases in cAMP activate cAMP-dependent protein kinases (protein kinase A) that phosphorylate various intracellular proteins that ultimately trigger acid secretion. Gastrin, released from G cells, binds to CCK_2 receptors on ECL and parietal cells that are coupled to activation of phospholipase C with conversion of phosphatidylinositol bisphosphate (PIP_2) to inositol triphosphate (IP_3). IP_3 in turn induces release of cytosolic calcium (Ca^{2+}), which activates various calcium-dependent enzymes, such as calmodulin kinases, that ultimately trigger acid secretion. The acid-stimulatory effects of gastrin are mediated primarily via release of histamine from ECL cells. ACh, released from intramural neurons, binds to M3 receptors that are coupled to an increase in intracellular calcium via similar signaling pathways as described earlier for gastrin. The intracellular cAMP- and calcium-dependent signaling systems activate downstream protein kinases ultimately leading to fusion and activation of H^+K^+-ATPase, the proton pump. Somatostatin, released from oxyntic D cells, is the principal inhibitor of acid secretion. Somatostatin, acting via the $SSTR_2$ receptor, inhibits the parietal cell directly and indirectly by inhibiting histamine release from ECL cells. +, Stimulatory; –, inhibitory. *(Redrawn from Schubert ML: Regulation of gastric acid secretion. In Johnson LR, Ghishan FK, Kavnitz JD, et al, editor:* Physiology of the gastrointestinal tract, *vol 2, ed 5. Boston, 2012, Academic Press.)*

the nucleus ambiguus and the dorsal motor nucleus of the vagus nerve are switched over to postganglionic neurons in the wall of the stomach and duodenum and with decreasing density in the mid and distal gut.[36] These neurons stimulate acid secretion either directly or indirectly by inhibiting somatostatin secretion and by stimulating histamine and gastrin. Overall, acid secretion is supported by paracrine histamine release from oxyntic enterochromaffin-like (ECL) cells, gastrin release from pyloric G cells, and ACh release from postganglionic intramural neurons. Histamine and either ACh or gastrin act synergistically at the parietal cell and potentiate hydrochloric acid release. Somatostatin is released from oxyntic and pyloric D cells in a paracrine fashion; this represents the major inhibitor of acid secretion. Synthetic somatostatin (octreotide) is used therapeutically among other treatments in acute bleeding peptic ulcer disease.

Bicarbonate Secretion and Mucus Barrier

Mucus and bicarbonate secretions, particularly in the stomach and the duodenum, represent the first line of defense against the hostile and acidic luminal milieu. Mucin is secreted from epithelial cells and polymerizes into large multimers to form a gel. Together with surfactant phospholipids and bicarbonate, it covers the epithelial cell surface and creates a steep pH gradient across the unstirred mucus layer. The hydrophobic luminal surface of this glycoprotein matrix is probably the major

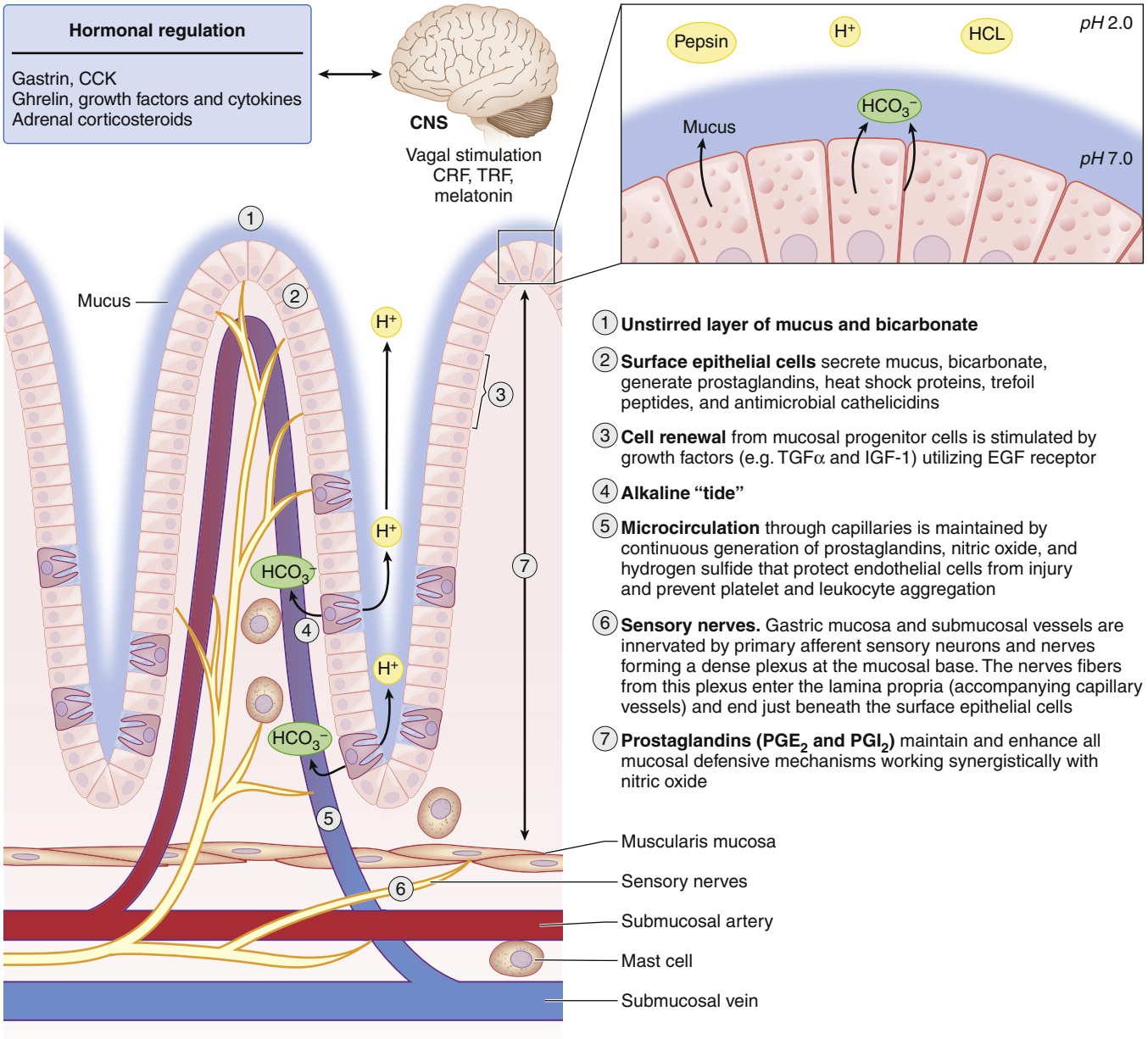


Figure 21-5. Gastric mucosal defense. Schematic diagram of the mucus–bicarbonate barrier of the acid-secreting gastric mucosa. *(Redrawn from Laine L, Takeuchi K, Tarnawski A: Gastric mucosal defense and cytoprotection: bench to bedside,* Gastroenterology *135:41, 2008.)*

reason for this gradient. Trefoil family peptides (TFFs) are stored in mucosal cells in the stomach (gastric pit and surface mucus cells) and in the duodenum (small and large intestinal goblet cells) and are secreted into the mucus gel, where TFFs increase viscosity and elasticity. In addition, TFFs are believed to play a pivotal role in mucosal cell differentiation and regeneration and add to the regulatory signals of acid production. Mucus secretion is stimulated by gastrin, secretin, prostaglandin E_2, and cholinergic agents. Ulcerogenic substances such as nonsteroidal antiinflammatory drugs (NSAIDs), aspirin, and bile salts dissolve the mucus gel and phospholipid layer and lead to mucosal injury (Fig. 21-5). Parietal cells in the oxyntic region of the stomach maintain a tandem production of equivalent numbers of hydrogen and bicarbonate ions. This astonishing and simplistic yet sophisticated principle results in self-regulation.[37] The more hydrochloric acid is produced, the more bicarbonate is secreted into the interstitium and fenestrated capillaries in the gastric glands from which it diffuses into the mucus layer, where it neutralizes hydrogen ions that have diffused into it from the gastric lumen. The driving force for bicarbonate diffusion is the rate of its neutralization in the mucus layer by hydrogen ions; however, most bicarbonate from parietal cells is secreted in the urine. The increase in blood and urine pH after a meal is known as the *alkaline tide*.[38]

Duodenal HCO_3^- secretion is stimulated by a wide variety of agonists (e.g., CCK, ghrelin, serotonin, uroguanylin) and is a much stronger and more sustained

occurrence compared with that of the stomach. Exposure of the duodenal mucosa to luminal acid results in a significant but segmental increase in bicarbonate secretion by mucosal enterocytes and by submucosal Brunner glands. This increase is augmented by a concomitant increase in PGE_2 secretion, which also stimulates bicarbonate secretion. The autonomic nervous system plays an important role in this acid-induced secretory response. The capsaicin-sensitive transient receptor potential vanilloid receptor 1 resides in the lamina propria, senses acidosis, and stimulates bicarbonate secretion. Local humoral factors such as melatonin, vasoactive intestinal peptide, and NO prove to be involved in up-regulation of bicarbonate secretion following exposure to luminal acid. Cystic fibrosis transmembrane conductance regulator (CFTR) is an ATP-binding cassette–class transporter ion channel for chloride and thiocyanate movement across epithelial cell membranes. In states of hypotonicity or low intracellular Cl^-, CFTR switches its selectivity from chloride to HCO_3^-.[39] At least three forms of the apical solute carrier (Slc-26) anion transporter family are expressed in the duodenum and contribute to HCO_3^- secretion.[40]

Prostaglandins (PGE_2, PGI_2) stimulate and facilitate mucosal defense by inhibiting acid secretion and by stimulating mucus, bicarbonate, and phospholipid secretion. They increase mucosal blood flow and support epithelial regeneration and mucosal healing. Prostaglandins (PGs) inhibit mast cell activation, leukocyte adhesion, and platelet adhesion to the vascular endothelium. The inhibition of cyclooxygenase (COX)-mediated PG synthesis by NSAIDs leads to gastroduodenal ulceration and is mainly a systemically mediated effect regardless of the route of NSAID administration. Gastric mucosal integrity at baseline is supported by COX-1–mediated PG synthesis. COX-1 is expressed in many tissues whereas COX-2 is rapidly induced in response to growth factors or cytokines. Only the combined inhibition of COX-1 and -2 causes mucosal damage, whereas mucosal blood flow decreases after selective COX-1 and COX-1/2 inhibition but not with COX-2 selective inhibition. The absence of PG renders hormonal, paracrine or neurocrine pathways (TRPV-1, afferent fibers, NO, CGRP) that stimulate mucus gel secretion ineffective, which underlines the importance of PG, especially in the up-regulation of mucus gel production and secretion. Interestingly, PG depletion results in vagus nerve–dependent gastric hypermotility and subsequent reduction of mucosal blood flow and neutrophil recruitment in the endothelium with the onset of oxygen-radical production.[38]

REGULATORY SECRETION

Hormones, Paracrine, and Neurocrine Compounds

Five peptides are considered GI hormones.[32] They are released following a stimulus, such as a meal, and act at a different location in the GI tract altering its function. This effect is maintained even if no nervous connections exist between the area where the hormone is released and the area where it acts. Hormones are chemically identified and reliably elicit the same functional change when injected into the blood stream. Secretin, gastrin, CCK, gastrin inhibitory peptide and motilin are today established gastrointestinal hormones.[32]

Histamine and somatostatin are released in close proximity to and reach their respective targets by diffusion and therefore represent paracrine agents.

Neurotransmitters are ACh, gastrin-releasing peptide (GRP), vasoactive intestinal peptide, and pituitary adenylate cyclase-activating polypeptide (PACAP). They are released from nerve terminals, and they reach their target receptors by traversing the synaptic cleft. Table 21-1 summarizes postpyloric compounds and their respective primary actions.

Gastrin is the major regulator for hydrochloric acid secretion in the stomach. It promotes mucosal proliferation and maturation, and it modulates innate mucosal immune function. Gastrin is secreted as precursor peptides by G cells in the antrum of the stomach and the duodenum. G cells are the hallmark of the pyloric gland mucosa in the antrum of the stomach. Gastrin is also produced, although in much smaller amounts, in the small intestine, colon, and pancreas. Gastrin release is stimulated by ACh, GRP, PACAP, secretin, serotonin, β_2/β_3-adrenergic agonists, calcium, luminal protein, capsaicin, alcoholic beverages made by fermentation, and bacterial lipopolysaccharide. Galanin, adenosine, and somatostatin inhibit gastrin release from G cells. Gastrin stimulates ECL cells and parietal cells directly via the CCK-2 receptor, which increases intracellular Ca^{2+} through the phospholipase C pathway. Gastrin is metabolized by the kidney, the intestine, and the liver and is found in higher plasma concentrations in patients with impaired renal function. At least two negative feedback loops regulate gastrin release. One loop is activated by intragastric acidity, which releases somatostatin via sensory CGRP neurons, and the second is a direct stimulus by gastrin to release somatostatin. Long-term use of medications that raise gastric pH can lead to hypergastrinemia.[41]

CCK-2 receptors are also found on oxyntic progenitor cells, implying that gastrin is also involved in differentiation, growth, and migration of parietal cells. Gastrin stimulates mucosal proliferation and increases the parietal and ECL cell mass, probably through the release of growth factors.

Gastrin modulates innate immune function through CCK-2 receptors that are found on macrophages in the intestinal lamina propria, peripheral blood mononuclear cells, and polymorphonuclear monocytes within the stroma of colorectal cancers. Proinflammatory actions appear to dominate with stimulation of chemotaxis, adherence, and phagocytosis at sites of active inflammation. In the mesenteric venous system, gastrin promotes leukocyte adherence and extravasation. CCK-2 receptor–expressing intestinal endothelial cells up-regulate their production of vascular cell adhesion molecule 1 (VCAM-1) and P-selectin glycoprotein ligand-1 (P-selectin) following a gastrin stimulus. Therefore, gastrin appears to act as a chemoattractant and recruits inflammatory cells to sites of inflammation within the GI tract.[41]

TABLE 21-1 **IMPORTANT FEATURES OF POSTPYLORIC PEPTIDES**

Peptide	Location	Hormone (H), Neuropeptide (N)	Secretagogues	Primary Activities
Secretin	"S" cells—small intestine	H	Luminal acid, fat	Bicarbonate secretion by biliary pancreatic ductular epithelium, Brunner's glands
Somatostatin (SRIF)	"D" cells—entire GI tract, nerves, and nerve plexuses	H, N	Luminal acid, dietary nutrients	Central inhibitor of gut hormone secretion, nutrient absorption, and exocrine secretion
Vasoactive intestinal polypeptide (VIP)	Superior and inferior mesenteric ganglia, Meissner's and Auerbach's plexuses	N	Unresponsive to meal	Smooth muscle relaxant
Pituitary adenylate cyclase activity peptide (PACAP)	Nerve fibers; myenteric and submucosal ganglia	N	Unresponsive to meal	Physiologic function not proved; relaxes colonic smooth muscle, stimulates pancreatic exocrine secretion
Neurotensin	"N" cells—cells in ileum and colon; myenteric plexus	H, N	Dietary fat	Physiologic functions not proved; influences pancreatic, gastric, and intestinal secretion
Neuropeptide Y (NPY)	Submucosal and myenteric plexuses; nerve fibers of entire GI tract; highest level in lower esophageal sphincter	N	Unresponsive to meal	Regulates GI blood flow, motility, and secretion
Motilin	"M" or "Mo" cells in duodendum	H	Cyclic elevations in plasma motilin during fasting stage; dietary fat in human increases plasma motilin	Stimulation of phase III–MMC contractions
Peptide YY (PYY)	"L" cells of terminal ileum and colon; nerve cell bodies and fibers of stomach; intestinal myenteric and submucosal plexuses	H, N	Mixed meal in humans, luminal fat	Enterogastrone; ileal break; reduces gastric and intestine motility, gastric acid, and pancreatic secretion

GI, Gastrointestinal; *MMC,* migrating myoelectric complex.
Reproduced from Greeley G: Postpyloric gastrointestinal peptides. In Johnson LR, Ghishan FK, Kavnitz JD, et al, editors: Physiology of the gastrointestinal tract, *vol 1, ed 5. Boston, 2012, Academic Press.*

Enteroendocrine I–type cells in the duodenum secrete CCK into the blood stream following a meal rich in fat and protein. This secretion stimulates gallbladder contractions and exocrine pancreatic secretion and inhibits further food intake, delays gastric emptying, and increases the travel time along the GI tract via CCK-receptor-1 acting on afferent vagal fibers. Overall, CCK promotes the optimal digestion of fat and protein in the small intestine and currently represents the most important anorexigenic signal in the complex control of food intake and in the long-term energy balance.[42] In addition, CCK has been found to act as an endogenous antiopioid and promotes the development of acute opioid tolerance.[43]

Secretin is released by S cells that line the mucosa of the small intestine in decreasing density from the duodenum to the ileum. It is released when the luminal pH in the duodenum falls to less than 4.5. Its major action is the stimulation of pancreatic and biliary duct cells to secrete bicarbonate.[1] In addition, secretin reduces the gastrin response to food intake, slows gastric emptying, and decreases colonic motility. Secretin is used to aid in the diagnosis of Zollinger-Ellison syndrome, a condition in which an often malignant neuroendocrine tumor produces gastrin. Elevated serum gastrin levels increase further by up to 100% after a secretin challenge.[32] Gastrin-inhibitory peptide or glucose-dependent insulinotropic peptide is a member of the secretin family; it is secreted by K cells, stimulates pancreatic insulin release, and decreases gastric acid release. Luminal carbohydrates, protein, and fat are triggers for the release of gastric inhibitory polypeptide. It also slows gastric emptying and reduces gastric motility.[32] Motilin is cyclically released in the small intestine during the fasting state; it promotes the "migrating motor complex," which is a phased peristaltic wave through the entire intestine

believed to serve a preparatory function to accommodate the next meal.[1]

Gastral histamine is mainly released from ECL cells that are found on the base of oxyntic glands. Some histamine is also released from mast cells. ECL cells, but not mast cells, contain L-histidine decarboxylase, which catalyzes the production of histamine from L-histidine, the major source for histamine in ECL cells. Four subtypes of histamine receptors exist and all of them are G-protein coupled. Parietal cells exhibit the histamine-2 receptor. Histamine release is stimulated by gastrin, PACAP, VIP, ghrelin, epinephrine, norepinephrine, and transforming growth factor alpha. Somatostatin, CGRP, PGE_1 and PGE_2, peptide YY, galanin, and interleukin-1β inhibit histamine secretion.[36]

ACh is released from postganglionic intramural neurons in the gastric body and fundus; it stimulates acid secretion directly by acting on M_3-ACh receptors on parietal cells and indirectly by inhibiting somatostatin release via M_2- and M_4-ACh receptors on D cells.[36]

Gastrin-releasing peptide (GRP) receptors are found on G cells and stimulate gastrin among other peptides.

PACAP is a regulatory peptide found in the gastric mucosa and released from enteric nervous system neurons. Its receptors are found on ECL and D cells. Whether it increases acid secretion or inhibits it depends on confounding factors such as calcium entry and the relative weight of ECL cell–derived histamine release versus D cell–derived somatostatin release.

NO acts as a neurotransmitter, intracellular messenger, and signaling molecule, and it appears to have a dose-dependent effect on net acid secretion.

Ghrelin

Ghrelin is present mainly within the oxyntic mucosa and to a lesser extent within the pyloric mucosa in A-like or Gr cells. These cells represent 20% to 30% of gastric neuroendocrine cells and produce approximately 80% of the body's ghrelin. It is released when the stomach does not contain calories and circulates systemically when fasting to stimulate appetite. ACh, glucagon, secretin, endothelin, and gastric inhibitory polypeptide stimulate ghrelin secretion as well. Ghrelin promotes food intake and appetite. It increases gastric motility, hydrochloric acid secretion, insulin secretion, and promotes adipogenesis. Ghrelin release decreases with intragastric calories, intravenous fat and dextrose, insulin, CCK, somatostatin, GRP, and IL-1β. Ghrelin stimulates growth hormone release in the pituitary gland.[41] The sustained weight loss after bariatric surgery or total gastrectomy is thought to be maintained by loss of ghrelin-secreting cells, 65% of which reside in the stomach. Additionally, ghrelin antagonists might be able to induce weight loss by reducing appetite. Offsetting the hormonal balance that regulates appetite (ghrelin, leptin, GLP-1) by removing parts of the stomach together with a significant drop in ghrelin-secreting cells can put patients at risk for addiction after bariatric surgery, because these mediators affect dopamine release in the addiction circuitry in the brain.[44]

IMMUNOMODULATORY SECRETION

Paneth Cells

Paneth cells reside at the base of Lieberkühn crypts in the small intestine and display a unique histologic morphology with their extensive endoplasmic reticulum and Golgi network.[45] Paneth cells secrete host defense proteins and peptides (e.g., α-defensins that modulate composition of small intestinal microflora, secretory phospholipase A2, lysozyme, lipopolysaccharide-binding protein, REG3-γ, xanthine oxidase, matrix metalloprotease 7, CD95 ligand, immunoglobulin A, CD1d, CRIP, CD15, and several proinflammatory mediators such as IL-17A, tumor necrosis factor α, IL-1β, and lipokines). As a result, these cells play various roles in innate mucosal immunity and maintenance of homeostasis in the lower GI tract. Paneth cells are particularly sensitive to endoplasmic reticulum stress and unfolded protein responses, which if unresolved, leads to apoptosis and disruption of crypt homeostasis with the result of increased sensitivity to ileitis and colitis.[45]

DIGESTION AND ABSORPTION

OVERVIEW

Digestion ensues in the mouth after the ingestion of food. Saliva lubricates the food bolus and mixes into the food as it is chewed. This action moistens the food and facilitates swallowing. Enzymes that are contained in saliva begin the breakdown of carbohydrates (α-amylase) and lipids (lipase). In addition, saliva protects the oral cavity by buffering and by diluting noxious substances, hot or cold liquids, or food. Saliva exhibits additional protective functions by its antibacterial compounds (lactoferrin, secretory immunoglobulin A). Salivary glands are highly effective in producing saliva and are under control of the autonomic nervous system. Muscarinergic receptors and β-adrenergic receptors of salivary glands are mostly stimulated by the parasympathetic as well as by the sympathetic nervous system. Antidiuretic hormone (ADH) and aldosterone decrease sodium and increase potassium concentrations; however, they do not affect the rate of saliva production.

The digestive process in the stomach begins with simple hydrolysis. The stomach secretes hydrochloric acid, which acidifies the luminal environment, denaturizes protein, and sterilizes the meal. Proteolytic enzymatic digestion begins in the stomach. Pepsin is secreted as an inactive precursor (pepsinogen), which is activated by autocatalytic cleavage in the low pH environment. Pepsin activity is optimal at low pH. This is referred to as *luminal digestion*.[32] As the bolus of food passes into the small intestine, membrane digestion ensues. Food contacts the small intestinal brush border and is further hydrolyzed by enzymes anchored in the apical membrane of the epithelial surface.

The small intestine with its brush border is the major area of digestion and absorption of all major dietary compounds, whereas the colon principally absorbs electrolytes and most of the remaining water that passes the ileocecal valve.

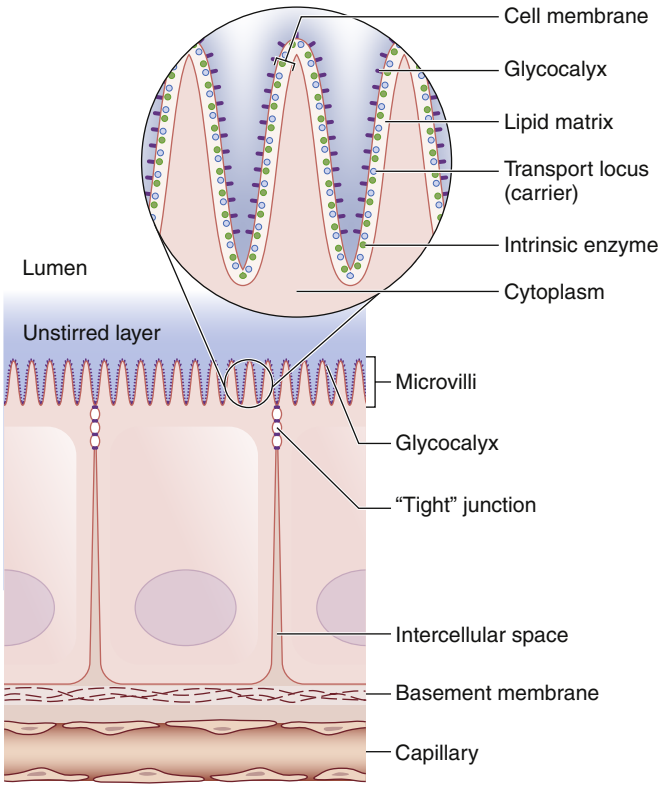


Figure 21-6. Mucosal barrier. Solutes moving across the enterocyte from the intestinal lumen to the blood must traverse an unstirred layer of fluid, a glycocalyx, the apical membrane, the cytoplasm of the cell, the basolateral cell membrane, the basement membrane, and finally the wall of the capillary of the lymphatic vessel. Microvilli are morphologic modifications of the cell membrane that comprise the brush border. The importance of this region in the digestion and absorption of nutrients is depicted by the enlarged microvillus *(inset)*, which illustrates the spatial arrangement of enzymes and carrier molecules. *(Redrawn from Johnson LR:* Gastrointestinal physiology: Mosby physiology monograph series*, ed 7. Philadelphia, 2006, Mosby.)*

The intestinal epithelial monolayer is composed mainly of four different cell types: absorptive enterocytes, mucus-secreting goblet cells, enteroendocrine cells, and Paneth cells. All cells are renewed continuously from pluripotent progenitor cells that reside in the Lieberkühn crypts. See Figure 21-6 for a schematic arrangement of the epithelium in villi and crypts and an illustration of its mucous barrier.

The intake of nutrients and water occurs through several mechanisms such as pinocytosis, passive diffusion, facilitated diffusion, and active transport.[32] Luminal tight junctions between apposing enterocytes seal the endothelium mechanically but are relatively leaky for ions and water in certain regions of the intestine. Digestive and absorptive processes are adaptable to functional changes within the intestine. Small bowel resections or bypasses are well tolerated because the remaining gut is able to compensate. An exception is the terminal ileum, which is the only area where bile salts and vitamin B_{12} are absorbed.

Sugars

Carbohydrates comprise approximately 50% of our daily ingested calories. Half of these calories are in the form of starch, a high-molecular-weight compound made of amylose and amylopectin. α-Amylase from salivary glands and from the pancreas luminally digests starch in the mouth and the small intestine. Amylase is inactivated by acid; therefore, only limited digestion of starch occurs in the stomach. Brush border hydrolases further break down starch and other carbohydrates into their monosaccharides. Those are absorbed throughout the small intestine passively either by paracellular diffusion facilitated by tight junction plasticity or by the passive facilitated diffusion using Glucose Transporters (GLUTs of the SLC2 gene family) at the brush border. More importantly, monosaccharides are absorbed into the enterocytes by the active sodium glucose symporter or cotransporter (SGLTs of the SLC5 gene family). Glucose and galactose are accumulated within the enterocyte and eventually exit at the basolateral membrane into the blood by either facilitated transport (GLUT2) or exocytosis.[46] The capacity to absorb sugars in the small intestine is extremely high**.** Usually, all monosaccharides are absorbed by the time they reach the mid ileum. Chemoreceptors and osmoreceptors within the brush border of the proximal small intestine sense luminal carbohydrate content and regulate the contact time of ingested sugars by modifying motility and gastric emptying.[32] The rate of carbohydrate-containing solutes leaving the stomach is inversely related to the carbohydrate content. The higher the carbohydrate load, the slower it is delivered into the duodenum with approximately 200 kcal/hr delivered to the duodenum.[5]

Proteins

Proteins are denaturized by hydrochloric acid and luminally digested by pepsin in the stomach. Pepsin is released as a precursor by the chief cells. Ingestion of a meal with protein in the stomach and low gastric pH (as more hydrochloric acid is secreted in response to protein in the meal) triggers pepsin release. With transition of the chyme to the duodenum, its polypeptide and fat content triggers CCK release from duodenal enteroendocrine cells (I cells), which stimulates the secretion of peptidases (trypsinogen, chymotrypsinogen, proelastase, procarboxypeptidase) from the pancreas in inactive precursor forms; they are activated by enterokinase in the brush border of duodenal enterocytes. Furthermore, membrane-bound digestion of peptides to free amino acids, and more importantly small dipeptides and tripeptides, occurs at the brush border, where absorption follows by secondary active transport processes along transmembrane ion gradients. The activity for dipeptide and tripeptide absorption is highest in the more proximal small intestine, whereas free amino acids are more efficiently absorbed more distally in the ileum. This activity coincides with a noticeable increase in brush border–bound proteases towards the ileum. Most protein is absorbed in the small intestine. Although able to absorb protein, the colon plays only a minor role in the uptake of amino acids derived from food. It can be involved in the absorption of dipeptides and tripeptides from bacterial proteins.[47] Enterocytes demonstrate high cytosolic peptidase activity that further hydrolyzes small peptides so that ultimately about 90% of all absorbed peptides exit the enterocyte at the basolateral membrane in the form of amino acids.

Lipids

Lipids are highly heterogeneous macromolecules and represent the most dense source of calories in the human diet. Lipids present predominantly as triacylglycerols (TAGs), phospholipids, and sterols; they are inherently insoluble in water and tend to form ester linkages. Digestion of lipids is a refined and efficient process that is intimately associated with the absorption of lipid-soluble vitamins. It involves three steps: emulsification, enzymatic hydrolysis, and the creation of water-soluble products of lipolysis that allows lipids to be absorbed.[32] The stomach mixes and churns lipids with hydrochloric acid, releases lipase in its corpus and fundus, and regulates the advancement of chyme into the duodenum. CCK is secreted to slow gastric motility and emptying when significant amounts of lipids reside in the small intestine. CCK also promotes the release of bile salts into the duodenum. With the exception of short-chain fatty acids, there is no absorption of lipids in the stomach.[32] In the small intestine, bile salts, phosphatidylcholine, fatty acids (FA), and other compounds emulsify lipids into small fat droplets of approximately 1 μm in diameter to allow enzymatic hydrolysis. Because products of lipolysis are poorly soluble in water, they are built together with lipid-soluble vitamins (vitamins A, D, E, and K) into micelles, which have a hydrophobic core but a hydrophilic surface.

CD36, a member of the class B scavenger receptor family of cell surface proteins, is found abundantly on the apical membrane of villi enterocytes of the proximal small bowel, where most FA absorption occurs. CD36 knockout animals shift absorption of FA to the more distal small bowel, where it is CD36 independent. Chylomicron production, however, is greatly impaired when CD36 is absent. Polymorphisms of the CD36 gene are relatively common and result in high blood FA levels and accelerated cardiovascular disease.[48] TAG is hydrolyzed to two FAs and monoacylglycerol and is subsequently reassembled to TAG in the endoplasmic reticulum of the enterocyte before moving as a prechylomicron transport vesicle into the Golgi apparatus. There, the chylomicrons mature and are subsequently released into the lymph and blood streams. This multistep process is usually accomplished quickly, and 500 g of fat can be processed daily. Fat-soluble vitamins are solubilized into micelles before absorption occurs by passive diffusion (vitamins A, D, E, food-derived K) into the enterocyte. Bacterially derived vitamin K is absorbed by an active process. The eventual distribution of vitamins throughout the body is achieved by embedding them (mostly unaltered) into chylomicrons, which demonstrates that the absorption of fat-soluble vitamins in fact depends on fat absorption.[32]

Intestinal lipid metabolism could have a significant effect on overall metabolic homeostasis in the body. High fatty intake and intestinal lipid metabolism disturbances can lead to hyperlipidemia and accelerated cardiovascular disease.[48]

WATER TRANSPORT

The GI tract handles 8 to 9 L of water in a 24-hour period; only the kidneys filter and process more water. Approximately 2 L are ingested with daily food and liquid intake, the remaining 6 to 7 L are derived in combination from the following: secretory products from salivary glands (1.5 L), gastric juices (2.5 L), pancreatic enzymes and bicarbonate-containing fluids (1.5 L), and bile salts (0.5 L). Most water is reabsorbed in the small intestine (7.5 to 9 L),[1,49] which illustrates that especially in the stomach and small intestine, water is secreted and absorbed at the same time, with a net flow in either direction depending on the location and the physiologic state. Compared with the small intestine, the colonic mucosa has a lower paracellular permeability and tighter epithelium with higher electrical resistance; therefore, it is relatively impermeable for water. It reabsorbs the remainder, leaving approximately 100 mL/day of hypertonic water for excretion with the feces. Hence, water flow in the colon is mostly absorptive and has to occur against substantial osmotic and hydraulic resistance imposed by the luminal content.[49] The colonic crypts are suggested to be the site where water is absorbed, because they are surrounded by a hypertonic milieu created by solute absorption (mostly sodium). A fenestrated sheath formed by myofibroblasts maintains the osmotic gradient and patency of the crypts as water is "sucked" into the pericryptal space.[49]

Mechanisms of Water Transport

The longstanding paradigm states that water moves across membranes driven by either osmotic forces created by active salt transport or hydrostatic pressure differences. The observation that water can be secreted or absorbed in the absence of both forces puzzles scientists even today and supports the theory of a dedicated active transport mechanism for water across GI epithelial membranes. The role of aquaporin water channels or water pumps such as the sodium/glucose co-transporter 1 is being investigated but remains elusive. Currently, the most widely accepted model, the "standing gradient model," assumes that sodium is actively transported into the hypertonic lateral intercellular space (LIS) between cells, resulting in transcellular movement of water into the LIS and isotonic transfer of fluid into the capillary circulation. However, the apical and basolateral membranes prove to be water permeable, and the osmotic gradient in the LIS is small and essentially immeasurable. The observation that most water transfer occurs through the cell rather than across intercellular tight junctions has led to the "revised standing gradient model" and the emergence of several other theories.[49]

Sodium and Potassium Transport

Sodium is absorbed by four mechanisms. It diffuses passively, either transcellular or paracellular, following electrochemical gradients and Starling forces. There is an active countertransport with H^+, cotransport with organic solutes such as sugars and amino acids, and cotransport with Cl^-. The luminal sodium content in the duodenum is equilibrated to plasma through net water secretion or absorption. The sodium content in the enterocyte is kept low as the basolateral Na^+, K^+-activated adenosine triphosphatase (ATPase) continues to move Na^+ out and K^+ into the cell. Advancing aborally, Na^+ and Cl^- concentrations decrease in the jejunum and further in the ileum, reaching their respective minima in the colon where luminal

Na^+ concentrations are as low as 35 to 40 mEq/L. Chloride is conserved in the colon and is exchanged for HCO_3^- which stems from the hydration of CO_2 by carbonic anhydrase.[32] Potassium is absorbed passively throughout the small intestine and is secreted actively in the colon.

There is little regulation of water and electrolyte absorption in the intestine, which simply absorbs what is presented. However, adrenergic (α-receptor) or anticholinergic stimuli increase absorption, whereas cholinergic and anti-adrenergic stimuli decrease it. Serotonin, dopamine, endorphins, and enkephalins alter the net transport across the epithelium and enhance secretion over absorption. Exogenous opiates such as morphine or codeine enhance absorption in the small and large intestine and increase transition time.[32]

In contrast to the small intestine, the large intestine is able to increase sodium absorption by decreasing sodium concentration in fecal water to as little as 2 mEq/L in a response to plasma sodium depletion or mineralocorticoid secretion. Simultaneously, the potassium secretion is stimulated. Aldosterone improves the sodium permeability of the brush border membrane by activating more sodium channels and increasing the number of sodium pump molecules in the basolateral membrane of the enterocyte. Osmotic retention of fluid in the gut and the increase in fecal water content is achieved by polyvalent ions such as magnesium sulfate ($MgSO_4$), which are only incompletely absorbed.[32] This principle is used when the bowel is "prepared" for endoscopies or colorectal surgery. For the latter, it has been suggested that this practice be abandoned because there is no benefit; moreover, the disturbances of electrolyte and water homeostasis may be significant.[50]

Calcium, Magnesium, and Phosphorus

Calcium, magnesium, and phosphorus stem from dietary sources and are essential elements required for multiple functions and structural tasks. Serum levels are tightly regulated, and the intestine along with kidney and bone play a major role in the homeostasis of those elements. Parathyroid hormone and vitamin D are the major regulating signals among a complex network of membrane transporters, associated proteins, and soluble mediators.[51] The ratio of absorbed to ingested calcium varies with age, level of Ca^{2+} intake, physiologic state (i.e., pregnancy), and GI factors, such as transit time of chyme along the gut, proportion of soluble form of calcium, and the rate of transport across the intestinal epithelium.[51] Solid food containing calcium must be digested first to make soluble calcium available. Overall, approximately 25% of all ingested calcium is enterically absorbed in the nonpregnant state by passive paracellular and active, ion-channel dependent transcellular pathways. When luminal calcium concentration is high, most of it is passively absorbed through the tight-junction regulated paracellular pathway. The major ion-channel protein responsible for transcellular calcium absorption is TRPV6. Several models have been proposed to explain how calcium can diffuse into the cytoplasm of the enterocyte, traverse it, and exit at the basolateral membrane without upsetting the tightly regulated intracellular calcium concentration. The "facilitated diffusion model" assumes binding of free calcium to an intracellular buffering protein and basolateral exclusion via a P-type ATPase with high affinity to Ca^{2+}. The "ER tunneling model" and the "vesicular transport model" suggest transport through the endoplasmic reticulum and exocytosis of calcium through vesicles, respectively, or Na^+/Ca^{2+} exchangers and Ca^{2+} ATPases.[51]

Phosphorus plays an important role in bone structure and as inorganic phosphate and phosphate esters in cell physiology. Phosphorus is extracted efficiently from food in the intestine, which maintains phosphate levels within a narrow range. Absorption occurs mostly in the duodenum and in the jejunum by passive paracellular diffusion and by active transcellular transport, which can be up-regulated when phosphate intake is reduced.

Magnesium is absorbed mostly in the small intestine by passive, gradient-driven, paracellular diffusion that is regulated by luminal magnesium concentration in a curvilinear fashion, which is probably the result of tight junction plasticity. [51] Similar to calcium and phosphorus, magnesium is also absorbed apically by an active transcellular transport involving TRP family of ion channels. Vitamin D_3 increases the capacity of both pathways and hence represents the major regulatory signal in intestinal calcium absorption and overall calcium homeostasis.

Iron

Iron is absorbed mainly in the proximal small intestine; less prominent sites include the stomach, ileum, and colon. Iron must be reduced before being transported across apical surfaces by the intestinal iron transporter-1 and stored as ferritin in mature enterocytes when iron stores in the body are filled. If iron stores are low, iron is exported from enterocyte storage via ferroportin 1 to bind to transferrin in interstitial fluid and plasma. This is regulated by liver-derived hepcidin, which is up-regulated by hemochromatosis protein.

Water-Soluble Vitamins

Dietary vitamin B_1 (thiamine) is mainly phosphorylated and thus needs to be hydrolyzed at the brush border before absorption through a mechanism in the small intestine that is pH dependent and mediated by an electroneutral carrier.[52] Another source of thiamine is the bacterial flora in the large intestine that synthesizes free thiamine to be used by enterocytes for their own metabolism in addition to adding to the body's supply. Prolonged vomiting and alcoholism are common causes for vitamin B_1 deficiency.

Vitamin B_2 (riboflavin) from dietary and bacterial sources in the large intestine is absorbed similarly to vitamin B_1 utilizing a Na^+-independent, carrier-mediated mechanism, whereas vitamin B_3 is absorbed only from dietary sources. Vitamin B_5 (pantothenic acid) and vitamin B_6 (pyridoxine) are hydrolyzed before they are absorbed in the small intestine.

Conjugated vitamin B_9 (folate) polyglutamates carry multiple negative charges, represent a large molecule, and are hydrophobic—all features that hinder absorption. Hence, folate hydrolases at the brush border hydrolyze it to its monoglutamate before it can be absorbed. Again, large intestine bacterial flora supplies folate locally to the colonic mucosa and supports its structural integrity.

Deficiencies in bacterially derived folate are being linked to malignant diseases of the colonic mucosa.[52]

Vitamin B_{12} (cobalamin) absorption requires the acidic gastric environment to isolate it from food to make it available for intrinsic factor to bind. Intrinsic factor is a glycoprotein secreted by parietal cells in the stomach. Cellular and functional gastric integrity is therefore vital for the cobalamin–intrinsic factor complex formation. This complex is recognized by the cubam receptor in the small intestine, which binds the complex and internalizes it into the enterocyte. Lack of intrinsic factor (e.g., atrophic gastritis, *Helicobacter pylori* infection) or decreased acid secretion (e.g., long-term antacid use) can render the patient deficient in vitamin B_{12}. In those patients, the use of NO, a potent and irreversible methionine synthase inhibitor, should be limited because it can cause acute vitamin B_{12} deficiency neuropathy and hyperhomocysteinemia.

Vitamin C is derived solely from the diet, and there is no bacterial source in the large intestine. Both luminal uptake and exit across the basolateral membrane involve concentrative, carrier-mediated, Na^+-dependent mechanisms.[52]

GASTROINTESTINAL BLOOD FLOW

This section discusses issues concerning control of regional blood flow within the GI tract and regulation of blood volume within the splanchnic vasculature.

ANATOMY

Celiac, superior mesenteric, and inferior mesenteric arteries leave the aorta and deliver arterial blood to the organs of the GI tract (Fig. 21-7). The celiac artery supplies the stomach, the proximal part of the duodenum, part of the pancreas, and the liver through the hepatic artery. The superior mesenteric artery delivers arterial blood to the remaining parts of the pancreas and duodenum, the jejunum and ileum, and the colon. The inferior mesenteric artery supplies blood to the remaining part of the colon and rectum, except the very distal part of the rectum, which is supplied by rectal arteries branching off the internal iliac artery.

The GI tract is richly supplied by blood. Blood flow to the stomach is approximately 11 mL/min per 100 g of tissue; in the small intestine it is 30 to 70 mL/min per 100 g[1]; and in the colon it is 8 to 35 mL/min per 100 g. For comparison, in resting skeletal muscle it is 2 to 5 mL/min per 100 g, whereas in the brain it is approximately 55 mL/min per 100 g.

Basic oxygen consumption in the GI tract is relatively low, between 1.5 and 2 mL/min per 100 g.[53] In comparison, in the liver it is up to 6 mL/min per 100 g; in the brain, it is 3.5 mL/min per 100 g; and in the heart it depends on heart rate and physical activity, reaching 7 to 9 mL/min per 100 g of tissue.

GASTRIC BLOOD FLOW

The celiac artery branches into smaller arteries, then into arterioles in the muscular layer and submucosa.

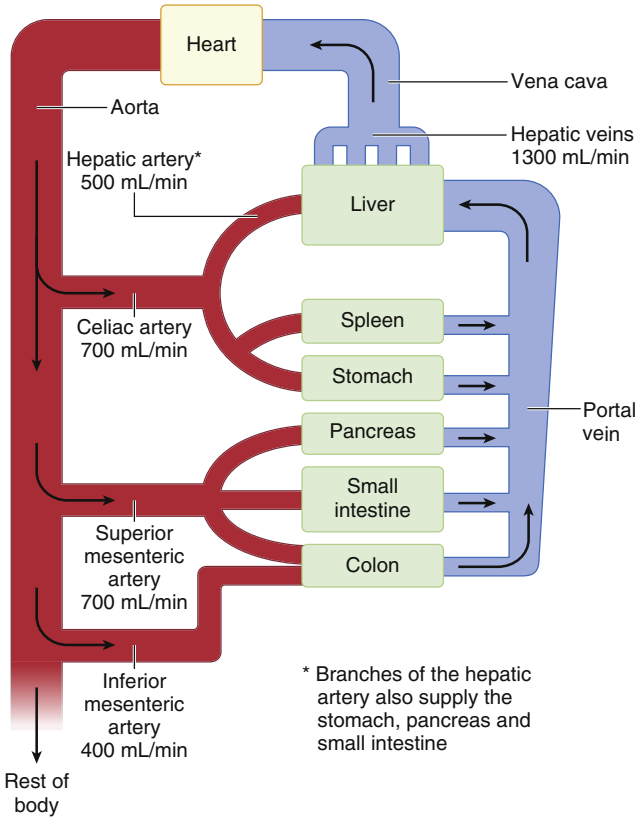


Figure 21-7. The schematic representation of the splanchnic circulation. Values of blood flow per gastrointestinal organs are identified. *(Redrawn with permission from Barrett KE:* Gastrointestinal physiology: Lange physiology series. *New York, 2005, McGraw-Hill.)*

Submucosal arterioles branch into capillaries at the base of the gastric glands and then travel to the luminal surface of the mucosa, forming a capillary network. The mucosal capillaries drain into venules that form venous plexuses in the submucosa. The muscular and mucosal blood flows are regulated independently according to tissue metabolism. Of the total blood flow through the stomach, 75% is distributed to the mucosa and 25% to the muscularis, although the distribution between muscular and mucosal layers is almost entirely dependent on their function at any particular moment.

INTESTINAL BLOOD FLOW

The three large arteries mentioned earlier (see Fig. 21-7) branch into smaller arteries, form arcades, and anastomose one with another, creating collateral flow. This is why an occlusion of one artery within the arcade does not usually lead to necrosis of tissue within the GI tract. These arcades give branches into the submucosal and mucosal layers. The blood flows to the different layers of the intestinal walls (mucosa, submucosa, and muscularis) through the arteriolar plexus within the submucosa. After flowing into arterioles and capillaries and exchanging metabolites through capillary walls, the blood flows through venules and larger veins. These veins enter the mesentery in parallel to the mesenteric arteries within the arcades, eventually forming three final preportal

veins: splenic, superior mesenteric, and inferior mesenteric. The splenic vein drains blood from the spleen, stomach, and pancreas; the superior mesenteric vein from small intestine and parts of the colon and pancreas; and the inferior mesenteric vein collects blood from the descending colon, sigmoid colon, and upper rectum. These three preportal veins combine to form the portal vein, from which blood flows through the liver and then enters the systemic circulation through hepatic veins and the inferior vena cava.

GASTROINTESTINAL BLOOD FLOW REGULATION

The main purpose of the GI blood flow is to deliver nutrients and hormones to the gut, to remove metabolic waste from the gut, and to maintain the mucosal barrier to prevent transepithelial migration of antigens, toxic chemicals, and pathogenic microbiota.[54] The blood flow within the GI tract varies over a wide range depending on need. GI organs periodically have high requirements for oxygen and therefore blood flow; for example, during food ingestion, the blood flow within the GI organs increases. On the other hand, the blood flow to the GI organs can decrease considerably to supply active muscles during physical exercise or to maintain viability of vitally important organs, such as the brain and heart, during blood loss. Such needs require a wide range of blood flow and sophisticated regulation. GI blood flow is regulated by extrinsic and intrinsic mechanisms that include the enteric nervous system.

Extrinsic control of the splanchnic circulation is achieved by activation of the sympathetic nervous system. The preganglionic sympathetic neurons are located mainly in the thoracolumbar area of the spinal cord at the T1-L2 level. The axons of the sympathetic preganglionic neuron synapse in celiac, superior mesenteric, or inferior mesenteric ganglia.[53] Blood vessels in GI organs are richly innervated by sympathetic and parasympathetic nerve fibers, which release neurotransmitters to affect vascular tone and blood flow. An increase in sympathetic discharge is usually associated with a constriction of the vessels and a decrease in blood flow. Although the parasympathetic nervous system is not directly involved in regulation of GI blood flow, vasodilating neurotransmitters can activate the appropriate receptors directly and indirectly through ACh. Compounds such as ACh, VIP, and the neuropeptide substance P are released from parasympathetic nerve fibers, and they can mediate vasodilation via NO. Parasympathetic fibers dilate vessels indirectly by stimulating the function of the GI organs. Many vasodilating and vasoconstricting substances affect GI blood flow. The main vasodilating factors include prostaglandins, adenosine, NO, bradykinin, VIP, and substance P. Vasoconstricting factors include mainly catecholamines that activate α-adrenergic receptors, the renin-angiotensin system, and vasopressin.

Intrinsic regulation of GI blood flow includes pressure-induced flow autoregulation, response to acute venous hypertension, reactive hyperemia, functional hyperemia, hypoxic vasodilation, and other internal factors. Overall, intrinsic regulation of blood flow is responsible for adjustment of blood flow to the demand at any time via myogenic, metabolic, or hormonal mechanisms.

Blood flow autoregulation is the ability of an organ to maintain relatively constant blood flow despite changes in blood pressure. Such regulation is strong in the heart and brain but much weaker in the GI organs. For example, a 50% decrease in blood pressure results in minimal changes in cerebral blood flow, whereas blood flow through the intestines is decreased by approximately 25%.

An increase in venous pressure is often used in experimental models to determine whether the regulation of flow is myogenic or metabolic in nature. If an increase in venous pressure is associated with an increase in arterial tone, vascular resistance, precapillary sphincter tone, and decrease in capillary density, the regulation is assumed to be myogenic. Otherwise, the control is assumed to be metabolic.[55]

Reactive hyperemia is defined as an increase in blood flow above baseline after temporary occlusion of an artery; it probably serves the need to repay oxygen debt after temporary oxygen deprivation and results, at least partially, from the accumulation of vasodilating metabolites (e.g., adenosine) produced by the preceding ischemia.

Stimulation of sympathetic nerves or an intra-arterial norepinephrine infusion leads to severe vasoconstriction and a decrease in intestinal blood flow. However, regardless of whether the infusion or stimulation continues, the blood flow partially returns to baseline level in a few minutes. This so-called autoregulatory escape is observed only in arterial but not in venous smooth muscle; it is not affected by β-adrenergic receptor antagonists or by muscarinergic antagonists. The mechanism most likely to be responsible for this phenomenon is the accumulation of different vasodilating factors during hypoperfusion. Adenosine and VIP have been implicated more often than other vasodilating compounds.

The metabolic mechanism of blood flow regulation assumes that an increase in oxygen demand or decrease in oxygen delivery, or both, decreases tissue oxygen tension and releases vasodilating metabolites. A decrease in oxygen content in arterial blood is associated with an increase in GI blood flow and capillary recruitment, even in a denervated intestinal preparation. A decrease in hematocrit is also associated with an increase in tissue blood flow. Oxygen deprivation leads to intracellular ATP breakdown and adenosine release, causing vasodilation. Adenosine has been shown to be a powerful vasodilator in the small intestine.[53]

An increase in function is associated with an increase in oxygen demand and a subsequent increase in blood flow. For example, an increase in acid secretion by the stomach induced by pentagastrin is associated with an increase in portal blood flow and in oxygen extraction. Similar responses have also been observed in other organs of the GI tract.[53] Functional (postprandial) hyperemia following food ingestion can increase blood flow within the small intestine by as much as 230% and can last 4 to 7 hours depending on the nature and quantity of the meal.[53] Redistribution of blood flow within the intestinal wall toward mucosa and submucosa has been observed. Many factors regulating the blood flow to the intestinal

mucosa are metabolic and include oxygen, pH, carbon dioxide, and adenosine. Other mediators include vasopressin, catecholamines, NO, VIP, substance P, histamine, prostaglandins, and bradykinin.[53]

An increase in intestinal motility (and associated increase in oxygen demand) drastically reduces the higher vascular resistance produced by elevated venous pressure**.** This change implies that metabolic factors play a more important role than myogenic mechanisms do in the regulation of GI flow.[55]

The enteric nervous system (as a part of intrinsic regulation) also plays a role in regulation of GI blood flow, particularly in the distribution of blood within the intestinal wall. The mucosa of the GI tract receives about 80% of total resting blood flow of the gut.[54] Such high blood flow is needed to meet the requirements of the gut for motility, secretion, and absorption. The submucosal plexus is the main control for blood flow within the gut, and vasoconstriction results primarily from activation of sympathetic efferents. Epinephrine increases blood flow through the GI tract mainly by activation of β_2-adrenergic receptors.

Vasodilation within the mucosa is controlled by three different types of neurons:

1. Extrinsic primary afferent neurons
2. Efferent neurons of the parasympathetic nervous system
3. Enteric neurons within the submucosal plexus[56]

The main afferent neurotransmitters are CGRP, substance P, and NO. Their release in the afferent pathways is associated with vasodilation of arterioles within the submucosa. These vasodilating signals are conducted through the sympathetic nervous system within the ganglia, where ACh is the main neurotransmitter.

Parasympathetic vasodilator pathways (within the vagus) include cholinergic mechanisms that probably play relatively minor roles: the gastric vasodilation caused by stimulation of the vagus nerve remains unchanged after atropine administration.[56] Parasympathetically mediated vasodilation is achieved through the myenteric plexus (where ACh is also the main neurotransmitter) and then, after synapsing there, the signals travel to the arterioles, where the main neurotransmitters are VIP and ACh.[56] ACh induces vasodilation by activating muscarinic receptors; their stimulation leads to release of NO within the arteriolar endothelium.[56]

Finally, arteries and arterioles in the submucosa and mucosa dilate in response to signals from enteric neurons that originate in the submucosal but not in the myenteric plexus; neither extrinsic denervation nor removal of the myenteric plexus alters these vasodilating effects, which are mediated by serotonin (5-hydroxytryptamine, 5-HT). In the submucosal plexus, afferent input is transmitted to the efferent reflex limb of the arch, which is composed of cholinergic vasodilator neurons; such reflex-mediated dilation of submucosal arterioles is blocked by atropine.

There are many interactions between enteric and sympathetic vasomotor neurons.[6,56] During exercise, portal blood flow may decrease by 80%, reaching only 20% of baseline. Such a decrease can be counteracted by ingestion of a meal. Superior mesenteric blood flow is reduced 43% by exercise but increased 60% by ingestion of a meal. When exercise was combined with a meal, the blood flow was actually increased by 40%, demonstrating that metabolic and humoral demands often override other influences.[57]

GASTROINTESTINAL MICROCIRCULATION

The mesenteric microcirculation is composed of isolated small microcirculatory units. Such units branch from the marginal arteries that are themselves branches of mesentery arcades. The blood flows within microvessels from arterioles to capillaries and then drains to low-flow venules, which then form high-flow venules of larger diameters. Some high-flow venules have direct anastomoses to other high-flow or low-flow venules.[58] The density of functioning capillaries depends on two factors working in concert: an increase in blood flow and the accumulation of the end products of cellular metabolism.

SPLANCHNIC BLOOD VOLUME

Splanchnic vasculature can be thought of as a devoted employee: it serves the boss (the body) enthusiastically and completely, sometimes sacrificing its own needs. Changes in the blood flow in one or another system generally serve the needs of a particular organ. However, alterations in the blood volume within the splanchnic veins serve overall hemodynamics rather than the GI organs themselves. Regulation of blood flow through the GI organs and the liver is described separately herein and in Chapters 22 and 23, respectively. However, regulation of blood volume within the GI organs and the liver has a common purpose: to maintain stable systemic hemodynamics. Therefore, the regulation of splanchnic blood volume as a whole is fully described in this chapter.

Approximately 70% of total blood volume is in the veins.[59] The splanchnic system receives 25% of cardiac output and contains approximately one third of the total blood volume.[59,60] Approximately 1 L of blood can be recruited from the splanchnic vasculature into the systemic circulation when needed (Table 21-2). Because veins are 30-fold more compliant than arteries, drastic changes in the blood volume within the splanchnic veins are associated with relatively small changes in the intravenous

TABLE 21-2 DISTRIBUTION OF BLOOD VOLUME AMONG ORGANS AND AMOUNT OF BLOOD THAT CAN BE RECRUITED FROM THEM

	Total (mL)	Mobilized (mL)
Liver	600	300
Spleen	700	600
Intestine	350	150
Total	**1650**	**1050**
Lungs	500	50
Skin	100	50
Muscle	850	250
Total	**3100**	**1400**

Adapted from Greenway CV, Lister GE: Capacitance effects and blood reservoir function in the splanchnic vascular bed during non-hypotensive haemorrhage and blood volume expansion in anaesthetized cats, J Physiol *237:279-294, 1974.*

pressure. Moreover, splanchnic veins can accumulate or lose a large amount of blood without significant change in systemic hemodynamic variables, such as blood pressure and cardiac output.

Definitions of at least two physiologic variables are needed for understanding the function of the compliant (splanchnic) veins in blood volume regulation. *Unstressed volume* is the volume of blood when transmural pressure equals zero. *Stressed volume* is the volume within the venous system under transmural pressures above zero. These two volumes cannot be measured directly; instead they are determined by extrapolation of the pressure-volume line to zero pressure[60] (Fig. 21-8). The difference between total volume and unstressed volume equals stressed volume. At rest, approximately one third of the total blood volume is stressed, and approximately 70% is unstressed, located mainly within the splanchnic venous system. The analogy with a tub can be helpful in understanding the relationship between stressed and unstressed volumes (Fig. 21-9).

The relationship between stressed and unstressed volumes explains why patients with up to 10% to 12% of blood volume loss maintain systemic hemodynamics without significant changes in heart rate, blood pressure, or central venous pressure (CVP). However, further blood loss, even if relatively small, leads to severe deterioration of hemodynamics. As the first 10% of blood volume is lost, compensation occurs mainly by moving unstressed volume into stressed volume. If the mechanism of transfer of blood from unstressed to stressed volume is already exhausted (no unstressed volume is left), further blood loss leads to decompensation.

Let us imagine that the heart is stopped, leading to cessation of blood flow. Pressure would be the same in all parts of the circulation, and is referred to as *mean circulatory filling pressure* (MCFP).[61] When the heart starts pumping again, the pressure in the aorta, arteries, capillaries, and finally in the small veins distal to capillaries increases, pushing blood back to the heart. Because arterial resistance is high (compared with other parts of the vasculature), the pressure in these small veins becomes the driving force for venous return and is called *pivotal pressure*; it turns out that this pressure is equal to the MCFP.[59,60]

It is the unstressed volume from which blood is mobilized into circulation (into stressed volume) when it is

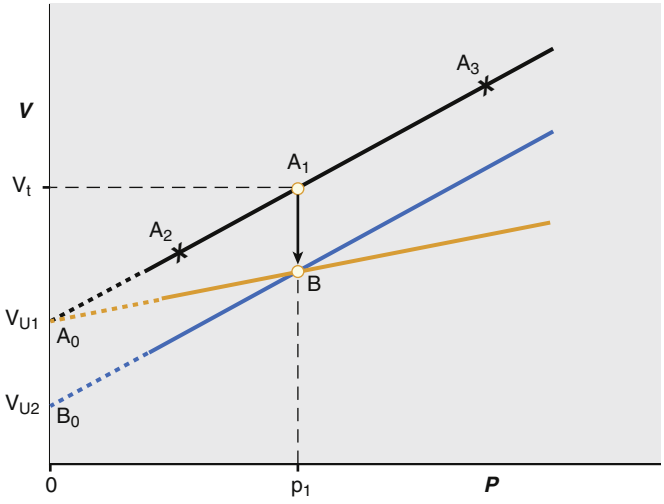


Figure 21-8. Venous capacitance and compliance, stressed and unstressed volumes. Point A1 represents volume of blood in veins at intramural pressure p_1. Points A2 and A3 represent change in volume induced by change in pressure within the veins. The *thick black line* represents baseline compliance. Point A_0 is obtained by extrapolation of the thick black line until it crosses the *y* axis; this point (A_0) represents volume of blood at transmural pressure zero, which is unstressed volume (Vu_1). The difference between total volume (Vt) and Vu_1 is stressed volume (Vs). When a certain amount of blood is mobilized from the veins, point A_1 moves to point B; the veins contain less blood at the same intramural pressure p_1. Removal of the volume of blood between points A_1 and B may be associated with no change in the slope of the pressure-volume relation (*blue line*); this means that venous compliance did not change, but capacity did. Point B_0 (*blue line extrapolated to the y-axis*) represents decreased unstressed volume (from Vu_1 to Vu_2). However, the pressure-volume relation within the veins might look like the *brown line*. The same amount of blood is mobilized (from point A1 to B), but Vu did not change. The *brown line* crossed the *y* axis at the same point A_0; the mobilized blood was recruited by a decrease in compliance rather than from a decrease in Vu. *(Redrawn with permission from Gelman S: Venous function and central venous pressure. A physiologic story.* Anesthesiology *108:735, 2008.)*

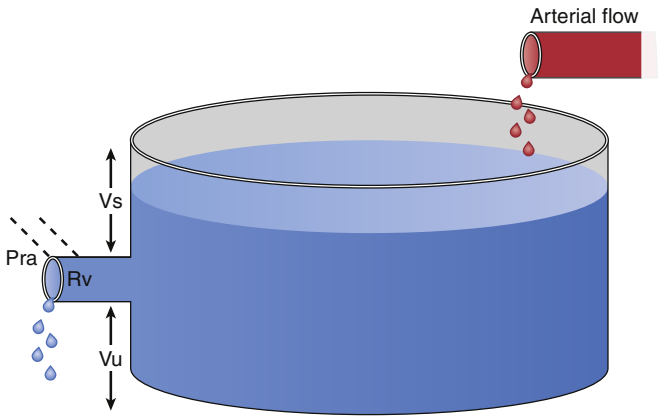


Figure 21-9. Stressed and unstressed volumes—tub analogy. Water in a tub represents total blood volume. A hole in the wall of the tub between the surface of the water and the bottom of the tub divides total volume into stressed (Vs) and unstressed (Vu) volumes, above and below the hole, respectively. The water leaves the tub through the hole at a certain rate that depends on the diameter of the hole (which would reflect venous resistance [VenR]), and on the height of the water above the hole, representing Vs. The larger the Vs, the higher the flow through the hole. The water between the hole and the bottom of the tub does not affect the flow of water through the hole; this is the Vu, which is a sequestered volume that does not directly participate in the rate of water flow (venous return). With the same amount of water in the tub (total blood volume in the venous system) the relationship between Vs and Vu can be changed by moving the hole up or down. Moving the hole down represents venoconstriction and increases Vs (and venous return). The distal end of the tube, attached to the hole in the tub wall, represents central venous pressure (CVP). The higher the distal end, the higher the CVP and the lower the pressure gradient for venous return, and vice versa. The inflow tap represents the arterial flow. The hydraulic disconnect between the tap and the tub represents functional disconnection between the two (arterial flow and the venous system) due to high arterial resistance. *(Redrawn with permission from Gelman S: Venous function and central venous pressure. A physiologic story,* Anesthesiology *108:735, 2008.)*

needed. Under physiologic conditions, the stressed volume is the main factor determining the MCFP (pivotal venous pressure) and (indirectly) venous return. Stressed volume, in turn, is determined by total blood volume and the arterial and venous tone within the splanchnic vasculature. The two-compartment model of the venous system helps to explain the relationships among stressed and unstressed volumes, MCFP, and venous return[60] (Fig. 21-10).

During sympathetic stimulation, the smooth muscles of the vasculature contract to produce vasoconstriction, leading to a decrease in flow through the arteries. When arteries are constricted, the blood flow into the veins through capillaries is decreased, lowering intramural (intraluminal) pressure within these veins. This decrease in intramural pressure leads to a passive recoil of the venous walls around the decreased volume and pressure, producing a short-lasting increase in flow out of the veins and an increase in venous return. The volume shifted out of the splanchnic vasculature stays in the main basic circuit (Fig. 21-11, see Fig. 21-10) until splanchnic arterial tone returns to baseline. In many instances active venoconstriction also occurs, squeezing blood out of the veins (reinforcing passive recoil) and increasing venous return and cardiac output.

In a canine model, an induced hemorrhage to lower blood pressure below 50 mm Hg was compensated for by three mechanisms: (1) transcapillary fluid shift from different tissues (one third of this volume), (2) shift of blood from passive elastic recoil of the veins, mainly splanchnic veins (an additional third of the lost volume), and (3) actively constricted capacitance vessels mediated by an increase in sympathetic discharge.[59] This means that approximately two thirds of the compensation for severe blood loss comes from the veins, mainly the splanchnic veins, regardless of whether it comes passively from venous recoil or actively from sympathetically mediated venoconstriction. The passive change in blood volume within the splanchnic veins is more typical of the intestines, whereas active venous constriction is more prominent within the liver.[62]

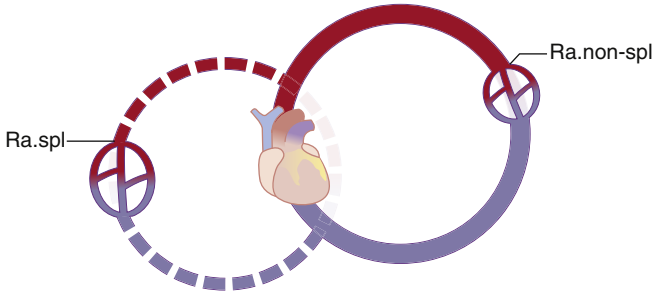


Figure 21-10. Two-compartment model of venous system. (*Two circuits* represent two compartments; the *solid red and blue lines* represent arterial and noncompliant venous compartments (the main, basic circuit). *Dashed red and blue lines* represent arterial and compliant (splanchnic) venous compartments. The compartment with compliant veins is outside the main circuit. Therefore, changes in arterial or venous resistance in compliant compartment do not directly affect arterial or venous resistance in the main circuit with noncompliant veins. *Thickness of the lines* reflects the amount of flow within the vessels under normal conditions. The *size of the junctions* between arteries and veins reflects the blood volumes contained in the two circuits. *(Adapted with permission from Gelman S: Venous function and central venous pressure. A physiologic story,* Anesthesiology *108:735, 2008.)*

ROLE OF α-ADRENERGIC AND β-ADRENERGIC RECEPTORS IN BLOOD VOLUME REGULATION

The splanchnic veins have a high population of α_1- and α_2-adrenergic receptors and are much more densely innervated than the corresponding arteries; this explains their more vigorous response to sympathetic stimulation compared to arteries.[60,63] Because of its high compliance and rich population of α-adrenergic receptors, the splanchnic venous system is the most effective blood reservoir in the body, capable of mobilizing (and accommodating) large amounts of blood. Low-frequency stimulation of sympathetic nerves or an infusion of α-adrenergic agonists at small doses leads to constriction of veins (particularly splanchnic veins) and shift of blood volume from the splanchnic vasculature to the systemic circulation. This "auto-transfusion" helps to maintain hemodynamics during situations such as blood loss, increase in intra-abdominal or intrathoracic pressure, general anesthesia, and positive-pressure breathing. Small doses of α-adrenergic agonist probably do not constrict arteries or jeopardize tissue perfusion; in many situations, this treatment can be preferable to infusion of extra blood volume.[64]

ROLE OF HEPATIC VEINS IN SPLANCHNIC BLOOD VOLUME REGULATION

An increase in resistance in the distal part of the splanchnic venous system might lead to sequestration of blood within the liver and more proximal part of the splanchnic venous vasculature. Therefore, a decrease in resistance to venous outflow within the liver or hepatic veins facilitates blood volume shift from the splanchnic vasculature into the inferior caval veins and right atrium, thereby increasing venous return. Activation of α-adrenergic receptors increases this resistance,[65] whereas activation of β_2-adrenergic receptors decreases it, facilitating a volume

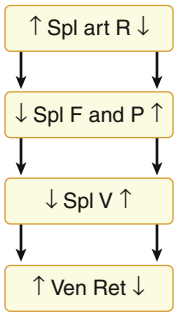


Figure 21-11. Role of splanchnic arteries in splanchnic blood volume (Spl V) regulation. An increase in resistance in the splanchnic arteries leads to a decrease in splanchnic venous flow and pressure within the splanchnic veins that leads to a decrease in splanchnic volume and subsequently to an increase in venous return. Decrease in resistance within splanchnic arteries leads to opposite chain of events. *Spl art R*, splanchnic arterial resistance; *Spl F+P*, splanchnic flow and pressure within the splanchnic veins.

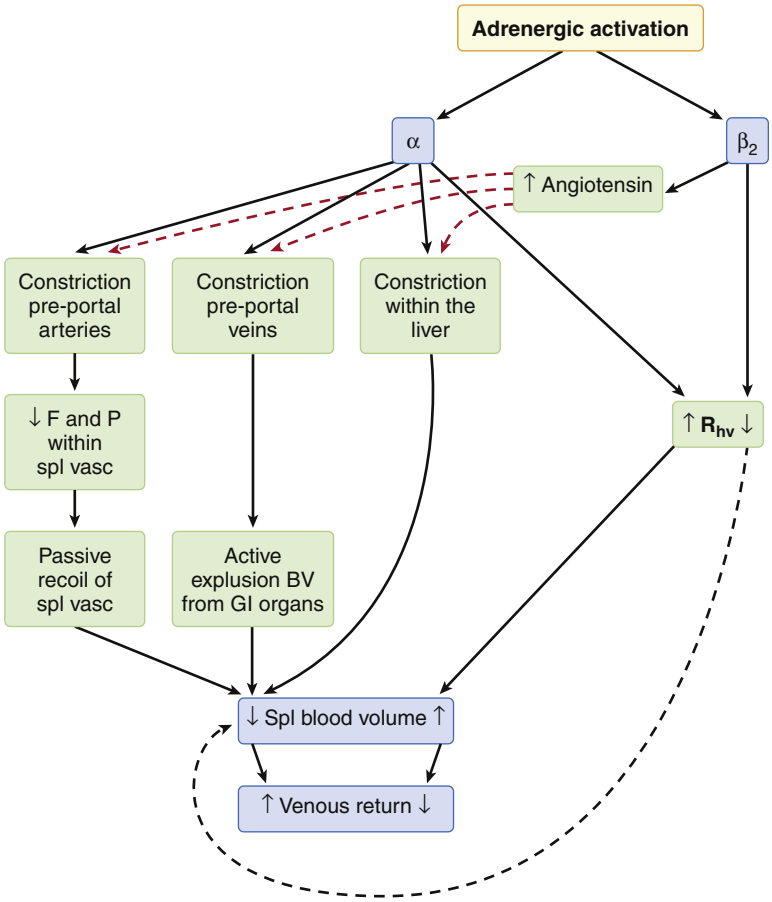


Figure 21-12. Effect of adrenergic activation on splanchnic blood volume regulation. ↑, increase; ↓, decrease; α, α-1 (including peripheral α-2) adrenergic receptors. β-2, β-2 adrenergic receptors; *BV*, blood volume; *GI*, gastrointestinal; *Rhv*, resistance in hepatic veins; *Spl vasc*, splnchnic vasculature; *Ven Ret*, venous return.

shift. A decrease in venous capacity (a shift of blood volume out of the splanchnic veins) induced by relatively small doses of α-adrenergic receptor agonists has a more dramatic effect than an increase in resistance within the hepatic veins (Fig. 21-12). However, large doses of α-adrenergic agonists can lead to sequestration of blood within the liver and decrease in venous return.[66] The combination of α- and β_2-adrenergic agonists can be useful in the treatment of hypotension in normovolemic patients, because it would facilitate the shift of blood volume from the splanchnic veins into the systemic circulation more effectively than an α-adrenergic agonist alone. Such a combination would decrease venous capacity, decrease resistance in the distal splanchnic venous system, and more effectively recruit unstressed volume into stressed volume. In cases of hypovolemia, the ability to recruit unstressed volume is diminished (or even absent, because unstressed volume has been completely mobilized), and an increase in blood pressure can be achieved only by administration of large doses of α-adrenergic agonists, which would lead to constriction of arteries, decreasing tissue blood flow, and tissue ischemia; therefore, the hypovolemia must be resolved as soon as possible.

ROLE OF REFLEXES IN SPLANCHNIC BLOOD VOLUME REGULATION

Increasing carotid sinus pressure from 50 to 200 mm Hg was associated with a volume increase within the splanchnic vasculature of approximately 50%.[60] Thus, when carotid sinuses and other arterial baroreceptors "sense" a decrease in blood pressure, sympathetic tone immediately increases, leading to an increase in arterial resistance throughout the body, including the splanchnic arteries. The latter is reinforced by concomitant constriction of splanchnic veins; both result in passive and active expulsion of blood from the splanchnic venous system. This expulsion leads to a decrease in unstressed volume and an increase in stressed volume, MCFP (or pivotal venous pressure), and both venous return and cardiac output; blood pressure returns toward normal values. Opposite changes occur when blood pressure increases. This reflex serves important functions in blood pressure regulation. General anesthesia impairs this reflex and significantly modifies such responses, decreasing the ability of the body to compensate for changes in blood pressure.

ROLE OF THE SPLEEN IN SPLANCHNIC BLOOD VOLUME REGULATION

Atrial natriuretic peptide (ANP) is released by atrial myocytes when the atrial wall is stretched. ANP increases the glomerular filtration rate by dilating the preglomerular and constricting the postglomerular vessels. Such an action is associated with a decrease in plasma volume and an increase in hematocrit values. Because this effect is almost completely abolished by splenectomy, we know that the major effect of ANP is achieved through

the spleen.[67] During ANP administration splenic venous blood flow is lower than arterial flow and venous hematocrit values are higher than arterial ones, indicating a loss of fluid from the splenic vascular bed. Thus, ANP has direct effects on the splenic microvasculature and intrasplenic hemodynamics to promote filtration of fluid out of the organ. NO affects splenic hemodynamics in concert with ANP; namely, NO decreases the arteriolar resistance within the intrasplenic microvasculature, increasing intracapillary pressure and fluid filtration. In conclusion, different mediators regulate the blood flow and filtration of fluid within the spleen, often leading to an increase in the filtration of fluid and an increase in hematocrit values within the splenic venous blood.

PATHOPHYSIOLOGIC VIGNETTES OF SPLANCHNIC CIRCULATION

Splanchnic Blood Volume During Aortic Cross-Clamping

Clamping of the aorta at the diaphragmatic level considerably decreases blood flow to the splanchnic organs. This decrease leads to a passive recoil of the splanchnic veins and a shift of blood volume from the splanchnic system into systemic circulation. Associated surgical stress and an increase in sympathetic discharge add an active component of venoconstriction. This is why in experimental conditions the clamping of the aorta at the diaphragmatic level is most often associated with an increase in venous return and cardiac output.[60,68] In the clinical setting, such an increase is rare because, unlike the experimental situation, other events that develop during surgical intervention affect volume shifts in different directions. A few examples are different depths of anesthesia, blood loss, and concomitant use of vasoactive drugs, including epidural anesthesia.

On the other hand, clamping of the aorta distal to celiac and mesenteric arteries is usually not associated with an increase in venous return and cardiac output, first because the leg veins are not compliant and therefore contain a relatively small amount of blood. Second, this volume usually shifts into the more compliant splanchnic veins (increasing the unstressed volume) rather than to the heart, which would increase venous return. This is why, even without serious blood loss, clamping of the aorta distal to the arteries supplying blood to splanchnic organs often decreases cardiac output (Fig. 21-13).

Effects of Increased Intra-abdominal Pressure on Gastrointestinal Blood Flow and Splanchnic Blood Volume

Spontaneous inspirations are associated with shifts of the diaphragm downwards, compression of the splanchnic vasculature, and shift of blood volume from the splanchnic system into the systemic circulation.[69] At the same time, venous flow from the lower extremities through the inferior caval vein decreases. During expiration the diaphragm shifts upwards, decreasing the flow from the splanchnic veins and increasing flow from the legs. More drastic increases in intra-abdominal pressure occur during other physiologic actions, such as defecation, coughing, and physical exercise. These changes occur acutely and are short in duration. Acute nonphysiologic increases occur during hemorrhage, perforation of a hollow organ within the abdominal cavity, pneumoperitoneum, and other abnormal states. Some conditions such as pregnancy and accumulation of ascites are associated with a relatively slow increase in intra-abdominal pressure. A drastic increase in intra-abdominal pressure might lead to abdominal compartment syndrome, which presents as a life-threatening hemodynamic instability and usually occurs when intra-abdominal pressure exceeds 25 mm Hg. Pneumoperitoneum induced for laparoscopic surgery decreases blood flow through the intra-abdominal organs.[70] Such increased intra-abdominal pressure compresses the GI organs and squeezes blood from the GI vasculature into the systemic circulation, increasing the stressed volume until the intra-abdominal pressure is normalized.

Any flow through the hepatic veins is maintained by the stressed blood volume within the splanchnic vasculature. In other words, the intravascular pressure within the splanchnic system must be higher than the intra-abdominal pressure, which is the perivascular pressure. When intra-abdominal pressure starts to increase, intravascular pressure increases with it, and stressed volume flows out of the splanchnic system through the hepatic veins, raising the intra-abdominal pressure by 5 mL/cm of fluid. A simultaneous increase in pressure within the inferior caval vein at the level of hepatic veins momentarily stops blood flow through the femoral veins. However, that high pressure also increases flow from the hepatic vein entry and delays the compression of the inferior caval vein by high intra-abdominal pressure. This increased pressure gradient from the inferior caval vein pressure to the right atrial pressure increases flow through the inferior caval vein and venous return, helping to counteract the effects of the compression of the inferior caval vein and possible decrease in preload.[69]

The final effect of these alterations depends on (1) the degree of the increase in intra-abdominal pressure (the larger the increase, the higher the probability of a decrease in venous return); (2) the baseline blood volume; and (3) the ability to develop sympathetically mediated vascular responses. If there is not enough blood volume within the splanchnic veins, or if intra-abdominal pressure is too high to be compensated for by the existing stressed volume, flow through the hepatic vein and then venous return will begin to decrease (Fig. 21-14). Thus, an increase in stressed volume is needed to overcome the increase in impedance to the venous return.[69] Such responses require activation of the sympathetic nervous system. An increase in concentrations of other vasoconstricting compounds such as vasopressin and endothelin, as well as activation of the renin-angiotensin system and release of aldosterone, adrenocorticotropic hormone (ACTH), and cortisol have been also observed.[70] These responses are reflected in increases in CVP, pulmonary wedge pressure, mean pulmonary arterial pressure, and systemic and pulmonary vascular resistances. Mean arterial pressure is usually slightly increased or decreased, cardiac output might be decreased or maintained.[71] A study of patients with American Society of

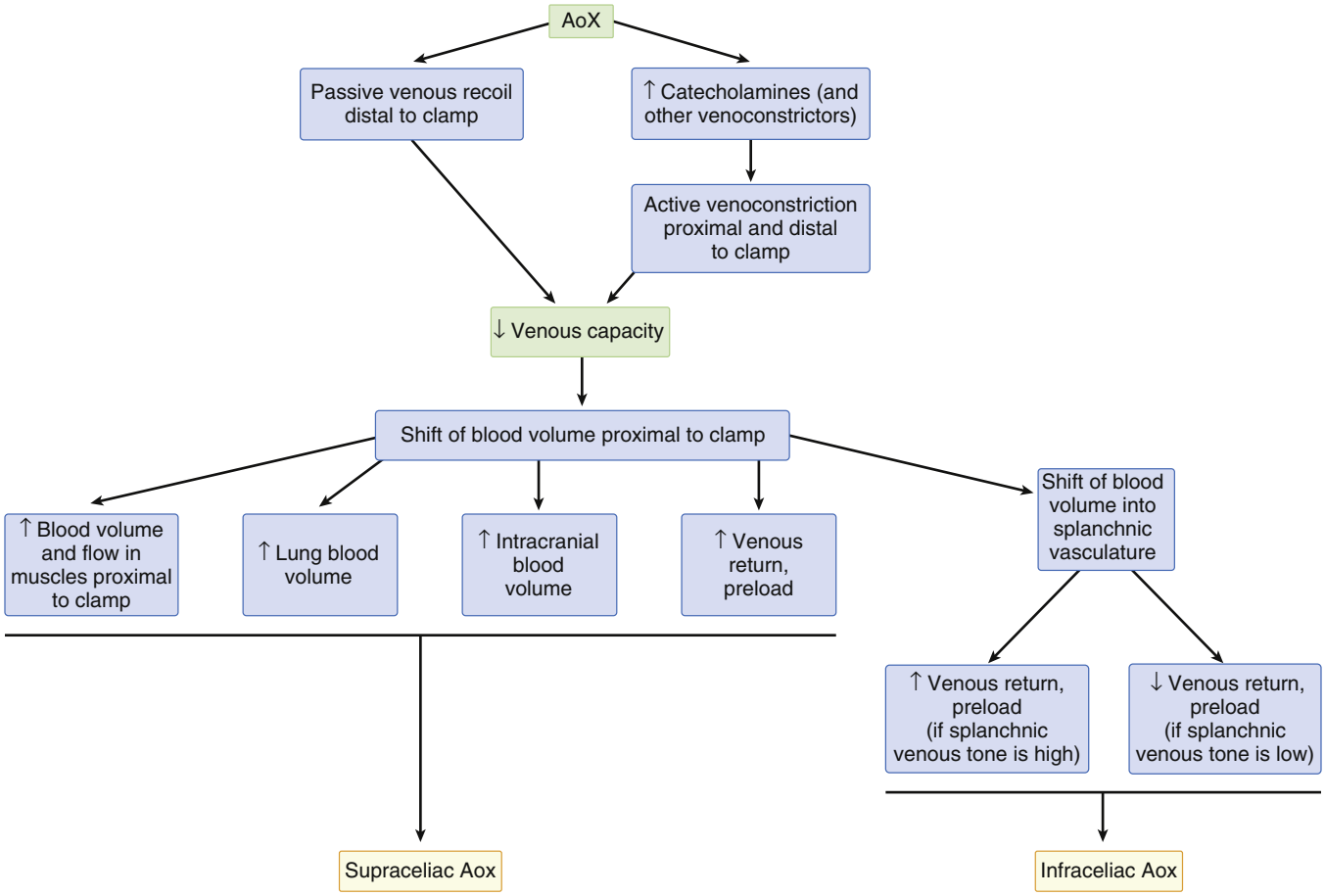


Figure 21-13. Blood volume redistribution during aortic cross-clamping. This scheme depicts the reason for the decrease in venous capacity, which results in blood volume redistribution from the vasculature distal to aortic occlusion to the vasculature proximal to aortic occlusion. If the aorta is occluded above the splanchnic system, the blood volume travels to the heart, increasing preload and blood volume in all organs and tissues proximal to the clamp. However, if the aorta is occluded below the splanchnic system, blood volume can shift into the splanchnic system or into the vasculature of other tissues proximal to the clamp. The distribution of this blood volume between the splanchnic and nonsplanchnic vasculature determines changes in preload. ↑, increase; ↓, decrease; *AoX*, aortic cross-clamping. *(Redrawn with permission from Gelman S: The pathophysiology of aortic cross-clamping and unclamping,* Anesthesiology *82:1026, 1995.)*

Anesthesiologists (ASA) physical status I and II showed that an increase in intra-abdominal pressure to 15 mm Hg was associated with increases in left and right ventricular end-diastolic area by 65% and 45%, respectively. The ejection fraction of both ventricles decreased by approximately 18%.[72] The reverse Trendelenburg position might improve the hemodynamics.[72]

Release of pneumoperitoneum and simultaneous drastic decrease in intra-abdominal pressure lead to opposite shifts in blood volume and possible hemodynamic instability (vasodilation, shift of blood volume into splanchnic veins, decrease in stressed volume and venous return, hypotension) and ischemia-reperfusion injury. The latter might lead to an increase in splanchnic free radical production, an increase in capillary permeability, and bacterial translocation from the intestine into the bloodstream.[70]

The hemodynamic changes observed during pneumoperitoneum with carbon dioxide are the result of the complex interaction of anesthesia, surgical insult, the patient's position (Trendelenburg or reverse Trendelenburg), carbon dioxide, and an increase (followed by a reduction at the end of surgery) in intra-abdominal pressure as well as oxidative stress, which plays an important role in the overall response to this procedure.[73] It is not surprising that some authors are replacing the term *minimally invasive surgery* with the more precise term *minimal-access surgery*. Fortunately, an increase in intra-abdominal pressure that does not cause it to reach 12 to15 mm Hg is usually well tolerated by most patients.

Splanchnic Blood Volume in Congestive Heart Failure

The majority of patients with congestive heart failure do not demonstrate an increase in body weight, but they do show volume overload and an associated decrease in cardiac output.[74] Some authors speculate that because the density of adrenergic terminals in veins is more than fivefold higher than in arteries,[63] and because vasomotor response induced by sympathetic stimulation is greater in veins than in arteries, the pathogenesis of congestive heart failure involves increases in sympathetic discharge, constriction of splanchnic vasculature, and translocation of blood volume into the systemic circulation.[74] Those researchers believe that this is the main mechanism

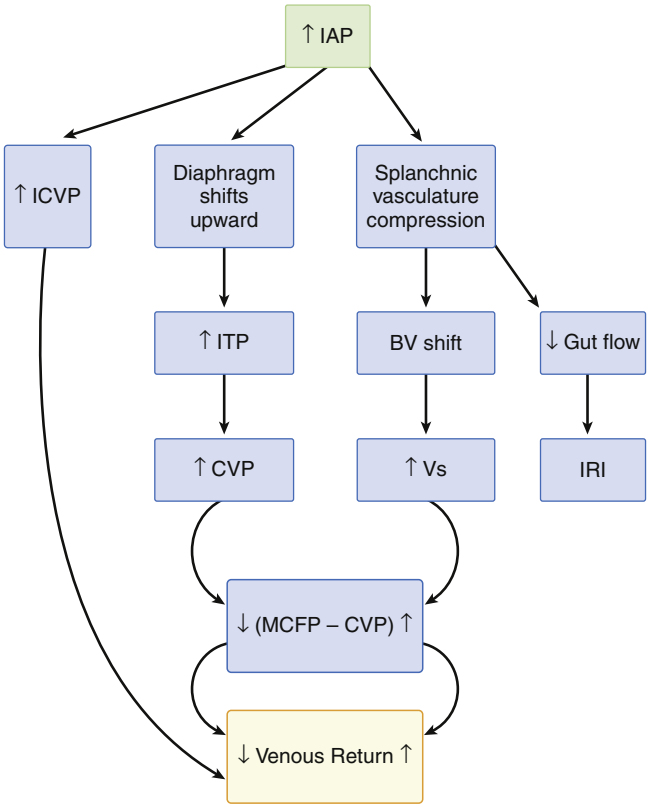


Figure 21-14. Hemodynamic responses to an increase in intra-abdominal pressure (IAP). ↑, Increase; ↓, decrease; *BV*, blood volume; *CVP*, central venous pressure; *ICVP*, inferior caval venous pressure; *IRI*, ischemia-reperfusion injury; *ITP*, intrathoracic pressure; *MCFP*, mean circulatory filling pressure; *Ven Ret*, venous return; *Vs*, stress volume.

responsible for congestive heart failure. It seems likely though that when the heart (myocardium) is able to handle an increased preload, such a translocation of blood volume does not lead to cardiac failure. However, when the myocardium is not able to handle this additional volume, congestive heart failure can ensue. Moreover, such an increase in preload (as a result of sympathetic activation) can be a compensatory mechanism necessary to maintain acceptable cardiac output. Different types of vasodilators can be used to treat cardiac failure.[75] Vasodilators (which decrease afterload and preload) should be administered carefully, because in cardiac failure an increased preload might be needed to maintain adequate cardiac output. In other words, a particular increase in stressed volume might be needed to maintain the heart at an appropriate position on the Starling curve (to the right of normal).

Role of Gastrointestinal Blood Flow in Gastroduodenal Mucosal Ulceration

Many compounds secreted within the stomach are ulcerogenic, the most important being hydrochloric acid and pepsin. Acute ulceration results from inflammatory response to physical or thermal trauma, shock, sepsis, and some others including emotional stress; these are called *stress ulcers*. These ulcers usually occur in the proximal, acid-secreting portion of the stomach.[76] The process starts with disturbances in microcirculation and focal ischemia. Focal ischemia can be observed as pallor and hyperemia, followed by petechiae and shallow ulcerations that progress to mucosal stress ulcers. Stress ulcers are superficial, limited only to the mucosa, and usually heal without serious consequences.

The etiology and course of drug-related ulcers are similar to those of stress ulcers. Aspirin and other NSAIDs can initiate that process. These drugs produce an imbalance between vasodilating and vasoconstricting prostaglandins, disturbing microcirculation within the mucosa that can be followed by ulceration.

The main pathogenetic factor in stress ulcers and in drug-related ulcers is a temporary decrease in gastric mucosal blood flow that can result in complications such as bleeding, endotoxemia, and sepsis. The role of blood flow and overall pathogenesis of stress ulcers has been well described.[76]

Splanchnic Circulation in Sepsis

Decrease in blood flow to the gut in general and to the intestinal mucosa in particular is the key event in the pathogenesis of sepsis and septic shock. Examination of the intravital microcirculation during sepsis reveals vascular wall edema, local hemorrhages, arteriole-venule shunting, reverse flow in capillaries and venules, blood flow redistribution within microunits, leukocyte-endothelial interaction, and transmigration through the capillary walls.[58] Reduction in blood velocity within the venules is closely correlated with the number of leukocyte-epithelium adhesions.[58] This disturbance in microcirculation is called *leukocyte adhesion stenosis*, because it is characterized by slowed capillary blood flow and a pattern of stop-and-go and no-flow venules; next, it progresses to leukocyte-endothelium adhesions within the lumen of the arterioles.[58] Thus, the microcirculation is severely disturbed and heterogeneous. Some micro-areas are hyperperfused and others are hypoperfused; arteriovenous shunting of blood is increased. This often is associated with a relatively normal or even increased total blood flow, but severely decreased nutritive blood flow to the intestinal walls, particularly to the mucosa. During sepsis, metabolic demand for oxygen within the intestines is increased, and nutritive blood flow is decreased despite profound vasodilation.

Sepsis is associated with severe inflammatory response leading to an increase in permeability and impaired immunologic barrier function within the intestines. Ischemia, increased permeability, and impaired intestinal barrier play an important role in subsequent amplification of distant organ dysfunction.[77] The use of dopamine and some other catecholamines might increase blood pressure and cardiac output, but also can increase arteriovenous shunting without any improvement in nutritive flow and microcirculation of GI organs. Such therapy often is ineffective and can actually exacerbate sepsis.[78] Despite an increase in oxygen delivery, the intramucosal pH, which is a marker of tissue oxygenation, decreases. The term *oxygen delivery* might not precisely reflect oxygen content in the arterial blood and flow (cardiac output). *Oxygen output* might be a better term, because in reality this oxygen is not delivered to cells, but bypasses them via arteriovenous shunting. The lack of oxygen uptake might

result not only from arteriovenous shunting, but in part from the inability of cells to consume oxygen because of impaired intracellular metabolism. In that case, "delivered" oxygen is not absorbed.

Effects of Spinal and Epidural Anesthesia on Gastrointestinal Blood Flow and Volume

The degree of arterial hypotension induced by spinal or epidural anesthesia is directly related to the extent of the blockade, the dose of local anesthetic used, and baseline hemodynamics.[79] Lumbar epidural anesthesia leads to arterial and venous dilation at the segments affected by the anesthetic. The constriction of the proximal part of the splanchnic vasculature shifts blood volume from the splanchnic system into the systemic circulation and usually results in preservation of stressed volume and blood pressure. Thoracic epidural anesthesia is associated with pronounced mesenteric vasodilation and arterial hypotension, whereas intestinal blood flow and oxygen consumption are maintained**.** A study using labeled red cells demonstrated that epidural anesthesia with sensory block at T4-T5 increased blood volume in both the intrathoracic and splanchnic vasculature.[80] The addition of a vasoconstrictor decreased volume within the splanchnic region, but increased volume within the thorax. The authors estimated that the use of a vasoconstrictor during thoracic epidural anesthesia led to a shift of approximately 1 L of blood from the splanchnic area into the thoracic and systemic circulation.[80]

Infusion of fluid or the use of adrenergic agonists apparently increases stressed volume. Infusion of fluid increases total (stressed and unstressed) blood volume, whereas adrenergic agonists move existing blood volume from unstressed to stressed. In many situations, the use of α-adrenergic agonists might be more beneficial than infusion of fluid.[64] Because veins are much more sensitive to adrenergic stimulation than arteries are, small doses of α-adrenergic agonists in normovolemic patients would constrict veins (increasing stressed volume) without affecting arteries or jeopardizing tissue perfusion.

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Chapter 22

Hepatic Physiology and Pathophysiology

PHILLIP S. MUSHLIN • SIMON GELMAN

Key Points

- Roughly 30% of cardiac output flows through the liver by a dual blood supply. The portal vein delivers 75% of total hepatic blood flow; the hepatic artery provides the rest. Each vessel delivers half of the total hepatic oxygen supply.
- Hepatic sinusoids are the capillaries of the liver. Postsinusoidal vessels are a major source of total hepatic vascular resistance. The liver has a highly compliant, distensible vasculature that is central to its role as an important, rapidly accessible reservoir of blood volume. Without this reservoir function, mild losses of intravascular volume can result in severe hypotension.
- The liver is integral to the monocyte-macrophage system. Kupffer cells reside in hepatic sinusoids; they filter the venous effluent of the gastrointestinal tract; and they avidly remove bacteria and other harmful substances, preventing their entry into the systemic circulation.
- The acinar concept describes the functional microvascular unit of the liver. Each acinus has three circulatory zones. Blood perfusing zone 1 is rich in O_2 and nutrients; zone 3 hepatocytes are perfused with effluent blood from zones 1 and 2, which is relatively O_2 poor.
- The hepatic arterial buffer response (HABR) induces a compensatory increase of hepatic arterial flow, thereby preserving hepatic O_2 delivery despite decreases of total hepatic blood flow. Pathologic disruptions of HABR increase the susceptibility of the liver to hypoxic injury.
- The liver metabolizes cholesterol to bile acids, which is the only means of eliminating cholesterol from the body. Hepatocytes secrete bile acids, which flow through a series of hepatobiliary ducts that drain into the duodenum via the common bile duct.
- Bile salts are amphipathic molecules with detergent-like properties; they emulsify lipophilic substances, promoting their enteric absorption. Enterocytes of the terminal ileum efficiently take up bile acids and return them to hepatocytes via the portal blood. Hepatocytes can then take up and secrete a single bile acid molecule many times; this gut–liver connection is called the enterohepatic circulation.
- The liver is the epicenter of intermediary metabolism and energy homeostasis. Depletion of liver glycogen during prolonged fasting, for example, promotes hepatic gluconeogenesis, enabling the liver to nourish glucose-dependent tissues. Starvation accelerates the oxidation of fatty acids and formation of ketoacids, which are released from the liver and used as energy substrates by most of the extrahepatic tissues.
- Hepatocytes oxidize myriad substances by cytochrome P450–mediated reactions; they also attach endogenous polar substrates to hydrophobic molecules. Such products, being more hydrophilic than their unconjugated precursors, are more readily excreted in the urine or feces.
- The liver has a vital role in nitrogen metabolism. Ammonia is highly toxic to the central nervous system and can be eliminated only by the liver. Hepatocytes are uniquely equipped with the urea cycle enzymes required to metabolize ammonia to urea, which is readily excreted and much less toxic than ammonia.

Key Points—cont'd

- The liver produces almost all of the plasma proteins, except γ-globulins. Albumin is the most abundant plasma protein; it is the main determinant of plasma oncotic pressure and an essential plasma transporter of exogenous substances and endogenous compounds, such as unconjugated bilirubin and free fatty acids.
- Hepatocytes synthesize most of the molecular participants in coagulation pathways; they also modify vitamin K–dependent proteins—such as factors II, VII, IX, and X; protein C; and protein S—enabling their participation in the coagulation cascade.
- Standard liver chemistry tests—which are useful for detecting and monitoring hepatic and biliary disorders—lack the specificity and sensitivity needed to identify any specific disease. For diagnostic purposes, results of such tests must be interpreted in clinical context and often with supplemental radiologic and endoscopic information.
- Cirrhosis-induced portal hypertension produces a hyperdynamic circulation: systemic blood pressure is slightly below normal, cardiac output increases, and total peripheral resistance decreases. Portosystemic shunting occurs, circumvents the hepatic filtering mechanism, and thereby allows drugs, nitrogenous waste, and toxins to enter the central circulation.
- The onset of cirrhosis-induced portal hypertension is a pivotal event; it coincides with loss of the huge physiologic reserve of the healthy liver. Additional liver injury leads to life-threatening pathophysiologic derangements, including variceal hemorrhage, hepatic encephalopathy, and the hepatorenal and hepatopulmonary syndromes. The only definitive treatment for end-stage hepatic disease is liver transplantation.

OVERVIEW

The liver is the most versatile and largest internal organ in the human body, comprising 2% of the total mass of healthy adults and 5% of neonates. The liver is an essential part of the gastrointestinal tract that filters, excretes, and modifies an enormity of gut-derived substances. It is also a key component of the monocyte-macrophage system; Kupffer cells within liver sinusoids avidly remove bacteria and other harmful substances from portal blood, preventing their entry into the systemic circulation. The liver is the most vascular organ in the body; it has a unique dual blood supply and receives nearly 30% of the total cardiac output. Because of its highly compliant, distensible vasculature, the liver serves as a rapidly exchangeable blood reservoir that promotes homeostasis of the circulating blood volume. Moreover, the liver is the epicenter of intermediary metabolism and energy homeostasis; it is uniquely equipped to meet the nutritional needs of tissues throughout the body during times of both feast and famine. The liver plays an indispensable role in the excretion of endogenous wastes—most notably, ammonia and bilirubin—and eliminates a wide range of xenophobic substances, including most of the drugs and toxins that enter the body. For these reasons, a fundamental understanding of hepatic physiology is a prerequisite for health care providers. Liver disease, particularly when severe, has pervasive clinical ramifications and imposes complex therapeutic challenges.

HEPATIC ANATOMY

TRADITIONAL ANATOMY

The liver looks like a reddish-brown boomerang and occupies the entire right subcostal space, most of the epigastrium, and part of the left subcostal space. Being highly malleable, the liver allows its less pliable neighbors to determine its topography. For example, on its posterior surface, the liver shows imprints of the inferior vena cava and diaphragmatic attachments, such as the coronary and triangular ligaments and the interstitial matrix at the bare area of the liver. The superior hepatic surface conforms to the underside of the diaphragm.

Topologic landmarks, which are at the core of traditional anatomy, provide the basis for separating the liver into four lobes, known as the left, right, caudate, and quadrate lobes. The liver, when viewed from its anterior, superior surface, reveals only the right and left lobes separated by the falciform ligament. The posterior-inferior hepatic surface provides the best vantage for viewing the relative positions of the four lobes. On this surface, the left and right lobes are separated by the left sagittal fossa (ligamenta venosum and teres hepatis). The quadrate and caudate lobes are not well delineated, but can be envisaged as follows: First, the midline boundary—the porta hepatis (transverse fissure) forms the posterior border of the quadrate lobe and the anterior border of caudate lobe. Second, the right-side boundary—for the quadrate lobe

it is the gallbladder fossa; for the caudate lobe it is the inferior vena cava. Third, the left-side boundary—for the quadrate lobe it is the ligamentum teres (umbilical vein fossa); for the caudate lobe it is the ligamentum venosum fissure (ductus venosus fossa).[1]

Knowledge of surface anatomy is indispensable for those who perform procedures involving the liver. Recent and marked advances in liver surgery—particularly with hepatic transplantation—have prompted the development of new classification systems of hepatic anatomy. This chapter provides a brief overview of the concepts of segmental anatomy, which focus on the spatial relationships among blood vessels and bile ducts within the liver. More specifically, physiologic anatomy seeks to identify singular portions of the liver (segments) that can be resected without compromising the viability of neighboring hepatic segments.[2,3]

PHYSIOLOGIC ANATOMY

Physiologic anatomy—also referred to as functional or segmental anatomy—separates the liver into independent, self-sufficient segments. Each segment is equipped with its own afferent blood supply and conduits to drain blood and bile from its parenchyma (Fig. 22-1).[4] At present, no system of physiologic anatomy is universally accepted, largely because of the considerable variability that exists in the interindividual anatomy of the portal vein, hepatic artery, and bile ducts. The Couinaud classification, which is in widespread clinical use, is depicted in Figure 22-1 and shows the general principles of segmental anatomy. The primary focus of the Couinaud system is on third-generation branches of the portal vein. This classification, similar to most others in common use, partitions the liver into eight physiologic segments (see Fig. 22-1).[2,4]

Advanced imaging techniques (e.g., contrast-enhanced helical computed tomography [CT]) are commonly used to determine the real anatomy of each patient's liver (Fig. 22-2).[5] These scans provide accurate correlative information about the topology and unique physiologic anatomy of the patient's liver.[4] Accordingly, liver operations (e.g., resection of tumors, repair of traumatic injuries), planned and guided by the principles of physiologic anatomy, result in lower rates of perioperative morbidity and mortality.

HEPATIC ARCHITECTURE

Portals for Hepatic Blood and Bile Flow

The hilum of the liver (porta hepatis) is where the afferent blood vessels enter and bile ducts exit the liver. The two main afferent blood vessels divide into first-order branches—the left and right portal veins and the left and right hepatic arteries. These vascular branches ramify and traverse the hepatic stroma in tandem. Their final branches—which are located within portal tracts—drain their blood into the liver sinusoids (hepatic capillaries). After perfusing the liver parenchyma, this blood drains into central hepatic veins (also called terminal hepatic venules). These tiny veins coalesce successively, giving rise to larger venous vessels that ultimately unite to form the right main, middle, and left main hepatic veins that connect directly to the inferior vena cava.

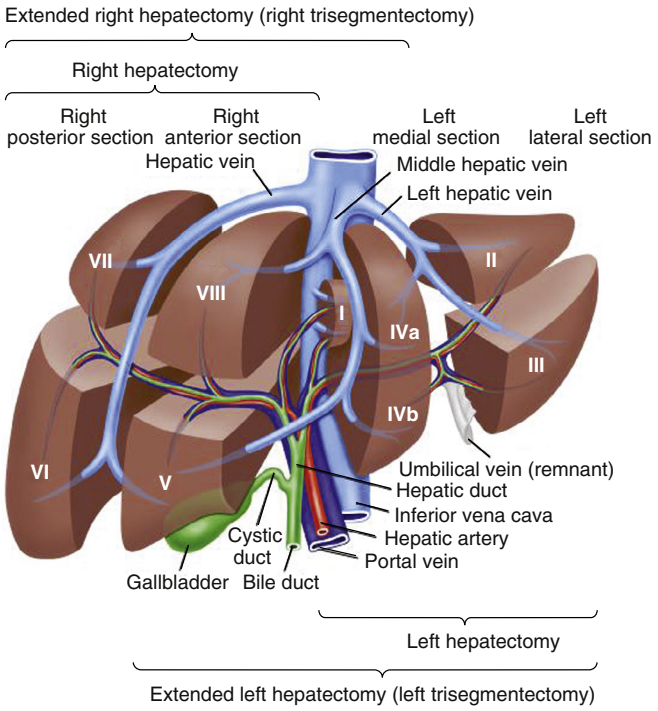


Figure 22-1. Schematic depiction of Couinaud segmental liver anatomy and the normal portal venous structures. *Bracketed text* shows hepatic segments resected during partial hepatectomies. *(Modified from Venook AP, Curley SA: Management of potentially resectable colorectal cancer liver metastases. Available at: http://www.uptodate.com/contents/management-of-potentially-resectable-colorectal-cancer-liver-metastases).*

Liver Lobule

The lobule is the basic anatomic unit of the liver (Fig. 22-3). An idealized classic liver lobule is a hexagonal prism that has six vertically aligned portal canals (see Fig. 22-3) at its apices and a terminal hepatic venule at its center. The portal canals contain a connective tissue matrix, nerve fibers, lymphatic vessels, and a portal triad, which consists of a bile ductule and the final branches of the portal vein and hepatic artery. Liver lobules are tiny; each has a circumference of 3 mm and is several millimeters in length. The human liver contains 50,000 to 100,000 lobules.

Liver Acinus: The Microvascular Unit of the Liver

The liver acinus is considered the functional microvascular unit of the liver. The acinus, as defined by Rappaport in the 1950s, is the parenchyma around terminal afferent portal and arterial vessels that supply blood to this group of hepatocytes. Figure 22-4 shows the three heterogeneous circulatory zones: zone 1 is periportal, zone 2 is the midzone, and zone 3 is pericentral. Blood supplied to zone 1, which is near the origin of the sinusoid, is rich in oxygen and nutrients. In contrast, zone 3, at the periphery of the acinus, receives blood that is O_2 poor because this blood has already perfused hepatocytes of zones 1 and 2 before it reaches zone 3.

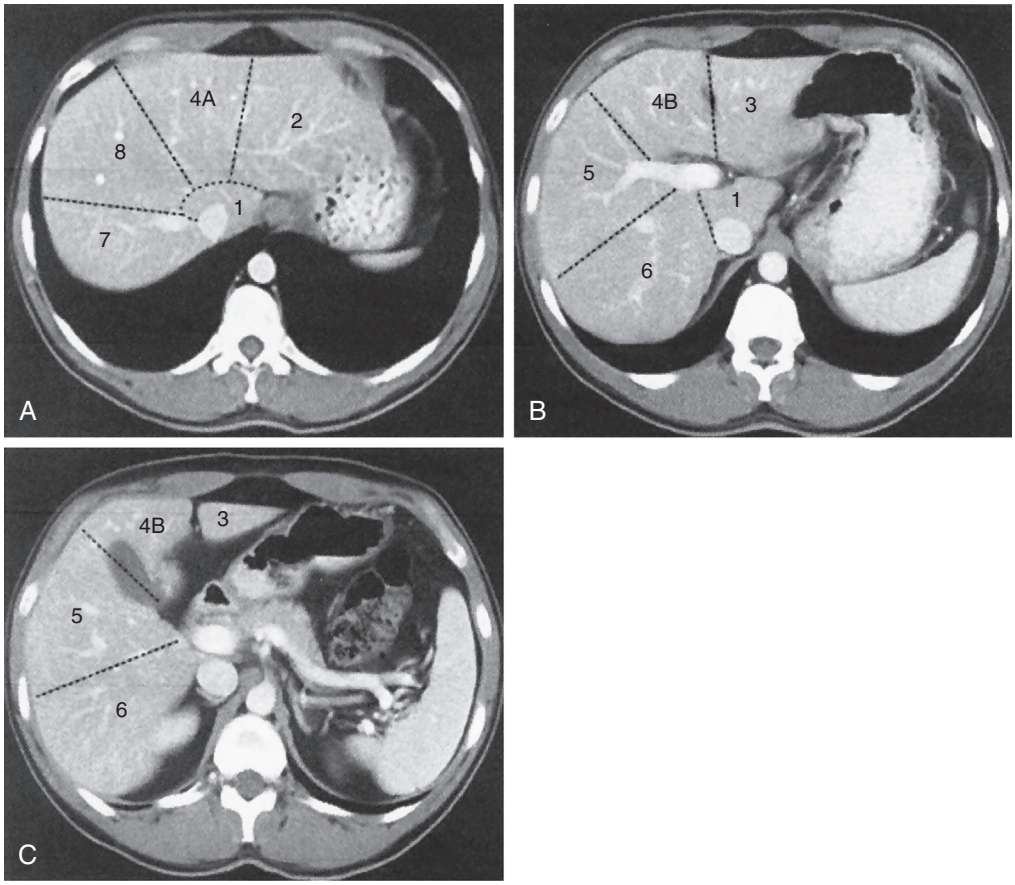


Figure 22-2. Segmental anatomy of the liver is demonstrated at three levels on contrast-enhanced CT images. **A,** At the level of the hepatic veins, the caudate lobe (segment 1) is seen posteriorly, embracing the vena cava. Segment 2 is separated from segment 4A by the left hepatic vein. Segment 4A is separated from segment 8 by the middle hepatic vein and segment 8 is separated from segment 7 by the right hepatic vein. **B,** At the level of the portal vein bifurcation, segment 3 is visible as it hangs inferiorly in its anatomic position and is separated from segment 4B by the umbilical fissure. Note that segment 2 is not visible at this level. Terminal branches of the middle hepatic vein separate segment 4B from segment 5 and terminal branches of the right hepatic vein separate segment 5 from segment 6. Note that Sements 4A, 8, and 7 are not visible at this level. Segment 1 is seen posterior to the portal vein and embracing the vena cava. **C,** Below the portal bifurcation, one can see the inferior tips of segments 3 and 4B. The terminal branches of the middle hepatic vein and the gallbladder mark the separation of segment 4B from segment 5. Segments 5 and 6 are separated by the distal branches of the right hepatic vein. Note how the right liver hangs well inferior to the left liver. *(From Townsend CM Jr, Beauchamp D, Evers BM, et al:* Sabiston textbook of surgery, *ed 19. Philadelphia, 2012, Saunders, Chap 54, Fig 54-6.)*

The microvascular architecture of the acinus allows increases in the efficiency of substrate usage and excretion of waste products.[6,7] Urea cycle enzymes are localized in zones 1 and 2. Hepatocytes within these zones convert amino acids to ketoacids and ammonia; the urea cycle (high capacity, low affinity) captures the ammonia and incorporates it into urea. Any ammonia that eludes the urea cycle is likely to encounter glutamine synthetase, which is expressed only in zone 3. This enzyme facilitates the capture of ammonia within the glutamine substrate. If glutamine substrate were present in zones 1 or 2, it would compete with urea cycle enzymes for ammonia and thereby decrease the liver's capacity to eliminate ammonia. By having glutamine synthetase localized in zone 3, pericentral hepatocytes more efficiently scavenge the ammonia that would otherwise reach the central circulation.

Periportal hepatocytes have the highest density of mitochondria and are the major site of oxidative metabolism and glycogen synthesis. In contrast, pericentral hepatocytes—which have an abundance of smooth endoplasmic reticulum, reduced nicotinamide adenine dinucleotide phosphate (NADPH), and cytochrome P450 (CYP) proteins—are the major site of anaerobic metabolism and xenobiotic biotransformation. Not surprisingly, pericentral hepatocytes bear the brunt of injuries induced by reactive xenobiotic metabolites or hypoxic episodes. The clinical message is that ischemic injury or necrosis of the centrilobular region decreases the liver's capacity to excrete many drugs and other xenobiotics.[4]

A Conceptual Alternative to the Acinar Concept

An alternative to the acinar concept, which is based on the angioarchitecture of the liver,[8] has recently been gaining popularity.[9] This concept divides the portal and hepatic venous systems into a conducting portion—which delivers and drains blood from the parenchyma—and a parenchymal portion, which is the basis for the primary lobule. Recent studies of hepatic enzymes and

pathologic processes suggest the presence of a continuous periportal network around portal tracts and terminal afferent vessels and a distinct concentric perivenous area around the central vein; such data support the idea that the liver architecture more closely resembles the classic lobule more than it does the acinus.[9]

Types of Liver Cells

Sinusoidal Endothelial Cells. Sinusoidal endothelial cells are different from the endothelium in the rest of the body. The large (~100 to 200 nm in diameter) pores between the cells are called fenestrae. The fenestrae permit passage of relatively large particles out of the blood; these include albumin with bound ligands, such as lipids and lipoproteins. But the fenestrae do not let red and white blood cells and platelets penetrate the sinusoidal endothelium. Another unusual feature of sinusoidal endothelium is that these cells lack basement membrane. This feature also increases the endothelium permeability to solute from the bloodstream. Thus, sinusoidal endothelium does not have a serious barrier to efflux of albumin and other molecules of similar size.

Kupffer Cells. The structure and function of Kupffer cells are similar to those of macrophages. Kupffer cells line the sinusoidal endothelium on the bloodstream side, have very high phagocytic properties, and represent the first line of host defense.[10]

Hepatic Epithelial Cells. The term *hepatocyte* is commonly used to denote the liver parenchymal cells. They are highly polarized epithelial cells and serve as the metabolic factories of the liver.[11] They have heterogeneous plasma membranes with three distinct specialized domains. For example, plasma membrane domains that face the hepatic sinusoids (called basolateral or sinusoidal membranes) are in direct contact with the perisinusoidal space of Disse; in contrast, apical domains of hepatocellular membranes that make up the lumina of the tiny channels (bile canaliculi) convey to bile ductules and ducts.

Lobular or acinar zonation is an important concept that explains morphologic and metabolic differences among hepatocytes based on their relative proximities to portal regions versus central veins. Hepatocytes close to portal regions are called zone 1 hepatocytes. They receive blood that is relatively high in O_2; the main function of these cells is detoxification and secretion. In conditions of compromised liver function, cells in zone 2 and 3 can be recruited; they represent the "anatomic reserve." Different zones determine the susceptibility of hepatocytes to injury. Hepatocytes in zone 3 are more sensitive to hypoxia; on the other hand, ischemia-reperfusion injury is more dramatic in zone 1. The histologic analysis of liver samples may help in diagnosis of the source of hepatic injury.

Hepatocytes can regenerate. After surgical removal of part of the liver, the remaining hepatocytes proliferate by undergoing mitosis. In animal models, up to 70% of total liver mass can be regenerated.[11]

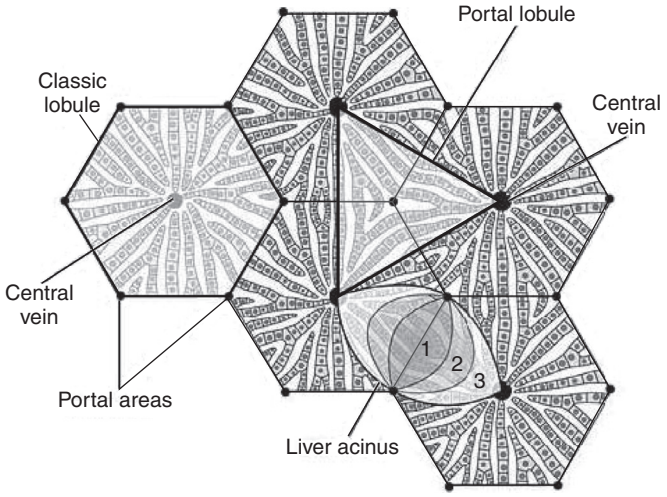


Figure 22-3. Schematic classifications of liver units: liver lobule, portal lobule, and liver acinus. Lobular units have well demarcated central structures (central vein or portal canal), whereas the liver acinus (zones *1, 2, 3*; see Fig. 22-4) contains a central axis derived from two adjacent classic lobules. *(From Henrickson R, Kaye GI, Mazurkiewicz J: Liver and gallbladder. In Henrickson R, Kaye GI, Mazurkiewicz, editors:* NMS Histology, *ed 3. Philadelphia, 1997, Lippincott Williams & Wilkins.)*

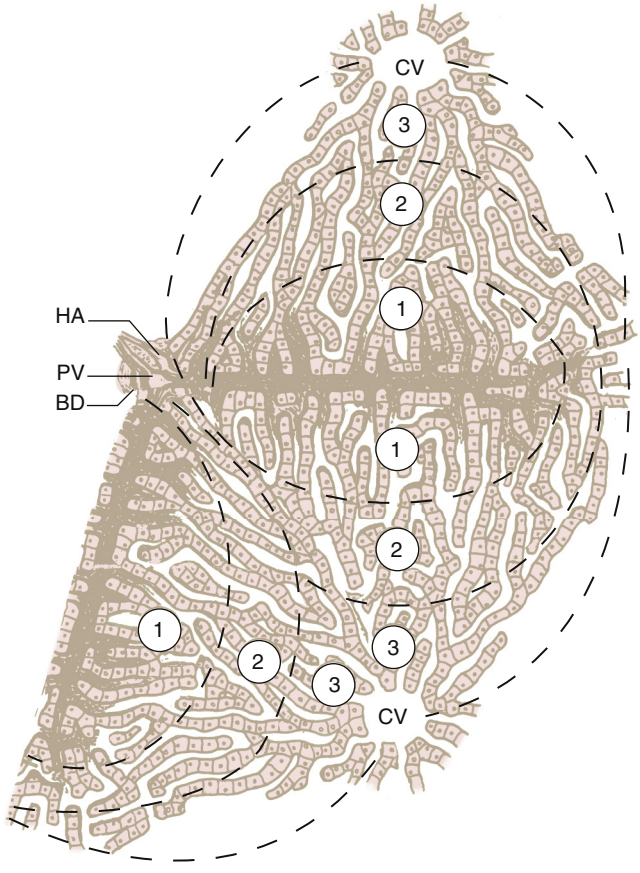


Figure 22-4. Blood supply of a liver acinus. Oxygen tensions and nutrient levels within sinusoids continuously decrease as blood flows from zone *1* through zone *3*. The lower part of this figure shows zones *1, 2,* and *3* of a neighboring acinus. *BD,* Bile ductule; *CV,* central vein; *HA,* hepatic artery; *PV,* portal vein. *(From Jones AL: Anatomy of the normal liver. In Zakim D, Boyer T, editors:* Hepatology: a textbook of liver disease, *ed 3. Philadelphia, 1996, Saunders, p 3.)*

FUNCTIONS OF THE LIVER

RESERVOIR FOR BLOOD VOLUME AND BLOOD FILTER

Vasculature of the Liver

The liver is the most vascular organ in the body; it receives nearly one third of the total cardiac output (1 mL of blood/1 g of liver) through a unique dual blood supply. Approximately 75% of the total hepatic blood flow arrives by the portal vein, and the remaining 25% is from the hepatic artery. Each of the two vessels brings half of the total O_2 content supplied to the liver. The hepatic artery has its origin at the celiac trunk of the abdominal aorta (Fig. 22-5).[1,12]

The portal vein—formed by the union of superior mesenteric and splenic veins—conveys the effluent venous blood from splanchnic organs, including the stomach, intestines, pancreas, and spleen. In other words, the portal veins transmit to the liver the entire venous drainage of the preportal splanchnic beds.[4,13]

Hepatic Blood Flow

Regulation of Hepatic Blood Flow. Intrinsic and extrinsic mechanisms play important roles in the regulation of hepatic blood flow. Intrinsic mechanisms—such as the hepatic arterial buffer response (HABR), metabolic control, and pressure-flow autoregulation—work independently of neurohumoral factors.

Intrinsic Regulation

Hepatic Arterial Buffer Response. The HABR is the most important intrinsic mechanism.[14] With an intact HABR, changes in portal venous flow cause reciprocal changes in hepatic arterial flow. That is, when portal venous flow decreases, the HABR compensates by increasing hepatic arterial flow and vice versa. The HABR mechanism involves the synthesis and washout of adenosine (i.e., a vasodilator) from periportal regions.[14,15] When portal venous flow decreases, adenosine accumulates in the periportal regions, which lowers arteriolar resistance and thereby increases hepatic arterial flow. Conversely, when portal venous flow increases, adenosine is washed out of the periportal regions, which increases arteriolar resistance and decreases hepatic arterial flow. At a maximum, the HABR can double hepatic arterial flow. Therefore, it cannot fully restore hepatic blood flow when portal venous flow falls by more than 50%. Yet, because hepatic arterial blood carries more O_2 than does portal venous blood, the HABR more effectively preserves hepatic O_2 supply than does hepatic blood flow. Various disorders (e.g., endotoxemia, splanchnic hypoperfusion) may decrease or even abolish the HABR and render the liver more vulnerable to hypoxic injury.[16-18]

Metabolic Control. Many constituents of blood affect hepatic arterial and portal venous blood flow. Decreases in O_2 tension or the pH of portal venous blood typically lead to increases in hepatic arterial flow. Postprandial hyperosmolarity increases hepatic arterial and portal venous flow. The underlying metabolic and respiratory status (e.g., hypercapnia, alkalosis, arterial hypoxemia) also modulate the distribution of blood flow within the liver.

Pressure-Flow Autoregulation. Pressure-flow autoregulation enables tissue-specific regulators to govern organ blood flow despite fluctuations in systemic arterial pressure.

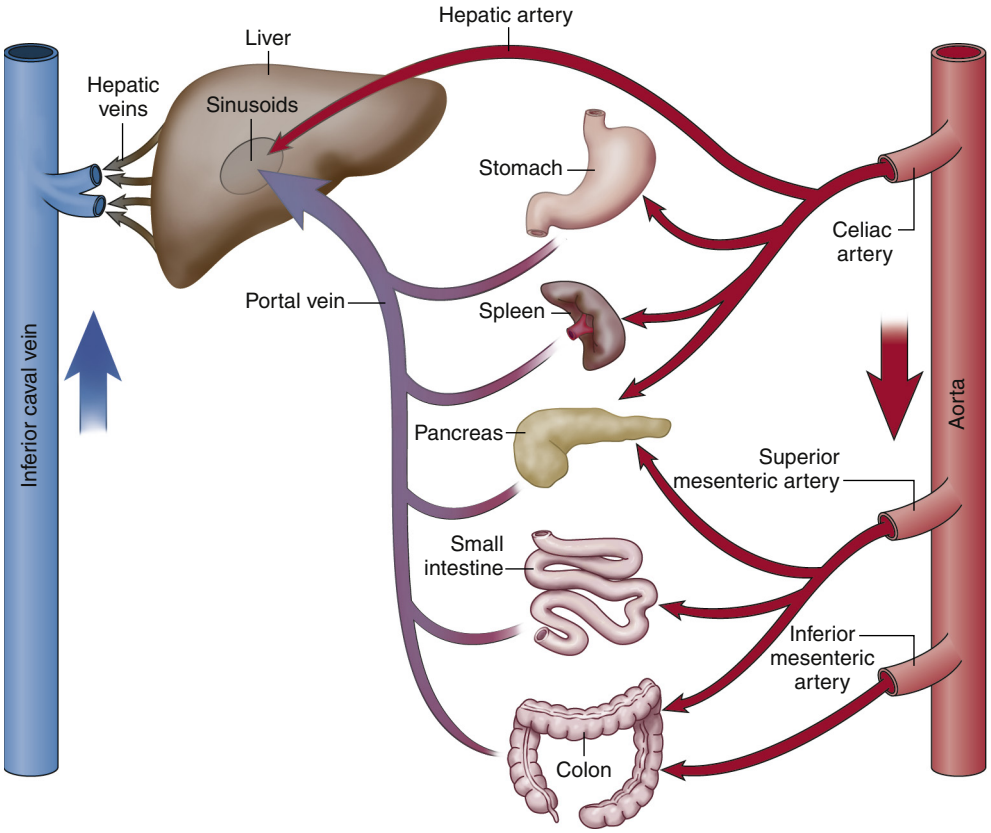


Figure 22-5. The splanchnic circulation. *(Redrawn from Gelman S, Mushlin PS: Catecholamine induced changes in the splanchnic circulation affecting systemic hemodynamics.* Anesthesiology *100:434-439, 2004.)*

The mechanism involves myogenic responses of vascular smooth muscle to stretch. For example, a hypertensive episode increases transmural pressure, thereby stretching arterial smooth muscle. The resultant increase in myogenic tone (i.e., vasoconstriction) prevents the increases in organ blood flow that would otherwise occur. Conversely, transient hypotension lowers transmural pressure and myogenic tone (i.e., vasodilation), which helps sustain organ perfusion during systemic hypotension. Decreases in systemic blood pressure, as often occur during anesthesia, typically lead to a proportional decrease in portal blood flow and often are compensated by an increase in hepatic arterial blood flow; anesthesia with volatile anesthetic decreases this response in a dose-related fashion.

Extrinsic Regulation

Neural Control. Fibers of the vagus, phrenic, and splanchnic nerves (postganglionic sympathetic fibers from T5 through T11) enter the liver at the hilum; they course through the liver alongside the afferent hepatic blood vessels and bile ducts. When sympathetic tone decreases, splanchnic reservoir volume increases. On the other hand, sympathoadrenal stimulation translocates blood volume from the splanchnic reservoir to the central circulation. Within seconds of splanchnic nerve stimulation, up to 80% of the hepatic blood volume (400 to 500 mL) could be transferred to the central circulation in dogs. The hepatic arterial bed has α_1-, α_2-, and β_2-adrenergic receptors, whereas the portal vein has only α-receptors (Fig. 22-6).[12,19]

Humoral Control. Glucagon induces dose-dependent relaxation of hepatic arterial smooth muscle and blocks the effects of physiologic vasoconstrictors on the hepatic artery. By contrast, angiotensin II constricts the hepatic arterial and portal venous beds. Pharmacologic doses of angiotensin II can cause hepatic blood flow to plummet because of its ability to markedly decrease both mesenteric arterial and portal venous flow. Vasopressin, on the other hand, elevates splanchnic arterial resistance, but it lowers portal venous resistance. Because of its vascular profile, vasopressin may have efficacy in treating portal hypertension.[4]

BIOCHEMICAL AND PHYSIOLOGIC ROLES OF THE LIVER

The liver removes particles from the portal blood, which usually contains numerous colonic bacteria that cross the wall of the intestine under normal circumstances. This "blood cleansing" is performed by Kupffer cells.[10]

The liver also has abundant specialized pathways and detoxifies gut-derived substances using CYP450 pathways and other enzymes. It converts xenobiotics, toxins, and other substances into harmless compounds. The effectiveness of many drugs is significantly decreased when taken orally because they are absorbed in the gastrointestinal (GI) tract, reach the liver through the portal blood, and are metabolized there. Their effectiveness is decreased by first-pass metabolism.

Hepatic metabolism of xenobiotics is achieved in two phases. The first phase is metabolism that includes oxidation and other reactions mediated by CYP450s. The second phase includes the esterification reaction that links the metabolites to other molecules such as sulfate, glucuronic acid, amino acids, and others. The liver metabolizes and synthesizes proteins, carbohydrates, lipids, and many other compounds.

Protein Metabolism

The liver plays a central role in the production and breakdown of amino acids, peptides, and proteins. Hepatocytes metabolize amino acids to ketoacids, glutamine, and ammonia by transamination and oxidative deamination

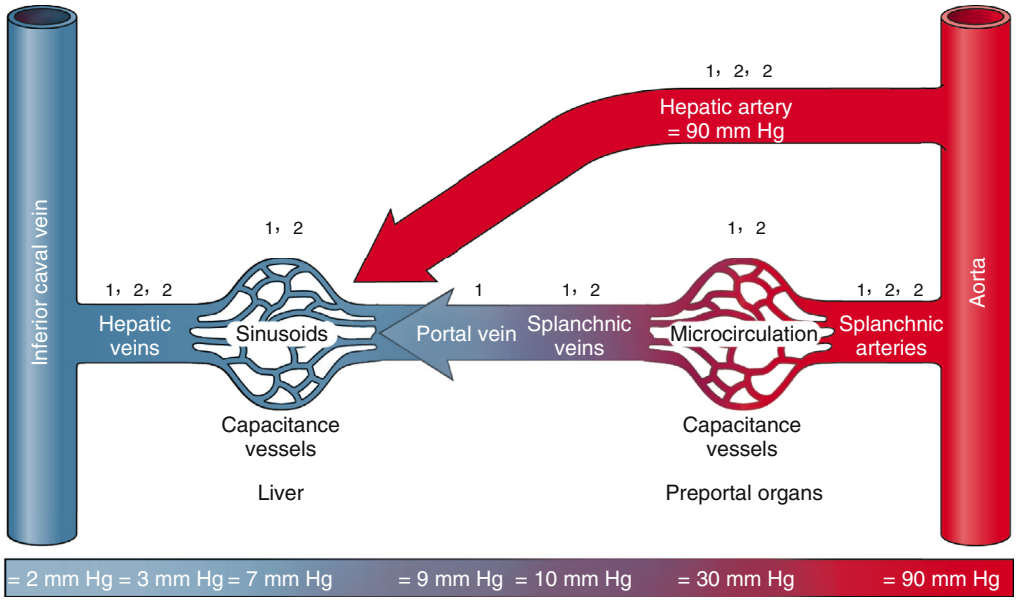


Figure 22-6. Adrenoceptor subtypes (α_1, α_2, β_2) and intravascular pressure within the splanchnic circulation. The splanchnic arteries represent the arterial supply to all preportal organs; the splanchnic veins represent the pooled venous blood from all these organs *(Redrawn from Gelman S, Mushlin PS: Catecholamine induced changes in the splanchnic circulation affecting systemic hemodynamics.* Anesthesiology *100:434-439, 2004.)*

reactions. The Krebs-Henseleit cycle is the major pathway for removing ammonia and other nitrogenous wastes from the body. This pathway captures nitrogen in the form of urea. Thus, with a failing liver (and normal renal function), blood urea nitrogen remains low, whereas nitrogenous wastes such as ammonia accumulate in blood and other tissues.

Liver-derived proteins have an impact on every organ in the body. Such proteins include procoagulants, hormones, cytokines, chemokines, acute-phase reactants, and transport proteins. The most abundant of them is albumin, which accounts for roughly 15% of the liver's total protein production. Healthy adults produce 12 to 15 g of albumin every day; the total-body pool of albumin has a mass of about 500 g. Factors that modulate the synthesis of albumin include plasma oncotic pressure, dietary amino acids, and hormones. The main regulator of intravascular albumin is oncotic pressure. Albumin binds to and transports a wide variety of substances—free fatty acids, unconjugated bilirubin, hormones, xenobiotics, and metals. In this way, albumin affects the biologic activity and clearance of a multiplicity of substances.[4]

Carbohydrate Metabolism

The liver is the epicenter of carbohydrate metabolism. Whether the liver is a net producer or consumer of glucose depends on many factors, including the neuroendocrine milieu (i.e., insulin, catecholamines, glucagon) and glucose concentration in sinusoidal blood. Hepatic production of glucose is inversely related to glycogen production by the liver. In the fed state, hepatocytes polymerize glucose and store it as glycogen; in the unfed state, hepatocytes depolymerize glycogen to glucose and release it into the bloodstream. Regulation of glycogen metabolism involves two rate-limiting enzymes: (1) glycogen synthase, which catalyzes the synthesis of glycogen from monomers of uridine diphosphate (UDP) glucose, and (2) glycogen phosphorylase, which catalyzes the sequential cleavage of glycogen to monomers of glucose 1-phosphate.

When liver glycogen stores are depleted the body depends on hepatic gluconeogenesis to replenish blood glucose. Substrates for gluconeogenesis include (1) lactate; (2) glycerol from the hydrolysis of triglycerides; and (3) glucogenic amino acids such as alanine and glutamine, which are derived from protein catabolism in skeletal muscle. Endocrine modulators of gluconeogenesis include glucagon, catecholamines, and insulin. Both glucagon and catecholamines stimulate gluconeogenesis. Glucagon works via cyclic adenosine monophosphate (cAMP)-dependent protein kinase, and catecholamines use both cAMP-dependent and cAMP-independent mechanisms. By contrast, insulin inhibits gluconeogenesis, and it blocks the stimulatory effects of catecholamines and glucagon on this pathway.

The four main functions of the liver in carbohydrate metabolism are glycogen storage, conversion of galactose and fructose to glucose, gluconeogenesis, and formation of many biochemical compounds from the intermediate products of carbohydrate metabolism. The liver removes excess glucose from the blood and returns it as needed. This function is often called glucose buffer function of the liver.[11]

Lipid Metabolism

The liver produces, takes up, retains, releases, and oxidizes fatty acids in accord with nutritional and endocrine influences. Dietary fatty acids absorbed in the small intestines reach the liver by blood and the lymphatics, mainly in the form of chylomicrons. When replete with glycogen, hepatocytes convert glucose to fatty acids and may store them as triglycerides (fat). Thus, the major sources of intrahepatic fatty acids include (1) free fatty acids extracted from blood, (2) de novo lipogenesis, (3) hydrolysis of cytoplasmic triglycerides, and (4) hepatocellular uptake and metabolism of blood-borne lipoproteins.

Esterification and β-oxidation pathways have pivotal roles in the hepatic disposition of fatty acids. Esterification of glycerol and fatty acids produces triglycerides—the main storage form of free fatty acids. The liver may either retain triglycerides or package them into lipoproteins, primarily very-low-density lipoproteins (VLDLs), for transport to other tissues. Free fatty acids regulate VLDL production, but endocrine and nutritional factors govern VLDL secretion. β-Oxidation is the pathway of fatty acid catabolism. Glucagon activates this pathway, whereas insulin inhibits it. β-Oxidation sequentially cleaves fatty acids to yield monomers of acetyl coenzyme A (acetyl-CoA). It is a building block for lipids (i.e., triglycerides, phospholipids, cholesterol) and a product of the oxidative breakdown of fatty acids and carbohydrates. Mitochondria oxidize acetyl groups to yield carbon dioxide, water, and adenosine triphosphate (ATP). If more acetyl-CoA is produced than the tricarboxylic acid cycle can handle, the surplus is metabolized to ketone bodies—namely, acetoacetate, β-hydroxybutyrate, and acetone.[7] Hepatocytes cannot extract energy from ketones, however, because they lack ketoacyl-CoA transferase (acetoacetate:succinyl-CoA transferase). This enzyme exists in all organs except the liver. Thus, ketones are an important extrahepatic energy source during catabolic states, most notably starvation. Insulin modulates ketogenesis by inhibiting lipolysis in adipocytes. Stress-induced ketosis is typically a self-limited process because ketones stimulate the release of insulin, thereby limiting availability of substrate (fatty acid) for hepatic ketogenesis.[20] Without insulin, this feedback loop is nonexistent and diabetic ketoacidosis may ensue.[77]

Thus, the liver plays an important role in lipid metabolism. An example is its major role in the high rate of fatty acid biotransformation that supplies energy for functions throughout the body. On the other hand, the liver converts amino acids and intermediate products of carbohydrates into fats and transports them to the adipose tissues.

GUT–LIVER INTERACTIONS: THE ENTEROHEPATIC CIRCULATION

Bile: Its Composition and Its Role in Enteric Absorption

Bile is a heterogeneous solution of variable composition; its main constituents are conjugated bile salts, cholesterol, phospholipids, conjugated bilirubins, and electrolytes.[21] After its release from the common bile duct into the duodenum, bile alkalinizes intestinal contents and its

detergent-like chemical properties promote the emulsification, absorption, and digestion of hydrophobic dietary lipids, including saturated long-chain fatty acids and fat-soluble vitamins. Furthermore, bile plays an indispensable role in the excretion of potentially toxic endogenous wastes and xenobiotics.[22]

Bile consists of a micellar solution in which bile acids, products of hepatocytes produced by the metabolism of cholesterol, form mixed micelles with phosphatidylcholine.[21] These mixed micelles solubilize molecules that would otherwise have minimal aqueous solubility, such as cholesterol itself and a variety of xenobiotics. In addition to its role in providing for excretion of hydrophobic waste products, bile also plays an important role in the digestion and absorption of lipids ingested in the diet. Bile acids form mixed micelles with the products of lipid digestion, increasing the rate at which they can diffuse across the aqueous environment of the gastrointestinal lumen. Although bile acids are not essential for the uptake of most fatty acids, which have appreciable aqueous solubility, they do markedly increase the efficiency of this process. On the other hand, in patients suffering from cholestasis, deficiencies of fat-soluble vitamins can occur.[23]

The liver transforms cholesterol into bile salts that are secreted by the liver as a vehicle to facilitate fat digestion and absorption; bile salts also allow the excretion of lipid-soluble waste products of metabolism and xenobiotics. Bile acids recycle several times daily from the intestine to the liver in the enterohepatic circulation; in their conjugated forms, they are actively reabsorbed in the terminal ileum, thereby generating a recycling pool of bile acids.[23]

Bile Formation and Intrahepatic Bile Flow

Bile secretion originates in pericentral hepatocytes and flows centrifugally through tiny channels that parallel the sinusoids. Hepatocytes around the sinusoids secrete bile acids into bile canaliculi that flow in a direction opposite to that of afferent blood. Bile canaliculi drain into small bile ductules that coalesce serially to form larger bile ducts. Ducts of liver segments unite and eventually form the right and left main hepatic bile ducts. The union of these two ducts is the common hepatic duct, which descends through the porta hepatis, where it combines with the cystic duct to create the common bile duct.

BILE PRODUCTION AND THE ENTEROHEPATIC CIRCULATION: GASTROINTESTINAL–HEPATIC INTERACTIONS

The liver produces 200 to 500 mg of primary bile acids per day, using cholesterol as the substrate. Chenodeoxycholic acid and cholic acid are the most important primary bile acids. These bile acids travel from the liver through the intestine. They are reabsorbed from either the terminal ileum or the colon, where bacterial enzymes metabolize them into secondary bile acids. Both types of bile acids enter the mesenteric venous blood and reach the liver sinusoids via the portal vein. Specific transporters on hepatocellular membranes internalize these bile acids, which are then conjugated with hydrophilic substrates (such as glycine or taurine); this facilitates their ATP-dependent secretion into bile canaliculi. Through this series of events, roughly 95% of bile acids are conserved and recycled via the enterohepatic circulation.

The bile acids activate lipases (bile acid dependent), promote micelle formation, and enable the intestinal uptake of fat-soluble vitamins, cholesterol, and other lipids. Bile acids also facilitate the excretion of numerous lipophilic substances, including exogenous compounds such as xenobiotics and endogenous molecules such as bilirubin, cholesterol, and steroid hormonal derivatives.

Bile salts also regulate lipid metabolism. Bile salts produce their regulatory effects by binding to and activating the farnesoid X receptor (FXR). When activated, hormone nuclear receptors (such as FXR) are transferred from cytoplasm to the nucleus; they bind to hormone response elements on DNA to induce either expression or transrepression of specific gene products. An important effect of FXR activation is the decrease in the transcription of cholesterol 7α-hydroxylase (CYP7A1), which catalyzes the rate-limiting step in the conversion of cholesterol to bile salts. Bile salts modulate plasma lipid levels by regulating the expression of lipoprotein receptors that enable hepatocytes to remove lipoprotein cholesterol from the bloodstream.

Cholesterol is so hydrophobic that the body is unable to excrete it without first increasing its water solubility. Remarkably, hepatocytes metabolize cholesterol to bile acids, creating amphipathic molecules that solve two problems. First, amphipathic metabolites of cholesterol are readily excreted in the bile. Second, such bile acid metabolites retain the hydrophobic regions of cholesterol while also containing newly added hydrophilic groups. Therefore, cholesterol metabolism yields effective detergents that facilitate enteric emulsification and digestion and absorption of dietary lipids, including long-chain fatty acids and fat-soluble vitamins.[11]

SYNTHESIS OF PROCOAGULANTS, ANTICOAGULANTS, AND FIBRINOLYTIC FACTORS

Hepatocytes make most of the procoagulants, with notable exceptions such as factors III (tissue thromboplastin), IV (calcium), and VIII (von Willebrand factor). The liver also makes protein regulators of coagulation and the fibrinolytic pathways. Such regulators include protein S, protein C, protein Z, plasminogen activator inhibitor (PAI), and antithrombin III. Protein Z facilitates the degradation of factor Xa, and protein S is a cofactor of activated protein C that inactivates factor Va and VIIIa complexes; a deficiency of protein S increases the risk for venous thrombosis. PAI-1 is an indirect inhibitor of fibrinolysis. This serine protease inhibitor blocks the effects of plasminogen activators, such as urokinase and tissue plasminogen activator, to convert plasminogen to plasmin; a deficiency of PAI increases the risk for uncontrolled fibrinolysis. To summarize, hepatocytes make most of the procoagulants and many proteins that modulate the consumption of clotting factors.[24]

Vitamin K Cofactor and γ-Carboxylation

Vitamin K–dependent proteins include factors II, VII, IX, and X and proteins C and S. Such proteins undergo

a vitamin K–dependent, posttranslational modification. This process involves carboxylation of the γ-position of glutamate residues at the amino terminus, which produces the amino acid carboxyglutamate.[20,25] This modification (termed γ-carboxylation) creates procoagulants capable of forming complexes with calcium or other divalent cations. Thus, γ-carboxylated procoagulants are primed for activation to serine proteases (e.g., via extrahepatic phospholipids) that participate in the clotting cascade.[20,26]

The γ-carboxylation pathway, which contains two steps, accounts for the anticoagulant effect of warfarin.[26] The first involves vitamin K–dependent γ-carboxylation of precursor proteins, during which vitamin K cofactor (naphthol hydroquinone) is oxidized to 2,3-epoxide vitamin K. In the second stage, vitamin K cofactor is regenerated via vitamin K 2,3-epoxide reductase. Warfarin blocks the second stage by inhibiting vitamin K epoxide reductase and thereby trapping vitamin K in the epoxide form. The eventual result is depletion of vitamin K cofactor, which shuts down the γ-carboxylation pathway.

Warfarin inhibits γ-carboxylation soon after its enteric absorption, but its anticoagulant effect takes at least 1 day to develop. This paradox reflects the slow clearance of blood-borne prothrombin complexes (i.e., half-life of ~14 hours) and the insensitivity of prothrombin time (PT) as a test for decreasing blood levels of procoagulants. As a rule, the PT will remain normal until the prothrombin complex in blood is less than 70% below the lower limit of normal.

Therapeutic use of vitamin K may help uncover the cause of an unexplained prolongation in PT. For example, PT abnormalities caused by malnutrition or warfarin are correctable with enteral or parenteral vitamin K therapy. When PT abnormalities result from malabsorption syndromes, parenteral vitamin K is superior to oral therapy. However, if PT abnormalities result from liver dysfunction (i.e., acute hepatitis, cirrhosis), vitamin K will be ineffective because the problem is not a deficiency of vitamin K but rather a deficiency of hepatic procoagulants.

SYNTHESIS AND DEGRADATION OF HEME: CYTOCHROMES, PORPHYRINS, AND BILIRUBIN

Heme synthesis begins with the condensation of glycine and succinyl-CoA to produce 5-aminolevulinic acid (ALA). This reaction, catalyzed by ALA synthase, is the rate-limiting step in the heme pathway. Heme inhibits ALA synthase and thereby regulates its own synthesis. ALA is made in mitochondria; it diffuses into the cytoplasm and encounters ALA dehydratase. This enzyme joins two ALA molecules together to form porphobilinogen (PBG). PBG molecules are positioned in a linear arrangement by PBG deaminase to form hydroxymethylbilane (HMB). HMB is transformed to uroporphyrinogen III, which is the precursor of coproporphyrinogen III. The latter is taken up by mitochondria and converted by coproporphyrinogen oxidase and protoporphyrin oxidase to protoporphyrin IX. In the final step of the pathway, ferrochelatase catalyzes the formation of a complex of ferrous iron and protoporphyrin IX to produce heme.[27,28]

Bilirubin Production and Excretion

The main source of serum bilirubin is heme metabolism. Healthy adults make approximately 300 mg of bilirubin daily, 80% of which is derived from phagocytosis of senescent erythrocytes by macrophages in the spleen, liver, and bone marrow. These reticuloendothelial cells extract protein from hemoglobin and convert heme to bilirubin.[29,30] The first step is rate limiting. Heme oxygenase, with O_2 as a substrate, oxidatively cleaves the porphyrin macrocycle of heme to yield biliverdin-IXα, carbon monoxide, and free divalent iron in equimolar amounts.

Most of the endogenous carbon dioxide production is derived from heme oxygenase reactions. Thus, the biologic importance of heme oxygenase may extend beyond the breakdown of heme. To clarify, carbon dioxide roles include regulation of vascular tone (vasodilator), platelet aggregation, vascular myocyte proliferation, and neurotransmitter release. Furthermore, carbon dioxide exerts cytoprotective, antiapoptotic, and antioxidant effects in organs throughout the body. Biliverdin also confers protection from oxidative stress[31]; it is rapidly converted to bilirubin by cytoplasmic reductases.[32]

After release from reticuloendothelial cells, bilirubin becomes tightly bound to plasma albumin. Hepatocytes avidly extract this bilirubin from albumin. They produce conjugates of bilirubin (through the action of glucuronic acid and bilirubin UDP-glucuronosyltransferase) and secrete these conjugates into canalicular bile. Although the gut excretes most of this bilirubin, a small amount returns to the liver in the enterohepatic circulation. Thus, the bloodstream normally has a modicum of bilirubin conjugates, which arrive directly by the enterohepatic circulation or indirectly from the bile ducts and lymphatics.

Porphyrias. Porphyrinogens exposed to O_2 are readily oxidized to the corresponding porphyrins. Accumulation of porphyrins in tissues leads to porphyrias. Porphyrias are rare, genetic diseases characterized by aberrations in heme production. Patients with these disorders are typically asymptomatic until some stressor (exogenous or endogenous) induces a porphyric crisis.[33]

The clinical syndrome includes recurrent, dramatic, and occasionally fatal neurologic reactions, accompanied by abdominal pain (90%) and dark urine (80%). Acute intermittent porphyria is the most common porphyria. Its prevalence in the general population is about 1 in 10,000, but it may reach 1 in 500 in psychiatric patients. Acute intermittent porphyria has a fivefold higher frequency in women than in men. Substances known to trigger porphyric crises include sex hormones, glucocorticoids, cigarette smoke, and various medications, most notably barbiturates and other CYP inducers.[29,34]

REGULATOR OF HEMATOGENOUS ENDOCRINE MEDIATORS

The liver is the largest gland in humans, and it plays important roles in the metabolism of hormones and hormone-binding proteins.[35] Hepatocytes produce a wide variety of endocrine substances, including angiotensinogen, thrombopoietin, and insulin-like growth factor I (IGF-I).[36] They take up thyroxine (T_4), the major product

of the thyroid gland, and may activate it to triiodothyronine (T_3) or inactivate it. The liver inactivates many other hormones, including aldosterone, antidiuretic hormone, estrogens, androgens, and insulin. Nearly half of the insulin released by the pancreas may not reach the systemic circulation because of hepatic degradation.

MODULATOR OF IMMUNE AND INFLAMMATORY PROCESSES

The liver is the largest reticuloendothelial organ in the human body. Hepatic macrophages (Kupffer cells) account for nearly 10% of the total liver mass. Kupffer cells protect and defend the body against foreign intrusions. Before splanchnic venous blood enters the central circulation, it is filtered by Kupffer cells, which degrade toxins, process antigens, and phagocytose bacteria.[10,37] In addition, Kupffer cells are important modulators of inflammation[38]; they attenuate inflammatory responses by removing inciting substances from the bloodstream; but they can also induce and intensify inflammation by producing and releasing proinflammatory mediators and recruiting neutrophils to the liver.[38] Among these mediators are various cytokines, chemokines, leukotrienes, proteases, nitroradicals, and reduced O_2 species. If not properly controlled, these same mediators can induce or aggravate injuries to parenchymal and other liver cells.[38,39] For example, because of their low glutathione content, endothelial cells of the sinusoids and terminal hepatic veins are highly vulnerable to oxidative stress and drug-induced vascular injury. Stellate cells reside mainly in the perisinusoidal spaces and are the liver's major source of matrix deposition. When activated by oxidative stress or toxic chemicals, stellate cells may be transformed to collagen-synthesizing myofibroblasts, which can cause extensive fibrosis of the liver (e.g., methotrexate-induced hepatic fibrosis).

METABOLISM AND EXCRETION OF ENDOGENOUS AND XENOBIOTIC MOLECULES

The myriad chemical reactions that hepatocytes use to eliminate drugs fit into three broad categories (or phases). Phase 1 metabolism uses CYP and mixed-function oxidases to increase the polarity of drugs. Phase 2 metabolism increases the polarity of drugs (or their metabolites) by conjugating them with endogenous water-soluble substrates. Phase 3 elimination uses energy-dependent transporters to excrete drugs into canalicular bile. The hepatic clearance of drugs involves at least one of these phases.[40-42]

Phase 1 Metabolism

Phase 1 reactions (e.g., oxidations, reductions, hydrolysis) convert drugs to more polar compounds by inserting polar groups (e.g., hydroxide, amine, sulfhydryl) or removing nonpolar groups. Generally, the products of phase 1 metabolism are more readily excreted in bile or urine than are their precursors. Such products also may be substrates for phase 2 conjugations.

Microsomal Oxidases and Cytochrome P450. More than 90% of drug biotransformations involve microsomal oxidases and hemoproteins of the CYP gene superfamily. The human liver has more than 20 different CYP isozymes that mediate redox reactions in diverse pathways, including steroid, lipid, and bile salt metabolism. Zone 3 (centrilobular) has the highest total CYP content. In fact, the acinar location of specific isozymes of CYP may clarify relationships between drug metabolism and liver injury. For example, centrilobular necrosis is the classic acetaminophen-induced injury; the probable explanation is that CYP2E—the CYP isoform involved in acetaminophen metabolism—is localized in zone 3.

CYP reactions generate metabolites that are highly reactive and potentially toxic. In brief, the CYP reaction cycle begins with O_2 binding to heme iron; this O_2 becomes activated after receiving an electron from a flavoprotein reductase—NADPH:hemoprotein oxidoreductase (CYP). Insertion of activated O_2 into lipophilic molecules (e.g., xenobiotics) produces substrates for mixed-function oxidase reactions. These oxidases transfer a singlet oxygen (atom) from O_2 to the target molecule; another substrate (e.g., NADPH) simultaneously delivers electrons that reduce the residual oxygen singlet, thereby enabling its incorporation into water. To summarize, oxidases promote the formation of highly active chemicals, including reduced O_2 species and free radical intermediates, which can cause or aggravate liver injury.[4]

Phase 2 Metabolism. Phase 2 reactions conjugate xenobiotics (or their metabolites) with endogenous hydrophilic molecules such as glucuronic acid, acetate, sulfates, amino acids, and glutathione.[40,43] Many conjugations involve glucuronic acid and UDP-glucuronosyltransferase. Other conjugations are catalyzed by sulfatases, glutathione-*S*-transferases, acetyl-*N*-transferases, or amino acid *N*-transferases. When compared with their precursors, conjugated xenobiotics are usually less efficacious, less toxic, more hydrophilic, and more readily excreted in bile or urine.

Phase 3 Elimination. Phase 3 reactions involve specific molecular transporters known as ATP-binding cassette (ABC) transport proteins that facilitate the excretion of xenobiotics and endogenous compounds. These proteins use ATP hydrolysis to drive molecular transport. Major ABC transport proteins include cystic fibrosis transmembrane conductance regulator, canalicular copper transporters, and multidrug resistance protein (MDR). MDR-1 (formerly referred to as P-glycoprotein) resides on the canalicular surfaces of hepatocytes and enables biliary excretion of cationic compounds, including anticancer drugs.[44,45]

Another family of ABC proteins—multidrug resistance–related protein (MRP)—excretes conjugated molecules. MRP-1, located on the lateral surfaces of hepatocytes, can transport drug conjugates into the sinusoids. MRP-2 (formerly termed canalicular multispecific organic anion transporter [cMOAT]), on the canalicular surfaces of hepatocytes, secretes conjugates of drugs and endogenous wastes (e.g., bilirubin diglucuronide, glutathionyl-leukotriene conjugates) into canalicular bile. Thus, dysfunction of ABC transport proteins can disrupt the flow of bile, impair excretion of xenobiotics and endogenous compounds, and induce cholestatic liver injury.[46,47]

Demographic Factors Affecting Metabolic Rates and By-products

Dose-related responses to drugs often vary considerably within individuals and populations. Much of this variability is due to the heterogeneity of drug disposition and metabolism, which is mainly influenced by genetic and environmental factors. Genetics control the expression of CYP isozymes. Environmental factors (e.g., drugs, other chemicals) modify genetic expression and thereby alter drug biotransformation.[40-42] Numerous conditions and disorders are capable of altering the production of CYP proteins. For example, obesity, fasting, and diabetes mellitus may lead to up-regulation of CYP2E1.[40-42] On the other hand, conditions that may result in down-regulation of CYP include systemic inflammatory disorders, fever, nitrogen-free solutions, nitrogen-rich solutions, and hepatic cirrhosis. Hypothyroidism and hypopituitarism may selectively down-regulate CYP1A and CYP3A4, respectively.[41,42]

Pharmacokinetics

Perfusion models of drug elimination generally focus on three major parameters: intrinsic hepatic clearance, hepatic blood flow, and protein binding. The intrinsic hepatic clearance of a drug divided by hepatic blood flow is the drug's extraction ratio; this provides a measure of the relative efficiency with which the liver extracts or eliminates a given drug.[48] Box 22-1 shows a compilation of drugs with high and low extraction ratios.[4,49] Such information enables general rules to be made about pharmacologic categories and intrinsic clearances. For example, hepatocytes are efficient extractors of calcium channel blockers, β-adrenoceptor blockers (except atenolol), opioid analgesics, tricyclic antidepressants, and organic nitrates. On the other hand, the liver poorly extracts warfarin, aspirin, alcohol, and many anticonvulsants. For drugs with a low extraction ratio, hepatic elimination rates are capacity limited. Such rates often change when protein binding or intrinsic hepatic clearance changes, but they are insensitive to fluctuations in hepatic blood flow. For drugs with a high extraction ratio, hepatic elimination rates are flow dependent. These elimination rates are highly dependent on and directly related to liver blood flow; they are unaffected by changes in either protein binding or the activity of drug-metabolizing enzymes (Table 22-1).[4]

BOX 22-1 *Drugs Efficiently Versus Poorly Extracted From Blood Flowing Through the Liver*

Efficiently Extracted Drugs	Poorly Extracted Drugs
Amitriptyline	Acetaminophen
Desipramine	Amobarbital
Imipramine	Antipyrine
Labetalol	Aspirin
Lidocaine	Clindamycin
Meperidine	Diazepam
Metoprolol	Digitoxin
Morphine	Ethanol
Nortriptyline	Hexobarbital
Pentazocine	Phenobarbital
Propoxyphene	Phenytoin
Propranolol	Tolbutamide
Ranitidine	Valproic acid
Verapamil	Warfarin
Zidovudine	

EVALUATION OF THE LIVER

CLINICAL ASSESSMENT

The only clues to liver disease may be mild, nonspecific symptoms, such as loss of appetite, easy fatigability, malaise, altered sleep patterns, or subtle changes in personality. The history addresses major risk factors for liver disease: (1) alcoholism; (2) illicit drug use; (3) sexual promiscuity; (4) blood transfusions; (5) occupational exposure to hepatotoxins; (6) prior bouts of jaundice, particularly after anesthesia; and (7) genetic diseases, such as hemochromatosis, α_1-antitrypsin deficiency, and Wilson disease. Clinical findings consistent with liver disease include nonspecific symptoms (as just mentioned), pruritus, abdominal pain, indigestion, and changes in urine or stool color. The physical examination focuses on stigmata of advanced liver disease, such as icterus, jaundice, ascites, spider angiomas, xanthelasma, encephalopathy, palmar erythema, and fetor hepaticus.

STANDARD LABORATORY TESTS

Standard test panels used to evaluate hepatobiliary status are often referred to as liver function tests (Table 22-2).[4,50,51] To be precise, this terminology is a misnomer because none of the tests measure any specific liver function. Instead, they point to broad categories of hepatobiliary pathology: hepatitis, hepatobiliary dysfunction, or insufficient protein synthesis. These categories include large subsets of diseases—for example, all possible causes of hepatitis.

Detection of Hepatocellular Injury

Aminotransferases. Hepatocellular injury is the usual cause of elevated serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), formerly termed serum glutamic-pyruvic transaminase (SGPT) and serum glutamic-oxaloacetic transaminase (SGOT), respectively. Both enzymes are involved in gluconeogenesis. They catalyze the transfer of an amine group to α-ketoglutarate to yield glutamate and either pyruvate (by ALT) or oxaloacetate (by AST). ALT is mainly a cytoplasmic liver enzyme. In contrast, cytoplasmic and mitochondrial isozymes of AST are found in most extrahepatic tissues, including the heart, skeletal muscle, brain, kidney, pancreas, adipose tissue, and blood. It is rare to encounter concomitant elevations in AST and ALT when the liver is normal and disease free. In those rare instances, the elevations in AST and ALT levels would most likely result from muscle injury.[51]

Elevated ALT and AST levels are sometimes described in qualitative terms: mild (100 to 249 International Units/L), moderate (250 to 999 International Units/L), large (1000 to 1999 International Units/L), and extreme

(>2000 International Units/L). Mild elevations in AST and ALT may arise from any disorder that injures hepatocytes. Common causes include steatosis, medications, alcohol consumption, hemochromatosis, cholestasis, chronic viral hepatitis, neoplasms, and cirrhosis. Moderate ALT and AST elevations are characteristic of acute viral hepatitis, drug-induced liver injury, and flare-ups of chronic liver disease (e.g., viral hepatitis, steatohepatitis). Large elevations often reflect acute hepatitis superimposed on chronic active liver disease. Extreme elevations signify massive hepatic necrosis. Typical causes are fulminant viral hepatitis, severe drug-induced liver injury (e.g., from acetaminophen), shock liver or hypoxic hepatitis, and, in rare instances, autoimmune hepatitis or acute biliary obstruction.[51]

Ratios of aminotransferases may hold keys to the diagnosis of hepatic disorders. For example, when both AST and ALT are elevated, an AST-to-ALT ratio higher than 4 is characteristic of Wilson disease, ratios between 2 and 4 are typical of alcoholic liver disease, and a ratio below 1 suggests nonalcoholic steatohepatitis (without cirrhosis). When elevations of AST and ALT are mild, ratios above 2 are consistent with alcoholic liver disease or cirrhosis of any etiology.[51] If the ratio is elevated and ALT is normal, the elevation in AST is most likely from an extrahepatic source of AST. Although concomitant elevations in AST and ALT are a reliable indicator of hepatocellular injury, aminotransferase levels by themselves seldom reveal the extent of liver damage. For instance, patients with florid liver failure can have normal enzyme levels when the liver damage is so extensive that too few viable hepatocytes remain to bring about increases in ALT or AST. In addition, chronic, smoldering liver diseases such as hepatitis C can destroy the liver, slowly and silently, without overt increases in ALT or AST.

Lactate Dehydrogenase. Elevated serum lactate dehydrogenase (LDH) levels may reflect hepatocellular injury, extrahepatic disorders, or both. Extreme increases signify massive liver damage, which may result from fulminant viral hepatitis, drug-induced liver failure, or hypoxic hepatitis. Prolonged, concurrent elevations in LDH and alkaline phosphatase (AP) suggest malignant infiltration of the liver. Notable extrahepatic disorders that cause moderate elevations in LDH include hemolysis, rhabdomyolysis, tumor necrosis, renal infarction, acute cerebrovascular accident, and myocardial infarction. Such disorders cause more pronounced LDH elevations in patients with acute

TABLE 22-1 FLOW-DEPENDENT VERSUS CAPACITY-LIMITED ELIMINATION OF DRUGS BY THE LIVER

Type of Hepatic Elimination	Extraction Ratio (ER)	Rate of Hepatic Drug Metabolism
Flow-dependent elimination	High ER: At clinically relevant concentrations, most of the drug in the afferent hepatic blood is eliminated on first pass through the liver.	Rapid: Because drugs with a high ER are metabolized so rapidly, their hepatic clearances roughly equal their rates of transport to the liver (i.e., hepatic blood flow).
Capacity-limited elimination (also referred to as dose-dependent, nonlinear, saturable, or zero-order elimination)	Low ER: Hepatic elimination of these drugs is determined by their plasma concentration.	Slow: When the capacity of the liver to eliminate a drug is less than the dosing rate, a steady state is unachievable; plasma levels of drug will continue to rise unless the dosing rate is decreased. Drug clearance has no real meaning in such settings.

TABLE 22-2 LIVER BLOOD TESTS AND THE DIFFERENTIAL DIAGNOSIS OF HEPATOBILIARY DISORDERS

	Predominant Abnormality		
Blood Test	Bilirubin Overload (Hemolysis)	Hepatocellular Injury	Cholestasis
Aminotransferases	Normal	Increased: May be normal or decreased in advanced stages	Normal: May be increased in advanced stages
Serum albumin	Normal	Decreased: May be normal in acute fulminant hepatic failure	Normal: May be decreased in advanced stages
Prothrombin time*	Normal	Prolonged	Normal: May be prolonged in advanced stages
Bilirubin (main form present)	Unconjugated (also mild increase in conjugates)	Conjugated	Conjugated
Alkaline phosphatase	Normal	Normal: May be increased by hepatic infiltrative disease	Increased
γ-Glutamyl transpeptidase 5′-nucleotidase	Normal	Normal	Increased
Blood urea nitrogen	Normal: May be increased by renal dysfunction	Normal: May be decreased by severe liver disease and normal kidney function	Normal
BSP/ICG (dye)	Normal	Retention of dye	Normal or retention of dye

BSP/ICG, Bromsulphalein and indocyanine green.
*Used interchangeably with the international normalized ratio.

liver injury (e.g., severe preeclampsia). An elevation in LDH that is due solely to hepatocellular injury is typically accompanied by elevations in AST and ALT. Thus, LDH rarely yields information about liver injury beyond that already provided by AST and ALT.[51]

Glutathione-*S*-Transferase. Glutathione-*S*-transferase (GST) is a sensitive and specific test for some patterns of drug-induced liver injury. The enzyme has a brief plasma half-life (90 minutes) and is released rapidly into the circulation after hepatocellular injury. Thus, serial GST measurements can reveal the time course of hepatic injury, from its onset to its resolution. In contrast to AST and ALT, which reside in acinar zone 1, GST localizes in acinar zone 3 (centrilobular region).[52] The zone contains the hepatocyte population with the highest susceptibility to injury from hypoxia or reactive drug metabolites. Accordingly, GST would be more sensitive than AST or ALT as a marker of centrilobular necrosis in its incipient stages.

Assessment of Hepatic Protein Synthesis

Serum Albumin. Serum albumin yields information about hepatocellular function (i.e., protein synthesis) and is used to evaluate chronic liver disease, with notable caveats. First, hypoalbuminemia has many causes besides low rates of albumin synthesis; examples include renal losses of albumin, increased albumin catabolism, expansion of plasma volume, and maldistribution of total body albumin. In fact, the total body mass of albumin (in the exchangeable pool) is often normal in patients with liver cirrhosis, ascites, and hypoalbuminemia.[53] Second, no clear relationship exists between serum albumin and the instantaneous rate of albumin synthesis because plasma albumin has a half-life of nearly 3 weeks. Thus, if hepatic protein synthesis came to an abrupt and permanent halt, this change would not be reflected as a decrease in the serum albumin level for at least a few days.

Prothrombin Time. When compared with albumin, liver-derived procoagulants have short half-lives, which range from 4 hours for factor VII to 4 days for fibrinogen. Plasma levels of such procoagulants start to descend shortly after the liver begins to fail. PT (or the international normalized ratio [INR]) is widely used to evaluate and monitor patients with acute liver dysfunction. A prolonged PT secondary to liver failure generally reflects a low blood level of factor VIIa, which has the shortest plasma half-life of hepatic coagulant factors.[51] Besides diagnostic utility, PT is used as a prognostic indicator. It is a common parameter of models or algorithms designed to facilitate timely, yet correct, decisions about the need for liver transplantation. In this regard, PT is of value for patients with drug-induced liver failure or those with active liver disease and a surgical condition that needs immediate attention.

Detection of Cholestatic Disorders

Alkaline Phosphatase. Serum AP is used to screen for disorders of the liver or biliary tree, including hepatitis, malignancies, and cholestatic diseases. Because AP isoenzymes exist in plasma membranes throughout the body, AP lacks specificity for hepatobiliary disease.[51] Mild, transient increases in AP may occur in up to a third of those subjected to routine laboratory testing. Major sources of AP include bone, intestine, kidney, leukocytes, placenta (third trimester of gestation), and neoplasms. Increased metabolic activity in one or more of these tissues may lead to elevations in AP. Increased serum AP usually reflects increased production or release of AP rather than decreased clearance of AP.

The AP elevations in cholestatic disorders may reflect the action of bile salt on the plasma membranes of hepatocytes. Serum AP may remain normal for a couple of days after the onset of biliary obstruction, not increasing until hepatocytes produce (and release) more AP. Because it has a half-life of nearly a week, serum AP may remain elevated for days after bile flow is restored.[51] Extreme increases in AP suggest (1) a major block in biliary flow as a result of disorders such as primary biliary cirrhosis and choledocholithiasis or (2) a hepatic malignancy (primary or metastatic) that is compressing small intrahepatic bile ducts.

Serum Bilirubin. Serum bilirubin is the most widely used test for hepatic excretory dysfunction. Total bilirubin is normally below 1 mg/dL, but up to 10% of healthy adults have higher levels, mainly in the form of unconjugated bilirubin. This is usually a benign condition (Gilbert syndrome) that reflects genetically low levels of bilirubin UDP-glucuronosyltransferase. Serum bilirubin levels above 4 mg/dL are readily detectable on physical examination as jaundice—a yellowish discoloration of body tissues. But with natural light, scleral icterus can be discerned at bilirubin levels of 3 mg/dL or even lower.[51]

Bilirubin is normally absorbed by hepatocytes, conjugated there with glucuronide, and transported across the bile canaliculi. Conjugated bilirubin is transported into the bile; both conjugated and unconjugated bilirubin can pass from hepatocytes into the plasma. Conjugation of bilirubin increases its solubility. Bilirubin is deconjugated and then metabolized by bacteria within the colon and converted into urobilinogen, which also can be passed into the urine.

Conjugated hyperbilirubinemia generally results from one or two fundamental problems: (1) flow of bile is blocked within the hepatobiliary tree, or (2) hepatocytes produce more bilirubin conjugates than they can efficiently transport into the canalicular space. Massive hemolysis causes unconjugated and conjugated hyperbilirubinemia. Increases in unconjugated bilirubin occur because hepatocytes are presented with more bilirubin than they can conjugate. Increases in conjugated bilirubin result because hepatocytes conjugate bilirubin faster than hepatocellular transporters can secrete them into canalicular bile. Bilirubinuria usually reflects conjugated hyperbilirubinemia. The kidneys readily excrete bilirubin conjugates, whereas unconjugated bilirubin, which binds tightly to plasma albumin, is neither filtered nor excreted by normal kidneys.[51,54]

Clinically it is important to distinguish conjugated from unconjugated bilirubin. Any bilirubin in the urine (which is easily diagnosed by color) must be conjugated because only conjugated bilirubin can pass through the kidney and be excreted in the urine. Jaundice without bilirubin in the urine can be due to overproduction of

bilirubin, impaired hepatic uptake, or impaired conjugation. Bilirubin in the urine suggests hepatobiliary disease (i.e., extrahepatic or intrahepatic cholestasis) or genetic defect in the excretion of bilirubin[11] (Fig. 22-7).

Thus, a patient with severe jaundice and no bilirubin in the urine suggests an increase in circulating bilirubin resulting from the unconjugated form. This is usually during the increase in heme production that overwhelms the conjugation pathway or when the process of conjugation is impaired. Hemolysis is one of the most common reasons for such a condition. Conjugated hyperbilirubinemia (jaundice and bilirubin in the urine) occurs because some of the bilirubin dissociates from albumin; the associated increase in water solubility of conjugated bilirubin leads to it being able to pass through the kidney into the urine. This means that bilirubin is formed within the hepatocytes but cannot be transported into the bile; a typical example is cholestasis.

Testing for Specific Diseases

Targeted testing is used to identify specific hepatic or biliary diseases. Examples include (1) serologic testing to identify viral, microbial, and autoimmune causes[55,56]; (2) genetic testing to diagnose heritable metabolic disorders; and (3) tumor marker assays to detect hepatic malignancies.

Identifying viral markers—antibodies, antigens, and genetic material—is the key for diagnosis of hepatitis from hepatotropic viruses (A, B, C, E) and herpesviruses such as cytomegalovirus and Epstein-Barr virus. Patients infected with hepatitis B or C virus often have markers of immune pathology, including anti–smooth muscle antibodies, antinuclear antibodies, and mixed cryoglobulins.[57] Autoimmune hepatitis and hepatitis A virus infection are commonly associated with anti–asialoglycoprotein receptor antibodies. Autoimmune cholangitides have distinctive serologic profiles.[58] For example, antimitochondrial antibodies usually develop with primary biliary cirrhosis[56,59-61] but are typically absent with primary sclerosing cholangitis. Characteristic findings of primary sclerosing cholangitis include anti–smooth muscle and antinuclear antibodies.[56,62,63]

Markers for hepatic malignancy include α-fetoprotein (AFP) and des-γ-carboxylated prothrombin.[64-67] As a test for hepatocellular carcinoma (HCC), plasma AFP is highly specific, with a sensitivity that ranges from 50% to 90%, depending on population subgroups.[66] Another test for HCC is the plasma γ-carboxylated prothrombin level. HCC cells usually make procoagulants without γ-carboxylating them.[64,67] High levels of des-γ-carboxylated, vitamin K–dependent proteins occur in up to 91% of patients with HCC. In at least two thirds of these patients, levels are above 300 ng/mL, which far exceeds the typical value in patients with liver cirrhosis or acute hepatitis. After surgical removal of HCC, levels of des-γ-carboxylated factors begin to decrease. Subsequent increases suggest tumor recurrence.[68]

QUANTITATIVE LIVER TESTS

Total hepatocellular mass can be estimated by measuring the clearance of a substance that is avidly extracted by the liver, such as bromsulphalein and indocyanine green (ICG). However, these are rough estimations because clearance is subject to many influences and unknown factors. For example, hepatic clearance of highly extracted substances (1) changes in direct proportion to variations in liver blood flow, (2) is altered by extrahepatic retention or clearance of the substance, and (3) may be affected by anomalous hepatobiliary function.

Drug-metabolizing capacity of the liver can be measured by several methods, such as caffeine clearance, galactose elimination capacity, aminopyrine breath test, antipyrine clearance, and monoethylglycinexylidide (MEGX).[51,69-72] Techniques are available for measuring caffeine clearance noninvasively. For example, patients take an oral dose of caffeine (150 to 300 mg), and caffeine metabolites in saliva are measured for up to 24 hours. MEGX is an invasive method that has recently gained popularity for measuring liver blood flow in critically ill patients. Fifteen minutes after an intravenous injection of lidocaine (1 mg/kg), a blood sample is obtained and assayed for MEGX, the major metabolite of lidocaine. Currently, quantitative tests are in the domain of research tools; when compared with standard liver chemistry tests, they are expensive and time consuming, with no compelling evidence of being superior, either diagnostically or prognostically.

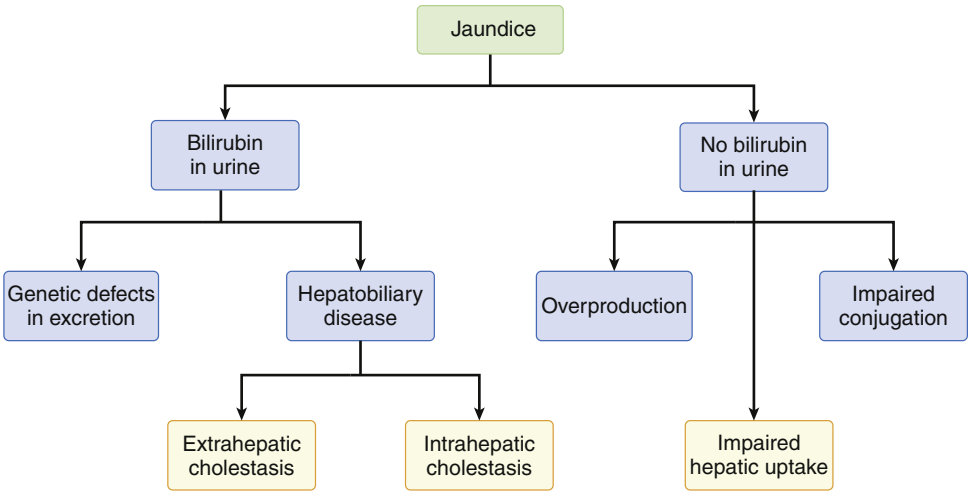


Figure 22-7. Differential diagnosis of jaundice depending on whether bilirubin is or is not present in the urine. *(From Barrett KE:* Gastrointestinal physiology. *New York, 2005,McGraw-Hill Medical, chap 13, p 222.)*

MEASUREMENT OF LIVER BLOOD FLOW

Methods used to measure hepatic blood flow fall into three broad categories: clearance techniques, indicator dilution techniques, and direct measurements.

Clearance Techniques

Extraction methods using the indirect Fick principle closely approximate hepatic blood flow and are valid for substances with high intrinsic hepatic clearance and total body clearance. Such substances include ICG dye, propranolol, lidocaine, and colloidal particles. Constant infusion of ICG is among the most reliable extraction methods. Hepatocytes take up nearly all of the ICG infused and excrete it unchanged in bile. Clearance methods also may be based on the ability of Kupffer cells to avidly phagocytose radiolabeled colloidal particles such as gold 198.

After injecting such particles, the area under the initial curve (of radioactivity versus time) can be computed to obtain a valid measurement of hepatic blood flow—assuming that the reticuloendothelial system is functioning normally.[73] The bottom line is that severe liver disease renders clearance techniques unreliable because of indeterminable disease-related effects on liver blood flow and hepatic capacity to eliminate substances. The latter decreases in direct proportion to the loss of hepatocellular mass.[74]

Indicator Dilution Techniques

Unlike clearance methods, measurements of liver blood flow by indicator dilution techniques are unaffected by liver disease. After a radiolabeled indicator (e.g., iodinated albumin) is injected into the spleen, hepatic flow is computed from indicator dilution curves. These curves are obtained by continuous sampling from one of the hepatic veins or by external γ-scintillation counting. For this technique to be valid, the indicator must be uniformly mixed on injection and resistant to hepatic clearance.[4]

Direct Measurements

Electromagnetic flow probes provide direct measurements of blood flow through the hepatic artery or portal vein. However, the surgical procedures used to implant the probes can themselves alter hepatic blood flow. Thus, the probes are often left in place after the implantation procedure and blood flow is subsequently measured by telemetry.

RADIOLOGIC AND ENDOSCOPIC METHODS

Radiologic and endoscopic techniques offer therapeutic alternatives to surgery. Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTHC) are used to evaluate hepatobiliary disorders. ERCP provides intraductal access to the biliary tree and pancreatic duct. Its main use is to diagnose and treat extrahepatic biliary disorders such as gallstones, tumors, inflammatory strictures, and postsurgical anastomotic leaks. Successful endoscopic papillotomy can obviate surgical removal of stones in the common bile duct.[75] ERCP is less invasive than surgery, but it too can lead to major complications, most notably pancreatitis. Radionuclide and ultrasonic scanning detect space-occupying lesions of the hepatobiliary tree.[75,76] PTHC provides a means of evaluating the intrahepatic bile ducts of patients with unexplained intrahepatic cholestasis or jaundice. Dilated intrahepatic bile ducts on PTHC indicate mechanical blockage of intrahepatic ducts. When no such blockage exists, the most likely cause of intrahepatic cholestasis is hepatic parenchymal disease.

Esophagogastroscopy is an important technique for evaluating and treating submucosal varices in patients with cirrhosis and portal hypertension. Splenoportography provides information about the status of the splenic and portal veins. Portal venography using three-dimensional CT with a multidetector row technique can render vascular maps that are superior to those obtained by classic angiography.[77] Such vascular maps show the extent and location of portosystemic collateral communications, which may include abnormalities in gastric, paraumbilical, and abdominal wall veins; esophageal varices; and splenorenal and gastrorenal shunts.

HEPATIC PATHOPHYSIOLOGY

PATTERNS OF LIVER PATHOLOGY

Cholestatic Disease

Cholestasis is impaired biliary flow and has a complex pathogenesis.[78] The usual cause of intrahepatic cholestasis, whether inherited or acquired, is dysfunction of the bile transporter.[79,80] In contrast, extrahepatic cholestasis most often results from mechanical blockage of the biliary tree. With cholestasis, high blood levels of biliary constituents are found, including hepatocellular enzymes (AP, γ-glutamyl transferase, 5′-nucleotidase, leukocyte alkaline phosphatase), immunoglobulin A, cholesterol, and various forms of bile salts and bilirubin. The most toxic of these is unconjugated bilirubin; high concentrations of unconjugated bilirubin cause membrane dysfunction and disrupt major metabolic pathways such as the tricarboxylic acid cycle and oxidative phosphorylation. Patients with cholestatic syndromes typically have marked increases in serum bile salts but normal or slightly elevated serum bilirubin. The clinical findings in cholestatic syndromes depend on the severity of the cholestatic disorder and its pathogenesis. Pruritus is a hallmark feature and results mainly from retained bile salts.[81] As cholestatic disorders increase in severity, jaundice develops. The stool becomes lighter in color and the urine darkens as bile pigments are diverted from the gut to the kidney for excretion. Some of the rest of the pathogenesis and symptomatology is often similar to that observed in hepatic cirrhosis.

Impairment can take place within the liver or distally within the biliary tract.[82] Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are classic examples of cholestasis. PBC is progressive inflammatory destruction of the cholangiocytes that line the bile ductus, and the disease is more common in women than men. PSC is associated with inflammation, and fibrosis of intrahepatic and extrahepatic bile ducts is more often

seen in men. It represents a severe inflammatory process and is often observed together with inflammatory bowel disease. Both PBC and PSC are associated with genetic and immunologic defects. Despite some differences between PBC and PSC, the end results are the same—bile ducts are destroyed, preventing bile from exiting the liver.

Obstructive Jaundice

A common reason for obstructive jaundice is gallstones. If gallstones block one of the hepatic ducts, the unobstructed side of the liver will increase its function to produce the necessary amount of bile. If the obstruction goes untreated, that part of the liver does not drain bile and the toxic effects of the retained bile eventually cause atrophy. If a gallstone occludes the common hepatic duct, bile cannot leave the liver and jaundice develops.

MECHANISMS OF CELL DEATH

Necrosis

Hepatocellular death often results from hypoxia or anoxia. Hypoxia decreases intracellular ATP. This stimulates breakdown of glycogen and anaerobic glycolysis, which raises lactic acid levels and lowers intracellular pH. Sudden precipitous decreases in ATP initiate a series of events that may culminate in hepatocellular necrosis. Such events include abrupt failure of the energy-dependent ion pumps that regulate intracellular fluid and electrolyte homeostasis. Plasma membranes become dysfunctional, and hepatocytes swell rapidly and then rupture and extrude their contents. This cellular debris, which contains hepatic enzymes and reactive chemicals such as aldehydes, lipid peroxides, and eicosanoids, incites an inflammatory response. The release of cytokines and chemoattractants recruits circulating neutrophils to the liver and augments the hepatic inflammation.[83]

Apoptosis

In contrast to necrosis, apoptosis is an energy-dependent process.[84] Most agents of liver disease (toxins, viruses, oxidants) can activate proapoptotic intracellular signaling pathways or proapoptotic cell-surface receptors such as Fas, tumor necrosis factor receptor (TNFR), and other members of the TNFR superfamily. Apoptosis has several ultrastructural hallmarks, including (1) a shrunken cell and nucleus; (2) condensed, marginated nuclear chromatin; (3) blebs on the plasma membrane; and (4) apoptotic bodies, which consist of membrane-bound cellular fragments and intact organelles. Epithelial and mesenchymal cells engulf the apoptotic bodies, and their lysosomes digest and recycle the contents of apoptotic bodies, such as intact mitochondria and nucleic acids. Apoptosis and necrosis may be related events at opposite ends of a spectrum of overlapping morphologic and mechanistic cell death processes.[84-86]

OXIDATIVE STRESS AND THE GLUTATHIONE SYSTEM

Hepatocytes continuously produce reactive O_2 species. During aerobic metabolism, mitochondria work nonstop transferring electrons from reduced substrates to O_2. This process involves the tetravalent reduction of O_2; the reduced O_2 atoms are incorporated into water. However, small amounts of O_2 undergo univalent or divalent reductions that give rise to superoxide and hydrogen peroxide. Nonparenchymal cells in the liver—Kupffer cells, endothelial cells, polymorphonuclear leukocytes, and macrophages—also can generate large amounts of reduced O_2 species and nitroradicals.[87]

In health, hepatocytes have many ways to keep oxidant concentrations within a safe range. Their defenses against oxidative injury include (1) micronutrients, such as vitamins C and E; (2) metal-sequestering proteins, such as ferritin; (3) enzymes that dispose of reactive O_2 species, such as catalase and superoxide dismutase; (4) enzymes that detoxify lipid peroxides, such as glutathione peroxidase; and (5) thiol-rich peptides, most notably glutathione (γ-glutamyl-cysteine-glycine). Glutathione is the single most important intracellular antioxidant.

The liver is the main site of glutathione synthesis. Accordingly, hepatocytes have high cytoplasmic concentrations of glutathione, ranging from 5 to 10 mmol/L.[40] Glutathione serves as a cofactor for major enzymes involved in the elimination of oxidants—notably glutathione peroxidase and thiol-disulfide exchangers. Glutathione peroxidase plays a key role as a detoxifier of organic peroxides and free radicals. Another enzyme, glutathione *S*-transferase, helps eliminate toxic electrophiles by attaching them to the free thiol of reduced glutathione (GSH). GSH also participates in nonenzymatic detoxification reactions, which yield oxidized glutathione and mixed disulfides of glutathione and protein.

ISCHEMIA-REPERFUSION INJURY

Ischemia-reperfusion injury results from both hypoxia during an ischemic episode and cytotoxic events during reperfusion.[88,89] Reperfusion induces the production of highly reactive chemicals that can cause necrosis or apoptosis, such as superoxide, hydrogen peroxide, and hydroxyl radicals. After relatively brief ischemic intervals, most of the injury is due to reperfusion. With more prolonged ischemia, hypoxia accounts for a larger fraction of the overall injury from ischemia-reperfusion.

Role of Xanthine Dehydrogenase/Xanthine Oxidase

The liver and intestines contain large amounts of xanthine dehydrogenase/xanthine oxidase (XDH/XO).[90] XDH catalyzes the rate-limiting step in nucleic acid degradation by using nicotinamide adenine dinucleotide (NAD) rather than O_2 as the electron acceptor. Thus, no O_2 radicals are produced in healthy tissue. However, ischemic conditions transform XDH to XO. Because XO reactions involve O_2, they produce free radicals. During reperfusion, XO-derived oxidants increase the production and release of leukotriene B_4 and platelet-activating factor, which promote neutrophil adherence and migration. When activated, neutrophils can wreak havoc on the microvascular circulation as they release proteases and physically disrupt the endothelial barrier. Liver injury, independent of the cause, imperils extrahepatic tissue because damaged hepatocytes spew out XO and other

inflammatory mediators. XO enters the bloodstream and binds to vascular endothelial cells in many organs. Endothelial cells produce superoxide, which reacts with nitric oxide (NO) to form peroxynitrite ($OONO^-$).[91] $OONO^-$ is intensely reactive and can increase the severity of injuries to local and remote tissues.[91]

Therapeutic agents that may confer protection from ischemia-reperfusion–induced injury include (1) antioxidants, (2) O_2 radical scavengers such as superoxide dismutase and dimethyl sulfoxide, (3) inhibitors of leukocyte adherence and migration, and (4) inhibitors of XO. For example, laboratory studies show that allopurinol (inhibits XO) treatment before induction of ischemia-reperfusion prevents the usual ischemia-reperfusion–related increases in microvascular permeability and epithelial cell necrosis.[4]

Hepatic Injury From Liver Transplantation

Preservation Injury. The University of Wisconsin solution protects the donor liver for approximately 24 hours. However, use of this solution for more than 24 hours may lead to microcirculatory disturbances (e.g., leukocyte and platelet adhesion) after liver transplantation. The adverse effects result from (1) depletion of hepatocellular antioxidants over time and (2) biochemical changes that lead to a profusion of reactive oxidants during reperfusion of the transplanted liver. Hypothermic preservation solutions also induce apoptotic changes in endothelial cells, which may engineer their destruction after graft implantation.

The pathogenesis of ischemia-reperfusion injury is complex.[91-94] Characteristic events include (1) Kupffer cell activation; (2) XO formation[95]; (3) profusion of oxidants—superoxide, NO, $OONO^-$) and hydroxyl radicals; (4) release of proinflammatory cytokines into the bloodstream; and (5) destruction of endothelial cells.[96]

BACTERIAL, VIRAL, AND IMMUNE INJURY

Endotoxins are lipopolysaccharide complexes of the outer membranes of gram-negative bacteria. All endotoxins have a common lipid component (lipid A), a core R antigen, and variable polysaccharide regions, which are bacterial strain–specific O-antigens. Lipid A binds to high-density lipoproteins in blood and other tissues, and it mediates the biologic actions common to endotoxins. Endotoxins bind more extensively to Kupffer cells than to hepatic parenchyma. They can induce hepatocellular or cholestatic injury directly or indirectly by activation of Kupffer cells and release of proinflammatory mediators (e.g., cytokines, eicosanoids). Like endotoxins, viruses may cause direct and indirect hepatocellular injury. Hepatotropic viruses and some herpesviruses can induce cytokine production, leading to lymphocyte- or macrophage-dependent cytotoxicity. Antigens on hepatocellular membranes may be primary targets of cell-mediated injury. Antibodies to such antigens are often increased selectively in patients with autoimmune hepatitis and primary biliary cirrhosis. Other potential antigenic foci for cell-mediated cytotoxicity include liver-specific lipoproteins and hepatic lectins, which may be targets in hepatitis B and other liver diseases.[4]

DRUG-INDUCED LIVER INJURY

Adverse reactions to drugs fall into two general categories: dose-related toxicity and idiosyncratic drug-induced injury. The former is predictable and develops in all individuals with escalation of the drug dose. The latter is a rare event, inducible with subclinical doses of the drug; it is most likely an immune-mediated injury that occurs in just a tiny fraction of those receiving the drug. Although obvious differences exist between the two categories of drug reactions, remarkable similarities also exist. For example, both categories involve covalent binding of drugs (or their metabolites) to endogenous macromolecules. This binding can lead to inactivation of important enzymes, depletion of intracellular antioxidants, and peroxidation of membrane lipids. The body's response to such molecular perturbations determines whether a drug-induced injury is categorized as dose related or idiosyncratic. When drug-induced subcellular damage induces immune sensitization, reexposure to even a very low dose of the sensitizing drug can cause severe liver injury (e.g., halothane hepatitis).[4]

The hepatotoxic effects of drugs and environmental substances usually involve CYP-mediated production of oxidants such as reduced O_2 species, carbon-based radicals, and nitroradicals. Examples include (1) carbon tetrachloride metabolism by CYP, which yields trichloromethyl radical—a highly toxic intermediate that induces centrilobular necrosis, and (2) metabolism of nitrofurantoin or other aromatic compounds, which generates free radical intermediates that induce hepatic injury. Similar to CYP of the smooth endoplasmic reticulum, mitochondrial electron transporters transform xenobiotics to reactive metabolites. For example, the nitroradicals that are formed during cocaine or nitrofurantoin metabolism reduce O_2 via flavoprotein reductases to yield superoxide and other oxidizing species. Redox cycling, as occurs with anthracycline chemotherapeutics and imidazole antimicrobials, is yet another source of toxic oxidizing species.

Oxidant formation during drug metabolism contributes to or causes liver injury by weakening the antioxidant defenses of hepatocytes. For example, acetaminophen and bromobenzene cause dose-related decreases in hepatocellular GSH, rendering the liver increasingly susceptible to necrosis. This increases the likelihood of oxidants damaging (1) proteins and enzymes, (2) phospholipids in membranes, and (3) nucleotides via activation of proteases, phospholipases, and endonucleases. Oxidative stress also can induce pathologic increases in cytosolic calcium by increasing Ca^{2+} uptake by hepatocytes while inducing release of Ca^{2+} from the endoplasmic reticulum or mitochondria. These events can lead to apoptosis, necrosis, or both.[4,84]

Drug-Induced Apoptosis

Apoptotic pathways can be activated by drug-induced mitochondrial injury.[84,97] The sequence of events may be (1) drug metabolism produces oxidants and depletes GSH; (2) oxidants induce mitochondrial injury, with release of cytochrome *c* and initiation of the mitochondrial membrane permeability transition; and (3) caspase is activated and triggers apoptosis.

Alcohol-Induced Disease

Alcoholism (five or more drinks per day) induces several patterns of liver injury—notably steatosis (fatty liver), alcoholic hepatitis, and cirrhosis. Steatosis develops in nearly everyone who drinks excessively, but cirrhosis develops in only 10% to 20% of these individuals. In contrast to the general population, people with alcoholic liver disease have a higher prevalence of health-related disorders—malnutrition, immune incompetence, and fluid and electrolyte imbalance. Such individuals are at increased risk for postoperative morbidity secondary to hemorrhage, sepsis, or cardiopulmonary decompensation (from alcoholic or cirrhotic cardiomyopathy).

Characteristic pathologic findings of alcoholic liver disease include (1) acetaldehyde-induced subcellular injury, (2) abnormalities in metabolism, (3) microvascular hypoxia, (4) increased O_2 and nitrogen radical formation, and (5) depletion of antioxidant defenses. Alcohol metabolism is integral to the pathology of alcoholic liver disease.[98-100] The rate-limiting step in ethanol metabolism is catalyzed by alcohol dehydrogenase (ADH).[101] This polymorphic zinc metalloenzyme has more than 20 different isozymes.[102] Although ADH activity exists in many tissues, hepatocytes metabolize more than 95% of the alcohol consumed. Genetic polymorphisms of ADH explain much of the variability in the relationship between ethanol consumption (dose) and liver disease (response). For example, the risk for alcoholic cirrhosis developing relates directly to polymorphisms at the *ADH2* gene locus (i.e., high frequency of the *B* allele). The oxidative metabolism of alcohol forms reduced nicotinamide adenine dinucleotide (NADH); these compounds inhibit the oxidation of fatty acids and 3-carboxyl acid cycles, promoting lipogenesis. Tumor necrosis factor-α (TNF-α) produced by Kupffer cells plays an important role in the genesis of alcoholic hepatitis.[103]

Hypoxic Liver Injury Resembles Alcohol-Induced Liver Injury

Hepatic injuries from hypoxic episodes and ingestion of ethanol are similar in many respects. Hypoxic injuries promote the release of proinflammatory cytokines, TNF-α, and interleukin-1 (IL-1) and IL-6. These signaling molecules lead to increased expression of adhesion molecules, decreased velocity and increased margination of neutrophils, increased platelet adherence, and decreased hepatic blood flow. Hepatoenteric ischemia releases cytokines and XO and leads to activation of complement. This intensifies the local inflammation and can induce systemic inflammatory responses, with subsequent pulmonary and cardiac injury.

Similarly, alcoholic-related liver injury promotes the release of proinflammatory mediators. Alcohol ingestion can markedly increase hepatic O_2 consumption, which would predispose to hypoxic injury. The earliest manifestations of ethanol-induced injury occur in acinar zone 3 (the centrilobular region), which has the highest ADH content and the lowest O_2 supply.

CIRRHOSIS AND PORTAL HYPERTENSION

Cirrhosis of the liver is a chronic condition that results from persistent hepatic injuries and is characterized by perturbations of the normal liver architecture by fibrotic scar tissue and regenerative nodules. The possible causes of cirrhosis include alcoholism, nonalcoholic steatohepatitis, viral hepatitides, and genetic disorders. Cirrhosis often progresses in an insidious, indolent manner. Hepatic fibrosis and vascular distortions cause continual, cumulative losses of liver function. Patients may remain unaware of their condition until approximately 70% of their liver is destroyed—that is, the innate and abundant physiologic reserves of the liver are depleted, and the body can no longer compensate for additional losses of viable hepatocytes.

The early clinical manifestations of cirrhosis include anorexia, abdominal discomfort, fatigue, weakness, nausea, vomiting, and jaundice. As the severity of cirrhosis increases, its signs and symptoms become overt; a common and serious complication is portal hypertension, which results in myriad and pervasive abnormalities that affect every tissue in the body. The most ominous changes include ascites, portosystemic shunting, renal and pulmonary dysfunction, hepatic encephalopathy, and gastroesophageal varices, which are associated with devastating events, including massive hemorrhage, sepsis, renal failure, coma, and death.

Pathogenesis of Portal Hypertension

Characteristic features of cirrhosis-induced portal hypertension include elevated resistance to sinusoidal blood flow, increased flow of blood through preportal vessels, and high rates of blood flow through portocaval collateral vessels.[104]

The complex pathogenesis of cirrhosis-induced portal hypertension has been explained using both "backward" and "forward" metaphors, which are not mutually exclusive. According to the backward concept, proliferation of perisinusoidal fibrous tissue leads to increased resistance to portal venous flow. Based on the physics of blood flow (i.e., pressure = flow × resistance), such an increase in resistance at a constant rate of portal venous flow increases portal venous pressure.

On the other hand, when portal hypertension is caused solely by prehepatic increases in portal venous resistance, such as that produced by experimental narrowing of the portal vein, the resultant changes include (1) increased mesenteric vascular resistance, (2) decreased mesenteric blood flow, (3) decreased splanchnic venous O_2 saturation, and (4) increased arteriovenous O_2 content gap in the mesenteric blood. Such changes are in diametric opposition to those associated with cirrhosis-induced portal hypertension. Yet, patients with liver cirrhosis have elevated blood levels of endogenous vasodilators, widespread arteriovenous shunt formation, and high cardiac output with low total peripheral resistance. Therefore, the forward concept could explain some portion of the portal pressure elevation that is caused by cirrhosis-induced changes in the systemic and splanchnic arterial circulation.

Cirrhosis-induced portal hypertension results from both increased intrahepatic vascular resistance (as a result of the development of fibrosis) and increased blood flow through the portal vein and hepatic artery. The deposition of collagen within the liver is the main mechanism

responsible for the increase in resistance within the liver as cirrhosis develops. In other words, the decrease in total cross-sectional area of hepatic sinusoids is one of the main reasons behind the increase in resistance to portal flow.[105] Fibrosis and tissue injury lead to endothelial dysfunction and intrahepatic vasoconstriction with development of intrahepatic vascular shunts between afferent and efferent vessels within the liver.[106,107]

An increase in portal pressure is one of the most important causes of hyperactivity in endothelial cells within the splanchnic and systemic circulation. The intestinal microcirculation is the first part of the vasculature to sense an increase in portal pressure. Responses follow from the arteries in the splanchnic and then the systemic circulation. An increase in splanchnic blood flow is the result of a decrease in splanchnic (mesenteric and splenic) arterial resistance.[105] Both local and systemic neurogenic and biochemical mechanisms contribute to the development of hyperdynamic circulatory syndrome, which is defined as the combination of decreased vascular resistance, increased cardiac output, and increased circulating blood volume.

NO has an indisputable role in the pathogenesis of hemodynamic disorders in liver cirrhosis. Chronic administration of a nitric oxide synthase (NOS) inhibitor may completely normalize the parameters of hyperdynamic circulation but only partially decrease the degree of mesenteric vasodilation.[108,109] This implies that other vasodilators participate in the decrease in mesenteric vascular resistance.

Prostacyclin (PGI_2) is a powerful vasodilator produced by endothelial and epithelial cells. Its production has been well documented in patients with liver cirrhosis.[105] CO, endocannabinoids, neuropeptide Y, and bradykinin are the endogenous vasodilators with the most important vasodilatory roles in patients with liver cirrhosis and portal hypertension. Other endogenous vasodilating factors include glucagon, histamine, vasoactive intestinal polypeptide, substance P, cholecystokinin, estrogen, ammonia, endotoxins, adenosine, and biliary acids. These numerous powerful compounds are responsible for the persistent vasodilation seen in advanced liver cirrhosis. A reduction in the release of some endogenous vasoconstrictors also may play a role in the development of vasodilation; for example, in patients with advanced liver disease, a decrease in vasopressin concentrations has been demonstrated.[110]

Collateral vessels connecting portal and systemic circulation are formed through the enlargement of preexisting vessels and angiogenesis.[111] These collaterals further increase already elevated portal blood flow and aggravate the symptoms of portal hypertension.[111]

An increase in the production of NO derived from endothelial nitric oxide synthase (eNOS) is responsible not only for vasodilation but also for thinning of arterial walls in the splanchnic systemic circulation. Arterial thinning is an important factor in the pathogenesis of hepatic cirrhosis. Treatment with a NOS inhibitor significantly improves wall thickness and attenuates hyperdynamic circulatory syndrome.[112,113]

Overall, hemodynamic disorders in patients with cirrhosis result not only from elevated levels of vasodilatory molecules but also from increased production of vasoconstrictive mediators. For example, by lowering arterial blood pressure, vasodilators trigger baroreceptor-mediated increases in sympathetic nervous system tone, activate the renin-angiotensin-aldosterone system, and promote the release of antidiuretic hormone. In addition, cyclooxygenase-1 production increases, increasing formation of PGH_2 and thromboxane A_2, which in turn augments vasoconstrictive responses to α-adrenergic stimulation.[114] The release of thromboxane A_2 by activated Kupffer cells along with endothelin-1 (ET-1), a potent vasoconstrictor produced by sinusoidal endothelial cells, is a major contributor to increases in portal pressure.[115] It is interesting to note that endothelins also participate in an autocrine loop that counteracts the development of liver fibrosis. Thus, administration of endothelin receptor antagonists as potential therapeutic agents could cause more harm than benefit in patients with liver cirrhosis.[105]

Vascular structures within cirrhotic livers can originate from preexisting sinusoids (in the postnecrotic area of connective tissue) or from pathologic angiogenesis.[116] The angiogenesis develops along two pathways. The first is the process of wound healing typical of fibrogenic chronic liver disease. It is characterized by overexpression of cytokines and several growth factors, such as platelet-derived growth factor, transforming growth factor-β1 (TGF-β1), fibroblasts, and others. The second is the neoangiogenesis that is stimulated in hepatic tissue by a progressive increase in tissue O_2 deprivation. This mechanism is enhanced by an increase in the contribution of the hepatic artery to sinusoidal blood flow, which becomes even more arteriole-like. Hepatocytes adjust to the high O_2 tension and bring about changes in the structure of sinusoids, leading to impairment in the diffusion of O_2 from the sinusoids to the hepatocytes, followed by up-regulation of proangiogenic pathways.[117] Persistent injury of hepatocytes eventually creates a vicious circle—hypoxia promotes angiogenesis, then fibrogenesis and cirrhosis, and back to hypoxia.[118]

The hepatic venous pressure gradient, which is the difference between wedge hepatic venous pressure and free hepatic venous pressure, is considered one of the most important determinants of the progression of hepatic cirrhosis and portal hypertension.[118] The normal hepatic venous pressure gradient is approximately 3 to 5 mm Hg; above 10 to 12 mm Hg, chronic liver disease becomes a serious systemic disorder with potentially life-threatening complications. Under these conditions, both systemic and extrahepatic collateral circulation develop enough to allow gut-derived antigenic matter to enter the systemic circulation. This leads to activation of the innate immune system and increased release of vasoactive compounds, particularly NO.[119] Reinforced and aggravated dilation within the splanchnic vasculature leads to sequestration of blood volume within the splanchnic vascular bed, producing both splanchnic hypervolemia and central hypovolemia.[118]

The described changes are associated with a failure of one of the most important functions of the liver, namely detoxification of potentially harmful compounds, including bacterial end products from the splanchnic and systemic circulation.[120]

Thus, splanchnic vasodilation results from the following mechanisms: (1) increased splanchnic arterial NO production; (2) release of other vasodilating compounds (e.g., endocannabinoids, CO, prostaglandins, glucagon, and others); (3) decreased ability of the splanchnic vasculature to constrict; (4) development of mesenteric angiogenesis mediated by vascular epithelial growth factors; and (5) development of portosystemic connections as a result of dilation of preexisting blood vessels, vascular remodeling, and angiogenesis.[111,121] These collaterals lead to even further increases in the already elevated portal venous blood flow, which exacerbates portal hypertension.[111]

Cardiovascular Dysfunction

The pathophysiologic changes within the splanchnic vasculature form the basis of subsequent changes in systemic hemodynamics. Hyperdynamic circulation (low total peripheral resistance, high cardiac output, and increased blood volume) is a hallmark of cirrhosis and portal hypertension.[122] Generally, systemic arterial pressure is slightly below normal, the heart rate is mildly increased, and central filling pressure is normal. Mixed venous O_2 saturation is elevated, and the arteriovenous O_2 content gap is low. Overall, the hemodynamic profile resembles a peripheral arteriovenous fistula. Indeed, advanced liver disease causes extensive, widespread arteriovenous communications (collateral vessels) within the splanchnic organs, lungs, muscle, and skin. As discussed earlier, high blood flow through these collateral vessels results from cirrhosis-induced increases in endogenous vasodilators.[123-127] Endogenous vasodilators also explain why severe liver disease diminishes cardiovascular responses to physiologic and pharmacologic vasoconstrictors. The main pathophysiologic feature for an anesthesiologist to keep in mind is that these patients are in a constant state of vasodilation, their vasoconstriction is impaired, and their response to vasoconstrictors is decreased. They exhibit both central hypovolemia (within the main, fast compartment of the vasculature) and splanchnic hypervolemia (within the secondary, slower circuit), and mobilization of blood from unstressed to stressed volume is also impaired (see Chapter 21, Figs. 21-9 to 21-11).

Control of Circulatory Volume and Renal Dysfunction

Renal dysfunction typically develops in patients with cirrhosis and portal hypertension. The glomerular filtration rate (GFR) steadily decreases, and the renal tubules avidly retain sodium, with no overt glomerular or tubular injury. Urinalysis is unremarkable except for a low sodium level.

Avid renal retention of sodium is integral to the pathophysiology of cirrhosis and portal hypertension. Volume receptors that detect low effective plasma volume stimulate the sympathetic nervous system and lead to release of renin from the kidney.[128-130] This increases the production of angiotensin II and aldosterone, which enhances renal tubular uptake of sodium. Blood norepinephrine levels are inversely correlated with renal blood flow. Both norepinephrine and angiotensin II redistribute intrarenal blood flow in a manner that increases retention of sodium by the kidney. Additional factors that may augment sodium retention include the kallikrein-kinin system and some potent renal vasoconstrictors, such as $F_{2\alpha}$-isprostanes[131] and ET-1. Renal vasoconstrictors are likely inducers of the renal dysfunction that accompanies cirrhosis and ascites.[132] Under such conditions, endogenous vasodilators (e.g., prostaglandins) become increasingly important to counteract intense vasoconstriction and protect renal blood flow. Accordingly, inhibitors of prostaglandin synthesis can significantly decrease renal blood flow and GFR, increasing the risk for acute renal injury.

The main causes of acute renal failure (ARF) in this patient population are prerenal failure and acute tubular necrosis (ATN). Prerenal failure usually results from hypovolemia, sepsis, or type 1 hepatorenal syndrome (HRS).[133-139] End-stage liver disease puts patients at high risk for systemic hypovolemia as a result of (1) the formation of profuse ascites,[132] (2) aggressive diuretic therapy, (3) gastrointestinal hemorrhage, and (4) sequestration of blood in the splanchnic vasculature. Therapy for prerenal ARF focuses on restoration of blood volume and renal blood flow. The most common cause of ATN is prerenal ARF—when it is protracted and severe enough to cause ischemic renal tubular injury. Other causes of ATN include nephrotoxic substances such as radiocontrast agents and nonsteroidal antiinflammatory drugs. Unlike prerenal ARF, no specific therapy exists for ATN; treatment is mainly supportive.[135,140,141]

Prerenal failure secondary to type 1 HRS has a poor prognosis. In many instances, the only effective therapy is liver transplantation. Interventions that may transiently improve renal performance in such patients include (1) intravenous vasoconstrictors, notably terlipressin, norepinephrine, and midodrine, in combination with octreotide, and (2) devices or procedures that support the liver, such as a molecular adsorbent recirculation system or transjugular intrahepatic portosystemic shunt.[135,140-143]

Thus, systemic vasodilation leads to a decrease in effective blood volume, a decrease in cardiac output followed by an increase in antidiuretic hormone production, sympathetic nervous system stimulation, and activation of the renin-angiotensin-aldosterone system. All this leads to sodium and water retention and finally to formation of ascites. In more extreme situations it is associated with severe renal arterial vasoconstriction, decrease in renal blood flow, and HRS.[144]

Pulmonary Dysfunction

Hepatopulmonary syndrome is presented as a defect in arterial oxygenation induced by dilation in the pulmonary vascular bed in the setting of hepatic cirrhosis.[145]

Pulmonary vasculature undergoes changes similar to those observed in the systemic circulation. Severe dilation of the pulmonary vasculature, intrapulmonary arteriovenous shunts, portopulmonary shunts, and decreased hypoxic pulmonary vasoconstriction can cause severe ventilation-perfusion abnormalities in the lung. Pulmonary vasodilation and increased flow through intrapulmonary shunts leads to increased passage of mixed venous blood from pulmonary arteries to pulmonary veins. An increase in wall thickness of small

veins and particularly capillary walls limits the alveolar-capillary diffusion. Atelectasis or restrictive pulmonary pathophysiology secondary to ascites or pleural effusion can further aggravate pulmonary function. Erythrocyte 2,3-diphosphoglycerate levels often increase and shift the oxyhemoglobin dissociation curve rightward. Ventilation-perfusion mismatching occurs because of atelectasis or restrictive pulmonary pathophysiology secondary to ascites or pleural effusion.

Orthodeoxia (a decrease in arterial oxygenation in standing position) is one of the characteristic symptoms of hepatopulmonary syndrome. Shunt flow, which cannot adjust easily to activation of baroreceptors through the sympathetic nervous system, leads to severe decrease in pulmonary flow and orthodeoxia, often associated with shortness of breath.[145]

Hematologic Dysfunction

Coagulopathies and other hematologic abnormalities are common with end-stage liver disease. Anemia often develops for many reasons, including gastrointestinal bleeding, hemolysis, hypersplenism, malnutrition, vitamin deficiencies, bone marrow depression, and plasma volume expansion. As the liver begins to fail, it cannot make enough vitamin K–dependent procoagulants. When factor VII drops by 70% of the normal level, the PT becomes prolonged. Thrombocytopenia and thrombopathy develop as a result of (1) splenic sequestration syndrome, (2) bone marrow suppression secondary to alcoholism or medications such as interferon, or (3) platelet destruction from immune-mediated, platelet-associated IgG. Dysfibrinogenemia—the activation of fibrinolysis—may develop. Laboratory results typically include increased D-dimer levels, increased fibrin degradation products, and normal or nearly normal fibrinogen levels. However, before attributing any fibrinolytic disorder to liver failure, it is essential to conduct a thorough search for all possible reversible causes of disseminated intravascular coagulation.

Gastrointestinal Complications

Gastrointestinal hemorrhage is always a concern; nearly a third of cirrhosis-related deaths are due to ruptured esophagogastric varices.[146] Portal hypertensive gastropathy, esophageal varices, or gastric varices develop in most patients with cirrhosis and portal hypertension.[147] Hemorrhage from esophageal varices occurs more often than hemorrhage from gastric varices, but the latter is generally more severe than the former. Variceal size is a good predictor of when varices will rupture, and rates of variceal enlargement parallel the severity of liver disease. Less than 2 years after cirrhosis and portal hypertension are diagnosed, 20% to 30% of patients experience a variceal hemorrhage.[147] The first hemorrhage is acutely lethal in approximately 7% of cases, with a 6-week mortality rate of approximately 30%. Untreated survivors of variceal hemorrhage have a 60% chance of rebleeding within 2 years; if this should occur, the death rate would be 40% to 50%.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis is another complication of hepatic cirrhosis. Impaired intestinal transport of food resulting in bacterial overgrowth in cirrhotic patients is probably one of the most important causes of bacterial translocation.[144,148] Observations that prokinetic drugs decrease intestinal overgrowth and bacteria translocation support this notion.[149] Mucosal hypoxia as a consequence of portal hypertension, vascular stasis, and intestinal mucosal congestion, combined with alteration in systemic immune defense systems, leads to development of bacterial peritonitis.[144]

Endocrinopathies

Because the liver produces, processes, and metabolizes many endocrine substances, advanced liver disease leads to endocrine abnormalities. For example, plasma levels of glucagon and growth hormone increase with liver disease and contribute to insulin resistance. Insulin-like growth factor–1 decreases in children with liver disease and adversely affects their growth and development. Gonadal dysfunction develops in men and women because of disruptions in the metabolism of sex hormones. Men undergo feminization, with the development of gynecomastia, testicular atrophy, infertility, and impotence. In women, oligomenorrhea, amenorrhea, and infertility are common.

Hepatic Encephalopathy

Hepatic encephalopathy is a complex neuropsychiatric syndrome that develops in 50% to 70% of patients with cirrhosis. Pathophysiologic phenomena that contribute to the syndrome include (1) hepatobiliary dysfunction, (2) decreased hepatic blood flow, and (3) extrahepatic diversion of portal venous flow through collateral vessels (i.e., portocaval blood flow). Various gut-derived chemicals, including mercaptans, phenols, ammonia, short-chain fatty acids, and manganese, may play a role in the pathogenesis of hepatic encephalopathy. Central nervous system depression may result from false neurotransmitters (e.g., octopamine) or endogenous ligands that increase central inhibitory outflow, such as activators of γ-aminobutyric acid and benzodiazepine receptors. Other possible contributors to encephalopathy are disruptions of the blood-brain barrier and defective cerebral energy metabolism. The pathogenesis and management of hepatic encephalopathy are described in detail elsewhere.

Pathogenesis of Ascites

Cirrhosis-induced portal hypertension leads to massive increases in total body water, edema, and ascites formation.[150] The problem can be traced to excessive sodium retention by the kidney (Fig. 22-8).[1,151] However, the principal driver of the sodium retention is unclear. One explanation—the overflow model—is that hepatic cirrhosis gives rise to chemicals that stimulate the kidney to retain sodium. A second explanation—the underfill model—is that renal retention of sodium is a normal physiologic response to a low effective blood volume.

The essence of the overflow model is that excessive renal retention of sodium causes intravascular volume to expand, with two major and direct consequences: (1) plasma oncotic pressure decreases, with the liver unable to produce sufficient albumin to correct the hypoalbuminemia, and (2) portal hydrostatic pressure increases (i.e., portal hypertension). The combination of low oncotic pressure and portal hypertension accelerates the formation

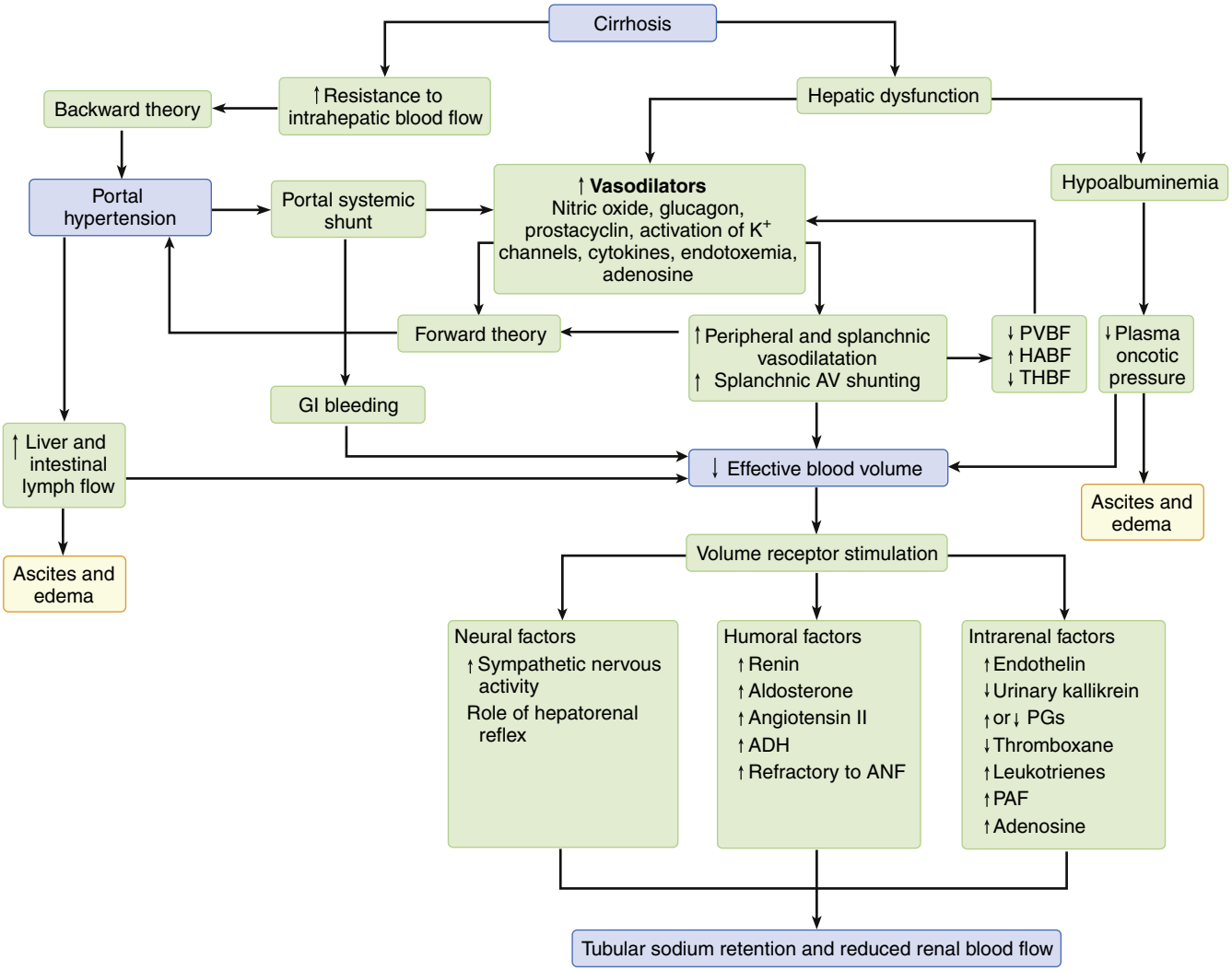


Figure 22-8. Schematic of pathways for cirrhosis-induced portal hypertension: the forward and backward theories. Cirrhosis and portal hypertension induce circulatory changes that decrease effective blood volume. This activates volume receptors and stimulates neurohumoral and intrarenal reflexes, which decreases renal blood flow and increases renal retention of sodium. *ADH,* antidiuretic hormone; *ANF,* atrial natriuretic factor; *AV,* arteriovenous; *HABF,* hepatic arterial blood flow; *PAF,* platelet-activating factor; *PGs,* prostaglandins; *PVBF,* portal venous blood flow; *THBF,* total hepatic blood flow. *(Reprinted with permission from Mushlin PS, Gelman S: Anesthesia and the liver. In Barash PG, Cullen BF, Stoelting RK, editors:* Clinical anesthesia, *ed 4. Philadelphia, 2001, Lippincott Williams & Wilkins, p 1088.)*

of edema and ascites. A pivotal assumption of the overflow model is that a cirrhosis-induced mediator causes normal kidneys to retain sodium and water despite an overfilled intravascular compartment. At present, no such mediator (or process) has been identified.

The underfill model recognizes that homeostatic reflexes work in concert with the kidney to tightly regulate intravascular volume. This model posits that cirrhosis causes the effective plasma volume to decrease, which activates homeostatic mechanisms to retain sodium and water. That is, with decreases in arterial volume, whether from arterial dilation or low cardiac output, the kidney is instructed to retain sodium and water. Cirrhosis-induced decreases in effective plasma (or arterial) volume can result from arterial dilation, intravascular volume depletion, or both. Although the latter has many possible causes, edema and ascites formation from unbalanced Starling forces are sufficient to significantly decrease intravascular volume. The overflow and underfill models are not mutually exclusive; a primary defect in sodium excretion could be the major factor in earlier stages of cirrhosis, whereas a low effective plasma volume could be the more important factor in progression to end-stage liver disease.

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Chapter 23

Renal Physiology, Pathophysiology, and Pharmacology

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Key Points

- To cross the filtration barrier between plasma and tubular fluid, a molecule must pass in succession through the endothelial fenestrations, glomerular basement membrane, and epithelial slit diaphragm. The capillary endothelium restricts the passage of cells, but the basement membrane filters plasma proteins. All three layers contain negatively charged glycoproteins, which retard the passage of other negatively charged proteins. Thus, the filtration barrier is size selective and charge selective.
- A primary determinant of glomerular filtration rate (GFR) is glomerular filtration pressure, which depends not only on renal artery perfusion pressure but also on the balance between afferent and efferent arteriolar tone. In the presence of decreased afferent arteriolar pressure or blood flow, low levels of catecholamines, angiotensin, and arginine vasopressin (AVP) induce preferential efferent arteriolar constriction, which maintains glomerular filtration pressure. This is reflected by an increase in calculated filtration fraction (FF), which is the GFR expressed as a fraction of the renal plasma flow (RPF). High levels of catecholamines and angiotensin (but not AVP) increase afferent arteriolar tone and decrease glomerular filtration pressure (and GFR) out of proportion to RPF, with a consequent reduction in FF.
- Tubuloglomerular feedback may be a primary mechanism in renal autoregulation. When GFR is increased, distal tubular NaCl delivery is enhanced. The increase in chloride is sensed by the macula densa, triggering release of renin from the adjacent afferent arteriole. Angiotensin is elaborated and arteriolar constriction ensues, which decreases GFR. When the thick ascending loop becomes ischemic, reabsorption of NaCl ceases, the ability of the tubule to concentrate urine is lost, and theoretically, intractable polyuria should result. However, the increased delivery of NaCl to the macula densa may be the trigger for angiotensin-mediated arteriolar constriction, which decreases GFR, induces oliguria, conserves intravascular volume, and protects the organism from dehydration—so-called acute renal success. Autoregulation enables the kidney to maintain solute and water regulation independently of wide fluctuations in arterial blood pressure. Urinary flow rate is not subject to autoregulation. Tubular water reabsorption determines urinary flow rate and is closely related to the hydrostatic pressure in the peritubular capillaries. Hypotension of any cause results in decreased urinary flow rate that may be correctable only when arterial blood pressure is restored toward normal.
- The tubule has an enormous capacity for reabsorption of water and NaCl. Each day, 180 L of protein-free glomerular ultrafiltrate is formed, of which almost 99% of the water and 99% of the sodium is reabsorbed. Many other filtered substances are completely reabsorbed, but some, such as glucose, have a maximum rate of tubular reabsorption (tubular maximum). Once this rate is exceeded, glycosuria results, increasing in proportion to the filtered load. The ability of the kidney to concentrate urine is dependent on the interaction of at least three processes: (1) generation of a hypertonic medullary interstitium by the countercurrent mechanism and urea recycling, (2) concentration and then dilution of tubular

KEY POINTS—cont'd

fluid in the loop of Henle, and (3) the action of antidiuretic hormone (now known as arginine vasopressin) in increasing water permeability in the last part of the distal tubule and collecting ducts. The juxtaglomerular apparatus consists of three groups of specialized tissues. In the afferent arteriole, modified fenestrated endothelial cells produce renin; in the juxtaposed distal tubule, cells of the macula densa act as chemoreceptors; and in the glomerulus, mesangial cells have contractile properties. Together these provide an important regulating system for arterial blood pressure, salt, and water homeostasis.

- Two mutually dependent but opposing neurohormonal systems maintain blood pressure, intravascular volume, and salt and water homeostasis. The sympathoadrenal axis, the renin-angiotensin-aldosterone system, and AVP defend against hypotension and hypovolemia by promoting vasoconstriction and salt and water retention. The prostaglandins and natriuretic peptides defend against hypertension and hypervolemia by promoting vasodilation and salt and water excretion.
- Hypothalamic osmoreceptors are sensitive to increases in serum osmolality of as little as 1% above normal. The threshold for AVP secretion (and sensation of thirst) is between 280 and 290 mOsm/kg. Even mild dehydration results in rapid antidiuresis, and urine osmolality can increase from 300 to 1200 mOsm/kg as plasma AVP levels rise from 0 to 5 pg/mL. Decreases in intravascular volume also stimulate AVP secretion, mediated by stretch receptors with vagal afferents from the left atrium and pulmonary veins.
- Serum creatinine reflects the balance between creatinine production from muscle and creatinine excretion by the kidney, which is dependent on GFR. Creatinine generation rate varies with muscle mass, physical activity, protein intake, and catabolism. However, when these processes are in equilibrium and renal function is stable, serum creatinine is a useful marker of GFR. The relationship between serum creatinine and GFR is inverse and exponential. A doubling of the serum creatinine implies a halving of GFR. However, limited sensitivity and specificity for renal injury combined with the delayed rise in creatinine that follows an acute reduction in GFR may limit the clinical utility of serum creatinine.
- Given the widely acknowledged limitations associated with traditional markers of renal injury, recent interest has focused on developing novel biomarkers to enable early detection of renal injury. Many candidate markers are currently under investigation to evaluate their validity and potential clinical utility. However, they remain investigational at the current time, and serum creatinine remains the imperfect gold standard for clinically relevant AKI.
- With an incidence of 20% to 25% following cardiac surgery, perioperative acute kidney injury (AKI) is associated with an increased incidence of adverse outcomes, including hospital mortality. Potential mechanisms are complex and multifactorial and may include ischemia-reperfusion injury, up-regulation of inflammatory cascades, endothelial dysfunction, multiple sources of embolic injury, and multiple nephrotoxins, including recent radiocontrast exposure and cardiopulmonary bypass–related hemolysis with associated hemoglobinuria.
- All anesthetic techniques and drugs tend to decrease GFR and intraoperative urine flow. Some drugs also decrease renal blood flow (RBF), but filtration fraction is usually increased, implying that angiotensin-induced efferent arteriolar constriction limits the decrease in GFR. However, these effects are much less significant than those caused by surgical stress or aortic cross-clamping and usually resolve promptly after emergence from anesthesia. Any anesthetic technique that induces hypotension will result in decreased urine flow because of altered peritubular capillary hydrostatic gradients, even if renal autoregulation is preserved (as is usually the case during anesthesia).
- Clinically significant renal injury with the use of low-flow sevoflurane anesthesia has not been reported in patients, even with moderate preexisting renal dysfunction. The relationship among compound A formation, biochemical injury, and clinically relevant renal dysfunction remains unclear and unproven. Nonetheless, the

KEY POINTS—cont'd

current U.S. Food and Drug Administration (FDA) guidelines, which recommend a fresh gas flow of at least 2 L/minute when using sevoflurane for longer than 2 MAC (minimal alveolar concentration of anesthetic)-hours to limit exposure to compound A, should be followed. Regardless of the position of an aortic cross-clamp, RBF may be significantly decreased during surgical manipulation of the aorta, presumably because of direct compression or reflex spasm of the renal arteries. After release of a suprarenal cross-clamp, RBF increases above normal (reflex hyperemia), but GFR may remain depressed to one third of control for up to 2 hours. After 24 hours, GFR may still be only two thirds of control. Urine flow may be maintained despite marked impairment of tubular functions (concentrating ability, sodium, and water conservation), resembling an attenuated form of acute tubular necrosis. Cross-clamp times longer than 50 minutes have been associated with prolonged depression of GFR and transient azotemia (also see Chapter 69).

- No intervention has proven effective for prevention or treatment of perioperative AKI. Although several therapies have shown some benefit in selected studies or meta-analyses (e.g., fenoldopam, goal-directed therapy), meaningful conclusions can be made only with additional large trials to clarify the potential role of such interventions.

The kidneys contain approximately 2×10^6 nephrons, each of which consists of a glomerulus and a tubule, which empties into a collecting duct. These functional units collectively enable the kidneys to maintain a remarkably stable interior milieu, despite large fluctuations in fluid and solute intake. Together they regulate intravascular volume, osmolality, and acid-base and electrolyte balance and excrete end products of metabolism and drugs. Urine is formed by the combination of glomerular ultrafiltration and tubular reabsorption and secretion. The nephron also elaborates hormones that contribute to fluid homeostasis (renin, prostaglandins, kinins), bone metabolism (1,25-dihydroxycholecalciferol), and hematopoiesis (erythropoietin). The function of the nephron is closely integrated with the vascular supply of the kidney (Fig. 23-1).

THE GLOMERULUS (RENAL CORPUSCLE)

The glomerulus consists of five distinct components: capillary endothelium, glomerular basement membrane, visceral epithelium (which together make up the filtration barrier), parietal epithelium (Bowman capsule), and mesangium (interstitial cells).[1,2] The glomerular tuft, a highly convoluted series of capillary loops, is fed by the afferent arteriole and drains into the efferent arteriole (Fig. 23-2).

The capillary endothelium synthesizes nitric oxide and endothelin-1, which, by governing vasodilation and vasoconstriction, control renal blood flow. The endothelium has fenestrations about 70 to 100 nm in diameter and lies atop the glomerular basement membrane, which has a total cross section of about 350 nm. The visceral epithelium, which is applied to the underside of the basement membrane, consists of podocytes with filamentous, interdigitating foot processes that contain contractile actin filaments. Filtration slits form 25- to 60-nm gaps between the foot processes and are bridged by a protein membrane slit diaphragm, whose size and permeability are altered by contraction of the foot processes.

The blind parietal epithelial sac of the renal tubule is invaginated around the capillary tuft as Bowman capsule and meets the visceral epithelium at the vascular pole of the glomerulus. Bowman space, between the visceral and parietal layers of the capsule, becomes the lumen of the proximal tubule at the urinary pole of the glomerulus, and the parietal endothelium merges with the cuboidal cells of the proximal tubule.

The central or interstitial mesangial cells are specialized pericytes with numerous functions, including structural support, matrix elaboration, and phagocytosis. They contain myofilament-like threads of actin and myosin. Mesangial contraction in response to vasoactive substances such as angiotensin II restricts blood flow to fewer capillary loops. The mesangial cells thereby regulate the effective glomerular surface area for filtration and, as a consequence, glomerular permeability.[3]

FORMATION OF THE GLOMERULAR ULTRAFILTRATE

To cross the filtration barrier between plasma and tubular fluid, a molecule must pass in succession through the endothelial fenestrations, the glomerular basement membrane, and the epithelial slit diaphragm. The capillary endothelium restricts the passage of cells, but the basement membrane filters plasma proteins. All three layers contain negatively charged glycoproteins, which retard the passage of other negatively charged proteins. Thus, the filtration barrier is both size selective and charge selective.[1] Molecules with an effective radius of less than 1.8 nm (e.g., water, sodium, urea, glucose,

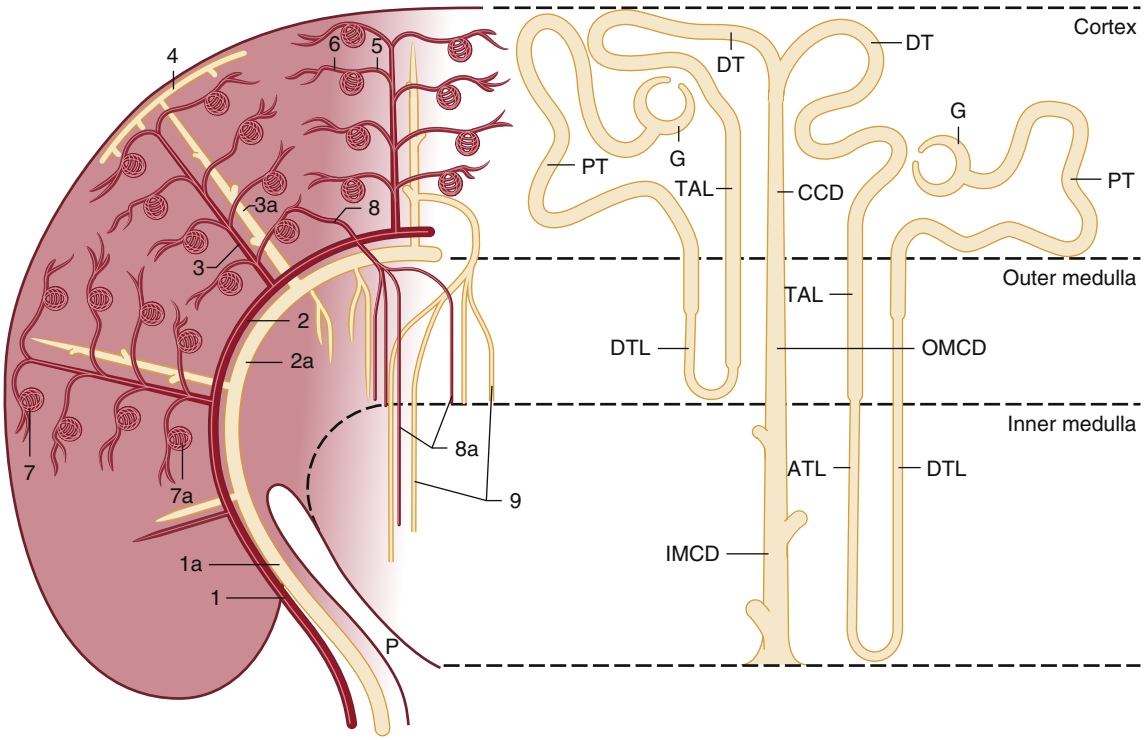


Figure 23-1. Anatomic relationships of the nephron and the renal vasculature. The left side of the diagram represents the renal vasculature as distributed through the inner medulla, outer medulla, and cortex. Arteries are drawn as *solid lines*, veins as hollow tubes. The renal artery divides serially into interlobar arteries (1), arcuate arteries (2), and interlobular arteries (3). The afferent arterioles (5) branch off laterally and provide the capillary tufts of the renal glomeruli in the outer cortex (7a), whose efferent arterioles (6) supply the cortical capillary network (not shown). In the juxtamedullary zone (7b), the efferent arterioles become the vasa recta, which are closely applied to the long loops of Henle (8, 8a, 9). The venous drainage consists of stellate veins (4), interlobular veins (3a), arcuate veins (2a), and interlobar veins (1a). The right side of the diagram represents two nephrons. On the left is the more numerous superficial cortical nephron with a short loop of Henle. On the right is the juxtamedullary nephron with a long loop of Henle, which dives deep into the inner medulla to generate the hyperosmotic interstitium required for tubular urine concentration. *ATL*, Ascending thin loop of Henle; *CCD*, cortical collecting duct; *DT*, distal tubule; *DTL*, descending thin loop of Henle; *G*, glomerulus; *IMCD*, inner medullary collecting duct; *OMCD*, outer medullary collecting duct; *PT*, proximal tubule; *TAL*, thick ascending loop. *(From Kriz W: A standard nomenclature for structures of the kidney,* Kidney Int *33:1-7, 1988.)*

inulin) are freely filtered. Molecules larger than 3.6 nm (e.g. hemoglobin, albumin) are not filtered. Filtration of molecules between 1.8 and 3.6 nm depends on their electrical charge. Cations are filtered, whereas anions are not. In glomerulonephritis the negatively charged glycoproteins are destroyed, polyanionic proteins are filtered, and proteinuria ensues.

Glomerular ultrafiltration is governed by the balance of Starling forces regulating fluid flux across the filtration barrier.[4] Glomerular filtration rate (GFR) depends on the permeability of the filtration barrier and the net difference between the hydrostatic forces pushing fluid into Bowman space and the osmotic forces keeping fluid in the plasma:

$$GFR = K_{uf}\,[(P_{gc} - P_{bs}) - (\pi_{gc} - \pi_{bs})] \qquad [1]$$

where uf = ultrafiltration, gc = glomerular capillary, and bs = Bowman space.

The ultrafiltration coefficient, K_{uf}, reflects capillary permeability and glomerular surface area. Renal arterial pressure determines the hydrostatic pressure in the glomerular capillary, P_{gc}. Afferent arteriolar plasma flow determines the plasma oncotic pressure (π_{gc}): rapid blood flow washes out osmotically effective molecules and lowers π_{gc}, and vice versa.

THE JUXTAGLOMERULAR APPARATUS

The juxtaglomerular apparatus provides a remarkable integration of tubular and glomerular structure and function (Fig. 23-3). A modified portion of the thick ascending limb, the macula densa, is applied to the glomerulus at the vascular pole between the afferent and efferent arterioles.[1] The cells of the macula densa are chemoreceptors and sense the tubular concentration of sodium chloride (NaCl). The juxtaposed segments of the afferent and efferent arterioles contain modified smooth muscle cells (granular cells), which produce renin. The arterioles are innervated by sympathetic nerve fibers and contain baroreceptors that respond to changes in intraluminal blood pressure. Renin catalyzes the formation of angiotensin, which modulates efferent and afferent arteriolar tone and GFR (see next section). The relationship of the juxtaglomerular apparatus to the sympathoadrenal system is discussed later in the section on neurohormonal regulation of renal function.

AFFERENT AND EFFERENT ARTERIOLAR CONTROL MECHANISMS

A primary determinant of GFR is the glomerular filtration pressure, which depends not only on the renal artery



Figure 23-2. Photomicrograph of a cast of a glomerulus without Bowman capsule. At lower left the afferent arteriole (A) originates from an interlobular artery and enters the glomerulus with its many capillary loops. At upper left the efferent arteriole (E) leaves the glomerulus and branches to form the peritubular capillary plexus. Magnification ×300. *(From Tisher CC, Madsen KM: Anatomy of the kidney. In Brenner BM, editor:* Brenner & Rector's The Kidney, *ed 6, Philadelphia, 2000, WB Saunders, pp 3-67.)*

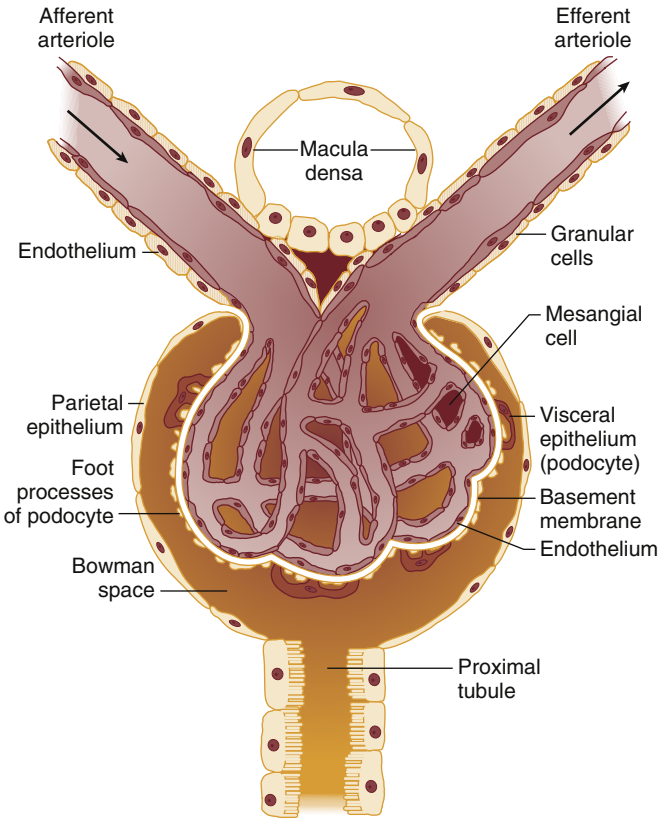


Figure 23-3. The juxtaglomerular apparatus. *(From Stanton BA, Koeppen BM: Elements of renal function. In Berne RM, Levy MN, editors:* Physiology, *ed 4, St Louis, 1998, Mosby, pp 677-698.)*

perfusion pressure but also on the balance between afferent and efferent arteriolar tone. In the face of decreased afferent arteriolar pressure or blood flow, low levels of catecholamines, angiotensin, and arginine vasopressin (AVP) induce preferential efferent arteriolar constriction, which maintains glomerular filtration pressure. This is reflected by an increase in calculated filtration fraction (FF), which is the GFR expressed as a fraction of the renal plasma flow (RPF)—FF = GFR/RPF. High levels of catecholamines and angiotensin (but not AVP) increase afferent arteriolar tone and decrease glomerular filtration pressure (and GFR) out of proportion to renal plasma flow, thus decreasing FF (Fig. 23-4). These mechanisms are described in more detail in the following sections.

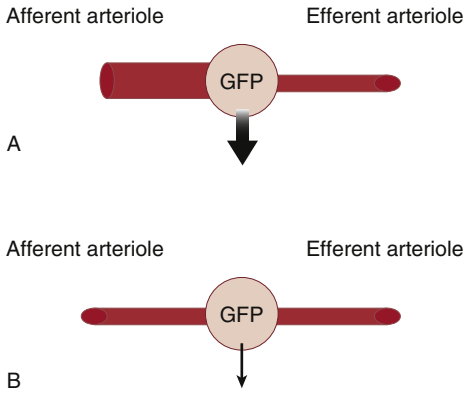


Figure 23-4. Afferent and efferent arteriolar control mechanisms. *(From Sladen RN, Landry D: Renal blood flow regulation, autoregulation, and vasomotor nephropathy,* Anesthesiol Clin North America *18:791-807, ix, 2000.)*

TUBULOGLOMERULAR FEEDBACK

Tubuloglomerular feedback is an important component of renal autoregulation.[3] When GFR is increased, distal tubular NaCl delivery is enhanced. The increase in chloride is sensed by the macula densa, which triggers the release of renin from the adjacent afferent arteriole. Angiotensin is elaborated, and arteriolar constriction ensues, which decreases GFR.

Tubuloglomerular feedback appears to prevent polyuria in acute renal failure. When the thick ascending loop becomes ischemic, reabsorption of NaCl ceases, the ability of the tubule to concentrate urine is lost, and theoretically, intractable polyuria should result. Thurau and Boylan[5] suggested that the increased delivery of NaCl to the macula densa triggers angiotensin-mediated arteriolar constriction, which decreases GFR, induces oliguria, conserves intravascular volume, and protects the organism from dehydration—so-called acute renal success.

RENAL AUTOREGULATION

Autoregulation enables the kidney to maintain solute and water regulation independently of wide fluctuations of arterial blood pressure. In 1951 the classic dog studies of Shipley and Study[6] demonstrated that the kidney

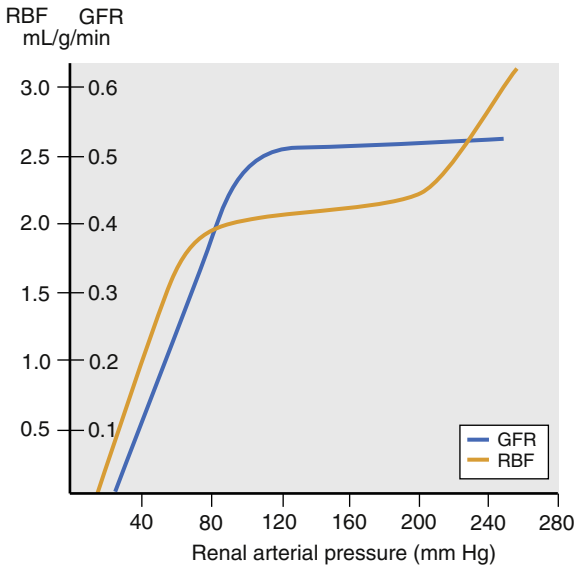


Figure 23-5. Autoregulation of glomerular filtration rate (GFR) and renal blood flow (RBF). Based on the original work of Shipley and Study.[5] GFR and RBF remain constant between renal arterial pressures of 80 and 180 mm Hg. *(From Pitts RF:* Physiology of the kidney and body fluids*, Chicago, 1974, Year Book Medical Publishers.)*

maintains a constant renal blood flow and GFR through an arterial pressure range of 80 to 180 mm Hg (Fig. 23-5). It is noteworthy that urinary flow rate is not subject to autoregulation. Tubular water reabsorption determines urinary flow rate and is closely related to the hydrostatic pressure in the peritubular capillaries. Hypotension, whether induced or inadvertent, results in decreased urinary flow rate that may be correctable only when the arterial blood pressure is restored toward normal.

There is considerable evidence to support two major mechanisms for renal autoregulation.[3] Renal vascular resistance appears to be mediated by variable resistance of the preglomerular afferent arteriole. As mean arterial pressure decreases, renal vascular resistance decreases and renal blood flow (RBF) is maintained. The most plausible explanation is a myogenic response (i.e., the arterioles constrict in response to increased arterial pressure and vice versa). Tubuloglomerular feedback via the juxtaglomerular apparatus also plays a role.[3,4,7] When arterial blood pressure increases through the autoregulatory range, delivery of sodium chloride to the chemosensors of the macula densa is enhanced, which generates ATP and adenosine that stimulate the adenosine A_1 receptor and induces afferent arteriolar constriction (Fig 23-6). This in turn decreases RBF and GFR back to the previous levels. The opposite effect occurs when arterial pressure declines. Local release of nitric oxide attenuates tubuloglomerular feedback, whereas release of angiotensin II enhances it.[4]

Autoregulation is impaired by calcium channel blockade, implying that a calcium-dependent mechanism is involved, but not by most anesthetic agents. It is reset in chronic hypertension and may be lost in the diabetic kidney. Experimental evidence shows that autoregulation is lost in acute renal failure[8]; in part, this may be due to endothelial dysfunction through excessive nitric oxide because inducible nitric oxide synthase is activated by renal ischemia-reperfusion injury.[9] Pressure-dependence of RBF is observed during cardiopulmonary bypass[10] and in severe sepsis,[11] but this may be due to hypotension below the autoregulatory range, rather than abnormal autoregulation per se. In these situations, restoration of renal perfusion pressure to normal levels improves RBF, even if this is achieved by vasoconstrictor therapy.

THE TUBULE

The tubule has four distinct segments: the proximal tubule, the loop of Henle, the distal tubule, and the connecting segment. The loop of Henle itself is divided into the pars recta (the straight portion of the proximal tubule), the descending and ascending thin limb segments, and the thick ascending limb. Each distal tubule drains into a collecting duct, which courses through the cortex, outer medulla, and inner medulla before entering the renal pelvis at the papilla (see Fig. 23-1).

Two populations of nephrons exist. The cortical nephrons, which populate the outer and middle renal cortex, are far more numerous, receive about 85% of the renal blood flow, and have short loops of Henle. Their efferent arterioles drain into a peritubular capillary plexus. The juxtamedullary nephrons populate the inner renal cortex, receive about 10% of the RBF, and have larger glomeruli and long loops of Henle, which dive deeply into the inner medulla.[2] Their efferent arterioles drain into elongated vascular conduits, the vasa recta, which are closely applied to the loops of Henle. Although the vasa recta receive less than 1% of the renal blood flow, they play an important role in generating the countercurrent mechanism for medullary hypertonicity and renal-concentrating ability (see later).

TUBULAR REABSORPTION AND SECRETION

The tubule has an enormous capacity for reabsorption of water and NaCl. Each day, 180 liters of protein-free glomerular ultrafiltrate is formed, of which almost 99% of the water and 99% of the sodium is reabsorbed.

Many other filtered substances are completely reabsorbed, but some, such as glucose, have a maximum rate of tubular reabsorption (tubular maximum). Tubular reabsorption of glucose increases at a rate equal to that of the filtered load. If the GFR is constant, the rate is directly proportional to the plasma glucose concentration. Once this concentration exceeds the tubular maximum (375 mg/dL), no further glucose is reabsorbed, and glycosuria results. Thereafter, the amount of glucose excreted in the urine increases in direct proportion to the filtered load.

Many important endogenous and exogenous solutes are secreted into the tubular lumen from the capillary blood. Some also have a tubular maximum for secretion, such as para-aminohippurate (PAH), which is used to calculate renal plasma flow. This is discussed further in the section on renal function tests.

There is a striking relationship between the structure and function of the different segments of the tubule (Fig. 23-7). The most metabolically active components of the tubule are the proximal tubule, the thick ascending loop of Henle, and the first part of the distal tubule.

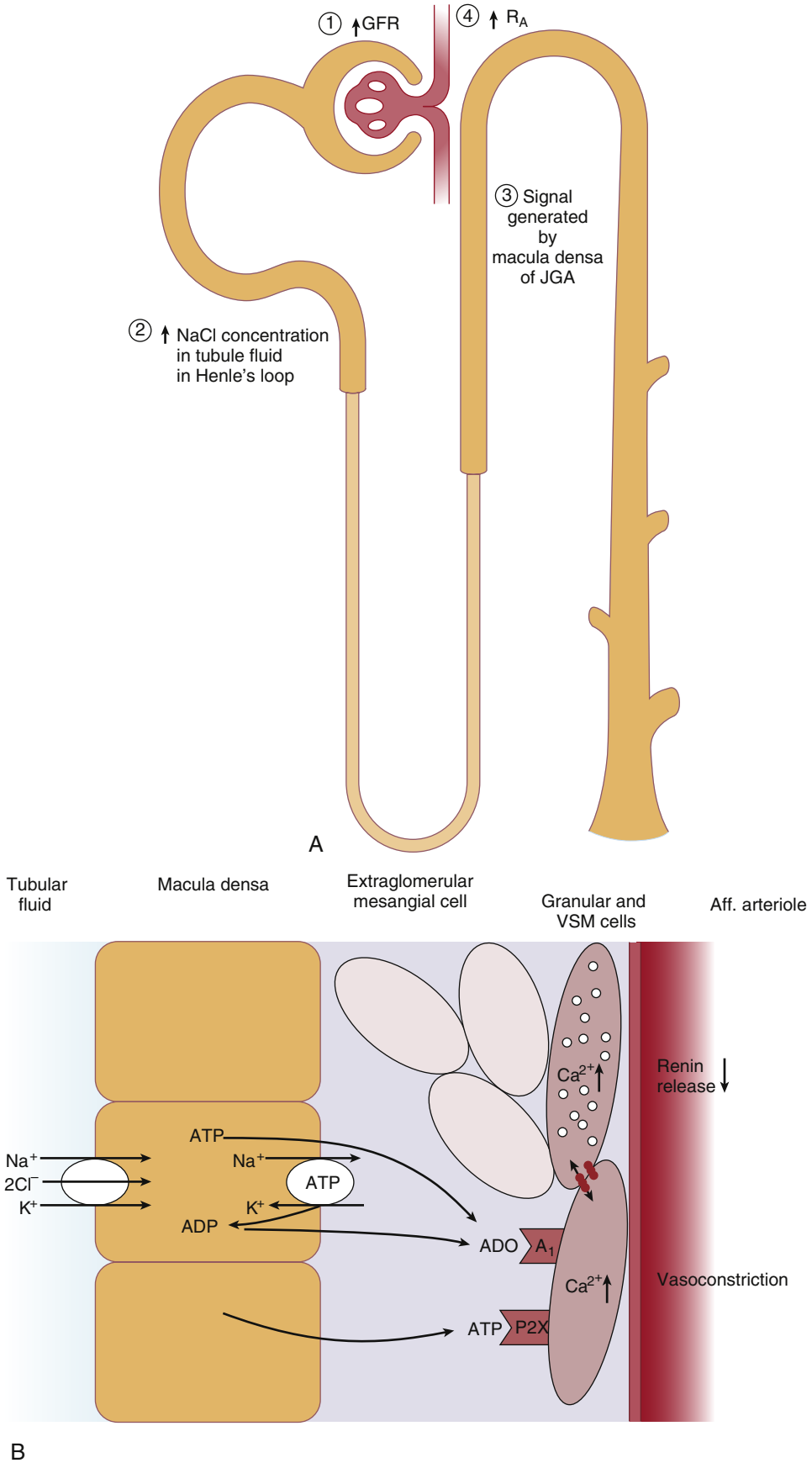


Figure 23-6. A and **B**, Tubuloglomerular feedback. An increase in glomerular filtration rate (GFR) (1) increases sodium chloride (NaCl) concentration in the tubular fluid in the loop of Henle. This is sensed by chemosensors in the modified distal tubular cells of the macula densa in the juxtaglomerular apparatus (JGA) (3). The cells of the macula densa generate adenosine triphosphate (ATP) and adenosine that induces afferent arteriolar constriction and increases its resistance (R_A) (4). This returns the GFR to its former level. A decline in the GFR has the opposite effect. *(From Koeppen BM, Stanton BA: Glomerular filtration and renal blood flow. In Koeppen BM, Stanton BA, editors:* Renal physiology, *ed 4, Philadelphia, 2007, Mosby, pp 31-46.)*

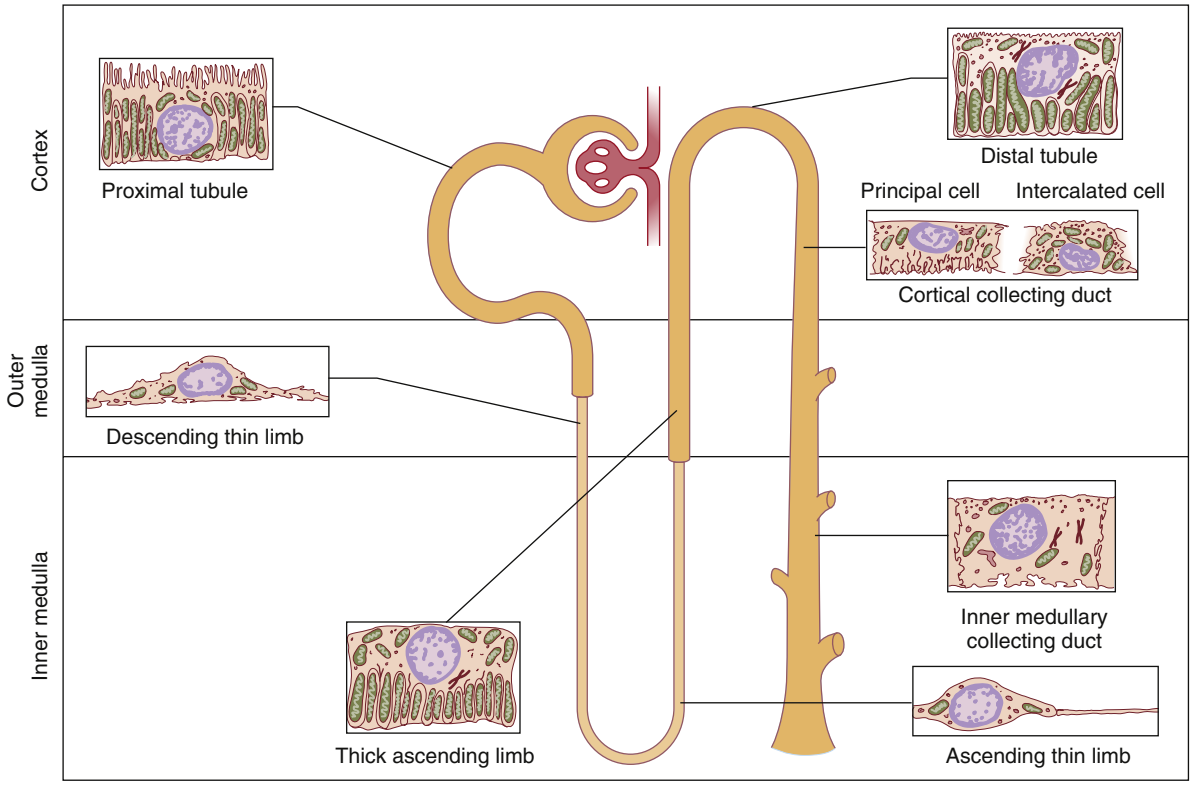


Figure 23-7. Structure-function relationships in the renal tubule. The most metabolically active components of the tubule are the proximal tubule, the thick ascending loop of Henle, and the first part of the distal tubule. Their cells are large, and on the capillary surface (basolateral membrane) there are many invaginations rich in mitochondria. The cells of the proximal tubule have a brush-border on the luminal surface (apical cell membrane), whereas the cells of the descending and thin ascending loops of Henle are flattened with few mitochondria. The second part of the distal tubule and collecting duct are intermediate in nature. The intercalated cells of the distal tubule have many mitochondria; the principal cells have few. *(From Stanton BA, Koeppen BM: Elements of renal function. In Koeppen BM, Stanton BA, editors:* Renal physiology, *ed 4, Philadelphia, 2007, Mosby, pp 677-698.)*

Figure 23-8 illustrates a tubular cell in the thick ascending loop of Henle, which encompasses all the major mechanisms of reabsorption and secretion. The tubular lumen abuts the apical cell membrane, which joins adjacent cells at the tight junctions. From each apical cell membrane protrudes a primary cilium equipped with a flow-sensitive mechanosensor and a chemosensor, both linked to calcium-dependent signaling pathways that control kidney cell function and apoptosis.[1] The remainder of the cell is lined by the basolateral cell membrane, which interfaces with the lateral interstitial spaces on either side and with the peritubular capillary at its base.

A number of protein-based active transport systems exist. The most important one is the sodium-potassium–adenosine triphosphatase (Na-K-ATPase) system, situated in the basolateral membrane. It pumps sodium out of the tubular cell into the interstitial fluid (and capillary blood) against a concentration and an electrical gradient, in exchange for potassium from inside the tubular cell. The consequent decrease in intracellular sodium concentration facilitates passive reabsorption of sodium from the tubular lumen into the cell. The transport of virtually all solutes is coupled to that of sodium.

Active transport systems that move solutes in the same direction into or out of the cell are called symporter systems, whereas those that move solutes in opposite directions are called antiporter systems. Solutes are transported by active and passive mechanisms, but water always diffuses passively along an osmotic gradient.

PROXIMAL TUBULE

The first part of the proximal tubule reabsorbs about 100% of the filtered glucose, lactate, and amino acids, as well as some phosphate by coupling with sodium-symporter systems.[12] Hydrogen ions (H^+) are extruded into the tubule in exchange for bicarbonate by a sodium-H^+ antiporter system. The absorption of organic anions and bicarbonate in the first part of the proximal tubule results in a relatively high chloride concentration downstream, promoting passive ingress of chloride. This leaves the tubular fluid positively charged relative to blood, further promoting the movement of sodium from the tubular fluid into the cell.

Most NaCl is absorbed transcellularly by a sodium-H^+ and chloride-based antiporter system in the apical cell membrane. The Na-K-ATPase system pumps sodium into the interstitial space, and a potassium-chloride symporter system pumps chloride. The resulting increase in osmolality also draws water across. In all, about two thirds of the filtered water, chloride, and potassium are reabsorbed by the proximal tubule, coupled with, and strongly influenced by, sodium absorption.[12]

The proximal tubule is also an important site of secretion of many endogenous anions (bile salts, urate), cations

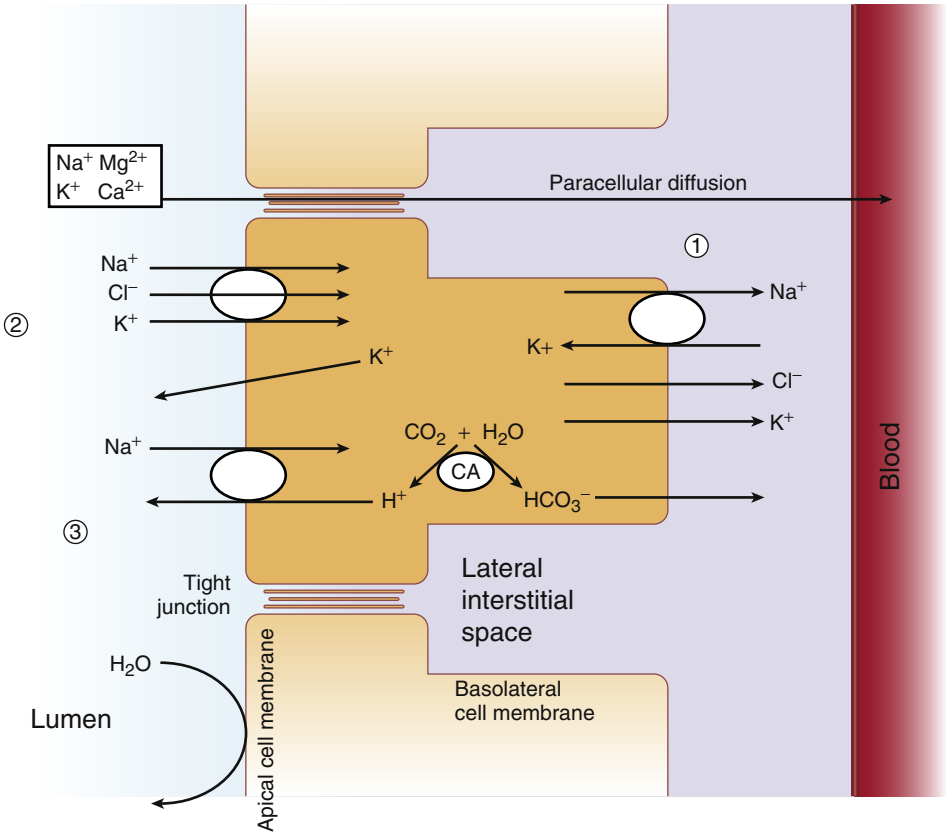


Figure 23-8. Mechanisms of tubular secretion and reabsorption. This tubular cell in the thick ascending loop of Henle encompasses the major mechanisms of secretion and reabsorption, one or more of which is used by various segments of the tubule. The most ubiquitous and important transport mechanism is the energy-requiring Na-K-ATPase pump in the basolateral cell membrane (1), which pumps sodium out into the interstitium against its concentration gradient and maintains a low intracellular concentration. This favors inward movement of sodium from the tubular lumen, facilitated by a sodium chloride symporter system on the apical cell membrane (2), which creates enough potential energy to draw in potassium against its concentration gradient and which is the primary inhibitory site of action of loop diuretics. A sodium-H^+ antiporter system on the apical cell membrane (3) aids sodium reabsorption and extrudes H^+, thereby promoting reaction of water with carbon dioxide to form H^+ and bicarbonate ion under the influence of carbonic anhydrase (CA). Bicarbonate diffuses out into the capillary. Sodium reabsorption is thereby coupled to H^+ loss and bicarbonate reabsorption. The transport proteins create a positive charge in the lumen, which drives ions such as sodium, calcium, potassium, and magnesium passively through the tight junctions by paracellular diffusion. The thick ascending loop of Henle is uniquely highly water-impermeable so that luminal osmolality progressively falls to less than 150 mOsm/kg (the "diluting segment"). *(From Stanton BA, Koeppen BM: Elements of renal function. In Koeppen BM, Stanton BA, editors:* Renal physiology, *ed 4, Philadelphia, 2007, Mosby, pp 677-698.)*

(creatinine, dopamine), and drugs (diuretics, penicillin, probenecid, cimetidine). Organic ions compete with each other for protein transport systems. Thus, administration of probenecid impairs tubular secretion of penicillin and prolongs its action. In chronic renal insufficiency there is an accumulation of organic acids that compete with drugs such as furosemide for secretor proteins, thereby conferring an apparent "resistance" to loop diuretics.

THICK ASCENDING LOOP OF HENLE

The metabolically active component of the loop of Henle is the thick ascending loop, which reabsorbs about 20% of the filtered sodium, chloride, potassium, and bicarbonate. Only the descending loop is permeable to water. In the water-impermeable thick ascending loop, sodium is actively reabsorbed, but water remains. In this so-called diluting segment of the kidney, tubular fluid osmolality decreases to less than 150 mOsm/kg H_2O.

As in the proximal tubule, the Na-K-ATPase pump in the basolateral membrane is the engine that drives the resorptive capacity of the thick ascending loop.[12] Sodium moves from the tubular lumen by passive diffusion along its concentration gradient. A sodium-H^+ antiporter system in the apical cell membrane mediates the net secretion of H^+ and reabsorption of bicarbonate.

An important symporter protein system couples the reabsorption of sodium, chloride, and potassium (the latter against its concentration gradient) across the apical membrane. Blockade of this system is the major site of action of loop diuretics that inhibit NaCl reabsorption in the thick ascending loop of Henle.

OXYGEN BALANCE IN THE MEDULLARY THICK ASCENDING LOOP

The kidneys receive 20% of the total cardiac output but extract relatively little oxygen. The renal arteriovenous oxygen difference (avO_2) is only 1.5 mL/dL. However, there is marked dissimilarity between the renal cortex and medulla with regard to blood flow, oxygen delivery,

and oxygen consumption (Fig. 23-9 and Table 23-1). The medulla receives only 6% of the RBF and has an average oxygen tension (PO_2) of 8 mm Hg. Thus, severe hypoxia could develop in the medulla despite a relatively adequate total RBF; the metabolically active medullary thick ascending loop of Henle (mTAL) is particularly vulnerable.[13]

The mTAL is also a potential site for nephrotoxic injury. Intrarenal blood flow is regulated by endogenous vasoactive compounds. In the outer cortex, at variance to its vasodilator actions elsewhere, adenosine induces vasoconstriction by stimulation of the adenosine A_1 receptor. In the deep juxtamedullary zone, endogenous prostaglandins and nitric oxide promote vasodilation. The net effect is to direct as much available blood flow to the medulla as possible. Drugs that inhibit prostaglandin synthesis, such as nonsteroidal antiinflammatory agents, can upset this compensatory mechanism and result in medullary ischemia.

Stress (e.g., pain, trauma, hemorrhage, hypoperfusion, sepsis, congestive heart failure) activates the sympathoadrenal system and results in renal cortical constriction and potential tubular ischemia. The kidney is relatively devoid of β_2 receptors, so epinephrine release induces predominant vasoconstriction through α receptor or angiotensin activation.

In hemodynamically mediated renal injury, the initial response to renal hypoperfusion is increased active NaCl absorption in the thick ascending limb. This increases oxygen consumption in the face of decreased oxygen delivery. Subsequent sympathoadrenal responses and renal cortical vasoconstriction may be a compensatory attempt to redistribute blood flow to the medulla. Ultimately, ATP stores become depleted and active NaCl reabsorption winds down. This increases the NaCl concentration in tubular fluid reaching the macula densa in the distal tubule, resulting in angiotensin release and afferent arteriolar constriction (i.e., tubuloglomerular feedback). Teleologically, the resultant decrease in GFR benefits renal oxygen balance by decreasing solute reabsorption and oxygen consumption in the medullary thick ascending loop of Henle.[13]

This hypothesis suggests that ischemic or nephrotoxic insults to the renal tubules might be alleviated by the administration of loop diuretics or dopaminergic agents. These drugs inhibit active sodium reabsorption in the thick ascending limb, thereby decreasing oxygen consumption and enhancing tubular oxygen balance. However, clinical trials have thus far been unable to demonstrate that these agents provide significant renoprotection.[14-17]

DISTAL TUBULE AND COLLECTING DUCT

The proximal segment of the distal tubule is structurally and functionally similar to the thick ascending loop. Sodium reabsorption is mediated by an apical cell membrane NaCl symporter system, which is the site of action of thiazide diuretics.[12]

TABLE 23-1 DISTRIBUTION OF RENAL BLOOD FLOW BETWEEN CORTEX AND MEDULLA

	Cortex	Medulla*
Percentage of renal blood flow	94	6
Blood flow (mL/minute/g)	5.0	0.03
PO_2 (mm Hg)	50	8
O_2 extraction ratio (VO_2/DO_2)	0.18	0.79

Data from Brezis M, Rosen S, Epstein F: The pathophysiological implications of medullary hypoxia, Am J Kidney Dis *13:253-258, 1989.*

DO_2, Oxygen delivery; *O_2*, oxygen; *PO_2*, oxygen tension; *VO_2*, oxygen consumption.

*The renal medulla receives only a small fraction of the total renal blood flow, and flow rates are extremely slow. As a result, the tissue oxygen tension is extremely low, and the medulla extracts almost 80% of the oxygen delivered to it. A very mild reduction in total and cortical renal blood flow may therefore induce ischemia and hypoxia in the renal medulla.

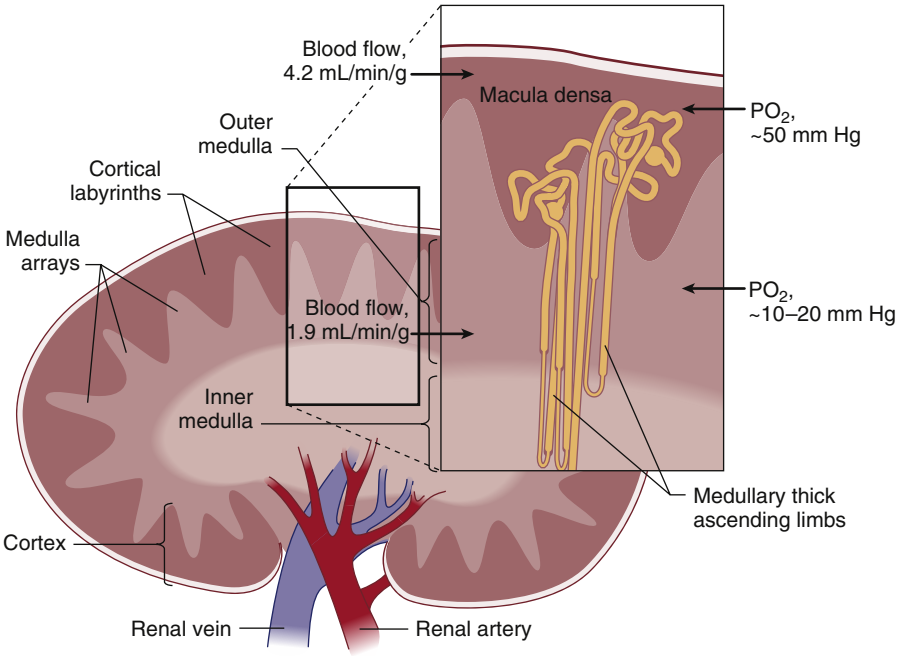


Figure 23-9. Medullary oligemia. To generate and maintain the countercurrent exchange that provides urinary concentrating ability, medullary blood flow must be slow. The juxtamedullary and medullary regions are zones of low blood flow and relative tissue hypoxia. Components of the nephron that have high oxygen consumption such as the medullary thick ascending limb (mTAL) are at high risk of oxygen supply-demand imbalance, and ischemic injury. *(From Brezis M, Rosen S: Hypoxia of the renal medulla—its implications for disease,* N Engl J Med *332:647-655, 1995.)*

The last part of the distal tubule is composed of two types of cells. Principal cells reabsorb sodium and water and secrete potassium via the Na-K-ATPase pump, and intercalated cells secrete H^+ and reabsorb bicarbonate by an H^+-ATPase pump in the apical cell membrane.

REGULATORY MECHANISMS IN SALT AND WATER REABSORPTION

OSMOTIC EQUILIBRIUM

The ability of the kidney to concentrate urine is dependent on the interaction of at least three processes. The first is generation of a hypertonic medullary interstitium by the countercurrent mechanism and urea recycling. The second is concentration and then dilution of tubular fluid in the loop of Henle. The third is the action of antidiuretic hormone (now known as arginine vasopressin or AVP) in increasing water permeability in the last part of the distal tubule and collecting ducts.

The medullary interstitium is rendered hypertonic by the countercurrent multiplier effect of the loop of Henle. The primary mechanism is the separation of solute from water (the single effect) by the combination of NaCl reabsorption and water impermeability in the ascending limb. This results in increased NaCl concentration and osmolality in the medullary interstitium. The descending limb is freely permeable to water, which diffuses into the interstitium along the osmotic gradient, and the tubular fluid becomes progressively hyperosmotic at the bend of the loop.

The vasa recta, which are closely applied to the long loops of Henle of juxtamedullary nephrons, maintain this condition by removing water and adding solute as they pass through the medullary interstitium. A standing osmotic gradient is thereby set up among the cortex (300 mOsm/kg), juxtamedullary zone (600 mOsm/kg), and deep medulla (1200 mOsm/kg). This process is enhanced by the passive recycling of urea, which diffuses out of the inner medullary collecting duct into the interstitium and then into the distal loop of Henle. These processes are summarized in Fig. 23-10.

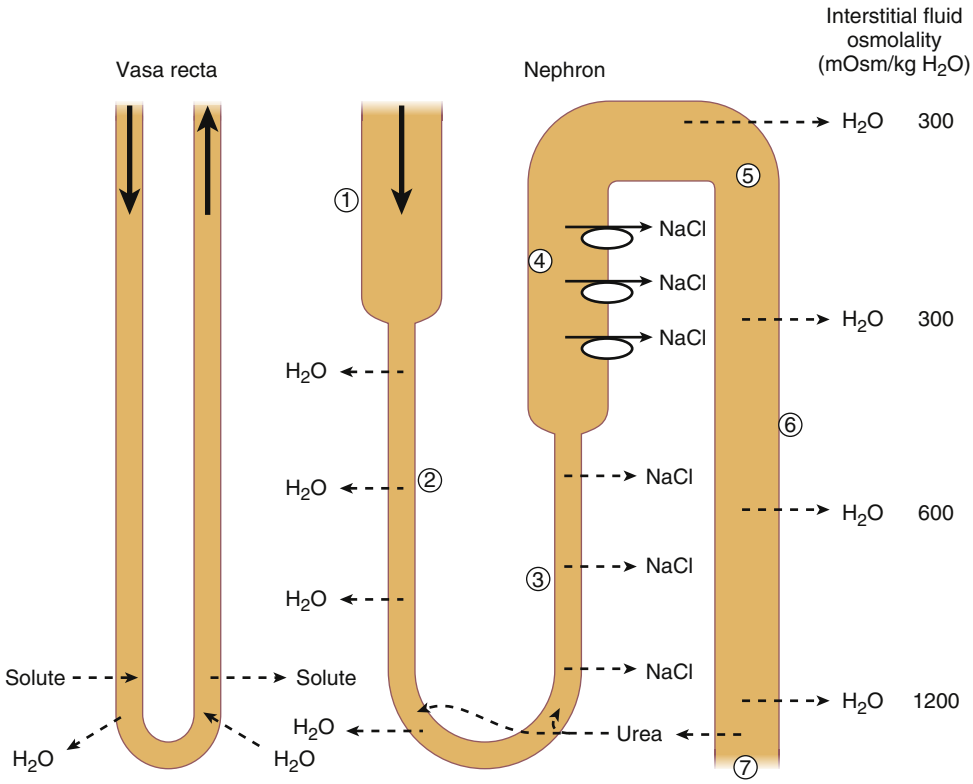


Figure 23-10. Tubular concentration of urine. The juxtamedullary nephrons have long loops of Henle associated with the vasa recta. *Dashed arrows* represent passive movement of fluid or solutes along concentration or osmolar gradients; *solid arrows* represent active transport. (1) Tubular fluid enters the distal proximal tubule iso-osmotic with plasma (300 mOsm/kg). In the descending limb of Henle (2), water rapidly diffuses out into the increasingly hypertonic medulla and is removed by the vasa recta so that the tubular fluid becomes hypertonic, owing largely to concentration of sodium chloride (NaCl). Urea diffuses in from the hypertonic interstitium, further increasing tubular fluid osmolality (1200 mOsm/kg). In the thin ascending loop of Henle (3), NaCl passively diffuses into the interstitium along its concentration gradient, but water is trapped in the water-impermeable tubule, which progressively decreases tubular fluid osmolality. Urea passively diffuses into the tubular fluid (urea recycling). Tubular dilution is accelerated by active reabsorption of NaCl in the thick ascending loop (the diluting segment) and proximal distal tubule (4). The fluid entering the distal tubule is quite hypo-osmotic (100 mOsm/kg). In the collecting segment (5), the osmolality of the tubular fluid returns to that of plasma (300 mOsm/kg), but unlike the contents of the proximal tubule, the solute component consists largely of urea, creatinine, and other excreted compounds. Increased plasma ADH renders the cortical and medullary collecting ducts (6) permeable to water, which passively diffuses into the hypertonic medullary interstitium. Even though some urea diffuses out into the medulla, the maximal osmolality of concentrated urine (7) approaches that of the hypertonic medullary interstitium, about 1200 mOsm/kg. In the absence of ADH, the collecting ducts remain impermeable to water, and the urine is diluted. *(From Stanton BA, Koeppen BM: Control of body fluid osmolality and volume. In Koeppen BM, Stanton BA, editors:* Renal physiology, *ed 4, Philadelphia, 2007, Mosby, pp 715-743.)*

TUBULAR CONCENTRATION AND DILUTION

Hypovolemia

Contraction of the extracellular volume by hypovolemia activates a series of vasoconstrictor, salt-retaining neurohormonal systems: the sympathoadrenal system, the renin-angiotensin-aldosterone axis, and AVP. Initially, the GFR and filtered load of sodium decrease. Sodium reabsorption in the proximal tubule is increased from about 66% to 80% by sympathetic activity and angiotensin II, as well as by the decline in peritubular capillary pressure induced by renal vasoconstriction. Sodium delivery to the thick ascending loop of Henle, distal tubule, and collecting duct is decreased, but aldosterone promotes reabsorption of sodium at these sites. Under the influence of AVP, water is also avidly reabsorbed in the collecting duct so that the urine becomes highly concentrated (osmolality 600 mOsm/kg) but with virtually no sodium (10 mEq/L).

Diuretic drugs abolish the kidney's ability to concentrate urine by washing out the hypertonic medulla. They do this either by an osmotic effect that prevents water reabsorption (e.g., mannitol) or by inhibition of active NaCl transport in the thick ascending loop (e.g., furosemide) or the first part of the distal tubule (e.g., hydrochlorthiazide). An early and important manifestation of acute kidney injury (AKI) is the loss of urinary concentrating ability caused by the breakdown of the energy-requiring Na-K-ATPase pump in the thick ascending loop of Henle.

Hypervolemia

Expansion of the extracellular volume by hypervolemia is countered by a series of vasodilator, salt-excreting neuropeptides, of which atrial, or A-type, natriuretic peptide (ANP) is predominant. The GFR and filtered sodium load increase because of a combination of reflex decreases in sympathetic and angiotensin II activity and the release of ANP. Together with the increase in peritubular capillary hydrostatic pressure, these responses cause sodium reabsorption in the proximal tubule to decrease from 67% to 50%. The decline in plasma aldosterone decreases sodium absorption from the thick ascending loop of Henle to the collecting duct. The presence of ANP and absence of AVP impairs water absorption at the collecting duct so that a dilute urine (osmolality 300 mOsm/kg) with abundant sodium (80 mEq/L) is produced.

It is noteworthy that loop diuretics, which depress tubular resorptive capacity, and acute kidney injury, which may abolish it completely, generate an identical urinary profile (low osmolality, high urinary sodium), even in the presence of hypovolemia.

EVALUATION OF RENAL FUNCTION

CLINICAL MARKERS OF RENAL FUNCTION

Urine Output

The mainstay of the clinical evaluation of renal function remains the measurement of urine output. Oliguria ("little urine") is a relative condition that depends on *expected* urine flow, and it may bear little, if any, relationship to GFR.

Perioperative oliguria is defined as a urine flow rate <0.5 mL/kg/hr, and it is often interpreted as a sign of renal dysfunction. Yet in the perioperative period, oliguria is almost inevitable, whether induced by hypotension, as an appropriate prerenal response to intravascular hypovolemia, or as a manifestation of the physiologic response to surgical stress[18] (see "Neurohormonal Regulation of Renal Function"). When arterial blood pressure and intravascular volume are restored to normal levels, and surgical stress abates postoperatively, the stimulus to the tubules abates and normal urinary flow resumes.

Complete, often abrupt, cessation of urine flow suggests postrenal obstruction. This can occur at the level of the renal pelvis, ureters, bladder, urethra, or urinary catheter. If the obstruction is subtotal, some urine flow may persist, even as AKI progresses.

In the past, acute renal failure was defined on the basis of urinary flow rate—as anuric (zero flow), oliguric (<15 mL/hr), nonoliguric (15 to 80 mL/hr), or polyuric (>80 mL/hr). More recently, urinary flow rate has been combined with changes in serum creatinine to create consensus definitions of AKI known as the RIFLE (risk, injury, failure, loss, end-stage renal disease) criteria[19] and the AKIN (Acute Kidney Injury Network) criteria[20] (Table 23-2). In both definitions, the first three stages of AKI (risk, injury, failure in RIFLE; stages 1, 2, and 3 in AKIN) are categorized on the basis of oliguria (<0.5 or <0.3 mL/kg/hr) of increasing duration.

At the present time, debate continues as to whether prerenal oliguria is an independent, reversible entity, or an early stage (*form fruste*) of AKI. In a study of oliguria as a predictive biomarker of AKI, low urine flow rate was almost inevitably (94% of the time) not a precursor of AKI, and most cases of AKI were not preceded by oliguria[21]. Oliguria was predictive of AKI only when it was associated with hemodynamic instability, which is not included in the RIFLE or AKIN criteria. In contrast, in a prospective observational study of 341 critically ill patients, the incidence of AKI increased from 24% to 52% and was diagnosed earlier when oliguria was added to elevated serum creatinine by the AKIN criteria.[22] The ICU mortality rate was 1.3% for patients without AKI, 8.8% for patients with oliguria without elevated serum creatinine, and 10.4% for patients with oliguria and increased serum

TABLE 23-2 ACUTE KIDNEY INJURY NETWORK (AKIN) DEFINITION

Stage of AKI	Change in SCr	Urine Output
1	>0.3 mg/dL Up to 1.5-2 × baseline	<0.5 mL/kg/hr × 6 hr
2	2-3 × baseline	<0.5 mL/kg/hr × 12 hr
3	>3 × baseline absolute SCr >4.0 mg/dL	<0.3 mL/kg/hr × 12 hr

Data from Mehta RL, Kellum A, Shah SV, et al: Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury, Crit Care *11:R31, 2007.*

AKI, Acute kidney injury; *SCr,* serum creatinine.

creatinine; the mortality rate was higher with increased severity and duration of oliguria.

In sum, perioperative oliguria is a frequent occurrence but almost always is prerenal in nature. On the other hand, the absence of oliguria does not exclude AKI, but its presence implies an increased severity of injury.

Blood Urea Nitrogen

Urea is continuously formed by the metabolism of ammonia in the liver. Hepatic deamination implies the splitting off of amide ($-NH_2$) groups from amino acids and their conversion to ammonia, which enters the arginine cycle and is converted to urea. Urea is a small uncharged molecule that is not protein bound and is rapidly cleared from the blood by glomerular filtration. It subsequently undergoes reabsorption by the tubules so the blood urea nitrogen (BUN) does not correlate directly with GFR.

The normal range of BUN is 5 to 10 mg/dL; given the normal range of serum creatinine (0.5-1.0 mg/dL), the normal ratio of BUN to serum creatinine is about 10:1. An increase in this ratio to 20:1 or higher implies the existence of a prerenal syndrome (prerenal azotemia). However, elevation of BUN out of proportion to decreases in GFR occurs whenever there is increased protein catabolism and formation of urea nitrogen. This scenario occurs with absorption of blood from the GI tract, steroid therapy, major trauma, and sepsis. In contrast, the BUN may be misleadingly low when its production is impaired by severe malnutrition (protein depletion) or severe liver disease (inability to convert ammonia to urea).

Serum Creatinine

Serum creatinine reflects the balance between creatinine production by muscle and creatinine excretion by the kidney, which is dependent on the GFR. Creatinine generation rate varies with muscle mass, physical activity, protein intake, and catabolism. However, when these processes are in equilibrium and renal function is stable, serum creatinine is a useful marker of GFR.

The relationship between serum creatinine and GFR is inverse and exponential. A doubling of the serum creatinine implies a halving of the GFR. An increase in serum creatinine from 0.8 to 1.6 mg/dL may not appear to be serious, but it indicates a 50% decrease in GFR. A much larger increase from 4 to 8 mg/dL also represents a 50% decrease in GFR, but by this time renal insufficiency is well established (Fig. 23-11).

Increases in serum creatinine from baseline are used to define the first three categories of the RIFLE and AKIN criteria for AKI (baseline × 1.5, 2 to 3, and >3 respectively).[19,20] The importance of small increases in serum creatinine are recognized by the AKIN criteria, which define stage 1 AKI by an increase of as little as >0.3 mg/dL. Indeed, there is evidence that this criterion alone predicts outcomes after AKI (hospital length of stay, dialysis, mortality) as accurately as do the full AKIN criteria.[23]

Limitations to Serum Creatinine as a Reflection of GFR. Serum creatinine is usually measured by the Jaffé reaction, a chromogenic assay based on the red color of the creatinine complex with alkaline picrate. It also picks up other normally occurring chromogens, such as glucose, protein, ketones, and ascorbic acid, which represent about 14% of total creatinine when renal function is normal, although substantially less when serum creatinine is elevated. Ketoacidosis, barbiturates, and cephalosporin antibiotics may artifactually increase serum creatinine by as much as 100%, and cimetidine and trimethoprim block its secretion by the tubule. *N*-acetylcysteine, an antioxidant advocated by some as a renoprotective agent in contrast nephropathy,[24] decreases serum creatinine levels, which may in part account for its apparently beneficial effect on renal function.[25]

Because of their nonlinear relationship, serum creatinine does not increase above the normal range until the GFR declines below 50 mL/minute. Large declines in GFR may occur above these levels without a concomitant increase in serum creatinine. The creatinine generation rate is relatively consistent in a given individual, but it varies with muscle mass, rate of catabolism, physical activity, and protein intake.[26] In a cachectic patient with very low muscle mass, creatinine generation may be so feeble that the serum creatinine remains "normal" (<0.9 mg/dL) even in the face of a GFR <25 mL/minute.[27]

The GFR declines progressively and predictably with age, from about 125 mL/minute in a healthy 20-year-old to about 60 mL/minute in an 80-year-old (or a 60-year-old

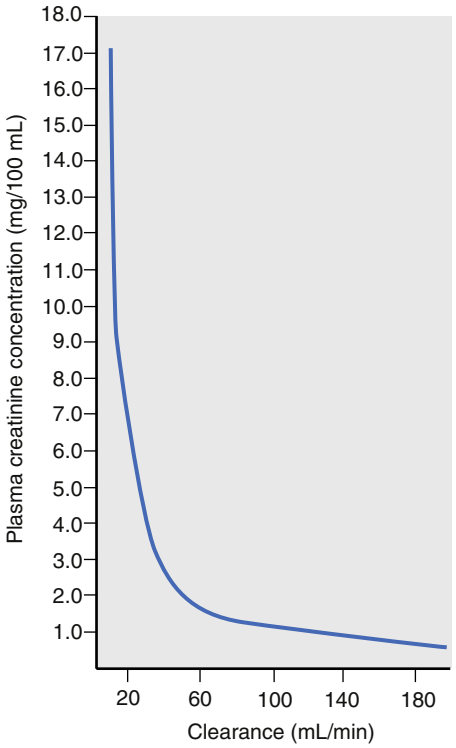


Figure 23-11. Relationship between serum creatinine and GFR. The relationship between serum creatinine and GFR as measured by creatinine clearance is reciprocal and exponential. Doubling of the serum creatinine corresponds to halving of the GFR. Relatively large declines in GFR from normal are associated with small increases in serum creatinine until GFR decreases below 60 mL/minute; further decrements are associated with large increases in serum creatinine. *(From Alfrey AC, Chan L: Chronic renal failure: manifestations and pathogenesis. In Schrier RW, editor:* Renal and electrolyte disorders, *ed 4, Boston, 1992, Little, Brown, p 541.)*

with atherosclerosis[28]) (also see Chapter 80). Because these changes occur at a GFR >50 mL/minute, the impairment induced by aging is not reflected by the serum creatinine. The implication is that a 20-year-old and 80-year-old patient may have an identical serum creatinine within the normal range, but compared with the younger, the older patient has half the GFR and renal reserve.

Creatinine is soluble, freely distributes through the total body water, and is diluted by the 10% to 15% increases in total body water that occur with fluid administration and retention during major surgery. It is not uncommon for serum creatinine to be decreased from baseline on the first postoperative day (e.g. 1.2 to 0.9 mg/dL). Subsequently, when total body water is decreased by fluid mobilization and diuresis, the serum creatinine increases (e.g., from 0.9 to 1.2 mg/dL). This does not necessarily imply AKI, but may simply represent hemoconcentration and a re-equilibration to baseline.

In a steady state the serum creatinine concentration represents an equilibrium between creatinine generation rate, which is dependent on muscle mass and catabolic activity, and creatinine excretion, which is dependent on (and reflective of) the GFR. However, serum creatinine is an unreliable marker of GFR when the GFR is rapidly changing.[26]

This point is lucidly illustrated by an intervention such as suprarenal aortic cross-clamping, which causes instantaneous cessation of renal blood flow, GFR and urinary creatinine excretion. However, measured serum creatinine would still be at baseline and would not detectably increase for several hours. Serum creatinine would then continue to increase as long as creatinine production exceeds creatinine excretion. Because it may take up to 48 hours for the GFR to return to baseline after cross-clamp release, after surgery the serum creatinine may still be increasing, even though the GFR is recovering.[28] In established oliguric acute renal failure, the serum creatinine is directly proportional to the creatinine generation rate, which may vary widely even though the GFR is consistently low.

Cystatin C

There is great interest in defining endogenous plasma markers that provide a more reliable, early indicator of changing GFR, especially in AKI.[29] One that has received prominence is cystatin C, a cysteine-protease inhibitor that is released into the circulation at a constant rate by all nucleated cells. It is completely filtered by the glomerulus and neither secreted nor resorbed by the tubular epithelium, so its serum levels bear a close relationship to serum creatinine and GFR.[30] Unlike creatinine, serum cystatin C is less subject to nonrenal variables such as muscle mass, age, or gender and in certain clinical situations appears to be a more accurate predictor of low GFR than serum creatinine.[31,32] Given the short half-life of cystatin C (approximately 2 hours), it should be anticipated that serum cystatin C will increase more rapidly than serum creatinine after an acute change in GFR. Indeed, evidence suggests that serum cystatin C is superior to creatinine in estimating GFR.[33,34]

However, more recent studies suggest that the relationship between serum cystatin C and GFR is affected by various anthropometric measures, as well as by cigarette smoking, inflammation (elevated C-reactive protein), corticosteroid use, and immunosuppressive therapy.[35,36] As a consequence, cystatin C remains an investigational marker that has not supplemented serum creatinine in clinical practice.

ASSESSMENT OF GLOMERULAR FILTRATION RATE

ESTIMATED GFR

In clinical investigation, serum creatinine-based nomograms derived from population studies are commonly used to calculate estimated GFR (eGFR), thus avoiding the necessity of a timed urine collection.

COCKROFT-GAULT EQUATION

The Cockcroft-Gault Equation utilizes age, weight, serum creatinine, and gender[37]:

$$\text{eGFR in mL/minute} = (140 - \text{age}) \times \text{weight in kg} \div (\text{serum creatinine} \times 72) \quad [2]$$

For females, the result is multiplied by 0.85 to obtain the derived GFR.

In this formula, the body weight that is used may substantially alter the derived GFR. In obese or edematous patients, the total body weight is much greater than the lean body mass from which creatinine is derived, and GFR is overestimated. In cachectic patients with depleted lean body mass, creatinine production is so low that serum creatinine is frequently less than 1.0 mg/dL and overestimates the true GFR. Robert and associates[38] adjusted the Cockroft-Gault Equation to incorporate ideal body weight from a nomogram and serum creatinine corrected to 1.0 mg/dL (if less than 1.0 mg/dL). Using this modification, they found that single measurements in hemodynamically stable patients correlate more closely with inulin clearance than either a 30-minute or a 24-hour creatinine clearance.

MODIFICATION OF DIET IN RENAL DISEASE (MDRD)

This is a complex nomogram based on a study called Modification of Diet in Renal Disease (MDRD)[39] that has the advantage of being independent of body weight:

$$\text{eGFR in mL/minute} = 175 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \quad [3]$$

For females, the derived eGFR is multiplied by 0.742, and for black patients, it is multiplied by 1.212.

The MDRD-derived eGFR is the basis of the National Kidney Foundation classification of chronic kidney disease (CKD)[40] (Table 23-3). In a landmark study on 1.2 million adult patients with CKD who did not undergo dialysis or transplantation, there was an exponential increase in

age-standardized rate of death from all causes, cardiovascular events, and hospitalizations with advancing stage of CKD[41] (Table 23-4). In cardiac surgery, the odds ratio for perioperative mortality increases to 1.18, 2.23, and 4.39 for preexisting CKD stages 3, 4, and 5, respectively.[42]

An important caveat is that when renal function is rapidly changing, eGFR based on serum creatinine is subject to the same limitations as serum creatinine itself (see earlier).

RENAL CLEARANCE TECHNIQUES

Clearance is the most commonly used technique to estimate GFR, using compounds that are predominantly filtered by the glomerulus and neither secreted nor reabsorbed by the renal tubules.[43] Based on the Fick principle, the amount of substance *x* excreted by the kidney equals the amount delivered in the arterial supply minus the amount in the venous return:

$$\text{Excretion}_x = \text{delivery}_x - \text{return}_x \quad [4]$$

Therefore,

$$\text{Delivery}_x = \text{return}_x + \text{excretion}_x \quad [5]$$

The amount of substance *x* delivered to the kidney is the product of the arterial plasma concentration (Pa_x) and RBF. The amount returning from the kidney is the product of the venous plasma concentration (Pv_x) and RBF. The urinary excretion rate of substance *x* is the product of its urinary concentration (U_x) and the urine flow rate in milliliters per minute (V). Therefore,

$$(Pa_x \times RBF) = (Pv_x \times RBF) + (U_x \times V) \quad [6]$$

TABLE 23-3 STAGES OF CHRONIC KIDNEY DISEASE

Stage of CKD	eGFR mL/kg/1.73m²	Description
1	>90	Kidney damage with normal GFR
2	60-89	Mildly decreased GFR
3	30-59	Moderately decreased GFR
4	15-29	Severely decreased GFR
5	<15	Kidney failure

Data from Levey AS, Coresh J, Balk E, et al: National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification, Ann Intern Med *139:137-147, 2003.*

CKD, Chronic kidney disease; *eGFR*, estimated glomerular filtration rate; *GFR*, glomerular filtration rate.

However, in practice, RBF and venous return are not measured. Instead, the removal of substance *x* from the plasma by the kidney is expressed in the concept of clearance. Clearance (C) is defined as the virtual volume of plasma cleared of substance *x* per unit time, in milliliters per minute. This allows the urinary excretion rate of *x* to be equated to its renal arterial plasma concentration:

$$Pa_x \times C = U_x \times V \quad [7]$$

If the assumption is made that the concentration of *x* in renal arterial and venous plasma is identical, the clearance of substance *x* may be calculated using a urine sample, arm venous sample, and measured urinary flow rate:

$$C_x \times = U_x \times Pa_x/V \quad [8]$$

Inulin Clearance

Inulin is an inert polyfructose sugar that is completely filtered by the glomerulus and is neither secreted nor reabsorbed by the renal tubules. The volume in milliliters of plasma cleared of inulin per minute represents the GFR (mL/minute). After an intravenous loading dose of 30 to 50 mg/kg, a continuous infusion of inulin is given to establish a steady-state plasma concentration of 15 to 20 mg/dL. The bladder is usually flushed with air to eliminate any pooled urine. After a carefully timed urine collection (which can be as short as 30 min), urine and plasma inulin concentration (U_{IN}, P_{IN}) are measured, and inulin clearance (C_{IN}) is calculated:

$$GFR = C_{IN} = U_{IN} \times V/P_{IN} \quad [9]$$

Normal values for inulin clearance are 110 to 140 mL/minute/1.73m² (males) and 95 to 125 mL/minute/1.37m² (females).

Although inulin clearance is the gold standard for measurement of GFR, it is seldom used clinically because its accurate measurement is laborious and requires meticulous attention to detail. Large changes in blood glucose during the test may interfere with its measurement. The inulin assay is time consuming, and inulin itself is in short supply because of lack of demand. Thus, although inulin meets all the criteria of an ideal filtration marker, its accuracy in reflecting GFR cannot be directly assessed, only inferred. The predicted variability of inulin clearance is 20% when measurements are compared at two different times in the same individual and 40% when measurements are compared between two individuals.[43]

TABLE 23-4 IMPACT OF STAGE OF CKD ON MORTALITY AND MORBIDITY*

EGFR mL/kg/1.73 m²	Death from All Causes (per 100 person-years)	Cardiovascular Events (per 100 person-years)	Hospitalizations (per 100 person-years)
>60	0.76	2.11	13.54
45-59	1.08	3.65	17.22
30-44	4.76	11.29	45.26
15-29	11.36	21.80	86.75
<15	14.14	36.60	144.61

Data from Go AS, Chertow GM, Fan D, et al: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization, New Engl J Med *351:1296-1305, 2004.*

eGFR, Estimated glomerular filtration rate.

*The risk analysis was performed on 1.12 million patients with CKD who did not undergo dialysis or renal transplantation. All data are age-standardized.

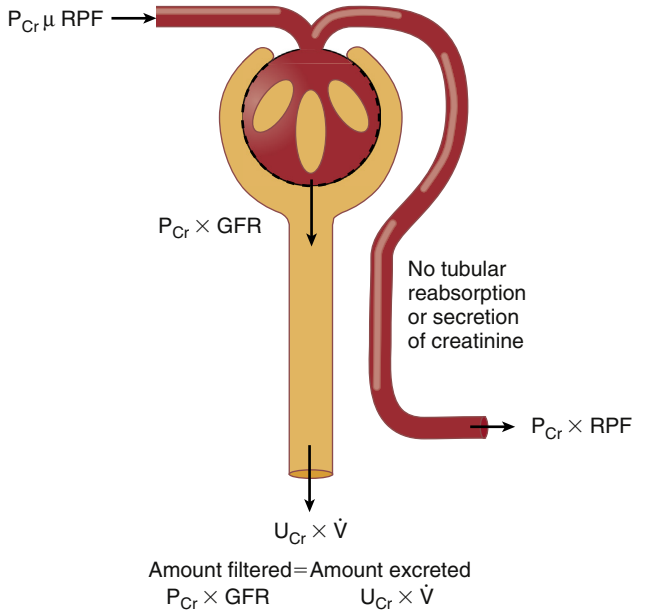


Figure 23-12. Renal handling of creatinine. Creatinine is freely filtered by the glomerulus, and there is normally an inconsequential amount secreted or reabsorbed by the tubules. Thus, the amount of creatinine filtered is equivalent to the amount excreted in the urine. For a more detailed explanation, see text. P_{Cr}, Plasma creatinine concentration; *RPF,* renal plasma flow; U_{Cr}, urinary concentration of creatinine; $\dot{V}$, urine flow rate. *(From Koeppen BM, Stanton BA: Glomerular filtration and renal blood flow. In Koeppen BM, Stanton BA, editors:* Renal physiology, *ed 4, Philadelphia, 2007, Mosby, pp 31-46.)*

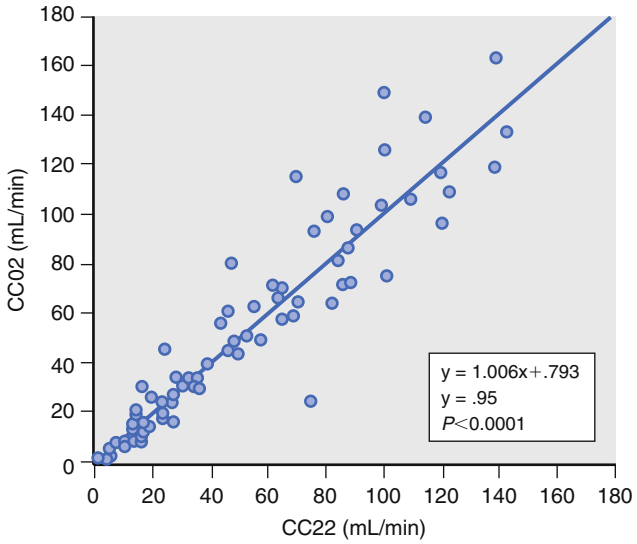


Figure 23-13. Creatinine clearance: 2-hour versus 22-hour values. There is a close and significant correlation in creatinine clearance estimation from a 2-hour and a 22-hour urine collection. *CC02,* 2-hour urine collection; *CC22,* 22-hour urine collection. *(From Sladen RN, Endo E, Harrison T: Two-hour versus 22-hour creatinine clearance in critically ill patients,* Anesthesiology *67:1013-1016, 1987.)*

Sodium iothalamate, a radiocontrast dye, has been substituted for inulin and facilitates accurate assessment of rapid changes in GFR in AKI.[44]

Creatinine Clearance

Creatinine, the endogenous end product of creatine phosphate metabolism, is normally generated from muscle at a very uniform rate and is handled by the kidney in a manner similar to that of inulin (Fig. 23-12). Thus, creatinine clearance (C_{CR}) provides a simple, inexpensive bedside estimate of GFR. A single blood sample is drawn at the midpoint of a carefully timed urine collection, and urine and plasma creatinine (U_{CR}, P_{CR}) and urinary flow rate in mL/minute (V) are used to calculate GFR:

$$GFR = C_{CR} = U_{CR} \times V/P_{CR} \quad [10]$$

The creatinine clearance is far more accurate in tracking rapid alterations in GFR than the serum creatinine alone, because changes in GFR immediately alter the creatinine excretion rate, which is incorporated into the equation above as $U_{CR} \times V$.

Bedside use of creatinine clearance was formerly restricted by the belief that a prolonged (12- to 24-hour) urine collection is necessary to eliminate error induced by residual urine in the bladder neck after spontaneous voiding. This practice is tedious and cumbersome, and it is inaccurate when renal function is rapidly changing. For example, if serum creatinine were to increase from 1 to 2 mg/dL from the beginning to the end of a 24-hour urine collection, clearance calculated on a serum creatinine drawn at the midpoint of the collection would mask the rapid deterioration in true GFR.

The precise timing, not the duration, of the urine collection is the critical issue.[45] If a brisk urine flow is induced by diuresis, and care is taken to empty the bladder, the variability of creatinine clearance is no greater with a 1-hour urine collection than with a 24-hour collection. In catheterized patients with urine flow rates of more than 15 mL/hour, creatinine clearance obtained with a 2-hour urine collection gives values equivalent to those obtained with a 22-hour collection.[46] In the example above, a 2-hour creatinine clearance obtained at the beginning and end of the 24-hour period would truly reflect the halving of GFR represented by a doubling of the serum creatinine from 1 to 2 mg/dL. In critically ill patients, a changing GFR can be closely tracked by serial estimations using a short, carefully timed urine collection (Figs. 23-13 to 23-15). In trauma patients, a 1-hour creatinine clearance of less than 25 mL/minute determined within 6 hours of surgery reliably predicted postoperative acute renal failure, despite the absence of oliguria.[47]

Considerable variation exists in the normal range of creatinine clearance. Tobias and associates[45] reported a variation in creatinine clearance between 88 and 148 mL/minute and in serum creatinine between 0.9 and 1.5 mg/dL in a single healthy individual over 5 years. There is also a diurnal variation, with higher values in the afternoon and a variance of up to 25% around mean values.[48] It is prudent to obtain short-collection creatinine clearance estimations at the same time each day to minimize diurnal variability. "Normal" creatinine clearance is related to body surface area and weight, so values may fluctuate widely in patients with cachexia or edema.

Creatinine clearance has a number of inherent limitations, even if collection error is carefully avoided. First, it is subject to many of the limitations imposed by the

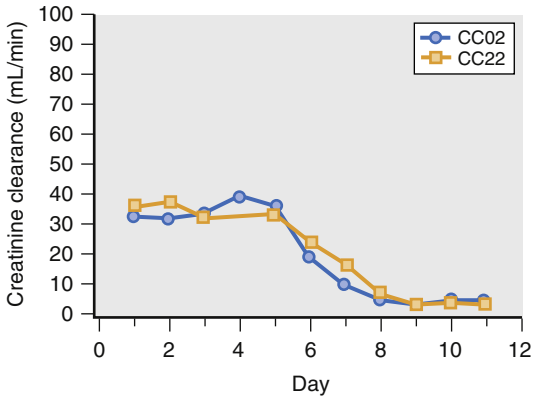


Figure 23-14. New-onset acute renal failure. In a patient developing acute renal failure in the intensive care unit, the exponential decline in creatinine clearance is tracked equally well whether a 2-hour (CC02) or a 22-hour (CC22) urine collection is used. However, data from the 2-hour collection are available well before those from the 22-hour collection.

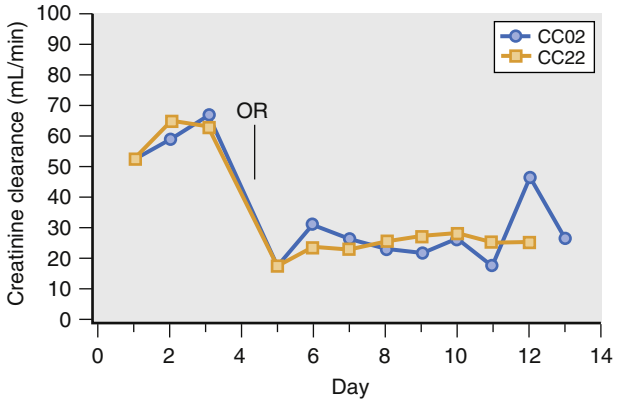


Figure 23-15. Renal revascularization. Patient with renovascular hypertension and renal insufficiency admitted to the intensive care unit for preoperative monitoring and stabilization. Bilateral renal revascularization was performed, and following return from the operating room there was a substantial decline in renal function. These changes were tracked equally well by creatinine clearance derived from a 2-hour (CC02) and a 22-hour (CC22) collection.

measurement of creatinine itself (see earlier). Unlike inulin, about 20% of creatinine is secreted by the proximal tubule, so that creatinine clearance overestimates GFR, and the ratio between the clearance of creatinine and inulin is 1.2:1. As the GFR declines, tubular secretion of creatinine increases. When GFR is less than 40 mL/minute/1.73m^2, a creatinine-to-inulin clearance ratio as high as 1.81 to 2.51 may be achieved.[49] In patients with normal renal function, the underestimate of GFR induced by the Jaffé reaction is balanced by the overestimate of GFR induced by tubular creatinine secretion, and creatinine clearance provides a reasonable representation of GFR. However, widely used drugs such as trimethoprim, H_2-antagonists, and salicylates block tubular secretion of creatinine and may elevate serum creatinine and decrease creatinine clearance. When serum levels of creatinine are very high, it is excreted into the gut and undergoes extrarenal metabolism by intestinal organisms.

Given these constraints, an isolated creatinine clearance estimation may not reveal early renal dysfunction. Nonetheless, serial estimations of creatinine clearance provide a useful clinical guide to alterations in renal function and prognosis. A preoperative creatinine clearance can provide a baseline for comparison with postoperative changes and also give a more accurate measure of effective renal reserve. Postoperatively, daily measurement of creatinine clearance is useful in guiding the dosing of renally excreted, potentially nephrotoxic aminoglycoside antibiotics (gentamicin, tobramycin, amikacin) or calcineurin antagonists (cyclosporine A, tacrolimus). Because the GFR may decline to less than 50% of normal before serum creatinine increases above the normal range, an observed decrease in creatinine clearance may allow down-adjustment of drug dosing before nephrotoxicity becomes established and the drug accumulates even further.

The variability of creatinine clearance diminishes as GFR declines; in fact, loss of variability is a clue to deteriorating renal function. If the GFR is rapidly declining, the creatinine clearance alerts the physician earlier and more compellingly than the serum creatinine because it reflects creatinine excretion rate (i.e., urine creatinine content times urine flow rate [$U_{CR} \times V$]). Directional changes between creatinine clearance and inulin clearance show good agreement.[49] At low levels of GFR a creatinine-to-inulin clearance ratio as high as 2:1 (e.g., 12 versus 6 mL/minute) would induce little actual difference in clinical management.

PLASMA CLEARANCE

Measurement of the rate of disappearance (plasma clearance) of a substance that is completely eliminated by glomerular filtration is an alternate method for measuring GFR without the need for a simultaneous urine collection. It involves an intravenous bolus dose and/or infusion of the marker, followed by measurement of multiple plasma levels to calculate its disappearance rate. The methodology does depend on the achievement of a steady-state plasma concentration of the marker, which is difficult to achieve with rapid changes in GFR.[44]

Numerous markers are used, including nonradioactive inulin and iothalamate, as well as radioisotopes such as Cr^{51}-ethylenediaminetetraacetic acid (EDTA), Tc^{99m}-diethylenetriaminepentaacetic acid (DTPA), and ^{125}I-iothalamate. The radioisotopes, which utilize measurement of decay in radiation, have shown promise in the rapid assessment of GFR.

TUBULAR FUNCTION TESTS

Tests of renal tubular function measure urinary concentrating ability, sodium handling, and urea handling. As such, they can potentially distinguish oliguria due to dehydration (prerenal syndrome) from that due to tubular injury (acute tubular necrosis).

In prerenal oliguria, tubular function is not only preserved but also activated to retain salt and water, resulting in concentrated urine that is low in sodium. With the exception of refractory prerenal states such as severe sepsis and end-stage liver failure (see later), restoration of

a normal hemodynamic status reverses oliguria and tubular activation. The administration of potent diuretics may override tubular conservation, resulting in dilute urine that is high in sodium (natriuresis), a profile that mimics that of acute tubular necrosis (see later). In this situation, analysis of urea handling is a more reliable indicator of a prerenal state. However, if intravascular hypovolemia is sufficiently severe, tubular sodium retention and low urinary sodium may persist despite the administration of diuretics such as small-dose dopamine.[50]

In established acute tubular necrosis, concentrating ability and sodium conservation are lost, resulting in dilute urine with high sodium that is not reversed by restoration of normal renal blood flow. However, in nonoliguric renal failure, which accounts for as much as 75% of cases of acute tubular necrosis encountered clinically,[51] the changes in tubular function are less distinct from those of the prerenal syndrome.

URINARY CONCENTRATING ABILITY

Concentrating ability is a very sensitive barometer of tubular function. In prerenal states, urinary osmolar concentration is markedly increased. In acute tubular necrosis, the ability to concentrate urine may be lost 24 to 48 hours before serum creatinine or BUN starts to increase.

Urine-to-Plasma Osmolar Ratio

The normal tubular response to dehydration or hypovolemia is to concentrate the urine and increase urine osmolality above 450 mOs/kg, compared with a normal serum or plasma osmolality of 280 to 300 mOs/kg. Thus, a prerenal syndrome is indicated by a urine-to-plasma osmolar ratio ($U:P_{OSM}$) of greater than 1.5. Loss of concentrating ability, or isosthenuria ($U:P_{OSM} = 1.0$), in the presence of oliguria implies tubular damage and established acute renal failure. However, isosthenuria can be induced in a prerenal state when diuretics are administered (see earlier).

Free Water Clearance

Free water clearance (C_{H_2O}) is a measure of renal water regulation by tubular dilution or concentration of urine. In essence, free water is cleared by the tubules in response to hypervolemia ("positive free water clearance"), or retained in response to hypovolemia ("negative free water clearance"). The kidney's capacity for water regulation is enormous, and daily C_{H_2O} can vary from 18L positive to 8L negative.[52]

C_{H_2O} is calculated by distinguishing the renal clearance of solute from that of free water. The solute or osmolar clearance (C_{OSM}) is calculated by standard methods, using urine osmolality in mOs/kg (U_{OSM}), plasma osmolality in mOs/kg (P_{OSM}), and urine flow in mL/minute (V):

$$C_{OSM} = (U_{OSM} \bullet V) / P_{OSM} \text{ mL/minute} \quad [11]$$

Then the osmolar clearance is subtracted from the urine flow rate to give free water clearance:

$$CH_2O = V - C_{OSM} \text{ mL/minute} \quad [12]$$

This implies that when urine is dilute and flow is more rapid than osmolar clearance, C_{H_2O} is positive and when urine is concentrated and flow is less than osmolar clearance, C_{H_2O} is negative. Negative free water clearance (i.e., free water retention), also known as tubular conservation of water (TC_{H_2O}), represents the volume of fluid that would have to be added to the urine to make its osmolality equivalent to that of plasma.[52]

With the onset of acute tubular necrosis and loss of concentrating ability, the urine becomes isosmotic and C_{H_2O} approaches zero (±0.25 mL/minute). However, in distinguishing between prerenal and intrarenal oliguria, C_{H_2O} does not really provide any more information about concentrating ability than $U:P_{OSM}$, and in addition, it requires a timed urine collection.

WATER CONSERVATION

Urine-to-Plasma Creatinine Ratio

The urine-to-plasma creatinine ratio ($U:P_{CR}$) represents the proportion of water filtered by the glomerulus that is abstracted by the entire tubule. Normally, about 98% of water is abstracted, and urine creatinine is much greater than plasma creatinine. The ratio can increase 100-fold in severe prerenal states. When tubular function is lost, the ratio declines to less than 20:1.

For example, assume that two patients have oliguria with a serum creatinine elevated to 2.0 mg/dL. In patient A, the urine creatinine is 100 mg/dL, and in patient B, it is 20 mg/dL. Patient A likely has a prerenal state, because tubular water abstraction is high (U:P creatinine = 50:1), whereas patient B likely has acute tubular necrosis, because tubular water abstraction is impaired (U:P creatinine = 10:1).

SODIUM AND UREA CONSERVATION

Urine Sodium

Dehydration or hypovolemia markedly stimulates tubular sodium reabsorption at the mTAL and distal tubule. In the prerenal syndrome, oliguria is characterized by very low urine sodium (U_{Na}), less than 20 mEq/L. Typically, this response is reversed by restoration of intravascular volume. However, in two situations, severe sepsis and the hepatorenal syndrome of liver failure, refractory oliguria with low urine sodium persists despite aggressive fluid resuscitation. The pathogenesis is multifactorial, but common to both syndromes is endotoxemia, which induces renal vasoconstriction and avid tubular sodium reabsorption.

In established acute renal failure, the tubular ability to conserve sodium and protect the intravascular volume is lost, and urine sodium exceeds 60 to 80 mEq/L. Note that after recent diuretic therapy, a high urine sodium cannot be interpreted as tubular injury, but a persistently low urine sodium implies the existence of an intense prerenal state (see earlier).[50]

Fractional Excretion of Sodium

Fractional excretion of sodium (FENa) is an additional means of evaluating tubular responses to hypo- and hypervolemia. FENa expresses sodium clearance as a

percentage of creatinine clearance. The implication is that in hypovolemia, sodium clearance (and thus FENa) declines to reflect tubular sodium conservation; in hypervolemia, the opposite occurs.

FENa is calculated as follows:

$$\text{FENa} = (\text{sodium clearance/creatinine clearance}) \times 100\,\% \quad [13]$$

Based on the relationship expressed earlier in Equation 7:

$$\text{FENa} = (U_{Na} \bullet V/P_{Na}) / (U_{Cr} \bullet V/P_{Cr}) \times 100\,\% \quad [14]$$

Urine flow rate (V) is identical in the numerator and denominator and thus cancels itself out:

$$\text{FENa} = (U_{Na}/P_{Na}) / (U_{Cr}/P_{Cr}) \times 100\,\% \quad [15]$$

Thus, FE_{Na} may be calculated from a spot sample of blood and urine without requiring a timed urine collection.

During dehydration or hypovolemia, sodium clearance and FENa are decreased to less than 1% of creatinine clearance. When tubular ability to conserve sodium is lost in acute renal failure, FENa increases to more than 3%. However, FENa increases with normal tubular function after diuretic therapy and during postoperative sodium mobilization. Sequential increases in FENa associated with a declining creatinine clearance provide a more reliable indicator of deteriorating renal function than does an isolated high FENa.

Fractional Excretion of Urea Nitrogen

Unlike sodium, handling of urea in the ascending loop of Henle and distal tubule is subject to passive forces, and is little influenced by loop diuretic therapy. Fractional excretion of urinary nitrogen (FE_{UN}) is related to water reabsorption in the proximal tubules, which increases to compensate for impaired renal perfusion in a prerenal state. Urea is also reabsorbed, leading to an increased BUN-to-SCr ratio and decreased FE_{UN}. Perhaps the FE_{UN} is more sensitive and more specific than the FENa in differentiating oliguria due to ATN from a prerenal syndrome, especially in the presence of loop diuretic therapy[53].

The FE_{UN} is calculated identically to FENa:

$$FE_{UN} = (U_{UN}/\text{BUN}) / (U_{Cr}/P_{Cr}) \times 100\,\% \quad [16]$$

where U_{UN} is the urinary urea nitrogen, U_{Cr} is urine creatinine, and P_{Cr} is plasma creatinine. In oliguric patients, a FE_{UN} of less than 35% indicates a prerenal syndrome, whereas a FE_{UN} of 50% to 65% suggests established acute renal failure, even in the presence of loop diuretic therapy.[53]

The major limitation to the FE_{UN} is the concomitant administration of proximal tubule diuretics, such as acetazolamide, and osmotic diuretics, such as mannitol. These agents impair water reabsorption in the proximal tubule and help to decrease FE_{UN} in a prerenal state. Excessive urea production in highly catabolic states may itself induce an osmotic diuresis and render the FE_{UN} inaccurate.

In conclusion, accurate diagnosis of a prerenal state should not be based on one test alone. The FE_{UN} reflects proximal tubule activity, the FENa reflects distal tubule activity, and the $U{:}P_{Cr}$ reflects water abstraction throughout the tubule. In difficult situations, a combination of tests is less likely to be subject to error than is a single estimation.[53]

BIOMARKERS OF RENAL INJURY

In contrast to serum creatinine, which is used as an indirect indicator of renal function or dysfunction (i.e., GFR), biomarkers are molecules or compounds that indicate direct tubular injury. Traditional biomarkers include β_2 microglobulin and *N*-acetyl-β-D-glucosaminidase. Their widely acknowledged limitations in the early and accurate detection of evolving renal injury have fostered an increasing interest in a new generation of biomarkers. Functional genomics and proteomics have created the possibility of identifying potential injury biomarkers with a precision and specificity not previously possible, and numerous candidate biomarkers are currently at various stages of clinical investigation. However, to supplant serum creatinine in clinical practice, new biomarkers of renal injury must reliably identify patients at risk for adverse outcomes across a range of clinical populations – a goal that has not yet been achieved.

B_2-MICROGLOBULIN

β_2-microglobulin is a small protein component of the major histocompatibility complex that is present on the surface of almost all cells. It is normally filtered by the glomerulus and then undergoes partial tubular reabsorption. The ratio of β_2-microglobulin between serum and urine may help distinguish glomerular from tubular injury, although the relationship between increased urinary β_2-microglobulin and subsequent ATN has not been characterized.

In glomerular injury, serum β_2-microglobulin levels increase and urine levels decrease. This assessment has been used as an early sign of rejection in renal transplantation.[54] In primary tubular injury, reabsorption of β_2-microglobulin is impaired, so urinary levels increase and serum levels decline. In a study in which cardiopulmonary bypass (CPB) with pulsatile flow was used, a significant decrease occurred in plasma renin activity but urinary β_2-microglobulin increased on CPB with pulsatile or non-pulsatile flow.[55] The implication is that although pulsatile flow maintains better renal perfusion, it does not prevent a subclinical renal tubular injury.

Urinary *N*-acetyl-*β*-D-glucosaminidase

A lysosomal enzyme, *N*-acetyl-β-D-glucosaminidase (NAG) is found abundantly in proximal tubular epithelial cells and increased urinary concentrations of the tubular enzyme NAG is a well-established method of identifying subclinical tubular injury. Urinary NAG levels, or the ratio of its isoenzymes, have been used in the early detection of rejection in transplant patients and to follow the course of chronic renal disease, such as lupus nephritis.[56] NAG was used extensively through the 1990s as a marker of subclinical tubular injury in association with sevoflurane and compound A exposure during anesthesia. However, a relationship between elevations in urinary NAG and histopathologic changes, increasing serum creatinine, or

adverse clinical outcomes has not been established, and the perioperative interpretation and clinical utility of NAG remains uncertain.[35]

Neutrophil Gelatinase–Associated Lipocalin

Neutrophil gelatinase–associated lipocalin (NGAL) is a small 25-kDA polypeptide expressed in distal tubular cells and collecting ducts, whose mRNA undergoes dramatic up-regulation after ischemic tubular injury.[57] Up-regulation can be detected within minutes of ischemia-reperfusion injury; it increases three- to fourfold within 2 to 3 hours and up to 10,000-fold by 24 hours. NGAL is protease resistant and is readily detected in tiny (nanogram/mL) amounts of urine almost immediately after renal injury, preceding the appearance of NAG and β_2-microglobulin.

Urinary NGAL has been demonstrated to increase significantly within 2 hours of CPB in pediatric or adult patients who subsequently went on to develop a 50% increase in postoperative serum creatinine, whose peak was delayed until 1 to 3 days after surgery.[58,59] However, the diagnostic performance of NGAL for AKI has varied widely and dramatically across clinical studies for reasons that remain unclear. Paradoxically, the very limitations of serum creatinine that have driven the search for better diagnostic measures of renal injury, also render creatinine-based measures of injury an unreliable gold standard by which to compare novel biomarkers.[60] Instead, novel biomarkers must demonstrate both validity and clinical utility for identifying individuals at increased risk for adverse clinical outcomes associated with renal injury.[61] Larger studies confirming a relationship between NGAL and adverse outcomes such as mortality, renal replacement therapy, and increased hospital length are beginning to emerge; these findings support a potential role for urinary NGAL as an early, sensitive, and noninvasive urinary biomarker for ischemic and nephrotoxic renal injury.[62,63]

Interleukin-18 (IL-18)

Synthesized as an inactive 23-kDa precursor by several cell types, including proximal tubular epithelial cells, macrophages, and monocytes, IL-18 is a proinflammatory cytokine.[35,64] Multiple studies demonstrate increased urinary IL-18 levels in association with acute kidney injury.[65-67] However, results have been inconsistent with limited data addressing a relationship with adverse clinical outcomes and its potential role as a diagnostic marker in clinical practice remains uncertain.

Other Candidate Biomarkers

Multiple other potential biomarkers of acute kidney injury have been identified. Liver fatty acid–binding protein (L-FABP), a component of the cytoplasm of proximal tubular cells, binds fatty acids for transport to mitochondria. It is released early into the urine following tubular injury, and there is some evidence that it may be more specific than NGAL.[68] In a study on 85 patients undergoing cardiac surgery, AKI was defined by stage 1 of the AKIN criteria. Urinary L-FABP was increased significantly earlier and to a greater extent than urinary NGAL.[69]

Hepcidin is a peptide hormone produced in the liver that regulates iron homeostasis. Its synthesis appears to be up-regulated by CPB and urinary hepcidin increases in patients with normal renal function. In the presence of AKI, 24-hour urinary hepcidin and hepcidin-to-creatinine ratios decrease and provide high sensitivity and specificity for its diagnosis.[70,71]

The true role of the previously mentioned biomarkers, as well as others such as retinol-binding protein and multiple forms of glutathione-S-transferase, awaits larger multicenter studies to characterize their validity and potential clinical utility. It may be practical to consider a panel of biomarkers that together define the course of AKI over time (Fig. 23-16).

At this point in time, an increased serum creatinine concentration, despite all the limitations enumerated earlier, remains the gold standard in the definition of AKI that is consistently and reliably associated with adverse clinical outcomes.[72-75] An emerging approach is the integration of serum creatinine (an indicator of renal function) with biomarkers (evidence of tubular injury). Thus, patients may be classified as having no evidence of injury and intact function (i.e., normal), evidence of injury but intact function (early AKI), loss of function without evidence of injury (CKD), or evidence of injury and loss of function (established AKI).

RENAL HEMODYNAMICS

RENAL PLASMA FLOW AND RENAL BLOOD FLOW

It is impractical to place renal flow probes in patients, so renal plasma flow (RPF) and renal blood flow (RBF) are most often measured indirectly by clearance techniques.

Para-Aminohippurate Clearance

Para-aminohippurate (PAH) is an organic anion filtered by the glomerulus, secreted by the tubule, and almost completely cleared from the plasma in a single pass through the kidney. Thus, clearance of PAH (C_{PAH}) represents RPF.

Like inulin clearance, the test is laborious and requires intravenous and urinary catheters. A PAH infusion is set up to maintain a steady-state PAH concentration of about 2 mg/dL, together with a carefully timed catheter urine collection[43]. Because 10% of the RPF bypasses the peritubular capillaries, C_{PAH} underestimates the true RPF, and is referred to as effective RPF.

$$\text{Effective RPF} = C_{PAH} = U_{PAH} \times V/P_{PAH} \quad [17]$$

In young healthy adults, effective RPF is 660 mL/minute/1.73 m^2.

Effective RBF may be derived if the hematocrit level (Hct) is known and expressed as a decimal (i.e., 35% = 0.35):

$$\text{Effective RBF} = \text{Effective RPF}/1 - \text{Hct} \quad [18]$$

As an example, if effective RPF is 600 mL/minute and Hct is 30% (0.3), effective RBF is 600 ÷ 0.7, or 860 mL/minute.

Unfortunately, C_{PAH} is an unreliable indicator of RPF during surgical stress, because hypovolemia and oliguria induce sequestration of PAH in the kidney. Ironically, the

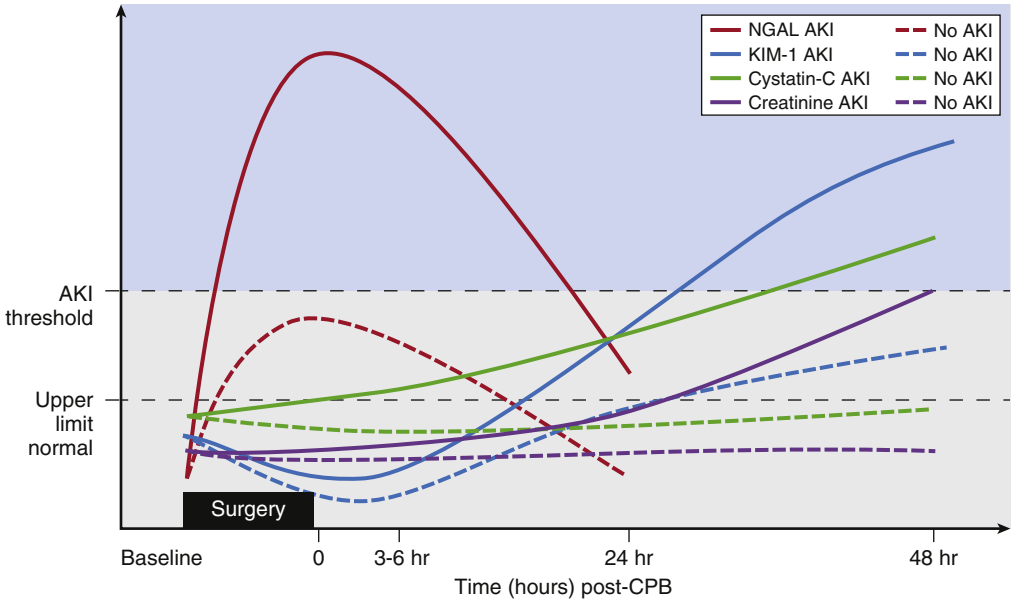


Figure 23-16. Renal biomarkers. Schematic representation of the possible time course of change in biomarker levels for the detection of acute kidney injury (AKI) after cardiac surgery in adults. Patterns of change represent ideal circumstances, which have not been consistently demonstrated in clinical studies. *AKI*, Acute kidney injury; *CPB*, cardiopulmonary bypass; creatinine, serum creatinine; *cystatin-C*, serum cystatin-C; *KIM-1*, urinary kidney injury molecule-1; *NGAL*, urinary neutrophil gelatinase–associated lipocalin. *(Modified from McIlroy D, Wagener G, Lee, HT: Biomarkers of acute kidney injury: an evolving domain,* Anesthesiology *112:998-1004, 2010.)*

most important limitation of C_{PAH} is acute kidney injury, because about 80% of PAH is cleared by tubular secretion. In the presence of proximal tubular injury, PAH secretion declines and C_{PAH} underestimates RPF.[76]

These errors can be overcome if renal vein sampling is accessible (e.g., during major abdominal vascular surgery). Measurement of the difference between arterial and renal vein PAH allows calculation of the renal extraction of PAH (E_{PAH}), an index of proximal tubular function:

$$E_{PAH} = \text{arterial PAH} - \text{renal vein PAH/arterial PAH} \quad [19]$$

When renal function is normal, renal vein PAH is close to zero and E_{PAH} approaches 100% (1.0). With worsening proximal tubular function, renal vein PAH concentration progressively increases and E_{PAH} progressively declines.

True RPF is calculated by dividing PAH clearance by PAH extraction:

$$RPF = C_{PAH}/E_{PAH} \quad [20]$$

In the presence of hypovolemia and oliguria, PAH is sequestered in the kidney. Even with the use of extraction techniques PAH clearance may misrepresent renal plasma flow under these conditions. Despite its relative convenience as an experimental tool, PAH clearance may be an unreliable indicator of RBF during the perturbations induced by anesthesia and surgical stress.

Filtration Fraction

The fraction of the RPF that is filtered by the glomerulus is called the filtration fraction (FF) and can be measured indirectly via the C_{PAH} and C_{IN}:

$$FF = GFR/RPF = C_{IN}/C_{PAH} \quad [21]$$

Normally, GFR is about 125 mL/minute and RPF is about 660 mL/minute, so the filtration fraction approximates 125/660, or about 0.2. Changes in filtration fraction are considered to represent changes in periglomerular arteriolar tone (see "Afferent and Efferent Arteriolar Control Mechanisms"). An increase in filtration fraction indicates that GFR is increased relative to RPF. This could be achieved by efferent arteriolar constriction or afferent arteriolar dilation and maintains glomerular filtration pressure in the face of decreased RPF. Conversely, a decrease in filtration fraction implies that GFR is decreased relative to RPF by afferent arteriolar constriction or efferent arteriolar dilation.

Total Renal Blood Flow

Real-time measurement of RBF is technically challenging and generally confined to the laboratory unless there is direct access to the renal arteries during surgery.

Flow Probes. Electromagnetic flow probes create a magnetic field around the circumference of the vessel that is disrupted by blood flow, and a voltage output proportional to blood velocity is generated.

Ultrasonic flow probes transmit high-frequency sound across the lumen of the vessel. A shift in sound frequency (Doppler effect) is created by the movement of blood and is proportional to blood velocity.

$$\text{Flow (mL/minute)} = \text{Blood velocity (cm/minute)} \times \text{Area of vessel } \left(\text{cm}^2\right) \quad [22]$$

Flow-probe placement is invasive and requires direct surgical exposure of the renal arteries. Probes must be calibrated in vitro before and after measurements. However, they are generally very accurate.

Investigational Methods of Measuring RBF. Numerous investigational methods have been or are being developed

to attempt to measure RBF. Some, such as thermodilution via direct renal vein cannulation, have been confined to animal studies.[77,78] Contrast ultrasonography with sonicated albumin microspheres has been used to measure RBF in animal studies.[79] More recently, this technique, utilizing microbubbles, has successfully measured RBF in healthy volunteers, and may lend itself to studies in patients.[80]

Transesophageal echocardiography (TEE) has been used to quantitate RBF in children and shows a high correlation with transabdominal ultrasonography.[81] Although this is more technically difficult in adults, the left renal artery can be visualized and interrogated by TEE.[82]

Positron emission tomography (PET) has been used to measure acute changes in RBF in patients with chronic renal failure using oxygen 15-radiolabeled water.[83]

Magnetic resonance imaging (MRI) shows some promise in the real-time, noninvasive assessment of RBF. Ungated spiral phase-contrast MRI is able to measure RBF within 6 seconds.[84] Cine phase–contrast magnetic resonance imaging (CPC-MRI) has been successfully used to assess renal blood flow as a fraction of cardiac output in septic patients with established dialysis-dependent AKI.[85] All metallic devices have to be removed before physical transport to an MRI suite, but this noninvasive approach does provide promise in the elucidation of changes in RBF under physiologic or pathologic conditions in patients.

NEUROHORMONAL REGULATION OF RENAL FUNCTION

The role of the kidney in controlling the interior milieu is modulated by a complex set of interactions. Two mutually dependent but opposing neurohormonal systems maintain blood pressure, intravascular volume, and salt and water homeostasis (Fig. 23-17). The sympathoadrenal axis, the renin-angiotensin-aldosterone system, and AVP defend against hypotension and hypovolemia by promoting vasoconstriction and salt and water retention. The prostaglandins and natriuretic peptides defend against hypertension and hypervolemia by promoting vasodilation and salt and water excretion (Fig. 23-18).

Anesthesia does not perturb these systems to any substantial degree. In the intact organism, anesthetics affect renal function through extrarenal circulatory changes, rather than by their direct actions on the kidney.[86] Surgical or traumatic injury, on the other hand, induces profound vasoconstriction and salt and water retention, which may persist for several days. The clinical sequel is postoperative oliguria and edema. Renal vasoconstriction also predisposes the kidney to further perioperative ischemic and nephrotoxic insults. Release of endogenous natriuretic peptides by atrial and ventricular stretch reinforces the notion that renal vasoconstriction can be prevented or modified by maintenance of normal or increased intravascular volume.

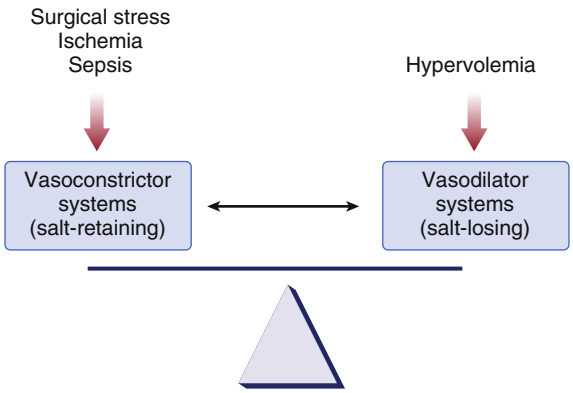


Figure 23-17. Neurohormonal regulation of renal function. Normally, there is a balance between those systems promoting renal vasoconstriction and sodium retention versus those systems promoting renal vasodilation and sodium excretion. Surgical stress, ischemia, and sepsis tip the balance in favor of vasoconstriction and sodium retention. On the other hand, hypervolemia (or the induction of atrial stretch) tips the balance in favor of vasodilation and sodium excretion.

SYSTEMS PROMOTING VASOCONSTRICTION AND SALT RETENTION

THE SYMPATHOADRENAL AXIS

Sympathetic effects on the kidney are mediated by circulating epinephrine and neuronal release of norepinephrine. The renal cortex has a dense plexus of autonomic nerve fibers derived from the T12 to L4 spinal segments via the celiac plexus. The primary stimulus to the sympathetic response is a decrease in arterial blood pressure sensed by baroreceptors in the aortic arch, carotid sinus, and afferent arteriole. Afferent fibers travel via the vagus nerve and decrease impulse transmission rate to the mediating centers in the hypothalamus, which results in increased adrenergic nerve activity. The kidney does not have any parasympathetic innervation.

A G protein–coupled phospholipase C receptor populates vascular smooth muscle and the mesangium, and it responds to α-adrenergic stimulation by epinephrine and norepinephrine. It also mediates vasoconstriction induced by a variety of other hormones and peptides, including angiotensin II, vasopressin, endothelin, platelet-activating factor, and leukotrienes.[3] The receptor subunit in the cell membrane is coupled through G_q protein

Vasoconstrictor Systems	Vasodilator Systems
Sympathoadrenal system Renin-angiotensin system Aldosterone Antidiuretic hormone (ADH)	Prostaglandins Kinins Atrial natriuretic peptide (ANP)
↓ RBF ↓ GFR ↓ Urine flow ↓ Na excretion	↑ RBF ↑ GFR ↑ Urine flow ↑ Na excretion

Figure 23-18. Neurohormonal renal regulatory systems. *GFR*, Glomerular filtration rate; *Na*, sodium; *RBF*, renal blood flow; *x*, decreased; *y*, increased. *(Modified from Sladen RN: Effect of anesthesia and surgery on renal function,* Crit Care Clin *3:380, 1987.)*

to phospholipase C, which hydrolyzes phosphatidylinositol biphosphate (PIP_2) to inositol triphosphate (IP_3) and diacylglycerol (DAG). In turn, DAG activates protein kinase, opening up a calcium channel in the membrane, and IP_3 triggers the release of calcium from the sarcoplasmic or endoplasmic reticulum. Both mechanisms result in a rapid increase in intracellular calcium, which binds with calmodulin and thereby activates myosin light-chain kinase, resulting in smooth muscle contraction. The calcium-calmodulin complex simultaneously activates phospholipase A_2, resulting in the production of vasodilator prostaglandins (see later).

Mild α-adrenergic stimulation appears to cause preferential efferent arteriolar constriction, which preserves the filtration fraction. Severe α-adrenergic stimulation causes predominant afferent arteriolar constriction and decreases filtration fraction.[87] Thus, the adrenergic response to a moderate decrease in renal perfusion (e.g., general anesthesia) favors the preservation of the GFR. In contrast, the adrenergic response to shock exacerbates the decrease in GFR already induced by renal hypoperfusion (see Fig. 23-4).

Adrenergic nerves also supply the proximal tubule, thick ascending limb of Henle, and collecting duct, and their stimulation enhances NaCl reabsorption at these sites. Gas tracer studies suggested that sympathetic activation caused sodium retention by intrarenal redistribution of RBF from the outer cortex to salt-retaining juxtamedullary nephrons, but this was not confirmed by microsphere studies.[88,89]

A close relationship exists between sympathetic stimulation and activation of the renin-angiotensin system. Adrenergic stimulation releases renin from the juxtaglomerular apparatus, and adrenergically induced vasoconstriction can be blocked by angiotensin-converting enzyme (ACE) inhibitor drugs such as captopril.

The effects of the administration of exogenous adrenergic drugs depend on their agonist activity. Drugs with predominantly α-adrenergic effects, such as norepinephrine, epinephrine, phenylephrine, and high-dose dopamine (>10 μg/kg/minute) exacerbate the endogenous sympathetic responses to hypotension. Drugs with predominantly β_1- and β_2-adrenergic activity, such as dobutamine or isoproterenol, cause marked increases in cardiac output and thus RBF, but it is difficult to ascertain their intrarenal effects. Dopaminergic agonists (Table 23-5) selectively increase RBF and may oppose α-adrenergic renal vasoconstriction.[78]

TABLE 23-5 DOPAMINE AND ITS ANALOGUES

Receptor	DA_1	DA_2	β_1	β_2	α_1
Dopamine	+++	++	++	±	+++
Dobutamine*	0	0	+++	++	±
Dopexamine*	++	+	±	+++	0
Fenoldopam*	++++	0	0	0	0

DA_1, Dopamine$_1$ receptor, *DA_2*, dopamine$_2$ receptor, *β_1*, beta$_1$ receptor, *β_2*, beta$_2$ receptor, *α_1*, alpha$_1$ receptor.
*Dobutamine, dopexamine, and fenoldopam are all pharmacologic analogues of dopamine. However, dobutamine is devoid of dopaminergic activity, dopexamine has about one third the dopaminergic activity of dopamine, and fenoldopam is a pure, selective dopamine$_1$ receptor agonist.

THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Renin and Angiotensin

The juxtaglomerular apparatus consists of three groups of specialized tissues. In the afferent arteriole, modified fenestrated endothelial cells produce renin; in the juxtaposed distal tubule, cells of the macula densa act as chemoreceptors; and in the glomerulus, mesangial cells have contractile properties (see Fig. 23-3). Together these provide an important regulating system for blood pressure, salt, and water homeostasis.[90]

Renin secretion is stimulated by hypovolemia that may be overt (hemorrhage, diuresis, or sodium loss or restriction) or covert (positive pressure ventilation, congestive heart failure, sepsis, or cirrhosis with ascites). Its release is controlled by several mechanisms. A decrease in renal artery perfusion pressure triggers baroreceptors in the afferent arterioles. Sympathetic nerve stimulation and circulating catecholamines act on β-adrenergic receptors in the afferent arterioles. An increase in chloride concentration in the distal tubular fluid activates the cells of the macula densa, which trigger renin release from the afferent arteriole. This tubuloglomerular feedback appears to play a role in modulating GFR during normal and abnormal renal function through a continuous feedback loop.[4,5]

Renin acts on angiotensinogen, a large circulating glycoprotein released from the liver, and cleaves off a decapeptide, angiotensin I. In the kidney and in the lung, angiotensin I is further cleaved by endothelial-based ACE to form an octapeptide, angiotensin II, which is a potent vasoconstrictor (Fig. 23-19). Renin is the rate-limiting enzyme in the production of angiotensin II[91].

Activation of modest amounts of angiotensin II causes renal cortical vasoconstriction predominantly at the level of the efferent arterioles (see Fig 23-4). This acts to maintain glomerular filtration fraction in the face of mild to moderate decreases in RBF or perfusion pressure. The importance of this protective mechanism is emphasized by the deterioration in GFR that occurs when ACE inhibitors are administered to patients with hypotension, renal insufficiency, or unilateral renal artery stenosis.[92,93] Severe stress induces the release of high levels of angiotensin

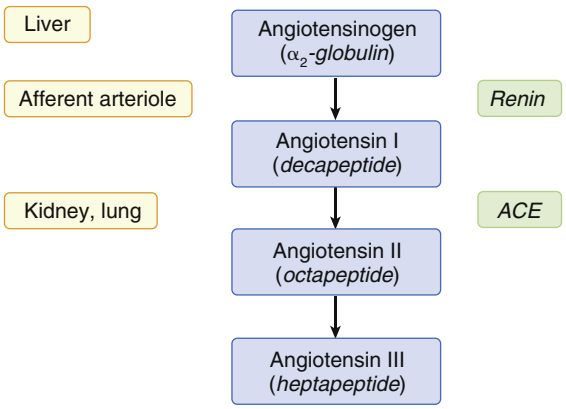


Figure 23-19. Renin-angiotensin system. For explanation, see text. *ACE,* Angiotensin-converting enzyme.

II, which constricts the glomerular mesangial cells and decreases the glomerular filtration fraction. Angiotensin II promotes systemic vasoconstriction at about one tenth of its renal effect. However, systemic arterial pressure and vascular resistance can be markedly decreased by ACE inhibitors (such as captopril, enalapril, or lisinopril) and by angiotensin receptor antagonists such as losartin. The effect of angiotensin II in causing salt and water retention is enhanced by its actions in stimulating aldosterone secretion by the adrenal cortex, AVP secretion by the posterior pituitary, and NaCl reabsorption by the proximal tubule.[90]

Angiotensin II triggers a number of responses that modulate or oppose its own actions. It inhibits renin secretion by a negative feedback mechanism. Blockade of angiotensin formation by ACE inhibitors causes vasodilation but increases plasma renin levels. Angiotensin II activates phospholipase A_2, which triggers the synthesis of intrarenal prostaglandins. Vasodilator prostaglandins modulate the action of angiotensin II and may be responsible for its preferential activity on the efferent arteriole at low plasma levels.[91] Angiotensin-induced vasoconstriction increases atrial pressure and releases ANP, which opposes the renin-angiotensin-aldosterone system.

The consequences of ACE inhibition on renal function depend on the patient's volume status, systemic hemodynamics, and baseline renal perfusion. In the long-term treatment of hypertension and CHF, especially in diabetics, the administration of ACE inhibitors decreases renal vascular resistance and appears to benefit renal function. Short-term pretreatment with captopril may prevent a decrease in RBF and GFR and preserve sodium excretion during cardiopulmonary bypass.[94] However, deterioration in renal function and hyperkalemia have been reported with the use of ACE inhibitors in patients with hypotension, renal insufficiency, or unilateral renal artery stenosis, probably related to the blockade of compensatory angiotensin-mediated efferent arteriolar constriction.[93] It may be prudent to avoid their use when hemodynamics are unstable in the immediate perioperative period.

Aldosterone

Aldosterone is a steroid hormone secreted by the zona glomerulosa of the adrenal cortex in response to hyperkalemia or hyponatremia. Angiotensin II and adrenocorticotropic hormone (ACTH) also trigger its release. It acts at the thick ascending limb of the loop of Henle, the principal cells of the distal tubule, and the collecting duct to increase active absorption of sodium and passive absorption of water, culminating in an expanded blood volume. Sodium retention in vessel walls appears to enhance their response to vasoconstrictor agents.

In contrast to the immediate sympathetic angiotensin II response to hypovolemia, there is a delay of about 1 to 2 hours from the secretion of aldosterone to its action on sodium reabsorption. As illustrated in Fig. 23-20, aldosterone forms a complex with a receptor at the cell membrane in the principal cells of the distal tubule. The aldosterone-receptor complex travels to the cell nucleus, where it induces cytoplasmic transcription of messenger ribonucleic acid (mRNA). This fosters synthesis of proteins that form sodium channels in the apical cell membrane and enhance the Na-K-ATPase pump in the basolateral cell membrane.[95] Sodium is transported from the tubular fluid into the peritubular capillary in exchange for potassium. Long-standing stimulation of aldosterone secretion, characteristically induced by the intravascular volume depletion of chronic ascites, culminates in potassium depletion and hypokalemic alkalosis.

Arginine Vasopressin (AVP)

Arginine vasopressin (AVP), previously known as antidiuretic hormone (ADH), regulates urinary volume and osmolality and controls diuresis and antidiuresis. It is a 9-amino-acid peptide, 8-arginine-vasopressin, which is synthesized in the supraoptic and paraventricular nuclei of the anterior hypothalamus.[95] These nuclei are essentially the cell bodies of neurons whose axons extend down into nerve terminals in the posterior pituitary, together composing the neurohypophysis (Fig. 23-21). When AVP is synthesized, it undergoes neuroaxonal transport to the posterior pituitary gland, where it is stored in granules. Neural stimulation of the cell bodies triggers exocytosis of AVP from the terminal vesicles into the circulation.

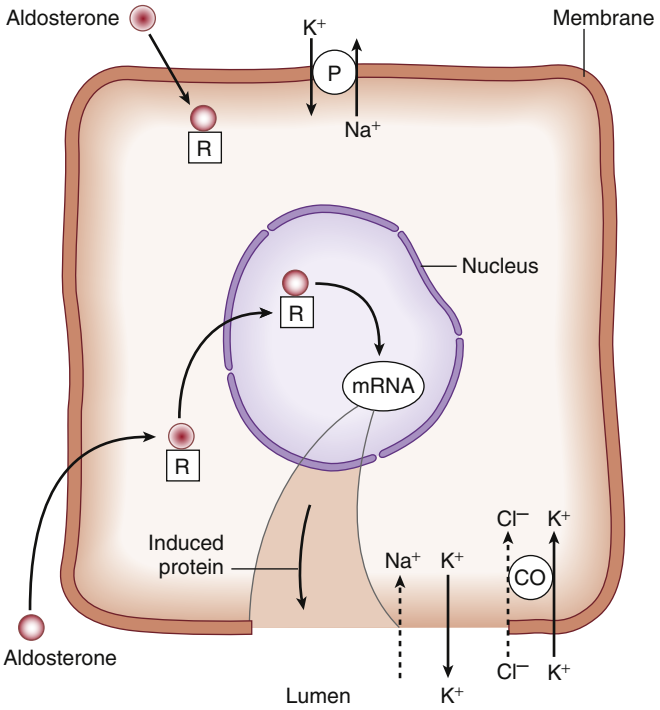


Figure 23-20. Action of aldosterone. Aldosterone enters the distal tubular cytoplasm and attaches to a receptor, then migrates to the nucleus, where it induces the formation of a messenger RNA (mRNA). The mRNA in turn induces the synthesis of a protein that enhances the permeability of the apical (luminal) membrane to sodium and potassium. The reabsorption of sodium stimulates the basolateral membrane Na-K-ATPase pump, the intracellular concentration of potassium rises, and it follows its concentration gradient out into the lumen. The net effect of aldosterone's action is sodium reabsorption and potassium loss. *Cl^-*, Chloride; *CO*, cotransporter (= symporter); *K^+*, potassium; *mRNA*, messenger ribonucleic acid; *Na^+*, sodium; *P*, sodium-potassium ATPase pump; *R*, receptor. *(From Wingard LB, Brody TM, Larner J, Schwartz A: Diuretics: drugs that increase excretion of water and electrolytes. In Wingard LB, Brody TM, Larner J, Schwartz A, editors:* Human pharmacology: molecular-to-clinical, *London, 1991, Wolfe Publishing Ltd, p 249, Fig 19-4.)*

AVP acts on specific V_2 receptors in the collecting ducts to induce water reabsorption and a decreased flow of concentrated urine. It also increases NaCl reabsorption from the thick ascending loop of Henle into the medullary interstitium, which maintains its hypertonicity and facilitates movement of water out of the collecting duct along the osmotic gradient. This results in tubular conservation of water and free water retention (i.e., negative free water clearance). The net effect is that AVP increases urine osmolality and decreases plasma osmolality, without significant alteration in solute excretion.

The V_2 receptor on the basolateral cell membrane of the collecting duct responds to AVP via a receptor mechanism analogous to the β-adrenergic receptor.[95] Through activation of G protein–coupled adenylyl cyclase, ATP is converted to cyclic adenosine monophosphate (cAMP). This in turn activates a protein kinase that causes preformed vesicles containing aquaporin-2 water channels to migrate and fuse with the apical cell membrane. This results in a dramatic increase in membrane permeability to water, which is reabsorbed into the cell and thence into the peritubular capillary. AVP has a short plasma half-life of between 5 and 15 minutes, and this process rapidly reverses as plasma AVP levels decline.

Regulation of AVP Secretion

Hypothalamic osmoreceptors are sensitive to increases in serum osmolality of as little as 1% above normal. As illustrated in Fig. 23-22, *A*, the threshold for AVP secretion (and the sensation of thirst) is between 280 and 290 mOsm/kg. Once this is exceeded, the secretion rate has a very steep gain.[96] Even mild dehydration results in a rapid antidiuresis, and urine osmolality can increase from 300 to 1200 mOs/kg as plasma AVP levels rise from 0 to 5 pg/mL (see Fig. 23-22, *B*).

Decreases in intravascular volume also stimulate AVP secretion, mediated by stretch receptors with vagal afferents in the left atrium and pulmonary veins. Hypovolemia-induced secretion of AVP overrides osmolar responses and contributes to the perioperative syndrome of inappropriate antidiuretic hormone secretion (SIADH): fluid retention, hypo-osmolality, and hyponatremia.[97] The situation is exacerbated by administration of large volumes of hypotonic solutions that decrease serum osmolality. Psychic stress, via cortical input, also induces AVP release and can override osmotic and volume sensors.

By far the most potent trigger for AVP release is systemic arterial hypotension, mediated by aortic and carotid baroreceptors. It overrides all other triggers, and plasma AVP may reach levels 10- to 1000-fold greater than normal (see Fig. 23-22, *C*). At these concentrations AVP acts as a vasoconstrictor, especially in the outer renal cortex. It does so by stimulating the V_{1a} receptor, which exists on vascular smooth muscle, glomerular mesangial cells, and the vasa recta and promotes vasoconstriction via the phosphatidylinositol pathway.[96] AVP maintains effective

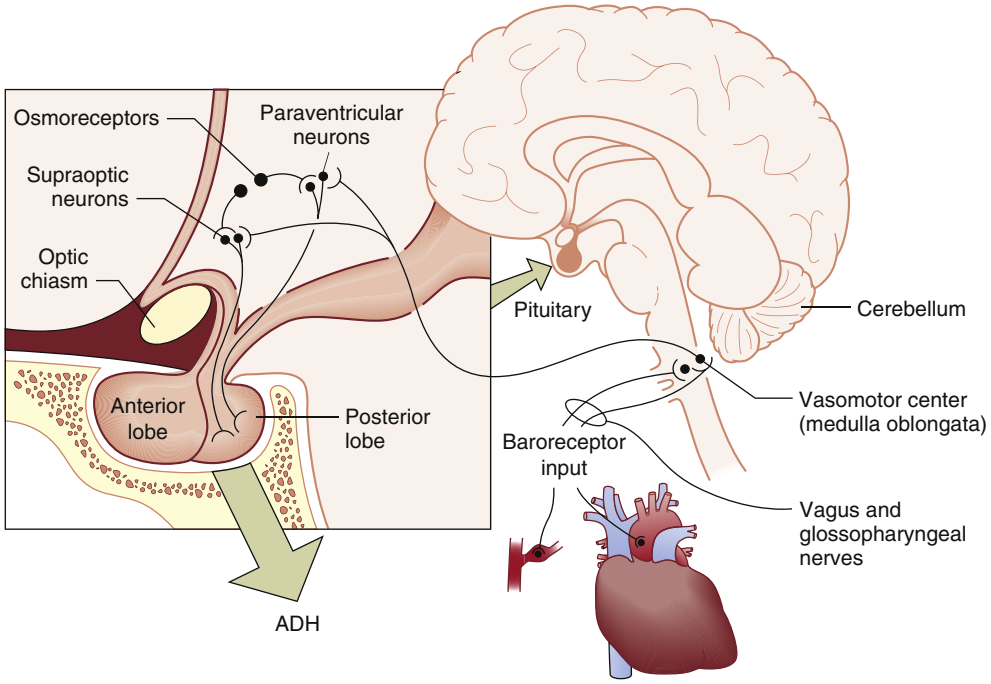


Figure 23-21. Elaboration and synthesis of arginine vasopressin (AVP). *Osmotic control:* An increase in serum osmolality is detected by osmoreceptors in the supraoptic and paraventricular neurons of the hypothalamus. Granules of AVP are elaborated and axonally transported to the posterior lobe of the pituitary gland. From there, they are released into the circulation to reach the V_2 receptors in the distal tubule, where they water retention and restore the serum osmolality. *Hemodynamic control:* Decreases in venous volume are sensed by stretch receptors in the atria and great veins, and decreases in arterial pressure are sensed by baroreceptors in the aortic arch and carotid sinus. The afferent arc is via the vagal and glossopharyngeal nerves to the solitary nucleus in the medulla oblongata (vasomotor center). The efferent arc, from the vasomotor center to the hypothalamic nuclei, induces AVP release. At low levels (<5 pg/mL), AVP stimulation of V_2 receptors may cause inappropriate water retention. At high levels (>20 pg/mL), AVP stimulation of V_{1a} receptors causes vasoconstriction and participates in the baroreceptor reflex. *(From Koeppen BM, Stanton BA: Regulation of body fluid osmolality: regulation of water balance. In Koeppen BM, Stanton BA, editors:* Renal physiology, *ed 4, Philadelphia, 2007, Mosby, pp 71-90.)*

glomerular filtration pressure because it is an extremely potent constrictor of the efferent arteriole, and unlike catecholamines and angiotensin, it has little effect on the afferent arteriole, even at high plasma levels.[98]

Anesthetics have little direct effect on AVP secretion, except via the changes that they induce in arterial blood pressure, venous volume, and serum osmolality. Surgical stimulation is a major stimulus to AVP secretion. This stress response, whether mediated by pain or by intravascular volume changes, is profound and lasts at least 2 to 3 days after the surgical procedure.

SYSTEMS PROMOTING VASODILATION AND SALT EXCRETION

PROSTAGLANDINS AND KININS

Prostaglandins

Intrarenal prostaglandins play an important role in endogenous renal protection, largely by vasodilating juxtamedullary blood vessels and maintaining inner cortical blood flow.[99] Prostaglandins are called autocoids because, unlike true hormones, they are produced in minute amounts and have a local, evanescent action. Because their structure is based on a 20-carbon fatty acid, they are also referred to as eicosanoids, after *eicosa*, the Greek word for the number twenty. The synthesis of intrarenal prostaglandins is summarized in Fig. 23-23.

Phospholipase A_2, which resides in the inner lipid layer of the cell membrane, controls prostaglandin production through its formation of the prime precursor, arachidonic acid. It is stimulated by ischemia and hypotension and also by norepinephrine, angiotensin II, and AVP. Thus, the factors that induce and mediate the stress response simultaneously activate prostaglandins, which defend the kidney against their actions. Cyclooxygenase-1 acts on arachidonic acid to form PGG_2, the precursor of the family of vasodilator prostaglandins that includes PGD_2, PGE_2, and PGI_2 (prostacyclin). They induce vasodilation through activation of cAMP, which blocks distal tubule sodium reabsorption, and they oppose the actions of norepinephrine, angiotensin II, and AVP. Prostaglandins may be particularly important in decreasing the vasoconstrictor activity of angiotensin II on the afferent arteriole and glomerular mesangial cells.[91] Production of prostaglandins promotes renal vasodilation, maintains intrarenal hemodynamics, and enhances sodium and water excretion. The renal vasodilator response to mannitol during hypoperfusion appears to be mediated through prostaglandin activation.[100] At the same time, prostaglandins also stimulate renin secretion so that there is a constant "yin and yang" between the two systems.[101]

Cyclooxygenase-2 forms derivatives of arachidonic acid that induce inflammation and renal vasoconstriction and are important in pathologic states. Thromboxane (TXA_2) is derived from cyclic endoperoxides by the action of thromboxane synthetase. It induces vasoconstriction and platelet aggregation, and in the kidney it causes mesangial cell contraction. This decreases GFR by diminishing the effective glomerular surface area and

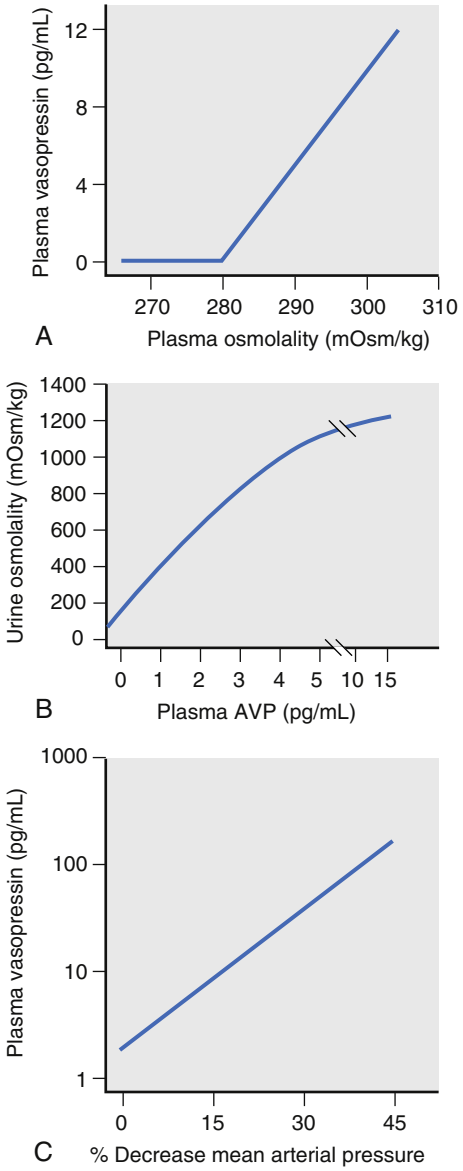


Figure 23-22. A, B, C, Physiologic regulation of arginine vasopressin (AVP). For explanation, see text. *(From Landry DW: Vasopressin deficiency and hypersensitivity in vasodilatory shock: discovery of a new clinical syndrome,* P & S Med Rev *3:3-7, 1996.)*

filtration constant (K_f). Renal levels of thromboxane are increased in experimental acute renal failure and sepsis. In animal experiments, the administration of a specific thromboxane synthetase inhibitor prevents the deterioration in renal function induced by injection of endotoxin.[102] Another vasoconstrictor prostaglandin, PGF_2, which acts on the thromboxane receptor, is formed when arachidonic acid is oxidized by free radicals liberated by leukostasis during acute inflammation. The leukotrienes, arachidonic acid derivatives formed by lipoxygenase, are also released from endotoxin-activated leukocytes. Like thromboxane, leukotrienes C_4 and D_4 induce mesangial cell contraction and decrease GFR.

Kinins

Kinins act as vasodilators that interact with and enhance the actions of prostaglandins, while modulating the

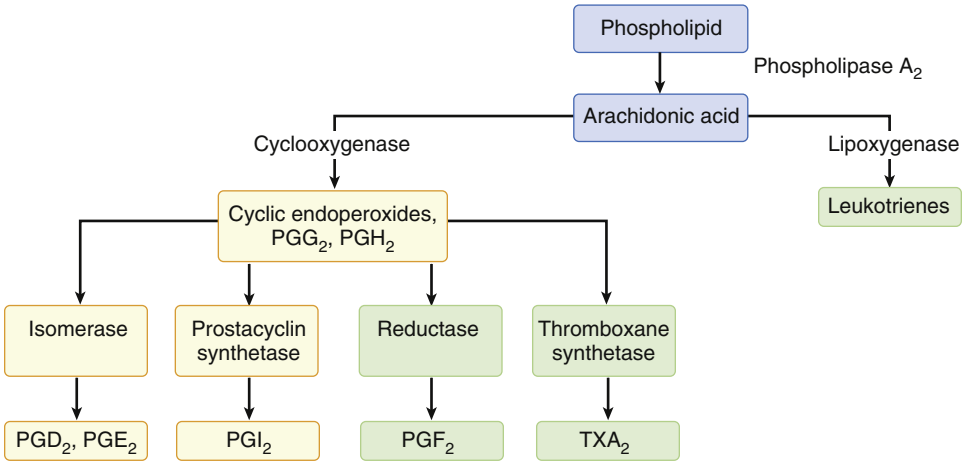


Figure 23-23. Synthesis of renal prostaglandins. Phospholipase A_2 is stimulated by ischemia, norepinephrine, and angiotensin II and cleaves arachidonic acid from its bond with membrane phospholipid. Cyclooxygenase acts on arachidonic acid to form evanescent cyclic endoperoxides (PGG_2 and PGH_2). Actions of isomerase and prostacyclin synthetase culminate in the formation of vasodilator prostaglandins PGD_2, PGE_2, and PGI_2 (prostacyclin), which oppose the actions of the renin-angiotensin system on the kidney and protect against ischemic stress. Inhibition of cyclooxygenase by nonsteroidal antiinflammatory drugs predisposes the kidney to damage. Under hypoxic or ischemic conditions, cyclic endoperoxides undergo reduction to the vasoconstrictor PGF_2, which acts on thromboxane receptors. Endotoxin increases the activity of leukocyte lipoxygenase and thromboxane synthetase. Leukotrienes (especially C_4 and D_4) and thromboxane (TXA_2) induce renal vasoconstriction and contribute to the vasomotor nephropathy of sepsis.

renin-angiotensin system.[103,104] For example, kinins stimulate phospholipase A_2 and prostacyclin formation, as well as endothelial nitric oxide formation. Kininase, which controls intrarenal kinin concentration, is blocked by ACE inhibitors, resulting in increased bradykinin levels. This may be beneficial in diseases such as diabetes and hypertension, because two important intrarenal kinins, bradykinin and kallidin, decrease renal vasoconstriction and sodium retention induced by adrenergic hormones and angiotensin II. On the other hand, it also explains the occasional occurrence of angioedema in patients who take ACE inhibitors.

NATRIURETIC PEPTIDES

The potential role of an endogenous natriuretic hormone was postulated for many years before ANP was identified. In 1972 Gorfinkel and colleagues[105] demonstrated a profound difference in the canine renal response to shock, depending on concomitant atrial pressure. Hypovolemic shock resulted in rapid diminution of RBF to 10% of control, whereas in cardiogenic shock RBF was preserved at 75% of control. The primary difference was that in cardiogenic shock atrial pressures were elevated, suggesting that atrial distention caused the release of a renal protective hormone. In 1981 de Bold and colleagues[106] confirmed the existence of ANP by demonstrating that an extract of atrial tissues caused natriuresis in rats, and the important actions of ANP on renal hemodynamics and sodium excretion were characterized.[107,108]

Subsequently, an entire series of peptides with a similar precursor was identified, with a common 25 to 32 amino acid core. These include ANP (atrial or A-type natriuretic peptide), released from electron-dense granules in atrial myocytes in response to local wall stretch and increased atrial volume; BNP (brain or B-type natriuretic peptide), released from the ventricles when they are distended; CNP (C-type natriuretic peptide) released from the endothelium of major vessels; and urodilatin, a natriuretic peptide produced in the lower urinary tract.[109] Human recombinant analogs have been developed for exogenous administration, including anaritide, derived from ANP, and nesiritide, derived from BNP. All these compounds induce arterial and venous dilation, increase RBF and GFR, and suppress the actions of norepinephrine, angiotensin, and endothelin.[110]

Natriuretic peptides dilate vascular smooth muscle through activation of guanylate cyclase and formation of cyclic guanosine monophosphate (GMP). At the phospholipase C–linked receptor, natriuretic peptides competitively block norepinephrine and noncompetitively block angiotensin II, thus reversing vascular smooth muscle constriction. They cause a prompt, sustained increase in GFR and glomerular filtration fraction, even when RBF is not increased or when arterial pressure is decreased. This suggests that natriuretic peptides promote afferent arteriolar dilation with or without efferent arteriolar constriction. The increased GFR increases the filtered load of sodium, but natriuresis may be due to increased medullary blood flow, which washes out the concentration gradient.

Natriuretic peptides have a mutually antagonistic interaction with endothelin, the endogenous vasoconstrictor peptide produced by vascular endothelium.[91] They oppose the renin-angiotensin-aldosterone system on several fronts (Fig. 23-24). Natriuretic peptides inhibit renin secretion and decrease angiotensin-stimulated aldosterone release. They also inhibit aldosterone release directly at the zona glomerulosa of the adrenal cortex and block the salt-retaining action of aldosterone at the distal tubule and collecting duct. Through cyclic GMP activation, they inhibit NaCl reabsorption at the medullary portion of the collecting duct.[12] Natriuretic peptides also promote diuresis by inhibiting AVP secretion from

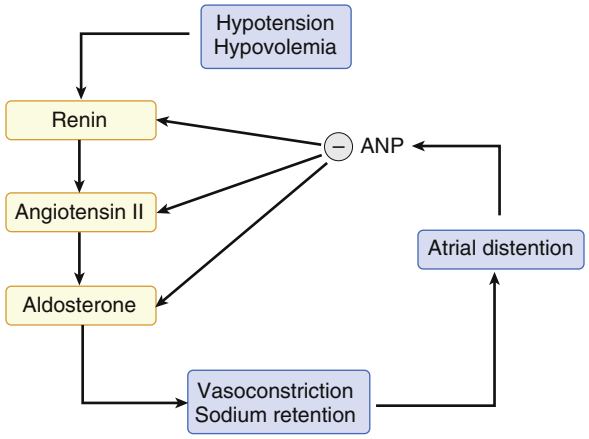


Figure 23-24. Interactions between ANP and the renin-angiotensin-aldosterone system. Hypotension or hypovolemia triggers release of renin from the afferent arteriole, causing the formation of angiotensin II, which stimulates release of aldosterone from the adrenal cortex. Angiotensin II and aldosterone cause vasoconstriction and sodium retention, ultimately resulting in reexpansion of the intravascular volume; this causes atrial distention, which triggers release of ANP. ANP inhibits release of renin, renin's action on angiotensinogen to form angiotensin II, angiotensin-induced vasoconstriction, stimulation of aldosterone secretion by angiotensin II, and the actions of aldosterone on the collecting duct. Thus, the actions of ANP promote vasodilation and sodium excretion. Therapeutic administration of fluids to distend the atrium and release ANP is an important intervention to curtail renal vasoconstriction and sodium retention.

the posterior pituitary and antagonizing its effect on the antidiuretic V_2 receptor in the collecting duct.

The renal protective role of endogenous ANP was elucidated by Shannon and colleagues,[111] who noticed that patients undergoing mitral valve replacement had lower urine output after cardiac surgery than those undergoing aortic valve replacement or coronary revascularization. They discovered that patients whose postoperative mean left atrial pressure declined by more than 7 mm Hg from preoperative values (which commonly occurs with correction of mitral valve disease) had significantly decreased postoperative urine sodium excretion and flow rate. Furthermore, a direct correlation was seen between the quantitative decrease in left atrial pressure and a postoperative decline in circulating ANP levels (Fig. 23-25). In other words, patients with mitral valve disease and high left atrial pressure have a constant stimulus to ANP release. Valve replacement or repair results in decreased left atrial pressure, decreased ANP, and thereby, decreased sodium excretion and urinary flow rate.

The advent of the total artificial heart (TAH), in which the ventricles are resected and replaced by prosthetic pumps, has highlighted the role of BNP in normal urine production. In TAH patients, urine flow declines despite stable hemodynamic status and responds to exogenous infusion of nesiritide.[112] After about 8 weeks, nesiritide can be weaned, suggesting that extraventricular sources of BNP become up-regulated.

THE DOPAMINERGIC SYSTEM

There are at least two subtypes of dopaminergic (DA) receptors.[113] At the end-organ, DA_1 receptors occur not

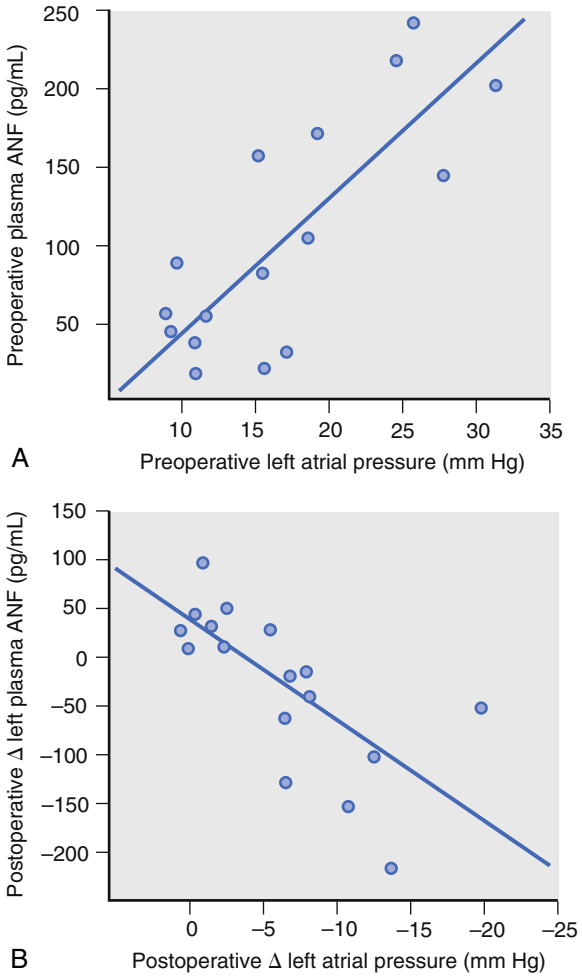


Figure 23-25. Correlation between left atrial pressure and plasma ANP in a group of patients undergoing cardiac surgery. **A,** Significant correlation ($r = 0.8$, $P < .001$) exists between absolute preoperative left atrial pressure and plasma ANP. **B,** Significant correlation ($r = 0.72$, $P < .002$) exists between the postoperative decrease in left atrial pressure and postoperative decrease in plasma ANP, ANF, and atrial natriuretic factor, synonymous with ANP. Δ, Change. *(From Shannon RP, Libby E, Elahi D, et al: Impact of acute reduction in chronically elevated left atrial pressure on sodium and water excretion,* Ann Thorac Surg *46: 430-437, 1988)*

only on the renal and splanchnic vasculature but also on the proximal tubule itself.[114] Stimulation of the DA_1 receptor activates cyclic AMP and induces renal vasodilation, increased RBF and GFR, natriuresis, and diuresis. However, natriuresis can occur independently of increases in RBF and GFR and is abolished by specific D_1 receptor antagonists.[115] In the proximal tubule, dopamine inhibits the sodium-hydrogen antiporter system at the brush-border membrane. In the mTAL, it also inhibits the Na-K-ATPase pump at the basolateral membrane.[115]

Neuronal DA_2 receptors exist on the presynaptic terminal of postganglionic sympathetic nerves. Stimulation inhibits the release of norepinephrine from presynaptic vesicles, a mechanism analogous to stimulation of the presynaptic α_2 receptor. Through inhibition of norepinephrine, DA_2-receptor activation facilitates vasodilation.

The dopaminergic system plays an integral role in the endogenous vasodilator-natriuresis system and the

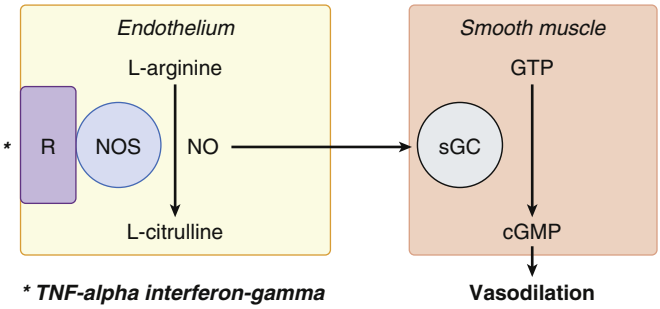


Figure 23-26. Synthesis of endogenous nitric oxide.

maintenance of normal blood pressure. Endogenous dopamine constitutively activates the DA_2 receptor, which synergistically enhances the activation of the DA_1 receptor.[116] It acts as an autocrine and paracrine natriuretic factor by inhibiting tubular Na^+-K^+-ATPase activity, especially when sodium intake is increased.[117] It also opposes the antinatriuretic effects of norepinephrine, angiotensin II, and aldosterone. Some evidence suggests that endogenous ANP acts via the renal dopamine system by recruiting "silent" DA_1 receptors from the interior of the cell toward the plasma membrane[117] and also enhances dopamine accumulation.[118]

Urinary dopamine excretion is increased with salt loading; decreased dopaminergic activity may contribute to the pathogenesis of idiopathic edema, which manifests as retention of salt and water in the upright position.[119] There is evidence that the endogenous dopamine system is activated in compensated cirrhosis and helps to maintain renal sodium excretion.[120]

NITRIC OXIDE

Endogenous formation of nitric oxide is controlled by the enzyme nitric oxide synthase (NOS), which catalyzes the hydroxylation of the nonessential amino acid L-arginine to L-citrulline.[121] Most actions of nitric oxide are mediated through its activation of soluble guanylate cyclase, which catalyzes the conversion of guanidine triphosphate (GTP) to cyclic GMP (Fig. 23-26). Cyclic GMP has two major actions: relaxation of vascular smooth muscle and suppression of the inflammatory response. It inhibits leukocyte adhesion, platelet activation and aggregation, and cellular proliferation. Cyclic GMP is converted to GMP by phosphodiesterase I and V. Thus, the local action of nitric oxide can be enhanced by the administration of a selective phosphodiesterase V inhibitor, such as sildenafil. Nitric oxide itself is rapidly inactivated by binding to intracellular heme and heme proteins (oxyhemoglobin, oxymyoglobin, guanylate cyclase, cyclooxygenase, cytochrome P_{450}).

Nitric Oxide Synthase (NOS)

There are several distinct subtypes of NOS, which determine the site and function of nitric oxide synthesis (also see Chapter 104). Constitutive NOS is calcium and calmodulin dependent and releases small amounts of nitric oxide for short periods of time ("tonic" release). Constitutive NOS has two subtypes: neuronal NOS, which acts as a peripheral neurotransmitter and induces cerebral vasodilation, and endothelial NOS, which exists in the vascular endothelium and mediates the activity previously ascribed to endothelium-derived relaxing factor (EDRF). The latter is an important modulator of systemic and pulmonary vascular resistance. In the kidney, endogenous nitric oxide preserves blood flow to the oligemic juxtamedullary cortex and medulla and may also provide endogenous protection against ischemic and nephrotoxic medullary injury.[122-124]

Inducible NOS is calcium and calmodulin independent and is induced by cytokines predominantly in inflammatory cells (macrophages, granulocytes) but also in vascular smooth muscle. At low levels of activation, inducible NOS enhances the response to infection and promotes inflammation and wound healing. In severe sepsis, inducible NOS produces huge amounts of nitric oxide for protracted periods of time (phasic release) and is largely responsible for its characteristically profound systemic vasodilation that is refractory to norepinephrine.[125] High levels of nitric oxide, as well as its reactive products nitrogen dioxide and peroxynitrite, induce lipid peroxidation and denaturation of proteins that drive the systemic inflammatory response syndrome (SIRS) and its attendant acute renal injury.

Duality of Nitric Oxide in Renal Function and Injury

Goligorsky and associates[126] have framed the hypothesis that an imbalance between the expression and activity of constitutive and inducible NOS plays an important role in the pathophysiology of acute renal failure. In experimental models of sepsis, nonselective inhibitors of both constitutive and inducible NOS improve blood pressure but worsen overall perfusion, including renal perfusion. Selective inhibitors of inducible NOS show promise in suppressing severe inflammation and vasodilation, while maintaining tonic perfusion to vital organs, including the kidneys.[127]

THE RENAL ADENOSINE SYSTEM

Adenosine Receptors

Adenosine, the endogenous degradation product of ATP, is produced by every mammalian cell type and is normally thought of as a potent vasodilator. However, in the kidney, it plays an essential role in regulating intrarenal blood flow by inducing outer cortical vasoconstriction and preserving juxtamedullary perfusion. This variance in function is explained by the identification of at least four subtypes of adenosine receptor: A_1, A_{2a}, A_{2b}, and A_3 (Table 23-6). Activation of the A_1 adenosine receptor induces outer cortical vasoconstriction; it also decreases renin release and inhibits diuresis and natriuresis. In contrast, A_{2a} adenosine receptors increase medullary renal blood flow and enhance renin release, diuresis, and natriuresis.

Ischemic Preconditioning and Adenosine

In a series of studies in an in vivo rat model of ischemic acute renal failure, Lee and Emala[128] characterized the role of adenosine and its receptor subtypes in ischemic

TABLE 23-6 ADENOSINE RECEPTOR SUBTYPES AND FUNCTIONS

Receptor	Agonist Function	Ischemic Injury
A_1	Outer cortical vasoconstriction Decreased renin release Inhibition of diuresis and natriuresis	Highly protective
A_{2a}	Juxtamedullary vasodilation Increased renin release Promotion of diuresis and natriuresis	Highly protective
A_{2b}	Unknown	
A_3	Unknown	Potentiates injury

From Fozard JR, Hannon JP: Adenosine receptor ligands: potential as therapeutic agents in asthma and COPD, Pulm Pharmacol Ther *12:111-114, 1999.*

preconditioning. Preischemic administration of adenosine and a selective A_1 adenosine receptor agonist protected the kidney against global renal ischemic reperfusion injury. The A_3 receptor appears to have polymorphic effects. In murine models of ischemic injury, pretreatment with a selective A_3 receptor activation potentiates renal injury; however, in murine septic peritonitis, activation of the A_3 receptor appears to protect the kidney by attenuating the hyperacute inflammatory response.[129] A selective A_{2a} adenosine receptor agonist had the greatest renal protective effects, even if its administration was delayed until the early reperfusion period after termination of renal ischemia.[130]

It is conceivable that A_1 adenosine receptor stimulation decreases renal oxygen consumption through a decrease in cortical blood flow, GFR and sympathetic tone, mediated by induction of cytoprotective sphingosine kinase and the synthesis of sphingosine-1-phosphate.[131] Adenosine has cytoprotective properties and promotes synthesis of protective heat shock proteins.[132] It is the key mediator of ischemic preconditioning in the heart and brain and is known to increase cellular resistance to ischemia in these organ systems. Pharmacologic development of a safe, specific A_{2a} adenosine receptor agonist might provide specific protection against renal ischemic injury.

PERIOPERATIVE ISCHEMIC AND NEPHROTOXIC INJURY

This section will review perioperative agents and events that may disrupt normal renal physiology. If the disruption is severe enough or occurs in susceptible individuals, it may induce ischemic or nephrotoxic acute tubular necrosis (ATN), a severe form of perioperative AKI. However, multiple studies indicate that even mild AKI (AKIN stage 1 or the R in RIFLE criteria) is associated with increases in hospital mortality, hospital lengths of stay, and resource utilization, as well as an increased risk of subsequent chronic kidney disease and long-term mortality.[72,73,75,133-137]

PATHOGENESIS

Ischemia-Reperfusion Injury

In many clinical situations (e.g., hypovolemic shock, suprarenal aortic cross-clamping), the kidney is subject to a classic ischemia-reperfusion injury that involves several distinct phases.[138] Acute injury to the tubular epithelium and vascular endothelium initiates a rapid decline in GFR. The injury is extended by epithelial and endothelial cell apoptosis and necrosis. The injury becomes stabilized during the maintenance phase, with the beginning of cellular reorganization that culminates in the recovery phase. The initiation phase is often transient, so the extension phase is the most important "window of opportunity" for therapeutic intervention that might reverse AKI. However, the timing of renal ischemia-reperfusion may be more subtle than in the above examples, emphasizing the importance of early, sensitive detection of rapid declines in GFR.[44]

Nephrotoxic Injury

The putative mechanisms of nephrotoxic tubular injury have been previously discussed (see "Oxygen Balance in the Medullary Thick Ascending Loop"). The risk of nephrotoxic AKI is exponentially related to the number of nephrotoxic insults.[13] An isolated nephrotoxin (e.g., radiocontrast dye) is unlikely to cause AKI when the kidney is well perfused. In animal models of nephrotoxic ATN, injection of radiocontrast dye predictably injures more than 50% of the renal mTAL only when the kidney is previously "primed" by a sequence of three other insults: dehydration, LMMA (a nitric oxide synthase inhibitor), and indomethacin (a prostaglandin synthesis inhibitor).[139]

ANESTHETIC DRUGS

The choice of an anesthetic technique to preserve renal function during and after surgery is predicated on the preservation of RBF and perfusion pressure, the suppression of vasoconstrictor, salt-retaining stress responses to surgical stimulation and postoperative pain, and the avoidance or curtailment of nephrotoxic insults. No single anesthetic drug alone meets these criteria (also see Chapters 69 and 74).

REGIONAL ANESTHESIA

Spinal or epidural anesthesia that achieves sympathetic blockade of the fourth through tenth thoracic segments is extremely effective in suppressing the sympathoadrenal stress response and release of catecholamines, renin, and AVP (also see Chapter 56). During major surgery, RBF and GFR are preserved as long as adequate renal perfusion pressure is maintained.[140-142] This implies careful titration of the block, especially in older adult patients with cardiovascular disease, and may necessitate a 25% to 50% increase in intraoperative intravenous fluid administration.[143] However, Gamulin and colleagues[144] found that renal sympathetic blockade obtained by epidural anesthesia did not block increases in renal vascular resistance induced by infrarenal aortic cross-clamping, nor

did it prevent postoperative decreases in creatinine clearance. Combined spinal-epidural anesthesia for nephrectomy in living related donors appeared to promote graft renal blood flow more than general anesthesia, but there was no difference in renal function or outcome in recipients[145] (also see Chapter 75). A large randomized controlled trial on patients undergoing major abdominal surgery compared general anesthesia plus perioperative epidural analgesia with general anesthesia and opiate-based postoperative analgesia; this study also revealed no difference in renal outcomes.[146]

GENERAL ANESTHESIA

All general anesthetics tend to decrease GFR and intraoperative urine flow as a consequence of decreased cardiac output and arterial blood pressure.[86] Some drugs also decrease RBF, but filtration fraction is usually increased, which implies that angiotensin-induced efferent arteriolar constriction limits the decrease in GFR. However, these effects are much less significant than those caused by surgical stress or aortic cross-clamping, and after emergence from anesthesia they usually resolve promptly. Any anesthetic technique that induces hypotension will result in decreased urine flow because of altered peritubular capillary hydrostatic gradients, even if renal autoregulation is preserved (as it usually is during anesthesia). Permanent injury seldom results, unless the kidneys are abnormal to begin with or the hypovolemic insult is prolonged and exacerbated by nephrotoxic injury.

Volatile anesthetics with nitrous oxide induce mild to moderate reductions in RBF and GFR, primarily because of their effects on the central circulation (myocardial depression, peripheral pooling).[147] These effects can be attenuated by prior intravenous hydration.

High-dose opioid techniques using fentanyl or sufentanil do not depress myocardial contractility and have minimal effect on RBF and GFR. They are also considerably more effective in suppressing the release of catecholamines, angiotensin II, aldosterone, and AVP during surgery than are volatile anesthetics. However, during cardiopulmonary bypass both AVP and catecholamine levels increase markedly despite high-dose opioid anesthesia[148] (also see Chapter 67). Intravenously administered anesthetics, such as thiopental and diazepam, cause minor changes in renal function, about 10% to 15% deviation from control. Ketamine increases RBF but decreases urine flow rate, possibly through sympathetic activation; it preserves RBF during hemorrhagic hypovolemia.[149]

Nephrotoxicity of Volatile Anesthetics

The potential nephrotoxicity of volatile anesthetics (also see Chapter 26) is due to their metabolic breakdown to free fluoride ions, which cause a tubular lesion that results in loss of concentrating ability and polyuric acute renal failure.[150] Toxicity is exacerbated by aminoglycosides or prior renal dysfunction. Peak fluoride levels less than 50 μm/L seldom induce injury, whereas levels >150 μm/L are associated with a frequent incidence of polyuric acute renal failure.[151] Administration of methoxyflurane at more than one (minimal alveolar concentration of anesthetic) (MAC) for more than 2 hours is capable of generating a peak fluoride level greater than 100 μm/L, and for this reason, this anesthetic is no longer used. Enflurane is metabolized more rapidly, and most studies indicated that peak fluoride levels seldom rose above 25 μm/L. The antituberculotic drug isoniazid enhances fluoride production, but only isolated reports of fluoride-induced nephrotoxicity due to enflurane ever appeared. Isoflurane produces peak fluoride levels less than 4 μm/L, and halothane is not metabolized to fluoride at all.[152]

The potential nephrotoxicity of sevoflurane remains controversial. Although its metabolism generates more fluoride than enflurane, clinically significant fluoride-induced nephrotoxicity has not been detected. Compound A, a vinyl ether formed by degradation of sevoflurane at low flow through carbon dioxide absorbents, is capable of inducing renal injury in rats. Although acute renal failure has not been reported in humans, Eger and associates reported evidence of transient renal injury (albuminuria, tubular enzymuria) in volunteers subjected to 8 hours of 1.25 MAC sevoflurane at 2 L/minute gas flow.[153] There were no changes in urinary concentrating ability, serum creatinine, or blood urea nitrogen (BUN). Subsequently, Eger and associates[154] described a dose-response relationship between biochemical markers of glomerular and tubular injury (urinary albumin, alpha-glutathione-S-transferase) and compound A exposure expressed as parts per million-hours (ppm/h). They suggested that the threshold of renal injury is 80 to 168 ppm/h based on their observation of altered biochemical markers with 1.25 MAC sevoflurane at 2 L/minute for 4 hours, which was not seen after 2 hours, and not at all with desflurane.

Other laboratories have disputed Eger's findings. Bito and colleagues compared 6-hour patient exposure to low- and high-flow sevoflurane with low-flow isoflurane and found no differences in BUN, creatinine, or tubular enzymes for 3 days postoperatively.[155] Kharasch and colleagues[156] had similar results with the use of sevoflurane or isoflurane at 1 L/minute in 73 patients undergoing procedures lasting longer than 2 hours. They concluded that moderate duration of low-flow sevoflurane anesthesia, even with the formation of compound A, is as safe as low-flow isoflurane anesthesia. Ebert and associates[157] attempted to duplicate the original 8-hour Eger sevoflurane study in volunteers at two sites with blinded laboratory analyses. Biochemical derangements were minimal and transient, and there were no significant changes in BUN, creatinine, or creatinine clearance. Despite the similarity in experimental design, the mean level of compound A was about 25% lower, and the mean arterial pressure about 10% higher than in the Eger study and may have accounted for the difference in results.

In summary, clinically significant renal injury with the use of low-flow sevoflurane anesthesia has not been reported in patients, even with moderate preexisting renal dysfunction. The relationship between compound A formation, biochemical injury, and clinically relevant renal dysfunction remains unclear and unproven. Nonetheless it appears prudent to follow current FDA guidelines, which recommend a fresh gas flow of at least 2 L/minute to inhibit compound A formation and its rebreathing and to enhance its washout.

Volatile Anesthetics and Ischemia-Reperfusion Injury

In direct contrast to the debate just described, experimental evidence suggests that volatile anesthetics can ameliorate ischemia-reperfusion injury in the kidney and beyond. In a murine model, Lee and Emala demonstrated that anesthesia with desflurane, sevoflurane, isoflurane, and halothane significantly attenuated the increase in serum creatinine compared with pentobarbital or ketamine.[158] The mechanism is independent of potassium-ATP channels but related to induction of cytoprotective factors and suppression of proinflammatory cytokine and chemokine activation in response to ischemia-reperfusion. In cultured renal tubule cells, sevoflurane induces the phosphorylation of cytoprotective kinases, up-regulates heat shock protein, and attenuates the proinflammatory transcription factor NF-κB, partly because of the release of transforming growth factor-β_1 (TGF-β_1).[159]

Isoflurane has similar protective effects, and in a murine model, it is able to protect against liver and intestinal injury associated with ischemia-reperfusion AKI.[160] As with adenosine receptor agonism described earlier, a major protective mechanism appears to be isoflurane-induced activation of sphingosine kinase-1 and production of sphingosine-1-phosphate.

These observations are consistent with the concept that volatile anesthetics confer protection only when administered during ischemia and reperfusion and do not appear to have a preconditioning effect.[161]

MECHANICAL VENTILATION

Mechanical ventilation and positive end-expiratory pressure (PEEP) may cause decreases in RBF, GFR, sodium excretion, and urine flow rate, or even acute renal injury.[162] There are several mechanisms for these effects (also see Chapter 103).

Hemodynamically mediated changes are the most common. Transmission of increased airway and intrapleural pressures to the intravascular space leads to decreases in venous return, transmural (i.e., effective) cardiac filling pressures, and cardiac output. Transmission may actually be attenuated in acute lung injury because of poor lung compliance. High levels of mean airway pressure may compress the pulmonary arterial circulation, increase right ventricular afterload, and induce the intraventricular septum to shift into the left ventricle and decrease its filling and cardiac output.[163] Positive pressure ventilation increases inferior vena caval pressure and renal venous pressure and may increase tubular sodium reabsorption by increases in peritubular capillary pressure.

The decrease in cardiac output and systemic arterial pressure results in a carotid and aortic baroreceptor-mediated increase in sympathetic nerve tone to the kidney, with renal vasoconstriction, antidiuresis, and antinatriuresis. Volume receptors in the atria respond to decreased filling by decreased ANP secretion, resulting in increased sympathetic tone, renin activation, and AVP activity.

Salt and water retention during airway pressure therapy was originally thought to be due to an AVP effect,[164] but it is now considered that sympathetic responses are more important and that sodium retention is largely the result of decreased sodium delivery to the tubules. The renin-angiotensin-aldosterone system undoubtedly augments the renal responses to positive pressure ventilation. Annat and colleagues[165] found that 15-cm H_2O PEEP depressed cardiac output, RBF, GFR, and urine volume by 20% to 30% and was associated with increases in renin and aldosterone but not AVP. The impairment in renal function induced by airway pressure therapy can be prevented or reversed by preserving normal circulatory status, either by hydration[166] or by use of dopamine.[167]

Although, theoretically, the extent of depression of renal function depends on the mean airway pressure, there is no difference in creatinine clearance and FENa, whether volume controlled- or pressure-support ventilation is used.[168] Therapeutic maneuvers used in severe acute lung injury, such as permissive hypercapnia or permissive hypoxemia, may promote renal vasoconstriction.[162]

Finally, in experimental lung injury there is evidence that an injurious ventilatory mode induces acute inflammation associated with renal epithelial cell apoptosis and dysfunction.[169] These findings appear to be in keeping with the clinical observation of multiorgan dysfunction in patients with acute respiratory distress syndrome and its amelioration when a lung protective strategy of mechanical ventilation is used.[162]

INDUCED HYPOTENSION

During anesthesia with induced hypotension, substantial reduction of GFR and urine flow rate is common. However, when the duration of hypotension is less than 2 hours, no permanent impairment of renal function occurs, even in older adult patients.[170] Vasodilators used to induce hypotension differ in their effect on RBF. Administration of sodium nitroprusside decreases renal vascular resistance but tends to shunt blood flow away from the kidney. Moreover, its administration is associated with marked renin-angiotensin activation and catecholamine release, which results in rebound hypertension if the infusion is suddenly discontinued. Nitroglycerin decreases RBF less than sodium nitroprusside.[171] The selective DA_1-dopaminergic agonist fenoldopam is capable of providing induced hypotension without any significant decrease in RBF.[172]

AORTIC CROSS-CLAMPING

The relative effects of suprarenal and infrarenal aortic cross-clamping on renal function in patients undergoing major vascular surgery have been studied (also see Chapter 69).[28] Regardless of the position of the aortic cross-clamp, RBF is decreased to 50% of normal during surgical preparation of the aorta, presumably due to direct compression or reflex spasm of the renal arteries. After release of the suprarenal cross-clamp, RBF increases above normal (reflex hyperemia), but GFR remains depressed to one third of control for up to 2 hours. After 24 hours GFR is still only two thirds of control. Tubular functions

(concentrating ability, sodium and water conservation) are markedly impaired, but urine flow is maintained. Myers and Moran[173] observed that these changes resemble an attenuated form of acute tubular necrosis. In this study all patients received mannitol pretreatment, which probably limited the tubular insult, because oliguria was uncommon and recovery was relatively rapid. Cross-clamp times longer than 50 minutes are associated with prolonged depression of GFR and transient azotemia.[28,174]

In animal models, suprarenal aortic cross-clamping induces a decrease in renal endothelial nitric oxide; nitric oxide synthesis and cortical blood flow is enhanced by the administration of its substrate, arginine.[175] Whether this intervention might attenuate the renal consequences of cross-clamping awaits further investigation.

Infrarenal aortic cross-clamping may also impair RBF and GFR by inducing decreases in cardiac output in response to increased systemic vascular resistance.[176] Atheromatous embolism of the renal arteries may be induced by cross-clamping or manipulation in areas of dense aortic plaque. Partial or complete cortical necrosis may occur, which is usually irreversible.

RENAL PROTECTION DURING AORTIC CROSS-CLAMPING

Mannitol has been used for more than 40 years to provide renal protection during aortic cross-clamping (also see Chapter 69).[177] Its protective effects have been clearly demonstrated in animal models of ischemic acute tubular necrosis (ATN),[178] but few prospective controlled human studies exist. Low-dose dopamine has commonly been used during major vascular surgery. In a canine study of thoracic aortic cross-clamping, RBF, GFR and urine flow remained impaired for a considerable time after cross-clamp release. This delay was not prevented by prophylactic dopamine.[179] In a human study of infrarenal cross-clamping, Paul and associates[180] compared diuretic therapy with a combination of mannitol and dopamine versus fluid loading with saline to a pulmonary artery occlusion pressure (PAOP) of 12 to 15 mm Hg. Although mannitol and dopamine substantially increased urine flow and sodium excretion during cross-clamping, they were no better than saline in attenuating residual GFR depression after cross-clamp release.

Fenoldopam, a synthetic phenolated dopamine analog that is a selective agonist of the dopamine-1 receptor, increases renal blood flow in a dose-dependent manner.[181] Infusion of fenoldopam has demonstrated a renoprotective effect in experimental suprarenal aortic cross-clamping.[182] In a controlled, randomized, blinded study in 28 patients undergoing infrarenal aortic cross-clamping, fenoldopam 0.1 mcg/kg/minute or placebo was infused intravenously before surgical skin incision and continued until release of the aortic cross-clamp.[183] Fenoldopam significantly attenuated the decrease in creatinine clearance and increase in serum creatinine observed in patients who received placebo.

However, in a different model of intraoperative renal ischemia, a randomized, double-blind study in 77 patients with a solitary functioning kidney undergoing partial nephrectomy, a 24-hour infusion of fenoldopam at 0.1 mcg/kg/minute did not attenuate the postoperative increase in serum creatinine.[184] Larger studies with this agent appear warranted.

CARDIAC SURGERY AND CARDIOPULMONARY BYPASS

The incidence of acute renal failure requiring renal replacement therapy after uncomplicated cardiac surgery in patients with previously normal renal function is infrequent (<2%).[185] However, the incidence of AKI defined by consensus definitions is about 20% to 30%.[186,187] Multiple risk factors have been identified, including preoperative renal dysfunction, hypertension, diabetes, impaired cardiac function, preoperative anemia, perioperative erythrocyte transfusion, combined surgical procedures, prolonged cardiopulmonary bypass, and advanced age (also see Chapter 67).[188,189]

Regardless of pathogenesis, AKI requiring renal replacement therapy after cardiac surgery has a profound impact on mortality, and even milder forms of AKI are consistently associated with increased mortality, length of stay, and hospital costs.[73,75,134,186] The potential mechanisms of cardiac surgery–associated renal injury are complex and multifactorial.

Preoperative hypertension is a major risk factor for AKI after cardiac surgery. This risk is increased by preexisting systolic (wide pulse pressure) hypertension. The risk of AKI increases by nearly 50% for every 20 mm Hg increase in pulse pressure above 40 mm Hg.[190] Increased variability of intraoperative blood pressure control also appears to be a risk factor.[191]

Most patients undergoing cardiac surgery will have undergone contrast angiography in preparation for surgery, and the time interval between this established nephrotoxin and surgery has been suggested as a potential contributory factor to perioperative AKI.[192]

Acute anemia (hemoglobin <9 g/dL) during cardiopulmonary bypass is associated with an increased risk of AKI, but so is red cell transfusion when hemoglobin is >8 g/dL[193] (also see Chapter 61). Decreased mean arterial pressure appears to be well tolerated, unless it is associated with anemia. On the other hand, a combination of patient factors and procedural factors result in a cumulative particulate, gaseous, micro- or macroscopic embolic load that may contribute to AKI.

During CPB, hypotension with nonpulsatile flow promote renal vasoconstriction and decreased RBF. Norepinephrine concentrations increase progressively during bypass, and the renin-angiotensin system is activated. Acute renal failure has been associated with persistent elevation of plasma renin levels.[173] Thromboxane, released from activated platelets, and vascular elaboration of endothelin could add to renal vasoconstriction during extracorporeal circulation.

Tubular enzymuria and microalbuminuria, an index of subclinical injury to the nephron, is consistently observed during cardiopulmonary bypass.[194] Inflammatory cascades initiated by surgery may be further amplified in response to CPB while the trauma of the CPB system causes hemolysis with release of free hemoglobin,

an established nephrotoxin, into the plasma.[195] Another consequence of hemolysis is the release of labile free iron that contributes to activation of reactive oxygen species, inflammation, and AKI.[196] A number of the tubular biomarkers released in AKI are associated with iron metabolism: NGAL participates in iron transport, L-FABP is a high-affinity heme binding protein, and hepcidin (which appears to be protective) sequesters free iron.[197] In a study specifically examining hemolysis during CPB for repair of thoracoabdominal aortic aneurysms, there was a direct association among peak plasma free hemoglobin, NAG, and perioperative AKI.[198]

Unfortunately, despite all the putative mechanisms described earlier, it still remains unclear exactly how much CPB itself contributes to AKI during cardiac surgery. The individual response to CPB varies greatly and may be the consequence of variable genetic polymorphisms that regulate the response to inflammatory and vasomotor processes.[199]

RENAL PROTECTION DURING CARDIOPULMONARY BYPASS

Pulsatile Perfusion During CPB

In animal and human studies, pulsatile perfusion during CPB enhances renal cortical blood flow and decreases circulating catecholamines, endothelin, and cytokine activation (also see Chapter 67).[200,201] Plasma renin activity is suppressed by pulsatile perfusion; however, evidence of glomerular injury (in this case, microalbuminuria) persists.[55] In a randomized prospective study on 215 pediatric patients undergoing repair of congenital heart disease, the use of pulsatile flow during CPB was associated with decreased inotropic drug requirement, shorter ICU and hospital lengths of stay, and increased urine output. Yet no difference was seen in serum creatinine.[202] Intraaortic balloon counterpulsation was used to provide pulsatile flow during CPB in a randomized, prospective study on 100 adult patients undergoing cardiac surgery.[203] Pulsatile flow attenuated the decline in GFR, but there was no difference in urine flow or renal outcome. In a large nonrandomized observational study, pulsatile flow was provided during CPB in 915 of 1820 patients but did not provide increased protection against perioperative renal injury.[204] Overall, results of clinical studies of pulsatile perfusion on CPB are inconsistent and further complicated by the absence of a precise and widely accepted definition of what constitutes pulsatile flow on CPB. Current evidence appears to be insufficient to allow recommendations either for or against the routine use of pulsatile perfusion on CPB to decrease the risk of renal injury.[205]

Avoidance of CPB

The benefit to renal function of off-pump coronary artery bypass (OPCAB, also known as beating heart surgery) also remains equivocal. In patients with a small risk, little difference has been observed in the incidence of acute kidney injury, regardless of whether CPB is used.[206] Most published studies to date have been small (< 60 patients), Although OPCAB is associated with less evidence of acute kidney injury, as manifested by lower levels of serum creatinine, cystatin C, microalbuminuria, and NAG, a clear benefit to renal outcome, morbidity, or mortality has not resulted.[207,208] A recent meta-analysis of randomized trials, found evidence to support a reduction in AKI with off-pump surgery but with no demonstrated reduction in dialysis or mortality.[209] However, the quality of included studies is variable, there is large interstudy variation in the definition of AKI, and the results and conclusions may have been skewed by one study. We need additional high-quality evidence that addresses clinically relevant end points to clarify the potential renal benefit of off-pump cardiac surgery.

Perfusion Pressure during CPB

Animal studies of cardiopulmonary bypass have shown that RBF is dependent on renal perfusion pressure, and infusion of dopamine does not increase RBF during low pressure states.[10] This suggests that autoregulation may be impaired during cardiopulmonary bypass. However, Hilberman and associates[210] found no relationship between low flow (<50 mL/kg/minute) and low mean arterial pressure (<50 mm Hg) and postoperative acute renal failure. Instead, the severity of postoperative renal dysfunction and its outcome correlated with the severity of cardiac dysfunction after cardiopulmonary bypass.[211]

These observations are supported by more recent ones that found no correlation between mean arterial pressure during cardiopulmonary bypass and AKI, unless hypotension was associated with severe anemia.[193] Perhaps the hemodilution of mild anemia preserves RBF at low perfusion pressure, but in severe anemia this is overcome by the deficit in oxygen delivery (also see Chapter 61 regarding anemia and the indications for blood transfusions).

Dopaminergic and Diuretic Drugs

In a study comparing equi-inotropic doses of dopamine and dobutamine after cardiac surgery, the two agents had similar effects on GFR, RBF, renal vascular resistance, and filtration fraction, but dopamine caused greater urine flow rate, natriuresis, fractional excretion of sodium, and potassium excretion, indicating a diuretic effect independent of changes in RBF and GFR.[212] However, there is no evidence that the prophylactic administration of low-dose dopamine has a protective role during CPB in patients with previously normal[213,214] or impaired renal function.[206,215]

In part, the lack of benefit may be due to the variable pharmacokinetic effect of dopamine. In a study on normal volunteers, McGregor and colleagues found a 30-fold intersubject variability in plasma dopamine levels.[216] Some subjects given an infusion of low-dose dopamine had plasma levels consistent with those associated with doses in the high, α-adrenergic range. Even at small doses it can cause unwanted tachycardia, and its postoperative infusion is associated with a more frequent incidence of supraventricular and ventricular arrhythmias.[217]

In contrast to dopamine, a renoprotective effect may occur from an infusion of low-dose fenoldopam infusion (0.1-0.3 mcg/kg/minute) during cardiac surgery[218] (also see Chapter 67). Echocardiographic studies using the Doppler technique have demonstrated a dose-dependent

increase in renal blood flow, especially in the cortical zones, when fenoldopam is administered in this dose range.[219] A meta-analysis of 13 randomized and case-matched studies on 1059 patients found that fenoldopam infusion is associated with a significant decrease in dialysis requirement, ICU length of stay, and in-hospital mortality.[16] However, most studies with fenoldopam have been relatively small and have identified improved serum creatinine and creatinine clearance rather than renal outcome.[220,221] The most convincing evidence thus far comes from a randomized, double-blinded study in 193 high-risk patients by Cogliati and colleagues.[222] Risk factors included increased preoperative serum creatinine concentrations (>1.5 mg/dL), age >70 years, diabetes, or previous cardiac surgery. Patients who received fenoldopam had a decreased incidence of acute kidney injury (12.6 versus 27.6%, $P = 0.02$) and requirement for dialysis (0 versus 8.2%, $P = 0.004$).

Prophylactic administration of diuretics during CPB may actually be harmful: in a study on 126 patients undergoing elective cardiac surgery, perioperative infusion of furosemide (0.5 mcg/kg/minute) worsened serum creatinine compared with low-dose dopamine and placebo.[213]

Natriuretic Peptides

Exogenous administration of anaritide (human recombinant ANP) decreases systemic arterial blood pressure through arterial and venous dilation. There has been considerable interest in the ability of infused anaritide to reverse established acute renal failure ("renal rescue"). Animal studies of ischemic and nephrotoxic acute tubular necrosis,[223,224] as well as preliminary clinical studies,[225] offer promise. A large prospective study demonstrated significantly increased dialysis-free survival with anaritide infusion in oliguric acute renal failure, but in nonoliguric acute renal failure, survival actually worsened.[51] Subsequently, a randomized, double-blind, placebo-controlled trial in 222 patients with oliguric acute renal failure found no differences in dialysis requirement, dialysis-free survival, or 60-day mortality between anaritide and placebo.[226] However, patients receiving anaritide had significantly more frequent incidence of hypotension during infusion of the study drug.

Infusion of anaritide has been studied during CPB.[227] Compared with controls, patients who received anaritide had significantly lower plasma levels of renin, angiotensin II, and aldosterone and higher GFR and urine output. A recent Cochrane review of ANP therapy concluded that although there was some evidence supporting a beneficial effect of low-dose ANP as a preventive strategy to reduce the risk of AKI requiring dialysis, the evidence is insufficient to make any strong recommendations.[228]

Nesiritide (human recombinant BNP) is approved by the FDA for the parenteral treatment of advanced decompensated congestive heart failure. It decreases increased cardiac preload and afterload, enhances cardiac function, and promotes diuresis and relieves symptoms related to pulmonary congestion and edema.[229] The major adverse effect is dose-related hypotension, which if excessive, can impair renal function.[230] A meta-analysis of studies of nesiritide infusion in patients with advanced decompensated heart failure indicated increasing serum creatinine levels.[231] However, a large prospective placebo-controlled study demonstrated no worsening of renal function in patients with advanced decompensated heart failure,[232] and similar results have been found when comparing nesiritide to nitroglycerin[233] or nitroprusside.[234]

Perioperative infusion of low-dose (0.01 mcg/kg/minute) nesiritide infusion in high-risk patients undergoing cardiac surgery may have a renoprotective effect.[235] In a prospective, randomized, blinded study of 279 patients with left ventricular dysfunction (EF <40%) undergoing coronary revascularization or mitral valve surgery, patients who received nesiritide had increased urine output, an attenuated postoperative increase in serum creatinine, and improved survival 6 months after surgery.

A meta-analysis of 15 trials of infusions of ANP or BNP in cardiovascular surgery found consistent benefits, including increased urine output and GFR, decreased diuretic use, decreased peak postoperative serum creatinine and requirement for dialysis, and decreased ICU and hospital length of stay.[236] These findings have yet to be confirmed by a large, multicenter, prospective randomized controlled trial.

N-Acetylcysteine

N-acetylcysteine is an antioxidant that directly scavenges reactive oxygen species, and it has been widely used to prevent radiocontrast nephropathy (see later discussion). On the other hand, no evidence exists that perioperative administration of *N*-acetylcysteine has any efficacy in the prevention of AKI during cardiac surgery. In two prospective, blinded, randomized studies neither intermittent injection[237] or continuous infusion[238] of *N*-acetylcysteine had any impact on renal function or outcome after cardiac surgery. A study on 254 patients with chronic renal insufficiency (GFR <60 mL/minute) was similarly unable to demonstrate any significant benefit from intermittent injection of *N*-acetylcysteine.[239] Most recently, a randomized controlled study on more than 2300 patients undergoing coronary or peripheral vascular angiography failed to show any benefit associated with *N*-acetylcysteine administration.[240]

Urinary Alkalinization

As described earlier, hemolysis is a common occurrence during CPB, the release of labile free iron may play a role in inducing activation of reactive oxidation species, and AKI in this situation could be considered a form of pigment nephropathy.[195] Under these circumstances, urinary alkalinization could prevent formation of methemoglobin and tubular casts, decrease endocytic hemoglobin uptake, and attenuate proximal tubular necrosis; bicarbonate may scavenge free iron-mediated reactive oxygen species such as hydroxyl ions and peroxynitrite.[196] Indeed, in a small, randomized, double-blind trial of in 100 patients undergoing cardiac surgery who were at increased risk of perioperative AKI, urinary alkalinization by a 24-hour infusion of sodium bicarbonate decreased the incidence of a 25% postoperative increase in SCr from 52% to 32%, with decreased urine NGAL.[241] These preliminary observations—and their impact on outcome—remain to be confirmed by larger prospective studies.

NEPHROTOXIC INSULTS

DRUG-INDUCED NEPHROTOXICITY

Nephrotoxic injury by drugs or contrast dyes seldom occurs without the presence of coexisting risk factors.[13] These may be acute (shock, hypovolemia, congestive heart failure) or chronic (advanced age, diabetes, chronic renal insufficiency). The risk of nephrotoxicity increases exponentially with the number of risk factors and nephrotoxic combinations.

Nephrotoxic acute renal failure is usually nonoliguric, with loss of concentrating ability and slowly progressive azotemia. As GFR declines, accumulation of renally excreted drugs exacerbates nephrotoxicity unless drug levels are carefully monitored and dosage repeatedly adjusted. However, the prognosis for recovery is good if these agents are discontinued in time and no coexistent organ failure exists.[242]

Aminoglycosides

Aminoglycosides (gentamicin, tobramycin, amikacin) are polycationic compounds that are filtered into the proximal tubule, where they bind to anionic brush-border membrane phospholipids. Their nephrotoxicity is directly related to their polycationic status, so that neomycin (six cationic sites) is more destructive than gentamicin (five sites) or streptomycin (three sites).[243] They are absorbed into intracellular lysosomes by endocytosis and thence released into the cytosol. Within the cell they induce the formation of reactive oxygen metabolites that injure lysosomes, plasma membranes, and mitochondria and, in particular, inhibit oxidative phosphorylation and the synthesis of high-energy phosphate compounds such as ATP. In animal studies, administration of antioxidants such as melatonin ameliorates nephrotoxicity.[244]

Aminoglycoside-induced nephrotoxicity is directly related to sustained high-trough serum levels, especially when associated with advanced age, preexisting renal disease, renal vasoconstrictive states (sepsis, hypovolemia, liver disease, congestive heart failure), adjuvant drug therapy (loop diuretics, vancomycin, cephalosporins, NSAIDs, cyclosporine A, amphotericin B), and electrolyte disorders (hypokalemia, hypomagnesemia, hypercalcemia, and metabolic acidosis).[245]

Prevention of aminoglycoside nephrotoxicity depends on maintenance of adequate hydration, avoidance or removal of the risk factors enumerated above, and careful monitoring of serum aminoglycoside levels. A daily 2-hour creatinine clearance can also be helpful in the early detection of aminoglycoside-induced nephrotoxicity and appropriate dose adjustment for GFR. Once-daily administration of aminoglycosides to achieve a high therapeutic level with an adequate trough period for renal recovery may limit the occurrence of nephrotoxicity.[246] Low-dose dopamine increases renal clearance of aminoglycosides, but it is not known whether this protects against tubular injury.

Nonsteroidal Antiinflammatory Drugs

Cyclooxygenase-1 is inhibited by nonsteroidal antiinflammatory drugs (NSAIDs) such as indomethacin, meclofenamate, and ketorolac for about 8 to 24 hours (also see Chapter 32). A single dose of aspirin causes its irreversible acetylation. In platelets, the impact lasts for the lifetime of these cells (7 to 10 days), but the kidney resynthesizes cyclooxygenase within 24 to 48 hours. The renal protective function of prostaglandins is "switched on" by injury, illustrated by the fact that NSAIDs cause nephrotoxicity in ischemic but not in normal kidneys. During conditions of stress, impaired prostaglandin activity results in decreased RBF and GFR, increased renal vascular resistance, attenuated diuretic responsiveness, and hyperkalemia.

Adverse effects of NSAIDs and aspirin (e.g., hemorrhage, endotoxemia, increased venous pressure, and low cardiac output) have occurred in animals and in humans with mild underlying renal dysfunction who also have congestive heart failure, ascites, or systemic lupus erythematosus.[247] However, in an individual patient, the risk of NSAID-induced nephrotoxicity is very much dependent on the milieu. Short-term postoperative analgesia with a single analgesic such as ketorolac is extremely unlikely to cause injury in a relatively young, healthy, well-hydrated patient. The risk of nephrotoxic injury increases exponentially with the addition of concomitant nephrotoxins (e.g., contrast dye, aminoglycosides) and in the presence of acute or chronic cardiovascular instability.

NSAIDs selective for cyclooxygenase-2 (celecoxib, rofecoxib, valdecoxib) are less likely to cause gastric irritation and erosion. However, the proposed decreased risk of nephrotoxic injury compared with nonselective cyclooxygenase inhibitors has not been shown.[248] Their use has been severely curtailed after reports of increased adverse cardiovascular events in clinical trials.

Calcineurin Antagonists (Cyclosporine A, Tacrolimus)

Cyclosporine A is a remarkably potent immunosuppressive drug; together with steroids and azathioprine, it is routinely used to prevent rejection after organ transplantation. Indeed, heart, lung, and liver transplantation increased exponentially after the release of cyclosporine A in 1981. It causes renal injury in part because it induces sympathetic hyperreactivity, hypertension, and renal vasoconstriction. Preexisting renal dysfunction, hypovolemia, and other nephrotoxic insults exacerbate its nephrotoxic effects. Many transplant patients must tolerate a moderately elevated serum creatinine (1.5-2 mg/dL) in order to sustain adequate immunosuppression.

A related calcineurin immunosuppressive agent, tacrolimus (FK506), has been considered somewhat less nephrotoxic than cyclosporine and has largely replaced it. However, renal biopsy studies in pancreas transplant patients indicate that the risk of nephrotoxicity does not differ between tacrolimus and cyclosporine A.[249] There is considerable genetic variability in the metabolism of tacrolimus by the hepatic CP450 enzyme system and its pharmacodynamic effects on immunosuppression; thus, the risk of nephrotoxicity also varies significantly.[250] For example, patients who express the CYP3A5*1 allele require higher tacrolimus doses to achieve therapeutic levels and have an increased risk of nephrotoxicity.[251]

Coadministration of calcium channel blockers competes for CP450 metabolism and results in higher levels

of cyclosporine A and tacrolimus. Most transplant immunologists will avoid this drug interaction, but it may actually be beneficial. In patients undergoing cadaveric renal transplantation, the calcium channel blocker diltiazem was added to the graft preservative solution, infused into the donor for 48 hours, and then given orally.[252] The incidence of transplant acute tubular necrosis decreased from 41% to 10%, and when AKI did occur, hemodialysis requirement was significantly less. Diltiazem impairs cyclosporine metabolism so that plasma cyclosporine levels are higher, but this results in fewer episodes of early acute rejection, and calcium channel blockade protects against cyclosporine nephrotoxicity.[253] Cyclosporine dosage may be reduced by 30% to achieve the same drug levels, representing a substantial cost savings to patients.

An alternative approach that is gaining some traction is to replace cyclosporine A or tacrolimus with a noncalcineurin agent, sirolimus, which appears to have similar immunosuppressive effects with considerable less potential to induced renal injury.[254]

CONTRAST-INDUCED NEPHROTOXICITY

The nephrotoxicity of contrast dye is likely mediated through intense renal vasoconstriction leading to medullary hypoxia, combined with oxidative stress (also see Chapter 90). Direct cytotoxicity almost certainly plays a role as well, because contrast agents are water soluble and readily gain access to the urinary space of the glomerulus and renal tubules.[255] Its likelihood is increased by intraarterial administration and use of large volumes of contrast. The risk of contrast-induced nephrotoxicity (CIN) is exacerbated in the setting of diabetic renal insufficiency, hypovolemia, congestive heart failure, and myeloma.[256]

Radiocontrast dyes are hypertonic and cause an osmotic diuresis, which induces a false sense of security but may actually exacerbate hypovolemia and renal damage. The potential toxicity of radiocontrast media was thought to be directly related to their osmolality. However, meta-analysis has failed to disclose a renoprotective benefit of iso-osmolar contrast compared with a pooled group of low-osmolar contrast agents.[257] The further finding that nephrotoxicity may vary among low-osmolar agents suggests that contrast-induced nephrotoxicity is mediated by other factors in addition to simply osmolality.

When CIN occurs, azotemia commences 24 to 48 hours after exposure and peaks at 3 to 5 days. This provides a clear warning to defer elective surgery to ameliorate the risk of perioperative acute renal failure. On the other hand, the impact of CIN may be missed when surgery immediately follows radiologic studies or when studies are performed during surgery.

The cornerstone of prophylaxis against CIN is adequate hydration—for instance, 1 mL/kg normal saline initiated at least 4 hours before and continued for 12 hours after radiocontrast administration.[258]

A number of pharmacologic agents have raised and then dashed hopes of their role in preventing or attenuating contrast-induced AKI, and nothing has replaced hydration as first-line protection. Intravenous mannitol has been used for many years but may exacerbate injury if it induces dehydration though excessive osmotic diuresis. In the last decade, most interest has focused on antioxidants and dopaminergic agonists.

N-Acetylcysteine

Tepel and associates reported that prophylactic administration of the antioxidant *N*-acetylcysteine (600 mg orally twice daily) attenuated CIN in a study on 83 patients with chronic renal insufficiency (mean serum creatinine 2.4 mg/dL) undergoing contrast radiography.[259] Only 2% of patients receiving *N*-acetylcysteine had an increase in serum creatinine of >0.5 mg/dL, compared with 21% of patients receiving saline placebo, and mean serum creatinine concentrations actually decreased.

Subsequent studies either did not confirm these results[260] or found that *N*-acetylcysteine provided better protection than saline alone only when a low dose of contrast dye was used.[261] *N*-acetylcysteine may itself decrease serum creatinine levels independent of changes in GFR.[25] The protective role of *N*-acetylcysteine clarified by a randomized controlled trial on more than 2300 patients with at least one risk factor for contrast-induced AKI (age >70 years, CKD, diabetes mellitus, heart failure, or hypotension).[240] The incidence of CIN was the same (about 13%), whether a standard *N*-acetylcysteine regimen or placebo was used before and after administration of radiocontrast.

Fenoldopam

An intravenous fenoldopam infusion prevented the decrease in RPF induced by radiocontrast media.[262] However, a large, multicenter RCT on 315 patients with preexisting renal insufficiency (creatinine clearance <60 mL/minute) showed that it had no benefit on renal function compared with placebo.[263] A more recent retrospective evaluation of a direct infusion of fenoldopam into the renal arteries in high-risk patients undergoing coronary angiography and percutaneous revascularization indicated a decrease in incidence of CIN from 31% to 12%.[264] As with many others, this intervention needs to be tested in a formal prospective, randomized, blinded study.

PIGMENT NEPHROPATHY

Pigment nephropathy implies AKI as a consequence of the nephrotoxic effects of the heme pigments myoglobin, hemoglobin, and bilirubin.

Rhabdomyolysis and Myoglobinemia

Muscle necrosis (rhabdomyolysis) occurs most commonly with direct trauma involving major crush or thermal injury. However, it also occurs with acute muscle ischemia induced by vascular disease or injury, or by prolonged immobilization. Compartment syndromes exacerbate rhabdomyolysis. They are particularly likely to occur with major hemorrhage in an extremity or when vascular insufficiency coexists with tissue edema (e.g., femoral placement of an intraaortic balloon after vein harvesting). Dramatic increases in metabolic rate (severe exercise, prolonged fever, status epilepticus, or myoclonus), severe hypophosphatemia, or direct proteolysis (acute pancreatitis) can all precipitate rhabdomyolysis.[265]

Myoglobin, the oxygen-carrying heme pigment of muscle, is released into the bloodstream (myoglobinemia)

and rapidly excreted by the glomerulus at a plasma threshold of 0.03 mg/dL. Delivery of myoglobin to the proximal tubule is greater in a well-muscled individual with normal GFR than in a cachectic patient with low GFR. At a urine pH less than 5.6, myoglobin is transformed into ferrihematin, which precipitates in the proximal tubule.[266] Renal damage is facilitated by hypovolemia (i.e., low tubular flow) and acidic urine. Because of the associated hypercatabolic state, oliguria is associated with acute hyperkalemia, hypocalcemia, anion-gap metabolic acidosis, and rapid azotemia. Serum creatinine and BUN increase very rapidly (1.0-1.5 mg/dL/day and 20-30 mg/dL/day, respectively).

The most important aid to the diagnosis of rhabdomyolysis is a high index of suspicion. The affected muscle may be obviously ischemic or swollen, painful, and edematous. Urine myoglobin often tests positive without reddish urine. The serum is clear because of the low renal threshold for myoglobin excretion, whereas in hemoglobinemia the larger hemoglobin molecule is poorly filtered and accumulates in serum, coloring it pink. Serial total creatinine phosphokinase (CPK) is a helpful guide to the severity of rhabdomyolysis (e.g., CPK-MM release).[267] AKI is much more likely when total CPK exceeds 10,000 U/L.

Prevention of myoglobin-induced AKI is dependent on the maintenance of high RBF and tubular flow. Urine flow should be kept between 100 to 150 mL/hour by osmotic diuresis with intravenous mannitol, 6.25 to 12.5 g every 6 hours, with or without intravenous furosemide, 10 to 20 mg as required.[268] Urine pH should be kept above pH 5.6 with intravenous sodium bicarbonate, 50 mEq intravenously, as required, and/or acetazolamide, 250 mg every 6 hours. However, because there are no prospective data that confirm the beneficial effect of urinary alkalinization, urine pH should not be increased at the expense of causing significant acid-base imbalance. Calcium should be given to treat hyperkalemia only.

Hemolysis and Hemoglobinemia

Hemolysis is induced by CPB, resulting in the release of free hemoglobin into the plasma, where it subsequently forms a complex with haptoglobin. This complex is too large to be filtered by the kidney and undergoes metabolism in the liver. When free hemoglobin production is excessive, it overwhelms the haptoglobin system and accumulates in the plasma. The hemoglobin molecule is small enough to be filtered by the glomerulus and enters the tubule, where it scavenges endothelium derived nitric oxide, subsequently releasing iron and causing tubular occlusion with hemoglobin cast formation. The released free iron is nephrotoxic, through the generation of reactive oxygen species.[195]

Preliminary evidence suggests that urinary alkalinization may attenuate AKI during CPB (see earlier).[241] Acute intravascular hemolysis due to mismatched blood transfusion (ABO incompatibility) represents a direct and devastating renal insult. However, renal damage is thought to be predominantly due to red blood cell stroma rather than to free hemoglobin. Protective renal management is essentially the same as for rhabdomyolysis (i.e., aggressive and sustained hydration, with or without osmotic diuresis, and urinary alkalinization).

Jaundice and Bilrubinemia

There is a direct correlation between the degree of preoperative obstructive jaundice and postoperative renal dysfunction.[269] When cholestasis causes the conjugated bilirubin to increase above 8 mg/dL, bile salt excretion effectively ceases, resulting in portal septicemia and renal damage. This situation is analogous to hepatorenal syndrome and sepsis, in which circulating endotoxins induce renal vasoconstriction and damage (vasomotor nephropathy).

Administration of preoperative oral bile salts (e.g., sodium taurocholate) or intravenous mannitol may provide perioperative renal protection in patients with severe obstructive jaundice. However, in a prospective, randomized study in patients with obstructive jaundice undergoing surgery, Plusa and Clark[270] found no difference in renal outcome between these two regimens. Nevertheless, mannitol provokes a brisk osmotic diuresis, and it is important to replace urinary losses appropriately. Diuresis-induced hypovolemia negates the protective effect of mannitol.[271]

SEPSIS

Sepsis is the most common cause of new-onset AKI in the postoperative period (also see Chapter 101). It may induce renal damage by altered hypotension and vasomotor nephropathy and through the direct and indirect effects of endotoxin, and renal function may deteriorate progressively without defined episodes of hypotension. In addition, sepsis predisposes the kidney to further ischemic and nephrotoxic insults (e.g., from concomitant aminoglycoside usage).[272] Acute renal failure itself and hemodialysis may both perpetuate sepsis by activating leukocytes.

Renal autoregulation may be impaired in sepsis, and RBF and GFR decrease pari passu with systemic vascular resistance and mean arterial pressure. Hypotension, in turn, sets off a cascade of neurohormonal responses (sympathoadrenal activity; renin-angiotensin, vasopressin, and thromboxane activation) that result in decreased RBF, GFR, sodium excretion, and urine flow. The severity of renal dysfunction is directly related to the severity of sepsis and the degree of plasma renin activation.[273]

Renal dysfunction in sepsis is characterized as a vasomotor nephropathy, which implies renal vasoconstriction in the face of increased total cardiac index. Renal vasoconstriction, mesangial cell contraction, decreased ultrafiltration coefficient, and decreased GFR are induced by endotoxin and by compounds activated in sepsis.[274] These include endothelin and eicosanoids, such as thromboxane, prostaglandin F_2, and the leukotrienes C4 and D4. Prostaglandin F_2, which mimics the action of thromboxane, is formed during leukostasis when arachidonic acid is oxidized by free oxygen radicals.

Endotoxin causes leukocyte arachidonic acid to undergo lipoxygenation to form leukotrienes; it also impairs their biliary elimination. In addition, experimental infusion of lipopolysaccharide (endotoxin) directly decreases RBF, GFR, and tubular concentrating ability and

increases urinary loss of tubular enzymes. It causes sequestration of leukocytes in peritubular capillaries, induces endothelial lesions by releasing neutrophil-derived elastase (enhanced by reperfusion injury), and potentiates renal ischemia such that brief hemodynamic instability causes rapid loss of renal function. It also potentiates nephrotoxicity. The changes caused by endotoxin are mimicked by the cytokine, tumor necrosis factor-α.

It has been estimated that about 10% to 26% of septic patients receiving aminoglycoside antibiotics will develop nephrotoxic renal insufficiency.[245] Aminoglycoside nephrotoxicity is enhanced by the interaction of fever, renal vasoconstriction, hypovolemia, and endotoxin. In the presence of these and other risk factors (see earlier), alternative nonnephrotoxic antibiotics should be considered to cover gram-negative infections, including penicillins (ticarcillin), cephalosporins (ceftazidime), carbapenems (imipenem), or monobactams (aztreonam).

RENAL PROTECTION IN SEPTIC SHOCK

Antiinflammatory Drugs

Cumming and associates[275] demonstrated a marked renal protective effect of a selective thromboxane synthetase inhibitor (U63557A) in laparotomy on a intravascularly volume-loaded sheep peritonitis model. Administration of the selective inhibitor either before or 30 minutes after surgery prevented deterioration in creatinine clearance, urinary sodium excretion, and urine flow rate. Beneficial effects have also been observed with aprotonin, perhaps through its antiinflammatory action.[102] In contrast, nonselective cyclooxygenase inhibition by NSAIDs worsens renal function in sepsis by decreasing the synthesis of the renal vasodilator prostacyclin.[276]

The use of pharmacologic doses of methylprednisolone in septic shock was discredited by two large multicenter studies showing no beneficial effect on outcome.[277,278] Moreover, patients who received steroids had significant increases in BUN but not in serum creatinine, suggesting a prerenal state induced by increased protein catabolism.[279] Other potentially adverse effects of large-dose steroids include impaired mitochondrial function, impaired leukocyte function, and inhibition of phospholipase A_2, resulting in decreased synthesis of intrarenal vasodilator prostaglandins.

Supranormal Oxygen Delivery

Over the last decade there has been considerable controversy in the concept of supranormal oxygen delivery to the tissues to overcome the defect that exists in oxygen utilization by septic tissues.[280] This approach uses inotropic support and blood transfusion to drive global oxygen delivery (DO_2) to one of three end points: (1) a DO_2 level consistently found in survivors (600 mL/minute/m^2), (2) a level at which global oxygen consumption (VO_2) no longer increases with increasing DO_2 (consumption independence), or (3) the point at which blood lactate levels start to decline. The benefits of supranormal oxygen delivery on outcome have been disputed, and high-dose inotropic and vasopressor support may themselves have adverse consequences. Moreover, renal DO_2 and VO_2 differ markedly from systemic indices. Renal VO_2 is largely determined by tubular metabolic function, which is regulated by fluid and electrolyte changes. In a volume-loaded septic porcine model, inotropic support with dobutamine increased systemic DO_2 and VO_2 but did not increase renal indices.[77] Furthermore, decreased global renal DO_2 does not appear to cause tubular damage, possibly because tubular work and VO_2 are decreased when GFR declines.[281]

Dopaminergic Agents

Low-dose dopamine (1 to 3 μg/kg/minute) is frequently administered to septic patients in the belief that it confers renal protection through renal vasodilation or perhaps by inhibition of the Na^+-K^+-ATPase pump and decreases in renal tubular VO_2.

In cases of sepsis, low-dose dopamine is also administered in combination with more potent pressors (dobutamine, epinephrine, and norepinephrine) in the hope of enhancing hepatic, renal, and mesenteric perfusion. There are limited animal data to support this practice. In a nonseptic dog study in which RBF was measured by thermodilution, the addition of low-dose dopamine to a norepinephrine infusion of 0.2-1.6 μg/kg/minute increased RBF by 40% to 50%.[78] However, a subsequent study demonstrated that although low-dose dopamine increased RBF when added to an epinephrine infusion in healthy sheep, this benefit could not be found in an intraperitoneal sepsis model.[282] Low-dose dopamine can increase hepatic DO_2, but possibly at the expense of splanchnic oxygenation.

In patients with sepsis syndrome (signs of sepsis without hypotension), low-dose dopamine infusion doubled urine flow rate and increased creatinine clearance by 60% without any change in systemic hemodynamics.[283] However, the renal response to dopamine decreased significantly after 48 hours of dopamine infusion, possibly due to down-regulation of the renal dopaminergic receptors or diuresis-induced contraction of the intravascular volume. In patients with established septic shock who required catecholamines for blood pressure support, low-dose dopamine did not alter systemic hemodynamics or renal function.

The prophylactic administration of low-dose dopamine in sepsis has been resolved by a large prospective controlled study conducted by the Australian and New Zealand Intensive Care Society (ANZICS). They randomized 328 patients with signs of the systemic inflammatory response syndrome (SIRS) and early renal dysfunction (oliguria or increasing serum creatinine) to dopamine 2 mcg/kg/minute or placebo. They found no differences in serum creatinine, dialysis requirement, ICU or hospital length of stay, or overall mortality.[284]

The potential role of dopexamine in septic shock remains speculative. Most studies have examined its role in splanchnic and hepatic perfusion rather than in renal protection. In animal models of sepsis, dopexamine improves splanchnic and hepatic DO_2, but its β_2-adrenergic activity in causing tachycardia and hypotension may limit its application in clinical sepsis. Smithies and colleagues[285] administered dopexamine to patients with sepsis syndrome, acute respiratory failure,

and at least one other organ system failure. Cardiac index increased and gastric intramucosal pH (an index of splanchnic perfusion) improved significantly.

In contrast, there is at least preliminary evidence that infusion of low-dose fenoldopam may have a renoprotective effect in sepsis. A pilot randomized, double-blind, placebo-controlled trial on 300 septic patients found that fenoldopam infusion (0.09 mcg/kg/minute) resulted in a significant decrease in AKI (defined as an increase in SCr >150 mM/L) and ICU length of stay, but not mortality.[286] These encouraging results await confirmation by a large multicenter study.

Norepinephrine

In the setting of severe vasodilatory shock, concern that infusions of norepinephrine may impair renal blood flow through α-adrenergic–induced vasoconstriction appears to be unfounded. In patients with septic shock, profound hypotension, and oliguria, vasopressor therapy with norepinephrine may actually improve renal function by enhancing renal perfusion pressure. Desjars and associates[11] evaluated a group of septic patients who remained oliguric despite volume resuscitation and the use of dopamine up to doses of 15 μg/kg/minute. The addition of norepinephrine and reduction of dopamine to a low-dose level resulted in an improvement in mean arterial pressure from 50 to 70 mm Hg, a tripling of urine flow, and a doubling of creatinine clearance. Norepinephrine increased the systemic vascular resistance (SVR) with little change in cardiac index or DO_2. Subsequent studies confirm that the use of norepinephrine to keep mean arterial pressure greater than 60 mm Hg results in improved cardiac function (increase in stroke volume and decrease in heart rate) and GFR without deleterious effects on cardiac index (CI), VO_2, or oxygen extraction.[287]

Large doses of norepinephrine may be required to achieve these goals, because in septic shock the peripheral vasculature is notoriously refractory to norepinephrine-induced vasoconstriction. This occurs because of massive inducible nitric oxide release and vasopressin deficiency (see later). Nonetheless, these findings strongly support the concept that renal autoregulation is impaired in sepsis and that maintenance of adequate renal perfusion pressure is an important component of renal protection.

Arginine Vasopressin

Patients in vasodilatory shock have inappropriately low plasma levels of arginine vasopressin (AVP) and marked vascular sensitivity to its exogenous administration at low doses.[288] Vasodilatory shock is defined as hypotension, increased cardiac index, and low systemic vascular resistance refractory to pressors such as norepinephrine. Septic shock is its most common manifestation, but it is also characteristic of the contact activation syndrome induced by cardiopulmonary bypass or ventricular assist devices.[289]

Landry and colleagues[290] observed unusual sensitivity to the vasoconstrictor effects of infused AVP in patients with septic shock and profound hypotension despite catecholamine infusion. Infusion of AVP at doses of 2.4 U/hour, less than one tenth of those used in the treatment of bleeding esophageal varices, resulted in a dramatic

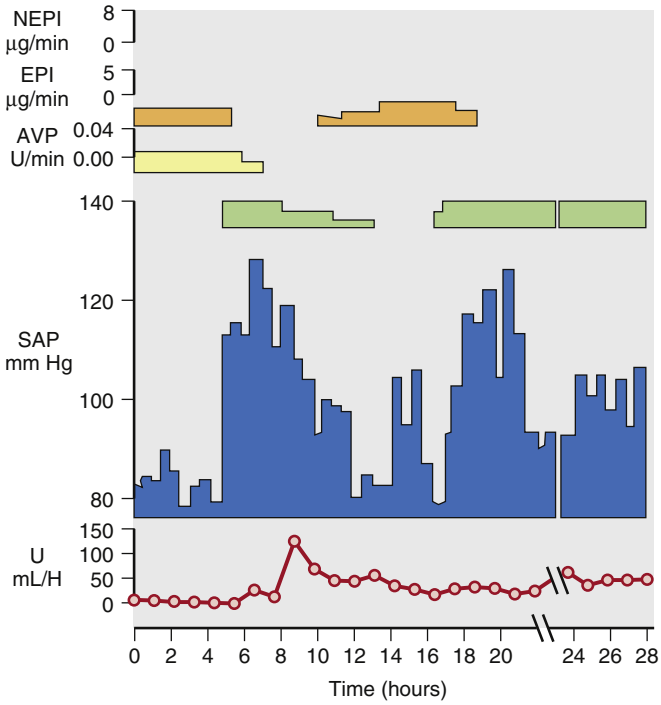


Figure 23-27. Effects of an infusion of AVP in vasodilatory shock.

increase in systolic blood pressure from 92 ± 4 mm Hg to 146 ± 4 mm Hg (mean ± SEM, $P < .001$), and catecholamine infusions were able to be discontinued (Fig. 23-27). In an associated report[291] the authors observed that urine flow increased concomitantly in three of five patients, from an average of 30 mL/hour to 110 mL/hour.

Plasma AVP levels were remarkably low (3.1 ± 1.0 pg/mL) and significantly lower than in a cohort of patients in cardiogenic shock also receiving catecholamines (22.7 ± 2.2 pg/mL, $P < 0.001$).[290] It has been postulated that this AVP deficiency may be the result of excessive baroreceptor-mediated AVP release from sustained hypotension. This is strongly supported by a canine study demonstrating almost complete depletion of radiolabeled AVP in the posterior pituitary following 1 hour of hemorrhagic shock.[288] In a human study in patients in vasodilatory shock we confirmed very low levels of endogenous plasma AVP (<2 pg/mL) that were corrected to the 20- to 30-pg/mL range by an infusion of AVP at 1 to 4 U/hour (Table 23-7).

A second mechanism for sensitivity to AVP in septic patients is explained by its effect on the potassium-ATP (K_{ATP}) channel.[288] Intracellular acidosis, lactic acid accumulation, and ATP depletion close K_{ATP} channels in the sarcolemma of vascular smooth muscle. This traps potassium outside the cell and hyperpolarizes the membrane, which in turn closes calcium channels essential for norepinephrine-induced vasoconstriction. AVP binds at the K_{ATP} channel and opens it, reversing membrane hyperpolarization and restoring sensitivity to norepinephrine.

The beneficial effect of AVP on renal function in sepsis may be due in part to its ability to increase low renal perfusion pressure back into the autoregulatory range. Another important factor is that, unlike norepinephrine, even at high local concentrations, AVP preferentially

TABLE 23-7 PLASMA VASOPRESSIN LEVELS IN VASODILATORY SEPTIC SHOCK

	Vasopressin Levels in pg/mL	
	T0*	T1
AVP (n = 12)	1.84 ± 0.59	32.3 ± 7.69
Placebo (n = 11)	1.72 ± 0.72	1.5 ± 0.5

From Kinster C, Germann P, Ullrich R, Landry D, Sladen RN: Infusion of arginine vasopressin (AVP) enhances blood pressure and renal function while preserving cerebral and splanchnic perfusion in patients in septic shock. Presented at Annual Meeting of American Society of Anesthesiologists (ASA), Orlando, FL, 2002.

AVP, Arginine vasopressin

*T0 represents mean baseline levels of plasma vasopressin in 23 patients in vasodilatory septic shock (hypotension requiring norepinephrine infusion to maintain mean arterial pressure [MAP] > 65 mm Hg, elevated cardiac index, decreased systemic vascular resistance, and three or more criteria of systemic inflammatory response syndrome). Mean plasma vasopressin levels are uniformly low, <2 pg/mL.

Patients were randomized in a blinded fashion to an infusion containing AVP (1-6 units/hr) or placebo, until norepinephrine infusion was no longer required to keep MAP >65 mm Hg, or the maximum infusion rate (6 mL/hr) was achieved, or the infusion had been administered for 2 hours.

Patients randomized to AVP infusion had a significant, 65% decrease in norepinephrine requirement, whereas it was unchanged in the placebo group. As indicated at T1—the point at which study end points were achieved—the mean plasma vasopressin that reflected a therapeutic effect of AVP infusion was about 32 pg/mL, which is in the range of the effective physiologic human vasopressin response to hypotension.

These observations support the concept that exogenous AVP infusion in vasodilatory septic shock restores the normal response to hypotension that is attenuated by posterior pituitary vasopressin depletion.

constricts the efferent arteriole, thereby improving filtration fraction and GFR.[292] In a large, prospective, randomized, blinded trial in 778 patients with severe septic shock, low-dose AVP (0.01-0.03 units/minute) did not provide an overall mortality benefit or decrease the requirement for dialysis, when compared with an infusion of norepinephrine (5-15 mcg/minute).[293] However, a post hoc analysis of the data found that in patients who entered the study with the R (risk) criterion of RIFLE-defined AKI, significantly fewer (21% versus 40%) progressed to the F (failure) or L (loss) categories or needed dialysis (17% versus 38%) when they were randomized to AVP rather than norepinephrine.[294]

RENAL CROSSTALK

Awareness and concern have increased that AKI may lead to acute injury in other, multiple organ systems, including the lung, brain, liver, and heart, through the phenomenon of organ "crosstalk."[295] The organ crosstalk that is initiated by AKI is mediated by acute inflammation, oxidative stress, and reactive oxygen species, resulting in activation of leukocytes and cytokines and induction of apoptosis and necrosis in distant organs. Multisystem organ dysfunction is common in patients developing AKI in the ICU, and it may account for a morbidity and mortality rate out of proportion to that anticipated by isolated AKI alone.

Crosstalk works both ways. For example, not only may AKI lead to acute lung injury, but the inflammatory processes induced by acute lung injury may themselves initiate or exacerbate AKI. Kidney-heart interactions involve much more than inflammatory pathways alone; they involve numerous neurohormonal interactions, resulting in a series of entities known as cardiorenal syndromes (CRS).[296] The most obvious kidney-brain interaction is uremic encephalopathy, but there also appear to be structural neuronal injuries caused by uremic toxins, especially NOS-modulating guanidine compounds, that are proexcitatory at the NMDA receptor.[297] Acute liver injury and transaminitis may be observed with severe AKI,[298] and in reverse, severe liver failure and vasoactive compound dysregulation may result in impaired kidney function (i.e., hepatorenal syndrome).

Complete references available online at expertconsult.com

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Chapter 24

Basic Principles of Pharmacology

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Key Points

- Pharmacokinetics describes the relationship between drug dose and drug concentration in plasma or at the site of drug effect over time. For anesthetic drugs, the processes of distribution and elimination (metabolism and excretion) govern this relationship.
- The time course of intravenously administered drugs is a function of distribution volume and clearance. Estimates of distribution volumes and clearances are described by pharmacokinetic parameters. These parameters are derived from mathematical formulas fit to measured blood or plasma concentrations over time following a known drug dose.
- Alterations in cardiac output substantially influence the pharmacokinetic behavior of anesthetic drugs in terms of onset and duration of effect.
- Biophase refers to the time delay between changes in plasma concentration and drug effect. Biophase accounts for the time required for drug to diffuse from the plasma to the site of action plus the time required, once drug is at the site of action, to illicit a drug effect.
- Pharmacodynamics describes what the drug does to the body. In particular, pharmacodynamics describes the relationship between drug concentration and pharmacologic effect.
- The effect-site concentration describes a mathematically derived virtual location where an anesthetic drug exerts its effect. This approach cannot describe a mechanism of drug action (e.g., drug-receptor interaction)
- A single anesthetic drug has multiple effects (i.e., analgesia, ventilatory depression, loss of response to laryngoscopy, and changes in the electroencephalogram) that typically occur at various effect-site concentrations.
- The concentration range where changes in drug effect occur is known as the dynamic range. Concentrations outside the dynamic range do not yield much change in drug effect. Levels below the dynamic range are ineffective and those above the dynamic range do not provide additional effect.
- Anesthesia is the practice of applied drug interactions. Anesthetics rarely consist of one drug, but rather a combination of drugs to achieve desired levels of hypnosis, analgesia, and muscle relaxation. Hypnotics, analgesics, and muscle relaxants all interact with one another such that rarely does one drug, when administered in the presence of other drugs, behave as if it were administered alone.
- Pharmacokinetic and pharmacodynamic principles characterize the magnitude and time course of drug effect, but because of complex mathematics, they have limited clinical utility. Advances in computer simulation have brought this capability to the point of real-time patient care in the form of drug displays.
- Special populations: Many aspects of a patient's demographics and medical history are considered in finding the correct dose. Some of these include age; body habitus; gender; chronic exposure to opioids, benzodiazepines, or alcohol; presence of heart, lung, kidney, or liver disease; and the extent of blood loss or dehydration.
- Some patient characteristics (e.g., obesity and age) influence anesthetic drug behavior, whereas other patient characteristics (chronic opioid use, hepatic and renal failure) remain poorly described.

The basic principles of pharmacology are fundamental to an anesthesia provider's knowledge base. The aim of this chapter is to provide an overview of key principles in clinical pharmacology used to describe anesthetic drug behavior. This chapter is divided into three major sections: pharmacokinetic principles, pharmacodynamic principles, and the importance of patient characteristics. Pharmacokinetics is the relationship between drug administration and drug concentration at the site of action. Core concepts include volumes of distribution, drug clearance, transfer of drugs between plasma and tissues, and binding of drugs to circulating plasma proteins. The section on pharmacokinetics introduces both the physiologic processes that determine pharmacokinetics and the mathematical models used to relate dose to concentration.

Pharmacodynamics is the relationship between drug concentration and pharmacologic effect. An anesthetic rarely consists of only one drug. In fact, most anesthetics are a combination of several drugs with specific goals in analgesia, sedation, and muscle relaxation. This section reviews common pharmacodynamic interactions and how they influence anesthetic effect.

The last section briefly addresses patient demographics and how they influence anesthetic behavior. When formulating an anesthetic, the following factors need to be considered in determining the correct dose: age; body habitus; gender; chronic exposure to opioids, benzodiazepines, or alcohol; the presence of heart, lung, kidney, or liver disease; and the extent of blood loss or dehydration. This section focuses on body habitus and age, both known to influence the pharmacology of many anesthetic drugs and both of which serve as excellent examples of altered pharmacokinetics and pharmacodynamics.

PHARMACOKINETICS PRINCIPLES

Pharmacokinetics describes the relationship between drug dose and drug concentration in plasma or at the site of drug effect over time. The processes of absorption, distribution, and elimination (metabolism and excretion) govern this relationship. Absorption is not relevant to intravenously administered drugs but is relevant to all other routes of drug delivery. The time course of intravenously administered drugs is a function of distribution volume and clearance. Estimates of distribution volumes and clearances are described by pharmacokinetic parameters. Pharmacokinetic parameters are derived from mathematical formulas fit to measured blood or plasma concentrations over time following a known drug dose.

FUNDAMENTAL PHARMACOKINETIC CONCEPTS

Volume of Distribution

An oversimplified model of drug distribution throughout plasma and tissues is the dilution of a drug dose into a tank of water. The volume of distribution (Vd) is the apparent size of the tank required to explain a measured drug concentration from the tank water once the drug has had enough time to thoroughly mix within the tank (Fig. 24-1). The distribution volume is estimated using the simple relationship between dose (e.g., mg) and measured concentration (e.g., mg/L) as presented in Equation 1.

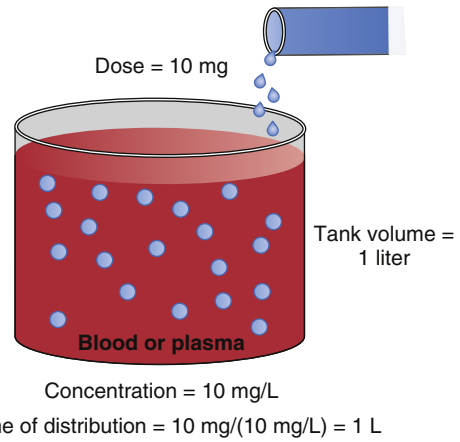


Figure 24-1. Schematic of a single-tank model of distribution volume. The group of blue dots at the top right represents a bolus dose that, when administered to the tank of water, evenly distributes within the tank.

$$\text{Volume of Distribution} = \frac{\text{Amount of dose}}{\text{Concentration}} \quad [1]$$

With an estimate of tank volume, drug concentration after any bolus dose can be calculated. Just as the tank has a volume regardless of whether there is drug in it, distribution volumes in people are an intrinsic property regardless of whether any drug has been given.

Human bodies are not water tanks. As soon as a drug is injected, it begins to be cleared from the body. To account for this in the schematic presented in Figure 24-1, a faucet is added to the tank to mimic drug elimination from the body (Fig. 24-2). Using Equation 1, to estimate the volume of distribution without accounting for elimination leads to volume of distribution estimates that become larger than initial volume. To refine the definition of distribution volume, the amount of drug that is present at a given time t is divided by the concentrations at the same time:

$$Vd = \frac{\text{Amount (t)}}{\text{Concentration (t)}} \quad [2]$$

If elimination occurs as a first-order process (i.e., elimination is proportional to the concentration at that time), the volume of distribution calculated by Equation 2 will be constant (Fig. 24-3; also see Fig. 24-2).

When a drug is administered intravenously, some drug stays in the vascular volume, but most of the drug distributes to peripheral tissues. This distribution is often represented as additional volumes of distribution (tanks) connected to a central tank (blood or plasma volume). Peripheral distribution volumes increase the total volume of distribution (Fig. 24-4).

The schematic in Figure 24-4 presents a plasma volume and tissue volume. The peripheral tank represents distribution of drug in peripheral tissues. There may be more than one peripheral tank (volume) to best describe the entire drug disposition in the body. The size of the peripheral volumes represents a drug's solubility in tissue

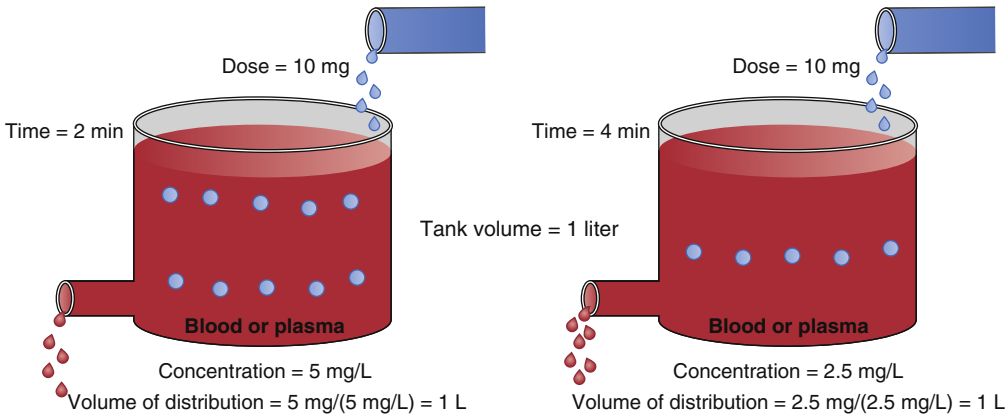


Figure 24-2. Schematic of a single-tank model of elimination as a first order process. At 2 minutes (*left panel*) and 4 minutes (*right panel*) following a 10-mg drug bolus, tank concentrations are decreasing from 5 to 2.5 mg/mL. Accounting for elimination, estimates of the distribution volume at each time point are both 1 liter.

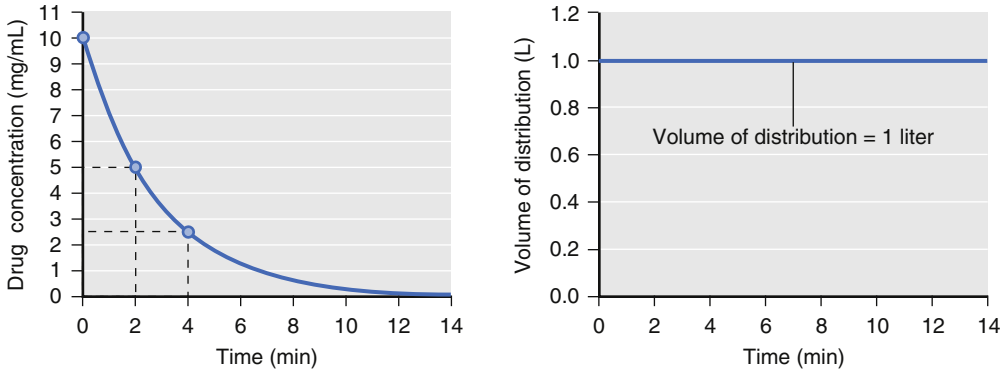


Figure 24-3. Simulation of concentration (*left panel*) and distribution volume (*right panel*) changes over time following a bolus dose for a single-tank (one-compartment) model. The distribution volume remains constant throughout.

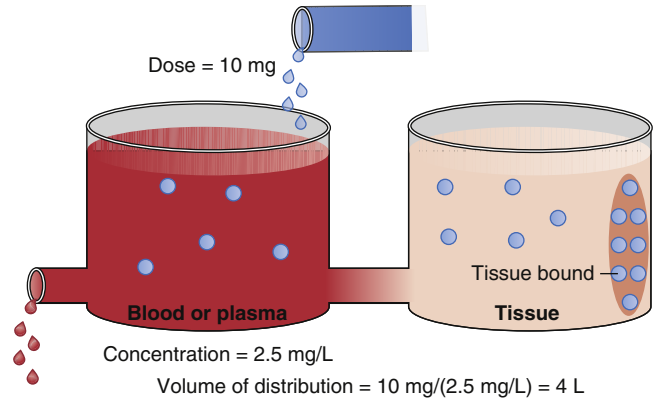


Figure 24-4. Schematic of a two-tank model. The total volume of distribution consists of the sum of the two tanks. The brown ellipse in the peripheral volume represents tissue that binds up drugs. The measured concentration in the blood or plasma is 2.5 mg/mL just after a bolus dose of 10 mg. Using Figure 24-1, this leads to a distribution volume of 4 liters.

relative to blood or plasma. The more soluble a drug is in peripheral tissue relative to blood or plasma, the larger the peripheral volumes of distribution.

An important point illustrated in Figure 24-4 is that drug not only distributes to the peripheral tank and thus increases the volume of distribution, but it also binds to tissue in that tank. This process further lowers the measureable concentration in the central tank. Thus, the total volume of distribution may even be larger than the two tanks added together. In fact some anesthetics have huge distribution volumes (e.g., fentanyl has an apparent distribution volume of 4 L/kg) that are substantially larger than an individual's vascular volume (0.07 L/kg) or extracellular volume (0.2 L/kg).

With an additional tank, the volume of distribution no longer remains constant over time. As illustrated in Figure 24-5, at time = 0, the volume of distribution is estimated as 4.3 L, the same as that of the model presented in Figure 24-3, which has only one tank. The volume of distribution then increases to 48 liters over the next 10 minutes. The increase is due to the distribution of drug to the peripheral volume and elimination once drug is in the body. The amount of drug that moves to the peripheral tissue commonly surpasses the amount that is eliminated during the first few minutes after drug administration. As an example, consider a simulation of a propofol bolus that plots the accumulation of propofol in peripheral tissues and the amount eliminated over time (Fig. 24-6). During the first 4 minutes, the amount distributed to the peripheral tissue is larger than the amount eliminated out of the body. Following 4 minutes, the amounts reverse.

Front-End Kinetics

Front-end kinetics refers to the description of intravenous drug behavior immediately following administration. How a drug rapidly moves from the blood into peripheral tissues directly influences the peak plasma drug concentration. With compartmental models, an important assumption is that an intravenous bolus instantly mixes in the central volume, with the peak concentration occurring at the moment of injection without elimination or

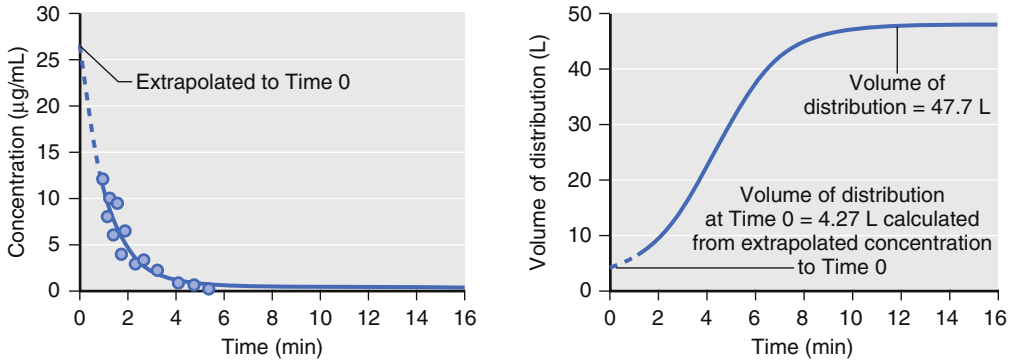


Figure 24-5. Simulation of concentration and apparent distribution volume changes over time following a bolus dose for a two-tank (two-compartment) model. *Left panel:* The dots represent measured drug concentrations. The *solid line* represents a mathematical equation fit to the measured concentrations. The *dotted line* represents an extrapolation of the mathematical equation (i.e., pharmacokinetic model) to time 0. *Right panel:* The apparent distribution volume is time dependent with the initial volume of distribution much small than the distribution volume at near steady state. The apparent distribution volume of time 0 is not true reflection of the actual volume of distribution.

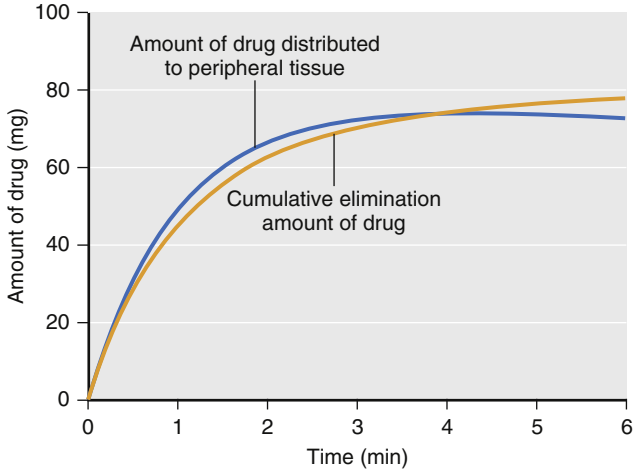


Figure 24-6. Simulation of propofol accumulation in the peripheral tissues (*blue line*) and the cumulative amount of propofol eliminated (*gold line*) following a 2-mg/kg propofol bolus to a 77-kg (170-lb), 53-year-old male who is 177 cm (5 ft 10 in) tall, using published pharmacokinetic model parameters.[1] *Drug* indicates propofol.

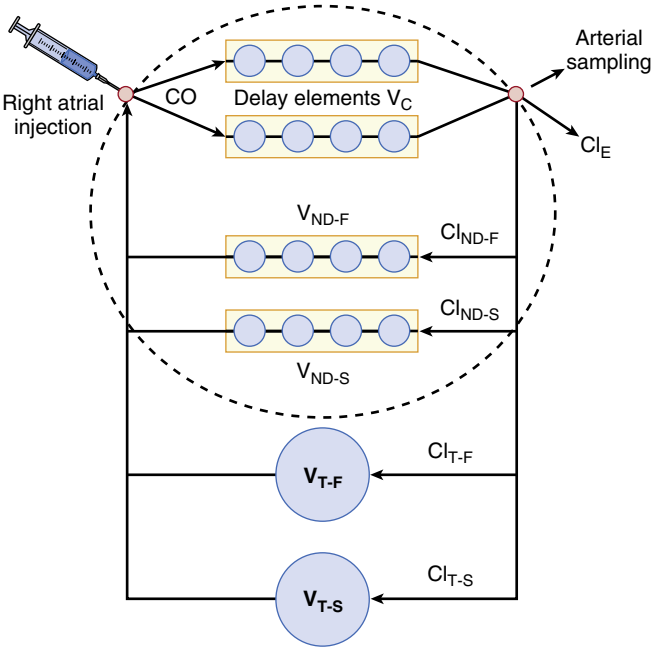


Figure 24-7. A recirculatory model accounting for cardiac output (CO), transit delays, pulmonary uptake (delay elements V and C), and nondistributive mixing pathways (V_{ND} and Cl_{ND}). All the components within the *dashed circle* are required to accurately model the central volume of distribution. In most situations, this complexity is not required, and the simpler approach of assuming instantaneous mixing within the central volume is an adequate approximation. Cl_{ND-F}, Fast nondistributive clearance; Cl_{ND-S}, slow nondistributive clearance; Cl_{T-F}, fast tissue clearance; Cl_{T-S}, slow tissue clearance; V_{ND-F}, fast nondistributive volume; V_{ND-S}, slow nondistributive volume; V_{T-F}, fast tissue volume; V_{T-S}, slow tissue volume.[2]

distribution to peripheral tissues. For simulation purposes, the initial concentration and volume of distribution at time = 0 are extrapolated as if the circulation had been infinitely fast. This, of course, is not real. If drug is injected into an arm vein and that the initial concentration is measured in a radial artery, drug appears in the arterial circulation 30 to 40 seconds after injection. The delay likely represents the time required for drug to pass through the venous volume of the upper part of the arm, heart, great vessels, and peripheral arterial circulation. More sophisticated models (e.g., a recirculatory model)[1] account for this delay and are useful when characterizing the behavior of a drug immediately following bolus administration, such as with induction agents where the speed of onset and duration of action are of interest (Fig. 24-7).

Clearance

Clearance describes the rate of drug removal from the plasma/blood. Two processes contribute to drug clearance: systemic (out of the tank) and intercompartmental (between the tanks) clearance (Fig. 24-8). Systemic clearance permanently removes drug from the body, either by eliminating the parent molecule or by transforming it into metabolites. Intercompartmental clearance moves drug between plasma and peripheral tissue tanks. By way of clarification, in this chapter, the words *compartment* and *tank* are interchangeable.

Clearance is defined in units of flow, that is, the volume completely cleared of drug per unit of time (e.g., liters/minute). Clearance is not to be confused with elimination rate (e.g., mg/minute). To explain why elimination rates

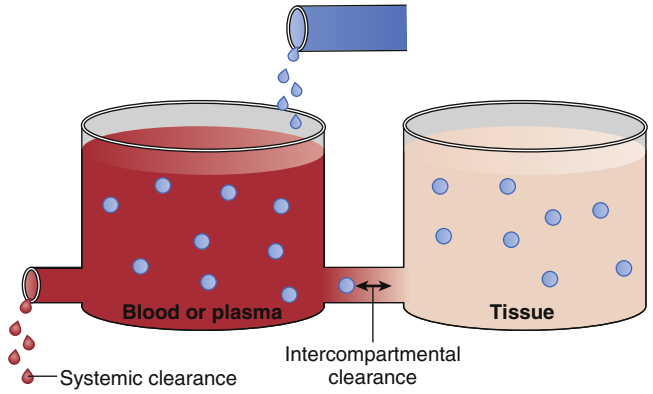


Figure 24-8. Schematic of a two-tank model illustrating two sources of drug removal from the central tank (blood or plasma): systemic and intercompartmental clearance.

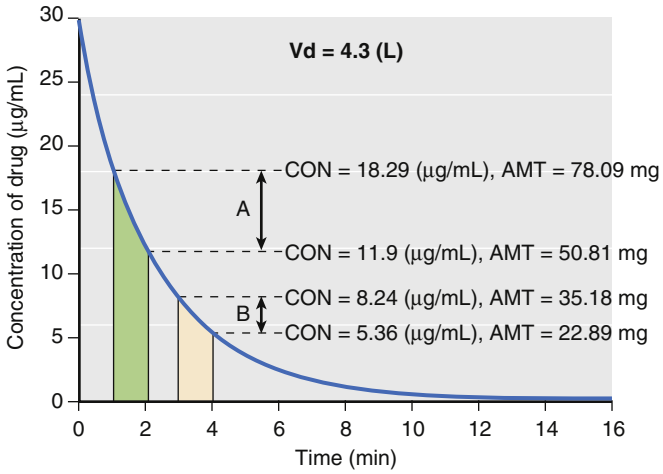


Figure 24-9. Simulation of drug concentration changes when a drug is administered to a single-tank model with linear elimination (see Fig. 24-2). The concentration changes for two time windows are labeled with diagonal lines from 1 to 2 minutes (*time window A*) and from 3 to 4 minutes (*time window B*), respectively. The concentrations (*CON*) at the beginning and end of each time window are used to calculate the amount (*AMT*) of drug that is eliminated (see text). *s* Volume of distribution.

do not accurately characterize clearance, consider the simulation presented in Figure 24-9. Using the volume of distribution, the total amount of drug can be calculated at every measured concentration. The concentration change in time window A is larger than in time window B even though they are both 1 minute in duration. The elimination rates are 27 and 12 mg/minute for time windows A and B, respectively. They are different and neither can be used as a parameter to predict drug concentrations when another dose of drug is administered. Because of this limitation with elimination rate, clearance was developed to provide a single number to describe the decay in drug concentration presented in Figure 24-9.

For discussion purposes, assume that concentration is the power necessary to push drug out of the water tank. The higher the concentration, the larger the amount of drug eliminated. To standardize the elimination rate, the eliminated amount of drug is scaled to concentration. For example, the elimination rate in time window A (27 mg/minute) scaled to the mean concentration during that time window (15 µg/mL) is 0.001807 mg/minute/mg/L. Reducing the units gives 0.002 L/minute. Normalizing the elimination rate in time window B to concentration gives the same as result as A. If the time interval is narrowed so that the time window approaches zero, the definition of clearance becomes:

$$\text{Clearance} = \frac{\frac{dA}{dt}}{C(t)} \qquad [3]$$

where dA/dt is the rate of drug elimination at given time and C(t) is the corresponding concentration at time. Rearranging Equation 3 and integrating both numerator and denominator, the following relationship holds:

$$\text{Clearance} = \frac{\int_0^\infty dA}{\int_0^\infty C(t)dt} \qquad [4]$$

because the term $\int_0^\infty dA$ is equal to the total amount of drug eliminated and $\int_0^\infty C(t)\,dt$ is the area under curve (AUC), then the following equation can be derived:

$$\text{Clearance} = \frac{\text{Dose}}{\text{AUC}} \qquad [5]$$

With long infusions, drug concentrations reach a steady-state condition where the rate of drug elimination (dA/dt) is in equilibrium with the rate of drug administration. Clearance in a steady-state condition can be obtained using Equation 3 as follows:

$$\text{Clearance} = \frac{\text{Infusion Rate}}{C_{ss}} \qquad [6]$$

where C_{ss} is the plasma concentration at steady state.

Physiologic Model for Clearance

Drug extraction by metabolic organs is illustrated in Figure 24-10. This model contains a metabolic organ system responsible for drug elimination. According to mass balance, the rate at which drug flows *out* of metabolic organs is the rate at which drug flows *into* them minus the metabolic rate. The elimination rate (dA/dt) can be expressed as $Q(C_{in} - C_{out})$. Rearranging C(t) in Equation 3 with C_{in}, clearance in Equation 3 can be expressed as

$$\text{Clearance} = \frac{Q(C_{in} - C_{out})}{C_{in}} \qquad [7]$$

where Q is the blood flow to metabolic organs, C_{in} is the concentration of drug delivered to metabolic organs, and C_{out} is the concentration of drug leaving metabolic organs. The fraction of inflowing drug extracted by the organ is $\frac{C_{in} - C_{out}}{C_{in}}$. This is called the extraction ratio (ER). Clearance can be estimated as organ blood flow multiplied by the ER. Equation 7 can be simplified to

$$\text{Clearance} = \frac{Q(C_{in} - C_{out})}{C_{in}} = Q \times \frac{C_{in} - C_{out}}{C_{in}} = Q \times ER \qquad [8]$$

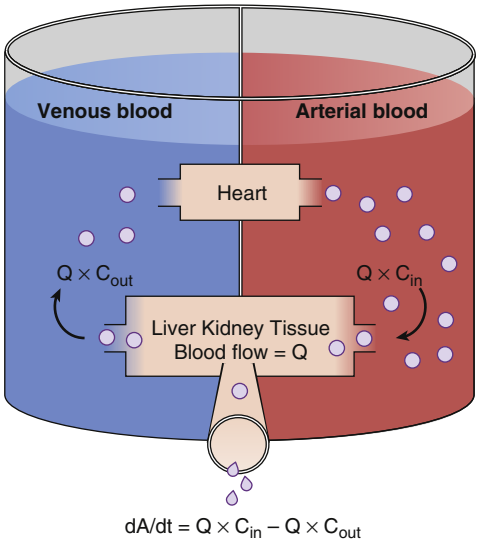


Figure 24-10. Schematic of drug extraction. *Q* indicates blood flow. C_{in} and C_{out} indicate drug concentrations presented to and leaving metabolic organs. *A* indicates the amount of drug, and *dA/dt* is the drug elimination rate.

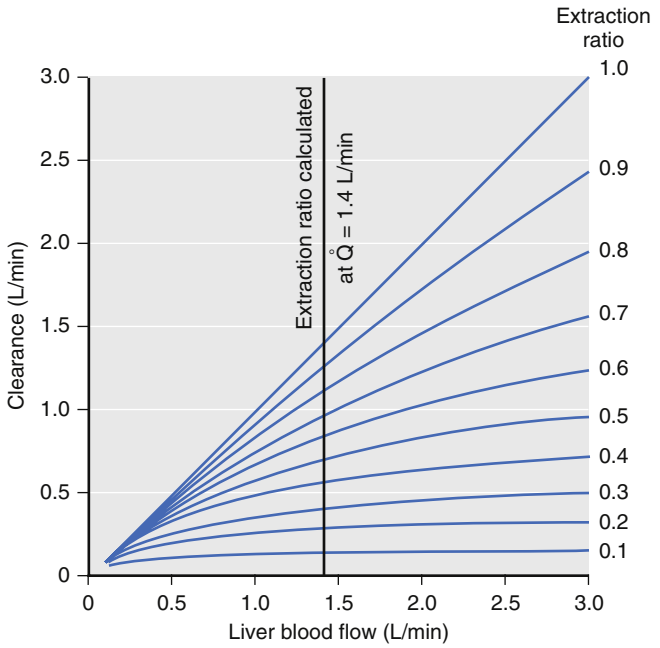


Figure 24-11. Relationship among liver blood flow (*Q*), clearance, and extraction ratio. For drugs with a high extraction ratio, clearance is nearly identical to liver blood flow. For drugs with a low extraction ratio, changes in liver blood flow have almost no effect on clearance.[3]

The total clearance is the sum of each clearance by metabolic organs such as the liver, kidney and other tissues.

Hepatic clearance has been well characterized. For example, the relationship among clearance, liver blood flow, and the extraction ratio is presented in Figure 24-11.[3] For drugs with an extraction ratio of nearly 1 (e.g., propofol), a change in liver blood flow produces a nearly proportional change in clearance. For drugs with a low extraction ratio (e.g., alfentanil), clearance is nearly independent of the rate of liver blood flow. If nearly 100% of the drug is extracted by the liver, this implies that the liver has a very large metabolic capacity for the drug. In this case, the rate-limiting step in metabolism is the flow of drug to the liver, and such drugs are said to be "flow limited." As a consequence, any reduction in liver blood flow due to circulatory effects of anesthetic agents or changes in circulatory volumes in cases of perioperative bleeding or other situations of excessive fluid loss can be expected to reduce liver-dependent drug clearance. However, moderate changes in hepatic metabolic function per se will have little impact on clearance because hepatic metabolic capacity is overwhelmingly in excess of demand.

For many drugs (e.g., alfentanil), the extraction ratio is considerably less than 1. For these drugs, clearance is limited by the capacity of the liver to take up and metabolize drug. These drugs are said to be "capacity limited." Clearance will change in response to any change in the capacity of the liver to metabolize such drugs, as might be caused by liver disease or enzymatic induction. However, changes in liver blood flow caused by the anesthetic regimen or other changes in splanchnic circulation usually have little influence on clearance because the liver handles only a fraction of the drug that it sees.

Hepatic Biotransformation

Most anesthetic drugs are cleared by hepatic biotransformation. The synthetic pathways for biotransformation are covered in detail in many biochemistry texts. Briefly, the liver metabolizes drugs through oxidation, reduction, hydrolysis, or conjugation. Oxidation and reduction occur in the cytochrome P450 system. These enzymes can be induced by exposure to certain drugs (e.g., the herbal remedy St. John's wort) and increase the liver's intrinsic metabolic capacity. Other drugs or hepatic disease can inhibit these enzymes (e.g., selected calcium channel blockers and selected antibiotics). Routes of oxidative metabolism include hydroxylation, dealkylation, deamination, desulfuration, epoxidation, and dehalogenation. Conjugation and hydrolysis often occur outside the P450 system, although glucuronidation involves the P450 system as well. The effect of conjugation is to transform hydrophobic molecules into water-soluble molecules through the addition of polar groups and thus render the metabolites easier to excrete via the kidneys. The metabolites generated by the liver are generally inactive, although some drugs (e.g., morphine, midazolam) have metabolites that are as potent as the parent drug. Genetic polymorphism can occur in all of these pathways, and this accounts for part of the variability in clearance in the population.

Extrahepatic Metabolism

Although most anesthetic drugs are cleared by hepatic metabolism, remifentanil, succinylcholine, and esmolol are cleared in the plasma and tissues by ester hydrolysis, and pancuronium is cleared via the kidney. The relationship between metabolism and clearance is complex. The following exploration of this relationship will assume hepatic metabolism, although the principles apply to the metabolism of drug in any tissue. The rate of metabolism for most anesthetic drugs is proportional

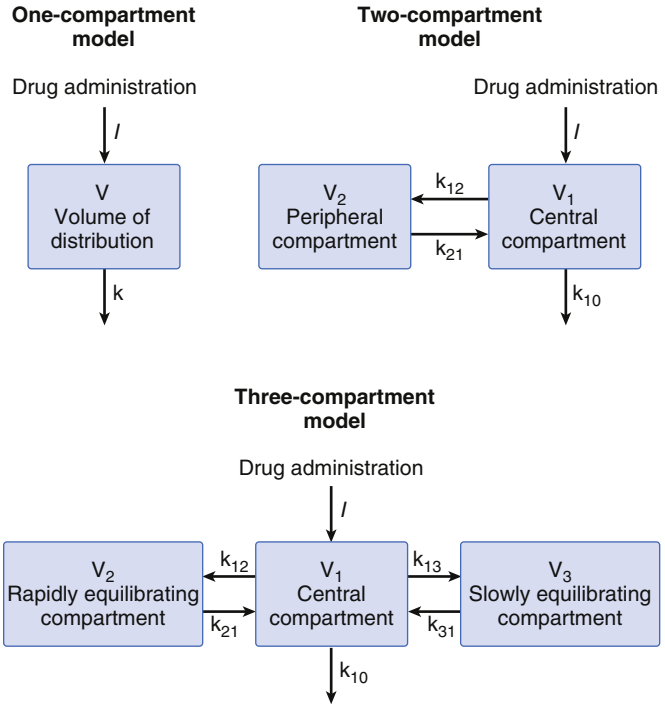


Figure 24-12. One-, two-, and three-compartment mammillary models.

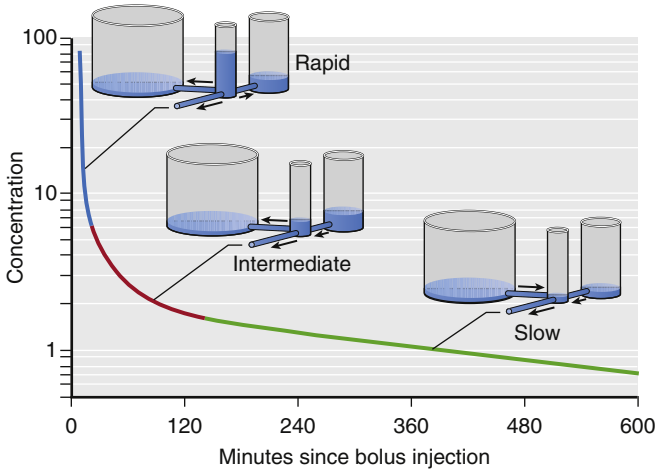


Figure 24-13. Hydraulic model of fentanyl pharmacokinetics. Drug is administered into the central tank, from which it can distribute into two peripheral tanks, or it may be eliminated. The volume of the tanks is proportional to the volumes of distribution. The cross-sectional area of the pipes is proportional to clearance.[5]

to the concentration of drug distributed via circulation to the liver. As was shown earlier, this means that metabolic clearance is usually constant and independent of dose.

Physiologic Pharmacokinetic Models

It is possible to analyze volumes and clearances for each organ in the body and construct models of pharmacokinetics by assembling the organ models into physiologically and anatomically accurate models of the entire animal.[4] Models that work with individual tissues are mathematically cumbersome and do not offer a better prediction of plasma drug concentration than models that lump the tissues into a few compartments. If the goal is to determine how to give drugs to obtain therapeutic plasma drug concentrations, all that is needed is to mathematically relate dose to plasma concentration. For this purpose, conventional compartmental models are usually adequate.

Compartmental Pharmacokinetic Models

Compartmental models are built on the same basic concepts as physiologic models, but with gross simplifications. The one-compartment model seen in Figure 24-12 contains a single volume and a single clearance, as though humans were built like tanks. For anesthetic drugs, human bodies resemble several tanks connected by pipes. These are usually modeled by two- or three-compartment models, also shown in Figure 24-12. The volume to the right in the two-compartment model—and in the center of the three-compartment model—is the central volume. The other volumes are peripheral volumes. The sum of all volumes is the volume of distribution at steady state, Vd_{ss}. Clearance in which the central compartment is left for the outside is the central, or metabolic, clearance. Clearances between the central compartment and the peripheral compartments are the intercompartmental clearances.

Multicompartment Models

Plasma concentrations over time after an intravenous bolus resemble the curve in Figure 24-13. This curve has the characteristics common to most drugs when given by intravenous bolus. First, the concentrations continuously decrease over time. Second, the rate of decline is initially steep but continuously becomes less steep, until we get to a portion that is log-linear.

For many drugs, three distinct phases can be distinguished, as illustrated in Figure 24-13. A rapid-distribution phase (blue line) begins immediately after injection of the bolus. Very rapid movement of the drug from plasma to the rapidly equilibrating tissues characterizes this phase. Frequently, there is a second, slow-distribution, phase (red line), which is characterized by movement of drug into more slowly equilibrating tissues and return of drug to plasma from the most rapidly equilibrating tissues. The terminal phase (green line) is a straight line when plotted on a semilogarithmic graph. The terminal phase is often called the elimination phase because the primary mechanism for decreasing drug concentration during the terminal phase is elimination of drug from the body. The distinguishing characteristic of the terminal elimination phase is that the plasma concentration is lower than tissue concentrations and the relative proportion of drug in plasma and peripheral volumes of distribution remains constant. During this terminal phase, drug returns from the rapid- and slow-distribution volumes to plasma and is permanently removed from plasma by metabolism or excretion.

The presence of three distinct phases after bolus injection is a defining characteristic of a mammillary model

with three compartments.[5] In this model, there are three tanks, corresponding (from left to right) to the slowly equilibrating peripheral compartment, the central compartment (the plasma, into which drug is injected), and the rapidly equilibrating peripheral compartment. The horizontal pipes represent intercompartmental clearance or (for the pipe draining onto the page) metabolic clearance. The volumes of each tank correspond to the volumes of the compartments for fentanyl. The cross-sectional areas of the pipes correlate with fentanyl systemic and intercompartmental clearance. The height of water in each tank corresponds to drug concentration. By using this hydraulic model, we can follow the processes that decrease drug concentration over time after bolus injection. Initially, drug flows from the central compartment to both peripheral compartments via intercompartmental clearance and completely out of the model via metabolic clearance. Because there are three places for drug to go, the concentration in the central compartment decreases very rapidly. At the transition between the blue line and the red line, a change occurs in the role of the most rapidly equilibrating compartment. At this transition, the concentration in the central compartment falls below the concentration in the rapidly equilibrating compartment, and the direction of flow between them is reversed. After this transition (red line), drug in plasma has only two places to go: into the slowly equilibrating compartment or out the drain pipe. These processes are partly offset by the return of drug to plasma from the rapidly equilibrating compartment. The net effect is that once the rapidly equilibrating compartment has come to equilibration, the concentration in the central compartment falls far more slowly than before.

Once the concentration in the central compartment falls below both the rapidly and slowly equilibrating compartments (green line), the only method of decreasing the plasma concentration is metabolic clearance, the drain pipe. Return of drug from both peripheral compartments to the central compartment greatly slows the rate of decrease in plasma drug concentration.

Curves that continuously decrease over time, with a continuously increasing slope (i.e., curves that look like Fig. 24-13), can be described by a sum of negative exponentials. In pharmacokinetics, one way of denoting this sum of exponentials is to say that the plasma concentration over time is

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t} \quad [9]$$

where t is the time since the bolus, C(t) is the drug concentration after a bolus dose, and A, α, B, β, C, and γ are parameters of a pharmacokinetic model. A, B, and C are called coefficients, whereas α, β, and γ are called exponents. After a bolus injection, all six of the parameters in Equation 9 will be greater than 0. The main reason that polyexponential equations are used is that they describe the plasma concentrations observed after bolus injection, except for the misspecification in the first few minutes mentioned previously. Compartmental pharmacokinetic models are strictly empirical. The models have no anatomic correlates. They are solely based on fitting equations to measured plasma concentrations following a known dose. Kinetic models are transformed into models that characterize concentration changes over time in terms of volumes and clearances. Although more intuitive, these models have no physiologic correlates.

Special significance is often ascribed to the smallest exponent. This exponent determines the slope of the final log-linear portion of the curve. When the medical literature refers to the half-life of a drug, unless otherwise stated, the half-life will be the terminal half-life. However, the terminal half-life for drugs with more than one exponential term is nearly uninterpretable. The terminal half-life sets an upper limit on the time required for the concentrations to decrease by 50% after drug administration. Usually, the time needed for a 50% decrease will be much faster than that upper limit.

Part of the continuing popularity of pharmacokinetic compartmental models is that they can be transformed from an unintuitive exponential form to a more intuitive compartmental form, as shown in Figure 24-12. Micro rate constants, expressed as k_{ij}, define the rate of drug transfer from compartment i to compartment j. Compartment 0 is the compartment outside the model, so k_{10} is the micro rate constant for processes acting through metabolism or elimination that irreversibly remove drug from the central compartment (analogous to k for a one-compartment model). The intercompartmental micro rate constants (k_{12}, k_{21}, etc.) describe movement of drug between the central and peripheral compartments. Each peripheral compartment has at least two micro rate constants, one for drug entry and one for drug exit. The micro rate constants for the two- and three-compartment models can be seen in Figure 24-12.

Back-End Kinetics

Using estimates of distribution volume and clearance, back-end kinetics is a useful tool to describe the behavior of intravenous agents when administered as continuous infusions. Back-end kinetics provides descriptors of how plasma drug concentrations decrease once a continuous infusion is terminated. An example is decrement time, which predicts the time required to reach a certain plasma concentration once an infusion is terminated. Decrement times are a function of infusion duration. Consider the example of decrement times for a set of continuous target controlled infusions (Fig. 24-14). In this simulation, target-controlled infusion of propofol is set to maintain a concentration of 4 μg/mL for 30, 60, and 120 minutes. Once the infusion is stopped, the time to reach 0.5 μg/mL is estimated. As illustrated, the longer the infusion, the longer the time required to reach 0.5 μg/mL. This example demonstrates how drugs accumulate in peripheral tissues with prolonged infusions. This accumulation prolongs the decrement time.

Another use of decrement times is as a tool to compare drugs within a drug class (e.g., opioids). As a comparator, plots of decrement times are presented as a function of infusion duration. When used this way, decrement times are determined as the time required to reach a target

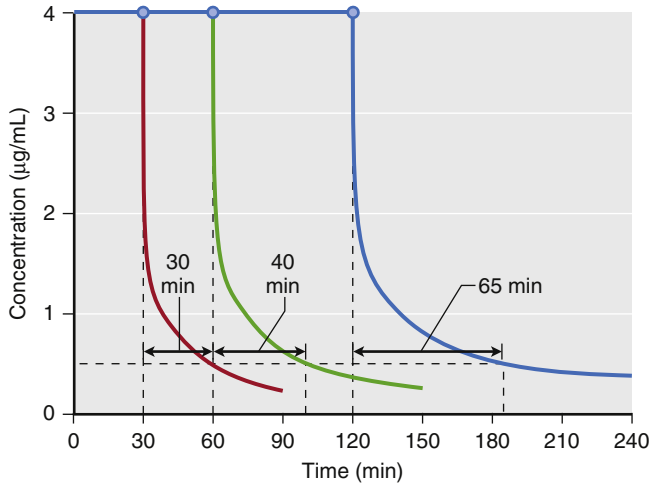


Figure 24-14. Simulation of decrement times for a target-controlled infusion set to maintain a target propofol concentration of 4 µg/mL for 30, 60, and 120 minutes. Once terminated, the time required to reach 0.5 µg/mL was 30, 40, and 65 minutes for each infusion, respectively. Simulations of the decrement times used a published pharmacokinetic model.[1]

percentage of the concentration just before the termination of a continuous infusion. Examples of 50% and 80% decrement times for selected opioids and sedatives are presented in Figure 24-15. Of note, for shorter infusions, the decrement times are similar for both classes of anesthetic drugs. Once infusion duration exceeds two hours, the decrement times vary substantially. A popular decrement time is the 50% decrement time, also known as the context-sensitive half-time.[6] The term *context-sensitive* refers to infusion duration. The term *half-time* refers to the 50% decrement time.

Biophase

Biophase refers to the time delay between changes in plasma concentration and drug effect. Biophase accounts for the time required for drug to diffuse from the plasma to the site of action plus the time required (once drug is at the site of action) to illicit a drug effect. A simulation of various propofol bolus doses and their predicted effect on bispectral index are presented in Figure 24-16. Of note, the time to peak effect for each dose is identical (approximately 1.5 minutes following the peak plasma concentration). The difference between each dose is the

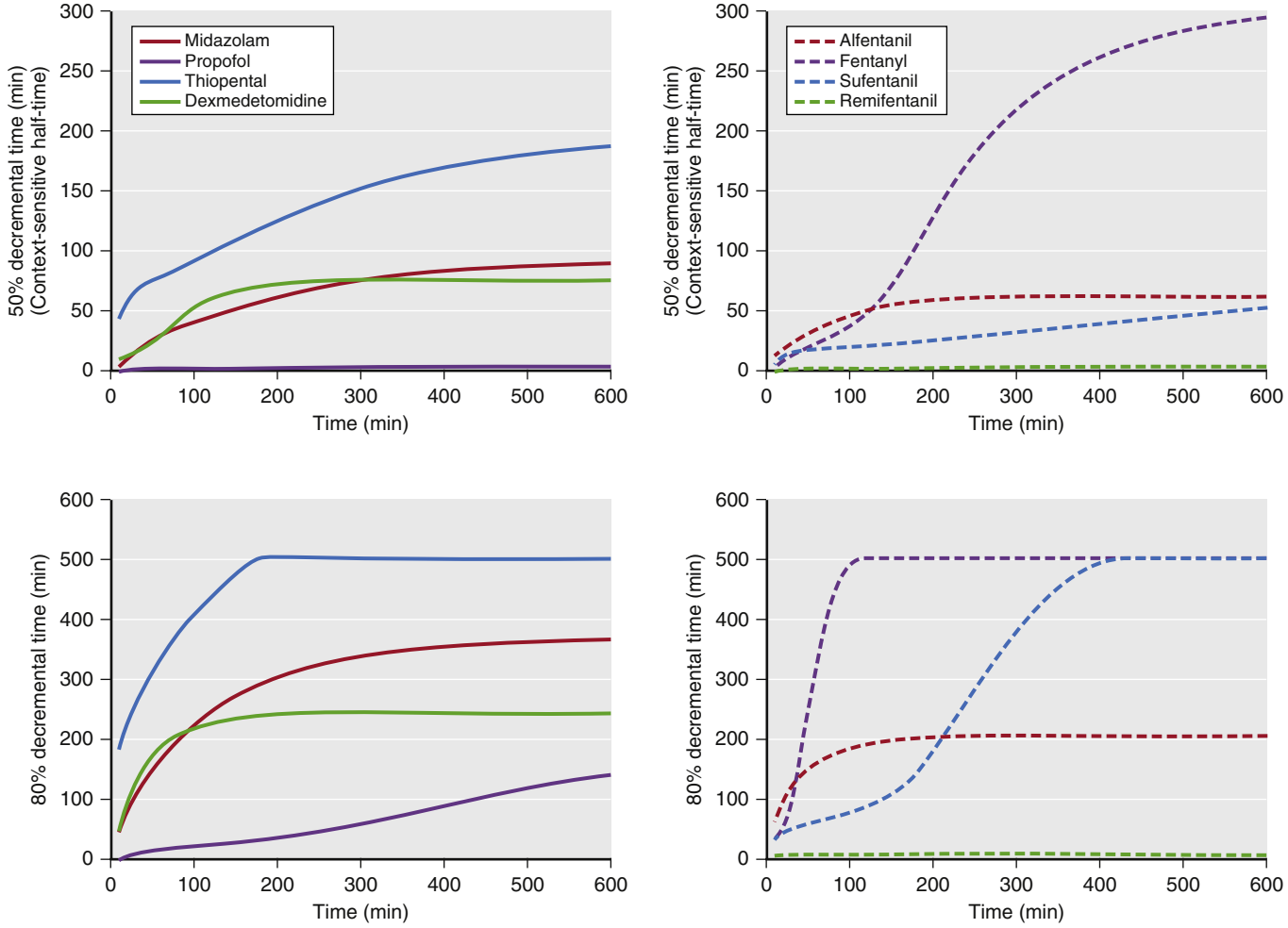


Figure 24-15. 50% and 80% decrement times for selected sedatives (*left side*) and opioids (*right side*). The vertical axis refers to the time required to reach the desired decrement time. The horizontal axes refer to infusion duration. Simulations of the decrement times used published pharmacokinetic models for each sedative and analgesic.[1,6-10]

magnitude and duration of effect. A key principle here is that when drug concentrations are in flux (e.g., during induction and emergence), changes in drug effect will lag behind changes in drug concentration. This lag between the plasma concentration and effect usually result in the phenomenon called hysteresis, in which two different plasma concentrations correspond to one drug effect or one plasma concentrations correspond to two drug effect. Figure 24-16 shows that different concentrations, C and c, correspond to the same bispectral image scale (BIS) score.

To collapse the hysteresis between plasma concentration and effect and to match one plasma concentration to one drug effect, this lag is often modeled with an effect-site compartment added to the central compartment. Kinetic micro rate constants used to describe biophase include k_{1e} and k_{e0}. The k_{1e} describes drug movement from the central compartment to the effect site, and k_{e0} describes the elimination of drug from the effect-site compartment. Two important assumptions must be understood with the effect-site compartment: (1) the amount of drug that moves from the central compartment to the effect-site compartment is negligible and vice versa, and (2) there is no volume estimate to the effect-site compartment.

Typically, the relationship between plasma and the site of drug effect is modeled with an effect-site model, as shown in Figure 24-17. The site of drug effect is connected to plasma by a first-order process. The equation that relates effect-site concentration to plasma concentration is

$$\frac{dCe}{dt} = k_{e0} \times (Cp - Ce) \qquad [10]$$

where Ce is the effect-site concentration, Cp is the plasma drug concentration, and k_{e0} is the rate constant for elimination of drug. The constant k_{e0} describes the rate of rise and off set of drug effect (Fig. 24-18).

In summary, although of interest to many clinicians, the conventional pharmacokinetic term *half-life* has limited meaning to anesthetic practice since the clinical behavior of drugs used in anesthesia is not well described by half-life. Instead, the pharmacokinetic principles discussed in this section (such as volume of distribution, clearance, elimination, front-end kinetics, back-end kinetics, context-sensitive half-time, and biophase) describe how drugs used in anesthesia will behave.

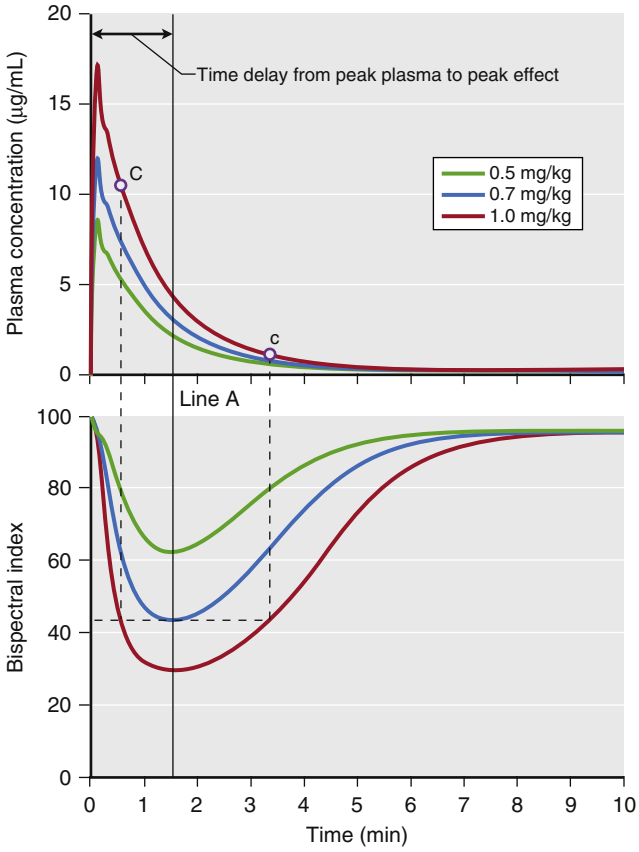


Figure 24-16. Illustration of biophase. The *top plot* presents a simulation of three propofol doses and the resultant plasma concentrations. The *bottom plot* presents a simulation of the predicted effect on the bispectral index scale (BIS). These simulations assume linear kinetics: regardless of the dose, effects peak at the same time (*line A*), as do the plasma concentration. The time to peak effect is 1.5 minutes. Even the plasma concentrations of points C and c are different; the BIS of those two points are same. It shows the hysteresis between plasma concentration and BIS. Simulations used published pharmacokinetic and pharmacodynamic models.[1,11]

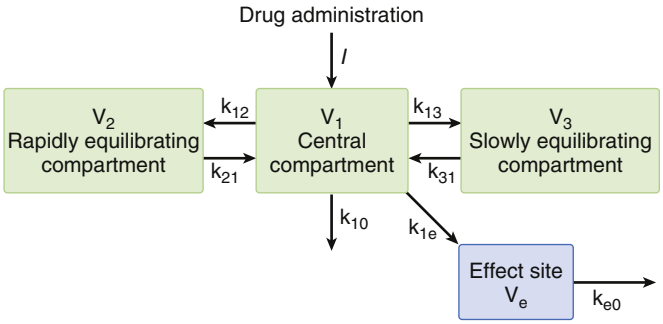


Figure 24-17. A three-compartment model with an added effect site to account for the delay in equilibration between the rise and fall in arterial drug concentrations and the onset and offset of drug effect. The effect site is assumed to have a negligible volume.

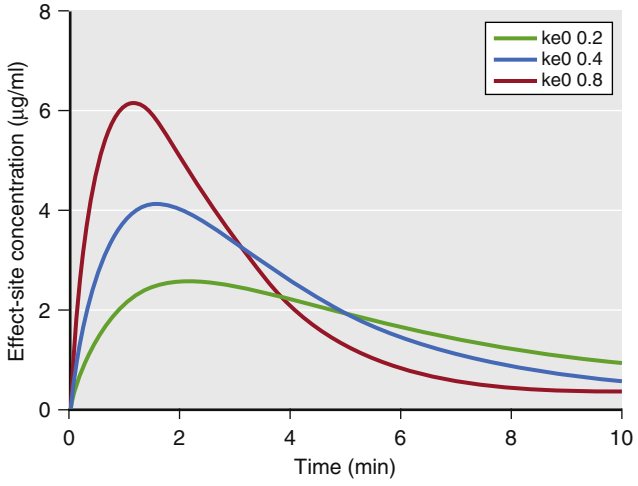


Figure 24-18. Effect of the k_{e0} changes. As the k_{e0} decreases, the time to peak effect is prolonged.[1,11-12]

PHARMACODYNAMIC PRINCIPLES

Simply stated, pharmacokinetics describes what the body does to the drug, whereas pharmacodynamics describes what the drug does to the body. In particular, pharmacodynamics describes the relationship between drug concentration and pharmacologic effect.

Models used to describe the concentration-effect relationships are created in much the same way as pharmacokinetic models; they are based on observations and used to create a mathematical model. To create a pharmacodynamic model, plasma drug levels and a selected drug effect are measured simultaneously. For example, consider the measured plasma concentrations of a drug following a bolus dose and the associated changes in the spectral edge from one individual presented in Figure 24-19. Spectral edge is an easily captured metric used to quantify the electroencephalogram (EEG). Shortly after the plasma concentration peaks, the spectral edge starts to drop, reaches a nadir, and then returns back to baseline as the plasma concentrations drop to near 0.

Combining data from several individuals and plotting the measured concentrations versus the observed effect (modified to be a percentage of the maximal effect across all individuals), the data create a hysteresis loop (Fig. 24-20). The ascending portion of the loop represents rising drug concentrations (see arrow). While rising, the increase in drug effect lags behind the increase in drug concentration. For the descending loop, the decrease in drug effect lags behind the decrease in drug concentration.

To create a pharmacodynamic model, the hysteresis loop is collapsed using modeling techniques that account for the lag time between plasma concentrations and the observed effect.[13] These modeling techniques provide an estimate of the lag time, known as the t1/2ke0, and an estimate of the effect-site concentration (Ce) associated with a 50% probability of drug effect (C_{50}). Most concentration effect relationships in anesthesia are described with a sigmoid curve. The standard equation for this relationship is the "Hill equation" also known as the sigmoid E_{max} relationship:

$$\text{Effect} = E_0 + \left(E_{max} - E_0\right) * \left(C^{\gamma} / \left(C_{50}{}^{\gamma} + C^{\gamma}\right)\right) \qquad [11]$$

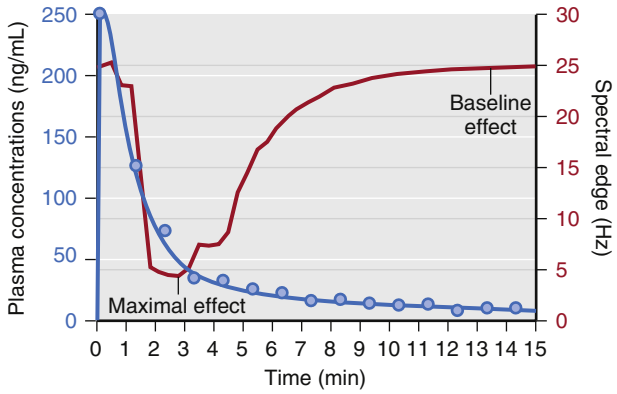


Figure 24-19. Schematic representation of drug plasma concentrations (*blue circles*) following a bolus and the associated changes in the electroencephalogram's spectral edge (*red line*) measured in one individual. Note that changes in spectral edge lag behind changes in plasma concentrations.

where E_0 is the baseline effect, E_{max} is the maximal effect, C is the drug concentration, and γ represents the slope of the concentration-effect relationship. Gamma (γ) is also known as the "Hill coefficient." For values of γ <1, the curve is hyperbolic; for values of γ >1, the curve is sigmoid. Figure 24-21 presents an example of this relationship: a fentanyl effect-site concentration-effect curve for analgesia. This example illustrates how C_{50} and γ characterize the concentration-effect relationship.

Potency and Efficacy

Two important concepts are relevant to this relationship: potency and efficacy. Potency describes the amount of drug required to elicit an effect. The C_{50} is a common

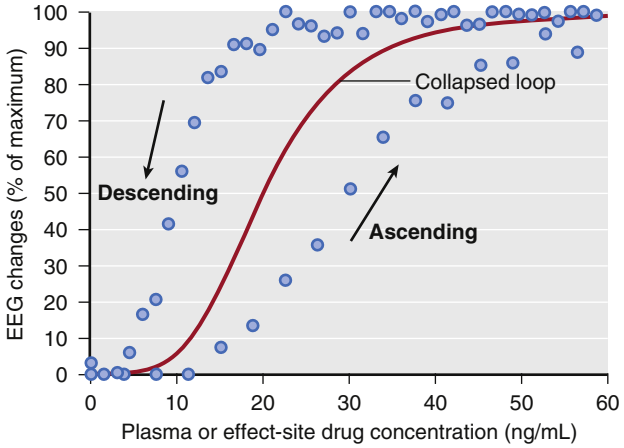


Figure 24-20. Schematic representation of plasma concentrations versus normalized spectral edge measurements (presented as a percentage of maximal effect) from several individuals (*blue circles*). The *black arrows* indicate the ascending and descending arms of a hysteresis loop that coincide with increasing and decreasing drug concentrations. The *red line* represents the pharmacodynamic model developed from collapsing the hysteresis loop.

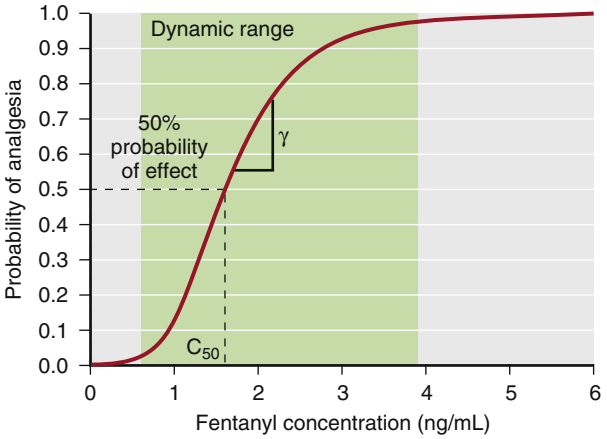


Figure 24-21. A pharmacodynamic model for the analgesic effect of fentanyl. The gray area represents the dynamic range, the concentration range where changes in concentration lead to a change in effect. Concentrations above or below the dynamic range do lead to changes in drug effect. The C_{50} represents the concentration associate with 50% probability of analgesia. Gamma (γ) represents the slop of the curve in the dynamic range.

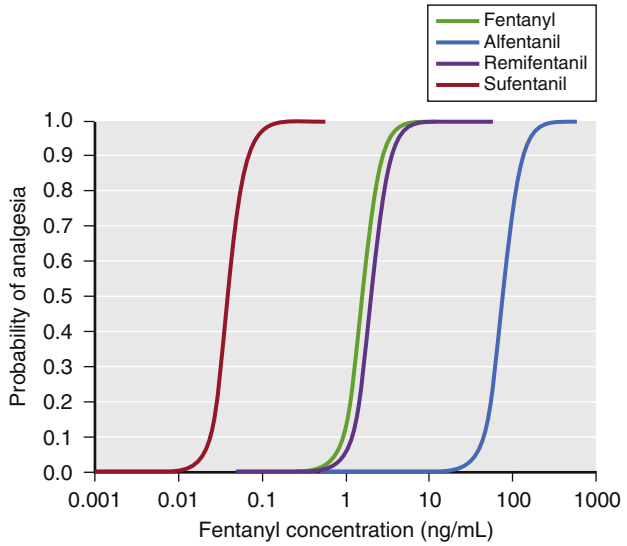


Figure 24-22. Pharmacodynamic models for fentanyl congeners. The C_{50} for each drug is different, but the slope and maximal effect are similar.[14]

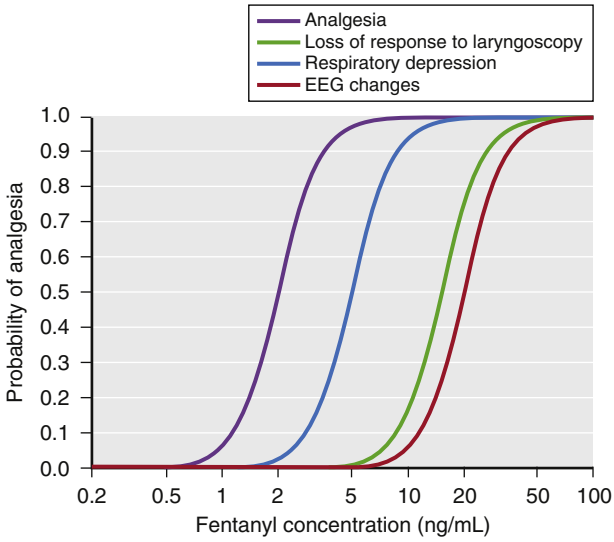


Figure 24-23. Pharmacodynamic models for various fentanyl effects.[14]

parameter used to describe potency. For drugs that have a concentration-versus-effect relationship that is shifted to the left (small C_{50}), the drug is considered to be more potent; the reverse is true for drugs that have a concentration-versus-effect relationship shifted to the right. For example, as illustrated in Figure 24-22, the analgesia C_{50} for some of the fentanyl congeners ranges from small for sufentanil (0.04 ng/mL) to large for alfentanil (75 ng/mL). Thus, sufentanil is more potent that alfentanil.

Efficacy is a measure of drug effectiveness at producing an effect once it occupies a receptor. Similar drugs that work through the same receptor may have varying degrees of effect despite having the same receptor occupancy. For example, with G-protein coupled receptors, some drugs may bind the receptor in such a way as to produce a more pronounced activation of second messengers causing more of an effect than others. Drugs that achieve maximal effect are known as full agonists, and those that have an effect less than maximal are known as partial agonists.

Effective Versus Lethal Doses

A single drug can have multiple effects. The C_{50} concept is used to compare various drug effects for a single drug. For example, as illustrated in Figure 24-23, fentanyl has a different C_{50} for analgesia (2 ng/mL), ventilatory depression (4 ng/mL), loss of response to laryngoscopy (15 ng/mL), and changes in the electroencephalogram (20 ng/mL).[14]

The concentration range where changes in drug effect occur is known at the dynamic range. In Figure 24-21, the dynamic range is from 0.6 to 3.9 ng/mL to cover a probability of analgesia ranging from 2% to 97%. Concentrations outside the dynamic range do not yield much change in drug effect. Levels below the dynamic range are ineffective, and those above the dynamic range do not provide additional effect.

Like other effects, the concentration-relationship for death is also described with a sigmoid E_{max} curve. The relationship between drug and effect is expressed differently in that the horizontal axis uses dose in place of concentration. Similar to the C_{50}, the ED50 is the dose at which there is a 50% probability of effect, and the LD50 is the dose with a 50% probability of death. The therapeutic index of a drug is defined as the ratio between the LD50 and the ED50 (Fig. 24-24). The larger the ratio, the safer the drug is for clinical use.

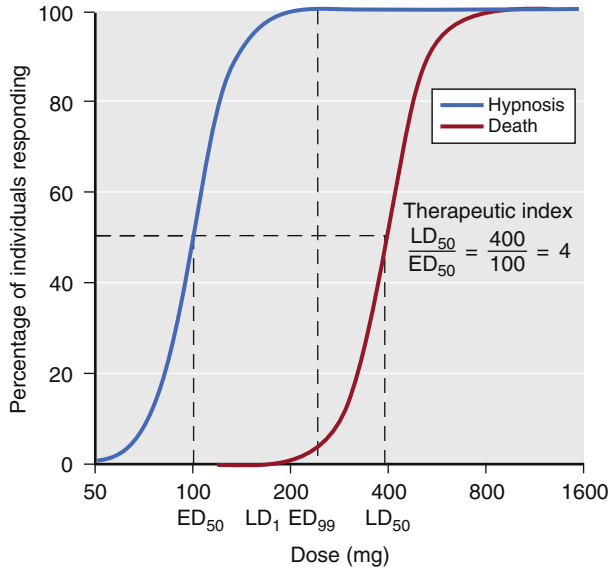


Figure 24-24. Median effective dose (ED_{50}), median lethal dose (LD_{50}), and the therapeutic index. The *blue curve* represents the dose-effect relationship for a sedative hypnotic to achieve unresponsiveness. The *red curve* represents the dose-effect relationship for the same sedative hypnotic to achieve death. The therapeutic index is the ratio of the LD50/ED50, which in this example is 400. Also of interest are the ED_{99} and LD_1. The ED_{99} is the dose with a 99% probability of unresponsiveness, and the LD_1 is the dose with a 1% probability of death. In this example, the LD_1 is less than the ED_{99}, which is clinically unacceptable.

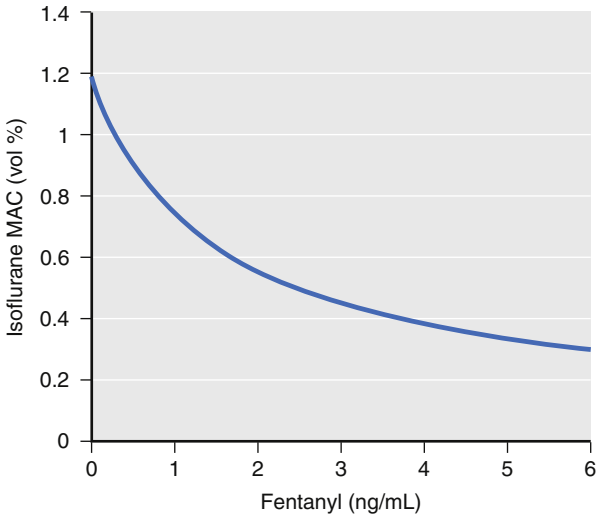


Figure 24-25. The influence of fentanyl on the isoflurane minimum alveolar concentration (*MAC*) associated with a 50% probability of movement with skin incision. *(Modified from McEwan AI, Smith C, Dyar O, et al: Isoflurane minimum alveolar concentration reduction by fentanyl,* Anesthesiology *78:864-869, 1993.)*

Anesthetic Drug Interactions

Anesthetics rarely consist of only one drug, but rather a combination of drugs to achieve desired levels of hypnosis, analgesia, and muscle relaxation. Hypnotics, analgesics, and muscle relaxants all interact with one another such that rarely does one drug, when administered in the presence of other drugs, behave as if it were administered alone. For example, when administering an analgesic in the presence of a hypnotic, analgesia is more profound with the hypnotic than by itself and hypnosis is more profound with the analgesic than by itself. Thus, anesthesia is the practice of applied drug interactions. This phenomenon is likely a function of each class of drug exerting an effect on different receptors.

Early work by McEwan and associates described interactions between two drugs and is illustrated in Figure 24-25.[15] It presents the interaction between isoflurane, a likely GABA agonist, and fentanyl, an opioid receptor agonist. This plot illustrates two key points: First, with a relatively low fentanyl concentration (<2 ng/mL), there is a substantial decrease (>50%) in the end tidal isoflurane concentration necessary to achieve minimum alveolar concentration (MAC) necessary to avoid movement with skin incision. Second, with fentanyl concentrations above 3 ng/mL, the end tidal concentration of isoflurane to maintain the MAC, although low, does not change much. Thus, a ceiling effect exists, indicating that some isoflurane is necessary regardless of the fentanyl concentration to maintain a MAC of anesthesia.

Work has been done to explore how anesthetic drugs interact with one another. As illustrated in Figure 24-26, interactions have been characterized as antagonistic, additive, and synergistic. When drugs that have an additive interaction are coadministered, their overall effect is the sum of the two individual effects. With antagonistic interactions, the overall effect is less than if the drug combination were additive; with synergistic interactions, the overall effect is greater than if the drug combination were additive.

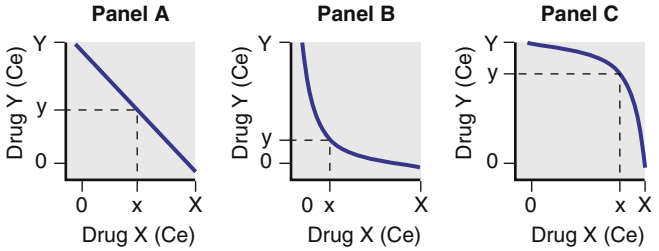


Figure 24-26. Drug interactions. For two drugs, X and Y, *Panel A* represents additive, *Panel B* represents synergistic, and *Panel C* represents antagonistic interactions.

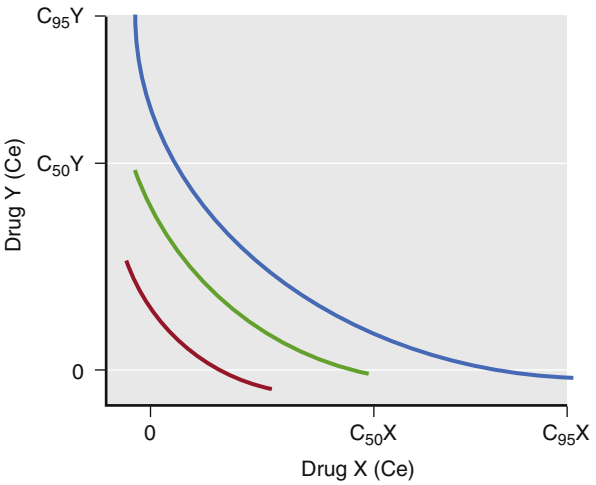


Figure 24-27. Schematic illustration of isoeffect (isobole) lines. The *red, green,* and *blue lines* represent the 50% and 95% isoboles for a synergistic interaction between drugs X and Y. Isoboles represent concentration pairs with an equivalent effect. A set of 5%, 50%, and 95% isoboles can be used to describe the dynamic range of the concentrations for drugs X and Y for a given effect. As with single concentration effect curves, the ideal dosing leads to concentration pairs that are near the 95% isobole.

A term used to characterize the continuum of drug concentrations across various combinations of drug pairs (X in combination with Y) is the *isobole*. The isobole is an isoeffect line for a selected probability of effect. A common isobole is the 50% isobole line. It represents all possible combinations of two-drug effect-site concentrations that would lead to a 50% probability of a given effect. Other isoboles are of more clinical interest. For example, the 95% isobole for loss of responsiveness represents the concentration pairs necessary to ensure a 95% probability of unresponsiveness. Similarly, the 5% isobole represents the concentration pairs in which the likelihood of that effect is low (i.e., most patients would be responsive). When formulating an anesthetic dosing regimen, dosing an anesthetic to achieve a probability of effect just above, but not far beyond, the 95% isobole is ideal (Fig. 24-27).

Work in both humans and animal models have described anesthetic drug interactions for opioids, sedative hypnotics, and inhalation agents for two anesthetic effects: (1) loss of responsiveness (humans) and loss of the righting reflex (animals) and (2) immobility defied as loss of movement response to noxious stimulus in a nonparalyzed subject.[16] First, based on these findings, inhalation

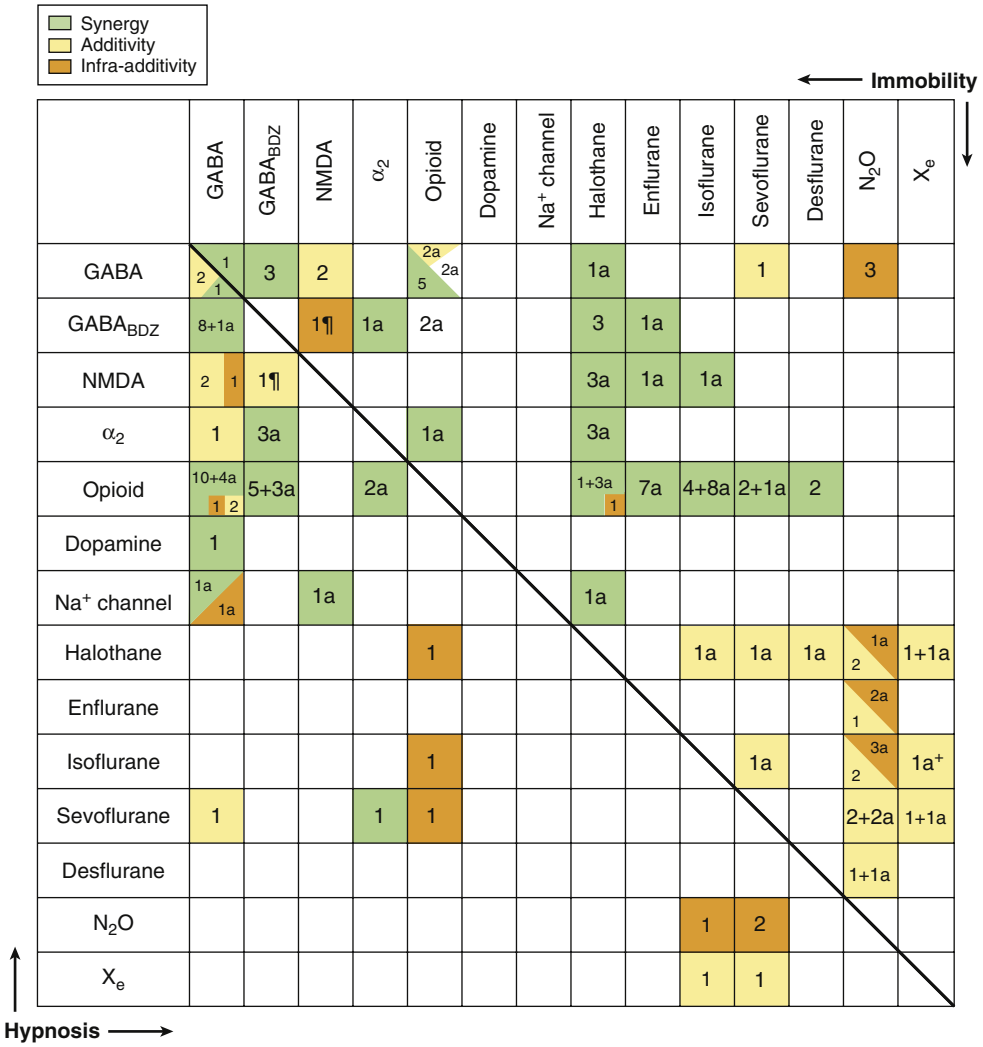
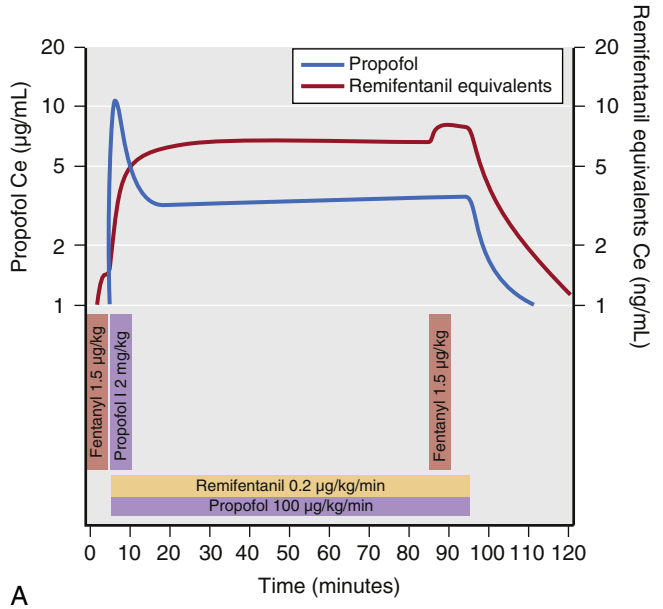


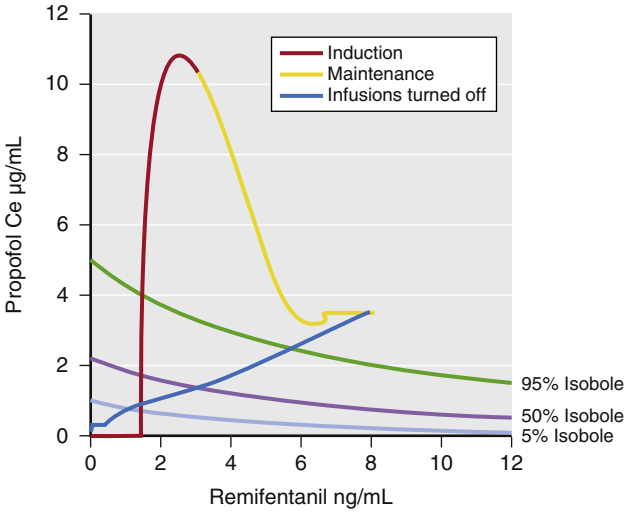
Figure 24-28. Summary of drug interactions in humans and animals for hypnosis (loss of responsiveness in humans, loss of righting reflex in animals) and immobility (loss of movement in response to a noxious stimulus). The numbers in each cell refer to the number of papers supporting the finding. α_2 Agonists include dexmedetomidine and clonidine. Opioid agonists include morphine, remifentanil, fentanyl, sufentanil, and alfentanil. Dopamine agonists include droperidol and metoclopramide. Na$^+$ (sodium) channel antagonists include lidocaine and bupivacaine. The letter *a* indicates the interaction was characterized in an animal model. The *thick diagonal line* separates studies characterizing drug-drug interactions of hypnosis (bottom half) and immobility (top half). *GABA,* Gamma aminobutyric acid (GABA agonist drugs include propofol, thiopental, methohexital, and etomidate; GABA$_{BDZ}$, agonist drugs that work via benzodiazepine binding site include midazolam and diazepam); *NMDA, N*-methyl-D-aspartate (NMDA receptor antagonists include ketamine). *(From Hendrickx JFA, Eger EI, Sonner JM, et al: Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility,* Anesth Analg *107:494-506, 2008.)*

agents, when combined, are strictly additive, suggesting a common mechanism of action—except for nitrous oxide, which has an infra-additive interaction with other inhalation agents. Second, interactions between various intravenous drugs and inhalation agents are synergistic, except for nitrous oxide and GABA sedative hypnotics. Third, interactions between different classes of intravenous agents (e.g., opioids and sedative hypnotics) are also primarily synergistic, except for ketamine and benzodiazepines (Fig. 24-28).

Several researchers have developed mathematical models that characterize anesthetic drug interactions in three dimensions. These models are known as response surface models and include effect-site concentrations for each drug, as well as a probability estimate of the overall effect. As an example, Figure 24-29 presents the propofol-remifentanil interaction for loss of responsiveness as published by Bouillon and associates.[17] The response surface presents the full range of remifentanil-propofol isoboles (0% to 100%) for loss of responsiveness. There are two common representations of the response surface model: the three-dimensional plot and the topographical plot. The topographic plot represents a top-down view of the response surface with drug concentrations on the vertical and horizontal axes. Drug effect is represented with selected isobole lines (i.e., 5%, 50%, and 95%).

Response surface models have been developed for a variety of anesthetic effects to include responses to verbal and tactile stimuli, painful stimuli, hemodynamic or respiratory effects, and changes in electrical brain activity. For example, with airway instrumentation, response surface models have been developed for loss of response





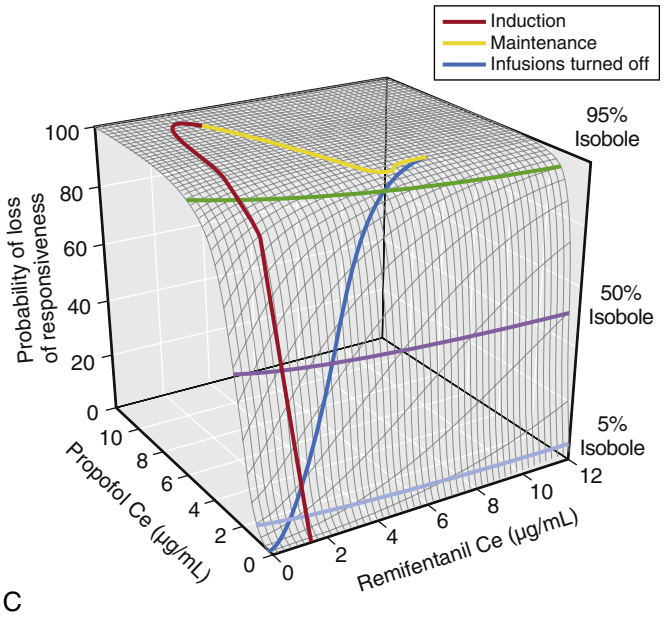


Figure 24-29. Simulation of a 90-minute total intravenous anesthetic consisting of propofol bolus (2 mg/kg) and infusion (100 µg/kg/minute), remifentanil (0.2 µg/kg/minute) and intermittent fentanyl boluses (1.5 µg/kg). **A,** Resultant effect-site concentrations (*Ce*) are presented. **B,** Predictions of loss of responsiveness are presented on a topographical (top-down) view. **C,** A three-dimensional response surface plot is shown. The *light blue, purple,* and *green lines* represent the 5%, 50%, and 95% isoboles. Each isobole presents the propofol-remifentanil pairs that yield the same effect. The inward bow of the isoboles indicates that the interaction is synergistic. The isoboles are in close proximity to one another, indicating a steep transition from responsive to unresponsive.

to placing a laryngeal mask airway,[18] laryngoscopy,[19,20] tracheal intubation,[21] and esophageal instrumentation[22] in selected combinations of anesthetic drugs. Although many response surface models exist, several gaps exist in available models, covering all common combinations of anesthetic drugs and various forms of stimuli encountered in the perioperative environment.

The interaction between sevoflurane and remifentanil has been characterized for a variety of drug effects, including loss of responsiveness, loss of response to several surrogates of surgical pain such as electrical tetany (up to 50 mA), pressure algometry (50 PSI pressure on the anterior tibial), loss of response to laryngoscopy, and temperature.[20] End tidal measurement of sevoflurane were inaccurate under non–steady-state conditions (i.e., with a change in vaporizer settings) End tidal concentrations did not account for the hysteresis (or time lag) between end tidal and effect-site concentrations. Improved model predictions were achieved when using estimated effect-site concentrations Overall, for sevoflurane-opioid interactions, analgesic effects are markedly synergistic, whereas sedative effects are somewhat synergistic.

Preliminary work has explored the adaptability of the sevoflurane-remifentanil interactions to other potent inhaled agent opioid combinations using MAC and opioid equivalencies.[23] Predictions from sevoflurane-remifentanil models adapted to isoflurane-fentanyl correlated well with observed effects in patients undergoing elective general surgery procedures. Also, models have been constructed that characterize the interactions between three or more drugs,[24] such as a model that accounts for nitrous oxide, sevoflurane, and remifentanil.[25] This is of clinical relevance because most anesthetics consist of more than two anesthetic drugs. In line with this, works has explored interactions between sedative hypnotics and opioids, primarily propofol with alfentanil[26] or remifentanil[17,19,22,27,28] for a variety of effects. As with potent inhaled anesthetics and opioids, the interactions between sedative hypnotics and opioids for analgesic effects are markedly synergistic, whereas sedative hypnotic effects are somewhat synergistic.

Interaction studies of different types of sedative hypnotics such as midazolam combined with propofol[29,30] and propofol combined with a volatile anesthetic[31-33] reveal that the interactions are primarily additive.

Drug Displays

The major disadvantage of response surface models is that they are complex and difficult to use in a clinical setting. These models have been adapted to drug displays that allow clinicians to use them in real-time patient care settings.

These displays provide estimates of not only drug concentrations (both plasma and effect site) but also various drug effects over time, such as loss of responsiveness, analgesia, and reduction in response to peripheral "train of four" stimulation (i.e., monitoring of muscle relaxant action), among others. With manual entry of patient demographics (age, gender, height, and weight) and drugs administered by syringe, either by bolus or continuous infusion along automated data collection from an anesthesia machine (end tidal potent inhaled anesthetic concentrations and, in some instances, infusion pump information), drug displays provide predictions of drug concentration and effects. Drug displays are currently available from several anesthesia machine manufactures (Navigator Suite from GE Healthcare, Wauwatosa, Wis, and SmartPilot View from Dräger, Lübeck, Germany). An example of a drug display is presented in Figure 24-30. All drug display examples are based on response surface interaction models.

A unique feature of the displays is that a given dosing regimen can be simulated before administration, which may be useful in identifying the optimal dose in challenging patients, especially when more than one drug is used. The drug displays use population models that, although generalizable, may not provide a good "fit" for every patient. For some drug display systems, observed patient responses are used to calibrate predictions of drug effect (see Fig. 24-30). For example, with older adults or debilitated patients, smaller doses are often required to achieve a desired effect (also see Chapter 80). Drug displays allow clinicians to identify concentrations that produce a desired response and can be used to titrate additional anesthetic.

Use of drug displays provides several other advantages. When titrating an anesthetic, it is often difficult to appreciate when effect-site concentrations are near steady state. Clinicians may be tempted to administer additional drug, assuming that drug concentrations have peaked (with bolus dosing) or are near steady-state conditions (with continuous infusions of potent inhaled agents). Clinicians may also be impatient, assuming that drug concentrations are near zero when in fact they are still increased, even after terminating delivery (e.g., the end tidal potent inhaled agent concentration is 0 mm Hg but there is persistent unresponsiveness).

A second advantage is that drug displays provide a means of delivering passive target-controlled infusions (TCI). Although widely used throughout the rest of the world, TCI is not used in the United States because of regulatory barriers.[34] TCI uses population pharmacokinetic models to drive infusion pumps. After entering the target plasma or effect-site concentration, a computer identifies the optimal infusion rate to achieve that concentration. With passive TCI, population models are used to display predicted effect-site concentrations and associated effects over time, but the models do not deliver information to drive infusion pumps as with TCI. With this approach, clinicians can test out dosing regimens (bolus doses and infusion rates) before administering them, thus allowing confirmation that they will achieve a desired effect. These features provide for a more consistent approach to drug delivery.

A third advantage of using drug displays is that they provide a better approach to dosing anesthetics. Instead of considering an anesthetic in terms of MAC, where 50% of patients may respond to surgical stimulus, drug displays provide a more refined characterization of anesthetic effect. Clinicians do not titrate an anesthetic to achieve a 50% probability of effect but rather aim for a 95% to 99% probability of effect. With response surfaces, anesthetic dosing regimens necessary to achieve this level of effect are easily visualized. Second, the concept of MAC does not fully embody the three elements of an anesthetic: analgesia, sedation and hypnosis, and muscle relaxation. Drug displays provide a means of visualizing all three effects simultaneously over a full 0% to 100% probability range.

SPECIAL POPULATIONS

When formulating an anesthetic, many aspects of patient demographics and medical history need to be considered to find the correct dose: age; body habitus; gender; chronic exposure to opioids, benzodiazepines, or alcohol; the presence of heart, lung, kidney, or liver disease; and the extent of blood loss or dehydration. Any of these factors can dramatically affect anesthetic drug kinetics and dynamics. Unfortunately, most studies characterizing anesthetic drug behavior have been conducted in healthy volunteers that rarely represent the general population presenting for surgery. Extensive work has explored how some patient characteristics (e.g., obesity) influence anesthetic drug behavior, whereas other patient characteristics remain difficult to assess (chronic opioid exposure). In addition, not all anesthetics have been studied. Most work has primarily focused on newer anesthetic drugs, such as propofol and remifentanil, whereas minimal work

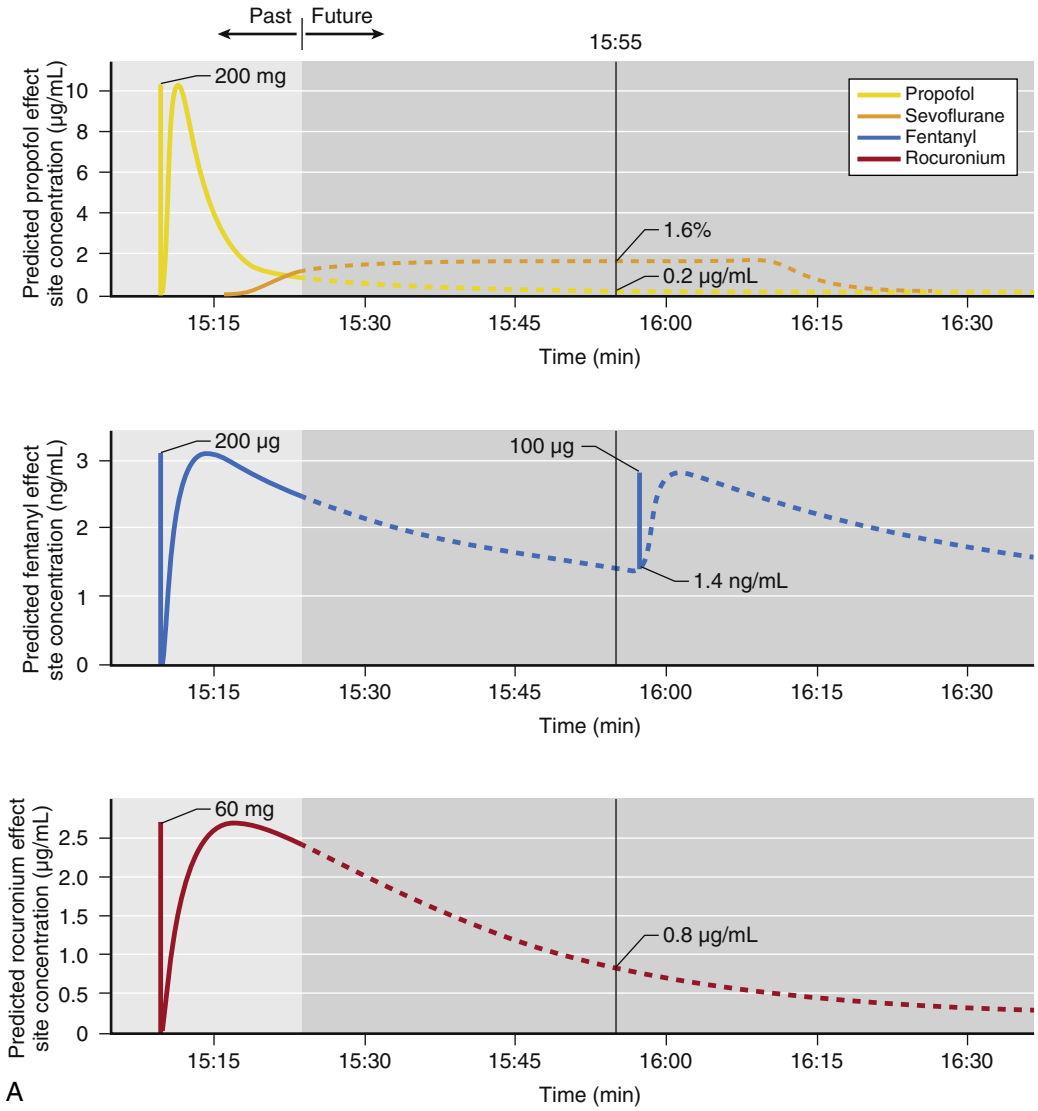


Figure 24-30. Example of a drug display. This example presents predictions of effect site concentrations (**A**) and drug effects (**B**) for a combined technique using fentanyl (2 µg/kg), propofol (2 mg/kg), and rocuronium (0.6 mg/kg) boluses and maintenance with sevoflurane (2%) and fentanyl bolus (1 µg/kg). This simulation assumes a 30-year-old, 100-kg male, 183 cm tall, with normal cardiac output and lung ventilation. **A,** Predicted effect site concentrations for propofol *(bright yellow line),* sevoflurane *(dark yellow line),* fentanyl *(blue line),* and rocuronium *(red line).* Bolus doses are represented as *vertical lines,* with the dose labeled adjacent to the line. Past predictions are *solid lines* and future predictions are dashed lines. The *vertical black line* represents a future prediction of effect-site concentrations at 15:55 PM. Concentrations are reported. (From Applied Medical Visualizations, Salt Lake City, Utah.)

has focused on many older, commonly used drugs, such as morphine. This section will briefly summarize work that has been done to characterize the pharmacokinetics and pharmacodynamics in a few unique special populations.

INFLUENCE OF OBESITY ON ANESTHETIC DRUGS

Obesity is a worldwide epidemic, and overweight patients frequently undergo anesthesia and surgery (also see Chapter 71). Furthermore, pharmacologic alterations of anesthetics occur in obese individuals. In general, manufacturer dosing recommendations are on a per-kg basis according to the actual total body weight (TBW). Anesthesia providers rarely use mg/kg dosing in obese patients for fear or administering an excessive dose (e.g., a 136-kg patient does not require twice as much drug as a patient of the same height who weighs 68 kg). To resolve this problem, several weight scalars have been developed in attempt to avoid excessive dosing or underdosing in this patient population. Some of these include lean body mass (LBM), ideal body weight (IBW), and fat-free mass (FFM). Table 24-1 presents the formulas used to estimate these weight scalars. Table 24-2 shows samples of the resultant scaled weight for a lean and obese individual. In general, the aim of weight scalars is to match dosing regimens for obese patients with what is required for normal-size patients. These scaled weights are usually smaller than TBW in obese patients and thus help prevent excessive drug dosing (Fig. 24-31). Scaled weights have been used in place of TBW for both bolus (mg/kg) and infusion (mg/kg/hr) dosing and also for TCI.

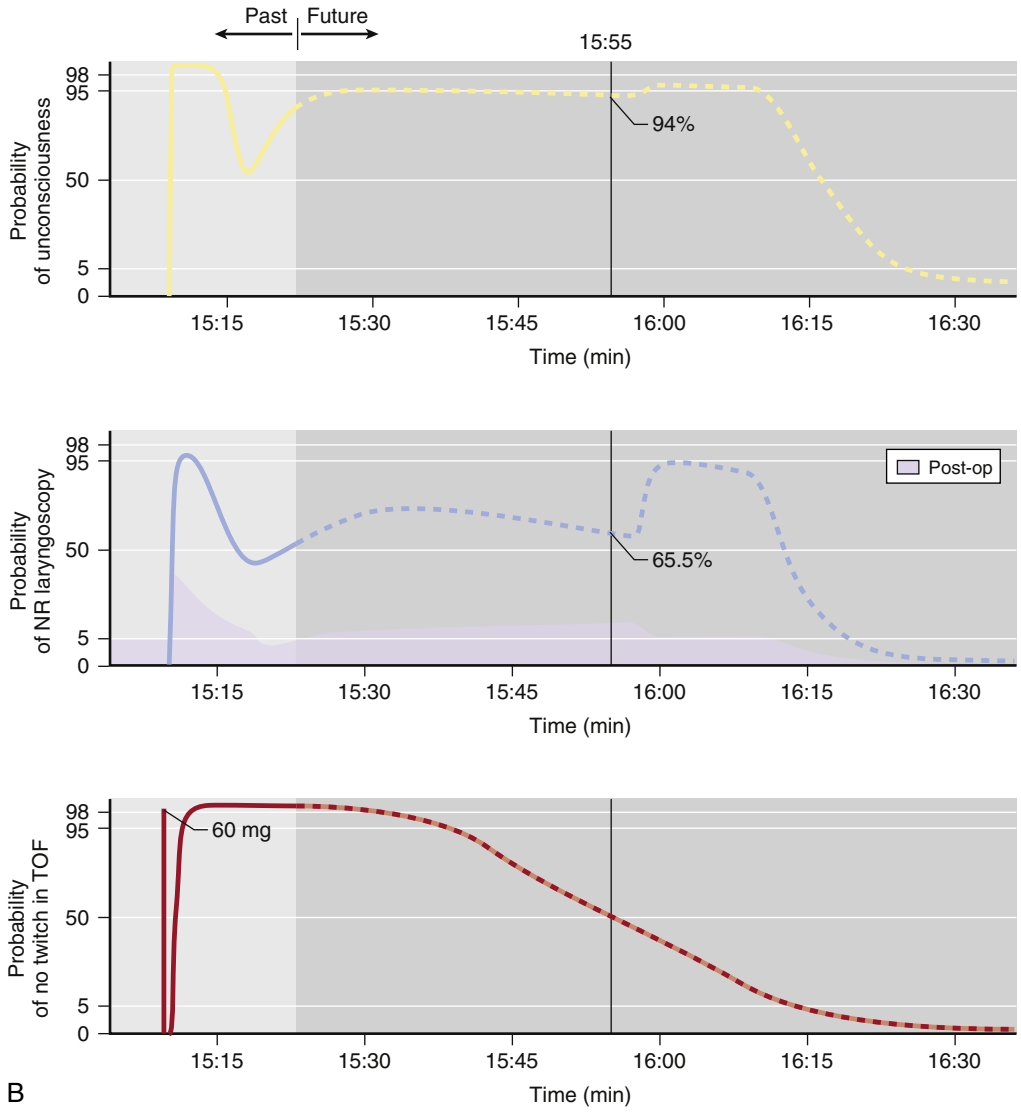


Figure 24-30, cont'd. B, Predicted drug effects. Probability of unresponsiveness *(yellow line),* probability of no response to laryngoscopy *(blue line),* and probability of loss of train of four *(red line)* from this combined technique. The *white horizontal lines* represent the 5%, 50%, 95%, and 98% probability of effect. The *vertical black line* represents a future prediction of drug effects at 15:55 PM. *NR laryngoscopy,* No response to laryngoscopy; *TOF,* train-of-four.

This section will discuss the pharmacologic (primarily pharmacokinetic) alterations of select intravenous anesthetic drugs (propofol, remifentanil, and fentanyl) in obese patients, review examples of weight scalars and their shortcomings when used in bolus and continuous infusion dosing, and when data are available, briefly describe pharmacologic models used to drive TCI.

Propofol

Dosing propofol in obese patients can be a challenge (also see Chapter 71). For bolus dosing and continuous infusions, the choice of weight scalar is specific to the dosing technique being used (i.e., one is best for bolus dosing and another for continuous infusions). Furthermore, of the available propofol pharmacokinetic models, the one built from observations in obese patients may be best for TCI.

The influence of obesity on propofol pharmacokinetics is not entirely clear. Generally, in obese patients, the blood distributes more to nonadipose than to adipose tissues. This may result in higher plasma drug concentrations in obese patients with mg/kg dosing than in normal patients with less adipose mass. Furthermore, propofol clearance increases because of the increased liver volume and/or liver blood flow associated with obesity (and increased cardiac output). Distribution likely influences concentration peaks with bolus dosing, and clearance likely influences concentrations during and following infusions

Dosing Scalars for Propofol. Simulations of an infusion using various weight scalars are presented in Figure 24-32. The simulations predict propofol effect-site concentrations from a 60-minute infusion (167 μg/kg/minute) in 176-cm (6-ft) males, obese (185 kg) and lean (68 kg).

TABLE 24-1 COMMON WEIGHT SCALARS

Name	Equations
Ideal body weight	Male: 50 kg + 2.3 kg for each 2.54 cm (1 in) over 152 cm (5 ft) Female: 45.5 kg + 2.3 kg for each 2.54 cm (1 in) over 152 cm (5 ft)
Lean body mass	Male: $1.1 \times TBW - 128 \times (TBW \div Ht)^2$ Female: $1.07 \times TBW - 148 \times (TBW \div Ht)^2$
Fat free mass[35]	Male: $(9.27 \times 10^3 \times TBW) \div (6.68 \times 10^3 + 216 \times BMI)$ Female: $(9.27 \times 10^3 \times TBW) \div (8.78 \times 10^3 + 244 \times BMI)$
Pharmacokinetic mass[36,37]	$52 \div [1 + (196.4 \times e^{-0.025\ TBW} - 53.66) \div 100]$ (fentanyl only)
Corrected body weight[38,39]	IBW + 0.4* (IBW – FFM)

BMI, Body mass index; *FFM,* fat-free mass; *Ht,* height in centimeters; *IBW,* ideal body weight; *LBM,* lean body mass; *MFFM,* modified fat-free mass; *TBW,* total body weight in kg.
*The dose/kg using IBW, TBW, or FFM in an obese person are all less than the dose/kg using TBW in a nonobese patient.

TABLE 24-2 DOSING WEIGHTS BASED ON VARIOUS DOSING SCALARS

	176-cm (6-ft) Male	
	68 kg (BMI = 22)	185 kg (BMI = 66)
Dosing Scalar	Dosing Weight (kg)	Dosing Weight (kg)
Total body weight (TBW)	68	185
Ideal body weight (IBW)	71	71
Lean body mass (LBM)	55	62
Fat-free mass (FFM)	55	87
Corrrected body weight (CBW)	68	115

BMI, Body mass index (kg/m^2).

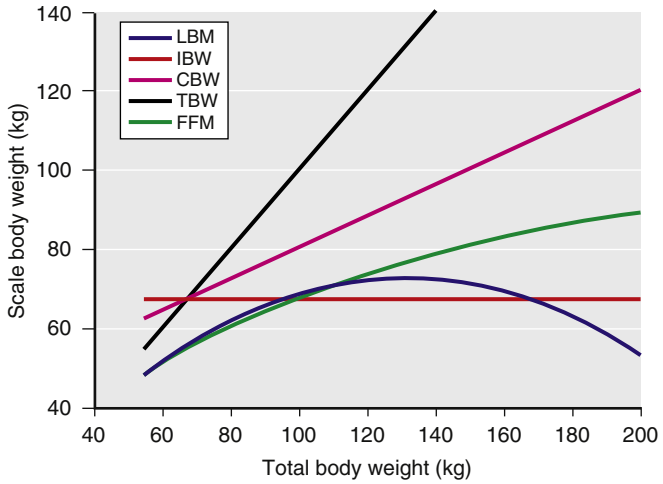


Figure 24-31. Scaled weights as a function of total body weight (TBW). Key points in this plot: IBW remains the same regardless of the TBW, and LBM starts to decline for weight increases above 127 kg. *CBW,* Corrected body weight; *FFM,* fat-free mass; *IBW,* ideal body weight; *LBM,* lean body mass (for a 40-year-old male, 176 cm tall).

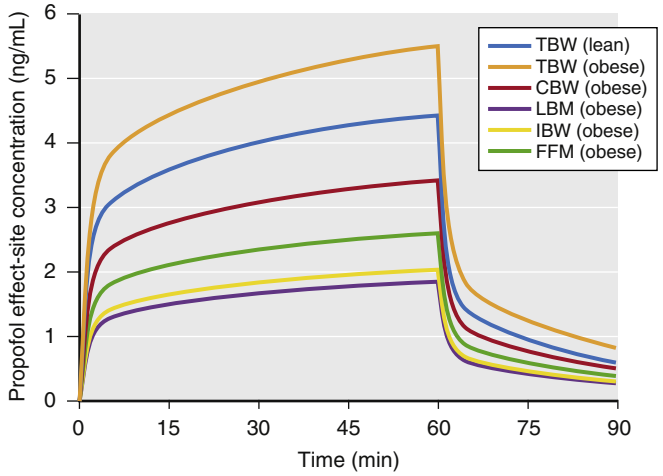


Figure 24-32. Simulations of propofol effect site concentrations that result from a 60-minute infusion (10 mg/kg/hour—167 μg/kg/minute) to a 40-year-old male who is 176 cm tall. Simulations include the following dosing weights: total body weights (TBW) of 68 kg and 185 kg (body mass indices of 22 and 60, respectively) and scaled weights for the 185 kg weight to include Servin's corrected body weight (CBW), lean body mass (LBM), ideal body weight (IBW), and fat-free mass (FFM). Key points: At the 185-kg weight, when dosed to TBW, the infusion leads to high propofol concentrations, whereas when dosed to IBW or LBM, the infusion leads to low propofol concentrations. When the 185-kg individual is dosed using CBW, it best approximates the propofol concentrations that result from TBW in a lean individual. Predictions of propofol effect site concentrations were made using the Cortinez model.

If dosed according to TBW, peak plasma concentrations in a lean and obese individual are different; their respective peak propofol concentrations are approximately 4.4 and 5.4 μg/mL, respectively. If the obese individual is dosed to CBW, the peak concentration is near 3.4 μg/mL. The other weight scalars lead to much lower concentrations with the infusion.

Of the many available dosing scalars, authors recommend LBM for bolus dosing (i.e., during induction) and TBW or corrected body weight (CBW) for infusions.[38,39] For continuous infusions, other weight scalars are likely inadequate (the most worrisome is LBM). When dosing to CBW, plasma concentrations may be lower than concentrations when dosed to TBW.

One concern with using TBW to dose continuous infusions is drug accumulation. Prior work, however, does not support this assumption. Servin and colleagues[38] performed pharmacokinetic analyses of propofol administration to normal and obese patients using TBW and CBW. The CBW was defined as IBW + 0.4 × (TBW – IBW).[40] They found similar concentrations at eye opening in both groups and absence of propofol accumulation in obese patients; in fact, obese patients showed earlier awareness after the termination of propofol infusions than did the normal subjects. Data suggest that dosing infusions according to Servin's CBW may markedly underdose obese patients.[41]

Propofol Kinetic Models for Target-Controlled Infusions. Of the many available models available, the two most widely used propofol kinetic models for TCI are those published by Marsh and associates[42] and Schnider and colleagues[1] In addition to model selection, as with bolus and continuous infusion dosing, identifying the ideal weight scalar to use is important.

The Marsh model, although useful in general, was built from data collected in a pediatric population. Researchers have explored different dosing weights using this model in morbidly obese patients when coadministered with remifentanil with varied results. Albertin and colleagues[40] used CBW to dose a propofol TCI using the Marsh model. They found predicted substantially overestimated measured propofol concentrations and expressed concern for intraoperative awareness when using CBW with the Marsh TCI model. The same group[43] compared the predictive performance of the TCI using CBW versus TBW and found that CBW performed worse than TBW. They concluded that TBW, not CBW, should be used to administer propofol via TCI to morbidly obese patients and then carefully titrate to targeted processed electroencephalographic values.

The Schnider model, although built from data collected in adults over a range of weights, heights, and age, does not specifically include obese patients. This model uses the weight scalar LBM, which has limited application in morbidly obese patients.[1] For comparison, the Marsh or the Schnider model has been applied on morbidly obese patients. Echevarria and colleagues[44] reported differences in effect-site propofol concentrations with a BIS of <60 between the two pharmacokinetic models when used for induction in morbidly obese patients. To achieve a 95% probability of effect, target concentrations of 4.2 and 5.5 μg/mL were required for the Marsh and Schnider models, respectively. This difference occurred because of the potential prediction errors in each pharmacokinetic model used (the actual drug concentrations in each patient are unknown).

Cortinez and colleagues used an international data repository called Open TCI (www.opentci.org) to build a model using propofol concentrations from a wide range of body weights.[39] They built a propofol kinetic model that scales normal-size to obese individuals using an empirically derived formula. In this formula, TBW accounts for differences in distribution and clearances in obese patients. TBW is divided by a standard patient size (70 kg) and raised to the power of 1 for distribution volumes and by the power of 0.75 for clearances. Van Kralingen and colleagues[45] further modified this approach and reported better model performance with exponents of 0.72 for clearance.

Figure 24-33 presents a simulation of propofol infusion rates and associated plasma concentrations using the Marsh, Schnider, and Cortinez models to drive a TCI to achieve a concentration of 3 μg/mL. Key points from this simulation include the following: TCI infusions based on the Marsh model are linear to TBW such that the infusion rates and plasma concentrations are identical across weights. With an increase in body weights, the degree of increase in total propofol amounts for TCI administrations is smaller with the Cortinez model than with the Marsh and Schnider models.

For propofol, the Cortinez model may be best suited for TCI in obese and morbidly obese patients. Unfortunately, this model is not yet available in many commercial TCI pumps. One caveat that is important to consider is that model differences are likely overshadowed by interindividual variability. In sum, any one of the three models will likely yield similar clinical results if titrated to effect in conjunction with processed EEG monitoring. Prospective external validation is warranted to explore how these new models will behave when used in TCIs.

Other Sedative-Hypnotics

Only limited information is available on the behavior of other sedatives (i.e. midazolam, ketamine, etomidate, and barbiturates) in obese patients.[46] In this study by Greenblatt and associates, the volume of distribution, even when normalized to weight (e.g., L/kg) was larger in obese patients, suggesting that lean tissue may take up less midazolam than adipose tissue. Thus, midazolam's distribution volume follows the TBW: as patient size increases, so does the distribution volume. In addition, midazolam elimination was the same in all study subjects (lean or obese). This suggests that regardless of dose, hepatic metabolism of midazolam is fixed and elimination will require more time in obese patients. Another interesting finding was that time to peak concentration and peak plasma drug concentrations were the same when administered in a weight-normalized fashion regardless of body habitus (also see Chapter 30).

Although not clinically validated in obese patients, bolus doses probably should be scaled to TBW and other dosing scalars may lead to inadequate effect. On the other hand, with a fixed elimination, continuous infusion rates should dosed to IBW.[46]

Opioids

With the exception of remifentanil, minimal work has explored the implication of obesity on the kinetic and dynamic behavior of opioids.

Remifentanil. In obese patients, largely because of its rapid metabolism by nonspecific esterases, the distribution volume and clearance of remifentanil are similar in lean and obese patients.[47] As with propofol, researchers have explored several scaled weights in an effort to optimize bolus dosing, continuous infusions, and TCIs.

Dosing Scalars. As above with propofol, simulation is used to present the predicted remifentanil effect-site concentrations and analgesic effect for a variety of scaled weights in individuals 176 cm in height, some obese (185 kg, BMI of 60) and some lean (68 kg, BMI of 22) (Fig. 24-34). Several key points are illustrated in these simulations:

1. For an obese patient, dosing scaled to FFM or IBW resulted in almost identical remifentanil effect-site concentrations as in the lean patient dosed according to TBW. Unlike propofol, dosing remifentanil to CBW (red line) leads to higher plasma concentrations compared with levels achieved when doing to TBW in a lean individual.

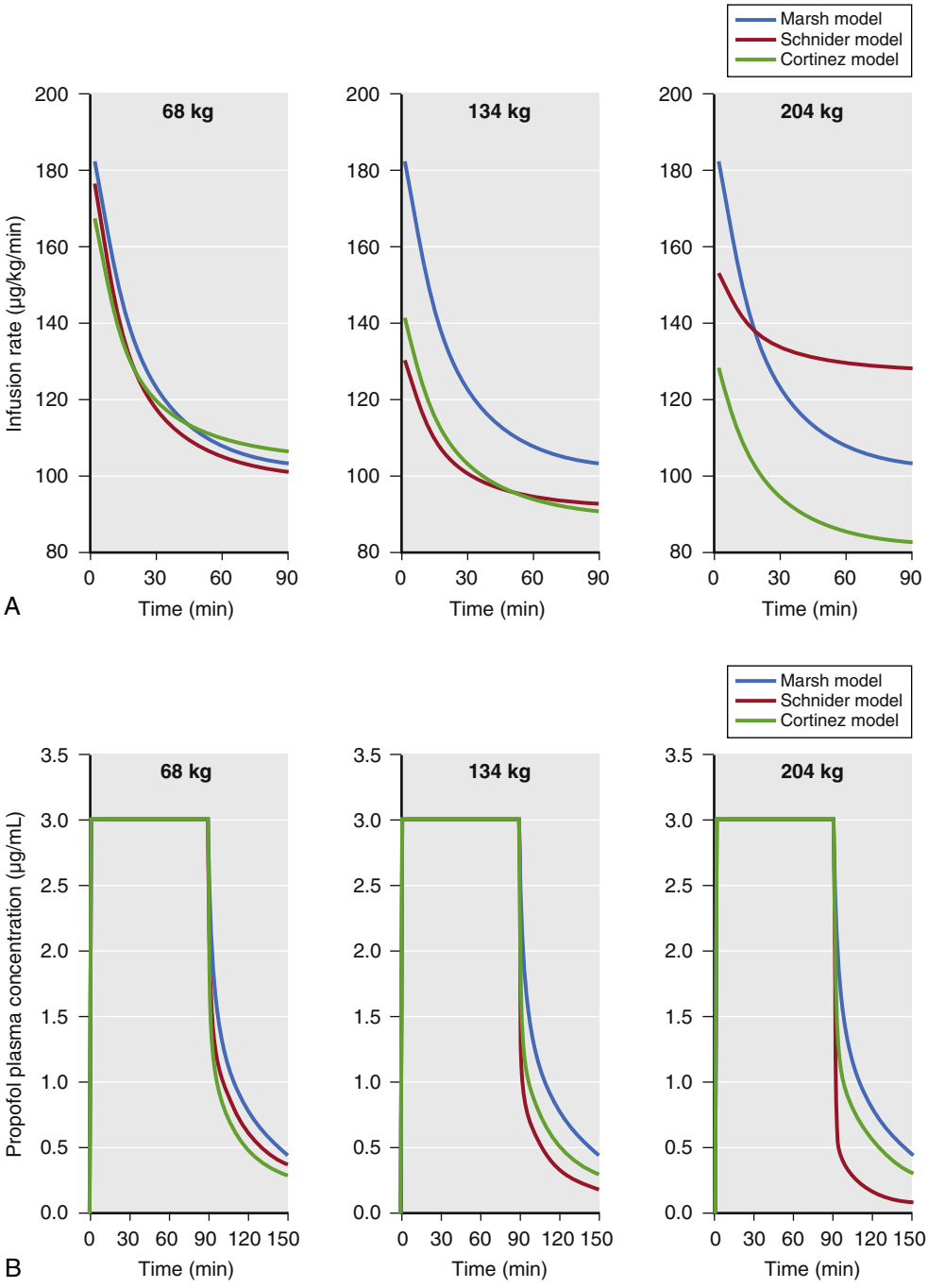


Figure 24-33. Simulations of a 90-minute propofol target-controlled infusion set to achieve and maintain a plasma concentration (*Cp*) of 3 µg/mL using three different published propofol pharmacokinetic models: Marsh and colleagues,[42] Schnider and associates,[1] and Cortinez and colleagues.[39] Simulations assumed 40-year-old males who are 176 cm tall and weigh 68, 136, or 204 kg. **A,** Propofol infusion rates for each model at each weight. **B,** Propofol plasma concentrations predicted by each model for each weight.

2. Dosing scaled to LBM in the obese individual resulted in lower effect-site concentrations than those in a lean individual dosed according to TBW.
3. Dosing the obese individual to TBW was excessive.
4. All dosing scalars, except LBM, provided effect-site concentrations associated with a high probability of analgesia.

As can be appreciated in Figure 24-34, LBM has substantial shortcomings in morbidly obese patients.[43] First, dosing remifentanil to LBM leads to plasma concentrations with a low probability of effect compared with the other dosing scalars. Second, with excessive weight (BMI over 40), LBM actually becomes smaller, with increasing TBW making it impractical to use (see Fig. 24-31). A modified LBM,[40] FFM eliminates the extremely small-dosing weight problem.[48] In this simulation, IBW also provides suitable effect-site concentrations, but this may not always be the case when using a weight scalar that is based only on patient height and not on body habitus, such as the FFM).

Remifentanil Kinetic Models for Target-Controlled Infusions. For remifentanil TCI, one pharmacokinetic model is currently available, published by Minto and

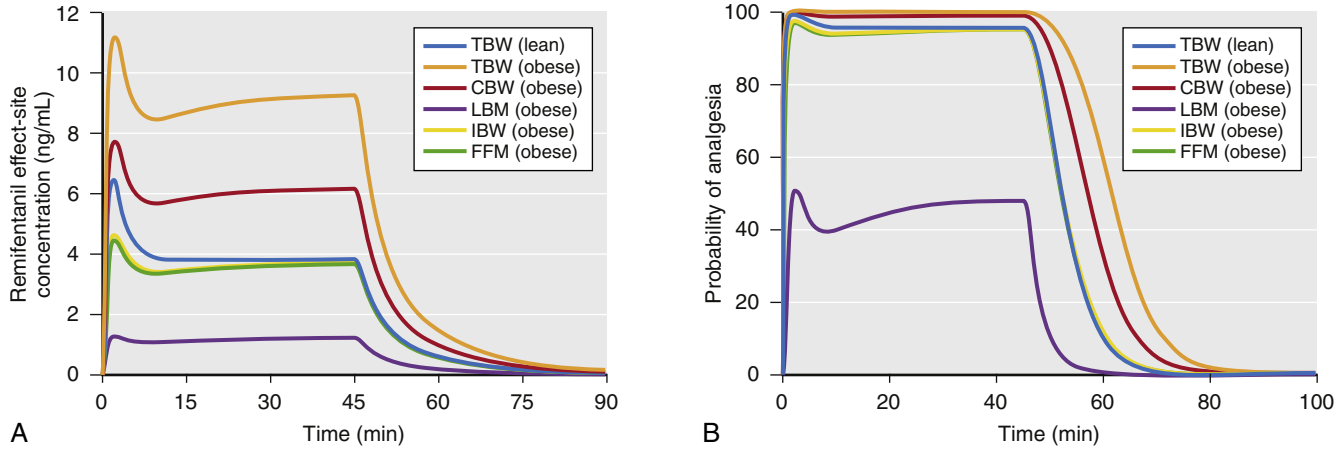


Figure 24-34. Simulations of remifentanil effect-site concentrations (**A**) and analgesic effect (**B**) that result from a 1 μg/kg bolus and a 60-minute infusion at a rate of 0.15 μg/kg/minute to a 40-year-old male who is 176 cm tall. Simulations include the following dosing weights: total body weights (TBW) of 68 kg and 185 kg (body mass indices of 22 and 60, respectively) and scaled weights for the 185-kg weight to include Servin's corrected body weight (CBW), lean body mass (LBM), ideal body weight (IBW), and fat-free mass (FFM). Remifentanil effect-site concentrations and estimates of analgesic effect were estimated using published pharmacokinetic models.[27,48] Analgesia was defined as loss of response to 30 PSI of pressure on the anterior tibia.

associates.[50] Although built from data collected in adults over a range of weights, heights, and age, obese and morbidly obese patients were not included. Many of the model parameters are scaled to LBM. As previously discussed, this may limit the application of this model in the morbidly obese. La Colla and colleagues propose using a weight-adjusted height to enter when programming a TCI pump for delivery of remifentanil to morbidly obese.[48] This adjusted height, based on FFM,[51] is designed to offset the inaccurate influence of LBM on model predictions used to drive the infusion pump. The fictitious weight-adjusted height uses actual height and weight to estimate a new (taller) height that will modify the Minto model to provide more remifentanil via TCI in overweight patients. For example, with a 176-cm 185-kg 40-51 year-old male, the adjusted fictitious height is 254 cm.

To illustrate the impact of the La Colla modification, Figure 24-35 presents a simulation of the predicted remifentanil plasma concentrations based on the Minto model and La Colla correction of the Minto model. The Minto model overestimates remifentanil concentrations with increasing weight. This is likely due to the use of LBM when estimating pharmacokinetic parameters.

A more reasonable approach would be to construct a new pharmacokinetic model based on data measured in obese patients rather than modifying an existing model that did not specifically include this patient population when it was built. A possible approach to constructing a new model is to use allometric body mass scaling as was described for propofol.[44,46]

In summary, available models (Minto or the La Colla modified Minto model) are appropriate for TCI in this patient group but will administer different amounts of remifentanil and require titration to achieve desired yet avoid adverse clinical effects.

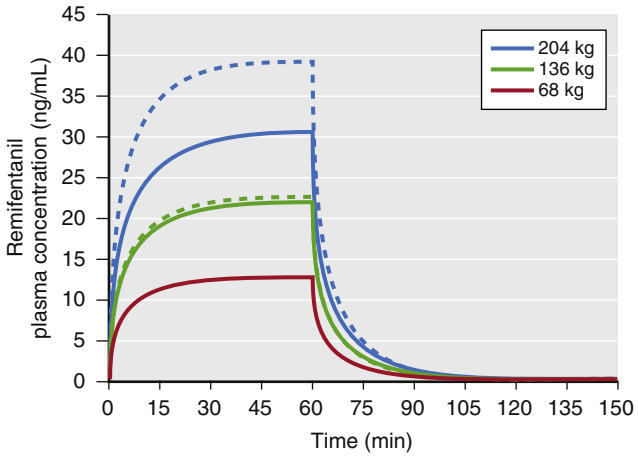


Figure 24-35. Simulations of remifentanil plasma concentrations that result from a 60-minute infusion (0.5 μg/kg/minute) in a 40-year-old male, 176 cm tall. The simulations include three total body weights: 68, 136, and 204 kg with body mass indices of 22, 44, and 66, respectively. Simulations were performed using pharmacokinetic parameters published by Minto and associates[39] (*dashed lines*) and with the La Colla's modification of Minto's model[38] (*solid lines*). In an extremely obese (204-kg) individual, Minto's model predicts very high remifentanil concentrations.

Fentanyl

Despite widespread use in the clinical arena, relatively little work has explored how obesity impacts fentanyl pharmacokinetics (also see Chapter 31). Published fentanyl pharmacokinetic models[52] tend to overestimate fentanyl concentrations as TBW increases. A fentanyl kinetic model based on data collected in obese subjects has not (yet) been published. As with La Colla and associates' work with remifentanil, Shibutani and colleagues[36,37] explored ways to improve predictions using published models by modifying demographic data (e.g., either height or weight). They characterized a nonlinear relationship between fentanyl clearance and TBW and recommended the use of a modified weight, called the pharmacokinetic mass, to improve the predictive performance of one of the many available fentanyl kinetic models, a model published by Shafer and colleagues. Shibutani and associates then explored the use of pharmacokinetic mass when

dosing obese patients with fentanyl in a postoperative setting. They found that dosing based on TBW may be excessive.[39]

Other Opioids

Even less information regarding the impact of obesity on drug behavior is available for opioids other than remifentanil and fentanyl. Sufentanil has been studied in obese patients, where its volume of distribution increases linearly with TBW[53] and clearance was similar between lean and obese individuals. It was recommended that bolus dosing use TBW and "prudently reduced" dosing for continuous infusions. For TCI, Slepchenko and colleagues found model estimates of sufentanil concentrations accurately predicted measured concentrations in morbidly obese patients[54] using a previously published mode of sufentanil kinetics by Gepts and associates.[55] This is likely due to the fact that the kinetic model was built from measured concentrations in patients with a weight range of 47 to 94 kg.

Inhaled Anesthetics

The perception of volatile anesthetics is that they accumulate more in obese than in lean patients and that this leads to prolonged emergence. Studies on inhaled anesthetics in obese individuals, however, has not confirmed this perception.[56] Two phenomena contribute to this observation: first, blood flow to adipose tissue *decreases* with increasing obesity,[57] and second, the time required to fill adipose tissue with volatile anesthetics is long. The times required to achieve 63% of the final equilibrium within adipose tissue for desflurane and isoflurane are longer than 22 and 35 hours, respectively.[58,59]

INFLUENCE OF INCREASING AGE ON ANESTHETIC DRUG PHARMACOLOGY

Clinicians are often faced with anesthetizing older adult patients adults and have long recognized that these patients usually require a smaller dosage of most anesthetics to produce the desired therapeutic effect while minimizing adverse effects. Age is one of the most valuable covariates to consider when developing an anesthetic plan (also see Chapter 80). The influence of age on pharmacokinetics and pharmacodynamics of many anesthetics has been well described. As with obesity, both remifentanil and propofol can serve as prototypes to understand how age influences anesthetic drug behavior. Studies specifically designed to assess the influence of age on remifentanil and propofol have characterized the influence of age in quantitative terms.[1,11,49,50]

With remifentanil, older patients require less drug to produce an opioid effect. Reduced doses are primarily a function of changes in pharmacodynamics but may also involve pharmacokinetic changes.[50] The concentration required to produce electroencephalographic changes is decreased. Based on previously published pharmacokinetic and pharmacodynamic models built from measurements over a wide age range,[1,11,49,50] simulations can be performed to explore how age may influence dosing. For example, to achieve equipotent doses in 20- and 80-year-olds, the dose for the 80-year-old should be reduced by 55%. A similar analysis for propofol recommends that the dose for an 80-year-old be reduced by 65% compared with that of a 20-year-old.

The mechanisms for these changes are not clear, especially for pharmacodynamic changes. One possible source of change in pharmacokinetic behavior may be decreased cardiac output. Lower cardiac output in older adults[60] results in slower circulation with subsequent changes in drug distribution and redistribution. This may lead to high peak concentrations[60,61] and decreased drug delivery to metabolic organs and reduced clearance. This is consistent with what has been described for many intravenous anesthetics (propofol, thiopental, and etomidate), which have slower clearance and a smaller volume of distribution.[1,62-64] Beyond age-related changes in cardiac output, other comorbidities may also reduce cardiovascular function.[65] Taking this into account, anesthesiologists often consider a patient's "physiologic" age instead of solely relying on actual age.[60,67] For some older adult patients, such as those with no significant coexisting disease, normal body habitus, and good exercise tolerance, a substantial reduction in dose may not be warranted.

SUMMARY

This chapter has reviewed the basic principles of clinical pharmacology used to describe anesthetic drug behavior: pharmacokinetics, pharmacodynamics, and anesthetic drug interactions. These principles provide the information needed to make rational decisions about the selection and administration of anesthetics. From a practical aspect, these principles characterize the magnitude and time course of drug effect, but because of complex math requirements, they have had limited clinical use in everyday practice. Advances in computer simulation, however, have brought this capability to the point of real-time patient care. Perhaps one of the most important advances in our understanding of clinical pharmacology is the development of interaction models that describe how different classes of anesthetic drugs influence one another. This is especially relevant to anesthesiologists, given that they rarely use just one drug when providing anesthesia.

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Chapter 25

Inhaled Anesthetics: Mechanisms of Action

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Key Points

- Anesthesia consists of separable and independent components or physiologic substates, each of which involves distinct, but possibly overlapping, mechanisms at different sites in the central nervous system.
- The potency of general anesthetics correlates with their solubility in oil, indicating the importance of interactions with hydrophobic targets.
- General anesthetics act by binding directly to amphiphilic cavities in proteins. Binding sites can be identified by a combination of site-directed mutagenesis and high-resolution structural analysis of anesthetic binding. Mutations rendering putative effector proteins insensitive to inhaled anesthetics have been constructed and expressed in mice but have not generated breakthroughs analogous to the success of this strategy with intravenous anesthetics.
- The effects of inhaled anesthetics cannot be explained by a single molecular mechanism. Rather, multiple targets contribute to the component actions comprising the anesthetic effects of each anesthetic. However, these effects do converge on a limited number of states underlying the behavioral effects.
- The immobilizing effect of inhaled anesthetics involves actions in the spinal cord, whereas sedation/hypnosis and amnesia involve supraspinal mechanisms that interact with endogenous memory, sleep, and consciousness pathways and networks.
- Volatile inhaled anesthetics enhance inhibitory synaptic transmission postsynaptically by potentiating ligand-gated ion channels activated by γ-aminobutyric acid (GABA) and glycine, extrasynaptically by enhancing GABA receptors and leak currents, and presynaptically by enhancing basal GABA release.
- Inhaled anesthetics suppress excitatory synaptic transmission presynaptically by reducing glutamate release (volatile anesthetics) and postsynaptically by inhibiting excitatory ionotropic receptors activated by glutamate (gaseous, and to some extent volatile, anesthetics).
- No comprehensive theory of anesthesia yet describes the sequence of events leading from the interaction between an anesthetic molecule and its targets to the behavioral effects.

Despite the widespread clinical use of general anesthetics, our current understanding of their molecular, cellular, and network mechanisms is incomplete. This critical gap in the pharmacology of one of medicine's most important drug classes not only impedes rational use of available anesthetics but also hinders the development of newer anesthetics that might selectively achieve the desirable end points of anesthesia with fewer adverse cardiovascular, respiratory, and possibly neuropathologic side effects. Although major progress has been made in understanding the pharmacology of the intravenous anesthetics by molecular genetic approaches (see Chapter 30), the actions of the inhaled anesthetics at the molecular and cellular levels are more enigmatic. It is still not possible to trace precisely the sequence of events that leads from inhaled anesthetic–target interactions, through ascending levels of biologic complexity, to the various behavioral effects that characterize the composite state of clinical anesthesia in humans. Nevertheless, investigations continue to reveal fundamental principles of action and have led to a framework for understanding anesthetic effects at different organizational levels. The focus of this chapter is on the mechanisms involved in the principal therapeutic effects (anesthesia) and on the side effects of the inhaled anesthetics (Fig. 25-1), a chemically and pharmacologically diverse group that includes the potent halogenated

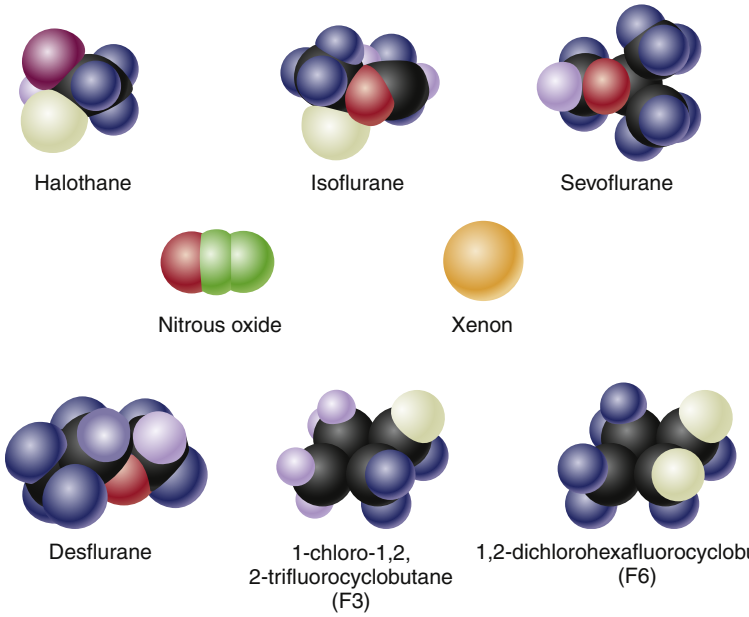


Figure 25-1. Structure of representative general anesthetics and a nonimmobilizer (F6) shown as space-filling models.

TABLE 25-1 **OVERVIEW OF CANDIDATE SITES OF ANESTHETIC ACTION**

	Site	Effect	Targets
Proteins	Amphiphilic binding sites	Conformational flexibility, ligand binding	Ion channels, receptors, signaling proteins
Action potential	Nervous system	Small reduction in amplitude	Na^+ channels
	Cardiovascular system	Reduced amplitude, duration	Ca^{2+} channels, K^+ channels
Synaptic transmission			
Inhibitory	Presynaptic terminal	Enhanced transmitter release	?
	Postsynaptic receptors	Enhanced transmitter effects	Glycine, $GABA_A$ receptors
Excitatory	Presynaptic terminal	Reduced transmitter release	Na^+ channels, K_{2P} channels
	Postsynaptic receptors	Reduced transmitter effects	NMDA receptors, nicotinic acetylcholine receptors
Neuronal networks	Neuronal circuit	Altered long-term potentiation (LTP)/ long-term depression (LTD)	Synaptic plasticity
	Neuronal integration	Altered rhythmicity, coherence	HCN channels, K_{2P} channels, extrasynaptic $GABA_A$ receptors, etc.
Central nervous system	Neocortex, hippocampus, amygdala	Sedation, amnesia	Slow 1-Slow 4, δ-, α-, θ-, γ-rhythms, cross-frequency coupling
	Diencephalon (thalamus), brainstem (reticular formation)	Unconsciousness	γ-band transfer entropy?, cross-frequency coupling? cortical integration capability?
	Spinal cord	Immobility	Thalamic deafferentation? Nocifensive reflex
Cardiovascular system	Myocardium	Negative inotropy	Excitation-contraction coupling
	Conduction system	Dysrhythmias	Action potential
	Vasculature	Vasodilation	Direct and indirect vasoregulation

HCN, Hyperpolarization-activated cyclic nucleotide; *NMDA, N*-methyl-D-aspartate.

ether (isoflurane, sevoflurane, desflurane, enflurane) and alkane (halothane) volatile anesthetics and the gaseous anesthetics (nitrous oxide and xenon). This critical summary of the current state of knowledge begins with an historical overview and a review of the behavioral end points of anesthesia. We then trace, where possible, inhaled anesthetic effects through ascending levels of organization from molecules, cells, circuits, networks, and organs to mammalian behavior; an overview is provided in Table 25-1. We also briefly address studies of anesthetic effects in model organisms, with anesthetic end points being identified that bear unclear relationships to those in mammals.[1]

HISTORY

THE UNIFIED PARADIGM OF ANESTHETIC THEORIES

The first monograph reporting experimental work on anesthetic mechanisms, proposing a soon-to-be

discredited lipid-elution theory of anesthetic action, was published only 6 months after Morton's Ether Dome demonstration. For decades thereafter, the phenomenon of anesthesia puzzled, inspired, and awed those who tried to understand it. A most influential paradigm of anesthetic action formulated by Claude Bernard in the 1870s posited that anesthesia was a "unified" phenomenon: a unitary mechanism applicable to all forms of life. Although the anesthetized state could be brought about by a variety of agents, its essence was the same in all living creatures. In fact, Bernard thought that life itself was defined by susceptibility to anesthesia. Bernard also proposed a more specific theory of anesthesia, coagulation of protoplasm, which competed with a number of coexisting theories entertained by the scientific community. In a major work published in 1919, Hans Winterstein summarized the perplexing diversity of anesthetic theories by listing more than 600 references, the majority to original laboratory work—a convincing testimony to the interest of the scientific world in this phenomenon. Of note, the work of Meyer and Overton at the end of the nineteenth century had only a limited effect on the trajectory of research until the 1960s.[1] Only then was the striking simplicity of the Meyer-Overton correlation (Fig. 25-2, *A*) of anesthetic potency with solubility in olive oil interpreted by the majority of researchers as an indicator that lipids are likely the anesthetic target. This interpretation focused attention on anesthetic effects on the bulk physical properties of cell membranes, which were known at that time to consist primarily of lipid molecules. Such nonspecific or "lipoid-based" anesthetic theories dominated the field from the 1960s to the 1980s.

MINIMUM ALVEOLAR CONCENTRATION: A BRIDGE BETWEEN PAST AND PRESENT

The potencies of inhaled anesthetics for immobilization were established in the classic studies in the 1960s of Eger and colleagues,[2,3] who defined the *minimum alveolar concentration* (MAC) as the inhaled anesthetic atmospheric pressure required to prevent movement in response to a defined noxious stimulus in 50% of subjects. The concept of MAC evolved within a unitary paradigm of anesthetic action and reflected the priorities of clinical practice. As a result, prevention of movement (immobility) became a universal yardstick for anesthetic effects, presumed to occur in the brain. Moreover, the simple elegance of the relationship between MAC and lipid solubility (see Fig. 25-2, *A*) graphically illustrated Meyer and Overton's conclusion that "All chemically indifferent substances that are soluble in fat are anesthetics … their relative potency as anesthetics will depend on their affinity to fat on the one hand and water on the other hand, that is, on the fat/water partition coefficient."[1] This was interpreted as favoring lipids as the primary targets of anesthetics and a single nonspecific theory to explain anesthesia. The appeal of a single unified mechanism to explain anesthesia was (and remains) intellectually appealing. This focused the bulk of research efforts on delineating how anesthetic interactions with lipid membranes might lead to the behavioral changes observed under anesthesia, the nonspecific lipoid theory.

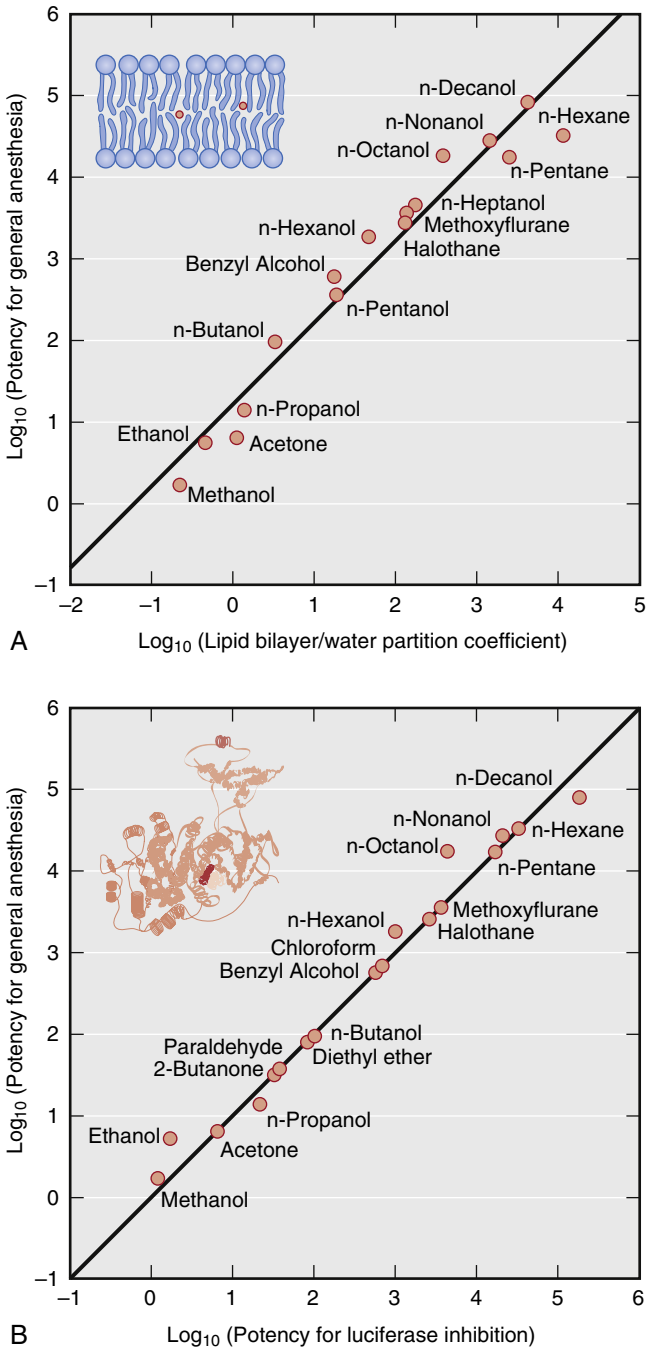


Figure 25-2. General anesthetics act by binding directly to proteins. **A,** The iconic Meyer-Overton correlation (ca. 1900) between anesthetic potency and the lipid-water partition coefficient was initially interpreted as evidence that lipids of nerve membranes were the principal anesthetic target sites. **B,** Progress in the twentieth century showed that general anesthetic potencies correlate equally well with their ability to inhibit activity of the soluble firefly enzyme luciferase, which is not a physiologically relevant anesthetic target itself but serves as a lipid-free model protein for anesthetic binding. *Inset,* The crystal structure of luciferase with bound anesthetic *(red). (Reprinted with permission from Franks NP, Lieb WR: Molecular and cellular mechanisms of general anesthesia,* Nature *367:607-614, 1994.)*

Because inhaled anesthetic concentrations reflect concentrations in the tissues after equilibration, which is most rapidly achieved for well-perfused organs such as the brain and heart, MAC is analogous to the plasma concentration for 50% effect (EC_{50}) for intravenous anesthetics. In clinical applications, MAC is usually expressed as volume percent (vol%), which varies considerably with temperature and atmospheric pressure caused by changes in aqueous solubility, whereas the equivalent liquid-phase molar concentration is temperature- and pressure-independent.[4] The MAC concept provided researchers and clinicians with a universal standard to measure a defined anesthetic end point (immobility), making meaningful comparisons of experimental results possible and accelerating clinical and laboratory research into anesthetic mechanisms. Today, a more nuanced understanding of MAC takes into account the structural and functional diversity of the physiologic targets for the different components of the anesthetic state.

SHIFT FROM LIPID- TO PROTEIN-CENTERED MECHANISMS

Lipid-centered mechanisms of anesthesia prevailed in the 2 decades after definition of the MAC concept. Alternative targets were repeatedly proposed but largely neglected by the scientific mainstream. Experimental inconsistencies of lipid targets,[5,6] as well as evidence compatible with proteins as primary sites of action,[7,8] remained largely unnoticed. A shift from lipid- to protein-centered mechanisms occurred in the 1980s, owing largely to the landmark discoveries by Franks and Lieb,[9,10] who in a classic series of publications demonstrated that protein targets were also compatible with the Meyer-Overton correlation (see Fig. 25-2, *B*)—a proof of concept that, within a couple of years, redirected the bulk of research efforts toward proteins. As a corollary of this reorientation, evidence against lipid-based theories was recognized. Examples include the cutoff in anesthetic potency in homologous series of long-chain anesthetic alcohols, and the identification of hydrophobic drugs that do not obey the Meyer-Overton correlation.[1,11] The enantiomeric selectivity of several anesthetics further strengthened the case for specific binding sites on proteins because stereoselectivity is difficult to reconcile with lipid targets.[12] Today, there is widespread (but not universal) acceptance of the notion that critical signaling proteins (e.g., ion channels or ligand-gated receptors) are the relevant molecular targets of anesthetic action, even though the submolecular mechanisms of their modulation by anesthetics are debated. The exact identity of proteins contributing to specific anesthetic end points continues to be sought, with research addressing not only the "where" (target) but also the "how" (process) of anesthetic mechanisms.

DIVERSITY OF POTENTIAL ANESTHETIC TARGETS

At high concentrations in vitro, most inhaled anesthetics affect the functions of multiple proteins, many of which can be plausibly connected to the components of the anesthetic state or anesthetic side effects. However, when considering a specific anesthetic end point, anesthetics are effective in vivo over quite a narrow concentration range. This makes the concentration at which a relevant anesthetic effect is observed a critical consideration for deciding potential relevance. The mechanistic relevance of small effects observed in vitro at relevant concentrations is less clear; that is, what effect is too small to be considered relevant to anesthesia?[13-15] Whether anesthesia results from the sum of minor perturbations at multiple sites that are amplified in cascades across multiple levels of integration to produce the macroscopic effect, or from strong effects on a small number of targets should be resolved as results of reductionist molecular studies are integrated into more complex molecular and cellular networks, and as genetic studies are extended to encompass inhaled anesthetics. The picture that is emerging includes multiple cellular and molecular targets in distinct brain regions that are involved in both the desired and adverse effects of general anesthetics.

ANESTHESIA: A COMPOSITE NEUROPHARMACOLOGIC STATE

Along with progress in identifying the molecular mechanisms of anesthesia, our understanding of the nature of the anesthetic state has evolved. Whereas a drug-induced comalike state of general anesthesia can be induced by inhaled anesthetics administered at appropriate concentrations (approximately 1.3 times MAC, equivalent to the EC_{95} of a volatile anesthetic), the use of such high concentrations can lead to short-, and possibly long-term, side effects. It is now clear that anesthesia consists of separable and at least partially independent components or substates, each of which involves distinct, but possibly overlapping, mechanisms in different regions of the central nervous system (CNS) and with variations in relative potencies between specific agents.[16] Immobilization, the core measure of MAC, is mediated largely at the level of the spinal cord by inhaled anesthetics[17,18] but not by barbiturates.[19] On the other hand, the spinal cord is unlikely to be the major site of such phenomena as amnesia, sedation, and unconsciousness, which rather are produced by anesthetic effects on cerebral cortical function (Fig. 25-3). A functional separation between amnesia and sedation has been demonstrated for intravenous anesthetics,[20] and it seems likely that this will apply to inhaled anesthetics as well. The state commonly referred to as "unconsciousness" is in itself heterogeneous, with evidence for distinct states of unresponsiveness and unconsciousness.[21] These and similar findings have led to the concept that general anesthesia consists of multiple independent components that can be resolved experimentally and clinically.

In principle, each component of anesthesia can be preferentially induced in a concentration- and agent-specific manner using individual cellular/molecular pathways in various regions of the CNS. For example, injections of pentobarbital into discrete sites in the mesopontine tegmentum induce a comatose state,[22] whereas sedation induced by systemic administration of propofol can be reversed by microinjections of γ-aminobutyric acid $(GABA)_A$ receptor antagonists into the tuberomammillary

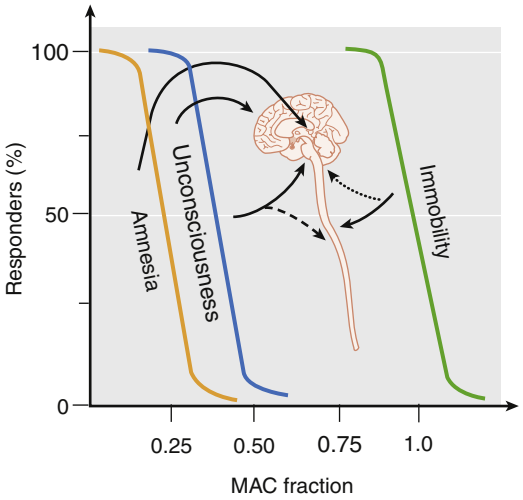


Figure 25-3. Multiple behavioral end points and sites of action underlie inhaled anesthetic action. Amnesia, the most sensitive anesthetic end point, probably involves the hippocampus, amygdala, mediotemporal lobe, and other cortical structures. Unconsciousness likely involves the cerebral cortex, thalamus, and reticular formation. Sedation and hypnosis (loss of responsiveness) are part of the consciousness-unconsciousness continuum and are not shown. Immobility occurs by anesthetic action in the spinal cord, although supraspinal effects *(dotted arrow)* are likely important for some anesthetics. Anesthetic action in the spinal cord blunts ascending impulses arising from noxious stimulation and might indirectly contribute to anesthetic-induced unconsciousness and amnesia *(dashed arrow)*. Cardiovascular responses occur at even greater MAC fractions (not shown). *(Courtesy Joseph Antognini, University of California, Davis.)*

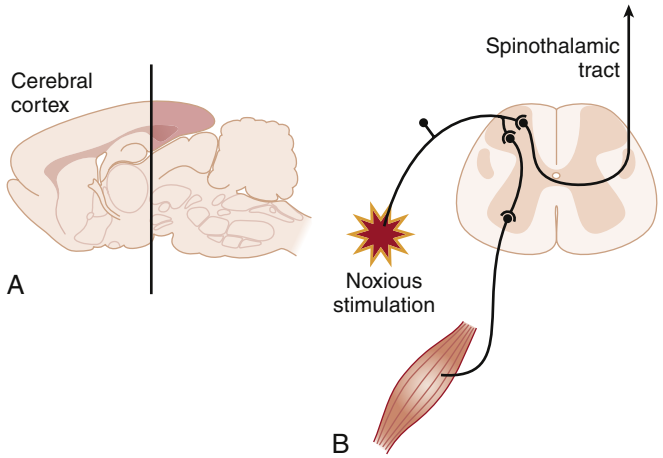


Figure 25-4. Inhaled anesthetics produce immobility at the spinal level. **A,** Decerebration by removal of the forebrain rostral to the *black line* does not alter the MAC of isoflurane in rats, indicating that volatile anesthetic immobilization does not depend on the cerebral cortex.[17,18] **B,** Anesthetics suppress the nocifensive withdrawal reflex response to noxious stimulation transmitted to the dorsal horn by sensory nerves at the spinal level. Current efforts are focused on identifying the molecular, cellular, and anatomic substrates for this effect.

nucleus, a sleep-regulating nucleus in the hypothalamus.[23] Thus, general anesthetics produce separate identifiable anesthetic substates via agent-specific actions at discrete anatomic sites in the CNS through different molecular targets. An important consequence of this complexity is that MAC, which is based exclusively on a motor response, might not proportionately reflect other components of anesthesia. Although this heterogeneity of anesthetic actions complicates a mechanistic understanding, it does open the possibility of developing substate-specific drugs.

INTEGRATED EFFECTS ON CENTRAL NERVOUS SYSTEM FUNCTION

IMMOBILITY

Electroencephalography as a monitor of brain activity has been applied both to the study of anesthetic mechanisms and as a monitor of the anesthetic state (also see Chapter 44). Failure to find a correlation between quantitative electroencephalographic activity and immobility in response to noxious stimulation led to the somewhat radical (at the time) hypothesis that immobility was not a cerebral cortex–mediated phenomenon.[24] Experimental demonstration that volatile anesthetics act on the spinal cord to suppress movement[17,18] supported this hypothesis and was a major factor leading to the contemporary separation of anesthetic substates, of which immobility requires the highest drug concentrations (see Fig. 25-3). Taking advantage of the unusual blood supply of goat CNS, which allows separate perfusion of brain and spinal cord, Antognini and associates[17,25] showed that immobility involves anesthetic effects at the spinal level because selective delivery of isoflurane or halothane only to the brain required 2.5-fold to 4-fold higher concentrations. At the same time, experiments by Rampil and co-workers[18] that used surgical separation of the forebrain and midbrain from the spinal cord in rats led to the conclusion that immobilization involves primarily suppression of the nocifensive withdrawal reflex arc at the level of the spinal cord (Fig. 25-4).

In the 20 years since the identification of the spinal cord as the site of anesthetic-induced immobility, research has centered on pharmacologic, genetic, and complex network approaches. The pharmacologic approach to identify receptor-level contributions to isoflurane-induced immobility (isoflurane being the standard potent ether for experimental purposes) yielded the surprising insight that actions at $GABA_A$ receptors appear to be unimportant.[26] Perhaps less surprisingly, inhibition of central nicotinic acetylcholine receptors also plays no role in immobilization.[27] A role for voltage-gated sodium (Na^+) channels was suggested by the finding that intrathecal administration of a selective inhibitor of Na^+ channels potentiates anesthetic immobility (reduces MAC), whereas a Na^+ channel activator does the opposite.[28] Anesthetic-resistant transgenic mice confirmed that $GABA_A$ receptors containing α1- or α3-subunits do not contribute to the immobilizing action of isoflurane.[29,30] In contrast, mutant mice lacking the TASK-1, TASK-3, or TREK-1 K_{2P} channels have higher MAC values for volatile anesthetics but not intravenous anesthetics,[31-33] indicating a role for these channels, possibly by a presynaptic mechanism.[34]

Work with physiologic preparations that attempt to preserve parts of the complex spinal cord circuitry suggests that anesthetic inhibition of afferent (noxious sensory) input to the dorsal horn plays a subordinate role to the suppression of the efferent (motor) output from the ventral horn, although this may vary by specific agent. This motor output is coordinated by neuronal networks organized in so-called central pattern generators that control the activity of cholinergic motoneurons.[35] Not unlike understanding the anesthetic effects on higher cognitive function, the key to understanding immobility will likely lie in resolving the effect of anesthetics on integrated spinal network activity.

UNCONSCIOUSNESS

Consciousness, as a quality of the mind, is easy to recognize but difficult to define (see Chapters 13 and 14). It has been described as "what abandons us every night when we fall into dreamless sleep and returns the next morning when we wake up or when we dream." This intuitive description applies equally as well to general anesthesia as it does to sleep; however, it does not provide a concrete definition that is useful for scientific studies. Consciousness consists of inner qualitative subjective states of sentience or awareness.[36] A recent suggestion that seeks to provide a quantitative measure of consciousness, and that may serve as a definition, is that consciousness is the capacity of a system to integrate information.[37] Loss of consciousness (or hypnosis) is a hallmark of the onset of anesthesia, and anesthetic drugs are being used as tools for understanding the neural correlates of consciousness (NCC).[38] However, what is commonly referred to as *unconsciousness* under anesthesia might be better described as *unresponsiveness*, which could obscure states of self- and environmental awareness lacking explicit memory traces.[21]

Although it is a relatively new field, particularly within the field of anesthesiology, the "science of consciousness" has generated considerable interest and has led to a number of specific hypotheses that are experimentally tractable. The "thalamic theory" of anesthesia proposes a somatosensory deafferentation by anesthetic action in the thalamus as a mechanism of unconsciousness.[39] In support of this hypothesis, isoflurane hyperpolarizes and shunts thalamic neurons,[40] an action consistent with impaired thalamic transfer of sensory information.[41] Functional human brain imaging shows preferential suppression of thalamic activity by some, but not all, anesthetics, and this has led to the "thalamic switch" hypothesis.[39] However, loss of consciousness occurs within a very narrow range of anesthetic concentrations,[42] typically up to 0.5 MAC,[43,44] whereas quantifiable effects in the thalamus occur above this concentration range and are typically incremental (dimmerlike) rather than sudden (switchlike). A comprehensive theory of anesthetic-induced unconsciousness must be more inclusive than a simple block of information transfer through the thalamus to be compatible with existing evidence[45,46] and must also explain the suppression of endogenous cortical activity that is generated without external stimulation.

Contemporary neuroscience has replaced the Cartesian view of an anatomically discrete brain structure as the center of consciousness with the concept that consciousness requires integration of information between multiple brain regions across large-scale cerebral networks.[45,47] The rich connectivity of the cerebral cortex and its hierarchical organization are especially suited to enable high levels of information integration in the human brain. Some brain areas present a "rich-club" organization (i.e., highly connected nodes tend to be preferentially connected to other highly connected nodes), which has been suggested to be optimal for information integration.[48,49] These hubs might be promising targets for the hypnotic action of general anesthetic drugs.

Anesthetics might act by interfering with the operational synchronicity and coherence of these networks. Consequent disruption of cortical functional and effective connectivity has been observed during natural slow wave sleep[50] and midazolam-induced loss of responsiveness.[51] This breakdown of cortical connectivity, rather than pharmacologic deafferentation from the environment, could underlie loss of consciousness.[45] Unconsciousness would then be characterized not by the absence but by the fragmentation of cortical processing. Although the mechanism of "binding" (i.e., creating the unity of perception) is uncertain, synchronicity of neuronal activity in the 40- to 90-Hz range across functionally connected cortical areas (commonly referred to as 40 Hz- or γ-rhythm) is a viable candidate. Animal[52,53] and human[42] data implicate activity in the γ-band throughout the cortex as a network-level target of general anesthetics. Anesthetic actions on cortical information processing probably consist not merely of suppression of responses but of reduced complexity and variability reflected counterintuitively in increased reliability and precision of evoked responses.[54,55]

LEARNING AND MEMORY

Anterograde amnesia, one of the core desirable anesthetic end points, is achieved at lower anesthetic concentrations (~0.25 MAC) than those required for unconsciousness (~0.5 MAC). Perhaps the closest analogue in rodents to explicit memory in humans is medial temporal lobe–dependent learning of temporal and spatial sequences known as *hippocampus-dependent spatial learning*. This can be tested by a variety of experimental paradigms, including fear conditioning to context (Fig. 25-5). Other learning paradigms, such as fear conditioning to tone, are by contrast independent of the hippocampus. Isoflurane and the nonimmobilizer F6 both inhibit hippocampus-dependent learning at about one-half the concentration necessary for disrupting hippocampus-independent learning.[56] Similarly, anesthetic concentrations that inhibit explicit memory in humans (memory that can be explicitly recalled as opposed to motor learning, classical conditioning, and so on) are similarly lower than concentrations that impair implicit memory (not subject to willful recollection).[46] Taken together, these findings implicate effects on function of the medial temporal lobe, including the hippocampus, in the suppression of explicit

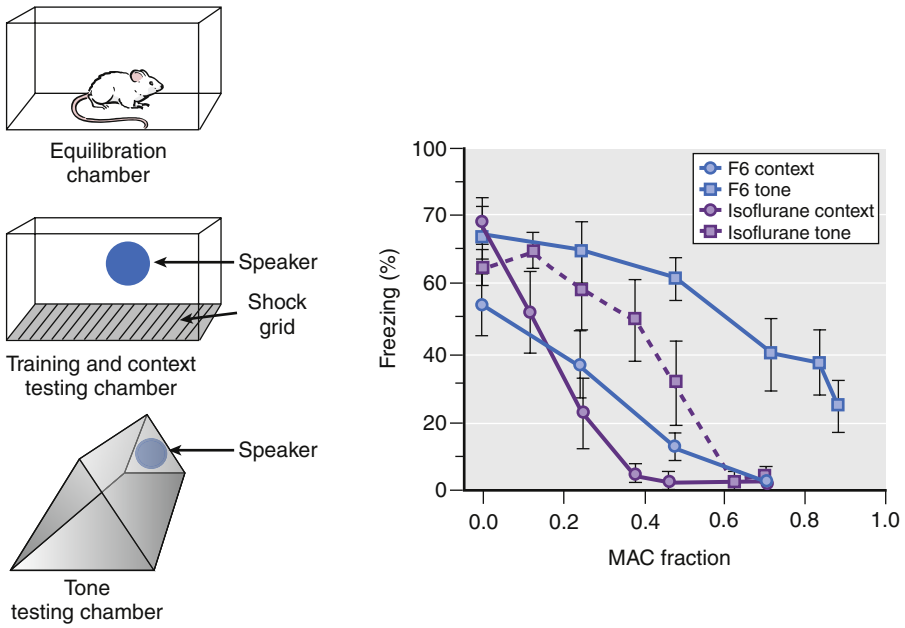


Figure 25-5. Differential sensitivity of different types of learning to anesthetics and nonimmobilizers. Freezing in anticipation of a noxious stimulus is a measure of learning in rats; less freezing indicates less learning. *Left,* The learning protocol involves pre-equilibration of rats in the equilibration chamber to isoflurane or the nonimmobilizer F6 at the desired concentration before placement into the training chamber. For testing of memory to context, the training and test chamber are identical. For testing of memory to tone, training and testing take place in different chambers. *Right,* Hippocampus-dependent learning (fear conditioning to context, *closed symbols*) is inhibited by isoflurane *(circles)* at lower concentrations than hippocampus-independent learning (fear conditioning to tone, *purple squares*). This differential sensitivity is mirrored by the nonimmobilizer F6 (*blue circles* and *blue squares* for context and tone, respectively). *(Left panel adapted with permission from Eger EI 2nd, et al: Isoflurane antagonizes the capacity of flurothyl or 1,2-dichlorohexafluorocyclobutane to impair fear conditioning to context and tone,* Anesth Analg *96: 1010-1018, 2003; right panel data points reconstructed from Dutton RC, et al: Short-term memory resists the depressant effect of the nonimmobilizer 1-2-dichlorohexafluorocyclobutane (2N) more than long-term memory,* Anesth Analg *94:631-639, 2002, and Dutton RC, et al: The concentration of isoflurane required to suppress learning depends on the type of learning,* Anesthesiology *94:514-519, 2001.)*

memory by anesthetics. Effects on other structures, such as the amygdala, may be relevant to anesthetic impairment of implicit or other types of memory.[57]

Comparison of the amnesic potency of five inhaled anesthetics using an inhibitory avoidance paradigm revealed that nitrous oxide was the most and halothane the least potent amnestic (expressed in MAC fractions), with the halogenated ethers of intermediate potency.[58] Because inhaled anesthetics affect multiple cellular targets at amnesic concentrations, it is difficult to attribute amnesia to specific cellular mechanisms. It is also unclear whether inhibition of learning and memory by drugs known to have different receptor affinities shares common mechanisms at some level of integration. Comparison with more selective drugs provides some insight. Yet, θ-rhythms (4-12/Hz) are clearly important for hippocampus-dependent learning and memory.[59] Benzodiazepines[60] and cannabinoids[61] slow and suppress hippocampal θ-rhythms in proportion to their ability to impair hippocampus-dependent learning (also see Chapters 13 and 30). Isoflurane and the nonimmobilizer F6 have comparable effects on θ-rhythms at amnesic concentrations while having different receptor-level profiles and opposite effects on sedation.[62] Thus alterations in neuronal synchrony provide a common network-level substrate for memory impairment. The synchronization between amygdalar and hippocampal θ-rhythms that occurs during fear memory retrieval indicates that this principle might also apply to other forms of memory and their impairment by anesthetics.[63] As with other components of the anesthetic state, the precise mechanisms of memory impairment by anesthetics, and of memory itself, remain to be fully elucidated.

SEDATION

Sedation (defined as a decrease in activity, alertness, arousal, and/or vigilance), which is on a behavioral continuum leading to hypnosis, is achieved at anesthetic doses similar to those that produce amnesia (<0.5 MAC). There is no clear mechanistic or clinical separation between sedation and hypnosis. By contrast, even though sedation can be difficult to separate from amnesia, for intravenous anesthetics (see Chapter 30) there may be separate but overlapping substrates for these two end points.[20,64] The mechanisms involved in these behavioral effects are likely to resemble those of less promiscuous drugs, for which genetic approaches have been informative. An amino acid knock-in mutation (H101R) in mice that renders the α_1 $GABA_A$ receptor subunit insensitive to modulation by benzodiazepines produces resistance to the sedative and amnesic effects of benzodiazepines while maintaining other behavioral effects, among them anxiolysis.[65] The α_1 subunit is abundantly expressed in the CNS, mainly in the cortical areas and thalamus. Volatile anesthetics have qualitatively similar

effects on α_1-containing $GABA_A$ receptors (but also those containing other subunits) at low concentrations. The observation that the nonimmobilizer F6, which is devoid of sedative properties,[62] is amnesic[66] but does not modulate benzodiazepine-sensitive α_1-containing $GABA_A$ receptors,[67,68] is compatible with a role for α_1-containing receptors in volatile anesthetic-induced sedation, because few other targets are affected at purely sedative concentrations. Possible targets for the sedative effects of the gaseous anesthetics nitrous oxide and xenon, which do not affect $GABA_A$ receptors, include *N*-methyl-D-aspartate (NMDA) receptor antagonism[69] and K_{2P} channel activation.[70] Consistent with this distinct pharmacologic profile, nitrous oxide has strikingly different effects from benzodiazepines in behavioral tests aimed at evaluating sedation in mice.[71]

Recognizing that there may be more than a superficial similarity between natural sleep and anesthetic-induced sedation and hypnosis, the effects of some anesthetics apparently share natural sleep mechanisms by directly activating discrete sleep-promoting nuclei in the hypothalamus.[23] Electroencephalographic patterns during natural slow-wave sleep and anesthesia show similarities,[72] and recovery from sleep deprivation can occur under propofol[73] and inhalational anesthesia,[74] supporting this concept (also see Chapter 14). Anesthetic effects on other cortical[75] and subcortical structures[21] may also contribute to anesthetic-induced sedation and hypnosis.

ANESTHETIC NEUROTOXICITY AND NEUROPROTECTION

Early Postnatal Neurotoxicity

General anesthetics can cause persistent neurologic effects beyond their classic reversible production of anesthesia. Yet its clinical significance remains unknown.[76-78] Since the discovery that postnatal exposure of the developing rodent brain to high doses of commonly used anesthetic drugs, in isolation or in combination, for a period of several hours, can induce apoptotic cell death with potentially long-term functional consequences,[78] the neonate rodent model has been extensively studied and discussed. Similar effects have been reproduced with all commonly used general anesthetic drugs. How the results translate quantitatively and qualitatively from short-lived altricial (such as rodents) to long-lived, more precocial (such as *Homo sapiens*) species remains to be defined. Interestingly, postexposure environmental factors appear to play a substantial role in the expression of neurotoxicity.[79]

Ischemic Neuroprotection

Pharmacologic neuroprotection from cerebral ischemia and reperfusion is a rapidly evolving area of research that is characterized by great potential, but comparable disappointments, because results from promising animal studies have failed to translate into clinical benefits. Despite considerable research, clinical evidence for ischemic brain protection by inhaled anesthetics remains controversial.[80] Ischemic neuronal injury results from early excitotoxic cell death mediated by excessive release of excitatory amino acid transmitters such as glutamate and oxidative stress caused by reperfusion injury together with delayed cell death as a result of apoptosis.[81,82] Volatile anesthetics (e.g., isoflurane) and xenon exhibit early neuroprotection in animal models that is sustained only for mild insults. This is consistent with a beneficial effect on excitotoxicity but minimal effects on delayed cell death caused by apoptosis. A therapeutic strategy to extend this early neuroprotection is suggested by the finding that isoflurane combined with caspase inhibitors to prevent apoptosis results in more sustained neuroprotection.[83] In contrast, xenon appears to have an intrinsic antiapoptotic action that contributes to its neuroprotective properties, consistent with its distinct molecular mechanisms.[84] Interestingly, "preconditioning" with ketamine appears to protect against ketamine-induced neurotoxicity.[85] In addition, volatile anesthetics probably protect by suppression of brain energy requirements owing to inhibition of excitatory transmission and potentiation of inhibitory receptors and ion channels.[81] The potential for beneficial effects from anesthetic-induced preconditioning has also received considerable recent attention. Similar to the protective effects of anesthetics administered before cardiac ischemia (anesthetic preconditioning; see later), protective effects have also been observed in animal models of focal cerebral ischemia (see also Chapters 67, 69, and 70).[86]

Postoperative Cognitive Effects

Adverse postoperative cognitive effects persisting beyond a duration explainable by pharmacokinetic factors have been attributed to anesthetics since the nineteenth century. Three clinical entities must be distinguished: delirium, dementia, and postoperative cognitive dysfunction (POCD). Contrary to delirium and dementia, POCD is not a clinical diagnosis but a result of comparison of pre- and postoperative scores on neuropsychological test batteries among patients undergoing surgery and matched control populations that did not undergo surgery. This is a highly complex experimental paradigm that is prone to artifacts. For example, as a result of these analyses, postoperative cognitive improvement coexists with POCD,[87] and whether either or both of these entities exists as pathologic entities and are clinically relevant remains an open question. The situation is fundamentally different with respect to delirium and neurodegeneration, which can be diagnosed by established criteria and standardized tools.

Although direct effects of inhalational anesthetics have been linked to memory deficits persisting for days in young adult mice, specifically via interaction with the α_5 subunit of the $GABA_A$ receptor,[88] postanesthesia changes in exploratory behaviour are dependent on interaction with central cholinergic signaling pathways.[89] Accumulating evidence, however, points to immune- and/or inflammation-mediated changes triggered by surgical trauma and anesthesia as potential mechanisms for delirium-like, short- or intermediate-term postoperative cognitive dysfunction (also see Chapter 99).[90,91]

Experimental evidence obtained using mice rendered genetically susceptible to Alzheimer disease–like neurodegeneration does not support a role of anesthetic agents per se in promoting neurodegenerative disease.[92] It provides experimental support for observational studies in humans that cognitive decline after surgery is caused by neither accelerated neurodegeneration nor anesthetic agents.[93]

Rather than an anesthetic-mediated effect, a determining role for the underlying disease trajectory (as opposed to the surgical/anesthetic intervention) in determining the long-term cognitive course of most patients is likely.[94] Short-term effects on cognition appear to be related to physiologic perturbations resulting from invasive interventions with either aggravating and/or mitigating roles of anesthetics.

INTEGRATED EFFECTS ON THE CARDIOVASCULAR AND RESPIRATORY SYSTEMS

Mechanisms of Cardiovascular Effects

The classic cardiovascular effects of the volatile anesthetics are usually undesired deleterious side effects that limit their safe use in the critically ill, but recent studies have shown that there are also direct cardioprotective effects.[95] All volatile anesthetics produce agent- and dose-dependent reductions in myocardial contractility, systemic vascular resistance, and cardiac preload, with consequent reduction in mean arterial pressure. However, significant differences do exist in the relative potencies of these effects between anesthetics (see Chapter 28).[96] Volatile anesthetics depress contractility by reducing Ca^{2+} availability and/or Ca^{2+} sensitivity of the contractile apparatus.[97] The major targets responsible for the negative inotropic effects of volatile anesthetics are cardiac Ca^{2+} channels, sarcoplasmic Ca^{2+} handling, and the contractile apparatus. Inhibition of depolarization-induced increases in myoplasmic Ca^{2+} concentration occur primarily via inhibition of cardiac L-type voltage-gated Ca^{2+} currents and shortening of action potential duration.[98] Volatile anesthetics also inhibit the sarcoendoplasmic Ca^{2+} adenosine triphosphatase (SERCA), whereas halothane, but not isoflurane or sevoflurane, opens sarcoplasmic reticulum (SR) Ca^{2+} release channels (ryanodine receptors), depleting SR Ca^{2+} content and reducing excitation-evoked SR Ca^{2+} release.[97] The resulting negative inotropic effect of this reduced Ca^{2+} availability is enhanced by reductions in the Ca^{2+} sensitivity of myofibrils. In contrast, xenon has no effect on ventricular contractility, conduction, or major cation currents.[98,99] consistent with its lack of significant cardiovascular effects. Nitrous oxide causes mild reductions in ventricular function[99] by poorly characterized effects on Ca^{2+} availability. This is usually accompanied by sympathetic nervous system stimulation that increases vascular resistance and counteracts the myocardial depression.[100,101]

Volatile anesthetics can produce vasodilation at clinical concentrations.[102] (Also see Chapter 28.) The vascular effects of volatile anesthetics are multifactorial and tissue specific, and the precise cellular mechanisms are poorly understood.[103,104] Peripheral vasodilation is mediated by both direct endothelium-independent vasodilating effects on vascular smooth muscle cells and indirect effects involving the sympathetic nervous system and the vascular endothelium. The mechanisms of these effects involve agent-specific effects on presynaptic norepinephrine release, inhibition of smooth muscle Ca^{2+} influx via L-type Ca^{2+} channels, activation of hyperpolarizing adenosine triphosphate (ATP)-sensitive K^+ (K_{ATP}) and K-Ca channels, and endothelium-dependent factors, including nitric oxide production.[105] As with the CNS, cardiovascular function depends on the integrated function of multiple ion channels, many of which are expressed in both of these excitable tissues. Volatile anesthetics have agent-specific effects on heart rate and induction of arrhythmias caused by actions on cardiac ion channels. Because multiple cardiac ion channels are sensitive to volatile anesthetics at clinical concentrations, and because most manipulations of cardiac ion channel function are potentially proarrhythmic, it is difficult to link anesthetic arrhythmogenicity to actions on specific channels.[106] Electrophysiologic studies indicate that cardiac L-type Ca^{2+} channels, which are critical to the plateau phase of the cardiac action potential and electromechanical coupling, are inhibited by volatile anesthetics, leading to shortening of the refractory period. Multiple voltage-gated K^+ channels are also inhibited and might predispose to arrhythmias by delaying repolarization. Alternatively, inhaled anesthetics can protect the heart against ischemia and reperfusion injury, possibly involving antioxidant, antiinflammatory, and/or preconditioning mechanisms.[107,108] Volatile anesthetics[109] and xenon[110] can mimic the strong cardioprotective effects produced by ischemic preconditioning (termed anesthetic preconditioning by analogy) through activation of various cytoprotective G-protein–coupled receptors and protein kinases, including protein kinase C (PKC), mitogen-activated protein kinases (MAP kinases), extracellular signal–regulated kinases (ERK), Akt (protein kinase B), and tyrosine kinases.[95,111] Although not entirely clarified, sarcolemmal and putative mitochondrial K_{ATP} channel activation, involving PKC activation and increased formation of free radicals and nitric oxide, are the likely end effectors of anesthetic preconditioning in the heart.

Mechanisms of Respiratory Effects

Inhaled anesthetics also have important effects on the respiratory system. All volatile anesthetics cause significant respiratory depression at concentrations necessary for surgical anesthesia. The peripheral chemo-reflexes and upper airway patency are particularly sensitive to subanesthetic concentrations of volatile anesthetics.[112] The mechanisms involved in these potentially serious effects involve depression of central respiratory networks mediated by depression of excitatory and facilitation of inhibitory transmission. The precise molecular targets responsible for the exquisite sensitivity of these networks to low concentrations of volatile anesthetics remain to be elucidated (see Chapters 19 and 27).

IDENTIFICATION OF MOLECULAR SITES OF ANESTHETIC ACTION

CRITERIA FOR IDENTIFYING SITES RELEVANT TO ANESTHESIA

Specific criteria have been proposed to evaluate the relevance of the many potential molecular targets of anesthetics.[113] These criteria include:

1. *Reversible alteration of target function at clinically relevant concentrations*. This criterion requires comparable in vivo and in vitro sensitivity and depends on the anesthetic end point under consideration. For example, targets involved in immobility must be sensitive to anesthetics near MAC, whereas targets mediating amnesia must be affected at a fraction of MAC. Recent evidence for persistent effects of inhaled anesthetics demonstrable in the absence of continued anesthetic exposure is challenging the notion of reversibility for certain effects.
2. *Expression of the target in appropriate anatomic locations to mediate the specific anesthetic end point*. For example, immobilization by inhaled agents appears to involve primarily actions in the spinal cord independent of actions in the brain.
3. *Concordant stereoselectivity of anesthetic effects in vivo and on the target in vitro*. Without a specific pharmacologic antagonist of anesthesia, correlation between the stereoselective actions of general anesthetics in vivo and in vitro is a useful test of pharmacologic relevance of putative molecular targets. Stereoselectivity data correlating in vivo potency and in vitro receptor actions implicate $GABA_A$ receptors as a target for the anesthetic actions of etomidate, pentobarbital, neurosteroid anesthetics, and possibly isoflurane.
4. Appropriate sensitivity or insensitivity to model anesthetic and nonanesthetic compounds. Anesthetic halogenated cyclobutanes together with structural analogs that do not produce anesthesia at concentrations predicted to be anesthetic by the Meyer-Overton correlation (nonimmobilizers) can be used to discriminate relevant volatile anesthetic targets in vitro. For example, the anesthetic F3 (1-chloro-1,2,2-trifluorocyclobutane), but not the structurally similar nonanesthetic F6 (1,2-dichlorohexafluorocyclobutane), affect $GABA_A$, glycine, AMPA, kainite, and 5-HT3 receptors, and Na^+ channels, consistent with possible roles in immobility, whereas both F3 and F6 affect neuronal nicotinic, M1 muscarinic, 5-HT2C, and mGluR5 receptors, indicating that these targets are not involved in immobility. F6 is interesting in that it lacks sedative and immobilizing effects but does possess amnesic effects, hence the more accurate term *nonimmobilizer*, making it a useful pharmacologic tool for discriminating targets for these actions.
5. *Predictable effects of genetic manipulations targeted to putative molecular targets*. The effects of targeted deletion of specific molecules implicated as anesthetic targets (knockout mutations) or genetic engineering to introduce specific mutations that modify anesthetic sensitivity (knock-in mutations) in model organisms provide powerful approaches to test the roles of putative molecular targets of anesthetic action. This approach has been particularly successful in implicating specific $GABA_A$ receptor subtypes in the effects of the GABAergic intravenous anesthetics propofol and etomidate, where single amino acid substitutions in specific receptor subtypes eliminates anesthetic effects both in vitro and in vivo.[114] Targeted mutations of putative anesthetic targets provide a bridge between in vitro observations and whole-animal experiments essential for demonstrating anesthetic end points. The existence of multiple targets and redundancy among ion channel subtypes make this a more challenging experimental approach for inhaled anesthetics compared with intravenous anesthetics (discussed later).

PHYSICOCHEMICAL PROPERTIES OF ANESTHETIC BINDING SITES

A convergence of x-ray crystallography, molecular modeling, and structure-function studies indicate that inhaled anesthetics bind in hydrophobic cavities formed within proteins.[14,115] The lipophilic (or hydrophobic) nature of these binding sites explains their adherence to the Meyer-Overton correlation. An element of amphiphilicity (possessing both polar and nonpolar characteristics) is also required for effective interaction with these cavities, as indicated by improvements in the Meyer-Overton correlation with more amphipathic solvents (possessing both hydrophobic and hydrophilic properties).

FROM MODEL PROTEINS TO RECEPTORS

Identifying inhaled anesthetic binding sites on plausible target proteins is difficult because of their low-affinity interactions, the paucity of atomic resolution structures of pharmacologically relevant target proteins, and the lack of specific antagonists. Consequently, most anesthetic binding sites have been identified in well-characterized model proteins for which three-dimensional atomic resolution structures are available, but which are not themselves relevant to anesthesia, such as luciferase and albumin.[14,115] These studies indicate that anesthetics bind in pockets with both nonpolar and polar noncovalent chemical interactions. Binding involves weak hydrogen bond interactions with polar amino acid residues and water molecules, nonpolar van der Waals interactions, and a polarizing effect of the amphiphilic binding cavity on the relatively hydrophobic anesthetic molecules. Internal cavities are important for the conformational flexibility required for ion channel gating and ligand-induced signal transduction of receptor proteins. Occupation of a critical volume within these cavities by anesthetics provides a plausible mechanism for alteration of receptor and ion channel function by selective stabilization of a particular confirmation (e.g., an open or inactivated state of an ion channel). Anesthetics also gain binding energy from the entropy generated by displacing bound water from these relatively promiscuous binding sites. Studies of glycine, $GABA_A$, and NMDA receptors provide convincing evidence for the existence of anesthetic binding sites in critical neuronal signaling proteins.[14] Amino acid

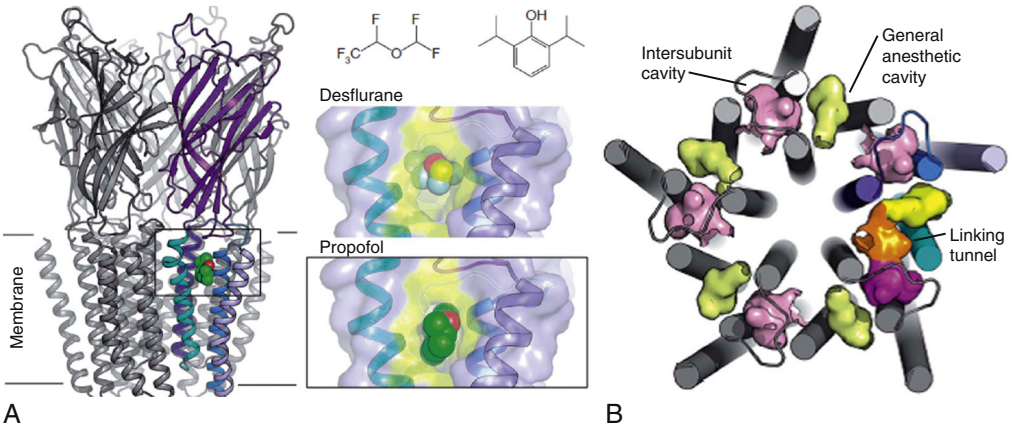


Figure 25-6. X-ray structures of propofol and desflurane bound to a pentameric ligand-gated ion channel. **A,** Cartoon of membrane-plane view of the bacterial homologue of mammalian pentameric ligand-gated ion channels (*Gloebacter violaceus* [GLIC]) with a bound general anesthetic molecule. **B,** Molecular surface of the general anesthetic intrasubunit cavities *(yellow)* and neighboring intersubunit cavities *(pink)* of the whole pentameric channel. *(Modified from Nury H, et al: X-ray structure of general anaesthetics bound to a pentameric ligand-gated ion channel,* Nature *469:428-433, 2011.)*

residues critical for volatile anesthetic actions, and, by inference, binding, have been identified in the α-subunit of the $GABA_A$ receptor.[14]

Structural studies using the more accessible prokaryotic homologues of eukaryotic ion channels have provided a powerful tool for the study of anesthetic binding sites in biologically plausible proteins. For example, both propofol and desflurane have been co-crystalized with GLIC, a bacterial homologue of eukaryotic inhibitory ligand-gated ion channels (glycine and $GABA_A$ receptors). Both anesthetics bind a common preexisting site in the upper part of the transmembrane domain between the transmembrane segments of a single subunit (Fig. 25-6).[116] Molecular modeling based on structurally homologous proteins has also been used to identify putative anesthetic binding sites in the transmembrane domains of vertebrate $GABA_A$ and glycine receptors (Fig. 25-7). These models suggest that different drugs may either bind in different orientations within a single amphiphilic cavity or occupy different cavities within the protein, causing similar functional effects. Refinement of these molecular models will continue to provide new insights in the molecular basis for general anesthetic action that can be experimentally tested. For example, potential sites of interaction of xenon and isoflurane with the NMDA receptor have also been identified using this approach. One site, which can contain up to three xenon atoms or one molecule of isoflurane, overlaps the known binding site for the co-agonist glycine in the NR1 subunit.[117] This suggests that two chemically dissimilar inhaled anesthetics inhibit NMDA receptors by direct competitive inhibition of co-agonist binding.

Molecular Targets of Inhaled Anesthetics

Ion channels have emerged as the most promising molecular targets for inhaled anesthetics. Neurotransmitter-gated ion channels, in particular $GABA_A$, glycine, and NMDA-type glutamate receptors, are leading candidates owing to their appropriate CNS distributions, essential physiologic roles in inhibitory and excitatory synaptic transmission, and sensitivities to clinically relevant concentrations of anesthetics.[16,118] Other ion channels that are sensitive to inhaled anesthetics include the hyperpolarization-activated cyclic nucleotide (HCN)-gated family of channels that give rise to pacemaker currents[118] and regulate dendritic excitability, two-pore domain (K_{2P}) "leak" K^+ channels that maintain resting membrane potential in many cells,[119] and voltage-gated Na^+ and Ca^{2+} channels.[118]

Inhaled anesthetics can be divided into two classes based on their distinct pharmacologic properties. The first class is the potent inhaled (volatile) anesthetics, which exhibit positive modulation of $GABA_A$ receptors and also produce significant, anesthesia-compatible effects on a number of other receptors/channels, including enhancement of inhibitory glycine receptors, inhibition of excitatory NMDA and neuronal nicotinic acetylcholine receptors, activation of K_{2P} channels, and inhibition of presynaptic Na^+ channels. Intravenous anesthetics such as propofol and etomidate represent more potent and specific positive modulators of $GABA_A$ receptors. The second class is the gaseous inhaled anesthetics, which include cyclopropane, nitrous oxide, and xenon. These anesthetics are inactive at $GABA_A$ receptors but block NMDA receptors and activate certain K_{2P} channels at clinical concentrations.

LIGAND-GATED ION CHANNELS

Potentiation of Inhibitory $GABA_A$ and Glycine Receptors

The ether anesthetics (including isoflurane, sevoflurane, and desflurane), the alkane anesthetic halothane, most intravenous anesthetics (including propofol, etomidate, barbiturates), and the neurosteroid anesthetics enhance $GABA_A$ and glycine receptor (GlyR) function. $GABA_A$ and GlyRs are members of the same cys-loop ligand-gated ion channel superfamily that also includes the cation-permeable nicotinic acetylcholine and $5HT_3$ receptors. $GABA_A$ receptors are the principal transmitter-gated Cl^- channels in the neocortex and allocortex, whereas GlyRs

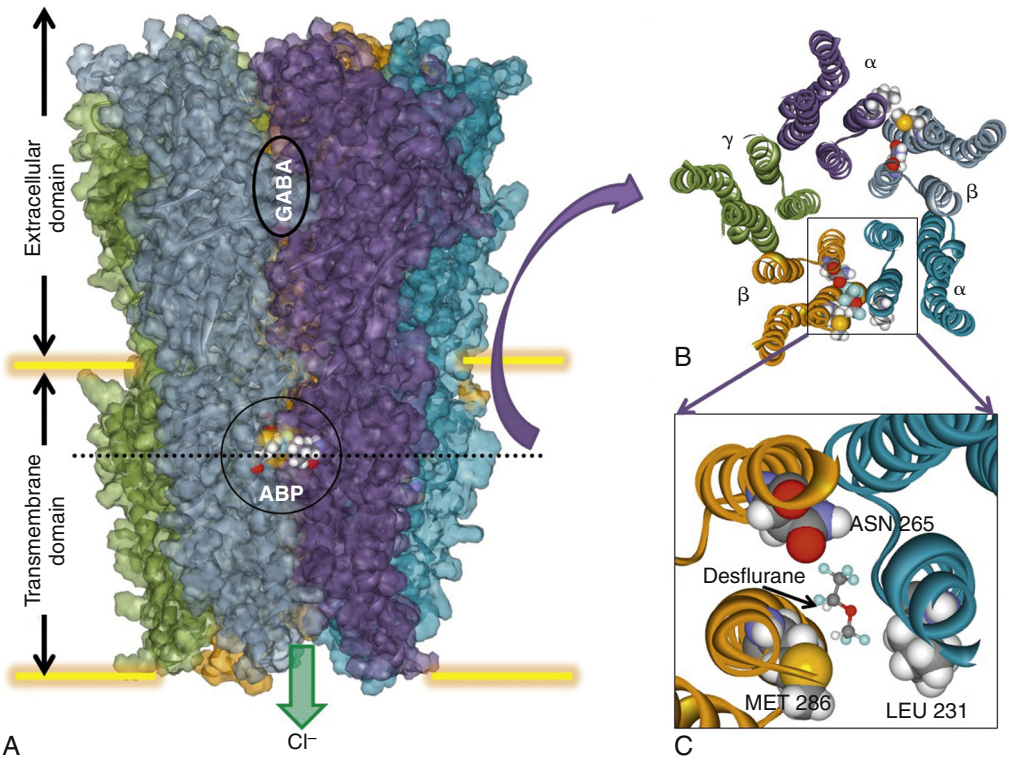


Figure 25-7. Putative anesthetic binding sites on $GABA_A$ receptors identified by molecular modeling. **A,** Molecular model of the mouse $GABA_A$ receptor built using homology modeling techniques with computational chemistry optimizations and molecular dockings. The amino acid backbone is displayed in ribbon format and outlined by the transparent solvent-accessible molecular surface. Each of the five subunits is colored uniquely. The GABA binding site is noted in the extracellular domain, whereas the putative anesthetic binding pocket (ABP) for potentiation is noted in the outer third of the transmembrane domain between the α and β subunits. Two binding sites are shown but only one has computationally docked desflurane. **B,** Cross-section at the *dotted line* level in **A** showing orientation of subunits with pentameric symmetry about a central ion pore. **C,** Magnified region of intersubunit anesthetic binding site derived from region in **B** showing relevant amino acid positions (in space-filling format) interacting with desflurane (in ball-and-stick format at the same scale). *(Courtesy the Bertaccini laboratory, Stanford University.)*

fulfill this function in the spinal cord, with some overlap in the diencephalon and brainstem. Activated receptors conduct chloride ions, driving the membrane potential toward the Cl^- equilibrium potential. Both receptors are inhibitory because the Cl^- equilibrium potential is usually more negative than the normal resting potential. Channel opening also reduces membrane resistance and "shunts" excitatory responses. Most functional $GABA_A$ and GlyRs are heteropentamers, typically consisting of three different $GABA_A$ subunits (e.g., two α, two β, and one γ or ∂) or two different GlyR subunits (three α and two β).[120] The subunit composition of $GABA_A$ receptors determines their physiologic and pharmacologic properties and varies between and within brain areas, as well as between different compartments of individual neurons. Examples are the preferential expression of the α_5-subunit in the dendritic field of the hippocampal CA1 area (a region important for memory formation), of the α_4-subunit in the thalamus, and of the α_6-subunit in the cerebellum. Presence of a γ-subunit is required for benzodiazepine modulation of $GABA_A$ receptors and can also influence modulation by inhaled anesthetics. Although the molecular mechanisms of receptor modulation by inhaled anesthetics are not clear, these receptors have been key to our understanding of anesthetic-receptor interactions. Using chimeric receptor constructs between anesthetic-sensitive $GABA_A$ and insensitive GlyR subunits, specific amino acid residues in transmembrane domains 2 and 3 critical to the action of inhaled anesthetics have been identified.[121] This laid the groundwork for the construction of anesthetic-resistant $GABA_A$ receptors and the generation of transgenic mice with altered anesthetic sensitivity (discussed later).

The related cation-permeable 5-hydroxytryptamine (serotonin)-3 ($5HT_3$) receptors are similarly potentiated by volatile anesthetics.[122] $5HT_3$ receptors are involved with autonomic reflexes and also probably contribute to the emetogenic properties of volatile anesthetics (see Chapter 97).

Inhibition of Excitatory Acetylcholine and Glutamate Receptors

Neuronal nicotinic acetylcholine receptors (nnAChRs), like the other members of the cys-loop family, are heteropentameric ligand-gated ion channels, but are cation selective. They are composed of α- and β-subunits, but functional homomeric receptors can be formed by certain α-subunits. In the CNS, nnAChRs are localized primarily presynaptically.[123] Homomeric α_7-receptors have high permeability to Ca^{2+} that can exceed that of NMDA receptors.[123] In contrast to $GABA_A$ and GlyRs, nnAChRs pass cations when activated and therefore depolarize

the membrane potential. Receptors containing $\alpha_4\beta_2$ subunits are very sensitive to block by isoflurane and propofol.[124,125] Relevance of nnAChR block to immobilization, sedation, and unconsciousness by inhaled anesthetics is unlikely because nnAChRs are also blocked by nonimmobilizers, although it is possible that they do contribute to amnesia.

NMDA receptors are a major postsynaptic receptor subtype of inotropic receptors for glutamate, the principal excitatory neurotransmitter in the mammalian CNS.[126] Typical NMDA receptors, defined pharmacologically by their selective activation by the exogenous agonist NMDA, are heteromers consisting of an obligatory GluN1 subunit and modulatory GluN2 subunits. Channel opening requires glutamate (or another synthetic agonist such as NMDA) binding to the GluN2 subunit while the endogenous co-agonist glycine binds to the GluN1 subunit. NMDA receptors also require membrane depolarization to relieve voltage-dependent block by Mg^{2+}. Depolarization is typically provided by binding of glutamate to non-NMDA glutamate receptors (discussed later). Because of this requirement for both presynaptic transmitter release and postsynaptic depolarization, synaptic NMDA receptors function as coincidence detectors, and this characteristic is thought to be central to their role in learning and memory. NMDA receptors are also involved in the development of chronic pain, perhaps because of mechanisms similar to those underlying synaptic plasticity, and in ischemia-induced excitotoxicity by virtue of their capacity to allow entry of the ubiquitous intracellular signal Ca^{2+}. The nonhalogenated inhaled anesthetics xenon, nitrous oxide, and cyclopropane have minimal effects on $GABA_A$ receptors but depress excitatory glutamatergic synaptic transmission postsynaptically via NMDA glutamate receptor blockade (see Fig. 25-8).[70,127] Volatile anesthetics can also inhibit isolated NMDA receptors at higher concentrations.[128] Along with presynaptic inhibition of glutamate release, this might contribute to their depression of NMDA receptor–mediated excitatory transmission.

A second class of inotropic glutamate receptors includes the non-NMDA receptors, which are subdivided into α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors based again on their sensitivities to selective exogenous agonists.[126] Inhaled anesthetics only weakly inhibit AMPA receptors, hence this action is unlikely to be important in their actions.[129] Interestingly, kainate receptors are enhanced by inhaled anesthetics, but this is unlikely to be involved in immobility because MAC is not altered in mice deficient in the GluR6 receptor subunit.[130] Most evidence suggests that the principal mechanism for depression of glutamatergic transmission by volatile anesthetics is presynaptic, with minor contributions from postsynaptic receptor blockade[131-133] (see "Cellular Mechanisms").

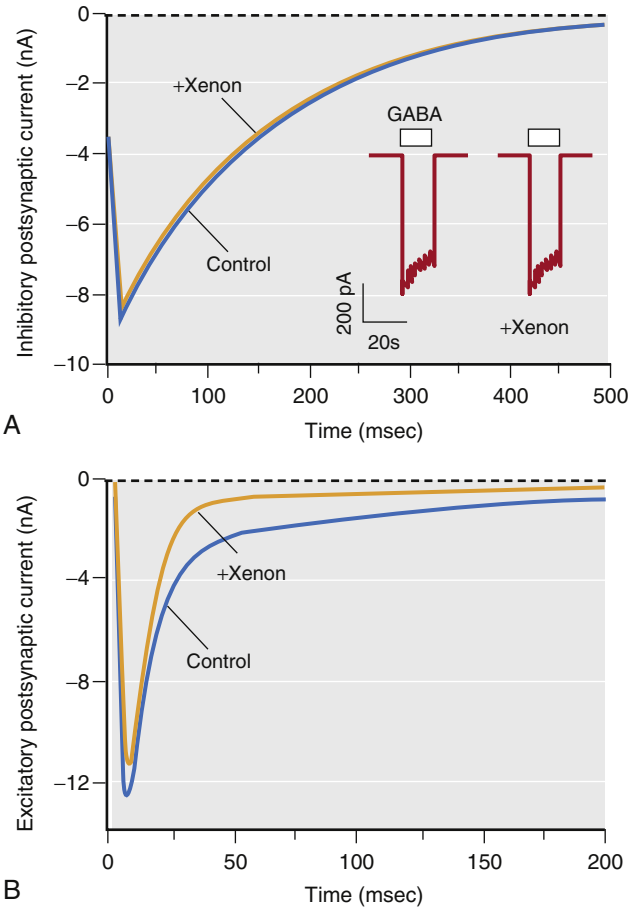


Figure 25-8. The actions of xenon on inhibitory GABAergic and excitatory glutamatergic synapses in cultured rat hippocampal neurons. Xenon (3.4 mM, ~1 MAC) has no significant effect on the inhibitory postsynaptic current (**A**) but depresses the excitatory glutamatergic synaptic current, almost exclusively the slow NMDA receptor-mediated component of the current (**B**). In contrast, the principal effects of ~1 MAC isoflurane are a prolongation in the inhibitory current decay and a reduction in excitatory current peak height, with little change in time course (not shown, see Fig. 25-10). *(Reprinted in modified form by permission from de Sousa SLM, et al: Contrasting synaptic activity of the inhalational general anesthetics isoflurane and xenon,* Anesthesiology *92:1055-1066, 2000.)*

VOLTAGE-GATED AND OTHER ION CHANNELS

Inhibition of Excitatory Na^+ Channels

Voltage-gated Na^+ channels are critical to axonal conduction, synaptic integration, and neuronal excitability. In contrast to findings in invertebrate giant axons,[134] axonal conduction in small (0.1 to 0.2 μm) unmyelinated hippocampal axons is depressed by volatile anesthetics,[135,136] and small reductions in preterminal action potential amplitude significantly depress transmitter release and hence postsynaptic responses at a mammalian synapse.[137] Heterologously expressed mammalian voltage-gated Na^+ channels are sensitive to clinically relevant concentrations of volatile anesthetics. The Na^+ channel family consists of nine homologous pore-forming α-subunits with distinct cellular and subcellular distributions.[138] Isoflurane and other volatile anesthetics inhibit the major mammalian Na^+ channel isoforms, including neuronal ($Na_v1.2$), skeletal muscle ($Na_v1.4$), cardiac ($Na_v1.5$), and peripheral ($Na_v1.8$) isoforms.[139] Volatile anesthetics, but not nonimmobilizers, also inhibit native neuronal and nerve terminal Na^+ channels,[140-143] lending support to the notion that Na^+

channel blockade contributes to the depression of synaptic neurotransmitter release.[143] In contrast, xenon has no detectable effect on Na^+, Ca^{2+}, or K^+ channels in isolated cardiomyocytes.[92] The demonstration that NaChBac, a prokaryotic homologue of voltage-gated Na^+ channels, is also inhibited by volatile anesthetics opens the way for structure-function studies of these channels.[141]

Inhibition of Ca^{2+} Channels

Multiple cellular functions depend on the tightly controlled concentration of intracellular free Ca^{2+} ($[Ca^{2+}]_i$), which is determined by the integrated activities of voltage-gated Ca^{2+} channels, capacitative Ca^{2+} channels, plasma membrane and sarcoplasmic/endoplasmic reticulum Ca^{2+}-adenosine triphosphatases (pumps), Na^+/Ca^{2+} exchangers, and mitochondrial Ca^{2+} sequestration. Alteration of any of these mechanisms by anesthetics can affect the many cellular processes regulated by the second messenger actions of Ca^{2+}, including synaptic transmission, gene expression, cytotoxicity, and muscle excitation–contraction coupling. Excitable cells translate their electrical activity into action by Ca^{2+} fluxes mediated primarily by voltage-gated Ca^{2+} channels in the plasma membrane. Distinct Ca^{2+} channel subtypes are expressed in various cells and tissues and are classified pharmacologically and functionally by the degree of depolarization required to gate the channel, such as low voltage–activated (LVA; T-type) and high voltage–activated (HVA; L-, N-, R-, and P/Q-type) channels. More recently, the molecular identity of their pore-forming α-subunits has been used for classification.[144] There is convincing evidence that volatile anesthetics inhibit certain Ca^{2+} channel isoforms but not others.[145]

Inhibition of presynaptic voltage-gated Ca^{2+} channels coupled to transmitter release has been proposed as a mechanism by which volatile anesthetics reduce excitatory transmission.[146] Indeed, N-type ($Ca_v2.2$) and P-type ($Ca_v2.1$) channels, which mediate Ca^{2+} entry coupled to neurotransmitter release, are modestly sensitive to volatile anesthetics,[147,148] but not in all neuron types,[149] suggesting the importance of auxiliary subunits, posttranslational modification, or other potential modulators of anesthetic sensitivity. A modest contribution of R-type Ca^{2+} channels ($Ca_v2.3$) to anesthesia is suggested by their sensitivity to volatile anesthetics and a small increase in MAC produced by genetic deletion in mice.[150] T-type Ca^{2+} channels are particularly sensitive to volatile anesthetics[151] and nitrous oxide.[152] However, mutant mice lacking a major neuronal T-type Ca^{2+} channel isoform ($Ca_v3.1$) have normal volatile anesthetic sensitivity, although the onset of anesthesia is delayed.[153] Thus the role that inhibition of these or other Ca^{2+} channels play in the CNS effects of inhaled anesthetics is unclear.

By contrast, a role for Ca^{2+} channel inhibition in the negative inotropic effects of volatile anesthetics, prominent at higher doses, is well established. The force of myocardial contraction is determined by the magnitude of cytosolic Ca^{2+} increase after electrical excitation, the responsiveness of the contractile proteins to Ca^{2+}, and sarcomere length. Negative inotropic effects of volatile anesthetics are mediated by reductions in Ca^{2+} availability, Ca^{2+} sensitivity of the contractile proteins, and rate of cytosolic Ca^{2+} clearance. Volatile anesthetics reduce the Ca^{2+} transient and shorten action potential duration in cardiomyocytes primarily by inhibiting L-type ($Ca_v1.2$) Ca^{2+} currents, resulting in a negative inotropic effect and arrhythmogenicity.[97,106,154] In contrast, xenon does not depress myocardial function or inhibit L-type Ca^{2+}, Na^+, or K^+ currents in isolated cardiomyocytes.[98,99] Inhibition of trans-sarcolemmal Ca^{2+} influx through cardiac L-type Ca^{2+} channels plays a major role in the negative inotropic effects of volatile anesthetics—greatest for halothane—along with contributions from effects on myofilament Ca^{2+} sensitivity and sarcolemmal Ca^{2+} release.[106,155]

In contrast to voltage-gated Ca^{2+} channels that regulate the influx of extracellular Ca^{2+}, intracellular Ca^{2+} channels regulate Ca^{2+} release from intracellular stores, particularly the endoplasmic reticulum (ER) and sarcoplasmic reticulum (SR). These include 1,4,5-trisphosphate receptors (IP_3Rs), regulated by the second messenger IP_3, and ryanodine receptors (RyRs), which mediate the rapid release of intracellular Ca^{2+} critical to excitation-contraction coupling in muscle. Volatile anesthetic–induced Ca^{2+} leak occurs via both IP_3R and RyR channels, which leads to depletion of intracellular Ca^{2+} stores from the SR and ER. This blunts changes in intracellular Ca^{2+} in response to stimulation and contributes to the smooth muscle–relaxing properties of volatile anesthetics that underlie bronchodilation and vasodilation.[156] Malignant hyperthermia susceptibility is a pharmacogenetic disorder that manifests as a potentially fatal hypermetabolic crisis triggered by volatile anesthetics, particularly halothane. It is often associated with mutations in RyR1 and the physically associated L-type Ca^{2+} channel ($Ca_v1.1$) that functions as the voltage sensor.[157] Volatile anesthetics activate the abnormal RyRs, resulting in uncontrolled intracellular Ca^{2+} release, muscle contraction, and metabolic activity[158] (see Chapter 43).

K^+ Channels and HCN Channels

Potassium (K^+) channels are an extremely diverse ion channel family noted for their varied modes of activation. They regulate electrical excitability, muscle contractility, and neurotransmitter release. They are important in determining input resistance and in driving repolarization, and thus they determine excitability and action potential duration. Given the large diversity in K^+ channel structure, function, and anesthetic sensitivity, it is not surprising that there is considerable diversity in their sensitivity and response to inhaled anesthetics[159]: from relatively insensitive (voltage-gated K^+ channels $K_v1.1$, K_v3)[160] to sensitive (some members of the 2-pore domain K^+ channels [K_{2P}] family), resulting in either inhibition, activation, or no effect on K^+ currents.

Volatile anesthetic activation of certain "leak" K^+ channels was first observed in the snail *Lymnaea*,[161] although the molecular identity of the affected ion channels was unknown. Activation of K_{2P} channels by volatile and gaseous anesthetics, including xenon, nitrous oxide, and cyclopropane, was subsequently observed in mammals.[162] Increased K^+ conductance can hyperpolarize neurons, reducing responsiveness to excitatory synaptic input and possibly altering network synchrony. Targeted deletion of the TASK-1, TASK-3, and TREK-1 K_{2P} channels

in mice reduces sensitivity to immobilization by volatile anesthetics in an agent-specific manner, implicating these channels as contributory anesthetic targets in vivo.[32-34] Other members of this large family of K^+ channels are also sensitive to volatile anesthetics.[163]

The recognition that inherited channelopathies are arrhythmogenic and constitute an important contributor to sudden cardiac death,[164] particularly in young children,[165] highlights the importance of analyzing anesthetic modulation of cardiac ion channels. Recombinant hERG (human ether-a-go-go related) channels are moderately inhibited by halothane, and their depression likely contributes to arrhythmogenic effects of volatile anesthetics[106,166]; they are also involved in acquired (drug-induced) and inherited long QT syndrome. Cardiac inward-rectifying (K_{IR}), voltage-gated (K_v), and Ca^{2+}-activated K^+ channels are generally relatively insensitive to clinical concentrations of volatile anesthetics and xenon.[98,106,167] In contrast, there is considerable evidence that volatile anesthetics and xenon activate cardiac mitochondrial and sarcolemmal K_{ATP} channels,[107] an effect that plays a critical role in anesthetic preconditioning. Direct electrophysiologic effects of anesthetics with preconditioning properties have been demonstrated on both mitochondrial and sarcolemmal K_{ATP} channels, although the precise mechanisms remain to be clarified.

Volatile anesthetics also inhibit HCN pacemaker channels, reducing the rate of rise of pacemaker potentials and the bursting frequency of certain neurons that show autorhythmicity. They decrease the I_h conductance in neurons[168] and modulate recombinant HCN1 and HCN2 channel isoforms at clinically relevant concentrations.[169] Because HCN channels contribute to resting membrane potential; control action potential firing, dendritic integration, neuronal automaticity, and temporal summation; and determine periodicity and synchronization of oscillations in many neuronal networks,[170] the anesthetic modulation of these channels could play an important role in anesthetic effects on neuronal integrative functions.

INTRACELLULAR SIGNALING MECHANISMS

Cell signaling mechanisms are critical to all phases of organ function and have been attractive targets for explaining the broad effects of general anesthetics. Anesthetics have poorly understood actions on intracellular cell signaling pathways, which include processes downstream from cell surface receptors and ion channels, such as effects of second messengers, protein phosphorylation pathways, and other regulatory mechanisms.[171]

G Protein–Coupled Receptors

A variety of signals, including hormones, neurotransmitters, cytokines, pheromones, odorants, and photons, produce their intracellular actions by interactions with metabotropic receptors that activate heterotrimeric guanine nucleotide–binding proteins (G proteins). In contrast to the inotropic receptors that directly couple to ion-selective channels, G proteins act as indirect molecular switches to relay information from activated plasma membrane receptors to appropriate intracellular targets. Heterotrimeric G proteins consist of a large α-subunit and a smaller β/γ-subunit dimer, each expressed as multiple isoforms with distinct properties and downstream targets. G proteins regulate a plethora of downstream effectors to control the levels of cytosolic second messengers such as Ca^{2+}, cyclic adenosine monophosphate, and inositol triphosphate. These in turn regulate effector proteins such as ion channels and enzymes, either directly or via second messenger–regulated protein phosphorylation pathways. Drugs that act through G protein–coupled receptors (GPCRs), such as agonists for μ-opioid and α_2-adrenergic receptors, can affect anesthetic sensitivity (reduce MAC). Inhaled anesthetics can also directly affect signaling via GPCRs.[172] For example, volatile anesthetics activate multiple olfactory GPCRs in the rat in vivo in a receptor- and agent-selective manner.[173] Analogous effects on related GPCRs more relevant to critical anesthetic end points are possible but remain to be demonstrated. The observation that both volatile anesthetics and nonimmobilizers inhibit mGluR5 glutamate receptors, 5-HT_{2A} serotonin receptors, and muscarinic acetylcholine receptors suggests that these GPCR effects do not contribute to anesthetic immobilization.[174-176]

Protein Phosphorylation

Phosphorylation of proteins on specific serine, threonine, or tyrosine hydroxyl groups, a posttranslational modification involved in the regulation of many anesthetic-sensitive receptors and ion channels, is pivotal to synaptic plasticity (e.g., long-term potentiation [LTP]). Phosphorylation is controlled by the balance of activity between protein kinases and phosphatases, several of which are plausible anesthetic targets. The protein kinase C (PKC) family of multifunctional protein kinases is activated by the lipid-signaling molecule diacylglycerol and is involved in the regulation of many ion channels and receptors. Halothane[177] and sevoflurane[178] enhance the activity of some PKC isoforms and stimulate phosphorylation of specific PKC substrates. Structural studies have identified a potential binding site in the diacylglycerol binding domain of PKCδ, consistent with the ability of certain anesthetics to mimic this natural regulator by binding to the activating site.[179] A specific role for a direct pharmacologically relevant effect mediated by anesthetic activation of PKC or of any other kinase has yet to be demonstrated. Intrathecal injection of isoform-specific inhibitors of PKC does not affect sensitivity to halothane in vivo.[180] Knock-out mice lacking the PKCγ isoform show normal sensitivity to halothane and desflurane while isoflurane MAC was increased,[181] suggesting that PKC is not critical to volatile anesthetic immobilization.

An important role for effects of volatile anesthetics and xenon on cell signaling mechanisms has been discovered for anesthetic-induced preconditioning in the heart (see Chapter 28) and brain against ischemic damage.[83,87,81,85,109] Anesthetic-induced and ischemic cardiac preconditioning share critical signaling mechanisms, including activation of multiple GPCRs (e.g., adenosine, opioid, adrenergic) and protein kinases (e.g., src kinase, PKCδ, PKCε, Akt, mitogen-activated protein kinases [MAPKs]) and their downstream targets, particularly sarcolemmal and/or mitochondrial K_{ATP} channels, possibly

initiated by changes in reactive oxygen species as the critical second messenger.[95] Volatile anesthetics and xenon share cardioprotective and neuroprotective effects involving these signaling pathways.[109]

The effects of anesthetics on the phosphorylation of individual residues in specific substrates can be studied using phosphorylation state–specific antibodies that are able to detect the phosphorylated forms of kinase substrates. A comparison of the effects of three mechanistically diverse anesthetics (isoflurane, propofol, and ketamine) on critical intracellular protein phosphorylation signaling pathways that are known to integrate multiple second messenger systems reveals both shared and agent-specific actions in vivo.[182] All three anesthetics reduce phosphorylation of activating sites on NMDA and AMPA glutamate receptors and of the downstream extracellular signal-regulated kinase ERK2, which are known to be involved in synaptic plasticity, consistent with depression of normal glutamatergic synaptic transmission in the anesthetized mouse cerebral cortex. These effects are somewhat selective in that several other PKA substrates examined are not affected, indicating substrate-specific effects rather than a general inhibition of PKA activity.[183] Additional studies will be required to determine which anesthetic effects on kinase pathways represent direct effects, as occurs with PKC, and which are indirect because of anesthetic-induced alterations in signaling molecules known to regulate protein kinase and phosphatase activity such as Ca^{2+} and other second messengers.

Gene Expression

The ability of general anesthetics to alter gene expression in the brain was first observed for the highly reactive immediate early genes c-*fos* and c-*jun*.[184] Anesthetic effects on gene expression have since been observed for multiple anesthetics and organs.[185] In the hippocampus of aged rats, changes in gene expression persisted for up to 2 days in rats exposed to isoflurane and nitrous oxide,[186] and changes in protein expression have been observed 3 days after exposure to desflurane.[187] The significance of these changes in gene and protein expression persisting after recovery from the classic signs of anesthesia remains to be established (see review[77]).

CELLULAR MECHANISMS

NEURONAL EXCITABILITY

Neuronal excitability is determined by resting membrane potential, threshold for action potential initiation, and input resistance (an indication of overall channel activity), which can differ between compartments within an individual neuron owing to subcellular specializations (e.g., soma versus dendrite). Neurons show considerable diversity, and therefore anesthetic effects vary between neuronal populations with the state of the individual neuron and its network—that is, whether it is hyperpolarized or depolarized, stimulated by synaptic inputs, or quiescent. Therefore it should be recognized that results obtained even from traditional acute slice preparations only incompletely reflect anesthetic effects on neurons in vivo.

The intrinsic excitability of lumbar spinal motoneurons in vivo appears to be little affected by halothane.[188] Anesthetic effects on the firing properties of hippocampal pyramidal neurons are complex: increased or decreased thresholds and regional differences and dose-dependent effects on firing patterns have been reported.[189,190] By contrast, neurons in the ventral-posterior nucleus of the thalamus (possibly thalamic relay neurons) hyperpolarize in the presence of isoflurane and are less likely to fire action potentials because of a decrease in input resistance (increased shunting), attributed to increased K^+ conductance.[191] Similar effects are observed in hypoglossal motoneurons and neurons from the locus coeruleus, where a TASK-type K_{2P} channel has been causally implicated.[192]

A role for $GABA_A$ receptors located at extrasynaptic sites may include volatile anesthetic effects (Fig. 25-9). Extrasynaptic $GABA_A$ receptors, which differ from synaptic receptors in their subunit composition, mediate tonic inhibition (as opposed to phasic inhibition mediated by synaptic $GABA_A$ receptors) and are remarkably sensitive to many general anesthetics. Extrasynaptic $GABA_A$ receptors have a high affinity for GABA, desensitize slowly, and are tonically exposed to low ambient GABA concentrations,[193] at which the potentiating effect of anesthetics is most significant. The effects of anesthetics on tonic inhibition have been characterized in the hippocampus, which is critically involved in learning and memory. Hippocampal neurons generate a robust tonic current via activation of α_5-subunit–containing $GABA_A$ receptors[194-197] that are highly sensitive to etomidate, propofol, midazolam, and isoflurane. $GABA_A$ receptors containing the α_5-subunit are highly sensitive to low concentrations of propofol and isoflurane that produce amnesia but not unconsciousness, and may also be involved in their longer-lasting cognitive effects (discussed earlier). (Also see Chapters 26, 30, and 99.) Receptors containing α_5-subunits also contribute to slow phasic (synaptic) currents that have been discovered in many brain regions.[198] In the hippocampus, these currents termed $GABA_{Aslow}$ are substantially modulated by both etomidate and isoflurane at amnesic concentrations. The slow time course and the location of $GABA_{Aslow}$ matches that of synaptic NMDA receptor–mediated inputs in hippocampal pyramidal cells, placing them therefore in an ideal position to modulate synaptic plasticity. Thus these receptors provide a potential substrate for the amnesic properties of anesthetics.

PRESYNAPTIC VERSUS POSTSYNAPTIC EFFECTS ON SYNAPTIC TRANSMISSION

General anesthetics have potent and specific effects on synaptic transmission, including presynaptic actions (by altering transmitter release) and postsynaptic actions (by altering the postsynaptic responses of neurons to specific transmitters). The relative contributions of presynaptic compared with postsynaptic anesthetic effects on synaptic transmission have been difficult to resolve, probably because the effects are transmitter and synapse specific. The net effect of anesthetics on synaptic transmission is

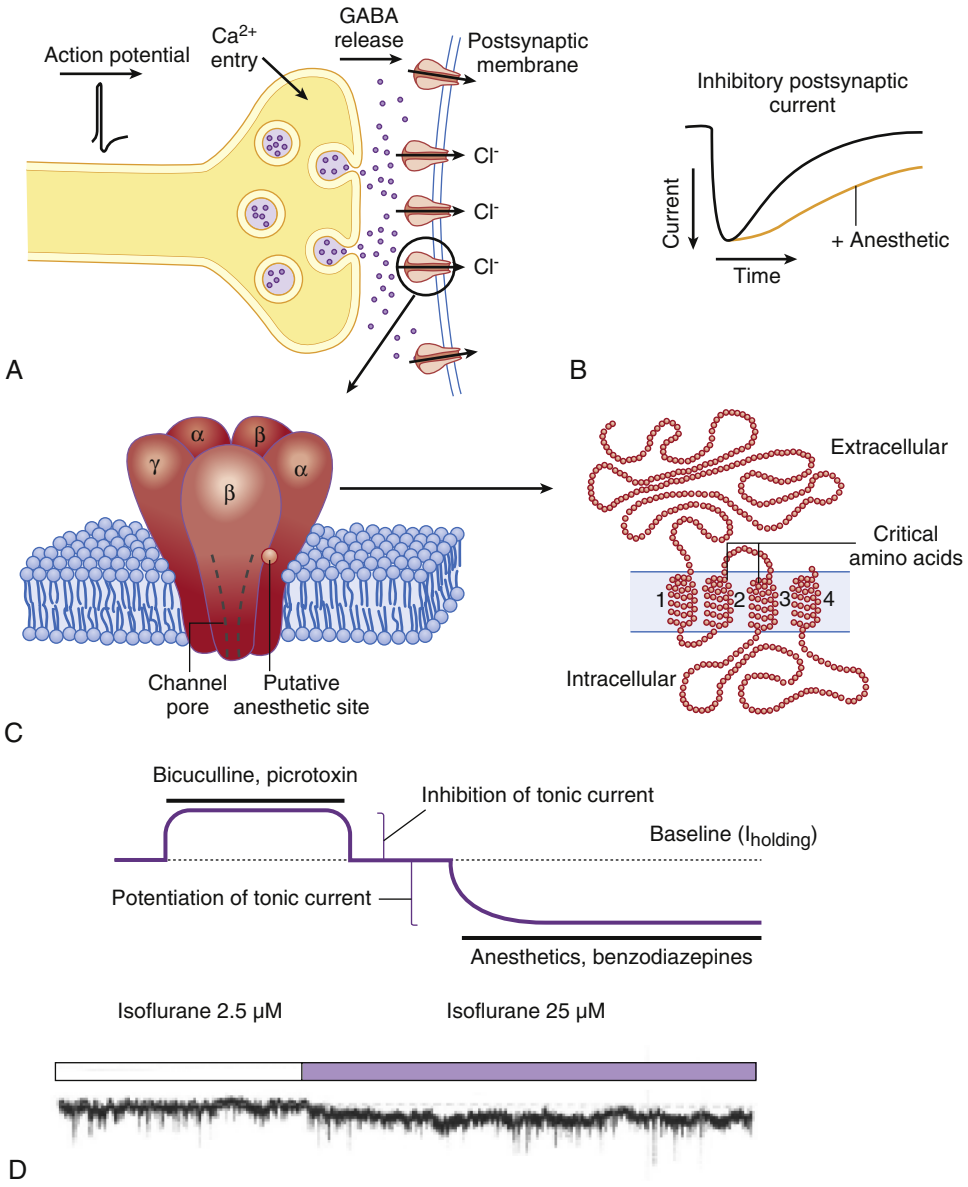


Figure 25-9. Synaptic and extrasynaptic $GABA_A$ receptors are targets for inhaled anesthetics. **A,** On binding of GABA (γ-aminobutyric acid) to the $GABA_A$ receptor, its chloride-permeable channel opens, leading to hyperpolarization. Volatile anesthetics have a relatively low potency but high efficacy at synaptic $GABA_A$ receptors and a high potency and low efficacy at extrasynaptic $GABA_A$ receptors. **B,** General anesthetics prolong channel opening and increase postsynaptic inhibition. The cartoon illustrates the prolongation of miniature inhibitory postsynaptic currents (mIPSCs) by the slowing of current decay. **C,** A pentameric $GABA_A$ receptor complex in the lipid bilayer membrane *(left),* with a blow-up of a single subunit showing the location of residues critical to anesthetic efficacy in the second and third transmembrane domains *(right).* **D,** A tonic inhibitory conductance is revealed by the application of a $GABA_A$ receptor antagonist (bicuculline or picrotoxin), as shown by the upward shift in the baseline current. Anesthetics and benzodiazepines increase the tonic conductance as indicated by the inward shift in the current. *(Modified from Hemmings HC Jr, Akabas MH, Goldstein PA, et al: Emerging molecular mechanisms of general anesthetic action,* Trends Pharmacol Sci *26:503-510, 2005.)*

determined by the relative magnitude and direction of both their presynaptic and postsynaptic effects.

Synaptic excitation is decreased by volatile anesthetics (Fig. 25-10). Experiments in various slice preparations indicate that reduced excitation is primarily caused by presynaptic mechanisms.[131,188,199-202] A postsynaptic mechanism is also involved because the response to directly applied glutamate is reduced to some degree.[202-204] Volatile anesthetics have inconsistent effects on cloned AMPA or NMDA glutamate receptors, but they potentiate kainite receptors,[117,205-207] which is consistent with a predominantly presynaptic mechanism for inhibition of glutamatergic synapses. By contrast, the effects of the nonhalogenated inhaled anesthetics (xenon, nitrous oxide, cyclopropane) appear to be mediated primarily by inhibition of postsynaptic NMDA receptors (discussed earlier). Augmentation of GABAergic inhibition by most general anesthetics is mediated by both presynaptic and postsynaptic mechanisms. Enhancement of postsynaptic and extrasynaptic $GABA_A$ receptors is well recognized.[118] Remarkably, however, volatile anesthetics also increase spontaneous GABA release and inhibitory postsynaptic current (IPSC) frequency[208-212]—that is, their presynaptic effects at GABAergic terminals are distinct from those at glutamatergic synapses.

The mechanisms for the presynaptic effects of inhaled anesthetics, like those for their postsynaptic effects, are complex and involve multiple targets. Although a synapse-specific contribution of presynaptic Ca^{2+} channels is likely, presynaptic Na^+ channels are more sensitive than the Ca^{2+} channels coupled to glutamate release. This is consistent with observations that the predominant Ca^{2+} channel coupled to neurotransmitter release at hippocampal glutamatergic synapses (P/Q-type) is insensitive to isoflurane.[149] Other presynaptic mechanisms have been proposed, including actions on the vesicle fusion process as demonstrated in the model organism *Caenorhabditis elegans*.[213,214] However, isoflurane effects on

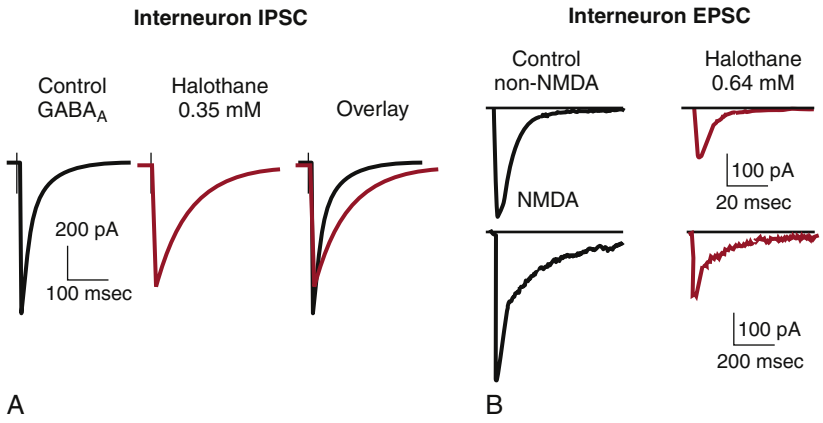


Figure 25-10. Halogenated anesthetics enhance inhibitory and depress excitatory synaptic transmission. Halothane slows the decay of $GABA_A$ receptor–mediated postsynaptic inhibitory currents (IPSCs) (**A**) and depresses the amplitude of glutamatergic excitatory postsynaptic currents (EPSCs) without affecting the decay (**B**) in hippocampal interneurons. (**A,** *Redrawn with permission from Nishikawa K, MacIver MB: Membrane and synaptic actions of halothane on rat hippocampal pyramidal neurons and inhibitory interneurons,* J Neurosci *20:5915-5923, 2000.* **B,** *Redrawn from Perouansky M, et al: Effects of halothane on glutamate receptor-mediated excitatory postsynaptic currents: a patch-clamp study in adult mouse hippocampal slices,* Anesthesiology *83:109-119, 1995.)*

exocytosis in rat hippocampal neurons occur primarily upstream of vesicle fusion.[137,215] (See review[117].)

The general effects of inhaled anesthetics are to increase inhibitory synaptic transmission and to inhibit excitatory synaptic transmission (Fig. 25-11). The relative importance of anesthetic effects on excitatory versus inhibitory synaptic transmission, and the mechanisms of these effects, is likely to differ for different anesthetics and for specific synapses and networks.[105,216] This concept extends to other putative targets and mechanisms and is incorporated in an "agent-specific multiple-site" hypothesis of anesthesia.[216,217]

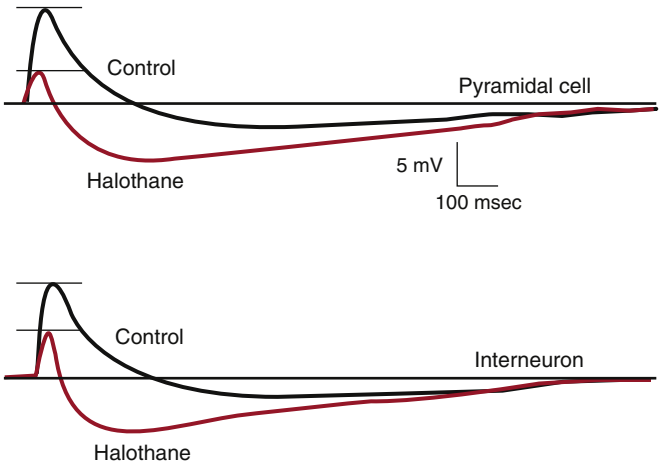


Figure 25-11. Anesthetics affect excitation and inhibition simultaneously in opposite directions. Halothane depresses the excitatory depolarization and augments the inhibitory hyperpolarization in both hippocampal pyramidal cells and interneurons. The net result will depend on the underlying neuronal state, the neuronal network, and its function. *(Redrawn form Nishikawa K, MacIver MB: Membrane and synaptic actions of halothane on rat hippocampal pyramidal neurons and inhibitory interneurons,* J Neurosci *20:5915-5923, 2000.)*

SIMPLE CIRCUITS AND COMPLEX NETWORKS

SIMPLE CIRCUIT PHENOMENA

The development of a mechanistic understanding of phenomena involving complex circuits has been greatly facilitated by the study of anatomically reduced (in vitro) or physiologically simplified (in vivo) preparations, complemented by computer simulations (in silico). These approaches are essential for integrating reductionist observations of the multiple molecular effects of anesthetics into functional models relevant to behavioral end points. Anesthetic effects have been studied in acute brain slice preparations from various regions of the CNS (hippocampus, amygdala, cortex, thalamus, brainstem, and spinal cord—most often from rodents). Brain slices preserve native connections but usually lack natural inputs and outputs. Slices from developing mammalian brain can be cultured in vitro. These "organotypic slice cultures" preserve a high degree of synaptic connectivity and display spontaneous network activity, typically absent from "acute slices." Simplified in vivo preparations involve phenomena (typically evoked responses) with *relatively* well-understood circuitry. Computer models and simulations can assist in generating hypotheses for experimental testing and developing hypotheses based on experimental data.

Synaptic Plasticity

Paired-pulse depression and paired-pulse facilitation are examples of short-term plasticity in response to external stimulation. Synaptic inhibition is prolonged by volatile anesthetics in vivo[218] and in vitro,[219] in general agreement with the notion that anesthetics enhance functional inhibition in the CNS. Enhancement of paired-pulse facilitation has been attributed to the presynaptic depressant effect of volatile agents (see Fig. 25-11).[131,201]

Long-term potentiation, a cellular model of learning and memory, consists of use-dependent strengthening of glutamatergic excitatory synaptic connections (see

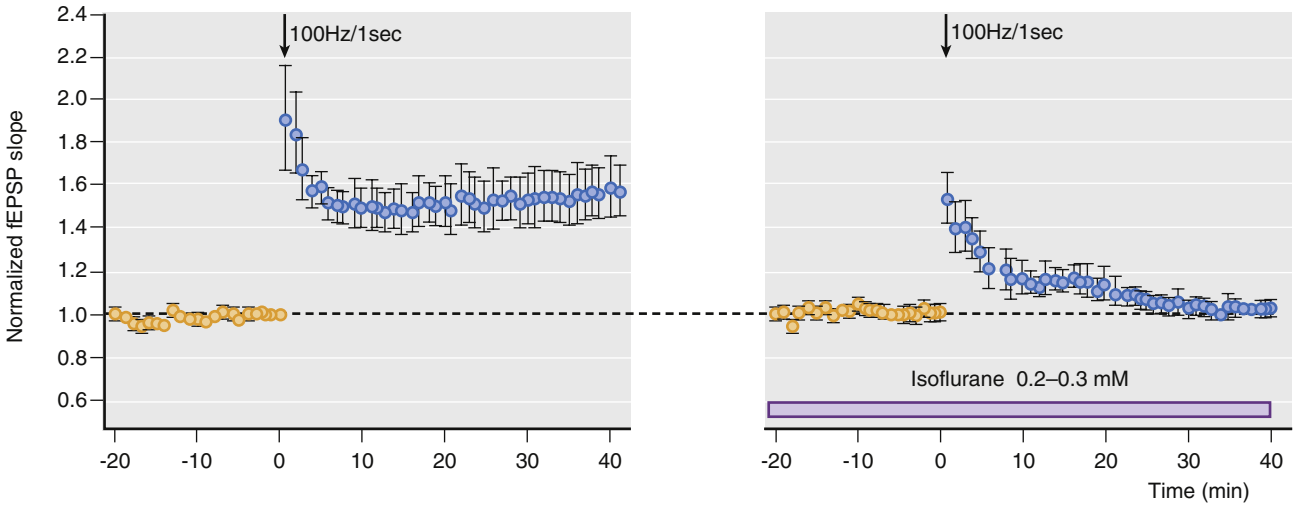


Figure 25-12. Isoflurane blocks the induction of synaptic plasticity in vitro (a model of learning and memory). Long-term potentiation (an increase in synaptic strength), indicated by the increase in normalized excitatory postsynaptic potential (EPSP) slope, in hippocampal slices evoked by tetanic stimulation of excitatory synapses, is blocked by 0.2 to 0.3 mM isoflurane. *(Redrawn from Simon W, et al: Isoflurane blocks synaptic plasticity in the mouse hippocampus,* Anesthesiology *94:1058-1065, 2001.)*

Chapter 13). Reported volatile anesthetic effects on LTP have been inconsistent: halothane, enflurane, and isoflurane do not block LTP induction in vivo, whereas ketamine does.[218] By contrast, isoflurane blocks LTP in the hippocampal slice by enhancing $GABA_A$ receptor–mediated inhibition (Fig. 25-12).[220] Long-term depression, a use-dependent weakening of excitatory connections that is effectively a homeostatic counterpart of LTP, is also blocked by isoflurane.[220] The discrepancy between these findings in vivo and in vitro remains unexplained.

Spontaneously Active Circuits

Spontaneous neuronal activity is decreased by volatile anesthetics both in vivo and in cortical brain slices. This effect is largely $GABA_A$ receptor dependent and marked even at low sedative concentrations.[76] Because the cortical brain slices lack subcortical input, these results suggest that volatile anesthetics can cause some effects (e.g., sedation) via direct cortical action. However, changes in raw neuronal firing rates do not provide a precise quantitative measure of higher cognitive function, which is better reflected by the relationship of firing patterns to strength and phase of cortical rhythms (see next section). Anesthetic effects have also been tested on the circuitry underlying locomotion, a well-studied central pattern generator. Effects of isoflurane on in vitro lamprey and rat spinal cord preparations support the spinal cord as the primary target for volatile anesthetic–induced immobility.[221,222]

RHYTHMS AND SIMULATIONS

The brain perpetually generates complex electrical rhythms (oscillations in extracellular field potentials) that range in frequency from fractions to hundreds of Hertz (Hz; cycles per second), as recorded on the surface of the scalp as the electroencephalogram (EEG; the higher frequency oscillations cannot be resolved in surface recordings). All oscillations are behavioral state dependent, and multiple oscillations coexist throughout the sleep-wake cycle. Lower frequency rhythms allow for integration over longer time periods and typically engage larger areas of the brain. By contrast, higher frequency rhythms allow for higher temporal resolution on local scales. Cross-frequency modulation allows for integration of both aspects of information processing. Although their physiologic roles are not clear, brain rhythms reflect, subserve, and/or constitute fundamental higher-order processing, such that their modulation by anesthetics is of great interest. The current nomenclature of brain rhythms reflects historical conventions and is not based on underlying mechanisms.

δ-Rhythms and Other Slow Rhythms

Oscillations with EEG frequencies from 1.5 to 4 Hz are generally referred to as δ-rhythms. Slower frequency rhythms are termed Slow-1 to Slow-4, with the higher numbers referring to slower rhythms.[223] Slow rhythms are prominent during non–rapid eye movement sleep (i.e., slow-wave sleep) and appear at loss of consciousness induced by propofol.[224] δ-Frequency rhythms are commonly observed under general anesthesia. During natural slow-wave sleep (SWS), δ-rhythms and sleep spindles are phase related to a slower oscillation, suggesting functional interaction.[225] Paroxysmal spindlelike waxing and waning oscillations overriding slower rhythms are also present in the cortical EEG under anesthesia, but the underlying physiology and functional significance are unknown.

θ-Rhythms

θ-Rhythms, present in various cortical structures but most prominent in the hippocampus, are thought to signal the "online state." They are associated with sensorimotor and mnemonic functions during waking behavior.[226] One component of the θ-rhythm (type I or atropine resistant) can be affected by amnestic concentrations of isoflurane as well as by the amnestic nonimmobilizer F6,[63] indicating a potential network-level signature effect for

anesthetic-induced amnesia. Type II θ-rhythm (atropine sensitive) can be evoked under anesthesia and is slowed and potentiated by halothane.[227]

γ-Rhythms

This designation includes an extremely broad and probably functionally and mechanistically heterogeneous spectrum of rhythms. It is frequently subdivided into slow γ (30 to 50 Hz; i.e., the spectrum above β-rhythms); γ (50 to 90 Hz), and fast-, ultra-γ, or ε-rhythms (>90 and up to hundreds of Hz).[224] Fast $GABA_A$-ergic synaptic inhibition and intrinsic resonant properties of neurons play important roles in γ-physiology, making these obvious candidates for anesthetic modulation. Isoflurane slows the frequency of evoked γ-oscillations (30 to 90 Hz, also known as "40- Hz rhythms") in humans.[228,229] Studies of γ-oscillations in vitro suggest that their frequency depends on the time constant of decay of $GABA_A$ receptor–mediated synaptic currents in inhibitory networks.[230] Isoflurane slows γ-rhythms in hippocampal[231] and neocortical slices[232] to a comparable degree as it does in humans,[229] providing a tentative link between receptor and circuit-level effects. However, the interaction between anesthetics and behaviorally relevant network effects is likely to be complex because flash-evoked γ-oscillations in the primary visual cortex are not affected by inhaled agents,[54] whereas feedback information transfer at γ-frequencies between the visual and frontal cortices is disrupted.[53,54] Moreover, brain rhythms are interlinked (e.g., θ-rhythms modulate γ-oscillations (θ–γ nesting). The nature of their modulation by anesthetics as well as relevance is far from clear.

Models and Simulations

On the atomic scale, modeling the interaction of anesthetic molecules with targets and model proteins has defined binding motifs that characterize the amphiphilic binding cavities for anesthetic molecules (see "Identification of Molecular Sites of Anesthetic Action," discussed earlier).[115] Modeling anesthetic interaction with firefly luciferase suggests that anesthetics act by disrupting the modes of motion essential for protein function.[233]

On the macroscopic scale, computer simulations can provide an integrated picture of modulation of dynamic neuronal and network activity. "Bottom-up" neuron-by-neuron approaches are based on computational models of individual neurons, known *anesthetic effects* on intrinsic and synaptic membrane conductances, and simple network models. Computer simulations of anesthetic effects on integrated outputs can thereby be generated (e.g., the firing of pacemaker neurons).[234] These models obviously rely on the accuracy of the derived characteristics of real neurons and networks as well as knowledge of the effects of anesthetics; the scale of simulations is limited by the complexity of its elements.[235] An alternative is a "top-down" approach, such as mean-field modeling, in which molecular and cellular individual accuracy detail is sacrificed in favor of global dynamics. Global cortical phenomena, such as anesthetic-induced seizures,[236] are modeled as phase transitions based on mean interactions between populations of averaged neurons (analogous to the EEG signal that also averages the signals of neuronal populations). This approach can be extended to other global cortical phenomena such as consciousness.[237] Neuronal modeling and computer simulations will likely gain importance in the future as bridges between theoretical and experimental studies of anesthesia.

RESEARCH STRATEGIES FOR THE FUTURE

The search for anesthetic mechanisms is driven by advances in the basic sciences. Some strategies that should facilitate understanding of anesthetic mechanisms include use of agonists or antagonists in vivo, nonanesthetics or nonimmobilizers, transgenic animals, and high-resolution imaging of the functioning brain.

PHARMACOLOGIC APPROACHES

Agonists, Antagonists, and Experimental Anesthetics

Use of receptor-specific agonists and antagonists provides a pharmacologic method for bridging in vitro with in vivo studies. In this approach, a receptor may be tested for its contribution to a specific end point (e.g., immobility) according to the criteria presented earlier. This approach was used to exclude an important role for NMDA receptor block in the immobilizing action of volatile anesthetics but did not yield conclusive results for the roles of $GABA_A$ and GlyR for immobilization,[238,239] probably owing to the intricacies of drug-receptor interactions on different levels of integration in complex networks like the spinal cord. A complementary pharmacologic approach using experimental anesthetics that inhibit NMDA receptors in vitro with different potencies supports the conclusion that NMDA receptor blockade does not contribute significantly to immobility by conventional volatile anesthetics.[240] Refinement of this strategy involves the anatomically discrete application of drugs to nuclei with known function. For example, the tuberomammillary nucleus (part of the endogenous sleep pathway) mediates the sedative component of anesthesia for some intravenous anesthetics (e.g., propofol).[23] A discrete site of general anesthetic action for GABAergic drugs in the mesopontine tegmentum has also been proposed based on this strategy.[22,241]

Nonimmobilizers

Nonimmobilizers are compounds with physicochemical characteristics similar to those of conventional inhaled anesthetics, but their predicted anesthetizing concentrations (based on their lipid solubility and the Meyer-Overton correlation [MAC_{pred}]) do not induce immobility.[11] Initially termed *nonanesthetics,* the terminology was revised when it was discovered that at least some of them cause amnesia at similar MAC_{pred} fractions as classic volatile anesthetics.[67] If a molecular or cellular process is affected in similar ways by an anesthetic and a nonimmobilizer, that process is not relevant for the anesthetic state, with the notable exception of amnesia. Despite this elegant rationale, only a limited number of receptors have been excluded because, compared with volatile anesthetics, nonimmobilizers are relatively

target selective. These compounds have the potential to provide insights beyond the initially envisaged receptor-level studies by allowing the separation of sedation from amnesia for the study of underlying network activity in vivo.[63]

Photoreactive Anesthetics

Recently, azi-isoflurane, a photoreactive analogue of isoflurane, was synthesized. This agent has similar (although not identical) physicochemical properties as isoflurane. When irradiated at a wavelength of 300 nm, azi-isoflurane reacts with amino acid residues surrounding putative isoflurane-binding sites. Use of azi-isoflurane and similar agents could help identify binding sites of inhaled agents on anesthesia-relevant molecular targets.[242]

GENETIC APPROACHES

Genetic strategies take two forms: forward and reverse.[243] The reverse genetic approach focuses on a particular gene, chosen because there are reasons to hypothesize that its product may be important to anesthesia. Examples of this strategy are targeted mutations that alter the sensitivity of specific neurotransmitter receptors to anesthetics.[121] Initially, these mutations were used to identify anesthetic binding sites. Subsequently, transgenic animals rendered resistant to anesthetics, either by deletion of a putative target protein from the genome or by expressing a target receptor engineered to be insensitive to an anesthetic, were used to test behavioral relevance of the altered gene product for the production of anesthesia. Forward genetics, by contrast, is a discovery process that involves the study of randomly generated mutations (either experimentally induced or naturally occurring polymorphisms) in a population that affect the phenotype of interest (i.e., anesthetic end points).

Knockout and Knock-in Animals

In the knockout approach, expression of the gene encoding a protein of interest is disrupted by a specific deletion or insertion. Nearly all such studies have been carried out in mice. A well-recognized problem with the global knockout approach is that extensive compensatory changes can be induced, from anomalies that are lethal in utero to insidious (but experimentally confounding) influences that might be expressed only at maturity. A complementary strategy is the conditional knockout, in which the genetic deletion is restricted—either anatomically (limited to certain brain regions) or temporally (at a known point in time). These strategies can minimize developmental anomalies and reduce the likelihood of compensatory changes. In the knock-in approach, a mutation, usually of a single amino acid residue, is targeted to produce a protein with altered sensitivity to a drug of interest. Ideally, this mutation remains completely silent in the absence of the drug—that is, it does not perturb the normal expression and function of the protein of interest or alter the expression of other genes.

$GABA_A$ Receptors. Results from transgenic animals illustrate both the utility and the difficulties of the genetic approach with respect to inhaled agents. The conditional forebrain-restricted $GABA_A$ receptor α_1-subunit knockout mouse was found to be less sensitive to isoflurane-induced amnesia than wild-type mice, and this led to the conclusion that action at these receptors contributes to its amnesic effects.[244] By contrast, a mouse harboring a mutation of the $GABA_A$ receptor α_1-subunit that renders the receptor insensitive to isoflurane in vitro did not show reduced sensitivity to either the amnesic or the immobilizing effects of isoflurane, leading to the conclusion that this subunit does not mediate the impairment of learning and memory by isoflurane.[31] Similar experiments indicate that action at the $GABA_A$ receptor β_3-subunit does not mediate immobility or amnesia by isoflurane.[30] This "bottom-up" genetic approach is a work-intensive but powerful tool that has yielded clear results with the receptor-specific intravenous anesthetics,[16] but it has proved more challenging to apply it to the more promiscuous inhaled agents.

Glycine α_1–Containing Receptors. Pharmacologic studies supported the notion that glycinergic neurotransmission might be the effector for the immobilizing action of inhaled anesthetics in the spinal cord, where glycine replaces GABA as the principal inhibitory transmitter. However, mice harboring mutations that render α_1 subunit–containing glycine receptors largely insensitive to alcohol and inhaled ether anesthetics did not demonstrate a concordant change in MAC values. Because α_1 is the most widely expressed subunit in adult animals, it is unlikely that action at glycine receptors plays an important part in the immobilizing action of inhaled agents.[245]

Two-Pore Domain K Channels. Use of mice harboring knockout mutations of several two-pore domain K^+ channel (K_{2P}) family members (TASK-1, TASK-3, TREK-1) has demonstrated a role for these channels in volatile anesthesia.[32-34] For example, TREK-1 knockout mice are partially resistant to all volatile anesthetics tested with respect to both loss of righting reflex (a measure of consciousness) and immobility, but anesthesia can still be induced, albeit at higher anesthetic concentrations. Interestingly, responses to pentobarbital are unaffected, indicating that the mutation does not cause a generalized resistance to anesthesia.

FORWARD AND POPULATION GENETICS

The nematode *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*, with 302 and 100,000 neurons, respectively, have also been used as model organisms in anesthesia research. Mutations in a number of *C. elegans* genes affect sensitivity to volatile anesthetics, such as *unc*[64,214] *stomatin*,[246] and *gas1*. Mutation of the latter gene confers hypersensitivity to enflurane. This gene encodes the worm homologue of a subunit of NADH hydrogenase expressed in neurons.[247] Yeasts have also been used as model organisms, with even more obvious limitations with respect to identification of appropriate anesthetic end points.

Sensitivity to anesthetics is a quantitative trait (varying continuously in a population). Quantitative genetics is the study of the heritability of continuous traits. These

traits are controlled by genes represented in quantitative trait loci (QTLs). A top-down population-based approach has been used to localize QTLs that govern susceptibility of individuals to anesthetics, in higher and lower organisms. Starting from the observation that inbred mouse strains vary in their sensitivity to isoflurane, microsatellite-based linkage analysis and, alternatively, single-nucleotide polymorphism–based analysis of genetic variation localized a QTL for isoflurane immobilization to the proximal part of mouse chromosome 7.248 This type of analysis promises to assist in defining the genetic basis for variability in the susceptibility to both primary anesthetic end points and side effects.

HIGH-DENSITY EEG AND FUNCTIONAL IMAGING

Identification of the anatomic and functional substrates for anesthetic effects on consciousness, memory, and immobility is now approachable with improved imaging techniques. Imaging is based on mapping of either metabolic or hemodynamic changes as surrogate measures of neuronal activity, as in positron emission tomography (PET) and functional magnetic resonance imaging, or on mapping electrical activity with high-density EEG, magnetoencephalography, and low-resolution brain electromagnetic tomography (see also Chapters 15, 17, and 49). Properties of receptors can also be probed with radioactive ligands (PET). These techniques have the capacity to identify neuroanatomic substrates of drug action, with method-specific limitations. Results from functional PET imaging suggest that propofol suppresses episodic memory by targeting the prefrontal and posterior parietal cortex as opposed to the medial temporal lobe,[249] and that suppression of consciousness is caused by anesthetic action in the thalamus, parts of the medial and posterior parietal cortex, and/or the posterior cingulate and medial parietal cortex.[250] Although observations of regionally specific and global suppressive effects of anesthetics on metabolic activity are unlikely to provide a definitive mechanistic understanding, such information can facilitate hypotheses and experimentally testable predictions.

Advanced analytical approaches based on theories from mathematical and statistical sciences are being increasingly applied to enhance the power of existing technologies. Magnetic resonance images and high-density EEG recordings of the brain reveal strong interregional connections, but the considerable potential of this connectivity information to better understand the brain's response to anesthesia has only recently begun to be tapped. The growing use of invasive recording techniques (e.g., brain surface electrode grids and microelectrodes implanted deep into the brain for functional neurosurgical therapies) is also advancing the frontiers of neuroscience in general and the understanding of anesthetic mechanisms in particular.

SUMMARY

The mechanisms of inhaled anesthetics have proved more difficult to explain than was envisaged a generation ago, when the paradigm shifted from lipids to amphiphilic cavities in proteins as targets for anesthetics. Despite a remarkable accumulation of information, a comprehensive theory of general anesthetic action has yet to be formulated. Progress toward this goal has been difficult for several reasons. Important pharmacologic characteristics of inhaled anesthetics that have impeded identification of their relevant molecular targets are their low potency (millimolar), promiscuous activity at multiple targets, lack of specific antagonists, and limitations in the neuroscience of memory and consciousness. This contrasts with the situation for intravenous anesthetics that exhibit more conventional receptor pharmacology. Moreover, accumulating evidence indicates that no universal target exists to explain the actions of every general anesthetic, or even of a single anesthetic agent. It is now clear that the composite state of anesthesia and its core components (amnesia, sedation/unconsciousness, immobility) are separable behavioral states in vivo that have limited reproducibility in vitro. Resolution of these phenomena at the molecular and cellular levels represents the cutting edge of contemporary neuroscience. Of the multiple molecular and cellular anesthetic effects identified, it is unclear which are critical for the desired behavioral end points, which are harmless or beneficial side effects (e.g., preconditioning), and which, if any, could have long-lasting or delayed undesirable consequences (e.g., cell death, cognitive dysfunction). Progress in identifying the molecular targets of general anesthetics provides a foundation for identification of the network and systems level effects relevant to their behavioral and peripheral end points. As the biologic foundations of behaviors once thought to be exclusively the realm of psychology are unraveled, for which anesthetics provide a valuable investigative tool, a comprehensive theory of anesthesia will also develop.

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Chapter 26

Inhaled Anesthetic Pharmacokinetics: Uptake, Distribution, Metabolism, and Toxicity

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Key Points

- The alveolar inhaled anesthetic concentration (F_A) or partial pressure (P_{alv}) is important, because it is the driving force determining anesthetic uptake into blood and target tissues in the central nervous system and it can be monitored as a readout of anesthetic dosage. P_{alv} is influenced by both delivery and uptake of anesthetic gas.
- Inhaled anesthetic delivery to patients can be augmented by increased fresh gas flows, vaporizer output settings, and minute ventilation.
- Initial anesthetic uptake into blood increases with increased pulmonary blood flow (cardiac output) and high blood solubility of anesthetic gas. Increased uptake (as with a highly blood-soluble drug or high cardiac output) slows the rate by which anesthesia is induced by slowing the rate of rise of P_{alv}. Conversely, low anesthetic solubility in blood is associated with rapid onset and offset of anesthesia.
- Uptake of anesthetic into blood slows as blood and tissue partial pressures increase, resulting in higher anesthetic partial pressure in mixed venous blood.
- The higher the inspired anesthetic concentration, the less it then diminishes because of uptake (the concentration effect). At 100% inspired concentration, uptake does not cause P_{alv} to change. Changes in alveolar volume result in a rapid initial uptake of N_2O, which sustains or increases concentrations of other alveolar gases (the second gas effect).
- Factors that affect anesthetic uptake similarly affect pulmonary clearance of anesthetics. The rate of clearance is also context sensitive; that is, equivalent decreases in alveolar and brain anesthetic concentrations are slower after a long exposure to inhaled anesthetics compared with a short period of exposure of equal depth.
- Toxicities of inhaled anesthetics are primarily related to their biotransformation (metabolism). Significant toxic effects are usually produced in the tissues, such as liver and kidney, in which metabolism occurs. Modern inhaled anesthetics undergo less metabolism than older drugs do, resulting in fewer toxicities.
- Halothane hepatitis is a potentially fatal syndrome of fulminant liver damage after exposure to reactive metabolites produced by oxidation of volatile anesthetics. These metabolites covalently modify liver proteins, creating neohaptens that elicit an immune response against hepatocytes. The incidence of the syndrome varies with different anesthetics, paralleling the extent of drug metabolism: halothane >> enflurane > isoflurane > desflurane.
- Defluorination of inhaled anesthetics occurs in both the liver and kidney. Free fluoride in blood can damage kidneys, resulting in high-output renal failure. Renal toxicity is almost exclusively associated with prolonged exposure to methoxyflurane. Sevoflurane metabolism also results in high fluoride levels in blood, but it does not damage kidneys. Factors that enhance the toxicity of methoxyflurane relative to sevoflurane include its high tissue solubility, slow clearance, and high degree of renal metabolism, resulting in high intrarenal fluoride levels for an extended time.

KEY POINTS—cont'd

- Anesthetics react with strong bases, particularly potassium hydroxide (KOH), in carbon dioxide (CO_2) absorbents, resulting in production of several potentially toxic substances. Sevoflurane degrades to form compound A, which is associated with renal damage in rodents, but not in humans. This differential toxicity is associated with differential renal metabolism in rodents versus humans. Dry CO_2 absorbents in the anesthetic machine (see Chapter 29) react with inhaled anesthetics, releasing carbon monoxide and heat. New CO_2 absorbent materials that lack strong base chemicals prevent these reactions and subsequent potential harm to patients.
- Nitrous oxide (N_2O) is unique among anesthetics in its ability to inhibit methionine synthase oxidation by oxidizing a cofactor, vitamin B_{12}. In certain susceptible patients and in patients receiving many anesthetics that include N_2O, methionine synthase inhibition can lead to hematologic and neurologic dysfunction. After prolonged N_2O exposure, methionine synthase inhibition also increases blood homocysteine, which can increase vascular inflammation and the risk of thrombosis. Definitive clinical trials assessing the effects of N_2O on morbidity in vasculopathic patients are lacking.
- Inhaled anesthetics, when scavenged and ejected into the atmosphere, contribute to both global warming and ozone depletion. The environmental impact of anesthetics can be lessened by reducing waste through the routine use of low fresh gas flows or with the use of new technologies that trap scavenged anesthetic gases. Reprocessing and reusing trapped anesthetic gases further reduces the environmental impact of drug production.
- In experimental models of the developing brain, including nonhuman primates, general anesthetics produce signs of neurotoxicity that are associated with later neurocognitive deficits. Results from clinical cohort studies in children within the United States and Europe remain inconclusive about an association between early anesthetic exposures and learning or behavioral problems later in life (see Chapter 93). Regarding long-term effects of anesthesia and surgery on the adult brain, see Chapter 99.

INTRODUCTION

Modern inhaled anesthetics are important pharmacologic tools for reversibly altering central nervous system functions in patients. Because inhaled anesthetics are both taken up and eliminated through alveolar blood–gas exchange, drug dosage can be monitored in expired alveolar gases, and tissue-dependent metabolism is unnecessary for drug clearance. Optimal delivery of systemic drugs via inhalation requires a full understanding of the factors influencing how gas-phase compounds move into and out of various body tissues and how they are metabolized (pharmacokinetics) together with where and how these drugs and their metabolism affect tissue functions. Reversible anesthetic effects on the nervous, respiratory, and cardiovascular systems (pharmacodynamics) are covered elsewhere in this textbook (see Chapters 25, 27, and 28).

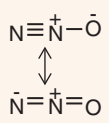
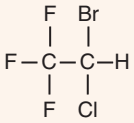
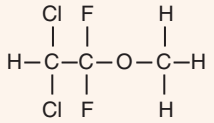
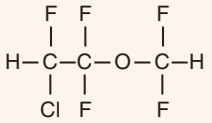
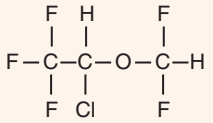
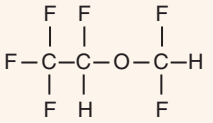
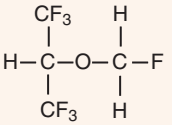
UPTAKE AND DISTRIBUTION OF INHALED ANESTHETICS

In the first part of this chapter, some of the basic concepts of chemical equilibria are reviewed and are applied to illuminate major factors influencing inhaled anesthetic uptake and distribution in patients. For this review, a physiologic model is used that closely simulates clinical observations. The model, an elaboration of that introduced in 1973 by Mapleson,[1] is described both qualitatively and quantitatively (using mathematical expressions) to convey important concepts to readers with different learning styles.

BIOPHYSICAL PROPERTIES OF INHALED ANESTHETICS: PARTIAL PRESSURE, HYDROPHOBICITY AND PARTITION COEFFICIENTS

Inhaled anesthetics are administered as a component of a gas mixture. The biophysical properties of inhaled anesthetics are summarized in Table 26-1. *Partial pressure* is the portion of total pressure contributed by one component of a gas mixture, where each component contributes pressure in direct proportion to its molar fraction. For example, 1.5% isoflurane in air (21% O_2 and 79% N_2) at 1 atm (760 mm Hg) is a mixture of O_2 at 157.2 mm Hg, N_2 at 591.4 mm Hg, and isoflurane at 11.4 mm Hg. The partial pressure of an anesthetic gas is a measure of thermodynamic activity of the gas and determines its pharmacologic effect. The partial pressure of an anesthetic is usually reported as the percentage (or fraction)

TABLE 26-1 **CHEMICAL STRUCTURES AND PROPERTIES OF INHALED ANESTHETICS***

Anesthetic	Nitrous Oxide	Halothane	Methoxyflurane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Year introduced into clinic	1840s	1956	1960	1966	1969	1990	1981
Chemical structure							
Molecular weight	44.0	197.4	165.0	184.5	184.5	168	200.1
Boiling point (° C)	–88.5	50.2	104.8	56.5	48.5	22.8	58.6
Density (g/mL)	1.84×10^{-3}	1.86	1.42	1.52	1.5	1.45	1.50
Vapor pressure (mm Hg)	43,880	243	22.5	175	238	664	157
Oil/gas partition coefficient at 37° C	1.3	197	950	98.5	90.8	19	47-54
Blood/gas partition coefficient at 37° C	0.47	2.5	12	1.9	1.4	0.45	0.65
MAC-immobility (% atm/mm Hg)†	104/800	0.75/5.7	0.2/1.52	1.58/12.0	1.28/9.7	6.0/45.6	2.05/15.6
MAC-awake†	71/540	0.41/3.21	0.081/0.62	0.51/3.88	0.43/3.27	2.4/19	0.63/4.79

Partition coefficients are from References 2-6.
MAC-immobility and MAC-awake values are from References 2, 8-11, 38.
*Properties are measured at standard temperature (20° C) and pressure (1 atm) unless otherwise specified.
†MAC is minimum alveolar concentration for subjects approximately age 40 years.

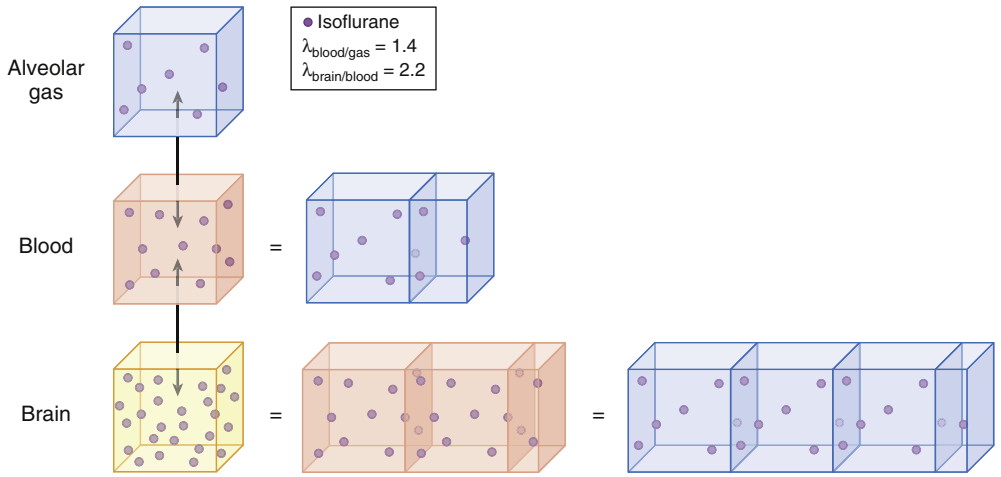


Figure 26-1. Partitioning of anesthetic gases between different biophases. *Left,* Depicts the partitioning of isoflurane between gas phase *(blue)*, blood *(red)*, and brain *(yellow)*. The blood/gas partition coefficient ($\lambda_{b/g}$) for isoflurane is 1.4. The brain/blood partition coefficient ($\lambda_{CNS/blood}$) is 2.2 (see Table 26-2). At equilibrium, defined as equal isoflurane partial pressure in all compartments, a volume of blood contains 1.4-fold the quantity of isoflurane as the same volume of alveolar gas, whereas a volume of brain tissue contains 2.2-fold the quantity of isoflurane as the same volume of blood. *Right,* We also Depicts partition coefficients as effective (equivalent) volumes of another biophase. For example, one volume of blood contains the same amount of isoflurane as 1.4 volumes of alveolar gas, whereas 1 volume of brain contains the same amount of isoflurane as 2.2 volumes of blood or 3.1 volumes of gas.

of the delivered gas mixture, where atmospheric pressure is near 1 atm (760 mm Hg). Correcting these values to absolute partial pressure is important under conditions when local atmospheric pressure differs significantly from standard, such as at high altitude, underwater, or in a hyperbaric chamber. The same inhaled concentration of an anesthetic gas results in a reduced pharmacologic effect at higher altitudes because the partial pressure of the anesthetic is lower. Because partial pressure is the thermodynamic force for gas movement in a system, anesthetics move from regions of high partial pressure to low partial pressure, unaffected by the other components of the gas mixture, and equilibrium is achieved when the partial pressure of an anesthetic is equal in the different compartments.

The maximal partial pressure of a volatile compound is its *vapor pressure*; this is the partial pressure of volatile anesthetic within the drug reservoir of a vaporizer. Vapor pressure is unique to each anesthetic and increases with increasing temperature. Volatile anesthetics are defined by a vapor pressure less than 1 atm at 20° C and a boiling point above 20° C (see Table 26-1). Gaseous anesthetics are defined by a vapor pressure greater than 1 atm at 20° C and a boiling point below 20° C (see Table 26-1). Volatile anesthetics typically account for a small fraction of the gas mixture delivered to patients. In contrast, gaseous anesthetics such as nitrous oxide (N_2O) and xenon, because of their relative lack of potency, typically compose a large fraction of an inhaled gas mixture and thus produce additional effects (e.g., concentration effect, second gas effect, and airspace expansion) that are negligible with potent volatile anesthetics.

Hydrophobicity is a molecular property of certain chemicals, including most general anesthetics that do not readily form hydrogen bonds and therefore display low water solubility. Hydrophobic compounds are also usually lipophilic, demonstrating high solubility in low polarity solvents such as oils. Common measures of hydrophobicity are *partition coefficients* between water and olive oil (which is mostly oleic acid, an 18-carbon fatty acid) or between water and *n*-octanol. Usually represented by the Greek letter lambda (λ), a partition coefficient is the ratio of two solute concentrations at equilibrium (i.e., at equal partial pressure) in two separate but adjacent solvents or compartments such that the solute moves freely between the compartments (Fig. 26-1). Another useful way to conceptualize a partition coefficient is that it represents the relative volume of two compartments that contain equal concentrations of the solute at equilibrium (see Fig. 26-1).

Anesthetic partition coefficients between blood and gas ($\lambda_{b/g}$) and between tissue and blood ($\lambda_{t/b}$) are important factors in uptake and distribution of inhaled anesthetics as they move from pulmonary airspace to pulmonary blood, then from blood to various tissues (Table 26-2). Blood solubility of anesthetic gases (and other gases such as O_2, N_2, and CO_2) increases as temperature decreases.[16,17] Because most anesthetics are hydrophobic, they tend to display high solubility in tissues with high lipid content (e.g., fat), and they bind to many proteins that form hydrophobic or amphiphilic pockets.[12] Anesthetic partitioning into blood (blood solubility) increases after ingestion of fatty foods[18] and may decrease in anemic or malnourished patients. Methoxyflurane (no longer in clinical use) and halothane are notable for high blood solubility. N_2O, sevoflurane, and desflurane are characterized by low blood solubility.

ANESTHETIC DELIVERY, UPTAKE, AND DISTRIBUTION: A MULTICOMPARTMENTAL MODEL

Delivering an inhaled anesthetic drug to patients is analogous to an intravenous drug infusion with two obvious

TABLE 26-2 UPTAKE AND DISTRIBUTION MODEL PARAMETERS FOR INHALED ANESTHETICS*

Tissue	Blood		Heart		Kidney		Liver		CNS		Muscle		Fat		VRG	
	Blood Flow (L/min)	Volume (L)	Blood Flow (L/min)	Volume (L)	Blood Flow (L/min)	Volume (L)	Blood Flow (L/min)	Volume (L)	Blood Flow (L/min)	Volume (L)	Blood Flow (L/min)	Volume (L)	Blood Flow (L/min)	Volume (L)	Blood Flow (L/min)	Volume (L)
	5	5	0.2	0.28	1.07	0.32	1.2	3.9	0.62	1.43	0.75	30	13	0.5	7	0.35

Anesthetic Agent	V_{eff} (L)	$\lambda_{Tissue/blood}$	V_{eff} (L)	τ (min)	$\lambda_{Tissue/blood}$	V_{eff} (L)	τ (min)	$\lambda_{Tissue/blood}$	V_{eff} (L)	τ (min)	$\lambda_{Tissue/blood}$	V_{eff} (L)	τ (min)	$\lambda_{Tissue/blood}$	V_{eff} (L)	τ (min)	$\lambda_{Tissue/blood}$	V_{eff} (L)	τ (min)	$\lambda_{Tissue/blood}$	V_{eff} (L)	τ (min)
Nitrous oxide	2.35	0.87	0.24	1.2	0.93	0.3	0.3	1.1	4.1	3.4	1.1	1.6	2.6	1.2	36	48	2.3	30	60	1.4	9.9	29
Halothane	12.5	2.9	0.8	4.0	1.5	0.5	0.4	2.5	9.8	8.0	2.7	3.9	3.3	2.5	75	100	65	840	1700	2.3	16	47
Methoxyflurane	60	1.2	0.34	1.7	2.3	0.74	.69	2.5	9.8	8	2	2.9	4.7	1.6	48	64	76	980	1960	1.2	8.5	25
Enflurane	9	1.3	0.36	1.8	2.0	0.64	0.6	2.1	8.2	6.7	1.4	2.0	3.3	1.7	51	68	36	464	930	2	14	41
Isoflurane	7	1.3	0.36	1.8	2.3	0.74	0.69	2.4	9.4	7.6	1.5	2.1	3.5	2.9	87	116	45	580	1160	2	14	41
Desflurane	2.25	1.3	0.36	1.8	1.0	0.32	0.3	1.4	5.5	4.5	1.3	1.9	3.0	2.0	60	80	27	350	670	2	14	41
Sevoflurane	3.25	1.3	0.36	1.8	2.3	0.74	0.69	2.4	9.4	7.7	1.7	2.4	4.0	3.1	93	120	48	620	1240	2	14	41

*Based on a 70-kg patient at rest. Blood and tissue partition coefficients are from References 6, 12-14. Tissue volumes and blood flow values are approximate (Levitt,[12] Kennedy and colleagues[15]). Effective volumes are calculated as Tissue volume × λTissue / Blood, and exchange time constant (τ) for each compartment is V_{eff} / Blood flow.

CNS, Central nervous system; *VRG,* vessel-rich group.

major differences: (1) entry of drug into the body is via transalveolar exchange from gas to blood and (2) clearance is mostly via the same route. Thus, inhaled anesthetic delivery is dependent on pulmonary ventilation, whereas uptake and clearance of inhaled anesthetics are dependent on pulmonary perfusion.

Upstream and Downstream Compartments and Anesthetic Transfer: Bulk Flow and Pressure Gradients

Uptake and distribution of inhaled anesthetic can be readily understood as a series of transfer steps from upstream compartments with high partial pressure to downstream compartments with low partial pressure as depicted in Figure 26-2. First, the drug is transferred from an anesthesia delivery device, typically an anesthesia machine with a vaporizer designed to deliver specified concentrations (in percent atm) of volatile anesthetic, into a fresh gas mixture flowing in a breathing circuit. Second, ventilation transfers gases from the circuit to the alveolar airspace in the lung. Third, the anesthetic moves by transcapillary diffusion into pulmonary venous blood. Fourth, arterial blood distributes the anesthetic to various tissues including the primary target tissue, the central nervous system (CNS). Fifth, venous outflow from tissues converges in the pulmonary artery, and sixth, the mixed venous blood passes through alveolar capillaries where it again equilibrates with alveolar gases.

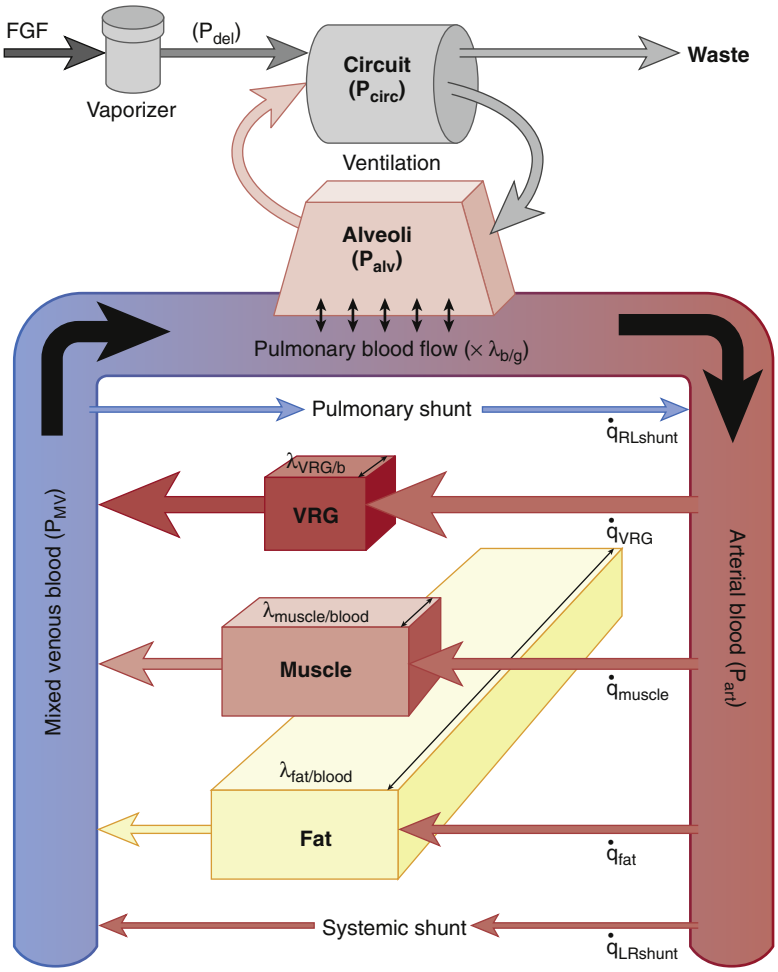


Figure 26-2. Flow diagram for uptake and distribution of inhaled anesthetics. Major compartments for anesthetic flow are depicted, including the breathing circuit, alveolar gas space, and three major tissue compartments: vessel-rich group (VRG), muscle, and fat. The physiologic volumes of the tissue compartments are approximately in proportion to the labeled face of the compartment, while the blood-tissue partition coefficients are depicted as the depth of the compartment. Thus, the effective volume of the VRG is much smaller than that of muscle, which in turn is much smaller than that of fat. Carrier flows and exchange in different parts of the model are depicted by arrows. Fresh gas flow (FGF) moves anesthetic from the vaporizer to the circuit; ventilation drives exchange of anesthetic between the circuit and alveoli; pulmonary blood flow transfers anesthetic from alveoli into the circulation, which then distributes drug to different compartments depending on blood flow to various tissues. Relative blood flow is approximately proportional to the width of the arrows into and out of tissue compartments, as well as for shunts. The diagram depicts an early phase of anesthetic uptake when organs of the VRG, including the brain, are approaching equilibrium with alveolar and arterial anesthetic partial pressure, while anesthetic partial pressures in muscle and fat remain relatively low. Quantitative modeling of anesthetic gas movement in this system was performed using numerical integration of equations describing anesthetic flow into and out of each compartment (Equations 5, 8, 9, 10, and 11). Figures 26-4, 26-5, 26-6, 26-7, 26-9, 26-10, and 26-12 were all generated using this model. Standardized parameters used in the model are summarized in Table 26-2. P_{circ}, Partial pressure in the circuit; P_{del}, delivered anesthetic partial pressure.

Gas flow from the machine into the breathing circuit is unidirectional. Blood circulation is also largely unidirectional. In transfers from machine (the fresh gas outlet) to breathing circuit and then to alveolar airspace, anesthetic flow can simply be understood as an exchange from upstream compartments into downstream gas phase compartments. In later steps, such as exchange between alveolar gases and pulmonary capillary blood, the flow of anesthetic molecules occurs via diffusion between adjacent compartments separated by a permeable membrane. For simplicity, we have not treated blood as a separate compartment in our model. Distribution of anesthetic to and from various tissues involves both bulk transfer via blood flow and diffusive equilibration across capillary membranes. Note that when anesthetic transfer occurs between gas and blood or between blood and tissue, the effective volume of the downstream compartment must be adjusted with the appropriate partition coefficient (see Table 26-2).

Rate of Wash-in of the Circuit: Equilibration between Vaporizer and Circuit

Equipment for controlled delivery of inhaled anesthetic drugs is described in Chapter 29. Wash-in of the ventilator breathing circuit represents an example of bulk transfer exchange, wherein the gas in the circuit components is replaced by fresh gases emerging from the gas outlet of the anesthesia machine.

Anesthetic Delivery from the Vaporizer. Volatile anesthetic delivery from a vaporizer is simply the product of the delivered anesthetic concentration (Fraction = F_{del} or Partial pressure = P_{del}) of the anesthetic gas and fresh gas flow (FGF).

$$dV_{del}/dt = P_{del} \times FGF \quad (1)$$

Thus, we can readily calculate the volume of delivered gas-phase anesthetic by simply integrating this function over time. In the simplest case where P_{del} and FGF remain constant:

$$V_{del}(t) = P_{del} \times FGF \times t \quad (2)$$

Fresh Gas Wash-in to the Breathing Circuit. The factors that affect the speed at which the gas mixture delivered from the anesthesia machine replaces gases in the breathing circuit (wash-in) are FGF and the breathing circuit volume (V_{circ}). Consider a typical situation in which FGF at the beginning of an anesthetic is 6 L/min and the gas volume inside the components of a breathing circuit is 6 L. If FGF is doubled to 12 L/min, then wash-in will proceed at twice the rate (halving the time). Conversely, if the V_{circ} doubles to 12 L, then wash-in will proceed at half the rate (doubling the time).

The gas exchange process is independent of the concentration of anesthetic in the circuit, because the exchange is simply through bulk flow and mixing. However, the difference between the delivered concentration and that in the circuit determines the magnitude and direction of net anesthetic gas flow. When the delivered anesthetic partial pressure (P_{del}) is greater than that in the circuit (P_{circ}), net anesthetic flow is into the circuit (and subsequently into the patient). To remove anesthetic from the circuit, P_{del} must be less than P_{circ}. When there is no concentration gradient (i.e., equal partial pressures), bulk flow exchange may replace all the old gas molecules with new ones, but there is no net flow and anesthetic concentrations in the circuit remain unchanged.

Mathematically, we can describe the breathing circuit exchange process as a differential equation that incorporates all of the above factors:

$$\frac{dP_{circ}}{dt} = \frac{FGF}{V_{circ}} \times (P_{del} - P_{circ}) \quad (3)$$

If P_{del} is constant, integrating this equation results in a single exponential function that defines P_{circ} at any given time following a change in P_{del} at $t = 0$:

$$P_{circ}(t) = P_{circ}(0) + (P_{del} - P_{circ}(0)) \times \left(1 - e^{-t/[Vcirc/FGF]}\right) \quad (4)$$

P_{circ} approaches P_{del} following an exponential time course with a time constant of $\tau = V_{circ}/FGF$. Thus, if V_{circ} = 6 L and FGF = 6 L/min, the exponential time constant will be 1 minute (Fig. 26-3). Each minute results in the fraction of old gas in the breathing circuit dropping by 63.1%, and after 4 minutes, less than 2% old gas remains. The half-life for the process (time for halving the vaporizer-circuit concentration difference) is 0.693 × τ.

Breathing circuit components, such as CO_2 adsorbents and the plastic or rubber of the circuit tubing and connectors, influence the rate of equilibration between vaporizer and circuit, because such materials can absorb volatile anesthetics, increasing the effective circuit volume.[19] The more hydrophobic volatile anesthetics absorb more into

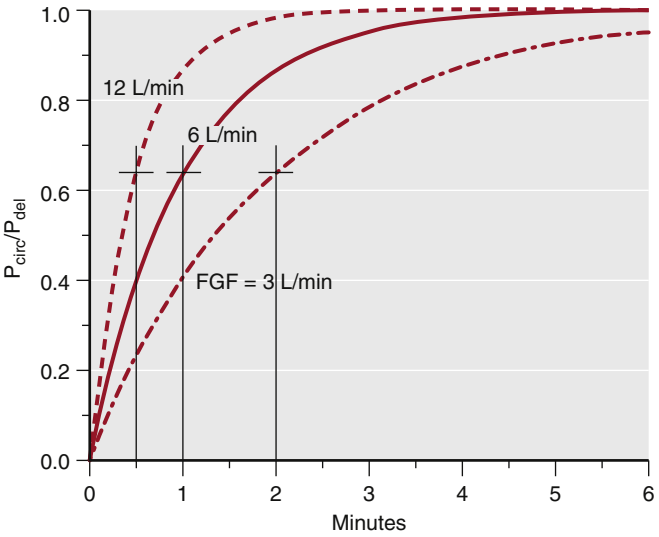


Figure 26-3. Wash-in of the breathing circuit depends on fresh gas flow (FGF). The *curves* depict the rate of rise of anesthetic concentration (partial pressure) in a breathing circuit with 6 L of gas volume, depending on FGF. Higher FGF results in more rapid exchange of circuit gases with fresh gas. The exponential time constant for the wash-in process is the circuit volume in liters divided by fresh gas flow in liters per minute (see Equation 4). *Cross marks* overlaying the curves indicate time constants under different gas flow rates. Each time constant correlates with a 63.1% exchange.

circuit components, whereas absorption negligibly affects wash-in and wash-out of low-solubility anesthetics.

The clinical relevance of the wash-in process is readily appreciated. An example of the importance of FGF is "priming" the anesthetic circuit for a single-breath induction technique. The FGF setting and the circuit volume influence the required duration of priming. More generally, whenever the vaporizer settings are altered, the speed at which the new settings influence the wash-in or wash-out of the circuit (and subsequently the patient) depend on FGF. Open (nonrebreathing) anesthetic breathing circuits are designed to have low exchange volumes and to be used with high fresh-gas flows. These features allow rapid changes in the delivered anesthetic concentration, while minimizing rebreathing of exhaled gases. The choice of an open versus rebreathing system influences the effects of various other factors that can affect uptake and distribution of inhaled anesthetics downstream from the breathing circuit. Some of the subsequent figures show models for both conditions.

Equilibration between Circuit and Pulmonary Airspace

Transfer of anesthetic gases from the breathing circuit to the pulmonary airspace is another bulk exchange process similar to that from vaporizer to breathing circuit. In this case, gas flow via ventilation is cyclical and bidirectional, and the factors that determine the rate of anesthetic exchange are minute ventilation (MV) and total pulmonary airspace volume (V_{pulm}).[20] Because transfer from the circuit to the lungs represents anesthetic flow out of the circuit, we alter Equation 3 to include both inflow to the circuit and outflow from the circuit:

$$\frac{dP_{circ}}{dt} = \frac{FGF}{V_{circ}} \times (P_{del} - P_{circ}) - \frac{MV}{V_{pulm}} \times (P_{circ} - P_{pulm}) \quad (5)$$

where P_{pulm} is a weighted average of the anesthetic partial pressure in deadspace and alveolar space.

Equation 5 describes how rebreathing affects the inhaled (breathing circuit) anesthetic concentration. Most inhaled anesthetics are delivered using a rebreathing circuit, which includes one-way flow valves and adsorbent material to remove exhaled CO_2 chemically. Rebreathing depends primarily on the balance between fresh gas flow and minute ventilation. The anesthetic gas in the breathing circuit represents a mixture of fresh gas and exhaled gases. Increased FGF reduces rebreathing, whereas increased MV increases rebreathing.

Alveolar Anesthetic Concentration

The alveolar anesthetic concentration (P_{alv} or F_A) is a critically important factor in anesthetic uptake and distribution because (1) it is in rapid equilibrium with circulating blood and highly perfused tissues, including target tissues in the CNS, and (2) P_{alv} can be measured in exhaled end-tidal gases. Thus, except during periods of rapid change, P_{alv} in exhaled breath represents a useful estimate of the anesthetic concentration in the patient's CNS and other highly perfused organs.

Because only alveolar gas is relevant to transpulmonary exchange of anesthetic into and out of the body, *alveolar ventilation* ($\dot{V}_{alv}$) is the proper gas flow to calculate anesthetic exchange into this part of the pulmonary airspace.

$$\frac{dP_{alv}}{dt} = \frac{\dot{V}_{alv}}{V_{alv}} \times (P_{circ} - P_{alv}) \quad (6)$$

where $\dot{V}_{alv}$ is MV corrected for deadspace ventilation.

Alveolar Uptake of Anesthetic into Pulmonary Blood

During inhaled anesthetic induction, anesthetic flows from alveolar gas to pulmonary blood across the alveolar–capillary interface separating these compartments and is driven by the partial pressure gradient between alveolar gas (P_{alv}) and mixed venous blood (P_{MV}) entering the pulmonary arteries. The net flow of anesthetic reverses during anesthetic wash-out when P_{alv} drops below P_{MV}. Anesthetic uptake into blood also depends on the pulmonary blood flow (which is typically close to cardiac output, $\dot{Q}$) and the blood's capacity to solvate anesthetic from the gas state (the blood/gas partition coefficient, $\lambda_{b/g}$):

$$\text{Uptake} = \dot{Q} \times \lambda_{b/g} \times (P_{alv} - P_{MV}) \quad (7)$$

We therefore correct Equation 6 to reflect both anesthetic inflow into alveolar airspace and its uptake into blood:

$$\frac{dP_{alv}}{dt} = \frac{\dot{V}_{alv}}{V_{alv}} \times (P_{circ} - P_{alv}) - \frac{\dot{Q} \times \lambda_{b/g}}{V_{alv}} \times (P_{alv} - P_{MV}) \quad (8)$$

Thus, during an inhaled induction of anesthesia, the rate of increase of P_{alv} relative to P_{circ} is governed by (1) alveolar ventilation, (2) cardiac output, and (3) anesthetic solubility in blood. Increased ventilation delivers more anesthetic from circuit to alveoli and increases P_{alv}/P_{circ} (Fig. 26-4). Yet increased pulmonary blood flow removes more anesthetic from alveoli, thereby decreasing the rate of increase in alveolar concentration of anesthetic (P_{alv}/P_{circ}; Fig. 26-5). Indeed, significant decreases in cardiac output are likely when end-tidal CO_2 ($ETCO_2$) decreases and end-tidal concentrations of volatile anesthetic increase.[21] The more soluble an anesthetic is in blood (i.e., the higher its $\lambda_{b/g}$), the more each volume of blood can take up anesthetic from alveolar gases (i.e., the larger the effective blood flow). Thus, as $\lambda_{b/g}$ increases, P_{alv}/P_{circ} increases more slowly (Fig. 26-6).

Other Factors That Affect the Rate of Rise of P_{alv}

Other factors affecting alveolar uptake of anesthetic include ventilation–perfusion matching and the absolute concentration of anesthetic in alveolar gases.

Deadspace. Deadspace (i.e., ventilated but not perfused pulmonary regions) reduces effective alveolar ventilation (see Equations 7 and 8), and thus slows anesthetic uptake. This effect is strongest under open-circuit (high FGF) conditions and with low blood-solubility inhaled anesthetics. Under conditions of limited anesthetic delivery and

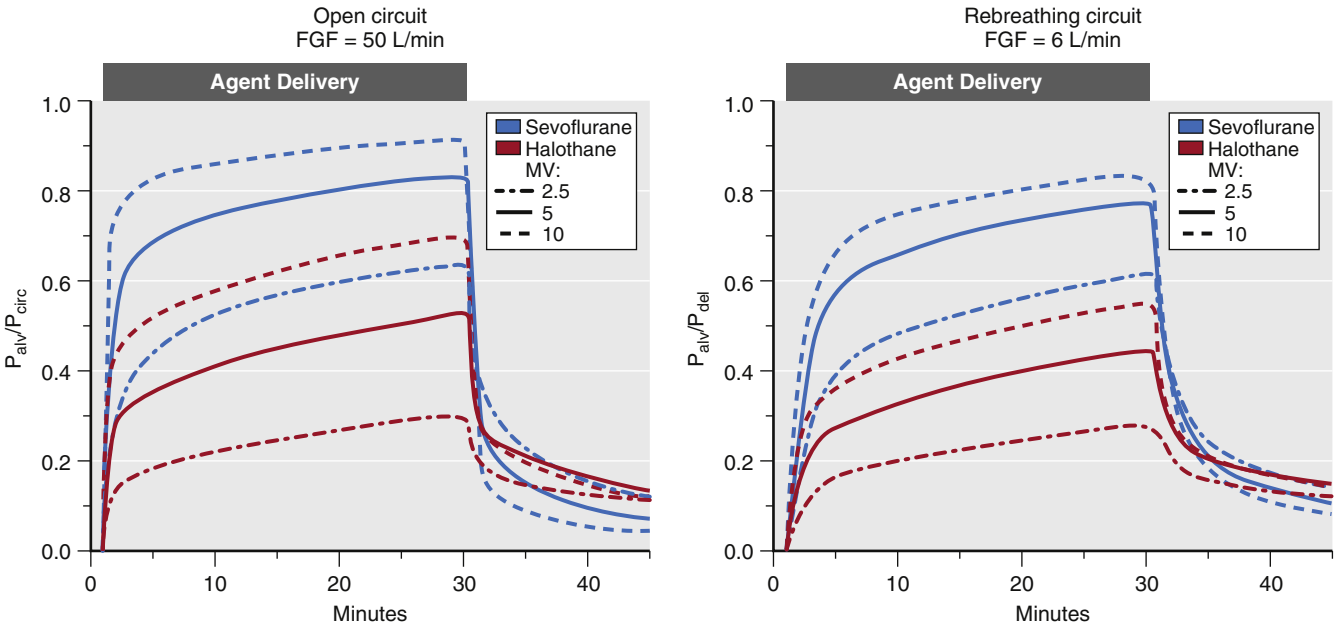


Figure 26-4. Effect of ventilation on the rise of alveolar anesthetic partial pressure (P_{alv}). *Left,* A traditional open-circuit model with very high fresh gas flow (FGF) and therefore constant $P_{del} = P_{circ}$. *Right,* A more common clinical situation with constant vaporizer output (P_{del}) and partial rebreathing at a 6 L/min fresh gas flow rate. Raising minute ventilation accelerates the rise of P_{alv} by delivering more anesthetic to the lungs. The effect is seen whether anesthetic is highly soluble in blood (e.g., halothane) or relatively insoluble (e.g., sevoflurane). However, the relative size of the ventilation effect is greater for soluble agents. Increased ventilation also accelerates clearance of anesthetic agents after delivery ceases. P_{circ}, Partial pressure in the circuit; P_{del}, delivered anesthetic partial pressure.

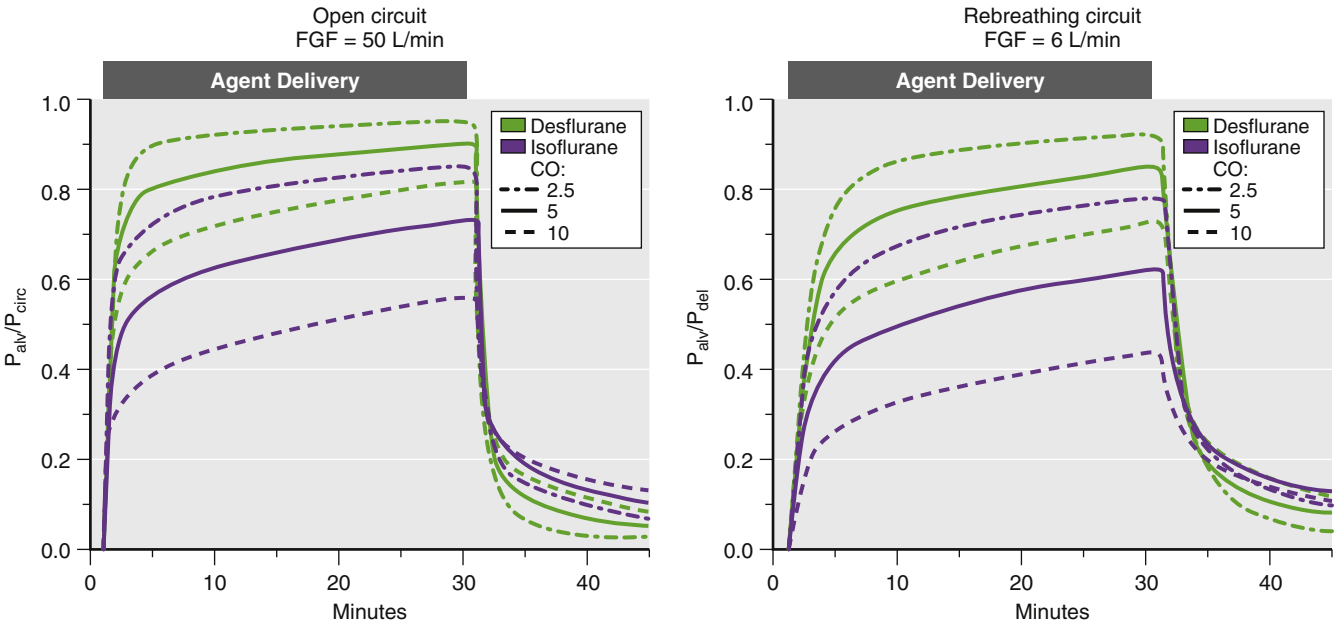


Figure 26-5. Effect of cardiac output on the rise of alveolar anesthetic partial pressure (P_{alv}). *Left,* A traditional open-circuit model with very high fresh gas flow (FGF) and therefore constant $P_{del} = P_{circ}$. *Right,* A common clinical situation with constant vaporizer output (P_{del}) and partial rebreathing at a 6 L/min FGF rate. Raising cardiac output slows the rise of P_{alv} by increasing anesthetic uptake into blood (removing anesthetic from alveolar gases). This effect is observed for both highly soluble and relatively insoluble (e.g., isoflurane) anesthetics, but the relative effect is greater for soluble agents. Cardiac output also affects clearance of anesthetics from the lungs in the same way it affects uptake (i.e., increased cardiac output slows anesthetic clearance rate). P_{circ}, Partial pressure in the circuit; P_{del}, delivered anesthetic partial pressure.

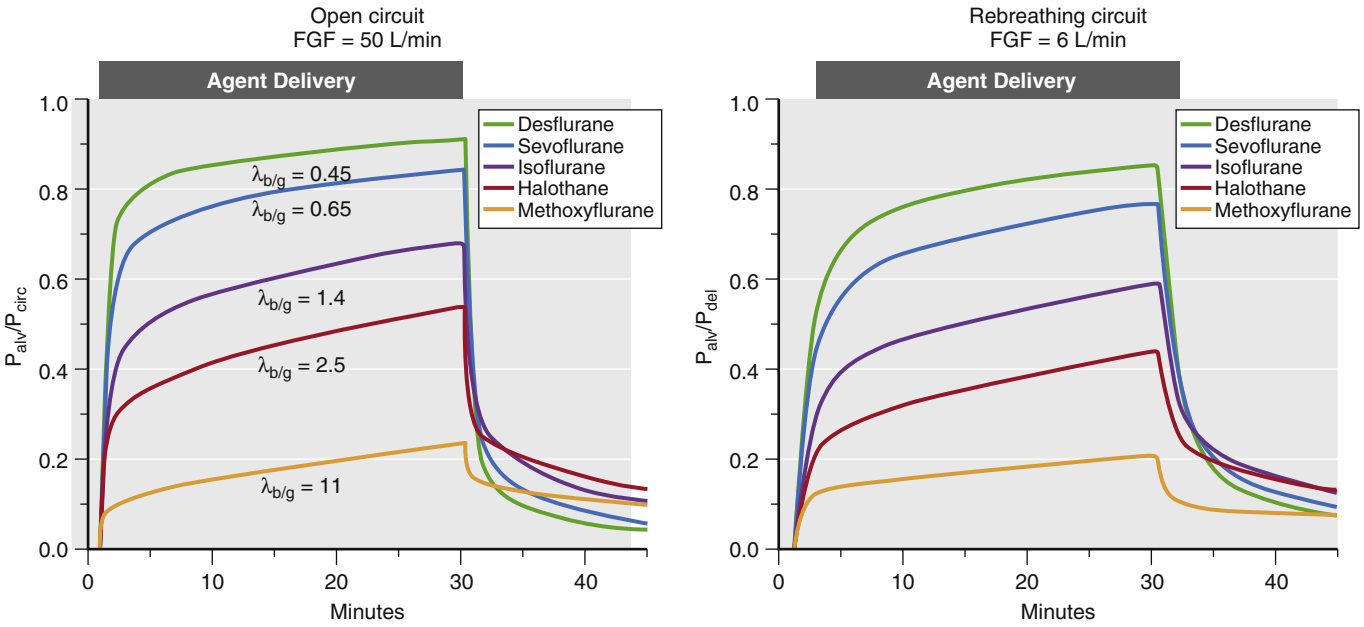


Figure 26-6. Effect of blood solubility on the rise of alveolar anesthetic partial pressure (P_{alv}). *Left,* A traditional open-circuit model with very high fresh gas flow (FGF) and therefore constant $P_{del} = P_{circ}$. *Right,* A more common clinical situation with constant vaporizer output (P_{del}) and partial rebreathing at a 6 L/min FGF rate. As blood solubility ($\lambda_{b/g}$) increases, the rate of rise in P_{alv} slows, because uptake into blood is greater for high solubility agents. The major effect of blood solubility is the magnitude of the rapid initial rise in P_{alv}, which represents a balance between anesthetic delivery and uptake into pulmonary blood. Blood solubility similarly affects clearance from alveoli after anesthetic delivery ceases (i.e., increased blood solubility results in slower clearance from alveolar gas). P_{circ}, Partial pressure in the circuit; P_{del}, delivered anesthetic partial pressure.

high uptake such as low FGF and a highly blood-soluble anesthetic, alveolar ventilation and therefore uptake are reduced. The inspired anesthetic concentration (P_{circ}) and the concentration gradient for alveolar exchange change very little. This compensates somewhat for the effect of deadspace on alveolar ventilation, reducing its overall effect on P_{alv}.

Pulmonary (Right to Left) Shunting. Pulmonary (right to left) shunting can be physiologic, pathologic, or iatrogenic, such as during one-lung ventilation. Right-to-left shunting results in a difference between P_{alv} and the partial pressure of anesthetic in arterial blood (P_{art}). This is because arterial blood represents a mixture of shunted mixed venous blood with blood that equilibrates with alveolar gases (Equation 9). Because such shunts also reduce transcapillary gas exchange in the lung and slow anesthetic uptake (Equations 7 and 8, after correcting pulmonary blood flow for shunt), right-to-left shunting, sustains P_{circ}, an effect that is more pronounced for highly soluble versus insoluble anesthetics. Thus, shunt reduces the ratio of P_{art}:P_{alv} more for insoluble anesthetics, such as N_2O[22,23] (Fig. 26-7).

$$P_{art} = P_{MV} \times \dot{q}_{RLshunt} + P_{alv} \times \left(\dot{Q} - \dot{q}_{RLshunt}\right) \quad (9)$$

Concentration and Second Gas Effects. The absolute concentration of an inhaled anesthetic influences its uptake. In the previous discussion and illustrations, an inhaled anesthetic has been assumed to represent a small fraction of the inhaled gas mixture, and that transalveolar uptake of the anesthetic results in a decrease in P_{alv}

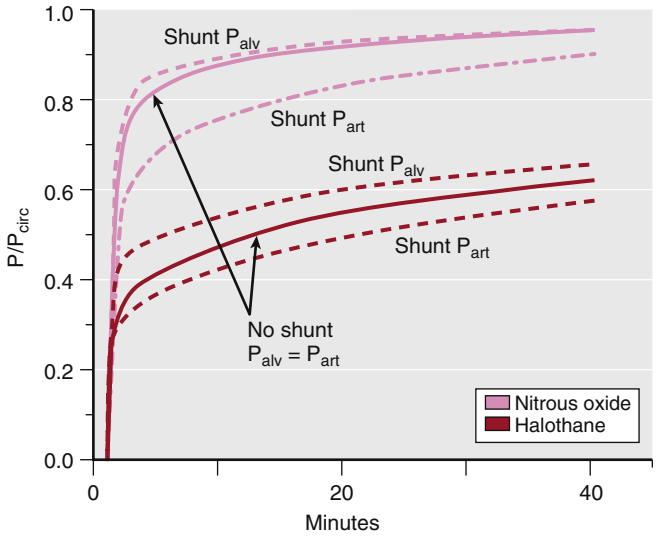


Figure 26-7. Effect of right-to-left pulmonary shunt on the anesthetic partial pressure in alveolar gas and arterial blood. The *curves* represent anesthetic partial pressures in alveolar gases (*dashed lines*) and arterial blood (*dash-dot lines*) under conditions of 40% right-to-left shunt and no shunt (*solid lines*). Pulmonary right-to-left shunting bypasses alveolar uptake, so that less anesthetic is removed from pulmonary gases; this accelerates the rise in P_{alv}. In addition, the anesthetic partial pressure in arterial blood (P_{art}) is a mixture of pulmonary venous blood at P_{alv} and shunted mixed venous blood at P_{MV}. Thus P_{art}, which determines the rate of anesthetic uptake into tissues, rises more slowly than P_{alv} when R-to-L shunting is present. The shunt effect on P_{art} versus P_{alv} is larger for insoluble anesthetics (e.g., N_2O) than for soluble anesthetics (e.g., halothane). Other model parameters were set for open circuit delivery (constant P_{circ}) with MV = 6 L/min and C.O. = 5 L/min. P_{alv}, Alveolar anesthetic partial pressure. *CO,* Cardiac output; *MV,* minute ventilation; P_{MV}, anesthetic partial pressure in mixed venous blood.

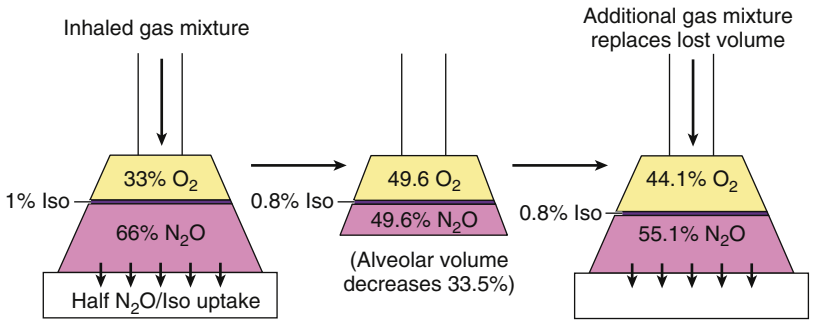


Figure 26-8. Concentration and second gas effects. The figure depicts alveolar gases at the beginning of an anesthetic. After an initial inspiratory breath, alveoli are filled with the gas mixture in the circuit (66% N_2O, 33% O_2, 1% isoflurane) at their normal end-inspiratory volume *(left panel)*. After half of the N_2O and isoflurane are absorbed into pulmonary blood, the alveolar gas volume is reduced by 33.5%. At this point, the volume of N_2O equals the volume of O_2, and the gas mixture is 49.6% N_2O, 49.6% O_2, and 0.8% isoflurane. Inflow of additional inspired gas mixture returns alveolar volume to its original value, resulting in a gas mixture of 55.1% N_2O, 44.1% O_2, and 0.8% isoflurane. The alveolar partial pressure of N_2O falls much less than the fractional uptake (the concentration effect). In addition, the partial pressure of O_2 increases relative to the inspired gas O_2 content, and the partial pressure of isoflurane is sustained close to the inspired value, increasing its rate of uptake (the second gas effect). *Iso,* Isoflurane.

and negligible changes in alveolar gas volume. However, when the inhaled anesthetic represents a large fraction of the inhaled gas mixture, its rapid uptake results in a smaller relative alveolar anesthetic concentration drop, because the volume of alveolar gas also decreases. This is known as the *concentration effect*.[24] In an imaginary situation in which a patient is breathing 100% anesthetic, uptake into pulmonary blood reduces the volume of anesthetic gas in the alveoli without altering its concentration or partial pressure (oxygen-induced atelectasis occurs through a similar mechanism). A typical situation, illustrated in Figure 26-8, is delivery of 66% N_2O with 33% O_2, and 1% isoflurane. Assuming cardiac output equals 5 L/min, the initial rates of N_2O uptake is given by Equation 7 as 5000 mL/min × 0.47 × 0.66 atm = 1550 mL/min N_2O, indicating that a large fraction of N_2O is initially taken up during the first few breaths. If we assume that half the N_2O and half the isoflurane are rapidly taken up following the first breath of this gas mixture, then alveolar volume drops by 33.5% and the remaining alveolar gas contains 33 parts N_2O, 33 parts O_2, and 0.5 parts isoflurane (49.6% N_2O, 49.6% O_2, and 0.8% isoflurane). Despite 50% uptake of N_2O, the significant reduction in alveolar gas volume results in a concentration of remaining alveolar N_2O that is only 24% less than its initial value.

The *second gas effect* is also evident in this example: the rapid uptake of N_2O and reduced alveolar gas volume sustains P_{iso} near its original inspired value and increases alveolar P_{O2}, thereby augmenting uptake of these gases.[25] Note also that the rapid uptake of N_2O into blood results in an effective increase in minute ventilation, because more circuit gas is passively drawn into alveoli as alveolar gas is absorbed rapidly. These effects have been demonstrated in humans[26] and animals,[25] and theoretically are short-lived and pertain only to the period of initial rapid transfer of N_2O from alveoli to blood. The second gas effect may persist beyond the initial rapid phase of N_2O uptake.[27]

Distribution of Anesthetic into Tissues

Blood exiting the pulmonary capillaries enters the pulmonary vein and the left heart. Inhaled anesthetics are then distributed via arterial blood to various body tissues. The rate of increase of anesthetic partial pressure within each tissue is determined by tissue-specific arterial blood flow ($\dot{q}$), effective volume (the product of anatomic volume and tissue/blood partition coefficient, $\lambda_{t/b}$), and the anesthetic partial pressure gradient between arterial blood and the tissue:

$$\frac{dP_i}{dt} = \frac{\dot{q}_i}{V_i \times \lambda_{i/b}} \times (P_{art} - P_i) \qquad (10)$$

where *i* designates a particular organ or type of tissue. Values used in model calculations are summarized in Table 26-2. The time required for anesthetic partial pressure equilibration between arterial blood ($P_{art} = P_{alv}$) and a specified tissue is shorter if its blood flow is high, and longer if that tissue has a large effective volume (Figs. 26-2, 26-9).

Traditionally, anesthetic distribution has been described for four distinct tissue groups. The vessel-rich group (VRG) includes the heart, brain, spinal cord, liver, and kidney. Together, these organs compose approximately 10% of the adult human body mass; however, they receive approximately 70% of cardiac output under normal resting conditions. As a result, time constants for anesthetic equilibration between blood and these organs are typically only a few minutes (see Table 26-2). Of particular interest is the equilibration time for the CNS, where anesthetic effects are mediated. After the highly perfused VRG tissues, skeletal muscle is the next compartment to equilibrate with inhaled anesthetics. Muscle composes approximately 40% of body mass in a healthy adult, making muscle the largest single compartment based on weight. Moreover, most inhaled anesthetics partition into muscle more than into brain, resulting in an increased effective volume for anesthetic uptake into this compartment. At rest, muscle receives 10% to 15% of cardiac output (20 mL/kg/min), but this value can increase dramatically during exercise, stress, fever, or other states associated with high cardiac output.[28] Taken together, these factors generally result in slow equilibration between anesthetic in blood and muscle, with typical time constants of hours (see Table 26-2). The third tissue

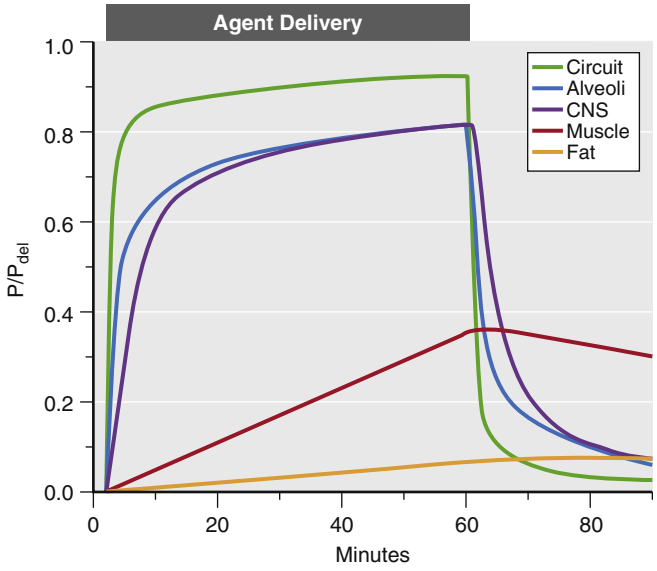


Figure 26-9. The rate of anesthetic partial pressure rise in different tissue compartments. The *curves* represent model calculations for sevoflurane delivered at 6 L/min fresh gas flow, with 5 L/min ventilation and 5 L/min cardiac output. The anesthetic partial pressure in the central nervous system (CNS; *purple line*), part of the vessel rich group, equilibrates rapidly with P_{alv} (*blue line*), although a lag-time of several minutes is evident when P_{alv} is rapidly rising or falling. The anesthetic partial pressures in both muscle *(red line)* and fat *(orange line)* rise and fall much more slowly, because muscle and fat compartments represent much larger effective volumes (see Fig. 26-2) and have lower blood flow than the vessel-rich group does. Note that anesthetic partial pressure in fat continues to rise after anesthetic delivery stops, as long as partial pressure in alveolar gas (and arterial blood) is greater than that in the fat compartment.

group is *fat*, which in a normal adult composes 25% of body mass and receives 10% of cardiac output.[29] Potent volatile anesthetics partition avidly into fat; therefore, fat represents the largest effective volume for uptake of these drugs (see Fig. 26-2, Table 26-2). The extremely large effective volume coupled with relatively low blood flow results in very slow equilibration of anesthetics between blood and fat, with time constants approaching days. A fourth group, including skin, cortical bone, and connective tissue, is referred to as *vessel poor tissues*. These tissues compose approximately 15% of an average adult body while receiving less than 5% of cardiac output at rest. Induction of general anesthesia impairs normal sympathetic nervous function, resulting in increased blood flow to normally cool skin in the extremities.[30] The blood volume represents approximately 7% of body mass and may be considered another compartment for anesthetic uptake, while also conveying drug to other tissue compartments.

As stated previously, increased cardiac output results in increased anesthetic uptake and a slower rate of rise of P_{alv}. Without confounding factors, increasing cardiac output slows the induction of general anesthesia with inhaled anesthetics.[21,31] This result can seem counterintuitive when increasing cardiac output increases uptake of anesthetic into the patient's body and hastens its delivery to the tissues. However, during induction the anesthetic partial pressure in blood and downstream tissue compartments cannot be higher than that in the upstream alveolar compartment. Increased cardiac output slows the rate of increase of P_{alv} and thus also slows the rate of increase of the anesthetic partial pressure in blood (P_{art}), the CNS (P_{CNS}), and other highly perfused tissues. The extra anesthetic uptake is primarily into muscle, which is a large tissue compartment with a high capacity for anesthetic and is where much of the excess cardiac output flows. For example, a 50% increase in cardiac output can more than double muscle blood flow, diverting the majority of anesthetic to muscle, lowering P_{alv}, and thus slowing anesthetic uptake into target tissues in the CNS. If one could manipulate inhaled anesthetic delivery to maintain constant P_{alv}, which may be achievable with automated feedback control of vaporizer output and FGF,[32] and then increasing cardiac output might have a different effect. Model simulations where P_{alv} is maintained at a constant level show that uptake into VRG tissues, including brain tissue, increases more rapidly as cardiac output increases.[33]

In pediatric patients (see Chapter 93), the balance of cardiac output to various tissue beds differs from that in adults. Thus, although cardiac output per kilogram body weight is larger in children than in adults, induction of anesthesia is more rapid in young children than in adults, because a disproportionate amount of perfusion goes to the vessel rich organs, such as the brain.[34]

The equilibrium distribution volumes for most inhaled anesthetics are extremely large, with the largest compartment by far being fat. However, equilibration with fat is so slow that this compartment usually plays a relatively minor role in the pharmacokinetics of inhaled anesthetics. During a typical general anesthetic lasting from 30 minutes to several hours, the blood, VRG organs, and muscle are the compartments into which inhaled anesthetics mostly distribute.

Although the model in Figure 26-2 illustrates anesthetic distribution only *via* arterial blood flow, intertissue diffusion takes place between abutting tissues that have large interfacial surface areas. In particular, direct diffusion from organs with high anesthetic partial pressures to abutting tissues with low partial pressure and high capacity for anesthetic uptake may also contribute to drug distribution. Examples of this process include anesthetic diffusion from the heart, liver, and kidneys to surrounding fat in the pericardium and abdomen.[35,36]

Mixed Venous Anesthetic Partial Pressure

The anesthetic partial pressure in mixed venous blood entering the pulmonary circulation is a weighted average of the venous outflows from all tissues and organs, which converge in the right ventricle:

$$P_{MV} = \sum_{i=1}^{n} \frac{\dot{Q}_i}{\dot{Q}} \times P_i \qquad (11)$$

As P_{MV} rises, the gradient driving uptake of inhaled anesthetics from alveoli weakens. The difference between the delivered (inspired) and the alveolar (end-expiratory) anesthetic concentrations also shrinks, causing transpulmonary uptake to slow (Equation 7). Systemic (left to right) shunting causes P_{MV} to increase more rapidly than it would in the absence of such shunts. When blood flow to other tissues remains normal and the left-to-right shunt

simply represents excess cardiac output, the resulting increase in anesthetic uptake (Equation 7) is offset by the increase in P_{MV}, resulting in a slight increase in the rate of anesthetic delivery or uptake into the brain, muscle, and other tissues. In cases where large left-to-right shunts result in reduced blood flow to other tissues, anesthetic equilibration in those tissues will be relatively slow.

SYNTHESIS OF THE MODEL AND INHALED ANESTHETIC INDUCTION: PK/PD

The rate of equilibration (pharmacokinetics) of inhaled anesthetics among the various compartments involved in delivery to a patient, vaporizer, circuit, lung, blood, and various tissues, has been discussed. However, in a clinical setting, the goal of the anesthesia provider is the reversible production of certain desired effects (amnesia, unconsciousness, and immobility) in the patient in a reasonable amount of time. To achieve these goals, pharmacokinetics must be combined with knowledge of the effects produced at different anesthetic partial pressures in target tissues (i.e., dose-response or pharmacodynamics). The most relevant pharmacodynamic guidelines are minimum alveolar concentration (MAC)–immobility,[37] the alveolar anesthetic concentration preventing movement response to surgical stimulus in 50% of subjects, and MAC-awake,[7] the alveolar anesthetic concentration preventing perceptive awareness in 50% of subjects, both measured under conditions where P_{alv} is in equilibrium with anesthetic partial pressure in the central nervous system (P_{CNS}). MAC-awake for potent volatile anesthetics is typically 0.34 × MAC-immobility,[38] whereas MAC-awake for N_2O is approximately 0.7 × MAC immobility (see Table 26-1). During induction of anesthesia, the goal may be achieving a high probability of immobility following incision ($P_{CNS} \approx 1.2 \times$ MAC-immobility) within 15 minutes, while avoiding the deleterious effects of overly deep anesthesia. At the end of an anesthetic, return of consciousness is likely to occur when P_{CNS} decreases to less than MAC-awake. The targets used for this illustrative model patient are estimates. In clinical practice, targets for anesthetic depth vary widely depending on patient factors, the presence of noxious stimuli, and other drugs that may be administered.

There are a variety of strategies to deliver inhaled anesthetics and meet the goals just discussed. The first important consideration is that P_{del} from the vaporizer must be higher than the target P_{alv} or P_{CNS} (overpressure). The more overpressure used, the more rapidly anesthetic is delivered. High fresh gas flows, large minute ventilation, and a low-solubility drug will also increase the rate of anesthetic delivery and the rate of rise of P_{alv} and P_{CNS}. These factors, and particularly overpressure, also increase the risk of delivering an overdose of anesthetic drug. A common strategy is to initiate inhaled anesthetic delivery with moderate to high fresh gas flows (≥6 L/min) and moderate overpressure ($P_{del} = 2 \times$ MAC-immobility), and reduce P_{del} after P_{alv} reaches or slightly exceeds the target level (Fig. 26-10, *left*). The need to maintain overpressure and slightly overshoot P_{alv} derives from the fact that distribution of drug to muscle maintains a high delivery requirement after the initial rapid phase of uptake. If P_{del} is decreased too quickly, then P_{alv} can decrease below the target. P_{del} or FGF is slowly adjusted downward as the anesthetic inspired-to-expired difference in anesthetic partial pressures ($P_{del} - P_{alv}$) decreases.

CLOSED-CIRCUIT OR LOW-FLOW DELIVERY OF ANESTHESIA

The use of high or moderate fresh gas flows, while enabling use of less overpressure, results in far more anesthetic drug being delivered than being taken up into tissues. Note in the left panel of Figure 26-10, the amount of isoflurane delivered is 4.5-fold more than that taken up, whereas delivered sevoflurane is 7.2-fold greater than absorbed drug. Thus, over 80% of delivered volatile anesthetic is waste using the moderately high FGF approach illustrated in this example. Rebreathing circuits allow the use of fresh gas flows well below minute ventilation, which results in reduced anesthetic discharge into the waste-scavenging system. Less waste discharge translates into both reduced costs and reduced global environmental impact of anesthetic gases within the atmosphere, where these anesthetics contribute to climate change (reviewed later). Additional benefits of low FGF and rebreathing include retention of expired heat and water vapor in rebreathed gas, improving airway epithelial health, and reducing accumulation of dried airway secretions.

Closed-circuit anesthesia represents the ultimate limit of low gas flows, where fresh gases are delivered only in quantities sufficient to replace those taken up into tissues, metabolized (especially O_2), or otherwise lost to the environment, and the vast majority of gas in the breathing circuit undergoes rebreathing.[39] Achieving this goal requires a leak-free breathing circuit, complete removal of CO_2, and careful attention to the inspired-to-expired values of oxygen and anesthetic gases, and even to the build-up of expired nitrogen that can slowly accumulate in the breathing circuit. Under these conditions, oxygen consumption in an anesthetized patient can be lower than 3 mL/kg/min, translating to O_2 replacement of around 200 mL/min in a patient weighing 70 kg. There are several significant limitations to this technique. Because all exhaled CO_2 must be removed by adsorbents, closed circuit anesthesia increases the risk of rebreathing CO_2 as adsorbent capacity diminishes. Anesthetic breakdown products, carbon monoxide (CO), and slowly degassing nitrogen from blood can accumulate in the breathing circuit.[40] Clinicians must be aware that patient metabolism may deplete oxygen from the breathing circuit and can result in delivery of a hypoxic gas mixture during use of closed circuit anesthesia. When using very low FGF values, changes in the vaporizer output (P_{del}) result in extremely slow changes in P_{circ} and the subsequent depth of anesthesia. Closed circuit anesthetic administration can be guided by the "square root of time" rule, proposed by Severinghaus[41] and detailed in now classic descriptions.[42] This rule states that the rate of anesthetic uptake decreases approximately at the square root of delivery time. We can estimate the uptake of 1.2 MAC isoflurane during the first minute of anesthesia using Equation 7. Thus, Cardiac output × $\lambda_{b/g}$ × 1.2 MAC = Initial uptake of isoflurane

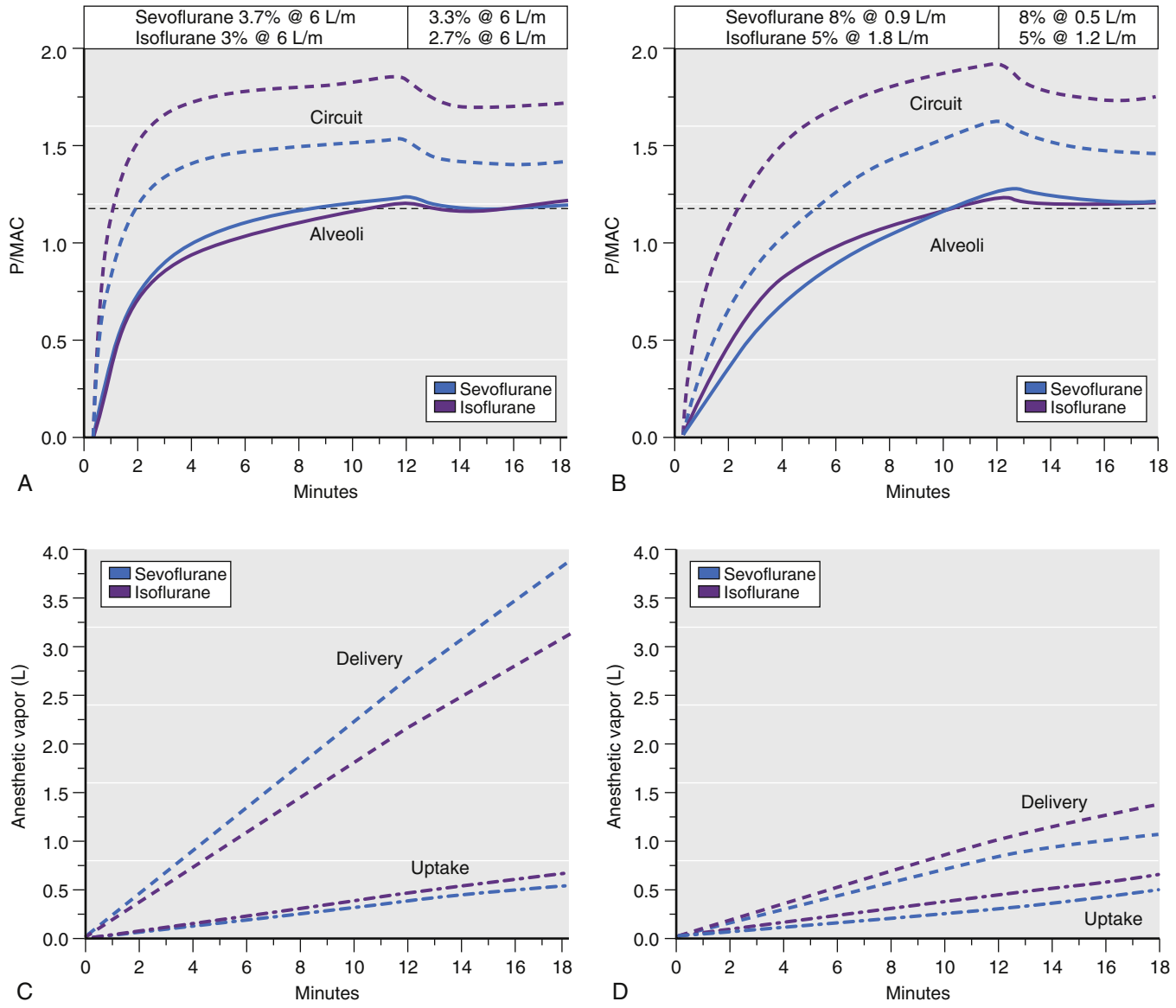


Figure 26-10. Effect of induction technique on uptake and delivery of inhaled anesthetics. **A,** Anesthetic partial pressures in both the circuit and alveoli during inhalation induction with moderate (6 L/min) fresh gas flows and modest (twofold to threefold) overpressure for sevoflurane *(blue)* and isoflurane *(purple)*. P_{alv} reaches 1.2 × MAC in approximately 12 minutes, and approximately 10% downward adjustment of vaporizer settings results in maintenance of P_{alv} near this target level. Additional downward adjustments in vaporizer setting or fresh gas flows, or both, would be needed to maintain this P_{alv} level. **B,** Anesthetic partial pressures in both the circuit and alveoli during inhalation induction with low (less than 2 L/min) fresh gas flows and maximal (fourfold) overpressure for sevoflurane *(blue)* and isoflurane *(purple)*. P_{alv} reaches 1.2 × MAC in approximately 12 minutes, and a downward adjustment of fresh gas flow results in maintenance of P_{alv} near this target level. **C,** The total anesthetic vapor delivered and taken up into the model patient from panel *A*. Note that delivery far exceeds uptake, more so for the low solubility anesthetic (sevoflurane). **D,** The total amount of anesthetic vapor delivered and taken up into the model patient from panel *B*. Note that uptake is similar, whereas delivery is much lower than that using a high-FGF technique. The low-FGF technique reduces waste more so for anesthetics with low blood solubility (e.g., sevoflurane) than for highly soluble drugs (e.g., isoflurane). $P_{alv,}$ Alveolar anesthetic partial pressure; *MAC,* minimum alveolar concentration.

vapor (5000 mL/min × 1.4 × 0.0128 atm = 90 mL/min). Using the square root of time rule, uptake at 4 minutes would be half of the initial rate (45 mL/min), and uptake at 9 minutes would be one third of the initial rate (30 mL/min). To deliver 90 mL/min of isoflurane vapor (0.54 mL of liquid isoflurane at 20° C) at a maximal vaporizer setting of 5% requires 1800 mL/min of fresh gas flow, far greater than the target flow for closed circuit. Anesthetists can overcome this limitation by directly injecting small volumes of liquid anesthetic into the expiratory limb of the breathing circuit[43]; however, this approach requires vigilant attention to the clock along with many other factors. In inexperienced hands, miscalculation or mistiming of anesthetic injection runs the risk of overdose.

Because of the challenges of closed-circuit administration, a more common practice is to use moderate to high fresh gas-flows to achieve rapid changes during induction of anesthesia, reserving closed-circuit anesthesia to periods where the P_{circ} to P_{alv} difference is small. Even so, changes in a patient's metabolism because of temperature variation, degree of muscle relaxation, or surgical stimulation can result in the need for frequent adjustments

to oxygen flow and anesthetic depth, making anesthesia delivery in a closed-circuit system relatively unstable and difficult.

Low-flow anesthetic delivery, typically with fresh gas flows of 0.5 to 1.0 L/min during maintenance, is a compromise between closed-circuit delivery of anesthesia and the use of high fresh gas flows. Much of the waste and other problems associated with high fresh gas flows are avoided, whereas the instability associated with a strict closed-circuit technique is also moderated. As noted earlier (see Equilibration between Circuit and Pulmonary Airspace), the inspired anesthetic concentration (P_{circ}) depends on both P_{del} and P_{pulm} when rebreathing occurs. Thus, as FGF diminishes, P_{del} must be adjusted upward to compensate for diminished delivery. Given that the maximal output setting on most vaporizers is approximately 4 × MAC-immobility, anesthetic delivery at 1 L/min and maximal P_{del} is still far less than the previous example with 6 L/min and P_{del} = 2 × MAC isoflurane. Higher FGF or a less soluble anesthetic drug, or both, are needed to achieve target P_{CNS} in less than 15 minutes, but as uptake diminishes, FGF can be gradually reduced (see Fig. 26-10, *right*). With soluble anesthetics such as isoflurane, maximal vaporizer settings and FGF near 2 L/min is required for reasonably rapid induction. FGF can be decreased incrementally as P_{alv} reaches the target level, and eventually vaporizer output is decreased as well. With low solubility anesthetics such as desflurane or sevoflurane, initial FGF values near 1.0 L/min can be used in combination with maximal vaporizer settings and a similar strategy of reducing FGF. As a result, vaporizer output results in reasonably rapid induction while minimizing waste of volatile anesthetics. Low FGF can be maintained until high FGF is again needed to achieve emergence at the end of the anesthetic administration.

When using high vaporizer output settings, diligence must be maintained to avoid overdosing the patient by reducing FGF and the vaporizer setting in a timely and deliberate manner. Thus, low-FGF techniques combined with significant overpressure should not be applied in situations when other clinical issues require the attention of the anesthesia provider.

PHARMACODYNAMIC EFFECTS OF ANESTHETICS ON UPTAKE AND DISTRIBUTION

The pharmacodynamic effects of most inhaled anesthetics also include changes in ventilatory and cardiac function that thereby introduce dynamic changes in the drug pharmacokinetics. Spontaneous ventilation is reduced by inhalation of potent volatile anesthetics in a dose-dependent manner.[44] As a result, spontaneously breathing patients will autoregulate to some degree by reducing their uptake of anesthetic as depth of anesthesia increases. This autoregulation provides a degree of safety that is absent in manually or mechanically ventilated patients, who may be subjected to excessive delivery of these anesthetics if a vaporizer is inadvertently set to deliver overpressure.[45] Inhaled anesthetics also reduce cardiac output, a pharmacodynamic effect that leads to a more rapid increase in P_{alv}/P_{circ} and consequently a more rapid increase in the anesthetic partial pressure in heart, brain, and other highly perfused tissues.[46] Halothane is the anesthetic associated with the greatest decrease in cardiac output. If anesthetic delivery continues with a decreasing cardiac output, a positive feedback loop of worsening cardiac depression and a rapid descent toward hemodynamic collapse can occur. For more details on the effects of inhaled anesthetics on the respiratory and circulatory systems, see Chapters 27 and 28.

EFFECT OF NITROUS OXIDE ON GAS-FILLED SPACES

Because N_2O is often used at high partial pressure, it diffuses into, and accumulates in, spaces containing air or other immobile gases, with potentially deleterious physiologic consequences. Clinically relevant examples include intravascular air emboli,[47] pneumothorax,[48] air in the inner chamber of the ear,[49] intravitreal gas bubbles (see Chapter 84),[50] intrathecal air, pneumoencephalus,[51] and air in the gastrointestinal tract.[48] Air-filled spaces contain mostly nitrogen, a gas that composes 78% of air, but is thirtyfold less soluble in blood than N_2O ($\lambda_{b/g}$ for N_2 is 0.015). Thus, N_2O diffuses down its pressure gradient from blood and surrounding tissues into air-filled spaces, whereas N_2 removal from these spaces is far slower, even with inspired $P_{N2} = 0$. As N_2O enters and the total number of gas molecules in an air space increases, it will expand in volume, increase in pressure, or both, depending on the compliance of the space.

In highly compliant air-filled spaces, such as intravascular air bubbles or small pneumothoraces, N_2O accumulation increases the total volume of gas (Fig. 26-11, *A*) with minimal changes in pressure. Air spaces expand as N_2O enters until the P_{N2O} within the air space matches that in surrounding blood, establishing equilibrium. The maximum potential gas volume expansion in a highly compliant space is:

$$\frac{V}{V_{init}} = \frac{1}{1 - P_{N2O}} \qquad (12)$$

Thus, administration of 50% N_2O can double air-space volume, whereas 67% can potentially triple air-space volume. N_2O can significantly worsen the cardiovascular or tissue consequences of intravascular air emboli, potentially making a nonlethal volume of venous air embolus lethal.[47] Expansion of intracranial air or gastrointestinal gas volume by N_2O can result in life-threatening intracranial expansion of this gas volume or impede surgical exposure or abdominal wound closure. Gas-space compartment compliance eventually decreases as volume expands, resulting in increased pressure. For example, N_2O can expand a small pneumothorax to a point where intrathoracic pressure increases, compressing lung, displacing the mediastinum, and reducing venous return (tension pneumothorax). The endotracheal tube cuff filled with air is also susceptible to expansion by N_2O. Increased tracheal cuff pressure can impair perfusion of surrounding mucosa.[52] Air-filled laryngeal mask airway

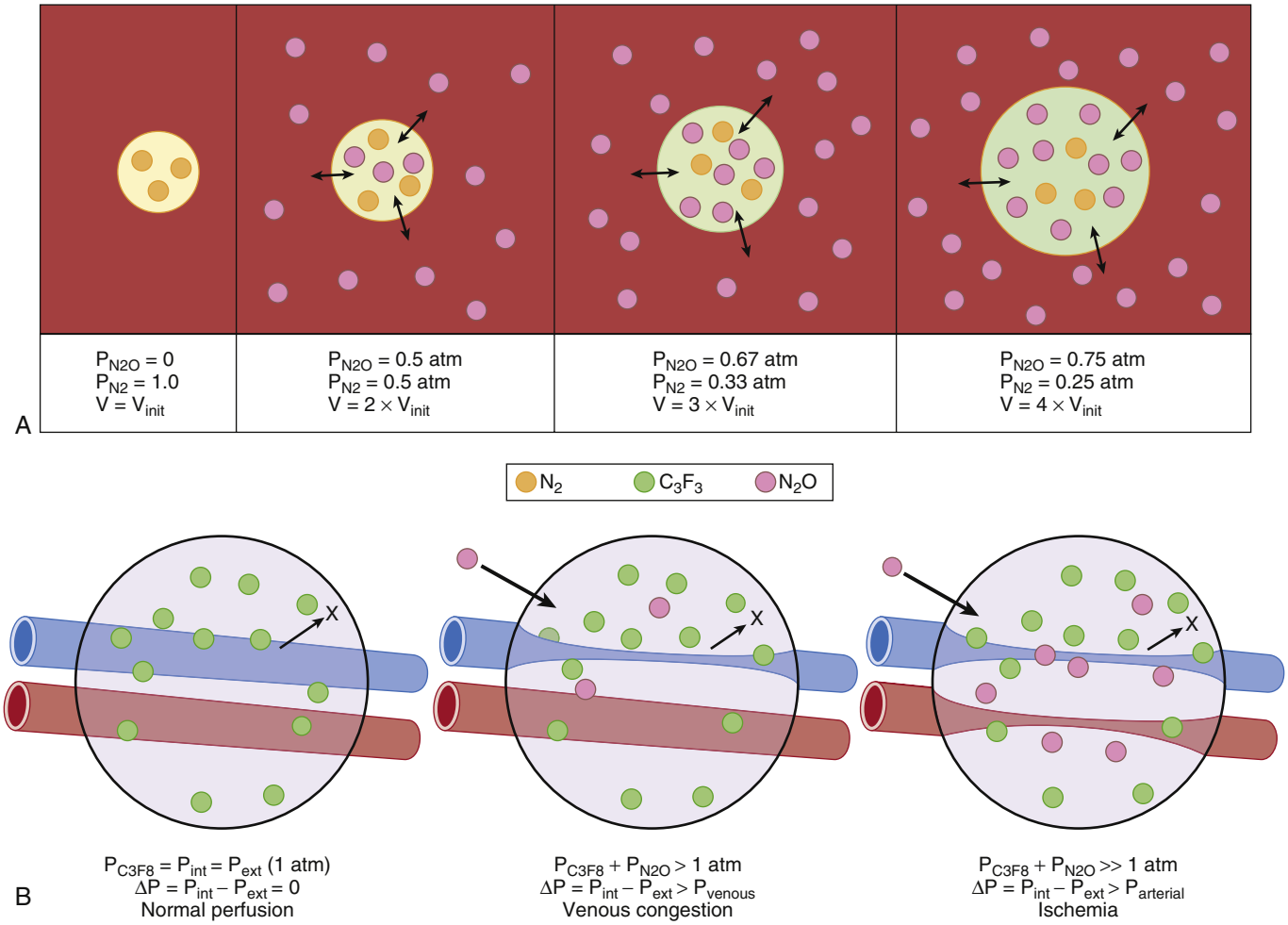


Figure 26-11. Nitrous oxide accumulation in gas-filled spaces. **A,** Expansion of a compliant air-filled space (a small vascular air embolus) occurs as the partial pressure of nitrous oxide in surrounding blood increases. Each panel depicts the equilibrium condition with P_{N2O} inside the bubble equal to that in blood. Labels below each panel summarize the partial pressures of N_2O and N_2 in the bubble as well as the bubble volume relative to its initial value (V_{init}). **B,** The increase in pressure inside a noncompliant, gas-filled compartment (e.g., an eye following perfluoropropane [C_3F_8] injection) with blood vessels passing through it. As N_2O accumulates, the pressure in the compartment increases, which can result in venous congestion *(middle panel)* or ischemia *(right panel)* in tissues that are perfused by the vessels in this compartment (e.g., the retina).

cuffs[53] and the air-filled balloon of a Swan-Ganz catheter[54] can similarly expand during N_2O administration.

In noncompliant gas-filled spaces, gas pressure rises as N_2O enters, until P_{N2O} within the air space matches that in blood. The maximal potential pressure in such a space, relative to surrounding ambient pressure, is therefore P_{N2O}. Thus, in a patient inhaling 50% N_2O, pressure in such a gas-filled compartment could approach 380 mm Hg, far greater than typical arterial perfusion pressures. A clinically important example is that of intravitreal sulfur hexafluoride (SF_6) or perfluoropropane (C_3F_8) bubbles, which are injected as the sclera is closed at the end of intraocular or retinal surgery[50] (see Fig. 26-11, *B*). These gases persist even longer than N_2 does because of their low blood solubility. If N_2O is administered to these patients at the time of intravitreal bubble injection, its diffusion into the bubble can rapidly increase intraocular pressure above that in retinal veins, producing retinal congestion. If the pressure in the eye further increases above systolic arterial pressure, retinal ischemia resulting in blindness might ensue (see Chapter 84).

The rate of N_2O diffusion into gas-filled spaces in the body depends on local blood flow and the surface-to-volume ratio of the space. Thus, small air emboli expand within seconds, because they have high surface/volume ratios and they are surrounded by a relatively infinite supply of blood containing dissolved N_2O. Larger air emboli expand more slowly, because their surface/volume ratio is smaller (spherical surface/volume is inversely proportional to radius). Small pneumothoraces typically have large surface/volume ratios and high local blood flow. Animal experiments show that inhalation of 75% N_2O approximately doubles pneumothorax volume in 10 minutes and triples it in 30 minutes (Fig. 26-12). Compared with pneumothorax air pockets, gastrointestinal air pockets have lower surface/volume ratios and lower blood flow. Thus, expansion of gas in the gastrointestinal tract is much slower than that in a pneumothorax. In animal studies (see Fig. 26-12), inhalation of 70% to 80% N_2O doubled intestinal gas volume after approximately 2 hours.[48]

N_2O is contraindicated in patients with pneumothorax, pneumocephalus, and closed dura or in those at high risk for vascular air embolus. Air-space expansion can impede surgery when substantial gastrointestinal air is present and N_2O exposure is prolonged, or it can be of

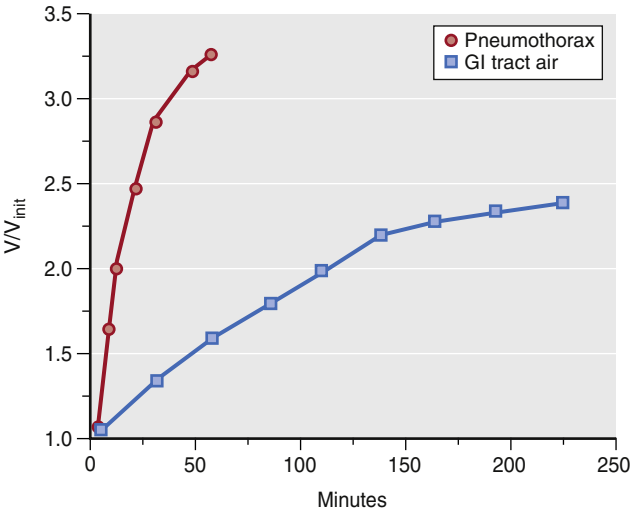


Figure 26-12. The rate of air-space expansion during nitrous oxide administration. The rate and extent of expansion of air pockets injected into either the pleural space *(red circles)* or the gastrointestinal tract *(blue squares)* of dogs during the inhalation of a 25% O_2/75% N_2O gas mixture is shown. Air pockets in stomach, small intestine, and colon expand more slowly than those in a pneumothorax do. *GI,* Gastrointestinal. *(Data are approximations from Eger EI II, Saidman LJ: Hazards of nitrous oxide anesthesia in bowel obstruction and pneumothorax,* Anesthesiology *26:61-66, 1965.)*

little consequence when the initial volume of gas in the gut is small or when the surgery is brief.

RECOVERY FROM ANESTHESIA

Similarities and Differences to Induction

Clearance of inhaled anesthetics from target tissues (brain and spinal cord) is primarily via the same pathways used for anesthetic induction: anesthetic gases flow from tissue into venous blood and then to the lungs. If P_{alv} is less than P_{MV}, then the net flow of anesthetic will be out of the blood and into alveoli, where it is subsequently exhaled. To achieve the fastest clearance possible, P_{circ} must therefore be as low as possible, and this is achieved using high flows of nonanesthetic carrier gases (oxygen and air) after discontinuing delivery of anesthetic. The same factors that affect transalveolar anesthetic exchange during induction also affect clearance via this route. Increasing ventilation will accelerate clearance (see Fig. 26-4), whereas increased cardiac output slows clearance, because more gas-exchange volumes are required to remove anesthetic from the larger blood flow (see Fig. 26-5). Highly blood-soluble anesthetics, which increase the effective blood flow, clear more slowly than insoluble anesthetics (see Fig. 26-6). Return to consciousness, which usually occurs after P_{CNS} drops below MAC-awake, is faster following desflurane or sevoflurane anesthesia than after isoflurane anesthesia. N_2O, which is characterized by blood solubility similar to that of desflurane, provides an even faster return to consciousness, because of two additional advantages. First, the concentration effect works in reverse during clearance for N_2O, increasing effective alveolar ventilation and maintaining the gradient for flow from pulmonary blood to alveoli. Second, MAC-awake for N_2O (0.71 atm at 40 years old) is near typical inhaled concentrations during general anesthesia; therefore, elimination of only a small fraction of this drug is associated with return to consciousness. This is also why N_2O as the sole hypnotic drug is associated with a high risk of intraoperative awareness, which can be prevented by using a balanced gas mixture of N_2O together with end-tidal concentrations of approximately 1 × MAC-awake of a second potent inhaled anesthetic.

Body composition has an increasing effect as the length of anesthetic exposure increases, especially for highly soluble anesthetics. Compared with standard models, patients with increased muscle or fat have larger volumes of anesthetic drug distribution over time, resulting in slower clearance rates.[55] One important difference between anesthetic uptake and clearance is that although overpressure can be used to hasten uptake and induction of anesthesia, the vaporizer setting cannot be set to less than zero. Thus, the most readily modifiable factors to affect the rate of anesthetic clearance are fresh gas flow and minute ventilation.

Context Sensitive Recovery from Anesthesia

Although the concept of context-sensitive half-time is typically applied to continuously infused intravenous drugs that distribute among multiple pharmacokinetic compartments, the concept also applies to inhaled anesthetics.[56] After a short period of inhalation and uptake, anesthetic clearance from blood is rapid through both exhalation and distribution to muscle and other tissues. As a result, P_{alv} decreases rapidly to a low value after discontinuing anesthetic delivery. After prolonged periods of inhalation and uptake, the anesthetic partial pressures in muscle and other compartments increase closer to that in blood, reducing the contribution of distributive clearance. Instead, clearance from the central blood compartment is slowed by the reverse flow of anesthetic from the high-capacity tissues. Thus, in comparison with a short period of inhalation, prolonged inhaled anesthesia is followed by a smaller initial decrease in P_{alv} and a more pronounced slow clearance phase, resulting in slower recovery from anesthesia (Fig. 26-13). As with other factors, context sensitivity is exaggerated in highly soluble anesthetics, and it has less impact with anesthetics that display low blood and tissue solubilities.[57] The relative advantage of low blood solubility anesthetics increases with the duration of anesthesia. There is only a small difference (2.5 minutes) between predicted times to awakening after a short anesthetic with isoflurane versus desflurane, but significantly faster awakening can be achieved using the low-solubility drug for long cases.

Percutaneous and Visceral Anesthetic Loss

Aside from pulmonary exchange, some portion of inhaled anesthetics is lost by diffusion through other large area interfaces between the body and surrounding air. The skin surface area of an average human is approximately 2 m^2, and blood flow through skin during general anesthesia may be substantial because of inhibition of normal thermoregulatory vasoconstriction.[30] Nonetheless, transcutaneous losses of general anesthetics probably contribute negligibly to their clearance.[58,59] During open abdominal or thoracic surgery, visceral surfaces are also

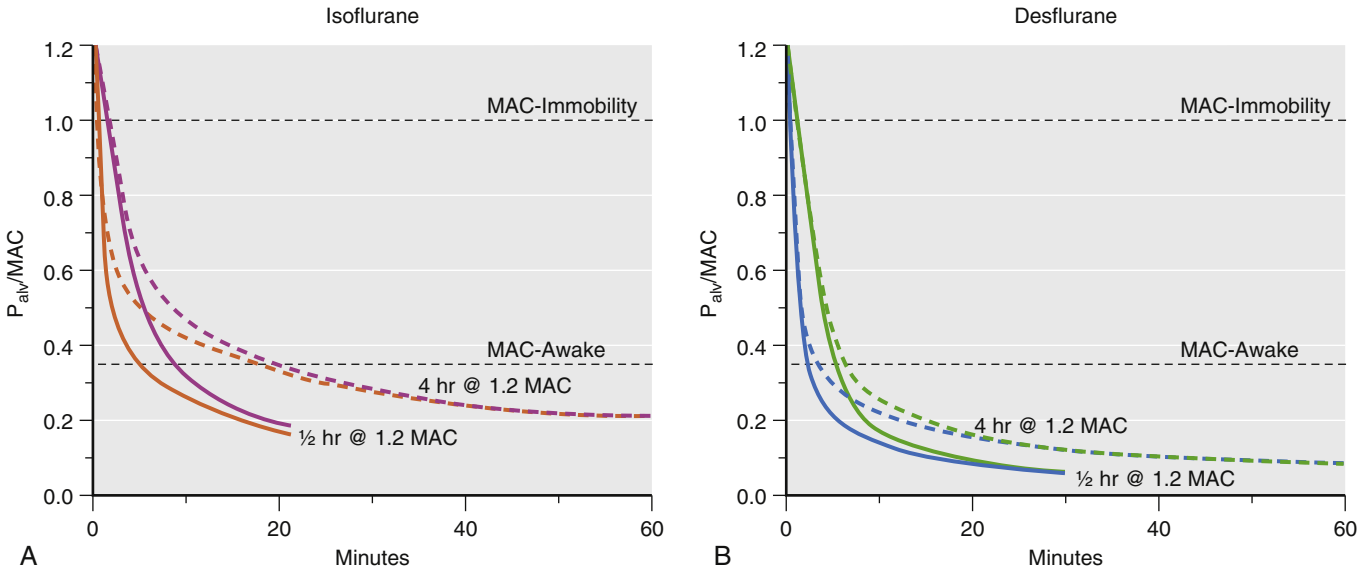


Figure 26-13. Inhaled anesthetic washout and time to awakening depends on duration of anesthesia. The panels depict model calculations of P_{alv} and P_{CNS} normalized to MAC during washout at 10 L/min FGF following anesthesia at approximately 1.2 × MAC-immobility for 30 minutes *(solid lines)* or 4 hours *(dashed lines).* The MAC-awake (approximately 0.34 × MAC-immobility) is shown to indicate the threshold below which typical patients regain perceptive awareness after general anesthesia. Although P_{alv} drops earlier than P_{CNS}, the clinically relevant endpoint (return of consciousness) is predicted when P_{CNS} falls below MAC-awake. **A,** Washout using a pharmacokinetic model for isoflurane (orange is P_{alv}, purple is P_{CNS}). The 30-minute isoflurane uptake was 990 mL of vapor, and the 4-hour isoflurane uptake was 3420 mL of vapor. Prolonged anesthesia with isoflurane dramatically increases the time required to wash out sufficient drug to achieve awakening. After a 30-minute anesthetic, P_{CNS} drops to MAC-awake in 9 minutes, whereas it takes more than 20 minutes of wash-out to reach the same P_{CNS} following a 4-hour anesthetic. **B,** Washout using a desflurane model (*blue* is P_{alv}, *green* is P_{CNS}). The 30-minute desflurane uptake was 1530 mL of vapor, and the 4-hour desflurane uptake was 4600 mL of vapor. The predicted times to awakening (5.2 versus 6.3 minutes) are much closer following different durations of desflurane anesthesia, because of its low blood solubility. Clinical studies demonstrate that emergence and recovery (time to extubation) following isoflurane anesthesia nearly doubles when exposure increases from 20 minutes to 75 minutes, while extubation is achieved in less than 10 minutes following desflurane anesthesia from 20 to 100 minutes' duration. P_{alv}, Alveolar anesthetic partial pressure; P_{CNS}, partial pressure in the central nervous system; *CO,* Cardiac output; FGF, fresh gas flow; *MAC,* minimum alveolar concentration; *MV,* minute ventilation; P_{alv}, alveolar anesthetic partial pressure; P_{CNS}, partial pressure in the central nervous system; P_{MV}, anesthetic partial pressure in mixed venous blood.

directly exposed to air, and under these circumstances, anesthetic losses via direct transfer and air movements are larger than those via skin, but are still a small fraction of total clearance.[60]

Effect of the Anesthetic Circuit

As mentioned earlier, circuit components, including tubing, connectors, manual ventilation bag, and CO_2-absorbent material, absorb inhaled anesthetics, effectively creating another compartment that fills while anesthetic is flowing and needs to be emptied during washout.[19] Low-level release of anesthetic gases from these components can continue for a considerable time.

Clearance via Metabolism of Anesthetics

Metabolism of inhaled anesthetics in tissues, particularly liver, contributes to a variable degree to drug clearance. Metabolism of inhaled anesthetics is reviewed in detail in the second part of this chapter (see Metabolism and Toxicity). Methoxyflurane, a drug that is no longer in clinical use, and halothane, an older drug that is rarely used in the United States, are highly metabolized inhaled anesthetics. Methoxyflurane undergoes extensive metabolism in humans, with only 19% of an inhaled dose recovered in exhaled gases.[61] Approximately 20% to 25% of inhaled halothane is metabolized through biotransformation in the liver. A high rate of metabolism will reduce the anesthetic partial pressure in tissues, resulting in reduced P_{MV} and increased rates of overall anesthetic clearance. Tissue-dependent breakdown contributes less to clearance of newer inhaled anesthetics.

Additional Considerations and Possibilities

Modern inhaled anesthetics such as sevoflurane and desflurane have low blood solubility, and therefore provide a distinct advantage for both anesthetic induction and recovery from anesthesia. However, they present no advantage over older drugs such as isoflurane for maintenance of anesthesia during long cases. What if anesthesia is induced with one drug, followed by a switch to isoflurane during the maintenance period and then back to the more soluble drug, such as desflurane, for a period preceding emergence? This might allow for rapid induction and wake-up. Although a fast wake-up can be achieved by allowing sufficient time for near total washout of isoflurane and its replacement with desflurane, this type of crossover requires significant lead-time and high fresh gas flows. As an illustration, Neumann and colleagues[62] compared 2-hour anesthetics at 1.25 × MAC (2 L/min FGF) with isoflurane alone, desflurane alone, or isoflurane with a crossover to desflurane during the last half hour. Although subjects awoke faster with desflurane alone, the crossover strategy did not result in acceleration of wake-up compared with isoflurane alone.

Diffusion Hypoxia

Diffusion hypoxia is an additional sequelae of rapid outgassing from the tissues of patients anesthetized with N_2O. During the initial 5 to 10 minutes after discontinuation of anesthesia, the flow of N_2O from blood into the alveoli can be several liters per minute, resulting in dilution of alveolar oxygen.[63] Another effect of rapid outgassing is dilution of alveolar P_{CO_2}, which can also reduce respiratory drive.[64] If the patient does not receive supplemental oxygen during this period, then the combined effects of respiratory depression from anesthesia, reduced alveolar P_{CO_2}, and reduced alveolar P_{O_2} can result in hypoventilation and oxyhemoglobin desaturation. This outcome is routinely avoided by providing supplemental O_2 for the first 1 to 10 minutes of recovery, together with vigilant attention to respiration.

METABOLISM AND TOXICITY OF INHALED ANESTHETICS

This portion of the chapter focuses on adverse effects that are attributable to inhaled anesthetics, excluding most of the acutely reversible pharmacodynamic effects of inhaled anesthetics on various physiologic systems (see Chapters 27, 28, and 29).

The inhaled anesthetics are a unique group of drugs that can enter and leave the body unchanged through the lungs. Thus, chemical transformation of inhaled anesthetics is unrelated to their therapeutic activities, such as amnesia, hypnosis, and immobilization. Nonetheless, the carbon-halogen and other bonds of volatile alkanes and ethers can break down under certain conditions: biotransformation by enzymes in various tissues, reactions with strong bases in CO_2 adsorbents, and exposure to ultraviolet radiation in the environment. Anesthetic breakdown resulting from decomposition in tissues or the breathing circuit can produce toxic reactive intermediates, which in sufficient amounts can harm patients directly or indirectly. N_2O gas is not biotransformed but selectively reacts with and inactivates vitamin B_{12} and perturbs B_{12}-dependent biochemical pathways. The breakdown of waste anesthetics in the atmosphere also has potential environmental and health consequences. There are potential long-term neurotoxic effects of anesthetic exposure that are not associated with chemical breakdown.

BIOTRANSFORMATION OF INHALED ANESTHETICS

The extent and location of inhaled anesthetic metabolism depends on multiple chemical factors. Inhaled anesthetics undergo varying degrees of biotransformation (Table 26-3) in various tissues. Methoxyflurane undergoes by far the greatest metabolism, estimated at 70%, and experiments indicate that only a small fraction of drug taken up into body tissues is exhaled.[61] Given the remarkable lipophilicity of methoxyflurane, respiratory clearance of this drug from muscle and fat extends over a period of days (see Tables 26-1 and 26-2). Halothane is the next most lipophilic drug and ranks second in metabolic clearance (see Table 26-3). Thus, prolonged residence in body tissues is an important factor in biotransformation of inhaled anesthetics. Chemical stability is another important factor. Isoflurane is an isomer of enflurane, and the two drugs display comparable respiratory uptake, distribution, and respiratory clearance. Nonetheless, isoflurane is metabolized only one tenth as much as enflurane. Although sevoflurane and desflurane represent another pair of anesthetics, both characterized by rapid uptake, distribution, and respiratory clearance, 5% of sevoflurane is biotransformed versus 0.02% of desflurane.

Of the major organs involved in anesthetic biotransformation, the liver and kidneys are exposed to the highest metabolite concentrations and thus are most susceptible to damage from toxic metabolites. Clinically significant hepatotoxicity is primarily associated with exposure to halothane, and nephrotoxicity is associated with methoxyflurane.[90] Investigations into the mechanisms of these toxicities have influenced drug development and provided important insights into human toxicology.[91]

Biotransformation in Liver

The liver is the major site of metabolism for most drugs, particularly lipophilic drugs, which typically are transformed into hydrophilic metabolites that are more readily excreted. The liver is large and contains high concentrations of many drug-metabolizing enzymes. Other organs that contribute to drug metabolism and clearance include the gastrointestinal tract, kidneys, and the lungs.[92,93] Drug biotransformation reactions include oxidation, hydrolysis, and conjugation. A single drug can be transformed into several metabolites, depending on the relative rates of various enzyme reactions, the drug concentration in different tissues expressing relevant enzymes, competition at enzyme sites with other drugs or endogenous substances, and other factors. Oxidation and hydrolysis are also known as *phase 1 reactions,* and they result in introduction or exposure of a polar group on the drug. The phase 1 enzymes that metabolize inhaled anesthetics in the liver are various cytochrome P450 (CYP) isoforms in the endoplasmic reticulum of hepatocytes. These enzymes catalyze oxidation reactions, such as dehalogenation, N- and O-dealkylation, N- and S-oxidation, and deamination. These reactions require oxygen and reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent cytochrome P450 reductase as cofactors. Under hypoxic conditions, some P450 enzymes can also catalyze reductive reactions. More than 50 CYP isoforms are active in humans, and CYP3A4 and CYP3A5 are the most abundant. Conjugations are also known as phase 2 reactions, and they often append highly polar groups such as glucuronic acid, sulfate, or glycine to polar groups on phase 1 metabolites. The resulting hydrophilic products are readily excreted in urine via the kidneys or in bile via the gastrointestinal tract. *N*-Acetylation reactions are an exception that result in metabolites that are less water soluble than the parent drug.

Many factors affect hepatic drug metabolism, including concomitant drugs, disease, age, and genetics.[57] Induction and inhibition of enzymes are associated with exposure to certain drugs or other exogenous substances. Induction of specific CYP isoforms is a gene-mediated response to chronic exposure to substrates of the enzyme, resulting in accelerated enzyme production or slowed turnover. For example, phenobarbital use results in increased production of CYP3A4 and NADPH-cytochrome P450 reductase, leading to dramatically increased metabolism of all CYP3A4

TABLE 26-3 METABOLISM OF HALOGENATED VOLATILE ANESTHETICS

Anesthetic	Halothane	Methoxyflurane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Extent of tissue metabolism (%)	25	70	2.5	0.2	0.02	5
Oxidating enzymes	CYP2E1, CYP2A6	CYP2E1, CYP1A2, 2C9/10, 2D6	CYP2E1	CYP2E1	CYP2E1	CYP2E1
Oxidative metabolites	F_3C-COOH, HBr, HCl	H_3C-O-CF_2-COOH, HCl_2C-COOH, HOOC-COOH, HF, HCl	HF_2C-O-CF_2-COOH, HCl, HF	HF_2C-O-CO-CF_3, F_3C-COOH, CF_2HOH, HCl	HF_2C-O-CO-CF_3, F_3C-COOH, CF_2HOH, HF	HO-$CH(CF_3)_2$, HF
Trifuoroacetylated hepatocellular proteins	+++++	n/a	++	+	+	none
Reducing enzymes	CYP2A6, CYP3A4	n/a	n/a	n/a	n/a	
Reductive metabolites	F^-, Br^- F_2C = CHCl F_3C-CH_2Cl	—	—	—	—	—
Tissue toxicities	Hepatic	Renal, hepatic	Renal, hepatic	Hepatic	Hepatic	Hepatic
Fulminant hepatitis incidence	1:20,000	Reported, incidence unknown	1:300,000	Rare	Rare	Few case reports
References	65-69	70-73	74-78	75, 79-81	82-85	71, 86-89

From Kharasch ED: Adverse drug reactions with halogenated anesthetics, Clin Pharmacol Ther *84:158-162, 2008.*
The plus signs indicate relative degree of protein modification.
n/a, The specific enzymes are not identified in these cases.

substrates. Enhanced metabolism can reduce drug efficacy (and therefore is one mechanism of drug tolerance) or, in cases of pro-drug transformation to active metabolites, increase efficacy. If metabolites are toxic, as is the case with volatile anesthetics, enhanced metabolism may increase toxicity. Conversely, CYP inhibition leads to enhanced activity of parent drugs and reduced metabolite effects. CYP enzyme inhibition is associated with hepatic disease and exposure to certain substances. An important example is CYP3A4 inhibition by grapefruit juice.[94] Regarding volatile anesthetics, the major oxidative enzyme CYP2E1 is inducible by ethanol and isoniazid and is inhibited by disulfiram.[95] Diseases such as hepatitis, various cirrhotic diseases, and hepatocarcinoma can also reduce enzymatic activity, as can cardiac failure with reduced hepatic perfusion.

Neonates have different dominant CYP isoforms compared with adults (see Chapters 93 and 94). Impaired hepatic metabolism is common in premature and full-term infants, notably in bilirubin glucuronidation, leading to hyperbilirubinemia of the newborn.[96,97] Pharmacogenomics is a growing area of pharmacologic research that has linked variable drug metabolism to genetic variability. A well-established example in anesthesiology is homozygous inheritance of atypical butyrylcholinesterase, resulting in slow hydrolysis of succinylcholine.[98] Genetic variations in CYP2D6 have clarified the basis for widely varying efficacies and toxicities of codeine, metoprolol, nortriptyline, dextromethorphan, and other substrate drugs.[99]

Hepatic CYP2E1 is particularly important in the oxidative metabolism of halogenated inhaled anesthetics (see Table 26-3). Under conditions of hypoxia or decreased blood flow, or in liver regions of low P_{O_2}, CYP2A6 and CYP3A4 catalyze the breakdown of volatile anesthetics via reductive pathways. Halothane metabolism is primarily oxidative, and under normal conditions, approximately 1% of halothane undergoes reductive metabolism. Oxidative metabolism of halothane results in release of chloride and bromide ions, resulting in trifluoroacetyl chloride, which reacts with water to form trifluoroacetic acid (Fig. 26-14). Reductive metabolism of halothane results initially in loss of bromide, and the intermediate either reacts with a hydrogen donor to form 2-chloro-1,1,1-trifluoroethane or captures an electron, further reducing the carbon-carbon bond to form 2-chloro-1,1-difluoroethylene (see Fig. 26-14). Halothane reduces hepatic blood flow and can cause hepatocellular hypoxia in some regions in the liver, potentially leading to an increase in its reductive metabolism.[90] All the ether anesthetics undergo similar oxidative metabolism catalyzed by CYP2E1 (see Table 26-3, Fig. 26-15). Oxidative metabolism of these drugs results in the release of fluoride (F^-) and chloride (Cl^-) ions and the formation of reactive intermediates that react with water to form carboxylic acids. Isoflurane and desflurane both produce trifluoroacetic acid, whereas enflurane forms 2-difluoromethoxy-2,2-difluoroacetic acid. Oxidative metabolism of methoxyflurane can follow several paths, releasing Cl^- or F^- in sequential steps and producing methoxy-difluoroacetic acid, dichloroacetic acid, and acetic acid (see Table 26-3).

Halothane Hepatotoxicity

The first modern halogenated volatile anesthetic, halothane, was introduced in 1955. Clinical exposure to halothane is associated with two distinct types of hepatic injury.[100,69,101] Subclinical hepatotoxicity occurs in 20% of adults who receive halothane. It is characterized by mild postoperative elevations in alanine aminotransferase and aspartate aminotransferase, but is reversible and innocuous. Anaerobic halothane reduction by CYP2A6 to a 2-chloro-1,1,1-trifluoroethyl radical (see Fig. 26-14) is thought to mediate this mild hepatic injury.[65] The fulminant form of hepatotoxicity, commonly known as halothane hepatitis, is characterized by elevated alanine aminotransferase, aspartate aminotransferase, bilirubin, and alkaline phosphatase levels, and massive hepatic

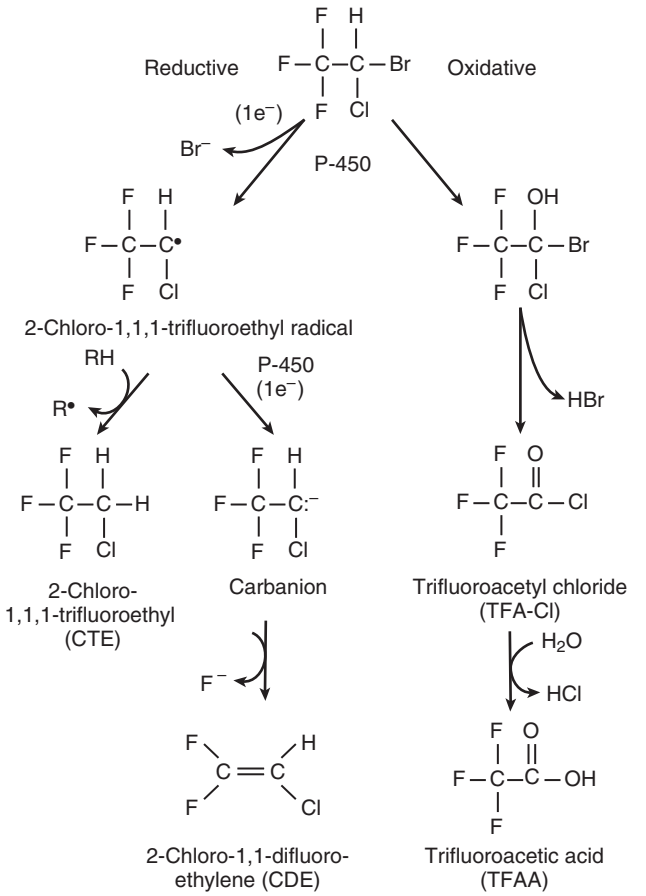


Figure 26-14. Oxidative and reductive metabolism of halothane. Major products of hepatic CYP2E1 catalyzed halothane metabolism are shown. Under normal conditions, 24% of halothane undergoes oxidative metabolism, and 1% undergoes reductive metabolism.

necrosis following the administration of halothane. Halothane hepatitis is rare (1 in 5000 to 35,000 administrations in adults), but is fatal in 50% to 75% of these cases. Because of the potential for fatal hepatitis, halothane is no longer used in adult patients in many countries.

Halothane hepatitis is caused by a hypersensitivity reaction associated with oxidative metabolism of halothane. The highly reactive trifluoroacetyl chloride metabolite of halothane oxidation can react with nearby liver proteins (see Table 26-3). In most patients who developed hepatic necrosis after halothane anesthesia, antibodies against TFA-modified proteins were detected, suggesting that the hepatic damage is linked to an immune response against the modified protein, which acts as a neoantigen (see Figure 26-16). Accordingly, patients who develop halothane hepatitis often have a history of prior exposures to halothane or other volatile anesthetics, together with symptoms suggestive of immune reactivity, such as fever, rash, arthralgia, and eosinophilia.[66] A current hypothesis is that TFA-protein adducts induce a cytotoxic T cell reaction in sensitized individuals, which leads to liver damage.[69] However, the immune responses observed in halothane hepatitis might not mediate liver injury.

Hepatotoxicity and massive hepatic necrosis has occurred after halothane anesthesia in pediatrics (see Chapter 93). However, two large retrospective studies have demonstrated that the clinical syndrome of halothane hepatitis is even more rare in the pediatric population (1 in 80,000 to 200,000) than in adults.[102-104] Halothane is metabolized to a similar degree in adults and children. The children are immune competent from birth. Pediatric cases of halothane hepatitis are also associated with multiple anesthetic exposures, suggesting a mechanism similar to that in adults. Why the incidence of halothane hepatitis is more frequent in the adult population is not known.

Other volatile anesthetics including enflurane, isoflurane, and desflurane have also been associated with fulminant hepatic necrosis,[82,105-109] but compared with halothane, the incidence of this potentially fatal toxicity is rare after administration of these newer volatile anesthetics. The mechanism of severe hepatitis following enflurane, isoflurane, and desflurane may be the same as for halothane, because all these drugs are oxidatively metabolized to highly reactive intermediates that can covalently modify hepatic proteins (Fig. 26-16). As with halothane, case investigations usually reveal that patients have had prior exposure to volatile anesthetics, and antibodies to modified hepatic proteins can be detected. The extremely infrequent incidence of severe hepatitis for modern volatile anesthetics is likely due to their lower degree of oxidative metabolism and subsequent immune sensitization. In fact, hepatitis was also commonly reported soon after introduction of methoxyflurane, another highly metabolized anesthetic that is metabolized to highly reactive acidic intermediates.[70,110] Unlike all other volatile anesthetics, sevoflurane is oxidized at the fluoromethoxy C-H bond and forms hexafluoroisopropanol and inorganic F^- (see Table 26-3; Fig. 26-17).[111,112] Hexafluoroisopropanol is relatively stable, and modified liver proteins are not formed after sevoflurane anesthesia. Cases of hepatitis and rapid death after sevoflurane anesthesia have been reported, but there was no evidence of an immune-mediated mechanism.[86]

Biotransformation in Kidneys

The kidneys are large organs that receive high blood flow. Renal physiologic activities include glomerular filtration of water-soluble metabolites, reabsorption of water and essential metabolites, urinary excretion of waste, and regulation of hormones involved in vascular tone (renin) and water balance (aldosterone). The kidneys clear most of the water-soluble metabolites resulting from biotransformation of inhaled anesthetics. Kidneys also contain CYP enzymes, including CYP2E1, that catalyze both phase 1 and phase 2 reactions and are therefore additional sites where inhaled anesthetic metabolism occurs. As in the liver, various CYPs in renal parenchyma can undergo induction or inhibition by exogenous substances.[113-116]

Fluoride-Associated Nephrotoxicity

The first modern halogenated ether anesthetic, methoxyflurane, was introduced in 1959. Methoxyflurane causes polyuric renal insufficiency, and it is no longer used in clinical practice.[117] The nephrotoxic effect of methoxyflurane is attributed to inorganic fluoride (F^-) released during its metabolism. Investigations have provided significant insights into potential nephrotoxic mechanisms by fluorinated volatile anesthetics and have influenced the development of subsequent halogenated anesthetic agents.

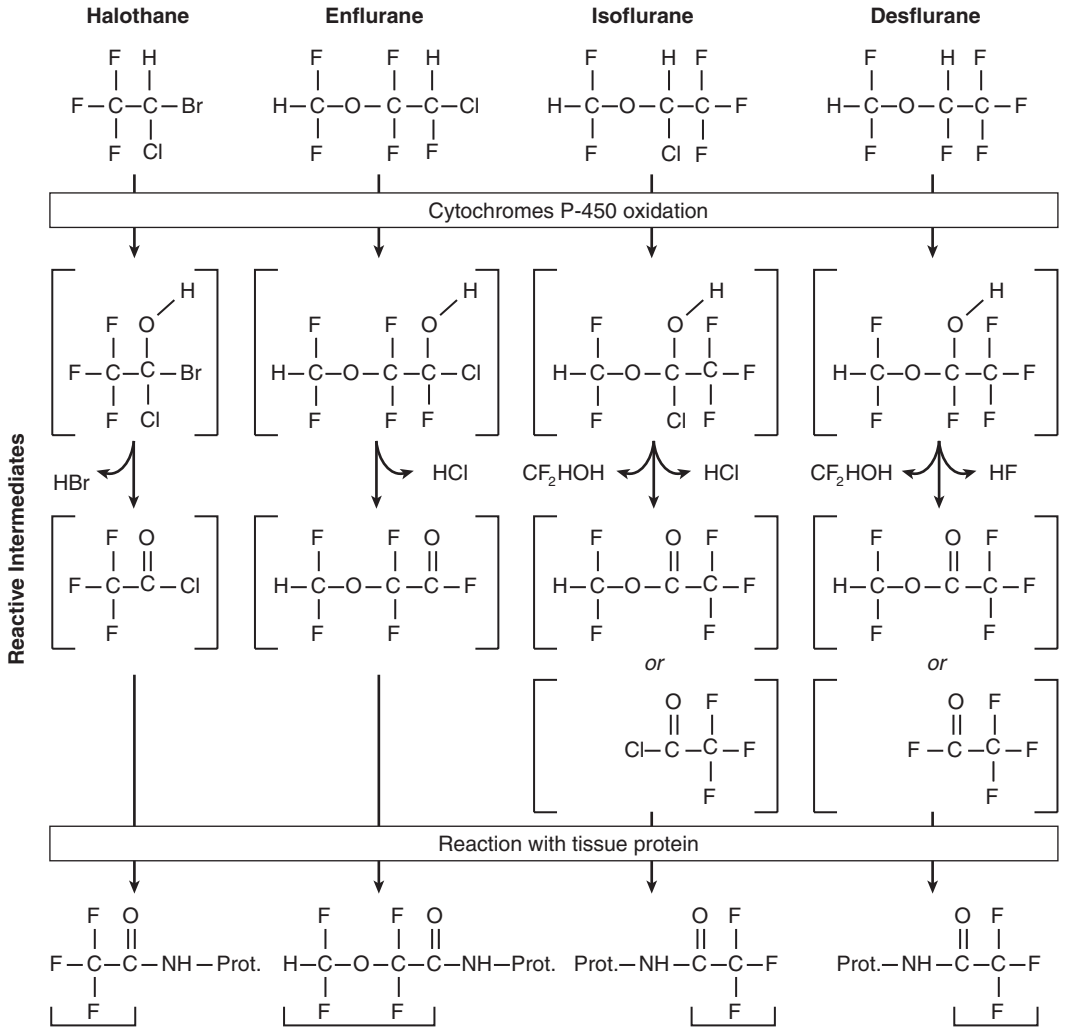


Figure 26-15. Proposed pathways for inhaled anesthetic metabolism to reactive intermediates. CYP2E1 catalyzes oxidative metabolism of halothane, enflurane, isoflurane, and desflurane to a variety of reactive intermediates that can form adducts with hepatocellular proteins. Trifluoroacetylated proteins are identical after halothane, isoflurane, and desflurane, whereas adducts following enflurane are immunologically similar.

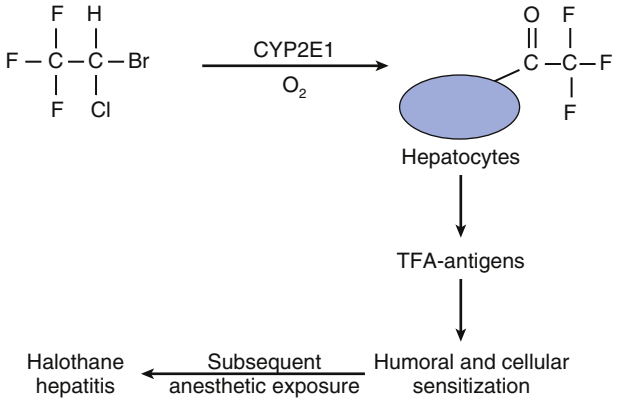


Figure 26-16. Pathways generating the immune response after exposure to inhaled anesthetics. Halothane is metabolized to a reactive trifluoroacetyl intermediate that forms an amide bond with hepatocellular proteins. The altered protein triggers an immune response, which on subsequent exposure to anesthetic results in hepatocellular damage and necrosis. A similar process may ensue after exposure to other fluorinated drugs metabolized to similar halo-acyl intermediates. *(Modified from Njoku D, Laster MJ, Gong DH, et al: Biotransformation of halothane, endflurane, isoflurane and desflurane to trifluoroacetylated liver proteins: association between protein acylation and liver injury,* Anesth Analg *84:173-178, 1997.)*

Absorbed methoxyflurane undergoes extensive biotransformation,[61] including cytochrome-catalyzed oxidation that releases inorganic fluoride ions (F^-) into blood. Animal studies provide clear evidence of the nephrotoxicity of methoxyflurane, which includes a strong relationship between methoxyflurane dose and renal injury,[118] increased nephrotoxicity with induction of CYP enzymes,[119,120] and decreased nephrotoxicity with inhibition of methoxyflurane metabolism.[75,121] Clinical data further indicate that severity of nephrotoxicity and mortality are associated with high plasma fluoride concentrations after methoxyflurane anesthesia.[122,123] Patients with serum inorganic fluoride levels below 50 μM had no evidence of renal injury, whereas patients with post-methoxyflurane serum F^- greater than 50 μM suffered high rates of renal dysfunction and increased mortality.[72,124] Moreover, serum F^- concentrations were significantly higher after the administration of methoxyflurane than with other halogenated volatile anesthetics, which are not associated with nephrotoxicity (Fig. 26-18). Inorganic fluoride released during methoxyflurane metabolism likely causes renal injury, and the nephrotoxic threshold for plasma F^- is approximately 50 μM. Individual variability among patients in the degree of apparent

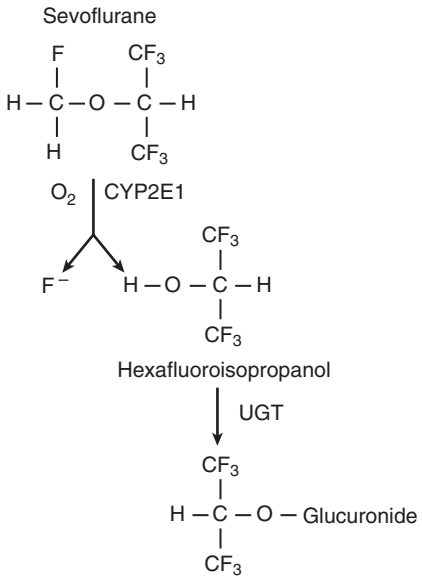


Figure 26-17. Metabolic oxidation of sevoflurane. CYP2E1 catalyzes phase 1 defluorination of sevoflurane, forming hexafluoroisopropanol. Phase 2 glucuronidation is catalyzed by uridine 5′-diphosphate glucuronosyltransferase.

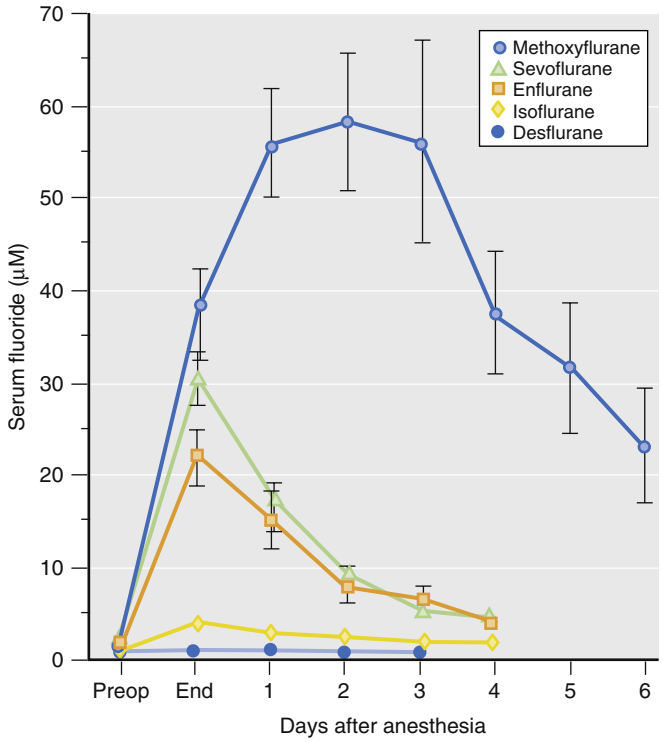


Figure 26-18. Serum inorganic fluoride (F^-) exposure before and after methoxyflurane anesthesia is much greater than with other anesthetics. Points represent serum F^- measurements (mean ± SD) from multiple subjects. After 2 to 3 MAC-hours of methoxyflurane anesthesia, F^- rises during and after drug administration ends, peaks above 60 μmol/L on postanesthesia days 2 and 3, then declines slowly, remaining elevated for more than 1 week. Sevoflurane anesthesia (3.7 MAC-hours) produces an early peak F^- concentration averaging 31 μmol/L, which declines over 3 to 4 days. Enflurane anesthesia (2.7 MAC-hours) results in an early average peak of 22 μmol/L which declines in 3 to 4 days. Isoflurane and desflurane result in small and negligible rises in serum F^- concentrations. Only methoxyflurane is associated with fluoride-associated renal toxicity. MAC, minimum alveolar concentration.

renal injury after methoxyflurane exposure was observed. Genetic heterogeneity, drug interactions, and preexisting renal disease probably account for these differences.

Since the introduction of methoxyflurane, all prospective halogenated anesthetic drugs have been extensively tested experimentally and clinically for their degree of defluorination and the resulting serum F^- concentrations. However, experience with newer drugs, particularly with sevoflurane, has caused investigators to reexamine the classical fluoride-induced nephrotoxicity hypothesis. Sevoflurane was initially synthesized in the 1970s, but because of its relatively large defluorination rate (2% to 5%), its introduction into clinical practice was delayed. It was first used widely in Japan in 1990. Subsequent clinical studies demonstrated no clinically significant nephrotoxicity after the administration of sevoflurane, even when high peak F^- concentrations greater than 50 μM were confirmed.[111] Typical peak fluoride concentrations after 2 to 3 MAC-hours of sevoflurane anesthesia are 20 to 30 μM, and less than 5 μM after isoflurane and desflurane (see Fig. 26-18). Enflurane metabolism also often results in peak F^- concentrations greater than 20 μM. Isoflurane and desflurane are metabolized minimally, and they produce lower plasma fluoride concentrations. However, none of these anesthetics is associated with clinically significant renal toxicity, suggesting that methoxyflurane is unique in its ability to harm kidneys. One difference between methoxyflurane and the current volatile anesthetics is its extreme lipophilicity and extremely long residence time in tissues. This results in prolonged elevated F^- concentrations in blood (see Fig. 26-18), suggesting that the length of F^- exposure is a key risk factor. However, prolonged, moderate increases of plasma fluoride (25 to 38 μM) during several days of isoflurane anesthesia have occurred without adverse renal effects.[125,126] Thus, neither the peak level nor the duration of high plasma fluoride concentration entirely explains the nephrotoxic effects by the halogenated anesthetics. It is also not clear whether the integrated concentration multiplied by time exposure to inorganic F^- represents the key risk factor; however, methoxyflurane is metabolized significantly within kidney parenchyma, producing high intrarenal inorganic fluoride concentrations (likely much higher than those measured in blood), which are proposed to cause renal injury.[71,73] Thus, compared with methoxyflurane, the absence of renal toxicity with current volatile anesthetics likely derives from a combination of factors: (1) their lower tissue solubilities, particularly in kidney (see Table 26-2), resulting in lower intrarenal fluoride production; (2) lower rates of biotransformation; and (3) more rapid respiratory clearance from the body.

ANESTHETIC DEGRADATION IN CARBON DIOXIDE ABSORBENTS

Sevoflurane, Compound A, and Renal Toxicity

Halogenated anesthetics can undergo chemical breakdown while interacting with CO_2 absorbents that contain strong bases such as sodium hydroxide (NaOH) and potassium hydroxide (KOH), which are present in soda lime and Baralyme.[127] Strong bases extract a proton from

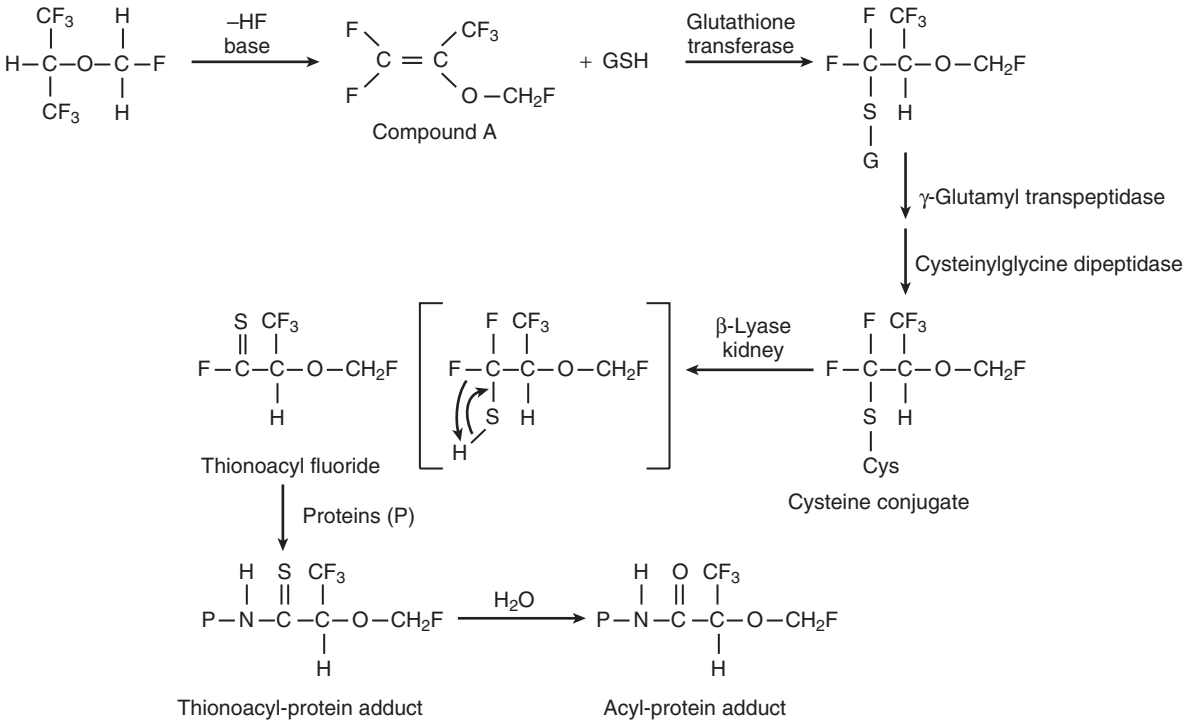


Figure 26-19. Proposed pathway mediating nephrotoxic effects of compound A in rodents. Sevoflurane degrades to compound A in the presence of strong base in some CO_2 absorbent materials. Compound A itself is not nephrotoxic but undergoes hepatic S-conjugation with glutathione. In the kidney, additional metabolic steps produce an S-cysteine compound A conjugate, which is metabolized by β-lyase to a reactive thionoacyl fluoride that is proposed to damage proteins essential for kidney function. Humans have very low β-lyase activity, which is hypothetically the basis for the lack of reported nephrotoxicity in patients. *GSH,* Glutathione; *HF,* hydrofluoric acid. *(Adapted from Martin JL, Kandel L, Laster MJ, et al: Studies of the mechanism of nephrotoxicity of comound A in rats,* J Anesth *11:32-37, 1997.)*

the isopropyl group of sevoflurane, primarily forming a haloalkene (fluoromethyl-2,2-difluoro-1-[trifluoromethyl] vinyl ether), known as *compound A* (Fig. 26-19). Compound A is volatile and can be absorbed via alveolar gas exchange. Compound A exposure is nephrotoxic in laboratory animals, causing proximal tubular necrosis and, with sufficient exposure, death. In rats, renal injury is observed with cumulative exposure to compound A above 150 parts per million (ppm)-hours (e.g., 50 ppm inhalation for 3 hours).[128,129] Moderately severe but reversible histopathologic damage was found in rats after 200 ppm-hour exposure, associated with increased blood urea nitrogen (BUN), creatinine, and other measures of renal damage. Compound A exposure greater than 1000 ppm-hours is lethal in half of exposed rats.

Patients given sevoflurane anesthesia are routinely exposed to compound A in rebreathing circuits, and the inhaled concentration is dependent on the fresh gas flow rate and the type of CO_2 absorbent present. Fresh gas flows of 1 L/min result in maximal compound A concentrations of approximately 20 ppm with soda lime and 30 ppm with Baralyme.[130] Higher FGF rates result in a smaller accumulation of compound A in the breathing circuit. However, compound A exposure is not associated with clinically significant nephrotoxicity in humans. There is no threshold exposure level known to cause more than subclinical renal damage. Numerous studies in which human subjects or patients were exposed to greater than 200 ppm-hours of compound A have reported that clinical measures of renal function (BUN, creatinine, urinary protein or glucose, and urine concentrating ability) and laboratory tests for subtle renal damage (*N*-acetyl-β-glucoaminidase, alanine aminopeptidase, γ-GTP, and β_2-microglobulin) remain unchanged.[74,131-134] Kharasch and colleagues[135] compared the effects of low-flow sevoflurane and isoflurane anesthesia in patients with stable renal insufficiency and found no significant difference in postoperative renal function tests. Other studies have reported normal BUN and creatinine, but transient reversible abnormalities in other renal function test values following prolonged sevoflurane anesthesia at low FGF (>330 ppm/hr compound A exposure in one study).[136-139]

The evidence of nephrotoxicity in rats compared with the remarkably benign results in humans suggests that mechanisms of sevoflurane metabolism and toxicity differ between these species. The difference in the nephrotoxic effects of compound A between humans and rats may be attributed to the doses of compound A, interspecies differences in metabolic toxification, and sensitivity of the proximal tubular cells to compound A cytotoxicity.[90] Detailed studies show that in rats, compound A undergoes S-conjugation to cysteine, and that the resulting cysteine conjugate is metabolized by renal β-lyase to form a reactive thionoacyl fluoride intermediate that acylates proteins and has been proposed to mediate the nephrotoxic effect[127,140] (see Fig. 26-19). Human kidneys have far lower β-lyase activity than rat kidneys, accounting for the differential toxicity of compound A in the two species. Inhibition of β-lyase using aminooxy-acetic

TABLE 26-4 **COMPOSITION OF BASE CHEMICALS AND WATER CONTENT OF CARBON DIOXIDE ABSORBENTS***

CO_2 Absorbent	$Ca(OH)_2$ (%)	$Ba(OH)_2$ (%)	KOH (%)	NaOH (%)	LiOH (%)	H_2O (%)
Baralyme†	70	10	4.6	—	—	14
Sodalime I	80	—	2.6	1.3	—	15
Sodasorb	90	—	0.0005	3.8	—	16
Drägersorb 800 plus	82	—	0.003	2.0	—	16
Sodalime II, Medisorb	81	—	0.003	2.6	—	16
Spherasorb	84.5	—	0.003	1.5	—	14
Amsorb	83.2	—	—	—	—	14.4
LofloSorb	84	—	—	—	—	16
Superia	79.5	—	—	—	—	17.5
Lithium hydroxide	—	—	—	—	99	1

Data from Keijzer C, Perez RSGM, De Lange JJ: Compound A and carbon monoxide production from sevoflurane and seven different types of carbon dioxide absorbent in a patient model, Acta Anaesthesiol Scand 51:31-37, 2007; and Kharasch ED, Powers KM, Artru AA: Comparison of Amsorb, sodalime, and Baralyme degradation of volatile anesthetics and formation of carbon monoxide and compound a in swine in vivo, Anesthesiology *96:173-182, 2002.*

*Various absorbents also contain other components, such as polyvinylpyrrolidine, calcium chloride, calcium sulfate, magnesium chloride, and aluminosilicate.

†Baralyme was withdrawn from the market in 2004.

acid (AOAA) protects rats from compound A nephrotoxicity,[141] whereas others have found no protective effect of AOAA or other inhibitors in the proposed pathway.[142] Alternative mechanisms underlying compound A toxicity have been proposed, including formation of reactive sulfoxides catalyzed by CYP3A isozymes,[143] which are also more active in rat than in human kidneys.

Although the mechanism underlying compound A toxicity in experimental animals remains uncertain, the clinical data are reassuring concerning the lack of significant sevoflurane nephrotoxicity in humans. Compound A exposure can be limited by careful selection of fresh gas flows, vaporizer output, and CO_2 absorbent materials. The use of 2 L/min fresh gas flows ensures that for the vast majority of patients, exposure to compound A will be below the most conservative threshold for nephrotoxicity. Although clinical studies indicate that sevoflurane is most likely safe even in patients with preexisting renal dysfunction, the drug should be administered in accordance with the approved package labeling guidelines.

Like sevoflurane, halothane degrades in the presence of CO_2 absorbents to form a reactive intermediate, bromochlorodifluoroethylene (BCDFE),[127] which has also been investigated as a possible nephrotoxin. Eger and colleagues[144] found that in comparison with compound A, BCDFE accumulates twentyfold to fortyfold less in breathing circuits and is fourfold less reactive.[144] Thus, the risk of BCDFE nephrotoxicity is negligible.

Carbon Monoxide and Heat

In the presence of strong bases in dry CO_2 absorbents (water content < 5%), some halogenated volatile anesthetics undergo degradation, resulting in the formation of CO, trifluoromethane (CF_3H), and hydrogen fluoride (HF).[127] The factors that determine the amount of CO produced include the chemical makeup of CO_2 adsorbent (KOH > NaOH >> $Ba(OH)_2$, $Ca(OH)_2$), dryness of the adsorbent material, the concentration of volatile agent, and its chemical structure.[145] Baralyme contains 4.6% KOH, whereas soda lime contains 2.5% KOH and 1.5% NaOH and reacts less vigorously with halogenated anesthetics. The relatively weak bases $Ba(OH)_2$ and $Ca(OH)_2$ are other major constituents in CO_2 absorbents, and do not catalyze CO formation (Table 26-4). The anesthetics that contain a difluoromethyl group (difluoromethyl-ethyl ethers) are most susceptible to this degradation and for this group CO production correlates with anesthetic concentration in the breathing circuit (desflurane > enflurane > isoflurane)[146] (Fig. 26-20). Sevoflurane, methoxyflurane, and halothane also degrade in the presence of strong bases, but do not produce CO. Production of CO appears to require nearly complete desiccation (i.e., removal of absorbent moisture) of the CO_2 absorbent, and typically occurs after high flow flushing of the breathing circuit for 1 to 2 days. Soda lime contains 15% water by weight, and Baralyme contains 13% water by weight (see Table 26-4). CO production is observed when water content of soda lime or Baralyme falls below 1.4% and 5%, respectively.[147] High ambient temperatures also accelerate desiccation of CO_2 absorbent materials and may increase the rate of CO producing reactions. As noted with compound A, CO accumulation in the breathing circuit is inversely related to the fresh gas flow.

Anesthetic degradation in the breathing circuit has resulted in CO poisoning during clinical anesthesia.[148,149] CO has 250-fold greater affinity for hemoglobin than O_2 does; therefore, the formation of carboxyhemoglobin reduces blood oxygen carrying capacity and tissue oxygen delivery, and is difficult to reverse. The detrimental effects and signs of CO toxicity are well known; however, with general anesthesia, signs of patient exposure to CO are masked, and hypoxia may be difficult to detect, because some pulse oximetry equipment cannot distinguish between carboxyhemoglobin and oxyhemoglobin.

The degradation of volatile anesthetics by bases in CO_2 absorbents is an exothermic reaction that results in the production of heat. Sevoflurane produces the most heat production when it is used with desiccated CO_2 absorbent. The absorbent canister and anesthetic circuit can reach extremely high temperatures, which can lead to explosion or fire, or both (see Chapter 109).[150,151]

Current recommendations to minimize anesthetic degradation to CO and heat include machine maintenance measures to avoid desiccation of CO_2 absorbent and the use of absorbents that contain less KOH and NaOH. Newer CO_2 absorbents (see Table 26-4) contain

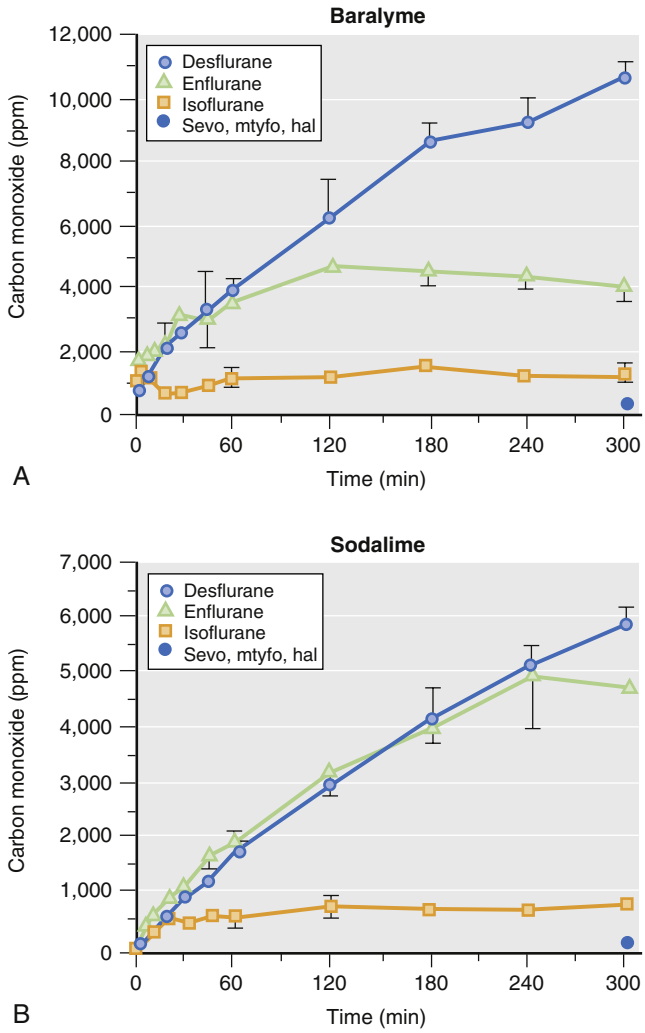


Figure 26-20. Inhaled anesthetic degradation and carbon monoxide production. Points represent mean ± SD of three measurements with equivalent anesthetic doses (1.5 × MAC) in the presence of dry CO_2 absorbents at identical fresh gas flows. **A,** Degradation and CO production with Baralyme. **B,** Degradation and CO production with soda lime. Degradation and CO production was observed with anesthetics containing difluoromethoxy groups (desflurane, enflurane, and isoflurane), but not halothane (hal) or those with monofluoromethoxy groups such as sevoflurane (sevo) and methoxyflurane (mtyfo). *MAC,* Minimum alveolar concentration. *(Adapted from Baxter PJ, Garton K, Kharasch ED: Mechanistic aspects of carbon monoxide formation from volatile anesthetics,* Anesthesiology *89:929-941, 1998).*

little or no strong base and do not degrade volatile anesthetics, regardless of hydration status.[130,152,153] The use of the newer CO_2 absorbents also reduces production of compound A during sevoflurane anesthesia.[154-156]

NITROUS OXIDE, VITAMIN B_{12}, AND HOMOCYSTEINE

N_2O is unique among anesthetics in irreversibly inhibiting cobalamins (vitamin B_{12}) by oxidizing the Co (I) ligand. Cobalamins are ingested or produced by bacteria in the gut, and they are critical cofactors together with 5-methyltetrahydrofolate in the activity of methionine synthase (Fig. 26-21). Methionine synthase catalyzes methylation of homocysteine to methionine, while also demethylating 5-methlytetrahydrofolate to produce tetrahydrofolate. Methionine, converted to S-adenosylmethionine, is the major substrate for methylation in biochemical pathways involved in the synthesis of DNA, RNA, myelin, and catecholamines.[157] Chronic vitamin B_{12} deficiency (as in pernicious anemia) results in hematologic and neurologic dysfunction. Long-term N_2O exposure, typically among individuals who frequently inhale it as a recreational drug, can also cause megaloblastic anemia, myelopathy, neuropathy, and encephalopathy, sometimes presenting as psychosis.[79,158,159] Risk factors that increase susceptibility to N_2O toxicity include pernicious anemia or other gastrointestinal malabsorption syndromes, extremes of age, alcoholism, malnutrition, a strict vegetarian diet, and inborn deficiencies in cobalamin or tetrahydrofolate metabolism.[79] Inhibitors of folate metabolism, such as methotrexate, can also enhance sensitivity to N_2O toxicity.[160]

In healthy surgical patients, megaloblastic changes in the bone marrow are rare, and reported only after a prolonged period of exposure (>12 hours) to N_2O. However, in seriously ill patients or those with risk factors noted earlier, shorter (or repetitive) periods of N_2O exposure can lead to significant subacute pathology. Megaloblastic bone marrow changes can be induced after a short period (2 to 6 hours) of N_2O exposure.[161] Vitamin B_{12} deficiency or reduced methionine synthase activity can also lead to subacute myelinopathy and neuropathy.[162-165] A case highlighting the potential importance of inborn metabolism was reported by Selzer and associates.[166] In this case, a 4-month-old child developed an irreversibly and ultimately fatal seizure disorder several weeks after receiving N_2O during anesthesia. Autopsy revealed widespread brain atrophy and demyelination, and biochemical investigations revealed reduced methyltetrahydrofolate reductase (MTHFR) activity, which eventually were linked to several mutations in the gene encoding MTHFR.

Another consequence of reduced methionine synthase activity is accumulation of its substrate, homocysteine (see Fig. 26-21). Homocystinuria caused by severe inborn deficiency of methionine synthase activity is associated with extremely increased blood homocysteine levels, early atherosclerosis of coronary and cerebral arteries, and premature death.[167] These observations led to the "homocysteine hypothesis," which postulates that homocysteine stimulates inflammation and atherosclerosis, and is a key modifiable factor in vascular morbidity and mortality. Increased homocysteine levels are an independent risk factor for cardiac and cerebrovascular morbidity,[168,169] but the association between homocysteine levels and atherothrombotic disease is weak.[170] Moreover, studies in which diet and vitamin supplementation were used to reduce homocysteine levels demonstrate improvement in some markers of vascular risk, but do not reduce the rate of myocardial infarction and atherosclerotic stroke.[170,171] Thus, the importance of chronic, moderate increases in homocysteine to cardiovascular outcomes is tenuous, or perhaps only pertinent to limited patient populations.

Do the rapid increase of homocysteine levels during N_2O anesthesia influence the risk of cardiovascular

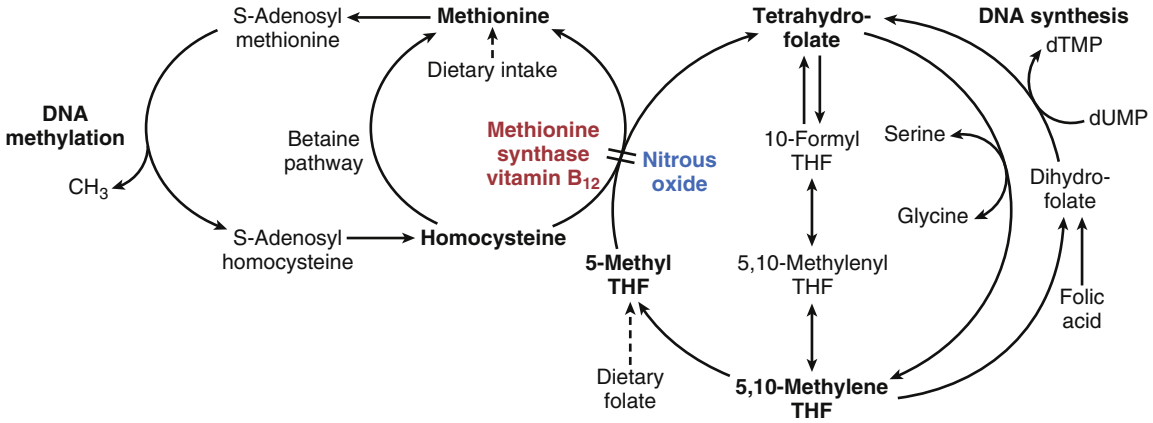


Figure 26-21. Nitrous oxide inhibition of methionine synthase. Biochemical cycles involved in methylation reactions are shown. Methionine synthase *(red)* catalyzes methylation of homocysteine with 5-methyl tetrahydrofolate as the donor, producing methionine and tetrahydrofolate (THF). Both vitamin B_{12} and folate are essential cofactors for methionine synthase. Nitrous oxide *(blue)* inhibits methionine synthase by oxidizing the cobalt of cobalamin (vitamin B_{12}). Methyl transfer pathways are important in synthesis of protein and DNA.

and neurovascular morbidity following surgery and anesthesia? Badner and colleagues[172] reported that N_2O administration significantly increased homocysteine levels and increased myocardial risk in carotid endarterectomy patients. The Evaluation of Nitrous Oxide in a Gas Mixture for Anaesthesia (ENIGMA) trial in over 2000 patients reported that avoidance of N_2O combined with increased inspired oxygen concentration during anesthesia decreased the incidence of a variety of complications after major surgery but found no reduction in death, myocardial infarction, stroke, or hospital length of stay.[173] A follow-up study of the ENIGMA trial patients reported that those exposed to N_2O for more than 2 hours were at increased risk (odds ratio, 1.6; 95% confidence interval, 1.01 to 2.5) of myocardial infarction up to 5.7 years after enrollment (ENIGMA-II).[174] No difference in rates of death or stroke were found. Unfortunately, diagnosis of myocardial infarction in ENIGMA-II was often based on data obtained in telephone interviews, rather than established diagnostic criteria. A recent post hoc study of 5133 enrollees in the Perioperative Ischemic Evaluation (POISE) trial[175] found no increase in rates of death, myocardial infarction, or stroke in approximately 1500 patients who received N_2O.

Homocysteine elevation following N_2O inhalation is a useful marker for assessing the sensitivity of methionine synthase and related biochemical pathways to N_2O inhibition. Nagele and colleagues[176] studied a small group of surgical patients with common mutations in the gene encoding MTHFR, and found that those with 667C→T and 1298A→C mutations were at risk of developing abnormally high homocysteine levels after N_2O exposures of at least 2 hours. However, a common gene variant (66A→G) associated with reduced methionine synthase reductase activity did not result in abnormally high homocysteine levels after anesthesia with N_2O.[177] Preoperative infusions of vitamin B_{12} and folate do not prevent the normal increases in homocysteine observed following anesthesia with N_2O.[178]

The continued value of N_2O, first used as an anesthetic in the early nineteenth century, has been questioned by some.[179,180] Given the ambivalence of currently available data, we recommend that anesthesia providers carefully screen patients to identify the few most likely to suffer N_2O side effects, and to avoid the drug in these cases.

INHALED ANESTHETICS AND NEUROTOXICITY

The ability of general anesthetics to ablate consciousness reversibly has benefitted millions of patients and enabled dramatic advances in health care. Although inhaled anesthetics were the first class of anesthetics and continue to be used in the vast majority of cases, the potential of long-lasting neurotoxic effects of inhaled and other general anesthetics does exist in patients of extreme ages[181-183] (see Chapters 80 and 93). The greatest concern surrounds the effects of general anesthetics in the youngest patients during periods of rapid brain development.[184] In a seminal study, Jevtovic-Tetrodovic and coworkers[185] demonstrated widespread neuronal apoptosis in the brains of 7-day-old rats after exposure to midazolam, isoflurane, and N_2O. Additional findings in these animals included long-lasting (up to 4.5 months) deficits in hippocampal long-term potentiation (a neurophysiologic correlate of learning and memory), and performance deficits in spatial learning tests. Subsequent animal studies in various species, including nonhuman primates, demonstrate that during sensitive periods of early brain development, exposure to most general anesthetics is associated with accelerated neuronal cell death (apoptosis) and degeneration.[186-190] Prolonged exposure to anesthetics can lead to neuroapoptosis and neurocognitive problems.[187,189] However, other studies suggest that even low nonapoptotic concentrations of general anesthetics may inhibit normal synapse formation and damage developing neuronal networks.[191] Mechanisms underlying neurodevelopmental toxicity are potentially linked to the same ion channels hypothesized to mediate general anesthesia. General anesthetic actions are attributed in part to both antagonism of *N*-methyl-D-aspartate receptor and potentiation of GABAA receptor signal transduction, and drugs with either or both of these activities damage developing brains.[183,192,193]

Early preclinical studies of neurodevelopmental toxicity of anesthesia demanded investigation of potential neurobehavioral correlates in humans. Current epidemiologic data (2013) are inconclusive. Clinical studies within the United States point to a possible association between anesthetic exposure in early childhood and the impairment of neurocognitive development,[181,194] in particular with cumulative anesthetic exposure.[195] In contrast, studies from Europe on the effects of a single exposure to anesthesia in early life that used combined data from national health data bases and educational registries within Denmark[196] found that early inguinal hernia repair was not associated with poor cognitive outcome; rather it is suggested that the poor academic performance of a subgroup of these children may be due to their being developmentally disadvantaged compared with the background population. In another study in sibling pairs in which one sibling received anesthesia before age 3 years, comparable test scores were reported for verbal, performance, and global intelligence between exposed and unexposed siblings.[197] Although some of the findings from the United States are concerning, potentially significant confounding factors were not controlled in these retrospective studies and firm conclusions cannot yet be drawn regarding the neurocognitive risks of general anesthesia in young children. Ongoing prospective clinical trials are expected to provide more definite information regarding this important issue[181,198] (see Chapter 93).

For updated recommendations to health care providers and parents regarding exposure to anesthesia and surgery in early life, please consult http://www.smarttots.org/resources/consensus.html or http://www.esahq.org. For a comprehensive description of the long-term impact on the adult brain, see Chapter 99.

INHALED ANESTHETICS AND ENVIRONMENTAL EFFECTS

Anesthetic gases in the workplace and in the outdoor environment have the potential to cause harm. Three potential sequelae have been investigated: global warming, ozone depletion, and health effects from workplace exposure (Table 26-5).

Global Warming Effects

Atmospheric trapping of thermal radiation from the earth's surface is known as the *greenhouse effect,* which the Intergovernmental Panel on Climate Change[203] deems a major contributor to global warming. Inhaled anesthetics are recognized greenhouse gases.[204,205] Isoflurane, sevoflurane, and desflurane, the most widely used current inhaled anesthetics, are minimally metabolized in the body, and are substantially eliminated through exhalation. Most anesthesia waste scavenging systems transfer these gases directly and unchanged into the atmosphere. Recently, attention to the ecotoxicologic properties of inhaled anesthetics has grown. The global warming potential takes into account the heat-trapping efficiency and lifespan of atmospheric gases (time for removal by chemical reaction with radicals, photolysis, and deposition). The global warming potential of volatile anesthetics ranges from 1230-fold (isoflurane) to 3714-fold (desflurane) that of an equal mass of CO_2. Recently Ryan and Nielsen[201] suggested that the most common volatile anesthetics can significantly influence global warming, with the greatest impact produced by atmospheric desflurane.

The global warming potential of N_2O is approximately 300-fold greater than that of an equal mass of CO_2.[206,207] N_2O is used in large quantities relative to volatile anesthetic gases and is remarkably stable, with an atmospheric lifespan of approximately 120 years.[208] Atmospheric N_2O is produced by natural sources in soil and water as well as human sources including agriculture (nitrogen-based fertilizers) and combustion of fossil fuels. Sherman and Cullen[209] first reported that N_2O could contribute to global warming and estimated that approximately 1% of man-made N_2O production was for anesthesia. More recently, the anesthetic use of N_2O may contribute 3.0% of total N_2O emissions in the United States.[205] Although the use of N_2O is declining in many countries, data on the worldwide medical use of N_2O are not available.

Ozone Depletion

The ozone layer of the earth's atmosphere, which has been declining 4% per decade since the 1970s, absorbs damaging ultraviolet B light (wavelengths 280 to 315 nm). The biologic consequences of increasing ultraviolet B radiation include increases in skin cancer, cataracts, damage to plants, and reduction of oceanic plankton populations. Halogenated volatile anesthetics are similar to chlorofluorocarbons (CFCs), which are major ozone depleting pollutants. Ozone depletion by halocarbons depends on molecular weight, number, and type of halogen atoms, and atmospheric lifespan.[210] The atmospheric lifespan of halogenated anesthetics is much shorter (4.0 to 21.4 years)[211] than that of many CFCs (up to 100 years). Fluorination is associated with longer atmospheric lifespan because of the stability of carbon-fluorine (C-F) bonds. Chemicals with a lifetime of more than 2 years are believed to reach the stratosphere in significant quantities. There they are exposed to intense ultraviolet radiation that can break carbon-halogen bonds, creating halogen radicals that catalytically destroy ozone. Chlorine-containing anesthetics such as halothane, isoflurane, and enflurane may be more destructive to the ozone layer than newer anesthetics, such as sevoflurane and desflurane, which contain only C-F bonds. Carbon-hydrogen bonds are susceptible to attack by hydroxyl radicals (OH·) in the troposphere,[212] making them less likely to reach the stratosphere. However, even compounds with a lifetime of a few months may potentially contribute to ozone destruction.[213] Contributions to total stratospheric ozone depletion were estimated as 1% for halothane and 0.02% for enflurane and isoflurane.[211]

N_2O is the primary source of stratospheric nitrogen oxides, NO and NO_2, and both destroy ozone. Because only 10% of N_2O is converted to NO_X, its ozone depleting potential is lower than that of an equal mass of CFCs. However, N_2O emission is the single largest ozone depleting human emission, and is expected to remain so for the rest of this century.[199] The use of N_2O could actually contribute additional environmental harm when used with halogenated anesthetics.

TABLE 26-5 ATMOSPHERIC LIFETIMES AND ENVIRONMENTAL EFFECTS OF INHALED ANESTHETICS

Compound		Lifetime (yr)	Ozone-Depleting Potential	Global Warming Potential (20 yr)	Global Warming Potential (100 yr)
CFC-12	CCl_2F_2	100	1	11,000	10,900
Carbon dioxide	CO_2	5-200	—*	1	1
Nitrous oxide	N_2O	114	0.017[199]	289	298
Halothane	$CF_3CHBrCl$	7[200]	0.36	—	218†
Isoflurane	$CHF_2OCHClCF_3$	2.6-3.6[201]	0.01	1230-1401[201]	350
Sevoflurane	$CH_2FOCH(CF_3)_2$	1.2-5.2 [201]	0	349-1980 [201]	575
Desflurane	$CHF_2OCHFCF_3$	10[201]	0	3714[201]	—

Ozone-depleting potential is the ratio of integrated perturbations to total ozone relative to an equal emission of CFC-12. Global warming potential is defined as the cumulative radiative retention integrated over a period of time from the emission of gas relative to reference gas (CO_2). The data are based on the Intergovernmental Panel on Climate Change Fourth Assessment Report [248] unless otherwise indicated.

*CO_2 unlikely reacts and depletes ozone; however, CO_2 producing the greenhouse effect in the troposphere is predicted to reduce stratospheric temperatures and cause further ozone depletion.[202]

†Computed value for halothane relative to global warming potential for CFC-12.

The environmental impact of all inhaled anesthetics could be reduced by up to 80% to 90% if closed-circuit anesthesia were widely employed, and to a lesser degree if low carrier gas flow rates were used routinely (see Fig. 26-13). Technologies that trap anesthetics in waste gas flows have the potential to reduce emissions into the environment, and can reduce drug costs by reusing (after redistillation) the trapped drugs.[214] Physician education warning that the medical use of N_2O can significantly contribute to both the greenhouse effect and ozone depletion should be maintained. Avoiding N_2O when it provides no clinical advantage is suggested as a more environmentally sound anesthetic practice.[204]

Exposure to Waste Anesthetic Gases

Health care personnel can be exposed to waste anesthetic gases both in and out of the operating room environment. Possible adverse health effects by chronic exposure to trace concentrations of inhaled anesthetics have caused concern among health care professionals for many years.[215,216] Laboratory studies suggest reproductive abnormalities in animals exposed to high concentrations of N_2O (1000 ppm or greater).[217,218] However, neither animal nor epidemiologic studies have shown any evidence for adverse effects attributable to the low levels of anesthetic gases in operating room air. A long-term prospective study found no causal relationship between adverse health effects and exposure to waste anesthetic gases with or without a scavenging system.[219] All inhaled anesthetics cross the placental-fetal exchange barrier. Teratogenicity, which has been demonstrated in animal fetuses chronically exposed to N_2O,[220,221] is of particular concern in pregnant health care workers, but there is no evidence of harm in humans. Furthermore, there is no evidence of harm to fetuses of women anesthetized while pregnant,[222] although general anesthesia is associated with neuroapoptosis during critical phases of brain development (see earlier, Inhaled Anesthetics and Neurotoxicity) warrant further clinical study of outcomes after anesthetic exposure during late-term pregnancy.[223] Currently, the U.S. Occupational Safety and Health Administration (OSHA) recommends that no worker should be exposed to concentrations of halogenated anesthetic greater than 2 ppm for a period not to exceed 1 hour during anesthesia administration (http://www.osha.gov/dts/osta/anestheticgases/index.html). OSHA also recommends that no worker should be exposed to 8-hour time-weighted average concentrations greater than 25 ppm. The recommended exposure level for N_2O is 25 ppm during anesthetic administration.

Potential postoperative exposure of health care workers to exhaled anesthetic gases in postanesthesia care units, intensive care units, and other patient care areas should also be recognized. Studies have documented excessive levels of waste anesthetic gases in poorly ventilated postanesthesia care units[224-226]; however, no studies have documented significant adverse health.

Xenon and Other Noble Gases

Current inhaled anesthetics represent vast improvements over earlier inhaled anesthetics, with N_2O representing the longest surviving widely used anesthetic. The noble gas xenon was first shown to produce general anesthesia in 1951,[227] and subsequent studies have revealed that it approaches the ideal closer than any other inhaled anesthetic.[228-230] It is most comparable to N_2O, but superior in a number of ways. Xenon is present as a minor constituent of air (50 parts per billion), and it is isolated by distillation of liquefied air, liquefied nitrogen, and oxygen. Xenon is entirely unreactive in the biosphere; therefore, it is the only inhaled anesthetic that is not an environmental pollutant, although its distillation from air uses considerable energy and thus creates CO_2 and other pollutants as byproducts.[205] It is odorless, tasteless, and nonflammable, and it has a limitless shelf-life. Its solubility in blood ($\lambda_{b/g}$ = 0.14) and body tissues is lower than that of any other inhaled anesthetic, including N_2O. As a result, it has extraordinarily rapid onset and respiratory clearance, with emergence times twofold to threefold faster when it replaces N_2O in clinical settings.[231,232] It undergoes no biotransformation or reactions with CO_2 absorbents or ultraviolet light. Moreover, xenon has favorable pharmacodynamic effects in comparison with most inhaled anesthetics. It produces minimal cardiovascular depression, and it is not arrhythmogenic.[233-235] As with N_2O, xenon has analgesic activity, and it reduces intraoperative opioid requirements.[236] It does not trigger malignant hyperthermia or produce any known toxicity.[237] In fact, xenon has cardioprotective and neuroprotective activities in preclinical models,[228,230] although clinical trials have

not demonstrated a reduction in postoperative delirium in high-risk patients receiving xenon.[238,239]

Given all these advantages, why is xenon not a commonly used inhaled anesthetic? The main reason is its cost.[240] At more than $15 per liter in the gas form, xenon is greater than 100-fold more expensive than N_2O and is far more expensive per patient than either desflurane or sevoflurane, which are currently the most expensive volatile anesthetics. Xenon has a MAC-immobility of 0.61 atm, and even with a strict closed-circuit technique, greater than 10 L is needed to anesthetize a typical patient. To perform closed-circuit anesthesia with xenon–oxygen also requires lengthy preanesthetic denitrogenation to prevent N_2 from accumulating in the rebreathing circuit.[241] Transitioning from 100% oxygen during denitrogenation to closed-circuit xenon–oxygen anesthesia is another slow process because xenon is added to the circuit as oxygen is metabolized in the patient at 200 to 250 mL/min. High-flow xenon is otherwise necessary to make this transition short. To make xenon a more affordable anesthetic, specialized anesthesia machines have been designed to enable its efficient delivery,[242] and new waste-scavenging systems are being introduced with cryogenic traps that can condense xenon in a liquid form from waste gases.[243] This process allows relatively inexpensive recycling of xenon after it has been redistilled to a pure form.

In addition to cost, xenon presents a few other downsides. Xenon gas has a much higher density (5.9 g/L) than either N_2O (1.5 g/L) or air (1.0 g/L), resulting in increased flow resistance and work of breathing.[244] Thus, it may be a poor choice for patients with compromised respiratory function. As with N_2O, high xenon partial pressures needed for anesthesia cause expansion of trapped air spaces and vascular air emboli.[245] Compared with propofol infusion, xenon anesthesia results in approximately twofold the incidence of nausea and vomiting.[246]

Currently, xenon remains an experimental anesthetic, with current research focusing on its potential as a clinical neuroprotectant and development of technologies to reduce its cost. Shifting the cost-benefit balance toward more xenon use in patients will depend on whether clinical studies ultimately support xenon's potential organ protection efficacy. Other noble gases also share some of xenon's neuroprotective actions in experimental model systems, and they are under investigation as potential clinical drugs.[247]

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Chapter 27

Inhaled Anesthetics: Pulmonary Pharmacology

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Key Points

- Inhaled anesthetics affect every facet of pulmonary physiologic function.
- Bronchodilatory actions of volatile anesthetics occur through decreases in intracellular calcium (ICa^{2+}) concentration and/or a reduction in calcium (Ca^{2+}) sensitivity. Volatile anesthetics attenuate increases in pulmonary airway resistance attributable to chemical or mechanical stimuli.
- Inhaled anesthetics diminish the rate of mucous clearance and alter type II alveolar cell function, which may play a role in postoperative pulmonary complications.
- Volatile anesthetics cause biphasic responses in pulmonary vascular smooth muscle that are mediated at multiple sites of a Ca^{2+}-mediated signaling pathway. Volatile anesthetic–induced inhibition of hypoxic pulmonary vasoconstriction (HPV) is small but may worsen hypoxemia.
- Components of the respiratory system include peripheral and central chemoreception, a central pattern generator, and motoneuronal output. Inspiratory efforts are closely coordinated with upper airway patency. Anesthetics depress these systems through a reduction of chemodrive and direct inhibition of neurotransmission, leading to a risk of respiratory depression and upper airway obstruction.
- During volatile anesthesia, maintenance of spontaneous ventilation is dependent on the carbon dioxide (CO_2)–mediated excitatory central chemoreceptor inputs to the central respiratory pattern generator. Peripheral chemoreceptor inputs and hypoxic arousal reflexes are severely impaired even during sedative levels of volatile anesthesia.
- Volatile anesthetics reduce tidal volume and minute ventilation and cause tachypnea in a dose-related fashion.
- Diaphragmatic function is relatively well preserved during volatile anesthesia, whereas inspiratory rib cage muscles are significantly depressed. Abdominal expiratory muscle activation contributes to less-coordinated respiratory muscle activation, which is pronounced during CO_2-stimulated breathing.
- Upper airway patency can be rapidly compromised during volatile anesthesia. Upper airway obstruction can even occur at sedative concentrations of volatile anesthetics in susceptible patients.
- Volatile anesthetics vary in their ability to irritate airways and enhance defensive airway reflexes. Sevoflurane is the anesthetic of choice for inhaled induction of anesthesia in infants and children (also see Chapter 93).
- Volatile anesthetics are immunomodulatory. In some models, they are proinflammatory. Yet, volatile anesthetics may reduce inflammation and improve both chemical and pulmonary physiologic function.
- Nitrous oxide may cause adverse pulmonary effects.
- The high-density and low blood-gas coefficient of xenon result in improved gas exchange and a *fast on and off action* without causing diffusion hypoxia.

INTRODUCTION

This chapter describes the pulmonary pharmacology of modern inhaled anesthetics (including isoflurane, desflurane, and sevoflurane), nitrous oxide, and the anesthetic noble gas, xenon. Comparison with older volatile anesthetics (e.g., halothane, enflurane, ethers) is made only when necessary because these drugs are no longer available in the developed world. The lungs are unique in their exposure to a wide variety of physical forces including ventilation, blood flow, and surface tension. The actions of inhaled anesthetics on airway tone, pulmonary vascular resistance (PVR), mucociliary function, surfactant production, ventilatory control, and acute lung injury are examined in detail.

INHALED ANESTHETICS

BRONCHOMOTOR TONE

Transient increases in airway resistance may be caused, at least in part, by an increase in bronchiolar smooth muscle tone. Asthma is one of the most common chronic airway diseases worldwide with an estimated annual death rate of 250,000 (also see Chapter 103). Patients without recent symptoms of asthma have a relatively low frequency of perioperative respiratory complications, yet perioperative bronchospasm develops in approximately 9% of patients with asthma.[1] Prospective studies have demonstrated 1.7% of patients with asthma experience a poor respiratory outcome[2] and 25% wheezed after the induction of anesthesia.[3] Of the 40 cases of bronchospasm resulting in settled malpractice claims reported by the American Society of Anesthesiologists Closed Claims Project,[4] 88% involved brain damage or death and only one-half of these patients had a history of asthma or chronic obstructive pulmonary disease (COPD). Adverse respiratory events accounted for 28% of claims dealing with anesthesia-related brain damage and death in the United States and are associated with the highest mean cost per closed claim. In France, 7% of anesthesia-related deaths were attributed to bronchospasm.[5] Of the 4000 reported adverse incidents in Australia, 3% (103) were related to perioperative bronchospasm.[6] Additionally, an allergic mechanism was far less frequently involved (21%) than a nonallergic mechanism (79%). Although bronchospasm caused by airway irritation occurred more frequently in patients who had one or more predisposing factors such as asthma, heavy tobacco smoking, or bronchitis, a history of asthma was only present in 50% and 60% of patients with nonallergic and allergic bronchospasm, respectively.

Pharmacology of Bronchial Smooth Muscle

Airway smooth muscle extends as far distally as the terminal bronchioles and is affected by autonomic nervous system activity. Nonadrenergic, noncholinergic mechanisms, activated by the stimulation of the afferent bronchopulmonary sensory C fibers, may play a role in airway smooth muscle constriction to tachykinins, vasoactive intestinal peptide, adenosine, and calcitonin gene-related peptides. However, this pathway may be less important in humans than in other animal models. Bronchiolar constriction associated with asthmatic exacerbations are complex and involve airway nerves, smooth muscle, epithelium, and inflammatory cells. Reflex-mediated bronchoconstriction, on the other hand, caused by upper airway irritation, is modulated by afferent sensory pathways in the nucleus of the solitary tract, projecting to vagal preganglionic neurons. The excitatory neurotransmitter glutamate modulates stimulation of the nucleus tractus solitarii (NTS) and vagal preganglionic neurons, whereas the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) project from the nucleus of the solitary tract to the vagal preganglionic neurons. The efferent pathway from the vagal preganglionic neurons back to the airway is via the vagus nerve and involves acetylcholine release, predominantly on M_3 muscarinic receptors of airway smooth muscle to induce airway constriction.

Parasympathetic nerves originating in the vagal centers within the central nervous system also mediate baseline airway tone. Changes in intracellular calcium (ICa^{2+}) levels and Ca^{2+} influx may be caused by alterations in cyclic nucleotides within bronchial smooth muscle. Agonist-induced contraction is mediated by an increase in myosin light-chain kinase activity, phosphorylation of the 20-KD regulatory myosin light chain, or an increase in Ca^{2+} sensitivity.[7] Ca^{2+}/calmodulin–dependent myosin light-chain kinase is a critical component of tonic smooth muscle contraction.[8] Exogenous administration of acetylcholine or the stimulation of the vagus nerve increases the relative amount of cyclic guanosine monophosphate (cGMP), compared with cyclic adenosine monophosphate (cAMP), and results in bronchial smooth muscle contraction. Agonist activation of bronchial smooth muscle cells also involves the second messenger, cyclic adenosine diphosphate ribose (cADPR), which results in inositol triphosphate (IP_3)–mediated release of Ca^{2+} from the sarcoplasmic reticulum (SR) by activating ryanodine channels.[9] This release is followed by activation of store- and receptor-operated nonselective cation channels, which, in turn, leads to sodium (Na^+) influx. This localized increase in Na^+ may switch the Na^+/Ca^{2+} exchanger into reverse mode, leading to even more Ca^{2+} influx and greater constriction. Several different cAMP signaling compartments exist in airway smooth muscle that are selectively responsive to different hormones and neurotransmitters.[10] The mechanical stretch of human bronchial smooth muscle cells also causes contraction via an influx of Ca^{2+} through unique stretch-activated nonselective cation channels.[11] Adenosine indirectly contracts airway smooth muscle via the release of contractile agents from mast cells and nerves by directly stimulating adenosine type I (A1) receptors on airway smooth muscle, thereby rapidly mobilizing ICa^{2+} stores through G proteins and IP_3 signaling.

Agonist-induced stimulation of particulate guanylyl cyclase relaxes bronchial smooth muscle by decreasing Ca^{2+} current. In contrast, stimulation of soluble guanylyl cyclase by substances such as nitric oxide (NO) reduces ICa^{2+} concentration and Ca^{2+} sensitivity.[12] In addition to Ca^{2+}, potassium (K^+) also plays a significant role in resting membrane potentials. The two-pore domain,

acid-sensitive K^+ (TASK-1) channel is a voltage-independent K^+ channel found in human pulmonary artery (PA) smooth muscle cells that helps set their resting membrane potential and plays a role in their sensitivity to a variety of vasoactive factors, including hypoxia, pH, G-protein coupled pathways, and volatile anesthetics.

Release of histamine in the airway or various forms of mechanical or chemical stimulation increases afferent vagal activity to produce reflex bronchoconstriction. This increase in bronchomotor tone is attenuated by the cholinergic antagonist atropine. M_2 and M_3 muscarinic receptors on airway smooth muscle mediate bronchoconstriction by increasing Ca^{2+} sensitivity.[13] Presynaptic M_2 muscarinic receptors have also been identified that inhibit acetylcholine release and thus drugs that preferentially inhibit M_2 receptors (e.g., ipratropium bromide) may paradoxically produce bronchoconstriction.[14] This effect is not commonly observed in patients. The histamine-degrading enzyme, histamine N-methyltransferase, has been localized to human airway epithelium and may play a protective role against histamine-mediated bronchoconstriction.[15] Cholinergic stimulation acting on muscarinic receptors primarily creates a central airway constriction, whereas antigen challenges usually provoke greater changes in the lung periphery.[16]

Adrenergic receptors in bronchial smooth muscle are classified into α and β_2 types. Although α-receptors have been characterized in the human bronchial tree, their clinical importance has not been demonstrated. In contrast, the β_2-receptor subtypes play an important role in bronchiolar smooth muscle responsiveness. Stimulation of β_2 adrenoceptors causes cAMP-mediated relaxation via activation of protein kinase A and subsequent Ca^{2+} efflux out of the cell and into the SR. Notably, asthma, as well as allergy- and methacholine-induced bronchospasm, do not appear to be genetically linked to a dominant β_2-adrenoceptor gene.[17]

Respiratory epithelium releases substances that modulate bronchial smooth muscle tone. Removal of the epithelium enhances contractile responses to acetylcholine, histamine, or serotonin in large airways and decreases relaxation responses to isoproterenol in small airways. These actions are analogous to the effect of endothelial damage on vascular smooth muscle tone. Notably, cardiopulmonary bypass does significantly affect porcine bronchiolar epithelium-mediated bronchomotor activity, in contrast to vascular endothelium-mediated smooth muscle dysfunction.[18] Although endogenous epithelial factors have been identified, NO may play an important vasodilatory role in respiratory epithelium similar to that of vascular endothelium. Endothelin-1 is also a potent endogenous bronchoconstrictor that functions by activation of the IP_3 pathway.[19] Endothelin-1 is a more potent constrictor of vascular than bronchial smooth muscle and has greater efficacy in the pulmonary than the systemic circulation.

Effects of Inhaled Anesthetics

Volatile anesthetics are all bronchodilators, but some controversy remains concerning which volatile anesthetic exerts the most potent bronchodilation. In animal models, halothane appears to have the most pronounced effect of relaxing airway smooth muscle. Eliminating indirect effects of arterial carbon dioxide (CO_2) tension is important when examining the actions of volatile anesthetics on bronchial tone, especially during spontaneous ventilation, as hypercapnia-induced bronchodilation and hypocapnia-induced bronchoconstriction are both attenuated by isoflurane.[20] What may be interpreted as a dose-dependent effect of deepening the level of volatile anesthetics may actually be attributable to an indirect action by a progressive increase in CO_2 tension. The structure of the respiratory epithelium changes from pseudostratified columnar cells of the large airways to thinner, cuboidal cells of the bronchioles, and thus a relatively large amount of histologic heterogeneity exists between these regions. Although all volatile anesthetics cause bronchodilation, their specific effects on the bronchioles depend on the location in and the structure of the respiratory tree. In vitro, isoflurane preferentially relaxes the bronchioles rather than the bronchi.[21] Park and colleagues[22] demonstrated that isoflurane and halothane dilate fourth order bronchi at equivalent minimum alveolar concentration (MAC) values. Isoflurane, sevoflurane, and desflurane at concentrations of up to 1 MAC similarly attenuated methacholine-induced bronchoconstriction in open-chest, pentobarbital-anesthetized rats.[23] Isoflurane and sevoflurane also appear to have greater inhibitory effects on bronchial contraction as compared with tracheal smooth muscle contraction.[24] Similarly, halothane, desflurane, and isoflurane relax distal airways (e.g., bronchioles) to a greater extent than proximal airways (e.g., bronchi).[25] These differential effects appear to be related to the type of voltage-dependent Ca^{2+} (VDC) channels that are present in these regions.

Inhalation of 1 or 2 MAC halothane, enflurane, sevoflurane, and isoflurane did not alter baseline pulmonary resistance and dynamic pulmonary compliance, but these anesthetics significantly attenuated increases in pulmonary resistance and decreases in dynamic pulmonary compliance in response to intravenous histamine. Halothane was most effective in altering indices of bronchodilation, whereas responses to isoflurane, enflurane, and sevoflurane were nearly identical.[26] In contrast, desflurane produced bronchodilation at 1 MAC but increased airway resistance at 2 MAC.[27] Halothane, enflurane, and sevoflurane are equivalent at dilating third- or fourth-generation bronchi as directly measured with a fiberoptic bronchoscope in vivo.[28]

A controversy remains regarding the role of desflurane in promoting or inhibiting airway constriction. Desflurane and sevoflurane (1 MAC) block the increases in central airway resistance after a cholinergic challenge to equivalent degrees in rabbits. However, neither anesthetic protected against the increases in tissue damping (a measure of heterogeneous deterioration of the peripheral airways), which occurred after the cholinergic stimulus. Both anesthetics inhibited basal bronchial tone by approximately 30% to 40%. This finding was consistently observed in the presence or absence of allergic inflammation of the airways and bronchial hyperresponsiveness.[29] When the mechanism of constriction is centrally mediated, such as with a cholinergic challenge,[23,30,31] desflurane appears to play a beneficial role in attenuating deleterious effects

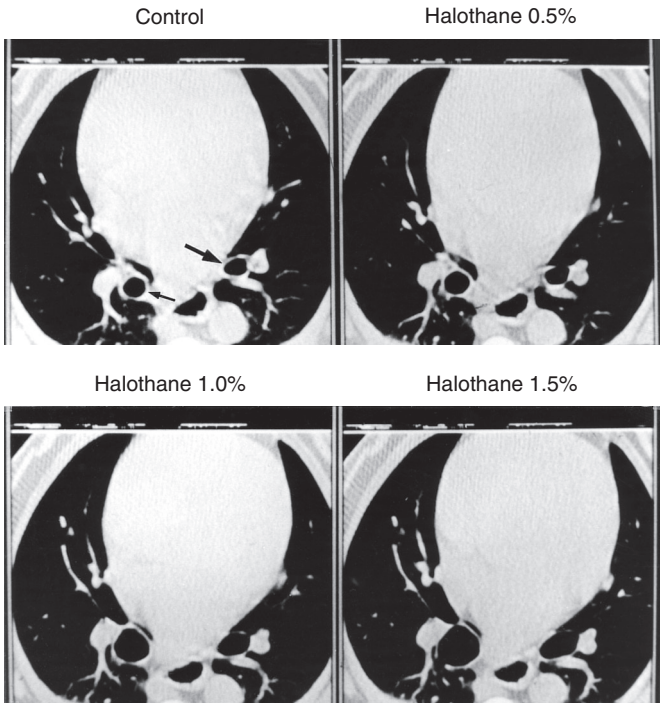


Figure 27-1. High-resolution computed tomography scans from one dog. *Upper left:* Control. *Upper right:* During 0.5% halothane. *Lower left:* During 1.0% halothane. *Lower right:* During 1.5% halothane. Note the progressive dilation of the airways as indicated by the arrows. *(Reproduced from Brown RH, Mitzner W, Zerhouni E, et al: Direct in vivo visualization of bronchodilation induced by inhalational anesthesia using high-resolution computed tomography,* Anesthesiology *78:295, 1993. Used with permission.)*

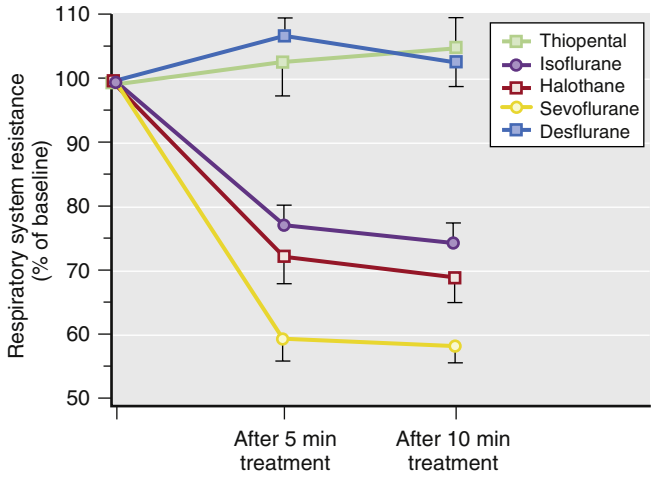


Figure 27-2. Percent change in respiratory system resistance in patients after 5 and 10 minutes of maintenance anesthesia with either 0.25 mg/kg/min thiopental plus 50% nitrous oxide or 1.1 minimum alveolar concentration (MAC) sevoflurane, halothane, or isoflurane or approximately 1 MAC desflurane. All volatile anesthetics except desflurane decreased resistance. Sevoflurane decreased resistance more than isoflurane. *(Modified from Rooke GA, Choi JH, Bishop MJ: The effect of isoflurane, halothane, sevoflurane, and thiopental/nitrous oxide on respiratory system resistance after tracheal intubation,* Anesthesiology *86:1294, 1997; and Goff MJ, Arain SR, Ficke DJ, et al: Absence of bronchodilation during desflurane anesthesia: a comparison to sevoflurane and thiopental,* Anesthesiology *93:404, 2000. Used with permission.)*

of bronchoconstriction. However, when the mechanism of airway constriction is from nonadrenergic, noncholinergic activation such as tachykinins, desflurane may augment and worsen constriction.[32,33] Clinically, anesthesiologists tend to avoid using desflurane in patients with reactive airway disease.

Effects of Inhaled Anesthetics on Bronchomotor Tone in Humans

Using computed tomography (CT), Brown and colleagues[34] showed that halothane causes greater bronchodilation than does isoflurane at low concentrations (Figure 27-1). Sevoflurane (1 MAC) reduced respiratory system resistance (determined using an isovolume technique) by 15% in patients undergoing elective surgery. In contrast, desflurane did not significantly alter resistance.[35] Rooke and associates[36] compared the bronchodilating effects of halothane, isoflurane, sevoflurane, and thiopental–nitrous oxide in 66 healthy patients undergoing induction of anesthesia and tracheal intubation (Figure 27-2). In contrast to thiopental–nitrous oxide, all volatile anesthetics significantly reduced respiratory resistance. An equivalent MAC value of sevoflurane and halothane decreased resistance to similar degrees, whereas isoflurane produced substantially less bronchodilation in vivo.

The work of breathing (expressed in joules) is defined as pressure or force multiplied by the tidal volume during inspiration. Respiratory work of the lung is further broken down into elastic work (required to overcome the recoil of the lung) and resistive work (required to overcome airway flow resistance and viscoelastic resistance of pulmonary tissues). The work of breathing is usually derived from transpulmonary pressure volume curves. Volatile anesthetics increase the work of breathing in adults and children. Some animal studies have suggested that volatile anesthetics *reduce* pulmonary compliance mediated at the lung periphery rather than at the airway level, thereby increasing viscoelastic and elastic pressures in the lung.[37] This finding was histologically supported by the observation of increased areas of alveolar collapse alternating with hyperinflation. In contrast, in a murine model of chronic asthma, sevoflurane anesthesia significantly decreased resistance in central and distal airways and also lowered resistance in the lung periphery. These data suggested that sevoflurane exerts a beneficial action in the presence of chronic airway obstruction and implied that volatile anesthetics reduce the work of breathing (Figure 27-3).[38] Indeed, most studies in humans demonstrate that low (small) concentrations of volatile anesthetics significantly reduce upper and lower respiratory system resistance (Figure 27-4).[39]

Expiration is passively affected by the recoil characteristics of the lung during normal breathing. In anesthetized patients, the ventilatory response to expiratory resistance is reduced to a greater extent than is the response to inspiratory resistance. Conscious and anesthetized humans exhibit decreases in respiratory rate during expiratory resistive loads, but only anesthetized subjects develop rib cage–abdominal wall motion dyssynchrony that causes less effective ventilation and increases

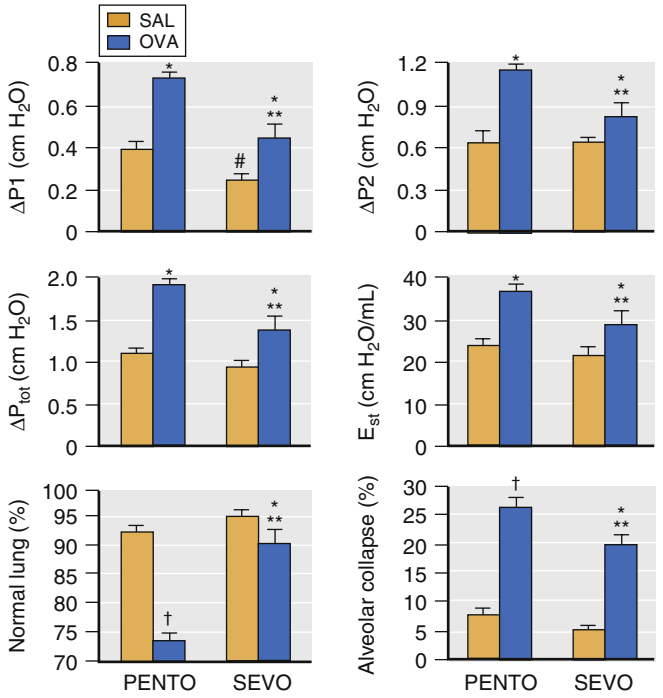


Figure 27-3. Mean ± standard error of the mean (SEM) for pressure to overcome airway resistance (ΔP1), viscoelastic lung properties (ΔP2), total of ΔP1 and ΔP2 (ΔP_{tot}), and static lung elastance (E_{st}). Also shown are the percent of normal area and the percent of alveolar collapse in mice repeatedly challenged with intratracheal instillation of saline (SAL) or ovalbumin (OVA). Animals were anesthetized with pentobarbital sodium (PENTO) or sevoflurane (SEVO), 1 minimum alveolar concentration (MAC). *, $P < 0.05$ versus corresponding SAL group; **, $P < 0.001$ versus OVA-PENTO group; #, $P < 0.05$ versus SAL-PENTO group; †, $P < 0.01$ versus the SAL-PENTO group. *(Modified from Burburan SM, Xisto DG, Ferreira HC, et al: Lung mechanics and histology during sevoflurane anesthesia in a model of chronic allergic rhinitis,* Anesth Analg *104:631, 2007. Used with permission.)*

in arterial CO_2 tension. This concept may be particularly important in spontaneously breathing, anesthetized patients who demonstrate expiratory obstruction, such as may be observed during partial breathing circuit occlusion, asthma, emphysema, or airway secretions.

Previously described experimental studies demonstrating the equal potency of sevoflurane and isoflurane and the relatively greater potency of halothane for bronchodilation must be extrapolated with caution because Ascaris- or histamine-mediated experimental bronchospasm may not precisely mimic tracheal intubation–induced bronchospasm in humans. In contrast to the findings in experimental animals, Arakawa and colleagues[40] showed that similar inspired concentrations of halothane, isoflurane, and sevoflurane produced nearly identical reductions in airway resistance in a patient with status asthmaticus. Indeed, volatile anesthetics may be an effective method of treating status asthmaticus when conventional therapy has failed.[40]

The use of β-adrenoceptor agonists may be beneficial for the treatment of acute bronchospasm in patients anesthetized with halothane,[41,42] but its use may not be beneficial with other volatile anesthetics. The β_2-adrenergic agonist, fenoterol, lowered respiratory system resistance after endotracheal intubation but did not further reduce resistance when administered in the presence of 1.3% isoflurane.[43] These data should be interpreted with caution because the technique used to determine respiratory system resistance incorporates alterations in lung and chest wall resistance, as well as tissue viscosity. The most important functional change that occurs in the presence of lung disease is increased resistance. Resistance to airflow is typically thought of as being determined by contraction and relaxation of airway smooth muscle. However, nonmuscle elements, such as lung inflammation, airway thickening, altered lung volumes, lung recoil, airway wall remodeling, mucous hypersecretion, and loss of lung elastance, also play a clinically significant role in the amount of airway narrowing.[44] The role of volatile anesthetics in altering many of those non–smooth-muscle elements responsible for airway resistance has not yet been studied.

The actions of volatile anesthetics on bronchomotor tone are also dependent on the substance used to elicit contraction in vitro.[45] Relaxation of tracheal smooth muscle by halothane and isoflurane is greatest in the presence of the endogenous mediator, serotonin, (potentially representing anaphylactoid or immunologic reactions) compared with acetylcholine (representing the neutrally derived mediator of reflex bronchospasm). Inhaled anesthetics may remain effective bronchodilators, even in the presence of severe serotonin- or histamine-induced bronchospasm that is refractory to β_2-adrenoceptor therapy. It is important to note that volatile anesthetic–induced decreases in bronchomotor tone and neurally mediated airway reflexes may be partially opposed by a simultaneous reduction in functional residual capacity (FRC) in the anesthetized patient. The well-known increased risk for morbidity and mortality in patients with asthma may be at least partially attributed to these FRC-mediated increases in airway resistance. Exposure of airway smooth muscle to low temperatures may abolish the inhibitory effects of volatile anesthetics on carbachol-induced contraction,[46] suggesting that intraoperative hypothermia also may attenuate volatile anesthetic–induced bronchodilation.

Bronchospasm may occur in respiratory diseases other than asthma. For example, healthy patients undergoing surgical stimulation of pulmonary parenchyma or airways (including tracheal stimulation by an endotracheal tube) are at risk of developing bronchospasm. The choice of preoperative medication, sedative-hypnotic, neuromuscular blocker, and volatile anesthetic are all important factors in determining the clinical appearance of bronchospasm in patients with known reactive airway disease. Iwasaki and colleagues[47] demonstrated that sevoflurane-induced relaxation of airway smooth muscle and VDC channels were dependent on the type of hyperreactive airway model. Sevoflurane had smaller effects in a model of chronic tobacco smoking (enlarged alveolar ducts and less muscarinic hyperreactivity), compared with an antigen-acute asthmatic (ovalbumin-sensitized) model. The morphologic changes in the peripheral airway may be responsible to some degree for a decrease in the efficacy of volatile anesthetics as bronchodilators in tobacco smokers, but sevoflurane and isoflurane decrease respiratory system resistance in patients with COPD.[48] In contrast to an acute asthmatic model that is characterized

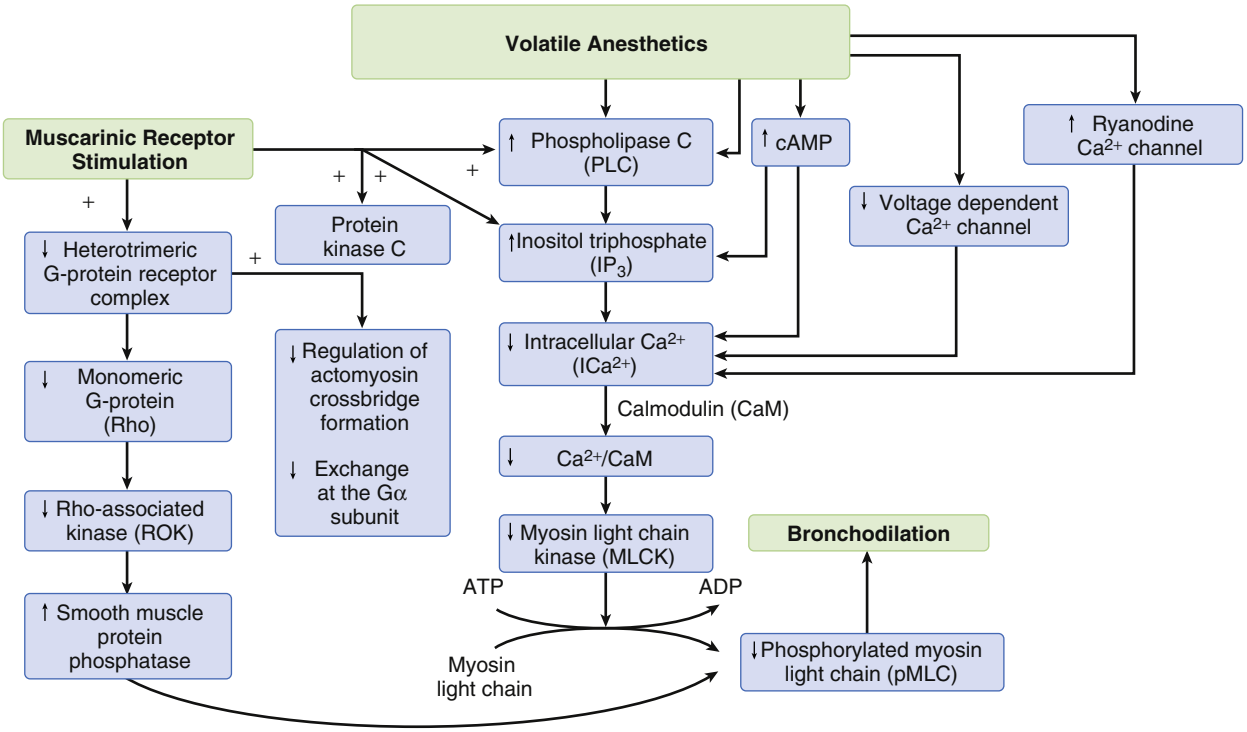


Figure 27-4. Isoflurane (ISO) at 0.6% reduced respiratory system elastance (E in cm H_2O/L) and resistance (R in cm H_2O/L/sec). *Total* represents the total respiratory system (lung and chest wall). Values are mean ± standard deviation (SD). No further reductions with increasing concentrations of isoflurane were observed. *, $P < 0.05$ versus baseline; *ADP*, adenosine diphosphate; *ATP*, adenosine triphosphate; *cAMP*, cyclic adenosine monophosphate. *(Modified from Ruiz P, Chartrand D: The effect of isoflurane 0.6% on respiratory mechanics in anesthetized-paralyzed humans is not increased at concentrations of 0.9% and 1.2%,* Can J Anaesth *50:67, 2003. Used with permission).*

by eosinophilic inflammation and airway wall changes, inflammation in chronic asthma involves many other cell types, including mast cells, macrophages, epithelial cells, and bronchial smooth muscle cells. In addition, chronic inflammation is associated with remodeling of bronchial epithelium to produce smooth muscle hypertrophy, gland hyperplasia, and neovascularization.

The administration of volatile anesthetics to children undergoing elective imaging studies was characterized by progressive reductions in the cross-sectional area of upper airway musculature, resulting in pharyngeal airway collapse[49] (also see Chapter 93). As observed with isoflurane in animal models, the effects of sevoflurane in children were not uniformly distributed along the upper airway. In healthy children, sevoflurane slightly decreased airway resistance, but desflurane had the opposite effect, presumably via reduced airway dimensions.[50] Children with documented airway susceptibility, such as those diagnosed with asthma or a recent upper respiratory tract infection, exhibited significant increases in respiratory system mechanical parameters such as respiratory impedance and elastance. In contrast to the beneficial effects of administering sevoflurane in these children, administration of desflurane caused greater deleterious changes in airway mechanics including an elevation in airway resistance, tissue damping, and elastance.[50]

Mechanisms of Action

Volatile anesthetics relax airway smooth muscle by directly depressing smooth muscle contractility. This action is the result of the anesthetics' direct effects on bronchial epithelium and airway smooth muscle cells, combined with the indirect inhibition of reflex neural pathways. The mechanisms responsible for the direct relaxation effects involve decreases in both ICa^{2+} concentration and Ca^{2+} sensitivity. Several intracellular mediators responsible for Ca^{2+} mobilization are potential sites for the action for volatile anesthetics. Inhibition of cell membrane-associated VDC channels by volatile anesthetics reduces Ca^{2+} entry into the cytosol.[47] Volatile anesthetic–induced increases in cAMP concentrations cause decreases in intracellular-free Ca^{2+} by stimulating Ca^{2+} efflux and increasing Ca^{2+} uptake into the SR. In addition, a volatile anesthetic–induced decrease in Ca^{2+} sensitivity attributable to the inhibition of protein kinase C activity,[51] inhibition of G-protein function, and attenuation of Rho and Rho-kinase signaling pathways also play important contributory roles.[52,53] Volatile anesthetics may differentially alter pulmonary resistance by affecting the density of the gas mixture (Figure 27-5).[51] In an experimental lung model of fixed pulmonary resistance, high concentrations of volatile anesthetics increased the density of the gas mixture and the calculated resistance, with desflurane producing the largest increase at all MAC values studied.

The effects of volatile anesthetics on proximal compared with distal airways may be related to the differential effects on VDC channels and the relative distribution of these channels. Long-lasting (L-type) VDC channels appear to be the predominant mechanism for Ca^{2+} entry in tracheal smooth muscle, whereas both transient

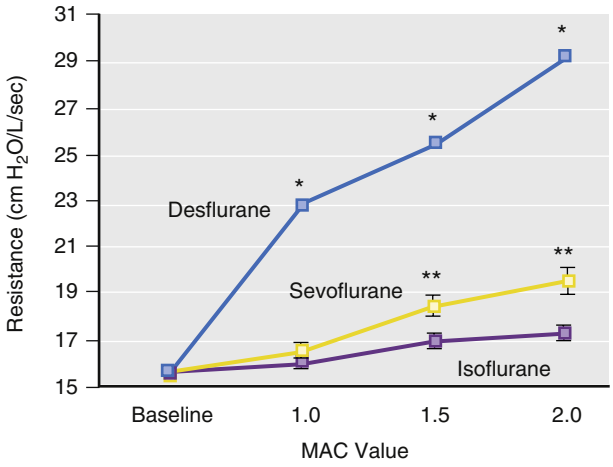


Figure 27-5. Comparison of the effect of different volatile anesthetics at equivalent concentrations on total pulmonary resistance. At 1 minimum alveolar concentration (MAC), only desflurane significantly increased pulmonary resistance, compared with isoflurane and sevoflurane. At 1.5 and 2 MAC, sevoflurane significantly increased total pulmonary resistance, compared with isoflurane, whereas desflurane caused a more pronounced increase than the other two agents. *, Increased pulmonary resistance in comparison with sevoflurane and isoflurane; **, increased pulmonary resistance in comparison with isoflurane. *(Reproduced from Nyktari VG, Papaioannou AA, Prinianakis G, et al: Effect of the physical properties of isoflurane, sevoflurane, and desflurane on pulmonary resistance in a laboratory lung model,* Anesthesiology *104:1202, 2006. Used with permission.)*

(T-type) and L-type VDC channels are present in bronchial smooth muscle.[24,54] Yamakage and coworkers[24] demonstrated that isoflurane and sevoflurane inhibit both types of VDC channels in a dose-dependent fashion, but their effects on T-type VDC channels in bronchial smooth muscle were substantially more pronounced (Figure 27-6). The differential effects of volatile anesthetics on tracheal smooth muscle, compared with bronchial smooth muscle, may also be related to actions on Ca^{2+}-activated chloride channel activity[55,56] or differential sensitivities of K^+ channel subtypes.[55]

The proposed signaling pathways underlying volatile anesthetic–induced bronchodilation are depicted in Figure 27-7. Volatile anesthetic–induced reductions in ICa^{2+} result from the inhibition of both VDC and receptor-gated Ca^{2+} channels. In addition, volatile anesthetics deplete SR Ca^{2+} stores by increasing Ca^{2+} leakage. Ca^{2+} influx occurring in response to depleted SR Ca^{2+} stores is known as store-operated Ca^{2+} entry (SOCE). By depleting SR Ca^{2+} stores, volatile anesthetics may be expected to enhance SOCE. Nevertheless, clinically relevant concentrations of volatile anesthetics (isoflurane more than sevoflurane) also inhibit SOCE in airway smooth muscle to further reduce available Ca^{2+}.[57] The cyclic nucleotides, cAMP and cGMP, also have similar inhibitory effects on SOCE in airway smooth muscle, and these effects are additive in the presence of isoflurane. In contrast, sevoflurane augments only the effects of cGMP on SOCE.

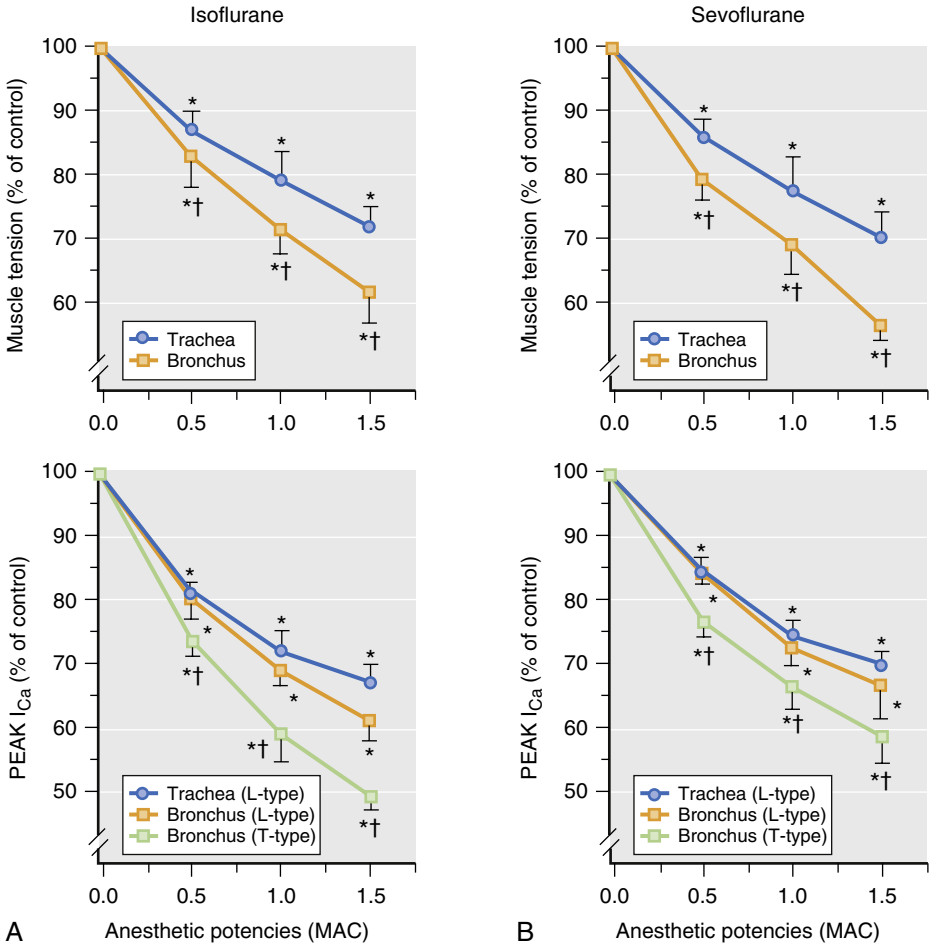


Figure 27-6. Effect of isoflurane and sevoflurane on porcine tracheal versus bronchial smooth muscle tension or inward calcium (Ca^{2+}) current intercellular calcium (ICa^{2+}) through T- and L-type voltage-dependent Ca^{2+} (VDC) channels. No differences were observed in the inhibition of L-type VDC channels. Both anesthetics had greater inhibitory effects on T-type VDC channels in bronchial smooth muscle. Symbols represent mean ± standard deviation (SD). **A,** *, $P < 0.05$ versus 0 minimum alveolar concentration (MAC). †, $P < 0.05$ versus tracheal smooth muscle. **B,** †, $P < 0.05$ versus L-type VDC channels. *(Reproduced from Yamakage M, Chen X, Tsujiguchi N, et al: Different inhibitory effects of volatile anesthetics on T- and L-type voltage dependent Ca^{2+} channels in porcine tracheal and bronchial smooth muscles,* Anesthesiology *94:683, 2001. Used with permission.)*

Volatile anesthetic–induced reductions in SR Ca^{2+} appear to occur through enhancement of IP_3 and ryanodine-receptor channel activities.[58] Kai and co-workers[52] demonstrated that halothane attenuates acetylcholine-induced Ca^{2+} sensitization in canine tracheal smooth muscle to a greater extent than does sevoflurane, whereas isoflurane showed no effect at concentrations equivalent to 2 MAC. These findings were analogous to the differential effects of volatile anesthetics on relaxing airway smooth muscle. This effect appears to be mediated, at least in part, by an increase in smooth muscle protein phosphatase,[59] modulation of G proteins (specifically G_q and G_I that exert actions on cGMP),[52,60] or modulation of the Rho and Rho-kinase signaling pathways. Volatile anesthetics interact with the muscarinic receptor–heterotrimeric G protein complex to prevent agonist-promoted nucleotide exchange at the Gα subunit of the G protein.[61,62] Perhaps volatile anesthetics, through this mechanism, inhibit signaling proteins such as phospholipase C, protein kinase C, and ion channels. Halothane, sevoflurane, and, minimally, isoflurane exert potent direct effects on muscarinic receptor–mediated contraction of isolated airway smooth muscle.[62] The inhibitory effects of volatile agents on the biochemical coupling between the M_3 muscarinic receptor and the $G\alpha_q$ heterotrimeric G protein is completely reversible with time. Isoflurane-induced relaxation of precontracted bronchial smooth muscles is significantly augmented by pretreatment with a Rho-kinase inhibitor, whereas sevoflurane-inhibited guanosine-5′-triphosphate (GTP) gamma S-stimulated contraction and membrane translocation of both Rho and Rho-kinase in a concentration-dependent manner. These latter actions play important roles in Ca^{2+} sensitization.[53] The final pathway in airway smooth muscle contraction is the generation of force and shortening of smooth muscles regulated by myosin crossbridge number and kinetics. Isoflurane modulates both crossbridge number and cycling rates of isolated rat airway smooth muscle.[63]

Volatile anesthetics are allosteric effectors of the action of GABA at the neuronal GABA A ($GABA_A$) channels. Thus the bronchodilatory action of volatile anesthetics is mediated by $GABA_A$ channels in the brainstem or GABA B ($GABA_B$) receptors on preganglionic

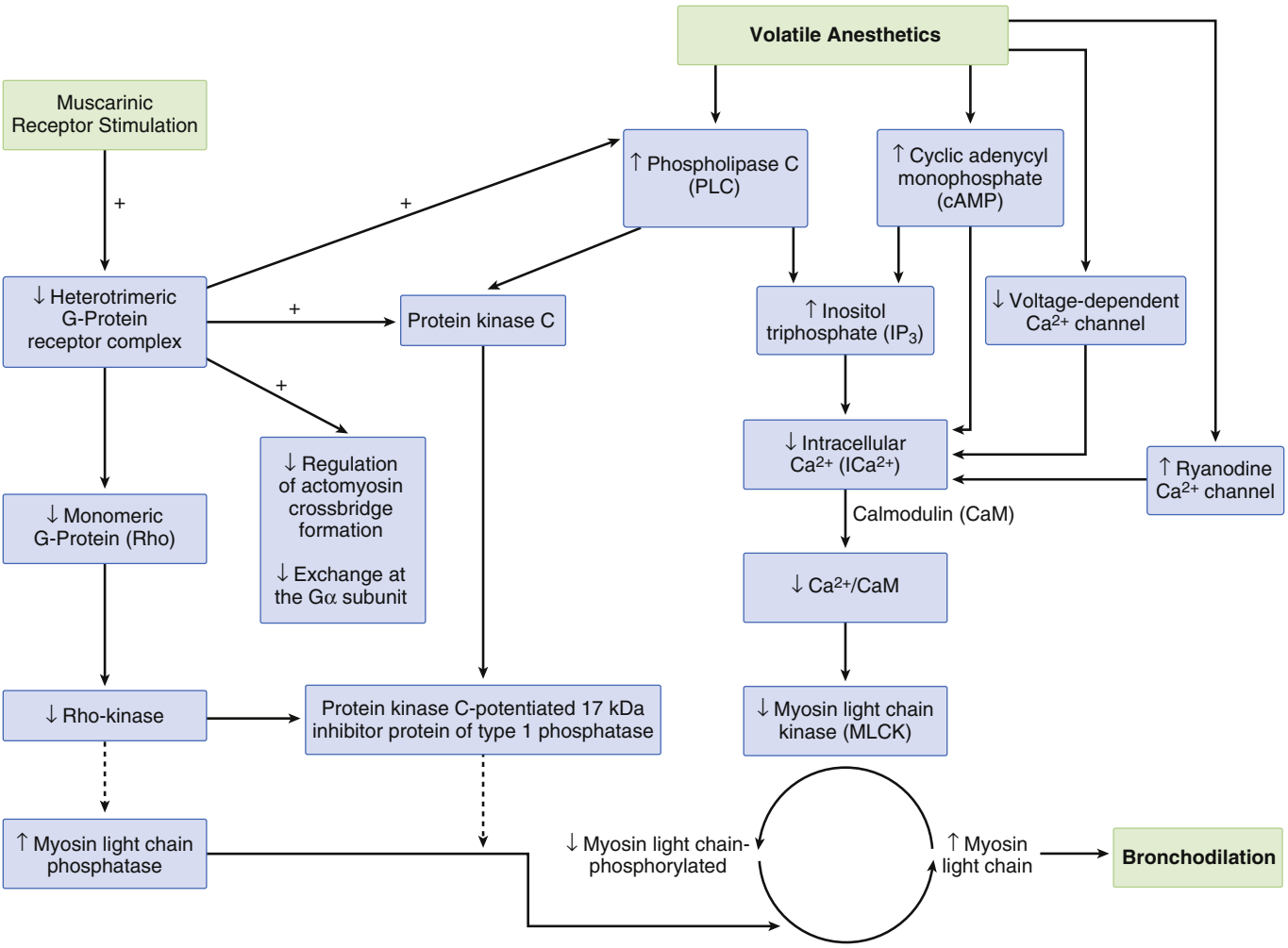


Figure 27-7. Proposed signaling pathways underlying volatile anesthetic-induced bronchodilation and/or inhibition of muscarinic agonist–induced contraction of airway smooth muscle. +, Excitatory action of muscarinic-receptor agonist. ↑, Activation or increase attributable to the volatile anesthetic. ↓, Inhibition or decrease attributable to the volatile anesthetic. Volatile anesthetics play a role in decreasing intracellular calcium (ICa^{2+}) levels and decreasing calcium (Ca^{2+}) sensitivity.

cholinergic nerves in the lung similar to the observations with propofol.[64] Indeed, $GABA_A$ and $GABA_B$ receptors, as well as glutamic decarboxylase (enzyme responsible for GABA synthesis), are located in airway epithelial and smooth muscle cells. Further, GABA levels increase and localize to airway smooth muscle after contractile stimuli in upper airways, and augmentation of cholinergic-induced tracheal ring contraction by GABA antagonism was shown to be reversed by a GABA agonist. These data suggest that volatile anesthetic–induced bronchodilation may also be mediated by the GABAergic airway system.[64,65]

The bronchoconstricting effects of low inhaled concentrations of CO_2 were attenuated by inhaled but not intravenous halothane, suggesting that the volatile anesthetic exerts a direct action on airway muscle tone or local neural reflex arcs rather than centrally controlled reflex pathways. Consistent with this hypothesis, halothane-, isoflurane-, sevoflurane-, and desflurane-induced dilation of distal bronchial segments is partially dependent on the presence of bronchial epithelium.[22,66] A prostanoid (e.g., prostaglandin E_2 or I_2) or NO may be responsible for the bronchodilatory effects of volatile anesthetics under these conditions. For example, isoflurane-mediated bronchodilation appears to be more dependent on NO than prostanoids, whereas the converse is true for halothane. Focal epithelial damage or inflammation may occur in small airways in patients with asthma or allergen exposure, and, as a consequence, the bronchodilatory response to volatile anesthetics may be reduced.[67] Nevertheless, the most pronounced bronchodilatory action of volatile anesthetics in patients with chronic reactive airway disease primarily occurs in the proximal rather than distal airways.

Direct stimulation of intrinsic airway nerves in vitro produces a contractile response that is inhibited by atropine. Volatile anesthetic–induced bronchodilation also occurs by modulation of this airway cholinergic neural transmission mediated through prejunctional and postjunctional mechanisms.[68,69] The combination of atropine and halothane did not increase airway caliber over that attained with either drug alone, suggesting that halothane dilates airways by blocking vagal tone during unstimulated conditions.[70] The release of histamine and the nonadrenergic, noncholinergic bronchodilatory neural reflex (believed to be mediated by NO[71]), do not appear to play a significant role in low-dose halothane-induced bronchodilation. Potent tracheal constriction also occurs in response to the endogenously produced endothelin-1. Isoflurane administration at a clinically relevant dose (2%) depressed endothelin-1–induced airway smooth muscle contraction in rat tracheal rings, suggesting another potential mechanism for airway smooth muscle relaxation.[72]

MUCOCILIARY FUNCTION AND SURFACTANT

Normal Mucociliary Function

The upward clearance of mucus from the tracheobronchial tree acts as a primary pulmonary defense mechanism to remove foreign particulate matter, microorganisms, and dead cells. Ciliated respiratory epithelium cells are present throughout the respiratory tract distally to the terminal bronchioles, but the density of ciliated respiratory epithelium progressively decreases from the trachea to the terminal bronchioles. Cilia are hairlike appendages, consisting of hundreds of proteins organized around a microtubular architecture. They are anchored to the apical cytoplasm by a basal body and extend from the cell surface into the extracellular space.[73,74] Cilia have historically been classified as either motile or immotile (primary). Motile cilia were thought to be responsible for generating extracellular fluid movement or propelling individual cells, whereas primary cilia were believed to be vestigial. However, primary cilia are actually important environmental sensors. Primary cilia localized to human bronchial smooth muscle play key roles in sensing and transducing extracellular mechanochemical signals and are also capable of identifying smooth muscle injury.[75] Indeed, ciliopathies are responsible for a variety of pediatric disorders such as primary ciliary dyskinesia and autosomal recessive polycystic kidney disease and research in ciliary physiologic function, morphologic structure, and pathologic disorders has rapidly evolved as a result.[73,76] The effects of volatile anesthetics on this complex primary ciliary physiologic function are currently unknown.

Ciliary motion consists of a rapid stroke in a cephalad direction, followed by a slower caudal recovery stroke. Movements of cilia are closely coordinated in a proximal-to-distal direction to move matter efficiently toward the trachea in a wave motion known as *metachronism*. Each motile cilium is organized in nine peripheral microtubule pairs surrounding a central pair (9 + 2). During a beat, dynein arms undergo an adenosine triphosphate (ATP)–dependent attachment, retraction, and release cycle with the adjacent doublet, which results in a sliding motion. The basal bodies of the motile cilia are anchored to the microtubules, nexin links, and radial spokes and are further restricted by the ciliary membrane. This anatomic constraint converts the sliding motion into a bend.

The quantity and physical properties of the mucous layer may also promote the coordination of ciliary beats. Mucus is a mixture of water, electrolytes, and macromolecules (e.g., lipids, mucins, enzymes) secreted by goblet cells and mucosal glands. Thicker layers of mucus slow the removal of surface particles from the airway, whereas low-viscosity mucus promotes more rapid ciliary transport. Mucociliary function may be assessed using high-speed videomicroscopy to examine the ciliary beat frequency. In vivo techniques in experimental animals have used a tracheal window model. In contrast, the velocity of mucous movement is typically measured with radioactive markers or fiberoptic bronchoscopy in humans. Impaired mucociliary function in the upper airways correlates with low levels of nasal NO, but the clinical significance of this finding is unclear.[77] Direct nervous system control of ciliary coordination has not been demonstrated in vertebrates, but mucociliary clearance is closely related to autonomic nervous system activity, most likely related to changes in physical characteristics of respiratory secretions[78] (also see Chapter 103).

Postoperative atelectasis and hypoxemia are common causes of perioperative morbidity. Many factors affect mucociliary function in the patient who is mechanically ventilated, and these factors contribute to the above complications. Poorly humidified inspired gases reduce ciliary movement and desiccate mucus. The flow rate of mucous movement was maintained within the normal range during a 40-minute exposure to inspired dry air at a temperature higher than 32° C in dogs. However, 3 hours of inhalation of dry air caused a complete cessation of the flow of tracheal mucus, which was restored by the subsequent use of inspired gases with 100% relative humidity at 38° C. Several anesthesia-related factors also reduce the rate of mucous movement, including the administration of high-inspired oxygen (O_2) concentrations and of adjuvant medications (e.g., corticosteroids, atropine, beta-adrenoreceptor antagonists) that affect bronchial tone, the presence of a cuffed endotracheal tube, and positive-pressure ventilation.[79]

Effects of Inhaled Anesthetics on Mucociliary Function

Volatile anesthetics and nitrous oxide diminish the rates of mucous clearance by decreasing ciliary beat frequency, disrupting metachronism, and altering the physical characteristics or quantity of mucus. Halothane, enflurane, isoflurane, and sevoflurane, in contrast to many intravenous anesthetics,[80,81] reduced ciliary movement and beat frequency in vitro.[80-84] Among the volatile anesthetics, sevoflurane exhibited the weakest cilioinhibitory effects in rat cultured tracheal epithelial cells in vitro (Figure 27-8).[84]

Gamsu and colleagues[85] compared the rate of tantalum (a powder that adheres to airway mucus) clearance from the lungs of postoperative patients who received general anesthesia for either intraabdominal or lower extremity surgical procedures. Tantalum retention was closely correlated with the retention of mucus (Figure 27-9) and was shown for as long as 6 days after intraabdominal surgery, with an average retention time three times greater than that observed in patients who underwent lower extremity surgery. Teflon discs placed on the tracheal mucosa and observed with fiberoptic bronchoscopy were used to examine tracheal mucous velocity in young women undergoing gynecologic surgery.[86] The administration of halothane (1% to 2%) and nitrous oxide (60%) rapidly decreased the rate of mucous movement. Little or no mucous motion was observed after 90 minutes of halothane–nitrous oxide inhalation. Inspired gases were humidified, but the use of high-inspired concentrations of O_2, a cuffed endotracheal tube, and positive-pressure ventilation were important confounding factors in this study. Bronchial mucosal transport velocity was also determined using radiolabeled albumin microspheres distally deposited in the mainstem bronchi using a fiberoptic bronchoscope in healthy patients.[87] In contrast to the findings of the study with halothane, mucous velocity was unchanged during the administration of 1.5 MAC isoflurane. Whether this relative lack of effect of isoflurane on mucous transport was specifically related to the type of volatile anesthetic was unclear. However, mucous pooling has been observed during and after anesthesia,

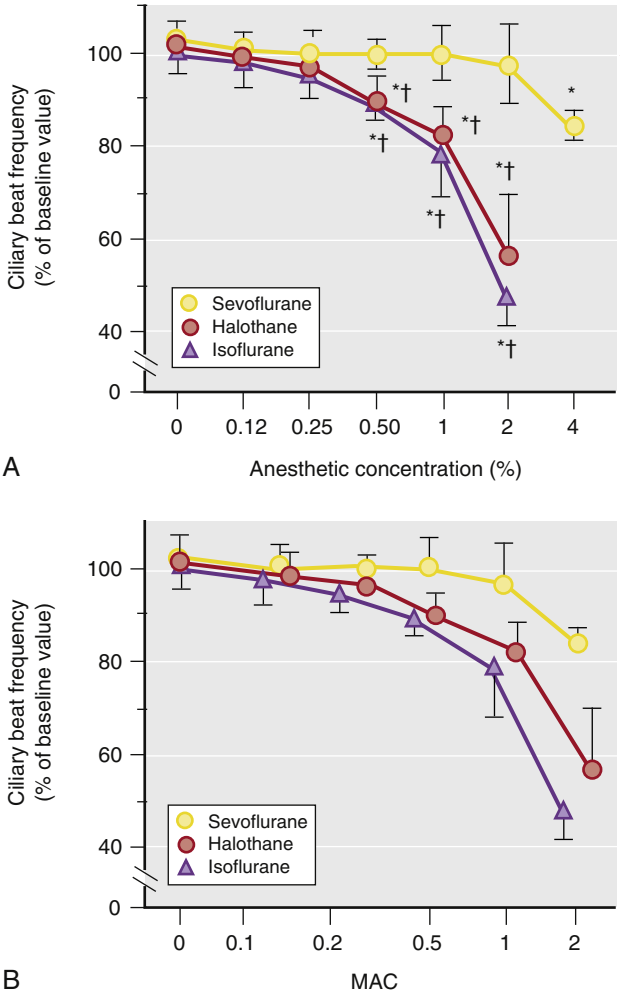


Figure 27-8. Effects of sevoflurane, halothane, and isoflurane on ciliary beat frequency (CBF) in cultured rat tracheal epithelial cells. CBF was measured at baseline and 30 minutes after exposure to various anesthetic concentrations. Values represent mean ± standard deviation (SD). **A**, Plot of percent baseline CBF versus anesthetic concentration. *, $P < 0.05$ versus 0% vehicle. †, $P < 0.05$ versus sevoflurane at the same concentration. **B**, Percent baseline CBF versus minimum alveolar concentration (MAC). *(Modified from Matsuura S, Shirakami G, Iida H, et al: The effect of sevoflurane on ciliary motility in rat cultured tracheal epithelial cells: a comparison with isoflurane and halothane,* Anesth Analg *102:1703, 2006. Used with permission.)*

and impaired bronchial mucous transport velocity is clearly associated with increased postoperative pulmonary complications.

The effects of sevoflurane and remifentanil on bronchial mucous transport were compared with total intravenous anesthesia (consisting of propofol and remifentanil) in patients undergoing general surgery.[88] In contrast to in vitro results,[84] bronchial mucous transport velocity was significantly reduced in patients receiving sevoflurane 30 minutes after endotracheal intubation. Desflurane is considered more irritating to the airways than sevoflurane, but both sevoflurane and desflurane, in combination with fentanyl, produced equivalent reductions in bronchial mucous transport velocity in patients undergoing general surgery. Unfortunately, velocity measurements were only obtained at a single time point 30 minutes

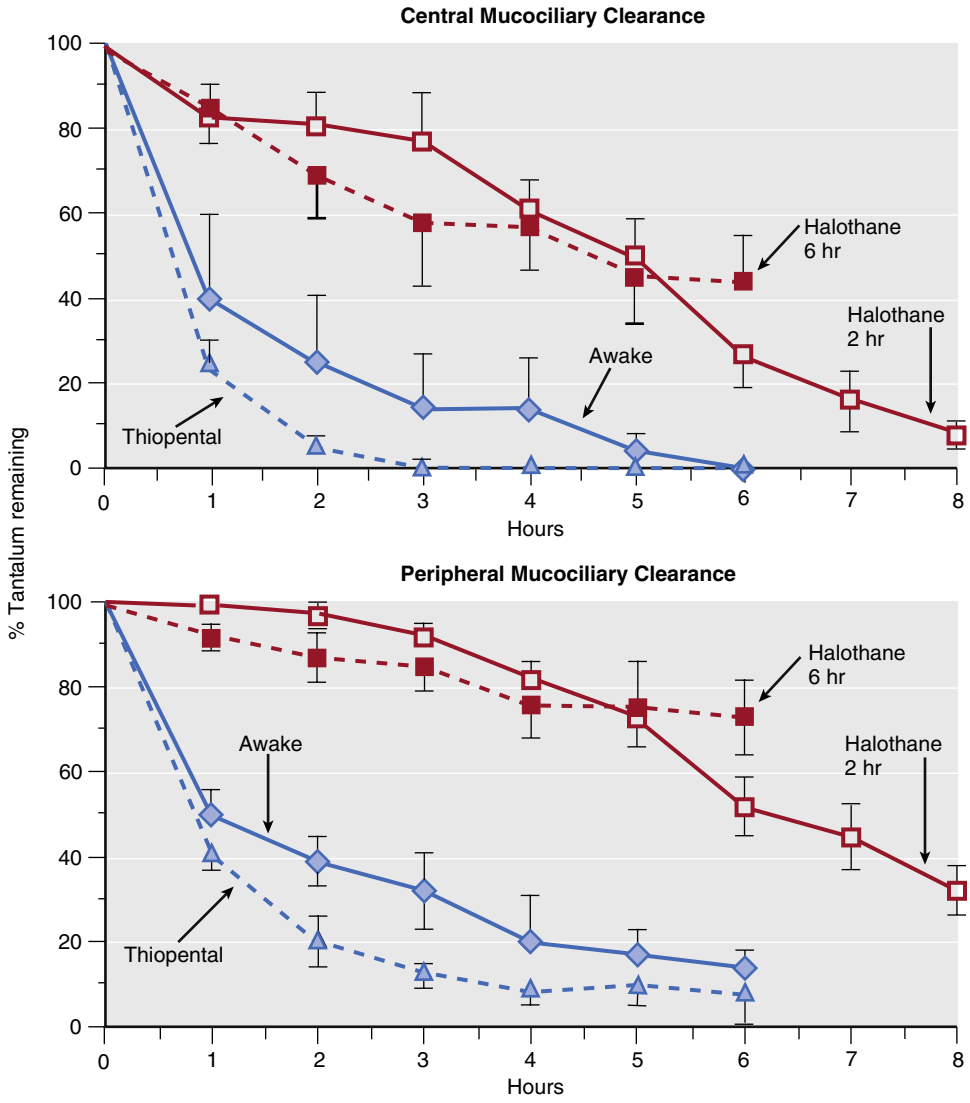


Figure 27-9. Mucociliary clearance measured as tantalum clearance in patients undergoing surgery with either general or local anesthesia (awake). Note the decrease in mucociliary clearance in both peripheral and central airways during halothane anesthesia. *(Modified from Forbes AR, Gamsu G: Mucociliary clearance in the canine lung during and after general anesthesia,* Anesthesiology *50:26, 1979. Used with permission.)*

after endotracheal intubation and a wide range of volatile anesthetic concentrations (0.8 to 1.5 MAC) were used in this study. These design deficiencies certainly limit interpretation of the results.

Impairment of ciliary beat frequency, mucociliary clearance, and bronchial mucous transport are associated with a high risk for pulmonary complications, including retention of secretions, atelectasis, and lower respiratory tract infection.[89] A reduction in bronchial mucous transport of as little as 3.5 mm per minute was associated with an increase in pulmonary complications in patients who were mechanically ventilated for 4 days in the intensive care unit (ICU). Thus pulmonary therapy directed at enhancing clearance of secretions from the airways may be beneficial in the immediate postoperative period, regardless of the type of volatile anesthetic chosen.

Tobacco smokers have significantly slower bronchial mucous transport velocities and more frequent pulmonary complications than nonsmokers undergoing major abdominal or thoracic surgery.[90] The specific effects of volatile anesthetics on mucous movement in smokers has not been well studied, but one may presume that an additive or synergistic negative effect on mucous transport may be present under these circumstances. Impairment of mucociliary function also occurs after lung transplantation. The mechanism for this dysfunction may be related to alterations in the surface properties of mucus and significant impairment of mucociliary transport distal to bronchial transection and reanastomosis.[91] The effects of volatile anesthetics on mucous transport in patients who underwent lung transplantation have not been described, but the baseline reductions in mucociliary movement would certainly be expected to predispose these patients to postoperative respiratory complications.

Effects of Inhaled Anesthetics on Surfactant

Pulmonary surfactant decreases the work of breathing by reducing surface tension at the fluid-gas interface. Surfactant is a mixture of proteins and phospholipids synthesized by alveolar type II cells. Similar to mucus, surfactant plays a role in removing foreign particles from airways while also enhancing the bactericidal actions of alveolar macrophages. Halothane[92] and isoflurane[93] transiently reduced phosphatidylcholine synthesis (a component of surfactant) by alveolar cells, in a dose-dependent manner during a 4-hour exposure. High concentrations of

halothane also disrupted the energy metabolism of cultured alveolar cells as indicated by reduced ATP content and enhanced glycolytic metabolism. Halothane and isoflurane potentiated hydrogen peroxide–mediated reduction of phosphatidylcholine content in alveolar type II cells[93,94] by affecting cell energetics. Halothane decreased the Na^+/K^+–adenosine triphosphatase (Na^+/K^+-ATPase), and Na^+ channel activity in alveolar type II cells, probably related to alterations in ICa^{2+} or ATP depletion.[95] A similar decrease in type II alveolar cell Na^+/K^+-ATPase occur after the administration of isoflurane.[96] Transepithelial Na^+ transport helps regulate alveolar fluid balance, and, as a result, impairment of this transport system may contribute to alveolar edema. This observation may be especially relevant in patients during surgery because volatile anesthetics decrease alveolar epithelial fluid clearance.[97]

The phospholipid makeup of surfactant is critical to its functional integrity. Another crucial component of surfactant is the hydrophobic surfactant-associated protein C. This protein is exclusively synthesized by alveolar type II cells, confers the properties of rapid surface adsorption and surface-tension reduction to phospholipids, facilitates the adsorption and spreading of phospholipids to form the surfactant monolayer, and enhances the lipid uptake into alveolar type II cells. Exogenous surfactants that contain surfactant-associated protein C are also effective at decreasing the rates of barotrauma and mortality in vivo. Clinically relevant concentrations of halothane increase surfactant-associated protein C messenger ribonucleic acid (mRNA) in vitro but cause the opposite effect in mechanically ventilated rats.[98] In contrast, thiopental administration increased the content of surfactant-associated protein C mRNA in both in vitro and in vivo models.[98] Extrapolation of these findings to patients undergoing anesthesia should be approached with caution, but these results may suggest that halothane and mechanical ventilation play a potentially additive and deleterious role on surfactant production and homeostasis of the alveolar space, particularly in the presence of acute lung injury. The actions of desflurane and sevoflurane on pulmonary surfactant metabolism have yet to be evaluated.

The specific roles of depressed mucociliary function and alterations in type II alveolar cells on pulmonary complications remain unclear, but impairment of ciliary motility, bronchial mucous transport, and surfactant production would certainly be expected to play significant roles in perioperative morbidity. As discussed in the following text, volatile anesthetics are also important immunomodulators of type II alveolar cell function during lung injury. Prolonged administration of volatile anesthetics may produce mucous pooling and adversely alter alveolar cell surfactant metabolism. These actions may result in adverse effects on pulmonary function including atelectasis and infection. Those at greatest risk appear to include patients with excessive or abnormal mucous or surfactant production or those with acute lung injury (e.g., chronic bronchitis, asthma, cystic fibrosis, chronic mechanical ventilation) (also see Chapter 103). Nevertheless, controlled studies of the effects of volatile anesthetics on mucociliary function, surfactant metabolism, and immunomodulation in patients with or experimental models of compromised pulmonary function have not been performed to date.

PULMONARY VASCULAR RESISTANCE

Determinants of Pulmonary Vascular Tone

The pulmonary vascular bed is a low-pressure, high-flow system. Normal PA pressure is approximately one-fifth of the systemic arterial pressure. As a result, calculated PVR is lower than systemic vascular resistance. The main PA and its major branches have a thinner medium and less vascular smooth muscle than the aorta and proximal arterial great vessels. PVR is increased with small (i.e., shorter, narrower, more tortuous alveolar blood vessels) or large lung volumes (compression of extraalveolar vessels), whereas PVR is lowest at a lung volume equivalent to the FRC. Changes in PA pressure and PVR exert important effects on pulmonary gas or fluid exchange. An increase in PVR occurs in conjunction with a corresponding increase in PA pressure and promotes interstitial fluid transudation. PVR is also increased by positive end-expiratory pressure (PEEP), alveolar hypoxia, hypercarbia, acidosis, and critical closing pressure. Hypoxia and acidosis have a synergistic effect on PVR. Clinically, the use of positive inotropic medications (e.g., milrinone) or expanded blood volume passively decreases PVR by increasing flow (cardiac output). Volatile anesthetics may also have indirect effects on PVR through a reduction in lung volumes during spontaneous ventilation.

Direct changes in pulmonary vascular smooth muscle tone alter PVR by affecting the slope of pressure-flow relation. Such direct changes may be produced by a rapid rise in ICa^{2+} or by alterations in sympathetic nervous system activity, arterial O_2 and CO_2 tension, acid-base balance, or plasma catecholamine concentrations. Hypercapnia at constant pH (i.e., isohydria) does not alter isolated PA tone, but normocapnic acidosis relaxes isolated PAs by an endothelium-independent mechanism.[99] Nevertheless, PA endothelial dysfunction potentiates hypercapnia-induced vasoconstriction.[100]

Activation of two primary endothelial-related enzymes affects pulmonary vascular tone: NO synthase and cyclooxygenase. Inducible, endothelial, and neuronal NO synthases are widely distributed in the lung, extensively involved in vascular homeostasis, and intimately linked to the pulmonary O_2 environment. NO synthase appears to play little role in the regulation of PVR in the healthy, normoxic lung,[101,102] but this enzyme and its metabolite NO are critical mediators of PVR during hypoxia.[103] In addition to producing vasodilation in ventilated, normoxic pulmonary regions during one-lung hypoxia, NO may also release an endogenous inhibitor of NO synthase that vasoconstricts nonventilated, hypoxic regions.[104] NO may be beneficial in the treatment of high-altitude pulmonary edema[105] and neonatal pulmonary hypertension resulting from a variety of congenital heart diseases, hypoplastic lung, and meconium aspiration. NO is also beneficial in the treatment of acute adult pulmonary hypertension, provided that the PVR is not *fixed* by remodeling and hypertrophy of pulmonary vascular smooth muscle. Thus NO may be useful in the management of severe mitral regurgitation, left ventricular dysfunction after myocardial infarction, and during heart or lung transplantation. Notably, NO inhalation during acute bronchospasm may paradoxically worsen

hypoxemia.[106] Whether this adverse action is mediated by direct bronchodilatory actions on less constricted peripheral airways or by worsening intrapulmonary shunt is unclear. Pulmonary endothelial dysfunction after cardiopulmonary bypass impairs endothelium-dependent vasodilation.[107] Nevertheless, the use of NO in pediatric and adult patients during cardiac surgeries has become a common means of reducing PVR in this setting (also see Chapters 67, 94, and 104). Similar to NO, carbon monoxide stimulates guanylyl cyclase and increases cGMP levels in pulmonary arterial vascular smooth muscle cells to regulate vascular tone. Inhaled carbon monoxide also attenuates hypoxemia-induced increases in PVR through this mechanism.[108]

Prostacyclin is another endogenous vasodilatory substance released from the endothelium that elicits smooth muscle relaxation through adenylyl cyclase stimulation and production of cAMP. Prostacyclin is clinically used as an inhaled or injected pulmonary vasodilator (Flolan or treprostinil). A role for endothelium-derived hyperpolarizing factor (EDHF) was identified as a third pathway for endothelium-mediated vasorelaxation.[109] EDHF produces relaxation by hyperpolarizing vascular smooth muscle in a process involving K^+ channel activation. EDHF production may be elicited by endothelial agonists (e.g., bradykinin, substance P) or alterations in wall shear stress.[109] EDHF may be an important regulator of pulmonary arterial blood flow, but its role in determining changes in PVR has not been well defined. Alterations in PVR may certainly be transient and occur in response to changes in acid-base balance and arterial blood gas tension. In contrast, the development of chronic pulmonary hypertension involves: (1) *endothelial dysfunction* with a resultant vasoconstriction, smooth muscle proliferation, and platelet aggregation; (2) *vascular remodeling*, attributable to a failure to eliminate endogenous vasoconstrictors (thromboxane A2, angiotensin 2, and endothelin-1), vascular smooth muscle hypertrophy, and protein kinase C–mediated fibroblast proliferation with collagen deposition; and (3) *formation of plexiform lesions* (i.e., complex vascular formations) that irreversibly obliterate pulmonary arterioles. Another pulmonary vasodilator, sildenafil citrate, acts by inhibiting cGMP-specific phosphodiesterase type 5 (an enzyme that promotes degradation of cGMP) and is clinically used to treat patients with refractory PA hypertension.

Mechanism of Hypoxic Pulmonary Vasoconstriction

Regional changes in PVR simultaneously affect the regional distribution of blood flow within the lung, produce changes in ventilation-perfusion matching, and gas exchange. The distribution of pulmonary arterial blood flow and ventilation in the lung is mainly a gravity-dependent phenomenon **(**also see Chapter 19) that is primarily mediated by the asymmetric branching of airways and blood vessels, thereby establishing regional heterogeneity.[110] An increase in PVR occurring within an area of atelectasis contributes to localized tissue hypoxia but also optimizes overall gas exchange (i.e., decreases the partial alveolar-arterial O_2 tension gradient [P_AO_2-PaO_2]) by shifting blood flow away from the atelectatic segment to well-ventilated regions of the lung. This phenomenon is termed hypoxic pulmonary vasoconstriction (HPV) and is unique to the pulmonary circulation because other vascular beds (e.g., coronary, cerebral) dilate (and do not constrict) in response to hypoxia. Thus HPV maintains oxygenation, and medications (including volatile anesthetics) that interfere with HPV may adversely affect gas exchange. HPV plays an especially important role in the presence of atelectasis, pneumonia, reactive airway disease, adult respiratory distress syndrome (ARDS), and one-lung ventilation. It usually does not contribute to pulmonary blood flow heterogeneity under normal conditions in supine humans.[111]

HPV is a locally mediated phenomenon that occurs independent of the autonomic nervous system control. HPV may be observed when alveolar O_2 tension falls below approximately 60 mm Hg and is maximal when O_2 tension is approximately 30 mm Hg. HPV was first identified in 1894, but the precise mechanisms underlying HPV remain unclear, despite many years of intensive research. Specialized O_2-sensing cells modulate respiratory and circulatory function to maintain a normal O_2 supply. Hypercapnia-induced acidosis increases PVR in intact animals and in isolated, perfused lungs. Acidosis-induced increases in PVR are relatively small at normal alveolar O_2 tensions but are dramatically enhanced during alveolar hypoxia. Local acidosis and increases in alveolar CO_2 tension may augment HPV and further improve arterial oxygenation in healthy lungs. High CO_2 concentrations reduce NO levels,[112] but whether this action is responsible for hypercarbia-induced improvements in the ratio of ventilation to perfusion is unclear.[113]

Although the hypoxia-mediated endothelial-derived vasoconstrictor has yet to be identified,[114] hypoxia clearly releases Ca^{2+} from smooth muscle SR via ryanodine receptors,[115] enhances Ca^{2+} sensitization,[114-116] and modulates voltage-gated K^+ channels in smooth muscles.[117] Heme oxygenase-2, hydrogen sulfide, CO, reactive O_2 species, and adenosine monophosphate–activated protein kinase (AMPK) have all been proposed as mediators of the hypoxic-response coupling.[116,118] Direct phosphorylation and regulation of O_2-sensitive ion channels by AMPK through inhibition of mitochondrial oxidative phosphorylation may also be responsible for hypoxia-response coupling.[116]

Inhaled Anesthetics and Hypoxic Pulmonary Vasoconstriction

All volatile anesthetics vasodilate the pulmonary vascular bed. Akata[119] presents a thorough review of the mechanisms by which inhaled anesthetics produce this vasodilation, including a reduction in free cytosolic Ca^{2+} and inhibition of myofilament Ca^{2+} sensitivity. Nevertheless, the pulmonary vasodilator effect of volatile anesthetics is relatively small in normal lungs, and the small decreases in PVR produced by volatile anesthetics are frequently offset by a concomitant reduction in cardiac output in vivo. The net effect of these hemodynamic changes result in little, if any, change in PA pressure concomitant with a small decrease in total pulmonary blood flow. In contrast to their action as direct pulmonary vasodilators, volatile anesthetics also attenuate K_{ATP} channel- and

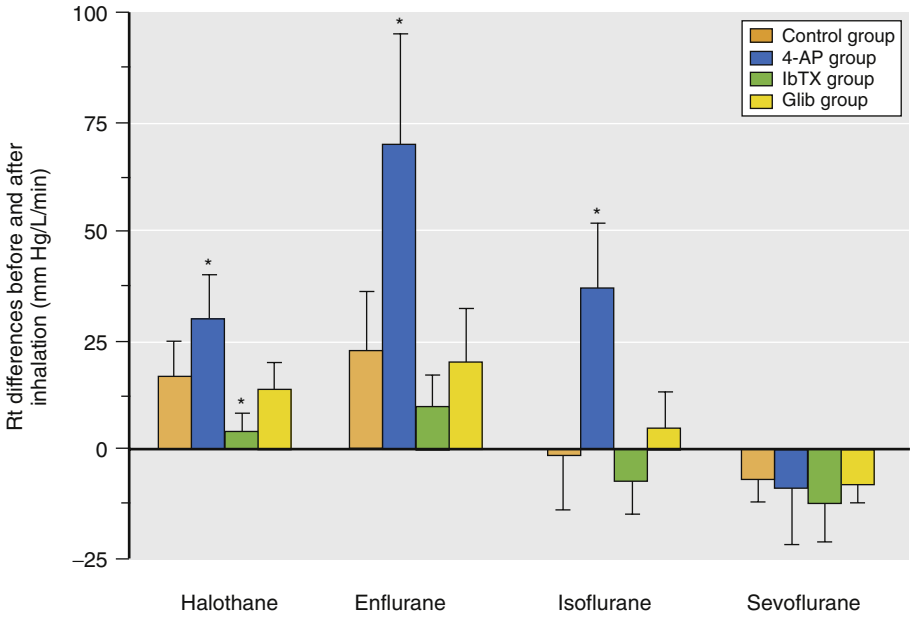
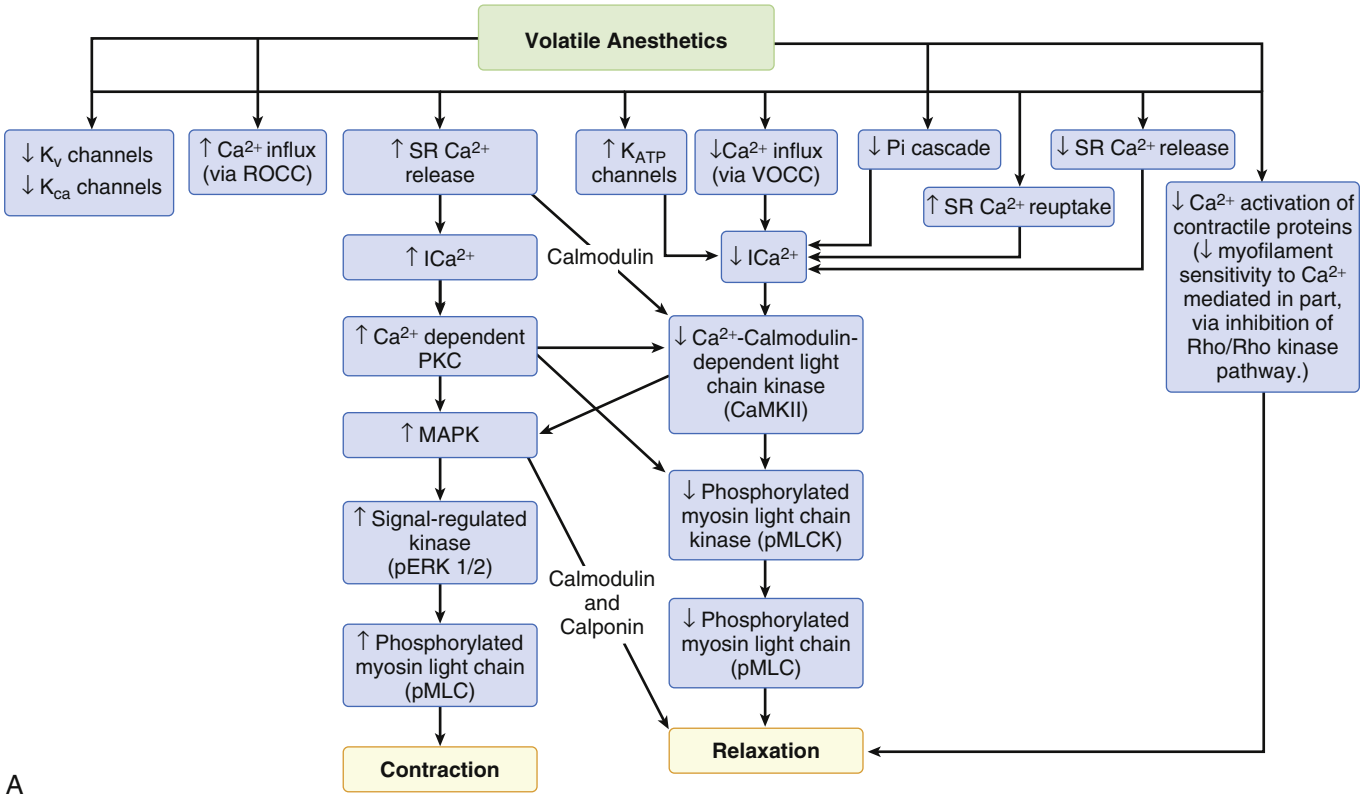


Figure 27-10. Total pulmonary vascular resistance *(Rt)* before and after anesthetic inhalation. Data are mean ± standard deviation (SD). *, $P < 0.01$ versus control group. *4AP*, voltage-sensitive K^+ channel inhibitor; *Glib*, glibenclamide, an adenosine triphosphate–sensitive K^+ channel inhibitor; *IbTX*, calcium-activated K^+ channel inhibitor; *Rt difference*, resistance after the administration of anesthetic minus resistance before administering the anesthetic. *(Modified from Liu R, Ishibe Y, Okazaki N, et al: Volatile anesthetics regulate pulmonary vascular tensions through different potassium channel subtypes in isolated rabbit lungs,* Can J Anaesth *50:301, 2003. Used with permission).*

endothelin-mediated pulmonary vasodilation in chronically instrumented dogs.[120-122] The inhibition of pulmonary vasodilation is not a uniform observation during the administration of volatile anesthetics under all conditions. For example, isoflurane and halothane, but not enflurane, enhance isoproterenol-mediated vasodilation.[123,124] Unlike the findings with other volatile anesthetics, K_{ATP} channel–mediated pulmonary vasodilation in response to lemakalim is preserved during sevoflurane anesthesia.[122] Indeed, evidence suggests that halothane, enflurane, and isoflurane, but not sevoflurane, differentially modulate pulmonary vascular tension through Ca^{2+}-activated or voltage-sensitive K^+ channels, at least in isolated rabbit lungs.[125] Halothane- and enflurane-induced constriction of pulmonary vessels were potentiated by voltage-gated potassium (Kv) channel inhibition in isolated lungs. In contrast, isoflurane did not affect pulmonary vessels when Kv channels were inhibited. Further, sevoflurane dilated pulmonary vessels and this dilation were not unaffected by K^+ channel subtype inhibitors (Figure 27-10). Isoflurane also attenuated hypotension-induced pulmonary vasoconstriction.[126] PA smooth muscle TASK-1 channels also appear to contribute to volatile anesthetic–induced PA dilation.[127] Rather than causing immediate vasodilation, volatile anesthetics produced a paradoxical initial dose-dependent increase in force in isolated pulmonary arterial strips as a result of Ca^{2+} release from intracellular stores (Figure 27-11). Subsequently, a decrease in force (associated with a Ca^{2+}/calmodulin–dependent protein kinase II activation) occurs.[128,129] Extrapolation of these results to humans in vivo must be approached with caution, but these studies suggest that vasodilatory responses of volatile anesthetics may be more profound in patients with reduced SR Ca^{2+} stores (e.g., neonates) or those with depressed protein kinase activity (e.g., primary pulmonary hypertension).

Several mechanisms contribute to the diminished FRC, reduced oxygenation, and increased alveolar-arterial O_2 gradient during anesthesia. Volatile anesthetics contribute to this process by affecting HPV. The effects of volatile anesthetics on HPV are multifactorial and involve direct actions on the pulmonary vasculature, combined with indirect effects mediated by systemic hemodynamics, the autonomic nervous system, and local humoral regulation. In general, in vitro studies have demonstrated that all volatile anesthetics attenuate HPV to some degree in isolated perfused lungs or in an in situ preparation with constant perfusion (Figure 27-12), whereas most intravenous anesthetics do not.[118] The combined administration of a Ca^{2+}-channel blocker and a volatile anesthetic further reduces HPV by an additional 35% to 40%, compared with either drug alone, suggesting that these medications inhibit HPV through differing mechanisms. Indeed, the mechanism of the direct inhibitory action of volatile anesthetics on HPV is unclear but may be related to an enhancement of arachidonic acid metabolism[130] or other endothelial-derived vasodilating factors.[131] Conversely, other evidence suggests that anesthetic-induced inhibition of HPV may occur independent of the presence of pulmonary vascular endothelium, NO, or guanylate cyclase.[132-134] Volatile anesthetics also disrupt Ca^{2+} homeostasis in vascular smooth muscle and thereby interfere with pulmonary vasoconstriction. Halothane and isoflurane attenuated endothelium-dependent vasodilation by inhibiting the accumulation of cGMP[134] and a K_{ATP} channel-mediated interaction between NO and prostacyclin in isolated canine PA rings.[135] In contrast, isoflurane modulated the HPV response, at least in part, through Ca^{2+}-activated and voltage-sensitive K^+ channels. Attenuation of HPV by sevoflurane occurred independent of K^+-channel function.[136]

The relative efficacy of volatile anesthetics on HPV in vivo is difficult to ascertain, in part, because of several factors that are known to impair HPV, including species, temperature, pH, CO_2 tension, relative degree of hypoxia, size of the hypoxic area, surgical trauma, and administration of medications. During one-lung ventilation, the direct inhibitory effects of volatile anesthetics on HPV may



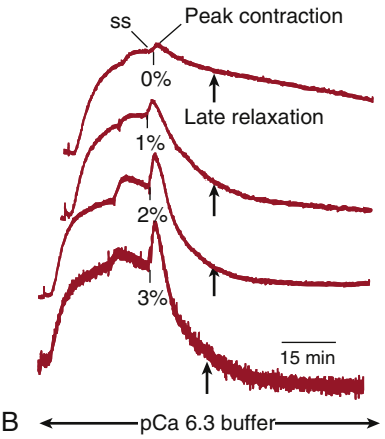


Figure 27-11. A, Proposed signaling pathways underlying volatile anesthetic-induced contraction and relaxation in pulmonary artery smooth muscle. Intracellular calcium (ICa^{2+}) may be increased by release from the sarcoplasmic reticulum (SR), by the inhibition of voltage-sensitive potassium (K_v) or calcium-activated potassium (K_{ca}) channels, or by receptor-operated Ca^{2+} channels (ROCC). Increased ICa^{2+} results in an initial dose-dependent increase in force (associated with activation of protein kinase C [PKC] and increased mitogen-activated protein kinase, [MAPK]). Volatile anesthetics also decrease ICa^{2+} by activating adenosine triphosphate–regulated potassium (K_{ATP}) channels, thereby inhibiting Ca^{2+} influx via voltage-operated Ca^{2+} channels (VOCC), decreasing SR-induced release of Ca^{2+}, inhibiting the phosphatidylinositol (Pi) cascade, and enhancing SR-mediated reuptake of Ca^{2+}. The resultant decrease in force is associated with activation of Ca^{2+}-calmodulin-dependent protein kinase II (CaMKII). It is important to note that there are many agent-specific effects of volatile anesthetics on each component of these pathways. *pERK,* Phosphorylated extracellular signal-regulated kinase. **B**, Example of a biphasic (contraction/relaxation) effect of halothane on pulmonary arterial smooth muscle. *0%, 1%, 2%, and 3%,* Halothane concentrations; *ss,* control force at steady state before halothane. Halothane dose dependently enhanced Ca^{2+}-activated peak force and late relaxation. *(Data from Akata,[119] Su and Vo,[128] and Zhong and Su.[129])*

increase perfusion in the nonventilated lung and worsen hypoxemia. However, volatile anesthetics may also affect HPV, lung perfusion, and oxygenation by indirect actions on cardiac output and mixed venous O_2 saturation.[137] Thus the direct effects of anesthetics on HPV, compared with indirect actions mediated through alterations in pulmonary perfusion, must be appreciated. The efficacy of HPV inversely varies with pulmonary arterial blood flow, and a direct inhibition of HPV by volatile anesthetics may be opposed by a simultaneous reduction in cardiac output such that HPV may appear to be unaffected. As a result, the net HPV response to volatile anesthetics

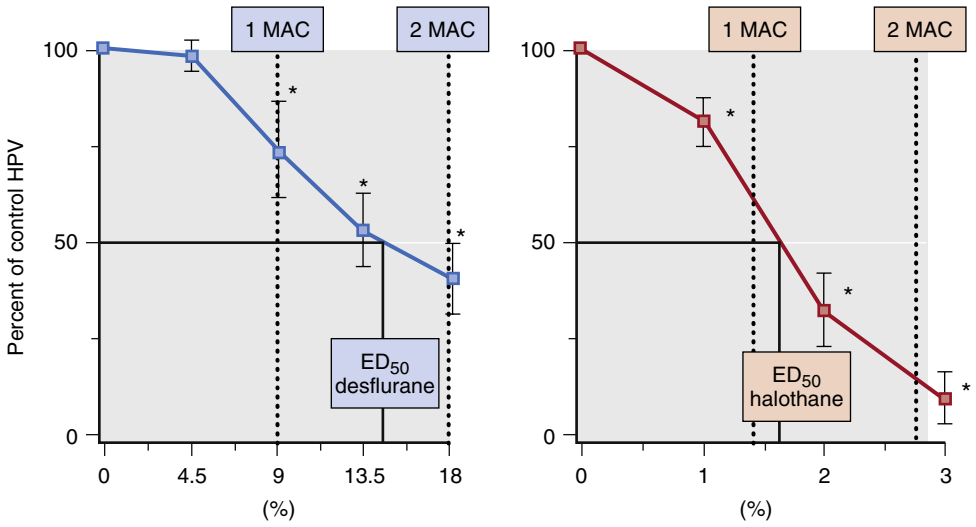


Figure 27-12. Concentration-dependent inhibition of hypoxic pulmonary vasoconstriction (HPV) in isolated rabbit lungs by desflurane *(blue squares)* and halothane *(red squares)*. Values are means ± standard error of the mean (SEM) and expressed as a percentage of control. *, $P < 0.05$ versus control HPV. The 50% effective dose (ED_{50}) values were within the range of 1 and 2 minimum alveolar concentrations (MAC) (for rabbits) for both agents. *(Reproduced from Loer SA, Scheeren T, Tarnow J: Desflurane inhibits hypoxic pulmonary vasoconstriction in isolated rabbit lungs,* Anesthesiology *83:552, 1995. Used with permission.)*

is unchanged when the cardiac output is reduced, but it may be fully intact or only minimally attenuated when pulmonary arterial blood flow is preserved. A reduction in cardiac output also decreases mixed venous oxygenation, which may enhance pulmonary vasoconstriction. These data emphasize the flow dependence of HPV during the administration of a volatile anesthetic. Baseline pulmonary arterial blood flow and pressure also modulate the effects of HPV. Elevated PA pressures may cause passive distension of constricted vascular beds and thereby reverse HPV. Alternatively, reflex pulmonary and systemic vasoconstriction in response to hypotension may increase PVR in healthy lung segments, leading to a favorable shift of pulmonary blood flow to hypoxic areas of lung.

Early studies suggested that nitrous oxide attenuates HPV in animal models in vivo. As opposed to the findings with isoflurane,[130] inhibition of HPV was not observed during sevoflurane or desflurane anesthesia (Figure 27-13)[138] in chronically instrumented dogs subjected to gradual occlusion of the right main PA. Nitrous oxide,[139] desflurane, and isoflurane,[140] but not xenon,[139] reduced the mixed venous O_2 saturation, cardiac output, and arterial oxygenation during one-lung ventilation in pigs. However, nitrous oxide,[139] xenon,[139] desflurane,[140,141] and isoflurane[140,142] did not alter perfusion of the nonventilated lung or reduce the shunt fraction during one-lung ventilation. In animals with a preexisting gas exchange defect attributable to a pneumoperitoneum, sevoflurane, but not isoflurane, caused more pronounced abnormalities in gas exchange than did propofol.[143] Thus although reductions in HPV by volatile anesthetics have been relatively small in vivo, coexisting pulmonary disease may worsen anesthetic-induced gas exchange abnormalities.

Effects of Volatile Anesthetics on Pulmonary Vasculature in Humans

In general, anesthesia is associated with some deterioration in pulmonary gas exchange. Attributing alterations in ventilation or perfusion to specific effects of volatile anesthetics is tempting. However, many other factors including gravity, posture, atelectasis, differences in vessel

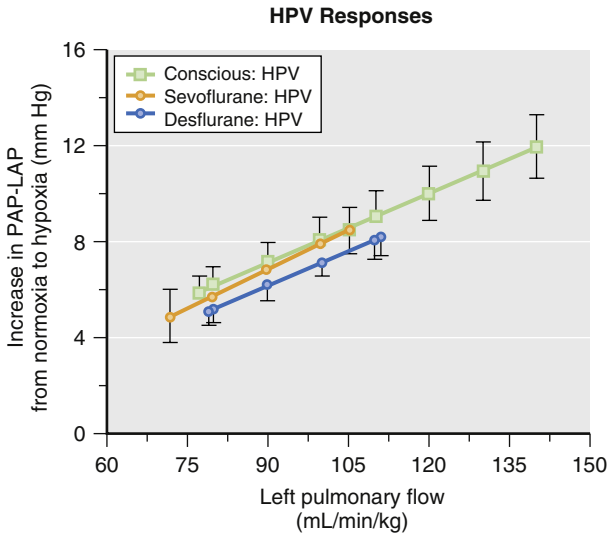


Figure 27-13. Composite hypoxic pulmonary vasoconstriction (HPV) responses (increase in pulmonary artery pressure [PAP] minus left atrial pressure [LAP] as a function of left pulmonary flow in the same seven chronically instrumented dogs in the conscious state and during sevoflurane and desflurane anesthesia. Neither anesthetic affected the magnitude of HPV when compared with the response in the conscious state. *(From Lesitsky MA, Davis S, Murray PA: Preservation of hypoxic pulmonary vasoconstriction during sevoflurane and desflurane anesthesia compared to the conscious state in chronically instrumented dogs,* Anesthesiology *89:1501, 1998. Used with permission)*

conductance between lung regions, intrathoracic pressure, and HPV may affect the distribution of pulmonary blood flow during the administration of volatile anesthetics. Alterations in regional ventilation are regulated by variations in alveolar compliance, inspiratory rate, flow rate, pleural pressures, and ventilatory strategies.[144]

In spontaneously breathing healthy volunteers, sevoflurane (1 MAC for 20 minutes) administered via a facemask did not alter the relative distribution of either ventilation or perfusion in a ventral to dorsal (front to back) direction measured by single photon–emission CT.[144] Similarly, no change in the distribution of ventilation (measured using electrical impedance tomography)

occurred in spontaneously breathing adults scheduled for elective orthopedic surgery given 0.7 MAC of sevoflurane via a laryngeal mask airway (LMA) (with higher tidal volumes and lower respiratory rates).[145] Interestingly, sevoflurane reduced regional heterogeneity of the perfusion distribution and widened the ventilation/perfusion ($\dot{V}/\dot{Q}$) ratio regional heterogeneity with a tendency toward lower ratios in spontaneously breathing volunteers.[144] This alteration may contribute to less effective pulmonary gas exchange, but these findings were relatively small compared with alterations in $\dot{V}/\dot{Q}$ distribution that occur during mechanical ventilation.[145,146] Whether the mode of ventilation is pressure-controlled or pressure-supported, sevoflurane caused similar ventral redistributions of ventilation.[145]

Isoflurane does not substantially alter pulmonary shunt in healthy patients even at concentrations that produce systemic hypotension.[147] Most clinical thoracic surgeries are usually undertaken in the lateral position with an open chest and dramatically affect the relative distribution of ventilation and perfusion. Under these circumstances, a diseased nondependent lung may affect the pulmonary vascular response to hypoxia, as may surgical manipulation of the lung itself. Most observations in experimental animals or patients undergoing single-lung ventilation fail to demonstrate clinically significant attenuation of HPV during the administration of a volatile anesthetic. Differences in shunt fraction, PVR, or oxygenation between isoflurane and sevoflurane anesthesia in patients undergoing one-lung ventilation for lobectomy for lung cancer do not appear to be significant.[148] Two studies demonstrated that shunt fraction is similar in patients receiving propofol or either isoflurane[149] or sevoflurane[150,151] during single-lung ventilation. No significant differences in shunt fraction or arterial O_2 tension were observed when pulmonary gas exchange was compared during intravenous infusions of ketamine (which does not inhibit HPV) and the administration of enflurane. In contrast, isoflurane[152,153] and sevoflurane[153] impaired oxygenation and decreased shunt fraction more than an intravenous infusion of propofol during single-lung ventilation in humans. However, the differences in oxygenation observed in these studies were small and clinically insignificant. Interpretation of the differences in oxygenation between intravenous and volatile anesthetics in these studies may be complicated by the relative depth of anesthesia. In contrast, when doses of propofol and sevoflurane were chosen based on similar depth of anesthesia (based on a bispectral index [BIS] monitor), similar reductions in arterial oxygenation were observed in patients undergoing one-lung ventilation.[151] Similar and rather modest changes in shunt fraction and oxygenation were shown to occur with halothane,[154] isoflurane,[148,154,155] desflurane[155] and sevoflurane[148] in patients undergoing thoracotomy and single-lung ventilation (Figure 27-14).

Convincing evidence suggests that all volatile anesthetics may be safely used in patients undergoing thoracotomy and single-lung ventilation (also see Chapter 66). The increase in shunt and the decrease in oxygenation caused by halothane or isoflurane[154] were consistent with an approximately 20% inhibition of HPV at

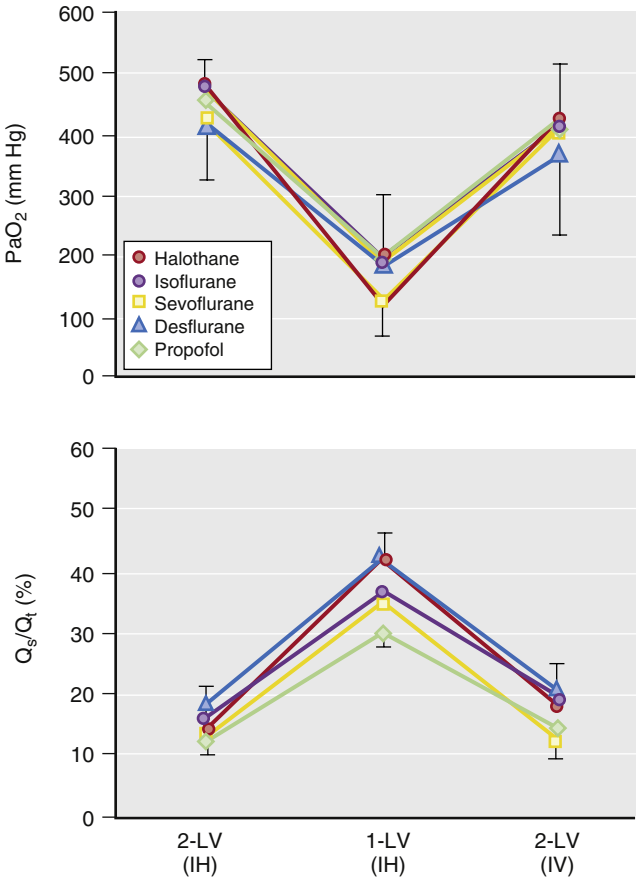


Figure 27-14. Partial arterial pressure of oxygen (PaO_2) and intrapulmonary shunt fraction (Q_s/Q_t) in patients with both lungs ventilated (2-LV) or with one lung ventilated (1-LV). Patients received an inhaled agent (IH) halothane, isoflurane, sevoflurane, or desflurane or the intravenous (IV) anesthetic propofol. Note the minimal effect on PaO_2 and shunt fraction that occurs in changing from a volatile anesthetic to an IV agent. *(Data modified from Abe and colleagues,[148,153] Benumof and colleagues,[154] and Pagel and colleagues.[155])*

1 MAC. Instead of the expected 50% reduction in pulmonary blood flow in a hypoxic lung in the absence of a volatile anesthetic, blood flow decreases by 40% during hypoxia in the presence of 1 MAC isoflurane. This change in flow corresponds to an increase in pulmonary shunt by approximately 4% of the cardiac output. Carlsson and colleagues[156] applied multiple inert gas elimination techniques to measure the true shunt fraction in humans anesthetized with volatile anesthetics and demonstrated a 2% to 3% increase in shunt fraction corresponding to approximately 20% HPV inhibition at 1.5% isoflurane. In addition, no significant effects on arterial oxygenation occurred with clinically relevant concentrations of isoflurane or enflurane. Indeed, the use of total intravenous anesthesia with propofol and alfentanil did not decrease the risk of hypoxemia during single-lung ventilation, compared with a volatile anesthetic.[149] Not only does isoflurane appear safe to use during single-lung ventilation, but the administration of isoflurane before pulmonary ischemia may also protect against ischemia-reperfusion injury. For example, isoflurane attenuated increases in PVR and blunted reductions in the coefficient of filtration

and the wet-to-dry ratio in isolated rabbit lungs subjected to ischemia and reperfusion.[157]

Isoflurane did not affect the pulmonary vasoconstrictor response to sympathetic α-adrenoreceptor activation or influence pulmonary vascular tone in the presence of increased PVR mediated by endothelin-mediated receptor activation[158] after single-lung transplantation.[159] These findings may have important implications for the intraoperative anesthetic management of patients with similar abnormalities in pulmonary vasoregulation because volatile anesthetics may produce smaller reductions in PVR than expected. The precise actions of volatile anesthetics on HPV and pulmonary shunt in patients with preexisting pulmonary disease remain to be defined, but the action of these drugs on the lung vasculature itself must be considered when evaluating causes of hypoxemia during anesthesia.

Volatile anesthetics exert only mild, if any, inhibitory effects on HPV and oxygenation[160,161] (also see Chapter 66). This relatively minor inhibition of HPV by volatile anesthetics should not significantly influence clinical decision making, especially considering the efficacy of drugs such as the peripheral chemoreceptor agonist, almitrine[162] (which enhances HPV) and inhaled NO (which causes localized vasodilation and increases perfusion to adequately ventilated pulmonary regions). In addition, ventilatory strategies (e.g., nondependent lung continuous positive airway pressure [CPAP], permissive hypercapnia) and fiberoptic bronchoscopy to check proper double-lumen endotracheal tube positioning help alleviate hypoxemia (also see Chapter 66). Thus the net effect of volatile anesthetics on HPV is multifactorial and not only depends on the direct effects of these agents on pulmonary vasomotor tone, but it is also determined by indirect actions that commonly occur during anesthesia and surgery.

CONTROL OF RESPIRATION

COMPONENTS OF THE RESPIRATORY SYSTEM

The main components of the respiratory system are located in the brainstem and include the medulla oblongata, pons, and midbrain (Figure 27-15). The neuronal networks in these areas are sufficient to generate involuntary, *automatic* breathing, which may be superseded by cortical centers for voluntary efforts such as speech, swallowing, and coughing. Respiration is also modulated by reflex inputs from the upper airways, lungs, and carotid bodies. Connections to the lateral hypothalamus convey *wakefulness* drive to the respiratory center. The anesthesiologist must be familiar with the main features of the respiratory system. Both physiologic sleep and exposure to volatile anesthetics may alter respiratory function to the point that mechanical ventilatory support becomes necessary. The following section does not describe anatomic features in detail, as these have been previously reviewed.[163-165] Rather, the focus is the major functional components of the respiratory system and how they are influenced by sleep and volatile anesthetics (Figure 27-16).

The effects of volatile anesthetics on the control of breathing have been summarized.[166,167] In general, the degree to which fast neurotransmission to individual respiratory neurons is affected by volatile anesthetics depends on the neurotransmitter inputs to the neuron. Volatile anesthetics decrease glutamatergic excitatory drive to bulbospinal respiratory neurons and increase $GABA_A$ergic inhibitory mechanisms at the postsynaptic neuronal membrane.[168] In hypoglossal upper airway motor neurons, volatile anesthetics hyperpolarize neuronal membrane resting potential by activating K^+ leak channels that are linked to serotonin or norepinephrine receptors.[169,170] The magnitude of volatile anesthetic depression may also depend on the position of the neuron in the *neuronal hierarchy*, which extends from the neurons generating excitatory respiratory drive to the respiratory pattern generator and down to the phrenic and hypoglossal respiratory output motor neurons (see Figure 27-16). For example, *downstream* phrenic motor neurons, which innervate the diaphragm, are significantly more depressed by volatile anesthetics than *upstream* bulbospinal respiratory premotor neurons that innervate the phrenic motoneurons. This suggests that either there are cascading anesthetic effects on synaptic neurotransmission from the premotor to the motor neuron or that there is additional direct anesthetic inhibition of the phrenic motor neuron (e.g., via TASK channel activation by volatile anesthetics).[168,169,171] Consequently, volatile anesthetics, which strongly affect synaptic neurotransmission, will have a greater depressant effect on polysynaptic neuronal circuits that include many synapses, compared with those comprised of only few neurons (paucisynaptic). Most connections between the single components of the respiratory system seem to be paucisynaptic, which has been proposed to explain a relative resistance of automatic breathing to the depressant effects of volatile anesthetics. As an example for the cascading effect of anesthetics on neurotransmission, we will assume a depression of 20% per synapse as has been shown for respiratory premotor neurons.[168] If this depression occurred at three different steps of the neuronal hierarchy (e.g., from chemoreceptor neuron to pre-Bötzinger neuron, from pre-Bötzinger neuron to inspiratory premotor neuron, from premotor neuron to phrenic motoneuron), then this would mean a total decrease in excitatory drive to 80% × 80% × 80% = 51% of the original drive. This concept has also been suggested for Ca^{2+} channels by Lynch and Pancrazio.[172]

Most experimental data are derived from animal models and must be extrapolated to humans with caution. For example, the area of the pre-Bötzinger complex, which is an important respiratory pacemaker cell–containing region in in vitro preparations, has not been conclusively demonstrated in adult mammals in vivo[173,174] and is impossible to demonstrate using current technology in humans.[175,176] Feldman,[177] who was instrumental in establishing the role of the pre-Bötzinger complex in respiratory rhythm generation and more recently proposed the existence of an inspiratory and expiratory oscillator, now emphasizes that the oscillator model of respiration is a working hypothesis that may not

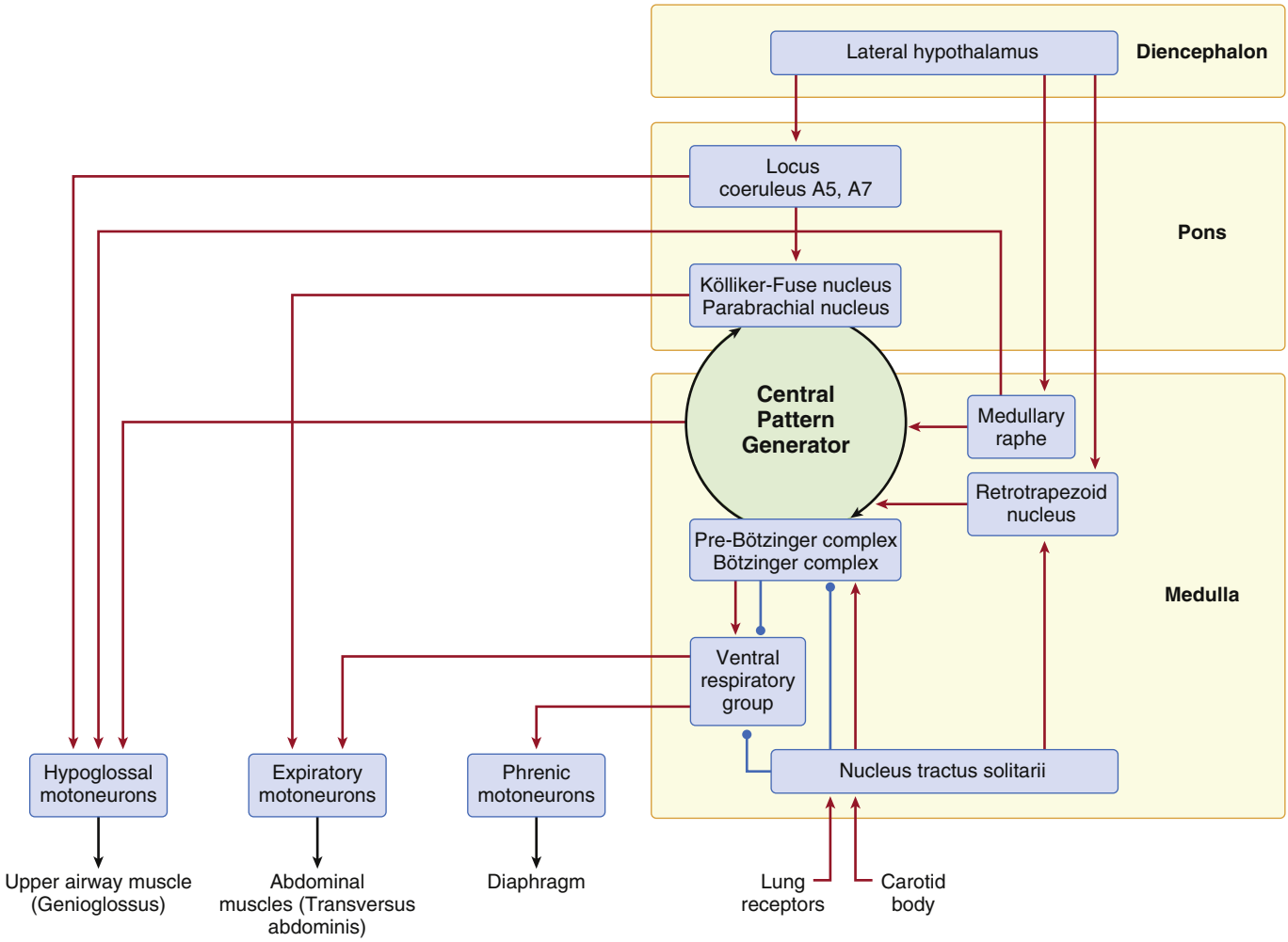


Figure 27-15. Anatomic components of the respiratory system and the main nuclei involved in the generation of respiration from chemoreception to motoneuron activation (see text for details). *Wakefulness drive* is derived from the lateral hypothalamus. The *central pattern generator*, where respiratory drive is converted into a respiratory pattern, is thought to consist of several nuclei in the medulla and pons. Potential sites of central chemoreception are the locus coeruleus, areas A5 and A7, in the pons, and the medullary raphé and retrotrapezoid nucleus in the medulla. Expiratory and inspiratory excitatory drive is relayed to premotor neurons (ventral respiratory group), which project to expiratory motoneurons and inspiratory motoneurons (e.g., phrenic nerve) in the spinal cord. These motor nerves innervate abdominal muscles (expiratory) and diaphragm (inspiratory). Respiratory pattern and chemoreception are influenced by afferents from the lungs and carotid bodies. Excitatory inputs *(red arrows)*; inhibitory inputs *(blue buttons)*.

reflect defined anatomical areas. Still, recent discoveries of genetic defects (e.g., in the pairedlike homeobox 2b (PHOX2B) transcription factor causing "Ondine's curse") suggest that important structural and functional defects in this area can increase sensitivity of patients (who remain undiagnosed) to anesthetic-induced depression of breathing.[178]

Animal data is presented first, as required for a basic understanding of respiratory function; then the focus of this chapter turns to the clinically applicable studies.

Central Chemoreception

In the healthy individual, automatic breathing under normoxic, normocapnic conditions depends on excitatory chemodrive, approximately two thirds of which results from stimulation of central chemoreceptors by CO_2 and pH and one third from peripheral chemoreceptors by O_2 and CO_2.[179] Although many brainstem nuclei contain neurons whose discharge responds to changes in extracellular pH, the locations of central chemoreceptors are still under intense debate.[180] In essence, chemoreceptors are thought to be neurons that (1) tonically and proportionally discharge to extracellular pH, (2) project to other areas of the respiratory system where they form excitatory synapses, and (3) are crucial to the function of the respiratory system (i.e., destruction of these neurons should decrease respiratory output).

Animal studies have pointed to multiple chemosensitive sites in the brainstem that fulfill these criteria[180] including the RTN, medullary raphé, locus coeruleus, NTS, lateral hypothalamus, and caudal ventrolateral medulla. Glial cells in these areas may also theoretically contribute to chemoreception through their effect on extracellular pH or by hypoxia- or CO_2-induced ATP release that may alter the function of *chemosensitive*

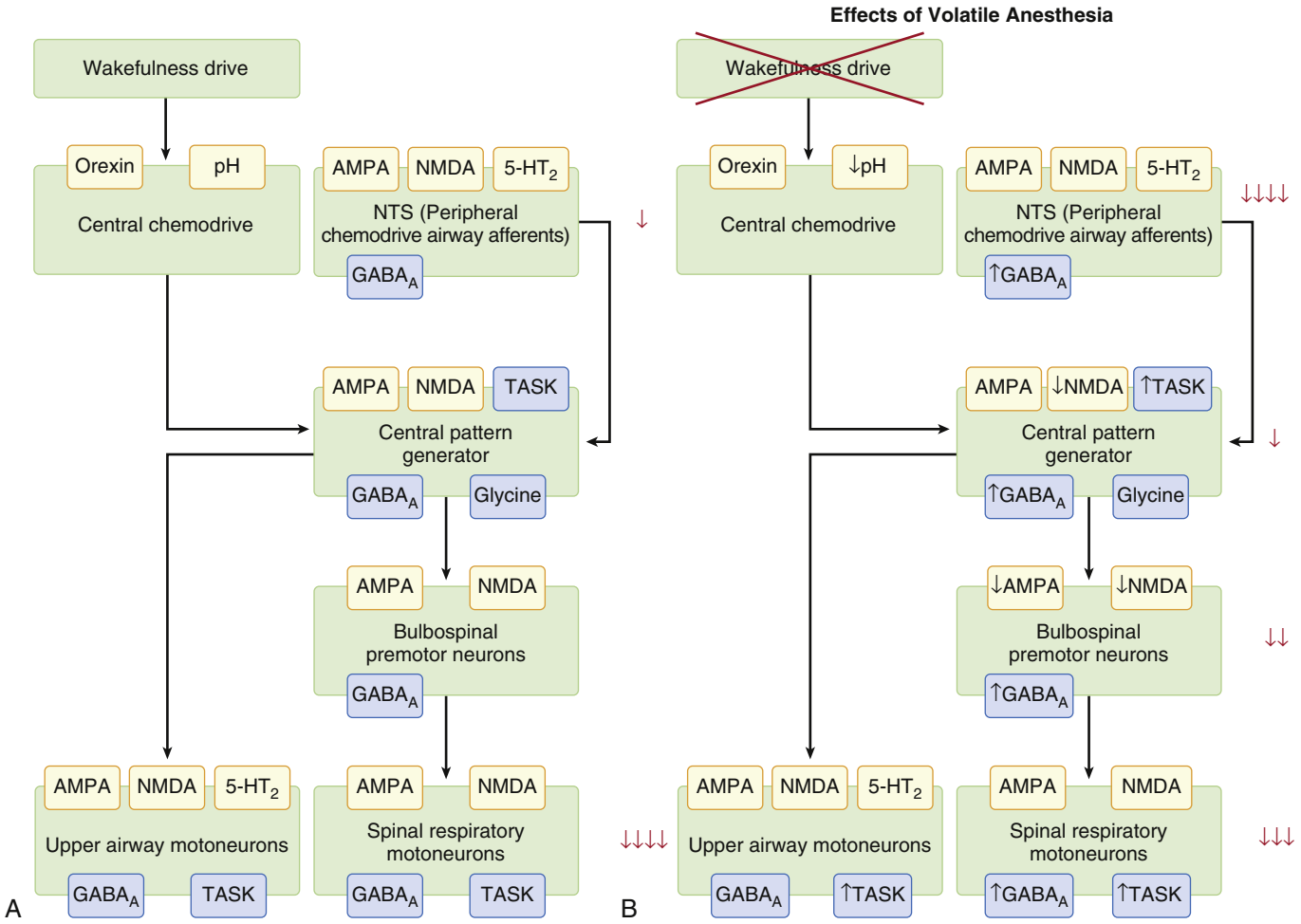


Figure 27-16. A, Ligand-gated receptors and ion channels on respiratory-related neurons. Excitatory receptors and channels are marked in *yellow*, inhibitory in *blue*. Opening of pH sensitive channels excites the neuron, whereas the opening of two-pore domain, acid-sensitive potassium (K^+) (TASK) channels causes membrane hyperpolarization and inhibition of neuronal discharge. **B**, Effects of volatile anesthetics on respiratory-related neurons. Volatile anesthetics eliminate wakefulness drive to the respiratory system *(red cross out)*. *Black arrows* indicate changes in receptor function (*up,* increase; *down*, decrease) that have been published in the literature. Volatile anesthetics reduce the presynaptic release of glutamate and gamma-aminobutyric acid A ($GABA_A$) in respiratory premotor neurons. The cumulative anesthetic effects on the respective neuron groups are depicted *(blue arrows)*. The relative magnitude of the depressant effect is visualized *(number of arrows)*. In humans, peripheral chemodrive is significantly more depressed than central chemodrive. Upper airway motoneurons are significantly more depressed than inspiratory motoneurons. *5-HT_2,* 5-Hydroxytryptamine; *AMPA,* alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate acid; *NMDA, N*-methyl-D-aspartate

neurons.[181] Interestingly, the state of cortical arousal (asleep or awake) appears to affect whether acidification of these areas is capable of producing an increase in ventilation.[180] The activity of orexin neurons located in the lateral hypothalamus are involved in sleep-wake regulation and feeding and may be partially responsible for this latter effect (see Figure 27-16). These neurons also project to and enhance the function of other chemoreceptor sites including the RTN and medullary raphé. In addition, central chemoreceptor sites seem to function interdependently; that is, the degree of change in ventilation caused by acidification of one site depends on the integrity or simultaneous acidification of other sites.[182] In opposition to this multiple site central chemoreceptor theory, Guyenet suggested that the RTN is singularly equipped to function as the primary if not the sole source of respiratory drive during automatic breathing (i.e., during sleep or volatile anesthesia).[183] The RTN may also serve as the major relay point for wakefulness drive from higher brain centers and regulate CO_2 homeostasis in the conscious state. Interestingly, the actual substrate for central chemosensitivity, namely a pH sensitive channel that is present on all chemoreceptive neurons and increases neuronal discharge under physiologic conditions in vivo, has not been specifically identified.

Chemoreception not only provides the tonic excitatory drive to the respiratory oscillator, premotor neurons, motor neurons, and respiratory muscles that underlie automatic breathing, but it also promotes excitatory drive to neurons regulating upper airway patency and arousal from sleep.[180] The genioglossus muscle, which is typically regarded as representative for the muscles maintaining upper airway patency, receives significant tonic and phasic excitatory drive in the conscious state. Genioglossal muscle activity is reduced during sleep, but high levels of inspiratory CO_2 (>5%) are capable of recruiting

near-normal levels of phasic activity. This phenomenon does not occur during rapid eye movement (REM) sleep because genioglossal muscle activity is absent. Hypercapnia may be another mechanism (aside from hypoxia) by which patients with obstructive sleep apnea (OSA) arouse from sleep and re-establish airway patency. Thus residual subanesthetic concentrations of volatile anesthetics, which may be present for hours in postoperative patients, inhibit both peripheral hypoxic[184] and CO_2 chemosensitivity[185] and may also substantially impair the spontaneous arousal and resolution of upper airway obstruction that would otherwise occur with severe hypoxia or hypercarbia. Interestingly, the level of CO_2 drive and the related orexinergic stimulation of airway vagal preganglionic neurons have also been linked to the patency of the small airways. This observation may be clinically reflected in the incidence of bronchoconstriction, which is highest in the early morning hours when CO_2 sensitivity and orexin levels are lowest.[180]

Central Pattern Generator

Tonic excitatory respiratory drive from the chemoreceptive neurons is conveyed to a central pattern generator that translates all excitatory and inhibitory inputs into a respiratory pattern that consists of distinct inspiratory and expiratory phases. The following description summarizes recent reviews.[186-188] The central pattern generator is currently believed to consist of several nuclei in the pontomedullary network (see Figure 27-15), including the Kölliker-Fuse nucleus and parabrachial nucleus in the pons and the Bötzinger complex, pre-Bötzinger complex, and rostral and caudal ventral respiratory groups in the medulla. In the intact, mature mammal under physiologic conditions, respiratory rhythm is most likely generated by groups of neurons engaged in reciprocal inhibition; that is, by two or more major groups of oscillating neurons that alternate their discharges by inhibiting each other. This alternating inhibition contributes to two distinctly separate respiratory phases. The basic oscillating pattern is reinforced in the pontine respiratory group, which plays a significant role in respiratory phase switching.[189] The connections between the medullary nuclei and the pons are very strong and are paucisynaptic. Notably, the actions of volatile anesthetic on the central respiratory rate are different, depending on the inclusion of the pons in the experimental preparation. This observation indicates that the pons exerts a general inhibitory effect on medullary respiratory rate response. Volatile anesthetics reduce this pontine inhibition and contribute to an increase in respiratory rate.

Integration of Peripheral Inputs

Many afferent inputs from the periphery reach the brainstem respiratory center and influence the respiratory drive and timing. The most important of these peripheral inputs originates from the carotid bodies, which are paired, highly perfused sensory organs located at the bifurcation of the common carotid arteries. Hypoxia or hypercapnia causes an increase in carotid sinus nerve discharge. After a neuronal relay in the NTS, part of this excitatory input directly projects to the central pattern generator and increases respiratory drive. Carotid body afferent signals also project to other chemoreceptive areas of the brainstem, including the RTN, thereby influencing central chemoreception.[190]

Afferent vagal inputs from the lungs and airways are also relayed through the NTS. Pulmonary stretch receptor inputs project to second order *pump* neurons in the NTS, which can provide both excitatory and inhibitory inputs to various parts of the medullary respiratory column. In general, pulmonary stretch receptor inputs promote the phase switch from inspiration to expiration. This vagal expiratory-facilitating reflex (Hering-Breuer reflex) is most prominent in immature mammals but also modulates respiratory phase-timing during resting ventilation in adult human volunteers.[191] Although some of these inputs directly influence the central pattern generator, others are integrated at the level of the bulbospinal or premotor neurons, which project to the motor neurons in the spinal cord.

Respiratory Motor Output and Upper Airway Patency

The excitatory input to phrenic motor neurons (the main inspiratory neurons in the spinal cord) is mediated by inspiratory bulbospinal neurons in the ventral respiratory group.[187] Expiratory motor neurons receive inputs from expiratory bulbospinal neurons and the pons.[187] Phrenic motor neurons are located at the levels C3-C5 of the spinal cord and innervate the diaphragm. Expiratory motor neurons are also located at approximately T7-T12 of the spinal cord and innervate truncal abdominal muscles that powerfully aid with expiration and with expiratory expulsive efforts such as coughing. The spinal motor neurons are the final neurons in the respiratory neuronal hierarchy, which means that their activity tends to be reduced by the cumulative effect of anesthetics on all previous steps of chemoreception and neurotransmission. Phrenic motor neurons are also directly depressed by volatile anesthetics.[192]

Inspiratory muscle activity is closely coordinated with upper airway patency. Genioglossal muscle activity is often chosen as an indicator for upper airway patency and the hypoglossal motor nerve as representative for the neural innervation of upper airway muscles. Hypoglossal motor neurons are located close to the obex in the medulla. The strength of excitatory and inhibitory drive to hypoglossal motor neurons strongly depends on the level of consciousness and differs between the REM and non-REM sleep phases. The primary excitatory drive of hypoglossal motor neurons (both tonic and phasic components) derives from noradrenergic neurons in the locus subcoeruleus and the pontine A5 or A7 region. Additional excitation results from glutamatergic drive from the raphé pallidus and is mediated by both *N*-methyl-D-aspartic acid (NMDA) and non-NMDA glutamate receptors.[193] Excitatory serotonergic inputs from the dorsal raphé nucleus and various histaminergic inputs appear to play only minor roles in conscious and nonvagotomized rodents. Interestingly, glutamate release may be reduced through presynaptic 5-hydroxytryptamine 1A (5-HT1A) and 1B (5-HT1B) receptors. Hypoglossal motor neuronal excitation is modulated by phasic GABAergic inhibition, but GABAergic or glycinergic inhibition does not appear

to produce significant suppression of hypoglossal motor neuronal activity during REM sleep.[194] Hypoglossal motor neurons also receive cholinergic inputs from the pedunculopontine tegmental neurons and the reticular formation. These inputs result in postsynaptic modulation of hypoglossal activity and presynaptic modulation of excitatory (glutamatergic) inputs.[195]

Importance of Sleep and Wake States

Two opposing systems determine the arousal state of an individual and with it the magnitude of respiratory drive and upper airway patency.

The *wakefulness-activating system* is an arousal system ascending from the brainstem that activates the forebrain and maintains consciousness. The orexinergic neurons from the lateral hypothalamus and the cholinergic neurons from the basal forebrain region project to the cortex to maintain cortical arousal. The orexinergic neurons also project to the brainstem to reinforce the activity of the ascending arousal system. The arousal system also increases the hypoglossal nerve activity by stimulating the locus coeruleus, which increases the excitatory noradrenergic input to the hypoglossal motor neurons. The ascending arousal system simultaneously inhibits neurons in the ventrolateral preoptic nucleus (VLPO), an area in which a group of hypothalamic neurons inhibit neurons involved in wakefulness.[195]

Opposing the wakefulness-activating system is the *sleep-activating system*, which consists of the anterior hypothalamus, basal forebrain, and VLPO. The sleep-activating system is responsible for nonREM sleep and directly suppresses the ascending cortical, as well as the brainstem arousal systems via $GABA_A$ergic neurons (also see Chapter 14).

These two antagonistic systems ensure that the brain is either awake or asleep without a partial transition state. GABAergic inhibition profoundly reduces the activity of the brainstem-arousal system mediated by noradrenergic, serotonergic, cholinergic, and histaminergic neurons during sleep. The withdrawal of activity from these neurons also causes a reduction of drive to the hypoglossal motor nucleus and thus a loss in upper airway tone.[195]

Reduced noradrenergic and serotonergic activity in the brainstem neurons leads to diminished presynaptic inhibition ($alpha_2$ and 5-HT1A) of pontine cholinergic neurons. The resultant increase in acetylcholine in the pontine reticular formation triggers REM sleep. During this phase, the locus coeruleus and dorsal raphé are inhibited via GABAergic inhibition. Spinal projections lead to glutamatergic activation of spinal inhibitory interneurons, which inhibit spinal motor neurons and lead to near-complete immobility except for respiration and REMs.

Upper airway patency is compromised by substantially lower concentrations of volatile anesthetics than diaphragmatic muscle activity.[196] This observation may be due, at least in part, to the arousal state—dependence of hypoglossal motor neuron activity. The near-complete loss of genioglossal activity during sleep may contribute to the development of OSA in patients with anatomic predisposition. These patients are at particular risk for upper airway obstruction during anesthesia because volatile anesthetics not only suppress the noradrenergic-mediated wakefulness drive to hypoglossal motor neurons, but they also profoundly depress the glutamatergic drive originating from peripheral and central chemoreception.

EFFECTS OF INHALED ANESTHETICS ON RESTING VENTILATION AND CHEMOREFLEXES IN HUMANS

Volitional control of breathing is reduced during sedation with concentrations of volatile anesthetic of less than 1 MAC and is completely abolished at higher concentrations. This phenomenon is similar to sleep in which breathing is largely controlled by automatic brainstem mechanisms and chemoreflex inputs. During sedation with most volatile anesthetics (in particular, those that undergo significant metabolism such as halothane), not only is there a loss of volitional control, but also a dose-dependent impairment of the peripheral chemoresponses to hypoxia and partial arterial pressure of carbon dioxide ($Paco_2$) occur. Interestingly, depression or enhancement of carotid body activity does not shift the central CO_2 threshold in an additive fashion; rather, it reduces or increases central CO_2 sensitivity, respectively.[197] From a clinical perspective, inhibition of carotid body activity by a volatile anesthetic increases the $Paco_2$ required to stimulate respiratory activity, compared with the conscious state. In the presence of volatile anesthetic concentrations of 1 MAC or higher, breathing in humans is entirely dependent on the automatic control from the pontomedullary respiratory center and afferent excitatory inputs from the *central* chemoreceptors. These anesthetic concentrations lead to a complete depression of the peripheral chemoreflex loop with further respiratory depression rather than stimulation in response to hypoxia.[198] A loss of upper airway muscle tone and function accompanies this process, as does differential depression of neurotransmission at the level of the spinal cord.[199]

EFFECTS OF INHALED ANESTHETICS ON RESTING VENTILATION

All volatile anesthetics cause a dose-dependent decrease in expiratory minute ventilation at concentrations greater than 1 MAC as a result of a decrease in tidal volume. Respiratory rate typically increases (Figure 27-17), but no evidence suggests that this increase in rate is a compensatory mechanism or that it is causally related to the reduction in tidal volume. Of note, the dose-dependent increase in respiratory rate observed with most volatile anesthetics is largely absent during isoflurane anesthesia concentrations greater than 1 MAC. Most volatile anesthetics cause an *increase* in respiratory rate by producing a decrease in both inspiratory and expiratory duration, whereas opioids cause a very prominent *decrease* in respiratory rate that primarily results from a large increase in expiratory duration. In general, the decrease in resting minute ventilation observed during the administration of volatile anesthetics is somewhat less than expected when compared with experiments performed under isocapnic conditions because the central chemoreflex feedback loop

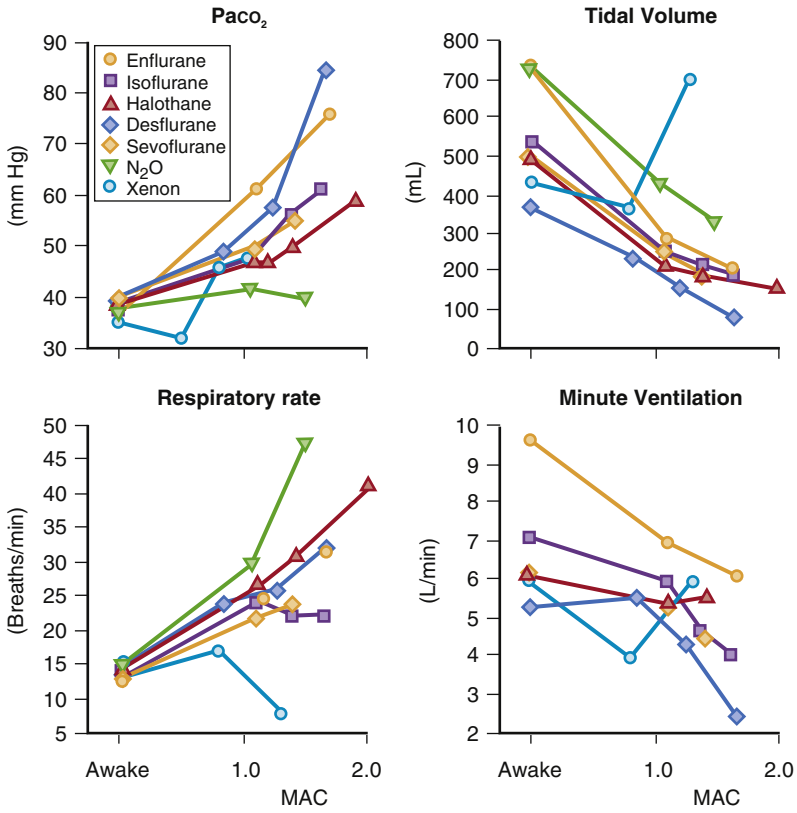


Figure 27-17. Comparison of mean changes in resting partial arterial pressure of carbon dioxide ($Paco_2$), tidal volume, respiratory rate, and minute ventilation in patients anesthetized with various inhaled agents. Most agents cause dose-dependent tachypnea, decreases in minute ventilation and tidal volume, and an increase in $Paco_2$. *MAC,* Minimum alveolar concentration, *N_2O,* nitrous oxide. *(Data are from references 297 and 299-304. Note the data for xenon has been extrapolated from references 291 and 305-307.)*

is *closed*; that is, central chemoreceptor feedback remains largely intact. Thus volatile anesthetic–induced hypoventilation increases $Paco_2$, which stimulates the central chemoreceptors, thereby increasing central chemodrive to the respiratory center.[200-205] As a result, the observed modest decrease in minute ventilation under closed loop conditions incompletely reflects the magnitude of the respiratory depressant effects of a volatile anesthetic and does not accurately predict the magnitude of the depressant effects of the anesthetic on the ventilatory response to either CO_2 or hypoxia. Nonetheless, the resultant elevation in resting $Paco_2$ observed with different volatile anesthetics at similar MAC values follows the order: halothane < sevoflurane < isoflurane < desflurane (see Figure 27-17). Volatile anesthetics also cause a rightward shift of the apneic threshold[206]; that is, the minimum $Paco_2$ required to initiate spontaneous respiration. Thus coordinated spontaneous breathing efforts do not occur if mechanical or assisted ventilation efforts drive the $Paco_2$ levels below the CO_2 threshold during anesthesia.[207]

EFFECTS OF INHALED ANESTHETICS ON THE HYPERCAPNIC VENTILATORY RESPONSE

Peripheral chemoreceptors contribute approximately one third of the CO_2-mediated minute ventilation in awake humans during normoxia. During hypoxia, the peripheral hypercapnic ventilatory response is augmented.[208] The CO_2-mediated component of the peripheral chemodrive remains largely intact, but the hypoxia-mediated component is rapidly abolished during the administration of volatile anesthetic concentrations under 1 MAC.[184,209-215] However, at higher anesthetic concentrations, chemical control of breathing is almost entirely mediated by the CO_2-responsive central chemoreceptors. Thus the central chemoreflex loop and not the hypoxic drive provides the primary excitatory chemodrive to the respiratory pattern generator to sustain respiration during deeper levels of volatile anesthesia.

The relative depressant effects of an equivalent MAC value of volatile anesthetics may be described by measuring the decrease of the sensitivity (slope) of the CO_2 response curve. The ventilatory CO_2 sensitivity is approximately 2 to 3 L/min/mm Hg[216] in conscious patients but significantly depressed by up to 70% during the administration of volatile anesthetics.[217]

EFFECTS OF INHALED ANESTHETICS ON THE HYPOXIC VENTILATORY RESPONSE IN HUMANS

The hypoxic ventilatory response (HVR) in conscious individuals is substantial and rarely observed because hypoxia is rarely encountered under normal circumstances. A mountaineer is exposed to an environmental barometric pressure of only 253 mm Hg at the summit of Mt. Everest (8848 m) without supplemental O_2 with an ambient O_2 tension of only approximately 50 mm Hg (one third of that at sea level). Arterial blood gases in one climber at this altitude showed a pH of 7.72, a partial arterial pressure of oxygen (PaO_2) of 37.6 mm Hg, and a $Paco_2$ of 7.5 mm Hg. These occurred as a result of severe hypoxic hyperventilation with the estimated minute ventilation

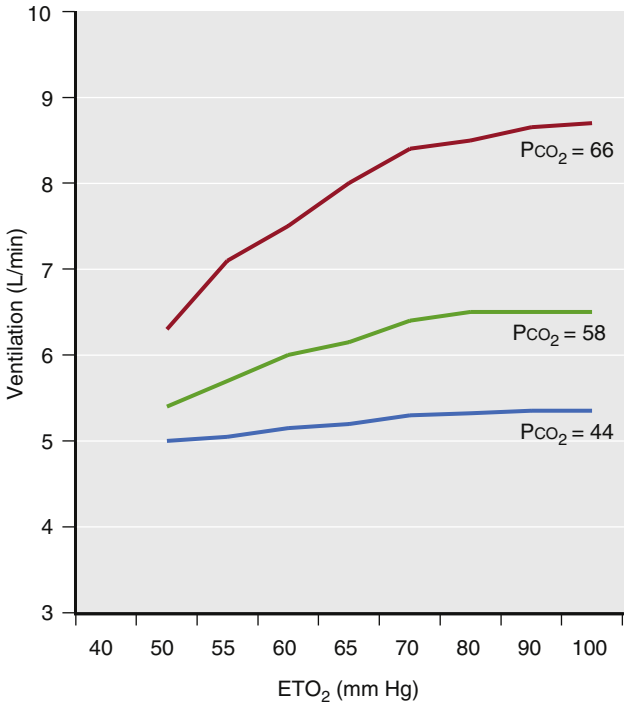


Figure 27-18. Effects of halothane anesthesia on the hypoxic ventilatory response in humans at three steady-state levels of partial pressure of carbon dioxide (P_{CO_2}). Halothane anesthesia (1.1 minimum alveolar concentration [MAC]) completely eliminates the hypoxic ventilatory response and the hypoxic hypercapnic interaction at the peripheral chemoreceptors. *ETO_2*, End-tidal oxygen. *(Modified from Knill RL, Gelb AW: Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anesthesia in man,* Anesthesiology *49:244, 1978. Used with permission.)*

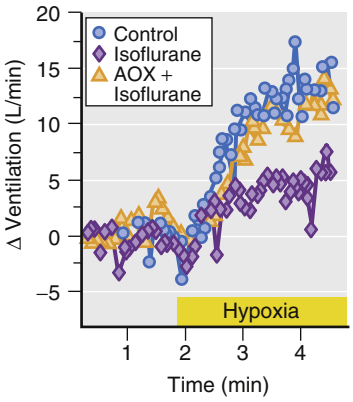


Figure 27-19. Subanesthetic concentrations of isoflurane strongly depress the acute hypoxic ventilatory response in humans. The depression of the hypoxic ventilatory response by subanesthetic isoflurane is prevented by antioxidant (AOX) pretreatment. *(Modified from Teppema LJ, Romberg RR, Dahan A: Antioxidants reverse reduction of the human hypoxic ventilatory response by subanesthetic isoflurane,* Anesthesiology *102:747, 2005. Used with permission.)*

of approximately 166 L/min.[218] Yet, 1.1 MAC halothane anesthesia is able to completely abolish this powerful ventilatory response to hypoxia. In fact, the direct effect of hypoxia on the respiratory centers during the administration of volatile anesthetics causes a reduction in minute ventilation. This central depressant effect of hypoxia in the presence of a volatile anesthetic is especially pronounced during hypercapnia (Figure 27-18). The depression of the HVR occurs at subanesthetic concentrations (0.1 MAC) of volatile anesthetics. In analyzing 37 separate studies investigating the effect of low-dose volatile anesthetics on HPV, Pandit proposed the rank order of potency as halothane > enflurane > sevoflurane = isoflurane > desflurane.[184] The depressant effect on the HVR is due to selective depression of the peripheral chemoreflex loop. The carotid body appears to be the most likely target. The clinical implications of volatile anesthetic–induced depression of HVR are important because subanesthetic concentrations of volatile anesthetics may be present in patients for several hours after a prolonged surgery. As a result, a hypoxia-mediated arousal response may not be present after administering a volatile anesthetic. This is especially the case in patients with OSA and premature infants who are at risk of respiratory depression or apnea during the perioperative period.

The mechanisms by which low concentrations of volatile anesthetics attenuate hypoxic ventilatory drive are not completely understood. The administration of antioxidants to healthy volunteers reversed the attenuation of the HVR to subanesthetic concentrations of halothane and isoflurane (Figure 27-19).[219] These results suggested that volatile anesthetics depress the hypoxic response by influencing the oxidation-reduction state of O_2-sensing elements in the carotid bodies. How antioxidants mediate this response is unclear, but modulation of the mitochondrial electron transport chain, volatile anesthetic binding sites, or K^+ channel function may be plausible explanations.

EFFECTS OF INHALED ANESTHETICS ON RESPIRATORY MUSCLES ACTIVITY

Humans are *bipeds*, unlike the *quadruped* mammals (cat, dog, and rats) in which most invasive in vivo and in vitro respiratory control studies have been performed. This difference in *posture* probably contributes to the divergent contribution of various muscle groups, in particular of the truncal muscles, to the normal respiratory effort and also likely contributes to the different changes in respiratory muscle function under anesthesia between mammalian species. Warner and colleagues performed extensive in vivo studies on the effects of volatile anesthetics, especially halothane, on respiratory muscle activation in dogs both in the presence and absence of CO_2-stimulated breathing.[220] Analogous studies using electromyography, fast CT scanning technology, and impedance plethysmography conducted in supine humans demonstrated that respiratory muscle activation during halothane anesthesia (1.2 MAC) significantly differed from the results observed in dogs.[217,221,222] Scalene and parasternal inspiratory activity are almost universally present during quiet breathing in conscious supine humans, but abdominal expiratory activity is absent. These inspiratory activities are enhanced, and abdominal expiratory activity is universally recruited during CO_2-stimulated rebreathing (which simulates increased chemodrive during exercise).

Halothane *differentially* depresses inspiratory muscle activity. The activity of the diaphragm as the main inspiratory pump muscle is relatively spared (Figure 27-20).

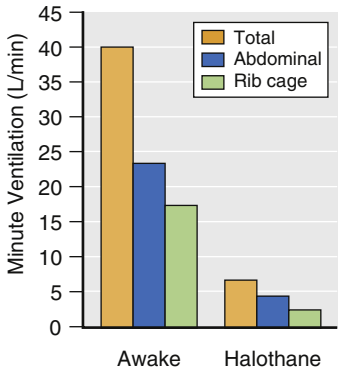


Figure 27-20. Effects of halothane anesthesia on rib cage and abdominal ventilation during hypercapnia (calculated ventilation at partial arterial pressure of carbon dioxide [Pa_{CO_2}] of 55 mm Hg). Compared with being awake, halothane anesthesia strongly depresses minute ventilation. Halothane depresses the rib cage component to ventilation more than the abdominal component (diaphragmatic). Data are means. *(Graph is based on data from Warner DO, Warner MA, Ritman EL: Mechanical significance of respiratory muscle activity in humans during halothane anesthesia,* Anesthesiology *84:309, 1996.)*

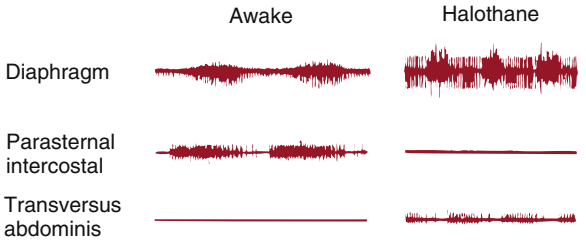


Figure 27-21. Representative record of respiratory electromyograms from one patient while awake and during halothane anesthesia. Halothane anesthesia selectively depresses inspiratory rib cage muscle activity and elicits expiratory abdominal muscle activity. *(From Warner DO, Warner MA, Ritman EL: Human chest wall function while awake and during halothane anesthesia. I. Quiet breathing,* Anesthesiology *82:6, 1995. Used with permission.)*

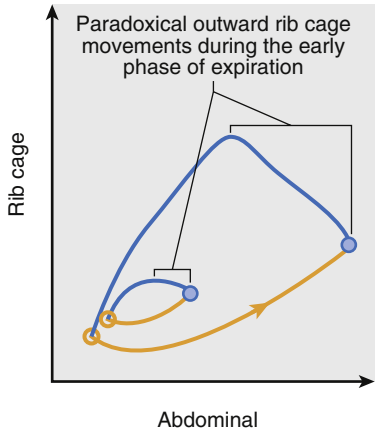


Figure 27-22. Chest wall and abdominal motion during anesthesia in a male patient are plotted as changes in thoracoabdominal movements and measured by respiratory impedance plethysmography at the onset *(small loop)* and conclusion *(large loop)* of rebreathing. Open and closed circles denote the beginning and end of inspiratory gas flow, respectively. After the termination of inspiration (i.e., during early expiration), the patient exhibits paradoxical rib cage motion with rib cage dimensions continuing to increase. *(From Warner DO, Warner MA, Ritman EL: Mechanical significance of respiratory muscle activity in humans during halothane anesthesia,* Anesthesiology *84:309, 1996. Used with permission.)*

Abdominal expiratory activity is routinely recruited during halothane anesthesia in male subjects. During quiet breathing, halothane anesthesia significantly depressed tidal volume (conscious, 707 ± 72 mL versus halothane, 288 ± 15 mL; mean ± standard error of the mean [SEM]) without any significant relative changes in abdominal versus rib cage contribution. An increase in respiratory rate (conscious, 10.6 ± 0.6 breaths/min versus halothane, 26.5 ± 2.8 breaths/min) and a reduction in FRC (335 ± 75 mL) were also reported. Halothane significantly reduced the slope of the expiratory minute ventilation to CO_2 response curve (conscious, 2.21 ± 0.34 L/min/mm Hg versus halothane, 1.49 ± 0.35 L/min/mm Hg). Thus expiratory minute ventilation at partial pressure of carbon dioxide (P_{CO_2}) = 55 mm Hg was dramatically reduced during halothane administration (conscious, 40.5 ± 7.5 L/min versus halothane, 6.7 ± 3.7 L/min). Furthermore, halothane strongly depressed the rib cage response to CO_2 during CO_2 rebreathing, whereas the abdominal (i.e., diaphragmatic) response was unaffected (Figure 27-21).[217]

Significant gender-related differences in respiratory muscle activity were observed during halothane anesthesia in spontaneously breathing humans. Women showed activation of inspiratory parasternal intercostal activity, which was enhanced during CO_2-induced rebreathing, whereas parasternal intercostal activity during halothane anesthesia did not change in men. Phasic inspiratory activity was present in the scalene muscle in the majority of subjects. CO_2-stimulated rebreathing uniformly increased scalene muscle phasic inspiratory activity. In contrast, inspiratory activity in internal intercostal muscles was present in men but not in women. Strong phasic expiratory activity in the transversus abdominis muscle was observed during halothane anesthesia in men but not in women, whereas CO_2 rebreathing elicited expiratory abdominal muscle activity in both genders. These observations demonstrate that, unlike in animals, there are important gender-specific differences on how volatile anesthetics affect respiratory muscles in humans. Indeed, caution should be used when extrapolating results from animal studies.

When expiratory transversus abdominis activity was present, the rib cage became significantly constricted (i.e., inward displacement of the rib cage), which reduced thoracic volume and partially contributed to the observed reduction of FRC during halothane anesthesia. A cephalad motion of the end-expiratory position of the diaphragm was also observed in supine halothane-anesthetized subjects. This alteration in diaphragm position also reduced FRC. Halothane distorted the normal phase relationships between the rib cage and abdominal movements observed in the conscious state with both rib cage and abdomen expanding during inspiration. *Paradoxical* rib cage motion developed in some subjects during halothane anesthesia, such that the rib cage continued to expand during the first portion of expiratory gas flow. Such paradoxical rib cage motion was exaggerated during CO_2-stimulated rebreathing (Figure 27-22).[217,222,223]

Similar to volatile anesthetics, nitrous oxide affects chest wall function and breathing by changing the distribution and timing of neural drive to the respiratory muscles.[224] Nitrous oxide decreases tidal volume as a result of a reduction in rib cage motion and increases phasic expiratory activity in humans.

EFFECTS OF INHALED ANESTHETICS ON THE UPPER AIRWAY

Pediatric anesthesiologists often conduct an inhaled induction of anesthesia (also see Chapter 93) and are very familiar with the upper airway collapse resulting from the administration of volatile anesthetics. As a result, pediatric anesthesia training is focused on mastering the skills of maintaining upper airway patency during mask induction and maintaining anesthesia in spontaneously breathing children. Inspiratory upper airway patency is maintained by the cortical wakefulness drive, fully preserved chemical chemoreceptor sensitivity and chemodrive transmission, and optimal reflex feedback from upper airway receptors in the conscious state. These upper airway receptors are activated by the negative pressure and airflow[225,226] that are generated by the pump muscles (e.g., diaphragm, respiratory chest wall muscles). During sleep, the cortical wakefulness drive is absent, and the sensitivity of the chemoreceptors and upper airway receptors is decreased. Thus both phasic and tonic inspiratory excitatory drives to the upper airway muscles are decreased or entirely absent during volatile anesthesia. The loss of tone in the upper airway muscles (genioglossus and other pharyngeal muscles) predisposes individuals with anatomic limitations (e.g., narrowed upper airway secondary to obesity or craniofacial abnormalities, adenotonsillar hypertrophy, macroglossia, micrognathia) to upper airway obstruction.

The cortical wakefulness drive, peripheral chemodrive from the peripheral chemoreceptors, and excitatory inputs from upper airway mechanoreceptors are already significantly impaired in the presence of subanesthetic concentrations of volatile anesthetics. Such conditions are often present in the immediate postoperative period and may lead to partial or even complete upper airway obstruction, a situation that is further complicated because subanesthetic concentrations of volatile anesthetics also strongly suppress hypoxia-mediated arousal reflexes. Higher anesthetic concentrations of volatile anesthetics cause further loss of upper airway muscle tone, which may lead to airflow limitation or complete airway obstruction, despite the continued function of respiratory pump muscles in patients with or without sleep-disordered breathing or anatomic airway abnormalities.[196,227]

Cortical control of breathing is absent, and respiration depends entirely on automatic brainstem mechanisms and blunted CO_2-mediated central chemoreceptor inputs at clinical levels of volatile anesthesia (≥1.0 to 1.3 MAC). Both tonic and phasic upper airway muscle tone is largely absent, and many anatomically normal patients will demonstrate air flow limitations, as indicated by flow-limited breathing secondary to partial or complete upper airway obstruction during negative inspiratory pressure. The airflow-limiting factor is almost invariably soft-tissue collapse at the level of the nasal velopharynx. The loss of velopharyngeal tone during surgical levels of volatile anesthesia can often be overcome with the simple application of CPAP. Collapse of the upper airway during inspiration, concomitant with inspiratory flow limitation during maximal inspiratory effort, rarely occurs in conscious patients or those with OSA because both phasic and tonic upper airway tone is robust. However, selective suppression of the upper airway reflexes alone (e.g., topical local anesthetics applied to the upper airway) may contribute to upper airway obstruction in some conscious patients with OSA or sleep-disordered breathing.

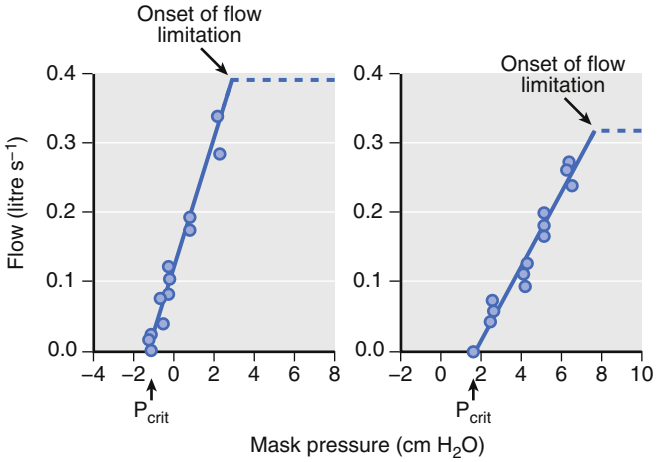


Figure 27-23. Relationship between maximal inspiratory flow and upper airway pressure for two subjects spontaneously breathing at end-tidal isoflurane levels of 1.2%. Both subjects exhibit inspiratory flow limitation as the positive upper airway pressure is lowered. The left panel demonstrates data from a subject with a relatively stable upper airway; note that the critical closing pressure (P_{crit}), indicating complete upper airway collapse is subatmospheric. The right panel demonstrates data from a subject with an unstable airway; note that P_{crit} exceeds atmospheric pressure. *(Modified from Hillman DR, Platt PR, Eastwood PR: The upper airway during anaesthesia,* Br J Anaesth *91:31, 2003. Used with permission.)*

The upper airway pressure proximal to the velopharynx, at which complete upper airway collapse occurs with no inspiratory flow during spontaneous breathing, is defined as the critical closing pressure (Pcrit). Pcrit is negative in normal, conscious individuals. As a result, it is difficult to cause complete airway collapse. Pcrit becomes less negative during sleep but remains typically slightly subatmospheric during the administration of a volatile anesthetic. Indeed, many patients who are anatomically normal show signs of inspiratory flow limitations at higher concentrations (≥1 to 1.3 MAC) of volatile anesthetics because Pcrit approaches zero (i.e., atmospheric pressure). Under these circumstances, CPAP may be required to maintain nasopharyngeal-velopharyngeal patency and to overcome the inspiratory flow limitation (Figure 27-23).[228,229] In patients with significant anatomic airway abnormalities (e.g., OSA, retrognathia), CPAP alone may be insufficient to maintain upper airway patency and additional measures (e.g., sniffing position, jaw thrust) may be required. If these standard maneuvers are insufficient to restore upper airway patency, then insertion of an airway device may be necessary to ensure upper airway patency.

EFFECTS OF INHALED ANESTHETICS ON DEFENSIVE AIRWAY REFLEXES

Vocal cord adduction and coughing in response to foreign material are important defensive reflex mechanisms that protect the airway from aspiration. Volatile anesthetics exert dose-dependent effects on defensive airway reflexes. Volatile anesthetics (≥1 to 1.3 MAC) progressively abolish defensive airway reflexes. The loss of airway protection against gastroesophageal reflux with consequent aspiration of orogastric content into the trachea are major adverse consequences of the loss of protective airway reflexes during the administration of volatile anesthetics. In contrast, lower concentrations of volatile anesthetics, such as those present during transitional states (e.g., mask induction, emergence), may paradoxically enhance and prolong the duration of protective defensive reflexes. Laryngospasm is the sustained and complete reflex glottic closure in response to foreign material (e.g., oral secretions), contacting the vocal cords, or to a poorly timed noxious stimulus (e.g., pain from incision, venipuncture) during the administration of inadequately low concentrations of a volatile anesthetic. Under such circumstances, therapeutic airway maneuvers, such as jaw thrust and sustained positive airway pressure, do not often relieve laryngospasm, and severe hypoxemia may ensue. Sedative-hypnotics or lidocaine may be used to *deepen* the plane of anesthesia rapidly or, alternatively, the administration of a neuromuscular blocker may be used to terminate the laryngospasm. In the absence of intravenous access (as may be the case during mask induction in infants and children), resorting to intramuscular, intraosseous, or intralingual injection of a neuromuscular blocker may be necessary to treat life-threatening laryngospasm. Clinical experience and experimental studies suggest that *severe* hypoxia ultimately silences laryngeal adductor motor neuron activity and terminates laryngospasm, but profound cardiovascular depression may precede relief of laryngospasm under these conditions.

Not all volatile anesthetics are equally prone to elicit unwanted sustained defensive airway reflexes. Desflurane and isoflurane appear to be most irritating to the airways; neither anesthetic is recommended for an inhaled induction of anesthesia. Lerman and associates[228] showed that the maintenance and emergence from desflurane anesthesia caused significantly more severe adverse airway events than did isoflurane anesthesia in spontaneously breathing infants and children with an LMA, especially when the LMA was removed before emergence. Another study in children confirmed the general clinical impression that isoflurane is more irritating to the airway than sevoflurane.[230] Children emerging from isoflurane anesthesia with an LMA in place had significantly more adverse airway reactions when compared with those anesthetized with sevoflurane (also see Chapter 93). Notably, higher concentrations (1.8 MAC) of isoflurane and sevoflurane produced similar attenuation of coughing, tachycardia, and hypertension associated with tracheal stimulation, but desflurane may continue to irritate the respiratory tract at concentrations that exceed 1 MAC. Removal of airway devices (e.g., LMA, endotracheal tube) during higher concentrations (>1.5 MAC) of a volatile anesthetic

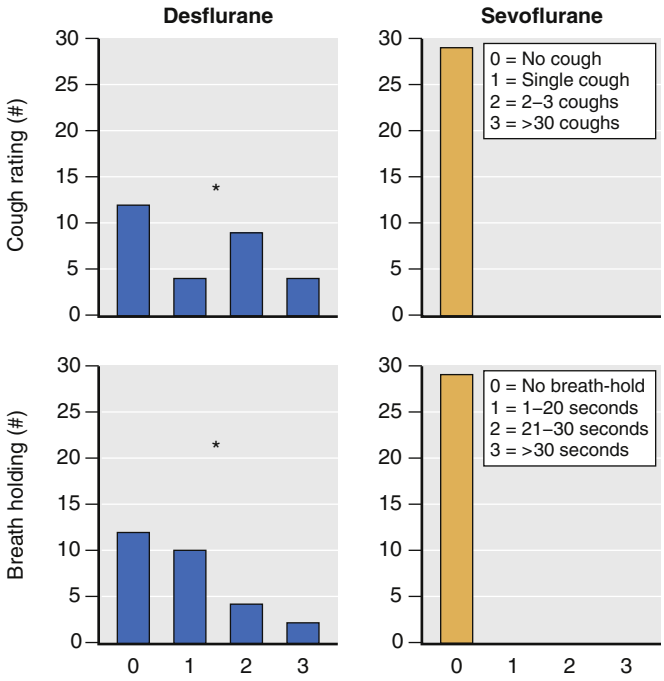


Figure 27-24. Graded responses to coughing and breath holding during transition to 2 minimum alveolar concentration (MAC) desflurane and sevoflurane anesthesia in elective surgical patients. Only desflurane caused adverse respiratory events, as indicated by an *asterisk*. *(Modified from Arain SR, Shankar H, Ebert TJ: Desflurane enhances reactivity during the use of the laryngeal mask airway,* Anesthesiology *103:495, 2005. Used with permission.)*

minimizes the risk of tracheal stimulation and laryngospasm related to the device. Nevertheless, desflurane caused significantly more adverse airway-related events, including coughing and breath holding, compared with sevoflurane,[231] even though patients had received adjuvant medications to blunt adverse airway reflexes (Figure 27-24). These findings contrasted with those of another study[232] that did not observe a difference in the airway-related complications in patients anesthetized with sevoflurane or desflurane. However, an average MAC value of less than 1 was used in this study. Klock and associates[233] confirmed the prevailing clinical opinion that sevoflurane may be better tolerated than desflurane at 1 MAC because cough responses to noxious airway stimulation (cuff inflation and deflation) were reduced. However, little difference was found between the two anesthetics at 1.8 MAC.[234] Anesthesia with desflurane, alone, probably leads to more airway-related adverse events than sevoflurane or halothane. Desflurane-related adverse airway reflexes may be mitigated by the use of adjuvant medications and the appropriate timing of airway device removal. Notably, significant increases in airway irritation were observed in tobacco smokers, independent of the specific volatile anesthetic.[235]

Unlike desflurane and isoflurane, sevoflurane and halothane are not pungent (irritants). This characteristic makes these volatile anesthetics the preferred medication for inhalational induction in infants and children. The mechanisms for the irritant effects of desflurane and isoflurane are not well understood. These volatile anesthetics

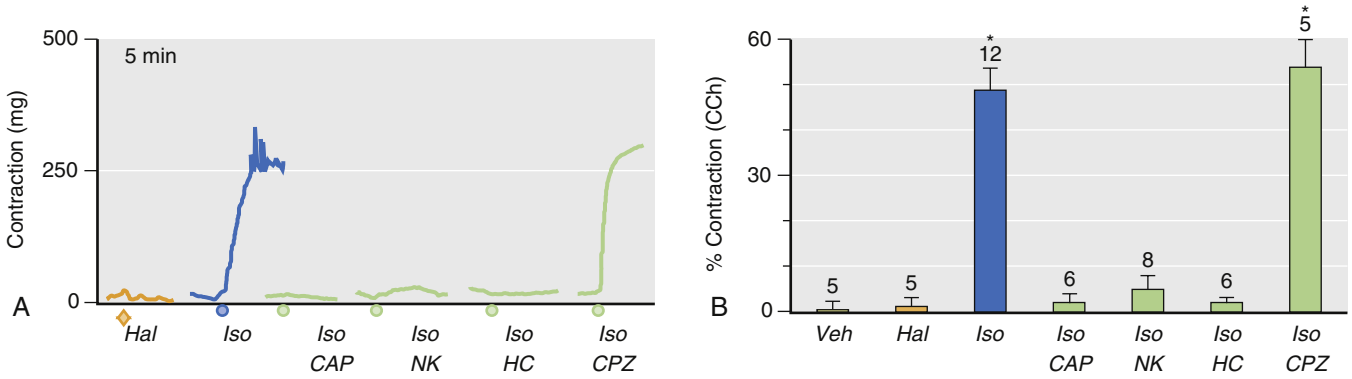


Figure 27-25. Isoflurane induces a contractile response in guinea pig bronchus. Typical traces (**A**) and pooled data (**B**) of the motor responses of guinea pig isolated bronchus to halothane (Hal) (◇) and isoflurane (Iso) *(filled circles)* or their vehicle (Veh) either alone or after pretreatment with capsaicin (CAP), the combination of neurokinin (NK)–receptor antagonists, the transient receptor potential cation channel, member A1, (TRPA1) antagonist (HC), or the transient receptor potential cation channel, subfamily V, member 1, (TRPV1) antagonist capsazepine (CPZ). Each column (in **B**) represents the mean ± standard error of the mean (SEM), and the number of observations for each group is listed in parenthesis. *, $P < 0.05$ versus Veh. *CCh,* Carbachol. *(Modified from Eilers H, Cattaruzza F, Nassini R, et al: Pungent general anesthetics activate transient receptor potential-A1 to produce hyperalgesia and neurogenic bronchoconstriction,* Anesthesiology *112:1452, 2010. Used with permission.)*

activate the excitatory, nonselective cation-channel transient-receptor potential (TRP)–A1, whereas the nonirritant anesthetics, halothane and sevoflurane, do not.[236] TRP-A1 channels detect endogenous and environmental chemical irritants and noxious stimuli. The channels play an important role in mediating protective airway responses. Desflurane and isoflurane also produce bronchoconstriction in experimental animals that is dependent on TRP-A1 activation of sensory neurons that are widely distributed throughout the respiratory tract. Thus it has been postulated that TRP-A1 channels in peripheral nociceptors mediate the irritant effects associated with desflurane and isoflurane (Figure 27-25).[236] Whether this nonadrenergic, noncholinergic (NANC)–mediated mechanism is important in humans remains unclear.

Halothane may be better than sevoflurane at suppressing airway reflexes during airway instrumentation (e.g., direct laryngoscopy, rigid bronchoscopy) because comparable MAC concentrations of halothane may cause stronger depression of noxious stimuli than sevoflurane.[237] However, closed claims outcome data suggest that the cardiovascular safety profile of halothane is inferior to that of sevoflurane[238,239] in infants and children during inhalational induction.[238,239] Endotracheal intubation of infants and children without a neuromuscular blocker after induction of anesthesia via mask is not recommended except under conditions in which maintenance of spontaneous breathing is preferred and when intravenous access cannot be readily achieved (also see Chapter 93). Administering small doses of a neuromuscular blocker significantly improves intubating conditions and decreases adverse airway reactions, compared with a *deep* inhaled sevoflurane anesthesia alone.[240]

Ishikawa and colleagues showed that infants and children who were spontaneously breathing with an LMA in place at a steady-state end-tidal concentration of 1% sevoflurane displayed strong *passive* (laryngospasm, apnea) and *active* (coughing, swallowing) airway reflexes in response to small amounts of water injected onto the vocal cords (Figure 27-26). At an end-tidal sevoflurane

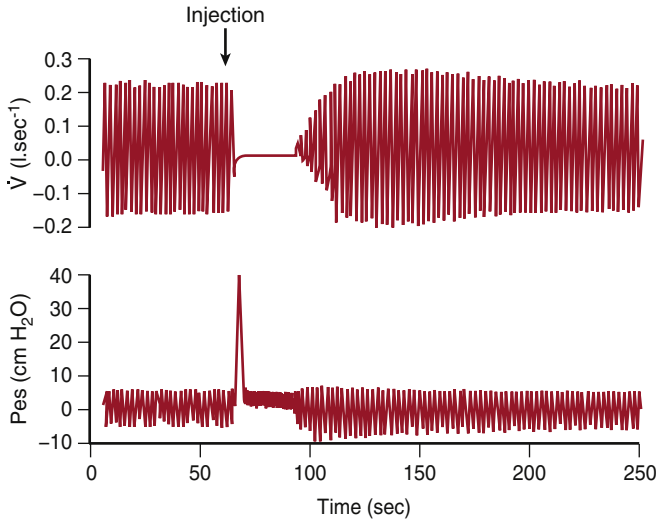


Figure 27-26. Demonstrable responses to laryngeal distilled water instillation. The subject was anesthetized with 1% of sevoflurane in oxygen. After only a few breaths after the instillation, laryngeal closure was observed, followed by laryngospasm and central apnea. Note no respiratory efforts occurred during apnea. A significant increase in esophageal pressure corresponded to the swallowing reflex. $\dot{V}$, Respiratory flow in L/sec.; *Pes,* esophageal pressure. *(From Ishikawa T, Isono S, Tanaka A, et al: Airway protective reflexes evoked by laryngeal instillation of distilled water under sevoflurane general anesthesia in children,* Anesth Analg *101:1615, 2005. Used with permission.)*

concentration of 2%, children continued to display passive responses, but active responses were completely depressed.[241] Thus transient or sustained glottic closures were routinely elicited during sevoflurane (1 MAC) anesthesia.

When volatile or intravenous anesthetics were used as the sole maintenance anesthetic in the absence of neuromuscular blockade, these medications had very different effects on active and passive upper airway reflexes in spontaneously breathing children. Oberer and coworkers[242] concluded that instillation of water onto the vocal

cords during light sevoflurane anesthesia (as determined using BIS monitoring) caused more laryngospasm and apnea than during propofol anesthesia. Conversely, active expiratory airway reflexes were greater when compared with sevoflurane at equivalent BIS values. Interestingly, neither passive nor active airway protective reflexes were completely depressed by 1.2 or 1.8 MAC sevoflurane anesthesia in adult women, results that are in contrast to those obtained in children.[243]

ACUTE LUNG INJURY

MECHANISMS OF ACUTE LUNG INJURY

Acute lung injury resulting from sepsis, pneumonia, ARDS, or asthma is common in patients who are critically ill and involves a vicious cycle of hypoxia and inflammation. Exposure to ambient hypoxia may cause pulmonary edema (e.g., high-altitude pulmonary edema) and an inflammatory response in the absence of pulmonary injury. Irrespective of the cause, acute lung injury is always accompanied by hypoxia and inflammation.[244] Hypoxia-induced inflammation results in enhanced vascular permeability and edema formation, atelectasis, airway plugging, microthrombi, $\dot{V}/\dot{Q}$ mismatch, apoptosis, and release of inflammatory mediators including tumor necrosis factor alpha (TNF-α), macrophage inflammatory protein-2 (MIP-2), monocyte chemoattractant protein-1 (MCP-1), interleukin (IL)–6 or IL-8, and cytokine-induced neutrophil chemoattractant-1 (CINC-1). Infiltration of neutrophils also occurs. Inflammation enhances metabolic and O_2 demand, further worsening the relative tissue hypoxemia, compromising gas exchange, and activating hypoxia-mediated signaling pathways, including those mediated by the A2B adenosine receptor[245,246] (also see Chapters 101 through 103).

The clinical condition of sepsis-induced acute lung injury is modeled in the laboratory by injection or inhalation of lipopolysaccharide (LPS), a component of the outer membrane of gram-negative bacteria. LPSs bind to Toll-like receptor 4 to activate nuclear factor κB, upregulate adhesion molecules, and stimulate cytokine-induced neutrophil migration into the pulmonary parenchyma. The alveolar epithelium may also be injured by endotoxin and may play a critical role in maintaining alveolar homeostasis by producing specific proteins, including surfactant and a variety of cytokines and by clearing excess alveolar liquid. Notably, failure of the alveolar epithelium is associated with increased mortality.[247]

Acute ventilator-induced lung injury (VILI) is manifested as severe distension of and damage to bronchoalveolar structures, lung overinflation, and bronchiectasis.[248] Caveolin-1, an integral membrane protein and component of endothelial caveolae (plasma membrane invaginations) regulates critical cell functions including endothelial uptake, albumin transport, and apoptosis.[249] Caveolin-1 plays an important role in the pathogenesis of acute lung injury. Inflammatory cytokines, including TNF-α, IL-1β and MIP-2, may be released from alveolar epithelial cells, neutrophils, and macrophages. Cytokines are important mediators of leukocyte recruitment and activation. In general, attenuation of the cytokine response is considered beneficial in terms of reducing potential lung injury. Alternatively, blunting the release of inflammatory mediators and attenuation of neutrophil migration into the inflamed lung may be detrimental and predispose immunocompromised patients to a greater risk of pulmonary infections. Unfortunately, the release of cytokines is highly variable, depending on experimental conditions. For example, altering the ventilation strategy may modify lung cytokine responses to LPS,[248] whereas positive pressure ventilation alone in the absence of anesthesia may exacerbate inflammatory responses.[250] NO is derived from inducible nitric oxide synthase (iNOS) in response to inflammation and endotoxin and also appears to play an important role in acute lung injury. Inhibition of iNOS substantially reduced pulmonary lymph filtration and improved oxygenation during endotoxemia in conscious sheep[251] (also see Chapter 104).

The presence of preexisting pulmonary disease, including chronic bronchitis, emphysema, and pneumonia, may exacerbate pulmonary damage that occurs in response to an acute lung injury.[235] As with acute lung injury, tobacco smoking induces an inflammatory state, but inhaled tobacco abuse decreases the response of macrophages and neutrophils. Thus these cells are less capable of releasing cytokines during an infection. In addition, goblet-cell hyperplasia, decreased mucociliary clearance, and increased airway reactivity occur in chronic tobacco smokers and contribute to potential infection, bronchospasm, and acute lung injury.

INHALED ANESTHETICS ENHANCE ACUTE LUNG INJURY

Volatile anesthetics both exacerbate and attenuate acute lung injury. Mechanical ventilation alone, in the absence of acute lung injury or volatile anesthetics, produces inflammatory pulmonary changes and injury known as VILI.[252-254] Cyclic stretching of the lung during mechanical ventilation (1) releases proinflammatory cytokines, such as IL-1 and MIP-2, leading to pulmonary neutrophil accumulation; (2) enhances activity of phospholipase A2, which degrades surfactant; and (3) results in pulmonary edema, hyaline membrane formation, and cellular infiltration. Reduced tidal volume with PEEP was successfully used to mitigate the adverse effects of VILI and ARDS. Nevertheless, inflammatory changes and lung injury still occur, despite this strategy. Thus studies investigating the specific effects of volatile anesthetics on acute lung injury must also account for concomitant damage caused by VILI. Volatile anesthetics enhance gene expression of proinflammatory cytokines and impair immune functions of alveolar macrophages in vitro and in vivo[255-257] (Figure 27-27). Halothane also caused DNA and cell damage, nuclear fragmentation, and apoptotic-like changes in isolated pulmonary epithelial cells.[258] Although desflurane and sevoflurane affect the function and distribution of lymphocytes[259,260] during one-lung ventilation, the clinical significance of this finding remains unclear. Volatile anesthetics exacerbated the extent of lung injury and increased mortality in a rat model of acid aspiration.[261]

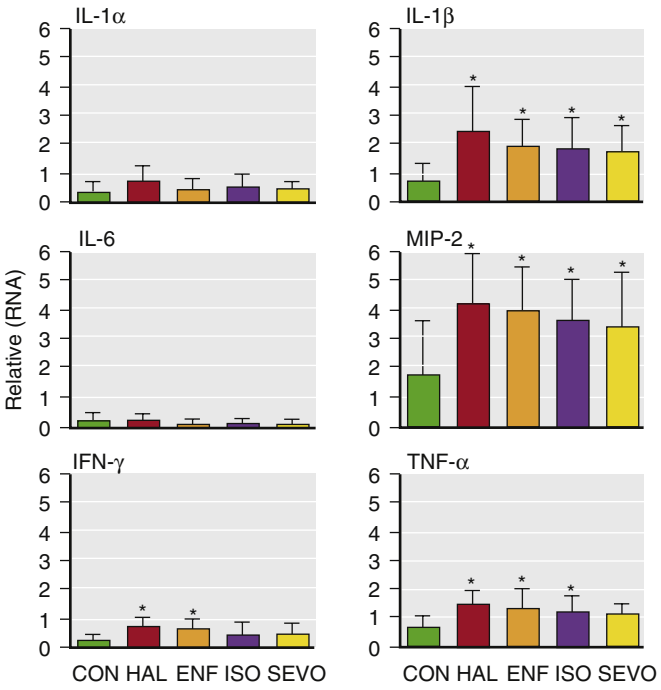


Figure 27-27. Changes in the expression of proinflammatory cytokines from macrophages during mechanical ventilation with and without volatile anesthetics. Values are the ratio of cytokine messenger ribonucleic acid (mRNA) to β-actin mRNA and presented as means ± standard deviation (SD). *, $P < 0.05$ versus the control group (mechanical ventilation without volatile anesthetics). Gene expression for interleukin-1β (IL-1β), macrophage inflammatory protein-2 (MIP-2), interferon-gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α) all significantly increased in comparison with mechanical ventilation alone. *CON,* Control; *ENF,* enflurane; *HAL,* halothane; *IL-1α,*interleukin-1α; *ISO,* isoflurane; *SEVO,* sevoflurane. *(Modified from Kotani N, Takahashi S, Sessler DI, et al: Volatile anesthetics augment expression of proinflammatory cytokines in rat alveolar macrophages during mechanical ventilation,* Anesthesiology *91:187, 1999. Used with permission.)*

The magnitude of the injury and mortality rate was dose dependent. The extent of injury was unaffected by the concomitant infusion of phenylephrine to avoid systemic and pulmonary hypotension. However, compromised pulmonary perfusion may have contributed to the results of this study. Volatile anesthetics may also augment the inflammatory response to mechanical ventilation.[256,262,263] Pigs were anesthetized for 4 hours with propofol or 1 MAC sevoflurane or desflurane.[263] Pigs anesthetized with sevoflurane or desflurane showed the following: (1) fewer alveolar macrophages in the bronchoalveolar lavage fluid (BALF), (2) greater percentage of lymphocytes in the BALF, and (3) greater apoptotic index (as measured by caspase-3 protein), compared with those anesthetized with propofol. Pigs receiving sevoflurane also showed significantly reduced levels of platelet-activating factor (PAF) acetylhydrolase, which limits the deleterious effects of PAF, and more pronounced atelectasis than propofol-anesthetized pigs. Of note, no differences were observed between groups in phospholipase-2 levels, intraalveolar septal thickening, alveolar edema, or wet-to-dry ratios, as indicators of pulmonary edema. In the absence of gross histologic effects, the deleterious effects of the volatile anesthetics appear to be predominantly functional. Similarly, no significant effects on alveolar integrity or ultrastructure were observed after administering high concentrations of sevoflurane in pigs.[264] The confounding factor of mechanical ventilation cannot be completely eliminated from the analysis because this factor alone may be associated with many of the inflammatory responses observed. A lack of PEEP may have also contributed to the observed exacerbation of lung injury in this study.[265] Although the results suggest that volatile anesthesia plays a detrimental, proinflammatory role, one cannot rule out a beneficial role for propofol. However, results from in vivo studies do not support a role for propofol in reducing acute lung injury.

Volatile anesthetics may worsen acute lung injury by increasing alveolar permeability. Using radionuclide scanning, halothane and isoflurane transiently increased pulmonary vascular endothelial damage.[266] Isoflurane also enhanced alveolar epithelial permeability in patients undergoing surgery.[267] Desflurane increased lipid peroxidation as measured in BALF samples from healthy surgical patients,[268] suggesting that the pulmonary alveolar membranes had been injured. Sevoflurane caused less-pronounced effects in this model, suggesting that this anesthetic may exert a protective effect, compared with desflurane. Furthermore, isoflurane, but not sevoflurane, increased albumin permeability and transport in isolated rat lungs.[249] These deleterious actions appeared to be related to an enhancement of caveolin-1–mediated albumin uptake. Similarly, pretreatment with isoflurane but not sevoflurane enhanced neurogenic pulmonary edema in rats.[269] Low concentrations of isoflurane also exacerbated impaired pulmonary gas exchange ($\dot{V}/\dot{Q}$ mismatch and shunting) and worsened O_2 delivery after oleic acid–induced lung injury in mechanically ventilated dogs.[270]

Proinflammatory responses and enhanced cytokine levels in healthy surgical patients undergoing tympanoplasty were more pronounced after desflurane, compared with sevoflurane anesthesia. Patients anesthetized with desflurane had more pronounced systemic and intrapulmonary inflammatory responses (as measured by mediators TNF-α, IL-1β, and IL-6) both before and after initiation of surgery, as compared with those anesthetized with sevoflurane.[255]

INHALED ANESTHETICS REDUCE ACUTE LUNG INJURY

Hypoxia is a common mechanism of acute lung injury. Hypoxia-inducible factor helps ameliorate lung injury via activation of hypoxia-responsive genes (e.g., iNOS, heme oxygenase, vascular endothelial growth factor) under conditions of low O_2 tension in the lung. Exposing isolated pulmonary cells to isoflurane significantly increased hypoxia-inducible factor 1α, and enhanced gene expression for hypoxia-responsive genes.[271] These actions suggest that volatile anesthetics are capable of producing a protective effect during acute lung injury.

Whether volatile anesthetics reduce or exacerbate pulmonary cytokine formation appears to be based on the type of cells studied and the conditions under which the cytokine expression is measured. Volatile anesthetics

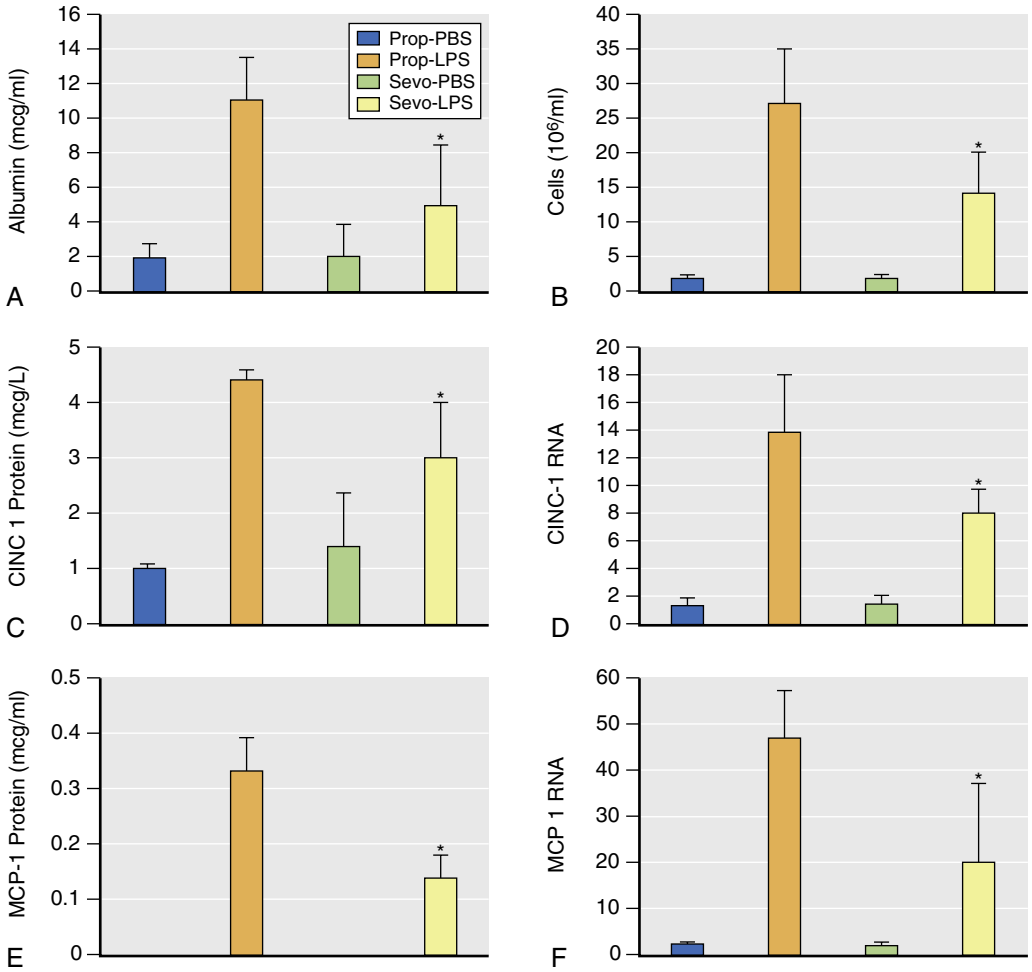


Figure 27-28. Instillation of phosphate-buffered saline (PBS) or lipopolysaccharide (LPS) intratracheally in rats, followed by ventilation and sedation with propofol (Prop) for 2 hours and continued with either propofol or with sevoflurane (SEVO) for an additional 4 hours. Evaluation of **A,** Lung hyperpermeability after 6 hours as measured by the amount of albumin in the bronchoalveolar lavage fluid (BALF). Sevoflurane inhibits the LPS-induced permeability. **B,** Total cell count in BALF. Cell count significantly increased in both LPS groups and were mostly neutrophils. The presence of sevoflurane was associated with a significantly lower total cell count. **C** and **D,** Cytokine-induced neutrophil chemoattractant-1 (CINC-1). CINC-1 protein in BALF and CINC-1 ribonucleic acid (RNA) in lung tissue were significantly increased in both LPS groups, as compared with PBS control groups. The presence of sevoflurane was associated with decreased RNA expression and decreased protein, compared with during propofol. **E** and **F,** Monocyte chemoattractant protein-1 (MCP-1). MCP-1 protein in BALF and MCP-1 RNA in lung tissue were significantly increased in both LPS groups, compared with PBS control groups. The presence of sevoflurane was associated with decreased RNA expression and decreased protein, compared with during propofol. Data are means ± standard deviation (SD). *, $P < 0.05$ versus propofol-LPS. *(Modified from Voigtsberger S, Lachmann RA, Leutert AC, et al: Sevoflurane ameliorates gas exchange and attenuates lung damage in experimental lipopolysaccharide-induced lung injury,* Anesthesiology *111:1238, 2009. Used with permission.)*

increased the secretion and gene expression of some cytokines in alveolar macrophages but reduced the formation of proinflammatory cytokines in alveolar type II cells.[250,272,273] Pretreatment with 1.1% sevoflurane also significantly reduced the inflammatory response and attenuated endotoxin-induced chemotaxis of neutrophils from alveolar type II cells exposed to LPS.[274] Several animal studies also suggest an important antiinflammatory role of volatile anesthetics in reducing acute lung injury. Compared with thiopental anesthesia, pigs anesthetized with sevoflurane exhibited a reduced expression of TNF and IL-1β in lung tissue.[275] Volatile anesthetics appear to exert antiinflammatory effects, including the inhibition of cytokine formation, reduction of neutrophil migration into the lung interstitium and alveolar space, and attenuation of protein leakage and pulmonary edema (Figure 27-28),[250,272,273,276,277] in models of acute lung injury induced with LPS, *Escherichia coli* endotoxin, or IL-1β. LPS-induced acute lung injury was significantly reduced in the presence of sevoflurane, compared with propofol anesthesia.[277] Sevoflurane, but not propofol, improved the oxygenation index and reduced the amount of pulmonary edema. Interestingly, the beneficial effect of sevoflurane on pulmonary edema resulted from a reduction in edema formation rather than water reabsorption or edema resolution. If this is indeed a critical mechanism, then sevoflurane would be expected to have little beneficial effect if the volatile anesthetic was administered after a pulmonary insult. In fact, however, this was not the case.[276] Rats anesthetized with thiopental were mechanically ventilated, anesthesia was continued with propofol infusion, and LPS was administered

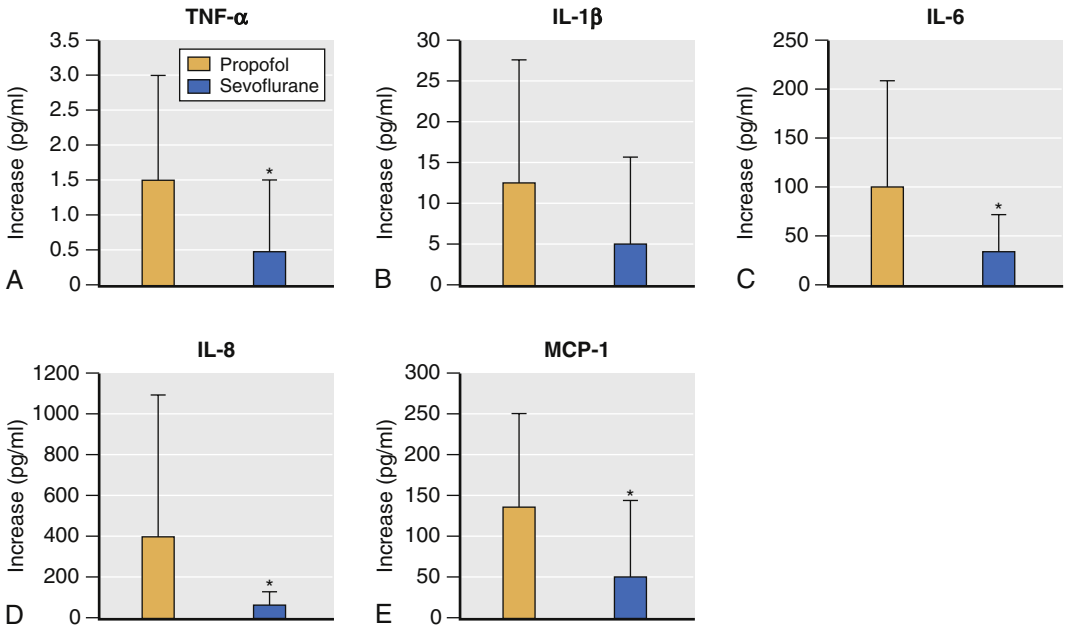


Figure 27-29. Increases in inflammatory mediators from bronchoalveolar lavage fluid in patients during one-lung ventilation receiving either propofol or sevoflurane. *, $P < 0.05$. Values are means ± standard deviation (SD). **A,** Increase in tumor necrosis factor alpha (TNF-α). **B,** Increase in interleukin-1β (IL-1β). **C,** Increase in interleukin-6 (IL-6). **D,** Increase in interleukin-8 (IL-8). **E,** Increase in monocyte chemoattractant protein-1 (MCP-1). Sevoflurane attenuates the release of inflammatory mediators during one-lung ventilation. *(Modified from De Conno E, Steurer MP, Wittlinger M, et al: Anesthetic-induced improvement of the inflammatory response to one-lung ventilation,* Anesthesiology *110:1316, 2009. Used with permission.)*

through an intratracheal approach. Two hours later, anesthesia was continued with either propofol or sevoflurane (0.5 to 1 MAC) for 4 hours, and several markers of lung injury were measured (see Figure 27-28). Rats receiving sevoflurane demonstrated the following: (1) improved gas exchange, (2) reduced amounts of albumin in BALF, (3) smaller total cell count in BALF (fewer neutrophils), and (4) lower cytokine levels in BALF and RNA levels in lung tissue, compared with rats receiving propofol. These data indicate that the administration of sevoflurane after the induction of pulmonary edema significantly attenuates lung injury and preserves lung function.[276] Similarly, isoflurane also protected against warm ischemia-reperfusion injury in an isolated, perfused rat lung model when the volatile anesthetic was administered after the onset of ischemia.[278]

In addition to improving lung function in sepsis, volatile anesthetics decrease lung injury attributable to mechanical ventilation[279] and ischemia-reperfusion.[280] The administration of isoflurane mitigated VILI as indicated by reduced inflammation, transmigration of neutrophils, and cytokine levels in mice.[279] Isoflurane also induced Akt (protein kinase B) phosphorylation; the beneficial effects of the volatile anesthetic were abolished by a selective phosphoinositide 3-kinase (PI3K) inhibitor. These findings strongly suggest that isoflurane-mediated pulmonary protection occurs through PI3K signaling. ATP-regulated K^+ (K_{ATP}) channels play important roles in cardioprotection and neuroprotection by volatile anesthetics, but blockade of these channels did not block the protective effects of isoflurane in this lung injury model.[279] Reductions in oxidative stress and inflammatory responses were also observed during sevoflurane, compared with propofol anesthesia in a porcine model of ischemia-reperfusion injury.[280]

Clinical investigations in patients support a beneficial role for volatile anesthetics in ameliorating lung injury (Figure 27-29).[281-284] For example, short-term positive pressure ventilation with high tidal volumes did not affect systemic proinflammatory or antiinflammatory cytokines in the lungs of healthy, isoflurane-anesthetized patients.[282] Three studies investigated the effects of volatile anesthetics in patients undergoing thoracic surgery using single-lung ventilation.[281,283,284] Single-lung ventilation increased the release of proinflammatory cytokines and mediators in both the dependent and the nondependent lungs. Volatile anesthetics suppressed local alveolar inflammatory responses and cytokine release, compared with propofol (see Figure 27-29). Furthermore, the anti-inflammatory effects of sevoflurane were greater in the dependent compared with the nondependent lung.[283] Patients receiving sevoflurane also had an improved postoperative course as indicated by a shorter ICU stay and fewer adverse events, compared with those treated with propofol.[284]

Whether the immunomodulatory effects of volatile anesthetics are mediated by the ether structure or the halogen, configuration was investigated using isolated pulmonary cells in an in vitro model of acute inflammation.[285] Cells were co-exposed to endotoxin and sevoflurane, diethyl-ether, or various other trifluorinated carbon (CF_3) groups. Expression of inflammatory mediators and chemotactic activity were modified by sevoflurane and molecules containing CF_3 groups but not by the diethyl-ether or structure-similar nonfluorinated molecules. This finding may have potential therapeutic importance; such

molecules may be theoretically provided in a hydrophilic, injectable formulation for the treatment of acute lung injury.[285]

NITROUS OXIDE

Data regarding the actions of nitrous oxide on bronchomotor tone, pulmonary vasculature, mucociliary function, control of ventilation, and acute lung injury have been previously presented. This section addresses specific concerns regarding nitrous oxide and the pulmonary system not included in other sections (also see Chapter 27).

Nitrous oxide, the least potent inhaled anesthetic, is also the oldest anesthetic currently in use, although its longevity is threatened by concerns of adverse effects and postoperative complications.[286] The Evaluation of Nitrous Oxide in a Gas Mixture for Anaesthesia (ENIGMA) trial[287] reported that more postoperative complications associated with use of nitrous oxide occur, compared with high concentrations of O_2 (80% plus 20% nitrogen); these complications include wound infections and adverse pulmonary events such as pneumonia and atelectasis. Notably, this large trial was not blinded and did not show a significant difference for the primary endpoint, that is, for the duration of the hospital stay. A thorough review of the potential toxicity of nitrous oxide suggests that no convincing data exist that document an increase in pulmonary complications.[286] As an inhibitor of methionine synthetase, nitrous oxide causes a long-lasting, dose-dependent increase in plasma homocysteine, reduces DNA and purine synthesis, and suppresses neutrophil chemotaxis. The consequences of an increase in plasma homocysteine are impaired endothelial function, enhanced platelet aggregation, and enhanced oxidative stress; all are potentially deleterious to the pulmonary system. Nevertheless, no randomized, controlled trials have investigated the effects of nitrous oxide in various models of acute lung injury.

In addition to other forms of hypoxia-induced lung injury previously discussed, diffusion hypoxia is a well-known phenomenon that may occur during recovery from nitrous oxide anesthesia. Rapid elimination of nitrous oxide from the blood to the alveoli, combined with slower nitrogen diffusion, reduces alveolar O_2 concentration, resulting in relative hypoxemia.

XENON

The anesthetic properties of the inert gas, xenon, have been known for more than 50 years, and advances in manufacturing technology and scavenging systems have made xenon more cost-effective.[288] Similar to volatile anesthetics, xenon exerts important neuroprotective and cardiovascular effects against ischemia-reperfusion injury.[289] Data on the interactions between xenon and the respiratory system are limited. The estimated MAC of xenon in humans is 63%, and xenon-induced respiratory depression occurs during inhalation of 33% xenon in radiology suites.[290] Xenon does not significantly affect transdiaphragmatic pressure or diaphragmatic electromyography because the gas preserves neuromuscular transmission.[291] The effects of xenon on airway resistance substantially differ from those of volatile anesthetics. Xenon has the lowest blood-gas partition coefficient (0.115) of all known inhaled anesthetics. As a result, induction and emergence from anesthesia is rapid. However, the anesthetic gas has a higher density and viscosity than air[291-293] (also see Chapter 26). Baseline airway resistance was significantly greater during 70% xenon-O_2 than during 70% nitrous oxide–O_2, in pentobarbital-anesthetized pigs, but the peak and mean airway pressures were unaffected. In contrast, airway pressures and resistance were moderately increased during xenon anesthesia in the presence of methacholine-induced bronchoconstriction.[293] In addition, pulmonary resistance during inhalation of 50% xenon was similar to that observed during 50% nitrous oxide or 70% nitrogen in methacholine-treated dogs.[294]

A randomized, double-blind comparison of xenon and nitrous oxide showed that both gases similarly increased expiratory lung resistance to a similar degree. However, patients receiving xenon were less likely to experience decreases in O_2 saturation than those treated with nitrous oxide.[295] Administration of 33% xenon in long-term mechanically ventilated patients may cause transient, elevations in peak airway pressure.[292] This increase in airway pressure was attenuated by reducing the inspiratory flow rate. The higher density and viscosity of xenon increases Reynolds number and probably causes the zone of transition from turbulent to laminar gas flow to move more distally to smaller airways. Arterial O_2 and CO_2 tensions were unaffected during the administration of xenon in anesthetized pigs.[296] However, breathing higher density gas mixtures may reduce the alveolar-arterial O_2 difference, improve the distribution of ventilation, and minimize $\dot{V}/\dot{Q}$ variances.[297] In morbidly obese patients scheduled for gastric bypass surgery, gas exchange (e.g., PaO_2/FiO_2) was enhanced in patients receiving xenon, compared with sevoflurane.[298]

Diffusion hypoxia may be less likely during xenon anesthesia, compared with nitrous oxide, because the blood-gas partition coefficient of the noble gas is similar to that of nitrogen and, as a result, diffusion into the alveoli may be slower. The specific effects of xenon on bronchomotor tone, mucociliary function, pulmonary vasculature, ventilatory control, or acute lung injury have not been described to date.

SUMMARY

Inhaled anesthetics affect every aspect of respiratory physiologic function. Volatile anesthetics are potent bronchodilators that reduce bronchiolar smooth muscle tone. Volatile anesthetics inhibit both ciliary function and bronchial mucous transport. Volatile anesthetics are pulmonary arterial vasodilators and inhibit HPV in vitro, but their net effect on HPV in vivo is minimal. Volatile anesthetics also significantly alter the activity of respiratory afferents, the respiratory control center, and the muscles of respiration. These effects are mediated by actions on pulmonary parenchyma and afferent, central, and efferent neural structures. The depressant effects

of volatile anesthetics are more pronounced in patients with lung disease and sleep-disordered breathing. Volatile anesthetics are also immunomodulatory. In some models, they appear to be proinflammatory, but the majority of studies show that volatile anesthetics ameliorate acute lung injury. The inhaled anesthetics, nitrous oxide and xenon, also affect the respiratory system. Although many actions of xenon have not been as well described, this gas is unusual in that it increases tidal breathing and decreases respiratory rate, an action that is opposite of other inhaled anesthetics. An understanding of the multiple actions of inhaled anesthetics on the respiratory system likely enhances the safe delivery of anesthesia.

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Chapter 28

Inhaled Anesthetics: Cardiovascular Pharmacology

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Key Points

- Volatile anesthetics produce dose-related depression of left ventricular (LV), right ventricular, and left atrial myocardial contractility, LV diastolic function, and LV-arterial coupling in the normal heart.
- The negative inotropic effects of volatile anesthetics are related to alterations in intracellular calcium homeostasis within the cardiac myocyte.
- Volatile anesthetics affect the determinants of LV afterload to varying degrees in the presence of normal and dysfunctional myocardium.
- The systemic hemodynamic effects of volatile anesthetics are complex and are determined by the interaction of myocardial effects, direct actions on the arterial and venous vasculature, and alterations in autonomic nervous system activity.
- Volatile anesthetics sensitize myocardium to the arrhythmogenic effects of epinephrine to varying degrees and may prevent or facilitate the development of atrial or ventricular arrhythmias during myocardial ischemia or infarction depending on the concentration of the agent, the extent of the injury, and the location affected within the conduction pathway.
- Volatile anesthetics are relatively weak coronary vasodilators that are not capable of producing coronary steal at typically used clinical concentrations, even in patients with steal-prone coronary artery anatomy.
- Volatile anesthetics exert myocardial protective effects against reversible and irreversible myocardial ischemia in experimental animals and humans when administered before, during, or immediately after the onset of coronary artery occlusion and reperfusion.
- Volatile anesthetics depress baroreceptor reflex control of arterial pressure to varying degrees.
- Nitrous oxide causes direct negative inotropic effects, does not substantially affect LV diastolic function, and produces modest increases in pulmonary and systemic arterial pressure via a sympathomimetic effect. These actions are dependent to some degree on the baseline anesthetic.
- Xenon is essentially devoid of cardiovascular effects but has been shown to protect myocardium against ischemic injury in experimental animals.

INTRODUCTION

This chapter comprehensively describes the cardiovascular pharmacology of modern volatile anesthetics (including isoflurane, desflurane, and sevoflurane), nitrous oxide, and the anesthetic noble gas xenon. Comparison to older volatile anesthetics (halothane and enflurane) will be made only when necessary because these drugs are no longer available in most countries. The actions of inhaled anesthetics on cardiovascular function, cardiac electrophysiology, the coronary circulation, and autonomic nervous system control of the circulation will be examined in detail.

VOLATILE ANESTHETICS

CARDIOVASCULAR FUNCTION

Myocardial Contractility

Isoflurane, desflurane, and sevoflurane depress myocardial contractility in vitro and in vivo. Investigations conducted

in the 1960s demonstrated that halothane and enflurane produce dose-related depression of force-velocity relations and Frank-Starling curves in isolated cardiac muscle preparations and intact hearts, respectively. Circulatory depression occurs during halothane and enflurane anesthesia in humans. Isoflurane produced direct negative inotropic effects as indicated by decreases in maximal velocity of shortening, peak developed force, and maximal rate of force development during isotonic contraction in isolated papillary muscles. These reductions in myocardial contractility by isoflurane also contribute to the cardiovascular depression observed with this anesthetic in humans. Similarly, desflurane and sevoflurane depress intrinsic inotropic state in isolated myocardium, which helps define the hemodynamic effects of these volatile anesthetics in humans with or without heart disease.

The relative degree of myocardial depression produced by volatile anesthetics in vivo is more difficult to establish because simultaneous alterations in systemic and pulmonary hemodynamics and autonomic nervous system activity complicate assessment of left ventricular (LV) systolic function. Early studies using isovolumic- and ejection-phase measures of myocardial contractility demonstrated that halothane and enflurane caused very similar negative inotropic effects in experimental animals and humans. These findings were confirmed using the slope of the LV end-systolic pressure–mid-axis diameter relation as a relatively heart rate– and load-independent index of inotropic state. In contrast, isoflurane produced less myocardial depression than the older anesthetics in vivo. For example, isoflurane caused smaller reductions in maximum rate of LV pressure development (dP/dt) than halothane when identical minimum alveolar concentrations (MACs) were directly compared in the presence and absence of autonomic nervous system function, suggesting that differences in myocardial depression caused by these anesthetics occurred independent of autonomic nervous system activity. Differences in the negative inotropic effects of halothane and isoflurane have been quantified using the slope of the regional preload recruitable stroke work relation derived from differentially loaded LV pressure–segment length diagrams. In these studies, isoflurane maintained contractility an average of 20% higher compared with identical MAC halothane. Differences in the relative degree of myocardial depression produced by isoflurane and the older volatile anesthetics were also inferred in humans using isovolumic- and ejection-phase measures of contractile state. The negative inotropic actions of all volatile anesthetics are exacerbated by hypocalcemia, calcium channel blockers, and β_1-adrenoceptor antagonists and may be reversed by administration of exogenous calcium (Ca^{2+}), cardiac phosphodiesterase fraction III inhibitors, β_1-adrenoceptor agonists, Ca^{2+} channel agonists, and myofilament Ca^{2+} sensitizers. The differential effects of isoflurane and halothane on myocardial contractility are maintained during changes in inotropic state produced by these vasoactive drugs.

Desflurane causes systemic and coronary hemodynamic effects that are similar to those produced by isoflurane. Desflurane and isoflurane depressed myocardial function to equivalent degrees using isovolumic- and ejection-phase measures of contractility in experimental animals and humans. These observations were verified using both end-systolic pressure-volume relations and preload recruitable stroke work (Fig. 28-1) in the presence and absence of autonomic nervous system activity. However, the unique cardiovascular stimulation associated with rapid increases in inspired desflurane concentration in humans may lead to transient increases in myocardial contractility resulting from stimulation of the sympathetic nervous system. The effects of sevoflurane on myocardial contractility are virtually indistinguishable from that produced by isoflurane in dogs. Sevoflurane caused less myocardial depression than equivalent MAC of halothane in pigs and produced less myocardial depression than enflurane in humans evaluated using echocardiography. Sevoflurane decreased contractile function to approximately 40% to 45% of control values at 1.75 MAC in the presence and absence of autonomic nervous system activity using regional preload recruitable stroke work. This magnitude of myocardial depression

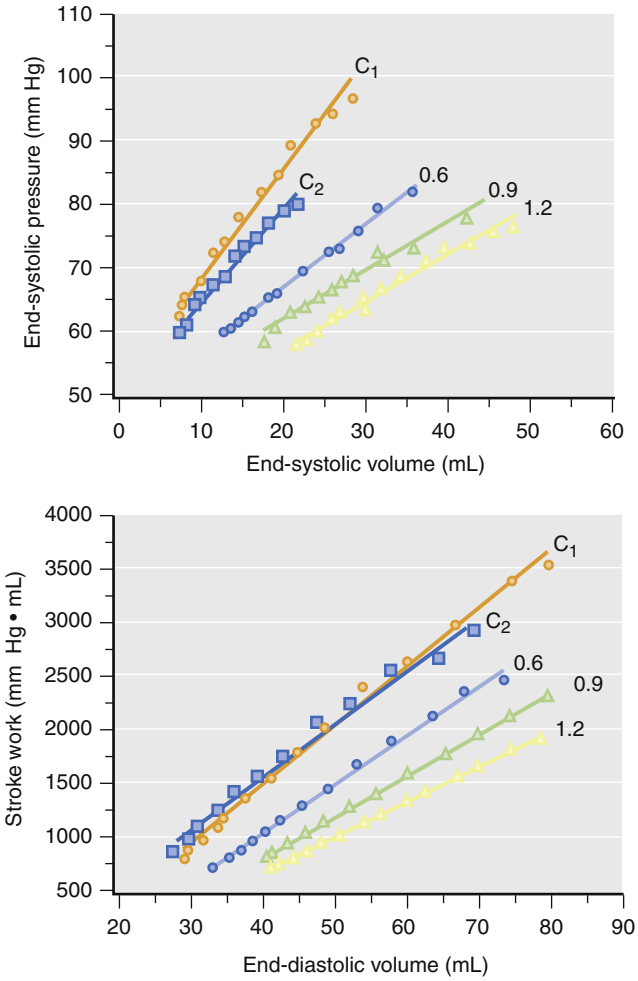


Figure 28-1. End-systolic pressure-volume *(top panel)* and stroke work–end-diastolic volume relationships *(bottom panel)* before (control 1; C_1), during 0.6, 0.9, and 1.2 minimum alveolar concentration, and after isoflurane (control 2; C_2) in an experiment in an open-chest dog. *(Modified from Hettrick DA, Pagel PS, Warltier DC: Desflurane, sevoflurane, and isoflurane impair canine left ventricular–arterial coupling and mechanical efficiency,* Anesthesiology *85:403-413, 1996.)*

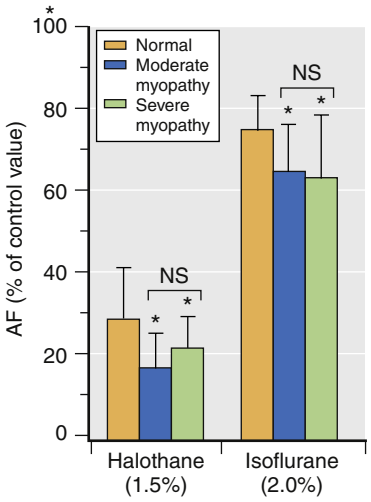


Figure 28-2. Comparison of the effects of halothane *(left)* and isoflurane *(right)* on isometric active force *(AF)* of papillary muscles from healthy hamsters *(yellow bars)* and those with cardiomyopathy *(blue and green bars)*. Probability values refer to between-group differences. *Significantly ($P < .05$) different from control values. *NS,* Not significant. *(Modified from Vivien B, Hanouz J-L, Gueugniaud P-Y, et al: Myocardial effects of halothane and isoflurane in hamsters with hypertrophic cardiomyopathy,* Anesthesiology *87:1406-1416, 1997.)*

is similar to isoflurane and desflurane using an identical experimental model. Thus, isoflurane, desflurane, and sevoflurane depress contractile state to similar degrees in normal LV myocardium.

The effects of volatile anesthetics on myocardial contractility in animal models or patients with LV dysfunction have been less extensively studied. An early in vitro study demonstrated that isoflurane causes greater reductions in maximum shortening velocity and the peak rate of force development in papillary muscles from failing compared with normal hearts subjected to chronic pressure overload. Halothane also produced more pronounced myocardial depression in ischemic in contrast to normal myocardium. Isoflurane and halothane caused relatively greater negative inotropic effects in ventricular myocardium obtained from cardiomyopathic hamsters than in normal hamsters (Fig. 28-2). Isoflurane and sevoflurane also produced greater depression of contractility in right ventricular (RV) papillary muscles obtained from ferrets with experimental pressure-overload hypertrophy compared with normal myocardium.[1] These findings suggested that myocardial depression caused by volatile anesthetics in failing or hypertrophied myocardium were accentuated and provided indirect evidence that patients with underlying contractile dysfunction may be more sensitive to the negative inotropic effects of volatile anesthetics. In contrast, isoflurane, sevoflurane, and desflurane caused similar declines in contractility in ventricular myocytes obtained from rats in the presence and absence of chemically induced chronic hyperglycemia.[2]

Volatile anesthetic–induced declines in contractile function were well tolerated and did not precipitate frank systolic dysfunction in experimental models of myocardial ischemia or infarction. In fact, volatile anesthetics exert important beneficial effects on mechanical function during myocardial ischemia and reperfusion injury. Volatile anesthetics reduced experimental myocardial infarct size, preserved metabolic and structural integrity during regional ischemia and reperfusion, enhanced the functional recovery of stunned myocardium, and improved indices of LV diastolic performance during brief coronary artery occlusion. Isoflurane produces beneficial decreases in LV preload and afterload in patients with ischemic heart disease. These improvements in loading conditions in patients with compromised LV function may serve to offset the direct negative inotropic effects of anesthetics and contribute to relative maintenance of cardiac performance by optimizing the Starling relationship or improving LV diastolic function. Isoflurane produced dose-related depression of myocardial contractility in a model of moderate LV dysfunction induced by chronic rapid LV pacing, but isoflurane anesthesia was well tolerated and did not precipitate LV failure. These findings with isoflurane were attributed to simultaneous improvements in LV loading conditions and filling dynamics that contributed to relative maintenance of cardiac output in the setting of moderate LV dysfunction despite concomitant reductions in contractility.

Cellular Mechanisms of Myocardial Depression

Volatile anesthetics depress myocardial contractility by alterations of intracellular Ca^{2+} homeostasis at several subcellular targets in the normal cardiac myocyte. Volatile anesthetics caused dose-related inhibition of the transsarcolemmal Ca^{2+} transient by affecting both L-type and T-type Ca^{2+} channels. Isoflurane produced less-pronounced reductions in intracellular Ca^{2+} transient than the older volatile ansethetics. The structural conformation and functional integrity of the voltage-dependent Ca^{2+} channel were directly altered by volatile anesthetics as indicated by attenuated binding of the Ca^{2+} channel blockers. The partial inhibition of Ca^{2+} influx via sarcolemmal Ca^{2+} channels has several important consequences, including declines in the availability of Ca^{2+} for contractile activation, depression of Ca^{2+}-dependent Ca^{2+} release from the sarcoplasmic reticulum (SR), and reduction of the amount of Ca^{2+} that can be subsequently stored in the SR. Notably, acute preconditioning by isoflurane triggers persistent changes in the inactivation of L-type Ca^{2+} channels that may contribute to attenuation of intracellular Ca^{2+} overload during ischemia-reperfusion injury.[3] In contrast to halothane and enflurane, isoflurane did not stimulate Ca^{2+} release from the SR or directly activate ryanodine-sensitive SR Ca^{2+} release channels, thereby reducing SR Ca^{2+} storage. Unlike halothane, isoflurane also did not cause a nonspecific leak of Ca^{2+} from the SR. When combined with decreases in transsarcolemmal Ca^{2+} flux, these alterations in SR function represent important mechanisms by which halothane and enflurane depressed the intracellular Ca^{2+} transient and reduced myocardial contractility more than isoflurane, desflurane, or sevoflurane. In addition, isoflurane and sevoflurane inhibited Ca^{2+} transport from the cell through the sarcolemmal Ca^{2+}-adenosine triphosphatase (ATPase), an action that partially offset reductions in SR Ca^{2+} stores. The partial preservation of the myocardial

positive frequency staircase effect observed with newer volatile anesthetics at physiologic excitation rates in vitro is due to this relative maintenance of SR function, in contrast to halothane or enflurane.

Volatile anesthetics also depress contractile function by inhibiting Na^+-Ca^{2+} exchange and reducing intracellular Ca^{2+} concentration independent of the voltage-dependent Ca^{2+} channel in vitro. This effect may be particularly important in neonatal myocardium, which may be more sensitive to the negative inotropic actions of volatile anesthetics than adult myocardium. The relative contribution of Na^+-Ca^{2+} exchange inhibition to anesthetic-induced depression of myocardial contractility in the intact heart remains controversial, but a role for Na^+-Ca^{2+} exchange inhibition in preconditioning by volatile anesthetics (see "Preconditioning and Postconditioning") was demonstrated.[4] Volatile anesthetics also may exert direct effects on the contractile apparatus and reduce myofilament Ca^{2+} sensitivity. Volatile anesthetics decreased tension development of skinned cardiac myofibrils and reduced myofibrillar ATPase activity. These actions may contribute to declines in actin-myosin cross-bridge kinetics during contraction, but not through a direct interaction with cardiac cross-bridge mechanics.[5] In addition, volatile anesthetics may modestly reduce myofilament Ca^{2+} sensitivity, but this mechanism probably plays a relatively minor role in the negative inotropic effects of these medications at clinically relevant concentrations in vivo.

The cellular mechanisms responsible for volatile anesthetic–induced depression of myocardial contractility in failing myocardium have not been studied in detail. However, the effects of isoflurane and sevoflurane on intracellular Ca^{2+} homeostasis have been studied in a model of RV pressure-overload hypertrophy.[1] These anesthetics produced more pronounced reductions in peak intracellular Ca^{2+} concentration and exaggerated decreases in myofilament Ca^{2+} sensitivity in ventricular myocytes obtained from hypertrophied compared with normal hearts. Whether similar alterations in intracellular Ca^{2+} regulation are produced by volatile anesthetics in other forms of heart failure remains to be determined. Profound abnormalities in Ca^{2+} homeostasis are characteristic features of failing myocardium, and volatile anesthetics may cause further reductions in contractile function by producing additive or synergistic effects on Ca^{2+} metabolism under these conditions.

Diastolic Function

Definitions of heart failure based solely on contractile dysfunction are inadequate because LV function during diastole significantly influences overall cardiac performance. The heart serves dual roles, propelling blood into the high-pressure arterial vasculature during systole and collecting blood from the low-pressure venous circulation during diastole. Thus, heart failure may occur not only from impaired contractility but also from altered LV diastolic function. The timing, rate, and extent of LV filling are determined by several major factors, including the rate and extent of myocardial relaxation, the intrinsic mechanical properties of the LV itself and those imposed by external constraints, and the structure and function of the left atrium, the pulmonary venous circulation, and the mitral valve.[6] Abnormalities in LV diastolic function may be linked to decreases in myocardial contractility, but heart failure also may result from primary diastolic dysfunction in the absence of or before the appearance of alterations in LV systolic function in a variety of pathologic conditions, including ischemic heart disease, pressure-overload or volume-overload hypertrophy, hypertrophic obstructive cardiomyopathy, and restrictive disease processes.

Volatile anesthetics produce dose-related prolongation of LV isovolumic relaxation in vivo. This delay of isovolumic relaxation is associated with declines in early LV filling but is not of sufficient magnitude to affect LV chamber stiffness. Coronary blood flow is elevated during isovolumic relaxation, and delays in relaxation produced by volatile anesthetics contribute to impairment of coronary flow during early diastole. Prolongation of LV relaxation probably occurs as a result of simultaneous depression of myocardial contractility and not because of a direct negative lusitropic effect. In fact, volatile anesthetics modestly enhanced the rate of relaxation of isolated myocardium in vitro. Volatile anesthetics also cause concentration-related decreases in the rate and extent of early LV filling concomitant with negative inotropic effects. Further, volatile anesthetics reduced LV filling during atrial systole.[7] Isoflurane, desflurane, and sevoflurane did not alter invasively derived indices of regional myocardial or chamber stiffness, indicating that LV distensibility was unaffected by these volatile anesthetics.

The effects of isoflurane and halothane on LV diastolic function in a canine model of dilated cardiomyopathy were described. In contrast to the findings in dogs with normal LV function, isoflurane improved several indices of LV relaxation and filling in cardiomyopathic hearts despite producing simultaneous negative inotropic effects. In addition, halothane did not exacerbate the preexisting diastolic dysfunction inherent in this experimental model. The findings with isoflurane and halothane were most likely related to favorable reductions in LV preload produced by these volatile anesthetics and were not due to direct positive lusitropic effects. Isoflurane-induced improvements of LV isovolumic relaxation and filling dynamics may contribute to relative maintenance of cardiac output in the presence of LV dysfunction despite simultaneous reductions in contractility. The findings in cardiomyopathic hearts supported earlier clinical observations reporting that patients with severe ischemic heart disease or congestive heart failure tolerate isoflurane or halothane anesthesia without acute hemodynamic decompensation.

The afterload dependence of LV relaxation is markedly enhanced in failing myocardium. Thus, afterload reduction may not only increase LV systolic performance by decreasing impedance to LV ejection but also may increase the rate of LV relaxation and contribute to improvements in LV diastolic filling and compliance. The effects of isoflurane and halothane on the afterload dependence of LV relaxation were explored in canine hearts before and after the development of rapid LV pacing–induced cardiomyopathy (Fig. 28-3). The afterload dependence of LV relaxation was unaffected by isoflurane and halothane

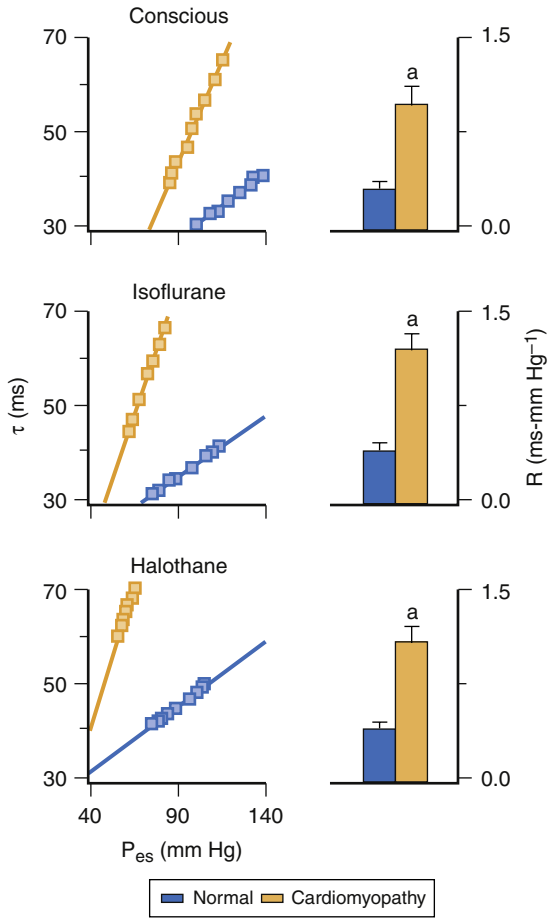


Figure 28-3. Linear relationship between the time constant of isovolumic relaxation (τ) and left ventricular end-systolic pressure (P_{es}) during inferior vena caval occlusion (*left panels*) in a typical dog before *(yellow squares)* and after *(blue squares)* the development of pacing-induced cardiomyopathy in the conscious state and during isoflurane and halothane anesthesia. The histograms on the right illustrate the slope *(R)* of the τ versus P_{es} relationship in the conscious state *(top right panel)* and during isoflurane *(middle right panel)* and halothane *(bottom right panel)* anesthesia before *(yellow bars)* and after *(blue bars)* pacing. *a,* Significantly ($P < .05$) different from normal myocardium. *(Modified from Pagel PS, Hettrick DA, Kersten JR, et al: Isoflurane and halothane do not alter the enhanced afterload sensitivity of left ventricular relaxation in dogs with pacing-induced cardiomyopathy,* Anesthesiology *87:952-962, 1997.)*

anesthesia in this model of dilated cardiomyopathy, further suggesting that these volatile anesthetics do not exert direct actions on LV isovolumic relaxation in failing myocardium independent of negative inotropic effects.

Left Ventricular–Arterial Coupling and Mechanical Efficiency

Optimum transfer of stroke volume from the left ventricle to the arterial circulation requires appropriate matching of these mechanical systems. LV-arterial coupling has most often been described by using a series elastic chamber model of the cardiovascular system. The elastances of the contracting left ventricle (E_{es}) and the arterial vasculature (E_a) are determined from LV end-systolic pressure-volume and end-systolic arterial pressure–stroke volume relationships, respectively. The ratio of E_{es} to E_a defines coupling between the left ventricle and the arterial circulation and provides a useful technique for assessment of the actions of drugs, including volatile anesthetics, on LV-arterial matching in vivo. Analysis of the pressure-volume relationship also creates a framework for the study of LV mechanical efficiency defined by the ratio of stroke work (SW) to pressure-volume area (PVA). LV-arterial coupling is initially maintained during anesthesia because declines in LV afterload may balance simultaneous reductions in myocardial contractility. Low concentrations of isoflurane (1 MAC), but not halothane, maintained E_{es}/E_a, consistent with preservation of mechanical coupling between the LV and arterial circulation. However, isoflurane decreased E_{es}/E_a at 2 MAC, suggesting that the vasodilating effects of this anesthetic were unable to compensate for the relatively greater declines in contractility. Desflurane, sevoflurane, and isoflurane maintained optimum LV-arterial coupling and mechanical efficiency as evaluated by E_{es}/E_a and SW/PVA at low anesthetic concentrations (<0.9 MAC) by producing simultaneous declines in myocardial contractility and LV afterload. However, mechanical matching between the LV and the arterial vasculature and efficiency of total LV energy transfer to external stroke work degenerates at higher anesthetic concentrations, indicating that anesthetic-induced reductions in contractility are not appropriately balanced by declines in afterload. Halothane (<1.0 MAC), but not isoflurane, also reduced the ratio of oscillatory to mean hydraulic power in vivo, indicating that this agent decreases LV mechanical efficiency as well. Detrimental alterations in LV-arterial coupling produced by volatile anesthetics contribute to reductions in overall cardiac performance observed with higher concentrations of the anesthetics in vivo.

Left Ventricular Afterload

A definition of LV afterload that describes the mechanical properties of the arterial vasculature opposing LV ejection is clear, but quantitative evaluation of afterload in vivo remains a difficult problem, the solution of which often confuses this clinically intuitive concept. Systemic vascular resistance, calculated as the ratio of mean arterial pressure to cardiac output, is the most commonly used estimate of LV afterload. However, systemic vascular resistance inadequately describes LV afterload because this index ignores the mechanical characteristics of the blood and arterial walls, fails to account for the frequency-dependent, phasic nature of arterial blood pressure and blood flow, and does not consider the potential effects of arterial wave reflection. As a result, systemic vascular resistance cannot be reliably used to quantify changes in LV afterload produced by drugs, including volatile anesthetics, or cardiovascular disease. Aortic input impedance ($Z_{in}[\omega]$) obtained from power spectral or Fourier series analysis of aortic pressure and blood flow waveforms provides a comprehensive description of LV afterload because $Z_{in}(\omega)$ incorporates arterial viscoelasticity, frequency dependence, and wave reflection. However, analysis of $Z_{in}(\omega)$ is conducted in the frequency domain and not as a function of time, and, as a result, $Z_{in}(\omega)$ is very difficult to apply in a clinical setting. $Z_{in}(\omega)$ is most often interpreted using an electrical three-element Windkessel model of the arterial circulation that describes characteristic aortic impedance (Z_c), total arterial

compliance (C), and total arterial resistance (R). Z_c represents aortic resistance to LV ejection, C is determined primarily by the compliance of the aorta and proximal great vessels and represents the energy storage component of the arterial circulation, and R is the combined resistances of the remaining arterial vasculature. The three-element Windkessel model has been shown to closely approximate $Z_{in}(\omega)$ under a variety of physiologic conditions.

Volatile anesthetics alter $Z_{in}(\omega)$ by affecting the mechanical properties of the arterial vascular tree. Isoflurane produced dose-related decreases in R in a canine model, consistent with isoflurane's effects on systemic vascular resistance, in contrast to the results obtained with halothane. Isoflurane and halothane also increased C and Z_c concomitant with reductions in mean arterial blood pressure. Thus, the major difference between the effects of isoflurane and halothane on LV afterload derived from the Windkessel model of $Z_{in}(\omega)$ was related to R, a property of arteriolar resistance vessels, and not to C or Z_c, the mechanical characteristics of the aorta. In contrast to the findings with sevoflurane, desflurane also reduced R, suggesting that this anesthetic was a more potent peripheral vasodilator, but sevoflurane and desflurane produce similar dose-related decreases in mean arterial pressure in anesthetized patients. Importantly, the inverse relationship between C and mean arterial blood pressure remains unchanged in the presence of a volatile anesthetic, unlike the findings with the arterial vasodilator sodium nitroprusside or the intravenous anesthetic propofol. These data emphasize that volatile anesthetics do not fundamentally affect aortic mechanical characteristics.

Isoflurane and halothane produced alterations in $Z_{in}(\omega)$ in an experimental model of heart failure that are somewhat different from those observed in the normal cardiovascular system. These volatile anesthetics decreased arterial pressure but did not affect C and Z_c in the presence of LV dysfunction. Isoflurane also did not reduce R in the presence of dilated cardiomyopathy, in contrast to the actions of this volatile anesthetic in the presence of normal LV performance. Thus, neither isoflurane nor halothane reduced arterial hydraulic resistance or favorably improved the rectifying properties of the aorta in the presence of a model of cardiomyopathy. The findings suggest that volatile anesthetics do not exert beneficial actions in LV afterload in the presence of heart failure.

Right Ventricular Function

The crescent-shaped right ventricle is composed of embryologically distinct inflow and outflow tracts that differ in their structure and response to autonomic nervous system activity. The sequential contraction of the RV inflow and outflow tracts establishes regional pressure gradients within the right ventricle and accounts for its peristaltic mechanical action during systole. True isovolumic relaxation does not occur in the right ventricle. Instead, ejection of blood from the outflow tract into the pulmonary artery continues after the inflow tract has begun to relax. The effects of volatile anesthetics on the function and contraction sequence of the RV inflow and outflow tracts have been incompletely studied. Halothane produced similar depression of contractile function in RV inflow and outflow tracts when a uniform definition of end-systole and end-diastole was used for both regions of the RV. Halothane also caused dose-related decreases in RV contractility as evaluated by using regional preload recruitable stroke work derived from RV pressure-segment length diagrams in the RV inflow and outflow tracts in the presence and absence of autonomic nervous system reflexes. Importantly, halothane also abolished the normal RV sequential contraction pattern without exerting differential negative inotropic effects in different regions of the RV, suggesting that volatile anesthetics may alter RV contraction dynamics by adversely affecting cardiac autonomic nervous system activity. Isoflurane also exerted qualitatively different effects on RV in contrast to LV afterload and hydraulic power generation that were also partially mediated by the autonomic nervous system. These data suggest that isoflurane produces fundamentally different actions on RV versus LV contraction dynamics in vivo.

Left Atrial Function

The left atrium serves three major roles that exert a profound effect on LV filling and overall cardiovascular performance. The left atrium is a contractile chamber that actively empties immediately before the onset of LV systole and establishes final LV end-diastolic volume. The left atrium is a reservoir that stores pulmonary venous return during LV contraction and isovolumic relaxation after the closure and before the opening of the mitral valve. The left atrium is also a conduit that empties its contents into the left ventricle down a pressure gradient after the mitral valve opens and continues to passively transfer pulmonary venous blood flow during LV diastasis. These contraction, reservoir, and conduit functions of the left atrium mechanically facilitate the transition between the almost continuous flow through the pulmonary venous circulation and the intermittent filling of the left ventricle. Advances in the understanding and clinical significance of left atrial (LA) mechanical function have been reviewed.[7]

The negative inotropic effects of an older volatile anesthetic—halothane—was initially described in atrial myocardium in vitro. Volatile anesthetics also depressed the contractile function of human atrial myocardium.[8] These actions have been attributed to reductions in transsarcolemmal Ca^{2+} influx through voltage-dependent Ca^{2+} channels and decreases in Ca^{2+} availability from the SR, mechanisms that are very similar to those responsible for anesthetic-induced depression of LV myocardium. The negative inotropic effects of volatile anesthetics in the intact left atrium were quantified using pressure-volume analysis.[9] Desflurane, sevoflurane, and isoflurane reduced LA contractility (i.e., E_{es}) by approximately 50% at an end-tidal concentration of 1.2 MAC. The magnitude of this effect in LA myocardium was similar to the degree of LV contractile depression produced by these anesthetics as quantified by LV end-systolic pressure-volume relationships. Desflurane, sevoflurane, and isoflurane also impaired LA and LV relaxation to similar degrees. These data indicate that volatile anesthetics produce equivalent alterations in contractility and relaxation in LA compared with LV myocardium. The magnitude of reductions in the LA inotropic and lusitropic state produced

by volatile anesthetics was also similar in the intact LA, supporting the results obtained in isolated human atrial myocardium.[8]

Desflurane, sevoflurane, and isoflurane altered the passive mechanical behavior of the left atrium.[9] LA reservoir function was maintained during the administration of anesthetic at concentrations less than 1.0 MAC. This preservation of reservoir function contributed to the relative maintenance of LV stroke volume by compensating for decreases in LV filling associated with a reduced contribution of LA contraction. The volatile anesthetics also reduced dynamic LA chamber stiffness, an action that most likely contributed to the preservation of reservoir function because the delays in LA relaxation and declines in LV systolic function that also occurred would be expected to decrease reservoir function. However, LA reservoir function was reduced during the administration of higher concentrations of volatile anesthetics because further impairment of LA relaxation and LV contractility occurred. Decreases in the ratio of LA SW to PVA and the increases in the ratio of LA conduit to total reservoir volume were also produced by desflurane, sevoflurane, and isoflurane. These data indicate that the LA contribution to LV filling becomes less active and more passive during the administration of the volatile anesthetics. Furthermore, desflurane, sevoflurane, and isoflurane decreased the ratio of LA to LV elastance (E_{es}/E_{LV}), consistent with impaired mechanical matching between these chambers. As described earlier, volatile anesthetics have been shown to produce LV diastolic dysfunction by delaying LV isovolumic relaxation and impairing early LV filling in association with direct negative inotropic effects. Thus, the attenuation of transfer of kinetic energy from the left atrium to the left ventricle probably resulted from the combination of LA contractile depression and LV systolic and diastolic dysfunction. Volatile anesthetic–induced abnormalities in LA-LV matching were greater than analogous impairment of LV-arterial coupling evaluated using a similar series elastic chamber model because these anesthetics produced beneficial alterations in the determinants of LV afterload that partially compensate for simultaneous depression of LV myocardial contractility.

The influence of isoflurane on LA function in the presence of preexisting LV dysfunction has also been examined.[10] Isoflurane depressed LA contractility, impaired LA-LV coupling, and reduced the active LA contribution to LV filling in a model of pacing-induced cardiomyopathy, findings that were similar in magnitude to those observed in normal hearts.[9] In contrast to the findings in normal hearts, LA reservoir function was reduced in the presence of LV dysfunction at lower isoflurane concentrations (0.6 and 0.9 MAC).[10] These findings indicated that the ability of the left atrium to act as a reservoir for pulmonary venous return is attenuated during isoflurane anesthesia. Such an isoflurane-induced reduction in LA storage ability suggested that quantity of blood transferred from the left atrium to the left ventricle when the mitral valve opens may be reduced, thereby providing another potential mechanism by which volatile anesthetics reduce early LV filling in the presence of preexisting LV dysfunction.

Systemic Hemodynamics

Volatile anesthetics cause direct negative chronotropic actions in vitro by depressing sinoatrial node activity, but alterations in heart rate in vivo are primarily determined by their interaction with baroreceptor reflexes. Halothane does not appreciably change the heart rate in humans because this anesthetic attenuates baroreceptor reflex responses. In contrast, isoflurane increases heart rate in response to simultaneous decreases in arterial pressure. These findings occur with this volatile anesthetic because baroreceptor reflexes are relatively preserved compared with the older anesthetics. Desflurane also causes dose-related increases in heart rate in humans. Desflurane- and isoflurane-induced tachycardia may be more pronounced in pediatric patients or in the presence of vagolytic drugs and, conversely, may be attenuated in neonates and geriatric patients or by the concomitant administration of opioids. Rapid increases in the inspired desflurane concentration above 1 MAC may be associated with further transient increases in heart rate and arterial pressure resulting from sympathetic nervous system activation. Interestingly, similar increases in heart rate were observed when the inspired isoflurane concentration was rapidly increased. The cardiovascular stimulation induced by rapid increases in desflurane or isoflurane concentration in humans resulted from activation of tracheopulmonary and systemic receptors and was attenuated by pretreatment with β_1-adrenoceptor antagonists, β_2-adrenoceptor agonists, or opioids. In contrast to the findings with isoflurane and desflurane, sevoflurane did not alter heart rate or cause cardiovascular stimulation during rapid increases in anesthetic concentration in humans.

All modern volatile anesthetics cause concentration-related decreases in arterial pressure. The mechanism by which these medications reduce arterial pressure differs among anesthetics. Decreases in arterial blood pressure produced by older volatile anesthetics were attributed to reductions in myocardial contractility and cardiac output, whereas isoflurane, desflurane, and sevoflurane reduce arterial pressure primarily as a result of reductions in LV afterload. Thus, isoflurane, desflurane, and sevoflurane maintain cardiac output because these anesthetics produce less pronounced reductions in myocardial contractility and greater decreases in systemic vascular resistance than halothane or enflurane in humans. Isoflurane and desflurane may preserve autonomic nervous system regulation of the circulation to a greater degree than other volatile anesthetics. The baroreceptor reflex–mediated tachycardia that occurs during isoflurane and desflurane anesthesia maintain cardiac output despite modest decreases in contractility and stroke volume. Declines in arterial pressure produced by volatile anesthetics may be attenuated by surgical stimulation or concomitant administration of nitrous oxide. Volatile anesthetics also cause modest, dose-related increases in right atrial pressure in humans. These effects probably occur as a result of direct negative inotropic actions. The cardiovascular effects of volatile anesthetics are altered by the duration of anesthesia. Increases in myocardial contractility and cardiac output and decreases in LV preload and afterload occur after several hours of constant MAC anesthesia. Recovery

from circulatory depression is greatest during halothane anesthesia but is somewhat less pronounced during prolonged administration of isoflurane and desflurane.

The systemic hemodynamic effects of volatile anesthetics in the presence of LV dysfunction are similar but not identical to those observed in the normal heart. Volatile anesthetics, including isoflurane, modestly increase or do not affect the heart rate in experimental animals with pacing- or doxorubicin-induced dilated cardiomyopathy and patients with coronary artery disease and LV dysfunction. These findings may be attributed to altered baroreceptor reflex activity, β_1-adrenoceptor down-regulation, increases in central sympathetic nervous system activity, and withdrawal of parasympathetic nervous system tone associated with heart failure. Isoflurane and halothane caused pronounced reductions in LV end-diastolic pressure and chamber dimension in cardiomyopathic hearts concomitant with decreases in mean arterial pressure. These findings supported previously observed declines in pulmonary artery pressures during isoflurane anesthesia in patients with coronary artery disease and heart failure and suggested that venodilation represents a major hemodynamic consequence of this volatile anesthetic in experimental and clinical heart failure. In contrast to the findings in normal hearts, isoflurane did not beneficially influence, and the older anesthetic halothane detrimentally affected, the determinants of LV afterload in cardiomyopathic hearts. As a result of these actions and the simultaneous declines in LV preload and myocardial contractility, cardiac output may be more profoundly reduced during isoflurane or halothane anesthesia in the presence of preexisting LV dysfunction.

CARDIAC ELECTROPHYSIOLOGY

Cardiac Conduction

Volatile anesthetics slow the rate of sinoatrial node discharge by direct and indirect effects on sinoatrial node automaticity. These actions may be altered in vivo by vasoactive drugs or autonomic nervous system activity. Older volatile anesthetics and, to a lesser extent, isoflurane shorten cardiac action potential and the effective refractory period duration in normal Purkinje fibers, but these medications prolong His-Purkinje and ventricular conduction times. Halothane, enflurane, and isoflurane also prolong atrioventricular conduction time and refractoriness. When combined with the direct actions of volatile anesthetics on sinoatrial node discharge, these data suggest that volatile anesthetics have the potential to produce bradycardia and atrioventricular conduction abnormalities. However, primary disturbances in atrioventricular conduction leading to second-degree or third-degree atrioventricular block in humans probably do not occur with volatile anesthetics in the absence of conduction disease or the concomitant administration of drugs that directly prolong the atrioventricular conduction time.

Volatile anesthetics may have proarrhythmogenic or antiarrhythmogenic actions against the abnormal cardiac electrophysiologic mechanisms produced by myocardial ischemia or infarction. Halothane, enflurane, and isoflurane have been shown to protect against ventricular fibrillation produced by coronary artery occlusion and reperfusion. Protective effects against ouabain-induced arrhythmias have been demonstrated with halothane. Volatile anesthetics may exert antiarrhythmic effects by opposing subsidiary pacemaker activity in infarcted myocardium. Conversely, halothane and, to a lesser extent, isoflurane may be arrhythmogenic in Purkinje fibers in experimental myocardial infarction by facilitating reentrant activity or increasing temporal dispersion of refractory period recovery. These actions may be related to inhibition of the slow Na^+ current in false tendon fibers and induction of reentry of premature impulses into more refractory Purkinje fibers in the border zone of an ischemic area. Halothane, enflurane, and isoflurane prolong the QT_c interval in humans, suggesting that patients with idiopathic or acquired long QT syndrome may be at greater risk for developing torsade de pointes ventricular tachycardia during anesthesia with these anesthetics.

Epinephrine-Induced Arrhythmias

Halothane and, to a lesser extent, other volatile anesthetics sensitize myocardium to the arrhythmogenic effects of epinephrine. Sensitization is the interaction between volatile anesthetics and catecholamines that leads to reductions in the threshold for both atrial and ventricular arrhythmias. Sequentially escalating doses of epinephrine produce premature ventricular contractions and sustained ventricular tachyarrhythmias during halothane anesthesia. Halothane-epinephrine–induced arrhythmias are attenuated by pretreatment with sodium thiopental, presumably by effects on the atrioventricular node or the upper His bundle. A synergistic interaction between α_1-adrenoreceptors and β-adrenoreceptors has been strongly implicated in the pathogenesis of halothane-epinephrine–induced ventricular arrhythmias. Stimulation of the α_{1A}-adrenoceptor in the His-Purkinje system by epinephrine during halothane anesthesia transiently slows Purkinje fiber conduction. This proarrhythmogenic effect is mediated by phospholipase C and the intracellular second messenger inositol triphosphate. Enhanced conduction in the Purkinje-ventricular muscle junction accompanied by simultaneous α_1-adrenoceptor–mediated depression of Purkinje conduction also plays an important role in halothane-epinephrine–induced arrhythmias. The doses of epinephrine required to produce ventricular arrhythmias during desflurane or sevoflurane anesthesia are similar to, but significantly less than, those observed during administration of isoflurane and halothane. Halothane-catecholamine sensitization also promotes abnormal automaticity of dominant and latent atrial pacemakers. These effects may produce premature ventricular contractions and arrhythmias originating from the His bundle. Intact sinoatrial node function reduces the incidence of epinephrine-induced ventricular escape during halothane anesthesia and is protective against His bundle arrhythmias.

CORONARY CIRCULATION

Coronary Vascular Effects In Vitro

Volatile anesthetics cause direct coronary artery vasodilation in vitro; however, simultaneous reductions in the

determinants of myocardial oxygen consumption (MVo_2), including heart rate, preload, afterload, and inotropic state, produced by these medications cause coronary vasoconstriction in vivo through metabolic autoregulation. Volatile anesthetic–induced alterations in coronary blood flow are also affected by reductions in coronary perfusion pressure. Thus, the combination of direct and indirect actions determines the net effect of volatile anesthetics on coronary vascular tone. Isoflurane and halothane caused vasodilation of isolated coronary arteries. Halothane produced greater coronary artery dilation than did isoflurane at similar MAC concentrations in isolated coronary arteries larger than 2000 μm. In contrast, isoflurane caused vasodilation of predominantly small (<900 μm) canine epicardial coronary arteries. Halothane may produce greater vasodilator effects in large coronary arteries than isoflurane because halothane causes more pronounced suppression of voltage-dependent Ca^{2+} current.

The direct negative inotropic effects of volatile anesthetics caused a reduction in coronary blood flow in isolated, contracting hearts during precise control of loading conditions via flow-metabolism coupling. Thus, a decrease in myocardial O_2 demand was accompanied by an increase in coronary vascular resistance, findings that may be incorrectly interpreted as coronary vasoconstriction. However, examination of the actions of volatile anesthetics on myocardial O_2 extraction and the ratio of myocardial O_2 delivery to MVo_2 revealed that these medications are coronary vasodilators. Halothane and isoflurane decreased myocardial O_2 extraction and increased the ratio of O_2 delivery to consumption in isolated hearts. These findings indicated that volatile anesthetics produce direct coronary vasodilation in isolated hearts because myocardial O_2 delivery exceeds MVo_2 and coronary sinus O_2 tension increases. Halothane, isoflurane, and sevoflurane also caused similar reductions in adenosine-induced coronary flow reserve in tetrodotoxin-arrested, isolated hearts. Because mechanical work was not performed in this preparation, these findings supported the hypothesis that volatile anesthetics cause direct coronary vasodilation of similar magnitude.

Coronary Vascular Effects In Vivo

Halothane has variable effects on coronary blood flow and coronary vascular resistance in vivo that occur concomitant with changes in MVo_2. Decreases in MVo_2 caused declines in coronary blood flow with relative maintenance or modest increases in coronary vascular resistance during halothane anesthesia. Despite the decreases in coronary blood flow, halothane increased coronary sinus O_2 tension and decreased O_2 extraction, indicating that halothane was a relatively weak coronary vasodilator. Like halothane, isoflurane variably altered coronary blood flow in vivo. Isoflurane reduced MVo_2 and simultaneously decreased O_2 extraction, indicating direct coronary vasodilation. Isoflurane also produced mild, transient increases in blood flow independent of changes in MVo_2 and autonomic nervous system activity during inhalation induction. Perfusion of the left anterior descending coronary artery with blood previously equilibrated with isoflurane dramatically increased coronary blood flow, but only mild coronary vasodilation occurred after a period of anesthetic equilibration in a similar experimental model. Isoflurane-induced increases in coronary blood flow were not accompanied by epicardial coronary artery dilation, verifying that isoflurane dilates predominantly small coronary arteries. In contrast, the potent coronary vasodilator adenosine caused considerably greater vasodilation in coronary microvessels than did isoflurane. Isoflurane produced more profound decreases in myocardial O_2 extraction than enflurane, indicating that isoflurane is a more potent coronary vasodilator than its structural isomer.

The influence of desflurane and sevoflurane on coronary blood flow in the intact cardiovascular system has been incompletely examined. Desflurane and isoflurane caused similar increases in the ratio of O_2 delivery to consumption and decreased O_2 extraction, consistent with coronary vasodilation. However, the increases in coronary blood flow produced by desflurane, but not isoflurane, were attenuated by pharmacologic blockade of the autonomic nervous system, suggesting that isoflurane causes relatively greater direct coronary vasodilation in vivo than desflurane. Sevoflurane did not appear to produce any significant degree of coronary vasodilation, in contrast to the findings with isoflurane and desflurane.

Coronary Vasodilator Reserve and Autoregulation

Volatile anesthetics alter coronary vasodilator reserve, defined as the ratio of peak coronary blood flow after brief coronary artery occlusion (reactive hyperemia) to baseline flow. Coronary vasodilator reserve was greater during isoflurane than halothane anesthesia. When considered from this perspective alone, this observation suggested that halothane may be a more potent coronary vasodilator than isoflurane because greater baseline coronary vasodilation should be accompanied by a reduced ability to further increase coronary blood flow in response to a brief ischemic episode. However, halothane also reduced the determinants of MVo_2 to a greater degree than isoflurane in vivo. Peak coronary blood flow during reactive hyperemia and percent flow debt repayment are directly related to the intensity of the ischemic stimulus and the magnitude of O_2 debt accumulated during coronary artery occlusion. Thus, differences in coronary vasodilator reserve produced by isoflurane and halothane may reflect differences in the intensity of ischemia during coronary occlusion and not the relative vasodilator efficacy of these two volatile anesthetics.

Dilation of coronary arteriolar resistance vessels by volatile anesthetics alters pressure autoregulation in the coronary vasculature. Changes in autoregulation produced by vasoactive drugs, including volatile anesthetics, are typically determined by the slope of the pressure-flow curve generated by progressive constriction of a coronary artery. Changes in these pressure-flow curves demonstrated that autoregulation is disrupted during anesthesia in contrast to the conscious state (Fig. 28-4). Isoflurane produced more profound alterations in autoregulation than the older volatile anesthetics, as indicated by greater increases in the slope of the pressure-flow relationship. Coronary perfusion pressure also played a more important role in the determination of coronary blood flow during anesthesia. Volatile anesthetics impaired coronary

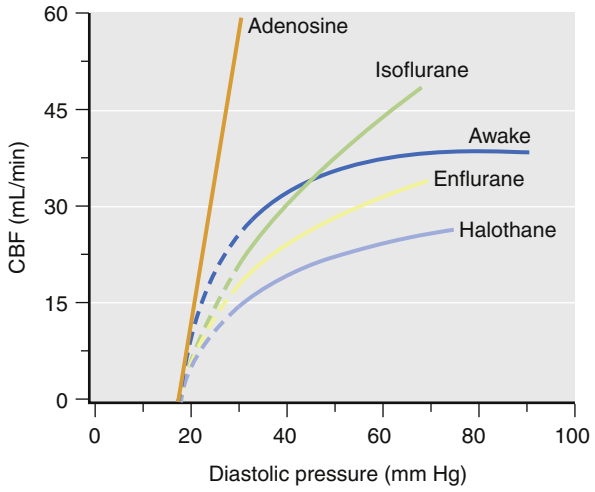


Figure 28-4. A qualitative description of the effects of volatile anesthetics on the coronary blood flow *(CBF)*–diastolic pressure relationship demonstrating the effect of adenosine-induced maximal coronary vasodilation in awake and anesthetized dogs. *Solid lines* are drawn from mean slopes determined by linear regression analysis. *Dashed lines* represent the nonlinear portion of the curve and are estimates. In contrast to the findings obtained in conscious dogs, the anesthetics affect absolute CBF variably but do not increase the slope of the CBF-pressure plots. *(Modified from Hickey RF, Sybert PE, Verrier ED, Cason BA: Effects of halothane, enflurane, and isoflurane on coronary blood flow autoregulation and coronary vascular reserve in the canine heart,* Anesthesiology *68:21-30, 1988.)*

autoregulation to some degree, but these medications did not produce the profound degree of coronary vasodilation and inhibition of autoregulation caused by adenosine or dipyridamole. In contrast to volatile anesthetics, adenosine caused maximal coronary vasodilation and inhibited pressure autoregulation to such a degree that coronary blood flow became directly dependent on coronary perfusion pressure. Thus, volatile anesthetics were shown to be weak coronary vasodilators.

Mechanisms of Coronary Vasodilation

Volatile anesthetics produce direct coronary artery relaxation by affecting intracellular Ca^{2+} regulation at several locations in the vascular smooth muscle cell. Volatile anesthetics inhibit Ca^{2+} influx through voltage-operated and receptor-operated Ca^{2+} channels in coronary vascular smooth muscle. Volatile anesthetics also reduce Ca^{2+} accumulation in, and release by, the coronary vascular smooth muscle SR; inhibit G proteins linked to phospholipase C; and decrease formation of inositol triphosphate. The coronary vasodilating actions of volatile anesthetics are probably not related to the production or release of nitric oxide (NO). Investigations conducted in isolated coronary and aortic vascular preparations and in the intact canine coronary circulation demonstrated that volatile anesthetic–induced coronary vasodilation occurs independent of NO. The weak direct coronary vasodilator effects of isoflurane may be mediated by the vascular endothelium, but, conversely, volatile anesthetics may adversely affect the release or action of NO. The results of one investigation demonstrated that NO-induced formation of cyclic guanylate monophosphate (cGMP) is partially attenuated by halothane, whereas other studies indicated that volatile anesthetics did not affect vasodilation produced by the NO donors sodium nitroprusside and nitroglycerin. Volatile anesthetics may also reduce the stability of NO by generating reactive O_2 species (ROS) while leaving NO release and its action on vascular smooth muscle unaffected. Whether the results of these latter studies conducted in isolated aortic preparations are applicable to the coronary circulation requires further evaluation, but these investigations provided important information about the potential interactions between NO metabolism and volatile anesthetic in the coronary circulation, which may be specifically relevant during myocardial protection (see "Preconditioning and Postconditioning").

Isoflurane and halothane cause coronary vasodilation by activation of adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels. Increases in coronary blood flow in response to halothane and isoflurane were attenuated by the nonselective K_{ATP} channel antagonist glyburide in isolated rat hearts and anesthetized pigs, respectively. Glyburide also partially blocked increases in coronary blood flow during intracoronary administration of volatile anesthetic–equilibrated blood in canine hearts in situ. Isoflurane-induced reductions in coronary vascular resistance were attenuated by a selective adenosine 1 (A_1) receptor antagonist. These data suggest that coronary vasodilation produced by isoflurane may partially occur as a result of stimulation of A_1 receptors coupled to K_{ATP} channels.

Ischemic Myocardium

Isoflurane and halothane decreased subendocardial blood flow and myocardial lactate extraction, produced contractile dysfunction, and caused electrocardiographic changes in the presence of a coronary stenosis concomitant with declines in coronary perfusion pressure. Regional ischemia during isoflurane- or halothane-induced reductions in perfusion pressure was functionally indicated by the appearance of paradoxical systolic lengthening and postsystolic shortening. Contractile dysfunction in the region distal to a critical coronary stenosis was more severe during isoflurane than halothane anesthesia coincident with higher flows in the normal zone and lower flows in the ischemic zone. These findings suggest that coronary vasodilation produced by isoflurane may cause a detrimental redistribution of coronary blood flow away from ischemic myocardium if hypotension is allowed to occur. This phenomenon is known as coronary steal. However, these potentially adverse effects of volatile anesthetics on ischemic myocardium were clearly avoided if coronary perfusion pressure was restored. Subendocardial blood flow in the perfusion bed distal to a critical coronary stenosis was reduced during isoflurane-induced declines in arterial pressure, but treatment of hypotension with phenylephrine restored subendocardial blood flow to values observed before administration of isoflurane. The transmural distribution of coronary blood flow between the subendocardium and subepicardium (endo/epi ratio) decreased during isoflurane anesthesia despite control of arterial pressure. Administration of phenylephrine to maintain arterial pressure increased subepicardial blood

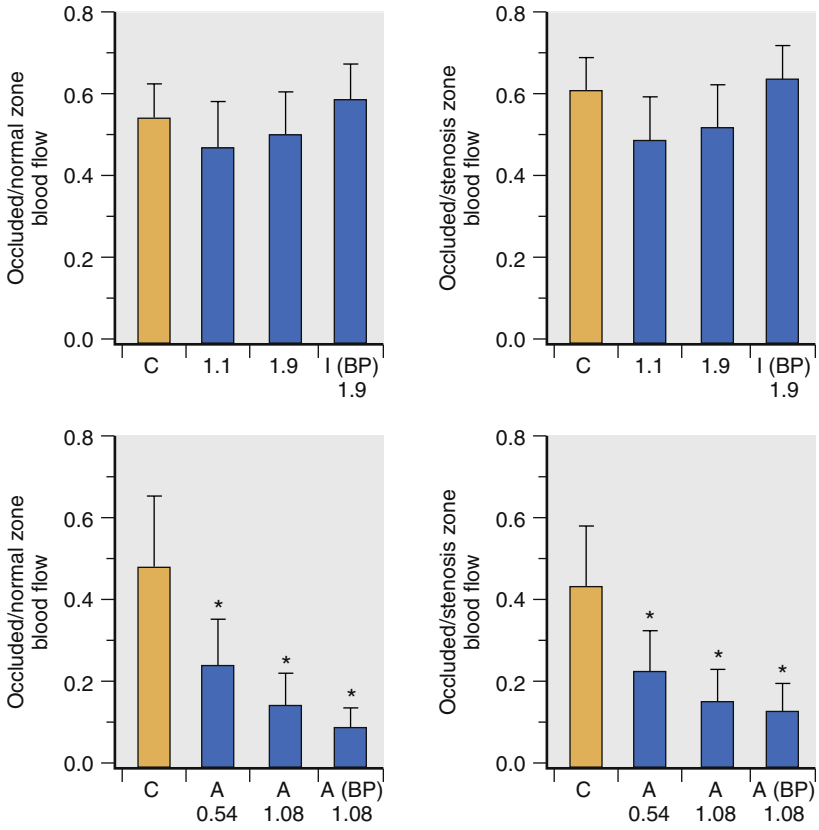


Figure 28-5. Comparison of occluded to normal and occluded to stenotic zone myocardial blood flow in dogs with steal-prone coronary artery anatomy in the conscious state *(C)*, during administration of isofurane at 1.1 and 1.9 minimum alveolar concentration *(I)*, during adenosine *(A)* infusions (0.54 and 1.08 mg/min), and during maintenance of heart rate and arterial pressure at conscious values during the highest doses *(BP)*. Isoflurane does not cause coronary steal, in contrast to significant ($P < .05$) reductions in blood flow to collateral-dependent myocardium produced by adenosine. *(Modified from Hartman JC, Kampine JP, Schmeling WT, Warltier DC: Actions of isoflurane on myocardial perfusion in chronically instrumented dogs with poor, moderate, or well-developed coronary collaterals,* J Cardiothorac Anesth *4:715-725, 1990.)*

flow more than subendocardial flow. This increase in subepicardial perfusion accounted for the decline in the endo/epi ratio in the absence of an absolute reduction in subendocardial flow. Restoration of coronary perfusion pressure to baseline levels during isoflurane anesthesia also increased coronary collateral blood flow and normalized myocardial O_2 tension in the ischemic zone.

Investigations in dogs with steal-prone anatomy (complete occlusion of a coronary artery with collateral flow from an adjacent vessel having a critical stenosis) have repeatedly demonstrated that isoflurane and halothane do not alter collateral-dependent or ischemic zone myocardial blood flow, endocardial-to-epicardial coronary blood flow distribution, or the electrocardiogram ST segment when diastolic arterial pressure is held constant. Coronary collateral perfusion was unchanged during isoflurane or halothane anesthesia in dogs at a mean arterial pressure of 50 mm Hg. Notably, no evidence of coronary steal was found in a chronically instrumented canine model of coronary artery disease with isoflurane, halothane, desflurane, or sevoflurane independent of coronary stenosis severity or coronary collateral development. These findings refuted earlier evidence in dogs with ameroid constrictor–induced augmentation of the coronary collateral circulation suggesting that isoflurane reduces collateral blood flow and causes coronary steal in vivo. The effects of volatile anesthetics are in contrast to those obtained with adenosine, a potent coronary vasodilator that produces coronary steal when arterial pressure is maintained at control levels in models of multivessel coronary artery disease (Fig. 28-5).

Preconditioning and Postconditioning

Acute Preconditioning. In 1986, Murry, Jennings, and Reimer[11] described a phenomenon in which a brief ischemic insult confers protection against a subsequent ischemic episode of similar or greater magnitude. Four brief 5-minute periods of coronary artery occlusion interspersed with 5-minute episodes of reperfusion reduced myocardial infarct size resulting from a subsequent, prolonged 40-minute episode of ischemia and reperfusion. This study demonstrated, for the first time, that the heart not only recognized but also rapidly adapted to stress and, in so doing, became more resistant to additional injury. This process is now known as ischemic preconditioning (IPC) and has been described as a type of "vaccination" that promotes the myocardium's "self-preservation" by altering its phenotype.[12] Since IPC was first reported, the mechanisms, limitations, and potential clinical applicability of this phenomenon have been extensively studied. For example, a recent PubMed search of the phrase "ischemic preconditioning" revealed that nearly 1100 research articles and reviews were published on this subject in 2011 alone.* Many other stimuli, including a wide variety of drugs, NO, ROS, endotoxins, inflammatory cytokines, heat stress, rapid pacing, and intense exercise, also stimulate the development of this prosurvival phenotype and protect the myocardium against ischemic injury without the need for a prior episode of ischemia.[13] Most notably from the perspective of this chapter, volatile anesthetics and the anesthetic gas Xe are among the drugs that

*PubMed: http://www.ncbi.nlm.nih.gov.

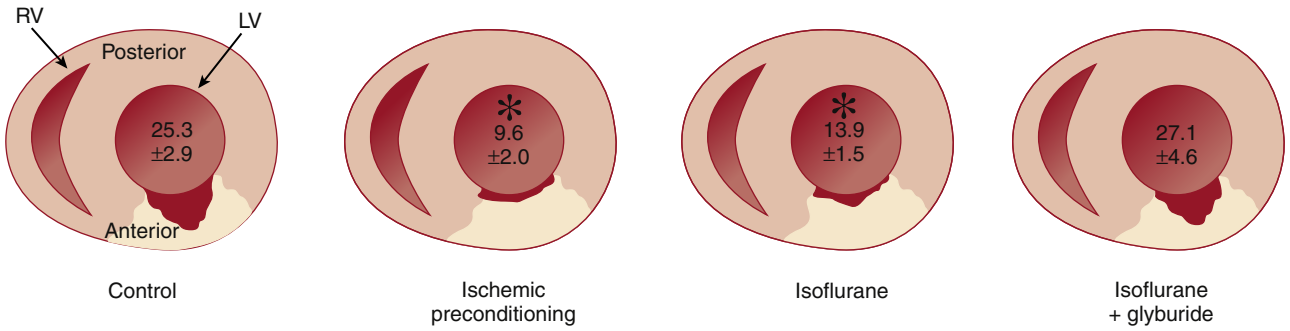


Figure 28-6. Schematic illustration of canine myocardium subjected to a 60-minute coronary artery occlusion and reperfusion and then stained to identify the region of myocardial infarction *(dark red area)* within the area of myocardium at risk for infarction *(light yellow area)*. Isoflurane decreased the extent of myocardial infarction. The protective effect of isoflurane was equivalent to that produced by ischemic preconditioning and was abolished by pretreatment with glyburide. *Significantly ($P < .05$) different from control. *LV,* Left ventricle; *RV,* right ventricle. *(Modified from Kersten JR, Schmeling TJ, Pagel PS, et al: Isoflurane mimics ischemic preconditioning via activation of KATP channels. Reduction of myocardial infarct size with acute memory phase,* Anesthesiology *87:361-370, 1997.)*

have been shown to mimic the beneficial effects of IPC through very similar intracellular mechanisms.[14,15]

It is important to recognize that the previously described controversy about volatile anesthetic–induced coronary vasodilation and coronary steal proved to be a fundamental distraction from other evidence indicating that volatile anesthetics exert *protective* (rather than detrimental) effects during myocardial ischemia and reperfusion injury. For example, the older anesthetic halothane attenuated ST-segment changes caused by brief coronary artery occlusion and decreased ST-segment elevation to a greater extent than propranolol and sodium nitroprusside despite producing similar hemodynamic effects.[16] These data suggested that volatile anesthetics may indeed produce antiischemic effects independent of simultaneous changes in coronary perfusion. Isoflurane and desflurane modestly improved LV diastolic function during acute regional myocardial ischemia. Isoflurane and sevoflurane decreased myocardial injury and improved functional recovery after global ischemia in isolated hearts. Isoflurane and halothane also hastened the functional recovery of postischemic-reperfused ("stunned") myocardium when these anesthetics were administered before brief periods of myocardial ischemia concomitant with preservation of high-energy phosphates. Volatile anesthetics attenuated the effects of ROS on LV pressure development in isolated hearts. Halothane preserved contractile function and ultrastructural integrity during reperfusion after normothermic cardioplegic arrest. Taken as a whole, the results of these studies raised the intriguing possibility that volatile anesthetics were capable of protecting myocardium against ischemia, suspicions that were subsequently confirmed in 1997 when three research groups independently reported that administration of halothane or isoflurane before prolonged coronary artery occlusion and reperfusion preconditioning reduced myocardial infarct size in vivo (Fig. 28-6). This beneficial effect was termed anesthetic preconditioning (APC) and was found to persist despite discontinuation of the volatile anesthetic before coronary artery occlusion, a short-term "memory" phase that mimicked observations during IPC. Indeed, the mechanisms responsible for APC are strikingly similar to those implicated in IPC, although relatively minor differences between these two phenomena were suggested when the results of microarray gene chip analysis were considered.[17]

APC is dose-related in experimental animals[18,19] and occurs independent of changes in systemic hemodynamics or coronary collateral blood flow. Isoflurane and sevoflurane also caused dose-dependent preservation of isolated ventricular myocyte viability after ischemia in vitro.[20] Isoflurane elicited protection when the volatile anesthetic was discontinued 15 or 30 minutes before prolonged coronary artery occlusion and reperfusion in rabbits and dogs, respectively. Dual as opposed to single exposure to sevoflurane further enhanced APC in guinea pigs, indicating that repetitive administration of a volatile anesthetic appears to cause an additional benefit,[21] but myocardial protection resulting from APC was shown to be restricted to ischemia durations between 25 and 40 minutes.[22] The mechanism of sevoflurane-induced myocardial protection was independent of the type of ischemic stimulus (hypoxia versus metabolic inhibition) in isolated cardiac muscle.[23] These results indirectly suggested that APC may be equally effective at preserving myocardial integrity during supply or demand ischemia in patients with coronary artery disease. Advanced age,[24,25] cardiomegaly,[26] obesity,[27] and hyperglycemia[28] in the presence[29] or absence[30] of diabetes mellitus attenuated the efficacy of APC. These experimental observations have potentially important clinical ramifications in elderly patients with diabetes at risk for the development of myocardial ischemia, such as those undergoing cardiac surgery. In contrast, sevoflurane was capable of exerting antiischemic effects in newborn myocardium.[31]

Volatile anesthetics also may produce beneficial effects on blood flow to, and neutrophil interaction with, ischemic myocardium. As discussed previously, volatile anesthetics cause coronary vasodilation by opening K_{ATP} channels or favorably affecting intracellular Ca^{2+} homeostasis in vascular smooth muscle. However, decreases in collateral blood flow after coronary occlusion were less pronounced than declines in flow to normal myocardium in the presence of the older anesthetic halothane. The ratio of myocardial O_2 delivery to consumption was also increased in collateral-dependent myocardium

during halothane anesthesia. Halothane inhibited platelet thrombi formation by increasing platelet cAMP concentration, thereby decreasing cyclical variations in coronary blood flow associated with a critical coronary stenosis. Sevoflurane increased blood flow to collateral-dependent myocardium when arterial pressure was maintained at conscious levels. Ca^{2+}-activated potassium (BK_{Ca}) channels mediated this process. Sevoflurane also improved recovery of coronary vascular reactivity and enhanced NO release in isolated hearts subjected to global ischemia and reperfusion. Volatile anesthetics attenuated adhesion of neutrophils and platelets in the coronary vasculature after ischemia and reperfusion. Isoflurane pretreatment also inhibited cytokine-induced cell death after ischemia-reperfusion injury in vitro.[32] Furthermore, isoflurane and sevoflurane preconditioned against neutrophil-induced contractile dysfunction through activation of adenosine receptors.[33] Finally, neutrophils pretreated with volatile anesthetics lost their ability to cause cardiac dysfunction through decreased superoxide dismutase production and reduced adherence to coronary vascular endothelium.[34] Collectively, the results of these investigations suggested that beneficial actions of volatile anesthetics on coronary perfusion and neutrophil function may, to some degree, be responsible for protection against ischemia-reperfusion injury.

Other mechanisms for APC have been intensively investigated. The beneficial effects of APC may be attributed to a favorable reduction in myocardial O_2 demand (reductions in ischemic burden) concomitant with preservation of energy-dependent vital cellular processes because volatile anesthetics cause direct negative inotropic, lusitropic, and chronotropic effects and are vasodilators. However, the older anesthetic halothane exerted protective effects during complete functional arrest of the heart induced by cardioplegia. Isoflurane, desflurane, and sevoflurane also protected against ischemic injury when administered solely during reperfusion. These data suggest that preferential alterations in myocardial O_2 supply-demand relationships are not solely responsible for the antiischemic actions of volatile anesthetics. Isoflurane and halothane may significantly lower excessive intracellular Ca^{2+} during reperfusion by directly reducing the net transsarcolemmal Ca^{2+} transient resulting from partially inhibited Ca^{2+} channel activity. Indeed, APC accelerated inactivation of cardiac L-type Ca^{2+} channels, an action that may attenuate intracellular Ca^{2+} overload during ischemia-reperfusion injury.[3] In contrast to this relatively nonspecific intracellular Ca^{2+} reduction hypothesis, other data convincingly demonstrated that APC occurs as a consequence of the activation of several redundant endogenous signaling pathways that lead to myocardial protection. To date, K_{ATP} channels, G protein–coupled receptor ligands, isoforms of protein kinase C (PKC), protein tyrosine kinase (PTK), reactive O_2 and nitrogen species, and key components of the prosurvival reperfusion injury salvage kinase (RISK) cascade including the mitochondrial permeability transition pore (mPTP) have all been shown to mediate APC. We will now discuss each of these elements in greater detail. Events within the myocardial cell itself are not solely responsible for APC, because paracrine crosstalk between factors produced by coronary vascular endothelium (e.g., NO, hypoxia-inducible factor) and the myocardium is essential to this process as well.[35]

The K_{ATP} channel plays a central role in IPC and APC. The K_{ATP} channel is a heteromultimeric complex consisting of an inward-rectifying K^+ channel (K_{ir}) and a sulfonylurea receptor (SUR). Pharmacologically distinct K_{ATP} channels have been identified in cardiac sarcolemmal and mitochondrial membranes. It was originally proposed that opening of sarcolemmal K_{ATP} protects ischemic myocardium by shortening action potential duration and preventing intracellular Ca^{2+} overload. However, subsequent studies performed after the discovery of the mitochondrial K_{ATP} indicated that the beneficial actions of K_{ATP} channel opening occurred independent of action potential duration. Nevertheless, IPC was not observed in the absence of the sarcolemmal K_{ir} channel in transgenic mice, suggesting that protection against ischemic injury requires sarcolemmal K_{ATP}. Despite this controversy about the relative role of sarcolemmal K_{ATP} in IPC, it is very clear that mitochondrial K_{ATP} is a primary mediator of IPC, because preservation of mitochondrial bioenergetic function appears to be vital for cellular protection against myocardial ischemia. Mitochondrial K_{ATP} openers maintained intracellular Ca^{2+} homeostasis and inhibited mitochondrial Ca^{2+} overload. These actions enhanced myocyte survival by preventing tissue necrosis and apoptosis (programmed cell death). Necrosis causes generalized cellular destruction and is associated with a profound inflammatory response, whereas apoptosis is a highly regulated, energy-dependent process in which cell membrane architecture is preserved, inflammation is absent, and DNA is selectively cleaved. Mitochondrial K_{ATP} opening inhibited apoptosis in rat ventricular myocytes by attenuating oxidant stress during reperfusion.[36] Alteration of the mitochondrial oxidation-reduction state by mitochondrial K_{ATP} opening may also promote cellular protection.[37] Experiments conducted in isolated cardiac mitochondria indicated that membrane depolarization, matrix swelling, and uncoupling of ATP synthesis occur as a result of increased O_2 consumption are associated with the opening of mitochondrial K_{ATP}. These actions may preserve cellular viability during IPC.[37] Opening of mitochondrial K_{ATP} depolarized the inner mitochondrial membrane and caused a transient swelling of the mitochondrial matrix, resulting from a shift in the ionic balance. Mitochondrial K_{ATP} opening initially reduced ATP production as a result of membrane depolarization, but subsequently stimulated a compensatory increase in respiration that optimizes the efficiency of oxidative phosphorylation, in part by regulating energy-dependent matrix volume. Potassium influx into the mitochondria occurred as a consequence of the balance between K^+ influx through mitochondrial K_{ATP} and K^+ efflux produced by the mitochondrial K^+-H^+ antiporter. The mitochondrial K_{ATP} opener diazoxide promoted K^+ influx and caused matrix alkalinization in isolated myocardium.[38] ATP and the selective mitochondrial K_{ATP} blocker 5-hydroxydecanoate (5-HD) abolished these effects. Thus, a moderate disturbance of mitochondrial homeostasis caused by mitochondrial K_{ATP} opening may promote myocardial tolerance to ischemic stress by altering bioenergetic systems to reduce Ca^{2+} overload, prevent

the activation of necrotic or apoptotic pathways, or attenuate oxidant stress.

It is hypothesized that a "trigger" (e.g., a brief ischemic episode, exposure to a volatile anesthetic) initiates a cascade of signaling events leading to activation of an "end-effector" that is responsible for resistance to injury. Both sarcolemmal K_{ATP} and mitochondrial K_{ATP} have been strongly implicated as important end-effectors in APC. Administration of isoflurane and sevoflurane preserved myocyte viability using a cellular model of ischemia in contrast to cells that were not exposed to a volatile anesthetic.[20] The selective mitochondrial K_{ATP} (5-HD) but not the selective sarcolemmal K_{ATP} antagonist HMR-1098 abolished this protective effect.[20] The nonselective K_{ATP} channel blocker glyburide attenuated the recovery of contractile function produced by isoflurane in stunned myocardium (Fig. 28-7). Isoflurane-induced reductions in canine myocardial infarct size and its ATP-sparing effects also were abolished by glyburide. 5-HD inhibited APC produced by exposure to isoflurane in rats,[18] rabbits,[39] and isolated human myocardium,[40] whereas both HMR-1098 and 5-HD abolished the protective effects of desflurane in dogs.[41] These latter data supported a role for both sarcolemmal K_{ATP} and mitochondrial K_{ATP} in APC. However, HMR-1098 did not affect APC in human atrial myocardium, suggesting that sarcolemmal K_{ATP} was not involved in this process.[42]

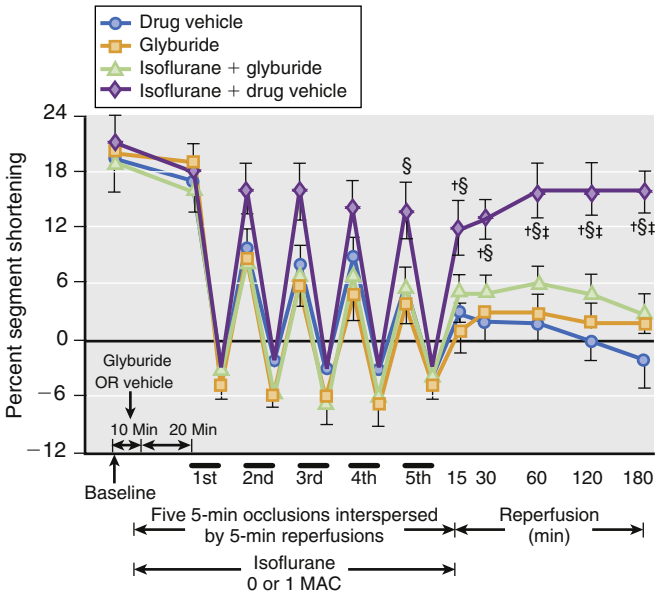


Figure 28-7. Percent segment shortening (%SS) in the intermittently ischemic and reperfused left anterior descending coronary artery (LAD) region. %SS decreases significantly ($P < .05$) from baseline during each 5-minute LAD occlusion and reperfusion in all groups. Significant decreases in %SS during each 5-minute reperfusion and throughout 180 minutes of final reperfusion are observed in dogs pretreated with glyburide, a nonselective K_{ATP} channel antagonist, in the presence or absence of isoflurane. %SS recovers to baseline values after reperfusion in dogs receiving isoflurane alone. †Significantly ($P < .05$) different from dogs pretreated with drug vehicle. ‡Significantly ($P < .05$) different from dogs receiving glyburide and isoflurane. §Significantly ($P < .05$) different from dogs pretreated with glyburide. *MAC,* Minimum alveolar concentration. *(From Kersten JR, Schmeling TJ, Hettrick DA, et al: Mechanism of cardioprotection by isoflurane: role of adenosine triphosphate–regulated potassium [KATP] channels,* Anesthesiology *85:794-807, 1996.)*

Despite some results suggesting that sarcolemmal K_{ATP} opening is not required for APC to occur in vivo, it is clear, based on findings obtained from many carefully conducted in vitro experiments, that volatile anesthetics have profound effects on sarcolemmal K_{ATP}. Isoflurane stimulated outward K^+ current through sarcolemmal K_{ATP} in isolated ventricular myocytes during patch-clamping.[43] Volatile anesthetics also reduced sarcolemmal K_{ATP} sensitivity to inhibition by ATP, thereby increasing the open state probability. Furthermore, volatile anesthetics enhanced sarcolemmal K_{ATP} current by facilitating channel opening after initial activation. The epsilon isoform of PKC (PKC-ε) was shown to prime sarcolemmal K_{ATP} to open in the presence of isoflurane.[44] Facilitation of sarcolemmal K_{ATP} current by isoflurane during reduced intracellular ATP concentrations (such as those observed during ischemia) was also dependent on PKC-dependent signaling.[45] ROS contributed to isoflurane-induced sensitization of sarcolemmal K_{ATP} to the opener pinacidil.[46] Isoflurane also directly opened sarcolemmal K_{ATP} during experimentally induced intracellular acidosis similar to that present during ischemia.[47] Sarcolemmal K_{ATP} acted as an effector during APC against oxidative stress in adult ventricular myocytes.[48] The effects of volatile anesthetics on sarcolemmal K_{ATP} function may persist beyond the duration of administration,[45] suggesting a cellular basis for the early "memory" phase of APC in vivo. Isoflurane APC produced prolonged sensitization of sarcolemmal K_{ATP} to opening through a δ isoform of PKC (PKC-δ–mediated mechanism)[49] or by enhancing PKC induction of sarcolemmal K_{ATP} current.[45] APC caused persistent reductions in the sensitivity of sarcolemmal K_{ATP} to inhibition by ATP and adenosine 5′-diphosphate.[50] The nucleotide-binding domains of the regulatory sulfonylurea receptor SUR2A were also shown to play important roles in isoflurane-induced facilitation of sarcolemmal K_{ATP} activity during moderate intracellular acidosis similar to that encountered during early ischemia.[51] These data provided support for the contention that isoflurane directly interacts with subunits of cardiac sarcolemmal K_{ATP}. Notably, age does not appear to affect the ability of isoflurane to interact with the sarcolemmal K_{ATP} in human atrial myocytes.[52]

It is also clear that volatile anesthetics directly or indirectly open mitochondrial K_{ATP} in vitro. Isoflurane and sevoflurane increased mitochondrial flavoprotein oxidation, an index of mitochondrial K_{ATP} open state, in guinea pig cardiac myocytes; 5-HD inhibited this increase in fluorescence.[53] Isoflurane directly opened mitochondrial K_{ATP} reconstituted in lipid bilayers[54] and protected human embryonic cardiac progenitor cells against oxidative stress through a mitochondrial K_{ATP}-mediated mechanism.[55] Isoflurane-induced increases in mitochondrial flavoprotein fluorescence were not blocked by pretreatment with adenosine, PKC, PTK, or mitogen-activated protein kinase (MAPK) inhibitors, suggesting that isoflurane may directly open mitochondrial K_{ATP}.[56] In contrast, isoflurane and sevoflurane failed to directly enhance flavoprotein fluorescence in rat ventricular myocytes, but these volatile anesthetics did enhance mitochondrial K_{ATP} agonist diazoxide-induced fluorescence.[20] The data suggested that volatile anesthetics indirectly

prime mitochondrial K_{ATP} by acting on other intracellular signaling elements that modulate the open state of the channel. Sarcolemmal K_{ATP} also may be linked to the function of the inner mitochondrial membrane. The ROS generated by mitochondria may act to open sarcolemmal K_{ATP}. An uncoupler of mitochondrial oxidative phosphorylation reversibly activated sarcolemmal current concomitant with nicotinamide adenine dinucleotide oxidation. These and other data led to the contention that crosstalk may occur between sarcolemmal K_{ATP} and mitochondrial K_{ATP} during IPC and pharmacologic preconditioning,[57] but such crosstalk has yet to be specifically demonstrated during APC. To summarize, experimental results collected to date provide somewhat conflicting results about a possible direct action of volatile anesthetics on sarcolemmal K_{ATP} and mitochondrial K_{ATP} open state. Nevertheless, it is clear that volatile anesthetics prime the opening of K_{ATP} channels in both sarcolemmal and mitochondrial membranes. It is also important to recognize that not all myocardial protection during APC is due to K_{ATP} channel opening. For example, APC preserved crucial Ca^{2+} cycling proteins (e.g., Ca^{2+}-release channels, Ca^{2+}-adenosine triphosphatase) independent of sarcolemmal K_{ATP} and mitochondrial K_{ATP} opening, suggesting that protection of major regulators of intracellular Ca^{2+} homeostasis against ischemia-reperfusion injury does not depend entirely on the actions of volatile anesthetics on K_{ATP} channel function.[58]

K_{ATP} channels in vascular smooth muscle cells are also essential regulators of coronary vascular tone when ATP production is reduced. Glyburide attenuated volatile anesthetic–induced coronary vasodilation,[59] indicating an important role for K_{ATP} channels in this process. Thus, it is possible that the beneficial actions of APC may be partially attributed to increases in myocardial O_2 supply mediated by K_{ATP} channel–dependent coronary vasodilation. However, sevoflurane increased coronary collateral blood flow in the presence of glyburide in vivo, indicating that this volatile anesthetic may enhance coronary collateral blood flow independent of K_{ATP} channel opening. Sevoflurane-induced increases in collateral perfusion also occurred as a result of BK_{Ca} and not K_{ATP} channel opening.[60] Thus, it appears highly unlikely that myocardial protection produced by volatile anesthetics is solely related to favorable alterations in coronary vascular tone mediated by K_{ATP} channels.

The sequential activation of several intracellular elements in a transduction pathway may facilitate amplification of the initial signal between other systems. This concept was clearly illustrated by the observation that the direct K_{ATP} channel opener nicorandil enhances the protective effects of isoflurane against ischemia-reperfusion injury. G protein–coupled receptor ligands and their downstream signaling elements converge on the K_{ATP} channel during APC. Pertussis toxin abolished reductions in infarct size produced by isoflurane, indicating that inhibitory guanine (G_i) nucleotide-binding proteins are linked to the signaling pathways that mediate APC.[61] In contrast, pertussis toxin did not prevent the beneficial effects of direct K_{ATP} channel opening produced by nicorandil. These data strongly supported the contention that volatile anesthetics modulate K_{ATP} channel activity through an action similar to that of a second messenger. Halothane-induced protection against infarction was completely abolished by A_1 receptor blockade, and a selective A_1 receptor antagonist also partially attenuated the beneficial effects of isoflurane in stunned myocardium. Isoflurane eliminated increases in interstitial adenosine during repetitive periods of coronary artery occlusion and reperfusion as demonstrated using a myocardial microdialysis technique. These findings suggested that both ATP preservation and a subsequent reduction of adenosine released into the interstitium occur during isoflurane anesthesia. The results were very similar to those obtained during IPC and pharmacologic preconditioning produced by bimakalim. Thus, volatile anesthetics may either directly activate A_1 receptors or indirectly enhance A_1 receptor sensitivity to diminished endogenous adenosine concentrations. The preservation of cardiac myocyte viability during ischemia produced by volatile anesthetics was also sensitive to adenosine receptor and G_i protein–mediated signaling blockade.[20] Moreover, adenosine enhanced APC through both mitochondrial K_{ATP}-dependent and K_{ATP}-independent mechanisms in isolated hearts.[62]

The nonselective opioid antagonist naloxone abolished APC in vivo,[18] indicating the existence of an important link between volatile anesthetics and another family of G_i protein–coupled receptors and their putative ligands. Volatile anesthetics competitively inhibited the ligand-binding site of G_i protein–coupled receptors.[63] Thus, APC appears to be associated with the activation of at least two separate receptor-mediated pathways (A_1 and opioid) that are linked to cell signaling through G_i proteins. Interestingly, the combination of isoflurane and a selective δ_1-opioid receptor agonist further amplified APC.[64] This effect was synergistic and sensitive to inhibition by glyburide. The combined administration of isoflurane and morphine also markedly reduced infarct size in vivo, and this protective effect was abolished by mitochondrial K_{ATP} blocker 5-HD.[18] Thus, combined administration of a volatile anesthetic and an opioid capable of agonist action at the δ_1-opioid receptor subtype may stimulate similar or cooperative signaling cascades that amplify mitochondrial K_{ATP} opening to profoundly augment myocardial protection beyond that produced by either drug alone. A G_s protein–coupled receptor ligand system, the β_1-adrenoceptor and its downstream target protein kinase A, also mediated APC,[65] suggesting that both G_i and G_s may play important roles in APC in vivo.

IPC produces translocation and phosphorylation of several protein kinases, most importantly PKC, involved in the signaling responsible for myocardial protection.[66] The diverse PKC isoform family is a large group of serine-threonine kinases that are distinguished by variable regulatory domains and cofactors. The PKC family displays diverse tissue and species distributions. G protein-coupled receptor ligands, including A_1, δ_1-opioid, and bradykinin, activate PKC during pharmacologic preconditioning. Volatile anesthetics stimulated PKC translocation and activity, possibly by interacting with the regulatory domain of the enzyme. Inhibition of PKC partially attenuated isoflurane-induced augmentation of the functional recovery of stunned myocardium. The beneficial

actions of halothane were entirely blocked by selective inhibition of PKC. Colchicine, a drug that depolymerizes microtubule assemblies, prevented isoflurane-induced reductions in myocardial infarct size. This result suggests that an intact cytoskeleton is essential for translocation of the PKC to occur. Indeed, volatile anesthetic–induced PKC translocation and activation appears to be required to open K_{ATP} channels. For example, a nonselective PKC antagonist abolished sevoflurane-induced increases in mitochondrial K_{ATP} open state and prevented protection against ischemic damage in rat ventricular myocytes.[20] Patch-clamp experiments demonstrated that isoflurane did not facilitate K_{ATP} channel opening in excised membranes but enhanced K_{ATP} channel current in a whole-cell configuration concomitant with PKC stimulation.[67] These observations were supported by findings that both adenosine and PKC enhance K_{ATP} channel open state during IPC. Specific PKC consensus sites were demonstrated on K_{ATP} channels, thereby suggesting a molecular basis for phosphorylation and opening of the channel by this enzyme.[68] Translocation of PKC-δ, but not PKC-ε, was initially shown to play an important role in APC in isolated hearts.[69] Phosphorylation of the serine 643 residue of PKC-δ appeared to mediate transfer of the preconditioning stimulus (exposure to 1.5 MAC isoflurane) to mitochondrial K_{ATP}. Both PKC-δ and PKC-ε translocation were implicated in APC produced by isoflurane in vivo, and opening of mitochondrial K_{ATP} and generation of ROS accompanied this PKC activation.[70] Another study implicated PKC-ε alone during APC produced by sevoflurane,[71] whereas PKC-α and PKC-ε, but not δ, specifically mediated the acute memory phase of sevoflurane APC in isolated guinea pig hearts.[72] PKC-α was shown to be important in sevoflurane-induced myocardial protection via production of ROS in rat myocardium.[73] A role for PKC-ε was also demonstrated in isoflurane APC in rats,[74] but only at lower concentrations (<0.5 MAC) of the volatile anesthetic. Desflurane APC produced time-dependent translocation of PKC-ε through activation of extracellular signal-regulated kinases 1 and 2 (ERK1/2).[75] In contrast, PKC-δ mediated APC by sevoflurane through ROS production independent of mitochondrial K_{ATP}.[76] This process depended on modulation of the reverse mode of the Na^+-Ca^{2+} exchanger.[73] When considered together, the data indicate that at least three different isoforms of PKC (α,ε, and δ) appear to be important mediators of APC, but PKC-ε has been most frequently implicated across various species, including humans.

PKC stimulates PTK and several MAPKs during IPC, and these latter proteins are also involved in APC independent of receptor activation. A nonselective PTK inhibitor and a *Src*-selective inhibitor abolished APC by isoflurane in rats,[70] but nonselective PTK inhibitors did not alter desflurane APC in rabbits.[77] These findings suggest that the role of PTK in APC may be species-dependent. The MAPK proteins are also serine-threonine kinases that are crucial for signal transduction from the cell surface to the nucleus and are key regulators of apoptosis. ERK1/2 is a MAPK (p42/p44) that mediates cell division, proliferation, and survival.[78] ERK1/2 is phosphorylated and activated by the upstream enzyme mitogen-activated protein kinase–extracellular signal-regulated kinase-1 (MEK-1) through occupation of PTK or G protein–coupled receptors. ERK1/2 was previously implicated in IPC and opioid-induced preconditioning. Reductions in infarct size and ERK1/2 phosphorylation produced by administration of desflurane before ischemia and reperfusion were abolished by a selective ERK1/2 inhibitor,[75] providing the first evidence suggesting that ERK1/2 mediates APC. ERK1/2 was also shown to trigger isoflurane APC in rabbits.[79]

ERK1/2-related signaling proteins control the expression of several genes essential for cell survival against ischemic stress, most notably, hypoxia-inducible factor-1α (HIF-1α), an important DNA-binding complex whose activity is influenced by intracellular O_2 tension. Myocardial hypoxia is a potent inducer of HIF-1α expression, and the combination of reduced O_2 tension and activation of ERK1/2 signaling are known to potentiate HIF-1α expression and activity.[80] HIF-1α also up-regulates transcription of vascular endothelial growth factor (VEGF), an important angiogenic protein that plays a central role in coronary collateral development in response to chronic myocardial ischemia.[81] Enhanced expression of both HIF-1α and VEGF occurs during myocardial ischemia.[82] ERK1/2-dependent up-regulation of HIF-1α and VEGF was shown during IPC and hypoxic preconditioning.[83] Isoflurane APC also produced temporal up-regulation of HIF-1α and VEGF protein expression by activating ERK1/2 in rabbit myocardium.[79,84] Another MAPK (p38) that was strongly implicated in IPC also mediated APC in isolated rat hearts.[85] p38 MAPK interacts with the actin cytoskeleton through MAPK-activated protein kinase-2 (MAPKAPK-2) and heat shock protein 27 (Hsp27). APC by isoflurane preconditioning was activated by both MAPKAPK-2 and Hsp27 downstream of PKC and p38 MAPK,[86] providing yet another link between APC and the cytoskeletal-specific translocation of signaling elements involved in myocardial protection. Two other protein kinases that deserve comment have been implicated in APC. 5′AMP-activated protein kinase (5′AMPK) is a regulator of cellular energy status known to mediate IPC. Sevoflurane APC phosphorylated 5′AMPK and its downstream target endothelial NO synthase (eNOS) concomitant with a reduction in myocardial infarct size in isolated rat hearts.[87] A selective 5′AMPK inhibitor abolished these effects. Finally, Pim-1 kinase is a regulator of cardiac myocyte survival during physiologic stress that was also shown to mediate desflurane APC in mice.[88]

Phosphatidylinositiol-3′-kinase (PI3K) has been shown to be responsible for the phosphorylation of a variety of subcellular targets implicated in cell survival, protein synthesis, and metabolism. Activation of this kinase pathway not only reduces cell necrosis but also contributes to the preservation of viable myocardium by inhibiting apoptosis and maintaining mitochondrial integrity.[78] PI3K converts phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3),[89] and PIP3-stimulated phosphorylation of the serine-threonine kinase Akt (protein kinase B) by phosphoinositide-dependent kinase 1 (PDK1) subsequently inhibits the formation of several proapoptotic proteins (e.g., Bad, Bax, caspases). PDK1 is a also a potent activator of other protein kinases,[89] including PKC and PTK, implicated in APC.[90] A role for PI3K signaling in APC by isoflurane was previously

demonstrated.[91] A selective inhibitor of PI3K abolished reductions in infarct size and also blocked phosphorylation of the downstream enzyme target Akt produced by administration of isoflurane before prolonged coronary occlusion and reperfusion in rabbits. Isoflurane preconditioning increased Akt phosphorylation and expression of the antiapoptotic B-cell lymphoma-2 (Bcl-2) protein and reduced expression of the apoptotic protein Bax in rabbits concomitant with decreases in infarct size and the number of apoptotic myocytes.[92] Selective PI3K antagonists abolished these actions, indicating that PI3K-induced modulation of proapoptotic and antiapoptotic protein balance plays a role in APC produced by isoflurane. Activation of Akt by isoflurane protected rat atrial and ventricular myocytes against apoptosis produced by exposure to hypoxia, hydrogen peroxide, or activated neutrophils concomitant with increased expression of Bcl-2.[93] The antiapoptotic effect of APC was also mediated by phosphorylation of the apoptosis repressor with caspase recruitment domain through a PI3K-dependent mechanism.[94] These results emphasize that APC-induced myocardial protection is at least partially caused by attenuation of apoptosis, similar to the findings during IPC.[95,96]

Opening of the nonspecific channel mPTP within the inner mitochondrial membrane abolishes the mitochondrial membrane potential ($\Delta\Psi_m$). This effect has several consequences that rapidly produce cell death, including inhibition of oxidative phosphorylation, unimpeded swelling of the mitochondria, and stimulation of the release or activation of several apoptotic proteins, including cytochrome c. The mPTP contains three major components: a voltage-dependent anion channel, the enzyme adenine nucleotide translocase, and cyclophilin D, a *cis/trans* peptidyl-propyl isomerase located within the mitochondrial matrix.[97] Cyclophilin D was proposed to bind to adenine nucleotide translocase in the presence of pathologic elevations in intramitochondrial Ca^{2+} concentration. The combination of these moieties prevented nucleotide transport and caused the channel of the mPTP to form. However, knockout mouse models suggest that neither the voltage-dependent anion channel nor adenine nucleotide translocase is truly essential for mPTP formation,[98,99] whereas cyclophilin D appears to be a critical component of mPTP.[100,101] Interestingly, the commonly used immunosuppressant medication cyclosporin A (CsA) binds cyclophilin D and prevents mPTP formation.[102,103] The combined effects of intramitochondrial Ca^{2+} overload, ROS, and inorganic phosphates accumulated during ischemia because of exhausted adenine nucleotide metabolism cause mPTP to open; these abnormalities are especially apparent during early reperfusion. In contrast, adenine nucleotides, magnesium and other matrix cations, and acidosis inhibit mPTP formation.

mPTP opening has been strongly implicated as an end-effector in myocardial necrosis and apoptosis resulting from ischemia-reperfusion injury.[104] Activation of the PI3K-Akt and ERK1/2 pathways exert regulatory control over the transition state of mPTP.[97] Administration of CsA reduced myocardial infarct size to a similar magnitude as IPC.[105] A radiolabeled 2-deoxyglucose entrapment technique was used to show that IPC directly inhibits mPTP opening during reperfusion.[106] Similarly, delayed mPTP opening in response to Ca^{2+} overload was observed in isolated cardiac mitochondria that had been previously exposed to IPC, CsA, or a cyclophilin D–selective CsA derivative. Delayed IPC regulated mPTP formation through enhanced expression of Bcl-2.[107] Pharmacologic preconditioning by mitochondrial K_{ATP} opener diazoxide[105] or volatile anesthetics[108] also involves mPTP inhibition. For example, APC improved the resistance of mPTP to Ca^{2+}-induced opening in rabbit mitochondria[108] through a PKC-ε–dependent mechanism.[109] CsA restored sevoflurane APC in the presence of hyperglycemia through inhibition of mPTP formation.[110] Isoflurane selectively phosphorylated the Tyr194 residue of the adenine nucleotide translocase component of mPTP, thereby favorably regulating mitochondrial bioenergetics.[111] APC was shown to modestly reduce $\Delta\Psi_m$ in stressed cardiac myocytes, thereby attenuating excess ROS production, delaying mPTP opening, and increasing cell survival through a decrease in mitochondrial Ca^{2+} uptake.[112,113] Notably, reductions in $\Delta\Psi_m$ were sustained after discontinuation of the volatile anesthetic, and this mitochondrial uncoupling may represent another contributing factor to the memory phase of APC.[112] Isoflurane also modified the response of the voltage-dependent anion channel to O-linked-β-N-acetylglucosamine; this modification inhibited mPTP opening and conferred protection against ischemia-reperfusion injury in cardiac myocytes.[114]

Reperfusion of ischemic myocardium is associated with the release of large quantities of ROS that disrupt intracellular Ca^{2+} homeostasis, cause lipid peroxidation, damage cell membranes, depress contractility, and produce reversible and irreversible tissue injury.[115] Volatile anesthetics, including isoflurane, have been shown to attenuate the toxic effects of O_2-derived free radicals on LV pressure development in isolated hearts. Isoflurane decreased hydroxyl radical generation in the ischemic rat heart, and halothane had a similar effect in dogs. The protective effects of sevoflurane were associated with reduced dityrosine formation, an indirect marker of reactive O_2 and N_2 species.[116] These results supported the contention that volatile anesthetics may reduce the release of deleterious quantities of ROS immediately after coronary artery occlusion and reperfusion. In contrast to these data implicating a pathologic role of large amounts of ROS, a variety of preconditioning stimuli, including brief ischemia, mitochondrial K_{ATP} openers, opioids, and volatile anesthetics, stimulate a small burst of ROS that initiates downstream signaling events and produces protection from subsequent ischemic injury. Pretreatment with low concentrations of ROS mimicked the beneficial effects of IPC, and free radical scavengers administered before or during ischemia attenuated this myocardial protection. These findings suggest that IPC is mediated by small quantities of ROS released during the preconditioning stimulus. Scavengers of superoxide anion and inhibition of nitric oxide synthase (NOS) abolished the beneficial actions of sevoflurane against ischemic damage.[116] Thus, small amounts of superoxide anion may act to trigger APC, whereas NO may scavenge larger quantities of superoxide anion on reperfusion to reduce injury. NO also mediated desflurane APC.[117] Scavengers of ROS attenuated isoflurane-induced

reductions in myocardial infarct size[118] and inhibited the salutary actions of mitochondrial K_{ATP} opening.[119] Isoflurane also directly increased superoxide anion formation in vivo independent of ischemia and reperfusion.[120] Thus, volatile anesthetics may be capable of producing small amounts of superoxide anion that exert protective effects during subsequent ischemia. These data provide compelling evidence that small quantities of ROS play a critical role in APC.

ROS are important regulatory mediators in many signaling processes that protect the cardiac myocyte from oxidative stress. ROS-induced PKC or MAPK activation[121] was implicated in IPC and pharmacologic preconditioning. ROS also activated G proteins that play a role in IPC.[122] Similarly, evidence connects ROS production by volatile agents to activation of protein kinases implicated in the signaling pathways responsible for APC. For example, administration of ROS scavengers inhibited isoflurane-induced PKC translocation and blocked APC.[70] Scavenging of ROS blocked desflurane and sevoflurane APC and attenuated mitochondrial uncoupling associated with these volatile anesthetics in vitro.[123] A cause-and-effect relationship between mitochondrial K_{ATP} opening and ROS production during IPC and APC also has been suggested. Mitochondrial K_{ATP} opening triggered IPC by generating ROS.[119] Similarly, agonist-induced mitochondrial K_{ATP} opening produced ROS that appeared to be essential for activation of MAPK and the subsequent beneficial effects against ischemic injury. For example, diazoxide enhanced cell viability after hypoxia and reoxygenation in vitro concomitant with ROS generation.[124] These beneficial actions were attenuated in cells pretreated with 5-HD or ROS scavengers, suggesting that myocardial protection produced by mitochondrial K_{ATP} agonists occurred as a result of triggering by ROS. The G protein–coupled receptor ligand morphine increased the fluorescence intensity of a hydrogen peroxide–sensitive probe. These effects were blocked by 5-HD,[125] thereby establishing a link between opioid-induced mitochondrial K_{ATP} opening and ROS production. Diazoxide and cromakalim (another mitochondrial K_{ATP} opener) directly caused release of superoxide anion from complex I of the electron transport chain in isolated rat heart mitochondria concomitant with matrix alkalinization.[126] In contrast to these studies indicating that mitochondrial K_{ATP} opening stimulates ROS production, other investigations suggest that ROS modulate mitochondrial K_{ATP} conformational state. For example, xanthine oxidase–derived superoxide anion opened mitochondrial K_{ATP} obtained from bovine ventricular myocardium and reconstituted in lipid bilayers.[127] ROS also triggered mitochondrial K_{ATP} opening, and this event subsequently generated additional quantities of both ROS and NO.[128] Thus, whether mitochondrial K_{ATP} opening acts as a trigger or effector of IPC or pharmacologic preconditioning may be unresolved to some degree, but it is clear that a complementary interaction between ROS and mitochondrial K_{ATP} exists during these preconditioning phenomena.

Whether mitochondrial K_{ATP} opening by volatile anesthetics precedes or follows ROS production during APC also remains in question. Pretreatment with 5-HD or a ROS scavenger before exposure to isoflurane abolished ROS production in rabbits,[39] whereas administration of 5-HD after discontinuation of isoflurane, but before prolonged coronary artery occlusion, only partially attenuated this effect. These results suggest that mitochondrial K_{ATP} opening acted as a trigger for APC by producing ROS. In direct contrast, sevoflurane-induced ROS production was not inhibited by 5-HD pretreatment in isolated guinea pig hearts.[129] Despite these equivocal findings, it is quite evident that ROS play a major role in APC in conjunction with mitochondrial K_{ATP}. Interestingly, a quantity of ROS that exceeds a critical threshold produced opening of the mPTP and a subsequent burst of ROS[130] that stimulated further release of additional ROS from other mitochondria.[131] This ROS-induced ROS release contributed to mPTP-dependent cell death in rat myocytes after ischemia-reperfusion.[132] Thus, volatile agents and other mitochondrial K_{ATP} openers may prevent opening of the mPTP in an oxidant-sensitive fashion to produce myocardial protection.

ROS derived from the mitochondrial electron transport chain have been shown to mediate IPC and pharmacologic preconditioning.[125] Whereas a complex III antagonist inhibited hypoxia-induced and acetylcholine-induced ROS production and abolished preconditioning in vitro, volatile anesthetics blocked complexes I and III in isolated cardiac mitochondria.[133,134] Sevoflurane-induced complex I inhibition was attenuated by a superoxide dismutase mimetic[134] and an NOS inhibitor,[135] suggesting that ROS, NO, or their reaction products may inhibit mitochondrial respiration through a positive feedback mechanism to amplify free radical signals for triggering APC. Conversely, a complex III inhibitor abolished isoflurane-mediated myocardial protection and ROS generation,[136] suggesting that complex III may be the source of ROS during APC. These data suggested the possibility that volatile anesthetics may modulate multiple sites of the electron transport chain either directly or indirectly through a ROS-mediated feedback mechanism. Indeed, the results of a recent study demonstrated that isoflurane produces ROS at complexes I and III of the electron transport chain by attenuating complex I activity in isolated mitochondria.[137] The actions of volatile anesthetics on complex I appear to reduce unfavorable reverse electron flow within the electron transport chain, thereby attenuating excessive ROS release in the mitochondria during reperfusion. Interestingly, it is this volatile anesthetic–induced inhibition of complex I activity that may be responsible for the production of small quantities of mitochondrial ROS known to trigger myocardial protection during APC.[138,139] A selective inhibitor of cyclooxygenase-2 (COX-2), but not COX-1 or COX-3, blocked isoflurane-induced myocardial protection in rabbits,[140] indicating that modulation of arachidonic acid metabolism by volatile anesthetics may represent another potential source of ROS during APC. Thus, at least three sources of O_2- or N_2-derived free radicals (mitochondrial electron transport, NOS, and COX-2) have been identified to date, but whether other enzymes (e.g., nicotinamide adenine dinucleotide oxidase, lipoxygenase, xanthine oxidase, cytochrome P450 [CYP450]) known to generate reactive intermediates are involved in APC remains to be determined.

The precise identity of the ROS involved in APC has not been defined. Superoxide anion directly opened mitochondrial K_{ATP} in vitro,[127] implicating this reactive intermediate in IPC. Isoflurane directly enhanced ethidium fluorescence in rabbit myocardium independent of subsequent ischemia and reperfusion.[39,120] Dihydroethidium is oxidized by intracellular superoxide anion to produce ethidium that subsequently binds to DNA, further amplifying its fluorescence. These data strongly suggested that superoxide anion mediates APC. Sevoflurane also generated superoxide anion before ischemia and reperfusion in isolated hearts.[129] In contrast to these findings implicating superoxide anion as a putative mediator of preconditioning, other results suggested that hydrogen peroxide may play a role in this phenomenon. Hydrogen peroxide stimulated PTK-dependent activation of phospholipase C in mouse embryonic fibroblasts, rendering these cells resistant to stress. Hydrogen peroxide has been shown to activate G_i and G_o proteins[122] and other protein kinases involved in reducing cellular injury. Hydrogen peroxide may be converted to more reactive species that subsequently modify cysteine residues specific to G proteins and selectively activate these proteins.[141] Thus, hydrogen peroxide or its immediate free radical metabolites represent another group of ROS known to affect many of the signaling molecules implicated in APC. Dismutation of superoxide anion leads to production of hydrogen peroxide, hydroxyl radical, and peroxynitrite, and these radicals may differentially alter channel or protein kinase activity. For example, superoxide anion and hydrogen peroxide enhanced, but peroxynitrite reduced, BK_{Ca} channel function.[1,42] Whether APC also produces other ROS that activate mitochondrial K_{ATP} or inhibit formation or intermediates such as peroxynitrite that adversely affect these channels has yet to be defined.

Heat shock proteins (Hsps) are constitutively expressed proteins that play essential roles in cell survival.[143] Hsps usually act as molecular chaperones by easing proper folding of other proteins, assisting in protein complex assembly, maintaining the structural integrity of steroid receptors, and helping move proteins throughout the cell. Hsps are also synthesized in response to tissue injury (most notably, hyperthermia, but also ischemia, inflammation, infection, and toxin exposure); this response stimulates restoration of denatured proteins and facilitates metabolism of proteins that are damaged beyond repair.[144,145] Importantly, induction of Hsps transiently protects the cell from damage by subsequent, potentially lethal insults of similar or differing origin or intensity, in part by inhibiting apoptosis.[144] Hsps are classified on the basis of molecular weight. The 70-kDa species (Hsp70) is one of the most thoroughly studied[146] because it has been strongly implicated in myocardial protection against reversible and irreversible ischemic injury.[147] For example, brief global or regional myocardial ischemia caused induction of Hsp70, and this increase in Hsp70 protected myocardium against subsequent ischemic damage. Repetitive, brief episodes of coronary artery occlusion conducted 24 hours before prolonged ischemia and reperfusion increased intracellular Hsp70 concentration concomitant with reductions in myocardial infarct size. Gene transfection of Hsp70 limited infarct size and preserved LV function after prolonged ischemia.[148] Furthermore, the viability of mitochondria isolated from transgenic mice overexpressing Hsp70 was enhanced after hypoxia-reoxygenation in contrast to those obtained from wild-type mice.[149] Hsp70 induction may also protect myocardium in patients undergoing coronary artery surgery.[150]

The role of Hsps in APC has been recently explored. Pharmacologic induction of Hsp70 24 hours before ischemia and reperfusion was shown to lower the threshold of sevoflurane APC in vivo.[151] Whereas 0.5 MAC sevoflurane failed to provide myocardial protection alone, administration of this concentration of the volatile anesthetic to rabbits pretreated with an Hsp70 inducer reduced myocardial infarct size to a significantly greater extent than observed with the Hsp70 inducer alone. Similar to the results of other studies in which exposure to volatile anesthetics did not affect Hsp70 expression,[152,153] sevoflurane APC failed to alter Hsp70 expression in the presence or absence of the Hsp70 inducer. Thus, it is unlikely that administration of a volatile anesthetic shortly before a prolonged ischemic episode produces myocardial protection by acutely enhancing Hsp70 transcription and translation. Like volatile anesthetics, Hsp70 exerts protective effects against ischemic injury through PKC activation and mitochondrial K_{ATP} opening. Thus, Hsp70 may enhance the beneficial actions of APC by simultaneously affecting these and other signaling components. In contrast to the findings with Hsp70, isoflurane APC was associated with up-regulation of lower molecular weight Hsps,[152] and an important role for Hsp27 (a key mediator of cytoskeletal integrity) has been reported during APC.[86] These results suggest that smaller Hsps also may be directly involved in APC. Finally, Hsp90-induced activation of eNOS colocalization has been shown to mediate APC through a tetrahydrobiopterin-dependent mechanism.[30,154]

Delayed Preconditioning. Seven years after the publication of Murry's original paper,[11] two groups[155,156] independently reported that two discrete chronologic phases of IPC exist: an acute or "early" phase of intense protection against infarction that occurs shortly after the inciting ischemic event and persists for a brief duration (1 to 2 hours) and a delayed, "late," or "second window" phase distinguished by a more protracted period (3 to 4 days) of myocardial protection against both reversible and irreversible injury that develops 6 to 12 hours after the initial ischemic event (Fig. 28-8). The mechanisms responsible for acute and delayed IPC are quite different. Whereas posttranslational modification of existing proteins mediates the early phase (thereby explaining its rapid onset and relatively short duration of protection), synthesis of new proteins is required for the late phase (explaining its delayed onset and more prolonged duration of protection).[12] An initial episode of ischemia is postulated to cause the release of small quantities of several molecules, including NO, ROS, and adenosine, that then stimulate a cascade of events culminating in delayed IPC. These molecules interact with endogenous signaling proteins, including PKC-ε, ERK1/2, the Src and Lck PTK isoforms, and the Janus-activated kinases 1 and 2, which then converge on and activate transcription factors, including nuclear factor κB(NF-κB), HIF-1α, and STAT1 and STAT3.

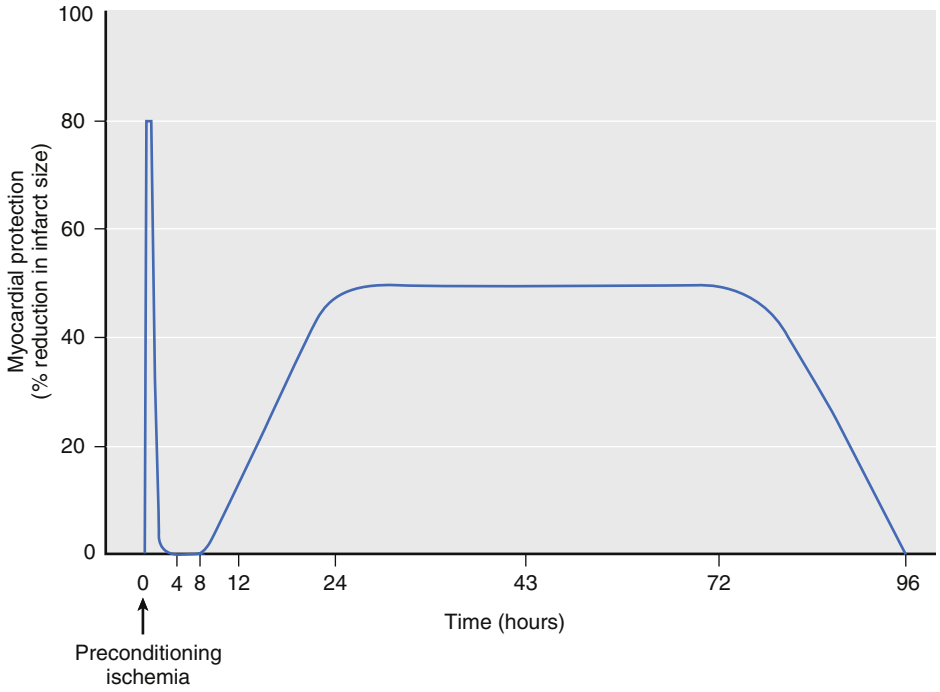


Figure 28-8. Schematic illustration depicting the two phases of ischemic preconditioning. Myocardial protection (expressed as a percentage reduction in infarct size) is plotted against time. After the application of a preconditioning (PC) stimulus (e.g., brief ischemia), rapid development of a preconditioned state occurs that confers powerful protection (80% to 90% reduction in infarct size in some models). However, the protection is transient, lasting only 1 to 2 hours. This is followed by the slower development of a late phase of protection, which becomes fully manifested at 24 hours after the PC stimulus and persists for approximately 72 hours. Thus, the duration of the late phase is 30- to 50-fold longer than that of the early phase of PC. *(From Bolli R: Preconditioning: a paradigm shift in the biology of myocardial ischemia,* Am J Physiol Heart Circ Physiol *292:H19-H27, 2007.)*

These transcription factors are usually quiescent, but cause genetic up-regulation and synthesis of iNOS, COX-2, heme oxygenase-1 (HO-1), and several antioxidants (e.g., extracellular superoxide dismutase, aldose reductase) in response to physiologic stress, including ischemia. These newly synthesized enzymes and their products, including NO, prostacyclin (prostaglandin I_2; PGI_2), and prostaglandin E_2, are considered to be the "mediators" of myocardial protection by inhibiting intracellular Ca^{2+} overload, producing antioxidant effects, opening mitochondrial or sarcolemmal K_{ATP} channels, blocking β-adrenoreceptor signaling, and preserving the closed conformation of mPTP.[157] Thus, a brief ischemic episode initiates several parallel and redundant events, including nuclear translocation of key transcription factors, stimulation of new protein synthesis, and release of new molecules, that produce late IPC through their actions on mitochondria and ion channels.

Remote administration of a volatile anesthetic before prolonged ischemia and reperfusion produces protective effects that are very similar to those of delayed IPC.[158] This "delayed" APC was first demonstrated in rabbit hearts subjected to a 2-hour exposure to 1% isoflurane 24 hours before prolonged ischemia and reperfusion.[159] Reduced myocardial infarct size and enhanced LV-developed pressure recovery were observed after this remote administration of isoflurane. The magnitude of the delayed protective effect was similar to that observed during acute APC. Pretreatment with 5-HD abolished the beneficial effects of remote isoflurane exposure in this model, whereas HMR-1098 attenuated them. As discussed earlier, both mitochondrial K_{ATP} and sarcolemmal K_{ATP} appear to be essential for acute APC,[90] and their involvement in delayed APC is certainly not surprising. Nevertheless, the relative roles of these channels in delayed APC have yet to be definitively established. Crosstalk between mitochondrial and sarcolemmal K_{ATP} may explain the apparent dual roles of these channels in acute and delayed IPC,[160] and a similar interaction between these channels may occur during delayed APC. Despite this minor controversy, it is abundantly clear that mitochondrial K_{ATP} plays a central role in late APC. For example, brief (5 minutes) administration of 1.0 MAC sevoflurane caused a further reduction in myocardial infarct size after delayed IPC in open-chest rabbits.[161] Pretreatment with 5-HD inhibited this beneficial effect of sevoflurane, indicating that the volatile anesthetic conferred additional protection in the presence of late IPC through mitochondrial K_{ATP} opening. Roles for BK_{Ca} channels and mPTP in desflurane-induced delayed APC have been recently suggested.[162]

In contrast to the aforementioned findings,[159] another group simultaneously reported that a 6-hour exposure to 1.0 MAC isoflurane did not cause late APC in a canine model, whereas acute APC was associated with substantial myocardial protection independent of alterations in systemic hemodynamics or coronary collateral blood flow.[163] The findings of this investigation appeared to contradict those of the previously discussed study[159] and suggested that isoflurane may not cause delayed APC in dogs or, alternatively, that late APC may be a species-specific phenomenon. Late IPC and other forms of delayed pharmacologic preconditioning were observed in several canine models,[164] but dogs may be less susceptible to preconditioning phenomena depending on the intensity of the initial stimulus, the temporal delay before the prolonged ischemic event, and the total duration of ischemia and reperfusion.[165] Thus, the duration and dose of isoflurane pretreatment may be crucial factors in determining whether delayed APC occurs. Interestingly, a 2-hour exposure to 1% isoflurane (≈0.5 MAC) caused robust myocardial protection in isolated rabbit hearts, but a 2-hour exposure to 2% isoflurane did not.

These results suggest that prolonged exposure to a greater isoflurane concentration did not cause a delayed APC effect, as suggested by the findings in dogs. Exposure to 1.0 MAC sevoflurane for 60 minutes followed by global ischemia and reperfusion 24 or 48 hours later decreased myocardial necrosis, enhanced recovery of LV function, maintained intracellular ATP concentrations, preserved intracellular pH, and maintained Na^+ and Ca^{2+} homeostasis in isolated rat hearts in contrast to those not receiving sevoflurane pretreatment.[166] Notably, the salutary actions of sevoflurane were greater 48 hours in contrast to 24 hours after exposure and may be functionally relevant for as long as 2 weeks after ischemia-reperfusion injury.[167] Similar findings were also described with isoflurane[168] and desflurane.[169] When considered collectively, these results suggest that a latency period greater than 24 hours after volatile anesthetic exposure may be needed to establish maximal protective effects in some experimental models of late APC. Considering these data, it is certainly plausible that myocardial protection may have been observed in dogs as well, if prolonged ischemia and reperfusion had occurred more than 24 hours after isoflurane pretreatment.

All investigations conducted after the single negative study in dogs demonstrated that remote administration of a volatile anesthetic before prolonged ischemia and reperfusion does, indeed, produce delayed protection against ischemic injury. For example, a 2-hour pretreatment with 1.0 MAC isoflurane conducted 24 hours before a 30-minute coronary artery occlusion and 3 hours of reperfusion reduced myocardial infarct size by 43% in rabbits.[170] The magnitude of the decreases in myocardial necrosis during late compared with early APC was nearly identical.[39] Additional studies from the same laboratory subsequently confirmed these findings.[171,172] Isoflurane (0.75 and 1.5 MAC) also caused dose-related and time-related delayed myocardial protection in rats.[168] Interestingly, pretreatment of rats with 1.5 MAC isoflurane 48 hours before ischemia and reperfusion caused the largest reductions in myocardial infarct size and the greatest recovery of LV-developed pressure during reperfusion.[168] Similar findings with desflurane- or sevoflurane-delayed APC were also reported.[169,173] Administration of a unique intravenous emulsified sevoflurane preparation did not produce sedation or respiratory depression in conscious rabbits, but the drug significantly reduced infarct size in contrast to lipid vehicle alone.[174] Notably, the plasma concentration of sevoflurane required for this beneficial effect was equivalent to a MAC value of approximately 0.17, suggesting that only a small amount of the volatile anesthetic may be required to produce delayed myocardial protection.

The mechanisms responsible for late APC in experimental animals have been incompletely studied to date. Bolli[175] proposed that iNOS plays a central role in delayed IPC because ischemia stimulates iNOS synthesis. The NO that is subsequently produced from newly synthesized iNOS may then exert protective effects. Bolli and associates[176] demonstrated that NO derived from eNOS triggers delayed IPC, whereas NO produced by iNOS mediates it. In contrast, targeted deletion of the *iNOS* gene also abolished late IPC. NO derived from neuronal NOS (nNOS; a regulator of catecholamine release expressed in sympathetic nerve terminals) may also mediate the late phase of IPC concomitant with activation of COX-2.[177] Similar to the findings with late IPC, NO has been shown to play an essential role in delayed APC, but the precise source of NO (iNOS, eNOS, or nNOS) is controversial. iNOS was shown to be important during late APC in rats exposed to 0.75 or 1.5 MAC isoflurane for 2 hours before global ischemia and reperfusion was conducted 24 to 96 hours later.[168] Remote exposure to isoflurane reduced infarct size, improved LV functional recovery, and enhanced iNOS expression and activity in a dose-dependent and time-dependent manner (Fig. 28-9). The maximal effects were observed 48 hours after exposure to 1.5 MAC isoflurane, and a selective iNOS inhibitor abolished myocardial protection in this model. These data strongly implicated iNOS as the primary enzymatic source for NO that mediates delayed APC.

Another group confirmed these findings in rats exposed to 1.0 MAC isoflurane for 1 hour followed by coronary artery occlusion and reperfusion 24 hours later.[178] Reduced infarct size, enhanced iNOS protein expression, increased myocardial NO content, translocation of the p65 subunit of NF-κB from the cytosol to the nucleus, and augmented NF-κB DNA-binding activity were observed. Pretreatment with a nonselective NOS antagonist or a NF-κB inhibitor before administration of isoflurane or a selective iNOS inhibitor immediately before ischemia abolished the protective effects of isoflurane. NF-κB is an important transcription factor involved in inflammatory response to oxidative stress that is activated during ischemia-reperfusion injury. The inhibitory protein IκB sequesters the major subunits of NF-κB (p50 and p65) within the myoplasm, thereby maintaining the transcription factor in its quiescent state under resting conditions. However, ischemia causes phosphorylation and degradation of IκB, allowing the p50 and p65 NF-κB subunits to associate and translocate to the nucleus, bind to promoter gene regions, and initiate transcription. IPC has been shown to reduce NF-kB activation and blunt production of inflammatory cytokines, chemokines, and adhesion molecules, thereby contributing to a reduction in myocardial necrosis. Sevoflurane preconditioning also attenuated NF-κB activation and reduced NF-κB–dependent inflammatory gene expression in isolated and intact hearts.[179,180] A reduction in apoptosis appears to play an important role in this NF-κB–mediated effect during APC.[181] Activation of NF-κB also was previously shown to play a central role in delayed IPC. The *iNOS* gene is a common target of NF-κB; binding of the transcription factor to the promoter-enhancer region of the gene initiates the protein's transcription. Thus, remote administration of isoflurane before prolonged ischemia and reperfusion generates NO and sequentially triggers activation of NF-κB, expression of iNOS, and synthesis of additional NO that the mediates delayed APC in rats. Administration of a NF-κB inhibitor before isoflurane exposure blocked the increases in NF-κB protein and its DNA-binding activity and inhibited myocardial protection. Thus, early activation of NF-κB may be an obligate step during delayed APC.

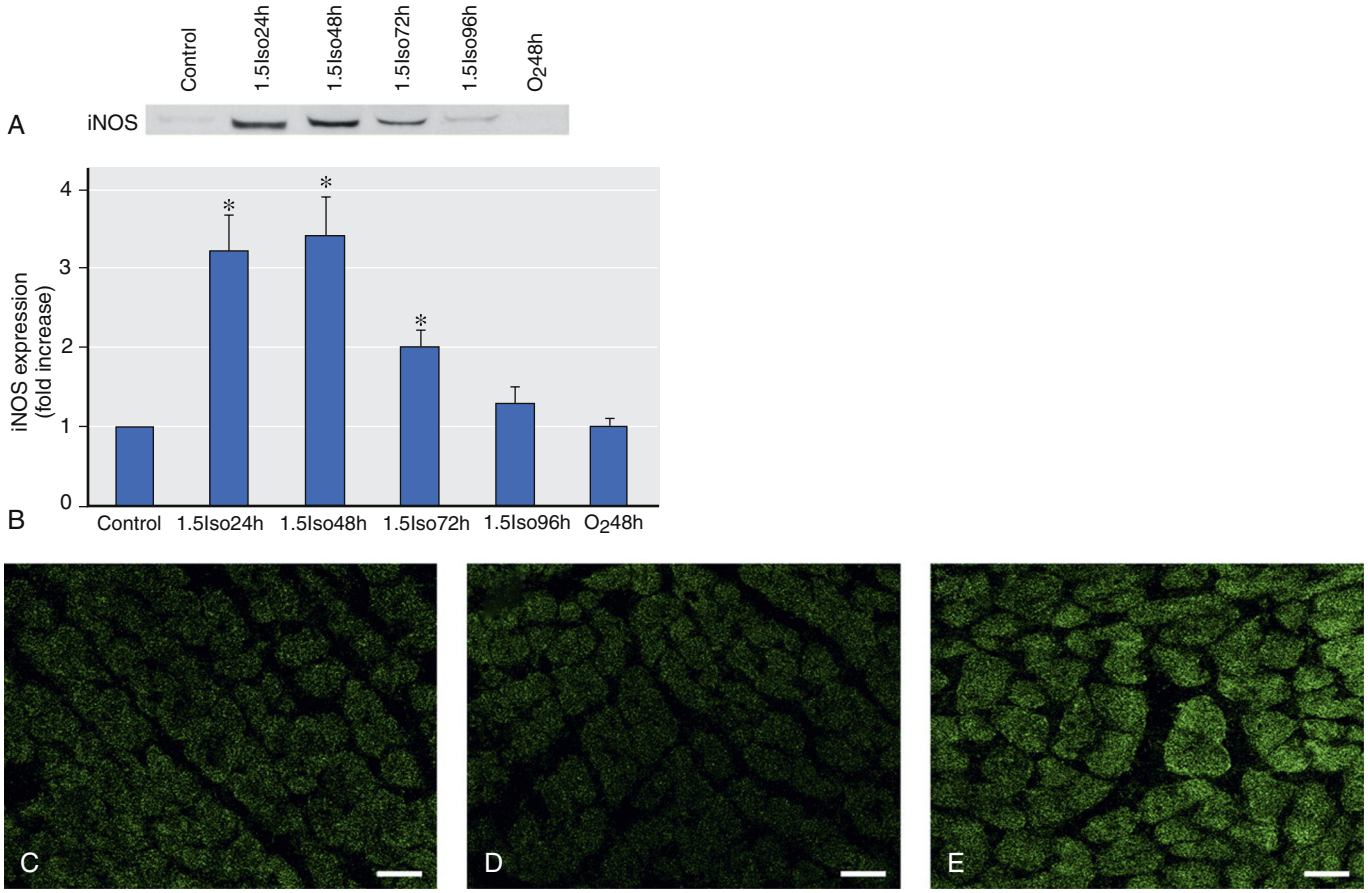


Figure 28-9. A, Immunoblot study of inducible nitric oxide synthase (iNOS) protein expression. **B,** Quantitative analysis of iNOS protein expression. Values are mean ± standard error of the mean of five experiments. $^{*}P < .05$ compared with control. **C** to **E,** Immunohistochemical analysis of iNOS protein expression in control heart (**C**), 48 hours after oxygen inhalation (**D**), and 48 hours after inhalation of 1.5 minimum alveolar concentration isoflurane (**E**). Scale bars, 20 μm. *(From Wakeno-Takahashi M, Otani H, Nakao S, et al: Isoflurane induces second window of preconditioning through upregulation of inducible nitric oxide synthase in rat heart,* Am J Physiol Heart Circ Physiol *289:H2585-H2591, 2005.)*

eNOS has been implicated in late APC. Administration of a nonselective NOS inhibitor, but not selective iNOS or nNOS inhibitors, either before remote isoflurane exposure or before coronary occlusion and reperfusion abolished reductions in infarct size produced by the volatile anesthetic concomitant with increases in eNOS but not iNOS transcription and translation in rabbits.[171] Delayed APC also was observed in only adult male, but not female, rabbits.[172] Estrogen enhances eNOS expression, favorably modulates endothelial NO release, and stimulates eNOS binding to Hsp90. The latter effect substantially increases eNOS activity. The interaction between eNOS and Hsp90 was demonstrated during acute APC.[154] Thus, the gender specificity of delayed APC is most likely related to the actions of estrogen on eNOS expression and activity in female rabbits that confers protection against infarction independent of any subsequent remote administration of a volatile anesthetic.[172] These findings also indirectly suggest that the protective effect of NO may be derived from eNOS and not iNOS.

The experimental disagreement about the specific source of NO (iNOS versus eNOS) that mediates delayed APC merits further discussion. NO derived from eNOS followed by iNOS acts as a trigger and mediator, respectively, of delayed IPC, but whether late pharmacologic preconditioning occurs through such a clearly defined sequence of events is not so clearly defined. For example, eNOS may "masquerade" as iNOS during delayed preconditioning produced by adenosine.[182] Selective iNOS inhibition before prolonged ischemia and reperfusion also did not alter the protective effects of remote administration of adenosine,[183] in contrast to the findings during the late IPC. Activation of eNOS by Akt also mediated late preconditioning produced by the mitochondrial K_{ATP} channel opener diazoxide.[184] A central role for the PI3K cascade was previously demonstrated in volatile anesthetic preconditioning and postconditioning.[185] Thus, the apparent predominance of eNOS-derived compared with iNOS-derived NO during delayed APC described in rabbits may be related, at least in part, to the relative importance of PI3K signaling in this species. Marked differences are seen in the type and distribution of NOS in rabbits, compared with rats and mice, which may profoundly influence cellular response to ischemia.[186] Thus, the animal species in which the studies were performed may partially account for observed variations in the source of NO. Nevertheless, experimental evidence accumulated to date indicates that NO is a critical trigger and mediator of delayed APC regardless of whether the source of the molecule is iNOS or eNOS.

ROS have been shown to trigger late APC.[187] A 2-hour exposure to 0.8% isoflurane conferred protection against

infarction and improved recovery of LV-developed pressure after global ischemia and reperfusion were imposed 24 hours later.[187] Administration of a superoxide anion scavenger 15 minutes before isoflurane abolished this myocardial protection. Isoflurane increased dihydroethidium fluorescence consistent with ROS production; pretreatment with a mitochondrial electron transport chain inhibitor attenuated this effect. These results suggested that the oxidative phosphorylation cascade was the source of ROS involved in delayed APC, similar to findings during acute APC and IPC.[96] For example, ROS triggered IPC through mitochondrial K_{ATP} opening in rabbits.[119] Isoflurane directly generated ROS independent of subsequent ischemia and reperfusion, and these reactive intermediates mediated myocardial protection[118] by opening mitochondrial K_{ATP}[39] and activating the electron transport chain.[136] However, it remains unclear whether ROS produced during remote volatile anesthetic exposure stimulates transcription and translation of new protein mediators of delayed APC similar to the triggering actions of NO. This mechanism appears likely because ROS activated PKC-ε and caused nuclear translocation of NF-κB during late IPC.[188]

COX-2 and its metabolites are also important mediators of delayed IPC.[12,189] COX-2 transcription and translation occurred 24 hours after an ischemic stimulus concomitant with elevated myocardial PGE_2 and 6-keto-$PGF_{1\alpha}$ (a PGI_2 metabolite) concentrations. Prostacyclin also was shown to produce salutary effects by stimulating mitochondrial K_{ATP} to open and abrogating oxidative damage as a result.[190] In contrast, pretreatment with a COX-2 inhibitor (e.g., celecoxib) abolished prostaglandin production and blocked reductions in myocardial necrosis during late IPC.[191] Coinduction of iNOS and COX-2 occurred after brief ischemia. This observation suggested that interaction of these two proteins is crucial for cellular defense in response to ischemia.[192] In fact, iNOS was shown to be an upstream regulator that modulates COX-2 expression and activity during delayed IPC.[192,193] COX-2 and its metabolites also mediated late pharmacologic preconditioning through the δ-opioid receptor.[194] COX-2 was shown to mediate acute and delayed APC in vivo.[140,170] Administration of celecoxib 2.5 hours before prolonged ischemia and reperfusion, but not immediately before isoflurane, abolished the myocardial protection associated with remote exposure to the volatile anesthetic. These data suggested that COX-2 functions as a mediator of delayed APC. Isoflurane exposure also produced time-dependent increases of COX-2 protein expression and activity that were associated with a decline in myocardial necrosis.[195] Thus, it is clear that COX-2 and metabolites are key mediators of late APC.

Arachidonic acid released during ischemia may be metabolized by lipoxygenases and CYP450 isoforms to generate other products that elicit myocardial protection.[196] For example, enhanced activity of 12-lipoxygenase and formation of 12-hydroxyeicosatetraenoic acid (12-HETE) mediated the cardioprotective effects of acute IPC through a PKC-dependent mechanism. Remote exposure to a selective δ-opioid receptor agonist reduced infarct size and enhanced 12-lipoxygenase transcription and translation, and these effects were attenuated by administration of a 12-lipoxygenase inhibitor.[197] A selective 12-lipoxygenase inhibitor also abolished the protective effect of exposure to 1.0 MAC isoflurane 24 hours before ischemia and reperfusion, suggesting that 12-lipoxygenase may be a mediator of delayed APC.[196] 12-Lipoxygenase expression was significantly increased 12 and 24 hours after isoflurane exposure; new protein was localized to the intercalated disk regions adjoining cardiac myocytes (Fig. 28-10). Conversely, another 12-lipoxygenase inhibitor did not appear to affect late APC.[195] Differences in experimental design and animal species may be responsible for these apparently contradictory results. However, it is clear that delayed APC up-regulates expression and enhances activity of a key enzyme (12-lipoxygenase) that metabolizes arachidonic acid to hydroxyeicosatetraenoic acid products that have been implicated in other forms of acute and delayed preconditioning.[197] Another arachidonic acid metabolite [15-deoxy-(12,14)-prostaglandin J_2] known to activate peroxisome-proliferator–activated receptor γ also was shown to mediate desflurane-induced delayed APC in rabbits.[198]

Lipid rafts are small regions (0.01 to 0.2 μm) suspended in membrane phospholipid bilayers that contain high concentrations of glycosphingolipids, sterols, and scaffolding proteins (termed caveolins).[199-201] Lipid rafts exist in myocardial sarcolemmal and mitochondrial membranes and are dynamic regulators of signal transduction molecules.[202] Caveolae are a type of lipid raft consisting of small membrane invaginations (0.06 to 0.08 μm) that bind and regulate the activity of G protein–coupled receptors, ERK1/2, and eNOS. Caveolins are required for caveolae to form. Thus, expression of caveolins directly influences the number of caveolae available for signal modulation.[203] Of the three known caveolin isoforms, caveolin-3 is the predominant type in myocardium.[202] Overexpression of caveolin-3 was shown to mimic IPC through a PI3K-mediated mechanism.[204] Similarly, caveolin-3 also played an obligate role in acute APC.[202,205] Remote exposure to isoflurane reduced infarct size in wild-type and caveolin-1, but not caveolin-3, knockout mice concomitant with up-regulation of caveolin-3 protein and microscopic evidence of caveolae.[206] These data implicated caveolin-3 in delayed APC. Late APC also increased expression of glucose transporter-4 (GLUT-4; the major transporter for cellular uptake of glucose), and this protein was colocalized with caveolin-3.[206] GLUT-4 translocation from the intracellular compartment to caveolae may facilitate substrate delivery for anaerobic glycolysis during ischemia. GLUT-4 was also previously shown to mediate acute and delayed IPC through its interaction with caveolin-3 and signaling proteins, including PKC, Akt, and eNOS.[207,208] Furthermore, NO and arachidonic acid metabolites caused transcription, translation, and translocation of GLUT-4.[209,210] Taken together, these results suggest the GLUT-4 is another important component of the delayed APC cascade that acts with caveolin-3 downstream from NOS and COX-2.[206]

The previously discussed studies of the efficacy of, and mechanisms responsible for, delayed APC were conducted in healthy adult experimental animals. Whether late APC occurs in models of cardiac disease has not been extensively studied. The effects of postinfarction remodeling

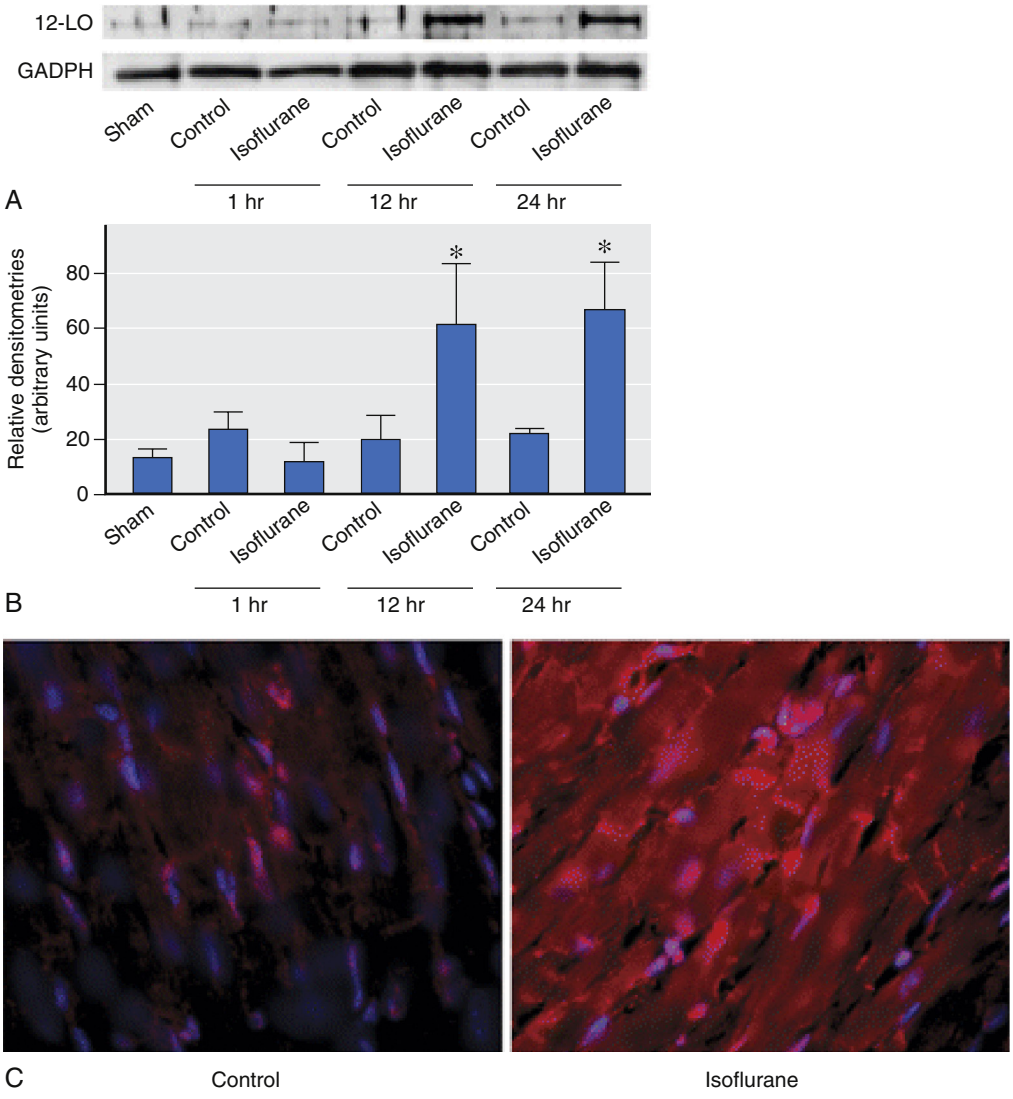


Figure 28-10. A, Immunoblots illustrating total 12-lipoxygenase (12-LO) after different recovery periods. Glyceraldehyde-3-phosphate dehydrogenase (GADPH) immunoblot was performed to determine equal protein loading. **B,** Densitometry of immunoblots in **A** was normalized to GADPH values. Isoflurane significantly increased 12-lipoxygenase protein at 12 and 24 hours of recovery (n = 3 in each group). Data are shown as mean ± standard error of the mean. $^{*}P < .05$ versus control. **C,** Immunofluorescence analysis of the expression and localization of 12-lipoxygenase (*red pixels*) in mouse ventricular tissue after 24-hour recovery period after isoflurane. *(From Tsutsumi YM, Patel HH, Huang D, Roth DM: Role of 12-lipoxygenase in volatile anesthetic-induced delayed preconditioning in mice,* Am J Physiol Heart Circ Physiol *291:H979-H983, 2006.)*

on delayed APC were examined in isolated Langendorff-perfused hearts 6 weeks after coronary artery ligation.[195] This model is characterized by compensatory LV hypertrophy and chamber dilatation. Late APC was observed in postinfarction remodeled hearts, and the magnitude of this protection was similar to that observed in normal hearts, but several differences were noted. The duration of late APC was limited to only 24 hours after brief isoflurane exposure in postinfarction remodeled hearts in contrast to at least 48 hours in normal hearts. Differences in COX-2 protein expression and activity between remodeled and normal hearts paralleled these findings. COX-2 inhibitors abolished delayed APC in both normal and postinfarction remodeled hearts. Thus, COX-2 plays an obligate role in late APC in both models. However, postinfarction remodeled hearts showed more pronounced sensitivity to COX-2 inhibitors compared with normal hearts (Fig. 28-11). Remote exposure to isoflurane also caused nuclear translocation of the COX-2–related transcription factor HIF-1α in normal and infarct remodeled hearts. However, nuclear translocation of another important transcription factor, cyclic adenosine monophosphate (cAMP) response element–binding protein (CREB), did not occur in remodeled hearts. In addition, increased expression of the CREB antagonist inducible cAMP early repressor (ICER) was observed.[195,211] It appears likely that the lack of isoflurane-induced CREB translocation after infarction may have contributed to the narrower window of delayed APC observed in this model.[195]

Two studies of isolated leukocytes provided evidence that remote exposure to a volatile anesthetic may abrogate the proinflammatory responses of white blood cells to ischemia-reperfusion injury.[212,213] Leukocytes were collected from healthy volunteers during and after a 60-minute inhalation of sevoflurane (0.5% to 1.0%) and analyzed using gene microarray analysis and flow cytometry. Sevoflurane produced dramatic alterations in gene expression, including several key transcripts implicated in late IPC. The temporal changes in gene expression resulting from sevoflurane exposure bore many similarities to those observed during late IPC.[214] Sevoflurane also reduced neutrophil surface receptor L-selectin (CD62L) expression and partially inhibited neutrophil responsiveness to inflammatory stimuli 24 and 48 hours after exposure to the anesthetic.

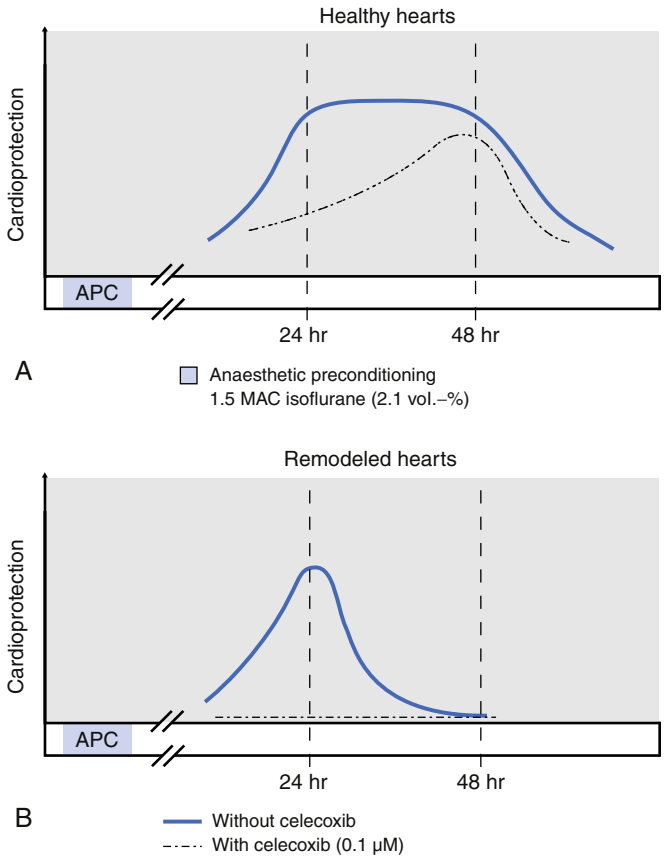


Figure 28-11. The second window of preconditioning is different in healthy and remodeled hearts. The panels show the second window of preconditioning at 24 and 48 hours after isoflurane exposure (anesthetic preconditioning *[APC]*) in healthy (**A**) and infarct remodeled (**B**) hearts in the absence *(solid line)* and presence *(dashed line)* of celecoxib (0.1 μM). *(From Feng J, Lucchinetti E, Fischer G, et al: Cardiac remodelling hinders activation of cyclooxygenase-2, diminishing protection by delayed pharmacological preconditioning: role of HIF1 alpha and CREB,* Cardiovasc Res *78:98-107, 2008.)*

BOX 28-1 ***Factors Implicated in Delayed Anesthetic Preconditioning***

TRIGGERS
NO (iNOS)
ROS (mitoK$_{ATP}$ or sarcK$_{ATP}$ opening; electron transport chain)

TRANSCRIPTION FACTORS
NF-κB
HIF-1α
CREB

NEW PROTEINS
iNOS
eNOS (?)
COX-2
12-Lipoxygenase
Caveolin-3
GLUT-4

MEDIATORS
NO
PGE_2/PGI_2
12-HETE
Caveolae
Neutrophil inhibition

From Pagel PS, Hudetz JA: Delayed cardioprotection by inhaled anesthetics. J Cardiothorac Vasc Anesth *25:1125-1140, 2011.*

COX-2, Cyclooxygenase-2; *CREB,* cyclic adenosine monophosphate response element–binding protein; *eNOS,* endothelial nitric oxide synthase; *12-HETE,* 12-hydroxyeicosatetraenoic acid; *HIF-1α,* hypoxia-inducible factor 1α; *iNOS,* inducible nitric oxide synthase; *mitoK$_{ATP}$* and *sarcK$_{ATP}$,* mitochondrial and sarcolemmal adenosine triphosphate–sensitive potassium channel, respectively; *NF-κB,* nuclear factor κB; *NO,* nitric oxide; *GLUT-4,* glucose transporter-4; *PGE$_2$* and *PGI$_2$,* prostaglandin E_2 and I_2, respectively;.

Adhesion molecules, including L-selectin and β_2-integrin, are responsible for neutrophil binding to injured vascular endothelium. These molecules stimulate leukocyte extravasation into the extravascular space during early reperfusion.[115] Specifically, L-selectin facilitates tethering and rolling of neutrophils on the endothelial surface that initiates the extravasation process.[215] Thus, inhibition of L-selectin expression by remote exposure to sevoflurane may contribute to a persistent reduction in neutrophil binding and activity during late APC, thereby abrogating the adverse effects of these leukocytes during reperfusion injury. Another research group examined superoxide anion production in response to receptor-dependent and receptor-independent stimuli in canine neutrophils after remote administration of 1.0 MAC isoflurane.[213] Exposure to isoflurane caused an immediate and sustained 50% reduction in superoxide anion formation in neutrophils activated by platelet activating factor or formyl-methionyl-leucyl-phenylalanine. Late APC was also recently shown to be associated with improved antioxidant defenses as indicated by enhanced activity of superoxide dismutase, catalase, and glutathione peroxidase and reductase.[216] When considered collectively, the results of these studies suggest that inhibition of neutrophil activity and enhanced antioxidant capability may be important contributors to delayed APC.

In summary, evidence accumulated over the past 10 years indicates remote exposure to a volatile anesthetic before prolonged ischemia and reperfusion protects against myocardial infarction. The mechanisms responsible for this late APC are very similar to those reported for delayed IPC. NO and ROS trigger synthesis of several proteins, including iNOS, COX-2, 12-lipoxygenase, caveolin-3, and GLUT-4, through the concerted actions of NF-κB, HIF-1α, and CREB. These newly synthesized proteins produce several crucial mediators of late APC, including NO, PGE_2 and I_2, and 12-HETE; contribute to caveolae formation; and enhance anaerobic metabolism (Box 28-1). In addition, late APC also inhibits the activity of neutrophils during early reperfusion through modulation of adhesion molecule expression. Sustained myocardial and mitochondrial proteome remodeling involving proteins related to ATP generation and transport has been demonstrated during late APC, suggesting that favorable alterations in bioenergetic balance may represent yet another mechanism by which delayed APC produces antiischemic effects.[217,218] Notably, the beneficial actions of delayed APC are attenuated in a model of chronic myocardial infarction, but whether other cardiac diseases adversely affect this process is currently unknown. Volatile anesthetics may have the potential to produce

delayed myocardial protection in patients at risk for ischemic injury, but the potential clinical applicability of late APC remains to be determined.

Postconditioning. Reperfusion after coronary artery occlusion is a double-edged sword—it is obviously required to salvage ischemic myocardium, but it also contributes to further injury.[115,219] Buckberg and colleagues first suggested that modification of reperfusion conditions favorably reduces the injury that occurs when coronary blood flow is restored. For example, selective low-pressure (40 to 50 mm Hg) reperfusion before full restoration of coronary blood flow reduced infarct size, enhanced LV systolic function, and mitigated myocardial tissue edema compared with abrupt reperfusion. Similarly, elimination of compensatory increases in blood flow resulting from coronary vasodilation after ischemia (reactive hyperemia) during early reperfusion maintained myocardial metabolism, reduced intracellular Ca^{2+} accumulation, and improved regional wall motion compared with conventional reperfusion. Gradual reperfusion of the ischemic territory during the first 30 minutes after prolonged coronary occlusion also preserved endothelial function in vitro. Thus, "gentle" or "staged" control of coronary blood flow during early reperfusion was shown to be important in preserving myocardial integrity and function after an ischemic episode. Nevertheless, these interesting observations were largely ignored because preconditioning, and not events occurring at the onset of reperfusion, was the primary focus of experimental and clinical research in myocardial protection during the late 1980s and 1990s. However, it is quite clear that coronary artery occlusion cannot be temporally predicted in the vast majority of patients with acute myocardial ischemia or infarction to any degree of certainty. As a result, application of preconditioning is limited primarily to conditions in which the onset of ischemia can be precisely determined. Inflation of an angioplasty balloon during cardiac catheterization, aortic cross clamp application during cardiopulmonary bypass, and temporary coronary artery occlusion for anastomosis during off-pump coronary artery bypass grafting (OP-CAB) are notable examples of clinical situations in which myocardial ischemia occurs in a predictable fashion. Under such circumstances, preconditioning strategies may be both clinically relevant and genuinely applicable.

The conditions during which reperfusion conditions may be altered to favorably reduce myocardial injury were reexamined in 2003.[220] In this seminal work, a series of brief (30-second) episodes of coronary artery occlusion interspersed with 30-second periods of complete reperfusion were used before coronary blood flow was fully reestablished in a canine model. This brief, repetitive occlusion-reperfusion technique (often termed "stuttering" reperfusion) reduced infarct size, decreased neutrophil accumulation, blunted ROS production, partially preserved endothelial function, and inhibited apoptosis.[220,221] The reductions in myocardial injury caused by this ischemic postconditioning (IPostC) phenomenon were very similar to those produced by IPC.[220] ERK1/2 activation and NO formation were initially shown to mediate IPostC.[220,222] Subsequently, PI3K-Akt signaling also was implicated, including the downstream enzymes eNOS and mammalian target of rapamycin 70-kDa ribosomal protein s6 kinase (mTOR/p70s6K).[223,224] The PI3K cascade modulates cellular necrosis and apoptosis by influencing the balance of proapoptotic and antiapoptotic proteins, the activity of the regulatory enzyme glycogen synthase kinase-3β (GSK-3β), and the transition state of mPTP[97,157] (Fig. 28-12). A large number of other studies demonstrated that administration of G protein–coupled receptor ligands (e.g., adenosine, bradykinin, opioid), insulin, statins, and growth factors immediately before or during early reperfusion mimicked the beneficial actions of IPostC. Many components of prosurvival signaling implicated in IPostC were shown to mediate this pharmacologic postconditioning.[78,225] Activation of the RISK pathway[78] by IPostC also occurred in a model of postinfarction ventricular hypertrophy,[226] suggesting that this phenomenon may be preserved in the presence of cardiac disease. Clinical evidence of IPostC was further demonstrated, because brief repetitive balloon inflation and deflation performed during coronary angioplasty preserved myocardial integrity and function in patients with acute myocardial infarction.[227] Furthermore, peak creatine kinase release was lower in patients with acute coronary syndrome who received four or more balloon inflations during angioplasty compared with those treated with one to three inflations.[228] These findings suggested that relief of sustained ischemia by stuttering reperfusion protected against permanent myocardial damage. Similarly, IPostC improved coronary artery blood flow velocity after final reperfusion, mitigated cellular necrosis, enhanced regional LV systolic function 8 weeks after intervention, and stimulated recovery of endothelial-dependent vasoreactivity compared with conventional reperfusion.[229,230] Since its initial description 10 years ago, IPostC has attracted intense interest because reperfusion is a controllable event in many patients with acute coronary syndrome.

Volatile anesthetics are capable of exerting protective effects when administered immediately before or during reperfusion. Halothane prevented hypercontracture of cardiac myocytes during reoxygenation after hypoxia and also reduced reperfusion injury after regional myocardial ischemia in rabbit hearts. Isoflurane enhanced the functional recovery of stunned myocardium, and desflurane and sevoflurane reduced infarct size, associated with brief and prolonged ischemia, respectively, when the volatile anesthetics were administered solely during reperfusion. Administration of sevoflurane after ischemia also improved contractile function, metabolism, and Ca^{2+} loading in guinea pig hearts.[231] Halothane abolished reoxygenation-induced attenuation of sarcoplasmic reticulum–dependent oscillations of Ca^{2+} concentration in cardiac myocytes, suggesting that volatile anesthetics may prevent intracellular Ca^{2+} overload during early reperfusion. Additionally, isoflurane and sevoflurane reduced postischemic adhesion of neutrophils to reduce Ca^{2+} overload or attenuate the deleterious effects of neutrophils during early reperfusion.

Isoflurane (1.0 MAC) administered during the final 3 minutes of coronary artery occlusion and the first 2 minutes of reperfusion was shown to reduce myocardial

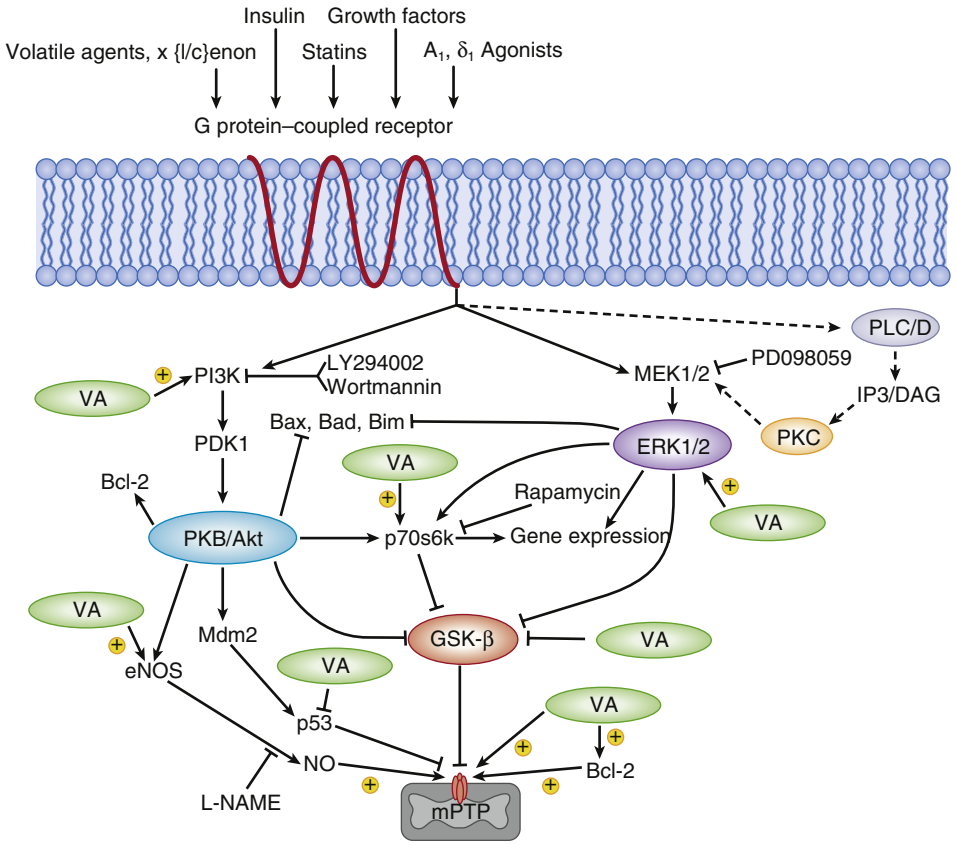


Figure 28-12. Schematic illustration depicting the potential sites of action of volatile anesthetics *(VA)* on myocardial protective signaling during early reperfusion. G protein–coupled receptor ligands (e.g., adenosine A_1, opioid δ_1), VA, insulin, statins, and growth factors activate parallel phosphoinositol-3-kinase *(PI3K)* or extracellular signal–regulated kinase *(ERK1/2)* cascades to produce protection. G protein–coupled activation of protein kinase C *(PKC)* by phospholipases *(PLC/D)* through the second messengers diacylglycerol *(DAG)* and inositol triphosphate *(IP3)* also contributes to activation of PI3K and ERK1/2. PI3K phosphorylates phosphoinositide-dependent kinase *(PDK1)*, which activates Akt (also known as protein kinase B *[PKB]*). This moiety stimulates the activity of antiapoptotic proteins (e.g., B-cell lymphoma-2 *[Bcl-2]*) and simultaneously inhibits activity of proapoptotic proteins (e.g., *Bax, Bad, Bim,* caspases). Akt/PKB also inhibits the β-isoform of glycogen synthase kinase *(GSK-β)* and activates endothelial nitric oxide synthase *(eNOS)*, 70-kDa ribosomal protein s6 kinase *(p70s6K)*, and murine double minute 2 *(Mdm2)* protein. p70s6K also inhibits GSK-β activity. Nitric oxide *(NO)* produced by eNOS inhibits whereas Mdm2-induced phosphorylation of the proapoptotic protein p53 opens the mitochondrial permeability transition pore *(mPTP)*. Inhibition of GSK-β and activation of mitochondrial K_{ATP} channels also act to close mPTP. The transition state of the mitochondrial pore is critical for the preservation of mitochondrial integrity and cell viability during ischemia and reperfusion. Activation of ERK1/2 also inhibits GSK-β and blocks the formation of proapoptotic proteins. LY294002 and wortmannin, rapamycin, PD 098059, and L-arginine methyl ester *(L-NAME)* block the activity of PI3K, p70s6K, ERK1/2, and eNOS, respectively. Volatile anesthetics have been proposed to enhance the activity of PI3K-Akt, p70s6k, ERK1/2, and eNOS. Volatile anesthetics have also been suggested to directly inhibit GSK-β and mPTP concomitant with enhanced expression of Bcl-2 and inhibition of p53. Volatile anesthetic–induced activation of mitochondrial K_{ATP} channels also inhibits mPTP. These actions of volatile anesthetics may contribute to the cardioprotective effects during early reperfusion.

infarct size in rabbits.[232] This experimental design was used to establish a plasma concentration of isoflurane and thereby create a pharmacologic effect immediately on reperfusion. The reductions in myocardial necrosis observed with this anesthetic postconditioning (APostC) were similar in magnitude to those obtained with IPostC and APC.[39,232] Postconditioning with 0.5 MAC isoflurane (an anesthetic concentration that did not decrease infarct size alone) also reduced the time threshold required for IPostC.[232] A selective PI3K antagonist (wortmannin) abolished the salutary actions of APostC and also blocked isoflurane-induced phosphorylation of the PI3K downstream enzyme Akt (protein kinase B). The data demonstrated that activation of the PI3K signaling pathway was responsible for the protective effects of APostC in vivo. Exposure to equivalent MAC concentrations of isoflurane, sevoflurane, and desflurane before and during early reperfusion were subsequently shown to produce almost identical reductions in myocardial infarct size in mice, indicating that the magnitude of APostC was very similar among modern volatile anesthetics.[233] APostC most likely reduces reperfusion injury by recruiting other endogenous signaling kinases and preventing apoptosis through PI3K.[232] APostC was also shown to be mediated by PI3K-Akt signaling in human atrial myocardium.[234] A central role for PI3K-Akt signaling in APostC was subsequently demonstrated in infarct-remodeled myocardium, suggesting that APostC may be preserved after myocardial infarction[235] (Fig. 28-13).

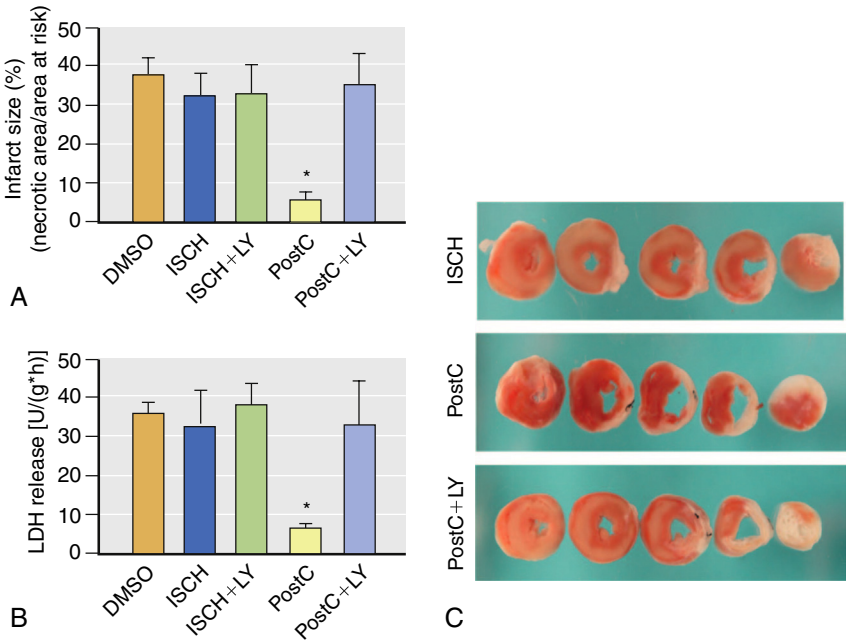


Figure 28-13. Infarct size was determined by using 1% triphenyltetrazolium chloride staining. Areas infarcted in vivo by coronary artery ligation were excluded from infarct size determination (**A**). The scarred chronic infarct *(white)* resulting from coronary ligation was clearly distinguished from fresh infarcts *(salmon pink)*. Release of lactate dehydrogenase (LDH) during reperfusion (**B**) served as an independent method to estimate infarct size. Transverse sections demonstrate representative experiments (**C**). *DMSO,* Dimethyl sulfoxide (< 0.1%; used to dissolve PI3K antagonist LY294002); *IPostC,* ischemic postconditioning; *ISCH,* unprotected remodeled hearts exposed to ischemia-reperfusion alone; *LY,* LY294002 (15 μM); *PostC,* anesthetic postconditioning. Data are mean ± standard deviation (n = 5 in each group). $^{*}P < .05$ versus ISCH. *(From Feng J, Fischer G, Lucchinetti E, et al: Infarct-remodeled myocardium is receptive to protection by isoflurane postconditioning: role of protein kinase B/Akt signaling,* Anesthesiology *104:1004-1014, 2006.)*

Reperfusion may initiate or accelerate apoptosis,[236] an observation that makes attenuation of apoptosis an especially important feature of postconditioning. Selective inhibition of apoptotic signaling by volatile anesthetics was crucial to minimize myocardial damage during early reperfusion. Brief administration of isoflurane immediately before and during early reperfusion reduced cytochrome c translocation from mitochondria (an important early marker of apoptosis) and decreased the number of terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling (TUNEL [another index of apoptosis])-positive ventricular myocytes in situ.[237] Isoflurane-induced PI3K activation also protected atrial and ventricular myocytes against apoptosis in models of oxidative stress.[93] Enhanced expression of Bcl-2 also was observed. Furthermore, volatile anesthetics abolished norepinephrine-induced apoptosis in ventricular myocytes (e.g., reductions in TUNEL-positive cell staining, attenuation of annexin V staining [an index of DNA laddering], and inhibition of caspase-9 activity).[238] More recently, APostC was shown to prevent activation of caspase-3 and caspace-9 by phosphorylation of antiapoptotic signaling proteins, including Akt, after ischemia-reperfusion injury.[239] Thus, volatile anesthetics have been shown to attenuate apoptosis associated with many forms of severe myocardial stress.

G protein–coupled receptor-mediated activation of PI3K and ERK1/2 signaling during several forms of postconditioning, including APostC, was recently emphasized.[237] For example, opioid-induced postconditioning was mediated by activation of δ_1-opioid receptors, PI3K-mediated signaling, and mitochondrial K_{ATP}.[240,241] Similar to the findings observed during opioid-induced preconditioning, morphine (when administered in a dose that does not affect infarct size alone) lowered the threshold of APostC by isoflurane in rabbits.[237] The protective effects were abolished by pretreatment with a selective PI3K antagonist and naloxone, indication that PI3K and G protein–coupled opioid receptors were required for APostC and its augmentation by morphine. Like PI3K, ERK1/2 also stimulates prosurvival signaling to favorably affect reperfusion injury.[78] ERK1/2 mediated ischemic[222] and pharmacologic postconditioning in vivo.[242] For example, activation of ERK1/2 during IPostC reduced infarct size in rabbit hearts.[243] Administration of G protein–coupled receptor ligands, including an adenosine A_1/A_2 agonist and bradykinin, on reperfusion decreased necrosis concomitant with phosphorylation of Erk1/2. These actions were blocked by pretreatment with a selective MEK-1 inhibitor.[242] Another A_1/A_2 receptor agonist also exerted protective effects during reperfusion through an ERK1/2-mediated mechanism.[244,245] Reductions in infarct size produced by APostC were abolished by pretreatment with a selective MEK-1 inhibitor in rabbit[246] and human myocardium.[247]

Both PI3K-Akt and ERK1/2 phosphorylate and activate mTOR and its target p70s6K. The latter enzyme is an important regulator of protein translation and a key inhibitor of GSK-3β. [248] A selective mTOR inhibitor abolished myocardial protection during IPostC.[223] mTOR/p70s6K was also implicated in pharmacologic postconditioning, because reductions in infarct size produced by administration of morphine or a δ_1-selective opioid agonist during early reperfusion were blocked by an mTOR inhibitor.[240] mTOR/p70s6K mediated the beneficial effects of an A_1/A_2 agonist[249] and insulin[250] during reperfusion. Similarly, isoflurane-induced APostC was mediated by mTOR/p70s6K in rabbits.[246] In addition, a selective PI3K inhibitor abolished isoflurane-induced phosphorylation of mTOR/p70s6K in infarct-remodeled rat myocardium when the volatile anesthetic was administered during the first 15 minutes of reperfusion.[235] These data suggested that APostC may retain its salutary actions in diseased myocardium through activation of the PI3K-Akt-mTOR/p70s6K axis. A role for mTOR was subsequently also implicated in APC.[84]

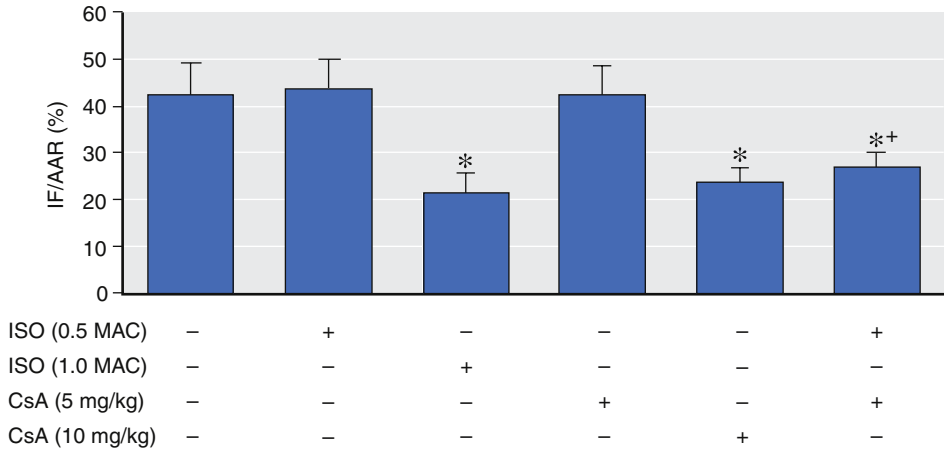


Figure 28-14. Histograms illustrating infarct size *(IF)* presented as a percentage of left ventricular area at risk *(AAR)* in rabbits in the presence (+) or absence (–) of postconditioning with isoflurane (*ISO;* 0.5 or 1.0 minimum alveolar concentration [MAC]) or the mPTP inhibitor cyclosporin A (*CsA;* 5 or 10 mg/kg). Isoflurane (1.0 but not 0.5 MAC) and cyclosporin A (10 but not 5 mg/kg) reduced infarct size compared with control. The combination of subthreshold doses of isoflurane (0.5 MAC) and cyclosporin A (5 mg/kg) also reduced infarct size to an equivalent degree as 1.0 MAC isoflurane and 10 mg/kg cyclosporin A. Data are mean ± standard deviation. *(From Pagel PS: Postconditioning by volatile anesthetics: salvaging ischemic myocardium at reperfusion by activation of prosurvival signaling,* J Cardiothorac Vase Anesth *22:753-765, 2008.)*

Other signaling molecules have been implicated in APostC. PI3K-Akt activates eNOS and thereby increases NO formation. A central role for eNOS-derived NO has been demonstrated in IPostC.[220,223] A nonselective NOS inhibitor *N*-nitro-L-arginine methyl ester, but not selective inducible or neuronal NOS antagonists, abolished reductions in infarct size produced by the administration of isoflurane before and during early reperfusion, suggesting that eNOS mediates APostC.[246] Thus, administration of isoflurane during early reperfusion enhanced the protective effect of IPostC through an NO-dependent mechanism. The eNOS-dependence of APostC was subsequently confirmed in knockout mice.[251] APostC also increased eNOS expression through PI3K in infarct-remodeled myocardium.[235] Thus, NO generated by eNOS mediated APostC through PI3K activation. NO is an important regulator of apoptosis, preserves ERK1/2 activity, nitrosates and inactivates several caspases, and blocks metabolism of Bcl-2. These actions combine to prevent mitochondrial disruption and cytochrome c release through inhibition of mPTP formation. These proposed intracellular actions of eNOS-derived NO were also implicated in APostC.[251]

mPTP opening is reperfusion-dependent, and inhibition of this process mediates IPostC.[103,252] IPostC and a cyclosporin A analogue reduced infarct size and decreased the quantity of Ca^{2+} loading necessary to open the mPTP to equivalent degrees in intact hearts and isolated mitochondria, respectively. Not surprisingly, a role for mPTP inhibition has been demonstrated during APostC. The mPTP opener atractyloside abolished, whereas cyclosporin A enhanced, decreases in myocardial necrosis produced by brief administration of isoflurane immediately before and during early reperfusion in rabbits[253] (Fig. 28-14). Atractyloside and a selective PI3K antagonist also abolished APostC in rats.[254] A PI3K inhibitor blocked phosphorylation of Akt and GSK-3β and opened mPTP, thereby demonstrating a critical link between prosurvival signaling and mPTP conformation during APostC.[254] APostC inhibited mitochondrial permeability transition, preserved $\Delta\Psi_m$, and maintained ATP synthesis during reperfusion by attenuating respiration, reducing pH, and causing depolarization of mitochondria.[255]

Mitochondrial K_{ATP} opening is also a postulated end-effector of APostC.[253,256] As described previously, volatile anesthetics either directly open mitochondrial K_{ATP} or prime their opening in response to other signaling molecules. Mitochondrial K_{ATP} opening during IPC alters intramitochondrial homeostasis and protects against subsequent ischemic damage by regulating matrix volume through an mPTP-dependent mechanism.[257] Mitochondrial K^+ influx through mitochondrial K_{ATP} also favorably regulated matrix volume and enhanced mitochondrial function during simulated ischemia and reperfusion.[258] A selective mitochondrial K_{ATP} antagonist inhibited APostC produced by isoflurane or sevoflurane.[253,256] A similar effect was observed in human atrial myocardium exposed to desflurane APostC in vitro.[247] A close interaction between mitochondrial K_{ATP} and mPTP was previously identified during APC.[108] The finding that reductions in cyclosporin A–induced decreases in myocardial infarct size were abolished by 5-HD pretreatment emphasized this interaction.[253] Adenine nucleotide translocase (a component of mPTP) was also shown to mediate H^+ and K^+ ion flux to the mitochondrial matrix produced by mitochondrial K_{ATP} openers. Thus, the effects of volatile agents on mitochondrial K_{ATP} may not be solely responsible for APostC, but may be dependent on an interaction between mitochondrial K_{ATP} opening and mPTP inhibition.

GSK-3β is a crucial regulator of cellular function. Activation of GSK-3β was implicated in the pathogenesis of diabetes mellitus and Alzheimer disease, whereas inhibition of the enzyme plays a key role in myocardial protection.[259,260] Reductions in infarct size during IPC were associated with inactivation of GSK-3β through a PI3K-dependent mechanism.[259] Inactivation of GSK-3β by PI3K also stimulated angiogenic and antiapoptotic signaling through the induction of VEGF, Bcl-2, and surviving during IPC.[261] GSK-3β inhibition also mediated the protective effects of opioids[240,262] and adenosine[260] administered either before ischemia or during early reperfusion.

Chronic hyperglycemia[263] and estrogen deficiency associated with age attenuated myocardial protection produced by PI3K-mediated GSK-3β inactivation associated with aging,[264] suggesting a mechanism by which diabetes mellitus and postmenopausal reductions in estrogen concentration may be associated with a reduced myocardial tolerance to ischemic events. GSK-3β was shown to be not only an important target of several prosurvival signaling enzymes but also a central regulator of mPTP formation.[248] Thus, it appears that several redundant signaling pathways converge on and reduce the activity of GSK-3β, thereby preventing mPTP opening and producing protection against reperfusion injury.[265] Administration of isoflurane during the first 15 minutes of reperfusion inactivated GSK-3β concomitant with reductions in myocardial infarct size in isolated hearts.[254] These actions were abolished by pretreatment with a selective PI3K antagonist. In contrast, the mPTP opener atractyloside failed to block isoflurane-induced phosphorylation of PI3K and GSK-3β, but the drug did abolish reductions in infarct size through its direct actions on the mPTP. Isoflurane preserved mitochondrial function as indicated by accumulation of a mitochondrial-specific probe, and this action was also blocked by atractyloside pretreatment. Thus, APostC protects against reperfusion injury in normal myocardium by preventing mPTP opening through GSK-3β inhibition.[254] Similar results were also reported in infarct-remodeled myocardium.[235] A selective inhibitor of GSK-3β lowered the threshold of APostC.[266] The beneficial effects of GSK-3β inhibition and its augmentation by isoflurane were inhibited by atractyloside but not the PI3K or mTOR/p70s6K antagonists. Thus, volatile anesthetics may also produce a direct inhibitory effect on GSK-3β independent of their actions on PI3K and mTOR/p70s6K activity to cause APostC. Interestingly, the serine protease inhibitor and antifibrinolytic drug aprotinin was shown to abolish APostC through a GSK-3β–mediated mechanism in isolated hearts.[267]

The mechanisms by which APostC inhibits GSK-3β to prevent mPTP opening and to cause protection during early reperfusion are unknown. Activated GSK-3β binds to and promotes the actions of p53, and this tumor suppressor protein subsequently causes mitochondrial disruption during apoptosis. Activated p53 translocates to mitochondria and opens the mPTP through an interaction with the apoptotic protein Bax, thereby abolishing $\Delta\Psi_m$ and causing the release of cytochrome c. Inhibition of p53 appears to play an important role in myocardial and neuronal protection against cellular injury. Hypoxia and ROS activated p53, which then stimulated apoptotic signaling,[268] enhanced transcription of other apoptotic proteins,[269] and caused cell death. IPC attenuated the increase in p53 expression that is typically observed after ischemia and reperfusion in isolated ventricular myocytes.[270] IPC also blunted p53 transcription and translation in hippocampal pyramidal neurons in a model of global forebrain ischemia and reperfusion. Inhibition of p53 using a selective antagonist or augmented degradation of the protein by the regulatory murine double minute 2 protein (Mdm2; an oncogenic factor[271]) protected against ischemic injury in isolated hearts.[272] Phosphorylated Mdm2 binds to and inactivates p53 by blocking its active site and promoting its degradation through formation of a ubiquitin complex.[273] These data suggested that IPC blocks the detrimental effects of p53 through PI3K-Mdm2 signaling.[272] A selective antagonist of p53 protected against ischemia-induced neuronal cell death.[274] Targeted deletion of p53 also prevented cardiac rupture after infarction in transgenic mice. This salutary effect most likely occurred because the protective effects of IPC were simulated by inhibition of p53-mediated apoptosis.[275]

Inhibition of p53 enhanced the beneficial actions of APostC in rabbits. Administration of a dose of a selective p53 inhibitor that did not affect the magnitude of irreversible ischemic injury alone lowered the threshold concentration of isoflurane required to cause APostC.[276] Atractyloside blocked this beneficial effect, suggesting that the myocardial protection was mediated by the combined actions of the selective p53 inhibitor and the volatile anesthetic on mPTP. Thus, APostC may favorably modulate the interaction between GSK-3β and p53 to prevent mPTP opening and thereby preserve myocardial integrity. A PI3K inhibitor also blocked decreases in infarct size produced by a combination of subthreshold doses of the p53 inhibitor and isoflurane, demonstrating that this phenomenon was PI3K-dependent. This process may depend on activation of Akt by isoflurane,[232] which leads to Mdm2 phosphorylation and subsequent inactivation and degradation of p53. Such an action may effectively prevent the latter protein's deleterious interaction with GSK-3β. IPC activated Mdm2 and enhanced phospho-Mdm2-p53 binding in a PI3K-dependent manner,[272] but whether APostC specifically causes a similar phospho-Mdm2-p53 interaction is unknown.

The effects of APostC on another important regulator of apoptosis during reperfusion were described.[93,277] The Bcl-2 protein is located in the outer mitochondrial membrane, regulates the transition state of mPTP, and has been implicated in myocardial protection against ischemia-reperfusion injury.[278] Bcl-2 reduced damage associated with ischemia by preventing mitochondrial cytochrome c release, attenuating intracellular Ca^{2+} overload, and preserving endoplasmic reticulum integrity. IPC also reduced apoptosis by up-regulating Bcl-2 expression in isolated hearts. Intermittent hypoxia mitigated reperfusion-induced apoptosis by favorably influencing the balance of Bcl-2 to Bax in ventricular myocytes.[279] Overexpression of Bcl-2 in transgenic mice attenuated apoptosis and protected against myocardial ischemia-reperfusion injury.[280] An interaction between Bcl-2 and mPTP closure was also postulated during delayed IPC.[107] A selective Bcl-2 inhibitor blocked increases in Bcl-2 expression and attenuated reductions in apoptosis produced by isoflurane in isolated myocytes subjected to cellular stress.[93] Furthermore, a Bcl-2 inhibitor blocked APostC and IPostC, but not cyclosporin A–induced myocardial protection in rabbits.[277] These results suggested that the salutary actions of APostC also may occur because the mPTP is maintained in its closed conformation by Bcl-2.[277] PI3K is known to phosphorylate and activate Bcl-2 in concert with inactivation of Bad, Bax, and p53. Thus, activation of PI3K signaling by APostC most likely produces favorable changes in apoptotic protein homeostasis to promote myocardial protection.

In summary, volatile anesthetics cause myocardial protection when exclusively administered immediately before or during early reperfusion after ischemia. The mechanisms responsible for APostC share many similarities with those recognized for APC. Research data collected to date emphasize that APostC activates many prosurvival proteins downstream from PI3K and ERK1/2 that favorably modulate mPTP. APostC also protects against apoptosis by shifting the balance between proapoptotic and antiapoptotic proteins. APostC will most likely protect the human heart from reperfusion injury in vivo because this process has been shown to occur in isolated human myocardium in the laboratory[234,247] and because IPostC has already been shown to do so in patients with acute myocardial infarction.[227] Notably, APostC most certainly has the potential to provide myocardial protection in clinical situations in which reperfusion is a predictable event.

Coronary Vascular Effects in Humans

Evaluation of the actions of volatile anesthetics on the human coronary circulation is difficult not only because the methods used to determine coronary blood flow in humans are limited but also because the interpretation of clinical findings during anesthesia are complicated by changes in hemodynamics, the impact of surgery, and the use of adjuvant anesthetics or vasoactive drugs. Halothane decreased MVo_2 and variably altered coronary blood flow in patients with coronary artery disease, but metabolic or electrocardiographic evidence of ischemia has not been observed during halothane anesthesia. A report published in 1983[281] described the occurrence of myocardial ischemia as indicated by new electrocardiographic changes and abnormal myocardial lactate extraction in 10 of 21 patients anesthetized with isoflurane undergoing major vascular surgery. Five patients were treated with phenylephrine and pacing to return arterial pressure and heart rate to control values, and after these interventions, electrocardiographic and metabolic derangements resolved in 2 of the 5 patients. Despite the apparent dependence of these new episodes of myocardial ischemia on alterations in systemic hemodynamics, the authors proposed that isoflurane had caused coronary steal in these patients, even though no specific evidence of blood flow redistribution between normal and collateral-dependent zones was presented. The data have not been uniformly supported by subsequent studies. Coronary blood flow remained unchanged during isoflurane anesthesia in patients undergoing coronary artery bypass graft surgery, but coronary sinus O_2 content increased consistent with modest coronary vasodilation. Isoflurane alone did not produce electrocardiographic or metabolic evidence of ischemia. Instead, myocardial ischemia occurring during isoflurane anesthesia was most often associated with tachycardia or hypotension. In addition, isoflurane actually increases the tolerance to pacing-induced ischemia in patients with coronary artery disease. Comparisons of studies examining the effects of isoflurane on the incidence of intraoperative myocardial ischemia were also complicated by differences in patient age, surgical procedure, operative time, and preoperative LV ejection fraction. Importantly, compelling evidence demonstrating redistribution of coronary blood flow away from ischemic to normal myocardium in humans anesthetized with isoflurane has yet to be reported.

The incidence of intraoperative myocardial ischemia in susceptible patients has been difficult to define. Less than 50% of intraoperative ischemic episodes have been linked to alterations in systemic hemodynamics.[282] The strongest predictor of intraoperative ischemia remains preexisting ischemia on arrival to the operating room and not anesthetic technique.[283] The only hemodynamic event definitively related to intraoperative ischemia in patients undergoing CABG surgery is tachycardia.[283] Perioperative use of β_1-adrenoceptor antagonists to prevent myocardial ischemia strongly supports this contention. Sternotomy caused greater increases in calculated indices of MVo_2, myocardial lactate production, and the incidence of hypertension requiring treatment with vasoactive drugs during morphine compared with halothane anesthesia. In contrast, induction of anesthesia with desflurane in patients undergoing CABG surgery may be associated with tachycardia, hypertension, and a greater incidence of ischemia than occurring during induction with sufentanil. Steal-prone anatomy was identified in 23% of patients with coronary artery disease, but patients with steal-prone coronary anatomy did not have a greater incidence of ischemia during desflurane anesthesia than with other forms of coronary artery disease. The incidence of myocardial ischemia and adverse cardiac outcomes has been shown to be similar in patients with cardiac disease undergoing noncardiac surgery during sevoflurane versus isoflurane anesthesia. New electrocardiographic changes, incidence of postoperative myocardial infarction, and mortality were similar in patients undergoing CABG surgery independent of anesthetic technique or the presence of steal-prone anatomy. Thus, despite the findings that volatile anesthetics are mild coronary vasodilators, these medications did not cause abnormal redistribution of myocardial perfusion resulting in ischemia when tachycardia and hypotension were avoided in patients with coronary artery disease.

Myocardial Protection in Humans

Volatile anesthetics protect human myocardium against ischemia-reperfusion or hypoxia-reoxygenation in vitro[40,42] through mechanisms that bear striking similarity to those described in experimental animals. However, whether laboratory data in isolated human myocardium may be translated into meaningful improvements in clinical outcome in patients at risk for myocardial ischemia remains open to question. In 1999, two groups independently suggested that volatile anesthetics had the potential to produce myocardial protection in cardiac surgical patients. Penta de Peppo and associates[284] reported that administration of enflurane (0.5% to 2.0%) before cardioplegic arrest enhanced postischemic functional recovery of contractility measured using LV pressure-area relations in 22 patients undergoing elective CABG.[284] Belhomme and colleagues[285] demonstrated that brief, 5-minute exposure to 2.5 MAC isoflurane during cardiopulmonary bypass (before aortic cross clamping; analogous to APC) reduced postoperative release of troponin I and the myocardial form of creatine kinase (CK-MB) in 20 patients undergoing CABG. The results of these two small clinical trials suggested that APC with

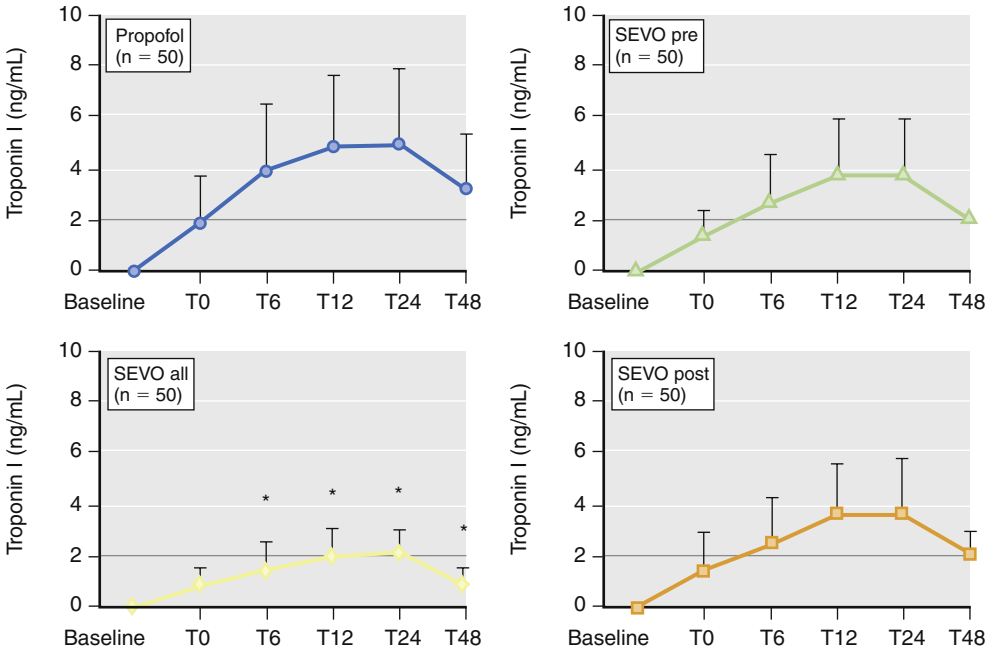


Figure 28-15. Cardiac troponin I concentrations observed in the four groups before surgery (baseline), at arrival in the intensive care unit *(T0)*, and after 6 *(T6)*, 12 *(T12)*, 24 *(T24)*, and 48 *(T48)* hours. Data are presented as mean ± standard deviation (SD). *Statistically significant difference with the propofol group ($P < .05$). In all groups, a transient increase in troponin I concentrations was observed. Only in the SEVO all group was this increase significantly less than in the propofol group. For the sake of clarity, the SD bars are represented in only one direction. *(From De Hert SG, ten Broecke PW, Mertens E, et al: Sevoflurane but not propofol preserves myocardial function in coronary surgery patients,* Anesthesiology *97:42-49, 2002.)*

enflurane or isoflurane may enhance contractile function after and decrease myocardial necrosis associated with cardiopulmonary bypass in patients with coronary artery disease.[284,285] These initial observations were extended by the findings of two subsequent studies in which sevoflurane or desflurane compared with propofol preserved myocardial function in patients undergoing CABG with or without preexisting LV dysfunction concomitant with a reduction in troponin I release.[286,287] Another study indicated that sevoflurane maintains postoperative LV myocardial contractility (as assessed using the maximum rate of increase of LV pressure; +dP/dt) and decreases plasma troponin I concentrations during the first 36 hours after surgery in contrast to a propofol-based anesthetic in patients with severe aortic valve stenosis (aortic valve area of 0.6 to 0.7 cm^2) undergoing aortic valve replacement.[288] The incidence of atrial fibrillation early after CABG also may be reduced by sevoflurane compared with propofol or midazolam.[289] Release of inflammatory mediators (interleukin-6 [IL-6], neutrophil integrins, and tumor necrosis factor-α [TNF-α]) was decreased and myocardial function (LV stroke work index) was preserved in patients undergoing CABG receiving sevoflurane compared with total intravenous anesthesia consisting of propofol, midazolam, and fentanyl.[290] Troponin I release was also less pronounced when sevoflurane or isoflurane was used as the primary anesthetic compared with propofol in patients undergoing CABG.[291] Notably, volatile or intravenous anesthetics were administered continuously throughout the operation in each of these studies, and a preconditioning technique per se was not examined. Thus, the salutary effects of sevoflurane or desflurane observed in these investigations may have been due, at least in part, to favorable alterations in the determinants of myocardial O_2 supply-demand relationships produced by the volatile anesthetic.

Myocardial protection associated with differing approaches to sevoflurane administration were examined and compared in 200 patients undergoing CABG.[292] As in the previously described investigations, two groups of patients received either propofol or sevoflurane throughout surgery, but in this trial, two additional groups also received sevoflurane either before cardiopulmonary bypass alone or solely after construction of coronary anastomoses to mimic the effects of APC and APostC, respectively (Fig. 28-15). Sevoflurane significantly reduced troponin I release and decreased intensive care unit and hospital length of stay only when the volatile anesthetic was administered throughout the operation and not when preconditioning or postconditioning methods of administration were used.[292] Nevertheless, other investigators have suggested that APC may occur in patients undergoing CABG. For example, Meco and associates[293] used a preconditioning protocol in which 28 patients undergoing CABG were exposed to 2.5 MAC desflurane or placebo for 5 minutes followed by a 10-minute washout period before aortic cross clamping and cardioplegic arrest. This desflurane APC reduced postoperative troponin I and N-terminal pro-brain natriuretic peptide (NT-proBNP; a biochemical marker of global LV contractility) release and also enhanced LV function assessed using mitral valve annulus tissue Doppler imaging. Inhalation of 4% sevoflurane for the first 10 minutes of cardiopulmonary bypass in 18 patients undergoing CABG during baseline propofol-opioid anesthesia reduced postoperative release of NT-proBNP compared with a control cohort (Fig. 28-16). These findings occurred concomitant with activation and translocation of PKC-δ and PKC-ε in atrial myocardial biopsies that had been obtained during cannulation[294] (Fig. 28-17). Similar translocation of PKC isoforms was previously demonstrated in experimental models of APC.[20,70] However, no differences in ST-segment changes, troponin T or CK-MB release, or arrhythmias were observed between groups in this study.[294] In contrast to the previous findings,[292] administration of sevoflurane before cardiopulmonary

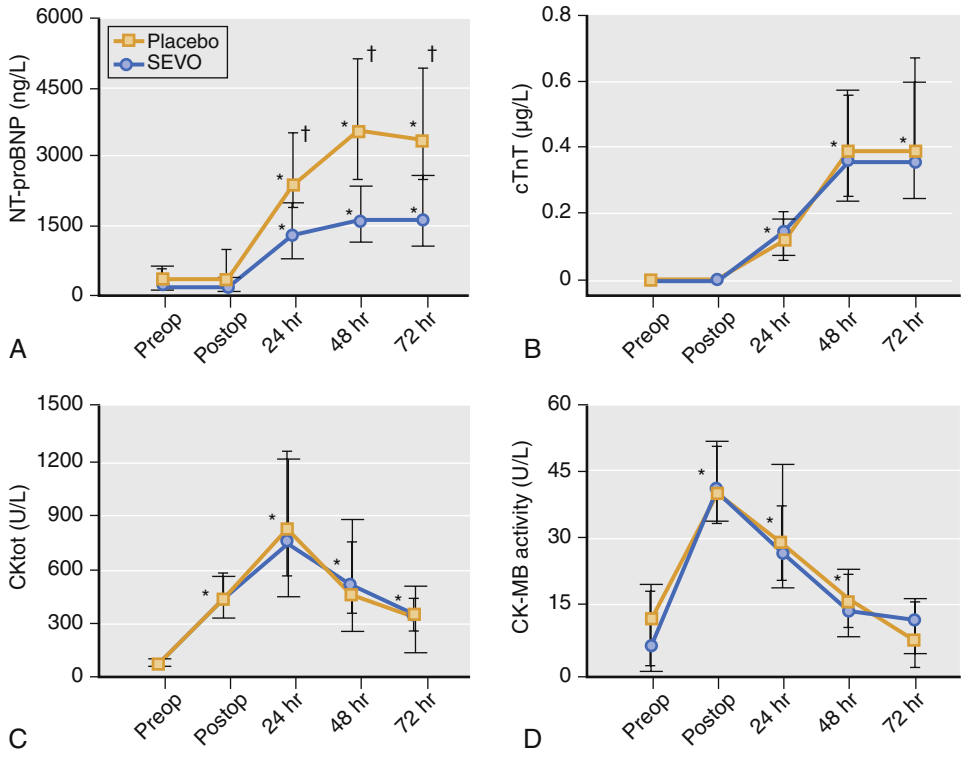


Figure 28-16. Biomarkers of myocardial injury at various time points for the placebo *(PLACEBO)*-treated and sevoflurane *(SEVO)*-treated groups: N-terminal pro-brain natriuretic peptide *(NT-proBP)* (**A**), cardiac troponin T *(cTnT)* (**B**), total creatine kinase *(CKtot)* (**C**), and creatine kinase–myocardial bound *(CK-MB)* isoenzyme activity (**D**). Two-factor repeated-measures analysis of variance indicated that the groups significantly differed in plasma NT-proBNP concentrations (time effect, $P < .001$; group effect, $P < .001$; group-time interaction, $P = .003$). No difference was found for cTnT, CKtot, and CK-MB activity concentrations. Multiple t tests with the Bonferroni correction for multiple comparisons were used to compare the plasma concentrations of the different biomarkers at each time point with the respective preoperative baseline value within groups and to compare plasma concentrations at each time point between groups. *(From Julier K, da Silva R, Garcia C, et al: Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: a double-blinded, placebo-controlled multicenter study,* Anesthesiology *98:1315-1327, 2003.)*

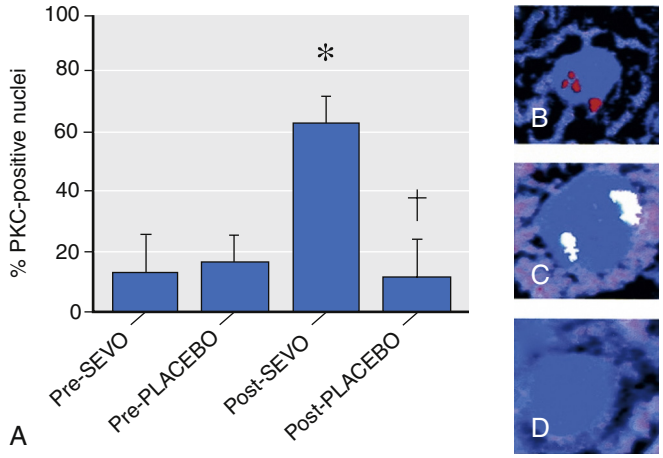


Figure 28-17. Translocation of protein kinase C ε (PKC-ε) to cardiac myocytes. **A,** Percentages of PKC-ε–positive myocytes. **B,** Representative nucleus of a PKC-ε–positive myocyte. **C,** Cardiac myocyte without PKC-ε but lipofuscin pigment in the nucleus. **D,** Cardiac myocyte with neither PKC-ε nor pigment in the nucleus. Pre-SEVO and post-SEVO, before and after sevoflurane preconditioning, respectively; pre-PLACEBO, before placebo preconditioning; post-PLACEBO, time-matched control after placebo preconditioning. *(From Julier K, da Silva R, Garcia C, et al: Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: a double-blinded, placebo-controlled, multicenter study,* Anesthesiology *98: 1315-1327, 2003.)*

bypass alone reduced postoperative myocardial necrosis (troponin T and CK-MB release) and enhanced global LV function (myocardial performance index) compared with continuous administration of sevoflurane or propofol throughout surgery.[295] However, cytokine release and lengths of stay in the intensive care unit and the hospital were similar between groups.[295] Indeed, the specific preconditioning protocol was shown to have an important impact on sevoflurane-induced myocardial protection in patients undergoing CABG. A single 5-minute exposure to 1.0 MAC sevoflurane followed by discontinuation of the volatile anesthetic for 10 minutes before beginning cardiopulmonary bypass did not reduce peak postoperative troponin I concentrations compared with continuous administration of propofol, whereas two cycles of sevoflurane preconditioning significantly attenuated postoperative release of this biochemical marker of myocardial necrosis.[296] Garcia and associates[297] reported their results in 36 CABG patients receiving brief (10-minute) administrations of 4% sevoflurane or placebo during cardiopulmonary bypass.[297] Patients exposed to 4% sevoflurane had reduced platelet-endothelial cell adhesion molecule-1 concentrations (PECAM-1; an important determinant of leukocyte migration through vascular endothelium during ischemia-reperfusion injury) and increased catalase expression in atrial biopsies.[297] Interestingly, late cardiac events during the first year after surgery occurred

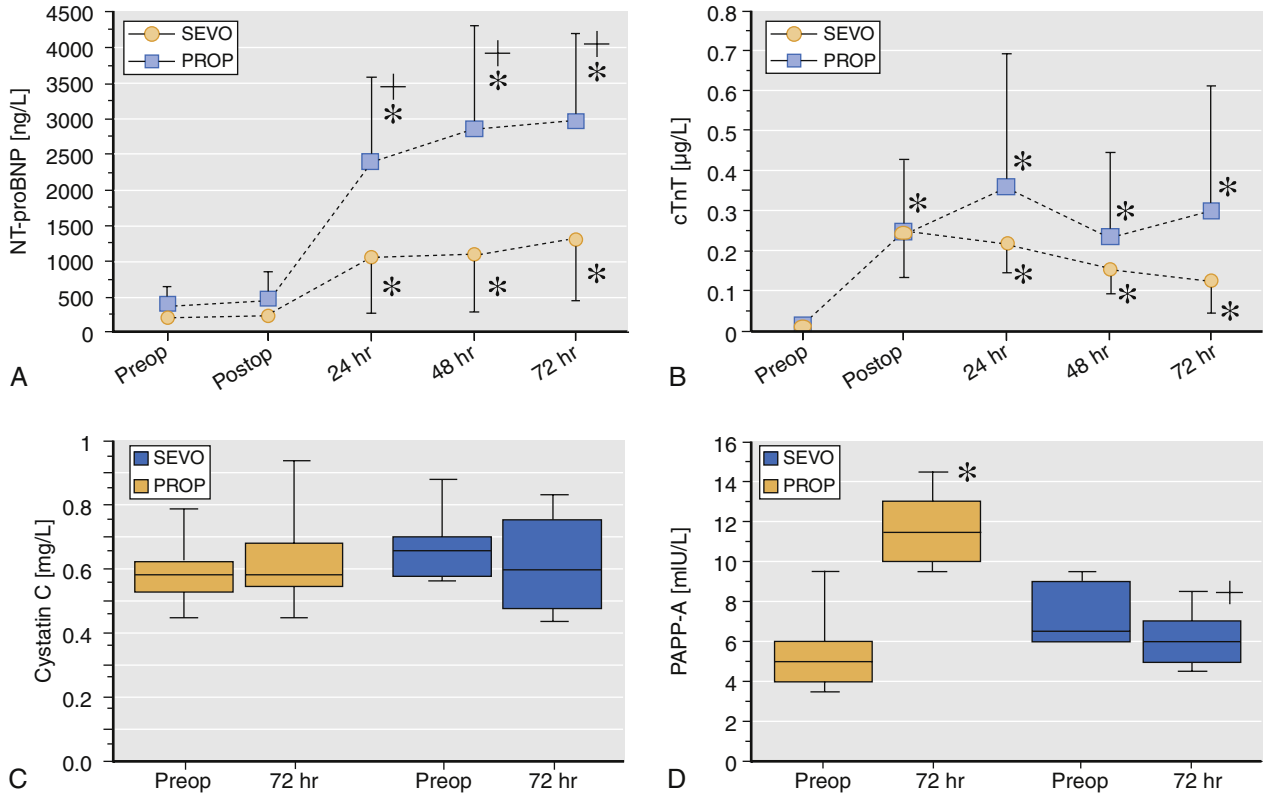


Figure 28-18. Cardiovascular biomarkers. Perioperative levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) were significantly more elevated in the propofol *(PROP)* group compared with the sevoflurane *(SEVO)* group (**A**). No difference between groups was found in cardiac troponin T (**B**) or cystatin (**C**), whereas pregnancy-associated plasma protein A *(PAPP-A)* was exclusively increased postoperatively in the PROP group (**D**). *(From Lucchinetti E, Hofer C, Bestmann L, et al: Gene regulatory control of myocardial energy metabolism predicts postoperative cardiac function in patients undergoing off-pump coronary artery bypass graft surgery: inhalational versus intravenous anesthetics.* Anesthesiology *106:444-457, 2007.)*

significantly less often in sevoflurane-treated patients than in controls (3% versus 17%, respectively; $P = .038$). Patients who suffered late cardiac events also had greater peak troponin T and NT-proBNP concentrations in contrast to those who did not sustain subsequent injury. The data supported the hypothesis that use of a volatile anesthetic in patients at risk for perioperative myocardial ischemia may exert a favorable long-term benefit by reducing the incidence of major adverse cardiac events. Nevertheless, it is essential to recognize that this small study[297] is the only prospective clinical trial conducted to date to specifically demonstrate a long-term cardiovascular benefit associated with administration of a volatile anesthetic to patients undergoing CABG. Finally, Amr and Yassin[298] randomized 45 patients scheduled for elective CABG to receive APC (a 10-minute exposure to 2.5% isoflurane followed by a 5-minute washout) or IPC (three episodes of brief aortic cross clamping interspersed with reperfusion).[298] The authors demonstrated that these protective strategies caused similar improvements in hemodynamics, reductions in postoperative CK-MB and troponin I release, and decreases in inotrope requirements, but patients who did not receive either intervention were not studied in a control group.

The potential for volatile anesthetics to produce myocardial protection in patients undergoing off-pump or minimally invasive direct CABG (OP-CAB or MID-CAB, respectively) has been examined. Transient coronary artery occlusion is often required to construct new vascular anastomoses during these procedures, thereby providing a predictable setting in which ischemia-reperfusion injury may occur in patients who are already at risk for myocardial ischemia because of preexisting flow-limiting coronary stenoses. Postoperative troponin I release was reduced in sevoflurane-treated compared with propofol-treated patients undergoing OP-CAB.[299] Desflurane also reduced troponin I release, use of positive inotropic medications, and the number of patients requiring prolonged hospitalization compared with a propofol-opioid–based anesthetic technique in patients undergoing OP-CAB.[300] Patients anesthetized with sevoflurane undergoing MID-CAB had preserved LV systolic (myocardial performance index) and diastolic (ratio of early-to-late transmitral blood flow velocity; E/A) function in contrast to those receiving propofol anesthesia, but no differences in troponin T and CK-MB release were observed between groups.[301] Postoperative NT-proBNP concentrations were lower and echocardiographically derived indices of LV function were preserved in patients undergoing OP-CAB who were anesthetized with sevoflurane compared with propofol.[302] The plasma concentrations of a biochemical marker of atherosclerotic plaque instability (pregnancy-associated plasma protein A) were also lower in sevoflurane-treated patients compared with those receiving propofol 72 hours after surgery (Fig. 28-18). In addition, sevoflurane-induced

alterations in genetic regulatory control of myocardial energy metabolism appeared to be favorably modified in such a way that postoperative cardiac function may be relatively preserved in OP-CAB patients receiving the volatile anesthetic compared with propofol.[302] Other studies also verified that sevoflurane and isoflurane may be used with equivalent protective efficacy in patients undergoing OP-CAB.[303,304]

Despite the generally compelling nature of the previously mentioned findings, the results of a number of other investigations have failed to show that volatile anesthetics exert any substantial myocardial protection in patients undergoing CABG with or without cardiopulmonary bypass. The effects of sevoflurane-remifentanil and propofol-remifentanil anesthesia adjusted to equivalent bispectral index values on intraoperative hemodynamics and postoperative myocardial necrosis (troponin I and CK-MB release) were examined and compared in two studies of patients undergoing OP-CAB.[305,306] No differences in these end points were observed between groups, although both studies were most likely underpowered to exclude β error from the analysis. Piriou and colleagues[307] randomized 72 patients to receive 1.0 MAC sevoflurane for 15 minutes followed by a 15-minute elimination period before cardiopulmonary bypass or placebo. Sevoflurane APC did not decrease postoperative troponin I release, nor did it affect the activities of several key protein kinases previously implicated in volatile anesthetic–induced myocardial protection, including ecto-5′-nucleotidase, PKC, PTK, and p38 MAPK, which were measured in atrial tissue biopsies. Fewer patients exposed to sevoflurane APC had reduced postoperative cardiac output, but the number of patients requiring inotropic support was similar between groups.[307] In the largest single-center, randomized clinical trial of its kind conducted to date, De Hert and colleagues[308] compared the effects of desflurane, sevoflurane, and propofol-based anesthesia on myocardial necrosis and long-term outcome in 414 patients undergoing CABG using cardiopulmonary bypass.[308] Maximal troponin T release and 1-year mortality were similar between groups, but hospital length of stay was shorter in patients receiving volatile anesthetic compared with total intravenous anesthesia. Postoperative troponin I release, intensive care unit and hospital length of stays, and short-term and long-term morbidity and mortality were also similar in a study of 100 patients undergoing CABG randomized to receive sufentanil with isoflurane or propofol.[309] Interpretation of these results requires qualification because naturally occurring (e.g., morphine) and synthetic opioids (e.g., fentanyl, sufentanil) also may be capable of producing myocardial protection in humans independent of volatile anesthetics or other medications implicated in pharmacologic preconditioning.[310,311] Peak troponin release and 1-year mortality were similar in 100 patients with coronary artery disease receiving continuous sevoflurane compared with propofol anesthesia for mitral valve surgery.[312] These data supported the findings of an earlier study demonstrating that desflurane APC (conducted using a 30-minute exposure before cardiopulmonary bypass) did not exert a selective myocardial protective effect compared with propofol in patients without coronary artery disease undergoing mitral valve surgery.[313]

Three meta-analyses emphasized that use of a volatile anesthetic during cardiac surgery most likely reduces the severity of myocardial necrosis associated with the procedure in contrast to intravenous anesthesia, but whether such a beneficial effect translates into an improvement in long-term clinical outcome was not definitively established. Symons and Myles[314] examined 27 clinical trials including 2979 patients undergoing CABG.[314] Postoperative troponin I release was decreased and cardiac index after cardiopulmonary bypass was greater, whereas the requirement for inotropic medications was diminished in patients receiving volatile compared with intravenous anesthetics, but no differences in the incidence of myocardial ischemia, postoperative myocardial infarction, intensive care unit length of stay, or hospital mortality were observed between groups. Yu and Beattie[315] analyzed 32 studies in which 2841 patients had been enrolled and confirmed that use of a volatile anesthetic during CABG surgery reduces postoperative troponin I release compared with an intravenous anesthetic technique.[315] Despite this observation, these authors were also unable to provide substantial evidence to support the hypothesis that a volatile anesthetic technique is linked to improved clinical outcome. In general, the overall conclusions of these two meta-analyses[314,315] concurred with the results of several large-scale clinical trials documenting the safety of volatile anesthetics compared with opioid-based anesthesia in cardiac surgical patients published more than 2 decades ago[282,283] in response to the isoflurane and coronary steal controversy. These latter studies continue to be vitally important because their results emphasized that anesthetic technique per se is not an important determinant of outcome in the setting of cardiac surgery.

In direct contrast to conclusions drawn by the two previously discussed meta-analyses,[314,315] another meta-analysis of 22 studies with 1922 patients undergoing cardiac surgery suggested that use of volatile anesthetics were, in fact, associated with significant reductions in the incidence of postoperative myocardial infarction (2.4% versus 5.1%; $P = .008$) and mortality (0.4% versus 1.6%; $P = .02$) compared with intravenous anesthesia.[316] The reasons for these divergent conclusions are unclear, especially considering that many of the same original clinical trials were included in all three meta-analyses. Nevertheless, two other studies have provided additional, albeit rather indirect, evidence that use of a volatile anesthetic may be capable of enhancing long-term outcome compared with intravenous anesthetic techniques. A longitudinal, risk-adjusted analysis of 64 Italian cardiac surgery centers examined whether a correlation existed between the use of volatile anesthetics and a decline in 30-day mortality in 34,310 patients undergoing CABG.[317] The authors concluded that use of a volatile anesthetic was weakly but significantly correlated with a decline in 30-day mortality ($r^2 = .07$; $P = .035$). The study's uncontrolled, retrospective design and the statistical methods used to estimate, rather than directly measure, 30-day mortality limited interpretation of the results. Nevertheless, the data suggest that there may be a positive relationship between the use of a volatile anesthetic and perioperative outcome in CABG patients. Similarly, a retrospective study of 10,535 patients also suggested that sevoflurane anesthesia was

associated with lower 30-day mortality in patients who had not suffered a recent myocardial infarction or did not have unstable angina (which mimics the beneficial effects of IPC) compared with a propofol-based anesthetic technique (2.28% versus 3.14%; $P = .015$).[318] However, no differences in 30-day mortality or the incidence of postoperative myocardial infarction were observed between groups when the entire cohort was examined as a whole.

Collectively, the results of these clinical trials and meta-analyses suggest that use of a volatile anesthetic during cardiac surgery may be associated with a reduction in the magnitude of myocardial necrosis and relative preservation of postoperative LV function compared with an intravenous anesthetic technique. Some evidence of clinical myocardial protection using an acute preconditioning strategy has been presented in the literature, but these data are certainly less convincing than the major findings from studies in which a volatile anesthetic was administered continuously throughout cardiac surgery. Whether delayed APC or APostC strategies have beneficial effects in cardiac surgical patients has yet to be examined. Perhaps most notably, few data have been presented to date directly indicating that use of a volatile anesthetic improves short-term or long-term outcome or decreases the incidence of major adverse cardiac events in patients undergoing cardiac or noncardiac surgery. When considered from the latter perspective, the recent American College of Cardiology Foundation and American Heart Association (ACCF/AHA) guidelines advocating the use of volatile anesthetics for myocardial protection in patients at risk for myocardial ischemia, including those undergoing noncardiac surgery,[319] may appear to be somewhat premature.[320,321] Whether such a strict interpretation of the accumulated data is truly valid will now be discussed in further detail.

Several reasons explain why the clearly advantageous protective effects of volatile anesthetics observed in laboratory settings of ischemia-reperfusion injury do not necessarily translate into equally robust clinical benefits.[322] First, volatile anesthetics may substantially alter the determinants of myocardial O_2 supply and demand through their direct and indirect effects on systemic, pulmonary, and coronary hemodynamics and autonomic nervous system activity in a dose-related manner. These changes may reduce myocardial O_2 consumption and ischemic burden under controlled conditions, but such beneficial effects may be offset or overcome in patients who are subjected to the profound stress associated with cardiac surgery and exposure to cardiopulmonary bypass. Most patients undergoing cardiac surgery are elderly and suffer from multiple coexisting diseases (e.g., hypertension, diabetes mellitus, hypercholesterolemia) that may cause abnormal cardiovascular homeostasis. Indeed, age[52] and diabetes[29] have been shown to attenuate or abolish APC in laboratory animals. Cardiac surgical patients are very often chronically treated with a variety of medications to manage their comorbid disease states and, in addition, receive other anesthetics, analgesics, and other vasoactive drugs that may influence the potentially salutary actions of volatile anesthetics during cardiac surgery. Coronary collateral blood flow, a key factor in determining the tolerance of susceptible regions of myocardium to ischemic stress, is relatively easy to quantify in experimental models of ischemia-reperfusion injury, but these alternative routes of myocardial perfusion are highly variable and are quite difficult to quantify in patients with coronary artery disease.

The relative amount of myocardium at risk for ischemic injury is probably the most important explanation why clinical investigations conducted to date have yet to demonstrate that volatile anesthetics favorably affect outcome in patients undergoing cardiac surgery. The intentional production of severe ischemia-reperfusion injury and the observation of its pathologic consequences without any intervention to mitigate them are characteristic features of virtually all laboratory studies. For example, a prolonged coronary artery ligation followed by several hours of reperfusion is commonly used to produce a large myocardial infarction in intact hearts, the size of which often exceeds more than 50% of the LV area at risk. This experimental model provides a clear, easily measured end point (infarct size) that may be used to discriminate whether administration of a volatile anesthetic reduces the magnitude of injury. Other commonly used models (e.g., Langendorff preparation, atrial or ventricular myocytes in vitro) may use other end points to quantify damage, but these models share the common feature that the heart or its cellular constituents are exposed to profound ischemic or hypoxic insult followed by reperfusion or reoxygenation. In contrast, substantially less myocardium is typically at ischemic risk during elective cardiac surgery unless an unanticipated intraoperative coronary artery occlusion occurs. This is the case because systemic and topical hypothermia, intermittent or continuous administration of antegrade and retrograde cardioplegia, and myocardial decompression are routinely used to minimize global ischemic damage during cardiopulmonary bypass in patients undergoing conventional CABG or valve surgery. Similarly, maintenance of coronary perfusion pressure with intravenous fluids or vasoactive medications during changes in cardiac position and use of intracoronary shunts to provide continuous coronary blood flow during construction of distal anastomoses are common techniques that also maintain global and regional myocardial integrity during OP-CAB or MID-CAB operations. The role of the vigilant anesthesiologist also cannot be overemphasized in these procedures because active prevention, prompt recognition, and immediate, aggressive treatment of myocardial ischemia are central objectives when caring for a patient undergoing cardiac surgery who is at risk for such an event. More subtle clinical end points (e.g., biochemical assays of myocardial necrosis or function, use of vasoactive medications, duration of intensive care unit or hospital stay) are also used to measure generally less intense ischemic injury.

The large differences in the amount of myocardium at risk for ischemia between experimental and clinical studies are emphasized when the following studies are considered. Peak and sustained troponins I and T release clearly predicted infarct size, LV dysfunction, and long-term clinical outcome in patients with acute ST-segment elevation myocardial infarction after an occluded coronary artery was reperfused in the cardiac catheterization laboratory.[323] Notably, the peak troponin I and

T concentrations (~450 and 4.7 ng/mL, respectively) observed in these patients with acute myocardial infarction after percutaneous coronary intervention[323] were at least several orders of magnitude greater than those that occur during sevoflurane or propofol anesthesia in patients undergoing CABG. For example, peak troponin I and T concentrations of approximately 6 and 1 ng/mL, respectively, were reported 24 hours after elective CABG in patients anesthetized with propofol.[286,308] These data clearly demonstrate that the amount of myocardium that may sustain ischemic damage during CABG surgery is relatively limited compared with evolving infarction. Under such circumstances, it may be very difficult, if not virtually impossible, to extrapolate small but statistically significant decreases in myocardial necrosis observed with volatile anesthetics into demonstrable improvements in short-term or long-term outcome without a well-conducted, large-scale, propensity-matched, randomized clinical trial in which thousands of patients are enrolled. The results of a recent study demonstrating that remote IPC combined with APC fails to provide additional myocardial protection in patients undergoing CABG may also be attributed to such an explanation because so little myocardium is actually at risk from the outset.[324] Alternatively, the general consensus of clinical data indicates that volatile anesthetics are capable of reducing injury and producing modest short-term benefits, even when only a small amount of myocardium is at risk.[320,321] Thus, when combined with the very clear conclusions of laboratory experiments, the observations of small clinical trials conducted to date provide compelling, albeit circumstantial, evidence suggesting that volatile anesthetics may indeed exert important protective effects and thereby improve outcome when larger areas of myocardium sustain ischemia-reperfusion injury. From this standpoint, the ACCF/AHA Guidelines appear to be justifiable based on this circumstantial evidence. Nevertheless, additional research will be required in the operating room to convincingly answer whether volatile anesthetics do indeed exert clinically relevant antiischemic effects by reducing the incidence and severity of major adverse cardiac events in patients undergoing cardiac or noncardiac surgery.

NEURAL CONTROL OF THE CIRCULATION

Volatile anesthetics have been shown to depress baroreceptor reflex control of arterial pressure in experimental animals to varying degrees. This inhibition of baroreceptor reflex activity occurs as a result of depression of central nervous system integration of afferent baroreceptor input, attenuation of efferent autonomic nervous system activity, and reductions in ganglionic transmission and end-organ response. Volatile anesthetics increased resting afferent nerve traffic and enhanced the sensitivity of arterial baroreceptors by a Ca^{2+}-dependent mechanism. These anesthetic-induced increases in baroreceptor sensitivity and discharge frequency tonically reduce overall sympathetic nervous system activity and attenuate sympathetic responses to declines in arterial pressure. Isoflurane, halothane, and enflurane inhibited preganglionic sympathetic efferent activity at clinically relevant concentrations in vivo. Volatile anesthetics reduced postganglionic sympathetic nerve activity, suggesting that attenuation of ganglionic transmission represents a major mechanism by which these medications depress sympathetic nerve traffic. Reduction of sympathetic outflow caused by volatile anesthetics has also been suggested by examination of endogenous plasma norepinephrine kinetics. Isoflurane and halothane decreased plasma concentrations of norepinephrine to varying degrees by causing a more pronounced decrease in norepinephrine spillover than clearance. Volatile anesthetics may also attenuate parasympathetic nervous system function. Halothane depressed vagal nerve efferent activity by direct measurement of parasympathetic nerve activity. These findings were supported by the results of several other studies demonstrating that volatile anesthetics inhibit reflex bradycardia in response to increases in arterial pressure. Parasympathetic and sympathetic nervous system outflows appear to be depressed to equivalent degrees during halothane or isoflurane anesthesia.

The effects of volatile anesthetics on neural control of the cardiovascular system have been incompletely examined in healthy humans and have not been described in patients with autonomic nervous system dysfunction. Halothane and enflurane produced greater attenuation of baroreceptor reflex regulation of heart rate than equivalent MAC concentrations of isoflurane. Depression of baroreceptor function by the older volatile anesthetics may be more profound compared with fentanyl, diazepam, and N_2O anesthesia. Baroreceptor-mediated control of peripheral arteriolar tone was also attenuated in young volunteers during halothane anesthesia. Steady-state anesthetic concentrations of sevoflurane were shown to cause greater depression of sympathetic nerve activity measured directly with microneurography in contrast to desflurane at equivalent levels of hypotension. These findings paralleled results demonstrating pronounced sympathetic hyperactivity during rapid increases in inspired desflurane concentration in humans. Importantly, the actions of volatile anesthetics on baroreceptor reflex control of the circulation may be profoundly altered during autonomic dysfunction in elderly patients or those with essential hypertension, diabetes mellitus, or heart failure.

NITROUS OXIDE AND CARDIOVASCULAR FUNCTION

CARDIOVASCULAR FUNCTION

Myocardial Contractility and Left Ventricular Diastolic Function

Experiments in papillary muscle and isolated heart preparations consistently demonstrated that N_2O produces a direct negative inotropic effect, but conflicting results about the influence of N_2O on contractility were observed in experimental animals and healthy volunteers. Several problems have contributed to apparently contradictory results in vivo. Observed changes in contractility may be influenced by the actions of N_2O on the systemic circulation or by autonomic nervous system reflex effects

because N_2O may increase sympathetic nervous system tone. Studies using N_2O alone are difficult to perform and interpret because the gas does not produce complete anesthesia at partial pressures less than 1 atm. The effects of N_2O on contractility also may be influenced by different baseline anesthetics. Furthermore, lack of use of load-insensitive measures of myocardial contractility has allowed only qualitative assessment of the effects of N_2O on intrinsic inotropic state in the intact heart.

Preload recruitable stroke work was used to demonstrate that N_2O depressed myocardial contractility in dogs anesthetized with isoflurane or sufentanil in the absence of autonomic nervous system activity. Seventy percent N_2O decreased this index of contractility by 28% and 41% during sufentanil and isoflurane anesthesia, respectively. Thus, 70% N_2O decreased contractility to approximately the same extent as 1 MAC isoflurane. Similar findings were reported using LV end-systolic pressure-dimension relations in acutely instrumented dogs. N_2O-induced myocardial depression may be offset by simultaneous increases in sympathetic nervous system tone. The negative inotropic effects of N_2O may be more pronounced in the presence of preexisting LV dysfunction. Moreover, N_2O-induced depression of contractile function appeared to overcome the mild sympathomimetic effect of the anesthetic gas in patients with coronary artery or valvular heart disease and LV dysfunction because increases in baseline sympathetic nervous system activity were not further augmented by N_2O under these clinical conditions.

The actions of N_2O on LV diastolic function have been incompletely studied. Modest increases in maximal lengthening velocity and maximal rate of decline of force were observed in ferret papillary muscle concomitant with decreases in contractile state. No changes in the rate of isometric or isotonic relaxation were observed, indicating that N_2O does not substantially modify myocardial relaxation. N_2O modestly increased indices of LV chamber stiffness and reduced early LV filling in acutely instrumented dogs. These findings were supported by evidence indicating that N_2O may produce LV diastolic dysfunction after cardiopulmonary bypass in patients undergoing CABG surgery. N_2O caused dose-related reductions in the intracellular Ca^{2+} transient in vitro. This finding indicated that N_2O-induced depression of myocardial contractility was related to decreases in Ca^{2+} availability for contractile activation. N_2O did not affect myofibrillar sensitivity to Ca^{2+} or Ca^{2+} uptake and release from the SR. In addition, the diastolic Ca^{2+} transient was unaffected by N_2O, suggesting that this anesthetic gas does not fundamentally alter myocardial relaxation kinetics.

Hemodynamics

Assessment of the hemodynamic effects of N_2O in humans is often complicated by administration of volatile anesthetics, opioids, or other medications in the presence or absence of cardiovascular disease. Typical clinical concentrations of N_2O (e.g., 40% to 70%) caused modest increases in heart rate in healthy volunteers. Small increases in heart rate also occurred when hyperbaric concentrations of N_2O were administered or when the gas was added to a volatile anesthetic. Declines in heart rate were observed with N_2O in patients with coronary artery disease anesthetized with isoflurane. Modest reductions in heart rate were reported in patients anesthetized with morphine or fentanyl undergoing cardiac surgery. Sixty percent N_2O caused small increases in arterial pressure in humans. Increases in arterial pressure also occurred under hyperbaric conditions or during volatile anesthesia in volunteers, consistent with a mild sympathomimetic effect. Other studies indicated that partial substitution of N_2O for a volatile anesthetic either did not affect or modestly increased arterial pressure during isoflurane or desflurane anesthesia in experiments conducted at constant MAC. In contrast, reductions in arterial pressure were observed in patients with coronary artery disease receiving N_2O in the presence and absence of opioids.

Small increases in cardiac output and stroke volume were noted during administration of 60% N_2O in O_2 in volunteers, but cardiac output remained unchanged in the presence of hyperbaric N_2O. Cardiac output was greater in volunteers anesthetized with N_2O and halothane than in those receiving halothane alone concomitant with increases in sympathetic nervous system outflow. The addition of N_2O to isoflurane or desflurane anesthesia also modestly increased cardiac output. In contrast, N_2O reduced cardiac output and stroke volume in healthy volunteers and patients with cardiac disease receiving opioids. Hyperbaric N_2O (1.5 MAC) caused a modest reduction in systemic vascular resistance. In contrast, systemic vascular resistance was higher during administration of a volatile anesthetic in the presence versus the absence of N_2O. Pretreatment with a ganglionic blocker attenuated the relative increase in systemic vascular resistance observed during administration of halothane and N_2O compared with halothane alone, findings that may be consistent with a reduction in sympathetic nervous system tone. N_2O-induced increases in systemic vascular resistance were reported in volunteers and patients with cardiac disease anesthetized with opioids.

N_2O increased venous tone and decreased venous capacitance in conscious volunteers. The gas also modestly increased pulmonary artery pressures and pulmonary vascular resistance in patients with coronary artery disease anesthetized with morphine and diazepam or a volatile anesthetic. Thus, the combined effects of enhanced venous return, elevated pulmonary vascular resistance, and depressed contractile function probably contributed to the increases in central venous pressure observed with N_2O in humans. Hyperbaric N_2O also enhanced central venous pressure in association with increases in pulmonary vascular resistance. N_2O inhibited norepinephrine uptake by the lung and subsequent increases in plasma norepinephrine levels detected in the pulmonary vasculature may be partially responsible for the characteristic increases in pulmonary vascular resistance observed during administration of this gas. N_2O-induced increases in pulmonary vascular resistance may be more pronounced in adults with pulmonary hypertension and children with increased pulmonary blood flow. Elevations in pulmonary artery pressures and vascular resistance were described during administration of N_2O in neonatal lambs. Such increases in pulmonary vascular resistance may potentially enhance right-to-left atrial or

ventricular shunts and thereby compromise arterial oxygenation in patients with congenital heart disease.

CARDIAC ELECTROPHYSIOLOGY

Reversible atrioventricular dissociation was reported in humans anesthetized with N_2O and volatile or opioid-based anesthetics. Addition of N_2O to halothane lowered the threshold at which arrhythmias occur. This observation may result from a combination of sympathetic nervous system stimulation by N_2O and myocardial sensitization by halothane. The incidence of arrhythmias was reduced during combined N_2O-opioid anesthesia compared with halothane alone.

CORONARY CIRCULATION

N_2O does not produce direct effects on the coronary vasculature in vitro. The gas altered coronary blood flow in parallel with changes in MVo_2 in dogs. N_2O decreased myocardial segment shortening, increased postsystolic shortening, and redistributed transmural coronary blood flow preferentially to the subepicardium (decreased endo/epi ratio) in experimental models of coronary artery disease. N_2O decreased the recovery of contractile function of canine stunned myocardium, and, in contrast to the findings with isoflurane, did not reduce myocardial infarct size in rats.[325] These data suggested that administration of N_2O before or during transient or prolonged coronary artery occlusion and reperfusion is not associated with myocardial protection. N_2O-induced sympathetic nervous system activation and imbalances of myocardial O_2 supply and demand represented potential mechanisms for the absence of a beneficial effect during reversible or irreversible ischemic injury. In the presence of a volatile anesthetic, N_2O decreased MVo_2 and myocardial O_2 extraction and may exacerbate myocardial ischemia during concomitant reductions in arterial pressure in patients with coronary artery disease. However, the addition of N_2O to volatile or opioid anesthetics did not increase the incidence of new regional wall motion abnormalities as assessed using transesophageal echocardiography in this patient population.

NEURAL CONTROL OF THE CIRCULATION

N_2O caused pupillary dilation, diaphoresis, and increases in systemic vascular resistance, central blood volume, and forearm vascular resistance in volunteers during volatile anesthesia, suggesting that N_2O activates the sympathetic nervous system. A subsequent study demonstrated that N_2O increases sympathetic nerve traffic measured using sympathetic microneurography in human volunteers, especially during the first 15 to 30 minutes of exposure to the gas. Baroreceptor reflex–mediated control of heart rate was impaired during administration of N_2O, but regulation of sympathetic outflow to peripheral blood vessels was preserved. This finding suggested N_2O does not alter sympathetic vasoconstrictor-induced maintenance of arterial pressure and may be partially responsible for the relative stability of hemodynamics during N_2O anesthesia.

XENON

In 1939, Behnke and Yarbrough reported that United States Navy divers developed "stupefaction," "mental fogginess," and neuromuscular impairment while breathing mixtures of argon or krypton and O_2 under hyperbaric conditions.[326] These seminal observations were the first to suggest that noble gases had the potential to produce anesthesia. Subsequent experiments with Xe conducted shortly after the end of World War II confirmed this hypothesis in mice[327] and human volunteers.[328] Xe has a very low blood-gas solubility coefficient (0.115) and produces rapid induction of and emergence from anesthesia. Xe is not teratogenic, does not undergo biotransformation, and exerts anesthetic and analgesic effects under normal atmospheric pressure conditions (1.0 MAC = 71%).[15] Xe is derived from α particle decay of radioactive heavy metals such as uranium and thorium. Xe naturally occurs in the atmosphere in trace amounts (1:11.5 million [8.7×10^{-6} %]) and is extracted from liquefied air by sequential cryogenic fractional distillation. Thus, Xe does not affect the ozone layer, unlike N_2O and volatile anesthetics. This latter effect may be particularly important because currently used inhaled anesthetics have been identified as strong greenhouse gases that contribute to total anthropogenic radiative forcing of global climate change.[329] Xe is expensive to produce because of its rarity; only a finite amount is available for use as a general anesthetic. Total world production of Xe is estimated to be approximately 9 to 12 million liters per year. Despite its relative scarcity and high production costs, Xe was approved for clinical use in Russia, Germany, France, and the United Kingdom during the past decade. A closed-circuit anesthetic technique using a relatively simple modification of a conventional anesthesia machine and a new miniature cryogenic waste gas recycling system have recently been described that may eventually make the use of Xe more cost-effective and competitive with other inhaled anesthetics.[330,331]

Unlike volatile anesthetics and N_2O, which produce diverse hemodynamic actions in the absence or presence of heart disease, Xe is essentially devoid of major cardiovascular effects.[15,332] For example, Xe did not alter the amplitudes of Na^+, L-type Ca^{2+}, and inward-rectifier K^+ channel currents over a range of voltages in the isolated cardiac myocyte nor did the anesthetic noble gas affect indices of cardiac function in a Langendorff heart preparation (Figs. 28-19 and 28-20).[333] No changes in the inotropic response to Ca^{2+}, isoproterenol, or increased stimulation rate were observed during administration of Xe in isolated ventricular myocytes.[334] In contrast to the equivalent MAC of halothane and isoflurane, Xe did not affect voltage-gated Ca^{2+} currents and caused minimal inhibition of transient outward K^+ currents in human atrial myocytes in vitro.[335] Xe anesthesia also did not adversely affect the circulatory response to moderate hypoventilation in vivo.[336] Administration of Xe did not alter invasively derived indices of LV systolic and diastolic function or systemic hemodynamics in isoflurane-anesthetized dogs before and after the development of congestive heart failure. Xe also produced minimal hemodynamic effects and did not affect

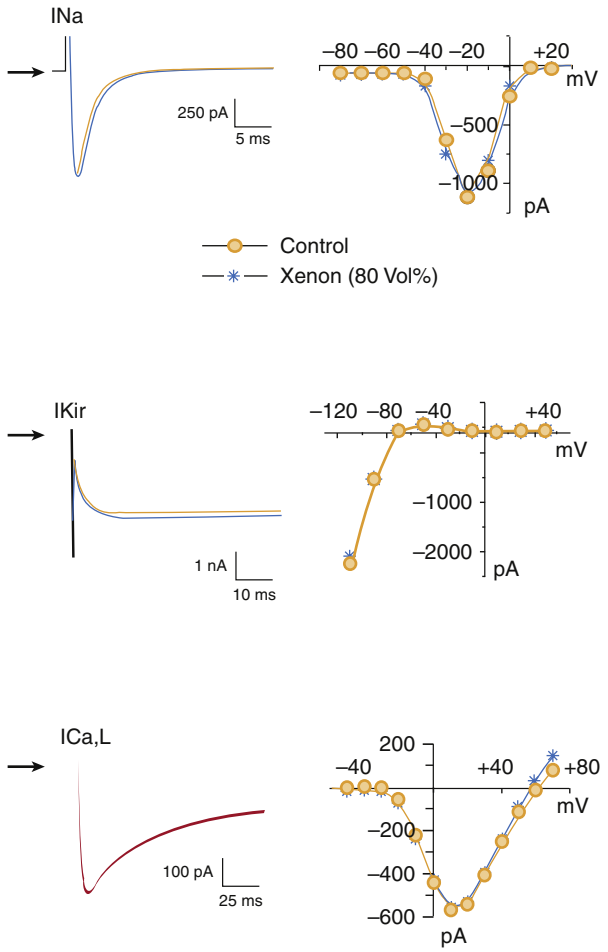


Figure 28-19. Effects of 80 vol% xenon on cardiac ionic currents in single cardiac myocytes *(left)*. Sample current traces recorded from three different myocytes were monitored at test potentials of –20 mV for I_{Na}, –110 mV for I_{Kir}, and +10 mV for $I_{Ca,L}$. Holding potentials were –110 mV for I_{Na}, –40 mV for I_{Kir}, and –50 mV for $I_{Ca,L}$. Corresponding current-voltage relationships for I_{Na}, I_{Kir}, and $I_{Ca,L}$ are shown. *(From Stowe DF, Rehmert GC, Kwok WM, et al: Xenon does not alter cardiac function or major cation currents in isolated guinea pig hearts or myocytes,* Anesthesiology *92:516-522, 2000.)*

contractile function in a rabbit model of myocardial infarction and chronic LV dysfunction.[337] In agreement with these experimental findings, the results of several clinical studies have also documented that Xe anesthesia is associated with remarkable cardiovascular stability in patients with or without heart disease. Xe anesthesia was shown to produce minimal effects on coronary blood flow dynamics and regional cerebral perfusion evaluated using positron emission tomography in healthy volunteers.[338,339] LV function assessed using transesophageal echocardiography was unchanged during 65% Xe-O_2 anesthesia in patients undergoing abdominal surgery. Systemic hemodynamics were unchanged and recovery from anesthesia was faster in patients who received 60% Xe-O_2 compared with 60% N_2O–0.5% isoflurane during elective surgery.[340] Similarly, mean arterial pressure was maintained at conscious values during Xe-remifentanil but not propofol-remifentanil anesthesia in another study of patients undergoing elective surgery.[341] Maintenance of autonomic nervous system–mediated regulation of the circulation during Xe anesthesia was most likely a major contributing factor to this preservation of hemodynamics.[342] Mean arterial pressure and LV function were preserved during Xe anesthesia in patients with coronary artery disease undergoing noncardiac surgery[343] and those with congestive heart failure in whom a cardioverter-defibrillator was implanted.[344] A phase I clinical trial further demonstrated the cardiovascular safety of Xe in patients undergoing CABG using cardiopulmonary bypass.[345]

When considered within the context of these laboratory and clinical findings, the ability of Xe to protect myocardium against ischemic injury is particularly striking. Preckel and associates[346] first demonstrated that administration of 70% Xe during the initial 15 minutes of reperfusion after prolonged coronary artery occlusion (postconditioning) reduced myocardial infarct size in rabbits.[346] Because Xe does not substantially affect the cardiovascular system, alterations in electrophysiology, inotropic state, coronary blood flow, and the hemodynamic determinants of myocardial O_2 supply-demand relations were most likely not responsible for the observed protective effects.[346] Another study demonstrated that administration of 75% Xe before and after brief coronary artery occlusion and reperfusion enhanced the functional recovery of stunned myocardium independent of changes in systemic hemodynamics and coronary collateral perfusion.[347] Weber and associates[348] subsequently demonstrated that three cycles of brief (5-minute) exposure to 70% Xe-O_2 interspersed with 5-minute periods of 70% N_2-O_2 before prolonged coronary occlusion and reperfusion reduced myocardial infarct size in vivo.[348] The magnitude of the myocardial protection resulting from this Xe preconditioning (XePC) was similar to that produced by IPC and APC. The authors further demonstrated that pretreatment with PKC or p38 MAPK inhibitors abolished XePC. In addition, Xe caused posttranslational modification and translocation of PKC-ε from the cytosol to the sarcolemmal membrane in a p38 MAPK–dependent fashion consistent with enzyme activation (Fig. 28-21). These results were also similar to findings observed during IPC and APC.

Additional evidence supports the hypothesis that the mechanisms responsible for XePC are indeed very similar to those of other forms of preconditioning. For example, two important downstream targets of p38 MAPK—MAPKAPK-2 and Hsp27—were shown to be essential for the beneficial effect of APC and XePC.[86] MAPKAPK-2 phosphorylates Hsp27, thereby promoting its translocation to, and facilitating its stabilization of, the actin cytoskeletal structure of the cardiac myocyte. Like APC, XePC phosphorylated MAPKAPK-2 and Hsp27, and these actions were abolished by pretreatment with PKC or p38 MAPK inhibitors. Furthermore, XePC also enhanced Hsp27 translocation, increased F-actin polymerization, and colocalized phospho-Hsp27 and F-actin. Thus, XePC was linked to the cytoskeleton through p38 MAPK-mediated activation of MAPKAPK-2 and Hsp27. These data implicated selective transportation of specific proteins to unique cellular locations to facilitate myocardial protection during XePC. Essential roles for mitochondrial K_{ATP} and other signaling kinases known to be of central importance in other forms

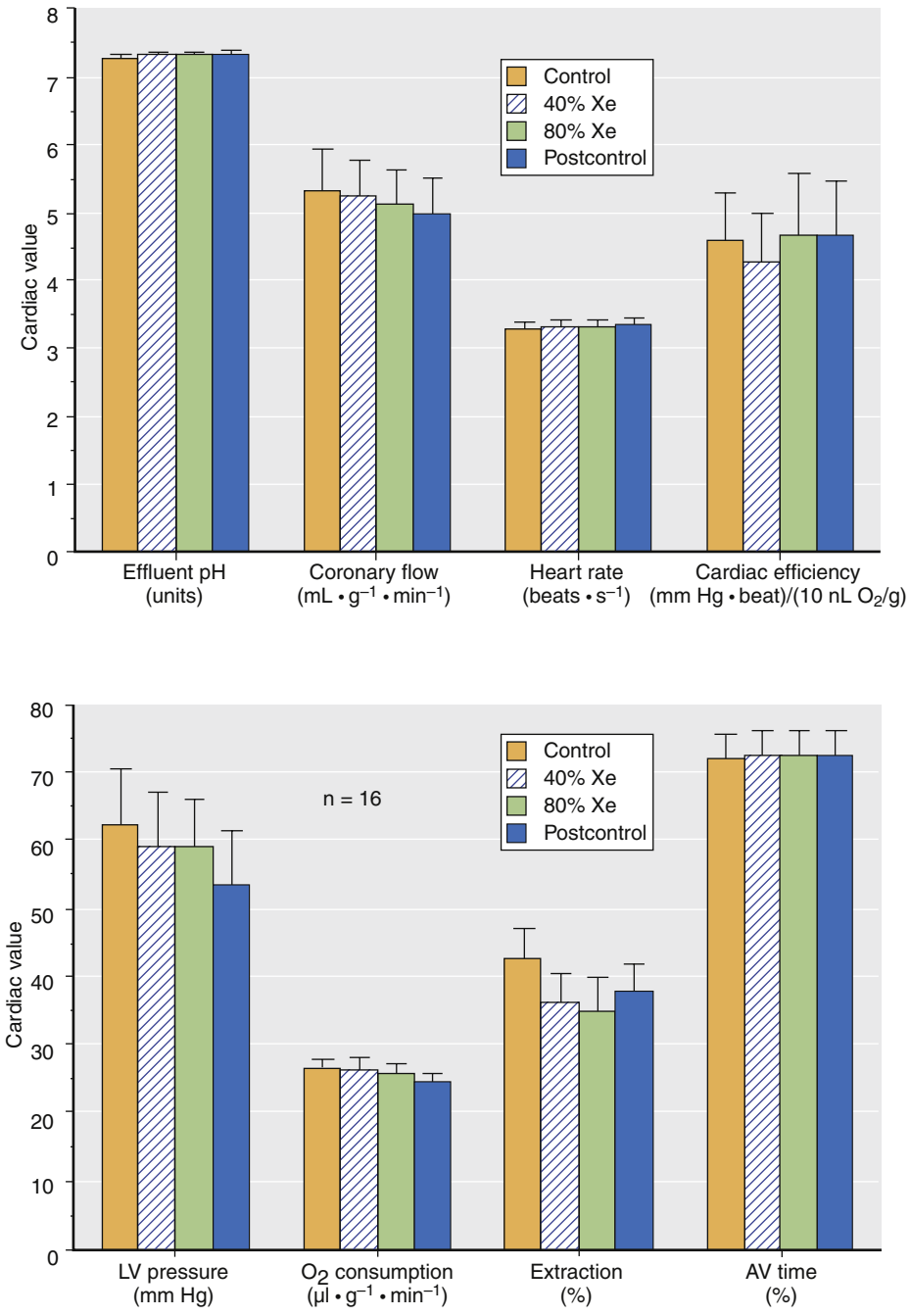


Figure 28-20. Lack of effect of two concentrations of xenon dissolved in erythrocyte-Krebs-Ringer solution on eight cardiac variables in guinea pig isolated hearts perfused at constant pressure. *AV,* Atrioventricular; *LV pressure,* left ventricular isovolumic pressure; *Postcontrol,* last control after Xe. *(From Stowe DF, Rehmert GC, Kwok WM, et al: Xenon does not alter cardiac function or major cation currents in isolated guinea pig hearts or myocytes,* Anesthesiology *92: 516-522, 2000.)*

of preconditioning and postconditioning also have been demonstrated in XePC. For example, a selective mitochondrial K_{ATP} antagonist blocked XePC-induced reductions in infarct size, phosphorylation of PKC-ε, and membrane translocation of PKC-ε in vivo.[349] Furthermore, a selective PI3K antagonist not only abolished myocardial protection produced by XePC but also inhibited phosphorylation of Akt and another PI3K-related enzyme.[350,351] XePC directly enhanced phosphorylation and translocation of ERK1/2 from the cytosol to the nucleus, whereas pretreatment with an antagonist of an upstream activator of this enzyme abolished XePC-induced protection against infarction.[350] Notably, XePC did not phosphorylate the stress-activated p46/p54 MAPK (also known as c-Jun-N-terminal kinases 1/2 and 3 [JNK 1/2 and 3]), nor did a specific inhibitor of this enzyme complex abolish reductions in infarct size produced by the noble gas. These findings suggested that not only is Xe capable of selectively activating some signaling kinases while leaving others unaffected, but also at least one important difference exists between XePC and IPC in which the involvement of p46/p54 was previously implicated.[350,352] Despite this relatively minor difference in signal transduction between XePC and IPC, Xe directly inhibited Ca^{2+}-induced mPTP opening in isolated ventricular mitochondria,[351] similar to the findings with APC[108] and IPC.[105] As mentioned earlier, mPTP is considered a primary end-effector of preconditioning and postconditioning phenomena. Thus, preservation of mitochondrial integrity appears to be of central importance during XePC, as well (Fig. 28-22).

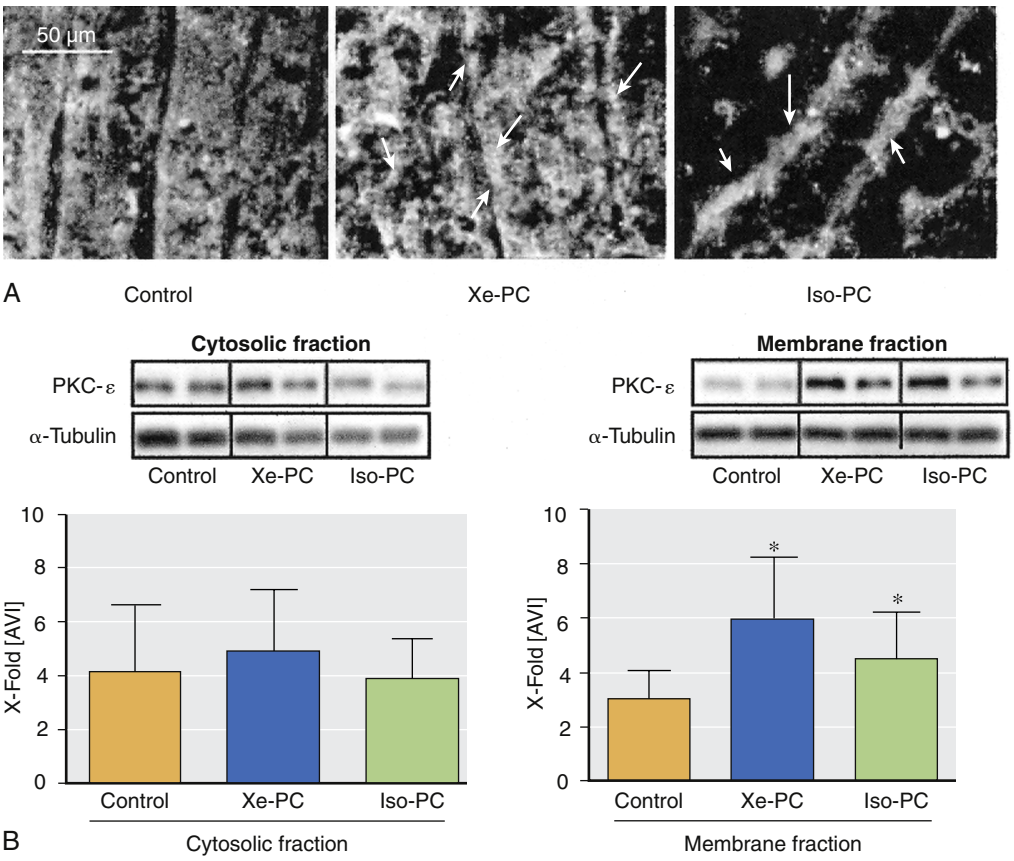


Figure 28-21. Representative Western blots (**A**) and histograms (**B**) illustrating phosphorylation and membrane translocation of the epsilon isoform of protein kinase C ε (PKC-ε) during control conditions and in the presence of xenon or isoflurane preconditioning (*Xe-PC* and *Iso-PC,* respectively). α-Tubulin was used as a standard to ensure uniform protein distribution on each blot. The histogram presents densitometric evaluation as times *(x)*-fold average light intensity (*AVI*). *Significantly ($P < .05$) different from control. *(From Weber NC, Toma O, Wolter JI, et al: The noble gas xenon induces pharmacological preconditioning in the rat heart in vivo via induction of PKC-epsilon and p38 MAPK,* Br J Pharmacol *144: 123-132, 2005.)*

Xe may cause myocardial protection against reversible or irreversible ischemic injury by favorably modulating endothelium-neutrophil interaction. The effects of Xe on cell adhesion molecule expression were examined in isolated human neutrophils in the absence or presence of known stimulants of enhanced neutrophil activity.[353] Xe decreased neutrophil expression of the adhesion molecules P-selectin glycoprotein ligand-1 (a regulator of neutrophil rolling on the endothelial surface) and L-selectin. Xe also inhibited exogenous stimulant-induced augmentation of L-selectin but not β_2-integrin (CD11a and CD11b) expression. Selectins initiate neutrophil-endothelial cell contact, whereas β_2-integrins are required for tight adhesion of neutrophils and their subsequent migration through endothelium. Thus, Xe may attenuate adhesion of neutrophils to endothelium, but the noble gas does not appear to affect their migration during ischemia-reperfusion injury.[353] Nevertheless, the results of another study failed to support these conclusions, because Xe did not affect cytokine and cell adhesion molecule expression in neutrophils activated by exposure to cardiopulmonary bypass.[354] More recently, the effects of Xe on TNF-α–induced cell adhesion molecule and NF-κB expression were studied in human umbilical vein endothelial cells.[28] Similar to the findings with volatile anesthetics, Xe blocked stimulated cell adhesion molecule expression by TNF-α and attenuated transcriptional activity of NF-κB, suggesting that Xe may protect against ischemic injury by favorably modulating these factors in vascular endothelium. In addition, Xe and isoflurane caused reductions in plasma TNF-α and IL-6 concentrations of similar magnitude in a porcine model of RV infarction.[355]

Like volatile anesthetics, Xe also causes delayed preconditioning in vivo. Weber and colleagues[356] demonstrated that a single 15-minute exposure to 70% Xe-O_2 performed 24 hours before prolonged coronary artery occlusion and reperfusion protects myocardium against infarction.[356] The magnitude of reductions in myocardial necrosis observed during this late XePC were similar to those observed during acute XePC.[348] Analogous to the findings during late APC,[170] pretreatment with a selective COX-2 antagonist blocked delayed XePC.[356] An increase in COX-2 activity was also shown to mediate late XePC. It is highly likely that other signaling molecules, protein kinases, and transcription factors previously implicated in delayed APC and IPC also play important roles in late XePC, but further studies will be required to confirm this hypothesis.

The mechanism(s) by which Xe selectively interacts with biologically active molecules to produce myocardial protection against ischemia-reperfusion injury remains a mystery.[15,332] Xe is not entirely inert despite completely filled electron orbitals and may be ionized or form covalent bonds in the presence of very strong oxidizing agents at low temperatures,[357] but the noble gas is essentially nonreactive under normal physiologic conditions. Intraatomic dipole formation within the outer electron orbitals ($[Kr]5s^2 4d^{10} 5p^6$) of the relatively large Xe atom may account for its ability to interact with ion channels, enzymes, or receptors, but this theory fails to account for

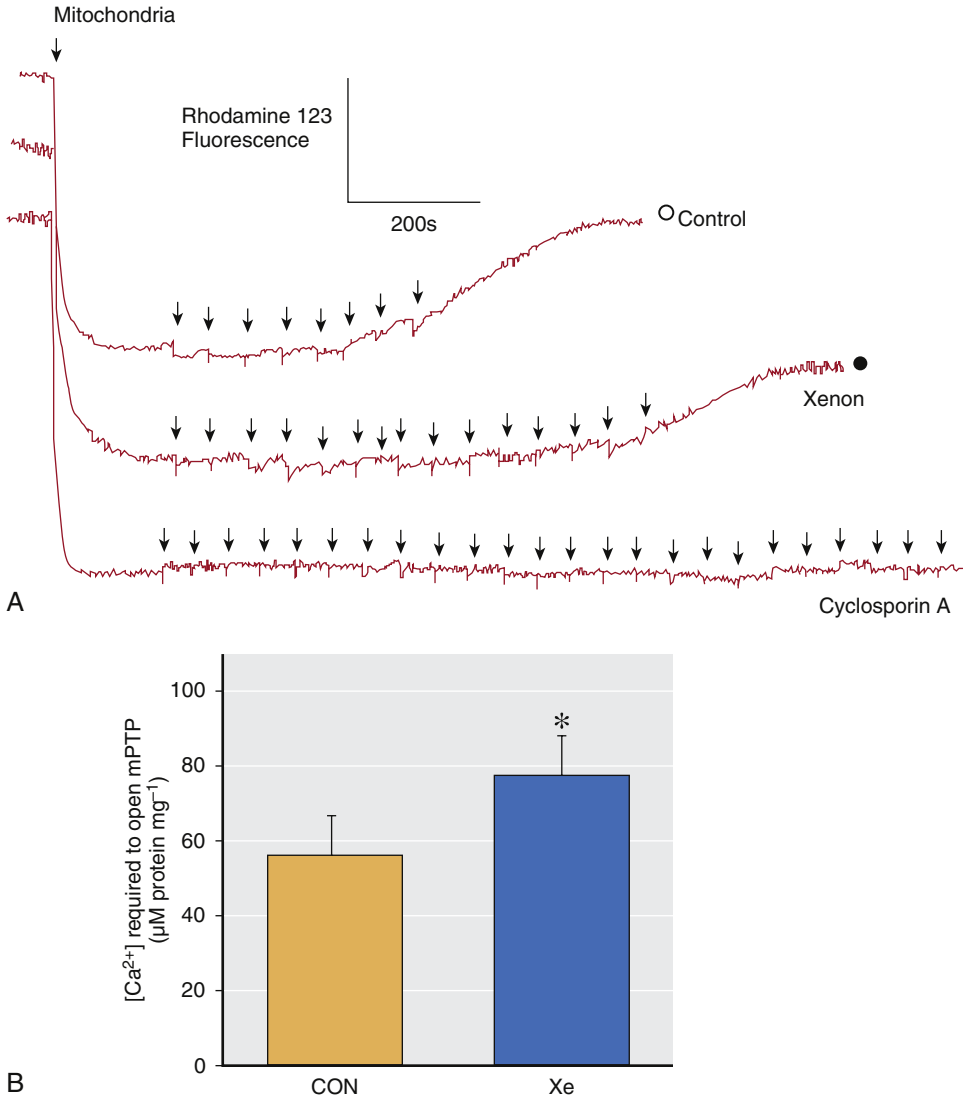


Figure 28-22. Effect of xenon preconditioning on isolated mitochondrial permeability transition pore *(mPTP)* opening. **A,** Typical chart recording showing mitochondrial membrane potential at state 2 with increasing calcium concentration ([Ca^{2+}]). The *arrows* denote the addition of Ca^{2+} in 5-μM increments. Depolarization was detectable by opening mPTP and releasing Ca^{2+} from mitochondria through the mPTP with sequential Ca^{2+} loading. Xe preconditioning delayed depolarization, indicating inhibition of mPTP opening. *Open circle,* Control; *solid circle,* Xe preconditioning. Depolarization was not observed in the presence of mPTP inhibitor cyclosporin A. **B,** Histograms summarizing the results. *CON,* Control; *Xe,* xenon preconditioning (n = 6 per group). *(From Mio Y, Shim YH, Richards E: Xenon preconditioning: the role of prosurvival signaling, mitochondrial permeability transition and bioenergetics in rats,* Anesth Analg *108:858-66, 2009.)*

the selectivity with which such an interaction may occur. Other nonanesthetic noble gases (e.g., helium, neon) have been shown to exert protective effects against myocardial ischemia-reperfusion injury,[358] and their electron orbital structures are not conducive to intraatomic dipole formation. X-ray crystallography studies demonstrated that the catalytic sites of several serine proteases contain specific binding cavities for Xe. Many of the prosurvival signaling kinases implicated in XePC are serine proteases that display conserved structural homology among species. These observations suggest a plausible mechanism by which Xe may activate protein kinases to mitigate ischemic injury. Nevertheless, extrapolation of x-ray crystallography findings to the intact heart may be difficult because the crystallography experiments were conducted using crystallized proteins under hyperbaric conditions (Xe pressures between 8 and 20 atm). Xe and N_2O were shown to occupy the heme pocket of CYP450 monooxygenase and competitively inhibit the enzyme's catalytic activity under standard atmospheric pressure conditions. However, only Xe, and not N_2O, is capable of producing myocardial protection.[325] Molecular modeling and electrophysiology studies suggested that Xe and isoflurane selectively inhibit the *N*-methyl-D-aspartate (NMDA) receptor by binding to its glycine agonist site[359] through the phenylalanine 758 residue.[360] These data suggested that Xe was capable of selectively interacting with a complex protein in vitro. However, it is unclear why Xe may activate some kinases or receptors while leaving others unaffected. As discussed, ERK1/2, but not c-Jun N-terminal kinases, mediated XePC in vivo,[350] whereas both kinase types are known to play roles in IPC. Thus, the precise biochemistry of selective Xe-protein interaction remains elusive, but strong pharmacologic evidence shows that Xe protects myocardium against ischemia-reperfusion injury by activating many of the same signaling pathways that are responsible for other forms of preconditioning and postconditioning. Whether Xe produces myocardial protection in humans is currently unknown and will require clinical trials to determine.

SUMMARY

Volatile anesthetics exert profound effects on the cardiovascular system by altering the inotropic, chronotropic,

dromotropic, and lusitropic state of the heart. Volatile anesthetics also produce significant actions on both the preload and afterload systems. These pharmacologic effects cause dramatic changes in hemodynamics that may be accentuated in patients with underlying cardiovascular disease. Less profound but equally important effects are observed with N_2O and Xe. Volatile anesthetics and Xe, but not N_2O, have been shown to cause myocardial protection, thereby directly reducing the sequelae of ischemia and reperfusion injury. The use of inhaled anesthetics requires a clear understanding of their complex cardiovascular pharmacology.

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Chapter 29

Inhaled Anesthetics: Delivery Systems

STEVEN G. VENTICINQUE • J. JEFFREY ANDREWS

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Key Points

- If there is any possibility that the workstation or the breathing circuit is a potential cause of difficulty with ventilation or oxygenation, switching to a self-inflating resuscitation bag is an appropriate decision. *Ventilate and oxygenate first — troubleshoot later.*
- The most important part of the preuse anesthesia workstation checkout procedure is verifying the presence of a self-inflating resuscitation bag.
- The Diameter Index Safety System (DISS) is designed to prevent the misconnection of hospital gas supply lines to the anesthesia workstation. The Pin Index Safety System (PISS) is designed to prevent incorrect gas cylinder connections in the anesthesia workstation. Neither system is immune from failure.
- If the hospital pipeline becomes crossed or contaminated, two actions must be taken. The backup oxygen cylinder valve must be opened, and the wall supply sources must be disconnected. Otherwise, hospital pipeline gas will continue to flow to the patient.
- Fail-safe valves and proportioning systems help minimize delivery of a hypoxic mixture, but they are not always effective. Delivery of a hypoxic mixture can result from (1) the wrong supply gas, (2) a defective or broken safety device, (3) leaks downstream from these safety devices, (4) administration of a fourth inert gas (e.g., helium), and (5) dilution of the inspired oxygen concentration by high concentrations of inhaled anesthetic agents (e.g., desflurane).
- The low-pressure section (LPS) of the gas supply system is a highly vulnerable area of the anesthesia machine because it is subject to breakage and leaks. The LPS is located downstream from all safety features of anesthesia machines, except the breathing circuit oxygen analyzer, and it is the portion of the machine that is missed if an inappropriate LPS leak test is performed.
- The LPS must be checked for leaks before an anesthetic agent is administered because leaks in the LPS can cause delivery of a hypoxic mixture or an inadequate concentration of anesthetic agent that could result in a patient's awareness during anesthesia (see also Chapter 44).
- Because many older Datex-Ohmeda anesthesia machines and some modern GE Healthcare machines have a one-way check valve in the LPS, a negative-pressure leak test is required to detect leaks in the LPS on these machines. On machines without a check valve in this location, manual positive-pressure testing or automated testing is used to test the LPS for leaks.
- Internal vaporizer leaks can be detected only when the vaporizer is turned on. This is true even during machine self-tests. The GE/Datex-Ohmeda Aladin cassette vaporizer and the Maquet FLOW-i anesthesia workstation vaporizer are exceptions to this rule.
- Saturated vapor pressure is a physical property of a liquid, and it depends on temperature. It is not affected by barometric pressure.
- The main purpose of the temperature compensation device within variable bypass vaporizers is to compensate for the liquid cooling that results from evaporation of volatile anesthetic liquid.
- Because of desflurane's low boiling point and high vapor pressure, controlled vaporization of desflurane is not possible using a variable bypass vaporizer.

Key Points—cont'd

- Misfilling a variable bypass vaporizer with desflurane could theoretically be catastrophic and potentially cause delivery of a hypoxic mixture and a massive overdose of inhaled desflurane.
- Increasing the fresh gas flow rate into the circle breathing system causes less rebreathing of volatile anesthetic gas and more waste gas.
- Before an anesthetic agent is administered, the circle system must be checked for leaks and flow. To test for leaks, the circle system should be pressurized to 30 cm H_2O, and the circle system airway pressure gauge should be observed (static test). An automated test may perform this function on many modern machines. To check for appropriate flow, to rule out obstruction and faulty valves, the ventilator or the breathing bag and a test lung (another breathing bag) can be used (dynamic test).
- Inhaled anesthetic agents can interact with carbon dioxide absorbents and produce potentially harmful degradation products. During sevoflurane anesthesia, compound A can be formed, particularly at low fresh gas flow rates. During desflurane anesthesia, carbon monoxide can be produced, particularly with desiccated absorbents (see also Chapter 26). The minimization of strong bases in absorbents decreases this risk.
- Anesthesia ventilators with ascending bellows (bellows ascending during the expiratory phase) are safer than descending bellows because disconnections are readily manifested by failure of ascending bellows to refill.
- Piston ventilators and descending bellows ventilators can potentially draw room air into the breathing circuit if a leak is present.
- With machines that do not have a fresh gas decoupling feature, oxygen flushing during the inspiratory phase can cause volutrauma or barotrauma, or both (particularly in pediatric patients) (see also Chapter 93). Therefore, the oxygen flush should never be activated during the inspiratory phase of mechanical ventilation.
- On older-generation anesthesia machines, tidal volume and airway pressure during positive-pressure ventilation are increased by increases in fresh gas flow rate. Most newer-generation machines compensate for changes in fresh gas flow rate. Obviously, anesthesia providers should know whether their machines compensate for these changes.
- Workstations that use bellows ventilators that scavenge gas from both the patient and the ventilator drive have substantially increased volumes of scavenged gas. Thus, the scavenging systems must be set appropriately (e.g., adequate vacuum) to accommodate the increased volume, or pollution of the operating room environment could result.
- Obstruction of the scavenging system transfer tubing (segment between the breathing circuit and the scavenging interface) can result in increased breathing circuit pressure and barotrauma.
- An inadequate vacuum to an open scavenging interface can cause leakage of anesthetic gases into the room.
- The American Society of Anesthesiologists *Recommendations for Pre-Anesthesia Checkout Procedures (2008)* serves as an excellent template for the creation of machine-specific checkout procedures. However, it is not a one-size-fits-all checklist.

Modern anesthesia delivery systems have evolved from the ether-soaked sponges and rags used in the mid-1800s. During that era, spontaneous breathing was the only mode of ventilation, no safety features existed besides vigilance, and the norm was uncertainty regarding the delivered anesthetic concentration. Today, anesthesia workstations are capable of safely delivering controlled concentrations of volatile anesthetic agents and other gases, along with providing positive-pressure ventilation, scavenging waste anesthetic gas, and monitoring for hazardous conditions or output failures. Newcomers to the specialty often find the anesthesia machine to be both mysterious and

intimidating, even though these practitioners often have some experience with other ventilation equipment, such as the intensive care unit (ICU) ventilator. The following requirements highlight the unique demands placed on the anesthesia workstation and help explain why it functionally differs from its ICU counterpart.

- Deliver volatile anesthetic gas at precise concentrations.
- Allow rebreathing of the exhaled anesthetic gases after removing carbon dioxide.
- Individually meter oxygen and two or more other breathing gases, and continuously enrich the inhaled gas with these vapors.
- Provide a manual mode of breathing ("bag" ventilation) with adjustable breathing circuit pressure control.
- Eliminate ("scavenge") excess gas from the patient's breathing circuit, and remove this gas from the room.
- Continuously measure the inspired oxygen concentration.
- Prevent hypoxic gas mixtures caused by operator error or gas supply failure.
- Provide a breathing circuit manual oxygen flush feature.
- Possess a backup supply of oxygen.
- Display gas pipeline and backup tank supply pressures.

Anesthesia workstations undergo steady innovation and change that make maintaining a current knowledge base difficult for many practitioners to achieve. Understanding anesthetic equipment is important because the workstation is one of the most essential pieces of equipment used by anesthesia care providers. Some design and engineering changes enhance ease of use and efficiency, and some enhance patients' safety. In fact, closed claims analysis of adverse anesthetic outcomes related to the anesthesia delivery system have declined and now account for only approximately 1% of the claims in the American Society of Anesthesiologists (ASA) closed claims database.[1] However, although claims related to the medical gas delivery system are infrequent, when they do occur they are usually severe, involving death or permanent brain injury.[2]

Although anesthesia workstation engineering advances may decrease the incidence of mishaps and injuries to patients, adverse events will never be eliminated. In addition, with new technologies come new potential problems. To prevent mishaps, providers must be aware of the operational characteristics and functional anatomy of their anesthesia workstations. Many workstations and their components share very similar characteristics, but the variation among them is growing. Similarly, the operational and preuse checkout procedures are becoming more divergent, thus mandating device-specific familiarity. Unfortunately, a lack of knowledge pertaining to the anesthesia workstation and a lack of understanding and application of a proper preuse check are common.[3-8] The increasing diversity in the design and function of these machines could potentially worsen the anesthesia provider's knowledge deficit. The safe use of today's anesthesia workstation requires a solid generic understanding, as well as knowledge of machine-specific features and checkout procedures.

Because anesthesia workstations consist of numerous subsystems, it is useful to learn about the machine in a manner that addresses each subsystem individually and as they relate to the system as a whole. This functional anatomy approach is familiar and useful. The chapter is therefore arranged as follows:

1. Standards and guidelines for anesthesia workstations
2. Functional anatomy sections
   a. Gas supply system
   b. Anesthetic breathing circuits
   c. Anesthetic vaporizers
   d. Waste gas scavenging systems
3. Anesthesia machine preuse checkout

For several decades, anesthesia workstation design remained fairly similar, barring some differences in subsystem design. In particular, the circle breathing circuits were virtually identical, and the schematic was requisite knowledge for the anesthesiology consultant. With moderate effort, a comprehensive understanding of the entire machine was attainable. Today, these workstations have increasing numbers of differences in terms of features and design nuance. Variability is now the norm. The ASA's current *Recommendations for Pre-Anesthesia Checkout* states more clearly than earlier versions that the checkout serves as a guide for users to *create their own machine-specific checkout procedures*, whereas the previous version could be more universally applied.[9,10] Earlier machines also tended to be more mechanical and less electronic. Further, with older machines the components were more exposed and therefore were easier to see and functionally understand. Newer workstations are more modular, and many of the components are concealed from view. An obvious analogy is the automobile. Arguably, our generic understanding and ability to troubleshoot issues with automobiles have diminished as a result of their increasing complexity, diversity, and component concealment.

Providing a detailed description of each gas system, subsystem component, and patient's breathing circuit is not practical within the scope of a single chapter. However, because anesthesia workstations must adhere to basic standards, a generic approach to learning is a suitable starting point. Although several subsystems are described in detail in this chapter, anesthesia providers must acquire a functional understanding of their own workstations and ensure that their local preuse checkout procedures are suitable for their machines.

STANDARDS AND GUIDELINES FOR ANESTHESIA WORKSTATIONS

Standards for medical devices and anesthesia workstations provide guidelines for manufacturers regarding device minimum performance, design characteristics, and safety requirements. For the anesthesia workstation, many of these requirements are outlined in the standards of ASTM International (formerly known as the American Society for Testing and Materials). ASTM International is a developer of international voluntary consensus standards.[11] The current standards are defined within the

Standard Specification for Particular Requirements for Anesthesia Workstations and Their Components F1850-00, found within ASTM volume 13.02, September 2012, *Medical and Surgical Materials and Devices*.[12] Additional ASTM International standards address anesthesia breathing systems, anesthetic gas scavenging systems, and alarm signals. ASTM International standards also apply the International Electrotechnical Commission (IEC) 60601-1 standards, which pertain to medical electrical equipment safety. The IEC 60601-1 serves as parent standards for numerous medical device standards. Additional key standards for machine subsystems arise from the Compressed Gas Association (CGA) and the Institute of Electrical and Electronics Engineers (IEEE), although other standards may directly or indirectly affect workstation design.[12]

The ASTM International specification describes the anesthesia workstation as a "system for administration of anesthesia to patients" consisting of "the anesthesia gas supply device, anesthesia ventilator, monitoring devices, and protection devices."[12] The standards define numerous aspects of design and construction, including protection against common hazards, protection against incorrect machine output, monitoring standards, alarm standards, and the requirements for several other safety systems. Although these standards are too long to describe here comprehensively, several of them are addressed in this chapter as they pertain to various subsystems.

The ASA publishes several guidelines pertaining to the anesthesia workstation.[9] The *Recommendations for Pre-Anesthesia Checkout,* which was updated last in 2008, serves as a general guideline for individual departments and practitioners to design preanesthesia checkout procedures specific to their anesthetic delivery systems.[9] The ASA *Guidelines for Determining Anesthesia Machine Obsolescence* helps to assist anesthesia providers and other health care personnel, administrators, and regulatory bodies determine when an anesthesia machine is obsolete by applying both absolute and relative criteria.[9] Finally, the ASA also publishes *Standards for Basic Anesthetic Monitoring,* which outlines minimal monitoring standards pertaining to oxygenation, ventilation, circulation, body temperature, and the requirements for the presence of anesthesia personnel. Standards and recommendations pertaining to the anesthesia workstation are published by several other national anesthesiology societies.[13,14]

FUNCTIONAL ANATOMY OF THE ANESTHESIA WORKSTATION

GAS SUPPLY SYSTEM

Regardless of the increasing electronic complexity of the anesthesia machine, it remains a fundamentally pneumatic device. Central to its function is the safe delivery and metering of the breathing gases, particularly oxygen, from the gas supply sources to the vaporizers and finally to the patient's breathing circuit. These are the functions of the gas supply system. Figures 29-1 and 29-2 demonstrate typical anesthesia workstation gas supply systems. The gas supply system of the workstation is usually concealed from view, with the exception of the pipeline gas inlets, the gas tanks and their mounts, the flowmeters, the vaporizers, and the oxygen flush button. Despite being cloaked within the anesthesia workstation, this section of the anesthesia machine contains numerous key pneumatic safety features. Although some diversity in gas supply systems exists among workstations, these systems do retain many similarities because of required safety standards and performance expectations.

The overview of the gas supply system is as follows: Oxygen and the other breathing gases flow from the hospital pipeline sources to the flow control valves, through the flowmeters (or flow sensors), and through or past an anesthetic vaporizer. From there they are introduced into the patient breathing circuit through a fresh gas supply line. Throughout this course, safeguards are present to detect low oxygen supply pressure and prevent a hypoxemic gas mixture from being delivered to the patient regardless of the flows selected by the user. Machine-mounted gas cylinders can be used as an alternate source of oxygen or of other gases. Permanent safeguards are in place to prevent connecting the wrong gas to the wrong inlet or connecting the wrong gas tank to the wrong tank receptacle. The machine can directly and rapidly flush 100% oxygen into the patient's breathing circuit, and oxygen is usually available from an auxiliary flowmeter. These two features are usually available even when the machine is not turned on.

The gas supply system can be divided functionally into high-pressure, intermediate-pressure, and low-pressure sections. The *high-pressure* section involves the segments exposed to the high pressures within the E-cylinder auxiliary gas tanks (e.g., ≤2000 pounds per square inch gauge [psig] for air and oxygen). This section extends from the tanks to the primary or high-pressure regulators. The *intermediate-pressure* section includes the segments exposed to hospital pipeline pressures (50 to 55 psig) and lower pressures in the range of 15 to 30 psig when secondary pressure regulators are used. The *low-pressure* section of the gas supply system extends from the flow control valves, through the flowmeters (or flow sensors), through the anesthetic vaporizers, and out the fresh gas supply line. This description begins with the gas supply source inlets and moves through to the fresh gas line that leads to the patient's breathing circuit.

High-Pressure Section

Auxiliary E-Cylinder Inlet. During normal operating conditions, the hospital's central gas supply system serves as the primary gas source for the anesthesia machine. However, it is a requirement to have at least one attachment for an oxygen cylinder to serve as a backup source of oxygen in case of failure of the hospital supply source. Many machines have up to three and sometimes four E-cylinder attachment points to accommodate oxygen, air, and nitrous oxide. Some machines have attachments for two oxygen tanks, and some rare systems can accommodate carbon dioxide or helium tanks used for special applications. The cylinders are mounted to the anesthesia machine by the hanger yoke assembly, as seen in Figure 29-3. The hanger yoke assembly orients and safely supports the cylinder, provides

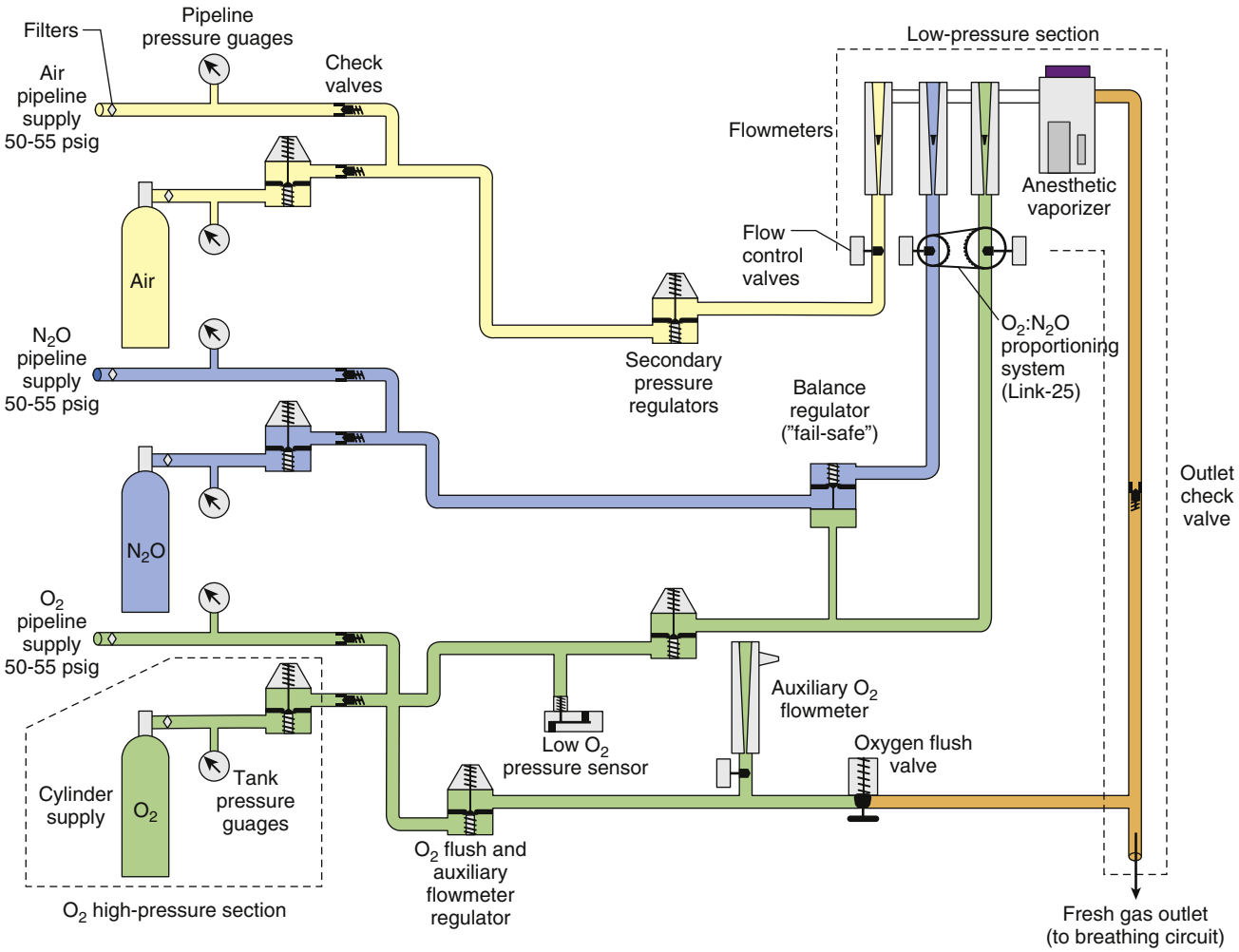


Figure 29-1. Anesthesia workstation gas supply system represented by the GE Healthcare Aespire anesthesia workstation. The high-pressure system extends from the gas cylinders to the high-pressure regulators (*dashed lines* around 0_2 high-pressure section). The intermediate-pressure section extends from the high-pressure regulators to the flow control valves and also includes the tubing and components originating from the pipeline inlets. The low-pressure section (*dashed lines*) extends from the flow control valves to the breathing circuit. See text for additional details. *(From Datex-Ohmeda:* S/5 Aespire anesthesia machine: technical reference manual, *Madison, Wis., 2004, Datex-Ohmeda.)*

a gas-tight seal, and ensures unidirectional flow of gases into the machine.[15] Each yoke assembly must have a label designating which gas it is intended to accept. Each hanger yoke is also equipped with the Pin Index Safety System (PISS), which is a safeguard to reduce the risk of a medical gas cylinder error caused by interchanging cylinders. Two metal pins on the yoke assembly are arranged to project precisely into corresponding holes on the cylinder head–valve assembly of the tank. Each gas or combination of gases has a specific pin arrangement.[16] Although infrequent, failures of the PISS have been reported, and like all safety systems, the PISS should be considered partial protection. Conditions in which failure occurred have included the following: excessive seating (jamming) of the pins back into the hanger yoke; the presence of bent or broken pins; and an excessive use of washers between the cylinder and the yoke that can override pin alignment, yet allow for a gas-tight seal.[17-19] Medical gas cylinder errors can have tragic outcomes, so it is critical to ensure that the proper gas is being connected to the proper inlet by also checking the tank and yoke labels.[20]

Once a gas cylinder valve is opened by the operator, gas flows first through a filter to entrap any particulate matter from the tank inflow. The maximum pressure in the E-cylinders ranges from approximately 750 psig for nitrous oxide, approximately 2000 psig for air, and approximately 2000 psig for oxygen. This pressure is much higher than the normal hospital pipeline supply pressure of 50 to 55 psig. Each cylinder supply source line must therefore have a pressure-reducing mechanism known as the *high-pressure regulator*, which reduces the variable high pressures present in the cylinders to a lower, nearly constant pressure suitable for use in the anesthesia machine (see Figs. 29-1 and 29-2). The high-pressure regulators are adjusted to provide gas from the E-cylinders at a pressure of approximately 45 psig (but it can be as low as 35 psig).[15,16,21] Although this specific value may vary among machines, the principle is to keep high-pressure regulator output pressure lower than the normal pipeline supply pressures. This approach ensures that the hospital's central gas supply will serve as the main supply of gas to the machine if a cylinder is open as long as the hospital supply line

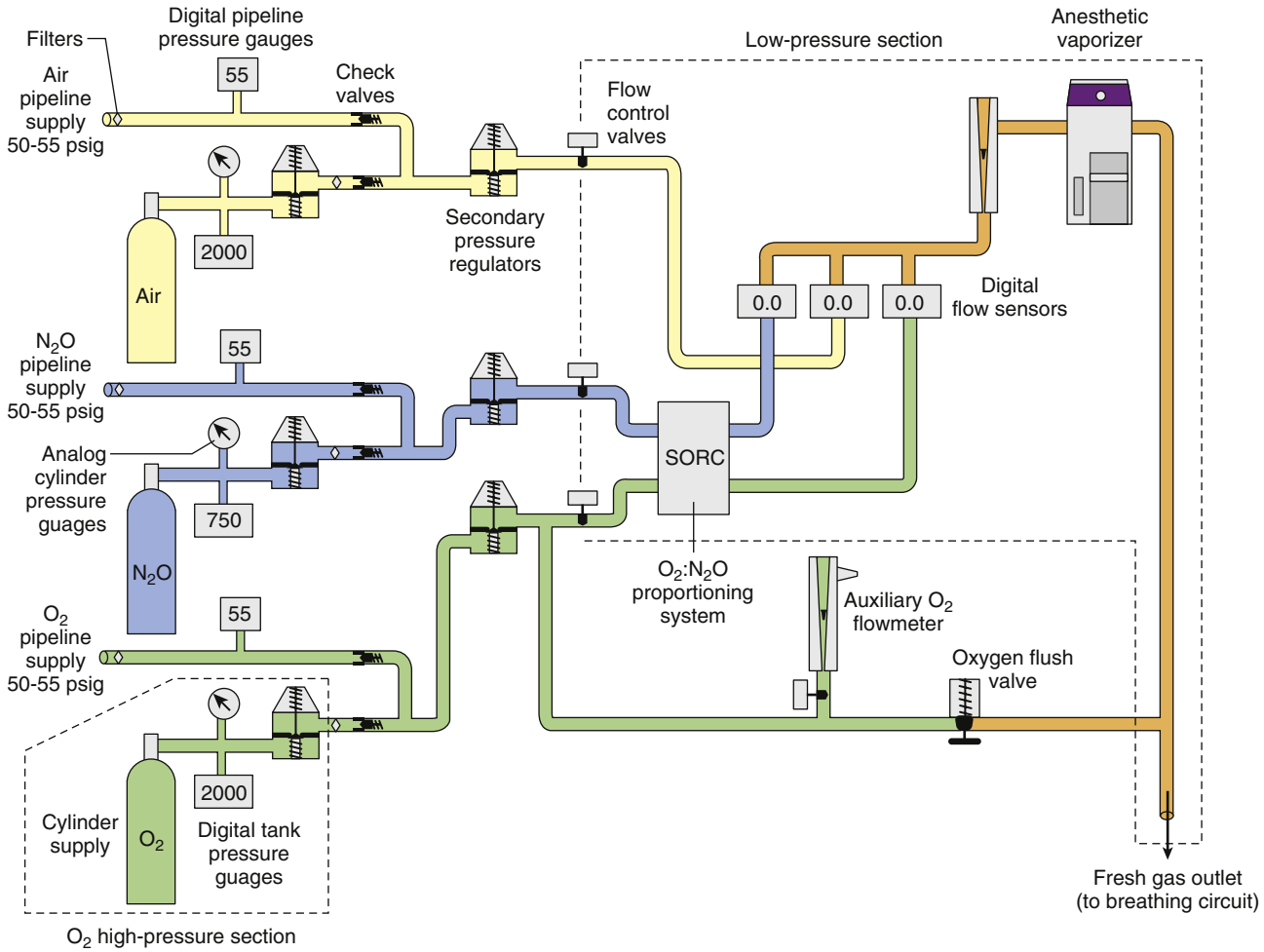


Figure 29-2. Anesthesia workstation gas supply system represented by the Dräger Apollo anesthesia workstation. The high-pressure system extends from the gas cylinders to the high-pressure regulators (*dashed lines* around 0_2 high-pressure section only). The intermediate-pressure section extends from the high-pressure regulators to the flow control valves and also includes the tubing and components originating from the pipeline inlets. The low-pressure section (*dashed lines*) extends from the flow control valves to the breathing circuit. See text for additional details. *(From Dräger Medical:* Instructions for use: Apollo, *Telford, Pa., 2012, Dräger Medical.)*

pressure remains higher than the regulator output pressure. In other words, the E-cylinders, even when open, will not provide gas to the anesthesia machine if the hospital supply line pressure is within or higher than the normal range. Therefore, in a case of known or suspected hospital pipeline oxygen supply contamination or pipeline crossover, in which oxygen is substituted for another gas but pipeline pressure maintained, only by *disconnection* of the oxygen pipeline source hose from the wall outlet will the machine be able to use E-cylinder oxygen.

After the high-pressure regulator, cylinder gas flows through a one-way valve called the cylinder check valve, which prevents any backflow of machine gas out through an empty yoke or back into a nearly empty cylinder (see Figs. 29-1 and 29-2). On some older machines, the yoke check valve is located before the high-pressure regulator. With this arrangement, and when two oxygen tanks could be mounted on the machine on a common manifold, the yoke check valve also (1) minimizes the transfer of gas from a cylinder at high pressure to one with lower pressure, (2) allows an empty cylinder to be exchanged for a full one while gas flow continues from the other cylinder into the machine, and (3) minimizes leakage from an open cylinder to the atmosphere if one cylinder is absent.[15,21] Note the location of the cylinder pressure gauges and pressure sample sites in Figures 29-1 and 29-2. Auxiliary tank pressure gauges (or electronic displays) must be located in plain sight on the front of the machine. In the gas supply system seen in Figure 29-2, electronic transducers relay tank pressure (when their valves are opened) to a display on the front of the machine.

Although gas usually does not flow from the open tanks when pipeline supply pressures are normal, the gas supply cylinder valves should be closed when they are not in use, except during the preoperative machine checkout. If the cylinder supply valves are left open, the reserve cylinder supply can be silently depleted if pressure inside the machine decreases to a value lower than the regulated cylinder pressure. For example, oxygen pressure within the machine can decrease to less than 45 psig with oxygen flushing or possibly even during use of a pneumatically driven ventilator, particularly at high

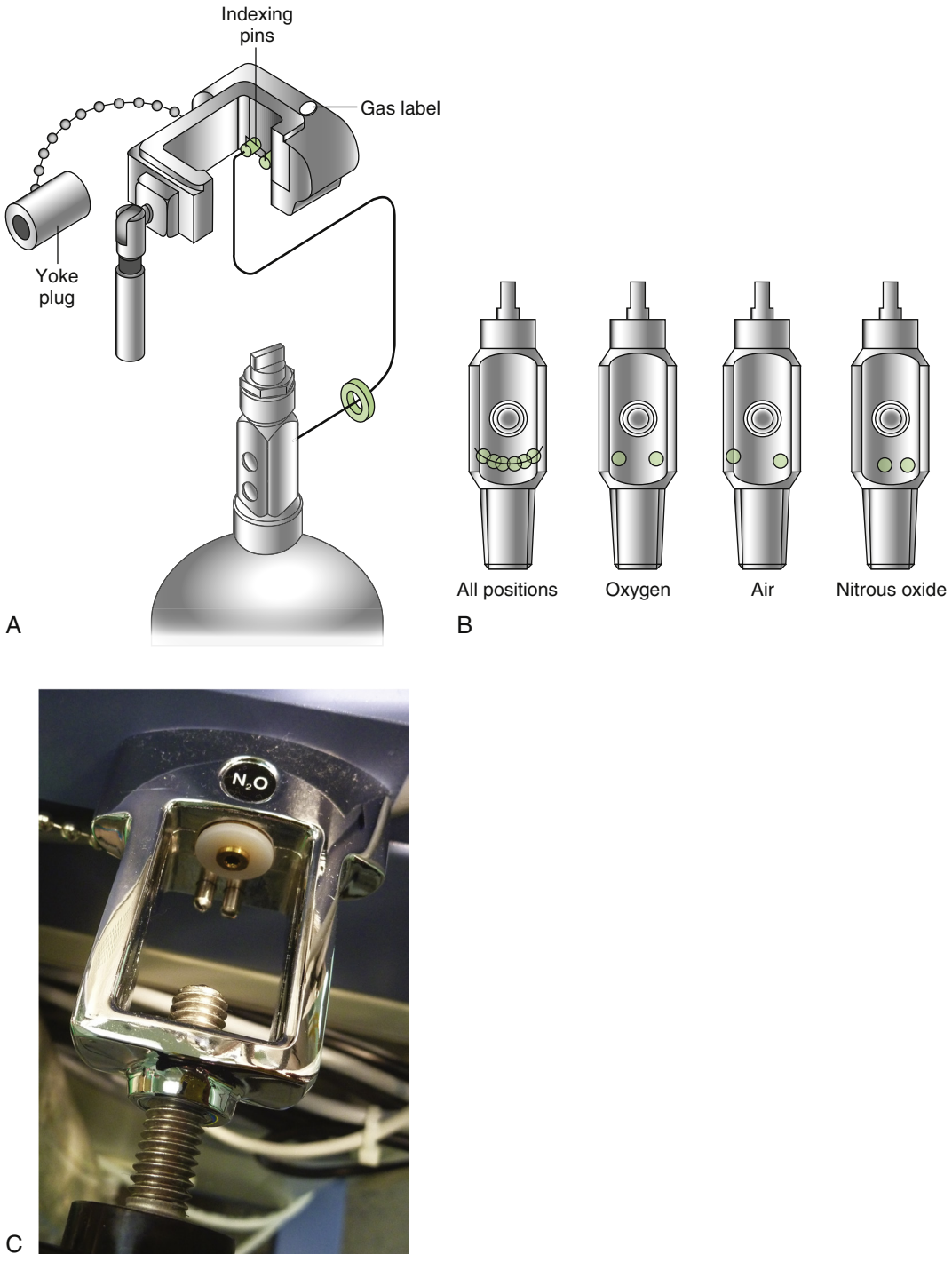


Figure 29-3. E-cylinder hanger yoke assembly. **A,** Standard E-cylinder hanger yoke assembly highlighting the gas-specific indexing pins, sealing gasket, and yoke plug. The yoke plug should be inserted when a tank is not in place. **B,** Pin Index Safety System holes machined into the cylinder head–valve mechanism of the compressed gas cylinders. **C,** Nitrous oxide yoke with indexing pins. Compare the image with the nitrous oxide pattern in **B.** *(**A** and **B,** From Yoder M: Gas supply systems. In* Understanding modern anesthesia systems, *Telford, Pa., 2009, Dräger Medical.)*

inspiratory flow rates. Additionally, the pipeline supply pressures of all gases can fall to less than 45 psig if problems exist in the central piping system. If the cylinders are left on when this occurs, they will eventually become depleted, and no reserve supply may be available if a pipeline failure occurs.[15,21] Moreover, the yoke hanger seal is vulnerable to leakage.

Intermediate-Pressure Section

Pipeline Inlet: Hospital Central Gas Supply Source. The main supply source of oxygen in a large hospital is usually a massive cryogenic bulk oxygen storage system, although some sites may use smaller cryogenic storage units or large H-type oxygen cylinders connected by manifold. Centrally supplied nitrous oxide arises from a bank

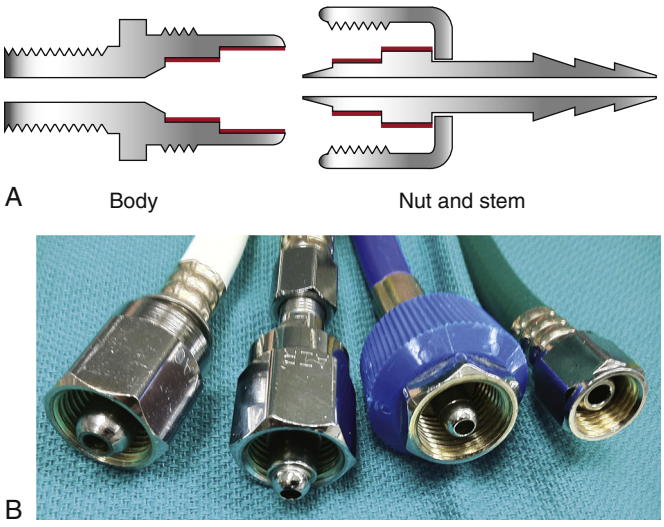


Figure 29-4. Diameter Index Safety System (DISS). DISS connectors are used for noninterchangeable, removable medical gas connections at pressures less than 200 psig. They are also used for suction and waste gas connections. Indexing is accomplished through differing diameters of the connection components, resulting in keylike fitting when matched connectors come together. The oxygen connector is additionally distinguished from the other gas connectors by a unique threaded fitting diameter and a unique thread count. **A,** DISS connector cross section. **B,** Nut and stem connectors for (*left* to *right*) vacuum, air, nitrous oxide, and oxygen. (***A,*** *Modified from Yoder M: Gas supply systems. In* Understanding modern anesthesia systems, *Telford, Pa., 2009, Dräger Medical.)*

of H-type cylinders. On-site compressors supply medical air, which is stored in holding tanks until needed. From these sources, a piping system delivers these gases to outlet points within patient care areas. The pipeline pressure for oxygen, medical air, and nitrous oxide in the United States is 50 to 55 psig.

The medical gas outlets throughout patient care areas in the hospital may have a variety of gas-specific connector types. However, medical gas from the hospital's central supply always enters the anesthesia machine through Diameter Index Safety System (DISS) connectors, as seen in Figure 29-4.[12] The purpose of these connectors is to prevent the connection of the wrong gas to the wrong inlet. DISS connectors work by matching the shoulders of the stem assembly on the end of the supply hose to the bores of the appropriate inlet receptacle on the anesthesia machine.[16] Once the gas enters the machine through the DISS connector, it encounters a filter followed by a pipeline check valve. This one-way valve prevents the reverse flow of machine gas from the machine into the medical gas pipeline system or into the atmosphere from an open inlet. Interposed between the DISS inlet and the pipeline check valves is a sample port to measure pipeline oxygen pressure by gauge or transducer. The pipeline pressure must always be clearly visible on the front of the machine.

Oxygen Flush Valve. The oxygen flush valve is probably one of the oldest safety features on the machine, and it remains a machine standard today.[12,22] The valve provides manual delivery of a high flow rate of 100% oxygen directly to the patient's breathing circuit. Flow from the oxygen flush valve bypasses the anesthetic vaporizers (see Figs. 29-1 and 29-2). The intermediate-pressure segment of the gas supply system feeds the valve, which remains closed until the operator opens it. The feature is usually available even when the machine is not turned on because the valve is usually located upstream from the machine's pneumatic power switch. Flow from the oxygen flush valve enters the low-pressure circuit downstream from the vaporizers at a rate between 35 and 75 L/minute, depending on the machine and the segment operating pressure.[12,22]

Several hazards have been reported with the oxygen flush valve. A defective or damaged valve can stick in the fully open position and result in barotrauma.[23] A valve sticking in a partially open position can result in a patient's awareness because oxygen flow from the incompetent valve dilutes the inhaled anesthetic.[24,25] Improper use of normally functioning oxygen flush valves also can cause problems. Overzealous intraoperative oxygen flushing can dilute inhaled anesthetic agents. Oxygen flushing during the inspiratory phase of positive-pressure ventilation can produce barotrauma if the anesthesia machine does not incorporate a fresh gas decoupling feature or an appropriately adjusted inspiratory pressure limiter. Fresh gas decoupling prevents the fresh gas inflow from either the flowmeters or the oxygen flush valve from increasing the delivered ventilator tidal volume presented to the patient's lungs (see the section on fresh gas decoupling). With most older anesthesia breathing circuits, excess volume could not be vented during the inspiratory phase of mechanical ventilation because the ventilator relief valve was closed and the breathing circuit adjustable pressure-limiting (APL) valve was either out of circuit or closed.[26]

The oxygen flush valve can potentially provide a high-pressure, high-flow oxygen source at the machine's fresh gas outlet suitable for jet ventilation, but it has potential limitations. First, on many modern anesthesia machines, the fresh gas outlet is no longer easy to access. Next, even on machines with accessible fresh gas outlets, not all are necessarily capable of generating pressures at the outlet that are sufficient to deliver jet ventilation.[27,28] If jet ventilation is going to be considered a contingency, it would be prudent to investigate whether it can be supported by the machine's oxygen flush function. If not, an alternate source of high-flow oxygen should be sought.

Pneumatic Safety Systems. The pneumatic safety devices within the gas supply system are engineered to help delivery of a hypoxemic gas mixture to the patient. Oxygen is the primary gas within the gas supply system circuitry, and it influences the flow of all other gases. On much older anesthetic delivery devices, the oxygen and nitrous oxide flows existed as independent entities, and they were not pneumatically or mechanically interfaced. Therefore, abrupt or insidious oxygen pressure failure had the potential to deliver a hypoxic gas mixture or possibly nitrous oxide alone. One of the primary safety goals of contemporary anesthesia machines is to prevent delivery of a hypoxemic gas mixture, and in particular to guard against the potential of delivering an excessive

concentration of nitrous oxide relative to oxygen. ASTM standards state the following: "The anesthesia gas supply device shall be designed so that whenever oxygen supply pressure is reduced to below the manufacturer specified minimum, the delivered oxygen concentration shall not decrease below 19% at the common gas outlet."[12] Gas supply systems have several safety devices that minimize the risk of delivery of a hypoxic gas mixture in case the oxygen pressure were to decrease significantly.

Oxygen Supply Failure Alarm Sensor. Within the oxygen circuit of the intermediate-pressure section of the machine is a sensor that will provide an audible and visual warning to the clinician if the oxygen pressure drops below a manufacturer-specified minimum (see Fig. 29-1). The alarm is an ASTM requirement, and it cannot be silenced until the pressure is restored to the minimum value.[12] An example is a loss or significant decrease of pipeline pressure, or a nearly empty oxygen tank if the machine were using the tank as an oxygen source. During normal operation, an alarm signal serves as a prompt for the operator to open the oxygen E-cylinder on the machine and troubleshoot the oxygen pipeline source. Numerous types of pneumatic-electrical switches can serve as this sensor. Because pipeline pressure standards vary significantly throughout the world, the minimum threshold pressure for an alarm condition differs among manufacturers and models. For example, early Dräger Narkomed (Dräger Medical, Lubeck, Germany) machines had a set point of 37 psig because they were designed for line pressures of 50 to 55 psig (the U.S. standard). However, Dräger Fabius series machines, which are sold internationally, are set to alarm at 20 psig to accommodate fluctuations in normal operating pressures as low as 41 psig, which can be seen in other countries.[22] The gas supply system seen in Figure 29-2 has no separate oxygen supply failure sensor component. The pipeline and tank electronic pressure transducers send information to a central processor, which will create an alarm if pressures drop below predetermined minimums.[22]

Oxygen Failure Protection Devices or Fail-Safe Valves. The so-called fail-safe valves are safeguards intended to link the flow of other gases in the gas supply system to the pressure of oxygen. They are present within some anesthesia workstations, but not all. Controlled by the oxygen supply pressure in the intermediate-pressure segment, the fail-safe valves shut off or proportionally decrease the flow of the other breathing gases before the flow control valves (e.g., nitrous oxide, air, helium) as the oxygen supply pressure decreases. Fail-safe valves either are binary (from open to closed at a threshold pressure) or close proportionally as the oxygen supply pressure decreases. Figure 29-1 demonstrates a proportioning-type fail-safe valve used on the nitrous oxide pathway within the GE Aespire (GE Healthcare, Little Chalfont, United Kingdom) gas supply system (called the "balance regulator" by the manufacturer). Unfortunately, the term *fail-safe* as it pertains to these valves is a misnomer and has led to the misconception that they can independently prevent the administration of a hypoxic mixture. In fact, if a gas other than oxygen adequately pressurizes the oxygen circuit as a result of hospital pipeline contamination or crossover, the fail-safe valves will remain open. In such a case, only the inspired oxygen concentration monitor and clinical acumen would protect the patient.

Auxiliary Oxygen Flowmeter. Although auxiliary oxygen flowmeters are not mandatory, they are commonly encountered. During normal operation, the auxiliary flowmeter is a convenience feature that allows the use of low-flow oxygen for devices independent of the patient's breathing circuit. Similar to the oxygen flush feature, oxygen flow from the flowmeter is usually accessible even when the machine is not turned on, because the flowmeter is typically fed before the pneumatic power switch in the intermediate-pressure section. Therefore, the auxiliary oxygen flowmeter can also serve as a safety feature because it allows the use of an oxygen delivery source (e.g., a manually powered self-inflating resuscitation bag) even in the case of a system power failure as long as oxygen is available from the pipeline inlet or from an attached E-cylinder. The auxiliary oxygen flowmeter may potentially serve as gas source for a jet ventilation contraption; however, not all machines can generate sufficient working pressure.[27]

The operator should be aware that the source of oxygen for the auxiliary flowmeter is the same as for the other oxygen flow control valves (see Figs. 29-1 and 29-2). This is an important consideration in cases of suspected hospital oxygen pipeline contamination or crossover. If the pipeline oxygen supply line is connected to the machine and the pressure is sufficient, the gas source will be the pipeline source even if the auxiliary oxygen tank valve is opened (described earlier). In a simulation experiment, a nitrous oxide–oxygen pipeline crossover situation was created whereby the inspired oxygen concentration became alarmingly low, and the "patient" became hypoxemic after turning the nitrous oxide flow off. Researchers noted that many study participants tried to make inappropriate use of the auxiliary oxygen flowmeter and oxygen E-cylinders on the machine as an external source of oxygen without disconnecting the pipeline source.[29] The participant's suboptimal management was attributed to a lack of knowledge of the anesthesia machine and its gas supply.

Second-Stage Pressure Regulators. Many machines have second-stage regulators located downstream from the gas supply sources in the intermediate-pressure circuit (see Figs. 29-1 and 29-2). These regulators supply constant pressure to the flow control valves and the proportioning system regardless of potential fluctuations in hospital pipeline pressures. They are adjusted to lower pressure levels than the pipeline supply, usually between 14 and 35 psig, depending on the workstation.[16,30-32]

Low-Pressure Section

The low-pressure section of the gas supply system begins at the flow control valves and ends at the outlet of the fresh gas line (see Figs. 29-1 and 29-2). Key components include the flow control valves, the flowmeters or flow sensors, the vaporizer manifold, and the anesthetic vaporizers. The low-pressure section is the most vulnerable section to leaks within the gas supply system.

Flowmeter Assemblies. The flowmeter assembly consists of the flow control valves and the flowmeters, and its purposes are precise control and measurement of gas flow traveling to the common gas outlet (Fig. 29-5). The valves themselves represent an important anatomic landmark within the anesthesia workstation because they separate the intermediate-pressure section from the low-pressure section. The operator regulates flow entering the low-pressure circuit by adjusting the flow control valves. Flow control valves have historically been controlled mechanically; however, on many newer workstations they are controlled by electronic interface. The oxygen and nitrous oxide flow control valves are either linked mechanically or affiliated pneumatically to a proportioning system to help prevent inadvertent delivery of a hypoxic mixture involving excess nitrous oxide (see the later section on proportioning systems). After leaving the flowmeters, the mixture of gases travels through a common manifold and may be directed through an anesthetic vaporizer if selected. The total fresh gas flow and the anesthetic vapor then travel toward the common gas outlet.[15,21]

Flow Control Valves. The flow control valve assembly consists of a flow control knob, a tapered needle valve, a valve seat, and a pair of valve stops.[15] The inlet pressure to the assembly is determined by the pressure characteristics of the intermediate-pressure segment of the respective machine. As described earlier, secondary pressure regulators are often used before the flow control valves to provide stable input pressure despite fluctuations in hospital pipeline supply pressure. The location of the needle valve in the valve seat changes to establish different orifices when the flow control valve is adjusted. Gas flow increases when the flow control valve is turned counterclockwise, and it decreases when the valve is turned clockwise. Because their use is frequent and the consequences of damage are significant, the controls must be constructed so extremes of rotation will not cause disassembly or disengagement. Some newer machines have a fully digital interface in which the control of flow is performed remote from the valve; however, even these workstations possess a backup manual oxygen flow control and valve flowmeter in case of system or electrical failure.[33,34]

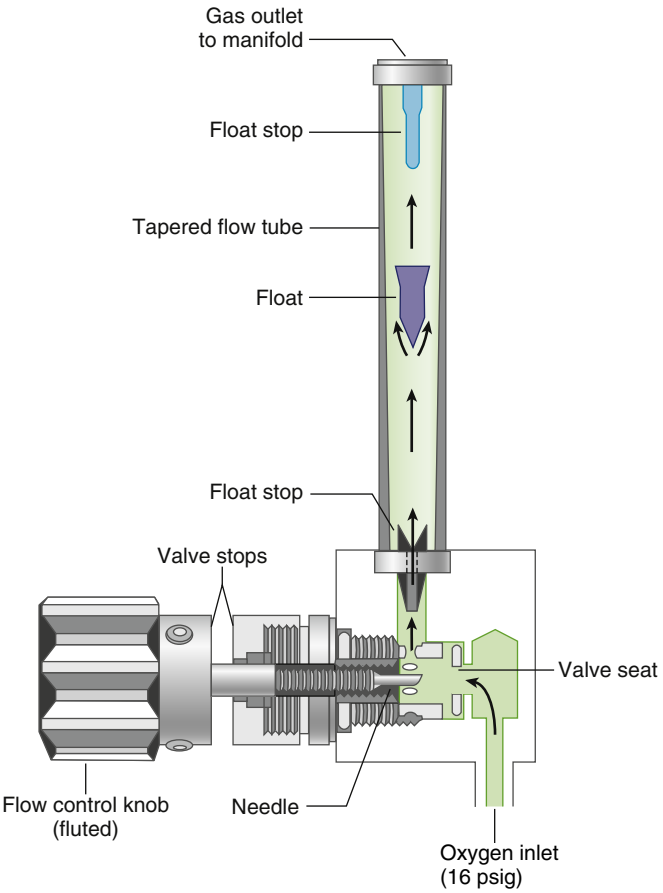


Figure 29-5. Oxygen flowmeter assembly. The oxygen flowmeter assembly is composed of the flow control valve assembly and the flowmeter subassembly. See text for details. *(From Bowie E, Huffman LM: The anesthesia machine: essentials for understanding, Madison, Wis., 1985, Ohmeda, BOC Group.)*

Safety Features. Contemporary flow control valve assemblies have numerous safety features. The oxygen flow control knob must be physically distinguishable from the other gas knobs. It is distinctively fluted, may project beyond the control knobs of the other gases, and is larger in diameter than the flow control knobs of other gases. All knobs are color coded for the appropriate gas, and the chemical formula or name of the gas must be permanently marked on each knob. Flow control knobs are recessed or protected with a shield or barrier to minimize inadvertent change from a preset position. If a single gas has two flow tubes, the tubes are arranged in series and are controlled by a single flow control valve.[12]

Flow Tubes. Although electronic flowmeters are becoming increasingly common, calibrated flow tubes historically have been the means of measuring gas flows on the anesthesia workstation and are still frequently encountered. With a traditional flowmeter assembly, the flow control valve regulates the amount of flow that enters a tapered, transparent flow tube known as a variable orifice flowmeter. A mobile indicator float inside the calibrated flow tube indicates the amount of flow passing through the associated flow control valve. The quantity of flow is indicated on a scale associated with the flow tube.[15,21] Referred to as *variable orifice area flow tubes* or *Thorpe tubes,* these glass tubes are narrowest at the bottom and widen vertically. An indicator float is housed within the tube that is free to move vertically. Opening the flow control valve allows gas to travel through the space between the float and the flow tube. This space is known as the *annular space,* and it varies in size depending on the position of the indicator in the tube (Fig. 29-6). The indicator float hovers freely in an equilibrium position in the tube where the upward force resulting from gas flow equals the downward force on the float resulting from gravity at a given flow rate. The float moves to a new equilibrium position in the tube when flow is changed. These flowmeters are commonly referred to as *constant-pressure* flowmeters because the decrease in pressure across the float remains constant for all positions in the tube.[15,35,36]

Flow through the annular space can be laminar or turbulent, depending on the gas flow rate (Fig. 29-7). The characteristics of a gas that influence its flow rate through a given constriction are viscosity (laminar flow)

and density (turbulent flow). Because the annular space behaves as a tube at low flow rates, laminar flow is present, and *viscosity* determines the gas flow rate. Conversely, at high flow rates the annular space behaves like an orifice with turbulent gas flow in which the *density* of the gas predominantly influences the flow. Because the viscosity and density of the gas affect flow through annular space around the float, the calibrated flow tubes are gas specific. The tube, the float, and the scale are inseparable. Although temperature and barometric pressure can influence gas density and viscosity, under normal clinical circumstances flow tube accuracy is not significantly affected by mild changes in temperature or pressure.

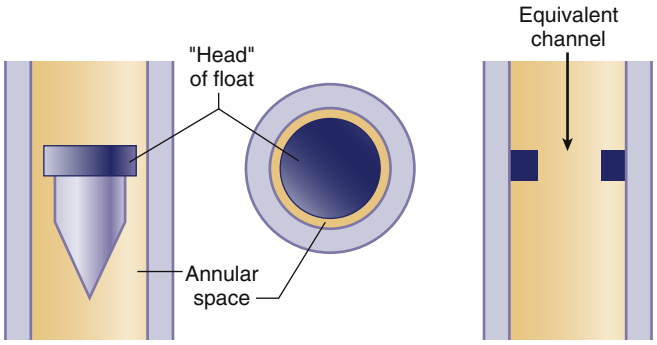


Figure 29-6. The annular space. The clearance between the head of the float and the flow tube is known as the annular space. It can be considered equivalent to a circular channel of the same cross-sectional area. *(Redrawn from Macintosh R, Mushin WW, Epstein HG, editors:* Physics for the anaesthetist, *ed 3, Oxford, 1963, Blackwell Scientific.)*

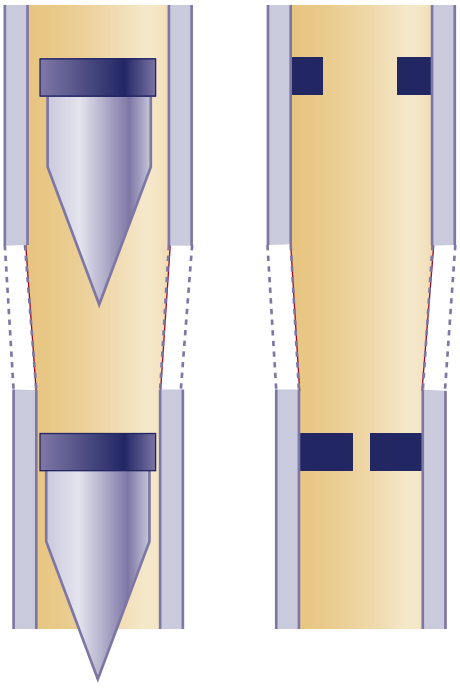


Figure 29-7. Flow tube constriction. The *lower pair* of illustrations represents the lower portion of a flow tube. The clearance between the head of the float and the flow tube is narrow. The equivalent channel is tubular because its diameter is less than its length. Viscosity is dominant in determining the gas flow rate through this tubular constriction. The *upper pair* of illustrations represents the upper portion of a flow tube. The equivalent channel is orificial because its length is less than its width. Density is dominant in determining the gas flow rate through this orificial constriction. *(Redrawn from Macintosh R, Mushin WW, Epstein HG, editors:* Physics for the anaesthetist, *ed 3, Oxford, 1963, Blackwell Scientific.)*

The float or bobbin within the flow tube is usually constructed so that it rotates to indicate that gas is flowing and that the indicator is not stuck in the tube. A stop at the top of the flowmeter tube prevents the float from occluding the outlet. Two flowmeter tubes are sometimes placed in series, with a fine flow tube displaying low flows and a coarse flow tube indicating higher flows.

Electronic Flow Sensors. As mentioned earlier, newer anesthesia workstations are increasingly equipped with electronic flow sensors instead of flow tubes with either conventional control knobs or an electronic interface to control gas flow. Flows can be displayed numerically or sometimes graphically in the form of a virtual, digitalized flowmeter. Numerous types flow sensor technologies can be applied, such as hot-wire anemometers, a differential pressure transducer method, or mass flow sensors. An example of an electronic mass flow sensor is seen in Figure 29-8. The illustrated device relies on the principle of specific heat to measure gas flow.[16] As gas streams through a heated chamber of known volume, a specific amount of electricity is required to maintain the chamber temperature. The amount of energy required to maintain the temperature is proportional to the flow of the gas and the gas's specific heat. Regardless of the mechanism of flow measurement, these systems depend on electrical power to provide a display of gas flow. When system electrical power is totally interrupted, some backup mechanical means usually exists to control (mechanical flow control) and display (flow tube) oxygen gas flow.

Problems with Flowmeters

Leaks. Flow tube leaks are a potential hazard because the flowmeters are located downstream from antihypoxemia safety devices, except the breathing circuit oxygen analyzer.[37] Leaks can occur at the O-ring junctions between the glass flow tubes and the metal manifold or from cracked or broken glass flow tubes, so these tubes have historically been a very fragile pneumatic component of the workstation. Even though gross damage to conventional glass flow tubes is usually apparent, subtle

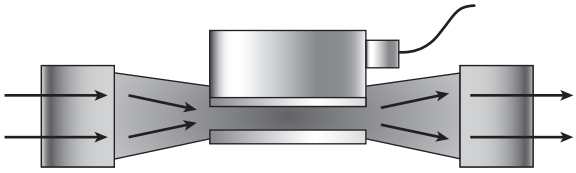


Figure 29-8. Electronic mass flow sensor. Gas flows past a heated chamber of known volume. The amount of heat (electrical energy) that is required to maintain a set chamber temperature is proportional to the specific heat of the gas and its rate of flow through the chamber. Because the specific heat of the gas is relevant to the calculation, each gas must have its own mass flow sensor. Flow is accurately extrapolated from the energy required to keep the chamber at a constant temperature. *(Modified from Yoder M: Gas supply systems. In* Understanding modern anesthesia systems, *Telford, Pa., 2009, Dräger Medical.)*

cracks and chips may be overlooked and can cause in errors in delivered flow.[38] The use of electronic flowmeters and removal of conventional glass flow tubes from many modern anesthesia workstations may help eliminate this potential source of leaks.

In the 1960s, investigators established that in the presence of a flowmeter leak, a hypoxic mixture is less likely to occur if the oxygen flowmeter is located downstream from all other flowmeters.[36,39] Figure 29-9 illustrates this potential problem. In the examples given in Figure 29-9, the unused air flow tube has a large leak, and the nitrous oxide and oxygen flow rates are assumed to be set at a ratio of 3:1. A potentially dangerous arrangement is shown in Figure 29-9, *A* and *B,* because the nitrous oxide flowmeter is located in the downstream position. A hypoxic mixture can occur because a substantial portion of the oxygen flow passes through the leak in the air flow tube, and mainly nitrous oxide is directed to the common gas outlet. Safer configurations are shown in Figure 29-9, *C* and *D,* in which the oxygen flowmeter is located in the downstream position. A portion of the nitrous oxide flow escapes through the leak, and the remainder goes toward the common gas outlet. A hypoxic mixture is less likely because all the oxygen flow is advanced by the nitrous oxide (this principle is known as the Eger flow sequence). ASTM standards state that "where oxygen and other gases are delivered by their respective flow indicators into a common manifold, the oxygen should be delivered downstream of all other gases."[12]

A leak in the oxygen flow tube may result in creation of a hypoxic mixture even when oxygen is located in the downstream position (Fig. 29-10).[37,38] Oxygen escapes through the leak, and nitrous oxide continues to flow toward the common outlet, particularly at high ratios of nitrous oxide to oxygen flow.

Inaccuracy. Flow measurement error can occur even when flowmeters are assembled properly with appropriate components. Dirt or static electricity can cause a float to stick, and the actual flow may be higher or lower than that indicated. Sticking of the indicator float is more common in the low-flow ranges because the annular space is smaller. A damaged float can cause inaccurate readings because the precise relationship between the float and the flow tube is altered. Backpressure from the breathing circuit can cause a float to drop so that it reads less than the actual flow. Finally, if flowmeters are not aligned properly in the vertical position (plumb), readings can be inaccurate because tilting distorts the annular space.[15,38,40]

Proportioning Systems. The proportioning system is probably the most important pneumatic safety component within the gas supply system of the machine. Manufacturers equip anesthesia workstations with proportioning systems in an attempt to prevent the creation and delivery of a hypoxic gas mixture. The ASTM standard states that the "the anesthesia workstation shall be provided with a device to protect against an *operator selected* delivery of a mixture of oxygen and nitrous oxide having an oxygen concentration below 21% oxygen (v/v%) in the fresh gas or in the inspiratory gas."[12] In other words, no matter how high the operator attempts to turn up the nitrous oxide, or how low the operator tries to turn down the oxygen flow when nitrous oxide is running, the machine will automatically limit the amount of nitrous oxide flow so that a hypoxemic gas mixture will not be delivered. This is accomplished by a pneumatic-mechanical interface between the oxygen and nitrous oxide flows or by mechanically linking the oxygen and nitrous oxide flow control valves. The specific devices used to accomplish this control vary among manufacturers in design. Two examples are discussed here.

North American Dräger Sensitive Oxygen Ratio Controller System. The North American Dräger sensitive oxygen ratio controller system (SORC) is a pneumatic-mechanical, oxygen–nitrous oxide interlock system designed to maintain a ratio of no less than 25% oxygen to 75% nitrous oxide flow into the breathing circuit by limiting the nitrous oxide flow when necessary.[22] The SORC is located between the flow control valves and the electronic flow sensors. A schematic of the SORC is shown in Figure 29-11. The SORC consists of an oxygen chamber with a diaphragm, a nitrous oxide chamber with a diaphragm, and a nitrous oxide proportioning valve. All are

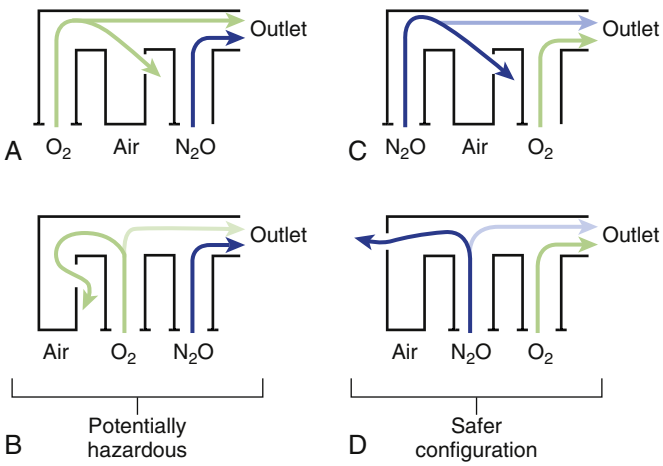


Figure 29-9. The flowmeter sequence is a potential cause of hypoxia. In the event of a flowmeter leak, a potentially dangerous arrangement exists when nitrous oxide is located in the downstream position (**A** and **B**). A safer configuration exists when oxygen is located in the downstream position (**C** and **D**). See text for details. *(Modified from Eger EI II, Hylton RR, Irwin RH, et al: Anesthetic flowmeter sequence: a cause for hypoxia,* Anesthesiology *24:396, 1963.)*

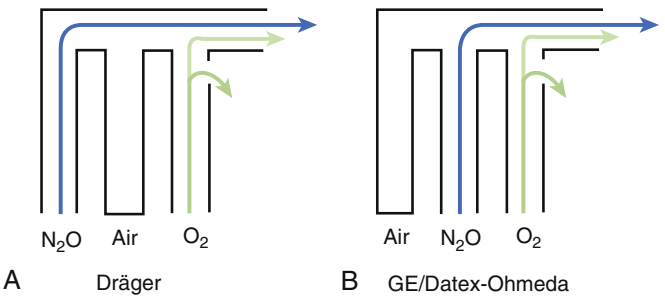


Figure 29-10. An oxygen leak from the flow tube can produce a hypoxic mixture regardless of the arrangement of the flow tubes (**A** shows a Dräger [Dräger Medical, Telford, Pa.] system, and **B** shows a GE Healthcare/Datex-Ohmeda [Datex Ohmeda, Madison, Wis.] system).

interconnected by a mobile horizontal shaft. Pneumatic input into the device comes from the oxygen and nitrous oxide flow control valves.

As oxygen flows out of the SORC, it encounters a resistor that creates backpressure. This backpressure is transmitted to the oxygen chamber diaphragm, which causes the diaphragm to move to the right, thereby opening the nitrous oxide proportioning valve. As the oxygen flow is increased, so too is the backpressure and the rightward motion of the shaft. If the nitrous oxide flow is now turned on, it will also flow into the SORC, through the proportioning valve, and past its resistor to create backpressure that will press on the diaphragm in its respective chamber. The counterbalance between the two gas flows (backpressures) determines the positioning of the nitrous oxide proportioning valve.[22] If the oxygen is turned down too low (<25% of the nitrous oxide flow), the shaft will move to the left and thus limit the nitrous oxide flow. If the operator tries to turn up the nitrous oxide too high relative to the oxygen flow, the SORC will limit the nitrous oxide flow regardless of how far the flow control valve is opened. If the oxygen flow is decreased to less than 200 mL/minute, the proportioning valve will close completely (see Fig. 29-11, *B*).[41]

Datex-Ohmeda Link-25 Proportion-Limiting Control System. A mechanical proportioning system that remains in use today on many conventional and modern anesthesia machines is the GE/Datex-Ohmeda Link-25 system (Datex-Ohmeda, Madison, Wis.). The system is based on a mechanical integration of the nitrous oxide and oxygen flow control valves and a difference in the taper of the needles of the oxygen and nitrous oxide flow control valves. It allows independent adjustment of either valve, yet it automatically intercedes to maintain a minimum oxygen concentration with a maximum nitrous oxide–oxygen flow ratio of 3:1. The Link-25 automatically increases oxygen flow when then nitrous oxide flow is increased to more than a certain point relative to oxygen flow to prevent delivery of a hypoxic mixture.

Figure 29-12 illustrates the Link-25 system. A 15-tooth sprocket is attached to the nitrous oxide flow control valve, and a 29-tooth sprocket is attached to the oxygen flow control valve. A chain physically links the sprockets. When the nitrous oxide flow control valve is turned through two revolutions, or 28 teeth, the oxygen flow control valve will revolve once because of the 2:1 gear ratio (see Fig. 29-12, *A*). The final 3:1 flow ratio results because the flow control valve needle for nitrous oxide

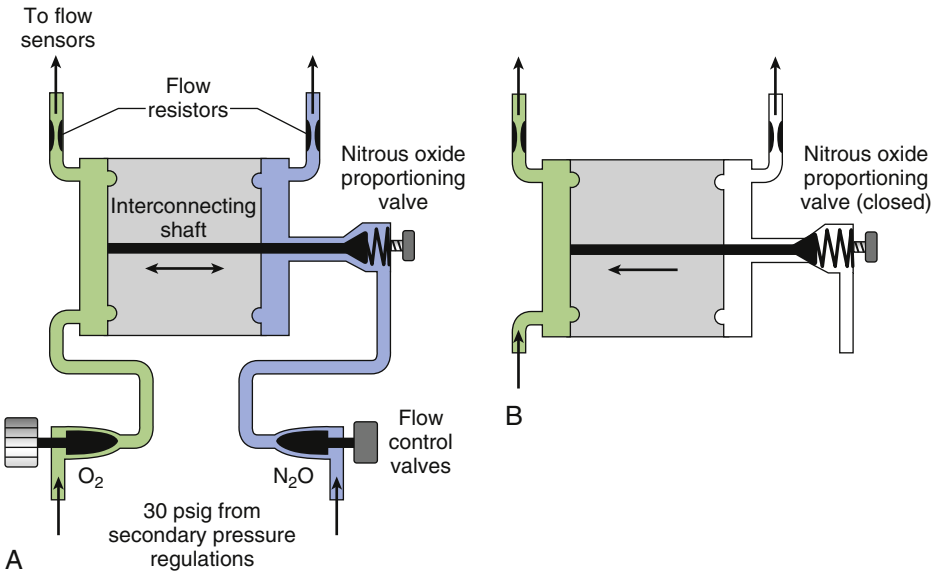


Figure 29-11. North American Dräger sensitive oxygen ratio controller system (SORC) (Dräger Medical, Telford, Pa.). The SORC is a pneumatic-mechanical interlock system designed to maintain a ratio of no less than 25%/75% nitrous oxide regardless of operator input. **A,** Main components. Differential oxygen and nitrous oxide flows and the resultant chamber backpressures determine the position of the nitrous oxide proportioning valve. See text for details**. B,** Complete closure of the proportioning valve when the oxygen flow is decreased to less than 200 mL/minute. *(Modified from Yoder M: Gas supply systems. In* Understanding modern anesthesia systems, *Telford, Pa., 2009, Dräger Medical.)*

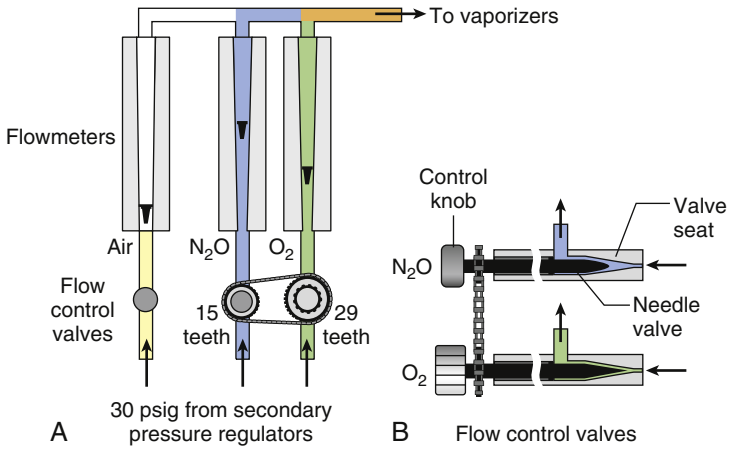


Figure 29-12. GE/Datex-Ohmeda Link-25 nitrous oxide: oxygen proportioning system. The system prevents the operator from selecting more than a 75% nitrous oxide–25% oxygen (3:1) mixture by two separate but interdependent means. **A,** Mechanical linkage of the control valves maintains no more than a 2:1 ratio. **B,** A faster taper of the nitrous oxide valve needle allows more gas flow through the valve per turn relative to flow through the oxygen valve per turn, thus resulting in the maximal 3:1 ratio. A stable and equal pressure supply to the valves is provided by the secondary pressure regulator for oxygen and a balance regulator for nitrous oxide. See text for additional details. *(Personal communication, GE Healthcare, Little Chalfont, United Kingdom, 28 February, 2013.)*

has a faster taper than does the oxygen valve needle (see Fig. 29-12, *B*). This situation results in more nitrous oxide flow per turn relative to flow through the oxygen valve per turn. Earlier versions of the system relied on a differential supply pressure to the valves rather than different needle tapers. With the current version, the pressure supplied to the valves is equal. Oxygen is supplied by a secondary regulator at 30 psig, and nitrous oxide is supplied by a balance regulator that is piloted by the oxygen supply pressure (see Fig. 29-1). If the oxygen pressure were to decrease, the nitrous oxide pressure would decrease by an equal amount. In this way, the balance regulator is also acting as a fail-safe valve. The Link-25 proportioning system can be thought of as a system that increases oxygen flow when necessary to prevent delivery of a fresh gas mixture with an oxygen concentration of less than 25%. In contrast, pneumatic systems such as the SORC work by limiting nitrous oxide flow.

Limitations. Proportioning systems are not immune from failure, and workstations equipped with proportioning systems can still deliver a hypoxic mixture under certain conditions. The following sections briefly present some situations in which this can occur.

Proportioning System Malfunction. Reports of proportioning system malfunction have described failures that resulted in an inability to administer oxygen without nitrous oxide or to increase oxygen flow or allowed creation of a hypoxic mixture.[42-46]

Wrong Supply Gas. Both mechanical and pneumatic proportioning systems can be defeated if a gas other than oxygen is present in the oxygen pipeline. If the pressure in the oxygen circuit is adequate, then the only device that will save the patient from experiencing a hypoxemic gas mixture is the oxygen analyzer within the patient's breathing circuit.

Leaks Downstream. Proportioning systems function at the level of the flow control valves. A leak downstream from these devices, such as a broken oxygen flow tube (see Fig. 29-10), can result in delivery of a hypoxic mixture to the common gas outlet. In this situation, oxygen escapes through the leak, and the predominant gas delivered is nitrous oxide. The inspired oxygen monitor is the only machine safety device that can detect this problem.

Dilution of Inspired Oxygen Concentration by Volatile Inhaled Anesthetic Agents. Volatile inhaled anesthetic agents are added to the mixed gases downstream from both the flowmeters and the proportioning system. Concentrations of less potent inhaled anesthetic agents such as desflurane may account for a larger percentage of the total fresh gas composition than is the case with more potent agents. This situation can be seen when the maximum vaporizer dial settings of the various volatile agents are examined (e.g., a desflurane maximum dial setting of 18% versus an isoflurane maximum dial setting of 5%). Because significant percentages of these inhaled anesthetic agents may be added downstream of the proportioning system, the resulting gas-vapor mixture may contain an inspired oxygen concentration less than 21% despite a functional proportioning system. The anesthesia care provider must be aware of this possibility, particularly when high concentrations of less potent volatile inhaled anesthetic agents are used.

Vaporizer Mount and Interlock System

Vaporizer Mounting Systems. Modern vaporizer mounts allow for detachment and replacement of the anesthetic vaporizers by the workstation operator. The benefits of detachable vaporizer mountings include ease of maintenance, the need for fewer vaporizer positions on the workstation, and the ability to remove the vaporizer in the setting of malignant hyperthermia.[47] The problems associated with detachable mounting systems stem from an increased potential for low-pressure systems leaks or fresh gas flow obstruction as a result of an inappropriately seated vaporizer or other connection-related failures.[47-51] After adding a vaporizer to the anesthesia machine, the operator should make sure it is properly and securely seated and cannot be removed once locked. The operator should then perform a low-pressure system leak test.[47] With all but the Datex-Ohmeda Anesthesia Delivery Unit (ADU) vaporizer and the Maquet (Maquet Critical Care, Solna, Sweden) vaporizer, the operator will need to turn the vaporizer on to test it for a leak.

Vaporizer Interlock Devices. All anesthesia workstations must prevent fresh gas from flowing through more than one vaporizer at time.[12] The design of vaporizer interlock devices varies significantly. Operators should be aware that these devices are not immune from to failure, and anesthetic overdose is the potential consequence.[52-55]

Outlet Check Valve. Many older Datex-Ohmeda anesthesia machines and a few contemporary workstations (e.g., GE/Datex-Ohmeda Aestiva and Aespire) have a one-way check valve located between the vaporizer and the common gas outlet in the mixed-gas pipeline (see Fig. 29-1). The purpose of this valve is to prevent backflow into the vaporizer during positive-pressure ventilation, thereby minimizing the effects of intermittent fluctuations in downstream pressure on the concentration of inhaled anesthetic (see the discussion of intermittent backpressure in the section on vaporizers). The presence or absence of this check valve historically influenced which *manual* preoperative leak test of the low-pressure system was indicated because it precluded positive-pressure tests to detect for leaks upstream of the valve (see the section on checking anesthesia workstations).

ANESTHETIC VAPORIZERS

In 1846, William T. G. Morton performed the first public demonstration of ether anesthesia using an ingenious, yet simple inhaler (Fig. 29-13).[56-58] Although the device was effective in delivering anesthetic vapor, Morton's ether inhaler had no means of regulating its output concentration or compensating for changes in temperature caused by vaporization of the liquid anesthetic and the ambient environment. These two issues were central to the subsequent development and evolution of modern anesthetic vaporizers. Modern variable bypass–type vaporizers are temperature compensated and can maintain desired outputs accurately over a wide range input gas flow rates. In 1993, with the introduction of desflurane to the clinical



Figure 29-13. Morton's ether inhaler: A replica of the inhaler used by William T.G. Morton during his public demonstration of ether anesthesia in October of 1846 at Massachusetts General Hospital in Boston. *(Courtesy the Wood Library–Museum of Anesthesiology, Park Ridge, Ill.)*

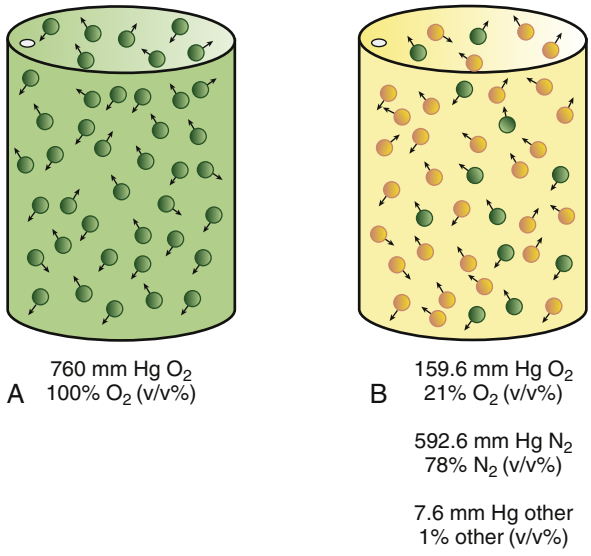


Figure 29-14. Partial pressures. **A,** Theoretical chamber containing 100% oxygen by volume at ambient pressure, which in this case is 1 atm (760 mm Hg). The oxygen molecules within the container account for the entirety of the wall tension. $P_{total} = P_{oxygen} = 760$ mm Hg. **B,** Pure oxygen is replaced with air, and now the sum of the nitrogen, oxygen, and the other molecules present in air accounts for the wall tension. $P_{total} = P_{oxygen} + P_{nitrogen} + P_{other} = 760$ mm. See text for more details.

setting, a unique and even more sophisticated vaporizer was introduced to handle the unique physical properties of this agent. Vaporizers blending both old technology and new computerized control technology also emerged in "cassette" vaporizer systems. An injection-type vaporizer has also been reintroduced. This vaporizer sprays precise amounts of liquid anesthetic agent into the fresh gas stream. Before discussing any of these systems, certain physical principles are briefly reviewed to facilitate an understanding of the operating principles, construction, and design of contemporary anesthetic vaporizers.

Physics

Dalton's Law of Partial Pressures. When a gas exists within a container, the gas molecules bombard the container walls and create a pressure that is proportional to the number of molecules of gas present within the space. The units usually used to express this pressure when describing the anesthetic breathing gases are millimeters of mercury (mm Hg) or kilopascals (kPa). In Figure 29-14, *A,* oxygen fills a theoretical container that is open to the ambient environment through a very small hole. The pressure in the container is equal to the ambient pressure, which in this case is 760 mm Hg. The oxygen molecules create all the wall tension within the space. In Figure 29-14, *B,* the container has now been filled with air, and the sum of the oxygen and nitrogen molecules creates the wall tension. If the container were to be sealed and only the oxygen molecules were removed, the pressure in the container would become subatmospheric, represented only by the pressure created by the nitrogen molecules (≈593 mm Hg). When a mixture of gases exists in a space such as the example container, each gas creates its own pressure, which is the same pressure as if it occupied the container alone (Dalton's law of partial pressures).[59] The individual gas tensions exerted by each of the constituent gases are referred to as *partial pressures*.

$$\text{Pressure}_{total} = P_1 + P_2 + P_3 + \ldots$$

In the context of describing the breathing gases in anesthesiology, the sum total of the partial pressures of the constituent gases is equal to the ambient or atmospheric pressure. At sea level, the ambient pressure is 760 mm Hg, which can also be expressed as 1 atm or 101.325 kPa.

Evaporation and Vapor Pressure. Inhaled anesthetic agents are termed volatile because, like other volatile liquids, they possess a high propensity to evaporate, or *vaporize*. When a liquid such as an inhaled anesthetic agent is exposed to air or other gases, molecules at the fluid surface that have sufficient energy escape from the liquid phase and enter the vapor phase. This process is known as evaporation, which is purely a surface phenomenon. If this process occurs within a contained environment, such as the vaporizing chamber of a variable bypass anesthetic vaporizer, the number of molecules entering the vapor phase will eventually equal those returning to the liquid phase (Fig. 29-15). The concentration of molecules in the vapor then remains constant, and the vapor is said to be "saturated" with anesthetic. At this point of evaporative equilibrium, the anesthetic molecules in the vapor phase are bombarding the walls of the container and creating a partial pressure known as the *saturated vapor pressure*, or simply *vapor pressure*. Substances with a high propensity to evaporate generate higher vapor pressures.

Vapor pressure is a physical property of a substance, with each substance having its own unique value at any

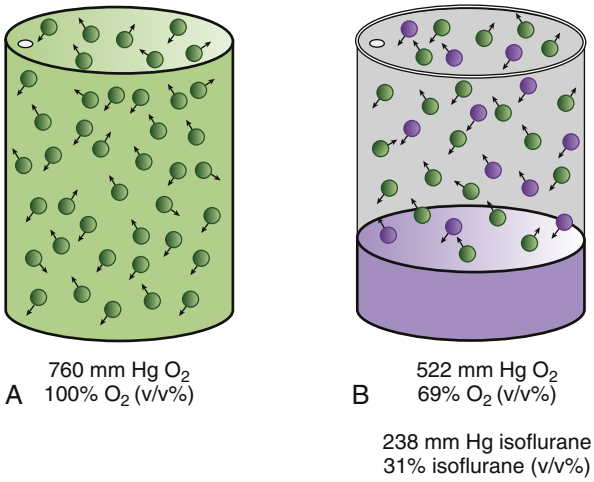


Figure 29-15. Evaporation (vaporization) and vapor pressure. **A,** Theoretical chamber containing 100% oxygen at 1 atm (760 mm Hg). The oxygen molecules within the container account for the entirety of the wall tension. $P_{total} = P_{oxygen} = 760$ mm Hg. **B,** Isoflurane is added to the container, and the temperature is maintained at 20° C (68° F). Evaporation commences, and isoflurane molecules begin to displace oxygen molecules out of the container. Once as many isoflurane molecules reenter the solution as leave it, the gas space above the liquid is said to be "saturated" with the vapor. The partial pressure of the isoflurane at this point is called the saturated vapor pressure (SVP), which at this temperature equals 238 mm Hg. $P_{total} = P_{oxygen} + P_{isoflurane} = 760$ mm.

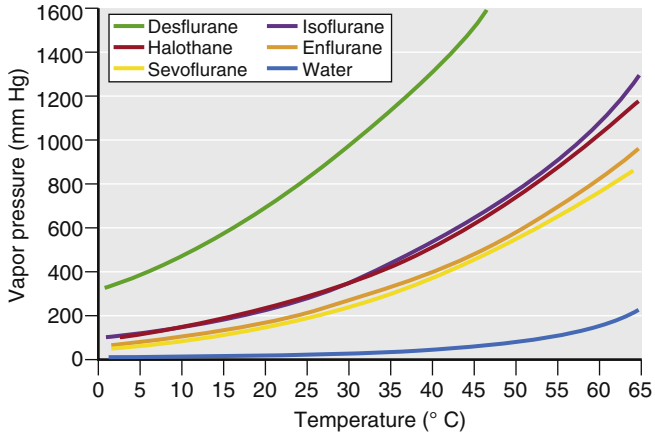
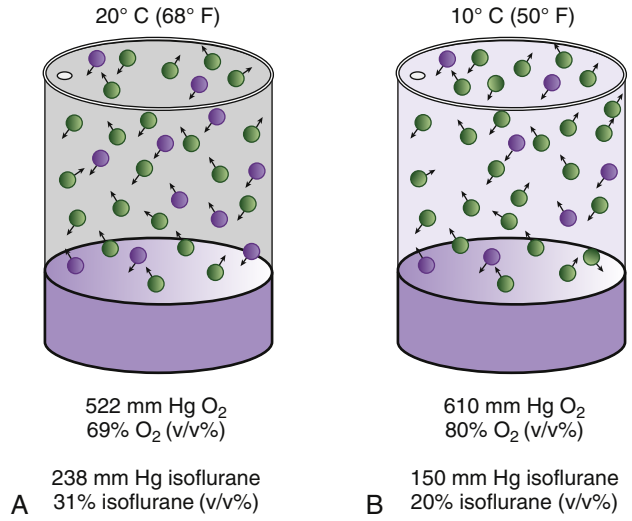


Figure 29-16. Vapor pressure–versus-temperature curves for desflurane, isoflurane, halothane, enflurane, sevoflurane, and water. Note that the vapor pressure curve for desflurane differs dramatically from that of the other contemporary inhaled anesthetic agents. Also note how the vapor pressure curves of the volatile agents compare with that of water *(From inhaled anesthetic package insert equations and Susay SR, Smith MA, Lockwood GG: The saturated vapor pressure of desflurane at various temperatures,* Anesth Analg *83:864-866, 1996.)*



$$P_{total} = P_{oxygen} + P_{isoflurane} = 760 \text{ mm Hg}$$

Figure 29-17. The impact of temperature on vapor pressure. **A,** Chamber containing oxygen and isoflurane at its SVP at 20° C (68° F). At evaporative equilibrium, the SVP of isoflurane in the container represents 31% of the entire gas composition by volume (v/v%). **B,** Decreasing the temperature by 10° C (16° F) to 10° C (50° F) substantially decreases the isoflurane vapor pressure to 150 mm Hg and causes isoflurane to represent only 20% of the entire gas volume (v/v%). This example assumes that some oxygen can enter the container to replace the liquefied isoflurane molecules.

given temperature (Fig. 29-16). Vapor pressure is temperature dependent and is *not* affected by changes in atmospheric pressure.[60] As illustrated in Figure 29-17, if the temperature of a liquid, such the anesthetic agent isoflurane, is decreased, evaporation is diminished because fewer molecules possess the energy to enter the vapor phase. Conversely, if the liquid temperature increases, evaporation is enhanced, and vapor pressure increases. Although ambient temperatures can alter liquid anesthetic vapor pressure, the cooling influence of evaporation has a far more pronounced and dynamic effect. The impact of evaporative temperature change on vaporizer and anesthetic inhaler output has been recognized since the mid-1800s, and addressing this phenomenon has been one of principal factors in the evolutionary design of anesthetic vaporizers.

Because vapor pressure values are unique to each liquid anesthetic agent, anesthetic vaporizers must be constructed in an agent-specific manner. If agent-specific vaporizers are inadvertently misfilled with incorrect liquid anesthetic agents, the resulting mixtures of volatile agents may demonstrate properties uniquely different from those of the individual component agents. The altered vapor pressure and other physical properties of the resulting azeotropic mixtures caused by combining various agents may change the output of the anesthetic vaporizer (see the discussion of misfilling in the section on variable bypass vaporizers).[61,62]

Expressing Gas Concentrations and Minimum Alveolar Concentration. When describing the proportion of a single gas in a sample containing a mixture of gases, we can refer to the individual gas in terms of its *partial pressure* (mm Hg) or by its percentage by volume relative to the sum volume of the all the gases present, which is known as *volume percent* or *volume-volume percent* (v/v%)[63]:

$$\text{Volume percent} = \frac{\text{Volume of gas } x}{\text{Total gas volume}}$$

The volume that a gas occupies at a given temperature and pressure is related to the number of molecules of gas present, not the size (type) of the molecules;

this is know as the *Avogadro Hypothesis*. Therefore, because partial pressure is directly proportional to the number of molecules of a gas that are present in the sample, we can also use partial pressure as a means to calculate the volume percent of any constituent gas[64]:

$$\text{Volume percent} = \frac{\text{Partial pressure of a gas (mm Hg)}}{\text{Atmospheric pressure (mm Hg)}}$$

Using air at sea level as an example:

Partial pressures

760 mm Hg ≈ 160 mm Hg oxygen + 592 mm Hg nitrogen + 8 mm Hg other gases

Volume percent (v/v%)

100 % air ≈ 21 % oxygen + 78 % nitrogen + 1 % other gases

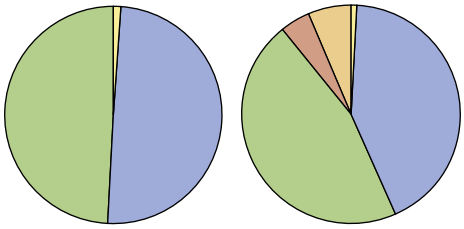
When anesthesiologists describe inhaled and exhaled anesthetic concentrations, they typically do so using volume percent. All anesthesiology practitioners understand the meaning of 1% isoflurane, but providing the value as 7.6 mm Hg isoflurane (the same amount at sea level) is typically out of context:

$$1\,\%\ \text{isoflurane} = \frac{7.6\ \text{mm Hg isoflurane}}{760\ \text{mm Hg (sea level)}}$$

The amount of oxygen and nitrous oxide in the breathing gas is also typically described in terms of volume percent. However, breathing gas carbon dioxide content (e.g., Et_{CO_2}) is usually displayed as a partial pressure (mm Hg). This was probably adopted because of the relatively close correlation between Et_{CO_2} and Pa_{CO_2}, and the latter's common expression as a partial pressure. Figure 29-18 illustrates a theoretical composition of the breathing gases during anesthesia in terms of concentration (v/v%) and partial pressures.

The minimum alveolar concentration (MAC) is described in terms of volume percent. MAC is the concentration of anesthetic that prevents movement from surgical stimulus in 50% of individuals.[65] MAC is an age-dependent phenomenon, and it can also be affected by other variables. MAC is a clinically useful value given that vaporizer control knobs are marked and calibrated in terms of anesthetic concentration. However, it is actually the anesthetic partial pressure (mm Hg) value in the brain that is responsible for anesthetic depth. MAC is simply an expression of gas concentration (v/v%), with the denominator being the barometric pressure where the MAC experiment was conducted (typically at sea level). The corresponding partial pressure for each MAC value is known as the minimal alveolar partial pressure (MAPP), as listed in Table 29-1.[66] When discussing anesthetic vaporizers, it is useful to think about their output in terms of partial pressure and how it relates to volume percent and MAC, especially when considering changes in ambient pressure. The impact of barometric pressure on vaporizer output is discussed later.

Latent Heat of Vaporization. When a molecule of liquid evaporates into the gaseous phase, energy is required because the molecules of a liquid are cohered. The amount of energy that is consumed by a specific liquid when it is converting to a vapor is referred to as the *latent heat of vaporization*. It is more precisely defined as the number of



	Inhalation		Exhalation	
Gas	mm Hg	v/v%	mm Hg	v/v%
Sevoflurane	9.5	1.25	7.6	1.0
Oxygen	378	49.75	323.2	42.5
N_2O	372.5	49	347.2	45.8
CO_2	–	–	35	4.5
H_2O	–	–	47*	6.2
Total	760	100	760	100

*Saturated vapor pressure of water at body temperature.

Figure 29-18. Common units of measure for breathing circuit gases: theoretical values for an oxygen-nitrous oxide-sevoflurane anesthetic. Anesthetic agent, oxygen, and nitrous oxide concentrations are typically expressed in volume percent (v/v%). Carbon dioxide is commonly described as a partial pressure (mm Hg).

calories required to change 1 g of liquid into vapor without a change in temperature. The energy for vaporization must come from the liquid itself, and in the absence of an outside energy source the temperature of the liquid decreases during vaporization. This energy loss can lead to significant decreases in temperature within the remaining liquid, which will reduce vapor pressure and subsequent vaporization.[47,60,67] Unless the evaporative cooling effect of the liquid anesthetic agent is mitigated and compensated for, vaporizer output will decrease.

Boiling Point. The *boiling point* of a liquid is defined as the temperature at which vapor pressure equals atmospheric pressure and the liquid begins to boil.[47,67] In Table 29-1, note the boiling points for the various anesthetic agents at 1 atm. Desflurane boils at 22.8° C, and the other four inhaled anesthetic agents boil at between 45° C and 60° C. Whereas evaporation is a surface phenomenon, boiling occurs throughout the body of the liquid. Unlike vapor pressure, the boiling point is directly proportional to atmospheric pressure. A liquid's boiling point is inversely related to its volatility. The lower the boiling point, the more likely a liquid is to vaporize. For comparison, the boiling point for water at sea level is 100° C (212° F), far in excess of the boiling point of the volatile anesthetic agents.

In reviewing the boiling points of contemporary volatile anesthetic agents, it becomes clear that under most clinical situations, the boiling point is not a functional issue. Desflurane, however, boils at 22.8° C (73° F), which is a temperature encountered in clinical settings. This unique physical characteristic, along with its high saturated vapor pressure, mandates a special vaporizer design to control the delivery of this agent (see the section on the desflurane vaporizer). Isoflurane and halothane could theoretically boil at high altitudes and very high temperatures. At least one manufacturer lowers its vaporizer's

TABLE 29-1 **PHYSICAL PROPERTIES OF INHALED VOLATILE ANESTHETIC AGENTS**

Property	Halothane	Isoflurane	Sevoflurane	Desflurane
SVP* @ 20° C (mm Hg)	243	238	157	669
SVC† @ 20° C at 1 atm‡ (v/v%)	32	31	21	88
MAC§ at age 40 yr (v/v%)	0.75	1.2	1.9	6.0
MAPP¶ (mm Hg)	5.7	9.1	14.4	45.6
Boiling Point @1 atm (° C)	50.2 (122.4° F)	48.5 (119.3° F)	58.6 (137.3° F)	22.8 (73° F)

v/v%, Volume percent.
*SVP, Saturated vapor pressure. From anesthetic prescribing information.
†SVC, Saturated vapor concentration: the percentage of anesthetic agent relative to ambient pressure within an equilibrated (saturated) container (SVP/ambient pressure).
‡1 atm, 1 atmosphere = ambient pressure at sea level (760 mm Hg).
§MAC, Minimum alveolar concentration: the alveolar concentration that produces immobility in response to a noxious stimulus in 50% of subjects.[65] The denominator is approximately sea level pressure (760 mm Hg).
¶MAPP, Minimum alveolar partial pressure. The alveolar partial pressure that produces immobility in response to a noxious stimulus in 50% of subjects (the numerator in the MAC calculation).[66] Not affected by altitude. Calculated as MAC (fraction) × 760 mm Hg (i.e., for isoflurane = 0.012 × 760 mm Hg).

maximum temperature operating range for these anesthetic agents.[68]

Specific Heat. The *specific heat* of a substance is the number of calories required to increase the temperature of 1 g of a substance by 1° C.[47,67] The concept of specific heat is important to the design, operation, and construction of vaporizers because it is applicable in two ways. First, the specific heat for an inhaled anesthetic agent is important because it indicates how much heat must be supplied to the liquid to maintain a constant temperature when heat is being lost during vaporization. Second, manufacturers select vaporizer component materials that have high specific heat because these materials better resist temperature changes associated with vaporization.

Thermal Conductivity. Thermal conductivity is a measure of the speed at which heat flows through a substance. The higher the thermal conductivity, the better the substance will conduct heat.[47] Vaporizers are constructed of metals that have relatively high thermal conductivity, which helps them maintain a uniform internal temperature during evaporation by allowing them to absorb environmental heat more effectively.

Modern Vaporizer Types

Generic vaporizer nomenclature can be somewhat confusing, especially if the historical context of vaporizer, workstation, and breathing circuit evolution is not considered. Vaporizers are first designated as *in-circuit* or *out-of-circuit*, which describes their relationship to the patient's breathing circuit. Virtually all modern vaporizers are located outside the patient's breathing circuit, and their controlled output is introduced into the breathing circuit through a fresh gas line. In-circuit vaporizers are found mainly within the so-called *draw-over* anesthesia systems, which are of great historical significance in anesthesiology and are still used in some settings.

The second designation involves the specific types of vaporizers, and these currently include the *variable bypass vaporizer*, the *dual-circuit vaporizer* (e.g., classic desflurane vaporizer), *the cassette vaporizer* (e.g., Datex-Ohmeda Aladin cassette), the *injection vaporizer* (e.g., the Maquet vaporizer), and the now historical *measured-flow vaporizer* (e.g., Copper Kettle). Variable bypass vaporizers can be subcategorized as *plenum type,* which are located out of the breathing circuit and have relatively high internal flow resistance, or *draw-over type,* which are located within the breathing circuit (in-circuit) and have low internal resistance. Within most modern clinical settings, variable bypass vaporizers are *plenum type* and are located out of the breathing circuit, like those seen in Figures 29-1 and 29-2. Draw-over–type variable bypass vaporizers are used with draw-over anesthesia circuits, which are very uncommon today. Variable bypass vaporizers are associated with some additional designations such as *agent-specific*, *flow-over*, *temperature-compensated*, and *pressure-compensated*, which are discussed later.

Variable Bypass Vaporizers. When volatile anesthetic agents evaporate, their resultant saturated gas concentrations greatly exceed those used clinically, so these concentrations must be diluted to safe ranges (Table 29-1). *Variable bypass* refers to the method of carefully regulating the concentration of vaporizer output by diluting gas fully saturated with anesthetic agent with a larger flow of gas. A diagram of a variable bypass vaporizer is shown in Figure 29-19, *A*. Basic vaporizer components include a vaporizer inlet port (fresh gas inlet), the concentration control dial, the bypass chamber, the vaporizing chamber, the vaporizer outlet port, and the filling assembly. The maximum safe level of the vaporizer corresponds to the filling port, which is situated to minimize the chance of overfilling. A concentration control dial determines the ratio of gas that flows through the bypass chamber and the vaporizing chamber, and a temperature-compensating device further adjusts that ratio. Vaporizer concentration control dials are labeled to set vaporizer output in terms of volume percent (v/v%), and the vaporizers are calibrated at sea level.

Figure 29-20 illustrates volatile anesthetic equilibrium concentrations within a theoretical vaporizing chamber of a variable bypass vaporizer. As can be seen, the anesthetic concentration within the chamber (21% sevoflurane) far exceeds the clinical concentration. Figure 29-20 also depicts the volume of anesthetic vapor that is added to the gas stream as it flows through the chamber. Although this example and others in the chapter imply that the gas flowing through the vaporizing chamber becomes fully saturated with anesthetic vapor, this is actually not

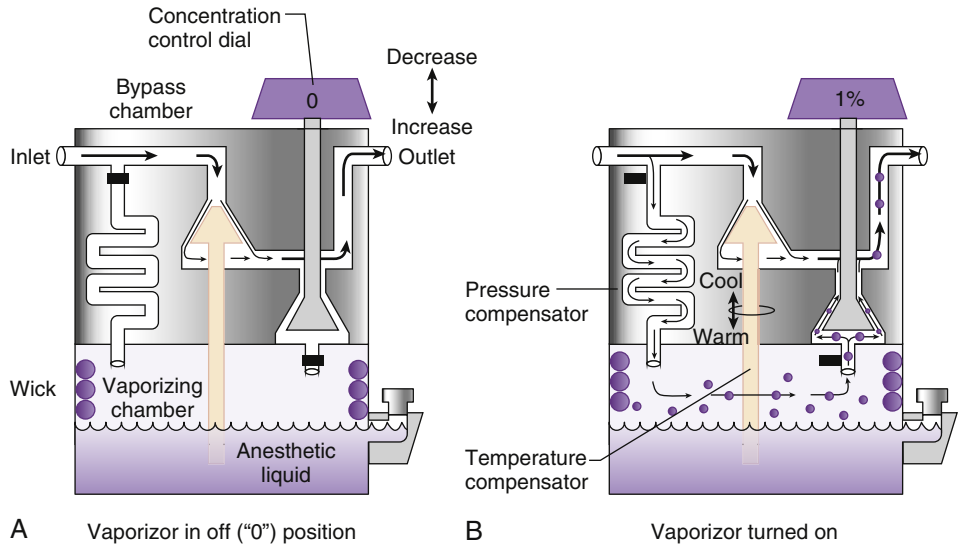


Figure 29-19. Variable bypass vaporizer. **A,** Basic component parts. Vaporizer in the off or "0" position. Fresh gas from the flowmeter assembly enters the vaporizer and then flows through the bypass chamber, around the temperature compensator, and out the vaporizer without passing through the vaporizing chamber. **B,** Selecting a vaporizer output (turning the vaporizer "on") diverts an agent-specific ratio of gas through the pressure-compensating labyrinth, into the vaporizing chamber where it becomes saturated with anesthetic vapor, and then past the concentration cone where it reunites with the fresh gas stream. The temperature compensation device further adjusts the ratio of bypass to vaporizing chamber flow, to compensate for changes in anesthetic vapor pressure resulting from temperature changes. As the liquid anesthetic cools by evaporation, more gas is diverted to the vaporizing chamber to compensate for the decrease in anesthetic vapor pressure. The pressure-compensating labyrinth compensates for pressure fluctuations within the vaporizer from the gas supply side and the breathing circuit side to stabilize vaporizer output. It is *not* present to compensate for changes in atmospheric pressure. Please see text for additional details.

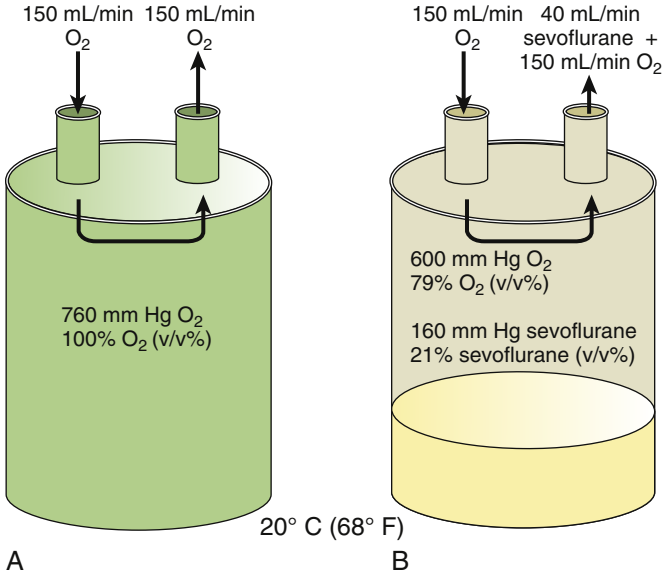


Figure 29-20. Theoretical vaporizing chamber demonstrating the volume of anesthetic gas added to the gas flow stream as a result of evaporation: **A,** 150 mL/minute of oxygen flows through the chamber at 1 atm (760 mm Hg) and 68° F (20° C). Oxygen represents 100% of chamber volume and output. **B,** Liquid sevoflurane is added to the chamber and evaporates to saturated vapor pressure SVP (160 mm Hg), which dilutes the oxygen to 79% of the chamber gas (600 mm Hg). The amount of gaseous sevoflurane that has been added to the chamber output can be calculated by simple equilibrium proportions: Step 1: 150 mL O_2/79% of container gas = *x* mL sevoflurane/21% of container gas Step 2: rearrange to solve for *x*: (150 mL/0.79) × 0.21 = *x* mL sevoflurane $x \approx 40$ mL sevoflurane.

the case. Vaporizing chamber gas becomes partly saturated as a result of constant gas flow.[69] However, for the purposes of this discussion, it is useful to assume that full saturation occurs.

Figure 29-21 illustrates a modern variable bypass vaporizer set to deliver 2% sevoflurane. Note how the majority of fresh gas flows straight through the bypass chamber. Figure 29-21 also illustrates how bypass flow and vaporizing chamber output combine to create the output concentration selected by the practitioner. The fresh gas that is diverted to the vaporizing chamber becomes saturated with anesthetic gas by flowing over liquid agent and the wicking system, hence the designation *flow-over*. The specific ratio of fresh gas flow divided between the bypass chamber and the vaporizing chamber is determined by the concentration control dial setting and the temperature compensation device (see the later discussion of temperature compensation). Because the physical properties and clinical concentrations of each agent are unique, the concentration-specific diverting ratios are specific to each agent, hence the vaporizer designation *agent specific*. The approximate variable bypass diverting or "splitting ratios" for the common anesthetic agents at 20° C are shown in Table 29-2. Variable bypass vaporizers can be used to deliver halothane, isoflurane, and sevoflurane, and older agents, but not desflurane, because of this agent's unique physical properties (see section on the desflurane vaporizer). Most variable bypass vaporizers are used in applications whereby their output is introduced into the patient's breathing circuit through a fresh gas line, hence the designation *out-of-circuit*. When these

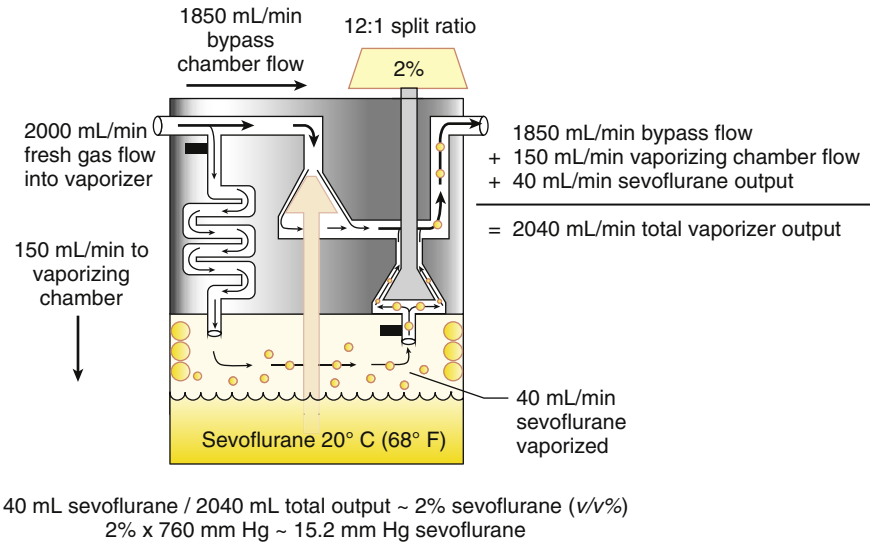


Figure 29-21. Vaporizer set to deliver 2% sevoflurane at 1 atm (760 mm Hg): 2% sevoflurane requires a splitting ratio of 12:1 (see Table 29-2). At 2000 mL/minute inflow, 1850 mL/minute flows through the bypass chamber and 150 mL/minute flows through the vaporizing chamber. The evaporation of sevoflurane contributes approximately 40 mL/minute of vapor:
Step 1: 150 mL O_2/79% of vaporizing chamber gas = *x* mL sevoflurane/21% of vaporizing chamber gas
Step 2: rearrange to solve for *x*: (150 mL/0.79) × 0.21 = *x* mL sevoflurane
$x \approx 40$ mL sevoflurane
Total vaporizer output is 2040 mL/minute. Sevoflurane represents ≈ 2% of that output.

TABLE 29-2 VARIABLE BYPASS VAPORIZER SPLITTING RATIOS

Concentration Control Dial Setting (v/v%)	Bypass Chamber–to–Vaporizing Chamber Splitting Ratios at 20° C (68° F)*		
	Halothane	Isoflurane	Sevoflurane
1	46:1	45:1	25:1
2	23:1	22:1	12:1
3	15:1	14:1	8:1

v/v%, Volume percent.
*Ratio of fresh gas flowing through the bypass chamber relative to the vaporizing chamber for the listed output concentrations. The temperature compensation device may alter the actual ratio. This applies to variable bypass vaporizers only. Calculated from: % volatile agent output = 100 × P_V × F_V / F_T (P_A – P_V) where P_A = atmospheric pressure, P_V = vapor pressure at 20° C, F_V = Flow of fresh gas through vaporizing chamber (mL/min), and F_T = total fresh gas flow (mL/min).
From Prescribing information Forane [isoflurane, USP]. *Deerfield, IL, 2009, Baxter Healthcare.*

agents are physically located within the patient's breathing circuit, they are designated as *in-circuit*, or *draw-over*.

Virtually all variable bypass vaporizers are classified as *temperature compensated*. Each of these vaporizers is equipped with an automatic temperature-compensating device that helps maintain constant vaporizer output over a wide range of operating temperatures by automatically altering the ratio of gas flowing to the bypass and vaporizing chambers. A representative temperature-compensating system is illustrated in Figure 29-19, *B*. Temperature compensation is accomplished by an expansion-contraction element, as seen in the image, or a bimetallic strip, that directs a greater proportion of gas flow through the vaporizing chamber as the liquid anesthetic cools from evaporation or a low ambient temperature, or both. In the example in Figure 29-19, *B*, as the liquid anesthetic agent cools, the temperature-compensating cone moves upward, which restricts bypass flow and diverts more gas to the vaporizing chamber. Cooler liquid anesthetic results in lower vapor pressure, so the net effect of temperature compensation is the maintenance of relatively stable vaporizer output. The inverse is also true, in that higher anesthetic temperatures result in lowering of the cone and less flow to the vaporizing chamber. The major temperature effect on vaporizers results from the evaporative cooling of the liquid anesthetic. The faster it evaporates, the more it cools. Rub some isopropyl alcohol on your skin, and feel your skin cool as the alcohol rapidly turns to vapor. Imagine the effect of this type of cooling on anesthetic agent vapor pressure! This knowledge has influenced vaporizer design for more than a century. Variable bypass vaporizers are also constructed from materials with high specific heat for temperature stability and high thermal conductivity to transfer ambient heat energy rapidly. Additionally, the wick systems previously mentioned are placed in contact with the metal wall of the vaporizer to absorb environmental heat better.

Factors That Influence Variable Bypass Vaporizer Output. An ideal variable bypass vaporizer at a given setting would maintain a constant concentration output regardless of varied conditions such as the fresh gas flow rate, temperature changes, intermittent backpressure from the breathing circuit, changes in carrier gas composition, and barometric pressure changes. ASTM standards state that the average output should not deviate from the dial setting by +30% or –20% or more than +7.5% or –5% of the maximum setting (ASTM). Although modern vaporizers generally have excellent performance characteristics, it is important to understand how these challenges could potentially influence vaporizer output.

Impact of Gas Flow Rate. Vaporizer output can vary with the rate of gas flowing through the vaporizer. As can be

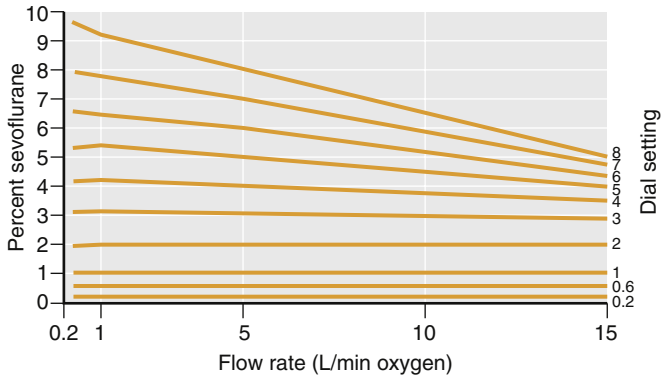


Figure 29-22. Effect of flow rate on vaporizer output. See text for explanation. *(From Datex-Ohmeda:* Tec 7 vaporizer: user's reference manual, *Madison, Wis., 2002, Datex-Ohmeda.)*

seen in Figure 29-22, this variation is notable only at the extremes of flow rates and at higher dial settings. The output of variable bypass vaporizers tends to be slightly less than the dial setting at low flow rates (<250 mL/minute) because of the relatively high density of volatile inhaled anesthetic agents. Insufficient turbulence is generated in the vaporizing chamber at low flow rates to advance the vapor molecules upwardly. At extremely high flow rates, such as 15 L/minute, the output of most variable bypass vaporizers is somewhat less than the dial setting at high anesthetic concentrations. This discrepancy is multifactorial, including cooling during rapid evaporation, incomplete mixing, and failure to saturate the carrier gas in the vaporizing chamber. In addition, the resistance characteristics of the bypass chamber and the vaporizing chamber can vary as flow increases.[68,70]

Impact of Temperature Change. Despite the impact of evaporative cooling and ambient conditions, modern vaporizer concentration output remains fairly linear over a wide range of vaporizer temperatures. Automatic temperature-compensating mechanisms in the bypass chamber strive to maintain constant vaporizer output with varying temperatures, although the linear change in these compensatory mechanisms does not correlate precisely with the shape of the vapor pressure curves.[21,68] As a result, a slight correlation between delivered concentration and vaporizer temperature may remain. This correlation is mainly apparent at higher temperatures and higher concentrations. A dangerous but highly unlikely circumstance could occur if the boiling point of a volatile agent within a variable bypass vaporizer were reached. In this situation, the vaporizer output would be impossible to control by any compensatory mechanism. Although it would be rare indeed to reach the ambient temperatures required at sea level to boil halothane, isoflurane, or sevoflurane, at higher altitudes, where boiling points are lower, isoflurane and halothane are theoretically vulnerable. In fact, the Dräger Vapor 2000 user's manual decreases the high-altitude operating specification for the vaporizer from 9880 to 4800 feet if halothane or isoflurane is used at higher ambient temperatures. Manufacturers' published vaporizer operating temperatures range from 10° C to 40° C (50° C to 104° F), although the specific ranges vary.[68,70-74]

Impact of Intermittent Backpressure. The intermittent backpressure that results from either positive-pressure ventilation or use of the oxygen flush valve may lead to higher than expected vaporizer output. This phenomenon, known as the *pumping effect*, is more pronounced at low flow rates, low dial settings, and low levels of liquid anesthetic in the vaporizing chamber.[47,68,75-77] Additionally, the pumping effect is increased by rapid respiratory rates, high peak inspired pressures, the use of anesthesia machines without fresh gas decoupling, and rapid drops in pressure during expiration.[47,60,67,68,78,79] Although contemporary variable bypass vaporizers are not highly vulnerable to the pumping effect, the proposed mechanism of the phenomenon and preventative design features should be understood. The pumping effect is caused by retrograde transmission of pressure from the patient circuit to the vaporizer during the inspiratory phase of positive-pressure ventilation or use of the oxygen flush function. Gas molecules are compressed in both the bypass and vaporizing chambers. When the backpressure is suddenly released during the expiratory phase of positive-pressure ventilation, vapor exits the vaporizing chamber both through the vaporizing chamber outlet and in the retrograde direction through the vaporizing chamber inlet because the output resistance of the bypass chamber is lower than that of the vaporizing chamber, particularly at low dial settings. The enhanced output concentration results from the increment of vapor that travels in the retrograde direction to the bypass chamber.[68,76,77,80]

To decrease the pumping effect, modern vaporizing chambers are smaller than those of early variable bypass vaporizers.[77] Therefore, no substantial volumes of vapor can be discharged from the vaporizing chamber into the bypass chamber during the expiratory phase. Additionally, some vaporizers, such as that shown in Figure 29-19, have a long spiral tube or labyrinth that serves as the inlet to the vaporizing chamber[77] (see Fig. 29-19, *B*). When the pressure in the vaporizing chamber is released, some of the vapor enters this tube but does not enter the bypass chamber because of tube length.[60] This serpentine passage also decreases the energy of the gas flow into the vaporizing chamber, thus dampening the pressure fluctuations. It can also compensate for fluctuations in gas supply pressure. Some designs may also include an extensive baffle system in the vaporizing chamber. Finally, a one-way check can be inserted past the vaporizers but before the breathing circuit inlet to minimize the pumping effect (see the discussion of the gas supply system). This check valve attenuates but does not eliminate the increase in pressure because gas still flows from the flowmeters to the vaporizer during the inspiratory phase of positive-pressure ventilation.[47,81] Although intermittent backpressure can result in transient rises in anesthetic concentration at the common gas outlet, dilution within the anesthetic breathing circuit tends to mitigate this effect.[82] The goal of all these pressure-compensating mechanisms is to provide an even flow of gas through the vaporizing chamber despite dynamic changes in outlet and inlet pressure. These devices lend the additional designation *pressure-compensated*. Clearly, these devices do not compensate for changes in ambient pressure, which is what some practitioners mistakenly infer from the term.

Impact of Carrier Gas Composition. Variable bypass vaporizer output can be influenced by the composition

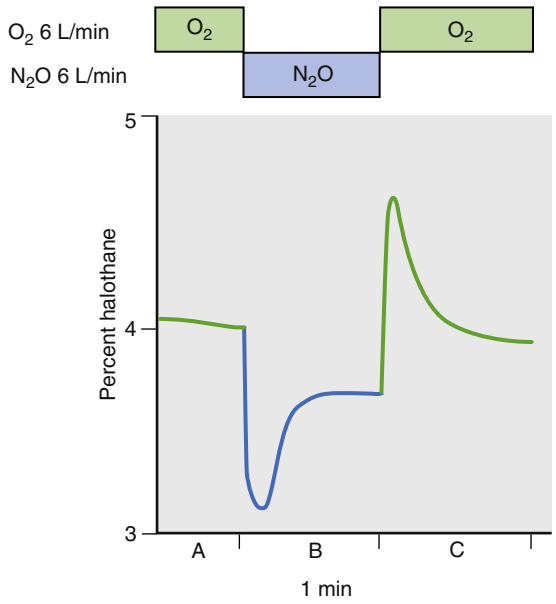


Figure 29-23. Halothane output of a North American Dräger Vapor 19.n vaporizer (Dräger Medical, Telford, Pa.) with different carrier gases. The initial output concentration is approximately 4% halothane when oxygen is the carrier gas at flows of 6 L/min (*A*). When the carrier gas is quickly switched to 100% nitrous oxide (*B*), the halothane concentration decreases to 3% within 8 sec. A new steady-state concentration of approximately 3.5% is then attained within about 1 min. When O_2 flow is reestablished, halothane output increases abruptly and then settles back to baseline (*C*). See text for details. *(Modified from Gould DB, Lampert BA, MacKrell TN: Effect of nitrous oxide solubility on vaporizer aberrance,* Anesth Analg *61:939, 1982.)*

of the fresh gas as a result of differences in solubility of anesthetic vapors in different carrier gas mixtures. This effect is most pronounced when nitrous oxide is introduced or removed as a carrier gas.[68,83-90] In the experimental example seen in Figure 29-23, a change in carrier gas from 100% oxygen to 100% nitrous oxide results in a sudden decrease in volume percent halothane output that is followed by a slow increase to a new steady-state value (see Fig. 29-23, label *B*).[88,89] Because nitrous oxide is more soluble than oxygen in the halogenated liquid within the vaporizer sump, the output from the vaporizing chamber is transiently reduced as some of the nitrous oxide is literally absorbed by the volatile agent, thus decreasing the vaporizing chamber volume output.[88] Once the anesthetic liquid becomes saturated with nitrous oxide, vaporizing chamber output increases, and a new steady state is established.

The explanation for the new steady-state output value is less well understood.[90] Although ongoing absorption of nitrous oxide may be contributory, differences in the density and viscosity of oxygen and nitrous oxide are also responsible. These gas properties can affect the relative amount of flows through the bypass and vaporizing channels within the vaporizer. This may explain difference in seen in the magnitude of this phenomenon when it is assessed using different vaporizers.[86,89,91] Helium, a gas with far lower density than either oxygen or nitrous oxide, has been shown to both decrease and increase vaporizer output, depending on the vaporizer model and study design, although the changes tend to be minimal.[92,93]

Although the carrier gas composition can be demonstrated experimentally to affect vaporizer output, deviations are often within vaporizer-specified accuracy ranges. Vaporizer user's manuals usually specify the anticipated response to a change in carrier gas relative to the calibration gas, which may be air or oxygen, depending on the vaporizer model.[68,70,71,94]

Impact of Barometric Pressure Changes. Understanding the influence of barometric pressure change on variable bypass vaporizer output is probably more important for comprehending vaporizer function than for actual clinical reasons. This is because, from a practical point of view, with *variable bypass* vaporizers the depth of anesthesia at a given dial setting is relatively independent of atmospheric pressure, and no adjustments must be made (Table 29-3).[68]

Hypobaric Conditions. As previously discussed, vapor pressure is not influenced by barometric pressure. Therefore, as altitude increases and the barometric pressure declines, the partial pressure of anesthetic agent in the variable bypass vaporizing chamber remains constant despite a decline in the partial pressures of other constituent breathing gases and the total ambient pressure. This situation results in significantly increased volume percent concentration of anesthetic agent within the vaporizing chamber and at the outlet of the vaporizer (see Table 29-3). However, because anesthetic depth is based on brain *partial pressure,* the clinical impact in minor (see MAPP in Table 29-1). With a constant dial setting of 0.89%, at 1 atm, a well-calibrated isoflurane variable bypass vaporizer would deliver 0.89 v/v% isoflurane, and the partial pressure of isoflurane would be 6.8 mm Hg. Maintaining the same dial setting and lowering the atmospheric pressure to 0.66 atm or 502 mm Hg (roughly equivalent to an elevation of 10,000 feet) would result in an increase in the concentration output to 1.75% (almost double), but the partial pressure would increase to only 8.77 mm Hg (a 29% increase). To put this change into familiar perspective, a similar partial pressure change at sea level, in terms of volume percent, would increase the isoflurane concentration by only 0.2%. To reemphasize, the anesthetic brain partial pressure is what is ultimately responsible for anesthetic depth. The anesthetic concentration (v/v%) is a relative phenomenon.

As described earlier, MAC values for contemporary inhalational anesthetic agents were determined at sea level. Similarly, anesthetic vaporizers are calibrated at sea level, thus ensuring that vaporizer output (v/v%) matches the dial setting. Using sevoflurane as an example, one can therefore see how confusing that using volume percent and MAC can be when considering barometric change. Knowing that sevoflurane MAPP = 12.9 mm Hg:

$$\text{Sevoflurane MAC at sea level (v/v\%)} = \frac{12.9\text{ mm Hg}}{760\text{ mm Hg}} \approx 1.7\%$$

$$\text{Sevoflurane MAC at } 10,000\text{ feet (v/v\%)} = \frac{12.9\text{ mm Hg}}{534\text{ mm Hg}} \approx 2.4\%$$

The MAPP at altitude is the same as at sea level because it is based on partial pressure, whereas the MAC has increased because it is a simple concentration. After viewing the examples in Table 29-3, it becomes clear that the

TABLE 29-3 COMPARATIVE PERFORMANCE OF AN ISOFLURANE VARIABLE BYPASS VAPORIZER AND THE TEC 6 DESFLURANE VAPORIZER DURING CHANGES IN BAROMETRIC PRESSURE

		Isoflurane Variable Bypass Vaporizer With a Dial Setting of 0.89% (*v/v*)			Tec 6 Desflurane Vaporizer With Dial Setting of 6%
atm	Ambient Pressure (mm Hg)	mL Isoflurane Vapor Entrained by 100 mL O_2	Vaporizer Isoflurane Output (v/v%)	Vaporizer Isoflurane Output (mm Hg)	Vaporizer Desflurane Output (mm Hg)
0.66	500 (≈10,000 ft)	91	1.7	8.7	30
0.74	560 (≈8,200 ft)	74	1.5	8	33.6
0.8	608 (≈6,000 ft)	64	1.2	7.6	36.5
1.0	760 (sea level)	46	0.89	6.8	45.6
1.5*	1,140	26	0.5	5.9	68.4
2*	1,520	19	0.36	5.5	91.2
3*	2,280	12	0.23	5.2	136

atm, Atmospheres (1 atm = 760 mm Hg); *v/v%,* volume percent.
*ATA or atmospheres absolute. ATA = atmospheric pressure + water pressure. Hyperbaric oxygen chamber protocols apply ATA. Many protocols use depths from 2.0 to 2.5 ATA, but some conditions such as gas embolus or carbon monoxide poisoning may require depths to 3.0 ATA.[262] 2 ATA ≈ 33 feet of sea water (fsw) ≈ 1520 mm Hg ambient pressure.
Modified from Ehrenwerth J, Eisenkraft J: Anesthesia vaporizers. In Ehrenwerth J, Eisenkraft J, editors: Anesthesia equipment: principles and applications, *St. Louis, 1993, Mosby, pp 69-71.*

partial pressure output of a variable bypass vaporizer changes proportionally less than the volume percent concentration as altitude increases. Because anesthetic partial pressure is what determines anesthetic depth, the operator *does not* need adjust the dial to a higher setting to compensate for barometric pressure change. This holds for variable bypass vaporizers, but it is not the case for the desflurane Tec 6–style vaporizer, which is discussed in section on desflurane vaporizers.

Although anesthesia is sometimes delivered in *hyperbaric conditions,* volatile agents are an unlikely choice in this setting given the advent of intravenous anesthesia. Under hyperbaric conditions, the anesthetic partial pressure in the vaporizing chamber also remains constant despite an increase in ambient pressure and the partial pressure of the other gases. The net theoretical effects on variable bypass vaporizers are a significant decrease in anesthetic concentration (v/v%) and a mild decrease in partial pressure output. However, the partial pressure of halothane was noted to increase slightly with increasing barometric pressure under experimental conditions.[95] Possible explanations for this finding include the effect of increased atmospheric gas density on the flow of gas through the vaporizer and the increased thermal conductivity of air at higher pressure. The clinical significance of these small changes in variable bypass vaporizer partial pressure output under hyperbaric conditions is unclear.

Safety Features and Potential Hazards. Contemporary variable bypass vaporizers incorporate many features that have minimized or eliminated many hazards once associated with these devices. Agent-specific, keyed filling devices help prevent filling a vaporizer with the wrong agent. Overfilling of these vaporizers is minimized because the filler port is located at the maximum safe liquid level. Finally, today's vaporizers are firmly secured to a vaporizer manifold on the anesthesia workstation. Thus, problems associated with vaporizer tipping have become much less frequent. Contemporary interlock systems prevent the administration of more than one inhaled anesthetic agent. However, virtually all safety systems have vulnerabilities, so understanding these potentially hazardous situations is important.

Misfilling. Misfilling of anesthetic vaporizers can result in potentially hazardous volatile agent outputs that can overdose or underdose anesthetic agents.[96,97] Vaporizer output in these circumstances depends on the erroneous agent's saturated vapor pressure and the splitting ratio of the vaporizer. Similarly, mixtures of anesthetic agents can result potentially harmful dosing as well.[61] The potential for misfilling anesthetic vaporizers with the wrong agent has been reduced but not eliminated with the use of agent specific filling devices; however, current standards recommend but do not mandate the use of these devices.[12] A potential for misfilling exists even in vaporizers equipped with keyed fillers, although few recent reports exist.[98-100] The use of breathing circuit gas analysis may alert the user to misfilling. If a variable bypass vaporizer such as an isoflurane or sevoflurane vaporizer is misfilled with desflurane, a substantial overdose could occur because of desflurane's high vapor pressure, particularly at normal operating temperatures.

Contamination. Although unusual and rarely reported, contamination of anesthetic vaporizer contents has occurred as a result of filling an isoflurane vaporizer with a contaminated bottle of isoflurane. A potentially serious incident was avoided because the operator did not use the contaminated vaporizer after detecting an abnormal acrid odor.[101]

Tipping. Tipping of a variable bypass vaporizer can occur when it is incorrectly removed, transported, or replaced. Excessive tipping can allow the liquid agent to enter the bypass chamber and cause an output with an extremely high concentration of agent.[102] Although some vaporizers may be more immune to tipping than others, most vaporizers should not be used until it they have been flushed for a period of time at high flow rates. Manufacturers' instructions differ regarding their

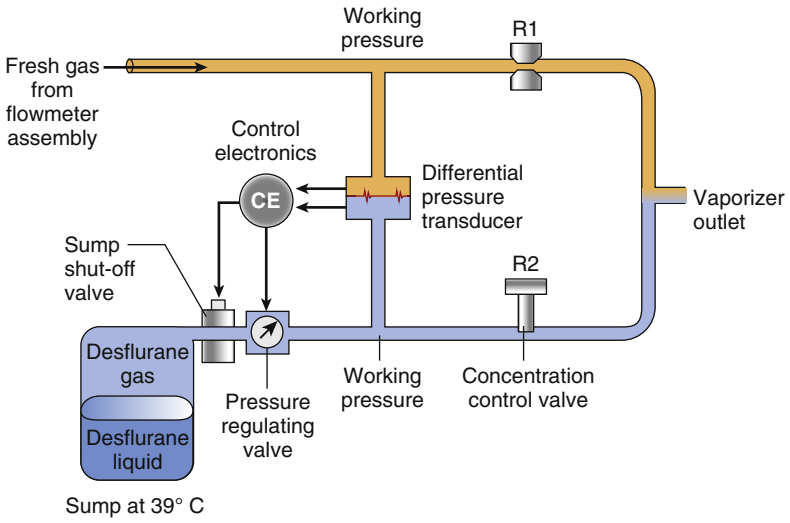


Figure 29-24. Simplified schematic of the Tec 6 desflurane vaporizer (Datex-Ohmeda, Madison, Wis.). Please see text for details. *(From Andrews JJ:* Operating principles of the Ohmeda Tec 6 desflurane vaporizer: a collection of twelve color illustrations, *Washington, D.C., 1996, Library of Congress.)*

posttipping procedures, precluding any generic recommendation.[68,70,71,94] The specific user's manual should be consulted. Following any of these specified procedures, a breathing gas analyzer should be used to assess vaporizer output before patient use. The Dräger Vapor 20.n series vaporizers have a transport ("T") dial setting that isolates the vaporizer chamber from the bypass chamber and eliminates the possibility of internal overflow.[68]

Overfilling. Improper filling procedures combined with failure of the vaporizer sight glass can cause overfilling and patient overdose. If overfilled, liquid anesthetic may enter the bypass chamber, and a harmful dose of vapor concentration can be delivered to the common gas outlet.[103] It is a design requirement that contemporary vaporizers cannot be overfilled when they are used in a normal operating position.[12] Side-fill variable bypass vaporizers, as opposed to top-fill devices, largely prevent overfilling because the maximum safe fill amount is predetermined by the level of the filler port, which is situated to minimize the chance of overfilling. In addition, some vaporizers are equipped with an overflow hole as an additional safeguard.[68] However, despite safeguards, vaporizer overfilling can still occur. Hazardous situations include tipping of the vaporizer while filling, filling of the vaporizer while it is turned on, and air entry at the bottle neck and filler adapter caused by a loose or faulty seal.[103-106] User's manuals for contemporary vaporizers warn specifically about these conditions.[68,70,71,94]

Leaks. Vaporizers and the vaporizer-machine interface are potential sources of gas leaks that can result in a patient's awareness during anesthesia. Loose filler caps, filler plugs, and drain valves are probably the most common sources of vaporizer leaks. Such a leak can be obvious as an audible gas leak with possible spillage of anesthetic agent or a more subtle presentation with lower than expected inhaled agent concentration or the odor of anesthetic gas.[107,108] Another common source of gas leak associated with vaporizers occurs at the junction of the vaporizer and the mounting bracket or manifold, where broken mounting assemblies or foreign bodies can compromise the seal between the vaporizer and its point of attachment.[109-112] Gas leaks can also occur within the vaporizer itself as a result of mechanical failure. Assessment for low-pressure system leaks, including the vaporizer mount, is addressed in the section on 'checking your anesthesia workstation.

Environmental Considerations. Today more than ever, anesthesia care providers are being asked to provide anesthesia to patients outside the operating room. One such location that has sometimes proved difficult to work in is the magnetic resonance imaging (MRI) suite. The presence of a powerful magnet field, significant noise pollution, and limited access to the patient during the procedure all complicate care in this setting. The anesthesia provider must have a clear understanding of the extremely powerful magnetic fields used in these devices and must know that only nonferrous (MRI-compatible) equipment can be used in these settings. Although some anesthesia vaporizers may appear nonferrous by testing with a horseshoe magnet, they may indeed contain substantial internal ferrous components. Inappropriate use of such devices in an MRI suite may potentially turn them into dangerous missiles if they are left unsecured.[113]

Desflurane Vaporizer. Because of its unique physical characteristics, the controlled vaporization of desflurane required a novel approach to vaporizer design. The first such system, the Datex-Ohmeda Tec 6 vaporizer, was released into clinical use in the early 1990s. The Tec 6 is an electrically heated, pressurized device specifically designed to deliver desflurane (Fig. 29-24).[114,115] The vapor pressure of desflurane is three to four times that of other contemporary inhaled anesthetic agents (669 mm Hg at 20° C), and it boils at 22.8° C (73.1° F),[116] which is basically room temperature (see Table 29-1). In 2004, Dräger Medical received approval from the U.S. Food and Drug Administration (FDA) for its own version of the Tec 6 desflurane vaporizer. The operating principles described in the following discussion are applicable to either system, although the discussion refers to the Tec 6 specifically. The

Datex-Ohmeda Aladin cassette vaporizer and the Maquet vaporizers are also capable of delivering desflurane, but their operational principles are different. These vaporizers are discussed in later sections.

Unsuitability of Contemporary Variable Bypass Vaporizers for Controlled Vaporization of Desflurane. Desflurane's high volatility and moderate potency preclude its use with contemporary variable bypass vaporizers for three main reasons[114]

1. Desflurane's high rate of evaporation would require excessive diluting gas (bypass chamber) flow. At 68° F (20° C), the vapor pressure of desflurane is nearly 1 atm. This pressure is significantly higher than the vapor pressure of the other conventional anesthetic agents (see Fig. 29-16 and Table 29-1).[116] If desflurane were placed in a variable bypass vaporizer, tremendous gas flow rates would be required to dilute the vaporizing chamber output to clinical concentrations. For example, at 1 atm and 68° F (20° C), 100 mL/minute passing through the vaporizing chamber would entrain 735 mL/minute of desflurane, as opposed to 29, 46, and 47 mL/minute of enflurane, isoflurane, and halothane, respectively.[114] Under these same conditions, to produce a 1% desflurane output, the amount of bypass flow necessary to achieve sufficient dilution of the large volume of desflurane-saturated anesthetic vapor would be approximately 73 L/minute, in contrast to 5 L/minute or less for the other three anesthetic agents. This would be neither practical nor possible using conventional anesthesia workstations.
2. Desflurane's high rate of evaporation would cause substantial anesthetic cooling. Variable bypass vaporizers require ambient sources heat to stay warm as they cool during vaporization. Although the latent heat of vaporization for desflurane is approximately equal to that of enflurane, isoflurane, and halothane, its MAC is four to nine times higher than those of the other three inhaled anesthetic agents. Thus, the absolute amount of desflurane vaporized over a given period is considerably greater than that of the other anesthetic drugs. Supplying desflurane through a variable bypass vaporizer in equivalent MAC concentrations would lead to excessive cooling of the vaporizer and significantly reduce its output. In the absence of an external heat source, temperature compensation with the traditional mechanical devices would be almost impossible. Because of the broad range of temperatures seen in the clinical setting and because of desflurane's steep vapor pressure–versus-temperature curve (V-P curve), delivery of desflurane in a conventional anesthetic vaporizer would be at best unpredictable.[114]
3. Desflurane is more likely to boil. At temperatures higher than 73° F (22.8° C) at 1 atm, desflurane boils. This temperature is at the higher end of normal operating room temperatures. If the anesthetic agent were to boil within a variable bypass–type vaporizer, the output would be uncontrollable because the amount of vapor produced would be limited only by the heat energy available from the vaporizer because of its specific heat.[114]

Operating Principles of the Tec 6 and Tec 6 Plus. The Tec 6 vaporizer was designed to achieve controlled vaporization of desflurane, and it was the first clinically available vaporizer ever to be electrically heated and pressurized. Although the physical appearance and operation of the desflurane vaporizers and the variable bypass vaporizers are similar, many aspects of their internal design and operating principles are radically different.

Functionally, operation of the Tec 6 is more accurately described as a dual-gas blender than as a vaporizer. A simplified schematic of the Tec 6 is shown in Figure 29-24. The vaporizer has two independent gas circuits arranged in parallel. The fresh gas circuit is shown in *orange,* and the vapor circuit is shown in *blue.* Fresh gas from the flowmeters enters at the fresh gas inlet, passes through a fixed restrictor (R1), and exits at the vaporizer gas outlet. The vapor circuit originates at the desflurane sump, which is electrically heated and thermostatically controlled to 39° C, a temperature much higher than desflurane's boiling point. The heated sump assembly serves as a reservoir of desflurane *vapor*. At 39° C, the vapor pressure in the sump is approximately 1300 mm Hg,[117] or approximately 2 atm. Just downstream from the sump is the shut-off valve. After the vaporizer warms up, the shut-off valve fully opens when the concentration control valve is turned to the "on" position. A pressure-regulating valve located downstream from the shut-off valve down regulates the pressure to approximately 1.1 atm absolute (74 mm Hg gauge) at a fresh gas flow rate of 10 L/minute. The operator controls the output of desflurane by adjusting the concentration control valve (R2), which is a variable restrictor.[114]

The vapor flow through R2 joins the fresh gas flow through R1 at a point downstream from the restrictors. Until this point, the two circuits are physically separated. They are interfaced pneumatically and electronically, however, through differential pressure transducers, a control electronics system, and a pressure-regulating valve. When a constant fresh gas flow rate encounters the fixed restrictor R1, a specific backpressure proportional to the fresh gas flow rate pushes against the diaphragm of the control differential pressure transducer. The differential pressure transducer conveys the pressure difference between the fresh gas circuit and the vapor circuit to the control electronics system. The control electronics system regulates the pressure-regulating valve so that the pressure in the vapor circuit equals the pressure in the fresh gas circuit. This equalized pressure supplying R1 and R2 is the working pressure, and the working pressure is constant at a fixed fresh gas flow rate. If the operator increases the fresh gas flow rate, more backpressure will be exerted on the diaphragm of the control pressure transducer, and the working pressure of the vaporizer will increase.[114]

Table 29-4 shows the approximate correlation of the fresh gas flow rate with working pressure for a typical vaporizer. At a fresh gas flow rate of 1 L/minute, the working pressure is 10 millibars, or 7.4 mm Hg gauge. At a fresh gas flow rate of 10 L/minute, the working pressure is 100 millibars, or 74 mm Hg gauge. Therefore, a linear relationship exists between the fresh gas flow rate and working pressure. When the fresh gas flow rate is increased 10-fold, the working pressure increases 10-fold.[114]

TABLE 29-4 FRESH GAS FLOW RATE VERSUS WORKING PRESSURE

Fresh Gas Flow Rate (L/min)	Working Pressure at R1 and R2 (Gauge) (Gas Inlet Pressure)		
	Millibar	cm H_2O	mm Hg
1	10	10.2	7.4
5	50	51.0	37.0
10	100	102.0	74.0

From Andrews JJ, Johnston RV Jr: The new Tec 6 desflurane vaporizer, Anesth Analg *76:1338, 1993.*

TABLE 29-5 DIAL SETTING VERSUS FLOW THROUGH RESTRICTOR R2

Dial Setting (vol%)*	Fresh Gas Flow Rate (L/min)	Approximate Vapor Flow Rate Through R2 (mL/min)
1	1	10
6	1	64
12	1	136
18	1	220

From Andrews JJ, Johnston RV Jr: The new Tec 6 desflurane vaporizer, Anesth Analg *76:1338, 1993.*

The following are two specific examples to demonstrate the operating principles of the Tec 6[114]:

Example A: *Constant fresh gas flow rate of 1 L/minute with an increase in the dial setting.* With a fresh gas flow rate of 1 L/minute, the working pressure of the vaporizer is 7.4 mm Hg. In other words, the pressure supplying R1 and R2 is 7.4 mm Hg. As the operator increases the dial setting, the opening at R2 becomes larger, thereby allowing more vapor to pass through R2. Specific vapor flow values at different dial settings are shown in Table 29-5.

Example B: *Constant dial setting with an increase in fresh gas flow from 1 to 10 L/minute.* At a fresh gas flow rate of 1 L/minute, the working pressure is 7.4 mm Hg, and at a dial setting of 6%, the vapor flow rate through R2 is 64 mL/minute (see Tables 29-4 and 29-5). With a 10-fold increase in the fresh gas flow rate, a concomitant 10-fold increase in the working pressure to 74 mm Hg occurs. The ratio of R2 to R1 resistance is constant at a fixed dial setting of 6%. Because R2 is supplied by 10 times more pressure, the vapor flow rate through R2 increases 10-fold to 640 mL/minute. Vaporizer output is constant because both fresh gas flow and vapor flow increase proportionally.

Factors That Influence Vaporizer Output. Varied altitude and carrier gas composition influence the Tec 6 vaporizer output. Each is discussed in the following paragraphs.

Varied Altitudes. Although ambient pressure changes affect *variable bypass vaporizer* output significantly in terms of volume percent, their effect on anesthetic potency (partial pressure) is minimal. However, the change in variable bypass vaporizer output with altitude is in stark contrast to the response of the Tec 6 style desflurane vaporizer at varied altitudes, as can be seen in Table 29-3. One must remember that the Tec 6 style desflurane vaporizer device is more accurately described as a dual-gas blender than a vaporizer. Regardless of ambient pressure, the Tec 6 will maintain a constant concentration of vapor output (v/v%), *not a constant partial pressure*. This means that at high altitudes, the partial pressure of desflurane will decrease in proportion to the reduction in atmospheric pressure divided by the calibration pressure (normally 760 mm Hg) per the following formula:

$$\text{Required dial setting } (\%) = \text{Normal dial setting} \times \frac{760 \text{ mm Hg}}{\text{Ambient pressure (mm Hg)}}$$

For example, at an altitude of 2000 m, or 6564 feet, where the ambient pressure is 608 mm Hg, the operator must advance the concentration control dial from 10% to 12.5% to maintain the required anesthetic partial pressure. In hyperbaric settings, the operator must decrease the dial setting to prevent delivery of an overdose. At 2 atm or 1520 mm Hg of pressure, the desflurane output in mm Hg is twice that at sea level (91.2 versus 45.6 mm Hg).

Carrier Gas Composition. Vaporizer output approximates the dial setting when oxygen is the carrier gas because the Tec 6 vaporizer is calibrated with 100% oxygen. At low flow rates when a carrier gas other than 100% oxygen is used, however, a clear trend toward reduction in vaporizer output emerges. This reduction parallels the proportional decrease in viscosity of the carrier gas. Nitrous oxide has lower viscosity than does oxygen, so the backpressure generated by resistor R1 (see Fig. 29-24) is less when nitrous oxide is the carrier gas, and the working pressure is reduced. At low flow rates and with nitrous oxide used as the carrier gas, vaporizer output is approximately 20% less than the dial setting. This suggests that at clinically useful fresh gas flow rates, gas flow across resistor R1 is laminar, and the working pressure is proportional to both the fresh gas flow rate and the viscosity of the carrier gas.[118]

Safety Features. Because desflurane's vapor pressure is nearly 1 atm, misfilling contemporary variable bypass vaporizers with desflurane could theoretically result in both desflurane overdose and creation of a hypoxic gas mixture.[119] Like most of its contemporaries, the desflurane vaporizer has a unique, anesthetic-specific filling system to minimize occurrence of this potential hazard. The agent-specific filler of the desflurane bottle, known as the "Saf-T-Fill" adapter, is intended to prevent its use with traditional vaporizers. The filling system also minimizes spillage of liquid or vapor anesthetic by maintaining a closed system during the filling process. Each desflurane bottle has a spring-loaded filler cap with an O-ring on the tip. The spring seals the bottle until it is engaged in the filler port of the vaporizer. Thus, this anesthetic-specific filling system interlocks the vaporizer and the dispensing bottle and thereby prevents loss of anesthetic agent to the atmosphere.

Major vaporizer faults cause the shut-off valve located just downstream from the desflurane sump (see Fig. 29-24) to close and produce a no-output situation. The valve is closed, and a no-output alarm is activated immediately if any of the following conditions occur: (1) the anesthetic level decreases to less than 20 mL,

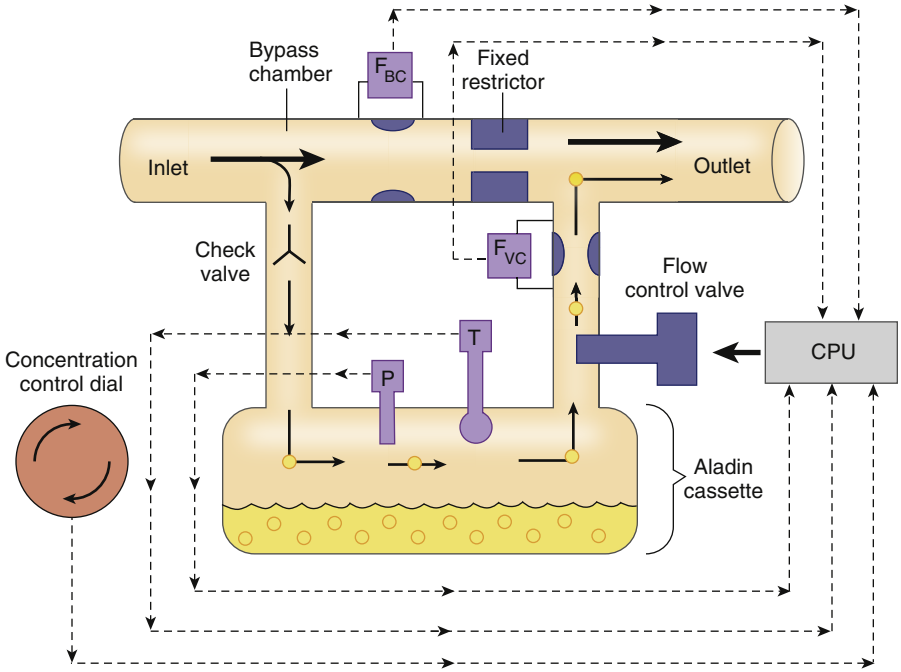


Figure 29-25. Simplified schematic of Datex-Ohmeda Aladin cassette vaporizer (Datex-Ohmeda, Madison, Wis.). The *black arrows* inside the vaporizer represent flow from the flowmeters, and the *yellow circles* represent anesthetic vapor. The heart of the vaporizer is the electronically controlled flow control valve located in the outlet of the vaporizing chamber. *CPU,* Central processing unit; F_{BC}, flow measurement unit that measures flow through the bypass chamber; F_{VC}, flow measurement unit that measures flow through the vaporizing chamber; *P,* pressure sensor; *T,* temperature sensor. Please see text for additional details. *(Modified from Andrews JJ:* Operating principles of the Datex-Ohmeda Aladin cassette vaporizer: a collection of color illustrations, *Washington, D.C., 2000, Library of Congress.)*

(2) the vaporizer is tilted, (3) a power failure occurs, or (4) a disparity between the pressure in the vapor circuit and the pressure in the fresh gas circuit exceeds a specified tolerance. Although such automated safeguards can enhance the patient's safety, they can sometimes have unintended consequences. For example, when a Datex-Ohmeda D-Tec "plus" was used with a new anesthesia machine that, by design, interrupted fresh gas flow during mechanical inspiration in the volume mode as means of fresh gas decoupling, the vaporizer was reported to provide a no output warning during mechanical ventilation.[120] These purposeful fresh gas flow interruptions, which occurred in the volume-mode of ventilation only, were sensed as a fault situation, and the vaporizer output was terminated. Although the vaporizer was subsequently modified, the circumstance serves as a reminder that new technology can bring about new problems.

Summary. The Tec 6 and Dräger D-Vapor vaporizers are electrically heated, thermostatically controlled, constant-temperature, pressurized, electromechanically coupled dual-circuit, gas vapor blenders. The pressure in the vapor circuit is electronically regulated to equal the pressure in the fresh gas circuit. At a constant fresh gas flow rate, the operator regulates vapor flow with a conventional concentration control dial. When the fresh gas flow rate increases, the working pressure increases proportionally. For a given concentration setting, even when varying the fresh gas flow rate, the vaporizer output is constant because the amount of flow through each circuit remains proportional.[114]

Datex-Ohmeda Aladin Cassette Vaporizer. The vaporizer system used in the Datex-Ohmeda S/5 ADU and GE Aisys anesthesia workstations is unique in that a single electronically controlled vaporizer is designed to deliver five different inhaled anesthetic agents, including halothane, isoflurane, enflurane, sevoflurane, and desflurane (Fig. 29-25). The vaporizer consists of a permanent internal control unit housed within the workstation and interchangeable cassettes that contain anesthetic liquid and serve as vaporizing chambers. The Aladin cassettes are color coded for each anesthetic agent, and they are also magnetically coded so the workstations can identify which anesthetic cassette has been inserted. The cassettes are filled using agent-specific fillers.[120]

Operationally, the Aladin cassette vaporizing system is best described, during most circumstances, as a computer-controlled variable bypass vaporizer because it consists of a bypass section and vaporizing chamber. Within the cassette, anesthetic agent vaporizes freely to saturated vapor pressure. A flow control valve, modulated by a central processing unit (CPU), precisely meters the amount of gas flow through the vaporizing chamber or cassette, which then joins the bypass flow after being saturated with anesthetic agent. The CPU receives input from multiple sources, including the concentration control dial, a pressure sensor located inside the vaporizing chamber, a temperature sensor located inside the vaporizing chamber, a flow measurement unit located in the bypass chamber, and a flow measurement unit located in the outlet of the vaporizing chamber. The CPU also receives input from the flowmeters regarding the composition of the carrier gas because this can affect vaporizer output, as described earlier. By using data from these multiple sources, the CPU is able to regulate the flow of fresh gas through the vaporizing chamber precisely with the flow control valve to obtain the desired vapor concentration output.[121]

A fixed restrictor located in the bypass chamber causes gas flow from the vaporizer system inlet to split into two flow streams. One stream passes through the bypass chamber, and the other portion enters the inlet of the vaporizing chamber and passes through a one-way check valve.

The presence of this check valve is unique to the Aladin system. This one-way valve prevents retrograde flow of the anesthetic vapor back into the bypass chamber, and its presence is crucial when delivering desflurane if room temperature is higher than the boiling point of desflurane (22.8° C).[47] A precise amount of vapor-saturated carrier gas passes through the flow control valve, which is regulated by the CPU. This flow then joins the bypass flow and is directed to the outlet of the vaporizer.[47]

As mentioned in the discussion of the Tec 6, controlled vaporization of desflurane presents a unique challenge, particularly when room temperature is higher than the boiling point of desflurane (73° F [22.8° C]). If the desflurane were to boil, the pressure inside the vaporizing chamber would increase to more than ambient pressure. When this pressure exceeds pressure in the bypass chamber, the one-way check valve located in the vaporizing chamber inlet closes to prevent carrier gas from entering the vaporizing chamber. At this point the carrier gas passes straight through the bypass chamber and its flow sensor. Under these conditions, the electronically regulated flow control valve simply meters in the appropriate flow of pure desflurane vapor needed to achieve the desired final concentration selected by the user. The vaporizer then begins functioning as an injector, as opposed to resembling a variable bypass unit. At least one case report has described failure of the vaporizing chamber inlet check valve to function as designed. In this case, an anesthetic overdose occurred as a result of regurgitation of desflurane from the vaporizing chamber in retrograde fashion back into the bypass chamber. Because of this report, ADU users should be cautious of this potential problem, especially when desflurane is used.[121]

During operating conditions in which high fresh gas flow rates or high dial settings (or both) are used, large quantities of anesthetic liquid are vaporized rapidly. As a result, the temperature of the remaining liquid anesthetic and the vaporizer itself decreases because of energy consumption or from the latent heat of vaporization. To offset this cooling effect, the S/5 ADU is equipped with a fan that forces warmed air from an "agent heating resistor" across the cassette (vaporizer sump) to raise its temperature when necessary. The fan is activated during two common clinical situations: (1) desflurane induction and maintenance and (2) sevoflurane induction.

The Aladin vaporizing system incorporates several important safety features. The electronic ratio control of the workstation is incorporated into the vaporizing system. This ensures no less than 25% oxygen at the common gas outlet regardless of the gas composition *and* the concentration of anesthetic agent. By contrast, anesthetic agent concentration does not affect conventional oxygen ratio controllers, so this feature is unique. The system is equipped with a safety relief valve that opens when the pressure within the cassette exceeds 2.5 bar (1899 mm Hg). When the Aladin cassette is removed from the unit, valves prevent the loss of fresh gas from the mount. Another valve prevents liquid anesthetic from entering the fresh gas line. This system also has an overfilling protection mechanism. Finally, because the Aladin cassette is immune from the problems associated with tipping that occur with conventional variable bypass vaporizers, it has no restrictions on tilting during handling or storage.[121]

Maquet Injection-Type Vaporizer. The Maquet vaporizer is an electronically controlled, injection-type vaporizer that is used exclusively with Maquet FLOW-i anesthesia workstations. Because these vaporizers are located upstream from the patient's breathing circuit, they are designated as out-of-circuit vaporizers, similar to the desflurane vaporizer and most variable bypass vaporizers. The Maquet injection vaporizers are also agent specific, with vaporizers available for isoflurane, sevoflurane, and desflurane. Agent-specific filling adapters are used for each anesthetic agent. Externally, the device has a lid, filling port, electronic level indicator, and alert indicators, but no concentration control dial. Vaporizer output adjustments are accomplished through an electronic interface on the workstation (personal communication, Maquet Critical Care, January 14, 2013).

The Maquet vaporizer principle of operation is illustrated in Figure 29-26. Gas from the anesthesia machine is used to pressurize an anesthetic liquid storage container. Pressurization of the reservoir provides the force to drive liquid anesthetic agent through the vaporizer injector and minimizes evaporation of the agent within the chamber. Liquid anesthetic agent is injected into a heated vaporizing chamber under microprocessor control in a pulsed and intermittent manner, and it rapidly evaporates. Anesthetic liquid is injected at small increments until the desired injection volume is obtained. The total amount of anesthetic injected at any given interval is based on the desired anesthetic concentration and the fresh gas flow through the vaporizer. A dedicated gas analysis line downstream from the vaporizer monitors the output. An optical sensor in the vaporizer monitors the integrity of the anesthetic injections (personal communication, Maquet Critical Care, January 14, 2013).

Fresh gas from the anesthesia workstation, under the control of operator and the fresh gas modules, flows through the vaporizing chamber and is enriched with gaseous anesthetic agent. Although some of the injected liquid anesthetic evaporates while in flight within the vaporizing chamber, the remaining liquid is deposited on an evaporative surface within the chamber. This evaporative surface is heated to ensure immediate evaporation. The heating of the surface is carefully regulated to compensate for the effect of evaporative cooling (personal communication, Maquet Critical Care, January 14, 2013).

During the daily workstation preuse check, the vaporizers are automatically tested with respect to functionality and leaks. This feature is unique relative to variable bypass vaporizers, which must be manually selected to participate in automated or manual leak testing. A safety valve stops the flow of liquid agent in the case of vaporizer malfunction. The vaporizer is not vulnerable to tipping because it has no wicks to saturate, and agent cannot spill into the vaporizing chamber. The vaporizer can be filled during use, although no vaporizer output occurs during filling. An alarm triggers when the vaporizer level is less than 10%, and a higher-priority alarm triggers when it reaches 5%. At this time, no published data are available

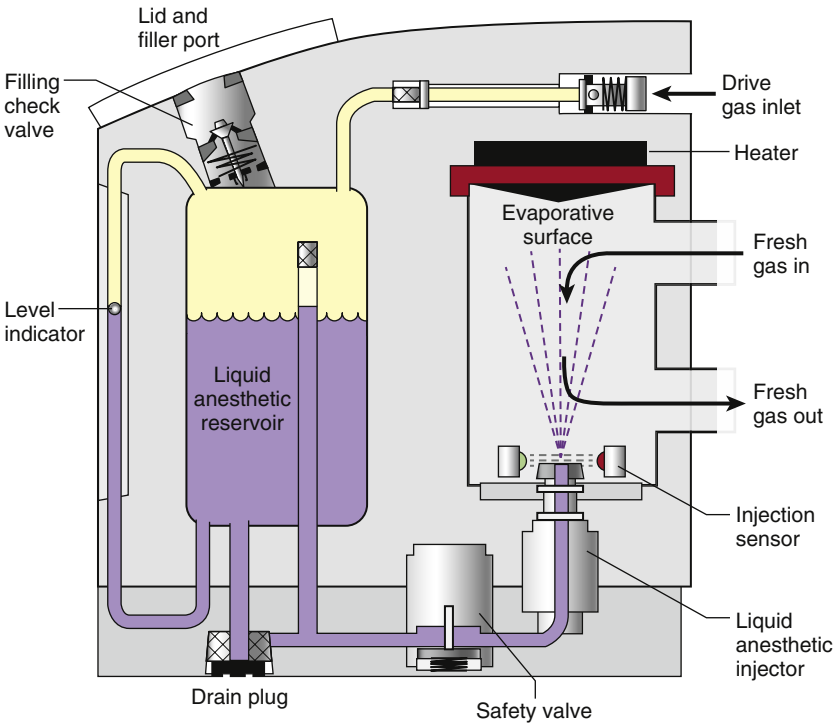


Figure 29-26. The Maquet anesthetic vaporizer. Drive gas from the anesthesia machine is used to pressurize a liquid anesthetic reservoir. Under microprocessor control, liquid agent is injected into a vaporizing chamber. Injection is carefully monitored. A heated surface within the vaporizing chamber facilitates evaporation of the anesthetic agent. Fresh gas flows through the chamber and is enriched with anesthetic gas. A safety valve stops the flow of liquid agent in the case of vaporizer malfunction. *(Personal communication, illustration adapted with permission from Maquet Critical Care, Solna, Sweden, January 14, 2013).*

on the vaporizer's performance at variable barometric pressure, temperature, flesh gas flow rates, or with variable fresh gas compositions (personal communication, Maquet Critical Care, January 14, 2013).

ANESTHETIC BREATHING CIRCUITS

Fresh gas departs from the gas supply system and enters the anesthetic breathing circuit through the fresh gas line. The functions of the breathing circuit are to deliver oxygen and other gases to the patient and to eliminate carbon dioxide. The breathing system must contain a low-resistance conduit for gas flow, a reservoir for gas that can meet the patient's inspiratory flow demand, and an expiratory port or valve to vent excess gas.[122] Applying these criteria as foundational for any anesthetic breathing system, one can then further categorize the circuits as those that use an absorber to eliminate carbon dioxide (the circle system) and those that do not (the Mapleson circuits).[123] Circle systems are the most common breathing circuits used for anesthetic delivery. However, certain Mapleson systems are used in anesthesia workstations, particularly in pediatrics, and they are often used by anesthesia providers for ventilation and oxygenation during transport of patients, procedural sedation, liberation from tracheal intubation (the T-piece), and preoxygenation during out-of-the-operating-room airway management. Therefore, both systems are discussed.

Leaks and obstruction represent the two most important hazards associated with the breathing circuit. Most of the time, these problems can be detected during the preuse checkout of the workstation. However, a firm understanding of the components and function of the breathing system is critical if one is to perform a proper preuse checkout of the workstation and troubleshoot acute problems. The operator should also be aware of the various standards and alarms associated with this critical part of the anesthesia workstation.

Circle Breathing Systems

For many years, the overall design of the classic circle breathing system changed very little (Figs. 29-27 to 29-29). From one anesthesia workstation to the next, the circle breathing circuits shared similar schematics and components. More recently, however, with the increasing technologic complexity of the anesthesia workstation, circle breathing systems have evolved and their diversity has increased. These changes have resulted in part from an effort to improve patients' safety, such as integration of fresh gas decoupling during positive-pressure ventilation.

The circle breathing system is so named because it allows circular, unidirectional gas flow, which is facilitated by unidirectional valves. Some of the main advantages of the circle system include (1) maintenance of relatively stable inspired gas concentrations, (2) conservation of respiratory moisture and heat, (3) elimination of carbon dioxide, (4) an economy of anesthetic gases resulting from rebreathing, and (5) prevention of operating room pollution. The capability to rebreathe and conserve anesthetic gases is a unique aspect of the circle breathing system as compared with an ICU ventilator breathing circuit, in which the entirety of each exhaled breath is vented into the room. To allow rebreathing of the exhaled gases, carbon dioxide must be removed. Another unique aspect of the circle system is that waste gases, which are composed of excess gas flows, anesthetic agent, and carbon dioxide, must able to be scavenged and eliminated. Circle systems also must allow for spontaneous ventilation, manual ventilation, and positive-pressure ventilation. Therefore, the circle system must function with both the anesthesia reservoir bag and a ventilator.

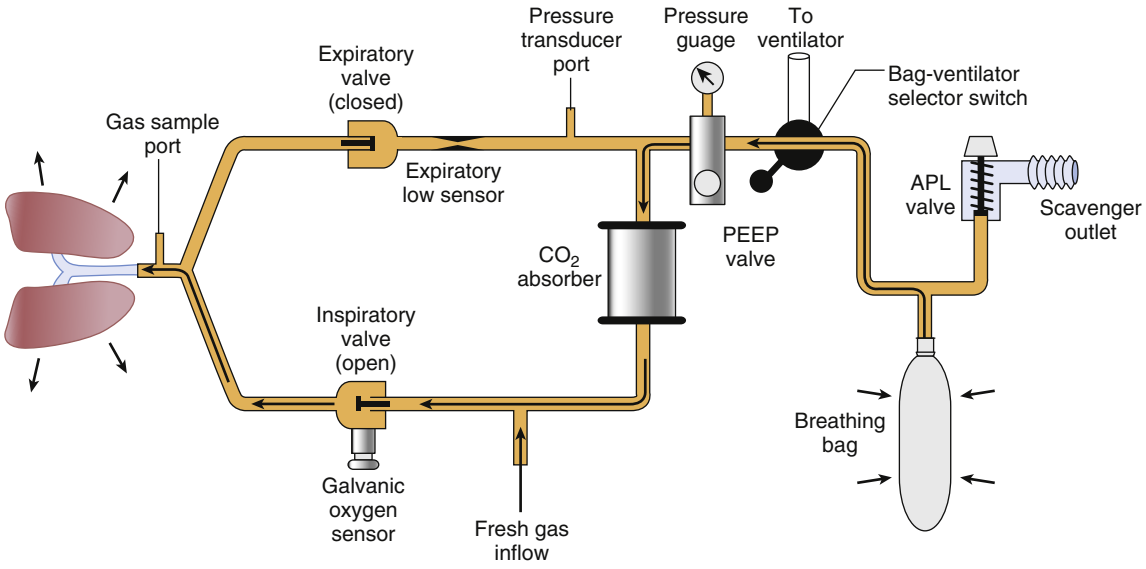


Figure 29-27. Classic circle breathing system. Spontaneous breathing-inspiratory phase (ventilator not shown). Gas is drawn by the patient from the breathing bag and through the carbon dioxide (CO_2) absorber. It is then mixed with the fresh gas inflow from the gas supply system, traverses the inspiratory valve, and flows to the patient. The expiratory valve prevents rebreathing by disallowing bypass of the CO_2 absorber. *PEEP,* Positive end-expiratory pressure. *(Courtesy Dr. Michael A. Olympio; modified with his permission.)*

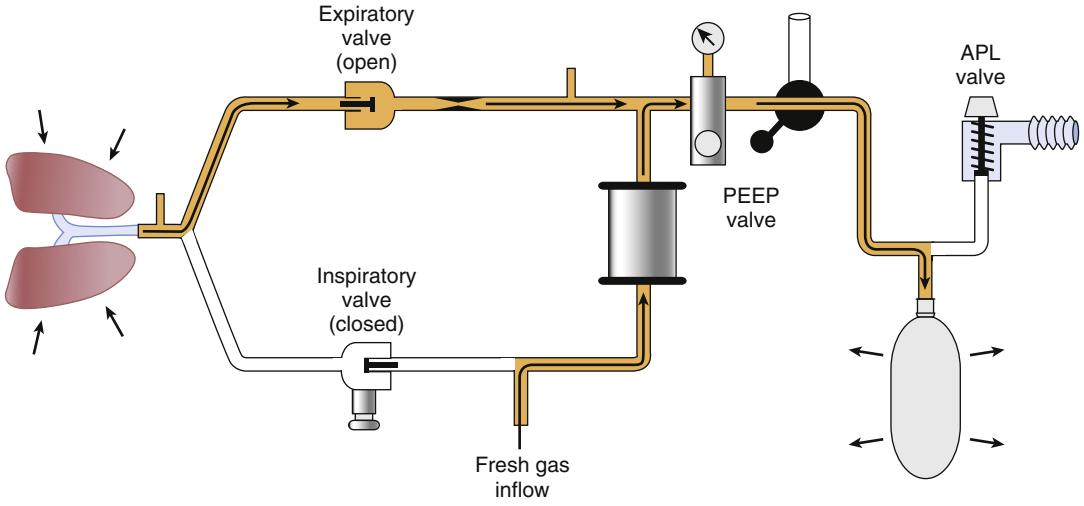


Figure 29-28. Spontaneous breathing: early expiratory phase. The inspiratory unidirectional valve ensures that all exhaled carbon dioxide (CO_2)–containing gas flows toward the breathing bag and adjustable pressure-limiting (APL) valve before being scrubbed of CO_2. Fresh gas continues to flow, but now in retrograde fashion, and combines with the exhaled breath. The APL valve remains closed in this example because circuit pressure is still lower than the practitioner-set APL valve pressure threshold (i.e., 10 cm H_2O). *PEEP,* Positive end-expiratory pressure. *(Courtesy Dr. Michael A. Olympio; modified with his permission.)*

The major disadvantage of the circle system stems from its complex design. Commonly, the circle system may have 10 or more different connections. These multiple connection sites set the stage for misconnections, disconnections, obstructions, and leaks. In a closed-claim analysis of adverse anesthetic outcomes arising from gas delivery equipment, 39% of malpractice claims resulted from breathing circuit misconnections or disconnection.[124] Malfunction of the circle system's unidirectional valves can cause life-threatening problems. Rebreathing can occur if the valves stick in the open position, and total occlusion of the circuit can occur if the valves are stuck shut. If the expiratory valve is stuck in the closed position, breath stacking and barotrauma can result. The circle breathing system is large compared with the Mapleson systems. Therefore, the overall compliance of the circuit tends to be higher, and this can decrease tidal volume delivery during controlled ventilation. Many newer anesthesia workstations assess circuit compliance to better deliver accurate tidal volumes, or they can compensate for disparities in set versus delivered tidal volume. Finally, because circle breathing systems use a carbon dioxide absorber, anesthetic degradation can occur (see the section on carbon dioxide absorbers).[125]

The circle system consists of several essential components, including (1) a fresh gas inflow source, (2) inspiratory and expiratory unidirectional valves, (3) inspiratory and expiratory corrugated tubes, (4) a Y-piece that connects to the patient, (5) an overflow or adjustable pressure limiting (pop-off) valve (the APL valve), (6) a reservoir or

breathing bag, and (7) a canister containing a carbon dioxide absorbent (see Fig. 29-27). Several additional common circuit components are added to enhance patients' safety, including a circuit pressure sensor, a circuit pressure gauge, an expiratory (and possibly an inspiratory) flow sensor, and an inspired oxygen concentration sensor. A separate positive end-expiratory pressure (PEEP) valve may be present. A ventilator serves as an alternate source of ventilation apart from the patient or the anesthesiology provider. The inspiratory and expiratory valves are placed in the system to ensure that gas flow through the circuit remains unidirectional. The fresh gas inflow enters the circle by a connection from the common gas outlet of the anesthesia machine. The major circle system components are described in the following subsections.

Unidirectional Valves. The one-way valves are essential elements of the circle breathing system (Fig. 29-30; see Fig. 29-57). They are usually constructed so that their function is not impaired by the humidity that sometimes accumulates in the breathing system. However, incompetence is one of the most common problems encountered with these usually reliable valves, and the expiratory valve seems to be most vulnerable because it is subject to greater moisture exposure. Stuck-open unidirectional valves result in rebreathing of carbon dioxide, and each valve demonstrates a characteristic incompetence pattern on the capnography tracing.[126] Assessing for proper unidirectional valve function should be part of the anesthesia workstation preuse check out procedure. Anesthesia machines are constructed so functioning of these valves is visible.[127]

Adjustable Pressure-Limiting Valve. The APL valve is an operator-adjustable relief valve that vents excess breathing circuit gas to the scavenging system and provides control of the breathing system pressure during spontaneous and manual modes of ventilation. Switching the workstation to a ventilator mode excludes or closes the valve.[127] Several other common names exist for these devices, including "pop-off" valve and pressure relief valve.[122] The two basic types of pressure-limiting valves are the variable-resistor (or variable-orifice) type and the pressure-regulating type. The variable-type functions as a needle valve, much like a flow control valve (Fig. 29-31). The operator adjusts the outlet orifice size, so the

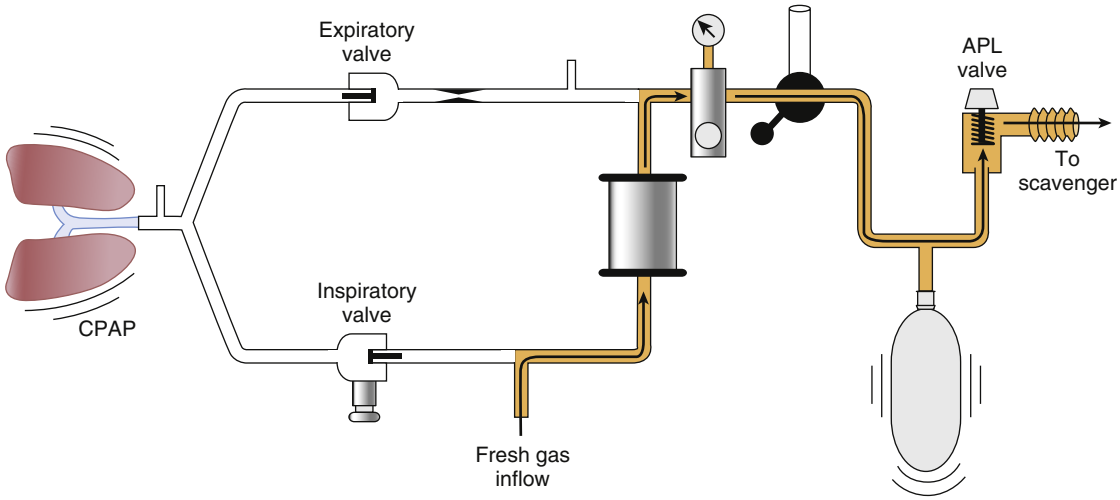


Figure 29-29. Spontaneous breathing: end-expiratory phase with continuous positive airway pressure (CPAP). Fresh gas continues to flow into the circuit generating pressure that maintains distention of the lungs (CPAP) and the breathing bag. Once the circuit pressure exceeds the adjustable pressure-limiting (APL) valve's set threshold (i.e., 10 cm H_2O), the valve opens, and excess gas flow is vented to the scavenger. *(Courtesy Dr. Michael A. Olympio; modified with his permission.)*

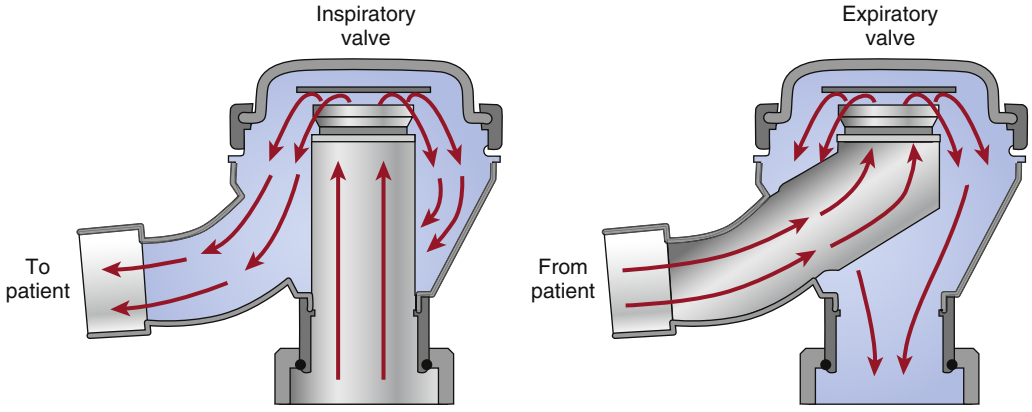


Figure 29-30. Circle breathing system unidirectional valves *(Modified from Yoder M: Absorbers and breathing systems. In* Understanding modern anesthesia systems, *Telford, Pa., 2009, Dräger Medical, pp 83-126.)*

resultant breathing system pressure at any given adjustment is directly related to the fresh gas flow rate. Modern machines now mostly use pressure-regulating–type APL valves (Fig. 29-32). This type of APL valve has an adjustable internal tension spring and an external scale indicating approximate or relative opening pressure. When the pressure in the system exceeds spring tension, a disk opens and gas is vented (see Fig. 29-32, *B*). In this manner, the operator can adjust the circuit pressure, which remains stable even as the fresh gas flow is increased. Continuous positive airway pressure (CPAP) can be more reliably controlled using this type of APL valve; however, circuit pressure should be carefully monitored. This type of valve usually has a fully open position for spontaneous breathing whereby the valve is open to the atmosphere (see Fig. 29-32, *C*). Gas is prevented from returning from the scavenging system by a downstream check valve. When the valve is placed in the manual mode, spring pressure is applied to the valve in an amount proportional to the desired maximal circuit pressure as described before.[41,122]

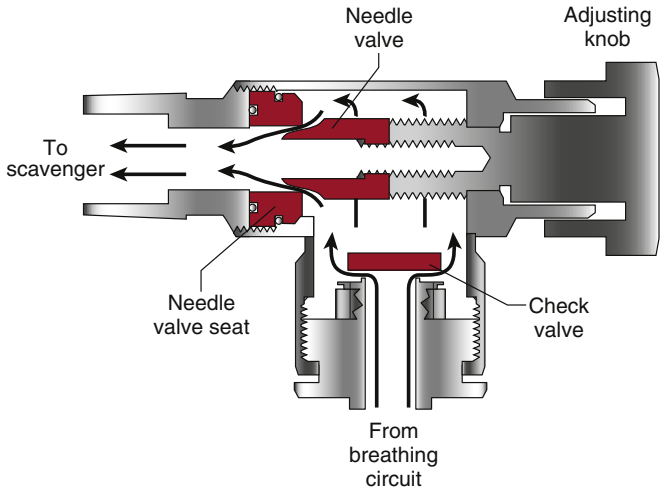


Figure 29-31. Adjustable pressure-limiting valve: variable orifice type. A weighted check valve prevents gas from flowing backward after being sent to the scavenger. A variable orifice needle valve controls rate of gas egress from the breathing circuit, thereby controlling the circuit pressure. At any given adjusted valve orifice, the pressure in the circuit will depend on the fresh gas flow rate. *(Modified from Yoder M: Absorbers and breathing systems. In* Understanding modern anesthesia systems, *Telford, Pa., 2009, Dräger Medical, pp 83-126.)*

Anesthesia Reservoir Bag or "Breathing Bag." The anesthesia reservoir bag, or "breathing bag," provides several important functions, including (1) serving as a reservoir for exhaled gas and excess fresh gas, (2) providing a means of delivering manual ventilation or assisting spontaneous breathing, (3) serving as a visual or tactile means of monitoring a patient's spontaneous breathing efforts, and (4) partially protecting the patient from excessive positive pressure in the breathing system such as in the case of inadvertent closure of the APL valve or an obstruction of the scavenge line (Fig. 29-33). The reservoir bag is the most compliant part of the breathing system. The pressure-volume characteristics of this bag are such that it inflates to a maximal pressure and then slightly decreases to a plateau as it continues to fill even to high volumes.[122,128,129] Anesthesia reservoir bags must adhere to pressure standards, which allow a minimal pressure of approximately 30 cm H_2O and a maximal pressure of approximately 60 cm H_2O when the bag is filled to four times its stated capacity.[130] Although most bags adhere to these standards, some latex-free bags have exceeded this maximal value.[129] Classically, the reservoir bag was excluded from the breathing circuit when the ventilator was in use. However, on some contemporary workstations, such as the Dräger Fabius and Dräger Apollo, the reservoir bag is integral to circuit function during mechanical ventilation, where it serves as an exhaled and fresh gas reservoir.[41,131]

Corrugated Breathing Circuit Tubing. The breathing circuit tubing, which accounts for most of the volume within the breathing, has certain vulnerabilities. First, these circuits are distensible; therefore, some of the volume to be delivered to the patient during positive-pressure ventilation is absorbed by the distention of the tubing. Many modern machines perform a compliance test to compensate for this distention, so it is important that these tests be performed with the circuit that is to be used. For instance, if an extension is to be used on the

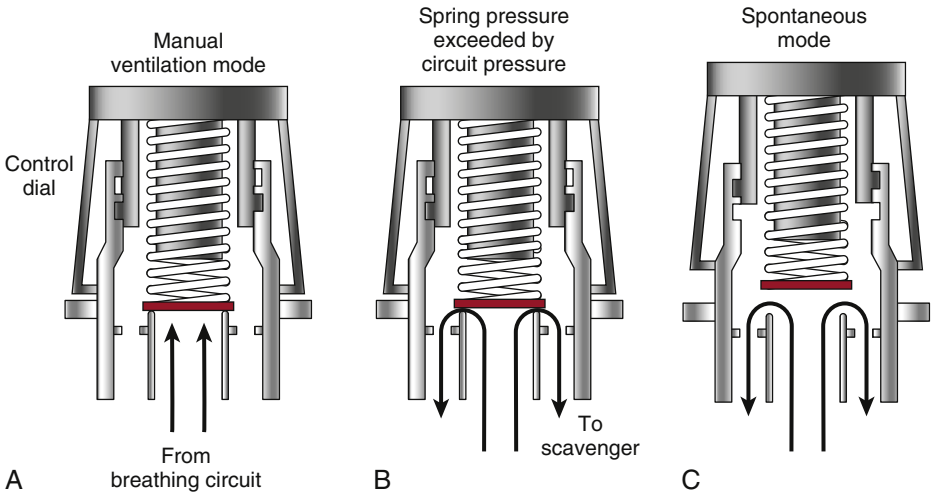


Figure 29-32. Adjustable pressure-limiting (APL) valve: pressure-regulating type. **A,** In the "manual" setting, the operator adjusts spring tension, thereby adjusting valve opening pressure. In this image the breathing circuit pressure has not yet exceeded spring tension. **B,** Breathing circuit pressure has exceeded the set pressure (spring tension), and gas is vented to the scavenger. With the pressure regulating type of APL valve circuit pressure is independent of the fresh gas flow rate. **C,** When the valve is placed in the spontaneous mode, the disk is lifted off the valve seat, and gas flows freely to the scavenger. A check valve downstream prevents waste gas from returning to the breathing circuit.

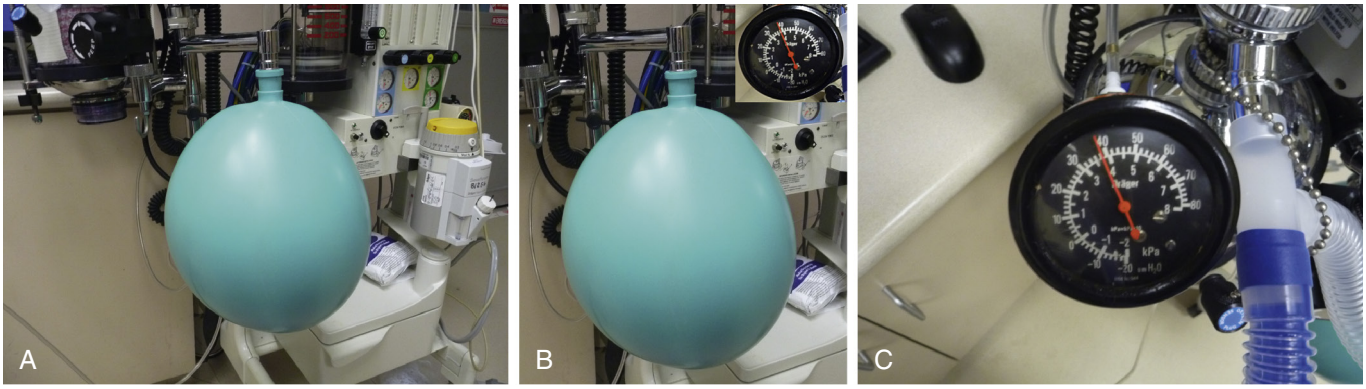


Figure 29-33. Breathing circuit reservoir bag or breathing bag. The standard for reservoir bags is that their maximum pressure should not exceed approximately 60 cm H_2O at four times their stated capacity.[130] However, many reservoir bags peak and plateau at lower pressures, and all should maintain plateau as they expand.[128] reservoir bags peak at lower pressures yet continue to expand. A peak pressure followed by a plateau is usually seen. In **A** and **B,** this breathing bag was allowed to inflate to several times its capacity. **C,** The breathing circuit pressure has plateaued at approximately 40 cm H_2O. Vigilance should prevent this from occurring because the continuing positive-pressure alarm should be sounding while the bag is inflating.

circuit to facilitate turning the operating room table 180 degrees**,** the compliance, leak, and flow tests should be performed with the extension in place. Another potential problem is that these circuits can leak or house an obstruction (see later).

Y-Piece. The Y-piece of the circuit is the distal part of the near the patient connection that merges the inspiratory and expiratory limbs of the circle breathing system. It has a distal inner 15-mm diameter to it can connect to an endotracheal tube or elbow connector, and a 22-mm outer diameter to connect to a face directly if needed. On modern anesthesia machines, the gas monitoring sample port is located at or near the Y-piece because inspiratory and expiratory gases can be sampled there. The anatomic dead space in the circle system begins at the Y-piece.

Inspired Oxygen Concentration Monitor. The ASTM standards state that the workstation must be provided with an oxygen monitor for the measurement of the oxygen concentration in the breathing circuit inspiratory limb or at the Y-piece. A low–oxygen concentration alarm must be associated with the device, and the alarm must activate within 30 seconds of an oxygen concentration drop below the set limit, which cannot be adjustable to less than 18% v/v%.[12] The oxygen sensor is truly the patient's last line of defense from receiving a hypoxemic gas mixture. Galvanic cell oxygen analyzers are often used for this purpose (see Fig. 29-55). A common location for this sensor is on the housing of the inspiratory unidirectional valve. Galvanic cell oxygen analyzers have a finite life span and are prone to drift. They therefore require daily calibration during the workstation preuse check (see the section on the Preuse check). Sidestream multigas analyzers are now used more often as the exclusive inspiratory oxygen monitor because machines are increasingly incorporating integrated gas monitoring capabilities. Paramagnetic oxygen analysis is typically employed within these monitors, and this analysis requires less frequent calibration. Multigas side-stream analysis is performed at the Y-piece.

Flow Sensors. Flow sensors are used on the anesthesia machine primarily to provide tidal volume measurement. In fact, ASTM standards state that the workstation must have a device that monitors the patient's exhaled tidal volume or minute ventilation, or both.[12] Some machines, if capable, also use the sensors to produce flow waveform or flow-volume loops, or both. Finally, some machines use tidal volume measurements as a feedback signal to maintain stable tidal volume delivery regardless of the total fresh flow rate. Although early flow sensors were usually mechanical respirometers, contemporary machines may employ differential pressure sensors, heated wire anemometers, ultrasonic flow sensors, and variable orifice flow sensors. The location of the flow sensor can vary, but the machine must have, at a minimum, a sensor for exhaled gas flow.

Breathing Circuit Pressure Sensors. The continuous measurement of airway pressure in the patient's breathing circuit is critical to the patient's safety, and it fulfills several requirements. First, anesthesia workstations must continuously display pressure in the breathing system. Second, operator-adjustable alarm conditions must exist for *high pressure*, as well as for *continuing positive pressure* for 15 seconds or longer. Excessive high pressure or prolonged positive airway pressure can compromise venous return, decrease cardiac output, interfere with ventilation, or cause barotrauma.[12] An alarm must also occur if the pressure in the breathing circuit becomes *less than –10 cm H_2O* for more than 1 second. Finally, when automatic ventilation is in use, the machine must alarm whenever the breathing pressure falls below a preset or adjustable pressure threshold for more than 20 seconds. Because the machine must also have a breathing system disconnection alarm, this low-pressure alarm may serve that purpose. However, low-volume or exhaled CO_2 monitoring may also be used.[12] The location of pressure sample site in the breathing system can be variable. It can be located in either the inspiratory or expiratory nondisposable circuitry, but it is usually close to one of the unidirectional valves. Anesthesia machines also have an analog breathing pressure gauge. Although it does not have any alarm

capabilities or an electronic interface, it continues to serve as a faithful adjunct.

Filters and Heat and Moisture Exchangers. The use of heat and moisture exchangers and filters within the anesthesia breathing circuit is common. The rationale for the use of heat and moisture exchangers is to replace the normal warming and humidifying function of the upper airway, which is bypassed by an artificial airway.[132] The basis for filter use is to prevent the transmission of microbes from the patient to the machine and hence potentially to other patients. Heat and moisture exchanging filters serve both purposes. Although a discussion of the benefits and potential hazards associated with these devices is beyond the scope of this chapter, no consensus agreement pertaining to the use of these devices exists. Further, current ASA recommendations endorse the use of filters only in the context of patients with tuberculosis, to protect the machine from contamination with airborne infectious disease.[133] If a filter is to be used for this purpose, it should have an efficiency rating higher than 95% for particle sizes of 0.3 um. The filter should be placed between the endotracheal tube and the Y-piece.[134]

Circle System Function. Classic circle system function is illustrated in Figures 29-27 to 29-29. The extent of rebreathing and the conservation of the other exhaled gases depend on the fresh gas flow rate. Higher fresh gas flow rates result in less rebreathing and greater waste gas. Contemporary circle systems are usually operated in a *semiclosed* manner, meaning that some waste flow is always vented through the APL valve or the waste gas valve associated with the ventilator. The use of low gas flows (≈1.0 L/minute) or minimal flows (≈0.5 L/minute) during anesthesia is an example. A *semiopen* system, as it pertains to the circle system, connotes higher fresh gas flows where minimal rebreathing would occur and more waste gas is vented. The potential advantages of conducting minimal fresh gas flow anesthesia include a decreased use of volatile anesthetic agents, improved temperature and humidity control, and reduced environmental pollution. The disadvantages include difficulty in rapidly adjusting anesthetic depth and the theoretical possibility of accumulation of endogenously released gases (e.g., carbon monoxide [CO], acetone, methane) or volatile anesthetic–absorbent related degradation products (e.g., compound A, CO).[135] A *closed* circuit is one in which the rate of oxygen inflow exactly matches metabolic demand, rebreathing is complete, and no waste gas is vented (APL valve remains closed). A volatile anesthetic agent is added to the breathing circuit in liquid form in precise amounts or is initially introduced through the vaporizer.[136] Closed-circuit anesthesia maximizes the advantages of low and minimal flow anesthesia. However, the technical demands of the technique relative to the benefits make it impractical for routine use with contemporary equipment, thus it is rarely employed.[137]

Potential Circle System Problems

Leaks and Disconnections. Breathing circuit leaks and disconnections continue to cause critical incidents in anesthesia.[138-140] Common sources of leaks include disposable tubing and components, as well as points of connection within the breathing circuit and at the carbon dioxide absorber canister.[141] Although leaks can develop during the course of anesthesia, such as a partial disconnection, most leaks can be detected during a thorough workstation preuse checkout. Leaks can be small, compensated only by increase in fresh gas flow to overcome the loss of volume, or they can be very large, prohibiting any ventilation at all. No matter the size, all leaks should be investigated. Several monitors can assist the anesthesia provider in detecting a leak or circuit disconnection during the course of anesthetic care (Table 29-6).

Breathing circuit pressure monitoring is an extremely important aid in diagnosing leaks and disconnections. As discussed earlier, breathing circuit pressure monitoring is a required feature, and alarms must be present for high-pressure, elevated sustained-pressure, and negative-pressure situations. The threshold pressure limit alarm is useful for detecting leaks and disconnections. Machines must be designed so that whenever the breathing system pressure remains lower than the threshold limit while in a controlled ventilation mode for more than 20 seconds, an audible and visual alarm is generated (Fig. 29-34, *A*).

TABLE 29-6 METHODS OF DETECTING LEAKS AND DISCONNECTIONS DURING THE COURSE OF ANESTHESIA

Method	Leak Indications
Breathing circuit pressure sensors	*Threshold pressure alarm** Pressure waveform evaluation Trend of peak pressures
Workstation tidal volume sensors	Low minute ventilation or low tidal volume alarm Failure to deliver set tidal volume Disparity between inhaled and exhaled tidal volumes Decreasing trend of tidal volume and minute ventilation
Exhaled gas analysis	Exhaled carbon dioxide automated monitoring Abnormal appearance and trend of capnography tracing
Physiologic sensors (e.g., SpO_2%, HR, BP)	*Late detection* of significant leaks and disconnections because the patient is already decompensating
A vigilant practitioner	Assesses breath sounds and chest wall excursion Pays close attention to alarms and responds promptly Observes workstation and physiologic monitors Notes that ventilator bellows is not refilling completely and tidal volumes are decreasing Notes that flow rate requirements are increasing to refill an ascending bellows Senses that breathing bag motion and feel are not normal Detects the odor of anesthetic gas Follows his or her instinct that something is not right

BP, Blood pressure; *HR,* heart rate; *SpO_2,* saturation of peripheral oxygen.
*ASTM standard.

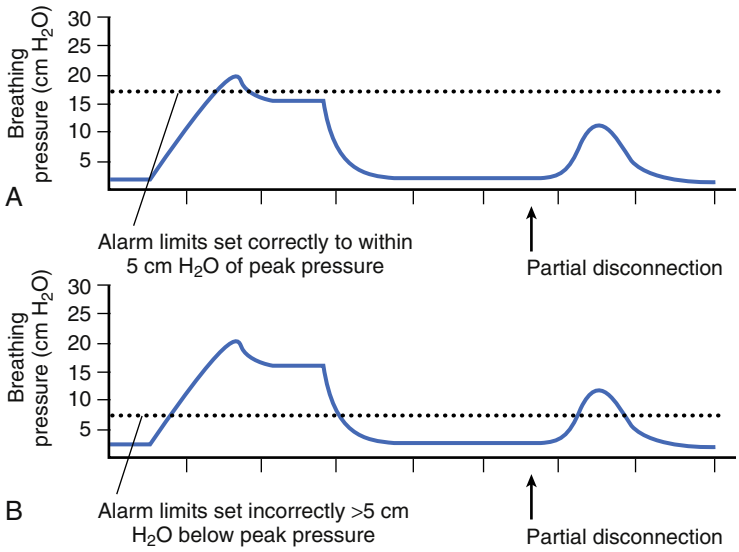


Figure 29-34. Threshold pressure alarm limit. **A,** The threshold pressure alarm limit (*dotted line*) has been set appropriately. An alarm is actuated when partial disconnection occurs (*arrow*) because the threshold pressure alarm limit is not exceeded by the breathing circuit pressure. **B,** Partial disconnection is unrecognized by the pressure monitor because the threshold pressure alarm limit has been set too low. *(Redrawn from North American Dräger:* Baromed breathing pressure monitor: operator's instruction manual, *Telford, Pa., 1986, North American Dräger.)*

Visual alarm examples include "Apnea Pressure," "Check Breathing Circuit," and "Low Pressure."[33,34,41] The specific pressure threshold alarm times on machines may vary slightly. The pressure threshold limit may be operator adjustable on some machines, and some may also have an "autoset" feature, which applies an algorithm to set an appropriate threshold limit based on the current airway pressures.[31,131] As can be seen in Figure 29-34, *B,* allowing the threshold limit to remain too low may allow a partial disconnection (leak) to go unrecognized. Conversely, allowing the threshold pressure limit to remain too high can result in an erroneous "apnea pressure" or "threshold low" alert.

Respiratory volume monitors are useful in detecting leaks or disconnections, and anesthesia workstations must be able to monitor exhaled tidal volume or minute ventilation. Alarms for low minute ventilation and low exhaled tidal volume alert the operator when these values drop to less than adjustable limits. The user should bracket the high and low threshold minute ventilation alarm slightly higher and lower than the patient's requirements. For example, if the exhaled minute volume of a patient is 10 L/minute, reasonable alarm limits would be 8 to 12 L/minute. An autoset feature may be available for minute ventilation monitoring as well.[131] Some workstations have an alarm if a significant disparity exists between inhaled and exhaled tidal volume, or when the measured tidal volume does not achieve the set tidal volume.[142] Finally, some workstations that have integrated gas monitoring may also use exhaled carbon dioxide as a means to alert the operator in the event of a loss of ventilation.

Misconnections. Misconnections of the breathing system are unfortunately not uncommon. Despite the efforts of standards committees to eliminate this problem by assigning different diameters to various hoses and hose terminals, they continue to occur. Anesthesia workstations, breathing systems, ventilators, and scavenging systems incorporate many of these diameter-specific connections. The ingenuity of some individuals in outwitting these "foolproof" systems has led to various hoses being cleverly adapted or forcefully fitted to inappropriate terminals and even to various other solid cylindrically shaped protrusions of the anesthesia machine.[143,144] Operators and technicians should be properly trained on their respective workstations, and workstation modification should be discouraged.

Occlusion. Occlusion (obstruction) of the breathing circuit may occur and can have severe consequences. Tracheal tubes can become kinked. Breathing circuit valves or other components can malfunction. Hoses throughout the breathing circuit are subject to occlusion by internal obstruction or external mechanical forces that can impinge on flow. Blockage of heat and moisture exchangers by secretions can cause significant obstruction, and blockage of a bacterial filter in the expiratory limb of the circle system has caused bilateral tension pneumothorax.[145,146] A misplaced disk in an expiratory valve also caused expiratory limb obstruction and tension pneumothorax.[147] Because retained carbon dioxide absorber canister wrapping has been associated with circuit obstruction, ASTM standards now require that absorbers be packaged in a way that immediately identifies the presence of a wrapper.[127,148,149] Defects associated with disposable circuit components or the disposable tubing itself have been associated with severe circuit obstruction and sometimes injury to the patient.[150-154] Misplaced Luer caps have made their way into the elbow connector of the circuit because of packaging or processing and have caused significant circuit obstruction.[155,156] Incorrect insertion of flow direction–sensitive components can result in a no-flow state. Examples of these components include some older PEEP valves and cascade humidifiers. Only the performance of manual circuit flow test, or a similar automated test, during the preuse checkout procedure reliably detects a circuit obstruction. *If you are struggling to ventilate a patient and are unsure regarding why, do not delay in switching to a self-inflating resuscitation bag.* Ventilate first, troubleshoot later.

Variations in Circle Breathing System Design. Numerous variations of the circle arrangement are possible, depending on the relative positions of the unidirectional

valves, the pop-off valve, the reservoir bag, the carbon dioxide absorber, and the site of fresh gas entry. However, to prevent rebreathing of carbon dioxide in a traditional circle system, three rules must be followed: (1) a unidirectional valve must be located between the patient and the reservoir bag on both the inspiratory and expiratory limbs of the circuit, (2) the fresh gas inflow cannot enter the circuit between the expiratory valve and the patient, and (3) the overflow (pop-off) valve cannot be located between the patient and the inspiratory valve. If these rules are followed, any arrangement of the other components will prevent rebreathing of carbon dioxide.[125] Design departures from the traditional circle breathing system are becoming more common as workstations evolve. Some of these designs are driven by the compensatory strategies intended to eliminate the impact of varying fresh gas flow rates or oxygen flush on inspiratory tidal volume and airway pressure during mechanical ventilations (fresh gas decoupling or compensation). Breathing system variations are addressed later, in the section on anesthesia ventilators.

Carbon Dioxide Absorbers

Circle breathing systems require a means of carbon dioxide removal from the exhaled gases to avoid carbon dioxide rebreathing and hypercapnia. Although increasing the fresh gas inflow to high levels can dilute out most carbon dioxide in the circle breathing circuit, this would be a very inefficient way to conduct an anesthetic regimen for reasons described earlier. Because gas flows through the anesthetic machine are less than minute ventilation, absorption of carbon dioxide prevents hypercarbia from occurring. If one could design an ideal carbon dioxide absorbent, its characteristics would include a lack of reactivity with common anesthetics, an absence of toxicity, low resistance to airflow, minimal dust production, small cost, ease of handling, and high efficiency carbon dioxide absorption. There should also exist a reliable method of assessing for absorbent depletion (i.e., a diminished ability to remove carbon dioxide). Finally, the container that houses the absorbent should be easy to remove and replace, should maintain breathing circuit integrity during rapid "in-flight" replacement, and should impose minimal risk of causing breathing system leaks or obstruction. Carbon dioxide absorbers are not unique to anesthesiology. They are also used in certain military and commercial diving equipment, submarines, space operations, mining and rescue operations, and hyperbaric facilities. In these environments, carbon dioxide absorbers are often referred to as *CO_2 scrubbers*.

Absorber Canister. Although anesthesia circuit absorber canister configurations vary considerably, they are all similar in that they must be visible to the operator and transparent to monitor for absorbent presence and color. Traditionally, the absorber canister has been composed of one or two clear plastic canisters arranged in series. Opening the canister assembly abolished the integrity of the breathing circuit, so ventilation had to be accomplished via other means if the absorbent had to be changed during the course of anesthesia and apnea could not be tolerated. Because of the multiple components and their compression assembly method, absorber canister assemblies of this type are not an uncommon source of leaks.[141] The canisters are filled either with loose bulk absorbent or with absorbent supplied by the factory in prefilled plastic disposable cartridges called *prepacks*. Free granules from bulk absorbent can create a clinically significant leak if they lodge between the clear plastic canister and the O-ring gasket of the absorber. Leaks have also been caused by defective prepacks that were larger than factory specifications.[157] Prepacks can also cause total obstruction of the circle system if the clear plastic shipping wrapper is not removed before use or if the prepack itself is defective.[148,154] Problems with rebreathing carbon dioxide have been caused by canister apparatus reassembly issues.[158-160] Many modern workstations now use single canister absorbers, with some being disposable and easily replaceable. Increasingly, workstation design allows the canister to be replaced during anesthesia without interfering with breathing system continuity, sometimes referred to as a *bypass* feature.[33] A potential risk imposed by this feature is that the machine may pass an automated or manual leak test *without* the absorber attached. This emphasizes the importance of actually inspecting the absorber before every anesthetic.

Chemistry of Absorbents. The process of removing carbon dioxide from the breathing circuit involves the absorption of the exhaled carbon dioxide by chemical absorbents contained within the absorber canister, whereby carbon dioxide is converted into water, heat, and other byproducts. Therefore, the removal of the acid gas carbon dioxide from the breathing circuit ultimately occurs via a series of chemical reactions; it is not merely a physical process like water soaking into a sponge. Most anesthesia machine absorbents use calcium hydroxide [$Ca(OH)_2$] to react with the expired carbon dioxide, producing insoluble calcium carbonate ($CaCO_3$). However, because carbon dioxide does not react quickly with $Ca(OH)_2$, water and small amounts of stronger bases have been used to speed up the carbon dioxide reaction. These calcium absorbents vary in terms of their contents of water; reaction catalysts such as sodium hydroxide (NaOH), potassium hydroxide (KOH), humectants (i.e., calcium chloride); and hardening agents such as silica. Many newer absorbents have only trace amounts of KOH, or it is absent altogether because this base has been associated with anesthetic degradation. Some have also limited or eliminated NaOH for the same reason. One absorbent brand replaces $Ca(OH)_2$ entirely with lithium hydroxide (LiOH), which does not require any additional catalysts to react with carbon dioxide. Key differences in absorbents include their absorptive capacity of carbon dioxide and their propensity to react with volatile anesthetics that produce potentially harmful degradation products (e.g., CO and compound A). The composition of several absorbents is shown in Table 29-7.[161-166]

The chemistry of carbon dioxide absorption by $Ca(OH)_2$-based absorbents is illustrated next using classic soda lime as an example. Carbon dioxide reacts relatively slowly with the $Ca(OH)_2$, so a few steps must occur first to catalyze the reaction. First, carbon dioxide reacts with liquid water present on and within the granules and

TABLE 29-7 CARBON DIOXIDE ABSORBER COMPARISONS

Absorbent (Reference)	$Ca(OH)_2$ (%)	LiOH (%)	H_20 (%)	NaOH (%)	KOH (%)	Other (%)
Classic soda lime (165)	80	0	16	3	2	-
Baralyme (164)*	73	0	11-16	0.0	5	11 $Ba(OH)_2$
Sodasorb (161)*	76.5	0	18.9	2.25	2.25	-
Dragersorb 800 Plus (162, 166)*	82	0	16	2	0.003	-
Medisorb (166)*	81	0	18	1-2	0.003	-
New soda lime*	73	0	<19	<4	0	-
Sodasorb LF (163)	>80	0	15-17	<1	0	-
Dragersorb Free (161, 164)	74-82	0	14-18	0.5-2	0	3-5 $CaCl_2$
Sofnolime*	>75	0	12-19	<3	0	-
Amsorb Plus (161, 165)	>75	0	14.5	0	0	<1 $CaCl_2$ and $CaS0_4$
Litholyme*	>75	0	12-19	0	0	<3 LiCl
SpiraLith*	0	≈ 95	0†	0	0	≤5 PE

$Ba(OH)_2$, Barium hydroxide; *$CaCl_2$*, calcium chloride; *$Ca(OH)_2$*, calcium hydroxide; *$CaS0_4$*, calcium sulfate; *KOH*, potassium hydroxide; *LiCL*, lithium chloride; *LiOH*, lithium hydroxide; *NaOH*, sodium hydroxide; *PE*, polyethylene.
*Materials Safety Data Sheets, Occupational Safety and Health Administration, U.S. Department of Labor.
†Up to 60% of LiOH is chemically bound 1:1 with H_20 as Lithium Hydroxide Monohydrate (see text for details).

creates weak carbonic acid (H_2CO_3). This step emphasizes the importance water in the reaction, thus all calcium hydroxide–based absorbents contain approximately 12% to 19% H_2O by weight. Because the H_2CO_3 also does not react quickly with $Ca(OH)_2$, the strong base additives NaOH and KOH are used to form sodium carbonate (Na_2CO_3) and potassium carbonate (K_2CO_3). This occurs in the second step of the reaction. Na_2CO_3 and K_2CO_3 are capable of reacting quickly with $Ca(OH)_2$, which is seen in the third reaction. This results in the formation of insoluble $CaCO_3$ and the liberation of NaOH and KOH for reuse. The rate of conversion of carbon dioxide to H_2CO_3 in the first reaction is determined by how fast H_2CO_3 can be consumed by the catalyst requiring a second reaction. Therefore the third reaction is the rate-limiting step. Some carbon dioxide may react directly with $Ca(OH)_2$, but as mentioned, this reaction is slower. Byproducts of the entire process are water and heat.[167,168] As it became apparent that the strong base catalysts such as NaOH and KOH were associated with potentially adverse effects, their proportions were reduced or they were removed altogether.

1. $CO_2 + H_2O \rightleftharpoons H_2CO_3$
2. $H_2CO_3 + 2NaOH\ (KOH) \rightleftharpoons Na_2CO_3\ (K_2CO_3) + 2H_2O + Heat$
3. $Na_2CO_3\ (K_2CO_3) + Ca(OH)_2 \rightleftharpoons CaCO_3 + 2NaOH\ (KOH) + Heat$

In contrast to the calcium hydroxide–based absorbents, lithium hydroxide (LiOH)-based absorbents do not require additives to react with carbon dioxide. LiOH is capable of reacting quickly with carbon dioxide by itself. Although liquid water is not required as in the classic $Ca(OH)_2$ reaction (where it combines with CO_2 to create H_2CO_3), H_2O molecules are still required for the reaction to take place. Traditionally, these water molecules come from exhaled breathing gases to complete the reaction of carbon dioxide with LiOH to produce lithium carbonate. Additionally, LiOH absorbents may contain molecules of water, where they are chemically bound to LiOH (1:1) through the following exothermic reaction:[168a]

$$2LiOH + 2H_2O \rightleftharpoons 2LiOH * H_2O + Heat$$

LiOH that does not contain water is referred to as *LiOH anhydrous*. LiOH containing chemically bound water is called *lithium hydroxide monohydrate*. Because the water addition reaction gives off heat, LiOH absorbents that already contain chemically bound water (lithium hydroxide monohydrate) react at a lower temperature than LiOH anhydrous absorbents.

Granular anhydrous LiOH is formed by removing the water from a granule of lithium hydroxide monohydrate. This provides greater surface area for reaction with carbon dioxide when the absorbent is of granular form. One manufacturer has a technique that creates a large surface area by using lithium hydroxide anhydrous powder instead of large granules and binds this fine powder within a nongranular polymer matrix. The fine powder is then partially hydrated, resulting in both a large surface area for carbon dioxide to quickly react while also reducing the reaction temperature (personal communication, Micropore, Inc., Elkton, MD, 2014). When LiOH is bound with water (lithium hydroxide monohydrate), it removes carbon dioxide from the breathing circuit through the following endothermic reaction, producing insoluble lithium carbonate:

$$2LiOH * H_2O + CO_2 \rightleftharpoons Li_2CO_2 + 3H_2O - Heat$$

Interactions of Inhaled Anesthetics With Absorbents

Formation of Potentially Harmful Degradation Products. The interaction of volatile anesthetic agents with the strong bases present in calcium hydroxide–based carbon dioxide absorbents, such as KOH and NaOH, has been long known to be associated with the formation of degradation products. For historical perspective, trichloroethylene, a volatile anesthetic introduced to clinical use in 1940, was found to be associated with neurologic toxicity, particularly cranial nerve neuropathies and encephalitis.[169,170] Experimental investigation determined that dichloroacetylene, a toxin, was being formed by a base-catalyzed reaction due to prior formulations of soda lime, particularly if the soda lime had a large base content and was dry. Today, the main degradation products of concern are compound A, associated with the use of sevoflurane, and CO, mainly associated with the use of desflurane, enflurane, and isoflurane.[171] Other degradation products include formaldehyde and methanol, but these are not discussed here.[165]

Compound A Production. Sevoflurane can undergo a base-catalyzed degradation within the breathing circuit into fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether, known as *compound A*. Compound A has been shown to be nephrotoxic in rats at concentrations that are capable of occurring in the breathing circuit during clinical conditions.[169,172] Moreover, in a limited number of volunteer studies, sevoflurane was associated with transient albuminuria and glucosuria.[173,174] To date, however, mounting data have shown no relationship between sevoflurane use and postoperative renal dysfunction in humans, including patients with preoperative renal insufficiency.[169,175-180] Several physical factors can contribute to an increase in the concentration of compound A in the breathing circuit, including the following:

- Low-flow or closed-circuit anesthetic techniques
- Higher concentrations of sevoflurane in the anesthetic circuit
- The type of absorbent
- Higher absorbent temperatures
- Fresh absorbent[171,172,175,181]

Sevoflurane product information states that, to minimize the risk of exposure to compound A, sevoflurane exposure should not exceed 2 MAC-hours at flow rates of 1 to less than 2 LPM, although this recommendation predates several studies demonstrating safety at lower flow rates.

The type and ratio of strong bases within the carbon dioxide absorbent seem to be related to the degree of degradation of sevoflurane and compound A formation. KOH seems to be a stronger precipitant of breakdown than is NaOH.[164,166] For example, the absorbent Baralyme, which has been voluntarily withdrawn from the market, and classic soda lime, which both contain KOH and NaOH, have a greater propensity to cause sevoflurane degradation to compound A than do newer absorbents that contain only trace amounts of KOH.[166] Calcium hydroxide–based absorbents that contain neither KOH nor NaOH produce negligible amounts of compound A in some studies, and none in others.[163,166,182] LiOH-based absorbent has negligible or no compound A production.[162,182,182a,182b] Given the safe track record of sevoflurane and the ongoing improvements in carbon dioxide absorbents, the risk to patients imposed by compound A during routine clinical practice must be minimal.[183]

Carbon Monoxide Production. Strong-base absorbents that are extremely dry (desiccated) can also degrade contemporary inhaled anesthetics to clinically significant concentrations of CO and can cause patient injury.[164] Under certain conditions, this process can produce very high carboxyhemoglobin concentrations that reach 35% or greater.[184] A typical scenario involving patient exposure to a high concentration of CO would involve the first case of the day on a Monday, where high continuous gas flows circulating through the breathing system during the weekend cause desiccation of the absorbent.[185,186] Machines in remote locations are also at a more frequent risk of absorbent desiccation.[186] In the absence of a patient connected to the circuit, prolonged fresh gas flow rates of 5 L/min or greater through the absorbent are sufficient to cause critical drying of the absorbent material. The situation is even worse when the breathing bag is left off the breathing circuit with conventional circle systems. An absence of a slight pressure building in the reservoir bag facilitates retrograde flow through the circle system.[184] Because the inspiratory valve leaflet produces some resistance to flow, fresh gas flow takes the retrograde path of least resistance through the absorbent and out the 22-mm breathing bag mount (see the classic circle breathing system in Fig. 29-27).

Several factors increase the production of CO and resultant increased carboxyhemoglobin levels, including the following:

- The inhaled anesthetic used (for a given MAC multiple, the magnitude of CO production from greatest to least is desflurane ≥ enflurane > isoflurane >> halothane = sevoflurane),
- The dryness of the absorbent
- The type of absorbent
- The temperature (increased temperature increases CO production)
- The anesthetic concentration (more CO is produced with higher anesthetic concentrations)[187]
- Low fresh gas flow rates
- Reduced experimental animal (patient) size per 100 g of absorbent.[188,189]

As with compound A production, the presence of strong bases like KOH and NaOH in the absorbent correlates to the ability of desiccated absorbent to degrade certain anesthetics and liberate CO. Therefore the now withdrawn agent Baralyme and, to a lesser extent, conventional soda lime and similar absorbents were more likely to produce CO when desiccated than are newer-generation absorbents, which have minimized or eliminated the presence of these bases.[190] Elimination of NaOH and KOH from the calcium hydroxide–based absorbents diminishes or eliminates degradation of desflurane to CO and sevoflurane to compound A, but it does seem to compromise carbon dioxide absorption.[182,191] LiOH absorbent

produces essentially no CO and maintains the same or higher carbon dioxide absorption.[162, 182b,191a]

Absorbent Heat Production. One extremely rare but potentially life-threatening complication related to carbon dioxide absorbent is the development extreme exothermic reactions that lead to fires and explosions within the breathing system.[192-194] Specifically, this seems to occur as a result of interactions between desiccated strong-base absorbents (particularly Baralyme) and the inhaled anesthetic sevoflurane. Under experimental conditions using desiccated Baralyme, absorber temperatures reached 200° C (392° F) and higher, and fire was noted in some of the breathing circuits.[195] The buildup of very high temperatures, the formation of combustible degradation byproducts (formaldehyde, methanol, and formic acid), and the oxygen- or nitrous oxide–enriched environment provide all the substrates necessary for a fire to occur.[196] Avoidance of the combination of sevoflurane with strong base–heavy absorbents like the now discontinued Baralyme, especially if they have become desiccated, is the best way to prevent this unusual, potentially life-threatening complication. Anhydrous lithium hydroxide absorbents reacting with moisture from expired gas also can generate high temperatures, but formulations containing lithium hydroxide monohydrate do not.

A consensus statement established by the Anesthesia Patient Safety Foundation provides guidance to reduce the risk adverse interactions between volatile anesthetics and conventional carbon dioxide absorbents that may degrade volatile anesthetics when absorbent desiccation occurs.[164] The recommendations include the following:

- Turning off all gas flow when the machine is not in use
- Changing the absorbent regularly
- Changing the absorbent whenever the color change indicates exhaustion
- Changing all absorbent, not just one canister in a two-canister system
- Changing the absorbent when uncertain about the state of hydration, such as if the fresh gas flow has been left on for an extensive of indeterminate period of time
- If used, changing compact canisters more frequently

Given the improvements in absorbent chemistry, selecting an absorbent that minimizes risk adverse reactions is a prudent risk reduction strategy. Finally, educating anesthesia personnel regarding these hazards and their preventive measures will also reduce the likelihood of an adverse event.

Indicators. Conventional absorbents contain an indicator dye, ethyl violet, that allows anesthesia personnel to visually assess the functional integrity of the absorbent. Ethyl violet is a substituted triphenylmethane dye with a critical pH of 10.3.[168] The dye changes from colorless to violet when the pH of the absorbent decreases as a surrogate indicator of exhaustion. When the absorbent is fresh, the pH exceeds the critical pH of the indicator dye, and it exists in its colorless form. However, as the absorbent becomes exhausted, the pH decreases below 10.3 and ethyl violet changes to its violet form because of alcohol dehydration. This change in color indicates that the absorptive capacity of the material has been consumed. Unfortunately, in some circumstances ethyl violet may not always be a reliable indicator of the functional status of the absorbent. For example, prolonged exposure of ethyl violet to fluorescent light can produce photodeactivation of this dye. When this occurs, the absorbent appears white even though it may have a reduced pH and its absorptive capacity has been exhausted.[197] Similarly, color reversion (purple back to white) can occur with some absorbents due to the strongly alkaline nature of NaOH. Many newer generation absorbent indicators are more resistant to color reversion, and several now endorse permanent color change. At least one absorbent contains no indicator and relies upon the measured increase in inspired carbon dioxide and/or a time schedule to trigger replacement.

Like absorbent exhaustion, desiccation of calcium hydroxide–based absorbents is also an occult phenomenon. Therefore some newer generation $Ca(OH)_2$ absorbents may also include indicators that reveal whether the material has become desiccated. Users should refer to the product manufacturer's literature to determine whether their absorbent material uses this type of indicator.

Carbon Dioxide Removal Capacity and Absorber Resistance. The ability of the workstation's absorber to remove carbon dioxide is related to three main factors: (1) the amount of surface area of the absorbent that the exhaled gas is exposed to, (2) the intrinsic capacity of the absorbent to remove carbon dioxide, and (3) the amount of functionally intact absorbent remaining in the absorber. The size and shape of the actual absorptive granules are intended to maximize absorptive surface and flow throughout the canister while trying to minimize the resistance to airflow.[198] The smaller the granule size, the greater the surface area that is available for absorption. However, as particle size decreases, airflow resistance increases. The size and shape of the granules is of a proprietary nature. The granule size is often referred to by mesh size. Mesh size refers to the number of openings per linear inch in a sieve through which the granular particles can pass. For example, a 4-mesh screen means that there are four quarter-inch openings per linear inch.[167] The granular size of some common absorbents is between 4 and 8 mesh, a size at which absorptive surface area and resistance to flow are optimized.

As the absorbent granules stack up in the absorber canisters, small passageways inevitably form. These small passages channel gases preferentially through low-resistance areas. Because of this phenomenon, known as *channeling,* the functional absorptive capacity of the absorbent may be substantially decreased.[199] At least one manufacturer makes a nongranular, molded absorbent that uses a polymer to bind the absorbent particles together. This absorbent has molded airflow channels, eliminating the phenomenon of channeling typical of granular systems (personal communication, Micropore, Inc., Elkton, MD, June 3, 2014).

If completely reacted, a pound of calcium hydroxide has the capacity to absorb 0.59 lb of carbon dioxide.

Lithium hydroxide has the ability to absorb 0.91 lb of carbon dioxide per pound.[199a] Lithium hydroxide absorbents typically neutralize or "scrub" more carbon dioxide by weight [199a,199b] because of their higher capacity to react with carbon dioxide.

Mapleson Breathing Systems

In 1954, Mapleson described and analyzed five different breathing circuits, and they are now classically referred to as the Mapleson systems.[200] These systems are similar to the circle breathing system in that they accept a fresh gas flow, supply the patient with a sufficient volume of gas from a reservoir to satisfy the inspiratory flow and volume requirements, and eliminate carbon dioxide. They differ from the circle system because they have bidirectional flow and do not use an absorber. Therefore, these systems depend on an appropriate rate of fresh gas inflow to eliminate carbon dioxide.

Mapleson described five circuits, designated A through E (Fig. 29-35).[200] Subsequently, in 1975, Willis and coauthors described the F system, which was added to the original five.[201] The Mapleson systems consist of several common components, including a connection point to a facemask or endotracheal tube, reservoir tubing, fresh gas inflow tubing, and an expiratory pop-off valve or port. All the Mapleson circuits except for the E version use a bag as an additional reservoir.

Three distinct functional groups can be seen: A, BC, and DEF groups. The Mapleson A, also known as the Magill circuit, has a spring-loaded pop-off valve located near the facemask, and fresh gas flow enters the opposite end of the circuit near the reservoir bag. In the B and C systems, the spring-loaded pop-off valve is located near the facemask, but the fresh gas inlet tubing is located near the patient. The reservoir tubing and breathing bag serve as a blind limb where fresh gas, dead space gas, and alveolar gas can collect. Finally, in the Mapleson D, E, and F, or "T-piece" group, fresh gas enters near the patient, and excess gas is vented off at the opposite end of the circuit.

Even though the components and their arrangement are simple, functional analysis of the Mapleson systems can be complex.[202,203] The amount of carbon dioxide rebreathing associated with each system is multifactorial, and variables that dictate the ultimate carbon dioxide concentration include the following: (1) the fresh gas inflow rate, (2) minute ventilation, (3) the mode of ventilation (spontaneous or controlled), (4) tidal volume, (5) the respiratory rate, (6) the inspiratory-to-expiratory ratio, (7) the duration of the expiratory pause, (8) the peak inspiratory flow rate, (9) the volume of the reservoir tube, (10) the volume of the breathing bag, (11) ventilation by mask, (12) ventilation through an endotracheal tube, and (13) the carbon dioxide sampling site.

The performance of the Mapleson systems is best understood by studying the expiratory phase of the respiratory cycle.[204] Illustrations of the various arrangements of Mapleson systems components may be found in Figure 29-35. During spontaneous ventilation, the Mapleson A has the best efficiency of the six systems because it requires a fresh gas inflow rate of only 1 times minute ventilation to prevent rebreathing of carbon dioxide.[205] However, it has the worst efficiency during controlled ventilation because a minute ventilation as high as 20 L/minute is needed to prevent rebreathing. Systems DEF are slightly more efficient than systems BC. To prevent rebreathing carbon dioxide, the DEF systems require a fresh gas inflow rate of approximately 2.5 times minute ventilation, whereas the fresh gas inflow rates required for BC systems are somewhat higher.[203]

The following summarizes the relative efficiency of different Mapleson systems with respect to prevention of rebreathing during spontaneous ventilation: A > DFE > CB. During controlled ventilation, DFE > BC > A.[200,203] The Mapleson A, B, and C systems are rarely used today, but the D, E, and F systems are commonly used. In the United States, the most popular representative from the DEF group is the Bain circuit.

Mapleson systems have low resistance to gas flow, they are small and contain few parts, and changes in the

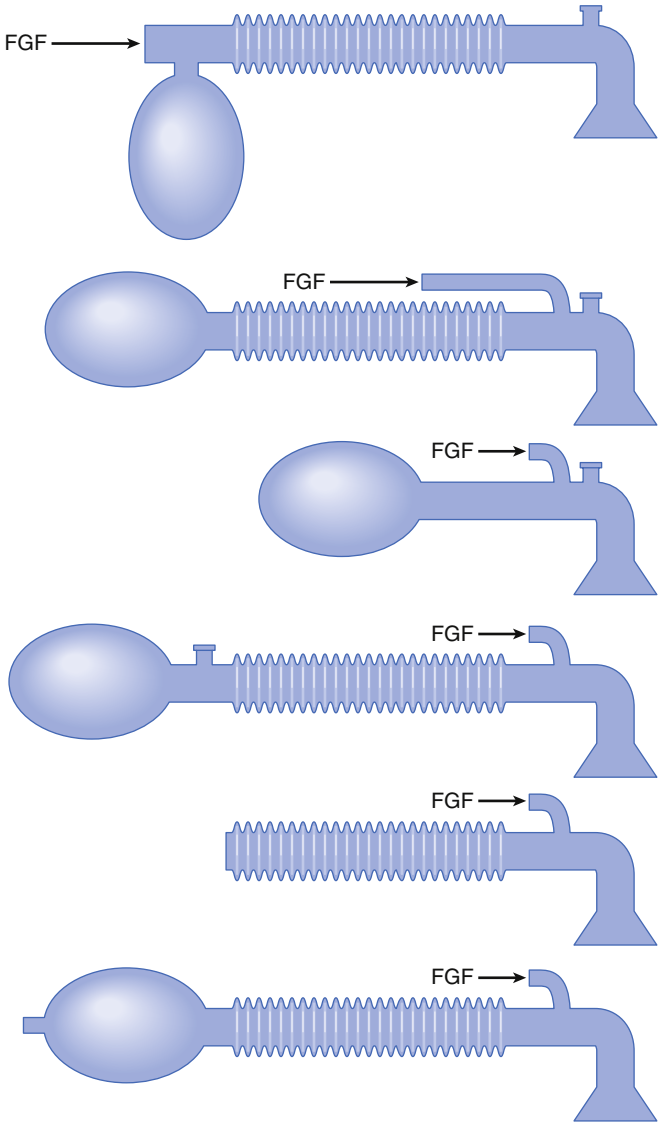


Figure 29-35. Mapleson breathing systems. *FGF,* Fresh gas flow. *(Redrawn from Willis BA, Pender JW, Mapleson WW: Rebreathing in a T-piece: volunteer and theoretical studies of the Jackson-Rees Modification of Ayer's T-piece during spontaneous respiration,* Br J Anesth *47:1239, 1975.)*

fresh gas flow composition result in rapid similar changes in the breathing circuit. In addition, the volatile anesthetic agents within a Mapleson breathing circuit have no chance of degradation because of the absence of a carbon dioxide absorber. However, given their need for higher gas flows, to dilute carbon dioxide their minimum required fresh gas flows are much higher than the circle system. Because of the higher gas flows, heat and humidity conservation is less efficient. Finally, scavenging can be challenging with these circuits, except for the Mapleson D, which has the pressure-limiting valve located away from the patient.[205]

Bain Circuit

The Bain circuit is a coaxial circuit and a modification of the Mapleson D system (Fig. 29-36). Fresh gas flows through a narrow inner tube within the outer corrugated tubing.[206] The central fresh gas tubing enters the outer corrugated hose near the reservoir bag, but the fresh gas actually empties into the circuit at the patient's end. Exhaled gases enter the corrugated tubing and are vented through the expiratory valve near the reservoir bag. The Bain circuit may be used for both spontaneous and controlled ventilation. The fresh gas inflow rate necessary to prevent rebreathing is 2.5 times minute ventilation.

The Bain circuit has many advantages over other systems. It is lightweight, convenient, easily sterilized, and potentially reusable. Being a Mapleson system, it has a very low resistance to breathing. Scavenging of gases from the expiratory valve is facilitated because the valve is located away from the patient. Exhaled gases in the outer reservoir tubing add warmth to the inspired fresh gases by countercurrent heat exchange. The main hazards related to use of the Bain circuit are an unrecognized disconnection and kinking of the inner fresh gas hose. These problems can cause hypercapnia as a result of inadequate gas flow or increased respiratory resistance. As with other circuits, an obstructed antimicrobial filter positioned between the Bain circuit and the endotracheal tube can result in increased resistance in the circuit. This may produce hypoventilation and hypoxemia that may even mimic the signs and symptoms of severe bronchospasm.[207]

The outer corrugated tube should be transparent to allow ongoing inspection of the inner tube. The integrity of the inner tube can be assessed as described by Pethick.[208] With his technique, high-flow oxygen is fed into the circuit while the patient's end is occluded until the reservoir bag is filled. The patient's end is opened, and oxygen is flushed into the circuit. If the inner tube is intact, the Venturi effect occurs at the patient's end. This causes a decrease in pressure within the circuit, and as a result, the reservoir bag deflates. Conversely, a leak in the inner tube allows fresh gas to escape into the expiratory limb, and the reservoir bag remains inflated. This test is recommended as part of the preanesthesia check if a Bain circuit is used.

ANESTHESIA VENTILATORS

Only a few decades ago, anesthesia ventilators were mere adjuncts to the anesthesia machine. Historical draw-over systems relied only on spontaneous breathing by the patient. Later, breathing bags were added to anesthetic delivery devices to allow manual ventilation. As the use of muscle relaxants and opiates became more common and the scope of surgery expanded, the need for automated mechanical ventilation increased. Today, ventilators have attained a prominent central role within the anesthesia workstation. Whereas early anesthesia ventilators provided only controlled mandatory ventilation that did not allow any patient-ventilator synchrony, many modern workstations incorporate ventilators with ICU-like capabilities that allow triggering by the patient's inspiratory effort, patient breath cycling, and multiple modes of ventilation. As the demands for precise, controlled ventilation and supported spontaneous ventilation increase, anesthesia workstation ventilator capability attempts to keep pace. However, incorporating an ICU-like ventilator on the anesthesia workstations is a challenging engineering endeavor because anesthesia ventilator requirements are unique. In particular, the anesthesia ventilator must act as a reservoir to receive and redeliver the patient's exhaled gas. For this reason, anesthesia machine ventilators incorporate either a bellows or piston-like design (or a volume reflector in the case of the Maquet FLOW-I

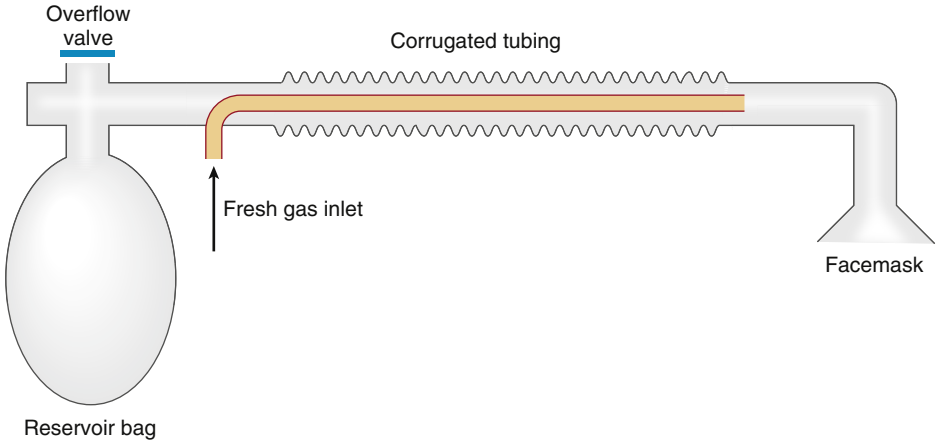


Figure 29-36. The Bain circuit. *(Redrawn from Bain JA, Spoerel WE: A streamlined anaesthetic system,* Can Anaesth Soc J *19:426, 1972.)*

Anesthesia System. See Maquet FLOW-i section). Further, the anesthesia ventilator system must function in the semiclosed environment of the circle breathing system and must be capable of venting excess circuit gas (waste gas). ICU ventilators are simply open circuit, venting all exhaled gas into the atmosphere. The demands imposed on the anesthesia ventilator systems mandate differences in circuit design and control. This discussion focuses on the classification, operating principles, and hazards associated with contemporary anesthesia ventilators.

Classification

Modern anesthesia ventilators can be best classified according to the type of reservoir that receives and delivers the breathing gas (bellows, piston, or volume reflector) and the drive mechanism of the reservoir (pneumatic or mechanical). The latter classification is almost unnecessary because bellows-type ventilators are virtually always pneumatically driven, and piston-type ventilators are usually mechanically driven. Bellows-type ventilators can be subclassified as ascending or descending. The direction of bellows movement during the *expiratory phase* determines the bellows classification. An ascending (standing) bellows *ascends* during the expiratory phase, whereas a descending (hanging) bellows *descends* during the expiratory phase. The implications of this difference are discussed later. Both types of bellows ventilators and a piston ventilator are illustrated in Figures 29-37 and 29-38.

Additional classifications involve the modes of ventilation that are available. Older anesthesia machine ventilators operated only in a time-triggered and time-cycled manner, or as "controller ventilators." Modern machines

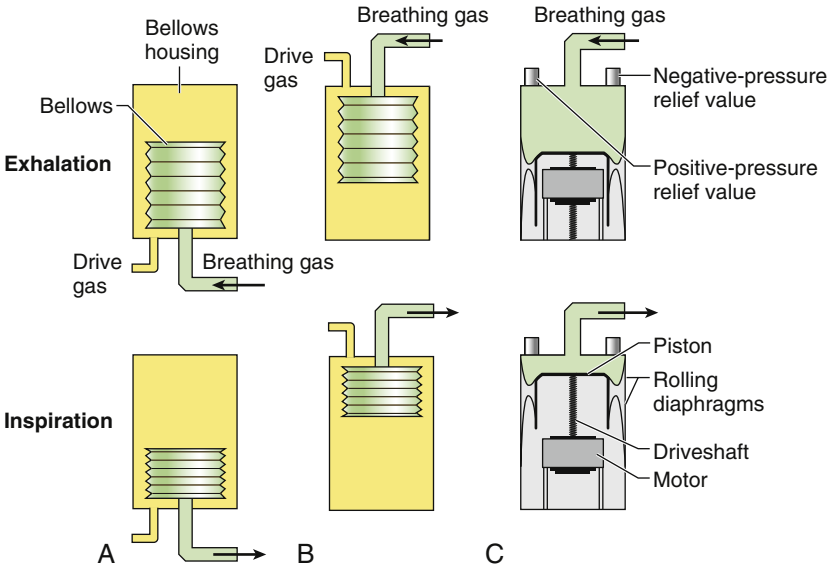


Figure 29-37. Three types of anesthesia ventilators during exhalation (**top row**) and inhalation (**bottom row**). Breathing gas is *green.* Ventilator drive gas is *yellow.* **A,** Ascending bellows **B,** Descending bellows. **C,** Piston ventilator. See text for additional details. *(Piston ventilator modified from Yoder M: Ventilators. In* Understanding modern anesthesia systems, *Telford, Pa., 2009, Dräger Medical.)*

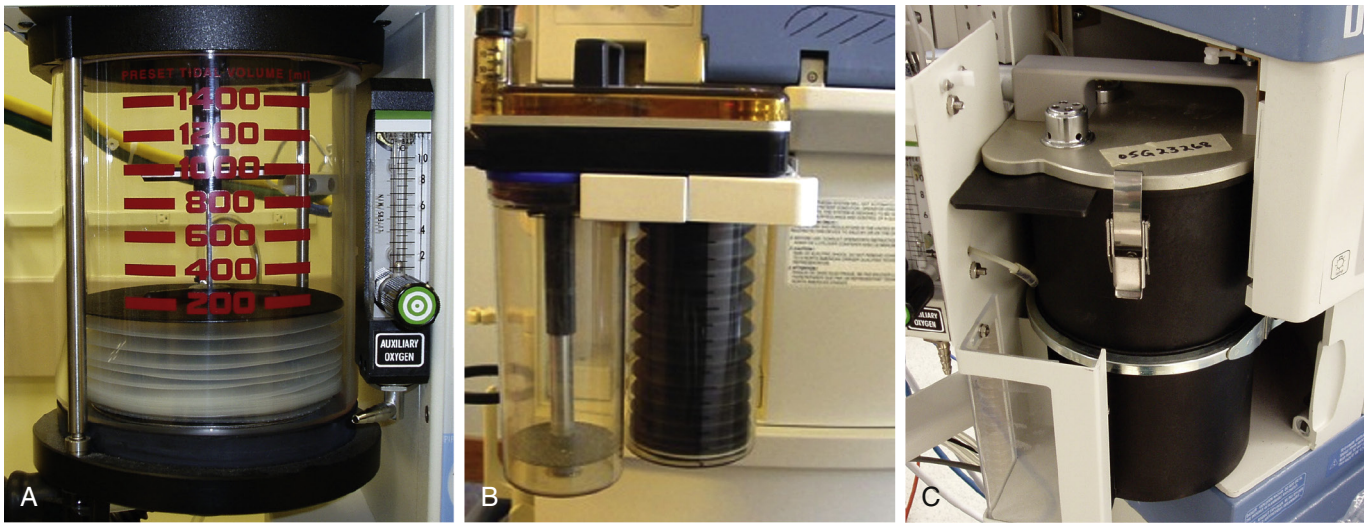


Figure 29-38. Anesthesia workstation ventilators. To allow rebreathing and the conservation of anesthetic gases, the anesthesia workstation ventilator must serve a reservoir for the patient's exhaled breathing gas, just as the breathing bag does in manual and spontaneous modes of ventilation. This is a unique requirement of ventilators in anesthesia workstations. Intensive care unit ventilators, conversely, can simply vent exhaled gases into the environment. **A,** Ascending bellows. **B,** Descending (hanging) bellows. **C,** Piston ventilator housing.

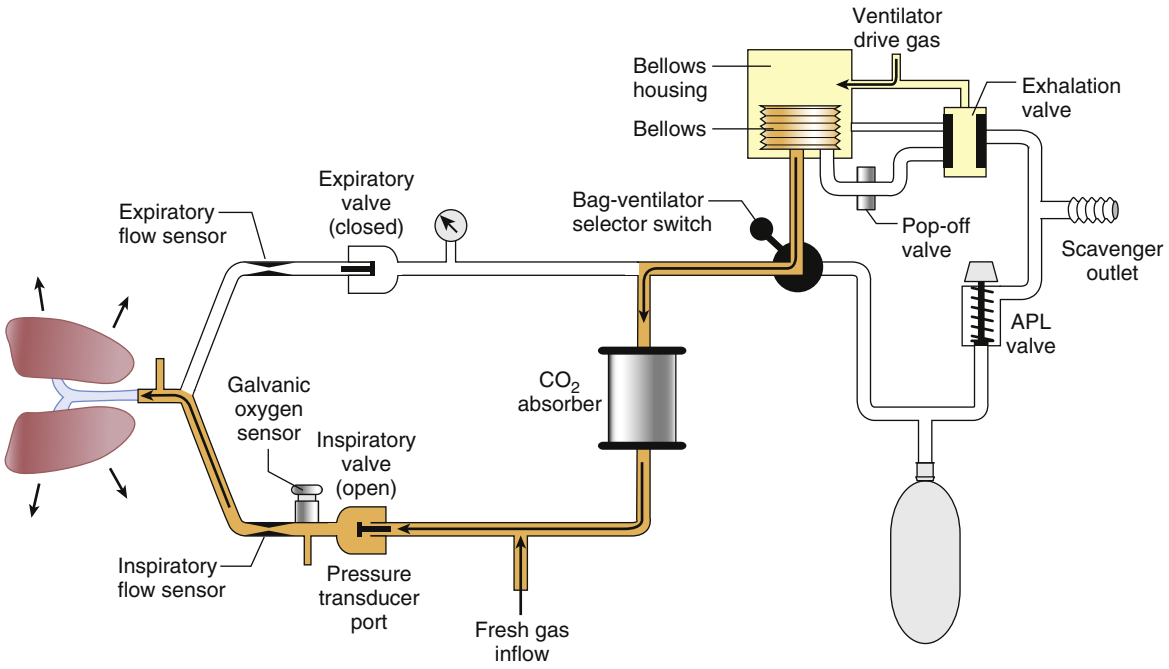


Figure 29-39. Inspiratory phases of ventilation with an ascending bellows ventilator represented by GE Aisys anesthesia workstation.. The ventilator drive gas circuit is located outside the bellows, and the patient's breathing circuit is inside the bellows. During the inspiratory phase the electronically controlled ventilator driving gas enters the bellows chamber and causes the pressure to increase, thereby compressing the bellows, which delivers gas to the patient's lungs. The drive gas also closes the exhalation valve and prevents the breathing gas from escaping into the scavenging system. Compensation for the impact of fresh gas flow on tidal volume accuracy is accomplished by monitoring the inhaled tidal volumes and adjusting ventilator drive gas volumes accordingly. *APL,* Adjustable pressure-limiting; *CO_2,* carbon dioxide. *(Image courtesy Dr. Michael A. Olympio; modified with his permission. Adapted from Datex-Ohmeda:* Aisys anesthesia machine: technical reference, *Madison, Wis., 2005, Datex-Ohmeda.)*

that offer synchronized intermittent mandatory ventilation (SIMV), assist control (A/C), and pressure support ventilation (PSV) must offer patient's triggering and patient's breath cycling and can be referred to as "noncontroller" ventilators. Many anesthesia ventilators can function in a volume-controlled or pressure-controlled modes. Finally, even though some ventilators may be pneumatically driven, all modern ventilators are under electronic control. The following sections review ventilator classification from a functional perspective, using specific workstations as examples.

Pneumatically Driven Bellows Ventilator

The operating principle of the bellows ventilator is that it functions as bellows in a box. The bellows, which is enclosed in an airtight housing, serves as reservoir for the patient's breathing gas. The driving force used to squeeze the gas out of bellows and back to the patient, as an anesthesia provider would squeeze a breathing bag, is pressurized gas that flows into the bellows housing under electropneumatic control. As the bellows is compressed, it delivers the breathing gas to the patient. The patient's exhalation and fresh gas flowing into the breathing circuit refill the bellows. Once the bellows is refilled, excess circuit gas is vented to the scavenging system during the expiratory pause. The mechanisms that vent breathing circuit waste gas during mechanical ventilation with bellows ventilators differ among manufacturers and models. The bellows ventilator is traditionally designated as a *double circuit*, meaning that the ventilator drive gas and the breathing gas exist in two separate circuits. The bellows serves as the interface between the breathing gas and the drive gas, much like the reservoir bag serves as the interface between the breathing gas and the anesthesia care provider's hands.[209] Figures 29-39 to 29-41 illustrate the inspiratory, early expiratory, and late expiratory phases of mechanical ventilation with an ascending bellows ventilator on the GE Aisys workstation. Many modern bellows ventilators, like the one shown in the example, can provide pressure- and volume-controlled ventilation, patient's triggering to support modes such as SIMV, and patient's cycling for pressure support ventilation.

The source of the drive gas for the bellows is either oxygen or air, which is obtained from the gas supply section of the workstation. Some workstations allow for the selection of either oxygen or air as the ventilator drive gas, and some can entrain room air through a Venturi effect into the oxygen drive gas flow, thereby decreasing the oxygen gas requirement. The type of gas used does have implications. First, if oxygen is used as the drive gas, the consumption of oxygen by the machine will equal that selected at the oxygen flow control valve *in addition to* an amount approximately equal to the minute ventilation being delivered by the ventilator. When oxygen is in finite supply (e.g., loss of hospital line supply, austere conditions), the use of the ventilator may rapidly deplete the oxygen supply. For example, a full E-cylinder contains approximately 625 L of oxygen. At an average oxygen

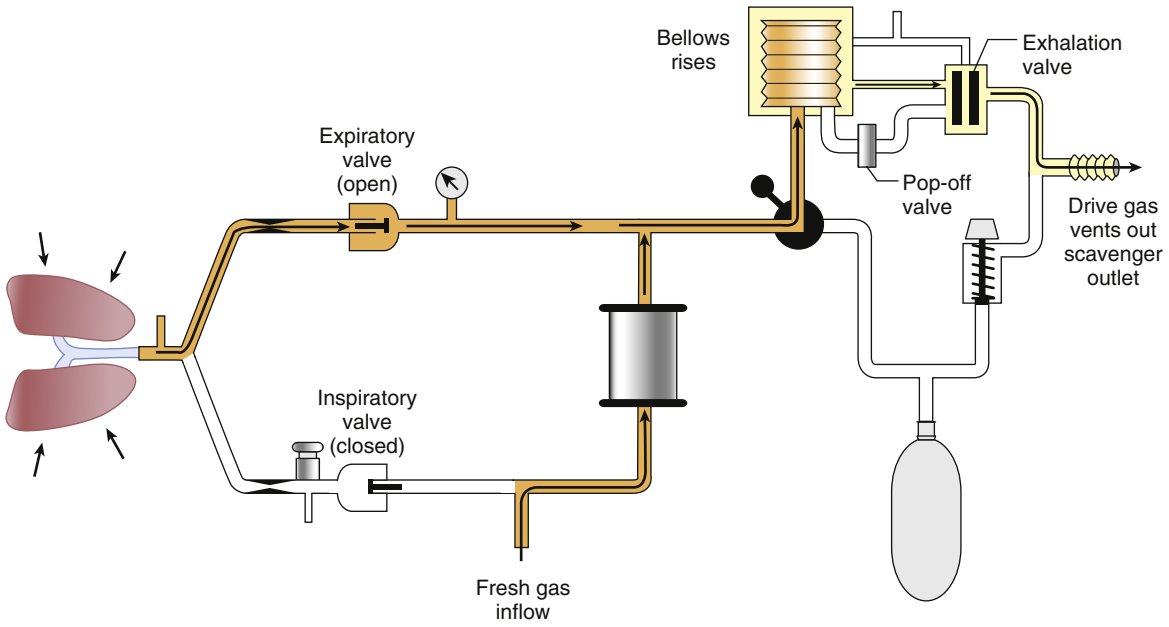


Figure 29-40. During the early expiratory phase, the patient is able to exhale into the bellows because the ventilator exhalation valve is now open, thus allowing the drive gas in the bellows housing to vent through the scavenger outlet. The pop-off or ventilator relief valve prevents bellows gas from escaping at this point so the bellows can fill. *(Courtesy Dr. Michael A. Olympio; modified with his permission. Adapted with permission from Datex-Ohmeda:* Aisys anesthesia machine: technical reference, *Madison, Wis., 2005, Datex-Ohmeda.)*

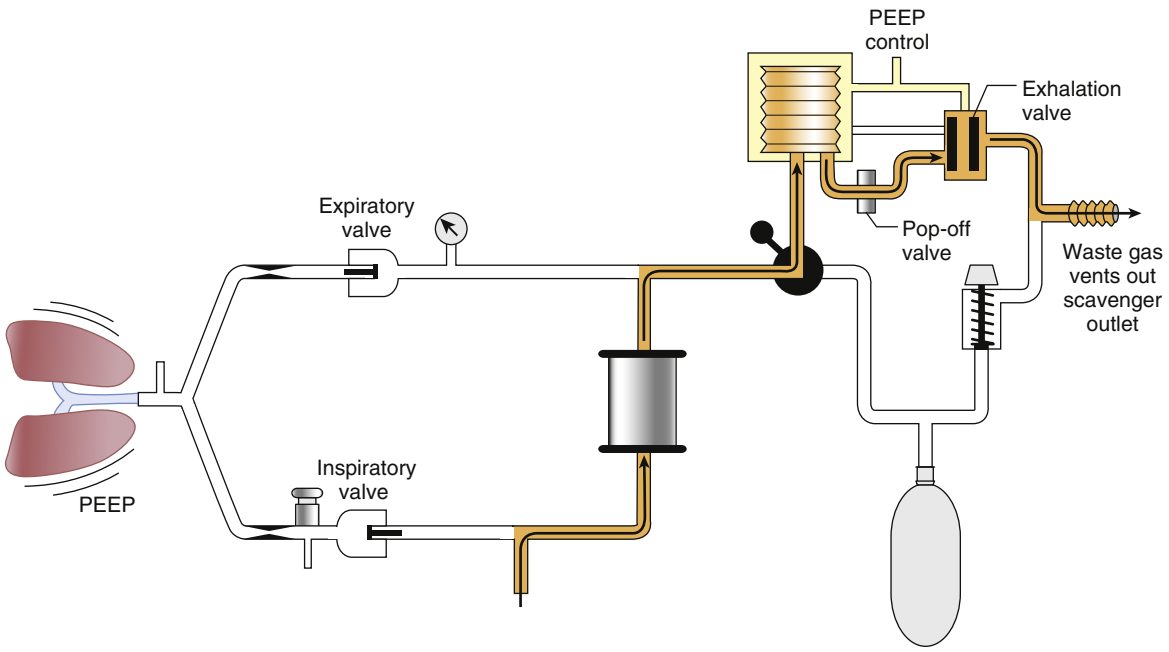


Figure 29-41. During the late expiratory phase, positive end-expiratory pressure (PEEP) is provided by pressurization of the bellows housing and pressure modulation of the expiratory valve. Whenever the pressure in the bellows exceeds the surrounding housing pressure by 2.5 cm H_2O, the pop-off or ventilator relief valve vents excess breathing gas to the scavenger. Bellows ventilator PEEP control and excess gas venting methods differ among manufacturers. *(Courtesy Dr. Michael A. Olympio; modified with his permission. Adapted from Datex-Ohmeda:* Aisys anesthesia machine: technical reference, *Madison, Wis., 2005, Datex-Ohmeda.)*

fresh gas flow rate of 1.5 L/minute, the tank would last almost 7 hours. However, if oxygen is *also* required as the ventilator drive gas, and the delivered minute ventilation is approximately 5.75 L/min, the tank would only last approximately 86 min.

As described earlier, bellows-type ventilators can be classified according to the direction that they move during patient exhalation. Ascending bellows rises with exhalation, and descending bellows falls with exhalation (see Fig. 29-37). Older pneumatic ventilators and some newer anesthesia workstations use weighted descending bellows, but most contemporary bellows ventilators employ an ascending bellows design. Of the two configurations, the ascending bellows is considered safer.

An ascending bellows will not fill if total disconnection occurs, or it may only partially fill if a circuit leak exceeds the fresh gas flow rate. However, the bellows of a descending bellows ventilator continues its upward and downward movement despite patient disconnection, so a descending bellows does not provide a visual cue for a circuit disconnect. The driving gas pushes the bellows upward during the inspiratory phase. During the expiratory phase, room air can entrained into the breathing system at the site of the disconnection because gravity acts on the weighted bellows. The disconnection pressure monitor and the volume monitor may be fooled even if disconnection is complete.[37] An essential safety feature of any anesthesia workstation that uses a descending bellows is an integrated carbon dioxide apnea alarm that cannot be disabled while the ventilator is in use. Some contemporary anesthesia workstation designs have returned to the descending bellows to integrate fresh gas decoupling.

Bellows Assembly Problems. Leaks can occur in the bellows assembly. Improper seating of the plastic bellows housing can result in inadequate ventilation because a portion of the driving gas is vented to the atmosphere. A hole in the bellows can lead to alveolar hyperinflation and possibly barotrauma in some ventilators because high-pressure driving gas can enter the patient's circuit. The oxygen concentration of the patient's gas may increase when the driving gas is 100% oxygen, or it may decrease if the driving gas is composed of air or an air-oxygen mixture.[210]

The ventilator relief valve can potentially cause problems. Hypoventilation can occur if the valve becomes incompetent because anesthetic gas is delivered to the scavenging system during the inspiratory phase instead of to the patient. Ventilator relief valve incompetency can result from a disconnected pilot line, a ruptured valve, or a damaged flapper valve.[211,212] A ventilator relief valve stuck in the closed or partially closed position can cause either barotrauma or undesired PEEP.[213] Excessive suction from the scavenging system can draw the ventilator relief valve to its seat and close the valve during both the inspiratory and expiratory phases.[37] In this case, breathing circuit pressure escalates because the excess anesthetic gas cannot be vented. During the expiratory phase, some machines (e.g., Datex-Ohmeda S/5 ADU, Many contemporary GE machines, Mindray AS 3000 [Mindray, Mahwah, NJ]) send to the scavenge interface both excess patient's gas and the exhausted ventilator drive gas. In other words, when the ventilator relief valve opens and waste anesthetic gases are vented from the breathing circuit, the drive gas from the bellows housing joins with these gases to enter the scavenging system. Under certain conditions, the large volume of exhaust gases could overwhelm the scavenging system and cause pollution of the operating room with waste anesthetic gases (see the section on scavenging systems). Other mechanical problems that can occur include leaks within the system, faulty pressure regulators, and faulty valves.

Mechanically Driven Piston Ventilator

A resurgence in the use of mechanically driven anesthesia ventilators has occurred. These "piston"-type ventilators use a computer-controlled stepper motor instead of compressed drive gas to drive the cylinder and actuate gas movement in the breathing system (see Fig. 29-37, *C*). They are classified, in anesthesia ventilator parlance, as piston-driven *single-circuit* ventilators because a separate ventilator drive gas circuit is not necessary The piston operates much like the plunger of a syringe to deliver the desired tidal volume or airway pressure to the patient. Computerized controls can provide advanced types of ventilation support in addition to the conventional control-mode ventilation such as SIMV, pressure-controlled ventilation (PCV), and pressure support–assisted ventilation.

Because the patient's mechanical breath is delivered without the use of compressed gas to actuate a bellows, these systems consume dramatically less compressed gas during ventilator operation than do traditional pneumatic ventilators. This improvement in efficiency may have clinical significance when the anesthesia workstation is used in a setting where no pipeline gas supply is available (e.g., remote locations or office-based anesthesia practices). Another advantage of the piston ventilator is the potential for very accurate tidal volume delivery. Because of the low compliance of the piston chamber, tidal volume delivery is closely related to piston movement. This is in contrast to bellows-type ventilators, in which the drive gas can be subject to varying degrees of compression. However, with either piston or bellows ventilators, feedback mechanisms that help maintain stable tidal volume delivery are becoming increasingly more common. These include circuit compliance compensation and the use of inspired tidal volume measurement as a feedback signal. Figures 29-42 to 29-44 illustrate the inspiratory and expiratory phases of mechanical ventilation with a piston ventilator on the Dräger Fabius workstation. Note the location of the ventilator within the breathing circuit on the Dräger Fabius system, the fresh gas decoupling valve (described later), and the fact that the breathing bag participates in the mechanical ventilation mode.

Piston ventilators tend to be hidden relative to their bellows ventilator counterparts because they are usually fully or partially concealed from view. Because of this concealment, visual feedback of the patient's exhaling back into the piston reservoir, as can easily be observed with the ascending bellows, is lost. In addition, piston ventilators tend to be extremely quiet, so the partially reassuring sound of the mechanical ventilator in operation is much more subtle. Some systems incorporate a breathing sound emulator that creates ventilator sounds to substitute for the traditional feedback noise (i.e., Dräger Apollo).

A potential hazard associated with piston ventilators is that, like descending bellows ventilators, they will refill even if a circuit disconnection occurs. Similarly, if a circuit leak is present, piston ventilators may entrain room air through the leak, thereby diluting oxygen and anesthetic agent. The associated risks are hypoxemia and awareness. The Dräger Fabius series piston ventilator will entrain room air through an auxiliary air valve, seen in Figure 29-37, *C,* to fill the piston chamber if the fresh gas flow fails or is inadequate (instead of causing negative pressure in the breathing circuit). However, if

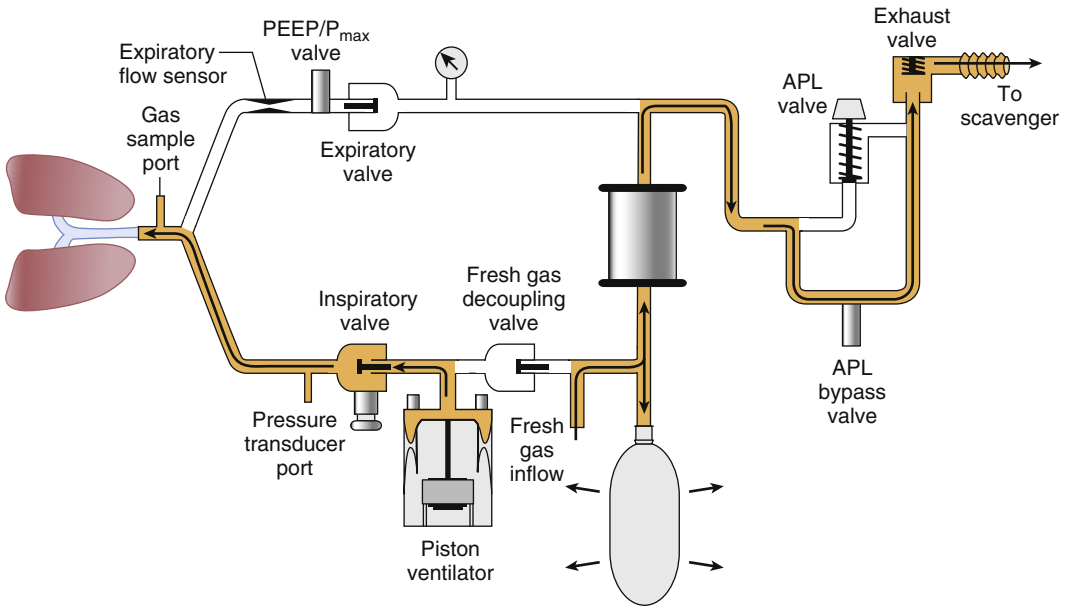


Figure 29-42. Inspiratory phase of ventilation with a piston ventilator represented by Dräger Fabius anesthesia workstation. During inspiration, the positive end-expiratory pressure (PEEP)/maximum pressure (P_{max}) valve is held closed. The pressure in the breathing circuit that is generated by the ventilator closes the fresh gas decoupling valve. This directs fresh gas flow toward the breathing bag during inspiration so it does not interfere with tidal volume accuracy. Excess gas fresh gas flows past the open adjustable pressure-limiting (APL) bypass valve, through the exhaust check valve, and to the scavenger. Note how the breathing bag is integral to circuit function during mechanical ventilation. In the manual and spontaneous modes of ventilation, the piston ventilator is held in the upward position, and the APL bypass valve closes, thus making the APL valve operable. *(Courtesy Dr. Michael A. Olympio; modified with his permission. Adapted from Dräger Medical:* Dräger technical service manual: Fabius GS anesthesia system, *Telford, Pa., 2002 Rev: E, Dräger Medical.)*

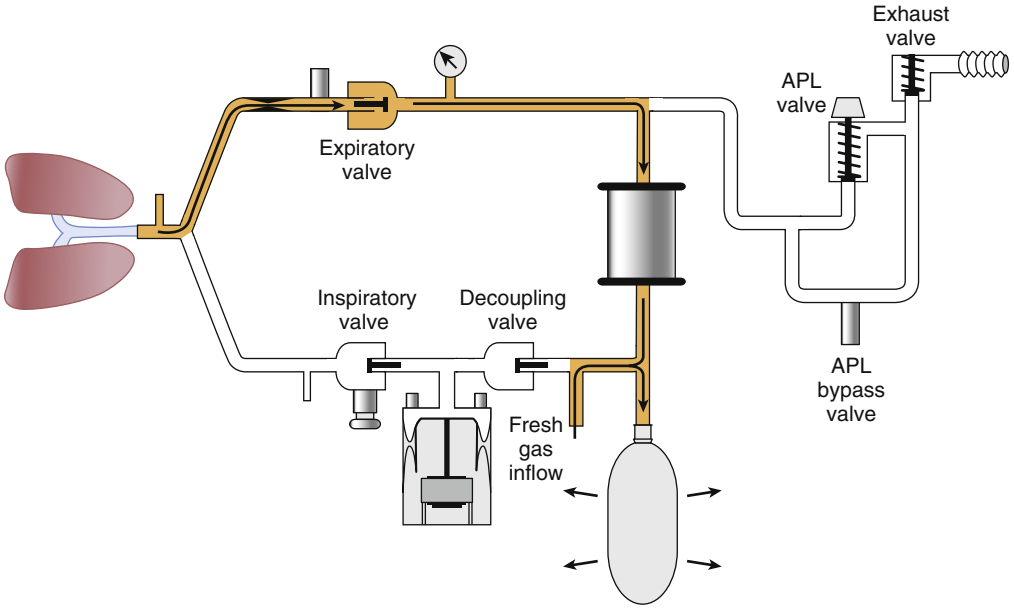


Figure 29-43. During the first step of exhalation the patient exhales into the breathing bag, and fresh gas continues to flow in retrograde fashion, as shown. *APL,* Adjustable pressure-limiting. *(Courtesy Dr. Michael A. Olympio; modified with his permission. Adapted from Dräger Medical:* Dräger technical service manual: Fabius GS anesthesia system, *Telford, Pa., 2002 Rev: E, Dräger Medical.)*

this occurs, an alarm will alert the operator. A positive-pressure relief valve on the ventilator prevents excessively high breathing circuit pressure (60 to 80 cm H_2O).[214]

Maquet FLOW-i Anesthesia System With Volume Reflector

Instead of employing a bellows or piston ventilator, the Maquet FLOW-i anesthesia workstation uses a device called the volume reflector (Figs. 29-45 and 29-46). The volume reflector is a coiled, 3.6-m plastic channel with an approximate 1.2-L capacity, which serves as reservoir for exhaled gases. The volume reflector is functional and "in-circuit" during all modes of ventilation. It is interposed between the patient and the reflector gas module during positive-pressure ventilation or between the patient and the breathing bag during spontaneous or assisted ventilation.

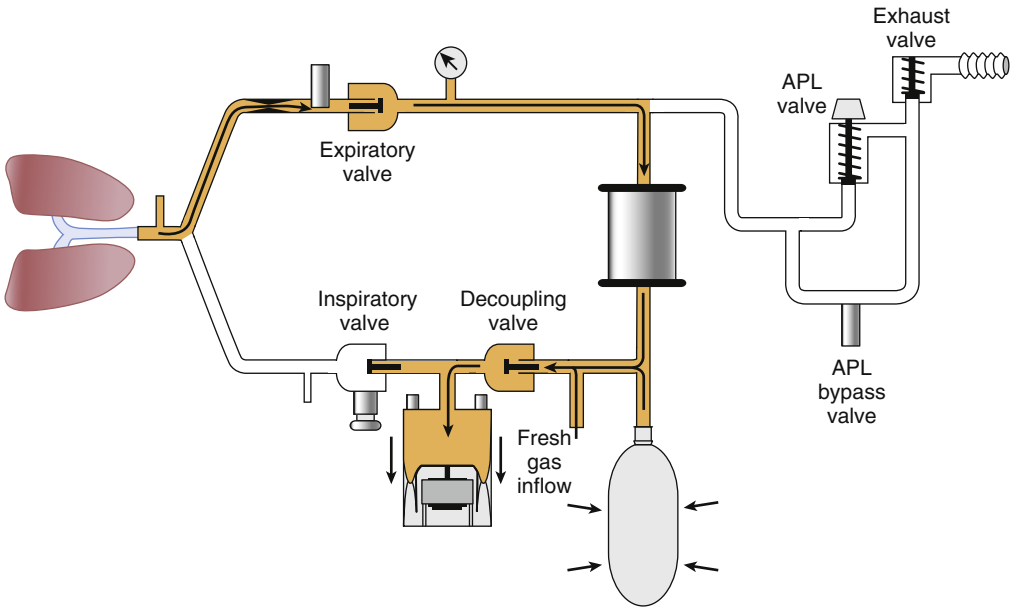


Figure 29-44. During the second step of exhalation the ventilator returns to its staring position, drawing in gas stored within the breathing bag and fresh gas from the gas supply system. Positive end-expiratory pressure (PEEP) is maintained by the PEEP/maximum pressure valve, which also prevents the ventilator from pulling in gas from the lungs. Once the piston reaches the bottom of its stroke, fresh gas flow reverses course and flows in retrograde fashion toward the breathing bag and the absorber (as in Figure 29-42). Excess gas vents through the exhaust valve to the scavenger (also depicted in right side of Figure 29-42). *APL,* Adjustable pressure-limiting. *(Courtesy Dr. Michael A. Olympio; modified with his permission. Adapted from Dräger Medical:* Dräger technical service manual: Fabius GS anesthesia system, *Telford, Pa., 2002 Rev: E, Dräger Medical.)*

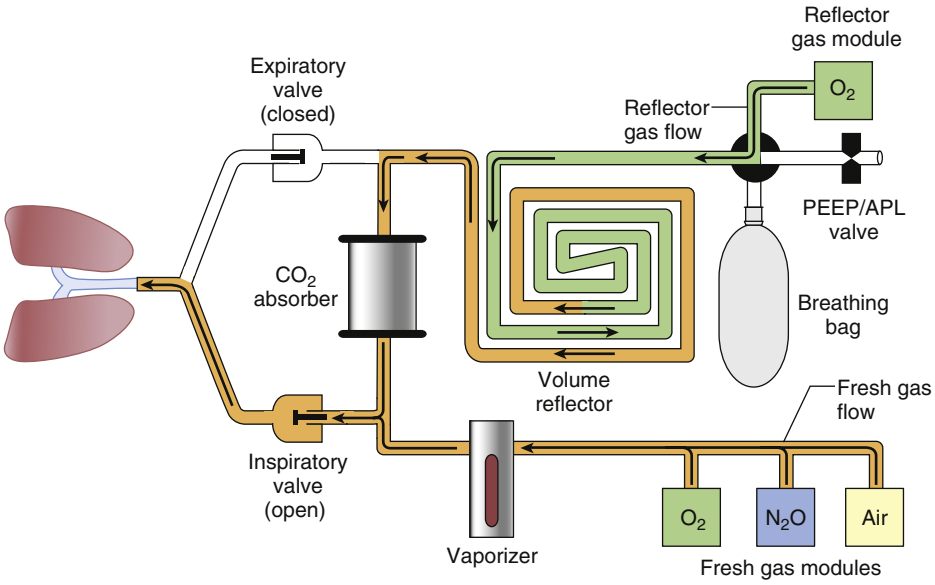


Figure 29-45. Simplified schematic of the Maquet FLOW-i anesthesia workstation breathing circuit and gas supply system. During controlled positive-pressure ventilation, the reflector gas module provides the driving force for ventilation by pushing gas out of the volume reflector to the patient. Volume reflector gas combines with the fresh gas flow downstream from the carbon dioxide (CO_2) absorber. *APL,* Adjustable pressure-limiting; *N_2O,* nitrous oxide; *O_2,* oxygen; *PEEP,* positive end-expiratory pressure. Please see text for additional details. *(Personal communication, Maquet Critical Care, January 14, 2013. Adapted from Maquet Critical Care:* User's manual: FLOW-i 1.2 anesthesia system, *Solna, Sweden, 2011, Rev: 11, Maquet Critical Care.)*

The reflector gas module serves as the controlled ventilation driving force. At the end of exhalation, the volume reflector is filled at its proximal end (nearer the patient) with exhaled gas and is filled distally with a mixture of exhaled gases and reflector gas. The reflector gas module is a solenoid-controlled oxygen flow source, which pushes the exhaled gas back out of the volume reflector during inspiration, much like a piston, through the carbon dioxide absorber to the patient. Fresh gas combines with the volume reflector outflow to maintain the desired oxygen and anesthetic concentration. The fresh gas modules and the reflector gas module work together in a coordinated manner to control gas flow and pressure in the breathing circuit so that operator determined ventilation parameters are maintained. All the gas modules use feedback loop–controlled, solenoid-actuated, pneumatic valves similar in function those found in a servo-controlled ICU ventilator (personal communication, Maquet Critical Care, January 14, 2013).

When the workstation is in the spontaneous mode of ventilation, the breathing bag is enabled, and the reflector gas module is disabled. The patient breathes in and out of the volume reflector, and circuit pressure controlled by the operator adjustable APL valve. Excess gases

in controlled and spontaneous modes of ventilation are vented to the scavenger through the dual-function PEEP-APL valve.

The FLOW-i system can compensate for breathing system leaks by increasing reflector gas module flow. The operator is informed if this occurs. Because the reflector gas module provides only 100% oxygen, dilution of anesthetic gas occurs in this circumstance. The machine is nearly entirely electronically interfaced; therefore, an emergency manual ventilation backup mode is provided for cases of system failure. This emergency backup mode provides mechanical oxygen flow adjustment and mechanical APL valve linkage (personal communication, Maquet Critical Care, January 14, 2013).

Fresh Gas Flow Compensation and Fresh Gas Decoupling

On most anesthesia workstations, gas flow from the fresh gas line into the breathing circuit is continuous and independent of ventilator activity. During the inspiratory phase of mechanical ventilation, the ventilator relief valve (also known as the ventilator pop-off valve) is typically closed, and the breathing system's APL valve is most commonly out of circuit. Therefore, during positive-pressure ventilation on most traditional machines, the patient's lungs received the volume from the bellows in addition to that from the flowmeters during the inspiratory phase. The amount of excess volume (and pressure) that the patient received was proportional to the direction and magnitude of the change in the fresh gas flow rate. As the practitioner turned up the fresh gas flow, the tidal volume increased. The opposite would occur if the flow rate were decreased from the baseline. It was therefore common knowledge that the operator needed to adjust the set tidal volume on the ventilator if the total fresh gas flow rate was changed to maintain stable tidal volumes and airway pressure. Many newer workstations have engineering features that provide compensation of fresh gas flow to maintain stable tidal volume delivery. The manner in which this is accomplished also accounts for much of the variation in breathing system design. Using GE Aisys as an example (see Fig. 29-39), inspiratory tidal volume measurement serves as a feedback signal for the automatic adjustment of ventilator drive gas volume to compensate for changes in fresh gas flow, small leaks, and compression upstream of the breathing circuit.[144] On the Dräger Fabius workstation, a principle called *fresh gas decoupling* is used to prevent changes in the fresh gas flow rate from altering positive-pressure tidal volumes and breathing circuit pressures. During the inspiratory phase of ventilation, a decoupling valve located upstream from the piston ventilator diverts the fresh gas stream toward the breathing bag and scavenge outlet during each positive-pressure breath (see Fig. 29-42).

On traditional and many contemporary workstations without a fresh gas decoupling feature, inappropriate activation of the oxygen flush valve during the inspiratory phase of mechanical ventilation can add a substantial amount of volume to the circuit and can result in barotrauma or volutrauma (or both) because excess pressure and volume may not be able to be vented from the breathing circuit.[26] Although the circuit high-pressure alarm may provide warning, unless an adjustable inspiratory pressure limiter is set to a relatively low value, high pressures can be realized. On workstations equipped with adjustable inspiratory pressure limiters, maximal

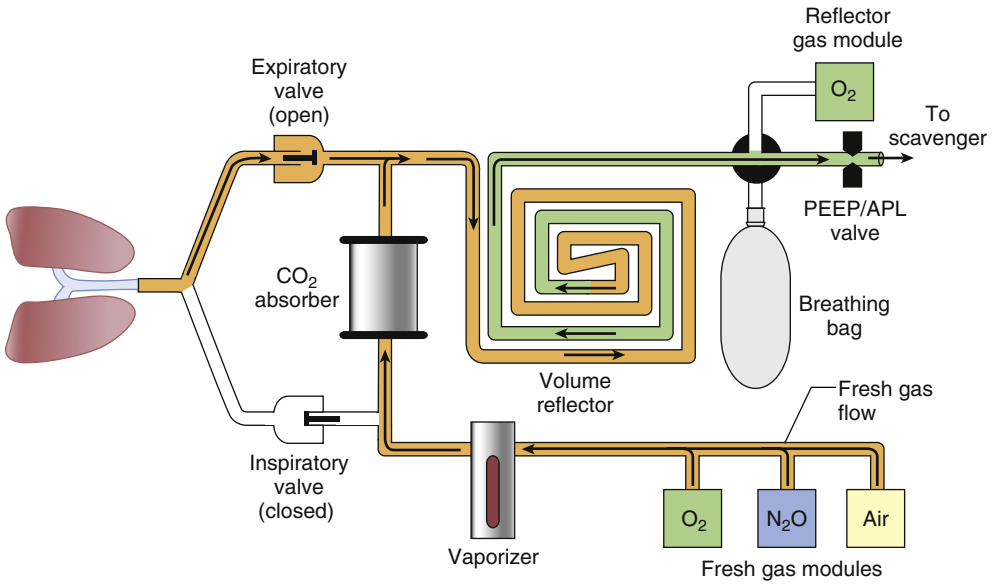


Figure 29-46. Maquet FLOW-i breathing circuit and gas supply during exhalation in a controlled ventilation mode. The patient exhales into the volume reflector, which serves as an exhalation reservoir. The patient only partially fills the volume reflector. Fresh gas flows in retrograde fashion and combines with the exhaled gas. Excess gas is vented to the scavenger through the positive end-expiratory pressure (PEEP)/adjustable pressure-limiting (APL) valve, which also controls breathing circuit pressure (PEEP). When the machine is placed in the manual mode of ventilation, the breathing bag is enabled and the reflector gas module is disabled. In the manual mode, the patient breathes in and out of the volume reflector and can be assisted with the breathing bag. The PEEP/APL valve vents excess gas to the scavenger and serves controls breathing circuit pressure (continuous positive airway pressure). CO_2, Carbon dioxide, N_2O, nitrous oxide; O_2, oxygen. *(Personal communication, Maquet Critical Care, January 14, 2013. Adapted from Maquet Critical Care:* User's manual: FLOW-i 1.2 anesthesia system, *Solna, Sweden, 2011, Rev: 11, Maquet Critical Care.)*

inspiratory pressure may be set by the user to a desired peak airway pressure. An adjustable pressure relief valve opens when the predetermined user-selected pressure is reached. This theoretically prevents the generation of excessive airway pressure. However, this feature depends on the user's having preset the appropriate pop-off pressure. If the setting is too low, insufficient pressure for ventilation may be generated and can result in inadequate minute ventilation; if set too high, the excessive airway pressure may still occur and result in barotrauma. Some machines may also include a factory-preset inspiratory pressure safety valve that opens at a preset airway pressure, such as 60 to 80 cm H_2O, to minimize the risk of barotrauma. Therefore, modern workstations without fresh gas decoupling usually reach a maximum pressure limit and terminate ventilation, release pressure, or sustain at the pressure limit.[215] In machines with a fresh gas decoupling feature, the oxygen flush inflow is diverted away from the patient during positive-pressure ventilation, thereby maintaining stable volumes and pressures (Fig. 29-47).

SCAVENGING SYSTEMS

Scavenging is the collection and subsequent removal of waste anesthetic gases from both the anesthesia machine and the anesthetizing location.[216] Scavenging is required because the fresh gas flow rates used during most anesthetic regimens deliver more volatile anesthetic agent and nitrous oxide than necessary, as well as more oxygen than is being consumed. When air is used, all the nitrogen is excess. Therefore, scavenging minimizes operating room pollution by removing these excess gases. In 1977, the National Institute for Occupational Safety and Health (NIOSH) prepared a document entitled *Criteria for a Recommended Standard: Occupational Exposure to Waste Anesthetic Gases and Vapors*.[217] Although it was maintained that a minimal safe level of exposure could not be defined, the NIOSH proceeded to issue the recommendations shown in Table 29-8. These same criteria remain in place today. ASTM International standard ASTM F1343-02 entitled *Standard Specification for Anesthetic Equipment: Scavenging Systems for Anesthetic Gases* established requirements for transfer and receiving systems of active anesthetic gas scavenging systems intended to reduce the exposure of

TABLE 29-8 NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH RECOMMENDATIONS FOR TRACE GAS LEVELS

Anesthetic Gas	Maximum TWA Concentration (ppm)*
Halogenated agent alone	2
Nitrous oxide	25
Combination of halogenated agent plus nitrous oxide	
Halogenated agent	0.5
Nitrous oxide	25
Dental facilities (nitrous oxide alone)	50

From U.S. Department of Health, Education and Welfare: Criteria for a recommended standard: occupational exposure to waste anesthetic gases and vapors, *Washington, DC, 1977, U.S. Department of Health, Education and Welfare.*

TWA, Time-weighted average.

*Time-weighted average sampling, also known as time-integrated sampling, is a sampling method that evaluates the average concentration of anesthetic gas over a prolonged period, such as 1 to 8 hours.

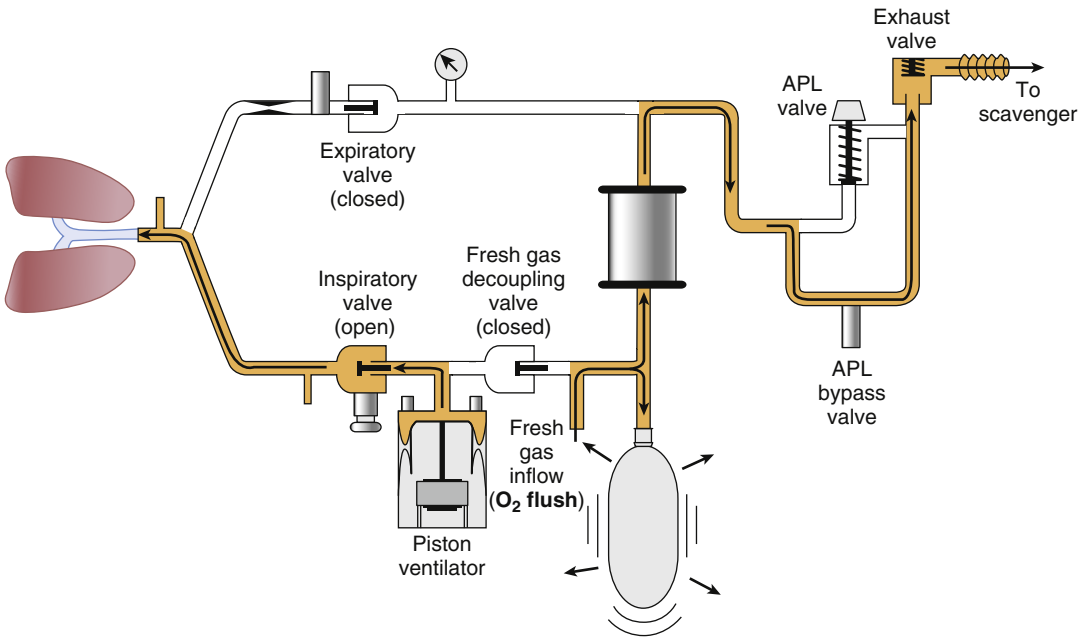


Figure 29-47. Fresh gas decoupling during an oxygen (O_2) flush shown on the Dräger Fabius workstation. During inspiration the positive end-expiratory pressure/maximum pressure valve is held closed. The pressure in the breathing circuit that is generated by the ventilator closes the fresh gas decoupling valve. This directs the high-volume oxygen flush flow toward the breathing bag during inspiration so it does not contribute to inhaled tidal volume and breathing circuit pressure. The O_2 flush gas also flows past the open adjustable pressure-limiting (APL) bypass valve, through the exhaust check valve, and to the scavenger. *(Modified image courtesy of Dr. Michael A. Olympio. Adapted from Dräger Medical:* Dräger technical service manual: Fabius GS anesthesia system, *Telford, Pa., 2002 Rev: E, Dräger Medical.)*

health care personnel to anesthetic gases and vapors.[218] In 1999, the ASA Task Force on Trace Anesthetic Gases developed a booklet entitled *Waste Anesthetic Gases: Information for Management in Anesthetizing Areas and the Postanesthesia Care Unit*. This publication describes the role of regulatory agencies, reviews scavenging and monitoring equipment, and provides recommendations.[219]

The two major causes of waste gas contamination in the operating room are the anesthetic technique used and equipment issues.[219,220] Regarding the anesthetic technique, the following are some of the causes of operating room contamination: (1) failure to turn off the gas flow control valves or the vaporizer when the circuit is disconnected from the patient; (2) use of poorly fitting masks; (3) flushing of the circuit into the room; (4) filling of anesthetic vaporizers, particularly if spillage occurs; (5) use of uncuffed endotracheal tubes; and (6) use of breathing circuits other than the circle system. Equipment failure or lack of understanding of proper equipment use can also contribute to operating room contamination. Leaks can occur in the high-pressure hoses, the nitrous oxide tank mounting, the high- or low-pressure circuits of the anesthesia machine, or the circle system, particularly at the carbon dioxide absorber assembly. The anesthesia care provider must be certain that the room suction and scavenging system is operational and adjusted properly to ensure adequate scavenging. Side-stream breathing gas analyzer waste flow (50 to 250 mL/minute) must be directed to the scavenging system or returned to the breathing system to prevent pollution of the operating room. [219,220]

Components

Scavenging systems classically have five components (Fig. 29-48): (1) the gas-collecting assembly, (2) the transfer tubing, (3) the scavenging interface, (4) the gas disposal assembly tubing, and (5) an active or passive gas disposal assembly.[216] An "active system" uses a central evacuation system to eliminate waste gases. With a "passive system," the pressure imposed by the venting of the breathing circuit produces flow. Although active systems are more common today, both are addressed here.

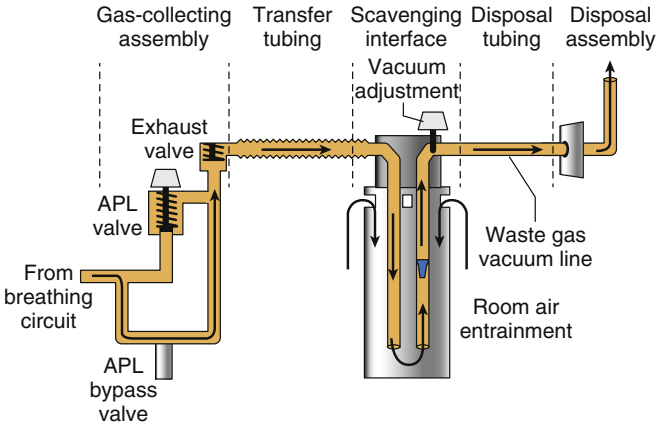


Figure 29-48. Components of a scavenging system using the example of a Dräger Fabius system (Dräger Medical, Telford, Pa.) connected to an open, active scavenging system. The transfer tubing has a connector size distinct from the breathing circuit to prevent misconnections. Obstructions in the gas-collecting assembly or transfer tubing can cause high pressure in the breathing circuit. Leaks, inadequate suction, or failure of the scavenging interface can cause environmental contamination. Closed systems can cause other problems. *APL,* Adjustable pressure-limiting. Please see text for details. *(From Brockwell RC: Delivery systems for inhaled anesthesia. In Barash PG, editor:* Clinical anesthesia, *ed 5, Philadelphia, 2006, Lippincott Williams & Wilkins, p 589.)*

Gas-Collecting Assembly. The gas-collecting assemblies are the points of waste gas exit from the breathing circuit that connect to the transfer tubing.[221] Waste anesthetic gases are vented from the anesthesia system either through the APL valve or through some sort of ventilator relief valve. Excess patient's gas either exits the breathing system through one of these valves or is shed into the room (e.g., poor facemask fit, endotracheal tube leak, machine leak). Conventional machines have separate outlet ports for these valves; however, many newer workstations only have one. Some anesthesia workstations may also exhaust the ventilator drive gas into the scavenging system (i.e., Datex-Ohmeda S/5 ADU, Mindray AS 3000). This is significant because under conditions of high fresh gas flow and high minute ventilation, the gases flowing into the scavenging interface may overwhelm the evacuation system. If this occurs, waste anesthetic gases may overflow the system through the positive-pressure relief valve (closed systems) or through the atmospheric vents (open systems) and pollute the operating room. In contrast, many other pneumatically driven ventilators exhaust their drive gas (100% oxygen or oxygen/air mixture) into the operating room through a small vent on the back of the ventilator control housing.

Transfer Tubing. The transfer means carries excess gas from the gas-collecting assembly to the scavenging interface. As specified by ASTM standard 1343-02, if the tubing is interchangeable, it must have 30-mm connectors on either end, which are distinct from the 22-mm connectors on the breathing system tubing.[218] Some manufacturers color-code the transfer tubing with yellow bands to distinguish it from 22-mm breathing system tubing. The tubing must be sufficiently rigid to prevent kinking to minimize the chance of occlusion, or it must contain some means of pressure relief in case of occlusion. Occlusion of the transfer means can be very problematic because it is upstream from the pressure-limiting features of the scavenging interface. If the transfer means is occluded by kinking or misconnection, breathing circuit pressure will increase and barotrauma can occur.[144,222-224] On machines that have separate transfer tubes for the APL valve and for the ventilator relief valve, the two tubes merge before or at the scavenging interface.

Scavenging Interface. The scavenging interface is the most important component of the system because it protects the breathing circuit or ventilator from excessive positive or negative pressure.[216] The interface should limit the pressure immediately downstream from the gas-collecting assembly to between –0.5 and +3.5 cm H_2O under normal working conditions.[218] Positive-pressure relief is mandatory irrespective of the type of disposal system used, so the system can vent excess gas in case

of occlusion (or inadequate suction with active systems) downstream from the interface. If the disposal system is an active system (see later), negative-pressure relief will be necessary to protect the breathing circuit or ventilator from excessive subatmospheric pressure. Subatmospheric pressure in the scavenging system could induce gas flow from the patient's breathing system. A reservoir is highly desirable with active systems because it stores waste gases until the evacuation system can remove them. Interfaces can be open or closed, depending on the method used to provide positive- and negative-pressure relief.[216]

An "active" anesthetic gas scavenging system relies on a hospital central evacuation system to remove gas from the anesthetic scavenging system. "Passive" systems simply vent the waste gas in to into a *nonrecirculating* heating, ventilation, and air conditioning (HVAC) system or through a hose to the building's exterior through a wall, ceiling, or floor (or out of a tent in the case of an austere setting). Passive systems rely only on the slight positive pressure of the gases leaving the gas-collecting assembly to provide the flow. Passive systems are less common in contemporary operating rooms. The other major classification of scavenging interfaces is "open" or "closed."

Open Interfaces. The open scavenge interface requires no positive- or negative-pressure relief valves because the canister is open to the atmosphere. Relief ports on the top of the canister provide positive- and negative-pressure relief. Open interfaces are active systems designed to operate only with a central vacuum or hospital waste gas elimination system. Open interfaces require a reservoir canister because waste gases are intermittently discharged in surges whereas flow from the evacuation system is continuous.[216] Many contemporary anesthesia machines are equipped with open interfaces, such as those in Figure 29-49. An open scavenging interface is also shown in Figure 29-48. An open canister provides reservoir capacity. Waste gas enters the system at the top of the canister and travels to the bottom through an inner tube, where a vacuum line removes waste gases. When adjusted properly, the vacuum rate should exceed the rate of waste gas flow into the chamber, and some room air should also be drawn into the canister through the relief port. The vacuum flow rate is usually adjusted on the scavenging interface using a flow control valve and flowmeter. Adjusting the scavenger vacuum flow rate is an important part of the workstation daily preuse checkout procedure. If vacuum flow is inadequate, waste gas can spill out into the room through the relief ports.

Closed Interfaces. Closed scavenging interfaces are isolated from the environment by pressure relief valves, so the relationship of waste gas flow, vacuum flow, and the size of the system's reservoir bag determines the effectiveness of the gas elimination. All closed interfaces must have a positive-pressure relief valve to vent excess system pressure if obstruction occurs downstream from the interface. A negative-pressure relief valve is mandatory to protect the breathing system from subatmospheric pressure if an active disposal system is used.[216] Two types of closed interfaces are used in clinical practice. One is used with passive scavenging systems and has positive-pressure relief only; the other is used with active scavenging systems and has both positive- and negative-pressure relief. Each type is discussed in the following paragraphs.

Positive-Pressure Relief Only. This interface has a single positive-pressure relief valve and is designed to operate only with passive disposal systems (Fig. 29-50, *A*). Waste gas enters the interface at the waste gas inlets. Transfer of the waste gas from the interface to the disposal system relies on the slight positive pressure of the gases leaving the patient's breathing system because a negative-pressure evacuation system is not used. Waste gases are then passively vented to a nonrecirculating HVAC system or to the outdoors. The positive-pressure relief valve opens at a preset value such as 5 cm H_2O if an obstruction between the interface and the disposal system occurs.[225] With this type of system, a reservoir bag is not required.

Positive- and Negative-Pressure Relief. This interface has a positive-pressure relief valve and at least one negative-pressure relief valve, in addition to a reservoir bag. It is designed to be used with active disposal systems. Figure 29-50, *B,* is a schematic of Dräger Medical's closed

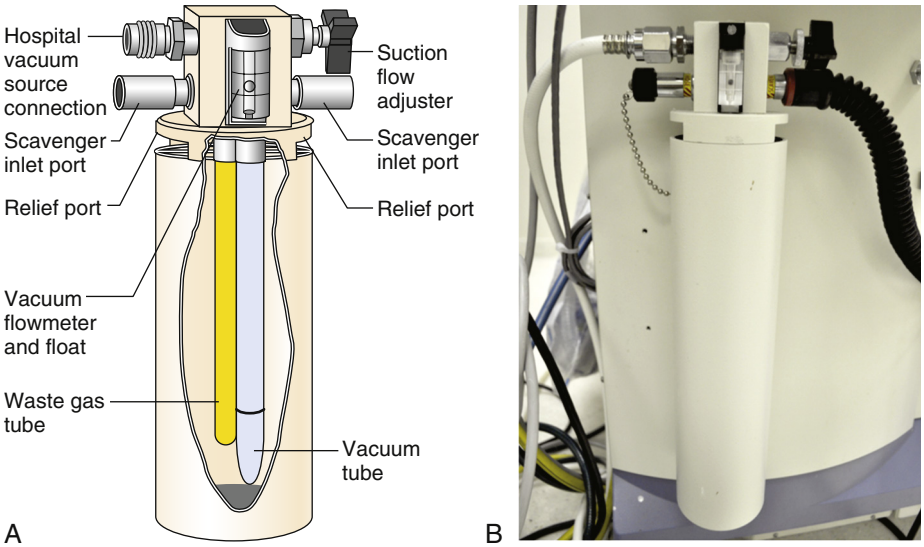


Figure 29-49. A and **B,** Open scavenge interface.

scavenge interface for active suction systems. A variable volume of waste gas intermittently enters the interface through the waste gas inlets. The reservoir bag intermittently accumulates excess gas until the evacuation system eliminates it. The operator must adjust the vacuum control valve so that the reservoir bag remains properly inflated (see Fig. 29-50, *B,* label *A*), and not overdistended (label *B*) or completely deflated (label *C*). Gas is vented to the atmosphere through the positive-pressure relief valve if the system pressure exceeds +5 cm H_2O. Room air is entrained through the negative-pressure relief valve if the system pressure is more negative than –0.5 cm H_2O. On some systems, a backup negative-pressure relief valve opens at –1.8 cm H_2O if the primary negative-pressure relief valve becomes occluded by dust or other causes. The effectiveness of a closed system in preventing spillage depends on the rate of waste gas inflow, the evacuation flow rate, and the size of the reservoir. Leakage of waste gases into the atmosphere occurs only when the reservoir bag becomes fully inflated and the pressure increases sufficiently to open the positive-pressure relief valve.

Gas Disposal Assembly Conduit or Extract Flow. The gas disposal assembly conduit conducts waste gas from the scavenging interface to the receiving end of the gas disposal system (see Fig. 29-48). It should be collapse-proof and should run overhead, if possible, to minimize the chance of accidental occlusion. The connection to the scavenging interface can be a permanent or proprietary connector, but the connection to an active gas disposal system should be a DISS-type connector.[218]

Gas Disposal System. The gas disposal assembly ultimately eliminates excess waste gas (see Fig. 29-48). The two types of environmental disposal mechanisms, active and passive, have been described.

Hazards

Scavenging systems minimize operating room pollution, yet they add complexity to the anesthesia system. A scavenging system functionally extends the anesthesia circuit all the way from the anesthesia machine to the ultimate disposal site. This extension increases the potential for problems. Obstruction of scavenging pathways can cause excessive positive pressure in the breathing circuit, and barotrauma can occur. Excessive vacuum applied to a scavenging system can cause undesirable negative pressures within the breathing system. In contrast, inadequate vacuum to the interface can cause venting of waste gas into the operating room. In one case report, inadequate suction caused a ventilator alarm condition resulting from backpressure caused within scavenge system.[226,227] In 2004, another unusual problem that resulted from waste gas scavenging was reported in the *ASA Newsletter* by Allen and Lees.[228] They reported fires in engineering equipment rooms that house the vacuum pumps used for evacuation of waste anesthetic gases. It seems that in some hospitals, waste gases are not directly vented outside but may be vented into machine rooms that have

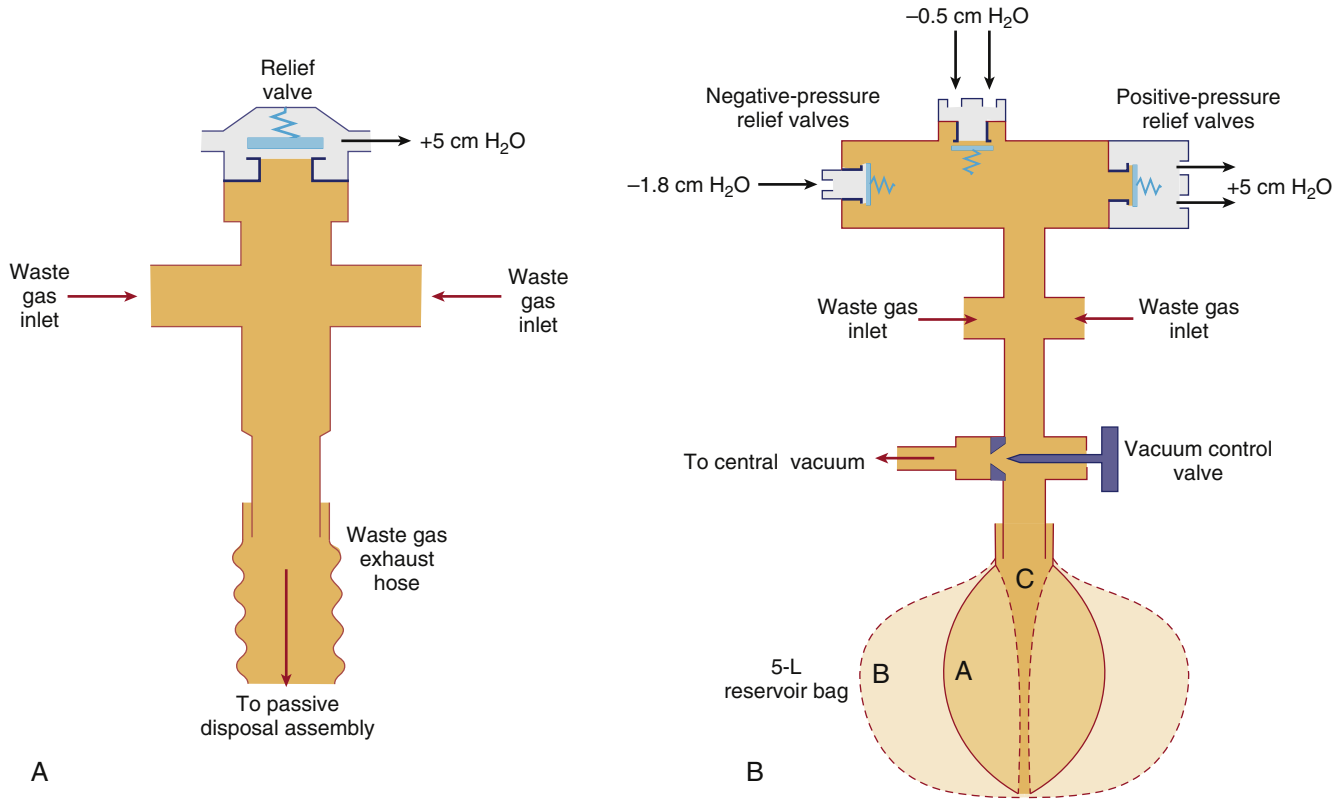


Figure 29-50. Closed scavenging interfaces. **A,** Interface used with a passive disposal system. **B,** Interface used with an active system. See text for details. (**A,** *Modified from North American Dräger:* Scavenger interface for air conditioning: instruction manual, *Telford, Pa., 1984, North American Dräger;* **B,** *from North American Dräger:* Narkomed 2A anesthesia system: technical service manual, *Telford, Pa., 1985, North American Dräger.)*

vents opening to the outside. Because some anesthesia machines scavenge ventilator drive gas (which is 100% oxygen in most cases) in addition to gas from the breathing system, the environments in these machine rooms may become highly enriched with oxygen gas. The result has been the production of fires in these spaces outside the operating room. These sites may contain equipment or materials such as petroleum distillates (pumps, oil, or grease) that in the presence of an oxygen-enriched atmosphere could be excessively combustible and a severe fire hazard.[228]

CHECKING YOUR ANESTHESIA WORKSTATION

HISTORICAL PERSPECTIVE

A complete anesthesia apparatus checkout procedure must be performed each day before the anesthesia workstation is first used, and an abbreviated version should be performed before each subsequent case. The preanesthesia machine checkout (PAC) is a *checklist*-oriented procedure. The obvious industry parallel is in aviation, in which strict adherence to prevent checklists (e.g., Before Start, Takeoff, Approach) is known to enhance compliance with important procedural steps and save lives. Similarly, the routine performance of a PAC procedure is associated with a decreased risk of perioperative morbidity and mortality.[229]

Data predating the 1986 publication of the FDA's first *Anesthesia Apparatus Checkout Recommendations* demonstrated a low level of proficiency by anesthesiologists in detecting life-threatening machine-related problems.[230] At that time, available preuse checkout procedures for anesthesia machines were provided and promoted by individual machine manufacturers. These procedures were not entirely user-friendly or well suited for clinical application. Prompted by a series of anesthesia machine related accidents, in 1984 the FDA met with representatives of the ASA, anesthesia equipment experts, and anesthesia machine manufacturers to discuss methods of reducing the risks to patients during anesthesia.[231,232] As result, the first anesthesia workstation preuse checkout was released in August of 1986. Limited information suggests that this detailed guideline did not appear to be extensively used, nor did it greatly improve the ability of anesthesiologists to detect anesthesia machine faults.[232-234] Recognizing the poor compliance with the 1986 guideline, the FDA revised the PAC in the early 1990s. Other factors, including the development of monitoring standards by the ASA, the retirement of many older machines, and the introduction of newer-generation anesthesia machines following the ASTM specifications also provided impetus for the update.[233] The revised checklist was issued in 1993.[10,235] Although the newer checklist was fairly comprehensive and universal, a stated intent of the authors, similar to the 1986 version, was to encourage users to "modify [the guideline] to accommodate differences in equipment design and variations in local clinical practice" and to subject modifications to local peer review.[10,235]

Although the data are limited, evidence that the 1993 PAC recommendations led to improved detection of machine faults was also not forthcoming. Researchers demonstrated that anesthesiologists demonstrated poor fault detection on sabotaged machines despite having the guideline in hand.[236,237] Larson and associates observed 87 participants at a "nationally attended anesthesia meeting" while they were asked to perform a checkout on an anesthesia machine with preset faults. In other studies within controlled settings, researchers noted limited machine fault detection and low checklist item compliance.[3-5]

As tempting as it is to implicate the checklists for this poor performance, human factors and machine knowledge issues are more likely to blame. In particular, a lack of cultural discipline in the routine use of a PAC (*a checklist*) seems to be a key problem. Surveys have demonstrated poor compliance with machine checks, as well as low self-admitted competence with the procedure.[7,8,238] Further, human error and failures to check and inspect equipment have been related to a significant percentage of anesthetic mishaps.[6,239] It seems that no matter how well conceived and strongly promoted PAC recommendations have been, adoption and routine use of the PAC have not been consistent. Increasing machine diversity could potentially compound the issue because the application of a simple, generic PAC is now unlikely.

2008 RECOMMENDATIONS FOR PREANESTHESIA CHECKOUT PROCEDURES

To improve PAC compliance and performance, it is recommended that individual anesthesia departments align the ASA's *Recommendations for Pre-Anesthesia Checkout Procedures (2008)* with their respective manufacturers' suggested checkout procedures to develop their own effective, workstation-specific PAC checklists (Box 29-1).[240] The recommendations were developed with the knowledge that the existing PAC was neither well understood nor reliably used by anesthesia providers and that anesthesia delivery systems have evolved to the point where one checkout procedure was no longer universally applicable. The recommendations are therefore designed as a template to develop "checkout procedures that are appropriate for each individual anesthesia machine design and practice setting."[240]

The 2008 recommendations warn against an overreliance on automated machine checkouts and assert that anesthesiology providers may be unaware of what is actually assessed by these features and may omit important preuse checkout items if they place all faith in an automated checkout. When developing a local PAC, a detailed understanding of what is actually checked by the machine should be determined. However, this is not always easy to ascertain by simply reviewing user's manuals.

The authors of the 2008 guideline recognized that using anesthesia technicians or biomedical technicians, or both, to perform some aspects of the checkout procedures may improve compliance with a department's PAC and could add redundancy to critical steps.[240] Although the 2008 guideline suggests which steps may be checked by "a qualified anesthesia technician, biomedical technician, or manufacturer-certified technician," this should be an institutional decision. Local skill levels, work flow patterns, and training requirements may vary greatly. According to the

BOX 29-1 *Summary Recommendations of the 2008 Preanesthesia Checkout Procedures*

Items to Be Completed Daily

Item #	Task	Responsible Parties?
1	Verify that auxiliary oxygen cylinder and self-inflating manual ventilation device are available and functioning	Provider *and* technician
2	Verify that patient suction is adequate to clear the airway	Provider *and* technician
3	Turn on the anesthesia delivery system and confirm that AC power is available	Provider *or* technician
4	Verify the availability of required monitors, including alarms	Provider *or* technician
5	Verify that pressure is adequate on the spare oxygen cylinder mounted on the anesthesia machine	Provider *and* technician
6	Verify that the piped gas pressures are ≥50 psig	Provider *and* technician
7	Verify that vaporizers are adequately filled and, if applicable, that the filler ports are tightly closed	Provider *only*
8	Verify that the gas supply lines have no leaks between the flowmeters and the common gas outlet	Provider *or* technician
9	Test the scavenging system function	Provider *or* technician
10	Calibrate, or verify the calibration of, the oxygen monitor, and check the low-oxygen alarm	Provider *or* technician
11	Verify that carbon dioxide absorbent is not exhausted	Provider *or* technician
12	Perform breathing system pressure and leak testing	Provider *and* technician
13	Verify that gas flows properly through the breathing circuit during both inspiration and exhalation	Provider *and* technician
14	Document the completion of checkout procedures	Provider *and* technician
15	Confirm the ventilator settings, and evaluate readiness to deliver anesthesia care (Anesthesia Time Out)	Provider *only*

Items to Be Completed Before Each Procedure

Item #	Task	Responsible Parties?
1	Verify that patient suction is adequate to clear the airway	Provider *and* technician
2	Verify the availability of required monitors, including alarms	Provider *or* technician
3	Verify that vaporizers are adequately filled and, if applicable, that the filler ports are tightly closed	Provider only
4	Verify that carbon dioxide absorbent is not exhausted	Provider *or* technician
5	Perform breathing system pressure and leak testing	Provider *and* technician
6	Verify that gas flows properly through the breathing circuit during both inspiration and exhalation	Provider *and* technician
7	Document the completion of checkout procedures	Provider *and* technician
8	Confirm the ventilator settings, and evaluate readiness to deliver anesthesia care (Anesthesia Time Out)	Provider only

Modified from Sub-Committee of American Society of Anesthesiologists Committee on Equipment and Facilities: Recommendations for pre-anesthesia checkout procedures (2008). <http://www.asahq.org/For-Members/Clinical-Information/2008-ASA-Recommendations-for-PreAnesthesia-Checkout.aspx>. (Accessed 01.03.11.)

guideline, the use of technician checks is not intended to be mandatory. Regardless of who participates in the PAC, the anesthesia care provider is ultimately responsible for the proper and safe functioning of the equipment.

The recommendations are intended to describe a basic approach to developing sound institution-specific PAC procedures designed "for the equipment and resources available." The method used to check each item depends on the specific equipment. The recommendations simply suggest the minimum machine-related items that should be assessed before use. A local PAC checklist should represent a workable merger of this guideline with the manufacturer's checkout recommendations.

In addition to developing effective PACs, it is also important that anesthesia providers remain knowledgeable about their equipment and embrace a "checklist culture." The 2008 guideline can be found at https://www.asahq.org/For-Members/Clinical-Information/2008-ASA-Recommendations-for-PreAnesthesia-Checkout.aspx.[240] Anesthesia workstation-specific PACs from individual departments can also be found at the site, which can be used for PAC development.

MINIMUM PREANESTHESIA CHECKLIST

Item 1: Verify Auxiliary Oxygen Cylinder and Self-Inflating Manual Ventilation Device Are Available and Functioning

Frequency: Daily
Responsible parties: Provider and technician

> "Failure to be able to ventilate is a major cause of morbidity and mortality related to anesthesia care. Because equipment failure with resulting inability to ventilate

the patient can occur at any time, a self-inflating manual ventilation device (e.g., an Ambu bag) should be present at every anesthetizing location for every case and should be checked for proper function. In addition, a source of oxygen separate from the anesthesia machine and pipeline supply, specifically an oxygen cylinder with regulator and a means to open the cylinder valve, should be immediately available and checked. After checking the cylinder pressure, it is recommended that the main cylinder valve be closed to avoid inadvertent emptying of the cylinder through a leaky or open regulator."[240]

This step was the most important item on the checklist on the 1993 PAC and remains so in the 2008 recommendations. No matter what happens to the machine, you should always be prepared to keep the patient alive without it. The auxiliary ventilation device should be self-inflating, which *excludes* Mapleson circuits that are often found in and out of the operating room. These devices should be located at "every anesthetizing location," and the guideline further recommends that they be checked for proper function. The recommendation also states that the auxiliary oxygen source should be separate from the machine and its pipeline supply, "specifically an oxygen cylinder." Ensuring that properly filled portable cylinders with attached flowmeters are available at specific locations requires an institutional logistic commitment and careful attention to detail by support staff.

Item 2: Verify Patient Suction Is Adequate to Clear the Airway

Frequency: Before each use
Responsible parties: Provider and technician

"Safe anesthetic care requires the immediate availability of suction to clear the airway if needed."[240]

Item 3: Turn on Anesthesia Delivery System and Confirm That AC Power Is Available

Frequency: Daily
Responsible party: Provider or technician

"Anesthesia delivery systems typically function with backup battery power if AC power fails. Unless the presence of AC power is confirmed, the first obvious sign of power failure can be a complete system shutdown when the batteries can no longer power the system. Many anesthesia delivery systems have visual indicators of the power source showing the presence of both AC and battery power. These indicators should be checked and connection of the power cord to a functional AC power source should be confirmed. Desflurane vaporizers require electrical power and recommendations for checking power to these vaporizers should also be followed."[240]

Item 4: Verify Availability of Required Monitors and Check Alarms

Frequency: Before each use
Responsible party: Provider or technician

"Standards for patient monitoring during anesthesia are clearly defined. The ability to conform to these standards should be confirmed for every anesthetic. The first step is to visually verify that the appropriate monitoring supplies (BP cuffs, oximetry probes, etc.) are available. All monitors should be turned on and proper completion of power-up self tests confirmed. Given the importance of pulse oximetry and capnography to patient safety, verifying proper function of these devices before anesthetizing the patient is essential. Capnometer function can be verified by exhaling through the breathing circuit or gas sensor to generate a capnogram, or verifying that the patient's breathing efforts generate a capnogram before the patient is anesthetized. Visual and audible alarm signals should be generated when this is discontinued. Pulse oximeter function, including an audible alarm, can be verified by placing the sensor on a finger and observing for a proper recording. The pulse oximeter alarm can be tested by introducing motion artifact or removing the sensor. Audible alarms have also been reconfirmed as essential to patient safety by ASA, AANA, APSF and JCAHO [The Joint Commission]. Proper monitor functioning includes visual and audible alarm signals that function as designed."[240]

Verifying the availability and proper functioning of standard and other required monitors is a relatively straightforward task. However, the process of checking alarm thresholds, and possibly resetting them, can be tedious. Monitor alarm settings may possibly vary within individual facilities as a result of provider manipulation of alarms for case requirements, a lack of standard default settings, and failure to reset alarm limits routinely. Departmental alarm default settings can be established and programmed into anesthesia workstation monitors. Alarm limit settings also include anesthesia machine alarms such as volume, pressure, and inspired oxygen concentration limits (Fig. 29-51). The practitioner should ensure that critical alarm limits are set to values that permit these alarms to do what they were intended to do.

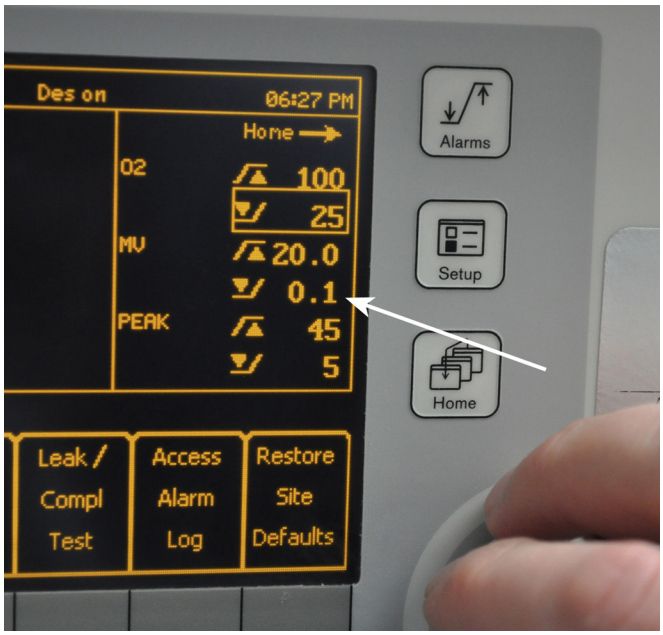


Figure 29-51. Setting machine alarm limits: Note the inappropriately low setting that was encountered on this machine's low minute ventilation alarm limit. Alarm limit values are easy to adjust, although this process can be time consuming during routine preuse checkout. Safe default values can be established locally and set by trained technicians, to help keep limits consistent.

Here, anesthesia technicians can improve the quality of the preuse checkout by checking the function of standard monitors and confirming that critical alarm thresholds are set to established default values.

Item 5: Verify That Pressure Is Adequate on the Spare Oxygen Cylinder Mounted on the Anesthesia Machine

Frequency: Daily
Responsible parties: Provider and technician

> "Anesthesia delivery systems rely on a supply of oxygen for various machine functions. At a minimum, the oxygen supply is used to provide oxygen to the patient. Pneumatically-powered ventilators also rely on a gas supply. Oxygen cylinder(s) should be mounted on the anesthesia delivery system and determined to have an acceptable minimum pressure. The acceptable pressure depends on the intended use, the design of the anesthesia delivery system and the availability of piped oxygen."[240]

Verification of oxygen cylinder pressure is accomplished by opening the oxygen cylinder or cylinders on the back of the machine and evaluating the tank gauge pressure, which is located on the front of the machine. Some newer machines may also have a tank gauge located on the back of the machine. The 1986 PAC guideline recommended to "replace any cylinder less than about 600 psig."[241] The 1993 PAC guideline recommended that the oxygen cylinder be "at least half full (about 1000 psi)" during checkout. The current recommendations do not provide a specific value, but some manufacturer's manuals still suggest the 1000 psi minimum.[242]

Additional bulleted comments in this item of the 2008 guideline include the following:

> "Typically, an oxygen cylinder will be used if the central oxygen supply fails."[240]

The auxiliary oxygen cylinder or cylinder will be used if the pipeline supply of oxygen fails or becomes contaminated. As discussed earlier, if the tank is to be used in the setting of a suspected oxygen pipeline contamination, the pipeline supply must be disconnected from the machine for tank gas to flow into the gas supply system.

> "If the cylinder is intended to be the primary source of oxygen (e.g., remote site anesthesia), then a cylinder supply sufficient to last for the entire anesthetic is required."[240]

It is always wise to estimate finite oxygen source needs (e.g., portable tank supply) by applying a wide margin on the side of safety.

> "If a pneumatically-powered ventilator that uses oxygen as its driving gas will be used, a full "E" oxygen cylinder may provide only 30 minutes of oxygen. In that case, the maximum duration of oxygen supply can be obtained from an oxygen cylinder if it is used only to provide fresh gas to the patient in conjunction with manual or spontaneous ventilation. Mechanical ventilators will consume the oxygen supply if pneumatically powered ventilators that require oxygen to power the ventilator are used. Electrically-powered ventilators do not consume oxygen so that the duration of a cylinder supply will depend only on total fresh gas flow."[240]

Generally speaking, mechanical ventilators using a bellows are typically gas driven (with either oxygen or air), the Maquet volume reflector is oxygen driven, and piston driven ventilators are electrically driven. This underscores the importance of machine familiarity.

> "The oxygen cylinder valve should be closed after it has been verified that adequate pressure is present, unless the cylinder is to be the primary source of oxygen (i.e., piped oxygen is not available). If the valve remains open and the pipeline supply should fail, the oxygen cylinder can become depleted while the anesthesia provider is unaware of the oxygen supply problem."[240]

The operator should remember to close the tank valve after checking the pressure so the tank does not slowly loose pressure (see the earlier discussion of the gas supply system).

> "Other gas supply cylinders (e.g., Heliox, CO_2, Air, N_2O) need to be checked only if that gas is required to provide anesthetic care." [240]

Item 6: Verify That Piped Gas Pressures Are 50 psig or Higher

Frequency: Daily
Responsible parties: Provider and technician

> "A minimum gas supply pressure is required for proper function of the anesthesia delivery system. Gas supplied from a central source can fail for a variety of reasons. Therefore the pressure in the piped gas supply should be checked at least once daily." [240]

Normal pipeline pressures in the United States for common gases (oxygen, air, nitrous oxide) are 50 to 55 psig.[243] Although the guideline suggests verifying gauge pressures, an inspection of the supply hoses and connections is also recommended by some manufacturers. Checking that "hoses are connected" was a checklist item on the 1993 PAC. Despite gas-specific connectors, misconnections of gas hoses have been reported.[244-246] Similarly, medical gas supply lines behind the walls of the operating room are not immune from misconnection or contamination.[247-251] A preuse check that includes a quick daily inspection of connections, supply hoses, gas pressures, and the presence of more than 90% oxygen in the inspiratory limb greatly minimizes risk. An important safety item on all machines is an audible and visual alarm that warns the operator of diminishing oxygen supply pressure. The only way to evaluate this pneumatic safety device is to disconnect the wall oxygen supply and shut off the oxygen supply tank or tanks. During development of the 1993 PAC, it was noted that provider failure to reconnect the main oxygen supply line during the PAC was not a rare occurrence. Concern also existed that daily removal and reconnection of oxygen supply line connector could contribute to wear or breakdown. Given these concerns, disconnection of the oxygen pipeline supply is not a specified recommendation within the 1993 and 2008 guideline (personal communication, Dr. J. Jeff Andrews, February 9, 2011).

Item 7: Verify That Vaporizers Are Adequately Filled and, If Applicable, That the Filler Ports Are Tightly Closed

Responsible parties: Provider (technician if redundancy desired)

> "If anesthetic vapor delivery is planned, an adequate supply is essential to reduce the risk of light anesthesia or recall. This is especially true if an anesthetic agent monitor with a low agent alarm is not being used. Partially open filler ports are a common cause of leaks that may not be detected if the vaporizer control dial is not open when a leak test is performed. This leak source can be minimized by tightly closing filler ports. Newer vaporizer designs have filling systems that automatically close the filler port when filling is completed. High and low anesthetic agent alarms are useful to help prevent over- or under-dosage of anesthetic vapor. Use of these alarms is encouraged and they should be set to the appropriate limits and enabled."[240]

Although not part of the 2008 PAC guideline, some manufacturers recommend a check of their machine's vaporizer interlock system, which, if present, prevents more than one vaporizer from being activated simultaneously. If this step is added to a local checklist, make sure that when one vaporizer hand wheel is turned to a setting greater than "0," the other vaporizer remains locked in its "0" position. Test the system for all mounted vaporizers; then ensure all vaporizers are placed back to their "0" position. This is also a good time to make certain that the vaporizers are firmly mounted.

Item 8: Verify That No Leaks Are Present in the Gas Supply Lines Between the Flowmeters and the Common Gas Outlet

Frequency: Daily and whenever a vaporizer is changed
Responsible party: Provider or technician

> "The gas supply in this part of the anesthesia delivery system passes through the anesthetic vaporizer(s) on most anesthesia delivery systems. To perform a thorough leak test, each vaporizer must be turned on individually to check for leaks at the vaporizer mount(s) or inside the vaporizer. Furthermore, some machines have a check valve between the flowmeters and the common gas outlet, requiring a negative-pressure test to check for leaks adequately. Automated checkout procedures typically include a leak test but may not evaluate leaks at the vaporizer especially if the vaporizer is not turned on during the leak test. When relying on automated testing to evaluate the system for leaks, the automated leak test would need to be repeated for each vaporizer in place. This test should also be completed whenever a vaporizer is changed. The risk of a leak at the vaporizer depends on the vaporizer design. Vaporizer designs where the filler port closes automatically after filling can reduce the risk of leaks. Technicians can provide useful assistance with this aspect of the machine checkout since it can be time consuming."[240]

This step checks the integrity of the so-called low-pressure section (LPS) of the workstation's gas supply system, which extends from the flow control valves to the fresh gas outlet. It evaluates the portion of the machine that is downstream from all safety devices except the oxygen analyzer. Leaks in this section of the machine are associated with hypoxemia or patient awareness under anesthesia.[23,25] The components located within this area are *precisely* the ones most subject to breakage and leaks, such as the anesthetic vaporizer, the vaporizer mounting, or the flowmeter tubes (Fig. 29-52). Loose filler caps on vaporizers are a common source of leaks, and these leaks can cause patient awareness under anesthesia.[230,238]

Because of significant machine design differences, several tests have been described to check for leaks within the LPS.[215] These tests use either positive pressure (assessing either leak flow or system pressure stability) or negative pressure to facilitate leak detection in this vulnerable part of the anesthesia machine. Selecting the proper test had been historically confusing because a few machines have an outlet check between the common gas outlet and the vaporizers, whereas most do not. An example of an anesthesia machine with an outlet check valve is

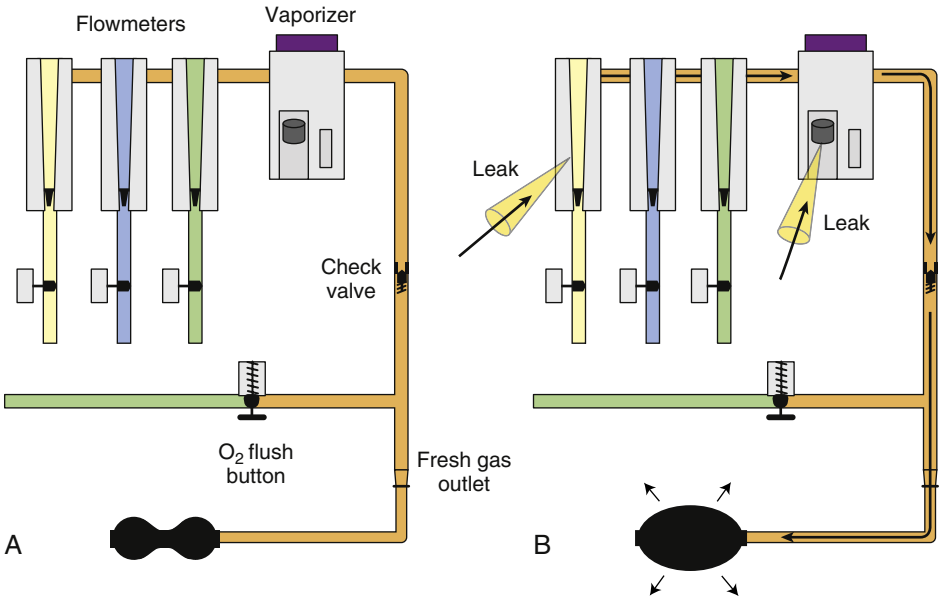


Figure 29-52. The negative-pressure "universal" low-pressure system leak test. **A,** A specially configured suction bulb is connected to the common (fresh) gas outlet and collapsed. Subatmospheric pressure is created in the low pressure circuit, thus opening the outlet check valve (if present) and exposing the vaporizers, tubing, and associated piping and connections to the vacuum. **B,** Leaks in the system draw in ambient air and inflate the suction bulb. O_2, Oxygen.

seen in Figures 29-1 and 29-52. The check valve is meant to minimize the effects of intermittent backpressure on vaporizer output. For machines without an outlet check valve, positive-pressure tests of the LPS are generally sufficient. These include simple pressurization of the patient's breathing circuit in the manner of performing a breathing circuit leak test as described later, or more complex positive-pressure testing of the low pressure system using specialized bulbs, manometers, or flowmeters.[5,32] Several mishaps have resulted from application of the wrong leak test to the wrong machine.[231-234] It is therefore mandatory that the appropriate low-pressure leak test be performed each day.

Again, the presence of an outlet check valve on some machines precludes manual positive-pressure testing of the LPS because the valve is held closed by downstream positive pressure (see Figs. 29-1 and 29-52). To eliminate confusion with this, the 1993 PAC's *Leak Check of the Machine Low Pressure System* prescribed the so-called *Universal Leak Test*. The universal leak test is a *negative-pressure* test that checks for leaks in the LPS regardless of whether or not an outlet check valve is present. The negative-pressure leak test is simple to perform and is highly sensitive, detecting leaks as small as 30 mL/minute. This simple test requires that the machine be turned off and that the flow control valves be fully closed to prevent any flow of gas into the low-pressure circuit. A specially configured suction bulb, which can either be constructed or obtained from the manufacturer, is then attached to the common gas outlet by tubing and a 15-mm adapter (Fig. 29-53; see also Fig. 29-52). The bulb is then squeezed repeatedly until it is fully collapsed. If the bulb does not stay collapsed for a specified period of time, then air is being sucked by the bulb into the machine through a leak that will allow gas to escape when the machine is pressurized. The same maneuver is carried out with each vaporizer opened in turn to check for associated leaks. The specified period of bulb collapse varies by reference, from 10 seconds in popular texts to 30 seconds in some workstation's user's manuals.[30,215,252-254] Although small leaks may require more than 10 seconds for bulb reinflation, it is likely that the collapsed bulb will be noted to be steadily expanding before that time.[32] The most important aspect about the universal negative-pressure leak test is that it eliminates any potential for error in which an operator might mistakenly apply a positive-pressure leak test to a machine with an outlet check valve. Suction bulbs for negative-pressure leak testing can be purchased or constructed as shown in Figure 29-54.

Many of the newer-generation anesthesia machines do not have an accessible common gas outlet; therefore, negative-pressure low-pressure system testing cannot be performed. On these machines, either manual positive-pressure testing of the LPS (and vaporizers) is performed during the preuse checkout, or LPS testing is accomplished as part of an automated checkout feature. Table 29-9 describes the LPS checkout requirement for several common anesthesia workstations. These machines test the integrity of the low-pressure system by means of an automated checkout. For machines that require manual LPS leak testing, the universal negative-pressure leak test can be applied unless the common gas outlet not readily accessible or the manufacturer specifies a positive-pressure test maneuver. A locally devolved PAC should indicate which method is required based on user's manual instructions. Regardless of what type of test is performed, the practitioner must understand that variable bypass anesthetic vaporizers and the Tec 6–style desflurane vaporizer will not be leak tested unless the concentration control dial is turned "on" during the leak test. If this step is not taken, large leaks that could potentially result in a patient's awareness, such as from a loose filler cap or cracked fill indicator, could go undetected. An exception to this rule applies to workstations that perform automated vaporizer leak testing on their unique vaporizers such as Maquet anesthesia machines and GE Healthcare workstations that use the ADU vaporizer.

Item 9: Test Scavenging System Function

Frequency: Daily

Responsible party: Provider or technician

> "A properly functioning scavenging system prevents room contamination by anesthetic gases. Proper function depends upon correct connections between the scavenging system and the anesthesia delivery system. These connections should be checked daily by a provider or technician. Depending upon the scavenging system design, proper function may also require that



Figure 29-53. The negative-pressure "universal" low-pressure system leak test. **A,** With the machine off and the flow control valves fully closed, a specially configured suction bulb is connected to the common (fresh) gas outlet. **B,** The bulb is pumped until it is fully collapsed. It is then observed to verify that it stays collapsed for more than 10 seconds, thus indicating that the low-pressure side of the machine is gas tight. Then, each vaporizer is opened in turn, and the maneuver is repeated to establish that no leak is associated with that vaporizer. **C,** The ventilator was intentionally tilted on its mount to cause a low-pressure system leak resulting in immediate inflation of the suction

the vacuum level is adequate which should also be confirmed daily. Some scavenging systems have mechanical positive and negative pressure relief valves. Positive and negative pressure relief is important to protect the patient circuit from pressure fluctuations related to the scavenging system. Proper checkout of the scavenging system should ensure that positive and negative pressure relief is functioning properly. Due to the complexity of checking for effective positive and negative pressure relief, and the variations in scavenging system design, a properly trained technician can facilitate this aspect of the checkout process."[240]

A test of the scavenging system begins by checking the proper assembly and integrity of each component and connection within system including the gas transfer tubes leading from the APL valve and the ventilator relief valve to the scavenging interface. In the case of many modern machines, a single transfer tube may lead from a compact breathing system to the scavenge interface. The integrity of the vacuum tubing leading from the wall outlet to the scavenging interface should also be checked. The different categories of scavenging systems, active versus passive and open versus closed, are discussed in a previous section.

A manufacturer's recommended test of the closed, passive scavenger system as seen in Figure 29-50, *A*, involves creating gas flow (pressure) within the breathing system by occluding the patient "Y-piece" (or short-circuiting the inspiratory and expiratory limbs of the breathing circuit with breathing hose), occluding the exhaust hose outlet on the scavenging interface, and ensuring that the flow of gas exits the system through the positive-pressure safety relief valve so excess pressure does not build up in the breathing circuit (e.g., <10 cm H_2O).

Checking a closed, active scavenger system as seen in Figure 29-50, *B*, involves two steps. A check of positive-pressure relief is conducted as described earlier for the passive, closed scavenger. Some manufacturers recommend that the suction needle valve be turned off for this step. A check of negative-pressure relief is conducted

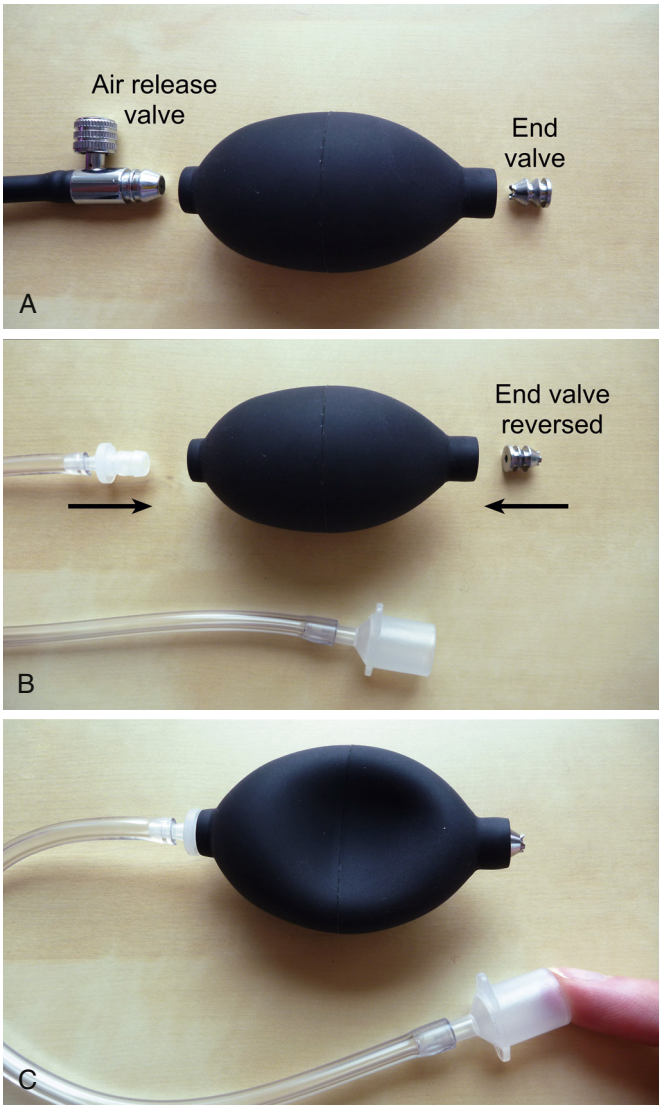


Figure 29-54. Constructing a negative-pressure system leak test suction bulb from a sphygmomanometer bulb. **A,** Remove the air release valve and discard. Remove the end valve. **B,** Reverse the end valve and reinsert it. Obtain a tight-fitting connector, some extra tubing, and a suitable endotracheal tube adapter. Insert the connector into the bulb. **C,** Squeeze the bulb, and occlude the adapter. The apparatus should remain collapsed for more than 60 seconds.

TABLE 29-9 LOW PRESSURE SYSTEM LEAK TEST TECHNIQUES OF VARIOUS ANESTHESIA WORKSTATIONS

Machine	Test Method
Dräger Narkomed 2B	Manual/positive pressure*†
Drä Narkomed M	Manual/positive pressure*†
Dräger Narkomed MRI	Manual/positive pressure*†
Drä Fabius MRI	Automated†
Drä Fabius Tiro	Automated†
Dräger Narkomed Julian	Automated†
Dräger Narkomed 6000 and 6400	Automated†
Dräger Fabius GS	Automated†
Dräger Apollo	Automated†
GE Aestiva/5	Manual/negative pressure†‡
GE Aisys	Automated
GE Aisys with ACGO	Manual/negative pressure†‡
GE S/5 Aespire	Manual/negative pressure†‡
GE ADU	Automated
GE Avance	Automated†
Maquet FLOW-i	Automated
Mindray Datascope AS 3000	Automated†
Mindray A5/A3	Manual/positive pressure†
Penlon Prima SP3	Manual/positive pressure†
Spacelabs Arkon	Automated†

Data from user's manuals from Datex-Ohmeda (Madison, Wis.), Dräger Medical (Telford, Pa.), GE Healthcare (Little Chalfont, United Kingdom), Maquet Critical Care (Solna, Sweden), Mindray (Mahwah, NJ), Penlon (Abingdon, United Kingdom), and Spacelabs Healthcare (Snoqualmie, Wash.).

ACGO, Auxiliary common gas outlet.

*Narkomed positive-pressure test using sphygmomanometer squeeze bulb, adapter, and inspiratory-expiratory port interconnection hose (Food and Drug Administration universal negative-pressure leak test can also be applied).

†Must manually open vaporizers to check them for leaks.

‡Alternatively, an "ISO 5358" or "BSI" flow test can be used, but an apparatus is required.



Figure 29-55. Testing the low–oxygen concentration alarm and calibrating the oxygen sensor. **A,** Removal of the oxygen sensor housing exposes the sensor to ambient air. **B,** When the oxygen concentration decreases to less than the alarm threshold value, which in this case is set at 25%, the visual and auditory low inspired oxygen concentration alarms should activate. **C,** After replacing the oxygen sensor, the oxygen flush button should be used to bring the fraction of inspired oxygen concentration (FiO_2) to at least 90%.

by setting scavenge interface suction to a routine setting, turning off all flow control valves on the anesthesia machine, and occluding inflow into the patient's breathing circuit at the patient's Y-piece (or short circuiting the inspiratory and expiratory limbs of the breathing circuit with breathing hose) and at the breathing bag mount. At this point, the breathing pressure gauge should indicate a negligible negative pressure (e.g., no lower than –1.0 cm H_2O). Generally speaking, the scavenging suction on active systems should be adjusted so the reservoir bag is never overinflated or underinflated, but it should remain slightly inflated during routine use. Because the volume of gas being passed into the scavenging system varies, it may be necessary to adjust the needle valve. Given the diversity of breathing systems, this check serves as another instance in which users must consider manufacturer-specified protocols when developing a local PAC.

Checking the function of an open, active system as seen in Figure 29-49 is relatively simple compared with checking a closed, active system. After ensuring that all gas transfer tubes and the suction lines are properly connected, the scavenger suction needle valve is adjusted to place the flowmeter bobbin between the indicator lines. A positive-pressure test and a negative-pressure test are then conducted as described earlier.

The 1993 PAC prescribed a simple procedure for checking the scavenging system that eliminated several steps described in manufacturer's user's manuals. It can be applied to both closed and open scavenging systems. For every machine, the evaluation of the scavenging system is a manual evolution. No automated checks are conducted.

Item 10: Calibrate, or Verify Calibration of, the Oxygen Monitor and Check the Low Oxygen Alarm

Frequency: Daily
Responsible Party: Provider or technician

> "Continuous monitoring of the inspired oxygen concentration is the last line of defense against delivering hypoxic gas concentrations to the patient. The oxygen monitor is essential for detecting adulteration of the oxygen supply. Most oxygen monitors require calibration once daily, although some are self-calibrating. For self-calibrating oxygen monitors, they should be verified to read 21% when sampling room air. This is a step that is easily completed by a trained technician. When more than one oxygen monitor is present, the primary sensor, which will be relied upon for oxygen monitoring should be checked. The low oxygen concentration alarm should also be checked at this time by setting the alarm above the measured oxygen concentration and confirming that an audible alarm signal is generated."[240]

The oxygen concentration analyzer is one of the most important monitors on the anesthesia workstation. It is the only monitor positioned to detect oxygen delivery problems downstream from the flow control valves.[215] All other oxygen related safety devices are located upstream from the flow control valves,[254] and it is the only monitor that evaluates the integrity of the low-pressure section of the gas supply system in an ongoing fashion. Other machine safety devices, such as fail-safe valves, oxygen pressure sensors, and proportioning systems are all upstream from the flow control valves. The only device that detects problems downstream from the flow control valves is the oxygen analyzer. Traditionally, most machines have used a galvanic cell oxygen sensor located near the patient's breathing circuit inspiratory valve (Fig. 29-55). These devices have a finite life span, which is inversely proportional to the amount of oxygen exposure.[255] They are also vulnerable to drift. Therefore, daily verification of calibration (and recalibration, if necessary) is recommended.

Galvanic oxygen sensors require that the sensor be removed from its mount during the recalibration procedure (see Fig. 29-55, *A*). At this time, the low-oxygen alarm should also be tested. The alarm should become activated if the low limit is set to more than 21% (see Fig. 29-55, *B*). A prudent default setting would be somewhere between 25% and 30%, unless oxygen concentrations lower than this value are used routinely. In any case, it is wise to keep it set to 21% or more. The steps involved in recalibrating the sensor to room air always involve removing the sensor from the breathing circuit. After calibration verification or recalibration, the breathing system is flushed with 100% oxygen. This should result in an oxygen concentration reading of more than 90% (see Fig. 29-55, *C*).

Some newer-generation anesthesia machines exclusively rely on side-stream gas analyzer to measure the inspired oxygen concentration. This is because the multigas analyzer on these workstations is an irremovable and permanent component. Thus, it fulfills the requirement

imposed on the manufacturer to provide inspired oxygen concentration monitoring. These monitors do not require daily calibration; however, the line should be disconnected from the circuit and sample room air to verify that it measures 21%.

Item 11: Verify Carbon Dioxide Absorbent Is Not Exhausted

Frequency: Before each use
Responsible Party: Provider or technician

> "Proper function of a circle anesthesia system relies on the absorbent to remove CO_2 from rebreathed gas. Exhausted absorbent as indicated by the characteristic color change should be replaced. It is possible for absorbent material to lose the ability to absorb CO_2 yet the characteristic color change may be absent or difficult to see. Some newer absorbents do change color when desiccated. Capnography should be utilized for every anesthetic and, when using a circle anesthesia system, rebreathing CO_2 as indicated by an inspired CO_2 concentration > 0 can also indicate exhausted absorbent."[240]

It is important for providers to know that absorbent color change is not as reliable as is the presence of *inspired* carbon dioxide on capnography in identifying exhausted absorbent. Absorbent "regeneration," indicator deactivation, inner canister channeling, and coloration of the absorbent canister wall are examples or circumstances that can mislead regarding the actual absorptive capacity.[197,216] Therefore, a normal-appearing absorbent may be significantly degraded in its ability to remove carbon dioxide, although some newer-generation absorbents are touted to maintain a permanent color change with exhaustion. It is no longer advised for providers to exercise (breathe in and breathe out of) the breathing circuit manually to assess the functionality of the absorbent during preuse checkout. Visual inspection and clinical suspicion of exhaustion or desiccation must suffice.

In addition to the exhaustion of carbon dioxide absorptive capacity, absorber desiccation is a potential hazard. Whereas colorimetric indicators identify the exhaustion of most absorbents, only few reportedly undergo color change with desiccation. Currently, no consistently reliable steps can be included in a PAC procedure to identify absorbent desiccation. However, certain situations increase the risk of absorbent desiccation, as described in the section on carbon dioxide absorbers.

Item 12: Breathing System Pressure and Leak Testing

Frequency: Before each use
Responsible parties: Provider and technician

> "The breathing system pressure and leak test should be performed with the circuit configuration to be used during anesthetic delivery. If any components of the circuit are changed after this test is completed, the test should be performed again. Although the anesthesia provider should perform this test before each use, anesthesia technicians who replace and assemble circuits can also perform this check and add redundancy to this important checkout procedure. Proper testing will demonstrate that pressure can be developed in the breathing system during both manual and mechanical ventilation and that pressure can be relieved during manual ventilation by opening the APL valve. Automated testing is often implemented in the newer anesthesia delivery systems to evaluate the system for leaks and also to determine the compliance of the breathing system. The compliance value determined during this testing will be used to automatically adjust the volume delivered by the ventilator to maintain a constant volume delivery to the patient. It is important that the circuit configuration that is to be used be in place during the test."[240]

It is not rare for either the disposable breathing circuit components or the fixed anesthesia machine components to leak. Therefore, a leak check of the breathing system is of paramount importance. Traditionally, this test has been performed manually after an inspection of the breathing circuit, removal of the gas sampling line, and capping of the gas sampling line port. With the machine set in the "bag" or the manual mode of ventilation, the gas flows are set to zero (or the minimal settings), the APL valve is closed, the patient's Y-piece is occluded, and breathing system is pressurized with the O_2 flush button to approximately 30 cm H_2O (Fig. 29-56). The circuit passes the leak test if it holds this pressure for at least 10 seconds. Some manufacturers may specify a low oxygen flow rate during the test.[256] A decrease in pressure during the test should prompt a check of all plug-in, push-fit, and screw connectors, the seal of the absorber canister, and a careful inspection of the disposable tubing. One of the most common locations of a circuit leak is at the absorber canister, and it is particularly important for the anesthesia provider to apply this check rigorously immediately after the absorbent has been changed.

On many modern anesthesia machines, breathing circuit leak testing is an automated feature, although manual steps are still required for test preparation. Circuit compliance is often also automatically assessed on some machines during this phase to guide ventilator tidal volume delivery. Therefore, the test should be performed with the circuit that is going to be used.

The APL valve can also assessed at this time by opening it widely after the pressure test and ensuring that the breathing circuit pressure decreases rapidly to zero. A prompt pressure drop should occur regardless of APL valve design. The ability of the pressure-limiting type APL valve to maintain stable circuit pressure can be easily assessed, if required, by setting the APL valve to 30 cm H_2O, occluding the patient's Y-piece in a manual mode of ventilation, increasing gas flow to approximately 5 L/minute, and ensuring the circuit pressure, once stable, remains within a range close to that set on the APL valve. This step may be specified in some user's manuals, whereas it is altogether absent in others.[257]

Item 13: Verify That Gas Flows Properly Through the Breathing Circuit During Both Inspiration and Exhalation

Frequency: Before each use
Responsible parties: Provider and technician

> "Pressure and leak testing does not identify all obstructions in the breathing circuit or confirm proper function

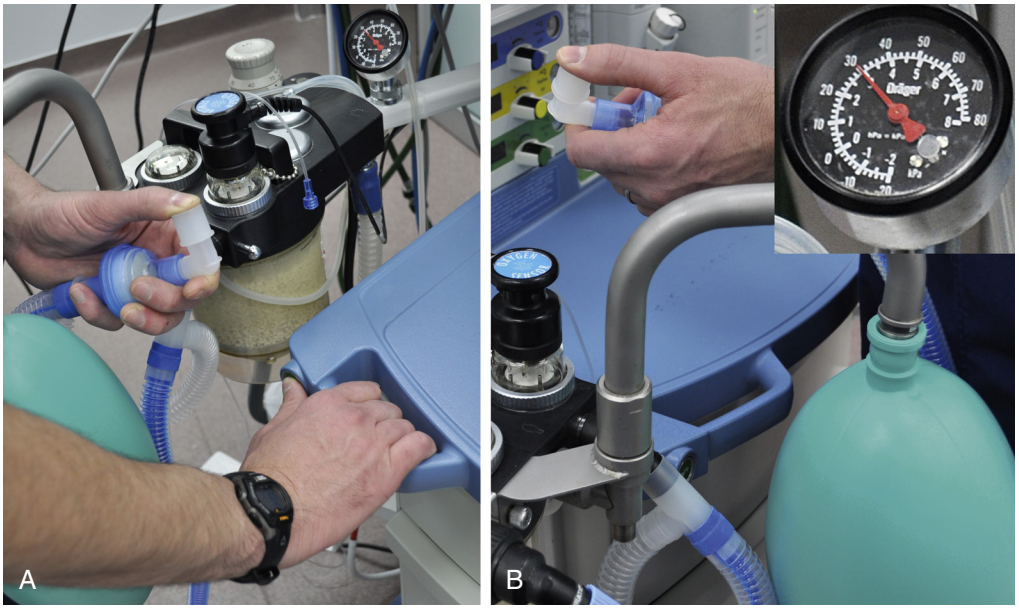


Figure 29-56. Manual breathing system pressure and leak testing. Breathing system pressure and leak testing should be performed with the circuit configuration that will be used during anesthetic delivery. **A,** The patient Y-piece or elbow is occluded, and the oxygen flush button is used to pressurize the breathing circuit to approximately 30 cm H_2O. **B,** The circuit should hold pressure at this level for at least 10 seconds. It is important to ensure that the gas flows are set to zero (or their minimal values), the gas sample line is removed, and its circuit port is occluded.

> of the inspiratory and expiratory unidirectional valves. A test lung or second reservoir bag can be used to confirm that flow through the circuit is unimpeded. Complete testing includes both manual and mechanical ventilation. The presence of the unidirectional valves can be assessed visually during the PAC. Proper function of these valves cannot be visually assessed since subtle valve incompetence may not be detected. Checkout procedures to identify valve incompetence which may not be visually obvious can be implemented but are typically too complex for daily testing. A trained technician can perform regular valve competence tests. Capnography should be used during every anesthetic and the presence of CO_2 in the inspired gases can help to detect an incompetent valve."[240]

The original 1986 FDA checklist recommended that the person checking the anesthesia machine inhale and exhale into the patient connector while observing the unidirectional valves for free gas flow in the correct direction and no flow in the opposite direction. Although it is controversial for the anesthesia provider to breathe in and out of the machine and through the next patient's breathing circuit, it is still important that the circuit be exercised to ensure that unidirectional flow is present and unimpeded. This test of circuit flow easily accomplished by placing a "test lung" or an extra breathing bag at the patient's elbow. In the "bag" or a manual mode of ventilation, the operator ventilates the artificial "lung" with the breathing bag, then actively "exhales" (squeezes) the test lung back to the breathing bag in a to-and-fro motion (Fig. 29-57). This is the so-called *flow test*. The inspiratory valve should open and the expiratory valve should close during inspiration, and vice versa for exhalation. A major malfunction of a unidirectional can be visually assessed, although subtle valve leaks (reverse flow) may be apparent only by capnography during anesthesia or through formal machine evaluation. Obstruction to flow during the flow test manifests as a "tight" breathing bag on "inspiration," whereas expiratory limb obstructions cause impeded "exhalation." Some form of flow test should be conducted because leak testing does not reliably identify circuit obstruction or unidirectional valve malfunction. Undetected circuit obstructions are particularly ominous and can manifest dramatically and sometimes immediately following induction.[147,148,150]

It cannot be stated definitively that all automated machine checks routinely assess for unimpeded circuit flow. Although most user's manuals for machines that perform automated aspects of the preuse checkout describe a leak test function, few specifically describe a flow test or an assessment of unidirectional valve function. In fact, some modern machines, which incorporate automated checkout steps, including a leak test, recommend a manual assessment of the inspiratory and expiratory valves.[257]

Item 14: Document Completion of Checkout Procedures

Responsible parties: Provider and technician

> "Each individual responsible for checkout procedures should document completion of these procedures. Documentation gives credit for completing the job and can be helpful if an adverse event should occur. Some automated checkout systems maintain an audit trail of completed checkout procedures that are dated and timed."[240]

Documentation of completion of the anesthetic checkout procedure by *providers* should occur within the anesthetic record. Currently, no guidance is available regarding where anesthesia or biomedical technician documentation of checkout procedures should occur. However, it would be prudent to maintain a detailed departmental log as a quality assurance tool.

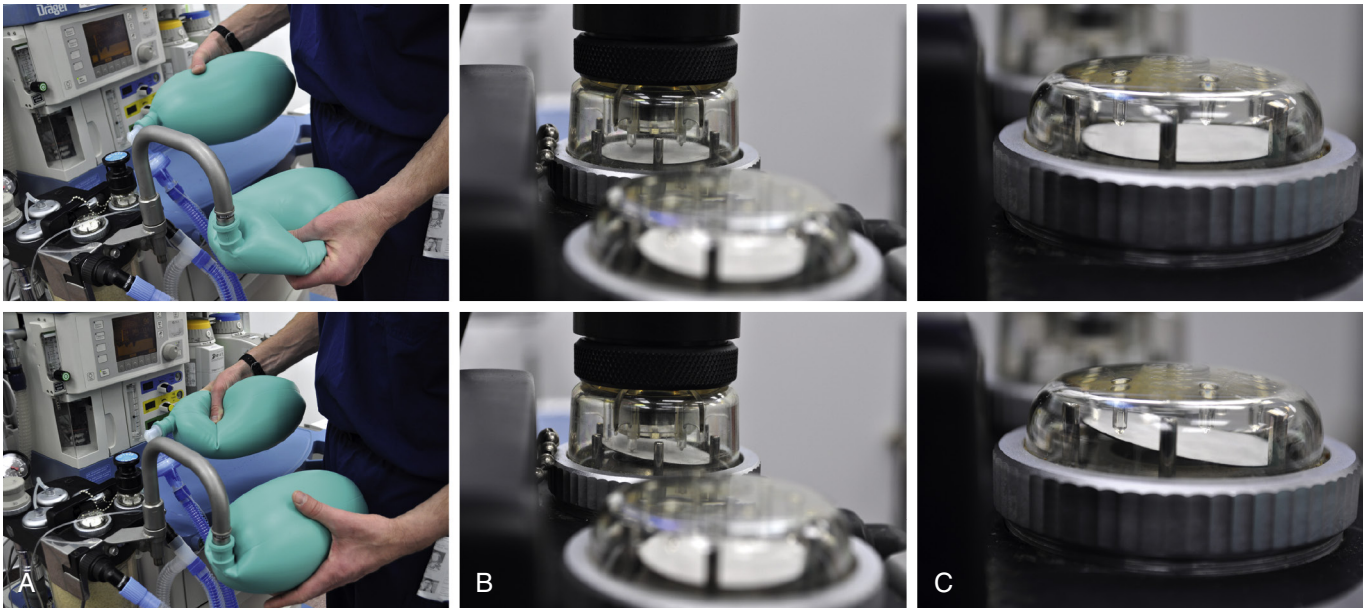


Figure 29-57. A to **C,** Verification that gas flows properly through the breathing circuit during both inspiration and exhalation with the to-and-fro "flow test." **Top row,** A test lung or second reservoir bag can is placed on the patient elbow piece. A squeeze of the breathing bag should cause flow through inspiratory limb, open the inspiratory valve, fill the test lung, and hold the expiratory valve closed. **Bottom row,** A reciprocal squeeze of the test lung should cause flow through expiratory limb, open the expiratory valve, fill the breathing bag, and hold the inspiratory valve closed. Circuit flow during the test should be smooth and unimpeded.

Item 15: Confirm Ventilator Settings and Evaluate Readiness to Deliver Anesthesia Care (Anesthesia Time Out)

Frequency: Immediately before initiating the anesthetic regimen

Responsible parties: Provider

> "This step is intended to avoid errors due to production pressure or other sources of haste. The goal is to confirm that appropriate checks have been completed and that essential equipment is indeed available. The concept is analogous to the "time out" used to confirm patient identity and surgical site prior to incision. Improper ventilator settings can be harmful especially if a small patient is following a much larger patient or vice versa. Pressure limit settings (when available) should be used to prevent excessive volume delivery from improper ventilator settings. Items to check: Monitors functional? Capnogram present? Oxygen saturation by pulse oximetry measured? Flowmeter and ventilator settings proper? Manual/ventilator switch set to manual? Vaporizer(s) adequately filled?"[240]

This last step serves as a recommended final preinduction check list of the machine and other important items including the application of essential monitors. It is a "pretakeoff" checklist for anesthesia providers. Some providers rely on final check mnemonic devices such as the MS MAIDS checklist (Box 29-2). Regardless of the specific steps, a final checklist that verifies the presence and function of key safety items is just as important in anesthesia as it is in aviation.

BOX 29-2 *The MS MAIDS Checklist**

- ❑ **Machine:** The machine checkout is complete; the vaporizers are filled, closed, and set to "0"; all gas flows knobs are set to zero flow; the ventilator and pressure settings are appropriate for the upcoming patient, with the machine in manual/spontaneous breathing mode, and the adjustable pressure-limiting valve is open.
- ❑ **Suction:** Patient suction is adequate to clear the airway.
- ❑ **Monitors:** All required standard monitors are present and ready to go.
- ❑ **Airway:** Primary airway equipment and appropriate backup equipment are ready to go.
- ❑ **IV:** Intravenous lines, fluids, and associated equipment are ready to go.
- ❑ **Drugs:** All necessary medications are available and are properly labeled.
- ❑ **Special:** Any special or unique items (i.e., additional monitors) required for the case are available and ready.

*An example of an "Anesthesia Time Out," which ensures that all appropriate checks have been completed, all essential equipment is available, and the machine is properly configured for the next patient.

Additional Comments Pertaining to the ASA's Pre-Anesthesia Checkout Procedure Recommendations (2008)

Although the 2008 PAC procedures are comprehensive, several steps that were part of the 1986 or 1993 recommendation did not appear in the current guideline; yet they are sometimes found within machine user's manuals. The use of these steps should be based on local needs or requirements because the 2008 recommendations are not restrictive or intended to be limiting. Some of these items are mentioned earlier in this section:

1. Disconnecting the central oxygen supply line to assess the low–oxygen supply pressure alarm and to purge the tank pressure gauges to zero
2. Inspecting the gas supply hoses for cracks or wear
3. Testing the flowmeters for smooth operation
4. Testing the proportioning system by attempting to create a hypoxic oxygen–nitrous oxide mixture

AUTOMATED ANESTHESIA MACHINE CHECKOUT PROCEDURES

Important points to consider regarding automated PAC features or "self-tests" are that (1) they differ between manufacturers and models, (2) it is sometimes difficult to determine precisely which segments or components are actually being checked by reading the user's manual, and (3) *no* machine automatically checks all the items on an effective PAC. At least some manual steps are required. Investigators have suggested that many providers do not understand exactly what is being checked by automated checks, or they make false assumptions regarding their respective machine's automated checkout procedure. It is easy to understand why the authors of the ASA's 2008 *Recommendations for Pre-Anesthesia Checkout Procedures* warned about an overreliance on the automated machine checkout. For example, one manufacturer's self-test screen reports a "leakage" amount, but the display or manual does not specify which section is responsible (e.g., the breathing circuit or the LPS). The operator must make an assumption that the low-pressure system is also being tested for leaks, and the manual does not state that any vaporizer should be turned "on" during leak testing. Finally, it is not clear in this unspecified manual whether the circuit is assessed for proper unidirectional flow or obstruction. When developing a local PAC procedure, providers should gain familiarity with their machine's automated checkout procedure through the user's manual. Once they are clear about the actual scope of the automated test, an effective departmental PAC checklist can be created. If an important item is not actually part of the described self-check or is not suggested in the user's manual, it should not be assumed that it is not important. Not requiring that conventional vaporizers be opened during a leak test of the low-pressure system is such an example.

MACHINE-IMBEDDED PREANESTHESIA MACHINE CHECKOUT CHECKLISTS

Some anesthesia machines have embedded PAC checklists, which are displayed during machine checkout. Like their paper counterparts, they help guide users through manual and self-test functions. If an embedded checklist provides a complete solution for a respective department, then it can be used exclusively. However, local requirements may exceed or depart, to some degree, from the workstation embedded checklist. In these cases, the use of the embedded checklist (or a modification thereof) can become a line item within the local PAC checklist.

DEVELOPING A LOCAL PREANESTHESIA MACHINE CHECKOUT CHECKLIST

The goal of a PAC is to evaluate and configure the anesthesia workstation properly so it performs its functions properly and safely. Similar to a pretakeoff checkout of an aircraft, it is a systematic task list with numerous critical steps. Therefore, it is the perfect situation in which to use a checklist. The goals of the PAC checklist are to guide the operator through an effective PAC and to promote compliance through ease of use. A checklist is a visual memory aid used to help overcome the limitations of short-term human memory, thus ensuring that particular series of specified actions or procedures are accomplished.[258] A PAC checklist can also serve as a quality control tool by codifying important items onto an organized list used by all providers.[258]

The essential items required for local PAC checklist development are the 2008 *Recommendations for Pre-Anesthesia Checkout Procedures,* the respective workstation user's manual, and an anesthesia machine reference text such as this book. PACs found in manufacturer's user's manuals tend to be several pages long and may contain items not specified in professional society recommendations, such as the ASA's guideline. Local PAC developers will quickly recognize the competing objectives of completeness and brevity during the design process. An excessively long checklist will probably not be routinely completed properly, and an underinclusive PAC could miss key items. Alternatively, some manufacturers omit important steps in their PAC recommendations. Not opening the vaporizers during leak testing is such an example.

Box 29-3 contains several checklist design principles, including many based on aviation standards. A checklist such as the PAC is a series of read-and-do tasks, which are either action items ("open the O_2 cylinder") or verification items ("…verify that the tank pressure reads >1000 psig").[259-261] In aviation it would be referred to as a "do-list," and like an aircraft checklist, it should avoid elaboration or explanation.[259,258] The design of the checklist must support its function to the fullest extent possible. The checkout procedure should be ergonomically ordered to minimize redundant movements and save time by placing procedures in a rational sequence. This is a well-recognized factor in the design of aviation checklists.[261] An example of an anesthesia workstation preuse checkout based on aviation checklist principles is shown in Box 29-4. The ASA's *Recommendations for Pre-Anesthesia Checkout Procedures (2008)* recommends an "Anesthesia Time Out," to ensure that appropriate checks have been completed, all essential equipment is available, and the machine is properly configured for the next patient. In the example checklist in Box 29-4, the MS MAIDS mnemonic is used to complete this step, which is further described in Box 29-2.

Finally, the checklist should be as short as possible, yet be detailed enough so critical items are not omitted. From a human perspective and performance point of view, a shorter and less elaborate checklist will encourage use, but it may not be sufficiently detailed to provide adequate guidance to personnel less familiar with the workstation. Unlike pilots, anesthesia providers do not spend countless hours on equipment-focused training, and this is where the aviation-anesthesia analogy weakens. PAC developers will quickly recognize this dilemma and may choose to create a slightly more detailed version for trainees or new employees, in addition to a standard version for those more familiar with their respective workstations. Because a PAC should be confined to one page, a laminated card with the detailed, instructional version on one side and the succinct, true checklist on the other may be optimal.

BOX 29-3 *Preanesthesia Machine Checkout Checklist Design and Use Tips*

PAC Checklist Design

- ❑ The PAC checklist should be designed in a read-and-do or read-and-confirm format (i.e., Ambu bag…Present and functional")
- ❑ The flow pattern of the checklist should lend itself to efficiency and compliance. The items should be in a logical sequence, to minimize redundant movements.
- ❑ The checklist should be as short as possible, yet it should include all key checks.
- ❑ When applicable, responses to checklist challenges should be provided to verify the value or status of an item, rather than simply confirm task completion (e.g., "Verify O_2 tank pressure…Done" is not adequate; "O_2 tank pressure…>1000 psig" is good).
- ❑ The challenges and responses on the checklist should be consistent with the labeling and text on the switches, screens, and controls of the machine.
- ❑ The font and character size should be pleasing.
- ❑ The overuse of *italics*, **bold**, underline, and UPPER CASE WORDS should be avoided.
- ❑ Language should be familiar, accessible, and unambiguous.
- ❑ Excessive verbiage should be avoided.
- ❑ For long checklists, pauses between key steps should be identified, or the checklist should be divided graphically into logical task groups, as opposed to one long continuous series of tasks.
- ❑ The checklist should fit onto one page. A large type size is preferred for legibility, but a small type size may be needed to keep the number of checklist pages to a minimum.

PAC Checklist Testing

- ❑ Rigorous testing and validation of the checklist should be performed before its implementation.
- ❑ Multiple individuals of different skill levels and backgrounds (e.g., technician, resident, CRNA, physician faculty) should give the checklist a trial.
- ❑ The checklist should be designed by a trial-and-error approach, with revisions anticipated.

PAC Checklist Use

- ❑ The checklist should be evaluated and updated periodically on the basis of user feedback, workstation modifications, manufacturer safety alerts, or compelling literature.
- ❑ PAC checklist users should be made aware that the PAC procedure is very vulnerable to production pressure. The checklist should not be relegated to a second level of importance.
- ❑ The checklist should be kept in sight each time it is used. Its benefit will be defeated if it dangles from the side of the machine during the checkout.
- ❑ A "checklist culture" should be developed through sound checklist design, leadership, and promotion of a positive departmental attitude regarding the procedure.

Data from references 258 to 261.
CRNA, Certified registered nurse anesthetist; *PAC*, preanesthesia machine checkout.

BOX 29-4 *Example of a Departmental Preanesthesia Machine Checkout for Dräger Fabius*

Ambu Bag	Present and Functional
AC power	Connected
Machine power	On
Breathing circuit	Intact
Vaporizers	Secured and filled
CO_2 absorbent color	White >½ the canister
Pipeline hoses	Properly connected
O_2 tank pressure	≥1000 psig
Pipeline pressures	Dark green range
"Run System Test"	Pass
"Calibrate Flow Sensor" test	Complete
O_2 sensor calibration	Complete
Inspiratory low O_2 alarm check	Alarm sounds (set low FiO_2 alarm limit between 25% and 30%)
"Leak/Compl Test" with vaporizer @ 1%	Pass
Vaporizer status after test	"0" volume % (off)
Deactivation of "DES COMP" if appropriate	Checked
APL valve function at 30 cm	Circuit pressure stays between 26 and 35 cm H_2O
APL valve function when open wide	Circuit pressure drops to 0 cm H_2O
Hand ventilation of breathing circuit	Unobstructed flow, good unidirectional valve function
Mechanical ventilation of breathing circuit	Test lung ventilates
O_2 flush	Gas flows from elbow

BOX 29-4 *Example of a Departmental Preanesthesia Machine Checkout for Dräger Fabius—cont'd*

Scavenger connections	Connected
Scavenger vacuum	Bobbin between the Min and Max marks
Scavenger integrity	<10 cm H_2O circuit pressure with O_2 flush button
Flow control valve function	Adjustable through full range
Attempt to create hypoxic mixture	Inability to create hypoxic mixture
Flow control valve position check	"0.0" flow after testing (off)
Test of CO_2 sample line	Exhaled CO_2 displayed
ASA standard and required monitors	Present and functional
ANESTHESIA TIME OUT: MS MAIDS CHECKLIST	
❑ **M**achine	Machine ready, vaporizers off and filled, ventilators set
❑ **S**uction	Functional
❑ **M**onitors	Present and functional
❑ **A**irway	Primary and alternate equipment ready
❑ **I**V	Lines, fluids, equipment ready
❑ **D**rugs	Ready and properly labeled
❑ **S**pecial	Special or unique items ready
ANESTHESIA APPARATUS CHECKOUT BEFORE EACH PROCEDURE	
CO_2 absorbent color	White >½ the canister
"Leak/Compl Test" with vaporizer @ 1%	Pass
Hand ventilation of breathing circuit	Unobstructed flow, good unidirectional valve function
Vaporizer status	Vaporizers set to "0," filled, ports closed
Flowmeters	Dialed clockwise to "0.0" flow
MS MAIDS Checklist	Completed

APL, Adjustable pressure-limiting; *ASA*, American Society of Anesthesiologists; *CO_2*, carbon dioxide; *IV*, intravenous; *O_2*, oxygen.

Complete references available online at expertconsult.com

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Chapter 30

Intravenous Anesthetics

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Key Points

- The introduction of thiopental into clinical practice in 1934 marked the beginning of modern intravenous (IV) anesthesia. Today, IV anesthetics are used for induction and maintenance of anesthesia and for sedation in a wide variety of circumstances.
- The most commonly used IV anesthetic is propofol, an alkylphenol currently formulated in a lipid emulsion. Propofol provides rapid onset and offset with context-sensitive decrement times of approximately 10 minutes when infused for less than 3 hours and of less than 40 minutes when infused for up to 8 hours. Its mechanism of action is likely the enhancement of γ-aminobutyric acid (GABA)-induced chloride currents. Propofol causes a dose-dependent decrease in arterial blood pressure through a decrease in cardiac output and systemic vascular resistance and produces moderate respiratory depression. A unique action of propofol is its antiemetic effect, even at concentrations less than those producing sedation.
- Barbiturates were the most commonly used IV drugs administered to induce anesthesia before the introduction of propofol. Thiopental provides rapid onset and offset when used as a single dose, but it accumulates rapidly with repeated or prolonged administration and thus postpones recovery from anesthesia. Methohexital has a rapid onset and offset similar to those of propofol for procedures lasting less than 2 hours. The barbiturates are administered as sodium salts diluted in a water base at an alkaline pH. Similar to propofol, the barbiturates provide their hypnotic effects largely through action on the $GABA_A$ receptor. Barbiturates provide cerebral protection (see also Chapter 70), and they are, apart from induction of anesthesia, used primarily for this purpose. They cause a moderate dose-dependent decrease in arterial blood pressure (primarily as a result of peripheral vasodilation) and respiratory drive. The barbiturates are contraindicated in patients with porphyria.
- The benzodiazepines are used primarily for anxiolysis and amnesia or for conscious sedation. The water-soluble benzodiazepine midazolam is most frequently used intravenously because of its rapid onset and offset compared with those of other benzodiazepines (e.g., diazepam). The onset time of midazolam is slower than that of propofol and barbiturates, and its offset, especially with larger doses or a prolonged infusion, is considerably longer than that of propofol and may be prolonged in hepatic and renal failure. The benzodiazepines act through the GABA receptor. Flumazenil is a specific benzodiazepine antagonist. It can be used to reverse the effects of benzodiazepines but should be used with caution because the duration of its antagonizing effect often is shorter than the benzodiazepine effect it is supposed to antagonize. The benzodiazepines generally produce only a mild decrease in arterial blood pressure and mild to moderate respiratory depression. Remimazolam is the most recent benzodiazepine, with an ultrashort duration of action resulting from its rapid clearance by plasma esterases.
- Ketamine is a phencyclidine derivative that acts primarily, but not entirely, as an antagonist of the *N*-methyl-D-aspartate receptor. It produces a dissociative state of hypnosis and analgesia. It has been used for induction and maintenance of anesthesia. Ketamine is associated with significant adverse psychological effects from larger doses and has several other side effects. It is used now primarily for its analgesic properties. It has rapid onset and relatively rapid offset, even after an infusion of several hours. Its sympathomimetic effects preserve cardiac function. Ketamine has minimal effect on respiration and tends to preserve autonomic reflexes.

KEY POINTS—cont'd

- Etomidate is an imidazole derivative used primarily for induction of anesthesia, especially in older patients and in patients with cardiovascular compromise (see also Chapter 80). It has a rapid onset of effect and a rapid offset even after a continuous infusion. A dose used to induce anesthesia results in inhibition of adrenocortical synthesis and possible mortality in patients in the intensive care unit (ICU). The major advantage of etomidate is its minimal effect on the cardiovascular and respiratory systems.
- Dexmedetomidine is the most recently released IV anesthetic. It is a highly selective α_2-adrenergic agonist that produces sedation, sympatholysis, hypnosis, and analgesia. Dexmedetomidine is currently approved only for brief (<24 hours) postoperative sedation. Its use as an adjunct or sole hypnotic agent is rapidly emerging, most frequently in an ICU setting. It may be advantageous for its ability to prevent delirium. Dexmedetomidine is used as a sedative during invasive or radiologic procedures and as an adjunct in central or peripheral neural blockade. Its primary action is as an agonist on α_2 receptors in the locus coeruleus. It has minimal effect on respiration. Heart rate and cardiac output show a concentration-dependent decrease.
- Droperidol, a butyrophenone and major tranquilizer, was initially used to produce a state of neuroleptanesthesia. Its prolongation of the QT interval has resulted in its withdrawal in several countries and its limitation to the treatment of postoperative nausea and vomiting (PONV). It has a black box warning in the United States. Because the use of low-dose droperidol (<1.25 mg) for PONV has not been approved by the U.S. Food and Drug Administration, the black box warning does not relate to this use. Clinically significant prolongation of the QT interval by doses used for PONV (0.625 to 1.25 mg) has been challenged by several editorials, and this effect has not been substantiated by review of the reported cases or other literature. Low-dose droperidol remains an effective antiemetic therapy and is used as such in many European countries (see also Chapter 97).

Intravenous (IV) anesthesia can be traced back to 1656, when Percival Christopher Wren and Daniel Johann Major first experimented with IV administration using a goose quill and bladder to inject wine and ale into a dog's vein. In 1665, German naturalist and physician Sigismund Elsholz made the first attempt at IV anesthesia in humans and investigated the possibilities of IV injection with opiates. IV anesthesia further evolved when Fedoroff started using hedonal in St. Petersburg in 1905 and entered the era of modern anesthesia with the release of thiopental in 1936.[1] Since these beginnings, and in particular since the 1980s, the pharmacokinetics and pharmacodynamics of IV anesthetics and their interactions have been described in increasingly greater detail. This body of knowledge and the availability of increasingly shorter-acting drugs now allow the anesthesia provider to administer anesthesia not on the basis of the needs of the population but on the individual needs of the patient. Today's anesthesia provider is supported by modern IV drug administration techniques, such as target-controlled infusion, and central nervous system (CNS) monitoring devices to further optimize and individualize the application of IV anesthesia. This chapter describes the current status of the pharmacology of IV anesthetics and their place in modern anesthesia.

PROPOFOL

HISTORY

Since its introduction in the 1970s, propofol has become the most widely used IV hypnotic today. Building on work on the sedative properties of phenol derivatives in mice, propofol was developed in the United Kingdom by Imperial Chemical Industries as ICI 35868. The initial solution of propofol was released in 1977 in Cremophor EL.[2] It was withdrawn because of anaphylactic reactions and was replaced and reformulated as an emulsion of a soybean oil–propofol mixture in water and relaunched in 1986. Propofol is used for induction and maintenance of anesthesia and for sedation in and outside the operating room.

PHYSICOCHEMICAL CHARACTERISTICS

Propofol is one of a group of alkylphenols that were explored for their hypnotic properties in animals (Fig. 30-1).[3-5] The

alkylphenols are highly lipid soluble and are insoluble in an aqueous solution.[6] Numerous formulations of propofol are marketed today. The formulation most commonly used is that of 1% propofol, 10% soybean oil, and 1.2% purified egg phospholipid added as emulsifier, with 2.25% of glycerol as a tonicity-adjusting agent, and sodium hydroxide to change the pH. Following concerns regarding microbial growth in the emulsion, ethylenediaminetetraacetic acid (EDTA) was added for its bacteriostatic activities. Propofol has a pH of 7 and appears as a slightly viscous, milky white substance, a result of small lipid droplets in solution. In Europe, a 2% formulation and a formulation in which the emulsion contains a mixture of medium-chain and long-chain triglycerides also are available. All formulations commercially available are stable at room temperature, are not light sensitive, and may be diluted with 5% dextrose in water. Propofol concentrations may be measured both in whole blood and in the exhaled air.[7-10]

In December 2008, the U.S. Food and Drug Administration (FDA) approved fospropofol disodium (Lusedra), for monitored anesthesia care in adult patients undergoing diagnostic and therapeutic procedures. Fospropofol is a water-soluble prodrug of propofol that is metabolized by alkaline phosphatases in the liver to the active metabolite propofol. One millimole of propofol is generated for each millimole of fospropofol sodium administered. Approximately 1.86 mg of fospropofol sodium is the molar equivalent of 1 mg propofol. In April 2010, six studies on the pharmacokinetics and pharmacodynamics of fospropofol were retracted as a result of an analytic assay inaccuracy that was discovered after publication of these studies.[11,12] Since then, few data on the pharmacokinetics and pharmacodynamics of fospropofol have been published. Although fospropofol remains available for monitored anesthesia care, available data are scarce, and most pharmacokinetic and pharmacodynamic data that are available come from the United States, as described in one review.[13] In contrast to propofol, fospropofol is not associated with pain on injection, although mild to moderate perineal paresthesias and pruritus minutes after a bolus injection of fospropofol have been reported and may result from a phosphate metabolite.

PHARMACOKINETICS

Propofol is oxidized to 1,4-diisopropyl quinol in the liver. Propofol and 1,4-diisopropyl quinol are conjugated with glucuronic acid to propofol-1-glucuronide and quinol-1-glucuronide and quinol-4-glucuronide, which then may be excreted by the kidneys.[14,15] After a 2.5-hour anesthetic regimen with propofol, patients excrete propofol and propofol metabolites for more than 60 hours.[15] Less than 1% propofol is excreted unchanged in urine, and only 2% is excreted in feces. The metabolites of propofol are thought to be inactive. Because clearance of propofol (>1.5 L/minute) exceeds hepatic blood flow, extrahepatic metabolism or extrarenal elimination may occur. Extrahepatic metabolism has been confirmed during the anhepatic phase of patients receiving a transplanted liver with the determination of propofol metabolites after propofol administration in the absence of liver tissue. The most important extrahepatic site of propofol metabolism is the kidney.[16,17] Renal metabolism of propofol accounts for up to 30% of propofol clearance, and this explains the rapid clearance of propofol, which exceeds liver blood flow. The lungs also may play a role in extrahepatic propofol metabolism.[18,19] In sheep, the lungs are responsible for approximately 30% of the uptake and first-pass elimination after a bolus dose. In humans, a 20% to 30% decrease in propofol concentration measured across the lung exists with a higher concentration of the metabolite 2,6-diisopropyl 1,4-quinol on the arterial side of the circulation.

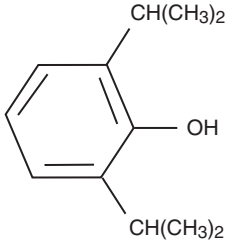


Figure 30-1. Structure of propofol, an alkylphenol derivative. *(From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

Propofol is generally known for its hemodynamic depressant effects and may reduce hepatic blood flow. As such, it may reduce the clearance of other drugs metabolized by the liver, in particular those with a high extraction ratio.[20] In addition, propofol is known as a CYP3A4 inhibitor.[21] In contrast to enzyme induction that may take several days or weeks to develop, competitive inhibition of cytochrome P450 system activity may occur almost instantaneously because of the competition of two drugs (e.g., propofol and midazolam) for the enzyme's active site. Short-term exposure to propofol at a blood concentration of 3 μg/mL already reduces CYP3A4 activity by approximately 37%.

Fospropofol is a water-soluble prodrug of propofol and is chemically described as phosphono-*O*-methyl-2, 6-diisopropylphenol, disodium salt ($C_{13}H_{19}O_5PNa_2$).[22-28] Fospropofol is metabolized by alkaline phosphatases to propofol, formaldehyde, and phosphate. Formaldehyde is further metabolized to formate, which is then eliminated, primarily by oxidation to carbon dioxide. More than 71% of fospropofol is recovered in the urine within 192 hours following a single 400-mg IV dose. Renal elimination is less than 0.02%, and total body clearance is on the order of 0.28 L/hour/kg. The terminal elimination half-life of fospropofol is 0.88 hours. The pharmacokinetics of fospropofol and liberated propofol is not affected by race, sex, or mild to moderate renal impairment. Furthermore, fospropofol pharmacokinetics is not affected by age or alkaline phosphatase concentration. So far, no pharmacokinetic interactions have been found between fospropofol and fentanyl, midazolam, morphine, or propofol. This is probably because fospropofol is not subject to cytochrome P450 enzyme-mediated metabolism.[13]

TABLE 30-1 PHARMACOKINETIC VARIABLES FOR COMMONLY USED INTRAVENOUS ANESTHETICS

Elimination	Elimination Half-Life (hr)	Clearance (mL/kg/min)	Vd_{SS} (L/kg)
Dexmedetomidine	2-3	10-30	2-3
Diazepam	20-50	0.2-0.5	0.7-1.7
Droperidol	1.7-2.2	14	2
Etomidate	2.9-5.3	18-25	2.5-4.5
Flumazenil	0.7-1.3	5-20	0.6-1.6
Ketamine	2.5-2.8	12-17	3.1
Lorazepam	11-22	0.8-1.8	0.8-1.3
Methohexital	2-6	10-15	1.5-3
Midazolam	1.7-2.6	6.4-11	1.1-1.7
Propofol	4-7	20-30	2-10
Thiopental	7-17	3-4	1.5-3

From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors: Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.*
Vd_{SS}, Apparent volume of distribution at steady state.

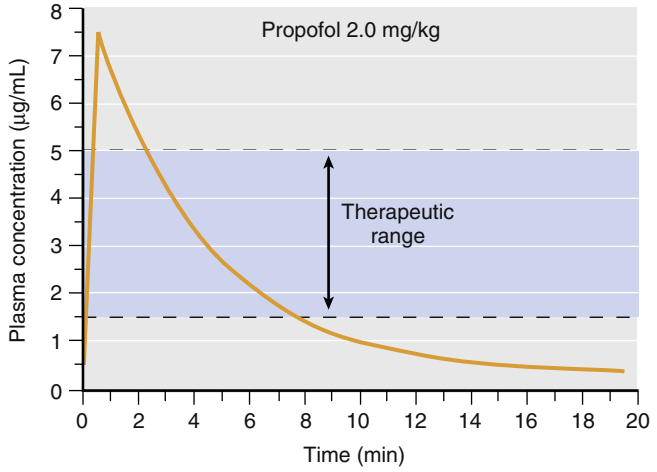


Figure 30-2. Simulated time course of whole blood levels of propofol after an induction dose of 2 mg/kg. Blood levels required for anesthesia during surgical procedures are 2 to 5 μg/mL, with awakening usually occurring at a blood level less than 1.5 μg/mL. *(From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

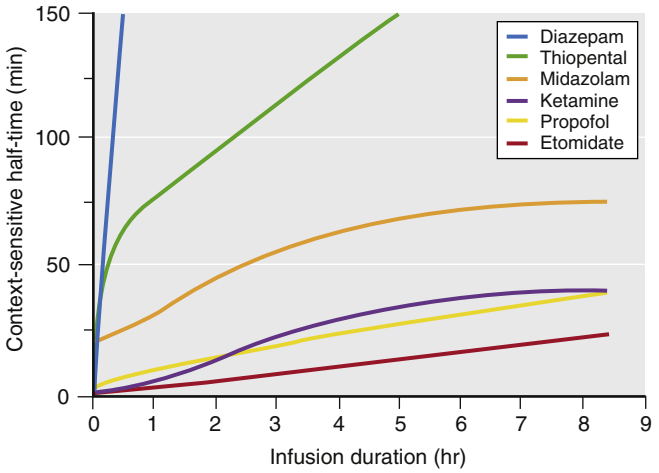


Figure 30-3. The context-sensitive half-times for commonly used intravenous anesthetic drugs. The context-sensitive half-time is the time for the plasma level of the drug to decrease 50% after cessation of infusion. The duration of infusion is plotted on the horizontal axis. The rapidity with which the drug level decreases is directly related to the time of infusion (i.e., the longer the drug is infused, the longer the half-time). Etomidate, propofol, and ketamine have significantly shorter half-times than do thiopental and diazepam, and this makes them more suitable for prolonged infusion. *(From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

The pharmacokinetics of propofol has been described by two-compartment and three-compartment models (Table 30-1). After a single bolus dose, whole blood propofol levels decrease rapidly as a result of redistribution and elimination (Fig. 30-2). The initial distribution half-life of propofol is 2 to 8 minutes. Studies in which the disposition of propofol is described by a three-compartment model give initial and slow distribution half-lives of 1 to 8 minutes and 30 to 70 minutes, respectively, and an elimination half-life of 4 to 23.5 hours.[29-34] The context-sensitive half-time for propofol for infusions of up to 8 hours is less than 40 minutes (Fig. 30-3).[35] Because the required decrease in concentration for awakening after anesthesia or sedation with propofol is generally less than 50%, recovery from propofol remains rapid even after prolonged infusion. The volume of distribution of the central compartment has been calculated at between 6 and 40 L, and the volume of distribution at steady state has been calculated as 150 to 700 L. The central compartment generally is smaller in older adults as a result of reduced cardiac output in these patients. Reduced cardiac output is associated with a higher peak plasma concentration, which is reflected by a smaller central compartment in the pharmacokinetic analysis. The clearance of propofol is extremely high, 1.5 to 2.2 L/minute. As discussed earlier, this exceeds hepatic blood flow, and extrahepatic metabolism has been shown.

The equilibrium constant for propofol based on suppression of the activity in the electroencephalogram (EEG) is approximately 0.3 minutes, and the half-life of equilibrium ($t_{½ke0}$) between plasma concentration and EEG effect is 2.5 minutes. The time to peak effect is 90 to 100 seconds. The onset of EEG effect with propofol seems to be independent of age. The onset of decreasing arterial blood pressure is much slower (double the time) and increases with age.[36] For EEG and blood pressure changes, older patients show a concentration-dependent increasing sensitivity (see also Chapter 80). The pharmacokinetics of propofol may be altered by various factors (e.g., gender, weight, preexisting disease, age, and concomitant medication).[37-39] Some studies suggest that propofol may exhibit nonlinear pharmacokinetics.[40] Because propofol has a high extraction ratio, this may impair its own clearance by decreasing cardiac output and thus hepatic blood flow.[41] As a result, a doubling of the dose of propofol may lead to a drug concentration that may be more than twice that initially experienced. In contrast, an increase

in cardiac output induced by sympathomimetic administration may lead to a decrease in the propofol plasma concentration. In a hemorrhagic shock model, propofol concentrations increased 20% until uncompensated shock occurred, when a rapid and marked increase in propofol concentrations was noted.[42]

In term and preterm neonates, variability of propofol clearance was accounted for largely by postmenstrual and postnatal age with very fast maturation of clearance in neonatal life. Dosage in these neonates must be calculated with extreme care.[43,44] Women have a larger volume of distribution and higher clearance rates, but the elimination half-life is similar for male and female patients. Older individuals have decreased clearance rates and a smaller central compartment volume.[45] Both changes may be the result of reduced cardiac output. Because of these conditions and the increased sensitivity to the effect of propofol in older adults, patients 80 years old or older generally need 50% of the propofol dose of patients 20 years old to target the same level of sedation or hypnosis.[29,38,45,46] Children have a relatively larger central compartment volume (50%) and a more rapid clearance (25%).[31,47] In children older than 3 years old, volumes and clearances should be weight adjusted (see also Chapter 93). Children younger than 3 years of age also show weight-proportional pharmacokinetic parameters, but with larger central compartment and systemic clearance values than in adults or older children. This finding explains the larger dose requirements in this age group.[48,49] Hepatic disease seems to result in larger steady-state and central compartment volumes; clearance is unchanged, but the elimination half-life is slightly prolonged, as is time to recovery.[50,51] In clinical practice, no significant dose adjustment is required in patients with hepatic disease. The extrahepatic clearance of propofol that may compensate for a reduced hepatic function may be responsible for this situation.

Midazolam affects the pharmacokinetics of propofol.[52] In the presence of a sedative midazolam concentration of 200 ng/mL, blood propofol concentrations become elevated by approximately 25%. Midazolam reduces propofol metabolic clearance from 1.94 to 1.61 L/minute, Cl_2 (rapid distribution clearance) from 2.86 to 1.52 L/minute, and Cl_3 (slow distribution clearance) from 0.95 to 0.73 L/minute. The high extraction ratio of propofol of 0.79 to 0.92 suggests that the metabolic clearance of propofol may not be affected by enzyme inhibition but may be susceptible to changes in hepatic perfusion. The changes in the pharmacokinetics of propofol induced by midazolam thus may be the result of the hemodynamic alterations induced by the coadministration of midazolam.

Propofol, in turn, affects midazolam pharmacokinetics.[20] In the presence of sedative concentrations of propofol, plasma midazolam concentrations increased by 27%. In the presence of propofol, midazolam is administered in a smaller central compartment from which midazolam is cleared and distributed less rapidly to peripheral tissues. For example, alfentanil has been shown to increase blood propofol concentrations through a reduction in the elimination and distribution clearance of propofol.[53] This finding is in line with other pharmacokinetic interactions between hypnotics and opioids when combined with propofol. Propofol has been shown to increase alfentanil concentrations by decreasing the elimination and the rapid and slow distribution clearances of alfentanil. Coadministration of propofol increased remifentanil concentrations through both a decrease in the central volume of distribution and distributional clearance of remifentanil by 41% and elimination clearance by 15%. Propofol kinetics is unaltered by renal disease.

As previously stated, pharmacokinetic data on the disposition of fospropofol are scarce. Phase I and phase II studies were conducted in Europe when a detection error became apparent that resulted in the retraction of six published manuscripts. Currently, no further pharmacokinetic studies have been initiated. The pharmacokinetics of fospropofol in humans remains largely unknown.

Fospropofol protein binding is extensive (98%).[13] This drug has a small volume of distribution of 0.3 L/kg and a total body clearance of 0.36 L/kg/hour with a terminal elimination half-life of 0.88 hours. After a bolus dose of 6 mg/kg of fospropofol, the parent drug peaks at 4 minutes and is rapidly metabolized to propofol with a peak plasma propofol concentration at 12 minutes after administration of fospropofol. With this fospropofol dose, the maximum concentration of fospropofol was 78.7 μg/mL and the maximum concentration of propofol was 1.08 μg/mL. The total body clearance of fospropofol and of propofol was 0.36 and 3.2 L/kg/hour, respectively. The terminal half-lives were 0.88 and 1.13 hours, respectively.

PHARMACODYNAMICS

Effects on the Central Nervous System

The hypnotic action of propofol is mostly mediated by enhancing γ-aminobutyric acid (GABA)-induced chloride current through its binding to the β subunit of the $GABA_A$ receptor. Sites on the β_1, β_2, and β_3 subunits of the transmembrane domains are crucial for the hypnotic action of propofol.[54,55] The α subunit and γ_2 subunit subtypes also seem to contribute to modulating the effects of propofol on the GABA receptor. The effects of propofol have been described as indirect and direct. Propofol exhibits an indirect effect by potentiation of the ion channel activation by GABA, thereby shifting the concentration-response relationship to the left. At higher propofol concentrations, propofol is also thought to activate $GABA_A$ receptor channels directly.[56-58]

The exact mechanism and location of changes that are associated with the change from consciousness to the unconscious state are not yet fully understood. Some experts suggest that proper functioning of the brainstem-thalamocortical arousal circuits is critical, whereas other investigators state that consciousness is more related to frontoparietal association cortex activity. Through its action on $GABA_A$ receptors in the hippocampus, propofol inhibits acetylcholine release in the hippocampus and prefrontal cortex.[59] The α_2-adrenoreceptor system also seems to play an indirect role in the sedative effects of propofol.[60] Resting-state functional magnetic resonance imaging (fMRI) studies suggest that propofol's

action may be related to a CNS that reduces its discriminable state and switches into stereotypic patterns of firing under propofol sedation.[61] The so-called default mode network (DMN), including the posterior cingulate, medial frontal, and bilateral parietal cortices, is the anatomic substrate in which these stereotypical patterns become visible. By using positron emission tomography, propofol hypnosis has been found to be related to reduced activity in the thalamic and precuneus regions. These regions likely play an important role in propofol-induced unconsciousness.[62]

Propofol results also in widespread inhibition of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor through modulation of sodium channel gating, an action that also may contribute to the drug's CNS effects.[63,64] Propofol has a direct depressant effect on neurons of the spinal cord. In acutely dissociated spinal dorsal horn neurons, propofol acts on $GABA_A$ and glycine receptors.[65] The sense of well-being in patients with propofol is related to the increase in dopamine concentrations in the nucleus accumbens (a phenomenon noted with drugs of abuse and pleasure-seeking behavior).[66] Propofol's antiemetic action may be explained by the decrease in serotonin levels it produces in the area postrema, probably through its action on GABA receptors.[67]

The onset of hypnosis after a dose of 2.5 mg/kg is rapid (one arm–brain circulation), with a peak effect seen at 90 to 100 seconds. The median effective dose (ED_{50}) of propofol for loss of consciousness is 1 to 1.5 mg/kg after a bolus. The duration of hypnosis is dose dependent and is 5 to 10 minutes after 2 to 2.5 mg/kg. Age markedly affects the induction dose, which is highest at younger than 2 years (95% effective dose [ED_{95}], 2.88 mg/kg) and decreases with increasing age. This is a direct result of the altered pharmacokinetics in children and in older adults. Children exhibit a relatively larger central compartment and thus need a higher dose to ensure a similar blood drug concentration.[68-70] In addition, the rapid clearance of propofol in children requires a larger maintenance dose. Increasing age decreases the propofol concentration required for loss of consciousness.

At subhypnotic doses, propofol provides sedation and amnesia. Propofol infusions of at least 2 mg/kg/hour were necessary to provide amnesia in unstimulated volunteers. Awareness during surgical procedures at higher infusion rates has been reported. During surgical procedures, extremely high infusion rates producing blood propofol concentrations in excess of 10 μg/mL may be necessary to prevent awareness if propofol is used as the sole anesthetic. Propofol also tends to produce a general state of well-being. Hallucinations, sexual fantasies, and opisthotonos occur after propofol administration.

The effect of propofol on the EEG, as assessed after 2.5 mg/kg followed by an infusion, shows an initial increase in alpha rhythm followed by a shift to gamma and theta frequency. Rapid infusion rates produce burst suppression at blood propofol concentrations higher than 8 μg/mL. Propofol causes a concentration-dependent decrease in the bispectral index (BIS), with 50% and 95% of patients unable to respond to a verbal command at a BIS of 63 and 51, respectively. The propofol concentration at which 50% of volunteers failed to respond to verbal command was 2.35 μg/mL. Lack of recall was observed in 95% of patients at a BIS value of 77.[71] Propofol effect-site concentrations provide similar correlation with decreases in the spectral entropy variable derived from the EEG as with BIS, as well as a similar ability to titrate propofol anesthetic effect. The effect of propofol on epileptogenic EEG activity is controversial. Propofol may suppress seizure activity through GABA agonism, inhibition of NMDA receptors (NMDARs), and modulation of slow calcium ion channels. However, the same GABA agonism and glycine antagonism may also induce clinical seizures and EEG epileptiform changes,[72] especially during induction of and emergence from anesthesia. Propofol has a dose-dependent anticonvulsant action. Propofol has even been used to treat epileptic seizures. However, propofol can cause grand mal seizures and has been used for cortical mapping of epileptogenic foci.[73]

Unfortunately, propofol can be addictive. An important issue in the potential of abuse is the development of tolerance. Tolerance to a drug creates circumstances for abuse. Propofol is used as a sedative in the intensive care unit (ICU); in 20% to 40% of patients, the propofol dosage regimen must be repeatedly adjusted upward to maintain the same effect.[74] Data on propofol abuse in the general public are unknown, but the incidence of abuse is likely to be low compared with other substances. For health care workers, propofol is easy to access, and case reports of lethal self-administration do occur. Some investigators have suggested a greater incidence of propofol abuse by health care providers,[75,76] and these investigators support stricter propofol regulation. In contrast to propofol, fospropofol was classified in 2009 by the U.S. Drug Enforcement Administration (DEA) as a controlled substance.

Propofol decreases intracranial pressure (ICP) in patients with either normal or increased ICP (see also Chapter 70). The decrease in ICP (30% to 50%) is associated with significant decreases in cerebral perfusion pressure (CPP).[77] The use of propofol in head-injured patients should be restricted to doses providing mild to moderate sedation (i.e., blood concentration of 2 μg/mL, infusion of 1.5-4.5 mg/kg/hr).[78] Anesthetics are neuroprotective because they reduce the metabolic oxygen use that is beneficial for the balance between energy supply and demand and because they increase the tolerance to hypoxia by the neuronal tissue. Propofol has no direct preconditioning effect but may attenuate glutamate-mediated excitotoxicity.[79-81] Propofol acutely reduces intraocular pressure by 30% to 40%. Compared with thiopental, propofol produces a larger decrease in intraocular pressure and is more effective in preventing an increase in intraocular pressure secondary to succinylcholine and endotracheal intubation. Normal cerebral reactivity to carbon dioxide and autoregulation are maintained during a propofol infusion.

The neuroprotective effects of propofol remain controversial.[82] In an incomplete ischemia model in rats, propofol administered to burst suppression resulted in significantly better neurologic outcome and less brain tissue injury compared with fentanyl. Propofol administered at sedative concentrations started either

TABLE 30-2 **INFUSION SCHEMES* OF PROPOFOL AND THE OPIOIDS COMBINED TO ENSURE ADEQUATE ANESTHESIA AND OPTIMAL RAPID RECOVERY FROM ABDOMINAL SURGERY**

Opioid	Alfentanil EC_{50}-EC_{95} (90-130 ng/mL)	Fentanyl EC_{50}-EC_{95} (1.1-1.6 ng/mL)	Sufentanil EC_{50}-EC_{95} (0.14-0.20 ng/mL)	Remifentanil EC_{50}-EC_{95} (4.7-8.0 ng/mL)
Bolus	25-35 μg/kg in 30 sec	3 μg/kg in 30 sec	0.15-0.25 μg/kg in 30 sec	1.5-2 μg/kg in 30 sec
Infusion 1	50-75 μg/kg/hr for 30 min	1.5-2.5 μg/kg/hr for 30 min	0.15-0.22 μg/kg thereafter	13-22 μg/kg/hr for 20 min
Infusion 2	30-42.5 μg/kg/hr thereafter	1.3-2 μg/kg/hr up to 150 min		11.5-19 μg/kg/hr thereafter
Infusion 3		0.7-1.4 μg/kg/hr thereafter		
Propofol	**Propofol EC_{50}-EC_{95} (3.2-4.4 μg/mL)**	**Propofol EC_{50}-EC_{95} (3.4-5.4 μg/mL)**	**Propofol EC_{50}-EC_{95} (3.3-4.5 μg/mL)**	**Propofol EC_{50}-EC_{95} (2.5-2.8 μg/mL)**
Bolus	2.0-2.8 mg/kg in 30 sec	2.0-3.0 mg/kg in 30 sec	2.0-2.8 mg/kg in 30 sec	1.5 mg/kg in 30 sec
Infusion 1	9-12 mg/kg/hr for 40 min	9-15 mg/kg/hr for 40 min	9-12 mg/kg/hr for 40 min	7-8 mg/kg/hr for 40 min
Infusion 2	7-10 mg/kg/hr for 150 min	7-12 mg/kg/hr for 150 min	7-10 mg/kg/hr for 150 min	6-6.5 mg/kg/hr for 150 min
Infusion 3	6.5-8 mg/kg/hr thereafter	6.5-11 mg/kg/hr thereafter	6.5-8 mg/kg/hr thereafter	5-6 mg/kg/hr thereafter

From Vuyk J, Mertens MJ, Olofsen E, et al: Propofol anesthesia and rational opioid selection: determination of optimal EC_{50}-EC_{95} propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness, Anesthesiology *87:1549-1562, 1997, with permission from Lippincott Williams & Wilkins, copyright 1997.*

EC_{50}, Half-maximal effective concentration; EC_{95}, 95% maximal effective concentration.

*These optimal infusion schemes have been derived from data in female patients undergoing lower abdominal surgical procedures. These should be used as guidelines and be adjusted to the individual needs of the patient.

immediately after or at 1 hour after an ischemic insult significantly reduced infarct size compared with awake controls infused with intralipid.[83,84] Subanesthetic doses of propofol also induced neuroapoptosis in the infant mouse brain.[85] In addition, anesthetic doses of propofol in rats induced complex changes accompanied by cell death in the cortex and thalamus of the developing rat brain.[86] The neuronal protective effect of propofol may result from the attenuation of changes in ATP, calcium, sodium, and potassium caused by hypoxic injury and its antioxidant action by inhibiting lipid peroxidation. Current evidence indicates that propofol can protect neurons against ischemic injury caused by excitotoxicity, but neuroprotection may be sustained only if the ischemic insult is relatively mild and is not sustained after a prolonged recovery period. Prolonged propofol sedation in children is associated with adverse neurologic sequelae.[87]

Many anesthetic-related drugs decrease the required dose or blood concentrations of propofol's pharmacologic action. The "required dose" is usually directly related to the required concentration for a given effect. The propofol Cp_{50} (blood concentration needed for 50% of subjects to not respond to a defined stimulus) for loss of response to verbal command in the absence of any other drug is 2.3 to 3.5 μg/ mL.[88-90] The propofol Cp_{50} to prevent movement on skin incision is 16 μg / mL; this is markedly reduced by increasing concentrations (i.e., doses) of fentanyl or alfentanil. The propofol Cp_{50} for skin incision when combined with benzodiazepine premedication (lorazepam, 1 to 2 mg) and 66% nitrous oxide is 2.5 μg/mL (venous).[91] This concentration is reduced to 1.7 μg/mL when morphine (0.15 mg/kg) rather than lorazepam is used for premedication. The concentration of propofol (when combined with 66% nitrous oxide) required during minor surgical procedures is 1.5 to 4.5 μg/mL, and the concentration for major operations is 2.5 to 6 μg/mL.[92] Awakening usually occurs at concentrations less than 1.6 μg/mL and orientation occurs at concentrations less than 1.2 μg/mL when the propofol concentration is decreasing. Not surprisingly, awakening is postponed in the presence of high blood concentrations of opioids. Optimal propofol blood concentrations have been defined when the drug is combined with several opioids, including remifentanil, alfentanil, sufentanil, and fentanyl, that ensure adequate anesthesia and the most rapid return to consciousness postoperatively (Table 30-2). In the presence of remifentanil, a relatively large-dose opioid anesthetic regimen is recommended, whereas with fentanyl, an accompanying large dose of propofol should be used to ensure rapid return to recovery postoperatively (Fig. 30-4). When equilibration between blood and effect site is allowed, awakening concentrations (2.2 μg/mL) are similar to concentrations associated with loss of verbal command.[93]

Effects on the Respiratory System

Apnea occurs after administration of an induction dose of propofol; the incidence and duration of apnea depend on dose, speed of injection, and concomitant premedication.[94] An induction dose of propofol results in a 25% to 30% incidence of apnea from the respiratory depressant effects of propofol and yet a normal partial pressure of carbon dioxide in the blood ($Paco_2$) at induction in the absence of surgical stimulation. Metabolic depression further prevents the $Paco_2$ to increase. However, the duration of apnea occurring with propofol may be prolonged to more than 30 seconds. The incidence of prolonged apnea (>30 seconds) is increased further by addition of an opiate, either as premedication or just before induction of anesthesia.[92,95] A maintenance infusion of propofol (100 μg/kg/minute) results in a 40% decrease in tidal volume and a 20% increase in respiratory frequency, with

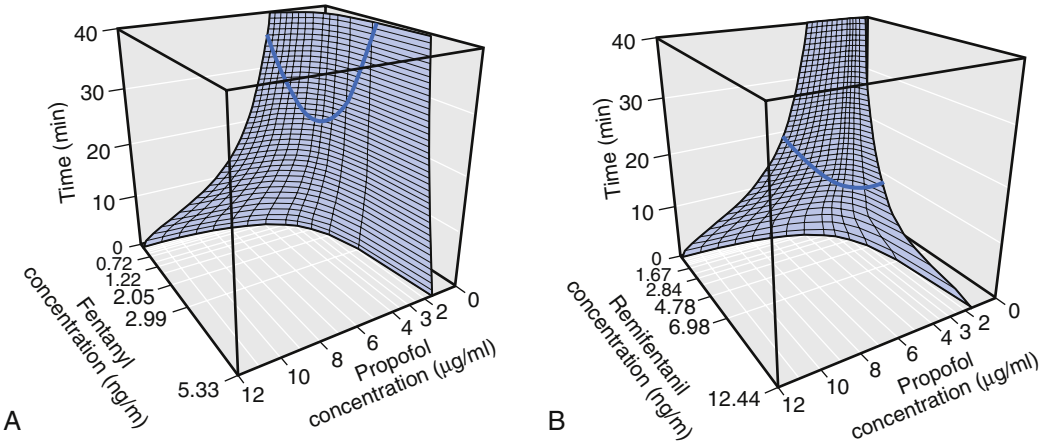


Figure 30-4. Computer simulation of effect-site propofol and fentanyl (**A**) or remifentanil (**B**) concentrations versus time during the first 40 minutes after termination of target-controlled infusions of propofol and fentanyl or remifentanil that had been maintained for 300 minutes at constant target blood or plasma concentration combinations associated with a 50% probability of no response to surgical stimuli. These concentration combinations are represented by the *curved line* on the bottom of the figure in the x-y plane. The decrease in concentrations following the intraoperative propofol-fentanyl and propofol-remifentanil combinations is represented by the curves running upward from the x-y plane. The *curved lines* parallel to the x-y plane represent consecutive 1-minute time intervals. The *bold blue curves* within the two figures represent the propofol-fentanyl-time and propofol-remifentanil-time relationships at which consciousness was regained in 50% of the patients. *(From Vuyk J, Mertens MJ, Olofsen E, et al: Propofol anesthesia and rational opioid selection: determination of optimal EC_{50}-EC_{95} propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness,* Anesthesiology *87:1549-1562, 1997.)*

an unpredictable change in minute ventilation. Doubling the infusion rate from 100 to 200 μg/kg/minute causes a further moderate decrease in tidal volume but no change in respiratory frequency.[96]

As with other hypnotic drugs, spontaneous ventilation is the result of the respiratory depressant effects of the hypnotic agents and the decrease in carbon dioxide production resulting from the metabolic depression versus the stimulatory effects of the increasing $Paco_2$ resulting from apnea and the level of nociception. Propofol (50 to 120 μg/kg/minute) also depresses the ventilatory response to hypoxia, presumably by a direct action on carotid body chemoreceptors.[97] Propofol induces bronchodilation in patients with chronic obstructive pulmonary disease. Propofol attenuates vagal (at low concentrations) and methacholine-induced (at high concentrations) bronchoconstriction, and it seems to have a direct action on muscarinic receptors. Propofol inhibits the receptor-coupled signal transduction pathway through inositol phosphate generation and inhibition of calcium mobilization. The preservative used with propofol is important because of its bronchodilator activity. Propofol with metabisulfite (compared with propofol without metabisulfite) does not inhibit vagal or methacholine-induced bronchoconstriction. Propofol potentiates hypoxic pulmonary vasoconstriction, an effect caused by inhibition of potassium–adenosine triphosphate (ATP)–mediated pulmonary vasodilatation. Propofol has an impact on the pulmonary pathophysiology of adult respiratory distress syndrome. In an animal model of septic endotoxemia, propofol (10 mg/kg/hour) significantly reduced free radical–mediated and cyclooxygenase-catalyzed lipid peroxidation. In addition, the partial pressure of arterial oxygen (Pao_2) and hemodynamics were maintained closer to baseline. These benefits of propofol have not yet been confirmed in humans.

Effects on the Cardiovascular System

The cardiovascular effects of propofol for induction and maintenance of anesthesia have been evaluated (Table 30-3).[98] The most prominent effect of propofol is a decrease in arterial blood pressure during induction of anesthesia. Independent of the presence of cardiovascular disease, an induction dose of 2 to 2.5 mg/kg produces a 25% to 40% reduction of systolic blood pressure. Similar changes are seen in mean and diastolic blood pressure. The decrease in arterial blood pressure is associated with a decrease in cardiac output and cardiac index (± 15%), stroke volume index (± 20%), and systemic vascular resistance (15% to 25%). Left ventricular stroke work index also is decreased (± 30%). When right ventricular function is considered specifically, propofol produces a marked reduction in the slope of the right ventricular end-systolic pressure-volume relationship.

In patients with valvular heart disease, pulmonary artery and pulmonary capillary wedge pressure also are reduced, a finding that implies the resultant decrease in pressure reflects a decrease in preload and afterload. Although the decrease in systemic pressure after an induction dose of propofol is caused by vasodilation, the direct myocardial depressant effects of propofol are more controversial. The decrease in cardiac output after propofol administration may result from its action on sympathetic drive to the heart. The hemodynamic response to propofol lags significantly behind that of the hypnotic effect. The effect-site equilibration half-life of propofol is on the order of 2 to 3 minutes for the hypnotic effect and approximately 7 minutes for the hemodynamic depressant effect.[36] This implies that hemodynamic depression increases the few minutes after a patient has lost consciousness from an induction of anesthesia.

High concentrations of propofol abolish the inotropic effect of α- but not β-adrenoreceptor stimulation, and

TABLE 30-3 **HEMODYNAMIC CHANGES % AFTER INDUCTION OF ANESTHESIA WITH NONBARBITURATE HYPNOTICS**

	Diazepam	Droperidol	Etomidat*	Ketamine	Lorazepam	Midazolam	Propofol
HR	–9 ± 13	Unchanged	–5 ± 10	0-59	Unchanged	–14 ± 12	–10 ± 10
MBP	0-19	0-10	0-17	0 ± 40	–7-20	–12-26	–10-40
SVR	–22 ± 13	–5-15	–10 ± 14	0 ± 33	–10-35	0-20	–15-25
PAP	0-10	Unchanged	–9 ± 8	+44 ± 47	—	Unchanged	0-10
PVR	0-19	Unchanged	–18 ± 6	0 ± 33	Unchanged	Unchanged	0-10
PAO	Unchanged	+25 ± 50	Unchanged	Unchanged	—	0-25	Unchanged
RAP	Unchanged	Unchanged	Unchanged	+15 ± 33	Unchanged	Unchanged	0-10
CI	Unchanged	Unchanged	–20 ± 14	0 ± 42	0 ± 16	0-25	–10-30
SV	0-8	0-10	0-20	0-21	Unchanged	0-18	–10-25
LVSWI	0-36	Unchanged	0-33	0 ± 27	—	–28-42	–10-20
dP/dt	Unchanged	—	0-18	Unchanged	—	0-12	Decreased

From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors: Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.*

CI, Cardiac index; *dP/dt,* first derivative of pressure measured over time; *HR,* heart rate; *LVSWI,* left ventricular stroke work index; *MBP,* mean blood pressure; *PAO,* pulmonary artery occluded pressure; *PAP,* pulmonary artery pressure; *PVR,* pulmonary vascular resistance; *RAP,* right atrial pressure; *SV,* stroke volume; *SVR,* systemic vascular resistance.

*The larger deviations are in patients with valvular disease.

enhance the lusitropic (relaxation) effect of β-adrenoreceptor stimulation. Clinically, the myocardial depressant effect and the vasodilation depend on the dose and on the plasma concentration.[99] Propofol is a vasodilator because it reduces sympathetic activity. The mechanism of this activity is a combination of a direct effect on intracellular smooth muscle calcium mobilization, inhibition of prostacyclin synthesis in endothelial cells, reduction in angiotensin II–elicited calcium entry,[100,101] activation of potassium ATP channels, and stimulation of nitric oxide. The stimulation of nitric oxide may be modulated by any intralipid rather than propofol itself.

Heart rate does not change significantly after an induction dose of propofol. Propofol either may reset or may inhibit the baroreflex, thus reducing the tachycardic response to hypotension. Propofol also decreases cardiac parasympathetic tone in a dose-dependent manner. The drug has a minimal direct effect on sinoatrial node function or on normal atrioventricular and accessory pathway conduction. Propofol attenuates the heart rate response to atropine in a dose-dependent manner. It also suppresses atrial (supraventricular) tachycardias and probably should be avoided during electrophysiologic studies. The peak plasma concentrations obtained after a bolus dose are substantially higher than the concentrations seen with a continuous infusion and may reach concentrations up to 80 to 100 μg/mL. Because the vasodilatory and myocardial depressant effects are concentration dependent, the decrease in arterial blood pressure from propofol during the infusion phase (maintenance of anesthesia) is much less than that seen after induction of anesthesia by an IV bolus administration of propofol. An infusion of propofol reduces myocardial blood flow and oxygen consumption. Thus, global myocardial oxygen supply-to-demand ratio is likely preserved.

The cardioprotective effect of propofol versus volatile anesthetics in patients who undergo cardiac surgical procedures on or off cardiopulmonary bypass is less debatable. In two large studies comparing propofol with sevoflurane in patients undergoing cardiac surgical procedures, postoperative troponin levels were lower and hemodynamic function was better in patients receiving sevoflurane. A study comparing desflurane with propofol in patients undergoing off-pump coronary artery bypass showed similar results. In contrast, administration of a large dose of propofol (120 μg/kg/minute) or a small dose of propofol (60 μg/kg/minute) during cardiopulmonary bypass, or titrating isoflurane throughout the operation, showed improved troponin levels and better hemodynamic function in the large-dose propofol group compared with the isoflurane or small-dose propofol group. This study suggests that cardioprotection with propofol is dose dependent.[102] Finally, combinations of propofol with inhaled anesthetics may offer an optimal preconditioning and postconditioning strategy in patients scheduled for coronary bypass surgery. Isoflurane preconditioning, when combined with propofol postconditioning, acts synergistically in attenuating postischemic myocardial reperfusion injury as determined by surrogate markers of myocardial injury and function.[103] Heart rate changes are variable when anesthesia is maintained with propofol. The extent of hypotension, the ability for the patient to compensate, and the use of any other concomitant drugs are likely the most important factors in determining what happens to the heart rate after propofol administration.

Other Effects

Propofol, similar to thiopental, does not enhance neuromuscular blockade produced by neuromuscular blocking drugs. Propofol produces no effect on the evoked electromyogram or twitch tension; however, good or acceptable tracheal intubating conditions after propofol alone have been reported. Propofol does not trigger malignant hyperthermia and is an appropriate choice in patients with this condition.[104-106] After a single dose or a prolonged infusion, propofol does not affect corticosteroid synthesis or alter the normal response to adrenocorticotropic hormone stimulation. Propofol in the emulsion formulation does not alter hepatic, hematologic, or fibrinolytic function. Lipid emulsion itself reduces in vitro platelet aggregation, however. Anaphylactoid reactions to the present

formulation of propofol have been reported. In at least some patients, the immune response was entirely caused by propofol and not by the lipid emulsion. Most patients developing the anaphylactoid response to propofol had a previous history of allergic responses. Perhaps propofol should not be used in patients with multiple drug allergies.[107-109] Propofol alone in intralipid does not trigger histamine release. Fospropofol is metabolized to propofol and formate. Formate concentrations do not increase after fospropofol administration. Propofol also possesses significant antiemetic activity with small (subhypnotic) doses (i.e., 10 mg in adults). The median concentration of propofol with an antiemetic effect was 343 ng/mL, which also causes a mild sedative effect.[110] This concentration can be achieved by an initial dose of propofol infusion of 10 to 20 mg followed by 10 μg/kg/minute. Propofol used as a maintenance anesthetic during breast surgical procedures was more effective than 4 mg of ondansetron given as prophylaxis in preventing postoperative nausea and vomiting (PONV) (see also Chapter 97). Propofol as an infusion of 1 mg/kg/hour (17 μg/kg/minute) also has provided excellent antiemetic action after anticancer chemotherapy. At subhypnotic doses, propofol relieves cholestatic pruritus and is likely as effective as naloxone in treating pruritus induced by spinal opiates.

Propofol decreases polymorphonuclear leukocyte chemotaxis, but not adherence phagocytosis and killing. This action contrasts with the effect of thiopental, which inhibits all these chemotactic responses. However, propofol inhibits phagocytosis and killing of *Staphylococcus aureus* and *Escherichia coli*. Life-threatening systemic infections have been associated with the use of propofol.[111] In hospitals where these infections occurred, opened vials and syringes of propofol had positive culture results. The intralipid that acts as the solvent for propofol is an excellent culture medium. Disodium edetate or metabisulfite has been added to the formulation of propofol in an attempt to retard such bacterial growth. Strict aseptic technique still must be observed.

The administration of propofol is associated with the development of pancreatitis,[112] which may be related to hypertriglyceridemia. Patients who developed hypertriglyceridemia tended to be older, had a longer ICU stay, and received propofol for a longer duration. When propofol is used for prolonged sedation or at higher infusion rates (especially in older patients), serum triglyceride concentrations should be routinely monitored.

USES

Induction and Maintenance of Anesthesia

Propofol is suitable for the induction and maintenance of anesthesia (Box 30-1). The IV induction dose is 1 to 2.5 mg/kg. Physiologic characteristics that best determine the appropriate dose to induce anesthesia are age, lean body mass, and central blood volume.[113] Propofol may be titrated on the basis of the BIS value for maintenance of anesthesia to ensure adequacy of anesthesia and prevention of overdosing. Premedication with an opiate or a benzodiazepine, or both, markedly reduces the necessary induction dose.[114-116] The induction dose must be reduced in older patients, and a dose of 1 mg/kg (with premedication) to 1.75 mg/kg (without premedication) is recommended for inducing anesthesia in patients who are older than 60 years old. Furthermore, older and sicker (American Society of Anesthesiologists [ASA] class III to IV) patients develop more profound hypotension, especially when propofol is combined with an opiate (see also Chapter 80). To prevent hypotension in sicker patients or in patients presenting for cardiac surgical procedures, IV fluids should be given as tolerated, and propofol should be titrated to achieve the desired anesthetic state. In general, for both pharmacokinetic and pharmacodynamic reasons older patients (>80 years old) require half the dose of young patients (<20 years)[117] (see also Chapter 80). For induction in children, the ED_{95} (2 to 3 mg/kg) is increased, primarily because of pharmacokinetic differences (see Chapter 93). Children have a smaller central compartment, increased metabolic clearance, and larger volumes of distribution of propofol relative to adult patients.[69] When used for induction of anesthesia in short-lasting procedures, propofol results in a significantly quicker recovery and an earlier return of psychomotor function compared with thiopental or methohexital, regardless of the anesthetic used for maintenance of anesthesia.

Several infusion schemes have been used to achieve adequate plasma concentrations of propofol. After an induction dose, an infusion of 100 to 200 μg/kg/minute is usually needed. The infusion rate is titrated to individual requirements and the surgical stimulus. When combined with propofol, the required infusion rate and concentration of opiates, midazolam, clonidine, or ketamine should be reduced.[20,118] Because opioids alter the concentration of propofol required for adequate anesthesia, the time to awakening and recovery can be influenced by these drug combinations. Also, opioids affect both the pharmacokinetics and the pharmacodynamics of propofol. Alfentanil decreases the elimination clearance of propofol from 2.1 to 1.9 L/minute, the distribution clearance from 2.7 to 2.0 L/minute, and the peripheral volume of distribution from 179 to 141 L. The pharmacokinetic parameters of propofol are affected by cardiac output, heart rate, and plasma alfentanil concentration.[39] Similarly, midazolam reduces propofol's metabolic clearance from 1.94 to 1.61 L/minute, Cl_2 from 2.86 to 1.52 L/minute, and Cl_3 from 0.95 to 0.73 L/minute. Consequently, in the presence

BOX 30-1 ***Uses and Doses of Intravenous Propofol***

Induction of general anesthesia	1-2.5 mg/kg IV, dose reduced with increasing age
Maintenance of general anesthesia	50-150 μg/kg/min IV combined with N_2O or an opiate
Sedation	25-75 μg/kg/min IV
Antiemetic action	10-20 mg IV, can repeat every 5-10 min or start infusion of 10 μg/kg/min

From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors: Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.*

IV, Intravenously; *N_2O,* nitrous oxide.

of both midazolam and alfentanil, propofol concentrations become elevated by 20% to 30%.[53] The infusion rate required to achieve the combination with the shortest recovery is propofol, 1 to 1.5 mg/kg followed by 140 μg/kg/minute for 10 minutes followed by 100 μg/kg/minute, and alfentanil, 30 μg/kg followed by an infusion of 0.25 μg/kg/minute, or fentanyl, 3 μg/kg followed by 0.02 μg/kg/minute.

As indicated previously, increasing age is associated with a decrease in propofol infusion requirements, whereas these requirements are larger in children and infants (see Chapter 93). The blood levels of propofol alone for loss of consciousness are 2.5 to 4.5 μg/mL, and the blood concentrations (when combined with nitrous oxide) required for surgery are 2.5 to 8 μg/mL. Similar concentrations are necessary when propofol is combined with an opioid for a total IV technique. The knowledge of these levels and of the pharmacokinetics of propofol has enabled the use of pharmacokinetic model–driven infusion systems to deliver propofol as a continuous infusion for the maintenance of anesthesia. A meta-analysis of recovery data after either propofol for maintenance or the newer volatile anesthetics indicated only minor differences in times to reach recovery goals; however, the incidence of nausea and vomiting remained significantly lower in the patients given propofol for maintenance of anesthesia (see also Chapter 97).

Propofol can be used as an infusion regimen for maintenance of anesthesia during cardiac surgical procedures (see also Chapter 67). With reduced and titrated doses of propofol for induction of anesthesia and titrated infusion rates of 50 to 200 μg/kg/minute combined with an opioid for maintenance, propofol provides intraoperative hemodynamic control and ischemic episodes similar to those with either enflurane combined with an opioid or a primary opioid technique.

Blood propofol concentrations increase in the presence of hemorrhagic shock. Shock affects the pharmacokinetics and pharmacodynamics of propofol. Shock also results in slower intercompartmental clearances and shifts the concentration effect relationship to the left, thereby demonstrating a 2.7-fold decrease in the effect-site concentration required to achieve 50% of the maximal effect in the BIS.[119] These pharmacokinetic changes may be reversed with IV fluid resuscitation. The propofol doses needed to reach a 50% decrease from baseline BIS and for no movement after noxious stimuli are reduced by hemorrhagic shock by 54% and 38%, respectively. Hemorrhagic shock decreases the effect-site concentration that produced 50% of the maximal BIS effect from 11.6 ± 3.8 to 9.1 ± 1.7 μg/mL and that producing a 50% probability of movement from 26.8 ± 1.0 to 20.6 ± 1.0 μg/mL.[120]

Sedation

Propofol has been evaluated for sedation during surgical procedures and for patients receiving mechanical ventilation in the ICU (see also Chapters 101 and 103).[121] As noted earlier, tolerance can occur with propofol. Increased propofol requirement occurs after repeated anesthetic administration in a limited time in individual patients and when propofol is infused for prolonged periods.[74] Infusion rates required for sedation to supplement regional anesthesia in healthy patients are half or less than the rates required for general anesthesia (i.e., 30 to 60 μg/kg/minute). In older patients (>65 years old) and in sicker patients, the necessary infusion rates are markedly reduced up to 50% compared with 20-year-old patients. The infusion should be individually titrated to the desired effect. The pharmacokinetic profile of propofol makes it a suitable choice for long-term (days) sedation. This choice should always be weighed, however, against the hemodynamic side effects, tolerance, and rare occurrences of hypertriglyceridemia (and potential pancreatitis) or propofol infusion syndrome. Maintaining the smallest possible dose required for the desired level of sedation with potential "sedation holidays" should be considered as part of a long-term propofol sedation regimen. In addition, the FDA has specifically recommended against the use of propofol for the prolonged sedation of pediatric patients (see also Chapter 93). The sedation guidelines of the American College of Critical Care Medicine also recommend "that patients receiving propofol for long term sedation should be monitored for unexplained metabolic acidosis or arrhythmias. Drugs other than propofol should be considered for patients with escalating vasopressor or inotrope requirements or cardiac failure during large-dose propofol infusions." The recommended maximal dose of propofol infusion rate is 80 μg/kg/minute (<5 mg/kg/hour).[122] Generally, at propofol infusion rates more rapid than 30 μg/kg/minute, patients are amnesic.

SIDE EFFECTS AND CONTRAINDICATIONS

Induction of anesthesia with propofol is often associated with pain on injection, apnea, hypotension, and, rarely, thrombophlebitis of the vein into which propofol is injected.[123] Pain on injection is reduced by using a large vein, avoiding veins in the dorsum of the hand, and adding lidocaine to the propofol solution or changing the propofol formulation. Multiple other drugs and distraction techniques have been investigated to reduce the pain on injection of propofol. Pretreatment with a small dose of propofol, opiates, nonsteroidal antiinflammatory drugs, ketamine, esmolol or metoprolol, magnesium, a flash of light, a clonidine-ephedrine combination, dexamethasone, and metoclopramide all have been tested with variable efficacy.

Propofol infusion syndrome is a rare but lethal syndrome associated with infusion of propofol at 4 mg/kg/hour or more for 48 hours or longer.[124] Yet, cases have been reported with smaller dosage schemes given for only 3 hours.[125] This syndrome was first described in children but subsequently has been observed in critically ill adults[126,127](see also Chapter 93). The clinical features of propofol infusion syndrome are acute refractory bradycardia leading to asystole in the presence of one or more of the following: metabolic acidosis (base deficit >10 mmol/L), rhabdomyolysis, hyperlipidemia, and enlarged or fatty liver. Other features include cardiomyopathy with acute cardiac failure, skeletal myopathy, hyperkalemia, hepatomegaly, and lipemia. The symptoms and signs are the result of muscle injury and the release of intracellular toxic contents. The major risk factors are poor oxygen delivery, sepsis, serious cerebral injury, and large propofol dosage.

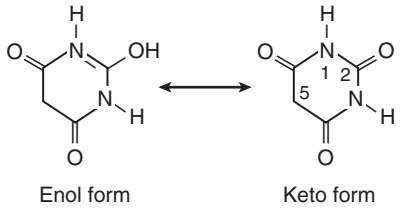


Figure 30-5. The keto and enol tautomeric forms of barbituric acid with the sites of substitution in the hypnotically active barbiturates identified as 1, 2, and 5. *(From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

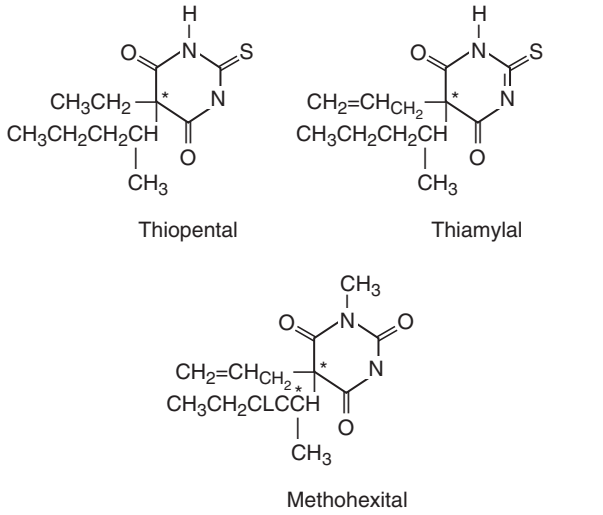


Figure 30-6. Hypnotically active barbiturates commonly used for induction, with their asymmetric centers indicated by an *asterisk. (From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

Predisposing factors are likely genetic disorders impairing fatty acid metabolism, such as medium-chain acyl coenzyme A (MCAD) deficiency and low carbohydrate supply. Because lipemia has been noted, a failure of hepatic lipid regulation, possibly related to poor oxygenation or a lack of glucose, may be the cause. In some cases, increasing lipemia was the first indication of impending propofol infusion syndrome onset; therefore, lipemia is a sign.

BARBITURATES

HISTORY

Barbiturates were discovered in the early twentieth century. The first barbiturate to cause loss of consciousness within one arm–brain circulation time was hexobarbital. After the clinical introduction of thiopental by Waters and Lundy in 1934, thiopental became preferred clinically because of its rapid onset of action and short duration, without the excitatory effects of hexobarbital.[128] Although criticized after many casualties during the attack on Pearl Harbor as "the cause of more fatal casualties among the servicemen at Pearl Harbor than were the enemy bombs," barbiturates continued to be widely used in clinical practice.[129] Many other barbiturate derivatives have been synthesized throughout the past decades, yet none have enjoyed the clinical success and popularity of thiopental.

PHYSICOCHEMICAL CHARACTERISTICS

Chemistry and Formulation

Barbiturates are hypnotically active drugs that are derivatives of barbituric acid (2,4,6-trioxohexahydropyrimidine), a hypnotically inactive pyrimidine nucleus that is formed by the condensation of malonic acid and urea (Fig. 30-5). The two major classes of barbiturates are the oxybarbiturates and thiobarbiturates with either an oxygen at position 2 or a sulfur in position 2, respectively. Through keto-enol tautomerization, the oxygen or sulfur in position 2 becomes a reactive species in the enol form. This process allows for the formation of water-soluble barbiturate salts in alkaline solutions and permits the IV use of barbiturates. Although tautomerization to the enol form allows for the creation of salts, the substitution of the hydrogen attached to the carbon atom in position 5 with aryl or alkyl groups gives the barbiturates their hypnotic activity. Only thiopental and thiamylal, thiobarbiturates, and methohexital, an oxybarbiturate, have been used for induction of anesthesia (Fig. 30-6). The formulation of barbiturates involves preparation as sodium salts (mixed with 6% by weight anhydrous sodium carbonate) and then reconstitution with water, glucose 5%, or normal saline to produce a 2.5% solution of thiopental, a 2% solution of thiamylal, or a 1% solution of methohexital. The thiobarbiturates are stable for 1 week if refrigerated after reconstitution, and methohexital remains available for use for 6 weeks after reconstitution. Barbiturates cannot be reconstituted with lactated Ringer's solution or mixed with other acidic solutions because a decrease in the alkalinity of the solution can result in precipitation of the barbiturates as free acids. Examples of drugs that are not to be coadministered or mixed in solution with the barbiturates are atracurium, vecuronium, rocuronium, suxamethonium, alfentanil, sufentanil, dobutamine, dopamine, S-ketamine, and midazolam. Mixing of thiopental with vecuronium or pancuronium results in the formation of precipitate, which may occlude the IV line during rapid-sequence induction of anesthesia.[130]

Structure-Activity Relationships

As noted earlier, substitutions at the 5, 2, and 1 positions confer different pharmacologic activities to the barbiturate nucleus. Substitutions at position 5 with either aryl or alkyl groups produce hypnotic and sedative effects; substitution at C5 with a phenyl group produces anticonvulsant activity. An increase in length of one or both side chains of an alkyl group at C5 increases hypnotic potency. Barbiturates used in clinical practice have either an oxygen or a sulfur at C2. Substitution of a sulfur at position 2 produces a more rapid onset of action, as with thiopental. The addition of a methyl or ethyl group at position 1 also may produce a more rapid onset of action,

as with methohexital. However, excitatory side effects, including tremor, hypertonus, and involuntary movement, may occur on administration.

PHARMACOKINETICS

Metabolism

The barbiturates (with the exception of phenobarbital) are metabolized hepatically. The metabolites are almost all inactive, water soluble, and excreted in the urine. Barbiturates are biotransformed by four processes: (1) oxidation of the aryl, alkyl, or phenyl moiety at C5; (2) *N*-dealkylation; (3) desulfuration of the thiobarbiturates at C2; and (4) destruction of the barbituric acid ring.[131] Oxidation, the most important pathway, produces polar (charged) alcohols, ketones, phenols, or carboxylic acids. These metabolites are readily excreted in the urine or as glucuronic acid conjugates in the bile. Hydrolytic cleavage of the barbituric acid ring forms a minimal contribution to the total metabolism of barbiturates because the ring is stable in vivo. Drugs that induce oxidative microsomes or long-term administration enhance the metabolism of barbiturates. The hepatic enzyme induction by barbiturates is the reason that they are not recommended for administration to patients with acute intermittent porphyria. Barbiturates may precipitate an attack by stimulating δ-aminolevulinic acid synthetase, the enzyme responsible for the production of porphyrins.[132]

As mentioned earlier, hepatic metabolism accounts for the elimination of all of the barbiturates with the exception of phenobarbital. Renal excretion accounts for 60% to 90% of phenobarbital excretion in an unchanged form. The alkalinization of urine with bicarbonate enhances the renal excretion of phenobarbital. Other barbiturates are excreted unchanged by the kidney only in trivial amounts.

Methohexital is metabolized in the liver by oxidation to an alcohol and *N*-dealkylation. Methohexital exhibits its distribution half-lives, volumes of distribution, and protein binding similar to those of thiopental. A marked difference exists, however, in plasma disappearance and elimination half-lives (4 hours for methohexital and 12 hours for thiopental). The reason for this difference is the threefold more rapid rate of hepatic clearance of methohexital (mean, 7.8 to 12.5 mL/kg/minute).[133] The hepatic extraction ratio of methohexital (clearance to hepatic blood flow) is approximately 0.5, indicating that the liver extracts 50% of the drug presented to it. This ratio differs from the smaller hepatic extraction ratio of thiopental (0.15).

Barbiturate pharmacokinetics has been described in physiologic and compartment models.[134] Both these pharmacokinetic models describe rapid redistribution as the primary mechanism that terminates the action of a single induction dose. Physiologic models of barbiturates describe a rapid mixing of the drug within the central blood volume followed by a quick distribution of the drug to highly perfused, low-volume tissues (i.e., brain), with a slower redistribution of the drug to lean tissue (muscle), which terminates the effect of the initial (induction of anesthesia) dose. In these models, adipose tissue uptake and metabolic clearance (elimination) play only minor roles in the termination of the effects of the induction dose. The reasons are the minimal perfusion ratio of adipose tissue compared with other tissues and the slow rate of removal. Compartment model values for thiopental and methohexital, the most commonly used barbiturates for induction of anesthesia, are given in Table 30-1. The compartment model explains the delay of recovery when a continuous infusion of a barbiturate is used. This model describes how the termination of effect becomes increasingly dependent on the slower process of uptake into and redistribution from adipose tissue and elimination clearance through hepatic metabolism. After prolonged infusions, the pharmacokinetics of barbiturate metabolism is best approximated by nonlinear Michaelis-Menten metabolism. In usual doses (4 to 5 mg/kg), thiopental exhibits first-order kinetics (i.e., a constant *fraction* of drug is cleared from the body per unit time); however, at very high doses of thiopental (300 to 600 mg/kg) with receptor saturation, zero-order kinetics occurs (i.e., a constant *amount* of drug is cleared per unit time). The volume of distribution is slightly larger in female patients, thus causing a longer elimination half-life.[135] Pregnancy also increases the volume of distribution of thiopental and prolongs the elimination half-life.[136] Even at advanced stages of liver cirrhosis, the clearance of thiopental is not altered. Because of its lipophilicity, relatively large volume of distribution, and low rate of hepatic clearance, thiopental can accumulate in tissues, especially if it is given in large doses over a prolonged period. The plasma drug level increases when repeated doses of drug are given. Although not used in routine clinical practice, appropriately designed infusion schemes ensure constant blood levels that maintain the desired hypnotic effect.

PHARMACOLOGY

Mechanism of Action

The mechanisms of action of barbiturates on the CNS are largely unknown, with the exception of their action on the $GABA_A$ receptor.[137,138] Perhaps the NMDARs are involved with the effects of barbiturates.[139-141] The effects of barbiturates on the CNS have been grouped into two categories: (1) enhancement of the synaptic actions of *inhibitory* neurotransmitters, and (2) blockade of the synaptic actions of *excitatory* neurotransmitters.[142] GABA is the principal inhibitory neurotransmitter in the mammalian CNS, and the $GABA_A$ receptor is the only site proven to be involved in barbiturate-induced anesthesia.[138] The $GABA_A$ receptor is a chloride ion channel, composed of at least five subunits, with specific sites of action for GABA, barbiturates, benzodiazepines, and other molecules. Barbiturate binding to the $GABA_A$ receptor enhances and mimics the action of GABA by increasing chloride conductance through the ion channel. This causes hyperpolarization of the cell membrane and increases the threshold of excitability of the postsynaptic neuron. At low concentrations, barbiturates enhance the effects of GABA, by decreasing the rate of dissociation of GABA from its receptor and increasing the duration of GABA-activated chloride ion channel openings. This

enhancement of the action of GABA is likely responsible for the sedative-hypnotic effects of the barbiturates. At larger concentrations, the barbiturates activate the chloride channels directly, without the binding of GABA, and act as agonists. The GABA-mimetic effect at slightly higher concentrations may be responsible for what is termed barbiturate anesthesia.[138]

The second mechanism of action of barbiturates involves the inhibition of the synaptic transmission of excitatory neurotransmitters, such as glutamate and acetylcholine. The actions of the barbiturates to block excitatory CNS transmission are specific for synaptic ion channels. Thiopental, however, may exert GABA-independent effects on the glutaminergic-NMDA system. In two studies of the effects in the rat prefrontal cortex, thiopental decreased extracellular glutamate levels in the CNS and decreased NMDA-gated currents in a concentration-dependent manner.[140,141]

Effects on Cerebral Metabolism

Barbiturates, like other CNS depressants, have potent effects on cerebral metabolism (see also Chapter 70). A dose-related depression of cerebral metabolic oxygen consumption rate ($CMRO_2$) progressively slows the EEG, reduces the rate of ATP consumption, and enhances protection from partial cerebral ischemia. The relationship between depressed metabolism and drug requirement was shown when thiopental was not eliminated (i.e., sustained with an extracorporeal circulation pump).[143] When the EEG became isoelectric, a point at which cerebral metabolic activity is roughly 50% of baseline,[144] no further decreases in $CMRO_2$ occurred. These findings support the hypothesis that metabolism and function of the brain are coupled. Barbiturates reduce the metabolic activity concerned with neuronal signaling and impulse traffic, not the metabolic activity corresponding to basal metabolic function. The only way to suppress baseline metabolic activity related to cellular activity is through hypothermia.[144] The effect of barbiturates on cerebral metabolism is maximized at a 50% depression of cerebral function, thus leaving all metabolic energy for the maintenance of cellular integrity. With the reduction in $CMRO_2$, a parallel reduction in cerebral perfusion occurs, as seen in decreased cerebral blood flow (CBF) and ICP. With reduced $CMRO_2$, cerebral vascular resistance increases, and CBF decreases.[145] The ratio of CBF to $CMRO_2$ remains unchanged. Even though the mean arterial pressure (MAP) decreases, barbiturates do not compromise the overall CPP because the CPP = MAP – ICP. In this relationship, ICP decreases more than MAP after barbiturate administration and thereby preserves CPP.

PHARMACODYNAMICS

Sufficient doses of barbiturates cause loss of consciousness, amnesia, and respiratory and cardiovascular depression, known as general anesthesia. The response to pain and other noxious stimulation during general anesthesia seems to be depressed. Pain studies reveal that barbiturates may decrease the pain threshold. This antianalgesic effect occurs only with low blood levels of barbiturates, which may be achieved with small doses of thiopental for induction of anesthesia or after emergence from thiopental. The amnestic effect of barbiturates is less pronounced than is that produced by benzodiazepines.

Effects on the Central Nervous System

Drugs with high lipid solubility and a low degree of ionization cross the blood-brain barrier rapidly and have a fast onset of action.[138] Most barbiturates exist in a nonionized form. Thiopental and methohexital are more lipid soluble than is pentobarbital, which is clinically reflected by the more rapid onset of action of thiopental and methohexital compared with pentobarbital.[146] Only the nonionized form of a drug can directly traverse the cellular membranes. Thiopental has a dissociation constant (pK_a) of 7.6. Approximately 50% of thiopental is nonionized at physiologic pH, which accounts partly for the rapid accumulation of thiopental in the cerebrospinal fluid (CSF) after IV administration.[147] Methohexital is 75% nonionized at pH 7.4, and this may explain the slightly more rapid effect of methohexital compared with thiopental. As pH decreases, with poor perfusion, barbiturates have a larger fraction of nonionized drug available to cross the blood-brain barrier.[147]

The onset of action in the CNS is affected by protein binding because only unbound drug (free drug) can cross the blood-brain barrier.[148] Barbiturates are highly bound to albumin and other plasma proteins, and the thiobarbiturates are more highly protein bound than are the oxybarbiturates. The degree of protein binding of a drug is influenced by the physiologic pH and disease states that alter the absolute amount of protein. Most barbiturates tend to experience peak protein binding at or near pH 7.5. The final factor governing the rapidity of drug penetration of the blood-brain barrier is the plasma drug concentration, which causes a concentration gradient. The two primary determinants of the plasma concentration are the *dose* administered and the *rate* (speed) of administration. As the dose of thiopental over the same time is increased, an increased percentage of patients will be anesthetized.[149] Concerning absolute dose, 2 mg/kg produced anesthesia in 20% of patients, whereas a dose of 2.4 mg/kg produced anesthesia in 80% of patients. Similarly, the speed of injection influences the effect of thiopental. A smaller amount of drug is required to produce anesthesia when the rate of the administration lasts 5 seconds as opposed to 15 seconds.

Because of the equilibrium between brain concentration and plasma concentration, factors that determine the rate of onset of barbiturate effects also affect their termination. Lipid solubility, degree of ionization, and CSF drug concentration affect the movement of drug from the CSF to plasma. As plasma levels decrease, drug levels in the brain and CSF decrease. The most important factors in the termination of drug effect are those that govern plasma disappearance of the drug. These are generally divided into a rapid redistribution phase and a slow metabolic and second redistribution phase. In a classic pharmacologic study, Brodie and co-workers showed that awakening from thiopental occurred because the plasma concentration rapidly declined.[150] These investigators further showed that the cause of the rapid plasma decay of thiopental was not metabolism of the drug, but was

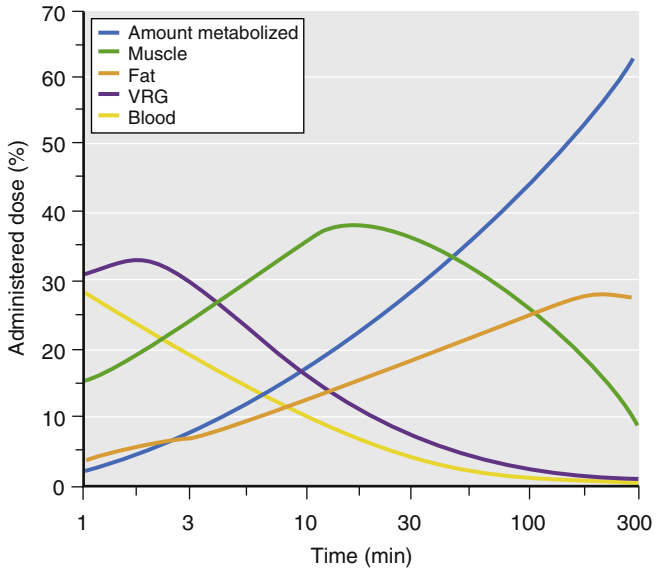


Figure 30-7. After delivery of an intravenous bolus, the percentage of thiopental remaining in blood rapidly decreases as drug moves from blood to body tissues. The time to attainment of peak tissue levels is a direct function of tissue capacity for barbiturate relative to blood flow. A larger capacity or smaller blood flow is related to a longer time to a peak tissue level. Initially, most thiopental is taken up by the vessel-rich group (VRG) of tissues because of their high blood flow. Subsequently, drug is redistributed to muscle and, to a lesser extent, to fat. Throughout this period, small but substantial amounts of thiopental are removed and metabolized by the liver. In contrast to removal by tissues, this removal is cumulative. The rate of metabolism equals the early rate of removal by fat. The sum of this early removal by fat and metabolism is the same as the removal by muscle. *(Redrawn from Saidman LJ: Uptake, distribution and elimination of barbiturates. In Eger EI, editor:* Anesthetic uptake and action. *Baltimore, 1974, Williams & Wilkins.)*

rather a redistribution of the drug to other tissues throughout the body. The relationship of the plasma drug level and drug redistribution with the onset and termination of effect is illustrated in Figure 30-7. Clinically, patients awaken from a single dose of thiopental 5 to 10 minutes after administration, as the drug is redistributed from highly perfused CNS tissues to well-perfused lean tissues. The termination of effect after multiple drug administrations or constant infusion depends on the elimination of the drug from the blood, which becomes increasingly more dependent on first-order metabolism than redistribution and is a function of its context-sensitive decrement time (see Fig. 30-3). Awakening may be delayed in older patients because of increased CNS sensitivity, alterations in metabolism, or decreased central volume of distribution relative to younger adults[151] (see also Chapter 80). The initial volume of distribution is less in older patients than in young patients, a feature that explains a smaller dose requirement for the onset effect. Pediatric patients (<13 years old) seem to have a more rapid rate of total clearance and a shorter rate of plasma thiopental clearance than do adults that theoretically could result in earlier awakening, especially after multiple doses of the drug[152] (see also Chapter 93).

The finding that little difference exists in distribution of thiopental and methohexital may explain the similar wakeup times. However, the rate of total body clearance is more rapid for methohexital. This disparity explains the difference found in the psychomotor skills of patients and the earlier full recovery after methohexital. Despite some residual effects, methohexital is cleared more rapidly than thiopental. This faster clearance explains why methohexital is preferred for use by some clinicians when rapid awakening is desirable, such as in outpatient anesthesia. Prolongation of early and late recovery by the barbiturates is the primary reason that these drugs have been largely replaced by propofol.

Effects on the Respiratory System

Barbiturates produce dose-related central respiratory depression. The evidence for central depression is a correlation between EEG suppression and diminished minute ventilation. Peak respiratory depression (as measured by the slope of carbon dioxide concentration in the blood) and maximum depression of minute ventilation after delivery of thiopental (3.5 mg/kg) occurs 1 to 1.5 minutes after administration. These variables return to predrug levels rapidly, and within 15 minutes the drug effects are barely detectable.[153] Patients with chronic lung disease are slightly more susceptible to the respiratory depression of thiopental. The ventilatory pattern with thiopental induction has been described as "double apnea," which is an initial episode of apnea lasting a few seconds on drug administration, succeeded by a few breaths of reasonably adequate tidal volume, and followed by a more prolonged period of apnea, typically lasting approximately 25 seconds. This apnea occurs in at least 20% of cases. During the induction of anesthesia with thiopental, ventilation must be assisted or controlled to provide adequate respiratory exchange. Like thiopental, methohexital is a central respiratory system depressant.[153] Induction doses (1.5 mg/kg) significantly decrease the slope of the ventilatory response to carbon dioxide, with a maximal reduction at 30 seconds after drug administration.[154] The peak decrease in tidal volume occurs 60 seconds after methohexital administration. All variables return to baseline within 15 minutes. In contrast to the effects on ventilation, patients awaken within approximately 5 minutes after the administration of methohexital (1.5 mg/kg).

Effects on the Cardiovascular System

Cardiovascular depression from barbiturates is a result of central and peripheral (direct vascular and cardiac) effects. The primary cardiovascular effect of a barbiturate during induction of anesthesia is peripheral vasodilation causing a pooling of blood in the venous system. Mechanisms for the decrease in cardiac output include (1) direct negative inotropic action resulting from a decrease of calcium influx into the cells, (2) decreased ventricular filling caused by increased capacitance, and (3) transiently decreased sympathetic outflow from the CNS.[155] The increase in heart rate (10% to 36%) that accompanies thiopental administration probably results from the baroreceptor-mediated sympathetic reflex stimulation of the heart in response to the decrease in output and pressure. The cardiac index, as well as the MAP, is unchanged or reduced. Hemodynamic changes depend on infusion rate of thiopental. In the dose ranges hitherto studied,

no relationship between plasma thiopental level and hemodynamic effect has been found. Little difference is noted in the responses after thiopental and methohexital administration in patients with heart disease. The increase in heart rate (11% to 36%) encountered in patients with coronary artery disease who are anesthetized with thiopental (1 to 4 mg/kg) is potentially deleterious because of the obligatory increase in myocardial oxygen consumption that accompanies the increased heart rate.

In a more recent study in dogs, thiopental prolonged the QT interval, flattened T waves, and increased QT dispersion during and after induction.[151] Thiopental may not be the most appropriate choice for patients with a susceptibility to ventricular dysrhythmias or a prolonged QT interval, such as acidotic patients or patients with conditions that prolong the QT interval, such as long-term dialysis or advanced cirrhosis. Patients who have normal coronary arteries have no difficulty in maintaining adequate coronary blood flow to meet the increased myocardial oxygen consumption.[156] Thiopental should be avoided in hypovolemic patients because of the significant reduction in cardiac output (69%) and the significant decrease in arterial blood pressure.[157] Patients without adequate compensatory mechanisms may have serious hemodynamic depression with thiopental induction of anesthesia.

Other Effects

The side effects of injecting barbiturates include a garlic or onion taste (40% of patients), allergic reactions, local tissue irritation, and rarely, tissue necrosis. A transient urticarial rash may develop on the head, neck, and trunk. More severe reactions, such as facial edema, hives, bronchospasm, and anaphylaxis, can occur. Treatment of anaphylaxis is symptomatic. Thiopental and thiamylal produce fewer excitatory symptoms with induction than does methohexital, which produces cough, hiccup, tremors, and twitching approximately five times more often. Tissue irritation and local complications may occur more frequently with the use of thiopental and thiamylal than with methohexital.

The consequences of accidental arterial injection may be severe. The degree of injury is related to the concentration of the drug. Treatment consists of (1) dilution of the drug by the administration of saline into the artery, (2) heparinization to prevent thrombosis, and (3) brachial plexus block. Overall, the proper IV administration of thiopental is remarkably free of local toxicity.

Phenobarbital is used experimentally as an inducer of the cytochrome P450 (CYP) system in rodents, in particular of the CYP2B enzymes. In human hepatocyte culture, phenobarbital acts as an inducer of the CYP2B6, CYP2C9, CYP2C19, and CYP3A4 enzymes through the constitutive androstane receptor (CAR).[158] This phenomenon may cause changes in the metabolism of drugs that are administered concomitantly.[159] Conversely, the metabolism of thiopental can be influenced by concomitant drugs such as selective serotonin reuptake inhibitors (SSRIs). These drugs are used frequently by patients who are treated by electroconvulsive therapy and in whom induction of anesthesia with thiopental or thiamylal is performed.[160]

USES

Induction and Maintenance of Anesthesia

Barbiturates are used clinically for induction and maintenance of anesthesia and premedication. Methohexital is the drug of choice for providing anesthesia during electroconvulsive therapy.[161] Other barbiturates used in this field are thiopental and thiamylal. Less frequently, barbiturates are used to provide cerebral protection in patients at risk of developing incomplete ischemia. The three barbiturates that are used most commonly for IV anesthesia induction and maintenance are thiopental, thiamylal, and methohexital. Thiopental is an excellent drug to use for induction of anesthesia. The prompt onset (15 to 30 seconds) of action and smooth induction are benefits of this drug. Rapid emergence, particularly after single use for induction, also is a reason for the widespread use of thiopental in this setting. Thiopental can be used to maintain general anesthesia because repeated doses reliably sustain unconsciousness and contribute to amnesia, but it should not be the drug of first choice as the hypnotic component in balanced anesthesia.

Methohexital is the only IV barbiturate used for induction of anesthesia that can compete with thiopental. With a dose of 1 to 2 mg/kg, induction and emergence from anesthesia are rapid. Methohexital also may be used as a hypnotic component to maintain anesthesia. Like thiopental, it is not an analgesic. Additional opioids or volatile anesthetics are required to provide a balanced technique satisfactory for general anesthesia during surgical procedures. Because methohexital is cleared more rapidly than thiopental, it may be preferred to thiopental for the maintenance of anesthesia, given that accumulation and saturation of peripheral sites take longer. For brief infusion (<60 minutes), recovery from a methohexital infusion titrated to maintain hypnosis (50 to 150 μg/kg/minute) is similar to that provided by propofol. The upper limits of safe infusion doses probably have yet to be defined, but seizures have occurred in neurosurgical patients after large doses of methohexital (24 mg/kg).[155] Methohexital may be given rectally and is absorbed rapidly, and it can be used for premedication in pediatric patients. The dose recommended for this use is 25 mg/kg by rectal instillation (10% solution through a 14-French catheter, 7 cm into rectum).[162] With this method of administration, sleep onset is rapid: mean peak plasma levels occur within 14 minutes.

DOSING

Dosing regimens for the two most commonly used barbiturates are listed in Table 30-4. The usual doses of thiopental (3 to 4 mg/kg) and thiamylal (3 to 4 mg/kg) are approximately twice the dose of methohexital (1 to 2 mg/kg). In dose-response studies, the ED_{50} for thiopental ranged from 2.2 to 2.7 mg/kg, and the ED_{50} for methohexital was 1.1 mg/kg.[148] Less interpatient variability is seen in the dose response to barbiturates than to benzodiazepines when used for anesthesia induction, but significant variability remains in the dose of thiopental required to induce anesthesia.[149] Interpatient dose variability is related to the presence of hemorrhagic shock, cardiac output, lean body mass, obesity, gender, and age (see

also Chapters 71 and 80). Hemorrhagic shock, lean body mass, age, and obesity explain the variability of patients' responses resulting from a decrease in the central volume of distribution. Finally, patients who have severe anemia, burns, malnutrition, widespread malignant disease, uremia, ulcerative colitis, or intestinal obstruction also require smaller induction doses of barbiturates.

CONTRAINDICATIONS

The following conditions should be considered contraindications to the use of IV barbiturates:

1. When the patient has respiratory obstruction or an inadequate airway, thiopental may worsen respiratory depression.
2. Severe cardiovascular instability or shock contraindicates barbiturate use.
3. Status asthmaticus is a condition in which airway control and ventilation may be worsened by thiopental.
4. Porphyria may be precipitated or acute attacks may be accentuated by the administration of thiopental.
5. Without proper equipment (IV instrumentation) and airway equipment (means of artificial ventilation), thiopental should not be administered.

TABLE 30-4 RECOMMENDED DOSES OF BARBITURATES FOR ANESTHESIA INDUCTION AND MAINTENANCE

Drug	Induction Dose (mg/kg)*†	Onset (sec)	Intravenous Maintenance Infusion
Thiopental	3-4	10-30	50-100 mg every 10-12 min
Methohexital	1-1.5	10-30	20-40 mg every 4-7 min

From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors: Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.*

*Adult and pediatric intravenous doses are roughly the same in milligrams per kilogram.

†Methohexital can be given rectally in pediatric patients as a 20 to 25 mg/kg/dose.

BENZODIAZEPINES

The benzodiazepines comprise a category of drugs widely used in anesthesia as anxiolytics, sedatives, and hypnotics. They exert their action through $GABA_A$ receptors, which are the key targets that mediate most of the clinically important effects of IV anesthetics.[163] In the clinical practice of daily anesthesia, midazolam is often used immediately before induction of anesthesia. The other agonists, diazepam, lorazepam, and temazepam and the antagonist flumazenil are sometimes used. Remimazolam, an ultrashort-acting $GABA_A$ receptor agonist, may be a useful benzodiazepine in future anesthetic practice.

Benzodiazepines were discovered in 1954 by Sternbach, and in 1959 chlordiazepoxide (Librium) was the first benzodiazepine patented. Diazepam was synthesized in 1963 in a search for a better compound and was used by the IV route to induce anesthesia in 1965.[164] Oxazepam (Serax), a metabolite of diazepam, was synthesized in 1961 by Bell. Lorazepam (Ativan), a 2′chloro-substitution product of oxazepam, was synthesized in 1971 in an attempt to produce a more potent benzodiazepine. The next major achievement was Fryer and Walser's synthesis in 1976 of midazolam (Versed, Dormicum), the first clinically used water-soluble benzodiazepine, produced primarily for use in anesthesia.[165]

PHYSICOCHEMICAL CHARACTERISTICS

Four benzodiazepine receptor agonists are commonly used in anesthesia: midazolam, diazepam, lorazepam, and temazepam (Fig. 30-8). The physicochemical characteristics of the benzodiazepines used in anesthesia are

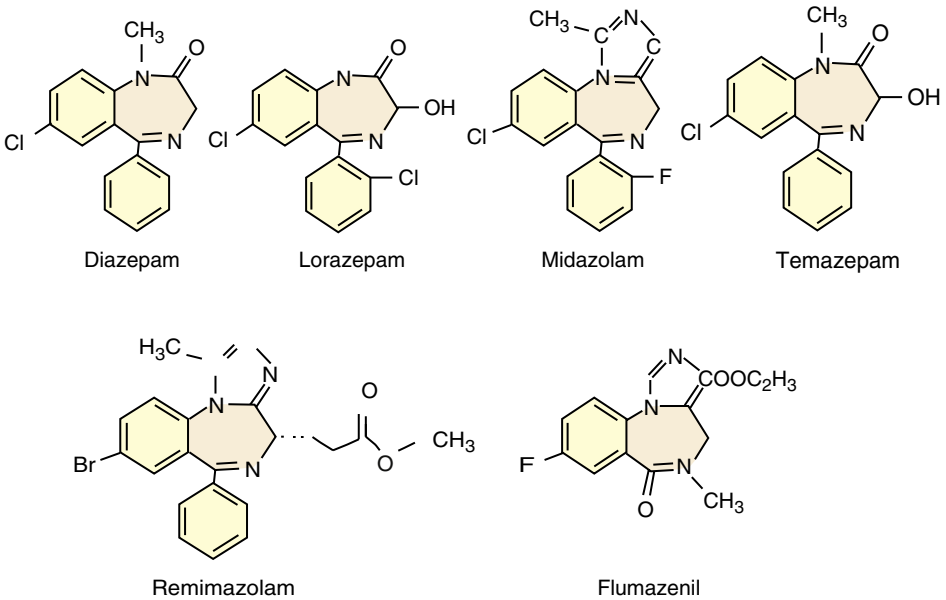


Figure 30-8. The structures of five benzodiazepines.

listed in Table 30-5. These six molecules are relatively small and are lipid soluble at physiologic pH.

Of the clinically used benzodiazepines, midazolam is the most lipid soluble in vivo,[166] but because of its pH-dependent solubility, it is water soluble when formulated in a buffered acidic medium (pH 3.5). The imidazole ring of midazolam accounts for its stability in solution and its lipophilicity as a result of rapid closing of the imidazole ring at physiologic pH. The high lipophilicity of the compounds is the basis for the rapid CNS effect and relatively large volumes of distribution.

PHARMACOKINETICS

The four benzodiazepines used in anesthesia are classified as a short-acting agent (midazolam), intermediate-acting agents (lorazepam, temazepam), and a long-acting agent (diazepam), according to their metabolism and plasma clearance (Table 30-6). The plasma disappearance curves of all benzodiazepines can be best described by a two- or three-compartment model.

Protein binding and volumes of distribution are not much different among these four benzodiazepines, but clearance is significantly different. Factors that may influence the pharmacokinetics of benzodiazepines are age, gender, race, enzyme induction, and hepatic and renal disease. In addition, the pharmacokinetics of the benzodiazepines is affected by obesity (see also Chapter 71). The volume of distribution is increased because drug diffuses from the plasma into the adipose tissue. Although clearance is not altered, elimination half-lives are prolonged by the increased volume of distribution and the delayed return of the drug to the plasma in obese patients.[167] Generally, sensitivity to benzodiazepines in some patient groups, such as older patients, is greater despite relatively modest pharmacokinetic changes; factors other than pharmacokinetics must be considered when these drugs are used.

Midazolam

After oral ingestion, midazolam is absorbed completely, and the peak plasma concentration is achieved in 30 to 80 minutes.[168] The bioavailability of less than 50% results from significant first-pass metabolism in the intestinal wall and the liver.[168,169] After IV administration, midazolam is rapidly distributed, with a distribution half-life of 6 to 15 minutes. [169] The plasma protein binding is high: 94% to 98%.

The hepatic extraction ratio is low, ranging from 0.30 to 0.44, but it is higher than the unbound free fraction of midazolam in plasma.[168] Thus, protein binding is not a restrictive factor in drug extraction by the liver. With this intermediate hepatic extraction ratio, the metabolic clearance of midazolam may be susceptible both to changes in enzyme activity and to changes in hepatic blood flow.

The elimination half-life ranges from 1.7 to 3.5 hours.[169,170] Plasma clearance ranges from 5.8 to 9.0 mL/kg/minute and is higher compared with that of the other benzodiazepines. This is related to the fused imidazole ring, which is rapidly oxidized in vivo, much more rapidly than the methylene group of the diazepine ring of other benzodiazepines.[171]

The pharmacokinetics of midazolam is affected by obesity, age (see also Chapters 71 and 80), and hepatic cirrhosis. Because of its high lipophilicity (at physiologic pH), midazolam distributes preferably to adipose tissue,

TABLE 30-5 PHYSICOCHEMICAL CHARACTERISTICS OF BENZODIAZEPINES

	Molecular Weight (Da)	pK_a	Water Solubility* (g/L)	Lipid Solubility (Log P)
Diazepam	284.7	3.4	0.051	2.801
Lorazepam	321.2	1.3	0.12	2.382
Temazepam	300.7	1.6, 11.7	0.28	2.188
Midazolam	325.8 (hydrochloride 362.2)	6.0	0.004 (2.0, pH 1)	3.798
Remimazolam	439.3 (besylate 597.5)	5.3	0.008 (7.5, pH 1)	3.724
Flumazenil	303.3	0.86	0.042	2.151

From Saari TI, Uusi-Oukari M, Ahonen J, Olkkola KT: Enhancement of GABAergic activity: neuropharmacological effects of benzodiazepines and therapeutic use in anesthesiology, Pharmacol Rev *63:243-267, 2011.*

pK_a, Dissociation constant.

*Water solubility values are in unbuffered water, maximal solubility at acidic pH in parenthesis. Data from http://scifinder.cas.org.

TABLE 30-6 PHARMACOKINETIC PARAMETERS OF THE BENZODIAZEPINES

	Elimination Half-life (hr)	Clearance (mL/kg/min)	Vd (L/kg)	Plasma Protein Binding (%)	Investigators (yr)
Midazolam	1.7-3.5	5.8-9.0	1.1-1.7	94-98	Dundee et al (1984)
Diazepam	20-50	0.2-0.5	0.7-1.7	98-99	Greenblatt et al (1980)
Lorazepam	11-22	0.8-1.5	0.8-1.3	88-92	Greenblatt et al(1979)
Temazepam	6-8	1.0-1.2	1.3-1.5	96-98	Fraschini and Stankov (1993)
Remimazolam*	0.4	4,521 mL/min	36.4 L	NA	Upton et al (2010)
Flumazenil	0.7-1.3	13-17	0.9-1.9	40-50	Klotz and Kanto (1998)

From Saari TI, Uusi-Oukari M, Ahonen J, Olkkola KT: Enhancement of GABAergic activity: neuropharmacological effects of benzodiazepines and therapeutic use in anesthesiology, Pharmacol Rev *63:243-267, 2011.*

NA, Not available.

*Noncompartmental analysis results from sheep.

with a resulting prolonged elimination half-life in obese patients.[167] Habitual alcohol consumption increases the metabolism of midazolam.[171a] While liver cirrhosis reduces plasma clearance of midazolam because of decreased metabolism.[172]

Midazolam is metabolized by CYP3A4 and CYP3A5 to its main metabolite 1-hydroxymidazolam and minor metabolite 4-hydroxymidazolam and 1,4-hydroxy midazolam.[173,174] These are subsequently conjugated to glucuronides and renally excreted. 1-Hydroxymidazolam possesses similar sedative activities compared to the parent compound. The metabolites are cleared more rapidly than midazolam, thus making them of little concern in patients with normal hepatic and renal function. In patients with renal impairment, however, the main metabolite and its conjugated metabolite can cause profound sedation.[175]

Diazepam

After oral ingestion, the bioavailability is approximately 94%.[176] Time to peak plasma concentrations after oral ingestion is approximately 60 minutes.[177] Diazepam is extensively bound to plasma proteins, and the volume of distribution ranges from 0.7 to 4.7 L/kg. The plasma clearance of diazepam ranges from 0.2 to 0.5 mL/kg/minute.[178]

The pharmacokinetics of diazepam is affected by obesity and liver dysfunction and particularly by age. Increasing age reduces the clearance of diazepam significantly.[179]

Metabolism occurs in the liver and is mediated mainly by CYP2C19 and CYP3A4. This accounts for 80% of the biotransformation of diazepam.[180-182] One of the main metabolites is *N*-desmethyldiazepam; it has pharmacodynamic characteristics similar to those of diazepam, but it has a much slower elimination half-life extending to 200 hours. *N*-desmethyldiazepam is further metabolized to oxazepam, which is also pharmacologically active; the metabolites add to and prolong the drug's effect.

Temazepam, another main metabolite of diazepam, is mainly conjugated to temazepam glucuronide, and a much smaller part is demethylated to oxazepam and thereafter conjugated to oxazepam glucuronide.[183]

Lorazepam

The oral bioavailability of lorazepam is high, nearly 90%. Peak plasma concentrations are reached approximately 2 hours after oral ingestion, and the mean elimination half-life is 15 hours, with a range of 8 to 25 hours.[184] Lorazepam has a large volume of distribution from 0.8 to 1.3 L/kg,[185] and it is highly bound to plasma proteins (>90%).

Clearance of lorazepam is 0.8 to 1.8 mL/kg/minute. Lorazepam is conjugated in the liver to an inactive glucuronide. This metabolite is water soluble and rapidly excreted in urine. The pharmacokinetics of lorazepam is not altered by age, gender, or renal disease, but clearance is decreased by hepatic dysfunction.[186]

Remimazolam (CNS 7056)

Remimazolam, a newer short-acting $GABA_A$ receptor agonist with high affinity to the GABA receptor, is rapidly degraded in plasma by nonspecific esterases to its carboxylic acid metabolite CNS 7054. The incorporation of a carboxylic ester moiety into the benzodiazepine core of remimazolam renders it susceptible to nonspecific tissue esterases.[187] Preclinical studies in sheep showed a more rapid onset of action, greater depth of sedation, and more rapid recovery than with midazolam. In sheep, remimazolam showed no dose-dependent depth of sedation such as occurs with propofol.[188] In humans, clearance of remimazolam was rapid (overall mean clearance, 70.3 ± 13.9 L/hour), and the volume of distribution was moderately large (steady-state volume of distribution, 34.8 ± 9.4 L). No clear relationship exists between body weight and systemic clearance. Level and duration of sedation are dose dependent in humans.[189]

PHARMACODYNAMICS

Benzodiazepines act selectively at the $GABA_A$ receptor, which mediates fast inhibitory synaptic transmission in the CNS. Benzodiazepines enhance the response to GABA by facilitating the opening of the GABA-activated chloride channels, with resulting hyperpolarization. Series of compounds (e.g., diazepam binding inhibitor and other substances) are candidates as endogenous ligands of the $GABA_A$ receptor. This is an area of ongoing research.[190]

Peripheral binding sites for benzodiazepines (renamed translocator protein (18kDa or TSPO), which are not associated with GABA receptors, exist in many tissues, including peripheral immune cells and the gastrointestinal tract. Although their precise function and pharmacologic significance remain only partly known, TSPO seems related to inflammatory activation.[191]

Effects on the Central Nervous System

All benzodiazepines have hypnotic, sedative, anxiolytic, amnestic, anticonvulsant, and centrally produced muscle-relaxing properties. They may differ to some extent in their potency and efficacy with regard to some of these pharmacodynamic actions (e.g., anticonvulsive action). The neurotransmitter GABA is an inhibitory neurotransmitter that controls the state of a chloride ion channel. Activation of this chloride ion channel results in neuronal hyperpolarization (increased membrane potential in the direction away from the threshold potential) and accounts for the classification of the GABA system as "inhibitory." Benzodiazepines bind to their receptors with high affinity. The binding is stereospecific and saturable; the order of receptor affinity (potency) of three agonists is lorazepam > midazolam > diazepam. Midazolam is approximately 3 to 6 times, and lorazepam 5 to 10 times, as potent as diazepam.[192] As indicated previously, the mechanism of action of benzodiazepines is reasonably well understood.[193,194] The interaction of benzodiazepine ligands with the $GABA_A$ receptor is one of the few examples in which the complex systems of biochemistry, molecular pharmacology, genetic mutations, and clinical behavioral patterns can to some extent be explained.

$GABA_A$ subtypes mediate the different effects (amnestic, anticonvulsant, anxiolytic, and sleep).[194] The $GABA_A$ receptor is a pentameric assembly built from 18 or more subunits (Fig. 30-9). Many different combinations of this pentameric assembly occur in different parts of the brain; linking this diversity to physiologic function and pharmacologic specificity may be possible. The α subunit of the pentameric complex occurs in six isoforms (α_1 to

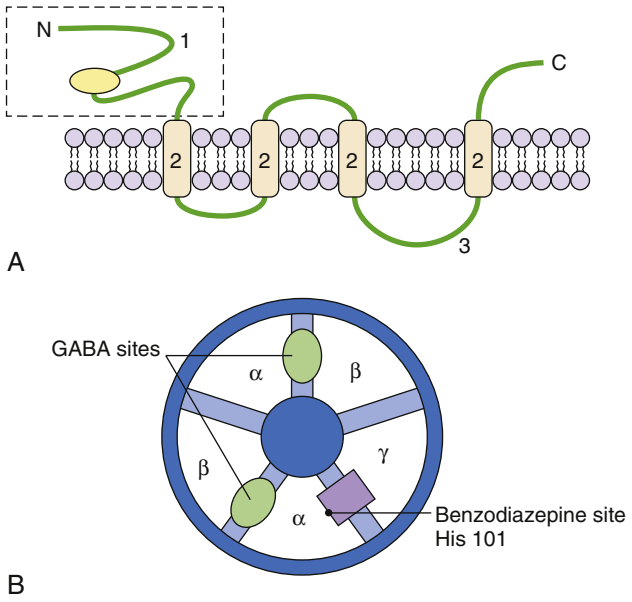


Figure 30-9. Schematics of γ-aminobutyric acid A ($GABA_A$) receptor structure and function. **A,** Topography of a $GABA_A$ receptor subunit partially embedded in the lipid bilayer: *1,* the N-terminal extracellular domain is responsible for transmitter and ligand binding and coupling of the binding sites with the ion channel; this part is also important for the assembly of various receptor subunits into functional receptors; *2,* four transmembrane segments forming the anion channel are responsible for binding of hydrophobic ligands, ion selectivity, and channel binding sites; *3,* an intracellular loop between transmembrane segments 3 and 4 forms the domain for regulatory phosphorylation sites and for the intracellular factors anchoring the receptors in appropriate locations. **B,** Hypothetic binding sites for GABA and benzodiazepine ligands in a pentameric receptor complex. *(From Saari TI, Uusi-Oukari M, Ahonen J, Olkkola KT: Enhancement of GABAergic activity: neuropharmacological effects of benzodiazepines and therapeutic use in anesthesiology,* Pharmacol Rev *63:243-267, 2011.)*

α_6).[186] Sedation, anterograde amnesia, and anticonvulsant properties are mediated by α_1 subunits of the $GABA_A$ receptors,[194] and anxiolysis and muscle relaxation are mediated by the α_2 subunits. The "benzodiazepine receptors" are found in highest densities in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantia nigra, and inferior colliculus, whereas lower densities are found in the striatum, lower brainstem, and spinal cord. Spinal cord benzodiazepine receptors can play an important role in analgesia; however, further elucidation of the mechanism of action of this drug class is required.[195] Intrathecal midazolam reduces excitatory GABA-mediated neurotransmission in interneurons and leads to a decrease in the excitability of spinal dorsal horn neurons.[195] A meta-analysis showed that intrathecal midazolam improves perioperative analgesia and reduces nausea and vomiting.[196]

The benzodiazepines reduce the $CMRO_2$ in a dose-related manner. Midazolam and diazepam maintain a relatively normal ratio of CBF to $CMRO_2$.[197] Midazolam, diazepam, and lorazepam all increased the seizure initiation threshold to local anesthetics and decreased the mortality rate in mice exposed to lethal doses of local anesthetics. Midazolam has neuroprotective effects by preventing lipid peroxidation and mitochondrial damage. Indications suggest that the peripheral benzodiazepine receptor is involved in these actions.[198]

Effects on the Respiratory System

Benzodiazepines, similar to most IV anesthetics, produce dose-related central respiratory system depression. The benzodiazepines affect respiration in two different ways. First, they have an effect on the muscular tone leading to an increased risk of upper airway obstruction.[199] Second, they flatten the response of the respiratory curve to carbon dioxide.[200] In addition, sedative doses of midazolam depress the hypoxic ventilatory response in humans.[201]

Benzodiazepines and opioids produce additive or supra-additive (synergistic) respiratory depression, even though they act at different receptors.[202] Old age, debilitating disease, and other respiratory depressant drugs increase the incidence and degree of respiratory depression and apnea by benzodiazepines.

Effects on the Cardiovascular System

The hypothalamic paraventricular nucleus is an important site for autonomic and endocrine homeostasis of the cardiovascular system. The paraventricular nucleus integrates afferent stimuli to regulate blood volume; the rostral ventrolateral medulla is the dominant brain region for tonic regulation of arterial blood pressure.[203] Under normal circumstances, the sympathetic nervous system is tonically inhibited. This inhibition depends on GABAergic signaling and nitric oxide.[204]

When used alone, benzodiazepines have modest hemodynamic effects. The predominant hemodynamic change is a modest decrease in arterial blood pressure resulting from a decrease in systemic vascular resistance. The mechanism by which benzodiazepines maintain relatively stable hemodynamics involves preservation of homeostatic reflex mechanisms, but the baroreflex may be impaired by midazolam and diazepam. The hemodynamic effects of midazolam and diazepam are dose related; however, a plateau plasma drug effect is seen above which little change in arterial blood pressure occurs. The plateau plasma level for midazolam is 100 ng/mL, and that for diazepam is approximately 900 ng/mL. Heart rate, ventricular filling pressures, and cardiac output are maintained after induction of anesthesia with benzodiazepines. In patients with increased left ventricular filling pressures, diazepam and midazolam produce a "nitroglycerin-like" effect by decreasing the filling pressure and increasing cardiac output. Notably, the stresses of endotracheal intubation and surgery are not blocked by midazolam.

DRUG INTERACTIONS

Pharmacokinetic Drug Interactions

The pharmacokinetics of benzodiazepines may be altered by drug interactions. Because cytochrome P450 is often involved in the metabolism of the benzodiazepines, drugs inducing or inhibiting CYP function often cause alterations in the pharmacokinetics of the benzodiazepines.

CYP-mediated drug interactions have extensively been examined using midazolam, which is almost completely metabolized by the CYP system, particularly CYP3A4.

The inhibition of CYP3A by concomitantly administered drugs such as the azole antifungal agents (among many others) results in significant inhibition of the metabolism of midazolam.[205] Orally administered midazolam is especially affected by these inhibitors because of a reduction of first-pass metabolism elimination.[206]

Diazepam is primarily metabolized by CYP2C19 and CYP3A4. Different CYP2C19 alleles have varying activity, which results in ultrarapid, extensive, intermediate, and poor metabolizer genotypes.[207,208] Pharmacokinetics and pharmacodynamics vary among these different metabolizers.[209,210] Strong inhibitors of CYP3A4 have a minor effect on the pharmacokinetics of diazepam.[211,212] Inhibitors of CYP2C19 such as omeprazole, fluvoxamine, and ciprofloxacin consequently increase the plasma half-life of diazepam substantially.[213-215] The clearance of lorazepam is affected by probenecid and valproic acid, both of which decrease the formation and clearance of lorazepam glucuronide.[216,217] Because remimazolam is not metabolized by CYP-dependent mechanisms, the chance of significant drug interactions is less.

Pharmacodynamic Drug Interaction

All benzodiazepines act on the CNS and interact with other drugs targeting the CNS, in particular those causing CNS depression.

In anesthetic practice, opioids are often combined with benzodiazepines, which interact in a synergistic manner.[218] The interaction between midazolam and ketamine is additive,[219] whereas the interaction between the hypnotic effects of thiopental and midazolam and those of propofol and midazolam is synergistic.[20,220]

USES

Premedication

Benzodiazepines are the most commonly applied drugs for premedication (see also Chapter 38). The goals of this application are anxiolysis, sedation, amnesia, vagolysis and sympatholysis and reduction of PONV.[221] The amnestic effects are anterograde; retrograde memory is not affected.

Diazepam, lorazepam, and midazolam are given by the oral or IV route for preoperative sedation. Midazolam is the most frequently used benzodiazepine for premedication in both adults and children.[222] The usual oral dose for adults ranges from 7.5 to 15 mg for midazolam, from 5 to 10 mg for diazepam and from 10 to 20 mg for temazepam.[223] Many factors such as age, ASA physical status, level of anxiety, and type and length of surgical procedure determine the dose. Lorazepam is mostly used when prolonged and intense anxiolysis is pursued, such as in cardiac surgery. Typically, 2 to 4 mg lorazepam is administered orally 2 hours before anesthesia and surgery.[224]

For pediatric patients, midazolam is available in several preparations (including a formulation for intranasal administration in some countries) and is well tolerated. The dose is effective from 0.25 mg/kg and produces sedation and anxiolysis in 10 to 20 minutes (see also Chapter 93).

TABLE 30-7 USES AND DOSES OF INTRAVENOUS BENZODIAZEPINES

	Midazolam	Diazepam	Lorazepam
Induction	0.05-0.15 mg/kg	0.3-0.5 mg/kg	0.1 mg/kg
Maintenance	0.05 mg/kg prn 1 μg/kg/min	0.1 mg/kg prn	0.02 mg/kg prn
Sedation*	0.5-1 mg repeated 0.07 mg/kg IM	2 mg repeated	0.25 mg repeated

From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors: Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.*

IM, Intramuscularly; *prn,* as required to keep patient hypnotic and amnesic.

*Incremental doses given until desired degree of sedation is obtained.

Midazolam has minimal effects on respiration and oxygen saturation, even in doses up to 1.0 mg/kg (maximum, 20 mg).

Sedation

Relief of anxiety and lack of recall of unpleasant events during minor surgical and diagnostic procedures are the primary objectives of good sedation. Appropriately used sedation improves patients' satisfaction.[221] Patients are seemingly conscious and coherent during sedation with benzodiazepines, yet they are amnesic for the procedure and events.[225] For this use, drugs should be given by titration; endpoints of titration are adequate sedation and dysarthria (Table 30-7). The onset of action is rapid with midazolam, usually with a peak effect reached within 2 to 3 minutes of administration; time to peak effect is slightly longer with diazepam and is even longer still with lorazepam.

The duration of action of these drugs is dose dependent. Although the onset is more rapid with midazolam than with diazepam after bolus administration, the recovery is similar, probably because both drugs have similar early plasma decay (redistribution) patterns[226] (Fig. 30-10). With lorazepam, sedation and particularly amnesia are slower in onset and are longer lasting than with the other two benzodiazepines.[227] Lorazepam is particularly unpredictable with regard to duration of amnesia, and this feature is undesirable in patients who wish or need to have recall in the immediate postoperative period. The degree of sedation and the reliable amnesia and the preservation of respiratory and hemodynamic function are better with benzodiazepines than with other sedative-hypnotic drugs used for conscious sedation. When midazolam is compared with propofol for sedation during procedures, the two are generally similar, except that emergence or wake-up is more rapid with propofol. Sedation with propofol is safe in the hands of well-trained professionals who are not anesthesia practitioners. However, decisions about which providers should administer propofol remain controversial. Although propofol is a wonderful drug, only individuals who are well trained should administer it, and training in airway management is an absolute requirement.[228,229]

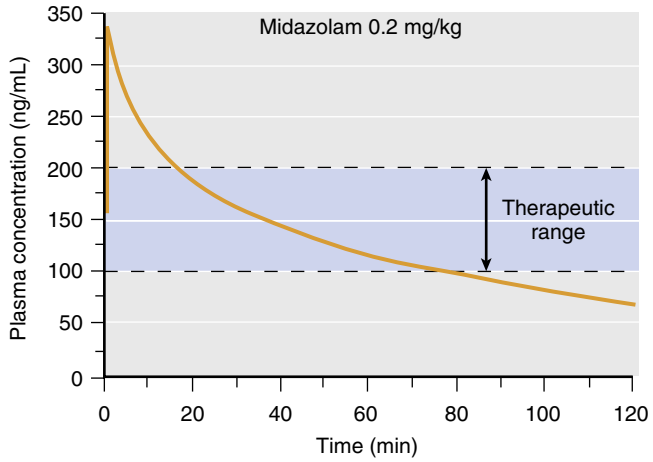


Figure 30-10. Simulated time course of plasma levels of midazolam after an induction dose of 0.2 mg/kg. Plasma levels required for hypnosis and amnesia during surgical procedures are 100 to 200 ng/mL, with awakening usually occurring at levels less than 50 ng/mL. *(From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

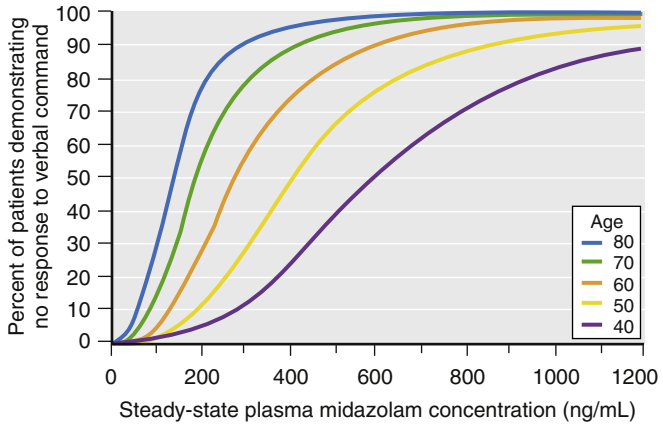


Figure 30-11. Simulated quantal concentration-response curves generated by the parameterized pharmacodynamic model for midazolam. *(Redrawn from Jacobs JR, Reves JG, Marty J, et al: Aging increases pharmacodynamic sensitivity to the hypnotic effects of midazolam,* Anesth Analg *80:143-148, 1995.)*

Reports suggested that remimazolam has a favorable profile as a sedative agent for upper gastrointestinal endoscopy in patients because the time to recovery was shorter and more consistent than that observed after the use of midazolam.[187,189] The use of midazolam for sedation during regional and epidural anesthesia requires vigilance with regard to depth of sedation and respiratory function.[230]

Two studies reported the use of midazolam during cesarean section either for sedation or prevention of nausea and vomiting; the results showed that use of a single IV dose of midazolam was a safe practice, with no detriment in Apgar scores, neurobehavioral scores, continuous oxygen saturation, or the ability of the mother to recall the birth events.[231] Nitsun and associates found that 0.005% of the maternal dose of midazolam is transferred into the breast milk during a 24-hour milk collection.[232] Although verification of these findings is needed, they highlight an important clinical use of midazolam that may be safe for mother and infant (see also Chapter 77).

Sedation for longer periods, such as in the ICU, can also be accomplished with benzodiazepines. The February 1, 2014 issue of the *New England Journal of Medicine* sets the standard for overall sedation in the ICU.[121] Prolonged infusion may result in accumulation of drug and, in the case of midazolam, significant concentration of the active metabolite. Reviews have pointed out both concerns and advantages of benzodiazepine sedation.[233] The main advantages are amnesia and hemodynamic stability, and the disadvantage is the potential lingering sedative effect after termination of the infusion, when compared with propofol. In 2013, the Society of Critical Care Medicine's (SCCM) American College of Critical Care Medicine (ACCM) published a revised version of its pain, agitation, and delirium clinical practice guidelines for adult patients in the ICU. These guidelines suggest that sedation strategies using nonbenzodiazepine sedatives may be preferred over sedation with benzodiazepines, either midazolam or lorazepam, to improve clinical outcome in mechanically ventilated patients in the ICU.[234] To prevent overdosing and prolonged mechanical ventilation, evidenced-based sedation algorithms have evolved. Daily interruption of sedation has not proven to decrease the time to extubation of the trachea or the length of hospital stay.[235]

Induction and Maintenance of Anesthesia

Midazolam is the benzodiazepine of choice for induction of anesthesia. Numerous factors influence the rapidity of action of midazolam and the other benzodiazepines when used for induction of general anesthesia, including dose, speed of injection, degree of premedication, age, ASA physical status, and concurrent anesthetic drugs. The usual induction dose of midazolam is 0.1 to 0.2 mg/kg in premedicated patients, and up to 0.3 mg/kg in unpremedicated patients. The onset of anesthesia is within 30 to 60 seconds. The half-time of equilibrium between the plasma concentration and the EEG effects is approximately 2 to 3 minutes.[236]

Older patients require smaller doses of midazolam than do younger patients[237] (Fig. 30-11) (see also Chapter 80).

When midazolam is combined with other anesthetic drugs (coinduction), often a synergistic interaction occurs, similar to that seen with propofol. This synergy is observed when midazolam is used with opioids or other hypnotics, similar to propofol in combination with opioids[20,52,238] (Fig. 30-12).

Emergence time is related to the dose of midazolam and to the dose of adjuvant anesthetic drugs.

Benzodiazepines lack analgesic properties and must be used with other anesthetic drugs to provide sufficient analgesia; however, as maintenance anesthetic drugs during general anesthesia, benzodiazepines provide hypnosis and amnesia. The amnesic period after an anesthetic dose is approximately 1 to 2 hours.

A plasma level of more than 50 to 100 ng/mL occurs when benzodiazepines are used with adjuvant opioids (e.g., fentanyl) or inhaled anesthetics (e.g., nitrous oxide, volatile anesthetics) with a bolus initial dose of 0.05 to 0.15 mg/kg and a continuous infusion of 0.25 to 1 μg/kg/minute.[239] This plasma level is sufficient to keep the

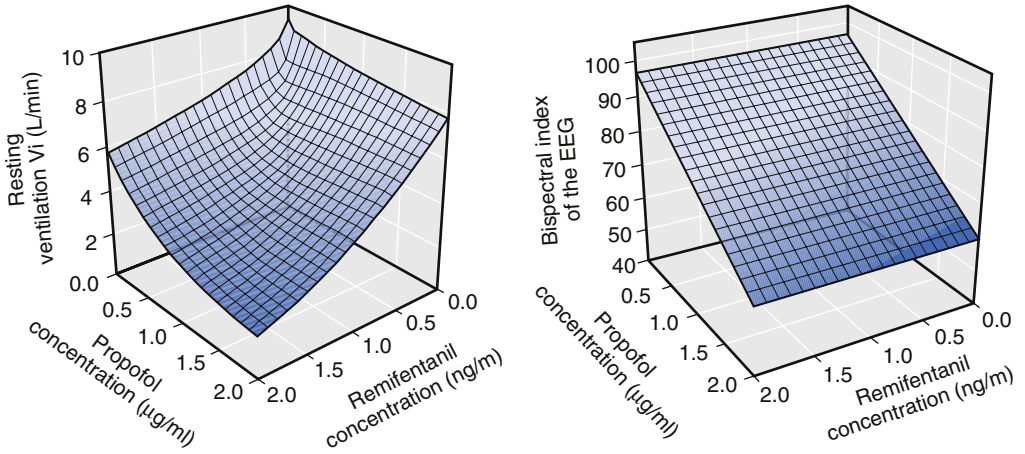


Figure 30-12. Response surface modeling of the interaction of remifentanil and propofol on resting ventilation and the bispectral index (BIS) of the electroencephalogram. Population response surface showing that the propofol-remifentanil interaction on respiration is synergistic and on BIS is inert because remifentanil had no effect on the BIS irrespective of the propofol concentrations. Over this dose range, propofol causes a linear decrease in BIS, with a 25% decrease occurring at 1.4 µg/mL. *(From Nieuwenhuijs DJ, Olofsen E, Romberg RR, et al: Response surface modeling of remifentanil-propofol interaction on cardiorespiratory control and bispectral index,* Anesthesiology *98:312-322, 2003.)*

patient asleep and amnesic but arousable at the end of surgery. Smaller infusion doses may be required in some patients or in combination with opioids. Midazolam, diazepam, and lorazepam accumulate in the blood after repeated bolus administrations or with continuous infusion. If the benzodiazepines do accumulate with repeated administration, prolonged arousal time can be anticipated. This is less of a problem with midazolam than with diazepam and lorazepam because of the shorter context-sensitive half-time and greater clearance of midazolam. Remimazolam may be a good alternative; it is rapidly metabolized and had a faster recovery profile than midazolam in sheep.[188,189]

Nausea and Vomiting Prophylaxis

Numerous studies have highlighted the role that benzodiazepines, and specifically midazolam, may play in the prevention of PONV (see also Chapter 97). Jung and colleagues found that in women undergoing middle ear surgery, IV midazolam, 0.075 mg/kg after induction of anesthesia, reduced the incidence of PONV and the need for rescue antiemetics, with no difference from placebo in pain intensity or drowsiness.[240] Furthermore, the combination of midazolam and dexamethasone proved more effective in preventing PONV than did midazolam alone.[241] The incidence of PONV after minor gynecologic or urologic surgical procedures was the same when comparing IV ondansetron, 4 mg, and IV midazolam, 2 mg.[242]

In children (see also Chapter 93), IV midazolam, 0.05 mg/kg, reduced PONV significantly after pediatric (4 to 12 years old) surgical procedures to treat strabismus compared with placebo or IV dexamethasone, 0.5 mg/kg. No child vomited with midazolam alone or with the midazolam-dexamethasone combination.[243,244]

Finally, in a 2010 three-arm, placebo-controlled, double-blind clinical trial, Fujii and associates compared midazolam 0.050 mg/kg with 0.075 mg/kg for PONV prophylaxis in patients undergoing laparoscopic gynecologic surgical procedures. The two doses of midazolam were not significantly different with regard to PONV (30% versus 27% of patients experienced PONV), and both proved better than placebo (67%).[245]

SIDE EFFECTS AND CONTRAINDICATIONS

Benzodiazepines have limited allergenic effects and do not suppress the adrenal gland. The most significant side effect of midazolam is respiratory depression. The major side effects of lorazepam and diazepam, in addition to respiratory depression, are venous irritation and thrombophlebitis, problems related to aqueous insolubility and requisite solvents.[165] When used as sedatives or for induction and maintenance of anesthesia, benzodiazepines may produce an undesirable degree or prolonged interval of postoperative amnesia, sedation, and, rarely, respiratory depression. These residual effects can be reversed with flumazenil.[246]

FLUMAZENIL

Flumazenil (Anexate, Romazicon) is the first benzodiazepine antagonist approved for clinical use.[247] It is a benzodiazepine receptor ligand with high affinity, great specificity, and by definition minimal intrinsic effect. Flumazenil, similar to the agonists it replaces at the benzodiazepine receptor, interacts with the receptor in a concentration-dependent manner. It is a competitive antagonist at the benzodiazepine receptor and produces antagonism that is reversible and surmountable. In humans, flumazenil has minimal agonist activity, which means that its benzodiazepine receptor agonist effects are very weak, significantly less than those of clinical agonists.[248] Flumazenil, like all competitive antagonists at receptors, does not displace the agonist, but rather occupies the receptor when an agonist dissociates from the receptor. The half-time (or half-life) of a receptor-ligand bond is a few milliseconds to a few seconds, and new ligand-receptor bonds are immediately formed. This

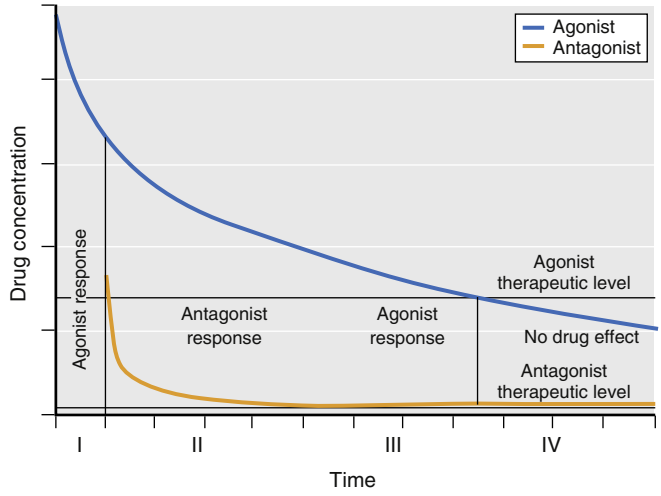


Figure 30-13. Schematic representation of the interaction of a short-acting antagonist with a longer-acting agonist, with resulting resedation. The *blue curve* shows disappearance of agonist from blood, and the *gold curve* shows disappearance of antagonist from plasma. Four conditions are represented: I, agonist response; II, antagonist response (the antagonist reverses the agonist effect); III, agonist response (resedation or resumption of agonist response with disappearance of short-lasting antagonist); and IV, no drug effect, with disappearance of agonist and antagonist (both drugs are below the therapeutic level). *(From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

dynamic situation accounts for the ability of either an agonist or an antagonist to occupy the receptor readily. The ratio of agonist to total receptors produces the effects of the agonist drug, but the antagonist can alter this ratio, depending on its concentration and dissociation constant. Flumazenil, which is an avid (high-affinity) ligand, replaces a relatively weak agonist, such as diazepam, as long as it is given in sufficient dose. Flumazenil is rapidly metabolically cleared, however, and the proportion of receptors occupied by the agonist then increases again, with the potential for rebound sedation and respiratory suppression (Fig. 30-13). This situation is less likely to occur when flumazenil is used to reverse midazolam, which has a more rapid clearance than that of the other benzodiazepine agonists.

Another important finding is that in the presence of extremely large doses of agonist (e.g., when a mistake in dosing has occurred or if suicide by means of an overdose is attempted), a small dose of flumazenil attenuates the deep CNS depression (loss of consciousness, respiratory depression) by reducing the fractional receptor occupancy by the agonist without decreasing the agonist effects that occur at low fractional receptor occupancy (drowsiness, amnesia).

Conversely, large doses of flumazenil in the presence of small doses of agonist completely reverse all the agonist effects. Flumazenil can precipitate withdrawal symptoms in animals or in humans physically dependent on a benzodiazepine receptor agonist.[249] However, this is not a problem when flumazenil is used to reverse clinical effects of benzodiazepine receptor agonists applied in the practice of anesthesia.

PHYSICOCHEMICAL CHARACTERISTICS

Flumazenil is similar to midazolam and other classic benzodiazepines except for the absence of the phenyl group, which is replaced by a carbonyl group (see Fig. 30-8). It forms a colorless, crystalline powder. It has a dissociation constant of 1.7 and weak but sufficient water solubility to permit its preparation in aqueous solution. Its octanol/aqueous buffer (pH 7.4) partition coefficient is 14, showing moderate lipid solubility at pH 7.4.[250]

PHARMACOKINETICS

Flumazenil, similar to the other benzodiazepines, is completely (99%) metabolized in the liver. It is rapidly cleared from the plasma, and it has three known metabolites: *N*-desmethylflumazenil, *N*-desmethylflumazenil acid, and flumazenil acid.[251] The metabolic end product (i.e., flumazenil acid) has no pharmacologic activity. The major metabolites identified in urine are the deethylated free acid and its glucuronide conjugate. Flumazenil is a short-lived compound. Table 30-5 includes a summary of its pharmacokinetic properties, which are described in various clinical settings. The volume of distribution is high, and extravascular distribution is rapid.

Compared with most benzodiazepine receptor agonists, flumazenil has very rapid clearance and a short elimination half-life.[252] Only remimazolam has more rapid clearance and a shorter half-life. The plasma half-life of flumazenil is approximately 1 hour, the shortest of all benzodiazepines used in anesthetic practice. The rapid blood clearance of flumazenil approaches hepatic blood flow, a finding that indicates that liver clearance partially depends on hepatic blood flow. Compared with other benzodiazepines, flumazenil has a high proportion of unbound drug; plasma protein binding is approximately 40%. The potential exists for the antagonist to be cleared, thus leaving sufficient concentrations of agonist at the receptor site to cause recurrent sedation.[253] To maintain a constant therapeutic blood level over a prolonged time, either repeated administration or a continuous infusion is required. An infusion rate of 30 to 60 μg/minute (0.5 to 1 μg/kg/minute) has been used for this purpose.[254]

PHARMACODYNAMICS

When given in the absence of a benzodiazepine receptor agonist, flumazenil has little discernible CNS effect. When given to healthy subjects and patients in clinically relevant doses, flumazenil has no effect on the EEG or cerebral metabolism. Flumazenil is free of anticonvulsant properties, and it reverses the anticonvulsant properties of benzodiazepines in local anesthetic–induced seizures.[255] When administered to patients who have benzodiazepine-induced CNS depression, flumazenil produces rapid and dependable reversal of unconsciousness, respiratory depression, sedation, amnesia, and psychomotor dysfunction.[256] Flumazenil can be given before, during, or after the agonist to block or reverse the CNS effects of the agonist.

Flumazenil has successfully reversed the effects of benzodiazepines such as midazolam, diazepam, lorazepam,

and flunitrazepam. It has also been used successfully to reverse the effects of chloral hydrate and cannabis intoxication in children (see also Chapter 95),[257,258] carbamazepine and alcohol overdose,[259] and antihistamine overdose.[260] The onset is rapid, with peak effect occurring in 1 to 3 minutes, which coincides with the detection of C-flumazenil in human brain.[256] Flumazenil reverses the agonist by replacing it at the benzodiazepine receptor, and its onset and duration are governed by the law of mass action. When flumazenil is given in the presence of agonists, it has significant respiratory effects because it reverses respiratory depression caused by the agonists (e.g., when given to volunteers made apneic with midazolam). For example, the reversal of midazolam-induced (0.13 mg/kg) respiratory depression with flumazenil (1 mg) lasts 3 to 30 minutes. Other agonists and other doses would have different durations of antagonism of respiratory depression.

Incremental IV doses up to 3 mg in patients with ischemic heart disease had no significant effect on cardiovascular variables.[256,261] Administration of flumazenil to patients given agonists is remarkably free of cardiovascular effects, in contrast to the experience of opioid reversal with naloxone.[262] Although flumazenil does reverse sedation, it does not increase blood concentrations of catecholamines. However, catecholamine levels may increase when arousal is more rapid after flumazenil.[263] The reversal of sedation by midazolam with flumazenil also restores the attenuated cardiac baroreflex function.[264]

In healthy subjects, flumazenil did not alter intraocular pressure but reversed the decrease in intraocular pressure observed after administration of midazolam (Romazicon package insert; www.fda.gov).

USES AND DOSES

Application of a benzodiazepine antagonist includes the diagnostic and therapeutic reversal of benzodiazepine receptor agonists (Box 30-2). For diagnostic use in suspected benzodiazepine overdose, flumazenil may be given in incremental IV doses of 0.2 to 0.5 mg up to 2 mg. More commonly in anesthesia, flumazenil is used to reverse residual sedation in a patient after administration of a benzodiazepine for premedication of a short surgical procedure, conscious sedation, or general anesthesia. Flumazenil reliably reverses the sedation, respiratory depression, and amnesia caused by benzodiazepines. Differential reversal effects on the different agonist actions are noted. Flumazenil tends to reverse the hypnotic and respiratory effects more than the amnestic effects of the benzodiazepine agonist.[265,266]

The dose varies with the particular benzodiazepine being reversed, and the duration of reversal depends on the kinetics of the agonist and of flumazenil. Surveillance is recommended if a long-lasting benzodiazepine is reversed with a single administration of flumazenil because of the relatively short-lived effect. If a patient shows no signs of recurrent sedation within 2 hours after a 1-mg reversal dose of flumazenil, serious recurrent sedation at a later time is unlikely. Flumazenil may be administered by continuous infusion to prevent recurrent sedation by longer-lasting benzodiazepine receptor agonists. The pharmacokinetic profile of flumazenil is unaltered in the presence of benzodiazepine agonists (diazepam, flunitrazepam, lormetazepam, midazolam) and vice versa.

BOX 30-2 *Uses and Doses of Flumazenil*

Reversal of benzodiazepines*	0.2 mg repeated† up to 3 mg
Diagnosis in coma	0.5 mg repeated up to 1 mg

From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors: Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.*

*The dose required to reverse each benzodiazepine (BZD) depends on residual BZD and the particular BZD (i.e., higher doses are required for more potent BZDs) (see text).

†The degree of reversal should be titrated by repeating 0.2-mg increments every 1 to 2 minutes until the desired level of reversal is achieved.

SIDE EFFECTS AND CONTRAINDICATIONS

Flumazenil has been given in large oral and IV doses with remarkably few toxic reactions.[256] It is free of local or tissue irritant properties, and it has no known organ toxicities. Like all benzodiazepines, flumazenil apparently has a high safety margin, probably higher than the safety margins of the agonists, because it does not produce prominent CNS depression. In patients using large doses of benzodiazepines over several weeks or longer, the administration of flumazenil may elicit symptoms of benzodiazepine withdrawal, including seizures.

PHENCYCLIDINES (KETAMINE)

HISTORY

Ketamine (Ketalar) was synthesized in 1962 by Stevens and was first used in humans in 1965 by Corssen and Domino. Ketamine was released for clinical use in 1970 and is still used in various clinical settings. It produces dissociative anesthesia, rather than generalized depression of the CNS, through antagonistic actions at the phencyclidine (PCP) site of the NMDAR. Ketamine is a racemic mixture of the isomers R(−)-ketamine and S(+)-ketamine. It usually does not depress the cardiovascular and respiratory systems, but it does have some of the adverse psychological effects found with the other phencyclidines.[267] The S(+)-isomer (Ketanest) is three to four times more potent as an analgesic with a faster clearance and recovery and with fewer psychomimetic side effects. Nonetheless, S-ketamine produces psychotropic effects, cognitive impairment, memory impairment, and a reduced reaction time, in addition to analgesia. Interest in ketamine has increased because of its effects on hyperalgesia and opiate tolerance, use in chronic pain states, potential neuroprotective effects, increasing popularity of total IV anesthesia, and the availability in some countries of S(+)-ketamine.[268]

PHYSICOCHEMICAL CHARACTERISTICS

Ketamine has a molecular weight of 238 kDa, is partially water soluble, and forms a white crystalline salt with a

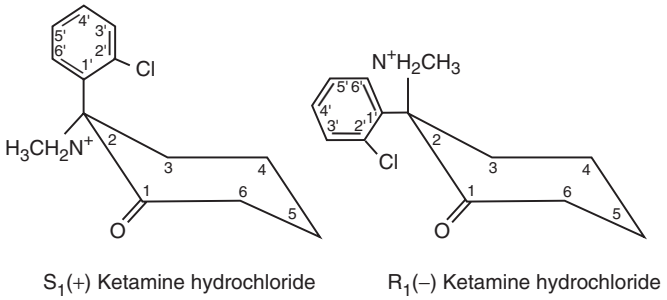


Figure 30-14. Stereoisomers of ketamine as it is formulated. *(From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

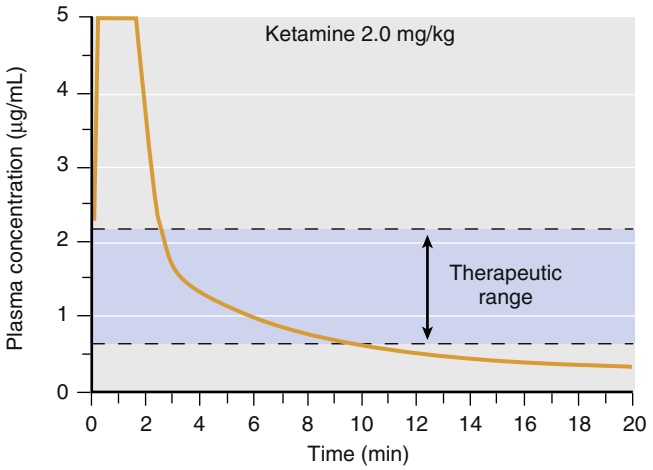


Figure 30-15. Simulated time course of plasma levels of ketamine after an induction dose of 2 mg/kg. Plasma levels required for hypnosis and amnesia during surgical procedures are 0.7 to 2.2 μg/mL, with awakening usually occurring at levels less than 0.5 μg/mL. *(From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

pK_a of 7.5 (Fig. 30-14). It has a lipid solubility 5 to 10 times that of thiopental. Ketamine is only for 12% bound to proteins. Its bioavailability is 93% after parenteral administration but only 20% after oral use, as a result of its high first-pass metabolism.[269]

PHARMACOKINETICS

Ketamine is metabolized by hepatic microsomal enzymes.[270,271] The major pathway involves *N*-demethylation to form norketamine (metabolite I), which is then hydroxylated to hydroxynorketamine, which is further conjugated to water-soluble glucuronide derivatives and excreted in the urine. The activity of the principal metabolites of ketamine has not been well studied, but norketamine (metabolite I) has significantly less (20% to 30%) activity than the parent compound. More recent modeling of norketamine suggests that it contributes in prolonging the analgesia provided by either a bolus or infusion of ketamine, although this conclusion is being questioned.[270,272,273] In contrast to previous reports, S-norketamine may have a negative contribution to S-ketamine–induced analgesia but shows absence of contribution to the cognitive impairment. This may explain the observation of ketamine-related excitatory phenomena (e.g., hyperalgesia and allodynia) upon the termination of ketamine infusions.[270,272,273]

Ketamine's pharmacokinetics has been examined after bolus administration of anesthetizing doses (2 to 2.5 mg/kg IV), after a subanesthetic dose (0.25 mg/kg IV), and after continuous infusion (steady-state plasma level 2000 ng/mL).

Regardless of the dose, the plasma disappearance of ketamine can be described by a two-compartment model. Table 30-1 contains the pharmacokinetic values from bolus administration studies. Of note is the rapid distribution reflected in the relatively brief distribution half-life of 11 to 16 minutes (Fig. 30-15). The high lipid solubility of ketamine is reflected in its large volume of distribution of nearly 3 L/kg.[271,274] Clearance also is high, 890 to 1227 mL/minute, which accounts for the short elimination half-life of 2 to 3 hours. Mean total body clearance (1.4 L/minute) is approximately equal to liver blood flow. Low-dose alfentanil increases the volume of distribution and clearance of ketamine. In addition, alfentanil increases the distribution of ketamine into the brain. The pharmacokinetic model of Clements provided the best accuracy when it was used to administer low-dose ketamine to volunteers using a target-controlled infusion device.[271] The pharmacokinetics of the two isomers is different. S(+)-ketamine has a larger elimination clearance and larger volume of distribution than R(–)-ketamine. When the pharmacokinetics of S(+)-ketamine was tested in a target-controlled infusion device for procedures of 1 hour and in combination with propofol, the investigators found that the accuracy of the pharmacokinetic parameters was improved with a much smaller Vc central volume of distribution (167 mL/kg).[275] The investigators also noted that ketamine clearance was not normally distributed, and this was not related to age. The S(+) enantiomer also seems to be more potent in suppressing the EEG than either R(–) or the racemic mixture. Ketamine is increasingly being given by alternative routes, especially orally and through an intranasal spray. Administration by either of these routes is subject to significant first-pass metabolism. The bioavailability by oral administration is 20% to 30%, and by the intranasal route it is approximately 40% to 50%. In clinical and experimental studies, hyperalgesic responses were noted after the withdrawal of S(+)-ketamine.[272-274,276,277] Furthermore, no delay between concentration and effect has been observed for any of the antinociceptive endpoints. This finding indicates an almost immediate passage of S(+)-ketamine across the blood-brain barrier and rapid receptor kinetics.

PHARMACODYNAMICS

Effects on the Central Nervous System

Ketamine produces dose-related unconsciousness and analgesia. Ketamine acts at multiple receptors, including the NMDARs, opioid receptors, and monoaminergic receptors. At high ketamine concentrations, σ opioid receptors

are also affected, muscarinic receptors are blocked, and GABA-ergic neurotransmission is facilitated. The most important action of ketamine is inhibition of NMDAR-mediated glutamergic input to the GABA-ergic system that leads to changing excitatory activity in the cortex and limbic system that in the end results in unconsciousness. At the spinal cord level, ketamine has potent antinociceptive effects on the NMDAR and inhibits acetylcholine release.[272-274] The anesthetized state has been termed *dissociative anesthesia* because patients who receive ketamine alone appear to be in a cataleptic state, in contrast to other states of anesthesia that resemble normal sleep. Patients anesthetized with ketamine have profound analgesia, but they keep their eyes open and maintain many reflexes. Corneal, cough, and swallow reflexes all may be present, but they should not be assumed to be protective. The patient has no recall of surgery or anesthesia, but amnesia is not as prominent with ketamine as with the benzodiazepines. Because ketamine has a low molecular weight, a pK_a near the physiologic pH, and relatively high lipid solubility, it crosses the blood-brain barrier rapidly and has an onset of action within 30 to 60 seconds of administration. The maximal effect occurs in approximately 1 minute.

After ketamine administration, pupils dilate moderately, and nystagmus occurs. Lacrimation and salivation are common, as is increased skeletal muscle tone, often with coordinated but seemingly purposeless movements of the arms, legs, trunk, and head. Although interindividual variability is great, plasma levels of 0.6 to 2 μg/mL are considered the minimum concentrations for general anesthesia; children may require slightly higher plasma levels (0.8 to 4 μg/mL) (see also Chapter 93). The duration of ketamine anesthesia after a single IV administration of a general anesthetic dose (2 mg/kg) is 10 to 15 minutes (see Fig. 30-15), and full orientation to person, place, and time occurs within 15 to 30 minutes. The S(+) enantiomer enables quicker recovery (by a couple of minutes) than does the racemic mixture,[278,279] as a result of the smaller dose necessary to produce an equianesthetic effect and the 10% faster hepatic biotransformation. Because of the good correlation between blood concentration of ketamine and the CNS effect, the relatively short duration of action of ketamine probably reflects its redistribution from the brain and blood to the other tissues in the body.

Concomitant administration of benzodiazepines, which is a common practice, may prolong the effect of ketamine. When used in combination with a benzodiazepine, the S(+) enantiomer was no different in terms of awareness at 30 minutes, but it was significantly better at 120 minutes than the racemic mixture. Analgesia occurs at considerably lower blood concentrations than does loss of consciousness.

Ketamine provides important postoperative analgesia. The plasma level at which pain thresholds are elevated is 0.1 μg/mL or greater.[276,280,281] This means that a considerable period of postoperative analgesia occurs after ketamine general anesthesia, and subanesthetic doses can consequently be used to produce analgesia. Ketamine inhibits nociceptive central hypersensitization. Ketamine also attenuates acute tolerance after opiate administration. The NMDAR plays an important role in the induction of hyperalgesia and antinociceptive tolerance as induced by opioids. Prophylactic ketamine administration may thus prevent both central sensitization and long-lasting enhancement in pain sensitivity as induced by opioids. Ketamine, like other NMDAR antagonists, may thus prevent opioid-induced hyperalgesia.[282] The primary site of CNS action of ketamine seems to be the thalamoneocortical projection system. The drug selectively depresses neuronal function in parts of the cortex (especially association areas) and thalamus while stimulating parts of the limbic system, including the hippocampus. This process creates what is termed a *functional disorganization* of nonspecific pathways in midbrain and thalamic areas. Ketamine acts by antagonism of the excitatory glutamatergic NMDAR. The NMDAR has high expression in the temporal cortex, hippocampus, basal ganglia, cerebellum, and brainstem, all regions significantly affected by ketamine.

Evidence also indicates that ketamine depresses transmission of impulses in the medial medullary reticular formation, which is important for transmission of the affective-emotional components of nociception from the spinal cord to higher brain centers. In volunteers experiencing heat pain, fMRI studies showed that ketamine produced a dose-dependent effect on pain processing by decreasing activation of the secondary somatosensory cortex (S2), insula, and anterior cingulate cortex. Ketamine occupies opiate receptors in the brain and spinal cord, and this property could account for some of the analgesic effects.[283,284] The S(+) enantiomer has some opioid μ-receptor activity, thus accounting for part of its analgesic effect. NMDAR interaction may mediate the general anesthetic effects and some analgesic actions of ketamine. The spinal cord analgesic effect of ketamine is postulated to be caused by inhibition of dorsal horn wide dynamic range neuronal activity. In a resting-state fMRI study, low-dose ketamine induced connectivity changes in brain areas involved in motor function, psychedelic effects, and pain processing. Ketamine's analgesic effect may arise from multiple pathways: decreased connectivity in regions of the pain matrix responsible for the perception of pain (pain sensing) and the affective processing of pain. In addition, ketamine affects connectivity in brain areas involved in endogenous pain inhibition.[285,286]

Although some drugs have been used to antagonize ketamine, no specific receptor antagonist reverses all the CNS effects of ketamine.

Ketamine increases cerebral metabolism, CBF, and ICP (see Chapter 70). Because of its excitatory CNS effects, which can be detected by generalized EEG development of theta wave activity and by petit mal seizure-like activity in the hippocampus, ketamine increases $CMRO_2$. The increase in CBF appears higher than the increase in $CMRO_2$ would mandate. With the rise in CBF and the generalized increase in sympathetic nervous system response, ICP increases after ketamine use. The increase in $CMRO_2$ and CBF can be blocked by the use of thiopental or diazepam. Cerebrovascular responsiveness to carbon dioxide seems to be preserved with ketamine; reducing $Paco_2$ attenuates the rise in ICP after ketamine.

S(+)-ketamine may influence the expression of apoptosis-regulating proteins in rat brains 4 hours after cerebral ischemia and reperfusion. The neuroprotection observed

with ketamine may involve antiapoptotic mechanisms in addition to reducing necrotic cell death.

In contrast, ketamine and other anesthetic agents such as propofol and volatile anesthetic agents accentuate apoptosis in the newborn brain of animals and cause changes in the morphology of dendritic spines. This finding has sparked controversy over the use of ketamine in neonates. An editorial in the journal *Anesthesiology* and the Anesthetic and Life Support Drugs Advisory Committee of the FDA cautioned changing clinical practice based on present available data (see also Chapter 93).

Ketamine, like other phencyclidines, produces undesirable psychological reactions, which occur during awakening from ketamine anesthesia and are termed *emergence reactions*. The common manifestations of these reactions, which vary in severity and classification, are vivid dreaming, extracorporeal experiences (sense of floating out of body), and illusions (misinterpretation of a real, external sensory experience). These incidents of dreaming and illusion are often associated with excitement, confusion, euphoria, and fear. They occur in the first hour of emergence and usually abate within 1 to several hours. These psychic emergence reactions are secondary to ketamine-induced depression of auditory and visual relay nuclei, thus leading to misperception or misinterpretation of auditory and visual stimuli. The incidence of the psychic emergence reactions ranges from 3% to 100%. A clinically relevant range is probably 10% to 30% of adult patients who receive ketamine as a sole or major part of the anesthetic technique. Factors that affect the incidence of emergence reactions are age, dose, gender, psychological susceptibility, and concurrent drugs. Pediatric patients do not report as high an incidence of unpleasant emergence reactions as do adult patients; men also report a less frequent incidence compared with women.

Larger doses and rapid administration of large doses seem to predispose patients to a frequent incidence of adverse effects. Finally, certain personality types seem prone to the development of emergence reactions. Patients who score high in psychotism on the Eysenck Personality Inventory are prone to develop emergence reactions, and individuals who commonly dream at home are more likely to have postoperative dreams in the hospital after ketamine. Although numerous drugs have been used to reduce the incidence and severity of postoperative reactions to ketamine, the benzodiazepines seem to be the most effective group of drugs.

Effects on the Respiratory System

Ketamine has minimal effects on the central respiratory drive as reflected by an unaltered response to carbon dioxide. A transient (1 to 3 minutes) decrease in minute ventilation can occur after the bolus administration of an induction IV dose of ketamine (2 mg/kg). Unusually large doses can produce apnea, but this is seldom seen. In a μ-opioid knockout mouse model, however, at supraspinal sites S(+)-ketamine interacted with the μ-opioid receptor system. This interaction contributed significantly to S(+)-ketamine–induced respiratory depression and supraspinal antinociception.[287,288] With the use of adjuvant sedatives or anesthetic drugs, respiratory depression may become clinically significant. Ketamine depresses ventilatory control in children, especially with bolus doses. Ketamine is a bronchial smooth muscle relaxant. When it is given to patients with reactive airway disease and bronchospasm, pulmonary compliance is improved.

Ketamine is as effective as halothane or enflurane in preventing experimentally induced bronchospasm. The mechanism for this effect is probably a result of the sympathomimetic response to ketamine, but isolated bronchial smooth muscle studies showed that ketamine can directly antagonize the spasmogenic effects of carbachol and histamine. Because of its bronchodilating effect, administration of ketamine can treat status asthmaticus unresponsive to conventional therapy. A potential respiratory problem, especially in children, is the increased salivation that follows ketamine administration; this effect can be modulated by an anticholinergic drug such as atropine or glycopyrrolate (see also Chapter 93).

Effects on the Cardiovascular System

Ketamine increases arterial blood pressure, heart rate, and cardiac output in a biphasic manner. It has a direct cardiodepressant, negative inotropic effect next to an indirect stimulatory effect secondary to activation of the sympathetic system. Ketamine causes the systemic release of catecholamines, inhibition of the vagal nerve, inhibition of norepinephrine reuptake at peripheral nerves and nonneuronal tissues such as the myocardium, and norepinephrine release from sympathetic ganglia.[289] Cardiodepression precedes stimulation after large-dose ketamine administration or occurs after repeated administrations when presynaptic catecholamine stores become depleted. Cardiovascular stimulation already occurs after small-dose ketamine infusion and is characterized by tachycardia, systemic and pulmonary hypertension, increases in cardiac output, and myocardial oxygen consumption. Whereas the cardiovascular stimulatory effects of ketamine generally are dominant, after termination of S-ketamine infusion, cardiovascular depression may become evident because cardiac output may decrease to less than preinfusion values.[272] The cardiovascular stimulatory effect of S(+)-ketamine is characterized by an increase in the cardiac output of 1 L/minute in the presence of 243 ng/mL S(+)-ketamine.[272] The cardiovascular stimulatory effect of S(+)-ketamine is induced very rapidly with a half-life for onset and offset of the effect of ketamine on cardiac output of 1 to 2 minutes.

The increase in hemodynamic variables is associated with increased work and myocardial oxygen consumption. The healthy heart augments oxygen supply by increased cardiac output and decreased coronary vascular resistance, so that coronary blood flow is appropriate for the increased oxygen consumption. Patients with congenital heart disease have no significant changes in shunt directions or fraction, or systemic oxygenation, after ketamine induction of anesthesia (see also Chapter 94). In patients who have increased pulmonary artery pressure (e.g., patients with mitral valvular and some congenital lesions), ketamine causes a more pronounced increase in pulmonary than systemic vascular resistance. Ketamine injected directly into the CNS produces an immediate sympathetic nervous system hemodynamic response. Ketamine also causes the sympathoneuronal release of

norepinephrine, which can be detected in venous blood. Blockade of this effect is possible with barbiturates, benzodiazepines, and droperidol. The centrally mediated sympathetic responses to ketamine usually override the direct depressant effects of ketamine. Some peripheral nervous system actions of ketamine play an undetermined role in the hemodynamic effects of the drug. Ketamine inhibits intraneuronal uptake of catecholamines by a cocaine-like effect, and it inhibits extraneuronal norepinephrine uptake.

Stimulation of the cardiovascular system is not always desirable, and certain pharmacologic methods have been used to block ketamine-induced tachycardia and systemic hypertension. Probably the most fruitful approach has been prior administration of benzodiazepines. Modest doses of diazepam, flunitrazepam, and midazolam all attenuate the hemodynamic effects of ketamine. It also is possible to decrease the tachycardia and hypertension caused by ketamine by using a continuous infusion technique with or without a benzodiazepine. Inhalation anesthetics and propofol blunt the hemodynamic effect of ketamine.

USES

The many unique features of ketamine pharmacology, especially its propensity to produce unwanted emergence reactions in 10% to 20% of patients, have limited its use for routine anesthesia. Nevertheless, ketamine has an important niche in the practice of anesthesiology when its unique sympathomimetic activity and bronchodilating capabilities are indicated during induction of anesthesia. It is used for premedication, sedation, induction, and maintenance of general anesthesia. Interest in the use of ketamine in small doses for preventive analgesia and for the treatment or prevention of opiate tolerance and hyperalgesia and in treatment of acute and chronic pain has increased.

Induction and Maintenance of Anesthesia

The cardiovascular stimulatory effects make ketamine a desirable drug for the induction of anesthesia in unstable cardiovascular patients suffering from hypovolemia, hemorrhagic shock, or cardiovascular depression in sepsis. Ketamine bronchodilation and profound analgesia allowing the use of high oxygen concentrations make ketamine an excellent choice for induction of anesthesia in patients with reactive airway disease. Patients who have sustained trauma with extensive blood loss are typical candidates for rapid-sequence anesthesia induction with ketamine (see also Chapter 81). Patients with septic shock also may benefit from ketamine. The intrinsic myocardial depressant effect of ketamine may manifest in this situation if trauma or sepsis has caused depletion of catecholamine stores before the patient's arrival in the operating room. Use of ketamine in these patients does not obviate the need for appropriate preoperative preparation, including restoration of intravascular blood volume.

Other cardiac diseases that can be well managed with ketamine anesthesia are cardiac tamponade and restrictive pericarditis. The finding that ketamine preserves heart rate and right atrial pressure through its sympathetic stimulating effects makes ketamine an excellent anesthetic induction and maintenance drug in this setting. Ketamine also is often used in patients with congenital heart disease, especially patients with a propensity for right-to-left shunting (see also Chapter 94). Ketamine has been successfully used in a patient susceptible to malignant hyperthermia. Ketamine combined with propofol or midazolam can be given by continuous infusion to produce satisfactory cardiac anesthesia for patients with valvular and ischemic heart disease. The combination of a benzodiazepine or of a benzodiazepine and sufentanil with ketamine attenuates or eliminates the unwanted tachycardia and hypertension and postoperative psychological derangements. With this technique, patients have minimal hemodynamic perturbations, profound analgesia, dependable amnesia, and an uneventful convalescence. The use of propofol in combination with small-dose ketamine also has gained increasing popularity as a total IV anesthesia technique for patients undergoing noncardiac surgical procedures. The advantages of this combination are maintenance of stable hemodynamics and minimal ventilatory depression when allowing spontaneous ventilation.

Pain Management

Postoperative pain is a major concern of many patients, and it is inadequately treated in as many as 30% to 50% of all postoperative patients (see also Chapter 98). Multimodal analgesia combining various analgesic agents that act through different pathways is the way to manage postoperative pain. Ketamine is increasingly used as one of the constituents of this multimodal analgesia therapy. Over the years, the ketamine dose used for perioperative analgesia has gradually been decreasing. Ketamine administered in small doses decreases postoperative analgesic consumption by 33%. Several meta-analyses of the use of small-dose ketamine (20 to 60 mg) perioperatively have been performed. These meta-analyses showed an overall decrease in opiate use or improved analgesia and a decrease in opiate-induced side effects, especially PONV. Side effects, especially psychomimetic effects, were minimal, especially if a benzodiazepine also was administered.

The action of ketamine on opiate tolerance and hyperalgesia combined with its direct analgesic activity has led to its use in chronic pain states. Ketamine may be effective in the treatment of cancer pain, chronic peripheral and central neuropathic pain, phantom and ischemic limb pain, fibromyalgia, complex regional pain syndrome, visceral pain, and migraine. The epidural or caudal administration of ketamine (0.5 to 1 mg/kg) is effective. Although the efficacy of these doses of ketamine seems to be established, the safety of this technique has not yet received regulatory approval. The preservative of racemic mixture is potentially neurotoxic, whereas studies to date indicate that preservative-free S(+)-ketamine may be safe. Epidural preservative-free S(+)-ketamine has been shown to be safe and of value as an adjunct to corticosteroids in patients for the treatment of chronic low back pain secondary to radiculopathy.[290] The favorable hemodynamic effects and conservation of respiration make ketamine, administered by the IV route and even intranasally, useful for analgesia after extremity fractures.

BOX 30-3 *Uses and Doses of Ketamine*

Induction of general anesthesia*	0.5-2 mg/kg IV 4-6 mg/kg IM
Maintenance of general anesthesia	0.5-1 mg/kg IV with N_2O 50% in O_2 15-45 μg/kg/min IV with N_2O 50-70% in O_2 30-90 μg/kg/min IV without N_2O
Sedation and analgesia	0.2-0.8 mg/kg IV over 2-3 min 2-4 mg/kg IM
Preemptive or preventive analgesia	0.15-0.25 mg/kg IV

From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors: Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.*

IM, Intramuscularly; *IV,* intravenously; *N_2O,* nitrous oxide.

*Lower doses are used if adjuvant drugs such as midazolam or thiopental also are given.

Sedation

Ketamine is often combined with premedication with a barbiturate or benzodiazepine and an antisialagogue (e.g., glycopyrrolate) to facilitate management. The premedications reduce the dose requirement for ketamine, and the antisialagogue reduces the sometimes troublesome salivation. In adults and children, ketamine can be used as a supplement or an adjunct to regional anesthesia, thereby extending the usefulness of the primary (local anesthetic) form of anesthesia. In addition, ketamine is increasingly used for short, painful procedures in the emergency department. The dose used then is between 0.1 and 0.6 mg/kg. As previously described, ketamine also may be considered for sedation of patients in a critical care unit because of its combined sedative and analgesic properties and favorable effects on hemodynamics. Ketamine can even be used safely in head-injured patients when they are adequately ventilated.[291,292]

Ketamine is particularly suitable for sedation of pediatric patients undergoing procedures outside the operating room. Pediatric patients have fewer adverse emergence reactions than adults, and this feature makes the use of ketamine in pediatric patients more versatile (see also Chapter 93).

DOSES AND ROUTES OF ADMINISTRATION

Ketamine has been administered by the IV, intramuscular (IM), transcutaneous, oral, nasal, and rectal routes and as a preservative-free solution epidurally or intrathecally. Most clinical use involves the IV and IM routes, by which the drug rapidly achieves therapeutic concentrations. The dose depends on the desired therapeutic effect and on the route of administration. Box 30-3 contains general recommended doses for the IV and IM administration of ketamine for various therapeutic goals. Intranasal administration has an onset closer to that of IV administration; an oral dose of 3 to 10 mg/kg generates a sedative effect in 20 to 45 minutes. For sedation, ketamine may be given in an IM dose of 2 to 4 mg/kg. It also has been administered orally in doses of 3 to 10 mg/kg, with 6 mg/kg providing optimal conditions in 20 to 25 minutes in one study and 10 mg/kg providing sedation in 87% of children within 45 minutes in another study.

SIDE EFFECTS AND CONTRAINDICATIONS

Contraindications to ketamine relate to specific pharmacologic actions and diseases. In patients with increased ICP who are breathing spontaneously, ketamine should be used with caution because it can increase ICP and has been reported to cause apnea. Ketamine is increasingly used clinically in emergency airway management in patients with brain injury with or without other bodily injuries. In this setting, the current knowledge of safe management of increased ICP is continuing to grow.[291,292]

In mechanically ventilated patients, ketamine retains the response of CBF to carbon dioxide, a property that makes it useful in head-injured patients because of its potential neuroprotective effect. Ketamine may be contraindicated in patients with an open eye injury or other ophthalmologic disorder, in which a ketamine-induced increase in intraocular pressure would be detrimental (see also Chapter 84). Because ketamine has a propensity to cause hypertension and tachycardia, with a commensurate increase in myocardial oxygen consumption, it may be contraindicated as the sole anesthetic agent in patients with ischemic heart disease. Similarly, it is unwise to give ketamine to patients with vascular aneurysms because of the possible sudden change in arterial blood pressure. Psychiatric disease, such as schizophrenia, and a history of adverse reaction to ketamine or one of its congeners also are contraindications. One also should consider carefully using ketamine when the patient may develop postoperative delirium from other causes (e.g., delirium tremens, possibility of head trauma), and a ketamine-induced psychomimetic effect would confuse the differential diagnosis.

As mentioned earlier, ketamine or other NMDAR antagonists accentuate apoptosis in the newborn brain of animals, and the clinical implications of this are unknown. Finally, because ketamine's preservative, chlorobutanol, is neurotoxic, this formulation of ketamine for subarachnoid or epidural administration is contraindicated. S(+)-ketamine is available in a preservative-free solution. The FDA has not approved the use of intrathecal or epidural ketamine. Caudal ketamine has been used for perioperative analgesia in children and neonates with 0.5 mg/kg as the optimal dose (see also Chapter 93). Caudal analgesia, by combinations of ketamine and a local anesthetic, prolongs analgesia from 2.26 to 5.3 hours and reduces the need for nonopioid analgesics.[293-297]

Finally, liver and renal toxicity occurs in the recreational abuse of ketamine. In addition, when ketamine was repeatedly administered in the treatment of chronic pain in patients with complex regional pain syndrome type 1, hepatotoxicity developed in patients who received two 100-hour infusions of S(+)-ketamine with a 16-day interval.[295,298,299]

ETOMIDATE

HISTORY

The first report of etomidate was published in 1965.[300] Etomidate was introduced into clinical practice in 1972. The unique properties of etomidate include hemodynamic stability, minimal respiratory depression, cerebral

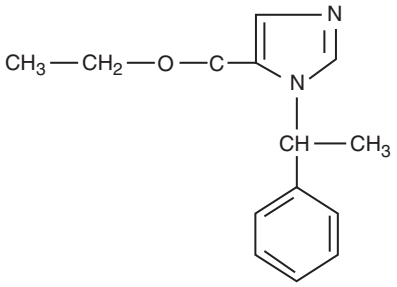


Figure 30-16. Structure of etomidate, an imidazole derivative. *(From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

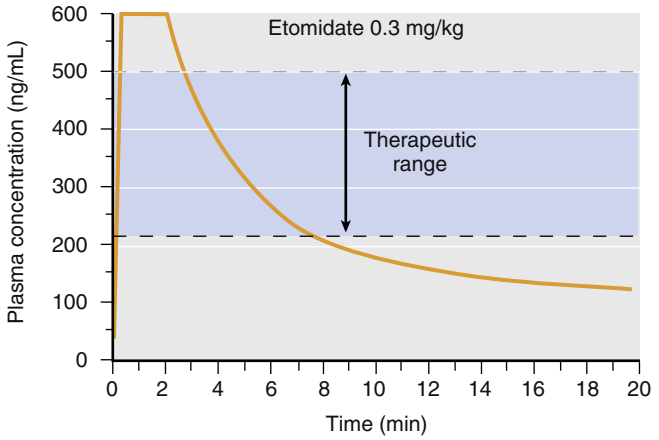


Figure 30-17. Simulated time course of plasma levels of etomidate after an induction dose of 0.3 mg/kg. Plasma levels required for hypnosis during surgical procedures are 300 to 500 ng/mL, with awakening usually occurring at levels less than 225 ng/mL. *(From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

protection, favorable toxicity profile, and pharmacokinetics enabling rapid recovery after either a single dose or a continuous infusion. In the 1970s, these beneficial properties led to widespread use of etomidate for induction, for maintenance of anesthesia, and for prolonged sedation in critically ill patients. The enthusiasm among clinicians for etomidate was tempered in the 1980s by reports that the drug can cause temporary inhibition of steroid synthesis after single doses and infusions.[301,302] This effect, combined with other minor disadvantages (e.g., pain on injection, superficial thrombophlebitis, myoclonus, and a frequent incidence of nausea and vomiting), led to several editorials questioning the role of etomidate in modern anesthetic practice.[303,304] Use of the drug decreased after those editorials, but it has expanded again as a result of the rediscovery of etomidate's beneficial physiologic profile and a widening use in emergency departments and ICUs, combined with a lack of novel reports describing clinically significant adrenocortical suppression after induction or brief infusions.

PHYSICOCHEMICAL CHARACTERISTICS

Etomidate is an imidazole derivative (R-(+)-pentylethyl-1H-imidazole-5 carboxylate sulfate). Its chemical structure is illustrated in Figure 30-16. Etomidate has a pK_a of 4.2 and is hydrophobic at physiologic pH. To increase its solubility, it is formulated as a 0.2% solution either in 35% propylene glycol (Amidate, Hospira, Inc., Lake Forest, Ill) or in a lipid emulsion (Etomidate-Lipuro, B. Braun, Melsungen, Germany).[305]

PHARMACOKINETICS

The pharmacokinetics of etomidate has been determined after single bolus doses and after continuous infusion. The time course of plasma disappearance after a 0.3 mg/kg bolus is shown in Figure 30-17. The pharmacokinetics of etomidate is best described by an open three-compartment model.[306]

The drug has an initial distribution half-life of 2.7 minutes, a redistribution half-life of 29 minutes, and an elimination half-life of 2.9 to 5.3 hours.[307] Clearance of etomidate by the liver is high (18 to 25 mL/kg/minute), with a hepatic extraction ratio of 0.5 ± 0.9.[306] Because redistribution is the mechanism whereby the effect after a bolus of etomidate is dissipated, hepatic dysfunction should not appreciably alter recovery from a single induction dose. Etomidate is 75% protein bound.

A hemorrhagic shock model in pigs bled to an MAP of 50 mm Hg did not alter etomidate pharmacokinetics or pharmacodynamics.[308] This finding contrasts with the marked changes seen in this same model with other IV anesthetics. In patients with cirrhosis, the volume of distribution is doubled, whereas clearance is normal; the result is an elimination half-life that is twice normal.[309] The initial distribution half-life and clinical effect are likely unchanged. Increasing age is associated with a smaller initial volume of distribution and decreased clearance of etomidate.[310]

The short elimination half-life and rapid clearance of etomidate did make it suitable for administration in a single dose, in multiple doses, or in a continuous infusion with its context-sensitive half-time being shorter than that of propofol.[311] However, continuous infusion was only practiced in the first decade of its clinical availability, but the now widely recognized adrenal suppression limits this application. Etomidate is mainly metabolized in the liver by ester hydrolysis to the corresponding carboxylic acid and an ethanol leaving group (main metabolite).[312] The main metabolite is inactive. Only 2% of the drug is excreted unchanged; the remaining part is excreted as metabolites by the kidney (85%) and bile (13%). Pathologic conditions altering serum proteins (e.g., hepatic or renal disease) affect the amount of the free (unbound) fraction and may cause a dose to have an exaggerated pharmacodynamic effect.[313]

PHARMACODYNAMICS

Effects on the Central Nervous System

The primary action of etomidate on the CNS is through the $GABA_A$ receptor and results in hypnosis,[314,315] which

is achieved in one arm–brain circulation after a normal induction dose (0.3 mg/kg). The mechanism by which etomidate produces hypnosis is almost exclusively through $GABA_A$ receptor facilitation.[315,316] This mechanism includes two effects produced by different concentrations of etomidate. The first is the positive modulation of the $GABA_A$ receptor: activation of the receptor by agonists at concentrations associated with clinical doses. A lower dose of GABA is required in the presence of etomidate to activate the $GABA_A$ receptor.[317] The second action is called the direct activation or allosteric agonism. In supraclinical concentrations, etomidate can directly, thus in absence of GABA, activate the $GABA_A$ receptor.[318] These two actions suggest two independent binding sites at the $GABA_A$ receptor.[315] The $GABA_A$ receptors containing β_2 and β_3 subunits are modulated and activated by etomidate, whereas those containing β_1 are much less affected.

At a dose of 0.2 to 0.3 mg/kg, etomidate reduces CBF by 34% and $CMRO_2$ by 45% without altering MAP. CPP is maintained or increased, and a beneficial net increase in the cerebral oxygen supply-to-demand ratio occurs.[319] When given in doses sufficient to produce EEG burst suppression, etomidate acutely decreases ICP by 50% in patients with already increased ICP, thereby returning increased ICP to almost normal values.[320] The decrease in ICP is maintained in the period immediately after intubation. To maintain the effects of etomidate on ICP, high infusion rates (60 μg/kg/minute) are necessary. Controversy remains on the neuroprotective qualities of etomidate. A dose-dependent increase in latency and a decreasing amplitude of the auditory evoked potentials are noted.[321]

Preliminary animal experiments suggested that in a case of acute fetal distress and hypoxic injury, propofol and midazolam may be preferred over etomidate to protect the fetal brain as the first-choice anesthetic agent in cesarean delivery.[198,322,323] Etomidate has been associated with grand mal seizures and produces increased EEG activity in epileptogenic foci. This feature has proven useful for intraoperative mapping of seizure foci before surgical ablation.[324,325] BIS monitor values decrease after etomidate bolus administration and return to baseline during recovery.[326] During etomidate infusion, the BIS values reliably predict the depth of sedation and hypnosis.[327]

Effects on the Respiratory System

Etomidate has less effect on ventilation than do other anesthetics used to induce anesthesia. It does not induce histamine release in healthy patients or in patients with reactive airway disease.[328] Ventilatory response to carbon dioxide is depressed by etomidate, but the ventilatory drive at any given carbon dioxide tension is greater than that following an equipotent dose of methohexital.[154] Induction of anesthesia with etomidate produces a brief period of hyperventilation, sometimes followed by a similarly brief period of apnea,[329] which results in a slight (± 15%) increase in $Paco_2$, but no change in Pao_2.[330] Etomidate's actions on pulmonary vascular tone are similar to the actions observed with ketamine and propofol; that is, they attenuate the vasorelaxant responses to acetylcholine and bradykinin.[331]

Effects on the Cardiovascular System

The hemodynamic stability seen with etomidate is caused by its lack of effect on the sympathetic nervous system and on the function of the baroreceptor.[332] The minimal effect of etomidate on cardiovascular function sets it apart from other rapid-onset anesthetics.[333,334] Etomidate has proven useful in patients with valvular or ischemic heart disease who are undergoing noncardiac surgical procedures and in patients with poor cardiac function.[335,336] In patients receiving etomidate during induction of anesthesia, more hypertension and tachycardia occur after etomidate compared with propofol.[337] The myocardial oxygen supply-to-demand ratio is well maintained.[338] Etomidate lacks analgesic efficacy, however, and must be combined with an opiate to prevent hemodynamic perturbations during laryngoscopy and intubation.

In the setting of hemorrhagic shock, etomidate has advantages for induction of anesthesia. In contrast to other drugs, the pharmacodynamics and pharmacokinetics of etomidate were minimally altered in a pig model of hemorrhagic shock.[308]

Endocrine Effects

In 1983, Ledingham and Watt reported retrospective data showing increased mortality among patients in the ICU who were receiving long-term etomidate infusion compared with patients receiving benzodiazepines.[301] These investigators postulated that adrenocortical suppression could be the cause of this increased mortality. Soon after this publication, clinical investigators confirmed the adrenocortical suppression by etomidate.[302,339]

The specific endocrine effects manifested by etomidate consist of a dose-dependent reversible inhibition of the enzyme 11β-hydroxylase, which results in decreased biosynthesis of cortisol. Blockade of the cytochrome P450–dependent enzyme 11β-hydroxylase also results in decreased mineralocorticoid production and increased formation of intermediaries (11-deoxycorticosterone) (Fig. 30-18). Subsequent research has shown that etomidate is far more potent as an inhibitor of steroid synthesis than as a sedative-hypnotic agent.[339,340] The etomidate concentrations associated with adrenocortical suppression are less than 10 ng/mL, which are much lower than the concentrations needed for hypnosis (>200 ng/mL). The disparate concentrations for hypnosis and adrenotoxicity may explain the dramatic difference in duration of these two actions.[57]

Concerns about the use of etomidate and etomidate-induced adrenal toxicity in critically ill patients have reemerged. The literature is conflicting regarding the potential benefits of etomidate over other induction agents in critically ill patients, and its safety in patients with sepsis is a matter of strong debate in the critical care community. As indicated earlier, etomidate is associated with suppression of adrenal steroidogenesis, which can last up to 72 hours. However, the clinical impact of this adrenal suppressive effect is not certain.[341]

The Corticosteroid Therapy of Septic Shock (CORTICUS) study followed 500 patients with septic shock who were randomized to receive either low-dose

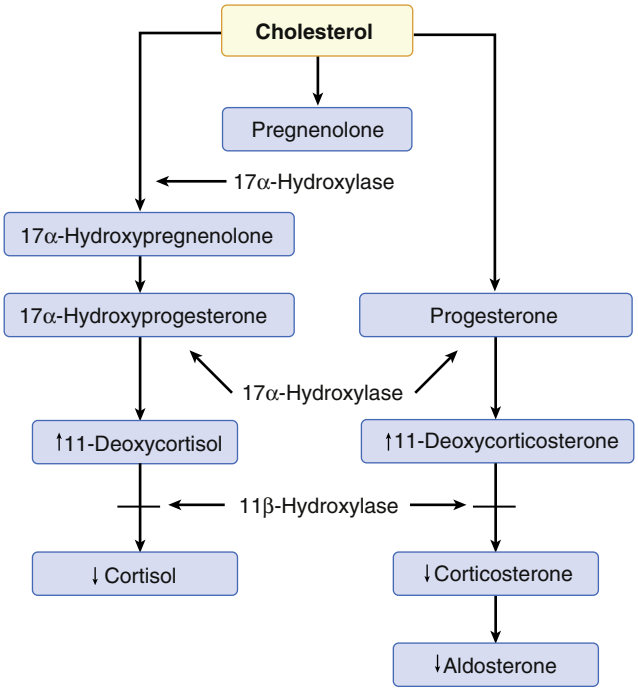


Figure 30-18. Pathway for the biosynthesis of cortisol and aldosterone. The sites at which etomidate affects cortisol-aldosterone synthesis by its action on 11β-hydroxylase (major site) and 17α-hydroxylase (minor site) are illustrated. *(From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

corticosteroid therapy or placebo. Twenty percent of the patients received etomidate. The study concluded that low-dose corticosteroid therapy had no benefit with regard to long-term outcome.[342] Retrospective analyses of the CORTICUS population suggest that patients receiving etomidate before enrollment had a 28-day mortality significantly higher and that steroid supplements provided no benefit.[343,344] Results of other studies designed to evaluate the effect of etomidate on morbidity and mortality and hospital and ICU length of stay are not conclusive.[345-348] In conclusion, the impact of the use of a single dose of etomidate in critically ill patients remains unclear.

USES

Induction of Anesthesia

The induction dose of etomidate is 0.2 to 0.6 mg/kg (Box 30-4).[349] The induction dose is reduced by premedication with an opiate, a benzodiazepine, or a barbiturate. Onset of anesthesia after a routine induction dose of 0.3 mg/kg of etomidate is rapid (one arm–brain circulation). In the past, various infusion schemes were devised to use etomidate as a maintenance anesthetic agent for the hypnotic component of anesthesia. After the publications on the adrenocortical suppressive effects of etomidate, continuous infusion was abandoned.

Etomidate is most appropriate in patients with cardiovascular disease, reactive airway disease, intracranial

BOX 30-4 *Uses and Doses of Etomidate*

Induction of general anesthesia	0.2-0.6 mg/kg IV
Sedation and analgesia	Limited to periods of brief sedation because of inhibition of corticosteroid synthesis

From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors: Miller's anesthesia, *ed 7, Philadelphia, 2010, Churchill Livingstone, pp 719-768.*
IV, Intravenously; N_2O, nitrous oxide.

hypertension, or any combination of disorders indicating the need for an induction agent with limited or beneficial physiologic side effects. The hemodynamic stability of etomidate is unique among the rapid-onset anesthetic agents used to induce anesthesia. In multiple studies, etomidate has been used for induction in patients with a compromised cardiovascular system who are undergoing coronary artery bypass surgery or valve surgery, as well as in patients requiring induction of general anesthesia for percutaneous transluminal coronary angioplasty, aortic aneurysm repair, and thoracic surgery. For cardioversion, the rapid onset, quick recovery, and maintenance of arterial blood pressure in these sometimes hemodynamically tenuous patients, combined with continued spontaneous respiration, make etomidate an acceptable choice.[350] Etomidate has been successfully used in neurosurgical procedures such as giant aneurysm clipping and is a reasonable choice during induction of anesthesia for neurosurgical procedures.[351] In addition, etomidate should be considered as an anesthetic induction agent to reduce increased ICP when maintenance of cerebral or coronary perfusion pressure is important.

Patients with trauma who have questionable intravascular volume status may be well served by an induction of anesthesia with etomidate. Although the indirect sympathomimetic effect seen with ketamine induction is absent, no direct myocardial depression occurs. When etomidate is used in patients with trauma, loss of consciousness by itself can be associated with decreased adrenergic output, and controlled ventilation can exacerbate the cardiovascular effects of a decreased preload. Both these factors may cause a significant decrease in arterial blood pressure during induction of anesthesia even though etomidate has no direct cardiovascular drug effect.

Short-term sedation with etomidate is useful in hemodynamically unstable patients, such as patients requiring cardioversion or patients requiring sedation after an acute myocardial infarction or with unstable angina for a minor operative procedure.[350] When used during electroconvulsive therapy, etomidate can produce longer seizures compared with other hypnotic agents.[352,353] Induction of anesthesia with etomidate is an independent risk factor in the development of emergence delirium.[354]

Treatment in Hypercortisolemia

Etomidate has a special place in the treatment of endogenous hypercortisolemia. It is proven to be an effective

parenteral treatment for this indication. In patients with unstable hemodynamic factors, patients with sepsis, or patients with psychosis, treatment should be performed under intensive care conditions.[355]

SIDE EFFECTS

Although etomidate provides stable hemodynamics and minimal respiratory depression, it is associated with several adverse effects when it is used for induction, including nausea and vomiting, pain on injection, myoclonic movement, and hiccups. Etomidate has been associated with PONV. More recently, etomidate in a lipid emulsion was associated with equal or an increased incidence of postoperative nausea compared with propofol.[356-358]

The lipid formulation of etomidate is associated with a much less frequent incidence of pain on injection, thrombophlebitis, and histamine release.[359,360] Pain on injection may be reduced by injecting IV lidocaine, 20 to 40 mg immediately before injection of etomidate.

The incidence of muscle movement (myoclonus) and of hiccups is highly variable (0% to 70%), but myoclonus is reduced by premedication with a hypnotic agent such as midazolam or a small dose of magnesium 60 to 90 seconds before the induction dose of etomidate is given.[361,362]

NOVEL ETOMIDATE DERIVATIVES

Etomidate is a well-known and widely used anesthetic agent for induction of anesthesia. The limitations of etomidate are, as mentioned earlier, adrenocortical suppression, myoclonus, and PONV. Modifying etomidate could improve its clinical utility and produce etomidate derivatives with a better profile.

Methoxycarbonyletomidate (MOC) is an etomidate derivative and is rapidly metabolized to methoxycarbonyletomidate carboxylic acid (MOC-ECA). The hypnotic potency of MOC is almost equal to that of etomidate, and the duration of the induced anesthesia is short because of rapid metabolism by nonspecific esterase enzymes. In preclinical studies, MOC may not act as an inhibitor of adrenal steroid synthesis.[363] Carboetomidate, another derivative, contains a five-membered pyrrole ring instead of an imidazole. In tadpoles and rats, carboetomidate reduced the adrenal suppression potency by three orders. Carboetomidate has potent hypnotic properties by activating $GABA_A$ receptors and thus causing minimal hemodynamic changes.[364]

DEXMEDETOMIDINE

HISTORY

The α_2-adrenergic receptor agonists have sedative, anxiolytic, hypnotic, analgesic, and sympatholytic effects. The potential for use in anesthesia was recognized in patients who were treated with clonidine.[365] Soon thereafter, a reduction of the minimum alveolar concentration (MAC) of halothane by clonidine was described.[366] Dexmedetomidine is a more selective α_2-agonist with a selectivity ratio for the α_2 receptor compared with the α_1 receptor of 1600:1, as compared with a ratio of 220:1 for clonidine. It was introduced in clinical practice in the United States in 1999 and was approved by the FDA only as a short-term (<24 hours) sedative for mechanically ventilated adult patients in the ICU. Dexmedetomidine is used for prolonged sedation and anxiolysis in the ICU, as well as outside the ICU in various settings, including sedation and adjunct analgesia in the operating room and sedation in diagnostic and procedure units, as well as for other applications such as withdrawal or detoxification amelioration in adult and pediatric patients.[367,368]

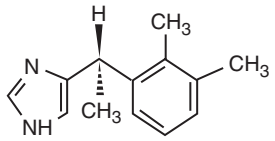


Figure 30-19. Chemical structure of dexmedetomidine. *(From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

PHYSICOCHEMICAL CHARACTERISTICS

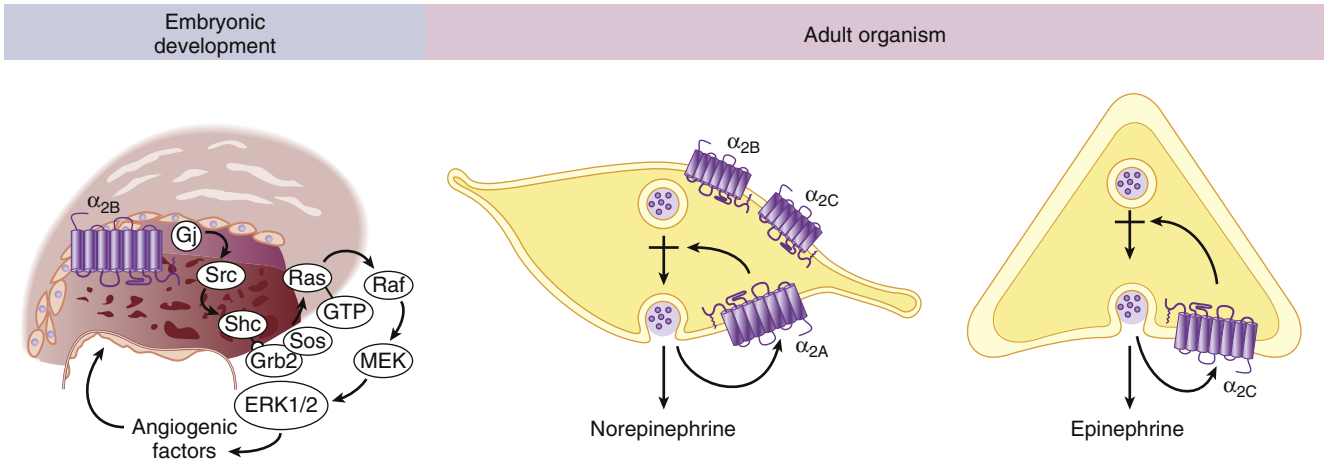
Dexmedetomidine is the S-enantiomer of medetomidine, a substance that has been used for sedation and analgesia in veterinary medicine for many years.[369] It shows a high ratio of specificity for the α_2 receptor (α_2/α_1 1600:1) compared with clonidine (α_2/α_1 220:1), thus making it a complete α_2-agonist.[370] The pK_a is 7.1. Dexmedetomidine belongs to the imidazole subclass of α_2-receptor agonists, similar to clonidine, and its structure is illustrated in Figure 30-19. It is freely soluble in water and is available as a clear isotonic solution containing 100 μg/mL and 9 mg sodium chloride per milliliter of water.

METABOLISM AND PHARMACOKINETICS

Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and feces. Biotransformation involves both direct glucuronidation and cytochrome P450–mediated metabolism. The major metabolic pathways of dexmedetomidine are direct *N*-glucuronidation to inactive metabolites, hydroxylation (mediated primarily by CYP2A6), and *N*-methylation.

Dexmedetomidine is 94% protein bound, and its concentration ratio between whole blood and plasma is 0.66. Dexmedetomidine has effects on cardiovascular variables, potentially causing bradycardia, transient hypertension or hypotension, and may alter its own pharmacokinetics. With large doses, marked vasoconstriction occurs and probably reduces the drug's volumes of distribution. In essence, dexmedetomidine displays nonlinear pharmacokinetics.[371] Its pharmacokinetics in volunteers is best described by a three-compartment model (see Table 30-1).

In subjects with varying degrees of hepatic impairment (Child-Pugh class A, B, or C), clearance values for dexmedetomidine are slower than in healthy subjects. The mean clearance values for patients with mild,



Physiologic functions of α_2-adrenergic receptor subtypes

α_{2B}	α_{2A}	α_{2C}
• Hypertension • Placental angiogenesis • Hypertensive effect of etomidate • Analgesic effect of nitrous oxide	• Presynaptic feedback inhibition of norepinephrine release • Hypotension • Analgesia • Sedation • Inhibition of epileptic seizures	• Feedback inhibition of adrenal catecholamine release • Analgesic effect of moxonidine • Modulation of behavior

Figure 30-20. The different physiologic functions of α_2 adrenoreceptors. The *top panel* depicts the three α_2-receptor subtypes acting as presynaptic inhibitory feedback receptors to control the release of norepinephrine and epinephrine from peripheral or central adult neurons. A negative feedback loop is also seen in the adrenal gland. α_{2B} Receptors have been shown to be involved in the development of the placental vascular system during prenatal development. The *lower panel* lists a series of physiologic effects with their associated α_2 adrenoreceptors. *(From Paris A, Tonner PH: Dexmedetomidine in anaesthesia,* Curr Opin Anaesthesiol *18:412-418, 2005.)*

moderate, and severe hepatic impairment are 74%, 64%, and 53% of those observed in the normal healthy subjects, respectively.

The pharmacokinetics of dexmedetomidine is not influenced by renal impairment (creatinine clearance <30 mL/minute) or age. In patients with severe renal disease, the sedative effect may be stronger as a result of a lower degree of plasma protein binding. Clearance is a function of height.[371,372] The elimination half-life of dexmedetomidine is 2 to 3 hours, with a context-sensitive half-time ranging from 4 minutes after a 10-minute infusion to 250 minutes after an 8-hour infusion. Postoperative patients sedated with dexmedetomidine display pharmacokinetic features similar to those seen in volunteers.[373] No clinically relevant cytochrome P450–mediated drug interaction has been found.

PHARMACOLOGY

Dexmedetomidine acts nonselectively on various subtypes of membrane-bound G protein–coupled α_2-adrenoreceptors. Intracellular pathways include inhibition of adenylate cyclase and modulation of calcium and potassium ion channels. Three subtypes of α_2 adrenoreceptors have been described in humans: α_{2A}, α_{2B}, and α_{2C} (Fig. 30-20).[374] The α_{2A} adrenoreceptors are primarily distributed in the periphery, whereas α_{2B} and α_{2C} are in the brain and spinal cord. Postsynaptic α_2 adrenoreceptors located in peripheral blood vessels produce vasoconstriction, whereas presynaptic α_2 adrenoreceptors inhibit the release of norepinephrine and potentially attenuate the vasoconstriction. The overall response to α_2-adrenoreceptor agonists is related to the stimulation of α_2 adrenoreceptors located in the CNS and spinal cord. These receptors are involved in the sympatholysis, sedation, and antinociceptive effects of α_2 adrenoreceptors.[375] The α_2-agonists have the advantage that their effects are readily reversible by α_2-adrenergic antagonists (e.g., atipamezole).[376] Atipamezole is currently not approved for use in humans.

Effects on the Central Nervous System

Sedation. The α_2-agonists produce their sedative-hypnotic effect by an action on α_2 receptors in the locus coeruleus and by an analgesic action at α_2 receptors within the locus coeruleus and within the spinal cord.[377] Dexmedetomidine produces a decrease in activity of the projections of the locus coeruleus to the ventrolateral preoptic nucleus. As a result, GABA and galanin release in the tuberomammillary nucleus is increased, producing a decrease in histamine release in cortical and subcortical projections.[378] The α_2-agonists inhibit ion conductance through L-type or P-type calcium channels and facilitate conductance through voltage-gated calcium-activated potassium channels. Dexmedetomidine induces sedation through different receptors than the sedative drugs propofol and benzodiazepines, which exert their action through the GABA system. The sedative effect of dexmedetomidine acts through the endogenous sleep-promoting pathways, thus generating natural sleep patterns (Fig. 30-21).[379] Patients have been described as being very easy to wake up

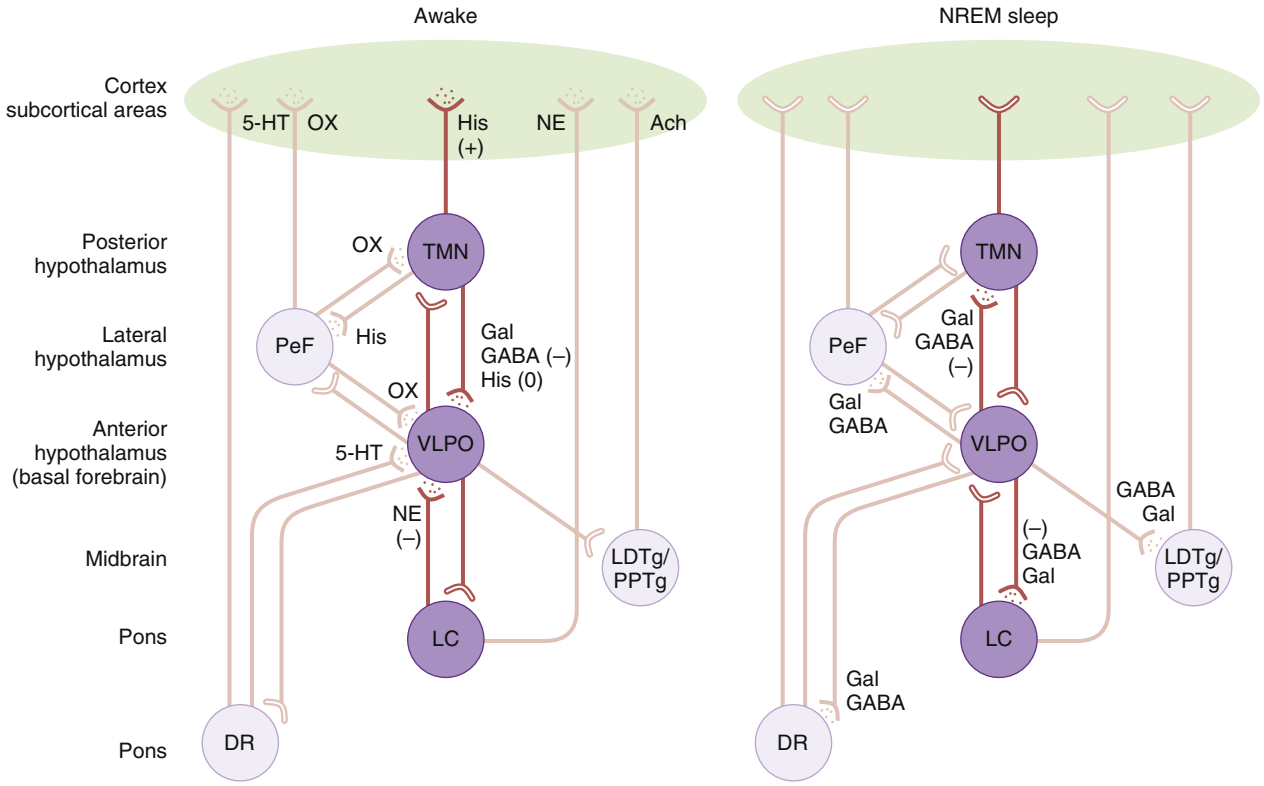


Figure 30-21. Dexmedetomidine has been shown to induce a non–rapid eye movement (NREM) sleeping pattern. The stimulation of the locus coeruleus (LC) by dexmedetomidine *(right)* releases the inhibition the LC has over the ventrolateral preoptic nucleus (VLPO). The VLPO subsequently releases γ-aminobutyric acid (GABA) onto the tuberomammillary nucleus (TMN). This inhibits the release of the arousal-promoting histamine on the cortex and forebrain, thus inducing the loss of consciousness. *Ach*, Acetylcholine; *DR,* dorsal raphae nuclei; *Gal,* galanin; *His,* histamine; *5-HT,* 5-hydroxytryptamine (serotonin); *LDTg,* laterodorsal tegmental nuclei; *NE,* norepinephrine; *OX,* orexin (hypocretin); *PeF,* perifornical area; *PPTg,* pedunculopontine tegmental nucleus; *TDTg,* laterodorsal tegmental nucleus. *(From Ebert T, Maze M: Dexmedetomidine: another arrow for the clinician's quiver,* Anesthesiology *101:569-570, 2004.)*

and having the ability to follow commands and cooperate while being tracheally intubated. Undisturbed, patients were noted to fall asleep momentarily.[380] This characteristic allows for "daily wake-up" tests to be done in a safe fashion. This critical test, in which ventilated patients in the ICU are taken off all sedatives to assess their mental status and titrate sedation, shortens their ventilated and ICU length of stay.[381,382] The number of patients experiencing delirium in the ICU is significantly lower when dexmedetomidine is used for sedation, compared with propofol or lorazepam[383] or with midazolam.[384]

Analgesia. The analgesic effect of the α_2-agonists is mediated through stimulation of the α_{2C} and α_{2A} receptor in the dorsal horn, thus directly suppressing pain transmission by reducing the release of pronociceptive transmitters, substance P and glutamate, and hyperpolarization of interneurons.[385] Systemic use of dexmedetomidine has an opioid-sparing effect during surgery and postoperatively.[386] This effect is advantageous in patients who are prone to postoperative apnea or hypoventilation, such as patients undergoing bariatric surgical procedures.[387] In the postoperative ICU setting, narcotic requirements are reduced by 50% when patients are receiving a dexmedetomidine infusion compared with placebo.[380] During general anesthesia, dexmedetomidine reduces the MAC of inhaled anesthetics.[388,389]

Like clonidine, dexmedetomidine is frequently used as an adjuvant in central or peripheral neural blockade. When it is administered caudally, 1 μg/kg as an adjuvant to bupivacaine 0.25% 1 mL/kg, in children undergoing inguinal hernia repair, response to hernial sac traction is reduced, and postoperative analgesia is prolonged.[390] Dexmedetomidine administered as an adjuvant to ropivacaine in ulnar nerve block[391] and tibial nerve block[392] was investigated in volunteers. Both studies showed intensification and foremost prolongation of the sensory blockade. This effect is likely elicited by prolonged hyperpolarization of the unmyelinated C fibers (sensory), and to a lesser extent the A fibers (motor function).

Central Nervous System Protection and Other Central Nervous System Effects. The CNS protective effects are not well defined. In animal models of incomplete cerebral ischemia and reperfusion, dexmedetomidine reduced cerebral necrosis and improved neurologic outcome. The prevalent idea is that dexmedetomidine reduces the intracerebral catecholamine outflow during injury. The neuroprotection may be attributed to modulation of proapoptotic and antiapoptotic proteins.[393] In addition, the reduction of the excitatory neurotransmitter glutamate during injury may explain some of the protective effects.[394]

In patients undergoing transsphenoidal hypophysectomy, dexmedetomidine had no effect on lumbar

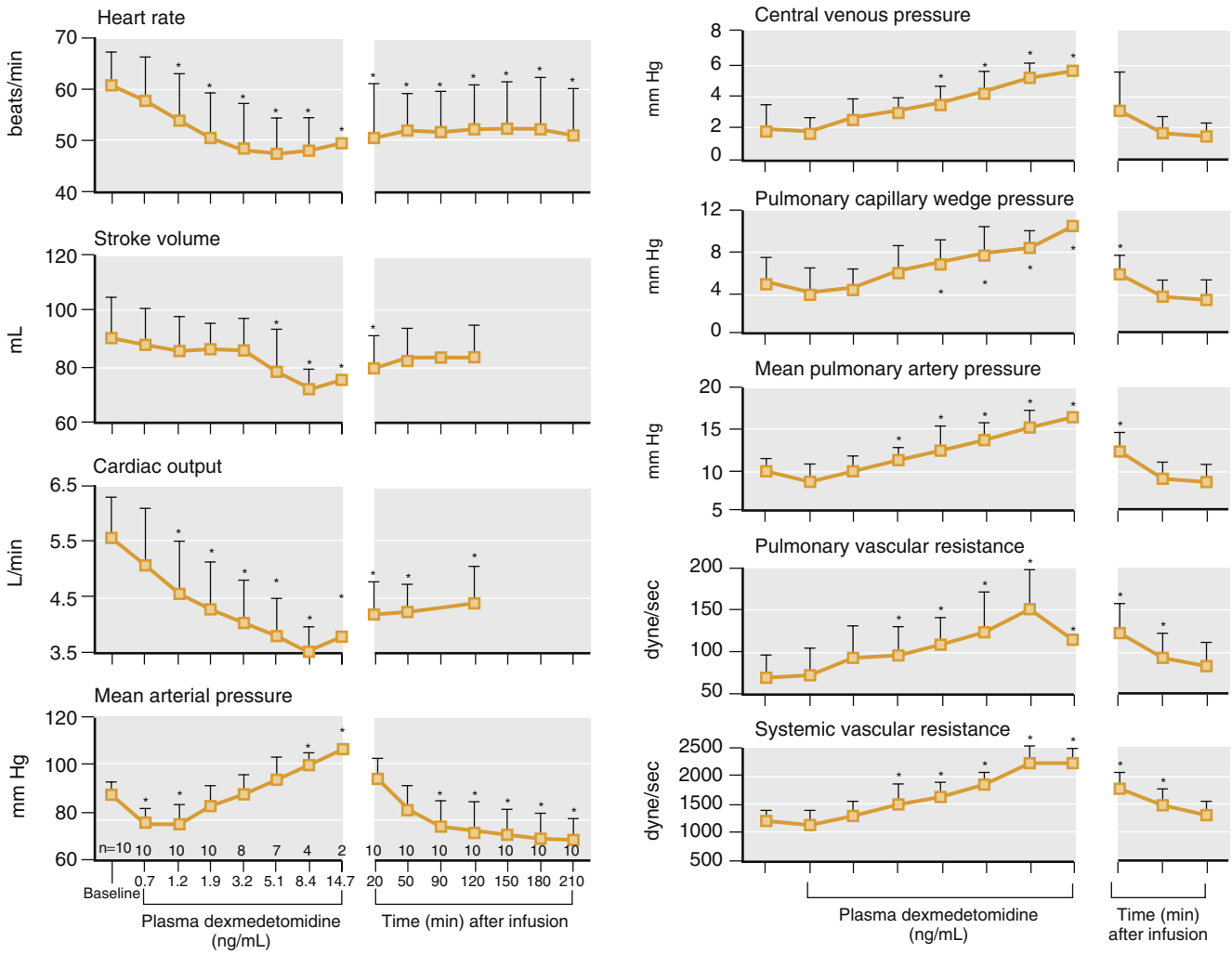


Figure 30-22. Effects of increasing plasma concentrations of dexmedetomidine. *(From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

cerebral spinal fluid pressure.[395] In other studies, CBF velocity at the middle cerebral artery, as measured by transcranial Doppler imaging, decreased with increasing concentrations of dexmedetomidine but carbon dioxide responsiveness and autoregulation were preserved.[396,397] The decrease in CBF was not accompanied by a reduction in $CRMO_2$. More recently, in a study of six normal volunteers, the administration of dexmedetomidine to achieve serum levels of 0.6 ng/mL and 1.2 ng/mL (with and without hyperventilation) produced the predicted reduction of CBF with a concomitant reduction in $CRMO_2$.[398] This finding suggests that further work in injured brains must be done on the maintenance of the cerebral oxygen supply-to-demand relationship.

Dexmedetomidine has been used in neurosurgical procedures involving neurophysiologic monitoring (see also Chapter 70). Cortical evoked potential amplitudes and latencies were minimally affected when dexmedetomidine was used intraoperatively. It may also be suitable as an anesthetic adjunct during surgical treatment of seizures because the epileptiform activity of seizure foci was not reduced by dexmedotomidine.[399]

Effects on the Respiratory System

In spontaneously breathing volunteers, dexmedetomidine at concentrations producing significant sedation reduced minute ventilation, but with no change in arterial oxygenation, pH, or the slope in the carbon dioxide ventilatory response curve.[332] In a study comparing the effects of remifentanil and dexmedetomidine on respiratory parameters in normal volunteers, the hypercapnic ventilatory response was unaffected even at doses that produced unresponsiveness to vigorous stimulation.[400] Dexmedetomidine-treated patients exhibited a hypercarbic arousal phenomenon, which has been described during normal sleep.

Effects on the Cardiovascular System

Ebert and colleagues performed a study in volunteers by using a target-controlled infusion system to provide increasing concentrations (0.7 to 15 ng/mL) of dexmedetomidine (Fig. 30-22).[332] The lowest two concentrations produced a decrease in MAP (13%) followed by progressive increase (12%). Increasing concentrations of dexmedetomidine also produced progressive decreases in heart rate (maximum 29%) and cardiac output (35%).[332]

The most commonly reported hemodynamic adverse reactions associated with dexmedetomidine in a phase III trial in 401 patients were hypotension (30%), hypertension (12%), and bradycardia (9%).[369] The initial increase in arterial blood pressure is probably caused by the vasoconstrictive effects of dexmedetomidine when stimulating peripheral α_2 receptors. The incidence of hypotension and bradycardia may be related to the administration of a large IV "loading" dose. Omitting the loading dose or not giving more than 0.4 μg/kg reduces the incidence of hypotension or makes it less pronounced. Giving the loading dose over 20 minutes also minimizes the transient hypertension.[401] In several studies after IM and IV administration, dexmedetomidine caused, in a small percentage of patients, profound bradycardia (<40 beats/minute) and occasionally sinus arrest or pause. Generally, these episodes resolved spontaneously or were readily treated without adverse outcome by anticholinergics. No rebound effects have been found when discontinuing a dexmedetomidine infusion, even when it was given for more than 24 hours.[402] Because clonidine and dexmedetomidine have shown to reduce perioperative oxygen consumption and blunt the sympathetic response to surgery, cardiac outcome may be improved.[403,404] However, more studies are needed to determine whether dexmedetomidine is beneficial in decreasing the risk of myocardial ischemia.

USES

Dexmedetomidine has been approved as a short-term sedative for adult intubated patients in the ICU. Given its well-documented beneficial effects of anxiolysis, sedation, analgesia, and sympatholysis with minimal respiratory depression, it also has been used in various other clinical situations. It is well used as a sedative during radiologic or invasive procedures, in adults as well as in children. Two studies, comprising 140 children 1 to 7 years old, reported successful sedation for MRI scans compared with midazolam or propofol.[405]

As a premedicant, dexmedetomidine, at IV doses of 0.33 to 0.67 μg/kg given 15 minutes before the surgical procedure, seems efficacious, while minimizing the cardiovascular side effects of hypotension and bradycardia.[389] Dexmedetomidine has high bioavailability when administered nasally or buccally. This improves better compliance and absorption in younger children. A dose of 3 to 4 μg/kg 1 hour preoperatively is safe and effective.

In a study comparing the efficacy of dexmedetomidine or propofol as a sedative agent in a group of 40 patients receiving local anesthesia or regional blocks, dexmedetomidine (1 μg/kg given over 10 minutes) when used for intraoperative sedation resulted in a slower onset than propofol (75 μg/kg/minute for 10 minutes), but had similar cardiorespiratory effects when titrated to equal sedation. The average infusion rate of dexmedetomidine intraoperatively to maintain a BIS value of 70 to 80 was 0.7 μg/kg/minute. Sedation was more prolonged after termination of the infusion, as was recovery of arterial blood pressure. Dexmedetomidine can also produce profound sedation, and it has been used as a total IV anesthetic when given at 10 times the normal sedation concentration range.[406] This characteristic, combined with the cooperative status of the patient at a lighter sedative level, and its analgesic effect with sparing of respiratory function, makes the drug suitable as hypnotic agent during surgical procedures such as awake craniotomy, deep brain stimulation, surgical procedures near speech areas, or awake carotid endarterectomies, with fewer fluctuations from the desired sedation level and more stable hemodynamics.[396] The opioid-sparing effects are advantageous in the performance of bariatric surgery in patients who are prone to postoperative respiratory depression.[387]

Dexmedetomidine can be employed for addiction treatment; it has been described for use in rapid opioid detoxification, cocaine withdrawal, and iatrogenically induced benzodiazepine and opioid tolerance after prolonged sedation.[407] The use of dexmedetomidine in opioid or benzodiazepine withdrawal therapy in pediatric patients during mechanical ventilation in intensive care areas has been described as well[408] (see also Chapter 95).

Dexmedetomidine may produce dry mouth secondary to a decrease in salivation. Combined with the sparing effect on respiratory function, this effect is beneficial for the facilitation of awake fiberoptic intubation, an application that is rapidly emerging.[409] Furthermore, dexmedetomidine decreases intraocular pressure and decreases the shivering threshold.[410]

Intensive Care Unit

Dexmedetomidine may have advantages over propofol for sedation in mechanically ventilated postoperative patients (see also Chapter 101). In one study, heart rate was slower in the dexmedetomidine group, whereas MAP was similar. The Pa_{O_2}/fraction of inspired oxygen (Fi_{O_2}) ratio was significantly higher in the dexmedetomidine group. Time to extubation of the trachea after discontinuation of the infusion was similar at 28 minutes. Patients receiving dexmedetomidine had greater recall of their stay in the ICU, but all described this as pleasant overall.[411] Several other studies confirmed the decreased requirement for opioids (>50%) when dexmedetomidine is used for sedation compared with propofol or benzodiazepines. Hemodynamics during weaning are more stable, and this benefits patients who are at high risk for myocardial ischemia.[412] For sedation in the ICU, loading doses of 0.5 to 1 μg/kg have been used. Omitting the bolus dose or giving the lower dose has been associated with fewer episodes of severe bradycardia and other hemodynamic perturbations. Infusion rates of 0.1 to 1 μg/kg/hour are generally needed to maintain adequate sedation.

Delirium in the ICU is a risk factor for increased length of stay and increased mortality.[413] In a double-blind, randomized controlled trial of sedation in ventilated patients with dexmedetomidine versus lorazepam, investigators found that dexmedetomidine infusions provided more days alive without delirium or coma and a greater amount of time spent at the appropriate sedation level compared with lorazepam.[383] Dexmedetomidine also improved the patient's ability to communicate pain, compared with midazolam or propofol in two trials.[381]

The unique characteristics of dexmedetomidine (i.e., providing adequate sedation with minimal respiratory depression) make this selective α_2-adrenoceptor agonist

very useful when weaning patients from the ventilator.[414] Although the FDA approved the use of dexmedetomidine infusions for 24 hours or less, multiple studies have shown the safety of using this agent for longer periods, even up to 30 days.[384]

DROPERIDOL

HISTORY

Janssen and Schnabel and their associates synthesized haloperidol, the first member of the butyrophenones, which became the primary neuroleptic component in neuroleptanesthesia.[295,298] In 1959, DeCastro and Mundeleer combined haloperidol with phenoperidine (a meperidine derivative also synthesized by Janssen) in the forerunner to the practice of neuroleptanesthesia.[414a] Droperidol, a derivative of haloperidol, and fentanyl (a phenoperidine congener), both synthesized by Janssen, were used by DeCastro and Mundeleer in a combination they reported to be superior to haloperidol and phenoperidine. This neuroleptanesthesia combination produced more rapid onset of analgesia, less respiratory depression, and fewer extrapyramidal side effects. The fixed combination of droperidol and fentanyl, marketed as Innovar in the United States, was the drug primarily used for neuroleptanesthesia. The use of neuroleptanesthesia has largely disappeared in modern anesthetic practice. The primary use of droperidol in anesthesia has been as an antiemetic and, to a lesser extent, as a sedative and antipruritic.

In 2001, the FDA issued a black box warning regarding the use of droperidol and its potential for fatal arrhythmias and recommended that it be administered only during continuous electrocardiogram monitoring. With the withdrawal of droperidol in certain countries and more stringent labeling regarding potentially lethal dysrhythmias in others, the use of droperidol has decreased markedly. The validity of the risk of low-dose droperidol in causing QT prolongation, dysrhythmias, and death has been challenged by numerous editorials, articles, and letters reviewing the cases that prompted this action.[295,415-419] In Europe, 19 of 25 countries with council members in the European Society of Anaesthesiologists reported that droperidol is regularly used in a dose of 0.5 to 2.5 mg for the prevention of PONV. Furthermore, in 2007, an international consensus panel recommended droperidol as a first-line antiemetic despite the FDA warning.[295,420]

Droperidol is a butyrophenone, a fluorinated derivative of phenothiazines (Fig. 30-23). Butyrophenones produce CNS depression, characterized by marked apparent tranquility and cataleptic immobility, and are potent antiemetics. Droperidol is a potent butyrophenone, and, similar to the others, it produces its action centrally at sites where dopamine, norepinephrine, and serotonin act.[295] Investigators have postulated that butyrophenones may occupy GABA receptors on the postsynaptic membrane, thereby reducing synaptic transmission and resulting in a buildup of dopamine in the synaptic cleft. In particular, droperidol results in submaximal inhibition of the $GABA_A$ α_1-, β_1-, and γ_2-acetylcholine receptors and full inhibition of α_2-acetylcholine receptors. This submaximal inhibition of GABA receptors by droperidol may explain the anxiety, dysphoria, and restlessness that may occur with its administration.[295,421] An imbalance in dopamine and acetylcholine is thought to occur with subsequent alteration in normal transmission of signals in the CNS. The chemoreceptor trigger zone is the emetic center, and "red" astrocytes transport neurolept molecules from the capillary to dopaminergic synapses in the chemoreceptor trigger zone, where they occupy GABA receptors. This is thought to be the mechanism by which droperidol exerts its antiemetic effect.

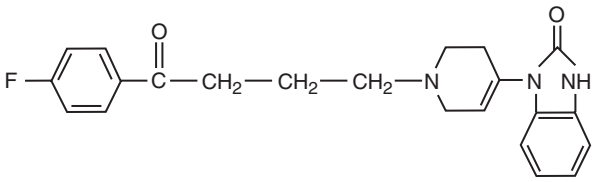


Figure 30-23. Structure of droperidol, a butyrophenone derivative. *(From Reves JG, Glass P, Lubarsky DA, et al: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleischer LA, et al, editors:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 719-768.)*

PHARMACOKINETICS

Droperidol is biotransformed in the liver into two primary metabolites. Its plasma decay can be described by a two-compartment model. The pharmacokinetics[295,422] is shown in Table 30-1.

PHARMACODYNAMICS

Effects on the Central Nervous System

The effects of neurolept anesthetics on human CBF and $CMRO_2$ have not been studied. In dogs, droperidol causes potent cerebral vasoconstriction, thus producing a 40% reduction in CBF. No significant change in $CMRO_2$ occurs during droperidol administration. The EEG in conscious patients shows some reduction in frequency, with occasional slowing. Low-dose droperidol also has been shown to cause balance disturbances at the time of discharge after doses used for antiemetic prophylaxis. Droperidol may produce extrapyramidal signs and worsens the symptoms of Parkinson disease. For this reason, the drug should be used with great caution in patients with this degenerative disorder. It also rarely may precipitate malignant neuroleptic syndrome.

Effects on the Respiratory System

When used alone, droperidol has little effect on the respiratory system. Droperidol (0.044 mg/kg) given to surgical patients produced a slight reduction in respiratory rate, and IV droperidol (3 mg) had no significant effect on tidal volume in volunteers. More detailed respiratory studies are unavailable.

Effects on the Cardiovascular System

Similar to most antipsychotics, droperidol may prolong the QT interval by delaying myocardial repolarization and precipitating torsades de pointes.[295,423] This effect

seems to be dose dependent and may be of clinical significance when other causes of QT prolongation also are present. Droperidol also may have some antiarrhythmic effects that are similar to those of quinidine. Droperidol produces vasodilation, with a decrease in blood pressure (see Table 30-3). This effect is considered to be a result of moderate α-adrenergic blockade. The dopamine-induced increase in renal blood flow (renal artery flowmeter methodology) is not significantly impaired by administration of droperidol. Droperidol has little effect on myocardial contractility.

USES

The use of droperidol today in the perioperative period is largely restricted to its antiemetic and sedative effects. It is an effective antiemetic; the dose for this use ranges from 10 to 20 μg/kg IV (typically 0.6 to 1.25 mg for a 70-kg individual).[295,424] Because droperidol in doses lower than 1 mg produce antiemetic effects and because the cardiac side effects may be dose dependent, an IV dose lower than 1 mg for prevention of PONV is advisable.[425] These doses of droperidol, given at the start of anesthesia for operations lasting 1 hour, reduce the incidence of nausea and vomiting by approximately 30%. These doses given at induction have little effect on wake-up time, but should they be given at the end of the surgical procedure, they could have some residual hypnotic effect. Overall, the antiemetic efficacy of droperidol alone is equal to that of ondansetron and results in an equal number of side effects, but droperidol is more cost effective. The efficacy of droperidol as an antiemetic is enhanced when it is used in combination with serotonin antagonists or dexamethasone, or both. Droperidol also has been shown to be effective in the treatment and prevention of pruritus secondary to opioid administration. It has been given by the IV route and into the epidural space for this purpose. When used in this fashion, droperidol also effectively reduces nausea, but it increases sedation. The safety of droperidol administration into the epidural space has not been fully evaluated, however, and it is not approved for administration by this route.

SUMMARY

Many different IV drugs are available for use in the care of patients requiring general anesthesia or sedation. The selection of a particular drug, but more often of a combination of drugs, must be based on the individual patient's need for hypnosis, amnesia, and analgesia. Drug selection must match the physiology or pathophysiology of the individual patient with the pharmacology of the particular drug or drugs. In addition, based on the pharmacokinetic and pharmacodynamic interactions now described, the optimal dosage of hypnotic-analgesic combinations may be selected. A patient in shock who requires induction of anesthesia should receive the drug that has a rapid onset of effect without causing further hemodynamic compromise. The knowledge of the clinical pharmacology of each of the IV anesthetic drugs enables the clinician to induce and maintain sedation or general anesthesia safely and effectively. No single perfect drug exists for any particular patient, but rather the informed practitioner wisely employs the appropriate drug or drugs in the practice of good anesthesia care.

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Chapter 31

Opioid Analgesics

KAZUHIKO FUKUDA

Key Points

- An increased understanding of the molecular pharmacology of opioid receptors and opioid-induced cellular responses allows utilization of new innovative techniques for analgesia.
- Opioids suppress pain by their action in the brain, spinal cord, and peripheral nervous system.
- Opioids affect multiple organ systems, including the respiratory and cardiovascular systems, and can cause a variety of adverse effects. Proper dosing and monitoring allow these adverse effects to be minimized.
- Pharmacokinetic and pharmacodynamic properties of opioids are affected by a variety of factors, such as age, body weight, organ failure, and shock. To use opioids appropriately, these factors should be taken into consideration.
- Opioids are a vital part of providing the analgesic component of anesthesia, especially total intravenous anesthesia. Short-acting opioids, such as remifentanil, allow even more rapid dissipation of total intravenous anesthetics/RDM than that of inhaled anesthetics.
- Newer opioid delivery systems, such as transdermal fentanyl patches, allow more flexibility in providing analgesia for perioperative patient care.
- Opioids can pharmacokinetically or pharmacodynamically interact with drugs used perioperatively. Drug interactions should be understood for proper management of patients receiving opioids.

The term *opioid* refers broadly to all compounds related to opium. The word *opium* is derived from *opos*, the Greek word for juice, because the drug is derived from the juice of the opium poppy, *Papaver somniferum*. Opiates are drugs derived from opium and include the natural products morphine, codeine, and thebaine, as well as many semisynthetic congeners derived from them.

The first undisputed reference to opium is found in the writings of Theophrastus in the third century B.C. During the Middle Ages, many of the uses of opium were appreciated. Opium contains more than 20 distinct alkaloids. In 1806, Sertürner reported the isolation of a pure substance in opium that he named morphine, after Morpheus, the Greek god of dreams. By the middle of the nineteenth century, the use of pure alkaloids, rather than crude opium preparations, began to spread throughout the medical world.

In addition to the remarkable beneficial effects of opioids, the toxic side effects and addictive potential of these drugs also have been known for centuries. Synthetic opioid analgesics without side effects were explored, but many of the synthetic opioids share the side effects of natural opioids. The search for newer opioid agonists led to the synthesis of opioid antagonists and compounds with mixed agonist-antagonist properties, which expanded the therapeutic options and provided important tools for exploring mechanisms of opioid actions. Furthermore, newer methods of opioid administration, including patient-controlled analgesia (PCA) and computer-based infusion techniques, were developed.

PHARMACOLOGY OF OPIOIDS

CLASSIFICATION OF OPIOID COMPOUNDS

Opioids can be classified as naturally occurring, semisynthetic, and synthetic (Box 31-1). The naturally occurring opioids can be divided into two chemical classes: phenanthrenes (morphine and codeine) and benzylisoquinolines (papaverine). The semisynthetic opioids are morphine derivatives in which one of several changes has been made. Synthetic opioids are classified into four groups: the morphinan derivatives (levorphanol), the diphenyl or methadone derivatives (methadone, *d*-propoxyphene), the benzomorphans (phenazocine, pentazocine), and the phenylpiperidine derivatives (meperidine, fentanyl, alfentanil, sufentanil, and remifentanil). Structures of opioid compounds are shown in Figure 31-1[1] and Table 31-1.[1]

BOX 31-1 *Classification of Opioid Compounds*

NATURALLY OCCURRING

Morphine
Codeine
Papaverine
Thebaine

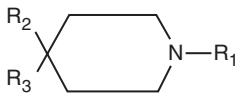
SEMISYNTHETIC

Heroin
Dihydromorphone, morphinone
Thebaine derivatives (e.g., etorphine, buprenorphine)

SYNTHETIC

Morphinan series (e.g., levorphanol, butorphanol)
Diphenylpropylamine series (e.g., methadone)
Benzomorphan series (e.g., pentazocine)
Phenylpiperidine series (e.g., meperidine, fentanyl, sufentanil, alfentanil, remifentanil)

From Bailey PL, Egan TD, Stanley TH: Intravenous opioid anesthetics. In Miller RD, editor: Anesthesia, *ed 5. Philadelphia, 2010, Churchill Livingstone, p 770.*



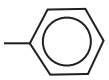
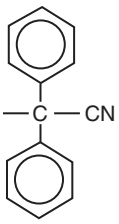
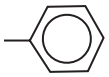
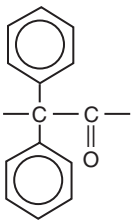
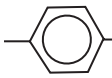
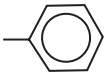
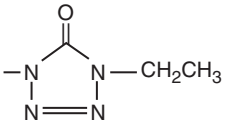
Compound	R_1	R_2	R_3
Meperidine	$-CH_3$		$-COCH_2CH_3$ (=O)
Diphenoxylate	$-CH_2CH_2-C(CN)$ 		$-COCH_2CH_3$ (=O)
Loperamide	$-CH_2CH_2-C(-C(=O)-N(CH_3)_2)$ 	 Cl	—OH
Fentanyl	$-CH_2CH_2-$ 	—H	—N—CCH_2CH_3 (=O)
Sufentanil	$-CH_2CH_2-$ 	$-CH_2OCH_3$	—N—CCH_2CH_3 (=O)
Alfentanil	$-CH_2CH_2-$  $-CH_2CH_3$	$-CH_2OCH_3$	—N—CCH_2CH_3 (=O)
Remifentanil	$-CH_2CH_2C(=O)-O-CH_3$	$-C(=O)-O-CH_3$	—N—CCH_2CH_3 (=O)

Figure 31-1. Chemical structures of piperidine and phenylpiperidine analgesics. *(From Gutstein HB, Akil H: Opioid analgesics. In Hardman JG, Limbird LE, editors:* Goodman and Gilman's the pharmacological basis of therapeutics, *ed 10. New York, 2001, McGraw-Hill, pp 569-619.)*

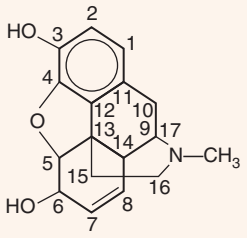
Opioids can be classified as agonists, partial agonists, mixed agonist-antagonists, and antagonists on the basis of their interaction with the opioid receptors.

OPIOID RECEPTORS

In 1973, three independent teams of investigators described the presence of opioid binding sites in the nervous system from the radioligand binding assays. From pharmacologic experiments, three types of opioid receptors were postulated. They were named μ for the morphine type, κ for the ketocyclazocine type, and σ for the SKF10047 (*N*-allylnormetazocine) type. In addition, a high-affinity receptor for enkephalins was found in the mouse vas deferens and was named the δ receptor. Furthermore, an ε receptor was proposed as the binding site for β-endorphin in the rat vas deferens. Pharmacologic actions of opioids and the involved receptors have been analyzed (Table 31-2).

Biochemical studies were performed to purify the opioid receptor protein but were not successful. Since the early 1990s, molecular biologic studies have elucidated the molecular structures and signal transduction mechanisms of the opioid receptors. Four different complementary DNAs (cDNAs) have been isolated as members of the opioid receptor family.[2] Investigators demonstrated that three of them correspond to the pharmacologically defined μ-, δ-, and κ-opioid receptors. The fourth receptor did not bind with opioid ligands with high affinities. Later, a novel peptide, nociceptin or orphanin FQ, was identified as an endogenous agonist of the fourth member of the opioid receptor family.[3,4] The μ-, δ-, and κ-opioid receptors and the nociceptin receptor share approximately 50% amino acid sequence homology with each other. Characteristics of the three opioid receptors and the nociceptin or orphanin FQ receptor are listed in Table 31-3. Hydropathy analysis of the primary structures of the opioid receptors predicted that the

TABLE 31-1 STRUCTURES OF OPIOIDS AND OPIOID ANTAGONISTS CHEMICALLY RELATED TO MORPHINE



Morphine

	Chemical Radicals and Position*			
Nonproprietary Name	**3**	**6**	**17**	**Other Changes†**
Morphine	—OH	—OH	—CH_3	—
Heroin	—$OCOCH_3$	—$OCOCH_3$	—CH_3	—
Hydromorphone	—OH	=O	—CH_3	(1)
Oxymorphone	—OH	=O	—CH_3	(1), (2)
Levorphanol	—OH	—H	—CH_3	(1), (3)
Levallorphan	—OH	—H	—$CH_2CH{=}CH_2$	(1), (3)
Codeine	—OCH_3	—OH	—CH_3	—
Hydrocodone	—OCH_3	=O	—CH_3	(1)
Oxycodone	—OCH_3	=O	—CH_3	(1), (2)
Nalmefene	—OH	=CH_2	—CH_2—	(1), (2)
Nalorphine	—OH	—OH	—CH_2CHKCH_2	—
Naloxone	—OH	=O	—$CH_2CH{=}CH_2$	(1), (2)
Naltrexone	—OH	=O	—CH_2—	(1), (2)
Buprenorphine	—OH	—OCH_3	—CH_2—	(1), (4)
Butorphanol	—OH	—H	—CH_2—	(1), (2), (3)
Nalbuphine	—OH	JOH	—CH_2—	(1), (2)

From Gutstein HB, Akil H: Opioid analgesics. In Hardman JG, Limbird LE, editors: Goodman and Gilman's the pharmacological basis of therapeutics, *ed 10. New York, 2001, McGraw-Hill, pp 569-619.*

*The numbers 3, 6, and 17 refer to positions in the morphine molecule, as shown above the table.

†Other changes in the morphine molecule are as follows:
(1)Single instead of double bond between C7 and C8
(2)OH added to C14
(3)No oxygen between C4 and C5
(4)Endoetheno bridge between C6 and C14; 1-hydroxy-1,2,2-trimethylpropyl substitution on C7

opioid receptors possess seven transmembrane domains (Fig. 31-2). This is a characteristic structural feature of the G-protein–coupled receptor. Crystallographic analysis revealed that the μ-opioid receptor actually possesses seven transmembrane domains and the morphinan ligand binds deeply within a large pocket.[5]

Further pharmacologic classification of the μ receptor as the μ_1, μ_2, and μ_3 subtypes has been proposed, but the molecular identity of these receptor subtypes remains to be clarified. Several possible molecular bases of the opioid receptor subtypes exist, including alternate splicing of a common gene product, receptor dimerization, and interaction of a common gene product with another receptor or signaling molecules.[6] Multiple μ-opioid receptor species can be produced from a gene product of the μ-opioid receptor gene by alternate splicing (Fig. 31-3).[7] Analysis of the alternate splicing products reveals differences in ligand binding and G-protein activation. Further research is necessary to clarify physiologic implications of the multiple alternate splicing products.

Several single nucleotide polymorphisms (SNPs) have been identified in the human μ-opioid receptor gene.[8] The A118G mutation, the most common of these SNPs, leads to a change in the gene product in the human μ-opioid receptors, which is an A-to-G substitution in exon 1 that results in an amino acid exchange at position 40 from asparagine to aspartate (N40D). Patients with cancer who are homozygous for the A118G variant require higher doses of oral morphine for long-term treatment of their pain.[9] A118G mutation of the human μ-opioid receptor gene reduces analgesic responses to morphine-6-glucuronide (M6G), but it does not significantly affect the respiratory depression induced by M6G.[10] Furthermore, morphine consumption with intravenous PCA after total abdominal hysterectomy is significantly greater in women homozygous for the A118G variant than in other patients.[11] Some studies have explored the relationship between gene-gene interactions and opioid responses. Kolesnikov and associates demonstrated that the heterozygous patients with μ-opioid receptor A118G and the catechol-*O*-methyltransferase G1974A mutation consumed significantly less morphine compared with homozygous patients of A118G.[12]

TABLE 31-2 PHARMACOLOGIC ACTIONS OF OPIOIDS AND OPIOID RECEPTORS IN ANIMAL MODELS

	Actions of		
	Receptor	**Agonists**	**Antagonists**
Analgesia			
Supraspinal	μ, δ, κ	Analgesic	No effect
Spinal	μ, δ, κ	Analgesic	No effect
Respiratory Function	μ	Decrease	No effect
Gastrointestinal Tract	μ, κ	Decrease transit	No effect
Psychotomimesis	κ	Increase	No effect
Feeding	μ, δ, κ	Increase feeding	Decrease feeding
Sedation	μ, κ	Increase	No effect
Diuresis	κ	Increase	—
Hormone Secretion			
Prolactin	μ	Increase release	Decrease release
Growth hormone	μ and/or δ	Increase release	Decrease release
Neurotransmitter Release			
Acetylcholine	μ	Inhibit	—
Dopamine	δ	Inhibit	—

ENDOGENOUS OPIOID PEPTIDES

Enkephalin, β-endorphin, and dynorphin were identified as endogenous agonists for the δ-, μ-, and κ-opioid receptors, respectively. Following purification of these peptides from mammalian tissues, cDNAs for the precursors of these peptides were cloned. cDNA cloning and amino acid determination of preproopiomelanocortin demonstrated that cleavage of this precursor protein produces not only β-endorphin but also several other neuropeptides, including methionine-enkephalin, adrenocorticotropic hormone (ACTH), and α-melanocyte stimulating hormone. Amino acid sequence of preproenkephalin indicates that four methionine enkephalins and one leucine-enkephalin are cleaved from this precursor. Furthermore, the primary structure of preprodynorphin, the precursor of dynorphin, was determined by cDNA cloning.

A novel endogenous opioid peptide with a significant sequence homology to dynorphin was isolated in 1995.[3,4] This peptide was called orphanin FQ, or nociceptin,

TABLE 31-3 CHARACTERISTICS OF OPIOID RECEPTORS

	μ	δ	κ	**Nociceptin**
Tissue bioassay	Guinea pig ileum	Mouse vas deferens	Rabbit vas deferens	—
Endogenous ligand	β-Endorphin, endomorphin	Leu-enkephalin, met-enkephalin	Dynorphin	Nociceptin
Agonist	Morphine, fentanyl, DAMGO	DPDPE, deltorphin,	Buprenorphine, pentazocine, U50488H	—
Antagonist	Naloxone, naltrexone	Naloxone, naltrindole	Naloxone, NorBNI	—
Coupled G protein	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Adenylate cyclase	Inhibition	Inhibition	Inhibition	Inhibition
Voltage-gated calcium channels	Inhibition	Inhibition	Inhibition	Inhibition
Inward rectifier potassium channels	Activation	Activation	Activation	Activation

DPDPE, [d-penicillamine2, d-penicillamine5]enkephalin; *DAMGO*, [d-Ala2, MePhe4, Gly-ol8]enkephaline; *NorBNI*, norbinaltorphimine.

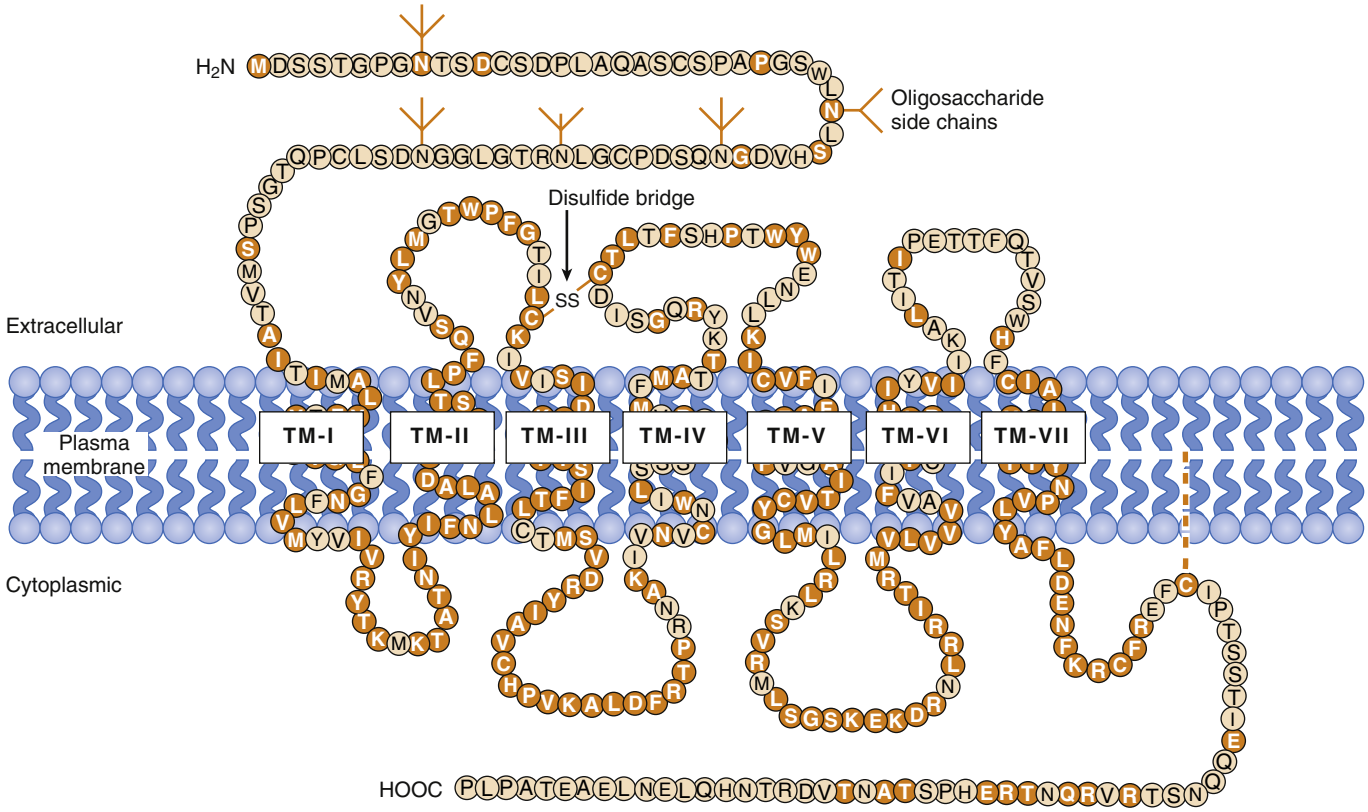


Figure 31-2. Proposed structure of the μ-opioid receptor. *Black circles* indicate amino acid residues identical in the μ- and δ-opioid receptors. TM-I to TM-VII show putative transmembrane segments composed of hydrophobic amino acid residues.

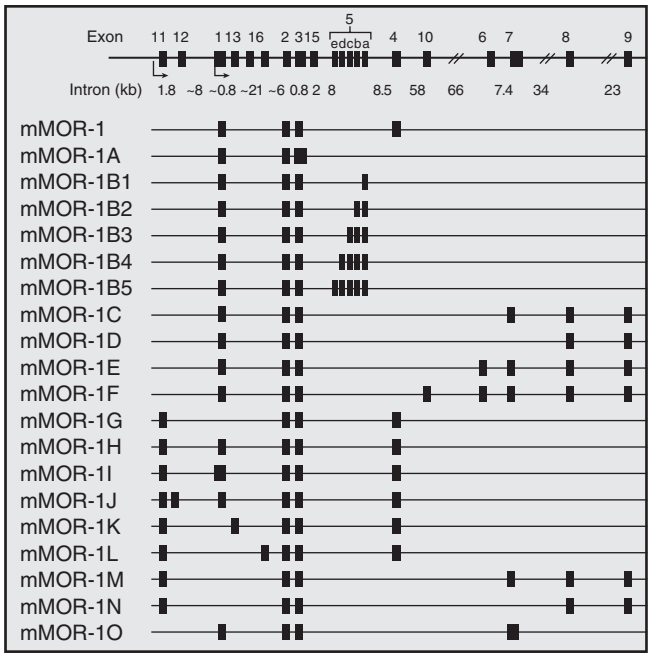


Figure 31-3. Alternate mRNA splicing of the mouse μ-opioid receptor gene leads to a combinatorial diversity of the μ-opioid receptor proteins. *(From Pasternak GW: Molecular insights into mu opioid pharmacology: from the clinic to the bench,* Clin J Pain *26[Suppl 10]:S3-S9, 2010.)*

because it lowered pain thresholds under certain conditions, in contrast to the other endogenous opioid peptides. Pharmacologic and physiologic studies demonstrated that orphanin FQ/nociceptin has behavioral and pain modulatory properties distinct from those of the three classic opioid peptides.[13] Studies of the effect of orphanin FQ/nociceptin on pain sensitivity produced conflicting results that may suggest that the effects of orphanin FQ/nociceptin on pain sensitivity depend on the underlying behavioral state of the animal. Prepronociceptin, the precursor of orphanin FQ/nociceptin, was cloned, and its amino acid sequence suggested the existence of prepronociceptin-derived neuropeptides other than orphanin FQ/nociception.[14]

The search for an endogenous ligand that binds with the μ receptor with high affinity and high selectivity led to the discovery of a class of novel endogenous opioids termed endomorphin-1 and endomorphin-2.[15] These peptides are tetrapeptides with the sequence Tyr-Pro-Trp-Phe and Tyr-Pro-Phe-Phe, respectively. An endomorphin gene has yet to be cloned, and much remains to be learned about the anatomic distribution, mode of interaction with the opioid receptors, function in vivo, and potential existence of other related peptides that are highly selective for each of the opioid receptors.

INTRACELLULAR SIGNAL TRANSDUCTION MECHANISM

The opioid receptors belong to the G-protein–coupled receptor family. Activation of the opioid receptors leads

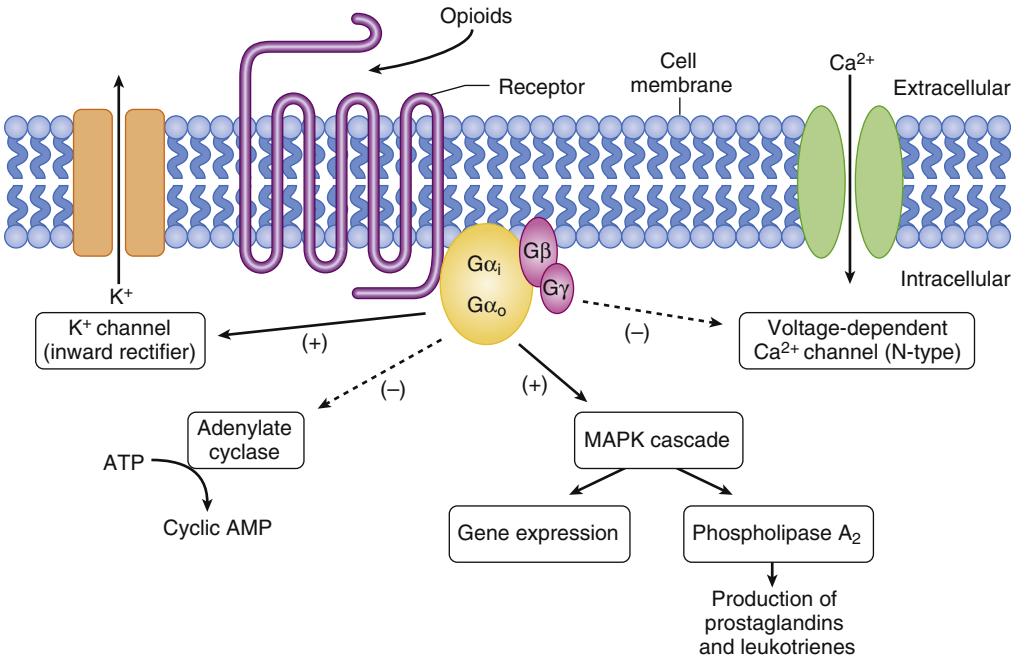


Figure 31-4. Intracellular signal transduction mechanisms linked with the opioid receptors. Opioid agonists bind with the opioid receptors, thus leading to activation of the G protein. Activity of adenylate cyclase and the voltage-dependent calcium (Ca^{2+}) channels is suppressed. Conversely, the inward rectifier potassium (K^+) channels and mitogen-activated protein kinase (MAPK) cascade are activated. *AMP,* Adenosine monophosphate; *ATP,* adenosine triphosphate.

to activation of the pertussis toxin–sensitive G proteins (G_i or G_o or both). Expression of the cloned opioid receptors in cultured cells by transfection of the cloned cDNAs has facilitated analysis of the intracellular signal transduction mechanisms activated by the opioid receptors[2] (Fig. 31-4). Adenylate cyclase is inhibited by opioid receptor activation, with a resulting reduction of the cellular cyclic adenosine monophosphate (AMP) content. Electrophysiologically, the voltage-gated Ca^{2+} channel is inhibited and the inwardly rectifying potassium (K^+) channels are activated by the opioid receptors. As a result, neuronal excitability is reduced by activation of the opioid receptors. In contrast, investigators reported that opioids also stimulate Ca^{2+} influx in neuronal cultured cells.[16] Extracellular signal-related kinase, a class of mitogen-activated protein kinases, is activated by the opioid receptors.[17] Opioid-induced activation of extracellular signal-related kinase can lead to an increase in arachidonate release[17] and expression of the immediate early genes, c-*fos* and *junB*.[18]

Long-term exposure of the opioid receptors to agonists induces cellular adaptation mechanisms, which may be involved in opioid tolerance, dependence, and withdrawal symptoms. Several investigators showed that short-term desensitization probably involves phosphorylation of the opioid receptors through protein kinase C.[19] Several other kinases also have been implicated, including protein kinase A and β-adrenergic receptor kinase (βARK), a member of the G-protein–coupled receptor kinase (GRK).[20] βARKs selectively phosphorylate agonist-bound receptors and thereby promote interactions with β-arrestins, which interfere with G-protein coupling and promote receptor internalization. β-Arrestin 2 functions as a scaffolding protein that interacts with signal transducers, and the recruitment of β-arrestin 2 induced by opioid receptor activation is involved in the regulation of activity of c-Src, Akt, and mitogen-activated protein kinases[21] (Fig.31-5). Acute morphine-induced analgesia was enhanced in mice lacking β-arrestin 2, a finding suggesting that this protein contributes to regulation of responsivity to opioids in vivo.[22]

Like other G-protein–coupled receptors, the opioid receptors can undergo rapid agonist-mediated internalization by a classic endocytic pathway.[23,24] These processes may be induced differentially as a function of the class of the ligand. For example, certain agonists, such as etorphine and enkephalins, cause rapid internalization of the μ receptor, whereas morphine, which decreases adenylyl cyclase activity equally well, does not cause μ-receptor internalization.[25] These findings may suggest that different ligands induce different conformational changes in the receptor that lead to divergent intracellular events. Furthermore, these observations may provide an explanation for differences in the efficacy and abuse potential of various opioids.[26]

Long-term tolerance to opioids is associated with superactivation of adenylyl cyclase activity, which is a counterregulatory response to the decrease in cyclic AMP levels seen after short-term opioid administration.[27] That this effect is prevented by pretreatment of cells with pertussis toxin demonstrates the involvement of G proteins (G_i or G_o or both).

MECHANISM OF ANALGESIA

Pain control by opioids must be considered in the context of brain circuits modulating analgesia and the functions of the various types of receptors in these circuits.[28] The analgesic effects of opioids arise from their ability to inhibit directly the ascending transmission of nociceptive information from the spinal cord dorsal horn and to activate pain control circuits that descend from the midbrain, through the rostral ventromedial medulla (RVM), to the spinal cord dorsal horn. Petrovic and associates used an experimental pain model and positron emission

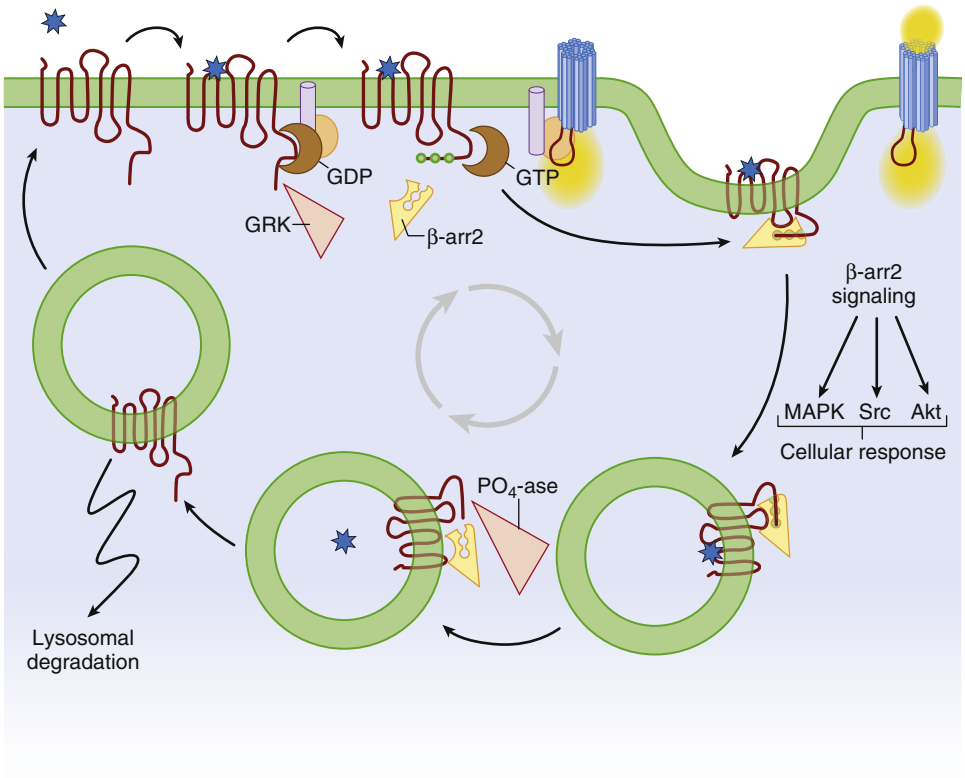


Figure 31-5. β-Arrestin 2 (β-arr2) and G protein in μ-opioid receptor recycling, signaling, and degradation. The *blue star* represents an opioid agonist and the trimeric membrane-associated complex in *brown, green,* and *blue* represents G protein α, β, and γ subunits, respectively. The α subunit is shown associated with guanosine diphosphate (GDP; resting state) or guanosine triphosphate (GTP; activated state). The βγ dimer interacts directly with the voltage-activated calcium (Ca^{2+}) channel to inhibit Ca^{2+} influx (indicated in *yellow*). *GRK,* G-protein–coupled receptor kinase; *MAPK,* mitogen-activated protein kinase; *PO_4-ase,* phosphatase. *(From Hales TG: Arresting the development of morphine tolerance and dependence,* Br J Anaesth *107:653-655, 2011.)*

tomography (PET) to study mechanisms of action of the short-acting μ-opioid agonist remifentanil and found drug-induced activation of the rostral anterior cingulate cortex, insula, orbitofrontal cortex, and brainstem areas.[29] The brainstem overlapped with brain areas that have been implicated in pain modulation, such as the periaqueductal gray (PAG). Surprisingly, placebo analgesia acts similarly on the activity of these brain areas, presumably by endogenous opioid release.[30]

Immunohistochemical studies and in situ hybridization analysis have demonstrated that opioid receptors are expressed in various areas in the central nervous system (CNS).[31] These areas include the amygdala, the mesencephalic reticular formation, the PAG, and the RVM. However, the role of the opioid receptors in all these areas has not been completely clarified.

Microinjection of morphine into the PAG or direct electrical stimulation of this area produces analgesia that can be blocked by naloxone. Opioid actions at the PAG influence the RVM, which in turn modulates nociceptive transmission in the dorsal horn of the spinal cord through the action of the descending inhibition pathway. Thus, opioids produce analgesia by direct actions on the spinal cord, as well as by neurally mediated action in the region separated from the site of opioid administration. Spinal serotonin type 7 ($5\text{-}HT_7$) receptors also play an important role on the antinociceptive effects of systemic morphine.[32]

The distribution of opioid receptors in descending pain control circuits indicates substantial overlap between μ and κ receptors. Interactions between the κ receptor and the μ receptor may be important for modulating nociceptive transmission from higher nociceptive centers, as well as in the spinal cord dorsal horn. The μ receptor produces analgesia within descending pain control circuits, at least in part, by the removal of γ-aminobutyric acidergic (GABAergic) inhibition of RVM-projecting neurons in the PAG and spinally projecting neurons in the RVM.[28] The actions of μ-receptor agonists are invariably analgesic, whereas those of κ-receptor agonists can be either analgesic or antianalgesic. The pain-modulating effects of the κ-receptor agonists in the brainstem appear to oppose those of μ-receptor agonists.[33]

Local spinal mechanisms, in addition to descending inhibition, underlie the analgesic action of opioids. In the spinal cord, opioids act at synapses either presynaptically or postsynaptically. Opioid receptors are abundantly expressed in the substantia gelatinosa, where substance P release from the primary sensory neuron is inhibited by opioids.

Although opioid receptor ligand binding is significant and little detectable receptor mRNA expression occurs in the spinal cord dorsal horn, high levels of opioid receptor mRNA are present in the dorsal root ganglia. This distribution may suggest that the actions of opioid receptor agonists relevant to analgesia at the spinal level are predominantly presynaptic. That opioids decrease the pain-evoked release of tachykinins from primary afferent nociceptors is well known. However, investigators demonstrated that at least 80% of tachykinin signaling in response to noxious stimulation remains intact after the intrathecal administration of large doses of opioids.[34] These results suggest that although opioid administration may reduce tachykinin release from primary afferent nociceptors, this reduction has little functional impact on the actions of tachykinins on postsynaptic pain-transmitting neurons.

The actions of opioids in bulbospinal pathways are critical to their analgesic efficacy. Opioid actions in the forebrain contribute to analgesia. Decerebration prevents analgesia when rats are tested for pain sensitivity using the formalin test,[35] and microinjection of opioids into several forebrain regions is analgesic in this test.[36] Analgesia induced by systemic administration of morphine in both the tail flick and formalin tests was disrupted either by lesioning or reversibly inactivating the central nucleus of the amygdala, thereby demonstrating that opioid actions in the forebrain contribute to analgesia after tissue damage, as well as after acute phasic nociception.[37,38]

Opioids may also produce analgesia through the peripheral mechanism.[39] Immune cells infiltrating the inflammation site may release endogenous opioid-like substances, which act on the opioid receptors located on the primary sensory neuron.[39] However, other findings do not support this conclusion.[40,41]

MECHANISM OF MOOD ALTERATIONS AND REWARDING PROPERTIES

The mechanisms by which opioids produce euphoria, tranquility, and other alterations of mood (including rewarding properties) are not entirely clear. Behavioral and pharmacologic evidence points to the role of dopaminergic pathways, particularly involving the nucleus accumbens (NAcc), in drug-induced reward. A functional magnetic resonance imaging study demonstrated that a small intravenous dose (4 mg) of morphine induces positive signal changes in reward structures, including the NAcc, sublenticular extended amygdala, orbitofrontal cortex, and hippocampus, and decreases signal in cortical areas similar to the action of sedative-hypnotics such as propofol and midazolam.[42] These observations are consistent with results of pharmacologic studies.

The shell of the NAcc is the site that may be involved directly in the emotional and motivational aspects of drug-induced reward. All three opioid receptor types are present on the NAcc and are thought to mediate, at least in part, the motivational effects of opiate drugs.[31] Selective μ- and δ-receptor agonists are rewarding when defined by place preference and intracranial self-administration paradigms. Conversely, selective κ-receptor agonists produce aversive effects. Positive motivational effects of opioids are partially mediated by dopamine release at the level of the NAcc.

The locus ceruleus contains both noradrenergic neurons and high concentrations of opioid receptors and is postulated to play a critical role in feelings of alarm, panic, fear, and anxiety. Neural activity in the locus ceruleus is inhibited by both exogenous opioids and endogenous opioid peptides.

ANALYSIS OF KNOCKOUT MICE

The physiologic roles of the opioid receptors and endogenous opioid peptides have been investigated mainly by pharmacologic and physiologic methods. However, analysis of the functional roles of these proteins has been difficult. More recently, knockout mice, in which a specific gene is inactivated by molecular biologic methods, have been produced. By analysis of knockout mice, the physiologic significance of the respective opioid receptors and endogenous opioid peptide precursors can be determined.[43]

In μ-receptor knockout mice, analgesia, the reward effect, and the withdrawal effect of morphine were lost.[44] Morphine-induced respiratory depression was not observed in μ-receptor knockout mice.[45] Therefore, the μ receptor is a mandatory component of the opioid system for morphine action. In μ-receptor knockout mice, ketamine-induced respiratory depression and antinociception were diminished,[46] a finding suggesting that ketamine interacts with the μ receptor to lead to these phenomena. Furthermore, minimum alveolar concentration (MAC) of sevoflurane was significantly higher in μ-receptor knockout mice than in wild-type mice, an observation suggesting the involvement of the μ receptor in the anesthetic potency of sevoflurane.[45] δ-Receptor knockout mice displayed a markedly reduced analgesic effect of opioids selective for δ receptors at the spinal cord level.[47] However, at the supraspinal level, analgesia could be induced by δ-receptor agonists in δ-receptor knockout mice, a finding suggesting the existence of a second δ-like analgesic system. Disruption of the κ receptor abolished the analgesic, hypolocomotor, and aversive actions of the κ-receptor agonists and induces hyperreactivity in the abdominal constriction test; this finding indicates that the κ receptor is involved in the perception of visceral chemical pain.[48]

In the mice lacking β-endorphin, morphine induced normal analgesia, but naloxone-reversible stress-induced analgesia could not be observed.[49] The preproenkephalin knockout mice were more anxious than wild-type mice, and males displayed increased offensive aggressiveness.[50] The mutant mice showed marked difference from controls in supraspinal, but not spinal, responses to painful stimuli.

Thus, the functional roles of individual components of the opioid system have been elucidated by analysis of knockout mice. However, many points remain to be clarified.

ACTIONS OF OPIOIDS ON TARGETS OTHER THAN OPIOID RECEPTORS

Opioids can interact with molecules other than the opioid receptors. In cardiac myocytes, morphine can inhibit voltage-dependent sodium (Na^+) current in a naloxone-insensitive manner, a finding suggesting the existence of a signal transduction mechanism that is not dependent on the opioid receptors.[51] Buprenorphine, a partial μ-opioid receptor agonist, also has a local anesthetic property and blocks voltage-gated Na^+ channels through the local anesthetic binding site.[52] Meperidine is an agonist of both μ and κ receptors. In addition, meperidine can block voltage-dependent Na^+ channels in amphibian peripheral nerves,[53] as well as in the *Xenopus* oocyte expression system (Fig. 31-6).[54] Furthermore, meperidine exerts agonist activity at the α_{2B}-adrenoreceptor subtype.[55] High concentrations of opioids, including meperidine, morphine, fentanyl, codeine, and naloxone, directly inhibit the *N*-methyl-D-aspartate (NMDA) receptor expressed in *Xenopus* oocytes.[56] Methadone is clinically used as a racemic

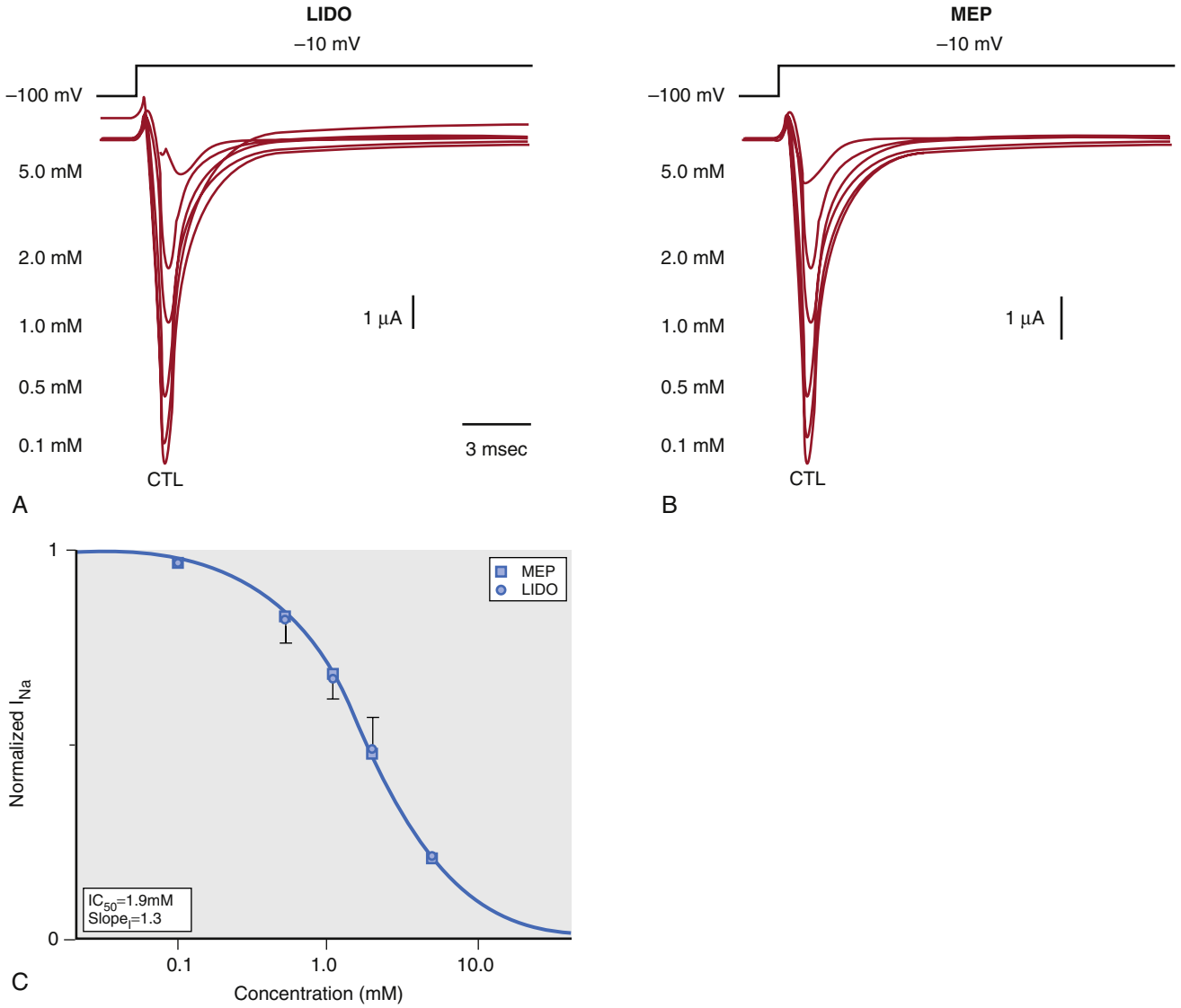


Figure 31-6. A to **C,** Meperidine blocks the sodium (Na^+) channels similarly to lidocaine. Na^+ currents induced by voltage jump were recorded from *Xenopus* oocytes expressing the Na^+ channels. Lidocaine (LIDO; **A**) and meperidine (MEP; **B**) dose dependently inhibited the current. *CTL,* Control. *(From Wagner LE 2nd, Eaton M, Sabnis SS, Gingrich KJ: Meperidine and lidocaine block of recombinant voltage-dependent Na^+ channels: evidence that meperidine is a local anesthetic,* Anesthesiology *91:1481-1490, 1999.)*

mixture of the *l* and *d* isomers. The opioid-like activity of the racemate seems to be almost entirely the result of *l*-methadone, whereas *d*-methadone acts as an NMDA antagonist.[57] The commercially available remifentanil solution (Ultiva), which contains glycine, directly activates the NMDA receptor expressed in *Xenopus* oocytes.[58] Furthermore, an electrophysiologic study in rat spinal cord showed that remifentanil hydrochloride does not directly activate NMDA receptors, the NMDA current recorded after application of Ultiva is related to the presence of glycine, and the glycine-induced NMDA current is potentiated by application of remifentanil hydrochloride through a pathway involving the μ-opioid receptor.[59] The serotonin type 3A (5-HT_{3A}) receptor, which is directly and indirectly linked to gastrointestinal motility, visceral pain, nausea, and vomiting, is competitively inhibited by morphine and hydromorphone, as well as by naloxone; however, investigators found that fentanyl-like opioids did not significantly affect activity of the 5-HT_{3A} receptor.[60,61] Tramadol acts as an agonist of transient receptor potential vanilloid-1 (TRPV1) heterologously expressed in cultured cells.[62] Tramadol may activate TRPV1 in sensory neurons, followed by local release of vasoactive neuropeptides and marked desensitization of the afferent fibers.

PHYSIOLOGIC ROLE OF NOCICEPTIN OR ORPHANIN FQ

Nociceptin or orphanin FQ is a 17-amino-acid peptide, the sequence of which resembles those of opioid peptides. Nociceptin or orphanin FQ precursor mRNA and peptide are present throughout the descending pain control circuits. In the spinal cord, nociceptin or orphanin FQ-receptor mRNA expression is stronger in the ventral horn than in the dorsal horn, but higher levels of ligand binding occur in the dorsal horn. Targeted disruption of the

nociceptin or orphanin FQ receptor in mice had little effect on basal pain sensitivity in several measures, whereas targeted disruption of the N nociceptin or orphanin FQ precursor consistently elevated basal responses in the tail flick test, findings suggesting an important role for nociceptin or orphanin FQ in regulating basal pain sensitivity.[63,64] Intrathecal injections of nociceptin or orphanin FQ have been shown to be analgesic[65]; however, supraspinal administration has produced hyperalgesia, antiopioid effects, or a biphasic hyperalgesic-analgesic response.[66] Nociceptin or orphanin FQ inhibits both pain-facilitating and analgesia-facilitating neurons in the RVM.[67] The effects of nociceptin or orphanin FQ on pain responses appear to depend on the preexisting state of pain in the animal. Physiologic implications of nociceptin or orphanin FQ remain to be elucidated.

Expression of opioid receptors on peripheral blood mononuclear cells is controversial. Williams and associates reported that human peripheral blood mononuclear cells express the nociceptin receptor, but not μ-, δ- or κ-opioid receptors.[68] Nociceptin, produced by the peripheral blood mononuclear cells, may be involved in the control of immune functions.

NEUROPHYSIOLOGIC EFFECTS OF OPIOIDS

ANALGESIC ACTION OF OPIOIDS

In human beings, morphine-like drugs produce analgesia, drowsiness, changes in mood, and mental clouding. A significant feature of opioid analgesia is that it is not associated with loss of consciousness. When morphine in the same dose is given to a normal, pain-free individual, the experience may be unpleasant. The relief of pain by morphine-like opioids is relatively selective in that other sensory modalities are not affected. Patients frequently report that the pain is still present, but they feel more comfortable. It is also important to distinguish between pain caused by stimulation of nociceptive receptors and transmitted over intact neural pathways (nociceptive pain) and pain that is caused by damage to neural structures, often involving neural supersensitivity (neuropathic pain). Although nociceptive pain usually is responsive to opioid analgesics, neuropathic pain typically responds poorly to opioid analgesics and may require larger doses. Not only is the sensation of pain altered by opioid analgesics, but also the affective response is changed.

The analgesic effects, as well as the side effects, of opioids vary among individuals. A pharmacogenomic twin study showed that the interindividual variations in opioid effects are likely the result of genetic and environmental factors.[69,70]

Animal and human studies indicated the existence of sex-related differences in opioid-mediated behavior.[71] Sarton and associates examined the influence of morphine on experimentally induced pain in healthy volunteers and demonstrated the gender differences in morphine analgesia, with greater morphine potency but slower speed of onset and offset in women.[72] In contrast, in a study examining interindividual variability in alfentanil analgesic sensitivity in experimental pain models in humans, no gender differences were detected.[73] The mechanism of the gender difference remains to be clarified.

The pharmacokinetic and pharmacodynamic characteristics of opioids often vary throughout the day, as demonstrated for oral morphine in chronic pain.[74] The duration of intrathecal sufentanil analgesia exhibited a temporal pattern, with 30% variation throughout the day in women in the first stage of labor.[75] The time of day of administration does not seem to influence the duration of labor analgesia with spinal-epidural administration of fentanyl or with systemic hydromorphone administration.[76] The potential impact of chronobiology on clinical practice is not clear, and research on the influence of circadian rhythms on the actions of opioids is warranted.

Some controversy remains regarding analgesia produced by the peripheral actions of opioids. One review concluded from meta-analysis that intraarticularly administered morphine has a definite but mild analgesic effect.[77] It may be dose dependent, and a systemic effect cannot be completely excluded. The addition of opioids in brachial plexus block improves the success rate and postoperative analgesia.[78,79] In contrast, the addition of sufentanil may not prolong the duration of brachial plexus block.[80]

EFFECTS OF OPIOIDS ON CONSCIOUSNESS

Cortical acetylcholine originates in the basal forebrain and is essential for maintaining normal cognition and arousal. Injection of morphine to the substantia innominata or intravenous morphine administration significantly decreased acetylcholine release within the prefrontal cortex in the rat, and this effect may be the neurochemical basis of opioid-induced change in consciousness.[81] Although unconsciousness in humans can be produced with high doses of opioids alone, opioid-based anesthesia can be unpredictable and inconsistent.[82] Therefore, opioids cannot induce anesthesia by themselves.[83] The anesthetic potential of opioids was tested by measurement of MAC.[84] Fentanyl can reduce the MAC of isoflurane at skin incision in patients by at least 80%.[85] The relationship between the plasma fentanyl concentration and reduction in MAC is not linear, and fentanyl has a sub-MAC ceiling effect on reduction of the MAC of isoflurane. The MAC of sevoflurane was also dose dependently reduced by fentanyl, with 3 ng/mL resulting in a 61% reduction in MAC[86] (see also Chapter 33). A ceiling effect was observed for MAC; 6 ng/mL fentanyl provided only an additional 13% reduction in the MAC of sevoflurane. Even potency ratios have been established for the "reduction of volatile anesthetic MAC" for most opioids such as sufentanil, fentanyl, alfentanil, and remifentanil. However, the MAC-reducing capabilites of the opioids are not complete; that is, these are not complete anesthetics. The opioids must be combined with other anesthetics to produce a "complete anesthetic."[85,87-89] Esmolol, a short-acting β_1-receptor antagonist, significantly decreased the MAC of isoflurane in the presence of alfentanil, although it did not significantly affect this parameter in the absence of alfentanil.[90] The mechanism of the interaction is unknown. Epidural fentanyl infusion reduces the awakening concentration of isoflurane more than does intravenous fentanyl infusion despite the lower plasma concentration, possibly by modulating the afferent nociceptive inputs in the spinal cord.[91]

The MAC that prevents movement in response to laryngoscopy and tracheal intubation in 50% of patients (MAC-TI) is higher than the MAC that prevents movement in response to surgical incision (MAC). The MAC-TI of sevoflurane was 3.55% and was reduced markedly to 2.07%, 1.45%, and 1.37% by the addition of fentanyl 1, 2, and 4 μg/kg, respectively, with no significant difference in the reduction between 2 and 4 μg/kg, thus showing a ceiling effect.[92] The MAC that prevents sympathetic responses to surgical incision in 50% of patients (MAC-BAR) decreased with increasing concentrations of fentanyl in plasma, and the initial steep reduction was followed by a ceiling effect.[86]

The bispectral index (BIS) was proposed as a measure of the effects of anesthetic agents on the brain (see also Chapter 50). In the presence of fentanyl, alfentanil, remifentanil, or sufentanil, loss of consciousness occurred at a lower effect-site concentration of propofol and at a higher BIS value than with propofol alone.[93] Furthermore, Wang and colleagues reported that infusion of remifentanil (0.1 to 0.4 μg/kg/minute) did not significantly change the median effective concentration (EC_{50}) of propofol necessary to lower the BIS value to 50 or less.[94] These results suggest that the hypnotic effect of propofol is enhanced by analgesic concentrations of opioids without changes in the BIS value. Conversely, infusion of remifentanil (effect-site target concentrations of 0.25, 2.5, and 10 ng/mL), combined with propofol infusion adjusted to a BIS of approximately 60, dose dependently decreased the BIS, thus suggesting a sedative or hypnotic effect of remifentanil.[95] Response surface analysis showed considerable synergy between opioids and hypnotics for sedation and suppression of responses to various noxious stimuli (see also Chapter 33).[96]

Opioids administered as a mainstay of surgical pain management can inhibit sleep on the first postoperative night. However, the effects of opioids on sleep and circadian rhythm are not clearly understood. A human study demonstrated that an overnight constant infusion of remifentanil inhibited rapid eye movement sleep without suppressing the nocturnal melatonin surge, findings that may suggest a minimal effect of opioids on the circadian pacemaker.[97]

ELECTROENCEPHALOGRAPHY

Increasing concentrations of inhaled anesthetic agents produce a continuum of electroencephalogram (EEG) changes and eventually result in burst suppression and a flat EEG. In contrast, a ceiling effect is reached with opioids. Once this ceiling has been obtained, increasing opioid dosage does not further affect the EEG.[98]

Although the potency and rate of equilibrium between plasma and brain are different among opioids, the effects of fentanyl, alfentanil, sufentanil, and remifentanil are consistent[99] (Fig. 31-7). Small doses of fentanyl (200 μg) produce minimal EEG changes, whereas higher doses (30 to 70 μg/kg) result in high-voltage slow (delta) waves suggesting a state consistent with anesthesia. Although transient isolated (usually frontotemporal) sharp wave activity can be observed after large doses of fentanyl and other opioids, it is not generalized (see also Chapter 49).

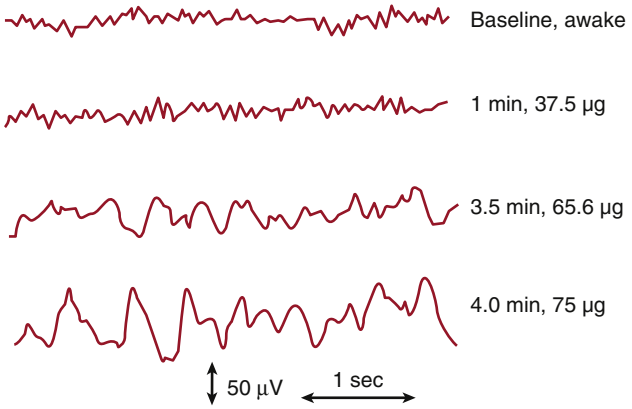


Figure 31-7. Representative 4-second electroencephalogram (EEG) tracings during infusion of sufentanil (total dose shown in the *right column*). The awake baseline EEG consists of mixed beta and alpha activity. At 1 minute, the EEG showed loss of beta activity and the presence of primarily alpha waves (8 to 13 Hz). At 3.5 minutes, the EEG consisted of mixed theta (4 to 7 Hz) and delta (<4 Hz) waves, and at 4.0 minutes, it consisted of delta waves of high amplitude. *(From Scott JC, Cooke JE, Stanski DR: Electroencephalographic quantitation of opioid effect: comparative pharmacodynamics of fentanyl and sufentanil,* Anesthesiology *74:34-42, 1991.)*

As an effect-site measure, the EEG can be employed to assess onset of drug action and drug potency ratios. The spectral edge and serum concentration are closely parallel for remifentanil,[100] whereas a significant time lag is found for recovery of the spectral edge for fentanyl and sufentanil[101] (Fig. 31-8). In healthy volunteers, approximate entropy derived from a parietal montage showed significant correlation with remifentanil concentration, and it was shown to be appropriate for the assessment of the remifentanil effect on the EEG.[102] Potency ratios based on EEG studies are similar to those obtained from studies determining the plasma drug levels of each opioid necessary to reduce the MAC of isoflurane by 50%.

EVOKED RESPONSES

Because opioids do not appreciably alter sensory-evoked potentials elicited at the posterior tibial or median nerve, sensory-evoked potentials can be used for spinal cord function monitoring during anesthesia with opioids.[103] Remifentanil produced dose-dependent reduction in auditory-evoked potentials.[104] Investigators also reported that remifentanil infusion (target plasma concentrations of 1, 2, and 3 ng/mL) did not affect evoked potential amplitudes and latencies.[105] In healthy human volunteers receiving 3 μg/kg fentanyl, amplitude and latency of motor-evoked responses to transcranial stimulation were not significantly affected.[106] Kawaguchi and associates reported that intraoperative myogenic motor-evoked potential monitoring is feasible during isoflurane or sevoflurane anesthesia with fentanyl.[107]

Middle latency auditory-evoked potentials (MLAEPs) and their derivatives are increasingly used as a surrogate measure of the level of anesthesia. Changes in MLAEPs following the administration of opioids occur and may result from either a direct depressant effect of opioids on MLAEPs itself or an indirect effect reflecting the action of

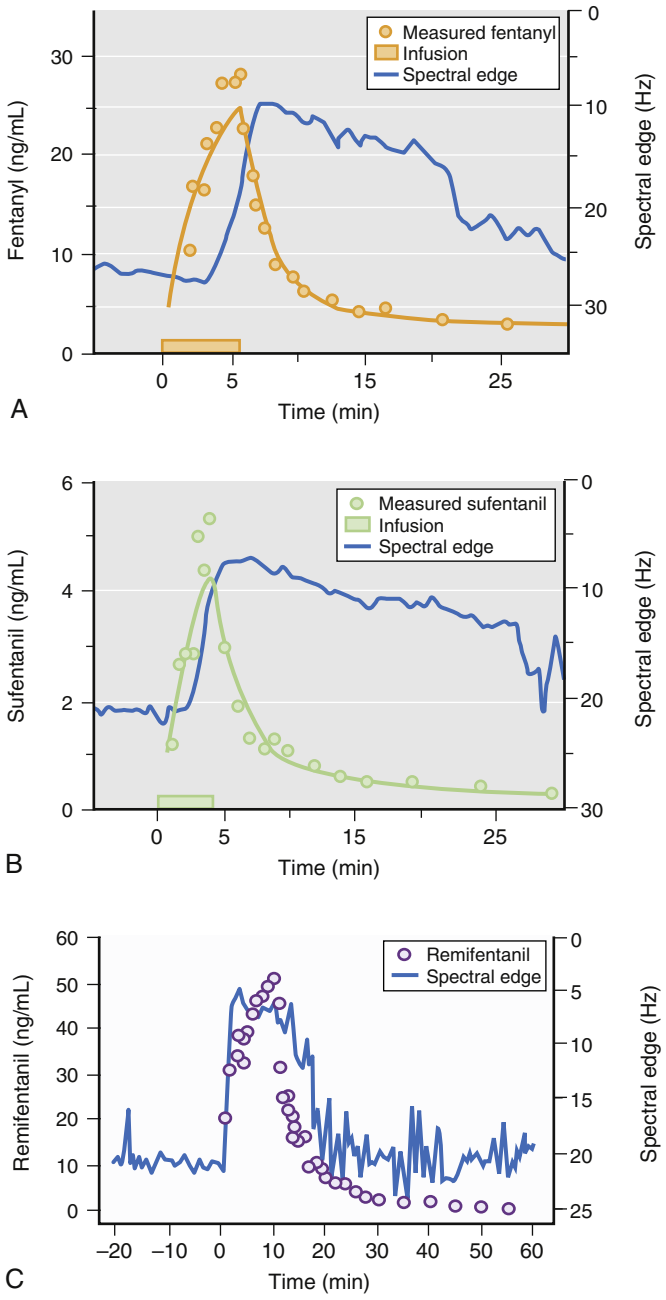


Figure 31-8. Time course of spectral edge and serum opioid concentration. Fentanyl (**A**) and sufentanil (**B**) were infused at 150 and 18.75 μg/minute, respectively. Remifentanil (**C**) was administered at 3 mg/kg/minute for 10 minutes. The spectral edge changes lag behind the serum concentration changes in the case of fentanyl and sufentanil, whereas the spectral edge and serum concentration closely parallel each other in the cases of remifentanil administration. *(From Scott JC, Ponganis KV, Stanski DR: EEG quantitation of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil,* Anesthesiology *62:234-241, 1985; and Egan TD, Minto CF, Hermann DJ, et al: Remifentanil versus alfentanil: comparative pharmacokinetics and pharmacodynamics in healthy adult male volunteers,* Anesthesiology *84:821-833, 1996.)*

opioids in attenuating CNS arousal associated with noxious stimuli. Wright and colleagues examined the effect of remifentanil (1 or 3 μg/kg/minute) on MLAEPs in tracheally intubated and nonintubated patients and showed that remifentanil has an effect on MLAEPs in attenuating the arousal associated with intubation of the trachea but has no effect in the absence of a stimulus.[108] Similarly, Schraag and associates found no significant contribution of remifentanil alone on MLAEPs, whereas increasing the concentration of remifentanil led to a significant decrease of the calculated propofol effect-site concentrations necessary for unconsciousness.[109]

CEREBRAL BLOOD FLOW AND CEREBRAL METABOLIC RATE

Opioids generally produce modest decreases in cerebral metabolic rate and intracranial pressure (ICP), although the changes are influenced by the concomitant administration of other agents and anesthetic drugs, as well as by patients' conditions (see also Chapters 49 and 70). When vasodilation is produced by coadministered anesthetic agents, opioids are more likely to cause cerebral vasoconstriction. Opioids also decrease cerebral blood flow (CBF) when they are combined with nitrous oxide (N_2O). When opioids are administered alone or when the coadministered anesthetic agents cause cerebral vasoconstriction, opioids usually have no influence or result in a small increase in CBF.

Endogenous opioid activity is present in the cerebral arteries, although exogenously administered opioids were found to exert little effect on pial artery diameter in several animal models.[110] In the piglet, fentanyl, alfentanil, and sufentanil decreased arteriolar diameter in a dose-dependent naloxone-reversible manner.[111] In human volunteers, PET demonstrated that CBF changes induced by fentanyl are regionally heterogenous.[112]

In healthy volunteers, sufentanil (0.5 μg/kg intravenously [IV]) produces no significant effect on CBF.[113] Alfentanil (25 to 50 μg/kg IV), administered to patients receiving isoflurane (0.4 to 0.6%)–N_2O anesthesia, produces minimal reductions in middle cerebral artery flow velocity.[114] A PET study in human volunteers showed that remifentanil induced dose-dependent changes in relative regional CBF in areas involved in pain processing, such as the lateral prefrontal cortex, inferior parietal cortex, and supplementary motor area.[115] In patients scheduled to undergo a supratentorial tumor surgical procedure and receiving N_2O, remifentanil (1 μg/kg/minute), similar to fentanyl (2 μg/kg/minute), reduced CBF and did not significantly affect cerebrovascular carbon dioxide (CO_2) reactivity.[116]

Opioid-induced neuroexcitation and focal seizure activity can cause regional increases in brain metabolism. Regional increases in glucose use induced by high doses of alfentanil in the rat were associated not only with epileptiform activity but also with neuropathic lesions.[117] In humans, PET evaluation demonstrated that a 1 to 3 μg/kg/minute infusion of remifentanil induces a significant increase in the cerebral metabolic rate for glucose.[118]

INTRACRANIAL PRESSURE

Opioids are generally thought to affect ICP minimally. During isoflurane-N_2O–based anesthesia, opioids do not cause significant increases in ICP in patients undergoing craniotomy for supratentorial space-occupying lesions (see also Chapters 17 and 70).[119,120] Opioid sedation does not alter ICP in patients with head injuries.[121] Light

sedation with remifentanil (4.2 ± 1.8 μg/kg/hour) does not result in higher ICP than that observed with propofol (4.3 ± 2.5 mg/kg/hour) in patients undergoing stereotactic brain tumor biopsy, and cerebral perfusion pressure may be better preserved with remifentanil.[122]

Opioids may produce increases in ICP in patients undergoing craniotomy for excision of supratentorial space-occupying lesions, especially if intracranial compliance is compromised (see also Chapter 70). In a study of patients with severe head injury who have preserved and impaired autoregulation, morphine (0.2 mg/kg) and fentanyl (2 μg/kg) moderately increased ICP, a finding suggesting that mechanisms other than vasodilation could be implicated in the opioid-induced ICP elevation.[123] Investigators also demonstrated no change in ICP in hydrocephalic children after alfentanil (70 μg/kg) administration.[124] Whether these discrepancies of the opioid effects on ICP reflect pressure assessment methods or the effects of other drugs is not clear.

NEUROPROTECTION

Although certain early studies suggested potentially adverse effects of μ-opioid agonists on ischemic brain, other studies documented that certain opioid agents, such as the κ-opioid agonists, can be neuroprotective, at least in animal models of focal ischemia (see also Chapter 70). Investigators also showed that activation of δ-opioid receptors increases the survival time of mice during lethal hypoxia. An in vitro study involving rat cerebellar brain slices demonstrated that pretreatment with morphine at clinically relevant concentrations induced acute neuroprotection mediated by activation of the δ_1-opioid receptors, activation of adenosine triphosphate (ATP)–sensitive K^+ channels, and free radical production in mitochondria.[125]

In contrast, Charchaflieh and associates demonstrated, using the rat hippocampal slice model, that fentanyl is neither neurotoxic nor protective against anoxic injury to neurons when used in concentrations comparable to those produced in clinical practice.[126]

In the rat focal ischemia model, in contrast to isoflurane, fentanyl neither increased nor decreased brain injury compared with awake unanesthetized rats.[127]

MUSCLE RIGIDITY

Opioids can increase muscle tone and may cause muscle rigidity. The incidence of rigidity noted with opioid anesthetic techniques varies greatly because of differences in dose and speed of opioid administration, the concomitant use of N_2O, the presence or absence of muscle relaxants, and the patient's age. Opioid-induced rigidity is characterized by increased muscle tone that sometimes progresses to severe stiffness with the potential for serious problems (Table 31-4). Clinically significant opioid-induced rigidity usually begins just as or after a patient loses consciousness. Mild manifestations of rigidity, such as hoarseness, can occur in conscious patients. Vocal cord closure is primarily responsible for the difficult ventilation with bag and mask that follows the administration of opioids. Delayed or postoperative rigidity is probably related to second peaks that can occur in plasma opioid concentrations, similar to the recurrence of respiratory depression.

TABLE 31-4 POTENTIAL PROBLEMS ASSOCIATED WITH OPIOID-INDUCED RIGIDITY

System	Problem
Hemodynamic	↑CVP, ↑ PAP, ↑ PVR
Respiratory	↓ Compliance, ↓ FRC, ↓ ventilation Hypercarbia, hypoxemia
Miscellaneous	↑ Oxygen consumption, ↑ intracranial pressure, ↑ fentanyl plasma levels

Modified from Bailey PL, Egan TD, Stanley TH: Intravenous opioid anesthetics. In Miller RD, editor: Anesthesia, *ed 5. Philadelphia, 2010, Churchill Livingstone, p 781.*

CVP, Central venous pressure; *FRC,* functional residual capacity; *PAP,* pulmonary artery pressure; *PVR,* pulmonary vascular resistance.

The precise mechanism by which opioids cause muscle rigidity is not clearly understood. Muscle rigidity is not the result of a direct action on muscle fibers because it can be decreased or prevented by pretreatment with muscle relaxants. Mechanisms of opioid-induced muscle rigidity involving the CNS have been postulated. Pharmacologic investigation using selective agonists and antagonists suggest that systemic opioid-induced muscle rigidity is primarily caused by activation of central μ receptors, whereas supraspinal δ_1 and κ_1 receptors may attenuate this effect.[128] Some aspects of opioid-induced catatonia and rigidity (increased incidence with age, muscle movements resembling extrapyramidal side effects) are similar to Parkinson disease and suggest similarities in neurochemical mechanisms. Patients with Parkinson disease, particularly if they are inadequately treated, may experience reactions such as dystonia following opioid administration.[129]

Pretreatment with or concomitant use of nondepolarizing muscle relaxants can decrease the incidence and severity of rigidity (see also Chapter 34). Induction doses of sodium thiopental and subanesthetic doses of diazepam and midazolam can prevent, attenuate, or successfully treat rigidity.

NEUROEXCITATORY PHENOMENA

Fentanyl causes seizure activity seen on the EEG in animals, but EEG evidence of seizure activity after fentanyl, alfentanil, and sufentanil is generally lacking in humans. Remifentanil induced generalized tonic-clonic seizure-like activity in an otherwise healthy adult.[130] Morphine produces tonic-clonic activity after epidural and intrathecal administration.[131] Focal neuroexcitation on the EEG (e.g., sharp and spike wave activity) occasionally occurs in humans after large doses of fentanyl, sufentanil, and alfentanil.

The mechanisms underlying opioid-induced neuroexcitatory phenomena are not completely clear. Excitatory opioid actions may be related to coupling to mitogen-activated protein kinase cascades.[132] Local increases in CBF and metabolism are also of theoretic concern because prolonged seizure activity, even if focal, could lead to neuronal injury or cellular death. Fentanyl, alfentanil, and sufentanil in large doses also induced hypermetabolism

and histopathologic alterations of the limbic system in rats.[133] Experimental study using excised mouse hippocampus showed that the proseizure effect of morphine is mediated by selective stimulation of the μ- and κ-opioid receptors but not the activation of the δ-opioid receptor.[134] In rats, midazolam, naloxone, and phenytoin prevented EEG seizure activity and histologically evident brain damage induced by large doses of fentanyl.[135]

Measurement of CBF by magnetic resonance imaging in human volunteers indicated that the cingulate cortex is the most susceptible to activation by remifentanil (0.05 to 0.2 μg/kg/minute), and susceptibility is affected by the apolipoprotein E genotype.[136] These findings support the notion that neuroactivation of limbic areas by the perioperative use of opioids may have a role in the genesis of postoperative cognitive dysfunction.

PUPIL SIZE

Morphine and most μ- and κ-agonists cause constriction of the pupil by an excitatory action on the parasympathetic nerve innervating the pupil. Opioids release cortical inhibition of the Edinger-Westphal nucleus, with resulting papillary constriction. After intravenous administration of morphine (0.125 mg/kg) in one report, a 26% decrease in pupil diameter occurred at 1 hour, and a period of more than 6 hours was necessary for complete recovery of pupil diameter.[137] The changes in pupil size associated with opioid action may be too slight to be of clinical utility in assessing the degree of opioid effect. The pupillary dilatation reflex has been successfully used to assess the analgesic component of a balanced anesthetic regimen. The pupillometer may be a valuable tool to guide morphine administration in the immediate postoperative period.[138]

PRURITUS

Histamine release is not causative because non–histamine-releasing opioids also produce pruritus. Intrathecal morphine-induced itching in monkeys was suggested to be mediated by the μ receptor.[139] Activation of a μ-opioid receptor isoform MOR1D by morphine induced activation of the gastrin-releasing peptide receptor that heterodimerized with MOR1D, thus resulting in activation of phospholipase β_3 and intracellular Ca^{2+} increase in neurons leading to itch sensation in mice.[140] Naloxone reverses opioid-induced itching, but opioid antagonists are not ideal therapeutic agents against pruritus because opioid analgesia is also reversed by these agents. A meta-analysis demonstrated that prophylactic use of serotonin type 3 ($5\text{-}HT_3$) antagonists significantly reduced the severity and the need for treatment of pruritus.[141] Activation of the κ-opioid receptor inhibits pruritus evoked by subcutaneous and intrathecal morphine in animal models.[142] Tamdee and colleagues reported that 15 mg of pentazocine, an agonist of the κ-opioid receptor and partial agonist of the μ-opioid receptor, is superior to 4 mg of ondansetron for the treatment of pruritus induced by intrathecal morphine in parturients undergoing cesarean delivery.[143] Tenoxicam, a nonsteroidal antiinflammatory drug (NSAID), was reported to be effective for pruritus induced by epidural fentanyl.[144] Intravenous administration of droperidol (1.25 mg), propofol (20 mg), or alizapride (100 mg) reduced the incidence of pruritus induced by the use of morphine 0.2 mg intrathecally in patients undergoing cesarean section with spinal anesthesia.[145] Preoperative gabapentin prevents pruritus induced by intrathecal morphine in patients undergoing lower limb operations with spinal anesthesia.[146]

Facial itching may not necessarily be a manifestation of direct opioid action at the level of the trigeminal nucleus, but rather, it may reflect opioid-triggered neural transmission at a distant site. Why the face is prone to pruritus even after spinal opioid administration is not known. Pruritus resulting from cholestasis is ameliorated by opioid antagonists.[147]

RESPIRATORY EFFECTS OF OPIOIDS

The respiratory depressant actions of opioids represent their most serious adverse effects (see also Chapter 51). Although some early studies indicated involvement of both μ- and δ-opioid receptors, a more recent report demonstrated that activation of the μ-opioid receptor in the caudal medullary raphe region, which is important for regulating pain and respiratory modulation, inhibits the ventilatory response to hypercapnia in anesthetized rats.[148] Furthermore, administration of morphine or M6G did not produce significant respiratory depression in the μ-opioid receptor knockout mice.[149] Polymorphism of the μ-opioid receptor at nucleotide position 118, which is known to affect M6G-induced analgesia, does not significantly change the susceptibility of respiratory depressive effect of M6G.[10] This result suggests that analgesia and respiratory depression may be mediated by different signal transduction mechanisms activated by the μ-opioid receptor.

Morphine depresses respiratory mucous transport, which is one of the most important defenses against respiratory tract infections. However, morphine had no effect on the beating frequency of nasal cilia in vitro.[150]

THERAPEUTIC EFFECTS

By decreasing pain and central ventilatory drive, opioids are effective agents in preventing hyperventilation induced by pain or anxiety. Because the lack of adequate pain relief can also cause postoperative respiratory dysfunction, opioids can be used as postoperative analgesics to prevent respiratory dysfunction. The antitussive actions of opioids are well known and central in origin. Investigators reported that an effect-site concentration of 2 ng/mL of remifentanil can suppress coughing induced by extubation after propofol or sevoflurane anesthesia.[151] In contrast, fentanyl, sufentanil, and alfentanil curiously elicit a brief cough in up to 50% of patients when the drug is injected by intravenous bolus. Fentanyl, administered through a peripheral intravenous cannula, provoked cough when it was injected rapidly, but the incidence of cough decreased significantly as the injection time was increased,[152] as well as by the administration of 1.5 mg/kg lidocaine 1 minute before fentanyl administration.[153] Investigators reported that preemptive use of 25 μg, administered 1 minute before bolus injection of

fentanyl (125 or 150 μg), can effectively suppress fentanyl-induced cough.[154] A prospective randomized controlled study demonstrated that a huffing maneuver, consisting of a forced expiration against an open glottis, just before intravenous fentanyl administration significantly reduced the incidence and severity of fentanyl-induced coughing in the majority of the patients.[155]

Opioids are also excellent agents for depressing upper airway, tracheal, and lower respiratory tract reflexes, but the mechanism is not clear. Although opioids can affect the contractile responses of airway smooth muscles, the clinical significance and relevance of opioid-induced effects on airway resistance remain controversial.[156] Opioids blunt or eliminate somatic and autonomic responses to tracheal intubation. They allow patients to tolerate endotracheal tubes without coughing or "bucking." Conversely, two successive dose of 1.5 μg/kg fentanyl did not effectively prevent laryngospasm in children 2 to 6 years old who were anesthetized with sevoflurane.[157] Opioids can also help avoid increases in bronchomotor tone in asthma. In addition, fentanyl also has antimuscarinic, antihistaminergic, and antiserotoninergic actions and may be more effective than morphine in patients with asthma or other bronchospastic diseases.

RESPIRATORY DEPRESSION

Opioids activating the μ receptor cause dose-dependent depression of respiration, primarily through a direct action on brainstem respiratory centers.[158] The stimulatory effect of CO_2 on ventilation is significantly reduced by opioids. Hypercapnic responses can be separated into central and peripheral components. In one report, morphine-induced changes in the central component were equal in men and women, whereas changes in the peripheral component were larger in women.[159] In addition, the apneic threshold and resting end-tidal partial pressure of CO_2 are increased by opioids (Fig. 31-9). Opioids also decrease hypoxic ventilatory drive.

Respiratory rate is usually drastically decreased in opioid overdose, although a hypoxic CNS insult can counter this effect. The prolonged expiratory time in the respiratory cycle induced by opioids frequently results in greater reductions in respiratory rate than in tidal volume. Monitoring of breath intervals can sensitively detect fentanyl-induced respiratory depression and can be used as a measure of dynamic opioid effect.[160] High doses of opioids usually eliminate spontaneous respirations without necessarily producing unconsciousness. Patients receiving high doses of opioids may still be responsive to verbal command and often breathe when they are directed to do so.

Peak onset of respiratory depression after an analgesic dose of morphine is slower than after comparable doses of fentanyl, and respiratory depression induced by small doses of morphine usually lasts longer than after equipotent doses of fentanyl. Sufentanil (0.1 to 0.4 μg/kg) produces shorter-lasting respiratory depression and longer-lasting analgesia than does fentanyl (1.0 to 4.0 μg/kg).[161] Plasma fentanyl concentrations of 1.5 to 3.0 ng/mL are associated with significant decreases in CO_2 responsiveness. With higher doses of fentanyl (50 to 100 μg/kg),

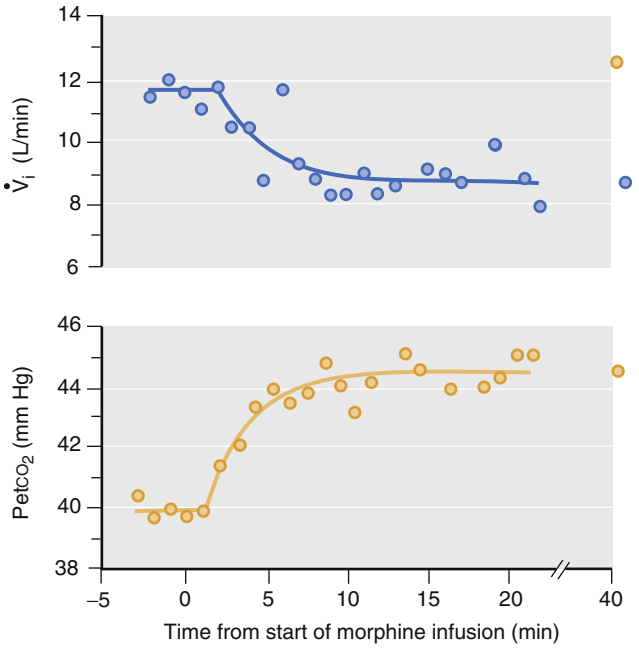


Figure 31-9. Influence of morphine administration (bolus dose of 100 μg/kg given at the start of the infusion [0 minute], followed by a continuous infusion of 30 μg/kg/hour) on resting inspired minute ventilation ($\dot{V}_i$) and resting pressure of end-tidal carbon dioxide ($Petco_2$) in a single subject. A one-component exponential was fitted to the data. The estimated time constant for the $\dot{V}_i$ data is 3.0 minutes and for $Petco_2$ data is 2.6 minutes. The time delays are between 1 and 2 minutes. *(From Sarton E, Teppema L, Dahan A: Sex differences in morphine-induced ventilatory depression reside within the peripheral chemoreflex loop,* Anesthesiology *90:1329-1338, 1999.)*

respiratory depression can persist for many hours. When moderately large doses (20 to 50 μg/kg or greater) of fentanyl are used, the potential need for postoperative mechanical ventilation should be anticipated. The effects of remifentanil, no matter what the dose, are attenuated rapidly and completely within 5 to 15 minutes following termination of its administration. In healthy humans, the EC_{50} for depression of minute ventilation with remifentanil and alfentanil was 1.17 ng/mL and 49.4 ng/mL, respectively.[162] In healthy volunteers, fentanyl 1 μg/kg and remifentanil 0.5 μg/kg had similar maximum decreases in minute ventilation (≈50%), but the onset of and recovery from ventilatory depression were faster with remifentanil.[163]

Naloxone has been accepted as a standard therapy for opioid-induced respiratory depression. However, reports have noted naloxone-resistant respiratory depression after intrathecal morphine administration.[164] Although serotonin agonists, ampakines, and the antibiotic minocycline may be considered newer treatments to prevent opioid-induced respiratory depression, more study is necessary before these treatments are used in humans.[158]

FACTORS AFFECTING OPIOID-INDUCED RESPIRATORY DEPRESSION

Many factors affect the magnitude and duration of opioid-induced respiratory depression (Box 31-2).

BOX 31-2 ***Factors Increasing the Magnitude and/or Duration of Opioid-Induced Respiratory Depression***

High dose
Sleep
Old age
Central nervous system depressant
  Inhaled anesthetics, alcohol, barbiturates, benzodiazepines
Renal insufficiency
Hyperventilation, hypocapnia
Respiratory acidosis
Decreased clearance
  Reduction of hepatic blood flow
Secondary peaks in plasma opioid levels
  Reuptake of opioids from muscle, lung, fat, and intestine
Pain

Older patients are more sensitive to the anesthetic and respiratory depressant effects of opioids (see also Chapter 80). Older patients also experience higher plasma concentrations of opioids administered on a weight basis. Morphine can produce greater respiratory depression on a weight basis in neonates than in adults because morphine easily penetrates the brain in neonates and infants with incomplete blood-brain barriers.

The respiratory depressant effects of opioids are increased or prolonged (or both) when these drugs are administered with other CNS depressants, including potent inhaled anesthetic agents, alcohol, barbiturates, benzodiazepines, most intravenous sedatives, and hypnotics. However, droperidol, scopolamine, and clonidine do not enhance the respiratory depressant effects of fentanyl or other opioids.

Although opioid action is usually dissipated by redistribution and hepatic metabolism, rather than by urinary excretion, the adequacy of renal function may influence the duration of opioid activity. In renal insufficiency, the respiratory depressant properties of the morphine metabolite M6G would become evident as it accumulated.

Hypocapnic hyperventilation enhances and prolongs postoperative respiratory depression after fentanyl (10 and 25 μg/kg). Intraoperative hypercarbia produces the opposite effects. Possible explanations for these findings include increased brain opioid penetration (increased un-ionized fentanyl with hypocarbia) and removal (decreased CBF with hypocarbia). In patients who hyperventilate because of anxiety or pain, even small doses of intravenous opioids can result in transient apnea because of acute shifts in apneic thresholds.

Delayed or recurring respiratory depression has been reported with most opioids. Mechanisms for this phenomenon may include augmented release of fentanyl or other opioids from skeletal muscle into the systemic circulation on rewarming, shivering, motion, or any other condition that enhances muscle perfusion.

CARDIOVASCULAR EFFECTS OF OPIOIDS

Numerous reports have demonstrated that large doses of opioid, administered as the sole or primary anesthetic agent, result in hemodynamic stability throughout the operative period.

NEUROLOGIC MECHANISMS

Key areas of the brainstem that integrate cardiovascular responses and maintain cardiovascular homeostasis are the nucleus solitarius, the dorsal vagal nucleus, the nucleus ambiguus, and the parabrachial nucleus. The nucleus solitarius and parabrachial nucleus play an important role in the hemodynamic control of vasopressin secretion. Enkephalin-containing neurons and opioid receptors are distributed in these regions. The direct administration of μ-agonists into the CNS of animals most commonly, but not always, produces hypotension and bradycardia.[165] The ventrolateral PAG region, a key central site mediating opioid analgesia, also affects hemodynamic control.[166] In addition, opioids can modulate the stress response through receptor-mediated actions on the hypothalamic-pituitary-adrenal axis. Most opioids reduce sympathetic and enhance vagal and parasympathetic tone. Patients who are volume depleted, or individuals depending on high sympathetic tone or exogenous catecholamines to maintain cardiovascular function, are predisposed to hypotension after opioid administration.

The predominant and usual effect of opioids on heart rate is bradycardia resulting from stimulation of the central vagal nucleus. Blockade of sympathetic actions may also play a role in opioid-induced bradycardia. Meperidine, in contrast to other opioids, rarely results in bradycardia, but it can cause tachycardia.

CARDIAC MECHANISMS

The direct cardiac actions of opioids, in particular the effects on myocardial contractile mechanisms, are significantly less pronounced than are those of many other intravenous and inhaled anesthetics. However, opioid receptors exist in cardiac myocytes of several species.

Contractility

Morphine decreases Ca^{2+} transients but not cardiac contraction and enhances myofilament Ca^{2+} sensitivity through the action on the δ_1-opioid receptor expressed in the heart.[167] In rabbit ventricular myocytes, morphine prolonged action potential duration by increasing L-type Ca^{2+} current, an effect mediated by δ- and κ-opioid receptors, and hyperpolarized cardiac resting membrane potential by increasing the inwardly rectifying K^+ current, which is not mediated by opioid receptors.[168] Conversely, investigators demonstrated that morphine decreased the isometric force of contraction in atrial muscles from nonfailing and failing human hearts through a naloxone-insensitive mechanism.[169] Fentanyl produces little or no change in myocardial contractility.[170] Usually, most hemodynamic variables remain unchanged after large doses of fentanyl. However, fentanyl has positive inotropic effects. Possible mechanisms of the dose-dependent positive inotropic effects of fentanyl, as well as those of sufentanil, include catecholamine release or direct myocardial adrenergic activation. Alfentanil, at concentrations achieved in clinical practice, increases contraction

in ventricular cells by a mechanism involving an increase in the sensitivity of the contractile apparatus to Ca^{2+}.[171] The negative inotropic effect of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) on ventricular myocytes caused by disruption of sarcoplasmic reticulum Ca^{2+} handling and the Ca^{2+} transient was reported to be ameliorated by alfentanil, but this response may not be mediated by opioid receptors.[172] Studies in dogs demonstrated little change in hemodynamics with moderate doses (160 μg/kg) of alfentanil and transient cardiac stimulation (increases in left ventricular contractility, aortic blood flow velocity, and acceleration) with very large doses (5 mg/kg). In dogs, remifentanil produced hemodynamic effects that include decreases in contractility and cardiac output, as well as reductions in heart rate and blood pressure.[173] However, a study using transthoracic echocardiography demonstrated that continuous target-controlled infusion of remifentanil (target effect-site concentration 2 ng/mL, infusion rate 0.08 to 0.09 μg/kg/minute) did not affect systolic and diastolic left ventricular function in young healthy subjects during spontaneous breathing.[174]

Cardiac Rhythm Conduction

Opioid-induced bradycardia is primarily mediated by the CNS (see also Chapter 45). However, some reports have noted direct effects of opioids on cardiac pacemaker cells. Alfentanil significantly decreased the frequency of contractions of the right atrial-sinoatrial node in a dose-related manner in isolated cardiac tissues from young adult rabbits.[175] Premedication with or concomitant administration of β-adrenergic or Ca^{2+} channel entry blockers can exacerbate the bradycardia and may result in asystole after the administration of opioids. Periods of asystole, 10 to 12 seconds in duration, may resolve spontaneously, but they usually respond to atropine (0.4 to 0.8 mg IV).

Fentanyl may depress cardiac conduction by a mechanism mediated by direct membrane actions, as opposed to opioid receptor interactions.[176] During induction of anesthesia in patients undergoing coronary artery bypass graft surgery, the QT interval increased significantly after the injection of fentanyl[177] (see also Chapter 67). However, pretreatment with fentanyl (2 μg/kg) or remifentanil (1 μg/kg) significantly attenuated QTc prolongation associated with laryngoscopy and tracheal intubation during propofol or sevoflurane induction.[178,179] Both sufentanil and alfentanil have been demonstrated to be devoid of electrophysiologic effects on the normal or accessory pathways in patients with Wolff-Parkinson-White syndrome.[180,181] Clinically, cardiac conduction disturbances attributable to opioids are rare, but they may be more likely to occur in the presence of Ca^{2+} channel or β-adrenergic blockers.

The overall effect of opioid anesthesia is antiarrhythmogenic. Naloxone, morphine, and levorphanol protected against arrhythmia induced by coronary artery occlusion in rats.[182] A direct effect on ionic currents in cardiac muscle was suggested as the mechanism of the antiarrhythmogenic activity of opioids. Opioid antagonists were more antiarrhythmogenic than were agonists in rats.[183] Some of the electrophysiologic actions of opioids resemble those of class III antiarrhythmogenic drugs.

Myocardial Ischemia

Determining the effects and consequences of opioid action on myocardial ischemia is complex because the results can depend on such factors as the species studied and experimental design (see also Chapter 67). In an experimental model of myocardial ischemia in rabbits, fentanyl had antiarrhythmic and antiischemic action with central and peripheral opioid receptor involvement.[184] Opioids can mimic ischemic preconditioning. Opioid receptor stimulation results in a reduction in infarct size similar to that produced by ischemic preconditioning.[185] Although the preconditioning effect of opioids is mediated mainly by the cardiac κ- and δ-opioid receptors,[186] part of the protective effect of remifentanil may be produced by μ-agonist activity outside the heart.[187] Preconditioning with small doses of intrathecal morphine can provide comparable cardioprotection to myocardial ischemic preconditioning and preconditioning with intravenous morphine, and the effect seems to involve δ-, κ- and μ-opioid receptors.[188] Late preconditioning, in which cardioprotective effects can be observed 24 hours after drug administration, was also produced by morphine-induced activation of the opioid receptor in rat hearts.[189] Remote preconditioning by brief ischemia of other distant organs, such as the intestine, kidney, and limb, similarly provides cardioprotection that is as effective as classic ischemic preconditioning. The myocardial κ-opioid receptors were demonstrated to mediate cardioprotection by remote preconditioning.[190] Brief cycles of ischemia and reperfusion during the early phase of reperfusion protect the heart from infarction. This phenomenon, termed *postconditioning*, was shown to be induced by activation of the κ-opioid receptor in the heart.[191] Volatile anesthetic agents may also be capable of producing protection against ischemic injury when these drugs are administered solely on reperfusion. This anesthetic-induced postconditioning can be enhanced by morphine through the activation of phosphatidyl-3-kinase and opioid receptors.[192]

Stimulation of δ_1-opioid receptor generates oxygen (O_2) radicals through mitochondrial ATP-sensitive K^+ channels, with resulting attenuation of oxidant stress and cell death in cardiomyocytes.[193] Involvement of adenosine A1 receptor and protein kinase C in the cardioprotective effect of opioids was also suggested.[194,195] Whether the experimental results showing protective effects of opioid against myocardial ischemia will translate into reductions in morbidity and mortality in patients with coronary artery disease has yet to be established by clinical trials.[196] Clinically, large doses of opioids can maintain myocardial perfusion and the O_2 supply-demand ratio as well as or better than can inhalation-based techniques.

Coronary Circulation

Opioids appear to have no significant effect on coronary vasomotion or myocardial metabolism; they do not produce steal phenomena, and they do not diminish the ability of large coronary arterioles to respond to vasoactive agents.[197] Coronary conductance is regulated by arterial baroreflex control, and a vasodilator response is induced by a rise in aortic pressure. This baroreflex control is enhanced by low plasma concentrations of

fentanyl (1 to 2 ng/mL), but it appears to be depressed with increasing plasma concentrations of fentanyl.[198] In a study of the effects of opioids and neuroendocrine modulators on porcine coronary arteries, fentanyl, but not sufentanil or morphine, antagonized acetylcholine-induced contractions.[199] The effect of fentanyl was not reversible by naloxone and thus was thought to represent a direct smooth muscle effect.

Circulatory Reflexes

In an experiment examining baroreceptor reflex responses induced by perfusion of the carotid sinus at predetermined levels, baroreceptor reflexes were well preserved with moderate doses of fentanyl, whereas high doses of fentanyl depressed the baroreceptor reflexes.[200] The oculocardiac reflex, which is caused by traction on the extraocular muscles during surgical procedures for strabismus, was significantly augmented by fentanyl, sufentanil, and remifentanil.[201] Among pediatric patients undergoing surgical procedures for strabismus and anesthetized with propofol (12 mg/kg/hour) and alfentanil (0.04 mg/kg/hour), virtually all patients developed oculocardiac reflex, and atrioventricular rhythm disorders were frequent.[202]

HISTAMINE RELEASE

Morphine causes histamine release and sympathoadrenal activation. Codeine and meperidine induce mast cell activation with the release of histamine, probably by a mechanism other than the μ-opioid receptors.[203]

Increases in plasma histamine after morphine administration cause dilatation of terminal arterioles and direct positive cardiac chronotropic and inotropic actions. In patients pretreated with both H_1- and H_2-antagonists, the cardiovascular responses are significantly attenuated despite comparable increases in plasma histamine concentrations. Meperidine also causes histamine release more frequently than do most other opioids. Unlike morphine or meperidine, fentanyl, alfentanil, and remifentanil do not produce increases in plasma histamine, and hypotension is less frequent with these opioids.

VASCULAR MECHANISMS

A more recent pharmacologically defined opioid receptor subtype, designated μ_3, is opiate alkaloid sensitive and insensntive to opioid peptides including peptides previously shown to have affinities for the μ-opioid receptors. This receptor is expressed in human endothelial cells and is coupled to vasodilation through nitric oxide production. Morphine-induced vasodilation may be partially caused by activation of the μ_3 receptor.[204] Pharmacologic studies evaluating alfentanil, fentanyl, and sufentanil in dogs demonstrated direct peripheral vessel smooth muscle relaxation.[205] Measurement of forearm blood flow after infusion of sufentanil into the brachial artery indicated that sufentanil has a direct vasodilatory effect on human vascular tissue that is probably independent of a neurogenic or systemic mechanism.[206] A supraclinical dose of alfentanil attenuated the phenylephrine-induced contraction through an inhibitory effect on calcium (Ca^{2+}) influx by blocking the L-type Ca^{2+} channels in rat aortic vascular smooth muscle.[207] Remifentanil can cause transient instability in hemodynamic variables. However, this change may not solely be the result of autonomic nervous system or CNS inhibition or centrally mediated vagal stimulation. A pharmacologic study using rat thoracic aortic rings indicated that remifentanil vasodilates by an endothelium-dependent mechanism involving prostacyclin and nitric oxide released from the endothelium and by an endothelium-independent vasodilation probably mediated by the suppression of voltage-sensitive Ca^{2+} channels.[208] In patients with total artificial hearts in which cardiac output is preload independent, remifentanil induces a dose-dependent and significant systemic vasodilation without significant effects on capacitance vessels.[209]

Opioids may affect the pulmonary vasculature, as well as the systemic circulation. Phenylephrine-induced contraction of the canine pulmonary artery was primarily mediated by α_{1B}-adrenergic receptor activation, and it was attenuated by fentanyl by binding to and directly inhibiting the α_{1B}-adrenergic receptor.[210] Pharmacologic studies in cats demonstrated that sufentanil and remifentanil have potent vasodepressor activity in the pulmonary vascular bed and that these responses may be mediated by the histamine and opioid receptor–sensitive pathway.[211,212]

Activation of muscarinic acetylcholine receptors expressed on endothelial cells results in the activation of nitric oxide synthase and release of nitric oxide, which relaxes vascular smooth muscle by activation of 3,5-cyclic guanosine monophosphate. Investigators showed that fentanyl attenuated acetylcholine-induced relaxation of rat aorta precontracted with phenylephrine by an inhibitory effect at a level proximal to nitric oxide synthase activation on the pathway involving endothelial M_3 muscarinic receptor activation.[213]

Opioids are often administered to patients requiring surgical intervention for the control of hemorrhage. An animal study demonstrated that pretreatment with morphine before inducing the shock state decreased leukocyte adhesion and vascular permeability in the microcirculation of the mesenteric venule, a finding suggesting the survival benefit for use of morphine during acute resuscitation[214] (see also Chapter 108).

ENDOCRINOLOGIC EFFECTS OF OPIOIDS

The main components of the neuroendocrine stress response are the corticotropin-releasing hormone brain centers (e.g., paraventricular hypothalamic nucleus) and the locus ceruleus–norepinephrine/autonomic nervous system. Increased levels of stress hormones are considered undesirable because they promote hemodynamic instability and intraoperative and postoperative metabolic catabolism. In some circumstances, the hormonal and metabolic responses to surgery are extreme and are thought to contribute to operative mortality.

Opioids are capable of reducing the stress response by modulating nociception at several different levels of the neuraxis, as well as by influencing centrally mediated neuroendocrine responses. Opioids are potent inhibitors

of the pituitary-adrenal axis.[215] Endogenous opioid peptides may serve as stress hormones themselves and not just as modulators of the secretion of other hormones. This activity is suggested by the finding that β-endorphin and ACTH are derived from the same precursor proopiomelanocortin and are cosecreted during stress.

Morphine modifies hormonal responses to surgical trauma in a dose-related fashion. Morphine can prevent ACTH release, suppress surgically induced increases in plasma cortisol, and attenuate the pituitary-adrenal response to surgical stress. Morphine can increase some stress-responding hormones by increasing plasma histamine release, adrenal medullary release mechanisms, and release of catecholamine from sympathetic nerve endings.

Fentanyl and its congeners are more effective than morphine in modifying hormonal responses to surgery. The efficacy of fentanyl in controlling the hormonal manifestations of the stress response can be dose dependent. Fentanyl doses of 50 μg/kg or larger can help reduce the hyperglycemic response to cardiac surgical procedures in pediatric patients to less than 200 mg/dL throughout the operation.[216] In contrast, neither fentanyl nor sufentanil alone can completely block the sympathetic and hormonal stress responses, and perhaps no dose-response relationship exists for opioid-associated control of the stress response.[217] The stress response to cardiopulmonary bypass (CPB) is difficult to suppress with sufentanil or fentanyl. Alfentanil can suppress increases in plasma cortisol and catecholamines before but not during CPB and may prevent increases in antidiuretic hormone (ADH) and growth hormone throughout coronary artery bypass surgery. A randomized controlled trial showed that remifentanil (0.85 μg/kg/minute), when compared with fentanyl (total doses of 15 and 28 μg/kg), blunts the hypertensive responses and cortisol excretion associated with cardiac surgery but is associated with more hypotension.[218]

STRESS REDUCTION AND OUTCOME

Anesthetic techniques or drugs that minimize the stress response may reduce morbidity and mortality in a variety of circumstances. Anand and colleagues evaluated the impact of sufentanil versus morphine-halothane anesthesia on hormonal and metabolic responses and morbidity and mortality in neonates undergoing cardiac surgical procedures.[219] Most strikingly, a statistically significant difference in postoperative mortality was observed (0 of 30 infants given sufentanil versus 4 of 15 infants given halothane plus morphine). Mangano and associates also reported that, after myocardial revascularization, patients receiving intense postoperative analgesia with sufentanil (1 μg/kg/hour) experienced a lower incidence and severity of electrocardiographically documented ischemia compared with patients receiving intermittent intravenous morphine (2.2 ± 2.1 mg/hour) for postoperative analgesia.[220] High-dose opioids (remifentanil 0.85 μg/kg/minute or fentanyl 28 μg/kg) are associated with a decreased rate of myocardial infarction after cardiac surgical procedures.[218]

Many different hormonal changes induced by surgery have been described. However, the concomitant neural, cellular, immune, and biochemical changes have been less well defined, and little is understood or proven with regard to how modifying hormonal responses alters outcome.[221] Additional studies are necessary for complete elucidation of the relationship between control of surgically induced hormonal responses and outcome.

OPIOID TOLERANCE AND OPIOID-INDUCED HYPERALGESIA

The mechanisms of dependence and tolerance involve genetic, molecular, cellular, physiologic, and functional factors. In the locus ceruleus, the major noradrenergic nucleus in the brain, long-term opioid exposure results in inhibition of adenylyl cyclase, reduced activity of protein kinase A, and up-regulation of the cyclic AMP pathway.[222] The changes in μ-receptor density that occur before or during the development of tolerance do not appear to be essential for the development of opioid tolerance.[223] Possible mechanisms involve protein kinase signal transduction cascades that link extracellular signals to cellular changes by regulating target gene expression. Central glucocorticoid receptors (GRs) have been implicated in the cellular mechanism of neuronal plasticity, which has many cellular steps in common with the mechanism of opioid tolerance. Investigators showed that the development of tolerance to the antinociceptive effect of morphine was substantially attenuated when a GR antagonist was coadministered with morphine, but the GR agonist dexamethasone facilitated the development of morphine tolerance; these findings suggest an important role of spinal GRs in the cellular mechanisms of morphine tolerance in rats.[224] Morphine tolerance occurs more rapidly in younger rats than in older rats and is unlikely to be the result of differences in drug metabolism or clearance, an observation suggesting that aging may have an impact on the molecular processes involved in the development of tolerance.[225] Activation of glial cells, including astrocytes and microglia, at the level of the spinal cord may play an important role in the development of opioid tolerance.[226,227]

Short-term administration of opioids results in analgesia and side effects, whereas tolerance and dependence were thought to occur only after long-term administration. However, tolerance can also develop rapidly after short-term opioid exposure in animals and humans. Intraoperative remifentanil infusion (0.3 μg/kg/minute) in patients undergoing major abdominal surgical procedures performed using desflurane anesthesia increased postoperative pain and morphine requirements when compared with low-dose remifentanil (0.1 μg/kg/minute); these findings suggest the development of acute remifentanil tolerance.[228] In contrast, there is a report that target-controlled infusion of alfentanil and remifentanil for postoperative analgesia does not lead to opioid tolerance.[229] In human volunteers, continuous infusion of remifentanil (0.08 μg/kg/minute) for 3 hours did not decrease the pain threshold.[230] Thus, the development of acute opioid tolerance in humans remains controversial.

Opioids can elicit hyperalgesia in experimental models after repeated opioid administration or continuous delivery.[231] This phenomenon seems to be related to opioid tolerance.[232] In rats, thermal hyperalgesia and mechanical

allodynia were observed for several days after cessation of morphine administration (40 mg/kg/day for 6 days).[233] The opioid-induced hyperalgesia resulted from spinal sensitization to glutamate and substance P.[234] Furthermore, cholecystokinin and the NMDA–nitric oxide system are responsible for the development of acute tolerance to opioids,[235] which is also affected by spinal serotonin activity.[236] Opioid-induced hyperalgesia and subsequent acute opioid tolerance can be prevented by ketamine, a finding suggesting involvement of the NMDA receptor.[237,238] Methadone is unique in possessing both μ-opioid and NMDA-antagonist properties. Opioid-induced hyperalgesia resulted from the presence of *l*-methadone (μ-opioid agonist) in the racemate and was antagonized by the presence of *d*-methadone (NMDA antagonist).[239] N_2O is an effective NMDA antagonist. Intraoperatively, 70% N_2O administration significantly reduced postoperative opioid-induced hyperalgesia in patients receiving propofol (≈120 μg/kg/minute) and remifentanil (0.3 μg/kg/minute).[240]

Spinal cyclooxygenase-2 (COX-2) protein was upregulated and release of prostaglandin E_2 in the spinal cord was increased after morphine withdrawal in rats.[241] In humans, hyperalgesia after 30-minute intravenous infusion of remifentanil (0.1 μg/kg/minute) could be prevented by the administration of parecoxib, a COX-2 inhibitor, before remifentanil infusion,[242] thereby suggesting the involvement of COX-2 in opioid-induced hyperalgesia.

Genetic analysis in mice suggested that genetic variants of the β_2-adrenergic receptor gene seem to explain some of the differences among various strains of mice in the development of opioid-induced hyperalgesia, and the selective β_2-adrenergic receptor antagonist butoxamine was shown to reverse opioid-induced hyperalgesia in a dose-dependent manner.[243] In mice, systemic or intrathecal injection of the 5-HT_3 receptor antagonist, ondansetron, was shown to prevent or reverse opioid-induced tolerance or hyperalgesia.[244]

The occurrence of opioid-induced hyperalgesia may possibly be affected by general anesthetic agents coadministered with opioids. When women undergoing surgical treatment of breast cancer were anesthetized with sevoflurane or propofol to keep the BIS value at 40 to 50, postoperative hyperalgesia induced by intraoperative remifentanil infusion (effect-site target of 4 ng/mL) was significant with sevoflurane anesthesia but not apparent with propofol anesthesia.[245] Human data generally support the existence of opioid-induced hyperalgesia in a few specific settings. The conditions under which opioid-induced hyperalgesia is expressed should be clarified, and its clinical significance remains to be elucidated.[246]

MANAGEMENT OF OPIOID-DEPENDENT PATIENTS

A variety of problems should be taken into consideration for anesthetic management of opioid-dependent patients.[247] Complications in opioid-addicted patients include cardiopulmonary problems, renal problems, and anemia. Long-term morphine administration causes adrenal hypertrophy and impairs corticosteroid secretion. Viral and nonviral hepatitis, acquired immunodeficiency syndrome, osteomyelitis, muscle weakness, and neurologic complications may be found in addicted patients. Because underestimation and undertreatment of pain are common in opioid-dependent patients, it is important to identify the goals of short-term pain management in these patients (Box 31-3).[248] Anesthetic management of the opiate-dependent or addicted patient should include adequate premedication with opioids, administration of supplemental intraoperative and postoperative opioids, and provision of nonopioid analgesics and neural blockade. No ideal anesthetic approach exists for a patient with a chronic addiction or a patient with an acute opiate overdose. One treatment for opioid addiction is rapid detoxification with a high dose of naloxone or naltrexone. For this treatment, general anesthesia is induced before the start of opioid antagonism and is maintained for several hours to prevent perception of withdrawal symptoms by the patient.[249,250] Blockade of μ-opioid receptors by naloxone (total dose of 12.4 mg) in opioid-addicted patients induces sympathetic neural activation, including an increase in plasma catecholamine concentration and cardiovascular stimulation, which is abolished by α_2-agonists.[251]

BOX 31-3 ***Goals of Acute Pain Management in Opioid-Dependent Patients***

1. Identification of the population of at-risk patients receiving long-term opioid therapy for various chronic pain situations (musculoskeletal disease, neuropathic conditions, sickle cell disease, HIV-related disease, palliative care), drug abusers, recovering addicts in opioid maintenance programs
2. Prevention of withdrawal symptoms and complications
3. Symptomatic treatment of psychological affective disorders such as anxiety
4. Effective analgesic treatment in the acute phase
5. Rehabilitation to acceptable and suitable maintenance opioid therapy

HIV, Human immunodeficiency virus.

RENAL AND URODYNAMIC EFFECTS OF OPIOIDS

μ-Receptor activation causes antidiuresis and decreases electrolyte excretion. κ-Receptor stimulation predominantly produces diuresis with little change in electrolyte excretion. Indirect actions may involve inhibiting or altering the secretion of ADH and atrial natriuretic peptide. The absence of increases in plasma ADH, renin, and aldosterone indicates that fentanyl, sufentanil, alfentanil, and probably remifentanil most likely preserve or minimally alter renal function in humans. If renal function does change during opioid anesthesia and surgery, this is probably the result of secondary changes in systemic and renal hemodynamics.

The mechanism by which opioids cause urinary retention is incompletely understood. Effects of opioids on the lower urinary tract include disturbances of micturition characterized by urinary retention, especially after intrathecal opioid administration. Intrathecal administration

of morphine and sufentanil caused dose-dependent suppression of detrusor contractility and decreased sensation of urge.[252] Mean times to recovery of normal lower urinary tract function were 5 and 8 hours after 10 or 30 μg sufentanil and 14 and 20 hours after 0.1 or 0.3 mg morphine, respectively. Not all opioid agonists behave similarly, and morphine appears to be particularly potent with regard to producing urodynamic problems. Malinovsky and associates compared the urodynamic effects of intravenous morphine (10 mg), buprenorphine (0.3 mg), fentanyl (0.35 mg), and nalbuphine (20 mg).[253] All the opioids altered bladder sensations, but detrusor contraction decreased only after the administration of fentanyl and buprenorphine. Urinary retention induced by intravenous infusion of remifentanil (0.15 μg/kg/minute) could be reversed by a single intravenous dose of methylnaltrexone (0.3 mg/kg) or naloxone (0.01 mg/kg).[254] Reversal of urinary retention by methylnaltrexone indicates that peripheral mechanisms may play a role in opioid-induced bladder dysfunction.

GASTROINTESTINAL EFFECTS OF OPIOIDS

Several opioid receptor types can be demonstrated on myenteric neurons, and both κ- and μ-receptor agonists regulate cholinergic transmission in the myenteric plexus. κ-Agonists appear to modulate release of acetylcholine more potently than do μ-agonists by inhibition of N-type voltage-sensitive Ca^{2+} channels through a pertussis toxin–sensitive G protein in guinea pig ileum.[255] The adverse gastrointestinal effects of exogenous opioid treatment include nausea, vomiting, altered fluid dynamics, inhibited gastric emptying, inhibited intestinal coordinated propulsive activity, and increased transit time, all of which may contribute to postoperative ileus (Box 31-4).[256]

The effect of morphine on esophageal motility has been extensively explored. Morphine (80 μg/kg) increased the velocity but did not alter the amplitude or duration of primary peristalsis of the esophagus, and it decreased the duration and magnitude of swallow-induced relaxation of the lower esophageal sphincter.[257] Gastric emptying is delayed by opioids through supraspinal (vagus nerve–mediated) and spinal, as well as peripheral, mechanisms. Intrathecal morphine (0.4 mg) significantly decreased the gastroduodenal propagation velocity and acetaminophen absorption, and intramuscular morphine (4 mg) resulted in additional effects.[258] Tramadol (1.25 mg/kg IV) has a measurable but smaller inhibitory effect on gastric emptying than does codeine (1 mg/kg IV) or morphine (0.125 mg/kg IV).[259] Opioids administered epidurally, as well as intrathecally, reduce gastrointestinal motility.[258] The translocation of enteric microorganisms from the intestinal tract to extraintestinal sites was promoted by reduction of gut propulsion after morphine treatment in rats.[260] Propofol (0.3 mg/kg bolus and 1.0 mg/kg/hour) abolished the decrease in gastric tone induced by morphine (0.1 mg/kg IV), but it did not abolish a morphine-induced delay of gastric emptying.[261]

Naloxone reverses opioid-induced delays in gastric emptying. Methylnaltrexone, a quaternary naloxone derivative that does not cross the blood-brain barrier, can attenuate morphine-induced delays in gastric emptying, thus suggesting a peripheral mechanism in the opioid effect on gastrointestinal tract.[262] Naloxone (0.7 mg/kg) significantly inhibited gastric emptying of saline and milk in rats.[263] This observation may suggest that opioids can affect the gastrointestinal tract by a mechanism independent of the opioid receptors. Intravenous, but not intramuscular, metoclopramide (10 mg) also can reverse morphine-induced delays in gastric emptying.[264]

Opioid effects on the intestine are complex. Transit time from mouth to ileum may not be significantly altered by morphine because morphine enhances ileal propulsion before decreasing motility. Opioids increase tone and decrease propulsive activity in most of the intestine. In rats, pretreatment with epidural or intraperitoneal morphine attenuated ischemia-induced inhibition of bowel motility.[265]

BOX 31-4 *Effects of Opioids on the Gastrointestinal Tract*

Pharmacologic Action	Clinical Effect
Decreased gastric motility and emptying	Decreased appetite; increased gastroesophageal reflux
Decreased pyloric tone	Nausea and vomiting
Decreased enzymatic secretion	Delayed digestion; hard, dry stools
Inhibition of small and large bowel propulsion	Delayed absorption of medication; straining; incomplete evacuation; bloating; abdominal distention; constipation
Increased fluid and electrolyte absorption	Hard, dry stools
Increased nonpropulsive segmental contractions	Spasms; abdominal cramps; pain
Increased anal sphincter tone	Incomplete evacuation

From Viscusi ER, Gan TJ, Leslie JB, et al: Peripherally acting mu-opioid receptor antagonists and postoperative ileus: mechanisms of action and clinical applicability, Anesth Analg *108:1811-1822, 2009.*

BILIARY AND HEPATIC EFFECTS

Opioid agonists increase biliary duct pressure and sphincter of Oddi (choledochoduodenal sphincter) tone in a dose- and drug-dependent manner through opioid receptor–mediated mechanisms. However, the clinical consequences of opioid-induced biliary tract actions are usually minimal. Although traditional teaching dictates that morphine induces "spasm" in the sphincter of Oddi and should not be used in patients with acute pancreatitis, no study or evidence indicates that morphine is contraindicated for use in acute pancreatitis.[266] Increases in biliary pressure caused by opioids are, with the exception of meperidine, reversible with naloxone. Oddi sphincter manometry through choledochoscopy demonstrated that the regular dose of morphine could increase common bile duct pressure, whereas pethidine had no effect, and tramadol inhibited motility of the sphincter of Oddi.[267] Fragen and associates studied the effect of remifentanil (0.1 mg/kg/minute) on the flow of dye from the gallbladder into

the duodenum and showed that remifentanil delays the drainage of dye from the gallbladder into the duodenum, but the delay is shorter than that reported after morphine or meperidine.[268]

Opioids have minimal effects on liver function during anesthesia and surgery. Remifentanil pretreatment can attenuate liver injury induced by ischemia and reperfusion. This effect is mediated by inducible nitric oxide synthase expression and exhausting reactive O_2 species but does not involve opioid receptors.[269]

NAUSEA AND VOMITING

Postoperative nausea and vomiting comprise a serious problem that often embarrasses patients and anesthesiologists[270,271] (see also Chapter 97). The etiology, treatment, and prevention of postoperative nausea and vomiting have been extensively investigated (Fig. 31-10).[272] Intraoperative use of opioids is a well-known risk factor for postoperative nausea and vomiting. Opioids stimulate the chemoreceptor trigger zone in the area postrema of the medulla, possibly through δ receptors, and thereby lead to nausea and vomiting. When compared with approximately equipotent doses of fentanyl and sufentanil, alfentanil is associated with a lower incidence of postoperative nausea and vomiting.[273]

The use of propofol in balanced anesthesia or total intravenous anesthesia (TIVA) significantly reduces the incidence of opioid-induced nausea and vomiting. When opioids are administered, antiemetic prophylaxis should be considered, including drugs with anticholinergic activity, butyrophenones, dopamine antagonists, serotonin antagonists, and acupressure. Ondansetron, a 5-HT_3 receptor antagonist, was found to be effective for postoperative opioid-induced nausea and vomiting.[274] A meta-analysis concluded that prophylactic use of 5-HT_3 receptor antagonists significantly reduced the incidence of postoperative nausea and vomiting and the need of rescue antiemetic therapy in parturient patients who received intrathecal morphine for cesarean delivery.[141] Nausea and vomiting after epidural morphine (3 mg) for postcesarean section analgesia could be prevented by dexamethasone (8 mg IV) as efficiently as droperidol (1.25 mg IV).[275] Cannabinoid receptor agonists are effective antiemetics in some clinical settings. Animal experiments showed that the cannabinoid agonist suppresses opioid-induced retching and vomiting by activation of the cannabinoid CB1 receptor.[276] A continuous low-dose naloxone infusion (0.25 μg/kg/hour) ameliorates some of the opioid-induced side effects, including nausea, vomiting, and pruritus, in many but not all patients without adversely affecting analgesia.[277] Transdermal scopolamine was shown to be effective for prophylactic use in parturient patients receiving intrathecal morphine while undergoing cesarean delivery, but it was associated with a higher incidence of side effects such as dry mouth and blurry vision.[278]

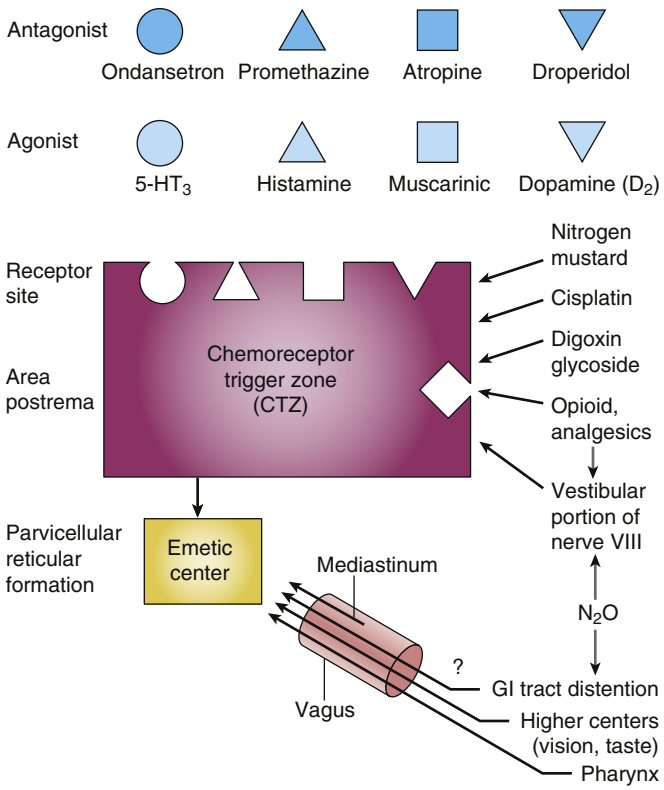


Figure 31-10. The chemoreceptor trigger zone and the emetic center with the agonist and antagonist sites of action of various anesthetic-related agents and stimuli. *GI,* Gastrointestinal. *(From Watcha MF, White PF: Postoperative nausea and vomiting: its etiology, treatment, and prevention,* Anesthesiology *77:162-184, 1992.)*

OTHER OPIOID EFFECTS

OBSTETRICS

Alfentanil and pethidine have been safely used as analgesics during the harvesting of human oocytes for subsequent in vitro fertilization[279] (see also Chapter 77). The teratogenic actions of opioids, including fentanyl, sufentanil, and alfentanil, at least in animal models, appear to be minimal. The parenteral administration of opioids before delivery remains a common method of analgesia. Nociception as a result of uterine cervical distention was able to be suppressed by μ- and κ-agonists in rats,[280] but the analgesic effect of μ-agonist but not κ-agonist was reduced by estrogen.[281] Aortocaval compression and associated hypotension may be exacerbated by parenteral opioids, especially following the use of morphine or meperidine. Fatal manifestations of maternal opioid administration include decreases in heart rate variability. Adverse neonatal effects can occur after administration of either morphine or meperidine to mothers. Fetal acidosis increases opioid transfer from the mother. Attempts to minimize neonatal effects of opioids include restricting opioid administration to the first stage of labor. In one report, the short-acting opioid alfentanil administered before cesarean delivery attenuated the maternal stress response but led to a slightly reduced Apgar score.[282] In a randomized double-blind controlled study, a single bolus of 1 μg/kg remifentanil administered to patients undergoing elective cesarean delivery effectively attenuated hemodynamic changes after induction of anesthesia and tracheal intubation, but remifentanil crosses the placenta and may cause mild neonatal depression.[283]

Because the fetus is capable of pain perception after the twenty-sixth week of gestation, adequate postoperative fetal pain management is essential after fetal surgery. Investigators showed that the sheep fetus absorbs sufentanil after intraamniotic instillation, and significantly greater plasma concentrations were achieved in the fetal lamb than in the ewe.[284]

Morphine and meperidine have been found in the breast milk of mothers receiving intravenous opioid analgesia.[285,286] Although both fentanyl and morphine are concentrated in breast milk in milk-to-plasma ratios of 2:1 to 3:1, newborn exposure is reported to be insignificant. Newborns of addicted mothers can exhibit opioid withdrawal and require observation and appropriate treatment.[287]

ANAPHYLACTOID REACTIONS

True allergic reactions and systemic anaphylactoid reactions to opioids are rare. More commonly, local reactions caused by preservatives or histamine may occur. In 32% of heroin addicts who died suddenly after heroin injection, the concentration of tryptase was elevated (>10 μg/L), but no correlation was found between the immunoglobulin E levels and tryptase, a finding supporting the hypothesis that mast cell degranulation was not mediated by allergic reactions.[288] This report suggests that many heroin fatalities are caused by an anaphylactoid reaction.

OCULAR EFFECTS

The use of fentanyl, sufentanil, and alfentanil during induction of anesthesia can help prevent increases in intraocular pressure. Fentanyl, alfentanil, and sufentanil doses as small as 2.5, 10, and 0.1 μg/kg, respectively, may be sufficient as long as appropriate anesthetic depth is achieved before tracheal intubation. Remifentanil (1 μg/kg) combined with propofol (2 mg/kg) or thiopental (5 mg/kg) was reported to be effective for prevention of intraocular pressure change after succinylcholine and tracheal intubation.[289,290]

IMMUNE EFFECTS

Opioids influence specific enzymatic degradation and regulation processes, as well as immune regulation through modulation of immune cell activity. Several immune cell populations, including T cells, macrophages, and natural killer (NK) cells, serve as targets for the effects of opioids. Investigators showed that the maximal suppression of NK cell activity, proliferation of splenic T and B cells, and interferon-γ production were observed 0.5 to 1 hour after the injection of 15 mg/kg of morphine in rats.[291] The time course was nearly concordant with the antinociceptive effect of morphine. Postoperative administration of morphine (10 mg intramuscularly [IM]) did not significantly affect NK cell activity, whereas tramadol (100 mg IM) enhanced NK cell activity.[292] Intravenous fentanyl causes a rapid increase in NK cell cytotoxicity, which is coincident with an increase in the percentage of $CD16^+$ and $CD8^+$ cells in peripheral blood.[293] When compared with fentanyl (1000 μg), administration of morphine (40 mg) as part of a balanced anesthetic technique suppressed several components of the inflammatory response (interleukin-6, CD11b, CD18, postoperative hyperthermia) to cardiac surgery and CPB.[294]

As a potential mechanism for the immunosuppressive effects of morphine, activation of nuclear factor NF-κB by an inflammatory stimulus was inhibited by morphine-induced activation of μ_3-opioid receptors in a nitric oxide–dependent manner.[295] Several investigators independently reported direct effects of morphine on apoptosis in cultured human peripheral blood lymphocytes that may result in compromised immune function.[296] However, another report noted that morphine has no effect on apoptosis-related molecules and does not promote apoptosis of human peripheral blood lymphocytes.[297]

CANCER PROGRESSION

Patients who receive general anesthesia with opioids have a greater rate of cancer recurrence than do patients who receive local or regional anesthetic agents.[298] Opioids may directly stimulate proliferation and invasion of tumor cells and inhibit apoptosis of tumor cells, or they may indirectly affect cancer recurrence by immunosuppression.[299] Overexpression of the μ-opioid receptor in human non–small cell lung cancer was suggested to promote tumor growth and progression.[300] Exploration of the opioid receptors in cancer cells could contribute to a diagnostic and therapeutic option of cancer. Furthermore, investigators reported that women with the A118G genotype of the μ-opioid receptor have decreased breast cancer–specific mortality, a finding suggesting that opioid pathways may be involved in tumor growth.[301]

WOUND HEALING

The topical application of opioids has been explored as a strategy for reducing pain associated with cutaneous wounds. Activation of peripheral opioid receptors on primary afferent neurons reduces the excitability of these neurons and suppresses the antidromic release of substance P and calcitonin gene–related peptide, which play an essential role in wound repair. Topical morphine application significantly reduced the number of myofibroblasts and macrophages in the closing wound.[302] These findings limit the topical application of opioids as an analgesic therapeutic strategy in the treatment of painful cutaneous wounds.

PHARMACOKINETICS AND PHARMACODYNAMICS OF OPIOIDS

Using modern drug assay technology and with the widespread availability of computers, investigators can analyze pharmacologic data with combined pharmacokinetic-pharmacodynamic models to separate drug responses into pharmacokinetic and pharmacodynamic components. Pharmacokinetic parameters govern the relationship between opioid dose and the opioid concentrations in blood (or other body fluid). Pharmacodynamic parameters describe the relationship between the

opioid concentration in blood (or other fluid) and opioid effect.

PHYSICOCHEMICAL PROPERTIES

Opioids are weak bases. When dissolved in solution, opioids are dissociated into protonated and free-base fractions, with the relative proportions depending on the pH and ion dissociation constant (pK_a). The free-base fraction is more lipid soluble than the protonated fraction. High lipid solubility facilitates transport of opioid into the biophase or site of action. Therefore, highly lipid-soluble opioids have a more rapid onset of action. However, because the opioid receptor "recognizes" an opioid molecule in the protonated form, the intensity of opioid effects is closely related to the ionized concentration of drug in the biophase.

All opioids are to some extent bound to plasma proteins, including albumin and α_1-acid glycoprotein. Only the un-ionized, unbound fraction constitutes the diffusible fraction and provides the concentration gradient that promotes diffusion of opioid from blood to the tissue of interest. Thus, the speed of onset of opioid effect is affected by both the lipid solubility and protein binding.

PHARMACOKINETIC FEATURES OF INDIVIDUAL DRUGS

Representative pharmacokinetic parameters for the opioids commonly used in anesthesia are displayed in Table 31-5.

Morphine

Morphine pharmacokinetics is notably different from that of the fentanyl congeners. This difference is in large part the result of morphine's comparatively low lipid solubility. Relatively little transient first-pass uptake of morphine by the lung occurs. The pK_a of morphine (8.0) is greater than physiologic pH, and thus after intravenous injection, only a small fraction (10% to 20%) of morphine is un-ionized. Penetration of morphine into and out of the brain is presumably slower than that of other opioids. Approximately 20% to 40% of morphine is bound to plasma proteins, mostly albumin.

Morphine is principally metabolized by conjugation in the liver, but the kidney plays a key role in the extrahepatic metabolism of morphine. Morphine-3-glucuronide (M3G) is the major metabolite of morphine, but it does not bind to opioid receptors and possesses little or no analgesic activity. M3G may actually antagonize morphine, and this effect may contribute to both variability in response and resistance to morphine analgesic therapy. M3G was reported to cause seizures in animals and allodynia in children.[303] M6G accounts for nearly 10% of morphine metabolite and is a more potent μ-receptor agonist than morphine, with a similar duration of action. Investigators reported that M6G contributes substantially to morphine's analgesic effects, even in patients with normal renal function.[304] Especially in patients with renal dysfunction, the accumulation of M6G can lead to an increased incidence of adverse effects, including respiratory depression. Except for renal function, M6G accumulation was shown to be affected by transmembrane transporters inhibited by probenecid.[305] M6G can induce respiratory depression in a manner similar to that of morphine, but the site of action in the ventilatory control system may be different between M6G and morphine.[306] Investigators suggested that SNP at the μ-opioid receptor affects the susceptibility to M6G-related opioid toxicity.[307] Because the hepatic extraction ratio of morphine is high, the bioavailability of orally administered morphine is significantly lower (20% to 30%) than after intramuscular or subcutaneous injection. M6G is in fact the primary active compound when morphine is administered orally (Fig. 31-11).[308] In contrast to the reports suggesting a high potency of M6G, other reports have shown that short-term intravenous administration of M6G does not provide effective analgesia.[309]

Fentanyl

A three-compartment model is typically used to describe decay of plasma fentanyl concentrations. The lungs exert a significant first-pass effect and transiently take up approximately 75% of an injected dose of fentanyl. Approximately 80% of fentanyl is bound to plasma

TABLE 31-5 PHYSICOCHEMICAL AND PHARMACOKINETIC DATA OF COMMONLY USED OPIOID AGONISTS

	Morphine	Fentanyl	Sufentanil	Alfentanil	Remifentanil
pK_a	8.0	8.4	8.0	6.5	7.1
% Un-ionized at pH 7.4	23	<10	20	90	67?
Octanol/H_2O partition coefficient	1.4	813	1778	145	17.9
% Bound to plasma protein	20-40	84	93	92	80?
Diffusible fraction (%)	16.8	1.5	1.6	8.0	13.3?
$t_{½\alpha}$ (min)	1-2.5	1-2	1-2	1-3	0.5-1.5
$t_{½\beta}$ (min)	10-20	10-30	15-20	4-17	5-8
$t_{½\gamma}$ (hr)	2-4	2-4	2-3	1-2	0.7-1.2
Vd_c (L/kg)	0.1-0.4	0.4-1.0	0.2	0.1-0.3	0.06-0.08
Vd_{ss} (L/kg)	3-5	3-5	2.5-3.0	0.4-1.0	0.2-0.3
Clearance (mL/min/kg)	15-30	10-20	10-15	4-9	30-40
Hepatic extraction ratio	0.6-0.8	0.8-1.0	0.7-0.9	0.3-0.5	NA

From Bailey PL, Egan TD, Stanley TH: Intravenous opioid anesthetics. In Miller RD, editor: Anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, p 791.*
NA, Not applicable; pK_a, ion dissociation constant; $t_{½\alpha}$, $t_{½\beta}$, $t_{½\gamma}$, half-lives of a three-compartment model; Vd_c, volume of distribution of the central compartment; Vd_{ss}, volume of distribution at steady state.

proteins, and significant amounts (40%) are taken up by red blood cells. Fentanyl is relatively long acting, in large part because of this widespread distribution in body tissues.

Fentanyl is primarily metabolized in the liver by *N*-dealkylation and hydroxylation. Metabolites begin to appear in plasma as early as 1.5 minutes after injection. Norfentanyl, the primary metabolite, is detectable in the urine for up to 48 hours after intravenous fentanyl administration in humans.

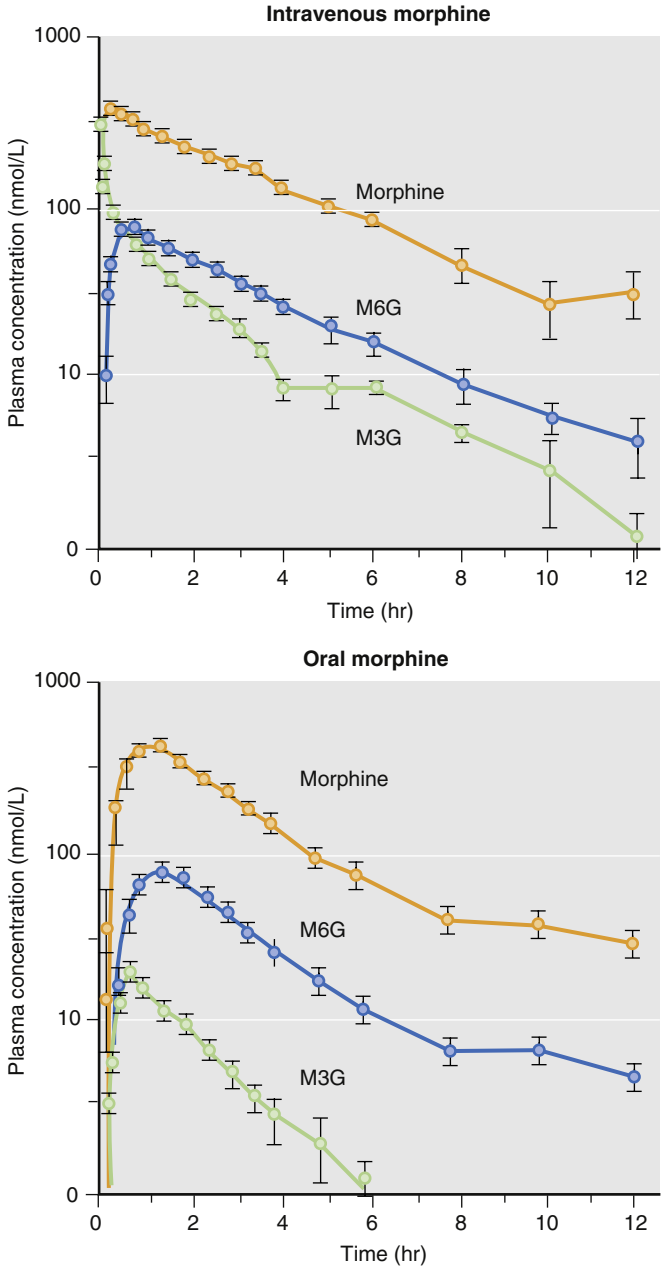


Figure 31-11. Mean plasma concentrations (± SEM) of morphine, morphine-6-glucuronide (M6G), and morphine-3-glucuronide (M3G) after intravenous and oral administration of morphine. *(From Osborne R, Joel S, Trew D, Slevin M: Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide,* Clin Pharmacol Ther *47:12-19, 1990.)*

Alfentanil

After intravenous injection, plasma concentrations of alfentanil are described by either a two-compartment or a three-compartment model. Alfentanil is bound to plasma proteins (mostly glycoproteins) in higher proportions (90%) than is fentanyl. At physiologic pH, alfentanil is mostly (90%) un-ionized because of its relatively low pK_a (6.5). Thus, despite more intense protein binding, the diffusible fraction of alfentanil is higher than is that of fentanyl. This explains, in part, the short latency to peak effect of alfentanil after intravenous injection.

The main metabolic pathways of alfentanil are similar to those of sufentanil and include oxidative *N*-dealkylation and *O*-demethylation, aromatic hydroxylation, and ether glucuronide formation. The degradation products of alfentanil have little, if any, opioid activity. Human alfentanil metabolism may be accomplished predominantly, if not exclusively, by cytochrome P450 3A3/4 (CYP3A3/4).[310] This enzyme is known to display at least an eightfold difference in activity in humans. Alfentanil is also metabolized by human liver microsomal CYP3A5, which shows more than a twentyfold pharmacogenetic variability in expression level and thus results in significant differences in human liver alfentanil metabolism.[311] An in vitro study demonstrated that propofol in clinically relevant concentrations interferes with oxidative metabolic degradation of alfentanil and sufentanil in the microsomal fraction of pig and human liver.[312]

Sufentanil

The pharmacokinetic property of sufentanil is adequately described by a three-compartment model. After intravenous injection of sufentanil, first-pass pulmonary extraction, retention, and release are similar to those of fentanyl.[313] The pK_a of sufentanil at physiologic pH is the same as that of morphine (8.0), and therefore only a small amount (20%) exists in the un-ionized form. Sufentanil is twice as lipid soluble as fentanyl and is highly bound (93%) to plasma proteins, including α_1-acid glycoprotein.

The major metabolic pathways of sufentanil include *N*-dealkylation, oxidative *O*-demethylation, and aromatic hydroxylation. Major metabolites include *N*-phenylpropanamide.

Remifentanil

Although chemically related to the fentanyl congeners, remifentanil is structurally unique because of its ester linkages. Remifentanil's ester structure renders it susceptible to hydrolysis by blood- and tissue-nonspecific esterases that results in rapid metabolism and rapid reduction of blood concentrations after cessation of infusion[314] (Fig. 31-12). Remifentanil thus constitutes the first "ultrashort"-acting opioid for use as a supplement to general anesthesia.

The pharmacokinetic properties of remifentanil are best described by a three-compartment model. Remifentanil clearance is several times more rapid than normal hepatic blood flow, consistent with widespread extrahepatic metabolism. However, remifentanil is not significantly metabolized or sequestered in the lungs.[315] It is a weak base with a pK_a of 7.07. It is highly lipid soluble, with an octanol-water partition coefficient of 19.9 at

pH 7.4. Remifentanil is highly bound (70%) to plasma proteins (mostly α_1-acid glycoprotein). The remifentanil free base is formulated with glycine. Because glycine has been shown to act as an inhibitory neurotransmitter that causes a reversible motor weakness when it is injected intrathecally in rodents, remifentanil is not approved for spinal or epidural use.[316]

The primary metabolic pathway of remifentanil is de-esterification to form a carboxylic acid metabolite, GI90291 (Fig. 31-13),[317] which is 0.003 to 0.001 times as potent as remifentanil. The low in vivo potency of GR90291 can be explained by a low affinity to the μ receptor in combination with poor brain penetration.[318] Excretion of GI90291 depends on renal clearance mechanisms. Evidence from dogs suggests that the remifentanil metabolites are, for practical purposes, completely inactive, even in patients with renal failure. The pharmacokinetics of remifentanil is not appreciably influenced by renal or hepatic failure. In blood, remifentanil is metabolized primarily by enzymes within erythrocytes. Remifentanil is not a good substrate for pseudocholinesterase and therefore is not influenced by pseudocholinesterase deficiency.[319]

SURROGATE MEASURES OF OPIOID POTENCY

Because a high-resolution measure of analgesia is not available, opioid potencies are usually estimated by some surrogate measures. Reduction of the MAC required to produce lack of movement to skin incision has been a frequently used surrogate measure for estimation of opioid potency (Fig. 31-14).[320] However, the MAC is not useful as a surrogate measure of opioid potency outside the operating room.

The EEG has been another widely used surrogate measure for estimating opioid potency. The EEG is advantageous because it is noninvasive and can be used as an effect

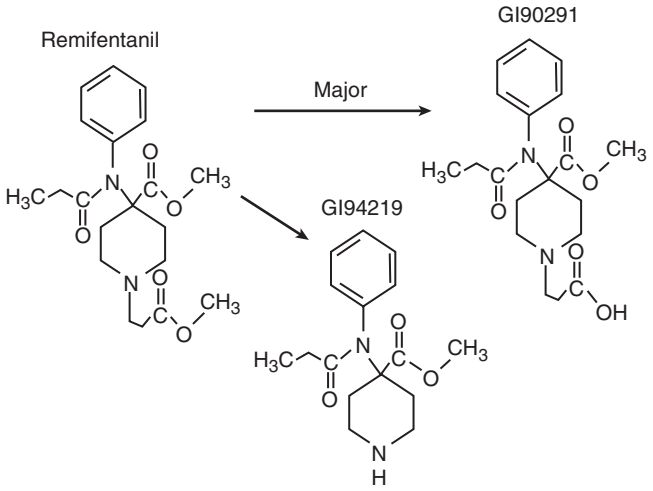


Figure 31-13. Metabolic pathway of remifentanil. De-esterification by nonspecific plasma and tissue esterases to form a carboxylic acid metabolite (GI90291) that has only 1/300 to 1/1000 the potency of the parent compound is the primary metabolic pathway. *N*-Dealkylation of remifentanil to G194219 is a minor metabolic pathway. *(From Egan TD, Lemmens HJ, Fiset P, et al: The pharmacokinetics of the new short-acting opioid remifentanil [GI87084B] in healthy adult male volunteers,* Anesthesiology *79:881-892, 1993.)*

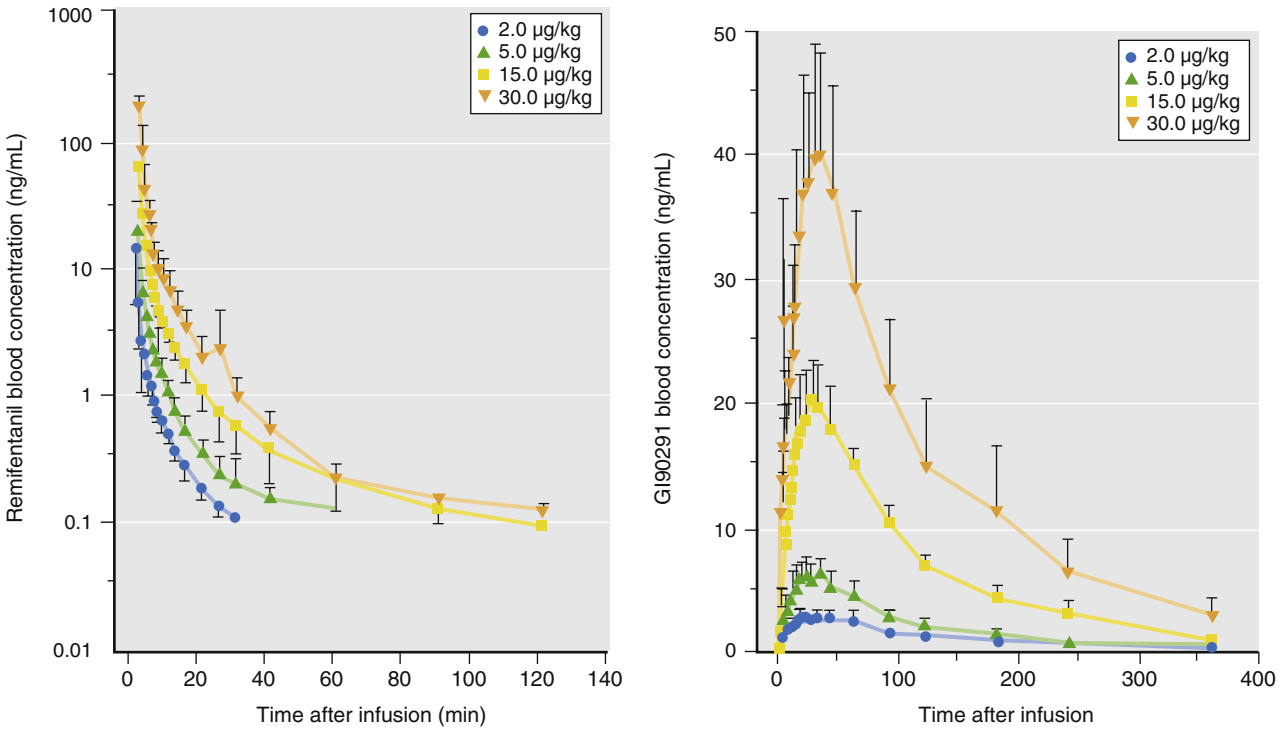


Figure 31-12. Mean (± standard deviation) blood concentration–time curves of remifentanil and its metabolite GI90291 after a 1-minute transfusion of remifentanil of 2, 5, 15, and 30 μg/kg (n = 6 for each dose). *(From Westmoreland CL, Hoke JF, Sebel PS, et al: Pharmacokinetics of remifentanil [GI87084B] and its major metabolite [GI90291] in patients undergoing elective inpatient surgery,* Anesthesiology *79:893-903, 1993.)*

measure when an experimental subject is unconscious or apneic. When processed by Fourier spectral analysis, the raw changes on the EEG translate into a significant decrease in the value of the spectral edge, a parameter that quantitates the frequency below which a given percentage (usually 95%) of the power in the signal of the EEG is found. Although the clinical meaning of the changes on the EEG produced by opioids is unclear, the opioid potencies estimated by using the EEG as a surrogate measure appear to be clinically reliable because they relate to clinically determined potencies in a proportional, reproducible fashion. However, because the surrogate measures do not always assess the drug effect of clinical interest (analgesia), estimations of potency based on surrogate measures must be interpreted with some caution.

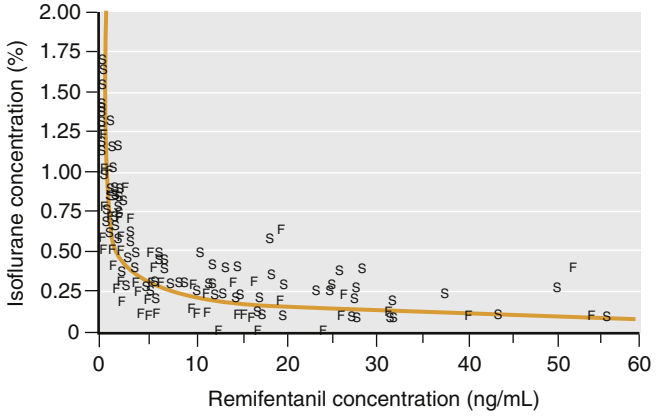


Figure 31-14. The reduction in isoflurane concentration to prevent movement at skin incision in 50% of patients by increasing measured remifentanil whole blood concentrations. *F* represents a patient who moved, and *S* represents a patient who did not move. The *solid line* is the logistic regression solution for a 40-year-old patient. *(From Lang E, Kapila A, Shlugman D, et al: Reduction of isoflurane minimal alveolar concentration by remifentanil,* Anesthesiology *85:721-728, 1996.)*

FACTORS AFFECTING PHARMACOKINETICS AND PHARMACODYNAMICS OF OPIOIDS

Age

The pharmacokinetics and pharmacodynamics of opioids can be influenced by age. Neonates clearly exhibit a reduced rate of elimination of essentially all opioids,[321] presumably because of immature metabolic mechanisms, including the cytochrome P450 system. The prolonged elimination of opioids observed in the neonatal period quickly normalizes toward adult values within the first year of life.[321]

Intraoperative requirements of opioids differ between adults and children. The infusion rate of remifentanil to block somatic and autonomic response to skin incision was almost twofold higher in children (2 to 11 years) than in adults (20 to 60 years).[322,323] With advanced age, although pharmacokinetic changes may play a minor role, pharmacodynamic differences are primarily responsible for the decreased dose requirement in older adults. In one report, age was inversely correlated with central volume of distribution, clearance, and potency of remifentanil[324] (Fig. 31-15). These combined pharmacokinetic

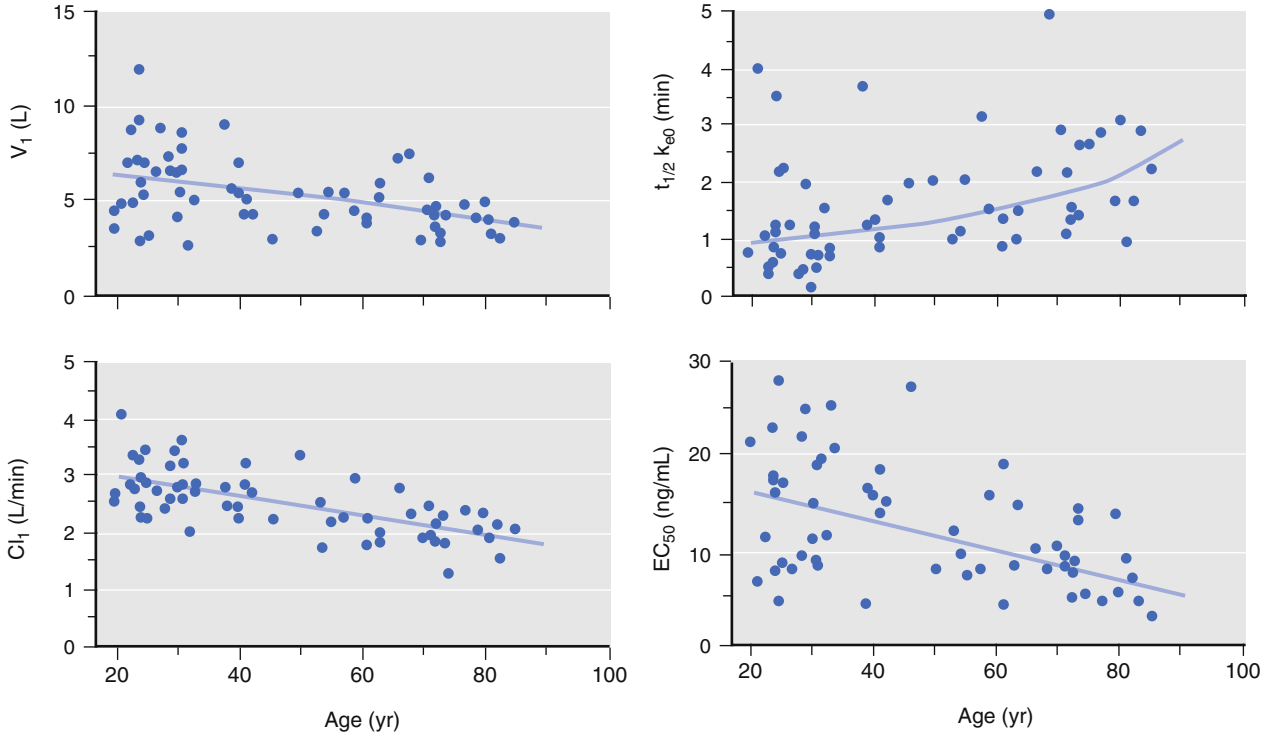


Figure 31-15. Relationship between pharmacokinetic and pharmacodynamic parameters and age for remifentanil. Volume of distribution (V_1) and clearance (Cl_1) are estimated using a three-compartment model. $t_{½}k_{e0}$ is a half-life corresponding to k_{e0}, a first-order rate constant for elimination of drug from the effect compartment. EC_{50}, Median effective concentration. *(From Minto CF, Schnider TW, Egan T et al: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology. 86:10-23, 1997.)*

and pharmacodynamic changes mandate a reduction in remifentanil dosage by at least 50% or more in older patients (see also Chapter 80).

Body Weight

Many opioid pharmacokinetic parameters, especially clearance, appear to be more closely related to lean body mass (see also Chapter 71). This means that opioid dosage regimens may best be based on lean body mass and not on total body weight. Total body weight–based dosing in an obese patient results in much higher remifentanil effect-site concentrations than does lean body mass–based dosing.[325] In contrast, for lean patients, the concentrations that result from total body weight–based dosing are not much greater than are those based on body mass (Fig. 31-16). Clinically, context-sensitive half-times are not significantly different between obese and lean subjects (Fig. 31-17). Mounting evidence suggests that lean body mass is a better predictor of metabolic capacity than is total body weight. Ideal body weight, a parameter closely related to lean body mass and one that is perhaps more easily estimated by the clinician, is probably an acceptable alternative.

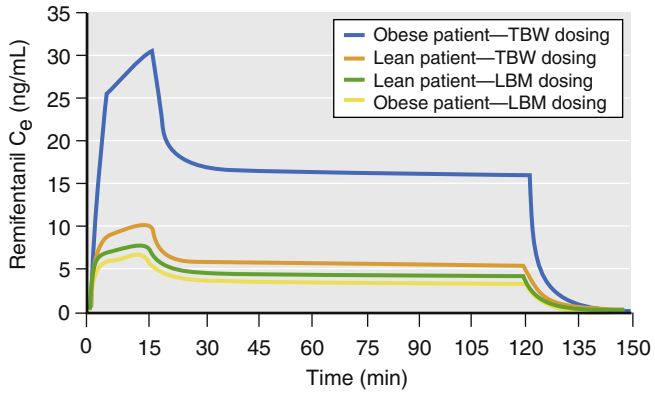


Figure 31-16. A computer simulation of the time course of remifentanil concentration change, when the dosage regimen is calculated based on lean body mass (LBM) or total body weight (TBW) for both obese and lean patients. TBW-based dosing in an obese patient results in dramatically higher drug concentrations. *(From Egan TD, Huizinga B, Gupta SK, et al: Remifentanil pharmacokinetics in obese versus lean patients,* Anesthesiology *89:562-573, 1998.)*

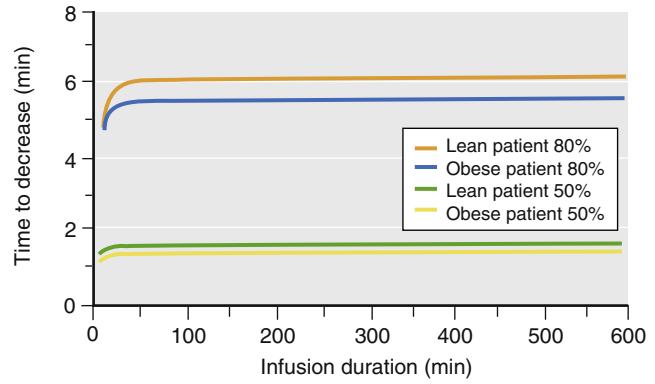


Figure 31-17. A computer simulation of the context-sensitive half-times (50% decrement times) and 80% decrement times of remifentanil in obese versus lean subjects. In clinical terms, the curves are not grossly different in obese and lean subjects. *(From Egan TD, Huizinga B, Gupta SK, et al: Remifentanil pharmacokinetics in obese versus lean patients,* Anesthesiology *89:562-573, 1998.)*

Renal Failure

Renal failure has implications of major clinical importance with respect to morphine and meperidine (see also Chapter 74). For the fentanyl congeners, the clinical importance of renal failure is less marked.

Morphine is an opioid with active metabolites that depend on renal clearance mechanisms for elimination. Morphine is principally metabolized by conjugation in the liver, and the water-soluble glucuronides (M3G and M6G) are excreted by the kidney. The kidney also plays a role in the conjugation of morphine and accounts for nearly 40% of the drug's metabolism.[326] Patients with renal failure can develop very high levels of M6G and life-threatening respiratory depression (Fig. 31-18).[327] In view of these changes induced by renal failure, morphine may not be a good choice in patients with severely altered renal clearance mechanisms.

The clinical pharmacology of meperidine is also significantly altered by renal failure. Normeperidine, the main metabolite, has analgesic and CNS excitatory effects. Because the active metabolites are subject to renal excretion, this potential CNS toxicity secondary to normeperidine accumulation is especially a concern in patients in renal failure.

The clinical pharmacology of the fentanyl congeners is not grossly altered by renal failure, although a decrease in plasma protein binding may potentially alter the free fraction of the fentanyl class of opioids. In the presence of renal impairment, fentanyl, alfentanil, sufentanil, and remifentanil do not deliver a high active metabolite load, and their clearance is not significantly prolonged.[328] Neither the pharmacokinetics nor the pharmacodynamics of remifentanil is altered by impaired renal function. Levels of GI90291 that develop during remifentanil infusion in patients with renal failure are not likely to produce any clinically significant effects.

Hepatic Failure

Even though the liver is the metabolic organ primarily responsible for opioid biotransformation, the degree of liver failure typically observed in perioperative patients, with the exception of patients undergoing liver transplantation, does not have a major impact on the pharmacokinetics of most opioids (see also Chapter 74). In addition to reduced metabolic capacity (i.e., cytochrome P450 system and conjugation), liver disease may also lead to reductions in hepatic blood flow, hepatocellular mass, and plasma protein binding. The increase in total body water and the edema of advanced liver disease may alter the distribution characteristics of a drug. Enzyme induction, such as that observed in early alcoholism, can actually increase the metabolic capacity of the liver.

Morphine pharmacokinetics is relatively unchanged by developing liver disease, such as liver cirrhosis and hepatic carcinoma, because of the substantial compensatory extrahepatic metabolism of morphine. A reduction in hepatic blood flow would be expected to slow the decline in morphine plasma concentrations. In one report, M6G-to-morphine and M3G-to-morphine ratios

were significantly reduced after liver resection, and the circulating morphine concentration was increased, mainly as a result of lower morphine clearance.[329] In patients with cirrhosis, the metabolism of meperidine is decreased, which leads to accumulation of the parent drug and possible CNS depressive effects similar to those observed in hepatic encephalopathy. Although the elimination of normeperidine is also decreased in these patients, the ratio of normeperidine to meperidine is generally low, and the narcotic effects of meperidine usually predominate.[330] The disposition of fentanyl and sufentanil appears to be unaffected by liver diseases.[331] The reductions in liver blood flow that result from either liver disease or some other disorder (e.g., shock) can affect the pharmacokinetic parameters of alfentanil, fentanyl, and sufentanil. A significant decrease in clearance of alfentanil was demonstrated in patients with mild to moderate cirrhosis when compared with volunteers from the historical control group.[332] Greater elimination half-lives ($t_{½}$; 3.7 ± 2.6 hours) have also been observed for alfentanil in patients undergoing abdominal aortic surgical procedures.[333] Remifentanil is an opioid whose pharmacokinetics is completely unchanged by liver disease (Fig. 31-19).[334] Its kinetics does not change during the anhepatic phase of orthotopic liver transplantation.[335] Investigators reported that 0.25 to 0.5 μg/kg/minute remifentanil could provide perioperative analgesia without neurologic deterioration in patients suffering from chronic hepatic failure with mild encephalopathy.[336]

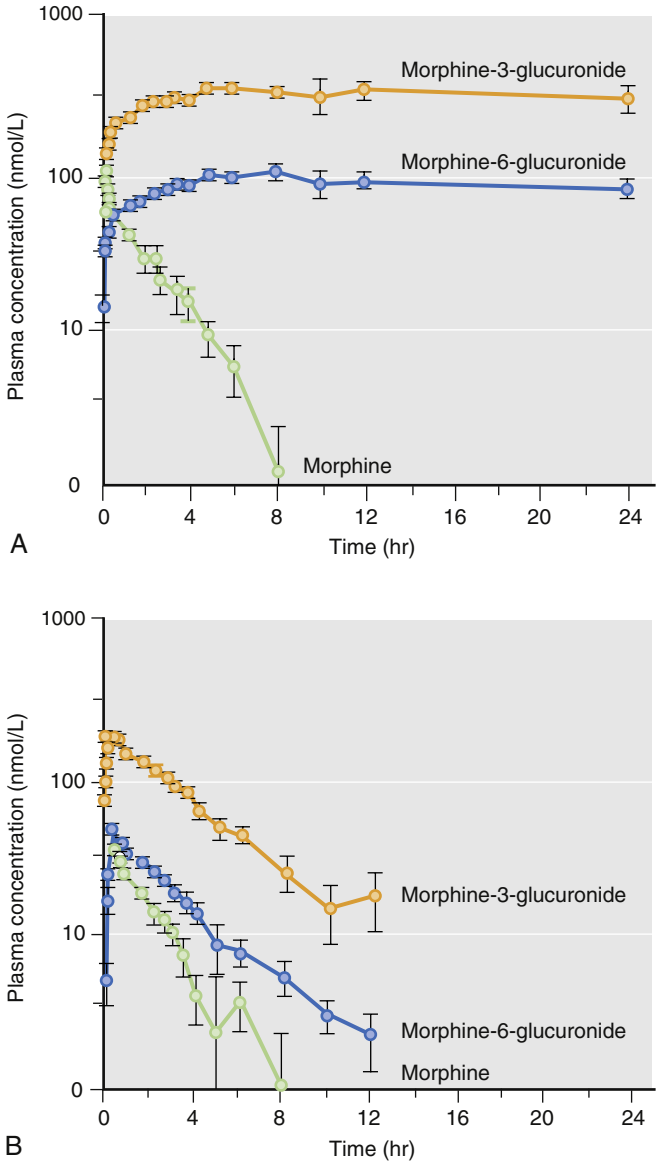


Figure 31-18. Effect of renal failure on the pharmacokinetics of morphine. The graphs show the time-dependent change of the serum concentration of morphine and its metabolites in patients with renal failure (**A**) and in patients with normal renal function (**B**) who received 0.1 mg/kg morphine intravenously. *(From Osborne R, Joel S, Grebenik K, et al: The pharmacokinetics of morphine and morphine glucuronides in kidney failure,* Clin Pharmacol Ther *54:158-167, 1993.)*

Cardiopulmonary Bypass

CPB produces significant alterations in the pharmacokinetics of most opioids (see also Chapter 67). These

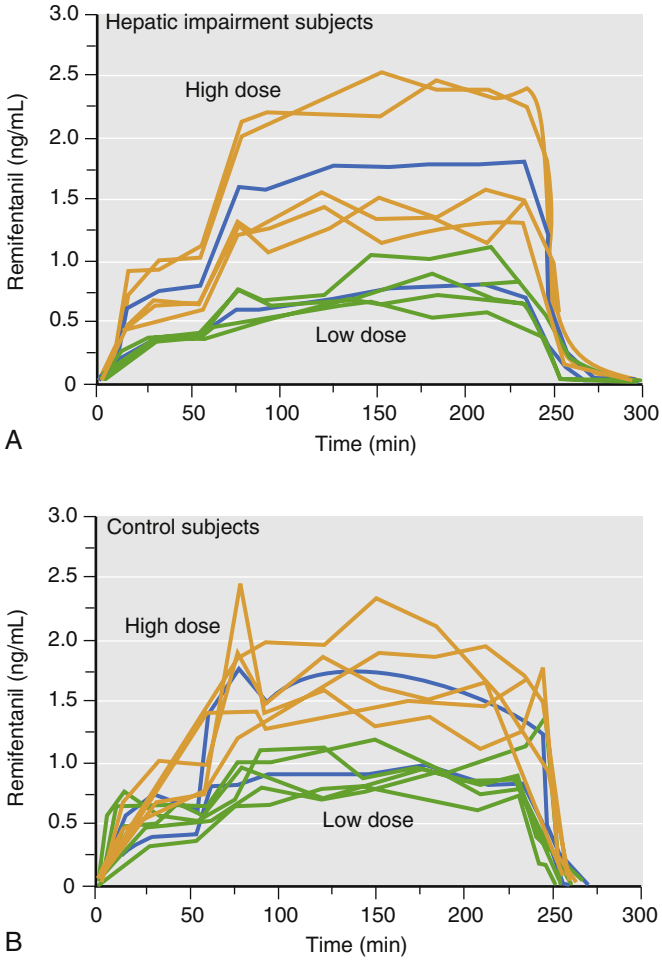


Figure 31-19. Time-dependent changes of blood concentration of remifentanil in patients with liver disease (**A**) and in control subjects (**B**). In the low-dose group, remifentanil was infused at 0.0125 μg/kg/minute for 1 hour and then at 0.025 μg/kg/minute for 3 hours. In the high-dose group, the infusion rate of remifentanil was 0.025 μg/kg/minute for 1 hour and then 0.05 μg/kg/minute for 3 hours. *(From Dershwitz M, Hoke JF, Rosow CE, et al: Pharmacokinetics and pharmacodynamics of remifentanil in volunteer subjects with severe liver disease,* Anesthesiology *84:812-820, 1996.)*

alterations are a result of CPB-induced modifications in distribution volumes (secondary to priming) and changes in acid-base balance, organ blood flow, plasma protein concentrations, and body temperature. Binding of drugs to components of the bypass circuit can also alter opioid pharmacokinetics.

When morphine is given as a premedication before cardiac anesthesia, its concentrations decline significantly on initiation of CPB. Miller and associates examined the effect of CPB on plasma fentanyl concentration and showed that the total concentration of fentanyl in plasma was significantly decreased and the unbound fraction of fentanyl rose on initiation of CPB.[337] The total fentanyl concentration remained relatively stable during bypass until near the end of CPB, at which time the mean total concentration increased, coincident with rewarming. Population pharmacokinetic modeling applied to concentration versus time data from patients undergoing coronary artery bypass grafting with CPB demonstrated that the effect of CPB on fentanyl pharmacokinetics is clinically insignificant and that a simple three-compartment model accurately predicts fentanyl concentrations throughout surgical procedures involving the use of CPB.[338] Elimination of alfentanil is prolonged by CPB primarily because of increased distribution. The volume of distribution in steady state (Vd_{ss}) and the volume of central compartment for alfentanil were significantly greater in the CPB groups than in the nonbypass group.[339] However, the elimination $t_{½\beta}$ of alfentanil did not differ significantly among the normothermic CPB, hypothermic CPB, and nonbypass groups. Between the normothermic and hypothermic CPB groups, no significant differences in Vd_{ss}, clearance, or $t_{½\beta}$ were found. The free fraction of alfentanil during CPB remains constant despite complex changes in binding protein concentrations.[340] In adult patients undergoing elective myocardial revascularization with hypothermic CPB who received continuous infusions of remifentanil 1.0 to 2.0 μg/kg/minute, no evidence of accumulation or sequestration was found.[315] Russell and colleagues reported that normothermic CPB did not significantly affect the clearance of remifentanil, but hypothermic CPB reduced it by an average of 20%, findings attributed to the effect of temperature on blood and tissue esterase activity.[341] In pediatric patients undergoing CPB for repair of atrial septal defects, no changes in the Vd_{ss}, volume of the central compartment, $t_{½\alpha}$, and $t_{½\beta}$ were noted, but clearance values increased 20% in the postbypass period.[342] In patients undergoing coronary artery bypass graft surgery with hypothermic CPB who received a continuous infusion of remifentanil, the volume of distribution increased by 86% with institution of CPB and remained increased after CPB, and elimination clearance decreased by 6.37% for each degree lower than 37°C.[343] Thus, although clearance of remifentanil reduced during CPB, remifentanil remains a very short-acting drug even during CPB.

Acid-Base Changes

Changes in pH influence the protein binding of fentanyl, sufentanil, and alfentanil. The results are an increase in protein binding with alkalosis and a decrease with acidosis (see also Chapter 60). These effects are more intense for fentanyl than for sufentanil and for sufentanil than for alfentanil. Relative changes in the free drug fraction with pH variation from 7.4 to 7.0 were much higher for fentanyl (52%) when compared with sufentanil (29%) and alfentanil (6%). The pH dependence of plasma protein binding of the opioids significantly correlates with their partition between an organic and aqueous phase, thus suggesting the hydrophobic character of the interaction between plasma proteins and opioids. Increased ionization decreases the amount of fentanyl available for hepatic metabolism or renal excretion. Intraoperative hyperventilation during surgical procedures can significantly influence the pharmacokinetics of sufentanil and can result in an increased distribution volume and prolonged elimination half-time.

Thus, both intraoperative respiratory alkalosis and respiratory acidosis, especially in the immediate postoperative period, can prolong and exacerbate opioid-induced respiratory depression.

Hemorrhagic Shock

Common practice is to administer reduced doses of opioids to patients in hemorrhagic shock to minimize adverse hemodynamic consequences and to prevent a prolonged opioid effect (see also Chapter 81). This prolonged drug effect is at least partially attributable to a pharmacokinetic mechanism. Analysis of pigs receiving fentanyl suggested that central clearance and central and second compartment distribution volumes were significantly reduced in hemorrhagic shock, with higher fentanyl concentrations for any given dosage and a prolonged context-sensitive half-time (Fig. 31-20).[344] Hemorrhagic shock also altered the pharmacokinetics of remifentanil, a finding suggesting that less remifentanil would be required to maintain a target plasma concentration (Fig. 31-21).[345] However, because of the rapid metabolism of remifentanil, changes in context-sensitive half-time are small. In a stepwise hemorrhagic model of pigs receiving TIVA with remifentanil (0.5 μg/kg/minute) and propofol (6 mg/kg/hour after 2 mg/kg bolus), the plasma remifentanil concentration showed a threefold greater increase than did

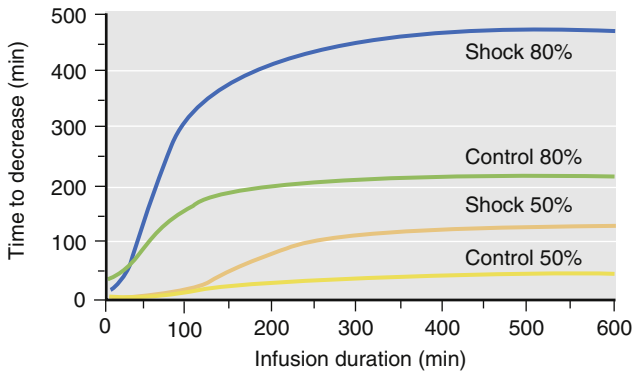


Figure 31-20. A computer simulation of the context-sensitive half-times (50% decrement times) and 80% decrement times of fentanyl in animals in shock versus control animals. *(From Egan TD, Kuramkote S, Gong G, et al: Fentanyl pharmacokinetics in hemorrhagic shock: a porcine model,* Anesthesiology *91:156-166, 1999.)*

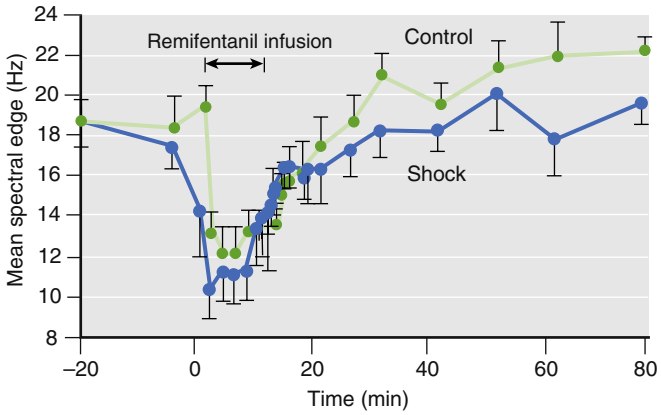


Figure 31-21. Mean spectral edge changes versus time during remifentanil infusion. The graph indicates spectral edge measurements for control animals and for animals in hemorrhagic shock, respectively. *(From Johnson KB, Kern SE, Hamber EA, et al: Influence of hemorrhagic shock on remifentanil: a pharmacokinetic and pharmacodynamic analysis,* Anesthesiology *94:322-332, 2001.)*

that of propofol.[346] Thus, the remifentanil dose should be reduced substantially compared with propofol during TIVA for patients with significant blood loss.

ANESTHETIC TECHNIQUES USING OPIOIDS

See also Chapters 56, 57, 64, 65, and 98.

ANALGESIA

Opioids are frequently used to relieve pain during monitored anesthesia care and regional anesthesia. A single bolus administration of opioids can provide significant pain relief. Morphine is slow in onset and does not allow rapid titration to effect. Meperidine (50 to 100 mg IV) produces variable degrees of pain relief and is not always effective in patients with severe pain. Intravenous boluses of fentanyl (1 to 3 μg/kg), alfentanil (10 to 20 μg/kg), or sufentanil (0.1 to 0.3 μg/kg) can produce potent and short-lasting analgesia. Infusion rates range from 0.01 to 0.05 μg/kg/minute for fentanyl, 0.0015 to 0.01 μg/kg/minute for sufentanil, 0.25 to 0.75 μg/kg/minute for alfentanil, and 0.05 to 0.25 μg/kg/minute for remifentanil. Plasma concentrations of opioids necessary for various purposes are listed in Table 31-6.

Changes in the excitability of central neurons play an important role in the establishment of pain. In rats, low doses of fentanyl blocked the synaptic form of central sensitization in the spinal cord in vivo, a finding suggesting the possibility of preemptive analgesia by fentanyl, but higher doses do not have this effect.[347] Reductions in postoperative pain and improved recovery have been attributed to preemptive analgesia with either epidural fentanyl or bupivacaine after radical prostatectomy.[348] In contrast, in patients undergoing transperitoneal tumor nephrectomy, preoperative intravenous administration of a combination of morphine, ketamine, and clonidine failed to exert a clinically relevant effect on postoperative pain.[349] Aida and colleagues reported that the effectiveness of preemptive analgesia varies according to the type of surgical procedure, and preemptive analgesia with epidural morphine was reliably effective in limb and breast operations but ineffective in abdominal surgical procedures.[350] A meta-analysis demonstrated that the results of preemptive analgesia with systemic administration of opioids are equivocal.[351] Thus, whether preemptive analgesia can be effectively achieved clinically by the early administration of opioids remains uncertain.

PCA with opioids is now a cornerstone of postoperative analgesia, but pharmacokinetic optimization of opioid treatment in acute pain is a complex matter. Without considering effect-site drug concentrations over time, the choice of opioid and the amount, method, and frequency of its administration cannot be optimal. Morphine remains a popular and rational choice for PCA therapy. A double-blind randomized study demonstrated that effect-compartment controlled remifentanil PCA with a slow and progressive adapted algorithm is feasible in young women undergoing uterine artery embolization.[352] The combination of opioids with other drugs may improve PCA. For thoracic surgical procedures, the addition of ketamine to opioids for intravenous PCA was superior to intravenous PCA opioids alone, whereas the effect of added ketamine was not significant for orthopedic or abdominal surgical procedures.[353]

BALANCED ANESTHESIA

The term *balanced anesthesia* was introduced by Lundy in 1926. Lundy suggested that a balance of anesthetic agents and techniques be used to produce the different components of anesthesia (i.e., analgesia, amnesia, muscle relaxation, and abolition of autonomic reflexes with maintenance of homeostasis). Anesthesia with a single agent can require doses that produce excessive hemodynamic depression. The inclusion of an opioid as a component of balanced anesthesia can reduce preoperative pain and anxiety, decrease somatic and autonomic responses to airway manipulations, improve hemodynamic stability, lower requirements for inhaled anesthetic agents, and provide immediate postoperative analgesia. Opioids interact synergistically and markedly reduce the dose of propofol and other sedative-hypnotics required for loss of consciousness and during noxious stimulation such as skin incision[354] (Fig. 31-22). Although the intent of combining opioids with sedative-hypnotics or volatile anesthetic agents is to produce anesthetic conditions with stable hemodynamics before and after noxious stimulation, this ideal is not always achieved.[355,356]

The timing, rate of administration, and dose of supplemental opioid should also be tailored to the specific condition of the patient and the expected duration of the operation, to avoid problems. Giving a large dose of any opioid shortly before the end of a surgical procedure is very likely to result in postoperative respiratory depression. However, analgesic concentrations of opioids have little effect on the MAC awake of inhaled anesthetic agents.[357]

The ideal opioid would permit rapid titration, successfully prevent unwanted responses to noxious stimuli, require little supplementation, not depress cardiovascular

TABLE 31-6 RANGE OF APPROXIMATE PLASMA (OR WHOLE BLOOD FOR REMIFENTANIL) OPIOID CONCENTRATION

	Fentanyl (ng/mL)	Sufentanil (ng/mL)	Alfentanil (ng/mL)	Remifentanil (ng/mL)
Predominant agent	15-30	5-10	400-800	—
Major surgery	4-10	1-3	200-400	2-4
Minor surgery	3-6	0.25-1	50-200	1-3
Spontaneous ventilation	1-3	<0.4	<200	0.3-0.6
Analgesia	1-2	0.2-0.4	50-150	0.2-0.4

From Bailey PL, Egan TD, Stanley TH: Intravenous opioid anesthetics. In Miller RD, editor: Anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, p 800.*

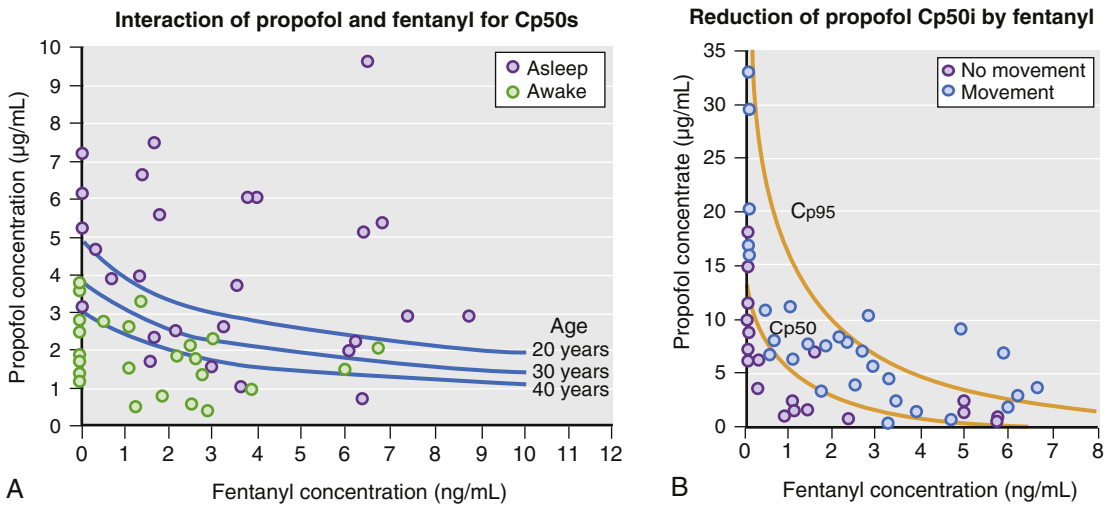


Figure 31-22. A, Measured arterial propofol and fentanyl concentrations at which patients did and did not respond to a verbal command at 10 minutes after the initiation of the infusion of these drugs. The *solid lines* represent the modeled concentration of propofol, according to decade of age when combined with the measured fentanyl concentrations, at which 50% of patients did not respond to verbal command (Cp50s). **B,** Reduction by increasing concentration of fentanyl of propofol concentration at which 50% or 95% of patients did not move at skin incision (Cp50i and CP95i, respectively). The *solid lines* represent the logistic regression solution. *(From Smith C, McEwan AI, Jhaveri R, et al: The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision,* Anesthesiology *81:820-828, 1994.)*

function, permit the return of adequate spontaneous ventilation in a timely manner, and produce residual if not complete postoperative analgesia with minimal side effects. Alfentanil and remifentanil provide the greatest ability to titrate opioids rapidly because of their extremely rapid time to onset (1 to 2 minutes) of peak effect. Sufentanil, alfentanil, and remifentanil are arguably superior to fentanyl in most respects. Antagonism of opioid action with naloxone for troublesome respiratory depression is required less frequently after alfentanil and sufentanil compared with fentanyl. Pharmacologic antagonism is rarely required after remifentanil administration.

Fentanyl

Anesthetic induction is usually achieved by combining a loading dose of fentanyl (2 to 6 µg/kg) with a sedative-hypnotic, most commonly thiopental or propofol, and a muscle relaxant. Maintenance of anesthesia can be achieved with N_2O (60% to 70%) in O_2, low concentrations of potent inhaled anesthetic agents, and additional fentanyl (intermittent boluses of 25 to 50 µg every 15 to 30 minutes or a constant infusion of 0.5 to 5.0 µg/kg/hour).

The plasma concentration of fentanyl required for postoperative analgesia was approximately 1.5 ng/mL,[358] but levels of at least 2 to 3 ng/mL are usually required during surgery if the only inhaled agent is N_2O. In unpremedicated patients anesthetized with a fentanyl infusion and N_2O in O_2, the CP_{50} (minimal steady-state plasma concentration of an intravenous analgesic or anesthetic agent required to prevent a somatic response in 50% of patients following skin incision) and the CP_{50}- BAR (minimal plasma concentration of an intravenous analgesic or anesthetic agent required to prevent a somatic, hemodynamic, or autonomic response in 50% of patients following skin incision) for fentanyl at skin incision are 3.26 and 4.17 ng/mL, respectively.[359] The MAC of isoflurane at skin incision can be reduced by 50% and 63% with plasma fentanyl concentrations of 1.67 and 3.0 ng/mL, respectively.[85] Increasing plasma fentanyl concentrations from 3.0 to 10 ng/mL only further reduced the MAC of isoflurane from 63% to 82%. The intraoperative requirement of propofol is also reduced by fentanyl. In patients undergoing spine fusion, to keep the mean arterial pressure within 15% of the control value when fentanyl was infused to maintain the plasma concentration at 0, 1.5, 3.0, and 4.5 ng/mL, average propofol infusion rates were 10.1 ± 2.5 (mean ± SD), 7.5 ± 1.2, 5.7 ± 1.1, and 4.9 ± 1.2 mg/kg/hour, respectively.[360]

Opioid pharmacokinetics and pharmacodynamics vary considerably among patients. Investigators reported that fentanyl dose based on total body weight may cause overdosing in obese patients.[358] Nevertheless, a balanced technique with fentanyl, by titrating the opioid in anticipation of various stimuli and patients' responses with pharmacokinetic guidelines in mind, often results in a stable hemodynamic course and rapid awakening of a pain-free patient. Repeated doses or continuous infusions of fentanyl are most likely to result in significant depression of spontaneous ventilation.

Alfentanil

Because alfentanil penetrates the brain so rapidly, equilibration of alfentanil between the plasma and the CNS can be achieved while plasma alfentanil levels are relatively high compared with sufentanil and fentanyl. This property explains how low doses (10 to 30 μg/kg) of alfentanil, administered just before or simultaneously with a sedative-hypnotic, are effective.

Alfentanil (25 to 50 μg/kg IV), followed by small titrated sleep doses of any sedative-hypnotic (e.g., 50 to 100 mg sodium thiopental), is usually successful in preventing significant hemodynamic stimulation from laryngoscopy and intubation. In one report, the optimum dose of alfentanil, coadministered with 2.5 mg/kg propofol, when inserting a classic laryngeal mask airway was 10 μg/kg.[361] Further opioid supplementation can be achieved with an alfentanil infusion (0.5 to 2.0 μg/kg/minute) or intermittent boluses of alfentanil (5 to 10 μg/kg) for shorter procedures. In balanced anesthetic techniques in which potent inhaled anesthetic agents are also employed, relatively low plasma alfentanil concentrations (e.g., 29 ng/mL) can reduce the MAC of isoflurane by approximately 50%.[87] In one report, the EC_{50} of alfentanil during propofol anesthesia, in which the plasma concentrations of propofol are kept at target concentrations of 3 μg/mL, was 92 ng/mL for intubation, 55 ng/mL for skin incision, 84 ng/mL for the opening of the peritoneum, and 66 ± 38 ng/mL for the intraabdominal part of surgery.[362] The hemodynamic changes induced by propofol may have an important influence on the pharmacokinetics of alfentanil. Propofol (target concentration, 1.5 μg/mL) decreased the elimination clearance of alfentanil by 15%, rapid distribution clearance by 68%, slow distribution clearance by 51%, and lag time by 62% in one report.[363] Alfentanil infusions or repeated doses should be minimized 15 to 30 minutes before the end of the surgical procedure, to avoid problematic residual respiratory depression.

Sufentanil

The mean plasma sufentanil concentration reported to be the CP_{50} for prevention of hemodynamic responses to laryngoscopy and tracheal intubation was 1.08 ng/mL with a range of 0.73 to 2.55 ng/mL. In combination with propofol for induction of anesthesia in children, bolus administration of sufentanil 0.3 μg/kg can completely abolish the cardiovascular response to tracheal intubation.[364] Maintenance of anesthesia can be achieved with N_2O (60% to 70%) in O_2 and further sufentanil (intermittent boluses, 0.1 to 0.25 μg/kg, or constant infusion, 0.5 to 1.5 μg/kg/hour). The CP_{50} for sufentanil during skin incision (2.08 ± 0.62 ng/mL) is twice as great as that for intubation in unpremedicated patients.[365] CP_{50} value ratios at skin incision for sufentanil, fentanyl, and alfentanil in N_2O-O_2 anesthesia are approximately 1:2:150 and represent different and probably more accurate potency ratios than those traditionally published based on drug dose. In patients undergoing coronary artery bypass grafting, sufentanil doses larger than 1.25 ± 0.21 ng/mL reduced isoflurane requirements to less than 0.5% through the operation.[366]

Remifentanil

Very short duration of action of remifentanil mandates that an infusion (0.1 to 1.0 μg/kg/minute) be started before or soon after the bolus dose to ensure a sustained opioid effect. Maintenance infusion rates of remifentanil range from 0.1 to 1.0 μg/kg/minute for balanced anesthesia. Remifentanil can reliably suppress automatic, hemodynamic, and somatic responses to noxious stimulation.

The use of remifentanil allows rapid (5 to 15 minute) emergence. Infusion rates of 0.1 ± 0.05 μg/kg/minute should permit the return of spontaneous ventilation and responsiveness with maintenance of analgesia. A randomized double-blind placebo-controlled study demonstrated that the combination of 0.05 to 0.1 μg/kg/minute remifentanil and 2 mg midazolam provided effective sedation and analgesia during outpatient surgical procedures performed using local anesthesia.[367] Administration of remifentanil 1 μg/kg followed by 0.5 μg/kg/minute with propofol and 66% N_2O provided sufficient anesthesia for craniotomy with stable hemodynamics and rapid tracheal extubation.[368] Associated with emergence from remifentanil anesthesia, the need for alternative analgesic therapies should be anticipated, and these medications should be administered in a timely fashion. Perioperative administration of morphine (0.15 or 0.25 mg/kg IV) or fentanyl (0.15 mg) did not provide entirely adequate immediate postoperative pain control after remifentanil-based anesthesia in patients undergoing major abdominal operations.[369,370] Administration of ketamine (0.15 mg/kg followed by 2 μg/kg/minute) decreased intraoperative remifentanil use during abdominal surgical procedures and reduced postoperative morphine consumption without increasing the incidence of side effects.[371] In children undergoing surgical correction of strabismus, a combination of sevoflurane (2.5%) and remifentanil (1 μg/kg followed by 0.1 to 0.2 μg/kg/minute) caused less frequent postoperative vomiting but higher postoperative pain scores, compared with fentanyl (2 μg/kg followed by 1 μg/kg every 45 minute).[372]

Postoperative pain relief with low-dose remifentanil infusion was also reported. After general anesthesia with propofol (75 μg/kg/minute) and remifentanil (0.5 to 1.0 μg/kg/minute) for abdominal or thoracic surgical procedures, continuous infusion of remifentanil (0.05 or 0.1 μg/kg/minute) provided adequate analgesia.[373]

NEUROLEPTANALGESIA-ANESTHESIA

In 1959, De Castro and Mundeleer derived the concept of *neuroleptanalgesia,* which involved the combination of a major tranquilizer (usually the butyrophenone

droperidol) and a potent opioid analgesic (fentanyl) to produce a detached, pain-free state of immobilization and insensitivity to pain. Neuroleptanalgesia is characterized by analgesia, absence of clinically apparent motor activity, suppression of autonomic reflexes, maintenance of cardiovascular stability, and amnesia in most patients. The addition of an inhaled anesthetic, usually N_2O, improves amnesia and has been called neuroleptanesthesia. Because of the frequent and serious postoperative adverse effects of the neurolept component, droperidol, this technique is rarely used today.

"Neuroleptic" drugs traditionally include the phenothiazines (e.g., chlorpromazine) and the butyrophenones (e.g., haloperidol and droperidol). Butyrophenones cause sedation, tranquility, immobility, antiemesis, an extrapyramidal syndrome with face and neck dyskinesia, oculogyric crises, torticollis, agitation, and hallucinations. Administering droperidol alone, without analgesics or other sedatives, often produces feelings of discomfort or dysphoria in patients. The cardiovascular effects of droperidol are most often limited to mild hypotension, probably mediated through α-adrenergic blockade. Little respiratory depression is induced by droperidol, although significant variability exists, and occasional respiratory depression may be noted. Droperidol and other butyrophenones may enhance hypoxia-induced increases in ventilation in humans because of their antidopaminergic effects at the carotid body. Droperidol was previously used as a premedication (0.025 to 0.075 mg/kg IM), as an antiemetic (0.01 to 0.02 mg/kg IV), as an adjunct for awake endotracheal intubations (0.025 to 0.1 mg/kg IV), and as treatment for agitated, belligerent, or psychotic patients (0.05 to 0.2 mg/kg IV or IM).

Neuroleptanalgesia or neuroleptanesthesia is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs), in patients who abuse drugs or alcohol, or in those with Parkinson disease.

TOTAL INTRAVENOUS ANESTHESIA

Many different intravenous compounds can be employed in numerous combinations to provide TIVA. Most commonly, an opioid is combined with another drug more likely to provide hypnosis and amnesia. For example, the combination of alfentanil and propofol produces excellent TIVA. Alfentanil provides analgesia and hemodynamic stability while blunting responses to noxious stimuli. Conversely, propofol provides hypnosis and amnesia and is antiemetic. Profound synergism also exists when more than two agents, such as propofol, alfentanil, and midazolam, are combined. Anesthetic induction with alfentanil (25 to 50 μg/kg) and propofol (0.5 to 1.5 mg/kg), followed by infusions of 0.5 to 1.5 μg/kg/minute of alfentanil and 80 to 120 μg/kg/minute of propofol, produce complete anesthesia in patients ventilated with air and O_2 with or without N_2O for a variety of procedures. Investigators proposed that alfentanil concentrations as low as 85 ng/mL, when combined with a blood propofol concentration of 3.5 μg/mL, can produce both optimal anesthetic conditions and speed of recovery.[374] Stanski and Shafer suggested that bolus doses and initial infusion rates would be 30 μg/kg and 0.35 μg/kg/minute for alfentanil and 0.7 mg/kg and 180 μg/kg/minute for propofol.[375] Recognizing that these calculations were based on EC_{50} data in patients undergoing only moderately painful procedures, anesthesiologists should adjust these doses accordingly. In patients undergoing ear, nose, throat surgical procedures, TIVA with remifentanil and propofol provided a more rapid respiratory recovery after brief surgical procedures, compared with TIVA with alfentanil and propofol.[376]

The optimal propofol-opioid concentrations that ensure adequate anesthesia and rapid emergence were determined by computer modeling. The optimal propofol concentration decreases in the order of fentanyl > alfentanil > sufentanil >> remifentanil. A shorter context-sensitive half-time allows the administration of greater amounts of opioid (and less propofol) during anesthesia without creating prolonged opioid effects.

Maintenance infusions vary according to the patient's condition and surgical stimuli. Propofol (75 to 125 μg/kg/minute) and alfentanil (1.0 to 2.0 μg/kg/minute) were initially recommended. Drug infusions should be terminated 10 to 20 minutes before the end of anesthesia if N_2O is employed. Otherwise, propofol infusions should be terminated 5 to 10 minutes before anticipated patient awakening. Alfentanil infusion rates do not need to be less than 0.25 to 0.5 μg/kg/minute until the surgical procedure is terminated. A multicenter evaluation demonstrated that, in patients undergoing elective inpatient surgical procedures, intravenous administration of remifentanil (1 μg/kg followed by 1.0 μg/kg/minute), when combined with propofol (75 μg/kg/minute), effectively controlled responses to tracheal intubation.[377] Reduction of the remifentanil infusion rate to 0.25 to 0.40 μg/kg/minute after tracheal intubation was also recommended.

Midazolam-opioid combinations can also provide complete anesthesia. However, midazolam-alfentanil TIVA has not been found to compare favorably with propofol-alfentanil TIVA even with flumazenil reversal of benzodiazepine actions.[378]

TIVA techniques are especially useful when delivery of inhaled anesthetic agents is compromised. By keeping the goals of balanced anesthesia in mind, combining modern opioids and other drugs, using infusion pumps, and employing an increased understanding of pharmacokinetics, clinicians can successfully perform a variety of TIVA techniques. Approximate opioid doses and infusion rates for TIVA are listed in Table 31-7.

TABLE 31-7 APPROXIMATE OPIOID LOADING (BOLUS) DOSES, MAINTENANCE INFUSION RATES, AND ADDITIONAL MAINTENANCE DOSES FOR TOTAL INTRAVENOUS ANESTHESIA

	Loading Dose (μg/kg)	Maintenance Infusion Rate	Additional Boluses
Alfentanil	25-100	0.5-2 μg/kg/min	5-10 μg/kg
Sufentanil	0.25-2	0.5-1.5 μg/kg/hr	2.5-10 μg
Fentanyl	4-20	2-10 μg/kg/hr	25-100 μg
Remifentanil	1-2	0.1-1.0 μg/kg/min	0.1-1.0 μg/kg

From Bailey PL, Egan TD, Stanley TH: Intravenous opioid anesthetics. In Miller RD, editor: Anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, p 803.*

OPIOID-BASED (HIGH-DOSE OPIOID) ANESTHESIA FOR CARDIAC SURGERY

Opioids can be administered as the primary or sole anesthetic in opioid-based anesthetic techniques (see also Chapter 67). High-dose opioid anesthesia was introduced as a stress-free anesthetic method for cardiac surgical procedures. High-dose opioid anesthesia was first performed with morphine; however, fentanyl and sufentanil were later recommended. Several factors have diminished the popularity of high-dose opioid anesthesia, even in cardiac anesthesia. These factors include the lack of evidence substantiating any significant outcome benefit associated with the use of large doses of opioids, the added drug costs, and the trend toward "fast track" approaches for cardiac patients that can be impeded with large doses of opioids. However, opioids, particularly when administered by continuous infusion, are still among the most effective anesthetic agents for patients undergoing cardiac or other extensive operations.

In an attempt to decrease the costs of cardiac surgery, fast-track programs have become popular. Engoren and colleagues reported that the more expensive but shorter-acting opioids, sufentanil and remifentanil, produced equally rapid extubation, similar stays, and similar costs when compared with fentanyl; these findings indicate that any of these opioids can be recommended for fast-track cardiac surgery.[379]

Fentanyl

Many different techniques have been used to achieve anesthesia with fentanyl.[380,381] Rapid or slow injections of fentanyl range from 5 to 75 μg/kg. These doses establish plasma fentanyl concentrations (10 to 30 ng/mL) that are often sufficient to provide stable hemodynamics throughout the induction and intubation sequence. Continuous infusions of fentanyl for cardiac surgery range from 0.1 to 1.0 μg/kg/minute up to or continuing through CPB. High-dose fentanyl anesthesia has also proved effective and safe for pediatric heart surgery. Investigators indicated that fentanyl (25 to 50 μg/kg) combined with isoflurane (0.2% to 0.4%) was sufficient to obtund hemodynamic and stress responses in the pre-CPB phase of open heart surgery in infants and young children[382] (Fig. 31-23). Investigators reported that 57 of 59 eligible patients were successfully extubated at 34 ± 14 minutes after termination of fentanyl administration (total dose, 127 ± 64 μg/kg) with naloxone (total bolus, 3.4 ± 2.6 μg/kg), and they recovered fully without ventilatory support under the naloxone infusion, which was terminated at 11 ± 7 hours.[383] These results suggest that naloxone infusion with individual dose titration facilitates the use of high-dose opioid anesthesia, thus maintaining the advantage of this anesthesia. Investigators also showed that high-dose fentanyl (50 μg/kg) is not associated with a difference in the incidence of postoperative cognitive dysfunction at 3 or 12 months after coronary artery bypass surgery in older adults, whereas low-dose fentanyl (10 μg/kg) leads to shorter postoperative ventilation times and may be associated with a greater incidence of postoperative cognitive dysfunction 1 week postoperatively.[384]

Alfentanil

The induction of anesthesia with large doses of alfentanil has been applied in cardiac surgery. Large doses of alfentanil (150 μg/kg) may be used with or without thiopental to induce anesthesia. However, some investigators claim that anesthesia cannot be reliably induced with alfentanil alone, at least in young and healthy adults. Continuous infusions of alfentanil (2 to 12 μg/kg/minute) have been employed to maintain moderate to very high plasma alfentanil concentrations (<3000 ng/mL) during cardiac surgical procedures. Enthusiasm for high-dose alfentanil anesthesia techniques is limited by the amount (and cost) of drug required and by suggestions that alfentanil anesthesia for cardiac surgery is inadequate and is associated with more cardiovascular adverse effects compared with

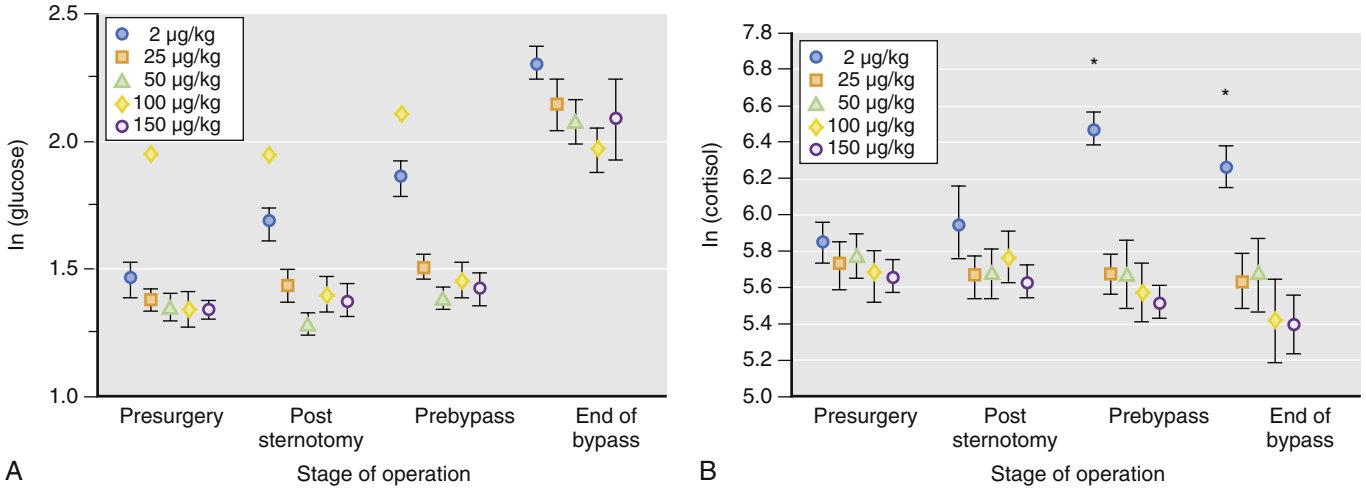


Figure 31-23. Suppression of stress responses in the prebypass phase of open heart surgery in infants and young children by fentanyl combined with a low concentration (0.2% to 0.4%) of isoflurane. Mean (± standard error) natural logarithm (ln) for glucose (**A**) or ln for cortisol (**B**) versus stage of surgery for each dose of fentanyl. The values for the 2 μg/kg group indicated by *asterisks* were significantly higher ($P < 0.01$) than in the other groups. *(From Duncan HP, Cloote A, Weir PM, et al: Reducing stress responses in the pre-bypass phase of open heart surgery in infants and young children: a comparison of different fentanyl doses,* Br J Anaesth *84:556-564, 2000.)*

fentanyl and sufentanil. More modest doses of alfentanil have been successfully administered in combination with sedative-hypnotics such as propofol for cardiac anesthesia.

Sufentanil

Advantages of high-dose sufentanil include more rapid induction, better blunting or elimination of hypertensive episodes, and greater reduction in left ventricular stroke work, with higher cardiac outputs and more stable hemodynamics intraoperatively and postoperatively. Induction doses of sufentanil range from 2 to 20 μg/kg administered as a bolus or infused over 2 to 10 minutes. Total doses of sufentanil administered in high-dose techniques usually range from 15 to 30 μg/kg. However, no additional benefit could be demonstrated in terms of hemodynamic control or EEG signs by increasing the dose of sufentanil from 3 to 15 μg/kg for the induction of anesthesia in patients premedicated with lorazepam.[385] Muscle rigidity during induction of anesthesia with high-dose opioid may cause difficult ventilation with a mask. During induction of anesthesia with sufentanil (3 μg/kg), upper airway closure occurs at the level of the glottis or above.[386]

The amount of sufentanil required can be markedly influenced by the supplements employed concomitantly. For patients undergoing coronary artery surgery, induction (0.4 ± 0.2 μg/kg) and total maintenance (2.4 ± 0.8 μg/kg) doses of sufentanil were used in combination with propofol (1.5 ± 1 mg/kg for induction and 32 ± 12 mg/kg total). Sufentanil requirements tripled when midazolam was used instead of propofol.[387] Etomidate combined with an opioid can provide excellent anesthetic conditions with few hemodynamic perturbations. Inducing anesthesia with sufentanil (0.5 to 1.0 μg/kg) and etomidate (0.1 to 0.2 mg/kg) frequently confers hemodynamic stability. Maintenance of anesthesia by using an infusion of sufentanil (1.0 to 2.0 μg/kg/hour) in a balanced anesthetic technique achieves the advantages of opioid-based anesthesia and avoids prolonged opioid action into the postoperative period.

Remifentanil

Remifentanil has been used in cardiac anesthesia[341] (see also Chapter 67). Induction with remifentanil (2 μg/kg) with propofol and maintenance with remifentanil at 0.25 or 0.5 μg/kg/minute provided appropriate anesthesia for minimally invasive coronary artery bypass surgery with rapid awakening and tracheal extubation (Fig. 31-24).[388] Kazmaier and associates compared high-dose remifentanil (2.0 μg/kg/minute) and remifentanil (0.5 μg/kg/minute) combined with propofol (target-controlled infusion aiming at a plasma concentration of 2.0 μg/mL) in patients undergoing elective coronary artery bypass grafting.[389] Their results showed that a high dose of remifentanil reduced stroke volume index, heart rate, mean arterial pressure, myocardial blood flow, and myocardial O_2 uptake, and the drug's effects did not differ from those of remifentanil-propofol anesthesia. Geisler and associates examined the efficacy and safety of high-dose remifentanil anesthesia in patients undergoing coronary artery bypass graft surgery.[390] Continuous infusions of remifentanil (1.0 to 2.0 μg/kg/minute) in combination with propofol (3 mg/kg/hour) caused profound suppression of responses to surgical stimuli in most patients, but muscle rigidity occurred when remifentanil was used to induce anesthesia. These investigators concluded that starting the remifentanil infusion rate higher than 1.0 μg/kg/minute had no apparent advantage, and remifentanil is not suitable for use as a sole induction agent.

OTHER APPLICATIONS OF OPIOIDS

See also Chapter 98.

Transdermal Therapeutic System

Transdermal drug delivery generally requires high solubility in both water and oil, low molecular weight, high potency, and little or no skin irritation. Fentanyl is available in a transdermal therapeutic system (TTS). Potential advantages of delivering fentanyl transdermally include no first-pass drug metabolism by the liver, improved patient compliance, convenience and comfort, and consistent analgesia. Doses of TTS fentanyl include 20, 50, 75 and 100 μg/hour and achieve blood levels ranging from less than 1.0 to 2.0 ng/mL, although significant variability exists.

The pharmacokinetics of transdermally delivered fentanyl (50 μg/hour) was compared in 10 young adult (25 to 38 years of age) and eight older adult (64 to 82 years of age) patients.[391] Investigators shown that the mean half-time (time for plasma concentrations to double after patch application) was 4.2 hours and 11.1 hours and the mean maximum plasma concentrations were 1.9 ng/mL

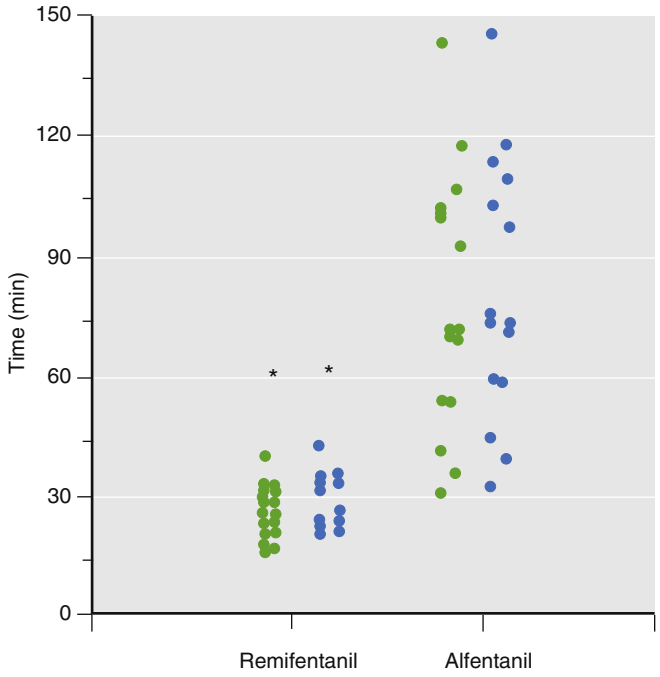


Figure 31-24. Times to awakening (*green circles*) and tracheal extubation (*blue circles*) in patients who underwent minimally invasive direct coronary artery bypass surgery after intravenous anesthesia with remifentanil and propofol or alfentanil and propofol. *(From Ahonen J, Olkkola KT, Verkkala K, et al: A comparison of remifentanil and alfentanil for use with propofol in patients undergoing minimally invasive coronary artery bypass surgery,* Anesth Analg *90:1269-1274, 2000.)*

and 1.5 ng/mL, in the younger and older groups, respectively. No differences were noted in the time at which maximum plasma concentrations occurred and the elimination $t_{½}$ after patch removal. Elevated body temperature accelerates either the release of fentanyl from the patch or the distribution from the subcutaneous fat depot. Portenoy and colleagues demonstrated that steady-state serum concentration was obtained by repeated application of TTS fentanyl, and the apparent $t_{½}$ following system removal after repeated application was relatively long, presumably because of ongoing absorption from a subcutaneous depot.[392]

Results of clinical trials using TTS fentanyl for postoperative analgesia demonstrated a high incidence of significant respiratory depression, and this application is not recommended.[393] In cancer pain, TTS fentanyl offers an interesting alternative to oral morphine, and its effectiveness and tolerability in this indication were demonstrated by several trials.[394] In general, TTS fentanyl has the same adverse effects as other opioids, mainly sedation, nausea, vomiting, and constipation. In comparison with oral morphine, TTS fentanyl causes fewer gastrointestinal adverse events. The risk of hypoventilation is comparatively low in patients with cancer. Sufentanil and buprenorphine may also be suitable for transdermal delivery, but clinical results are not yet available. Transdermal morphine is useful only if it is applied to de-epithelialized skin.

Iontophoresis

Iontophoresis is a technique by which drug passage through the skin is augmented by an external electric current. Clinically significant doses of morphine and fentanyl can be delivered iontophoretically. The fentanyl HCl iontophoretic transdermal system (fentanyl ITS) is a novel PCA system that has been approved in the United States and Europe for the management of acute moderate to severe postoperative pain.[395] This system allows patients to self-administer preprogramed doses of fentanyl noninvasively through the use of iontophoretic technology. To assess the efficacy and safety of patient-controlled ITS using fentanyl hydrochloride (40-μg infusion over 10 minutes) compared with standard intravenous morphine PCA (1-mg bolus every 5 minutes; maximum of 10 mg/hour), a prospective randomized controlled parallel-group trial was performed.[396] The results indicated that the fentanyl ITS can provide pain control equivalent to that observed with standard morphine PCA, with a similar incidence of opioid-related adverse events. The fentanyl ITS may offer certain clinical advantages over existing PCA modalities.[395] Its method of drug delivery avoids the risk of complications of needle-related injuries and infection, and its preprogramed electronics eliminate the potential for manual programing errors and excessive dosing. In addition, the compact size of the system enables more patient mobility postoperatively. The patient-controlled ITS with fentanyl has the potential to become a valuable option in the management of acute postoperative pain. Panchal and colleagues reported that fentanyl ITS was associated with a significantly lower incidence of analgesic gaps, which are defined as periods during which the patient does not access analgesia, thus contributing to ineffective postoperative pain management relative to morphine intravenous PCA.[397]

Transmucosal Drug Delivery

Similar to transdermal drug delivery, transmucosal delivery through the oropharynx and nasopharynx eliminates hepatic first-pass metabolism (drugs are absorbed directly into the systemic circulation) and improves patient comfort, convenience, and compliance.

Buprenorphine, a potent, synthetic morphine analogue with mixed opioid agonist-antagonist properties and a long half-time, is readily absorbed from sublingual mucosal tissues. The portion of the drug that is swallowed is almost completely metabolized by the liver, and only a small fraction can reach the systemic circulation when swallowed. Systemic bioavailability after sublingual buprenorphine is approximately 50% of that following intravenous administration. In several studies, sublingual buprenorphine (0.4 mg) was compared with conventional intramuscular morphine or meperidine and found to provide comparable and satisfactory analgesia.

Oral transmucosal fentanyl citrate (OTFC) is a solid dosage form of fentanyl that consists of fentanyl incorporated into a sweetened lozenge on a stick. A portion of fentanyl is absorbed through the oral mucosa, and the rest is swallowed and absorbed through the gastrointestinal tract. The recommended doses range from 5 to 20 μg/kg.[398] OTFC should be administered approximately 30 minutes before the surgical procedure (or painful procedure) to obtain peak effect. Plasma concentrations after OTFC administration peak at 2.0 ± 0.5 ng/mL, 15 to 30 minutes after OTFC administration, and then decline to less than 1 ng/mL an hour later.[399] Unlike transdermal fentanyl, OTFC leaves no significant depot in the mucosal tissues after it is removed. The systemic bioavailability of OTFC is 50% and reflects both buccal and gastrointestinal absorption. OTFC bioavailability is similar to that of buprenorphine (55%), but it is much greater than that of buccal morphine and other opioids with low lipid solubility. Egan and associates demonstrated that the pharmacokinetics of OTFC did not change with repeated dosing, and the decline of plasma concentration was as rapid as when the drug was administered by intravenous infusion[400] (Fig. 31-25). Furthermore, Kharasch and colleagues reported that the pharmacokinetics of OTFC was not altered in older volunteers (67 ± 6 years of age), and no change in OTFC dosing in older adults would appear necessary.[401] Peak fentanyl concentration and clinical effects after OTFC were minimally affected by hepatic or intestinal CYP3A induction by rifampicin and intestinal CYP3A inhibition by grapefruit juice, findings suggesting that first-pass metabolism minimally influences OTFC bioavailability.[402] Perioperative OTFC was reported to be effective for postoperative analgesia in pediatric patients undergoing tonsillectomy.[403] However, OTFC can induce perioperative emesis and respiratory depression. It is also being evaluated for the treatment of breakthrough cancer pain.[404] OTFC may be ideally suited to treat breakthrough cancer pain because fentanyl is rapidly absorbed from OTFC, and patients can easily self-administer OTFC.

Delivery of opioids through the nasal mucosa has also been investigated. No difference was noted in the efficacy of intranasal fentanyl (2 μg/kg), intramuscular morphine (0.1 mg/kg), and intravenous morphine

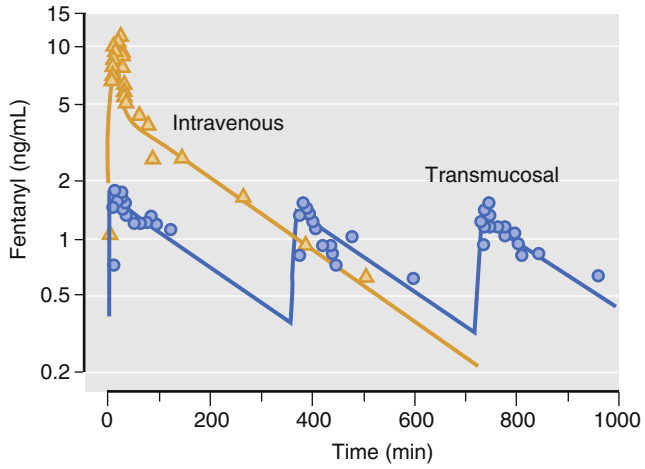


Figure 31-25. A typical result of time-dependent change in plasma concentration of fentanyl after oral transmucosal fentanyl citrate (OTFC) application and intravenous administration. Three 800-μg doses of OTFC were administered with 6-hour intervals between doses, and fentanyl was infused at a constant rate of 50 μg/minute to a total of 15 μg/kg. *(From Egan TD, Sharma A, Ashburn MA, et al: Multiple dose pharmacokinetics of oral transmucosal fentanyl citrate in healthy volunteers,* Anesthesiology *92:665-673, 2000.)*

(0.1 mg/kg) in controlling postoperative pain and emergence delirium in children undergoing bilateral myringotomy and placement of ventilating tubes.[405] A novel transnasal morphine formulation composed of morphine monohydrate and chitosan, a nontoxic, naturally occurring mucoadherent derived from shellfish, was shown to offer a noninvasive alternative to intravenous morphine for postoperative analgesia in patients after third molar extraction.[406] Intranasal administration of remifentanil (4 μg/kg) produces good intubating conditions in 2 to 3 minutes after induction of anesthesia with sevoflurane in children.[407]

Fentanyl (300 μg) inhalation produces low plasma drug level (0.1 ng/mL) after 15 minutes and analgesia that may be disproportionately greater than expected.[408] Inhaled liposome-encapsulated fentanyl was also demonstrated to provide a noninvasive route of administration with a rapid increase and prolonged maintenance of plasma fentanyl concentration.[409] In patients terminally ill with cancer, inhalation of nebulized fentanyl citrate significantly improved patients' perception of breathing, respiratory rate, and O_2 saturation.[410] This inexpensive and readily available treatment may offer substantial relief of end-of-life dyspnea. The advent of specialized and efficient pulmonary drug delivery systems has facilitated the evaluation of inhaled opioids, such as morphine and fentanyl, for management of severe pain associated with surgery or malignant disease.[411]

The rectal mucosa is another site for transmucosal drug delivery. The bioavailability of 30 mg morphine sulfate controlled-release suppository formulation was significantly greater than that of 30 mg oral controlled-release morphine sulfate tablets; this increase may be the result of partial avoidance of hepatic biotransformation with rectal administration.[412] The hydrogel formulation of rectal morphine may also be useful for premedication and analgesia in pediatric patients.[413]

Oral Controlled-Release Medications

Despite the high first-pass metabolism of opioid analgesics, morphine has been formulated into an oral, sustained-release tablet (MST) and has been evaluated for premedication, for postoperative analgesia, and as an analgesic for chronic cancer pain. MST provides unreliable preoperative anxiolysis and postoperative pain relief, possibly because of delayed time to onset of peak effects (3 to 5 hours), which can be increased by impaired gastric emptying and absorption from the small intestine. As an analgesic for chronic cancer pain, MST was shown to be an excellent formula.[414]

The relative analgesic potency of single doses of oral controlled-release oxycodone (20 or 40 mg) and oral controlled-release morphine (45 or 90 mg) was compared in a randomized double-blind trial in women with moderate to severe pain following abdominal hysterectomy.[415] Controlled-release oxycodone at doses of 20 mg or 40 mg was comparable with controlled-release morphine at doses of 45 mg or 90 mg, respectively, for total and peak analgesic effects, thus indicating that oral controlled-release oxycodone was twice as potent as oral controlled-release morphine. A randomized double-blind crossover trial indicated that controlled-release oxycodone is as safe and effective as controlled-release morphine in the treatment of cancer pain.[416]

Extended-Release Epidural Morphine (DepoDur)

DepoDur is a novel drug that delivers morphine by using DepoFoam technology, a drug-delivery system composed of multivesicular lipid particles containing nonconcentric aqueous chambers that encapsulate the active drug. When the plasma morphine concentration after epidural administration of 5 mg of standard morphine was compared with that of 5 mg of DepoDur, the terminal $t_{½}$ was comparable, but the peak concentration was significantly smaller, and peak systemic absorption occurred later with DepoDur. Randomized controlled studies demonstrated that 5 to 15 mg of DepoDur can be a potentially beneficial analgesic after elective cesarean delivery with no significant increases in adverse events for the period from 24 to 48 hours postoperatively.[417,418] A large dose of epidural lidocaine before DepoDur administration alters the pharmacokinetics and drug effects of DepoDur.[419]

OTHER OPIOID AGONISTS

CODEINE

Codeine (methylmorphine) is one half as potent as morphine, has a high oral-parenteral potency ratio (2:3), and has a plasma $t_{½}$ of 2 to 3 hours. Codeine has mild to moderate analgesic but strong cough-suppressant properties after oral administration. Cytochrome P450 2D6 (CYP2D6) is the enzyme responsible for *O*-demethylation of codeine to morphine.[420] Intravenous codeine produces profound hypotension and is neither approved nor recommended.

OXYCODONE

Oxycodone is extensively metabolized in humans mainly by hepatic cytochrome P450, and only 10%

of oxycodone is excreted in unchanged form in urine. Rifampin, a strong inducer of several drug-metabolizing enzymes, induces cytochrome P450, reduces the plasma concentration of intravenous and oral oxycodone, and modestly attenuates the pharmacologic effects of oxycodone.[421] The role of several metabolites in oxycodone's analgesic activity is still not fully understood.[422] Oxycodone is a potent analgesic after systemic administration, but its analgesic potency is poor after intrathecal administration.[423] Investigators showed that oxycodone is more potent than morphine for visceral pain relief in intravenous PCA after laparoscopic hysterectomy.[424] With respect to pharmacologic effects other than analgesic effects, investigators reported that the extent and speed of onset of oxycodone-induced respiratory depression were dose dependent and greater than those of an equivalent dose of morphine.[425]

MEPERIDINE (PETHIDINE)

Meperidine is predominantly a μ-opioid receptor agonist that produces pharmacologic effects similar but not identical to those of morphine. Meperidine sometimes causes excitation of the CNS that is characterized by tremors, muscle twitches, and seizures largely caused by accumulation of a metabolite, normeperidine. Meperidine has well-known local anesthetic properties.

Unlike morphine, after intravenous injection, first-pass uptake of meperidine by the lungs is approximately 65%. Meperidine is more highly bound to plasma proteins than is morphine, principally (70%) to α_1-acid glycoprotein. As with morphine, a relatively high hepatic extraction ratio results in biotransformation that depends on hepatic blood flow. The major metabolite normeperidine has analgesic activity and is roughly twice as potent as meperidine in producing seizures in animals. The elimination $t_{½}$ of normeperidine is considerably greater than that of meperidine, and thus repeated doses can easily produce accumulation of this toxic metabolite in patients with renal disease, with the potential for inducing seizures.

Meperidine is frequently used for postoperative pain management. A comparative study demonstrated that morphine, meperidine, and tramadol resulted in equivalent pain scores in intravenous PCA after abdominal hysterectomy.[426] Meperidine (12.5 to 35 mg) is also effective for prevention and treatment of postoperative shivering.[427,428]

HYDROMORPHONE

Hydromorphone is structurally related to morphine but is approximately 5 to 10 times as potent. Hydromorphone may be better tolerated than morphine in patients with renal failure; because of the keto-group in position 6 of the benzol ring, an active 6-glucuronate metabolite is not formed as in morphine.[429] A bolus dose of hydromorphone reaches its peak effect in approximately 20 minutes, whereas an equivalent morphine bolus requires 94 minutes to reach peak. Analgesia after hydromorphone lasts 4 to 5 hours. Hydromorphone has been used for both acute and chronic pain conditions in adults and children.[430] Hydromorphone PCA provides adequate postoperative analgesia in patients who have undergone gynecologic surgical procedures, and no systematic difference is noted between morphine and hydromorphone in opioid-related side effects.[431]

LEVORPHANOL

Levorphanol is the only available semisynthetic opioid agonist of the morphinan series with a long (12 to 19 hours) $t_{½}$. It is five times as potent as morphine, with an intramuscular-to-oral potency ratio of 1:2. Levorphanol may have particular utility in patients with chronic pain who demonstrate morphine tolerance, perhaps because of differences in opioid receptor activity. Analgesia produced by levorphanol is mediated by its interactions with μ-, δ-, and κ-opioid receptors. Levorphanol is also an NMDA receptor antagonist. The long $t_{½}$ of the drug increases the potential for drug accumulation.[432]

METHADONE

Methadone has an equivalent potency but longer duration of action than morphine. The plasma $t_{½}$ of methadone is very long and variable (13 to 100 hours). Despite this property, many patients require doses every 4 to 8 hours to maintain analgesic effects. The major clinical applications of methadone are in the prevention of opioid withdrawal symptoms and in the treatment of chronic pain. Investigators showed that the same dose of intravenous methadone (20 mg) that is effective for postoperative pain is also suitable for the induction of anesthesia in combination with etomidate, and that methadone may have the potential for producing histamine release.[433]

OXYMORPHONE

Oxymorphone is a semisynthetic opioid agonist that is specific for the μ-opioid receptor and is approved to treat both acute and chronic pain. Because of its extensive liver metabolism, oral oxymorphone is contraindicated in patients with moderate to severe hepatic impairment.[434] Oxymorphone is structurally related to morphine and is almost 10 times as potent, but with a similar duration of action. In patients with acute moderate to severe postsurgical pain, oral immediate-release oxymorphone (10, 20, or 30 mg) provided significant dose-related pain relief compared with placebo, and this relief was maintained over several days, with a safety profile comparable to that of immediate-release oxycodone.[435]

PIRITRAMIDE

Piritramide, a synthetic opioid structurally related to meperidine, is devoid of emetic activity and is used for postoperative analgesia in several European countries.[436] Pharmacokinetic analysis showed that piritramide is distributed extensively and is eliminated slowly and recommended intermittent bolus administration.[437] A randomized controlled trial showed that intravenous PCA with piritramide can produce pain management as satisfactory as that observed with oral oxycodone after cesarean section.[438]

TRAMADOL

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine with a dual mechanism of action. Tramadol stimulates the μ receptor and, to a lesser extent, the δ- and κ-opioid receptors. Like tricyclic antidepressants, tramadol also activates spinal inhibition of pain by decreasing the reuptake of norepinephrine and serotonin.[439] Investigators suggested that tramadol may have direct serotonin-releasing action.[440] Tramadol is one fifth to one tenth as potent as morphine. In rats, tramadol reduced the MAC of isoflurane in a naloxone-sensitive manner.[441] Intravenous tramadol was effective for postthoracotomy pain relief.[442] Analgesic doses of tramadol may produce less respiratory depression, in part because of its nonopioid receptor–mediated actions, and may have minimal effects on gastrointestinal motor function.[443] Seizures have been reported in patients taking the drug. Caution should be exercised when combining tramadol with MAOIs, neuroleptic agents, and other drugs that lower the seizure threshold. Investigators suggested that tramadol has local anesthetic properties on peripheral nerves when it is used alone.[444]

Tramadol used as a sole drug cannot be considered the drug of choice after moderately painful surgical procedures. The doses needed to relieve pain in 80% of patients are much larger than the usual dose of 100 mg.[445] Tramadol added to lidocaine for intravenous regional anesthesia provided a shorter onset time of sensory block.[446] Tramadol added to 1.5% mepivacaine for brachial plexus block enhances the duration of analgesia in a dose-dependent manner with acceptable side effects.[447] Intraarticular tramadol was also used for management and prevention of pain after arthroscopic knee surgery. The intraarticular admixture of tramadol 100 mg with 0.25% bupivacaine provides pronounced prolongation of analgesia than with either drug alone in patients undergoing arthroscopic knee surgery.[448] Clinical studies to determine the analgesic efficacy of neuraxial tramadol added to epidural anesthesia in adults have yielded contradictory results.[449,450]

Tramadol has dose- and time-dependent bactericidal activity against *Escherichia coli* and *Staphylococcus epidermidis*, as well as antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The antibacterial properties of tramadol may be useful for reduction of bacterial infection after regional anesthesia.[451]

MORPHINE-6-GLUCURONIDE

M6G is a potent metabolite of morphine. In contrast to morphine, M6G is not metabolized but is excreted by the kidneys and exhibits enterohepatic cycling because it is a substrate for multidrug resistant transporter proteins in the liver and intestines.[452] M6G exhibits a delay in its analgesic effect (blood–effect-site equilibration $t_{½}$ 4 to 8 hours), which is partly related to slow passage through the blood-brain barrier and distribution within the brain compartment. In humans, M6G's potency is just half that of morphine. Trials to use M6G as an analgesic have been reported. Osborne and co-workers reported that 0.5 to 4 mg of intravenous M6G was effective for treatment of cancer pain for 2 to 24 hours without causing nausea and vomiting.[453] M6G (100 mg given intrathecally) provided excellent analgesia after total hip replacement, as did intrathecal morphine sulfate (500 mg).[454] In a randomized double-blind study, M6G had an analgesic effect similar to that of morphine over the first 24 hours postoperatively. However, the initial onset of M6G effect may be slower than that of morphine.[455] M6G can paradoxically increase pain sensitivity in mice and humans. The pronociceptive effect of M6G can be shown in knockout mice lacking μ-, κ- and δ-opioid receptors, and it may result from activation of the NMDA receptors.[456]

AGONIST-ANTAGONIST OPIOID COMPOUNDS

Nalorphine, the first agonist-antagonist opioid, was successfully synthesized by Weijland and Erickson in 1942 and was found to be strongly antagonistic to almost all the properties of morphine. Although nalorphine was found to possess strong analgesic actions, it was unsuitable for clinical use because of its psychotomimetic effects. Nalorphine was used in lower doses as an opioid antagonist.

Agonist-antagonist opioids are usually produced by alkylation of the piperidine nitrogen and the addition of a three-carbon side chain such as a propyl, allyl, or methyl allyl to morphine. Buprenorphine is a partial agonist at the μ receptor. The other compounds are μ-receptor antagonists and full or partial agonists at the κ receptors. Agonist-antagonist opioids are less prone (but not immune) to abuse because they cause less euphoria and are associated with less drug-seeking behavior and physical dependence.

Dosing data of these compounds are shown in Table 31-8. The agonist-antagonist compounds depress respiration in a manner similar to that of morphine, but ceiling effects exist (Table 31-9). Effects on the cardiovascular system differ among these compounds (Table 31-10).

PENTAZOCINE

Analgesia produced by pentazocine is primarily related to κ-receptor stimulation. Pentazocine is one half to one fourth as potent as morphine. Ceilings to both analgesia and respiratory depression occur after administration of 30 to 70 mg of pentazocine. Although the potential for abuse is less than with morphine, prolonged use of

TABLE 31-8 DOSING DATA FOR AGONIST-ANTAGONIST OPIOIDS AND MORPHINE

	Equianalgesic IM Dose (mg)	Duration of Analgesia (hr)	Oral-IM Efficacy Ratio
Morphine	10	4-5	1:6
Buprenorphine	0.3-0.4	>6	1:2*
Butorphanol	2	3-4	—
Nalbuphine	10	3-6	1:4-5
Pentazocine	40	3	1:3

IM, Intramuscular.
*Sublingual-intramuscular ratio.

TABLE 31-9 RESPIRATORY DEPRESSANT EFFECTS OF AGONIST-ANTAGONISTS COMPARED WITH MORPHINE

Drug	Correlation of Respiratory Depression With Dose
Morphine	Increases proportionally with dose
Buprenorphine	Ceiling effect at 0.15-1.2 mg in adults
Butorphanol	Ceiling effect at 30-60 μg/kg
Nalbuphine	Ceiling effect at 30 mg in adults
Pentazocine	Ceiling effect suggested, but difficult to study because of psychotomimetic effects

From Zola EM, McLeod DC: Comparative effects of analgesic efficacy of the agonist-antagonist opioids, Drug Intell Clin Pharm *17:411, 1983.*
*Low or moderate naloxone doses readily reverse the respiratory effects produced by therapeutic doses of all drugs listed, except buprenorphine.

TABLE 31-10 HEMODYNAMIC EFFECTS OF AGONIST-ANTAGONIST COMPOUNDS COMPARED WITH MORPHINE

Drug	Cardiac Workload	Blood Pressure	Heart Rate	Pulmonary Artery Pressure
Morphine	↓	↓	=↓	=↓
Buprenorphine	↓	↓	↓	?
Butorphanol	↑	=↑	=	↑
Nalbuphine	↓	=	=↓	=
Pentazocine	↑	↑	↑	↑

From Zola EM, McLeod DC: Comparative effects of analgesic efficacy of the agonist-antagonist opioids, Drug Intell Clin Pharm *17:411, 1983.*

pentazocine can lead to physical dependence. Nalorphine-like dysphoric side effects are common, especially after high doses (>60 mg) of pentazocine in older patients. The dysphoric effects of pentazocine can be reversed with naloxone. Pentazocine depresses myocardial contractility and increases arterial blood pressure, heart rate, systemic vascular resistance, pulmonary artery pressure, and left ventricular work index. Pentazocine also increases blood catecholamine levels. Pentazocine inhibits gastric emptying and gastrointestinal transit in rats, whereas U50488H, a pure κ-agonist, did not significantly inhibit either.[457] Therefore, one may speculate that pentazocine affects gastrointestinal function through a mechanism other than the opioid receptors.

Pentazocine has limited application because it is associated with a high incidence of postoperative nausea and vomiting, it provides limited analgesia, it partially antagonizes other opioids, and it can produce undesirable cardiovascular and psychotomimetic effects.

BUTORPHANOL

Butorphanol is an agonist at κ receptors. Its activity at μ receptors is either antagonistic or partially agonistic. It is five to eight times as potent as morphine and is available only in parenteral form. After intramuscular injection, the onset of effect is rapid, and peak analgesia occurs within 1 hour. Whereas the duration of action of butorphanol is similar to that of morphine, its plasma $t_{1/2}$ is only 2 to 3 hours. Although butorphanol (10 mg IM) causes as much respiratory depression as the same dose of morphine, higher doses reach a ceiling. Side effects after butorphanol include drowsiness, sweating, nausea, and CNS stimulation. In healthy volunteers, butorphanol (0.03 or 0.06 mg/kg IV) produces no or minimal cardiovascular changes. However, in patients with cardiac disease, butorphanol causes significant increases in cardiac index, left ventricular end-diastolic pressure, and pulmonary artery pressure.

Because butorphanol decreases the MAC for enflurane by only a small fraction, it cannot serve like the fentanyl congeners as an anesthetic. Butorphanol is subject to less abuse and has less addictive potential than does morphine or fentanyl. Acute biliary spasm can occur after butorphanol administration, but increases in biliary pressure are lower than after equipotent doses of fentanyl or morphine.

Transnasal butorphanol is effective in relieving migraine and postoperative pain.[458]

BUPRENORPHINE

Buprenorphine is a thebaine derivative, μ-receptor partial agonist, and it is similar in structure to morphine but approximately 33 times more potent. Whereas fentanyl dissociates rapidly from μ receptors ($t_{1/2}$ of 6.8 minutes), buprenorphine has a higher affinity and takes much longer ($t_{1/2}$ of 166 minutes). The onset of action of buprenorphine is slow, its peak effect may not occur until 3 hours, and the duration of effect is prolonged (<10 hours). The volume of distribution of buprenorphine is 2.8 L/kg, and its clearance is 20 mL/kg/minute. Plasma concentrations of the metabolites of buprenorphine (norbuprenorphine, buprenorphine-3-glucuronide, and norbuprenorphine-3-glucuronide) may approximate or exceed those of the parent drug. Glucuronide metabolites are biologically active and may contribute to the overall pharmacology of buprenorphine.[459]

Subjective effects (e.g., euphoria) of buprenorphine are similar to those of morphine. Buprenorphine produces depression of minute ventilation that levels off at doses higher than 3.0 μg/kg to approximately 50% of baseline, in contrast to the case of fentanyl, in which dose-dependent respiratory depression results in apnea at doses higher than 2.9 μg/kg[460] (Fig. 31-26). Buprenorphine has been successfully used for premedication (0.3 mg IM), as the analgesic component in balanced anesthesia (4.5 to 12 μg/kg), and for postoperative pain control (0.3 mg IM). Buprenorphine, like the other agonist-antagonist compounds, is not acceptable as a sole anesthetic, and its receptor kinetic profile restricts its usefulness if other μ-agonists are used. Opioid withdrawal symptoms develop slowly (5 to 10 days) after buprenorphine is discontinued following long-term use.

NALBUPHINE

Nalbuphine is an agonist-antagonist opioid that is structurally related to oxymorphone and naloxone. It binds to μ receptors as well as to κ and δ receptors. Nalbuphine acts as an antagonist at the μ receptor and an agonist at the κ receptor. Activation of supraspinal and

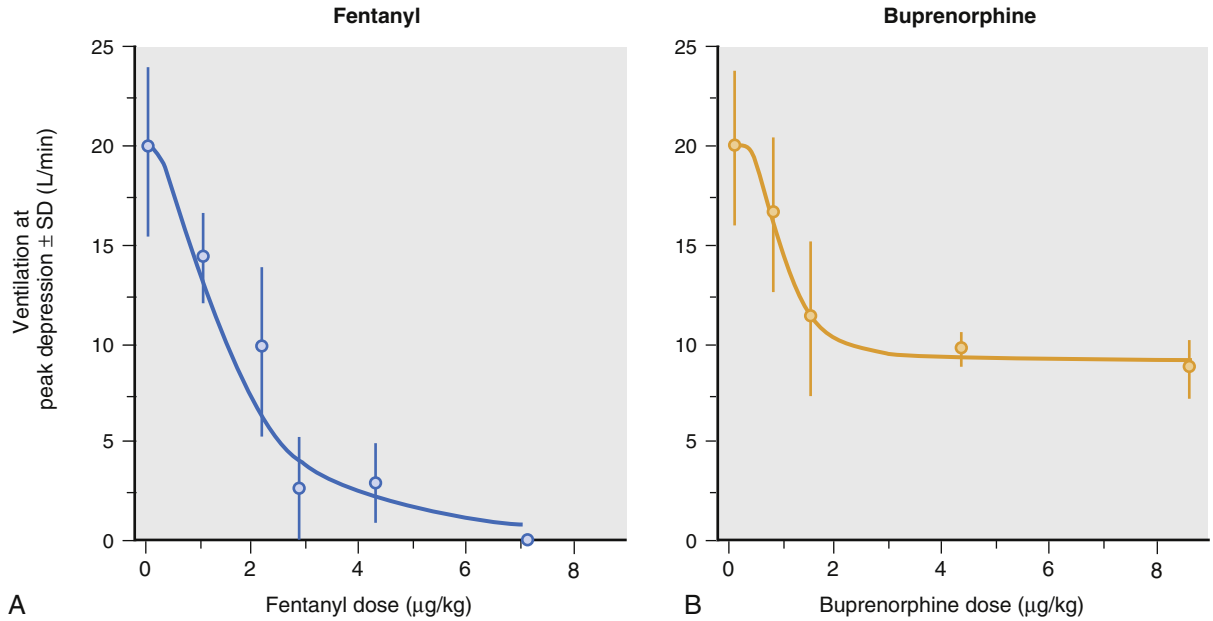


Figure 31-26. Dose-response relationships for reduction of minute ventilation induced by fentanyl (**A**) and buprenorphine (**B**). The response is the peak ventilatory depression at each dose. The *line through the data* is the fit to the Hill equation. Placebo is 0 μg/kg. Data are mean ± standard deviation. *(From Dahan A, Yassen A, Bijl H, et al: Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats,* Br J Anaesth *94:825-834, 2005.)*

spinal κ receptors results in limited analgesia, respiratory depression, and sedation. Nalbuphine, like other agonist-antagonist compounds, interferes with the analgesia produced by pure μ-agonists. In rats, coadministration of nalbuphine with morphine dose dependently blocked the development of morphine tolerance and dependence, without attenuation of the antinociceptive effect of morphine.[461] Nalbuphine is available only for parenteral use. The onset of effect is rapid (5 to 10 minutes), and its duration is long (3 to 6 hours) because of a long plasma elimination $t_{½}$ (5 hours).

Nalbuphine has been administered as an analgesic supplement for conscious sedation or balanced anesthesia and as an analgesic for postoperative and chronic pain problems. In patients undergoing myocardial revascularization, continuous infusion of nalbuphine (0.05 to 0.1 mg/kg/minute) and that of fentanyl (0.15 to 0.3 μg/kg/minute) were compared.[462] Nalbuphine lacked the ability to attenuate cardiovascular and hormonal responses to tracheal intubation and surgical procedures. The investigators concluded that continuous infusion of nalbuphine cannot be recommended for anesthesia in patients undergoing myocardial revascularization. For postoperative epidural PCA, the combination of hydromorphone (0.075 mg/mL) and nalbuphine (0.04 mg/mL) resulted in a lower incidence of nausea and a decreased need for bladder catheterization compared with hydromorphone alone.[463] A randomized double-blind controlled study in patients undergoing gynecologic surgical procedures demonstrated that the interaction between morphine and nalbuphine in an intravenous PCA admixture is additive, and the combination of the two drugs can decrease the incidence of pruritus.[464]

A prospective randomized double-blind study demonstrated that nalbuphine (4 mg IV) was as effective as ondansetron (4 to 8 mg IV) for prevention of intrathecal morphine-induced pruritus after cesarean delivery.[465] Whereas one study reported that nalbuphine provides a rapid and potent antishivering effect similar to that of meperidine,[466] a quantitative systematic review of randomized controlled trials did not support this conclusion.

DEZOCINE

Dezocine is slightly more potent and acts faster than morphine, with a similar duration, and it is a partial agonist of the μ receptors. Side effects are similar to those of morphine. Although dezocine was shown to be an effective alternative to fentanyl when administered during outpatient laparoscopy with propofol and N_2O, dezocine was associated with a high incidence of postoperative nausea and a delayed discharge time.[467] In adult patients who underwent arthroscopic surgical procedures performed using general anesthesia, dezocine (5 mg IV) and morphine (5 mg IV) were similarly effective for postoperative analgesia and caused similar side effects.[468] One report showed that intravenous dezocine (0.1 mg/kg) can effectively suppress cough induced by 5 μg/kg fentanyl.[469]

MEPTAZINOL

Meptazinol has been reported to cause minimal respiratory depression because of its selectivity for $μ_1$ receptors. In patients receiving meptazinol (2.5 mg/kg) with a barbiturate, no cardiovascular changes were observed during tracheal intubation, whereas blood pressure and heart rate were significantly increased in patients receiving fentanyl (5 μg/kg).[470] Side effects (nausea and vomiting) limit its use to the relief of severe pain.

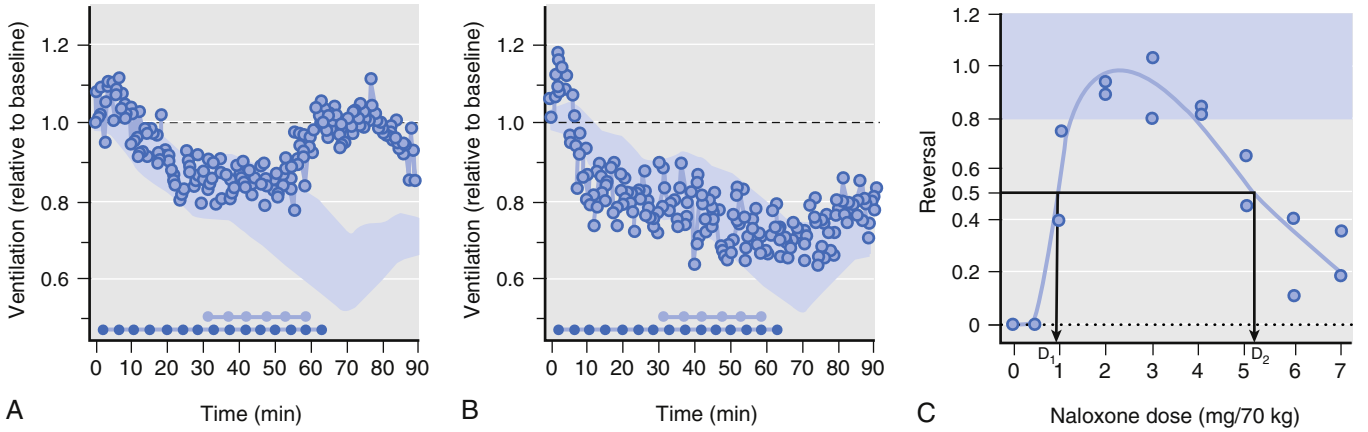


Figure 31-27. Reversal of buprenorphine-induced respiratory depression with naloxone depends on the correct naloxone dose window. Respiratory depression induced by 0.2 mg buprenorphine was reversed by naloxone 2 mg (**A**) and 6 mg (**B**) given over 30 minutes in one subject. The *blue field in the background* is the result of the placebo group in which saline was infused instead of naloxone. *Light blue dots* and *dark blue dots* represent buprenorphine and naloxone infusion, respectively. **C,** Influence of 0 (placebo) and 0.5 to 7 mg naloxone on 0.2 mg intravenous buprenorphine-induced respiratory depression. Reversal was calculated from the naloxone-induced change in ventilation, and it ranges from 0 (effect not different from placebo) to 1 (reversal to predrug baseline level). *(From van Dorp E, Yassen A, Sarton E, et al: Naloxone reversal of buprenorphine-induced respiratory depression,* Anesthesiology *105:51-57, 2006.)*

OPIOID ANTAGONISTS

NALOXONE

Clinically, opioid antagonists are used to restore spontaneous ventilation in patients who breathe inadequately after opioid overdoses or opioid anesthesia. In addition, opioid antagonists can reduce or reverse opioid-induced nausea and vomiting, pruritus, urinary retention, rigidity, and biliary spasm associated with numerous therapies employing opioids, such as neuraxial analgesic techniques. The reported potency ratio of naloxone to nalbuphine for antagonism of pruritic effects of epidural morphine was approximately 40:1.[471]

In one report, morphine requirements were significantly less in patients receiving naloxone, a finding suggesting that naloxone enhanced analgesia.[472] Proposed possible mechanisms for this apparent paradoxical effect of naloxone include enhanced release of endogenous opioids and opioid receptor up-regulation.

Although naloxone is generally considered a pure opioid receptor antagonist, it delays gastric emptying of saline or milk, as does morphine in the rat.[263] Furthermore, high-dose naloxone has partial agonistic activity on the μ- and κ-opioid receptors in cultured cells.[473]

Reversal of Respiratory Depression

In the early 1950s, nalorphine and levallorphan were evaluated as opioid antagonists. They were often found unacceptable because of a high incidence of side effects, as well as incomplete reversal of respiratory depression. Naloxone was introduced into clinical practice in the late 1960s. Side effects (increases in heart rate and blood pressure) and more serious complications (e.g., pulmonary edema) have been reported. The initial naloxone dose recommendations ranged from 0.4 to 0.8 mg. The onset of action of intravenous naloxone is rapid (1 to 2 minutes), and $t_{½}$ and duration of effect are short, approximately 30 to 60 minutes. If intravenous access is not available, naloxone, in doses similar to those given by the intravenous route, is effectively absorbed after intratracheal administration. Reversal with naloxone is limited by high affinity for and slow dissociation from the μ-opioid receptor of buprenorphine, and it depends on the buprenorphine dose and the correct naloxone dose window[474] (Fig. 31-27). Because respiratory depression from buprenorphine may outlast the effects of naloxone boluses or short infusions, a continuous infusion of naloxone may be required to maintain reversal of respiratory depression.[474]

Several mechanisms produce increases in arterial blood pressure, heart rate, and other significant hemodynamic alterations after naloxone reversal of opioids. These include pain, rapid awakening, and sympathetic activation not necessarily caused by pain. When patients receiving naloxone for opioid agonist reversal are hypothermic secondary to intraoperative heat loss, O_2 consumption and minute ventilation can increase two- to threefold.[475] Such metabolic demands also stress the cardiovascular system and increase cardiac output. In addition, greater degrees of hypercapnia at the time of opioid antagonism result in greater degrees of cardiovascular stimulation because of associated sympathetic stimulation. Opioid reversal may be particularly hazardous in patients with pheochromocytoma or chromaffin tissue tumors. However, investigators also reported that intravenous administration of 10 mg naloxone did not significantly change plasma catecholamine concentration and blood pressure.[476]

Recurrence of respiratory depression after naloxone results from the short $t_{½}$ of naloxone. "Renarcotization" occurs more frequently after the use of naloxone to reverse longer-acting opioids such as morphine. Although naloxone is active at μ, δ, and κ receptors, the drug has the greatest affinity for μ receptors, which mediate most potent opioid effects, including respiratory depression and analgesia. Careful titration of naloxone often can restore adequate spontaneous ventilation without reversal of adequate analgesia.

Other Applications

Naloxone may ameliorate the neurologic deficit following an ischemic or traumatic neurologic insult in animals.[477] In humans, a randomized controlled trial demonstrated that naloxone (a bolus of 5.4 mg/kg, followed by infusion at 4.0 mg/kg/hour for 23 hours) does not improve neurologic recovery after acute spinal cord injury.[478] However, the combined use of cerebrospinal fluid drainage and naloxone reduces the risk of paraplegia in thoracoabdominal aneurysm repair.[479] Naloxone may also have a therapeutic role in heat stroke disorders,[480] as well as in cholestasis-induced pruritus.[481] Although intravenous naloxone has been claimed to produce pain relief in opioid-resistant central poststroke pain, a double-blind trial concluded that intravenous naloxone was of no value in alleviating central poststroke pain.[482]

NALTREXONE

Naltrexone is a μ-, δ- and κ-opioid receptor antagonist. It is longer acting than naloxone (plasma $t_{½}$ of 8 to 12 versus 0.5 to 1.5 hours), and it is active when taken orally. A double-blind placebo-controlled study for patients undergoing cesarean section indicated that naltrexone (6 mg) was an effective oral prophylactic against the pruritus and vomiting associated with intrathecal morphine, but it was associated with a shorter duration of analgesia.[483]

NALMEFENE

Nalmefene has a greater preference for μ than δ or κ receptors. Nalmefene is equipotent to naloxone. Nalmefene is long acting after oral (0.5 to 3.0 mg/kg) and parenteral (0.2 to 2.0 mg/kg) administration. Bioavailability after oral administration is 40% to 50%, and peak plasma concentrations are reached in 1 to 2 hours. The mean terminal elimination $t_{½}$ of nalmefene is 8.5 hours, compared with 1 hour for naloxone. Prophylactic administration of nalmefene significantly decreased the need for antiemetics and antipruritic medications in patients receiving intravenous PCA with morphine.[484]

METHYLNALTREXONE

Methylnaltrexone is the first quaternary ammonium opioid receptor antagonist that does not cross the blood-brain barrier.[256] It can reverse the effects of opioid medications mediated by peripheral opioid receptors, whereas the opioid effects mediated by opioid receptors in the CNS, such as analgesia, are not affected. Delayed gastric emptying induced by 0.09 mg/kg morphine could be attenuated by 0.3 mg/kg methylnaltrexone in healthy volunteers.[262] Investigators also reported that methylnaltrexone was effective for reversal of constipation resulting from long-term methadone use.[485] Because methylnaltrexone does not cross the dura, it could have the potential to reverse peripherally mediated side effects of epidural opioids.[486] Randomized double-blind placebo-controlled studies have shown the effectiveness of methylnaltrexone and alvimopan, another peripherally acting opioid receptor antagonist, in the management of postoperative ileus.[256]

DRUG INTERACTONS WITH OPIOIDS

GENERAL PRINCIPLES

Opioids are frequently combined with other anesthetic drugs to produce optimal anesthetic conditions. In anesthesia, most drugs concomitantly administered interact. Although some of these interactions are intentionally sought, others are unwanted and adverse. The three general types of mechanisms of drug interactions are pharmaceutical, pharmacokinetic, and pharmacodynamic.[487]

Pharmaceutical interactions are chemical, as illustrated when an alkaline solution of thiopental and an acidic solution of succinylcholine precipitate when they are simultaneously administered by the intravenous route.

Pharmacokinetic interactions occur when the administration of one agent alters the pharmacokinetics or disposition of another. Hemodynamic changes induced by one agent can affect the pharmacokinetic behavior of the other agent. Sufentanil, which has a greater hepatic extraction ratio than does alfentanil, is more likely to be affected by decreases in hepatic blood flow. Cimetidine can prolong opioid effects by decreasing hepatic blood flow or by diminishing hepatic metabolism. Opioid plasma levels also increase in the presence of propofol.[488] Decreased opioid metabolism, by the CYP3A4 isoform of the cytochrome P450 enzyme responsible for the oxidative metabolism of more than 50 drugs, may also underlie pharmacokinetic interactions. A wide range of chemical compounds, including many drugs, can interact with the cytochrome P450 system and cause either increased activity (enzyme induction) or enzyme inhibition (Box 31-5).[487] Alfentanil, but not sufentanil, may have prolonged action as a result of impaired metabolism in patients receiving erythromycin.[489,490]

Pharmacodynamic interactions between opioids and inhaled anesthetic agents were assessed with classic MAC reduction evaluations in animals and humans. Although marked synergism between opioids and inhaled anesthetic agents occurs with analgesic doses of opioids, the MAC reduction by opioids has a ceiling effect. The pharmacodynamic synergism between opioids and sedative-hypnotics such as propofol is profound. Choosing an opioid with a short context-sensitive $t_{½}$ allows greater doses of that opioid to be administered, along with reduced doses of propofol, without compromising the time for recovery from anesthesia. Thus, the optimal plasma level of propofol is estimated to be approximately 30% less when it is combined with remifentanil instead of alfentanil.[488]

Drug dosing regimens and plasma concentrations of opioid and sedative-hypnotics that provide optimal hemodynamic control during a range of noxious stimuli are necessary. However, complicating our understanding of drug interactions is the observation that the same degree of interaction does not apply across different types of stimuli.

BOX 31-5 *Drugs That Inhibit or Induce Cytochrome P450 Enzymes*

INHIBITORS

Antibiotics
- Macrolides
- Troleandomycin
- Erythromycin
- Fluoroquinolones
- Isoniazid

Azole antifungal drugs
- Ketoconazole
- Itraconazole

Calcium entry blockers
- Diltiazem
- Verapamil

Omeprazole
Cimetidine
Propofol
Grapefruit juice

INDUCERS

Barbiturates
Antiepileptics
- Carbamazepine
- Phenytoin
- Primidone

Rifampicin
Dichloralphenazone
Ethanol
Tobacco smoke

From Bovill, JG: Adverse drug interactions in anesthesia, J Clin Anesth *9(Suppl):3S, 1997.*

SEDATIVE-HYPNOTICS

See also Chapter 30.

Benzodiazepines

Alfentanil reduces the median effective dose (ED_{50}) of midazolam for the induction of anesthesia in a dose-dependent fashion. On the contrary, with regard to the antinociceptive effect, the interaction between these two types of drugs may be less than additive.[491] Midazolam enhances opioid-induced antinociception at the spinal level but inhibits it at the supraspinal level.[492] Many studies reveal that benzodiazepine-opioid interactions for many properties other than analgesia are synergistic (supraadditive). Both the cardiovascular and respiratory actions of opioids can be significantly altered by the concomitant administration of benzodiazepines.[493] In anesthetized rabbits, fentanyl and midazolam synergistically caused depression of phrenic nerve activity.[494] Combinations of benzodiazepines and opioids, although occasionally preserving ventricular function, can cause significant and at times profound decreases in blood pressure, cardiac index, heart rate, and systemic vascular resistance. Fluid loading may attenuate circulatory depression that occurs when benzodiazepines and opioids are combined.

Barbiturates

Barbiturates can potentiate or produce hypotension if a large dose is administered with opioids. Hypotension after barbiturate-opioid combination results from venodilatation, decreased cardiac filling, myocardial depression, and decreased sympathetic nervous system activity. Reducing induction doses of barbiturates administered concomitantly with opioids is recommended.

Propofol

Administration of propofol-opioid combinations provides unconsciousness and block responses to noxious stimuli. However, when given as an intravenous bolus for induction of anesthesia, propofol can create moderate to severe preintubation hypotension. Propofol-fentanyl and propofol-sufentanil anesthesia for coronary artery bypass surgery may provide acceptable conditions, but mean arterial pressure can decrease to levels that may jeopardize coronary perfusion, especially during induction of anesthesia. In healthy volunteers, the addition of alfentanil (effect-site concentration of 50 or 100 ng/mL) did not affect the changes in the BIS induced by propofol, but it blocked the BIS increase induced by painful stimuli.[495] In patients undergoing spine fusion, infusion of fentanyl (blood levels of 1.5 to 4.5 ng/mL) reduced the infusion rate of propofol necessary to maintain mean arterial pressure but delayed spontaneous eye opening and recovery of orientation.[360] In patients undergoing ambulatory gynecologic laparoscopy, the administration of fentanyl (25 to 50 μg IV) at the time of induction of anesthesia reduced the maintenance propofol requirement but failed to provide effective postoperative analgesia and increased the need for postoperative use of antiemetics.[496] Pharmacokinetic interaction, as well as pharmacodynamic interaction, between propofol and opioids has been reported. Target-controlled infusion of alfentanil (target concentration of 80 ng/mL) was shown to increase the blood propofol concentration by 17% and decrease the elimination clearance, distribution clearance, and peripheral volume of distribution of propofol.[497]

Etomidate

Etomidate can be combined in low doses with opioids with little loss of cardiovascular stability. In patients scheduled for coronary artery bypass grafting, etomidate (0.25 mg/kg) combined with fentanyl (6 μg/kg) resulted in less hypotension after induction and intubation than did propofol (1 mg/kg) combined with fentanyl (6 μg/kg).[498]

Ketamine

A prospective randomized double-blind controlled study demonstrated that intraoperative and postoperative administration of ketamine for the first 48 hours postoperatively (2 μg/kg/minute after a 0.5 mg/kg bolus) improved postoperative analgesia with a significant decrease of morphine consumption.[499] Furthermore, investigators reported that small doses of ketamine and memantine, a long-acting oral NMDA-receptor antagonist, were effective in managing intractable pain in an opioid-tolerant patient.[500] Webb and co-workers reported that low-dose ketamine could be a useful addition to perioperative tramadol administration in patients undergoing abdominal surgical procedures.[501]

INHALED ANESTHETIC AGENTS

Volatile anesthetic agents are frequently combined with opioids to ensure amnesia and to promote immobility and hemodynamic stability (see Chapter 26). Clinical trials of opioids supplemented with volatile anesthetic agents for cardiac surgery demonstrated well-preserved cardiac output and minimal decreases in mean arterial blood pressure.[502] Myocardial ischemia may not, however, always be ameliorated by approaches that combine opioids with potent inhaled anesthetic agents in spite of apparent "good" hemodynamic control. Some of the potent inhaled anesthetic drugs can increase sympathetic nervous system activity and may increase the risk of myocardial ischemia in the patient with cardiac disease.[503] Prior administration of fentanyl, in doses as low as 1.5 μg/kg, can markedly attenuate such responses. Alfentanil (10 μg/kg) is also effective in attenuating these effects.

MUSCLE RELAXANTS

Pancuronium bromide has been frequently used for muscle relaxation during high-dose opioid anesthesia (see also Chapter 34). The vagolytic action of pancuronium can attenuate opioid-induced bradycardia and support blood pressure. In patients undergoing coronary artery bypass grafting who were administered sufentanil (3 to 8 μg/kg), pancuronium (120 μg/kg) caused significant increases in mean arterial pressure, heart rate, and cardiac output but did not induce myocardial ischemia.[504]

Combinations of vecuronium and high doses of opioids may produce negative chronotropic and inotropic effects that result in decreases in heart rate, cardiac output, and blood pressure and increases in the need for vasopressor support. In patients scheduled for coronary artery surgery who received 40 μg/kg sufentanil in combination with vecuronium (0.1 mg/kg), heart rate, mean arterial pressure, and systemic vascular resistance decreased from baseline values after tracheal intubation, with no significant change in cardiac output or evidence of new myocardial ischemia.[505]

In patients anesthetized with fentanyl (50 μg/kg) and scheduled to undergo elective coronary artery bypass grafting, rocuronium (0.6 mg/kg; approximately equivalent to 2 × ED_{95} doses) was associated with minimal changes in hemodynamic variables, including increases in stroke volume index (+15%) and cardiac index (+11%) and a decrease in pulmonary capillary wedge pressure (–25%).[506] In patients undergoing coronary artery bypass surgery performed using fentanyl anesthesia, mivacurium (0.15 or 0.2 mg/kg) produced decreases in mean arterial pressure and systemic vascular resistance index possibly mediated by histamine release, whereas atracurium (0.5 mg/kg) produced no significant hemodynamic changes.[507]

MONOAMINE OXIDASE INHIBITORS

MAOIs can underlie the most serious and potentially fatal opioid-other drug interaction. The combination of meperidine and MAOIs can induce the serotonin syndrome, which is caused by excess serotonin availability in the CNS at the serotonin type 1A (5-HT_{1A}) receptor. The serotonin syndrome is characterized by confusion, fever, shivering, diaphoresis, ataxia, hyperreflexia, myoclonus, or diarrhea. The phenylpiperidine series opioids, including meperidine, tramadol, and methadone, appear to be weak serotonin reuptake inhibitors and have all been involved in serotonin toxicity reactions with MAOIs, whereas morphine, codeine, oxycodone, and buprenorphine are known not to be serotonin reuptake inhibitors and do not precipitate serotonin toxicity with MAOIs.[508] Alfentanil can be used with MAOIs without complications.[509,510]

CALCIUM CHANNEL BLOCKERS

Because opioids can inhibit voltage-dependent Ca^{2+} channel activity through the activation of G proteins, [2]opioid action may possibly be potentiated by Ca^{2+} channel blockers. Numerous animal studies and a few clinical studies documented that opioid-induced analgesia is potentiated by L-type Ca^{2+} channel blockers. However, another report noted that L-type Ca^{2+} channel blockers do not potentiate morphine analgesia at clinically relevant doses.[511] N-type Ca^{+} channels are involved in the release of neurotransmitters from sensory neurons in the spinal cord. The intrathecal administration of a blocker of this channel, ω-conotoxin GVIA, produced antinociception and interacted synergistically with opioids at the spinal cord level.[512]

MAGNESIUM

Magnesium has antinociceptive effects, probably because of its antagonistic action on the NMDA receptor. Intravenous administration of magnesium sulfate (50 mg/kg preoperatively and 8 mg/kg/hour intraoperatively) significantly reduced intraoperative and postoperative fentanyl requirement.[513] However, passage of magnesium across the blood-brain barrier is limited. Intrathecal administration of fentanyl (25 μg) in combination with magnesium sulfate (50 mg) provided significantly prolonged analgesia compared with fentanyl alone in patients requesting analgesia for labor.[514] It is likely that magnesium can potentiate opioid analgesia by both central and peripheral mechanisms.[515] A randomized double-blind prospective study showed that a relatively high dose of remifentanil (0.2 μg/kg/minute) enhances periincisional hyperalgesia in patients undergoing thyroidectomy, and intraoperative magnesium sulfate (30 mg/kg at induction, followed by 10 mg/kg/hour) can prevent remifentanil-induced hyperalgesia.[516]

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

NSAIDs, such as ibuprofen, diclofenac, or ketorolac, have been perioperatively administered to reduce opioid requirement. Perioperative administration of diclofenac (75 mg twice daily) reduced morphine consumption and the incidence of adverse effects such as sedation and nausea after total abdominal hysterectomy.[517] In a randomized double-blind trial, 0.1 mg/kg morphine was superior to 30 mg ketorolac in providing postoperative pain relief; however,

the addition of ketorolac to morphine reduced the postoperative opioid requirement and opioid-related side effects in the early postoperative period.[518] NSAIDs are thought to prevent opioid-induced hyperalgesia or acute opioid tolerance that could cause an increase in postoperative opioid requirement. A randomized double-blind placebo-controlled study showed that 8 mg of lornoxicam prevented an increase in postoperative morphine consumption induced by intraoperative fentanyl in female patients undergoing abdominal hysterectomy with spinal anesthesia.[519]

Acetaminophen has analgesic and antipyretic effects similar to those of NSAIDs, but it has a weak antiinflammatory effect. Acetaminophen has significant fentanyl-sparing effects and reduces side effects when it is combined with fentanyl in intravenous parent- or nurse-controlled analgesia for postoperative pediatric pain management.[520]

GABAPENTIN

Gabapentin, a structural analogue of γ-aminobutyric acid, binds to the $\alpha_2\delta$ subunit of the spinal voltage-gated Ca^{2+} channel and has analgesic effects in neuropathic pain. Investigators suggested that both pharmacodynamic and pharmacokinetic interactions between morphine and gabapentin lead to increased analgesic effects.[521] Furthermore, intrathecal administration of gabapentin prevents the development of opioid tolerance induced by repeated intrathecal injections of morphine.[522] Systemic and intrathecal applications of gabapentin may possibly prevent the development of opioid-induced hyperalgesia.[523]

ANTIDEPRESSANTS

Tricyclic antidepressants may cause respiratory depression in patients with chronic obstructive pulmonary diseases, and reduced CO_2 sensitivity has also been reported in patients receiving tricyclic antidepressants. An animal study demonstrated that pretreatment with amitriptyline increases morphine-induced hypercarbia through pharmacodynamic processes.[524] This finding suggests that morphine doses should be reduced with careful titration if patients are receiving concomitant treatment with tricyclic antidepressants.[524] Perioperative administration of duloxetine, a potent selective serotonin and norepinephrine reuptake inhibitor, can reduce the requirement for morphine after knee replacement surgery.[525]

DIPHENHYDRAMINE

Diphenhydramine, a histamine H_1-receptor antagonist, is used as a sedative, an antipruritic, and an antiemetic agent. When administered alone, this drug modestly stimulates ventilation by augmenting the interaction of hypoxic and hypercarbic ventilatory drives. Diphenhydramine counteracts the alfentanil-induced decrease in the slope of the ventilatory response to CO_2.[526]

LOCAL ANESTHETIC AGENTS

Systemic administration of local anesthetic agents can significantly reduce pain and allow more rapid discharge. Perioperative systemic lidocaine significantly reduced opioid requirements in the ambulatory setting.[527]

Complete references available online at expertconsult.com

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Chapter 32

Nonopioid Pain Medications

LUCY CHEN • JIANREN MAO

Key Points

- With a better understanding of pain pathways and mechanisms, it has been recognized that ion channels play an important role in the transduction, transmission, and modulation of nociceptive signals. This opens a new avenue of developing novel therapeutic agents for the treatment of chronic pain, particularly neuropathic pain.
- Although the exact mechanism of action remains unclear for many drugs listed in this chapter, they often are a component of a multidrug treatment strategy that has been increasingly used for the management of chronic pain conditions.

INTRODUCTION

Recent advances in our understanding of pain mechanisms allow treatment of chronic pain conditions by a variety of nonopioid pain medications. Besides acetaminophen and nonsteroidal antiinflammatory drugs, several new categories of nonopioid pain medications can be used for the management of chronic pain, particularly neuropathic pain. Examples of nonopioid pain medications include drugs that block voltage-sensitive sodium channels and voltage-sensitive calcium channels, facilitate opening of chloride channels, increase function of the endogenous γ-aminobutyric acid (GABA) system, and modulate the N-methyl-D-aspartate (NMDA) receptor activity. In particular, ion channel blockers possess the antihyperalgesic effect by targeting specific mechanisms of pathologic pain, although most analgesics in this category do not necessarily produce the typical analgesic effect (i.e., raising the pain threshold above the normal baseline).[1]

This chapter focuses on describing several ion channel blockers that are commonly used in the treatment of chronic pain conditions, as listed in Box 32-1. They are grouped into two categories: calcium channel blockers and sodium channel blockers.

CALCIUM CHANNEL BLOCKERS

Opening of calcium channels is an important step of synaptic transmission because it facilitates release of neurotransmitters and neuromodulators from presynaptic sites. Changes in intracellular calcium concentration also modulate cell membrane excitability and initiate a cascade of intracellular responses. Therefore, blocking calcium channels can play a significant role in modulating both nociceptive and antinociceptive processes. Drugs that reduce calcium influx into the intracellular compartment of neuronal or glial cells may be used as adjunctive or alternative medications for the treatment of various pain conditions, particularly chronic neuropathic pain conditions. Gabapentin, pregabalin, zonisamide, ziconotide, and levetiracetam are examples of drugs that block calcium channels as a part of their mechanisms of action.

GABAPETIN

Gabapentin was initially approved by the U.S. Food and Drug Administration (FDA) as an anticonvulsant and later for the treatment of neuropathic pain conditions. Although gabapentin's mechanism of action is unclear, it does block voltage-gated calcium channels by binding to the α_2-δ subunit,[2] producing a reduced calcium influx. The blocking calcium influx reduces the release of glutamate and substance P from primary nociceptive afferents, thereby modulating nociceptive transmission. Gabapentin can treat painful diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, complex regional pain syndrome, and painful peripheral neuropathies caused by human immunodeficiency virus (HIV), cancer, multiple sclerosis, and spinal cord injury (see also Chapters 31 and 64).

Painful diabetic neuropathy is a debilitating condition commonly seen in patients with diabetes mellitus (see also Chapter 39). Up to 25% of patients with diabetes may suffer from spontaneous pain, allodynia, hyperalgesia, paresthesias, and other pain symptoms.[3] Postherpetic neuralgia is another common neuropathic pain condition (see also Chapter 64). The incidence of postherpetic neuralgia is estimated to be 9% to 34%, which increases significantly with age (see also Chapter 80). Multiple classes of drugs have been tried to treat pain associated with painful diabetic neuralgia and postherpetic neuralgia, including tricyclic antidepressants (TCAs) such as amitriptyline, nortriptyline, imipramine, and desipramine. Because of the significant

BOX 32-1 *Ion Channel Blockers as Pain Medications (Recommended Dosing)*

Calcium Channel Blockers

Gabapentin: Starting dose 100-300 mg/day; titrating up to 1800-3600 mg/day
Pregabalin: Starting dose: 75-150 mg/day; titrating up to 450-600 mg/day
Zonisamide: Starting dose: 50-100 mg/day; titrating up to 450 mg/day
Ziconotide: Starting dose: 0.1 mcg/hr; titrating up to 0.4 mcg/hr
Levetiracetam: Starting dose: 250-500 mg/day; titrating up to 2000 mg/day

Sodium Channel Blockers

Lidocaine: Used in a lidocaine test: 1 mg/kg via slow intravenous push or drip
Mexiletine: Starting dose: 150-300 mg/day; titrating up to 600 mg/day
Carbamazepine: Starting dose: 100 mg/day; titrating up to 600 mg/day
Oxcarbazepine: Starting dose: 150 mg/day; titrating up to 900 mg/day
Lamotrigine: Starting dose: 25-50 mg/day; titrating up to 250-500 mg/day
Topiramate: Starting dose: 50-100 mg/day; titrating up to 300-400 mg/day

side effects of TCAs, gabapentin has been increasingly used in these pain conditions.

Gabapentin is effective in reducing several salient symptoms of neuropathic pain such as burning and shooting pain, allodynia, and hyperalgesia.[4,5] The number needed to achieve at least 50% pain relief with antidepressants and gabapentin are 3.4 and 2.7, respectively.[6] Although both antidepressants and gabapentin may provide moderate pain relief, antidepressants have major side effects.

The recommended gabapentin dose range is 1800 to 3600 mg/day, starting at 100 to 300 mg/day and increasing 100 to 300 mg every 1 to 3 days. Adverse effects are usually mild to moderate and typically subside within 7 to 10 days after the treatment is started. In general, a slow titration process can significantly reduce some otherwise intolerable side effects, such as dizziness. In addition to its use as a monotherapy, gabapentin has been extensively used in multidrug therapy in conjunction with TCAs and other anticonvulsants.[1] Multidrug therapy provides better pain control, requiring a smaller dose range for each drug included in the regimen. Gabapentin also can treat complex regional pain syndrome, phantom pain, trigeminal neuralgia, cancer-related neuropathic pain, multiple sclerosis, spinal cord injury, HIV-associated painful sensory neuropathy, and glossopharyngeal neuralgia (see also Chapter 64). The role of gabapentin in postoperative pain management remains unclear (see also Chapter 98).

PREGABALIN

Pregabalin is an anticonvulsant that has a high affinity to the α_2-δ subunit of voltage-sensitive calcium channels. The mechanism of action of pregabalin is similar to that of gabapentin. Pregabalin decreases calcium influx, thereby reducing the release of excitatory neurotransmitters, including glutamate, substance P, and calcitonin gene-related peptide. Pregabalin has no activity on GABA or benzodiazepine receptors; therefore, it has no significant drug-drug interactions with such agents.

Pregabalin has been used to treat painful diabetic neuropathy and postherpetic neuralgia with a significant therapeutic effect.[7,8] It has a quick onset, and, in some cases, pain reduction can be expected on the first day of treatment with pregabalin (300 mg/day). Sustainable sleep improvement is also observed 1 week after the therapy is initiated. Common side effects are dizziness, somnolence, and mild to moderate peripheral edema.[9] Moreover, pregabalin (at an average dose of 450 mg/day) is effective with patients with fibromyalgia, who often have clinical presentations including diffuse musculoskeletal pain, sleep disturbance, and fatigue.

ZONISAMIDE

Zonisamide blocks both voltage-sensitive sodium channels and N-type calcium channels. Recent studies suggest that zonisamide may be used to treat mania, Parkinson disease, and central poststroke pain or to provide migraine prophylaxis.[10,11] Its possible mechanisms of action include modulation of monoamine neurotransmitter release and free radical scavenging. Zonisamide is effective for the treatment of painful diabetic neuropathy (540 mg/day). The tolerability of zonisamide is difficult to assess because it is often used in multidrug therapy. Thus, the effectiveness and side effects of zonisamide remain limited.

ZICONOTIDE

Ziconotide is a synthetic peptide analogue of omega conotoxin derived from a marine snail, *Conus magus*. Ziconotide potently and selectively blocks N-type voltage-sensitive calcium channels. This drug is approved by the FDA only for intrathecal use in patients with severe pain who are refractory to other treatment options, including intrathecal morphine. In early clinical trials, ziconotide exhibited severe central nervous system and psychiatric adverse effects with an initial intrathecal infusion rate of 0.4 mcg/hr and frequent dosing titration.[12] More recently, ziconotide has been shown to be effective for chronic pain conditions resulting from cancer, acquired immunodeficiency syndrome, and trigeminal neuralgia.[13,14] The role of ziconotide in postoperative pain management is less clear. Given ziconotide's significant side effects and restrictive delivery route, its routine use in acute postoperative pain management is not well justified (see also Chapter 98).

The initial infusion rate of ziconotide should start at 0.1 mcg/hr, with a slow titration of no more than 2 to 3 times the initial dose per week. An implanted intrathecal infusion system is required for the long-term use of this therapy if the initial ziconotide trial is effective.[15] Patients with severe psychiatric disorders may not be proper candidates for this therapy. Ziconotide may be advantageous over intrathecal morphine because patients do not develop tolerance after a prolonged use of ziconotide.

However, adverse neurologic effects associated with ziconotide therapy will require careful patient selection and monitoring. Using a smaller dose increment will help avoid systemic toxicity.

LEVETIRACETAM

Levetiracetam is an anticonvulsant that has recently received approval from the FDA for epilepsy treatment.[16] Its mechanisms of action are less clear because it may have effects on several neurotransmitter systems, including dopaminergic, glutamatergic, and GABAergic systems. But at least one of its mechanisms of action is due to inhibition of N-type voltage-sensitive calcium channels. Levetiracetam improves neoplastic plexopathies, painful peripheral neuropathy, and postherpetic neuralgia. Levetiracetam also has been used in migraine headache prophylaxis. The dose range is 500 to 2000 mg/day. At this dose range, levetiracetam is well tolerated in clinical trials. Common adverse effects are dry eyes and dizziness.[19]

SODIUM CHANNEL BLOCKERS

Sodium channels are primarily involved in nerve conduction. Sodium channels can be divided into two general categories based on their sensitivity to tetrodotoxin (TTX): TTX-sensitive (TTX-S) and TTX-resistant (TTX-R) sodium channels. TTX-S sodium channels are expressed mainly in large and medium dorsal root ganglion neurons, whereas TTX-R sodium channels are expressed mainly in small-diameter dorsal root ganglion neurons, including C-afferent neurons. Expression of both TTX-S and TTX-R sodium channels is likely to be altered when peripheral nerves are injured or severed (axotomy), producing aberrant high-frequency spontaneous ectopic discharges. Sodium channel blockers at a proper dose range are believed to suppress ectopic discharges without blocking normal nerve conduction. Several representative sodium channel blockers include lidocaine, mexiletine, carbamazepine, oxcarbazepine, lamotrigine, and topiramate.[20]

LIDOCAINE

Lidocaine is a local anesthetic and cardiac antiarrhythmic (see also Chapters 36 and 38). Since the 1980s, intravenous administration of lidocaine has been used as a diagnostic tool and, in some cases, a therapeutic tool for intractable neuropathic pain[20] (see also Chapter 64). This treatment modality has been shown to improve chronic pain conditions induced by neurologic diseases, including stroke, neurogenic facial pain, and myofascial pain.[21,22] Up to 78% of cases are associated with a positive outcome when intravenous lidocaine is used.[23] A major pitfall of intravenous lidocaine treatment is its short duration, which requires rather frequent treatment sessions.

Topical 5% lidocaine patch provides a local analgesic effect with a minimum systemic effect. Lidocaine patch has been used in patients with neuropathic pain conditions such as painful diabetic neuropathy, postherpetic neuralgia, and peripheral neuropathies. It reduces allodynia and hyperalgesia associated with such conditions.[24] Although the evidence remains weak and unclear, lidocaine patch has been used to treat chronic lower back pain. In some cases, lidocaine patch has become a part of multidrug therapy, such as a combination of topical lidocaine patch and gabapentin.[1]

MEXILETINE

Mexiletine is an oral lidocaine congener. It may be used to overcome the shortcoming of transient pain relief with intravenous lidocaine. In many cases, intravenous lidocaine is used as a test to determine whether the intended lidocaine treatment is effective. When a positive response is achieved, oral mexiletine is administered to maintain the therapeutic effect.[17,18] This treatment regimen reduces pain related to painful diabetic neuropathy refractory to other therapies.[25] Mexiletine alone has been used to treat phantom pain and pain after spinal cord injury.[25]

Fibromyalgia and myofascial pain are other clinical conditions that may be responsive to a lidocaine and mexiletine treatment regimen. In addition, anecdotal reports suggest that oral mexiletine may be used to treat primary erythromelalgia, metastasis bone pain, and headaches.

CARBAMAZEPINE

A primary mechanism of action of carbamazepine is sodium channel blockade, which is considered to decrease spontaneous firing of Aδ-fibers and C-fibers. Carbamazepine was approved by the FDA to treat trigeminal neuralgia, a neuropathic pain condition characterized by episodic lightning, lancinating, or shooting pain along the trigeminal nerve distribution.[26] Carbamazepine has been used for over 4 decades and was superior to placebo in a number of clinical trials. It was once considered a gold standard and remains a treatment of choice for trigeminal neuralgia, with a response rate of 89% within 5 to 14 days after the treatment is initiated. However, carbamazepine has significant drug-drug interactions and includes a long list of adverse effects, such as central nervous system side effects. The FDA has issued black box warnings about this drug, including aplastic anemia and agranulocytosis. Therefore, its clinical utility is rather limited considering newer anticonvulsants are available with fewer and less severe side effects.

OXCARBAZEPINE

Oxcarbazepine is an analogue of carbamazepine, which acts as a sodium channel blocker and stabilizes neuronal membrane. In contrast to carbamazepine, oxcarbazepine has fewer drug-drug interactions and side effects, particularly severe blood dyscrasias. The most common side effects of oxcarbazepine are dizziness, drowsiness, hypotension, nausea, and asymptomatic mild hyponatremia. Oxcarbazepine has been used to treat intractable trigeminal neuralgia refractory to other anticonvulsants.[27] With a median dose of 750 mg/day, this new drug appears to have the same efficacy as carbamazepine in the treatment of trigeminal neuralgia but a much lower incidence of side effects.

Oxcarbazepine also reduces pain associated with painful diabetic neuropathy and complex regional pain syndrome. For patients with postherpetic neuralgia that is unresponsive to carbamazepine and gabapentin, oxcarbazepine, starting at 150 mg/day and titrating up to a maintenance dose of 900 mg/day, may be a promising drug because it significantly reduces allodynia related to postherpetic neuralgia. Oxcarbazepine appears to be well tolerated and may serve as a reasonable alternative to other sodium channel blockers.

LAMOTRIGINE

Lamotrigine has multiple mechanisms of action although it also blocks both sodium and calcium channels.[28] Lamotrigine is effective in the treatment of trigeminal neuralgia, neuralgia after nerve section, and pain related to HIV neuropathy. With a daily dose of lamotrigine 75 to 300 mg, the intensity of burning and shooting pain is relieved by 33% to 100%, and the frequency of shooting pain attack is reduced by 80% to 100%. In patients with spinal cord injury, lamotrigine decreases overall pain sensation below the level of injury in patients with incomplete spinal cord injury but has little effect on spontaneous and evoked pain in patients with complete spinal cord injury.

A typical starting dose for lamotrigine is 25 to 50 mg/day, which can be slowly titrated up over 2 to 3 weeks to 250 to 500 mg/day in divided doses. Tolerability is usually low at high doses (>300 mg/day). Up to 10% of patients may have rashes after taking this medication, with a 3 in 1000 incidence of Stevens-Johnson syndrome. Other side effects are mild dizziness, somnolence, nausea, and constipation.

TOPIRAMATE

Topiramate is another drug that has multiple mechanisms of action. However, at least one of its actions is to block voltage-sensitive sodium channels. It also may potentiate GABA inhibitory action, block voltage-sensitive calcium channels, and inhibit subtypes of glutamate receptors (non-NMDA receptors). Topiramate can cause significant weight loss (up to 7%), a side effect that could be beneficial for certain patient populations. Topiramate, at a daily dose of 400 mg or above, attenuates neuropathic pain, improves sleep quality, and reduces body weight.[27] When used to treat chronic lumbar radicular pain, the effect of topiramate is inconclusive because of a high dropout rate and frequent side effects. However, topiramate 30 to 80 mg/day is superior to placebo for the treatment of chronic tension, migraine, and cluster headaches with a substantial tolerability.[29]

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Chapter 33

Intravenous Drug Delivery Systems

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Key Points

- The pharmacokinetics of anesthetic drugs is described by multicompartment models. Accurate intravenous drug delivery requires adjusting the maintenance infusion rates to take into account the accumulation of the drug in the peripheral tissues.
- *Biophase* is the site of action of a drug. Initiation, maintenance, and titration of intravenous anesthetics must account for the delay in equilibration between plasma and the site of drug effect.
- Some drug effects directly reflect the concentration of the drug in the biophase (direct effect models). Other drug effects reflect the alteration of feedback systems by anesthetics (indirect effect models). The influence of opioids on ventilation reflects the dynamic influence of opioids on the feedback between ventilation and carbon dioxide and is thus an example of an indirect drug effect.
- The target concentration in the effect site is the same as the target concentration in plasma at steady state. Effect-site requirements are influenced by patient physiologic characteristics, surgical stimulation, and concurrent drug administration. Ideally, target concentrations should be set for the hypnotic (volatile anesthetic or propofol) and the analgesic (opioid) that properly accounts for the synergy between them.
- To achieve an effective target concentration, the conventional teaching of administering an initial dose as calculated by the product of target concentration and volume of distribution, followed by a maintenance rate as calculated as the product of target concentration and clearance, is inaccurate. The initial dose may be calculated as the product of target concentration and volume of distribution at peak effect. Maintenance rates must initially account for the distribution of drug in peripheral tissues and should only be reduced to the product of target concentration and clearance after equilibration of plasma and peripheral tissue concentrations.
- The terminal half-life does not reflect the clinical time course of drug plasma concentration. The context-sensitive decrement time is the time for a given decrement in drug concentration, as a function of the duration of infusion that maintains a steady plasma concentration. Context-sensitive decrement times properly incorporate the multicompartment behavior of intravenous anesthetics. The context-sensitive half-time is the time for a 50% decrement in concentration.
- Alfentanil, fentanyl, sufentanil, remifentanil, propofol, thiopental, methohexital, etomidate, ketamine, midazolam, and dexmedetomidine can all be administered as a continuous intravenous infusion. Specific caveats, infusion rates, and titration guidelines are presented in this text.
- Target-controlled infusions (TCIs) use pharmacokinetic models to titrate intravenous anesthetic administration to achieve specified plasma or effect-site drug concentrations. Various plasma and effect-site targeting TCI systems are commercially available worldwide (except within the United States) to administer hypnotics and opioids.
- Closed-loop drug delivery systems have used the median electroencephalographic frequency, bispectral index (BIS), or auditory-evoked potentials to control intravenous anesthetic delivery. Although these systems have generally performed well clinically, they remain under investigation.

INTRODUCTION

Drugs must reach their site of action to be effective. In 1628, William Harvey proved in *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* that venous blood was transported to the arterial circulation and thus to body organs by the heart. That drugs injected into veins could be rapidly carried to the entire body was rapidly recognized. Consequently, for intravenous drug delivery to be successful, predictable intravenous access is essential.

The development of intravenous methods of anesthetic drug delivery has been made possible by technologic advances. In the middle of the seventeenth century, Christopher Wren and his Oxford contemporaries applied a feather quill and animal bladder to inject drugs into dogs and humans and rendered them unconscious. The hollow hypodermic needle and a functional syringe were developed by Frances Rynd (1801-1861) and Charles Pravaz (1791-1853), respectively. Contemporary needles, catheters, and syringes are descendants of these early devices. In the twentieth century, equipment began to be made of plastics, first polyvinyl chloride, then Teflon, and later, polyurethane. In 1950, Massa invented the Rochester needle (Fig. 33-1),[1] which led to the revolutionary concept of the "over-the-needle" catheter, which is still the gold standard for intravenous access for nearly all intravenous drug delivery today.[2]

Although fundamental principles of intravenously administering drugs were known in the eighteenth century, intravenous induction of anesthesia became common only in the 1930s after the discovery of barbiturates. Maintenance of anesthesia by intravenously administered anesthetics has become practical, safe, and popular in the past 2 decades. Intravenous drugs such as methohexitone and thiopental, although suitable for intravenous induction of anesthesia, are not suitable for use by infusion for the maintenance of anesthesia. In the case of thiopental, accumulation can lead to cardiovascular instability and delayed recovery, whereas methohexitone is associated with the excitatory phenomenon and epileptiform electroencephalographic (EEG) changes. Although the next generation of intravenous drugs, such as ketamine, althesin, and etomidate, possessed desirable pharmacokinetic characteristics, their use has been limited as a result of other side effects, including hallucinations, anaphylaxis, and adrenal suppression, respectively. The discovery of propofol in 1977 provided the anesthetic practice an intravenous drug suitable for both induction and maintenance of anesthesia; currently, propofol is one of the most frequently used drugs for this purpose.[3] Other drugs suitable for continuous infusion used today are some of the opioids such as alfentanil and sufentanil and certainly the short-acting opioid remifentanil (also see Chapter 30). In addition, some of the nondepolarizing muscle relaxants are used as continuous infusions in specific situations (also see Chapter 34).

Drugs are still predominantly injected as a bolus or continuous infusion using standard dosing guidelines, thereby ignoring the large interindividual variability in the dose-response relationship.[4] In contrast to inhaled anesthetics, for which the inspired and end-tidal concentrations can be continuously measured in real time

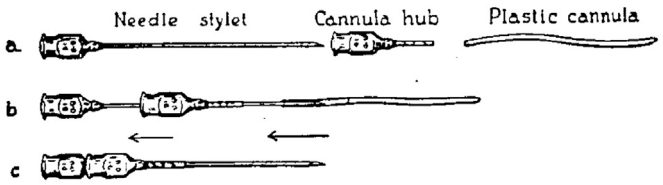


Figure 33-1. Details of the assembly of the Massa plastic needle, sold by Rochester Products Company, Rochester, Minnesota. *(From Massa DJ: A plastic needle,* Anesthesiology *12:772-773, 1951. Used with permission.)*

("online"), the actual plasma or effect organ concentration of an intravenously administered drug is not immediately measurable in clinical practice. Therefore manually adjusting the intravenous drug injection regimens to maintain an online measured plasma concentration is impossible. It becomes even more complex if a specific effect-site concentration is the target. Optimal patient-individual dosing may be achieved by the application of pharmacokinetic-pharmacodynamic principles. Additionally, recent findings suggest that the pharmacokinetic and pharmacodynamic interactions during intravenous administration of various drugs are important and, as such, should be taken into account when optimizing drug administration.[5,6] Computer technology can be used to assist the clinician in titrating intravenous drug administration by using the therapeutic end point as the feedback signal for dosing (Fig. 33-2).

The development of the first mechanical syringe pumps in the 1950s improved the quality of intravenous drug administration. A more recent technologic development in intravenous anesthesia is the introduction of computerized pharmacokinetic model–driven continuous-infusion devices, enabling the attainment of desired plasma levels of an intravenous anesthetic drug by using a computer-controlled infusion pump operated in accordance with the published pharmacokinetics of the drug.[7] These efforts have resulted in the release of the first commercial target-controlled infusion (TCI) device in Europe, developed by Zeneca specifically for the administration of propofol. Since that time, several countries (with the exception of the United States) have approved the use of TCI devices for the delivery of anesthetic drugs.

The ultimate development in anesthetic delivery systems will be devices for closed-loop administration of intravenous drugs during anesthesia. Systems have been developed for closed-loop administration of various drugs such as muscle relaxants, hypnotics, and opioids. The control variables for these systems have included various pharmacodynamic measures derived from techniques such as acceleromyography, automated blood pressure measurement, and electroencephalography.

The dose-response relationship can be divided into three parts (see Fig. 33-2): (1) the time course of the relationship between the given dose and the plasma concentration is defined as *pharmacokinetics*, (2) the relationship between the plasma concentration and/or effect-organ concentration and the clinical effect is defined as *pharmacodynamics*, and (3) the coupling between pharmacokinetics and pharmacodynamics is required when the blood is not the site of drug effect.

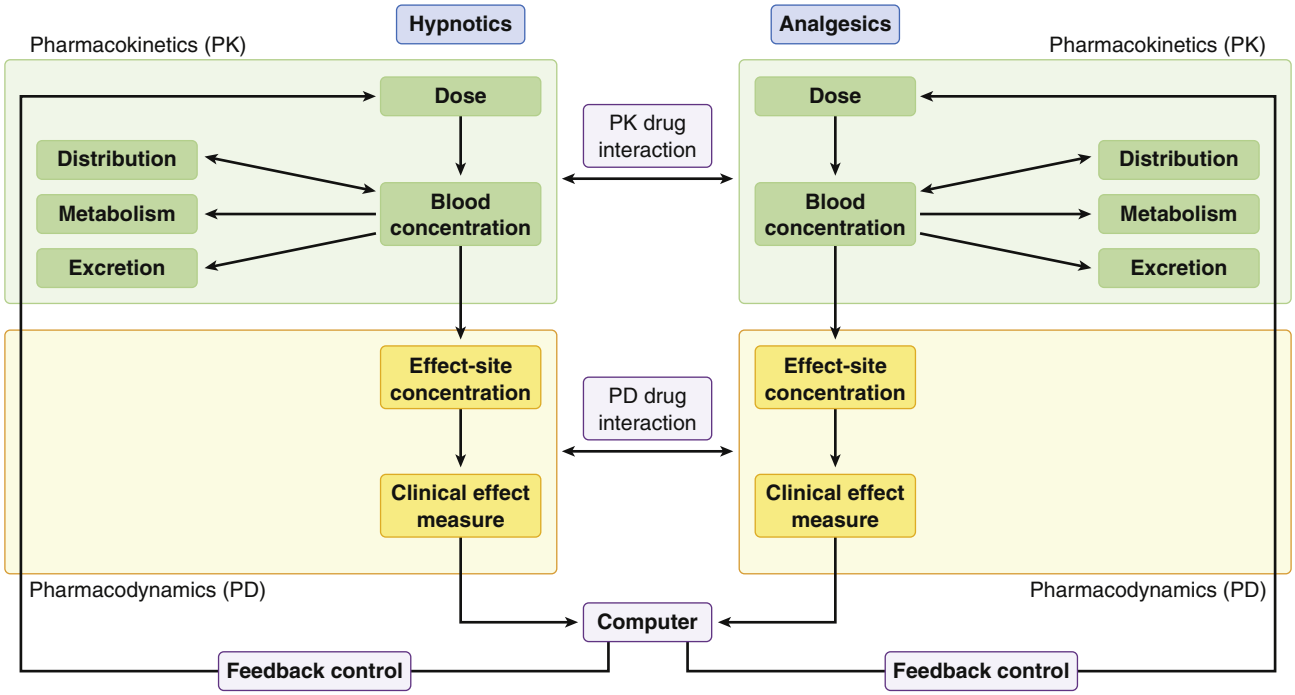


Figure 33-2. Schematic representation of the dose-response relationship for both hypnotics and opioids. The pharmacokinetic (PK) (*green area*) and the pharmacodynamic (PD) (*yellow area*) parts of this relationship are shown. Closed-loop control of drug administration using the clinical measure is indicated as *feed-back control*. Pharmacokinetic and pharmacodynamic drug interactions are indicated. *(From Sahinovic MM, Absalom AR, Struys MM: Administration and monitoring of intravenous anesthetics,* Curr Opin Anaesthesiol *23:734-734, 2010. Used with permission.)*

Before reviewing delivery techniques and devices for intravenous anesthesia, this chapter presents some pharmacokinetic and pharmacodynamic principles as background for understanding how to administer intravenous drugs to their best advantage. Further discussion of the principles of pharmacokinetics and pharmacodynamics can be found in Chapter 30.

PHARMACOKINETIC CONSIDERATIONS

The aim of optimal intravenous drug dosing is to reach and maintain a desired time course of therapeutic drug effect as accurately as possible, thereby preventing dose-related adverse drug effects. To be useful in anesthesia, this time course should include a rapid onset of clinical effects, smooth maintenance, and fast recovery after the termination of drug administration. The pharmacokinetics of many intravenous drugs can be described using mammillary multicompartment pharmacokinetic models. These models assume that the drug is directly given and mixed in the plasma, resulting in an immediate peak in its plasma concentration.

The easiest clinical technique is to administer a single dose, calculated to keep the plasma concentration above the therapeutic target concentration for the required time (Fig. 33-3). A constant concentration cannot be maintained, but it should not decrease to less than the therapeutic concentration. Unfortunately, when one single bolus is used, the initial dose must be large enough to maintain a concentration above the lowest therapeutic concentration even at the end of surgery. However, this sometimes very large dose of drug may cause numerous side effects attributable to the initially high concentrations in the body. It might be less harmful to keep the drug concentration above the lowest therapeutic level without very high initial concentrations by repeatedly injecting smaller doses; even with this technique, however, maintaining a stable plasma concentration is still impossible.

To produce a time course of drug effect that follows the time course of anesthetic requirement, a continuous infusion titrated to the perceived anesthetic requirement should be used. Typically, just enough amount of drug is given to achieve the therapeutic blood or plasma drug concentration. Drug administration thereafter should be continuously titrated throughout surgery. Although such a regimen does not overshoot the required concentration (and therefore avoids the risk of concentration-related side effects), yet another difficulty exists. Whereas, the large bolus approach produces an effective concentration (EC) from the onset, albeit with an excessive overshoot, a continuous infusion takes a long time to become effective because of the slow increase in concentration. Reaching steady state (see Fig. 33-3) takes a very long time during which the increase in concentration is rapid at first but then slows down as equilibrium is approached. For example, it will take longer than 1 hour for the propofol infusion to generate a plasma concentration that is at least 95% of the steady-state concentration. Consequently, although simple infusions are obviously very effective for maintaining constant blood concentrations once steady state is reached and for avoiding overshoot, infusions do not offer a clinically realistic approach. Therefore a combination of an initial bolus followed by a stepwise decreasing continuous infusion is more useful.[8,9]

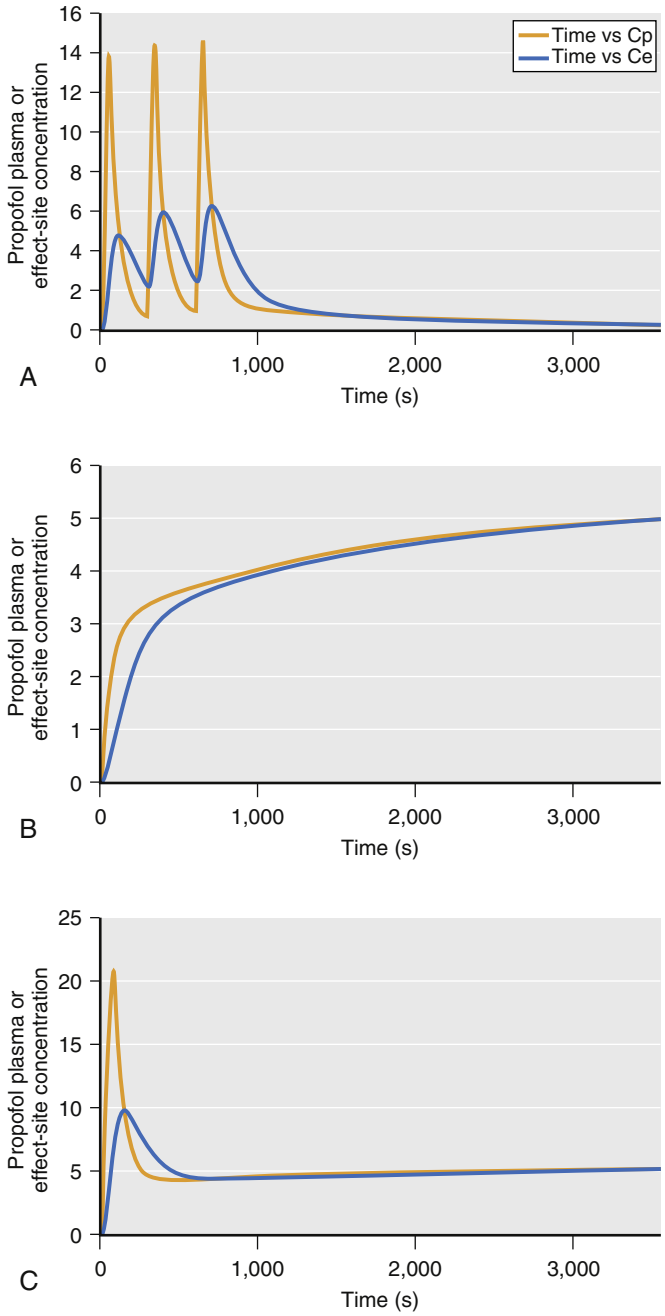


Figure 33-3. Predicted propofol plasma concentration (Cp) and effect-site concentration (Ce) for a repeated bolus dose (1 mg/kg given at time 0 and after 5 and 10 minutes) (**A**), continuous infusion (10 mg/kg/hr) (**B**), and a bolus (2 mg/kg) followed by a continuous infusion (10 mg/kg/hr). **C**, Simulated patient is a man, 45 years of age, 80 kg, 175 cm; Schnider model).

Pharmacokinetic models can be used to calculate the required drug-dosing regimen to reach and maintain a therapeutic drug concentration as fast as possible without overshooting or accumulation. In this chapter, an explanation of how pharmacokinetic models can be used to calculate accurate dosing schemes for use with intravenous drug delivery systems is offered.

Pharmacokinetic models are mathematical descriptions of how the body *disposes* of drugs. The parameters describing this process are estimated by administering a known dose of the drug and measuring the resulting plasma concentrations. A mathematical model then relates the input over time, I(t), with the concentrations over time, C(t). These models can take many forms. Figure 33-4 shows concentrations in plasma and effect site over time after a single intravenous bolus of drug at time 0. Drug concentrations continuously decrease after the bolus, and the rate of decrease is approximately proportional to the amount of drug in plasma. Typically, this behavior can be described with the use of exponential models. The curve might have a single exponent, in which case the plasma concentrations over time might be described by the function $C(t) = Ae^{-kt}$, where A is the concentration at time 0 and k is a constant that describes the rate of decrease in concentration. The relationship appears to be a straight line when graphed as the log of concentration versus time. The pharmacokinetics of intravenous anesthetic drugs is more complex because after the bolus, a period of rapid decline is observed before the terminal *log-linear* portion (i.e., the part that is a straight line when described as log concentration versus time). This process can be modeled by taking several monoexponential curves and adding them together. The result is a polyexponential curve. For example, the concentrations after an intravenous bolus might be described by an equation with two exponents, $C(t) = Ae^{-\alpha t} + Be^{-\beta t}$, or an equation with three exponents, $C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$.

The aforementioned is applied to single bolus dosing, which is, of course, only one way of administering intravenous anesthetic drugs. A more general way to think of pharmacokinetics is to decompose the input into a series of small bits (boluses) and consider each bit of drug separately. The general pharmacokinetic model of drug disposition commonly used in anesthesia independently considers each bit of drug and analyzes its contribution by means of polyexponential decay over time. The formal mathematic description of each bit of drug in terms of polyexponential decay over time is the relationship.

$$C(t) = I(t) * \sum_{i=1}^{n} A_i e^{-\lambda_i t} \qquad (1)$$

where C(t) is the plasma concentration at time t and I(t) is drug input (i.e., a bolus or infusion). The summation after the asterisk (described later in this chapter) is the function describing how each bit of drug is disposed (hence the name, *disposition function*). Note that this is again a sum of *n* exponentials, as described in the previous paragraph.

Pharmacokinetic modeling is the process of estimating the parameters within this function. The integer *n* is the number of exponentials (i.e., compartments) and is usually two or three. Each exponential term is associated with a coefficient A_i and an exponent λ_i. The λ values are inversely proportional to the half-lives (half-life = $\ln 2/\lambda = 0.693/\lambda$), with the smallest λ representing the longest (terminal) half-life. The A values are the relative contribution of each half-life to overall drug disposition. If a drug has a very long terminal half-life but a coefficient that is significantly smaller than the other coefficients, then the long half-life is likely to be clinically meaningless. Conversely, if a drug has a very long half-life with a relatively large coefficient, then the drug will be long lasting even

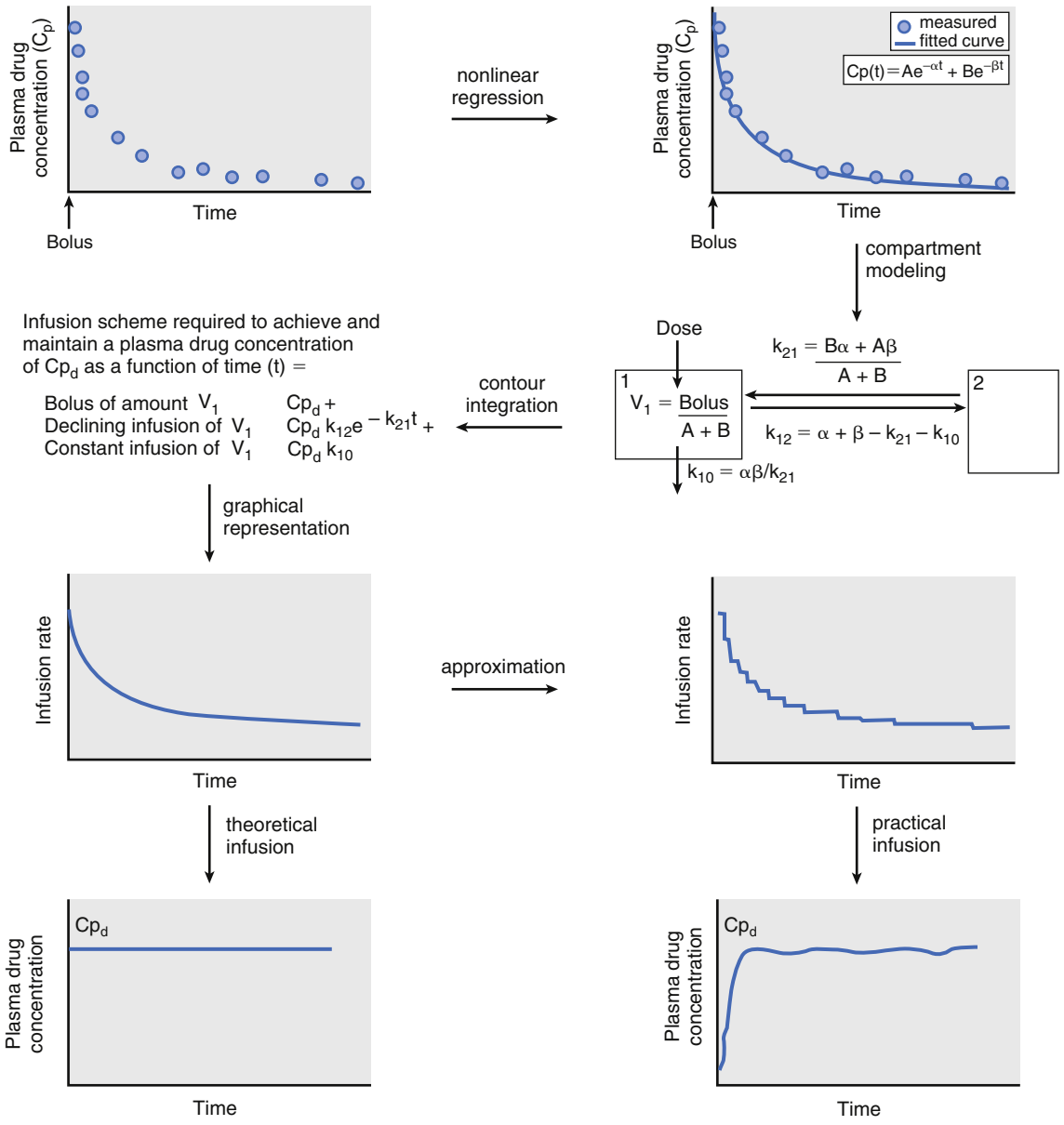


Figure 33-4. Steps involved in pharmacokinetic model–driven infusion. Typically, pharmacokinetic models are derived from experiments in which plasma drug concentrations are measured at intervals after bolus administration of the drug. Nonlinear regression is used to fit a mono-exponential, biexponential, or triexponential curve to the resulting concentration-versus-time data. An algebraic relationship exists between the exponential decay curves and a one-, two-, or three-compartment pharmacokinetic model. The bolus-elimination-transfer (BET) infusion scheme is developed and consists of a bolus, a continuous infusion to replace drug eliminated from the body, and an exponentially declining infusion to replace drug transferred out of plasma to other body compartments. BET infusion results in the maintenance of a constant specified plasma drug concentration. Practical implementation of the BET scheme with real infusion pumps and infusion rates that change only at discrete intervals of time results in a plasma drug concentration profile that approximates that resulting from a BET infusion.

after brief administration. The asterisk (*) operator is the mathematic process called *convolution*, which is simply the process of breaking the infusion into *bits* of drug and then adding up the results to observe the overall concentrations resulting from the disposition of the different bits up to a time point t.

The pharmacokinetic model shown has some useful characteristics that account for its enduring popularity in pharmacokinetic analysis. Most important, the model describes observations from studies reasonably well, the *sine qua non* for models. Second, these models have the useful characteristic of *linearity*. Simply stated, if the dose, I, is doubled (e.g., administering a bolus twice as large or an infusion twice as fast), then the resulting concentrations should be doubled.

More generally, linearity implies that the system (i.e., the body acting to produce a plasma drug concentration output from a drug dosage input) behaves in accordance with the principle of superposition. The superposition principle states that the response of a linear system with multiple inputs can be computed by determining the response to each individual input and then summing

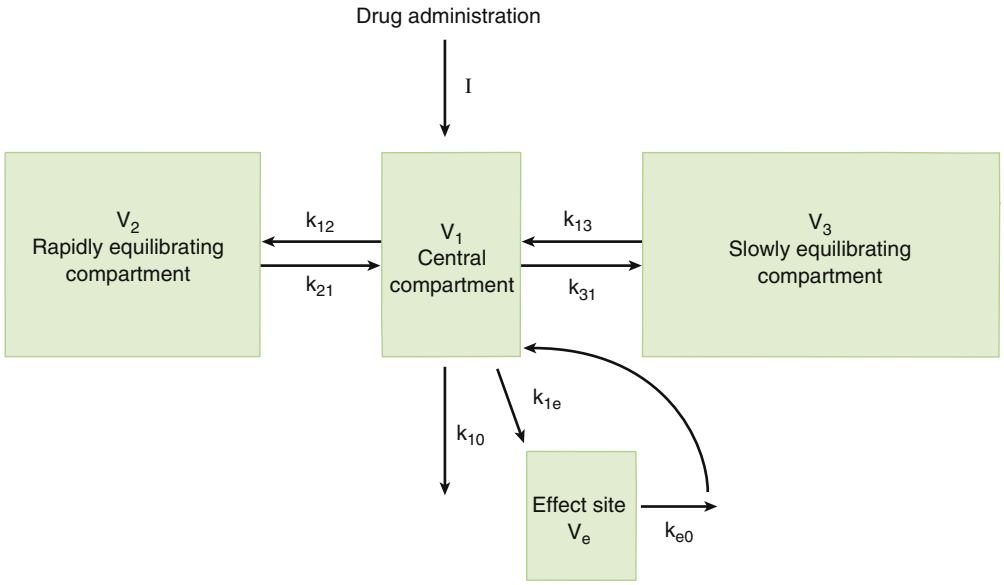


Figure 33-5. Three-compartment model (including the biophase) illustrating the basic pharmacokinetic processes that occur after intravenous drug administration. *I*, Dosing scheme as a function of time; k_{10}, rate constant reflecting all processes acting to remove drug irreversibly from the central compartment; *k*, intercompartment rate constants; V_1, central compartment volume, usually expressed in liters or liters per kilogram.

the individual responses. In other words, when the body treats each bit of drug by polyexponential decay over time, the *disposing* of each bit of drug does not influence the disposing of other bits of drug.

The third reason for the continuing popularity of these models is that they can be mathematically transformed from the admittedly nonintuitive exponential form shown earlier to a more intuitive compartment form (Fig. 33-5). The fundamental parameters of the compartment model are the volumes of distribution (central, rapidly equilibrating, and slowly equilibrating peripheral volumes) and clearances (systemic, rapid, and slow intercompartment). The central compartment (V_1) represents a distribution volume and includes the rapidly mixing portion of the blood and first-pass pulmonary uptake. The peripheral compartments are made up of tissues and organs that show a time course and extent of drug accumulation (or dissipation) different from that of the central compartment. In the three-compartment model, the two peripheral compartments may roughly correspond to splanchnic and muscle tissues (rapidly equilibrating) and fat stores (slowly equilibrating). The sum of the compartment volumes is the apparent volume of distribution at steady state (Vd_{ss}) and is the proportionality constant relating the plasma drug concentration at steady state to the total amount of drug in the body. The intercompartment rate constants (k_{12}, k_{21}, and so on) describe the movement of drug between the central and peripheral compartments. The elimination rate constant (k_{10}) encompasses processes acting through biotransformation or elimination that irreversibly removes drug from the central compartment.

Despite their physiologic flavor, compartment models are simply mathematic transformations of the polyexponential disposition functions computed from observed plasma concentrations. Thus physiologic interpretation of volumes and clearances (with the possible exception of systemic clearance and Vd_{ss} [the algebraic sum of the volumes]) is entirely speculative.

The last reason behind the popularity of these models is that they can be used to design infusion regimens. If the disposition function

$$\sum_{i=1}^{n} A_i e^{-\lambda_i t} \tag{2}$$

is abbreviated as simply D(t), then the relationship among concentration, dose, and the pharmacokinetic model D(t) can be rewritten as

$$C(t) = I(t)*D(t) \tag{3}$$

where * is the convolution operator, as noted earlier. In the usual pharmacokinetic study, I(t) is known, the dose that is given the patient, and C(t) is measured, the concentrations over time. The goal is to find D(t), the pharmacokinetic disposition function. Pharmacokinetic analysis can be thought of as a simple rearrangement of Equation 3 to solve for D(t)

$$D(t) = \frac{C(t)}{\overrightarrow{\leftarrow} I(t)} \tag{4}$$

where the symbol $\rightarrow\leftarrow$ means *deconvolution*, the inverse operation of convolution. Deconvolution is similar to division, but of functions rather than simple numbers. When dosing regimens are designed from known pharmacokinetic models and a desired course for the plasma concentration over time, the known values are D(t) (the pharmacokinetics) and $C_T(t)$ (the desired target concentrations), and the drug dosing scheme is

$$I(t) = \frac{C_T(t)}{\overrightarrow{\leftarrow} D(t)} \tag{5}$$

Thus the necessary infusion rates, I(t), can be calculated, given the desired target concentrations, $C_T(t)$, and the pharmacokinetics, D(t), by applying the same tools used to calculate the original pharmacokinetics. Unfortunately, such a solution might require some negative infusion rates, which are obviously impossible. Because drug cannot be retracted from the body (i.e., give inverse

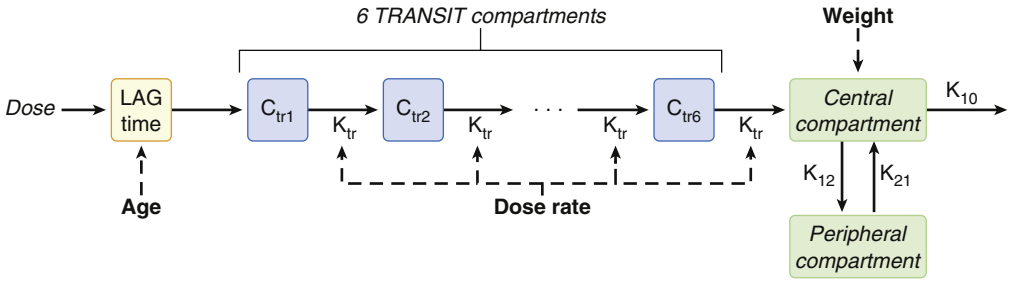


Figure 33-6. Scheme of the final two-compartment pharmacokinetic model with a LAG time and six TRANSIT compartments (C_{tr} *n*). The equilibration rate constants between the central and peripheral compartments were calculated using the following equations: $k_{12} = Cl_2 \div V_1$, $k_{21} = Cl_2 \div V_2$. The elimination rate constant was calculated using the following equation: $k_{10} = Cl_1 \div V_1$. Cl_1, Clearance of central compartment; Cl_2, clearance of peripheral compartment; V_1, distribution volume of central compartment; V_2, distribution volume of peripheral compartment. LAG time represents the time shift of dosing as if the drug was, in fact, administered to the pharmacokinetic model at a later time. TRANSIT compartments depict a multiple-step process represented by a chain of presystemic compartments. *(From Masui K, Kira M, Kazama T, et al: Early phase pharmacokinetics but not pharmacodynamics are influenced by propofol infusion rate,* Anesthesiology *111:805-817, 2009. Used with permission.)*

infusions), clinicians must restrict themselves to plasma concentrations over time that can be achieved with non-inverse infusion rates.

The standard pharmacokinetic model has one glaring shortcoming. It assumes that after a bolus injection there is complete mixing within the central compartment such that the peak concentration occurs precisely at time 0. It actually takes approximately 30 to 45 seconds for the drug to make its transit from the venous injection site to the arterial circulation. This model misspecification over the first minute or so may not seem significant, but it can cause problems in attempts to relate the drug effect after a bolus to drug concentrations in the body,[10] which becomes even more important when using effect-site TCI.[11] The standard polyexponential pharmacokinetic models are being modified to provide more accurate models of plasma drug concentration in the first minute after bolus injection, also taking into account infusion rate. Recently, Masui and associates[12] found that a pharmacokinetic model consisting of a two-compartment model with a LAG (the time shift of dosing as if the drug were, in fact, administered to the pharmacokinetic model at a later time) and presystemic compartments model accurately described the early pharmacologic phase of propofol during infusion rates between 10 and 160 mg/kg/h. The infusion rate has an influence on kinetics. Age was a covariate for LAG time (Fig. 33-6). Besides compartment models, various physiologically based models have been developed to model the pharmacokinetic behavior of anesthetics.[13] So far, these models are not superior at predicting the time course of drug concentration.[12] None of these models have been used to control intravenous drug delivery devices.

PHARMACODYNAMIC CONSIDERATIONS

THE BIOPHASE

The goal of drug titration during anesthesia is to reach and maintain a stable therapeutic drug concentration at the site of drug effect, also defined as the *effect site* or *biophase*. For most drugs used in anesthesia, the plasma is not the biophase and thus, even after the drug has reached the arterial circulation, a further delay occurs before a therapeutic effect is observed. The reason is that additional time is required for the drug to be transported to the target organ, penetrate the tissue, bind to a receptor, and induce intercellular processes that ultimately lead to the onset of drug effect. This delay between peak plasma concentration and peak concentration at the effect site is called *hysteresis*. Figure 33-7 illustrates an example of hysteresis revealed during an experiment published by Soehle and co-workers.[14] Two periods of continuous propofol infusions were given. The time course of the plasma concentration and effect-site concentration are simulated using pharmacokinetics and pharmacodynamics models. The cerebral drug effect was measured using the EEG-derived bispectral index (BIS). A clear delay between the time course of the plasma concentration and that of the BIS can be observed. The plasma concentration versus effect curve forms a counterclockwise hysteresis loop. This loop represents the plasma concentration but is not the site of drug effect. Using nonlinear mixed effect modeling, the hysteresis is minimized to reveal the effect-site concentration versus clinical effect relationship. The typical sigmoidal population model is also depicted in Figure 33-7.

The concentration of drug in the biophase cannot be measured because it is usually inaccessible, at least in human subjects. The time course of drug effect can be calculated by using rapid measures of drug effect. Knowing the time course of drug effect, the rate of drug flow in and out of the biophase (or effect site) can be calculated with the use of mathematic models. As such, the time course of the plasma concentration and the measured effect can be linked using the concept of the *effect compartment*, developed by Hull[15] and Sheiner.[16] The effect-site concentration is not a real measurable concentration but rather a virtual concentration in a theoretic compartment without a volume and, as such, also without any significant amount of drug present. For any concentration in this virtual compartment, a corresponding assumed effect is observed. This relationship between the effect-site concentration and effect is usually nonlinear and static (i.e., does not explicitly depend on time). If the plasma concentration is maintained at a constant level, then the

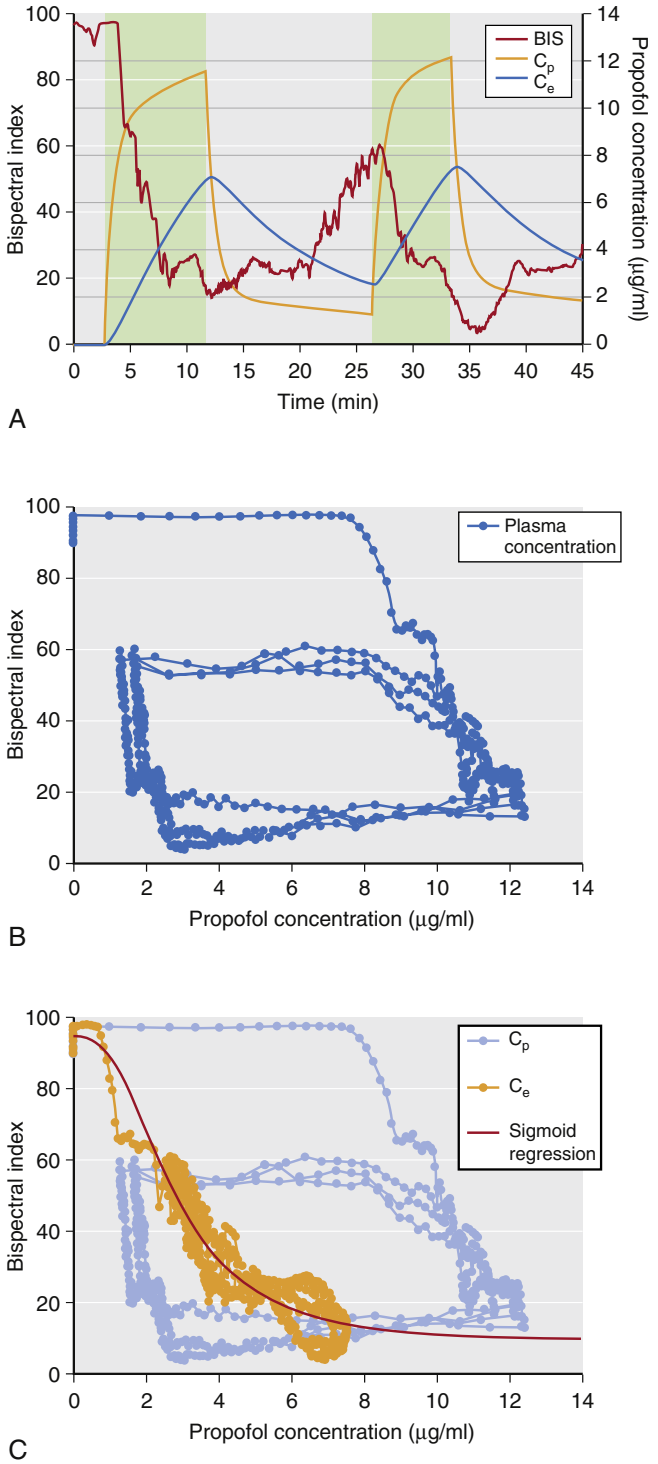


Figure 33-7. A, Time course of an experiment showing the hysteresis between plasma concentration (C_p) and hypnotic effect as measured by the electroencephalographic (EEG)-derived bispectral index (BIS). Propofol was given at a constant rate during the shaded periods, resulting in C_p (*orange line*) and effect-site concentration (C_e) (*blue line*). The corresponding BIS values are shown as a *solid blue line.* **B,** Relation between C_p and BIS using data from the experiment reveals a hysteresis loop. **C,** After modeling, this hysteresis is minimized as shown in the relation between the effect-site concentration and BIS. (**A,** *Adapted from Soehle M, Kuech M, Grube M, et al: Patient state index vs bispectral index as measures of the electroencephalographic effects of propofol,* Br J Anaesth *105:172-178, 2010. Used with permission;* **B** and **C,** *Courtesy of M. Soehle, Bonn, Germany).*

model assumes that, at equilibrium, the effect-compartment concentration equals the plasma concentration. The delay between the plasma and the effect compartment is mathematically described by a single parameter, defined as *ke0*, the effect-site equilibration rate constant[17] (see Fig. 33-5).

Measures of drug effect used to characterize the time course of drug between plasma and the biophase vary with the drug being evaluated. For some drugs, a direct measure of drug effect can be applied. For neuromuscular blocking drugs, the response from peripheral nerve stimulation (i.e., the twitch) is an ideal measure of effect. Various authors have used the T1% (percentage change of the T1 response compared with baseline T1 response during supramaximal stimulus) derived from electromyogram to measure the drug effect of newer drugs such as rocuronium[18] and cisatracurium.[19] For other categories of drugs such as opioids and hypnotics, the real clinical effects (e.g., unconsciousness, amnesia, memory loss, antinociception) are not measurable. For these reasons, surrogate measures are used to quantify the time course of clinical effects. These surrogate measures can be categorical or continuous. For example, the Observer's Assessment of Alertness/Sedation (OAA/S) scale was used to measure quantal changes in hypnotic drug effects during propofol administration.[20] Egan and colleagues[21] applied a noxious pain stimulus and used an algometer to measure the balance between nociception and antinociception during remifentanil infusion. Various spontaneous and evoked EEG-derived and processed measures were used to measure cerebral drug effects for opioids and hypnotics.[14,22-26] Ludbrook and associates measured propofol concentrations in the carotid artery and jugular bulb to establish movement of propofol into and equilibration with the brain. They simultaneously measured the BIS and found a close correlation between brain concentration (calculated by mass balance) and changes in the BIS (also see Chapter 50).[27]

DIRECT-EFFECT MODELS

As with plasma pharmacokinetics, the biophase concentration is the convolution of an input function (in this case, the plasma drug concentration over time) and the disposition function of the biophase. This relationship can be expressed as

$$C_{biophase}(t) = C_{plasma}(t) * D_{biophase}(t) \quad (6)$$

The disposition function of the biophase is typically modeled as a single exponential decay

$$D_{biophase}(t) = K_{e0} e^{-K_{e0} t} \quad (7)$$

The monoexponential disposition function implies that the effect site is simply an additional compartment in the standard compartment model that is connected to the plasma compartment (see Fig. 33-5). The effect site is the hypothetical compartment that relates the time course of plasma drug concentration to the time course of drug effect, and k_{e0} is the rate constant of elimination of drug from the effect site. By convention, the effect compartment is assumed to receive such small amounts of drug from the central compartment that it has no influence on plasma pharmacokinetics.

Neither $C_{biophase}(t)$ nor $D_{biophase}(t)$ can be directly measured, but the drug effect can be measured. Knowing that the observed drug effect is a function of the drug concentration in the biophase, the drug effect can be predicted as

$$Effect = f_{PD}\left[C_{plasma}(t)*D_{biophase}(t)\,,\,P_{PD}\,,\,K_{e0}\right] \quad (8)$$

where f_{PD} is a pharmacodynamic model (typically sigmoidal in shape), P_{PD} represents the parameters of the pharmacodynamic model, and k_{e0} is the rate constant for equilibration between plasma and the biophase. Nonlinear regression programs are used to find values of P_{PD} and k_{e0} that best predict the time course of drug effect. This method is called *loop-collapsing* (see Fig. 33-7). Knowledge of these parameters can then be incorporated into dosing regimens that produce the desired time course of drug effect.[28,29]

If a constant plasma concentration is maintained, then the time required for the biophase concentration to reach 50% of the plasma concentration ($t_{1/2}k_{e0}$) can be calculated as $0.693/k_{e0}$. After a bolus dose, the time to peak biophase concentration is a function of both plasma pharmacokinetics and k_{e0}. For drugs with a very rapid decline in plasma concentration after a bolus (e.g., adenosine with a half-life of several seconds), the effect-site concentration peaks within several seconds of the bolus, regardless of k_{e0}. For drugs with a rapid k_{e0} and a slow decrease in concentration after a bolus injection (e.g., pancuronium), the peak effect-site concentration is determined more by k_{e0} than by plasma pharmacokinetics.

An accurate estimation of k_{e0} demands an integrated pharmacokinetic-dynamic study combining rapid blood sampling with frequent measurements of drug effect, yielding an overall model for the dose-response behavior of the drug. Historically, the time constants of pharmacokinetic models and the k_{e0} of pharmacodynamic studies were sometimes naively merged, possibly leading to inaccurate predictions of the clinical drug effect. Coppens and colleagues proved that pharmacodynamic models of BIS in children developed by using estimates of plasma propofol concentrations from published pharmacokinetic models and estimating the pharmacodynamic model do not ensure good pharmacokinetic accuracy or provide informative estimates for pharmacodynamic parameters.[30] If no integrated pharmacokinetic-dynamic model exists, then the time to peak effect (t_{peak}) after a bolus injection can be used to recalculate k_{e0} using the pharmacokinetic model of interest to yield the correct time to peak effect. Under these circumstances, this alternative approach might lead to a more accurate prediction of the dose-response time course.[31,32] However, the correct covariates for t_{peak} should be estimated in a specific population.[33] A second caveat is that the time course of drug effect is specific for a given effect (e.g., cerebral drug effect as measured by a specific processed EEG). The time course of other side effects (e.g., hemodynamic effect for hypnotics) most frequently follows a different trajectory.[34,35] The time to peak effect and the $t_{1/2}$ k_{e0} for several intravenous anesthetics are listed in Table 33-1.

All methods explained so far incorporate k_{e0} values calculated on the assumption that hysteresis between plasma concentration and clinical effect is explained by a delay in drug transfer between plasma and biophase and thus that anesthesia is a smooth, path- and state-independent, symmetric process. Although still commonly used, this assumption might be suboptimal. Data from animal experiments suggest that neural processes and pathways involved in anesthesia induction and recovery are different.[36,37] In an animal study, measured brain drug concentrations at loss of consciousness and at return of consciousness were significantly different.[38] If these data are confirmed, then a more complex model (e.g., one incorporating a second, serial effect-site model) might be required to depict the time course of drug effect.

TABLE 33-1 TIME TO PEAK EFFECT AND $t_{1/2}k_{e0}$ AFTER A BOLUS DOSE*

Drug	Time to Peak Drug Effect (min)	$t_{1/2}$ k_{e0} (min)
Morphine	19	264
Fentanyl	3.6	4.7
Alfentanil	1.4	0.9
Sufentanil	5.6	3.0
Remifentanil	1.8	1.3
Ketamine	—	3.5
Propofol	1.6	1.7
Thiopental	1.6	1.5
Midazolam	2.8	4.0
Etomidate	2.0	1.5

$t_{1/2}$ k_{e0} = $0.693/k_{e0}$, Rate constant for transfer of drug from the site of drug effect to the environment.
*Measured by electroencephalography.

INDIRECT-EFFECT MODELS

Thus far, clinical effects that are an instantaneous function of drug concentration at the site of drug effect have been discussed, as implied by Equation 8. For example, once a hypnotic drug reaches the brain or a neuromuscular-blocking drug reaches the muscles, drug action is almost immediately observed. On the other hand, some effects are significantly more complex. For example, consider the effect of opioids on ventilation. Initially, opioids depress ventilation, and carbon dioxide (CO_2) gradually accumulates. Yet, the accumulation of CO_2 at normal conditions is a strong stimulant for ventilation, thereby partly counteracting the ventilatory depressant effects of opioids. Ventilatory depression is an example in which direct and indirect drug effects are incorporated. The direct effect of the opioid is to depress ventilation, and the indirect effect is to increase arterial tension of CO_2. Modeling the time course of opioid-induced ventilatory depression requires consideration of both components. Bouillon and colleagues developed a model of ventilatory depression that incorporates both direct and indirect effects.[19,20] As is generally the case with indirect-effect models, characterizing drug-induced ventilatory depression requires a consideration of the entire time course of drug therapy, which is embodied by the following differential equation:

$$\frac{d}{dt}Pa_{CO_2} = k_{el} \cdot \left[1 - \frac{Cp(t)\gamma}{C_{50}\gamma + C_p(t)\gamma}\right] \cdot \left[\frac{P_{biophase_{CO_2}}(t)}{P_{biophase_{CO_2}}(0)}\right]^F \cdot Pa_{CO_2}(t) \quad (9)$$

where partial pressure of arterial carbon dioxide (Pa_{CO_2}) is arterial CO_2, $P_{biphase_{CO_2}}$ is CO_2 in the biophase (i.e., brainstem respiratory control circuits), k_{el} is the rate constant for the elimination of CO_2, C_{50} is the effect-site opioid concentration associated with a 50% reduction in ventilatory drive, and F is the steepness or *gain* of the effect of CO_2 on ventilatory drive.

DOSE IMPLICATIONS OF THE BIOPHASE

The delay in onset of clinical effects has important clinical implications. After a bolus, the plasma concentration peaks nearly instantly and then steadily declines. The effect-site concentration starts at zero and increases over time until it equals the descending plasma concentration. The plasma concentration continues to decline. After the moment of identical concentrations, the gradient between plasma and the biophase favors removal of drug from the biophase, and the effect-site concentration decreases. The rate at which the effect-site concentration rises toward the peak after a bolus dictates how much drug must be injected into plasma to produce a given effect. For alfentanil, its rapid plasma effect-site equilibration (large k_{e0}) causes the effect-site concentration to rise rapidly, with a peak produced in approximately 90 seconds. At the time of the peak, approximately 60% of the alfentanil bolus has been distributed into peripheral tissues or eliminated from the body. For fentanyl, the effect-site concentration rises significantly more slowly and peaks 3 to 4 minutes after the bolus.[39] At the time of the peak, more than 80% of the initial bolus of fentanyl has been distributed into tissues or eliminated. As a result of slower equilibration with the biophase, relatively more fentanyl than alfentanil must be injected into plasma, which makes the rate of offset of drug effect after a fentanyl bolus slower than after an alfentanil bolus.

This difference in pharmacokinetics indicates that k_{e0} must be incorporated into dosing strategies on which rational drug selection is dependent. For rapid onset of effect, a drug with a large k_{e0} (short $t_{1/2}$ k_{e0}) should be chosen. For example, for rapid-sequence induction of anesthesia, alfentanil or remifentanil may be the optimal opioid because its peak effect-site concentration coincides with the likely time of endotracheal intubation. However, for a slower induction of anesthesia in which a nondepolarizing neuromuscular blocking drug is used, an opioid with a slower onset of drug effect should be selected to coincide with the peak effect of the neuromuscular blocking drug. In this case, a bolus of fentanyl or sufentanil at the time of induction may be more appropriate. The time to peak effect for the commonly used opioids is shown in Figure 33-8. Knowing k_{e0} (or time to peak effect) also improves titration of the drug by identifying the time at which the clinician should make an assessment of drug effect. For example, midazolam has a slow time to peak effect, and repeat bolus doses should be spaced at least 3 to 5 minutes apart to avoid inadvertent overdosing.

An accurate k_{e0} is also crucial during TCI titrating to a specific effect-site concentration because the initial bolus given to reach the targeted effect-site concentration depends on both the pharmacokinetics and the k_{e0}.[40]

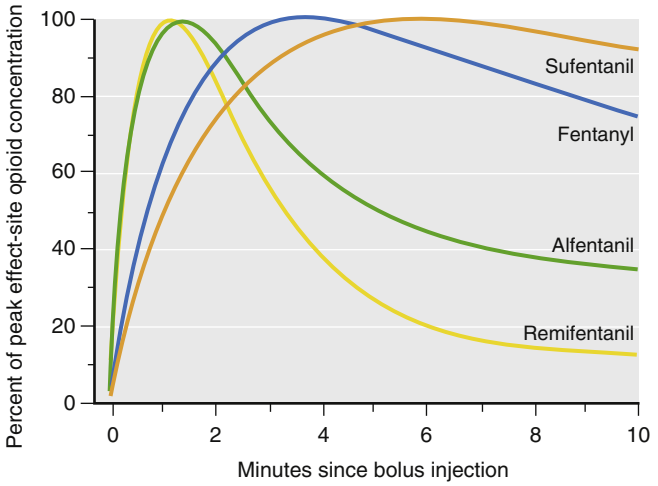


Figure 33-8. Simulated onset and time to peak effect of commonly used opioids based on their k_{e0} and pharmacokinetic parameters. k_{e0}, Rate constant for the transfer of drug from the site of drug effect to the environment.

DRUG POTENCY

Single Drugs

Knowledge about adequate therapeutic drug concentration is crucial to achieve the aim of providing optimal anesthetic conditions. Therefore information on drug potency is essential. Analagous to the concept of minimum alveolar concentration (MAC), the concentration associated with a 50% likelihood of movement in response to skin incision for inhaled anesthetics,[41] is the C_{50}, which is the concentration that produces 50% of the maximum possible drug effect. Defining the C_{50}, similar to the MAC, provides a measure of relative potency between intravenous anesthetics.

There are many ways to look upon C_{50}, taking into consideration whether the clinical effect is a binary or continuous effect. When considering binary effects, the C_{50} might be the drug concentration that prevents response (e.g., movement, hypertension, release of catecholamines) to a particular stimulus (e.g., surgical incision, endotracheal intubation, spreading of the sternum) in 50% of patients. In this case, each combination of stimulus and response may have a unique C_{50}. When C_{50} is defined as the drug concentration that produces a given response in 50% of patients, a 50% probability of response is also likely in a given patient. Defining C_{50} as the concentration that produces a given drug effect in 50% of individuals implicitly assumes that the effect can be achieved in all individuals. Some drugs exhibit a ceiling effect. For example, a ceiling effect may exist on the ability of opioids to suppress response to noxious stimulation. When a ceiling in drug effect exists, some patients may not exhibit the drug effect even at infinitely large doses. In this case, C_{50} is not the concentration that causes the drug effect in 50% of patients but is the concentration associated with the drug effect in one half of whatever fraction of patients is able to respond.

Several studies have been performed to establish appropriate concentrations of intravenous anesthetics

TABLE 33-2 **STEADY-STATE CONCENTRATIONS FOR PREDEFINED EFFECTS***

Drug	C_{50} for EEG Depression†	C_{50} for Incision or Painful Stimulus‡	C_{50} for Loss of Consciousness§	C_{50} for Spontaneous Ventilation‖	C_{50} for Isoflurane MAC Reduction	MEAC
Alfentanil (ng/mL)	500-600	200-300	—	170-230	50	10-30
Fentanyl (ng/mL)	6-10	4-6	—	2-3	1.7	0.5-1
Sufentanil (ng/mL)	0.5-0.75	(0.3-0.4)	—	(0.15-0.2)	0.15	0.025-0.05
Remifentanil (ng/mL)	10-15	4-6	—	2-3	1.2	0.5-1
Propofol (μg/mL)	3-4	4-8	2-3	1.33	—	—
Thiopental (μg/mL)	15-20	35-40	8-16	—	—	—
Etomidate (μg/mL)	0.53	—	0.55	—	—	—
Midazolam (ng/mL)	250-350	—	125-250	—	—	—

EEG, Electroencephalography; *MAC,* minimum alveolar concentration; *MEAC,* minimum effective plasma concentration providing postoperative analgesia.
*Values in parentheses are estimated by scaling to the alfentanil C_{50} (see text for details).
†C_{50} for depression of the EEG is the steady-state serum concentration that causes a 50% slowing of the maximal EEG, except for midazolam, in which the C_{50} is associated with 50% activation of the EEG.
‡C_{50} for skin incision is the steady-state plasma concentration that prevents a somatic or autonomic response in 50% of patients.
§C_{50} for loss of consciousness is the steady-state plasma concentration for absence of a response to a verbal command in 50% of patients.
‖C_{50} for spontaneous ventilation is the steady-state plasma concentration associated with adequate spontaneous ventilation in 50% of patients.

and opioids for various clinical endpoints and the effect of drug interactions (Table 33-2).[42-49]

Another interpretation of C_{50} is the concentration that produces 50% of the maximum possible physiologic response. For example, the C_{50} for an EEG response is the drug concentration that provides 50% depression of the maximal EEG effect. The C_{50} for EEG response has been measured for the opioids alfentanil,[50] fentanyl,[50] sufentanil,[51] and remifentanil.[52-54] It has also been determined for thiopental,[44,55,56] etomidate,[48] propofol,[26] and benzodiazepines[57] (see Table 33-2). Other measures such as pupillary dilation in response to a noxious stimulus[58] and pressure algometry[21] were used to measure opioid potency and revealed slightly different values for C_{50}, which indicates that observation of drug potency also depends on the applied measure of drug effect.

As mentioned, C_{50} can be used to compare potency among drugs. For example, Glass and colleagues[59] determined the potency of remifentanil compared with alfentanil using ventilatory depression as the measure of opioid effect. In their study, the C_{50} for depression of minute ventilation was 1.17 ng/mL and 49.4 ng/mL for remifentanil and alfentanil, respectively. Using this difference in C_{50}, they concluded that remifentanil is approximately 40 times more potent than alfentanil.

To be entirely independent of dosing history, C_{50} must be determined at steady state, which is rarely possible because most anesthetic drugs do not reach steady state during a continuous infusion until many hours have passed. However, if the drug exhibits rapid equilibration between plasma and the effect site and the investigator waits long enough after starting the infusion, then this choice can be reasonably satisfactory. For example, Ausems and colleagues[60,61] used a continuous infusion of alfentanil in their experiments, which quickly equilibrated. They also recorded their measurements after the effect-site concentration had equilibrated with plasma.

A second alternative to performing a true steady-state experiment is to use mathematic modeling to calculate the effect-site concentrations of drug at the time of measurement, as proposed by Hull and colleagues[15] and Sheiner and colleagues.[16] The relationship between effect-site and plasma concentrations is graphically represented in Figure 33-5 and mathematically in Equation 6. Calculating effect-site concentrations is the same as attempting to determine the steady-state plasma concentrations that produce the observed drug effect. When the C_{50} reflects effect-site concentrations, it is represented as Ce_{50} to distinguish it from values of C_{50} that are based on plasma concentrations, which are then termed Cp_{50}. However, the distinction is artificial. In both cases, C_{50} is intended to represent the steady-state plasma drug concentration associated with a given drug effect.

A third alternative to performing a steady-state experiment is to establish a pseudo–steady state with the use of computer-controlled drug delivery. This method has become the state-of-the-art for determining the C_{50} for anesthetic drugs, and many of the C_{50} values referenced earlier were determined at pseudo–steady state with the use of computer-controlled drug delivery. Typically, maintaining a constant plasma steady-state concentration for four to five plasma effect-site equilibration half-lives (e.g., 10 to 15 minutes for fentanyl) is required. Such a long delay is not necessarily needed when computer-controlled drug delivery is used. Effect-compartment TCIs can be used to target the concentration at the effect site rather than the plasma concentration and thereby rapidly establishing plasma–effect site equilibration.[28,62] For example, Kodaka and associates reported predicted values of propofol effect-site concentration C_{50} between 3.1 μg/mL and 4.3 μg/mL for insertion of various laryngeal airway masks, depending on the type of laryngeal mask.[63] Cortinez and associates used TCI to determine the C_{50} of remifentanil and fentanyl for accurate pain relief during extracorporeal shock wave lithotripsy in relation with possible side effects and found that remifentanil and fentanyl C_{50} were 2.8 ng/mL and 2.9 ng/mL, respectively.[64] At C_{50}, the probability of having a respiratory rate less than 10 breaths per minute was 4% for remifentanil and 56% for fentanyl. Thus several ways can establish C_{50} in terms of steady-state concentrations. C_{50} can be estimated through mathematic effect-site modeling or can be experimentally measured with the use of computer-controlled drug delivery to establish a pseudo–steady

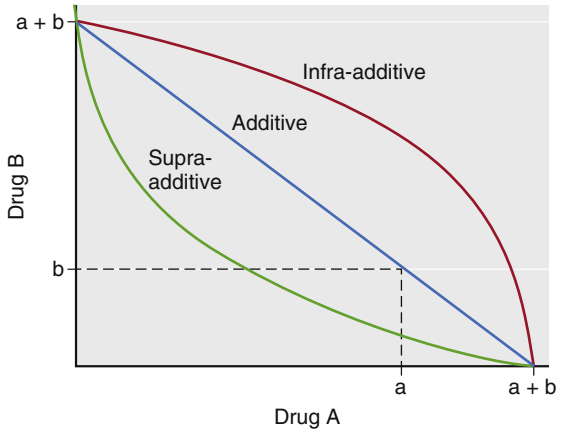


Figure 33-9. Pharmacodynamic drug interactions.

state quickly. Either way, when performing studies to define the concentration-effect relationship, equilibrium must exist or be modeled between the biophase (the site of effect) and plasma or blood (where the concentration is actually measured).

When C_{50} is defined in terms of the concentration associated with a response in one half of a population, that same C_{50} is the concentration associated with a 50% probability of response in a typical individual. However, individual patients are not typical individuals but rather will have their own value for C_{50}. Expressed in clinical terms, different patients have different anesthetic requirements for the same stimulus. For example, the minimal effective analgesic concentration of fentanyl is 0.6 ng/mL, but it varies among patients from 0.2 to 2.0 ng/mL.[65] The minimal effective analgesic concentrations of alfentanil[66] and sufentanil[67] similarly vary among patients by a factor of 5 to 10. This range encompasses both variability in the intensity of the stimulus and variability of the individual patient. However, this wide range reflects the clinical reality that must be accounted for when dosing regimens are designed. Because of this variability, intravenous anesthetics should be titrated to each patient's unique anesthetic requirement for the given stimulus.

Pharmacodynamic Drug Interactions

Drug interactions cause the C_{50} of one drug to shift in response to the administration of a second drug. This drug interaction can be additive, supra-additive (synergistic) or infra-additive (antagonistic). As observed in the isobologram (Fig. 33-9), for additive drugs with equal potency, the cumulative effect resulting from doses a and b for substances A and B, respectively, equals the effect obtained with the injection of either drug A or B solely in a dose a + b. If the drugs interact synergistically, then the combination of A and B will generate a more pronounced effect than additive. For antagonistic drug interaction, the combination of A and B will result in a less pronounced effect than additive. In general, additive drug interactions occur when combining drugs acting by the same mechanism and synergistic or antagonistic interaction when combining drugs acting by a different mechanism.[68] Hendrickx and co-workers (Fig. 33-10) reviewed the available literature and summarized the available data on drug interactions in humans and animals for hypnosis and immobility.[68]

Investigating one isobole of the interaction spectrum (at the 50% probability level of a specific drug response) provides a rudimentary insight on the interaction characteristics but reveals only limited information about other levels of drug effect (e.g., at the clinically more important level of 95% probability of drug response). As drug interactions may vary among drug effect levels (e.g., additive at the 50% level but synergistic at the 95% level), the ultimate aim is to characterize the response surface describing all levels of effect. Pharmacodynamic response surface models generate figures that are three- (or even higher) dimensional structures that have been developed to describe the relationship quantitatively between two or more drug concentrations and their combined clinical effect (Fig. 33-11). Response surface models are powerful representations of drug interactions as they combine information about the full range of isoboles resulting from the concentration response curves of all combinations of the drugs involved.[69,70] Using the mathematically defined response surface, the corresponding drug effect for any two or more drug concentrations of the interacting drugs can be predicted.[69,71] Various methodologic approaches to response surface models are found in the literature.[72]

Intravenous opioids are frequently combined with volatile anesthetics during anesthesia. The reduction of the MAC for a given volatile by a given opioid dose can be applied to investigate the potency and efficacy of opioids.[73-75] These MAC reduction studies reveal a general pattern, irrespectively of which opioid or volatile anesthetic has been used. Low concentrations of an opioid result in a substantial reduction of MAC (Fig. 33-12). With increasing concentrations of the opioid, MAC continues to decrease until a plateau is reached and, consequently, a further increase of the opioid dose is futile.[76]

The previously mentioned MAC reduction studies show the effect of a single opioid dose on a single point of a dose-response curve but, nonetheless, form the basis for more detailed surface interaction studies.[77] To characterize the interaction between sevoflurane and remifentanil in blunting responses to verbal (OAA/S scale) and painful stimuli (pressure algometry, electrical tetanic stimulus, and thermal stimulation), Manyam and coworkers constructed a response surface for each pharmacodynamic response using a Logit model approach and found synergy between sevoflurane and remifentanil for all responses. More specifically, a remifentanil effect-site concentration of 1.25 ng/mL was able to more than halve the sevoflurane requirements for preventing movement to pain.[78] Because this study suffered from nonsteady-state conditions at the moment of measurements, the authors improved their data using calculated effect-site sevoflurane concentrations and a Greco model instead of a Logit approach.[79] Accounting for the time lag between sevoflurane effect-site concentration and end-tidal concentration improved the predictions of responsiveness during anesthesia but had no effect on the accuracy of prediction of a response to a noxious stimulus in recovery. They concluded that models may be useful in predicting events of clinical interest, but large-scale evaluations with numerous patients are needed to better characterize

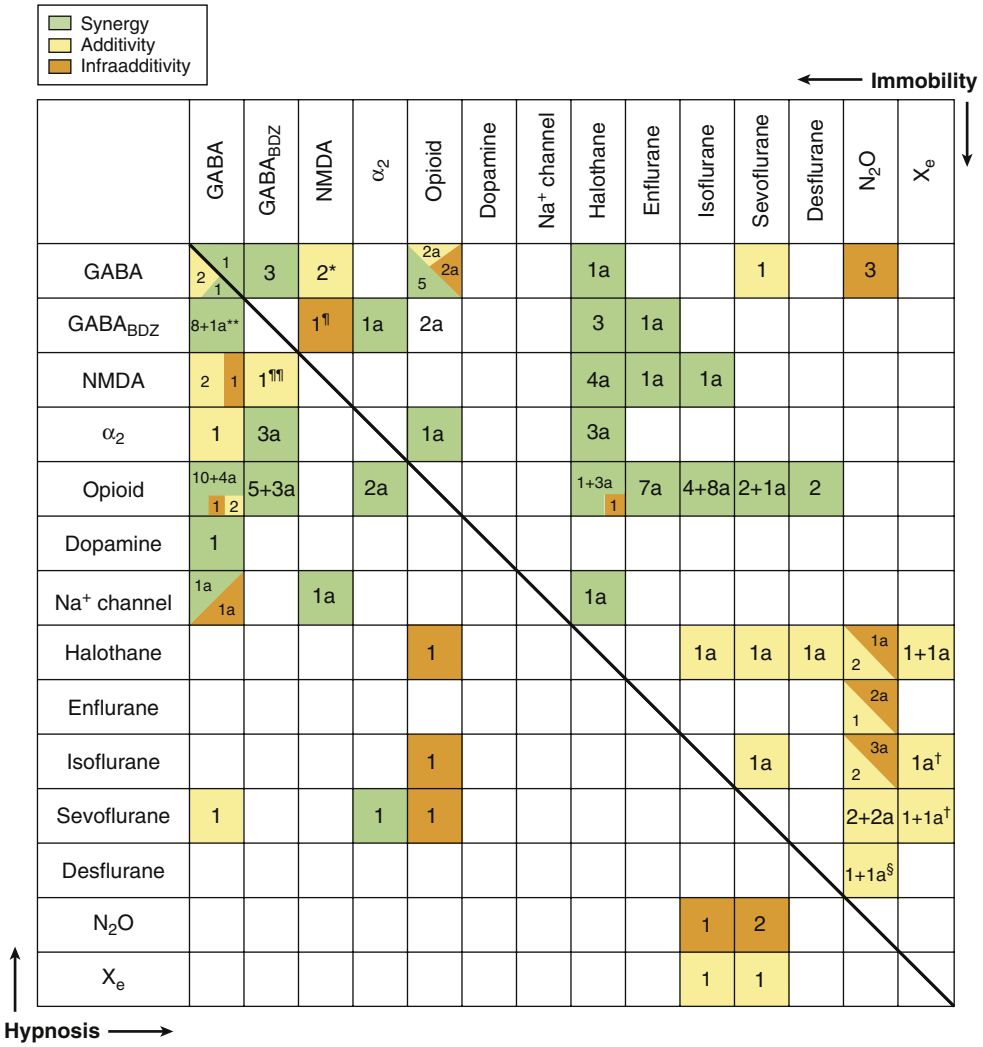


Figure 33-10. Interaction grid summarizing the available data on drug interactions in humans and animals for hypnosis and immobility. Drugs are organized by pharmacologic class: gamma-aminobutyric acid (GABA)–acting drugs (propofol, thiopental, methohexital, and etomidate); GABA agents acting at the benzodiazepine ($GABA_{BDZ}$)-binding site (midazolam, diazepam); *N*-methyl-D-aspartate (NMDA)-receptor antagonist (ketamine); adrenergic agonists (α_2) (dexmedetomidine, clonidine); opioid-acting drugs at opioid receptor (morphine, alfentanil, fentanyl, sufentanil, and remifentanil); dopamine at dopamine antagonists (droperidol, metoclopramide); sodium (Na^+) channel blockers (lidocaine, bupivacaine); and anesthetic gases. The right upper half of the grid *(above the thick diagonal)* summarizes the interactions for the endpoint of immobility; the left lower half *(below the thick diagonal)* summarizes the interactions for the endpoint of hypnosis. Synergy is coded as *green,* additivity as *yellow*, and infra-additivity as *dark orange.* The number refers to the number of studies attesting to a particular interaction; if one study documents two interactions (e.g., isoflurane with both fentanyl and alfentanil), then they are counted separately. Animal data carry the suffix *a* after the number of studies, human data have no suffix.

*Reanalysis: propofol-ketamine interaction in humans is infra-additive for immobility.

**Reanalysis: thiopental-midazolam interaction in humans is additive for hypnosis.

¶Reanalysis: ketamine-midazolam interaction in humans is infra-additive for hypnosis and additive for immobility.

§Infra-additivity between desflurane and nitrous oxide (N_2O) has been suggested in a small subgroup of 18- to 30-year-old patients.

(From Hendrickx JF, Eger EI 2nd, Sonner JM, et al: Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility, Anesth Analg *107:494-506, 2008. Used with permission.)*

model performance. Heyse and colleagues (Fig. 33-13) found that the pharmacodynamic interaction between sevoflurane and remifentanil for tolerance to shaking and shouting (TOSS), tetanic stimulation (TTET), laryngeal mask airway insertion (TLMA), and laryngoscopy (TLAR) using the Fixed C50(O) Hierarchical model was strongly synergistic for both the hypnotic and the analgesic components of anesthesia and showed the importance of exploring various surface model approaches when studying drug interactions.[72]

For total intravenous anesthesia, interactions associated with various drug combinations and concentrations have been described. The concept of *balanced* anesthesia is based on the assumption that drug combinations will be synergistic in anesthetic effect (however defined) but not in toxicity. Such synergism has been demonstrated for a variety of drug combinations but not for others[68,80] (see Fig. 33-10). Zanderigo and colleagues[81] developed the *well-being model*, a new interaction model to describe both positive and negative effects of drug combinations (Fig. 33-14).

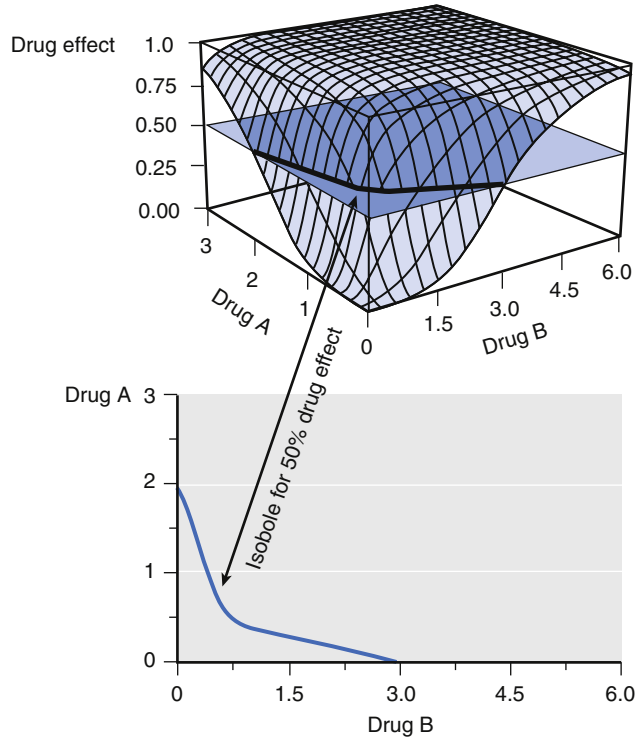


Figure 33-11. Relationship between a response surface and a standard isobologram. Conventional isobolographic analysis, whether for doses or concentrations, describes only the concentration of both drugs that yields a 50% drug effect and thus fails to capture the entire response surface. *(From Minto CF, Schnider TW, Short TG, et al: Response surface model for anesthetic drug interactions,* Anesthesiology *92:1603-1616, 2000. Used with permission.)*

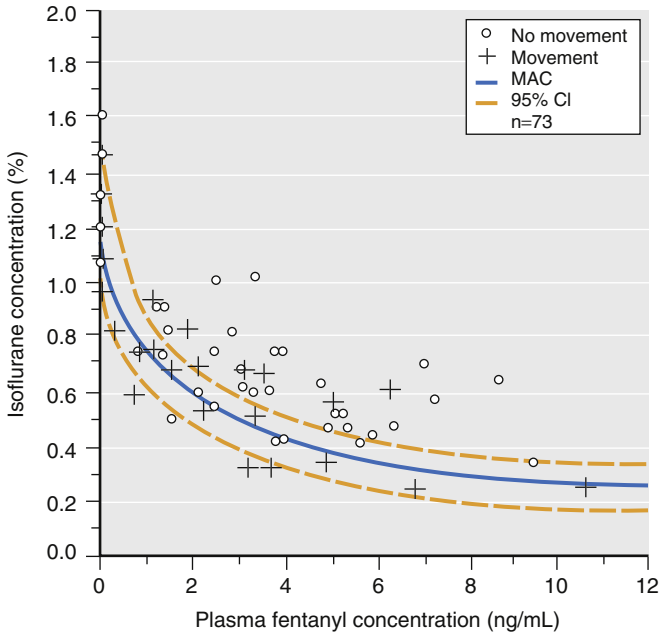


Figure 33-12. Interaction of isoflurane and fentanyl in preventing a somatic response at skin incision (i.e., minimum alveolar concentration [MAC] reduction of isoflurane). The *blue line* represents the concentrations of isoflurane and fentanyl when administered together that are required to prevent purposeful movement in 50% of patients at skin incision. The *dotted gold lines* represent the 95% confidence interval (CI) of the MAC at each combination of fentanyl and isoflurane. *(From McEwan AI, Smith C, Dyar O, et al: Isoflurane MAC reduction by fentanyl,* Anesthesiology *78:864-869, 1993. Used with permission.)*

More profound synergy for specific endpoints related to analgesia and hypnosis has also been demonstrated for the interaction between propofol and opioids. Thus when anesthetic regimens are designed that rely on synergy to produce the anesthetic state, distinguishing the desired endpoint—loss of consciousness or ablation of response to noxious stimulation—is important. Different combinations of drugs may be required to achieve each endpoint. Vuyk and colleagues characterized the interaction between propofol and alfentanil for several endpoints: loss of response to endotracheal intubation, loss of response to incision and retraction of the peritoneum, and emergence from anesthesia (Fig. 33-15).[82] The most profound stimulation was tracheal intubation, and the abolition of that stimulus required a propofol concentration equal to or more than 2 μg/mL. More details for optimal drug combinations based on the findings from Vuyk and co-workers[82] are provided in Table 33-3.

Minto and colleagues published *response surfaces* for combinations of midazolam-alfentanil, propofol-alfentanil, and midazolam-propofol associated with the loss of response to verbal command (Fig. 33-16).[83] They also extended response surface methodology to describe the simultaneous interaction of three drugs. Rendering the full interaction surface for three drugs would require drawing the graph in four dimensions. If the graph is limited to the interaction at 50% drug effect, then it can be rendered in three dimensions (Fig. 33-17).

In addition to the quantal responses, various studies investigated the interaction between hypnotics and opioids as measured with continuous measures. The effect of combined drug administration on spontaneous and evoked EEG–derived indices was found to be important and existing but often in studies that did not provide sufficient data for full response surface model development.[26,84,85] Fortunately, more accurate designed studies[71] using surface modeling techniques revealed the interaction between hypnotics and opioids. Bouillon and colleagues found synergy between propofol and remifentanil regarding hypnosis as measured by the BIS and EEG approximate entropy. They also found that both indices were more sensitive to propofol than remifentanil.[86] Others found conflicting results for the effect of opioids on the BIS.[87] More recently, Gambus and colleagues modeled the effect of propofol and remifentanil combinations for sedation-analgesia in endoscopic procedures using an adaptive neurofuzzy inference system. Both spontaneous and evoked EEG–derived indices (e.g., BIS or autoregressive auditory-evoked potential index [AAI/2] and index of consciousness [IoC]) were used. They found, based on these models, that the propofol and remifentanil effect-site concentration pairs provide a Ramsay Sedation Score of 4 ranging from (1.8 $\mu g/mL^{-1}$, 1.5 ng/mL^{-1}) to (2.7 $\mu g/mL^{-1}$, 0 ng/mL^{-1}), associated with a BIS of 71 to 75, AAI/2 values of 25 to 30, and IoC of 72 to 76, respectively. The presence of noxious stimulation increases the requirements of propofol and remifentanil

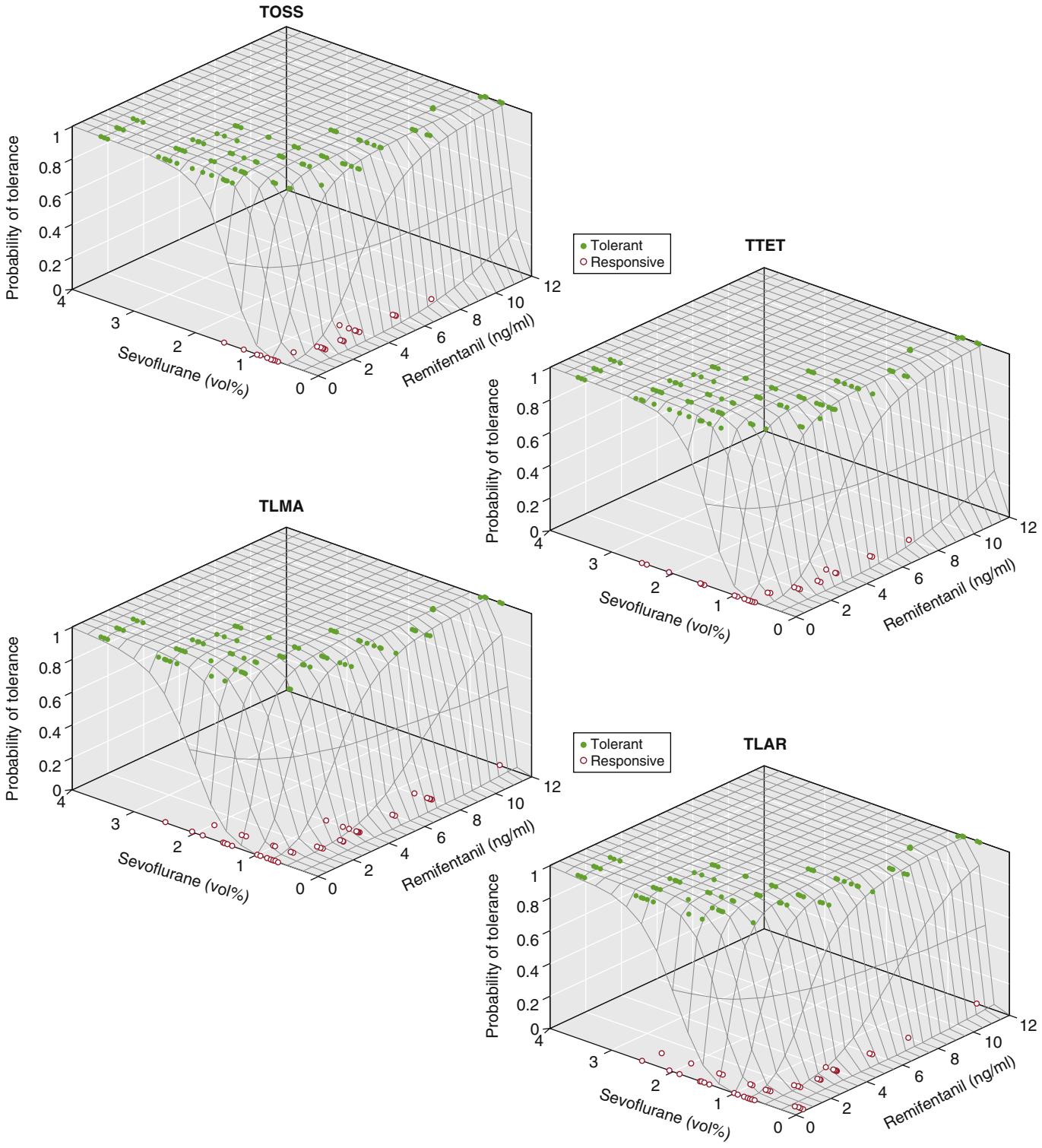


Figure 33-13. Response surface for probability of tolerance to shaking and shouting (TOSS), tetanic stimulation (TTET), laryngeal mask airway insertion (TLMA), and laryngoscopy (TLAR) for the Fixed C50(O) Hierarchical model. The solid lines at probability 0.5 represent the 50% isoboles. *(From Heyse B, Proost JH, Schumacher PM, et al: Sevoflurane remifentanil interaction: comparison of different response surface models,* Anesthesiology *116:311-323, 2012. Used with permission.)*

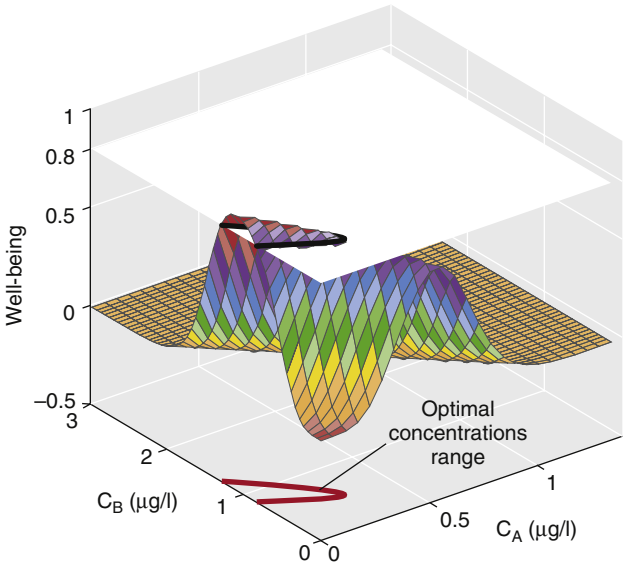


Figure 33-14. Definition of the optimal concentrations range for the combined administration of drugs A and B, in the case of zero interactions. The optimal concentrations range results from the intersection between the well-being surface and the plane representing a well-being value of 0.8. *(From Zanderigo E, Sartori V, Sveticic G, et al: The well-being model: a new drug interaction model for positive and negative effects,* Anesthesiology *104:742-753, 2006. Used with permission.)*

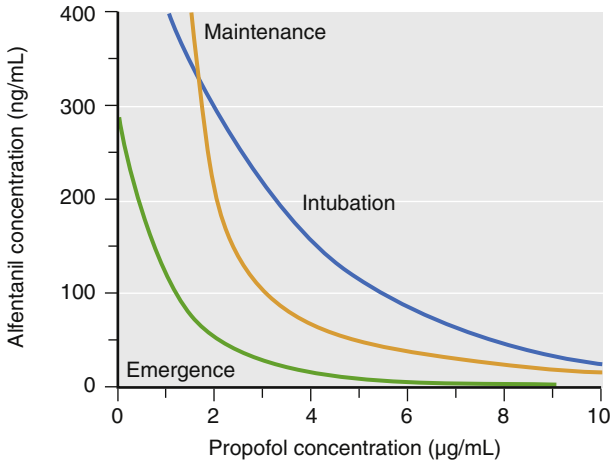


Figure 33-15. Interaction between alfentanil and propofol on three different endpoints: response to intubation (*blue line*), maintenance of anesthesia (*gold line*), and concentrations associated with emergence from anesthesia (*green line*). The curve shows the concentrations associated with a 50% probability of the respective endpoint. *(Adapted from Vuyk J, Lim T, Engbers FH, et al: The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women,* Anesthesiology *83:8-22, 1995.)*

to achieve the same degree of sedative effects.[88] Other effects of drug combinations were studied. Bouillon and associates and Nieuwenhuijs and associates investigated the effects of hypnotic-opioid combinations on cardiorespiratory control.[87,89] These data show dose-dependent effects on respiration at relatively low concentrations of propofol and remifentanil. When combined, their effect on respiration is strikingly synergistic, resulting in severe respiratory depression.

Surface models were also used to optimize drug administration in challenging situations such as short-duration procedures in spontaneous breathing patients. LaPierre and co-workers[90] explored remifentanil-propofol combinations that led to a loss of response to esophageal instrumentation, a loss of responsiveness, and/or an onset of ventilatory depression requiring intervention. They found that the combinations that allowed esophageal instrumentation and avoided intolerable ventilatory depression and/or loss of responsiveness primarily clustered around remifentanil-propofol effect-site concentrations ranging from 0.8 to 1.6 ng/mL and 1.5 to 2.7 µg/mL, respectively. However, blocking the response to esophageal instrumentation and avoiding both intolerable ventilatory depression and/or a loss of responsiveness is difficult. It may be necessary to accept some discomfort and blunt, rather than block, the response to esophageal instrumentation to consistently avoid intolerable ventilatory depression and/or loss of responsiveness.

The interactions between hypnotics such as propofol and sevoflurane should be understood, because these drugs are frequently used sequentially. Schumacher and colleagues[91] used response surface methodology to examine the influence of this interaction on the probability of TOSS and three noxious stimuli (TTET, TLMA, and TLAR). They found that for both EEG suppression and tolerance to stimulation, the interaction of propofol and sevoflurane were additive. Others found similar results on the C_{50} level.[92] Hammer and colleagues[93] determined the pharmacodynamic interaction of propofol and dexmedetomidine during pediatric esophagogastroduodenoscopy and concluded that the concentration of propofol at which 50% of patients are adequately anesthetized (EC_{50}) in children was unaffected by a concomitant intravenous infusion of dexmedetomidine 1 µg/kg body weight given over 10 minutes.

DESIGNING DOSING REGIMENS

BOLUS DOSE CALCULATIONS

The definition of concentration is drug mass per unit of volume. The definition of concentration can be rearranged to find the amount of drug required to produce any desired concentration for a known volume.

$$Amount = C_T \cdot Volume \qquad (10)$$

where C_T is the desired or *target* concentration. This formula is often used to calculate the initial (loading) bolus dose required to achieve a given concentration. The problem with applying this concept to anesthetic drugs is that there are several volumes of distribution: V_1 (central compartment), V_2 and V_3 (the peripheral compartments), and Vd_{ss} (the sum of the individual volumes). V_1 is usually significantly smaller than Vd_{ss}, and thus saying that the loading dose should be something between $C_T \times V_1$ and $C_T \times Vd_{ss}$ is tempting.

Consideration should be given to the dose of fentanyl required to attenuate the hemodynamic response to endotracheal intubation when combined with thiopental. The C_{50} for fentanyl, combined with thiopental for intubation, is approximately 3 ng/mL. The V_1 and Vd_{ss} for fentanyl are 13 L and 360 L, respectively. The aforementioned

TABLE 33-3 PROPOFOL/OPIOID COMBINATIONS ASSOCIATED WITH THE FASTEST RECOVERY FROM ANESTHESIA

Infusion Duration (min)		Propofol/Alfentanil (μg/mL; ng/mL)	Propofol/Sufentanil (μg/mL; ng/mL)	Propofol/Remifentanil (μg/mL; ng/mL)
15	$C_{optimal}$	3.25/99.3	3.57/0.17	2.57/4.70
	$C_{awakening}$	1.69/65.0	1.70/0.10	1.83/1.93
	Time to awakening (min)	8.2	9.4	5.1
60	$C_{optimal}$	3.38/89.7	3.34/0.14	2.51/4.78
	$C_{awakening}$	1.70/64.9	1.70/0.10	1.83/1.93
	Time to awakening (min)	12.2	11.9	6.1
300	$C_{optimal}$	3.40/88.9	3.37/0.14	2.51/4.78
	$C_{awakening}$	1.70/64.9	1.70/0.10	1.86/1.88
	Time to awakening (min)	16.0	15.6	6.7

$C_{optimal}$ represents combinations associated with a 50% probability of a response to surgical stimuli; $C_{awakening}$ concentrations represent the estimated concentrations at which consciousness will be regained; and Time to awakening represents the estimated time from termination of the infusion to return of consciousness in 50% of patients.

(From Vuyk J, Mertens MJ, Olofsen E, et al: Propofol anesthesia and rational opioid selection: determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness, Anesthesiology *87:1549-1562, 1997; and modified from Absalom A, Struys MMRF:* An overview of TCI and TIVA*, ed 2, 2007. Gent, Belgium, Academia Press. Used with permission.)*

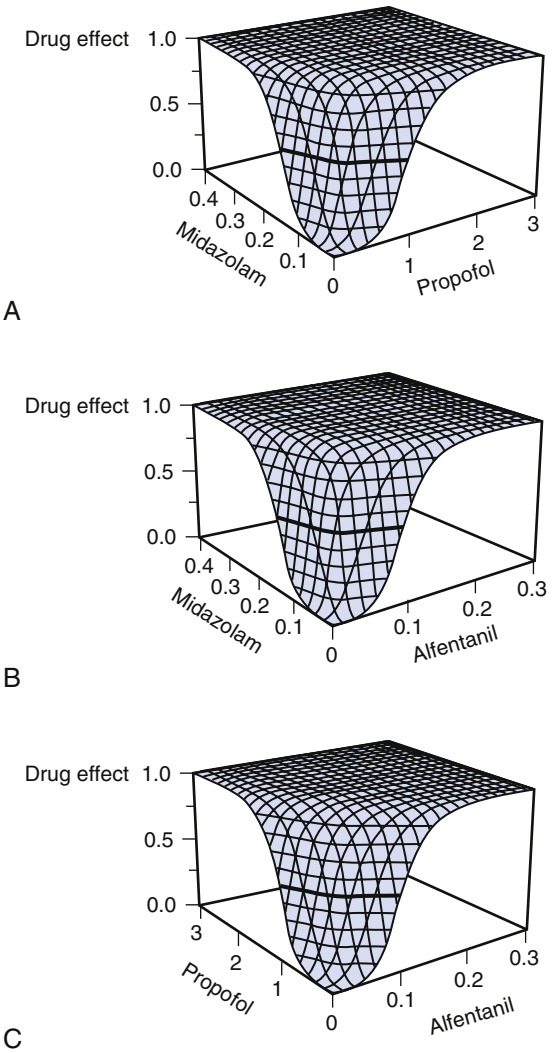


Figure 33-16. Response surface for each of the paired interactions between propofol and midazolam (**A**), alfentanil and midazolam (**B**), and alfentanil and propofol (**C**) on the probability of opening eyes to a verbal command. The isoboles for a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, and 90% response are shown. *(From Minto CF, Schnider TW, Short TG, et al: Response surface model for anesthetic drug interactions,* Anesthesiology *92:1603-1616, 2000.)*

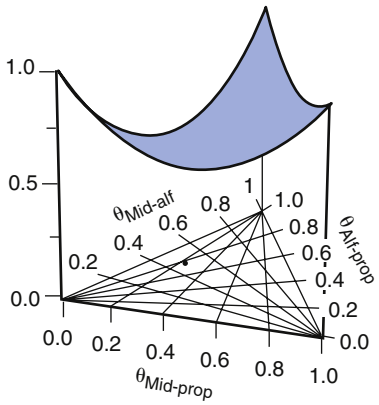


Figure 33-17. Interaction at 50% drug effect (C_{50}) among propofol, midazolam, and alfentanil. Downward deflection of the surface represents synergy, in units of fractional reduction in C_{50}. The three edges represent relative amounts of propofol to midazolam ($\theta_{Mid\text{-}prop}$), alfentanil to midazolam ($\theta_{Mid\text{-}alf}$), and alfentanil to propofol ($\theta_{Alf\text{-}prop}$). The surface between the edges represents the relative synergy of all three drugs taken together. *(From Minto CF, Schnider TW, Short TG, et al: Response surface model for anesthetic drug interactions,* Anesthesiology *92:1603-1616, 2000.)*

equations can thus be interpreted as suggesting that an appropriate dose of fentanyl to attenuate the hemodynamic response is between 39 μg (3 ng/mL × 13 L) and 1080 μg (3 ng/mL × 360 L). A fentanyl bolus of 39 μg achieves the desired concentration in plasma for an initial instant, but plasma levels almost instantly decrease below the desired target. Levels at the effect site will never be close to the desired target concentration of 3 ng/mL. A fentanyl bolus of 1080 μg, not surprisingly, produces a significant overshoot in plasma levels that persists for hours (Fig. 33-18). Additionally, using equations to calculate the fentanyl dose if the resulting recommendation is to "use a fentanyl dose between 39 and 1080 μg" is absurd.

The usual dosing guidelines for a bolus dose, presented earlier, are designed to produce a specific plasma concentration. Because plasma is not the site of drug effect, calculating the initial bolus on the basis of a desired plasma concentration is irrational. By knowing the k_{e0}

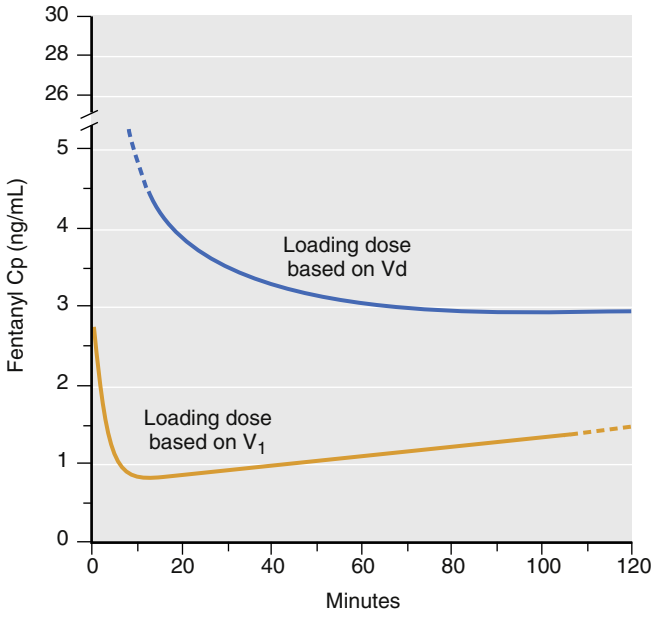


Figure 33-18. Pharmacokinetic simulation demonstrating the limitations of infusion regimens based on simple pharmacokinetic parameters with fentanyl used as an example. These infusion schemes were designed to achieve a fentanyl plasma concentration (Cp) of 3 ng/mL. The *upper blue curve* shows that a regimen using a loading dose based on the volume of distribution followed by a constant infusion based on clearance results in a transient period of very high plasma concentrations. If the same maintenance infusion is given but the loading dose is based on the volume of the central compartment, then the distribution of drug to the peripheral compartments causes the plasma concentration to fall below the desired level until the compartments reach steady-state concentrations as shown in the *lower gold curve*.

of an intravenous anesthetic, a dosing regimen can be designed that yields the desired concentration at the site of drug effect. To avoid an overdose for the patient, a bolus should be selected that produces the desired peak concentration at the effect site.

The decline in plasma concentration between the initial concentration after the bolus (amount/V_1) and the concentration at the time of peak effect can be thought of as dilution of the bolus into a larger anatomic volume than the volume of the central compartment. This introduces the concept of Vd_{pe}, the apparent volume of distribution at the time of peak effect,[28,94] or pseudoequilibration between plasma and the site of drug effect.[95] The size of this volume can be readily calculated from the observation that the plasma and effect-site concentrations are the same at the time of peak effect.

$$Vd_{pe} = \frac{Bolus\ amount}{C_{pe}} \qquad (11)$$

where C_{pe} is the plasma concentration at the time of peak effect.

If the clinical goal is to select the dose required to achieve a certain drug effect without producing an overdose, then Equation 11 can be rearranged by substituting C_T, the target concentration (which is the same in plasma and the effect site at the moment of peak effect), for C_{pe} to calculate the size of the initial bolus

$$Loading\ dose = C_T \cdot Vd_{pe} \qquad (12)$$

The Vd_{pe} for fentanyl is 75 L. To achieve a peak fentanyl effect-site concentration of 3.0 ng/mL requires 225 µg, which produces a peak effect in 3.6 minutes. This dosing guideline is more reasonable, compared with the previous recommendation of a dose between 39 and 1080 µg. Table 33-4 lists V_1 and Vd_{pe} for fentanyl, alfentanil, sufentanil, remifentanil, propofol, thiopental, and midazolam. Table 33-1 lists the time to peak effect and the $t_{1/2}$ k_{e0} of the commonly used intravenous anesthetics.

TABLE 33-4 VOLUME OF DISTRIBUTION AT THE TIME OF PEAK EFFECT

Drug	V_1 (L)	Vd_{pe} (L)
Fentanyl	12.7	75
Alfentanil	2.19	5.9
Sufentanil	17.8	89
Remifentanil	5.0	17
Propofol	6.7	37
Thiopental	5.6	14.6
Midazolam	3.4	31

V_1, Volume of the central compartment; Vd_{pe}, apparent volume of distribution at the time of peak effect.

MAINTENANCE INFUSION RATES

By definition, the rate at which active drug exits the body is systemic clearance (Cl_S) times the plasma concentration. To maintain a given target concentration (C_T) drug must be delivered at the same rate that it is exiting the body. Thus

$$\text{Maintenance infusion rate} = C_T \cdot Cl_s \qquad (13)$$

For drugs with multicompartment pharmacokinetics, which includes all of the intravenous drugs used in anesthetic practice, drug is distributed into the peripheral tissues, as well as cleared from the body. The rate of distribution into tissues changes over time as the tissues equilibrate with plasma. Equation 13 is correct only after the peripheral tissues have fully equilibrated with plasma, which requires many hours. At all other times, this maintenance infusion rate underestimates the infusion rate necessary to maintain a target concentration.

Yet, in some situations, this simple maintenance rate calculation may be acceptable. For example, if an infusion at this rate is used along with a bolus dose based on Vd_{pe} and the drug has a long delay between the bolus and peak effect, then most of the distribution of drug into tissues may have occurred by the time that the effect-site concentration reaches the target concentration. In this case, the maintenance infusion rate calculated as clearance times target concentration may be accurate because Vd_{pe} is sufficiently higher than V_1 to account for the distribution of drug into peripheral tissues. Unfortunately, most drugs used in anesthesia achieve sufficiently rapid equilibration between plasma

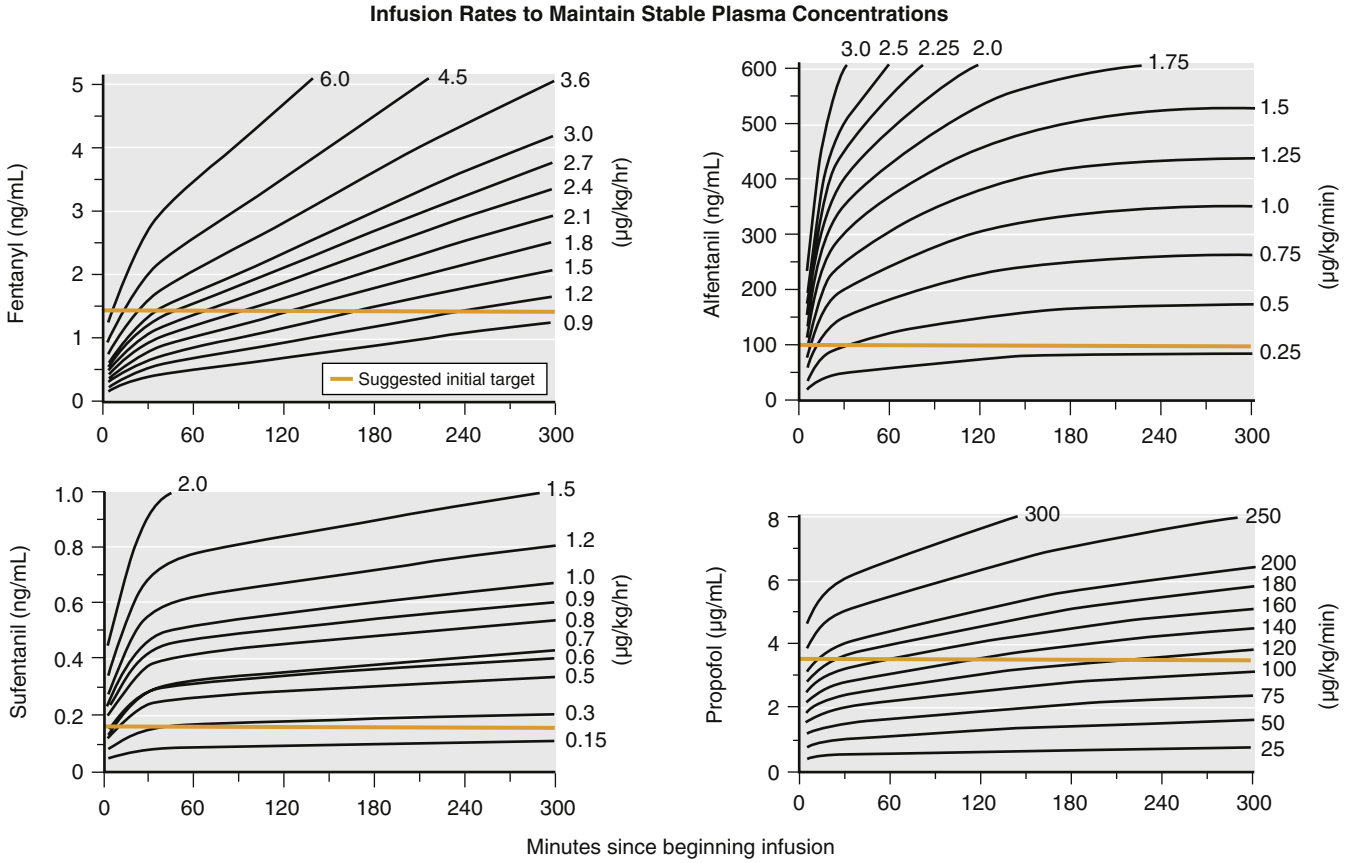


Figure 33-19. Nomogram for calculating maintenance infusion rates to maintain a stable concentration of fentanyl, alfentanil, sufentanil, or propofol. The *y* axis is the desired concentration. The *x* axis is the time relative to the initial bolus. The *diagonal lines* show the infusion rates at different times required to maintain the desired concentration selected on the *y* axis.

and the effect site that Vd_{pe} does not adequately encompass the distribution process, thus making this approach unsuitable.

As such, approaches need to be used that are mathematically and clinically sound. Because the net flow of drug into peripheral tissues decreases over time, the infusion rate required to maintain any desired concentration must also decrease over time. If the initial bolus has been based on Vd_{pe}, no infusion needs be administered until the effect-site concentration peaks. After the peak in effect-site concentration, the (nearly) correct equation to maintain the desired concentration is

$$\text{Maintenance infusion rate} = C_T \cdot V_1 \cdot \left(k_{10} + k_{12}e^{-k_{21}t} + k_{13}e^{-k_{31}t}\right) \qquad (14)$$

This equation indicates that a rapid infusion rate is initially required to maintain C_T. Over time, the infusion rate gradually decreases (see Fig. 33-14). At equilibrium ($t = \infty$), the infusion rate decreases to $C_T \times V_1 \times k_{10}$, which is the same as $C_T \times Cl_S$. Few clinicians would choose to solve such an equation during the administration of an anesthetic. Fortunately, simple techniques can be used in place of solving such a complex expression.

Figure 33-19 is a nomogram in which Equation 14 has been solved; the infusion rates at different times necessary to maintain any desired concentration of fentanyl, alfentanil, sufentanil, and propofol are shown. Because this nomogram is complex, the following review is provided:

The *y* axis represents the target concentration C_T. The *x* axis is the time since the beginning of the anesthetic (i.e., since the initial bolus). The suggested initial target concentrations (shown in gold) are based on the work of Vuyk and colleagues[82] with propofol and alfentanil (see Fig. 33-15) and are scaled to fentanyl and sufentanil according to their relative potencies.[94] The intersections of the target concentration line and the diagonal lines indicate the infusion rate appropriate at each point in time. For example, to maintain a fentanyl concentration of 1.5 ng/mL, the appropriate rates are 4.5 µg/kg/hr at 15 minutes, 3.6 µg/kg/hr at 30 minutes, 2.7 µg/kg/hr at 60 minutes, 2.1 µg/kg/hr at 120 minutes, and 1.5 µg/kg/hr at 180 minutes. Of course, selecting target concentrations and different times of rate adjustment is possible, depending on the clinical circumstances and an assessment of how accurately the intravenous drug needs to be titrated.

RECOVERY FROM ANESTHESIA

Recovery from anesthesia is determined by the pharmacokinetic principles that govern the rate of decrease in drug from the effect compartment once drug administration is terminated, as well as by the pharmacodynamics

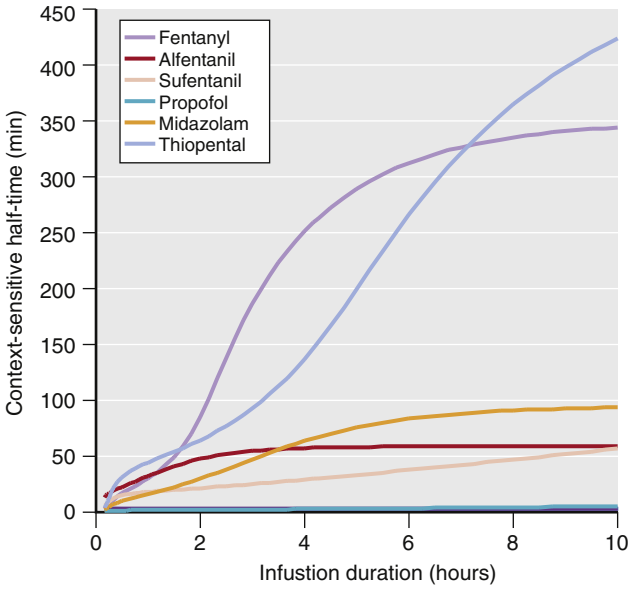


Figure 33-20. Context-sensitive half-times as a function of infusion duration (*context*) derived from pharmacokinetic models of fentanyl, sufentanil, alfentanil, remifentanil, propofol, midazolam, and thiopental. *(From Hughes MA, Glass PSA, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs,* Anesthesiology *76:334-341, 1992.)*

of the drug. Although the terminal elimination half-life is often interpreted as a measure of how short- or long-lasting a drug is, the rate at which drug plasma concentration decreases is dependent on both elimination and redistribution of the drug from the central compartment. The contribution of redistribution and elimination toward the rate of decrease in drug concentration varies according to the duration for which the drug has been administered[94,96] and also the time since the infusion has stopped, because these processes have different rate constants.

In 1985, Schwilden[97] developed a mathematic model to relate the time course of offset of action of inhaled anesthetics to the duration of anesthetic drug delivery. Similarly, Fisher and Rosen[98] demonstrated how the accumulation of muscle relaxants in peripheral volumes of distribution results in slowed recovery with increasing duration of administration. They introduced two measures of the time course of recovery, the time for twitch tension to recover from 5% to 25% and the time for twitch tension to recover from 25% to 75%.

Since then, the time for the plasma concentration to decrease by 50% from an infusion that maintains a constant concentration (e.g., infusion given by Equation 14) has been termed the *context-sensitive half-time*[96] (Fig. 33-20), with the context being the duration of the infusion. The 50% decrease was chosen both for tradition (e.g., half-lives are the time for a 50% decrease with a one-compartment model) and because, very roughly, a 50% reduction in drug concentration appears to be necessary for recovery after the administration of most intravenous hypnotics at the termination of surgery. Depending on circumstances, decreases other than 50% may be clinically relevant. Additionally, sometimes it is the plasma concentration that is of interest, and sometimes it is the effect-site concentration that is of interest. A more general term is the context-sensitive *decrement time*,[99] in which the decrement in concentration is specifically noted, as is the compartment where the decrease is modeled (plasma or effect site). For example, the relationship between infusion duration and the time required for a 70% decrease in fentanyl effect-site concentration is the *context-sensitive 70% effect-site decrement time*.

Context-sensitive effect-site decrement times for varying percent decreases in alfentanil, fentanyl, sufentanil, and remifentanil concentration are illustrated in Figure 33-21. To determine when an infusion should be terminated (to enable awakening of the patient at the end of surgery), the clinician needs to bear in mind the decrease in concentration necessary for recovery, the duration of the infusion (the context), and the context-sensitive, effect-site decrement time required for the necessary decrease.

Context-sensitive decrement times are fundamentally different from the elimination half-life. With monoexponential decay, each 50% decrease in concentration requires the same amount of time, and this time is independent of how the drug is given. This is not true for the context-sensitive half-time. First, as the name is intended to imply, the time needed for a 50% decrease is absolutely dependent on how long the drug was given, with infusion duration being the context to which the name refers. In addition, small changes in percent decrement can result in surprisingly large increases in the time required. The time required for a 60% decrease in drug concentration can be more than twice the time required for a 50% decrease in some situations (see Fig. 33-21).

Context-sensitive decrement times are based on the assumption that plasma or the effect site is maintained at a constant concentration. Such is rarely the case clinically, but the maintenance of constant concentrations is a necessary assumption to provide a unique mathematic solution to the time required for a given percent decrement in plasma or effect-site concentration. Because plasma and effect-site concentrations are rarely kept constant, it is important that context-sensitive decrement times are used as *general* guidelines for interpreting the pharmacokinetics of intravenous drugs and not as *absolute* predictions for any given case or infusion regimen. Automated drug delivery systems can provide more precise predictions of the time required for the plasma or effect-site concentration to decrease to any desired concentration, based on the actual drug dosing in the individual patient, which provides the clinician with guidance for the most appropriate time to terminate the infusion.

Context-sensitive decrement times focus on the role of pharmacokinetics in recovery from anesthesia. Pharmacodynamics plays an important role in recovery as well. Bailey[100] used integrated pharmacokinetic-pharmacodynamic models to define the *mean effect time* as the average time to responsiveness after maintenance of anesthesia at the 90% probability of unresponsiveness. The mean effect time demonstrates that when drugs have a very shallow concentration-versus-response relationship, concentrations must decrease by a significant fraction to provide adequate emergence, which delays recovery from anesthesia. In contrast, recovery is hastened by a steep

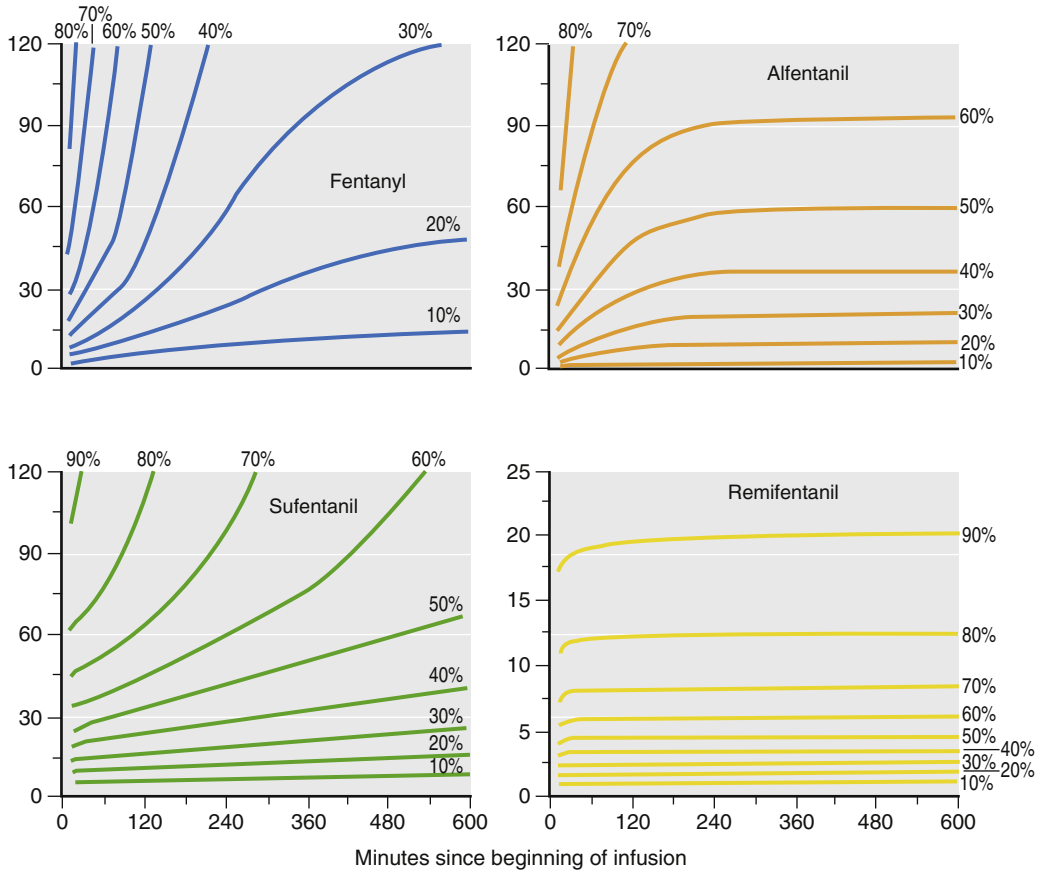


Figure 33-21. Context-sensitive effect-site decrement times for alfentanil, fentanyl, sufentanil, and remifentanil showing the time required for decreases of a given percentage (*labeled for each curve)* from the maintained effect-site concentration after termination of the infusion.

concentration-versus-response relationship, in which emergence from anesthesia occurs after a relatively small fractional decrease in concentration. Most intravenous hypnotics have a moderately steep concentration-versus-response relationship.

Pharmacodynamic drug interactions also play a role in recovery from anesthesia. Interaction relationships predict that the same anesthetic state can be achieved by different ratios of two drugs. One way of selecting the best ratio might be the combination that offers the most rapid recovery. For example, when an opioid is combined with a hypnotic, the rate of recovery from anesthesia depends on the opioid and hypnotic concentrations, the rate of decrease in both drug concentrations, and the relative synergy between them for loss of response to noxious stimulation (i.e., the state maintained during anesthesia) versus the relative synergy for loss of consciousness. Although the time course of decreases in opioid and hypnotic concentrations can be approximately described by their respective context-sensitive decrement times for both drugs (Fig. 33-22; see Fig. 33-15]), the influence of relative synergy for different endpoints must be captured by separate models of the interaction of the drugs for adequate anesthesia and emergence from anesthesia.

Vuyk and co-workers[43] modeled the predicted time to awakening from adequate anesthesia when propofol is combined with fentanyl, sufentanil, alfentanil, or

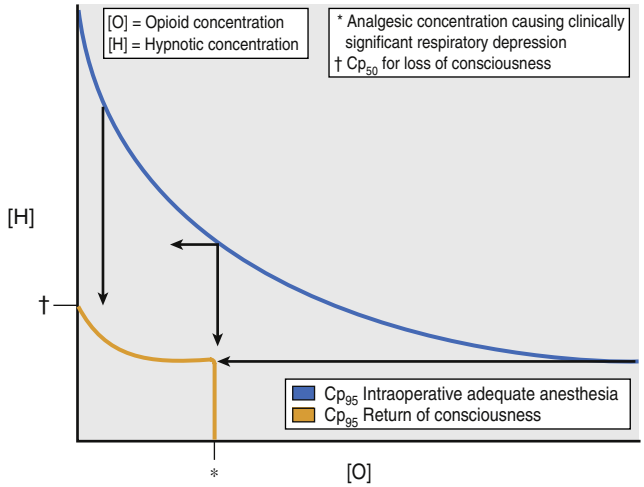


Figure 33-22. Interaction between hypnotics and opioids for the prevention of movement after a noxious stimulus and for awakening and adequate spontaneous ventilation at the end of a surgical procedure. The time to recover at the end of a procedure is dependent on the concentration of both drugs used during surgery and the time for both to decrease below that required for consciousness and adequate spontaneous ventilation (i.e., their context-sensitive decrement times).

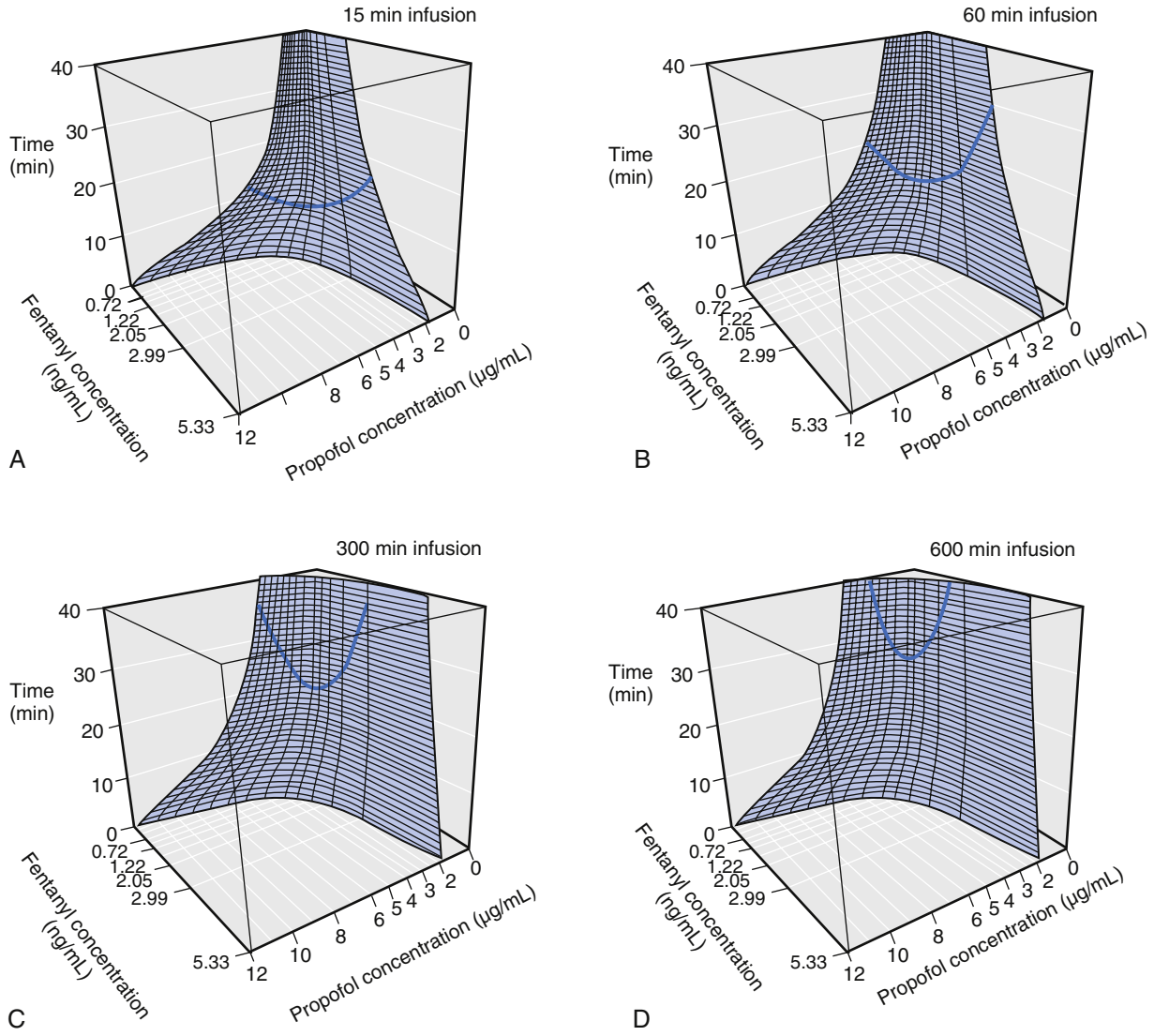


Figure 33-23. Simulation of the interaction of propofol and fentanyl in preventing a somatic response at skin incision and time to recovery. On the *x* axis is the fentanyl concentration, and on the *y* axis is the propofol concentration. The *blue curve* in the lower plane shows the propofol-fentanyl interaction required to provide adequate anesthesia. When the infusion is turned off, the concentrations of each drug decrease, as shown on the *z* axis. The *blue curve* drawn on the recovery surface shows the time to emergence from anesthesia for combinations of fentanyl and propofol after an anesthetic of 15 minutes' (**A**), 60 minutes' (**B**), 180 minutes' (**C**), and 600 minutes' (**D**) duration. The optimal combination for the most rapid recovery is a propofol concentration of 3.0 to 3.5 μg/mL, combined with 1.5 ng/mL fentanyl. As the concentration of propofol or fentanyl increases, the time for recovery increases. In addition, the longer the duration of drug infusion, the longer recovery takes, especially if the optimal combination is not used. *(Modified from Vuyk J, Mertens MJ, Olofsen E, et al: Propofol anesthesia and rational opioid selection: determination of optimal EC_{50}-EC_{95} propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness,* Anesthesiology *87:1549-1562, 1997.*)

remifentanil. Their calculations took into account the interaction between propofol and these opioids to provide adequate anesthesia and the interaction between propofol and opioids on consciousness levels on emergence from anesthesia (Figs. 33-23 and 33-24). Recovery times vary with the choice of opioid and the relative balance of opioid and propofol during maintenance of anesthesia. For example, the upper left of Figure 33-23 simulates the emergence from a propofol-fentanyl anesthetic of 15-minute duration. The simulations assume a steady concentration of fentanyl and propofol throughout the anesthesia, similar to the underlying assumption of context-sensitive decrement times. The blue curve in the lower plane is the interaction curve between fentanyl and propofol; it ranges from no fentanyl and 12 μg/mL of propofol on the left to 6 ng/mL of fentanyl and 1.8 μg/mL of propofol on the right. In theory, any point along this curve would ensure maintenance of equivalent depth of anesthesia. When the infusion is turned off after 15 minutes of anesthesia, the concentrations of both drugs decrease. The decreasing concentrations of propofol and fentanyl when the infusion is turned off can be found by the upward lines drawn from different points on the interaction curve, with the distance away from the lower plane representing time. Taken together, these upward lines represent a *recovery surface*. The blue line drawn on

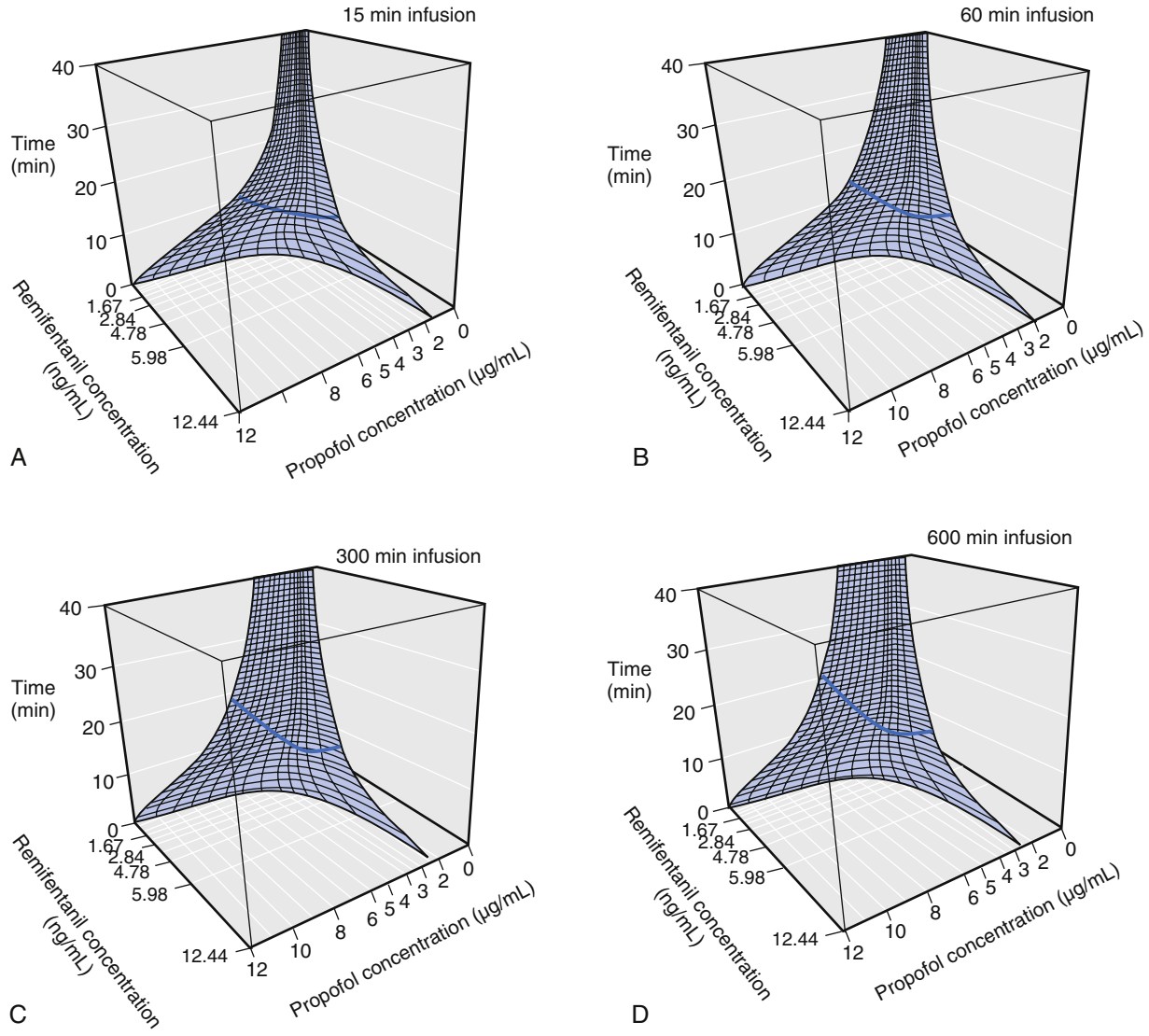


Figure 33-24. Simulation of the interaction of propofol and remifentanil in preventing a somatic response at skin incision and time to recovery. The remifentanil concentration is on the *x*-axis, and the propofol concentration is on the *y*-axis. The *blue curve* in the lower plane shows the propofol-remifentanil interaction required to provide adequate anesthesia. When the infusion is turned off, the concentrations of each drug decrease, as shown on the *z*-axis. The *blue line* drawn on the recovery surface shows the time to emergence from anesthesia for combinations of remifentanil and propofol after an anesthetic of 15 minutes' (**A**), 60 minutes' (**B**), 180 minutes' (**C**), and 600 minutes' (**D**) duration. With remifentanil, the optimal combination is a propofol concentration of 2.5 μg/mL and, with remifentanil, 5 to 7 ng/mL. In addition, increasing the duration of the infusion has minimal impact on recovery time if the optimal dose of remifentanil is not used. However, if the propofol dose is increased, then recovery is prolonged. *(Modified from Vuyk J, Mertens MJ, Olofsen E, et al: Propofol anesthesia and rational opioid selection: determination of optimal EC_{50}-EC_{95} propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness,* Anesthesiology *87:1549-1562, 1997.)*

the recovery surface shows the points at which the fentanyl-propofol interaction model predicts emergence.

After 15 minutes of maintaining 1.8 μg/mL of propofol and 6 ng/mL of fentanyl (right margin of the interaction curve), approximately 12 minutes is needed for the concentrations of both drugs to decrease sufficiently to permit emergence (see Fig. 33-23). However, if one maintains concentrations of 3.5 μg/mL of propofol and 1.5 ng/mL of fentanyl (toward the middle of the interaction curve), then emergence can be expected only 8 minutes after the infusions are turned off. Examination of the curves for 60, 300, and 600 minutes of propofol-fentanyl anesthesia suggests that the fentanyl target concentration that provides the most rapid emergence is approximately 1.0 to 1.5 ng/mL, which requires a propofol concentration of approximately 3.0 to 3.5 μg/mL to maintain adequate anesthesia. In similar simulations, Vuyk and colleagues demonstrated that maintaining alfentanil and sufentanil concentrations in excess of the analgesic range (i.e., approximately 80 ng/mL for alfentanil and 0.15 ng/mL for sufentanil) is of little clinical benefit and can be expected to delay recovery from anesthesia. A second conclusion from these simulations is that if the patient demonstrates inadequate anesthesia, increasing the hypnotic concentration rather than increasing the opioid concentration beyond the analgesic range is preferable, so as to prevent prolongation of recovery.

The situation is different for remifentanil because of its unusual pharmacokinetic properties (see Fig. 33-24). When

a remifentanil infusion is terminated, the extraordinarily fast clearance of remifentanil results in a very rapid offset of opioid drug effect. The lower plane again shows equivalent anesthetic states during maintenance with remifentanil and propofol (see Fig. 33-24). High doses of remifentanil permit a modest reduction in the dose of propofol needed for adequate anesthesia.[101] However, the recovery surfaces show that high doses of remifentanil, with a modest reduction in the propofol dose, permit considerably faster emergence from anesthesia. For example, it takes approximately 12 minutes to awaken from 600 minutes of anesthesia maintained with 3 μg/mL of propofol and 2.5 ng/mL of remifentanil (see Fig. 33-24, *D*). On the other hand, if the remifentanil concentration is increased to 5 ng/mL, then the propofol concentration can be reduced to between 2 and 2.5 μg/mL, and emergence can be anticipated within 6 minutes of discontinuation of the infusions. One might be concerned that such a technique places patients at increased risk for awareness because a propofol concentration of 2 μg/mL is below the C_{50} value for wakefulness.[102] Therefore combining such a technique with intraoperative EEG monitoring to assess anesthetic adequacy is reasonable.[20,102]

DISPLAYING PHARMACOLOGIC INFORMATION

Integrating all sources of pharmacologic information including drug interaction together with measurements of patient response to a specific drug dose might offer a powerful advisory tool to depict the complete dose-response relationship of multiple drugs, thereby optimizing drug administration and improving patient care.[103,104] For example, Figure 33-25 shows a drug interaction advisory display. Schumacher and colleagues proposed an advisory system for clinical use that offers real-time information about predicted drug concentrations, predicted combined effect, and predicted wake-up time resulting from these actions, as well as displaying the optimal drug concentration ratio for a given effect in this typical patient.[105] Others have described similar systems.[104]

INTRAVENOUS INFUSION DEVICES AND TECHNOLOGIES

MANUAL INTRAVENOUS INFUSION

When an infusion of an intravenous anesthetic is administered, the infusion regimen can be controlled by a variety of mechanisms varying from the simple Cair clamp or Dial-a-Flo (Abbott Laboratories) to complex computer-controlled infusion pumps. Simplicity of mechanical design, however, is not necessarily correlated with ease of use, which has prompted ongoing advances in infusion device technology over the past decades.

Infusion devices can be classified as either controllers or positive displacement pumps. Explicit in their title, controllers contain mechanisms that control the rate of flow produced by gravity, whereas positive displacement pumps contain active pumping mechanisms.

The most commonly used pumps for administration of intravenous anesthetics are positive displacement syringe pumps that use a variety of mechanisms. These pumps have acceptable accuracy and have several features that make them particularly suitable for anesthetic delivery. An important advance has been the introduction of a calculator feature within the pump so that the clinician can input the weight of the patient, the drug concentration, and the infusion rate in dose/unit weight/unit time and the pump will then calculate the infusion in volume/unit time. These pumps also permit simple application of a staged infusion scheme by allowing an initial dose and a maintenance infusion rate to be programmed into the pump. Numerous syringe pumps also include automated recognition of syringe size. Further enhancements are drug libraries by class of drug, suggested dosing schemes, and maximal dosing alerts. These modest advances in pump technology and design enable intravenous anesthetics to be conveniently and safely delivered.

In addition to the pumps, the complete intravenous delivery systems' hardware must perform perfectly,[5] which means that the correct amount of drug should be delivered to the venous circulation in each unit of time. When the drug administration set has too large a *dead-space*, the actual delivery rate can be altered, depending on the flow rate of co-administered fluid.[106] The use of an antireflux valve is certainly advisable to prevent flow of the medication backward into the intravenous fluid bag rather than into the patient. Other factors include excessive compliance within the administration system (in the syringe plunger or in the administration lines) and the use of syringes with suboptimal lubrication, causing the plunger to advance in small jumps when infusion rates are slow; that is, with small patients, low target concentrations, concentrated drug solutions, or large syringes.[5]

Manual intravenous drug delivery consists of a combination of a bolus dosage and a continuous infusion, as explained earlier when discussing the pharmacokinetic considerations. Table 33-5 offers recommendations for delivering intravenous anesthetics via conventional infusion pumps based on integrated pharmacokinetic-pharmacodynamic models. Ultimately, the adequate rate of drug administration is based on observation and examination. Individual patients vary significantly in their response to a given drug dose or concentration; therefore titrating to an adequate drug level for each individual patient is essential. Drug concentrations required to provide adequate anesthesia also vary according to the type of surgery (e.g., surface surgery versus upper abdominal surgery). Drug concentration requirements are often smaller during the end phase of surgery; therefore titration often involves judicious reduction of the infusion rate toward the end of surgery to facilitate rapid recovery.

If the infusion rate is insufficient to maintain adequate anesthesia, then both an additional loading (bolus) dose and an increase in infusion are required to increase the plasma (biophase) drug concentration rapidly. Various interventions also require larger drug concentrations, usually for brief periods (e.g., laryngoscopy, endotracheal intubation, skin incision). Therefore the infusion scheme should be tailored to provide peak concentrations during these brief periods of intense stimulation. An adequate drug level for endotracheal intubation is often achieved with the initial loading dose; however, for procedures such as skin incision, an additional bolus dose may be necessary.



Figure 33-25. On-line advisory displays including characteristics of drug behavior and interaction. The SmartPilot (Dräger, Lübeck, Germany) *(upper display)* is a two-dimensional display that shows the effect-site concentrations of combined drugs (opioids and intravenous or inhalation hypnotics), based on pharmacokinetic models and the resulting anesthetic effect and on pharmacodynamic models. Grey shaded areas indicate different levels of anesthesia. The *orange point* indicates the current combination of effect-site concentrations; the *white line* shows the retrospective concentrations; and a 10- and 15-minute prediction is marked by a *black point* and *arrow*—already calculated during presetting of delivery. Event markers may be set to show specific states of the patient related to the level of anesthesia: the time-based real-time curves, trends, and prediction of effect-site concentrations of individual drugs; resulting anesthetic effect (noxious stimulus response index [NSRI]) and correlated bispectral index (BIS), vital signs, and event markers as reference for interpretation. The Medvis display (Medvis, Salt Lake City, Utah) *(lower display)* shows a real-time visualization of anesthetic using pharmacokinetic and pharmacodynamic models to predict drug effect-site concentrations and drug effects in the past, current time, and 10 minutes into the future. Drug doses as boluses and infusions are administered via a separate data interface or user interface. Drugs are categorized according to sedation (*top plot*), analgesia (*middle plot*), and muscle relaxation (*bottom plot*). Effects are depicted as a population-based probability of unconsciousness (*top plot*), no response to tracheal intubation (*middle plot*), and no twitch response to a train of four stimulus *(bottom plot)*. In addition, a second pharmacodynamic endpoint, POST-OP ANALG, represents a guideline therapeutic window for postoperative pain. Synergistic interactions of sedative-hypnotics and analgesics are shown by the *white curves* in the plot. For example, the top plot shows that with only propofol, the probability of unconsciousness is between 50% and 95% *(yellow curve)*, but because propofol interacts with the opioids, the probability of unconsciousness is greater than 95% *(white curve)*. Similarly, propofol potentiates the effect of the opioids in the middle plot.

TABLE 33-5 **MANUAL INFUSION SCHEMES***

	Anesthesia		Sedation or Analgesia	
Drug	Loading Dose (μg/kg)	Maintenance Infusion (μg/kg/min)	Loading Dose (μg/kg)	Maintenance Infusion (μg/kg/min)
Alfentanil	50-150	0.5-3	10-25	0.25-1
Fentanyl	5-15	0.03-0.1	1-3	0.01-0.03
Sufentanil	0.5-5	0.01-0.05	0.1-0.5	0.005-0.01
Remifentanil	0.5-1.0	0.1-0.4	†	0.025-0.1
Ketamine	1500-2500	25-75	500-1000	10-20
Propofol	1000-2000	50-150	250-1000	10-50
Midazolam	50-150	0.25-1.5	25-100	0.25-1
Methohexital	1500-2500	50-150	250-1000	10-50
Dexmedetomidine			0.5-1 over 10 min	0.2-0.7

*After the loading dose, an initially high infusion rate to account for redistribution should be used and then titrated to the lowest infusion rate that will maintain adequate anesthesia or sedation. When using opiates as part of a nitrous-narcotic technique or for cardiac anesthesia, the dosing scheme listed under anesthesia is used. When the opiate is combined as part of balanced anesthesia, dosing listed for analgesia is needed.

†For analgesia or during sedation, an initial loading dose of remifentanil should not be given because its very rapid onset may result in apnea or muscle rigidity.

Infusion schemes (see Table 33-5) do not approach the convenience and precision of use associated with the delivery of an inhaled anesthetic via a calibrated vaporizer. This level of precision can be achieved by using TCI devices, such as the commercially available TCI pumps. These devices range from simple calculator pumps to pumps with automated drug delivery (see "Target-Controlled Infusion").

A particular method of intravenous drug administration is patient-controlled analgesia (PCA ; also see Chapter 98), mostly used for the postoperative administration of analgesics or for patient-controlled sedation (PCS) during therapeutic procedures. Although PCA can be considered as a method of computer-controlled or even closed-loop drug administration, most of these pumps do not include pharmacokinetic or pharmacodynamic algorithms. In some cases, the pump is set to deliver a low, constant or *background* flow of medication. Additional doses of medication can be self-administered by the patient pressing a button as needed. Most commonly, no background infusion is provided, and the patient controls when he or she receives an analgesic bolus. To avoid overdosing, these pumps have built-in safety mechanisms such as lock-out times and limitations of the total amount of drug delivered per time unit. PCA is a common technique for delivery of postoperative pain medication such as morphine, piritramide, fentanyl, tramadol, and other agents.[107-111] In a systematic review, Walder and colleagues showed that the literature presented some evidence that in the postoperative pain setting, PCA with opioids, compared with conventional opioid treatment, improved analgesia and decreased the risk of pulmonary complications; in general, the patients preferred the technique.[112] Strict hospital guidelines may help avoid side effects such as oversedation and respiratory depression.[113] When epidural analgesia is contraindicated during labor, remifentanil PCA has been suggested as an alternative. Pilot trials have suggested that this alternative is safe under strict observation.[114-119]

Studies on the quality and outcomes after PCS have shown that it reduces discomfort and fear by inducing sedation and amnesia during uncomfortable therapeutic procedures such as colonoscopy. Additionally, PCS facilitates the procedure by increasing the patient's tolerance. Although propofol offers no analgesic effect, several studies of patient control of propofol administration (bolus or short infusions) during procedures were performed and showed that it provided reasonably safe, light sedation, and that patients expressed a preference for being in control.[120-122] As this manual infusion regimen might produce fluctuating levels of sedation, Kenny and colleagues combined PCS with TCI of propofol to overcome this problem. Using this system, the patient can set a specific propofol target concentration. A lock-out time is set by the clinician (commonly with the default being approximately the equilibration time between plasma and effect-site concentrations). When the patient stops pushing the delivery button, the target concentration automatically decreases (see also "Target-Controlled Infusion" later in this chapter). In various applications requiring sedation, their experimental system was shown to be feasible; however, even when using an effect-site controlled TCI system, some volunteers rendered themselves unconscious. It is possible that safety can be improved further, particularly if a test or measure of responsiveness to a stimulus is added and if the control algorithm is incorporated to allow the facility to stop the infusion should the response become inadequate.[123-126] Doufas and colleagues tested an automatic response test to optimize propofol administration for conscious sedation.[127,128] Although volunteers were required to push a delivery button in response to auditory and tactile stimuli, a TCI-like algorithm guided the propofol administration. The study showed that failure to respond to automated responsiveness monitoring precedes potentially serious adverse effects of sedation such as loss of responsiveness, and that the monitor was not susceptible to false-positive responses.[129]

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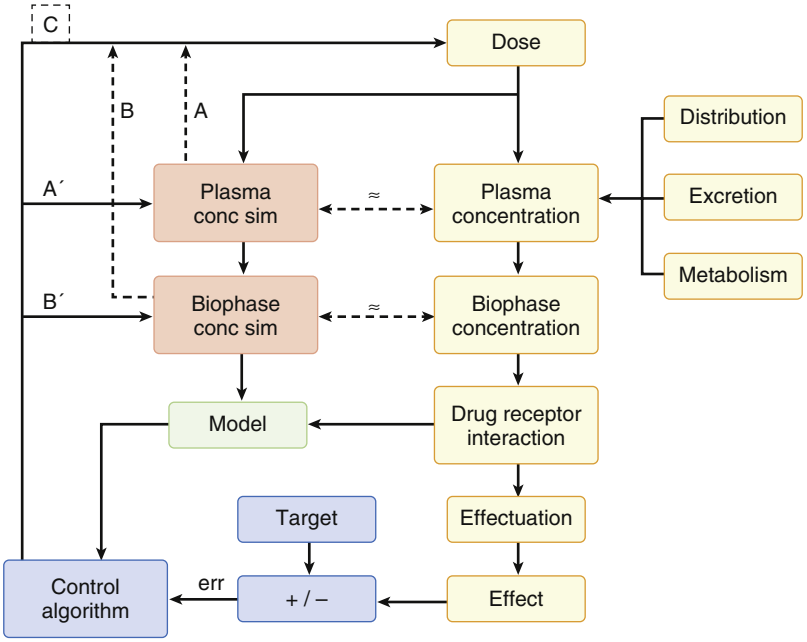


Figure 33-26. Schematic representation of the pharmacokinetic and pharmacodynamic processes determining the relationship between administered doses and resulting effect intensity of a drug *(yellow)*. Pharmacokinetic factors such as distribution, metabolism, and/or excretion determine the relationship between drug dose and drug concentration in the biophase. In the biophase, the drug interacts with the receptor, and the pharmacologic effect is accomplished via effectuation processes. Target-controlled infusion (TCI) will use a model to estimate the plasma or biophase drug concentration *(red)*, and will calculate the dose needed to approach a target concentration in plasma *(A)* or biophase/effect-site *(B)*. Computer-controlled, closed-loop feedback measures the error between the effect and the target effect to control the dose administration *(blue)*. Better closed-loop performance can result if, rather than using the dose as a direct actuator, the *simulated* variable of a TCI system is used as actuated variable *(A/A′, B/B′)*. The TCI system then compensates for part of the complexity of the dose-interaction relationship. Advanced control algorithms may take into account a continuously updated model of the interaction *(light green) (Modified from Struys M, de Smet T: Principles of drug actions: target-controlled infusions and closed-loop administration. In Evers AS, Maze M, Kharasch ED, editors:* Anesthetic pharmacology: basic principles and clinical practice. *Cambridge, 2011, Cambridge University Press, pp, 103-122. Used with permission.)*

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COMPUTER-CONTROLLED DRUG DELIVERY

As discussed in the introduction of this chapter, optimal patient-individual dosing may be achieved by the application of pharmacokinetic and pharmacodynamic principles. Using the dose-response relationship, drug titration should be performed as close as possible to the drug effect. Titrating to a specific effect or, if not possible, a specific effect-site concentration offers advantages. Because the effect-site or plasma concentrations are not continuously measurable online for most intravenous anesthetics (in contrast to inhaled anesthetics), a drug model using a computer that continuously updates the anesthetic administration rate to maintain an estimated drug effect or drug concentration is required (Fig. 33-26).

If a specific plasma or effect-site concentration is titrated, then this technique is called TCI. TCI is a *closed-loop control* system. However, in this system the clinician serves as the *human controller* in the loop and, as a consequence, the control actions are intermittent and irregular in time.[132] Control theory is increasingly being applied in the development of computer-controlled drug delivery systems, among others in anesthetic closed-loop control applications. The aim of computer-controlled closed-loop systems is to formalize this process of observation and intervention to provide finer and more accurate control. Such systems use a near continuous signal of drug effect, calculate the error between the observed value and the set point value (selected by the user), and use this error figure in an algorithm to make frequent and regular adjustments to drug administration rates. Some computer-controlled drug delivery systems try to predict the future drug effect to make appropriate adjustments well in advance.[132]

TARGET-CONTROLLED INFUSION

Devices

The development of microprocessor-controlled syringe pumps and a better understanding of the dose-response relationship have enabled the development of TCI systems. TCI is an infusion controlled system that achieves a user-defined estimated drug concentration in a body compartment or tissue. A clinician using a TCI system to administer an anesthetic drug is thus able to set and adjust a desired drug concentration, usually referred to as the *target concentration*, based on clinical observation of the patient or measurement of drug effect. Multicompartment

pharmacokinetic-dynamic models are used by TCI systems to calculate the infusion rates required to achieve the target concentration (see Fig. 33-4). A computer or microprocessor is required to perform the complex calculations and to control the infusion pump. Typically, plasma or effect-site concentrations are targeted.[3,133]

TCI originates from the theoretic approach to achieve and maintain a steady-state blood concentration of a drug whose pharmacokinetic trajectory is a multicompartment model as described by Kruger-Thiemer[134] and first clinically implemented by Schwilden and colleagues.[7] The applied infusion schemes, better known as bolus-elimination-transfer (BET) schemes (see Fig. 33-4), were initially designed for two-compartment models. Briefly, the infusion starts with an initial bolus of drug required to achieve the initial target concentration. Second, an infusion is administered to replace drug lost by elimination. Since the elimination rate constant is fixed, the amount of drug eliminated in each unit of time is proportional to the plasma concentration; thus at steady-state plasma concentrations, drug removal by elimination can be compensated for by a constant rate infusion. Third, a second infusion is administered to replace drug distributed or transferred to peripheral tissues. The amount redistributed exponentially declines over time as the gradient between the central compartment and the peripheral compartment decreases. Replacing distributed drug requires an infusion at an exponentially declining rate to replace drug *lost* from the central compartment by distribution until steady state.[4]

BET schemes have some disadvantages such as the requirement of a no-drug status before infusion, which disables a change in the target concentration. In addition, more recent research concluded that the pharmacokinetics of most anesthetics is better described using a three- instead of a two-compartment model. Lastly, as previously discussed in this chapter, the plasma is not the site of drug effect. Therefore effect compartment–controlled TCI algorithms were developed.[28] During the 1990s, various computer-based TCI prototypes were developed by researchers at Stanford (STANPUMP, California), Stellenbosch (STELPUMP, South Africa), Duke (computer-assisted continuous infusion [CACI], North Carolina), and Ghent (RUGLOOP, Belgium) universities. Groups in Erlangen, Germany, and Leiden, The Netherlands, produced software able to simulate pharmacokinetic trajectories (IVA-SIM and TIVA Trainer, respectively). Finally, the Diprifusor (AstraZeneca, London) became the first commercially available TCI pump. It was based on a prototype from the Kenny group[135] and was able to control a set plasma target concentration using specific prefilled syringes from AstraZeneca. Although the technology never became available in the United States,[136] this TCI pump was the first breakthrough in an attempt to optimize drug administration in daily clinical practice in many countries. More recently, various companies have commercialized more flexible *open TCI* pumps capable of administering multiple drugs in both plasma and effect compartment–control mode (Fig. 33-27).

Effect compartment–control requires a rate constant that accurately describes the rate of equilibration between plasma (Fig. 33-28, *A*) and effect-site concentrations (Fig. 33-28, *B*). The benefits of effect compartment-controlled TCI were demonstrated for propofol by Wakeling and associates[137] and Struys and associates.[62] This mode is commonly used throughout Europe.

Evaluation of Target-Controlled Infusion Delivery

Acceptance of target-controlled drug delivery of intravenous anesthetics requires evaluation of accuracy (defined as the difference between predicted and measured concentrations) and outcomes among patients in whom automated drug delivery has been used. The inaccuracies associated with pharmacokinetic model–driven devices are attributed to both the software and hardware, as well as to pharmacokinetic variability (Fig. 33-29).

Inaccuracy in the software results from incorrect mathematic implementation of the pharmacokinetic model. Computer simulations can be used to test the infusion rates as calculated by a software program, and thus software errors are fairly simple to identify and correct.[138] Inaccurate drug delivery from the infusion pump

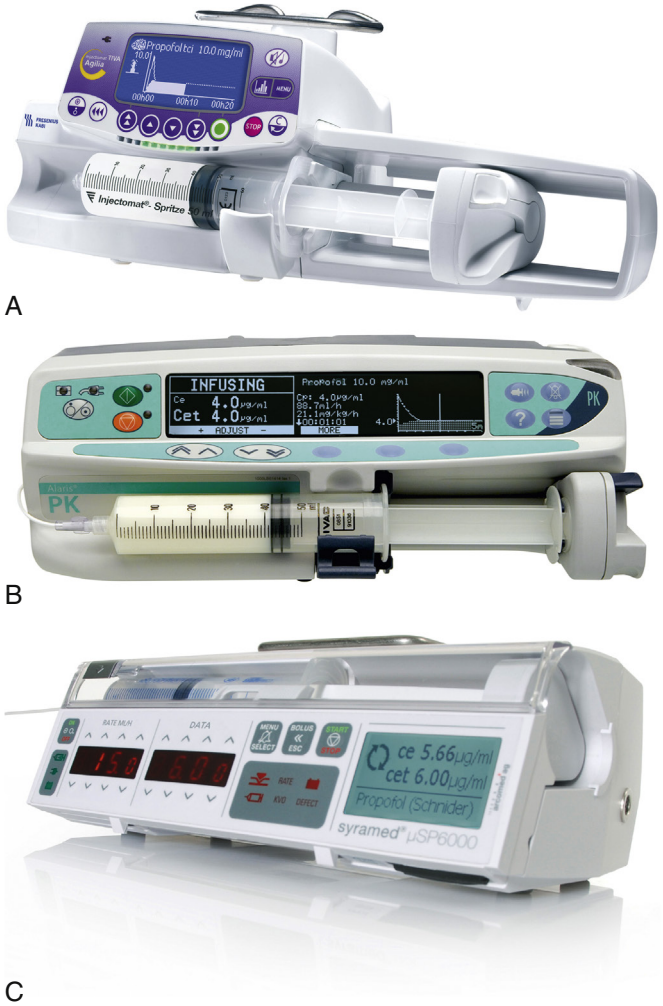


Figure 33-27. Target-controlled infusion (TCI) pumps. **A,** Injectomat TIVA Agilia from Fresenius Kabi (Bad Homburg, Germany). **B,** Alaris PK Syringe pump from Carefusion (Basingstoke, UK). **C,** Syramed µSP6000 from Arcomed (Regensdorf, Switzerland).

infrequently occurs with present syringe-pump technology and contributes little to the overall inaccuracy of these devices.[139] The major cause of inaccuracy is biologic variability, of which there are two sources: (1) the pharmacokinetic model is always wrong,[140] and (2) the pharmacokinetics of the patient is not as programmed into the model. The pharmacokinetic model is always wrong because individuals are far more complex than implied by simple compartment models, and no model can precisely predict the concentrations, even if the pharmacokinetic parameters in the individual were known with absolute precision. However, even if the pharmacokinetic model truly reflected the underlying biologic variables, the parameters of the model would be average parameters for the population and not the exact parameters of the patient. Even if the parameters were modified to reflect the influence of demographic factors such as age, gender, hypovolemia, and co-administration of other drugs, the parameters would still deviate from the true pharmacokinetic parameters in the individual. Thus biologic variability fundamentally precludes the possibility of precisely achieving the desired target concentration when automated drug delivery devices are used. Realizing that biologic variability always exists, no matter how drugs are given, and that this same biologic variability affects all methods of drug delivery is important. Nonetheless, the variability with TCI devices will always be less than the variability observed after a single bolus injection.[141] The performance of computer-controlled drug administration must be interpreted in terms of the therapeutic expectations of the clinician. Possible goals include accurately producing a desired concentration in plasma, precisely titrating the plasma drug concentration, achieving the desired drug effect, and producing the desired time course of drug effect. Over the past decade, investigators have addressed each of these goals and have refined the performance of automated drug delivery devices accordingly.

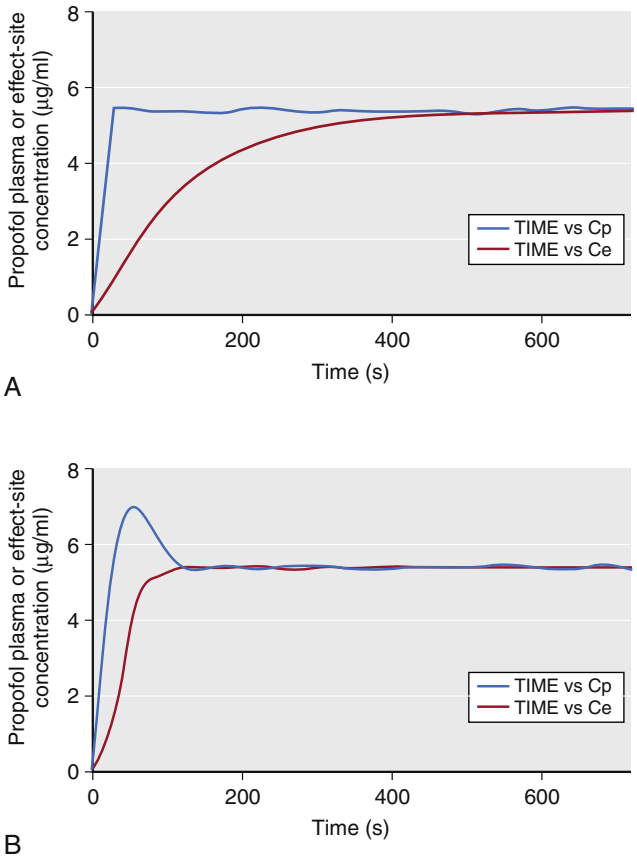


Figure 33-28. Simulation of propofol plasma (**A**) versus effect compartment–controlled (**B**) target-controlled infusion (TCI).

The ability of an automated drug delivery system to rapidly achieve and then maintain a selected target concentration is a logical measure of the performance of such a device. The difference between the measured and target concentrations can be expressed in several ways. Classic graphic representations are X-Y plots depicting predicted versus measured blood (plasma) drug concentrations (Fig. 33-30) or the relationship of the measured and predicted drug concentration versus time of administration (Fig. 33-31). Numerically, the primary concern is how far the measured concentration is from the predicted one; this relationship is now most frequently described in terms of performance error, which is the difference between the measured

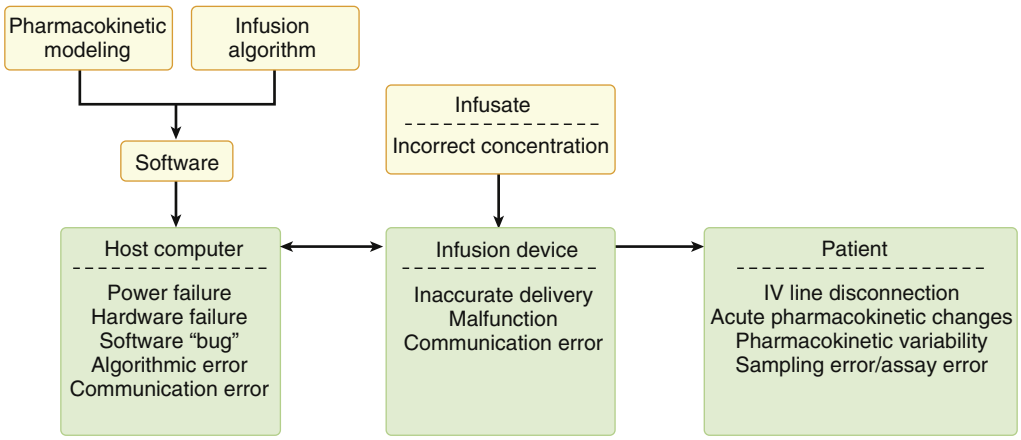


Figure 33-29. Major sources of potential error in pharmacokinetic model–driven drug delivery. In a commercial device, the computer functions are incorporated into the infusion device. *IV,* Intravenous.

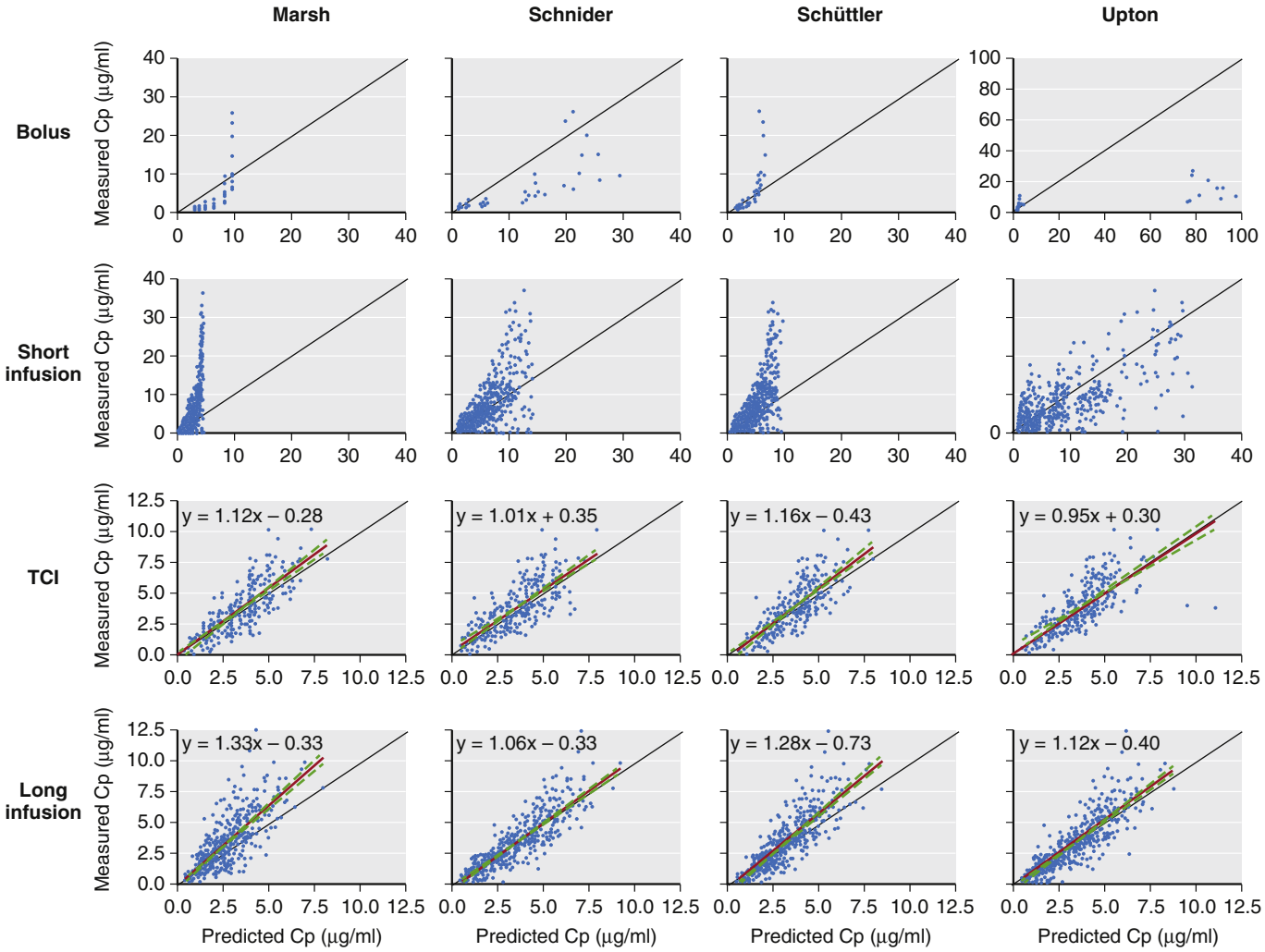


Figure 33-30. Predicted versus measured propofol plasma concentration for the four pharmacokinetic models. Each point represents a single sample. *Thin black line* represents the line of identity. For target-controlled infusion (TCI) and long infusion conditions, the bold *red line* shows the regression line and the bold *dashed green line* indicates the 95% confidence interval for the regression line. The formula represents the equation from the linear regression. *(From Masui K, Upton RN, Doufas AG, et al: The performance of compartmental and physiologically based recirculatory pharmacokinetic models for propofol: a comparison using bolus, continuous, and target-controlled infusion data,* Anesth Analg *111:368-379, 2010. Used with permission.)*

and the target concentrations as a percentage of the desired target—for example, [(measured – target) ÷ (target × 100%)].[142] The median value of the performance error for a patient or population is referred to as the median performance error (MDPE) and represents the average overshoot or undershoot of the system. The median absolute performance error (MDAPE) is the median of the absolute values of all performance errors. The MDAPE is commonly used as a measure of the inaccuracy of an automated drug delivery device. An MDAPE of zero is perfect performance, and an MDAPE of 20% means that one half the plasma concentrations will be within 20% of the target and one half will be outside that range. A further assessment of accuracy is whether the system maintains a stable target concentration, which is best measured by the wobble of the system. Varvel and colleagues[142] asked a group of clinicians to evaluate the performance of automated drug delivery devices and demonstrated that the MDAPE best predicted the adequacy of performance of the automated delivery device, as judged by experienced clinicians.

As observed earlier, expecting all performance errors to be zero is not reasonable. However, it would be desirable if positive and negative errors offset each other so that the MDPE of an automated drug delivery device were 0%. The MDPE does not indicate the range of performance errors (because positive and negative performance errors offset each other), but it does indicate whether the plasma concentrations achieved with the device tend to overshoot (+MDPE) or undershoot (–MDPE) the desired target.

Many groups have evaluated the accuracy of many different pharmacokinetic sets for virtually all the intravenous hypnotics and analgesics.[12,30,61,143-155] Based on many of these studies, the expected performance of such devices, at best, tends to be around 20% to 30% MDAPE.

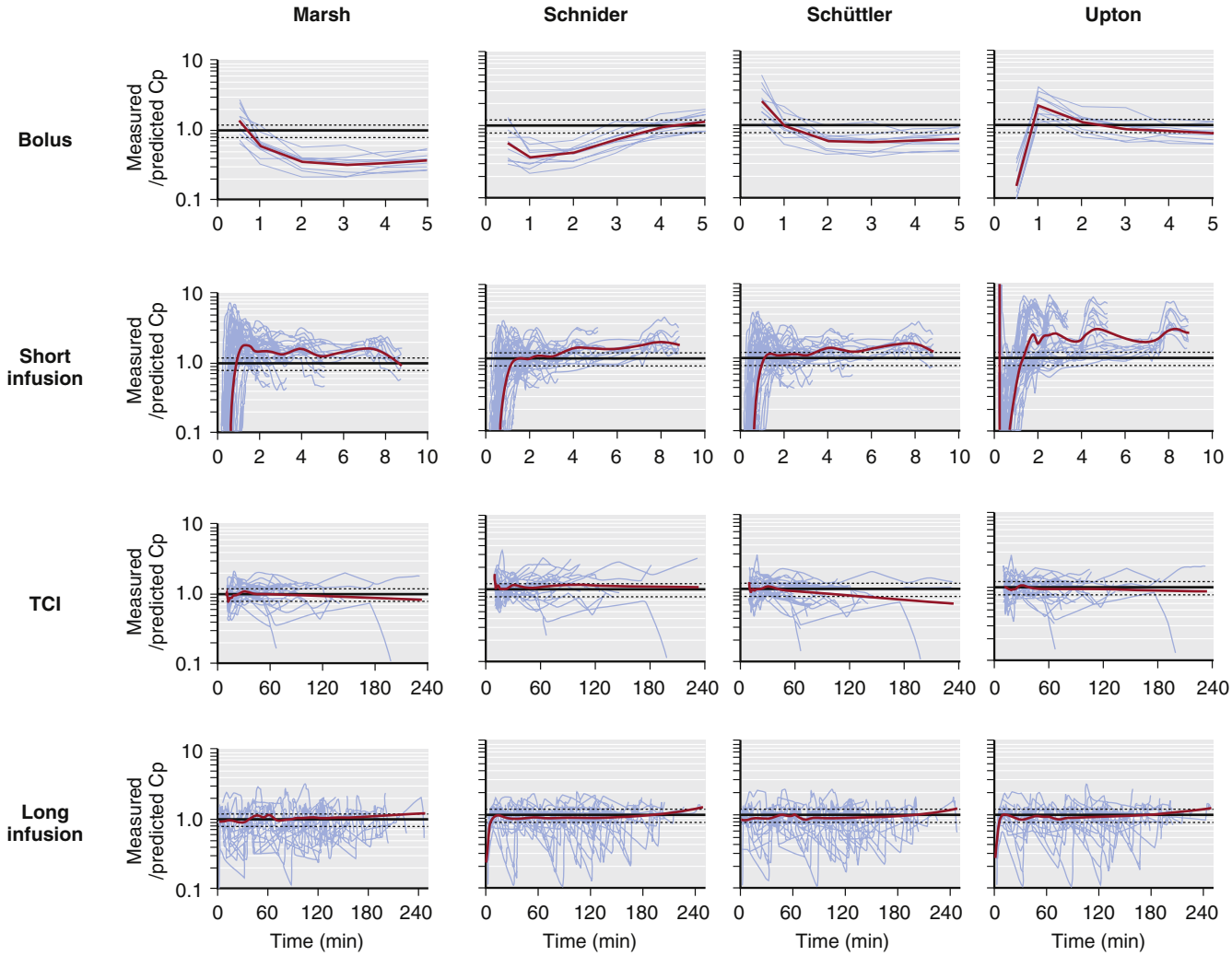


Figure 33-31. Time course of the measured/predicted concentration relationship versus time of drug administration. The *dotted lines* indicate an acceptable range of measured/predicted plasma drug concentration (Cp). The *red line* indicates the Friedman Super Smoother curve for the population data. *(From Masui K, Upton RN, Doufas AG, et al: The performance of compartmental and physiologically based recirculatory pharmacokinetic models for propofol: a comparison using bolus, continuous, and target-controlled infusion data,* Anesth Analg *111:368-379, 2010. Used with permission.)*

Model Selection for Target-Controlled Infusion

For most intravenous drugs, various multicompartment pharmacokinetic-dynamic models have been published. The pharmacokinetics of propofol have been the most frequently tested (see Fig. 33-6). Coetzee and co-workers compared the accuracy of some of the models published before 1995 and found that propofol TCI using the model published by Marsh and co-workers resulted in acceptable performance (MDPE −7%; MDAPE 18%).[148]

The Marsh model was incorporated in the first commercially available TCI system (Diprifusor). Clinical studies using this plasma-controlled TCI system showed that the technique and model were clinically useful in various clinical situations.[156-160] The major drawback of the Marsh model is the lack of effect compartment information and the fact that weight is the only covariate. More recently, Schnider and co-workers[54,161] evaluated age, height, weight, and lean body mass as covariates in a new combined pharmacokinetic-dynamic three-compartment model. The large variability of the study population (18 to 81 years of age and weighing 44 to 123 kg) provides a wide applicability of the model. Several validation studies rated this model accurate under various conditions. For example, Masui and colleagues[12] studied the measured propofol plasma concentrations versus predicted by the four published models and revealed bias in all three compartment models during the bolus and short infusion regimens (see Figs. 33-30 and 33-31).

In the long infusion, a worse measured/predicted propofol plasma concentration at higher concentration was observed for the Marsh and Schüttler[162] models than for the two other models. Less biased measured/predicted propofol plasma concentration was found for all models during TCI. In the bolus group, after 1 minute, a clear overprediction was observed for all three-compartment models for the entire 5-minute period; however, this initial error resolved after 4 minutes in the Schnider model. During the bolus and short infusion conditions, the Marsh model demonstrated worse MDPE and MDAPE

when compared with the other models. During short infusion, MDAPE for the Schnider and Schüttler models was better. All models showed similar MDPE and MDAPE during TCI simulations. During long infusion, the Marsh and the Schüttler models underestimated the higher plasma concentrations. Interestingly, the physiologically based recirculatory model developed by Upton and co-workers[13] did not reveal a better description of the pharmacokinetic time course. The Schüttler model has a major practical drawback; it defined the infusion characteristics, being bolus or infusion, as a significant covariate, thereby discouraging TCI applicability.

When comparing the Schnider and Marsh model during effect compartment–controlled TCI, Coppens and co-workers[163] found a significant difference in behavior. When targeting the effect-site concentration detected at the moment of loss of consciousness, patients in the Marsh model group woke up and those in the Schnider model group showed a further deepening of anesthesia as measured by the BIS. They concluded that targeting the effect-site concentration at which patients lose consciousness with effect-site controlled TCI does not translate into an immediate constant effect. Others have observed contradictory findings.[164] As a result, more fundamental research is required to better understand the mechanisms of anesthetic-induced loss of consciousness and to subsequently fine tune the pharmacometric principles governing effect-site modeling.[132]

An additional drawback of the Schnider model is the use of lean body mass as calculated using the equation developed by James.[165] The quadratic behavior of the lean body mass function makes it invalid (negative values!) when used in patients who are very obese. Therefore as changing population demographics such as obesity might influence the pharmacokinetics of propofol, models should ideally be applicable to a broad range of population demographics before being used in clinical practice. Recently, Cortinez and co-workers[166] derived a population pharmacokinetics model using obese and nonobese data to describe the pharmacokinetics of propofol over a wide range of body weights. A model using allometric scaling of total body weight as the size descriptor of volumes and clearances was superior to other size descriptors to characterize propofol pharmacokinetics in patients who are obese. When using allometric scaling, growth and development can be studied using classic covariates (e.g., weight, age, sex). Size is the primary covariate and can be referenced to a 70-kg person with allometric scaling using a coefficient of 0.75 for clearance and 1 for volume. Anderson and Holford[167] promote this approach because the use of these coefficients is supported by fractal geometric concepts and observations from biologically diverse areas.[168]

Two pharmacokinetic models for propofol in children are available in clinical TCI systems. Kataria and colleagues described the time course of propofol plasma concentration in a population of children between ages of 3 and 11 years using a three-compartment model with weight as the sole significant covariate. Weight-adjusting the volumes and clearances significantly improved the accuracy of the pharmacokinetics. Adjusting the pharmacokinetics for inclusion of additional patient covariates or using a mixed-effects model did not further improve the ability of the pharmacokinetic parameters to describe the observations.[169] An alternative propofol TCI model called *Paedfusor*, developed by the Glasgow research group, incorporated a preliminary model published by Schüttler and co-workers[162] and was recently found to be more accurate than the Kataria model. In this recent study, Coppens and associates[30] were the first to publish a combined pharmacokinetic-pharmacodynamic model for propofol in children, revealing a k_{e0} of 0.79 min^{-1} and a Ce_{50} of 3.85 μg/mL as measured using the BIS (Table 33-6).

Table 33-7 shows the clinically used pharmacokinetic-pharmacodynamic models for remifentanil, fentanyl, sufentanil, and alfentanil. For sufentanil, the covariate model developed by Gepts and colleagues[170] is accurate with MDPE between −2.3% and 22.3% and MDAPE between 18.5% and 29%, even in patients who are obese[150-152] (also see Chapter 71). Multiple pharmacokinetic models were developed for alfentanil. A combined analysis of these early study results using a true population analysis was used to develop a new alfentanil model.[171] A comparison showed a better performance for the Maitre alfentanil model (MDPE, 35%; MDAPE 36%) than the Scott model (MDPE, 12%; MDAPE, 28%).[154] Other studies found contradictory results.[145]

A compartment fentanyl model without covariates specifically aiming for TCI was developed[147] and tested in both lean and obese patients.[172] A simulated plasma concentration required a specific correction in patients who were obese.[172] Various three-compartment combined pharmacokinetic-pharmacodynamic models for remifentanil were developed from studies with both volunteers and patients; however, only the model published by Minto and colleagues is applied in TCI.[54,173] Evaluation of this model showed an acceptable performance, with an MDPE of −15% and an MDAPE of 20%.[155] Because combined pharmacokinetic-pharmacodynamic models are lacking for some of the opioids, the times to peak effect after a bolus administration of alfentanil (1.4 min), fentanyl (3.6 min), and sufentanil (5.6 min) can be applied to calculate the effect-site concentration using the *tpeak algorithm*.[31]

Preliminary remifentanil models in children have been developed (also see Chapter 93). For example, Rigby-Jones and colleagues[174] applied allometric scaling during a study of remifentanil pharmacokinetics in children and reported a single fixed allometric function scaled to a body mass of 10.5 kg that performed well across a broad range of patient weights. In addition to propofol and the opioids, compartment models have been published describing the time course of the plasma concentration and clinical effect of benzodiazepines, neuromuscular-blocking drugs, ketamine, and dexmedetomidine, although these drugs have not yet been included in the commercially available TCI pumps.

Rational Target Concentration Selection

No single regimen, concentration, or drug combination applies to all patients. Most of the previously mentioned pharmacokinetic-pharmacodynamic models have been derived from population pharmacologic studies. Interpatient variability limits the accuracy of the estimated drug

TABLE 33-6 **COMMONLY APPLIED PHARMACOKINETIC-PHARMACODYNAMIC MODELS FOR TARGET-CONTROLLED INFUSION SYSTEMS FOR HYPNOTICS**

Drug/Model	V1	V2	V3	K_{10} (min^{-1})	K_{12} (min^{-1})	K_{13} (min^{-1})	K_{21} (min^{-1})	K_{31} (min^{-1})	K_{e0} (min^{-1})	TPPE (min)
Propofol/Marsh[149]	0.228 L/kg	0.363 L/kg	2.893 L/kg	0.119	0.112	0.042	0.055	0.0033	0.26 [a]	NA
Propofol/Schnider[226,227]	4.27 L	18.9 – 0.391 (age 53) L	238 L	0.443 + 0.0107 × (weight – 77) – 0.0159 × (LBM – 59) + 0.0062 × (height – 177)	0.302 – 0.0056 (age 53)	0.196	(1.29 – 0.024 × [age – 53] ÷ (18.9 – 0.391 × [age – 53])	0.0035	0.456	1.69
Propofol/Paedfusor[228]	0.458 L/kg	1.34 L/kg	8.20 L/kg	$70 \times weight^{-0.3} \div 458.3$	0.12	0.034	0.041	0.0019	NA	NA
Propofol/Kataria[229]	0.52 L/kg	1.0 L/kg	8.2 L/kg	0.066	0.113	0.051	0.059	0.0032	NA	NA
Ketamine/Domino[230]	0.063 L/kg	0.207 L/kg	1.51 L/kg	0.4381	0.5921	0.59	0.2470	0.0146	NA	NA

[a] K_{e0} derived independently from the PK model by Schüttler and colleagues.[231]
LBM, Lean body mass; *TPPE,* time to peak effect.

TABLE 33-7 COMMONLY APPLIED PHARMACOKINETIC-PHARMACODYNAMIC MODELS FOR TARGET-CONTROLLED INFUSION SYSTEMS FOR ANALGESICS

Drug	Remifentanil	Sufentanil	Fentanyl	Alfentanil
Model	**Minto[54,173]**	**Gepts[170]**	**Shafer[147]**	**Maitre[171]**
V1	(5.1 – 0.0201 [age – 40]) + 0.072 × (LBM – 55) L	14.3 L	6.09 L	♂ = 0.111 L/kg ♀ = 1.15 × 0.111 L/kg
V2	(9.82 – 0.0811 [age – 40]) + 0.108 (LBM – 55) L	63.4 L	28.1 L	12.0 L
V3	5.42 L	251.9 L	228 L	10.5 L
K_{10} (min^{-1})	(2.6 – 0.0162 [age – 40]) + 0.0191 (LBM – 55) ÷ V1	0.0645	0.083	<40 year = 0.356/V1 >40 year = 0.356 – (0.00269 [age – 40]) ÷ V1
K_{12} (min^{-1})	(2.05 – 0.0301 [age – 40])/V1	0.1086	0.4713	0.104
K_{13} (min^{-1})	(0.076 – 0.00113 [age – 40])/V1	0.0229	0.22496	0.017
K_{21} (min^{-1})	K_{12} × V1 ÷ V2	0.0245	0.1021	0.067
K_{31} (min^{-1})	K_{13} × V1 ÷ V2	0.0013	0.00601	< 40 year = 0.0126 > 40 year = 0.0126-0.000113 (age – 40)
K_{e0} (min^{-1})	0.595 – 0.007(age-40)	NA	0.147[a]	0.77[a]

[a]K_{e0} is derived independently from the PK model by Scott and colleagues.[39]
LBM, Lean body mass.

concentration for the individual but can be counteracted if the model is built while exploring a wide variety of possible covariates using parametric modeling, optionally nonlinear mixed-effects modeling. Consequently, caution is needed when applying these models to patients who are obese, older, very young, diabetic, alcoholic, or unwell if similar participants were not part of the study population. The current commercial implementations of TCI therefore do not function with patients with characteristics beyond the range of the model's development study population. As illustrated by Absalom and co-workers, the use of specific TCI algorithms outside the original studied population might result in dangerous drug infusion profiles.[11] These investigators compared two currently used methods for calculating the effect-site concentration for propofol in patients who were obese, one using a fixed k_{e0} and the other using a fixed t_{peak} (see also "Direct Effect Models" earlier in this chapter).

Other obvious sources of reduced single-drug model accuracy are errors such as drug spills, excessive blood loss causing shock, or pharmacokinetic drug interaction.[175-177]

Growing evidence suggests that gender, ethnic, and racial differences may be important sources of population pharmacokinetic-pharmacodynamic variability and should be considered when designing dosage regimens.[178] Xu and co-workers[47] evaluated the C_{50} for propofol-remifentanil TCI and the BIS at loss of consciousness and the response to noxious stimulus in patients of Chinese ethnicity and revealed that the predicted blood and effect-site concentrations at loss of consciousness were lower than those in previous publications involving Caucasian populations.

An additional caveat is required with the use of different formulations of a drug. For propofol, Calvo and colleagues[179] found that pharmacokinetics and pharmacodynamics were not equal for all formulations, which contributed to an increase in variability of the observed effect. Because of the aforementioned factors, no single regimen, concentration, or drug combination applies to all patients. Some guidance can be found in the effective concentrations at which 50% and 95% of patients have accurate clinical effect (see Table 33-3). As with all drug administration in anesthesia, clinical judgment is always required, and the target concentration should be titrated according to the clinical response of the patient.

The ability of TCI to rapidly achieve and maintain a steady concentration facilitates attaining a desired drug effect, irrespective of the absolute achieved drug concentration in the target compartment. The application of TCI in most cases even reduces the variability of intersubject drug-response curves.[141] As a result, clinical outcomes when comparing TCI versus manual infusion were found to be improved in various early studies, although contradictions exist in the literature. Two decades ago, Ausems and co-workers[180] compared pharmacokinetic model–driven administration with intermittent bolus administration of alfentanil. Automated drug delivery produced fewer episodes of muscular rigidity, hypotension, and bradycardia on induction. Automated drug delivery during maintenance resulted in a significantly less frequent incidence of hemodynamic response, which resulted in a larger percentage of anesthesia time within 15% of the desired arterial blood pressure and heart rate. Recovery after TCI was associated with significantly less use of naloxone for adequate ventilation. Pharmacokinetic model–driven infusion of fentanyl during cardiac surgery resulted in better hemodynamic control with fewer additional drug interventions and significantly fewer episodes of either hypotension or hypertension than with bolus dose administration.[181] Theil and colleagues[182] compared double-blind manual administration of fentanyl-midazolam with pharmacokinetic model–driven infusion of these two drugs in a small group of patients undergoing cardiac surgery. Both systems were simultaneously titrated (one containing placebo), with the aim of maintaining hemodynamics within 20% of baseline values. Both systems were equally effective in providing hemodynamic control as dictated by the protocol. The most significant difference between the two modes of delivery was the greater variability in drug plasma concentrations in the manual group, which suggested that pharmacokinetic model–driven infusion maintained patients within

a more narrow therapeutic range. Using the first commercially available TCI system (Diprifusor), early studies administering propofol by plasma-targeted TCI showed some benefits.[157,183,184] These revealed a significant preference of clinicians for the TCI system, although this was their first use of the device. Equal results between manual infusion and TCI were only observed when targeting propofol to a specific BIS value.[185,186] In a Cochrane review systemically including most studies using propofol plasma–targeting TCI devices, Leslie concluded that the evidence was insufficient to make firm recommendations about the use of target- versus manual-controlled infusion in clinical anesthetic practice.[126] The primary reason for these contradictory results is that early TCI devices targeted the plasma, which is not the site of drug effect (see also "Pharmacodynamic Considerations" earlier in this chapter).

Using experimental systems, Glass[137] and Struys[62] and their colleagues conducted similar studies in which they targeted either plasma or effect-site concentration of propofol and then observed the time and plasma versus effect-site concentration at loss of consciousness. In both studies, regardless of whether the effect-site or plasma concentration was targeted, loss of consciousness occurred when the appropriate *effect-site* concentration for loss of consciousness was achieved, thus validating the concept. Two other important observations were made during these studies. First, hemodynamic factors were not different whether plasma or the effect site was targeted, although higher plasma concentrations were achieved in the effect-site group. This finding implies, at least for propofol, that the time course for its hemodynamic effects is similar or longer[187] to that for its anesthetic effects. Second, k_{e0} is dependent on the pharmacokinetic set from which it is derived.[31] A k_{e0} value cannot be taken from one pharmacokinetic set and used with another pharmacokinetic set.[30] Just as various demographics may alter the pharmacokinetics, they may also alter k_{e0}. Therefore using the k_{e0} best adapted for the clinical milieu is desirable. An ideal test of whether targeting plasma or the effect site is better is to compare their use in a closed-loop system in which a measure of effect (e.g., the BIS) is used as the target of control. In a small study of 10 patients per group, Absalom and Kenny showed that maintenance of the targeted BIS (as measured by MDPE, MDAPE, and wobble) was somewhat improved and induction times were significantly shorter when the pharmacokinetic model was for the effect site rather than for the plasma.[188] Effect compartment–controlled TCI systems are currently commercially available in many countries (not the United States).

TCI remifentanil provided improved hemodynamic control both intraoperatively and postoperatively with less remifentanil and similar propofol infusion rates.[189] Age dramatically influences the pharmacokinetics of remifentanil; consequently, a TCI model that includes age will result in a beneficial drug titration compared with a standard μg/kg/min infusion (also see Chapter 80). For deep sedation in spontaneously breathing patients, Moerman and associates[190] found that the combination of remifentanil and propofol offered better conditions for colonoscopy than propofol alone; and that TCI remifentanil administration was associated with reduced propofol dosing and a less frequent incidence of apnea and respiratory depression, compared with manually controlled administration. Others have confirmed this finding.[191] In addition, effect compartment–controlled TCI may offer better control of the dose-response relationship.[62,192,193]

Pharmacokinetic model–driven infusion of propofol compares favorably with inhaled anesthetics. Sneyd and co-workers compared TCI propofol with sevoflurane in patients undergoing neurosurgical procedures and found little difference between the two techniques[194] (also see Chapter 70). This finding implies that given the appropriate means for administration, intravenous anesthesia can be equivalent to inhaled anesthetics in achieving the objectives of anesthesia; that is, rapid induction and recovery with stable maintenance. Passot and coworkers[195] compared TCI, manual propofol infusion, and etomidate/desflurane in high-risk older patients undergoing hip fracture surgery and concluded that TCI improved the time course of propofol-induced hemodynamic effects in these patients.

In noncomparative studies, pharmacokinetic model–driven infusion has been used to administer most of the potent opioids, as well as the hypnotics. Different anesthetic techniques have also been tested with pharmacokinetic model–driven infusion devices, including nitrous oxide–opioid anesthesia, supplementation of volatile anesthetics, total intravenous anesthesia, sedation for monitored anesthesia care, and intensive care unit (ICU) sedation. In all these studies, outcome as measured by hemodynamics and recovery has been within the expectations of normal clinical care. Etomidate, methohexital, midazolam, propofol, thiopental, dexmedetomidine, alfentanil, fentanyl, remifentanil, and sufentanil have all been used with TCI. When these drugs were used with target-controlled drug delivery systems for total intravenous anesthesia or to supplement nitrous oxide or volatile anesthetics, hemodynamics were well maintained during induction and intubation, as well as during maintenance. Recovery milestones were reached at times comparable with those achieved with similar drug combinations used in manual infusion schemes. None of these studies have reported adverse outcomes resulting from target-controlled drug delivery. TCI devices have also been used to provide PCA. For example, Van den Nieuwenhuyzen and colleagues demonstrated advantages of PCA-TCI with alfentanil over routine morphine PCA.[66,154,196,197] Analgesia support using effect-site targeted TCI of remifentanil or fentanyl during extracorporeal shock-wave lithotripsy was tested by Cortinez and colleagues. They found a remifentanil and fentanyl EC_{50} of 2.8 ng/mL and 2.9 ng/ mL. At EC_{50}, the probability of having a respiratory rate less than 10 was 4% for remifentanil and 56% for fentanyl. Hypoxemia, vomiting, and sedation were more frequent in the fentanyl group, making this drug less suitable for this clinical application than remifentanil. Lipszyc and associates[111] accurately used remifentanil effect-site PCA-TCI with a slow and progressive adapted algorithm for treatment of acute pain after uterine artery embolization and showed that it provided better care than PCA morphine in the first 4 hours of administration

Preliminary results have been published for the use of propofol TCI in the ICU (also see Chapter 101). McMurray and co-workers[198] proposed propofol plasma targets between 0.2 and 2.0 μg/mL for ICU sedation. In their study, acceptable sedation levels occurred in 84% of the sedation period and predicted propofol concentrations were close to measured concentrations.

The authors have concluded that automated drug delivery of intravenous anesthetics is at least equal to manual delivery of these drugs. Intravenous drug administration via target-controlled drug delivery is analogous to inhaled volative anesthetic delivery via a calibrated vaporizer. Similar to the vaporizer, pharmacokinetic model–driven infusion facilitates drug delivery based on plasma or biophase concentration rather than on drug dosage. Variability exists with the use of a calibrated vaporizer, including the variability in the accuracy of drug delivery with vaporizers, slow equilibration between the fresh gas flow and the circuit at low flow rates, and variable uptake by the patient. This variability does not particularly complicate the titration of inhaled anesthetics. The variability with target-controlled drug delivery is of a similar magnitude and can be demonstrated to be less than the variability associated with vaporizers and, likewise, does not particularly complicate titration of intravenous anesthetics. Indeed, the variations in surgery-dependent and patient-dependent stress responses require titrated administration of potent inhaled anesthetics by using the calibrated vaporizer as a tool. These same factors require that the clinician carefully titrate the infusion of intravenous anesthetic drugs when using automated drug delivery as a tool.

No real-time plasma concentration measurements of intravenous drugs are available for clinical use. If available, such measurements may improve drug delivery or might optimize TCI administration for the individual patient.[199] Recently, efforts have been made to measure expired air propofol concentrations and to correlate these with plasma concentrations. Several promising techniques have been described. Miekisch and co-workers have used proton transfer mass spectrometry and headspace solid-phase microextraction coupled with gas chromatography-mass spectrometry.[200] Perl and colleagues[201] used an ion mobility spectrometer coupled to a multicapillary column for preseparation (multicapillary column–ion mobility spectrometer), and Grossherr and colleagues used gas chromatography mass spectrometry.[202] The latter group also described the difference between blood/gas partition coefficient and pulmonary extraction ratio for propofol between species, which will be important when studying this technique in an animal setting.[203] More research is required before these measurements can be applied to clinical practice.

Closed-Loop Controlled Intravenous Drug Delivery

The next step in computer-controlled drug delivery is to feed a continuous measure of drug effect directly back to the automated drug delivery device, thus providing a continuous closed-loop system. This system avoids the requirement of a clinician to titrate the target concentration manually, based on intermittent observations of the desired therapeutic effect. With manual control, attempts to achieve tight titration of hypnosis require high clinical expertise and a labor-intensive process and may divert the clinician's attention from critical actions resulting in a suboptimal therapy or even threatening the patient's safety. Applying closed-loop drug administration techniques could optimize this process of dose titration.[4] The application of closed-loop systems for drug administration is complex and requires a perfect balance for all the basic components of such a system: (1) a control variable representative for the targeted therapeutic effect; (2) a clinically relevant set-point or target value for this variable; (3) a control actuator which is, in this case, the infusion pump driving the drug; (4) a system, in this case a patient; and (5) an accurate, stable control algorithm.[204]

Control algorithms are all based on measuring the error between the target and the observed effect. Various control strategies are described in the literature to steer this closed-loop administration. Proportional-integral differential (PID) controllers are frequently used in engineering applications. This controller will adjust the infusion rates in a manner that is proportional to the magnitude of the error, the integral of the error over time, and the derivative of the error over time. The fine-tuning of a PID controller might be difficult in this particular setting because of the complexity of the system to control and the interindividual pharmacologic variability and because directly counteracting the administration of excessive drug is not possible. A more appropriate approach could be to use a PID control system connected to a TCI system to decrease the order of complexity between dose and response (see Fig. 33-26).[205] An alternative control strategy is called *model-based adaptive control*. This controller has an internal model of the system, typically set up as an integrated pharmacokinetic-pharmacodynamic model that relates dose to concentration (pharmacokinetics) and concentration to drug effect (pharmacodynamics). The model is updated to explain the difference between the measured and predicted drug effect.

A reliable physiologic signal, which is a measure of the clinical drug effect, is the most important component of closed-loop technology. Vital signs such as arterial blood pressure or muscle activity have been used to guide intravenous closed-loop drug administration. For example, Kenny and co-workers[206] successfully evaluated closed-loop control of arterial blood pressure using a mixture of trimethaphan camsylate and sodium nitroprusside during controlled hypotensive anesthesia for local resection of intraocular melanoma. In the 1980s and the 1990s, various researchers investigated the accuracy of closed-loop controlled administration of atracurium[207,208] and vecuronium.[209] However, since the introduction of the novel reversal drug, sugammadex, interest in closed-loop administration of vecuronium or rocuronium has significantly declined.

The commercialization of various EEG-based *depth of anesthesia* monitors, such as the BIS, spectral entropy, and auditory-evoked potential, has renewed the interest of various research groups in closed-loop administration of intravenous hypnotics. Using an early version of

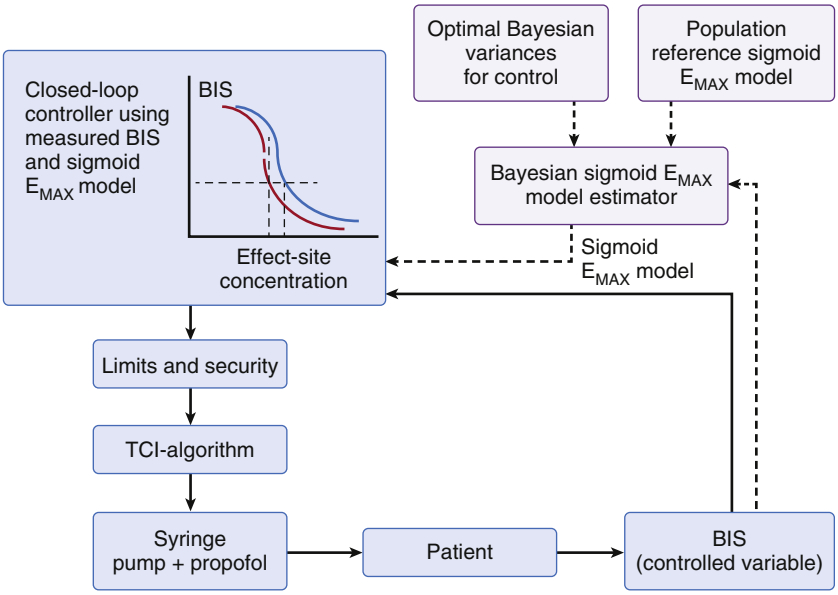


Figure 33-32. Flow chart of the closed-loop system. The *solid lines* represent the closed-loop control system. At each time the required effect-site concentration is calculated by the controller. This value is sent to an additional algorithm, taking the safety limits into account. The result of these calculations is the required effect-site concentration sent to the target-controlled infusion (TCI) algorithm, which steers a pump injecting propofol to the patient. The measured bispectral index (BIS) is used as the input of the closed-loop controller. The *dotted lines* represent the Bayesian sigmoid E_{MAX} model estimator. The estimator receives a priori information from the population sigmoid E_{MAX} model, the optimal Bayesian variances for control and the patient-measured BIS values *(From De Smet T, Struys MM, Greenwald S, et al: Estimation of optimal modelling weights for a Bayesian-based closed-loop system for propofol administration using the bispectral index as a controlled variable: a simulation study,* Anesth Analg *105:1629-38, 2007. Used with permission.)*

the BIS as the control variable, Sakai and colleagues[210] concluded that their closed-loop system provided intraoperative hemodynamic stability and a prompt recovery from sedative-hypnotic effects of propofol. A similar propofol closed-loop system using the BIS and PID control of a plasma-controlled TCI system showed acceptable control during major orthopedic surgery[211] and during sedation.[212] Although these investigators improved the performance of their control system by switching toward effect-site targeted TCI, they also concluded that the PID controller might still face some stability problems. Similarly, Liu and colleagues used a closed-loop titration of TCI based on a proportional-differential algorithm guided by the BIS, allowing induction and maintenance of general anesthesia and compared this with manual propofol TCI. They found that closed-loop control resulted in smaller propofol consumption and longer induction times but with better hemodynamic stability, less excessive anesthetic levels (BIS <40), similar hemodynamic stability, and faster recovery.[205,213] More recently, the same researchers tested a more advanced version of their system, now using full PID control, for closed-loop co-administration of both propofol and remifentanil, using the BIS as the controlled variable. A rule-based algorithm decides when to change the propofol or remifentanil targets. In a multicenter study, this system showed a better overall performance versus manual administration.[214] A similar approach was used with an alternative EEG-derived index, spectral entropy.[215]

Model-based adaptive control of BIS-guided propofol administration was previously used by Struys and colleagues for sedation during spinal anesthesia and for general anesthesia.[216,217] The control algorithm is based on a patient-specific pharmacodynamic profile estimated during induction. Compared with manually titrated propofol administration, patients in the closed-loop group reached the target BIS at a somewhat slower rate, but this resulted in less BIS overshoot and better hemodynamics after induction. During the maintenance phase, improved control of the BIS and systolic blood pressure was found in the closed-loop group and recovery was faster. Using simulations, these authors compared their model-based control system with a previously published PID controller and found that the model-based controller outperformed, even under extreme control conditions such as low and high BIS levels and abrupt changes in the BIS levels.[218] More recently, De Smet and Struys developed the adaptive part of the controller using Bayesian optimization (Fig. 33-32)[219] and compared the feasibility and accuracy of this system with manually controlled BIS-guided, effect compartment–controlled propofol TCI during ambulatory gynecologic procedures. They found that the closed-loop control system accurately titrated propofol administration resulting in BIS values close to the set point. The closed-loop control system was able to induce anesthesia in the patients within clinically accepted time limits and with less overshoot than the manual control group. Automated control resulted in beneficial recovery times. This closed-loop control group showed similar acceptable clinical performance specified by similar hemodynamic, respiratory stability, comparable movement rates, and quality scores as the manual control group.[220]

Alternative closed-loop systems have been developed for isoflurane administration using a controller with a cascade structure, originally described by Gentilini and

associates.[221,222] Recently, Moore and Doufas designed a closed-loop system using an intelligent system technique called *reinforcement learning*, known as a mathematically robust method of achieving optimal control in systems challenged with noise, nonlinearity, time delay, and uncertainty.[223,224]

So far, all developed closed-loop systems have been used under strict experimental conditions. The challenge is now to prove their safety and utility when applied in clinical practice.[225] Finally, clinicians will have to determine whether adaptive, intelligent computer systems with dual, interacting, closed-loop systems will facilitate better control and improve patient outcomes.[132]

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Chapter 34

Pharmacology of Neuromuscular Blocking Drugs

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Key Points

- Two different populations of nicotinic acetylcholine receptors exist at the mammalian neuromuscular junction. In the adult, the nicotinic acetylcholine receptor at the postsynaptic (muscular) membrane is composed of $\alpha_2\beta\delta\varepsilon$ subunits. Each of the two α subunits has an acetylcholine-binding site. The presynaptic (neuronal) nicotinic receptor is also a pentameric complex composed of $\alpha_3\beta_2$ subunits (see also Chapter 18).
- Nondepolarizing muscle relaxants produce neuromuscular blockade by competing with acetylcholine for the postsynaptic α subunits. In contrast, succinylcholine produces prolonged depolarization that results in decreased sensitivity of the postsynaptic nicotinic acetylcholine receptor and inactivation of sodium channels so that propagation of the action potential across the muscle membrane is inhibited.
- Different forms of neuromuscular stimulation test for neuromuscular blockade at different areas of the motor end plate. Depression of the response to single twitch stimulation is likely caused by blockade of postsynaptic nicotinic acetylcholine receptors, whereas fade in the response to tetanic and train-of-four stimuli results from blockade of presynaptic nicotinic receptors.
- Succinylcholine is the only available depolarizing neuromuscular blocker. It is characterized by rapid onset of effect and ultrashort duration of action because of its rapid hydrolysis by butyrylcholinesterase.
- Available nondepolarizing neuromuscular blockers can be classified according to chemical class (the steroidal, the benzylisoquinolinium, or other compounds) or, alternatively, according to onset or duration of action (long-, intermediate-, and short-acting drugs) of equipotent doses.
- The speed of onset is inversely proportional to the potency of nondepolarizing neuromuscular blocking drugs. With the exception of atracurium, molar potency is highly predictive of a drug's rate of onset of effect. Rocuronium has a molar potency ($ED_{95} \approx 0.54$ μM/kg) that is approximately 13% that of vecuronium and 9% that of cisatracurium. Its onset of effect is more rapid than either of these muscle relaxants.
- Neuromuscular blockade develops faster, lasts a shorter time, and is recovered from more quickly in the more centrally located neuromuscular units (e.g., laryngeal adductors, diaphragm, and masseter muscle) than in the more peripherally located adductor pollicis.
- The long-acting neuromuscular blockers undergo minimal or no metabolism, and they are primarily eliminated, largely unchanged, by renal excretion. Neuromuscular blockers of intermediate duration of action have more rapid clearances than the long-acting blockers because of multiple pathways of degradation, metabolism, and elimination. Mivacurium, a short-acting neuromuscular blocker, is cleared rapidly and almost exclusively by metabolism by butyrylcholinesterase.
- After the administration of nondepolarizing neuromuscular blocking drugs, it is essential to ensure adequate return of normal neuromuscular function. Residual paralysis decreases upper esophageal tone, coordination of the esophageal musculature during swallowing, and hypoxic ventilatory drive. Residual paralysis can increase morbidity and mortality.

HISTORY AND CLINICAL USE

In 1942, Griffith and Johnson described *d*-tubocurarine (dTc) as a safe drug to provide skeletal muscle relaxation during surgery.[1] One year later, Cullen described the use of this drug in 131 patients who had received general anesthesia for surgery.[2] In 1954, Beecher and Todd reported a sixfold increase in mortality in patients receiving dTc compared with patients who had not received a muscle relaxant.[3] The increased mortality resulted from a general lack of understanding of the clinical pharmacology and effects of neuromuscular blocking drugs (NMBDs). The effect of residual neuromuscular blockade postoperatively was not appreciated, guidelines for monitoring muscle strength had not been established, and the importance of pharmacologically antagonizing residual blockade was not understood.

Succinylcholine, introduced by Thesleff[4] and Foldes and associates[5] in 1952, changed anesthetic practice drastically because the drug's rapid onset of effect and ultrashort duration of action allowed for both rapid endotracheal intubation and rapid recovery of neuromuscular strength.

In 1967, Baird and Reid first reported on the clinical administration of the first synthetic aminosteroid, pancuronium.[6] The development of the intermediate-acting NMBDs built on the compounds' metabolism and resulted in the introduction of vecuronium,[7] an aminosteroid, and atracurium,[8] a benzylisoquinolinium, into clinical practice in the 1980s. Vecuronium was the first muscle relaxant to have an intermediate duration of action and minimal cardiovascular actions. Mivacurium, the first short-acting nondepolarizing NMBD, was introduced into clinical practice in the 1990s,[9] as was rocuronium,[10] an intermediate-acting nondepolarizing blocker with a very rapid onset of neuromuscular blockade. Other NMBDs have been introduced into clinical practice since the use of dTc was first advocated. These include pipecuronium, doxacurium, cisatracurium, and rapacuronium. Although all do not remain in use, each represented an advance or improvement in at least one aspect over its predecessors. Still other NMBDs, such as gantacurium and CW 002,[11] are undergoing investigation.

NMBDs should be administered only to anesthetized individuals to provide relaxation of skeletal muscles. Because this class of drugs lacks analgesic or amnestic properties, these drugs should not be administered to prevent patient movement. Awareness during surgery[12] and in the intensive care unit (ICU)[13] has been described in multiple publications. As stated by Cullen and Larson, "muscle relaxants given inappropriately may provide the surgeon with optimal [operating] conditions in…a patient[14] [who] is paralyzed but not anesthetized—a state that [is] wholly unacceptable for the patient."[15] Additionally, "muscle relaxants used to cover up deficiencies in total anesthetic management…represent an…inappropriate use of the valuable adjuncts to anesthesia."[15] Administration of NMBDs intraoperatively to maintain neuromuscular block requires that the time course of block be monitored and the depth of anesthesia be continuously assessed.

NMBDs have been integrated into most anesthetic techniques for major surgery and have become key components in the continuous improvement of safe anesthetic practice and the development of advanced surgical techniques. As earlier stated by Foldes and colleagues,[5] "…[the] first use of…muscle relaxants…not only revolutionized the practice of anesthesia but also started the modern era of surgery and made possible the explosive development of cardiothoracic, neurologic, and organ transplant surgery." Certainly, NMBDs are now used routinely to facilitate endotracheal intubation and mechanical ventilation and are commonly used to maintain neuromuscular blockade through any number of different surgical procedures. This chapter reviews the pharmacology and clinical use of NMBDs and anticholinesterases in anesthesia and intensive care settings.

PRINCIPLES OF ACTION OF NEUROMUSCULAR BLOCKERS AT THE NEUROMUSCULAR JUNCTION

A brief description of the physiology of neuromuscular blockade is presented in this chapter. A more comprehensive overview is provided in Chapter 18.

POSTJUNCTIONAL EFFECTS

In adult mammalian skeletal muscle, the nicotinic acetylcholine receptor (nAChR) is a pentameric complex of two α subunits in association with single β, δ, and ε subunits (Fig. 34-1). These subunits are organized to form a transmembrane pore, or channel, as well as extracellular binding pockets for acetylcholine and other agonists or antagonists.[16] Each of the two α subunits has an acetylcholine-binding site. These sites are located in pockets within the receptor protein, approximately 3.0 nm above the surface membrane at the interfaces of the α_H-ε and α_L-δ subunits.[17] α_H and α_L indicate the high- and low-affinity binding sites for dTc and probably result from the contribution of the different neighboring subunits.[18] For instance, the binding affinity of dTc for the α_H-ε site is approximately 100 to 500 times higher than that for the α_L-δ site.[18] The fetal nAChR contains a γ subunit instead of an adult ε subunit. Once activated by acetylcholine, the mature nAChR has a shorter opening time and a higher conductance to sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}) than does the fetal nAChR, which has a considerably longer opening time.[16]

Functionally, the ion channel of the acetylcholine receptor is closed in the resting state. Simultaneous binding of two acetylcholine molecules to the α subunits initiates conformational changes that open the channel. If one molecule of a nondepolarizer NMBD (i.e., a competitive antagonist) is bound to a subunit at the AChR, two agonists cannot bind, and neuromuscular transmission is inhibited.[19]

Succinylcholine, a depolarizing NMBD, produces prolonged depolarization of the end plate region, which results in (1) desensitization of the nAChR, (2) inactivation of voltage-gated Na^+ channels at the neuromuscular junction, and (3) increases in K^+ permeability in the surrounding membrane.[19] The end results are failure of action potential generation and neuromuscular blockade.

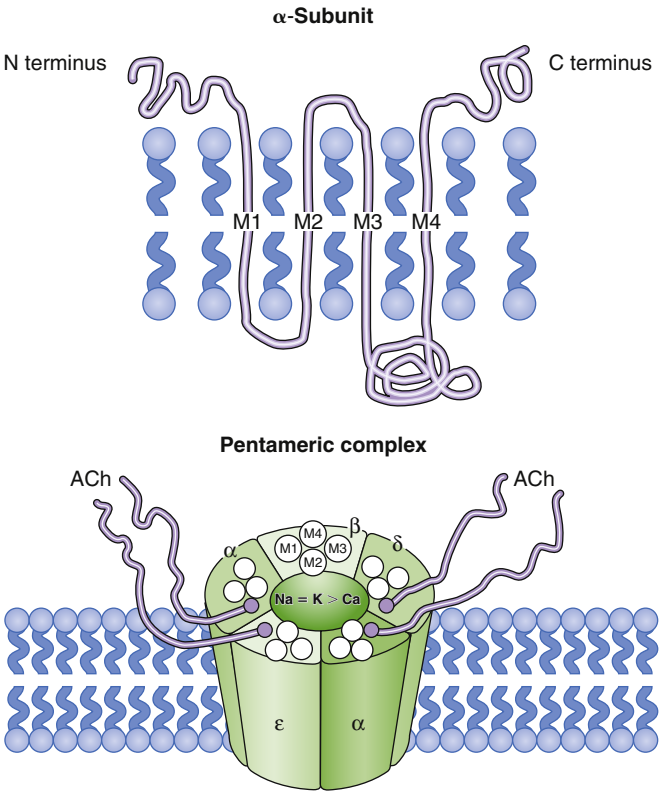


Figure 34-1. Subunit composition of the nicotinic acetylcholine receptor (nAChR) in the end plate surface of adult mammalian muscle. The adult AChR is an intrinsic membrane protein with five distinct subunits ($\alpha_2\beta\delta\varepsilon$). Each subunit contains four helical domains, labeled M_1 to M_4. The M_2 domain forms the channel pore. The *upper panel* shows a single α subunit with its N and C termini on the extracellular surface of the membrane lipid bilayer. Between the N and C termini, the α subunit forms four helices (M_1, M_2, M_3, and M_4), which span the membrane bilayer. The *lower panel* shows the pentameric structure of the nAChR of adult mammalian muscle. The N termini of two subunits cooperate to form two distinct binding pockets for acetylcholine. These pockets occur at the ε-α and the δ-α subunit interface. The M_2 membrane-spanning domain of each subunit lines the ion channel. The doubly liganded ion channel has equal permeability to sodium (Na) and potassium (K); calcium (Ca) contributes approximately 2.5% to the total permeability. *(From Naguib M, Flood P, McArdle JJ, Brenner HR: Advances in neurobiology of the neuromuscular junction: implications for the anesthesiologist,* Anesthesiology *96:202-231, 2002, with permission from* Anesthesiology.*)*

The fetal nAChR is a low-conductance channel, in contrast to the high-conductance channel of the adult nAChR. Thus, acetylcholine release causes brief activation and a reduced probability of the channel's opening.[16] The up-regulation of nAChRs found in states of functional or surgical denervation is characterized by the spreading of predominantly fetal-type nAChRs. These receptors are resistant to nondepolarizing NMBDs and are more sensitive to succinylcholine.[20] When depolarized, the immature isoform has a prolonged open channel time that exaggerates the K^+ efflux.[21] The neuronal nicotinic α7 receptor, which also is expressed after muscle denervation, has an exaggerated response to agonists associated with excessive release of K^+ from cells.[22]

PREJUNCTIONAL EFFECTS

Prejunctional receptors are involved in the modulation of acetylcholine release in the neuromuscular junction. The existence of both nicotinic and muscarinic receptors on the motor nerve endings has been described. Bowman suggested that the prejunctional nicotinic receptors are activated by acetylcholine and function in a positive-feedback control system that serves to maintain availability of acetylcholine when demand for it is high (e.g., during tetany).[23] It is now demonstrated that these presynaptic receptors are the $\alpha_3\beta_2$ neuronal subtype receptor. Although most clinically used nondepolarizing NMBDs have a distinct affinity to the $\alpha_3\beta_2$ cholinergic receptor, succinylcholine lacks affinity for this presynaptic receptor subtype. The action of nondepolarizing versus depolarizing NMBDs at this neuronal cholinergic receptor explains the typical fade phenomenon after any nondepolarizing drugs and the lack of such effect in the clinical dose range for succinylcholine.

The G-protein–coupled muscarinic receptors are also involved in the feedback modulation of acetylcholine release.[24] The prejunctional M_1 and M_2 receptors are involved in facilitation and inhibition of acetylcholine release, respectively, by modulation of Ca^{2+} influx.[24] The prejunctional nicotinic receptors are involved with mobilization of acetylcholine but not directly with the release process.[25] Hence, blockade of the prejunctional nicotinic receptors by nondepolarizing NMBDs prevents acetylcholine from being made available fast enough to support tetanic or train-of-four (TOF) stimulation. In contrast, the prejunctional muscarinic receptors are involved with up-modulation or down-modulation of the release mechanism.

PHARMACOLOGY OF SUCCINYLCHOLINE

STRUCTURE-ACTIVITY RELATIONSHIPS

All NMBDs contain quaternary ammonium compounds and as such are structurally closely related to acetylcholine. Positive charges at the quaternary ammonium sites of NMBDs mimic the quaternary nitrogen atom of acetylcholine and are the structural reason for the attraction of these drugs to muscle- and neuronal-type nAChRs at the neuromuscular junction. These receptors are also located at other sites throughout the body where acetylcholine is the transmitter. These sites include the neuronal-type nicotinic receptors in autonomic ganglia and as many as five different muscarinic receptors on both the parasympathetic and sympathetic sides of the autonomic nervous system. In addition, populations of neuronal nicotinic and muscarinic receptors are located prejunctionally at the neuromuscular junction.[19]

The depolarizing NMBD, succinylcholine, is composed of two molecules of acetylcholine linked through the acetate methyl groups (Fig. 34-2). As described by Bovet,[26] succinylcholine is a small, flexible molecule, and like the natural ligand acetylcholine, succinylcholine stimulates cholinergic receptors at the neuromuscular junction and muscarinic autonomic sites, thus opening the ionic channel in the acetylcholine receptor.

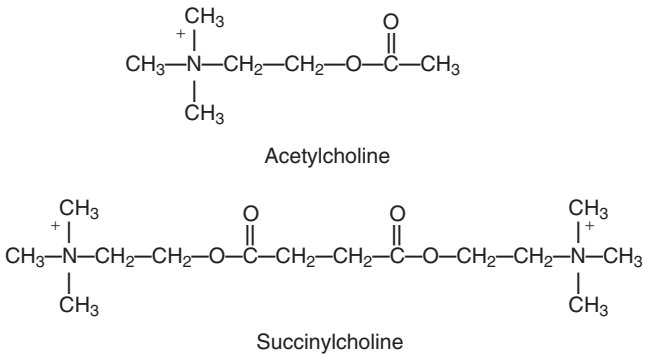


Figure 34-2. Structural relationship of succinylcholine, a depolarizing neuromuscular blocking drug, and acetylcholine. Succinylcholine consists of two acetylcholine molecules linked through the acetate methyl groups. Like acetylcholine, succinylcholine stimulates nicotinic receptors at the neuromuscular junction.

PHARMACOKINETICS AND PHARMACODYNAMICS

Succinylcholine is the only available NMBD with a rapid onset of effect and an ultrashort duration of action. The ED_{95} (the dose causing on average 95% suppression of neuromuscular response) of succinylcholine is 0.51 to 0.63 mg/kg.[27] Using cumulative dose-response techniques, Kopman and co-workers estimated that its potency is far greater,[28] and it has an ED_{95} of less than 0.3 mg/kg.

Administration of 1 mg/kg of succinylcholine results in complete suppression of response to neuromuscular stimulation in approximately 60 seconds.[29] In patients with genotypically normal butyrylcholinesterase (also known as plasma cholinesterase or pseudocholinesterase), recovery to 90% muscle strength following administration of 1 mg/kg succinylcholine requires 9 to 13 minutes.[30]

The short duration of action of succinylcholine results from its rapid hydrolysis by butyrylcholinesterase to succinylmonocholine and choline. Butyrylcholinesterase has a large enzymatic capacity to hydrolyze succinylcholine, and only 10% of the administered drug reaches the neuromuscular junction.[31] The initial metabolite, succinylmonocholine, is a much weaker NMBD than succinylcholine and is metabolized much more slowly to succinic acid and choline. The elimination half-life of succinylcholine is estimated to be 47 seconds.[32]

Because little or no butyrylcholinesterase is present at the neuromuscular junction, the neuromuscular blockade of succinylcholine is terminated by its diffusion away from the neuromuscular junction into the circulation. Butyrylcholinesterase therefore influences the onset and duration of action of succinylcholine by controlling the rate at which the drug is hydrolyzed before it reaches and after it leaves the neuromuscular junction.

DIBUCAINE NUMBER AND BUTYRYLCHOLINESTERASE ACTIVITY

Butyrylcholinesterase is synthesized by the liver and found in the plasma. The neuromuscular blockade induced by succinylcholine is prolonged when the concentration or activity of the enzyme is decreased. The activity of the enzyme refers to the number of substrate

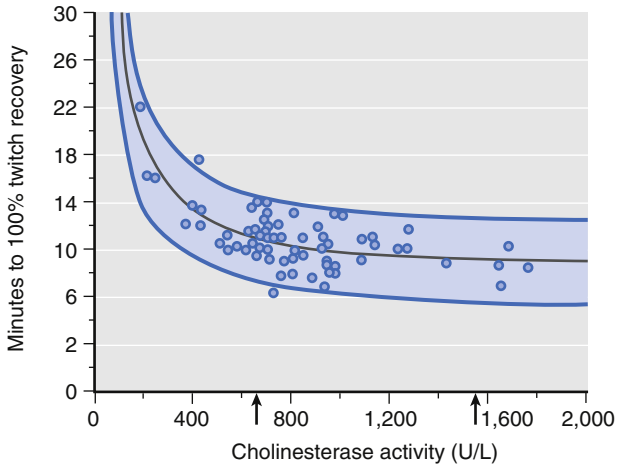


Figure 34-3. Correlation between duration of succinylcholine neuromuscular blockade and butyrylcholinesterase activity. The normal range of activity lies between the *arrows. (From Viby-Mogensen J: Correlation of succinylcholine duration of action with plasma cholinesterase activity in subjects with the genotypically normal enzyme,* Anesthesiology *53:517-520, 1980.)*

molecules (μmol) hydrolyzed per unit of time, and it is often expressed in International Units. The normal range of butyrylcholinesterase activity is quite large[30]; significant decreases in butyrylcholinesterase activity result in only modest increases in the time required to return to 100% of baseline muscle strength (Fig. 34-3).

Factors that lower butyrylcholinesterase activity include liver disease,[33] advanced age,[34] malnutrition, pregnancy, burns, oral contraceptives, monoamine oxidase inhibitors, echothiophate, cytotoxic drugs, neoplastic disease, anticholinesterase drugs,[35] tetrahydroaminacrine,[36] hexafluorenium,[37] and metoclopramide.[38] Bambuterol, a prodrug of terbutaline, produces marked inhibition of butyrylcholinesterase activity and causes prolongation of succinylcholine-induced blockade.[39] The β-blocker esmolol inhibits butyrylcholinesterase but causes only a minor prolongation of succinylcholine-induced blockade.[40]

Decreased butyrylcholinesterase enzyme activity is not a major concern in clinical practice because even large decreases in butyrylcholinesterase activity result in only moderate increases in the duration of action of succinylcholine. When butyrylcholinesterase activity is reduced to 20% of normal by severe liver disease, the duration of apnea after the administration of succinylcholine increases from a normal duration of 3 minutes to only 9 minutes. When glaucoma treatment with echothiophate decreased butyrylcholinesterase activity from 49% of control to no activity, the increase in duration of neuromuscular blockade varied from 2 to 14 minutes. In no patient did the total duration of neuromuscular blockade exceed 23 minutes.[41]

DIBUCAINE NUMBER AND ATYPICAL BUTYRYLCHOLINESTERASE ACTIVITY

Succinylcholine-induced neuromuscular blockade can be significantly prolonged if a patient has an abnormal genetic variant of butyrylcholinesterase. The variant was found by Kalow and Genest to respond to dibucaine

TABLE 34-1 RELATIONSHIP BETWEEN DIBUCAINE NUMBER AND DURATION OF SUCCINYLCHOLINE OR MIVACURIUM NEUROMUSCULAR BLOCKADE

Type of Butyrylcholinesterase	Genotype	Incidence	Dibucaine Number*	Response to Succinylcholine or Mivacurium
Homozygous typical	$E_1^uE_1^u$	Normal	70-80	Normal
Heterozygous atypical	$E_1^uE_1^a$	1/480	50-60	Lengthened by 50-100%
Homozygous atypical	$E_1^aE_1^a$	1/3200	20-30	Prolonged to 4-8 hr

*The dibucaine number indicates the percentage of enzyme inhibited.

differently than did normal butyrylcholinesterase.[42] Dibucaine inhibits normal butyrylcholinesterase to a far greater extent than the abnormal enzyme. This observation led to the establishment of the dibucaine number. Under standardized test conditions, dibucaine inhibits the normal enzyme approximately 80% and the abnormal enzyme approximately 20% (Table 34-1). Many other genetic variants of butyrylcholinesterase have since been identified, although the dibucaine-resistant variants are the most important. A review by Jensen and Viby-Mogensen provides more detailed information on this topic.[43]

Although the dibucaine number indicates the genetic makeup of an individual with respect to butyrylcholinesterase, it does not measure the concentration of the enzyme in the plasma substrate. This is determined by measuring butyrylcholinesterase activity in plasma, and it may be influenced by comorbidities, medications, and genotype.

The molecular biology of butyrylcholinesterase is well understood. The amino acid sequence of the enzyme is known, and the coding errors responsible for most genetic variations have been identified.[43] Most variants result from a single amino acid substitution error or sequencing error at or near the active site of the enzyme. For example, in the case of the "atypical" dibucaine-resistant (A) gene, a mutation occurs at nucleotide 209, where guanine is substituted for adenine. The resultant change in this codon causes substitution of glycine for aspartic acid at position 70 in the enzyme. In the case of the fluoride-resistant (F) gene, two amino acid substitutions are possible, namely, methionine for threonine at position 243 and valine for glycine at position 390. Table 34-1 summarizes many of the known genetic variants of butyrylcholinesterase: the amino acid substitution at position 70 is written as Asp ∅ Gly. New variants of butyrylcholinesterase genotypes continue to be discovered.[44]

SIDE EFFECTS

Cardiovascular Effects

Succinylcholine-induced cardiac dysrhythmias are many and varied. The drug stimulates cholinergic autonomic receptors on both sympathetic and parasympathetic ganglia[45] and muscarinic receptors in the sinus node of the heart. At low doses, both negative inotropic and chronotropic responses may occur. These responses can be attenuated by prior administration of atropine. With large doses of succinylcholine, these effects may become positive,[46] causing tachycardia. The clinical manifestation of generalized autonomic stimulation is the development of sinus bradycardia, junctional rhythms, and ventricular dysrhythmias. Clinical studies have described these dysrhythmias under various conditions in the presence of the intense autonomic stimulus of tracheal intubation. It is not entirely clear whether the cardiac irregularities are caused by the action of succinylcholine alone or by the added presence of extraneous autonomic stimulation. An in vitro study using ganglionic acetylcholine receptors subtype $\alpha_3\beta_4$ expressed in *Xenopus laevis* oocytes suggested that succinylcholine at clinically relevant concentrations had no effect on the expressed receptors.[47] Only high doses of succinylcholine caused inhibition of ganglionic acetylcholine receptors.[47] Whether or not these findings are applicable to clinical practice is unclear because the methodology (*Xenopus laevis* oocytes expression model) has no clinical equivalent.

Sinus Bradycardia. Stimulation of cardiac muscarinic receptors in the sinus node causes sinus bradycardia. This side effect is particularly problematic in individuals with predominantly vagal tone, such as in children who have not received atropine. Sinus bradycardia can occur in adults and appears more commonly after a second dose of the drug administered approximately 5 minutes after the initial dose.[48] The bradycardia may be prevented by administration of atropine, ganglion-blocking drugs, and nondepolarizing NMBDs.[49] The ability of these drugs to prevent bradycardia implies that direct myocardial effects, increased muscarinic stimulation, and ganglionic stimulation may all be involved in the bradycardic response. The greater incidence of bradycardia after a second dose of succinylcholine suggests that the hydrolysis products of succinylcholine (succinylmonocholine and choline) may sensitize the heart to a subsequent dose.

Nodal (Junctional) Rhythms. Nodal rhythms commonly occur following administration of succinylcholine. The mechanism responsible for this likely involves relatively greater stimulation of muscarinic receptors in the sinus node, thus suppressing the sinus mechanism and allowing the emergence of the atrioventricular node as the pacemaker. The incidence of junctional rhythm is greater after a second dose of succinylcholine but is prevented by prior administration of dTc.[49]

Ventricular Dysrhythmias. Under stable anesthetic conditions, succinylcholine decreases the threshold of the ventricle to catecholamine-induced dysrhythmias in monkeys and dogs. Circulating catecholamine concentrations increase fourfold, and K^+ concentrations increase by one third after succinylcholine administration to dogs.[50] Similar increases in catecholamine levels occur following

administration of succinylcholine to humans.[51] Other autonomic stimuli, such as endotracheal intubation, hypoxia, hypercarbia, and surgery, may be additive to the effect of succinylcholine. The possible influence of drugs such as digitalis, tricyclic antidepressants, monoamine oxidase inhibitors, exogenous catecholamines, and anesthetic drugs such as halothane, which may lower the ventricular threshold for ectopic activity or increase the arrhythmogenic effect of the catecholamines, should also be considered. Ventricular escape beats may also occur as a result of severe sinus bradycardia and atrioventricular nodal slowing secondary to succinylcholine administration. The incidence of ventricular dysrhythmias is further enhanced by the release of K^+ from skeletal muscle as a consequence of the depolarizing action of the drug.

Hyperkalemia

The administration of succinylcholine to an otherwise healthy individual for an elective surgical procedure increases the plasma K^+ levels by approximately 0.5 mEq/dL. This increase in K^+ results from the depolarizing action of the compound. With activation of the acetylcholine channels, movement of Na^+ into the cells is accompanied by movement of K^+ out of the cells. This slight increase in K^+ is well tolerated by most individuals and generally does not cause dysrhythmias.

Patients with renal failure are no more susceptible to an exaggerated response to succinylcholine than are those with normal renal function.[52] Patients who have uremic neuropathy may possibly be susceptible to succinylcholine-induced hyperkalemia, although the evidence supporting this view is scarce.[52,53]

However, severe hyperkalemia may follow the administration of succinylcholine to patients with severe metabolic acidosis and hypovolemia.[54] In rabbits, the combination of metabolic acidosis and hypovolemia results in a high resting K^+ level and an exaggerated hyperkalemic response to succinylcholine.[55] In this situation, the K^+ originates from the gastrointestinal tract, rather than from muscle.[56] In patients with metabolic acidosis and hypovolemia, correction of the acidosis by hyperventilation and sodium bicarbonate administration should be attempted before succinylcholine administration. Should severe hyperkalemia occur, it can be treated with immediate hyperventilation, 1.0 to 2.0 mg of calcium chloride intravenously, 1 mEq/kg of sodium bicarbonate, and 10 units of regular insulin in 50 mL of 50% glucose for adults or, for children, 0.15 units/kg of regular insulin in 1.0 mL/kg of 50% glucose.

Kohlschütter and associates found that four of nine patients with severe abdominal infections had an increase in serum K^+ levels of as much as 3.1 mEq/L after succinylcholine administration.[57] The likelihood of a hyperkalemic response to succinylcholine increases in patients who have had intraabdominal infections for longer than 1 week.

Stevenson and Birch described a single, well-documented case of a marked hyperkalemic response to succinylcholine in a patient with a closed head injury without peripheral paralysis.[58]

Hyperkalemia after administration of succinylcholine is also a risk in patients who have had physical trauma.[59] The risk of hyperkalemia occurs 1 week after the injury, at which time a progressive increase in serum K^+ occurs during an infusion of succinylcholine. The risk of hyperkalemia can persist. Three weeks after injury, three of the patients studied in this series, who had especially severe injuries, became markedly hyperkalemic with an increase in serum K^+ of more than 3.6 mEq/L. Birch and co-workers also found that the prior administration of 6 mg of dTc prevented the hyperkalemic response to succinylcholine.[59] In the absence of infection or persistent degeneration of tissue, a patient is susceptible to the hyperkalemic response for likely at least 60 days after massive trauma or until adequate healing of damaged muscle has occurred.

Additionally, patients with conditions that result in the proliferation of extrajunctional acetylcholine receptors, such as neuromuscular disease, are likely to have an exaggerated hyperkalemic response following the administration of succinylcholine. The response of these patients to NMBDs is reviewed in detail later in this chapter. Some of these disease states include cerebrovascular accident with resultant hemiplegia or paraplegia, muscular dystrophies, and Guillain-Barré syndrome (see also Chapter 42). The hyperkalemia following administration of succinylcholine may be severe enough that cardiac arrest ensues. For a review of succinylcholine-induced hyperkalemia in acquired pathologic states, see Martyn and Richtsfeld.[22]

Increased Intraocular Pressure

Succinylcholine may cause an increase in intraocular pressure (IOP). The increased IOP develops within 1 minute of injection, peaks at 2 to 4 minutes, and subsides by 6 minutes.[60] The mechanism by which succinylcholine increases IOP has not been clearly defined, but it is known to involve contraction of tonic myofibrils and/or transient dilatation of choroidal blood vessels. Sublingual administration of nifedipine may attenuate the increase in IOP caused by succinylcholine, a finding suggesting a circulatory mechanism.[61] Despite this increase in IOP, the use of succinylcholine for eye operations is not contraindicated unless the anterior chamber is open. Although Meyers and colleagues were unable to confirm the efficacy of precurarization in attenuating increases in IOP following succinylcholine,[62] numerous other investigators have found that prior administration of a small dose of nondepolarizing NMBD (e.g., 3 mg of dTc or 1 mg of pancuronium) prevents a succinylcholine-induced increase in IOP.[63] Furthermore, Libonati and associates described the anesthetic management of 73 patients with penetrating eye injuries who received succinylcholine.[64] Among these 73 patients, no extrusion occurred. Thus, despite the potential concerns, the use of succinylcholine in patients with penetrating eye injuries, after pretreatment with a nondepolarizing NMBD and with a carefully controlled rapid-sequence induction of anesthesia, can be considered. Succinylcholine is only one of many factors that may increase IOP.[62] Other factors include endotracheal intubation and "bucking" on the endotracheal tube once it is positioned. Of prime importance in minimizing the chance of increasing IOP is ensuring that the patient is well anesthetized and is not straining or coughing. Because a nondepolarizing NMBD with a short onset of effect, rocuronium, is available, it is possible to perform

a rapid sequence induction of anesthesia and endotracheal intubation without administering succinylcholine. Finally, should a patient become too lightly anesthetized during intraocular surgery, succinylcholine should not be given to immobilize the patient. Rather, the surgeon should be asked to pause while anesthesia is deepened. If necessary, the depth of neuromuscular blockade can also be increased with nondepolarizing NMBDs.

Increased Intragastric Pressure

Unlike the rather consistent increase in IOP following administration of succinylcholine, increases in intragastric pressure (IGP) are much more variable. The increase in IGP from succinylcholine is presumed to result from fasciculations of the abdominal skeletal muscle. This is not surprising because more coordinated abdominal skeletal muscle activity (e.g., straight-leg raising) may increase the IGP to values as high as 120 cm H_2O. In addition to skeletal muscle fasciculations, the acetylcholine-like effect of succinylcholine may be partly responsible for the observed increases in IGP. Greenan observed consistent increases in IGP of 4 to 7 cm H_2O with direct vagal stimulation.[65]

Miller and Way found that 11 of 30 patients had essentially no increase in IGP after succinylcholine administration, yet 5 of the 30 had an increase in IGP of greater than 30 cm H_2O.[66] The increase in IGP from succinylcholine appeared to be related to the intensity of the fasciculations of the abdominal skeletal muscles. Accordingly, when fasciculations were prevented by prior administration of a nondepolarizing NMBD, no increase in IGP was observed.

Are the increases in IGP following succinylcholine administration enough to cause incompetence of the gastroesophageal junction? Generally, an IGP greater than 28 cm H_2O is required to overcome the competence of the gastroesophageal junction. However, when the normal oblique angle of entry of the esophagus into the stomach is altered, as may occur with pregnancy or an abdomen distended by ascites, bowel obstruction, or a hiatus hernia, the IGP required to cause incompetence of the gastroesophageal junction is frequently less than 15 cm H_2O.[66] In these circumstances, regurgitation of stomach contents following succinylcholine administration is a distinct possibility, and precautionary measures should be taken to prevent fasciculation. Endotracheal intubation may be facilitated with administration of either a nondepolarizing NMBD or a defasciculating dose of nondepolarizing relaxant before the succinylcholine. Although the increase in IGP from succinylcholine is well documented, the evidence of clinical harm is not clear.

Apparently, succinylcholine does not increase IGP appreciably in infants and children. This may be related to the minimal or absent fasciculations from succinylcholine in these young patients.[67]

Increased Intracranial Pressure

Succinylcholine has the potential to increase intracranial pressure.[68] The mechanisms and clinical significance of this transient increase are unknown, but the rise in intracranial pressure does not occur after pretreatment with nondepolarizing NMBDs.[68]

Myalgias

The incidence of muscle pain following administration of succinylcholine varies widely, from 0.2% to 89%.[69] Muscle pain occurs more frequently after minor surgery, especially in women and in ambulatory rather than bedridden patients.[70] Waters and Mapleson postulated that pain is secondary to damage produced in muscle by the unsynchronized contractions of adjacent muscle fibers just before the onset of paralysis.[70] This concept has been substantiated by finding myoglobinemia and increases in serum creatine kinase following succinylcholine administration.[71] Prior administration of a small dose of a nondepolarizing NMBD clearly prevents fasciculations from succinylcholine.[71] The efficacy of this approach in preventing muscle pain is not clear, however; most investigators claim that pretreatment with a nondepolarizing NMBD has no effect.[69] Pretreatment with a prostaglandin inhibitor (e.g., lysine acetyl salicylate) has been shown to be effective in decreasing the incidence of muscle pain after succinylcholine.[72] This finding suggests a possible role for prostaglandins and cyclooxygenases in succinylcholine-induced myalgias. Other investigators have found that myalgias following outpatient surgery occur even in the absence of succinylcholine.[73]

Masseter Spasm

An increase in tone of the masseter muscle is a frequent response to succinylcholine in adults,[74] as well as in children.[75] Meakin and associates suggested that the high incidence of spasm in children may result from inadequate dosage of succinylcholine.[75] In all likelihood, this increase in tone is an exaggerated contractile response at the neuromuscular junction and cannot be used to establish a diagnosis of malignant hyperthermia. Although an increase in tone of the masseter muscle may be an early indicator of malignant hyperthermia, this finding is not consistently associated with that syndrome.[76] Currently, no indication exists to change to a "nontriggering" anesthetic in instances of isolated masseter spasm.[77]

CLINICAL USES

In spite of its many adverse effects, succinylcholine remains commonly used. Its popularity is likely the result of its rapid onset of effect, the profound depth of neuromuscular blockade it produces, and its short duration of action. Succinylcholine may not be used as regularly as in the past for routine endotracheal intubation, but it is still a muscle relaxant for rapid-sequence induction of anesthesia. Although 1.0 mg/kg of succinylcholine is recommended to facilitate endotracheal intubation at 60 seconds, as little as 0.5 to 0.6 mg/kg allows for adequate intubating conditions 60 seconds after administration.[78] Reduction in the succinylcholine dose from 1.0 to 0.6 mg/kg decreases the incidence of hemoglobin desaturation but does not shorten the time to spontaneous diaphragmatic movements.[79] Decreasing the dose of succinylcholine is appealing as long as it does not interfere with provision of adequate conditions for endotracheal intubation and subsequent adequate ventilation.[79]

Typically, after administering succinylcholine for intubation, a nondepolarizing NMBD is given to maintain

neuromuscular blockade. Prior administration of succinylcholine enhances the depth of blockade caused by a subsequent dose of nondepolarizing NMBD.[80,81] However, the effect on duration of action is variable. Succinylcholine has no effect on the duration of pancuronium,[82] but it increases the duration of atracurium and rocuronium.[80,83] The reasons for these differences are not clear.

With administration of large doses of succinylcholine, the nature of the block, as determined by a monitor of neuromuscular blockade, changes from that of a depolarizing drug to that of a nondepolarizing drug. Clearly, both the dose and the duration of administration of succinylcholine contribute to this change. The relative contribution of each has not been established, however.

Posttetanic potentiation and fade in response to TOF and tetanic stimuli can be demonstrated after bolus administration of different doses of succinylcholine.[84] It seems that some characteristics of phase 2 blockade are evident from an initial dose (i.e., as small as 0.3 mg/kg) of succinylcholine.[84] Fade in response to TOF stimulation has been attributed to the presynaptic effects on NMBDs. The etiology of the appearance of fade phenomenon in the TOF response following excessive administration of succinylcholine has been suggested to be dependent on a concentration-dependent affinity for succinylcholine to the presynaptic $\alpha_3\beta_2$ neuronal subtype AChR in concentrations exceeding the normal clinical concentration range seen after routine doses.[47]

INTERACTIONS WITH ANTICHOLINESTERASES

Neostigmine and pyridostigmine inhibit butyrylcholinesterase, as well as acetylcholinesterase. If succinylcholine is administered after antagonism of residual neuromuscular block, as it may be with laryngospasm, the effect of succinylcholine will be pronounced and significantly prolonged. Sunew and Hicks found that the effect of succinylcholine (1 mg/kg) was prolonged from 11 to 35 minutes when it was given 5 minutes after administration of neostigmine (5 mg).[35] Ninety minutes after neostigmine administration, butyrylcholinesterase activity will have returned to less than 50% of its baseline value.

NONDEPOLARIZING NEUROMUSCULAR BLOCKERS

The use of NMBDs in anesthesia has its origin in the arrow poisons or curares of South American Indians. Several nondepolarizing NMBDs were purified from naturally occurring sources. For example, dTc can be isolated from the Amazonian vine *Chondodendron tomentosum*. Similarly, the intermediates for the production of metocurine and alcuronium, which are semisynthetic, are obtained from *Chondodendron* and *Strychnos toxifera*. Malouetine, the first steroidal NMBD, was originally isolated from *Malouetia bequaertiana*, which grows in the jungles of the Democratic Republic of Congo in central Africa. The widely used drugs pancuronium, vecuronium, pipecuronium, rocuronium, rapacuronium, atracurium, doxacurium, mivacurium, cisatracurium, gantacurium, and gallamine are all synthetic compounds.

Available nondepolarizing NMBDs can be classified according to chemical class, based on structure (steroids, benzylisoquinoliniums, fumarates, and other compounds), or, alternatively, according to onset or duration of action (long-, intermediate-, and short-acting drugs) of equipotent doses (Table 34-2).

STRUCTURE-ACTIVITY RELATIONSHIPS

Nondepolarizing NMBDs were originally classified by Bovet as pachycurares,[26] or bulky molecules having the amine functions incorporated into rigid ring structures. Two extensively studied chemical series of synthetic nondepolarizing NMBDs are the aminosteroids, in which the interonium distance is maintained by an androstane skeleton, and the benzylisoquinolinium series, in which the distance is maintained by linear diester-containing chains or, in the case of curare, by benzyl ethers. For a detailed account on structure-activity relationships, see Lee.[85]

Benzylisoquinolinium Compounds

dTc is an NMBD in which the amines are present in the form of two benzyl substituted tetrahydroisoquinoline structures (Fig. 34-4). Using nuclear magnetic resonance spectroscopy and methylation–demethylation studies, Everett and associates demonstrated that dTc contains three *N*-methyl groups.[86] One amine is quaternary (i.e., permanently charged with four nitrogen substituents),

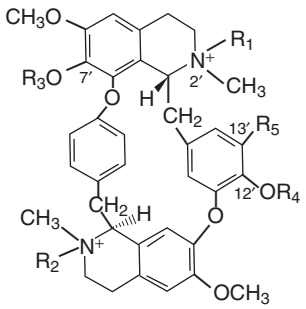
TABLE 34-2 **CLASSIFICATION OF NONDEPOLARIZING NEUROMUSCULAR BLOCKERS ACCORDING TO DURATION OF ACTION (TIME TO T1 = 25% OF CONTROL) AFTER TWICE THE DOSE CAUSING ON AVERAGE 95% SUPPRESSION OF NEUROMUSCULAR RESPONSE***

	Clinical Duration			
	Long-acting (>50 min)	Intermediate-acting (20-50 min)	Short-acting (10-20 min)	Ultrashort-acting (<10 min)
Steroidal compounds	Pancuronium	Vecuronium Rocuronium		
Benzylisoquinolinium compounds	*d*-Tubocurarine	Atracurium Cisatracurium	Mivacurium	
Asymmetric mixed-onium fumarates		CW 002		Gantacurium

T1, First twitch of train-of-four.
*Most nondepolarizing neuromuscular blockers are bisquaternary ammonium compounds. *d*-Tubocurarine, vecuronium, and rocuronium are monoquaternary compounds.

and the other is tertiary (i.e., pH-dependent charge with three nitrogen substituents). At physiologic pH, the tertiary nitrogen is protonated so that it is positively charged. The structure-activity relationships of the bis-benzylisoquinolines (see Fig. 34-4) have been described by Waser[87] and by Hill and associates,[88] and these relationships are as follows:

1. The nitrogen atoms are incorporated into isoquinoline ring systems. This bulky molecule favors a nondepolarizing rather than a depolarizing activity.
2. The interonium distance (distance between charged amines) is approximately 1.4 nm.
3. Both the ganglion-blocking and the histamine-releasing properties of dTc probably result from the presence of the tertiary amine function.
4. When dTc is methylated at the tertiary amine and at the hydroxyl groups, the result is metocurine, a compound and greater potency (by a factor of two in humans) with much weaker ganglion-blocking and histamine-releasing properties than dTc (see Fig. 34-4). Metocurine contains three additional methyl groups, one of which quaternizes the tertiary nitrogen of dTc; the other two form methyl ethers at the phenolic hydroxyl groups.
5. Bisquaternary compounds are more potent than their monoquaternary analogues. The bisquaternary derivative of dTc, chondocurine, is more than twice as potent as dTc (see Fig. 34-4).
6. Substitution of the methyl groups on the quaternary nitrogen with bulkier groups causes a reduction in both potency and duration of action.



Cyclic benzylisoquinoline

Cyclic benzylisoquinoline derivatives

Name	R_1	R_2	R_3	R_4	R_5	1	1′
d-Tubocurarine	CH_3	H	H	H	H	*S*	*R*
Metocurine	CH_3	CH_3	CH_3	CH_3	H	*S*	*R*
Chondocurine	CH_3	CH_3	H	H	H	*S*	*R*

R and S represent the stereochemical configuration about the designated carbon

Figure 34-4. Chemical structures of *d*-tubocurarine, metocurine, and chondocurine.

Atracurium is a bis-benzyltetrahydroisoquinolinium with isoquinolinium nitrogens connected by a diester-containing hydrocarbon chain (Fig. 34-5). The presence (in duplicate) of two-carbon separations between quaternary nitrogen and ester carbonyl renders it susceptible to the Hofmann elimination reaction.[89] The compound can also undergo ester hydrolysis. In a Hofmann elimination reaction, a quaternary ammonium group is converted into a tertiary amine through cleavage of a carbon-nitrogen bond. This is a pH- and temperature-dependent reaction in which higher pH and temperature favor elimination.

Atracurium has 4 chiral centers at each of the chiral carbons adjacent to the 2 amines. It is composed of 10 isomers.[89] These isomers have been separated into 3 geometric isomer groups that are designated *cis-cis*, *cis-trans*, and *trans-trans* according to their configuration about the tetrahydroisoquinoline ring system.[89] The ratio of the *cis-cis*, *cis-trans*, and *trans-trans* isomers is approximately 10:6:1, corresponding to 50% to 55% *cis-cis*, 35% to 38% *cis-trans*, and 6% to 7% *trans-trans* isomers.

Cisatracurium, the 1R *cis*–1′R *cis* isomer of atracurium, comprises approximately 15% of atracurium by weight but more than 50% in terms of neuromuscular blocking activity (see Fig. 34-5). R designates the absolute stereochemistry of the benzyl tetrahydroisoquinoline rings, and *cis* represents the relative geometry of the bulky dimethoxy and 2-alkyester groups at C(1) and N(1), respectively.[90,91] Like atracurium, cisatracurium is metabolized by Hofmann elimination. It is approximately four times as potent as atracurium, and in contrast to atracurium, it does not cause histamine release,[90,92] thus indicating that histamine release may be stereospecific.[90,93]

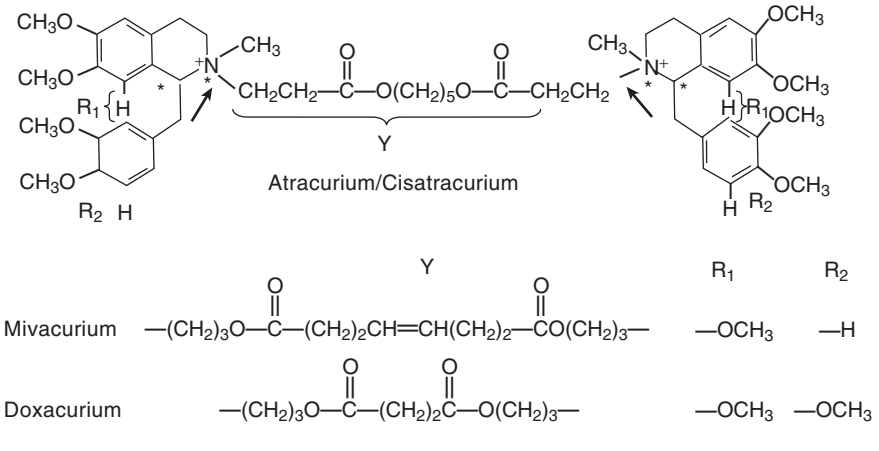


Figure 34-5. Chemical structures of atracurium, cisatracurium, mivacurium, and doxacurium. The *asterisk* indicates the chiral centers; *arrows* show cleavage sites for Hofmann elimination.

Mivacurium differs from atracurium by the presence of an additional methylated phenolic group (see Fig. 34-5). Compared with other isoquinolinium NMBDs, the interonium chain of mivacurium is longer (16 atoms).[88] Mivacurium consists of a mixture of three stereoisomers.[94] The two most active are the *trans-trans* and *cis-trans* isomers (57% and 37% weight/weight, respectively), which are equipotent; the *cis-cis* isomer (6% weight/weight) has only one tenth the neuromuscular blocking activity of the more potent isomers in cats and monkeys.[94] Mivacurium is metabolized by butyrylcholinesterase to a monoester and a dicarboxylic acid at 70% to 88% the rate at which succinylcholine is metabolized by the same enzyme.[9]

Steroidal Neuromuscular Blockers

For the steroidal compounds to have neuromuscular blocking potential, it is likely that one of the compound's two nitrogen atoms be quaternized. The presence of an acetyl ester (acetylcholine-like moiety) facilitates their interaction with nAChRs at the postsynaptic muscle membrane.

Pancuronium is characterized by the presence of two acetyl ester groups on the A and D rings of the steroidal molecule. Pancuronium is a potent NMBD with both vagolytic properties. It is also an inhibitor of butyrylcholinesterase (Fig. 34-6).[95] Deacetylation at the 3 or 17 positions decreases its potency.[96]

Vecuronium, in which the 2-piperidine substituent is not methylated, is the *N*-demethylated derivative of pancuronium (see Fig. 34-6).[7] At physiologic pH, the tertiary amine is largely protonated, as it is in dTc. The minor molecular modification results in the following: (1) a slight increase in the potency when compared with pancuronium; (2) a marked reduction in its vagolytic properties; (3) molecular instability in solution; and (4) increased lipid solubility, which results in a greater biliary elimination of vecuronium than pancuronium.[88]

Vecuronium is degraded by the hydrolysis of the acetyl esters at the C3 and the C17 positions. Hydrolysis at the C3 position is the primary degradation pathway because the acetate at the 3 position is more susceptible to hydrolysis in aqueous solutions than the acetate at the 17 position. This is because of the adjacent basic piperidine at the 2 position that facilitates hydrolysis of the 3-acetate. Therefore, vecuronium cannot be prepared as a ready-to-use solution with a sufficient shelf life, even as a buffered solution. In contrast, the 2-piperidine of pancuronium is quaternized and no longer alkaline and therefore does not facilitate hydrolysis of the 3-acetate.

Rocuronium lacks the acetyl ester that is found in the A ring of the steroid nucleus of pancuronium and vecuronium (see Fig. 34-6). The introduction of cyclic substituents other than piperidine at the 2 and 16 positions results in a compound with a more rapid onset of effect than vecuronium or pancuronium.[97] The methyl group attached to the quaternary nitrogen of vecuronium and pancuronium is replaced by an allyl group in rocuronium. As a result of this change, rocuronium is approximately 6 and 10 times less potent than pancuronium and vecuronium, respectively.[97-99] The replacement of the acetyl ester attached to the A ring by a hydroxy group means that rocuronium is stable in solution. At room temperature, rocuronium is stable for 60 days. In contrast, pancuronium is stable for 6 months. The reason for this difference in shelf life is related to the fact that rocuronium is terminally sterilized in manufacturing, and pancuronium is not. Terminal sterilization causes some degree of degradation.

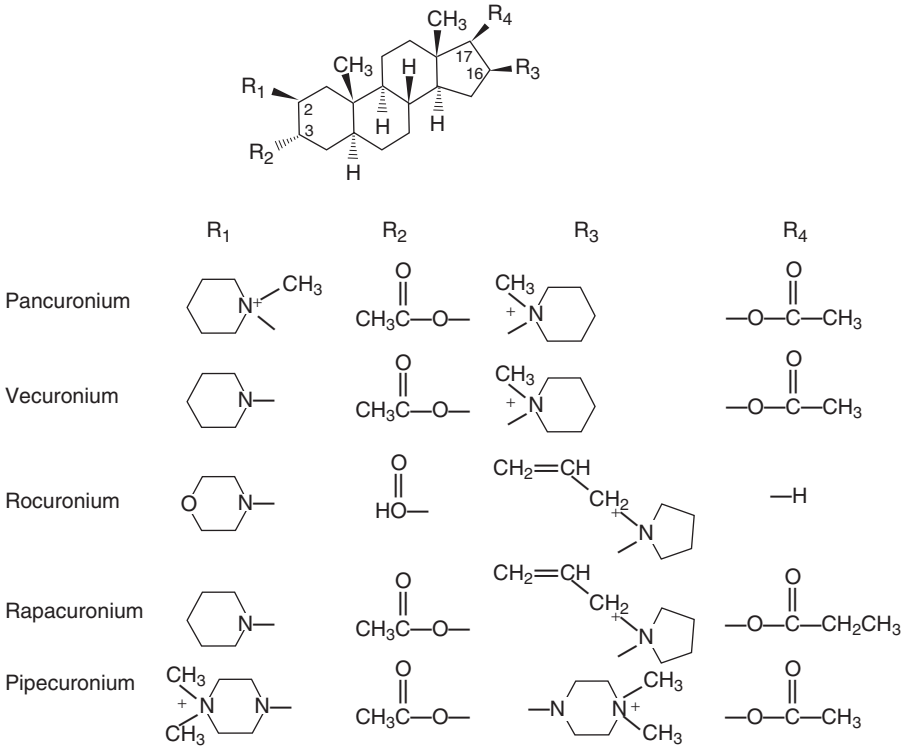


Figure 34-6. Chemical structures of different steroidal neuromuscular blockers.

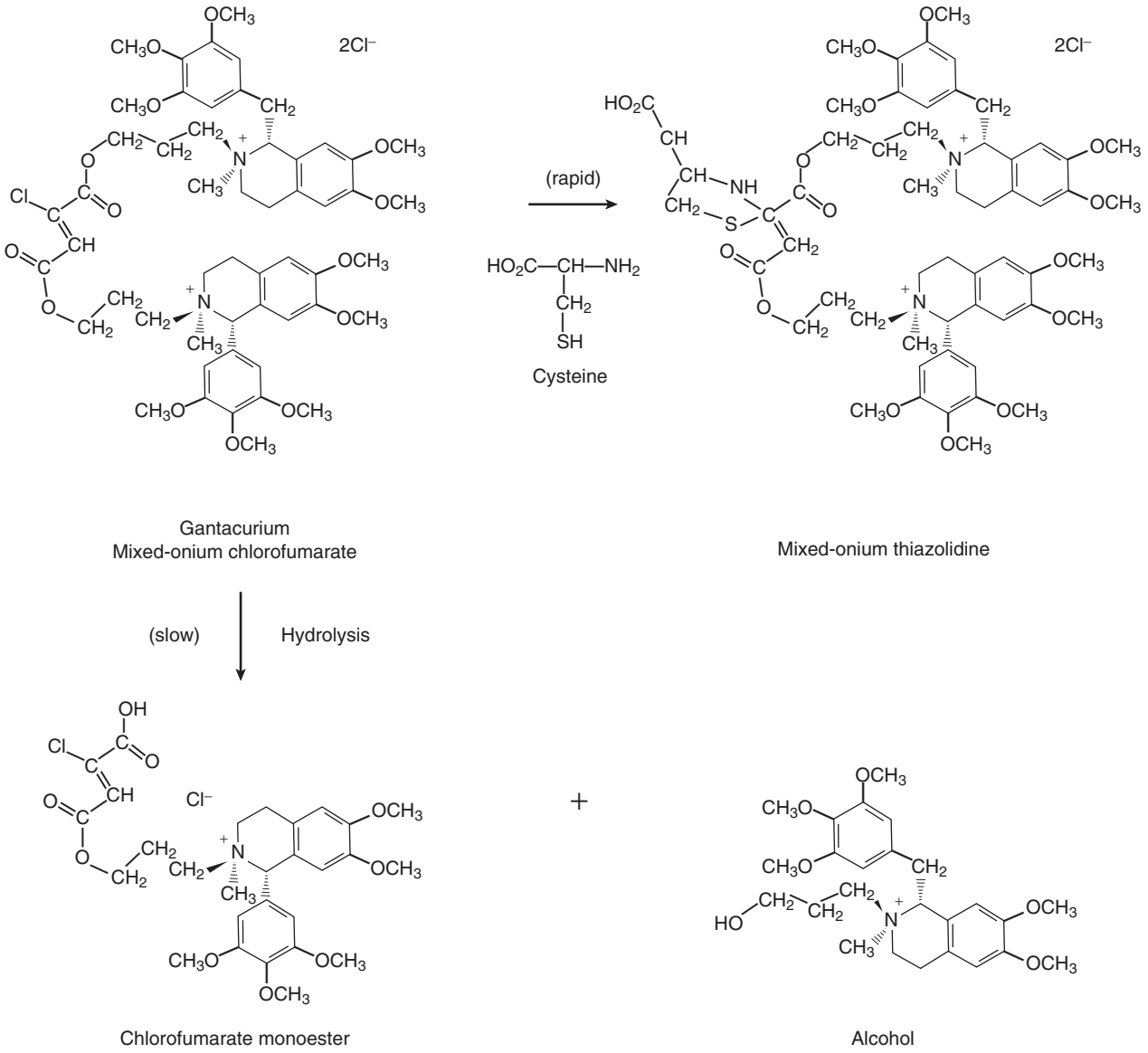


Figure 34-7. Chemical structure of gantacurium (a mixed-onium chlorofumarate). In whole human blood, two pathways of deactivation occur, neither of which is enzymatic: (1) rapid formation of an apparently inactive cysteine adduction product, with cysteine replacing chlorine, and (2) slower hydrolysis of the ester bond adjacent to the chlorine substitution to chlorofumarate monoester and alcohol. *(From Boros EE, Samano V, Ray JA, et al: Neuromuscular blocking activity and therapeutic potential of mixed-tetrahydroisoquinolinium halofumarates and halosuccinates in rhesus monkeys,* J Med Chem *46:2502-2515, 2003.)*

Asymmetric Mixed-Onium Fumarates

Gantacurium and CW 002 represent a new class of bisquaternary nondepolarizing NMBDs (Fig. 34-7). Gantacurium, an asymmetric mixed-onium chlorofumarate, is unique among nondepolarizing compounds in terms of its rapid onset of effect, its short duration of action, and its unique means of inactivation.[11,100] Because of the presence of three methyl groups between the quaternary nitrogen and oxygen atom at each end of the carbon chain, this compound does not undergo Hofmann elimination.[100]

Gantacurium has an ultrashort duration of action in human volunteers and in different animal species. In human volunteers receiving a nitrous oxide–opioid anesthetic, the ED_{95} of gantacurium is 0.19 mg/kg.[100] Onset of and recovery from block resemble that following administration of succinylcholine. Following administration of approximately 2.5 times the ED_{95} dose, onset of maximal block occurs in 1.5 minutes. Spontaneous recovery to a TOF of 0.9 or greater occurs 10 minutes after administration of an ED_{95} dose, and complete spontaneous recovery occurs in 14 to 15 minutes after administration of doses ranging from 2 to 3.5 times the ED_{95}. Recovery is accelerated by administration of edrophonium at the beginning of spontaneous recovery. Transient hypotension and tachycardia occur following administration of doses 3 times the ED_{95} and greater, a finding suggesting that histamine release occurs with administration of these doses.[100]

Gantacurium appears to undergo two pathways of inactivation. One is a slower ester hydrolysis, and the

TABLE 34-3 DOSE-RESPONSE RELATIONSHIPS OF NONDEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS IN HUMAN SUBJECTS*

	ED_{50} (mg/kg)	ED_{90} (mg/kg)	ED_{95} (mg/kg)	References
Long-acting				
Pancuronium	0.036 (0.022-0.042)	0.056 (0.044-0.070)	0.067 (0.059-0.080)	98, 103
d-Tubocurarine	0.23 (0.16-0.26)	0.41 (0.27-0.45)	0.48 (0.34-0.56)	103
Intermediate-acting				
Rocuronium	0.147 (0.069-0.220)	0.268 (0.200-0.419)	0.305 (0.257-0.521)	98, 104-106
Vecuronium	0.027 (0.015-0.031)	0.042 (0.023-0.055)	0.043 (0.037-0.059)	103
Atracurium	0.12 (0.08-0.15)	0.18 (0.19-0.24)	0.21 (0.13-0.28)	103
Cisatracurium	0.026 (0.015-0.031)	—	0.04 (0.032-0.05)	107-109, 371
Short-acting				
Mivacurium	0.039 (0.027-0.052)	—	0.067 (0.045-0.081)	9, 110-112
Ultrashort-acting				
Gantacurium	0.09	—	0.19	100

*Data are the medians and ranges of reported values. ED_{50}, ED_{90}, and ED_{95} are the doses of each drug that produce, respectively, 50%, 90%, and 95% decrease in the force of contraction or amplitude of the electromyogram of the adductor pollicis muscle following ulnar nerve stimulation.

second one, which occurs much more quickly, occurs through the adduction of cysteine, a nonessential amino acid, to create a new compound that can no longer bind to the acetylcholine receptor of the neuromuscular junction.[101] This unique means of inactivation likely accounts for the drug's ultrashort duration of effect. It also provides a novel means of shortening recovery from gantacurium-induced neuromuscular block.[102]

An analogue of the asymmetric fumarate gantacurium, CW 002, has been synthesized to undergo slower L-cysteine adduction. Because of its slower metabolism, it has an intermediate duration of action. In animals, it causes a nondepolarizing block that can be antagonized by neostigmine. Administration of L-cysteine 1 minute after administration of CW 002 effectively speeds recovery of neuromuscular function, whereas neostigmine does not.[22] Volunteer trials are required to determine whether onset, recovery, and ease of antagonism are improved over those using compounds that are currently available.

POTENCY OF NONDEPOLARIZING NEUROMUSCULAR BLOCKERS

Drug potency is commonly expressed by the dose-response relationship. The dose of an NMBD required to produce an effect (e.g., 50%, 90%, or 95% depression of twitch height, commonly expressed as ED_{50}, ED_{90}, and ED_{95}, respectively) is its potency.[9,98,103-114] The NMBDs have different potencies, as illustrated in Table 34-3 and Figure 34-8. For factors affecting the potency of NMBDs, see the section on drug interactions later in this chapter. The dose-response relationship for nondepolarizing NMBDs is sigmoidal (see Fig. 34-8) and has been derived in various ways. The simplest method is to perform linear regression over the approximately linear portion of a semilogarithmic plot between 25% and 75% neuromuscular blockade. Alternatively, the curve can be subjected to probit or logit transformation to linearize it over its whole length, or the data can be subjected to nonlinear regression using the sigmoid E_{max} model of this form:

$$\text{Effect}\,(e) = .\backslash F\left(\text{dose}_e{}^{\gamma}, \text{dose}_e{}^{\gamma} + \text{dose}_{e50}{}^{\gamma}\right)$$

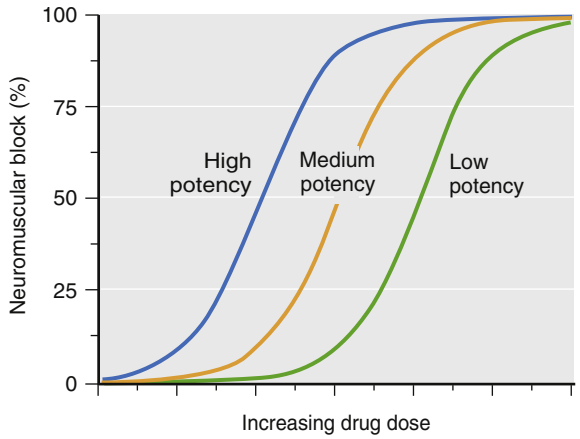


Figure 34-8. Schematic representation of a semilogarithmic plot of a muscle-relaxant dose versus neuromuscular blockade. A drug of high potency is doxacurium, one of medium potency is atracurium, and one of low potency is gallamine. The graph illustrates that the relative potencies of the muscle relaxants span a range of approximately two orders of magnitude.

More complex models relating the concentration of NMBDs at the neuromuscular junction to their pharmacologic effect have been developed, and they are discussed later.[115,116]

CLINICAL MANAGEMENT

The main goal of neuromuscular blockade during induction of anesthesia includes paralysis of the vocal cords and muscles of the jaw to facilitate endotracheal intubation. Relaxation of the respiratory muscles, particularly the diaphragm, allows controlled ventilation. Paralysis of the abdominal muscles and the diaphragm is often required intraoperatively, particularly during abdominal or laparoscopic surgery. During recovery from neuromuscular block, restoration of complete neuromuscular strength is essential to ensure adequate spontaneous ventilation with normal regulation of breathing during hypoxia and the patency of the musculature of the upper airway with maintained airway protection. The choice of

the initial dose of NMBD, timing of readministration of NMBD, timing of administration of anticholinesterase, and interpretation of monitoring require an understanding of the varying sensitivities of different muscle groups to NMBDs.

Although the practice of administering an NMBD to facilitate tracheal intubation may be routine, it has been suggested that the combination of propofol with a rapid-acting opioid may provide good to excellent intubating conditions in most patients. However, relatively large doses of opioids are required to obtain satisfactory intubating conditions. Mencke and co-workers demonstrated that adding atracurium to a propofol-fentanyl induction regimen significantly improved the quality of intubating conditions and decreased the frequency of vocal cord lesions following intubation from 42% to 8%.[117] The rate of postoperative hoarseness was also significantly decreased to 16% from 44%.[117] Combes and associates confirmed that the use of NMBD for tracheal intubation decreased the incidence of adverse postoperative upper airway symptoms, resulted in better intubating conditions, and also reduced the rate of adverse hemodynamic effects caused by deeper levels of anesthesia.[118] Patients intubated without an NMBD had three to four times more Cormack scores of 3 to 4, and difficult intubation was more common (12% versus 1%).

Several alternative approaches are available to enhance surgical relaxation when administration of additional NMBDs may be inappropriate. These options include increasing the depth of general anesthesia with a drug such as a volatile anesthetic or propofol, administering lidocaine, using regional anesthesia, positioning the patient properly on the operating table, and appropriately adjusting the depth of neuromuscular blockade. The choice of one or several of these options is determined by the estimated remaining duration of surgery, the anesthetic technique, and the surgical maneuver required. It is important to keep these options in mind to avoid relying on only neuromuscular blockade to achieve a desired degree of relaxation.

Varying Sensitivities of Different Muscle Groups

The sensitivity of the neuromuscular junctions to the effects of neuromuscular relaxants among various muscle groups varies greatly. Paton and Zaimis[118a] demonstrated in 1951 that some of the muscles of respiration, such as the diaphragm, were more resistant to curare than others. The dose of nondepolarizing NMBDs needed to block the diaphragm is 1.5 to 2 times that of the adductor pollicis. Thus, complete paralysis of the diaphragm is not expected with doses of NMBDs used to block neuromuscular transmission at the adductor pollicis.[119] Similarly, the laryngeal adductor muscles are more resistant to nondepolarizing NMBDs than the more peripheral muscles such as the adductor pollicis,[120] at which all dosing recommendations for NMBDs and their antagonists have been made. The sparing effect on the laryngeal adductor muscles has been documented with vecuronium, rocuronium, cisatracurium, and mivacurium.[120-122] Plaud and colleagues studied the pharmacokinetic-pharmacodynamic relationship of blocking drugs at the adductor pollicis and the laryngeal adductors.[123] These investigators found that the concentration in the effect compartment producing 50% of the maximum block was significantly greater at the laryngeal adductor muscles (1.5 μg/mL) than that at the adductor pollicis (0.8 μg/mL). Convincing evidence indicates that the EC_{50} for almost all drugs is 50% to 100% higher at the diaphragm or larynx than it is at the adductor pollicis. These differences may be caused by any of several factors. Waud and Waud found that following curare administration, neuromuscular transmission occurs when approximately 18% of the receptors are free at the diaphragm, whereas it does not occur at the peripheral muscles unless 29% of receptors are free.[124] The reason may be higher receptor density, greater release of acetylcholine, or less acetylcholinesterase activity. The lower density of acetylcholine receptors in slow muscle fibers, such as found in the peripheral muscles, explains, in part, the lower margin of safety for neuromuscular transmission when compared with that in the faster muscle fibers in the laryngeal adductors. Muscle sensitivity to succinylcholine is different from that of other NMBDs. Succinylcholine is the only muscle relaxant that, at equipotent doses, causes greater neuromuscular block at the vocal cords than at the adductor pollicis. Some data suggest that in contrast to nondepolarizing NMBDs, succinylcholine is more effective in blocking the muscles composed of primarily fast contracting fibers.[125]

In spite of the relative resistance to NMBDs, the onset of neuromuscular block is significantly faster at the diaphragm and the laryngeal adductors than at the adductor pollicis. Fisher and associates postulated that more rapid equilibration (shorter effect site equilibration half-life [$t_{½}k_{e0}$]) of the NMBD between plasma[126] and the effect compartment at these more centrally located muscles was the explanation for this observation. The accelerated rate of equilibrium probably represents little more than differences in regional blood flow. Therefore, muscle blood flow, rather than a drug's intrinsic potency, may be more important in determining the onset and offset time of nondepolarizing NMBDs. Greater blood flow per gram of muscle at the diaphragm or larynx results in receipt of a higher peak plasma concentration of drug in the brief period of time before rapid redistribution occurs. Plaud and colleagues confirmed this hypothesis by demonstrating a faster transfer rate constant (i.e., $t_{½}k_{e0}$) at the laryngeal adductors (2.7 minutes) than at the adductor pollicis (4.4 minutes).[123] Greater resistance to neuromuscular blockade accounts for the faster recovery of the respiratory muscles and the muscles of the abdominal wall than at the adductor pollicis. Recovery occurs more rapidly because blood concentration of the NMBD must decrease more in the muscles of respiration than in the adductor pollicis for recovery of neuromuscular function to begin.

In contrast, the muscles of the upper airway are particularly sensitive to the effects of muscle relaxants. The masseter is 15% more sensitive to nondepolarizing NMBDs than is the adductor pollicis.[127] Significant weakness of the muscles of the upper airway may exist even when strength at the adductor pollicis has recovered almost to baseline values. A TOF ratio less than 0.9 at the

TABLE 34-4 **GUIDE TO NONDEPOLARIZING RELAXANT DOSAGE (MG/KG) UNDER DIFFERENT ANESTHETIC TECHNIQUES***

	ED_{95} Under N_2O/O_2	Dose for Intubation	Supplemental Dose After Intubation	Dosage for Relaxation	
				N_2O	Anesthetic Vapors†
Long-acting					
Pancuronium	0.07	0.08-0.12	0.02	0.05	0.03
d-Tubocurarine	0.5	0.5-0.6	0.1	0.3	0.15
Intermediate-acting					
Vecuronium	0.05	0.1-0.2	0.02	0.05	0.03
Atracurium	0.23	0.5-0.6	0.1	0.3	0.15
Cisatracurium	0.05	0.15-0.2	0.02	0.05	0.04
Rocuronium	0.3	0.6-1.0	0.1	0.3	0.15
Short-acting					
Mivacurium	0.08	0.2-0.25	0.05	0.1	0.08
Continuous Infusion Dosage (μg/kg/min) Required to Maintain 90-95% Twitch Inhibition Under N_2O/O_2 With Intravenous Agents					
Mivacurium	3-15				
Atracurium	4-12				
Cisatracurium	1-2				
Vecuronium	0.8-1.0				
Rocuronium	9-12				

ED_{95}, Dose causing on average 95% suppression of neuromuscular response; *N_2O*, nitrous oxide.
*Suggested dosages provide good intubating conditions under light anesthesia. Satisfactory abdominal relaxation may be achieved at dosages listed after intubation without a relaxant or with succinylcholine. This table is intended as a general guide to dosage. Individual relaxant requirement should be confirmed with a peripheral nerve stimulator.
†The potentiation of nondepolarizing relaxants by different anesthetic vapors has been reported to vary from 20% to 50%. More recent data suggest, however, that this variation may be much less, particularly in the case of the intermediate- and short-acting relaxants. Therefore, for the sake of simplicity, this table assumes a potentiation of 40% in the case of all volatile anesthetics.

adductor pollicis is associated with impaired pharyngeal function, reduced resting tone in the upper esophageal sphincter muscle, and decreased coordination of the muscles involved in swallowing, all of which cause an increased incidence of misdirected swallows, or aspiration.[128] Because of the resistance of the muscles of respiration to neuromuscular block, patients may be weak but able to breathe as long as an endotracheal tube is in place. Once extubated, however, they may not be able to maintain a patent airway or protect their airway.[129] This is likely the reason that patients with a TOF less than 0.9 in the postanesthesia care unit (PACU) are more likely to develop respiratory events than those whose TOF ratio is 0.9 or greater.

DOSAGE

General Dosage Guidelines

Proper selection of the dose of nondepolarizing NMBD is required to ensure that the desired effect is achieved without overdose of the relaxant (Tables 34-4 and 34-5). The intensity of maximum blockade is directly affected by dose. If a small dose of NMBD is administered, neuromuscular block may not occur because the amount administered is inadequate to overcome the margin of safety at the neuromuscular junction. When doses lower than those required to cause 100% neuromuscular block are administered, the time required to reach maximum effect is a function of the NMBD and blood flow to the muscles. It is independent of the dose administered. However, if the administered dose is high enough to cause 100% neuromuscular block, the time required for maximum block will depend on the dose of NMBD administered. Larger doses will, up to a certain point, produce a faster onset of effect.[130] Increasing the dose of NMBD beyond that point will not decrease the time to onset of maximal effect and may contribute to postoperative neuromuscular block.

In addition to a general knowledge of the pharmacodynamics and pharmacokinetics of NMBDs and understanding of the guidelines for dosing, optimal practice requires that dosing be adjusted to account for variability in individual patients' responses to NMBDs. This adjustment cannot be made without using a monitor of neuromuscular blockade any time that an NMBD is administered to a patient. Overdosage must be avoided for two reasons: to limit the duration of drug effect so that it matches the anticipated length of surgery and to avoid unwanted cardiovascular side effects.

Initial and Maintenance Dosage

The initial dose of NMBD is determined by the reason it is being administered. Traditionally, doses used to facilitate tracheal intubation are twice the ED_{95} (see Table 34-4). If, however, the trachea has been intubated without the use of an NMBD and the purpose in administering an NMBD is to produce surgical relaxation, a dose that is slightly less

than the ED_{95} (see Table 34-5) should be given. Administration of NMBDs solely for surgical relaxation does not prevent vocal cord lesions and postoperative hoarseness caused by intubation without NMBD. Administering a smaller initial dose may be necessary in the presence of any of the potent inhalational anesthetics (see the later section on drug interactions).

To avoid prolonged residual paralysis, inadequate antagonism of residual blockade, or both, the main goal in dosing NMBDs should be to use the lowest possible dose that provides adequate relaxation for surgery. Moreover, clinical management of individual patients should be guided by monitoring of the neuromuscular block, ideally with an objective neuromuscular monitoring technique (see also Chapter 53), to allow safe intraoperative administration of the NMBD and its antagonism by neostigmine or sugammadex. In an adequately anesthetized and monitored patient, little reason exists to abolish the TOF responses to peripheral nerve stimulation completely. However, if deep levels of block are required to maintain paralysis of the diaphragm and the abdominal wall muscles, response of the adductor pollicis to stimulation of the ulnar nerve may disappear. In this case, monitoring the depth of neuromuscular block can be accomplished using the posttetanic count (PTC) at the adductor pollicis or TOF at the corrugator supercilii[131,132] (see Chapter 53). Supplemental (maintenance) doses of NMBDs should be approximately one tenth (in case of long-acting NMBDs) to one fourth (in the case of intermediate- and short-acting NMBDs) the initial dose and should not be given until clear evidence of beginning recovery from the previous dose is present.

Relaxation can be maintained by continuous infusion of intermediate- and short-acting drugs. This approach is useful in maintaining a stable depth of neuromuscular block and allows adjustment of the depth of relaxation according to surgical needs. The depth of neuromuscular block maintained is moderate, if possible, to ensure complete spontaneous recovery of neuromuscular function at the end of a surgical procedure or prompt antagonism of residual effects. Table 34-4 lists the approximate dose ranges that are typically required during infusions to maintain 90% to 95% blockade of the twitch (one twitch visible on TOF stimulation) during a nitrous

TABLE 34-5 **PHARMACODYNAMIC EFFECTS OF SUCCINYLCHOLINE AND NONDEPOLARIZING NEUROMUSCULAR BLOCKERS**

	Anesthesia	Intubating Dose (mg/kg)	Approximate ED_{95} Multiples	Maximum Block (%)	Time to Maximum Block (min)	Clinical Duration*(min)	References
Succinylcholine	Opioids or halothane	0.5	1.7	100	—	6.7	372
Succinylcholine	Desflurane	0.6	2	100	1.4	7.6	373
Succinylcholine	Opioids or halothane	1.0	2	100	—	11.3	372
Succinylcholine	Desflurane	1.0	3	100	1.2	9.3	373
Succinylcholine	Opioids	1.0	3	—	1.1	8	374
Succinylcholine	Opioids	1.0	3	—	1.1	9	375
Succinylcholine	Isoflurane	1.0	3	100	0.8	9	140
Steroidal Compounds							
Rocuronium	Opioids	0.6	2	100	1.7	36	142
Rocuronium	Isoflurane	0.6	2	100	1.5	37	140
Rocuronium	Isoflurane	0.9	3	100	1.3	53	140
Rocuronium	Isoflurane	1.2	4	100	0.9	73	140
Vecuronium	Isoflurane	0.1	2	100	2.4	41	140
Vecuronium	Opioids	0.1	2	100	2.4	44	376
Pancuronium	Opioids	0.08	1.3	100	2.9	86	148, 377
Pancuronium	Opioids	0.1	1.7	99	4	100	378
Benzylisoquinolinium Compounds†							
Mivacurium	Opioids	0.15	2	100	3.3	16.8	9
Mivacurium	Opioids	0.15	2	100	3	14.5	142
Mivacurium	Halothane	0.15	2	100	2.8	18.6	379
Mivacurium	Opioids	0.2	2.6	100	2.5	19.7	9
Mivacurium	Opioids	0.25	3.3	100	2.3	20.3	9
Mivacurium	Opioids	0.25	3.3	—	2.1	21	375
Atracurium	Opioids	0.5	2	100	3.2	46	107
Cisatracurium	Opioids	0.1	2	99	7.7	46	323
Cisatracurium	Opioids	0.1	2	100	5.2	45	107
Cisatracurium	Opioids	0.2	4	100	2.7	68	107
Cisatracurium	Opioids	0.4	8	100	1.9	91	107
d-Tubocurarine	Opioids	0.6	1.2	97	5.7	81	378

ED_{95}, Dose causing on average 95% suppression of neuromuscular response.
*Time from injection of the intubating dose to recovery of twitch to 25% of control.
†For atracurium and mivacurium, slower injection (30 seconds) is recommended to minimize circulatory effects.

oxide–oxygen anesthetic supplemented with intravenous anesthetics. Infusion dosage is usually decreased by 30% to 50% in the presence of potent volatile anesthetics.

NEUROMUSCULAR BLOCKERS AND TRACHEAL INTUBATION

Rapid onset of neuromuscular blockade is one of the requirements for securing an airway promptly. It is affected by several factors, including muscle blood flow, rate of delivery of the drug to the neuromuscular junction, receptor affinity, plasma clearance, and the mechanism of neuromuscular blockade (depolarizing versus nondepolarizing).[96,133,134] The speed of onset is inversely proportional to the potency of nondepolarizing NMBDs.[96,133] A high ED_{95} (i.e., low potency) is predictive of rapid onset of effect and vice versa (see Table 34-5 and Fig. 34-9). Onset time decreases as ED_{50} increases. This relationship can be explained on the basis of the density of receptors at the neuromuscular junction. Irrespective of their potency, NMBDs must bind to a critical number of acetylcholine receptors for blockade to occur. These receptors are concentrated at the neuromuscular junction where access is limited. When a potent NMBD is administered, fewer molecules are administered than in the case of an equipotent dose of a less potent drug. Because of this lower concentration gradient, more time is required for enough molecules of a potent drug to be delivered to the neuromuscular junction. Thus, onset time is longer. This concept was verified by Kopman and colleagues, who demonstrated that, when giving equipotent doses of gallamine, dTc, and pancuronium, onset time was slower with the more potent pancuronium and faster with the less potent gallamine. Except for atracurium,[135] the molar potency (the ED_{50} or ED_{95} expressed as μM/kg) is highly predictive of a drug's initial rate of onset of effect (at the adductor pollicis).[133] A drug's measured molar potency is the end result of many contributing factors: the drug's intrinsic potency (the CE_{50}, which is the biophase concentration resulting in 50% twitch depression), the rate of equilibration between plasma and biophase (k_{e0}), the initial rate of plasma clearance, and probably other factors as well.[136] Notably, rocuronium has a molar potency (ED_{95}) of 0.54 μM/kg, which is approximately 13% that of vecuronium and only 9% that of cisatracurium; this finding illustrates the expected faster onset of rocuronium at the adductor pollicis, as opposed to vecuronium and cisatracurium.

Donati and Meistelman proposed a model to explain this inverse potency–onset relationship.[134] Nondepolarizing NMBDs of low potency (e.g., rocuronium) have more molecules to diffuse from the central compartment into the effect compartment. Once in the effect compartment, all molecules act promptly. Weaker binding of the low-potency drugs to receptors prevents buffered diffusion,[134] a process that occurs with more potent drugs. Buffered diffusion causes repetitive binding and unbinding to receptors, thus keeping potent drugs in the neighborhood of the effector sites and potentially lengthening the duration of effect.

The times to 95% blockade at the adductor pollicis after administration of the ED_{95} dose of succinylcholine, rocuronium, vecuronium, atracurium, mivacurium, and cisatracurium are shown in Figure 34-10.[114,133,135] The illustration shows that the most potent compound, cisatracurium, has the slowest onset, and the least potent compound, rocuronium, has the most rapid onset.[114,133,135] Bevan also proposed that rapid plasma clearance is associated with a rapid onset of action.[137] The fast onset of succinylcholine's action is related to its rapid metabolism and plasma clearance.

The onset of neuromuscular blockade is much faster in the muscles that are relevant to obtaining optimal intubating conditions (laryngeal adductors, diaphragm, and masseter) than in the muscle that is typically monitored (adductor pollicis) (Fig. 34-11).[121] Thus, neuromuscular blockade develops faster, has a shorter duration of effect, and recovers more quickly in these muscles (Table 34-6).[120-122,138,139]

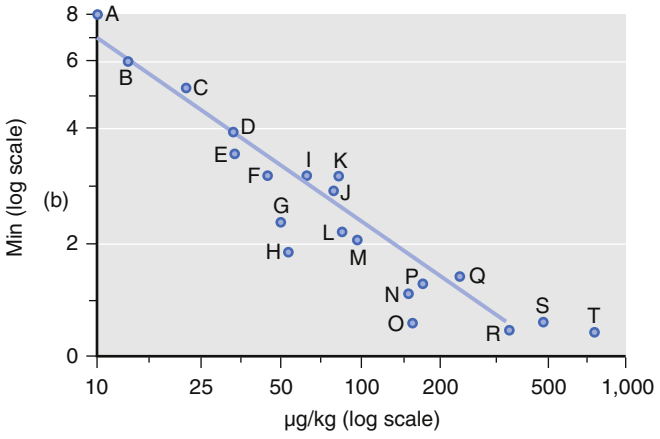


Figure 34-9. Linear regression of onset of neuromuscular blockade (ordinate) versus potency of a series of steroidal relaxants studied in the cat model by Bowman and associates.[96] The data show that onset may be increased in compounds of low potency and encouraged the eventual development of rocuronium and rapacuronium (ORG 9487). *A,* Pipecuronium; *C,* pancuronium; *D,* vecuronium.

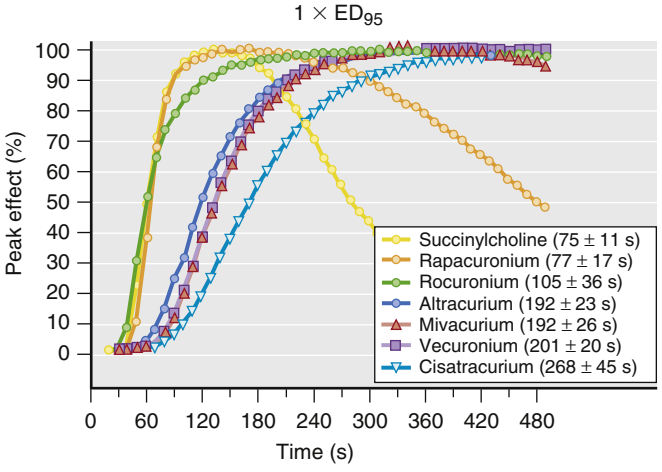


Figure 34-10. Percentages of peak effect after a dose causing on average 95% suppression of neuromuscular response (ED_{95}) of succinylcholine, rocuronium, rapacuronium, vecuronium, atracurium, mivacurium, and cisatracurium at the adductor pollicis muscle. Times (mean ± standard deviation) in seconds to 95% of peak effect are shown in parentheses. *(Data from references 114, 133, and 135.)*

Paralysis following injection does not occur instantaneously even with large doses of muscle relaxants. Onset of blockade occurs 1 to 2 minutes earlier in the larynx than at the adductor pollicis after administration of nondepolarizing NMBDs. The pattern of blockade (onset, depth, and speed of recovery) in the corrugator supercilii is similar to that in the larynx,[119] the diaphragm, and the muscles of the abdominal wall. By monitoring the onset of neuromuscular blockade at the corrugator supercilii, one can predict the quality of tracheal intubating conditions. Good to excellent intubating conditions are observed in more than 90% of patients after disappearance of the TOF at the corrugator supercilii.[131] The onset of maximal blockade in the larynx also corresponds with the point at which the adductor pollicis begins to show palpable evidence of weakening.

Rapid Tracheal Intubation

Succinylcholine is commonly used when rapid tracheal intubation is needed because it consistently provides muscle relaxation within 60 to 90 seconds. When succinylcholine is considered undesirable or contraindicated, high doses of rocuronium can be administered.[140] The onset of action of other nondepolarizing NMBDs can be accelerated by administering a priming dose of the NMBD[141] or by using combinations of NMBDs.[142] Although combinations of mivacurium and rocuronium can achieve rapid onset without undue prolongation of action and without undesirable side effects,[142] combinations of compounds of different structures may result in a marked prolongation of neuromuscular blockade. Additionally, combining different NMBDs may not consistently result in a rapid onset of neuromuscular block.

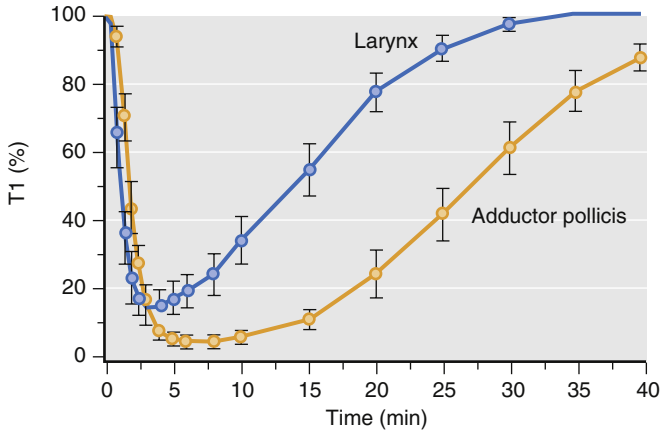


Figure 34-11. Evolution of neuromuscular blockade in the larynx and thumb (adductor pollicis) after a 0.07-mg/kg dose of vecuronium. Onset and recovery from blockade occur more rapidly in the larynx. *T1*, First twitch of train-of-four. *(From Donati F, Meistelman C, Plaud B: Vecuronium neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis,* Anesthesiology *74:833-837, 1991.)*

Priming Technique. Since the introduction of rocuronium into clinical practice, the use of priming has almost disappeared. When priming, a small, subparalyzing dose of the nondepolarizer (≈20% of the ED_{95} or ≈10% of the intubating dose) is administered 2 to 4 minutes before the intubating dose of the compound.[141] This procedure accelerates the onset of blockade for most nondepolarizing NMBDs only by 30 to 60 seconds, thereby indicating that intubation can be performed within 90 seconds of the second dose. However, the intubating conditions that occur after priming are only marginally improved and do not match those that occur after succinylcholine. The size of the priming dose is limited by its effects on the awake patient. Further, priming doses can cause subtle degrees of neuromuscular blockade and increase the patient's discomfort, the risks of aspiration, and difficulty swallowing and breathing.[143] This technique is contraindicated in patients with abnormal airway anatomy or increased sensitivity to NMBDs such as patients with myasthenia gravis or those taking magnesium.

Large-Dose Regimen for Rapid Tracheal Intubation. Large doses of NMBDs are usually recommended when intubation must be accomplished in less than 90 seconds. High-dose regimens are associated with considerably prolonged duration of action and potentially increased cardiovascular side effects, however (see Table 34-5).[140,144] Increasing the dosage of rocuronium from 0.6 mg/kg (twice the ED_{95}) to 1.2 mg/kg (four times the ED_{95}) shortens the onset time of complete neuromuscular block from 89 seconds to 55 seconds but essentially doubles the clinical duration of action of the compound (the recovery

TABLE 34-6 **TIME COURSE OF ACTION AND PEAK EFFECT DATA AT THE LARYNGEAL ADDUCTORS AND ADDUCTOR POLLICIS**

		Laryngeal Adductors			Adductor Pollicis			
Dose (mg/kg)	Anesthesia	Onset Time (sec)	Maximum Block (% Depression)	Clinical Duration (min)	Onset Time (sec)	Maximum block (% Depression)	Clinical Duration (min)	Reference
Succinylcholine, 1.0	Propofol-fentanyl	34 ± 12	100 ± 0	4.3 ± 1.6	56 ± 15	100 ± 0	8 ± 2	122
Rocuronium, 0.25	Propofol-fentanyl	96 ± 6	37 ± 8	—	180 ± 18	69 ± 8	—	121
Rocuronium, 0.4	Propofol-fentanyl	92 ± 29	70 ± 15	—	155 ± 40	99 ± 3	24 ± 7	122
Rocuronium, 0.5	Propofol-fentanyl	84 ± 6	77 ± 5	8 ± 3	144 ± 12	98 ± 1	22 ± 3	121
Vecuronium, 0.04	Propofol-fentanyl	198 ± 6	55 ± 8	—	342 ± 12	89 ± 3	11 ± 2	120
Vecuronium, 0.07	Propofol-fentanyl	198 ± 12	88 ± 4	9 ± 2	342 ± 18	98 ± 1	22 ± 2	120
Mivacurium, 0.14	Propofol-alfentanil	137 ± 20	90 ± 7	5.7 ± 2.1	201 ± 59	99 ± 1	16.2 ± 4.6	138
Mivacurium, 0.2	Propofol-alfentanil	89 ± 26	99 ± 4	10.4 ± 1.5	202 ± 45	99 ± 2	20.5 ± 3.9	139

*Clinical duration is the time until the first twitch of train-of-four (T1) has recovered to 25% of its control value. Mean and standard deviation[122,138,139] or standard error of the mean.[120,121]

of the first twitch of TOF [T1] to 25% of baseline values) from 37 minutes to 73 minutes.[140]

Whatever technique of rapid-sequence induction of anesthesia and intubation is chosen, the following four principles are important: (1) preoxygenation must be performed, (2) sufficient doses of intravenous drugs must be administered to ensure that the patient is adequately anesthetized, and (3) intubation within 60 to 90 seconds must be considered acceptable; and (4) cricoid pressure should be applied subsequent to injection of the induction agent.

Small-Dose Relaxants for Tracheal Intubation

Small doses of NMBDs can be used for routine tracheal intubation. The use of smaller doses of NMBDs has the following two possible advantages: (1) it shortens the time to recovery from neuromuscular blockade, and (2) it reduces the requirement for anticholinesterase drugs. Rocuronium has the shortest onset time of all the nondepolarizing NMBDs currently available.[121,122] The maximal effect of either 0.25 or 0.5 mg/kg of rocuronium at the laryngeal muscles occurs after 1.5 minutes.[121] This interval is shorter than the 3.3 minutes reported after administration of equipotent doses of vecuronium (0.04 or 0.07 mg/kg),[120] and it is only slightly more than the 0.9 minutes reported after 0.25 or 0.5 mg/kg of succinylcholine (see Table 34-6).[125]

With a better understanding of the multiple factors that contribute to satisfactory conditions for intubation, it is now possible to administer NMBDs thoughtfully in this fashion. Intubating conditions are related more closely to the degree of neuromuscular blockade of the laryngeal adductor muscles than to the degree of blockade typically monitored at the adductor pollicis. Figure 34-12 demonstrates this principle.[136] In the presence of an adequate depth of anesthesia, complete blockade at the larynx or diaphragm, or both, may not be a prerequisite for satisfactory intubating conditions. Kopman and colleagues noted that 0.5 mg/kg of rocuronium (1.5 times the ED_{95}) provided very satisfactory conditions for intubation in patients anesthetized with 12.5 μg/kg of alfentanil and 2.0 mg/kg of propofol if laryngoscopy was delayed for 75 seconds after drug administration.[145] It was furthermore estimated that 1.5 times the ED_{95} of rocuronium would produce at least 95% blockade in 98% of the population.[145] A similar or lower multiple of rocuronium's ED_{95} was shown to have a faster onset and shorter duration of action than those of atracurium[146] or cisatracurium.[109] In most patients receiving 15 μg/kg of alfentanil followed by 2.0 mg/kg of propofol and 0.45 mg/kg of rocuronium, good to excellent conditions for intubation are present 75 to 90 seconds after the completion of drug administration.

METABOLISM AND ELIMINATION

The specific pathways of the metabolism (biotransformation) and elimination of NMBDs are summarized in Table 34-7. Of the nondepolarizing NMBDs listed, pancuronium, pipecuronium, vecuronium, atracurium, cisatracurium, and mivacurium are the only drugs that are metabolized or degraded. Nearly all nondepolarizing NMBD molecules contain ester linkages, acetyl ester groups, and hydroxy or methoxy groups. These substitutions, especially the quaternary nitrogen groups, confer a high degree of water solubility with only slight lipid solubility. The hydrophilic nature of relaxant molecules enables easy elimination in the urine through glomerular filtration, with no tubular resorption or secretion. Therefore, all nondepolarizing NMBDs show elimination of the parent molecule in the urine as the basic route of elimination; those with a long duration of action thus have a clearance rate that is limited by the glomerular filtration rate (1 to 2 mL/kg/minute).

Steroidal Compounds

Long-Acting Neuromuscular Blocking Drugs. Pancuronium is cleared largely by the kidney[147] and, to a limited extent, by hepatic uptake and elimination. A small amount (15% to 20%) is deacetylated at the 3 position in the liver, but this makes a minimal contribution to the total clearance. Deacetylation also occurs at the 17 position but to such a small extent as to be clinically

	Muscle X	Adductor pollicis
EC_{50} (μg/mL)	3.00	1.18
$t_{1/2}k_{e0}$ (min)	1.93	3.85
Hill coefficient	4.00	4.50

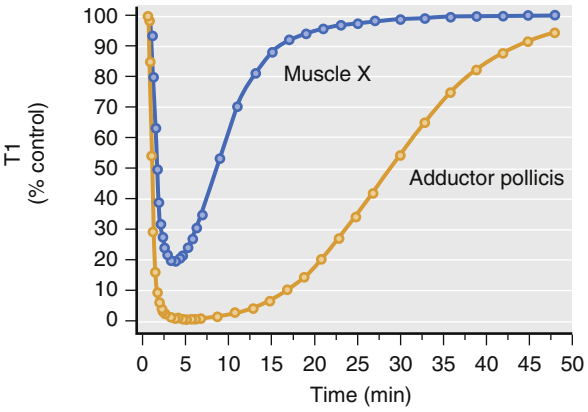


Figure 34-12. A computer simulation based on Sheiner's model[115] and data reported by Wierda and colleagues. The dose causing on average 95% suppression of neuromuscular response (ED_{95}) of rocuronium at the adductor pollicis from this model is 0.33 mg/kg. Rocuronium, 0.45 mg/kg, is given as a bolus at time zero. Muscle X represents a muscle (e.g., the diaphragm or the laryngeal adductors) that is less sensitive to the effects of nondepolarizing relaxants than the adductor pollicis but has greater blood flow. In this example, the concentration of rocuronium producing 50% block (EC_{50}) of muscle X is 2.5 times that of the adductor pollicis, but the half-life of transport between the plasma and effect compartment ($t_{½}k_{e0}$) of muscle X is only half as long. The rapid equilibration between plasma concentrations of rocuronium and muscle X results in the more rapid onset of blockade of muscle X than of the adductor pollicis. The greater EC_{50} at muscle X explains the faster recovery of this muscle than of the adductor pollicis from neuromuscular blockade. Lower blood concentrations of rocuronium must be achieved at the adductor pollicis than at muscle X before recovery begins. *T1,* First twitch of train-of-four *(From Naguib M, Kopman AF: Low dose rocuronium for tracheal intubation,* Middle East J Anesthesiol *17:193-204, 2003, with permission from the* Middle East Journal of Anesthesiology.*)*

TABLE 34-7 METABOLISM AND ELIMINATION OF NEUROMUSCULAR BLOCKING DRUGS

Drug	Duration	Metabolism (%)	Elimination		Metabolites
			Kidney (%)	Liver (%)	
Succinylcholine	Ultrashort	Butyrylcholinesterase (98-99%)	<2%	None	Monoester (succinyl monocholine) and choline; the monoester is metabolized much more slowly than succinylcholine
Gantacurium	Ultrashort	Cysteine (fast) and ester hydrolysis (slow)	?	?	Inactive cysteine adduction product, chloroformate monoester, and alcohol
Mivacurium	Short	Butyrylcholinesterase (95-99%)	<5% (Metabolites eliminated in urine and bile)	None	Monoester and quaternary alcohol; the metabolites are inactive and most likely are not metabolized any further
Atracurium	Intermediate	Hofmann elimination and nonspecific ester hydrolysis (60-90%)	10-40% (Metabolites eliminated in urine and bile)	None	Laudanosine, acrylates, alcohols, and acids; although laudanosine has CNS-stimulating properties, the clinical relevance of this effect is negligible
Cisatracurium	Intermediate	Hofmann elimination (77%?)	Renal clearance is 16% of total		Laudanosine and acrylates; ester hydrolysis of the quaternary monoacrylate occurs secondarily; because of the greater potency of cisatracurium, laudanosine quantities produced by Hofmann elimination are 5 to 10 times lower than in the case of atracurium, thus making this a nonissue in practice
Vecuronium	Intermediate	Liver (30-40%)	40-50% (Metabolites excreted in urine and bile) ≈40%	50-60% ≈60%	The 3-OH metabolite accumulates, particularly in renal failure; it has ≈80% the potency of vecuronium and may be responsible for delayed recovery in ICU patients
Rocuronium	Intermediate	None	10-25%	>70%	None
Pancuronium	Long	Liver (10-20%)	85%	15%	The 3-OH metabolite may accumulate, particularly in renal failure; it is approximately two thirds as potent as the parent compound
d-Tubocurarine	Long	None	80% (?)	20%	None

CNS, Central nervous system; *ICU,* intensive care unit.

irrelevant. The three known metabolites have been individually studied in anesthetized humans.[148] The 3-OH metabolite is the most potent of the three, being approximately half as potent as pancuronium, and is the only one present in detectable concentrations in the plasma. This metabolite has pharmacokinetics and duration of action similar to those of pancuronium.[148] The 3-OH metabolite is most likely excreted largely by the kidney.[148] The parent compound and the 3-OH metabolite are also cleared in small amounts through a minor liver pathway. The total clearance is delayed, and the duration of action is significantly lengthened by severe disorders of renal or hepatic function.[149-151]

Intermediate-Acting Neuromuscular Blockers. Vecuronium, the 2-desmethyl derivative of pancuronium, is more lipid soluble than pancuronium because of the absence of the quaternizing methyl group at the 2 position. It undergoes two to three times more metabolism than does pancuronium. Vecuronium is taken up into the liver by a carrier-mediated transport system,[152] and it is then deacetylated at the 3 position by liver microsomes. Approximately 12% of vecuronium clearance is through conversion to 3-desacetylvecuronium,[153] and 30% to 40% of the drug is cleared in the bile as the parent compound.[154] Although the liver is the principal organ of elimination for vecuronium, the drug also undergoes significant (up to 25%) renal excretion, and this combined organ elimination gives it a clearance rate of 3 to 6 mL/kg/minute.[153,155]

The principal metabolite of vecuronium, 3-desacetylvecuronium, is a potent (≈80% of vecuronium) NMBD in its own right. The metabolite, however, has slower plasma clearance and longer duration of action than vecuronium.[153] 3-Desacetylvecuronium has a clearance rate of 3.5 mL/kg/minute, and renal clearance accounts for approximately one sixth of its elimination.[153] In patients with renal failure in the ICU, 3-desacetylvecuronium can accumulate and produce prolonged neuromuscular blockade.[156] Other putative metabolites are 17-desacetylvecuronium and 3,17-bisdesacetylvecuronium, neither of which occurs in clinically significant amounts.

Rocuronium is eliminated primarily by the liver, with a small fraction (≈10%) eliminated in the urine.[157] It is taken up into the liver by a carrier-mediated active transport system.[158] The putative metabolite, 17-desacetylrocuronium, has not been detected in significant quantities.

Benzylisoquinolinium Compounds

Short-Acting Neuromuscular Blocking Drugs. Mivacurium is hydrolyzed in the plasma by butyrylcholinesterase to a monoester and an amino alcohol,[9] which are excreted in urine and bile. They have less than 1% of the neuromuscular blocking activity of the parent compound. Less than 5% of mivacurium is excreted in the urine as the parent compound.

Mivacurium consists of three stereoisomers, and the clearances of the two most pharmacologically active isomers, the *cis-trans* and *trans-trans*, are approximately 100 and 50 to 70 mL/kg/minute, respectively.[94,159,160] These two isomers show elimination half-lives of 2 to 3 minutes.[94] The third stereoisomer, the *cis-cis*, is present as only 4% to 8% of the mivacurium mixture and has less than 10% of the neuromuscular blocking potency of the other two isomers.[94] Consequently, even though it has a much longer elimination half-life (55 minutes) and lower clearance (≈4 mL/kg/minute) than the two other isomers, it does not contribute significantly to the duration of action of mivacurium.[94] This rapid enzymatic clearance of mivacurium accounts for its short duration of action.[9,94] When butyrylcholinesterase activity is significantly decreased, however, as in the rare patient who is homozygous for genetically atypical enzymes, the duration of action of mivacurium is prolonged for up to several hours.[161-164]

Intermediate-Acting Neuromuscular Blocking Drugs. Atracurium is metabolized through two pathways: Hofmann elimination and nonspecific ester hydrolysis. Hofmann elimination is a purely chemical process that results in loss of the positive charges by molecular fragmentation to laudanosine (a tertiary amine) and a monoquaternary acrylate, compounds that are thought to have no neuromuscular and little or no cardiovascular activity of clinical relevance.[165]

Because it undergoes Hofmann elimination, atracurium is relatively stable at pH 3.0 and 4° C and becomes unstable when it is injected into the bloodstream. Early observations of the breakdown of the drug in buffer and plasma showed faster degradation in plasma, a finding suggesting a possible enzymatic hydrolysis of the ester groups. Further evidence suggested that ester hydrolysis may be more important than originally realized in the breakdown of atracurium.[166] By using a pharmacokinetics analysis, Fisher and associates concluded that a significant amount of clearance of atracurium may be by routes other than ester hydrolysis and Hofmann elimination.[167] Thus, it appears that atracurium's metabolism is complicated and may not be completely understood.[167]

Laudanosine, a metabolite of atracurium, has central nervous system (CNS)–stimulating properties. However, adverse effects are unlikely to occur with atracurium use in either the operating room or the ICU.

Atracurium is a mixture of 10 optical isomers. Cisatracurium is the 1R *cis*–1′R *cis* isomer of atracurium.[90] Like atracurium, cisatracurium is metabolized by Hofmann elimination to laudanosine and a monoquaternary acrylate.[168,169] In contrast, however, no ester hydrolysis of the parent molecule occurs. Hofmann elimination accounts for 77% of the total clearance of 5 to 6 mL/kg/minute. Twenty-three percent of the drug is cleared through organ-dependent means, and renal elimination accounts for 16% of this.[169] Because cisatracurium is approximately four or five times as potent as atracurium, approximately five times less laudanosine is produced, and, as with atracurium, accumulation of this metabolite is not thought to be of any consequence in clinical practice.

Long-Acting Neuromuscular Blocking Drugs. dTc has no active metabolism. The kidney is the major pathway of elimination, with approximately 50% of a dose eliminated through renal pathways. The liver is likely a secondary route of elimination.

Asymmetric Mixed-Onium Fumarates

Gantacurium and CW 002 are degraded by two chemical mechanisms, neither of which is enzymatic: (1) rapid formation of an apparently inactive cysteine adduction product and (2) slower hydrolysis of the ester bond to presumably inactive hydrolysis products (see Fig. 34-7).[11,170]

In summary, the only short-acting nondepolarizing NMBD, mivacurium, is cleared rapidly and almost exclusively by metabolism by butyrylcholinesterase, thus resulting in much greater plasma clearance than that of any other nondepolarizing NMBD.[9] NMBDs of intermediate duration, such as vecuronium, rocuronium, atracurium, and cisatracurium, have clearance rates in the range of 3 to 6 mL/kg/minute because of multiple pathways of degradation, metabolism, and/or elimination. Atracurium is cleared two to three times more rapidly than the long-acting drugs.[171-174] Similar clearance values have been obtained for rocuronium[175-179] and cisatracurium.[168,169,180] Finally, the long-acting NMBDs undergo minimal or no metabolism, and they are eliminated largely unchanged, mostly by renal excretion. Hepatic pathways are less important in their metabolism.

ADVERSE EFFECTS OF NEUROMUSCULAR BLOCKERS

NMBDs seem to play a prominent role in the incidence of adverse reactions that occur during anesthesia. The Committee on Safety of Medicines in the United Kingdom reported that 10.8% (218 of 2014) of adverse drug reactions and 7.3% of deaths (21 of 286) were attributable to the NMBDs.[181]

Autonomic Effects

NMBDs may interact with nicotinic and muscarinic cholinergic receptors within the sympathetic and parasympathetic nervous systems and at the nicotinic receptors of the neuromuscular junction.

Dose-response ratios comparing the neuromuscular blocking potencies of these drugs (the ED_{95}) with their potencies in blocking vagal (parasympathetic) or

TABLE 34-8 APPROXIMATE AUTONOMIC MARGINS OF SAFETY OF NONDEPOLARIZING NEUROMUSCULAR BLOCKERS*

Drugs	Vagus†	Sympathetic Ganglia†	Histamine Release‡
Benzylisoquinolinium Compounds			
Mivacurium	>50	>100	3.0
Atracurium	16	40	2.5
Cisatracurium	>50	>50	None
d-Tubocurarine	0.6	2.0	0.6
Steroidal Compounds			
Vecuronium	20	>250	None
Rocuronium	3.0-5.0	>10	None
Pancuronium	3.0	>250	None

*Definition: number of multiples of the dose causing on average 95% suppression of neuromuscular response (ED_{95}) for neuromuscular blockade required to produce the autonomic side effect (ED_{50}).
†In cats.
‡In human subjects.

TABLE 34-9 CLINICAL AUTONOMIC EFFECTS OF NEUROMUSCULAR BLOCKING DRUGS

Drug Type	Autonomic Ganglia	Cardiac Muscarinic Receptors	Histamine Release
Depolarizing Substance			
Succinylcholine	Stimulates	Stimulates	Slight
Benzylisoquinolinium Compounds			
Mivacurium	None	None	Slight
Atracurium	None	None	Slight
Cisatracurium	None	None	None
d-Tubocurarine	Blocks	None	Moderate
Steroidal Compounds			
Vecuronium	None	None	None
Rocuronium	None	Blocks weakly	None
Pancuronium	None	Blocks moderately	None

sympathetic ganglionic transmission (the ED_{50}) can be constructed (Table 34-8). These ratios are termed the autonomic margin of safety of the relaxant in question. The higher the dose ratio, the lower is the likelihood of, or the greater the safety ratio for, the occurrence of the particular autonomic effect. The side effect is considered absent (none) in clinical practice if the safety ratio is greater than 5; it is weak or slight if the safety ratio is 3 or 4, moderate if 2 or 3, and strong or prominent if the ratio is 1 or less.

These autonomic responses are not reduced by slower injection of the muscle relaxant. They are dose related and additive over time if divided doses are given. If identical to the original dose, subsequent doses will produce a similar response (i.e., no tachyphylaxis will occur). This is not the case, however, when the side effect of histamine release is in question. Cardiovascular responses secondary to histamine release are decreased by slowing the injection rate, and the response undergoes rapid tachyphylaxis. The autonomic effects of NMBDs are summarized in Table 34-9.

Histamine Release. Quaternary ammonium compounds (e.g., NMBDs) are generally weaker histamine-releasing substances than are tertiary amines such as morphine. Nevertheless, when large doses of certain NMBDs are administered rapidly, erythema of the face, neck, and upper torso may develop, as well as a brief decrease in arterial pressure and a slight to moderate increase in heart rate. Bronchospasm in this setting is very rare. The clinical effects of histamine are seen when plasma concentrations increase 200% to 300% of baseline values, and these effects involve chemical displacement of the contents of mast cell granules containing histamine, prostaglandin, and possibly other vasoactive substances.[182] The serosal mast cell, located in the skin and connective tissue and near blood vessels and nerves, is principally involved in the degranulation process.[182]

The side effect of histamine release is most often noted following administration of the benzylisoquinolinium class of muscle relaxants, although it has also been noted in steroidal relaxants of low potency. The effect is usually of short duration (1 to 5 minutes), is dose related, and is clinically insignificant in healthy patients. Hatano and colleagues showed that the hypotensive cardiovascular response to 0.6 mg/kg of dTc in humans is prevented not only by antihistamines but also by nonsteroidal anti-inflammatory drugs (e.g., aspirin).[183] Those investigators concluded that the final step in dTc-induced hypotension is modulated by prostaglandins that are vasodilators.[183] This side effect can be reduced considerably by using a slower injection rate. It is also prevented by prophylaxis with combinations of $histamine_1$ and $histamine_2$ blockers.[184] If a minor degree of histamine release such as described earlier occurs after an initial dose of an NMBD, subsequent doses will generally cause no response at all, as long as they are no larger than the original dose. This is clinical evidence of tachyphylaxis, an important characteristic of histamine release. A much more significant degree of histamine release occurs during anaphylactic or anaphylactoid reactions; these reactions are very rare.

Clinical Cardiovascular Manifestations of Autonomic Mechanisms

Hypotension. The hypotension seen with the use of atracurium and mivacurium results from histamine release, whereas dTc causes hypotension by histamine release and ganglion blockade.[185,186] The effects of dTc occur closer to the dose required to achieve neuromuscular blockade.[113] The safety margin for histamine release is approximately three times greater for atracurium and mivacurium than it is for dTc.[182,183,186] Rapid administration of atracurium in doses greater than 0.4 mg/kg and of mivacurium in doses greater than 0.15 mg/kg has been associated with transient hypotension secondary to histamine release (Fig. 34-13).

Tachycardia. Pancuronium causes a moderate increase in heart rate and, to a lesser extent, in cardiac output, with little or no change in systemic vascular resistance.[187] Pancuronium-induced tachycardia has been attributed to the following: (1) vagolytic action,[187] probably from inhibition of M_2 receptors; and (2) sympathetic stimulation that involves both direct (blockade of neuronal uptake of norepinephrine) and indirect (release of norepinephrine from adrenergic nerve endings) mechanisms.[188] In studies in humans, Roizen and associates surprisingly found decreases in plasma norepinephrine levels after administration of either pancuronium or atropine.[189] These

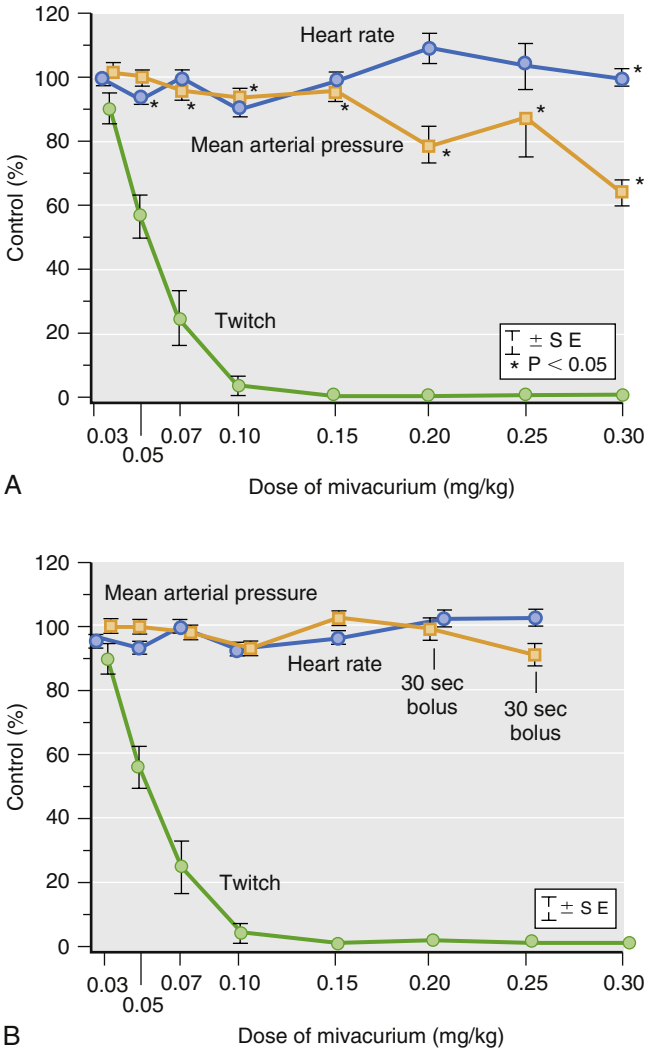


Figure 34-13. Dose response to mivacurium in patients under nitrous oxide–oxygen–opioid anesthesia. Maximum changes at each dose are shown; $n = 9$ subjects per group. **A,** With fast injection, a 15% to 20% decrease in arterial pressure occurred at 2.5 to 3 times the ED_{95} (0.20 to 0.25 mg/kg). **B,** The changes were less than 10% when slower injection (30 seconds) was done. *(From Savarese JJ, Ali HH, Basta SJ, et al: The cardiovascular effects of mivacurium chloride (BW B1090U) in patients receiving nitrous oxide–opiate-barbiturate anesthesia,* Anesthesiology *70:386-394, 1989.)*

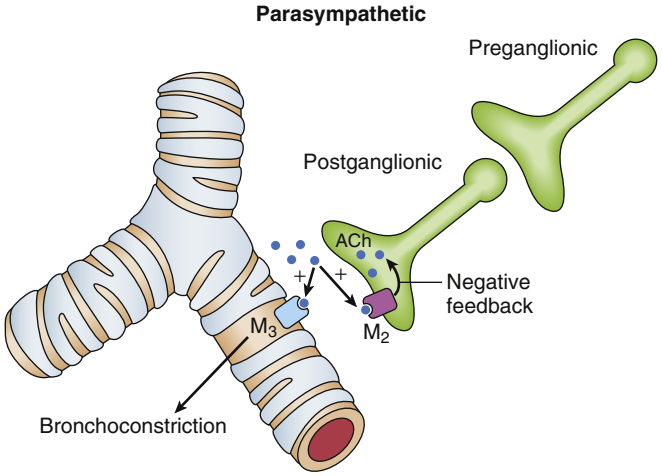


Figure 34-14. The muscarinic (M_3) receptors are located postsynaptically on airway smooth muscle. Acetylcholine (ACh) stimulates M_3 receptors to cause contraction. M_2 muscarinic receptors are located presynaptically at the postganglionic parasympathetic nerve endings, and they function in a negative-feedback mechanism to limit the release of ACh.

investigators postulated that the increase in heart rate or rate-pressure product occurs because pancuronium (or atropine) acts through baroreceptors to reduce sympathetic outflow.[189] More specifically, the vagolytic effect of pancuronium increases heart rate and hence blood pressure and cardiac output, in turn influencing the baroreceptors to decrease sympathetic tone. Support for this concept is provided by the finding that prior administration of atropine attenuates or eliminates the cardiovascular effects of pancuronium.[187] However, a positive chronotropic effect that places emphasis on the vagolytic mechanism has not been found in humans.[190] The tachycardia seen with benzylisoquinolinium compounds is the result of histamine release.

Dysrhythmias. Succinylcholine and dTc actually reduce the incidence of epinephrine-induced dysrhythmias.[191] Possibly because of enhanced atrioventricular conduction,[192] the incidence of dysrhythmias caused by pancuronium appears to increase during halothane anesthesia.[187] Edwards and colleagues observed rapid tachycardia (>150 beats/minute) that progressed to atrioventricular dissociation in two patients anesthetized with halothane who also received pancuronium.[193] The only other factor common to those two patients was that both were taking tricyclic antidepressant drugs.

Bradycardia. Several case reports described the occurrence of severe bradycardia and even asystole after vecuronium or atracurium administration.[194,195] All these cases were also associated with opioid administration. Subsequent studies indicated that administration of vecuronium or atracurium alone does not cause bradycardia.[196] When combined with other drugs that do cause bradycardia (e.g., fentanyl), however, the nonvagolytic relaxants such as vecuronium, cisatracurium, and atracurium allow this mechanism to occur unopposed. Thus, the moderate vagolytic effect of pancuronium is often used to counteract opioid-induced bradycardia (see also Chapter 31).

Respiratory Effects. The muscarinic cholinergic system plays an important role in regulating airway function. Five muscarinic receptors have been cloned,[197] three of which (M_1 to M_3) exist in the airways.[198] M_1 receptors are under sympathetic control, and they mediate bronchodilation.[199] M_2 receptors are located presynaptically (Fig. 34-14), at the postganglionic parasympathetic nerve endings, and they function in a negative-feedback mechanism to limit the release of acetylcholine. The M_3 receptors, which are located postsynaptically (see Fig. 34-14), mediate contraction of the airway smooth muscles (i.e., bronchoconstriction).[199] Nondepolarizing NMBDs have different antagonistic activities at both M_2 and M_3 receptors.[200] For example, blockage of M_3 muscarinic receptors on airway smooth muscle inhibits vagally induced bronchoconstriction (i.e., causes bronchodilation), whereas

blockage of M_2 receptors results in increased release of acetylcholine that acts on M_3 receptors, thus causing bronchoconstriction.

The affinity of the compound rapacuronium to block M_2 receptors is 15 times higher than its affinity to block M_3 receptors.[200] This explains the high incidence (>9%) of severe bronchospasm[201-203] seen with this drug and that resulted in its withdrawal from the market.

The administration of benzylisoquinolinium NMBDs (with the exception of cisatracurium) is associated with histamine release, which may result in increased airway resistance and bronchospasm in patients with hyperactive airway disease.

Allergic Reactions. The frequency of life-threatening anaphylactic (immune-mediated) or anaphylactoid reactions occurring during anesthesia has been estimated at 1 in 10,000 to 20,000 anesthetic procedures, whereas it is estimated at 1 in 6500 administrations of NMBDs in some countries.[204,205] In France, the most common causes of anaphylaxis in patients who experienced allergic reactions were reported to be NMBDs (58.2%), latex (16.7%), and antibiotics (15.1%).[206] Anaphylactic reactions are mediated through immune responses involving immunoglobulin E antibodies fixed to mast cells. Anaphylactoid reactions are not immune mediated and represent exaggerated pharmacologic responses in very rare and very sensitive individuals.

However, anaphylaxis to nondepolarizing NMBDs is not uncommon in patients without any previous exposure to any nondepolarizing NMBDs. Cross-reactivity occurs between NMBDs and food, cosmetics, disinfectants, and industrial materials.[207] Sensitization to nondepolarizing NMBDs may be related to pholcodine, a cough-relieving medicine. Cross-reactivity is seen in 70% of patients with a history of anaphylaxis to an NMBD.[206]

Steroidal compounds (e.g., rocuronium, vecuronium, or pancuronium) result in no significant histamine release.[186] For example, four times the ED_{95} of rocuronium (1.2 mg/kg) causes no significant histamine release.[208] Nevertheless, rocuronium and succinylcholine are reportedly associated with a 43.1% and 22.6% incidence, respectively, of anaphylaxis in France.[206] Rose and Fisher classified rocuronium and atracurium as having intermediate levels of risk for causing allergic reactions.[209] These investigators also noted that the increased number of reports of anaphylaxis with rocuronium is in line with the market share of that drug's usage. Watkins stated, "The much higher incidence of rocuronium reactions reported in France is currently inexplicable and is likely to remain so if investigators continue to seek a purely antibody-mediated response as an explanation of all anaphylactoid reaction presentations."[210] All nondepolarizing NMBDs may elicit anaphylaxis. More recent publications have highlighted the need for standardization of diagnostic procedures of anaphylactic reactions. Biochemical tests should be performed rapidly after occurrence of an anaphylactic reaction. An early increase in plasma histamine is observed 60 to 90 minutes after anaphylactic reactions. Serum tryptase concentrations typically reach a peak between 15 and 120 minutes, depending on the severity of the reaction. It is highly suggestive of mast cell activation. Skin testing remains the gold standard for detection of the culprit agent.[211] For many years, dilution thresholds have been debated. For instance, Laxenaire used a 1:10 dilution of rocuronium for interdermal skin testing,[212] whereas Rose and Fisher used a 1:1000 dilution.[209] Levy and associates showed that rocuronium in a 1:10 dilution can produce false-positive results in intradermal testing and suggested that rocuronium be diluted at least 100-fold to prevent such results.[213] Those authors also reported that high concentrations ($\geq 10^{-4}$ M) of both rocuronium and cisatracurium were capable of producing a wheal-and-flare response to intradermal testing, which was associated with mild to moderate mast cell degranulation in the cisatracurium group only.[213] However, in contrast to control patients, skin tests with nondepolarizing NMBDs that were performed in patients who had an anaphylactic reaction were considered reliable.

All NMBDs can cause noncompetitive inhibition of histamine-*N*-methyltransferase, but the concentrations required for that inhibition greatly exceeds those that would be used clinically, except in the case of vecuronium, with which the effect becomes manifest at 0.1 to 0.2 mg/kg.[214] This finding could explain the occurrence of occasional severe bronchospasm in patients after receiving vecuronium.[215] For goals of treatment of anaphylactic reactions, see Chapters 6 and 7.

DRUG INTERACTIONS AND OTHER FACTORS AFFECTING RESPONSE TO NEUROMUSCULAR BLOCKERS

A drug-drug interaction is an in vivo phenomenon that occurs when the administration of one drug alters the effects or kinetics of another drug. In vitro physical or chemical incompatibilities are *not* considered drug interactions.[216]

Many drugs interact with NMBDs or their antagonists, or both, and it is beyond the scope of this chapter to review them all.[216,217] Some of the more important drug interactions with NMBDs and their antagonists are discussed in the following sections.

Interactions Among Nondepolarizing Neuromuscular Blocking Drugs

Mixtures of two nondepolarizing NMBDs are considered to be either additive or synergistic. Antagonistic interactions have not been reported in this class of drugs. Additive interactions have been demonstrated after administration of chemically related drugs, such as atracurium and mivacurium,[218] or after coadministration of various pairs of steroidal NMBDs.[98] Conversely, combinations of structurally dissimilar (e.g., a steroidal with a benzylisoquinolinium) NMBDs, such as the combinations of pancuronium and dTc,[219] pancuronium and metocurine,[219] rocuronium and mivacurium,[142] or rocuronium and cisatracurium,[109] produce a synergistic response.

The administration of two NMBDs in combination was first introduced by Lebowitz and associates in an attempt to reduce the cardiovascular side effects of NMBDs by giving smaller doses of each drug in combination.[219] An additional advantage (rapid onset and short duration) is noted for mivacurium-rocuronium

combinations.[142] Although the precise mechanisms underlying a synergistic interaction are not known, hypotheses that have been put forward include the existence of multiple binding sites at the neuromuscular junction (presynaptic and postsynaptic receptors)[220] and the nonequivalence of binding affinities of the two α subunits (α_H and α_L). Further, inhibition of butyrylcholinesterase by pancuronium results in decreased plasma clearance of mivacurium and marked potentiation of the neuromuscular blockade.[221]

The pharmacodynamic response to the use of two different nondepolarizing NMBDs during the course of anesthesia depends not only on the specific drugs used but also on the sequence of their administration.[222,223] Approximately three half-lives are required for a clinical changeover (so that 95% of the first drug has been cleared) and for the duration of the blockade to begin to take on the characteristics of the second drug. After the administration of pancuronium, recovery from the first two maintenance doses of vecuronium is reportedly prolonged, although this effect becomes negligible by the third dose.[222] Similarly, Naguib and colleagues noted that the mean duration of the first maintenance dose of mivacurium to 10% recovery of the first twitch was significantly longer after atracurium (25 minutes) than after mivacurium (14.2 minutes).[218] However, the duration of the second maintenance dose of mivacurium after atracurium (18.3 minutes) was similar to that of mivacurium after mivacurium (14.6 minutes).

The apparent prolongation of action of the first maintenance dose of mivacurium administered after atracurium,[218] and of those reported with vecuronium after pancuronium,[222,223] is not related to synergism. Combinations of atracurium and mivacurium[218] and of vecuronium and pancuronium[98] are simply additive. However, this prolongation in the duration of action could be attributed to the relative concentrations of these drugs at the receptor site. Because most receptors remain occupied by the drug administered initially, the clinical profile depends on the kinetics or dynamics (or both) of the drug administered first rather than on those of the second (maintenance) drug. However, with further incremental doses of the second drug, a progressively larger proportion of the receptors is occupied by that drug, and its clinical profile becomes evident.

Interactions Between Succinylcholine and Nondepolarizing Neuromuscular Blocking Drugs

The interaction between succinylcholine and nondepolarizing NMBDs depends on the order of administration and the doses used.[81,224,225] Small doses of different nondepolarizing NMBDs administered before succinylcholine to prevent fasciculations have an antagonistic effect on the development of subsequent depolarizing block produced by succinylcholine.[27,81] Therefore, it is recommended that the dose of succinylcholine be increased after the administration of a defasciculating dose of a nondepolarizing NMBD.[27]

Studies of the effects of administering succinylcholine before nondepolarizing NMBDs have produced conflicting results. Several investigators reported potentiation of the effects of pancuronium,[224] vecuronium, and atracurium[225] by prior administration of succinylcholine. In contrast, other investigators found no significant influence of succinylcholine on subsequent administration of pancuronium, rocuronium, or mivacurium.[81,226,227]

Interactions with Inhaled Anesthetics

Deep anesthesia induced with potent volatile anesthetics (in the absence of neuromuscular blockade) may cause a slight reduction of neuromuscular transmission, as measured by depression of sensitive indicators of clinical neuromuscular function, such as tetanus and TOF.[228] Inhaled anesthetics also enhance the neuromuscular blocking effects of nondepolarizing NMBDs. Inhaled anesthetics decrease the required dose of NMBDs, as well as prolong both the duration of action of the blocker and recovery from neuromuscular block,[229] depending on the duration of anesthesia,[228,230,231] the specific inhaled anesthetic,[232] and the concentration (dose) given.[233] The rank order of potentiation is desflurane > sevoflurane > isoflurane > halothane > nitrous oxide–barbiturate–opioid or propofol anesthesia (Fig. 34-15).[234-236]

The greater clinical muscle-relaxing effect produced by less potent anesthetics is mainly caused by their larger aqueous concentrations.[237] Desflurane and sevoflurane have low blood-gas and tissue-gas solubility, so equilibrium between the end-tidal concentration and the neuromuscular junction is reached more rapidly with these anesthetics than with older inhaled anesthetics.

The interaction between volatile anesthetics and NMBDs is one of pharmacodynamics, not pharmacokinetics.[238] The proposed mechanisms behind this interaction include (1) a central effect on α motoneurons and interneuronal synapses,[239] (2) inhibition of postsynaptic nAChR,[240] and (3) augmentation of the antagonist's affinity at the receptor site.[237]

Interactions with Antibiotics

Most antibiotics can cause neuromuscular blockade in the absence of NMBDs. The aminoglycoside antibiotics, the

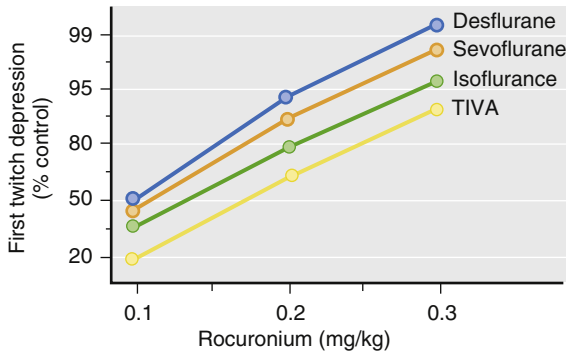


Figure 34-15. Cumulative dose-response curves for rocuronium-induced neuromuscular blockade during 1.5 minimum alveolar concentration (MAC) anesthesia with desflurane, sevoflurane, isoflurane, and total intravenous anesthesia (TIVA). *(From Wulf H, Ledowski T, Linstedt U, et al: Neuromuscular blocking effects of rocuronium during desflurane, isoflurane, and sevoflurane anaesthesia,* Can J Anaesth *45:526-532, 1998, with permission from the* Canadian Journal of Anaesthesia.*)*

polymyxins, and lincomycin and clindamycin primarily inhibit the prejunctional release of acetylcholine and also depress postjunctional nAChR sensitivity to acetylcholine.[241] The tetracyclines, in contrast, exhibit postjunctional activity only. When combined with NMBDs, the aforementioned antibiotics can potentiate neuromuscular blockade.[242] The cephalosporins and penicillins have not been reported to potentiate neuromuscular blockade. Because antagonism of neuromuscular blockade has been reported to be more difficult after the administration of aminoglycosides,[243] ventilation should be controlled until the neuromuscular blockade terminates spontaneously. Ca^{2+} should not be used to hasten the recovery of neuromuscular function for two reasons: the antagonism it produces is not sustained, and it may prevent the antibacterial effect of the antibiotics.

Temperature

Hypothermia prolongs the duration of action of nondepolarizing NMBDs.[244-246] The force of contraction of the adductor pollicis decreases by 10% to 16% per degree Celsius decrease in muscle temperature lower than 35.2° C.[247,248] To maintain the muscle temperature at or higher than 35.2° C, the central temperature must be maintained at 36.0° C.[244] The recovery to 10% twitch height with 0.1 mg/kg of vecuronium increases from 28 minutes at a mean central temperature of 36.4° C to 64 minutes at 34.4° C.[244] The mechanism or mechanisms underlying this prolongation may be pharmacodynamic or pharmacokinetic, or both.[246] They include diminished renal and hepatic excretion, changing volumes of distribution, altered local diffusion receptor affinity, changes in pH at the neuromuscular junction, and the net effect of cooling on the various components of neuromuscular transmission.[244,249] Hypothermia decreases the plasma clearance and prolongs the duration of action of rocuronium and vecuronium.[246] Temperature-related differences in the pharmacodynamics of vecuronium have also been reported. The k_{e0} decreases (0.023/minute/° C) with lower temperature, a finding suggesting slightly delayed equilibration of drug between the circulation and the neuromuscular junction during hypothermia.[246] The Hofmann elimination process of atracurium is slowed by a decrease in pH and especially by a decrease in temperature.[250] In fact, atracurium's duration of action is markedly prolonged by hypothermia.[245] For instance, the duration of action of a dose of 0.5 mg/kg atracurium is 44 minutes at 37° C but 68 minutes at 34.0° C.

Changes in temperature also affect the interpretation of the results of monitoring neuromuscular blockade. For example, the duration of action of vecuronium measured in an arm cooled to a skin temperature of 27° C is prolonged, and monitoring by PTC in that arm is unreliable.[251] In the same patient, TOF responses are different if the arms are at different temperatures, and the correlation of responses in the two arms becomes progressively poorer as the temperature difference between the arms increases.[252]

The efficacy of neostigmine is not altered by mild hypothermia.[253-255] Hypothermia does not change the clearance, maximum effect, or duration of action of neostigmine in volunteers.[255]

Interactions with Magnesium and Calcium

Magnesium sulfate, given for treatment of preeclampsia and eclamptic toxemia, potentiates the neuromuscular blockade induced by nondepolarizing NMBDs[256,257] (see Chapter 77). After a dose of 40 mg/kg of magnesium sulfate, the ED_{50} of vecuronium was reduced by 25%, the onset time was nearly halved, and the recovery time nearly doubled.[257] Neostigmine-induced recovery is also attenuated in patients treated with magnesium.[256] The mechanisms underlying the enhancement of nondepolarizing block by magnesium probably involve both prejunctional and postjunctional effects. High magnesium concentrations inhibit Ca^{2+} channels at the presynaptic nerve terminals that trigger the release of acetylcholine.[16] Further, magnesium ions have an inhibitory effect on postjunctional potentials and cause decreased excitability of muscle fiber membranes. In patients receiving magnesium, the dose of nondepolarizing NMBDs must be reduced and carefully titrated using a nerve stimulator to ensure adequate recovery of neuromuscular function at the end of surgery.

The interaction between magnesium and succinylcholine is controversial. However, more recent results suggest that magnesium antagonizes the block produced by succinylcholine.[258]

Ca^{2+} triggers the release of acetylcholine from the motor nerve terminal and enhances excitation-contraction coupling in muscle.[16] Increasing Ca^{2+} concentrations decreased the sensitivity to dTc and pancuronium in a muscle-nerve model.[259] In hyperparathyroidism, hypercalcemia is associated with decreased sensitivity to atracurium and thus a shortened time course of neuromuscular blockade.[260]

Interactions with Lithium

Lithium remains the drug of choice for treatment of bipolar affective disorder (manic-depressive illness). The lithium ion resembles Na^+, K^+, magnesium, and Ca^{2+} ions and therefore may affect the distribution and kinetics of all these electrolytes.[261] Lithium enters cells via Na^+ channels and tends to accumulate within the cells.

By its activation of K^+ channels, lithium inhibits neuromuscular transmission presynaptically and muscular contraction postsynaptically.[262] The combination of lithium and pipecuronium results in a synergistic inhibition of neuromuscular transmission, whereas the combination of lithium and succinylcholine results in additive inhibition.[262] Prolongation of neuromuscular blockade was reported in patients taking lithium carbonate and both depolarizing and nondepolarizing NMBDs.[263] Only one report did not demonstrate prolongation of recovery from succinylcholine in patients receiving lithium.[264] In patients who are stabilized on lithium therapy and undergoing surgery, NMBDs should be administered in incremental and reduced doses and titrated to the degree of blockade required.

Interactions with Local Anesthetic and Antidysrhythmic Drugs

Local anesthetics act on the presynaptic and postsynaptic part of the neuromuscular. In large intravenous doses, most local anesthetics block neuromuscular transmission;

in smaller doses, they enhance the neuromuscular blockade produced by both nondepolarizing and depolarizing NMBDs.[265] The ability of neostigmine to antagonize a combined local anesthetic–neuromuscular blockade has not been studied. Procaine also inhibits butyrylcholinesterase and may augment the effects of succinylcholine and mivacurium by decreasing their hydrolysis by the enzyme.

In small intravenous doses, local anesthetics depress posttetanic potentiation, and this is thought to be a neural prejunctional effect.[266] With larger doses, local anesthetics block acetylcholine-induced muscular contractions, a finding suggesting that local anesthetics have a stabilizing effect on the postjunctional membrane.[267] Procaine displaces Ca^{2+} from the sarcolemma and thus inhibits caffeine-induced contracture of skeletal muscle.[268] Most of these mechanisms of action probably apply to all the local anesthetics.

Several drugs used for the treatment of dysrhythmias augment the blockade induced by NMBDs. Single-fiber electromyography disclosed that verapamil and amlodipine impair neuromuscular transmission in subjects without neuromuscular disease.[269] Clinical reports suggested potentiation of neuromuscular block with verapamil[270] and impaired reversal of vecuronium in a patient receiving disopyramide.[271] However, the clinical significance of these interactions is probably minor.

Interactions with Antiepileptic Drugs

Anticonvulsants have a depressant action on acetylcholine release at the neuromuscular junction.[272,273] Patients receiving long-term anticonvulsant therapy demonstrated resistance to nondepolarizing NMBDs (except mivacurium[274] and probably atracurium as well[273]), as evidenced by accelerated recovery from neuromuscular blockade and the need for increased doses to achieve complete neuromuscular blockade. Vecuronium clearance is increased twofold in patients receiving long-term carbamazepine therapy.[275] Other investigators, however, attribute this resistance to the increased binding (i.e., decreased free fraction) of the NMBDs to α_1-acid glycoproteins or to up-regulation of neuromuscular acetylcholine receptors (or to both mechanisms).[276] The latter could also explain the hypersensitivity seen with succinylcholine.[277] The slight prolongation of succinylcholine's action in patients taking anticonvulsants has few clinical implications. Conversely, the potential hyperkalemic response to succinylcholine in the presence of receptor up-regulation is of concern.

Interactions with Diuretics

Early results showed that in patients undergoing renal transplantation, the intensity and duration of dTc neuromuscular blockade was increased after a dose of furosemide (1 mg/kg intravenously).[278] Furosemide reduced the concentration of dTc required to achieve 50% twitch tension depression in the indirectly stimulated rat diaphragm and intensified the neuromuscular blockade produced by dTc and succinylcholine.[279] Furosemide appears to inhibit the production of cyclic adenosine monophosphate. In addition, the breakdown of adenosine triphosphate is inhibited, resulting in reduced output of acetylcholine. Acetazolamide antagonized the effects of anticholinesterases in the rat phrenic-diaphragm preparation.[280] However, in one report, 1 mg/kg of furosemide facilitated recovery of the evoked twitch response after pancuronium.[281] Long-term furosemide treatment had no effect on either dTc- or pancuronium-induced neuromuscular blockade.[282]

In contrast, mannitol appears to have no effect on a nondepolarizing neuromuscular blockade. Furthermore, increasing urine output by the administration of mannitol or other osmotic or tubular diuretics has no effect on the rate at which dTc and presumably other NMBDs are eliminated in the urine.[283] However, this lack of effect on the excretion of dTc should not be surprising. Urinary excretion of all NMBDs that are long acting depends primarily on glomerular filtration. Mannitol is an osmotic diuretic that exerts its effects by altering the osmotic gradient within the proximal tubules so that water is retained within the tubules. An increase in urine volume in patients with adequate glomerular filtration therefore would not be expected to increase the excretion of NMBDs.

Interactions with Other Drugs

Dantrolene, a drug used for the treatment of malignant hyperthermia, prevents Ca^{2+} release from the sarcoplasmic reticulum and blocks excitation-contraction coupling (see Chapter 43). Although dantrolene does not block neuromuscular transmission, the mechanical response to stimulation is depressed, resulting in potentiation of the nondepolarizing neuromuscular blockade.[284]

Azathioprine, an immunodepressant drug that is used in patients undergoing renal transplantation, has a minor antagonistic action on muscle relaxant–induced neuromuscular blockade.[285]

Steroids antagonize the effects of nondepolarizing NMBDs in both humans[286] and animals.[287] Possible mechanisms for this interaction include facilitation of acetylcholine release because of the effect of steroids on the presynaptic motor nerve terminal[288] and channel blockade of the nAChR.[289] Endogenous steroids act noncompetitively on nAChRs.[290] Prolonged treatment with a combination of corticosteroids and NMBDs can result in prolonged weakness in patients receiving critical care (see the later section on NMBDs and weakness syndromes in critically ill patients).

Antiestrogenic drugs such as tamoxifen appear to potentiate the effects of nondepolarizing NMBDs.[291]

SPECIAL POPULATIONS

PEDIATRIC PATIENTS

The development of the neuromuscular junction is not complete at birth.[16] In humans, maturation of neuromuscular transmission occurs after the first 2 months of age, although immature junctions have been found up to 2 years of age The main evolution during the first months of life is that the fetal receptors located outside the neuromuscular junction will disappear and will be replaced by mature receptors with ε subunits instead of γ

subunits. These changes suggest that that the neonate's neuromuscular junction may exhibit evidence of its immaturity by changes in response to NMBDs, although NMBDs can be used safely in term and preterm infants (see also Chapter 93).

The routine administration of succinylcholine to healthy children should be discontinued. In apparently healthy children, intractable cardiac arrest with hyperkalemia, rhabdomyolysis, and acidosis may develop after succinylcholine administration, particularly in patients with unsuspected muscular dystrophy of the Duchenne type[292] (see the section on complications of succinylcholine).

Significant age-related differences in the potency of nondepolarizing NMBDs exist in infants and children when compared with adults. Children require higher doses of nondepolarizing NMBDs than any other age group of patients. In infants less than 1 year old, the ED_{95} at the adductor pollicis is approximately 30% less than in older children. It is not apparent from older studies whether the neonate is more sensitive than adults to nondepolarizing NMBDs,[293] although most of the studies showed a wider range of dosage requirement in the neonate. These apparent discrepancies were been explained by studies by Fisher and associates on the pharmacokinetics and pharmacodynamics of NMBDs in infants, children, and adults,[294-296] and they made it possible to understand the clinical pharmacology of these drugs in pediatric patients more clearly (see Chapter 93). Neonates and infants are more sensitive than adults to the neuromuscular blocking effects of dTc.[294] Plasma concentrations required to achieve a desired level of neuromuscular blockade are 57% and 32% lower in neonates and infants, respectively, when compared with children. However, the dosage should not be decreased as much because neonates and infants have a larger volume of distribution at steady state. This increased volume of distribution results from the increase in extracellular fluid volume during the first months of life. This increase, in association with a lower elimination clearance, contributes to a longer elimination half-life.[294,297] In infants, less frequent dosing (longer dosing intervals) of nondepolarizing NMBDs may be required than in older children.

Atracurium, vecuronium, cisatracurium, rocuronium, and mivacurium are commonly administered to children because many surgical procedures are of short duration in children and are compatible with the duration of action of a single intubating dose. Onset time of neuromuscular block is faster in infants (30%) and children (40%) when compared with adults. This age-related effect is probably caused by circulatory factors such as the relative decrease of cardiac output and increase of circulation time with age.

As with the long-acting NMBDs, the sensitivity of infants to vecuronium is more intense than in children (ED_{95} 0.047 mg/kg versus 0.081 mg/kg, respectively).[298,299] An increased duration of action in infants is most likely secondary to the increased volume of distribution of vecuronium because its clearance is unchanged.[295,297] An age-dependent prolongation of action has been demonstrated in infants. A dose of 0.1 mg/kg of vecuronium produces almost a complete neuromuscular block of approximately 60 minutes' duration in infants but of only 20 minutes' duration in children and adults. Vecuronium therefore acts as a long-acting muscle NMBD in the neonate.[295,297]

In contrast, the duration of action of atracurium is not significantly different in the pediatric patient from that in the adult.[300] As with vecuronium and dTc, the volume of distribution is increased in infants.[296] However, the clearance of atracurium is also more rapid.[296] Therefore, the same dose (0.5 to 0.6 mg/kg) can be used in infants, children, and adults for tracheal intubation without any major differences among the three groups in the drug's duration of action. Atracurium recovery from neuromuscular block is little affected by age in pediatric patients more than 1 month old. Histamine release and the occurrence of an untoward reaction caused by atracurium are less frequent in children than in adults. In children, a dose of 0.1 µg/kg of cisatracurium has an onset just longer than 2 minutes and a clinical duration of approximately 30 minutes during balanced or halothane anesthesia.[301] The calculated ED_{95} doses of cisatracurium in infants and children are 43 and 47 µg/kg, respectively.[302] The mean infusion rate necessary to maintain 90% to 99% neuromuscular block is also similar in infants and children.[302]

Rocuronium in adults is an intermediate-acting NMBD with a faster onset of action than other nondepolarizing NMBDs, and this is also true in infants and children.[303,304] The ED_{95} is approximately 0.4 mg/kg in children; it is approximately 20% to 30% greater than that in adults, but its onset is faster in adults.[304] In children, 0.6 mg/kg of rocuronium produces better conditions for rapid tracheal intubation (60 seconds) than does 0.1 mg/kg of vecuronium (100 seconds) or 0.5 mg/kg of atracurium (180 seconds).[303] Evidence indicates that, even during sevoflurane induction in infants, the addition of 0.3 mg/kg rocuronium significantly improves intubating conditions and significantly decreases the frequency of respiratory adverse events such as desaturation of laryngospasm during induction.[305] As with adults, for rapid-sequence intubation (60 seconds) in the presence of a full stomach, a 1.2 mg/kg dose of rocuronium is suggested to provide excellent intubating conditions in patients.

OLDER PATIENTS

The pharmacodynamics of NMBDs may be altered in older patients (see also Chapter 80). Certain physiologic changes that accompany the aging process occur, including decreases in total body water and lean body mass, increases in total body fat, decreases in hepatic and renal blood flow and hepatic enzyme activity, and decreases in glomerular filtration rate (≈20%/year in adults). These changes may account for the altered responses of older adults to NMBDs. Some physiologic and anatomic changes at the neuromuscular junction also occur with aging. These include an increase in the distance between the junctional axon and the motor end plate, flattening of the folds of the motor end plate, a decreased concentration of acetylcholine receptors at the motor end plate, a decrease of the amount of acetylcholine in each vesicle in the prejunctional axon, and decreased release of

acetylcholine from the preterminal axon in response to a neural impulse.[16]

Several studies found no differences in the initial dose requirement for nondepolarizing muscle relaxants in older adults. The dose-response curves of atracurium, pancuronium, and vecuronium were slightly to the right of the curves for the younger adult subjects; however, no significant differences were noted. After a bolus dose of pancuronium, no significant difference was observed at any of the plasma concentrations corresponding to a fixed degree of neuromuscular block. Such results confirm that nondepolarizing muscle relaxants are as potent in older as in young adult patients. The onset of neuromuscular block can be delayed and can be correlated with age.[306] This age-related effect is probably caused by circulatory factors such as the decrease in cardiac output and increase in circulation time in older adults. These factors induce slower biophase equilibration. The onset of rocuronium neuromuscular block was prolonged to 3.7 from 3.1 minutes in older adults. Similarly, the onset of cisatracurium is approximately 1 minute longer in this age group.

A prolongation of the duration of action of nondepolarizing muscle relaxants and a decrease in dose requirements for the maintenance of neuromuscular block have been observed with several currently available muscle relaxants in older adults. These results are explained by pharmacokinetic changes in this population. The distribution and elimination may be altered by any of the multitude of physiologic changes that accompany the aging process. The effect of aging alone, as opposed to disease states often associated with the aging process, may be difficult to distinguish in identifying mechanisms of altered NMBD action in older adults.

Pancuronium,[307] vecuronium,[295,308] and rocuronium[177] depend on the kidney or the liver (or both) for their metabolism and elimination. Therefore, they all show altered pharmacodynamics and pharmacokinetics in older patients. Pancuronium has delayed recovery in older adults because of decreased plasma clearance secondary to delayed urinary excretion. The clinical duration of action is prolonged from 44 to 73 minutes in this age group.[2] Vecuronium dose requirements to maintain a constant neuromuscular block are decreased by approximately 36% in patients more than 60 years old, and spontaneous recovery is significantly longer in older patients.[25] Lien and co-workers showed that plasma clearance was reduced by more than 50% and elimination half-life prolonged by 60% in older patients.[308] The prolongation of vecuronium action appears to be secondary to decreased drug elimination consistent with age-associated decreases in hepatic and renal blood flows. The duration of action of rocuronium and the recovery index are also increased in older adults. The prolongation of action can be explained by a 27% decrease in plasma clearance.

In the case of drugs whose elimination is independent of hepatic or renal blood flow, pharmacokinetics and pharmacodynamics should not be significantly altered by age. Atracurium has multiple routes of elimination. Degradation by Hofmann elimination and ester hydrolysis is independent of the liver and the kidney and is not affected by age. The only pharmacokinetic change is a slight increase of the volume of distribution at steady state leading to a modestly increased elimination half-life. Consequently, the duration of action, the recovery index, and the dose requirement during a continuous infusion are independent of age. Cisatracurium exhibits a slightly delayed onset of effect in older patients because of slower biophase equilibration. Clearances are not decreased in patients of advanced age. The slight prolongation of the elimination half-life of the drug in older adults is secondary to an increased volume of distribution at steady state (+10%). These minor pharmacokinetic changes are not associated with changes in the recovery profile of older patients.

Butyrylcholinesterase activity in older adults, although still in the normal range, is approximately 26% lower than that in young adults.[309] Because mivacurium is metabolized by butyrylcholinesterase, its clearance is likely to be slightly reduced in older patients, thus resulting in a 20% to 25% longer duration of action,[310] as well as a decreased infusion requirement to maintain a stable depth of block. Succinylcholine metabolism is unaffected by these changes.

In general, when maintaining neuromuscular blockade with nondepolarizing NMBDs in older patients, one can expect that, with the exception of atracurium and cisatracurium, the dosing interval will be increased to maintain the desired depth of neuromuscular blockade. The choice of drug and monitoring the depth of blockade are exceptionally important in this population because recovery of neuromuscular function is generally delayed in older patients. Inadequate or incomplete recovery of muscle strength after the use of pancuronium is associated with an increased incidence of perioperative pulmonary complications in this patient population.[129] The clear relationship between incomplete recovery from neuromuscular block and occurrence of critical respiratory events in the PACU highlights the need for objective recovery of neuromuscular block in older patients.

OBESE PATIENTS

The level of plasma pseudocholinesterase activity and the volume of extracellular fluid, which are the main determinants of the duration of action of succinylcholine, are increased in obese patients (see also Chapter 71). Lemmens and Brodsky demonstrated that for complete neuromuscular paralysis and a predictable intubating condition, a 1 mg/kg dose based on total-body weight (TBW) was recommended.[311]

Initial studies showed that obese subjects needed significantly more pancuronium than nonobese patients to maintain a constant 90% depression of twitch height. However, when corrected for body surface area (BSA), no significant difference was noted in dose requirement to maintain neuromuscular block.

The use of NMBDs with an intermediate duration of action should be preferred. Vecuronium doses based on TBW induce a prolonged duration of action in obese patients, although vecuronium pharmacokinetics is unaltered by obesity. The prolonged recovery in obese patients can be explained by the larger total dose administered in these patients. With larger doses, when administration is based on TBW, recovery occurs during the elimination

phase when plasma concentration decreases more slowly than during the distribution phase.[312] The pharmacokinetics of rocuronium is not altered by obesity. In the same way, the duration of action of rocuronium is significantly prolonged when the dose is calculated according to TBW. In contrast, when rocuronium is dosed according to ideal body weight (IBW), the clinical duration is less than half.[313,314]

A correlation exists between the duration of action of atracurium and TBW when the dose is given as milligrams per kilogram of TBW. The clinical duration of action is doubled when the drug is given based on TBW versus IBW. Varin and colleagues reported the lack of difference between obese and normal-weight patients in atracurium elimination half-life (19.8 versus 19.7 minutes), volume of distribution at steady state (8.6 versus 8.5 L), and total clearance (444 versus 404 mL/minute).[315] The finding that IBW avoids prolonged recovery of atracurium-induced blockade can be explained by an unchanged muscle mass and an unchanged volume of distribution in morbidly obese patients compared with normal-weight patients.[316] The duration of cisatracurium is also prolonged in obese patients when the drug is given on the basis of TBW versus IBW.

Nondepolarizing NMBDs should be given to obese patients on the basis of IBW rather than on their actual body weight, to ensure that these patients are not receiving relative overdoses and to avoid prolonged recovery. When using maintenance doses, objective monitoring is strongly recommended to avoid accumulation.

SEVERE RENAL DISEASE

NMBDs contain quaternary ammonium groups that make them very hydrophilic (see also Chapters 72 and 74). They are therefore usually completely ionized at 7.4 pH and are poorly bound to plasma proteins. The predominant pathway of elimination of steroidal muscle relaxants is ultrafiltration by the glomeruli before urinary excretion. Renal failure influences the pharmacologic characteristics of nondepolarizing NMBDs by producing either decreased elimination of the drug or its metabolites through the kidney. Only atracurium, cisatracurium, and, to some extent, vecuronium are independent of renal function. Succinylcholine elimination is mainly independent of kidney function. However, succinylcholine is metabolized by plasma cholinesterases, and concentrations may be slightly decreased in patients with severe renal failure (Table 34-10). The decrease in plasma cholinesterase activity is always moderate (30%) and does not result in prolongation of succinylcholine-induced neuromuscular block. Succinylcholine induces a transient increase in plasma K^+ concentration (<0.5 mmol/L). Therefore, succinylcholine is not contraindicated in severe renal failure when plasma K^+ concentrations are within the normal range. Consequently, the duration of action of NMBDs may be prolonged in patients with renal failure.

Renal failure does not alter the sensitivity (dose response) of patients to the neuromuscular blocking action of pancuronium,[317] atracurium,[318] vecuronium,[319] or rocuronium.[320] All long-lasting muscle relaxants are eliminated predominantly through the kidney, and renal failure is associated with reduced plasma clearance and increased elimination half-life for these drugs as well.[103] The elimination half-life of pancuronium is increased by 500% in patients with severe renal failure. As a consequence of these pharmacokinetic changes, the duration of neuromuscular blockade produced by these drugs is longer and more variable than in patients with normal renal function. Because of the potential for prolonged

TABLE 34-10 **PHARMACOKINETICS OF NEUROMUSCULAR BLOCKING DRUGS IN PATIENTS WITH NORMAL RENAL FUNCTION OR RENAL FAILURE**

	Plasma Clearance (mL/kg/min)		Volume of Distribution (mL/kg)		Elimination Half-life (min)		
	Normal Function	Renal Failure	Normal Function	Renal Failure	Normal Function	Renal Failure	References
Short-acting Drugs							
Mivacurium isomers							160
Cis-trans	106	80	278	475	2.0	4.3	
Trans-trans	57	48	211	270	2.3	4.3	
Cis-cis	3.8	2.4*	227	244	68	80	
Intermediate-acting Drugs							
Atracurium	6.1	6.7	182	224	21	24	172
	5.5	5.8	153	141	19	20	173*,†
	10.9	7.8	280	265	17.3	19.7	322
Cisatracurium	5.2	—	31	—	—	—	169
Vecuronium	3.0	2.5	194	239	78	97	324
	5.3	3.1*	199	241	53	83*	325
Rocuronium	2.9	2.9	207	264*	71	97*	175
Long-acting Drugs							
d-Tubocurarine	2.4	1.5	250	250	84	132	115
Pancuronium	74	20*	148	236*	97	475*	149†
	1.7	0.9	261	296*	132	257*	380

*Significant difference normal renal function versus renal failure.
†Values expressed as mL/min, not weight adjusted.

blockade and the availability of intermediate- and short-acting NMBDs, long-acting NMBDs should not be used in patients with renal failure.

The pharmacokinetics and duration of action of atracurium are unaffected by renal failure.[321,322] This lack of effect is in part because Hofmann elimination and ester hydrolysis[173] account for 50% of its total clearance.[167] Laudanosine, the principal metabolite of atracurium, is eliminated unchanged by the kidney. The elimination half-life of laudanosine increases in renal failure.[322] Even during continuous administration of atracurium, laudanosine plasma concentrations are 10 times less than concentrations associated with convulsions in dogs.

In patients with chronic renal failure, the duration of action of cisatracurium is not prolonged.[323] Hofmann elimination accounts for 77% of the total clearance of cisatracurium,[169] and renal excretion accounts for 16% of its elimination.[169] The peak plasma laudanosine concentration is 10 times lower than after equipotent doses of atracurium. In patients with end-stage renal failure, the volume of distribution is unchanged, but Eastwood found a 13% reduction in clearance and an increase from 30 to 34 minutes in the elimination half-life in the renal failure group.

Vecuronium relies principally on hepatic mechanisms for its elimination. However, its clearance is reduced and its elimination half-life is increased in patients with renal failure.[324,325] In one study, the duration of action of 0.1 mg/kg of vecuronium was both longer and more variable in patients with renal failure than in those with normal renal function.[325] In three other studies, the duration of action of 0.05 to 0.14 mg/kg of vecuronium was not prolonged by renal failure, but this result was likely caused by the use of relatively small doses or inadequate sample sizes.[324] The principal metabolite of vecuronium, 3-desacetylvecuronium, has 80% of the neuromuscular blocking activity of vecuronium[153]; it may cause prolonged paralysis in patients with renal failure in the ICU.[156] In patients with renal failure, the duration of action and the rate of recovery from vecuronium- or atracurium-induced neuromuscular blockade during surgery are similar.[326]

The major routes of elimination of rocuronium are biliary and urinary excretion. Rocuronium is taken up by the liver and metabolized, excreted, or both, in bile and feces in high concentrations. After 0.6 mg/kg rocuronium, up to one fifth of the dose is recovered unchanged from the urine within 24 hours, and no active metabolites can be found in humans. More recent pharmacokinetic studies showed that the clearance of rocuronium was reduced by 33% to 390% in patients with renal failure. The distribution volume of this drug remained unchanged or slightly increased.[175] The elimination half-life was 70 and 57 minutes in patients with and without renal failure, respectively. The duration of action of single and repeated doses, however, was not significantly affected.[320]

HEPATOBILIARY DISEASE

In comparison with renal elimination, liver function is a modest determinant of the pharmacokinetics of nondepolarizing muscle relaxants (see also Chapters 73 and 74). The influence of hepatobiliary disease on the pharmacokinetics of NMBDs can be complex because of the different types of liver failure (Table 34-11). Cirrhosis is associated with an increased extracellular water

TABLE 34-11 **PHARMACOKINETICS OF NEUROMUSCULAR BLOCKING DRUGS IN PATIENTS WITH NORMAL LIVER FUNCTION OR HEPATOBILIARY DISEASE**

	Plasma Clearance (mL/kg/min)		Volume of Distribution (mL/kg)		Elimination Half-life (min)		Hepatic Pathology	References
	Normal	Disease	Normal	Disease	Normal	Disease		
Short-acting Drugs								
Mivacurium isomers							Cirrhosis	159
Cis-trans	95	44*	210	188	1.53	2.48*		
Trans-trans	70	32*	200	199	2.32	11.1*		
Cis-cis	5.2	4.2	266	237	50.3	60.8		
Intermediate-acting Drugs								
Atracurium	5.3	6.5	159	207*	21	22	Hepatorenal	318
	6.6	8.0*	202	282*	21	25	Cirrhosis	174
Cisatracurium	5.7	6.6*	161	195*	23.5	24.4	Transplantation	
Vecuronium	4.26	2.73*	246	253	58	84*	Cirrhosis	154
	4.30	2.36*	247	206	58	98*	Cholestasis	381
	4.5	4.4	180	220	58	51	Cirrhosis	155
Rocuronium	2.79	2.41	184	234	87.5	96.0	Cirrhosis	176
	217	217	16.4	23.4*	76.4	111.5*	Mixed	178†
	296	189	151	264*	56	98*	Cirrhosis	382†
	3.70	2.66*	211	248	92	143*	Cirrhosis	179
Long-acting Drugs								
Pancuronium	123	59*	261	307*	133	267*	Cholestasis	151†
	1.86	1.45*	279	416*	114	208*	Cirrhosis	150
	1.76	1.47	284	425*	141	224*	Cholestasis	383

*Significant difference normal hepatic function versus hepatobiliary disease.
†Values expressed as mL/min, or L, not weight adjusted.

compartment, edema, and often kidney dysfunction. Cholestasis induces decreased biliary excretion but is not associated with significant liver failure, contrary to acute hepatic failure.

A delayed onset of action and an apparent resistance to nondepolarizing muscle relaxants occur in patients with cirrhosis, although studies demonstrated that the sensitivity of the neuromuscular junction was unaltered. This is the consequence of the increased volume of distribution, which induces greater dilution of muscle relaxants in cirrhotic patients. The increase of terminal half-life can be secondary to either the increased volume of distribution or decreased biliary excretion for muscle relaxants dependent on hepatic function for elimination. Following a single dose of nondepolarizing muscle relaxant, in most of the cases, no prolongation of the duration of action occurs because it is dependent on distribution. However, for muscle relaxants dependent on hepatic elimination, prolongation of neuromuscular block can be observed following repeated doses or continuous infusion.

Pancuronium is mainly eliminated through the kidney, although one third of a dose is metabolized and excreted through the liver. The elimination half-life increases from 114 to 208 minutes in cirrhotic patients. This is the consequence of a 50% increase of the volume of distribution in conjunction with a 22% decrease in plasma clearance. Cholestasis induces a 50% decrease in pancuronium clearance leading to a prolonged elimination half-life of 270 minutes. Severe acute hepatic failure also induces reduced plasma clearance and a prolonged elimination half-life.

Vecuronium elimination is mainly through the bile. Only a small fraction is metabolized to 3-hydroxyvecuronium, which still has 60% of the potency of vecuronium. This metabolic process is presumed to occur in the liver because 40% of the total dose of vecuronium is found in the liver and bile as both parent drug and metabolite.[147] The elimination half-life is increased in mildly decompensated cirrhotic patients as the result of a decreased clearance, whereas the volume of distribution of the central compartment and the volume of distribution at steady state can be increased. In cirrhotic patients, the duration of action of vecuronium is related to the dose. A dose of 0.1 mg/kg has a slower onset of action and a shorter duration of action because the volume of distribution is increased. In contrast, after 0.2 mg/kg vecuronium, the duration of action is increased from 65 minutes to 91 minutes in cirrhotic patients because elimination is impaired. Cholestasis can increase plasma concentration of bile salts and thus reduce the hepatic uptake of vecuronium,[147] as well as pancuronium. This may explain the decreased clearance observed by some investigators. The duration of action of vecuronium is increased by 50% in patients with biliary obstruction.

Rocuronium is mainly excreted into the bile. The volume of both the central compartment (+33%) and the volume of distribution at steady state (+43%) are increased in cirrhotic patients, whereas clearance may be decreased. The duration of action is prolonged in patients with hepatic disease, and a correlation exists between the increased volume of distribution and the slower onset of action when compared with controls.

Atracurium and cisatracurium share organ-independent modes of elimination.[165,168,169] As a consequence, their clearance should be little affected by hepatic disease. In fact, and in contrast to all other NMBDs, the plasma clearances of atracurium and cisatracurium are slightly increased in patients with liver disease (see Table 34-11).[174,180] Because elimination of atracurium and cisatracurium occurs outside of, as well as from within, the central compartment, investigators have suggested that a larger distribution volume should be associated with greater clearance.[169] In two studies,[174,180] volumes of distribution and clearances of the drugs increased with liver disease, thereby lending support to this hypothesis.[169] The increased clearance of the relaxant in patients with liver disease is not reflected in a decrease in the drug's duration of action.[174,180]

One concern raised about administering atracurium to patients with hepatic disease is the possible accumulation of laudanosine. Although laudanosine relies principally on hepatic mechanisms for its elimination, the concentrations encountered during liver transplantation are unlikely to be associated with clinical sequelae.[327]

Because of the wide interindividual variations seen in the response to nondepolarizing muscle relaxants in patients with hepatic disease, monitoring of neuromuscular block is required with titration of doses.

In patients with severe liver disease, butyrylcholinesterase activity is decreased because of decreased synthesis of the hepatic enzymes. Consequently, the plasma clearance of the isomers of mivacurium is decreased by approximately 50%[159] (see Table 34-11), and the drug's duration of action is prolonged and may be almost tripled.[159]

BURNS

In patients with burn injuries, muscle relaxants can be used to facilitate mechanical ventilation, which can be associated with sustained improvement in oxygenation (see also Chapter 101). After a period of immobilization, burn injury causes up-regulation of both fetal ($\alpha_2\beta\gamma\delta$) and mature ($\alpha_2\beta\varepsilon\delta$) nAChRs.[328] This up-regulation of nAChRs usually is associated with resistance to nondepolarizing NMBDs and increased sensitivity to succinylcholine.[329] Causes of up-regulation of nAChRs are listed in Table 34-12. A significant increase in the quantal content of

TABLE 34-12 CONDITIONS ASSOCIATED WITH UP-REGULATION AND DOWN-REGULATION OF ACETYLCHOLINE RECEPTORS

nAChR Up-regulation	nAChR Down-regulation
Spinal cord injury	Myasthenia gravis
Stroke	Anticholinesterase poisoning
Burns	Organophosphate poisoning
Prolonged immobility	
Prolonged exposure to neuromuscular blockers	
Multiple sclerosis	
Guillain-Barré syndrome	

nAChR, Nicotinic acetylcholine receptor.
From Naguib M, Flood P, McArdle JJ, Brenner HR: Advances in neurobiology of the neuromuscular junction: implications for the anesthesiologist, Anesthesiology *96:202-231, 2002, with permission from* Anesthesiology.

evoked acetylcholine release is noted by 72 hours after scald injury in rats.[330] This increase also contributes to the resistance to NMBDs in patients with burn injuries. In mice, thermal injury induces changes in diaphragm acetylcholinesterase with respect to total content and specific molecular forms.[331]

Resistance to the effects of nondepolarizing NMBDs is usually seen in patients with burns over at least 25% of their total body surface area.[329,332,333] Recovery of neuromuscular function to preburn levels may take several months or even years after the burn injury.[334] The increase in serum K^+ concentration that normally follows succinylcholine administration is markedly exaggerated in burned patients.[335] K^+ concentrations as high as 13 mEq/L, resulting in ventricular tachycardia, fibrillation, and cardiac arrest have been reported.[335] The magnitude of the hyperkalemic response does not appear to correlate closely with the magnitude of the burn injury. Potentially lethal hyperkalemia was seen in a patient with only an 8% total body surface area burn.[336] Succinylcholine has been safely administered within 24 hours of a burn injury. It is the drug of choice for prehospital or emergency room intubation, particularly when patients have a full stomach. After an initial 24-hour interval, however, sufficient alteration in muscle response may have occurred. Because of the unpredictability of occurrence of hyperkalemia, the use of succinylcholine is best avoided 48 to 72 hours after a burn injury.

The time course of abnormal muscle membrane function corresponds with that of the healing process. Once normal skin has regrown and any infection subsides, the normal acetylcholine receptor populations appear to return.[334] Although normal responses to succinylcholine have been demonstrated in burned patients studied 3 years after injury,[334] the actual length of time during which a patient with a burn injury may be at risk for the hyperkalemic response is not well defined. A conservative guideline therefore would be to avoid the use of succinylcholine in patients 24 to 48 hours after a thermal injury and for at least 1 or 2 years after the burned skin has healed.

USE OF NEUROMUSCULAR BLOCKING DRUGS AND WEAKNESS SYNDROMES IN CRITICALLY ILL PATIENTS

NMBDs are frequently used in conjunction with sedatives and analgesics in ICUs (see also Chapter 101). The indications for the use of NMBDs in the ICU are outlined in Box 34-1. Few available data support their use, and evidence for a beneficial effect on pulmonary function or patient oxygenation is inconclusive.[337] However, a multicenter, double-blind trial showed that, in a subset of patients with acute respiratory distress syndrome, early and short-term administration of cisatracurium for 48 hours could be beneficial.[338] Half of the patients in the placebo group in that study received one or more doses of cisatracurium. The study was underpowered, and the effect on mortality was statistically borderline, with no between-group difference in crude mortality rate. Yet, nondepolarizing NMBDs are sometimes used in ICU patients. Of particular concern in intensive care settings is the risk that paralyzed patients receive inadequate analgesia and sedation.[339] This reason for this concern may be that ICU nurses and physicians are unfamiliar with the pharmacology of the NMBDs.[339,340] For instance, pancuronium was thought to be an anxiolytic by 50% to 70% of ICU nurses and house staff, and 5% to 10% thought it was an analgesic.[339] In the United Kingdom, the erroneous use of NMBDs as sedatives in intensive care was not uncommon in the 1980s.[341] Approximately 96% of ICU patients received NMBDs to aid mechanical ventilation in 1980. By 1986, their use had fallen to 16% of ventilated patients.[341] Currently, intensivists are aware of the side effects and avoid giving NMBDs to critically ill ICU patients unless these drugs are needed to facilitate mechanical ventilation.

A prolonged ICU stay during critical illness is associated with disorders of neuromuscular function that contribute to morbidity, length of hospital stay, weaning difficulties, and prolonged rehabilitation.[342] The complications of long-term administration of NMBDs in the ICU are outlined in Box 34-2. In the ICU, duration of mechanical ventilation, sepsis, the dysfunction of two or more

BOX 34-1 ***Reported Indications for the Use of Muscle Relaxants in the Intensive Care Unit***

- Facilitation of mechanical ventilation
  - Facilitation of endotracheal intubation
  - Enabling patient to tolerate mechanical ventilation
  - High pulmonary inflation pressures (e.g., acute respiratory distress syndrome)
- Hyperventilation for increased intracranial pressure
- Facilitation of therapeutic or diagnostic procedures
- Tetanus
- Status epilepticus
- Reduction of oxygen consumption
  - Abolishing shivering
  - Reduction of work of breathing

BOX 34-2 ***Complications of Muscle Paralysis in the Intensive Care Unit***

- Short-term use
  - Specific, known drug side effects
  - Inadequate ventilation in the event of a ventilator failure or circuit disconnection
  - Inadequate analgesia and/or sedation
- Long-term use
  - Complications of immobility
    - Deep vein thrombosis and pulmonary embolus
    - Peripheral nerve injuries
    - Decubitus ulcers
  - Inability to cough
    - Retention of secretions and atelectasis
    - Pulmonary infection
- Dysregulation of nicotinic acetylcholine receptors
- Prolonged paralysis after stopping relaxant
  - Persistent neuromuscular blockade
  - Critical illness myopathy
  - Critical illness polyneuropathy
  - Combination of the above
- Unrecognized effects of drug or metabolites
  - Succinylcholine and metabolic acidosis or hypovolemia
  - 3-Desacetylvecuronium and neuromuscular blockade
  - Laudanosine and cerebral excitation

BOX 34-3 ***Causes of Generalized Neuromuscular Weakness in the Intensive Care Unit***

- Central nervous system
  - Septic or toxic-metabolic encephalopathy
  - Brainstem stroke
  - Central pontine myelinolysis
  - Anterior horn cell disorders (e.g., amyotrophic lateral sclerosis)
- Peripheral neuropathies
  - Critical illness polyneuropathy
  - Guillain-Barré syndrome
  - Porphyria
  - Paraneoplasia
  - Vasculitis
  - Nutritional and toxic neuropathies
- Neuromuscular junction disorders
  - Myasthenia gravis
  - Lambert-Eaton myasthenic syndrome
  - Botulism
  - Prolonged neuromuscular junction blockade
- Myopathies
  - Critical illness myopathy
  - Cachectic myopathy
  - Rhabdomyolysis
  - Inflammatory and infectious myopathies
  - Muscular dystrophies
  - Toxic myopathies
  - Acid maltase deficiency
  - Mitochondrial
  - Hypokalemia
  - Hypermetabolic syndromes with rhabdomyolysis (e.g., neuroleptic malignant syndrome)

From Lacomis D: Critical illness myopathy, Curr Rheumatol Rep *4:403-408, 2002.*

organs, female sex, administration of steroids, and hypercapnia are known risk factors for developing neuromuscular dysfunction. Syndromes of weakness in critically ill patients are relatively common and likely polymorphic in origin. In a retrospective study of 92 critically ill patients with clinically diagnosed weakness, electromyographic studies indicated that acute myopathy (critical illness myopathy [CIM]) is 3 times as common as acute axonal neuropathy (critical illness neuropathy): 43% versus 13%, respectively.[342] The additional health care cost of a single case of persistent weakness was estimated at approximately $67,000.[343] Conditions to consider when making a differential diagnosis of neuromuscular weakness in the ICU are listed in Box 34-3.

Critical Illness Myopathy

Lacomis and colleagues suggested using the term *critical illness myopathy* (CIM),[344] instead of the current terms used in the literature, such as acute quadriplegic myopathy,[345] acute (necrotizing) myopathy of intensive care, thick filament myopathy, acute corticosteroid myopathy, and critical care myopathy (see also Chapters 81 and 101).

Initial published reports of CIM in the ICU focused on patients with status asthmaticus.[346] Affected individuals typically had been treated with corticosteroids and nondepolarizing NMBDs. Nevertheless, myopathy has also been documented in asthmatic patients and in patients with chronic lung disease without paralysis who received corticosteroids,[347] as well as in critically ill patients with sepsis who received neither corticosteroids nor nondepolarizing NMBDs.[348] Animal studies revealed that the number of cytosolic corticosteroid receptors is increased in immobilized muscles relative to that in contralateral controls.[349] It seems—at least in some patients—that prolonged immobility may be the key risk factor for myopathy in corticosteroid-treated patients,[350] and selective muscle atrophy is a result of changes in glucocorticoid sensitivity.[349]

Sepsis, immobility, and the catabolism associated with negative nitrogen balance may also result in myopathy.[16] Skeletal muscle hypoperfusion is noted in patients with severe sepsis despite normal or elevated whole blood oxygen delivery.[351] Antibodies to nAChRs were demonstrated in a rodent model of sepsis.[352] Thus, myasthenia-like syndrome is also seen in critically ill patients. Evidence for local immune activation by cytokine expression in the skeletal muscle was reported in patients with CIM.[353]

The major feature of CIM is flaccid weakness that tends to be diffuse and sometimes also includes the facial muscles and diaphragm.[344] The clinical features of CIM overlap with those of critical illness polyneuropathy (CIP) and prolonged neuromuscular blockade.[344] Electrophysiologic studies and increases in serum creatine kinase concentrations may differentiate neuropathy from myopathy.[344] Lacomis and colleagues stated, "muscle biopsy should be considered if another myopathic process such as an inflammatory myopathy is suspected or if the histologic findings would affect management."[344]

Critical Illness Polyneuropathy

CIP is the polyneuropathy seen in critically ill patients. It affects both sensory and motor nerves and occurs in 50% to 70% of patients with multisystem organ failure and systemic inflammatory response syndrome.[354] Investigators have postulated that systemic inflammatory response syndrome contributes to CIP by releasing cytokines and free radicals that damage the microcirculation of the central and peripheral nervous systems.[353] Dysregulation of the microcirculation may render the peripheral nervous system susceptible to injury.

Although no pharmacologic treatment for muscle weakness syndromes in the critically ill patient currently exists, increasing evidence indicates the positive effects of early physical rehabilitation during ICU stay. Previously, intensive insulin therapy during critical illness was found to decrease the risk of CIP, and the maintenance of blood glucose at or below 110 mg/mL in critically ill patients may reduce the risk of CIP.

The outcomes from CIM and CIP appear to be similar. The reported mortality rate of patients with CIP syndrome is approximately 35%. In one study, 100% (13 of 13) of the patients who survived had abnormal clinical or neurophysiologic findings 1 to 2 years after the onset of the CIP syndrome, and quality of life was markedly impaired in all patients.[355]

Clinical Implications

Nondepolarizing NMBDs are the most common chemical agents producing immobilization and inducing a

denervation-like state. In such circumstances, besides the mature or junctional nAChR formed of two α and one each of β, ε, and δ subunits, two other isoforms, the immature AChR or γAChR and the neuronal α7AChR, are expressed in the muscle. The immature AChR is also referred as extrajunctional because it is expressed mostly in the extrajunctional part of the muscle. Up-regulation of nAChRs was noted in the muscles of deceased critically ill adults who had received long-term infusions of vecuronium.[356] Up-regulation refers to changes in the number of available receptors, but these changes usually do not involve a change in isoform changes. These three types of receptors can coexist in the muscle.

Should Succinylcholine Be Used in Patients in the Intensive Care Unit?

It is likely that up-regulation of nAChRs induced by immobilization and by prolonged administration of nondepolarizing NMBDs contributes to (1) the higher incidence of cardiac arrest associated with the use of succinylcholine in ICU patients[356] and (2) increased requirements for nondepolarizing NMBDs in ICU patients.[357] Even more important, succinylcholine more easily depolarizes immature nAChRs that may induce profound K^+ flux outward, with subsequent hyperkalemia. Moreover, the α7AChR can also be depolarized by succinylcholine, thus contributing to the K^+ efflux from the cell to the extracellular space. Therefore, succinylcholine should be avoided in ICU patients in whom total body immobilization exceeds 24 hours.[16]

Should Nondepolarizing Neuromuscular Blockers Be Used in Patients in the Intensive Care Unit?

NMBD-associated persistent weakness appears to be a distinct pathologic entity and is not simply a manifestation of weakness syndromes in critically ill patients (see also Chapter 101). In a prospective study, Kupfer and associates showed a 70% incidence of persistent weakness in ICU patients who received NMBDs for more than 2 days, compared with a 0% incidence in similar ICU patients who received no NMBD.[358] This is compelling evidence for the effects of nondepolarizing NMBDs in this complication.

Long-term weakness has been described after nondepolarizing NMBDs.[156,359,360] Approximately 20% of patients who received NMBDs for more than 6 days,[359] 15% to 40% of asthmatic patients who also received high-dose steroids,[346] and 50% of patients with renal failure who received vecuronium developed prolonged weakness.[156] Clinically, it appears that prolonged recovery from neuromuscular blockade occurs more frequently when steroidal NMBDs are used.[156,359]

However, prolonged weakness was also noted after the use of atracurium in ICU patients.[360] Further, the use of atracurium has raised concerns about its metabolite, laudanosine. Laudanosine, also detected in the cerebrospinal fluid (CSF) of ICU patients given atracurium,[361] is an analeptic and can trigger seizures in animals.[362] The toxic dose in humans is not known, but case reports have noted patients having seizures while receiving atracurium, and laudanosine has not been ruled out as a cause of these seizures.[363-365] Evidence also indicates that laudanosine can activate neuronal nicotinic receptors.[366] Cisatracurium is a single isomer of atracurium, and because it is four to five times more potent than atracurium, it is given in smaller doses. Therefore, the risk of laudanosine-related adverse effects should be minimal.[367]

Nondepolarizing NMBDs are polar molecules and do not readily cross the blood-brain barrier, but vecuronium and its long-acting active metabolite, 3-desacetylvecuronium, have been detected in the CSF of patients in the ICU. The CNS effects of NMBDs and their metabolites in humans have not been well studied, but in rats, atracurium, pancuronium, and vecuronium injected into the CSF caused dose-related cerebral excitation culminating in seizures.[362] Cerebral excitation with consequent increased cerebral oxygen demand is undesirable in ICU patients at risk of cerebral ischemia. Investigators have also suggested that nondepolarizing NMBDs can gain access to nerves during systemic inflammatory response syndrome, thus resulting in direct neurotoxicity.[362]

When nondepolarizing NMBDs are necessary, the use of a peripheral nerve stimulator is recommended, and periodic return of muscle function should be allowed. However, routine monitoring of neuromuscular function alone is insufficient in eliminating prolonged recovery and weakness syndromes in ICU patients.[368] Adjusting the dosage of NMBDs by peripheral nerve stimulation versus standard clinical dosing in critically ill patients reduces drug requirements, produces faster recovery of neuromuscular function, and results in a total cost savings of $738 per patient.[369] Daily interruption of sedative-drug infusions decreases the duration of mechanical ventilation and the length of stay in the ICU.[370] The effect of such an approach on the weakness syndromes in the ICU patient is unknown. When nondepolarizing NMBDs are used, the guidelines in Box 34-4 may help minimize the incidence of complications. As stated in the clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient,[337] "*Independent of the reasons for using neuromuscular blockers, we emphasize that all other modalities to improve the clinical situation must be tried, using neuromuscular blockers only as a last resort.*"

BOX 34-4 ***Recommendations for the Use of Neuromuscular Blockers in the Intensive Care Unit***

- Avoid the use of neuromuscular blockers by
  - Maximal use of analgesics and sedatives
  - Manipulation of ventilatory parameters and modes
- Minimize the dose of neuromuscular blocker
  - Use a peripheral nerve stimulator with train-of-four monitoring
  - Do not administer for more than 2 days continuously
  - Administer by bolus rather than infusion
  - Administer only when required and to achieve a well-defined goal
  - Continually allow recovery from paralysis
- Consider alternative therapies

Complete references available online at expertconsult.com

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Chapter 35

Reversal (Antagonism) of Neuromuscular Blockade

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Key Points

- Appropriate reversal of a nondepolarizing neuromuscular blockade is essential to avoid adverse patient outcomes. Complete recovery of muscle strength should be present, and the residual effects of neuromuscular blocking drugs (NMBDs) should be fully pharmacologically reversed (or spontaneously recovered).
- Sufficient recovery from neuromuscular blockade for tracheal extubation can be confirmed by an adductor pollicis train-of-four (TOF) ratio of at least 0.90 (or 1.0 if acceleromyography [AMG] is used). Quantitative neuromuscular monitoring is the only method of assessing whether a safe level of recovery of muscular function has occurred.
- Residual neuromuscular blockade is not a rare event in the postanesthesia care unit (PACU). Approximately 30% to 50% of patients can have TOF ratios less than 0.90 following surgery.
- Patients with TOF ratios less than 0.90 in the PACU are at increased risk for hypoxemic events, impaired control of breathing during hypoxia, airway obstruction, postoperative pulmonary complications, symptoms of muscle weakness, and prolonged PACU admission times. Appropriate management of neuromuscular blockade can decrease the incidence of, or eliminate, residual blockade, which will reduce the risks of these adverse postoperative events.
- Neostigmine, pyridostigmine, and edrophonium inhibit the breakdown of acetylcholine, resulting in an increase in acetylcholine in the neuromuscular junction. However, there is a "ceiling" effect to the maximal concentration of acetylcholine that can be achieved with these drugs. Reversal of neuromuscular blockade with these drugs should not be attempted until some evidence of spontaneous recovery is present. Neostigmine in the dose range of 30 to 70 μg/kg body weight antagonizes moderate to shallow levels of neuromuscular blockade. However, if these reversal drugs are given in the presence of full neuromuscular recovery, paradoxical muscle weakness theoretically may be induced.
- Sugammadex is a modified γ-cyclodextrin that shows a high affinity for the steroidal NMBDs rocuronium and vecuronium. Sugammadex is able to form a tight inclusion complex with either of these steroidal NMBDs, thereby inactivating the effects of rocuronium and vecuronium, resulting in rapid reversal of neuromuscular blockade.
- Sugammadex is able to reverse a moderate/shallow and a profound neuromuscular blockade with a dose of 2.0 mg/kg and 4.0 mg/kg, respectively. An immediate reversal of neuromuscular blockade induced by rocuronium is possible with a dose of sugammadex 16 mg/kg. Reversal of neuromuscular blockade by sugammadex is rapid and without side effects encountered with anticholinesterase drugs.
- Fumarates (gantacurium [GW280430A, AV430A], CW002, and CW011) represent a new class of NMBDs in development that are inactivated primarily via adduction of cysteine to the double bond of the compounds, resulting in inactive breakdown products. Laboratory studies have shown that the administration of exogenous L-cysteine results in complete reversal of deep neuromuscular blockade within 2 to 3 minutes.

HISTORY

The paralytic effects of curare have been recognized since the time of Sir Walter Raleigh's voyage on the Amazon in 1595.[1] In 1935, the name *d*-tubocurarine was assigned to an alkaloid isolated from a South American vine (*Chondrodendron tomentosum*). At approximately the same time, experiments from pharmacology and physiology laboratories in London suggested that acetylcholine was the chemical neurotransmitter at motor nerve endings.[2] Investigations from these same laboratories demonstrated that eserine (physostigmine)-like substances could reverse the effects of curare at the neuromuscular junction of frog nerve-muscle preparations.[2] In the clinical setting, Bennett (1940) described the use of curare in the prevention of traumatic complications during convulsive shock therapy.[3] In l942, Griffith and colleagues described the use of an extract of curare in 25 surgical patients; all patients appeared to recover fully without administration of an antagonist such as neostigmine.[4]

The importance of pharmacologic reversal of neuromuscular blockade was suggested in 1945. Specifically, use of neostigmine or physostigmine to antagonize curare was recognized and was recommended to be available whenever muscle relaxants were given in the operating room.[5] The first large case series examining the use of curare was published by Cecil Gray in 1946.[1] A crystalline extract, *d*-tubocurarine chloride, was administered in 1049 general anesthesia cases. No postoperative complications directly attributable to *d*-tubocurarine were noted, and physostigmine was administered to only two patients in the series. However, in a later review article (1959) from the same anesthesia department, the authors concluded that "it is safer to always use neostigmine when nondepolarizing relaxants have been administered."[6] By the mid-1960s, significant differences in neuromuscular management existed between the United States and Europe. As noted in an editorial from this time, "In Great Britain the majority of anesthetists have arbitrarily adopted the attitude that the dangers of reversal are far less than those of latent paresis, so that most patients receive at least some anticholinesterase drug at the end of anesthesia." In the United States, however, where smaller doses of curare were used, the emphasis was more on the mortality and morbidity associated with reversal drugs. Emphasis was placed on using muscle relaxants in smaller doses so reversal drugs were not necessary.[7] In fact, in the senior author's training (Miller), the prevailing thinking was that emphasis in anesthesia should be on "properly anesthetizing rather than paralyzing" a patient; it was commonly said that "curare is not an anesthetic."

Despite more than 7 decades of research, significant differences in opinion still exist regarding management of neuromuscular blockade at the conclusion of surgery and anesthesia. Some clinicians routinely pharmacologically antagonize a nondepolarizing neuromuscular blocking drug (NMBD), whereas others antagonize neuromuscular blockade only when obvious clinical muscle weakness is present. The issue is whether clinically important weakness exists when it is not clinically apparent. Will monitoring of neuromuscular blockade improve patient care? The aim of this chapter is to review the consequences of incomplete neuromuscular recovery, the use of anticholinesterase agents in clinical practice (benefits, risks, and limitations), and the recent developments in novel drugs to reverse/antagonize residual neuromuscular blockade.

ANTAGONISM OF NEUROMUSCULAR BLOCKADE: CURRENT MANAGEMENT PRACTICES

A number of survey studies have been conducted to determine how clinicians evaluate and manage neuromuscular blockade in the perioperative period. In the late 1950s, a survey was sent to anesthetists in Great Britain and Ireland.[6] Forty-four percent of the respondents used neostigmine "always" or "almost always" when *d*-tubocurarine chloride or gallamine was used. Two thirds of respondents administered 1.25 to 2.5 mg when antagonizing these NMBDs.[6] Despite accumulating data demonstrating a continued frequent incidence of residual neuromuscular blockade, more-recent surveys indicate that attitudes toward reversal of neuromuscular blockade have changed little over the intervening decades. A questionnaire sent to German anesthesiologists in 2003 revealed routine reversal with neostigmine at the end of surgery was not practiced in 75% of anesthesia departments.[8] A similar survey of 1230 senior anesthetists in France reported that pharmacologic antagonism of neuromuscular blockade was "systematic" or "frequent" in only 6% and 26% of surgical cases, respectively.[9] In contrast, reversal of nondepolarizing NMBDs was routinely performed in Great Britain.[10]

A large-scale, comprehensive survey of neuromuscular management practices in the United States and Europe was conducted in order to better understand attitudes about doses of NMBDs, monitoring, and pharmacologic reversal.[11] Only 18% of European respondents and 34.2% of respondents from the United States "always" administered an anticholinesterase drug when a nondepolarizing relaxant was used. The findings from these surveys suggest that there is little agreement about best practices related to reversal of neuromuscular blockade. Despite perioperative guidelines from several national organizations, surveys from many countries reveal that most clinicians do not monitor or reverse a neuromuscular blockade in the operating room. Surprisingly, most anesthesiologists have not witnessed obvious adverse events directly attributable to incomplete recovery from neuromuscular blockade.[11] Therefore, the potential hazards of reversal of neuromuscular blockade using an anticholinesterase drug (see later) are likely estimated to be more frequent than the risks of residual neuromuscular blockade. In the following sections, the definitions, incidence, and clinical implications of residual neuromuscular blockade are reviewed.

RESIDUAL NEUROMUSCULAR BLOCKADE

Assessment of Residual Neuromuscular Blockade

In order to optimize patient safety, tracheal extubation in the operating room should not occur until complete

recovery of muscle strength is present and the residual effects of NMBDs have been fully reversed (or spontaneously recovered). Therefore, clinicians have methods to detect and treat residual muscle weakness. Three methods are commonly used in the operating room to determine the presence or absence of residual neuromuscular blockade: clinical evaluations for signs of muscle weakness, qualitative neuromuscular monitors, and quantitative neuromuscular monitors. A more detailed description of the types of neuromuscular monitors used perioperatively is provided in Chapter 53.

Clinical Evaluation for Signs of Muscle Weakness. Following the introduction of *d*-tubocurarine into clinical practice, residual paralysis and the need for neostigmine was determined primarily by the observation of "shallow, jerky movements of the diaphragm" at the end of surgery.[12] In the absence of any clinically observable respiratory impairment, neuromuscular function was assumed to be adequate, and no reversal drugs were administered. A peripheral nerve stimulator was first used in the 1960s by Harry Churchill-Davidson in the United Kingdom and later in the United States. However, routine use of a peripheral nerve stimulator did not occur. In fact, several decades later, the most commonly applied technique for evaluation of recovery of neuromuscular function continues to be the use of clinical tests for signs of apparent muscle weakness.[13] Furthermore, one of the primary factors that determines whether clinicians elect to administer a reversal drug at the end of surgery is the presence of signs of muscle weakness.[11] However, for decades clinical studies have consistently shown that tests of muscle strength are not sensitive or reliable indices of adequate neuromuscular recovery. The most commonly applied criteria used to determine suitability for extubation of the trachea are a "normal" pattern of ventilation and a sustained head lift.[13] Unfortunately, the sensitivity of each test in detecting residual blockade is poor. At a level of neuromuscular recovery that allows for adequate ventilation in a patient whose trachea is intubated, the muscles responsible for maintaining airway patency and protection are significantly impaired.[14] Other investigators have observed that the majority of subjects could maintain a 5-second head lift at a train-of-four (TOF) ratio of 0.50 or less.[15,16] Additional clinical tests of muscle strength, such as sustained hand-grip, leg-lift, or eye opening, have been demonstrated to have a low sensitivity in predicting recovery of neuromuscular function[17,18] (Table 35-1).

Qualitative Neuromuscular Monitoring. Qualitative neuromuscular monitors—or more accurately, peripheral nerve stimulators—deliver an electrical stimulus to a peripheral nerve, and the response to nerve stimulation is subjectively assessed by clinicians either visually or tactilely (i.e., placing a hand on the thumb to detect the muscle contraction after ulnar nerve stimulation) (Fig. 35-1; also see Chapter 53). Three patterns of nerve stimulation are used in the clinical setting to assess patients for residual blockade: TOF, tetanic, and double-burst stimulation. TOF stimulation delivers four supramaximal stimuli every 0.5 seconds, tetanic stimulation consists of a series of extremely rapid (usually 50 or 100 Hz) stimuli typically applied over 5 seconds, and double-burst stimulation delivers two short bursts of 50-Hz tetanic stimuli separated by 750 msec (see Chapter 53). The presence of fade with these patterns of nerve stimulation indicates incomplete neuromuscular recovery. Although qualitative monitoring may guide management during early recovery from neuromuscular blockade, the sensitivity of these devices in detecting small degrees of residual paresis (TOF ratios between 0.50 and 1.0) is limited (Fig. 35-2). When using TOF stimulation, investigators have consistently observed that clinicians are unable to detect fade when TOF ratios exceed 0.30 to 0.4.[19-21] Similarly, the observation of fade during a 5-second, 50-Hz tetanic stimulation is difficult when TOF ratios are greater than 0.30.[21-22] The ability of clinicians to detect fade is improved with double-burst stimulation; the threshold for detection of fade is approximately

TABLE 35-1 SENSITIVITY, SPECIFICITY, POSITIVE, AND NEGATIVE PREDICTIVE VALUES OF AN INDIVIDUAL CLINICAL TEST FOR A TRAIN-OF-FOUR <90% IN 640 SURGICAL PATIENTS

Variable	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Inability to smile	0.29	0.80	0.47	0.64
Inability to swallow	0.21	0.85	0.47	0.63
Inability to speak	0.29	0.80	0.47	0.64
General weakness	0.35	0.78	0.51	0.66
Inability to lift head for 5 sec	0.19	0.88	0.51	0.64
Inability to lift leg for 5 sec	0.25	0.84	0.50	0.64
Inability to sustain hand grip for 5 sec	0.18	0.89	0.51	0.63
Inability to perform sustained tongue depressor test	0.22	0.88	0.52	0.64

From Cammu G, De Witte J, De Veylder J, et al: Postoperative residual paralysis in outpatients versus inpatients, Anesth Analg *102:426-429, 2006.*

The sensitivity of a test is the number of true positives ÷ the sum of true positives + false negatives; the specificity is the number of true negatives ÷ the sum of true negatives + false positives. True positives are patients scoring positive for a test and having a train-of-four (TOF) <90%. False negatives are patients with a negative test result but a TOF <90%. True negatives have a negative test score and a TOF not <90%; false positives score positively but have a TOF not <90%. A *positive* test result means *inability* to smile, swallow and speak, general muscular weakness, and so on.

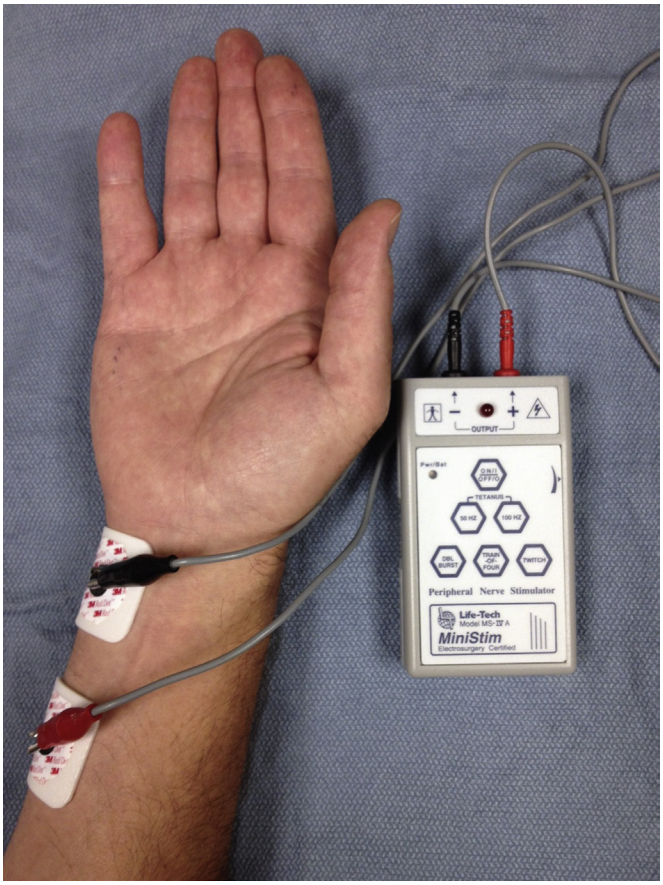


Figure 35-1. Example of a qualitative neuromuscular monitor (or more appropriately, a peripheral nerve stimulator). A peripheral nerve is stimulated, and the response to nerve stimulation is subjectively (qualitatively) assessed using either visual or tactile (hand placed on the muscle) means. In this illustration, the ulnar nerve is stimulated, and movement of the thumb subjectively evaluated.

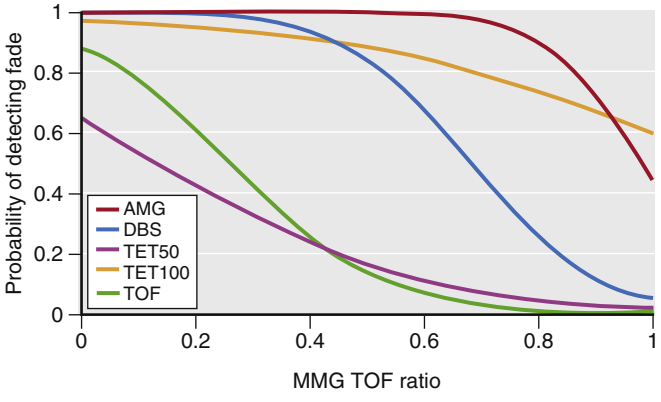


Figure 35-2. Detection of fade with various neuromuscular monitoring techniques. Residual neuromuscular blockade was evaluated using acceleromyography (AMG), tactile assessment of train-of-four (TOF), double-burst stimulation (DBS), 50-Hz tetanus, or 100-Hz tetanus. The mechanomyographic (MMG) adductor pollicis TOF ratio was measured at one extremity. During recovery, a blinded observer estimated tactile fade in the other extremity. Probability of detection of fade by logistic regression is presented. *(From Capron F, Fortier LP, Racine S, Donati F: Tactile fade detection with hand or wrist stimulation using train-of-four, double-burst stimulation, 50-hertz tetanus, 100-hertz tetanus, and acceleromyography,* Anesth Analg *102:1578-1584, 2006.)*

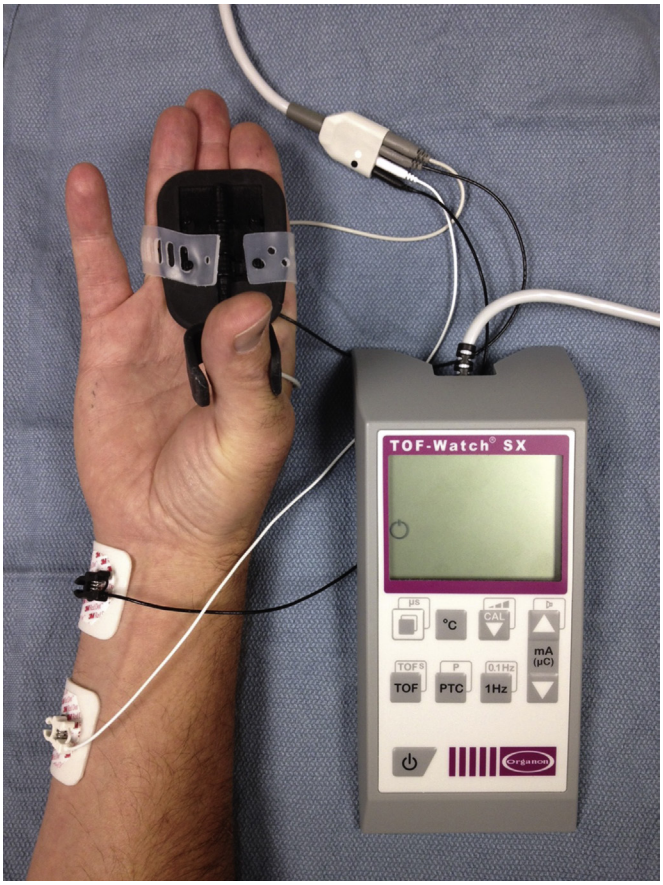


Figure 35-3. Example of a quantitative neuromuscular monitor (acceleromyography [AMG]). Ulnar nerve stimulation results in thumb movement, which is sensed by a piezoelectric sensor attached to the thumb. To improve the consistency of responses, a hand adapter applies a constant preload. Acceleration of the thumb is sensed by the piezoelectric sensor, and is proportional to the force of muscle contraction.

0.6 to 0.7 using this mode of stimulation.[20,21,23] However, regardless of the mode of nerve stimulation used, residual neuromuscular blockade cannot always be reliably excluded using qualitative monitoring.

Quantitative Neuromuscular Monitoring. Quantitative neuromuscular monitors are instruments that permit both stimulation of a peripheral nerve and the quantification and recording of the evoked response to nerve stimulation. Quantitative monitors allow an accurate assessment of the degree of muscle weakness using either TOF stimulation (TOF ratio displayed) or single-twitch stimulation (response compared with control "twitch" as a percentage). Although five different methods of quantifying neuromuscular function in the operating room have been developed, only one technology, acceleromyography (AMG, available as the TOF-Watch, Bluestar Enterprises), is commercially produced as a stand-alone monitor (Fig. 35-3). In a study comparing AMG with standard qualitative tests (tactile fade to TOF, double-burst, 5-Hz tetanic, and 100-Hz tetanic stimulation), AMG was the most accurate technique in detecting residual paralysis[21] (see Fig. 35-2). In addition, the use of AMG in the operating room has been demonstrated to reduce the risk of residual

neuromuscular blockade in the postanesthesia care unit (PACU)[24-27] and to decrease adverse respiratory events and symptoms of muscle weakness associated with incomplete neuromuscular recovery.[26,27] In clinical practice, AMG is a valuable monitor in determining whether full recovery of neuromuscular function has occurred before tracheal extubation, and provides objective data to guide dosing of reversal agents at the conclusion of surgery (see later).

A careful evaluation of the degree of residual blockade at the conclusion of a general anesthetic is essential in order to avoid the potential hazards of incomplete neuromuscular recovery following tracheal extubation. However, the methods used by most clinicians (ability to perform a head lift or maintain a stable pattern of ventilation; no fade observed to TOF or tetanic nerve stimulation) are insufficient in assuring safe recovery. At the present time, quantitative neuromuscular monitoring is the only method of determining whether full recovery of muscular function has occurred and reversal drugs safely avoided. In order to exclude with certainty the possibility of residual paresis, quantitative monitoring should be used.

Definitions of Residual Neuromuscular Blockade

Quantitative Neuromuscular Monitoring: TOF Ratio Less Than 0.70 and Less Than 0.90. Traditionally, residual neuromuscular blockade has been defined using quantitative neuromuscular monitoring. Although peripheral nerve stimulation was used in the l960s, Ali and colleagues first described the application of peripheral nerve stimulation for neuromuscular monitoring using the ulnar nerve–adductor pollicis unit as the site of monitoring in the early 1970s.[28,29] By comparing the amplitude of the fourth (T4) to the first (T1) evoked mechanical or electromyographic response (TOF response), the degree of neuromuscular recovery could be measured. Shortly thereafter, these same investigators performed several studies examining the association between the degree of residual blockade in the hand (defined using quantified T4/T1 ratio, i.e., TOF ratio) with symptoms of peripheral muscle weakness and spirometry measurements.[30-32] At adductor pollicis TOF ratios less than 0.60, signs of muscle weakness, tracheal tug, and ptosis were observed. When TOF ratios recovered to 0.70, the majority of patients were able to sustain head lift, eye opening, hand grasp, tongue protrusion, and a vital capacity exceeding 15 mL/kg. On the basis of these data, a TOF ratio of 0.70 was previously agreed on to represent acceptable neuromuscular recovery at the end of a general anesthetic that included administration of nondepolarizing NMBDs. Yet, more recently, clinically significant muscle weakness and impaired respiratory control have been observed at TOF ratios of up to 0.90. At TOF ratios less than 0.90, awake volunteers exhibit impaired pharyngeal function, airway obstruction, an increased risk of aspiration of gastric contents, an impaired hypoxic ventilatory control, and unpleasant symptoms of muscle weakness.[33-37] In surgical patients, an association between TOF ratios less than 0.90 and adverse respiratory events and prolonged PACU length of stay has been observed.[38,39] At the present time, it is generally agreed that adequate recovery of neuromuscular function is represented by an adductor pollicis TOF ratio of at least 0.90 (or even 1.0 when AMG is used).

Clinical Signs and Symptoms. A variety of clinical signs may be present in patients with residual neuromuscular blockade, including the following: inability to perform a head lift, hand grip, eye opening, or tongue protrusion; inability to clench a tongue depressor between the incisor teeth; inability to smile, swallow, speak, cough, track objects with eyes; or inability to perform a deep or vital capacity breath.[40] Symptoms of residual blockade that have been reported include subjective difficulty performing the aforementioned tests, as well as blurry vision, diplopia, facial weakness, facial numbness, and general weakness.[37,40] Although the majority of patients with TOF ratios of 0.90 to 1.0 will have recovered satisfactory strength in most muscle groups, signs and symptoms of muscle weakness may be present in some of these patients. In contrast, a few patients with significant residual blockade (TOF ratios <0.70) may exhibit no apparent muscle weakness. The most inclusive and precise definition of residual neuromuscular blockade should include not only objective and quantifiable monitoring data (a TOF ratio <0.90 demonstrated with AMG, mechanomyography, or electromyography) but also clinical evidence of impaired neuromuscular recovery (swallowing impairment, inability to speak or perform a head lift, diplopia, and/or general weakness).

Incidence of Residual Neuromuscular Blockade

Residual neuromuscular Blockade is not a rare event in the PACU. In 1979, Viby-Mogensen examined the efficacy of neostigmine in reversing *d*-tubocurarine, gallamine, or pancuronium blockade.[41] On arrival to the PACU, 42% of patients had a TOF ratio less than 0.70, and 24% were unable to perform a 5-second head lift (the majority of these subjects had TOF ratios <0.70). The authors concluded that the average dose of neostigmine given (2.5 mg) was insufficient for reversing neuromuscular blockade. Subsequent studies demonstrated a similarly frequent incidence of residual blockade in patients receiving long-acting NMBDs; 21% to 50% of patients in the early postoperative period had TOF ratios less than 0.70.[42-44] Subsequently, the risk of postoperative residual blockade was reduced if intermediate-acting NMBDs were used instead of long-acting drugs.[44-46] As the use of long-acting NMBDs began to decrease in clinical practices, many investigators hoped that residual blockade would become an uncommon occurrence in the PACU. However, incomplete neuromuscular recovery continues to be a common postoperative event. Large-scale studies (150 to 640 subjects) have demonstrated that approximately 31% to 50% of patients have clinically significant residual neuromuscular blockade with adductor pollicis TOF ratios less than 0.90 following surgery.[17,47,48] In a meta-analysis of data from 24 clinical trials, Naguib and colleagues calculated the incidence of residual blockade by NMBD type and TOF ratio.[44] The pooled rate of residual blockade, defined as a TOF ratio less than 0.90, was 41% when studies using intermediate-acting NMBDs were analyzed (Table 35-2). In conclusion, a frequent incidence of residual neuromuscular blockade still occurs worldwide in the immediate postoperative period; with current practice and inadequate monitoring, the incidence of this complication is not decreasing over time.

The observed incidence of postoperative residual blockade varies widely between studies, ranging from 5% to 93%.[44] A number of factors may influence the degree

of neuromuscular recovery measured following tracheal extubation, accounting for the reported variability in the incidence of residual blockade (Box 35-1). The observed incidence of residual blockade is more frequent if a threshold definition of 0.90 is used (versus the previous threshold of 0.70) (see Table 35-2). Similarly, a frequent incidence of residual paralysis is observed if there is a short time interval between reversal of NMBDs and quantification of TOF ratios (TOF ratios measured at the time of extubation versus measurement in the PACU).[49] Furthermore, the technology used to quantify neuromuscular recovery may influence the percentage of patients with TOF ratios less than 0.90 following surgery. For example, when compared with mechanomyography (MMG), AMG frequently overestimates the degree of neuromuscular recovery.[21] Additional factors influencing the degree of residual paralysis are discussed later.

Adverse Effects of Residual Blockade

Many investigations have demonstrated that approximately one half of patients will be admitted to the PACU with TOF ratios less than 0.90, as measured with AMG, MMG, or electromyography (EMG).[44] The impact of this residual muscle weakness on clinical outcomes has been less well-documented. Yet even minimal levels of neuromuscular blockade may have clinical consequences. The following section reviews the effects of residual blockade in both awake volunteer studies and in postoperative surgical patients.

TABLE 35-2 POOLED ESTIMATED INCIDENCE OF RESIDUAL NEUROMUSCULAR BLOCKADE BY MUSCLE RELAXANT TYPE AND TRAIN-OF-FOUR RATIO

Sub-population	Pooled Rate of RNMB*	Confidence Interval	Heterogeneity	
			P-value	Inconsistency† (%)
Long-acting MR (TOF <0.70)	0.351	(0.25-0.46)	<.001	86.7
Intermediate-acting MR (TOF <0.70)	0.115	(0.07-0.17)	<.001	85.9
Long-acting MR (TOF <0.90)	0.721	(0.59-0.84)	<.001	88.1
Intermediate-acting MR (TOF <0.90)	0.413	(0.25-0.58)	<.001	97.2

From Naguib M, Kopman AF, Ensor JE: Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis, Br J Anaesth *98:302-316, 2007.*
MR, Muscle relaxant; *RNMB*, residual neuromuscular blockade; *TOF*, train-of-four.
*Pooled rate of RNMB is the weighted average. The weight in the random-effect model takes into account both between and within studies variation.
†Inconsistency is the proportion of between studies variability that cannot be explained by chance.

BOX 35-1 ***Factors Influencing the Measured Incidence of Postoperative Residual Neuromuscular Blockade***

Preoperative Factors

1. Definition of residual neuromuscular blockade
   - TOF ratio <0.70 (before 1990)
   - TOF ratio <0.90 (after 1990)
   - Presence of signs or symptoms of muscle weakness
2. Patient factors
   - Age (higher risk in older adults)
   - Gender
   - Preexisting medical conditions (renal or liver dysfunction, neuromuscular disorders)
   - Medications known to affect neuromuscular transmission (antiseizure medications)

Intraoperative Anesthetic Factors

1. Type of NMBD administered intraoperatively
   - Intermediate-acting NMBD (lower risk)
   - Long-acting NMBD (higher risk)
2. Dose of NMBD used intraoperatively
3. Use of neuromuscular monitoring
   - Qualitative monitoring (studies inconclusive)
   - Quantitative monitoring (lower risk)
4. Depth of neuromuscular blockade maintained
   - "Deeper blockade" (TOF count of 1-2) (higher risk)
   - "Lighter blockade" (TOF count of 2-3) (lower risk)
5. Type of anesthesia used intraoperatively
   - Inhalational agents (higher risk)
   - TIVA (lower risk)

Factors Related to Antagonism of Residual Blockade

1. Use of reversal agents (lower risk)
   - Neostigmine
   - Pyridostigmine
   - Edrophonium
   - Sugammadex
2. Dosage of reversal agent used
3. Time interval between reversal agent administration and quantification of residual blockade

Factors Related to Measurement of Residual Blockade

1. Method of objective measurement of residual neuromuscular blockade
   - Mechanomyography (MMG)
   - Electromyography (EMG)
   - Acceleromyography (AMG)
   - Kinemyography (KMG)
   - Phonomyography (PMG)
2. Time of measurement of residual neuromuscular blockade
   - Immediately before tracheal extubation (higher risk)
   - Immediately after tracheal extubation (higher risk)
   - On arrival to PACU (lower risk)

Postoperative Factors

1. Respiratory acidosis and metabolic alkalosis (higher risk)
2. Hypothermia (higher risk)
3. Drug administration in the PACU (antibiotics, opioids) (higher risk)

NMBD, Neuromuscular blocking drug; *PACU*, postanesthesia care unit *TIVA*, total intravenous anesthetic; *TOF*, train-of-four.

Adverse Effects of Residual Blockade—Awake Volunteer Studies. Surgical patients receive a variety of anesthetics in the perioperative period, which complicates an assessment of the particular effect of residual neuromuscular blockade on clinical outcomes. Conducting awake volunteer trials allows investigators to more precisely quantify the impact of NMBDs and various degrees of neuromuscular blockade on physiologic systems in the absence of anesthetics. In general, these studies have titrated NMBDs to various TOF ratios in awake subjects, and measured the effects on the respiratory system and on signs and symptoms of muscle weakness.

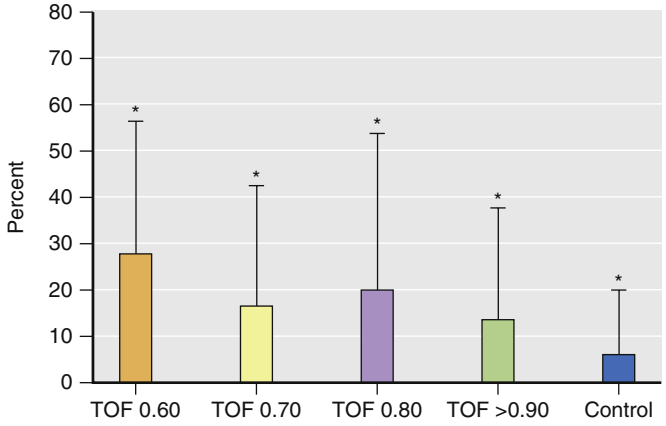


Fig 35-4. Incidence of pharyngeal dysfunction during atracurium-induced partial neuromuscular blockade corresponding to steady-state adductor pollicis TOF ratio of 0.70, 0.80, >0.90 and control in young volunteers. *(Modified from Sundman E, Witt H, Olsson R, et al: The incidence and mechanisms of pharyngeal and upper esophageal dysfunction in partially paralyzed humans,* Anesthesiology *92:977-984, 2000.)*

Early volunteer investigations concluded that respiratory impairment was minimal at TOF ratios of 0.60 to 0.70.[32] Respiratory frequency, tidal volume, vital capacity, and peak expiratory flow rates were not altered during the study, although vital capacity and inspiratory force were both significantly reduced compared with control values at a TOF ratio of 0.60.[32] The authors concluded that these changes were of minor clinical importance. Subsequent investigations have revealed that pharyngeal and respiratory function is impaired at TOF ratios as high as 0.90 to 1.0. Return of pharyngeal muscle function is essential for airway control following tracheal extubation. In series of human studies from the Karolinska Institutet, Sweden, a functional assessment of the pharynx, upper esophageal muscles, and the integration of respiration with swallowing was performed during various levels of neuromuscular blockade.[33-34] At adductor pollicis TOF ratios less than 0.90, pharyngeal dysfunction was observed in 17% to 28% of young adult volunteers[33] (Fig. 35-4), increasing more than twofold in patients older than 60 years and associated with reduced upper esophageal sphincter resting tone and misdirected swallowing and aspiration (laryngeal penetration) of oral contrast material.[33-34a] Eikermann and colleagues conducted several investigations examining the effect of residual paresis on respiratory muscle function in awake volunteers. Awake subjects were administered a rocuronium infusion, which was titrated to a TOF ratio 0.50 to 1.0. At a minimal level of residual blockade (approximately 0.80), the authors observed impaired inspiratory air flow and upper airway obstruction,[35] a marked decrease in upper airway volumes and upper airway dilator muscle function,[50] and increased upper airway closing pressure and collapsibility[51] (Fig. 35-5). In addition, evidence from human studies of respiratory control suggest that residual blockade inhibits hypoxic ventilatory control while leaving the ventilatory

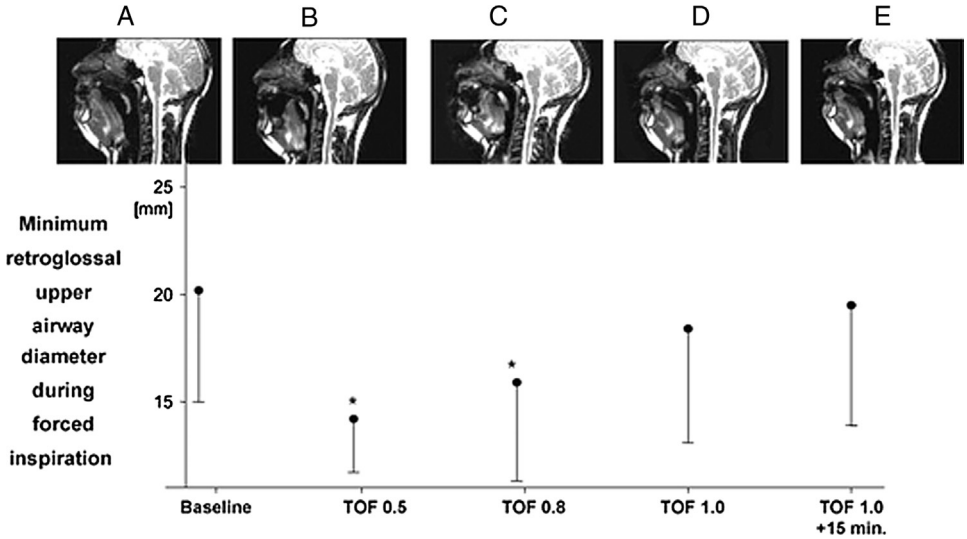


Figure 35-5. An investigation examining the effect of residual neuromuscular blockade on respiratory muscle function in awake volunteers. Subjects were administered a rocuronium infusion, which was titrated to a train-of-four (TOF) ratio 0.5 to 1.0. Supraglottic airway diameter and volume was measured by respiratory-gated magnetic resonance imaging. Minimum retroglossal upper airway diameter during forced inspiration (**A**) before neuromuscular blockade (baseline), at a steady-state TOF ratio of (**B**) 0.50 and (**C**) 0.80, (**D**) after recovery of the TOF ratio to 1.0, and (**E**) 15 minutes later. Images from the volunteer show that a partial paralysis evokes an impairment of upper airway diameter increase during forced inspiration. **P* <.05 versus baseline. *(From Eikermann M, Vogt FM, Herbstreit F, et al: The predisposition to inspiratory upper airway collapse during partial neuromuscular blockade,* Am J Respir Crit Care Med *175:9-15, 2007.)*

control during hypercapnia unaffected. In human volunteers, the hypoxic ventilatory response was attenuated by 30% after administration of either atracurium, vecuronium, or pancuronium at an adductor pollicis TOF ratio of 0.70, returning to normal after spontaneous recovery to a TOF ratio of greater than 0.90[52] (Fig. 35-6). An increase in ventilatory drive during hypoxia is primarily mediated by afferent input from peripheral chemoreceptors in the carotid bodies located bilaterally at the carotid artery bifurcation, whereas ventilatory regulation during hypercapnia is mediated via CO_2 interaction with brainstem chemoreceptors. In experimental animals, the firing frequencies of carotid body chemoreceptors is almost abolished by the administration of a nondepolarizing NMBD because of a cholinergic blockade of nicotinic acetylcholine receptors within the carotid body oxygen signaling pathway.[53]

Awake volunteer studies have also revealed that unpleasant symptoms of muscle weakness are present in subjects with small degrees of residual neuromuscular blockade. Conscious subjects given a small "priming" dose of pancuronium noted blurred vision, difficulty swallowing and keeping their eyes open, and jaw weakness at a TOF ratio of 0.81.[54] Symptoms of diplopia, dysarthria, and subjective difficulty swallowing were reported by subjects at TOF ratios of 0.60 and 0.70.[34] Reduced clarity of vision was described in all subjects receiving a mivacurium infusion at a TOF ratio of 0.81.[55] Kopman and associates examined 10 volunteers for symptoms and signs of residual paralysis at various TOF ratios.[37] Testing was performed at baseline (before an infusion of mivacurium), at a TOF ratio of 0.65 to 0.75, at 0.85 to 0.95, and at full recovery (1.0). All subjects had significant signs and symptoms at a TOF ratio of 0.70 (inability to maintain incisor teeth apposition, sit without assistance, or drink from a straw, visual disturbances, facial numbness, difficulty speaking and swallowing, general weakness), and in seven subjects, visual symptoms persisted for up to 90 minutes after the TOF ratio had recovered to unity.

Adverse Effects of Residual Blockade—Postoperative Surgical Patients. Awake volunteers have impairment of respiratory function and a variety of symptoms of muscle weakness at TOF ratios of 0.50 to 0.90. Similar adverse events have been observed in postoperative surgical patients with TOF ratios less than 0.90 measured in the PACU. Incomplete neuromuscular recovery is a risk factor for hypoxemic events, airway obstruction, unpleasant symptoms of muscle weakness, delayed PACU length of stay, and pulmonary complications during the early postoperative period.

Clearly, an association exists between neuromuscular management characteristics and postoperative morbidity and mortality. Beecher and colleagues collected data from 10 university hospitals between the years 1948 to 1952 to determine anesthetic-related causes of mortality.[56] Risk of death related to anesthesia was six times more frequent in patients receiving NMBDs (primarily tubocurarine and decamethonium) compared with those administered no NMBDs (1:370 versus 1:2100). Although the authors conclude that there is "an important increase in anesthesia death rate when muscle relaxants are added"[56] to an anesthetic, the use or omission of pharmacologic reversal in patients receiving NMBDs was not reported or analyzed. In another large-scale study, mortality data associated with anesthesia were collected over a 10-year period (1967-1976) at a single institution in South Africa.[57] An analysis of 240,483 anesthetics revealed that "respiratory inadequacy following myoneural blockade" was the second-most common cause of death. Again, data relating to the use of pharmacologic reversal drugs were not provided. A study from the Association of Anaesthetists of Great Britain and Ireland examined deaths that were judged "totally due to anesthesia" and reported that postoperative respiratory failure secondary to neuromuscular management was a primary cause of mortality.[58] Rose and associates examined patient, surgical, and anesthetic factors associated with critical respiratory events in the PACU.[59] Of the anesthetic management factors assessed,

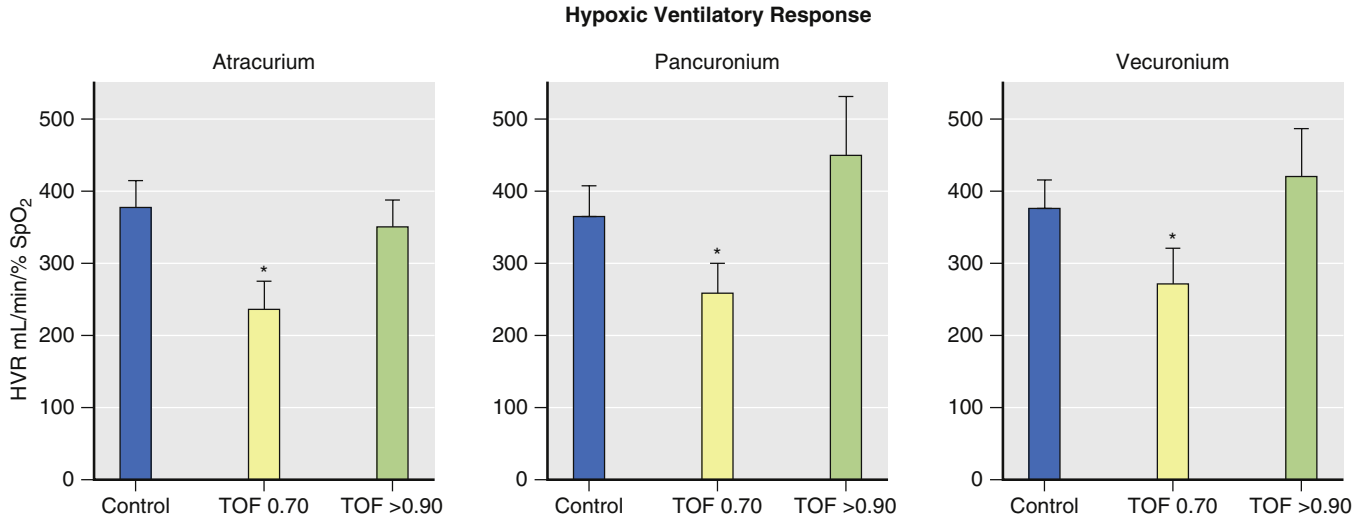


Figure 35-6. Hypoxic ventilatory response (HVR) before (control); during steady-state infusion at train-of-four (TOF) ratio 0.70 of atracurium, pancuronium and vecuronium; and after recovery (TOF ratio >0.90). Data presented as means ± SD. * = $P < .01$. *(From Eriksson LI: Reduced hypoxic chemosensitivity in partially paralysed man: a new property of muscle relaxants,* Acta Anaesthesiol Scand *40:520-523, 1996.)*

the most frequent rate of critical respiratory events was observed in patients receiving large doses of NMBDs (the use of reversal drugs was not analyzed). Two investigations of anesthetic complications resulting in admissions to the intensive care unit determined that "failure to reverse after muscle relaxants" and "ventilatory inadequacy after reversal of muscle relaxants" were the most common causes of admission.[60,61] Sprung and colleagues reviewed the medical records of patients who experienced a cardiac arrest over a 10-year period (223 of 518,284 anesthetics).[62] The most important category was the use of NMBDs, involving either hypoxia caused by inadequate pharmacologic reversal or asystole induced by anticholinesterase drugs. A large case-control investigation was performed of all patients undergoing anesthesia over a 3-year period (n = 869,483) in The Netherlands assessing the impact of anesthetic management characteristics on the risk of coma or death within 24 hours of surgery.[63] Reversal of the effects of NMBDs was associated with a significant reduction (odds ratio, 0.10, 95% CI, 0.03-0.31) in the risk of these complications. Epidemiologic studies thus suggest an association between incomplete neuromuscular recovery and adverse events in the early postoperative period. Notably, an important limitation of these outcome studies is that residual paresis was not quantified at the end of surgery. Therefore, causality (residual blockade results in postoperative complications) can only be suggested but not proven.

In order to address these limitations, more recent studies have quantified TOF ratios in the PACU and documented a relationship between residual blockade and adverse outcomes. Several clinical investigations have documented an association between postoperative residual blockade and adverse respiratory events. In an observational study by Bissinger and colleagues, patients with TOF ratios less than 0.70 in the PACU had a more frequent incidence of hypoxemia (60%) compared with patients with TOF ratios 0.70 or greater (10%, $P < .05$).[64] Another small study of orthopedic surgical patients randomized to receive either pancuronium or rocuronium revealed that patients with TOF ratios less than 0.90 on arrival to the PACU were more likely to develop postoperative hypoxemia (24 of 39 patients) than those with TOF ratios greater than 0.90 (7 of 30 patients, $P = .003$).[65] Murphy and associates conducted a case-control study examining the incidence and severity of residual blockade in patients who developed critical respiratory events in the PACU.[38] Seventy-four percent of patients in the group with critical respiratory events had TOF ratios less than 0.70, compared with 0% in the matched control group (matched for age, sex, and surgical procedure). Because the two cohorts did not differ in any perioperative characteristics with the exception of neuromuscular recovery, these findings suggest that unrecognized residual paralysis is an important contributing factor to postoperative adverse respiratory events. Another investigation by this same group examined the effect of AMG monitoring on postoperative respiratory events.[26] Few patients randomized to AMG monitoring had postoperative TOF ratios less than 0.90, and a less frequent incidence of early hypoxemia and airway obstruction was observed in this group (compared with patients randomized to standard qualitative monitoring). A study of 114 patients randomized to neostigmine reversal or placebo (saline) documented a significantly more frequent incidence of both postoperative residual blockade and hypoxemia in the placebo group.[66] Residual blockade in the PACU may also result in pulmonary complications within the first postoperative week. Berg and colleagues randomized 691 patients to receive pancuronium, atracurium, or vecuronium.[67] TOF ratios were quantified in the PACU, and subjects followed for 6 days for pulmonary complications. In the pancuronium group, significantly more patients with TOF ratios less than 0.70 developed a pulmonary complication (16.9%) compared with patients with TOF 0.70 or greater (4.8%). Notably, the study also demonstrated a continuously increased risk for postoperative pulmonary complications with increased age, a finding of significant clinical relevance for older adult patients, a growing part of the surgical patient population.

Residual blockade causes unpleasant symptoms of muscle weakness. This symptom of "general weakness" was the most sensitive "test" for determining whether patients had a TOF ratio of less than 0.90 in the PACU.[17] Orthopedic surgical patients given pancuronium had a more frequent risk of exhibiting both TOF ratios less than 0.90 and symptoms of blurry vision and general weakness during the PACU admission, compared with patients randomized to receive rocuronium.[65] Similar findings were observed in a cardiac surgical patient population not receiving anticholinesterase drugs.[68] The subjective experience of residual neuromuscular blockade after surgery was determined by examining 155 patients for 16 symptoms of muscle weakness during the PACU admission.[27] The presence of symptoms of muscle weakness was predictive of a TOF ratio less than 0.90 (good sensitivity and specificity).

The residual effects of NMBDs on postoperative muscle strength may impair clinical recovery and prolong PACU discharge times. In a small study of patients randomized to receive either pancuronium or rocuronium, the times required to meet and achieve discharge criteria were significantly longer in the pancuronium group, and patients in the cohort as a whole with postoperative TOF ratios less than 0.90 were more likely to have a prolonged PACU stay compared with those with TOF ratios greater than 0.90.[65] A larger investigation measured TOF ratios in 246 consecutive patients on arrival to the PACU.[39] The PACU length of stay was significantly longer in patients with TOF ratios less than 0.90 (323 minutes) compared with patients with adequate recovery of neuromuscular function (243 minutes). Multiple regression analysis revealed that only age and residual blockade were independently associated with PACU length of stay.

In conclusion, a number of studies conducted over the past 5 decades have documented the effects of small degrees of residual blockade in human volunteers and surgical patients. Awake volunteer investigations have demonstrated that subjects with TOF ratios less than 0.90 have reduced upper airway tone and diameters, upper airway obstruction, pharyngeal dysfunction with impaired airway integrity, decreased upper esophageal tone, and an increased risk of aspiration, impaired hypoxic ventilatory control, and unpleasant symptoms of muscle weakness. Epidemiologic outcome investigations have suggested an association between incomplete neuromuscular recovery and major morbidity and mortality. Prospective clinical

trials have revealed that patients with TOF ratios less than 0.90 in the PACU are at increased risk for hypoxemic events, airway obstruction, postoperative pulmonary complications, symptoms of muscle weakness, and prolonged PACU admission times. These data suggest that residual blockade is an important patient safety issue in the early postoperative period. Therefore, appropriate management of reversal of neuromuscular blockade is essential to optimize patient outcomes.

DRUGS USED TO ANTAGONIZE (REVERSE) NEUROMUSCULAR BLOCKADE

Reversal of neuromuscular blockade is theoretically possible by three principal mechanisms: (1) an increase in presynaptic release of acetylcholine; (2) a decrease in enzymatic metabolism of acetylcholine by cholinesterase, thereby increasing receptor binding competition; and (3) a decrease in the concentration of the NMBD at the effect-site, freeing the postsynaptic receptors.

ANTICHOLINESTERASE REVERSAL OF NEUROMUSCULAR BLOCK ADE

Nondepolarizing NMBDs inhibit neuromuscular transmission primarily by competitively antagonizing or blocking the effect of acetylcholine at the postjunctional nicotinic acetylcholine receptor (nAChR). Binding of nondepolarizing NMBDs to the nAChR occurs in a competitive fashion. If larger concentrations of acetylcholine are present at the neuromuscular junction, acetylcholine will attach to the postsynaptic receptor and facilitate neuromuscular transmission and muscle contraction. Conversely, if larger concentrations of a nondepolarizing NMBD are present at the neuromuscular junction, binding to α subunits of the receptor will preferentially occur, preventing central pore opening and muscle depolarization from occurring. A more detailed description of the neuromuscular junction is provided in Chapter 18.

One mechanism of reversing the effects of NMBDs is by an increase in the concentration of acetylcholine at the neuromuscular junction. This can be accomplished using an inhibitor of cholinesterase, which constrains the enzyme that breaks down acetylcholine at the neuromuscular junction (acetylcholinesterase). Three anticholinesterase drugs are commonly used in clinical practice: neostigmine, edrophonium, and pyridostigmine. Neostigmine is likely the most commonly administered drug. Over the prior 6 decades, anticholinesterases have been the only drugs used clinically to reverse neuromuscular blockade (until the recent introduction of sugammadex).

Mechanism of Action of Anticholinesterases

Acetylcholine is the primary neurotransmitter that is synthesized, stored, and released by exocytosis at the distal motor nerve terminal. Acetylcholinesterase is the enzyme responsible for the control of neurotransmission at the neuromuscular junction by hydrolyzing acetylcholine. Rapid hydrolysis of acetylcholine removes excess neurotransmitter from the synapse, preventing overstimulation and tetanic excitation of the postsynaptic muscle. Nearly half

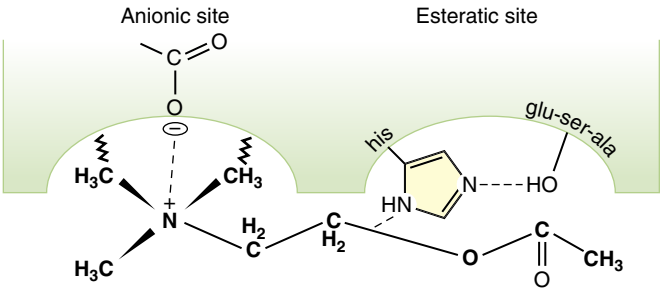


Figure 35-7. Active binding sites on acetylcholinesterase. The positively charged quaternary nitrogen group on acetylcholine (Ach) binds by electrostatic forces to the negatively charged anionic site on the enzyme. The carbamate group at the opposite end of the Ach molecule forms covalent bonds with and is metabolized at the esteratic site. *(From Caldwell JE: Clinical limitations of acetylcholinesterase antagonists,* J Crit Care, *24:21-28, 2009.)*

of the acetylcholine molecules released from the presynaptic nerve membrane are hydrolyzed by acetylcholinesterase before reaching the nAChR.[69] The action of acetylcholinesterase is quite rapid; acetylcholine molecules are hydrolyzed in approximately 80 to 100 μs (microseconds). Acetylcholinesterase is concentrated at the neuromuscular junction, and there are approximately 10 enzyme-binding sites for each molecule of acetylcholine released.[70] However, lower concentrations of acetylcholinesterase are present along the length of the muscle fiber. Each molecule of acetylcholinesterase has an active surface with two important binding sites, an anionic site and an esteratic site. The negatively charged anionic site on the acetylcholinesterase molecule is responsible for electrostatically binding the positively charged quaternary nitrogen group on the acetylcholine molecule. The esteratic site forms covalent bonds with the carbamate group at the opposite end of the acetylcholine molecule and is responsible for the hydrolytic process[70] (Fig. 35-7). In addition, a secondary or peripheral anionic site has been proposed. Binding of ligands to the peripheral anionic site results in inactivation of the enzyme.

The anticholinesterase drugs used by anesthesiologists interact with the anionic and esteratic sites of acetylcholinesterase. These drugs are characterized as either prosthetic inhibitors (edrophonium) or oxydiaphoretic (acid-transferring) inhibitors (neostigmine, pyridostigmine) of the enzyme. Edrophonium rapidly binds to the anionic site via electrostatic forces and to the esteratic site by hydrogen bonding.[69,70] Rapid binding may account for the short onset of action of edrophonium in clinical practice. During the time edrophonium is bound, the enzyme is inactive and edrophonium is not metabolized. However, the interaction between edrophonium and acetylcholinesterase is weak and short-lived. The dissociation half-life of this interaction is approximately 20 to 30 seconds, and the interaction between drug and enzyme is competitive and reversible. Because the nature of the binding is relatively brief, the efficacy of edrophonium in reversing neuromuscular blockade may be limited. Neostigmine and pyridostigmine are oxydiaphoretic inhibitors of acetylcholinesterase, which also bind to the anionic site. In addition, these drugs transfer a carbamate group to acetylcholinesterase, creating a covalent bond at the esteratic site.[69,70] This reaction results in an inactivation of the enzyme, as

well as the hydrolysis of the drug. The stronger interaction between neostigmine and enzyme results in dissociation half-life of approximately 7 minutes.[70] Therefore, the duration of enzyme inhibition is longer with neostigmine and pyridostigmine compared with edrophonium. These interactions at the molecular level likely have little impact on the duration of action in clinical practice. Duration of clinical effect is primarily determined by removal of anticholinesterase from the plasma.[71]

The administration of anticholinesterases has also been reported to produce presynaptic effects.[71] Laboratory investigations have demonstrated that these prejunctional effects may actually facilitate neuromuscular transmission. Anticholinesterases produce a reversible increase in the duration of the action potential and refractory period of the nerve terminal. Because the quantity of acetylcholine released is a function of the extent and duration of the depolarization of the terminal membrane, the period of acetylcholine release in response to nerve stimulation may be increased by anticholinesterase agents.[71] Excessive release of acetylcholine, coupled with decreased hydrolysis due to acetylcholinesterase inhibition, results in prolonged end-plate potentials and repetitive firing of muscle fibers. These prejunctional effects appear to account for the observations that spontaneous contractions of muscles can occur when anticholinesterases are given in the absence of NMBDs.[71]

Although neostigmine, pyridostigmine, and edrophonium inhibit the breakdown of acetylcholine, resulting in an increase in acetylcholine in the neuromuscular junction, there is a clinically relevant "ceiling" effect to the maximal concentration of acetylcholine. As concentrations of acetylcholine increase, some of the neurotransmitter diffuses away from the neuromuscular junction, while additional acetylcholine undergoes reuptake into motor nerve terminals. As the processes of diffusion and reuptake reach equilibrium with augmented release by enzyme inhibition, a "peak" level at the neuromuscular junction is reached.[70] Once the acetylcholinesterase enzyme is maximally inhibited by an anticholinesterase agent and peak concentrations of acetylcholine are present, the administration of additional drug will not further increase acetylcholine levels or enhance recovery of neuromuscular blockade. This "ceiling" effect of anticholinesterases is an important limitation of all clinically used agents; neuromuscular blockade cannot be adequately reversed if high concentrations of NMBDs are present at the neuromuscular junction.

Pharmacokinetic and Pharmacodynamic Properties of Anticholinesterases

A large number of clinical studies have examined the pharmacokinetic and pharmacodynamic characteristics of neostigmine, pyridostigmine, and edrophonium. Neostigmine has been the most extensively investigated anticholinesterase agent over the past 5 decades. The favorable pharmacokinetic profile of neostigmine likely explains its popularity in clinical practice as a reversal drug.

The pharmacokinetic profiles of neostigmine, pyridostigmine, and edrophonium are presented in Table 35-3. Most studies have used a two-compartment model to establish pharmacokinetic characteristics of each agent. Following a bolus administration, plasma concentrations peak rapidly and decline significantly within the first 5 to 10 minutes. This is followed by a slower decline in plasma concentrations due to the elimination phase.[71] In general, the pharmacokinetic profiles of all three muscle relaxants are similar. Early studies suggested that the duration of edrophonium was too short for clinical use. However, studies using larger doses (0.5 or 1.0 mg/kg) demonstrated that the elimination half-life of edrophonium was not significantly different from that of neostigmine or pyridostigmine and that edrophonium could produce prompt and sustained reversal of neuromuscular blockade.[72,73] The longer elimination half-life of pyridostigmine likely accounts for the longer duration of action compared with the other anticholinesterase drugs.[74]

TABLE 35-3 PHARMACOKINETICS OF NEOSTIGMINE, PYRIDOSTIGMINE, AND EDROPHONIUM IN PATIENTS WITHOUT AND WITH RENAL FAILURE

	Without Renal Failure			With Renal Failure		
	N	P	E	N	P	E
Distribution half-life ($T_{1/2\alpha}$, min)	3.4	6.7	7.2	2.5	3.9	7.0
Elimination half-life ($T_{1/2\beta}$, min)	77	113	110	181	379	304
Volume of central compartment (L/kg)	0.2	0.3	0.3	0.3	0.4	0.3
Total plasma clearance (mL/kg/min)	9.1	8.6	9.5	4.8	3.1	3.9

From Naguib M, Lien CA: Pharmacology of muscle relaxants and their antagonists. In Miller RD, editor: Miller's Anesthesia, *ed 7. Philadelphia, 2010, Saunders.*
Data from references 73-76.

The pharmacokinetics of anticholinesterases can be influenced by renal function, age, and body temperature. The elimination half-lives of all three agents are altered by the presence of renal insufficiency or failure (see Table 35-3). Renal excretion accounts for approximately 50% of plasma clearance of neostigmine; elimination half-life is significantly prolonged and serum clearance decreased in anephric patients.[75] Similarly, renal function accounts for 70% to 75% of serum clearance of pyridostigmine and edrophonium.[74,76] The reduced plasma clearance of the anticholinesterases in renal failure patients provides a "margin of safety" against the risk of postoperative "recurarization" (the effects of the NMBD persist longer than that of the reversal agent, resulting in a worsening of residual paresis). The pharmacokinetics of edrophonium have been examined in older adult (age >70 years) patients. When compared with a younger cohort, older adult patients exhibited a significant decrease in plasma clearance (5.9 ± 2 versus 12.1 ± 4 mL· kg^{-1}· min^{-1}) and a prolonged elimination half-life (84.2 ± 17 versus 56.6 ± 16 minutes).[77] Mild hypothermia (reduction in core

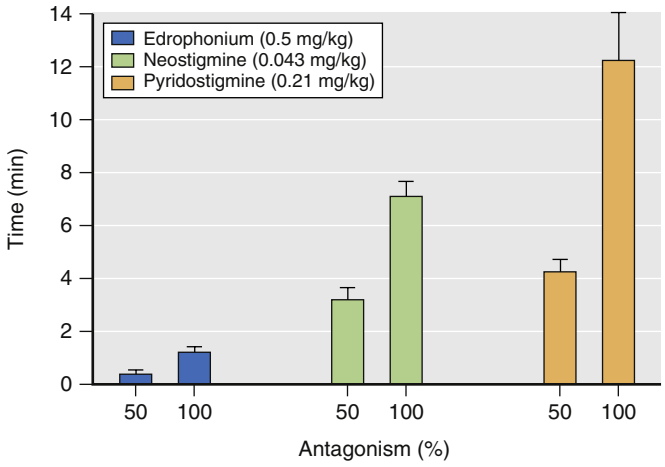


Figure 35-8. Comparison of onset of action for edrophonium, neostigmine, and pyridostigmine. Values plotted are means ± SE. Edrophonium's onset was significantly faster than neostigmine or pyridostigmine. *(From Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia,* Anesthesiology *57:261-266, 1982.)*

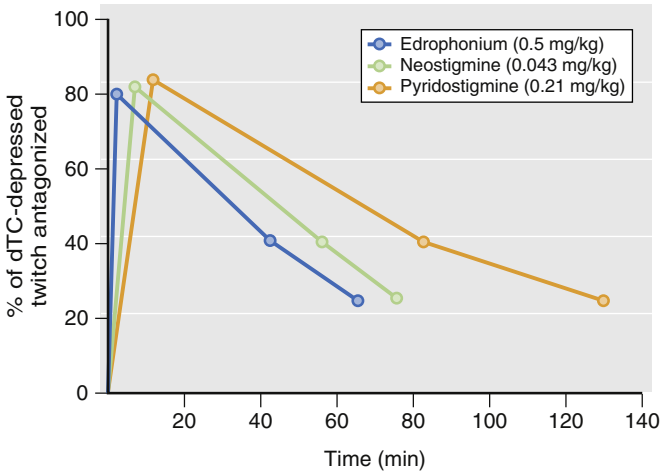


Figure 35-9. Duration of antagonism compared at equipotent doses of neostigmine, pyridostigmine, and edrophonium. Values plotted are means. Edrophonium did not differ from neostigmine in duration, however, both were shorter than pyridostigmine. *(From Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia,* Anesthesiology *57:261-266, 1982).*

temperature of 2° C) more than doubles the duration of action of intermediate-acting NMBDs.[78] In a study of human volunteers cooled to 34.5° C, the central volume of distribution of neostigmine decreased 38% and the onset time of maximal blockade increased from 4.6 to 5.6 minutes.[79] However, the clearance, maximal effect, and duration of action of neostigmine were not altered by a reduction in body temperature. Therefore, if hypothermia influences the degree of neuromuscular recovery, it is likely secondary to an effect on the pharmacology of NMBDs (not the anticholinesterase).

Onset of action may be more rapid with edrophonium than with either neostigmine or pyridostigmine. When *d*-tubocurarine neuromuscular blockade was reversed with approximately equipotent doses of the three clinically used anticholinesterases, the peak effect of antagonism was reached significantly faster with edrophonium (0.8 to 2.0 minutes) than with neostigmine (7 to 11 minutes) or pyridostigmine (12 to 16 minutes)[72] (Fig. 35-8). Similar findings have been observed in patients receiving other long- and intermediate-acting NMBDs. When larger doses (0.5 to 1.0 mg/kg) of edrophonium are administered during moderate levels of neuromuscular blockade (10% recovery of single-twitch height after pancuronium or atracurium), the onset time of edrophonium was faster than neostigmine.[80,81] During deeper levels of blockade (<10% recovery of single twitch), edrophonium 1.0 mg/kg and neostigmine 0.04 mg/kg had similar onset times when vecuronium was used (and both were faster than edrophonium 0.5 mg/kg).[82] When pancuronium was antagonized during deep blockade, edrophonium 1.0 mg/kg had a shorter onset time than neostigmine 0.04 mg/kg.[82] These findings suggest that onset time of antagonism is influenced by the type and dose of anticholinesterase used, the choice of NMBD administered intraoperatively, and the depth of neuromuscular blockade at the time of antagonism.

The duration of action of anticholinesterases is determined not only by the pharmacokinetic properties of the drugs, but also by the concentration of NMBD present at the neuromuscular junction at the time of reversal. Duration of neuromuscular blockade will naturally decrease over time as a result of metabolism and elimination of NMBDs. To accurately assess the duration of action of anticholinesterases during a stable, constant level of neuromuscular blockade, investigators have administered these agents to patients receiving an infusion of *d*-tubocurarine titrated to a 90% depression of single-twitch height.[72] The investigators observed that the duration of action of equipotent doses of neostigmine (0.043 mg/kg) and edrophonium (0.5 mg/kg) were similar (Fig. 35-9). The duration of both drugs, however, was significantly less than with pyridostigmine (0.21 mg/kg).

The comparative potencies of clinically used anticholinesterases have been calculated by constructing dose-response curves. In general, neostigmine is more potent than pyridostigmine, which is more potent than edrophonium. Neostigmine-to-pyridostigmine potency ratios of 4.4 to 6.7 have been reported (neostigmine is 4.4 to 6.7 times more potent than pyridostigmine).[72,83] Neostigmine is even more potent than edrophonium, with potency ratios of 5.7 to 19.5 estimated from dose-response curves.[72,83,84] The great variability in potency ratios described in the literature is related to several factors, which include the type of NMBD used in the studies, the endpoint selected to represent neuromuscular recovery, and the depth of blockade at the time of anticholinesterase administration.

In conclusion, pharmacokinetic and pharmacodynamic studies suggest that neostigmine, pyridostigmine, and edrophonium are all effective in reversing neuromuscular blockade when used in appropriate and equipotent doses. The following section will review factors that determine the efficacy of these agents in reversing neuromuscular blockade in the clinical setting.

Factors Determining the Adequacy of Recovery Following Administration of Anticholinesterases

Depth of Neuromuscular Blockade or Train-of-Four Count at the Time of Reversal. The primary anesthetic management variable determining the effectiveness of anticholinesterase agents in completely antagonizing neuromuscular blockade at the end of surgery is the depth of neuromuscular blockade at the time of reversal. As opposed to sugammadex (see later in this chapter), reversal of blockade by anticholinesterases should not be attempted until some evidence of spontaneous recovery is present. Kirkegaard-Nielsen and associates examined the optimal time for neostigmine reversal of an atracurium blockade.[85] Administration of neostigmine 0.07 mg/kg during deep blockade (before the first twitch height reached 8%) resulted in significant prolongation of reversal times. In a similar investigation, atracurium was antagonized with neostigmine during intense blockade (posttetanic count [PTC] of 1 to >13).[86] Early administration of neostigmine did not shorten total recovery time and offered no clinical advantages. Similar findings have been observed during reversal of deep vecuronium blockade.[87] The total time to achieve a TOF ratio of 0.75 was the same whether neostigmine (0.07 mg/kg) was given 15 minutes after an intubating dose of vecuronium or whether single-twitch height had recovered to 10% of control.

The time required to achieve a TOF ratio of 0.90 after anticholinesterase administration is significantly shorter when a higher TOF count is present at reversal. Two studies have examined the efficacy of antagonizing residual blockade at varying TOF counts. Kirkegaard and colleagues randomized patients receiving cisatracurium to reversal with neostigmine (0.07 mg/kg) at the reappearance of the first, second, third, and fourth tactile TOF response (TOF count 1-4).[88] The median (range) time required to achieve a TOF ratio of 0.90 was 22.2 (13.9 to 44.0) minutes when reversal was attempted at a TOF count of 1. However, even when four responses were present, the time needed to attain a TOF ratio of 0.90 was 16.5 (6.5 to 143.3) minutes (Table 35-4). Kim and associates performed a similar study in which patients administered rocuronium were randomized to be reversed at the first through fourth tactile TOF responses.[89] In those patients receiving sevoflurane for anesthetic maintenance, the median (range) time required to achieve a TOF ratio of 0.90 was 28.6 (8.8 to 75.8) minutes when reversed at a TOF count of 1 and 9.7 (5.1 to 26.4) minutes when reversed at a TOF count of 4. In both investigations, a large interindividual variability in reversal times was observed.[88,89] This is likely a reflection of the individual response to the NMBD administered. The reason for marked prolongation of reversal times in some patients (up to 143 minutes) was not determined, but may be due to the "ceiling effect" with respect to the blockade (peak effect of the antagonist is followed by a plateau phase in which the balance between diminishing anticholinesterase activity and spontaneous recovery determines the slope of the recovery curve).[88] Both studies demonstrated that it was not possible to reliably achieve full neuromuscular recovery (TOF ratio of >0.90) in the majority of patients within 10 minutes of anticholinesterase administration.

TABLE 35-4 TIME (MIN) FROM NEOSTIGMINE ADMINISTRATION TO A TOF RATIO 0.70, 0.80, AND 0.90 WHEN GIVEN AT A TOF COUNT OF 1-4

	Group*			
TOF Ratio	I	II	III	IV
0.70				
Median	10.3†	7.6‡	5.0	4.1
Range	5.9-23.4	3.2-14.1	2.0-18.4	2.4-11.0
0.80				
Median	16.6†	9.8‡	8.3	7.5
Range	8.9-30.7	5.3-25.0	3.8-27.1	3.0-74.5
0.90				
Median	22.2	20.2	17.1	16.5
Range	13.9-44.0	6.5-70.5	8.3-46.2	6.5-143.3

From Kirkegaard H, Heier T, Caldwell JE: Efficacy of tactile-guided reversal from cisatracurium-induced neuromuscular block, Anesthesiology *96:45-50, 2002.*

TOF, Train-of-four.

*Group I was reversed at a TOF count of 1, group II was reversed at a TOF count of 2, group III was reversed at a TOF count of 3, and group IV was reversed at a TOF count of 4.

†$P < .05$, group I > group II, III, and IV.

‡$P < .05$, group II > group IV.

Time Interval Between Anticholinesterase Administration and Tracheal Extubation. As noted in the studies by Kirkegaard and Kim, if four responses to TOF nerve stimulation are present, approximately 15 minutes are needed to reach a TOF ratio of 0.90 in most patients.[88,89] Achieving a TOF ratio of 0.90 will require significantly longer (20 to 30 minutes) if a TOF count of 1 to 3 is observed at the time of reversal. In order to ensure patient safety, full recovery of neuromuscular function should be present at the time of tracheal extubation. Therefore, anticholinesterase drugs should be given, on average, 15 to 30 minutes before clinicians anticipate removal of the endotracheal tube in the operating room. In many clinical situations, however, anticholinesterases are often administered at the conclusion of surgical closure, with tracheal extubation performed shortly thereafter. A survey of anesthesiologists from Europe and the United States revealed that approximately one half of respondents allowed only 5 minutes or less between anticholinesterase administration and tracheal extubation.[11] In a study of 120 surgical patients, TOF ratios were quantified at the time of tracheal extubation when clinicians had determined that full recovery of neuromuscular function had occurred using clinical criteria and qualitative neuromuscular monitoring (Fig. 35-10).[49] Mean TOF ratios of 0.67 were observed immediately before extubation, with 88% of patients exhibiting TOF less than 0.90. Of note, the median TOF count at reversal was 4, and the average time interval between neostigmine administration and tracheal extubation was only 8 minutes. The frequent incidence of residual blockade reported in multiple studies is likely attributable to the fact that anticholinesterases are not given early enough during the intraoperative anesthetic to ensure full neuromuscular recovery.

Type of NMBD Used Intraoperatively (Long-Acting Versus Intermediate-Acting). Two separate processes

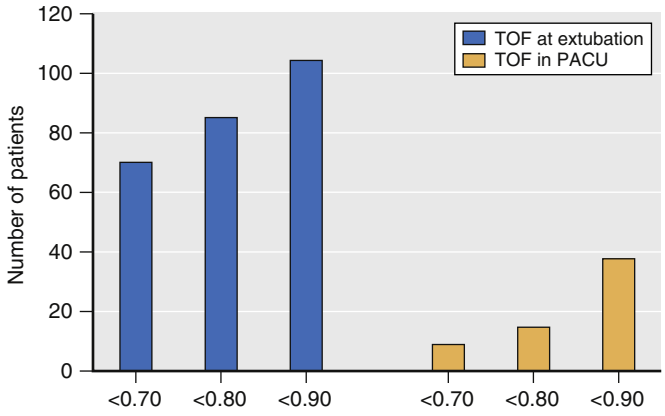


Figure 35-10. Train-of-four (TOF) ratios measured immediately before tracheal extubation and again on admission to the postanesthesia care unit (PACU). The graphs illustrate the number of patients (of a total of 120) with TOF ratios <0.70, 0.80, and 0.90 at each measurement interval. *(From Murphy GS, Szokol JW, et al: Residual paralysis at the time of tracheal extubation.* Anesth Analg *100:1840-1845, 2005.)*

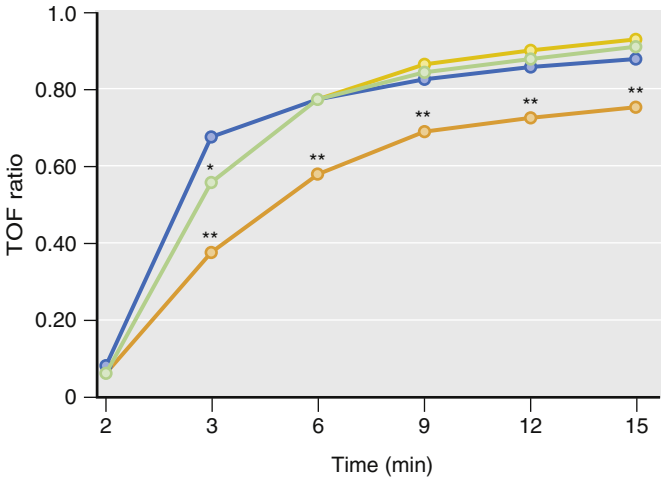


Figure 35-11. Evolution of the train-of-four (TOF) ratio (mean) recorded at 3-minute intervals after administration of neostigmine 40 μg kg^{-1} when twitch height had returned to 25% of its initial value in groups of Roc (*green*), Vec (*blue*), Atr (*yellow*) and Pan (*orange*). *$P < .05$, one-way analysis of variance and Duncan multiple classification range tests (group Vec versus groups Roc and Atr). **$P < .01$, one-way analysis of variance and Duncan multiple classification range tests (group Pan versus groups Vec, Roc, Atr). *(From Baurain MJ, Hoton F, D'Hollander AA, et al: Is recovery of neuromuscular transmission complete after the use of neostigmine to antagonize block produced by rocuronium, vecuronium, atracurium and pancuronium?* Br J Anaesth *77: 496-499, 1996.)*

contribute to recovery of neuromuscular function following anticholinesterase administration. The first is the inhibition of acetylcholinesterase at the neuromuscular junction produced by neostigmine, pyridostigmine, or edrophonium. The second is the spontaneous process of decrease in the concentration of the NMBD at the neuromuscular junction over time due to redistribution and elimination. Therefore, NMBDs that are redistributed and eliminated more rapidly from the plasma should be associated with more rapid recovery profiles after anticholinesterase use. Not surprisingly, the probability of satisfactorily antagonizing neuromuscular blockade is a function of the NMBD used to provide muscle relaxation. The ability of edrophonium (0.75 mg/kg) and neostigmine (0.05 mg/kg) to antagonize neuromuscular blockade produced by atracurium, vecuronium, and pancuronium following termination of steady-state infusions (single-twitch depression 10% of control) has been examined.[90] TOF ratios 20 minutes postreversal were 0.80 and 0.95 (atracurium with edrophonium or neostigmine), 0.76 and 0.89 (vecuronium with edrophonium or neostigmine), and 0.44 and 0.68 (pancuronium with edrophonium or neostigmine). Another clinical study investigated recovery of neuromuscular function in patients randomized to receive either intermediate-acting (rocuronium, vecuronium, atracurium) or long-acting (pancuronium) NMBDs.[91] Neostigmine (0.04 mg/kg) was given at 25% recovery of control twitch height, and TOF ratios were measured for 15 minutes. Mean TOF ratios had recovered to 0.88 to 0.92 in patients receiving intermediate-acting NMBDs, versus only 0.76 in the pancuronium group (Fig. 35-11).

A number of clinical investigations have examined the incidence of residual blockade in the PACU in patients receiving either intermediate- or long-acting NMBDs. These studies have consistently demonstrated that fewer patients given intermediate-acting NMBD have residual blockade compared with those receiving long-acting agents. A meta-analysis of 24 clinical trials examined the pooled estimated incidence of residual blockade (defined as a TOF ratio <0.90) by muscle relaxant type.[44] The risk of residual blockade was significantly less in patients given intermediate-acting NMBDs (41%) versus long-acting NMBDs (72%). In conclusion, the probability of incomplete neuromuscular recovery in the early postoperative period is decreased when shorter-acting NMBDs are used intraoperatively.

Type and Dose of Anticholinesterase. Complete recovery of neuromuscular function within 10 to 15 minutes with neostigmine, edrophonium, or pyridostigmine is difficult to achieve when profound neuromuscular blockade is present. Some investigations have suggested that edrophonium is less effective than neostigmine when reversing deep blockade; this may occur because the slopes of the dose-response relationships of neostigmine and edrophonium are not parallel (flatter dose-response curves are observed with edrophonium; Fig. 35-12).[82,84] In contrast, the recovery profile of edrophonium with larger doses (approximately 1.0 mg/kg) does not differ from neostigmine and pyridostigmine, and edrophonium can produce rapid and sustained reversal of neuromuscular blockade.[80,82] At moderate levels of neuromuscular blockade all three agents appear to be similarly effective in reversing blockade, although the onset of edrophonium may occur more quickly.

In general, larger doses of anticholinesterases result in more rapid and complete reversal of neuromuscular blockade than smaller doses. This relationship remains true until the maximal dose of anticholinesterase has been administered. At this point, acetylcholinesterase is maximally inhibited, and additional amounts of anticholinesterase will result in no further antagonism. Maximal effective doses of neostigmine and edrophonium have not been clearly defined, but likely vary in relation to depth of blockade and type of NMBD used

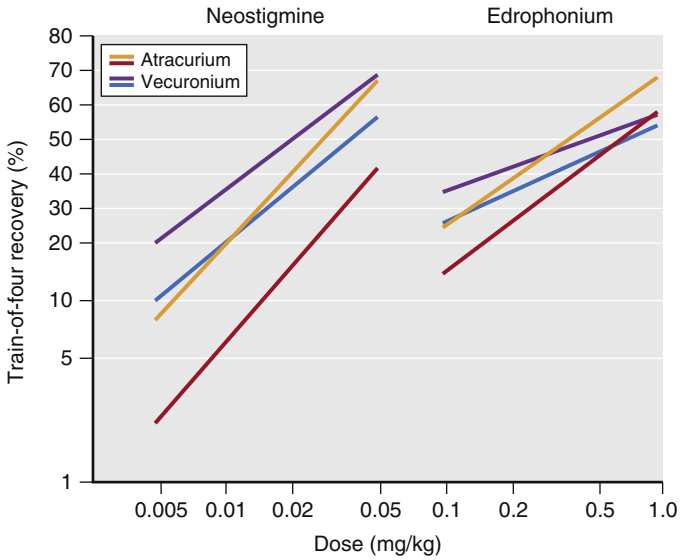


Figure 35-12. Dose-response relationships of train-of-four assisted recovery evaluated 5 minutes *(blue lines)* or 10 minutes *(purple lines)* after administration of the antagonist as a function of the dose of neostigmine or edrophonium. The slopes of the curves obtained with edrophonium were usually flatter than the corresponding curves for neostigmine. *(From Smith CE, Donati F, Bevan DR: Dose-response relationships for edrophonium and neostigmine as antagonists of atracurium and vecuronium neuromuscular blockade,* Anesthesiology *71: 37-43, 1989).*

intraoperatively. Providing additional anticholinesterase beyond these maximum dose limits (neostigmine 60 to 80 μg/kg, edrophonium 1.0 to 1.5 mg/kg) provides no further benefit. When administered during deep neuromuscular blockade, a second dose of neostigmine (70 μg/kg) usually does not enhance recovery times beyond that observed with a single dose.[87]

Age

Infants and Children. The dose of neostigmine producing 50% antagonism of a *d*-tubocurarine neuromuscular blockade was slightly smaller in infants (13 μg/kg) and children (15 μg/kg) compared with adults (23 μg/kg) (also see Chapter 93).[92] The times to peak antagonism and duration of antagonism did not differ between infants, children, and adults. Pharmacokinetic modeling revealed that distribution half-lives and volumes were similar in all three cohorts, although elimination half-life was shorter in infants and children than adults. As in adults, the depth of neuromuscular blockade at the time of antagonism was a primary factor determining adequacy of recovery.[93,94] Spontaneous recovery from neuromuscular blockade is more rapid in children compared with adults.[94] However, when neostigmine was administered at various levels of blockade, the times to achieve neuromuscular recovery were similar in children and adults (the times to reach a TOF ratio of 0.90 were reduced by 30% to 40% compared with spontaneous recovery).[94] Thus, in the clinical setting, reversal of neuromuscular blockade does not appear to differ significantly between children and adults.

Older Adults. Physiologic changes occur during the aging process that result in alterations in the response of older patients to NMBDs (also see Chapter 80). These changes include an increase in body fat, a decrease in total body water, and declines in cardiac, hepatic, and renal function. In addition, anatomic alterations occur at the neuromuscular junction in older adults, such as a decrease in the concentration of nAChRs at the motor endplate and a reduction in the release of acetylcholine from the preterminal axon. All of these factors contribute to a prolongation of effect of most NMBDs in older patients (see also Chapter 34). In a study comparing older adults (age >70) to younger controls, plasma clearance of edrophonium was decreased and elimination half-life prolonged in the aged cohort.[77] Despite higher plasma concentrations of edrophonium, however, duration of antagonism was not increased. In contrast, Young and colleagues observed that the duration of action of both neostigmine and pyridostigmine was significantly longer in older adults (age >60) compared with younger subjects.[95] These findings suggest that plasma concentrations and/or duration of action of both NMBDs and anticholinesterases (neostigmine and pyridostigmine) are prolonged in older patients, which should reduce the risk of recurarization. Whether older patients who have received anticholinesterases are at greater risk for residual blockade in the PACU is not documented.

Type of Anesthesia

Volatile anesthetics intensify the action of nondepolarizing NMBDs when compared with intravenous anesthetics. Furthermore, volatile anesthetics interfere with the antagonism of neuromuscular blockade.[96] Kim and colleagues randomized patients to receive a propofol or sevoflurane anesthetic (Table 35-5).[89] The times required to achieve a TOF ratio of 0.70, 0.80, and 0.90 were significantly longer in patients given the sevoflurane-based anesthetic compared with the propofol-based technique. Similar findings have been observed in patients randomized to receive either isoflurane or propofol (neuromuscular recovery was delayed when a volatile anesthetic was used).[96,97] These findings suggest that the probability of achieving a TOF ratio greater than 0.90 within 10 to 15 minutes of anticholinesterase administration is increased if a total intravenous anesthetic technique is administered as opposed to a volatile anesthetic.

Continuous Infusion Versus Bolus Administration of NMBDs. Recovery from neuromuscular blockade may also be influenced by mode of NMBD administration. Jellish and colleagues examined recovery characteristics of rocuronium and cisatracurium when given as either a bolus or continuous infusion.[97] The time required to reach a TOF ratio of 0.75 in the cisatracurium group was similar whether bolus or infusion techniques were used, whereas recovery was delayed when rocuronium was given as an infusion.[97] The authors conclude that cisatracurium may be the agent of choice for prolonged procedures since its recovery is not affected by length of infusion.

Renal Function. As previously noted, renal excretion accounts for 50% to 75% of plasma clearance of neostigmine, pyridostigmine, and edrophonium. In anephric patients, elimination half-life of all three anticholinesterases is prolonged, and total plasma clearance of these agents is decreased (see Table 35-3). Similar changes in the pharmacokinetics characteristics of nondepolarizing NMBDs have been noted in patients with renal failure. Therefore, management of anticholinesterase reversal should be similar in patients with normal and impaired renal function. Postoperative residual neuromuscular

TABLE 35-5 TIME (MIN) FROM NEOSTIGMINE ADMINISTRATION TO A TOF RATIO OF 0.70, 0.80, AND 0.90 DURING PROPOFOL- OR SEVOFLURANE-BASED ANESTHESIA

	Group*			
TOF ratio	**I**	**II**	**III**	**IV**
Propofol				
0.70	4.7 (2.5-7.8)†	4.0 (1.5-7.5)	3.4 (0.9-5.5)	2.1 (0.6-3.8)‡§
0.80	6.4 (3.1-10.8)	5.5 (2.2-9.3)	4.4 (0.9-7.1)‡	3.3 (0.7-4.9)‡§
0.90	8.6 (4.7-18.9)	7.5 (3.4-11.2)	5.4 (1.6-8.6)‡	4.7 (1.3-7.2)‡§
Sevoflurane				
0.70	10.9 (3.6-28.9)¶	8.3 (2.5-22.3)¶	6.6 (2.4-18.5)‡¶	5.4 (2.2-14.3)‡§¶
0.80	16.4 (5.9-47.5)¶	13.5 (5.1-37.2)¶	10.8 (4.2-29.2)‡¶	7.8 (3.5-19.3)‡§¶
0.90	28.6 (8.8-75.8)¶	22.6 (8.3-57.4)¶	15.6 (7.3-43.9)‡¶	9.7 (5.1-26.4)‡§¶

From Kim KS, Cheong MA, Lee HJ, Lee JM: Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or sevoflurane anesthesia, Anesth Analg *99:1080-1085, 2004.*

TOF, Train-of-four.

*Group I was reversed at a TOF count of 1, group II was reversed at a TOF count of 2, group III was reversed at a TOF count of 3, and group IV was reversed at a TOF count of 4.

†Values are median and (range).

‡$P < .05$ compared with group I.

§$P < .05$ compared with group II.

¶$P < .0001$ compared with propofol groups.

blockade in patients with renal failure is more likely secondary to improper titration of NMBDs intraoperatively rather than to inappropriate dosing of anticholinesterase agents.

Acid-Base Status. The influence of metabolic status and respiratory acid-base balance on reversal of neuromuscular blockade has been investigated in the laboratory setting. Miller and associates noted that respiratory alkalosis and metabolic acidosis did not alter the dose of neostigmine needed to reverse a *d*-tubocurarine or pancuronium blockade. However, during respiratory acidosis and metabolic alkalosis, the dose of neostigmine needed to produce a comparable level of neuromuscular recovery was nearly twice as large.[98,99] Although clinical studies have not been performed, the findings from laboratory investigations suggest that complete reversal of neuromuscular blockade may be difficult in the presence of respiratory acidosis and metabolic alkalosis. In particular, clinicians should be aware of the risk of residual blockade in the setting of respiratory acidosis. A number of anesthetics (opioids, benzodiazepines, volatile anesthetics) can potentially depress the ventilatory drive in the early postoperative period. This respiratory depression may result in respiratory acidosis, which limits the ability of anticholinesterases to reverse neuromuscular blockade. The resultant residual blockade may further depress the respiratory muscle strength and ventilatory drive and increase the risk of adverse postoperative events.

Neuromuscular Monitoring. Qualitative and quantitative neuromuscular monitoring (also see Chapter 53) should be used to guide dosing of both NMBDs and their reversal in the operating room. In general, if deeper levels of neuromuscular blockade are present at the end of surgery (1 to 2 responses to TOF stimulation), larger doses of anticholinesterases should be given. In these clinical scenarios, maximal doses of neostigmine (70 μg/kg), edrophonium (1.0 to 1.5 mg/kg), or pyridostigmine (350 μg/kg) should be considered. If three to four responses to TOF stimulation are present with observable fade of the fourth response, moderate doses of anticholinesterase should be administered (40 to 50 μg/kg of neostigmine, 0.5 mg/kg of edrophonium, 200 μg/kg pyridostigmine). If four responses are present with no fade, low doses of anticholinesterases can be considered (e.g., 20 μg/kg of neostigmine; see later).

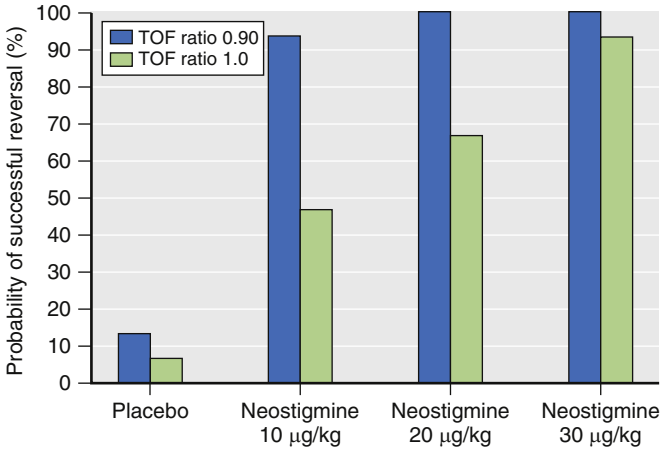


Figure 35-13. Probability of successful reversal within 10 minutes after different doses of neostigmine or placebo. Neostigmine or placebo was given at a train-of-four ratio of 0.40. *(From Fuchs-Buder T, Meistelman C, Alla F, et al: Antagonism of low degrees of atracurium-induced neuromuscular blockade: dose-effect relationship for neostigmine,* Anesthesiology *112:34-40, 2010).*

Quantitative monitoring is also useful in guiding the dosing of anticholinesterases. Fuchs-Buder and colleagues investigated the dose-response relationship of neostigmine when administered at shallow levels of an atracurium neuromuscular blockade (Fig. 35-13).[100] Neuromuscular function was monitored with AMG, and neostigmine (10, 20, or 30 μg/kg) was given at a TOF ratio of 0.40 or 0.60. All patients were able to achieve a TOF ratio of 0.90 within 10 minutes of receiving 20 μg/kg of neostigmine. These findings demonstrate that small doses of neostigmine can be safely used if neuromuscular recovery is measured with quantitative monitoring. If muscle

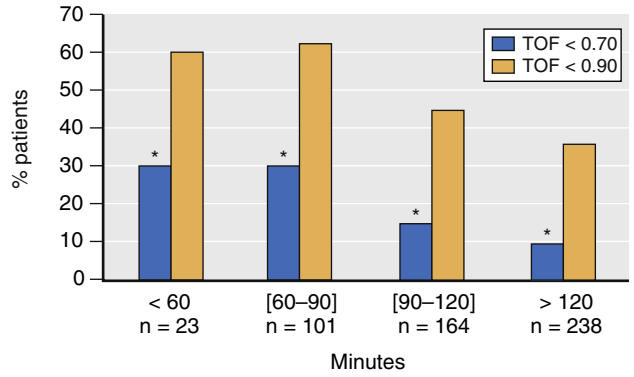


Figure 35-14. The incidence of residual neuromuscular blockade after a single intubating dose of intermediate-duration nondepolarizing relaxant (rocuronium, vecuronium, or atracurium). Partial paralysis rate (percent) according to the delay between the administration of muscle relaxant and the arrival in the postanesthesia care unit (PACU). Partial paralysis was defined as a train-of-four (TOF) ratio less than 0.70 or less than 0.90. *n* = number of patients. *Significantly different from TOF <0.90. *(From Debaene B, Plaud B, Dilly MP, Donati F: Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action,* Anesthesiology *98:1042-1048, 2003.)*

function is monitored with a simple nerve stimulator and no fade is detected with TOF stimulation, the TOF ratio is likely at least 0.40, but may be as high as 0.90 or 1.0. In the setting of full neuromuscular recovery, neostigmine administration may produce paradoxical muscle weakness (see later). This potential risk should be considered if neostigmine is used to reverse shallow blockade based on the results of qualitative neuromuscular monitoring.

In many clinical settings neuromuscular monitoring is unfortunately not utilized and decisions relating to the administration of anticholinesterases are based on the time that has elapsed between the last dose of NMBD and the conclusion of the anesthetic. Clinical studies do not support this practice. In a study of patients receiving a single intubating dose of vecuronium (0.1 mg/kg), 8.4% of patients had TOF ratios less than 0.80 4 hours after NMBD administration.[101] Debaene and colleagues examined the incidence of residual blockade in a large cohort of patients given a single intubating dose of vecuronium, rocuronium, or atracurium.[47] Of the 239 patients who were tested 2 or more hours after administration of the NMBD, 37% had a TOF ratio less than 0.90 (Fig. 35-14). These investigations, as well as a number of pharmacokinetic and pharmacodynamic studies, demonstrate that the time course of spontaneous neuromuscular recovery is extremely variable from patient to patient. In order to detect and appropriately manage patients in whom delayed neuromuscular recovery may be present, quantitative neuromuscular monitoring is required.

Patients With Cholinesterase Deficiency. The duration of neuromuscular blockade following the administration of either succinylcholine or mivacurium is primarily determined by their rate of hydrolysis by plasma cholinesterase (also see Chapter 34). Patients with abnormal plasma cholinesterase phenotypes and activity can demonstrate significant prolongation of clinical effect of these NMBDs. Mivacurium is four to five times more potent in patients phenotypically homozygous for the atypical plasma cholinesterase gene than in patients with normal cholinesterase activity.[102] Following standard intubating doses of mivacurium, recovery of neuromuscular function may require up to 4 to 8 hours in patients with cholinesterase deficiency.[103] Similar prolonged recovery times have been observed in patients administered succinylcholine who have atypical plasma cholinesterase genes.[104]

Human plasma cholinesterase has been used clinically to reverse neuromuscular blockade in patients with atypical serum cholinesterase. In 1977, Scholler and associates reported data on 15 patients with unexpected prolonged apnea lasting several hours after a dose of succinylcholine.[105] Adequate spontaneous ventilation was restored within an average time of 10 minutes in all subjects following the administration of human serum cholinesterase. Naguib and associates reported successful reversal of a profound mivacurium-induced neuromuscular blockade with three doses of a purified human plasma cholinesterase preparation and, in a subsequent study, established a dose-response relationship for plasma cholinesterase as a reversal agent for mivacurium in normal subjects.[103,106] The efficacy of exogenously administered plasma cholinesterase in antagonism of a mivacurium neuromuscular blockade was assessed in 11 patients phenotypically homozygous for atypical plasma cholinesterase.[107] A purified concentrate of cholinesterase (2.8 to 10 mg/kg) was administered 30 or 120 minutes after an intubating dose of mivacurium. Administration of cholinesterase restored plasma cholinesterase to normal levels, resulting in a 9- to 15-fold increased clearance and a shorter elimination half-life of mivacurium. The first response to TOF stimulation was observed in 13.5 minutes, and the time to achieve a TOF ratio of 0.80 ranged from 30 to 60 minutes. These data suggest that prolonged neuromuscular blockade secondary to low or abnormal plasma cholinesterase activity can be successfully managed with purified human plasma cholinesterase. Decisions relating to management of prolonged neuromuscular blockade in patients with atypical plasma cholinesterase should be based on the availability and cost of human plasma cholinesterase versus delaying tracheal extubation until spontaneous neuromuscular recovery has occurred.

Box 35-2 summarizes clinical management strategies that can be used by clinicians to reduce the risk of residual blockade when NMBDs are antagonized with anticholinesterases.

Complications Associated With Inhibitors of Acetylcholinesterase

Anticholinesterase-Associated Muscle Weakness. Anticholinesterases can antagonize moderate to shallow levels of neuromuscular blockade. However, if given when neuromuscular function is completely recovered, paradoxical muscle weakness theoretically may be induced. Large doses of neostigmine, pyridostigmine, and edrophonium may result in cholinergic hyperactivity and more intense fade in response to multiple nerve stimuli (decrease in TOF ratio) in an in vitro model.[108] The administration of a second dose of neostigmine (2.5 mg) to patients with small degrees of residual blockade resulted in a decrease in TOF ratios, tetanic height, and tetanic fade.[109,110] Caldwell

BOX 35-2 *Clinical Management Strategies to Reduce the Risk of Residual Neuromuscular Blockade When Anticholinesterase Reversal Agents Are Used*

Quantitative Monitoring Used (e.g., acceleromyography)

1. TOF count of 1 or no TOF response—delay reversal until neuromuscular recovery is more complete (TOF count of 2 or greater).
2. TOF count of 2 or 3—administer doses of anticholinesterases (neostigmine [70 μg/kg], edrophonium [1.0-1.5 mg/kg], or pyridostigmine [350 μg/kg]). Extubate when the adductor pollicis TOF ratio has reached 0.90.
3. TOF ratio ≥ 0.40—administer moderate pharmacologic reversal doses of anticholinesterases (neostigmine [40-50 μg/kg], edrophonium [0.5 mg/kg], or pyridostigmine [200 μg/kg]). Extubate when the adductor pollicis TOF ratio has reached 0.90.
4. TOF ratio between 0.40 and 0.70—administer pharmacologic reversal, consider a low dose of neostigmine (20 μg/kg).
5. TOF ratio > 0.70—avoid anticholinesterase reversal; risk of anticholinesterase-induced muscle weakness if given.

Qualitative Monitoring Used (Peripheral Nerve Stimulator)

1. TOF count of 1 or no TOF response—delay reversal until neuromuscular recovery is detectable (TOF count of 2 or greater)
2. TOF count of 2 or 3 at the end of surgery—administer anticholinesterases (neostigmine [70 μg/kg], edrophonium [1.0-1.5 mg/kg], or pyridostigmine [350 μg/kg]). Allow at least 15-30 minutes before tracheal extubation is performed.
3. TOF count of 4 with observable fade at the end of surgery (likely adductor pollicis TOF ratio < 0.40)—administer anticholinesterases (neostigmine [40-50 μg/kg], edrophonium [0.5 mg/kg], or pyridostigmine [200 μg/kg]). Allow at least 10-15 minutes before tracheal extubation is performed.
4. TOF count of 4 with no perceived fade at the end of surgery (likely adductor pollicis TOF ratio ≥ 0.40)—administer pharmacologic reversal, consider a low dose of neostigmine (20 μg/kg).

No Neuromuscular Monitoring Used

1. Anticholinesterases should be considered. Spontaneous recovery of neuromuscular function may require several hours in a significant percentage of patients, even after a single intubating dose of an intermediate-acting NMBD.
2. Anticholinesterases should not be given until some evidence of recovery of muscle strength is observed since administration of an anticholinesterase during deep levels of paralysis may delay neuromuscular recovery.
3. Decisions relating to the use or avoidance of anticholinesterases should not be based upon clinical tests of muscle strength (5-second head lift). Many patients can perform these tests even in the presence of profound neuromuscular blockade (TOF ratio < 0.50). Other muscle groups may be significantly impaired (pharyngeal muscles) at the time when patients can successfully perform these tests.

Modified in part from Brull SJ, Murphy GS: Residual neuromuscular block: lessons unlearned. Part II: methods to reduce the risk of residual weakness, Anesth Analg *111:129-140, 2010.*

NMBD, Neuromuscular blocking drug; *TOF*, train-of-four.

and co-workers examined neostigmine reversal (20 or 40 μg/kg) of residual neuromuscular blockade 1 to 4 hours after a single dose of vecuronium.[101] TOF ratios increased in 52 patients and decreased in 8 patients; TOF ratio decreases were only observed in patients with TOF ratios 0.90 or greater at the time of reversal (with 40 μg/kg doses of neostigmine but not 20 μg/kg dosing).

The clinical implications of administration of neostigmine after neuromuscular recovery has occurred have been examined in studies by Eikermann and colleagues. Rats were administered neostigmine after TOF ratios recovered to 1.0. Neostigmine administration resulted in decreases in upper airway dilator muscle tone and volume, impairment of diaphragmatic function, and reductions in minute ventilation.[111,112] In healthy volunteers given rocuronium, the administration of neostigmine after the recovery of the TOF to 1.0 induced genioglossus muscle impairment and increased upper airway collapsibility.[113] The adverse physiologic effects of neostigmine in the setting of complete neuromuscular recovery can potentially have negative respiratory consequences in postoperative surgical patients. The mechanisms proposed for this effect include sensitivity of the upper airway muscles to an overabundance of acetylcholine with desensitization of the ACh receptor, depolarizing blockade, or an open channel blockade. In contrast, sugammadex does not appear to produce adverse effects on upper airway tone or normal breathing when given after neuromuscular recovery.[111]

Nausea and Vomiting. The impact of anticholinesterases on the incidence of postoperative nausea and vomiting remains controversial (also see Chapter 97). Systemic anticholinesterases produce effects outside of the neuromuscular junction that may influence the risk of unwanted side effects following anesthesia and surgery. In addition to the action within the neuromuscular junction, anticholinesterase drugs result in muscarinic effects on the gastrointestinal tract, resulting in stimulation of secretion of gastric fluid and increases in gastric motility. The use of smaller doses of neostigmine in combination with atropine decreases lower esophageal sphincter tone.[114] Furthermore, neostigmine may produce nausea and vomiting via a central effect. Intrathecal neostigmine increases the incidence of nausea and vomiting, likely through a direct effect on the brainstem.

Anticholinergic drugs (e.g. atropine, glycopyrrolate) are routinely administered with anticholinesterases in order to attenuate the undesirable muscarinic effects of these reversal agents. Perhaps anticholinergic drugs have antiemetic properties.[115] When given to children receiving sedation (in the absence of anticholinesterases), atropine was associated with significantly less vomiting (5.3%) than either glycopyrrolate (10.7%) or no anticholinergic (11.4%)[116] (also see Chapter 93). Similarly, surgical patients who were randomized to receive atropine had significantly less nausea than those given glycopyrrolate.[117] Atropine is a tertiary amine that can readily cross the blood-brain barrier and produce central effects, whereas glycopyrrolate is a quaternary amine that does not penetrate the blood-brain barrier. The beneficial effects of atropine on nausea and vomiting are likely secondary to a central nervous system effect.

TABLE 35-6 **EARLY AND DELAYED POSTOPERATIVE NAUSEA AND VOMITING WITH NEOSTIGMINE VERSUS CONTROL—RESULTS OF A META-ANALYSIS**

Outcome	Anticholinergics	Number of Studies	Number of Participants	Relative Risk (95% CI)
Early nausea (0-6 hr)	Atropine and Glycopyrrolate	6	584	1.24 (0.86-1.80)
	Atropine	1	79	0.67 (0.36-1.26)
	Glycopyrrolate	5	505	1.39 (0.97-1.99)
Early vomiting (0-6 hr)	Atropine and Glycopyrrolate	8	768	1.05 (0.72-1.55)
	Atropine	2	199	0.75 (0.52-1.08)
	Glycopyrrolate	6	568	1.35 (0.88-2.06)
Delayed nausea (6-24 hr)	Glycopyrrolate	4	337	1.09 (0.76-1.57)
Delayed vomiting (6-24 hr)	Glycopyrrolate	4	337	1.01 (0.58-1.78)

From Cheng CR, Sessler DI, Apfel CC: Does neostigmine administration produce a clinically important increase in postoperative nausea and vomiting? Anesth Analg *101:1349-1355, 2005.*
CI, Confidence interval.

Several randomized clinical trials have been performed to determine whether anticholinesterase administration results in an increase in the incidence of postoperative nausea and vomiting. Unfortunately, most study populations were small (39 to 120 patients). Two systematic reviews have been conducted to address this limitation. Tramer and Fuchs-Buder analyzed eight trials with data on 1134 patients that compared reversal with neostigmine or edrophonium with spontaneous recovery from long- or intermediate-acting NMBDs.[118] An analysis of the neostigmine data across all trials and doses revealed no evidence of an increased risk of early and late nausea and vomiting when neostigmine was administered. However, some evidence in adults suggested that antagonism with larger doses of neostigmine (2.5 mg) might increase the incidence of these events. No evidence was found for this effect with edrophonium. A later systematic review evaluated the effect of neostigmine on postoperative nausea and vomiting while considering the different anticholinergics as confounding variables.[115] Ten randomized trials (933 patients) that compared neostigmine to inactive control were included. The combination of neostigmine with either glycopyrrolate or atropine did not increase the incidence of nausea or vomiting, nor was there an increased risk when large doses of neostigmine were compared with smaller doses (Table 35-6). Atropine was associated with a reduction in the risk of vomiting, but glycopyrrolate was not. In conclusion, there is at present insufficient evidence to conclude that neostigmine or edrophonium is associated with an increased risk of postoperative nausea and vomiting.

Cardiovascular Effects. Pronounced vagal effects are observed following the administration of anticholinesterases—bradycardia and other bradyarrhythmias, such as junctional rhythms, ventricular escape beats, complete heart block, and asystole, have been reported. The time course of these bradyarrhythmias parallels the onset of action of the anticholinesterases, with the most rapid onset observed with edrophonium, slower for neostigmine, and slowest for pyridostigmine.[71] In order to counteract these cardiovascular effects, atropine and glycopyrrolate are administered concurrently with anticholinesterases. Atropine and glycopyrrolate have muscarinic (parasympathetic) blocking effects, but do not block nicotinic receptors. Atropine has a more rapid onset of action (approximately 1 minute) compared with glycopyrrolate (2 to 3 minutes), although the duration of action of both agents is similar (30 to 60 minutes). Despite the concurrent administration of anticholinergic drugs, a high incidence of bradyarrhythmias is observed following anticholinesterase reversal (up to 50% to 60% of patients in some studies).[72,119] The risk of arrhythmias is influenced by the type of anticholinesterase and anticholinergic used, the dose of anticholinesterase and anticholinergic administered, and background anesthetic used (opioid-based versus volatile anesthetic and type of NMBD).

Several investigations have examined the heart rate and rhythm responses to various anticholinesterase/anticholinergic combinations. In general, it is preferable to use atropine with edrophonium, because the onset of action of both drugs is rapid. Edrophonium-atropine mixtures induced small increases in heart rate, whereas edrophonium-glycopyrrolate mixtures caused decreases in heart rate and occasionally severe bradycardia.[120] Similarly, the onset of cholinergic effects of neostigmine coincides with the onset of the anticholinergic effects of glycopyrrolate; glycopyrrolate is superior to atropine in protecting against neostigmine-induced bradyarrhythmias.[121] When atropine is given with edrophonium (0.5 to 1.0 mg/kg), doses of 5 to 7 μg/kg are recommended, although larger doses may be used in certain circumstances.[120,122] If glycopyrrolate is given with neostigmine, minimal changes in heart rate are observed if a dose equivalent of one fourth the dose of neostigmine is used (e.g., 1 mg glycopyrrolate with 4 mg of neostigmine).[71,121] Because the onset of action is slow with pyridostigmine, tachycardia may be observed when either atropine or glycopyrrolate is coadministered.[71]

More recent investigations have examined the impact of atropine and glycopyrrolate, given with neostigmine, on autonomic control in the postoperative period. During physiologic stressful events, control of heart rate and arterial blood pressure is regulated by the sympathetic and parasympathetic nervous systems. Anticholinergic drugs attenuate the efferent parasympathetic regulation of heart rate and suppress cardiac baroreflex sensitivity and heart rate variability. This suppression of the parasympathetic system may predispose patients to cardiac arrhythmias following

surgery. Marked decreases in baroreflex sensitivity and high-frequency heart rate variability have been observed in healthy volunteers given either atropine (20 μg/kg) or glycopyrrolate (7 μg/kg).[123] Although the times required to return to baseline values were prolonged in both groups, recovery times were significantly longer in the subjects given atropine (177 to 212 minutes) compared with those administered glycopyrrolate (82 to 111 minutes). Similar effects have been observed in healthy patients undergoing general anesthesia reversed with neostigmine and anticholinergics.[124] Neuromuscular blockade was antagonized with neostigmine 50 μg/kg and either atropine 20 μg/kg or glycopyrrolate 8 μg/kg. Two hours after giving neostigmine, patients given atropine had persistent impairment of baroreflex sensitivity and high-frequency heart rate variability, whereas these variables had returned to baseline values in patients receiving glycopyrrolate. These investigations demonstrate that the parasympathetic nervous system control of heart rate is less impaired by glycopyrrolate than by atropine.

Bronchoconstriction. Bronchospasm can occur after the administration of neostigmine in surgical patients.[125,126] Anticholinesterases (e.g., neostigmine) stimulate muscarinic receptors in airway smooth muscle; stimulation of these receptors can provoke bronchoconstriction. Neostigmine and pyridostigmine induce a phosphatidylinositol response (a reflection of smooth muscle contraction induced by a muscarinic agonist) in airway muscle, which can result in bronchoconstriction.[127] This response was inhibited in the presence of atropine, a direct bronchodilator. Edrophonium did not induce a phosphatidylinositol response. In patients with cervical spinal cord injuries, neostigmine alone caused bronchoconstriction, whereas neostigmine combined with glycopyrrolate caused bronchodilation.[128] The risk of perioperative bronchospasm appears low if anticholinesterases are administered concurrently with anticholinergics.

SUGAMMADEX REVERSAL OF NEUROMUSCULAR BLOCKADE

Sugammadex (Org 25969) is a modified γ-cyclodextrin and the first selective relaxant–binding agent based on an encapsulating principle for inactivation of a neuromuscular blocking agent (*su* refers to sugar, and *gammadex* refers to the structural molecule γ-cyclodextrin). This principle for reversal of rocuronium- and vecuronium-induced neuromuscular blockade was first introduced into clinical practice in 2008 and is now available for pediatric and adult anesthesia in most countries worldwide. The complex formation of sugammadex and rocuronium or vecuronium occurs at all levels of neuromuscular blockade (profound through shallow) and results in a more fast-acting pharmacologic reversal when compared with anticholinesterase drugs. Consequently, sugammadex may markedly reduce postoperative residual neuromuscular blockade in the PACU.[129]

Structure-Activity Relationships and Mechanism of Action

The three natural unmodified cyclodextrins consist of six, seven, and eight cyclic oligosaccharides (i.e., dextrose units joined through one to four glycosyl bonds) and are

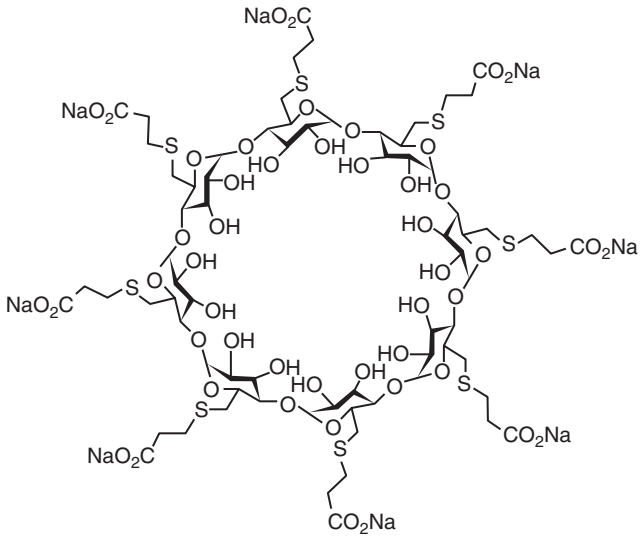


Figure 35-15. Structure of the synthetic γ-cyclodextrin sugammadex (Org 25969). *(From Bom A, Bradley M, Cameron K, et al: A novel concept of reversing neuromuscular block: chemical encapsulating of rocuronium bromide by a cyclodextrin-based synthetic host,* Angew Chem *41:266-270, 2002.)*

called α-, β-, and γ-cyclodextrins, respectively.[130, 131] Their three-dimensional structure resembles a hollow, truncated cone or a doughnut. The structure has a hydrophobic cavity and hydrophilic exterior because of the presence of polar hydroxyl groups. Hydrophobic interactions trap the lipophilic molecules in the cyclodextrin cavity, thereby resulting in the formation of a water-soluble guest-host complex. Sugammadex is built on this principle ring structure but is a modified γ-cyclodextrin. Although an unmodified γ-cyclodextrin possesses a larger lipophilic cavity (7.5 to 8.3 Å) than α- or β-cyclodextrins, it is still not deep enough to accommodate the larger rigid structure of the rocuronium molecule. Therefore, the cavity is modified by adding eight side chains to extend it to 11 Å for better accommodation of the four hydrophobic steroidal rings of rocuronium. Furthermore, at the end of these side chains, negatively charged carboxyl groups are added to enhance electrostatic binding to the positively charged quaternary nitrogen of rocuronium (Fig. 35-15).[131,132] The stability of the rocuronium-sugammadex complex is a result of the combination of intermolecular forces (van der Waals forces), including thermodynamic (hydrogen bonds) and hydrophobic interactions.[131-133] Sugammadex forms a rigid complex in a 1:1 ratio with steroidal neuromuscular blocking drugs (rocuronium and vecuronium) (Fig. 35-16).[131] There is some binding affinity with pancuronium, but this interaction is too low to have a significant clinical effect. The molecular mass of the sugammadex-rocuronium complex is 2532 g/mol (sugammadex 2002 g/mol and rocuronium 530 g/mol), and that of the sugammadex-vecuronium complex is 2640 g/mol (vecuronium 638 g/mol).[131] The rocuronium-sugammadex complex exists in an equilibrium with an association/dissociation rate of 1 molar concentration of sugammadex and rocuronium of 25,000,000:1, which

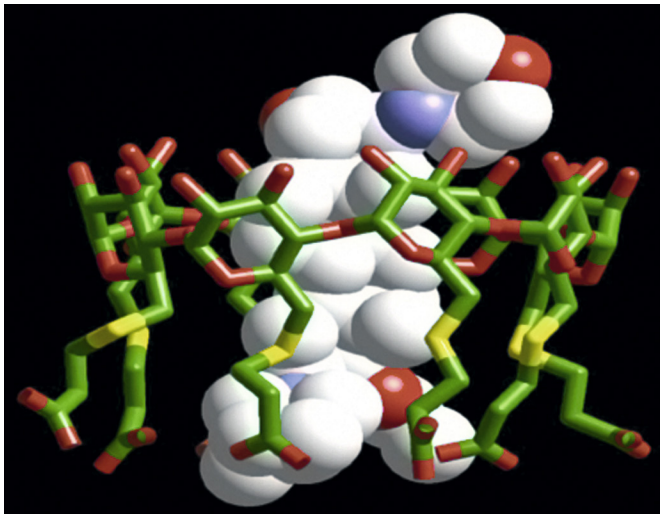


Figure 35-16. The sugammadex-rocuronium complex. *(From Bom A, Bradley M, Cameron K, et al: A novel concept of reversing neuromuscular block: chemical encapsulating of rocuronium bromide by a cyclodextrin-based synthetic host,* Angew Chem *41:266-270, 2002.)*

means that sugammadex forms a very rigid complex and encapsulates rocuronium at 25 million times the rate that one molecule complex dissociates. The affinity of sugammadex toward vecuronium is 2.5 times smaller, but still high enough to form a tight complex.[131] Rapid binding of rocuronium and sugammadex results in removal of free rocuronium molecules from the plasma. This creates a concentration gradient favoring movement of the remaining rocuronium molecules from the effect site at the neuromuscular junction into plasma, where the drug is encapsulated by free sugammadex molecules. Neuromuscular blockade is quickly reversed as rocuronium is removed from the binding sites at the neuromuscular junction. Sugammadex administration results in an increase in the total plasma concentration of rocuronium (free and that bound to sugammadex).[134] Because sugammadex acts as a selective binding agent and has no direct or indirect action on the molecular components of cholinergic transmission (cholinesterase, nicotinic receptors, or muscarinic receptors), the need for coadministration of anticholinergic drugs is eliminated.[135]

Pharmacokinetics

The pharmacokinetic profile of sugammadex and rocuronium has been investigated in healthy volunteers and surgical patients.[136] Sugammadex, in a dose range of 0.1 to 8.0 mg/kg in healthy adult volunteers (without neuromuscular blockade), exhibited a dose-linear pharmacokinetic profile, a volume distribution of 18 L, an elimination half-life of 100 minutes, and a plasma clearance rate of 120 mL/min, with up to 80% of the dose being excreted in urine over 24 hours.[136] After encapsulation by sugammadex, rocuronium is less free to distribute to compartments other than those associated with the compartment in which sugammadex resides. During an infusion of rocuronium to maintain a stable depth of neuromuscular blockade, administration of sugammadex increased the measured plasma concentration of rocuronium; rocuronium redistributed from the effect compartment (including the neuromuscular junction) to the central compartment (mostly as the sugammadex complex) as it was encapsulated by sugammadex.[134] The volume of distribution of rocuronium decreases with increasing doses of sugammadex until the volume of distribution of rocuronium approaches the volume of distribution of sugammadex at higher doses.[134] Encapsulation changes the pharmacokinetics of rocuronium. In the absence of sugammadex, rocuronium is eliminated mainly by biliary excretion (>75%) and to a lesser degree by renal excretion (10% to 25%).[137] The main difference in the pharmacokinetic profile of sugammadex and rocuronium is that the clearance of sugammadex is approximately three times slower than that of rocuronium.[136] The rate and amount of urinary excretion of rocuronium when administered alone is slow and small, but when sugammadex (a dose of 2.0 mg/kg or more) is administered, the plasma clearance of rocuronium was decreased by a factor of more than two.[136] This decreased clearance occurs because the biliary route of excretion becomes unavailable for the rocuronium-sugammadex complex as the large size of this complex prohibits additional renal excretion. The clearance of rocuronium after binding by sugammadex decreases to a value approaching the glomerular filtration rate (120 mL/min).[137] However, the renal excretion of rocuronium is increased by more than 100% after administration of 4.0 to 8.0 mg/kg of sugammadex.[137] Following the administration of sugammadex, encapsulation of rocuronium in the plasma results in a rapid decrease in free rocuronium in this compartment, although the total plasma concentration of rocuronium (both free and bound by sugammadex) increases. This results in a concentration gradient between the relatively high level of free rocuronium in the effect compartment (the neuromuscular junction) and the low level in the plasma compartment.[134] As a result, free rocuronium molecules return to the plasma compartment and are encapsulated by sugammadex. Thus, the increase in plasma levels of rocuronium after sugammadex administration illustrates the mechanism responsible for the rapid reversal of neuromuscular blockade by sugammadex.

Because renal excretion is the primary route for the elimination of sugammadex and the rocuronium-sugammadex complex, studies on elimination by dialysis have considerable relevance in clinical practice. In a small subset of patients with severe renal impairment, an investigation on dialysis showed that the clearance of sugammadex and rocuronium in blood was 78 and 89 mL/min, respectively. Therefore, hemodialysis using a high-flux dialysis method is effective in removing sugammadex and the sugammadex-rocuronium complex in patients with severe renal impairment.[138]

Pharmacodynamics

Clinical Use of Sugammadex in Healthy Patients. The first human exposure of sugammadex in male volunteers showed a large dose-dependent, more rapid recovery time from a rocuronium-induced neuromuscular blockade with sugammadex (0.1 to 8.0 mg/kg) as compared with placebo.[136] Administration of 8 mg/kg of sugammadex 3 minutes after a bolus dose of 0.6 mg/kg of rocuronium resulted in a recovery of the TOF ratio to 0.90 within 2 minutes compared with

52 minutes for placebo. Decreasing the dose of sugammadex to 4 mg/kg resulted in recovery of the TOF ratio to 0.90 in less than 4 minutes.[136] Similar recovery times were found in a study in which surgical patients received 0.6 mg/kg rocuronium, followed by different doses of sugammadex or placebo administered at a TOF count of 2.[139] Sugammadex reduced the median recovery time in a dose-dependent manner from 21 minutes in the placebo group to 1.1 minutes in the group receiving 4.0 mg/kg of sugammadex.[139] In another study, administration of sugammadex resulted in a more rapid and effective recovery from a rocuronium (0.6 mg/kg) or vecuronium (0.1 mg/kg) neuromuscular blockade.[140] After a dose of 4.0 mg/kg of sugammadex, the mean recovery time to a TOF ratio of 0.90 was 1.1 minutes and 1.5 minutes after rocuronium and vecuronium, respectively (Figs. 35-17 and 35-18).[140] Reversal of neuromuscular blockade with larger doses of rocuronium (1.0 to 1.2 mg/kg) by different doses of sugammadex (2.0 to 16.0 mg/kg) at different time points (3 to 15 minutes after rocuronium) showed a dose dependent, rapid, and effective reversal compared with placebo.[141-144]

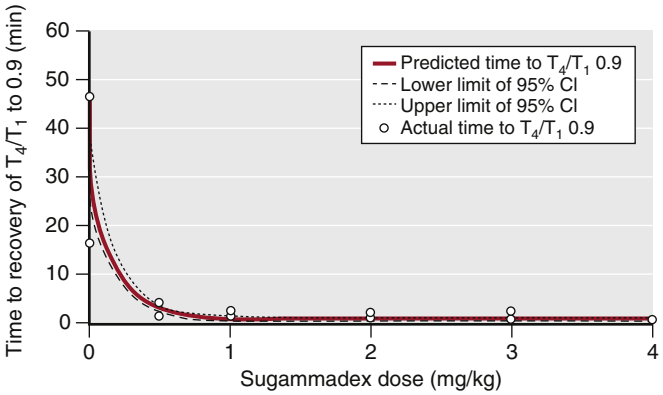


Figure 35-17. The dose-response relation of sugammadex dose and time to recovery of the T4/T1 ratio to 0.9 with rocuronium 0.6 mg/kg. *(From Suy K, Morias K, Cammu G, et al: Effective reversal of moderate rocuronium- or vecuronium-induced neuromuscular block with sugammadex, a selective relaxant binding agent,* Anesthesiology *106:283-288, 2007.)*

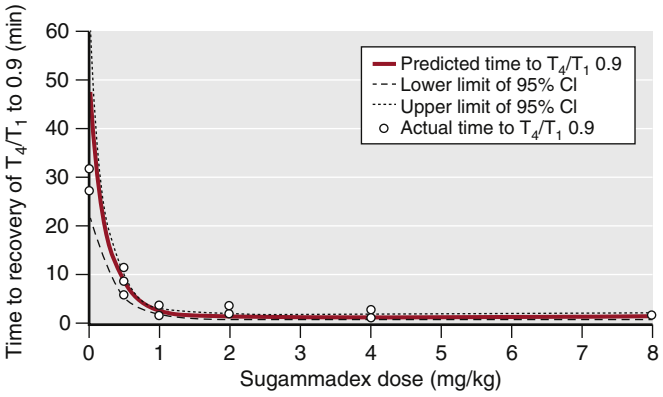


Figure 35-18. The dose-response relation of sugammadex dose and time to recovery of the T4/T1 ratio to 0.9 with vecuronium 0.1 mg/kg. *(From Suy K, Morias K, Cammu G, et al: Effective reversal of moderate rocuronium- or vecuronium-induced neuromuscular block with sugammadex, a selective relaxant binding agent,* Anesthesiology *106:283-288, 2007.)*

Whereas anticholinesterase drugs, such as neostigmine, are unable to reverse deeper levels of neuromuscular blockade (e.g., posttetanic count of 1 to 2) because of a ceiling effect, sugammadex is effective in reversing profound neuromuscular blockade.[141,145] Optimal doses of sugammadex of 4.0 mg/kg produced prompt recovery of the TOF ratio to 0.90 within minutes (Table 35-7).[140-145] Therefore, reversal of moderate and profound rocuronium and vecuronium neuromuscular blockades can be reliably achieved by administration of sugammadex, provided a dose of 2.0 and 4.0 mg/kg, respectively, is used. Because neostigmine has neuromuscular effects when given alone, some spontaneous recovery of the TOF should be evident before it is given. In contrast, sugammadex has no neuromuscular effects when given alone. Accordingly, sugammadex can be given even if there is no response to TOF stimulation. Sugammadex allows a profound neuromuscular blockade to continue until the end of surgery.

In contrast to the anticholinesterase drugs (e.g., neostigmine), intense neuromuscular blockade (no response to TOF and PTC stimulation) can be reversed by sugammadex immediately after the administration of rocuronium. In a multicenter investigation, patients were randomized to receive 1.2 mg/kg of rocuronium followed 3 minutes later by 16 mg/kg of sugammadex or a dose of 1.0 mg/kg of succinylcholine.[146] The mean time to 90% recovery of the first twitch (T1) from the start of sugammadex administration was 2.9 minutes and to a recovery of the TOF ratio to 0.90 was 2.2 minutes.[146] In contrast, the spontaneous recovery time from a succinylcholine neuromuscular blockade to 90% recovery of T1 was 10.9 minutes. Thus, reversal of large doses of rocuronium with 16 mg/kg sugammadex was significantly faster than spontaneous recovery from succinylcholine (Fig. 35-19).[146]

TABLE 35-7 **RECOVERY TIMES* OF REVERSAL OF A ROCURONIUM-INDUCED (1.2 mg/kg) NEUROMUSCULAR BLOCKADE WITH EITHER SUGAMMADEX OR PLACEBO (NaCl 0.9%)**

		Sugammadex				
	Placebo (*n* = 4)	2.0 mg/kg (*n* = 5)	4.0 mg/kg (*n* = 5)	8.0 mg/kg (*n* = 12)	12.0 mg/kg (*n* = 7)	16.0 mg/kg (*n* = 7)
Mean (SD)	122.1 (18.1)	56.5 (5.4)	15.8 (17.8)	2.8 (0.6)	1.4 (0.3)	1.9 (2.2)
Median	126.1	55.3	12.3	2.5	1.3	1.3
Min-max	96.8-139.4	50.5-65.1	3.3-46.6	2.2-3.7	1.0-1.9	0.7-6.9

From de Boer HD, Driessen JJ, Marcus MA, et al: Reversal of a rocuronium-induced (1.2 mg/kg) profound neuromuscular block by sugammadex: a multicenter, dose-finding and safety study, Anesthesiology *107:239-244, 2007.*

SD, Standard deviation.

*Recovery times (minutes) from the start of administration of sugammadex or placebo to recovery of the TOF ratio to 0.90.

These findings were confirmed in a randomized trial that assessed how rapidly spontaneous ventilation could be reestablished after rapid sequence induction of anesthesia and intubation of the trachea, using either the combination of rocuronium (1.0 mg/kg)–sugammadex (16 mg/kg) or succinylcholine (1.0 mg/kg).[147] The median time from tracheal intubation to spontaneous ventilation was 406 seconds with succinylcholine and 216 seconds with rocuronium-sugammadex (Table 35-8).[147] These data demonstrated that sugammadex reversal of a large-dose rocuronium neuromuscular blockade was not only significantly faster than spontaneous recovery from succinylcholine, but that spontaneous ventilation could be restored more rapidly (i.e., this dose can be used to replace succinylcholine for endotracheal intubation). In clinical practice and during an unexpected difficult airway (cannot intubate, cannot ventilate scenario), a rocuronium neuromuscular blockade may be reversed by sugammadex immediately in order to restore spontaneous ventilation.

When sugammadex was compared with neostigmine or edrophonium, the time course of neuromuscular recovery was markedly different.[148-150] In a clinical study, patients received 0.6 mg/kg of rocuronium after which neuromuscular blockade was sustained with supplemental boluses of rocuronium given at the reappearance of the second twitch (second response to TOF stimulation or T2).[148] Fifteen minutes after the last dose of rocuronium either 70 μg/kg of neostigmine, 1 mg/kg of edrophonium, or 4.0 mg/kg sugammadex was administered. The average time to achieve a TOF ratio of 0.90 was 10 times longer after the administration of neostigmine than it was after sugammadex (1044 seconds versus 107 seconds) and 3 times longer after the administration of edrophonium (331 seconds). In another study by Blobner and associates, similar differences were found when comparing reversal of rocuronium at the reappearance of the second twitch in the TOF response using 2 mg/kg sugammadex versus neostigmine 50 μg/kg.[149] This was also confirmed in an investigation that assessed the efficacy of sugammadex versus neostigmine for reversal of profound rocuronium-induced neuromuscular blockade.[150] More than 97% of patients reversed with sugammadex (4.0 mg/kg) at a PTC of 1 to 2 recovered to a TOF ratio of 0.90 within 5 minutes. In contrast, 73% of the patients administered neostigmine (70 μg/kg)

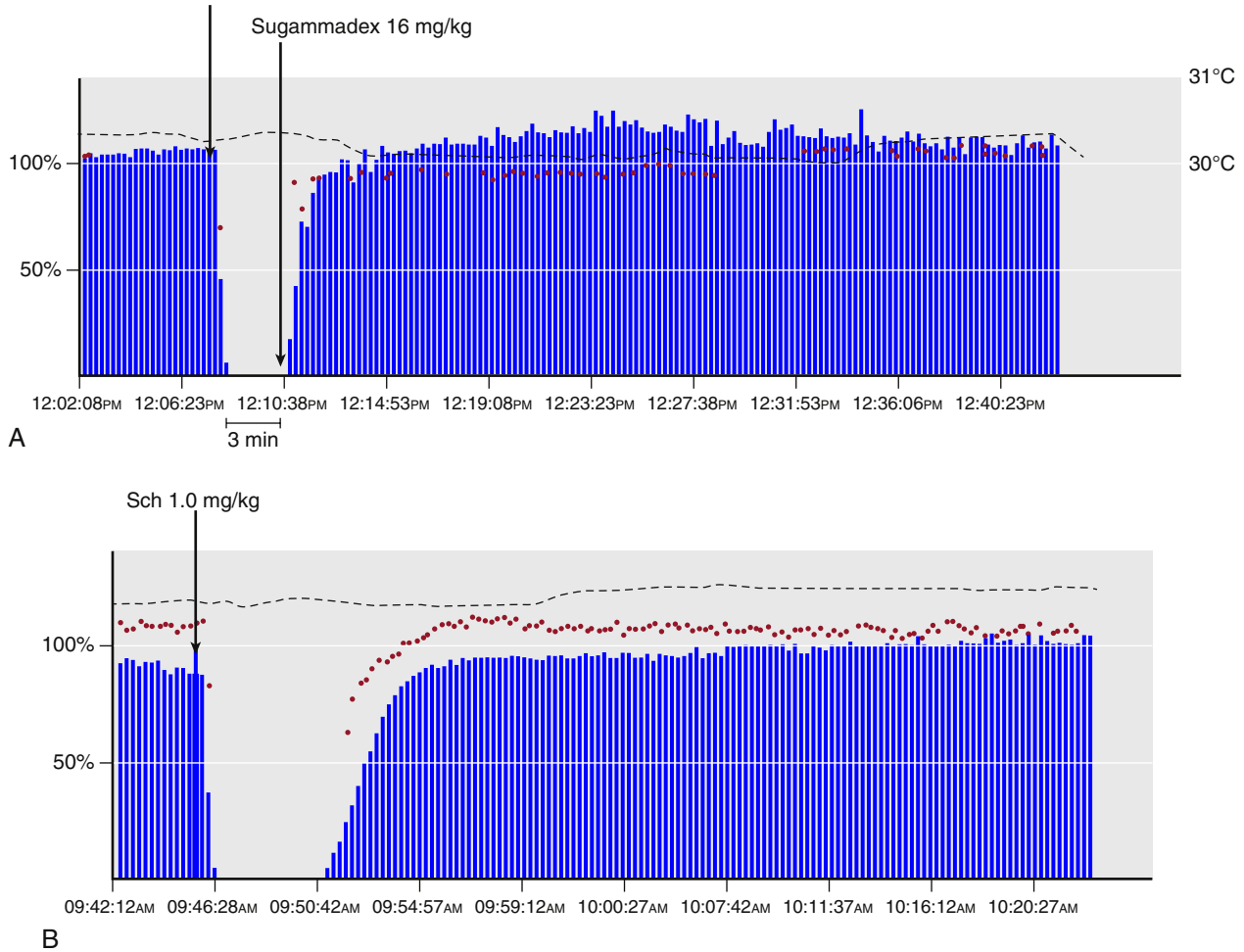


Figure 35-19. A, Recovery of T1 twitch height (*blue tracings*) and the train-of-four (TOF) ratio (*red dots*) after the administration of 1.2 mg/kg of rocuronium, followed 3 minutes later by 16 mg/kg of sugammadex, both given intravenously. Recovery to a first twitch height (T1) of 90% and a TOF ratio of 0.94 occurred 110 seconds later. The onset-offset time with this sequence (i.e., time from the end of the injection of rocuronium until T1 recovery to 90%) was 4 minutes, 47 seconds. **B,** Effects of administering 1.0 mg/kg of succinylcholine (Sch) with spontaneous recovery to a T1 recovery to 90% occurring after 9 minutes, 23 seconds. *Black dashed line* represents hand skin temperature (degrees Celcius). *(From Naguib M: Sugammadex: another milestone in clinical neuromuscular pharmacology,* Anesth Analg *104:575-581, 2007.)*

TABLE 35-8 HOW RAPIDLY CAN SPONTANEOUS VENTILATION BE REESTABLISHED AFTER A RAPID SEQUENCE INDUCTION AND INTUBATION OF ANESTHESIA USING EITHER SUCCINYLCHOLINE- OR ROCURONIUM-SUGAMMADEX*

	Succinylcholine (1 mg kg^{-1}) (n = 26)	Rocuronium (1 mg kg^{-1}) Sugammadex (16 mg kg^{-1}) (n = 29)	P-value
Time from start of procedure to tracheal intubation (sec)	330 (313-351)	324 (312-343)	.45
Intubation conditions			.13
Excellent	20 (76%)	27 (93%)	
Good	6 (24%)	2 (7%)	
Poor	0 (0%)	0 (0%)	
Intubation difficulty score			.23
≤ 5	24 (92%)	28 (100%)	
> 5	2 (8%)	0 (0%)	
Time from tracheal intubation to spontaneous ventilation (sec)	406 (313-507)	216 (132-425)	.002
Time from tracheal intubation to T1 90% (sec)	518 (451-671) (n = 17)	168 (122-201) (n = 27)	<.0001
Time from injection of NMBD to T1 90% (sec)	719 (575-787) (n = 17)	282 (242-319) (n = 27)	<.0001

From Sørensen MK, Bretlau C, Gätke MR, et al: Rapid sequence induction and intubation with rocuronium-sugammadex compared with succinylcholine: a randomized trial, Br J Anaesth *108:682-689, 2012.*

**These data include tracheal intubation conditions, time to reappearance of spontaneous ventilation, and recovery of neuromuscular function from either succinylcholine or the combination of rocuronium-sugammadex.*

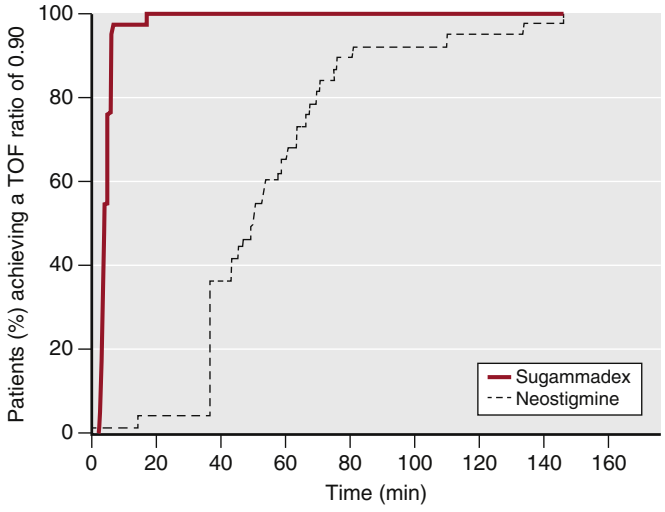


Figure 35-20. Time to recovery of the train-of-four ratio to 0.90 from profound rocuronium-induced neuromuscular blockade after administration of sugammadex 4 mg/kg or neostigmine 70 μg/kg. *(From Jones RK, Caldwell JE, Brull SJ, et al: Reversal of profound rocuronium-induced blockade with sugammadex: a randomized comparison with neostigmine,* Anesthesiology *109:816-824, 2008.)*

recovered between 30 and 60 minutes after administration, with 23% requiring more than 60 minutes to recover to a TOF ratio of 0.90 (Fig. 35-20).

A randomized trial compared the efficacy of sugammadex reversal of a rocuronium (0.6 mg/kg) neuromuscular blockade with that of neostigmine reversal of a cisatracurium (0.15 mg/kg) neuromuscular blockade.[151] Time from the start of administration of reversal agent sugammadex 2.0 mg/kg or neostigmine 50 μg/kg) to recovery of the TOF ratio to 0.90 was 4.7 times faster with sugammadex than with neostigmine, 1.9 versus 9.0 minutes, respectively.

Unlike with neostigmine or edrophonium, the choice of anesthetic (e.g., propofol versus sevoflurane) does not influence the ability of sugammadex to reverse rocuronium-induced neuromuscular blockade.[152,153] Provided that sugammadex is used in recommended dosages according to the level of neuromuscular blockade, a small risk exists of incomplete neuromuscular recovery or reoccurrence of neuromuscular blockade following surgery.

Clinical Use of Sugammadex in Pediatric and Older Adult Patients

Pediatrics. The use of sugammadex in pediatric patients (also see Chapter 93) was examined in a study enrolling 8 infants (28 days to 23 months), 24 children (2 to 11 years), and 31 adolescents (12 to 17 years).[154] Patients were anesthetized with propofol and opioids and received rocuronium 0.6 mg/kg. At the reappearance of T2 (second twitch), patients were given sugammadex 0.5, 1.0, 2.0 or 4.0 mg/kg or placebo. Recovery time to a TOF ratio of 0.90 decreased in a dose-dependent manner in all age groups. Residual neuromuscular blockade or recurarization was not observed, and no side effects were reported. In a more recent case report, sugammadex was used successfully in reversing a vecuronium-induced neuromuscular blockade in a 7-month-old infant.[155] Another case report described a 2-year-old patient who received readministration of rocuronium for reoperation after an initial successful reversal with sugammadex.[156] Sugammadex can be used safely in children and adolescents (2 to 17 years old). Information on the use of sugammadex in pediatric patients less than 2 years old is still limited.

Older Adult Patients. Reversal of neuromuscular blockade by sugammadex has been assessed in older patients (also see Chapter 80). One hundred and fifty patients were divided into three groups; an adult group (18 to 64 years old),

TABLE 35-9 **ROCURONIUM RECOVERY TIME (min) FROM THE ADMINISTRATION OF SUGAMMADEX (2 mg/kg AT APPEARANCE OF T2) UNTIL THE RECOVERY OF TRAIN-OF-FOUR RATIOS AS INDICATED IN PATIENTS WITH AND WITHOUT RENAL FAILURE**

	Patient Group		
	CL_{CR} <30 mL min^{-1} (n = 15)	CL_{CR} ≥80 mL min^{-1} (n = 14)*	ANOVA
Recovery to TOF ratio 0.7, mean (SD)	1.45 (0.47)	1.17 (0.38)	NS
Recovery to TOF ratio 0.8, mean (SD)	1.60 (0.57)	1.32 (0.45)	NS
Recovery to TOF ratio 0.9, mean (SD)	2.00 (0.72)	1.65 (0.63)	NS

From Staals LM, Snoeck MM, Driessen JJ, et al: Multicenter, parallel-group, comparative trial evaluating the efficacy and safety of sugammadex in patients with end-stage renal failure or normal renal function, Br J Anaesth *101:492-497, 2008.*

ANOVA, Analysis of variance; CL_{CR}, total plasma creatinine clearance; NS, not significant; SD, standard deviation.

*One patient was excluded from the control group (normal renal function) because of unreliable TOF traces.

an older adult group (65 to 75 years old), and an oldest adult group (75 years or older).[157] Patients received an intubating dose of rocuronium 0.6 mg/kg with maintenance doses of 0.15 mg/kg as required. Sugammadex 2.0 mg/kg was administered after the last dose of rocuronium at the reappearance of T2. Recovery of neuromuscular blockade by sugammadex was slightly (0.7 minutes) faster in patients younger than 65 years of age. In general, a prolonged circulation time secondary to a reduced cardiac output in older patients was anticipated to result in a longer recovery time from neuromuscular blockade after administration of sugammadex.[158,159] However, based on these results, no dose adjustments are needed in older patients.[157]

Clinical Use of Sugammadex in Special Patient Populations

Cardiac Disease. Studies evaluating the safety and efficacy of sugammadex in patients with underlying cardiovascular disease have not demonstrated an effect of sugammadex on electrocardiogram (no indication of a possible prolongation effect on the QTc interval).[160,161] A study designed to evaluate the effects of sugammadex on QTc prolongation in healthy subjects (in doses up to 32 mg/kg, alone or in combination with rocuronium or vecuronium) revealed that the administration of sugammadex was not associated with QTc prolongation.[161] In a case report of a patient with long QT syndrome, a vecuronium neuromuscular blockade was reversed with sugammadex 2 mg/kg without adversely affecting the QT interval.[162] Based on current data, sugammadex reversal is not associated with cardiovascular side effects in healthy patients or in those with cardiovascular comorbidities (also see "Complications Associated With Inhibitors of Acetylcholinesterase").

Pulmonary Disease. Patients with a history of pulmonary disease have an increased risk of postoperative pulmonary complications such as pneumonia, respiratory failure, and exacerbation of the underlying pulmonary disease.[163] Sugammadex has been studied in patients with pulmonary disease.[163] Seventy-seven surgical patients with a diagnosis or known history of pulmonary disorders received sugammadex in doses up to 4 mg/kg in order to reverse a rocuronium neuromuscular blockade. As in other adult patient groups, reversal of a rocuronium-induced neuromuscular blockade was rapid, and there were no signs of residual neuromuscular blockade or recurarization.[164] Of the 77 patients treated with sugammadex, 2 patients developed bronchospasm, 1 minute and 55 minutes respectively, after the administration of sugammadex. Both patients were asthmatic, and there was no evidence that these symptoms were related to sugammadex. In other subsets of high-risk pulmonary patients (cystic fibrosis and end-stage lung disease), the successful use of sugammadex has been reported.[165] Reversal of a neuromuscular blockade with sugammadex has potential advantages compared with anticholinesterase drugs (e.g., neostigmine) in patients with pulmonary disease, because sugammadex lacks interactions with the muscarinic cholinergic system, and there is no need for coadministration of anticholinergic compounds (also see "Complications Associated With Inhibitors of Acetylcholinesterase").

Renal Failure. The use of sugammadex to reverse rocuronium neuromuscular blockade was investigated in 15 patients with severe renal impairment (creatinine clearance <30 mL/min) and compared with 15 patients with normal renal function (creatinine clearance >80 mL/min).[166] Sugammadex 2 mg/kg was administered at the reappearance of T2. There were no differences between groups in the recovery profile or the incidence of residual blockade after sugammadex (Table 35-9). Because complete elimination of the sugammadex-rocuronium complex remains poorly understood in renal impairment, sugammadex is at present not recommended for use in patients with severe renal failure. However, it can be used in patients with mild or moderate renal dysfunction.[166] Theoretically, because of the molecular mass of the rocuronium/vecuronium-sugammadex complex, it is possible to decrease the plasma levels of this complex by dialysis. Hemodialysis using a high-flux dialysis method has been demonstrated to be effective in removing sugammadex and the sugammadex-rocuronium complex in patients with severe renal impairment.[138]

Hepatobiliary Disease. Sugammadex has not been studied in animal models or in patients with hepatic impairment. However, it is known that the biliary route of excretion becomes unavailable for either sugammadex or the rocuronium/vecuronium-sugammadex complex, because the large size of this complex prohibits such excretion.[167] A population pharmacokinetic/pharmacodynamic (PK-PD)

model was used to simulate the scenario of an immediate reversal and reversal of a profound rocuronium-induced neuromuscular blockade in patients with hepatic impairment.[167] Under such study conditions, hepatic impairment had little effect on the reversal time when sugammadex (16 mg/kg) was administered 3 minutes after rocuronium (1.2 mg/kg). However, in other scenarios (sugammadex 2 mg/kg at reappearance of T2 and 4 mg/kg after 15 minutes), recovery from a rocuronium-induced (1.2 mg/kg) neuromuscular blockade was predicted to be longer than that seen in healthy patients.[167] In patients with hepatobiliary disease, the recovery of neuromuscular function after sugammadex administration will likely be faster than reversal with anticholinesterase drugs (but not be as rapid as patients without hepatobiliary disease). The explanation of the slower reversal is not yet fully understood and needs to be investigated in clinical studies. Based on limited available data, sugammadex should be used with caution in patients with hepatobiliary disease.

Obesity. Patients with obesity, particularly morbid obesity (body mass index [BMI] > 40 kg/m^2), are at risk for cardiovascular and respiratory complications perioperatively (also see Chapter 71).[168] These patients are susceptible to critical respiratory events in the postoperative period, including hypoventilation, hypoxia, airway obstruction, and acute respiratory failure.[38,67] The presence of postoperative residual neuromuscular blockade may further increase the risk for postoperative complications in these patients by producing impairment of the integrity of the upper airway and upper airway collapse.[33,34] Therefore, a rapid and complete reversal of neuromuscular blockade must be achieved before tracheal extubation is attempted. In this setting, sugammadex may have a more favorable recovery profile than traditional anticholinesterase drugs because it provides a more reliable recovery of neuromuscular functions and a less frequent risk of incomplete neuromuscular recovery.[168] A key issue is determining the appropriate dose of sugammadex to administer in a morbidly obese patient that is sufficient to capture remaining NMBD molecules. Whereas the dosing of NMBDs in obese patients should be based on lean/ideal body weight (because these drugs are hydrophilic and their volume of distribution is minimally affected by obesity), the dosing of sugammadex in obese patients is currently under debate. In order to ensure complete neuromuscular recovery, the dose of sugammadex must be sufficient to affect the gradient between the peripheral and central compartments and effectively encapsulate all rocuronium molecules. An inadequate dose of sugammadex may be incapable of sustaining this redistribution of rocuronium and lead to reoccurrence of the neuromuscular blockade.

The current product monograph recommends calculating the sugammadex dose based on the patient's actual body weight. However, because the low volume of distribution at steady state (estimated at 0.16 L/kg) restricts distribution to the intravascular space, it might be relevant to determine the dose of sugammadex based on the lean/ideal body weight and not on the actual body weight.[166] Several studies have investigated the dosage of sugammadex based on lean or variations on the lean/ideal body weight.[169-172] In one investigation, a sugammadex dose of 4 mg/kg based on a lean/ideal body weight calculation was administered to morbidly obese patients during a profound rocuronium neuromuscular blockade.[171] Approximately 40% of these patients were inadequately reversed with a lean/ideal body weight–based dose of sugammadex. In these patients, an additional dose of sugammadex 2 mg/kg based on lean/ideal body weight was required to achieve a TOF ratio 0.90. The conclusion of the authors was that a sugammadex dose calculated according to lean/ideal body weight was insufficient for reversing both profound and moderate blockade in a considerable number of morbidly obese patients.[171]

In another study in morbidly obese patients, investigators examined reversal of a moderate level of a rocuronium neuromuscular blockade (at T1-T2) using a dose of sugammadex of 2.0 mg/kg.[170] Four different weight corrections were used: lean/ideal body weight, lean/ideal body weight +20%, lean/ideal body weight +40%, and actual body weight. This study demonstrated that a moderate rocuronium neuromuscular blockade could be effectively reversed with sugammadex 2.0 mg/kg using the calculation lean/ideal body weight +40%.[170] However, longer and great interindividual variability of recovery times occur when dosing is based on lean/ideal body weight compared with dosing based on actual body weight.[170,171] Additionally, reoccurrence of neuromuscular blockade after suboptimal dosing of sugammadex has been reported in a morbidly obese patient.[172] Therefore, the dosing of sugammadex in obese patients is still under debate. Until more data are available, the dose of sugammadex should be based on the actual body weight.

Cesarean Section and Pregnant Patients. Induction of general anesthesia in late pregnancy and for patients undergoing cesarean section typically involves a rapid sequence induction of anesthesia with either thiopental or propofol and a rapid-onset neuromuscular blocking drug (also see Chapter 77). For decades, succinylcholine has been the prototypic NMBD used in these procedures to produce optimal endotracheal intubation conditions.[173] Rocuronium is an acceptable alternative to succinylcholine in rapid sequence induction of anesthesia procedures; rocuronium in doses larger than 1.0 mg/kg not only provides onset of action within 60 seconds, but also identical intubation conditions compared with succinylcholine.[174] However, the duration of action of rocuronium in dosages of 1.0 mg/kg or greater will result in a profound neuromuscular blockade of long duration (often more than 2 hours). Furthermore, the risk of failed intubation in the obstetric population is at least eight times higher compared with nonpregnant females.[175] In case of a failed endotracheal intubation scenario or a "cannot intubate, cannot ventilate" situation, rocuronium, even in dosages up to 1.2 mg/kg, can be immediately reversed with sugammadex 16 mg/kg.[146]

Preclinical animal data demonstrated that uteroplacental transfer of sugammadex is very small (<2% to 6%). Sugammadex does not have negative effects on pregnancy or on embryonic, fetal, or postnatal development.[173,176,177] Although no data are available about the excretion of sugammadex in human breast milk, excretion in breast milk is likely minimal, with insignificant clinical impact because oral absorption of cyclodextrins

in general is small. Therefore, sugammadex can be used in breastfeeding females. In two case series examining obstetric patients who received rocuronium and sugammadex (7 and 18 patients), no side effects were observed.[176,177] The efficacy and safety of sugammadex in obstetric anesthesia has not been determined; yet serious adverse events for the mother or the neonate have not been reported after sugammadex.

Neuromuscular Disorders. Neuromuscular disorders are frequently associated with an increased incidence of perioperative respiratory complications due to muscle weakness.[178,179] In these patient groups, administration of succinylcholine is often contraindicated and associated with potential life-threatening side effects. The use of nondepolarizing NMBDs can on occasion be associated with prolonged spontaneous neuromuscular recovery, even after a single dose. Consequently, these patients have an increased risk for postoperative muscle weakness of multifactorial origin, one being residual neuromuscular blockade.[178,179] Prompt recovery of neuromuscular function is essential in order to optimize patient safety and reduce the risk of pulmonary complications. However, reversal with anticholinesterase (e.g., neostigmine), especially in neuromuscular disorders, can be associated with postoperative complications.[179]

Multiple case reports describe the use of sugammadex in patients with various neuromuscular disorders such as myasthenia gravis, myotonic dystrophy, and spinal muscular atrophy (Fig. 35-21).[180-184] In general, dosing regimens for sugammadex were consistent with recommended doses adjusted to actual body weight and based on the level of neuromuscular blockade at the time of reversal. Sugammadex administration resulted in prompt reversal of neuromuscular blockade with a similar recovery profile as observed in normal patients. Although no studies have been performed in patients with neuromuscular disorders, the reported cases indicate that sugammadex should be considered as an alternative reversal drug (e.g., instead of neostigmine) in this patient population. These observations need to be confirmed in a larger series of patient studies.

Side Effects and Drug Interactions

Sugammadex is contraindicated in patients with known hypersensitivity to the drug. The potential for hypersensitivity is currently under investigation. At the time this chapter was written, sugammadex had been approved in many countries in the world, but not in the United States or Canada. Hypersensitivity was the major concern; however, this is difficult to study because hypersensitivity reactions occur rarely. Other reported side effects include coughing, movement, parosmia (abnormal sense of smell), and elevated levels of *N*-acetyl-glucosaminidase in the urine.[167] Coughing and movement after the administration of sugammadex may have been due to the unmasking of inadequate anesthesia rather than a direct side effect of sugammadex. These observations recall the old saying that patients are often "adequately paralyzed, but not anesthetized." This concern has existed for decades, well before the introduction of sugammadex. Cyclodextrins, such as sugammadex, are well known for their ability to form inclusion complexes with other compounds. Sugammadex forms a very tight complex with rocuronium or vecuronium in a 1:1 molecular ratio; however, because of its mechanism of action, it is possible that other relevant drug interactions may occur.[185] Theoretically, two important drug interactions can take place. First, sugammadex is capable of encapsulating endogenous or pharmaceutical molecules other than steroidal neuromuscular blocking drugs, resulting in reduced efficacy of the encapsulated molecules. However, the ability to form complexes with steroidal or nonsteroidal molecules such as cortisone, atropine, and verapamil is clinically insignificant, because the affinity for sugammadex is 120 to 700 times less than that of rocuronium.[185] In preclinical studies, an interaction of sugammadex with other steroidal compounds could be excluded up to a dose of sugammadex of 500 mg/kg/day.[186] Second, if the affinity of sugammadex for another molecule is very high, this molecule may displace rocuronium or vecuronium from the complex with sugammadex, resulting in reoccurrence of neuromuscular blockade. Both drug interactions may have potential clinical safety implications.[185] A modeling approach has been developed to evaluate 300 compounds (including the most commonly used drugs in the perioperative period) for possible displacement interactions with sugammadex.[185] In this screening, three compounds were identified as having possible displacement interactions: toremifene, fusidic acid, and flucloxacillin.[185] However, no clinically relevant reoccurrence of neuromuscular blockade was identified when sugammadex was used in combination with these drugs.[185] A clinical study reported that flucloxacillin did not cause reoccurrence of neuromuscular blockade after

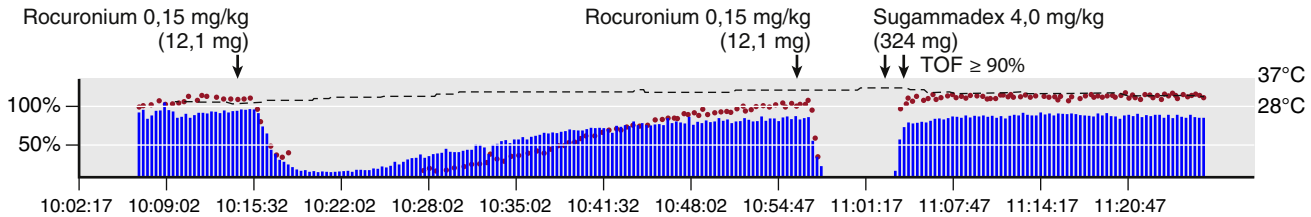


Figure 35-21. Original tracing of sugammadex reversal in a patient with myasthenia gravis. The time to spontaneous recovery from the first profound rocuronium-induced neuromuscular blockade to a TOF ratio was 36.5 minutes. The time from the start of the administration of sugammadex 4.0 mg/kg after the second dose of rocuronium to the recovery of the TOF ratio to 0.90 was 2.7 minutes. *Blue tracing* represent T1 recovery while *red dots* represent TOF ratio recovery. *Black dashed line* indicates hand skin temperature (degrees Celcius). *(From de Boer HD, van Egmond J, Driessen JJ, et al: A new approach to anesthesia management in myasthenia gravis: reversal of neuromuscular blockade by sugammadex,* Rev Esp Anesthesiol Reanim *57: 81-84, 2010.)*

reversal with sugammadex; no clinically important displacement interaction was observed.[187]

Special Considerations

Reintubation of the Trachea After Initial Reversal of Neuromuscular Blockade With Sugammadex. Patients receiving sugammadex before extubation of the trachea who need reintubation require special consideration because the remaining circulating sugammadex molecules may potentially interfere with readministration of rocuronium or vecuronium. In this setting, two alternate strategies can reestablish a neuromuscular blockade. Within 24 hours of sugammadex administration, it is currently recommended that a nonsteroidal NMBD be used instead of rocuronium or vecuronium. This conservative approach is based on the maximum clearance time for sugammadex. However, preclinical and clinical studies have shown that it is possible to safely reestablish neuromuscular blockade with rocuronium earlier than 24 hours.[188] A modeling-based study in healthy volunteers revealed that high-dose rocuronium given 5 to 60 minutes after sugammadex reversal produced a complete neuromuscular blockade (T1 = 0%).[189] Rocuronium (1.2 mg/kg) administrated 5 minutes after sugammadex reversal produced a rapid onset of neuromuscular blockade (T1 = 0%), with a mean onset time of approximately 3 minutes. Thirty minutes after administration of sugammadex, an onset time of 1.5 minutes can be achieved with rocuronium (1.2 mg/kg). Hence an inverse relationship exists between the onset time and the time interval between sugammadex and the repeat dose of rocuronium, and a direct relationship exists between the duration of neuromuscular blockade and the time interval between sugammadex and the repeat dose of rocuronium.

Based on dose calculations using a model in which the equilibrium is described in the common volume of distribution of rocuronium and sugammadex, even a second reversal is possible using sugammadex with large doses between 8 and 20 mg/kg.[188]

Incomplete Reversal of Neuromuscular Blockade. Although sugammadex encapsulates rocuronium and vecuronium to form a rigid complex, case reports have described incomplete reversal of neuromuscular blockade.[141,190] In a dose-finding study, a case was described in which a temporary decrease in the TOF response was observed in a healthy patient after reversal with 0.5 mg/kg sugammadex.[190] The TOF ratio initially reached 0.70 before decreasing to 0.30 and then gradually increasing to 0.90 (Fig. 35-22). The authors hypothesized that the decrease in TOF ratio occurred because of redistribution of unbound rocuronium from the peripheral compartments, with insufficient sugammadex available for additional encapsulation of rocuronium. Similarly, incomplete reversal was reported in two healthy patients given suboptimal doses of sugammadex (0.5 mg/kg) during profound rocuronium-induced neuromuscular blockade.[141] Therefore, the recommended dose adjusted to the depth of neuromuscular blockade should be administered.

Female Patients. Sugammadex may interact with hormonal contraceptive drugs. Possible capturing interactions, whereby unwanted encapsulation of a third drug by sugammadex reduces its clinical efficacy, have been investigated. In pharmacokinetic-pharmacodynamic simulations, it was predicted that 34% of (free) etonogestrel might be captured by 4 mg/kg sugammadex under very conservative modeling assumption conditions.[186] The interaction with this bolus dose of sugammadex resulted in a decrease in etonogestrel exposure, which was similar to the decrease seen after one missed daily dose of an oral contraceptive. Patients using hormonal contraceptives should be informed about the possible reduced effectiveness of hormonal contraceptive drugs after the administration of sugammadex. The use of an additional nonhormonal contraceptive method for the next 7 days should be considered in this patient population.

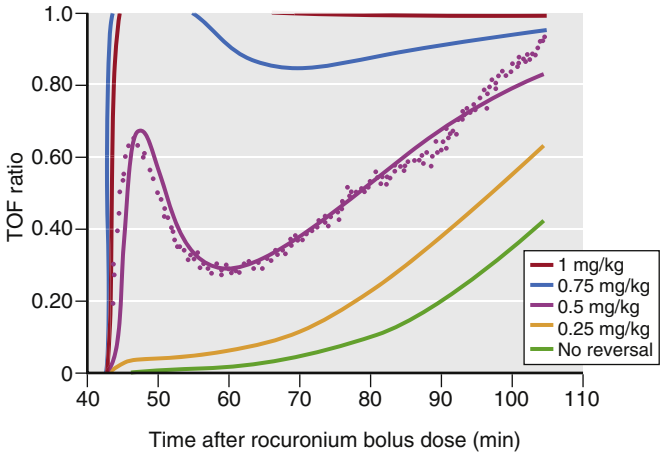


Figure 35-22. The train-of-four data *(dots)* and the results of simulations *(solid lines)* of various sugammadex dosing amounts. Muscle relaxation rebound only occurs for sugammadex doses in a limited range. The simulations indicate that for this patient, doses larger than about 1 mg/kg are sufficient to achieve rapid muscle relaxation reversal and avoid muscle relaxation rebound. *(From Eleveld DJ, Kuizenga K, Proost JH, et al: A temporary decrease in twitch response during reversal of rocuronium-induced muscle relaxation with a small dose of sugammadex,* Anesth Analg *104:582-584, 2007.)*

Electroconvulsive Therapy. Electroconvulsive therapy is the transcutaneous application of small electrical stimuli to the brain for treatment of selected psychiatric disorders like major depression. The tonic-clonic convulsions associated with electroconvulsive therapy can result in injuries such as limb fractures and compression fractures of vertebral bodies. The introduction of anesthesia, especially neuromuscular blockade, can mitigate tonic-clonic motor activity and reduce the physiologic trauma associated with uncontrolled tetanic muscle contractions.[191] Succinylcholine is commonly used as a neuromuscular blocking drug in these patients, and its use is associated with well-known unwanted side effects.[191] Rocuronium has similar efficacy as succinylcholine in electroconvulsive therapy, making it an appropriate alternative to succinylcholine.[192] However, the increased doses of rocuronium required to decrease the onset time are associated with a prolonged duration of neuromuscular blockade. Several reports have evaluated the use of sugammadex in electroconvulsive therapy. These investigations demonstrated that sugammadex produced a complete and rapid reversal of neuromuscular blockade

induced by rocuronium, without signs of residual blockade or other safety concerns.[192-195] Therefore, the combination of rocuronium and sugammadex may be an alternative to succinylcholine for electroconvulsive therapy. However, the required dose of sugammadex in this clinical situation is not well established.

Historically, an important strategy in anesthesia has been to ensure that neuromuscular blockade is sufficiently recovered to achieve adequate antagonism by neostigmine. Having an intense neuromuscular blockade at the end of surgery would more likely result in residual blockade. With the availability of sugammadex, a profound, or deep, neuromuscular blockade has been recommended for the entire duration of laparoscopy. A profound neuromuscular blockade increases surgical space with smaller pressures for the pneumoperitoneum.[196] It is even possible that reducing insufflation pressures may improve patient outcomes.[196] Furthermore, Staehr-Rye and associates[197] have postulated that a deep or profound neuromuscular blockade is associated with more optimal surgical conditions, which leads to less postoperative pain and nausea and vomiting. Sugammadex, at doses of 2 to 8 mg/kg, was given to reverse the blockade when the TOF ratio was less than 0.90.

In Japan, the use of sugammadex is widespread, and Japanese anesthesiologists have one of the largest clinical experiences with sugammadex in the world. A recently published report describes the clinical experience in Japan and provides a look at the role of sugammadex in clinical practice.[198] Notably, although neuromuscular blockade was not routinely monitored intraoperatively, the TOF ratio was determined after tracheal extubation. A total of 249 patients were studied in three separate groups: patients with spontaneous recovery (n = 23) were compared with patients being reversed with either neostigmine (n = 109) or sugammadex 2.7 mg/kg (n = 117). Although the sugammadex group had the least frequent incidence of residual neuromuscular blockade, all three groups had a surprisingly frequent incidence of residual neuromuscular blockade.[198]

A scholarly editorial written by Naguib and associates[199] placed prime emphasis on the dose of sugammadex used for reversal in combination with the lack of neuromuscular monitoring. Although proper monitoring is strongly advisable, an adequate dose of sugammadex is under current debate. Although the reversal effect of neostigmine is not improved by increasing the dose above the recommended dose interval, there are strong reasons to believe that sugammadex in doses larger than 2.7 mg/kg would be more effective for reversal. Others argue that a dose of sugammadex larger than 2.0 mg/kg would not be necessary if proper monitoring were used. Of course, another possibility exists. It would seem that a larger dose of sugammadex plus neuromuscular monitoring would be ideal.

In conclusion, sugammadex is an innovative addition to the armamentarium of reversal of neuromuscular blockade options. Although the expense of sugammadex continues to be an important factor that may limit its use, many institutions currently use sugammadex for routine reversal of neuromuscular blockade. We speculate whether, in the future, larger doses of sugammadex will likely be used and whether routine neuromuscular monitoring will finally be mandatory in anesthetic practice among countries worldwide.

CYSTEINE REVERSAL OF FUMARATE NEUROMUSCULAR BLOCKING DRUGS

A new class of nondepolarizing NMBDs called fumarates has been recently developed. These NMBDs are olefinic (double-bonded) isoquinolinium diester compounds that differ from symmetric benzylisoquinolines such as mivacurium in their unique method of inactivation. The developed drugs (gantacurium [GW280430A, AV430A], CW002, and CW011) bind to L-cysteine to form less active degradation products (Fig. 35-23). The administration of L-cysteine can rapidly inactivate fumarate compounds and reverse neuromuscular blockade.

Gantacurium is an asymmetric α-chlorofumarate that was developed to be a replacement for succinylcholine.[200] Gantacurium has a rapid onset and short duration of effect. The brief duration of gantacurium is primarily due to rapid reaction and subsequent inactivation of the drug with free cysteine in the plasma. The process of adduction of cysteine to gantacurium occurs at the central fumarate double bond. The adduction changes the stereochemistry of gantacurium so that it can no longer bind to the nAChR at the neuromuscular junction. Degradation also occurs through a slower secondary route (pH-sensitive ester hydrolysis) that yields two products without neuromuscular blocking properties.[200,201] CW 002 (a symmetrical fumarate) and CW 011 (an asymmetric maleate) are investigational NMBDs with no halogen (chlorine) substitution at the central double-bonded carbons. The absence of chlorine results in a slower adduction with cysteine; the inactivation of CW 002 and CW 011 is slower than gantacurium, resulting in a duration of action consistent with an intermediate-acting NMBD.

Cysteine is a nonessential endogenous amino acid derived from one molecule of serine and one molecule of methionine. It is composed of L- and D-enantiomers. L-cysteine is a normal building block of protein and is a conditionally essential amino acid in infants.[202] Several therapeutic applications of cysteine in medicine are common. It is often added to total parenteral nutrition solutions for pediatric patients in doses of approximately 80 mg/kg/day. An acetylated derivative of cysteine (*N*-acetyl L-cysteine) is approved for use in the treatment of acute acetaminophen toxicity. In the doses used clinically for these applications, there does not appear to be obvious toxicity. L-cysteine has also been studied for reversal of the neuromuscular blockade for fumarate NMBDs. Several laboratory investigations have attempted to define the L-cysteine dose necessary to effectively reverse gantacurium, CW 002, and CW 011 neuromuscular blockade.

The first of the fumarate NMBDs studied was gantacurium. In monkeys, the total duration of action was one half to one third that of mivacurium at equipotent doses; at three times the ED_{95} doses, the time until 95% twitch recovery was 8.5 ± 0.5 minutes versus 22.0 ± 2.6 minutes, respectively.[201] The administration of edrophonium 0.5 mg/kg accelerated the recovery of blockade. In a human volunteer trial, the time from administration of 0.40 mg/kg of gantacurium (2 × ED_{95}) until a TOF ratio

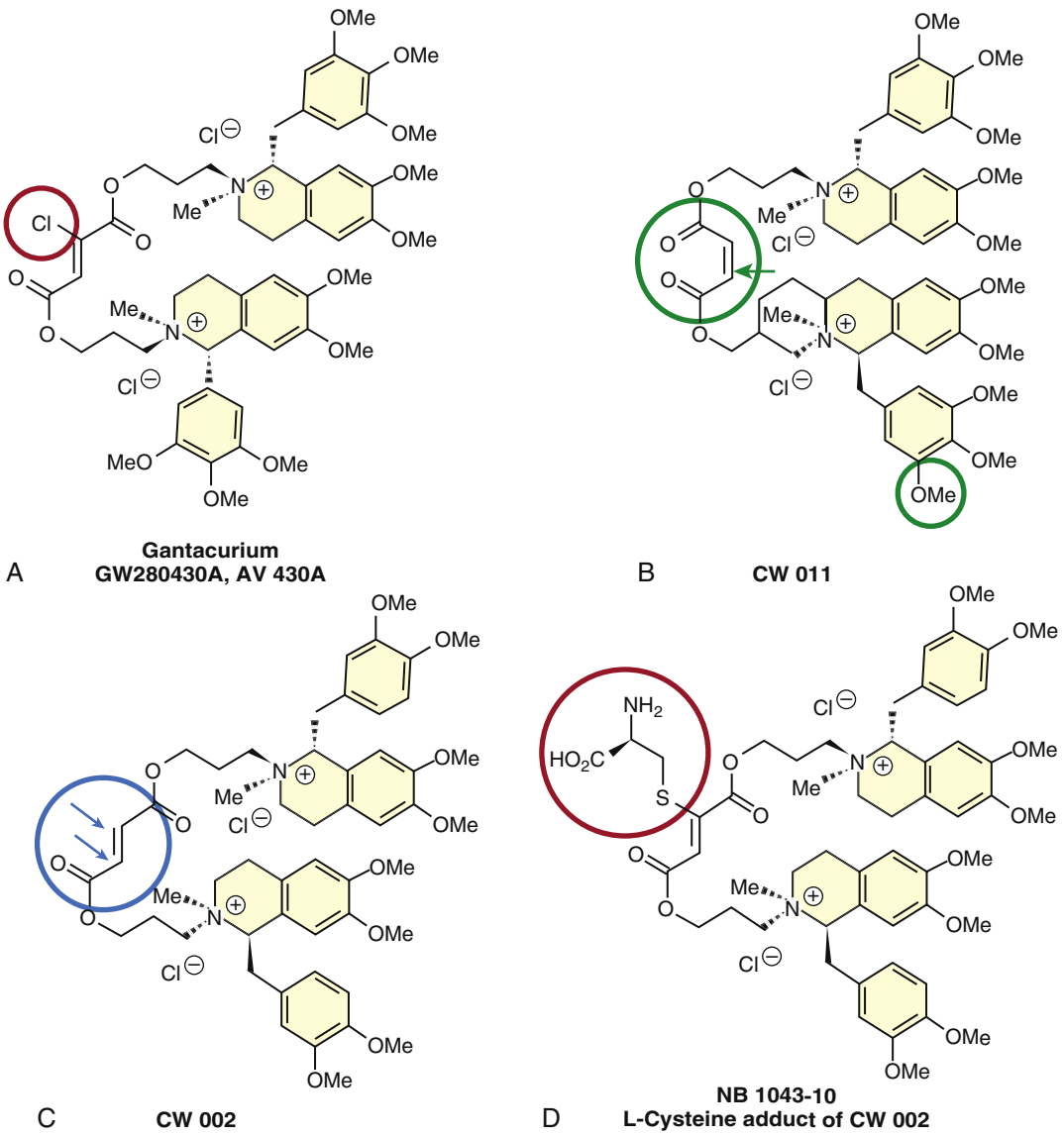


Figure 35-23. The chemical formulas of gantacurium (**A**), CW 011 (**B**), and CW 002 (**C**). Chemical features are as follows: chlorine substitution *(red circle)* on the olefinic double bond of gantacurium, a chlorofumarate, is designed to accelerate the L-cysteine adduction reaction. The fumarate CW 002 is symmetrical with no halogen (chlorine) substitutions and undergoes L-cysteine adduction more slowly than gantacurium, at either olefinic carbon *(blue arrows)*, enabled by the adjacent α-carboxyl (ester) groups. The maleate CW 011 is asymmetric in that one isoquinolinium group contains an extra methoxy substitution *(green circle)*. This may reduce access of L-cysteine to the olefin *(green arrow)* and may decrease the rate of the adduction reaction. The chemical formula of NB 1043-10, the L-cysteine adduct of CW 002, is also shown (**D**). The L-cysteine adduction is highlighted by the *red circle. (From Savarese JJ, McGilvra JD, Sunaga H, et al: Rapid chemical antagonism of neuromuscular blockade by L-cysteine adduction to and inactivation of the olefinic (double-bonded) isoquinolinium diester compounds gantacurium (AV430A), CW 002, and CW 011*, Anesthesiology *113:58-73, 2010.)*

0.90 or greater was achieved was studied during spontaneous recovery or reversal with edrophonium 0.5 mg/kg.[203] Mean recovery time was significantly more rapid in the reversal group (3.8 minutes) compared with the spontaneous recovery group (14.3 minutes). The reversal of gantacurium with cysteine was investigated in monkeys.[202] A bolus of L-cysteine (10 mg/kg) given 1 minute after gantacurium reduced duration from 10.4 ± 3.1 minutes (spontaneous recovery) to 3.0 ± 1.0 minutes ($P < .001$). Antagonism of gantacurium was significantly faster at 1 minute with L-cysteine than edrophonium. These studies suggest that although gantacurium is a short-acting NMBD, recovery can be further enhanced by the administration of L-cysteine.

In contrast to gantacurium, CW 002 and CW 011 have a duration of action between a short-acting and intermediate-acting NMBD. In monkeys given four to five times the ED_{95} of CW 002 and CW 011, the duration of blockade was three times longer than gantacurium (28.1 and 33.3 minutes versus 10.4 minutes), but only half the duration of cisatracurium.[202] The administration of neostigmine 1 minute after CW 002 did not accelerate neuromuscular recovery. Immediate reversal of CW 002 with cysteine (50 mg/kg), however, was highly effective in antagonizing

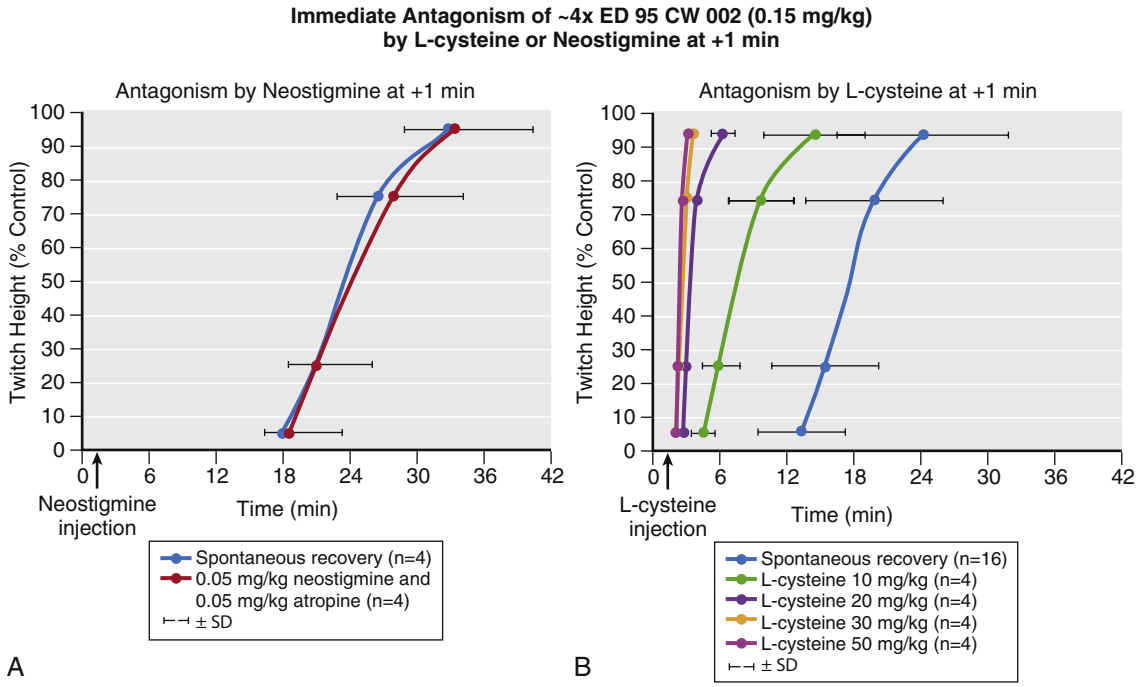


Figure 35-24. Immediate antagonism of CW 002 blockade 1 minute after CW 002 dosage of 0.15 mg/kg, or ≈4 × ED95, injected at $t = 0$. Neostigmine (0.05 mg/kg + atropine 0.05 mg/kg) or L-cysteine (10, 20, 30, or 50 mg/kg) was given at +1 min. Neostigmine did not shorten recovery (**A**), whereas L-cysteine produced a dose-related acceleration of recovery (**B**), peaking at 50 mg/kg. Data were taken from anesthetized rhesus monkeys. *(From Savarese JJ, McGilvra JD, Sunaga H, et al: Rapid chemical antagonism of neuromuscular blockade by L-cysteine adduction to and inactivation of the olefinic (double-bonded) isoquinolinium diester compounds gantacurium (AV430A), CW 002, and CW 011,* Anesthesiology *113:58-73, 2010.)*

neuromuscular blockade (95% of baseline twitch height within 2.2 ± 0.3 minutes and to a TOF ratio of 100% 1 to 2 minutes later)[202] (Fig. 35-24). Similar findings were observed with CW 011 using this model. Larger doses of L-cysteine were needed to optimally reverse CW 002 and CW 011 (50 mg/kg) compared with gantacurium (10 mg/kg); this is likely related to the slower rate of adduction of L-cysteine to these compounds, as well as the greater potency of CW 002 and CW 011. L-Cysteine reversal of CW 002 has also been investigated in a dog model given a dose of 9 × ED_{95}.[204] L-Cysteine (50 mg/kg) reduced the median duration of blockade from 70 minutes (spontaneous recovery) to less than 5 minutes. Doses of up to 200 mg/kg produced minimal hemodynamic changes and resulted in no anatomic, biochemical, or histologic evidence of organ toxicity.

In summary, fumarates are a new class of NMBDs that are inactivated primarily via adduction of cysteine to the double bond of the compounds, resulting in breakdown products that do not bind to the neuromuscular junction. Initial laboratory studies have shown that the administration of exogenous L-cysteine results in complete reversal of deep neuromuscular blockade within 2 to 3 minutes. These studies suggest that chemical antagonism of fumarate NMBDs will allow clinicians to rapidly and completely antagonize neuromuscular blockade, even when large doses of an NMBD have been recently administered. Early clinical trials in human volunteers have examined the pharmacology of gantacurium, and investigations of CW 002 in volunteers are currently ongoing. The optimal dose of L-cysteine is 50 mg/kg in an animal model. The dosing of L-cysteine needed to reverse the effects of gantacurium, CW 002, and CW 011 in humans has not been established. Additional investigations are also needed to determine whether large doses of cysteine produce adverse effects in humans. If future studies are consistent with these early findings, fumarate NMBDs may allow clinicians to maintain profound neuromuscular blockade throughout the surgical procedure with little risk of postoperative residual paralysis.

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Chapter 36

Local Anesthetics

CHARLES B. BERDE • GARY R. STRICHARTZ

Key Points

- Local anesthetics block voltage-gated sodium channels thereby interrupting the initiation and propagation of nerve impulses in axons. Based on this mechanism of action, local anesthetics provide a wide variety of biologic actions, both desirable and unwanted, and have side effects through other mechanisms.
- Currently available local anesthetics are of two chemical classes: aminoesters and aminoamides.
- The low potency and lack of specificity of available local anesthetics are in part due to the weak structural constraints at their binding site on the sodium channel. Most of their features are derived from the requirement for high solubility and rapid diffusion in both aqueous environments and the lipid phases of biologic membranes.
- Reversible protonation of the tertiary amine group tends to make local anesthetics less charged at more basic pH values and more charged at neutral or acidic pH; the neutral base forms are more soluble in lipid environments, whereas the charged acid forms are more soluble in aqueous environments.
- Aminoesters are metabolized primarily by plasma esterases, and aminoamides are metabolized primarily by hepatic cytochrome P450–linked enzymes.
- The principal systemic toxicities of local anesthetics involve the heart (including atrioventricular conduction block, arrhythmias, myocardial depression, and cardiac arrest) and the brain (including agitation, lethargy, seizures, and generalized central nervous system depression). Hypoxemia and acidosis exacerbate these toxicities. Cardiopulmonary resuscitation (see Chapter 108) after bupivacaine overdose is particularly difficult. Therefore, prevention of intravascular injection or overdose is crucial, and major nerve blockade should involve incremental and fractionated delivery rather than bolus administration.
- Local anesthetics are directly toxic to nerve at the concentrations supplied in commercial solutions. Intraneural concentrations during regional anesthesia are generally (but not always) less than a threshold for toxicity because of local vascular removal, and dilutional effects due to spread of solutions through tissues and into nerve. Hence, injection into a constrained tissue space increases the risk for local toxicity.
- Optimal use of local anesthetics in regional anesthesia requires an understanding of (1) the individual patient's clinical situation, (2) the location, intensity, and duration of regional anesthesia and analgesia required, (3) anatomic factors affecting deposition of drug near nerves, (4) proper drug selection and dosing, and (5) repeated assessment of clinical effects after administration of a local anesthetic.
- There are several new formulations for topical anesthesia. Single-stereoisomer (as opposed to a racemic mixture) formulations can reduce systemic toxicity and improve sensory selectivity.
- Local anesthetics are increasingly being used as postoperative infusions and via both local and systemic administration for the management of chronic pain. Further research and development could lead to safe, more selective local anesthetics that will facilitate prolonged administration in the setting of acute or chronic pain.

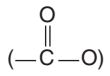
Local anesthesia results from the blockade of nerve impulses to abolish sensation. All currently available, clinically useful anesthetics are either aminoesters or aminoamides. These drugs, when applied in sufficient concentration near the site of action, prevent conduction of electrical impulses by the membranes of nerve and muscle. In addition to blockade of impulses, local anesthetics can inhibit various receptors, enhance release of glutamate, and depress the activity of certain intracellular signaling pathways. When local anesthetics are given systemically, the functions of cardiac, skeletal, and smooth muscle, as well as transmission of impulses in the central and peripheral nervous systems and within the specialized conducting system of the heart, can all be altered. Local anesthetics can abolish sensation in various parts of the body by topical application, injection near peripheral nerve endings and major nerve trunks, or instillation within the epidural or subarachnoid space. Toxicity may be local or systemic. The central nervous and cardiovascular systems are most commonly the targets for acute clinical toxicity caused by local anesthetics.

BASIC PHARMACOLOGY

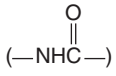
CHEMISTRY

Local Anesthetic Molecule

The typical local anesthetic molecule, exemplified by lidocaine and procaine (Fig. 36-1), contains a tertiary amine attached to a substituted aromatic ring by an intermediate chain that almost always contains either an ester



or an amide linkage.



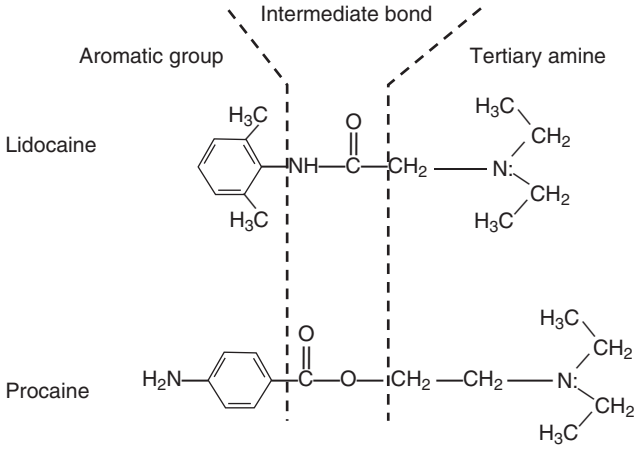


Figure 36-1. Structures of two local anesthetics: the aminoamide lidocaine and the aminoester procaine. In both drugs, a hydrophobic aromatic group is joined to a more hydrophilic base, the tertiary amine, by an intermediate amide or ester bond.

Local anesthetics can therefore be classified as aminoester or aminoamide compounds. The aromatic ring system gives a lipophilic (membrane-liking) character to its portion of the molecule, whereas the tertiary amine end is relatively hydrophilic, particularly since it is partially protonated and thus bears some positive charge in the physiologic pH range (Fig. 36-2). The structures of commonly administered local anesthetics are given in Table 36-1, and their physicochemical properties are given in Table 36-2.

STRUCTURE-ACTIVITY RELATIONSHIPS AND PHYSICOCHEMICAL PROPERTIES

The intrinsic potency and duration of action of local anesthetics are clearly dependent on certain features of the molecule.

Lipophilic-Hydrophilic Balance

The lipophilic versus hydrophilic character of a local anesthetic depends on the size of alkyl substituents on or near the tertiary amine and on the aromatic ring. *Lipophilicity* expresses the tendency of a compound to associate with lipids, and in this case membrane lipids in particular—a property usually approximated by equilibrium partitioning into a hydrophobic solvent such as octanol.[1] Although octanol/buffer partition coefficients are comparable to membrane/buffer partition coefficients for the uncharged species of local anesthetics, they severely underestimate membrane partitioning for the charged, protonated species—octanol being a poor model for the polar regions near the membrane surface where local anesthetics are concentrated.[2]

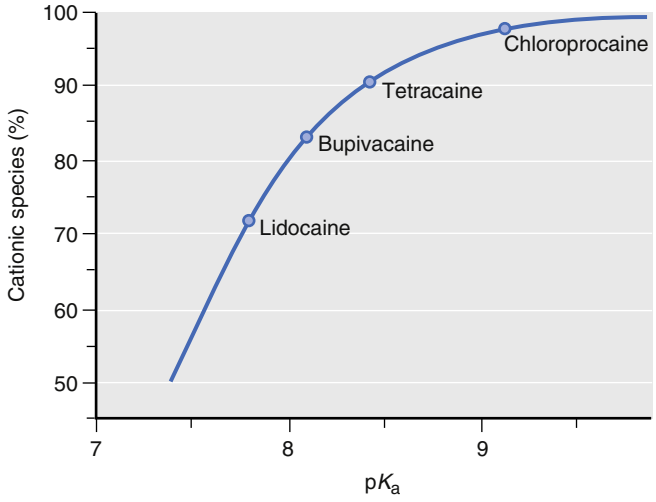


Figure 36-2. Fraction of local anesthetic in the protonated, cationic form of an aqueous solution at physiologic pH (7.4) as a function of the pK_a of the drug. Lidocaine, the drug with the lowest pK_a, has the smallest fraction of its molecules protonated, the largest in the neutral form, and vice versa for chloroprocaine, the local anesthetic with the highest pK_a. Individual drug molecules become protonated and deprotonated in thousandths of a second in solution.

TABLE 36-1 **REPRESENTATIVE LOCAL ANESTHETICS IN COMMON CLINICAL USE**

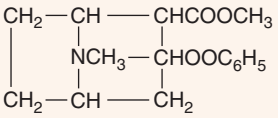
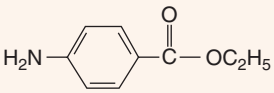
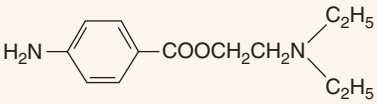
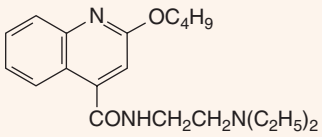
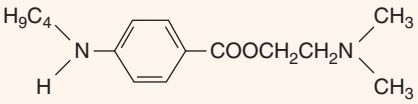
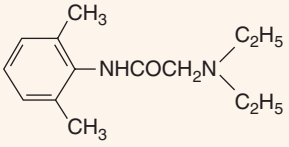
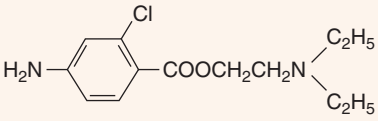
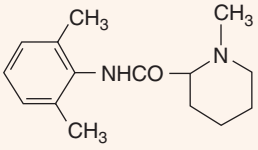
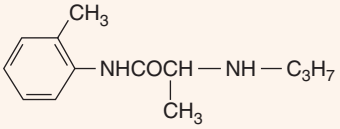
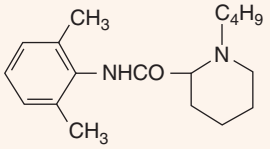
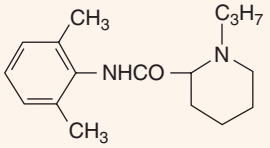
Generic* and Common Proprietary Names	Chemical Structure	Approximate Year of Initial Clinical Use	Main Anesthetic Use	Representative Commercial Preparation
Cocaine		1884	Topical	40-mg/mL solution
Benzocaine (Americaine)		1900	Topical	200 mg/mL
Procaine (Novocain)		1905	Topical Infiltration Spinal	200 mg/mL 10- and 20-mg/mL solutions 100-mg/mL solution
Dibucaine (Nupercaine)		1929	Spinal	0.667-, 2.5-, and 5-mg/mL solutions
Tetracaine (Pontocaine)		1930	Spinal	Niphanoid crystals—20- and 10-mg/mL solutions
Lidocaine (Xylocaine)		1948	Infiltration Peripheral nerve blockade Epidural Spinal Topical Topical	5- and 10-mg/mL solutions 10-, 15-, and 20-mg/mL solutions 10-, 15-, and 20-mg/mL solutions 50-mg/mL solution 20-mg/mL jelly, viscous 25-, 50-mg/mL ointment
Chloroprocaine (Nesacaine)		1955	Infiltration Peripheral nerve blockade Epidural	10-mg/mL solution 10- and 20-mg/mL solutions 20- and 30-mg/mL solutions
Mepivacaine (Carbocaine)		1957	Infiltration Peripheral nerve blockade Epidural	10-mg/mL solution 10- and 20-mg/mL solutions 10-, 15-, and 20-mg/mL solutions
Prilocaine (Citanest)		1960	Infiltration Peripheral nerve blockade Epidural	10- and 20-mg/mL solutions 10-, 20-, and 30-mg/mL solutions 10-, 20-, and 30-mg/mL solutions

TABLE 36-1 REPRESENTATIVE LOCAL ANESTHETICS IN COMMON CLINICAL USE—cont'd

Generic* and Common Proprietary Names	Chemical Structure	Approximate Year of Initial Clinical Use	Main Anesthetic Use	Representative Commercial Preparation
Bupivacaine (Marcaine)		1963	Infiltration Peripheral nerve blockade Epidural Spinal	2.5-mg/mL solution 2.5- and 5-mg/mL solutions 2.5-, 5-, and 7.5-mg/mL solutions 5- and 7.5-mg/mL solutions
Ropivacaine (Naropin)		1992	Infiltration Peripheral nerve blockade Epidural	2.5- and 5-mg/mL solutions 5- and 10-mg/mL solutions 5- and 7.5-mg/mL solutions

Modified from Covino B, Vassallo H: Local anesthetics: mechanisms of action and clinical use. *Orlando, Fla, 1976, Grune and Stratton.*
*United States Pharmacopeia nomenclature.

TABLE 36-2 RELATIVE IN VITRO CONDUCTION-BLOCKING POTENCY AND PHYSICOCHEMICAL PROPERTIES OF LOCAL ANESTHETIC DRUGS

Drug	Relative Conduction-Blocking Potency*	Physiochemical Properties	
		pK_a†	Hydrophobicity†
Low Potency			
Procaine	1	8.9	100
Intermediate Potency			
Mepivacaine	1.5	7.7	136
Prilocaine	1.8	8.0‡	129
Chloropro-caine	3	9.1	810
Lidocaine	2	7.8	366
High Potency			
Tetracaine	8	8.4	5822
Bupivacaine	8	8.1	3420
Etidocaine	8	7.9	7320

From Strichartz GR, Sanchez V, Arthur GR, et al: Fundamental properties of local anesthetics. II. Measured octanol : buffer partition coefficients and pK_a values of clinically used drugs, Anesth Analg *71:158-170, 1990.*
*Data derived from C fibers of isolated rabbit vagus and sciatic nerve.
†pK_a and hydrophobicity at 36° C; hydrophobicity equals the octanol/buffer partition coefficient of the base. Values are ratios of concentrations.
‡Values at 25° C.

The term *hydrophobicity*, expressed as octanol/buffer partitioning, describes a physicochemical property of local anesthetics.

Compounds with a more hydrophobic nature are obtained by increasing the size of the alkyl substituents. These agents are more potent and produce longer-lasting blocks than their less hydrophobic congeners do.[3-5] For example, etidocaine, which has three more carbon atoms than lidocaine does in the amine end of the molecule, is fourfold as potent and fivefold as long lasting as lidocaine when compared using impulse blockade in the isolated sciatic nerve.

Hydrogen Ion Concentration

Local anesthetics in solution exist in a rapid chemical equilibrium between the base, uncharged form (B) and the charged cationic form (BH^+). At a certain hydrogen ion concentration ($\log_{10}^{-1}$ [−pH]) specific for each drug, the concentration of local anesthetic base in solution is equal to the concentration of charged cation. The logarithm of this hydrogen ion concentration is called pK_a. The relationship between the fraction of charged drug and the pH is defined by

$$\frac{[BH^+]}{[B]} = 10^{pK_a - pH}$$

The pK_a values of local anesthetic agents in aqueous solution are listed in Table 36-2. The tendency to be protonated also depends on environmental factors, such as temperature and ionic strength, and on the medium surrounding the drug. In the relatively apolar milieu of a membrane, the average pK_a of local anesthetics is lower than in solution.[6] This is chemically equivalent to saying that the membrane concentrates the base form of the local anesthetic more than it concentrates the protonated cation form.

The pH of the medium containing the local anesthetic influences drug activity by altering the relative percentage of the base and protonated forms. For example, in inflamed tissues the pH is lower than normal, and local anesthetics are more protonated than in normal tissue and consequently penetrate the tissue more slowly (discussed later).

The relationship between pK_a and the percentage of local anesthetic present in the cationic form is shown in Figure 36-2. As described later, there are dual effects of pH on clinical effectiveness, depending on where the local anesthetic is injected and the importance of the base form for tissue penetration.

ANATOMY OF THE PERIPHERAL NERVE

Each peripheral nerve axon possesses its own cell membrane—the axolemma. Nonmyelinated nerves, such as

autonomic postganglionic efferent and nociceptive afferent C fibers, contain many axons encased in a single Schwann cell sheath. In contrast, all large motor and sensory fibers are enclosed in many layers of myelin, which consists of the plasma membranes of specialized Schwann cells that wrap themselves around the axon during axonal outgrowth. Myelin markedly increases the speed of nerve conduction by insulating the axolemma from the surrounding conducting salt medium and forcing the "action current" generated by an impulse to flow through the axoplasm to the nodes of Ranvier, which are periodic interruptions in the myelin sheath where the active impulse is regenerated (Fig. 36-3). The Na^+ channels that serve to propagate impulses are highly concentrated at the nodes of Ranvier of myelinated fibers,[7] but are distributed all along the axon of nonmyelinated fibers (see Fig. 36-3). A classification of peripheral nerves according to fiber size and physiologic properties is presented in Table 36-3.

A typical peripheral nerve consists of several axon bundles, or fascicles. Each axon has its own connective tissue covering—the *endoneurium*. Each fascicle of many axons is encased by a second connective tissue layer—the epithelial-like *perineurium*—and the entire nerve is wrapped in a loose outer sheath called the *epineurium* (Fig. 36-4). To reach the nerve axon, a local anesthetic molecule must traverse four or five layers of connective tissue or lipid membranous barriers, or both.

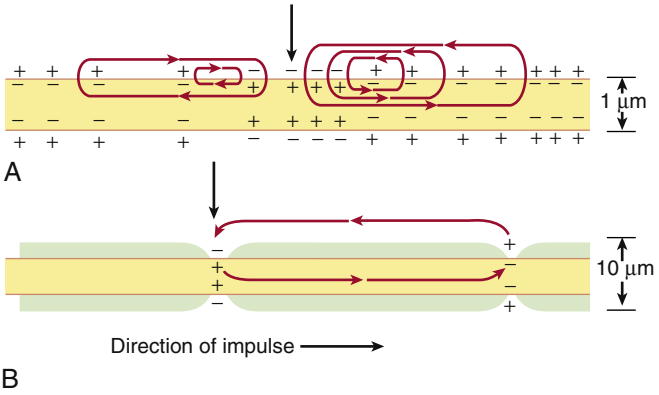


Figure 36-3. Pattern of local circuit currents flowing during propagation of an impulse in a nonmyelinated C fiber's axon (**A**) and a myelinated axon (**B**). During propagation of impulses, from left to right, current entering the axon at the initial rising phase of the impulse *(large vertical arrows)* passes through the axoplasm (local circuit current) and depolarizes the adjacent membrane. Plus and minus signs adjacent to the axon membrane indicate the polarization state of the axon membrane: negative inside at rest, positive inside during active depolarization under the action potential, and less negative in regions where local circuit currents flow. This ionic current passes relatively uniformly across the nonmyelinated axon, but it is restricted in the myelinated axon to entry at the nodes of Ranvier, several of which are simultaneously depolarized during a single action potential.

STRUCTURE OF THE AXONAL MEMBRANE

Biologic membranes consist of a molecular lipid bilayer containing proteins adsorbed on the surfaces, as well as embedded in or spanning the hydrocarbon core (Fig. 36-5). The character of the bilayer is determined by the phospholipids, which have long hydrophobic fatty acyl tails that lie in the center of the membrane, connected to polar hydrophilic head groups, which are usually composed of zwitterionic portions (containing both positive and negative charges) that project into the cytoplasm or the extracellular fluid. Within the membrane, there is both lateral and rotational diffusion, which allows lipids and certain proteins to migrate in a fluid mosaic, but most membrane proteins are fixed within specific regions of a membrane, anchored by connections to specific proteins of the cell's cytoskeleton.[6]

A dynamic interaction exists between cell membrane and cytoplasm. Although this chapter focuses on the channel-blocking actions of local anesthetics, it is noteworthy that many other cellular activities, including both metabolic and signal transduction pathways, are inhibited by these drugs.

PHYSIOLOGY OF NERVE CONDUCTION

The neural membrane constantly maintains a voltage difference at rest of –60 to –90 mV between the intracellular medium and the cell's outside, because during rest it is relatively impermeable to sodium ions but selectively permeable to potassium ions. The Na^+/K^+ pump, an active, energy-dependent mechanism, sustains the ion gradients that drive this potential difference by constant extrusion of sodium from within the cell in exchange for a net uptake of potassium, with adenosine triphosphate used as an energy source. Although the membrane is relatively permeable to potassium ions, an intracellular-to-extracellular potassium ratio of 150 to 5 mM, or 30:1, is maintained by active removal of potassium as it leaks passively across the plasma membrane.

The nerve at rest behaves largely as a potassium electrode, according to the Nernst equation:

$$E_m \approx E_K = \left(\frac{-RT}{F}\right) \ln \left(\frac{[K^+]_i}{[K^+]_o}\right)$$

where E_m is the membrane potential, E_K is the potassium equilibrium potential, R is the gas constant, T is temperature (Kelvin), F is Faraday's constant, and $[K^+]$ is the potassium ion concentration inside (i) and outside (o) the cell. For potassium, therefore,

$$E_K = -58 \log 30, \text{ or } -85.7 \text{ mV}$$

An opposite situation exists for Na^+, which is at higher concentration outside the cell and has a Nernst potential (E_{Na}) of approximately +60 mV. During an action potential, the nerve membrane transiently switches its higher permeability from K^+ to Na^+, thereby changing the membrane potential from negative to positive and back again.[7] The progress of this potential change and the underlying events are graphed in Figure 36-6. These events provide a basis for understanding local anesthetic conduction block.

Permeation of ions through membranes occurs via specialized proteins called *ion channels*.[8] The conformation of these channels is typically sensitive to the membrane potential; both Na^+ and K^+ channels in nerve membranes are activated to an "open" conformation by

TABLE 36-3 CLASSIFICATION OF PERIPHERAL NERVES ACCORDING TO ANATOMY, PHYSIOLOGY, AND FUNCTION

Fiber Class	Subclass	Myelin	Diameter (μm)	Conduction Velocity (m/sec)	Location	Function	Susceptibility to Local Anesthetic Block
A	alpha	+	6-22	30-120	Efferent to muscles	Motor	++
	beta	+	6-22	30-120	Afferent from skin and joints	Tactile, proprioception	++
	gamma	+	3-6	15-35	Efferent to muscle spindles	Muscle tone	++++
	delta	+	1-4	5-25	Afferent sensory nerves	Pain, cold temperature, touch	+++
B		+	<3	3-15	Preganglionic sympathetic	Various autonomic functions	++
C	sC	–	0.3-1.3	0.7-1.3	Postganglionic sympathetic	Various autonomic functions	++
	dC	–	0.4-1.2	0.1-2.0	Afferent sensory nerves	Various autonomic functions Pain, warm temperature, touch	+

Modified From Bonica JJ: Principles and practice of obstetric anesthesia and analgesia. *Philadelphia, 1967, FA Davis.*

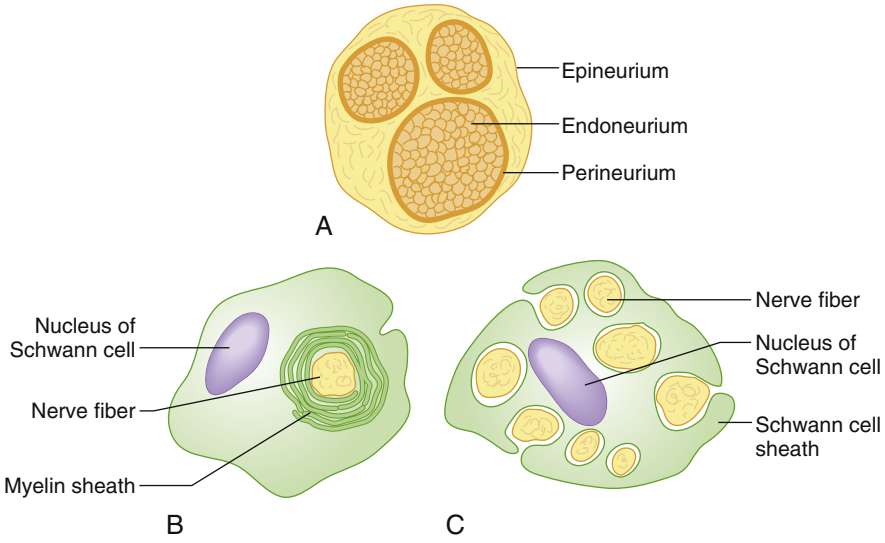


Figure 36-4. A, Transverse sections of a peripheral nerve showing the outermost epineurium; the inner perineurium, which collects nerve axons in fascicles; and the endoneurium, which surrounds each myelinated fiber. **B,** Each myelinated axon is encased in the multiple membranous wrappings of myelin formed by one Schwann cell, each of which stretches longitudinally more than approximately 100 times the diameter of the axon. The narrow span of axon between these myelinated segments, the node of Ranvier, contains the ion channels that support action potentials. **C,** Nonmyelinated fibers are enclosed in bundles of 5 to 10 axons by a chain of Schwann cells that tightly embrace each axon with but one layer of membrane.

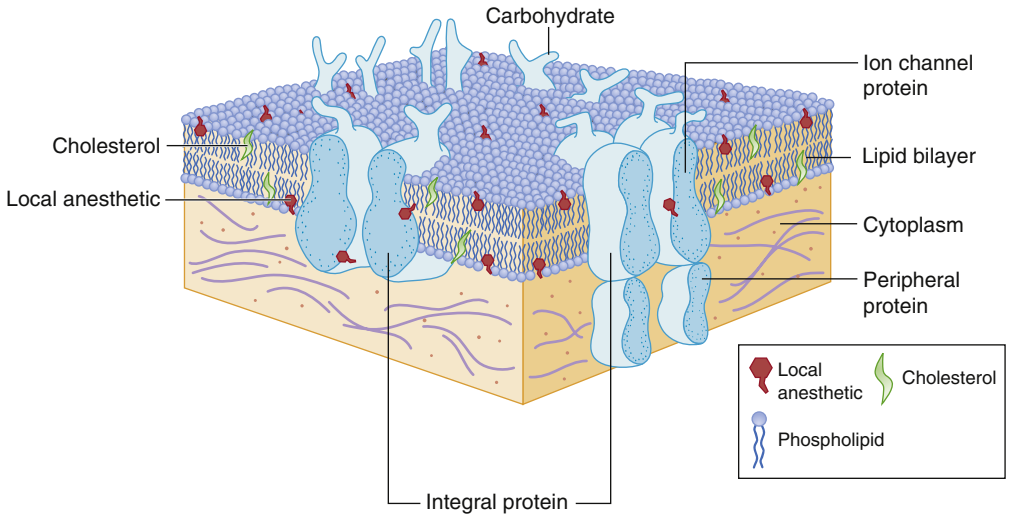


Figure 36-5. A typical plasma membrane has at its core the lipid bilayer, composed of phospholipids and cholesterol molecules (in an approximately 5:1 ratio) embedding the membrane integral proteins, which are most often glycosylated by extracellular carbohydrates and include receptors and ion channels essential for intercellular communication. "Peripheral proteins" regulate the functions of membrane proteins, chaperone them to the plasma membrane, and stabilize them in the cell through interactions with both the cytoskeleton and the extracellular matrix. Probable membrane locations and protein sites for local anesthetics are also shown.

membrane depolarization. Sodium channels, in addition, close to an "inactivated" conformation after their initial activation. A small membrane depolarization, extending along an axon from a region of excited membrane, for example, will begin to open both Na^+ and K^+ channels. The Na^+ channels open faster, however, and the inwardly directed Na^+ current (see Fig. 36-6) depolarizes the membrane further, thereby leading to opening of more Na^+ channels and increasing the inward Na^+ current even further (Fig. 36-7). This sequence of events continues during the depolarizing phase until some of the Na^+ channels have become inactivated and enough of the K^+ channels have opened to change the balance of current and result in a net outward current that produces membrane repolarization (see Fig. 36-7). After one action potential, the concentrations of Na^+ and K^+ have changed little for the large myelinated fibers, but by as much as 10% for the small, nonmyelinated axons. The Na^+ ions entering and K^+ ions leaving the cell because of this process are restored by the Na^+/K^+ pump.

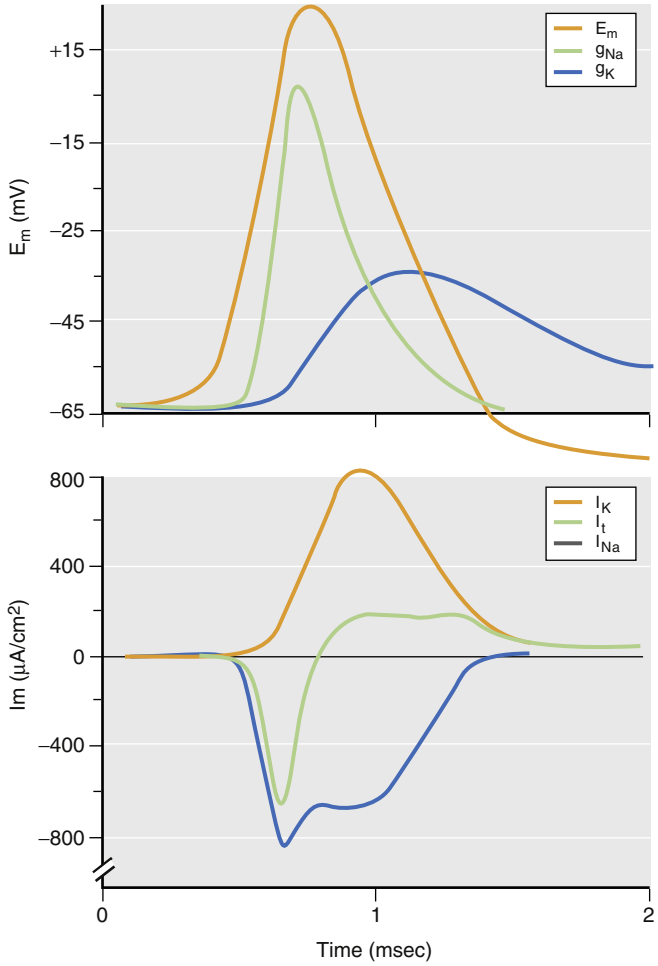


Figure 36-6. Membrane potential (E_m) and the voltage-gated ionic conductance of sodium (g_{Na}) and potassium (g_K), which determine the corresponding membrane currents Im (I_{Na} and I_K) during a propagated action potential. Modeled from the original studies of Hodgkin and Huxley on the squid giant axon (see Hodgkin[7]), these relationships hold for almost all invertebrate and vertebrate nerve fibers. The direction of the total ionic current (I_t), which is the sum of I_{Na} and I_K, is inward (negative values) for the depolarizing phase of the action potential and outward (positive values) for the repolarizing phase.

Depolarizations too weak to activate enough Na^+ channels to produce a net inward current are below the membrane's excitability threshold. The precise value of the threshold varies in different regions of the cell and changes with time. For example, directly after an impulse, when some Na^+ channels are still inactivated and some K^+ channels are still activated, the threshold is above its resting value and the membrane is refractory to stimulation. Over time, however, as Na^+ inactivation decays and K^+ channels return to their closed conformation, the original resting threshold value is restored.

The action potential is a wave of depolarization that is propagated along the axon by continuous coupling between excited and nonexcited regions of membrane. Ionic current (the action current) enters the axon in the excited, depolarized region and then flows down the axoplasm and exits through the surrounding membrane, thereby passively depolarizing this adjacent region (see Fig. 36-3). Although this local circuit current spreads away from the excited zone in both directions, the region behind the impulse, having just been depolarized, is absolutely refractory, and propagation of impulses is thus unidirectional.

The local circuit current spreads rapidly along a length of insulated internode in a myelinated axon (see Fig. 36-3), and many nodes of Ranvier in sequence are depolarized to threshold with little intervening delay. Single impulses do not jump from node to node as separate, discrete events; instead, active depolarization occurs simultaneously along several centimeters of the largest axons (see Fig. 36-3). Indeed, the local circuit current is so robust that it can skip past two completely nonexcitable nodes (e.g., blocked by local anesthetic) and successfully stimulate a third node. If excitability is partially reduced, such as by inhibition of some of the Na^+ channels, the amplitude of impulses in successive nodes falls decrementally in a process that can continue for many centimeters.[9] This situation most likely occurs during certain phases of local

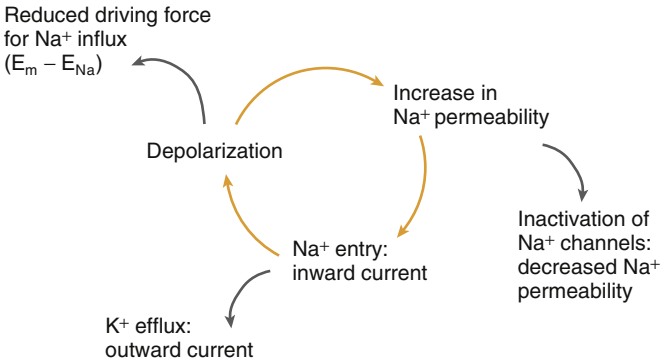


Figure 36-7. The action potential can be understood in terms of the cyclic relationships between factors contributing to the regenerative, depolarizing phase and the passive, repolarizing phase. Positive factors *(yellow arrows)* increase the rate of depolarization in a positive-feedback loop, with each element in the cycle favoring the subsequent one. Negative factors *(gray arrows)* decrease the depolarization rate by reducing or opposing the related positive factor, with efflux of K^+ eventually dominating the ionic flow and repolarizing the membrane.

anesthesia, as discussed later. However, when enough of the Na^+ channels are blocked, local circuit current fails to bring the adjacent resting region to threshold, and the impulse is fully extinguished.

MECHANISM OF ACTION OF LOCAL ANESTHETICS (PHARMACODYNAMICS)

ACTIVE FORM

Local anesthetic bases are poorly to sparingly soluble in water, but are soluble in relatively hydrophobic organic solvents. Therefore, as a matter of chemistry (and to optimize shelf life), most of these drugs are formulated as hydrochloride salts. The pK_a of the drug and tissue pH determine the amount of drug that exists in solution as free base or as positively charged cation when injected into living tissue (discussed earlier). Furthermore, uptake of the drug by tissue, largely via lipophilic adsorption, will also alter its activity, both by shifting the effective pK_a downward, thereby favoring the neutral base form, and by limiting diffusion of the anesthetic away from the site of injection. Moderately hydrophobic local anesthetics block faster than either hydrophilic or highly hydrophobic ones, delivered at the same concentration, for the following reasons. Moderately hydrophilic molecules, such as lidocaine, are less bound to tissues than highly hydrophobic drugs are (e.g., tetracaine) but are still more membrane permeant than highly hydrophilic ones (e.g., 2-chloroprocaine). The hydrophobic local anesthetics, having higher intrinsic potencies (see Table 36-2), are therefore used in lower concentrations and their diffusion-controlled rate of onset is correspondingly reduced.

Which form of the local anesthetic—charged cation or neutral base—is actually responsible for blockade of impulses? More alkaline solutions of local anesthetics block nerve conduction more effectively. On sheath-free nerves, the rate of inhibition by tertiary amine anesthetics is greater at alkaline than at neutral external pH because membrane permeation, favored by the base over the cationic species, determines the rate of access to the binding site.[10] Direct control of axoplasmic pH (or internal perfusion with permanently charged quaternary amine homologues) shows that the dominant potency derives from the cationic species acting from the cytoplasmic surface.[11,12] The uncharged base also has intrinsic pharmacologic activity, however, which explains the effectiveness of benzocaine as a topical local anesthetic.

ELECTROPHYSIOLOGIC EFFECT OF LOCAL ANESTHETICS

The nerve resting membrane potential is little affected by local anesthetics. As the concentration of local anesthetic applied to the nerve is increased, a decrease in the rate of depolarization and in the peak amplitude of the action potential occurs until the impulse is abolished. It is not possible, however, to derive data on the binding of local anesthetics to Na^+ channels from measurement of the changes in nerve impulses.

By using a "voltage-clamp" procedure, Na^+ currents and their inhibition by local anesthetics can be directly assayed (Fig. 36-8, *A*). When the membrane of isolated neurons is rapidly depolarized to a constant value, the time course of ionic currents is observed. Sodium currents during one initial depolarization are reduced by subclinical doses of local anesthetic (e.g., 0.2 mM lidocaine) and totally abolished by clinical doses (e.g., 1% lidocaine, ≈40 mM). If the test depolarization is applied repeatedly, for example, at frequencies higher than 5 Hz (five pulses per second), the partially depressed (tonically inhibited) Na^+ current is further reduced incrementally

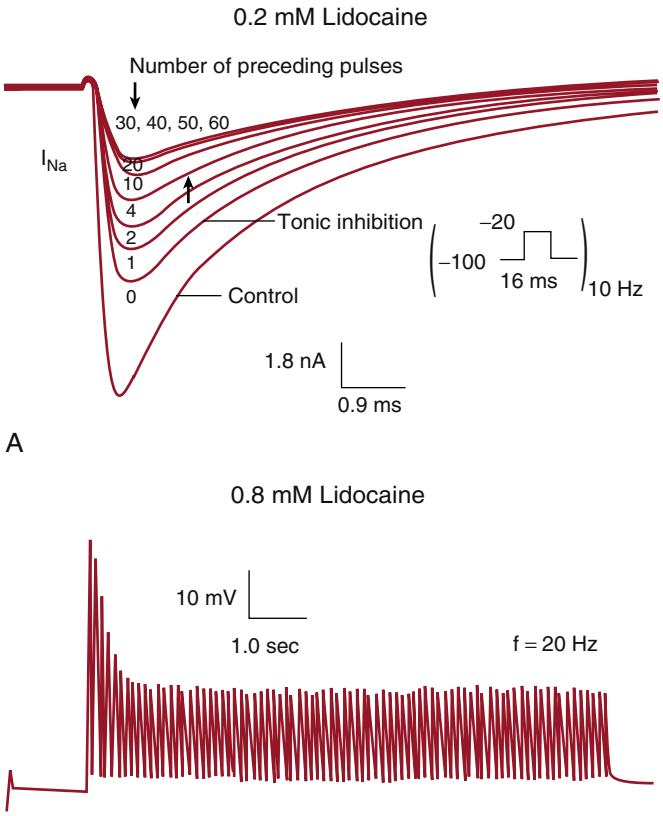


Figure 36-8. Use-dependent actions of local anesthetics on excitable membrane properties. **A,** Ionic Na^+ currents measured by a voltage-clamping technique are transiently activated by brief steps of depolarization applied infrequently (tonic test) or in a train at 10 times per second (phasic test, see E_m pattern in parentheses). After equilibration with 0.2 mM (0.005%) lidocaine, the currents measured tonically are reduced by approximately 30% from the control currents. Application of the phasic train of depolarizations results in a dynamic reduction of currents after each depolarization, with a steady-state value of phasic inhibition reached during the train of 75% of control currents. Recovery of currents to the tonic value occurs within a few seconds when phasic testing stops (not shown). **B,** Action potentials are also inhibited in a phasic manner by local anesthetics. After equilibration with 0.8 mM lidocaine (0.02%), the action potential is tonically reduced by approximately 20% from its amplitude in drug-free solution (not shown). Stimulation by a train at 20 stimuli per second induces a phasic inhibition that further reduces the amplitude by about 70% from the control value. As with the ionic currents (**A**), phasic inhibition of the action potential recovers rapidly when high-frequency stimulation stops.

for each pulse until a new steady-state level of inhibition is reached.[13,14] This frequency-dependent inhibition, also called *phasic inhibition,* is reversed when stimulation is slowed or stopped, and currents return to the level of tonic inhibition observed in the resting nerve. Paralleling the phasic inhibition of Na^+ currents in voltage-clamped membranes is a "use-dependent" blockade of action potentials during normal physiologic function (see Fig. 36-8, *B*).

The potency of local anesthetics to produce tonic and phasic inhibition is similarly dependent on their structure, hydrophobicity, and pK_a. At its simplest, there appears to be a single binding site for local anesthetics on the Na^+ channel, with a tonic affinity at rest and increased phasic affinity occurring because of depolarization. The phasic blocking phenomenon can thus be used to reveal the true kinetics of binding of local anesthetic to the functional receptor, the Na^+ channel itself.

Phasic actions are a manifestation of the selective affinity of local anesthetics for conformations of the Na^+ channel that result from depolarization. Both open and inactivated states of the channel bind local anesthetics more avidly than the resting state does. Repeated depolarization thus increases the fraction of drug-bound channels; dissociation of these bound drug molecules is usually a slower process than the normal recovery from inactivation (discussed earlier) and results in the use-dependent accumulation of channels in the blocked condition and the phenomenon of phasic block.

By its selective binding to a channel state, the local anesthetic stabilizes that state. During phasic block, therefore, more inactivated channels become drug bound, and reciprocally, less activation can occur. This relationship between state-dependent affinities and modification of transitions among states through drug binding is known as the *modulated receptor model*.[15] Overall binding of anesthetic is increased by membrane depolarization for two reasons: more binding sites become accessible during activation (the guarded receptor model) and drug *dissociation* from inactivated channels is slower than from resting channels (the modulated receptor model).

The specific binding rates and affinities for the different conformations of the sodium channel depend on the particular local anesthetic drug. When the details of this dependence are correlated with the physicochemical properties of the drug and with the experimental conditions, they provide insight into the molecular features of the local anesthetic binding site.

THE NATURE OF THE LOCAL ANESTHETIC BINDING SITE

Intentional mutation of specific amino acids of the Na^+ channel has allowed definition of regions that interact directly with local anesthetics. The major functional protein of the Na^+ channel (the α-subunit) is composed of four homologous domains (D-1 to D-4), each of which contains six helical regions (S1 to S6) that span the core of the membrane (Fig. 36-9, *A*). Each domain also has a loop, termed the *P region,* that links the extracellular ends of its S5 and S6 transmembrane segments. The P regions extend inward between the transmembrane regions such that when the α-subunit folds together, each P loop contributes a quarter of the cylindrical ion selectivity pore, the narrowest passage of an open channel (see Fig. 36-9, *B*). Voltage sensitivity derives from the positive charges located on S4 segments, which slide or swing outward in response to membrane depolarization. By linkages that are still unknown, this movement of S4 results in a conformational rearrangement of the S6 segments, which form the inner, cytoplasmic entry to the channel. Closed-to-open channel gating results from movement of the S6 segments, whereas inactivation gating results from binding of the cytoplasmic loop located between D-3 and D-4 to the cytoplasmic opening of the channel.

Local anesthetics bind in the inner vestibule of the closed Na^+ channel (see Fig. 36-9, *C*). Amino acid mutations in the S6 segments of D-1, D-3, and D-4 all modify local anesthetic action, thus suggesting either that these regions form a pharmacophore small enough to simultaneously contact the drug at three surfaces or that the local anesthetic molecule moves rapidly among these three segments.

The rate constant for binding of local anesthetic to the closed Na^+ channel is larger for the more hydrophobic molecules, which suggests that drug molecules can reach the binding site (and depart from it) through a hydrophobic pathway. This path could be movement from the membrane phase laterally, into the channel, or through hydrophobic amino acid residues that limit access through a pathway in the closed pore. The slow block of closed and inactivated channels appears to use such a hydrophobic access and thus accounts for tonic inhibition.

The charged species of local anesthetics dissociates much more slowly from closed and inactivated Na^+ channels than the neutral form does, which suggests that an ionic bond may be involved in drug binding or that the charged molecule moves only slowly along the hydrophobic pathway.

In brief, hydrophobicity delivers the drug to the receptor and charge keeps it there.

NEUROPHYSIOLOGIC ASPECTS OF PHASIC INHIBITION

Different fiber types in the nerve are affected differently during local anesthesia. At least part of this difference arises from pharmacokinetic factors. At the onset of and during recovery from clinical block, in particular, longitudinal and radial diffusion of drug will produce concentration variations within and along the nerve. This variation is superimposed on the dynamic use-dependent inhibition to provide variable propagation, which depends on a fiber's geometry, position within the nerve, and functional and electrophysiologic properties.

Different fiber types are also differentially sensitive to local anesthetic blockade. In vivo experiments in which continuous superperfusion of peripheral nerve allows equilibration with drug, and experiments in

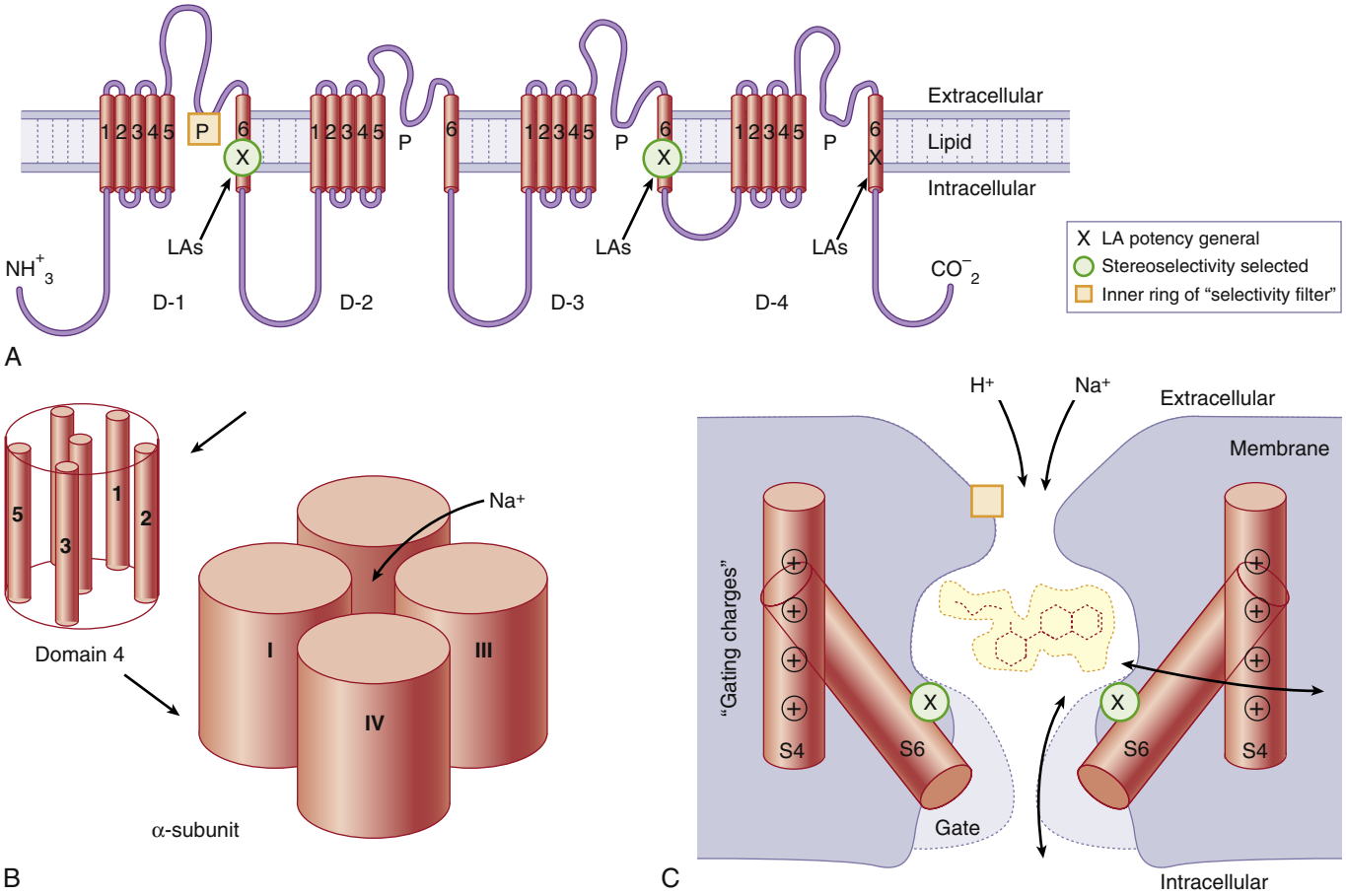


Figure 36-9. Structural features of the Na^+ channel that determine local anesthetic (LA) interactions. **A,** Consensus arrangement of the single peptide of the Na^+ channel α-subunit in a plasma membrane. Four domains with homologous sequences (D-1 through D-4) each contain six α-helical segments that span the membrane (S1 to S6). **B,** Each domain folds within itself to form one cylindrical bundle of segments, and these bundles converge to form the functional channel's quaternary structure. **C,** Activation gating leading to channel opening results from primary movement of the positively charged S4 segments in response to membrane depolarization. Fast inactivation of the channel follows binding to the cytoplasmic end of the channel of part of the small loop that connects D-3 to D-4. Ions travel through an open channel along a pore defined at its narrowest dimension by the P region formed by partial membrane penetration of the four extracellular loops of protein connecting S5 and S6 in each domain. Intentional, directed mutations of different amino acids on the channel indicate residues that are involved in LA binding in the inner vestibule of the channel (X on S6 segments), at the interior regions of the ion-discriminating selectivity filter (*square* on the P region), and also are known to influence stereoselectivity for phasic inhibition (*circle*, also on S6 segments). Schematic cross section of the channel speculating on the manner in which S6 segments, forming a "gate," may realign during activation to open the channel and allow entry and departure of a bupivacaine molecule by the hydrophilic pathway. The closed (inactivated) channel has a more intimate association with the LA molecule, whose favored pathway for dissociation is no longer between S6 segments (the former pore) but now, much more slowly, laterally between segments and then through the membrane, the hydrophobic pathway. Na^+ ions entering the pore will compete with the LA for a site in the channel, and H^+ ions, which pass slowly through the pore, can enter and leave from the extracellular opening, thereby protonating and deprotonating a bound LA molecule and thus regulating its rate of dissociation from the channel.

which a drug bolus is delivered by percutaneous injection,[16] analogous to clinical peripheral nerve block, show unequivocally that small myelinated axons (A gamma motor and A delta sensory fibers) are the most susceptible to impulse annihilation. Next in order of block are the large myelinated (A alpha and A beta) fibers, and the least susceptible are the small, nonmyelinated C fibers. In fact, in this last group, impulses in the slowest conducting population (conduction velocity of 0.5 to 0.8 m/sec) are the most resistant to local anesthetic.[16] The widespread notion that local anesthetics block the smallest fibers first or most is thus clearly wrong.

Selective Susceptibility of Na^+ Channel Isoforms

Ten different Na^+ channels have been physiologically identified and biochemically sequenced. At least four of them are found in peripheral neurons, and some are associated exclusively with nociceptive afferents. Obviously, it would be clinically advantageous to inhibit these channels selectively and thus prevent or reduce pain while sparing other functions. Although selective channel blockade has been attained with naturally occurring small peptide toxins,[17] relatively little selective blockade by local anesthetics occurs,[18] probably because the local anesthetic pharmacophore is too similar among the different channel isoforms

and the local anesthetic molecules themselves have several rotational axes, which makes them poor structural templates for selecting among static binding pockets.

Sodium Channel Isoforms in Human Diseases Characterized by Pain or Pain Insensitivity

Mutations in sodium channel isoform $Na_V1.7$ can produce disease states with either spontaneous pain[19,20] or profound and selective impairment of pain sensitivity.[21] Erythromelalgia is characterized by episodes of severe burning pain, predominantly in the feet and hands. In these subjects, pain is exacerbated by heat and relieved by cold. This disorder can occur as an isolated problem or can coexist with certain rheumatologic disorders. In a small subgroup of these patients, the disorder has a clear familial pattern with an autosomal dominant pattern of inheritance. A second autosomal dominant disorder characterized by spontaneous pain is known initially as *familial rectal pain disorder* or *paroxysmal extreme pain disorder*. Recent molecular studies have shown that these disorders involve several distinct types of mutations in $Na_V1.7$ sodium channels.[19,20] When these channels are inserted into cells that lack sodium channels, they generate spontaneous, temperature-sensitive, inward currents.

Perhaps even more remarkable is the recent report of several consanguineous families in Pakistan in which certain members exhibit profound insensitivity to pain while being neurologically normal in almost all other respects.[21] Genetic, biochemical, and electrophysiologic studies have demonstrated an autosomal recessive pattern of inheritance. Molecular studies have shown that these mutations are of the nonsense type and generate functionally impaired $Na_V1.7$ sodium channels; when placed into cell membranes in vitro, they fail to generate inward currents in response to depolarizing stimuli.

Aberrant impulses, which are often considered the hallmarks of various diseases of excitable membranes such as abnormal repetitive firing in neuropathic pain or in certain types of inherited skeletal myotonia, are abolished by systemic lidocaine in doses that do not block normal propagating impulses. Conditions for the sensitivity of such impulses to local anesthetics, such as lidocaine, appear to result from the patterns of impulse spikes superimposed on slow membrane depolarizations caused by abnormal expression of Na^+ channels rather than from selective sensitivity of certain subtypes of channels to these drugs.[22]

SUMMARY OF LOCAL ANESTHETIC MECHANISMS

Impulse blockade by local anesthetics may be summarized by the following chronology[4]:

1. Solutions of local anesthetic are deposited near the nerve. Removal of free drug molecules away from this locus is a function of tissue binding, removal by the circulation, and local hydrolysis of aminoester anesthetics. The net result is penetration of the nerve sheath by the remaining free drug molecules.
2. Local anesthetic molecules then permeate the nerve's axon membranes and accumulate within the axoplasm. The speed and extent of these processes depend on a particular drug's p*K*a and on the lipophilicity of its base and cation species.
3. Binding of local anesthetic to sites on voltage-gated Na^+ channels prevents opening of the channels by inhibiting the conformational changes that underlie channel activation. Local anesthetics primarily bind to the channel's pore and occlude the pore path for Na^+ ions.
4. During onset of and recovery from local anesthesia, impulse blockade is incomplete, and partially blocked fibers are further inhibited by repetitive stimulation, which produces an additional, use-dependent binding to Na^+ channels.
5. One local anesthetic binding site on the Na^+ channel may be sufficient to account for the drug's resting (tonic) and use-dependent (phasic) actions. Access to this site may potentially involve multiple pathways, but for clinical local anesthesia, resting block predominates and, the primary route is the hydrophobic approach from within the axon membrane.
6. The clinically observed rates of onset and recovery from blockade are governed by the relatively slow diffusion of local anesthetic molecules into and out of the whole nerve, not by their much faster binding and dissociation from ion channels. A clinically effective block that may last for hours can be accomplished with local anesthetic drugs that dissociate from Na^+ channels in a few seconds.

CLINICAL PHARMACOLOGY

The successful use of regional anesthesia requires knowledge of the pharmacologic properties of the various local anesthetic drugs, as well as technical skill in performing the nerve block. Local anesthetic requirements vary considerably, depending on factors such as the type of block, surgical procedure, and physiologic status of the patient.

Commonly used aminoester local anesthetics include procaine, chloroprocaine, tetracaine, and cocaine. The clinically used aminoamides include lidocaine, mepivacaine, prilocaine, bupivacaine (racemic and its levoenantiomer), ropivacaine, and etidocaine. The ester and amide local anesthetics differ in their chemical stability, locus of biotransformation, and allergic potential. Amides are extremely stable, whereas esters are relatively unstable in solution. Aminoesters are hydrolyzed in plasma by cholinesterase enzymes, but the amides undergo enzymatic degradation in the liver. Two exceptions to this trend include cocaine, an ester that is metabolized predominantly by hepatic carboxylesterase, and articaine, an amide local anesthetic widely used in dentistry that is inactivated by plasma carboxylesterase-induced cleavage of a methyl ester on the aromatic ring.

p-Aminobenzoic acid is one of the metabolites of ester-type compounds that can induce allergic-type reactions in a small percentage of patients. The aminoamides are not metabolized to *p*-aminobenzoic acid, and reports of allergic reactions to these agents are extremely rare.

GENERAL CONSIDERATIONS

Clinically important properties of the various local anesthetics include potency, speed of onset, duration of anesthetic action, and differential sensory vs motor blockade. As previously indicated, the profile of individual drugs is determined by their physicochemical characteristics (see Table 36-2).

Anesthetic Potency

Hydrophobicity is a primary determinant of intrinsic anesthetic potency[5] because the anesthetic molecule must penetrate into the nerve membrane and bind at a partially hydrophobic site on the Na^+ channel. Clinically, however, the correlation between hydrophobicity and anesthetic potency is not as precise as in an isolated nerve. Differences between in vitro and in vivo potency may be related to a number of factors, including local anesthetic charge and hydrophobicity (which influence partitioning into and transverse diffusion across biologic membranes) and vasodilator or vasoconstrictor properties (which influence the initial rate of vascular uptake from injection sites into the central circulation).

Onset of Action

The onset of conduction block in isolated nerves is related to the physicochemical properties of the individual agents. In vivo latency is also dependent on the dose or concentration of local anesthetic used. For example, 0.75% bupivacaine has more rapid onset than 0.25%. Chloroprocaine demonstrates a rapid onset of action in humans because its low systemic toxicity permits its use in high concentrations (i.e., 3%).

Duration of Action

The duration of action of the various local anesthetics differs markedly. Procaine and chloroprocaine have a short duration of action. Lidocaine, mepivacaine, and prilocaine produce a moderate duration of anesthesia, whereas tetracaine, bupivacaine, ropivacaine, and etidocaine have the longest durations.

In humans, the duration of anesthesia is markedly influenced by the peripheral vascular effects of the local anesthetic drugs. Many local anesthetics have a biphasic effect on vascular smooth muscle. These agents tend to cause vasoconstriction at low concentrations, whereas they cause vasodilation at higher, clinically administered concentrations.[23] There are, however, differences in the degree of vasodilator activity of the various drugs. The effects of local anesthetics on vascular tone and regional blood flow are complex and vary according to concentration, time, and the particular vascular bed near the site of application, among other factors. As a practical example, the topical local anesthetic formulation EMLA (a eutectic mixture of the local anesthetics lidocaine and prilocaine) vasoconstricts cutaneous vessels initially and through most of the first hour of application, but vasodilation is observed after 2 or more hours of application.

Differential Sensory and Motor Blockade

Another important clinical consideration is the ability of local anesthetic agents to cause differential inhibition of sensory and motor activity. Bupivacaine became popular in the 1980s for epidural blocks because it was better than the previously available long-acting agents were (e.g., etidocaine) in producing adequate antinociception without profound inhibition of motor activity, particularly when dilute solutions were used. Bupivacaine is widely used epidurally for obstetric analgesia and postoperative pain management because it can provide adequate analgesia or pain relief with only mild muscle weakness (see Chapters 56, 77, and 98). Additional observations on the sensory selectivity of newer local anesthetics are detailed later in the section on chiral local anesthetics.

Small-diameter axons, such as C fibers, are often stated to be more susceptible to local anesthetic block than larger-diameter fibers are. However, when careful measurements are made of single-impulse annihilation in individual nerve fibers, exactly the opposite differential susceptibility is noted (discussed earlier).[24,25] Repetitive stimulation, such as occurs during propagation of trains of impulses, produces further, phasic inhibition of excitability, but it is not clear how this will affect a functionally selective failure of impulses. The length of drug-exposed nerve in the intrathecal space, imposed by anatomic restrictions, can perhaps explain clinically documented differential spinal or epidural blockade, with longer drug-exposed regions yielding block by lower concentrations of local anesthetic.[26] However, this reasoning does not explain the functionally differential loss from peripheral nerve block. Other factors can include actual spread of the drug along the nerve or its selective ability to inhibit Na^+ channels over K^+ channels,[27] which in itself can produce a differential block because these channels are present in different proportions in different types of nerves. Because of these confounding factors, clinicians should be discouraged from making conclusions about fiber-type involvement in chronic pain syndromes based on the dose or concentration requirement for pain relief in diagnostic nerve blockade.[28]

FACTORS INFLUENCING ANESTHETIC ACTIVITY IN HUMANS

Dosage of Local Anesthetic

As the dose of local anesthetic is increased, the probability and duration of satisfactory anesthesia increase, and the time to onset of block is shortened. The dose of local anesthetic can be increased by administering either a larger volume or a more concentrated solution. For example, increasing the concentration of epidurally administered bupivacaine from 0.125% to 0.5%, while maintaining the same volume of injectate (10 mL), resulted in more rapid onset, an improved incidence of satisfactory analgesia, and a longer duration of sensory analgesia.[29] The volume of anesthetic solution probably influences the spread of anesthesia. For example, 30 mL of 1% lidocaine administered into the epidural space produces a level of anesthesia that is 4.3 dermatomes higher than that achieved when 10 mL of 3% lidocaine is given.

In selecting the volume and concentration for a specific block in a particular patient, clinicians must balance the risk of adverse effects from overdosing (e.g., systemic

toxicity, excessive motor or autonomic blockade) against the increased risk of block failure if an inadequate volume or concentration is chosen. The degree to which additional volume can compensate for imprecise needle placement varies among different blocks.

With the advent of extremely precise needle placement using ultrasound-guided blockade (see Chapter 58), the median effective volume for obtaining successful blockade can be achieved with smaller volumes than have been recommended previously as compared with techniques not using ultrasound. For example, in a recent dose-finding randomized trial for femoral nerve blockade, the median volumes for 50% or 95% success in obtaining dense sensory and motor block at 30 minutes under ultrasound guidance were 57% and 54% of the corresponding volumes with the use of nerve stimulation.[30] Confidence intervals (i.e., variability) were large in this study. Statistical design issues for dose-response studies involving all types of anesthetics are well described.[31] As limited by toxicity considerations, the aim in most clinical situations should be to choose doses that provide frequent and predictable success rates; that is, a dose effective in 95% of patients (ED_{95}) is generally a more relevant guide to dose selection than an ED_{50} dose. In other words, one should not aim for failure 50% of the time.[32]

Addition of Vasoconstrictors

Vasoconstrictors, usually epinephrine (5 μg/mL or 1:200,000), are frequently included in local anesthetic solutions to decrease the rate of vascular absorption, thereby allowing more anesthetic molecules to reach the nerve membrane and thus improve the depth and duration of anesthesia, as well as to provide a marker for inadvertent intravascular injection.[33] Test dosing with epinephrine can generate false negative and false positive results. Some of these sources of error have been described for specific patient groups, such as adults and children under general anesthesia, parturients in labor, and patients receiving β-adrenergic blockers. Despite these limitations, test dosing has utility in a wide range of clinical situations.[34]

Epinephrine in a concentration of 1:200,000 provides the optimal degree of vasoconstriction when used with lidocaine for epidural or intercostal blockade.[35] Other vasoconstrictor drugs, such as norepinephrine and phenylephrine, have been used but do not appear to be superior to epinephrine.

The extent to which epinephrine prolongs the duration of anesthesia depends on the specific local anesthetic used and the site of injection. Epinephrine will significantly extend the duration of both infiltration anesthesia and peripheral nerve blockade with shorter-duration agents (e.g., lidocaine); epinephrine produces mild intensification of blockade, but only most modest prolongation of epidural or peripheral blocks with bupivacaine.[36] α_2-Adrenergic receptors in the spinal cord are known to activate endogenous analgesic mechanisms, and the increased depth of analgesic action produced by epinephrine and the α_2-agonist clonidine[37] with both epidural and intrathecal local anesthetics may arise from this pharmacodynamic mechanism and from the pharmacokinetic (vasoconstrictive) action.

Site of Injection

The most rapid onset but the shortest duration of action occurs after intrathecal or subcutaneous administration of local anesthetics. The longest onset times and durations occur after brachial plexus blocks. For example, intrathecal bupivacaine will usually produce anesthesia with an onset time within 5 minutes that will persist for 3 to 4 hours. However, when bupivacaine is administered for brachial plexus blockade, the onset time is approximately 20 to 30 minutes, and the duration of anesthesia (or at least analgesia) averages 10 hours.[38] These differences in the onset and duration of anesthesia and analgesia are due in part to the particular anatomy of the area of injection, which will influence the rate of diffusion and vascular absorption and, in turn, affect the amount of local anesthetic used for various types of regional anesthesia. In the subarachnoid space, for example, the lack of a nerve sheath around the spinal cord and deposition of the local anesthetic solution in the immediate vicinity of the spinal cord are responsible for the rapid onset of action, whereas the relatively small amount of drug used for spinal anesthesia probably accounts for the short duration of conduction block.

In contrast, the onset of brachial plexus blockade is slow because the anesthetic is usually deposited at some distance from the nerve, and it must diffuse through various tissue barriers before reaching the nerve membrane. The prolonged block with brachial plexus blockade may be related to several factors, including comparatively slower rates of vascular absorption from the brachial plexus sheath, larger doses of drug required for this regional anesthetic technique, and comparatively long segments of nerves exposed to local anesthetic.

Carbonation and pH Adjustment of Local Anesthetics

The addition of sodium bicarbonate to a solution of local anesthetic applied to an isolated nerve accelerates the onset and decreases the minimum concentration required for conduction blockade.[39] Although the effect of carbon dioxide on local anesthetic activity is easily demonstrable in isolated nerve, controversy exists concerning the clinical utility of carbonated local anesthetic solutions.[40]

The addition of sodium bicarbonate to local anesthetic solutions decreases the onset time of conduction blockade.[40] An increase in the pH of the local anesthetic solution increases the amount of drug in the uncharged base form, which should enhance the rate of diffusion across the nerve sheath and nerve membrane and result in a more rapid onset of anesthesia. Alkalinization of solutions of bupivacaine or lidocaine accelerated the onset of brachial plexus and epidural blockade in some studies[40] but not others.[41]

Mixtures of Local Anesthetics

Mixtures of local anesthetics for regional anesthesia are sometimes used in an effort to compensate for the short duration of action of certain rapidly acting anesthetics such as chloroprocaine and lidocaine, and the long latency of longer-acting anesthetics such as tetracaine and bupivacaine. Mixtures of chloroprocaine and bupivacaine theoretically offer significant clinical advantages

because of the rapid onset and infrequent incidence of systemic toxicity of chloroprocaine and the long duration of action of bupivacaine; however, clinical results in studies of combinations have been mixed.[42] In addition, the use of catheter-based techniques for many forms of regional anesthesia makes it possible to begin with a rapid-onset local anesthetic such as lidocaine, mepivacaine, or chloroprocaine followed by an infusion of either a shorter-acting or longer-acting local anesthetic thereafter. Conversely and even more importantly, clinicians should be cautioned not to use maximum doses of two local anesthetics in combination in the mistaken belief that their toxicities are independent.[43] In the absence of additional data, the toxicities should be presumed to be additive.

Pregnancy

The spread and depth of epidural and spinal anesthesia are more in pregnant than in nonpregnant women (see Chapter 77). The effects of pregnancy on local anesthetic potency may reflect a combined effect of mechanical factors associated with pregnancy (i.e., dilated epidural veins decrease the volume of the epidural and subarachnoid spaces) and direct effects of hormones, especially progesterone, on the susceptibility of nerves to conduction blockade by local anesthetics.[44] Hormonal alterations are probably the more important of these two factors because greater spread of epidural anesthesia occurs during the first trimester of pregnancy,[45] before any gross change in vascular dimensions within the epidural or subarachnoid spaces. The dosage of local anesthetics probably should be decreased in patients in all stages of pregnancy.

CHOICE OF LOCAL ANESTHETIC FOR VARIOUS REGIONAL ANESTHETIC PROCEDURES

On the basis of anatomic considerations, regional anesthesia can be divided into infiltration anesthesia, intravenous regional anesthesia, peripheral nerve blockade (including plexus blockade), central neural blockade, and topical anesthesia (see Chapters 56, 57, 58, 77, 79, 92, and 98). An additional method of local anesthetic injection—tumescent anesthesia—is included because it is widely used in office plastic surgery practice.

INFILTRATION ANESTHESIA

Any local anesthetic can be used for infiltration anesthesia. Onset of action is almost immediate for all agents after intradermal or subcutaneous administration; however, the duration of anesthesia varies (Table 36-4). Epinephrine will prolong the duration of infiltration anesthesia by all local anesthetic drugs, although this effect is most pronounced when epinephrine is added to lidocaine. The choice of a specific drug for infiltration anesthesia largely depends on the desired duration of action.

The dose of local anesthetic required for adequate infiltration anesthesia depends on the extent of the area to be anesthetized and the expected duration of the surgical procedure. When large surface areas have to be anesthetized, large volumes of dilute anesthetic solutions should be used. These considerations are particularly important when performing infiltration anesthesia in infants and smaller children. For example, consider a 4-kg infant receiving infiltration anesthesia with the maximum safe dose of lidocaine of 5 mg/kg (see Chapter 92). Dosing to 5 mg/kg in a 4-kg infant permits 20 mg, which is 1 mL of a 2% solution or 4 mL of a 0.5% solution. Lidocaine is effective for infiltration in concentrations as dilute as 0.3% to 0.5%; therefore, the more dilute solution can be used more safely to anesthetize a larger area.

Patients frequently experience pain immediately after subcutaneous injection of local anesthetic solutions, in part because of the acidic nature of these solutions. For example, neutralization of lidocaine solutions by the addition of sodium bicarbonate immediately before injection reduces pain on skin infiltration[46] and can improve onset (discussed earlier).

Infiltration analgesia and indwelling wound catheters are used increasingly as components of multimodal postoperative analgesia.[47-49]

INTRAVENOUS REGIONAL ANESTHESIA

Intravenous regional anesthesia involves the intravenous administration of a local anesthetic into a tourniquet-occluded limb (i.e., Bier block; see Chapter 79). The local anesthetic diffuses from the peripheral vascular bed to nonvascular tissue such as axons and nerve endings. Both the safety and the efficacy of this regional anesthetic

TABLE 36-4 **INFILTRATION ANESTHESIA**

	Plain Solution			Epinephrine-Containing Solution	
Drug	**Concentration (%)**	**Maximum Dose (mg)**	**Duration (min)**	**Maximum Dose (mg)**	**Duration (min)**
Short Duration					
Procaine	1-2	500	20-30	600	30-45
Chloroprocaine	1-2	800	15-30	1000	30
Moderate Duration					
Lidocaine	0.5-1	300	30-60	500	120
Mepivacaine	0.5-1	300	45-90	500	120
Prilocaine	0.5-1	350	30-90	550	120
Long Duration					
Bupivacaine	0.25-0.5	175	120-240	200	180-240
Ropivacaine	0.2-0.5	200	120-240	250	180-240

procedure depend on interruption of blood flow to the involved limb and gradual release of the occluding tourniquet. Intravenous regional anesthesia has been used primarily for surgical procedures on the upper limbs. Shorter surgical procedures on the foot can also be performed successfully with intravenous regional anesthesia. If a lower-leg tourniquet is used, it should not be applied over the superficial peroneal nerve, which can cause nerve injury; in general, use of an upper-leg tourniquet is preferred over lower-leg tourniquets.[50]

Lidocaine has been the drug used most frequently for intravenous regional anesthesia. Prilocaine, mepivacaine, chloroprocaine, procaine, bupivacaine, and etidocaine have also been used successfully. One might suppose a safety advantage with the aminoester-linked compounds because of their hydrolysis in blood; however, thrombophlebitis has been reported with chloroprocaine. Cardiovascular collapse has occurred after the use of bupivacaine for intravenous regional anesthesia, and this use of bupivacaine is discouraged.[51]

In general, approximately 3 mg/kg (40 mL of a 0.5% solution) of preservative-free lidocaine without epinephrine is used for upper extremity procedures. For surgical procedures on the lower limbs, 50 to 100 mL of a 0.25% lidocaine solution can be used.

PERIPHERAL NERVE BLOCKADE

Regional anesthetic procedures that inhibit conduction in fibers of the peripheral nervous system can be classified together under the general category of peripheral nerve blockade (see Chapters 57 and 58). This form of regional anesthesia has been subdivided arbitrarily into minor and major nerve blocks. Minor nerve blocks are defined as procedures involving single nerve entities such as the ulnar or radial nerve, whereas major nerve blocks involve the blockade of two or more distinct nerves or a nerve plexus or the blockade of very large nerves at more proximal sites (i.e., the femoral and sciatic nerves).

Most local anesthetic drugs can be used for minor nerve blocks. The onset of blockade is rapid with most drugs, and the choice of drug is determined primarily by the required duration of anesthesia. A classification of the various drugs according to their duration of action is shown in Table 36-5. The duration of both sensory analgesia and motor blockade is prolonged significantly when epinephrine is added to the various local anesthetic solutions in some, but not all applications.[52]

In 1986, a technique of interpleural regional analgesia was described as an alternative to multiple intercostal nerve blocks.[53] This procedure involves the administration of local anesthetic solution into the pleural space, either by percutaneous placement or by placement through the open chest by the surgeon during thoracotomy. The risk of pneumothorax has varied in published case series. Although interpleural analgesia appeared to be useful for unilateral postoperative analgesia after open cholecystectomy, mastectomy, and nephrectomy, its efficacy for post-thoracotomy pain is doubtful.[54] This technique has been associated with extremely high plasma concentrations of anesthetic, and a subsequently associated risk of convulsions. Interpleural analgesia has also been used to provide analgesia for chronic pain conditions as diverse as upper extremity complex regional pain syndromes, pancreatitis, and cancer of the thorax and abdomen. In many centers, interpleural analgesia has largely been supplanted by thoracic epidural analgesia for the majority of thoracic and abdominal procedures.

Two related approaches for unilateral somatic blockade in the thorax are continuous extrapleural catheters[55] (placed by the surgeon through the chest dorsal to the parietal pleura) and continuous thoracic paravertebral somatic blockade.[56] One advantage of these two approaches over interpleural analgesia is that little of the administered solution leaks from the chest into chest tubes. The risk-benefit ratio of thoracic epidural analgesia versus thoracic paravertebral analgesia or extrapleural analgesia remains controversial.[57,58]

Brachial plexus blockade for upper limb surgery is the most common major peripheral nerve block technique. A significant difference exists between the onset times of various agents when these blocks are used (Table 36-6). In general, agents of intermediate potency exhibit a more rapid onset than the more potent compounds do. Onset times of approximately 14 minutes for lidocaine and mepivacaine have been reported, versus approximately 23 minutes for bupivacaine. A variety of approaches to the brachial plexus are available; the choice among these approaches is dictated by several factors, including the site of surgery and the ability of the patient to tolerate spillover to other nerves, including the phrenic nerve. These considerations are detailed in Chapters 57, 58, and 79.

TABLE 36-5 **MINOR NERVE BLOCKS***

Drug	Usual Concentration (%)	Usual Volume (mL)	Dose† (mg)	Average Duration (min)	
				Plain Solutions	Epinephrine-Containing Solutions
Procaine	2	5-20	100-400	15-30	30-60
Chloroprocaine	2	5-20	100-400	15-30	30-60
Lidocaine	1	5-20	50-200	60-120	120-180
Mepivacaine	1	5-20	50-200	60-120	120-180
Prilocaine	1	5-20	50-200	60-120	120-180
Bupivacaine	0.25-0.5	5-20	12.5-100	180-360	240-420
Ropivacaine	0.2-0.5	5-20	10-100	180-360	240-420

*See also Chapter 57.
†Doses are for a 70-kg adult. For pediatric doses, see Chapter 92.

Similarly, the lumbar plexus can be approached via several routes, including a posterior approach, an anterior perivascular "3 in 1" approach, and an anterior fascia iliaca compartment approach.[59]

The variation in duration of anesthesia after brachial plexus blockade is also considerably greater than that observed with other types of conduction block. For example, durations of anesthesia varying from 4 to 30 hours have been reported for bupivacaine. It is prudent to warn patients before a major nerve block about the possibility of prolonged sensory and motor block in the involved region, particularly when agents such as bupivacaine, levobupivacaine, and ropivacaine are used.

PERINEURAL AND PLEXUS INFUSIONS

Local anesthetics are increasingly being administered by continuous infusion for several days after surgery[48,60] or for periods of weeks to months for the treatment of chronic malignant and nonmalignant pain (see Chapters 64 and 98). With prolonged infusions, there is the potential for delayed systemic accumulation and toxicity. Continuous bupivacaine infusions of up to 30 mg/hr in adults for as long as 2 weeks produced no overt central nervous system (CNS) or cardiac toxicity despite total plasma bupivacaine concentrations in the range of 2 to 5 μg/mL in several patients.[61]

CENTRAL NEURAL BLOCKADE

Any of the local anesthetic drugs can be used for epidural anesthesia (Table 36-7), although procaine and tetracaine are rarely used because of their long onset times (see Chapter 56). Drugs of intermediate potency produce surgical anesthesia of 1 to 2 hours' duration, whereas long-acting drugs usually produce 3 to 4 hours of anesthesia. The duration of short- and intermediate-acting drugs is significantly prolonged by the addition of epinephrine (1:200,000), but the duration of long-acting drugs is only minimally affected by epinephrine. The onset of lumbar epidural anesthesia occurs within 5 to 15 minutes after the administration of chloroprocaine, lidocaine, mepivacaine, and prilocaine. Bupivacaine has a slower onset of action.

Bupivacaine epidural bolus doses at a concentration of 0.125% produce adequate analgesia in many clinical settings with only mild motor deficits.[62] Continuous epidural infusions of bupivacaine as dilute as 0.0625% to 0.1% are useful for labor epidural analgesia, especially when administered in combination with opioids and other additives. Bupivacaine 0.25% can be used for more intense analgesia (particularly during combined epidural–light general anesthesia cases) with moderate degrees of motor block. Bupivacaine at concentrations of 0.5% to 0.75% is associated with a more profound degree of motor block, which makes these solutions most suitable for major surgical procedures, particularly when epidural anesthesia is not combined with general anesthesia. It should be emphasized that although high concentrations of local anesthetics may be appropriate for episodic bolus dosing for surgery, these concentrations (i.e., >0.2% for bupivacaine) should generally be avoided for continuous epidural infusions. Bolus injections produce much more cephalocaudad spread than infusions do. When concentrated bupivacaine solutions are used for infusions, the potential exists for excessive local effect with an associated risk for unwanted and very prolonged motor blockade. Etidocaine produces adequate sensory analgesia and

TABLE 36-6 MAJOR NERVE BLOCKS*

Drug	Usual Concentration (%)	Usual Volume (mL)	Maximum Dose (mg) Without/With Epinephrine	Onset (min)	Duration (min)
Lidocaine	1-2	30-50	350/500	10-20	120-240
Mepivacaine	1-1.5	30-50	350/500	10-20	180-300
Prilocaine	1-2	30-50	400/600	10-20	180-300
Bupivacaine	0.25-0.5	30-50	175/225	20-30	360-720
Levobupivacaine	0.25-0.5	30-50	200/225	20-30	360-720
Ropivacaine	0.2-0.5	30-50	200/250	20-30	360-720

*See also Chapter 57. Doses are for a 70-kg adult receiving epinephrine-containing solutions. Doses should be reduced, as detailed in Chapter 92, for children, for patients with specific risk factors, and for blocks in specific locations (e.g., interscalene). When two or more blocks are performed together, the sum of the doses for each of the individual blocks should not exceed the max dose listed here.

TABLE 36-7 EPIDURAL ANESTHESIA*

Drug With Epinephrine (1:200,000)	Usual Concentration (%)	Usual Volume (mL)	Maximum Dose (mg) Without/ With Epinephrine	Usual Onset (min)	Usual Duration (min)
Chloroprocaine	2-3	15-30	700/900	5-15	30-90
Lidocaine	1-2	15-30	350/500	5-15	
Mepivacaine	1-2	15-30	350/500	5-15	60-180
Prilocaine	1-3	15-30	350/500	5-15	
Bupivacaine	0.25-0.5	15-30	175/225	15-20	180-350
Levobupivacaine	0.25-0.75	15-30	200/250	15-20	180-350
Ropivacaine	0.2-0.75	15-30	200/250	15-20	180-350

*See also Chapter 56. Doses are for a 70-kg adult receiving epinephrine-containing solutions. Doses should be reduced, as detailed in Chapter 92, for children, for patients with specific risk factors, and for specific catheter tip locations (e.g., upper thoracic).

TABLE 36-8 **SPINAL ANESTHESIA***

Drug	Usual Concentration (%)	Usual Volume (mL)	Total Dose (mg)	Baricity	Glucose Concentration (%)	Usual Duration (min)
Procaine	10.0	1-2	100-200	Hyperbaric	5.0	30-60
Lidocaine	1.5, 5.0	1-2	30-100	Hyperbaric	7.5	30-90
Mepivacaine	4.0	1-2	40-80	Hyperbaric	9.0	30-90
Tetracaine	0.25-1.0	1-4	5-20	Hyperbaric	5.0	90-200
	0.25	2-6	5-20	Hypobaric		90-200
	1.0	1-2	5-20	Isobaric		90-200
Dibucaine	0.25	1-2	2.5-5.0	Hyperbaric	5.0	90-200
	0.5	1-2	5-10	Isobaric		90-200
	0.06	5-20	3-12	Hypobaric		90-200
Bupivacaine	0.5	3-4	15-20	Isobaric		90-200
	0.75	2-3	15-20	Hyperbaric	8.25	90-200
Levobupivacaine	0.5	3-4	15-20	Isobaric		90-200
	0.75	2-3	15-20	Hyperbaric		90-200
Ropivacaine	0.5	3-4	15-20	Isobaric		90-200
	0.75	2-3	15-20	Hyperbaric		90-200

*Doses are for a 70-kg adult. Dosing may be reduced during pregnancy (see Chapter 77) and with advancing age (see Chapter 80). Pediatric dosing is detailed in Chapter 92.

profound, long-lasting motor block. Use of etidocaine has decreased in recent years, and currently it is primarily restricted to surgical procedures for which profound muscle relaxation is required.

Drugs available for subarachnoid administration are shown in Table 36-8.

Although lidocaine has long been used for spinal anesthesia as a 5% solution, recent studies of local anesthetic neurotoxicity have led some to question this practice. This issue is discussed later in the chapter in the section on the neurotoxicity of local anesthetics.

Tetracaine is available both as crystals and as a 1% solution, which may be diluted with 10% glucose to obtain a 0.5% hyperbaric solution. Hypobaric solutions of tetracaine (tetracaine in sterile water) can be used for specific operative situations, such as anorectal or hip surgery. Isobaric tetracaine obtained by mixing 1% tetracaine with cerebrospinal fluid or normal saline is useful for lower limb surgical procedures.

Bupivacaine is widely used as a spinal anesthetic, either as a hyperbaric solution at a concentration of 0.75% with 8.25% dextrose or by using the nearly isobaric 0.5% solution. Intrathecal bupivacaine possesses an anesthetic profile similar to that of tetracaine.[63]

The addition of vasoconstrictors can prolong the duration of spinal anesthesia. For example, the addition of 0.2 to 0.3 mg of epinephrine to lidocaine, tetracaine, or bupivacaine solutions will produce a 50% or greater increase in duration.[64,65] The duration of spinal anesthesia produced by tetracaine can also be increased to a similar extent by adding 1 to 5 mg of phenylephrine. The addition of epinephrine to bupivacaine or lidocaine may be more effective in prolonging the duration of spinal anesthesia in lumbosacral segments than in thoracic segments.

TOPICAL ANESTHESIA

A number of local anesthetic formulations are available for topical anesthesia (Table 36-9), with lidocaine, dibucaine, tetracaine, and benzocaine being the drugs used most commonly. In general, these preparations provide effective but relatively short durations of analgesia when applied to mucous membranes or abraded skin. Lidocaine and tetracaine sprays are commonly used for endotracheal anesthesia before endotracheal intubation or for mucosal analgesia for bronchoscopy or esophagoscopy.

Several topical local anesthetic formulations can penetrate intact skin. EMLA, which is a eutectic mixture of 2.5% lidocaine base and 2.5% prilocaine base, is widely used for venipuncture, intravenous cannulation, skin grafting, and a range of other uses, including circumcision.[66] This preparation must be applied under an occlusive bandage for 45 to 60 minutes to obtain effective cutaneous anesthesia. Longer application times increase the depth and reliability of skin analgesia. EMLA is safe in neonates, and methemoglobinemia with the use of prilocaine is exceedingly uncommon. EMLA is more effective for newborn circumcision than placebo is but less effective than dorsal penile nerve block.[66,67] Several alternative topical local anesthetic formulations also are in use, including tetracaine gel[68] and liposomal lidocaine.[69] Physical methods to accelerate local anesthetic transit across skin, including iontophoresis, local heating, electroporation, and a variety of forms of needleless pressure injection, can lead to more rapid onset of cutaneous analgesia.[70] Synera (originally studied as S-Caine) is a formulation of lidocaine and tetracaine that was developed with a heating element (activated by opening the package to initiate an oxygen-dependent exothermic reaction). This formulation has a rapid onset and evokes vasodilatation.[71]

Topical anesthesia through cut skin is commonly used in pediatric emergency departments for liquid application into lacerations that require suturing. Historically, this had been provided by a mixture of tetracaine, epinephrine (adrenaline), and cocaine, known as TAC. TAC is usually supplied as tetracaine 0.5%, epinephrine 1:2000, and cocaine 10% to 11.8%, although studies suggest that more dilute concentrations may be almost equally effective and less likely to cause toxicity. The generally

TABLE 36-9 **VARIOUS PREPARATIONS INTENDED FOR TOPICAL ANESTHESIA**

Anesthetic Ingredient	Concentration (%)	Pharmaceutical Application Form	Intended Area of Use
Benzocaine	1-5	Cream	Skin and mucous membrane
	20	Ointment	Skin and mucous membrane
	20	Aerosol	Skin and mucous membrane
Cocaine	4	Solution	Ear, nose, throat
Dibucaine	0.25-1	Cream	Skin
	0.25-1	Ointment	Skin
	0.25-1	Aerosol	Skin
	0.25	Solution	Ear
	2.5	Suppositories	Rectum
Cyclonine	0.5-1	Solution	Skin, oropharynx, tracheobronchial tree, urethra, rectum
Lidocaine	2-4	Solution	Oropharynx, tracheobronchial tree, nose
	2	Jelly	Urethra
	2.5-5	Ointment	Skin, mucous membrane, rectum
	2	Viscous	Oropharynx
	10	Suppositories	Rectum
	10	Aerosol	Gingival mucosa
Tetracaine	0.5-1	Ointment	Skin, rectum, mucous membrane
	0.5-1	Cream	Skin, rectum, mucous membrane
	0.25-1	Solution	Nose, tracheobronchial tree
EMLA	Lidocaine, 2.5 Prilocaine, 2.5	Cream	Intact skin
TAC	Tetracaine, 0.5 Epinephrine, 1:200,000 Cocaine, 11.8	Solution	Cut skin
LET	Lidocaine, 4% Epinephrine, 1:20,000 Tetracaine, 0.5%	Solution	Cut skin

Modified from Covino B, Vassallo H: Local anesthetics: mechanisms of action and clinical use. *Orlando, Fla, 1976, Grune and Stratton.*
EMLA, Eutectic mixture of lidocaine and prilocaine; *LET,* lidocaine-epinephrine-tetracaine; *TAC,* tetracaine-epinephrine-cocaine.

recommended safe maximum dose is 3 to 4 mL for adults or 0.05 mL/kg for children. TAC is ineffective through intact skin; in contrast, its rapid absorption from mucosal surfaces can lead to toxic, even fatal reactions.

Because of concerns regarding cocaine toxicity and the potential for diversion and abuse, several groups have investigated alternative cocaine-free topical preparations. Non–cocaine-containing formulations, especially lidocaine-epinephrine-tetracaine and tetracaine-phenylephrine, have largely supplanted TAC.[72] Similarly, otolaryngologists previously administered cocaine routinely as a solution or aerosol into the nasal passages to provide mucosal analgesia and vasoconstriction. In recent years, cocaine has increasingly been replaced for nasal application by the combined use of an α_1-adrenergic agonist (oxymetazoline or phenylephrine) and a local anesthetic such as 2% to 4% lidocaine, with more dilute solutions being recommended for infants and children (see Chapter 92). Systemic absorption of phenylephrine can cause severe hypertension and reflex bradycardia. Oxymetazoline is associated with much less systemic effect and has a wider margin of safety, although it can still produce peripheral vasoconstriction, hypertension, and reflex bradycardia. In the authors' view, there is no clinical setting for which the benefits of cocaine clearly outweigh the potential risks when compared with alternative approaches involving combined administration of a local anesthetic and a topical vasoconstrictor such as oxymetazoline.

TUMESCENT ANESTHESIA

A technique of local anesthesia most commonly used by plastic surgeons during liposuction procedures involves the subcutaneous injection of large volumes of dilute local anesthetic in combination with epinephrine and other drugs. Total doses of lidocaine ranging from 35 to 55 mg/kg produce safe plasma concentrations, which can peak more than 8 to 12 hours after infusion.[73] Despite these seemingly huge doses, good outcomes have been reported in several case series.[74] Conversely, there have been several case series of cardiac arrest and death during plastic surgery procedures in which multiple risk factors, including high local anesthetic concentrations and concomitant use of sedatives, may have contributed to the patients' instability and deterioration.[75] Factors governing uptake and clearance from this method of local anesthetic delivery deserve further study. Clinicians should exercise great caution when administering additional local anesthetics by infiltration or other routes for at least 12 to 18 hours after the use of this technique.

SYSTEMIC LOCAL ANESTHETICS FOR NEUROPATHIC PAIN

A broad variety of local anesthetics, antiarrhythmics, anticonvulsants, and other Na^+ channel blockers are administered intravenously, orally, or both to relieve a number of forms of neuropathic pain (see Chapter 64).[76] Clinical

results are unpredictable.[77] Although successful responses from intravenous lidocaine are often taken as a positive indication for oral mexiletine, some patients find mexiletine difficult to tolerate. When the signs of neuropathic pain are reversed by lidocaine infusion, normal nociception and other sensory modalities are unaffected, suggesting that the neurophysiologic correlate of the disease has an unusually high susceptibility to these drugs, present in plasma at concentrations 50- to 100-fold lower than that required to block normal impulses in peripheral fibers. Laboratory studies suggest that ectopic impulse activity arising at a site of injury or elsewhere, such as the dorsal root ganglion, contributes to the neuropathic pain and that such impulses are particularly sensitive to use-dependent Na^+ channel blockers. It is noteworthy that relief of preexisting neuropathic pain, both clinically and in animal models,[78] can in some cases persist for days, weeks, or months after a single intravenous infusion of drug (e.g., lidocaine), far beyond the lifetime of the drug in vivo or any nerve block that it might affect. The mechanism of this remarkable action remains a mystery.

PHARMACOKINETICS

The concentration of local anesthetics in blood is determined by the amount injected, the rate of absorption from the site of injection, the rate of tissue distribution, and the rate of biotransformation and excretion of the specific drug.[79,80] Patient-related factors such as age, cardiovascular status, and hepatic function influence the physiologic disposition and resultant blood concentration of local anesthetics.

ABSORPTION

The systemic absorption of local anesthetics is determined by the site of injection with its tissue blood perfusion, dosage and volume, addition of a vasoconstrictor agent, and the pharmacologic profile of the agent itself.[79,80] Comparison of the blood concentration of local anesthetics after various routes of administration reveals that the anesthetic drug concentration is highest after intercostal nerve blockade, followed in order of decreasing concentration by injection into the caudal epidural space, lumbar epidural space, brachial plexus, and subcutaneous tissue. When a local anesthetic solution is exposed to an area of greater vascularity, a greater rate and degree of absorption occur. This relationship is of clinical significance because use of a fixed dose of a local anesthetic agent can be potentially toxic in one area of administration but not in others. For example, the use of 400 mg of lidocaine without epinephrine for an intercostal nerve block results in an average peak venous plasma level of approximately 7 μg/mL, which is sufficiently high to cause symptoms of CNS toxicity in some patients. By comparison, this same dose of lidocaine used for a brachial plexus block yields a mean maximum blood level of approximately 3 μg/mL, which is rarely associated with signs of toxicity.

The maximum blood concentration of local anesthetic drugs is related to the total dose of drug administered for any particular site of administration. For most drugs, there is a proportionality between the amount of drug administered and the resultant peak anesthetic blood concentration. Epinephrine decreases the rate of vascular absorption of certain local anesthetics from various sites of administration and thus decreases their potential systemic toxicity. A 5-μg/mL concentration of epinephrine (1:200,000) significantly reduces the peak blood levels of lidocaine and mepivacaine irrespective of the site of administration. Peak blood levels of bupivacaine and etidocaine are minimally influenced by the addition of a vasoconstrictor after injection into the lumbar epidural space. However, epinephrine will significantly reduce the rate of vascular absorption of these drugs when they are used for peripheral nerve blocks such as brachial plexus blockade.

Differences also exist in the rate of absorption of various local anesthetics.

DISTRIBUTION

The systemic distribution of local anesthetics in many settings can be described sufficiently by a two-compartment model.[81,82] The rapid-disappearance phase is believed to be related to uptake by rapidly equilibrating tissues (i.e., tissues that have high vascular perfusion). The slower phase of disappearance from blood is mainly a function of the particular compound.[82]

Local anesthetic drugs are distributed throughout all body tissues, but the relative concentration in different tissues varies. In general, more highly perfused organs show higher concentrations of local anesthetic drug than less well-perfused organs do. Because local anesthetics are rapidly extracted by lung tissue, the whole blood concentration of local anesthetics decreases markedly as they pass through the pulmonary vasculature.[83]

BIOTRANSFORMATION AND EXCRETION

The pattern of metabolism of local anesthetic agents varies according to their chemical classification. The ester, or procainelike, drugs undergo hydrolysis in plasma by the pseudocholinesterase enzymes; clearance of chloroprocaine is especially rapid.[84,85]

The aminoamide drugs undergo enzymatic degradation primarily in the liver. Lidocaine is metabolized somewhat more rapidly than mepivacaine, which in turn is more rapidly metabolized than bupivacaine.[67,86,87]

Excretion of the metabolites of amide-type local anesthetics occurs via the kidney. Less than 5% of the unchanged drug is excreted via the kidney into urine.

PHARMACOKINETIC ALTERATIONS BY PATIENT STATUS

Patient age can influence the physiologic disposition of local anesthetics (see Chapters 80 and 92). In a report by Nation and colleagues,[88] the half-life of lidocaine after intravenous administration averaged 80 minutes in human volunteers varying in age from 22 to 26 years, whereas volunteers 61 to 71 years of age demonstrated a significantly prolonged lidocaine half-life that averaged 138 minutes.

Newborn infants have immature hepatic enzyme systems and hence prolonged elimination of lidocaine, bupivacaine, and ropivacaine.[89-91] Bupivacaine, for example, has a terminal elimination half-life in adults that averages 3.5 hours. In neonates and some younger infants, terminal elimination half-lives can be as long as 8 to 12 hours. Prolonged elimination is particularly an issue for continuous infusions of local anesthetics in infants, and seizures have been associated with high bupivacaine infusion rates.[92] Based on analysis of these cases, a maximum infusion rate of 0.4 mg/kg/hr for prolonged bupivacaine infusions has been proposed for children and adults, whereas prolonged infusion rates for neonates and young infants should not exceed 0.2 mg/kg/hr.[93] Even at 0.2 mg/kg/hr, plasma bupivacaine concentrations were found to be rising toward a toxic range in some younger infants after 48 hours.[94] Similarly, prolonged lidocaine infusions in neonates should not exceed 0.8 mg/kg/hr. The potential for toxicity with lidocaine infusions in neonates is also increased by the accumulation of its principal metabolite, monoethylglycinexylidide, which can cause seizures. Chloroprocaine may offer unique advantages for epidural infusion in neonates in that it is rapidly cleared from plasma, even in preterm neonates.[95]

Decreased hepatic blood flow or impaired hepatic enzyme function can produce a substantial elevation of blood levels of the aminoamide local anesthetics. An average lidocaine half-life of 1.5 hours was reported in volunteers with normal hepatic function, whereas patients with liver disease demonstrated an average half-life of 5.0 hours. The rate of disappearance of lidocaine from blood is markedly prolonged in patients with congestive heart failure.[96]

TOXICITY

Local anesthetic drugs are generally considered safe if administered in an appropriate dosage and in the correct anatomic location. However, systemic and localized toxic reactions can occur because of accidental intravascular or intrathecal injection or administration of an unwanted excessive dose. In addition, specific adverse effects are associated with the use of certain drugs, such as allergic reactions to the aminoester drugs and methemoglobinemia after the use of prilocaine.

SYSTEMIC TOXICITY

Systemic reactions to local anesthetics primarily involve the CNS and the cardiovascular system (see Chapters 56 to 58 and 92). In general, the CNS is more susceptible to the actions of systemic local anesthetics than the cardiovascular system is, and thus the dose or blood level of local anesthetic required to produce CNS toxicity is usually lower than that resulting in circulatory collapse.

Central Nervous System Toxicity

The initial symptoms of local anesthetic–induced CNS toxicity are feelings of lightheadedness and dizziness followed frequently by visual and auditory disturbances such as difficulty focusing and tinnitus. Other subjective CNS symptoms include disorientation and occasional feelings of drowsiness. Objective signs of CNS toxicity are usually excitatory in nature and include shivering, muscular twitching, and tremors initially involving muscles of the face and distal parts of the extremities. Ultimately, generalized convulsions of a tonic-clonic nature occur. If a sufficiently large dose or rapid intravenous injection of a local anesthetic is administered, the initial signs of CNS excitation are rapidly followed by a state of generalized CNS depression. Seizure activity ceases, and respiratory depression and ultimately respiratory arrest may occur. In some patients, CNS depression is seen without a preceding excitatory phase, particularly if other CNS depressant drugs have been administered.

CNS excitation may be the result of an initial blockade of inhibitory pathways in the cerebral cortex by local anesthetic drugs,[97] but it can also result from the net stimulation of release of glutamate, an excitatory amino acid neurotransmitter. Blockade of inhibitory pathways allows facilitatory neurons to function in an unopposed fashion, which results in an increase in excitatory activity leading to convulsions. Further increase in the dose of local anesthetic leads to inhibition of activity of both the inhibitory and facilitatory circuits, which results in a generalized state of CNS depression.

In general, the potency of the local anesthetic is correlated with intravenous CNS toxicity.[98] Convulsions caused by an inadvertent intravenous bolus of local anesthetic can generally be terminated by small intravenous doses of a benzodiazepine, such as midazolam, or by small intravenous doses of thiopental. Respiratory or metabolic acidosis increases the risks for CNS toxicity from local anesthetics.[99]

Increased $Paco_2$ enhances cerebral blood flow and thus the anesthetic is delivered more rapidly to the brain. In addition, diffusion of CO_2 into neuronal cells decreases intracellular pH, which facilitates conversion of the base form of the drugs to the cationic form. The cationic form does not diffuse well across the nerve membrane, so that ion trapping will occur, which will increase the apparent CNS toxicity of local anesthetics.

Hypercapnia and acidosis also decrease the plasma protein binding of local anesthetic agents.[100] Accordingly, an increase in $Paco_2$ or a decrease in pH will increase the proportion of free drug available for diffusion into the brain. On the other hand, acidosis increases the cationic form of the local anesthetic, which should decrease the rate of diffusion through lipid barriers.

The clinical implication of this effect of hypercapnia and acidosis on toxicity deserves emphasis. Seizures produce hypoventilation and a combined respiratory and metabolic acidosis, which further exacerbates the CNS toxicity. In the setting of local anesthetic toxic reactions, it is essential to provide prompt assisted ventilation and circulatory support as needed to prevent or correct hypercapnia and acidosis and to prevent or correct hypoxemia, which also exacerbates CNS toxicity.

Based on the preceding discussion and a number of national guidelines for safe perioperative care, it is generally agreed that clinicians performing major conduction blockade should make a routine practice of having the following ready at hand:

1. Routine vital sign monitoring equipment
2. An oxygen tank or wall oxygen outlet

3. Airway equipment, including a bag-mask circuit for delivery of positive-pressure ventilation
4. Drugs to terminate convulsions, should they occur, preferably midazolam, lorazepam, diazepam, or thiopental.

Cardiovascular System Toxicity

Local anesthetics can exert direct actions on both the heart and peripheral blood vessels, as well as indirect actions on the circulation by blockade of sympathetic or parasympathetic efferent activity.

Direct Cardiac Effects. The primary cardiac electrophysiologic effect of local anesthetics is a decrease in the rate of depolarization in the fast conducting tissues of Purkinje fibers and ventricular muscle.[101] This reduction in rate is believed to be due to a decrease in the availability of fast sodium channels in cardiac membranes. Action potential duration and the effective refractory period are also decreased by local anesthetics.

The electrophysiologic effects of various local anesthetics differ qualitatively. Bupivacaine depresses the rapid phase of depolarization (Vmax) in Purkinje fibers and ventricular muscle more than lidocaine does. In addition, the rate of recovery from a use-dependent block is slower in bupivacaine-treated papillary muscles than in lidocaine-treated muscles. This slow rate of recovery results in incomplete restoration of Na^+ channel availability between action potentials, particularly at high heart rates. These differential effects of lidocaine and bupivacaine have been advanced as explanations of the antiarrhythmic properties of lidocaine and the arrhythmogenic potential of bupivacaine.

Electrophysiologic studies have shown that high blood levels of local anesthetics will prolong conduction time through various parts of the heart, as indicated on the electrocardiogram (ECG) by an increase in the PR interval and duration of the QRS complex. Extremely high concentrations of local anesthetics depress spontaneous pacemaker activity in the sinus node, thereby resulting in sinus bradycardia and sinus arrest.

All local anesthetics exert dose-dependent negative inotropic action on cardiac muscle[102]; the depression of cardiac contractility is roughly proportional to conduction blocking potency. Thus, bupivacaine and tetracaine are more potent cardiodepressants than lidocaine is.

Local anesthetics may depress myocardial contractility by affecting calcium influx and triggered release from the sarcoplasmic reticulum,[97] as well as by inhibiting cardiac sarcolemmal Ca^{2+} currents and Na^+ currents.

Direct Peripheral Vascular Effects. Local anesthetics exert biphasic effects on peripheral vascular smooth muscle.[103] Low concentrations of lidocaine and bupivacaine produced vasoconstriction in the cremaster muscle of rats, whereas high concentrations produced vasodilation in both isolated tissue models and in vivo.

Cocaine is the only local anesthetic that consistently causes vasoconstriction at all concentrations because of its ability to inhibit the uptake of norepinephrine by premotor neurons and thus to potentiate neurogenic vasoconstriction.

COMPARATIVE CARDIOVASCULAR TOXICITY

All local anesthetics, but especially bupivacaine, can cause rapid and profound cardiovascular depression (see Chapters 56 to 58 and 92). The cardiotoxicity of bupivacaine appears to differ from that of lidocaine in the following manner:

1. The ratio of the dosage required for irreversible cardiovascular collapse (CC) and the dosage that will produce CNS toxicity (convulsions; i.e., the CC/CNS ratio) is lower for bupivacaine and etidocaine than for lidocaine.[104]
2. Ventricular arrhythmias and fatal ventricular fibrillation can occur more often after the rapid intravenous administration of a large dose of bupivacaine, but far less frequently with lidocaine. The CNS effects of local anesthetics may contribute to the generation of arrhythmias (see Chapter 68).
3. A pregnant animal or patient may be more sensitive to the cardiotoxic effects of bupivacaine than a nonpregnant animal or patient[105] (see Chapter 77). The 0.75% solution of bupivacaine is no longer recommended for use in obstetric anesthesia in the United States.
4. Cardiac resuscitation is more difficult after bupivacaine-induced cardiovascular collapse, and acidosis and hypoxia markedly potentiate the cardiotoxicity of bupivacaine.[106]

Many resuscitation drugs, including atropine, epinephrine, bretylium, lidocaine, amrinone, and phenytoin, have been used in animal studies, and occasionally in humans, for the treatment of bupivacaine overdose and cardiovascular collapse. As with other forms of cardiovascular collapse, basic CPR should be started immediately and defibrillation should be performed as indicated according to advanced cardiac life support (ACLS) algorithms.[107] In the authors' view—beyond the established uses of low-dose epinephrine and atropine in their designated steps in ACLS protocol[107] and beyond the use of lipid emulsions as detailed later—there is no established role for antiarrhythmic drugs or other traditional cardiac resuscitation drugs in the setting of bupivacaine-induced cardiac arrest. It is *not* recommended to treat bupivacaine-induced ventricular arrhythmias with lidocaine or amiodarone. Rapid institution of extracorporeal cardiopulmonary support has been lifesaving in a small number of cases of bupivacaine cardiotoxicity. There is a growing use of rapid-response extracorporeal membrane oxygenator and/or cardiopulmonary bypass teams in some tertiary hospitals. In selected cases, these teams should be activated even while initiating ACLS and infusing lipid emulsions.

The clinical implications for cardiac resuscitation after intravascular injection or overdose of local anesthetic are the following:

1. No medications are uniformly effective in facilitating resuscitation from bupivacaine-induced cardiac arrest or severe ventricular tachycardia (despite our recommendations regarding Intralipid later). Basic principles of cardiopulmonary resuscitation should be

emphasized first, including attention to securing the airway, providing oxygenation and ventilation, and performing chest compressions if needed.
2. Because resuscitation after local anesthetic-induced circulatory collapse is so difficult, prevention of massive intravascular injection or excessive dosing is crucial.
3. Negative aspiration of the syringe does not always exclude intravascular placement. Incremental, fractionated dosing should be the rule for all patients undergoing major conduction blockade. Although changes on the ECG are not always present before circulatory collapse, they often are, and continuous attention to the ECG (including changes in QRS morphology, rate, rhythm, or ectopy) may be lifesaving by terminating injection before a lethal dose is administered.
4. Based on animal studies[108] and a growing number of human case reports,[109-111] hospitals and clinics that perform major conduction blockade should keep available for emergency use a supply of lipid emulsion, such as Intralipid 20%.[111] If a patient experiences profound cardiovascular depression or circulatory arrest after the administration of bupivacaine, ropivacaine, or by extrapolation, other local anesthetics, then along with initiation of basic life support and the ACLS protocol we support the recommendation for a rapid bolus of Intralipid 20%, 1.5 mL/kg (or approximately 100 mL in adults), administering without delay, followed if necessary by an infusion of 0.25 mL/kg/min for the next 10 minutes.

Chiral Local Anesthetics: Ropivacaine and Levobupivacaine

Commercial bupivacaine is a racemic mixture of (*R*)- and (*S*)-stereoisomers. In response to the problem of cardiovascular toxicity resulting from accidental intravenous injection of bupivacaine, single enantiomers were developed in the hope that they would be potentially safer local anesthetics. Ropivacaine (Naropin)[112] and levo-(*S*)-bupivacaine (Chirocaine)[113] were formulated to exploit this stereoselectivity. Ropivacaine is a single (*S*)-stereoisomer that differs from levobupivacaine in the substitution of a propyl for the butyl group on the piperidine ring (see Table 36-1). With these designed changes in molecular structure, it was hoped that ropivacaine and levobupivacaine would be less intrinsically cardiotoxic. Conversely, it appears that the (*S*)-enantiomers of mepivacaine and bupivacaine are metabolized by the liver more slowly than the corresponding (*R*)-enantiomers, which would lead to somewhat greater systemic accumulation with prolonged infusions.

The slow reversal of Na^+ channel blockade after a cardiac action potential, which is a hallmark of bupivacaine, is considerably faster with ropivacaine. In addition to these electrical differences, the negative inotropic potency of ropivacaine on isolated cardiac tissue appears to be considerably less than that of bupivacaine. Both electrical and mechanical differences in the toxic profiles can arise from the selective inhibition of Ca^{2+} currents by bupivacaine.

Is there a greater therapeutic index for ropivacaine than bupivacaine, particularly regarding cardiotoxicity? In clinical studies comparing potencies of ropivacaine and bupivacaine administered for brachial plexus[114] or lumbar epidural block,[115] the anesthetic profiles of the drugs were almost identical. A third study comparing lumbar epidural 0.5% bupivacaine with 0.75% ropivacaine also found no significant differences in motor or sensory effects between the drugs at these different concentrations.[116] Overall, it appears that ropivacaine is slightly less potent than (1:1.3 to 1:1.5) bupivacaine for regional anesthesia. In some laboratory animal studies and in some human studies, ropivacaine also produced blocks of shorter duration than those induced by bupivacaine. Other studies in animals and humans have found equal durations of sensory and motor block for the two drugs.

At the projected equipotent doses for nerve block, are the drugs equally toxic? The overall impression is that ropivacaine is less cardiotoxic than bupivacaine. Studies in animals have generally found that bupivacaine more readily produces conduction disturbances, cardiac collapse, or ventricular fibrillation than ropivacaine does and that aggressive cardiac resuscitation after an intentional intravenous bolus in dogs leads to effective reversal of the toxic effects far more frequently with ropivacaine than with bupivacaine.[117]

The greater safety of ropivacaine than bupivacaine may be related both to the reduced toxicity of the single (*S*)-isomer and to the difference between the propyl- and butyl-*N*-piperidine substituent. In contrast to bupivacaine, the cardiotoxic profile of ropivacaine in pregnant ewes is the same as the corresponding profile in nonpregnant ewes.[118]

Levobupivacaine has been studied in a range of clinical settings and sites of administration.[119-121] Although many publications have compared levobupivacaine with racemic bupivacaine and ropivacaine,[120,121] conclusions differ among studies regarding the relative potency and duration of block of these three drugs at different sites of administration with respect to sensory and motor endpoints. Levobupivacaine is formulated as a weight percentage in regard to its free base content, whereas the weight percentage of most other local anesthetics is calculated on the basis of the hydrochloride salt.[122]

Acidosis and Hypoxia

As with CNS toxicity, hypercapnia, acidosis, and hypoxia potentiate the negative chronotropic and inotropic actions of lidocaine and bupivacaine in isolated cardiac tissue, and the combination of hypoxia and acidosis markedly potentiates the cardiodepressant effects of bupivacaine.[123] Hypoxia and acidosis also increased the frequency of cardiac arrhythmias and the mortality rate in sheep after the intravenous administration of bupivacaine. Hypercapnia, acidosis, and hypoxia occur very rapidly in some patients after seizure activity caused by the rapid accidental intravascular injection of local anesthetic agents.[124] Thus, the cardiovascular depression observed in some patients after the accidental intravenous injection of bupivacaine may be related in part to the effect of seizures producing acidosis and hypoxia and thereby leading to an exacerbation of bupivacaine's intrinsic cardiotoxicity.

Indirect Cardiovascular Effects

High levels of spinal or epidural blockade can produce severe hypotension. A follow-up study of closed claims of patients who suffered perioperative cardiac arrest confirmed previous reports of a series of cardiac arrests involving generally healthy patients undergoing spinal or epidural anesthesia.[125] These events frequently occurred in conjunction with high dermatomal levels of blockade, liberal use of sedatives, and progression to cardiac arrest after a period of hypotension accompanied by bradycardia, often involving delays in recognition of the problem, delays in instituting airway support (particularly in sedated patients), and delays in administration of direct-acting combined α- and β-adrenergic agonists, such as epinephrine. Whereas mild to moderate degrees of hypotension generally respond well to indirect-acting sympathomimetics, such as ephedrine or incremental dosing of phenylephrine, the combination of severe hypotension and severe bradycardia under spinal anesthesia should in most clinical settings be treated promptly with incremental dosing of epinephrine, initially at doses of 0.1 to 1 μg/kg, or roughly 20- to 200-fold less than those used in the ACLS cardiac arrest algorithm (see Chapter 108).

METHEMOGLOBINEMIA

A unique systemic side effect associated with a specific local anesthetic is the development of methemoglobinemia after the administration of large doses of prilocaine.[126] In general, 600-mg doses are required for the development of clinically significant levels of methemoglobinemia in adults. Hepatic metabolism of prilocaine generates *O*-toluidine, which oxidizes hemoglobin to methemoglobin. Methemoglobinemia, if severe, can be treated with intravenous administration of methylene blue. Standard dosing of the topical local anesthetic EMLA (a mixture of lidocaine and prilocaine) in term newborns produces minimal amounts of methemoglobin, and EMLA when used in this manner should thus be regarded as safe in the great majority of newborns. It should be noted that risk is increased in newborns with rare metabolic disorders or after the concomitant administration of other drugs that impair reduction of methemoglobin.

ALLERGIES

Although patients receiving local anesthetics may experience a range of local and systemic symptoms, prospective studies indicate that few of these reactions are confirmed as allergic reactions.[127] Aminoester drugs such as procaine produce allergic-type reactions more commonly than the aminoamides do, although even with aminoesters, the vast majority of reactions are not allergic. Aminoesters, unlike aminoamides, are derivatives of *p*-aminobenzoic acid, which is known to be allergenic. Some aminoamide solutions contain a preservative, methylparaben, whose chemical structure is similar to that of *p*-aminobenzoic acid, but for most aminoamides, preservative-free solutions are available. Contamination of vials with latex antigen has been suspected in some allergic reactions, although it is difficult to confirm. In the rare patient for whom confirmed allergy to both aminoamides and aminoesters precludes their use for spinal anesthesia, meperidine can be considered as an alternative.[128]

LOCAL TISSUE TOXICITY

All the clinically used aminoamide and aminoester local anesthetics can produce direct toxicity to nerves if they achieve sufficiently high intraneural concentrations. Conversely, in most clinical applications, no damage to nerves occurs. Although local anesthetics are usually packaged and injected at concentrations well above their physiologically effective range, in the process of delivery they are generally diluted sufficiently so that no harm is done. If such dilution does not occur, however, long-term or permanent neural deficits do result. Thus, the application of 5% (200 mM) lidocaine in viscous, dense solutions through narrow intrathecal catheters has been associated with a high frequency of transient or longer-term radicular symptoms, or even cauda equina syndrome.[129] Laboratory investigations have shown that such high concentrations of local anesthetics alone applied directly to bare nerve fibers produce an irreversible conduction block in less than 5 minutes.[130] Clinicians should be aware that the concentrations of formulated local anesthetic solutions are neurotoxic and that their dilution, in situ or in tissue, is essential for safe use without local toxic reactions.

In the late 1970s and early 1980s, prolonged sensory and motor deficits were reported in some patients after the epidural or subarachnoid injection of large doses of chloroprocaine.[131] Studies in animals have proved somewhat contradictory regarding the potential neurotoxicity of chloroprocaine.[132,133] Some studies suggest that the combination of low pH, sodium bisulfite, and inadvertent intrathecal dosing is responsible in part for the neurotoxic reactions observed after the use of large amounts of chloroprocaine solution; other studies have disputed this claim and note that chloroprocaine itself at high concentrations can also be neurotoxic,[132,133] but these concentrations are probably rarely achieved during properly positioned epidural anesthesia, as opposed to inadvertent spinal anesthesia. The currently available commercial solutions of chloroprocaine do not contain sodium bisulfite. This was initially replaced by ethylene glycol-bis-(β-aminoethyl ether)-*N*,*N*-tetraacetic acid (EGTA), a preservative and high-affinity calcium chelator that occasionally causes local muscle spasms after epidural administration. More recently, chloroprocaine has become available in an entirely preservative-free preparation. Chloroprocaine has unique utility in situations in which rapid plasma clearance is required to prevent excessive systemic accumulation of local anesthetic. Chloroprocaine has been given by epidural infusion to neonates and young infants in settings in which lidocaine and bupivacaine do not provide an effective therapeutic index,[95] and it has also recently become popular as a short-duration spinal anesthetic.

Single-shot spinal anesthesia with commonly recommended doses and concentrations of many different local anesthetics can produce more limited and transient neurologic symptoms (back pain, paresthesias, radicular pain, or hypoesthesia).[134] Some studies and systematic

reviews have found that mepivacaine and lidocaine at a range of dilutions cause more frequent symptoms than bupivacaine and prilocaine do.[135] The risk of transient neurologic symptoms after spinal anesthesia was not diminished by dilution of lidocaine from 5% to 1% or 2%. Differences in study design, method of questioning, and criteria for inclusion may be partially responsible for differences in the prevalence of radicular sequelae in various studies. Despite these differences in study design, a meta-analysis concluded that the pooled relative risk for transient neurologic symptoms after spinal anesthesia with lidocaine was 6.7-fold higher than with bupivacaine and 5.5-fold higher than with prilocaine.[135] The addition of vasoconstrictors to local anesthetic solutions can also increase risk.[136] Neurotoxicity appears to be unrelated to conduction block, because saxitoxin, neosaxitoxin, and tetrodotoxin, which are highly potent blockers of sodium channels, can produce intense conduction blockade without histologic or behavioral signs of nerve injury.[137]

With the recent widespread use of ultrasound guidance of peripheral nerve blockade, there is an expectation, not yet fully demonstrated,[138] that this approach will reduce the frequency of neurologic sequelae from peripheral nerve blockade. This issue is discussed in detail in Chapter 58.

Intraoperative positioning in association with nerve blockade appears to be a risk factor (see Chapter 41). For example, patients undergoing surgery in the lithotomy position appear to be at increased risk for neurologic symptoms after either spinal or epidural anesthesia. It is unknown at present why this association produces increased risk; nerve compression or stretch or reduced perfusion pressure in the vasa nervorum may possibly exacerbate the toxicity from local anesthetics. The lithotomy position can produce neurologic sequelae and lower extremity compartment syndrome, particularly with prolonged surgery and use of the Trendelenburg position.[139]

Skeletal muscle changes occur after the intramuscular injection of local anesthetics such as lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine. In general, the more potent, longer-acting agents bupivacaine and etidocaine cause more localized skeletal muscle damage than the less potent, shorter-acting anesthetics lidocaine and prilocaine do. This effect on skeletal muscle is reversible, and muscle regeneration occurs rapidly and is complete within 2 weeks after the injection of local anesthetic agents. Local anesthetic-induced myotoxicity may involve actions on mitochondria.[140]

DEVELOPMENT OF PROLONGED-DURATION AND SENSORY- OR NOCICEPTIVE-SELECTIVE LOCAL ANESTHETICS

Several methods for producing long-duration nerve blockade are under investigation. Liposomal encapsulation can prolong nerve blockade, depending on the dose and the physical properties of the liposome (surface charge, size, lamellar structure).[141-143] Local anesthetics can be incorporated into biodegradable polymer microspheres for sustained release.[144] These preparations produce peripheral nerve blockade in animal models and human volunteers,[145] ranging from 2 to 8 days, depending on the dose, site, and species. Because of the intrinsic neurotoxicity of all aminoamide and aminoester local anesthetics, there is likely to be some irreducible potential for neurotoxicity with most of these approaches to controlled release of aminoamide and aminoester local anesthetics in proximity to major nerve trunks. Thus, these formulations will have the most favorable risk-benefit ratio when used in nonprotective locations, such as intercostal nerve blockade, where prolonged numbness may be a benefit rather than a complication of the intervention. This risk is also likely to be less clinically important for infiltration analgesia. Exparel is a lipid depot formulation that has recently been approved in the U.S. for infiltration analgesia, not for perineural administration.[146] Posidur is another lipid depot formulation currently in clinical trials.[147]

Prolonged-duration local anesthesia also appears to be feasible with the use of site 1 sodium channel blockers in combination with either local anesthetics or adrenergics.[148] The site 1 blocker neosaxitoxin has been used in humans in phase 1 and phase 2 clinical trials.[149-151] A combination of site 1 toxins with either local anesthetics or adrenergics results in prolongation of blockade and improvement in the therapeutic index.[149] Theoretically, attractive features of site 1 toxins include their apparent lack of local tissue toxicity on nerves[137] or muscles[152] and their minimal cardiotoxicity.[153]

Other drugs have been examined for use as local anesthetics, including tricyclic antidepressants,[154] although neurotoxicity may limit the clinical utility of this group of drugs.

Prolonged duration local anesthetics are expected to be useful for providing prolonged postoperative analgesia for a wide range of surgeries, both via wound infiltration and by peripheral nerve and plexus blockade. For peripheral nerve and plexus blocks for the extremities, clinical application will require careful consideration of the potential consequences of prolonged motor blockade. For thoracic and abdominal surgeries, prolonged-duration paravertebral and transversus abdominis plane blockades should be useful, and motor blockade should be a nonissue.

Sensory (or nociceptive) selectivity has been another long-sought goal for local anesthetics. A novel approach to targeting small sensory fibers involved routing a quaternary lidocaine derivative, QX-314, through transient receptor potential (TRP) channels, which are preferentially located in small sensory fibers.[155,156] These channels are involved in the transduction of heat pain and are activated by a vanilloid, such as capsaicin.

BIOLOGIC MECHANISMS OF LOCAL ANESTHETIC FAILURE: INFLAMMATION, HYPERALGESIA, TACHYPHYLAXIS, AND GENETIC VARIANTS

Failure of local anesthesia is commonly ascribed to technical failure of delivery, insufficient volume or concentration of drug, or erroneous clinical decisions in selection of techniques. However, there are many clinical situations in which biologic processes contribute to failed local anesthesia, even with proper technique and drug selection.

For example, in patients going to the dentist with infections such as a tooth abscess or severe pulpitis, failure rates of standard doses of local anesthetic have been reported to be as high as 70%. Local anesthetic failure at a site of inflammation appears to reflect a combination of pharmacokinetic and pharmacodynamic factors. Pharmacokinetic factors include (1) increased local blood flow leading to accelerated removal of drug from perineural injection compartments; (2) local tissue acidosis leading to a greater proportion of the drug in the hydrochloride form, which diffuses more poorly across biologic membranes; and (3) local tissue edema, which increases diffusion distances for drug into nerves and promotes further dilution. Pharmacodynamic factors include the effects of inflammation on both peripheral sensitization of nerves and central sensitization.[157,158] In the setting of an infected mandibular tooth, inferior alveolar nerve block (performed proximally at a site presumably remote from the infected area) also has an unexpectedly frequent failure rate.

Local anesthetics and regional anesthesia, in turn, can suppress components of inflammatory responses by a complex interplay of local, spinal, and systemic mechanisms.[159,160]

Apparent reductions in the effectiveness of local anesthetic infusions over time may be due to many causes unrelated to tolerance, including dislodgement of catheters and changes in the dermatomal origin or intensity of nociceptive input. In obstetric patients receiving epidural bolus injections, recurrence of pain before the next injection resulted in a reduction in the intensity and duration of blockade, whereas repeated injection before the return of pain prevented this rapidly occurring form of tolerance, or tachyphylaxis.[161] In postoperative patients, coadministration of systemic opioids prevented regression of segmental block in patients receiving thoracic epidural bupivacaine infusions.[162] Studies in rats suggest that both pharmacokinetic and pharmacodynamic mechanisms are involved. In a rat model, tachyphylaxis was linked to the development of hyperalgesia,[163] and drugs that inhibit hyperalgesia, including *N*-methyl-D-aspartate receptor antagonists and nitric oxide synthase inhibitors,[164] also prevented tachyphylaxis. Conversely, repeated sciatic injections of lidocaine resulted in reduced intraneural lidocaine content and reduced duration of block.[165]

Occasionally, patients report "local anesthetics don't work for me." Although this claim may reflect previous technical failures or a variety of other processes and patient- or procedure-specific factors, it is possible that these failures may involve genetic variation in local anesthetic responsiveness in some cases. For example, a subgroup of patients with the connective tissue disorder Ehlers-Danlos syndrome appears to have a diminished response to topical local anesthesia.[166]

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Chapter 37

Risk of Anesthesia

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Key Points

- Perioperative risk is multifactorial and may occur as a result of anesthesia-, surgery-, and/or patient-specific factors.
- Anesthesia-related (and surgery-related) risk is typically defined as morbidity and mortality occurring within 30 days of surgery, although events that occur at later points may still be related to anesthesia and/or surgery.
- The overall risk of anesthesia relates to both specific, organ-based complications and the rapidity with which they are managed (i.e., rescued).
- In the literature on anesthesia-related risk, the rates of morbidity and mortality reported across studies show a substantial variability in part attributable to the wide variety of definitions used in these studies.
- Historical studies of anesthesia-related risk identified anesthesia-related respiratory depression as the major cause of death and coma totally attributable to anesthesia. This finding prompted the creation of postanesthesia care units (PACUs).
- Research into anesthesia-related cardiac arrest has found it to be attributable to medication administration, airway management, and technical problems of central venous access.
- Multivariate modeling can be used to determine specific factors associated with an increased likelihood of adverse postoperative events, and it has been used to define a range of clinical risk indices to predict postoperative outcomes.
- Surveys of maternal mortality suggest that although the absolute rate of complications attributable to anesthesia has not decreased over time, the increased use of regional anesthesia may have led to improvements in outcome.
- Medication-related and cardiovascular events were the most common causes of cardiac arrest in the Pediatric Perioperative Cardiac Arrest (POCA) Registry.
- Growth in the number and variety of surgical procedures performed in hospital outpatient departments, ambulatory surgery centers, and physician offices creates novel challenges for assessing and managing perioperative risk.
- Initiatives established over time by the Anesthesia Patient Safety Foundation, the American Society of Anesthesiologists (ASA), and others have sought to decrease the potential risks of anesthesia through systems-level improvements, standardization of care processes, human-factors engineering, and simulation-based training.

INTRODUCTION

Since the beginning of its modern history, the administration of anesthesia has been recognized as a hazardous enterprise,[1] with distinct risks to the patient and occupational risks to anesthesia providers. From the perspective of public health, understanding both the nature and the magnitude of these risks is important on multiple levels. For individual patients, receiving accurate information on the probability of specific perioperative complications is a prerequisite for informed decision making related to anesthesia and surgery. More broadly, understanding the extent to which rates of perioperative morbidity and mortality vary across patients, physicians, and hospitals provides an important opportunity for assessing and improving quality in health care.

Efforts to determine the risks of anesthesia are complicated by many potential perspectives from which such risks can be defined. The use of alternate periods of observation for morbidity and mortality—the intraoperative period alone, the first 48 hours after surgery, the duration of the hospital stay, or the first 30 days or longer

TABLE 37-1 TIME PERSPECTIVE OF ANESTHETIC MORBIDITY AND MORTALITY STUDIES

Study	Study Year	Time Perspective
Beecher and Todd	1954	All deaths on the surgical services
Dornette and Orth	1956	Deaths in the surgical unit or after failure to regain consciousness
Clifton and Hotten	1963	Any death under or attributable to anesthesia or without return of consciousness after anesthesia
Harrison	1978	Death within 24 hours
Marx et al	1973	Death within 5 days
Hovi-Viander	1980	Death within 3 days
Lunn and Mushin	1982	Death within 6 days
Tiret and Hatton	1986	Complications within 24 hours
Mangano et al	1996	Death within 2 years
Monk et al	2005	Death within 1 year

Adapted from Derrington MC, Smith G: A review of studies of anaesthetic risk, morbidity and mortality, Br J Anaesth *59:827, 1987.*

TABLE 37-2 EXAMPLES OF COMMON OUTCOME MEASURES

Outcome	Example
Mortality	
Failure-to-rescue	Mortality after a postoperative complication
Morbidity	
Major	Myocardial infarction
	Pneumonia
	Pulmonary embolism
	Renal failure or insufficiency
	Postoperative cognitive dysfunction
Minor	Nausea
	Vomiting
	Readmission
Patient satisfaction	
Quality of life	

after surgery—complicate simple conclusions about the risks faced by any individual patient undergoing anesthesia and surgery and at what point after surgery the likelihood of further adverse events has returned to baseline (Table 37-1). For example, patients undergoing ambulatory surgery have the lowest risk of death the day of surgery as opposed to 1 month later.[2] At the opposite end of the spectrum, asymptomatic release of cardiac enzymes in the perioperative period can have implications for months to years.[3-5] Divergent conclusions would also be expected from studies that consider adverse events that are solely attributable to the administration of anesthesia versus those that examine the overall rates of morbidity and mortality after surgery, which anesthesia care may modify. Studies exclusively focusing on the intraoperative period have characterized contemporary anesthesia care as a patient safety "success story" as a result of the low rates of death directly attributable to anesthesia care. As a result, anesthesia has been hailed by the Institute of Medicine as "an area in which very impressive improvements have been made" in terms of patient safety.[6]

Nonetheless, a broader perspective on perioperative outcomes presents a more complicated story. For example, in the case of a patient with established coronary artery disease who sustains a myocardial infarction after experiencing tachycardia during high-risk surgery, the cause of the patient's adverse outcome could arguably be attributed to both the patient's underlying coronary artery disease and to the absence of intraoperative heart rate control. In this situation, the decision to view the perioperative infarction primarily as a consequence of patient disease or as an event that could be prevented by anesthesia care carries vastly different implications for efforts to define and reduce the risks of anesthesia.

Finally, the diverse array of outcomes considered as hazards of anesthesia complicate the interpretation of the literature on the risks of anesthesia. Traditionally, investigators have focused on issues of death and major morbidity such as myocardial infarction, pneumonia, and renal failure. More recently, however, this view has been broadened to include economic outcomes, as well as patient-centered outcomes such as functional independence, quality of life, and satisfaction (Table 37-2). For example, unanticipated rehospitalization after ambulatory surgery or a delay in discharge as a result of postoperative nausea and vomiting are both potentially important from the perspectives of the patient's quality of life, as well as economics (also see chapter 89).

In this chapter, current theories regarding the underlying causes of adverse events in the perioperative period are reviewed, and the historical and contemporary literature regarding the nature and magnitude of risk related to both intraoperative anesthesia care and perioperative care are more broadly examined in detail. Next, historical and recent efforts to characterize the patient-, provider-, and facility-level determinants of anesthetic and perioperative risk are reviewed through statistical risk indices and are clinically based approaches to patient classification, and available literature on the determinants of risk unique to the obstetric, pediatric, and geriatric populations are discussed. Finally, future directions in research and clinical care related to anesthetic risk are discussed, with a focus on the health policy implications of changing knowledge regarding the hazards of anesthesia.

FRAMEWORK OF PERIOPERATIVE RISK

Perioperative risk is multifactorial and depends on the interaction of anesthesia-, patient-, and surgery-specific factors (Fig. 37-1). With respect to anesthesia, the selection and effects of medications, including volatile and intravenous anesthetic agents, and the skills of the practitioner are important. Similarly, the surgeon's skills and the surgical procedure itself also affect perioperative risk. Further, practitioners may influence outcomes at multiple points in the postoperative course. Although the incidence of specific local or organ-based complications, such as perioperative myocardial infarction or central line–related bloodstream infection, may be modified by anesthetic or surgical care, variations in the adequacy of

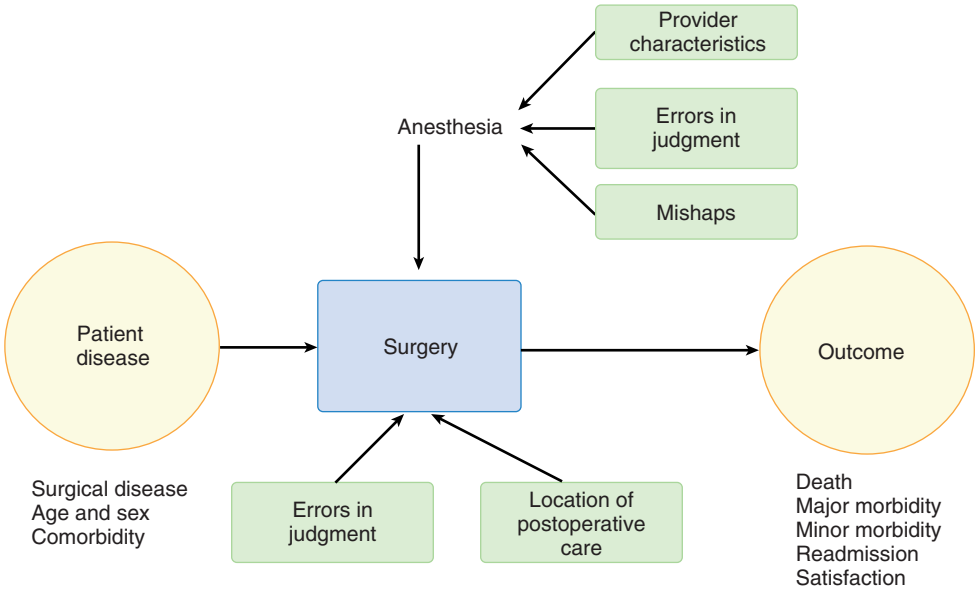


Figure 37-1. Representation of the influences of various components on poor perioperative outcomes. Surgical, anesthetic, and patient characteristics all contribute to outcome. Anesthesia-related contributions can include issues of judgment and mishaps, as well as characteristics of the provider. The surgical procedure itself affects outcome, as does the location of intraoperative and postoperative care.

care delivered to patients who have already experienced a complication (i.e., failure to rescue) may largely explain hospital-to-hospital differences in surgical outcomes.[7-9] Notably, although past investigators have pointed to volume-outcome relationships as potentially mitigating these hospital-to-hospital outcome differences,[10,11] more recent data have suggested that local quality-improvement efforts, rather than large-scale efforts, at regionalization of care for elective surgeries hold the greatest potential to yield meaningful improvements in operative outcomes.[12]

The potential for anesthetic care to influence the overall hazard of surgery at multiple time points highlights both the complexity of measuring the risks of anesthesia and surgery and the range of potential opportunities that may exist to reduce such risks. Given these challenges and opportunities, the goal of the next section is to summarize the current state of knowledge in this area, including the relative strengths and weaknesses of randomized and nonrandomized (i.e., observational) study designs used in efforts to understand patterns of outcomes after surgery and anesthesia.

ISSUES RELATED TO STUDY DESIGN

TYPES OF STUDIES

To interpret the literature related to anesthetic and perioperative risk, the strengths and limitations of various study designs must be understood. Prospective cohort studies involve the identification of a group of subjects who are monitored over time for the occurrence of an outcome of interest. The goal is to identify patients in whom the outcome develops. For studies of perioperative mortality, individual cases can be reviewed to determine the cause of mortality. Alternatively, data on all patients in the cohort study can be obtained, and discrete factors associated with the development of morbidity or mortality can be determined, often using multivariate regression techniques. An example of a prospective cohort study to identify factors associated with perioperative cardiac morbidity and mortality is that of Goldman and colleagues,[13] which led to development of the Cardiac Risk Index.

Although prospective cohort studies have important value in identifying risk factors for perioperative outcomes, they also have significant limitations. The range of patients enrolled in the cohort study, both in terms of baseline characteristics and the care they receive, may positively or negatively impact the generalizability of the study findings more broadly to the population. Additional biases may be introduced by loss of patients to follow-up for assessment of outcomes. Finally, failure to anticipate the potential impact of some variables and collect data on them may limit the insights gained from a cohort study. For example, if a cohort study focusing on predictors of postoperative myocardial infarction failed to collect data on preoperative angina, the study's findings could be limited by the investigators' inability to examine this factor as a potential predictor of postoperative outcomes. Similarly, the inability to collect data on all potential confounders of the relationship between a putative risk factor and a given outcome limits the extent to which cohort studies can support causal inferences.

Randomized clinical trials offer stronger evidence of causality than do observational cohort studies. In a randomized trial, subjects are assigned by random allocation to one of two or more treatments (potentially including a placebo) and are observed for the development of a particular outcome. In the context of perioperative risk, randomized trials may be used to determine the efficacy of an intervention or anesthetic regimen intended to improve postoperative outcomes. For example, hypothermia in the perioperative period has been associated with an increased incidence of perioperative ischemia, a surrogate marker for morbidity.[14] In a randomized clinical trial, the use of forced-air warming to maintain normothermia was associated with a significantly less frequent incidence of perioperative morbid cardiac events.[15] Randomized clinical trials often build on hypotheses generated in cohort studies regarding the determinants of outcomes by testing

interventions directed at a specific risk factor associated with adverse outcomes.

Randomized clinical trials derive their strength from their high degree of internal validity; the randomization scheme and the use of placebo (or accepted alternative treatments) provide strong evidence that the results are related to the intervention. Importantly, these trials may have a lower degree of external validity because the intervention tested in a particular trial may not work as well or in the same manner as when it is diffused into a more heterogeneous population. Further, as a result of sample size limitations, clinical trials may often be unable to detect subtle differences in outcomes among study groups or differences in rare events.

Retrospective studies involve the identification of patients who have sustained an outcome and definition of risk factors associated with the outcome. An example of a retrospective design is a case-control study. Case-control studies identify patients with the outcome of interest. Frequently, these patients are included as part of a prospective cohort study. The prevalence of a risk factor in patients with the outcome (i.e., cases) is compared with the prevalence of the risk factor in matched control participants to maximize the efficiency and power of the results. The ratio of cases to control participants can be varied to yield greater power with an increasing number of controls. An alternative retrospective design involves the systematic review of identifiable adverse events for patterns of error. For example, Cheney and colleagues[16] developed the American Society of Anesthesiologists' Closed Claims Project (ASA-CCP) to assess the risks associated with anesthesia care. By obtaining the records of major events that led to legal litigation, they were able to identify factors that contributed to bad outcomes. With this methodology, selected morbidities that led to litigation can be identified. The limitation of this methodology is that the actual rates of complications in the overall population are not known; only the number of closed legal claims is identified. Cases that do not result in litigation are not included in the database.

PROBLEMS INHERENT IN STUDYING ANESTHESIA-RELATED RISK

Studying anesthesia-related risk involves a range of methodologic challenges. On the most basic level, multiple definitions exist for key outcomes, such as perioperative mortality. In particular, the timeframe in which a death can be attributed to the surgery or the delivery of anesthesia or both varies. Notably, many events related to surgery may occur after discharge when monitoring of outcomes becomes more challenging. For this reason, the National Surgical Quality Improvement Program (NSQIP), a large, prospectively collected United States registry of surgical care and outcomes, requires 30-day follow-up on all patients to allow for consistent assessments of outcomes for all patients.

A second major challenge in any study of postoperative outcomes is the low observed rate of many key outcomes in the population of interest. Although some recent writers have called into question the safety of contemporary anesthesia care,[17] anesthesia-related death remains relatively uncommon in absolute terms. For example, the rate of anesthesia-related mortality described in the Confidential Enquiry into Perioperative Deaths (CEPOD) of 1987 was 1 in 185,000 patients as opposed to the 1 in 2680 cases reported by Beecher and Todd approximately 30 years earlier.[18,19] As a result, efforts to identify the range of factors that now contribute to anesthetic mortality are likely to require large patient cohort studies available either from administrative sources or collected over several years from multiple institutions. Several attempts have been made to establish large epidemiologic databases to address this challenge. One example of such an approach has been the work of Dennis Mangano and the Multicenter Study of Perioperative Ischemia Research Group with regard to cardiac surgery. This group used its database to evaluate issues such as the rate and importance of atrial fibrillation after cardiac surgery and the association of perioperative use of aspirin with cardiac surgical outcomes.[20,21] Other approaches include the development of cardiac surgery databases by the Society of Thoracic Surgeons, the U.S. Veterans Administration NSQIP, and the Northern New England Cardiovascular Disease Study Group.[22-25] These databases are used to define risk factors for poor outcome, to compare local with national complication rates, and as educational tools. In the United States, the Multicenter Perioperative Outcomes Group has undertaken such an enterprise by pooling electronically collected intraoperative and postoperative data.[26] Although these databases may provide extremely important information to improve care, the ability to generalize results to centers that do not have sufficient infrastructure to participate in such projects (e.g., smaller hospitals) is unknown.

Variations in care and outcomes across institutions may further complicate efforts to develop meaningful estimates of perioperative risk for use in clinical decision making by individual patients. Beyond the impact of patient illness, type of surgery, or anesthetic approach, hospital-level differences in postoperative care may have a profound impact on outcome. For example, the incidence of pulmonary embolism may be related to nursing care and the frequency of patient ambulation after surgery[27]; similarly, the presence of an intensivist who makes daily rounds and higher nurse staffing ratios may also affect outcome.[28]

Finally, issues of risk adjustment complicate efforts to determine changes in anesthesia risk over time. Common endpoints, such as mortality, are influenced by patient factors as well as by anesthesia and surgical care; as such, temporal trends in patient acuity may influence the apparent adverse outcomes associated with anesthesia and surgery in a given period. With appropriate risk adjustment, changes in mortality rates over short periods may provide some indication of changes in the quality of anesthesia or surgical care. When viewed over longer periods, however, it may be more difficult to reach firm conclusions regarding temporal changes in the safety of anesthesia or surgery based on differences in mortality rates over time. For example, if improvements in anesthetic technology have allowed for older and sicker patients to undergo surgery, then the safety of anesthesia may have improved without any apparent change in mortality rates because a sicker

patient population is now offered surgery that, in the past, would have been avoided. Similarly, the rapid adoption of new but relatively high-risk procedures, such as coronary artery bypass grafting or liver transplantation, complicates simple comparisons of anesthesia-related complications over time.

STUDIES OF ANESTHESIA-RELATED MORTALITY BEFORE 1980

Efforts to understand the specific risks imposed by anesthesia care, above and beyond the surgical procedure itself, have represented an important dimension of research in anesthesia since the early 20th century. Although more recent trends in anesthesia research have emphasized a broad view of perioperative outcomes not strictly limited to events primarily caused by anesthesia care,[30] the history of efforts to determine the safety of anesthesia management, per se, represents an important chapter in the development of modern perioperative medicine. This history also serves as important background for understanding current research and practice.

Research performed before 1980 demonstrated wide variation in reported rates of anesthesia-related mortality (Table 37-3). Beecher and Todd's 1954 report of anesthesia-related deaths at 10 institutions represents the earliest published major analysis of anesthesia outcomes.[18] Their study included 599,548 anesthesia procedures and found a rate of all-cause mortality of 1 per 75 cases (1.3%). In 1 out of every 2680 procedures, anesthesia represented the primary cause of mortality, and it was a primary or contributory cause of mortality in 1 of 1560 procedures. Surgical error in diagnosis, judgment, or technique was the primary cause of death in 1 in 420 cases, and patient disease was the primary cause in 1 in 95 cases.

Beecher and Todd's findings were confirmed by the work of Dornette and Orth,[31] who reported on deaths occurring in the surgical department at their institution over 12 years from 1943 through 1954. The rate of mortality totally attributable to anesthesia was 1 in 2427 cases, and the rate of mortality totally or partially attributable to anesthesia was 1 in 1343 cases. In contrast, Dripps and colleagues, working at the University of Pennsylvania, observed a higher rate of anesthetic mortality over a 10-year period from 1947 through 1957.[32] Whereas Beecher and Todd reported 1 incident of anesthesia-attributable mortality for every 2680 cases observed, Dripps and colleagues found the anesthesia-attributable mortality rate to be 1 in 852. Although definitive conclusions were not offered concerning the differences between the Dripps and Beecher studies, they may have been partially explained by Dripps' observation of 30-day, rather than intraoperative or 48-hour mortality, or differences in patient severity across studies.

Multiple additional studies on anesthetic risk appeared between 1960 and 1980.[33] In the United States, these included the Baltimore Anesthesia Study Committee,[34] which reviewed 1024 deaths occurring on the day of or the day after a surgical procedure; the study of Schapira and co-authors[35] who reported on mortality occurring within 24 hours after surgery between the years 1952 and 1956 at Montefiore Hospital in New York; and the study of Marx and colleagues[36] who evaluated the incidence of death within 7 days after surgery in 34,145 consecutive patients at the Bronx Municipal Hospital Center between 1965 and 1969. Overall, the rate of anesthesia-related mortality in these studies varied widely, ranging from 1 in 1232 cases in the Schapira study to 1 in 7692 cases in the Baltimore Anesthesia Study Committee report.

Internationally, Clifton and Hotten identified a total of 162 deaths associated with anesthesia in 205,640 surgical procedures performed at the Royal Prince Alfred Hospital in Sydney, Australia, between 1952 and 1962.[37] In 1964, Dinnick published a report, sponsored by the Association of Anaesthetists in London, on 600 deaths associated with anesthesia,[38] followed by a report on anesthesia-related mortality from Bodlander,[39] who observed a progressive decrease in the contribution of anesthesia to operative mortality at the Royal Prince Alfred Hospital for the years 1963 to 1972. Finally, Harrison[40] evaluated mortality associated with 240,483 anesthesia procedures performed between 1967 and

TABLE 37-3 **ESTIMATES OF THE INCIDENCE OF MORTALITY RELATED TO ANESTHESIA BEFORE 1980**

Study	Year	Number of Anesthetics	Primary Cause	Primary and Associated Causes
Beecher and Todd	1954	599,548	1:2680	1:1560
Dornette and Orth	1956	63,105	1:2427	1:1343
Schapira et al	1960	22,177	1:1232	1:821
Phillips et al	1960	—	1:7692	1:2500
Dripps et al	1961	33,224	1:852	1:415
Clifton and Hotton	1963	205,640	1:6048	1:3955
Memery	1965	114,866	1:3145	1:1082
Gebbie	1966	129,336	—	1:6158
Minuck	1967	121,786	1:6766	1:3291
Marx et al	1973	34,145	—	1:1265
Bodlander	1975	211,130	1:14,075	1:1703
Harrison	1978	240,483	—	1:4537
Hovi-Viander	1980	338,934	1:5059	1:1412

From Ross AF, Tinker JH: Anesthesia risk. In Miller RD, editor: Anesthesia, *ed 3. New York, 1990, Churchill Livingstone, p 722.*

1976 at Groote Schuur Hospital in Cape Town, South Africa. Data were prospectively collected, beginning in 1956. Anesthesia was the cause of death or a major contributory factor in 0.22 cases per 1000 procedures, as opposed to 0.33 per 1000 procedures in the previous 10 years.

In summary, studies of anesthetic risk published before 1980 varied widely in the definitions used for anesthesia-related mortality and in the mortality rates they reported. Nonetheless, these studies did offer several important insights for anesthesia care. First, they suggested that death related solely to anesthesia was a relatively uncommon event; moreover, an overall trend toward lower rates of anesthesia-related mortality across studies over time suggested potential improvements in anesthesia safety.

STUDIES OF ANESTHESIA-RELATED MORTALITY SINCE 1980

Whereas studies conducted before 1980 typically focused on one institution or a small number of institutions, studies since then have frequently been performed on a regional or national basis with a particular emphasis on documenting changes over time in anesthesia-related mortality. For example, Holland[41] reported deaths occurring within 24 hours after anesthesia in New South Wales, Australia. A committee of six anesthesiologists, three surgeons, an obstetrician, a general practitioner, and a medical administrator was established in 1960 and reviewed all such cases except those that occurred during a 3-year period between 1980 and 1983. Four categories were established to define the relationship of anesthesia to operative morbidity and mortality (Table 37-4). Between 1960 and 1985, information was available on 92% to 96% of all cases. The incidence of anesthesia-attributable deaths decreased from 1 in 5500 procedures performed in 1960 to 1 in 10,250 in 1970 and then to 1 in 26,000 in 1984. Based on these estimates, the investigators asserted that for all patients receiving surgery, it was more than five times safer to undergo anesthesia in 1984 than it was in 1960.[42]

Under the direction of the French Ministry of Health, Tiret and colleagues[43] carried out a prospective survey of complications associated with anesthesia in France between 1978 and 1982 from a representative sample of 198,103 anesthesia procedures chosen at random from hospitals throughout the country. The sample included a survey of 460 public and private hospitals. The investigators evaluated the occurrence of death or coma within 24 hours after surgery. In the group studied, 268 patients had major complications, 67 patients died, and 16 patients suffered persistent coma. Death was solely related to anesthesia in 1 in 13,207 procedures and partially related in 1 in 3810 (Table 37-5). The French survey confirmed previous findings that major complications occur more frequently in older patients, those undergoing emergency surgical procedures, and those with more extensive comorbid conditions as measured by ASA physical status classification.

A key finding of the French survey was that postanesthesia respiratory depression was the leading principal cause among cases of death and coma that were solely attributable to anesthesia. Moreover, almost all the patients who had had respiratory depression leading to a major complication had received narcotics, as well as neuromuscular blocking drugs, but they had not received anticholinesterase medications for reversal of the agents.

Despite these observations, the low rates of anesthesia-attributable mortality documented in the French study offered compelling evidence of improvements in anesthesia safety. Such findings were reinforced by the work of Tikkanen and Hovi-Viander,[44] who studied deaths associated with anesthesia and surgery in Finland and compared the results in 1986 with those collected in 1975. Mortality related to anesthesia decreased during the 9-year period; the incidence of anesthesia-related mortality was 0.15 per 10,000 procedures in 1986.

The next major step forward in efforts to understand the risks of anesthesia came through the pioneering work of Lunn[45] in the United Kingdom. Reporting on 197 fatalities occurring within 6 days after anesthesia during 1981, Lunn found 43% of the deaths to have been unrelated to anesthesia, 41% to be partly attributable to anesthesia, and 16% to be totally attributable to anesthesia. Of the

TABLE 37-4 EDWARDS CLASSIFICATION OF THE RELATIONSHIP OF ANESTHESIA TO OPERATIVE MORBIDITY AND MORTALITY

Category	Definition
I	Cases in which it is reasonably certain that the event or death was caused by the anesthetic agent or technique of administration or in other ways directly within the anesthetist's province
II	Similar to type I cases but ones in which some element of doubt exists concerning whether the agent or technique was entirely responsible for the result
III	Cases in which the patient's adverse event or death was caused by the anesthetic and the surgical technique
IV	Cases in which the events were entirely referable to the surgical technique

From Holland R: Anaesthetic mortality in New South Wales, Br J Anaesth *59:834, 1987.*

TABLE 37-5 INCIDENCE OF COMPLICATIONS PARTIALLY OR TOTALLY RELATED TO ANESTHESIA

Complications	Partially Related	Totally Related	Total*
All complications	1:1887	1:1215	1:739
Death	1:3810	1:13,207	1:1957
Death and coma	1:3415	1:7924	1:2387

From Tiret L, Desmonts JM, Hatton F, et al: Complications associated with anaesthesia—a prospective survey in France, Can Anaesth Soc J *33:336-344, 1986.*

*Total number of anesthetics: 198,103.

32 cases for which death was totally attributable to anesthesia, most were caused by faulty anesthesia technique or postoperative respiratory failure.

One important result of Lunn's work was the development of the United Kingdom CEPOD, which assessed almost 1 million anesthetics during a 1-year period in 1987 in three large regions of the United Kingdom. Unique to this study was the establishment of "crown privilege" by the government to protect data submitted to the enquiry from further subpoena.[19]

Beyond confirming earlier work, CEPOD's findings suggested that anesthesia care may have been far safer than had been found in prior studies. Examining deaths within 30 days of surgery, CEPOD investigators observed 4034 deaths in an estimated 485,850 surgeries for a crude mortality rate of 0.7% to 0.8%. CEPOD reviewers concluded that surgery contributed totally or partially in 30% of all cases. Progression of the present disease contributed to death in 67.5% of the cases, and progression of an intercurrent disease was relevant in 44.3%. Anesthesia was considered the sole cause of death in only three individuals, for a rate of 1 in 185,000 cases, and anesthesia was contributory in 410 deaths, for a rate of 7 in 10,000 cases (Table 37-6).[19] The five most common causes of death in the CEPOD cohort study are shown in Table 37-7. Notably, of the 410 perioperative deaths, gastric aspiration was identified in 9 cases and cardiac arrest in 18 cases. Further, CEPOD identified potential health-system factors that conceivably contributed to the risk of surgery and anesthesia. Among patients with femoral neck fracture, for example, CEPOD researchers observed that the mortality rate was inversely related to the seniority of the surgeon and to preoperative preparation. The surgeon was a consultant in only 19% of the orthopedic cases, as compared with 47% overall. Ultimately, CEPOD researchers concluded that avoidable factors were present in approximately 20% of the perioperative deaths. Contributing factors for anesthesiologists and surgeons tended to be failure to act appropriately with existing knowledge (rather than a lack of knowledge), equipment malfunction, fatigue, and inadequate supervision of trainees, particularly in off-hours shifts (Table 37-8).

Large national studies performed since the 1987 CEPOD report vary in the extent to which their findings agree with those of the CEPOD investigators. Pedersen and colleagues[46] performed a series of studies in the late 1980s in Denmark to examine anesthesia-related factors contributing to serious morbidity or mortality. In a prospective study of 7306 anesthesia procedures, they found complications attributable to anesthesia in 43 patients (1 in 170) and 3 deaths (1 in 2500), an incidence far higher than that documented by the CEPOD investigators. Complications in the 43 patients, in order of incidence, included cardiovascular collapse in 16 (37%), severe postoperative headache after regional anesthesia in 9 (21%), and awareness under anesthesia in 8 (19%).

In the United States, Li and colleagues[47] conducted a population-level study to estimate epidemiologic patterns of anesthesia-related deaths, using International Classification of Diseases (ICD) codes listed in the United States multiple-cause-of-death data files for the years 1999 through 2005. Although the interpretation of Li's study is complicated by questions surrounding the sensitivity of ICD codes for anesthesia-related mortality,[48] their findings are in accord with those of the CEPOD report in presenting anesthesia-related mortality to be an extremely rare cause of death at the population level. In particular, the authors found anesthesia to be the underlying cause of death in 34 patients each year in the United States and a contributing factor in another 281 deaths annually, resulting in a 97% decrease in anesthesia-related death rates since the 1940s.

More recent studies conducted on the local and national level have sought to emphasize room for improvement in anesthesia-related mortality. Lagasse[17] reviewed perioperative deaths (i.e., deaths occurring within 2 days after surgery) at a suburban university hospital network between 1992 and 1994 and at an urban university hospital network between 1995 and 1999. A total of 347 deaths occurred in 184,472 cases. Anesthesia-related mortality (i.e., death to which error by an anesthesia practitioner

TABLE 37-6 DEATH TOTALLY ATTRIBUTABLE TO EACH COMPONENT OF RISK IN THE CONFIDENTIAL ENQUIRY INTO PERIOPERATIVE DEATHS

Component	Mortality Rate Contribution
Patient	1:870
Operation	1:2860
Anesthetic	1:185,056

Adapted from Buck N, Devlin HB, Lunn JL: Report of a confidential enquiry into perioperative deaths, Nuffield Provincial Hospitals Trust, *London, 1987, The King's Fund Publishing House.*

TABLE 37-7 MOST COMMON CLINICAL CAUSES OF DEATH IN THE CONFIDENTIAL ENQUIRY INTO PERIOPERATIVE DEATHS

Cause of Death	Percent of Total
Bronchopneumonia	13.5
Congestive heart failure	10.8
Myocardial infarction	8.4
Pulmonary embolism	7.8
Respiratory failure	6.5

Adapted from Buck N, Devlin HB, Lunn JL: Report of a confidential enquiry into perioperative deaths, Nuffield Provincial Hospitals Trust. *London, 1987, The King's Fund Publishing House.*

TABLE 37-8 GRADE OF PHYSICIAN ACCORDING TO TIME OF SURGERY IN THE CONFIDENTIAL ENQUIRY INTO PERIOPERATIVE DEATHS

	Anesthetist		Surgeon	
Grade	Day*	Night†	Day*	Night†
Consultant	50	25	45	34
Others	50	75	55	66

Adapted from Buck N, Devlin HB, Lunn JL: Report of a confidential enquiry into perioperative deaths, Nuffield Provincial Hospitals Trust. *London, 1987, The King's Fund Publishing House.*

**Represents Monday through Friday, 9 AM to 7 PM.*

†Represents Monday through Friday, 7 PM to 9 AM, and Saturday and Sunday.

contributed) occurred in 1 in every 12,641 procedures in the suburban setting and in 1 in 13,322 procedures in the urban setting. Mortality increased with increasing ASA physical status (Fig. 37-2). In reviewing data over the previous decade, Lagasse estimated that anesthesia-related mortality had remained stable at approximately 1 death per 13,000 procedures.

Recent European studies, including those from the successor to CEPOD, Britain's National Confidential Enquiry into Patient Outcomes and Death (NCEPOD), have taken a broader focus beyond anesthesia-related events to examine perioperative outcomes more generally, particularly among high-risk patients who Lagasse and others previously observed to account for the majority of postoperative deaths. In a 2011 report, NCEPOD investigators prospectively collected data on all patients undergoing inpatient surgery, excluding obstetric, cardiac, transplant, or neurosurgery cases, in United Kingdom National Health Service facilities between March 1 and March 7, 2010.[49] In addition to prospectively collected patient-level data on clinical care and outcomes, which were available for 13,513 surgical patients, the authors conducted a detailed institution-level survey of resources and practices. Although the authors observed an overall 30-day mortality rate of 1.6%, a subset of high-risk patients—approximately 20% of the full cohort—experienced a disproportionate share of adverse outcomes, accounting for 79% of all perioperative deaths. Notably, the authors identified important gaps in the perioperative management of these patients. A minority of the high-risk patients were monitored using an arterial line, a central line, or cardiac output monitoring; still more concerning was their observation that 48% of all high-risk patients who died were never admitted to a critical care unit for postoperative management.

Similar findings were obtained in another study of surgical outcomes conducted across 28 European countries between April 4 and April 11, 2011.[50] Observing

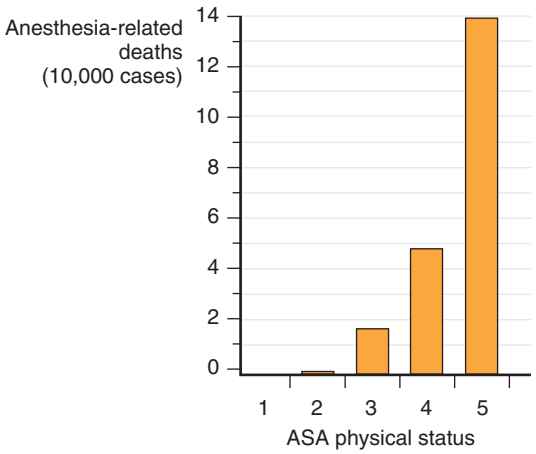


Figure 37-2. Relationship between the American Society of Anesthesiologists (ASA) physical status classification and perioperative mortality (within 2 days of surgery) related to anesthesia provided in urban and suburban institutions. *(Adapted from Lagasse RS: Anesthesia safety: model or myth? A review of the published literature and analysis of current original data,* Anesthesiology *97:1609, 2002.)*

perioperative care and outcomes for 46,539 adults undergoing inpatient noncardiac surgery, the authors noted an overall in-hospital mortality rate of 4%. Further, the investigators noted severity-adjusted operative mortality rates to differ significantly by country; for example, relative to the United Kingdom, the risk of death after surgery was highest in Poland (odds ratio [OR] 6.92, P = 0.0004) and lowest in Finland (OR 0.44, P = 0.06). Despite these national differences, the authors observed patterns of critical care use consistent with the 2011 NCEPOD report, noting that only 5% of all patients in the sample underwent a planned admission to critical care; still more concerning, of the patients who died, most (73%) were not admitted to critical care at any point. Such patterns, which the authors describe as a "systematic failure in the process of allocation of critical care resources" in Europe, highlight the potential importance of "rescue"—the prevention of mortality among patients who experience postoperative complications[8]—in determining the outcomes of surgical care. Further, to the extent that critical care use among patients who die after surgery is higher in the United States than in the United Kingdom,[51] such differences may offer insight into potential reasons for earlier observations of lower risk-adjusted postoperative mortality among American versus British surgical patients.[52]

In summary, research between 1980 and the present on anesthesia-related mortality offers a complex and still incomplete picture regarding the risks of anesthesia. Taken from the perspective of the 1987 CEPOD report or the findings of Li and colleagues, modern operative anesthesia could be characterized as an exceedingly safe enterprise with bad outcomes occurring as truly rare events. Nonetheless, subsequent research disputed the quantitative findings of CEPOD's 1987 study, making the argument that anesthesia-related mortality was common enough to represent an ongoing public health concern. Finally, more recent work has sought to go beyond efforts to quantify the contribution of anesthesia per se to overall operative risk to explore how anesthesia providers might be able to improve outcomes among high-risk patients; in essence asking not "how safe is anesthesia?" but instead "how can anesthesia providers help make surgery safer?" Ultimately, these studies' differing messages emphasize not only the dynamic nature of anesthesia risk over time, but they also highlight important changes in how anesthetic risk has been defined across different periods and how alternate approaches to evaluating, describing, and mitigating such risk may be more or less relevant at a given moment in time.

ANALYSIS OF INTRAOPERATIVE CARDIAC ARREST

In an alternative approach to evaluating perioperative mortality specific to anesthesia, several studies have evaluated intraoperative fatal and nonfatal cardiac arrest (Table 37-9). In contrast to efforts to estimate the mortality attributable to anesthesia per se, studies of intraoperative cardiac arrest may offer a broader picture of the potential hazards of anesthesia by examining an adverse outcome that is far more common than mortality yet remains highly consequential for long-term outcomes.

TABLE 37-9 **SELECTED CARDIAC ARREST SERIES WHEN THE DENOMINATOR IS GREATER THAN 40,000 ANESTHETICS**

Study	Years	Total Number of Anesthetics	Rate of Arrest
Hanks and Papper	1947-1950	49,728	1:2162
Ehrenhaft et al	1942-1951	71,000	1:2840
Bonica	1945-1952	90,000	1:6000
Blades	1948-1952	42,636	1:21,318
Hewlett et al	1950-1954	56,033	1:2061
Briggs et al	1945-1954	103,777	1:1038
Keenan and Boyan	1969-1978	107,257	1:6704 (P)
Cohen et al	1975-1983	112,721	1:1427 (C)
Tiret et al	1978-1982	198,103	1:3358 (C)
Tiret et al	1978-1982	198,103	1:11,653 (P)
Keenan and Boyan	1979-1988*	134,677	1:9620 (P)
Newland et al	1989-1999	72,959	1:14,493 (P)
Newland et al	1989-1999	72,959	1:7299 (C)
Olsson et al	1967-1984	250,543	1:33,000
Biboulet et al	1989-1995	101,769	1:7828
Kawashima et al	1994-1998	2,363,038	1:10,000 (P)
Sprung et al	1990-2000	518,294	1:20,000 (P)
Braz et al	1996-2005	53,718	1.9:10,000 (P)

Adapted from Brown DL: Anesthesia risk: a historical perspective. In Brown DL, editor: Risk and outcome in anesthesia*, ed 2. Philadelphia, 1992, Lippincott, p 14.*

C, Contributory cause; P, primary cause.

*Since pulse oximetry was introduced in 1984, no preventable respiratory cardiac arrests have occurred.

These studies offer a range of perspectives on the incidence of intraoperative cardiac arrest and the causes of such events. For example, Keenan and Boyan[53] studied the incidence and causes of cardiac arrest related to anesthesia at the Medical College of Virginia between 1969 and 1983. A total of 27 cardiac arrests occurred during 163,240 procedures, for an incidence of 1.7 per 10,000 cases. Fourteen patients died, for an incidence of 0.9 per 10,000 cases. Pediatric patients had a threefold higher risk of arrest than did adults, and emergency cases had a sixfold greater risk. Importantly, specific errors in anesthesia management could be identified in 75% of the cases; most common among these were inadequate ventilation and overdose of an inhaled anesthetic. Notably, the investigators identified progressive bradycardia preceding all but 1 arrest, suggesting that early identification and treatment may prevent complications.

Similar findings were reported by Olsson and Hallen[54] who studied the incidence of intraoperative cardiac arrest at the Karolinska Hospital in Stockholm, Sweden, from 1967 to 1984. A total of 170 arrests occurred in 250,543 anesthesia procedures performed. Sixty patients died, for a mortality rate of 2.4 per 10,000 procedures. After eliminating cases of inevitable death (e.g., rupture of a cerebral aneurysm, trauma), the rate of mortality caused by anesthesia was 0.3 per 10,000 procedures. The most common causes of anesthesia-related cardiac arrest were inadequate ventilation (27 patients), asystole after succinylcholine (23 patients), and postinduction hypotension (14 patients). The incidence of cardiac arrest was highest in the patients with significant comorbid disease, as assessed by the ASA physical status classification. Also of note is the finding that the incidence of cardiac arrest decreased over the study period.

Biboulet and colleagues[55] studied fatal and nonfatal cardiac arrests encountered during anesthesia and during the first 12 postoperative hours in the postanesthesia care unit (PACU) or intensive care unit (ICU) in a single hospital in France. Eleven cardiac arrests related to anesthesia were identified in 101,769 anesthesia procedures (1.1 per 10,000). The mortality rate related to anesthesia was 0.6 per 10,000 cases. The major causes of death were anesthetic overdose, hypovolemia, and hypoxemia; 10 of the 11 cases had at least one avoidable error.

Newland and associates[56] reported anesthesia-related cardiac arrests during 72,959 procedures between 1989 and 1999 in a teaching hospital in the United States. They judged that 15 of the 144 cardiac arrests were related to anesthesia (0.69 per 10,000 procedures); in an additional 10 cases, anesthesia was considered contributory, for a total rate of 1.37 per 10,000 procedures (95% confidence interval [CI], 0.52 to 2.22). The risk of death from perioperative cardiac arrest that was attributable to anesthesia was 0.55 per 10,000 procedures. Most of the arrests were related to medication administration, airway management, or technical problems of central venous access.

Kawashima and colleagues sent confidential questionnaires to all Japan Society of Anesthesiologists Certified Training Hospitals every year from 1994 through 1998.[57] A total of 2,363,038 cases were documented over a 5-year period. The average yearly incidence of cardiac arrest during surgery that was totally attributable to anesthesia was 1 per 10,000 cases (95% CI, 0.88 to 1.12). The average mortality per year in the surgical unit or within 7 postoperative days that was totally attributable to anesthesia was 0.21 (0.15 to 0.27) per 10,000 cases. The two principal causes of cardiac arrest solely attributable to anesthesia were drug overdose or selection error (15.3%) and serious arrhythmia (13.9%). Preventable human errors caused 53.2% of cardiac arrests and 22.2% of deaths in the surgical unit that were totally attributable to anesthesia. The outcomes of cardiac arrests totally attributable to anesthesia are shown in Table 37-10.

TABLE 37-10 CARDIAC ARREST TOTALLY ATTRIBUTABLE TO ANESTHESIA DURING ANESTHESIA AND SURGERY AND ITS OUTCOMES, 1994-1998

		Outcomes				
	Number of Arrests	Uneventful Recovery	Death in Surgical Unit	Death Within 7 Days	Vegetative State	Others
5-year total	237	185	13	15	9	15
Incidence per 10,000	1.00	0.78	0.05	0.08	0.04	0.06
95% CI	0.88- ≈1.12	0.66- ≈0.89	0.2- ≈0.08	0.02- ≈0.13	0.03- ≈0.05	0.02- ≈0.10
Ratio	100%	78.1%	5.5%	6.3%	3.8%	6.3%
95% CI		55.3- ≈100	1.7- ≈9.3	3.0- ≈9.7	2.5- ≈5.3	1.7- ≈11.0

Reproduced with permission from Kawashima Y, Takahashi S, Suzuki M, et al: Anesthesia-related mortality and morbidity over a 5-year period in 2,363,038 patients in Japan, Acta Anaesthesiol Scand *47:809-817, 2003.*
N = 2,363,038.
CI, Confidence interval.

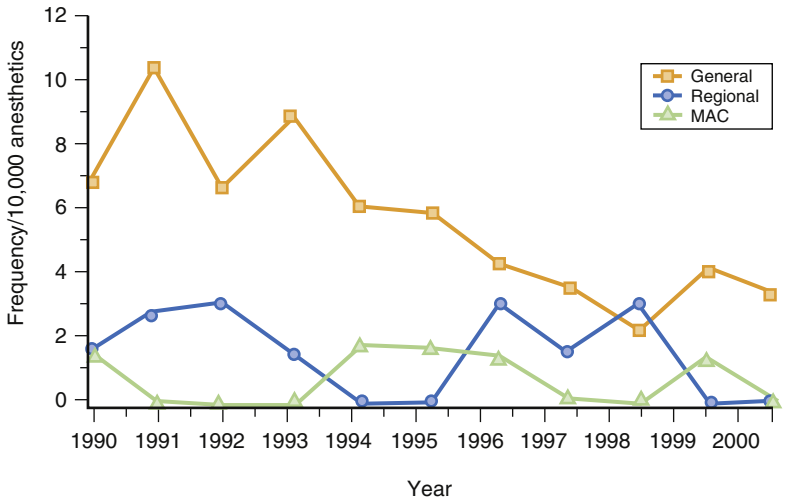


Figure 37-3. Frequency of cardiac arrest by calendar year and type of anesthesia. *MAC,* Monitored anesthesia care. *(From Sprung J, Warner ME, Contreras MG, et al: Predictors of survival following cardiac arrest in patients undergoing noncardiac surgery: a study of 518,294 patients at a tertiary referral center,* Anesthesiology *99:259-269, 2003.)*

Between 1990 and 2000, Sprung and colleagues studied patients who experienced cardiac arrest in the surgical unit, during transport to the PACU or ICU, or in the PACU after noncardiac surgery.[58] Cardiac arrest occurred in 223 of 518,294 anesthesia procedures (4.3 per 10,000) during the study period. The frequency of arrest in patients receiving general anesthesia decreased over time (7.8 per 10,000 during 1990 to 1992; 3.2 per 10,000 during 1998 to 2000). The frequency of arrest during regional anesthesia (1.5 per 10,000) and monitored anesthesia care (0.7 per 10,000) remained the same during the study period (Fig. 37-3). The hospital survival rate after cardiac arrest was 34.5%. Twenty-four patients (0.5 per 10,000) had cardiac arrest primarily related to anesthesia, 19 of whom (79.2%) survived to hospital discharge. The in-hospital mortality attributable to anesthetic-related cardiac arrest was 0.1 per 10,000 anesthetics.

Braz and co-workers[59] studied perioperative cardiac arrest that occurred during induction of anesthesia for 53,718 anesthetics between 1996 and 2005 in a Brazilian teaching hospital.[58] In this study, 186 cardiac arrests (34.6 per 10,000) and 118 deaths (21.97 per 10,000) were reported. Major risk factors for cardiac arrest were neonates, children younger than 1 year of age, and older adults; male patients with ASA III or poorer physical status; emergency surgery; and general anesthesia. There were 18 anesthesia-related cardiac arrests (3.35 per 10,000), 10 totally attributed to anesthesia (1.86 per 10,000) and 8 partially related to anesthesia (1.49 per 10,000). There were 6 anesthesia-related deaths (1.12 per 10,000), 3 totally attributable and 3 partially related to anesthesia (0.56 per 10,000 in both cases). The main causes of anesthesia-related cardiac arrest were respiratory events (55.5%) and medication-related events (44.5%).

More recently, Kheterpal and colleagues at the University of Michigan examined predictors of cardiac adverse events—including cardiac arrest, myocardial infarction, and clinically significant arrhythmia—among 7700 patients undergoing noncardiac surgery. Eighty-three patients (1.1%) experienced an adverse event. The authors identified nine independent predictors of an adverse event: (1) age 68 years or older, (2) body mass index of 30 or greater, (3) emergency surgery, (4) previous coronary intervention or cardiac surgery, (5) active congestive heart failure, (6) cerebrovascular disease, (7) hypertension, (8) operative time of 3.8 hours or longer, and (9) the intraoperative administration of one or more units of packed red blood cells.[60]

In summary, perioperative cardiac arrest is a relatively rare event whose incidence may be decreasing over time. Further, research in this area has highlighted the role of both patient factors and intraoperative care

as contributing to the risk of intraoperative and postoperative cardiac arrest and emphasized the management of ventilation and the selection and dosing of anesthetic medications as key areas of focus for the prevention of such events.

PERIOPERATIVE MORTALITY AND MORBIDITY IN OUTPATIENT SURGERY

At least in the United States, an estimated 60% of all surgical procedures are performed on an outpatient basis, and this percentage is increasing annually. The type and extent of surgical procedures performed in an outpatient setting are constantly changing, and more complicated procedures associated with greater perioperative risk are increasingly being performed on an outpatient basis (also see Chapter 89).

Notably, early research on the safety of two ambulatory surgical procedures—tonsillectomy and simple mastectomy—presented a negative view of the hazards of surgery in the outpatient setting. One of the first procedures advocated to be performed on an ambulatory basis was tonsillectomy (also see Chapter 85). Although a 1968 case series of 40,000 outpatient tonsillectomies reported no deaths,[61] details on patient selection and length of postoperative monitoring were vague. Based on insurance company and state mandates, performance of tonsillectomy on an outpatient basis became routine.[62] Beginning in the mid-1980s and continuing in the 1990s, a number of articles evaluated outcomes with early discharge after tonsillectomy. For example, Carithers and colleagues[63] in 1987 at Ohio State University reported on 3000 tonsillectomies and argued that early discharge might be hazardous and economically unwarranted. The rate of readmission for active bleeding between 5 and 24 hours after surgery was reported to be between 0.2% and 0.5%.[64-67] Notably, although these findings are important from a historical perspective, they may not reflect current practice; therefore they may or may not suggest the need for delayed discharge and prolonged postoperative monitoring for all patients undergoing tonsillectomy in the ambulatory setting.

Mastectomy represents a second important case study in the development of surgery as an outpatient procedure. An analysis of Medicare claims demonstrated that the rate of outpatient mastectomy increased from a negligible proportion of all mastectomies in 1986 to 10.8% of all mastectomies performed among Medicare beneficiaries in 1995.[68] Within this population, simple mastectomies performed on an outpatient basis had a significantly higher rate of readmission than did those undergoing a 1-day hospital stay, with an adjusted OR of 1.84. When compared with the group treated on an outpatient basis, rates of readmission after 1-day stays were significantly lower for infection (4.1 versus 1.8 per 1000 cases), nausea and vomiting (1.1 versus 0 per 1000 cases), and pulmonary embolism or deep venous thrombosis (1.1 versus 0 per 1000 cases).

In contrast to these earlier studies, the 1993 publication of Warner and colleagues[69] on major morbidity and mortality within 1 month of ambulatory surgery strongly argued for the safety and feasibility of surgery in the outpatient setting. Among the 38,598 patients included in Warner's study, 4 died. Of these 4 deaths, 2 were due to myocardial infarctions occurring more than 1 week after surgery; the other 2 deaths occurred in automobile accidents (Fig. 37-4).

In part, as a result of such findings, the use of ambulatory surgery has dramatically grown between the early 1990s and the present, with a concurrent increase in the number and type of sites for ambulatory surgery. Such sites now include not only freestanding ambulatory surgery centers (ASCs) and physician's offices, but they also include interventional radiology units and other diagnostic and therapeutic sites not affiliated with any other health care facility.

In the context of such growth, investigators have sought to examine the relative safety of similar procedures performed across different outpatient settings. For example, Fleisher and co-workers[2] performed a claims analysis of patients undergoing 16 different surgical procedures in a nationally representative (5%) sample of Medicare beneficiaries for the years 1994 through 1999. A total of 564,267 procedures were studied, with 360,780 in an outpatient hospital, 175,288 in an ASC, and 28,199 in a physician's office. On the day of surgery, no deaths occurred in the office, but four deaths occurred in the ASC (2.3 per 100,000) and nine deaths occurred in the outpatient hospital (2.5 per 100,000). The 7-day mortality rate was 35 per 100,000 in the office setting, 25 per 100,000 in the ASC, and 50 per 100,000 in the outpatient hospital. The rate of admission to an inpatient hospital within 7 days was 9.08 per 1000 in the office, 8.41 per 1000 in the ASC, and 21 per 1000 in the outpatient hospital. Notably, the inferences of this study are limited by an inability to distinguish fully whether these differences in outcomes are related to the differences in the types of patients selected to have surgery in each setting versus the differences in the care patients received in each setting.

In a related report, Fleisher's group analyzed data from surgical procedures performed in hospital-based and freestanding ASCs in New York during 1997 that were obtained from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project.[70] Of the 783,558 patients eligible for inclusion in this study, 4351 were discharged directly for short-term hospitalization (1 in 180), and 19 died (1 in 41,240).

Subsequent work by Chukmaitov and colleagues compared quality outcomes between ASCs and hospital-based outpatient departments in the state of Florida between the years 1997 and 2004.[71] They used 7- and 30-day mortality and unexpected hospitalization as the outcomes of interest in 12 surgical procedures. The importance of location of care varied by surgical procedure and the number of comorbid conditions included in the analysis. Although their conclusions were limited by differences in the data available for patients treated in each setting, they postulated that the difference in outcomes between the two locations may be related to variations in organizational structure, processes, and strategies.

In contrast to the growing literature on the safety of anesthesia and surgery in ASCs, limited information exists to quantify the incidence of complications in office-based settings. The American Association for Ambulatory Plastic

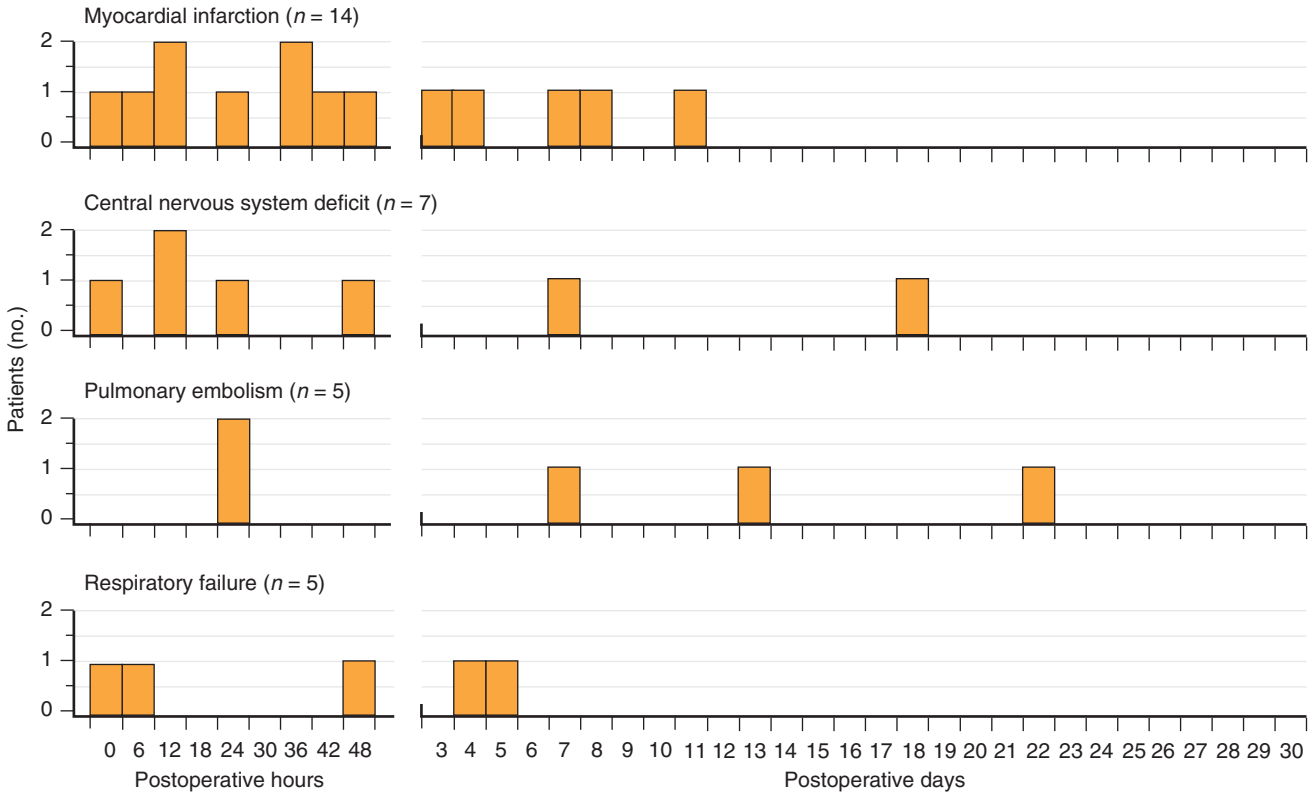


Figure 37-4. Timing of perioperative events in patients undergoing ambulatory surgery. Many of the events occurring within the first 48 hours are probably related to the stress of surgery. A subset of events occurring after this period may be related to background event rates. The overall rate of morbidity was lower than expected for a similar cohort of age-matched nonsurgical patients. *(From Warner MA, Shields SE, Chute CG: Major morbidity and mortality within 1 month of ambulatory surgery and anesthesia,* JAMA *270:1437, 1993.)*

Surgery Facilities mailed a survey to their members to determine the incidence of complications occurring in office facilities.[72] The overall response rate was 57%. The findings showed that 0.47% of patients had at least one complication, including bleeding, hypertension, infection, and hypotension, and 1 in 57,000 patients died. Although low in absolute terms, the observation of a rate of mortality after minor outpatient procedures that is three times the current estimate for anesthesia-related complications is concerning in this context.

Vila and colleagues reviewed all adverse incident reports to the Florida Board of Medicine for procedures dated April 1, 2000, to April 1, 2002.[73] The numbers of office procedures performed during a 4-month period were used to estimate the total number of procedures. Adverse incidents occurred at a rate of 66 and 5.3 per 100,000 procedures in offices and ASCs, respectively. The death rate per 100,000 procedures performed was 9.2 in offices and 0.78 in ASCs. The relative risk for injury and death for procedures performed in offices versus ASCs was 12.4 (95% CI, 9.5 to 16.2) and 11.8 (95% CI, 5.8 to 24.1), respectively. As a result, the authors concluded that if all office procedures had been performed in ASCs, approximately 43 injuries and 6 deaths per year could have been prevented. In contrast, Coldiron and colleagues studied office-based surgeries in Florida and showed that the greatest danger to patients lies not with the surgical procedures in office-based settings per se but with cosmetic procedures that are performed in office-based settings, particularly when under general anesthesia.[74] Several other groups have analyzed the Florida data and have been unable to document the increased risk in the office setting.[75,76]

In summary, although early research on ambulatory surgery placed an emphasis on the undue risks created by premature discharge, more recent analyses confirm that a range of surgeries can be safely performed in properly selected patients; moreover, although some variations in outcomes have been observed across settings (i.e., hospital outpatient department versus ASC), available literature suggests that, given proper patient selection, outpatient surgeries can be performed with a low rate of adverse events in multiple practice environments. Finally, given the gradual expansion of outpatient surgery over time to include patients with greater burdens of comorbid disease and more extensive procedures, ongoing evaluations will be essential to characterize the dynamic, evolving nature of anesthetic risk in the ambulatory setting.

USE OF ANESTHESIA INFORMATION MANAGEMENT SYSTEMS

Over the past 4 decades, the use of computerized databases has enhanced the ability to assess perioperative risk and complications (see also Chapter 5).

In one of the earliest computer analyses of postanesthesia deaths, Marx and associates[36] identified 645 individuals who died within 7 days after surgery out of a total cohort

of 34,145 consecutive surgical patients. More recently, the growth of electronic anesthesia record systems has allowed for better insights into the causes of anesthesia-related events within the surgical unit, and, when used in combination with other data sources, on postoperative outcomes. An early example of such an analysis was that of Sanborn and colleagues,[77] who used a computer anesthesia record to identify intraoperative incidents. They were able to demonstrate that perioperative deaths occurred more frequently in patients who sustained an intraoperative incident of any type than in those who did not.

Similarly, Reich and colleagues used computerized anesthesia records to evaluate hemodynamic variables and their relationship to risk.[78] Among 2149 patients, 50 deaths, 51 strokes, and 85 perioperative myocardial infarctions occurred. By multivariate analysis, they identified pulmonary hypertension, hypotension during cardiopulmonary bypass, and post–cardiopulmonary bypass pulmonary diastolic hypertension as independent predictors associated with mortality, stroke, and perioperative myocardial infarction over and above the effects of other preoperative risk factors.

More recently, data from the University of Michigan anesthesia information management system have been used to identify predictors of perioperative risk. For example, they evaluated factors related to adequacy of mask ventilation in 22,660 patients.[79] Limited or severely limited mandibular protrusion, abnormal neck anatomy, sleep apnea, snoring, and a body mass index of 30 kg/m^2 or greater were independent predictors of grade 3 or 4 mask ventilation and difficult intubation. In another publication, the same group examined a total of 15,102 patients who had a normal preoperative creatinine clearance and underwent noncardiac surgery.[80] Acute renal failure developed in 121 patients (0.8%), and 14 patients required renal replacement therapy (0.1%). Seven independent preoperative predictors were identified: age, emergency surgery, liver disease, body mass index, high-risk surgery, peripheral vascular occlusive disease, and chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy. They found that acute renal failure was associated with increased mortality from any cause at 30 days, 60 days, and 1 year.

In an effort to expand upon the insights gained from single-institution studies, two major efforts have since been initiated to pool electronic data on anesthesia care from multiple sites as a means of more effectively comparing outcomes and defining risk factors related to outcomes after anesthesia. The first of these, the Multicenter Perioperative Outcomes Group, was initiated in 2008 under the leadership of investigators at the University of Michigan. This project currently collects electronic anesthesia data from over 30 participating anesthesia departments and has released initial data related to the incidence of epidural hematoma across member practices.[26] The second of these, the National Anesthesia Clinical Outcomes Registry, is maintained by the Anesthesia Quality Institute, a nonprofit organization established by the ASA. This large-scale data warehouse collects both paper and electronic anesthesia case data that will be used to assess anesthesia practices to optimize local efforts to assess both the risk and the quality of care and for research purposes for the specialty as a whole.

OTHER APPROACHES TO DISCERN THE ROOT CAUSE OF MORBIDITY AND MORTALITY

Although mortality directly attributable to anesthesia appears to have declined over time, the exact causes of this decline remain unclear. Numerous factors have been implicated in the improved outcome, including new monitoring modalities, new anesthetic drugs, and changes in the anesthesia workforce. However, relating the reduced risk to any one factor on the basis of available epidemiologic data is difficult. Further, although the use of newer monitoring modalities, particularly pulse oximetry, would be expected to improve outcomes, no randomized trial has been able to document such a conclusion. This limitation supports the need for continued monitoring of complications and their root cause through a number of approaches.

Initiated by the Professional Liability Committee of the ASA, the ASA-CCP represents one important approach to understanding the root causes of important complications of anesthesia care (also see Chapter 11). The ASA-CCP constitutes an ongoing, nationwide survey of closed insurance claims for major anesthesia-related adverse events. In an early publication based on data collected by the ASA-CCP, Caplan and colleagues reviewed both fatal and nonfatal outcomes resulting in claims against anesthesia providers. Among the fatal events, unexpected cardiac arrest during spinal anesthesia was observed in 14 healthy patients from the initial 900 claims.[81] These cases were analyzed in detail to identify patterns of care that might have led to the event. Two patterns were identified: oversedation leading to respiratory insufficiency and inappropriate resuscitation of high spinal sympathetic blockade.

Tinker and co-workers[82] queried the ASA-CCP to determine the role of monitoring devices in the prevention of anesthesia mishaps. They reviewed 1097 anesthesia-related claims and determined that 31.5% of the negative outcomes could have been prevented by the use of additional monitors, primarily pulse oximetry and capnography. Injuries that were deemed preventable with additional monitoring resulted in dramatically more severe injury and cost of settlement than did those judged to be nonpreventable with additional monitoring. In nearly 90% (305 of 346) of the preventable cases, at least one clinical sign of abnormality was identified by the existing monitors.

In a subsequent report, Caplan and colleagues[83] reviewed the ASA-CCP for respiratory events (Table 37-11). These claims represented the single largest class of injury (34%), with death or brain damage occurring in 85% of cases. They identified inadequate ventilation, esophageal intubation, and difficult tracheal intubation as the primary causes of respiratory events. The investigators believed most of the outcomes to be preventable with better monitoring, such as pulse oximetry or capnography (Fig. 37-5).

More recently, the ASA-CCP has focused on such topics as monitored anesthesia care.[84] More than 40% of 121 claims associated with monitored anesthesia care involved death or permanent brain damage. Respiratory

depression, after an absolute or relative overdose of sedative or opioid drugs, was the most common (21%, $n = 25$) of the complications.

A similar registry was developed by the Danish Patient Insurance Association.[85] For the years of 1996 through 2004, 1256 files were related to anesthesia, and 24 deaths were considered to be a result of the anesthetic procedure: 4 deaths were related to airway management, 2 to ventilation management, 4 to central venous catheter placement, 4 as a result of medication errors, 4 from infusion pump problems, and 4 after complications from regional blockade. Severe hemorrhage caused one death, and the cause was uncertain in one case.

Cooper and colleagues[86,87] took an alternate approach to examining perioperative mortality through the study of critical incidents, which were defined as those that were potentially preventable and could lead to undesirable outcomes. This definition included events that led to no harm or only transient effects. The investigation involved collecting data on anesthesia-related human errors and equipment failures from anesthesiologists, residents, and certified registered nurse anesthetists (CRNAs). In a series of reports, the authors identified frequent incidents, such as disconnections in breathing circuits, and causes of discovery of errors, such as intraoperative relief. They confirmed that equipment failure was a small cause of anesthesia mishaps (4%), whereas human error was a predominant factor. They suggested that future studies of anesthesia-related mortality and morbidity should classify events according to a strategy for prevention rather than outcome alone.

The Australian Incident Monitoring Study was developed by the Australian Patient Safety Foundation and has been in existence since the early 1990s. It is a method of reporting and analyzing critical incidents so that corrective strategies can be implemented. Similar to the ASA-CCP, there is no rate of occurrence, only an analysis of reported cases. Numerous reports have looked at the cause of critical incidents, including problems with ventilation, with vascular access, and in the postanesthesia care unit.[88,89]

Buffington and co-workers[90] studied the ability of attendees of an anesthesia meeting to identify five faults intentionally created in a standard anesthesia machine. A survey was distributed, and the answer sheets were scored with respect to the number of correct answers. Only 3.4% of the respondents found all five faults. The average number of faults detected was 2.2. The professional background of the participants did not influence the ability to find the faults; distributions were similar between physicians and CRNAs. A small improvement in fault-finding ability was found in those with more than 10 years of experience. Studies such as these highlight the problem of the practitioner's ability to identify conditions that may lead to anesthesia mishaps. Whether improved technology or education can reduce some basal level of mishaps is unknown.

TABLE 37-11 DISTRIBUTION OF ADVERSE RESPIRATORY EVENTS IN THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS' ANESTHESIA CLOSED CLAIMS STUDY

Event	Number of Cases	Percent of 522 Respiratory Claims
Inadequate ventilation	196	38
Esophageal intubation	94	18
Difficult tracheal intubation	87	17
Inadequate inspired oxygen concentration	11	2

From Caplan RA, Ward RJ, Posner K, et al: Unexpected cardiac arrest during spinal anesthesia: a closed claims analysis of predisposing factors, Anesthesiology *68:5, 1988.*

ISSUES ASSOCIATED WITH ANESTHESIA-RELATED MORTALITY

The studies detailed in the previous text focus on intraoperative or inhospital deaths directly attributable to anesthesia care; nonetheless, perioperative complications may contribute to the risk of mortality beyond the immediate postoperative period. For example, a perioperative stroke or myocardial infarction may lead to death after the period of analysis. Notably, recent research has suggested that even small myocardial infarctions or unstable

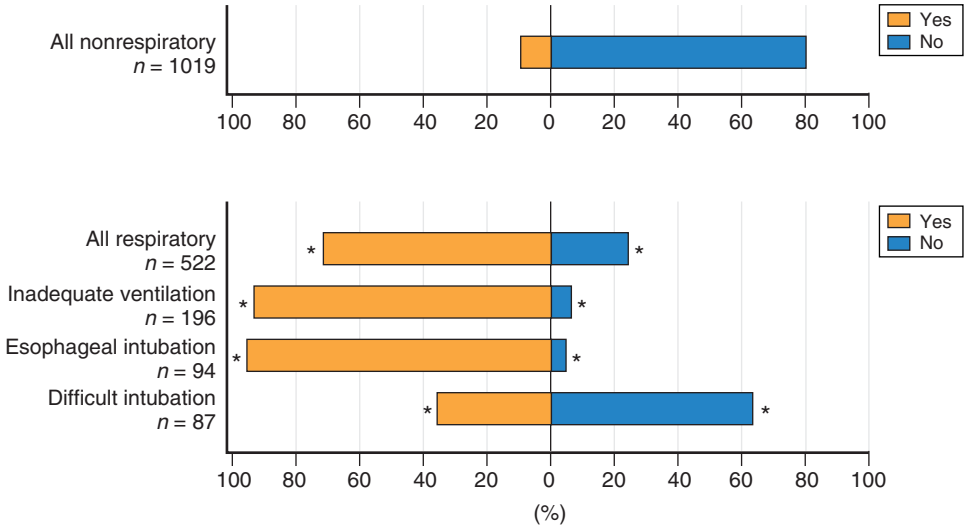


Figure 37-5. Relationship between adverse events in the American Society of Anesthesiologists' Anesthesia Closed Claims Study and preventable complications. Preventable events related to respiratory complications were significantly more common than those related to all nonrespiratory complications. Of the respiratory complications, difficult intubation had the least number of preventable complications (*$P < .05$ versus nonrespiratory claims). *(From Caplan RA, Posner KL, Ward RJ, et al: Adverse respiratory events in anesthesia: a closed claims analysis,* Anesthesiology *72:828, 1990.)*

angina during the perioperative period have been associated with worsened long-term survival.[91] Should these *late* deaths be attributed to anesthesia complications for the purpose of such analyses? The answer depends on the outcome and its relationship to anesthesia management.

The potential effects of anesthesia on long-term survival were suggested by Monk and colleagues.[92] Using multivariate Cox proportional hazards models, these investigators identified three variables as significant independent predictors of mortality: patient comorbidity (relative risk [RR], 16.116), cumulative deep hypnotic time (bispectral index < 45) (RR, 1.244/hr), and intraoperative systolic hypotension (RR, 1.036/min). They reported that cumulative deep hypnotic time and intraoperative hypotension were significant, independent predictors of increased mortality. Further work is required to determine whether these results reflect a true pathophysiologic link between perioperative (anesthesia) management and long-term outcome or a simple statistical association. This study and others, however, emphasize the importance of evaluating all aspects of anesthesia care and short- and long-term outcomes to try to optimize both long- and short-term patient outcomes.

RISKS RELATED TO PATIENT CHARACTERISTICS

Multiple past studies have demonstrated that perioperative morbidity and mortality are increased in the presence of coexisting medical diseases (also see Chapter 39). The ASA physical status classification system, originally proposed in 1941,[93] represents a widely used method of classifying the severity of coexisting disease among surgical patients. Since its introduction, this classification system has introduced a standardized terminology for anesthesia practice and has aided in developing valid statistical comparisons of outcomes among sites.[94]

The correlation between ASA physical status and mortality offers a simple illustration of the link between comorbidities and adverse operative outcomes. In 1961, Dripps and co-workers demonstrated that mortality increased as the severity of comorbid disease increased, as assessed by the ASA physical status classification.[32] Several investigators have reevaluated the relationship between operative mortality and ASA physical status. Studies by Pedersen[46] and Tiret[43] and their colleagues demonstrated such relationships. Vacanti and co-workers[95] also demonstrated the relationship between increasing mortality and decreasing physical status in 68,388 cases.

In Canada, Cohen and colleagues[96] analyzed 100,000 anesthesia procedures and determined mortality within 7 days of surgery by using governmental vital statistics mortality data between the years 1975 and 1984. They collected information for each patient on age, preoperative conditions, ASA physical status, anesthetic technique, monitors, and other factors. The overall 7-day mortality rate was 71.04 deaths per 10,000 procedures. The mortality rate increased with advanced age, and it showed a significant increase in those older than 80 years of age. Rates were low for normal, healthy individuals and for those undergoing minor procedures. The investigators developed a multiple logistic regression model to determine the independent predictors of mortality. Significant risk markers for increasing mortality were advanced age, male gender, increasing physical status score, major or intermediate surgery, emergency procedure, having a complication in the surgical unit, narcotic anesthetic techniques, and having received only one or two anesthetic drugs (Table 37-12).

One of the limitations of the ASA physical status classification system is that the ranking is determined by individual anesthesia providers; as such, it might differ from one practitioner to another. Owens and co-workers[97] evaluated this hypothesis by asking 255 anesthesiologists to classify 10 hypothetical patients. In six of the cases there was general agreement among the practitioners about classification of the patient; in the other four cases, opinion diverged.

TABLE 37-12 RISK FACTORS ASSOCIATED WITH INCREASED ODDS OF DYING WITHIN 7 DAYS FOR ALL CASES

Variable	All Procedures: Relative Odds of Dying Within 7 Days	95% Confidence Limits
Patient related		
Age (yr)		
60-79 vs <60	2.32	1.70-3.17
80+ vs <60	3.29	2.18-4.96
Sex (female vs male)	0.77	0.59-1.00
ASA physical status classification (3-5 vs 1-2)	10.65	7.59-14.85
Surgery related		
Major vs minor	3.82	2.50-5.93
Intermediate vs minor	1.76	1.24-2.5
Length of anesthesia (≤2 hr vs <2 hr)	1.08	0.77-1.50
Emergency vs elective	4.44	3.38-5.83
Other factors		
Year of surgery (1975-1979 vs 1980-1984)	1.75	1.32-2.31
Complication in the surgical or recovery unit (yes vs no)	1.42	1.06-1.89
Anesthesia related*		
Experience of the anesthetist (>600 procedures for ≥8 yr vs <600 procedures for <8 yr)	1.06	0.82-1.37
Inhalation with narcotic vs inhalation alone	0.76	0.51-1.15
Narcotic alone vs inhalation alone	1.41	1.01-2.00
Narcotic with inhalation vs inhalation alone	0.79	0.47-1.32
Spinal vs inhalation alone	0.53	0.29-0.98
Number of anesthetic drugs (1-2 vs 3)	2.94	2.20-3.84

Adapted from Cohen MM, Duncan PG, Tate RB: Does anesthesia contribute to operative mortality? JAMA *260:2861, 1988.*

**All cases performed with the five most frequently used anesthetic techniques.*

In contrast to the ASA physical status classification, which offers a general assessment of the severity and extent of a patient's coexisting illnesses, other studies have attempted to define the specific patient characteristics that are most strongly associated with perioperative adverse events related to a particular organ system. In evaluating the risk directly related to the patient's condition, the limitations of the methodology must be understood. All such studies evaluate the predictive value of a clinical or laboratory risk factor for a defined perioperative complication. In this approach, a cohort of individuals of interest is defined. In the optimal state the study is performed prospectively, and the outcome of interest is assessed in a rigorous, blinded fashion. Despite this, many available studies of perioperative risk factors focus on selected patients and include a retrospective design, methods that greatly limit their generalizability and validity.

Many studies have identified a cohort of individuals, determining their clinical and laboratory risk factors and using multivariate modeling to determine the factors associated with increased risk. A major limitation in the use of multivariate modeling for this purpose is the assumption that the intraoperative period is a *black box* and that care is not modified by the knowledge of the risk factor (Fig. 37-6). However, anesthesiologists modify intraoperative care of high-risk patients in an attempt to minimize the likelihood of complications. Changes in medical care over time and better knowledge about high-risk patients should result in a reduction of the risk related to specified clinical factors. For this reason, many of the indices defined in previously published studies may no longer be valid because of changes in clinical practice. Such considerations make it difficult to design and complete formal investigations to validate individual management strategies in the context of current practice.

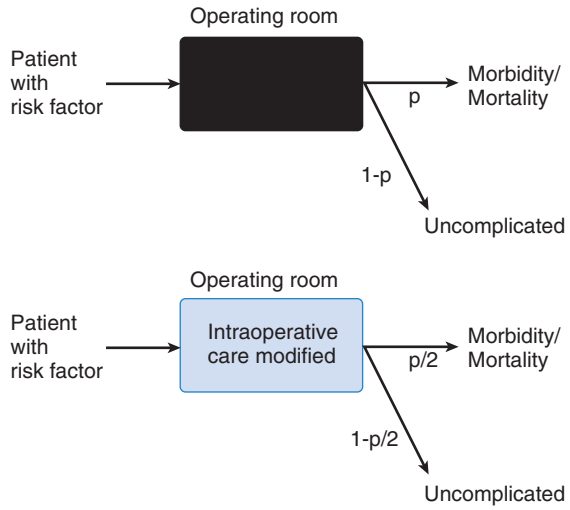


Figure 37-6. The concept of the black box for risk indices. In developing a risk index, patients with a specific risk factor enter the operating room and have a complication at a rate *p*. If the anesthesiologist is aware of the importance of the risk factor and can modify care to reduce such risk (*p/2*), then the risk factor may no longer be significant. If the risk factor is ignored, then complications may again occur in such patients.

One common approach taken in past efforts to quantify operative risk has been to examine the relationship between a single risk factor and a broad range of adverse perioperative outcomes (also see Chapter 39). For example, numerous studies have evaluated the importance of hypertension on perioperative risk. Goldman and Caldera[98] evaluated a cohort of patients undergoing noncardiac surgery under general anesthesia. Hypertension was not associated with increased perioperative risk, although the number of patients with diastolic blood pressure greater than 110 mm Hg was too small to draw any statistically significant conclusions. In contrast, Hollenberg and co-workers[99] identified hypertension and the presence of left ventricular hypertrophy as predictors of perioperative ischemia, but they did not consider their independent relationship to perioperative major morbidity.

An alternative to examining the impact of a single risk factor on perioperative outcomes involves a more general effort to identify multiple risk factors for one or more adverse perioperative outcomes. As such, multiple researchers have undertaken prospective and retrospective cohort studies with the goal of identifying patients at greatest risk for fatal and nonfatal myocardial infarction. One of the earliest attempts to define cardiac risk was performed by Goldman and colleagues at the Massachusetts General Hospital.[13] They studied 1001 patients older than 45 years of age who were undergoing noncardiac surgery, excluding those who underwent transurethral resection of the prostate under spinal anesthesia. Using multivariate logistic regression, they demonstrated nine clinical factors associated with increased morbidity and mortality. Each risk factor was weighted in the logistic regression equation and converted into points in the index. An increasing number of points was associated with increasing perioperative cardiac morbidity or mortality.

Several attempts have been made to validate the Goldman Cardiac Risk Index. Zeldin[100] prospectively determined the Cardiac Risk Index for 1140 surgical patients and reported that the overall accuracy of the index was as high as in the original study, although the rate of complications in the highest risk group was less than originally reported. Larsen and co-workers[101] also found that the Cardiac Risk Index demonstrated good accuracy in 2609 consecutive unselected patients older than 40 years of age. The validity of the Cardiac Risk Index is more controversial for patients undergoing vascular surgery. Domaingue and colleagues[102] studied patients undergoing various vascular surgery procedures and reported a higher probability of major cardiac complications than that reported by Goldman and associates; however, they also demonstrated a higher rate of complications with increasing cardiac risk class. Jeffrey and colleagues[103] evaluated the rate of cardiac complications in 99 patients undergoing elective abdominal aortic surgery and demonstrated a similar pattern of increased overall complication rates with increasing cardiac risk. A higher percentage (7%) of patients in the lowest category in their study sustained a cardiac complication. White and associates[104] demonstrated the value of the Goldman Cardiac Risk Index for long-term survival after vascular surgery. Several other studies, however, were unable to

demonstrate any relationship between the Cardiac Risk Index and perioperative cardiac complications, with a high incidence of complications found in patients with a Cardiac Risk Index of I or II.[105,106] When the ASA physical status classification system was compared with the Goldman Cardiac Risk Index in a cohort of 16,277 patients undergoing noncardiac surgery,[106] both indices demonstrated predictive value, although the objective Goldman Cardiac Risk Index provided little additional value over the more subjective ASA physical status classification.

Since the introduction of the Goldman Cardiac Risk Index, other investigators have put forward alternative risk indices for cardiac events after noncardiac surgery. Detsky and co-workers[107] studied a cohort of individuals who were referred to an internal medicine service for preoperative evaluation. Many of the factors identified by Goldman were confirmed or slightly modified in the Detsky Modified Risk Index, and angina was added to the risk factors. The researchers advocated the calculation of a pretest probability of complications based on the type of surgery, after which the Detsky Modified Risk Index is applied with the use of a nomogram. In this manner, the overall probability of complications can be determined as a function of the surgical procedure and patient disease. The Detsky Modified Risk Index was advocated as the starting point for risk stratification in the American College of Physicians guidelines on preoperative evaluation.[108] In an attempt to update Goldman's original index, Lee and colleagues[109] at the Brigham and Women's Hospital studied 4315 patients 50 years of age or older who were undergoing elective major noncardiac procedures in a tertiary care teaching hospital. Six independent predictors of complications were identified and included in a Revised Cardiac Risk Index (RCRI): high-risk type of surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine level higher than 2.0 mg/dL. The rate of major cardiac complications increased with the number of risk factors. The performance of the RCRI was examined in a meta-analysis conducted by Ford and colleagues.[110] In a review of 24 studies including over 700,000 patients, they found that although the RCRI showed moderate discrimination for patients at low versus high risk for cardiac events after noncardiac surgery, it did not perform well at predicting death or at predicting cardiac events after vascular surgery.

More recently, Gupta and colleagues[111] used data collected by the NSQIP to develop the risk for cardiovascular events after noncardiac surgery. They developed a risk-prediction model using all 211,410 patients recorded in the 2007 version of the NSQIP database and subsequently validated this model on the 257,385 patients in the 2008 dataset. This model, which included five variables—type of surgery, dependent functional status, abnormal creatinine level, ASA physical status, and increasing age—demonstrated improved discrimination over the RCRI, which did not improve with the addition of the RCRI score to the model.

Beyond the efforts at identifying those patients most at risk of postoperative cardiovascular events, recent research has sought to develop statistical models for a range of other organ-based preoperative outcomes. These have included risk models for acute kidney injury in cardiac[112] and noncardiac surgery patients,[60] postoperative respiratory failure,[113,114] and stroke after cardiac surgery[115] and carotid endarterectomy.[116]

In contrast to the efforts to determine risk factors for specific organ-based complications, other investigators have sought to develop risk-prediction models to identify those patients at risk of death from any cause in the immediate postoperative period. For example, Glance and colleagues from the University of Rochester used data from the NSQIP to derive and validate a predictive score for 30-day all-cause mortality for noncardiac surgery. Studying 298,772 patients undergoing surgery between 2005 and 2007, Glance and colleagues identified three factors that were highly predictive of death at 30 days after surgery: (1) ASA physical status, (2) emergency status, and (3) surgery type. Patients with ASA physical status I, II, III, IV or V were assigned 0, 2, 4, 5, or 6 points, respectively; intermediate- or high-risk procedures were assigned 1 or 2 points, respectively; and emergency procedures were assigned 1 point. Patients with risk scores less than 5 had a predicted risk of mortality less than 0.5%, whereas patients with a risk score of 5 to 6 had a risk of mortality between 1.5% and 4%. Patients with a risk score greater than 6 had risk of mortality more than 10%.[117]

Beyond their clinical applicability, such risk indices have become important in the context of health policy by allowing for comparisons of risk-adjusted mortality rates across hospitals and physicians providing cardiac surgery. For example, the state of New York annually publishes data on mortality rates associated with coronary bypass grafting by surgeon and by hospital.[118-120] For comparison of rates across institutions, institutional mortality rates are typically risk-adjusted so that high-performing institutions that treat a high percentage of medically complex patients are not spuriously categorized as *poor performers* simply because of the features of their patient mix.

Beyond identifying clinical indicators of perioperative risk, historic and current research has focused on the role of genetics and genomics on the outcomes of major surgical procedures. Notably, the impact of genotype on perioperative risk has been well known since elucidation of the inheritance pattern of malignant hyperthermia. With malignant hyperthermia, a clear link exists between the autosomal dominant disease and an adverse outcome after administration of an anesthetic.[121] Interest in evaluating the impact of genetic polymorphism on overall perioperative outcome is increasing, even if the link to anesthesia is less well defined. For example, apolipoprotein E4 has been shown to modulate neurologic injury and recovery after a variety of acute ischemic insults, including coronary artery bypass grafting.[122] Polymorphism of the glycoprotein IIIa constituent of the platelet integrin receptor has also been correlated with postoperative cognitive decline.[123,124] Further research will be required to determine specific genetic profiles that will impact anesthetic management strategies, drug selection, and other aspects of care.

SPECIAL PATIENT GROUPS

OBSTETRICS

Anesthesia for the obstetric patient carries unique challenges, since both the mother and the fetus are potentially at risk for complications. Fortunately, maternal mortality is rare, and the anesthesia-related component of maternal delivery represents only a small fraction of all maternal deaths. As a result, studies of peripartum complications require a large number of patients from a diversity of clinical settings (also see Chapter 77).

In parallel to the early efforts to determine the overall risk of anesthesia for surgery, a series of studies were performed between 1974 and 1985 that sought to determine the rate of obstetric complications in the United States and England and to assess the contribution of anesthesia per se to the risk of adverse events in this group. One of the first reports included the period of 1974 through 1978. Kaunitz and coauthors[125] reported an anesthesia-related death rate of 0.6 per 100,000 births with data from all 50 states. Endler and co-workers[126] studied births in Michigan between 1972 and 1984 and reported 15 maternal deaths in which anesthesia was the primary cause and 4 deaths in which anesthesia was contributory. This resulted in a rate of 0.82 anesthesia-related deaths per 100,000 live births. Eleven of the 15 deaths were associated with cesarean section. Obesity and emergency surgery were risk factors in many patients. Complications related to regional anesthesia were identified as a problem in the earlier years of the study, whereas failure to secure a patent airway was the primary cause of mortality in the later years. No anesthesia-related maternal deaths occurred in the final 2 years of the study. Rochat and colleagues[127] studied 19 areas of the United States between 1980 and 1985 and reported 0.98 anesthesia-related deaths per 100,000 live births. They observed that maternal mortality did not decrease over the time of the study.

The Confidential Enquiry into Maternal Deaths in England and Wales has been assessing maternal deaths since 1952.[128] Records of all maternal deaths are sent to a district medical officer, who sends an inquiry form to all health practitioners involved in the care of these patients. These forms are evaluated by a senior obstetrician and an anesthesia assessor. Morgan[128] reported the maternal deaths from anesthesia between 1952 and 1981 (Table 37-13). The total maternal mortality rate decreased over time, but the percentage of deaths related to anesthesia increased, although the absolute number of deaths associated with anesthesia decreased. During the early years of the study, endotracheal intubation was rarely performed during obstetric anesthesia. Later reports advocated the use of endotracheal intubation after the induction of thiopental and suxamethonium, and technical difficulties with intubation were identified. The other major finding of this study was that the experience of the anesthesia provider in obstetric anesthesia was the most important factor in anesthesia-related maternal mortality.

More recent investigations have confirmed ongoing decreases over time in the hazards of obstetric anesthesia. Hawkins and associates[129] obtained data from the ongoing National Pregnancy Mortality Surveillance System of the Centers for Disease Control and Prevention on births and fetal deaths from 1979 through 1990 to determine the possible risk related to anesthesia for obstetrics. They identified a total of 129 women who died of anesthesia-related causes during the study period, most (82%) of the deaths occurred during cesarean section, and the incidence of anesthesia-related maternal mortality decreased over time (Table 37-14), possibly the result of a trend toward a greater use of neuraxial techniques. Importantly, among maternal deaths that occurred in the context of general anesthesia for cesarean delivery, 73% were related to airway problems.

In a subsequent study, Panchal and colleagues[130] conducted a retrospective case-control study using patients' records from a state-maintained anonymous database of all nonfederal Maryland hospitals that performed deliveries between 1984 and 1997. Variables studied included patient demographics and the International Classification of Diseases, Clinical Modification (ICD-9 CM) diagnosis and procedure codes. Of the 822,591 hospital admissions for delivery during the 14-year study period, 135 maternal deaths occurred. The most common diagnoses associated with mortality during hospital admission for delivery were preeclampsia or eclampsia (22.2%), postpartum hemorrhage or obstetric shock (22.2%), pulmonary complications (14%), blood clot or amniotic embolism

TABLE 37-13 **MATERNAL MORTALITY FIGURES OBTAINED FROM THE CONFIDENTIAL ENQUIRY INTO MATERNAL DEATHS IN ENGLAND AND WALES**

Years	Maternal Mortality per 1000 Total Births	Number of Deaths From Anesthesia	Percent of True Maternal Deaths From Anesthesia	Percent With Avoidable Factors
1952-1954	0.53	49	4.5	—
1955-1957	0.43	31	3.6	77
1958-1960	0.33	30	4.0	80
1961-1963	0.26	28	4.0	50
1964-1966	0.20	50	8.7	48
1967-1969	0.16	50	10.9	68
1970-1972	0.13	37	10.4	76
1973-1975	0.11	31	13.2	90
1976-1978	0.11	30	13.2	93
1979-1981	0.11	22	12.2	100

From Morgan M: Anaesthetic contribution to maternal mortality, Br J Anaesth *59:842, 1987.*

or both (8.1%), and anesthesia-related complications (5.2%). Notably, Panchal's study noted differences by race in the rate of maternal death per 100,000 live births per year (Fig. 37-7). Although the potential causes of this difference remain to be elucidated, Panchal's findings also suggested potential improvements over time in both the overall risk of maternal mortality, as well as the degree to which such risk differed by race.

More recent studies have continued to portray maternal mortality related to anesthesia as an important, although exceedingly rare event. Importantly, contemporary analyses of adverse maternal outcomes of anesthesia emphasize the particular risks associated with airway management in this population. For example, Mhyre and colleagues reviewed maternal mortality in Michigan between 1985 and 2003.[131] Of 855 pregnancy-associated deaths, 8 were related to anesthesia, and anesthesia was considered to be contributory in 7. All anesthesia-related deaths from airway obstruction or hypoventilation took place during emergence and recovery, not during induction of general anesthesia. Lapses in postoperative monitoring and inadequate supervision by an anesthesiologist seemed to contribute to more than one half of the deaths. In a similar study, Bloom and associates studied anesthesia-related morbidity and mortality as part of a prospective observational study conducted in women (N = 37,142) with singleton gestations undergoing cesarean delivery in the clinical centers comprising the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network.[132] One maternal death was caused by failed intubation in which the anesthetic procedure was directly implicated.

In summary, extensive past research has indicated that the risks of major morbidity and mortality attributable to obstetric anesthesia care have decreased over time; nonetheless, recent research indicates that adverse outcomes continue to occur and may be of particular concern for patients receiving general anesthesia for cesarean delivery. Looking forward, further research is needed, potentially using national and international databases, to define more clearly the current risks of anesthesia for obstetrics, as well as the variability in the care delivered (including the use of differing anesthetic techniques) and the maternal outcomes across institutions and practice environments.

PEDIATRICS

There are few studies of anesthesia-related risk in the pediatric population (also see Chapters 92 to 95). Two themes emerge from these studies: very young infants are at increased risk, and anesthesia-related risk is reduced in centers with specialized pediatric anesthesia facilities.

TABLE 37-14 NUMBERS, CASE FATALITY RATES, AND RISK RATIOS OF ANESTHESIA-RELATED DEATHS DURING CESAREAN SECTION DELIVERY BY TYPE OF ANESTHESIA IN THE UNITED STATES, 1979-1984 AND 1985-1990

	Number of Deaths		Case-Fatality Rate		Risk Ratio	
Population	1979-1984	1985-1990	1979-1984	1985-1990	1979-1984	1985-1990
General	33	32	20.0* (95% CI, 17.7-22.7)	32.3* (95% CI, 25.9-49.3)	2.3 (95% CI, 1.9-2.9)	16.7 (95% CI, 12.9-21.8)
Regional	19	9	8.6† (95% CI, 1.8-9.4)	1.9† (95% CI, 1.8-2)	Referent	Referent

Adapted from Hawkins JL, Gibbs CP, Orleans M, et al: Obstetric anesthesia work force survey, 1981 versus 1992, Anesthesiology *87:135, 1997.*
CI, Confidence interval.
*Per million general anesthetics for cesarean section.
†Per million regional anesthetics for cesarean section.

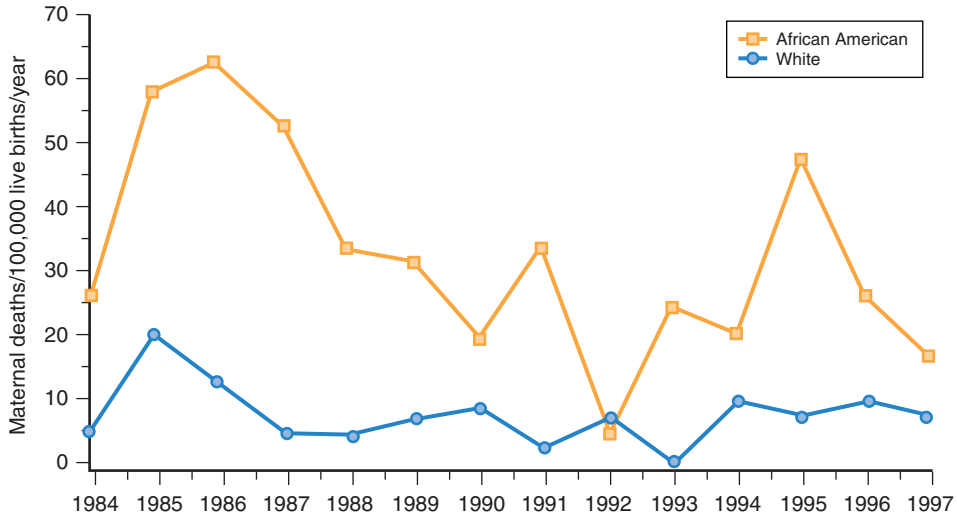


Figure 37-7. Delivery mortality ratios by race in Maryland, from 1984 to 1997, according to discharge summaries. *(From Panchal S, Arria AM, Labhsetwar SA: Maternal mortality during hospital admission for delivery: a retrospective analysis using a state-maintained database,* Anesth Analg *93:134, 2001.)*

In Beecher and Todd's classic 1954 study on anesthesia outcomes,[18] a "disproportionate number" of anesthesia-related deaths occurred in children younger than 10 years of age. Similarly, Graff and colleagues[133] from the Baltimore Anesthesia Study Committee reported 335 operative deaths in the pediatric age group. Of these, 58 were thought to be primarily or partially attributable to anesthesia. The percentage of operative deaths attributable to anesthesia was relatively constant among age groups at 16.6% to 21.7%. The estimated anesthesia-associated mortality rate was 3.3 deaths per 10,000 surgeries for those younger than 15 years of age versus 0.6 for those between 15 and 24 years of age and 11.7 for those older than 64 years. Notably, the majority of pediatric anesthetic deaths occurred in children with low anesthesia risk and among those undergoing tonsillectomy, a common surgical procedure in this age group. In an effort to understand the causes of pediatric anesthetic mortality, the authors noted errors in anesthesia management as accounting for approximately one half of the cases. Respiratory complications (e.g., underventilation, aspiration of vomitus or blood) were apparent in 82% of the anesthesia-related deaths. Notably, since this study was completed at a time when anesthetic management and monitoring techniques were quite different, its applicability to modern practice remains limited.

The studies that followed those of Beecher and Todd and the Baltimore Anesthesia Study Committee provided further detail on the risks associated with pediatric anesthesia over time. Tiret and coauthors[134] prospectively studied major anesthesia-related complications in pediatric patients in 440 hospitals in France between 1978 and 1982. There were 27 major complications in 40,240 cases, which included 12 cardiac arrests and 1 death. The incidence of major complications and cardiac arrest was significantly higher in infants than in older children. The rate of cardiac arrest related to anesthesia was highest in infants (19 per 10,000) and lowest in children (2.1 per 10,000). Most complications in infants involved the respiratory system and predominantly consisted of airway problems and aspiration. Older children experienced respiratory and cardiac complications, which occurred most frequently during induction and recovery.

Cohen and colleagues[135] studied 29,220 anesthesia procedures at the Winnipeg Children's Hospital. Data were collected from mid-1982 through 1987 and stored in a databank. Data on patients' coexisting medical conditions and postoperative follow-up were obtained within 72 hours. Complications included death, cardiac arrest, drug reactions, airway obstruction, and minor complications such as nausea and vomiting, arrhythmias, and sore throat. Neonates underwent a higher percentage of major vascular or cardiac and intraabdominal procedures, and older children had a higher incidence of extremity procedures. Intraoperative cardiac arrest occurred most frequently in patients younger than 1 year of age (4 in 2901 procedures). Postoperatively, minor events such as nausea and vomiting were more common in older children, whereas respiratory events were more common in infants and younger children (Table 37-15). When compared with adult patients, children experienced different complications, which frequently extended well into the postoperative period. In a comparison of 2-year periods between 1982 and 1987, rates of intraoperative events were found to be stable, and the rate of postoperative complications decreased.

More recently, van der Griend and colleagues reported on 24-hour and 30-day mortality associated with 101,885 anesthetics administered to 56,263 children at the Royal Children's Hospital in Melbourne, Australia. They noted a rate of all-cause 24-hour mortality of 13.4 per 10,000 anesthetics and a 30-day all-cause mortality of 34.5 per 10,000 anesthetics. The incidence of deaths related to anesthesia was far lower, occurring at a rate of 1 in 10,188 or 0.98 cases per 10,000 anesthetics performed. In all of the 10 anesthetic-related deaths that the authors observed, preexisting medical conditions were assessed to have been a significant contributing factor.[136]

In contrast to efforts to determine the incidence and predictors of mortality among pediatric surgical patients, a number of investigators have focused on cardiac arrest in the context of pediatric anesthesia. For example, Flick and associates[137] studied patients younger than 18 years of age who underwent surgery at the Mayo Clinic and

TABLE 37-15 SUMMARY OF PERIOPERATIVE EVENTS BY AGE GROUP*

	<1 Month (*n* = 361)	1-12 Months (*n* = 2544)	1-5 Years (*n* = 13,484)	6-10 Years (*n* = 7184)	11+ Years (*n* = 5647)
Any intraoperative event	14.96	7.31	7.10	12.22	9.69
Any recovery room event	16.61	7.23	12.20	14.88	15.23
Any postoperative event					
Minor event†	13.57	10.30	20.32	31.49	32.44
Major event‡	23.82	7.51	3.26	3.37	3.33
Any event§					
Among patients seen	48.89	25.92	37.50	50.52	51.33
Among all patients	41.55	23.47	33.16	45.04	45.78

Adapted from Cohen MM, Cameron CB, Duncan PG: Pediatric anesthesia morbidity and mortality in the perioperative period, Anesth Analg *70:160, 1990.*

**All figures are given as the percentage of events per total anesthetics.*

†Includes nausea and vomiting, sore throat, muscle pain, headache, dental conditions, positional conditions, conditions involving extremities, eye conditions, croup, temperature, behavioral problems, thrombophlebitis, arterial line problem, awareness, and "other" problems.

‡Includes "other respiratory" conditions, cardiovascular disorders, nerve palsy, hepatic disorders, renal disorders, seizures, surgical complications, and death.

§Percentage of total anesthetics in which at least one event occurred in the intraoperative unit, recovery unit, or later during the postoperative period.

experienced perioperative cardiac arrest between November 1, 1988, and June 30, 2005. A total of 92,881 anesthetics were administered during the study period, 4242 (5%) of which were for the repair of congenital heart malformations. The incidence of perioperative cardiac arrest during noncardiac procedures was 2.9 per 10,000, and the incidence during cardiac procedures was 127 per 10,000. The incidence of perioperative cardiac arrest attributable to anesthesia was 0.65 per 10,000 anesthetics. The incidence of cardiac arrest and mortality was highest in neonates (0 to 30 days of life) undergoing cardiac procedures (incidence, 435 per 10,000; mortality, 389 per 10,000).

Investigators at the Children's Hospital of Boston used an established data registry that included all cardiac arrests from January 2000 through December 2005 related to surgery for congenital heart disease.[138] Over this time period, 41 cardiac arrests occurred in 40 patients during 5213 anesthetics for an overall frequency of 0.79%. Eleven cardiac arrests (26.8%) were classified as either likely ($n = 6$) or possibly related ($n = 5$) to anesthesia (21.1 per 10,000 anesthetics) but with no mortality; 30 cardiac arrests were categorized as being related to the procedure.

Efforts to understand the causes and outcomes of cardiac arrest in pediatric anesthesia patients have been aided by the development of large-scale clinical registries for research and quality improvement. In 1994, the Pediatric Perioperative Cardiac Arrest (POCA) Registry[139] was formed to determine the clinical factors and outcomes associated with cardiac arrest in anesthetized children. Institutions included in the registry submitted standardized data from each cardiac arrest occurring in an anesthetized child 18 years of age or younger. A total of 289 cardiac arrests occurred in the 63 institutions in the database during the first 4 years of the registry, 150 of which were judged to be related to anesthesia (1.4 per 10,000 anesthesia procedures), with a 26% mortality rate. Medication-related causes and cardiovascular causes of cardiac arrest were most common. Anesthesia-related cardiac arrest occurred most often in patients younger than age 1 year and in patients with severe underlying disease. The goal of the registry is similar to that of the closed claims studies—to identify the causes in this unique population and thereby formulate preventive strategies.

An update from the POCA Registry was published in 2007.[140] From 1998 through 2004, 193 arrests (49%) were related to anesthesia. Medication-related arrests accounted for 18% of all arrests. Cardiovascular causes of cardiac arrest (41%) were the most common, with hypovolemia from blood loss and hyperkalemia from transfusion of stored blood being the most common identifiable cardiovascular causes (Fig. 37-8). Among respiratory causes of arrest (27%), airway obstruction from laryngospasm was the most common. Vascular injury incurred during placement of central venous catheters was the most frequent equipment-related cause of arrest. Cardiovascular and respiratory causes occurred most commonly in the surgical and postsurgical phases, respectively.

In 2010, POCA investigators reported on anesthesia-related cardiac arrest in children with preexisting cardiac disease, comparing 245 cardiac arrests in children without heart disease with 127 cardiac arrests in children with cardiac conditions. Compared with children without cardiac disease, children with cardiac conditions were more often ASA physical status III, IV, or V and more often arrested from cardiovascular causes. Mortality was higher in children with heart disease than among children without heart disease (33% vs 23%) but did not differ when adjusted for ASA physical status classification.[141]

GERIATRICS

The relationship of age to operative risk has been a subject of scientific and clinical debate since the early days of modern surgery (also see Chapter 80). As the proportion of United States adults aged 65 years and older is anticipated to increase rapidly over the next 3 decades as a result of the aging of the post–World War II *baby boomer* generation, the nature of operative and anesthetic risk in older patients remains a vital area of inquiry.

A key issue in research on the safety of surgery and anesthesia among older adults is the determination of what constitutes *old age* from the perspective of perioperative risk. Multiple definitions have been used for advanced age, including age older than 65, 70, 80, or 90 years. For example, Denney and Denson[142] evaluated risk associated with surgery in patients older than 90 years of age. They reported 272 patients undergoing 301 operations at the University of Southern California Medical Center, finding a high perioperative mortality rate among older patients with serious bowel obstruction (63%). Taking a slightly different approach, Djokovic and Hedley-Whyte[143] studied outcome after surgery in 500 patients older than 80 years of age. They found that mortality was predicted by ASA physical status classification, with greater comorbid conditions associated with increasing risk. Myocardial infarction was the leading cause of postoperative death. Patients without significant comorbid diseases (ASA I classification) had a mortality rate of less than 1%.

Del Guercio and Cohn[144] investigated the value of preoperative invasive monitoring in obtaining hemodynamic and cardiopulmonary variables for predicting operative risk in the older adult. Among 148 consecutive

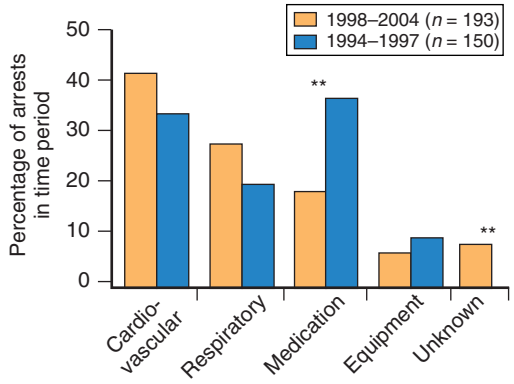


Figure 37-8. Causes of anesthesia-related cardiac arrest in the Pediatric Perioperative Cardiac Arrest (POCA) Registry from 1998 to 2004 versus 1994 to 1997. (**$P < .01$ 1998-2004 vs 1994-1997 by Z test). *(From Bhananker SM, Ramamoorthy C, Geiduschek JM, et al: Anesthesia-related cardiac arrest in children: update from the Pediatric Perioperative Cardiac Arrest Registry,* Anesth Analg *105:344-350, 2007.)*

patients older than 65 years of age who were treated in a surgical ICU, only 13.5% had normal physiologic measurements. Advanced and uncorrectable functional deficits were found in 63% of patients, and all in this group who underwent the planned surgery died.

Del Guerico and Cohn's work represented one of several studies that emphasized coexisting diseases, rather than aging itself, as the cause of apparently increased perioperative mortality among older adults. More recently, a growing body of literature has focused on the importance of functional disability and chronic geriatric syndromes, such as frailty and dementia, as determinants of postoperative outcomes among older individuals. Robinson and colleagues examined a cohort of 110 surgical patients with a mean age of 74 years, finding a 15% 6-month rate of mortality. Statistically significant predictors of 6-month mortality included impaired cognition, a recent fall, hypoalbuminemia, anemia, functional dependence, and comorbidity. Notably, functional dependence was the strongest predictor of 6-month mortality. Four or more markers in any one patient effectively predicted 6-month mortality (sensitivity, 81%; specificity, 86%).[145] Similarly, Finlayson and colleagues observed high rates of mortality after major gastrointestinal surgery among older nursing home residents versus the overall Medicare population; the high rates of mortality were likely attributable to high rates of comorbidity and functional disability within this population.[146]

In this context, research on the risks of surgery and anesthesia in the older adult now focuses on broader definitions of *risk* that include functional outcomes and quality of life, in addition to traditional morbidity and mortality outcomes. Most recently, Finlayson and colleagues examined 6822 older nursing home residents undergoing intestinal resections for colon cancer, noting a 53% 1-year mortality rate and a 24% rate of sustained decline in functional independence in activities of daily living among survivors. In multivariate regression, age older than 80 years, hospital readmission after surgical discharge, surgical complications, and functional decline before surgery all predicted functional decline at 1 year.[147] As this population continues to grow, these measures of outcome relative to patient goals of care will become increasingly important in determining optimal strategies for perioperative management.

RISKS DIRECTLY RELATED TO THE ANESTHETIC DRUG

Numerous studies have evaluated the influence of the choice of anesthetic on outcome, a question that is discussed throughout this book. From a global perspective, there does not appear to be a single best anesthesia technique for a particular surgery or group of surgeries. In a multivariate analysis by Cohen and co-workers[96] of 100,000 anesthesia procedures performed in Canada, the choice of drug did not provide any additional prognostic information for predicting mortality beyond that of patient disease and the surgical procedure. In univariate analysis, monitored anesthesia care appeared to be associated with worse outcomes; however, this association was attributable to the use of monitored anesthesia in sicker patients (see Table 37-12).

One question that has persisted within the anesthesia literature is the issue of whether anesthetic medications carry inherent toxicity (also see Chapter 26). For example, numerous recent discussions have focused on the potential toxicity of halothane and sevoflurane. In the case of halothane, concern focused on the potential for fulminant, potentially fatal, hepatic necrosis with this medication. After several case reports of hepatic necrosis after halothane anesthesia, a large retrospective study of 856,500 anesthesia procedures at 34 institutions was undertaken.[148-150] In all but nine cases, hepatic necrosis could be explained by other causes. Of the remaining nine cases, only seven received halothane. Halothane could be associated with hepatitis and hepatic failure, but the incidence was very low.

In the case of sevoflurane, concern has centered on the potential nephrotoxicity of its metabolite compound A. Although some laboratory studies have supported the contention that sevoflurane reacts with soda lime to form compound A and that this metabolite can lead to renal toxicity,[151,152] clinical studies have been unable to confirm this potentially detrimental effect[153,154] in the United States (also see Chapter 26) .

Numerous studies have attempted to define the *safest* anesthetic for high-risk patients. In the late 1980s, there was particular concern that isoflurane caused coronary steal in patients with coronary stenosis and collaterals and that this could result in myocardial ischemia.[155,156] A series of studies were conducted to evaluate the rate of perioperative cardiac morbidity and mortality in patients undergoing coronary artery bypass grafting to determine the importance of the agent used for general anesthesia.[157-160] Taken together, these studies demonstrated negligible differences in outcome, thus supporting the contention that multiple safe approaches to general anesthesia may exist for an individual context. Other studies have focused on the relative safety of general anesthesia versus neuraxial or regional techniques. Notably, multiple randomized trials and observational studies demonstrated improved outcome with regional rather than general anesthesia.[161,162] For lower extremity and pelvic surgery, regional anesthesia was associated with a lower incidence of graft thrombosis and deep venous thrombosis, as well as decreased bleeding. For patients undergoing vascular surgery, the primary finding was a lower incidence of graft thrombosis and the need for reoperation in patients undergoing infrainguinal bypass surgery; however, the largest of these studies was unable to demonstrate any difference in outcome based on anesthesia technique.[163-165] The rate of this complication was low in the total cohort in the largest trial, which made it impossible to detect any difference based on technique. Summarizing findings from several of these studies, Rodgers and co-workers[162] published an influential meta-analysis of regional versus general anesthesia. Neuraxial blockade was found to reduce postoperative mortality and other serious complications. The magnitude of some of these benefits remained uncertain. Discussion of regional versus general anesthesia is presented in Chapters 56 and 57.

RISKS RELATED TO SURGERY

The surgical procedure itself significantly influences perioperative risk. In virtually every study performed, emergency surgery is associated with additional risk. For example, in the study of Goldman and Caldera,[98] emergency surgery was associated with the second highest weight (i.e., number of points) after active signs of congestive heart failure. In this same study, intrathoracic and abdominal procedures were determined to have higher risk.

In some cases, the risk related to surgery is a function of the underlying disease processes and the stress related to the surgical procedure. As a category of surgical procedures, cardiovascular surgery has historically been associated with the highest risk of mortality and major morbidity. (The risks related to cardiac surgery are reviewed in Chapter 67.) Vascular surgery is among the highest-risk group of noncardiac procedures. Although aortic reconstructive surgery has traditionally been considered the procedure with the highest risk, infrainguinal procedures have shown a similar rate of cardiac morbidity in several studies.[166,167] In an attempt to analyze the cause of the high complication rate with a relatively peripheral procedure, L'Italien and associates[167] demonstrated that the extent of coronary artery disease is higher in patients undergoing infrainguinal procedures and most likely accounts for the excess morbidity and mortality.

Ashton and colleagues[168] evaluated perioperative morbidity and mortality in a cohort of patients at a Veterans hospital. Although vascular surgery was among the highest risk procedures, amputation was associated with the highest inhospital cardiac complication rate within this subgroup. This finding most likely represents the more severe nature of the cardiovascular disease in these patients and the prolonged hospitalization needed to facilitate recuperation. As in the study by Goldman and co-workers,[13] intraabdominal, thoracic, and orthopedic procedures were associated with increased risk. In another report, Ashton and colleagues[169] evaluated the rate of perioperative myocardial infarction in patients undergoing transurethral resection of the prostate. Despite the high frequency of coronary artery disease in this population, the incidence of perioperative myocardial infarction was only 1%.

Numerous studies have evaluated the perioperative complication rate related to superficial procedures. Backer and associates[170] evaluated the rate of perioperative myocardial reinfarction in patients who had histories of preexisting coronary artery disease and who underwent ophthalmologic surgery. They demonstrated that the rate of perioperative cardiac morbidity after ophthalmologic surgery was extremely low, even in patients with a recent myocardial infarction. Similar findings of the safety of ophthalmologic surgery have been reported by multiple other investigators.[69,171]

Eagle and associates[172] evaluated perioperative cardiac morbidity and mortality among patients who had been treated for coronary artery disease and subsequently underwent major noncardiac surgery. Among these patients, major vascular surgery was associated with the highest risk of myocardial infarction or death, with a combined incidence of morbidity and mortality greater than 5%. Procedures associated with a combined complication rate of 1% to 5% included intraabdominal, thoracic, and head and neck surgical procedures. Low-risk procedures included breast, skin, urologic, and orthopedic surgeries. Ultimately, these groupings of surgical procedures came to form the basis for the definitions of surgical risk published in the American College of Cardiology/American Heart Association joint guidelines on perioperative cardiovascular evaluation for noncardiac surgery.[173]

More recent statistical modeling efforts aimed at predicting postoperative outcomes have recognized the important contribution of the type of surgical procedure to the overall operative risk. Gupta and colleagues,[111] who reported on efforts to model the risk of cardiac events after noncardiac surgery, identified the type of surgical procedure as one of five key predictors of postoperative cardiac events. Glance and colleagues[117]developed a risk-prediction model for 30-day mortality after noncardiac surgery incorporating three key risk factors, one of which was an indicator of the risk associated specifically with the surgical procedure. Although these groups each used different methods of grouping procedures into categories of higher and lower risks, their common incorporation of information on procedure type into risk models to predict operative outcomes highlights the important contribution of the surgical procedure itself to overall operative risk.

RISKS RELATED TO THE LOCATION OF SURGERY AND POSTOPERATIVE MONITORING

Perioperative risk varies among hospitals for major procedures such as coronary artery bypass grafting and abdominal aortic aneurysm repair[9,10,174] (also see Chapters 67 and 69). Multiple studies have documented a relationship between surgical volume and mortality. Although surgical skill most certainly plays a role in the rate of complications and mortality, local factors may also play an important role. For example, low surgical volume may lead to less skilled anesthesia and postoperative care. The influence of each of these factors on overall morbidity and mortality is unknown.

Although the value of postoperative monitoring and care in an ICU has never been documented in a randomized clinical trial, many investigators have suggested that such care is one of the primary reasons for the improved morbidity and mortality in recent years. For patients undergoing major vascular surgery, several investigators have suggested that more intense postoperative monitoring could obviate the need for preoperative cardiac testing and revascularization.[173] One potential value of risk assessment is the identification of patients who could benefit from referral to clinical centers with more extensive perioperative resources. Patients with a low probability of perioperative morbidity and mortality could have surgery performed locally, and individuals at higher risk could receive benefit from transfer to a center with high surgical volume.

RISKS RELATED TO THE ANESTHESIA PROVIDER

Over the past decade a great deal of attention has been paid to the role and skill of the anesthesia provider on patient outcome. Since the initial introduction of ether, anesthesia has been administered by a diverse group of providers with variable levels of supervision including anesthesiologists, general medical officers, residents, CRNAs, and anesthesia assistants. The extent to which the skills and training of the individual anesthesia provider may affect outcomes has been assessed in a number of studies. In a now-classic paper, Slogoff and Keats[175] studied the association of perioperative myocardial ischemia and cardiac morbidity in patients undergoing coronary artery bypass grafting across multiple anesthesiologists working in a single practice. Notably, the rate of perioperative ischemia and infarction varied by anesthesiologist; for example, the care delivered by the seventh anesthesiologist in their sample was associated with a significantly higher rate of complications than the average for the rest of the group. The authors concluded that operator technique and experience may affect risk. Subsequent work has moved beyond efforts to demonstrate variability in anesthesia outcomes at the level of the individual practitioner to examine whether outcomes might vary across different models of anesthesia care. Arbous and coauthors reported a case-control study of major morbidity (coma) and mortality affecting a total of 869,463 procedures over a 1-year period in the Netherlands.[176] In this study, 807 cases of coma or death within 24 hours of anesthesia were identified and matched by age and sex to randomly selected control participants who underwent anesthesia temporally in close proximity to the matched case. The Hospital Characteristics Questionnaire, Procedure Questionnaire, and anesthesia and recovery records were used to examine the intraoperative and postoperative characteristics of cases and controls. Anesthesia practice in the Netherlands is described as a *flexible* system with one-on-one anesthesiologist coverage of induction and emergence, assisted by a nurse anesthetist or resident, and a two-on-one system during maintenance anesthesia, with a nurse or resident present in the room and an anesthesiologist in the vicinity. The authors elected to use multivariate analysis on data sets rather than match cases and controls for the anesthesia and physical risk categories or the type of surgical procedure (or both).

Included in the analysis were 807 cases and 883 control participants. Cases and controls, however, were not comparable for ASA classification, and controls were more likely than cases to have undergone minor elective procedures during regular working hours. Cases more frequently underwent cardiac and major vascular procedures, and controls more often underwent orthopedic, urologic, and ophthalmologic procedures. Of the 807 cases, 95% died within 24 hours, and 5% remained comatose, all of whom eventually died in the hospital. Postoperative mortality was 8.8% per 10,000 anesthetics, and postoperative coma occurred in 0.5% of 10,000 anesthetics. Confounding factors were, expectedly, ASA physical status, type of procedure, anesthetic technique, and hospital. Practice-level independent variables that were associated with a decreased risk for coma and death in 24 hours were (1) anesthesia equipment check performed with a checklist; (2) direct availability of an anesthesiologist during maintenance anesthesia by telephone, beeper, or walkie-talkie; (3) no change of anesthesiologist during the case (OR, 0.46); (4) presence of a full-time nurse anesthetist versus a part-time anesthetist during maintenance anesthesia; and (5) presence of two persons (anesthesiologist plus resident or nurse anesthetist) versus one person during emergence.

This study is one of very few that attempts to identify practice characteristics rather than specific drugs or techniques that have an impact on anesthesia outcomes. The size of this study and the nonambiguity of outcomes followed are important characteristics. The study suffers from several significant problems, however. Study groups were not comparable in important ways. The estimated incidence of underreporting of coma and death was 13% to 47%, and selective underreporting could have occurred. The finding that a change of anesthesiologist during maintenance anesthesia adversely affected patient outcomes contradicts findings in previous studies and requires further explanation. Confounding variables associated with a change of anesthesiologist during maintenance anesthesia could include case length and the time of day in which cases are performed. An intriguing finding is that practitioner characteristics affect outcomes; for example outcomes are better with more availability of an anesthesiologist and when nurse anesthetists practice full time rather than part time. This finding warrants further follow-up.

Several studies have attempted to evaluate the complication rates and risks associated with various care provider models. Bechtoldt,[177] as a member of the North Carolina Anesthesia Study Committee, evaluated 900 perioperative deaths that occurred in an estimated 2 million anesthesia procedures performed in North Carolina between 1969 and 1976. Data were obtained from the medical examiner's report, routine death certificates, and a questionnaire completed by the person who administered the anesthetic. The committee concluded that 90 of these deaths were related to anesthesia. Approximately one half of the anesthesia-related deaths took place in the surgical unit, including 19 that occurred on induction. With information obtained from a survey of hospitals, the committee then determined the relationship between mortality and anesthesia provider, based on the total number of procedures administered by each group. The lowest rate of anesthesia-related deaths (1 per 28,166 procedures) occurred in patients who received anesthesia from an anesthesia care team (physician anesthesiologist and CRNA), and the highest rate (1 per 11,432 procedures) was associated with anesthesia administered by a dentist; the rate for the nurse anesthetist–only cohort was intermediate (1 per 20,723). The large number of cases in which the care provider was unknown and reliance on hospital estimates of the number of cases performed by each group made interpretation of this study difficult.

The Stanford Center for Health Care Research[178] also evaluated the impact of the provider on the outcome of care. This group prospectively collected data

from 8593 patients undergoing 15 surgical procedures over a 10-month period (May 1973 through February 1974). Using a risk adjustment methodology, the actual patient outcome was compared with that predicted by the patient's health status and surgical procedure. The investigators reported that death plus severe morbidity was 11% higher than predicted in patients who received their care in a nurse anesthetist–only setting, 3% lower than predicted for physician-only care, and 20% lower than predicted for an anesthesia care team environment. Because of the small sample size, these findings did not reach statistical significance between groups.

The differences in outcome among anesthesia providers are extremely difficult to study from a methodologic standpoint. The impact of specific provider types may be greatest in specific situations. For example, there may be no difference in outcome for healthy individuals, particularly if no complications occur. In contrast, patients with significant comorbid diseases and those who sustain perioperative complications may benefit from having providers with specific skill sets. One way to study such issues is to evaluate the rate of survival after complications. Silber and colleagues[7] at the University of Pennsylvania studied the medical records of 5972 surgical patients randomly selected from 531 hospitals. They evaluated patient and hospital characteristics, including the number and type of physicians, board certification status, and ratio of care providers. The 30-day mortality rate correlated with patient characteristics. Failure to rescue (i.e., failure to prevent death) after an adverse event was inversely associated with the proportion of board-certified anesthesiologists on staff in each facility. Improved perioperative survival was significantly associated with the presence of an increased number of board-certified anesthesiologists.

As a follow-up to this study, Silber[179] used an administrative data set to compare the outcomes of surgical patients for whom anesthesia care was or was not personally performed or medically directed by an anesthesiologist. All older patients in Pennsylvania who underwent general surgical or orthopedic procedures between 1991 and 1994 were analyzed. The 30-day mortality rate and the mortality rate after complications (e.g., failure to rescue) were lower when anesthesiologists directed anesthesia care, even after adjustment for patient and hospital characteristics. Interpretation of the study was limited because the undirected group was small and included a large percentage of procedures in which no bill was submitted for anesthesia services. Administrative data sets, such as Medicare claims, allow the investigator to study a large number of patients, but significant limitations exist, related to the robustness of the data and the potential uncontrolled confounding factors. Therefore most investigators suggest that such studies are best at generating hypotheses rather than defining best practices.[180]

Silber and colleagues[181] used similar methodology to determine the importance of board certification on perioperative risk. Adjusted ORs for death (1.13; 95% CI, 1.00 to 1.26; $P < .04$) and for failure to rescue (1.13; 95% CI, 1.01 to 1.27; $P < .04$) were greater when care was delivered by noncertified, midcareer anesthesiologists.

Pine and co-workers evaluated mortality after eight specific surgical procedures.[182] Procedure-specific risk adjustment models (including institutional and geographic factors) were derived by stepwise logistic regression. Observed and predicted values by type of provider were not statistically significantly different. Hospitals without anesthesiologists had results similar to those facilities in which anesthesiologists provided or directed anesthesia care. The authors did not evaluate failure to rescue or cause of mortality.

More recently, work by Needleman and Minnick has appeared in the health services research literature comparing obstetric outcomes in facilities with different obstetric anesthesia staffing patterns[183]; although the authors observed consistent differences in maternal mortality or other quality indicators at facilities where nurse anesthetists practiced with minimal or no supervision by anesthesiologists versus anesthesiologist-only facilities, questions regarding risk adjustment and study design limit definitive interpretations of this work for policy making.[184] Similarly, a 2010 study by Dulisse and Cromwell suggested no changes in overall surgical patient outcomes in states that had enacted laws allowing nurse anesthetists to practice independently versus states that required anesthesiologist supervision.[185] However, as such new legislation was not associated with major changes in the number or types of surgery conducted without anesthesiologist supervision, Dulisse and Cromwell's work does not speak directly to the question of the gains or losses in safety associated with any specific provider type for a given type of surgery.

Ultimately, as concluded by Smith and associates[186] in a review of available published studies through 2004 on the influence of anesthesia providers, the relationship of patient outcomes to the type of anesthesia provider has not yet been conclusively demonstrated. Nurse anesthetists and other nonphysician providers are vital to the delivery of anesthesia care in the United States and elsewhere, and determining the optimal scope of practice for such providers remains an ongoing area of academic research and political debate.

RISKS TO THE ANESTHESIOLOGIST

Several potential risks to the anesthesiologist are related to the provision of care (also see Chapter 110), including medicolegal risk, the risk of an allergic reaction, and the risk of a needlestick injury and transmission of disease from the patient to the practitioner. (Medicolegal risks are described in Chapter 11.)

The risk for latex allergy, which can lead to a life-threatening reaction, is becoming increasingly apparent for anesthesiologists. Many anesthesiologists are sensitized to latex and need to apply appropriate precautions. The problem is that many sensitized individuals are asymptomatic. Brown and co-workers[187] studied 168 eligible anesthesiologists and nurse anesthetists working in the anesthesia department of The Johns Hopkins Hospital. The prevalence of latex allergy with clinical symptoms was 2.4% and that of latex sensitization without clinical symptoms was 10.1%. The prevalence of irritant or contact dermatitis was 24%. These data suggest that latex is an important problem to the anesthesiologist and that

transforming the hospital to a latex-free environment is needed.

The fact that anesthesiologists are at risk for contracting a disease from a patient has always been a concern. In a review of the literature, Berry and Greene[188] reported that at least 20 different pathogens have been transmitted through accidental needlestick injuries. In the past the risk was primarily hepatitis, but human immunodeficiency virus (HIV) is now also a great concern. Among anesthesia personnel in several studies conducted in the United States, hepatitis B seropositivity ranged from 12.7% to 48.6%, a rate at least four times greater than that in the general population.[189-191] The development of the hepatitis B vaccine has substantially reduced this risk. Hepatitis C virus has been identified as a major cause of posttransfusion hepatitis. Several cases of occupationally acquired hepatitis in health care workers have been reported.[192] Because signs of chronic liver infection develop in up to 50% of infected individuals, this represents a potentially serious problem.

Among the greatest fears of health care workers is the HIV infection. The risk of acquiring HIV is approximately 0.4% from a single percutaneous exposure to blood or bloody fluid from an HIV-infected patient.[193] At least one case of an anesthesiologist who was infected with HIV from a needlestick injury during the insertion of a central venous catheter into an HIV-positive patient has been reported.[194]

Several strategies have been developed to reduce the transmission of communicable diseases (also see Chapter 110). Although anesthesiologists traditionally think of the risk to the patient, they must now be aware of the risk to themselves. Widespread adoption of Universal Precautions should reduce the rate of infection; however, anesthesiologists have not widely accepted these recommendations. In a study of nine hospitals, 59% of the contaminated percutaneous injuries were preventable.[195] In a theoretic model of the risk for HIV infection, the 30-year occupational risk was estimated at 0.10% to 0.22% in low-prevalence areas and 8.26% to 13% in high-prevalence areas.[196] The researchers suggested that double-gloving practices may lead to reduced risk.

IMPROVING ANESTHESIA SAFETY

Over the past several decades, major improvements to the safety of anesthesia have been initiated. In 1984, Cooper, Kitz, and Pierce hosted a landmark International Symposium on Preventable Anesthesia Mortality and Morbidity in Boston. Approximately 50 anesthesiologists from around the world attended the meeting and, after much debate, established a series of definitions of outcome, morbidity, and mortality (Box 37-1). Beyond its specific conclusions, however, the symposium remains an event of major historical importance as a seminal early event in the movement to improve patient safety and as the context out of which the Anesthesia Patient Safety Foundation (APSF) was established. After its formal incorporation in October 1985, the APSF has since actively promoted a range of initiatives focused on fulfilling its mission to improve continually the safety of patients during anesthesia care by encouraging and conducting: (1) safety research and education, (2) patient safety programs and campaigns, and (3) national and international exchange of information and ideas. To this end, the APSF has focused on promoting research, practice improvement, and knowledge dissemination across a range of priority areas (Box 37-2). Overall, these efforts have stressed the potential for systems-level improvements, standardization of care processes, human-factors engineering, and simulation-based training to limit harms caused by preventable adverse events and errors in crisis management in the context of anesthesia care. Through this work, the APSF has come to serve as a leader in patient safety, not only in the context of anesthesia and perioperative care, but also more generally within medicine by establishing *patient safety* as a formal concept and discipline in medical care and serving as a model for other organizations such as the U.S. National Patient Safety Foundation.[197]

Alongside the efforts of the APSF, other prominent organizations, such as the ASA, have sought to improve the safety of anesthesia care through the creation and dissemination of standards and guidelines for clinical practice. In general, both standards and guidelines represent summations by clinicians of the available evidence about the benefits and risks of particular approaches to treatment. Typically, a practice standard implies that a therapy or practice should be performed for patients with a particular condition. Standards are approved only if an assessment of the probabilities and utilities of the group indicate that the decision to choose the treatment or a strategy would be virtually unanimous. At present, the ASA has established one set of practice standards for anesthesia care, which outline basic requirements for intraoperative monitoring.[198]

In contrast to practice standards, guidelines are intended to be more flexible than standards, but they should be followed in most cases. Depending on the patient, setting, and other factors, guidelines can and should be tailored to fit individual needs. Similar to standards, guidelines should be cost-effective methods. Specific guidelines have been created by the ASA for diverse

BOX 37-1 ***Proposed Definitions From the 1984 International Symposium on Preventable Anesthesia Morbidity and Mortality***

Outcome
- Normal
- Abandoned procedure
- Morbidity
- Death

Morbidity
- Unplanned, unwanted, undesirable consequence of anesthesia

Mortality
- Death that occurs before recovery from the effects of a drug or drugs given to facilitate a procedure
- Death that occurs during an attempt to relieve the pain of a condition
- Death that results from an incident that occurs while the drugs are effective

Adapted from Pierce EC Jr: The 34th Rovenstine Lecture. 40 years behind the mask: safety revisited, Anesthesiology *84:965, 1996.*

BOX 37-2 ***Selected Areas of Focus of the Anesthesia Patient Safety Foundation, 1985-2012***

- Use of anesthesia simulators for training and evaluation
- Improvement of standards for intraoperative monitoring
- Application of patient safety checklists to intraoperative care
- Promotion of standardized approaches to difficult airway management
- Prevention of medication-related adverse events
- Reuse and attempted resterilization of disposable anesthesia equipment
- Risks of outdated anesthesia machines without modern safety features
- Aiding the development of practice standards by the World Federated Societies of Anesthesiologists
- Surgery department crisis management, including teamwork, team training, and resource management
- *Production pressure*, causing dangerous omissions and cutting corners
- Intravenous procedural sedation by nonanesthesia personnel
- Contamination of medical gases and disruption of pipeline flow
- Contamination of intravenous medications
- Special risks of office-based anesthesia
- Patients with obstructive sleep apnea and their postoperative care
- Postoperative cognitive dysfunction (particularly in older adults)
- Possible long-term increase in morbidity and mortality after extensive general anesthesia
- Postoperative vision loss, especially in extensive prone spine surgery
- Wrong-site surgery
- Residual neuromuscular blockade and postoperative complications
- Protocols for assessing and managing adverse events
- Persistence of deaths from malignant hyperthermia
- Dangers and challenges in patients with coronary artery stents
- Maintenance of current protocols for the anesthesia machine checkout
- Possible impact of anesthesia management on cancer recurrence
- Persistence of surgical unit fires

Adapted from Eichhorn JH: The Anesthesia Patient Safety Foundation at 25: a pioneering success in safety, 25th anniversary provokes reflection, anticipation, Anesth Analg *114: 791-800, 2012.*

issues such as a difficult airway,[199] the use of the pulmonary artery catheter,[200] and the use of blood components[201] with the goal of defining the evidence on which optimal practice can be based. In a similar vein, the World Health Organization has recently placed an emphasis on the potential for a simple preoperative checklist, modeled on the processes used in other high-risk industries such as aviation, to reduce the rates of adverse events in the perioperative period.[202] Driven in part by the findings of improved outcomes with checklist use in a multicenter, international study by Haynes and co-authors,[203] such expanding interest in the use of standardized safety checks offers new potential opportunities to decrease the risk of anesthesia further.

Applying further insights gained from the aviation industry to anesthesia care, the APSF and other organizations have focused on developing simulation-based approaches to train anesthesia providers and to evaluate their decision-making capabilities in crisis situations.[204-208] To date, an extensive array of standardized scenarios have been developed for making comparisons among individuals, and research is ongoing to examine how best to use this technology in anesthesia training and recertification. Ultimately, such efforts, combined with improved monitoring of adverse outcomes through large outcomes databases and those now being assembled by the Multicenter Perioperative Outcomes Group and the Anesthesia Quality Institute, hold potential to improve the safety of anesthesia care continually on both a national and an international level.

SUMMARY

The risks related to anesthesia appear to have dramatically decreased over the past several decades. Clearly, death solely attributable to anesthesia is rare; rather, underlying patient disease and the nature and extent of surgery have a greater effect on overall outcome than do risks attributable to the anesthetic per se. Although these changes in the risk attributable to anesthesia could justifiably be considered a major achievement on the part of anesthesia providers over time, they also present a novel challenge to anesthesia providers to identify new opportunities to aid in more broadly decreasing both the morbidity and the mortality of surgical procedures and to aid in aligning the results of surgical interventions with individual patients' goals of care. At the same time, vigilance must be continued to maintain high standards of basic anesthesia care across both hospital- and nonhospital-based settings. Finally, anesthesia providers should play a role in systems-based thinking to improve perioperative care and the short- and long-term outcomes of patients undergoing surgery and anesthesia.

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Chapter 38

Preoperative Evaluation

DUMINDA N. WIJEYSUNDERA • BOBBIE-JEAN SWEITZER

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Key Points

- The anesthesia preoperative evaluation, which is the clinical foundation for guiding perioperative patient management, reduces perioperative morbidity and enhances patient outcome.
- The fundamental purpose of preoperative evaluation is to obtain pertinent information regarding the patient's medical history, formulate an assessment of the patient's perioperative risk, and develop a plan for any requisite clinical optimization.
- The preanesthesia evaluation should include a focused clinical examination, documentation of comorbid illness, reduction of patients' anxiety through education, assurance that preexisting medical conditions are optimally managed, selective referrals to medical specialists, ordering of preoperative investigations, initiation of interventions intended to decrease risk, discussion of aspects of perioperative care, arrangements for appropriate postoperative care, and recommendations to delay or cancel the surgical procedure, if deemed appropriate.
- Basic and complex medical diseases and syndromes that can influence anesthetic perioperative management require the anesthesiologist to be clinically knowledgeable and current in many aspects of internal medicine.
- Patients require appropriate preoperative diagnostic and laboratory studies consistent with their medical history, the proposed surgical procedure, and possible intraoperative blood loss. Routine preoperative testing is costly, is often clinically inappropriate, and cannot be justified.
- The anesthetic preoperative evaluation clinic can enhance operating room efficiency, decrease day-of-surgery cancellations or delays, reduce hospital costs, and enhance the quality of patient care.
- New and updated preoperative evaluation consensus and evidence-based guidelines published by multiple medical specialties have important influences on the preparation of patients for anesthesia and surgery.
- Anesthesiologists must be aware of, and be compliant with, increasing regulatory and reporting requirements involving preoperative issues by agencies such as The Joint Commission.
- The anesthesiologist is the perioperative medical specialist and thus is uniquely positioned to evaluate the risks associated with anesthesia or surgery, discuss these risks with the patient, and manage them perioperatively in collaboration with the surgical team and sometimes the referring physician.

Preoperative evaluation is a requisite component to administering any anesthetic. The practice and scope of preanesthesia evaluation have changed dramatically, largely because of a rapid transformation in hospital practice from admission of patients to the hospital the night before surgical procedures to admission on the morning of surgery. This practice led to a new approach to preoperative evaluation, which is a vital role of the perioperative physician. Accordingly, many anesthesiologists have expanded their responsibilities from providers of intraoperative anesthesia care to *perioperative medical specialists* who use their unique knowledge and experience to

manage medical complexities related to surgery.[1] Within the context of preoperative evaluation, this expanded role entails that anesthesiologists assume the leadership role in the assessment and optimization of patients who are being prepared for surgery.[2] This chapter provides a comprehensive discussion of the fundamental practice of preoperative assessment, as well as a review of related concepts, regulatory requirements, consensus-based guidelines, and clinical options.

EVOLUTION OF PREANESTHESIA EVALUATION

All patients requiring anesthesia for surgery undergo a preoperative evaluation by their anesthesia provider. Clinical practice with regard to this evaluation has changed substantially. Historically, anesthesiologists assessed their patients for the first time either just before the surgical procedure or on the day before it, whereas the remainder of preoperative evaluation and preparation was the responsibility of surgeons, primary care providers, or other medical specialists. In some countries, this approach remains the standard model of preanesthesia evaluation. Once the surgical procedure has been contemplated or actually decided, the trend has been for anesthesiologists increasingly to take on a leadership role in preoperative evaluation and preparation, well in advance of the scheduled surgical procedure.

Several factors have contributed to this change. First, few patients are admitted to the hospital before surgical procedures. Currently, most surgical procedures in the United States are performed on an outpatient or same-day admission basis, including major neurosurgical, cardiac, and radical cancer procedures. Little financial justification exists for the previous model of admitting patients to the hospital at least 1 day before surgery. Second, the increasing burden of medical comorbidity among surgical patients entails sufficient time between the preanesthesia evaluation and the planned surgical procedure to facilitate required testing, interventions, and medical optimization. Third, anesthesia care is no longer limited to the operating room. Indeed, many departments of anesthesiology have changed their official departmental titles to include anesthesia and perioperative care. The leadership role of anesthesiologists in preoperative evaluation is a logical extension of their role in perioperative medicine, especially given their unique expertise in the management of medical complexities related to anesthesia and surgery.

The development of the outpatient preoperative assessment clinic has been instrumental in facilitating increasing involvement of anesthesiologists in preoperative evaluation. These clinics also impose new clinical and organizational challenges. In an institution where most surgical patients are evaluated in the preoperative assessment clinic, anesthesiologists may have less time to evaluate often medically complex patients. Consequently, anesthesiologists must achieve a high level of efficiency and accuracy in the assessment of a patient's history, physical examination, and differential diagnosis, as well as in the planning of perioperative management. Conversely, in a hospital where only the highest-risk patients are referred for consultation at a preoperative assessment clinic, the anesthesia department must interact with surgical departments to establish general protocols that ensure capture of the information needed to perform anesthesia safely, as well as the appropriate selection of individuals who require preoperative anesthesia consultation.

In addition to changes in the scope and timing of the preanesthesia evaluation, this assessment has increasingly been influenced and governed by practice guidelines. For example, The Joint Commission mandates documentation of a history and physical examination for any surgical patient within 30 days before the planned procedure, as well as reassessment within the 48-hour period immediately preceding the surgical procedure. The American Society of Anesthesiologists (ASA) published specific standards for the conduct of preoperative anesthesia evaluation.[3] In addition, several other specialty societies published practice guidelines specifically relating to the preoperative management of medical issues in surgical patients.[4-7]

GOALS AND BENEFITS OF PREANESTHESIA EVALUATION

The preoperative evaluation can help influence and thereby improve perioperative care (Fig. 38-1). Conversely, *inadequate* preoperative evaluation was identified as a clear contributing factor for 3% of perioperative adverse events captured by the Australian Incident Monitoring Study (AIMS) database.[8]

The goals of the preanesthesia evaluation are twofold: first, to ensure that patients can safely tolerate anesthesia for planned surgical procedures; and second, to mitigate risks associated with the overall perioperative period, such as postoperative pulmonary or cardiac complications. In pursuit of these goals, the preanesthesia evaluation offers opportunities to perform focused clinical examinations, better document comorbid illness, reduce the patient's (and family's) anxiety through education, optimize preexisting medical conditions, make selective referrals to medical specialists (e.g., pulmonologists, cardiologists), order specialized preoperative investigations (e.g., cardiac stress tests), initiate interventions intended to decrease perioperative risk (e.g., β-adrenergic blockers), discuss aspects of perioperative care (e.g., anticipated risks, fasting guidelines, regional anesthesia), and arrange appropriate levels of postoperative care (e.g., admission to a critical care unit). When the patient is at very high risk for adverse perioperative outcomes, the anesthesiologist may recommend an alternative nonoperative or less invasive treatment. The preanesthesia evaluation may sometimes identify previously unrecognized medical conditions (e.g., hypertension) that may not significantly affect immediate perioperative risks, but that warrant subsequent follow-up by appropriate health care professionals.[5]

Preanesthesia evaluation has measurable benefits. Anesthesiologist-led preoperative evaluation is associated with more selective ordering of laboratory tests and

specialist referrals than is evaluation led by surgeons or primary care physicians, thereby leading to reduced health care costs.[9-12] Additional benefits have been shown when patients are assessed in an outpatient preoperative assessment clinic, including reduced levels of patients' anxiety,[13] improved acceptance by patients of regional anesthesia,[14] fewer case cancellations on the day of surgery,[9,15-17] shorter duration of hospitalization,[14,16,17] and lower hospital costs.[16]

ROLE OF THE MEDICAL CONSULTANT IN PREOPERATIVE EVALUATION

The use of preoperative medical consultation for surgical patients varies across institutions, likely depending on the expertise in perioperative medicine among clinicians performing preanesthesia assessments. Given the inadequate degree of exposure to preoperative assessment at many anesthesia residency programs,[18] some anesthesiology departments may prefer that medical specialists and hospitalists take primary responsibility for most preoperative evaluations at their centers. When anesthesiologists who perform preoperative evaluations do have improved comfort levels with respect to the ordering and interpretation of electrocardiograms (ECGs), special tests, or stress ECGs, rates of preoperative medical consultations are substantially reduced.[12]

Medical consultants have a clear role in the preoperative care of selected surgical patients. Potential reasons for medical consultations include management of unstable medical conditions before elective surgery (e.g., unstable angina), preoperative optimization of poorly controlled medical diseases (e.g., treatment of asthma exacerbation), facilitation of clinically relevant preoperative diagnostic workups (e.g., coronary angiography following high-risk stress test results), or guidance regarding the perioperative management of an uncommon medical disorder (e.g., severe hyponatremia). Preoperative consultation by medical specialists or hospitalists can also help facilitate postoperative comanagement by these same individuals.[19] The comanagement model for postoperative care of surgical patients is increasingly common,[20] although its benefits for patients' outcomes and costs remains unclear.[21-24]

The effects of preoperative medical consultation on patients' outcomes are also mixed. A randomized trial of outpatient preoperative evaluation demonstrated fewer last-minute cancellations of surgical procedures but no difference in hospital length of stay, as well as an increase in consultations.[25] In addition, medical consultation was associated with increases in specialized testing,[26] costs,[27] hospital length of stay,[26,27] and mortality.[26] Conversely, a transition from an anesthesiologist-led to a hospitalist-led preoperative assessment clinic reduced hospital length of stay in high-risk patients.[28] Potential reasons

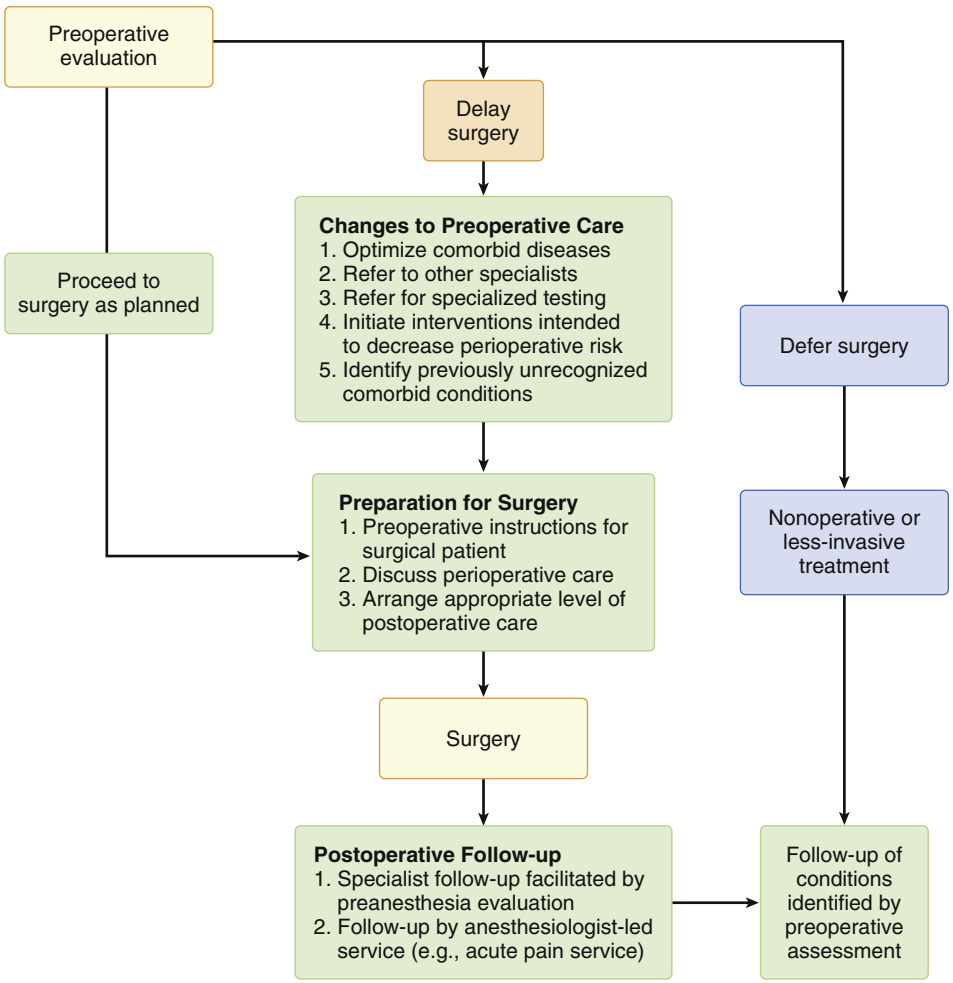


Figure 38-1. Mechanisms by which preoperative evaluation can help influence and improve perioperative care.

for this variable effect may be the absence of actual recommendations in many medical consultations,[29] as well as disagreements among medical specialists, anesthesiologists, and surgeons on the intended purpose of these consultations.[30] In addition, increased burden of comorbidity is a very small determinant of whether patients are referred for preoperative medical consultations,[31] a finding suggesting that most consultations are not sought for higher-risk patients who most warrant the involvement of medical specialists.

DETECTING DISEASE IN PREOPERATIVE EVALUATION

The *clinical examination*, consisting of the history and physical examination, is often all that is required to make a diagnosis or eliminate alternative hypotheses. In a study of patients in a general medical clinic, 56% of correct diagnoses were made on the basis of the history alone; this percentage increased to 73% with the physical examination. In patients with cardiovascular disease, the history established the diagnosis two thirds of the time, with physical examination contributing to one fourth of diagnoses.[32] Diagnostic tests, such as chest radiographs (x-ray studies) and ECGs, helped with only 3% of diagnoses, whereas special tests (e.g., cardiac stress tests) assisted with 6%. In respiratory, urinary, and neurologic conditions, history taking is the most important diagnostic method. The skill of performing a clinical examination derives from pattern recognition acquired by seeing patients and assimilating their stories and outcomes. The diagnostic acumen of physicians reflects their ability to integrate and develop an overall impression, rather than just reviewing a compilation of facts.

IMPORTANCE OF THE MEDICAL HISTORY

The variability in the words that patients and physicians use to describe symptoms is a common problem. The use of lay language and the recording of symptoms in ordinary words lead to greater interobserver agreement among practitioners and can prevent communication errors that are common in medical care. Common errors occur when diagnostic labels such as "angina" are written in the medical record when the patient actually complained of "chest pain." Conversely, patients rarely describe true angina or myocardial infarction (MI) as chest *pain*. More likely, they present with complaints of tightness or squeezing, often in their upper abdomen, shoulder, or neck. Medical interviewers should therefore not be surprised that patients may deny ever having chest *pain* when this is the only noun used when inquiring about symptoms of angina. Obtaining the patient's history is not simply asking questions but asking the right questions, often in a variety of ways, and interpreting and carefully recording the answers. Thorough histories assist in planning appropriate safe anesthesia care and are more accurate and cost effective in establishing diagnoses than are screening laboratory tests.

COMPONENTS OF THE MEDICAL HISTORY

The important components of the anesthesia history are shown in Figure 38-2. The form can be completed by anesthesia staff during an in-person or telephone interview with the patient. Alternatively, the patient can complete the form, either in person (paper or electronic version) or remotely through a Web-based program.

The classic history of present illness, or HPI, as it relates to preanesthesia evaluation starts with the indication for surgery and the planned procedure. The development of the surgical condition and any prior related therapies need to be clear. Current and past medical problems, previous surgical procedures, types of anesthesia, and any anesthesia-related complications must be noted. A simple notation of diseases or symptoms such as hypertension, diabetes mellitus, coronary artery disease (CAD), shortness of breath, or chest pain is rarely sufficient. Rather, the severity, stability, exacerbations (current or recent), prior treatments, and planned interventions should be clear. The extent, degree of control, and the activity-limiting nature of the problems are equally of interest. The patient's responses to these initial questions elicit further inquiry to establish a complete history.

Prescription and over-the-counter medications (including supplements and herbal medications) should be carefully recorded, along with their dosages and schedules. This includes any recent but currently interrupted medications because this could lead to the recognition of important issues (e.g., recent corticosteroid therapy). It is necessary to inquire about allergies to medications and other substances (e.g., latex, radiographic dye), with special emphasis on the patient's response to the exposure. Patients often claim an "allergy" to a substance when, in reality, the reaction was an expected side effect (e.g., nausea or vomiting with narcotics). The patient's use of tobacco, alcohol, or illicit drugs must be documented. Quantitative documentation of tobacco exposure using pack-years (number of packs of cigarettes smoked per day, multiplied by the number of years of smoking) is best. For example, if an individual has smoked 2 packs of cigarettes daily for the last 10 years, this is recorded as 20 pack-years of tobacco use.

A personal or family history of pseudocholinesterase deficiency, malignant hyperthermia (MH), or a suggestion of MH (hyperthermia or rigidity during anesthesia) in a patient or family member must be clearly documented to allow appropriate arrangements to be made before the day of surgery (see also Chapter 43). Records from previous anesthetic experiences may clarify an uncertain history.

A screening review of systems may identify symptoms that could lead to the establishment of previously undiagnosed conditions. Prime emphasis is on airway abnormalities; a personal or family history of adverse events related to anesthesia; and symptoms of cardiovascular, pulmonary, hepatic, renal, endocrine, or neurologic disease. A report of a patient who has experienced excessive sore throat, dental injuries, or "the need to have a small tube" with previous anesthetic cases may be an indication of previous difficulty with airway management. Questioning the patient about snoring and daytime

somnolence may suggest undiagnosed sleep apnea, which has implications for anesthesia management (see the later section on obstructive sleep apnea [OSA] and also Chapter 14). The presence of any two of the following findings increases the chance that a patient has sleep apnea: snoring, daytime somnolence, sleepiness, hypertension, and obesity. The presence of chest discomfort (pain, pressure, tightness), as well as its duration, precipitating factors, associated symptoms, and relieving factors, could be important. All diagnoses, diagnostic tests, therapies, and names of treating physicians should be documented. Any history of shortness of breath, both with exertion or when lying flat (i.e., orthopnea), and peripheral edema could signal potential postoperative problems. Does the patient have a history of heart murmurs? Were diagnostic studies performed to evaluate the murmur? The cardinal symptoms of severe aortic stenosis are angina, heart failure, and syncope, although decreased exercise tolerance and exertional dyspnea are more likely. A history of significant heartburn or reflux, especially after a fasting duration comparable to preoperative fasting, is important. Women of childbearing age need to recall their last menstrual period and their likelihood of being pregnant. This history is more reliable if the female patient, especially if a minor child, is questioned in privacy.

Patient's name_____Age_____Sex_____Date of surgery_____

Planned operation _____Surgeon_____

Primary care doctor/phone #_____ Other physicians/phone #s_____

1. Please list **all operations** (and approximate dates)

a. _____ d. _____

b. _____ e. _____

c. _____ f. _____

2. Please list any **allergies** to medicines, latex, or other (and your reactions to them)

a. _____ c. _____

b. _____ d. _____

3. Please list **all medications** you have taken in the last month (include over-the-counter drugs, inhalers, herbals, dietary supplements, and aspirin)

Name of Drug	Dose and How Often	Name of Drug	Dose and How Often
a.		f.	
b.		g.	
c.		h.	
d.		i.	
e.		j.	

(Please check YES or NO and circle specific problems)	YES	NO
4. Have you taken steroids (prednisone or cortisone) in the last year?	☐	☐
5. Have you *ever* smoked? (Quantify in _____ packs/day for _____ years)	☐	☐
Do you still smoke?	☐	☐
Do you drink alcohol? (If so, how much?) _____	☐	☐
Do you use or have you ever used any illegal drugs? (we need to know for your safety)	☐	☐
6. Can you walk up one flight of stairs without stopping?	☐	☐
7. Have you had any problems with your heart? **(circle)** (chest pain or pressure, heart attack, abnormal ECG, skipped beats, heart murmur, palpitation, heart failure [fluid in the lungs], require antibiotics before routine dental care)	☐	☐
8. Do you have high blood pressure?	☐	☐
9. Have you had any problems with your lungs or your chest? **(circle)** (shortness of breath, emphysema, bronchitis, asthma, TB, abnormal chest x-ray)	☐	☐
10. Are you ill now or were you recently ill with a cold, fever, chills, flu or productive cough? Describe recent changes _____	☐	☐

A

Figure 38-2. A and **B,** Sample patient preoperative history form. *ECG,* Electrocardiogram; *TB,* tuberculosis; *TMJ,* temporomandibular joint.

(Please check YES or NO and circle specific problems)	**YES**	**NO**
11. Have you or anyone in your family had serious bleeding problems? **(circle)** (prolonged bleeding from nosebleed, gums, tooth extractions, or surgery)	☐	☐
12. Have you had any problems with your blood (anemia, leukemia, sickle cell disease, blood clots, transfusions)?	☐	☐
13. Have you ever had problems with your: **(circle)**	☐	☐
Liver (cirrhosis, hepatitis, jaundice)?	☐	☐
Kidney (stones, failure, dialysis)?	☐	☐
Digestive system (frequent heartburn, hiatus hernia, stomach ulcer)?	☐	☐
Back, neck or jaws (TMJ, rheumatoid arthritis)?	☐	☐
Thyroid gland (underactive or overactive)?	☐	☐
14. Have you ever had: **(circle)**	☐	☐
Seizures, epilepsy, or fits?	☐	☐
Stroke, facial, leg or arm weakness, difficulty speaking?	☐	☐
Cramping pain in your legs with walking?	☐	☐
Problems with hearing, vision or memory?	☐	☐
15. Have you ever been treated for cancer with chemotherapy or radiation therapy? **(circle)**	☐	☐
16. Women: Could you be pregnant? Last menstrual period began: _____	☐	☐
17. Have you ever had problems with anesthesia or surgery? **(circle)** (severe nausea or vomiting, malignant hyperthermia [in blood relatives or self], prolonged drowsiness, anxiety, breathing difficulties, or problems during placement of a breathing tube)	☐	☐
18. Do you have any chipped or loose teeth, dentures, caps, bridgework, braces, problems opening your mouth, swallowing or choking? **(circle)**	☐	☐
19. Do your physical abilities limit your daily activities?	☐	☐
20. Do you snore?	☐	☐

21. Please list any medical illnesses not noted above:

_____

_____

_____

_____

22. Additional comments or questions for nurse or anesthesiologist?

_____

_____

B

Figure 38-2, cont'd

The status of the patient's cardiorespiratory fitness or functional capacity helps determine whether additional preanesthetic evaluation should be performed and may predict perioperative outcomes. Exercise or work activity can be quantified in metabolic equivalents of the task (METs), which is a measure of the volume of oxygen consumed during an activity. A proposed scheme for estimating METs is presented in Table 38-1. Poor exercise capacity may be the cause or result of cardiopulmonary disease. Although lack of exercise may increase the risk of developing cardiac disease, preexisting cardiopulmonary disease can also prevent an individual from exercising. For example, patients with peripheral arterial disease (PAD) are limited by intermittent claudication, and patients with ischemic heart disease may complain of chest discomfort with exertion. Patients may not volunteer this information until asked why they cannot walk more than a certain distance or climb stairs. A patient's self-reported inability to perform average levels of exercise (i.e., 4 to 5 METs) increases the risk of perioperative complications.[33,34] Nonetheless, the magnitude of the association is relatively weak.

A general review of all organ systems should also be done. For example, asking patients whether they ever had problems with their heart, lungs, kidneys, liver, nervous system or whether they have had cancer, anemia, bleeding problems or have ever been hospitalized for any reason often prompts recall of medical problems.

Similarly, obtaining a complete list of previous surgical procedures can help complete the medical history. Finally, a review of records from primary care physicians, specialists, or the hospital can reveal any issues the patient may not recall.

PHYSICAL EXAMINATION

At a minimum, the preanesthetic examination includes vital signs (i.e., arterial blood pressure [BP], heart rate [HR], respiratory rate, oxygen saturation), height, and weight. Body mass index (BMI) is calculated from the height and weight and is more accurate than weight in establishing obesity. Online BMI calculators are found at http://www.cdc.gov/nccdphp/dnpa/bmi/index.htm or http://www.nhlbi.nih.gov/guidelines/obesity/BMI/bmicalc.htm. The formulas for calculating the BMI are as follows:

English formula:

$$\text{BMI} = \left(\frac{\text{Weight in pounds}}{(\text{Height in inches}) \times (\text{Height in inches})} \right) \times 703$$

Metric formula:

$$\text{BMI} = \left(\frac{\text{Weight in kilograms}}{(\text{Height in meters}) \times (\text{Height in meters})} \right)$$

or:

$$\text{BMI} = \left(\frac{\text{Weight in kilograms}}{(\text{Height in centimeters}) \times (\text{Height in centimeters})} \right) \times 10^4$$

A BMI of 40 or more defines extreme obesity, a BMI of 30 to less than 40 defines obesity, and a BMI of 25 to less than 30 defines an overweight person. A scheme for classifying children and adults based on BMI is presented in Table 38-2. An increased BMI is predictive of difficulties with airway management, both bag-mask ventilation and endotracheal intubation. In addition, obesity is associated with development of chronic diseases such as heart disease, cancer, or diabetes[35] (see also Chapter 71).

Patients often have increased arterial BP during the preoperative visit, even without a prior history of hypertension. This finding may be caused by anxiety, or the patient may have forgotten to take his or her usual dose of antihypertensive medication before an appointment or procedure. Thus, this single reading may not reflect the patient's usual BP control. Repeating the BP measurement or obtaining previous readings, either from medical records or asking the patient what his or her "usual" BP measurements are, can be informative.

From the anesthesiologist's perspective, inspection of the airway may be the single most important component of the physical examination (see Chapter 55). Without specialized training in airway evaluation and management, it is challenging for nonanesthesiologists to perform an adequate assessment. The components of the airway examination are presented in Box 38-1. Documentation of an airway examination includes the Mallampati score (Fig. 38-3), status of teeth, degree of neck mobility (especially extension), neck circumference (increased size predicts difficulty with laryngoscopy), thyromental distance, body habitus, and pertinent deformities.[36] Because of the potential for occasional dental injuries during anesthesia, a thorough documentation of preexisting tooth abnormalities is useful (Fig. 38-4). Patients with the following characteristics have potential difficulty with ventilation through a bag-mask apparatus.

- Age of 55 years or more
- BMI exceeding 26
- Lack of teeth
- Beard
- History of snoring

Patients with the following characteristics may pose a challenge to ventilate by any mechanism:

- OSA (see also Chapter 14)
- History of snoring
- Obesity (see also Chapter 71)

TABLE 38-1 METABOLIC EQUIVALENTS OF FUNCTIONAL CAPACITY

METs	Equivalent Level of Exercise
1	Eating, working at computer, or dressing
2	Walking down stairs, walking in your house, or cooking
3	Walking one or two blocks on level ground
4	Raking leaves or gardening
5	Climbing one flight of stairs, dancing, or bicycling
6	Playing golf or carrying clubs
7	Playing singles tennis
8	Rapidly climbing stairs or slowly jogging
9	Jumping rope slowly or cycling moderately
10	Swimming quickly, running, or jogging briskly
11	Skiing cross country or playing full court basketball
12	Running rapidly for moderate to long distances

Modified from Jette M, Sidney K, Blumchen G: Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity, Clin Cardiol *13:555-565, 1990.*

MET, Metabolic equivalent (1 MET is equivalent to oxygen consumption of 3.5 mL/minute/kg body weight).

TABLE 38-2 CLASSIFICATION SCHEME FOR BODY MASS INDEX

Body Mass Index	Weight Status
Adults >20 Yr Old	
BMI <18.5	Underweight
BMI 18.5-24.9	Normal
BMI 25.0-29.9	Overweight
BMI ≥30.0	Obese
For Children and Teens	
BMI for age <5th percentile	Underweight
BMI for age 5th-<85th percentile	Normal
BMI for age 85th-<95th percentile	At risk of overweight
BMI-for-age ≥95th percentile	Overweight

From Centers for Disease Control and Prevention: <http://www.cdc.gov/> (Accessed 26.02.14.)

BMI, Body mass index.

- Increased neck circumference (>17 inches in men or >16 inches in women)
- Thyromental distance less than 7 cm with head in maximum extension
- Higher Mallampati scores (see Fig. 38-3)
- Large tongue
- Inability to protrude the mandible or lower teeth in front of the upper teeth
- Facial and neck deformities from previous surgery
- Previous head and neck radiation
- Head and neck trauma
- Congenital abnormalities of the head and neck
- Rheumatoid arthritis
- Down syndrome
- Scleroderma
- Cervical spine disease or previous cervical spine surgery

Examination of previous anesthetic records is critical, and extensive effort should be expended to obtain these records. Patients with documented difficult airways should be urged to obtain proper medical alert identification. When challenging airways are identified, advance planning ensures that necessary equipment and skilled personnel are available on the day of surgery.

An evaluation of the heart, lungs, and skin is necessary, as well as further focus on the organ systems involved with disease as reported by the patient. Auscultation of the heart and inspection of arterial pulses, veins (peripheral and central), and any edema in the extremities help establish diagnoses and predict perioperative risk. In addition, inspection of peripheral veins can help assess the ease of intravenous access. If intravenous access sites are limited, possible central line placement can be discussed with the patient, or arrangements can be made for assistance from the interventional radiology department. The auscultatory examination should assess for murmurs, rhythm disturbances, and evidence of volume overload. Important physical findings include third or fourth heart sounds, rales, jugular venous distention, ascites, hepatomegaly, and dependent edema. As opposed to patients' self-reporting of exercise tolerance, direct observation of a patient climbing flights of stairs can provide very useful prognostic information. The observed inability to climb one to two flights of stairs predicts a significantly increased risk of postoperative morbidity or mortality,[37] and it may help guide the need for further specialized testing, such as pulmonary function tests (PFTs) or cardiac stress testing. Examination of the pulmonary system should include auscultation for wheezing and for decreased or abnormal breath sounds, as well as inspection for cyanosis, clubbing, accessory muscle use, and respiratory effort. Obesity, hypertension, and large neck circumference are associated with an increased risk of OSA.[38]

A basic neurologic examination includes documenting deficits in mental status, speech, cranial nerves, gait, and motor and sensory function. For selected patients (e.g., those with deficits or disease or patients undergoing neurosurgery), a more extensive or focused neurologic examination should document specific preexisting abnormalities that may aid in diagnosis or interfere with positioning. In addition, definition of a baseline state can be compared with the postoperative state for identification of new deficits and to aid in defense of any future legal claims. Auscultation for carotid bruits is also important, especially in patients with a history of head or neck irradiation, strokes, or transient ischemic attacks.

BOX 38-1 ***Components of the Airway Examination***

Length of the upper incisors
Condition of the teeth
Relationship of the upper (maxillary) incisors to the lower (mandibular) incisors
Ability to advance the lower (mandibular) incisors in front of the upper (maxillary) incisors
Interincisor or intergum (if edentulous) distance
Visibility of the uvula
Presence of heavy facial hair
Compliance of the mandibular space
Thyromental distance
Length of the neck
Thickness or circumference of the neck
Range of motion of the head and neck

PREOPERATIVE EVALUATION OF PATIENTS WITH COEXISTING DISEASE

For some conditions commonly seen in the preanesthetic assessment clinic, preoperative intervention may be important (see also Chapter 39). Identification of these comorbid conditions often presents an opportunity for the anesthesiologist to intervene to decrease risk. These conditions are best managed before the day of surgery,

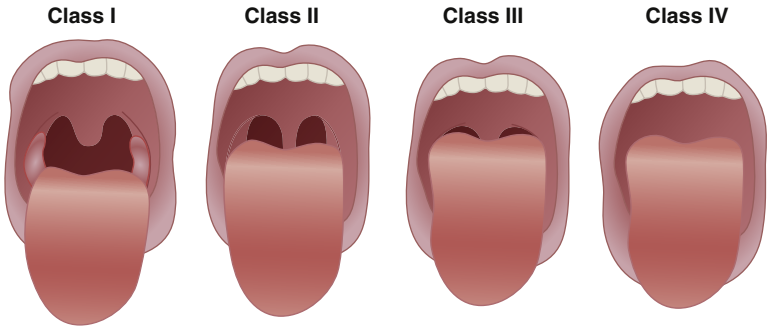


Figure 38-3. Mallampati classification: class I, soft palate, fauces, entire uvula, pillars; class II, soft palate, fauces, portion of uvula; class III, soft palate, base of uvula; class IV, hard palate only. *(Redrawn from Bair AE, Caravelli R, Tyler K, et al: Feasibility of the preoperative Mallampati airway assessment in emergency department patients,* J Emerg Med *38:677-680, 2010.)*

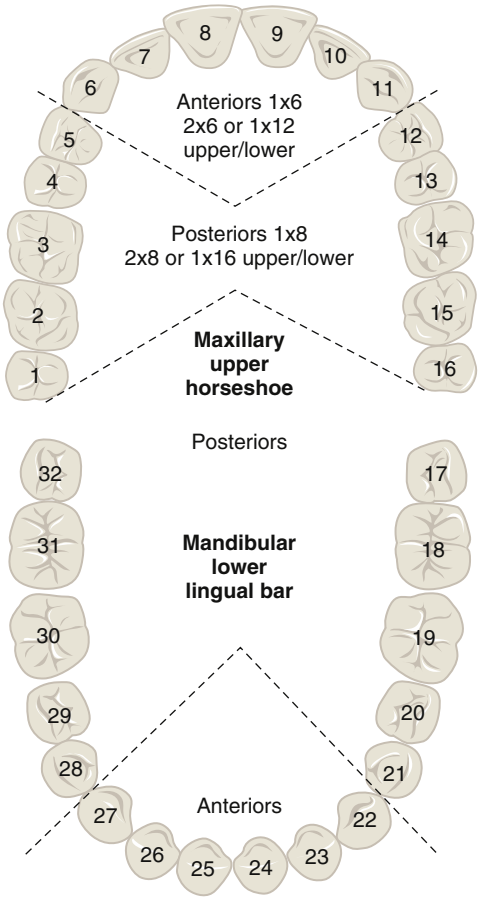


Figure 38-4. Tooth numbering.

thus allowing ample time for thoughtful evaluation, consultation, and planning.

CARDIOVASCULAR DISEASE

Cardiovascular complications are very common serious perioperative adverse events (see Chapter 37), and they account for almost half of all perioperative deaths.[39] In addition, serious myocardial injury occurs in approximately 8% of patients who undergo major surgery.[39] Some perioperative interventions may modify risks for cardiovascular morbidity and mortality.[5,40,41]

Hypertension

Hypertension, which is defined by two or more arterial BP measurements greater than 140/90 mm Hg, affects 1 billion individuals worldwide and increases with age. In the United States, 25% of adults and 70% of patients more than 70 years old have hypertension; of these individuals, less than 30% are adequately treated. The duration and severity of hypertension are highly correlated with subsequent end-organ damage, morbidity, and mortality. Ischemic heart disease is the most common form of organ damage associated with hypertension. Each incremental increase of systolic BP of 20 mm Hg or diastolic BP of 10 mm Hg above 115/75 doubles the lifetime risk for cardiovascular disease in individuals 40 to 70 years of age. Although the degree of preoperative hypertension is associated with increased risks of postoperative death and MI,[42] hypertension is associated only with a relatively small 1.3-fold increase in perioperative cardiac risk.[43] Other end-organ manifestations of hypertension are heart failure, renal insufficiency, and cerebrovascular disease.

Preoperative evaluation can help identify causes of hypertension, other cardiovascular risk factors, and end-organ damage. Paroxysmal hypertension or hypertension in young individuals should prompt a search for coarctation, hyperthyroidism, pheochromocytoma, or illicit drug use (e.g., cocaine, anabolic steroids). The physical examination focuses on the cardiovascular system, pulses, vital signs (BP measurement must be repeated and previous records obtained to establish long-term values), thyroid gland, and signs of excessive intravascular volume. Other than essential hypertension, the patient should be asked about episodic tachycardia, palpitations, and syncope. In addition, the physical examination should include BP measurements in both arms, auscultation of bruits, and examination of pulses in both upper and lower extremities. Additional testing should be directed by history and physical examination. Patients with long-standing, severe, or poorly controlled hypertension need an ECG and determinations of blood urea nitrogen (BUN) and creatinine, depending on the surgical procedure. Individuals receiving diuretics may require evaluation of electrolytes. Patients with significant left ventricular hypertrophy (LVH) on their ECG, especially with strain pattern, should be assessed for associated CAD. Patients suspected of hyperthyroidism require thyroid function tests (see also Chapter 39).

Elective surgery should be delayed for severe hypertension (diastolic BP >115 mm Hg or systolic BP >200 mm Hg) until BP is less than 180/110 mm Hg. Nonetheless, current guidelines from the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) instead suggest that the potential benefits of delaying surgery to optimize antihypertensive treatment should be weighed against the risks of delaying the surgical procedure.[5] Specifically, the literature is generally unclear on whether such delays help improve perioperative outcomes.[43] For example, a randomized trial of 898 patients with inadequately treated chronic hypertension without acute symptoms demonstrated no advantage of delaying surgery to optimize long-term BP control, when compared with simply proceeding to surgery with short-term BP treatment.[44]

The perioperative period should also be viewed as an excellent opportunity to alter both long-term and short-term consequences of diseases.[5] Thus, although surgery may not have to be delayed to optimize BP control, appropriate referrals should be made so that patients will have future appropriate postoperative management of inadequately managed hypertension. In general, all long-term antihypertensive treatment should be continued preoperatively. The only potential exceptions are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Preoperative administration of these medications is associated with increased risks for intraoperative hypotension.[45]

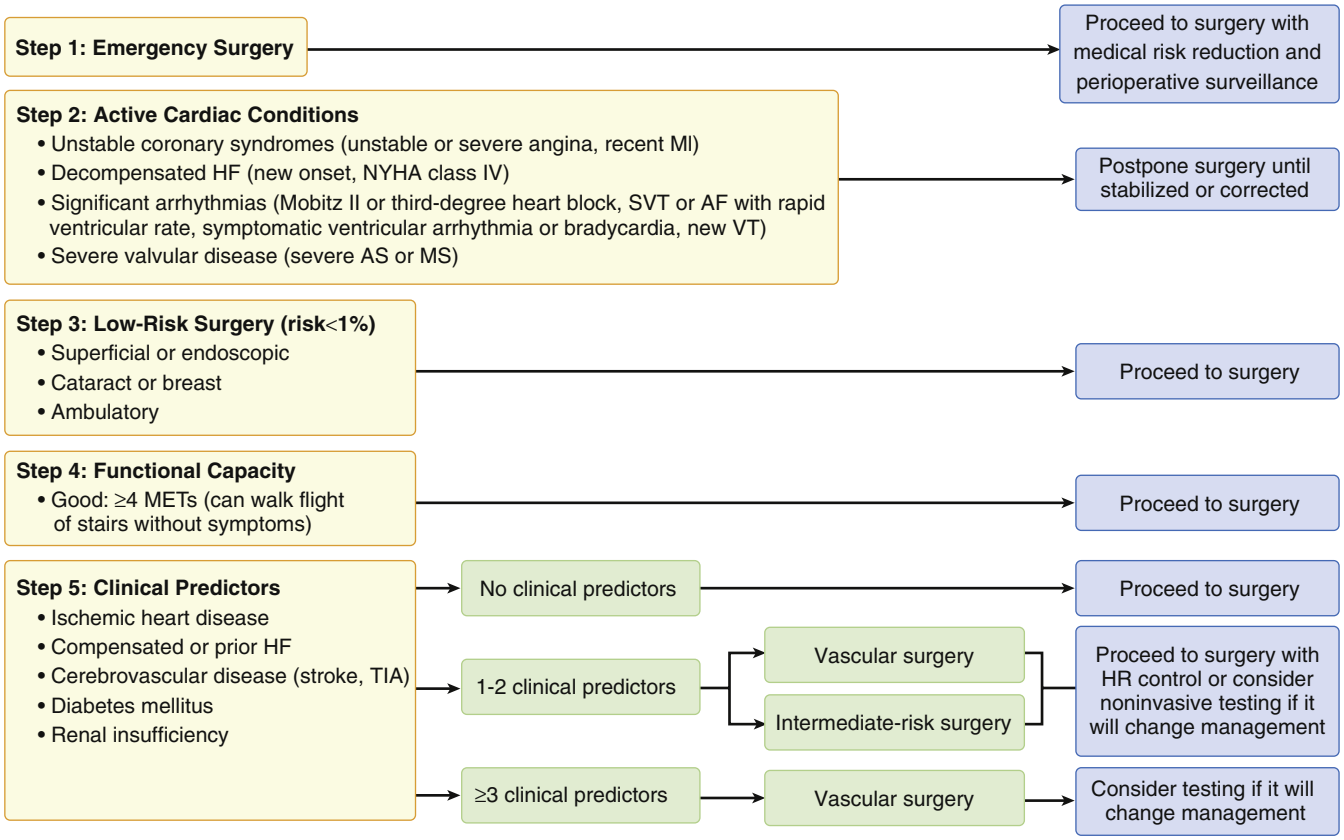


Figure 38-5. Simplified cardiac evaluation for noncardiac surgery. *AF,* Atrial fibrillation; *AS,* aortic stenosis; *HF,* heart failure; *HR,* heart rate; *METs,* metabolic equivalents of the task; *MI,* myocardial infarction; *MS,* mitral stenosis; *NYHA,* New York Heart Association; *SVT,* supraventricular tachycardia; *TIA,* transient ischemic attack; *VT,* ventricular tachycardia. *(From Fleisher LA, Beckman JA, Brown KA, et al: 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines,* Circulation *120:e169-e276, 2009.)*

Ischemic Heart Disease

The goals in the preanesthetic evaluation of patients with ischemic heart disease are as follows:

- Identify the risk of heart disease based on risk factors (Fig. 38-5 and Table 38-3).
- Identify the presence and severity of heart disease based on symptoms, physical findings, or diagnostic tests.
- Determine the need for preoperative interventions.
- Modify the risk of perioperative adverse events.

The primary basis of cardiac assessment comprises the history, physical examination, and ECG. Evaluation of risk factors for CAD is important because 40% of men and 65% of women are not diagnosed before their first acute coronary syndrome (unstable angina, acute MI, or sudden death). The traditional risk factors for CAD (i.e., smoking, hypertension, increased age, male sex, hypercholesterolemia, family history) are not the same risk factors that increase perioperative cardiac events (see Fig. 38-5 and Table 38-3). However, traditional risk factors are important in assessing the significance of chest pain, dyspnea, or an abnormal ECG identified during the preoperative evaluation. The Revised Cardiac Risk Index (RCRI) has been extensively validated for predicting perioperative cardiac risk in noncardiac surgery (see Table 38-3).[46,47]

TABLE 38-3 REVISED CARDIAC RISK INDEX COMPONENTS AND EXPECTED CARDIAC RISK

Components of Revised Cardiac Risk Index*	Points Assigned
High-risk surgery (intraperitoneal, intrathoracic, or suprainguinal vascular procedure)	1
Ischemic heart disease (by any diagnostic criteria)	1
History of congestive heart failure	1
History of cerebrovascular disease	1
Diabetes mellitus requiring insulin	1
Creatinine >2.0 mg/dL (176 μmol/L)	1
Revised Cardiac Risk Index Score	Risk of Major Cardiac Events†‡
0	0.4%
1	1.0%
2	2.4%
≥3	5.4%

*Data from Lee TH, Marcantonio ER, Mangione CM, et al: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery, *Circulation* 100:1043-1049, 1999.
†Data from Devereaux OJ, Goldman L, Cook DJ, et al: Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk, *CMAJ* 173:627-634, 2005.
‡Defined as cardiac death, nonfatal myocardial infarction, or nonfatal cardiac arrest.

The components of the RCRI, all of which are assigned equal weights, are a history of ischemic heart disease, heart failure, diabetes, cerebrovascular disease, renal insufficiency (creatinine concentration >2.0 mg/dL), and high-risk surgery (intraperitoneal, intrathoracic, and suprainguinal vascular procedures).

The presence of chest discomfort (pain, pressure, tightness) and its duration, precipitating factors, associated symptoms, and relieving factors should be determined. The reporting of shortness of breath with exertion may represent an angina equivalent; nonetheless, dyspnea with exertion is nonspecific and can be the result of physical deconditioning, pulmonary disease, or heart failure. Even in the absence of angina symptoms, patients should be assessed for known risk factors for clinically silent ischemic heart disease. Thus, dyspnea in patients with risk factors for CAD may necessitate an investigation for ischemic heart disease. Women are particularly likely to have atypical symptoms of ischemic heart disease.

Preoperative laboratory tests for patients with known or suspected CAD include determination of the blood creatinine and hemoglobin concentrations. Renal insufficiency is a component of the RCRI and a risk factor for perioperative cardiac complications.[47] Preoperative anemia is associated with increased perioperative cardiac risk.[48,49] Anemia can decrease the effects of β-adrenergic blocker therapy in patients undergoing noncardiac surgery, with evidence of increased harm when this therapy is used in patients with perioperative anemia or significant bleeding.[50,51] However, increasing the blood transfusion rate in anemic surgical patients does not decrease perioperative cardiac risk.[52]

Patients with risk factors for CAD or symptoms (typical or atypical) suggestive of ischemia may require an ECG, especially for intermediate- to high-risk surgical procedures. Routine preoperative ECGs are not indicated (Box 38-2), particularly in patients without known cardiovascular disease or risk factors.[53] Specific abnormalities that are associated with increased perioperative cardiac risk include Q waves, right bundle branch blocks (RBBBs), and left bundle branch blocks (LBBBs).[47,54] Nonetheless, when considered *in combination* with known clinical risk factors, such as the components of the RCRI, these ECG abnormalities do not enable clinicians to identify patients with increased perioperative cardiac risk more accurately.[54] A preoperative ECG should not be ordered simply because of a patient's advanced age. Although ECG abnormalities are more common with advanced age, such as a 34% prevalence of Q waves in surgical patients 70 years old or older,[55] these abnormalities themselves provide minimal additional prognostic information (see also Chapter 80). Establishing a baseline for postoperative comparison is often the most important reason to obtain a preoperative ECG; however, this decision should be based on the patient's likely risk of postoperative adverse effects. Specifically, a baseline ECG is unlikely to be helpful in an individual who is already at very low risk for postoperative cardiac events. In addition, if a previous ECG is available and no intervening change in clinical status has occurred, a repeat ECG is unlikely to be useful.

BOX 38-2 ***Recommendations for Preoperative Resting 12-Lead Electrocardiogram***

Class I Recommendation: Procedure *Should* Be Performed

Preoperative resting 12-lead ECG is recommended for patients with one or more clinical risk factors* who are undergoing vascular surgical procedures.

Preoperative resting 12-lead ECG is recommended for patients with known CAD, PAD, or CVD who are undergoing intermediate-risk surgical procedures.

Class IIa Recommendation: It Is Reasonable to Perform the Procedure

Preoperative resting 12-lead ECG is reasonable in persons with no clinical risk factors who are undergoing vascular surgical procedures.

Class IIb Recommendation: The Procedure May Be Considered

Preoperative resting 12-lead ECG may be reasonable in patients with one or more clinical risk factors who are undergoing intermediate-risk operative procedures.

Class III Recommendation: The Procedure Should Not Be Performed Because It Is Not Helpful

Preoperative and postoperative resting 12-lead ECGs are not indicated in asymptomatic persons undergoing low-risk surgical procedures.

From Fleisher LA, Beckman JA, Brown KA, et al: 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, Circulation *120:e169-e276, 2009.*

CAD, Coronary artery disease; CVD, cerebrovascular disease; ECG, electrocardiogram; PAD, peripheral arterial disease.

*Risk factors are history of ischemic heart disease, a history of heart failure, a history of cerebrovascular disease, diabetes mellitus, and renal insufficiency.

The preoperative evaluation should include a review of medical records and previous diagnostic studies, especially stress tests and coronary angiography results. It is important not to rely on a patient's history of a "normal" test result because many patients are unaware of mild abnormalities not requiring revascularization. In many cases, a phone call to the primary care physician or cardiologist yields important information and obviates the need for further testing or consultation. Any further consultation initiated by the preoperative physician should seek specific advice regarding the diagnosis and status of the patient's condition. Asking specific questions such as "Does this patient have CAD?" or "Is this patient optimized for planned radical nephrectomy?" is the first step. Specialist consultations that simply state that a patient is "cleared for surgery" are not sufficient to design a safe anesthetic plan. The specialist's consultation report should summarize the medical problems, therapies, and results of any necessary diagnostic tests.

The goal of the preoperative evaluation is to identify patients who have a high perioperative cardiac risk or those who have *modifiable* risk. The ACCF/AHA practice guidelines for cardiac evaluation before noncardiac surgery have become the national standard of care.[5] In general, the guidelines emphasize the use of functional capacity, surgical risk, and clinical predictors for

preoperative diagnostic and therapeutic interventions. At the time of this writing, new guidelines are in development and should be published after mid 2014.

The 2009 guidelines propose an algorithm for preoperative cardiac risk evaluation that is followed in stepwise fashion and stops at the first point that applies to the patient (see Fig. 38-5).

Step 1 in this guideline algorithm considers the urgency of surgery. For emergency surgery, the focus is on perioperative surveillance (e.g., serial ECGs, cardiac enzymes, monitoring) and risk reduction (e.g., β-adrenergic blockers, statins, pain management).

Step 2 focuses on active cardiac conditions such as acute MI, unstable or severe angina, decompensated heart failure, severe valvular disease (e.g., critical aortic stenosis), or significant arrhythmias (e.g., atrial fibrillation with rapid ventricular rate, sustained ventricular tachycardia). Active cardiac conditions warrant postponement of surgery for all except lifesaving emergency procedures. After identification and treatment of these conditions, surgery can be reconsidered if the benefit is substantial and the risk acceptable. Traditionally, patients who experienced an MI within the previous 3 to 6 months were considered high risk and necessitated delay of surgery in step 2. Instead, the ACCF/AHA guidelines now suggest postponement of surgery if a patient had an *acute MI*, defined as occurring within the past 7 days. Patients who had a *recent MI*, defined as occurring within 7 to 30 days before surgery, are also considered at high risk if they have *evidence of myocardium at risk*, based on persistent symptoms or stress testing results. Such individuals should also delay any nonemergency surgery.

Step 3 considers the surgical risk or severity (Table 38-4). Patients without active cardiac conditions who undergo low-risk surgery can proceed without further cardiac testing. All ambulatory surgery is in the low-risk category.

Step 4 assesses the patient's functional capacity based on METs (see Table 38-1). Asymptomatic patients with average functional capacity, defined as the ability to walk one to two flights of stairs or four blocks on a level surface, can proceed directly to surgery.

Step 5 considers patients who have poor or indeterminate functional capacity and need intermediate-risk or vascular surgery (see Table 38-4). The number of patient-level clinical predictors from the RCRI (CAD, heart failure, cerebrovascular disease, diabetes, renal insufficiency) determines the likely benefit of further cardiac testing among individuals who reach step 5. Patients with no clinical predictors proceed to surgery. Those with risk predictors may benefit from further testing, but only if the results *alter management*. Selective testing in individuals with risk factors may also help improve postoperative survival. Data suggest that preoperative stress testing in patients with RCRI scores of 3 or more is associated with a moderate reduction in 1-year mortality.[267]

Preoperative cardiac stress testing can help identify the presence and severity of preexisting CAD. These tests also provide some prognostic information with respect to predicting risks of perioperative cardiac complications. Given the relatively infrequent incidence of postoperative cardiac events, the prognostic performance of these tests should not be evaluated on the basis of positive or negative predictive values. Rather, the prognostic performance of these tests is better assessed based on positive likelihood ratio, negative likelihood ratio, sensitivity, or specificity. For context, positive test results must have likelihood ratios exceeding 2 to provide clinically meaningful information, whereas negative test results should have associated likelihood ratios of 0.5 or less.[56] Exercise ECG testing has a sensitivity of 74% and a specificity of 69% for predicting postoperative cardiac events.[57] These values correspond to a positive likelihood ratio of 2.4 and a negative likelihood ratio of 0.4. In contrast, dobutamine stress echocardiography has a positive likelihood ratio of 4.1 and a negative likelihood ratio of 0.2, whereas myocardial perfusion scintigraphy has a positive likelihood ratio of 1.8 and a negative likelihood ratio of 0.4.[58] Thus, overall, dobutamine stress echocardiography provides the most accurate prognostic information (for both positive and negative test results), whereas myocardial perfusion scintigraphy may be predisposed to more false-positive results. The prognostic value of myocardial perfusion scintigraphy may be improved by considering the extent of reversible ischemia found on these tests. Significant increases in perioperative cardiac risk are associated with reversibility affecting more than 20% of the myocardium.[59] The presence of fixed defects alone on perfusion imaging is not associated with increased perioperative cardiac risk. Coronary angiography, which is considered the gold standard for diagnosing CAD, may not absolutely risk stratify patients either. Specifically, many perioperative cardiac events may be related to noncritical coronary lesions rupturing within the context of the hypercoagulable perioperative state.[60] Nonetheless, a randomized trial

TABLE 38-4 STRATIFICATION OF PERIOPERATIVE CARDIAC RISK FOR NONCARDIAC SURGICAL PROCEDURES

Risk Stratification	Estimated Risk of Cardiac Death or Nonfatal MI	Examples of Procedures
Vascular	>5%	Aortic and other major vascular surgery Peripheral vascular surgery
Intermediate	1-5%	Intraperitoneal and intrathoracic surgery Carotid endarterectomy Head and neck surgery Orthopedic surgery Prostate surgery
Low*	<1%	Endoscopic procedures Superficial procedure Cataract surgery Breast surgery Ambulatory surgery

From Fleisher LA, Beckman JA, Brown KA, et al: 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, Circulation *120:e169-e276, 2009.*

MI, Myocardial infarction.

*These procedures do not require further preoperative cardiac testing unless the patient has an unstable cardiac condition.

of 208 intermediate- to high-risk patients undergoing vascular surgery found that a strategy of routine preoperative coronary angiography led to superior long-term survival when compared with the selective use of angiography in individuals with high-risk stress test results.[61]

When considering the choice of cardiac stress test, exercise ECG testing can be ordered for patients with normal ECGs who can exercise and are likely to achieve an adequate HR response (see also Chapter 47). An adequate test result is obtained when patients can exercise to at least 85% of their target HR (target HR is defined as 220 minus age). Pharmacologic stress tests, such as dobutamine echocardiography or dipyridamole myocardial perfusion scintigraphy, are indicated for individuals who cannot exercise, have pacemakers or significant bradycardia, or receive high-dose β-adrenergic blockers. A combination of exercise and imaging (e.g., exercise stress echocardiography) can be used in patients who can exercise but have significant ECG abnormalities (e.g., LVH with a strain pattern or LBBB) that may interfere with ECG interpretation for ischemia. Exercise echocardiography can lead to many false-positive results in patients with LBBB because of associated septal abnormalities[5] (see also Chapter 46). For most patients, the choice of pharmacologic stress test is immaterial. Because dobutamine uncovers ischemia by increasing contractility, HR, and BP, it may not be the best choice in patients with pacemakers, significant bradycardia, aortic or cerebral aneurysms, or poorly controlled hypertension. Adenosine or dipyridamole myocardial scintigraphy relies on the vasodilatory properties of adenosine or dipyridamole (stenotic vessels are maximally vasodilated at rest) and uptake of the radioisotope by viable myocardium. Although these tests do not depend on HR response, they may exacerbate bronchospasm in patients taking theophylline or may cause dangerous reductions in preload for patients with severe aortic valve disease or hypertrophic cardiomyopathy (HCM).

Echocardiography, combined with exercise or a pharmacologic agent, is used to look for wall motion abnormalities (see also Chapter 46). Abnormalities present at rest (baseline) indicate scar tissue from previous infarction. Areas of myocardium that are normal at rest but show abnormalities with increased inotropy and chronotropy (i.e., inducible wall motion abnormalities) indicate stenotic coronary lesions and limited blood flow. Similarly, nuclear imaging perfusion abnormalities at rest are consistent with prior infarction. Normal coronary arteries vasodilate with adenosine or exercise, and uptake of isotope is normal. Myocardium with flow limiting lesions is normal at rest, but it shows decreased uptake of isotope with exercise or adenosine administration. If a patient had a specific test in the past, it is most useful to obtain the same test for comparison. The ACCF/AHA guidelines also state that a patient who had a favorable stress test result within the previous 2 years does not require repeat testing if no subsequent change in symptoms has occurred.

By applying the ACCF/AHA recommendations and using the predictive value of the RCRI, practitioners in preanesthetic clinics are well positioned to initiate preoperative cardiac evaluation with stress tests. Results may obviate the need for subsequent cardiology consultation or ensure that relevant test results will be available at the time of the consultation. The preoperative period is also an opportunity to identify patients with CAD who will benefit from long-term risk modification with statins, aspirin, exercise, and diet adjustment. Patients with symptoms consistent with ischemia or significant risk factors without medical management may benefit from evaluation by a cardiologist, regardless of whether they are having surgery. Preoperative evaluation should therefore not simply focus on the immediate perioperative risk.

However, concerns exist over the predictive value, costs, risks, and benefits of the ACC/AHA guidelines for cardiac evaluation for noncardiac surgery. An important controversy pertains to the benefits versus risks of coronary revascularization before noncardiac surgery. Two randomized trials of preoperative coronary revascularization versus medical management in intermediate- to high-risk patients undergoing vascular surgery found no benefit to a strategy of revascularization.[62,63] The revascularization strategies employed in these studies included both coronary artery bypass grafting and percutaneous coronary intervention (PCI) with stenting. The larger of the two trials excluded individuals found to have left main coronary artery stenosis on preoperative coronary angiography, a finding present in 5% to 15% of intermediate- to high-risk patients undergoing vascular surgery.[61,62,64] Such patients with unprotected left main coronary artery stenosis may be the only subgroup of patients deriving a perioperative benefit from preoperative coronary revascularization.[64] These patients would usually require revascularization by coronary artery bypass graft.[65]

Patients already receiving statins and β-adrenergic blockers must continue taking these drugs without interruption throughout the perioperative period (Boxes 38-3 and 38-4). Patients already taking β-adrenergic blockers need their dosages adjusted to achieve an HR of less than 70 beats/minute, if at all possible. The role of initiating β-adrenergic blockers de novo in patients at increased perioperative cardiac risk is unclear, especially given the results of the Perioperative Ischemic Evaluation Study-1 (POISE-1) trial.[40] The patients most likely to benefit are individuals undergoing vascular surgery with evidence of inducible ischemia on preoperative testing.[5,41] β-Adrenergic blockers should be initiated at least several days before surgery,[66,67] and they should be titrated to achieve HR control without precipitating hypotension. Caution should be exercised in individuals with known cerebrovascular disease because of the potential for β-adrenergic blockers to increase rates of perioperative acute stroke.[40,68] In intermediate- to high-risk surgical patients, consideration should also be given to initiating statins, which reduce perioperative cardiac risk with few safety concerns.[69,70] Randomized trials to date have not clearly shown benefits from routinely continuing aspirin before noncardiac surgery.[71-73] The largest trial to-date, the Perioperative Ischemic Evaluation Study-2 (POISE-2), found that continuing low-dose aspirin (100 mg/day) did not prevent cardiac events but also increased rates of major bleeding.[71] Since only one-third of these participants had known vascular disease, it may

BOX 38-3 *Preoperative Management of Medications*

Instruct patients to take these medications with a small sip of water, even if fasting.

1. **Antihypertensive medications**
   Continue on the day of surgery.
   - **Possible exception:** For patients undergoing procedures with major fluid shifts, or for patients who have medical conditions in which hypotension is particularly dangerous, it may be prudent to discontinue ACEIs or ARBs before surgery.
2. **Cardiac medications (e.g., β-blockers, digoxin)**
   Continue on the day of surgery.
3. **Antidepressants, anxiolytics, and other psychiatric medications**
   Continue on the day of surgery.
4. **Thyroid medications**
   Continue on the day of surgery.
5. **Birth control pills**
   Continue on the day of surgery.
6. **Eye drops**
   Continue on the day of surgery.
7. **Heartburn or reflux medications**
   Continue on the day of surgery.
8. **Narcotic medications**
   Continue on the day of surgery.
9. **Anticonvulsant medications**
   Continue on the day of surgery.
10. **Asthma medications**
    Continue on the day of surgery.
11. **Steroids (oral and inhaled)**
    Continue on the day of surgery.
12. **Statins**
    Continue on the day of surgery.
13. **Aspirin**
    Consider selectively continuing aspirin in patients where the risks of cardiac events is felt to exceed the risk of major bleeding. Examples would be patients high-grade CAD or CVD. If reversal of platelet inhibition is necessary, aspirin must be stopped at least 3 days before surgery. Do not discontinue aspirin in patients who have drug-eluting coronary stents until they have completed 12 months of dual antiplatelet therapy, unless patients, surgeons, and cardiologists have discussed the risks of discontinuation. The same applies to patients with bare metal stents until they have completed 1 month of dual antiplatelet therapy. In general, aspirin should be continued in any patient with a coronary stent, regardless of the time since stent implantation.
14. **Thienopyridines (e.g., clopidogrel, ticlopidine)**
    Patients having cataract surgery with topical or general anesthesia do not need to stop taking thienopyridines. If reversal of platelet inhibition is necessary, then clopidogrel must be stopped 7 days before surgery (14 days for ticlopidine). Do not discontinue thienopyridines in patients who have drug-eluting stents until they have completed 12 months of dual antiplatelet therapy, unless patients, surgeons, and cardiologists have discussed the risks of discontinuation. The same applies to patients with bare metal stents until they have completed 1 month of dual antiplatelet therapy.
15. **Insulin**
    For all patients, discontinue all short-acting (e.g., regular) insulin on the day of surgery (unless insulin is administered by continuous pump). Patients with type 2 diabetes should take none, or up to one half of their dose of long-acting or combination (e.g., 70/30 preparations) insulin, on the day of surgery. Patients with type 1 diabetes should take a small amount (usually one third) of their usual morning long-acting insulin dose on the day of surgery. Patients with an insulin pump should continue their basal rate only.
16. **Topical medications (e.g., creams and ointments)**
    Discontinue on the day of surgery.
17. **Oral hypoglycemic agents**
    Discontinue on the day of surgery.
18. **Diuretics**
    Discontinue on the day of surgery (exception: thiazide diuretics taken for hypertension, which should be continued on the day of surgery).
19. **Sildenafil (Viagra) or similar drugs**
    Discontinue 24 hours before surgery.
20. **COX-2 inhibitors**
    Continue on the day of surgery unless the surgeon is concerned about bone healing.
21. **Nonsteroidal antiinflammatory drugs**
    Discontinue 48 hours before the day of surgery.
22. **Warfarin (Coumadin)**
    Discontinue 4 days before surgery, except for patients having cataract surgery without a bulbar block.
23. **Monoamine oxidase inhibitors**
    Continue these medications and adjust the anesthesia plan accordingly.

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; CAD, coronary artery disease; *COX-2,* Cyclooxygenase-2; CVD, cerebrovascular disease.

still be reasonable to continue aspirin in select patients where the risk of cardiac events is felt to exceed the risk of major bleeding. Examples would be patients with high-grade CAD (including coronary stents) or cerebrovascular disease. (see Box 38-3).

Coronary Stents

Patients who have undergone PCI, especially those with drug-eluting stents, require several months, if not a lifetime, of antiplatelet therapy to avoid restenosis or acute in-stent thrombosis. The presence and type (drug-eluting or bare metal) of any coronary stent must be identified in the preanesthetic clinic, and subsequent management must be performed in collaboration with a cardiologist. A scientific advisory from major national medical and dental associations, including the ACCF and the AHA, provides recommendations for managing patients with coronary stents.[74] Patients with a recent bare metal stent implantation, defined as occurring within the previous 30 days, should absolutely *not* undergo elective surgery. If urgent surgery is needed, strong consideration is given to continuing dual antiplatelet therapy (i.e., thienopyridine and aspirin) throughout the perioperative period (see Box 38-3),[5] as well as close monitoring for postoperative myocardial injury (i.e., serial troponin measurement).

Current guidelines also clearly recommend against elective surgery within 1 year after drug-eluting stent implantation.[74] Conversely, perioperative cardiac risk is

BOX 38-4 ***Recommendations for Use of Perioperative β-Blockers From the American College of Cardiology Foundation and American Heart Association***

Class I Indications*

- β-Blockers should be continued in patients undergoing surgery who are already receiving β-blockers for treatment of conditions with ACCF/AHA class I guideline indications for the drugs.

Class IIa Indications†

- β-Blockers titrated to heart rate and blood pressure are probably recommended for patients undergoing vascular surgery who are at high cardiac risk as a result of coronary artery disease or the finding of cardiac ischemia on preoperative stress testing.
- β-Blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk, as defined by the presence of more than one clinical risk factor.
- β-Blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment identifies coronary artery disease or high cardiac risk, as defined by the presence of two or more clinical risk factors, who are undergoing intermediate-risk surgery.

Modified from Fleisher LA, Beckman JA, Brown KA, et al: 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, Circulation *120:e169-e276, 2009.*

ACCF/AHA, American College of Cardiology Foundation and American Heart Association.

*Class I indication: Conditions for evidence and general agreement indicate that a given procedure or treatment is beneficial, useful, and effective.

†Class IIa indication: Conditions for conflicting evidence and a divergence of opinion exist about the usefulness and efficacy of a procedure or treatment, but the weight of evidence or opinion is in favor of usefulness and efficacy

relatively low if elective surgery is performed more than 6 months after drug-eluting stent implantation.[75-78] Nonetheless, surgery within 1 year must involve consultation with a cardiologist who is familiar with the implanted stent type and the details of the patient's coronary artery anatomy. In general, elective surgery should *not* be performed until at least 1 year following drug-eluting stent implantation. If urgent surgery is needed, strong consideration is given to continuing dual antiplatelet drug therapy throughout the perioperative period (see Box 38-3).

Antiplatelet drugs should not be interrupted in patients with coronary stents without consultation with a cardiologist familiar with coronary stents, as well as an in-depth discussion with the surgeon and the patient regarding the risks of stopping these drugs. The major concern with premature discontinuation of dual antiplatelet therapy, especially during critical time windows following bare metal stent implantation (30 days) or drug-eluting stent implantation (1 year), is the risk of precipitating catastrophic stent thrombosis, MI, or death. Every effort should be made to ensure that surgical procedures are performed following these critical time windows, aspirin is continued throughout the perioperative period, and thienopyridine (typically clopidogrel) therapy is restarted as soon as possible postoperatively. Unfractionated heparin and low-molecular-weight heparin (LMWH) are not appropriate for "bridging" patients with coronary stents who have been withdrawn from all antiplatelet therapy. Specifically, heparin administration can paradoxically *increase* platelet aggregation and thereby may actually increase risk.[79] Stent thrombosis is best treated with PCI, which can be performed safely even in the immediate postoperative period.[80] High-risk patients are thus likely best managed in facilities with immediate access to interventional cardiology.

Heart Failure

Heart failure affects 4 to 5 million people in the United States and is a significant risk factor for postoperative mortality and adverse events.[39,81,82] Decompensated heart failure is also a high-risk characteristic that warrants postponement of surgery for all except lifesaving emergency procedures.[5] Heart failure may result from systolic dysfunction (decreased ejection fraction from abnormal contractility), diastolic dysfunction (increased filling pressures from abnormal relaxation but normal contractility and ejection fraction), or a combination. Diastolic failure accounts for almost half of all cases, but little science guides the perioperative care of these individuals. Hypertension is a cause of diastolic dysfunction, and LVH on an ECG raises suspicion. Ischemic heart disease is the most common cause of systolic dysfunction in developed countries (50% to 75% of cases). Cardiomyopathies have a variety of causes including infections (human immunodeficiency virus [HIV], coxsackievirus, influenza virus, adenovirus, Chagas or Lyme disease), toxins, alcohol, sarcoidosis, peripartum cardiomyopathy, drugs (e.g., doxorubicin [Adriamycin], cocaine), muscular dystrophy, and idiopathic causes. Cardiac magnetic resonance imaging (MRI) or endomyocardial biopsy may be used to establish a diagnosis.

The goal in the preoperative evaluation is to identify and minimize the effects of heart failure. Recent weight gain, complaints of shortness of breath, fatigue, orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough, peripheral edema, hospitalizations, and recent changes in management are all significant. Patients with decompensated heart failure feel like they are "suffocating" or have "air hunger."

The physical examination focuses on finding third or fourth heart sounds, tachycardia, a laterally displaced apical pulse, rales, jugular venous distention, ascites, hepatomegaly, and peripheral edema. Classifying the patient's medical status according to the New York Heart Association (NYHA) categories is also useful:

- NYHA class I: no limitation of physical activity; ordinary activity not a cause of fatigue, palpitations, or syncope
- NYHA class II: slight limitation of physical activity; ordinary activity resulting in fatigue, palpitations, or syncope
- NYHA class III: marked limitation of physical activity; less than ordinary activity resulting in fatigue, palpitations, or syncope; comfort at rest
- NYHA class IV: inability to do any physical activity without discomfort; symptoms at rest

Brain natriuretic peptide (BNP), which is released from the atria and ventricles in response to ischemia or strain, is useful in evaluating patients suspected of having decompensated heart failure. [83] The plasma concentration of BNP is a powerful marker of cardiovascular risk in nonsurgical patients, including individuals who are at risk for CAD, have CAD, or have heart failure.[83] In patients undergoing noncardiac surgery, preoperative BNP levels predict risk for cardiac complications and death.[84,85] A particular use for BNP is screening individuals whose functional capacity is difficult to estimate.[86,87] Specifically, a low BNP concentration is very reassuring with respect to predicting a low perioperative cardiac risk. Among patients undergoing vascular surgery, a BNP level less than 30 pg/mL has a negative likelihood ratio of 0.11 with respect to predicting postoperative MI or death; the negative likelihood ratio associated with a level less than 116 pg/mL is 0.41.[87]

An ECG and determination of electrolytes, BUN, creatinine, and possibly BNP are indicated in patients with or suspected of having heart failure. Digoxin levels are not routinely determined unless toxicity, undertreatment, or noncompliance is suspected. One must determine trough levels of digoxin, and this is not always possible in a preoperative evaluation setting. Paroxysmal atrial tachycardia with a 2:1 atrioventricular (AV) block is pathognomonic of digoxin toxicity. Junctional tachycardia, ventricular ectopic beats, bigeminy, second-degree AV block, nausea, lethargy, altered color perception, and mental status changes or agitation are symptoms of digoxin toxicity. Chest radiography is useful in patients suspected of having pulmonary edema. The use of echocardiography to obtain objective measures of left ventricular ejection fraction, ventricular performance, and diastolic function may be helpful, especially in patients with NYHA class III or IV heart failure (Box 38-5). Normal left ventricular ejection fraction is greater than 50%; mildly diminished is 41% to 49%, moderately diminished is 26% to 40%, and severely diminished is 25% or less. The current ACCF/AHA guidelines recommend preoperative echocardiography (or other noninvasive measure of ventricular function) to assess dyspnea of unknown origin or recent altered clinical status in an individual with known heart failure.[5] Conversely, routine preoperative assessment of ventricular function is discouraged. Patients with class III or IV heart failure should be evaluated in conjunction with a cardiologist before they undergo general anesthesia or any intermediate- or high-risk procedure. In addition, severely affected individuals or those with decompensated heart failure may need the help of a heart failure specialist. Very minor procedures performed using monitored anesthesia care may proceed as long as the patient's condition is stable.

Medical therapy, including β-adrenergic blockers, hydralazine, nitrates, and digoxin, must be optimized and continued preoperatively. ACEIs, ARBs, and diuretics (including aldosterone antagonists such as spironolactone) may be beneficial, even on the day of surgery. Continuation of loop diuretics on the day of surgery does not increase the risk of intraoperative hypotension or adverse cardiac events.[88] Conversely, preoperative administration of ACEIs or ARBs is a risk for intraoperative hypotension.[45] Thus, selective continuation or discontinuation of these drugs depends on the intravascular volume and hemodynamic status of the patient, the degree of cardiac dysfunction, and the anticipated surgical procedure and intravascular volume challenges (see Box 38-3). Continuing all medications for patients with severe dysfunction who are scheduled for minor procedures is probably best. The other extreme occurs when patients with well-compensated NYHA class I heart failure are scheduled for lengthy high-risk procedures with projected significant blood loss or fluid requirements. In these cases, potent diuretics should be discontinued on the morning of surgery. Patients with pacemakers or implantable cardioverter-defibrillators (ICDs) have their own special perioperative considerations (see the later section on cardiovascular implantable electronic devices [CIEDs]: pacemakers, and ICDs; see also Chapter 48).

As indicated previously, surgery should be postponed in patients with decompensated or untreated heart failure, unless the situation is truly an emergency. No consensus exists on how long such patients remain at risk after resolution of an acute exacerbation of heart failure.

BOX 38-5 ***Recommendations for Preoperative Noninvasive Evaluation of Left Ventricular Function***

Class IIa: Reasonable to Perform

- It is reasonable for patients with dyspnea of unknown origin to undergo preoperative evaluation of LV function.
- It is reasonable for patients with current or prior heart failure with worsening dyspnea or other change in clinical status to undergo preoperative evaluation of LV function if such evaluation was not performed within 12 months.

Class IIb: May Be Considered

- Reassessment of LV function in clinically stable patients with previously documented cardiomyopathy is not well established.

Class III: Should Not Be Performed Because It Is Not Helpful

- Routine perioperative evaluation of LV function in patients is not recommended.

Modified from Fleisher LA, Beckman JA, Brown KA, et al: 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, Circulation *120:e169-e276, 2009.*

LV, Left ventricle.

Murmurs and Valvular Abnormalities

Clinical goals in preoperative assessment include determining the cause of cardiac murmurs and distinguishing between significant murmurs and those that are clinically unimportant[89] (see Chapter 67). Functional murmurs occur from turbulent flow across the aortic or pulmonic outflow tracts. These benign murmurs occur with high-flow states such as hyperthyroidism, pregnancy, or anemia. It is often not easy for noncardiologists to distinguish benign from pathologic murmurs. Indications for echocardiography to assess a murmur include increased

BOX 38-6 ***American College of Cardiology and American Heart Association Guidelines Recommendations for Echocardiography in Asymptomatic Patients With Cardiac Murmurs***

Class I: Evidence and general agreement indicate that echocardiography is useful in asymptomatic patients with the following cardiac murmurs:

- Diastolic murmurs
- Continuous murmurs
- Late systolic murmurs
- Murmurs associated with ejection clicks
- Murmurs that radiate to the neck or back
- Grade 3 or louder systolic murmurs

Class IIa: The weight of evidence or opinion is in favor of usefulness of echocardiography in asymptomatic patients with the following cardiac murmurs:

- Murmurs associated with other abnormal physical findings on cardiac examination
- Murmurs associated with an abnormal electrocardiogram or chest radiograph

Class III: Evidence and general agreement indicate that echocardiography is not useful in asymptomatic patients with the following murmurs:

- Grade 2 or softer midsystolic murmurs considered innocent or functional by an experienced observer

Modified from Bonow, RO, Carabello, BA, Chatterjee, K, et al: ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Circulation *114:e84-e231, 2006.*

age, risk factors for heart disease, other abnormal heart sounds, history of rheumatic fever, anorectic drug use, evidence of excessive intravascular volume, pulmonary disease, cardiomegaly, or abnormal ECG (Box 38-6). Diastolic murmurs are always pathologic and require further evaluation. In general, regurgitant valvular lesions are better tolerated perioperatively than is stenotic disease. Murmurs can be graded according to loudness, as shown in Table 38-5. Nonetheless, the usefulness of this approach is debatable because severe lesions can be associated with soft murmurs and vice versa. The location of the murmur, as well as changes in intensity associated with maneuvers, can guide diagnosis (Table 38-6). A Valsalva maneuver decreases filling of the right and left heart chambers and reduces the intensity of most murmurs, except those associated with mitral valve prolapse (MVP) and HCM. Standing also decreases preload and thereby increases the intensity of murmurs of MVP and HCM. Conversely, squatting increases venous return and afterload and therefore increases most murmurs, except those of MVP and HCM. Having the patient repeatedly perform a hand grip increases HR and arterial BP and thereby augments murmurs of mitral regurgitation, mitral stenosis, and aortic insufficiency; however, this maneuver decreases murmurs of aortic stenosis and HCM. Significant abnormalities found by history, physical examination, or ECG may require a preoperative echocardiogram or cardiology consultation.

TABLE 38-5 **GRADING THE INTENSITY OF CARDIAC MURMURS**

Grade	Description
I	Faintest that can be heard with difficulty
II	Faint but easily heard
III	Moderately loud without a thrill
IV	Loud with a palpable thrill
V	Very loud but still need stethoscope (thrill present)
VI	Heard without a stethoscope

Aortic Stenosis. Severe aortic stenosis is associated with increased perioperative cardiac risk, especially in combination with other risk factors for perioperative cardiac complications.[90] Patients with bicuspid valves typically develop stenosis at a younger age (fourth and fifth decades of life), whereas patients with stenosis of nonbicuspid valves are usually 60 years old or older. Aortic *sclerosis,* which also causes a systolic ejection murmur similar to that of aortic stenosis, is present in 25% of people 65 to 74 years old and in almost half of those 84 years old or older. Aortic sclerosis is associated with a 40% increase in the risk of MI and a 50% increase in the risk of cardiovascular death in patients without a prior history of CAD.[91] No hemodynamic compromise occurs in aortic sclerosis.

The cardinal symptoms of severe aortic stenosis are angina, heart failure, and syncope, although patients are much more likely to complain of a decrease in exercise tolerance and exertional dyspnea. Aortic stenosis causes a systolic ejection murmur, best heard in the right upper sternal border and often radiating to the neck. A delayed carotid upstroke and a paradoxically split S_2 (second heart sound) are noted. Exercise increases HR and decreases an aortic stenosis murmur. The pattern of radiation of the murmur can help rule out aortic stenosis; specifically, the absence of murmur radiation to the right clavicle is associated with a negative likelihood ratio of 0.1 for aortic stenosis.[92] Any patient with a previously undiagnosed suspicious murmur needs an ECG, and any ECG abnormality warrants an echocardiogram (see Box 38-6). ECG abnormalities may consist of LVH, often with a strain pattern, left axis deviation, or LBBB. Because of the difficulties noncardiologists have in distinguishing murmurs of aortic stenosis from those of aortic sclerosis, an echocardiogram is often useful, even without ECG abnormalities. This is especially true if general anesthesia or an intermediate- or high-risk procedure is planned.

Aortic stenosis severity is based on the valve area and mean transvalvular pressure gradient (Table 38-7). A limitation of using the pressure gradient alone to assess severity is that the gradient may decrease if the left ventricle begins to fail. Echocardiography is recommended annually for patients with severe aortic stenosis, every 2 years for moderate stenosis, and every 5 years for mild stenosis. Patients with aortic stenosis are at risk for sudden death, arrhythmias, heart failure, ischemia, and MI; ischemia may result from concomitant CAD or a supply-demand mismatch. Aortic sclerosis or stenosis is an indicator of CAD, regardless of other risk factors. Severe or critical stenosis should preclude noncardiac surgery (unless it is an

TABLE 38-6 DESCRIPTIONS OF MURMURS ASSOCIATED WITH CARDIAC ABNORMALITIES

Lesion	Location	Timing	Description
Aortic stenosis	Second parasternal interspace	Midsystolic	Crescendo-decrescendo, radiates to the carotid arteries; with or without S_3, S_4; Valsalva maneuver and sustained hand grip exercise decrease intensity
Aortic insufficiency	Third and fourth parasternal interspaces	Holodiastolic	Decrescendo, blowing, high pitched, radiates to the carotid arteries; Austin-Flint rumble at the apex; squatting, hand grip exercise, and leaning forward increase intensity
Mitral stenosis	Apex	Middiastolic	Opening snap; low-pitched rumble radiates to the axilla; squatting and hand grip exercise increase intensity
Mitral regurgitation	Apex	Holosystolic	High pitched, blowing, radiates to the axilla; loud S_3; standing decreases intensity; squatting and hand grip exercise increase intensity
Mitral valve prolapse	Apex	Late systolic	Crescendo, midsystolic click; Valsalva maneuver and standing increase intensity; squatting decreases intensity
Hypertrophic cardiomyopathy	Apex, lower left sternal border	Midsystolic	S_4, single S_2; Valsalva maneuver and standing increase intensity; squatting, passive leg raising, and hand grip exercise decrease intensity

TABLE 38-7 GRADING SEVERITY OF AORTIC STENOSIS

Grade	Velocity of Aortic Jet (m/sec)	Mean Pressure Gradient (mm Hg)	Valve Area (cm^2)
Mild	<3	<25	≥1.5
Moderate	3-4	2-40	1.0-1.5
Severe	4-4.5	40-50	0.7-1.0
Critical	>4.5	50	<0.7

emergency and lifesaving procedure) without cardiology evaluation, careful consideration of risks, or valve replacement. Patients with moderate to severe aortic stenosis have an increased risk of bleeding. The cause appears to be *acquired* von Willebrand syndrome, resulting from mechanical disruption of von Willebrand multimers during turbulent blood flow through a narrowed valve.[93] An activated partial thromboplastin time (aPTT) is indicated. Prophylaxis for infective endocarditis in patients with aortic stenosis is no longer recommended.[94]

Aortic Insufficiency. Insufficiency of the aortic valve occurs with true valvular disease affecting the leaflets, aortic root dilation, or both. Rheumatic heart disease, bicuspid valves, collagen vascular diseases, and endocarditis can all lead to valvular disease. Aortic root dilation can complicate ankylosing spondylitis, osteogenesis imperfecta, syphilis, hypertension, age-related degeneration, Marfan syndrome, and collagen vascular diseases. Acute aortic insufficiency can also result from trauma, infections, or aortic dissection; this is an emergency. The murmur of aortic insufficiency is described in Table 38-6. The intensity of the murmur does not correlate with the severity of regurgitation.[95] Patients typically have a widened pulse pressure, which manifests as Corrigan or water-hammer pulses (bounding carotid pulse with a rapid downstroke). Other signs include de Musset sign (head bob with each heart beat), Duroziez sign (systolic and diastolic bruit heard over the femoral artery when it is partially compressed), Quincke pulses (capillary pulsations in the fingertips or lips), and Mueller sign (systolic pulsations of the uvula).

An ECG is needed and an echocardiogram may be useful (see Box 38-6). LVH with ST-segment and T-wave changes as a result of excessive intravascular volume, or underlying chronic ischemia, may be present. Left atrial hypertrophy and left axis deviation along with premature atrial and ventricular contractions are not uncommon. Generally, chronic aortic insufficiency is well tolerated in the perioperative period. Patients with good functional status and preserved left ventricular systolic function have a low risk of complications of anesthesia. Prophylaxis for infective endocarditis is no longer recommended.[94]

Mitral Stenosis. Mitral stenosis is much less common than aortic stenosis and is usually associated with a history of rheumatic heart disease. Mitral stenosis causes a diastolic murmur and is always evaluated with an ECG and an echocardiogram (see Box 38-6). This disorder can occur with aortic valvular disease or mitral regurgitation. A normal mitral valve has an area of 4 to 6 cm^2; stenosis is mild when the area is 1.5 to 2.5 cm^2, moderate with an area of 1.1 to 1.5 cm^2, and critical when the area is 0.6 to 1.0 cm^2. A resting mean transvalvular gradient of 10 mm Hg or more also denotes severe stenosis. Symptoms typically occur 10 to 20 years after acute rheumatic fever and often are precipitated by pregnancy or illness. Unrecognized mitral stenosis should be included in the differential diagnosis of pulmonary edema.

Dyspnea, fatigue, orthopnea, pulmonary edema, and hemoptysis result from increased left atrial pressures and decreased cardiac output. Atrial fibrillation can result from a dilated left atrium, which can precipitate heart failure in the short term and cause thrombosis in the long term. Patients with atrial fibrillation also require anticoagulation to avoid a left atrial thrombus. Pulmonary

hypertension (suggested by a loud S_2 heart sound) and right-sided heart failure may occur in patients with significant stenosis. The characteristics of the murmur are described in Table 38-6. Sustained hand grip exercise increases HR and arterial BP, thereby increasing the intensity of the murmur. Physical examination involves looking for rales and for signs of right-sided heart failure such as jugular venous distention, peripheral edema, hepatomegaly, right ventricular heave, and ascites.

An ECG and an echocardiogram are necessary (see Box 38-6). β-Adrenergic blockers are used to control HR, and antiarrhythmic agents prevent or control atrial fibrillation. These medications should be continued preoperatively. HR must be controlled preoperatively. Anticoagulation is managed in conjunction with the treating cardiologist and surgeon. Prophylaxis for infective endocarditis is no longer recommended.[94]

Mitral Regurgitation. Mitral regurgitation can be acute in the setting of ischemia and infarction or chronic and associated with mitral stenosis, MVP, collagen vascular diseases, and cardiomyopathies. The course is typically very gradual, with symptoms developing late and only after left ventricular dysfunction occurs. The symptoms are vague and are often attributed to other causes. Fatigue, dyspnea, and atrial fibrillation can be present. A description of the murmur is presented in Table 38-6. A loud murmur associated with a thrill (grade 4 murmur or higher) has a specificity of 91% for severe regurgitation, but a sensitivity of 24%.[95] Severe regurgitation is rarely present with a grade 1 to 2 murmur; however, the range of severity is wide with a grade 3 murmur. An ECG and an echocardiogram may be necessary (see Box 38-6). Chronic mitral regurgitation is generally well tolerated perioperatively, unless other valvular lesions (e.g., mitral or aortic stenosis) or left ventricular dysfunction coexist. Prophylaxis for infective endocarditis is no longer recommended.[94]

Mitral Valve Prolapse. Also known as click-murmur or floppy valve syndrome, MVP is commonly diagnosed in young women during evaluation for atypical chest pain, palpitations, or syncope. Whether these symptoms are truly related is questionable. Men who are more than 55 years old and who have MVP are more likely to have regurgitation and complications, and they are at greatest risk for infective endocarditis. The important preoperative issue is to differentiate patients with clinically significant mitral valve degeneration and regurgitation from those with an incidental finding of prolapse that does not warrant further evaluation or management. Patients taking β-adrenergic blockers for control of palpitations or atypical chest pain should continue taking these drugs perioperatively. Prophylaxis for infective endocarditis is no longer recommended.[94]

Tricuspid Regurgitation. Tricuspid regurgitation is a relatively common abnormality; however, because it is usually asymptomatic and not audible on physical examination, it is most commonly noted by echocardiography performed for other reasons. A small degree of tricuspid regurgitation is present in approximately 70% of normal adults. Tricuspid regurgitation is most commonly caused by dilatation of the right ventricle and the tricuspid annulus. Right ventricular dilatation results from conditions that directly involve the right ventricle (ischemia, cardiomyopathy) or from pulmonary hypertension and resulting elevations in right ventricular systolic pressure. Tricuspid regurgitation and mitral regurgitation often occur together. Tricuspid regurgitation is less often caused by processes that directly affect the tricuspid valve, such as Ebstein anomaly (congenital malformation), infective endocarditis (typically in intravenous drug users), rheumatic fever, carcinoid syndrome, connective tissue disorders (Marfan syndrome), myxomatous degeneration, or injury (e.g., pacemaker lead, central venous line, ICD lead). Drugs such as anorectics (i.e., fenfluramine, phentermine) and pergolide (dopamine agonist) may cause tricuspid regurgitation by a mechanism similar to carcinoid syndrome. These drugs are no longer available in the United States.

Tricuspid regurgitation is classically associated with a holosystolic murmur that is best heard at the right or left midsternal border or at the subxiphoid area. When the right ventricle is greatly enlarged, the murmur may even be appreciated at the apex. Usually, little radiation of the murmur occurs, and a thrill is not palpable. The murmur of tricuspid insufficiency is often soft or absent, even when regurgitation is severe. Interventions that result in an increase in venous return (e.g., leg raising, exercise, hepatic compression) augment the murmur of tricuspid regurgitation. The murmur may also become louder after a premature beat and prolonged diastole (secondary to augmented preload). In contrast, reducing venous return (e.g., standing, amyl nitrate) diminishes the intensity of the murmur. In patients with pulmonary hypertension, the intensity of the murmur may change with changes in pressure in the pulmonary artery and therefore the right ventricle. Patients with, or suspected of having, pulmonary hypertension must be managed by a pulmonary hypertension specialist (see the later section on pulmonary hypertension). An ECG, echocardiogram, and often a chest radiograph may be indicated. Prophylaxis for infective endocarditis is no longer recommended.[94]

Hypertrophic Cardiomyopathy. Previously known as hypertrophic obstructive cardiomyopathy or idiopathic hypertrophic subaortic stenosis, HCM can have either a familial or a nonfamilial basis. Patients with HCM are often young male patients who may be asymptomatic and without murmurs. An ECG and an echocardiogram should be obtained if the patient has a personal or family history of syncope with exertion or sudden death or when a murmur consistent with this disorder is detected. Characteristics of the murmur are described in Table 38-6. A maneuver that decreases diastolic volume or increases contractility increases the intensity of the murmur. Thus, passive leg raising and squatting decrease the intensity, whereas the Valsalva maneuver increases it. Other indicators may be LVH and ST-segment and T-wave abnormalities on an ECG in an otherwise healthy nonhypertensive patient, and further evaluation with echocardiography is warranted. These patients are at risk for sudden cardiac

death, likely from arrhythmias. An ECG and an echocardiogram are indicated (see Box 38-6). Holter monitoring may be useful in some patients. Many patients are treated with β-adrenergic blockers to decrease contractility; these medications should be continued perioperatively. An ICD may be in place to prevent sudden death. Prophylaxis for infective endocarditis is no longer recommended.[94]

Prosthetic Heart Valves. The most important preoperative issues in patients with prosthetic heart valves are determinations of the underlying condition requiring replacement, the type of prosthesis, the need for anticoagulation, and the planned anticoagulation management of such patients in the perioperative period. Patients may also have valve-related hemolysis. In descending order of risk, the risk of thrombosis is greatest with multiple valves, mitral valve replacements, and aortic valve replacements. Caged-ball valves (e.g., Starr-Edwards) have the highest risk, single tilting-disk valves (e.g., Björk-Shiley, Medtronic-Hall, Omnicarbon) have an intermediate risk, and the lowest risk is with bileaflet tilting-disk prostheses (e.g., St. Jude, CarboMedics, Edwards Duromedics). Bioprosthetic valves such as Carpentier-Edwards or Hancock brands generally do not require long-term anticoagulation. Decisions about stopping anticoagulants, the duration of anticoagulant discontinuance, the use of "bridging" with a shorter-acting drug, and the type of bridging agent (intravenous heparin or LMWH) are made in conjunction with the treating cardiologist and surgeon. Prophylaxis for infective endocarditis is recommended for specific procedures and is discussed in the next section.[94]

Infective Endocarditis Prophylaxis

Patients at risk for infective endocarditis (e.g., valve replacements, complex congenital heart disease, previous endocarditis) and scheduled for procedures with the potential for transient bacteremia must be identified preoperatively. Current guidelines have dramatically scaled back the range of conditions and procedures warranting prophylaxis.[94] Prophylaxis is now recommended only for patients with cardiac conditions with the highest risk of major adverse outcomes (Box 38-7), not necessarily the highest risk of acquiring endocarditis. For example, MVP is the most common underlying condition predisposing to endocarditis in industrialized countries, yet infection in the setting of MVP is rarely associated with severe complications. The absolute risk rate for infective endocarditis with MVP is thought to be 1 in 1.1 million procedures. Prophylaxis to prevent endocarditis is also no longer recommended for patients with valvular abnormalities (other than transplant recipients). Prophylaxis is recommended only for a limited number of "dirty" procedures. Patients who are having procedures on infected skin or musculoskeletal tissues and who also have one of the conditions listed in Box 38-7 receive prophylaxis. Many procedures involving the gastrointestinal and genitourinary tracts may cause transient bacteremia; however, reports of endocarditis associated with these procedures are anecdotal. The current guidelines recommend prophylaxis only for at-risk patients (see Box 38-7) undergoing urinary tract procedural manipulation (e.g., cystoscopy) in the presence of enterococcal urinary infection or colonization. If the procedure is elective, infection should be eradicated before the procedure is performed. No prophylaxis is recommended for upper and lower gastrointestinal diagnostic endoscopic procedures.

BOX 38-7 ***Cardiac Conditions Associated With the Highest Risk of Adverse Outcome From Endocarditis, for Which Prophylaxis Is Recommended***

- Previous infective endocarditis
- Congenital heart disease*
  - Unrepaired cyanotic congenital heart disease, including palliative shunts and conduits
  - Completely repaired congenital heart defects with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†
  - Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibited endothelialization)
- Cardiac valvulopathy that develops in cardiac transplantation recipients

Modified from Wilson W, Taubert K, Gewitz M, et al: Prevention of infective endocarditis: guidelines from the American Heart Association. A Guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group, Circulation *16:1736-1754, 2007.*

*Antibiotic prophylaxis is no longer recommended for forms of congenital heart disease not listed in this table.

†Prophylaxis is recommended because prosthetic material is endothelialized within 6 months after the procedure.

Rhythm Disturbances on the Preoperative Electrocardiogram

Arrhythmias and conduction disturbances are common in the perioperative period. Supraventricular and ventricular arrhythmias are associated with a higher risk of perioperative adverse events, both because of the arrhythmias themselves and because they are markers for cardiopulmonary disease. Uncontrolled atrial fibrillation and ventricular tachycardia are high-risk clinical predictors, and elective surgery is postponed until evaluation and stabilization are complete. New-onset atrial fibrillation, uncontrolled atrial fibrillation (rates >100 beats/minute), symptomatic bradycardia, or high-grade heart block (second- or third-degree heart block), warrants postponement of elective procedures and referral to cardiology for further evaluation.

First-degree AV block is defined as a PR interval exceeding 0.20 msec with an HR of 50 to 100 beats/minute, and it is generally benign. Second-degree heart block occurs when the PR interval exceeds 0.20 msec and some atrial beats are blocked, resulting in a dropped or missing QRS complex after a P wave. Two types of second-degree block exist. Mobitz type I, or Wenckebach block, is more benign, rarely progresses to complete heart block, and is easily responsive to atropine. Because of AV nodal delay, it is characterized by progressive lengthening of the PR interval until the dropped beat occurs. Mobitz type II block results

from an infranodal block, can progress to complete heart block, and is generally treated with a pacemaker unless the condition is secondary to a reversible cause such as ischemia or drugs. Mobitz type II block is characterized by a fixed, prolonged PR interval that does not change before the dropped QRS complex. Third-degree or complete heart block is complete dissociation between the atrial and ventricular beats and requires a pacemaker unless a reversible source is identified. Two general factors are considered when determining the need for a pacemaker: an arrhythmia associated with symptoms and the location of the conduction abnormality. Syncope or near syncope associated with bradycardia or conduction delays is generally an indication for pacemaker placement. Disease below the AV node, in the His-Purkinje system, is also ominous. Such conduction disease is suggested by a normal or minimally prolonged PR interval, Mobitz type II block, and QRS abnormalities (BBB, fascicular block, or both). Disease in the His-Purkinje system is generally less stable and likely benefits from permanent pacemaker placement. Indications for perioperative pacemaker placement are the same as those in nonsurgical patients (Box 38-8).[96]

BBBs are complete or incomplete, and they manifest as either RBBB or LBBB. They can be normal variants, or they can result from aging or fibrosis of the conducting system, ischemia, pulmonary disease, radiation, and cardiomyopathies. A recent onset (or no previous evaluation) of BBB prompts a more extensive consideration of cardiac risk. A previous ECG for comparison helps differentiate a long-standing abnormality from a new development. Nonetheless, even if the LBBB was present in a previous ECG, the patient should be appropriately assessed if no prior cardiac evaluation was performed. An LBBB on an ECG necessitates a detailed history and examination to ascertain the presence of cardiac disease and associated risk factors. Traditionally, LBBB has been considered more ominous and is associated with CAD and heart failure.[97,98] RBBB is more likely than LBBB to be related to congenital causes, pulmonary disease, or degeneration of the conduction system. Brugada syndrome is a congenital disease characterized by RBBB with ST-segment elevation in the right precordial leads and is associated with sudden death and lethal arrhythmias. If the history and physical examination do not suggest significant pulmonary, congenital, or ischemic heart disease or Brugada syndrome, no further evaluation of an isolated RBBB is warranted. An RBBB in a patient with pulmonary symptoms (including pulmonary hypertension) may suggest severe respiratory or vascular compromise; consideration should be given to pulmonary evaluation and echocardiography if intermediate- or high-risk surgery is planned. If congenital heart disease, pulmonary hypertension, or Brugada syndrome is suspected, a cardiology consultation is indicated.

A prolonged QT interval should prompt an evaluation of electrolytes, magnesium, and calcium, as well as a search for potentiating drugs. Syncope, presyncope, or a family history of sudden death in a patient with a prolonged QT interval mandates cardiology consultation.

Atrial Fibrillation. Atrial fibrillation can occur in the setting of increased age, thyrotoxicosis, and valvular heart disease. It also occurs in the perioperative setting. Atrial fibrillation can be intermittent (i.e., paroxysmal), persistent (i.e., capable of being cardioverted), or permanent (i.e., cannot be converted). In general, HR control is more important than rhythm control.[99,100] Patients with rapid ventricular rates, exceeding 100 beats/minute, require rate control before elective surgical procedures.[5] Patients with slow ventricular rates without any rate-controlling medications may have sick sinus syndrome; these individuals should be questioned carefully regarding any previous syncopal or presyncopal episodes. In addition, Holter monitor testing may be warranted. Most patients with atrial fibrillation require long-term anticoagulation, which entails perioperative management. The requirement for bridging anticoagulation therapy during the perioperative period is based on a patient's expected risk for stroke related to the atrial fibrillation. Patients with atrial or ventricular thrombi, mechanical heart valves, or a history of previous thromboembolic events are at higher risk for stroke. In addition, the $CHADS_2$ (congestive heart failure, hypertension, age, diabetes, stroke) index can more accurately estimate the risk of stroke in individuals with nonrheumatic atrial fibrillation.[101] This index consists of five components: congestive heart failure, hypertension (BP >140/90 mm Hg), age 75 years or older, diabetes, and prior thromboembolism (including stroke or transient ischemic attack). Each risk factor is assigned

BOX 38-8 *Indications for a Pacemaker*

Class I Indications*

- Sinus bradycardia with symptoms clearly related to the bradycardia (usually with a heart rate <40 beats/minute or frequent sinus pauses)
- Symptomatic chronotropic incompetence
- Complete (third-degree) AV block†
- Advanced second-degree AV block (block of >2 consecutive P waves)
- Symptomatic Mobitz I or II second-degree AV block
- Mobitz II second-degree AV block with a widened QRS complex or chronic bifascicular block, regardless of symptoms

Class 2 Indications‡

- Sinus bradycardia (heart rate <40 beats/minute) with symptoms suggestive of bradycardia but without a clear association between bradycardia and symptoms
- Sinus node dysfunction with unexplained syncope
- Chronic heart rates <30 beats/minute in an awake patient

Modified from Gregoratos, G, Abrams, J, Epstein, AE, et al: ACC/AHA/NASPE 2002 Guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines), Circulation *106:2145-2161, 2002.*

AV, Atrioventricular.

*Class I indications: Conditions in which permanent pacing is definitely beneficial and effective, provided the condition does not have a transient cause.

†Controversy exists concerning complete AV block without symptoms. The current American College of Cardiology Foundation and American Heart Association guidelines classify asymptomatic third-degree AV block with average awake ventricular rates ≥40 beats/minute as a class 2a indication, although others recommend definite pacemaker placement.

‡Class II indications: Conditions in which permanent pacing may be indicated but conflicting evidence and a divergence of opinon exist.

one point except for prior thromboembolism, which is assigned two points. Guidelines from the American College of Chest Physicians recommend consideration of bridging therapy for patients who have $CHADS_2$ scores of 3 or more.[102] In general, the perioperative management of a patient's long-term anticoagulant therapy is made in concert with the treating physician. Any β-adrenergic blockers, digoxin, calcium channel blockers, or antiarrhythmic medications used for atrial fibrillation should be continued perioperatively.

Supraventricular Arrhythmias. Supraventricular tachycardia results from rapidly firing ectopic atrial foci with rapid conduction through the AV node or from a reentry mechanism through accessory pathways. In a reentry mechanism, the cycle self-perpetuates because conduction occurs down one pathway and up the other, involving both the AV node-Purkinje system and the accessory pathway. Various degrees of AV block may slow the ventricular rate. Wolff-Parkinson-White (WPW) syndrome is characterized by the presence of an accessory pathway (called bundle of Kent) that permits both retrograde and antegrade conduction. Antegrade conduction over the accessory pathway results in a short PR interval (<0.12 msec) and a slurring of the upstroke of the QRS complex (termed a delta wave). Individuals with WPW syndrome are predisposed to supraventricular tachycardia. In individuals with WPW syndrome, treatment of supraventricular tachycardia with AV nodal blocking drugs (e.g., β-adrenergic blockers, calcium channel blockers, digoxin) can paradoxically increase conduction over the accessory pathway, thus potentially causing ventricular fibrillation. Lidocaine and procainamide are the preferred drugs for treating supraventricular tachycardia in patients with WPW syndrome. Patients with WPW syndrome typically undergo ablation for long-term management of their conduction before any elective surgery.

Ventricular Arrhythmias. Ventricular ectopic beats can be differentiated from atrial ectopic beats by a wide QRS complex (>0.12 msec) and lack of a P wave. Classifying ventricular arrhythmias according to the type of rhythm disturbance and the presence of coexisting heart disease helps predict the risk of sudden death, as follows:

- Benign: isolated ventricular premature beats (VPBs) without associated heart disease
  - No need for further evaluation
  - No risk of sudden cardiac arrest
- Potentially lethal: more than 30 VPBs/hour or nonsustained ventricular tachycardia with underlying heart disease
  - Requires cardiology evaluation with echocardiography, as well as possible stress testing, coronary angiography, and electrophysiology testing
  - Moderately high risk of sudden cardiac arrest; possible benefit from an ICD
- Lethal: sustained ventricular tachycardia, ventricular fibrillation, syncope, or hemodynamic compromise associated with VPBs with underlying heart disease and depressed cardiac function
  - Requires cardiology evaluation with echocardiography, as well as possible stress testing, coronary angiography, and electrophysiology testing
  - High risk of sudden cardiac arrest; likelihood of benefiting from an ICD

Reversible causes such as hypokalemia, ischemia, acidosis, hypomagnesemia, drug toxicity, and endocrine dysfunction must be sought out and treated. Antiarrhythmic medication must be continued perioperatively.

Prolonged QT Syndrome. The long QT syndrome (LQTS) is a disorder of myocardial repolarization that can be either genetic or acquired. It is associated with *torsades de pointes*, a polymorphic ventricular tachycardia with frequent variations of the QRS axis or morphology. Symptoms include palpitations, syncope, seizures, and sudden cardiac death. The ECG in individuals with LQTS shows a prolonged QT interval. The QT interval is measured in lead II of a 12-lead ECG from the onset of the QRS complex to the end of the T wave. Because the QT interval varies inversely with HR, the QT_c (corrected for HR) can be calculated (QT_c = QT interval + square root of the RR interval). In children 1 to 15 years old, a QT_c exceeding 0.46 seconds is considered prolonged. Otherwise, a QT_c is prolonged if exceeding 0.47 seconds in women and 0.45 seconds in men.

Acquired LQTS results from hypokalemia, hypomagnesemia, and eating disorders, as well as specific drugs such as antiarrhythmic drugs (quinidine) and psychotropic drugs (haloperidol, droperidol, methadone). Concerns over methadone prompted a safety alert by the U.S. Food and Drug Administration in 2006, and reports of adverse events with droperidol resulted in a black box warning and subsequent removal of the drug from the U.S. market. Amiodarone markedly prolongs the QT interval but is rarely associated with *torsades de pointes*, except in association with hypokalemia. The ACCF/AHA scientific statement on the prevention of *torsades de pointes* suggests that QT_c be documented before initiation of QT-prolonging drugs and thereafter at least every 8 to 12 hours.[103] Other components of treating individuals with LQTS include β-adrenergic blockers (congenital LQTS), ICD implantation, and correction of underlying metabolic disorders.

Brugada Syndrome. Brugada syndrome is a rare cause of sudden cardiac arrest that occurs without structural heart disease. Most affected individuals are of Asian ethnicity. Brugada syndrome is an autosomal dominant disorder that is much more common in men and rarely diagnosed in children. It is associated with a peculiar ECG consisting of a pseudo-RBBB and persistent ST-segment elevation in V_1 to V_3 (Fig. 38-6). The widened S wave in the left lateral leads, as is typical of usual RBBB, is absent in most patients with Brugada syndrome. In some patients, these ECG changes are transient and provoked by medications. The website www.brugadadrugs.org lists drugs that are associated with adverse events in Brugada syndrome. Some are commonly used anesthetic drugs, including propofol and bupivacaine. Findings on echocardiography, stress testing, and cardiac MRI in these individuals

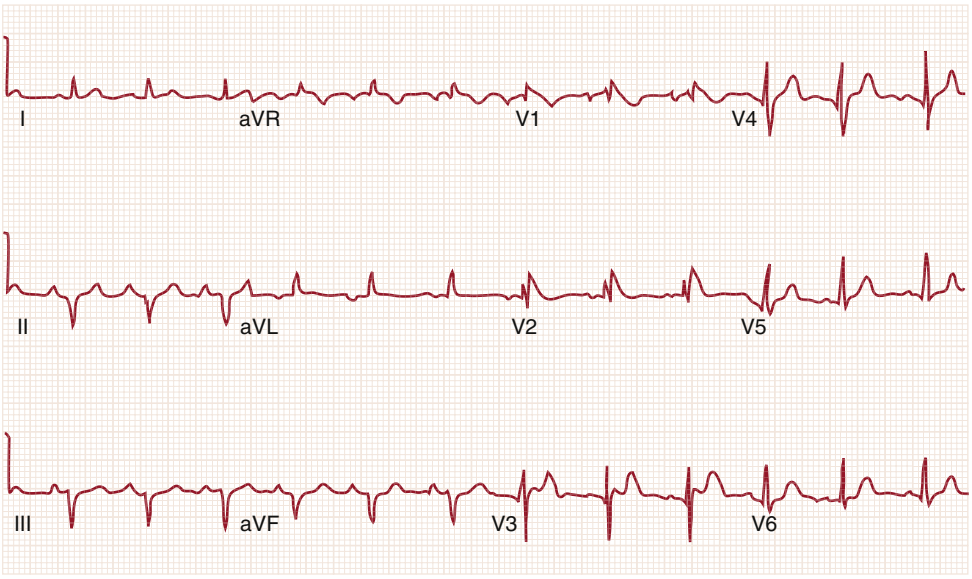


Figure 38-6. Typical 12-lead electrocardiogram in a patient with Brugada syndrome.

TABLE 38-8 **PACEMAKER NOMENCLATURE**

Position I	Position II	Position III	Position IV	Position V
Chamber(s) paced **O** = None **A** = Atrium **V** = Ventricle **D** = Dual (A+V)	Chamber(s) sensed **O** = None **A** = Atrium **V** = Ventricle **D** = Dual (A+V)	Response to sensing **O** = None **I** = Inhibited **T** = Triggered **D** = Dual (T+I)	Rate modulation **O** = None **R** = Rate modulation	Multisite pacing **O** = None **A** = Atrium **V** = Ventricle **D** = Dual (A+V)

From Bernstein AD, Daubert JC, Fletcher RD, et al: The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing: North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group, Pacing Clin Electrophysiol *25:260-264, 2002.*

are usually normal. The most significant clinical manifestations are ventricular arrhythmias, syncope, and sudden death. These patients may also be at increased risk of atrial arrhythmias, especially atrial fibrillation. The syndrome has no proven pharmacologic treatment; indeed, class I antiarrhythmic medications (e.g., flecainide, procainamide) and β-adrenergic blockers can worsen the risk of lethal arrhythmias. ICD implantation is the standard of care.

Cardiovascular Implantable Electronic Device: Pacemakers and Implantable Cardioverter-Defibrillators

More than 100,000 new CIEDs are implanted yearly in the United States (see also Chapters 48 and 68). The preoperative evaluation should determine the type of device, as well as features (e.g., rate modulation) likely to malfunction with perioperative electromagnetic interference. Patients frequently carry a wallet card with important designations and phone numbers. Equally important is the need to evaluate the coexisting cardiac disease because these patients invariably have conditions such as heart failure, ischemic heart disease, valvular heart disease, or potentially lethal arrhythmias.

Pacemakers are designated with a five-letter code (Table 38-8),[104] and consultation with the device manufacturer, cardiologist, or the electrophysiology or CIED service may be needed (Box 38-9). Ideally, patients with CIEDs have these devices interrogated preoperatively. Special features such as rate-adaptive mechanisms and antitachyarrhythmia functions must be disabled, or the device must be reprogrammed to an asynchronous pacing mode before surgical procedures where interference may occur.[105] Electromagnetic interference is likely to occur with electrocautery, radiofrequency ablation, MRI, and radiation therapy; it can result in malfunction or adverse events.[105] Patient monitors, ventilators, vibrations, or chest preparation can be misinterpreted by the sensors such that the pacing rate is increased, with the possibility of tachycardia, ischemia, or inappropriate shocks. An ICD can also misinterpret electrocautery as an arrhythmia and can inappropriately shock a patient. During delicate surgical procedures (e.g., intracranial, spinal, ocular), an unexpected discharge with movement of the patient can have catastrophic results. Central line placement can also trigger cardioversion.

Given the complexity of newer-generation CIEDs, reliance on a magnet without specific information about the CIED is not recommended, except in emergency situations. In fact, some CIEDs from certain manufacturers are programmed to ignore magnet placement or have antitachyarrhythmia therapy *permanently* disabled by magnet placement. Depending on the available resources, it may

BOX 38-9 ***Proposed Principles for Cardiovascular Implantable Electronic Device Management***

The perioperative management of CIEDs must be individualized to the patient, the type of CIED, and the procedure being performed. A single recommendation for all patients with CIEDs is not appropriate.

The CIED team is defined as the physicians and physician extenders who monitor the CIED function of the patient.

The surgical or procedural team should communicate with the CIED team to identify the type of procedure and the likely risk of EMI.

The CIED team should communicate with the procedure team to deliver a prescription for the perioperative management of patients with CIEDs.

For most patients, the prescription can be made from a review of the records of the CIED clinic. A few patients may require consultation with CIED specialists if the information is not available.

It is inappropriate to have industry-employed allied health professionals independently develop this prescription.

From Crossley GH, Poole JE, Rozner MA, et al: The Heart Rhythm Society (HRS)/American Society of Anesthesiologists (ASA) expert consensus statement on the perioperative management of patients with implantable defibrillators, pacemakers and implantable monitors: facilities and patient management: executive summary, Heart Rhythm *8:e1-e18, 2011.*

CIED, Cardiovascular implantable electronic device; *EMI,* electromagnetic interference.

not be appropriate to care for these patients in some facilities. These individuals require a preoperative ECG, while a chest radiograph can reveal the manufacturer's code. Communication and guidance with an electrophysiology specialist comprise the preferred approach for managing these patients. Preoperative recommendations for CIEDs are presented in Box 38-10.

Peripheral Arterial Disease

Formerly called peripheral vascular disease, PAD refers to aneurysmal or occlusive arterial disease of the extremities, visceral organs, head, neck, and brain. In many patients, PAD is secondary to tobacco use, diabetes, hyperlipidemia, and hypertension. Patients with Marfan syndrome or Ehlers-Danlos syndrome may have aneurysmal disease without other risk factors. Renal insufficiency and cerebrovascular disease are also common in these patients. Patients with PAD frequently have concomitant CAD. For example, in a study of 1000 consecutive patients scheduled for major vascular surgery, almost 60% had critical stenosis in at least one major coronary vessel.[106] Although the high perioperative cardiac risk of vascular surgery is well appreciated, patients with PAD have a high cardiac risk even when undergoing nonvascular surgery. For example, a reduced ankle-to-arm BP index, which indicates PAD, is independently associated with an increased perioperative cardiac risk following noncardiac surgery.[107] In addition, claudication related to PAD generally limits functional capacity and thereby masks the symptoms of underlying ischemic heart disease. If significant vascular disease is diagnosed during an examination for nonvascular surgery, referral to a vascular specialist is needed.

BOX 38-10 ***Preoperative Recommendations for Cardiovascular Implantable Electronic Devices***

- Inactivation of ICDs is not absolutely necessary for all procedures.
- Not all pacemakers need to be altered to pace asynchronously in all patients or for all procedures.
- Pacemakers can be reprogrammed or magnets can be used to force pacemakers to pace asynchronously to prevent inhibition.
- ICDs can be reprogrammed or magnets can be used to inhibit ICD arrhythmia detection and tachyarrhythmia functions.
- Magnets *cannot* or *will not* force pacemakers in ICDs to pace asynchronously.
- Inactivation of ICDs is recommended for all procedures above the umbilicus involving electrocautery or radiofrequency ablation.
- It is preferable to change to asynchronous pacing in pacemaker-dependent patients for procedures involving electrocautery or radiofrequency ablation above the umbilicus.

The procedure team provides the following information to the CIED team:

- Type of procedure
- Anatomic site of the procedure
- Patient position during the procedure
- Whether electrocautery will be used (and if so, type of cautery)
- Whether other sources of EMI are present
- Other issues such as likelihood of damage to leads (e.g., chest procedures), anticipated large blood loss, and surgery in close proximity to the CIED

The CIED team provides the following information to the procedure team:

- Type of device (e.g., pacemaker, ICD)
- Indication for the device (e.g., sick sinus syndrome, primary or secondary prevention of lethal arrhythmias)
- Programming (e.g., pacing mode, rate, rate responsive, heart rates for shock delivery)
- Whether the patient is pacemaker dependent and the patient's underlying heart rate and rhythm
- Magnet response
  - Pacing rate
  - Whether the device is responsive to a magnet
  - Whether ICD functions will resume automatically after magnet removal
  - Whether the magnet must be placed off-center

Modified from Crossley GH, Poole JE, Rozner MA, et al: The Heart Rhythm Society (HRS)/American Society of Anesthesiologists (ASA) expert consensus statement on the perioperative management of patients with implantable defibrillators, pacemakers and implantable monitors: facilities and patient management: executive summary, Heart Rhythm *8:e1-e18, 2011.*

CIED, Cardiovascular implantable electronic device; *EMI,* electromagnetic interference; *ICD,* implantable cardioverter-defibrillator.

Arterial BPs should be measured in both upper extremities, and the presence of peripheral pulses in these patients should be assessed. Auscultation for bruits over the abdomen and femoral arteries, as well as palpation for abdominal masses, should be part of the vascular examination. A creatinine concentration should be determined before procedures involving injection of radiocontrast dye. These dyes can damage an already compromised kidney. Many patients take aspirin or dipyridamole,

a vasodilator with antiplatelet effects that are reversible on discontinuation. Dipyridamole's elimination half-life is approximately 10 hours, and its discontinuation for 48 hours is sufficient to eliminate its antiplatelet effect. Nonetheless, the risks of stopping antiplatelet drugs must be also considered. Continuation of antiplatelet drugs is preferable for almost all vascular procedures.

PULMONARY DISORDERS

See also Chapters 19 and 66.

Asthma

Asthma is a chronic inflammatory disease characterized by obstruction of the airways that is partially or completely reversible with treatment or spontaneously.[108] Bronchoconstriction is precipitated by irritants (e.g., smoke), allergens, infections, medications, or airway instrumentation. Asthma is classified as intermittent, persistent mild, persistent moderate, and persistent severe, based on the degree of impairment and on whether symptoms are intermittent or constant. Patients with mild, well-controlled asthma have no greater perioperative risk than do individuals without asthma.

A history of asthma should be associated with further questioning about shortness of breath, chest tightness, cough (especially nocturnal), recent exacerbations, therapy (especially steroids), prior hospitalizations or emergency department visits, critical care unit admissions, and endotracheal intubations. The patient's best exercise level is important information for risk assessment. Previous exacerbations with anesthesia must be explored. Patients with asthma can estimate their breathing capacity based on their estimated percentage at which they are currently functioning. Medical therapy must be determined. The quality of breath sounds, quantity of air movement, and degree of wheezing are important. The degree of wheezing does not always correlate with the severity of bronchoconstriction. With severe obstruction, airflow is dangerously restricted, and wheezing diminishes. Wheezing is common in asthmatic patients, but it is not specific for this disease. Patients with chronic obstructive pulmonary disease (COPD), gastroesophageal reflux disease, vocal cord dysfunction, tracheal stenosis, bronchial stenosis, cystic fibrosis, allergic bronchopulmonary aspergillosis, and heart failure may also wheeze. Observing the degree of accessory muscle use helps gauge severity of the bronchoconstriction. Determining oxygen saturation by pulse oximetry is needed.

Analysis of arterial blood gases is *not* necessary unless the patient is having a severe acute exacerbation. Patients taking oral steroids must have their blood glucose checked. Chest radiography is necessary only to evaluate infections or pneumothorax. Spirometry is the preferred diagnostic test for asthma, but a normal result does not exclude asthma. A methacholine challenge test or a trial of bronchodilator therapy is indicated if results of spirometry are normal but a strong suspicion of asthma still exists. PFTs have no perioperative predictive value for asthmatic patients. Typical findings on PFTs include reduced forced expiratory volume in 1 second (FEV_1) and normal to slightly reduced forced vital capacity (FRC). Bronchodilators, inhaled and oral steroids, and antibiotics (if taken) must be continued on the day of surgery. The use of β-adrenergic agonists is the most useful prophylactic intervention to lower the risk of bronchospasm on induction of anesthesia. A short course of steroids (20 to 60 mg of prednisone daily for 3 to 5 days) preoperatively may be considered in any patient who is not "as good as they can be." Specifically, a 5-day course of 40 mg oral methylprednisolone daily before surgery decreases posttracheal intubation wheezing in a newly diagnosed or poorly compliant asthmatic patient.[109] Inhalers and any long-term medications for asthma should be continued on the day of surgery.

Chronic Obstructive Pulmonary Disease

COPD is characterized by persistent (sometimes partially reversible) airflow obstruction (see also Chapters 19 and 39). It is often the result of smoking, environmental pollutants (e.g., air pollution, dust), α_1-antitrypsin deficiency, chronic infections, and long-standing asthma. Historically, COPD was characterized as "chronic bronchitis" and "emphysema." Chronic bronchitis is a persistent productive cough for at least 3 months per year in 2 consecutive years. The *contemporary* definition of COPD, based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD), is a preventable and treatable disease with a pulmonary airflow limitation that is progressive, not fully reversible, and associated with an abnormal inflammatory response of the lung to noxious particles or gases (see http://www.goldcopd.org). This definition is largely consistent with that proposed by the American Thoracic Society and the European Respiratory Society.[110] Dyspnea, cough, wheezing, and sputum production are common features. The severity of COPD is classified based on spirometry findings, specifically forced vital capacity (FVC) and FEV_1. In patients with an FEV_1/FVC ratio of 0.7 or less, COPD is *mild* if FEV_1 is at or greater than 80% of predicted, *moderate* if FEV_1 is between 50% and 80% of predicted, *severe* if FEV_1 is between 30% and 50% of predicted, and *very severe* if less than 30% of predicted. An acute exacerbation is defined as an "acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication" (see http://www.goldcopd.org).

The history and physical examination for patients with COPD are similar to those for patients with asthma, with an additional emphasis on changes in sputum amount, color, or other signs of infection. A barrel chest and pursed-lip breathing suggest advanced disease. Typically, the FEV_1 is reduced secondary to obstruction of airflow, whereas the FRC is increased because of reduced airflow, loss of elasticity, and overexpansion. Diffusing capacity of the lung for carbon monoxide (D_{LCO}) is often decreased, with the severity of decrease often correlating with the degree of hypoxia and hypercarbia. PFT results are generally not predictive of perioperative outcomes in patients with COPD.[111] A preoperative determination of oxygen saturation by pulse oximetry is important to establish a baseline. Patients found to be hypoxic, or requiring supplemental oxygen, benefit from further testing, including arterial blood gas determinations. A chest

radiograph is useful only when infection or bullous disease is suspected. Right axis deviation, RBBB, or peaked P waves on an ECG suggest right ventricular changes and pulmonary hypertension. Inhalers and other long-term medications for COPD should be continued on the day of surgery.

Restrictive Pulmonary Disorders

Restrictive lung disease is characterized by a reduction in total lung capacity. Both pulmonary and extrapulmonary conditions can cause restrictive disease. Pulmonary causes include idiopathic interstitial pneumonia, prior lung resection, pulmonary fibrosis, and interstitial lung disease secondary to connective tissue disease. Extrapulmonary disorders may be related to chest wall limitations (e.g., kyphoscoliosis, obesity, ankylosing spondylitis), muscle dysfunction (e.g., muscular dystrophies, myasthenia gravis, paralyzed diaphragm), and pleural disease (e.g., mesothelioma, effusion, pneumothorax). The medical history of associated diseases or symptoms prompts the directed evaluation. Chest radiograph and PFTs may be indicated to establish a diagnosis or evaluate acute or progressive worsening; however, preoperative PFTs are not routinely necessary. Typically, the FEV_1 and the FVC are reduced proportionally such that the FEV_1/FVC ratio is normal (i.e., >0.7). These patients are at risk of pulmonary hypertension, which may not be recognized because of overlapping symptoms with restrictive lung disease.

Dyspnea

Dyspnea is a subjective experience of breathing discomfort. It is a symptom of deconditioning, obesity, and disorders of ventilation, cardiac function, perfusion, and oxygen delivery. Dyspnea is also associated with cardiac, pulmonary, hematologic, and neuromuscular diseases (Fig. 38-7). Patients with an insidious onset may not seek attention until quite late; often, they and their caregivers assume that the dyspnea results from being "out of shape." Dyspnea should not simply be attributed to deconditioning without a thorough investigation to rule out other causes. Most patients with chronic dyspnea of unclear etiology have one of four diagnoses: asthma, COPD, interstitial lung disease, or cardiac dysfunction.[112] The severity of dyspnea symptoms is classified using the NYHA functional class categories (see the section on heart failure).

The important facts to determine in the preoperative evaluation of dyspnea are its onset, progression, precipitating factors, associated symptoms (e.g., chest pain, leg edema, fatigue, syncope, or near syncope), associated conditions (e.g., arthritis, connective tissue disease, cardiac disease, smoking), and drug (or toxin) exposure. Asking about the quality of dyspnea can differentiate causes. Dyspnea secondary to deconditioning is usually described as "heavy breathing." Bronchoconstriction in asthma exacerbations is more commonly described as "tightness" or "air hunger," whereas patients with COPD complain of "not being able to take a deep breath" or an "increased effort to breathe." Patients with heart failure feel like they are "suffocating" or have "air hunger."[113] Orthopnea (dyspnea while recumbent) suggests heart failure. Coughing can be a symptom of heart failure, asthma, or COPD. Concomitant angina or a history of CAD in a dyspneic patient may indicate heart failure. Prior anorectic drug exposure

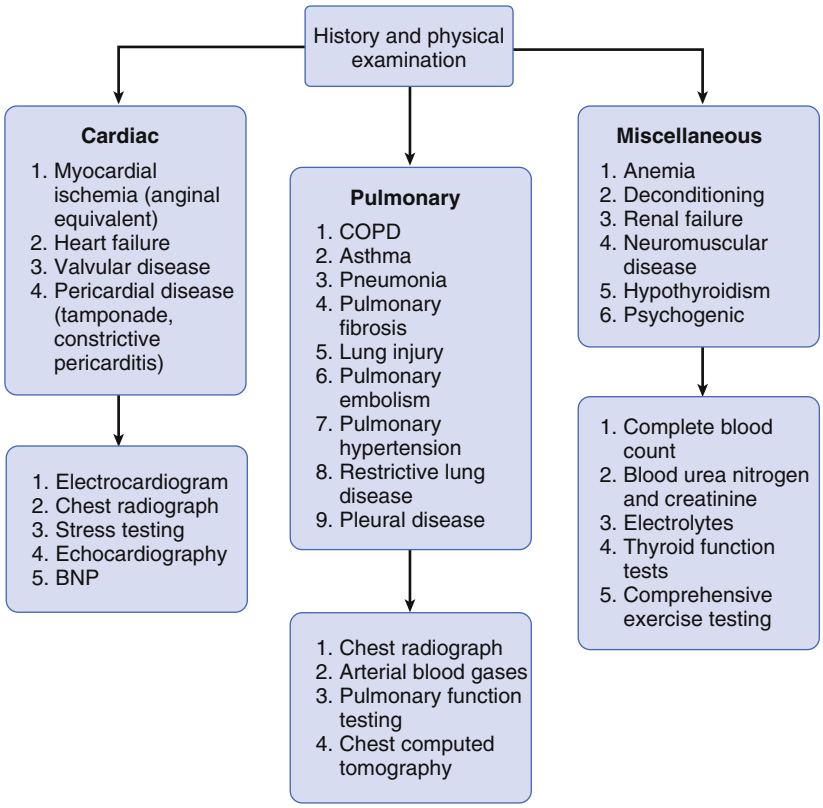


Figure 38-7. Classification scheme for causes of dyspnea. *BNP,* Brain natriuretic protein; *COPD,* chronic obstructive pulmonary disease.

may suggest pulmonary hypertension or valvular abnormalities as causes of dyspnea. Dyspnea in an individual with connective tissue disease may suggest secondary interstitial lung disease. Physical examination should assess for pallor, cyanosis, barrel chest, rales, wheezing, crackles, murmurs, abnormal heart sounds or rhythms, cardiomegaly, tachycardia, jugular venous distention, joint involvement, clubbing, fibrotic skin changes, and peripheral edema. Patients with severe airflow obstruction may have pursed lips and a slow deep breathing pattern, whereas patients with interstitial fibrosis or kyphoscoliosis typically have rapid shallow breathing.

The preoperative history and physical examination lead to accurate diagnoses in two thirds of cases. Initial testing includes an ECG, hematocrit (to exclude anemia), arterial blood gas analysis, thyroid function tests, chest radiograph, spirometry, and oximetry (at rest and after walking several feet). BNP levels may be useful. Most dyspneic patients with heart failure have BNP values exceeding 400 pg/mL, although plasma BNP concentrations between 100 and 400 pg/mL in a dyspneic patient should raise suspicions about compensated left ventricular dysfunction, pulmonary embolism, and cor pulmonale. Other specialized testing should be directed by the history, physical examination, and initial test results. Computed tomography (CT) scans and cardiopulmonary exercise testing (CPET) are rarely necessary, but they can be useful if the aforementioned tests are not diagnostic.

Patients Scheduled for Lung Resection

Most patients scheduled for lung resection operations have underlying lung disease, and PFTs may be useful in predicting risk or in excluding patients who lack adequate pulmonary reserve after resection (see also Chapter 66). The amount of residual lung function after resection can be estimated by using a combination of spirometry and radionuclide quantitative lung scanning. The estimated residual FEV_1 is predicted by multiplying the baseline FEV_1 by the percentage of radioactive counts from the nonoperative lung or lung region, as presented here[114]:

$$\text{Predicted postoperative } FEV_1 = FEV_1 \times \frac{\text{Radioactive counts in nonoperative lung}}{\text{Radioactive counts from both lungs}}$$

A predicted postoperative FEV_1 exceeding 0.8 L, or greater than 40% of predicted, indicates that sufficient lung tissue and ventilatory capacity will remain.[115] A postoperative FEV_1 or D_{LCO} less than 40% of predicted indicates increased perioperative risk. In patients undergoing pneumonectomy, a preoperative FEV_1 less than 2 L or 50% of predicted, maximal voluntary ventilation less than 50% of predicted, or D_{LCO} less than 60% indicates increased risk.[116]

If preoperative PFTs and ventilation-perfusion $\dot{V}/\dot{Q}$ scanning suggest that the patient is at great risk or may not be an operative candidate, additional information can be obtained with CPET and determinations of peak oxygen consumption (VO_{2peak}). Patients with preoperative VO_{2peak} greater than 20 mL/kg/minute have a low risk of complications or death, those with VO_{2peak} less than 15 mL/kg/minute have an increased risk; and those with VO_{2peak} less than 10 mL/kg/minute are at very high risk of postoperative complications. Stair climbing can also help predict VO_{2peak}. Patients who can climb five flights of stairs likely have a VO_{2peak} exceeding 20 mL/kg/minute. Conversely, patients who cannot climb one flight of stairs likely have a VO_{2peak} less than 10 mL/kg/minute.[117] Hypoxia with exertion or hypercarbia at rest is also associated with increased postoperative complications in patients having lung resection procedures.[117] This topic is covered in more detail in Chapter 66.

Obstructive Sleep Apnea

Sleep-disordered breathing affects up to 9% of middle-aged women and 24% of middle-aged men; less than 15% of these cases have been diagnosed (see also Chapters 19 and 39). OSA, which is the most common serious manifestation of sleep-disordered breathing, is caused by intermittent airway obstruction. It is characterized by total collapse of the airway with complete obstruction for more than 10 seconds. Obstructive hypopnea is partial collapse (30% to 99%) associated with at least a 4% arterial oxygen desaturation. Snoring, daytime sleepiness, hypertension, obesity, and a family history are risk factors for OSA.[118] The severity of OSA is measured based on the apnea-hypopnea index (AHI), which is the number of apneic and hypopneic episodes per hour of sleep. Patients with severe OSA have 30 or more episodes per hour.

Cardiovascular disease is common in patients with OSA. Patients have an increased prevalence of hypertension, atrial fibrillation, bradyarrhythmias, ventricular ectopy, stroke, heart failure, pulmonary hypertension, dilated cardiomyopathy, and CAD.[119] Mask ventilation, direct laryngoscopy, endotracheal intubation, and fiberoptic visualization of the airway are more difficult in patients with OSA (see Chapters 55 and 71). Such patients are likely to have perioperative airway obstruction, hypoxemia, atelectasis, ischemia, pneumonia, and prolonged hospitalizations.[120] Patients with OSA are more sensitive to the respiratory depressant effects of opioids. Once their coexisting comorbidities are accounted for, patients with OSA are *not* at increased risk for postoperative mortality.[39]

Preoperative evaluation focuses on identifying patients at risk for OSA and optimizing associated comorbid conditions. The STOP-Bang questionnaire, which was developed and validated in an anesthesia preoperative clinic, screens for OSA (Fig. 38-8).[38] Echocardiography may be indicated if heart failure or pulmonary hypertension is suspected. Patients should be instructed to bring their continuous positive airway pressure (CPAP) devices to the hospital on the day of operation.

Pulmonary Hypertension

Pulmonary hypertension may occur in isolation or with associated medical conditions and is defined as a persistent increase of mean pulmonary artery pressure of 25 mm Hg or more with a pulmonary artery occlusion pressure less than 15 mm Hg. According to the World Health Organization, pulmonary hypertension is classified into five groups (Box 38-11). Idiopathic pulmonary arterial hypertension, formerly called primary pulmonary hypertension, is relatively

STOP-Bang
Screening for Sleep Apnea

Have you been diagnosed with sleep apnea by a sleep study? Yes ☐ No ☐

Have you received treatment for sleep apnea, such as CPAP or Bi-PAP? Yes ☐ No ☐

Please answer the following four questions with a *yes* or *no* answer:

1) Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?
Yes ☐ No ☐

2) Do you often feel tired, fatigued, or sleepy during daytime?
Yes ☐ No ☐

3) Has anyone observed you stop breathing during your sleep?
Yes ☐ No ☐

4) Do you have or are you being treated for high blood pressure?
Yes ☐ No ☐

FOR STAFF USE ONLY, DO NOT WRITE BELOW THIS LINE

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5) Is the BMI ≥35 kg/m^2?
Yes ☐ No ☐

6) Is the patient ≥50 years of age?
Yes ☐ No ☐

7) Is the neck circumference greater than 15.7 inches (40 cm)?
Yes ☐ No ☐

8) Is the patient male?
Yes ☐ No ☐

Total number of questions answered YES: _____ Is the patient at high risk for OSA? Yes ☐ No ☐

High risk of OSA: Yes to >3 items

Figure 38-8. STOP-Bang questionnaire to screen patients for obstructive sleep apnea (OSA). *BMI,* Body mass index. *(From Chung F, Yegneswaran B, Liao P, et al: STOP questionnaire: a tool to screen patients for obstructive sleep apnea,* Anesthesiology *108:812-821, 2008.)*

rare. Other more common forms occur with a variety of diseases including cardiac, pulmonary, liver, thromboembolic, and collagen vascular diseases. Pulmonary hypertension is associated with HIV infection, anorectic drug exposure (e.g., fenfluramine), sleep apnea, chronic liver disease (especially with portal hypertension), and collagen vascular diseases (e.g., scleroderma, systemic lupus erythematosus [SLE]). Occult pulmonary hypertension is more problematic than fully recognized disease because symptoms may be attributed to other diseases, and perioperative decompensation may occur unexpectedly. The onset of pulmonary hypertension is usually nonspecific, insidious, and associated with delayed diagnosis. Dyspnea is the initial symptom in 60% of patients, but it is present in 98% by the time of diagnosis. Presyncopal or syncopal episodes portend severe disease.

Patients with pulmonary arterial hypertension have a high rate of perioperative morbidity and mortality.[121] Hypoxia, hypercarbia, vasoconstrictors, and increased sympathetic tone (even from anxiety) increase pulmonary vascular resistance, with the potential for acute decompensation with right-sided heart failure. Mild pulmonary hypertension rarely affects anesthetic management, but moderate to severe disease increases the risk of right-sided heart failure. Signs and symptoms of disease severity include dyspnea at rest, metabolic acidosis, hypoxemia, right-sided heart failure (peripheral edema, hepatomegaly, jugular venous distention), and syncope.[122] Physical examination may reveal a split S_2 with a loud second component, right ventricular heave, tricuspid regurgitation murmur, ascites, hepatomegaly, jugular venous distention, and peripheral edema. An ECG and a chest radiograph are useful in patients with more than mild disease. Typical ECG findings include right axis deviation, RBBB, right ventricular hypertrophy, and tall R waves in leads V_1 and V_2. Right atrial hypertrophy and "P-pulmonale" may be present in severe pulmonary hypertension, with peaked P waves, usually in leads II, III, aVF, and V_1. Enlargement of the main pulmonary artery and a globular heart shape with a loss of the retrosternal airspace from right ventricular dilation can be seen on a chest radiograph. In addition, testing for complete blood count (CBC); determination of electrolyte, BUN, and creatinine levels; and liver function tests (LFTs; may be elevated from congestion or bosentan) are needed. An echocardiogram is the initial screening test of choice and can assess the pulmonary artery pressure and right ventricular function, identify left-sided heart failure, and valvular or congenital heart disease[122] (see also Chapter 46). Patients with significant findings usually require right and left cardiac catheterizations, especially

BOX 38-11 *Classification Scheme for Pulmonary Hypertension*

Pulmonary Arterial Hypertension
- Primary pulmonary hypertension
  - Sporadic
  - Familial
- Associated with other conditions
  - Collagen vascular disease
  - Congenital shunts
  - Portal hypertension
  - Human immunodeficiency virus infection
  - Drugs or toxins
  - Persistent pulmonary hypertension of the newborn

Pulmonary Venous Hypertension
- Left-sided heart disease
- Extrinsic compression of the central pulmonary veins
- Pulmonary venoocclusive disease

Pulmonary Hypertension Related to Lung Disease or Hypoxemia
- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Sleep-disordered breathing
- Neonatal lung disease
- Chronic exposure to high altitude

Pulmonary Hypertension Caused by Chronic Thromboembolic Disease
- Pulmonary thrombosis or embolism
- Sickle cell disease

Pulmonary Hypertension From Disorders Directly Affecting the Pulmonary Vasculature
- Schistosomiasis
- Sarcoidosis

given the potential inaccuracy of estimating right-sided pressures by echocardiography alone.

Patients may be treated with diuretics, anticoagulation, calcium channel blockers, supplemental oxygen, sildenafil (phosphodiesterase inhibitor), endothelin receptor antagonists (e.g., bosentan), and prostanoids (e.g., iloprost, epoprostenol). Some of these drugs are given by continuous intravenous infusions, and even momentary interruption of therapy can be catastrophic. All drugs must be continued preoperatively. Management of these patients in conjunction with a pulmonary hypertension specialist is advised.

Smokers and Patients Exposed to Second-Hand Smoke

Exposure to tobacco, directly or through "second-hand" smoke, increases the risk of many perioperative complications. Smokers are more likely to experience wound infections, respiratory complications (including oxygen desaturation), and severe coughing.[123] Patients without ischemic heart disease who smoked shortly before operation have significantly more episodes of ST-segment depression than do nonsmokers, former smokers, or chronic smokers who do not smoke in the immediate preoperative period.[124] Smoking decreases macrophage function; negatively affects coronary flow reserve; and causes vascular endothelial dysfunction, hypertension, and ischemia. Smokers require longer hospital stays and often need more postoperative intensive care than do nonsmokers.

The greatest benefit of smoking abstinence is probably realized only after several months of cessation. In addition, the perioperative clinical benefits of preoperative smoking cessation demonstrated in systematic reviews are evident only when cessation occurred at least 3 to 4 weeks before the surgical procedure.[125] These benefits include reduced respiratory and wound healing complications. Despite an early study reporting an increased perioperative risk (this association was not statistically significant) in recent quitters,[126] a systematic review found no increased risk of adverse events with quitting smoking soon before surgical procedures (i.e., within 8 weeks).[127] Thus, motivated patients should quit smoking at any point before surgery. Quitting has many potential benefits, even within a few days before operation. Soon after a patient quits smoking, carbon monoxide levels decrease, thereby improving oxygen delivery and use. Cyanide levels decrease, and this benefits mitochondrial oxidative metabolism. Lower nicotine levels improve vasodilatation, and many toxic substances that impair wound healing decrease.

The U.S. Public Health Service recommends that "*all* physicians should strongly advise every patient who smokes to quit because evidence shows that physician advice to quit smoking increases abstinence rates."[128] Nearly 70% of smokers want to quit. Effective interventions include medical advice and pharmacotherapy, such as nicotine replacement therapy, which is safe in the perioperative period. Nicotine patches, gum, and lozenges are available without a prescription; nasal spray, bupropion (i.e., Zyban), and varenicline (i.e., Chantix) require prescriptions. Clonidine is also effective. Bupropion, varenicline, or clonidine is started 1 to 2 weeks before a quit attempt; nicotine replacement therapy is effective immediately. Individual and group counseling may increase rates of long-term abstinence. Many hospitals, insurance companies, and communities offer smoking cessation programs. Excellent resources are available on the Internet and from the U.S. government. Advice and guidelines are available at 1-800-QUITNOW and http://www.cdc.gov/TOBACCO/quit_smoking/index.htm. Tobacco intervention training during medical school and residency can significantly improve the quality of physician counseling and rates of abstinence.

Interventions in the preoperative clinic can cause significantly higher rates of short-term cessation of smoking (i.e., within 3 to 6 months after surgery).[129] The long-term benefits are less clear, although a randomized trial demonstrated reduced nicotine dependence of up to 1 year postoperatively with the institution of a perioperative smoking cessation intervention using varenicline.[130]

Upper Respiratory Tract Infections

Traditionally, elective surgical procedures were cancelled when patients, especially children, presented with current or recent upper respiratory tract infections (see also Chapter 93). With modern anesthetic practices, cancellation is not routine. In patients with severe symptoms, especially those with underlying conditions (e.g., significant asthma, heart disease, immunosuppression) that may further compromise a safe anesthetic regimen, elective surgical procedures are postponed for at least 4 weeks.[131]

When an infection is mild or uncomplicated in healthy patients, the risk in proceeding with a procedure to avoid the inconvenience of a cancellation is low. The dilemma lies with the patients between these two extremes. Decisions regarding suitability to proceed are made on an individual basis.

Cystic Fibrosis

Cystic fibrosis is an autosomal recessive disease caused by altered chloride and water transport across epithelial cells. It can result in a progressive chronic airway disease with airway obstruction, destruction, and frequent infections. Exocrine pancreatic insufficiency (i.e., malnutrition, diabetes, pancreatitis), bowel obstruction, sinusitis, and liver disease (biliary cirrhosis, portal hypertension) can also be present. The diagnosis is established on the basis of a sweat chloride concentration exceeding 60 mEq/L (sweat chloride test), in addition to one of the following: chronic airway disease, exocrine pancreatic insufficiency, or cystic fibrosis in a first-degree relative. A history and physical examination similar to those for patients with asthma and nutritional and hepatic assessments are necessary. Optimization of pulmonary status (treatment of secretions, infections, bronchospasm) is key. Electrolytes, LFTs, and chest radiographs are useful. Continuation of most medications is recommended. Management of these patients with a pulmonologist or a cystic fibrosis specialist is best.

Postoperative Pulmonary Complications

Postoperative pulmonary complications develop in 5% to 10% of patients undergoing nonthoracic surgery and in 22% of high-risk patients. Established risk factors for pulmonary complications include the following[132]:

- History of cigarette use (current or exceeding 40 pack-years)
- ASA-PS scores of 2 or more
- Age 70 years or more
- COPD
- Neck, thoracic, upper abdominal, aortic, or neurologic surgical procedures
- Anticipated prolonged procedures (≥2 hours)
- Planned general anesthesia (especially with endotracheal intubation)
- Albumin concentration less than 35 g/dL
- Inability to walk two blocks on the level or to climb one flight of stairs
- BMI of 30 or more

Surprisingly absent in the foregoing list are asthma, analysis of arterial blood gases, or PFT results. The risk of complications is surprisingly low in patients with well-controlled asthma or in those treated preoperatively with corticosteroids.[133] The risk is higher in asthmatic patients with recent exacerbations, prior postoperative pulmonary complications, recent hospitalizations, or endotracheal intubations for asthma. Analysis of arterial blood gases is useful in predicting pulmonary function after lung resection operations, but it does not predict the risk of complications. The degree of airway obstruction, measured by the FEV_1, is not predictive of pulmonary complications.[111] The role of PFTs may be for diagnosis ("Is dyspnea caused by lung disease or heart failure?") or to assess management ("Can dyspnea or wheezing be improved further?"), but PFTs should *not* be used as a risk assessment tool or to deny a beneficial procedure.[111]

BOX 38-12 ***Risk Factors for Postoperative Pulmonary Complications***

PATIENT-RELATED

- Age ≥60 yr
- ASA-PS class ≥2
- Heart failure
- Partial or total functional dependence
- Chronic obstructive pulmonary disease
- Weight loss
- Delirium
- Cigarette smoking
- Alcohol use
- Abnormal chest examination findings

PROCEDURE-RELATED

- Thoracic surgery
- Abdominal surgery
- Neurosurgery
- Head and neck surgery
- Emergency surgery
- Vascular surgery
- Use of general anesthesia
- Blood product transfusion

LABORATORY TEST–RELATED

- Albumin level <35 g/L
- Abnormal chest radiograph
- BUN level >7.5 mmol/L (>21 mg/dL)

From Smetana GW, Lawrence VA, Cornell JE, et al: Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians, Ann Intern Med *144:581-595, 2006.*
ASA-PS, American Society of Anesthesiologists physical status; *BUN,* blood urea nitrogen.

Box 38-12 lists the laboratory results and the patient-related, procedure-related, and laboratory test–related determinants of perioperative pulmonary complications.[111] Some of these factors can be modified to alter risk. The pulmonary status of patients with recent exacerbations or infections must be improved whenever possible. Patients at high risk may require prescriptions for antibiotics, bronchodilators, and steroids; referrals to pulmonologists or internists; or delayed surgical procedures. Effective measures to decrease pulmonary complications include the following: a change in perioperative management, including altering the planned surgical procedure, if possible; discussing alternatives to general anesthesia, especially when a regional technique (see also Chapters 56 and 57) is an option; and educating the patient about the benefits of epidural pain management (see also Chapter 98).

ENDOCRINE DISORDERS

See also Chapter 39.

Diabetes Mellitus

Type 1 diabetes is an autoimmune disease resulting in destruction of pancreatic insulin-producing (β) cells. These patients, who have an absolute deficiency of insulin but normal sensitivity to insulin, are at risk of ketoacidosis and generally have an onset of disease at a younger

age. Because of the often difficult nature of control of type 1 diabetes and its long duration, by the time these individuals reach adulthood they are at increased risk of premature vascular disease, especially myocardial ischemia, even in the second decade of life. Type 2 diabetes is initially a result of insulin resistance, which can eventually result in pancreatic "burnout." It is usually found in older, overweight adults. Classifying diabetes with terms such as "insulin dependent," "non–insulin dependent," or "adult onset" is confusing and not recommended.

In the United States, 25.8 million persons (8.3% of the population) have diabetes, and 2 million new cases occur each year. Up to one third of patients are diagnosed only after developing significant diabetes-related complications. Unfortunately, the symptoms of diabetes are nonspecific, so the history, other than a family history of the disease, does not reliably screen for disease. Patients who are overweight, have excessive abdominal fat (even if BMI is normal), take steroids, or have polycystic ovarian syndrome are at increased risk. Certain ethnic groups (Native American, non-Hispanic black, Hispanic, South Asian) are also at higher risk.

Diabetic patients are at risk for multiorgan dysfunction, including renal insufficiency, stroke, peripheral neuropathy, autonomic dysfunction, and cardiovascular disease. Delayed gastric emptying, retinopathy, and reduced joint mobility occur in these patients. Diabetes is considered a CAD equivalent,[134] and it is a risk factor for perioperative cardiac complications on a par with previous MI.[47] Autonomic neuropathy and erectile dysfunction are strong predictors of silent ischemia in these patients. Poorly controlled blood glucose concentrations and longer duration of disease also correlate with cardiac risk.

Heart failure is twice as common in men and five times as common in women with diabetes as in persons without diabetes. Poor glycemic control is associated with an increased risk for heart failure, with both systolic and diastolic dysfunction. Diabetic patients are at increased risk for renal failure perioperatively and for postoperative infections. Chronic kidney disease (CKD) is usually asymptomatic until quite advanced. Diabetes is responsible for almost half of the patients requiring dialysis in the United States. "Screening" for kidney disease is accepted practice in patients with diabetes, likely using serum creatinine measurement and an estimated glomerular filtration rate (eGFR).[135] Patients with poorly controlled diabetes develop stiff joint syndrome with reduced cervical mobility that may affect airway management.

The preoperative evaluation should assess organ damage and blood glucose control. The history and physical examination focus on the cardiovascular, renal, and neurologic systems. Ischemic heart disease is often asymptomatic in the diabetic patient. Inquiring about early satiety, erectile dysfunction, numbness in extremities, and postprandial vomiting is important. Documenting pulses, skin breakdown, sensory examination, and orthostatic vital signs is important in most diabetic patients, particularly in those with long-standing disease or poor diabetes control. Patients with autonomic dysfunction (or hypovolemia) have more than a 20-mm Hg decrease in systolic BP, or more than a 10-mm Hg decrease in diastolic BP when changing from a supine to standing position. An ECG, in addition to determinations of electrolytes, BUN, creatinine, and blood glucose, is needed. Frequently, patients are not fasting when they are evaluated in a preoperative clinic, and relying on reported glucose values is problematic. If patients bring a diary of multiple glucose values at varying times of the day (preprandial and postprandial), one can estimate the adequacy of therapy. The glycosylated hemoglobin (HbA_{1c}) level is not influenced by fasting and can identify patients with poor diabetes control.[136] The American Diabetes Association recommends a target HbA_{1c} of less than 7%. Suggestions for hypoglycemic medication management on the day of surgery are shown in Box 38-3 and are discussed in Chapter 39. Poor long-term control of the disease is associated with infections and worse outcomes, especially for certain procedures such as joint replacements. Optimization of glucose control is a goal even before these patients proceed with surgery. The goals of perioperative diabetic management include avoidance of hypoglycemia and marked hyperglycemia. Tight perioperative glucose control in the immediate perioperative period is controversial. Patients with poor preoperative management of glucose are more likely to have diabetes that is out of control intraoperatively and postoperatively.[136] Thus, aggressive management of hyperglycemia may theoretically help decrease postoperative complications. However, these theoretical clinical benefits of intraoperative intensive glucose control have not been observed in randomized trials of surgical patients.[137]

Thyroid Disease

Thyroid hormones are important for metabolism and its regulation (see also Chapter 39). Mild to moderate thyroid dysfunction probably has minimal impact perioperatively.[138] Significant hyperthyroidism or hypothyroidism appears to increase perioperative risk. Hyperthyroid patients may have tachycardia, arrhythmias, palpitations, tremors, weight loss, and diarrhea. Hypothyroid patients may be hypotensive, bradycardic, and lethargic and may demonstrate weight gain, depressed cardiac function, pericardial effusions, and impaired ventilatory response to hypoxia and hypercarbia. Symptoms and findings of both hypothyroidism and hyperthyroidism can be subtle and nonspecific, particularly in older adults. Patients may have goiters with related symptoms such as dysphagia, dyspnea, wheezing, and orthopnea. Graves ophthalmopathy (or proptosis) is more common in smokers. Patients taking amiodarone are at risk of hypothyroidism and need evaluation of thyroid function before surgery.

Determination of medical therapy is important. Patients with a history of chronic thyroid disease need preoperative thyroid function tests. If symptoms and therapy have not changed, tests within the 6 months before the surgical procedure are generally adequate. Thyroid-stimulating hormone (TSH) assays are best to evaluate for hypothyroidism. Measuring free triiodothyronine (T_3), free thyroxine (T_4), and TSH levels is useful in hyperthyroid patients and avoids the confusion of protein-binding effects seen with total hormone levels. Elective surgical procedures should be postponed until patients are euthyroid. Surgery, stress, or illness can precipitate myxedema

or thyroid storm in patients with untreated or severe thyroid dysfunction. Consultation with an endocrinologist is necessary if surgery is urgent in patients with thyroid dysfunction. Hyperthyroid patients can be treated with β-adrenergic blockers, antithyroid medications, and steroids if surgery is urgent. Chest radiography or CT is useful to evaluate tracheal or mediastinal involvement by a goiter. Continuation of medications, such as thyroid replacement and antithyroid drugs (e.g., propylthiouracil), on the day of the surgical procedure is important.

Parathyroid Disease

Parathyroid hormone regulates calcium; most cases of hyperparathyroidism are discovered when an elevated calcium level is found incidentally during diagnostic testing. *Primary* hyperparathyroidism is caused by a primary disorder of the parathyroid glands (adenomas or hyperplasia). *Secondary* hyperparathyroidism is parathyroid gland hyperplasia caused by hyperphosphatemia and hypocalcemia related to chronic renal failure. *Tertiary* hyperparathyroidism occurs when the parathyroid hyperplasia in secondary hyperparathyroidism functions autonomously, resulting in hypercalcemia. Hypercalcemia from parathyroid disease is associated with osteoporosis and bone loss. Rarely do the parathyroid glands become enlarged enough to compromise the airway. Hypoparathyroidism is rare, but it can result from total parathyroidectomy.

Hypothalamic-Pituitary-Adrenal Disorders

Corticotropin-releasing hormone is released by the hypothalamus and regulates adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, which in turn regulates cortisol from the adrenal cortex. A key component is the negative feedback suppression imposed by endogenous or exogenous glucocorticoids. Cortisol secretion varies with the circadian rhythm, and it is highest in the morning; it also increases with stress, fever, hypoglycemia, and surgery. Surgery is one of the most potent activators of the hypothalamic-pituitary-adrenal (HPA) axis. ACTH concentrations increase with incision and during the surgical procedure, but the greatest ACTH secretion occurs during termination of anesthesia, extubation of the trachea, and the immediate postoperative period.[139]

Adrenal hormone excess results from glucocorticoid treatment of disorders such as asthma or inflammatory diseases or from pituitary or adrenal tumors. Cushing disease denotes the constellation of findings associated with a pituitary tumor; Cushing syndrome refers to the same findings resulting from an adrenal tumor or hyperplasia, ectopic ACTH from neoplasms, or exogenous steroids. Its major manifestations are hypertension, weight gain, myopathy, diabetes, "moon facies," and "buffalo hump," all of which can affect airway management. Striae, easy bruising, and virilization in female patients are common. Exogenous steroids suppress the adrenals and thus blunt the normal hypersecretion expected from stress or surgery. Therefore, patients at risk need "steroid coverage." An ECG and electrolyte and glucose determinations are necessary preoperatively. In spite of bruising easily, patients have normal coagulation profiles.

Adrenal insufficiency results from destruction of the pituitary, destruction of the adrenal glands, or long-term exogenous glucocorticoid administration. Tuberculosis and HIV infection can cause primary hypoadrenalism. Prednisone or its equivalent in doses higher than 20 mg/day for more than 3 weeks suppresses the HPA axis. The axis is not suppressed with doses lower than 5 mg/day of prednisone or its equivalent. Intermediate doses of steroids taken for more than 3 weeks have equivocal effects on the HPA axis. This risk remains for up to 1 year after cessation of steroids. Patients with adrenal insufficiency have weakness, weight loss, hypotension, orthostasis, hypovolemia, hyperpigmentation, and electrolyte abnormalities. Electrolytes and orthostatic vital signs therefore must be checked.

Serum cortisol and plasma ACTH can establish the diagnosis and cause of adrenal insufficiency in most cases. If the serum cortisol concentration is inappropriately low and a simultaneous plasma ACTH concentration is very high, primary adrenal insufficiency (primary adrenal disease) is the cause. Secondary (pituitary disease) or tertiary (hypothalamic disease) is the diagnosis if both the serum cortisol and plasma ACTH concentrations are inappropriately low. In more urgent situations, one may not be able to wait for results of the ACTH determination, in which case, an ACTH stimulation test can be performed (unless the diagnosis has been ruled out by a basal serum cortisol value in the upper end of the reference range or higher).[140] Cosyntropin is synthetic ACTH, and it can be administered in either a high-dose or a low-dose stimulation test. The time of the day is not important because in patients with adrenal insufficiency, the response to cosyntropin is the same in the morning and the afternoon. A normal response to the high-dose (250 μg as an intravenous bolus) ACTH stimulation test is a rise in serum cortisol concentration, measured after 30 to 60 minutes, to a peak greater than 18 to 20 μg/dL. Low-dose (1-μg intravenous bolus) ACTH causes an increase in cortisol concentrations of more than 16 to 20 μg/dL after 20 to 30 minutes. For both tests, a subnormal response confirms the diagnosis of adrenal insufficiency, but further studies are necessary to establish the type and cause. Patients continue steroids on the day of surgery and may need supplementation with additional doses.

Aldosterone, which is produced by the adrenal cortex, regulates volume and electrolytes (absorption of sodium and chloride; secretion of potassium and hydrogen ions). It is controlled by the renin-angiotensin system, not the HPA axis.

Multiple Endocrine Neoplasia Syndromes

The multiple endocrine neoplasia (MEN) syndromes are rare, but recognition is important both for treatment and for evaluation of family members.[141] Multiple endocrine neoplasia type 2 (MEN 2) is subclassified into three distinct syndromes: MEN 2A, MEN 2B, and familial medullary thyroid cancer. The inheritance of MEN 1 and 2 is autosomal dominant. Hyperparathyroidism is the most common manifestation of MEN 1, with almost 100% penetrance by the age of 40 to 50 years. Hypersecretion of gastrin in the Zollinger-Ellison syndrome in MEN 1 often manifests with multiple peptic ulcers. The MEN 1

gene has been identified, and therefore testing for MEN 1 mutations is possible. Little evidence indicates that early presymptomatic detection reduces morbidity or mortality in MEN 1. Screening of asymptomatic family members can also be done by measurement of serum calcium because of the high penetrance of hyperparathyroidism in MEN 1.

Because undiagnosed pheochromocytoma can cause substantial morbidity or even death during surgical procedures, it is important to consider this diagnosis as a component of possible MEN 2 and, if present, to remove the tumor before removing other endocrine tumors. Extraadrenal pheochromocytoma is rare in MEN 2, but bilateral adrenal disease is common. It is unusual for pheochromocytoma to precede the development of medullary thyroid carcinoma or be the initial manifestation of MEN 2. Hyperparathyroidism in MEN 2A is often clinically occult. In contrast to MEN 1, in which the long-term benefit of early diagnosis by genetic screening is not well established, early diagnosis by screening of at-risk family members in MEN 2 kindred is essential because medullary thyroid carcinoma is a life-threatening disease that can be cured or prevented by early thyroidectomy.

Pheochromocytoma

Catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla or sympathetic ganglia are referred to as pheochromocytomas and extraadrenal catecholamine-secreting paragangliomas (extraadrenal pheochromocytomas), respectively.[142] Nonetheless, the term *pheochromocytoma* is often used for both types of tumors. Pheochromocytomas are discovered when patients present with symptoms, a suggestive family history, or an incidental adrenal mass. Approximately 3% to 10% of adrenal "incidentalomas" prove to be pheochromocytomas. The classic triad of symptoms includes episodic headache, sweating, and tachycardia. Paroxysmal hypertension occurs in half of patients, whereas most of the remaining patients have what appears to be essential hypertension. Approximately 5% to 15% of patients have *normal* BP. Headache, which is variable in severity and duration, occurs in up to 90% of symptomatic patients. *Paroxysmal* hypertension is a classic sign of pheochromocytoma, but it is nonspecific for the disorder. Sweating occurs in up to 60% to 70% of patients. Other symptoms include palpitations, dyspnea, weakness, and panic attacks (particularly in patients with tumors that produce an increase in epinephrine). Pallor, orthostatic hypotension, blurred vision, weight loss, polyuria, polydipsia, hyperglycemia, psychiatric disorders, cardiopulmonary dysfunction (particularly with the initiation of β-adrenergic blockers), dilated cardiomyopathy (from excess catecholamines), and marked hypertension have been reported. Pheochromocytoma is suspected in patients who have one or more of the following:

- Hyperadrenergic spells (nonexertional palpitations, diaphoresis, headache, tremor, pallor)
- Hypertension that is difficult to control
- Familial syndrome that includes catecholamine-secreting tumors (e.g., MEN 2, neurofibromatosis type 1, von Hippel–Lindau disease) (These individuals often have bilateral disease.)
- Family history of pheochromocytoma
- Incidentally discovered adrenal mass
- Unusual BP response during anesthesia, surgery, or angiography
- Hypertension at a young age (e.g., <20 years old)
- Idiopathic dilated cardiomyopathy
- A history of gastric stromal tumor or pulmonary chondromas (Carney triad)

Measurements of urinary and plasma fractionated metanephrines and catecholamines generally establish the diagnosis. History and physical examination should focus on the cardiovascular system (including findings of heart failure) and evaluation of vital signs (including orthostatic BP). An ECG and determinations of electrolytes, BUN, creatinine, and glucose are needed. CT, echocardiography, and cardiac consultation may be useful.

All patients with pheochromocytoma must be managed with preoperative α-adrenergic blockade at least 7 to 10 days before the surgical procedure, with the goal of normalizing BP and volume status. Phenoxybenzamine is the preferred drug for preoperative preparation to control arterial BP and arrhythmias. It is an irreversible, long-acting, nonspecific α-adrenergic blocking agent. The initial dose is 10 mg once or twice daily, and the dose is increased by 10 to 20 mg every 2 to 3 days as needed to control BP and spells. Most patients need between 20 and 100 mg daily. BP is measured twice daily with the patient lying, sitting, and standing. The target BP is less than 120/80 mm Hg seated, with systolic BP less than 90 mm Hg while standing. Patients should be warned about common side effects of orthostasis, marked fatigue, and nasal congestion. Selective α_1-adrenergic blocking agents (e.g., prazosin, terazosin, doxazosin) are preferable to phenoxybenzamine when long-term pharmacologic treatment is indicated (e.g., metastatic pheochromocytoma) because of the favorable side effect profiles of these drugs. The disadvantage of using these agents preoperatively is their incomplete degree of α-adrenergic blockade, thus resulting in more episodes of intraoperative hypertension.[143] Conversely, preoperative preparation with phenoxybenzamine is associated with more postresection hypotension than is preparation with selective α_1-adrenergic blocking agents.[143]

After adequate α-adrenergic blockade is achieved, β-adrenergic blockade may be started cautiously with short-acting drugs. For example, 10 mg of propranolol every 6 hours can be used. After 24 to 48 hours, if the patient tolerates β-adrenergic blockade, a long-acting preparation (e.g., metoprolol, atenolol) can be substituted. The dose is then adjusted to control tachycardia with an HR goal of 60 to 80 beats/minute. β-Adrenergic blockade should *never* be initiated before α-adrenergic blockade because blockade of vasodilatory peripheral β-adrenergic receptors with unopposed α-adrenergic receptor stimulation can lead to a further elevation in BP. Additionally, depression of cardiac function with sustained hypertension can precipitate acute heart failure and death. Chronic catecholamine excess can also

produce cardiomyopathy that may become evident with the initiation of β-adrenergic blockade, with resulting acute pulmonary edema.

Although perioperative α-adrenergic blockade is most commonly used, another option involves the administration of a calcium channel blocker.[144] Nicardipine is the most commonly used calcium channel blocker for pheochromocytoma management. The starting dose of the sustained release preparation is 30 mg orally twice a day. The exclusive use of calcium channel blockers for the perioperative management of patients with catecholamine-secreting tumors does not prevent all hemodynamic changes; however, morbidity and mortality remain low with this class of drug. The main role for calcium channel blockers is likely to supplement α- and β-adrenergic blockade when BP control is inadequate or in patients with intolerable side effects. Patients with acute hypertensive crises require hospitalization and treatment with intravenous sodium nitroprusside, phentolamine, or nicardipine.

RENAL DISEASE

The type and degree of renal impairment are important. Patients with renal dysfunction have many associated comorbidities, generally related to the accompanying vasculopathy. Hypertension, cardiovascular disease, and electrolyte disturbances are most common. CKD is defined as a decreased GFR of less than 60 mL/minute/1.73 m^2 for at least 3 months, or significant proteinuria. Chronic renal failure is defined as a GFR less than 15 mL/minute/1.73 m^2. End-stage renal disease (ESRD) is loss of renal function for 3 or more months. Acute kidney injury (AKI) is a sudden decrease in renal function with the possible decrease in urine output. Two consensus-based criteria for classifying AKI are the RIFLE (risk, injury, failure, loss of function, ESRD) and Acute Kidney Injury Network (AKIN) classification schemes.[145,146] Diabetes accounts for almost half of all ESRD cases, and hypertension accounts for more than one fourth. Polycystic kidney disease (autosomal dominant 90% of time) is the causative factor in 10% of ESRD cases and can be associated with intracranial aneurysms and MVP.

AKI may be reversible if precipitating factors are identified and corrected. Classifying AKI into prerenal, renal, and postrenal causes allows for a systematic approach. Prerenal causes can often be differentiated by calculating the BUN-to-creatinine ratio. A ratio less than 20 suggests prerenal etiologies, with hypovolemia or hypotension the most common. A fractional excretion of sodium (FEN_a) less than 1% also suggests prerenal azotemia (in the absence of concomitant diuretic administration) and can be calculated using the following formula:

$$FEN_a = \frac{PCr/UCr}{PNa/UNa}$$

Obstruction results in dilated ureters and enlarged kidneys, and it is always considered in the differential diagnosis of AKI. Prompt identification with ultrasound should lead to attempts to decompress the outflow tract. Rhabdomyolysis can cause AKI and is treatable.

GFR decreases with age; the renal reserve of a normal 80-year-old person is less than half that of a 40-year-old person. The creatinine level is often not an accurate indicator of renal function, especially in older individuals.[147] The GFR can be reduced by 50% without a rise in creatinine. Creatinine does not exceed the normal limits until GFR has fallen to less than 50 mL/minute. The Cockcroft-Gault equation can be used to calculate an eGFR:

$$\text{Creatinine clearance} = \frac{(140 - \text{Age}) \times \text{Weight (kg)} \times (0.85 \text{ If female})}{72 \times \text{Serum creatinine(mg/dL)}}$$

Another formula is the Modification of Diet in Renal Disease (MDRD)[135] equation, which is likely more accurate:

$$\text{eGFR (mL/kg/minute)} = \frac{1086 \times \text{Serum creatinine} \times \text{Age}}{(0.742 \text{ If female}) \times (1.210 \text{ If African descent})}$$

Online calculators to estimate renal function are available at www.nephron.com. Calculating an eGFR is necessary in older patients, those with an elevated serum creatinine, or with other risk factors for CKD.[147] Given the inaccuracy of these equations at lower creatinine concentrations, values of eGFR that are greater than 60 mL/kg/minute/1.73m^2 should simply be reported as ">60 mL/kg/minute/1.73m^2 ."

CKD is a significant risk factor for perioperative cardiovascular morbidity and mortality. For example, a creatinine concentration higher than 2.0 mg/dL is a risk factor in the RCRI.[47] The incidence of death from CAD in patients with both diabetes and ESRD requiring hemodialysis is 8.2% per year. Pericarditis, pericardial effusions, and diastolic and systolic dysfunction can also be present. Valvular heart disease is common in patients undergoing maintenance dialysis. Abnormalities include valvular and annular thickening, as well as calcification of the heart valves that results in regurgitation or stenosis.[148] Mitral or aortic valve calcifications (40% and 55% of patients, respectively) and stenosis (11% to 13%) occur. Valvular calcifications progress to stenosis at an accelerated rate in patients undergoing dialysis.[47] Systemic hypertension is almost ubiquitous in these patients, but it is generally easier to manage with initiation of dialysis. Pulmonary hypertension and increased cardiac output occur in many patients with an arteriovenous fistula.

Renal failure results in anemia from lack of erythropoietin production by the kidneys; however, excessive treatment of this anemia with erythropoietin may actually increase morbidity and vascular events.[149] Patients with CKD can have platelet dysfunction and increased bleeding, despite normal platelet counts, prothrombin times (PTs), and aPTT. Once dialysis is begun, patients become more prone to hypercoagulable states. Chronic metabolic acidosis is common, but it is usually mild and compensated for by chronic hyperventilation. Patients may have electrolyte (including calcium) abnormalities, pulmonary edema, peripheral edema, hypercholesterolemia, and hypoalbuminemia. Hyperkalemia is the most serious electrolyte disturbance. Hypocalcemia is common in patients undergoing dialysis, although with long-term disease, secondary and tertiary hyperparathyroidism eventually develops. Chronically elevated troponin and creatine kinase levels are common in patients undergoing dialysis. Worsening renal function should be suspected in

diabetic patients with ESRD who develop improved glycemic control or unexpected hypoglycemia because insulin is metabolized by the kidneys. Autonomic and peripheral (sensory and motor) neuropathies can occur.

Among individuals undergoing cardiac surgery, several simple preoperative risk indices have been developed for accurately predicting postoperative AKI requiring dialysis.[150,151] Important risk factors in these indices include complex surgery, nonelective surgery, preexisting renal insufficiency, diabetes, heart failure, female gender, and COPD. In the setting of noncardiac surgery, identified risk factors for AKI include increased age, male gender, symptomatic heart failure, hypertension, liver disease (including ascites), preexisting renal insufficiency, PAD, COPD, nonelective surgery, and intraperitoneal surgery.[152,153] Preoperative identification of at-risk patients can help facilitate care, such as preoperative hydration and avoidance of hypovolemia. This approach may require preoperative hospital admission. Nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors interfere with renal perfusion autoregulation; they should be avoided or discontinued in patients with renal insufficiency. The use of these drugs in patients with normal renal function does not increase the risks of postoperative AKI.[154] Although long-term ACEI and ARB use prevents deterioration of renal function in patients with diabetes or renal insufficiency, the use of these drugs may worsen function during hypoperfusion states and AKI.

Many drugs are metabolized or cleared by the kidneys. Drugs with particular implications for anesthesia and surgery are the LMWHs because no easy method of monitoring the anticoagulation effects exists. All the LMWHs available in the United States are cleared by the kidneys and are not removed during dialysis; thus, they have a prolonged duration of action in patients with CKD.

The emphases of the preoperative evaluation of patients with renal insufficiency are on the cardiovascular system, cerebrovascular system, fluid volume, and electrolyte status. The early stages of CKD typically cause no symptoms. Inquiring about the cardiovascular systems (i.e., chest pain, orthopnea, paroxysmal nocturnal dyspnea), urine output, associated comorbidities, medications, and dialysis schedules is vital. Monitoring of patients' weight is important for assessing volume status. Patients with or at risk of renal disease (especially if they have 2 or more of the following risk factors: diabetes, poorly controlled hypertension, advanced age) need an ECG and determinations of electrolytes, calcium, glucose, albumin, BUN, and creatinine function. Further evaluation is needed if the ECG shows LVH (hypertension), peaked T waves (hyperkalemia), flattened T waves, a prolonged PR interval, or a prolonged QT interval (hypokalemia). A chest radiograph (infection, volume overload), echocardiogram (murmurs, heart failure), and cardiology evaluation may be necessary. Venous access sites or blood draws from the brachial, cephalic (antecubital), and central veins in the nondominant upper extremity are avoided in patients who may eventually need fistulas in those locations for dialysis.

Preoperative renal replacement therapy (dialysis) schedules are coordinated, with scheduling of the surgical procedure ideally within 24 hours after dialysis. In elective surgical cases, dialysis should be performed within 24 hours of surgery but not immediately before, given the risks of acute volume depletion and electrolyte alterations. Dialysis is associated with fluid shifts and electrolyte (sodium, potassium, magnesium, phosphate) imbalance, especially related to shifting of electrolytes between intracellular and extracellular compartments. Dialysis is performed to correct volume overload, hyperkalemia, and acidosis. Coordination of the timing of dialysis in relation to elective surgery is an important aspect of preoperative care.

Contrast-Induced Nephropathy

Contrast-induced nephropathy is defined as a 25% increase in creatinine above baseline after radiocontrast administration. Patients with diabetes and CKD are at greatest risk, although radiocontrast media cause a transient decrease in GFR in most individuals. Renal failure requiring dialysis after contrast-induced nephropathy is associated with a poor prognosis, with less than a 20% 2-year survival and one third of patients dying during the initial hospitalization. A proposed preventive strategy has been developed for patients with CKD (GFR <60 mL/kg/minute) who are undergoing PCI (Box 38-13), which may be beneficial for patients undergoing any procedure involving contrast administration. However, more recent large randomized trials did not find that *N*-acetylcysteine decreased rates of contrast-induced nephropathy (see Box 38-13).[155]

HEPATIC DISORDERS

Liver disease can affect the hepatocytes, the biliary system, or both (see Chapters 22 and 73). Liver disease affects protein synthesis (e.g., coagulation factors, albumin), bile

BOX 38-13 ***Checklist for Contrast-Induced Nephropathy Risk Stratification and Prevention***

1. Calculate the eGFR: the risk is high if the eGFR is <60 mL/min/1.73 m^2.
2. If the eGFR is <15 mL/min/1.73 m^2, consider a nephrology consultation to plan for the possible need for dialysis after the procedure.
3. Determine the patient's history of diabetes (the risk is increased five times with diabetes).
4. Discuss the contrast-induced nephropathy risk in the informed consent process.
5. Discontinue nonsteroidal antiinflammatory drugs and other nephrotoxic drugs.
6. Discontinue diuretics the day before and the day of the procedure.
7. Administer hydration with intravenous saline or sodium bicarbonate at 1.5 mL/kg/hr starting 3 hours before contrast and continuing 6 hours after contrast administration.
8. Administer *N*-acetylcysteine, 1200 mg orally twice a day before contrast administration and 1600 mg orally twice a day after contrast administration.
9. The preferred urine output is >150 mL/hr after the procedure.
10. Avoid additional contrast media for 10 days.

Modified from McCullough Pa, Soman SS: Contrast-induced nephropathy, Crit Care Clin *21:261-280, 2005.*
eGFR, Estimated glomerular filtration rate.

regulation, and metabolism of drugs or toxins. Hepatocellular diseases, including hepatitis (viral, alcoholic, autoimmune hepatitis) and hepatocellular carcinoma, affect the hepatocytes and synthetic function of the liver. Obstructive disorders, including choledocholithiasis, bile duct tumors (extrahepatic), primary biliary cirrhosis (intrahepatic), and primary sclerosing cholangitis (extrahepatic and intrahepatic), cause bile stasis. Most drug-induced liver disease, as well as some forms of viral hepatitis, affect both hepatocytes and the biliary system.

The patient's history uncovers the underlying disease etiology, therapies, and associated complications. Important issues to explore include the cause and degree of hepatic dysfunction. Some patients with liver disease may be asymptomatic, whereas others may complain of fatigue, weight loss, dark urine, pale stools, pruritus, right upper quadrant pain, bloating, and jaundice. Weight and vital signs (including oxygen saturation) are needed. Physical examination may reveal jaundice, bruising, ascites, pleural effusions, peripheral edema, or hypoxia. The presence of encephalopathy, coagulopathy, ascites, volume overload, and infection need to be determined before surgery. The bilirubin level generally must exceed 2.5 mg/dL before icterus can be seen in mucous membranes and sclerae. Examination may find hepatomegaly, splenomegaly, and altered mental status. New-onset or worsening encephalopathy should prompt an evaluation for precipitating factors such as worsening liver disease, infection, drug effects, bleeding, or electrolyte disturbances.

An ECG, CBC (with platelet count), electrolytes, BUN, creatinine, LFTs, albumin, and PT are helpful. Patients suspected of having hepatitis may require screening for the hepatitis A immunoglobulin M (IgM) antibody, the hepatitis B surface and core antigens, the hepatitis B surface antibody, and the hepatitis C antibody. A chest radiograph can identify effusions, whereas ammonia levels may help in the patient with encephalopathy. Coagulopathy can be a result of vitamin K deficiency (from cholestasis), factor deficiency (from loss of synthetic function), or thrombocytopenia (from splenomegaly and portal hypertension). Therapy to correct coagulopathy should be directed at the cause. Vitamin K, fresh frozen plasma, or platelets may correct deficiencies. Vitamin K, taken at 1 to 5 mg orally or subcutaneously daily for 1 to 3 days, may correct a prolonged PT and carries minimal risk. The coagulopathy in patients with synthetic failure is not likely to correct, thus necessitating fresh frozen plasma transfusion aiming for an international normalized ratio (INR) of less than 1.5. Although anemia is a predictor of poor perioperative outcome in patients with cirrhosis,[156] correction of any anemia with transfusion remains controversial. Lactulose (30 mL orally every 6 hours for 3 days preoperatively) with the last dose within 12 hours of surgery, or oral bile salts with intravenous hydration beginning the night before the operation, may reduce perioperative progression of renal disease in patients at risk.[157] Reduction of ascites preoperatively may decrease the risk of wound dehiscence and improve pulmonary function. Sodium restriction (in diet and intravenous solutions), diuretics (especially spironolactone), and even paracentesis are useful. If ascites fluid is aspirated, it is important to analyze it for infection. Encephalopathy is frequently precipitated by an additional acute insult such as infection, gastrointestinal bleeding, hypovolemia, or sedatives. It is therefore important to determine reversible factors and treat them accordingly. Lactulose (30 mL every 6 hours orally) is first-line therapy. Addressing nutritional deficiencies with enteral or parental supplementation may have benefits, especially in alcoholic patients. Patients who abuse alcohol may be at risk for neurologic deterioration (i.e., Wernicke-Korsakoff syndrome) if thiamine, folate, and vitamin B_{12} supplements are not provided, especially when these patients are given nutrition or glucose. These patients are also at risk of alcohol withdrawal syndromes.

In some cases, it may be appropriate to delay elective surgical procedures until an acute episode of hepatitis (or exacerbation of chronic disease) has resolved or until a diagnosis is established for newly discovered hepatic dysfunction. Elective surgery is contraindicated in patients with acute or fulminant liver disease, including alcoholic, viral, or undefined hepatitis. The perioperative risk of patients with chronic hepatitis or cirrhosis is predicted by histologic severity (i.e., bridging or multilobular necrosis on biopsy), portal hypertension (i.e., ascites, varices, bleeding), and impairment of liver function (both synthetic and excretory function). Patients with severe liver disease have increased perioperative morbidity and mortality; common adverse events are bleeding, infection, liver failure, and hepatorenal syndrome. Predictors of poor perioperative outcome in patients with liver disease include the following:

- Child-Turcotte-Pugh class C cirrhosis, which is calculated using bilirubin level, albumin concentration, PT, severity of ascites, and severity of encephalopathy (Table 38-9)
- Model for end-stage liver disease (MELD)[158] score of 15 or more (The MELD score is calculated using serum bilirubin, INR, and serum creatinine concentrations.)
- Acute hepatitis (viral or alcoholic)
- Chronic active hepatitis with jaundice, encephalopathy, coagulopathy, or elevated liver enzymes
- Abdominal surgical procedures
- PT prolongation of 3 seconds or more that is refractive to vitamin K therapy

Patients with significant abnormalities or at high risk are best managed by a liver specialist.

Hepatitis

Hepatitis is defined by inflammation of hepatocytes, and it can be caused by drugs, alcohol, viruses (hepatitis A, B,

TABLE 38-9 **CHILD-TURCOTTE-PUGH CLASSIFICATION***

Parameter	1 Point	2 Points	3 Points
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (seconds over control)	<4	4-6	>6
Encephalopathy	None	Grade 1-2	Grade 3-4

*Class A, <7 points; class B, 7 to 9 points; class C, >9 points.

C, D, and E), and autoimmune diseases (see also Chapter 74). All these disorders have both an acute phase and a chronic phase, which can progress to cirrhosis (irreversible fibrosis of the liver). Risk factors for hepatitis are alcohol use, sexual activity (multiple partners, sex industry workers, sex with sex industry workers, men who have sex with men), intravenous drug use, blood transfusions administered before 1992, obesity (i.e., nonalcoholic steatohepatitis), tattoos, body piercing, and travel to developing countries. Hepatitis A, which is caused by contaminated food or water or by contact with an infected person, rarely progresses beyond the acute illness. A remote history of hepatitis A has no perioperative significance. Hepatitis B is transmitted by sexual activity or contact with blood (rarely after implementation of screening in 1986). It varies in severity, but it has become much less common since the widespread use of hepatitis B vaccination. Hepatitis C is transmitted primarily through blood exposure (all blood has been screened since 1992), most often among intravenous drug users. Many patients are unaware of infection because the acute phase is often asymptomatic. Hepatitis C infection can then advance to cirrhosis. Hepatitis D occurs only in conjunction with hepatitis B infection, whereas hepatitis E is rare in developed countries. Alcoholic hepatitis generally occurs after at least 10 years of moderate to heavy daily alcohol intake (i.e., three or more drinks per day for women, and five or more drinks per day for men) and may progress to cirrhosis. Autoimmune hepatitis primarily affects young women, and its etiology remains unknown. Many different drugs, including herbal and over-the-counter preparations, can cause hepatitis; examples of inciting medications are statins, isoniazid, and acetaminophen.

Obstructive Jaundice

Extrahepatic bile duct obstruction may be caused by gallstones, tumors (e.g., pancreatic, gallbladder, bile duct, ampulla of Vater), or scarring. Patients can present with jaundice, pruritus, and abdominal pain. Predictors of surgical mortality are a hemoglobin concentration of less than 10 g/dL, serum bilirubin exceeding 20 mg/dL, and serum albumin lower than 2.5 g/dL.[159] Perioperative AKI occurs in up to 8% of these patients,[160] and it may be prevented with administration of bile salts or lactulose.[157]

Miscellaneous Liver Diseases

Wilson disease, hemochromatosis, and α_1-antitrypsin deficiency are uncommon hereditary causes of liver disease. Gilbert disease, which is a benign hereditary disorder characterized by a mildly elevated bilirubin level, has no perioperative significance. Obesity can result in nonalcoholic steatohepatitis, also known as "fatty liver," which progresses to abnormal LFTs, fibrosis, cirrhosis, and end-stage liver disease. Primary biliary cirrhosis is an autoimmune disorder that most frequently affects women and is characterized by intrahepatic biliary obstruction and antimitochondrial antibodies. Primary sclerosing cholangitis, which most frequently affects young male patients, is characterized by bile duct destruction that can eventually progress to cirrhosis. It may be idiopathic or associated with inflammatory bowel disease. Acute nonhepatic events, such as sepsis, surgery, and anesthesia, can also cause hepatic dysfunction.

Remote History of "Hepatitis"

Patients may recount a remote history of "having hepatitis" but may be unable to recall little other related medical information. One must take a careful history to determine the circumstances surrounding the onset (e.g., transfusions, travel, high-risk exposures) and whether any sequelae of chronic liver disease are present. It is important to clarify whether the episode occurred during or soon after a surgical procedure. Although halothane is not used in adults in the United States in contemporary practice, individuals who previously had halothane hepatitis may be at risk of cross-sensitivity to other volatile anesthetics with trifluoroacetyl metabolites (e.g., enflurane, isoflurane, desflurane).

Unexpected Elevated Liver Function Tests

Elevated alanine aminotransferase and aspartate aminotransferase reflect damage to hepatocytes; bilirubin measures the liver's ability to conjugate and excrete bile salts; alkaline phosphatase rises with impaired hepatic excretion, whereas albumin or PT measures the synthetic function of the liver. Approximately 1 in 700 preoperative patients are unexpectedly found to have liver diseases, most of which are not severe.[161] Nonetheless, if abnormal LFT values are unexpectedly found, further testing or referral may be necessary. Elevations in alanine transferase or aspartate transferase should prompt hepatitis screening with hepatitis A IgM antibody, hepatitis B surface and core antigens, hepatitis B surface antibody, and hepatitis C antibody. Elevations of alkaline phosphatase or bilirubin, in association with normal or mild to moderate increased transaminase levels, may indicate obstruction in the biliary system. In these cases, abdominal ultrasound, CT scans, or endoscopic retrograde cholangiopancreatography may establish a diagnosis.

Cirrhosis

Cirrhosis is the end result of most hepatotoxic conditions. Cirrhosis often leads to portal hypertension, which is characterized by splenomegaly, esophageal varices, ascites, dependent edema, and pleural effusions. The liver has impaired synthetic (i.e., synthesis of proteins and clotting factors) and metabolic (i.e., clearance of toxins and drugs) functions. Patients may have encephalopathy, bleeding, thrombocytopenia, low albumin levels, and prolonged PT. Pulmonary shunting may cause hypoxemia and pulmonary hypertension (i.e., hepatopulmonary syndrome). Hepatorenal syndrome is renal insufficiency in patients with hepatic disease in the absence of primary renal disease; it may be related to renal hypoperfusion. Jaundiced patients are at particular risk of hepatorenal syndrome. Patients with ascites may also develop spontaneous bacterial peritonitis, which is associated with increased perioperative mortality. Patients with end-stage liver disease also develop a high–cardiac output state, characterized by increased cardiac output and decreased systemic vascular resistance.

The Child-Turcotte-Pugh classification can predict perioperative morbidity and mortality, with especially

high risks in patients assigned to class C (see Table 38-9). The MELD score can also predict perioperative risks, perhaps better than the Child-Turcotte-Pugh classification.[156] Increased perioperative risk is associated with a MELD score exceeding 14.[156] Online calculators are available to calculate MELD scores readily (see www.unos.org).

HEMATOLOGIC DISORDERS

Anemia

Anemia is a very common preoperative hematologic disorder. Preoperative anemia is a recognized risk factor (see also Chapter 61). It may be a known problem or suspected based on a patient's underlying medical conditions or indication for surgery. The goal in the preoperative clinic is to determine its etiology, duration, stability, related symptoms, and therapy (especially transfusions). Inquiring about a personal or family history of anemia is important. Patients at risk for anemia include those with histories of colon cancer, gastrointestinal bleeding, genitourinary bleeding, menorrhagia, chronic infections, inflammatory diseases, nutritional deficiencies, and prior weight reduction procedures (e.g., bariatric surgery). One should also consider the type of surgical procedure, anticipated blood loss, and comorbid conditions that may either affect oxygenation or be affected by hypoxia (e.g., pulmonary, renal, hepatic, cerebrovascular, cardiovascular disease). In addition, an accurate determination of the patient's medications is required, especially because anemia has implications for the risk-to-benefit profile of some medications in the perioperative period, such as β-adrenergic blockers.[50,51] Important components of the preoperative evaluation include assessing for palpitations, fatigue, chest pain, melena, bloody stools, weight loss, pallor, murmurs, hepatosplenomegaly, or lymphadenopathy.

The World Health Organization defines anemia as a hemoglobin level less than 13 g/dL in adult men and less than 12 g/dL in adult women. Risk is directly proportional to the degree of anemia and independent of the patient's other comorbidities.[48,49,162] In addition, any value outside of normal is associated with risk. Nonetheless, simply treating all anemic patients with red blood cell transfusions is not the solution because transfusion itself carries inherent risks.[163] The ASA Task Force on Blood Component Therapy concluded that red blood cells should not be transfused based solely on a hemoglobin level, but rather they should be used to address risks for complications from inadequate oxygenation.[164] A new report will be published by the ASA in 2015. Transfusion is rarely indicated when the hemoglobin level is higher than 10 g/dL and is almost always needed when hemoglobin is less than 6 g/dL[165](see also Chapter 61). In general, the balance of risks versus benefits of transfusing patients with hemoglobin levels between these two thresholds largely depends on comorbid conditions, especially cardiopulmonary disease states. A randomized trial found no advantage of routinely transfusing older patients who were undergoing hip fracture repair to a hemoglobin concentration of 10 g/dL as opposed to 8 g/dL.[52]

Patients with anemia or suspected anemia must have a CBC. In general, a primary care physician or hematologist performs further evaluation of newly diagnosed anemia. Usual initial studies include peripheral smear, mean corpuscular volume (MCV), and reticulocyte count; subsequent studies, such as iron studies, vitamin B_{12}, or folate levels, are guided by findings on the smear and the MCV. In iron deficiency anemia, the MCV, iron, and ferritin are low, whereas total iron binding capacity (TIBC) is high. Although the MCV and TIBC are low or normal, iron and ferritin are normal or high in anemia associated with chronic disease. The MCV is high and the vitamin B_{12} or folate levels are low in macrocytic anemia associated with these deficiencies. Blood type and screening, and in selected cases, preoperative transfusion may be necessary depending on the level of anemia and the degree of anticipated surgical blood loss.

Elective procedures must be postponed in patients found to have significant anemia, regardless of the anticipated blood loss of the planned procedure. This delay allows for evaluation for causes of the anemia, such as occult blood loss (colonoscopy), vitamin deficiencies, or undiagnosed chronic conditions (e.g., CKD). In special circumstances, such as a patient's refusal to receive perioperative blood transfusions or elective procedures with expected significant blood loss in anemic patients, postponement of surgery to facilitate preoperative treatment with recombinant human erythropoietin and iron may be warranted.

Sickle Cell Disease

Sickle cell disease is a hereditary hemoglobinopathy with associated vasoocclusive episodes that are responsible for most associated complications. Patients homozygous for hemoglobin S (HbS) have symptomatic disease; they are at risk for major morbidity and have a shortened life expectancy. Patients with SC disease, who have both HbS and HbC, have a much less severe clinical course with moderate anemia. Heterozygous patients (HbS and HbA) have sickle cell trait and rarely have any related consequences. Preoperative assessment should focus on identification of organ dysfunction and acute exacerbations.[166] Patients may have renal insufficiency, loss of renal concentration ability (and therefore are prone to dehydration), splenomegaly, pulmonary hypertension, pulmonary infarctions, acute stroke, and heart failure. They are at increased risk for infections because of splenic infarctions. Predictors of perioperative vasoocclusive complications include a recent increase in hospitalizations, advanced age, preexisting infections, and pulmonary disease.[166]

The preoperative examination focuses on the frequency, severity, and pattern of vasoocclusive crises, as well as the degree of pulmonary, cardiac, renal, and central nervous system damage. Oxygen saturation, hematocrit, measurement of BUN and creatinine, an ECG, and chest radiographs are indicated. Additional testing (e.g., echocardiogram, arterial blood gases) may be needed. Preoperative prophylactic transfusion is controversial. The objective of any red cell transfusion is to reduce the proportion of abnormal hemoglobin in the affected patient. The observational Cooperative Study of Sickle Cell Disease concluded that preoperative transfusion was associated

with fewer complications among surgical patients with sickle cell disease; nonetheless, complication rates were low following low-risk surgical procedures, even without transfusion.[167] Conversely, a randomized trial found that a conservative transfusion regimen (correcting anemia by increasing total hemoglobin to ≥10 g/dL) was as effective as a more aggressive approach (transfusing to decrease HbS to <30% and increase hemoglobin to ≥10 g/dL).[168] Thus, the decision to transfuse preoperatively should be made only in concert with a hematologist familiar with the disease. Any benefits are likely to apply only to intermediate- to high-risk surgical procedures.

Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a type of X-linked hereditary Coombs-positive hemolytic anemia. Hemolysis may occur with exposure to drugs (e.g., antipyretics, nitrates, sulfonamides), infections, hypoxia, hypothermia, or blood products. The severity of the hemolysis varies based on the individual patient and the underlying etiology. Steroid therapy is usually effective. The preoperative history should focus on previous episodes of hemolysis, identification of predisposing factors, and determination of the current hematocrit.

Coagulopathies

Hypocoagulable states may be inherited (e.g., hemophilia) or acquired (e.g., liver disease, malnutrition, drug exposure) disorders. To determine the diagnosis and the risk of bleeding, one should inquire about known diagnoses, tests, treatments, previous bleeding episodes, and family history. Asking about excessive bruising, prolonged bleeding after cuts, heavy menstrual cycles, and bleeding gums is sensitive but not specific. A *change* in these symptoms is more meaningful than a long-term history (because what one individual considers excessive may actually be normal). Excessive bleeding after previous procedures or childbirth (especially if transfusions were unexpectedly required) is more definitive but not diagnostic. Petechiae, multiple bruises, hematomas, jaundice, and frank bleeding are important findings. Diagnostic testing may include a platelet count, CBC, PT, and aPTT. *Routine* screening for coagulopathies is not indicated. If a specific cause of bleeding is suspected or known (e.g., liver disease, malnutrition), then appropriate targeted testing (e.g., liver enzymes, protein, albumin levels, PT) should be conducted.

Occasionally, a patient has an abnormal PT or PTT result on presentation for preoperative evaluation. The most common causes of a prolonged PT without a history of warfarin use are laboratory error, liver disease, and malnutrition. One should first repeat the test. If the test result is again abnormal, then evaluation of liver enzymes and a hepatitis panel are warranted, in addition to referral to a hematologist or primary care physician. A trial of vitamin K (1 to 5 mg orally once a day for 3 days) can be initiated. A prolonged aPTT can result from both hypocoagulable and hypercoagulable (e.g., antiphospholipid antibody syndrome) conditions. The first steps are to repeat the test and ascertain exposure to heparin. Even small amounts of heparin present in indwelling catheters, especially if the blood is drawn from that site, can inadvertently prolong the aPTT. Other than heparin exposure, the most common cause of a prolonged aPTT is von Willebrand disease (vWD), but other hemophilias can prolong the aPTT. In addition, an aPTT mixing study (in which normal blood is mixed with the subject's blood) allows for differentiation between factor deficiencies (aPTT will be corrected) and inhibitors (aPTT will not be corrected). Some hypercoagulable states can cause a prolonged aPTT, including factor V Leiden, anticardiolipin antibody, and lupus anticoagulants. Elective surgical procedures should be postponed until the etiology of abnormal tests is determined and corrections are made.

Hemophilias. Hemophilia A (factor VIII deficiency) and hemophilia B (or Christmas disease) are X-linked recessive inherited disorders that almost exclusively manifest in male patients. Hemophilia A accounts for 85% of all patients with hemophilia. Patients with hemophilia have prolonged aPTT and normal PT results. The severity of bleeding varies among individuals but tends to be similar among relatives and is directly related to the degree of factor deficiency. Even mild trauma can result in significant hemorrhage. Intramuscular injections are to be avoided. Orthopedic procedures account for 50% of operations in patients with hemophilia because recurrent intra-articular bleeding destroys joints.

A hematologist must be involved in the perioperative care of these patients. A detailed plan to monitor and replace deficient factors is paramount. Typically, factors VIII and IX are maintained at 75% to 100% of usual levels in the immediate perioperative period and then at 50% until any risk of bleeding is past. Each unit of recombinant or purified factor concentrate raises the factor level by 2% per kilogram.

von Willebrand Disease. vWD is an inherited disorder of factor VIII and von Willebrand factor (vWF) that affects both sexes. It is the most common congenital coagulopathy, occurring in approximately 1% of individuals.[169] Several types (1, 2A, 2B, 2M, and 2N) are autosomal dominant, and type 3 is autosomal recessive (Table 38-10). Factor VIII and vWF circulate as a complex, with disease resulting from both quantitative and qualitative deficiencies. Most patients have a prolonged aPTT, although patients with mild disease may have normal aPTT. The most common cause of a prolonged aPTT in patients not taking heparin is vWD. The condition is diagnosed by measuring ristocetin cofactor (functional assay for vWF, which causes platelet aggregation in the presence of ristocetin), vWF antigen, and factor VIII levels. vWF is an acute phase reactant and increases with conditions such as stress or surgery, thereby making the diagnosis sometimes difficult. Most patients with vWD have a history of bleeding, but some do not receive a diagnosis until a challenge to coagulation occurs with major surgery or antiplatelet drug exposure (e.g., aspirin, NSAIDs). A hematologist must be involved in the care of these patients. Desmopressin acetate (1-desamino-8-D-arginine vasopressin [DDAVP]) increases factor VIII, vWF, and plasminogen activator release from endothelial cells. An intravenous dose of 0.3 μg/kg (given over 15 to 30 minutes to avoid

TABLE 38-10 **CLASSIFICATION OF VON WILLEBRAND DISEASE**

Type	Characteristics	Treatment
1	80% of cases; quantitative defect	Desmopressin*
2A	Quantitative and qualitative defect	Desmopressin*
2B†	Rare; quantitative and qualitative defect, autosomal dominant	Cryoprecipitate or factor VII concentrates with vWF
2M	Qualitative defect	Desmopressin*
2N	Qualitative defect; vWF levels normal; factor VIII reduced	Desmopressin* effect may be too short-lived
3	Rare; low to undetectable levels of vWF	Desmopressin* usually not effective

vWF, Von Willebrand factor.
*Desmopressin acetate (DDAVP).
†With type 2B, desmopressin acetate may cause thrombocytopenia. If desmopressin is not effective, factor VIII concentrates containing vWF or cryoprecipitate may be used.

hypotension, flushing, and tachycardia) typically raises the vWF by three- to fourfold. Nonetheless, considerable variation in response exists among individuals, so vWF and factor VIII levels must be monitored. Desmopressin acetate is also available as a nasal spray. It should not be given more frequently than every 48 hours to prevent depletion of endothelial stores. To avoid the release of plasminogen activator by desmopressin acetate, antifibrinolytics such as ε-aminocaproic acid or tranexamic acid can be given. Desmopressin acetate is contraindicated in patients with type 2B disease because it increases abnormal vWF and may cause thrombocytopenia. For these individuals, cryoprecipitate or factor VIII concentrates containing vWF can be used to replace abnormal vWF.

Thrombocytopenia. Thrombocytopenia is defined as a platelet count of less than 150,000/mm^3, and it results from decreased production, increased destruction, or sequestration (see also Chapter 61). Causes include malignant diseases, drugs, autoimmune disorders, preeclampsia, hereditary disease, and disseminated intravascular coagulation. In patients who are unexpectedly found to have low platelet counts, the initial steps are to repeat the test, examine the peripheral smear, and collect blood for the platelet count in a tube without ethylenediaminetetraacetic acid (EDTA). This chemical, which is a chelating agent often used to prevent clotting in tubes used for determining CBC, can also cause clumping of platelets (termed pseudothrombocytopenia).

Recent exposure to heparin raises the concern of heparin-induced thrombocytopenia (HIT), which generally occurs within 5 to 10 days after heparin exposure.[170] HIT is an immune-mediated disorder characterized by antibodies directed against platelets. The disorder can result in arterial thromboses, venous thromboses, stroke, amputations, and death in up to 30% of patients. Immediate discontinuation of heparin is required, followed by testing for heparin-induced platelet antibodies. LMWH is less likely than unfractionated heparin to cause HIT; nonetheless, LMWH is contraindicated in any patient with established HIT. Alternative anticoagulants that can be used in these patients include danaparoid sodium, lepirudin, and argatroban.

Idiopathic thrombocytopenic purpura (ITP) is a chronic autoimmune disorder characterized by antiplatelet autoantibodies that cause platelet destruction. Usual treatment for ITP includes corticosteroids, splenectomy (eliminates the major site of platelet removal), and intravenous immunoglobulin. Patients with ITP often have less bleeding than expected, even at very low platelet levels, likely because of increased platelet turnover with a resulting predominance of young platelets.

Neuraxial anesthesia is considered safe in patients with platelet counts higher than 100,000/mm^3.[171] Surgery can be safely performed in patients with platelet counts higher than 50,000/mm^3. The risk of bleeding increases progressively as the count falls further, to less than 50,000/mm^3. Anemia, fever, infections, and antiplatelet drugs can increase bleeding at any platelet count. A patient with newly discovered thrombocytopenia should undergo hematology consultation before elective surgery. When platelet transfusions are used to treat thrombocytopenia, the platelet count generally rises by 10,000/mm^3 for every unit transfused.

Thrombocytosis. Thrombocytosis is defined as a platelet count of more than 500,000/mm^3. It may be physiologic (e.g., exercise, pregnancy), primary (e.g., myeloproliferative disorder), or secondary (e.g., iron deficiency, neoplasm, surgery, chronic inflammation). Platelet counts greater than 1,000,000/mm^3 can increase risks for thrombotic events such as strokes, MIs, pulmonary emboli, mesenteric emboli, and venous clots. Conversely, patients with primary thrombocytosis (also known as essential thrombocythemia) have a tendency toward increased bleeding, which is worsened with exposure to antiplatelet medications such as aspirin. Risk factors include increased age and a previous history of bleeding or thrombosis. Treatments include medications (e.g., hydroxyurea, anagrelide) that decrease platelet production and hence reduce platelet counts over 7 to 10 days. Plasmapheresis, which removes platelets from the circulation, can also be used if an immediate lowering in platelet count is required. In cases of secondary thrombocytosis, treatment of the underlying disorder usually results in normalization of the platelet level.

Polycythemia. Polycythemia is defined as a hematocrit greater than 54%. It has both primary causes (i.e., polycythemia vera) and secondary causes (e.g., COPD, high altitude, congenital heart disease), usually related to chronic hypoxia. A steep increase in blood viscosity occurs once the hematocrit increases to more than 50%, resulting in an increased thrombogenic risk. High hematocrits are associated with increased atherosclerosis (e.g., carotid stenosis, stroke) and cardiac disease (e.g., heart failure, MI). Reports on whether polycythemia increases perioperative risk are contradictory. For example, an increase in hematocrit to more than 51% was associated with increased postoperative mortality in a large study of 310,311 patients.[49] Conversely, a previous smaller study of 200 patients did

not find an increased rate of perioperative complications in individuals with secondary polycythemia.[172]

The preoperative history and physical examination of these patients should focus on the pulmonary and cardiovascular systems. Examination for cyanosis, clubbing, wheezing, and murmurs is necessary. Pulse oximetry and an ECG are required in patients with polycythemia, with analysis of arterial blood gases and a chest radiograph. An unexpected finding of polycythemia should prompt an investigation for possible causes, which if not readily apparent, should raise the possibility of polycythemia vera. In such cases, elective surgical procedures should be postponed pending an evaluation by a hematologist.

Thromboembolic Disorders. The rate of fatal pulmonary embolism is 0.1% to 0.8% after elective general surgery, 2% to 3% after elective hip replacement, and 4% to 7% after repair of a fractured hip, if prophylaxis is not administered. Primary thromboembolic prophylaxis is beyond the scope of this chapter and is covered extensively in specialty society practice guidelines.[173,174] Nonetheless, patients should be stratified preoperatively for their risks of perioperative venous thromboembolism, so appropriate measures can be implemented on the day of surgery. These risks depend on both patient-related (e.g., inflammatory bowel disease, acute illness, smoking, malignant disease, obesity, increased age, prior thromboembolism, estrogen use, hypercoagulable state, inherited thrombophilia) and procedure-related (e.g., invasiveness, trauma, immobilization) factors (Box 38-14).[175] Factor V Leiden, the most common inherited thrombophilia, accounts for 40% to 50% of cases. The remaining cases are caused by prothrombin gene mutation, as well as deficiencies in protein S, protein C, or antithrombin. Because of the high risk of thromboembolism in patients undergoing elective lower extremity joint replacement, these patients are often given a dose of warfarin the night before the surgical procedure. The American Society of Regional Anesthesiologists (ASRA) guidelines specifically state that neuraxial anesthesia can be safely performed when a single dose of warfarin has been administered within the previous 24 hours.[171]

Specific subgroups of patients are at considerably higher risk for perioperative venous thromboembolism. Recent arterial or deep vein thromboembolism (DVT) entails postponement of procedures that are not lifesaving. Without anticoagulation, the risk of recurrent DVT within 3 months following a proximal DVT is approximately 50%. A month of warfarin treatment reduces that risk to 10%, whereas a 3-month course of treatment reduces it to 5%. Elective surgery should therefore be postponed in the first month after an episode of venous or arterial thromboembolism. Ideally, a 3-month course of anticoagulation is recommended before elective surgery. If postponement is not possible, then the patient must receive preoperative bridging therapy while the INR is less than 2.0.[176] Patients who have a hereditary hypercoagulable state (e.g., antithrombin III, protein C or S deficiencies, prothrombin gene mutation, factor V Leiden), cancer, or multiple episodes of venous thromboembolism are considered at high risk indefinitely. Other high-risk subgroups include patients with nonvalvular atrial fibrillation who have had previous cerebral emboli, as well as patients with mechanical heart valves. Among patients with mechanical heart valves, multiple valves and mitral valves (as opposed to aortic valves) are associated with greater risk. Although surgery is associated with an increased risk for DVT, a similar increased risk does not occur for postoperative arterial embolism in patients with atrial fibrillation or mechanical valves.[176]

Patients having minor procedures such as dental, endoscopic, cataract, or superficial operations usually do not require interruption of anticoagulant therapy. In other individuals, withholding warfarin for 5 days typically allows the PT or INR to decrease to normal if the INR is maintained at the usual therapeutic target (2.0 and 3.0) in the long term. More doses should be withheld if the INR is more prolonged, and fewer doses should be withheld if the INR is subtherapeutic. Thus, INR should be checked during the preoperative visit to guide cessation of therapy. During the time without warfarin (Coumadin), patients may be at risk for recurrent thromboembolism; however, the risk

BOX 38-14 ***Categories of Risk for Venous Thromboembolism in Surgical Patients***

Low Risk

Minor surgery in patients <40 years of age with no additional risk factors present*

- Risk of calf DVT: 2%
- Risk of proximal DVT: 0.4%
- Risk of clinical PE: 0.2%
- Risk of fatal PE: <0.01%

Moderate Risk

Minor surgery in patients with additional risk factor present* **or** surgery in patients 40 to 60 years old with no additional risk factors

- Risk of calf DVT: 10-20%
- Risk of proximal DVT: 2-4%
- Risk of clinical PE: 1-2%
- Risk of fatal PE: 0.1-0.4%

High Risk

Surgery in patients ≥60 years old **or** surgery in patients 40 to 60 years old with additional risk factors*

- Risk of calf DVT: 20-40%
- Risk of proximal DVT: 4-8%
- Risk of clinical PE: 2-4%
- Risk of fatal PE: 0.4-1.0%

Highest Risk

Surgery in patients ≥40 years old with multiple risk factors,* hip or knee arthroplasty, hip fracture surgery, **m**ajor trauma, or spinal cord injury

- Risk of calf DVT: 40-80%
- Risk of proximal DVT: 10-20%
- Risk of clinical PE: 4-10%
- Risk of fatal PE: 0.2-5%

Data from Geerts WH, Pineo GF, Heit JA, et al: Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy, Chest *126:338S-340S, 2004.*

DVT, Deep vein thrombosis; *PE,* pulmonary embolism.

*Additional risk factors include one or more of the following: advanced age, cancer, prior venous thromboembolism, obesity, heart failure, paralysis, or molecular hypercoagulable state (e.g., protein C deficiency, factor V Leiden).

is relatively small in all but the highest-risk patients. The decision to bridge with intravenous unfractionated heparin or with LMWH subcutaneously, or not to bridge at all, in high-risk patients must be made in concert with the treating physician or a cardiologist. Previously, the only option for bridging was costly hospital admission for intravenous heparin therapy. With the availability of LMWH in contemporary clinical practice, patients can now receive bridging therapy with subcutaneous (usually self-administered) LMWH at home, without the need for monitoring.

Anticoagulant Therapy. Warfarin may increase perioperative bleeding, except for minor procedures such as cataract surgery without bulbar blocks. No consensus exists on the optimal perioperative management of patients receiving warfarin. The usual recommendation is to withhold warfarin starting 4 to 5 days preoperatively (if the INR is between 2.0 and 3.0) to allow the INR to decrease to less than 1.5, which is a level considered safe for surgical procedures and neuraxial blockade.[171] If the INR is greater than 3.0, it is usually necessary to withhold warfarin longer than 4 to 5 days. If the INR is measured the day before the surgical procedure and remains higher than 1.8, a small dose of vitamin K (1 to 5 mg administrated orally or subcutaneously) can reverse anticoagulation.[176] Vitamin K has an effect within 6 to 10 hours after oral or subcutaneous administration (more predictable with oral administration), and it peaks within 24 hours to 48 hours. Administration of higher doses may lead to warfarin resistance when therapy is initiated again.

Decisions to use bridging therapy with unfractionated heparin or LMWH must be individualized and made in concert with the treating physician or a cardiologist. If bridging is planned, the INR must be checked 2 days after the last warfarin dose. When the INR drops to less than 1.5, the patient is either admitted for intravenous heparin, or LMWH therapy (thromboprophylaxis dose: enoxaparin 40 mg once daily, dalteparin 2500 to 5000 International Units once daily, or tinzaparin 175 International Units/kg once daily) can be initiated. Adjustments in LMWH doses are necessary for patients with impaired renal function (eGFR <30 mL/minute). Intravenous unfractionated heparin is usually discontinued approximately 6 hours before the surgical procedure to allow for normal intraoperative coagulation. The last dose of *therapeutic* LMWH is given 24 hours (prophylactic doses must be held for just 12 hours) preoperatively to allow normalization of coagulation. Factor Xa levels are not usually monitored, with the possible exception of patients with an eGFR of less than 30 mL/minute. Both unfractionated heparin and LMWH are contraindicated in patients with a history of HIT. Fondaparinux is a synthetic pentasaccharide that inhibits factor X, and it can be given subcutaneously once daily (thromboprophylaxis dose: 2.5 mg) in patients with a history of HIT. It is not recommended for patients with an eGFR of less than 30 mL/minute. Aspirin does reduce the risk of perioperative venous thromboembolism,[177] but not to the same degree as anticoagulants.

Caution is used when performing neuraxial techniques in patients who have recently discontinued long-term warfarin therapy (see also Chapter 56). The anticoagulant therapy must be stopped (ideally 4 to 5 days before the planned procedure) and PT or INR measured before initiation of neuraxial block. Adequate levels of factors II, VII, IX, and X may not be present until the PT or INR is within normal limits. For patients receiving an initial preoperative dose of warfarin, practice guidelines recommend checking the PT or INR before neuraxial block if either the first dose was given more than 24 hours before the surgical procedure or more than one dose of oral anticoagulant had been administered.[171]

Prophylactic LMWH is stopped 12 hours before any planned neuraxial block, whereas therapeutic LMWH doses should be stopped 24 hours before neuraxial blocks. The subsequent dose of LMWH must occur 2 or more hours after the neuraxial block.[171] Monitoring of the anti-Xa level is not recommended because the anti-Xa level is generally not predictive of the risk of bleeding. Subcutaneous (minidose) unfractionated heparin prophylaxis is not a contraindication to the use of neuraxial techniques.[171] Combining neuraxial techniques with intraoperative anticoagulation by intravenous unfractionated heparin is acceptable, provided the patient has no other coagulopathies and heparin administration is delayed for at least 1 hour after needle placement.[171] Preoperative unfractionated intravenous heparin is generally stopped 6 to 8 hours before planned spinal or epidural anesthesia; in addition, return to normal coagulation can be monitored with aPTT, and further reversal can be achieved with protamine. Epidural catheters can be safely left in place while patients receive a single daily dose of prophylactic LMWH, but not with larger doses. When removing epidural catheters, the optimal time is 12 hours after the last prophylactic dose *and* 2 hours before the next dose. Any patients receiving fibrinolytic and thrombolytic drugs should be cautioned against receiving neuraxial anesthesia, except in highly unusual circumstances.[171]

Antiplatelet Therapy. Traditionally, aspirin has been discontinued leading up to surgery (often 7 to 10 days before the operation) because of concern about increased bleeding. The 7- to 10-day withdrawal period is itself likely excessive, especially given that new platelets formed after the discontinuation of aspirin (its half-life is ≈15 minutes) are not inhibited. Given that approximately 10% of platelets are turned over every 24 hours, and the minimum (normal functioning) platelet count needed to control surgical bleeding is 50,000 per mm^3, it is likely that aspirin must be stopped only 3 to 4 days preoperatively.

Although a systematic review of patients undergoing noncardiac surgery found that perioperative aspirin increased bleeding complications by approximately 50%,[71] aspirin was not associated with increased severity of bleeding complications, except in intracranial surgery and possibly transurethral resection of the prostate. Nonetheless, low-dose aspirin (100 mg/day) was shown to increase major bleeding in the POISE-2 trial of 10,010 surgical patients.[71] Notably, when surgeons are blinded to aspirin administration, they cannot differentiate between patients who were taking aspirin and those who were not, based on clinical inspection of perioperative bleeding.[178]

Withdrawing aspirin itself has important potential risks. A rebound hypercoagulable state results when

long-term aspirin therapy is withdrawn,[179] and withdrawal or noncompliance with aspirin is associated with a threefold increase in the risk of major cardiac events.[180] When considered in combination with a hypercoagulable state induced by many surgical procedures, preoperative aspirin withdrawal has important theoretical risks. Observational studies,[181,182] as well as a randomized trial of 220 participants,[73] support an increased risk of vascular events when long-term aspirin is stopped perioperatively.

Despite these promising reasons for continuing aspirin during noncardiac surgery, the actual benefits are uncertain. For example, a randomized trial of 291 participants found no benefit from continuing, as opposed to withdrawing, aspirin therapy before elective noncardiac surgery.[72] Most recently, the POISE-2 trial found no differences in rates of cardiac complications in patients receiving aspirin.[71] Thus, aspirin should neither be continued or withdrawn *routinely*. Any benefits from continuing aspirin are most likely to be seen in patients for whom the risk of cardiac events is felt to outweigh the risk of bleeding (e.g., high-risk CAD).

The risk of dual antiplatelet therapy with respect to increasing perioperative bleeding and mortality, especially in noncardiac surgery, is not well established.[5] The usual recommended time point for discontinuing clopidogrel is 5 days to 7 days preoperatively. This interval is consistent with pharmacokinetic data showing complete restoration of platelet function in healthy volunteers by 7 days following discontinuation of clopidogrel.[183] In some selected cases, the best overall option for a patient may be to proceed to surgery while continuing thienopyridine therapy (e.g., drug-eluting stent within 1 year before urgent surgical procedures). Decisions regarding the perioperative management of such a case must be individualized and based on extensive discussion with the patient's cardiologist and surgeon. A newer antiplatelet drug, prasugrel, may be more potent than aspirin or thienopyridines. Studies support the safety of neuraxial and peripheral anesthesia in patients taking long-term aspirin,[184] and the ASRA endorses this opinion.[171] The risk of spinal hematoma with ticlopidine or clopidogrel is unknown. Based on labeling, ASRA guidelines, and surgical reviews, the suggested time interval between discontinuation of thienopyridine therapy and neuraxial blockade is 14 days for ticlopidine and 7 days for clopidogrel.[171]

Information on the perioperative safety of continuing other antiplatelet therapies, such as glycoprotein IIb/IIIa inhibitors, is limited. Platelet glycoprotein IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, tirofiban) exert profound effects on platelet aggregation. Following administration, the time to restoration of normal platelet aggregation is 24 to 48 hours for abciximab and 4 to 8 hours for eptifibatide and tirofiban. Neuraxial techniques should be avoided until platelet function has recovered.[171]

NEUROLOGIC DISEASE

For a patient with neurologic disease, the detailed history should focus on recent events, exacerbations, and evidence of poor control of the underlying medical condition. Information about prior investigations or therapy is important. A basic neurologic examination evaluating deficits in mental status, speech, cranial nerves, gait, motor function, and sensory function is important. This baseline determination also allows for comparison of possible new deficits postoperatively.

Cerebrovascular Disease

If a stroke or transient neurologic deficit has occurred recently or has not been fully evaluated, elective surgical procedures should be delayed pending complete evaluation, especially because a history of cerebrovascular disease is a very strong predictor of subsequent perioperative stroke.[185,186] No good data are available on the safe interval required between an acute stroke and subsequent surgery. Investigators have suggested that the appropriate interval is at least 1 to 3 months, although research is needed to define this optimal duration more clearly.[187] The etiology and treatment of previous strokes or transient ischemic attacks should guide further perioperative management. For example, an embolic stroke from a patent foramen ovale may require correction of the defect or strict attention to avoid air emboli. A left atrial or ventricular thrombus, as well as an embolic stroke believed secondary to atrial fibrillation, requires a minimum of 1 month and preferably 3 months of anticoagulation therapy (in addition to possible bridging with unfractionated heparin or LMWH).

Cerebrovascular disease is a predictor of perioperative cardiac complications, and attention is required to determine the risk of ischemic heart disease.[47] In addition, the presence of concomitant cerebrovascular disease should be carefully considered in any decision to initiate new β-adrenergic blocker therapy in a patient awaiting a noncardiac surgical procedure. Although β blockade does decrease perioperative cardiac risk, it may also significantly increase the risk for acute stroke following noncardiac surgery.[40,68]

Asymptomatic Bruit

A newly discovered carotid bruit requires a careful search for symptoms of cerebral ischemia or transient ischemic attack, especially if the procedure involves manipulation of the neck or if the patient has a potentially difficult airway. Patients often fail to volunteer pertinent symptoms until they are specifically probed, especially if the symptoms were transient. Patients with risk factors for carotid atherosclerosis, including patients who received head and neck irradiation at younger ages, should be questioned specifically about *amaurosis fugax*, dysphagia, dysarthria, and other symptoms of cerebrovascular insufficiency.

Carotid Doppler ultrasound studies are simple, effective tools to evaluate at-risk patients with suspicious carotid bruits. Significant abnormalities on Doppler studies should prompt a referral to a neurologist or vascular surgeon. In patients who have truly asymptomatic bruits, significant carotid lesions are present 40% to 60% of cases. The risk of stroke in this group is 1% to 2% per year, with most strokes preceded by transient symptoms.[188] Carotid endarterectomy for asymptomatic carotid stenosis should be considered only if the patient has 80% or greater stenosis and the operating surgeon has a low (i.e., ≤3%) perioperative complication rate.[188,189] No evidence

indicates that truly asymptomatic bruits increase the risk of *perioperative* stroke.[187]

Seizure Disorder

The type of seizure (e.g., *grand mal*, absence) and specific symptoms (e.g., staring, focal findings) are important to document. Absence (previously *petit mal*) seizures may be particularly difficult to recognize because they lack generalized motor signs. More typical symptoms such as staring and obtundation may be misinterpreted as residual anesthetic effects in the postoperative period. Determining the etiology of the seizure disorder is also important because of possible associated morbidities. Important associated comorbidities include brain tumors, aneurysms, arteriovenous malformations (AVMs), classic epilepsy, drug toxicity, electrolyte disorders, infections, cerebrovascular disease, sickle cell disease, and SLE.

Careful documentation of anticonvulsants and adequacy of seizure control is necessary. Routine measurement of serum drug levels of anticonvulsants is not indicated unless toxicities or ongoing breakthrough seizures pose a concern. Indeed, patients with good control of seizures may have levels outside the therapeutic range. Drug levels are highly influenced by when the blood draw occurs relative to the timing of drug administration. In general, trough levels should be measured. Medications to control seizures have multiple side effects (e.g., bone marrow suppression, macrocytic anemia, leucopenia, hyponatremia), and testing should be directed based on suspected abnormalities. The most commonly ordered tests are CBC and electrolyte levels. Poorly controlled or new-onset seizures entail a consultation with a neurologist before the patient undergoes anything other than emergency surgery. Continuation of anticonvulsant therapy in the perioperative period is necessary.

Multiple Sclerosis

Multiple sclerosis is believed to be an inflammatory immune disorder with two general clinical patterns: exacerbating-remitting and chronic progressive. Symptoms can include ataxia, motor weakness, sensory deficits, autonomic dysfunction, emotional lability, bladder or bowel dysfunction, and visual disturbances. Exacerbations of multiple sclerosis can be triggered by stress, infections, pregnancy, and elevated temperatures. Various treatments have been tried, including steroids, immunosuppressants, monoclonal antibodies, plasmapheresis, benzodiazepines, and baclofen. During the preoperative assessment, the history and pattern of disease, especially symptoms and physical deficits affecting the respiratory system (including oxygen saturation), should be documented. Medications, previous triggers, and preexisting neurologic deficits should be documented. Testing is generally directed toward associated disturbances (e.g., chest radiography and white blood cell count if pulmonary infection is suspected) and possible medication side effects. For example, azathioprine can suppress bone marrow or affect liver function, cyclophosphamide may cause electrolyte abnormalities, and steroids can cause hyperglycemia. Patients with minor, stable disease require no special testing. Medications should be continued on the day of surgery. No clear association has been shown between the type of anesthetic or a specific anesthetic drug and disease exacerbations.[190] Regional anesthesia may offer advantages for patients with respiratory compromise or cognitive dysfunction.

Aneurysms and Arteriovenous Malformations

Cerebral and spinal vascular lesions consist of aneurysms and AVMs, which may be intact, ruptured, symptomatic, or incidental findings. Risk factors include polycystic kidney disease, fibromuscular dysplasia, type IV Ehlers-Danlos syndrome, and a family history of aneurysms. An AVM may also be large enough to cause a mass effect. Pregnancy increases the risk of aneurysmal and possibly AVM bleeding. Before rupture, most patients have minimal symptoms other than headache or seizures, but it is important to document complaints in all patients. Any rupture can result in altered mental status, syncope, increased intracranial pressure, inappropriate antidiuretic hormone secretion, and hemodynamic perturbations. The hemodynamic changes include bradycardia, tachycardia, and ectopic beats. Usual tests ordered include an ECG and determination of electrolytes, glucose, BUN, and creatinine. Chest radiography and echocardiography are also often needed. The ECG changes, often ST-segment and T-wave changes, commonly mimic those seen with myocardial ischemia. Significant cardiac dysfunction with depressed contractility and wall motion abnormalities can also be present on echocardiography. Although the bleeding may be responsible for these cardiovascular changes, concomitant CAD or preexisting cardiomyopathy should also be considered. Measures aimed at controlling increased intracranial pressure, arterial BP, and blood glucose are most important.

Parkinson Disease

Parkinson disease is a degenerative disorder of the basal ganglia characterized by failure of dopamine secretion that results in diminished inhibition of the extrapyramidal motor system.[191] Patients typically have diminution of spontaneous movements, rigidity (cogwheel rigidity is classic), resting tremor, masked facies, difficulty speaking, difficulty walking, depression, and dementia. Autonomic dysfunction with orthostatic hypotension, excessive salivation, and impaired thermoregulation may also occur. Patients are at risk of pulmonary complications resulting from difficulty swallowing, altered mental status, increased aspiration risk, and ventilatory muscle dysfunction. Standard treatments include levodopa (often combined with carbidopa), anticholinergic agents, bromocriptine, amantadine, and selefiline. Levodopa can cause dyskinesias (i.e., dystonic and myoclonic involuntary movements). Selefiline is a monoamine oxidase inhibitor (MAOI) that inhibits dopamine degradation. Some individuals also undergo implantation of deep brain stimulators to manage their symptoms.

Preoperative evaluation focuses on the pulmonary system, signs of dysphagia, and degree of disability. Both room air saturation and orthostatic vital signs are important to document. Evidence of significant pulmonary symptoms or possible infection requires chest radiography, pulmonary consultation, and possible delay of the

procedure for improvement. Individuals with deep brain stimulators require deactivation of the devices before any procedures in which electrocautery will be used. All associated medications should be continued, including MAOIs. Abrupt withdrawal of levodopa may exacerbate symptoms (especially dysphagia and chest wall rigidity) or precipitate neuroleptic malignant syndrome. The latter disorder is characterized by autonomic instability, altered mental status, rigidity, and fever. Some medications encountered in the perioperative setting, such as metoclopramide and phenothiazines, may exacerbate symptoms of Parkinson disease by interfering with dopamine.

Neuromuscular Junction Disorders

Myasthenia gravis is an autoimmune disorder of skeletal muscle neuromuscular junctions that is caused by antibodies against nicotinic acetylcholine receptors (see also Chapter 42).[192] The disease is characterized by muscle weakness that worsens with activity and improves with rest. Box 38-15 presents a classification system for myasthenia gravis with increasing numeric classes indicating increasing levels of involvement and debilitation. Weakness is exacerbated by stress, infections, hypokalemia, medications (e.g., aminoglycosides, propranolol, ciprofloxacin, clindamycin), and surgery. Cardiac and smooth muscles are unaffected. Patients with myasthenia gravis commonly have other autoimmune diseases, such as rheumatoid arthritis, polymyositis, and thyroid disorders.

Affected individuals may have thymic hyperplasia and tumors. Because the thymus is located in the anterior mediastinum, thymic enlargement has implications for anesthesia care. Cranial nerve and bulbar involvement are common, with an associated increase in aspiration risk resulting from pharyngeal and laryngeal muscle weakness. Ocular symptoms (i.e., diplopia, ptosis) are almost always present; often, they are the presenting or only complaints. Patients are usually treated with thymectomy, anticholinesterase, and immunosuppressant medications. Worsening symptoms may reflect worsening disease (i.e., myasthenic crisis) or excessive anticholinesterase treatment (i.e., cholinergic crisis). A short-acting anticholinesterase (edrophonium) can help distinguish the two states. Specifically, only a myasthenic crisis improves with more anticholinesterase. Plasmapheresis and intravenous immunoglobulins have been used to treat myasthenic crises and prepare patients for surgery, but they require several days to weeks to produce signs of improvement.

Documentation of medication dosages and continuation of medications until the surgical procedure are paramount. Patients taking azathioprine require a CBC and LFTs because of drug-induced bone marrow suppression and liver dysfunction. Patients treated with steroids need glucose measurement, as well as steroid supplementation in the perioperative period. Because ventilatory function can be compromised, preoperative PFTs may also be indicated for selected patients, particularly those with severely affected ventilatory function. These tests may also be helpful if patients are being considered for ambulatory surgery, especially in freestanding surgical centers. Even though anticholinesterases may cause bradycardia, salivation, and altered effects of neuromuscular blocking drugs, these agents must be continued in the perioperative period.[193] Avoidance of drugs that can exacerbate myasthenic symptoms is also necessary.

Lambert-Eaton syndrome is similar to myasthenia gravis, with muscle weakness including oculobulbar involvement and dysautonomia. It is caused by antibodies against voltage-gated calcium channels that result in a decrease in acetylcholine release. Lambert-Eaton syndrome is not associated with thymic abnormalities, but it commonly occurs in patients with malignant diseases, especially small cell lung cancer and gastrointestinal tumors. The other distinguishing feature of this disorder is that the muscle weakness classically improves with activity and is worse after inactivity. Therapies for Lambert-Eaton syndrome are similar to those used for myasthenia gravis. In addition, a selective potassium channel blocker, namely 3,4-diaminopyridine, is used and should be continued perioperatively. Preoperative evaluation and management are similar to those for myasthenia gravis.

BOX 38-15 ***Osserman Classification System for Myasthenia Gravis***

Class I: Ocular myasthenia
Class IIA: Mild generalized myasthenia with slow progression: no crises, responsive to drugs
Class IIB: Moderately severe generalized myasthenia: severe skeletal and bulbar involvement but no crises; drug response less than satisfactory
Class III: Acute fulminating myasthenia: rapid progression of severe symptoms, with respiratory crises and poor drug response
Class IV: Late severe myasthenia, same as class III but progression over 2 years from class I to II

Data from Osserman KE, Genkins G: Studies in myasthenia gravis: review of a twenty-year experience in over 1200 patients. Mt Sinai J Med 1971; 38: 497–537.

Muscular Dystrophies and Myopathies

Muscular dystrophies and myopathies are inherited disorders that affect the neuromuscular junction. They share many similarities but do have a few differences. The hallmark of these disorders is progressive skeletal muscle weakness that commonly leads to respiratory failure. No effective therapy is available. Many individuals have associated cardiomyopathies and possible association with MH.

Duchenne and Becker muscular dystrophies are X-linked recessive disorders that occur primarily in male patients. Affected individuals have elevated creatine phosphokinase (CK) levels, often preceding the onset of symptoms. Male patients with a family history of either Duchenne or Becker muscular dystrophy should be considered at risk (even when they have not been formally tested), and they require precautions similar to those in patients with diagnosed disease. Cardiomyopathy and respiratory failure are the usual causes of death. Female carriers of the abnormal gene may have dilated cardiomyopathy despite having no other manifestations of the disease. The focus of the preoperative history is on eliciting details pertaining to palpitations, dyspnea, chest pain, syncope, orthopnea, dependent edema, aspiration, and pneumonia. The physical examination generally concentrates on the cardiopulmonary system, whereas

important additional preoperative tests include an ECG, PFTs, and echocardiography.

Facioscapulohumeral muscular dystrophy (also known as faciohumeroscapular or Landouzy-Dejerine muscular dystrophy) is an autosomal dominant disorder that affects both sexes and causes a slow, progressive weakness of muscles in the shoulders and face. Cardiomyopathy occurs much less frequently than in other dystrophies, but arrhythmias have been reported. Limb-girdle dystrophies have a variable genetic inheritance pattern and primarily affect the muscles of the shoulders and pelvis. Conduction abnormalities are present in some patients, although frank cardiomyopathies are less frequent. The preoperative evaluation is largely similar to that described previously for Duchenne muscular dystrophy.

Myotonic Dystrophies. Myotonia consists of prolonged contraction and delayed relaxation of muscles. It is a common symptom of several dystrophies, including classic myotonic dystrophy, congenital myotonic dystrophy, myotonia congenital, and central core disease. Myotonic dystrophy, which is the most common of these conditions, is an autosomal dominant inherited disorder affecting both sexes. Congenital myotonic dystrophy is a severe form of this disease that manifests in infancy, often in the children of affected mothers. The classic findings are severe muscle wasting, typically involving the diaphragm, as well as muscles in the face, hands, pharynx, and larynx. Cold temperatures can often trigger myotonia. The disease severity is variable, with symptoms often not apparent until the second or third decade of life; therefore, obtaining a family history is important. Cardiomyopathies, arrhythmias, and conduction abnormalities are common, while some patients also have cardiac valvular abnormalities. Cardiac involvement may not correlate with the degree of atrophy or weakness in skeletal muscle. Once an affected individual shows any evidence of second- or third-degree AV block, a pacemaker should be implanted (even if the patient is asymptomatic) because an unpredictably rapid progression of the cardiac conduction disease may occur. Given this potential for rapid disease progression, pacemaker placement may even be considered in patients with first-degree AV block, regardless of symptoms. Affected individuals are also at risk for aspiration, pneumonia, respiratory failure, and postoperative pulmonary complications.[194]

Central core disease is a rare disorder caused by deficiency of mitochondrial enzymes. The name derives from findings of muscle biopsies, which reveal "cores" of abnormalities. Affected individuals have proximal muscle weakness, scoliosis, and sometimes cardiomyopathies. As with myotonic dystrophy, patients are at risk for respiratory failure and aspiration. Myotonia congenita is a hereditary disorder that involves only skeletal muscles, causes less severe symptoms, and does not cause cardiac abnormalities.

Patients with myotonia may be at increased risk for MH, although this association is controversial. They may have a clinical presentation similar to that in patients with MH as a result of uncontrolled myotonic contraction with elevated metabolism and rhabdomyolysis.[195]

Symptomatic treatments for myotonic contractions include steroids, quinine, and procainamide; otherwise, these diseases have no cure. These treatments should be continued during the perioperative period. The preoperative evaluation focuses on the cardiopulmonary system, with special emphasis on evaluating for pulmonary infection, heart failure, palpitations, syncope, conduction abnormalities, and valvular abnormalities. Preoperative testing includes an ECG, an echocardiogram (except for myotonia congenita), and a chest radiograph (if symptoms of pulmonary disease are present). Any evidence of a conduction abnormality on ECG should trigger a cardiology consultation. Myotonia is not inhibited by regional anesthesia, but local anesthetic infiltration into muscle may provide symptomatic relief.

Central Nervous System Tumors

Pituitary tumors may be classified as functioning (associated with endocrine abnormalities) versus nonfunctioning, as well as benign (adenomas are the most common pituitary lesion) versus malignant (see also Chapter 70). The mass effect of the tumor can also lead to some associated symptoms, such as headaches, visual field defects, and increased intracranial pressure (with associated gait disturbances, vomiting, cranial nerve deficits, and bladder or bowel incontinence). Other symptoms may be related to pituitary insufficiency (e.g., hypoadrenalism, hypothyroidism, infertility) or overactivity. Manifestations of pituitary overactivity include the following: Cushing syndrome from ACTH-secreting tumors; acromegaly from growth hormone secretion; hyperthyroidism from TSH production; and gynecomastia, lactation, and sex hormone–related changes from prolactin and gonadotropin (follicle stimulating and luteinizing hormones) secretion. These hormones are all produced by the anterior lobe of the pituitary and are controlled by a feedback loop from the hypothalamus. The posterior pituitary stores and secretes vasopressin and oxytocin, which are synthesized in the hypothalamus.

Acromegaly results in enlargement of connective tissue, bone, and visceral organs. Patients have an enlarged jaw (i.e., macrognathia), nose, feet, hands, pharyngeal, and laryngeal tissues (including macroglossia and enlarged epiglottis). Affected individuals have increased risks of sleep apnea (both central and obstructive), neuropathies (from nerve entrapment), hypertension, LVH, diastolic dysfunction, and valvular abnormalities. CAD, heart failure, diabetes, hypothyroidism, and difficulty with airway management (mask ventilation, laryngoscopy, intubation) may also occur. The preoperative evaluation should document any chest pain, dyspnea, snoring, numbness, polydipsia, headaches, and visual disturbances. The physical examination focuses on BP, airway examination, murmurs, neurologic findings, and peripheral edema. It is important to plan for possible difficult airway management and to make the patient aware of the possible use of awake fiberoptic intubation. Preoperative testing may include ECG, electrolytes, glucose, and thyroid function tests. TSH increases production of thyroid hormones (T_3 and T_4) by the thyroid gland (see the earlier section on thyroid disease). Prolactin- and gonadotropin-secreting tumors have little impact on anesthetic management, but associated symptoms may alert clinicians to an undiagnosed pituitary tumor.

Posterior pituitary tumors result in failure to secrete vasopressin or antidiuretic hormone (ADH), which regulates renal water excretion. A deficiency results in diabetes insipidus, which is characterized by excessive urine output from a failure to reabsorb water. Unless treated with DDAVP, these patients may develop hypernatremia and volume depletion. Therefore, the need exists for a careful evaluation of their intravascular volume status, including orthostatic vital signs and blood testing for electrolytes, BUN, and creatinine levels. Patients with pituitary tumors, pituitary apoplexy (hemorrhage into pituitary, associated with hypertension, trauma, or pregnancy), or previous resection of a pituitary tumor may require hormone replacement therapy, such as with steroids, thyroid replacement, or DDAVP. These medications must not be interrupted during the perioperative period. The adequacy of replacement therapy can be determined based on the history and physical examination, as well as by determining electrolyte, BUN, and creatinine levels and performing thyroid function tests and an ECG.

Other intracranial tumors include gliomas (45% of tumors), astrocytomas, ependymomas, medulloblastomas, oligodendrocytomas (malignant and highly lethal), benign meningiomas (15% of tumors), schwannomas, craniopharyngiomas, and dermoid tumors. Metastatic lesions (6% of intracranial tumors) can also occur with virtually all types of primary malignant diseases. Common primary sources of metastatic intracranial lesions include breast, colorectal, and lung cancers. Most intracranial tumors are detected either incidentally or when patients develop seizures of symptoms related to mass effect. Symptoms of mass effect include headaches, strokelike symptoms, vomiting, visual disturbances, altered cognitive function, and ataxia. If the intracranial pressure becomes elevated, hypertension, bradycardia, arrhythmias, ECG abnormalities, and brainstem herniation may occur. Careful questioning and documentation of neurologic deficits are important. For patients with metastatic lesions, issues pertaining to the primary malignant disease and previous treatment (e.g., chemotherapy, radiation, steroids, anticonvulsants) must be clarified. Continuation of preexisting steroids (for decreasing brain edema) and anticonvulsant medications is important.

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

These disorders are characterized by deformities and chronic inflammation. Assessment of any deformities is important, given their potential implications on airway management and regional anesthetic technique. Chronic inflammation, which is associated with rheumatoid arthritis, SLE, and systemic sclerosis, can result in vasculopathy and associated multiorgan dysfunction. Organ systems that may be affected include the cardiovascular, pulmonary, renal, hematologic, integumentary, gastrointestinal, central nervous, and peripheral nervous systems.

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic autoimmune disorder that primarily affects joints, but it often also affects multiple organ systems.[196] The disease affects approximately 1% of the population, and women are more than twice as likely to be affected as are men.[196] Distal joints are involved more often than proximal, often in a symmetric pattern. Joint involvement is characterized by inflammation that can progress to severe deformity, although the disease course can vary dramatically. The temporomandibular joints and cricoarytenoid cartilage can be involved, resulting in limited mouth opening, hoarseness, and possible difficulties with airway management. Atlantodens subluxation and instability of the cervical spine can also occur. Subluxation, which is caused by ligamentous laxity, as opposed to joint disease, may occur in as many as 46% of patients.[197] Cervical spine disease can be asymptomatic. CAD, pericardial effusions, aortic regurgitation, and conduction abnormalities may be present in affected individuals. Symptoms of cardiac ischemia may be masked in patients with rheumatoid arthritis because of impairment of functional status by concomitant joint disease. In addition, dyspnea, which can be an anginal equivalent, may be confused with pulmonary involvement. Pulmonary manifestations include restrictive lung disease secondary to decreased thoracic mobility, pulmonary fibrosis, and pleural effusions. Patients have an increased risk of renal dysfunction secondary to both vasculitis and long-term NSAID use. Peripheral neuropathy can result from vasculitis or entrapment. Anemia, leukocytosis, thrombocytosis (from chronic inflammation), and thrombocytopenia (from splenomegaly) may be present. Patients may also have rheumatoid nodules that occur subcutaneously (usually over extensor joints) or in the lungs.

The preoperative examination must document symptoms related to the many organ systems affected by rheumatoid arthritis. Special detail is directed to the neurologic, airway, pulmonary, and cardiovascular systems. Documentation of deformities and neurologic deficits is important to establish a baseline level of function. Significant hoarseness should prompt an evaluation by an otolaryngologist to assess the mobility of the vocal cords and the presence of cricoarytenoid arthritis. A careful history may elicit neurologic deficits, neck pain, upper extremity pain, or crunching sound with neck movement. Indications for preoperative cervical spine radiographs include neurologic findings, long-standing severely deforming disease, or procedures requiring prone positioning or manipulation of the cervical spine. The specific radiographs required are anteroposterior and lateral cervical spine films with flexion, extension, and open-mouth odontoid views.[197] Significant abnormalities (i.e., anterior atlas-dens interval >9 mm or posterior interval <14 mm) require consultation with a neurologist or neurosurgeon. However, the disease duration, severity, and symptoms do not correlate with cervical spine subluxation. New or worsening pulmonary symptoms should trigger further evaluation with pulse oximetry, chest radiographs, PFTs, or possibly a pulmonary consultation. Muffled heart sounds, pericardial rubs, enlarged heart (examination or radiograph), and low voltage on an ECG suggest the presence of a pericardial effusion, which necessitates an echocardiogram. Any suspicious murmur merits further investigation in these patients. Because rheumatoid arthritis is associated with a very high prevalence of CAD, patients require ECGs, as well as possible cardiac stress

testing, with cardiology referral as indicated. Other preoperative tests should include blood sampling for a CBC and determination of BUN and creatinine levels.

Advanced planning for management of potential difficult airways is important, including discussion of regional anesthetic options and possible awake fiberoptic intubation. When possible, steroids, analgesic and antiplatelet medications should be continued. Patients with complex treatment regimens (especially immunosuppressant therapy) or severe disease are best managed in concert with their rheumatologist or primary physician.

Ankylosing Spondylitis

Ankylosing spondylitis is a progressive, inflammatory arthropathy that primarily affects the spine and sacroiliac joints, although peripheral joints may be involved as well. It usually occurs in male patients and can have extraarticular manifestations, including uveitis, vasculitis, aortitis, and aortic insufficiency. Affected individuals may develop restrictive lung disease secondary to pulmonary fibrosis or chest wall movement restriction (secondary to joint fixation and kyphosis). Kyphosis can be so extreme that patients are unable to face forward, thereby making mask ventilation, direct laryngoscopy, and intubation very difficult. The patient's history and physical examination should focus on the skeletal and cardiopulmonary systems, with the physical examination including measurement of oxygen saturation on room air. The presence of a murmur on physical examination warrants an ECG and an echocardiogram. If ventilatory compromise is suspected or present, a chest radiograph and PFTs are necessary. Any acute change must be managed preoperatively. Any NSAID therapy is usually discontinued for 2 days before the surgical procedure, but other drugs can be continued unless laboratory tests suggest complications. Patients receiving treatment with leflunomide should undergo LFTs, whereas patients receiving NSAIDs should undergo CBC, BUN, and creatinine testing. Planning for perioperative airway management and discussion with the patient about the possibility of awake fiberoptic intubation are important. Peripheral nerve blocks are an option, but neuraxial anesthesia is often unsuccessful in the presence of severe spinal involvement.

Systemic Lupus Erythematosus

SLE is a systemic autoimmune disease that is predominantly caused by vasculitis and has a variable course with flares and periods of remissions. It affects mainly female patients and is typically more severe in African Americans than in other ethnic groups. Common manifestations include fever, chronic fatigue, and migratory arthritis affecting the small joints of the hands and feet. The fevers may be explained by disease activity itself, as well as frequent infections attributable to disease-induced immune dysfunction and immunosuppressant treatment. Many patients have dermatologic conditions including alopecia, photosensitivity, and the typical "butterfly rash" across the cheeks and nose. Vasospasm of the digits (i.e., Raynaud phenomenon), often associated with atrophy of nails and fingernails, can make it difficult to obtain pulse oximetry readings. Interstitial lung disease, pleural effusions, frequent infections, and pulmonary hypertension may be present. Pulmonary hypertension, which can result from recurrent pulmonary emboli, pulmonary vasculopathy, and interstitial lung disease, carries a high risk of perioperative complications.[198] Cardiac involvement includes premature CAD, pericarditis, myocarditis, coronary artery vasculitis, cardiomyopathy, aseptic endocarditis, and pleural effusions. Hypertension is almost ubiquitous and is often difficult to control. Neurologic disease includes cerebral vasculitis, stroke, cerebrovascular disease, cognitive dysfunction, seizures, peripheral neuropathy, headache, neuropsychiatric manifestations, and affective disorders. Lupus nephritis is a common end-organ complication that carries a poor prognosis and often results in renal failure. Patients with SLE are frequently anemic and may also have leukopenia and thrombocytopenia. Affected individuals frequently have antiphospholipid antibodies, which can result in pulmonary emboli, stroke, and recurrent venous or arterial thromboses. Despite their prothrombotic tendency, these patients typically have a prolonged aPTT. Antinuclear antibodies are present in most cases, and these antibodies can help establish a diagnosis.

The history and physical examination should evaluate all major organ systems and describe all relevant medications. Patients with severe disease, infections, or exacerbations are best managed in concert with their rheumatologist or primarily responsible physician. Detailed questioning regarding cough, dyspnea, chest pain, orthopnea, neurologic symptoms, fever, disease course, and medications is paramount. A description of any prior thromboembolic events, precipitating factors, and treatment (type and duration) is important, especially to plan preoperative anticoagulant discontinuation and the need for bridging therapy. Given the prevalence of CAD and cerebrovascular disease in patients with SLE, the evaluation should include careful questioning about exercise capacity, atypical symptoms of ischemia, and the results of any previous relevant diagnostic studies (e.g., cardiac stress testing, echocardiography, CT, MRI).

The preoperative physical examination concentrates on the pulmonary (rales, decreased breath sounds), cardiac (pericardial rubs, murmurs, arrhythmias, jugular venous distention, peripheral edema), and nervous (motor deficits, sensory deficits, visual disturbances) systems. Preoperative ECG, CBC, electrolyte, glucose, BUN, creatinine levels, and aPTT (unless the patient has a known antiphospholipid syndrome) are often necessary. Significant ECG abnormalities (e.g., conduction delays, arrhythmias, Q waves, low voltage) should prompt consideration for further testing, cardiology consultation, or pulmonology consultation. Other tests that may be considered include a PT (patients receiving warfarin), echocardiogram (murmurs, suspected heart failure, suspected effusion), chest radiograph (pulmonary symptoms or suspected heart failure), and PFTs (worsening or undiagnosed dyspnea). Patients with advanced cardiomyopathy, decompensated heart failure, pulmonary hypertension, systemic vasculitis, and recent or recurrent thromboembolism are considered to be at high risk, and they are best managed in concert with the appropriate specialists. Most medications, with the exception of anticoagulants, are continued into the perioperative period (see Box 38-3).

Systemic Sclerosis

Systemic sclerosis (previously known as scleroderma) is an autoimmune disease that is characterized by excessive fibrosis and occurs more commonly in female patients.[199] Aside from skin thickening, the most common skin manifestation is Raynaud phenomenon. Scleroderma has several variants. *Localized scleroderma* involves just the skin and not any other organs. *Limited systemic sclerosis* has cutaneous manifestations "limited" to the skin of the face and upper extremities, as well as systemic involvement in the gastrointestinal tract (e.g., dysphagia, reflux) and lungs (e.g., interstitial lung disease, pulmonary hypertension). *Diffuse systemic sclerosis* has generalized skin involvement and causes multiple end-organ damage. Manifestations include myocardial fibrosis, pericarditis, heart failure, coronary artery fibrosis, severe hypertension, renal failure, dysphagia, fatigue, weight loss, gastroesophageal reflux, and right-sided heart failure. Pulmonary hypertension, which may result from interstitial lung disease or vasculopathy, is a leading cause of death in systemic sclerosis and is associated with increased perioperative risk.[198]

The preoperative evaluation focuses on the organ systems in the manner outlined before in the section on systemic lupus erythematosus, with special attention to evidence of pulmonary hypertension (see the earlier section on pulmonary hypertension). A careful history to elicit symptoms of pulmonary disease (e.g., cough, dyspnea) or cardiac disease (e.g., dyspnea, orthopnea, chest pain) is vital. Patients may develop limited mouth opening (i.e., microstomia), limited neck mobility, poor dentition, and oropharyngeal lesions secondary to skin involvement. Careful airway evaluation and planning for airway management are essential in such individuals, especially because they may also be at high risk for aspiration secondary to gastroesophageal reflux. Dermal involvement, edema, and contractures may also make venous access and regional anesthesia technically challenging. Thus, it is helpful to discuss central venous access and possible awake fiberoptic intubation during the preoperative assessment; in some cases, consideration should be given to arranging for interventional radiology to place intravenous lines.

Patients with systemic sclerosis usually need an ECG, CBC (especially if receiving immunosuppressant therapy), and determinations of BUN and creatinine levels. A chest radiograph and PFTs can be useful for evaluating patients with evidence of possible interstitial lung disease or pulmonary fibrosis. Echocardiography is useful as a screening tool in patients suspected of having pulmonary hypertension. Antihypertensive agents (including calcium channel blockers used to treat Raynaud phenomenon) and immunosuppressant therapy must be continued into the perioperative period.

Raynaud Phenomenon

Raynaud phenomenon is an exaggerated vascular response to cold or emotional stress that results in color changes of the digits (typical sequence is pallor to cyanosis to rubor).[200] It is classified as primary (termed *Raynaud disease*) or secondary (termed *Raynaud phenomenon*, and associated with connective tissue diseases, autoimmune disorders, drugs, and use of vibrating tools). The prevalence of Raynaud phenomenon is 95% or more in patients with systemic sclerosis, 20% to 30% in patients with Sjögren disease or SLE, but less than 5% in patients with rheumatoid arthritis.[201] Raynaud phenomenon most often affects the hands, typically resulting in a sudden onset of cold digits with sharply demarcated pallor or cyanosis. Cutaneous vasospasm is also common in other sites such as the face and ears, where it causes pain and numbness. Criteria for the diagnosis of Raynaud disease (primary disease) include symmetric episodic attacks, absence of PAD, absence of tissue injury or gangrene, normal nail fold capillary examination, normal erythrocyte sedimentation rate, and negative antinuclear antibody test. Raynaud disease requires no special preoperative evaluation. Secondary Raynaud phenomenon should prompt an assessment for associated disease states. It is also important to distinguish Raynaud phenomenon from PAD, especially given the difference in associated comorbidities. Calcium channel blockers are useful treatments in many patients and should be continued in the perioperative period.

Inherited Connective Tissue Disorders

Ehlers-Danlos syndrome is a disorder of collagen synthesis. It consists of several subtypes that have various manifestations but are almost all characterized by joint hypermobility. Type IV disease is more serious because affected individuals may have vascular fragility and skin fragility, as well as predisposition to vascular rupture, visceral rupture, and pneumothoraces. Patients with type VI Ehlers-Danlos syndrome have muscle weakness, scoliosis, ocular fragility, skin fragility, and osteopenia.

Marfan syndrome is characterized by tall stature, arachnodactyly (i.e., long digits), scoliosis, pectus excavatum, valvular disease (e.g., aortic insufficiency, MVP, mitral regurgitation), arrhythmias, and ascending aortic dilatation. These patients are at risk for aortic dissection. Ocular (e.g., ectopia lentis, strabismus, glaucoma) and pulmonary (e.g., spontaneous pneumothoraces) complications can also occur.[202] Other manifestations include retrognathia and high arched palates. Careful auscultation for the diastolic murmur of aortic insufficiency is important (see Table 38-6). If such a murmur is detected, subsequent tests should include an ECG, an echocardiogram, and a chest radiograph.

The most distinguishing feature of osteogenesis imperfecta is the propensity for fractures from extremely fragile bones. These patients may have blue sclerae, short stature, scoliosis, joint hypermobility, hearing loss, pulmonary complications, muscle weakness, MVP, aortic insufficiency, and platelet dysfunction. An ECG and an echocardiogram are necessary if physical examination reveals a murmur.

Epidermolysis bullosa is distinguished by blistering, skin fragility, and scarring caused by abnormal epidermal-dermal anchoring. Even measurement of BP may cause skin blistering and breakdown in an affected individual.

Kyphoscoliosis

Kyphoscoliosis is a curvature of the spine in both lateral and posterior directions. It can involve the thoracic region, the lumbar region, or both. Kyphoscoliosis may

occur alone or as a manifestation of other diseases such as collagen vascular disorders, Marfan syndrome, neurofibromatosis, muscular dystrophies, and cerebral palsy. Therefore, the preoperative evaluation should focus on identifying any coexisting abnormalities. Severe thoracic deformity may cause cardiopulmonary compromise as a consequence of restrictive lung disease, pulmonary hypertension, heart failure, tracheobronchial compression, or cardiac compression. The history should focus on assessing functional capacity and cardiopulmonary symptoms. The ability of the patient to lie supine, to permit airway access and management, must also be determined. The physical examination should include evaluation of vital signs (including oxygen saturation), pulmonary system (rales, decreased air entry), and cardiovascular system (murmurs, additional heart sounds, edema, jugular venous distention). A CBC, as well as a blood type and screen, is required in any patient scheduled to undergo spine correction surgery for kyphoscoliosis, and an ECG and a chest radiograph may be useful. If symptoms or signs of heart failure are present, a preoperative echocardiogram should be considered. Any reversible lung disease or heart failure must be optimized preoperatively.

CANCERS AND TUMORS IN PREOPERATIVE PATIENTS

Patients With Cancer

Patients with a history of cancer may have complications related to the disease or the treatment. Typically, patients are aware of the side effects of their cancer treatments. It is often helpful to ask patients whether any unexpected complications occurred during treatment or whether chemotherapy or radiation therapy had to be interrupted because of adverse effects. A hypercoagulable state is common in patients with cancer, particularly those with advanced disease, primary brain tumors, ovarian adenocarcinoma, pancreatic cancer, colon cancer, gastric cancer, lung cancer, prostate cancer, and kidney tumors. The risk of thromboembolic events is increased sixfold in patients with cancer, and active cancer accounts for 20% of new cases of thromboembolism.

The preoperative evaluation focuses on cardiac, pulmonary, neurologic, and hematologic systems. Previous head and neck irradiation may cause carotid artery disease, hypothyroidism, or difficulty with airway management. Auscultation for bruits, thyroid function tests, and carotid Doppler studies are therefore recommended. Mediastinal, chest wall, or left breast irradiation can cause pericarditis, conduction abnormalities, cardiomyopathy, valvular abnormalities, and premature CAD, even in the absence of traditional cardiovascular risk factors.[203] Thus, younger patients with a history of radiation therapy, even if they may not otherwise be at risk for heart disease, should be assessed for symptoms of cardiac disease and should undergo a preoperative ECG. Based on these initial results, stress testing and echocardiography may be indicated. Previous irradiation to the lungs, breast, or mediastinum may also cause radiation pneumonitis. In such individuals, an oxygen saturation measurement and chest radiograph may be required, with consideration for PFTs if appropriate.

Other important chemotherapy-associated side effects include cardiomyopathy with doxorubicin (Adriamycin), pulmonary toxicity with bleomycin, hemorrhagic cystitis with cyclophosphamide, and peripheral neuropathy with vincristine or cisplatin. Many chemotherapeutic agents are toxic to the kidneys, liver, and bone marrow, and patients commonly exhibit preoperative anemia. Patients who received steroids as part of their cancer treatment may be at risk for adrenal insufficiency. These individuals can be assessed with an ACTH stimulation test (see the earlier section on hypothalamic-pituitary-adrenal disorders) or given supplemental perioperative steroids (Table 38-11). Based on the type of chemotherapy, a CBC; determinations of electrolytes, BUN, and creatinine levels; LFTs; an ECG; and a chest radiograph may be needed. In some cases, consideration may be given to delaying the surgical procedure to allow resolution of neutropenia and thrombocytopenia. In general, advance planning of blood component replacement (including type and screening in the preoperative clinic) can avoid delays on the day of surgery.

TABLE 38-11 RECOMMENDATIONS FOR PERIOPERATIVE GLUCOCORTICOID COVERAGE

Surgical Stress	Target Hydrocortisone Equivalent	Preoperative Steroid Dose	Intraoperative Steroid Dose	Postoperative Steroid Dose	Postoperative Steroid Dose Day 1	Postoperative Steroid Dose Day 2
Minor (e.g., inguinal hernia repair)	25 mg/day for 1 day	Usual daily dose of steroid	None*	None*	Usual daily dose*	Usual daily dose*
Moderate (e.g., colon resection, total joint replacement, lower extremity revascularization)	50-75 mg/day for 1-2 days	Usual daily dose of steroid	50 mg hydrocortisone	20 mg hydrocortisone every 8 hr	20 mg hydrocortisone every 8 hr†	Usual daily dose
Major (e.g., esophagectomy, pancreatoduodenectomy)	100-150 mg/day for 2-3 days	Usual daily dose of steroid	50 mg hydrocortisone	50 mg hydrocortisone every 8 hr	50 mg hydrocortisone every 8 hr	50 mg hydrocortisone every 8 hr †

From Salem M, Tainsh RE, Bromberg J, et al: Perioperative glucocorticoid coverage: a reassessment 42 years after emergence of a problem, Ann Surg *219: 416-425, 1994.*

*If the postoperative course is uncomplicated, the patient can resume his or her usual steroid dose on postoperative day 1.

†If postoperative complications occur, continued glucocorticoid administration will be necessary commensurate with the level of stress.

The direct effects of cancers depend on the specific organ systems involved. Issues pertaining to intracranial tumors are discussed in the section on central nervous system tumors. Bone and liver involvement with metastases can commonly occur in patients with breast, colorectal, lung, and head and neck tumors. The resulting bony lesions can in turn cause hypercalcemia or pancytopenia. Head and neck tumors, as well as associated therapy (e.g., surgery, radiation), may cause difficulty with airway management and thyroid dysfunction. Lung cancer can cause airway problems, compromised pulmonary function, or mediastinal masses (see the next section, on mediastinal masses). In these cases, CT scans of the head, neck, or chest may be indicated. Paraneoplastic syndromes can also complicate almost any type of malignant disease, but these syndromes are most commonly seen with lung cancer. Typical manifestations of these syndromes include hypercalcemia, inappropriate antidiuretic hormone secretion, Lambert-Eaton syndrome, Cushing syndromes, and neuropathies.

Patients who are receiving opioids on a long-term basis for cancer pain are likely to require larger than usual doses of medication for postoperative pain control (see the later section on planning for postoperative pain management). On the day of surgery, these patients typically take their usual analgesic medications, with the exception of NSAIDs.

Mediastinal Masses

Tumors that may occur in the anterior mediastinal space include lymphomas, thymomas, teratomas, thyroid goiters, and metastatic disease. Anterior mediastinal masses can obstruct the great vessels (i.e., aorta, pulmonary arteries, pulmonary vein, superior vena cava), heart, trachea, and bronchi. Patients may complain of dyspnea, dysphagia, stridor, wheezing, coughing (especially when recumbent), and orthopnea. Superior vena cava syndrome is the consequence of the compression of the superior vena cava, and it results in jugular venous distention and edema in the face, neck, chest, and upper extremity. Evidence of increased intracranial pressure and airway compromise may also be present. Imaging of the chest (CT or MRI) and echocardiography are needed if airway, cardiac, or vascular compression is suspected. Flow-volume loops may also be useful to assess the location (extrathoracic versus intrathoracic) and degree of airway obstruction. Patients with tracheobronchial, cardiac, or major vessel compression require special anesthetic precautions, including possible awake fiberoptic intubation.

Von Hippel–Lindau disease

von Hippel–Lindau disease is an inherited, autosomal dominant syndrome characterized by a variety of benign and malignant tumors. Associated tumors include hemangioblastomas, retinal angiomas, clear cell renal cell carcinomas, pheochromocytomas, and neuroendocrine tumors of the pancreas. Preoperative evaluation of these patients includes an evaluation of renal function and assessment of symptoms compatible with pheochromocytomas or neuroendocrine tumors. Findings from a thorough patient history and physical examination (with vital signs) should guide any further testing (e.g., electrolytes, ECG, BUN, creatinine, glucose).

Carcinoid Tumors

Carcinoid tumors are rare neuroendocrine tumors that release mediators. They are associated with MEN 1. These tumors typically occur in the gastrointestinal tract and are the most common neoplasms of the appendix; in addition, carcinoid tumors can also occur in the pancreas and bronchi. Carcinoid syndrome is caused by vasoactive amines (e.g., serotonin, norepinephrine, histamine, dopamine), polypeptides (e.g., bradykinin, somatostatin, vasoactive intestinal peptide, glucagon), and prostaglandins released by the tumors. Typical manifestations include flushing, tachycardia, arrhythmias, diarrhea, malnutrition, bronchospasm, and carcinoid heart disease. Nonetheless, most patients are asymptomatic because the liver inactivates the bioactive products of carcinoid tumors. Thus, patients with gastrointestinal carcinoid tumors have manifestations of carcinoid syndrome only if they have hepatic metastases. Carcinoid heart disease is characterized by endocardial fibrosis of pulmonic and tricuspid valves. Affected individuals may then develop tricuspid regurgitation, pulmonic stenosis, pulmonic regurgitation, right-sided heart failure, peripheral edema, and hepatomegaly. Some individuals may also develop *carcinoid crisis*, which is associated with profound flushing, bronchospasm, tachycardia, and hemodynamic instability. These life-threatening episodes can occur with induction of anesthesia, intraoperative handling of a tumor, or other invasive procedure on a tumor (e.g., tumor embolization).[204]

The initial evaluation should focus on possible dyspnea, orthopnea, wheezing, edema, arrhythmias, and murmurs; subsequent diagnostic tests are guided by the initial assessment. Patients with chronic diarrhea need measurement of orthostatic vital signs, electrolytes, BUN, and creatinine. Patients with cardiac involvement must have an ECG, electrolyte determinations, and an echocardiogram. Malnourished patients need measurement of orthostatic vital signs, an ECG, and electrolyte and albumin levels. Predictors of perioperative adverse events in these patients are elevated urinary 5-hydroxyindoleacetic acid levels and the presence of carcinoid heart disease. [205] Histamine receptor blockers (both H_1 and H_2), ketanserin (serotonin receptor antagonist), and octreotide are useful in blocking mediator release or their associated effects. Preoperative treatment with an intravenous infusion of octreotide, starting 12 hours preoperatively, may help mitigate the risks of intraoperative carcinoid crises.[204,206]

SPECIAL ISSUES IN PREOPERATIVE EVALUATION

PSEUDOCHOLINESTERASE DEFICIENCY

A personal or family history of pseudocholinesterase, or butyrylcholinesterase, deficiency should be identified preoperatively (see Chapter 34). Pseudocholinesterase, which is found in the plasma, liver, pancreas, heart, and brain, is distinct from acetylcholinesterase, which is

found in erythrocytes. Patients reporting an "allergy to succinylcholine" should be suspected of having either this disorder or MH. Inquiring whether the patient was intubated postoperatively, gravely ill, or in need of intensive care may help differentiate these disorders. Previous anesthetic records may also help clarify an uncertain history.

Pseudocholinesterase activity may be reduced permanently because of abnormal genotypes or transiently altered because of disease, drugs, pregnancy, or infancy. In patients with a history suggestive of pseudocholinesterase deficiency, plasma cholinesterase activity, as well as the dibucaine number and fluoride number, should be measured. Plasma cholinesterase activity is a *quantitative* measure of enzyme activity, whereas the dibucaine number and fluoride number are *qualitative* measures. Plasma cholinesterase activity should not be confused with acetylcholinesterase activity, which is an assessment of erythrocyte cholinesterase. The *dibucaine number* represents the percentage inhibition of the enzyme by the local anesthetic dibucaine, and the fluoride number represents the percentage inhibition by fluoride. Normal individuals, who are homozygous for the wild-type gene have a dibucaine number of 80 because their plasma cholinesterase is 80% inhibited by dibucaine. Individuals who are homozygous for the atypical genes have a dibucaine number of 20 (corresponding to 20% inhibition) and can be paralyzed for up to 4 to 8 hours after receiving succinylcholine. In heterozygous individuals who have a dibucaine number of 60 (corresponding to 60% inhibition), the duration of action of succinylcholine is prolonged by 50% to 100%. The combination of dibucaine number and plasma cholinesterase activity can therefore help differentiate genetic from acquired causes of prolonged apnea after succinylcholine administration. Patients with known or suspected pseudocholinesterase deficiency should be urged to obtain proper medical alert identification and be educated that this enzyme also metabolizes ester-linked local anesthetics.

MALIGNANT HYPERTHERMIA

A history of MH or a suggestion of it (e.g., hyperthermia or rigidity during anesthesia) in a patient or family member must be clearly documented in the preoperative assessment, as well as communicated to the surgeon and eventual anesthesia provider. This is critical to ensure that special arrangements are made preoperatively (see Chapter 43). Individuals who are genetically predisposed to MH are asymptomatic until they are exposed to triggering agents. Certain neuromuscular diseases are also associated with a risk for MH, including specific muscular dystrophies (i.e., Duchenne, Becker, myotonic), King-Denborough syndrome, central core disease, periodic paralysis, osteogenesis imperfecta, myelomeningocele, and strabismus.

MORBIDLY OBESE PATIENTS

The morbidly obese patient presents a special set of preoperative risks (see Chapter 71). Obesity is associated with several important comorbidities, including diabetes, hypertension, cardiovascular disease, cerebrovascular disease, cancer, OSA (see the earlier section on obstructive sleep apnea), and poor functional capacity. Obese individuals are also at risk for nonalcoholic steatohepatitis (or "fatty liver"), which can result in abnormal LFTs; liver fibrosis; and, in some cases, end-stage liver disease. In addition, patients with extreme obesity are at risk for right-sided heart failure and pulmonary hypertension. Such individuals can have obesity-hypoventilation syndrome (OHS), also known as pickwickian syndrome. Obesity-hypoventilation syndrome is characterized by impaired central ventilatory drive and is distinct from OSA. It is associated with awake, chronic hypoxemia (PaO_2 <65 mm Hg) without a diagnosis of COPD or primary lung disease. In the perioperative setting, obese patients experience higher rates of difficult bag-mask ventilation and difficult tracheal intubation.

The preoperative evaluation focuses on relevant coexisting diseases, airway, cardiopulmonary system, and vital signs (including pulse oximetry). When measuring BP, the BP cuff should have a width that is approximately two thirds of the arm and a length that can adequately encircle the extremity. Assessment of neck circumference can also identify individuals at risk for difficulty with endotracheal intubation. Treatments for obesity can have important perioperative implications. For example, drugs or methods of weight reduction (e.g., purging, diuretics, laxatives, gastric bypass procedures) may result in electrolyte abnormalities, vitamin deficiencies, malnutrition, anemia, and cardiopulmonary disorders. Two previously available antiobesity medications, fenfluramine and dexfenfluramine (both were withdrawn from the market in 1997), had significant cardiac side effects, including regurgitant valvular lesions and pulmonary hypertension. Any individual who was ever exposed to these drugs should undergo a cardiovascular evaluation, including an ECG and an echocardiogram.

PATIENTS WITH TRANSPLANTED ORGANS

The number of patients with transplanted organs who require nontransplant surgical procedures increases yearly. During preoperative evaluation, these patients present special issues relating to transplant function, allograft denervation, immunosuppression, and other posttransplant physiologic and pharmacologic issues (see Chapter 74). Close interaction with the transplant team is one of the most important steps in the perioperative care of these patients. Clinicians performing the preoperative assessment should ensure that the transplant care providers are made aware of the upcoming procedure and are given an opportunity to make recommendations.

Some general preoperative considerations apply to all transplant recipients, as well as additional concerns based on the specific organ transplanted.[207] In all transplant recipients, the level of function of the transplanted organ and the presence of any rejection should be evaluated. The dosage regimen of all immunosuppressant medications should be noted, and patients should be instructed to continue taking all these medications through the perioperative period. However, these drugs can modify the pharmacology of many other agents administered during the

perioperative period, as has been extensively summarized in the literature.[208,209] Patients should also be assessed for complications related to immunosuppressant therapy. These complications include the following: hyperglycemia and adrenal suppression (steroids); increased risks of infection, hypertension, and renal insufficiency (steroids, cyclosporine, tacrolimus); and myelosuppression causing anemia, thrombocytopenia, and leukopenia (azathioprine, sirolimus). Although transplant recipients are at increased risk for postoperative infectious complications, no evidence indicates that higher doses of antibiotic prophylaxis provide added benefit. Instead, usual preoperative recommendations for antibiotic prophylaxis should be followed. Despite the controversy regarding the need for "stress-dose" supplementation in patients taking low-dose corticosteroids, it is still used frequently because of the low risks involved.

Careful cardiac evaluation is important in all transplant recipients because of their increased risk for cardiovascular disease. The bases for this increased risk include the impact of underlying diseases that led to the initial organ failure (e.g., diabetes, hypertension) and the potential for drug regimens, transplantation, and rejection episodes to create or worsen traditional cardiovascular risk factors. Preoperative renal function should also be assessed because long-term immunosuppressive regimens often lead to chronic renal insufficiency. Although the effects of transplantation and immunosuppressive regimens on intravascular coagulation are controversial, appropriate thromboprophylaxis should be considered in all transplant recipients.

Kidney transplant recipients present some specific issues for preoperative evaluation. Despite the presence of a normal creatinine concentration, the average GFR in these individuals is generally decreased. This impairment in renal function predisposes these patients to electrolyte abnormalities and altered drug metabolism.[208,209] Nephrotoxic drugs, including NSAIDs and COX-2 inhibitors, should be avoided in all renal transplant recipients. In addition, their risk for cardiovascular disease is increased to approximately twice that of the general population. Careful preoperative cardiac evaluation is essential.

Successful liver transplantation usually results in resolution of the hepatic and cardiovascular effects of end-stage liver disease. Nonetheless, some pretransplant disturbances present in these patients may not resolve after transplantation, thus necessitating careful evaluation of pulmonary function. These disturbances can include hepatopulmonary syndrome, which involves hypoxemia from intrapulmonary vascular shunting. Other patients may demonstrate ventilation-perfusion mismatch secondary to pulmonary effusions, ascites, or diaphragmatic dysfunction, as well as diffusion abnormalities resulting from interstitial pneumonitis or impaired hypoxic pulmonary vasoconstriction.

Following successful lung transplantation, recipients may require months to achieve peak pulmonary function. Compared with all other allografts, the transplanted lung is especially susceptible to infection and rejection as a result of its unique exposure to the external environment. Careful preoperative evaluation with PFTs should be considered in all lung transplant recipients, with postponement of elective surgical procedures when allograft rejection or infection is suspected. Other perioperative considerations include airway hyperresponsiveness, the loss of the cough reflex, and the potential for injury to the airway anastomosis with intubation. These patients are also at increased risk for pulmonary edema, which has been attributed to disruption of the lymphatic drainage in the transplanted lung.

Most issues relating to heart transplant recipients relate to the absence of autonomic innervation in the transplanted heart. This denervation has multiple physiologic effects, such as a higher than normal resting HR (from absence of vagal tone); the absence of cardiac baroreflexes; and the lack of response to carotid sinus massage, Valsalva maneuver, laryngoscopy, or tracheal intubation. Denervation also affects responses to medications; the allograft demonstrates a normal or augmented response to direct-acting drugs (e.g., epinephrine), a blunted response to indirect-acting agents (e.g., ephedrine), and no response to vagolytic agents. Chronic allograft rejection can manifest as accelerated coronary heart disease and as both systolic and diastolic dysfunction. Because allograft denervation causes any myocardial ischemia to be silent, typical manifestations of chronic rejection include fatigue, ventricular dysrhythmias, congestive heart failure, and silent MI on the ECG. Should preoperative evaluation raise clinical suspicions of worsening rejection, the patient's recent cardiac testing must be reviewed. Heart transplant recipients undergo routine periodic evaluation for CAD (stress testing or coronary angiography) and cardiac function (echocardiogram or radionuclide angiography). With respect to other preoperative cardiac investigations in these patients, the preoperative ECGs often reveal conduction abnormalities and may show two P waves (a nonconducted P wave from the native atria and a conducted P wave from the donor atria). Many heart transplant recipients also require permanent pacemakers, and pacemaker function should be confirmed during the preoperative assessment.

PATIENTS WITH ALLERGIES

The patient's preoperative record should include careful documentation of any history of allergies and adverse drug reactions. True anaphylactic reactions should be distinguished from adverse side effects (e.g., nausea with opioid use), especially because a patient's definition of an allergy may differ significantly from the true clinical definition. In some cases, patients may incorrectly attribute previous perioperative difficulties to "allergies" to anesthetic or analgesic medications. The true incidence of anaphylactic and anaphylactoid reactions during anesthesia is probably underestimated because reactions are generally underreported. The reported incidence ranges from 1 in 10,000 to 1 in 20,000 procedures, with an increased incidence of 1 in 5200 to 1 in 6500 in cases involving administration of neuromuscular blocking agents[210] (see also Chapter 34). The most common precipitating drugs are neuromuscular blocking agents (50% to 70% of cases), followed by latex and antibiotics.[210] Anaphylaxis also accounts for up to 3% of perioperative deaths that are totally or partially related to anesthesia.[211] Nonetheless,

a careful history generally allows for avoidance of precipitating agents; thus, premedication with histamine blockers and steroids is not generally recommended. In selected cases in which the clear diagnosis of a specific allergy is required to guide perioperative management, skin testing may also be considered.

Latex is the second most common precipitant of anaphylaxis during anesthesia. Although the rate of latex sensitization continues to increase, the development of better ways to identify at-risk patients has led to a decreased incidence of latex-induced anaphylaxis.[212] The diagnosis of a latex allergy during preoperative evaluation is based on a careful history. Individuals at particular risk for latex allergy include those with a history of multiple surgical procedures, health care workers, and those with atopic histories. In Europe, this history may be supplemented using commercially available skin tests (not currently approved in the United States).[210] When latex allergy is identified during the preoperative evaluation, the operative team should be notified in advance to ensure that all appropriate equipment is available. The ASA Task Force outlines detailed intraoperative considerations for these patients.[213]

Among antibiotics, penicillins and cephalosporins are the most common causes of anaphylaxis. A small risk of cross-reactivity exists between penicillins and cephalosporins, but most of these reported reactions involve rashes, not anaphylaxis. Reported allergies to vancomycin should be distinguished from "red man syndrome." This histamine-induced side effect, which is associated with rapid injection of vancomycin, consists of flushing, pruritus, erythematous rash, and hypotension.

With respect to other medications commonly encountered in the perioperative setting, anaphylactic reactions to amide local anesthetics are extremely rare. Most true anaphylactic reactions following exposure to ester local anesthetics do not involve an allergy to the local anesthetic, but rather to associated preservatives (e.g., *para*-aminobenzoic acid). Patients may incorrectly interpret adverse side effects from epinephrine in local anesthetic solutions as allergies, especially with dental procedures. Such reports should be carefully distinguished from true allergies. Similarly, true allergies to opioids are rare, with most reports of such "allergies" being simply opioid-related side effects, such as nausea and vomiting. No reports of anaphylactic reactions to volatile anesthetics have been published. Most reactions to commonly used antiseptic solutions such as bacitracin or povidone-iodine involve contact dermatitis; in contrast, true anaphylactic reactions have only rarely been reported.[214]

The scientific status of multiple chemical sensitivity disorder, or idiopathic environmental intolerance syndrome, is controversial. These individuals report chronic, diffuse, nonspecific symptoms with low levels of multiple chemical substances. Symptoms involve multiple organ systems and include fatigue, headache, memory loss, palpitations, and gastrointestinal symptoms. The symptoms are not generally accompanied by biologic test abnormalities or changes on physical examination, but they are frequently associated with psychiatric symptoms, notably depression and anxiety.[215] This disorder is also often associated with fibromyalgia. Preoperative evaluation of these patients can be extremely challenging because they have significant concerns about the multiple exposures involved during the perioperative period and the potential impact on their symptoms. No current recommendations are available on the perioperative care of these patients.

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Acute infection with HIV causes a mononucleosis-like illness, which then progresses to chronic lymphadenopathy (lasting 3 to 5 years). Infection can culminate in cell-mediated immune deficiency characterized by opportunistic infections, malignant diseases (e.g., Kaposi sarcoma, non-Hodgkin lymphoma), and death (usually secondary from infections, wasting, or cancer). Although the prognosis of untreated HIV infection is very poor,[216] outcomes have improved substantially in individuals compliant with highly active antiretroviral therapy (HAART).[217] Risk factors for HIV infection include sexual contact with an infected individual, bloodborne contamination, men who have sex with men, sexual workers, and those having contact with sexual workers. Most infection transmitted by blood exposure occurs in intravenous drug users, whereas infection through blood product transfusion in the United States is very rare (1 per 1.5 to 2 million blood transfusions). Mothers can transmit the disease to infants, which occurs usually during breastfeeding or delivery.[218] Many patients infected with HIV are unaware of their status.

HIV infection can affect all organs and cause multiple complications.[219] Cardiac complications include myocarditis, dilated cardiomyopathy, valvular disease, pulmonary hypertension, pericardial effusions, and tamponade. Pulmonary effects include lymphoid interstitial pneumonitis, as well as drug-resistant infections with *Pneumocystis jiroveci*, *Mycobacterium avium* or *Mycobacterium tuberculosis*, cytomegalovirus, and *Cryptococcus*. Nervous system manifestations include central nervous system tumors, infections, aseptic meningitis, and acquired immunodeficiency syndrome (AIDS)–related dementia. Malignant diseases can occur, such as lymphomas, Kaposi sarcoma, and cervical cancer. These tumors can also have direct consequences for anesthetic management. For example, supraglottic or intraoral Kaposi sarcoma may interfere with ventilation and intubation, whereas non-Hodgkin lymphoma can cause mediastinal masses. Gastrointestinal manifestations include dysphagia, diarrhea, and esophagitis, which can in turn cause malnutrition, dehydration, and electrolyte imbalance. Renal complications include acute tubular necrosis, glomerulonephritis, renovascular disease, and HIV-associated nephropathy with nephritic syndrome. Antiretroviral medications used to treat HIV infection also have important side effects. The major classes of antiretroviral medications include nucleoside reverse transcriptase inhibitors (e.g., lamivudine, zidovudine, tenofovir, abacavir), nonnucleoside reverse transcriptase inhibitors (e.g., nevirapine, efavirenz, rilpivirine), protease inhibitors (e.g., atazanavir, darunavir, lopinavir, fosamprenavir, saquinavir), attachment inhibitors (e.g., maraviroc), and integrase strand transfer inhibitors

(e.g., raltegravir).[220] Side effects of relevance to anesthesiologists include lactic acidosis (nucleoside reverse transcriptase inhibitors), hepatotoxicity (nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors), hyperlipidemia (protease inhibitors), insulin resistance (protease inhibitors), and bone marrow suppression (all classes). [221] Protease inhibitors are also associated with premature CAD[222] and cardiac conduction abnormalities (especially PR interval prolongation). Patients' antiretroviral therapy must be continued through the perioperative period.

If the preoperative evaluation of a relatively young, otherwise healthy individual elicits a history of thrush, fever of unknown origin, chronic diarrhea, lymphadenopathy, or herpes zoster in more than one dermatome, these findings should raise concern of undiagnosed HIV infection. In these cases, the enzyme-linked immunosorbent assay (ELISA) is the primary initial screening test. It demonstrates very high sensitivity exceeding 99% but yields a high number of false-positive results. The Western blot technique is used as the confirmatory test following an initial positive ELISA result. Patients with known HIV infection frequently require further evaluation, including an ECG, a chest radiograph, and blood sampling for CBC, determination of electrolytes, creatinine, and LFTs. If the patient shows evidence of malnourishment or nephrotic syndrome, further blood tests for albumin, total protein, and magnesium levels may be beneficial. The patient's perioperative prognosis may be estimated based on the CD4 lymphocyte count and viral load, which reflect the patients' immunologic status during the previous 3 months. In general, rates of postoperative complications and mortality are higher among patients with CD4 counts lower than 200 cells/mm^3 and viral loads greater than 10,000 copies/mL.[223,224]

PATIENTS WITH A HISTORY OF SUBSTANCE ABUSE

A patient with a history of current or previous alcohol or drug addiction presents special challenges for the perioperative team (see Chapter 110). The lifetime prevalence of these addictions is significant, at 14% for alcohol addiction and 7% for drug addiction in the United States population.[225] Nonetheless, very limited data from clinical trials are available to help guide the perioperative management of these individuals.

The preoperative evaluation is an opportunity to obtain a detailed history of addiction and recovery. In a suggested classification system, abused drugs can be categorized as central nervous system depressants (e.g., heroin, alcohol, sedatives, hypnotics), stimulants (e.g., cocaine, amphetamines), and other psychotropic substances (e.g., cannabis).[226] Many addicts are polysubstance abusers. Addictive disease should be considered *permanent* even in patients who have had long periods of abstinence. Some patients in the process of recovery from addiction may be receiving specific medications to maintain recovery. For example, previous opioid abusers may be receiving methadone, clonidine, or buprenorphine (a partial μ-agonist). The dosage of any such medications should be documented and verified. Patients in recovery may also have heighted anxiety regarding upcoming surgical procedures because of concerns about relapse into addiction and inadequate pain treatment, given their history of addiction. Such concerns may be appropriate. Patients receiving opioid substitution therapy do experience normal pain responses to nociceptive stimuli but require additional analgesia for control of postprocedural pain.[227] These patients should therefore be reassured that anxiety and pain will be adequately treated. The clinicians performing preoperative evaluation may have prejudicial attitudes and lack the educational background to formulate appropriate perioperative pain management plans. For example, pain medication may be underdosed and inappropriately restricted because of concerns about provoking relapses. Early involvement of the acute pain service and addiction specialists to assist in the management of these at-risk patients may be helpful.

The preoperative period should be used to develop appropriate management plans based on the types of abused drugs. All pertinent preoperative information and management plans should be transmitted to members of the perioperative team. Individuals addicted to alcohol, sedatives, or hypnotics may require stabilization with benzodiazepines, whereas heroin addicts may require substitution with methadone. It is important to document the dosage of opioids consumed by individuals abusing these drugs, especially to help guide postoperative pain management. To avoid inadequate analgesia (which could potentially activate addiction) in these patients, the preoperative evaluation should be used to discuss and plan the optimal use of nonopioid analgesics and regional techniques. Patients actively abusing cocaine and amphetamines are at especially high risk during anesthesia because of the potential for intraoperative hemodynamic instability. Urine testing, especially on the day of surgery, may be appropriate to ensure the absence of abused substances in such patients.

Addicts are at risk for myriad perioperative complications, including withdrawal, acute intoxication, infections, end-organ damage, and altered tolerance of anesthetic or opioid medications.[228] A history of intravenous drug use should prompt an evaluation for cardiovascular, pulmonary, neurologic, and infectious complications such as endocarditis, abscesses, osteomyelitis, hepatitis, and HIV infection. Opioid (including heroin) users have a tolerance to narcotics. Patients with alcoholism are at risk for delirium tremens, a potentially life-threatening form of withdrawal characterized by autonomic instability and hyperpyrexia. These patients may also have liver disease (alcoholic hepatitis, cirrhosis, portal hypertension, end-stage liver disease), alcohol-induced cardiomyopathy, arrhythmias, seizures, neuropathies, dementia, Wernicke-Korsakoff syndrome (ataxia and cognitive dysfunction secondary to thiamine deficiency), macrocytic anemia, and coagulopathies (from hepatic dysfunction or vitamin K deficiency). Cocaine and amphetamine addicts can develop cerebrovascular accidents, cardiomyopathy, and arrhythmias. Additionally, cocaine and amphetamine inhibit the uptake of sympathomimetic neurotransmitters, thereby increasing risks for hypertension, tachycardia, paranoia, anxiety, seizures, and myocardial ischemia. Long-term use can result in ventricular hypertrophy, MI,

and nasal septal perforation. Solvents can cause cardiac dysrhythmias, pulmonary edema, cerebral edema, diffuse cortical atrophy, and hepatic failure. Hallucinogens, such as lysergic acid diethylamide (LSD), can cause autonomic dysregulation and paranoia. Ecstasy, or more specifically 3,4-methylenedioxymethamphetamine (MDMA), can cause excessive thirst that results in hyponatremia, pulmonary edema, or cerebral edema. Marijuana can cause tachycardia, vasodilatation, and increased cardiac output. The risk of pulmonary complications in patients who smoke marijuana is similar to that of individuals who smoke tobacco.[229]

During the preoperative evaluation interview, patients who abuse alcohol or drugs may not give a reliable history. The subsequent physical examination must include careful measurement of vital signs, including temperature. For example, cocaine and amphetamines may cause hypertension and tachycardia, whereas acute opioid use may result in a slow respiratory rate. Acute opioid use may also manifest as lethargy and pinpoint pupils, and recent alcohol consumption can often be detected by smell. Especially in individuals suspected of being intravenous drug abusers, examination of venous access sites for signs of abscesses and skin and soft tissue infections is important. In addition, careful auscultation for murmurs is essential because of the risk of bacterial endocarditis in these patients. Cocaine or alcohol abusers can also exhibit important findings in their cardiovascular examination, such as symptoms and signs of heart failure or arrhythmias. Long-term alcohol abuse may manifest with physical findings of chronic liver disease. In addition to identifying the presence of substance abuse and its related complications, clinicians should ascertain whether, and for how long, patients can stop consuming alcohol or addictive drugs. If patients do stop consumption occasionally, it is especially important to determine what complications, if any, occur. When an alcoholic patient reports previously interrupting drinking for several days, the interviewer should inquire whether agitation, seizures, delirium tremens, or other signs of withdrawal developed. Preoperative testing largely depends on symptoms and findings from the history and physical examination, as well as the specific drug that is being abused. For example, an ECG may be warranted to assess for previous MI in an individual with a history of cocaine abuse or in an individual receiving methadone (which prolongs the QT interval) to treat opioid addiction.

Ideally, patients with drug or alcohol dependence should be drug free well before elective surgical procedures. A randomized trial of a preoperative alcohol cessation program demonstrated significant reductions in postoperative complications,[230] although these benefits were not replicated in a subsequent similar trial.[231] Preanesthesia clinic staff should be prepared to refer patients to addiction specialists or to prescribe medications to prevent withdrawal in the preoperative period if patients agree to abstinence. For example, benzodiazepines can be useful in preventing or treating alcohol withdrawal symptoms.

Some medications used to manage withdrawal or facilitate recovery have specific perioperative considerations.[225] Patients taking selective serotonin reuptake inhibitors (SSRIs) or methadone should continue maintenance doses in the perioperative period. Patients who are taking disulfiram because of a history of alcohol abuse may have an altered response to sympathomimetic drugs; some authors therefore suggest that disulfiram be discontinued 10 days before the surgical procedure.[225] If disulfiram is continued, users can experience flushing, nausea, and tachycardia in response to small amounts of alcohol, such as amounts encountered in skin preparations or medications. For patients taking naltrexone for a history of alcohol abuse, consideration should be given to discontinuing it 3 days preoperatively.[225] Naltrexone alters responses to opioid analgesics and may make postoperative pain management very challenging. Buprenorphine-containing medications (i.e., Suboxone, Subutex), which are used to treat opioid addiction, should also be discontinued 3 days before surgical procedures because they too alter responses to opioid analgesics. If medications needed to manage recovery from addiction are discontinued preoperatively, patients may require substitution with alternative medications that can be continued perioperatively (e.g., SSRIs).

BREASTFEEDING PATIENTS

Research data to help guide recommendations for the safety of anesthetics and medications in the babies of breastfeeding mothers who receive these agents are limited. For elective surgical cases, women should be advised to pump and store milk preoperatively; this milk can be used in the first 24 hours after administration of an anesthetic or for the duration of breast milk exposure to potentially harmful agents. The mother should discard milk produced within the first 24 hours after anesthesia and should generally resume breastfeeding after this period. Very young or premature babies, especially those at risk for apnea, may have complications if the mother continues to take opioid or sedating drugs. Mothers should be advised to first discuss the safety of breastfeeding while taking medications with their child's pediatrician.

PATIENTS WITH DO NOT RESUSCITATE ORDERS

Some patients scheduled for procedures have advance directives or a do not resuscitate (DNR) status (see Chapter 108). The ASA adopted guidelines for the care of these patients and updated them in 2013 (Box 38-16).[232] Frequently, in circumstances with DNR orders, care providers are focused on a procedure-directed approach (i.e., do not intubate, do not administer resuscitative drugs). This approach is problematic in the perioperative period because much of anesthesia care involves such procedures. Within the context of anesthesia care, some authors have proposed that a better approach is to discuss DNR status in a goal-directed approach (i.e., from the perspective of the patient's values and objectives, such as quality-of-life concerns).[233] The ideal time to have this emotional and complex discussion is during the preoperative evaluation. Short discussions in the preoperative clinic have been shown to foster dialogue among patients, their proxies, and physicians regarding advance directives concerning

BOX 38-16 ***Do Not Resuscitate Orders in the Perioperative Period***

Policies automatically suspending DNR orders or other directives that limit treatment before procedures involving anesthetic care may not sufficiently address a patient's rights to self-determination in a responsible and ethical manner. Such policies, if they exist, should be reviewed and revised, as necessary, to reflect the content of these guidelines.

- **Full attempt at resuscitation:** The patient or designated surrogate may request the full suspension of existing directives during the anesthetic and immediate postoperative period, thereby consenting to the use of any resuscitation procedures that may be appropriate to treat clinical events that occur during this time.
- **Limited attempt at resuscitation defined with regard to specific procedures:** The patient or designated surrogate may elect to continue to refuse certain specific resuscitation procedures (e.g. chest compressions, defibrillation, or tracheal intubation). The anesthesiologist should inform the patient or designated surrogate about (1) which procedures are essential to the success of the anesthesia and the proposed procedure and (2) which procedures are not essential and may be refused.
- **Limited attempt at resuscitation defined with regard to the patient's goals and values:** The patient or designated surrogate may allow the anesthesiologist and surgical team to use clinical judgment in determining which resuscitation procedures are appropriate in the context of the situation and the patient's stated goals and values. For example, some patients may want full resuscitation procedures to be used to manage adverse clinical events that are believed to be quickly and easily reversible but to refrain from treatment for conditions that are likely to result in permanent sequelae, such as neurologic impairment or unwanted dependence on life-sustaining technology.

Modified from Committee on Ethics, American Society of Anesthesiologists: Ethical guidelines for the anesthesia care of patients with do-not-resuscitate orders or other directives that limit treatment, 2013. Available at http:// http://www.asahq.org/For-Members/Standards-Guidelines-and-Statements.aspx

DNR, Do not resuscitate.

end-of-life care, as demonstrated by a randomized trial of 397 patients at a preoperative evaluation clinic.[234] Individuals who received the information session were significantly more likely to complete a durable power-of-attorney (27% versus 10%) and discuss end-of-life care with their proxy decision makers (87% versus 66%).

PREOPERATIVE LABORATORY AND DIAGNOSTIC STUDIES

The value of preoperative diagnostic testing has become a central issue in delivering cost-effective health care to surgical patients. The role of preoperative testing to screen for disease and to evaluate the patient's fitness for surgery has been extensively studied. Research in this field has largely concluded that a practice of routine preoperative testing in all surgical patients, without consideration for their age or medical condition, cannot be justified. Unnecessary testing is inefficient and expensive, and it entails additional technical resources. In addition, it may lead to costly evaluation of borderline or false-positive test abnormalities. Aside from potentially causing operating room delays or cancellations, these unnecessary follow-up tests may pose risks to patients that are attributable to both the tests and any associated interventions. Therefore, the targeting of testing in appropriate patients has both clinical and economic benefits.

At many hospitals where surgeons and primary care physicians order all preoperative tests, the common practice has been to order tests without any diagnostic focus, other than speculation that the anesthesiologist may "require them" for surgery to proceed without delay or cancellation. Other justifications offered for this nonselective ordering of tests include routine screening for disease states, establishment of a diagnostic baseline, personal habit (e.g., "standard" testing checklist for all patients), physician reassurance, and a perceived medicolegal necessity "not to miss anything." Routine preoperative testing in asymptomatic healthy patients has very poor diagnostic yield, provides little to no additional prognostic information, and has not shown any beneficial effect on outcomes.[235-238] This practice can therefore no longer be justified. Indeed, Medicare and most private insurance carriers no longer reimburse routine preoperative screening tests without specific indications.

The ordering of preoperative diagnostic tests should be based on a patient's medical history, the proposed surgical procedure, and the potential for intraoperative blood loss. Testing should be targeted to detecting specific clinical indications that may increase perioperative risk. Randomized trials have demonstrated that such a shift in strategy from nonselective to selective preoperative testing in low-risk surgical procedures can reduce costs while preserving patients' safety.[239,240] As experts in perioperative medicine, anesthesiologists are in a unique position to appropriately select the preoperative laboratory tests needed to guide perioperative care. Indeed, anesthesiologist-led preoperative evaluation has been shown to result in more selective ordering of laboratory tests than evaluation led by surgeons or primary care physicians.[9-12] Thus, by educating and providing specific guidance to surgeons and other physician specialists on the appropriate ordering of preoperative tests, anesthesiologists can expedite patient care, reduce health care costs, and enhance the standing of the specialty in perioperative medicine.

A proposed framework for ordering preoperative diagnostic tests based on a patient's medical history is presented in Table 38-12. These disease-specific recommendations are not intended as absolute or standard. Indeed, many individual hospitals, as well as certain regional jurisdictions (e.g., Ontario Pre-Operative Testing Grid),[241] have developed their own specific recommendations for preoperative laboratory testing. In addition, the National Institute for Health and Care Excellence (NICE) has developed explicit guidelines for preoperative testing in the United Kingdom, following an extensive systematic review of the literature.[237,238] Although the most recent ASA "Practice Advisory for Preanesthesia Evaluation" did recommend against routine preoperative testing,[242] it did not make explicit recommendations about which tests should be ordered for specific clinical conditions. The practice advisory stated that the indications for

TABLE 38-12 **FRAMEWORK FOR PREOPERATIVE DIAGNOSTIC TESTING BASED ON PATIENTS' MEDICAL HISTORY**

Preoperative Diagnosis	ECG	Chest Radiograph	Hct/ Hb	CBC	Electrolytes	Creatinine	Glucose	Coagulation	LFTs	Drug Levels	Ca
Cardiac disease											
History of MI	X			X	±						
Chronic stable angina	X			X	±						
CHF	X	±									
HTN	X	±			X*	X					
Chronic atrial fibrillation	X									X†	
PAD	X										
Valvular heart disease	X	±									
Pulmonary disease											
COPD	X	±		X						X‡	
Asthma	(PFTs only if symptomatic; otherwise no tests required)										
Diabetes	X				±	X	X				
Liver disease											
Infectious hepatitis								X	X		
Alcohol or drug induced hepatitis								X	X		
Tumor infiltration								X	X		
Renal disease			X		X	X					
Hematologic disorders				X							
Coagulopathies				X				X			
CNS disorders											
Stroke	X			X	X		X			X	
Seizures	X			X	X		X			X	
Tumor	X			X							
Vascular disorders or aneurysms	X		X								
Malignant disease				X							
Hyperthyroidism	X		X		X						X
Hypothyroidism	X		X		X						
Cushing disease				X	X		X				
Addison disease				X	X		X				
Hyperparathyroidism	X		X		X						X
Hypoparathyroidism	X				X						X
Morbid obesity	X	±					X				
Malabsorption or poor nutrition	X			X	X	X	X				
Select drug therapies											
Digoxin (digitalis)	X				±					X	
Anticoagulants			X					X			
Phenytoin (Dilantin)										X	
Phenobarbital										X	
Diuretics					X	X					
Corticosteroids				X			X				
Chemotherapy				X		±					
Aspirin or NSAIDs											
Theophylline										X	

±, *Ca,* Calcium; *CBC,* complete blood count; *CHF,* congestive heart failure; *CNS,* central nervous system; *COPD,* chronic obstructive pulmonary disease; *ECG,* electrocardiogram; *Hb,* hemoglobin; *Hct,* hematocrit; *HTN,* hypertension; *LFTs,* liver function tests; *MI,* myocardial infarction; *NSAID,* nonsteroidal antiinflammatory drug; *PAD,* peripheral arterial disease; *PFT,* pulmonary function test; *X,* obtain.

*If the patient is taking diuretics.

†If the patient is taking digoxin.

‡If the patient is taking theophylline.

testing should be "based on information obtained from medical records, patient interview, physical examination, and type and invasiveness of the planned procedure." In addition, it described patient-related and surgery-related factors that anesthesiologists should consider when deciding to order a specific laboratory test.[242] Specific preoperative laboratory tests are discussed in the following subsections, with an emphasis on clinical indications for testing.

COMPLETE BLOOD COUNT, HEMOGLOBIN, AND HEMATOCRIT

The proposed surgical procedure, associated potential blood loss, and individualized patient-level clinical indications should determine the requirement for a preoperative blood count. Primary clinical indications include a history of increased bleeding, hematologic disorders, renal disease, recent chemotherapy or radiation treatment, corticosteroid or anticoagulant therapy, poor nutritional status, surgical procedures with anticipated high blood loss, and trauma.

RENAL FUNCTION TESTING

Tests of renal function measure the degree of renal tubular dysfunction and glomerular filtration. Primary clinical indications include diabetes, hypertension, cardiac disease, potential dehydration (e.g., vomiting, diarrhea), anorexia, bulimia, fluid overload (e.g., congestive heart failure, peripheral edema, ascites), renal disease, liver disease, relevant recent chemotherapy (e.g., cisplatin, carboplatin), hematuria, nocturia, polyuria, oliguria, anuria, and renal transplantation.

LIVER FUNCTION TESTING

The ordering of LFTs should be based on a history of liver injury and physical examination findings. Primary clinical indications include a history of hepatitis (viral, alcohol, drug-induced, autoimmune), jaundice, cirrhosis, portal hypertension, biliary or gallbladder disease, hepatotoxic drug exposure, tumor involvement of the liver, and bleeding disorders.

COAGULATION TESTING

Clotting studies are not indicated in routine preoperative evaluation, even in patients undergoing regional procedures, unless an indication exists of a known or suspected coagulopathy. A careful history and physical examination provide guidance on whether coagulation testing is indicated. Primary clinical indications include a known bleeding disorder, previous excessive intraoperative surgical bleeding, hepatic disease, poor nutritional status, and use of anticoagulants or other drugs that affect coagulation.

URINALYSIS

No indication exists for routine urinalysis during preoperative evaluation. Primary clinical indications could include a suspected urinary tract infection or unexplained fever or chills.

PREGNANCY TEST

Pregnancy testing is often determined by hospital-specific protocols and can be based on findings in the history. Clinical indications relate to the date of the last menstrual period, sexual activity, use (and type) of birth control, and patient or physician intuition.

SICKLE CELL TEST

Individuals at risk for sickle cell disease include those of African, Caribbean, Eastern Mediterranean, and Middle Eastern origin. Consideration should be given to offering the sickle cell test to *previously untested* patients from at-risk ethnic groups. Given the very low yield of routine testing in these at-risk populations,[243] testing should also be guided by other factors. These factors include patient-related (e.g., family history of sickle cell disease, unknown family history, anemia, sickle cell symptoms) and surgery-related (e.g., deliberate hypothermia, cardiopulmonary bypass, intrathoracic procedures, intraabdominal procedures, orthopedic procedures involving tourniquet use) indications. The test should be accompanied by pretest and posttest counseling, so that patients are aware of the implications of both positive and negative test results for themselves and family members.

ELECTROCARDIOGRAM

The ECG can help determine a previous history of MI, conduction or rhythm disturbances, ischemia, chamber hypertrophy, and electrolyte disorders. Nonetheless, when combined with usual clinical examination, the preoperative ECG may not provide additional prognostic information to identify individuals at risk for postoperative cardiac complications.[54] Primary clinical indications preoperatively include a history of CAD, hypertension, diabetes, congestive heart failure, chest pain, palpitations, abnormal valvular murmurs, peripheral edema, syncope, dizziness, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and cerebrovascular disease. The ACCF/AHA 2009 guidelines on perioperative cardiovascular evaluation provide additional recommendations about when to order preoperative resting ECGs (see Box 38-2).[5]

CHEST RADIOGRAPH

No compelling evidence indicates that routine preoperative chest radiographs provide prognostically important information for assessing patients' perioperative risk.[244] A preoperative chest radiograph should therefore be ordered only to assess concerning abnormalities that are present in the history or physical examination. Clinical indications for a preoperative chest radiograph include auscultation of rales or rhonchi, advanced COPD, bullous lung disease, suspected pulmonary edema, suspected pneumonia, suspected pulmonary or mediastinal masses, suspicious findings on physical examination (e.g., rales,

rhonchi, tracheal deviation), aortic aneurysm, cardiomegaly, pulmonary hypertension, or dextrocardia.

PREOPERATIVE RISK ASSESSMENT

A critical objective for the preanesthesia evaluation is assessment of a patient's risk for undergoing anesthesia and surgery. This assessment improves patients' understanding of the risks inherent to the perioperative period and better informs health care providers' clinical decision making. For example, these risk assessments can help identify individuals who warrant potentially beneficial interventions, enhanced levels of postoperative monitoring, or consideration for alternative nonoperative treatment for their underlying condition. An anesthesiologist's designation of a surgical patient as being high risk is clinically important. Specifically, when an initial preanesthesia evaluation deems that a patient is an unacceptably high risk for anesthesia and surgery, this assessment is accurate, and adherence to the anesthesiologist's recommendations for further perioperative management is associated with lower postoperative complication rates.[245] In addition, accurate risk assessments facilitate fairer comparisons of perioperative outcomes across different health care providers and institutions; specifically, estimates of patients' risks are required by statistical methods that can adjust for case-mix differences across providers and institutions.[246]

The most commonly used method by anesthesiologists to assess overall perioperative risk is the ASA physical status (ASA-PS) classification system (Table 38-13). This classification system, which was developed in 1941 by Meyer Sakland at the request of the ASA,[247] was originally intended to facilitate collection and comparison of statistical data in anesthesia. The ASA-PS classification system seeks to describe a patient's preoperative medical status, but it does not consider risks inherent to the planned surgical procedure. Although *not* intended to guide estimation of patients' risks for anesthesia and surgery, the ASA-PS is often used for this very purpose, especially given its simplicity of use.

Indeed, several studies have shown a correlation of ASA-PS scores with postoperative mortality and major complications.[47,111,248,249] An important limitation to the classification system is its inherent subjectivity; consequently, previous research has shown only fair to modest interrater agreement when different individuals attempt to assign to an ASA-PS category to the same patient.[250-252]

In addition to patients' preoperative medical status, which is described by the ASA-PS system, operative procedure is an important determinant of perioperative risk.[249,253,254] Overall perioperative risk is necessarily a function of both the risk associated with the specific operative procedure and the risk associated with a patient's underlying medical status. For example, ambulatory surgical procedures are very safe with respect to risks of postoperative mortality and major adverse events,[255-257] as evidenced by a 7-day postoperative mortality rate of only 41 per 100,000 procedures in a large cohort of Medicare beneficiaries 65 years old or older.[255] Thus, although older patients with an increased burden of comorbidity do have increased relative risks of mortality and morbidity following ambulatory surgery, their *absolute* risks remain very low. The inherent importance of operative risk also explains why specialty society practice guidelines recommend that, in the absence of an unstable cardiac condition, patients can proceed directly to elective low-risk ambulatory surgical procedures without any additional preoperative cardiac workup.[5] Classification schemes have been proposed for assessing operative risk, such as the Johns Hopkins risk classification system (Table 38-14) and the strata proposed by the ACCF/AHA (see Table 38-4).[5] Although these consensus-based classification schemes are clinically sensible, their accuracy in predicting outcomes is less clear.

Several commonly used and methodologically sound clinical indices can predict mortality and major morbidity after cardiac surgery with reasonable accuracy, such as the EuroSCORE,[258] or Society of Thoracic Surgeons (STS) risk score.[259-261] For noncardiac surgery, the American

TABLE 38-13 AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION

Category*	Definition
ASA-PS 1	A normal, healthy patient
ASA-PS 2	A patient with mild systemic disease
ASA-PS 3	A patient with severe systemic disease
ASA-PS 4	A patient with severe systemic disease that is a constant threat to life
ASA-PS 5	A moribund patient who is not expected to survive without the operation
ASA-PS 6	A declared brain-dead patient whose organs are being removed for donor purposes

ASA-PS, American Society of Anesthesiologists physical status.
*The addition of "E" to the classification category indicates emergency surgery.

TABLE 38-14 JOHNS HOPKINS SURGERY RISK CLASSIFICATION SYSTEM

Category	Description
1	Minimal risk to the patient independent of anesthesia; minimally invasive procedure with little or no blood loss; procedures often done in an office setting, with the operating room used principally for anesthesia and monitoring
2	Minimal to moderately invasive procedure, with expected blood loss not exceeding 500 mL; mild risk to patient independent of anesthesia
3	Moderately to significantly invasive procedure, with expected blood loss of 500 to 1500 mL; moderate risk to patient independent of anesthesia
4	Highly invasive procedure, with expected blood loss exceeding 1500 mL; major risk to patient independent of anesthesia
5	Highly invasive procedure, with expected blood loss exceeding 1500 mL; critical risk to patient independent of anesthesia; usually requiring postoperative critical care unit stay with invasive monitoring

From Paternak LR, Johns A: Ambulatory gynaecological surgery: risk and assessment, Best Pract Res Clin Obstet Gynaecol *19:663-679, 2005.*

College of Surgeons National Surgical Quality Improvement Project (NSQIP) risk calculator is available on the Internet and provides an estimate of risk based on patients' comorbidities and proposed surgical procedures (http://riskcalculator.facs.org). Large multinational prospective epidemiologic studies of surgical patients, which included accurate capture of perioperative characteristics and outcomes,[39,249] will likely help lead to the development of similar indices for noncardiac surgery. Initial results from the VISION study, a multinational prospective cohort study of 15,133 individuals who were 45 years old or older and who underwent noncardiac surgical procedures, identified several independent predictors of postoperative 30-day mortality, including age, operative procedure, nonelective surgery, and specific comorbid conditions (Table 38-15).

Despite the paucity of clinical risk indices for predicting postoperative mortality following noncardiac surgery, high-quality indices have been developed for predicting other major postoperative complications such as cardiovascular events,[47] pneumonia,[132] respiratory failure,[262] and AKI.[153] Among these indices, the RCRI is likely the most commonly used (see Table 38-3), especially because it is simple (an important determinant of uptake into clinical practice), is strongly recommended by ACCF/AHA practice guidelines, and has consistently predicted cardiac complications across many different surgical samples.[46]

TABLE 38-15 PREOPERATIVE PREDICTORS OF 30-DAY MORTALITY AFTER NONCARDIAC SURGERY

Characteristic	Adjusted Hazard Ratio for 30-day Mortality	95% Confidence Interval
Age		
45-64 yr	Reference group	
76-74 yr	1.67	1.18-2.36
≥75 yr or older	3.03	2.20-4.18
Urgent or Emergency Surgery	4.62	3.57-5.98
Operative Procedure		
Major intraabdominal or head and neck surgery	3.25	1.64-6.45
Craniotomy or multilevel spine surgery	3.72	1.68-8.20
Major vascular surgery	2.38	1.04-5.47
Comorbid Disease		
High-risk coronary artery disease in previous 6 months*	3.12	1.71-5.68
History of congestive heart failure	1.60	1.09-2.36
History of stroke	2.01	1.42-2.84
History of peripheral arterial disease	2.13	1.47-3.10
Chronic obstructive pulmonary disease	2.15	1.61-2.89
Active cancer†	2.38	1.79-3.18

Data from VISION Study Investigators: Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery, JAMA *307:2295-2304, 2012.*

*Defined as acute myocardial infarction, acute coronary syndrome, or severe (Canadian Cardiovascular Society class 3 or 4) angina within 6 months before surgery.

†Defined as active treatment (chemotherapy, radiation or surgery) for cancer within 6 months before surgery, known metastatic disease, or planned surgery for cancer.

ROLE OF SPECIALIZED TESTING IN PREOPERATIVE RISK ASSESSMENT

Based on an initial preoperative clinical evaluation, anesthesiologists may order subsequent specialized tests to help define a patient's perioperative risk more accurately. Such tests may include noninvasive cardiac stress tests (see the earlier section on ischemic heart disease), coronary angiography (see the earlier section on ischemic heart disease), echocardiography, CPET, and PFTs.

Resting echocardiography can provide information related to valvular lesions, pulmonary hypertension, fixed wall motion abnormalities, and ventricular function. Especially in cases of a suspicious murmur or other clinical indication, a preoperative echocardiogram can help diagnose prognostically important valvular or other cardiac lesions, such as aortic stenosis or pulmonary hypertension.[263,264] Similarly, an echocardiogram can identify fixed wall motion abnormalities suggestive of a previous MI. Nonetheless, in the absence of concurrent reversible wall abnormalities (which are identified instead by noninvasive stress testing), fixed wall motion abnormalities are not associated with increased perioperative cardiac risk.[59] Systolic ventricular dysfunction is associated with increased cardiac risk.[264-266] However, this finding may not provide additional prognostic information when it is combined with routine preoperative clinical evaluation.[266] Aside from the assessment of suspicious murmurs, current ACCF/AHA practice guidelines recommend preoperative echocardiography (or other noninvasive measure of ventricular function) to help assess dyspnea of unknown origin or recent altered clinical status in an individual with known heart failure.[5] Conversely, these guidelines also specifically discourage routine preoperative assessment of ventricular function. Unlike noninvasive stress testing,[267] preoperative resting echocardiography is not associated with improved short- or long-term postoperative outcomes.[268]

CPET is a noninvasive global assessment of exercise capacity; it involves a patient exercising on a bicycle or treadmill for 8 to 12 minutes while undergoing continuous measurement of respiratory gas exchange (i.e., oxygen uptake and carbon dioxide production).[269] In some geographic settings,[270] CPET is also used to aid preoperative risk assessment. Limited available data suggest that poor exercise capacity during CPET, based on low peak oxygen consumption or low anaerobic threshold, may be associated with increased postoperative mortality and morbidity.[271,272] CPET has been used by some practitioners to guide the decision regarding the appropriateness of undergoing a surgical procedure.

The role of PFTs for guiding preoperative assessment in the setting of specific comorbidities is discussed previously in this chapter. These tests do have an established and important role for assessing perioperative risk in

lung resection surgery, as discussed in detail in Chapter 66.[273] These tests also play an important diagnostic role. For example, PFTs may help differentiate between pulmonary and cardiac causes of dyspnea of unknown origin. Aside from these specific circumstances, the *prognostic* value of preoperative PFTs is limited. Indeed, practice guidelines from the American College of Physicians recommend against routine preoperative spirometry for predicting risks for pulmonary complications of noncardiothoracic surgical procedures. Research has *not* found a consistent link between poor PFT results and increased risks for perioperative pulmonary complications,[111] with older studies being generally limited by important methodologic flaws.[274] A critical PFT threshold below which patients should not be offered surgical treatment does not appear to exist.[111] For example, a previous study of patients with severe obstructive findings on preoperative PFTs (i.e., FEV_1 <50% of predicted and an FEV_1/FVC ratio <70%) demonstrated rates of mortality (5.6%) and respiratory failure (5.6%) that were not unacceptably high.[275]

PREOPERATIVE MEDICATION MANAGEMENT

The patient's comorbidities and planned procedure must be considered when managing medications in the perioperative period. Some medications have beneficial effects during surgical procedures, whereas others may be detrimental. In some cases, withdrawal of medications suddenly can have a negative effect. Box 38-3 outlines the medications to continue or discontinue preoperatively. Although issues pertaining to many of these drugs are covered in other sections of this chapter (e.g., the section on ischemic heart disease), several issues deserve special mention.

Antihypertensive medications should generally be continued preoperatively. Stopping β-blockers or α_2-agonists (e.g., clonidine) may be associated with rebound hypertension. For patients who cannot tolerate hypotension, consideration may be given to discontinuing ACEI or ARB agents 12 to 24 hours preoperatively. Continuation of these agents up to the morning of surgery can lead to increased risks for intraoperative hypotension,[45] especially in individuals receiving concomitant diuretic therapy.[276] This hypotension can be refractory to fluid administration and typical vasopressors, although vasopressin has been used successfully to treat hypotension in these instances. The benefit of withholding ACEI and ARB agents may be especially pertinent for cardiac surgery, complex spine surgery, procedures involving significant blood loss or fluid shifts, patients taking multiple antihypertensive medications, or procedures involving intraoperative positioning that may impair hemodynamics. Both ARBs and ACEIs may have long-term protective effects in patients with CAD or associated risk factors, and the negative consequences of abrupt preoperative discontinuation are not clear. Thus, the potential for intraoperative hypotension must be balanced against possible benefits of continuing these agents up to the time of the surgical procedure. Thus, decisions about withholding ACEIs or ARBs are better made on a case-by-case basis, as opposed to a uniform approach for all patients.

Diuretics are generally discontinued preoperatively, with the exception of thiazide diuretics (e.g., hydrochlorothiazide, chlorthalidone) if taken for hypertension. Loop diuretics, which may cause volume depletion and hypokalemia, have generally been discontinued on the day of surgery. Nonetheless, a randomized trial found no increased risk of intraoperative hypotension when loop diuretics were continued, as opposed to withdrawn, on the day of surgery.[88] Thus, it is reasonable to continue loop diuretics in patients with significant volume overload, severe heart failure, or ascites, especially if the scheduled procedure is minor and unlikely to involve major fluid shifts or blood loss.

Patients with heart disease or associated cardiovascular risk factors may be taking a variety of medications, such as β-blockers, statins, digoxin, and antiarrhythmic medications. These agents are generally continued up until the time of the surgical procedure because of their beneficial effects and the potential for negative consequences if discontinued. The perioperative use of these medications is discussed in detail in the section of this chapter on cardiovascular disease.

NSAIDs have *reversible* antiplatelet effects; hence, once the drugs have been eliminated, platelet function returns to normal. Concomitant NSAID use does not appear to increase the risk of spinal hematoma with neuraxial anesthesia.[171] Preoperative discontinuation of NSAIDs may be of value in patients at risk for perioperative AKI. Typically, NSAIDs are discontinued 24 to 72 hours preoperatively. Earlier discontinuation does not increase safety, and it may be burdensome to many patients with significant arthritis or chronic pain. COX-2 inhibitors (e.g., celecoxib) have minimal effect on platelet function and can usually be continued in the perioperative period. However, the long-term use of COX-2 inhibitors in the nonoperative setting does increase the risk of cardiac events, in comparison with placebo or naproxen.[277] Conversely, COX-2 inhibitors have a cardiac risk profile similar to that of ibuprofen or diclofenac.[277] In general, no clear evidence indicates increased cardiac risk from *short-term* perioperative administration of COX-2 inhibitors. The only exception is a randomized trial of valdecoxib (now withdrawn from the market) in cardiac surgery in which the drug caused an excess of cardiac events.[278]

Patients with either type 1 or type 2 diabetes should discontinue short-acting insulin while fasting. The exception to this rule pertains to diabetic patients with continuous subcutaneous insulin infusion pumps. Such individuals should instead continue their infusion at the lowest basal rate, which is usually the nighttime fasting rate. On the day of surgery, patients with type 1 diabetes typically need to take a small amount (one third to one half) of their usual morning dose of intermediate-acting or long-acting insulin (e.g., lente, NPH) to avoid diabetic ketoacidosis. Patients with type 2 diabetes can either take no insulin or up to one half of their usual dose of intermediate-acting, long-acting, or combination (e.g., 70/30 preparations) insulin on the morning of surgery.

Metformin does not have to be routinely discontinued before the day of surgery. No data support such a recommendation, and routine discontinuation before the day of surgery may increase the risk of poor perioperative

glycemic control. Conversely, a very low risk of lactic acidosis exists in patients who then go on to develop renal and hepatic failure while taking metformin. Thus, withholding metformin before the day of surgery may be considered if the anticipated procedure poses a high risk of acute kidney or liver injury (e.g., intravenous contrast exposure, significant hemodynamic instability). In addition, metformin should likely not be restarted in patients postoperatively until any important risk of hepatic or renal failure has passed. Sulfonylurea agents with very long half-lives (e.g., chlorpropamide) can cause hypoglycemia in the fasting patient and should therefore be withheld on the day of surgery. Several newer oral agents (e.g., acarbose, pioglitazone) do not carry a risk of hypoglycemia in the fasting patient when they are used as single-agent therapy. Nonetheless, to avoid confusion, oral hypoglycemic agents are generally held the day of surgery except for minor, short procedures performed during the morning in ambulatory patients who are able to resume oral intake soon after the procedure. Hyperglycemia in the immediate perioperative period is best managed with insulin.

Patients taking steroids on a long-term basis should take their usual dose on the day of surgery. Stress-associated adrenal insufficiency may occur in patients taking steroids unless additional steroid therapy is instituted perioperatively. Approximately 5 to 7.5 mg of prednisone is equivalent to the normal daily adrenal output of cortisol, which is approximately 30 mg. The HPA axis is not suppressed in patients who take less than 5 mg/day of prednisone or its equivalent. In patients who take 5 to 20 mg/day of prednisone or its equivalent for 3 or more weeks, the HPA axis may or may not be suppressed. Patients who take more than 20 mg/day of prednisone or its equivalent for 3 or more weeks have suppression of their HPA axis. The risk of adrenal insufficiency remains for up to 1 year after the cessation of high-dose steroid therapy. The stress associated with surgery, trauma, or infection leads an intact HPA to increase adrenal output of glucocorticoids. In most patients, the circulating cortisol concentration then returns to normal within 24 to 48 hours.[279] Surgical procedures also induce a range of stress from minimal to severe; thus, the amount of supplementation should vary based on the estimated amount of surgical stress and the long-term daily dose of steroid (see Table 38-11). The risks of infection, psychosis, decreased wound healing, and hyperglycemia outweigh the benefits of unnecessarily high doses of perioperative steroids.[279]

Postmenopausal hormone replacement therapies that contain estrogen increase the risk of thromboembolic events.[280] It may therefore be reasonable to discontinue these medications before operations. Estrogens must be stopped approximately 1 month preoperatively for coagulation function to return to baseline. Most modern oral contraceptives contain low doses of estrogen that minimally increase thromboembolic risk. Because the risk of unanticipated pregnancy may outweigh the benefits of discontinuing oral contraceptives preoperatively, it is reasonable to continue oral contraceptives in the perioperative period.

Most medications for psychiatric and psychological problems should be continued into the preoperative period. Thus, antidepressants, antipsychotics, and benzodiazepines are best maintained to avoid exacerbations of symptoms. Anxiolytics are continued up until the time of the procedure. Historically, MAOI antidepressants were discontinued preoperatively; however, elimination of the risks associated with many of these drugs required drug discontinuation at least 3 weeks before surgical procedures. This long withdrawal period specifically applied to MAOIs that caused *irreversible* inhibition of MAO. Some newer agents, such as moclobemide, cause *reversible* enzyme inhibition and have effects lasting less than 24 hours. Preoperative withdrawal of these drugs has potential risks. Specifically, case reports of suicides or severe depression following discontinuation of MAOIs have been reported in the literature. Thus, the safest approach may be to continue these drugs and adjust the anesthetic plan to make changes such as avoiding meperidine and indirect-acting vasopressors (e.g., ephedrine). Details regarding a patient's MAOI use must be clearly communicated to health care providers on the day of the surgical procedure. Patients receiving tricyclic antidepressants require a preoperative ECG, given the potential for associated prolongation of the QT interval. Because tricyclic antidepressants block the reuptake of norepinephrine and serotonin, high doses may also result in augmented responses to vasopressor drugs, with the potential for exaggerated hemodynamic changes. Patients taking lithium require evaluation of electrolytes, BUN, and creatinine. Discontinuation of lithium has also been associated with suicide. Similarly, abrupt discontinuation of SSRIs can also cause adverse effects, including dizziness, headache, nausea, irritability, visual disturbances, and sensations of electric shocks.

Complementary and alternative medications may interact with anesthetic agents, alter effects of prescription medications, and increase bleeding. In addition, many patients do not consider these agents "medications" and hence do not include them in a list of their medications unless specifically asked. The perioperative management of complementary and alternative medications is discussed in further detail in Chapter 40.

PLANNING FOR ANESTHESIA

PREOPERATIVE FASTING STATUS

The primary goal of preoperative fasting recommendations has been to reduce the occurrence of pulmonary aspiration. The ASA published practice guidelines pertaining to preoperative fasting in nonlaboring individuals undergoing elective procedures.[281] The recommended fasting period following clear fluids for all patients is 2 hours. In general, the volume of liquid ingested is less important than the type of liquid ingested. For neonates and infants, the recommended fasting period is 4 hours following breast milk, and 6 hours following formula and solids. For patients other than infants, a fasting period of 6 hours after a light meal is recommended; this period may have to be increased to 8 hours or more if the meal includes fried or fatty foods. In addition to implementing these fasting intervals, these guidelines recommend that the preoperative evaluation include assessment of

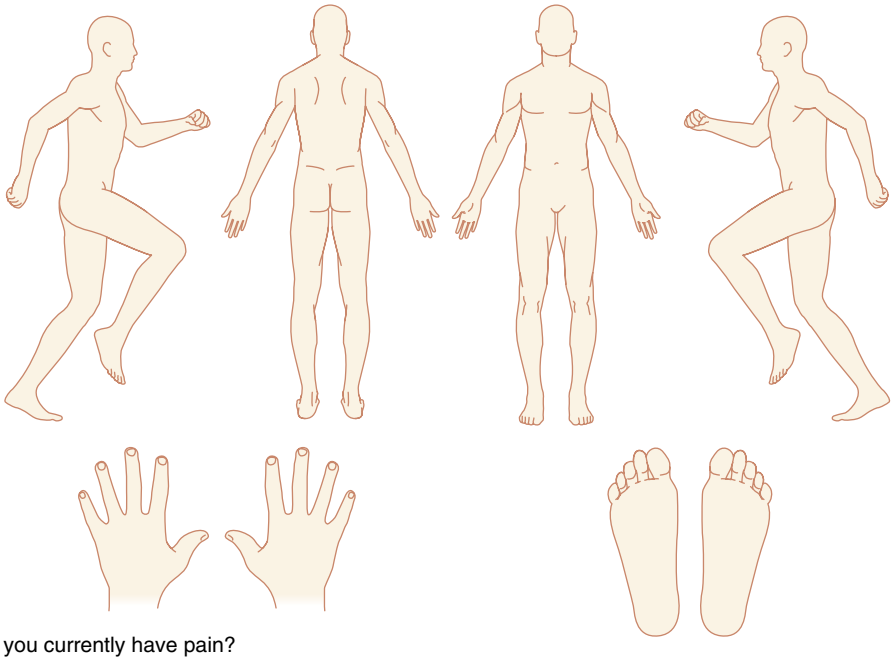
the potential for difficult airway management, as well as factors that may increase the risk for aspiration (e.g., gastrointestinal motility disorders, diabetes).

PLANNING FOR POSTOPERATIVE PAIN MANAGEMENT

The Joint Commission recognizes that all patients have the right to appropriate assessment and treatment of pain and mandates assessment of pain in all patients. A preoperative evaluation should therefore always include baseline pain assessment, which often occurs as part of the preoperative nursing assessment.

Standardization of pain measurement is difficult because of the subjective nature of the variable. The scales used fall into the categories of single-dimension scales, such as visual analog and numeric rating scales, and multidimensional scales, such as the McGill pain questionnaire.[282] Figure 38-9 shows one example used for pain assessment in a preoperative evaluation. The location of the pain is noted on the figure; the character, duration, and frequency are documented, and intensity is recorded with a numeric rating scale from 1 to 10, with 1 being no pain and 10 being the worst pain imaginable. If a numeric scale cannot be used, a scale using faces can be substituted. Use of these scales readily allows comparison when reassessments are performed postoperatively.

The preoperative evaluation provides an important opportunity to discuss and plan for the management of acute postoperative pain (see Chapter 98), for several reasons. First, adequacy of perioperative pain control is a frequent concern for patients during preoperative evaluation.[283,284] Second, intensive preoperative pain instructions may help improve postoperative pain control in surgical patients.[285] Third, preoperative anesthesia consultation is associated with improved patient acceptance of perioperative regional techniques,[14] which themselves can help improve the quality of postoperative analgesia.[286] Fourth, preoperative evaluation facilitates planning the perioperative care of patients with chronic pain conditions, who often present significant challenges with respect to managing postoperative analgesia. Specific issues include their tolerance to usual doses of opioid analgesics and the potential for acute withdrawal reactions if they receive



Do you currently have pain?

☐ Yes ☐ No If Yes, location: _____

Character: ☐ sharp ☐ throbbing ☐ dull ☐ burning

Duration: _____

Frequency: _____

Intensity scale: _____

☐ Numeric

☐ Faces

What makes the pain better? _____

What makes the pain worse? _____

What is an acceptable pain level to you? _____

Figure 38-9. Pain status and history form.

insufficient doses of opioids postoperatively. The preoperative consultation should therefore be used to carefully document their usual baseline opioid requirements (to ensure adequate postoperative dosing), facilitate early involvement of an acute pain service or chronic pain specialist, encourage regional analgesic techniques, and plan adjunct analgesic medications (e.g., NSAIDs, gabapentin, pregabalin, clonidine). Patients with preexisting chronic pain should be encouraged to develop reasonable goals for adequacy of postoperative pain control. They should be informed that although care providers will do everything possible to maintain comfort postoperatively, patients should not expect to have no pain at all.

In general, patients do not have to be weaned from pain medications preoperatively. If patients are instructed by the surgeon to discontinue NSAIDs or COX-2 analgesics, they may have to be transitioned to alternative analgesics leading up to the surgical procedure. Patients should be instructed to take their usual morning doses of pain medication, including the continued use of any transdermal fentanyl patch.

REGULATORY ISSUES

Providers must be aware of various governmental regulatory requirements. These requirements may be driven by quality regulations such as those developed by The Joint Commission or by payment requirements as set by the Centers for Medicare and Medicaid Services (CMS) in the United States. Local regulations may also be in effect. These regulations often differ by individual municipalities and countries, meaning that one needs to stay abreast of updates. For example, the CMS has determined that a comprehensive anesthesia evaluation can be done within 30 days, and a focused update is required within 48 hours of a procedure requiring anesthesia services. At a minimum, the preanesthesia evaluation must include the following:

- Notation of anesthesia risk (e.g., ASA-PS classification)
- Review of the medical, anesthesia, drug, and allergy history
- Interview and examination of the patient
- Potential anesthesia problems (e.g., difficult airway, limited intravascular access)
- Additional evaluation, if deemed necessary (e.g., stress tests, specialist consultation)
- Development of a plan for anesthesia, including the type of medications for induction, maintenance, and postoperative care
- Discussion of the risks and benefits of anesthesia with the patient or the patient's representative

A practitioner qualified to provide anesthesia must perform this evaluation.

PREOPERATIVE EVALUATION CLINIC

Many anesthesia groups and medical centers have developed preoperative evaluation programs and clinics, with the objectives of improving patient care and operating room efficiency.[9,17,287] Although these programs may differ with respect to staffing, structure, financial support, and daily operations, they all share a common goal of preventing delays, last-minute cancellations, and adverse patient outcomes that could have been addressed before the day of surgery.

The decision to develop a preoperative evaluation clinic depends on several key factors. They include the anticipated daily volume of surgical patients, the predominant level of medical acuity among these patients, the availability of clinic facilities, relevant patient demographics (e.g., average travel distances from patients' homes to the clinic), and requisite support from the anesthesia department, perioperative staff, and hospital administration. If the decision to implement a preoperative evaluation program is made, anesthesiologists must play a key role in its leadership and management. When this role is instead undertaken by other specialties, such as internal medicine, anesthesiologists' expertise in perioperative patient management often becomes secondary. This shift to a secondary role can result in interdepartmental conflicts concerning patients' preoperative evaluation, risk stratification, and fitness to proceed with anesthesia and surgery. These conflicts can, in turn, result in unplanned delays or cancellations of planned surgical procedures, despite the completion of an assessment in an outpatient preoperative evaluation clinic.

Such conflicts often relate to surgeons' interpretation of a nonanesthesia specialist's judgment that a patient is "cleared for surgery" as evidence that the patient is fit for anesthesia. Unfortunately, this "clearance" is frequently made with limited knowledge of factors critical to the responsible anesthesiologist in the operating room, such as current anesthesia practice and intraoperative patient management. Indeed, previous research has shown that preoperative histories, physical examinations, and assessments performed by medical specialists often fail to address specific anesthesia-related concerns.[30] As the specialist who makes the final determination of whether a patient is fit to proceed with anesthesia and surgery, the responsible anesthesiologist is a critical "end-user" of any assessment performed in a preoperative evaluation clinic. Consequently, a reliance on nonanesthesia specialists can result in preoperative assessments that are deemed inadequate by the responsible anesthesia providers and that lead to potential last-minute surgical delays and cancellations, with associated significant frustration among both patients and surgeons. Conversely, preoperative-to-intraoperative communication is likely significantly improved when anesthesiologists are responsible for most outpatient preanesthesia evaluations, as confirmed by previous studies showing fewer last-minute case cancellations,[9,15-17] shorter durations of hospitalization,[16,17] and lower hospital costs,[16] with institution of anesthesia-led preoperative evaluation programs.

Awareness of the local hospital context is critical if a preoperative evaluation program is to have good outcomes. In a hospital with limited resources that has mostly healthy outpatient and same-day-admission surgical patients, the anesthesia group may be unable to evaluate all patients preoperatively in a clinic before the day of surgery. In this situation, the preoperative program must develop a means for accurate screening and

triage of patients based on their current health status. An accurate triage process helps target the use of preoperative clinic visits only among selected higher-risk patients without compromising patients' quality of care and outcomes. An example of such a triage process may involve having patients initially complete an anesthesia questionnaire (see Fig. 38-2) in their surgeons' office. This questionnaire can be a Web-based online document or even a paper version that would then be faxed to the anesthesia group before the date of surgery. In the case of a patient with a questionable medical history, a telephone call by the anesthesiologist could clarify any issues of concern. This opportunity to review a patient's medical history before the day of surgery helps reduce unresolved or unexpected medical concerns on the day of surgery. It also helps determine whether a patient requires formal preoperative consultation in advance of the surgical procedure, as opposed to evaluation on the day of surgery itself.

Conversely, anesthesia groups at hospitals with many medically complex surgical patients may benefit from the establishment of a formal preoperative evaluation facility with multiple examination rooms, dedicated staffing, and a full-time operational system. The establishment of a successful preoperative evaluation clinic requires commitment, collaboration, and support from several hospital disciplines.[9] At a minimum, the departments of anesthesia, surgery, nursing, and hospital administration must agree that such a clinic has value for the hospital, and they must commit to support its operational goals (Box 38-17).

BOX 38-17 ***Operational Goals for a Preoperative Evaluation Clinic***

- Improve patients' perception of the preoperative evaluation experience by increasing personalized care, comfort, and convenience.
- Provide a centralized site for preoperative evaluation.
- Institute a clinic scheduling system for timely patient access and flow.
- Ensure the presence of an anesthesiologist on site when patients are present.
- Appoint a medical director to coordinate all activities.
- Ensure the availability of medical records and surgical notes at the time of the preoperative evaluation.
- Decrease logistic shuffling of patients to multiple other hospital service areas.
- Integrate and coordinate services through on-site facilities for admission, registration, insurance authorization, laboratory tests, radiographs, and electrocardiographic studies.
- Educate patients and families about the elements of their surgical procedure and the proposed anesthesia care, including postoperative pain control options.
- Educate patients about what to expect regarding postoperative feeding and discharge needs.
- Ensure medically appropriate and cost-effective ordering of preoperative laboratory and diagnostic studies.
- Provide a medical consultation service for evaluation of medically complex surgical patients.
- Decrease the number of cancellations and delays on the day of surgery.
- Enlist nurses or mid-level providers to assist in preoperative evaluation and in patient and family education.
- Develop protocols, policies, and clinical pathways for preoperative care.
- Perform quality assurance reviews.
- Maximize efficiency in operating room function by coordinating all preoperative information at one location in the preoperative evaluation clinic.
- Enhance patient and surgeon satisfaction.

COLLABORATION, COMMITMENT, AND TEAMWORK

The preoperative evaluation clinic is a visible partnership among the departments of anesthesia, surgery, nursing, and hospital administration to achieve common goals, as illustrated in Figure 38-10. This collaboration conveys the important theme that the new clinical program is an integrated enterprise that requires shared obligation, endeavor, and financial responsibility. Although these clinics are best led by anesthesiologists,[9,15-17] engagement with medical specialists and hospitalists remains important to the success of any preoperative program. These nonanesthesia specialties provide unique expertise in the preoperative management of selected medically complex patients; furthermore, they can facilitate enhanced postoperative monitoring of high-risk patients through, for example, the comanagement model of postoperative care (see the earlier section on the role of the medical consultant in preoperative evaluation).

Surgeons may be initially reluctant to send their patients to a newly established anesthesia-led preoperative evaluation clinic. This reluctance often stems from

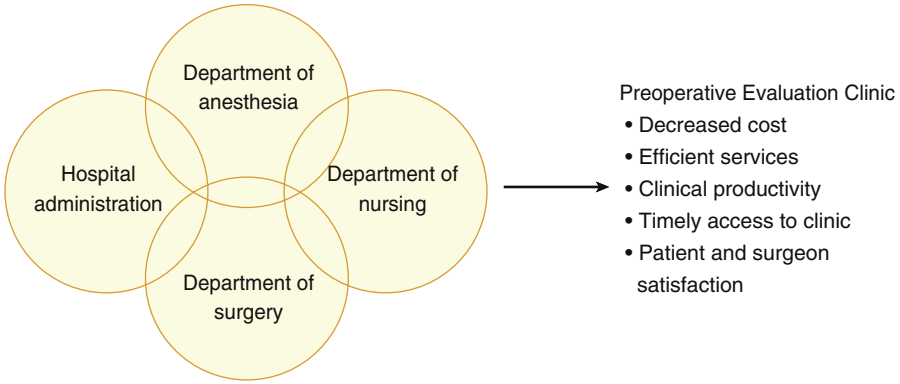


Figure 38-10. The anesthesia preoperative evaluation clinic is a constructive partnership working toward common goals.

an unclear understanding of the benefits of outpatient preoperative anesthesia evaluation. Consequently, the surgeons' hesitation can be reduced by clearly identifying the specific advantages of an integrated anesthesia-led preoperative evaluation program. First, the proven benefits of anesthesia-led preoperative evaluation should be highlighted.[9,14-17] Second, anesthesiologists should emphasize the important practical advantages of an integrated assessment of medically complex surgical patients. Specifically, when relevant medical concerns are identified before the surgical procedure, the preoperative program can acquire all relevant prior medical data, coordinate any additional workup or consultation, prearrange any required specialized postoperative monitoring, and discuss the case beforehand with the surgeon and responsible anesthesiologist. This approach ensures that when such a patient presents for the operation, the responsible anesthesia provider is satisfied to proceed with the surgical procedure, and the perioperative team has all required medical information to manage the patient optimally during the hospitalization.

Third, informal assurances should be made to the surgical services that, if a patient is managed by the preoperative evaluation program, surgery will proceed without cancellation or delay by the assigned anesthesiologist unless an intervening illness or adverse medical event occurs between the outpatient evaluation and the scheduled operation. Because cancellations and delays on the day of surgery can be a prominent source of aggravation for surgeons and patients, these informal assurances would be viewed as a key strength of the newly developed preoperative program. Such assurances depend heavily on the anesthesia department's addressing relevant clinical practice variations. Specifically, issues that are subject to important interpractitioner differences, such as what fasting blood glucose level or degree of preoperative hypertension would merit cancelling a surgical case, must be discussed to achieve a departmental consensus standard. The absence of consensus standards can lead to situations in which half the anesthesia providers may proceed with a higher-risk surgical case, whereas the other half would cancel it instead. Wide inconsistency in practice will foster a lack of support among surgeons and will lead to reluctance to have their patients evaluated. Such a preoperative program is unlikely to be successful.

STRUCTURES AND ACTIVITIES OF THE PREOPERATIVE EVALUATION CLINIC

The daily operations of a preoperative evaluation clinic vary based on the patient volume, the general level of medical complexity among surgical patients, the type of available clinic facilities, and staffing resources. Nonetheless, a general operational structure can be proposed based on examination of several preoperative clinic models currently in practice.

Centers with large surgical case volumes should have their patients formally scheduled in the clinic before the day of evaluation, to allow for medical records and relevant outside information to be acquired and collated. The surgeon's office should schedule this clinic appointment at the same time that it books the operating room case. To ensure timely patient access and flow through the facility, these appointments should be booked using an efficient clinic scheduling system. Ideally, appointments should be scheduled to allow sufficient time between the clinic visit and the scheduled surgical procedure, to facilitate any additional preoperative testing, consultations, or interventions. Some degree of flexibility in the clinic schedule is also needed, especially to accommodate patients who have urgent indications for surgery. One approach for incorporating some flexibility is to include a few open appointment slots in the daily clinic schedule that can be used as needed for last-minute patient referrals. Such flexibility is required for individuals residing in rural and remote areas, who have been reported to have reduced rates of access to preoperative evaluation clinic facilities.[288] Anesthesiologists at some centers have also adopted telemedicine technology (defined as health care delivery and sharing of medical knowledge over a distance using telecommunications systems)[289] so that patients residing at remote locations can undergo preanesthesia consultations without traveling long distances to the clinic.[290]

At the clinic, a clinician interviews and examines the patient, obtains historical medical information and outside records, and determines whether (and which) additional laboratory tests, ECGs, radiographs or other diagnostic tests are required. Phlebotomy, ECG, and hospital admitting and insurance registration services are typically available in the preoperative clinic facility. The ECGs are assessed during the clinic visit itself, whereas laboratory test results are evaluated at the end of each clinic day, with follow-up of abnormal findings as needed. In this manner, significant abnormalities can be addressed immediately; thus, any required delays or cancellations of surgical cases can occur well in advance of the scheduled day of surgery. This centralization of multiple services is also a significant convenience for patients, who no longer have to visit multiple hospital locations to complete their preoperative requirements. This arrangement should also centralize all medical data relevant to the scheduled hospital admission into a single chart, which remains in the preoperative evaluation clinic area until the date of surgery. In addition to addressing medical aspects relevant to the scheduled surgery, the preoperative evaluation program plays an important role in educating surgical patients. Typically, both the clinician performing the preoperative assessment and a specifically trained nurse educator discuss the forthcoming perioperative process with each patient and family members. By increasing patients' awareness of important components pertaining to their scheduled hospital admission (e.g., analgesic options, risks of anesthesia), this education process can decrease patients' anxiety,[13] as well as increase their willingness to receive regional analgesia.[14] The types of clinicians who perform the preanesthesia assessment include anesthesiologists and specially trained nurse practitioners. Some authors have questioned whether the responsible anesthesiologist in the operating room would be satisfied with preanesthesia assessments performed by another individual.[291] Patients themselves often report a preference for having the same anesthesiologist in both the preoperative clinic and the operating room.[292] Nonetheless, it

is simply not feasible for all patients in the preoperative clinic to be evaluated by their eventual anesthesia providers. Furthermore, a large Dutch study of 21,454 surgical patients demonstrated that responsible anesthesia providers were satisfied with 95% of outpatient preanesthesia assessments performed by other anesthesiologists or trained nurses.[293]

Preoperative programs must adopt several strategies to ensure that anesthesia providers in the operating room will be satisfied with the quality of outpatient preoperative assessments. First, the anesthesia department must develop consensus standards for determining when patients should have scheduled surgery cancelled for medical reasons. Second, the documentation required for all preanesthesia assessments in the clinic should be standardized. This standardization helps prevent situations in which an assessment does not contain information needed by the anesthesia provider in the operating room to determine a patient's fitness for surgery or to develop an anesthetic management plan. Some national anesthetic groups have initiated work on consensus-based documentation standards for all preanesthesia assessments.[294] Strategies for improving the consistency of documentation across preanesthesia assessments include the use of checklists, as well as structured electronic or paper-based forms for documenting preanesthesia assessments. Third, all nurse practitioners or other nonanesthesia clinicians assessing patients in the clinic should undergo an intensive and ongoing education in preoperative assessment. Anesthesiologists with strong interest and expertise in preoperative evaluation should lead this education program. Previous research has shown that well-trained nurses do perform effectively in both screening and evaluating patients in preoperative clinics.[295-297]

IMPACT ON OPERATING ROOM EFFICIENCY AND OUTCOMES

Anesthesia-led preoperative assessment clinics have been shown to have a positive impact on operating room efficiency and outcomes (see the earlier section on the goals and benefits of preanesthesia evaluation). The demonstrated benefits of these clinics include fewer case cancellations on the day of surgery[9,15-17] and a shorter duration of hospitalization.[14,16,17] Other mechanisms whereby preoperative evaluation clinics reduce health care costs include more selective ordering of preoperative laboratory tests and specialist referrals.[9,11,12] Thus, although preoperative evaluation programs do incur costs (e.g., facility development costs, staff salaries), they can still lead to an overall reduction in hospital costs as a result of these associated cost savings.[16]

PATIENT SATISFACTION WITH PREOPERATIVE EVALUATION CLINICS

In addition to addressing perioperative efficiencies and clinical outcomes, preoperative programs should also consider the experience and satisfaction of patients attending their clinics. During development of strategies to improve patient satisfaction, the key underlying determinants of improved satisfaction should be considered. They include being assessed by the same anesthesiologist who will administer anesthesia in the operating room, shorter wait times in the clinic, and good quality of communication from the clinic staff.[292,298,299] Because it is simply not feasible to have all patients in the clinic seen by their eventual anesthesia providers, the major focus should be on improving wait times and the quality of communication. Changes in appointment booking systems,[300] process flows, and clinic operations can decrease wait times,[295] which in turn can substantially improve patients' satisfaction.[295] In addition, preoperative programs can ensure that patients receive an accurate estimate of average waiting times before their scheduled clinic visit and use any encountered wait times to conduct other clinic-related activities (e.g., physical therapy instructions, video-based preoperative education).

The development of an ongoing patient survey and feedback system is an important initial step to help improve patients' experience and satisfaction with preoperative evaluation programs. Specifically, such surveys can be used to measure the baseline level of patients' satisfaction, identify opportunities for improvement, and determine responses to any subsequent interventions. When attempting to choose a survey instrument, preoperative programs will find that most currently available surveys, such as the Press Ganey Patient Satisfaction Survey and Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) patient satisfaction survey, reflect the overall perioperative experience. These surveys are not effective for discerning patients' satisfaction with particular elements of the preoperative process. Therefore, several studies developed specialized questionnaires to measure and help drive improvement in patient-reported quality of care in preoperative evaluation clinics.[295,301]

CONCLUSION

The practice of anesthesiology has changed.[2] The expanding role of the anesthesiologist outside the operating room will redefine our specialty's contribution to high-quality patient care in the health care system. Within the context of preoperative evaluation, anesthesiologists must be knowledgeable and adept at assessing patients of highly varying medical complexity, whether in an outpatient preoperative evaluation clinic before the day of the surgical procedure or at the bedside immediately before induction of anesthesia. Anesthesiologists must be familiar with the impact of a broad range of chronic and acute medical conditions on patients' risks for anesthesia and surgery. In addition, this role entails awareness of multiple practice guidelines, regulatory requirements, and approaches for efficient management of outpatient clinics. Despite this evolving and expanding role of anesthesiologists in preoperative care, the primary purpose of preoperative evaluation will never change. It is the clinical foundation for guiding perioperative patient management, and it has the potential to reduce perioperative morbidity and enhance patient outcome.

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Chapter 39

Anesthetic Implications of Concurrent Diseases

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Key Points

- The history and physical examination most accurately predict the risks of anesthesia and the likelihood of required changes in monitoring or therapy.
- For diabetic patients, end-organ dysfunction and the degree of glucose control in the perioperative and periprocedural periods are the critical issues with regard to risk.
- The keys to managing blood glucose levels in diabetic patients perioperatively are to set clear goals and then monitor blood glucose levels frequently enough to adjust therapy to achieve these goals.
- Obesity is associated with multiple comorbid conditions, including diabetes, hyperlipidemia, and cholelithiasis, but the primary concern is derangements of the cardiopulmonary system.
- Obstructive sleep apnea is important to recognize because of the increased sensitivity to and the consequence of the depressing effects of hypnotics and opioids on airway muscle tone and respiration, as well as the difficulty with laryngoscopy and mask ventilation.
- Although no controlled, randomized prospective clinical studies have been performed to evaluate the use of adrenergic receptor blocking drugs in patients undergoing resection of pheochromocytoma, the preoperative use of such drugs is generally recommended.
- For patients with hypertension, the routine administration of all drugs preoperatively is recommended, except angiotensin-converting enzyme inhibitors and angiotensin II antagonists.
- Evaluation of a patient with cardiovascular disease depends on clinical risk factors, the extent of surgery, and exercise tolerance.
- In patients with pulmonary disease, the following should be assessed: dyspnea, coughing and the production of sputum, recent respiratory infection, hemoptysis, wheezing, previous pulmonary complications, smoking history, and physical findings.
- In patients with pulmonary disease, several strategies have been suggested, including cessation of smoking 8 weeks or more preoperatively.
- Risk factors for perioperative renal dysfunction include advanced age, congestive heart failure, previous myocardial revascularization, diabetes, and increased baseline blood creatinine concentration.
- One of the primary objectives for a patient with renal disease is ensuring that the renal dysfunction is not augmented and thereby increasing the chance for renal failure, coma, and death.
- Mild perioperative anemia may be clinically significant only in patients with ischemic heart disease.
- Careful management of long-term drug administration should include questions about the effects and side effects of alternative as well as prescription drugs.

This chapter reviews many conditions requiring special preoperative and preprocedure evaluation, intraoperative or intraprocedure management, or postprocedure care. Patients undergoing surgical procedures move through a continuum of medical care to which a primary care physician, an internist or pediatrician, an anesthesiologist, and a surgeon, radiologist, or obstetrician-gynecologist contribute to ensure the best outcome possible. No aspect of medical care requires greater cooperation among physicians than does performance of a surgical operation or a complex procedure involving multiple specialists and the perioperative care of a patient. Moreover, nowhere else can counseling make so huge a difference in so many lives. The preoperative evaluation also represents a time when education on tobacco cessation, physical inactivity, and poor food choices can be discussed (see also Chapter 38). The importance of integrating physicians' expertise is even greater within the context of the increasing life span of our population. As the number of older adults and very old adults (those >85 years old) grows, so does the need of surgical patients for preoperative consultation to help plan for comorbidity and multiple drug regimens, knowledge of which is crucial to successful patient management (see also Chapter 80). At a time when medical information is encyclopedic, it is difficult, if not impossible, for even the most conscientious anesthesiologist to keep abreast of the medical issues relevant to every aspect of perioperative or periprocedure patient management. This chapter reviews such issues with primary emphasis on the anesthesiologist providing preoperative evaluation and care, rather than transferring these responsibilities to other providers.

As with "healthy" patients (see also Chapter 38), the history and physical examination most accurately predict not only the associated risks but also the likelihood that a monitoring technique or change in therapy will be beneficial or necessary for survival. This chapter emphasizes instances in which specific information should be sought in history taking, physical examination, or laboratory evaluation. Although controlled studies designed to confirm that optimizing a patient's preoperative or preprocedure physical condition would result in a less frequent rate of morbidity have not been performed for most diseases, it is logical to assume that such is the case. That such preventive measures would cost less than treating the morbidity that would otherwise occur is an important consideration in a cost-conscious environment.

Minimally invasive procedures such as cataract extraction, magnetic resonance imaging (MRI), or diagnostic arthroscopy, performed in conjunction with the best current anesthetic practices, may pose no greater risk than daily living and thus may not be considered an opportunity for special evaluation. Nevertheless, the preoperative evaluation may identify conditions that could change perioperative management and that may improve both throughput of surgery and the speed of recovery. Examples include the following: ensuring the administration of long-term medications such as a β-adrenergic blocking drug, aspirin for patients with coronary stents, or a statin (or any combination); administering a histamine type 2 (H_2) antagonist 1 to 2 hours before entry into the operating room; ensuring the availability of equipment to measure blood glucose levels; obtaining a history of the patient's diabetic course and treatment from the primary care physician, as well as from the patient; and performing a fiberoptic laryngoscopic examination or procuring additional skilled attention.

The following conditions are discussed in this chapter:

1. Diseases involving the endocrine system and disorders of nutrition (discussed first because of its increasing importance to care)
2. Diseases involving the cardiovascular system
3. Disorders of the respiratory and immune system
4. Diseases of the central nervous system (CNS), neuromuscular diseases, and mental disorders
5. Diseases involving the kidney, infectious diseases, and disorders of electrolytes
6. Diseases involving the gastrointestinal (GI) tract or the liver
7. Diseases involving hematopoiesis and various forms of cancer
8. Diseases of aging or those that occur more commonly in older adults, as well as chronic and acute medical conditions requiring drug therapy (see also Chapter 80)

ROLE OF THE PRIMARY CARE PHYSICIAN OR CONSULTANT

The roles of the primary care physician or consultant are not to select and suggest anesthetic or surgical methods but rather to optimize the patient's preoperative and preprocedure status regarding conditions that increase the morbidity and mortality associated with surgery and to alert the anesthesia care team about these conditions.

Quotations and a box in a Medical Knowledge Self-Assessment Program published by the leading organization representing internists, the American College of Physicians, highlight this role for the consultant[1]:

Effective interaction with colleagues in other specialties requires a thorough grounding in the language and science of these other disciplines as well as an awareness of basic guidelines for consultation [Box 39-1]. The consulting internists' role in perioperative care is focused on the elucidation of medical factors that may increase the risks of anesthesia and surgery. Selecting the anesthetic technique for a given patient, procedure, surgeon, and anesthetist is highly individualized and remains the responsibility of the anesthesiologist rather than the internist.

Optimizing a patient's preoperative and preprocedure condition and, in settings with a preoperative clinic, counseling a patient about needed future lifestyle changes such as walking, food choices, and tobacco cessation are cooperative ventures between the anesthesiologist and the internist, pediatrician, surgeon, or family physician (see also Chapter 38). If available, the primary

BOX 39-1 *Guidelines for Consultation Practice*

- Complete a prompt, thorough, generalist-oriented evaluation.
- Respond specifically to the question or questions posed.
- Indicate clearly the perioperative importance of any observations and recommendations outside the area of initial concern.
- Provide focused, detailed, and precise diagnostic and therapeutic guidance.
- Emphasize verbal communication with the anesthesiologist and surgeon, particularly to resolve complex issues.
- Avoid chart notations that unnecessarily create or exacerbate regulatory or medicolegal risk.
- Use frequent follow-up visits in difficult cases to monitor clinical status and compliance with recommendations.

From American College of Physicians: Medical consultation. In Medical knowledge self-assessment program IX, *part C, book 4. Philadelphia, 1992, American College of Physicians, p 939.*

care physician should affirm that the patient is in the very best physical state attainable (for that patient), or the anesthesiologist and primary care physician should do what is necessary to optimize that condition. Statements that describe the preoperative and preprocedure physical condition of the patient (e.g., "This patient is in optimum shape" and "I believe the mitral stenosis is more severe than the slight degree of mitral insufficiency") are much more useful to the anesthesiologist than statements that suggest overall clearance ("cleared for surgery") or perioperative procedures ("prevent hypoxia and hypotension").

Primary care physicians can prepare and treat a patient to provide optimal conditions for daily life. However, they often do not have the depth of understanding of the anesthesiologist regarding the physiologic changes brought on by surgery and the manipulations in function that must be made to facilitate surgery and procedures and to optimize perioperative and periprocedure outcomes. One example is the induction of some degree of prerenal azotemia in a patient with congestive heart failure (CHF) by the primary care physician. The intravascular volume depletion associated with prerenal azotemia may make a patient with a cardiac condition more comfortable in daily life but would predispose that patient to hypovolemic problems during and after surgery and complex procedures. The preoperative clinic should collaborate with the primary care physician to start the process of preparing the patient for the needs of surgery or complex procedures (see Chapter 38). Although such education is more readily available and of better quality than in previous decades and although cardiologic organizations have provided considerable data on the importance of this aspect of care,[2-4] the primary care physician's training, knowledge, and ability must be verified when he or she is part of the preoperative evaluation process. Without understanding the physiologic changes that occur perioperatively, appropriate therapy is difficult to prescribe. It is therefore part of the anesthesiologist's job to instruct the patient's consultants about the type of information needed from the preoperative and preprocedure consultation.

DISEASES INVOLVING THE ENDOCRINE SYSTEM AND DISORDERS OF NUTRITION

PANCREATIC DISORDERS

Preoperative and Preprocedure Diabetes Mellitus

Diabetes mellitus is a heterogeneous group of disorders that have the common feature of a relative or absolute lack of insulin. The disease is characterized by a multitude of hormone-induced metabolic abnormalities, by diffuse microvascular lesions, and by long-term end-organ complications. The diagnosis of diabetes is made with a fasting blood glucose level greater than 110 mg/dL (6.1 mmol/L), and impaired glucose tolerance is diagnosed if the fasting glucose level is less than 110 mg/dL (6.1 mmol/L) but greater than 100 mg/dL (5.5 mmol/L). Diabetes can be divided into two very different diseases that share these end-organ abnormalities. Type 1 diabetes is associated with autoimmune diseases and has a concordance rate of 40% to 50% (i.e., if one of a pair of monozygotic twins had diabetes, the likelihood that the other twin would have diabetes is 40% to 50%). In type 1 diabetes, the patient is insulin deficient and susceptible to ketoacidosis if insulin is withheld. In type 2 diabetes, the concordance rate is 100% (i.e., genetic material is both necessary and sufficient for the development of type 2 diabetes). How markedly the aging and end-organ effects of these genes are expressed is based on lifestyle choices of food and physical activity. These patients are not susceptible to the development of ketoacidosis in the absence of insulin, and they have peripheral insulin resistance. Patients with non–insulin-dependent (type 2) diabetes now account for most (>90%) of the diabetic patients in Europe and North America. These individuals tend to be overweight, relatively resistant to ketoacidosis, and susceptible to the development of a hyperglycemic-hyperosmolar nonketotic state. Plasma insulin levels are normal or increased in type 2 diabetes but are relatively low for the level of blood glucose. This hyperinsulinemia by itself is postulated to cause accelerated cardiovascular disease. Gestational diabetes develops in more than 3% of all pregnancies and increases the risk of type 2 diabetes by 17% to 63% within 15 years.

Type 1 and type 2 diabetes differ in other ways as well. Contrary to long-standing belief, a patient's age does not allow a firm distinction between type 1 and type 2 diabetes; type 1 diabetes can develop in an older person, and clearly, type 2 diabetes can develop in overnourished children. Type 1 diabetes is associated with a 15% prevalence of other autoimmune diseases, including Graves disease, Hashimoto thyroiditis, Addison disease, and myasthenia gravis.

Over the next decade, the prevalence of diabetes is expected to increase by 50%. This growth is primarily the result of the increase in type 2 diabetes caused by excessive weight gain in adults (see also Chapter 71) and now also in the pediatric population (see also Chapter 93). Large clinical studies show that long-term, strict control of blood glucose levels and arterial blood pressure, along with regular physical activity, results in a major delay in microvascular complications and perhaps indefinite postponement of type 2 diabetes in patients.[5,6]

The common orally administered drugs can be classified into six major groups: acarbose, meglitinide (e.g., repaglinide or nateglinide), metformin, sulfonylureas (e.g., glibenclamide, glipizide, glimepiride, gliuidone), thiazolidinediones (e.g., pioglitazone), and dipeptidyl peptidase-4 (DPP-IV) inhibitors (e.g., sitagliptin, saxagliptin, vildagliptin). Physicians advocating tight control of blood glucose levels usually give insulin to "maturity-onset" insulin-dependent diabetic patients twice a day or even more frequently.

Patients with insulin-dependent diabetes tend to be young, nonobese, and susceptible to the development of ketoacidosis. Plasma insulin levels are low or not measurable, and therapy requires insulin replacement. Patients with insulin-dependent diabetes experience an increase in their insulin requirements in the postmidnight hours, which may result in early morning hyperglycemia (dawn phenomenon). This accelerated glucose production and impaired glucose use reflect nocturnal surges in secretion of growth hormone (GH). Physiologically normal patients and diabetic patients taking insulin have steady-state levels of insulin in their blood. (Unfortunately, traditional values for insulin pharmacokinetics are derived from studies designed as though the diabetic patient received only one shot of insulin in a lifetime.) Absorption of insulin is highly variable and depends on the type and species of insulin, the site of administration, and subcutaneous blood flow. Nevertheless, attainment of a steady state depends on periodic administration of the preparations received by the patient. Thus, it seems logical to continue the combinations of preparations perioperatively that the patient had been receiving on a long-term basis after examining the patient's blood glucose monitoring logbook for the degree of control.

The major risk factors for diabetic patients undergoing surgery are the end-organ diseases associated with diabetes: cardiovascular dysfunction, renal insufficiency, joint collagen tissue abnormalities (limitation in neck extension,[7] poor wound healing), inadequate granulocyte production, and neuropathies.[8-15] Thus, a major focus of the anesthesiologist should be the preoperative and preprocedure evaluation and treatment of these diseases to ensure optimal preoperative and preprocedure conditions. Poor preoperative glucose control, as measured by the hemoglobin A_{1C} (glycosylated hemoglobin) level, is an independent predictor of worse perioperative outcome.[16-18]

Glucotoxicity

Long-term tight control of blood glucose has been motivated by a theoretic concern about three potential glucotoxicities, in addition to the results from major randomized outcome studies involving diabetic patients.[5-13]

1. Glucose itself may be toxic because high levels can promote nonenzymatic glycosylation reactions that lead to the formation of abnormal proteins. These proteins may weaken endothelial junctions and decrease elastance, which is responsible for the stiff joint syndrome (and difficult intubation secondary to fixation of the atlanto-occipital joint), as well as decrease wound healing tensile strength.
2. Furthermore, elevations in glucose may increase macroglobulin production by the liver (which would increase blood viscosity) and promote intracellular swelling by favoring the production of nondiffusible, large molecules (e.g., sorbitol). Some drug therapies (e.g., aldose reductase inhibitors) endeavor to decrease intracellular swelling by inhibiting the formation of such large molecules.
3. Glycemia also disrupts autoregulation. Glucose-induced vasodilation prevents target organs from protecting against increases in systemic blood pressure. A glycosylated hemoglobin level of 8.1% is the threshold at which the risk for microalbuminuria increases logarithmically. A person with type 1 diabetes who has microalbuminuria of greater than 29 mg/day has an 80% chance of experiencing renal insufficiency. The threshold for glycemic toxicity differs for various vascular beds. For example, the threshold for retinopathy is a glycosylated hemoglobin value of 8.5% to 9.0% (12.5 mmol/L or 225 mg/dL), and that for cardiovascular disease is an average blood glucose value of 5.4 mmol/L (96 mg/dL). Thus, different degrees of hyperglycemia may be required before different vascular beds are damaged, or certain degrees of glycemia are associated with other risk factors for vascular disease. Another view is that perhaps severe hyperglycemia and microalbuminuria are simply concomitant effects of a common underlying cause. For instance, diabetic patients in whom microalbuminuria develops are more resistant to insulin, insulin resistance is associated with microalbuminuria in first-degree relatives of patients with type 2 diabetes, and persons who are normoglycemic but subsequently have clinical diabetes are at risk for atherogenesis before the onset of disease.

Diabetes itself may not be as important to perioperative outcome as are its end-organ effects. Epidemiologic studies segregated the effects of diabetes itself on the organ system from the effects of the complications of diabetes (e.g., cardiac, nervous system, renal, and vascular disease) and the effects of old age and the accelerated aging that diabetes causes. Even in patients requiring intensive care unit (ICU) management, long-standing diabetes does not appear to be as important an issue as the end-organ dysfunction that exists and the degree of glucose control in the perioperative or periprocedure and ICU periods.[8-13]

The World Health Organization's surgical safety checklist bundle suggests control with a target perioperative blood glucose concentration of 6 to 10 mmol/L (acceptable range, 4 to 12 mmol/L).[19] Poor perioperative glycemic control has a significant impact on the risk of postoperative infection across a variety of surgical specialities.[20] Different regimens permit almost any degree of perioperative control of blood glucose levels, but the tighter the control desired, the greater the risk of hypoglycemia. Therefore, debate regarding optimal control during the perioperative period has been extensive. Tight control retards all these glucotoxicities and may have other benefits in retarding the severity of diabetes itself.[5-13,21] Management of intraoperative glucose may be influenced by specific situations, such as the following: the type of operation, pregnancy,[22] expected global CNS insult, the bias of the patient's primary care physician, or the type of diabetes.

Much of the research on perioperative control is derived from studies in the ICU, as opposed to the operating

TABLE 39-1 RECOMMENDED GLUCOSE TARGET RANGES FOR INTENSIVE CARE PATIENTS AND RELATED SUBGROUPS

Society, Guideline	Patient Group	Trigger Blood Glucose Value to Start Insulin Infusion (mM [mg/dL])	Target range, (mM [mg/dL])	Rationale
Society of Critical Care Medicine's clinical practice guideline[26]	General recommendation	8.3 (150)	5.6-8.3 (100-150)	
	Cardiac surgical patients		<8.3 (150)	Decreased risk for deep sternal wound infection and death[73,118-121]
	Critically ill trauma patients	8.3 (150)	<10 (180)	
	Patients with traumatic brain injury	8.3 (150)	<10 (180)	
	Neurologic ICU patients Ischemic stroke Intraparenchymal hemorrhage Aneurysmal subarachnoid hemorrhage	8.3 (150)	<10 (180)	
American Diabetes Association guidelines[471]	General recommendation	10 (180)	7.8-10 (140-180)	
	Adaptation		6.1-7.8 (110-140)	Adjust to lower target range in documented low rate of severe hypoglycemia
American Association of Clinical Endocrinologists[472]	General recommendation		7.8-10 (140-180)	
	Surgical patients		Lower range	Only in units showing low rates of hypoglycemia
Surviving Sepsis Campaign[473]	General recommendation	10 (180)	<10 (180)	Based on the NICE-SUGAR study
Clinical Practical Guideline from the American College of Physicians[474]	General recommendation		7.8-11.1 (140-200)	If insulin infusion is applied; however, guideline does not recommend intensive insulin therapy
Spanish Society of Intensive Care Medicine and Coronary Units[476]	General recommendation		<8.3 (150)	
French Society of Anaesthesia and Intensive Care[475]	General recommendation		10 (180)	
	Surgical patients		<6.1 (110)	
	Cardiac patients		<6.1 (110)	
Society of Thoracic Surgeons[477]	Cardiac surgical patients		<10 (180) except <8.3 (150) for those with devices in place	

Data from Sebranek JJ, Lugli AK, Coursin DB: Glycaemic control in the perioperative period, Br J Anaesth *111(Suppl 1):i18-34, 2013; and Jacobi J, Bircher N, Krinsley J, et al: Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients,* Crit Care Med *40:3251-3276, 2012.*
ICU, Intensive care unit; *NICE-SUGAR,* Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation.

room. The first major trial demonstrating the benefit of tight glucose control was in medical ICU patients in Leuven, Belgium.[23] The most recent trial was from the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) group.[24] In this randomized controlled trial, the investigators examined the associations between moderate and severe hypoglycemia (blood glucose, 41 to 70 mg/dL [2.3 to 3.9 mmol/L] and ≤40 mg/dL [2.2 mmol/L, respectively) and death among 6026 critically ill patients in ICUs. Intensive glucose control leads to moderate and severe hypoglycemia, both of which are associated with an increased risk of death. The association exhibits a dose-response relationship and is strongest for death from distributive shock. The optimal perioperative management has been reviewed elsewhere.[25] Guidelines have been developed on the use of insulin infusions in the critical care unit to achieve these goals[26] (Table 39-1).

Diabetes and Accelerated Physiologic Aging

Adverse perioperative outcomes have repeatedly and substantially correlated with the age of the patient,[2,3,27-30] and diabetes does cause physiologic aging. When one translates the results of the Diabetes Control and Complications Trials into age-induced physiologic changes, a patient with type 1 diabetes who has poor control of blood glucose ages approximately 1.75 years physiologically for every chronologic year of the disease and 1.25 years if blood glucose has been controlled tightly.[27-29] A patient with type 2 diabetes ages approximately 1.5 years for every chronologic year of the disease and approximately 1.06 years with tight control of blood glucose and blood pressure.[6,27-29,31] Thus, when providing care for a diabetic patient, one must consider the associated risks to be those of a person who is much older physiologically; the physiologic age of a diabetic patient is considerably older than that person's calendar age just by virtue of having the disease.[1]

The pervasiveness of obesity and the lack of physical exercise seem to be major contributors to the increased prevalence of type 2 diabetes. As with type 1 diabetes, tight control of blood glucose, increased physical activity, and reduction in weight appear to reduce the accelerated aging associated with type 2 diabetes and even to delay the appearance of the disease and aging from it substantially.[27-29,31] Although such a reduction in aging should reduce the perioperative risk for diabetic patients, no controlled trials have confirmed this theory.

The key to managing blood glucose levels perioperatively in diabetic patients is to set clear goals and then monitor blood glucose levels frequently enough to adjust therapy to achieve these goals.

Other Conditions Associated With Diabetes

Diabetes is associated with microangiopathy (in retinal and renal vessels), peripheral neuropathy, autonomic dysfunction, and infection. Diabetic patients are often treated with angiotensin-converting enzyme (ACE) inhibitors, even in the absence of gross hypertension, in an effort to prevent the effects of disordered autoregulation, including renal failure.[5,6,32]

Preoperatively, assessment and optimization of treatment of the potential and potent end-organ effects of diabetes are at least as important as assessment of the diabetic patient's current overall metabolic status. The preoperative evaluation of diabetic patients is also discussed in Chapter 38.

The presence of autonomic neuropathy likely makes the operative period more hazardous and the postoperative period crucial to survival. Evidence of autonomic neuropathy may be routinely sought before the surgical procedure. Patients with diabetic autonomic neuropathy are at increased risk for gastroparesis (and consequent aspiration of gastric contents) and for perioperative cardiorespiratory arrest. Diabetic patients who exhibit signs of autonomic neuropathy, such as early satiety, lack of sweating, lack of pulse rate change with inspiration or orthostatic maneuvers, and impotence, have a very frequent incidence of painless myocardial ischemia,[15,33] as well as gastroparesis. Administration of metoclopramide, 10 mg preoperatively to facilitate gastric emptying of solids, may be helpful (Fig. 39-1). Interference with respiration or sinus automaticity by pneumonia or by anesthetic agents, pain medications, or sedative drugs is likely the precipitating cause in most cases of sudden cardiorespiratory arrest. Measuring the degree of sinus arrhythmia or beat-to-beat variability provides a simple, accurate test for significant autonomic neuropathy. The difference between the maximum and minimum heart rate on deep inspiration is normally 15 beats/minute, but it is 5 beats/minute or less in all patients who subsequently sustain cardiorespiratory arrest.[15,33]

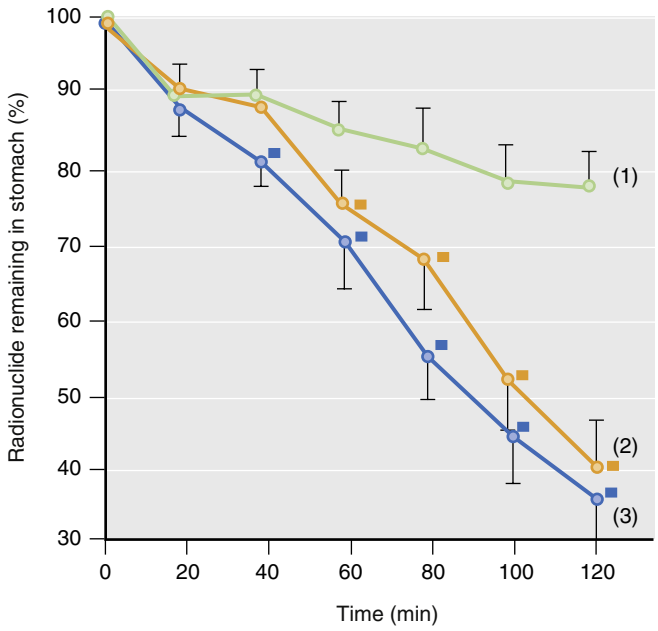


Figure 39-1. Gastric emptying time (mean ± standard deviation) of a solid test meal in three groups of patients: diabetic patients *(line 1)*, diabetic patients given metoclopramide (10 mg intravenously) 1.5 hours before the test meal *(line 2)*, and nondiabetic patients *(line 3)*. *(From Wright RA, Clemente R, Wathen R: Diabetic gastroparesis: an abnormality of gastric emptying of solids,* Am J Med Sci *289:240, 1985.)*

Other characteristics of patients with autonomic neuropathy include postural hypotension with a decrease in arterial blood pressure of more than 30 mm Hg, resting tachycardia, nocturnal diarrhea, and dense peripheral neuropathy. Diabetic patients with significant autonomic neuropathy may have impaired respiratory responses to hypoxia and are particularly susceptible to the action of drugs that have depressant effects. These patients may warrant very close, continuous cardiac and respiratory monitoring for 24 to 72 hours postoperatively, although such logical treatment has not been tested in a rigorous, controlled trial.[15] In the absence of autonomic neuropathy, outpatient surgery is preferred for a diabetic patient if possible (see Table 39-1).

Emergency Surgery

Many diabetic patients requiring emergency surgery for trauma or infection have significant metabolic decompensation, including ketoacidosis (see also Chapter 81). Frequently, little time is available to stabilize the patient, but even a few hours may be sufficient for correction of any fluid and electrolyte disturbances that are potentially life-threatening. It is futile to delay surgery in an attempt

to eliminate ketoacidosis completely if the underlying surgical condition will lead to further metabolic deterioration. The likelihood of intraoperative cardiac arrhythmias and hypotension resulting from ketoacidosis will be reduced if intravascular volume depletion and hypokalemia are at least partially treated.

Insulin therapy is initiated with a 10-unit intravenous bolus of regular insulin, followed by continuous insulin infusion. The rate of infusion is determined most easily if one divides the last serum glucose value by 150 (or 100 if the patient is receiving steroids, has an infection, or is considerably overweight [body mass index ≥35]). The actual amount of insulin administered is less important than is regular monitoring of glucose, potassium, and arterial pH. Because the number of insulin binding sites is limited, the maximum rate of decline in glucose is fairly constant and averages 75 to 100 mg/dL/hour, regardless of the dose of insulin.[34] During the first 1 to 2 hours of fluid resuscitation, the glucose level may decrease more precipitously. When serum glucose reaches 250 mg/dL, the intravenous fluid should include 5% dextrose.

The volume of intravenously administered fluid required varies with the overall deficit; it ranges from 3 to 5 L and may be as large as 10 L. Despite losses of water in excess of losses of solute, sodium levels are generally normal or reduced. Factitious hyponatremia caused by hyperglycemia or hypertriglyceridemia may result in this seeming contradiction. The plasma sodium concentration decreases by approximately 1.6 mEq/L for every 100 mg/dL increase in plasma glucose greater than normal. Initially, normal saline solution is infused at a rate of 250 to 1000 mL/hour, depending on the degree of intravascular volume depletion and cardiac status. Some measure of left ventricular volume should be monitored in diabetic patients who have a history of myocardial dysfunction. Approximately one third of the estimated fluid deficit is corrected during the first 6 to 8 hours and the remaining two thirds over the next 24 hours.

The degree of acidosis is determined by analysis of arterial blood gases and detection of an increased anion gap (see also Chapter 60).

Acidosis with an increased anion gap (≥16 mEq/L) in an acutely ill diabetic patient may be caused by ketones in ketoacidosis, lactic acid in lactic acidosis, increased organic acids from renal insufficiency, or all three disorders. In ketoacidosis, plasma levels of acetoacetate, β-hydroxybutyrate, and acetone are increased. Plasma and urinary ketones are measured semiquantitatively with Ketostix and Acetest tablets. The role of bicarbonate therapy in diabetic ketoacidosis is controversial. Myocardial function and respiration are known to be depressed at a blood pH lower than 7.0 to 7.10, yet rapid correction of acidosis with bicarbonate therapy may result in alterations in CNS function and structure. These alterations may be caused by (1) paradoxical development of cerebrospinal fluid and CNS acidosis from rapid conversion of bicarbonate to carbon dioxide and diffusion of the acid across the blood-brain barrier, (2) altered CNS oxygenation with decreased cerebral blood flow, and (3) the development of unfavorable osmotic gradients. After treatment with fluids and insulin, β-hydroxybutyrate levels decrease rapidly, whereas acetoacetate levels may remain stable or even increase before declining. Plasma acetone levels remain elevated for 24 to 42 hours, long after blood glucose, β-hydroxybutyrate, and acetoacetate levels have returned to normal; the result is continuing ketonuria.[34] Persistent ketosis with a serum bicarbonate level less than 20 mEq/L in the presence of a normal glucose concentration is an indication of the continued need for intracellular glucose and insulin for reversal of lipolysis.

The most important electrolyte disturbance in diabetic ketoacidosis is depletion of total-body potassium. Deficits range from 3 to 10 mEq/kg body weight. Serum potassium levels decline rapidly and reach a nadir within 2 to 4 hours after the start of intravenous insulin administration. Aggressive replacement therapy is required. The potassium administered moves into the intracellular space with insulin as the acidosis is corrected. Potassium is also excreted in urine because of the increased delivery of sodium to the distal renal tubules that accompanies volume expansion. Phosphorus deficiency in ketoacidosis as a result of tissue catabolism, impaired cellular uptake, and increased urinary losses may give rise to significant muscular weakness and organ dysfunction. The average phosphorus deficit is approximately 1 mmol/kg body weight. Replacement is needed if the plasma concentration decreases to less than 1.0 mg/dL.[34]

Anticipated Newer Treatments of Diabetes

At least three major changes in the care of diabetic patients have made it to the clinical trial stage:

- Implanted (like a pacemaker) glucose analyzer with electronic transmission to a surface (watch) monitor
- New islet transplantation medication that makes islet cell transplants much more successful and rejection medication less hazardous
- Medications such as INGAP (islet neogenesis–associated protein) peptide, which may cause regrowth of normally functioning islet cells (without the need for transplantation)

Some of these treatments may radically change the therapies used in the perioperative period. If regrowth of islet cells becomes common, type 1 diabetes could all but disappear; if implanted minute-to-minute glucose reading is possible, tight control may be much easier and more expected.

Insulinoma and Other Causes of Hypoglycemia

Hypoglycemia in persons not treated for diabetes is rare. Hypoglycemia in nondiabetic patients can be caused by such diverse entities as pancreatic islet cell adenoma or carcinoma, large hepatoma, large sarcoma, alcohol ingestion, use of β-adrenergic receptor blocking drugs, haloperidol therapy, hypopituitarism, adrenal insufficiency, altered physiology after gastric or gastric bypass surgery, hereditary fructose intolerance, ingestion of antidiabetic drugs, galactosemia, or autoimmune hypoglycemia.[35] The last four entities cause postprandial reactive hypoglycemia. Because restriction of oral intake prevents severe hypoglycemia, the practice of keeping the patient NPO (nothing by mouth) and infusing small amounts of a solution containing 5% dextrose greatly lessens the

possibility of perioperative postprandial reactive hypoglycemia. The other causes of hypoglycemia can cause serious problems during the perioperative period.[35]

Symptoms of hypoglycemia fall into one of two groups: adrenergic excess (tachycardia, palpitations, tremulousness, or diaphoresis) or neuroglycopenia (headache, confusion, mental sluggishness, seizures, or coma). All these symptoms may be masked by anesthesia, so blood glucose levels should be determined frequently in such patients to ensure that hypoglycemia is not present. Because manipulation of an insulinoma can result in massive insulin release, this tumor should probably be operated on only at centers equipped with a mechanical pancreas. Perioperative use of the somatostatin analogue octreotide, which suppresses insulin release from such tumors, makes the perioperative period a logarithm safer in anecdotal experience.

DISORDERS OF NUTRITION, INCLUDING OBESITY

Hyperlipoproteinemia, Hyperlipidemia, and Hypolipidemia

Hyperlipidemia may result from obesity, estrogen or corticoid therapy, uremia, diabetes, hypothyroidism, acromegaly, alcohol ingestion, liver disease, inborn errors of metabolism, or pregnancy. Hyperlipidemia may cause premature coronary or peripheral vascular disease or pancreatitis.

Coronary events can be decreased by treating individuals with even normal levels of low-density lipoprotein (LDL) cholesterol with the "statins" (3-hydroxy-3-methylglutaryl–coenzyme A [HMG-CoA] reductase inhibitors)—drugs that increase high-density lipoprotein (HDL) and decrease LDL cholesterol levels. This approach has markedly decreased the rate of myocardial reinfarction in high-risk patients.[36-38] Secondary prevention efforts were successful when these high-risk patients stopped smoking, reduced their arterial blood pressure, controlled stress, increased physical activity, and used aspirin, folate, β-blocking drugs, angiotensin inhibitors, diet, and other drugs to reduce their levels of LDL and increase their levels of HDL.

Although controlling the diet remains a major treatment modality for all types of hyperlipidemia, the drugs fenofibrate and gemfibrozil, which are used to treat hypertriglyceridemia, can cause myopathy, especially in patients with hepatic or renal disease; clofibrate is also associated with an increased incidence of gallstones. Cholestyramine binds bile acids, as well as oral anticoagulants, digitalis drugs, and thyroid hormones. Nicotinic acid causes peripheral vasodilation and should probably not be continued through the morning of the surgical procedure. Probucol (Lorelco) decreases the synthesis of apoprotein A-1; its use is associated on rare occasion with fetid perspiration or prolongation of the QT interval, or both, and sudden death in animals.

The West of Scotland Coronary Prevention Study and its congeners produced convincing evidence that drugs in the statin class prevent the morbidity and mortality related to arterial aging and vascular disease, as well as their consequences, such as coronary artery disease (CAD), stroke, and peripheral vascular insufficiency.[37] Thus, the statins—lovastatin (Mevacor), pravastatin (Pravachol), simvastatin, fluvastatin, atorvastatin (Lipitor), and rosuvastatin (Crestor)—are mainstays of therapy.

However, the report of Downs and co-workers from the Air Force/Texas Coronary Atherosclerosis Prevention Study went further.[37] This report showed a 37% reduction in the risk for first acute major coronary events in patients who had no risk factors and normal (average) LDL cholesterol levels. In this study lovastatin did not alter mortality rates, but that had been true for many early short-term trials with the statins. Although much of the effect of the statins has been attributed to their lipid-lowering effects, statins also influence endothelial function, inflammatory responses, plaque stability, and thrombogenicity. In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) released a new clinical practice guideline for the treatment of blood cholesterol in people at high risk for cardiovascular diseases.[39] They now advocate statin therapy for the following:

- Patients who have cardiovascular disease
- Patients with an LDL, or "bad" cholesterol, level of 190 mg/dL or higher
- Patients with type 2 diabetes who are between 40 and 75 years old
- Patients with an estimated 10-year risk of cardiovascular disease of 7.5% or higher who are between 40 and 75 years old (the report provides formulas for calculating 10-year risk)

Statins are drugs that block HMG-CoA reductase, the rate-limiting enzyme of cholesterol synthesis. Their use is occasionally accompanied by liver dysfunction, CNS dysfunction, and severe depression not related to the high cost of each drug and its congeners. Based on the available evidence, statin therapy should be continued in patients already taking these drugs.[40] Other drugs that reduce LDL and increase HDL cholesterol and decrease triglycerides are docosahexaenoic acid (an ω-3 fatty acid) and niacin. Statins also provide the substantial benefit of reversing inflammation in arteries, as evidenced by their ability to decrease highly specific C-reactive protein and pull cholesterol from plaque.[41]

Hypolipidemic conditions are rare diseases often associated with neuropathy, anemia, and renal failure. Although anesthetic experience with hypolipidemic conditions has been limited, some specific recommendations can be made: continuation of caloric intake and intravenous administration of protein hydrolysates and glucose should be continued throughout the perioperative period.

Obesity

Although many conditions associated with obesity (diabetes, hyperlipidemia, cholelithiasis, gastroesophageal reflux disease, cirrhosis, degenerative joint and disk disease, venous stasis and thrombotic or embolic disease, sleep disorders, and emotional and altered body image disorders) contribute to chronic morbidity in obese patients, the main concerns for the anesthesiologist have been the same since the 1970s—derangements of the cardiopulmonary system (see also Chapter 71).

Morbid obesity with minimal or no coexisting pulmonary conditions (e.g., no obesity-hypoventilation

syndrome or chronic obstructive pulmonary disease [COPD]) is referred to here as "simple" obesity. In simple obesity, the pathophysiology of mild alterations in daytime gas exchange and pulmonary function may also result from compression and restriction of the chest wall and diaphragm by excess adipose tissue.[42] Typically, in obese patients, the expiratory reserve volume and functional residual capacity are most affected and are reduced to 60% and 80% of normal, respectively.

Other Eating Disorders: Anorexia Nervosa, Bulimia, and Starvation

Many endocrine and metabolic abnormalities occur in patients with anorexia nervosa, a condition characterized by starvation to the point of 40% loss of normal weight, hyperactivity, and a psychiatrically distorted body image. Many anorectic patients exhibit impulsive behavior, including suicide attempts, and intravenous drug use is much more common than in the general population. Acidosis, hypokalemia, hypocalcemia, hypomagnesemia, hypothermia, diabetes insipidus, and severe endocrine abnormalities mimicking panhypopituitarism need attention before patients undergo anesthesia and surgery. Similar problems occur in bulimia (bulimorexia), a condition that may affect as many as 50% of female college students and is even unintentionally present in many older adults. As in severe protein deficiency (kwashiorkor), anorexia nervosa and bulimia may be accompanied by the following: alterations on the electrocardiogram (ECG), including a prolonged QT interval, atrioventricular (AV) block, and other arrhythmias; sensitivity to epinephrine; and cardiomyopathy.[43] Total depletion of body potassium makes the addition of potassium to glucose solutions useful; however, fluid administration can precipitate pulmonary edema in these patients. Esophagitis, pancreatitis, and aspiration pneumonia are more frequent in these patients, as is delayed gastric emptying. One review reported that in patients with severe anorexia with a body mass index less than 13 kg/m^2, marked hypoglycemia or leukocytopenia lower than 3.0 × 10^9/L, or both, potentially fatal complications frequently occur.[44] Accordingly, patients need strict nutritional support to avoid refeeding syndrome until the surgical procedure. Intraoperatively, glucose or catecholamine administration may lead to disturbance of electrolytes or fatal arrhythmia. Intensive care and early feeding as soon as possible postoperatively are important to prevent surgical site infection.

HYPERALIMENTATION (TOTAL PARENTERAL OR ENTERAL NUTRITION)

Hyperalimentation (i.e., total parenteral nutrition [TPN]) consists of concentrating hypertonic glucose calories in the normal daily fluid requirements (see also Chapter 106). The solutions contain protein hydrolysates, soybean emulsions (i.e., Intralipid), or synthetic amino acids (or any combination of these ingredients). The major benefits of TPN or enteral nutrition have been fewer complications postoperatively and shorter hospital stays for patients scheduled to have no oral feeding for 7 days or who were malnourished preoperatively.[45,46] Starker and colleagues found that the response to TPN, as monitored by serum albumin levels, predicted the postoperative outcome.[47] The group of patients demonstrating an increase in serum albumin concentrations from TPN had diuresis, weight loss, and fewer complications (1 of 15 patients) than did the group that gained weight and had a decrease in serum albumin (8 of 16 patients had 15 complications) (Fig. 39-2). The Veterans Administration (former name for Veterans Affairs [VA used for both]) studies also found that the serum albumin level was one of the most powerful predictors of perioperative outcome.[45]

The major complications of hyperalimentation are sepsis and metabolic abnormalities. The central lines used for TPN require application with an absolutely aseptic technique and should not be used routinely as an intravenous route for drug administration. Major metabolic complications of TPN relate to deficiencies and the development of hyperosmolar states. Complications of hypertonic dextrose can develop if the patient has insufficient insulin (diabetes mellitus) to metabolize the sugar or if insulin resistance occurs (e.g., because of uremia, burns, or sepsis).

A gradual decrease in the infusion rate of TPN prevents the hypoglycemia that can occur on abrupt discontinuance. Thus, the infusion rate of TPN should be decreased the night before anesthesia and surgery or should be continued throughout the operation at its current rate. The main reason for slowing or discontinuing TPN before anesthesia is to avoid intraoperative hyperosmolarity secondary to accidental rapid infusion of the solution or hypoglycemia if the infusion is discontinued because of high levels of endogenous insulin and lower levels of glucose present in the usual crystalloid solutions.[45] Hypophosphatemia is a particularly serious complication that results from the administration of phosphate-free or phosphate-depleted solutions for hyperalimentation.

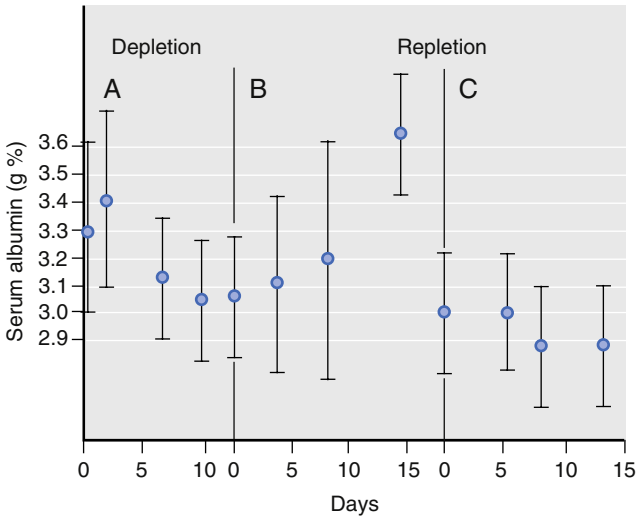


Figure 39-2. The response to hyperalimentation (*A,* repletion), as measured by variation in serum albumin levels, predicted the outcome of surgery. Patients who responded (*B*) to nutritional support with increased albumin levels had a significantly better outcome than did those whose albumin level did not increase (*C*). See the text for a more complete explanation. *(Modified from Starker PM, Group FE, Askanazi J, et al: Serum albumin levels as an index of nutritional support,* Surgery *91:194, 1982.)*

The low serum phosphate level causes a shift of the oxygen dissociation curve to the left. The resulting low 2,3-diphosphoglycerate and adenosine triphosphatase levels mean that cardiac output must increase for oxygen delivery to remain the same. Hypophosphatemia of less than 1.0 mg/dL of blood may cause hemolytic anemia, cardiac failure, tachypnea, neurologic symptoms, seizures, and death. In addition, long-term TPN is associated with deficiencies in trace metals such as copper (refractory anemia), zinc (impaired wound healing), and magnesium.

ADRENOCORTICAL MALFUNCTION

Three major classes of hormones—androgens, glucocorticoids, and mineralocorticoids—are secreted by the adrenal cortex. For each class, an excess or a deficiency of hormone produces a characteristic clinical syndrome. The widespread use of steroids can also make the adrenal cortex unable to respond normally to the demands placed on it by surgical trauma and subsequent healing. The increase in unindicated (scanning) computed tomography (CT) abdominal imaging procedures has meant that many adrenal masses have unfortunately been discovered only incidentally. These adrenal "incidentalomas," as they are termed because they were initially thought a nuisance discovered by unindicated body scans, have proved more serious. As many as 30% are hormonally active; in a review of 2000 such masses, 82% were not hormonally active, 5.3% proved to be cortisone-secreting adenomas, 5.1% were pheochromocytomas, 4.7% were adrenal carcinomas, 2.5% were unsuspected metastatic disease, and 1% were aldosterone-secreting adenomas. Incidentalomas may therefore require serious pursuit. Several points relative to adrenal cortical management deserve attention.

Controlled comparisons of the perioperative management of patients who have disorders of adrenal function are lacking, although steroids are used more and more commonly, with the results of some controlled trials available for specific uses. However, a review of the possible pathophysiologic changes in the adrenal cortex and techniques for their management should enable physicians to improve the perioperative care of patients with adrenal abnormalities.

Physiologic Properties of Adrenocortical Hormones

Androgens. Androstenedione and dehydroepiandrosterone, weak androgens arising from the adrenal cortex, constitute major sources of androgen in women (and have gained prominence for their use or abuse by baseball players seeking to hit more home runs). Excess secretion of androgen causes masculinization, pseudopuberty, or female pseudohermaphroditism. With some tumors, androgen is converted to an estrogenic substance, in which case feminization results. No special anesthetic evaluation is needed for such patients. Some congenital enzyme defects that cause androgen abnormalities also result in glucocorticoid and mineralocorticoid abnormalities that should be evaluated preoperatively. Most of these patients are treated with exogenous glucocorticoids and mineralocorticoids and consequently require supplementation of these hormones perioperatively (see later).

Glucocorticoids. The principal glucocorticoid, cortisol, is an essential regulator of carbohydrate, protein, lipid, and nucleic acid metabolism. Cortisol exerts its biologic effects through a sequence of steps initiated by binding of hormone to stereospecific intracellular cytoplasmic receptors. This bound complex stimulates nuclear transcription of specific mRNA molecules. These molecules are then translated to give rise to proteins that mediate the ultimate effects of hormones.

Most cortisol is bound to corticosterone-binding globulin (CBG, transcortin). The relatively small amounts of unbound cortisol enter cells to induce actions or to be metabolized. Conditions that induce changes in the amount of CBG include liver disease and nephrotic syndrome, both of which result in decreased circulating levels of CBG, and estrogen administration and pregnancy, which result in increased CBG production. Total serum cortisol levels may become elevated or depressed under conditions that alter the amount of bound cortisol, and yet the unbound, active form of cortisol is present in normal amounts. The most accurate measure of cortisol activity is the level of urinary cortisol (i.e., the amount of unbound, active cortisol filtered by the kidney).

The serum half-life of cortisol is 80 to 110 minutes. However, because cortisol acts through intracellular receptors, pharmacokinetic data based on serum levels are not good indicators of cortisol activity. After a single dose of glucocorticoid, serum glucose is elevated for 12 to 24 hours; improvement in pulmonary function in patients with bronchial asthma can still be measured 24 hours after glucocorticoid administration. Treatment schedules for glucocorticoid replacement are therefore based not on the measured serum half-life but on the well-documented prolonged end-organ effect of these steroids. Hospitalized patients requiring long-term glucocorticoid replacement therapy are usually treated twice daily, with a slightly higher dose given in the morning than in the evening to simulate the normal diurnal variation in cortisol levels. For patients who require parenteral "steroid coverage" during and after surgery (see later paragraphs), administration of glucocorticoid every 12 hours is appropriate.[48] The relative potencies of glucocorticoids are listed in Table 39-2. Cortisol is inactivated

TABLE 39-2 RELATIVE POTENCIES AND EQUIVALENT DOSES FOR COMMONLY USED GLUCOCORTICOIDS

Steroids	Relative Glucocorticoid Potency	Equivalent Glucocorticoid Dose (mg)
Short Acting		
Cortisol (hydrocortisone)	1.0	20.0
Cortisone	0.8	25.0
Prednisone	4.0	5.0
Prednisolone	4.0	5.0
Methylprednisolone	5.0	4.0
Intermediate Acting		
Triamcinolone	5.0	4.0
Long Acting		
Betamethasone	25.0	0.60
Dexamethasone	30.0	0.75

Data from Axelrod L: Glucocorticoid therapy, Medicine (Baltimore) *55:39, 1976.*

primarily in the liver and is excreted as 17-hydroxycorticosteroid. Cortisol is also filtered and excreted unchanged into urine.

The synthetic glucocorticoids vary in their binding specificity in a dose-related manner. When given in supraphysiologic doses (>30 mg/day), cortisol and cortisone bind to mineralocorticoid receptor sites and cause salt and water retention and loss of potassium and hydrogen ions. When these steroids are administered in maintenance doses of 30 mg/day or less, patients require a specific mineralocorticoid for electrolyte and volume homeostasis. Many other steroids do not bind to mineralocorticoid receptors, even at high doses, and have no mineralocorticoid effect (see Table 39-2).

Secretion of glucocorticoids is regulated by pituitary adrenocorticotropic hormone (ACTH). ACTH is synthesized from a precursor molecule (pro-opiomelanocortin) that is metabolized to form an endorphin (β-lipotropin) and ACTH. Episodic secretion of ACTH has a diurnal rhythm that is normally greatest during the early morning hours in men and later in women and is regulated at least in part by light-dark cycles. Its secretion is stimulated by release of corticotropin-releasing factor (CRF) from the hypothalamus. (An abnormality in the diurnal rhythm of corticoid secretion has been implicated as a cause of so-called jet lag.) Cortisol and other glucocorticoids exert negative feedback at both the pituitary and hypothalamic levels to inhibit the secretion of ACTH and CRF. If the CRF- or ACTH-producing cells are destroyed, the adrenal gland takes more than 30 days to atrophy to the point at which short-term administration of exogenous ACTH will cause almost no adrenal responsiveness.

Mineralocorticoids. Aldosterone, the major mineralocorticoid secreted in humans, comes from the zona glomerulosa of the adrenal cortex and causes reabsorption of sodium and secretion of potassium and hydrogen ions, thereby contributing to electrolyte and volume homeostasis. This action is most prominent in the distal renal tubule but also occurs in the salivary and sweat glands. The major regulator of aldosterone secretion is the renin-angiotensin system. Juxtaglomerular cells in the cuff of renal arterioles are sensitive to decreased renal perfusion pressure or volume and, consequently, secrete renin. Renin transforms the precursor angiotensinogen (from the liver) into angiotensin I, which is further converted by a converting enzyme, primarily in the lung, to angiotensin II. Angiotensin II binds to specific receptors to increase mineralocorticoid secretion, which is also stimulated by an increased potassium concentration and, to a lesser degree, by ACTH.

Adrenocortical Hormone Excess

Glucocorticoid Excess. Glucocorticoid excess (Cushing syndrome) resulting from either endogenous oversecretion or long-term treatment with glucocorticoids at higher than physiologic doses produces a moon-faced plethoric individual with a centripetal distribution of fat (truncal obesity and skinny extremities), thin skin, easy bruising, and striae. Muscle wasting is common, but the heart and diaphragm are usually spared. A test for this syndrome is to ask the patient to get up from a chair without using the hands. An inability to do so indicates proximal muscle weakness consistent with Cushing syndrome. These patients often have osteopenia as a result of decreased formation of bone matrix and impaired absorption of calcium. Fluid retention and hypertension (because of increases in renin substrate and vascular reactivity caused by glucocorticoid) are common. Such patients may also have hyperglycemia and even diabetes mellitus from inhibition of peripheral use of glucose, as well as antiinsulin action and concomitant stimulation of gluconeogenesis (Table 39-3).

The most common cause of Cushing syndrome is the administration of glucocorticoids for such conditions as arthritis, asthma, and allergies. In these conditions, the adrenal glands atrophy and cannot respond to stressful situations (e.g., the preoperative and preprocedure period) by secreting more steroid. Thus, additional glucocorticoids may be required perioperatively (see the later section "Patients Taking Steroids for Other Reasons"). Spontaneous Cushing syndrome may be caused by pituitary production of ACTH (65% to 75% of all spontaneous cases), which is usually associated with pituitary microadenoma, or by nonendocrine ectopic ACTH production (principally by tumors of the lung, pancreas, or thymus).[49] Ten percent to 20% of cases of spontaneous Cushing syndrome are caused by an ACTH-independent process, either an adrenal adenoma or carcinoma.

Special preoperative and preprocedure considerations for patients with Cushing syndrome include regulating diabetes and hypertension and ensuring that intravascular fluid volume and electrolyte concentrations are normal. Ectopic ACTH production may cause marked hypokalemic alkalosis. Treatment with the aldosterone antagonist spironolactone stops the potassium loss and helps mobilize excess fluid. Because of the high incidence of severe osteopenia and the risk of fractures, meticulous attention must be paid to positioning of the patient. In addition,

TABLE 39-3 CLINICAL FEATURES OF HYPERADRENALISM (CUSHING SYNDROME) AND HYPOADRENALISM

Cushing Syndrome	Hypoadrenalism
Central obesity	Weight loss
Proximal muscle weakness	Weakness, fatigue, lethargy
Osteopenia at a young age	Muscle and joint pain and back pain
Hypertension	Postural hypotension and dizziness
Headache	Headache
Psychiatric disorders	Anorexia, nausea, abdominal pain, constipation, diarrhea
Purple striae	
Spontaneous ecchymoses	
Plethoric facies	
Hyperpigmentation	Hyperpigmentation
Hirsutism	
Acne	
Hypokalemic alkalosis	Hyperkalemia, hyponatremia
Glucose intolerance	Occasional hypoglycemia
Kidney stones	Hypercalcemia
Polyuria	Prerenal azotemia
Menstrual disorders	
Increased leukocyte count	

glucocorticoids are lympholytic and immunosuppressive and thus increase the patient's susceptibility to infection. The tensile strength of healing wounds decreases in the presence of glucocorticoids, an effect that is at least partially reversed by the topical administration of vitamin A.

Specific considerations pertain to the surgical approach for each cause of Cushing syndrome. For example, nearly three fourths of cases of spontaneous Cushing disease result from a pituitary adenoma that secretes ACTH. In the experience of Dr. Michael Roizen, a previous author of this chapter in earlier editions, perioperative treatment of patients who have Cushing disease and a pituitary microadenoma differs from that of patients who have a pituitary adenoma associated with amenorrhea and galactorrhea. A patient with Cushing disease is inclined to bleed more easily and (on the basis of anecdotal evidence) tends to have higher central venous pressure (CVP). Thus, during transsphenoidal tumor resection in such patients, routine practice is to monitor CVP and maintain it at the low end of the normal range. In other cases of transsphenoidal resection of microadenoma, such monitoring is needed only infrequently.

Ten percent to 15% of patients with Cushing syndrome exhibit adrenal overproduction of glucocorticoids from an adrenal adenoma or carcinoma. If either unilateral or bilateral adrenal resection is planned, the physician should begin administering glucocorticoids at the start of resectioning of the tumor. Despite the absence of definitive studies, 100 mg of hydrocortisone hemisuccinate or hydrocortisone phosphate every 24 hours intravenously is reasonable. This amount can be reduced over a period of 3 to 6 days until a maintenance dose is reached. Beginning on day 3, the surgeons may also give a mineralocorticoid, 9α-fluorocortisol (0.05 to 0.1 mg/day). In certain patients, both steroids may require several adjustments. This therapy continues if the patient has undergone bilateral resection. For a patient who has undergone unilateral adrenal resection, therapy is individualized according to the status of the remaining adrenal gland. The incidence of pneumothorax in open adrenal resection approach can be as high as 20%; the diagnosis of pneumothorax is sought and treatment is initiated before the wound is closed. The use of the laparoscopic technique has markedly decreased this complication.

Bilateral adrenalectomy in patients with Cushing syndrome is associated with a high incidence of postoperative complications and a perioperative mortality rate (higher than that of even cardiac surgery) of 5% to 10%; this procedure often results in permanent mineralocorticoid and glucocorticoid deficiency. Ten percent of patients with Cushing syndrome who undergo adrenalectomy have an undiagnosed pituitary tumor. After cortisol concentrations are decreased by adrenalectomy, the pituitary tumor will likely enlarge. These pituitary tumors are potentially invasive and may produce large amounts of ACTH and melanocyte-stimulating hormone, thereby increasing pigmentation.

Approximately 85% of adrenal tumors are discovered incidentally during screening CT scans. Nonfunctioning adrenal adenomas are found in patients on autopsy, ranging from 1% to 32% in different series. Functioning adenomas are generally treated surgically; often, the contralateral gland resumes functioning after several months. Frequently, however, the effects of carcinomas are not cured surgically. In such cases, administration of inhibitors of steroid synthesis, such as metyrapone or mitotane (*o*,*p*′-DDD[2,2-bis(2-chlorophenyl4-chlorophenyl)-1, 1-dichloroethane]), may ameliorate some symptoms but may not improve survival. These drugs and specific aldosterone antagonists may aid in reducing symptoms in the case of ectopic ACTH secretion if the primary tumor proves unresectable. Patients given these adrenal suppressants are also prescribed long-term glucocorticoid replacement therapy (i.e., the goal of therapy is complete adrenal suppression). These patients should be considered to have suppressed adrenal function, and glucocorticoid replacement should be increased perioperatively.

Mineralocorticoid Excess. Excess mineralocorticoid activity (common with glucocorticoid excess because most glucocorticoids have some mineralocorticoid properties) leads to potassium depletion, sodium retention, muscle weakness, hypertension, tetany, polyuria, inability to concentrate urine, and hypokalemic alkalosis. These symptoms constitute primary hyperaldosteronism, or Conn syndrome (a cause of low-renin hypertension because renin secretion is inhibited by the effects of the high levels of aldosterone).

Primary hyperaldosteronism is present in 0.5% to 1% of hypertensive patients who have no other known cause of hypertension. Primary hyperaldosteronism most often results from unilateral adenoma, although 25% to 40% of patients have been found to have bilateral adrenal hyperplasia. Intravascular fluid volume, electrolyte concentrations, and renal function should be restored to within normal limits preoperatively by administering the aldosterone antagonist spironolactone. The effects of spironolactone are slow in onset and increase for 1 to 2 weeks. A patient who has a serum potassium level of 2.9 mEq/L may have a total-body potassium deficit of as little as 40 mEq or as much as 400 mEq. Frequently, a period of at least 24 hours is required to restore potassium equilibrium. A normal serum potassium level does not necessarily imply correction of a total-body deficit of potassium. In addition, patients with Conn syndrome have a high incidence of hypertension and ischemic heart disease; hemodynamic monitoring should be appropriate for the degree of cardiovascular impairment.

A retrospective anecdotal study indicated that intraoperative hemodynamic status was more stable when arterial blood pressure and electrolytes were controlled preoperatively with spironolactone than when other antihypertensive drugs were used. However, the efficacy of optimizing the perioperative status of patients who have disorders of glucocorticoid or mineralocorticoid secretion has not been clearly established. We have assumed that gradual restoration of a normal condition is good medicine and that it would decrease perioperative morbidity and mortality.

Adrenocortical Hormone Deficiency

Glucocorticoid Deficiency. Withdrawal of steroids or suppression of synthesis by steroid therapy is the leading cause of underproduction of corticosteroids. Management of this type of glucocorticoid deficiency is discussed in the later section "Patients Taking Steroids for Other

Reasons". Other causes of adrenocortical insufficiency include the following: defects in ACTH secretion and destruction of the adrenal gland by autoimmune disease, tuberculosis, hemorrhage, or cancer; some forms of congenital adrenal hyperplasia (see previous discussion); and administration of cytotoxic drugs.

Primary adrenal insufficiency (Addison disease) is associated with local destruction of all zones of the adrenal cortex and results in both glucocorticoid and mineralocorticoid deficiency if the insufficiency is bilateral; common symptoms and signs are listed in Table 39-3. Autoimmune disease is the most common cause of primary (nonexogenous) bilateral ACTH deficiency in the United States, whereas tuberculosis is the most common cause worldwide. Tuberculosis is associated with decreased adrenal function but large adrenal glands, as is also common in sarcoidosis, histoplasmosis, amyloidosis, metastatic malignant disease, and adrenal hemorrhage. Destruction or partial destruction by trauma and by human immunodeficiency virus (HIV) and other infections, such as cytomegalovirus, mycobacteria, and fungi, is being recognized more frequently.

An increasingly common cause of adrenal insufficiency associated with large adrenal glands is heparin-induced thrombocytopenia, which may be considered in every patient who has received heparin and has hypotension.

Autoimmune destruction of the adrenal glands may be associated with other autoimmune disorders, such as some forms of type 1 diabetes and Hashimoto thyroiditis. Enzymatic defects in cortisol synthesis also cause glucocorticoid insufficiency, compensatory elevations in ACTH, and congenital adrenal hyperplasia. Because adrenal insufficiency usually develops slowly, such patients are subject to marked pigmentation (from excess ACTH trying to stimulate an unproductive adrenal gland) and cardiopenia (apparently secondary to chronic hypotension).

Secondary adrenal insufficiency occurs when ACTH secretion is deficient, often because of a pituitary or hypothalamic tumor. Treatment of pituitary tumors by surgery or radiation therapy may result in hypopituitarism and subsequent adrenal failure.

If unstressed, glucocorticoid-deficient patients usually have no perioperative problems. However, acute adrenal crisis (addisonian crisis) can occur when even a minor stress is present (e.g., upper respiratory infection). Preparation of such a patient for anesthesia and surgery should include treatment of hypovolemia, hyperkalemia, and hyponatremia. Because these patients cannot respond to stressful situations, it was traditionally recommended that they be given a stress dose of glucocorticoids (≈200 mg hydrocortisone/70 kg body weight/day) perioperatively. However, Symreng and colleagues gave 25 mg of hydrocortisone phosphate intravenously to adults at the start of the operative procedure, followed by 100 mg intravenously over the next 24 hours.[50] Because using the minimum drug dose that would produce an appropriate effect is desirable, this latter regimen seems attractive. Such a regimen has proved to be as successful as a regimen using maximum doses (≈300 mg hydrocortisone/70 kg body weight/day—see the later section "Patients Taking Steroids for Other Reasons"). Thus, we now recommend giving 100 mg of hydrocortisone phosphate intravenously every 24 hours.

Mineralocorticoid Deficiency. Hypoaldosteronism, a less common condition, can be congenital or can occur after unilateral adrenalectomy or prolonged administration of heparin. In addition, it can also be a consequence of long-standing diabetes and renal failure. Nonsteroidal inhibitors of prostaglandin synthesis may also inhibit renin release and exacerbate this condition in patients with renal insufficiency. Plasma renin activity is lower than normal and fails to increase appropriately in response to sodium restriction or diuretic drugs. Most symptoms are caused by hyperkalemic acidosis rather than hypovolemia; in fact, some patients are hypertensive. These patients can have severe hyperkalemia, hyponatremia, and myocardial conduction defects. These defects can be treated successfully by administering mineralocorticoids (9α-fluorocortisol, 0.05 to 0.1 mg/day) preoperatively. Doses must be carefully titrated and monitored to avoid an increase in hypertension.

Patients Taking Steroids for Other Reasons

Perioperative Stress and the Need for Corticoid Supplementation. The adrenal responses of normal patients to the perioperative period, as well as those responses of patients taking steroids for other diseases, indicate the following:

1. Perioperative stress is related to the degree of trauma and the depth of anesthesia. Deep general or regional anesthesia delays the usual intraoperative glucocorticoid surge to the postoperative period.
2. A few patients with suppressed adrenal function will have perioperative cardiovascular problems if they do not receive supplemental steroids perioperatively.
3. Although a patient who takes steroids on a long-term basis may become hypotensive perioperatively, glucocorticoid or mineralocorticoid deficiency is rarely the cause.
4. Acute adrenal insufficiency rarely occurs, but it can be life-threatening.
5. Giving these patients steroid coverage equivalent to 100 mg of hydrocortisone hemisuccinate perioperatively has little risk.

In a well-controlled study of glucocorticoid replacement in nonhuman primates, the investigators clearly defined the life-threatening events that can be associated with inadequate perioperative corticosteroid replacement.[48] An alternative dose regimen has altered management methods that will likely improve patients' safety. In this study, adrenalectomized primates and sham-operated controls were given physiologic doses of steroids for 4 months. The animals were then randomly allocated to groups that received subphysiologic (one tenth of the normal cortisol production), physiologic, or supraphysiologic (10 times the normal cortisol production) doses of cortisol for 4 days preceding abdominal surgery (cholecystectomy). Hemodynamic variables were measured by means of arterial and pulmonary artery catheters. The animals were maintained on their randomized dosage schedules during and after the surgical procedures. The group given subphysiologic doses of steroid perioperatively had a significant increase in postoperative mortality. Death rates

TABLE 39-4 RECOVERY OF HYPOTHALAMIC-PITUITARY-ADRENAL FUNCTION AFTER WITHDRAWAL OF STEROIDS

Recovery Time (mo)	Plasma 17-Hydroxycorticoid Values	Plasma ACTH Values	Adrenal Response to Exogenous ACTH	Response to Metyrapone
1	Low*	Low	Low	Low
2-5	Low	High†	Low	Low
6-9	Normal	Normal	Low	Low
>9	Normal	Normal	Normal	Normal

Data from Graber AL, Ney RI, Nicholson WE, et al: Natural history of pituitary-adrenal recovery following long-term suppression with corticosteroids, J Clin Endocrinol Metab *25:11, 1965.*

ACTH, Adrenocorticotropic hormone.

*Various subjective manifestations of mild adrenal insufficiency occur during this stage.

†The diurnal rhythm of plasma concentrations is qualitatively normal during this stage.

for the physiologic and supraphysiologic replacement groups were the same and did not differ from the rate for sham-operated controls. Death in the subphysiologic replacement group was related to severe hypotension associated with a significant decrease in systemic vascular resistance and a reduced left ventricular stroke work index. Filling pressures of the heart were unchanged when compared with those in control animals. No evidence of hypovolemia or severe CHF was observed. Despite the low systemic vascular resistance, the animals did not become tachycardic. All these responses are compatible with the previously documented interaction of glucocorticoids and catecholamines and thus suggest that glucocorticoids mediate catecholamine-induced increases in cardiac contractility and maintenance of vascular tone.

The investigators used a sensitive measure of wound healing involving accumulation of hydroxyproline. All treatment groups, including the group given supraphysiologic doses of glucocorticoids, had the same capacity for wound healing. Furthermore, perioperative administration of supraphysiologic doses of corticosteroids produced no adverse metabolic consequences.

This well-conducted study confirms several longstanding intuitive impressions concerning patients who have inadequate adrenal function as a result of either underlying disease or administration of exogenous steroids. Inadequate replacement of corticosteroids perioperatively can lead to addisonian crisis and death. Administration of supraphysiologic doses of steroids for a short time perioperatively caused no discernible complications. However, at least theoretic negative consequences can occur when large doses of steroids are given (see later). It is clear that inadequate corticosteroid coverage can cause death. What is not so clear is what dose of steroid should be recommended for replacement therapy. Yong and colleagues reviewed the randomized controlled trials for a Cochrane Systemic Review and reported only 2 trials involving 37 patients that met the inclusion criteria.[51] These studies reported that supplemental perioperative steroids were not required during surgery for patients with adrenal insufficiency, but neither study reported any adverse effects or complications in the intervention and control groups. The authors concluded that they were unable to support or refute the use of supplemental perioperative steroids for patients with adrenal insufficiency during surgery.

Because the risk is low, physicians should consider providing supplementation for any patient who has received steroids within a year.[48,50] Data indicate that topical application of steroids (even without the use of occlusive dressings) can suppress normal adrenal responses for as long as 9 months to 1 year (Table 39-4).

How can one determine when adrenal responsiveness has returned to normal? The morning plasma cortisol level does not reveal whether the adrenal cortex has recovered sufficiently to ensure that cortisol secretion will increase adequately to meet the demands of stress. Inducing hypoglycemia with insulin has been advocated as a sensitive test of pituitary-adrenal competence, but it is impractical and is probably a more dangerous practice than simply administering glucocorticoids. If the plasma cortisol concentration is measured during acute stress, a value of greater than 25 μg/dL assuredly (and a value >15 μg/dL probably) indicates normal pituitary-adrenal responsiveness. In another test of pituitary-adrenal sufficiency, the baseline plasma cortisol level is determined. Then, 250 μg of synthetic ACTH (cosyntropin) is given, and plasma cortisol is measured 30 to 60 minutes later. An increase in plasma cortisol of 6 to 20 μg/dL or more is normal.[52,53] A normal response indicates recovery of pituitary-adrenal axis function. A lesser response usually indicates pituitary-adrenal insufficiency, possibly requiring perioperative supplementation with steroids.

It is unusual for laboratory data defining pituitary-adrenal adequacy to be available preoperatively. Rather than delay surgery or test most patients, we assume that any patient who has taken steroids at any time during the preceding year has suppressed pituitary-adrenal function and will require perioperative supplementation.

Under perioperative conditions, the adrenal glands secrete 116 to 185 mg of cortisol daily. Under maximum stress, they may secrete 200 to 500 mg/day. Good correlation exists between the severity and duration of the operation and the response of the adrenal gland. "Major surgery" would be represented by procedures such as laparoscopic colectomy and "minor surgery" by procedures such as herniorrhaphy. In a study of 20 patients during major surgery, the mean maximal concentration of cortisol in plasma was 47 μg/dL (range, 22 to 75 μg/dL). Values remained higher than 26 μg/dL for a maximum of 72 hours postoperatively. During minor surgery, the mean maximal concentration of cortisol in plasma was 28 μg/dL (range, 10 to 44 μg/dL).

Although the precise amount required has not been established, we usually intravenously administer the maximum amount of glucocorticoid that the body manufactures in response to maximal stress (i.e., approximately 200 mg/day of hydrocortisone phosphate/70 kg body weight). For minor surgical procedures, we usually give hydrocortisone phosphate intravenously, 100 mg/day/70 kg body weight. Unless infection or some other perioperative complication develops, we decrease this dose by approximately 25% per day until oral intake can be resumed. At this point, the usual maintenance dose of glucocorticoids can be administered.

Risks of Supplementation. Rare complications of perioperative steroid supplementation include aggravation of hypertension, fluid retention, inducement of stress ulcers, and psychiatric disturbances. Two common complications of short-term perioperative supplementation with glucocorticoids are abnormal wound healing and an increased rate of infections. This evidence is inconclusive, however, because it relates to short-term glucocorticoid administration and not to long-term administration of glucocorticoids with increased doses at times of stress. In contrast to a deleterious effect of perioperative glucocorticoid administration on wound healing in rats, a study involving primates suggested that large doses of glucocorticoids, administered perioperatively, do not impair sensitive measures of wound healing.[48] An overall assessment of these results suggests that short-term perioperative supplementation with steroids has a small but definite deleterious effect on wound healing that is perhaps partially reversed by topical administration of vitamin A.

Information on the risk of infection from perioperative glucocorticoid supplementation is also unclear. In many studies of long-term use by patients and supplementation, no increased risk of serious infections was reported with long-term use of steroids alone. Data indicate that the risk of infection in a patient taking steroids on a long-term basis is real, but whether perioperative supplementation with steroids increases that risk is not clear.

Adrenal Cortex Function in Older Adults

Production of androgens by the adrenal gland progressively decreases with age; this change has no known implications for anesthesia (see also Chapter 80). Plasma levels of cortisol are unaffected by increasing age. Levels of CBG are also unaffected by age, a finding suggesting that a normal fraction of free cortisol (1% to 5%) is present in older patients. Older patients have a progressively impaired ability to metabolize and excrete glucocorticoids. In normal individuals, the quantity of 17-hydroxycorticosteroids excreted is reduced by half by the seventh decade. This decreased excretion undoubtedly reflects the reduced renal function that occurs with aging. When excretion of cortisol metabolites is expressed as a function of creatinine clearance, the age difference disappears. Further reductions in cortisol clearance may reflect impaired hepatic metabolism of circulating cortisol.

The rate of secretion of cortisol is 30% slower in older adults. This reduced secretion may be an appropriate compensatory mechanism for maintaining a normal cortisol level in the presence of decreased hepatic and renal clearance of cortisol. The reduced cortisol production can be overcome during periods of stress, and even extremely old patients (>100 years old) display an entirely normal adrenal response to the administration of ACTH and to stresses such as hypoglycemia.

Both underproduction and overproduction of glucocorticoids are generally considered diseases of younger individuals. The highest incidence of Cushing disease of either pituitary or adrenal origin occurs during the third decade of life. The most common cause of spontaneous Cushing disease is benign pituitary adenoma. However, in patients older than 60 years in whom Cushing disease develops, the most likely cause is adrenal carcinoma or ectopic ACTH production from tumors usually located in the lung, pancreas, or thymus.

ADRENAL MEDULLARY SYMPATHETIC HORMONE EXCESS: PHEOCHROMOCYTOMA

Less than 0.1% of all cases of hypertension are caused by pheochromocytomas, or catecholamine-producing tumors derived from chromaffin tissue.[54] Nevertheless, these tumors are clearly important to the anesthesiologist inasmuch as 25% to 50% of hospital deaths in patients with pheochromocytoma occur during induction of anesthesia or during operative procedures for other causes.[55] Although usually found in the adrenal medulla, these vascular tumors can occur anywhere, such as in the right atrium, the spleen, the broad ligament of the ovary, or the organs of Zuckerkandl at the bifurcation of the aorta. Malignant spread, which occurs in less than 15% of pheochromocytomas, usually proceeds to venous and lymphatic channels with a predisposition for the liver. This tumor is occasionally familial or part of the pluriglandular-neoplastic syndrome known as multiple endocrine adenoma type IIa or type IIb and is manifested as an autosomal dominant trait. Type IIa consists of medullary carcinoma of the thyroid, parathyroid adenoma or hyperplasia, and pheochromocytoma. What used to be called type IIb is now often called pheochromocytoma in association with phakomatoses such as von Recklinghausen neurofibromatosis and von Hippel–Lindau disease with cerebellar hemangioblastoma. Frequently, bilateral tumors are found in the familial form. Localization of tumors can be achieved by MRI or CT, metaiodobenzylguanidine (MIBG) nuclear scanning, ultrasonography, or intravenous pyelography (in decreasing order of combined sensitivity and specificity).

Symptoms and signs that may be solicited before surgery or procedures and are suggestive of pheochromocytoma are as follows: excessive sweating; headache; hypertension; orthostatic hypotension; previous hypertensive or arrhythmic response to induction of anesthesia or to abdominal examination; paroxysmal attacks of sweating, headache, tachycardia, and hypertension; glucose intolerance; polycythemia; weight loss; and psychological abnormalities. In fact, the occurrence of combined symptoms of paroxysmal headache, sweating, and hypertension is probably a more sensitive and specific indicator than any one biochemical test for pheochromocytoma

TABLE 39-5 **CHARACTERISTICS OF TESTS FOR PHEOCHROMOCYTOMA**

Test/Symptoms	Sensitivity (%)	Specificity (%)	Likelihood Ratio	
			Positive Result*	Negative Result†
Vanillylmandelic acid excretion	81	97	27.0	0.20
Catecholamine excretion	82	95	16.4	0.19
Metanephrine excretion	83	95	16.6	0.18
Abdominal computed tomography	92	80	4.6	0.10
Concurrent paroxysmal hypertension, headache, sweating, and tachycardia‡	90	95	18.0	0.10

Modified from Pauker SG, Kopelman RI: Interpreting hoofbeats: can Bayes help clear the haze? N Engl J Med *327:1009, 1992.*
*The ratio representing the likelihood of a positive result is obtained by dividing the sensitivity by 1 and then subtracting the specificity.
†The ratio representing the likelihood of a negative result is obtained by subtracting the sensitivity from 1 and the dividing by the specificity.
‡Data for concurrent paroxysmal symptoms are best estimates from available data.

(Table 39-5). Despite more than 2000 articles in the literature on pheochromocytoma, little is known about what factors in care affect perioperative morbidity.

The value of preoperative and preprocedure use of adrenergic receptor blocking drugs probably justifies the use of such drugs preoperatively. These drugs probably reduce the complications of hypertensive crisis, the wide arterial blood pressure fluctuations during manipulation of the tumor (especially until venous drainage is obliterated), and the myocardial dysfunction that occurs perioperatively. Mortality is decreased with resection of pheochromocytoma (from 40% to 60% to the current 0% to 6%) when adrenergic receptor blockade is introduced as preoperative and preprocedure preparatory therapy for such patients.[56-60]

α-Adrenergic receptor blockade with prazosin or phenoxybenzamine restores intravascular plasma volume by counteracting the vasoconstrictive effects of high levels of catecholamines. This reexpansion of intravascular fluid volume is often followed by a decrease in hematocrit. Because some patients may be very sensitive to the effects of phenoxybenzamine, this drug should initially be given in doses of 20 to 30 mg/70 kg orally once or twice a day. Most patients usually require 60 to 250 mg/day. The efficacy of therapy should be judged by the reduction in symptoms (especially sweating) and stabilization of arterial blood pressure. For patients who have carbohydrate intolerance because of inhibition of insulin release mediated by α-adrenergic receptor stimulation, α-adrenergic receptor blockade may reduce fasting blood glucose levels. For patients who exhibit ST-T changes on the ECG, long-term preoperative and preprocedure α-adrenergic receptor blockade (1 to 6 months) has produced ECG and clinical resolution of catecholamine-induced myocarditis.[56,57,59-63]

β-Adrenergic receptor blockade with propranolol is suggested for patients who have persistent arrhythmias or tachycardia,[56,57,59-63] the reason being that these conditions can be precipitated or aggravated by α-adrenergic receptor blockade. β-Adrenergic receptor blockade should not be used without concomitant α-adrenergic receptor blockade lest the vasoconstrictive effects of the latter go unopposed and thereby increase the risk of dangerous hypertension.

The optimal duration of preoperative therapy with phenoxybenzamine has not been studied. Most patients require 10 to 14 days, as judged by the time needed to stabilize arterial blood pressure and ameliorate symptoms. Because the tumor spreads slowly, little is lost by waiting until medical therapy has optimized the patient's preoperative condition. The following criteria are reasonable for assessing the adequacy of treatment:

1. No in-hospital arterial blood pressure reading higher than 165/90 mm Hg should be evident for 48 hours preoperatively. We often measure arterial blood pressure every minute for 1 hour in a stressful environment (our postanesthesia care unit). If no blood pressure reading is higher than 165/90 mm Hg, this criterion is considered satisfied.
2. Orthostatic hypotension is acceptable as long as arterial blood pressure when the patient is standing is not less than 80/45 mm Hg.
3. The ECG should be free of ST-T changes that are not permanent.
4. No more than one premature ventricular contraction (PVC) should occur every 5 minutes.

Other drugs, including prazosin, calcium channel blocking drugs, clonidine, dexmedetomidine, and magnesium, have also been used to achieve suitable degrees of α-adrenergic blockade preoperatively. Multiple case series have confirmed the clinical utility of this approach in adults before tumor excision, including in a hemodynamic catecholamine crisis.[64] Magnesium therapy has shown efficacy for the resection of pheochromocytoma or paraganglioma during pregnancy. The dosing of magnesium for the management of pheochromocytoma has been reviewed elsewhere.[65]

The key clinical components of ideal patient care include optimal preoperative preparation, gentle (slow) induction of anesthesia, and good communication between the surgeon and the anesthesiologist. Virtually all anesthetic drugs and techniques (including isoflurane, sevoflurane, sufentanil, remifentanil, fentanyl, and regional anesthesia) have been used with success. In fact, all drugs studied are associated with a high rate of transient intraoperative arrhythmias.[59]

Because of ease of use, the preference is to give phenylephrine hydrochloride (Neo-Synephrine) or dopamine for hypotension and nitroprusside or theoretically, clevidipine, for hypertension. Phentolamine (Regitine) has too long an onset and duration of action. Painful or stressful events such as intubation often cause an exaggerated stress response in less than perfectly anesthetized patients who have pheochromocytoma. This response is caused by release of catecholamines from nerve endings that

are "loaded" by the reuptake process. Such stresses may result in catecholamine levels of 200 to 2000 pg/mL in normal patients. For a patient with pheochromocytoma, even simple stress can lead to blood catecholamine levels of 2000 to 20,000 pg/mL. However, infarction of a tumor, with release of products onto peritoneal surfaces, or surgical pressure causing release of products, can result in blood levels of 200,000 to 1,000,000 pg/mL—a situation that should be anticipated and avoided (ask for a temporary stay of surgery, if at all possible, while the rate of nitroprusside infusion is increased). Once the venous supply is secured and if intravascular volume is normal (as measured by pulmonary wedge pressure or echocardiography), normal arterial blood pressure usually results. However, some patients become hypotensive and occasionally require massive infusions of catecholamines. Vasopressin has also been used for hemodynamic rescue in catecholamine-resistant vasoplegic shock after resection of a massive pheochromocytoma.[66] On rare occasion, patients remain hypertensive intraoperatively. Postoperatively, approximately 50% of patients remain hypertensive for 1 to 3 days—and initially have markedly increased but declining plasma catecholamine levels—at which time all but 25% will become normotensive. Other family members should be advised to inform their future anesthesiologist about the potential for such familial disease.

HYPOFUNCTION OR ABERRATION IN FUNCTION OF THE SYMPATHETIC NERVOUS SYSTEM (DYSAUTONOMIA)

Disorders of the sympathetic nervous system include Shy-Drager syndrome, Riley-Day syndrome, Lesch-Nyhan syndrome, Gill familial dysautonomia, diabetic dysautonomia, and the dysautonomia of spinal cord transection.

Although individuals can function well without an adrenal medulla, a deficient peripheral sympathetic nervous system occurring late in life poses major problems for many facets of life; nevertheless, perioperative sympathectomy or its equivalent is often recommended.[67-73] A primary function of the sympathetic nervous system appears to be regulation of arterial blood pressure and intravascular fluid volume during changing of body position. Common features of all the syndromes of hypofunctioning of the sympathetic nervous system are orthostatic hypotension and decreased beat-to-beat variability in heart rate. These conditions can be caused by deficient intravascular volume, deficient baroreceptor function (as also occurs in carotid artery disease[74]), abnormalities in CNS function (as in Wernicke or Shy-Drager syndrome), deficient neuronal stores of norepinephrine (as in idiopathic orthostatic hypotension[75] and diabetes), or deficient release of norepinephrine (as in traumatic spinal cord injury[76]). These patients may have an increased number of available adrenergic receptors (a compensatory response) and an exaggerated response to sympathomimetic drugs. In addition to other abnormalities, such as retention of urine or feces and deficient heat exchange, hypofunctioning of the sympathetic nervous system is often accompanied by renal amyloidosis. Thus, electrolyte and intravascular fluid volume status should be evaluated preoperatively. Because many of these patients have cardiac abnormalities, intravascular fluid volume may be assessed preoperatively with a Swan-Ganz catheter or intraoperatively via transesophageal echocardiography rather than measurement of CVP.

Because the functioning of the sympathetic nervous system is not predictable in these patients, gentle induction of anesthesia and treatment of sympathetic excess or deficiency by infusing drugs that directly constrict (phenylephrine) or dilate (nitroprusside) blood vessels or that stimulate (isoproterenol) or depress (esmolol) the heart rate are suggested. A 20% perioperative mortality rate for 2600 patients after spinal cord transection has been reported, thus indicating that such patients are difficult to manage and deserve particularly close attention.

After reviewing 300 patients with spinal cord injuries, Kendrick and co-workers concluded that autonomic hyperreflexia syndrome does not develop if the lesion is below spinal dermatome T7.[77] If the lesion is above that level (splanchnic outflow), 60% to 70% of patients experience extreme vascular instability. The trigger to this instability, or a mass reflex involving noradrenergic and motor hypertonus, can be a cutaneous, proprioceptive, or visceral stimulus (a full bladder is a common initiator). The sensation enters the spinal cord and causes a spinal reflex, which in normal persons is inhibited from above. Sudden increases in arterial blood pressure are sensed in the pressure receptors of the aorta and carotid sinus. The resulting vagal hyperactivity produces bradycardia, ventricular ectopia, or various degrees of heart block. Reflex vasodilation may occur above the level of the lesion and result in flushing of the head and neck. Two newer techniques to help reduce acute injury or aid in repair (high-dose docosahexaenoic acid and acute cooling) may also have anesthetic implications, but reports of these effects, if any, have not been published.

Depending on the length of time since spinal cord transection, other abnormalities may occur. In the short term (i.e., <3 weeks from the time of spinal injury), retention of urine and feces is common and, by elevating the diaphragm, may impair respiration. Disimpaction of the intestine alleviates this respiratory problem. Hyperesthesia is present above the lesion; reflexes and flaccid paralysis are present below the lesion. The intermediate period (3 days to 6 months) is marked by a hyperkalemic response to depolarizing drugs.[78] The chronic phase is characterized by return of muscle tone, Babinski sign, and, frequently, the occurrence of hyperreflexia syndromes (e.g., mass reflex [see earlier]).

Thus, in addition to meticulous attention to perioperative intravascular volume and electrolyte status, the anesthesiologist should know—by history taking, physical examination, and laboratory data—the status of the patient's myocardial conduction (as revealed by the ECG), the status of renal functioning (by noting the ratio of creatinine to blood urea nitrogen [BUN]), and the condition of the respiratory muscles (by determining the ratio of forced expiratory volume in 1 second [FEV_1] to forced vital capacity [FVC]) (see also Chapter 44). The anesthesiologist may also obtain a chest radiograph if atelectasis or pneumonia is suspected on the basis of history taking or the physical examination. Temperature control, the presence of bone fractures or decubitus ulcers, and normal

TABLE 39-6 BIOCHEMICAL MEASUREMENTS OF THYROID FUNCTION THAT ACCOUNT FOR VARIATION IN PRODUCTION OF THYROXINE-BINDING GLOBULIN

	Examples of Normal Thyroid Status*					
	FT_4E	=	T_4	×	THBR	TSH
Normal	0.19 (0.12-0.25)	=	0.6 (0.4-0.9)	×	31% (25%-35%)	0.2 (0.2-0.8)
During use of oral contraceptives	0.19	=	1.3	×	15%	0.3
During use of corticosteroids	0.18	=	0.3	×	60%	0.3

*FT_4E is the free T_4 (thyroxine) estimate. It is usually obtained by multiplying the total T_4 concentration (the free amount and the amount bound to protein) by the thyroid hormone–binding ratio (THBR, formerly called the resin T_3 uptake). THBR is a measure of the bound thyroid hormone–binding protein. TSH is the thyroid-stimulating hormone secreted by the pituitary in the negative feedback loop. (TSH increases when FT_4E is low in hypothyroidism.)

functioning of the urination and defecation systems must be assessed. Confirmation of the latter prevents postoperative pneumonia or atelectasis caused by high positioning of the diaphragm.

THYROID DYSFUNCTION

The major thyroid hormones are thyroxine (T_4), a prohormone product of the thyroid gland, and the more potent 3,5,3-triiodothyronine (T_3), a product of both the thyroid and extrathyroidal enzymatic deiodination of T_4. Under normal circumstances, approximately 85% of T_3 is produced outside the thyroid gland. Production of thyroid secretions is maintained by secretion of thyroid-stimulating hormone (TSH) in the pituitary, which in turn is regulated by secretion of thyrotropin-releasing hormone (TRH) in the hypothalamus. Secretion of TSH and TRH appears to be negatively regulated by T_4 and T_3. Many investigators believe that all effects of thyroid hormones are mediated by T_3 and that T_4 functions only as a prohormone.

Because T_3 has greater biologic effect than does T_4, one would expect the diagnosis of thyroid disorders to be based on levels of T_3. However, this is not usually the case. The diagnosis of thyroid disease is confirmed by one of several biochemical measurements: levels of free T_4 or total serum concentrations of T_4 and the "free T_4 estimate." This estimate is obtained by multiplying total T_4 (free and bound) by the thyroid-binding ratio (formerly called resin T_3 uptake) (Table 39-6). Free T_4 can be accurately measured by many laboratories. Direct measurement of free T_4 obviates the need to account for changes in binding protein synthesis and affinity caused by other conditions. The T_3-binding ratio measures the extra quantity of serum protein-binding sites. This measurement is necessary because thyroxine-binding globulin (TBG) levels are abnormally high during pregnancy, hepatic disease, and estrogen therapy (all of which would elevate the total T_4 level) (Box 39-2). Reliable interpretation of measurements of the total hormone concentration in serum necessitates data on the percentage of bound hormone. The thyroid hormone–binding ratio test provides this information. In this test, iodine-labeled T_3 is added to a patient's serum and is allowed to reach an equilibrium binding state. A resin is then added that binds the remaining radioactive T_3. Resin uptake is greater if the patient has fewer TBG-binding sites. In normal patients, resin T_3 uptake (the thyroid hormone–binding ratio) is 25% to 35%. When serum TBG is elevated, the thyroid hormone–binding ratio is diminished (see Table 39-6). When serum TBG is diminished, as in nephrotic syndrome, in conditions in which glucocorticoids are increased, or in chronic liver disease, the thyroid hormone–binding ratio is increased.

BOX 39-2 ***Factors Influencing Serum Levels of Thyroxine-Binding Globulin***

Conditions Increasing Serum Levels

- Use of oral contraceptives
- Pregnancy
- Use of estrogen
- Infectious hepatitis
- Chronic active hepatitis
- Neonatal state
- Acute intermittent porphyria
- Inherited conditions

Conditions Decreasing Serum Levels

- Testosterone
- Use of corticosteroids
- Severe illness
- Cirrhosis
- Nephrotic syndrome
- Inherited conditions

The free T_4 estimate and the free T_3 estimate are frequently used as measures of a patient's serum T_4 and T_3 hormone concentrations, respectively. To obtain these estimates, the concentration of total serum T_4 or total serum T_3 is multiplied by the measured thyroid hormone–binding ratio. Values of these two indices are normal in the event of a primary alteration in binding but not with an alteration in secretion of thyroid hormone.

Hyperthyroidism can be diagnosed by measuring levels of TSH after the administration of TRH. Although administering TRH normally increases TSH levels in blood, even a small increase in the T_4 or T_3 level in blood abolishes this response. Thus, a subnormal or absent serum TSH response to TRH is a very sensitive indicator of hyperthyroidism. In one group of disorders involving hyperthyroidism, serum TSH levels are elevated in the presence of elevated levels of free thyroid hormone.

Measurement of the α-subunit of TSH has been helpful in identifying the rare patients who have a pituitary

neoplasm and who usually have increased α-subunit concentrations. Some patients are clinically euthyroid in the presence of elevated levels of total T_4 in serum. Certain drugs, notably gallbladder dyes, propranolol, glucocorticoids, and amiodarone, block the conversion of T_4 to T_3 and thereby elevate T_4 levels. Severe illness also slows this conversion. Levels of TSH are often high in situations in which the rate of conversion is decreased. In hyperthyroidism, cardiac function and responses to stress are abnormal; return of normal cardiac function parallels the return of TSH levels to normal.

Hyperthyroidism

Although hyperthyroidism is usually caused by the multinodular diffuse enlargement in Graves disease (also associated with disorders of the skin or eyes, or both), it can also occur with pregnancy, thyroiditis (with or without neck pain), thyroid adenoma, choriocarcinoma, or TSH-secreting pituitary adenoma. Five percent of women have thyrotoxic effects 3 to 6 months postpartum and tend to have recurrences with subsequent pregnancies. Major manifestations of hyperthyroidism are weight loss, diarrhea, warm and moist skin, weakness of large muscle groups, menstrual abnormalities, osteopenia, nervousness, jitteriness, intolerance to heat, tachycardia, cardiac arrhythmias, mitral valve prolapse, and heart failure. When the thyroid is functioning abnormally, the entity most threatened is the cardiovascular system. When diarrhea is severe, dehydration should be corrected preoperatively. Mild anemia, thrombocytopenia, increased serum alkaline phosphatase, hypercalcemia, muscle wasting, and bone loss frequently occur in hyperthyroidism. Muscle disease usually involves the proximal muscle groups; it has not been reported to cause respiratory muscle paralysis. In the apathetic form of hyperthyroidism (seen most commonly in persons >60 years old), cardiac effects dominate the clinical picture. Signs and symptoms include weight loss, anorexia, and cardiac effects such as tachycardia, irregular heart rhythm, atrial fibrillation (in 10%), heart failure, and occasionally, papillary muscle dysfunction.

Although β-adrenergic receptor blockade can control the heart rate, its use is fraught with hazard in a patient already experiencing CHF. However, a decreasing heart rate may improve heart-pumping function. Thus, hyperthyroid patients who have fast ventricular rates, who are in CHF, and who require emergency surgery are given short-acting β-blockers guided by changes in pulmonary artery wedge pressure and their condition. If slowing the heart rate with a small dose of esmolol (50 μg/kg) does not aggravate the heart failure, the physician should administer more esmolol. Antithyroid medications include propylthiouracil and methimazole, both of which decrease the synthesis of T_4 and may enhance remission by reducing TSH receptor antibody levels (the primary pathologic mechanism in Graves disease). Propylthiouracil also decreases the conversion of T_4 to the more potent T_3. However, the literature indicates a trend toward preoperative preparation with propranolol and iodides alone.[79] This approach is quicker (i.e., 7 to 14 days versus 2 to 6 weeks); it shrinks the thyroid gland, as does the more traditional approach; it decreases conversion of the prohormone T_4 into the more potent T_3; and it treats symptoms but may not correct abnormalities in left ventricular function. Regardless of the approach, antithyroid drugs should be administered on a long-term basis and on the morning of the surgical procedure. If emergency surgery is necessary before the euthyroid state is achieved, if subclinical hyperthyroidism progresses without adequate treatment, or if hyperthyroidism is out of control intraoperatively, intravenous administration of esmolol, 50 to 500 μg/kg, could be titrated to restore a normal heart rate (assuming the absence of CHF) (see earlier). In addition, intravascular fluid volume and electrolyte balance should be restored. However, administering propranolol or esmolol does not invariably prevent "thyroid storm."

No specific anesthetic drug is preferred for surgical patients who are hyperthyroid. Anticholinergic drugs (especially atropine) are sometimes not used because they interfere with the sweating mechanism and cause tachycardia; yet atropine has been given as a test for the adequacy of antithyroid treatment. Because patients are now subjected to operative procedures only (or almost only) when euthyroid, the traditional "steal" of a heavily premedicated hyperthyroid patient in the operating room has vanished.

A patient with a large goiter and an obstructed airway can be managed in the same way as any other patient with a problematic airway (see also Chapter 55). In this type of case, reviewing CT scans of the neck preoperatively may provide valuable information regarding the extent of compression. Maintenance of anesthesia usually presents little difficulty. Postoperatively, extubation of the trachea should be performed under optimal circumstances for reintubation in the event that the tracheal rings have been weakened and the trachea collapses.

Of the many possible postoperative complications (nerve injury, bleeding, and metabolic abnormalities), thyroid storm (discussed in the next section), bilateral recurrent nerve trauma, and hypocalcemic tetany are the most feared. Bilateral recurrent laryngeal nerve injury (secondary to trauma or edema) causes stridor and laryngeal obstruction as a result of unopposed adduction of the vocal cords and closure of the glottic aperture. Immediate endotracheal intubation is required, usually followed by tracheostomy to ensure an adequate airway. This rare complication occurred only once in more than 30,000 thyroid operations at the Lahey Clinic. Unilateral recurrent nerve injury often goes unnoticed because of compensatory overadduction of the uninvolved cord. However, we often test vocal cord function before and after this operation by asking the patient to say "e" or "moon." Unilateral nerve injury is characterized by hoarseness and bilateral nerve injury by aphonia. Selective injury to the adductor fibers of both recurrent laryngeal nerves leaves the abductor muscles relatively unopposed, and pulmonary aspiration is a risk. Selective injury to the abductor fibers leaves the adductor muscles relatively unopposed, and airway obstruction can occur. Bullous glottic edema, an additional cause of postoperative respiratory compromise, has no specific cause or known preventive measure.

The intimate involvement of the parathyroid gland with the thyroid gland can result in inadvertent

hypocalcemia during surgery for thyroid disease. Complications related to hypocalcemia are discussed in the later section on this disorder.

Because postoperative hematoma can compromise the airway, neck and wound dressings are placed in a crossing fashion (rather than vertically or horizontally) and should be examined for evidence of bleeding before a patient is discharged from the recovery room.

Thyroid Storm

Thyroid storm is the name for the clinical diagnosis of a life-threatening illness in a patient whose hyperthyroidism has been severely exacerbated by illness or surgery. Thyroid storm is characterized by hyperpyrexia, tachycardia, and striking alterations in consciousness. It clinically manifests in a manner similar to that of malignant hyperthermia, pheochromocytoma, and neuroleptic malignant syndrome. No laboratory tests are diagnostic of thyroid storm, and the precipitating (nonthyroidal) cause is the major determinant of survival. Therapy can include blocking the synthesis of thyroid hormones by administering antithyroid drugs and the release of preformed hormone with iodine. Blocking the sympathetic nervous system with reserpine, α- and β-receptor antagonists, or α_2 drugs may be exceedingly hazardous and requires skillful management and constant monitoring of the critically ill patient.

Thyroid dysfunction, either hyperthyroidism or hypothyroidism, develops in more than 10% of patients treated with the antiarrhythmic agent amiodarone.[80] Approximately 35% of the drug's weight is iodine, and a 200-mg tablet releases approximately 20 times the optimal daily dose of iodine. This iodine can lead to reduced synthesis of T_4 or increased synthesis. In addition, amiodarone inhibits the conversion of T_4 to the more potent T_3.

Patients receiving amiodarone may be considered to be in need of special attention preoperatively and intraoperatively, not just because of the arrhythmia that led to such therapy but also to ensure that no perioperative dysfunction or surprises result from unsuspected thyroid hyperfunction or hypofunction.[81] Many patients with amiodarone-induced thyrotoxicosis receive steroids for a period, another area of questioning that may be triggered by the use of amiodarone in a preoperative patient.

Hypothyroidism

Hypothyroidism is a common disease that has been detected in 5% of a large population in Great Britain, in 3% to 6% of a healthy older population in Massachusetts, and in 4.5% of a medical clinic population in Switzerland. The apathy and lethargy that often accompany hypothyroidism frequently delay its diagnosis, so the perioperative period may be the first opportunity to spot many such hypothyroid patients. However, hypothyroidism is usually subclinical, serum concentrations of thyroid hormones are in the normal range, and only serum TSH levels are elevated. The normal range of TSH is 0.3 to 4.5 milliunits/L, and TSH values of 5 to 15 milliunits/L are characteristic of this entity. In such cases, hypothyroidism may have little or no perioperative significance. However, a retrospective study of 59 mildly hypothyroid patients found that more hypothyroid patients than control subjects required prolonged postoperative intubation (9 of 59 versus 4 of 59) and had significant electrolyte imbalances (3 of 59 versus 1 of 59) and bleeding complications (4 of 59 versus 0 of 59).[82] Because only a few charts were examined, these differences did not reach statistical significance. In another study, overt hypothyroidism later developed in a high percentage of patients with a history of subclinical hypothyroidism.[83,84] Thus, a previous history of subclinical hypothyroidism may be a clue to the possibility of overt hypothyroidism.

Overt hypothyroidism may cause slow mental functioning, slow movement, dry skin, arthralgias, carpal tunnel syndrome, periorbital edema, intolerance to cold, depression of the ventilatory responses to hypoxia and hypercapnia, impaired clearance of free water with or without hyponatremia, "hung-up reflexes," slow gastric emptying, sleep apnea,[85] and bradycardia. In extreme cases, cardiomegaly, heart failure, and pericardial and pleural effusions manifest as fatigue, dyspnea, and orthopnea. Hypothyroidism is often associated with amyloidosis, which may produce an enlarged tongue, abnormalities of the cardiac conduction system, and renal disease. Hypothyroidism decreases the anesthetic requirement slightly. The tongue may be enlarged in a hypothyroid patient even in the absence of amyloidosis, and such enlargement may hamper endotracheal intubation.

An increasing TSH level is the most sensitive indicator of failing thyroid function. Ideal preoperative and preprocedure management of hypothyroidism consists of restoring normal thyroid status: the physicians should consider administering the normal dose of levothyroxine the morning of the surgical procedure, even though these drugs have long half-lives (1.4 to 10 days). Reduced GI absorption of levothyroxine may occur with the coadministration of cholestyramine or aluminum hydroxide, iron, a high-bran meal, or sucralfate or colestipol. For patients in myxedema coma who require emergency surgery, liothyronine can be given intravenously (with fear of precipitating myocardial ischemia, however) while supportive therapy is undertaken to restore normal intravascular fluid volume, body temperature, cardiac function, respiratory function, and electrolyte balance.

In hypothyroidism, respiratory control mechanisms do not function normally. However, the response to hypoxia and hypercapnia and clearance of free water become normal with thyroid replacement therapy. Drug metabolism is anecdotally reported to be slowed, and awakening times from sedatives are reported to be prolonged by hypothyroidism. However, few formal studies and none in humans of the pharmacokinetics and pharmacodynamics of sedatives or anesthetic drugs have been published. These concerns disappear when thyroid function is normalized preoperatively. Addison disease (with its relative steroid deficiency) is more common in hypothyroidism, and some endocrinologists routinely treat patients with noniatrogenic hypothyroidism with stress doses of steroids perioperatively because both conditions are commonly caused by autoimmune responses. The possibility that this steroid deficiency exists should be considered if the patient becomes hypotensive perioperatively. Body heat mechanisms are inadequate in hypothyroid patients, so temperature should be monitored and

maintained, especially in patients requiring emergency surgery. Because of an increased incidence of myasthenia gravis in hypothyroid patients, it may be advisable to use a peripheral nerve stimulator to guide administration of muscle relaxants.

Thyroid Nodules and Carcinoma

More than 90% of thyroid nodules are benign, yet identifying malignancy in a solitary thyroid nodule is a difficult and important procedure. Male patients and patients with previous radiation therapy to the head and neck have an increased likelihood of malignant disease in their nodules. Often, needle biopsy and scanning are sufficient for the diagnosis, but occasionally excisional biopsy is needed. Papillary carcinoma accounts for more than 70% of all thyroid carcinomas. Simple excision of lymph node metastases appears to be as efficacious as radical neck procedures for the patient's survival. Follicular carcinoma accounts for approximately 15% of thyroid carcinomas, is more aggressive, and has a less favorable prognosis.

Medullary carcinoma, the most aggressive form of thyroid carcinoma, is associated with a familial occurrence of pheochromocytoma, as are parathyroid adenomas. For this reason, a history may be obtained from patients who have a surgical scar in the thyroid region so that the possibility of occult pheochromocytoma can be excluded.

DISORDERS OF CALCIUM METABOLISM

The three substances that regulate serum concentrations of calcium, phosphorus, and magnesium—parathyroid hormone (parathyrin, PTH), calcitonin, and vitamin D—act on bone, kidney, gut, and their own receptors (the last has led to an important advance in treatment). Calcium excess in blood is caused by either malignant disease or hyperparathyroidism in more than 90% of patients.[86] PTH stimulates bone resorption, inhibits renal excretion of calcium, and increases conversion to active vitamin D, three conditions that lead to hypercalcemia. Calcitonin can be considered an antagonist to PTH. Through its metabolites, vitamin D aids in the absorption of calcium, phosphate, and magnesium from the gut and facilitates the bone resorptive effects of PTH. Secretion of PTH is modulated through the calcium-sensing receptor on the cell surface of parathyroid cells. An increase in ionized calcium stimulates this receptor and thus causes a decrease in PTH secretion. Recognition of this effect has led to reevaluation of the therapy for hyperparathyroidism inasmuch as a drug up-regulating this receptor's sensitivity reduces PTH levels.[87]

Hyperparathyroidism and Hypercalcemia

Primary hyperparathyroidism occurs in approximately 0.1% of the population, most commonly begins in the third to fifth decades of life, and occurs two to three times more frequently in women than in men. Primary hyperparathyroidism usually results from enlargement of a single gland, commonly an adenoma and very rarely a carcinoma. Hypercalcemia almost always develops.

Calcium is the chief mineral component of the body; it provides structure to the skeleton and performs key roles in neural transmission, intracellular signaling, blood coagulation, and neuromuscular functioning. Ninety-nine percent of the 1000 g of calcium present in the average human body is stored in the bone mineral reservoir. The normal total serum calcium level is 8.6 to 10.4 mg/dL, as measured in most laboratories. Fifty percent to 60% is bound to plasma proteins or is complexed with phosphate or citrate. The value depends on the albumin level, with a decline of 0.8 mg/dL for each 1 g/dL drop in albumin. Binding of calcium to albumin depends on pH: binding decreases with acidic pH and increases with alkaline pH. Serum calcium, not ionized calcium, decreases with reductions in albumin levels. Although ionized calcium is the clinically significant fraction, the cost and technical difficulties of stabilizing the electrodes used for measurement have limited the available assays. Nevertheless, PTH and vitamin D_3 work to keep the level stable within 0.1 mg/dL in any individual.

Many of the prominent symptoms of hyperparathyroidism are a result of the hypercalcemia that accompanies it. Regardless of the cause, hypercalcemia can produce any of a number of symptoms, the most prominent of which involve the renal, skeletal, neuromuscular, and GI systems—anorexia, vomiting, constipation, polyuria, polydipsia, lethargy, confusion, formation of renal calculi, pancreatitis, bone pain, and psychiatric abnormalities. Free intracellular calcium initiates or regulates muscle contraction, release of neurotransmitters, secretion of hormones, enzyme action, and energy metabolism.

Nephrolithiasis occurs in 60% to 70% of patients with hyperparathyroidism. Sustained hypercalcemia can result in tubular and glomerular disorders, including proximal (type II) renal tubular acidosis. Polyuria and polydipsia are common complaints.

Skeletal disorders related to hyperparathyroidism are osteitis fibrosa cystica, simple diffuse osteopenia, and osteoporosis. The rate of bone turnover is five times higher in patients with hyperparathyroidism than in normal controls. Patients may have a history of frequent fractures or may complain of bone pain, especially pain in the anterior margin of the tibia.

Because free intracellular calcium initiates or regulates muscle contraction, neurotransmitter signaling, hormone secretion, enzyme action, and energy metabolism, abnormalities in these end organs are often symptoms of hyperparathyroidism. Patients may experience profound muscle weakness, especially in proximal muscle groups, as well as muscle atrophy. Depression, psychomotor retardation, and memory impairment may occur. Lethargy and confusion are frequent complaints.

Peptic ulcer disease is more common in these patients than in the rest of the population. Production of gastrin and gastric acid is increased. Anorexia, vomiting, and constipation may also be present.

Approximately one third of all hypercalcemic patients are hypertensive, but the hypertension usually resolves with successful treatment of the primary disease. Neither hypertension nor minimally invasive surgery seems to alter the perioperative risk associated with surgery in such patients in comparison with the usual hypertensive patients.[88,89] Even octogenarians with asymptomatic hyperparathyroidism can be operated on without

mortality and with morbidity no different from that in younger individuals, thus encouraging the use of parathyroidectomy as preventive therapy.[90] Long-standing hypercalcemia can lead to calcifications in the myocardium, blood vessels, brain, and kidneys. Cerebral calcifications may cause seizures, whereas renal calcifications lead to polyuria that is unresponsive to vasopressin.

The most useful confirmatory test for hyperparathyroidism is radioimmunoassay for PTH. In fact, two changes have radically reduced anesthesia involvement in the care of patients with primary hyperparathyroidism. One, use of the calcimimetic drug class, which modulates the calcium-sensitive PTH cell receptor and thereby decreases calcium levels, discussed earlier, has been emphasized in older individuals (see later). The other change is use of minimally invasive approaches after imaging procedures with just local anesthesia or a cervical plexus block—as with thyroidectomy.[91,92] Most surgeons now performing minimally invasive parathyroid removal monitor PTH levels intraoperatively to determine whether the causative adenoma has been resected. The baseline PTH level should be determined before induction of anesthesia because even monitored anesthesia care increases PTH levels.[93] In hyperparathyroid patients, hormone levels are abnormal for a given level of calcium. The level of inorganic phosphorus in serum is usually low, but it may be within normal limits. Alkaline phosphatase levels are elevated if considerable skeletal involvement is present.

Glucocorticoid administration reduces the level of calcium in blood in many other conditions that cause hypercalcemia, but not usually in primary hyperparathyroidism. In sarcoidosis, multiple myeloma, vitamin D intoxication, and some malignant diseases, all of which can cause hypercalcemia, administration of glucocorticoids may lower serum calcium levels through an effect on GI absorption. This effect occurs to a lesser degree in primary hyperparathyroidism.

Hypercalcemia may also occur as a consequence of secondary hyperparathyroidism in patients who have chronic renal disease. When phosphate excretion decreases as a result of decreased nephron mass, serum calcium levels fall because of deposition of calcium and phosphate in bone. Secretion of PTH subsequently increases, and this causes the fraction of phosphate excreted by each nephron to increase. Eventually, the chronic intermittent hypocalcemia of chronic renal failure leads to chronically high levels of serum PTH and hyperplasia of the parathyroid glands—one of the entities termed secondary hyperparathyroidism.

Symptomatic primary hyperparathyroidism in patients younger than 50 years or with serum calcium levels more than 1 mg/dL higher than the upper limit of normal, a 30% or greater reduction in the glomerular filtration rate (GFR), or severe bone demineralization is usually treated surgically. If the patient refuses surgery or if other illnesses render surgery inadvisable, medical management with the calcimimetic cinacalcet makes management much more feasible. The difficulty with such management is that the hyperfunctioning parathyroid glands secrete more hormone as the serum calcium concentration is lowered—as though the calcium set point for feedback regulation of PTH secretion had been raised. Blanchard and colleagues

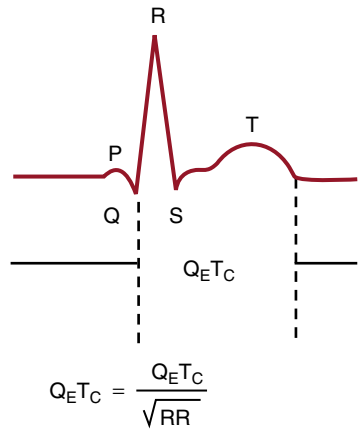


Figure 39-3. Measurement of the QTc interval (properly termed Q_ET_C to indicate that it begins with the start of the Q wave, lasts throughout the QT interval, ends with the end of the T wave, and is corrected for heart rate). RR is the RR interval in seconds. *(From Hensel P, Roizen MF: Patients with disorders of parathyroid function,* Anesthesiol Clin North Am *5:287, 1987.)*

demonstrated that patients with "asymptomatic" primary hyperparathyroidism have clinical improvement of their symptoms postoperatively even after 1 year.[94] Younger patients and those with higher preoperative calcium levels show the best improvement.

Patients with moderate hypercalcemia who have normal renal and cardiovascular function present no special preoperative and preprocedure problems. The ECG can be examined preoperatively and intraoperatively for shortened PR or QT intervals (Fig. 39-3). Because severe hypercalcemia can result in hypovolemia, normal intravascular volume and electrolyte status should be restored before commencement of anesthesia and surgery.

Management of hypercalcemia preoperatively should include (even in urgent or emergency situations) treatment of the underlying cause—a frequent strategy in surgical patients with malignancy-associated hypercalcemia. Antitumor therapy preoperatively for both malignant and nonmalignant causes of hypercalcemia can include hydration and diuresis to increase urinary calcium excretion. Restoration of intravascular volume, augmentation and excretion of urinary sodium (with saline infusion), and administration of diuretics (furosemide is commonly used) generally increase urinary calcium excretion substantially. Infusion rates of 200 to 400 mL/hour preoperatively are commonly used, but monitoring is needed to avoid administration of an excessive amount of intravenous fluids, especially because many patients have compromised cardiac pumping ability. Other complications of these interventions include hypomagnesemia and hypokalemia.

In emergency situations, vigorous expansion of intravascular volume usually reduces serum calcium to a safe level (<14 mg/dL); administration of furosemide is also often helpful in these situations. Phosphate should be given to correct hypophosphatemia because it decreases calcium uptake into bone, increases calcium excretion, and stimulates breakdown of bone. Hydration and diuresis, accompanied by phosphate repletion, suffice in the management of most hypercalcemic patients. Other

measures to decrease reabsorption of bone include the bisphosphonates pamidronate sodium (90 mg intravenously) and zoledronate (4 mg intravenously), salmon calcitonin (100 to 400 units every 12 hours).

Calcitonin lowers serum calcium levels through direct inhibition of bone resorption. It can decrease serum calcium levels within minutes after intravenous administration. Side effects include urticaria and nausea. It is so rapid acting that it can be used to reduce calcium levels while waiting for hydration and a bisphosphonate to take effect. Dialysis can also be used when appropriate.

It is especially important to know whether the hypercalcemia has been chronic because serious cardiac, renal, or CNS abnormalities may have resulted.

Hypocalcemia

Hypocalcemia (caused by hypoalbuminemia, hypoparathyroidism, hypomagnesemia, hypovitaminosis D, hungry bones after correction of hyperparathyroidism, anticonvulsant therapy, citrate infusion, or chronic renal disease) is not usually accompanied by a clinically evident cardiovascular disorder. The most common cause of hypocalcemia is hypoalbuminemia. In true hypocalcemia (i.e., when the free calcium concentration is low), myocardial contractility is affected. In other words, myocardial contractility varies directly with levels of blood ionized calcium, although contractility decreased only 20% when ionized calcium levels changed from 1.68 to 1.34 mmol/L. The clinical signs of hypocalcemia are as follows: clumsiness; convulsions; laryngeal stridor; depression; muscle stiffness; paresthesia (oral and perioral); parkinsonism; tetany; Chvostek sign; dry and scaly skin, brittle nails, and coarse hair; low serum concentrations of calcium; prolonged QT intervals; soft tissue calcifications; and Trousseau sign.

Hypocalcemia delays ventricular repolarization, hence increasing the QTc interval (normal, 0.35 to 0.44 second). With electrical systole prolonged, the ventricles may fail to respond to the next electrical impulse from the sinoatrial node, and a second-degree heart block results. Prolongation of the QT interval is a moderately reliable ECG sign of hypocalcemia, not for the population as a whole, but for the individual patient.[95] Thus, monitoring the QT interval as corrected for the heart rate is a useful, but not always accurate means of monitoring hypocalcemia in any individual patient (see Fig. 39-3). CHF may also occur with hypocalcemia, but this is rare. Because CHF in patients with coexisting heart disease is reduced in severity when calcium and magnesium ion levels are restored to normal, these levels may be normalized preoperatively in a patient with impaired exercise tolerance or signs of cardiovascular dysfunction; normalization can be achieved intravenously over a 15-minute period if absolutely necessary. Sudden decreases in blood levels of ionized calcium (as with chelation therapy) can result in severe hypotension.

Patients with hypocalcemia may have seizures. They may be focal, jacksonian, petit mal, or grand mal in appearance, indistinguishable from such seizures in the absence of hypocalcemia. Patients may also have a type of seizure called cerebral tetany, which consists of generalized tetany followed by tonic spasms. Therapy with standard anticonvulsants is ineffective and may even exacerbate these seizures (by an anti–vitamin D effect). In long-standing hypoparathyroidism, calcifications may appear above the sella; these calcifications represent deposits of calcium in and around small blood vessels of the basal ganglia. They may be associated with a variety of extrapyramidal syndromes.

The most common cause of acquired hypoparathyroidism is surgery of the thyroid or parathyroid glands. Other causes include autoimmune disorders, therapy with iodine-131, hemosiderosis or hemochromatosis, neoplasia, and granulomatous disease. Idiopathic hypoparathyroidism has been divided into three categories: an isolated persistent neonatal form, branchial dysembryogenesis, and autoimmune candidiasis related to multiple endocrine deficiency.

Pseudohypoparathyroidism and pseudopseudohypoparathyroidism are rare hereditary disorders characterized by short stature, obesity, rounded face, and shortened metacarpals. Patients with pseudohypoparathyroidism have hypocalcemia and hyperphosphatemia despite high serum levels of PTH. These patients have a deficient end-organ response to PTH as a result of abnormalities in G-protein function.

Because treatment of hypoparathyroidism is not surgical, hypoparathyroid patients who come to the operating room are those who require surgery for unrelated conditions. Their calcium, phosphate, and magnesium levels should be measured both preoperatively and postoperatively. Patients with symptomatic hypocalcemia may be treated with intravenous calcium gluconate preoperatively. Initially, 10 to 20 mL of 10% calcium gluconate may be given at a rate of 5 mL/minute. The effect on serum calcium levels is of short duration, but a continuous infusion with 10 mL/minute of 10% calcium gluconate in 500 mL of solution over a period of 6 hours helps keep serum calcium at adequate levels. Magnesium and phosphate levels may also require normalization to normalize cardiovascular and nervous system function.

The objective of therapy is to bring the symptoms under control before the surgical procedure and anesthesia. For patients with chronic hypoparathyroidism, the objective is to keep the serum calcium level in the lower half of the normal range. A preoperative and preprocedure ECG is useful for maintaining the QTc interval. The preoperative and preprocedure QTc value may be used as a guide to the serum calcium level if rapid laboratory assessment is not possible. Changes in the calcium level may alter the duration of muscle relaxation, so such alterations may be monitored by using a twitch monitor in these (as well as all other) patients.

The intimate involvement of the parathyroid gland with the thyroid gland can result in unintentional hypocalcemia during surgery for diseases of either organ. Because of the affinity of their bones for calcium, this relationship is crucial in patients with advanced osteitis. Internal redistribution of magnesium, calcium, or both ions may occur (into "hungry bones") after parathyroidectomy and may cause hypomagnesemia, hypocalcemia, or both conditions. Because the tendency to tetany increases with alkalosis, hyperventilation is usually

assiduously avoided. The most prominent manifestations of acute hypocalcemia are distal paresthesias and muscle spasm (tetany). Potentially fatal complications of severe hypocalcemia include laryngeal spasm and hypocalcemic seizures. The clinical sequelae of magnesium deficiency include cardiac arrhythmias (principally ventricular tachyarrhythmias), hypocalcemic tetany, and neuromuscular irritability independent of hypocalcemia (tremors, twitching, asterixis, and seizures).

In addition to monitoring total serum calcium or ionized calcium postoperatively, one can test for the Chvostek and Trousseau signs. (Serum calcium, not ionized calcium, depends on the albumin level, with a decline of approximately 0.8 mg/dL for each 1 g/dL drop in serum albumin level.) Because the Chvostek sign can be elicited in 10% to 15% of patients who are not hypocalcemic, an attempt should be made to elicit this sign preoperatively to ensure that its appearance is meaningful. The Chvostek sign is a contracture of the facial muscles produced by tapping the ipsilateral facial nerve at the angle of the jaw. The Trousseau sign is elicited by applying a blood pressure cuff at a level slightly above the systolic level for a few minutes. The resulting carpopedal spasm, with contraction of the fingers and inability to open the hand, stems from the increased muscle irritability in hypocalcemic states, aggravated by ischemia produced by the blood pressure cuff.

Osteoporosis

Fifty percent of women who are older than 65 years sustain an osteoporotic fracture. (Because men are living longer, osteoporosis has become an increasing problem for them, too, and reports indicate a 15% per decade hip fracture rate for men >65 years old).[95] Men with COPD (even without steroid treatment) are at high risk for vertebral fractures and thus may be allowed to position and move themselves onto and off surgical tables. Furthermore, in either gender, each vertebral fracture is associated with a 10% decrease in lung capacity. Diagnosis and treatment of these conditions have increased with routine use of dual-energy x-ray absorptiometry or quantitative ultrasonography. Because T-scores and Z-scores were developed to relate changes in white postmenopausal women to those at age 21 years, care must be used in interpreting the results. Known risk factors include age, relative lifetime estrogen deficiency (late menarche, amenorrhea, early menopause, nulliparity), deficiency of dietary calcium, tobacco use, increased aerobic exercise in combination with decreased weight-bearing exercise, decreased weight-bearing exercise by itself, use of soft drinks, and Asian or white ancestry. Although therapy for osteoporosis (use of biphosphates, bone mineral depositors, weight-bearing exercises, calcium, vitamin D, estrogen, and now designer estrogens that may be useful for men, such as raloxifene [Evista]) does not have major known implications for anesthesia care,[96-98] bone fractures in such patients have occurred on movement to and from an operating table. Recombinant PTH and calcitonin are also used, but again, no reports of perioperative interactions have been prominent. Thus, the precautions mentioned earlier for hyperparathyroid patients relative to self-positioning and careful positioning may be useful.

PITUITARY ABNORMALITIES

Anterior Pituitary Hypersecretion

The anterior pituitary gland (or master endocrine gland) consists of five identifiable types of secretory cells (and the hormones that they secrete): somatotrophs (GH), corticotrophs (ACTH), lactotrophs (prolactin), gonadotrophs (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), and thyrotrophs (TSH). Secretion of these pituitary hormones is largely regulated by a negative-feedback loop by hypothalamic regulatory hormones and by signals that originate from the target site of pituitary action. Six hypothalamic hormones have been characterized: dopamine, the prolactin-inhibiting hormone; somatostatin, the GH release–inhibiting hormone; GH-releasing hormone (GHRH); corticotropin-releasing hormone (CRH); gonadotropin-releasing hormone (GnRH or LHRH); and TRH. Most pituitary tumors (>60%) are hypersecretory and are classified according to the excess production of a specific anterior pituitary hormone.

The most common disorders of pituitary hypersecretion are those related to excesses of prolactin (amenorrhea, galactorrhea, and infertility), ACTH (Cushing syndrome), and GH (acromegaly). In addition to knowing the pathophysiologic processes of the disease involved, the anesthesiologist must determine whether the patient recently underwent air pneumoencephalography (almost obsolete, but still used rarely). If so, nitrous oxide should not be used to lessen the risk of intracranial hypertension from gas collection. CT or MRI of the sella has largely replaced neuroencephalography.

More than 99% of cases of acromegaly are attributable to pituitary adenoma (or use of recombinant GH for unapproved aging prevention, for which this substance is not effective, as of current data). Thus, the primary treatment of acromegaly is transsphenoidal surgery (or withdrawal of drug) and symptomatic treatment of the carpal tunnel or other syndromes provoked. If the pituitary tumor is not totally removed, patients are often offered external pituitary irradiation. In the case of suprasellar extension, conventional transfrontal hypophysectomy is often performed. The dopaminergic agonist bromocriptine can lower GH levels, but the long-term follow-up with this drug is not favorable. Octreotide, a long-acting analogue of somatostatin, now given in depot form approximately once a month, produces effective palliation in 50% of patients. Other medical therapies such as pegvisomant or somatostatin analogues are also medications that have been tried before surgical intervention. In 2011, new guidelines were published with few changes to the available recommendations.[99] However, the new guidelines reported some evidence that medication taken preoperatively may result in a better postoperative outcome.

Difficulty with endotracheal intubation should be anticipated in a patient with acromegaly; lateral neck radiographs or CT scans of the neck and direct or indirect visualization can identify patients with subglottic stenosis or an enlarged tongue, mandible, epiglottis, or vocal cords. If placement of an arterial line is necessary, a brachial or femoral site may be preferable to a radial site.[100]

Anterior Pituitary Hypofunction

Anterior pituitary hypofunction results in deficiency of one or more of the following hormones: GH, TSH, ACTH, prolactin, or gonadotropin. No special preoperative and preprocedure preparation is required for a patient deficient in prolactin or gonadotropin; deficiency in GH, however, can result in atrophy of cardiac muscle, a condition that may necessitate preoperative and preprocedure cardiac evaluation. Nonetheless, anesthetic problems have not been documented in patients with isolated GH deficiency. Acute deficiencies are another matter.

Acute pituitary deficiency is often caused by bleeding into a pituitary tumor. In surgical specimens of resected adenomas, as many as 25% show evidence of hemorrhage. These patients often have acute headache, visual loss, nausea or vomiting, ocular palsy, disturbances of consciousness, fever, vertigo, or hemiparesis. In such patients, rapid transsphenoidal decompression should be accompanied by consideration of replacement therapy, including glucocorticoids, and treatment of increased intracranial pressure.

Obstetric anesthesiologists are often aware of these pituitary failure problems (see also Chapter 77); Sheehan syndrome is the clinical manifestation of pituitary infarction associated with hypotension after or during obstetric hemorrhage. Conditions that strongly suggest this diagnosis are failure to start postpartum lactation, increasing fatigue, cold intolerance, and especially hypotension unresponsive to volume replacement and pressors.

Posterior Pituitary Hormone Excess and Deficiency

Secretion of vasopressin or antidiuretic hormone (ADH) is enhanced by increased serum osmolality or the presence of hypotension. Inappropriate secretion of vasopressin, without relation to serum osmolality, results in hyponatremia and fluid retention. This inappropriate secretion can result from the following: a variety of CNS lesions; drugs such as nicotine, narcotics, chlorpropamide, clofibrate, vincristine, vinblastine, and cyclophosphamide; and pulmonary infections, hypothyroidism, adrenal insufficiency, and ectopic production from tumors. Preoperative and preprocedure management of a surgical patient with inappropriate secretion of vasopressin includes appropriate treatment of the causative disorders and restriction of water. Occasionally, drugs that inhibit the renal response to ADH (e.g., lithium or demeclocycline) should be administered preoperatively to restore normal intravascular volume and electrolyte status.

Most of the clinical features associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) are related to hyponatremia and the resulting brain edema; such features include weight gain, weakness, lethargy, mental confusion, obtundation, and disordered reflexes and may culminate in convulsions and coma. This form of edema rarely leads to hypertension.

Investigators have recognized that 10% to 20% of long-distance and marathon runners have SIADH with increased vasopressin secretion. Because such people not infrequently undergo surgical treatment of injuries, SIADH symptoms and laboratory evaluation may be routine for that group as well.

SIADH should be suspected in any patient with hyponatremia who excretes urine that is hypertonic relative to plasma. The following laboratory findings further support the diagnosis:

1. Urinary sodium greater than 20 mEq/L
2. Low serum levels of BUN, creatinine, uric acid, and albumin
3. Serum sodium lower than 130 mEq/L
4. Plasma osmolality lower than 270 mOsm/L
5. Urine hypertonic relative to plasma

Noting the response to water loading is a useful way of evaluating patients with hyponatremia. Patients with SIADH are unable to excrete dilute urine even after water loading. Assay of ADH in blood can confirm the diagnosis. Too vigorous treatment of chronic hyponatremia can result in disabling demyelination.[101,102] The increase in serum sodium should not be greater than 1 mEq/L/hour[101,102] (see the discussion of hyponatremia in the later section on electrolyte disorders).

Patients with mild to moderate symptoms of water intoxication can be treated with restriction of fluid intake to approximately 500 to 1000 mL/day. Patients with severe water intoxication and CNS symptoms may need vigorous treatment consisting of intravenous administration of 200 to 300 mL of a 5% saline solution over a period of several hours, followed by fluid restriction.

Treatment should be directed at the underlying problem. If SIADH is drug induced, use of the drug should be withdrawn. Inflammation should be treated with appropriate measures, and neoplasms should be managed by surgical resection, irradiation, or chemotherapy, whichever is indicated.

No drugs are available that can suppress release of ADH from the neurohypophysis or from a tumor. Phenytoin (Dilantin) and narcotic antagonists such as naloxone and butorphanol have some inhibiting effect on physiologic ADH release but are clinically ineffective in patients with SIADH. Drugs that block the effect of ADH on renal tubules include lithium, which is rarely used because its toxicity often outweighs its benefits, and demethylchlortetracycline in doses of 900 to 1200 mg/day. Demethylchlortetracycline interferes with the ability of the renal tubules to concentrate urine, thereby causing excretion of isotonic or hypotonic urine and lessening the hyponatremia. This drug can be used in ambulatory patients with SIADH when it is difficult to restrict fluids.

When a patient with SIADH comes to the operating room for any surgical procedure, fluids are managed by measuring central volume status by CVP, pulmonary artery lines, or the cross-sectional left ventricular area at end-diastole on transesophageal echocardiography and by frequent assays of urine osmolarity, plasma osmolarity, and serum sodium, including the period immediately after the surgical procedure. Despite the common impression that SIADH is frequently seen in older patients in the postoperative period, studies have shown that the patient's age and the type of anesthetic used have no bearing on the postoperative development of SIADH. It

is not unusual to see several patients in the neurosurgical ICU suffering from this syndrome. The diagnosis is usually one of exclusion. Patients with SIADH generally require only restriction of intravenous fluids; very rarely is hypertonic saline needed.

Lack of ADH, which results in diabetes insipidus, is caused by pituitary disease, brain tumors, infiltrative diseases such as sarcoidosis, head trauma (including trauma after neurosurgery), or lack of a renal response to ADH. The last can result from such diverse conditions as hypokalemia, hypercalcemia, sickle cell anemia, obstructive uropathy, and renal insufficiency. Preoperative or preprocedure treatment of diabetes insipidus consists of restoring normal intravascular volume by replacing urinary losses, administering desmopressin acetate (DDAVP) nasally, and giving daily fluid requirements intravenously.

Perioperative management of patients with diabetes insipidus is based on the extent of the ADH deficiency. Management of a patient with complete diabetes insipidus and a total lack of ADH does not usually present any major problem as long as the side effects of the drug are avoided and the presence of the condition is known preoperatively. Just before the surgical procedure, the patient is given the usual dose of DDAVP intranasally or an intravenous bolus of 100 milliunits of aqueous vasopressin, followed by a constant infusion of 100 to 200 milliunits/hour.[1] The dose is usually adjusted to permit the daily breakthrough polyuria that prevents the iatrogenic syndrome of SIADH. All the intravenous fluids given intraoperatively should be isotonic to reduce the risk of water depletion and hypernatremia. Plasma osmolality should be measured every hour, both intraoperatively and immediately postoperatively. If plasma osmolality rises much higher than 290 mOsm/L, hypotonic fluids can be administered; the rate of the intraoperative vasopressin infusion can be increased to greater than 200 milliunits/hour.

For patients who have a partial deficiency of ADH, it is not necessary to use aqueous vasopressin perioperatively unless plasma osmolality rises to more than 290 mOsm/L. Nonosmotic stimuli (e.g., volume depletion) and the stress of surgery usually cause the release of large quantities of ADH perioperatively. Consequently, these patients require only frequent monitoring of plasma osmolality during this period.

Because of side effects, the dose of vasopressin should be limited to that necessary for control of diuresis. The oxytocic and coronary artery–constricting properties of vasopressin make this limit especially applicable to patients who are pregnant or have CAD.

DISEASES INVOLVING THE CARDIOVASCULAR SYSTEM

HYPERTENSION

Analysis of the perioperative treatment of hypertension is important because of the prevalence of the condition (30% of the general population in the United States), the great risk in perioperative care of a hypertensive patient, and the high cost of unnecessary delays in surgical treatment. Numerous studies over the years have evaluated the impact of hypertension as one of the risk factors for cardiac morbidity. More recently, the need to delay surgery because of poorly controlled hypertension has been questioned. Weksler and colleagues studied 989 hypertensive patients who were treated on a long-term basis and who underwent noncardiac surgery with diastolic blood pressure between 110 and 130 mm Hg and no previous myocardial infarction (MI), unstable or severe angina pectoris, renal failure, pregnancy-induced hypertension, left ventricular hypertrophy, previous coronary revascularization, aortic stenosis, preoperative dysrhythmias, conduction defects, or stroke.[103] The control group had their surgical procedures postponed and remained in the hospital for control of blood pressure, and the study patients received 10 mg of nifedipine intranasally. No statistically significant differences in postoperative complications were observed, thus suggesting that this subset of patients without significant cardiovascular comorbid conditions can proceed with surgery despite elevated blood pressure on the day of the operation.

Several studies have assessed the relationship between cardiovascular disease and preoperative hypertension. In a multicenter study of patients undergoing coronary artery bypass graft (CABG), the presence of isolated systolic hypertension was associated with a 30% increased incidence of perioperative cardiovascular complications when compared with normotensive individuals.[104] Kheterpal and colleagues integrated data from their anesthesia information system (AIMS) and the American College of Surgeons National Surgical Quality Improvement Project (NSQIP) and found hypertension to be one of the independent predictors of events.[105] Wax and colleagues used their AIMS to identify independent predictors of troponin elevation or death, and independent predictors of adverse outcome included increased baseline systolic blood pressure, intraoperative diastolic blood pressure lower than 85 mm Hg, increased intraoperative heart rate, blood transfusion, and anesthetic technique, controlling for standard risk factors.[106] A delay of surgery did not result in interval normalization of blood pressure.

Although preoperative blood pressure (both systolic and diastolic) is a significant predictor of postoperative morbidity, no data definitively establish whether preoperative treatment of hypertension reduces perioperative risk. Until a definitive study is performed, we recommend letting the weight of evidence guide preoperative treatment of a patient with hypertension. Such treatment would be based on three general beliefs: (1) the patient should be educated regarding the importance of lifelong treatment of hypertension, even isolated systolic hypertension; (2) perioperative hemodynamic fluctuations occur less frequently in treated than in untreated hypertensive patients (as demonstrated by Prys-Roberts and colleagues[107] and confirmed by Goldman and Caldera[108] and Mangano and associates[109]); and (3) hemodynamic fluctuations have some relation to morbidity. Kheterpal and colleagues demonstrated that patients who sustained a cardiac adverse event were more likely to experience an episode of mean arterial pressure lower than 50 mm Hg,

an episode of 40% decrease in mean arterial pressure, and an episode of heart rate higher than 100 beats/minute.[105] The data of Pasternack and colleagues and Weksler and associates imply that rapid correction of blood pressure or prevention of increases in heart rate may be all that is needed.[103,110] Taken together, these data suggest that maintenance of normal blood pressure is critical in patients with hypertension.

Preoperative data should be used to determine the individualized range of suitable arterial blood pressure values that are tolerable by a particular patient during and after a surgical procedure. That is, if blood pressure is 180/100 mm Hg and the heart rate is 96 beats/minute on admission with no signs or symptoms of myocardial ischemia, these levels can likely be tolerated during a surgical procedure. Conversely, if during the night blood pressure decreases to 80/50 mm Hg and the heart rate to 48 beats/minute and a new cerebral deficit does not occur, the patient can probably safely tolerate such levels during anesthesia. Therefore, on the basis of preoperative data, we derive an individualized set of values for each patient. However, hypotension in patients at risk for a cerebrovascular event should be avoided. For example, the POISE (Perioperative Ischemic Evaluation) study demonstrated that short-term β-blocker administration resulted in an increased incidence of stroke and death that was associated with an increased rate of hypotension.[111]

Preoperative Administration of All Antihypertensive Drugs

Continuation of all antihypertensive drugs preoperatively should be considered, except ACE inhibitors or angiotensin II antagonists, for which no clear consensus exists. Coriat and colleagues found that ACE inhibitors were associated with hypotension in 100% of patients during induction versus approximately 20% in whom ACE inhibitors were withheld on the morning of the surgical procedure.[112] Bertrand and co-workers performed a prospective randomized study that demonstrated that more severe hypotensive episodes requiring vasoconstrictor treatment occurred after induction of general anesthesia in patients treated on a long-term basis with an angiotensin II antagonist and receiving the drug on the morning before the operation than in those in whom angiotensin II antagonists were discontinued on the day before the surgical procedure.[113] Kheterpal and colleagues performed a propensity-matched analysis of 12,381 noncardiac surgical cases.[114] Patients with long-term ACE inhibitor or angiotensin receptor blocker and diuretic therapy showed more periods with a mean arterial blood pressure lower than 70 mm Hg, periods with a 40% decrease in systolic blood pressure, periods with a 50% decrease in systolic blood pressure, and vasopressor boluses than did patients receiving diuretic therapy alone. If these drugs are continued, vasopressin is the drug of choice for refractory hypotension. Investigators at the Cleveland Clinic evaluated 79,228 patients (9905 ACE inhibitor users [13%] and 66,620 [87%] non–ACE inhibitor users) who had noncardiac surgery between 2005 and 2009.[115] These investigators did not find any association between use of ACE inhibitors and intraoperative or postoperative upper airway complications. ACE inhibitor use was not associated with in-hospital complications or increased 30-day mortality.

ISCHEMIC HEART DISEASE

Preoperative evaluation of a patient with ischemic heart disease (see also Chapter 67) and a discussion of the AHA/ACC guidelines can be found in Chapter 38.[116] New guidelines were published in 2014 by both the AHA/ACC and the European Society of Cardiology.[116a,166b]

Role of Coronary Artery Bypass Graft or Percutaneous Coronary Interventions Before Noncardiac Surgical Procedures

Coronary revascularization may reduce the perioperative risk before noncardiac surgery (see also Chapter 67). Earlier successful preoperative revascularization may decrease postoperative cardiac risk twofold to fourfold in patients undergoing elective vascular surgery.[117,118] The strongest retrospective evidence comes from the Coronary Artery Surgery Study (CASS) registry, which enrolled patients from 1978 to 1981. Operative mortality in patients with CABG performed before noncardiac surgery was 0.9% but was significantly higher at 2.4% in patients without previous CABG. However, a 1.4% mortality rate was associated with the CABG procedure itself.

Eagle and colleagues reported on a long-term analysis of patients entered into the CASS.[119] These investigators studied patients assigned to medical or surgical therapy for CAD for more than 10 years who subsequently underwent 3368 noncardiac operations in the years after assignment of coronary treatment. Intermediate-risk surgery such as abdominal, thoracic, or carotid endarterectomy were associated with a combined morbidity and mortality rate of 1% to 5% and a small but significant improvement in outcome in patients who had previously undergone revascularization. The most significant improvement in outcome occurred in patients who underwent major vascular surgery such as abdominal or lower extremity revascularization. However, this observational study did not randomize patients and was undertaken in the 1970s and 1980s, before significant advances in medical, surgical, and percutaneous coronary strategies.[119]

Landesberg and coauthors retrospectively reviewed long-term outcomes in 578 major vascular procedures.[120] By multivariate analysis, age, type of vascular surgery, presence of diabetes, previous MI, and moderate to severe ischemia on preoperative thallium scanning independently predicted mortality, and preoperative coronary revascularization predicted improved survival. Long-term survival after major vascular surgery was significantly improved if patients with moderate to severe ischemia on preoperative thallium scanning underwent selective coronary revascularization.

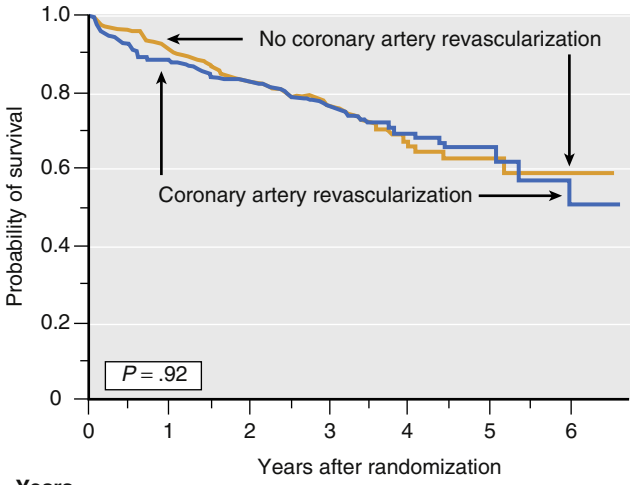
The benefit of percutaneous coronary intervention (PCI) before noncardiac surgery has also been examined in several cohort studies. Posner and colleagues used an administrative data set of patients who underwent PCI and noncardiac surgery in Washington State.[121] These

investigators matched patients with coronary disease who were undergoing noncardiac surgery with and without previous PCI and looked at cardiac complications. In this nonrandomized design, Posner and colleagues noted a significantly lower rate of 30-day cardiac complications in patients who underwent PCI at least 90 days before the noncardiac surgery. However, PCI within 90 days of noncardiac surgery did not improve outcome. Although the explanation for these results is unknown, they may support the notion that PCI performed "to get the patient through surgery" may not improve perioperative outcome because cardiac complications may not occur in patients with stable or asymptomatic coronary stenosis. PCI may actually destabilize coronary plaque, which becomes manifest in the days or weeks after noncardiac surgery.

Godet and associates studied a cohort of 1152 patients after abdominal aortic surgery in which 78 patients underwent PCI.[122] In the PCI group, the observed percentages of patients with a severe postoperative coronary event (9.0%; 95% confidence interval [CI], 4.4 to 17.4) or death (5.1% [95% CI, 2.0 to 12.5]) were not significantly different from the expected percentages (8.2% and 6.9%, respectively), which was confirmed by propensity analysis. PCI did not seem to significantly limit cardiac risk or death after aortic surgery.

Several randomized trials have addressed the value of testing and CABG or PCI, or both, in a subset of patients. McFalls and colleagues reported the results of a multicenter randomized trial in the VA Health System in which patients with documented CAD on coronary angiography, excluding those with left main CAD or a severely depressed ejection fraction (<20%), were randomized to CABG (59%) or percutaneous transluminal coronary angioplasty (PTCA) (41%) versus routine medical therapy.[123] At 2.7 years after randomization, mortality in the revascularization group was not significantly different (22%) from that in the no-revascularization group (23%) (Fig. 39-4). Within 30 days after the vascular operation, postoperative MI, defined by elevated troponin levels, occurred in 12% of the revascularization group and in 14% of the no-revascularization group (P = .37). The authors suggested that coronary revascularization is not indicated in patients with stable CAD, and their results further support the lack of efficacy of PCI or CABG for single- or double-vessel disease before noncardiac surgery. However, in a follow-up analysis, Ward and coauthors reported improved outcome in the subset of patients who underwent CABG versus PCI.[124]

Poldermans and colleagues randomized 770 patients about to undergo major vascular surgery and considered to have intermediate cardiac risk, defined as the presence of 1 or 2 cardiac risk factors, to either undergo further risk stratification with stress imaging or proceed directly to surgery.[125] All patients received bisoprolol with a targeted heart rate of 60 to 65 beats/minute initiated before and continued after the surgical procedure. The 30-day incidence of cardiac death and nonfatal MI was similar in both groups (1.8% in the no-testing group versus 2.3% in the tested group). The conclusions of the authors were that further risk stratification in this group of patients considered to be at intermediate risk based on clinical history alone was unnecessary as long as perioperative β-blockers



Years	1	2	3	4	5	6
No. at risk						
Revascularization	226	175	113	65	18	7
No revascularization	229	172	108	55	17	12

Figure 39-4. Long-term survival in patients randomized to coronary revascularization or routine care in patients with coronary artery disease on angiography and undergoing major vascular surgical procedures in the Coronary Artery Revascularization Prophylaxis trial. *(From McFalls EO, Ward HB, Moritz TE, et al: Coronary-artery revascularization before elective major vascular surgery,* N Engl J Med *351:2795-2804, 2004.)*

were used and that testing only delayed necessary vascular surgery. In a pilot study, Poldermans and associates tested patients with more than 3 risk factors; 101 (23%) showed extensive ischemia and were randomly assigned to revascularization (n = 49) or no revascularization.[126] Revascularization did not improve 30-day outcome; the incidence of the composite end-point was 43% versus 33% (odds ratio [OR], 1.4; 95% CI, 0.7 to 2.8; P = .30). In addition, no benefit during 1-year follow-up was observed after coronary revascularization (49% versus 44%; OR, 1.2; 95% CI, 0.7 to 2.3; P = .48). Concern was expressed by Erasmus University (Rotterdam, the Netherlands) regarding the scientific integrity of studies led by Poldermans, as detailed in Erasmus MC Follow-up Investigation Committee: *Report on the 2012 follow-up investigation of possible breaches of academic integrity, September 30, 2012* (http://www.erasmusmc.nl/5663/135857/3675250/3706798/Integrity_report_2012-10.pdf?lang=en). At the time of writing this chapter, the articles have not been retracted, but these data should be viewed with some skepticism. The authors of the 2014 AHA/ACCF Guidelines decided that the nonretracted decrease publications and/or other derivative studies by Poldermans that are relevant to the topic can only be cited in the text with a comment about the finding compared with the current recommendation but did not form the basis of that recommendation.

One issue in interpreting the results is that the length of time between coronary revascularization and noncardiac surgery most likely has an impact on its protective effect and potential risks. Back and co-workers studied 425 consecutive patients undergoing 481 elective major vascular operations at an academic VA Medical Center.[127] Coronary revascularization was classified as recent (CABG <1 year; PTCA <6 months) in 35 cases (7%),

prior (CABG >1 year and ≤5 years; PTCA >6 months and ≤2 years) in 45 cases (9%), and remote (CABG ≥5 years; PTCA ≥2 years) in 48 cases (10%). Outcomes in patients with previous PTCA were similar to those after CABG (P = .7). Significant differences in adverse cardiac events and mortality were found among patients with CABG performed within 5 years or PTCA within 2 years (6.3%, 1.3%, respectively), individuals with remote revascularization (10.4%, 6.3%), and nonrevascularized patients stratified at high risk (13.3%, 3.3%) or intermediate/low risk (2.8%, 0.9%). The authors concluded that previous coronary revascularization (CABG <5 years; PTCA <2 years) may provide only modest protection against adverse cardiac events and mortality after major arterial reconstruction.

PCI using coronary stenting poses several special issues. Kaluza and associates reported on the outcome of 40 patients who underwent prophylactic coronary stent placement less than 6 weeks before major noncardiac surgery requiring general anesthesia.[128] Among these patients, 7 MIs, 11 major bleeding episodes, and 8 deaths were noted. All deaths and MIs, as well as 8 of the 11 bleeding episodes, occurred in patients subjected to surgical procedures less than 14 days after stenting. Four patients died after undergoing surgical procedures 1 day after stenting. Wilson and colleagues reported on 207 patients who underwent noncardiac surgery within 2 months of stent placement.[129] Eight patients died or suffered an MI, all of whom were among the 168 patients who had surgical procedures 6 weeks after stent placement. Vicenzi and co-workers studied 103 patients and reported that the risk of suffering a perioperative cardiac event was 2.11-fold greater in patients with recent stents (<35 days before surgery) than in those who underwent PCI more than 90 days before surgical procedures.[130] Leibowitz and associates studied a total of 216 consecutive patients who underwent PCI within 3 months of noncardiac surgery (PTCA, 122; stent, 94).[131] A total of 26 patients (12%) died, 13 in the stent group (14%) and 13 in the PTCA group (11%), a nonsignificant difference. The incidence of acute MI and death within 6 months was not significantly different (7% and 14% in the stent group and 6% and 11% in the PTCA group, respectively). Significantly more events occurred in the 2 groups when noncardiac surgery was performed within 2 weeks of PCI. Based on the accumulating data, elective noncardiac surgery after PCI, with or without stent placement, should be delayed for 4 to 6 weeks.

Drug-eluting stents may represent an even greater problem during the perioperative period based on case reports. Nasser and coauthors described two patients with in-stent thrombosis occurring 4 and 21 months after the implantation of sirolimus-eluting stents.[132] Drug-eluting stents may represent an additional risk over a prolonged period (≤12 months), particularly if antiplatelet drugs are discontinued.[133] One study demonstrated that although the frequency of major noncardiac surgery in the year after drug-eluting stent placement was more than 4%, the overall risk of adverse outcomes was less than previously reported when surgical procedures were performed months after drug-eluting stent placement.[134] However, the risk was significantly increased in the week after major noncardiac surgery. A population-based study in Canada using administrative health care databases demonstrated that the earliest optimal time for elective surgery is 46 to 180 days after bare metal stent implantation or more than 180 days after drug-eluting stent implantation.[135] Hawn and colleagues used a national, retrospective cohort study of 41,989 VA and non-VA operations occurring in the 24 months after coronary stent implantation between 2000 and 2010.[136] Among patients undergoing noncardiac surgery within 2 years of coronary stent placement, major adverse cardiac events were associated with emergency surgery and advanced cardiac disease but not stent type or timing of surgery beyond 6 months after stent implantation (Fig. 39-5).

Perioperative Risk Factors for Cardiac Morbidity and Mortality

A thorough history should focus on cardiovascular risk factors and symptoms or signs of unstable cardiac disease states, such as myocardial ischemia with minimal exertion, active CHF, symptomatic valvular heart disease, and significant cardiac arrhythmias. The presence of unstable angina is associated with a 28% incidence of perioperative MI.[137] Such patients would benefit from delaying elective surgery to address their CAD. For those patients with chronic stable angina, exercise tolerance appears to be a good method of assessing perioperative risk.

In virtually all studies, the presence of active CHF has been associated with increased perioperative cardiac morbidity.[138] In addition, multiple studies have demonstrated that reduced ejection fraction is associated with an increased incidence of perioperative cardiac events.[139,140] Flu and colleagues performed echocardiography in patients undergoing vascular surgery and found that for open surgical procedures, asymptomatic systolic left ventricular dysfunction and asymptomatic diastolic left ventricular dysfunction were both associated with increased 30-day cardiovascular event rates (OR, 2.3; 95% CI, 1.4 to 3.6; and OR, 1.8; 95% CI 1.1 to 2.9, respectively) and long-term cardiovascular mortality (hazard ratio, 4.6; 95% CI 2.4 to 8.5; and hazard ratio, 3.0; 95% CI 1.5 to 6.0, respectively).[141] In patients undergoing endovascular surgery (n = 356), only symptomatic heart failure was associated with an increase in 30-day cardiovascular events and long-term cardiovascular mortality. These results suggest that stabilization of ventricular function and treatment of pulmonary congestion is prudent before elective surgery.

A recent MI has traditionally been an important predictor of perioperative risk. The more recent the MI, particularly within 3 to 6 months, the greater is the perioperative risk. However, like the Goldman Cardiac Risk Index, medicine has changed and outcomes are improved. The classic article by Rao and associates that was published in 1983 cited a reinfarction rate of nearly 30% if noncardiac surgery occurred within 3 months of a prior infarction.[142] These reinfarctions had a very high mortality rate. With the advent of dedicated postoperative ICUs, more vigilant monitoring, and early intervention, the postoperative reinfarction rate has decreased by almost an order of magnitude. The 2014 AHA/ACC Foundation (AHA/ACCF) guidelines advocate the use of 60 days as being high risk.[116a] After that time, further risk stratification depends on clinical symptoms.

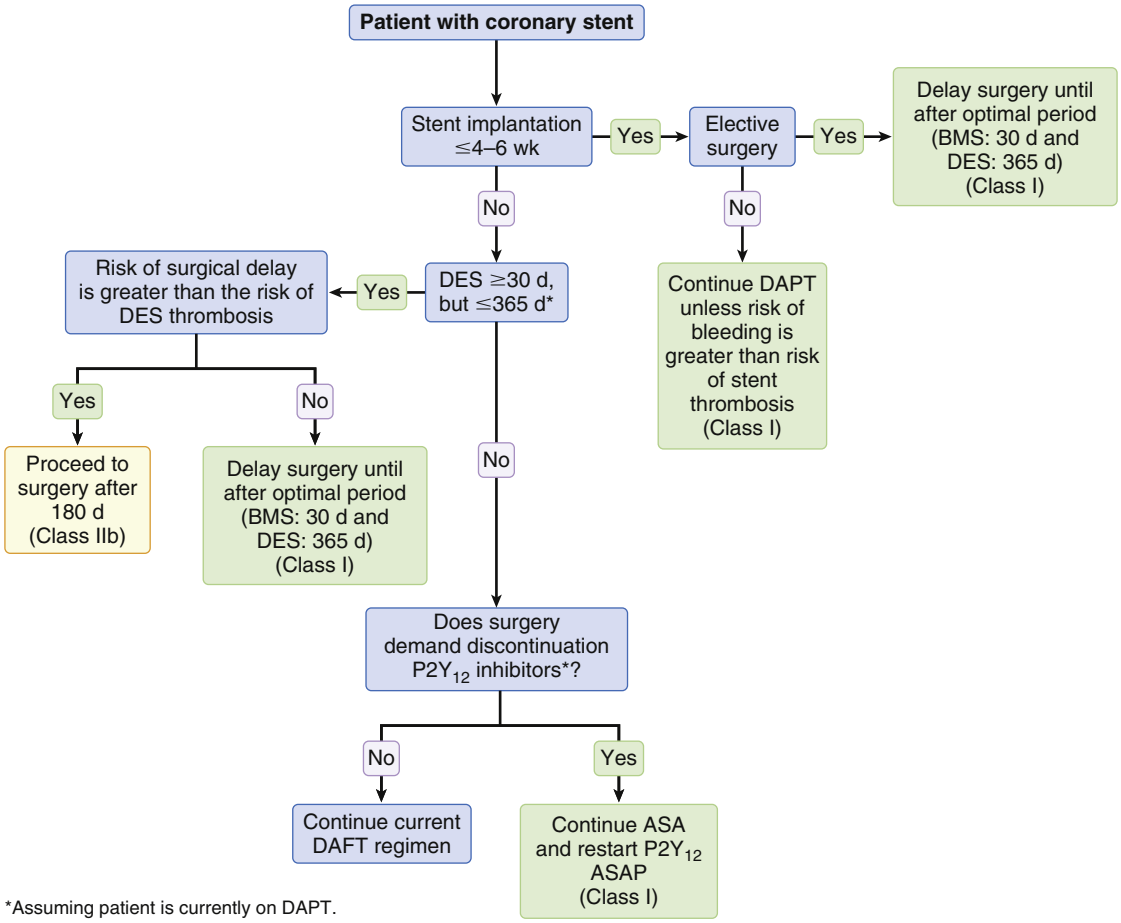


Figure 39-5. Proposed algorithm for antiplatelet management in patients with PCI and noncardiac surgery. *ASA,* Aspirin; *BMS,* bare metal stent; *DAPT,* dual antiplatelet therapy; *DES,* drug-eluting stent; *PCI,* percutaneous coronary intervention. *(From Fleisher LA, Fleischmann KE, Auerbach AD, et al: 2014 ACC/AHA guidelines on perioperative cardiovascular evaluation and management of patients undergoing noncardiac srgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines,* J Am Coll Cardiol *2014 Jul 29. [Epub ahead of print.])*

For those patients without overt symptoms or a history of CAD, the probability of CAD varies with the type and number of atherosclerotic risk factors present. Diabetes accelerates the progression of atherosclerosis, which can frequently be silent, leading many clinicians to assume that diabetes is a CAD equivalent and treating patients as such. Diabetes is an independent risk factor for perioperative cardiac morbidity, and the preoperative treatment with insulin has been included in the Revised Cardiac Risk Index (RCRI). In attempting to determine the degree of the increased risk associated with diabetes, the treatment modality, duration of the disease, and other associated end-organ dysfunction should be taken into account.

Significant intraoperative factors that correlate with perioperative risk and that may be avoided or altered are (1) unnecessary use of vasopressors,[143,144] (2) unintentional hypotension[145-147] (this point is controversial, however, because some investigators have found that unintentional hypotension does not correlate with perioperative morbidity[144]), (3) hypothermia,[148] (4) too low or too high a hematocrit,[149,150] and (5) lengthy operations.[146]

Significant intraoperative factors that correlate with perioperative morbidity and probably cannot be avoided are (1) emergency surgery and (2) thoracic or intraperitoneal surgery or above-the-knee amputations.[146,151-164]

Several risk indices were developed in a prospective cohort study by Lee and asociates.[165] They studied 4315 patients 50 years old or older who were undergoing elective major noncardiac procedures in a tertiary care teaching hospital. The 6 independent predictors of complications included in a RCRI were high-risk type of surgery, history of ischemic heart disease, history of CHF, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine greater than 2.0 mg/dL; increasing cardiac complication rates were noted with an increasing number of risk factors.[165] The RCRI has become the standard tool in the literature for assessing perioperative cardiac risk in a given individual and has been used to direct the decision to perform cardiovascular testing and implement perioperative management protocols. It has been validated for both short-term and long-term cardiovascular outcomes.[166] It has also been shown to predict long-term quality of life.[166] Therefore, the RCRI can be used to help define both the short-term and long-term risks of cardiovascular disease in the surgical patient.

The American College of Surgeons NSQIP created a Surgical Risk Calculator from 525 participating hospitals

and more than 1 million operations.[167] This risk calculator uses the specific current procedural terminology code of the procedure being performed to enable procedure-specific risk assessment and includes 21 patient-specific variables (e.g., age, sex, body mass index, dyspnea, previous MI). From this input, it calculates the percentage of risk of a major adverse cardiac event, death, and 8 other outcomes. Use of this risk calculator may offer the best estimation for surgery-specific risk of a major adverse cardiac event and death.

The American College of Surgeons NSQIP Myocardial Infarction and Cardiac Arrest (MICA) risk prediction rule is more specific for cardiac complications.[168] Using these definitions of outcome and chart-based data collection methods, the authors derived a risk index that was robust in the derivation and validation stages and appeared to outperform the RCRI (which was tested in the same data set) in terms of discriminative power, particularly among patients undergoing vascular surgery.

A primary issue with all these indices is that a simple estimate of risk does not help in refining perioperative management for an individual patient. Therefore, the consultant must communicate the extent and stability of the patient's CAD, rather than make a simple statement of risk classification.

The goal in providing anesthesia to patients with ischemic heart disease is to achieve the best preoperative condition obtainable by treating conditions that correlate with perioperative risk. The next step is to intraoperatively monitor for conditions that correlate with perioperative risk and avoid circumstances that lead to perioperative risk.

Preoperative and Preprocedure Therapy

The only way known to increase oxygen supply to the myocardium of patients with coronary artery stenosis is to maintain adequate diastolic blood pressure, hemoglobin concentration, and oxygen saturation (see also Chapter 38). The main goals of anesthesia practice for these patients have been to decrease the determinants of myocardial oxygen demand, heart rate, ventricular wall tension, and contractile performance and to improve plaque stabilization. Thus, medical management designed to preserve all viable myocardial tissue may include the following:

1. Continuation of β-adrenergic receptor blocking drugs (propranolol, atenolol, esmolol, or metoprolol) to avoid β-blocker withdrawal leading to increased contractility and heart rate. Multiple studies have demonstrated improved outcome in patients given perioperative β-adrenergic blockers, especially if the heart rate is controlled.[169,170] However, newer studies have demonstrated that β-adrenergic blockers may not be effective if the heart rate is not well controlled or in lower-risk patients.[171-173] The POISE trial enrolled 8351 high-risk β-blocker–naive patients who were randomized to high-dose continuous-release metoprolol versus placebo.[111] A significant reduction in the primary outcome of cardiovascular events was reported, along with a 30% reduction in the MI rate, but with a significantly increased rate of 30-day all-cause mortality and stroke. The current ACC/AHA guidelines on perioperative β blockade advocate that perioperative β blockade is a class I indication and should be used in patients previously taking β-blockers and those with a positive stress test who are undergoing major vascular surgery, although short-term administration without titration may be associated with harm (Box 39-3).
2. Vasodilation (with nitroglycerin or its "long-acting" analogues nitroprusside, hydralazine, or prazosin) to decrease ventricular wall tension may be beneficial, although currently no randomized trials support the prophylactic use of these agents.[109,110,174] The use of Swan-Ganz catheters and transesophageal echocardiography for this type of patient is described in Chapter 45,[159,175] and the intraoperative management of patients with ischemic heart disease is discussed in further detail in Chapter 67 and in published guidelines.[116]
3. Aspirin, statins, exercise, and diet. These choices seem to be indicated in many patients. Briefly, we believe that drugs given on a long-term basis (e.g., antihypertensive medications and some ACE inhibitors) should be continued through the morning of the surgical procedure (see earlier). The topic of long-term drug

BOX 39-3 *2014 ACCF/AHA Recommendations for Perioperative β-Blockade*

Class I

- β-Blockers should be continued in patients undergoing surgery who have been on β-blockers chronically.[111-117] **(Level of Evidence: B)**

Class IIa

- It is reasonable for the management of β-blockers after surgery to be guided by clinical circumstances, independent of when the agent was started.[110,117,118] **(Level of Evidence: B)**

Class IIb

- In patients with intermediate- or high-risk myocardial ischemia noted in preoperative risk stratification tests, it may be reasonable to begin perioperative β-blockers.[119] **(Level of Evidence: C)**
- In patients with three or more RCRI risk factors (e.g., diabetes mellitus, heart failure, coronary artery disease, renal insufficiency, cerebrovascular accident), it may be reasonable to begin β-blockers before surgery.[117] **(Level of Evidence: B)**
- In patients with a compelling long-term indication for β-blocker therapy but no other RCRI risk factors, initiating beta blockers in the perioperative setting as an approach to reduce perioperative risk is of uncertain benefit.[111,117,120] **(Level of Evidence: B)**
- In patients in whom β-blocker therapy is initiated, it may be reasonable to begin perioperative β-blockers long enough in advance to assess safety and tolerability, preferably more than 1 day before surgery.[110,121-123] **(Level of Evidence: B)**

Class III: Harm

- β-Blocker therapy should not be started on the day of surgery.[110] **(Level of Evidence: B)**

From Fleisher LA, Fleischmann KE, Auerbach AD, et al: 2014 ACC/AHA guidelines on perioperative cardiovascular evaluation and management of patients undergoing noncardiac srgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, J Am Coll Cardiol *2014 Jul 29. [Epub ahead of print]*

RCRI, Revised Cardiac Risk Index.

therapy is discussed in more detail in the last section of this chapter, on drug therapy.

4. Perioperative transfusion therapy is discussed in more detail in Chapter 61. The FOCUS (Functional Outcomes in Cardiovascular Patients Undergoing Surgical Repair of Hip Fracture) trial was unable to demonstrate benefit in high-risk patients with hip fracture between a high and low transfusion trigger.[176]

VALVULAR HEART DISEASE

Major alterations in the preoperative management of patients with valvular heart disease have been made regarding the use of anticoagulant therapy and are now based on the causes of the disease. Preoperative and intraoperative management of patients with valvular heart disease is discussed in Chapters 38 and 67.

The prognosis and, presumably, the perioperative risk for patients with valvular heart disease depend on the stage of the disease. Although stenotic lesions progress faster than do regurgitant lesions, regurgitant lesions secondary to infective endocarditis, rupture of the chordae tendineae, or ischemic heart disease can be rapidly fatal. Left ventricular dysfunction is common in the late stage of valvular heart disease.

Preoperative maintenance of drug therapy can be crucial; for example, the condition of a patient with aortic stenosis can deteriorate rapidly with the onset of atrial fibrillation or flutter because the atrial contribution to left ventricular filling can be critical in maintaining cardiac output. One of the most serious complications of valvular heart surgery and of preoperative valvular heart disease is cardiac arrhythmia. Conduction disorders and long-term therapy with antiarrhythmic and inotropic drugs are discussed elsewhere in this chapter. The reader is referred to Chapter 94 and to other sources for discussion of the management of a child with congenital heart disease who is undergoing noncardiac surgery.[177]

Preoperative Antibiotic Prophylaxis for Endocarditis

Patients who have any form of valvular heart disease, as well as those with intracardiac (ventricular septal or atrial septal defects) or intravascular shunts, should be protected against endocarditis at the time of a known bacteremic event. Endocarditis has occurred in a sufficiently significant number of patients with hypertrophic cardiomyopathy (subvalvular aortic stenosis, asymmetric septal hypertrophy) and mitral valve prolapse to warrant the inclusion of these two conditions in the prophylaxis regimen.

Bacteremia occurs after the following events: dental extraction, 30% to 80%; brushing of teeth, 20% to 24%; use of oral irrigation devices, 20% to 24%; barium enema, 11%; transurethral resection of the prostate (TURP), 10% to 57%; upper GI endoscopy, 8%; nasotracheal intubation, 16% (4 of 25 patients); and orotracheal intubation, 0% (0 of 25 patients). The most recent guidelines from the AHA consisted of an update in 2008 from the AHA/ACC on endocarditis in patients with valvular heart disease, with changes from the 2006 document shown in Table 39-7.[178]

Cardiac Valve Prostheses and Anticoagulant Therapy and Prophylaxis for Deep Vein Thrombosis

In patients with prosthetic valves, the risk of increased bleeding during a procedure in a patient receiving antithrombotic therapy must be weighed against the increased risk of thromboembolism caused by stopping the therapy. Common practice in patients undergoing noncardiac surgery with a mechanical prosthetic valve in place is cessation of anticoagulant therapy 3 days preoperatively. This time frame allows the international normalized ratio to fall to less than 1.5 times normal. The oral anticoagulants can then be resumed on postoperative day 1. Using a similar protocol, Katholi and colleagues found no perioperative episodes of thromboembolism or hemorrhage in 25 patients.[179] An alternative approach in patients at high risk for thromboembolism is conversion to heparin during the perioperative period. The heparin can then be discontinued 4 to 6 hours preoperatively and resumed shortly thereafter. Current prosthetic valves may have a lower incidence of this complication, and the risk associated with heparin may outweigh its benefit in the perioperative setting. According to the AHA/ACC guidelines, heparin can usually be reserved for patients who have had a recent thrombus or embolus (arbitrarily within 1 year), those with demonstrated thrombotic problems when previously off therapy, those with a Björk-Shiley valve, and those with more than three risk factors (atrial fibrillation, previous thromboembolism, hypercoagulable condition, and mechanical prosthesis).[180] A lower threshold for recommending heparin should be considered in patients with mechanical valves in the mitral position, in whom a single risk factor would be sufficient evidence of high risk. Subcutaneous low-molecular-weight heparin offers an alternative outpatient approach.[181] It is appropriate for the surgeon and cardiologist to discuss the optimal perioperative management for such a patient, including a review of the most recent guidelines.[182] A new guideline publication was published in 2014.[182a]

Regional anesthetic techniques may be avoided, although this issue is controversial.[183] Many practitioners do not hesitate to use regional anesthesia in patients who are receiving prophylaxis for deep vein thrombosis.[184-186] However, epidural hematoma has been associated with anticoagulant therapy in many reports. Large retrospective reviews of outcome after epidural or spinal anesthesia, or both, during or shortly before initiation of anticoagulant therapy with heparin have not reported neurologic dysfunction related to hematoma formation in any patient.[187,188] This paucity of damaging epidemiologic evidence, although reassuring, does not reduce the need for frequent evaluation of neurologic function and a search for back pain in the perioperative period after regional anesthesia in any patient receiving any clotting function inhibitor, including aspirin.[183,189-191] The risk of regional anesthesia concurrent with prophylaxis for deep vein thrombosis with heparin is greater with the use of low-molecular-weight heparin. (Heparin-induced thrombocytopenia has been treated successfully with intravenous immunoglobulin.[185]) The American Society of Regional Anesthesia and Pain Management has issued a consensus statement on the use of regional anesthesia in anticoagulated patients.[192] They

TABLE 39-7 CHANGES RELATED TO ENDOCARDITIS PROPHYLAXIS: AMERICAN COLLEGE OF CARDIOLOGY/ AMERICAN HEART ASSOCIATION GUIDELINES ON VALVULAR HEART DISEASE

2006 VHD Guideline Recommendations	2008 VHD Focused Update Recommendations	Comments
Class I	**Class IIa**	
Prophylaxis against infective endocarditis is recommended for the following patients: • Patients with prosthetic heart valves and patients with a history of infective endocarditis (*level of evidence: C*) • Patients who have complex cyanotic congenital heart disease (e.g., single-ventricle states, transposition of the great arteries, tetralogy of Fallot) (*level of evidence: C*) • Patients with surgically constructed systemic pulmonary shunts or conduits (*level of evidence: C*) • Patients with congenital cardiac valve malformations, particularly those with bicuspid aortic valves, and patients with acquired valvular dysfunction (e.g., rheumatic heart disease) (*level of evidence: C*) • Patients who have undergone valve repair (*level of evidence: C*) • Patients who have hypertrophic cardiomyopathy when there is latent or resting obstruction (*level of evidence: C*) • Patients with MVP and auscultatory evidence of valvular regurgitation and/or thickened leaflets on echocardiography* (*level of evidence: C*)	Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: • Patients with prosthetic cardiac valves or prosthetic material used for cardiac valve repair *(level of evidence: B)* • Patients with previous infective endocarditis *(level of evidence: B)* • Patients with CHD *(level of evidence: B)* • Unrepaired cyanotic CHD, including palliative shunts and conduits *(level of evidence: B)* • Completely repaired congenital heart defect repaired with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure *(level of evidence: B)* • Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (both of which inhibit endothelialization) *(level of evidence: B)* • Cardiac transplant recipients with valve regurgitation as a result of a structurally abnormal valve *(level of evidence: C)*	Modified recommendation (changed class of recommendation from I to IIa, changed text); no class I recommendations exist for infective endocarditis prophylaxis

CHD, Congenital heart disease; *MVP,* mitral valve prolapse; *VHD,* valvular heart disease.

*This footnote is obsolete. Please see 2006 VHD Guideline 3 for footnote text, in Bonow RO, Carabello BA, Kanu C, et al: ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease). Developed in collaboration with the Society of Cardiovascular Anesthesiologists: Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons, Circulation 114:e84-e231, 2006.

From Nishimura RA, Carabello BA, Faxon DP, et al: ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, Circulation *118:887-896, 2008.*

suggest that the decision to perform spinal or epidural anesthesia or analgesia and the timing of catheter removal in a patient receiving antithrombotic therapy should be made on an individual basis, with the small but definite risk of spinal hematoma weighed against the benefits of regional anesthesia for a specific patient.

Deep vein thrombosis is so common in postoperative patients that almost 1% of postsurgical patients die of fatal pulmonary embolism (Table 39-8).[193] Because of this high mortality risk, prophylaxis against deep vein thrombosis has attained widespread acceptance; thus, prophylaxis often begins with 5000 units of heparin given subcutaneously 2 hours preoperatively.[193-195] Other trials have shown equal effect with external pneumatic compression.[194,196] Persuading surgeons to use this technique may provide greater assurance in using regional anesthesia. Such an option, however, is not available for patients with a prosthetic valve. Newer recommendations are available from the American College of Chest Physicians for prophylaxis against venous thromboembolism.[197]

Another problem that can arise is managing a pregnant patient with a prosthetic valve during delivery. It is recommended that warfarin be replaced by subcutaneous heparin during the peripartum period. During labor and delivery, elective induction of labor is advocated with discontinuance of all anticoagulant therapy, as indicated for the particular valve prosthesis (discussed earlier).[198]

Auscultation of the prosthetic valve should be performed preoperatively to verify normal functioning. Abnormalities in such sounds warrant preoperative consultation and verification of functioning.

CARDIAC CONDUCTION DISTURBANCES: CARDIAC ARRHYTHMIAS

Bradyarrhythmias, especially if profound or associated with dizziness or syncope, are generally managed with pacemakers (see also Chapters 45 to 47). However, chronic bifascicular block (right bundle branch block with a left anterior or posterior hemiblock or left bundle

TABLE 39-8 **INCIDENCE OF DEEP VEIN THROMBOSIS AND FATAL PULMONARY EMBOLISM**

Type of Surgery	Incidence of Deep Vein Thrombosis (%)	Incidence of Proximal Deep Vein Thrombosis (%)	Incidence of Fatal Pulmonary Embolism (%)
General			
Age >40 yr	10	<1	0.1
Age >60 yr	10-40	3-15	0.8
Malignancy	50-60		
Thoracic	30		
Vascular			
Aortic repair	26		
Peripheral	12		
Urologic			
Open prostatectomy	40		
TURP	10		
Other urologic	30-40		
Major Gynecologic			
With malignancy	40		
Without malignancy	10-20		
Neurosurgery			
Craniotomy	20-80		
Laminectomy	4-25		1.5-3.0
Orthopedic			
Total hip replacement	40-80	10-20	1.0-5.0
Hip fracture	48-75		1.0-5.0
Tibial fracture	45		
Total knee replacement	60-70	20	1.0-5.0
Head, neck, chest wall	**11**		
Medical			
Acute myocardial infarction	30	6	
Stroke	60-75		
Acute spine injury	60-100		
Other bed bound	26		

TURP, Transurethral resection of the prostate.

branch block with combined left anterior and posterior hemiblocks), even when only a first-degree heart block is present, can progress to complete heart block and sudden perioperative death on rare occasion. In 6 studies, less than 2% of the approximately 266 patients with bifascicular block progressed to complete heart block perioperatively.[199] Conversely, these patients have a high 5-year mortality rate (160 of 554 patients, or 29%). Most of the deaths were related to tachyarrhythmias or MI—events not usually preventable by traditional pacemakers.[200] Thus, the presence of a bifascicular block on the ECG should make the anesthesiologist more worried about associated CAD or left ventricular dysfunction. Nevertheless, these patients rarely have complete heart block perioperatively. Therefore, prophylactic preoperative insertion of temporary pacing wires for bifascicular block does not seem warranted. However, a central route can be established in advance in the event that a temporary pacemaker needs to be inserted (most operating rooms do not rely on transthoracic pacing, although it may be attempted if available).[201] The actual pacemaker equipment and appropriate personnel should be immediately available, and the equipment should be tested regularly, because symptomatic heart block does occur perioperatively in more than 1% of patients. One study appears to have confirmed this rate of at least 1% for patients undergoing cardiac surgery.[202] One percent of patients in whom a pacing pulmonary artery catheter was not inserted preoperatively subsequently required pacing before cardiopulmonary bypass. By contrast, 19% of patients who had such a catheter in place underwent cardiac pacing before cardiopulmonary bypass. Predictors of the need for pacing included previous symptomatic bradyarrhythmia, a history of transient complete AV block, and aortic valve disease.

Older studies demonstrated that a rate of more than five PVCs per minute on preoperative examination correlates with perioperative cardiac morbidity.[146,153-155] To the classic criteria for treating PVCs (the presence of R-on-T couplets, the occurrence of more than three PVCs per minute, and multifocality of PVCs) must be added frequent (>10/hour over a 24-hour period) and repetitive ventricular beats. Electrophysiologic and programmed ventricular stimulation studies are being used to indicate and guide treatment of patients with ischemic heart disease or recurrent arrhythmias and survivors of out-of-hospital cardiac arrest. Although such patients are often treated with antiarrhythmic therapy, attention to their underlying condition should be a focus of our preoperative management. Long-term antiarrhythmic therapy is discussed in the last section of this chapter, on drug therapy. Torsades de pointes is an arrhythmia characterized by episodes of alternating electrical polarity such that the major vector of the QRS complex seems to alternate around an isoelectric line. The hallmark enabling differential diagnosis from ventricular tachycardia is the unusual response of this arrhythmia to commonly used antiarrhythmic drugs. In other words, the use of drugs that prolong the QT interval (e.g., quinidine, procainamide, disopyramide, some of the antihistamines, and the antipsychotic phenothiazines) may well make the arrhythmia more frequent or of longer duration. Reports of the sudden occurrence of torsades de pointes during surgical procedures have been rare in the anesthesia literature. Immediate therapy consists of the administration of magnesium or electrical cardioversion, followed by overdrive cardiac pacing or the administration of β-adrenergic agonists and discontinuation of drugs that prolong the QT interval.

Premature atrial contractions and cardiac rhythm other than sinus also correlate with perioperative cardiac morbidity.[146,154] These arrhythmias may be more a marker of poor cardiovascular reserve than a specific cause of perioperative cardiac complications.

Preexcitation syndrome is the name for supraventricular tachycardias associated with AV bypass tracts.[203]

Successful treatment, which is predicated on an understanding of the clinical and electrophysiologic manifestations of the syndrome, consists of either catheter ablation techniques[200] or surgery using preoperative and intraoperative techniques that avoid release of sympathetic and other vasoactive substances and therefore tachyarrhythmias.[204,205] Anesthesia for electrophysiologic procedures is discussed in Chapter 68.

DISORDERS OF THE RESPIRATORY AND IMMUNE SYSTEMS

GENERAL PREOPERATIVE AND PREPROCEDURE CONSIDERATIONS

Pulmonary complications after procedures requiring anesthesia are as common as cardiovascular complications—even more common if deep vein thrombosis is included. Moreover, pulmonary complications are equally important or more important to the patient and the health system in terms of morbidity, mortality, length-of-stay extension, and cost.

Although little may seem to have changed in the preoperative preparation of patients with respiratory disease, this impression is not true. Major changes in drug therapy have occurred, and appreciation of the effects of smoking and sleep apnea on perioperative and long-term care has increased.[206-223] (Preoperative and preprocedure identification and perioperative care of patients with sleep apnea are discussed in the earlier section on obesity and in Chapter 71.)

The main purpose of preoperative testing is to identify patients at risk for perioperative complications so that appropriate perioperative therapy can be instituted to foster return to functional status. Preoperative assessment can also establish baseline function and the feasibility of surgical intervention. Whereas numerous investigators have used pulmonary function tests to define inoperability or high-risk versus low-risk groups for pulmonary complications, few have been able to demonstrate that the performance of any specific preoperative or intraoperative measure, except perhaps smoking cessation and physical activity such as a walking program, reliably decreases perioperative pulmonary morbidity or mortality. Because routine preoperative pulmonary testing and care are discussed extensively in Chapter 51, the current discussion is limited to an assessment of the effectiveness of this type of care.

In fact, few randomized prospective studies indicate an outcome benefit of preoperative preparation. Stein and Cassara randomly allocated 48 patients to undergo preoperative therapy (cessation of smoking, administration of antibiotics for purulent sputum, and use of bronchodilating drugs, postural drainage, chest physiotherapy, and ultrasonic nebulizer) or no preoperative therapy.[219] The no-treatment group had a mortality of 16% and morbidity of 60%, as opposed to 0% and 20%, respectively, for the treatment group. In addition, the treatment group spent an average of 12 postoperative days in the hospital as compared with 24 days for the 21 survivors in the no-treatment group.

Collins and colleagues prospectively examined the benefits of preoperative antibiotics, perioperative chest physiotherapy and therapy with bronchodilating drugs, and routine postoperative analgesia (morphine) on postoperative respiratory complications in patients with COPD.[224] Of these therapies, only preoperative treatment with antibiotics had a beneficial effect.

Hulzebos and colleagues performed a single-center randomized trial of intensive inspiratory muscle training.[225] Preoperative inspiratory muscle training reduced the incidence of postoperative pulmonary complications and the duration of postoperative hospitalization in patients at high risk of developing a pulmonary complication who were undergoing CABG surgery.

Warner and co-workers collected data retrospectively about smoking history and prospectively (concurrently) about pulmonary complications for 200 patients undergoing CABG.[226] These investigators documented that 8 weeks or more of smoking cessation was associated with a 66% reduction in postoperative pulmonary complications. Smokers who stopped for less than 8 weeks actually had an increase (from 33% for current smokers to 57.1% for recent quitters) in the rate of 1 or more of the 6 complications surveyed: purulent sputum with pyrexia; need for respiratory therapy care; bronchospasm requiring therapy; pleural effusion or pneumothorax (or both) necessitating drainage; segmental pulmonary collapse, as confirmed by radiography; or pneumonia necessitating antibiotic therapy. Other investigators have found that both shorter and longer periods of cessation of smoking were needed before achieving cardiovascular[227] and hematologic benefit.[228] Bluman and associates performed a retrospective chart review of 410 patients undergoing noncardiac surgery at a VA hospital.[229] Current smoking was associated with a nearly 6-fold increase in the risk of a postoperative pulmonary complication. Reduction in smoking within 1 month of surgery was not associated with a decreased risk for postoperative pulmonary complications. Nakagawa and coauthors also reported higher pulmonary complication rates in patients undergoing pulmonary surgery who quit within 4 weeks of surgery than in current smokers or those who had stopped smoking for more than 4 weeks.[230] Wong and colleagues performed a systematic review of 25 studies of smoking cessation.[231] At least 4 weeks of abstinence from smoking reduced respiratory complications, and abstinence of at least 3 to 4 weeks reduced wound healing complications. Short-term (<4 weeks) smoking cessation did not appear to increase or reduce the risk of postoperative respiratory complications.

Two randomized trials focused on smoking cessation. Wong and colleagues performed a prospective, multicenter, double-blind, placebo-controlled trial, in which 286 patients were randomized to receive varenicline or placebo.[232] A perioperative smoking cessation intervention with varenicline increased abstinence from smoking 3, 6, and 12 months after elective noncardiac surgery with no increase in serious adverse events. Lee and colleagues randomized patients to a group receiving no specific smoking cessation intervention or to an intervention group that received (1) brief counseling by the preadmission nurse, (2) brochures on smoking cessation, (3) referral to the Canadian Cancer Society's Smokers' Helpline, and (4) a free 6-week supply of transdermal nicotine replacement therapy.[233] All outcome assessors and caregivers

on the operative day were blinded to group assignment. Smoking cessation occurred in 12 patients (14.3%) in the intervention group as compared with 3 patients (3.6%) in the control group (relative risk, 4.0; 95% CI, 1.2 to 13.7; $P = .03$). The overall rate of combined intraoperative and immediate postoperative complications was not significantly different between intervention and control groups. At follow-up 30 days postoperatively, smoking cessation was reported in 22 patients (28.6%) in the intervention group compared with 8 patients (11%) in controls (relative risk, 2.6; 95% CI, 1.2 to 5.5; $P = .008$).

When Skolnick and co-workers studied 602 children prospectively, exposure to passive smoking (as measured by urinary cotinine, the major metabolite of nicotine) correlated directly with airway complications. Children with the least exposure to passive smoke had the fewest complications.[217] Second-hand smoke may be a model for particulate air pollution with PM 2.5 particles, which have immediate and long-term effects in increasing lung dysfunction and inflammatory stimuli throughout the body.[234,235] In this sense, reducing particulate and diesel exhaust exposure in the 2 weeks before surgical procedures may make sense, but such a hypothesis has not been tested (and outpatient surgery centers located next to busy freeways may prove to be appropriate sites for studying such subtle inhibition of healing secondary to diesel particles).

Celli and associates performed a randomized prospective controlled trial of intermittent positive-pressure breathing (IPPB) versus incentive spirometry and deep-breathing exercises in 81 patients undergoing abdominal surgery.[236] The groups exposed to a respiratory therapist (regardless of the treatment given) had more than a 50% lower incidence of clinical complications (30% to 33% versus 88%) and shorter hospital stays than did the control group. Thus, this third prospective study indicates that outcome improves when any concern about lung function is shown by someone knowledgeable in maneuvers designed to clear lung secretions.

Bartlett and co-workers randomly assigned 150 patients undergoing extensive laparotomy to 1 of 2 groups.[237] One group received preoperative instruction in and postoperative use of incentive spirometry (10 times/hour). The other group received similar medical care but no incentive spirometry. Only 7 of 75 patients using incentive spirometry had postoperative pulmonary complications, as opposed to 19 of 75 in the control group. However, other studies have not shown a benefit for specific treatments or have been too contaminated with bias to have a clear result emerge. Lyager and colleagues randomly assigned 103 patients undergoing biliary or gastric surgery to receive either incentive spirometry with preoperative and postoperative chest physiotherapy or only preoperative and postoperative chest physiotherapy.[238] No difference in the postoperative course or pulmonary complications was found between the groups. Other studies have shown a specific benefit (i.e., greater than that provided by routine care) for chest physiotherapy and IPPB. These studies are usually poorly controlled, not randomized, or retrospective in design (or any combination); these deficiencies probably substantially bias the results toward finding a benefit in reducing postoperative pulmonary complications. Although randomized prospective studies showed no benefit or actual harm from chest physiotherapy and IPPB on the resolution of pneumonia or postoperative pulmonary complications, the studies cited earlier[219,224,236,237] and numerous retrospective studies strongly suggest that preoperative evaluation and treatment of patients with pulmonary disease actually decrease perioperative respiratory complications, even if only by causing a change in anesthetic techniques.

Meta-analyses have suggested a benefit of anesthetic and pain management with respect to respiratory outcomes. Rodgers and associates reviewed 141 trials involving 9559 patients who had been randomized to receive neuraxial blockade or general anesthesia. Overall mortality was significantly less frequent in the neuraxial blockade group (2.1% versus 3.1%) (see also Chapter 56). The relative risk of pneumonia in the neuraxial blockade group was 0.61 (CI, 0.48 to 0.81), and the relative risk of respiratory depression was 0.41 (CI, 0.23 to 0.73).[218] Neuman and colleagues examined a retrospective cohort of 18,158 patients undergoing surgery for hip fracture in 126 hospitals in New York in 2007 and 2008.[239] Patients receiving regional anesthesia experienced fewer pulmonary complications (359 [6.8%] versus 1040 [8.1%]; $P < .005$). Regional anesthesia was associated with a lower adjusted odds of mortality (OR, 0.710; 95% CI, 0.541, 0.932; $P = .014$) and pulmonary complications (OR, 0.752; 95% CI, 0.637, 0.887; $P < .0001$) relative to general anesthesia. In subgroup analyses, regional anesthesia was associated with improved survival and fewer pulmonary complications among patients with intertrochanteric fractures but not among patients with femoral neck fractures (see also Chapter 56).

Not all studies demonstrate beneficial effects of pharmacologic pretreatment. In afebrile outpatient American Society of Anesthesiologists (ASA) class I and II children with no lung disease or findings who underwent noncavitary, nonairway surgery lasting less than 3 hours, neither albuterol nor ipratropium premedication decreased adverse events (see also Chapter 94).[240]

Evaluation of dyspnea is especially useful (see also Chapter 96). Boushy and co-workers found that grades of preoperative dyspnea correlated with postoperative survival.[241] (Grades of respiratory dyspnea are provided in Table 39-9.) Mittman demonstrated an increased risk of

TABLE 39-9 GRADE OF DYSPNEA CAUSED BY RESPIRATORY PROBLEMS (ASSESSED IN TERMS OF WALKING ON A LEVEL SURFACE AT A NORMAL PACE)

Category	Description
0	No dyspnea while walking on a level surface at a normal pace
I	"I am able to walk as far as I like, provided I take my time"
II	Specific (street) block limitation ("I have to stop for a while after one or two blocks")
III	Dyspnea on mild exertion ("I have to stop and rest while going from the kitchen to the bathroom")
IV	Dyspnea at rest

Modified from Boushy SF, Billing DM, North LB, et al: Clinical course related to preoperative pulmonary function in patients with bronchogenic carcinoma, Chest *59:383, 1971.*

TABLE 39-10 CLASSIFICATION OF RISK OF PULMONARY COMPLICATIONS FOR THORACIC AND ABDOMINAL PROCEDURES

Category	Points
I. Expiratory Spirogram	
A. Normal (% FVC + [% FEV_1/FVC] > 150)	0
B. % FVC + (% FEV_1/FVC) = 100-150	1
C. % FVC + (% FEV_1/FVC) <100	2
D. Preoperative FVC <20 mL/kg	3
E. Postbronchodilator FEV_1/FVC <50%	3
II. Cardiovascular System	
A. Normal	0
B. Controlled hypertension, myocardial infarction without sequelae for >2 yr	0
C. Dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, dependent edema, congestive heart failure, angina	1
III. Nervous System	
A. Normal	0
B. Confusion, obtundation, agitation, spasticity, discoordination, bulbar malfunction	1
C. Significant muscular weakness	1
IV. Arterial Blood Gases	
A. Acceptable	0
B. $Paco_2$ >50 mm Hg or PaO_2 <60 mm Hg on room air	1
C. Metabolic pH abnormality >7.50 or <7.30	1
V. Postoperative Ambulation	
A. Expected ambulation (minimum, sitting at bedside) within 36 hr	0
B. Expected complete bed confinement for ≥36 hr	1

Modified from Wong DH, Weber EC, Schell MJ, et al: Factors associated with postoperative pulmonary complications in patients with severe COPD, Anesth Analg *80:276, 1995.*

FEV_1, Forced expiratory volume in 1 second; *FVC,* forced vital capacity; *$Paco_2$,* arterial partial pressure of carbon dioxide; *PaO_2,* arterial partial pressure of oxygen.

TABLE 39-11 PREOPERATIVE PREDICTORS OF POSTOPERATIVE RESPIRATORY FAILURE

Variable	Odds Ratio (95% Confidence Interval)
Type of Surgery	
Abdominal aortic aneurysm	14.3 (12.0-16.9)
Thoracic	8.14 (7.17-9.25)
Neurosurgery, upper abdominal, or peripheral vascular	4.21 (3.80-4.67)
Neck	3.10 (2.40-4.01)
Other surgery*	1.00 (reference)
Emergency surgery	3.12 (2.83-3.43)
Albumin <30 g/L	2.53 (2.28-2.80)
Blood Urea Nitrogen >30 mg/dL	2.29 (2.04-2.56)
Partially or Fully Dependent Status	1.92 (1.74-2.11)
History of COPD	1.81 (1.66-1.98)
Age (yr)	
≥70	1.91 (1.71-2.13)
0-69	1.51 (1.36-1.69)
<60	1.00 (reference)

From Arozullah AM, Daley J, Henderson WG, et al: Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery: the National Veterans Administration Surgical Quality Improvement Program, Ann Surg *232:242-253, 2000.*

COPD, Chronic obstructive pulmonary disease.

*Other surgery includes ophthalmologic, ear, nose, mouth, lower abdominal, extremity, dermatologic, spine, and back surgery.

death after thoracic surgery, from 8% in patients without dyspnea to 56% in patients who were dyspneic.[242] Similarly, Reichel found that no patients died after pneumonectomy if they were able to complete a preoperative treadmill test for 4 minutes at the rate of 2 mph on level ground.[243] Other studies have found that the history and physical examination of an asthmatic subject can also predict the need for hospitalization.[208] Wong and colleagues found that the risk index correlated with postoperative pulmonary complications (Table 39-10).[244]

Arozullah and associates developed the first validated multifactorial risk index for postoperative respiratory failure, defined as mechanical ventilation for more than 48 hours after surgical procedures or reintubation and mechanical ventilation after postoperative extubation.[245] In a prospective cohort study of 181,000 male veterans as part of the National Veterans Administration Surgical Quality Improvement Program, 7 factors independently predicted risk (Table 39-11). With increasing numbers of risk factors present, the rate of complications increased from 0.5% (class 1) to 26.6% (class 4). Arozullah and colleagues subsequently developed a risk index for postoperative pneumonia by using data on 160,805 patients undergoing major noncardiac surgery and validated the index by using data on an additional 155,266 patients.[246] Patients were divided into 5 risk classes by using risk index scores (Table 39-12). Pneumonia rates were 0.2% in patients with 0 to 15 risk points, 1.2% in those with 16 to 25 risk points, 4.0% in those with 26 to 40 risk points, 9.4% in those with 41 to 55 risk points, and 15.3% in those with more than 55 risk points.

Gupta and colleagues used the American College of Surgeons NSQIP to develop a risk model for postoperative respiratory failure.[168] On multivariate logistic regression analysis, five preoperative predictors of postoperative respiratory failure were identified: type of surgery, emergency case, dependent functional status, preoperative sepsis, and higher ASA class (Table 39-13).

SPECIFIC DISEASES

Pulmonary Vascular Diseases

Pulmonary vascular diseases include pulmonary hypertension secondary to heart disease (postcapillary disorders), parenchymal lung disease (pulmonary precapillary disorders), pulmonary embolism, and cor pulmonale from COPD.[247] Optimal preoperative management of these conditions requires treatment of the underlying disease.[247-249] Because pulmonary embolism can be particularly difficult to diagnose, it is crucial to be especially alert to the possibility of this disease. The clinical findings of pulmonary emboli are not always present or specific for the diagnosis. The history may include tachypnea, dyspnea, palpitations,

TABLE 39-12 **POSTOPERATIVE PNEUMONIA RISK INDEX**

Preoperative Risk Factor	Point Value
Type of Surgery	
Abdominal aortic aneurysm repair	15
Thoracic	14
Upper abdominal	10
Neck	8
Neurosurgery	8
Vascular	3
Age	
80 yr	17
70-79 yr	13
60-69 yr	9
50-59 yr	4
Functional Status	
Totally dependent	10
Partially dependent	6
Weight loss >10% in past 6 mo	7
History of COPD	5
General anesthesia	4
Impaired sensorium	4
History of cerebrovascular accident	4
Blood Urea Nitrogen Level	
<2.86 mmol/L (0.8 mg/dL)	4
7.85-10.7 mmol/L (22-30 mg/dL)	2
≥10.7 mmol/L (≥30 mg/dL)	3
Transfusion >4 Units	3
Emergency Surgery	3
Steroid Use for Chronic Condition	3
Current Smoker Within 1 Yr	3
Alcohol Intake >2 Drinks/Day in Past 2 Wk	2

From Arozullah AM, Khuri SF, Henderson WG, et al: Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery, Ann Intern Med *135:847-857, 2001.*
COPD, Chronic obstructive pulmonary disease.

TABLE 39-13 **PREOPERATIVE VARIABLES SIGNIFICANTLY ASSOCIATED WITH AN INCREASED RISK FOR POSTOPERATIVE RESPIRATORY FAILURE IN 2007 MODEL FROM THE AMERICAN COLLEGE OF SURGEONS NATIONAL SURGICAL QUALITY IMPROVEMENT PROJECT***

Parameter	Adjusted OR	95% Wald CI
Totally dependent functional status†	4.07	3.68-4.51
Partially dependent functional status†	2.16	1.98-2.34
ASA class 1‡	0.03	0.02-0.05
ASA class 2‡	0.14	0.11-0.17
ASA class 3‡	0.54	0.44-0.67
ASA class 4‡	1.28	1.04-1.57
Preoperative sepsis (none)§	0.46	0.42-0.50
Preoperative sepsis§	1.32	1.16-1.49
Preoperative septic shock§	2.47	2.16-2.82
Emergency case (absence versus presence)	0.56	0.52-0.61
Anorectal¶	0.26	0.15-0.44
Aortic¶	2.94	2.35-3.68
Bariatric¶	0.36	0.27-0.49
Brain¶	2.08	1.15-3.78
Breast¶	0.07	0.04-0.12
Cardiac¶	1.32	0.92-1.88
Ear, nose, and throat¶	1.11	0.26-4.71
Foregut/ hepatopancreatobiliary¶	2.64	2.13-3.27
Gallbladder, appendix, adrenals, and spleen¶	0.57	0.45-0.71
Intestinal¶	1.78	1.44-2.18
Neck¶	0.59	0.33-1.07
Obstetrics and gynecology¶	0.29	0.09-0.94
Orthopedic¶	0.42	0.33-0.55
Other abdominal¶	1.27	1.001-1.62
Peripheral vascular¶	0.79	0.63-0.98
Skin¶	0.73	0.55-0.95
Spine¶	0.593	0.25-1.39
Thoracic¶	1.96	1.43-2.68
Venous¶	0.134	0.05-0.37
Urologic¶	1.36	0.82-2.28

From Gupta H, Gupta PK, Fang X, et al: Development and validation of a risk calculator predicting postoperative respiratory failure, Chest *140:1207-1215, 2011.*
ASA, American Society of Anesthesiologists; *CI,* confidence interval; *OR,* odds ratio.
*The estimate and the standard error (SE) refer to the estimate of the logistic regression coefficient for the specific variable and its associated SE. C-statistic, 0.894.
†Reference group, independent functional status.
‡Reference group, ASA class 5.
§Reference group, preoperative systemic inflammatory response syndrome.
¶Reference group, hernia surgery.

syncope, chest pain, or hemoptysis. Physical examination can reveal a pleural rub, wheezing, rales, a fixed and split second heart sound, right ventricular lift, or evidence of venous thrombosis, none of which are present in most patients. If the ECG shows an S_1Q_3 pattern, spiral CT or lung perfusion scans can be obtained to rule out the diagnosis of pulmonary emboli. A high degree of suspicion is necessary to warrant angiography and anticoagulation or fibrinolytic therapy. If possible, the reactivity of the pulmonary vasculature should be determined because it may be enhanced or decreased by such drugs as nifedipine, hydralazine, nitroglycerin, prazosin, tolazoline, phentolamine, sildenafil citrate, and nitric oxide. Monitoring of pulmonary artery pressure is often required. Preoperative measures should be undertaken to ensure that the patient is not exposed to conditions that elevate pulmonary vascular resistance (e.g., hypoxia, hypercapnia, acidosis, lung hyperinflation, hypothermia)[250] or that decrease blood volume (prolonged restriction of fluid intake) or systemic vascular resistance.

Infectious Diseases of the Lung

Preoperative evaluation and treatment should follow the basic guidelines outlined in the introduction to this section and in Chapter 38. Treatment of the underlying disease should be completed before all but emergency surgery is performed.

Even though elective surgery should be postponed whenever infectious diseases of the lung are present, patients undergoing emergency surgery often have nosocomial infections and immunocompromised systems. The predominant pathogens for nosocomial pneumonia are gram-negative bacilli, *Staphylococcus aureus*, *Haemophilus influenzae*, anaerobes, and pneumococci. Furthermore,

BOX 39-4 *Procedures for Correct Use of a Metered-Dose Inhaler*

Remove the cap and hold the inhaler upright.
Shake the inhaler.
Tilt the head back slightly and exhale steadily to functional residual capacity.
Position the inhaler by using a spacer between the actuator and the mouth.
Press down on the inhaler while taking a slow, deep breath (3 to 5 seconds).
Hold the full inspiration for at least 5 and up to 10 seconds, if possible, to allow the medication to reach deeply into the lungs.
Repeat inhalations as directed. Waiting 1 minute after inhalation of the bronchodilator may permit subsequent inhalations to penetrate more deeply into the lungs and is necessary to ensure proper delivery of the dose. Rinse your mouth and expectorate after using the inhaler.

the incidence of tuberculosis increased rapidly in the late 1980s and in the 1990s, probably because of reactivation in patients infected with HIV. Increased funding and directly observed antituberculosis therapy have more than offset immigrant and travel risk to cause the incidence of tuberculosis to decrease. Tuberculosis leads to chronic pulmonary and systemic symptoms. Affected patients may have malaise, headache, fever, hemoptysis, and extrapulmonary diseases affecting the skin, cervical lymph nodes, kidneys, pericardium, and meninges. Active disease is treated with four-drug therapy: isoniazid, pyrazinamide, ethambutol or streptomycin, and rifampin for 9 months. Therapy should probably be started preoperatively. Management of these emergency patients (many of whom have adult respiratory distress syndrome [ARDS]) before they are brought to the operating room may include initiation of antiinfective therapy, optimization of fluid status and gas exchange, and therapy for the underlying pathophysiologic process.

Chronic Diseases of the Lung

Treatment of COPD (reactive airways) may include the use of β-adrenergic drugs, parasympatholytic agents (especially for exercise-induced asthma), systemic or inhaled corticosteroids, and leukotriene antagonists. An estimated 5% of the population has bronchospasm. Some investigators recommend using inhaled bronchodilators as first-line drugs and reducing the dose of inhaled steroids, such as beclomethasone dipropionate, budesonide, mometasone, and fluticasone, which are inactivated after absorption. However, in large doses, these "inhaled" steroids can suppress adrenal function, and supplemental systemic corticosteroids may be needed at times of stress (see the earlier discussion in the section on adrenocortical malfunction). Preoperative assessment must include gaining knowledge of drug regimens and their effects and education of the patient regarding proper use of an inhaler (Box 39-4), given that these drugs can interact dangerously with anesthetics (see the last section of this chapter) or can be used inappropriately and therefore produce side effects without maximum benefit.[206-216] No known interaction between the inhaled anticholinergic ipratropium bromide and muscle relaxants has been reported. Patients can feel fine at rest but must be tested by exercise or spirometry to document the degree of current bronchospasm. Furthermore, a symptomatic response to bronchodilators in an asymptomatic patient may not predict whether the patient will respond to bronchodilator therapy. An estimated 10% of asthmatic patients exhibit sensitivity to aspirin and may react not only to compounds containing aspirin but also to tartrazine, yellow dye number 5, indomethacin, other nonsteroidal antiinflammatory drugs, and aminopyrine.[251]

Cystic fibrosis is characterized by dilatation and hypertrophy of the bronchial glands, mucous plugging of the peripheral airways, and frequently, bronchitis, bronchiectasis, and bronchiolectasis. For all these conditions, the measures recommended earlier in this section, as well as appropriate hydration to allow mobilization of secretions, constitute optimal preprocedure therapy.

Surgical resection is the primary therapy for non–small cell carcinomas (e.g., adenocarcinoma, squamous cell carcinoma, and large cell carcinoma). These carcinomas account for 75% of all lung carcinomas, 12% of all malignant tumors, and 20% of all cancer deaths in the United States.[252] Success of surgery can be predicted by the stage of the tumor.

The combination of chemotherapy and radiation therapy is the current treatment of choice for small cell carcinomas of the lung.[253] Oat cell (small cell) carcinoma of the lung and bronchial adenomas are known for their secretion of endocrinologically active substances, such as ACTH-like hormones. Squamous cell cancers in the superior pulmonary sulcus produce Horner syndrome, as well as characteristic pain in areas served by the eighth cervical nerves and first and second thoracic nerves. These tumors are now treated with preoperative radiation; surgical resection leads to an almost 30% "cure" rate.

Anaphylaxis, Anaphylactoid Responses, and Allergic Disorders Other Than Those Related to Lung Diseases and Asthma

Anaphylactic and Anaphylactoid Reactions. Anaphylaxis is a severe life-threatening allergic reaction. *Allergic* applies to immunologically mediated reactions, as opposed to those caused by pharmacologic idiosyncrasy, by direct toxicity or drug overdosage, or by drug interaction.[254-256] Anaphylaxis is the typical immediate hypersensitivity reaction (type I). Such reactions are produced by immunoglobulin E (IgE)–mediated release of pharmacologically active substances. These mediators in turn produce specific end-organ responses in the skin (urticaria), the respiratory system (bronchospasm and upper airway edema), and the cardiovascular system (vasodilation, changes in inotropy, and increased capillary permeability). Vasodilation occurs at the level of the capillary and postcapillary venule and leads to erythema, edema, and smooth muscle contraction. This clinical syndrome is called *anaphylaxis*. By contrast, an *anaphylactoid reaction* denotes an identical or very similar clinical response that is not mediated by IgE or (usually) an antigen-antibody process.[255,256]

In anaphylactic reactions, an injected or inhaled (or ingested) substance—usually drugs, food, or insect venom—can serve as the allergen itself. Low-molecular-weight agents are believed to act as haptens that form

immunologic conjugates with host proteins. The offending substance, regardless of whether it is a hapten, may be the parent compound, a nonenzymatically generated product, or a metabolic product formed in the patient's body. When an allergen binds immunospecific IgE antibodies on the surface of mast cells and basophils, histamine and eosinophilic chemotactic factors of anaphylaxis are released from storage granules in a calcium- and energy-dependent process.[255,256] Other chemical mediators are rapidly synthesized and are subsequently released in response to cellular activation. These mediators include the following: slow-reacting substance of anaphylaxis, which is a combination of three leukotrienes; other leukotrienes[255,256]; kinins; platelet-activating factors; adenosine; chemotactic factors; heparin; tryptase; chymase; and prostaglandins, including the potent bronchoconstrictor prostaglandin D_2; eosinophil growth and activating factors; mast cell growth factors; and proinflammatory and other factors that contribute to the IgE isotype switch.

The end-organ effects of the mediators produce the clinical syndrome of anaphylaxis. Usually, a first wave of symptoms, including those caused by vasodilation and a feeling of impending doom, is quickly followed by a second wave as the cascade of mediators amplifies the reactions. In a sensitized patient, onset of the signs and symptoms caused by these mediators is usually immediate but may be delayed 2 to 15 minutes or, in rare instances, as long as 2.5 hours after the parenteral injection of antigen.[257,258] After oral administration, manifestations may occur at unpredictable times.

Mast cell proliferation, together with severe progressive inflammation, contributes to the worsening of symptoms that occurs even after an allergen load is no longer present. The antigen present in cells and lymphocytes, as well as activated mast cells, starts to induce the production of cytokines. These proinflammatory cytokines recruit more inflammatory cells, a process that leads to tissue edema and mediates a second wave of mast cell degranulation. This second wave can promote the recurrence of severe symptoms 6 to 8 hours later and necessitates, some believe, at least 8 hours of continued ICU-like observation.

In addition, biologically active mediators can be generated by multiple effector processes to produce an anaphylactoid reaction. Activation of the blood coagulation and fibrinolytic systems, the kinin-generating sequence, or the complement cascade can produce the same inflammatory substances that result in an anaphylactic reaction. The two mechanisms known to activate the complement system are called classical and alternative. The classical pathway can be initiated through IgG or IgM (transfusion reactions) or plasmin. The alternative pathway can be activated by lipopolysaccharides (endotoxin), drugs (Althesin), radiographic contrast media,[259] membranes (nylon tricot membranes for bubble oxygenators), cellophane membranes of dialyzers, vascular graft material,[260] latex or latex-containing products,[261,262] and perfluorocarbon artificial blood. The most common drugs responsible for intraoperative anaphylaxis are muscle relaxants (see also Chapters 34 and 35).[262] In addition, one of the primary concerns regarding the delayed approval of sugammadex in the United States has been "hypersensitivity reactions," which includes anaphylaxis. However, latex accounts for a significant number of these reactions, and the incidence of intraoperative anaphylaxis caused by latex is increasing. It is now probably the second most important cause of intraoperative anaphylaxis. In addition, histamine can be liberated independent of immunologic reactions.[263] Mast cells and basophils release histamine in response to chemicals or drugs. Most narcotics can release histamine,[263] and they can produce an anaphylactoid reaction, as can radiographic contrast media,[259] *d*-tubocurarine, and thiopental. What makes some patients susceptible to release of histamine in response to drugs is unknown, but hereditary and environmental factors may play a role.

Intravenous contrast material is probably the most frequently used agent that causes anaphylactoid reactions. Because diagnostic (skin and other) tests are helpful only in IgE-mediated reactions, pretesting is not useful for contrast reactions. Pretreatment with diphenhydramine, cimetidine (or ranitidine), and corticosteroids has been reported to be useful in preventing or ameliorating anaphylactoid reactions to intravenous contrast material,[259,264] as well as perhaps to narcotics. Unfortunately, very large doses of steroids (1 g of methylprednisolone intravenously) may be necessary to obtain a beneficial effect.[265] The efficacy of large-dose steroid therapy has not been confirmed. Other common substances associated with anaphylactic or anaphylactoid reactions that may merit preoperative therapy include antibiotics, intravascular volume expanders, and blood products (see also Chapters 61 and 62).[255] The anesthesiologist should always be prepared perioperatively to treat an anaphylactic or anaphylactoid response.

In some cases, a patient with a history of an anaphylactic or anaphylactoid reaction must receive a substance suspected of producing such a reaction (e.g., iodinated contrast material). In addition, some patients have a higher than average likelihood of having a reaction, thus warranting well-planned pretreatment and therapy for possible anaphylactic and anaphylactoid reactions.[259]

Minimizing Risks Preoperatively. Although virtually all evidence on this subject is merely anecdotal, enough consistent thought recurs through the literature to justify proposing an optimal approach to these problems. First, predisposing factors should be sought; patients with a history of atopy or allergic rhinitis should be suspected of being at risk. Because anaphylactic and anaphylactoid reactions to contrast media occur 5 to 10 times more frequently in patients with a previously suspected reaction, consideration should be given to the administration of low-osmotic agents and both H_1- and H_2-receptor antagonists for 16 to 24 hours before exposing these patients to a suspected allergen. H_1-receptor antagonists appear to require this much time to act on the receptor. Volume status can be optimized,[255] and perhaps large doses of steroids (1 g of hydrocortisone) should also be administered before exposing patients to agents associated with a high incidence of anaphylactic or anaphylactoid reactions.[265] Older patients and patients taking β-adrenergic blocking drugs present special problems; they are at higher risk of having complications from both pretreatment (especially vigorous hydration) and therapy for anaphylactic reactions

(glucagon is useful here) and are less responsive to treatment regimens.[266] One approach is to avoid drugs likely to trigger anaphylactic or anaphylactoid reactions or alter the treatment protocol for this group. Drawing blood for later analysis, especially of tryptase, can be useful in clarifying the diagnosis.[267]

With the increasing incidence of latex hypersensitivity, attempts have been made to make much of the operating room environment latex free; however, costs and preferences have resulted in the continued use of latex-containing gloves in many hospitals. Nonetheless, more hospitals are totally latex free. In allergic patients, care should be taken to ensure that no latex-containing products are present in the operating room.

Primary Immunodeficiency Diseases

Primary immunodeficiency diseases usually manifest early in life as recurrent infections. Along with survival achieved with antibiotic and antibody treatment have come new prominent features: cancer and allergic and autoimmune disorders. Hereditary angioneurotic edema is an autosomal dominant genetic disease characterized by episodes of angioneurotic edema involving the subcutaneous tissues and submucosa of the GI tract and airway and often manifested as abdominal pain. These patients have a functionally impotent inhibitor or deficiency of an inhibitor to complement component C1. Treatment of an acute attack is supportive because epinephrine, antihistamines, and corticosteroids often fail to work. Plasma transfusions have been reported to resolve attacks or make them worse (theoretically by supplying either C1 esterase inhibitor or previously depleted complement components). The severity of attacks can be prevented or decreased by drugs that are either plasmin inhibitors (e.g., ε-aminocaproic acid [EACA] and tranexamic acid) or androgens (e.g., danazol). Because trauma can precipitate acute attacks, prophylactic therapy with danazol, intravenous EACA, plasma, or all three is recommended before elective surgery. A partially purified C1 esterase inhibitor has been used in two patients.

Most of the 1 in 700 persons who have selective IgA deficiency (i.e., <5 mg/dL) have repeated serious infections or connective tissue disorders. These infections commonly involve the respiratory tract (e.g., sinusitis, otitis) or GI tract (manifested as diarrhea, malabsorption, or both). If the patient has rheumatoid arthritis, Sjögren syndrome, or systemic lupus erythematosus, the anesthetist should consider the possibility of isolated IgA deficiency. However, patients with this disorder can be otherwise healthy. Because antibodies to IgA may develop in these patients if they were previously exposed to IgA (as could occur from a previous blood transfusion), subsequent blood transfusions can cause anaphylaxis, even when they contain washed erythrocytes. Transfusions should therefore consist of blood donated by another IgA-deficient patient.

Many immunomodulators are now being given to augment cancer treatments[268]; no interactions among these modulators, no effects on the incidence of immune reactions during anesthesia, and no interactions with anesthetic effects have been reported except those regarding immunosuppressant drugs (see the last section of this chapter).

Immunonutrition is increasingly being used preprocedurally by patients and prescribed by providers to decrease inflammatory responses.[261] Whereas excellent data on the benefits of probiotics in changing the intestinal milieu to decrease inflammation can be found, limited data are available on their effects on periprocedural recovery or outcomes.

DISEASES OF THE CENTRAL NERVOUS SYSTEM, NEUROMUSCULAR DISEASES, AND PSYCHIATRIC DISORDERS

Evaluation of a patient with neurologic or psychiatric disease can be found in Chapter 38. Information gathered from the history that warrants further investigation includes a previous need for postoperative ventilation in a patient without inordinate lung disease, which indicates the possibility of metabolic neurologic disorders such as porphyria, alcoholic myopathy, other myopathies, neuropathies, and neuromuscular disorders such as myasthenia gravis. Other historical information warranting further investigation includes the use of drugs such as the following: steroids; guanidine; anticonvulsant, anticoagulant, and antiplatelet drugs; lithium; tricyclic antidepressants; phenothiazines; and butyrophenones.

Although preoperative treatment of most neurologic disorders may not lessen perioperative morbidity, knowledge of the pathophysiologic characteristics of these disorders is important in planning intraoperative and postoperative management. Thus, preoperative knowledge about these disorders and their associated conditions (e.g., cardiac arrhythmias with Duchenne muscular dystrophy or respiratory and cardiac muscle weakness with dermatomyositis) may reduce perioperative morbidity. A primary goal of neurologic evaluation is to determine the site of the lesion in the nervous system. Such localization to one of four levels (supratentorial compartment, posterior fossa, spinal cord, peripheral nervous system) is essential for accurate diagnosis and appropriate management. (Disorders accompanied by increased intracranial pressure and cerebrovascular disorders are discussed in Chapters 17 and 70.)

COMA

Little is known about specific anesthetic or perioperative or periprocedural choices that alter outcome for a comatose patient, but as for all other conditions, the cause of the coma should be known so that drugs can be avoided that may worsen the condition or that may not be metabolized because of organ dysfunction (see also Chapters 96 and 101). First, the patient should be observed. Yawning, swallowing, or licking of the lips implies a "light" coma with major brainstem function intact. If consciousness is depressed but respiration, pupillary reactivity to light, and eye movements are normal and no focal motor signs are present, metabolic depression is likely. Abnormal pupillary responses may indicate hypoxia, hypothermia, local eye disease, or drug intoxication with belladonna alkaloids, narcotics, benzodiazepines, or glutethimide; pupillary responses may also be abnormal, however, after the

use of eye drops. Other metabolic causes of coma include uremia, hypoglycemia, hepatic coma, alcohol ingestion, hypophosphatemia, myxedema, and hyperosmolar nonketotic coma. Except in extreme emergencies, such as uncontrolled bleeding or a perforated viscus, care should be taken to render the patient as metabolically normal as possible before the surgical procedure. This practice and documenting the findings on the chart preoperatively lessen any confusion regarding the cause of intraoperative and postoperative problems. However, too rapid correction of uremia or hyperosmolar nonketotic coma can lead to cerebral edema, a shift of water into the brain as a result of a reverse osmotic effect caused by dysequilibrium of the urea concentration.

The physical examination can be extremely helpful preoperatively in assessing the prognosis. Arms flexed at the elbow (i.e., decorticate posture) imply bilateral hemisphere dysfunction but an intact brainstem, whereas extension of the legs and arms (bilateral decerebrate posture) implies bilateral damage to structures at the upper brainstem or deep hemisphere level. Seizures are often seen in patients with uremia and other metabolic encephalopathies. Hyperreflexia and upward-pointing toes suggest a structural CNS lesion or uremia, hypoglycemia, or hepatic coma; hyporeflexia and downward-pointing toes with no hemiplegia generally indicate the absence of a structural CNS lesion.

EPILEPTIC SEIZURES

Epileptic seizures result from paroxysmal neuronal discharges of abnormally excitable neurons. Six percent to 10% of individuals younger than 70 years old will experience a seizure at some time during their lifetime. Fifty percent to 70% of patients with one seizure will never have another. However, 70% of people with two seizures will have an epileptic focus, be candidates for antiseizure medications, and be subject to withdrawal seizures after anesthesia if such medications are not continued.[269] A *seizure* is the term for the clinical event defined as a paroxysmal alteration in neurologic function caused by a synchronous, rhythmic depolarization of brain cortical neurons. *Epilepsy* is the condition manifested by recurrent, unprovoked seizures. Sometimes syncopal episodes can be mistaken for seizures, especially when interviews are compressed in the short time frame of a preoperative visit. Twenty-five percent of patients with a seizure have a normal electroencephalogram (EEG) when they are interictal. Thus, a negative EEG result does not indicate that someone with a seizure will not have a withdrawal seizure when emerging from anesthesia. Seizures can be generalized (arising from deep midline structures in the brainstem or thalamus, usually without an aura or focal features during the seizure), partial focal motor, or sensory (the initial discharge comes from a focal unilateral area of the brain, often preceded by an aura). As with cerebrovascular accidents and coma, knowing the origin may be crucial to understanding the pathophysiologic processes of the disease and to managing the patient's intraoperative and postoperative course.

Epileptic seizures can arise from discontinuation of sedative-hypnotic drugs or alcohol, use of narcotics, uremia, traumatic injury, neoplasms, infection, congenital malformation, birth injury, drug use (e.g., amphetamines, cocaine), hypercalcemia or hypocalcemia, blood in the ventricle or hypoxia, and vascular disease and vascular accidents. Thirty percent of epileptic seizures have no known cause. Most partial seizures are caused by structural brain abnormalities (secondary to tumor, trauma, stroke, infection, and other causes).

An epileptic patient requires no special anesthetic management other than that for the underlying disease. Most authorities believe that anticonvulsant medications should be given in the therapeutic range,[269-271] and they should be continued through the morning of the surgical procedure, even in pregnant women. They should also be given postoperatively, even in mothers who plan to breastfeed, according to guidelines published by the American Academy of Neurology. Many of the epileptic drugs, including phenytoin, carbamazepine, and phenobarbiturate, alter the hepatic metabolism of many drugs and induce cytochrome P450 enzyme activity. Drug-drug interactions are much less problematic with the newer epileptic drugs such as gabapentin and topiramate.[269] Appropriate treatment of status epilepticus may include general anesthesia.[271] In one controlled trial, phenobarbital was more rapidly effective in controlling status epilepticus than was diazepam followed by phenytoin.[271] The frequency of side effects and of required tracheal intubation was similar for both regimens. Thus, other than the use of current drug therapy and heeding precautions taken for the underlying disease, no known changes in perioperative management seem to be indicated.

INFECTIOUS DISEASES OF THE CENTRAL NERVOUS SYSTEM, DEGENERATIVE DISORDERS OF THE CENTRAL NERVOUS SYSTEM, AND HEADACHE

Many degenerative CNS disorders have been traced to slowly developing viral diseases or even the presence of certain proteins or viral particles ("prions"). No special perioperative anesthetic considerations appear to apply for infectious disorders of the CNS other than those for increased intracranial pressure and avoidance of occupational exposure and transmission of disease to health care workers (see also Chapter 110). The appropriate prophylactic measures to take if one comes in contact with meningococcal disease or other infectious CNS diseases are still not well established. The use of *H. influenzae* type b vaccine has made meningitis an adult disease.[272]

Parkinson disease is a degenerative disorder of the CNS that may or may not be caused by a virus (see also Chapters 38 and 80). Clinically, Parkinson disease, chronic manganese intoxication, phenothiazine or butyrophenone toxicity, Wilson disease, Huntington chorea, traumatic boxing injury, the effects of street drug toxins such as methylphenyltetrahydropyridine (MPTP), and carbon monoxide encephalopathy all have similar initial features: bradykinesia, muscular rigidity, and tremor.

Newer therapies have been developed to arrest or even reverse the progression of Parkinson disease. Therapy is directed at (1) increasing the neuronal release of dopamine

or the receptor's response to dopamine, (2) stimulating the receptor directly with bromocriptine and lergotrile, (3) implanting dopaminergic tissue, or (4) decreasing cholinergic activity. Newer therapies using the monoamine oxidase inhibitor (MAOI) deprenyl or adrenal medullary transplants to slow the progression of disease appear promising,[273,274] and even treatment with high-dose coenzyme Q10 seems to be strikingly beneficial.[28] Experience with deprenyl in the perioperative milieu is insufficient to make proscriptions about its use. Anticholinergic agents have been the initial drugs of choice because they decrease tremor more than muscle rigidity. Dopamine does not pass the blood-brain barrier, so its precursor L-dopa (levodopa) is used. Unfortunately, L-dopa is decarboxylated to dopamine in the periphery and can cause nausea, vomiting, and arrhythmia. These side effects are diminished by the administration of α-methylhydrazine (carbidopa), a decarboxylase inhibitor that does not pass the blood-brain barrier. Refractoriness to L-dopa develops, and it is now debated whether the drug should be used only when symptoms cannot be controlled with other anticholinergic medications. "Drug holidays" have been suggested as one means of restoring the effectiveness of these compounds, but cessation of such therapy may result in marked deterioration of function and need for hospitalization. Therapy for Parkinson disease should be initiated preoperatively and be continued through the morning of the surgical procedure; such treatment seems to decrease drooling, the potential for aspiration, and ventilatory weakness.[275,276] Reinstituting therapy promptly after surgery is crucial,[270,273-277] as is avoiding drugs such as the phenothiazines and butyrophenones (droperidol, and perhaps alfentanil), which inhibit the release of dopamine (and perhaps alfentanil) or compete with dopamine at the receptor.[275] Carbidopa or levodopa in low doses (20 to 200 mg nightly versus the usual 60 to 600 mg/day for Parkinson disease) is commonly used in the nonparkinsonian restless leg syndrome of older adults (present in 2% to 5% of individuals >60 years old). This drug also should be given the night before and the night immediately after the surgical procedure. Clozapine (a benzodiazepine) does not appear to worsen the movement disorders of Parkinson disease and has been used postoperatively to stop levodopa-induced hallucinations. Patients with Parkinson disease may also undergo deep brain stimulation under monitored anesthesia care.

Dementia, a progressive decline in intellectual function, can be caused by treatable infections (e.g., syphilis, cryptococcosis, coccidioidomycosis, Lyme disease, tuberculosis), depression (a trial of antidepressants is indicated in most patients), side effects of medications (digitalis has slowed brain function more than the heart rate), myxedema, vitamin B_{12} deficiency, chronic drug or alcohol intoxication, metabolic causes (liver and renal failure), neoplasms, partially treatable infections (HIV), untreatable infections (Creutzfeldt-Jakob syndrome), or decreased acetylcholine in the cerebral cortex (Alzheimer disease). This last condition occurs in more than 0.5% of Americans.[278-281] Although these patients are often given cholinergic agonists, controlled trials of these drugs have not as yet shown major significant benefit.[279,280,282] Gingko has improved subjective symptoms in 37% of patients versus 23% of those given placebo. Although later controlled trials failed to confirm its benefit in early Alzheimer disease or in healthy older individuals, gingko is still popular. However, the prevalence of Alzheimer disease and the desperation of the patients and their families have now widened such therapies. Cholinergic medications improve functioning in patients with Alzheimer disease.[283] These families often desire surgery, but the interactions of these drugs and therapies with perioperative analgesic and anesthetic drug therapies are not well established. One case report noted intraoperative bradycardia in such patients with two cholinergic drugs.[284] A link may exist among Alzheimer disease, postoperative cognitive dysfunction, and inhaled anesthetics.[285] Deposition of β-amyloid can occur in animals exposed to inhaled anesthetics.[286-288] Whether this link is clinically relevant in humans remains to be determined. Most reversible dementias represent either drug-induced delirium or depression.[279,280,289] At present, early results with stimulation at "threshold testing" are promising and seem to stimulate dendritic regrowth and may reverse some or much of the cognitive decline. Creutzfeldt-Jakob disease has been transmitted inadvertently by surgical instruments and corneal transplants; the causative virus or protein particle is not inactivated by heat, disinfectants, or formaldehyde.

More than 90% of patients with chronic recurring headaches are categorized as having migraine, tension, or cluster headaches. The mechanism of tension or cluster headaches may not differ qualitatively from that of migraine headaches; all may be manifestations of labile vasomotor regulation.[290] A headache is said to be migraine if it is characterized by four of the following five "POUNDing" conditions: if it is Pulsating, if it lasts One day or more, if it is Unilateral, if Nausea occurs, and if it Disturbs daily activities.[291]

Treatment of cluster and migraine headaches centers on the use of serotonin drugs such as sumatriptan or ergotamine and its derivatives.[290-292] Other drugs that may be effective are propranolol, calcium channel inhibitors, cyproheptadine, prednisone, antihistamines, tricyclic antidepressants, phenytoin, and diuretic drugs, as well as biofeedback. Giant cell arteritis, glaucoma, and all the meningitides, including Lyme disease, are other causes of headache that may benefit from preoperative treatment.[293] No other special treatment is indicated preoperatively for a patient who has a well-delineated cause for the headaches. Acute migraine attacks can sometimes be terminated by ergotamine tartrate aerosol or by injection of sumatriptan or dihydroergotamine mesylate intravenously; general anesthesia has also been used. We normally continue all prophylactic headache medicine, although the decision to continue aspirin through the morning of the surgical procedure is usually left to the surgeon.

BACK PAIN, NECK PAIN, AND SPINAL CANAL SYNDROMES

Acute spinal cord injury is discussed earlier in the section on autonomic dysfunction. Although it is a common problem, little is written about the anesthetic

management of syndromes related to herniated disks, spondylosis (usually of advancing age), and the congenital narrowing of the cervical and lumbar spinal canal that gives rise to symptoms of nerve root compression. One report stresses the importance of the vascular component in the mechanism of damage to the spinal cord and hence the theoretic desirability of slight hypertension perioperatively.[294] Another report suggests the use of awake intubation, a fiberoptic bronchoscope, and monitoring of evoked potentials.[295] Other than the commonsense approach of seeking neurologic consultation or, if necessary, using awake positioning of patients in a comfortable position before emergency root decompression procedures, no special procedures appear to be necessary. Patients with back pain may be receiving large doses of narcotics that may influence the anesthetic plan.

DEMYELINATING DISEASES

Demyelinating diseases constitute a diffuse group of diseases ranging from those with uncertain cause (e.g., multiple sclerosis, in which genetic, epidemiologic, and immunologic factors are probably all involved and interferon-β appears to be a promising treatment[296]) to those that follow infection, vaccination (e.g., Guillain-Barré syndrome), or antimetabolite treatment of cancer. Therefore, demyelinating diseases can have very diverse symptoms. Apparently, a risk of relapse of these diseases exists immediately after surgery. Because relapse may occur as a result of rapid electrolyte changes in the perioperative period, such changes may be avoided. In addition, perioperative administration of steroids may be a protective measure.[100] Both spinal anesthesia and epidural anesthesia have been administered without problems.[297,298] Multiple sclerosis and demyelinating diseases in general are the most common causes of nontraumatic disability in young adults. The age-adjusted survival rate is 80% of that of unaffected individuals, or put another way, the average patient with multiple sclerosis ages 1.2 years for every year with the disease. However, the variability of the disease makes this average rate of aging almost meaningless. No treatment alters most of these disease processes, although ACTH, steroids, interferon-β, glatiramer acetate (Copaxone), and plasmapheresis may ameliorate or abbreviate a relapse, or even alter disease progression, especially progression of multiple sclerosis and (if started within 2 weeks of onset) Guillain-Barré syndrome.[299] Such an effect is consonant with the hypothesis of an immunologic disorder as the cause of these diseases. Care should be taken to avoid succinylcholine in these patients because of the risk of hyperkalemia.

METABOLIC DISEASES

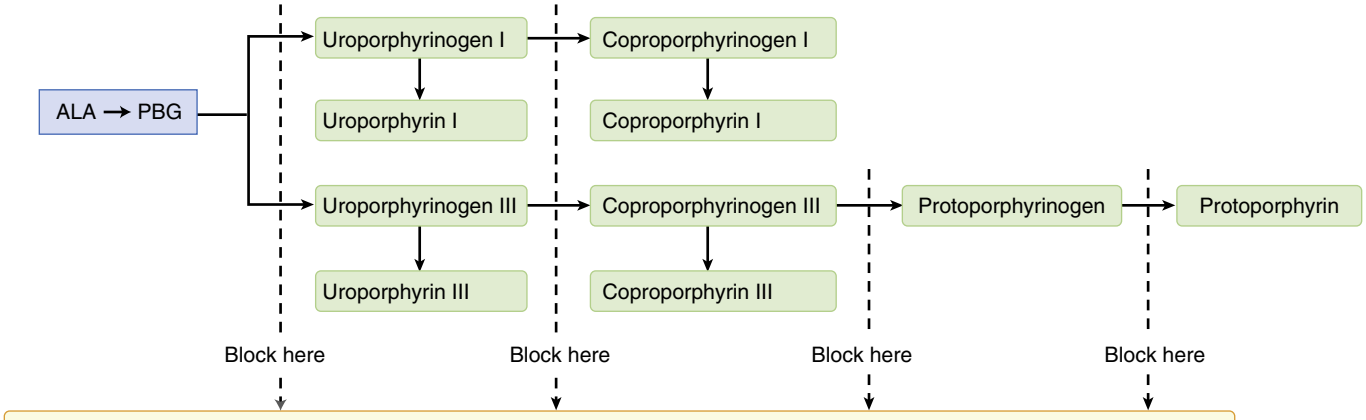
Included in the category of metabolic diseases is nervous system dysfunction secondary to porphyrias, alcoholism, uremia, hepatic failure, and vitamin B_{12} deficiency. The periodic paralysis that can accompany thyroid disease is discussed in the later section on neuromuscular disorders.

Alcoholism or heavy alcohol intake is associated with the following: acute alcoholic hepatitis (see also Chapter 73), the activity of which declines as alcohol is withdrawn; myopathy and cardiomyopathy, which can be severe; and withdrawal syndromes. Within 6 to 8 hours of withdrawal, the patient may become tremulous, a state that usually subsides within days or weeks. Alcoholic hallucinosis and withdrawal seizures generally occur within 24 to 36 hours. These seizures are generalized grand mal attacks; when focal seizures occur, other causes should be sought. Delirium tremens usually appears within 72 hours of withdrawal and is often preceded by tremulousness, hallucinations, or seizures. These three symptoms, combined with perceptual distortions, insomnia, psychomotor disturbances, autonomic hyperactivity, and, in a large percentage of cases, another potentially fatal illness (e.g., bowel infarction or subdural hematoma), are components of delirium tremens. This syndrome is now treated with benzodiazepines. Nutritional disorders of alcoholism include alcoholic hypoglycemia and hypothermia, alcoholic polyneuropathy, Wernicke-Korsakoff syndrome, and cerebellar degeneration. In patients with alcoholism (i.e., those who drink at least two six packs of beer or 1 pint of whiskey/day or the equivalent), emergency surgery and anesthesia (despite alcoholic hepatitis) are not associated with worsening abnormalities in liver enzymes. In addition, approximately 20% of patients with alcoholism also have COPD. A patient who has a history of alcohol abuse therefore warrants careful examination of many systems for quantification of preoperative physical status.

Although hepatic failure can lead to coma with high-output cardiac failure, unlike uremia, it does not lead to chronic polyneuropathy. Uremic polyneuropathy is a distal symmetric sensorimotor polyneuropathy that may be improved by dialysis. The use of depolarizing muscle relaxants in patients with polyneuropathies has been questioned (see also Chapter 34). We believe that patients who have neuropathy associated with uremia should not be given succinylcholine because of a possible exaggerated hyperkalemic response.

Pernicious anemia caused by vitamin B_{12} deficiency may result in subacute combined degeneration of the spinal cord; the signs are similar to those of chronic nitrous oxide toxicity. Both pernicious anemia and nitrous oxide toxicity are associated with peripheral neuropathy and disorders of the pyramidal tract and posterior column (which governs fine motor skills and the sense of body position). Combined-system disease can also occur without anemia, as can nitrous oxide toxicity in dentists and nitrous oxide abusers. Patients with vitamin B_{12} deficiency and anemia, if treated with folate, improve hematologically but progress to dementia and severe neuropathy. It may thus be prudent to give an intramuscular injection of 100 μg of vitamin B_{12} or 800 μg orally before giving folate to a patient who has signs of combined-system degeneration.[300]

The porphyrias are a constellation of metabolic diseases that result from an autosomally inherited lack of functional enzymes active in the synthesis of hemoglobin. Figure 39-6 schematically depicts the abnormalities that result from these enzyme deficits. Type 1, 3, and 4 porphyrias can cause life-threatening neurologic abnormalities. These conditions are characterized by the presence of aminolevulinic acid (ALA) or porphobilinogen,



Diagnosis:	Acute intermittent porphyria	Porphyria cutanea tarda	Coproporphyria (hereditary porphyria)	Variegate porphyria
In urine:	ALA PBG	Uroporphyrin	ALA PBG	ALA PBG
Neurologic sequelae:	Yes	No	Yes	Yes
Drug sensitization:	Yes	No	Yes	Yes

Figure 39-6. Schematic depiction of the functional enzyme deficits that occur in some of the porphyrias. *ALA,* Aminolevulinic acid; *PBG,* porphobilinogen.

or both, in urine; these substances do not occur in porphyria cutanea tarda, a disease that does not incur neurologic sequelae.[301] In acute intermittent porphyria, the typical pattern consists of acute attacks of colicky pain, nausea, vomiting, severe constipation, psychiatric disorders, and lesions of the lower motoneuron that can progress to bulbar paralysis. Certain drugs can induce the enzyme ALA synthetase and thereby exacerbate the disease process.[302-304] Such sensitizing drugs include barbiturates, meprobamate, chlordiazepoxide, glutethimide, diazepam, hydroxydione, phenytoin, imipramine, pentazocine, birth control pills, ethyl alcohol, sulfonamides, griseofulvin, and ergotamine preparations. Patients often have attacks during infection, fasting, or menstruation. Administration of glucose suppresses ALA synthetase activity and prevents or ablates acute attacks. Drugs used in anesthetic management that are reported to be safe for patients with porphyria include neostigmine (Prostigmin), atropine, gallamine, succinylcholine, *d*-tubocurarine, pancuronium, nitrous oxide, procaine, propofol, propanidid, etomidate, meperidine, fentanyl, morphine, droperidol, promazine, promethazine, and chlorpromazine.[302-304] Although ketamine has been used, postoperative psychoses attributable to the disease may be difficult to distinguish from those possibly caused by ketamine. In addition, although ketamine and etomidate are reported to be safe in humans, they seem to be porphyrinogenic in rats. Propofol has been used without provoking porphyria in at least two susceptible patients.[302,303]

NEUROMUSCULAR DISORDERS

Neuromuscular disorders consist of conditions affecting any major component of the motor unit: motoneuron, peripheral nerve, neuromuscular junction, and muscle. Neuropathies may involve all components of the nerve, thereby producing sensory, motor, and autonomic dysfunction, or only one component. Myopathies may involve the proximal muscles, the distal muscles, or both.

Myasthenia gravis is a disorder of the muscular system caused by partial blockade or destruction of nicotinic acetylcholine receptors by IgG antibodies (see also Chapters 34, 38, and 80). The severity of the disease correlates with the ability of antibodies to decrease the number of available acetylcholine receptors.[305] Treatment of myasthenia is usually begun with anticholinesterase drugs, but in moderate and severe disease, treatment progresses to steroids and thymectomy.[305,306] Immunosuppressive drugs and plasmapheresis are initiated if the more conservative measures fail, and intravenous immunoglobulin, a rapid-onset therapy, is reserved for acute exacerbations and myasthenic crises.[305,306]

One major problem for the anesthesiologist involves the use of muscle relaxants and their reversal[307] (see also Chapter 35). Because much of the care of patients with myasthenia gravis involves tailoring the amount of anticholinesterase medication to the maximal muscle strength of the patient, derangement of the course of the patient during the surgical procedure could necessitate

reassessment of the drug dosage. For that reason, all anticholinergic drugs may be withheld for 6 hours preoperatively, and medication should be reinstituted postoperatively with extreme caution because the sensitivity of these patients to such drugs may have changed. Small doses of succinylcholine can be used to facilitate endotracheal intubation; extremely small doses of nondepolarizing drugs can be used for intraoperative relaxation not achieved by regional anesthesia or volatile anesthetics. Of prime importance is monitoring neuromuscular blockade as the guide for muscle relaxant administration and their reversal (see Chapter 53). Although controlled ventilation was frequently required for at least 24 to 48 hours postoperatively, immediate extubation has become more common.[306-308] Postoperative ventilation is especially important in patients with myasthenia gravis of more than 6 years' duration, COPD, a daily pyridostigmine requirement of 750 mg in association with significant bulbar weakness, and vital capacity of less than 40 mL/kg.[308] One study in myasthenic patients found rapid recovery of neuromuscular function in patients receiving rocuronium when sugammadex was used for reversal.[309] The authors suggest that the combination could be a rational alternative for myasthenic patients for whom neuromuscular blockade is mandatory during surgical procedures.

Lambert-Eaton syndrome (myasthenic syndrome) is characterized by proximal limb muscle weakness and is associated with antibodies directed against the voltage-gated calcium channels in presynaptic nerve terminals. Strength or reflexes may increase with repetitive effort. Affected patients exhibit decreased release of acetylcholine at the neuromuscular junction. Guanidine therapy enhances the release of acetylcholine from nerve terminals and improves strength. Men with this syndrome generally have small cell carcinoma of the lung or other malignant disease, whereas women often have malignant disease, sarcoidosis, thyroiditis, or a collagen-related vascular disease. In addition, these patients have increased sensitivity to both depolarizing and nondepolarizing muscle relaxants.[310] Lambert-Eaton syndrome is also associated with an autonomic nervous system defect manifested by gastroparesis, orthostatic hypotension, and urinary retention.

Dermatomyositis and polymyositis are characterized by proximal limb muscle weakness with dysphagia. These conditions are associated with malignant disease or collagen-related vascular disease and often involve respiratory and cardiac muscle.

Periodic paralysis is another disease in which sensitivity to muscle relaxants increases. Periodic weakness starts in childhood or adolescence and is precipitated by rest after exercise, sleep, cold, surgery, or pregnancy. Hypokalemic and hyperkalemic forms exist and are associated with cardiac arrhythmias. Like thyrotoxic periodic paralysis, these hypokalemic and hyperkalemic forms usually spare the respiratory muscles. Anesthetic management consists of minimizing stress and maintaining normal fluid and electrolyte status and body temperature.[310-313]

Patients with muscular dystrophy now survive into their late 20s or early 30s. Because the disease involves the muscles themselves and not their innervation, conduction anesthesia cannot produce adequate relaxation of tonic muscles. Gastric dilation is also a problem, as is malignant hyperthermia. As with the other forms of muscular dystrophy, most problems in myotonic dystrophy arise from cardiac arrhythmias and inadequacy of the respiratory muscles.[314] For all the forms of muscular dystrophy, as for all the neuropathies (discussed earlier), problems have been related to exaggerated release of serum potassium after the administration of depolarizing muscle relaxants.

Malignant hyperthermia in the patient or in a relative of the patient merits careful history taking and at least consideration of performing a test for susceptibility to the condition (see also Chapter 43). Prophylaxis with intravenous dantrolene sodium (Dantrium) may also be warranted. In some cases, malignant hyperthermia has been associated with recognizable musculoskeletal abnormalities such as strabismus, ptosis, myotonic dystrophy, hernias, kyphoscoliosis, muscular dystrophy, central core disease, and marfanoid syndrome. Appropriate preparation for a patient with previous masseter spasm, or trismus, is a matter of considerable debate. Malignant hyperthermia occurs most frequently in children and adolescents; the incidence is 1 in 14,000 administrations of anesthesia. The incidence increases to 1 in 2500 patients requiring strabismus (squint) surgery.

DOWN SYNDROME

Down syndrome (trisomy 21) occurs once in 1000 live births. It is associated with congenital cardiac lesions such as endocardial cushion defects (40%), ventricular septal defects (27%), patent ductus arteriosus (12%), and tetralogy of Fallot (8%). Prophylactic antibiotics should be used before predictable bacteremic events. Down syndrome is also associated with upper respiratory infections, with atlanto-occipital instability (in ≈15% of patients,[315-318] in whom it is asymptomatic in most cases, but all patients should be treated as though they have atlanto-occipital instability) and laxity of other joints, with thyroid hypofunction (50%), with an increased incidence of subglottic stenosis, and with enlargement of the tongue (or a decreased oral cavity size for a normal-sized tongue).[317,319] No abnormal responses to anesthetic agents or anesthetic adjuvants have been substantiated. A reported sensitivity to atropine has been disproved, although administration of atropine to any patient receiving digoxin for atrial fibrillation should be done with care.[319] Examination for the conditions associated with Down syndrome should precede surgery.

PREOPERATIVE PREDICTION OF INCREASED INTRACRANIAL PRESSURE DURING NEUROSURGERY

Symptoms and signs of increased intracranial pressure include morning headache or headache made worse by coughing, nausea, vomiting, disturbances in consciousness, history of large tumors, tumors involving the brainstem, neck rigidity, and papilledema. Patients with these signs, large ventricles (as seen on radiography or images of the brain), or edema surrounding supratentorial

tumors should be considered at risk for intraoperative intracranial hypertension. These patients may benefit from preoperative treatment or anesthetic management that assumes this possibility (see also Chapter 70).[320]

Other preoperative considerations for patients with neurologic disease that can cause intracranial hypertension are the associated hypoventilation and hypoxia in patients who have severe hemiplegia and the presence of subarachnoid bleeding or other forms of intracranial hemorrhage (especially likely in women given heparin who have two or more cerebral infarcts noted on CT). Many strokes or transient ischemic attacks have a possible cardiac origin.

MENTAL DISORDERS

Perhaps the most important preoperative consideration for patients with mental disorders, in addition to developing rapport, is understanding their specific drug therapy and its effects and side effects. Lithium, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), other antidepressants that defy classification (e.g., bupropion), phenothiazines, butyrophenones, and MAOIs are used in these patients.[321] These drugs have potent effects and side effects that are discussed in the last section of this chapter, on drug therapy.

RENAL DISEASE AND ELECTROLYTE DISORDERS

The anesthesiologist has an important role to play in preventing the onset and consequences of renal failure and its initiators. The linking of renal failure to electrolyte disorders is more obvious: the kidney is the primary organ for regulating body osmolality and fluid volume and has a major role in excretion of the end products of metabolism. In performing these functions, the kidney becomes intimately involved in the excretion of electrolytes.

A patient with renal insufficiency whose own kidneys are still functioning is distinct not only from a patient with end-stage renal disease whose renal functions are provided by dialysis but also from a patient who has a transplanted kidney. These three groups of patients require very different preoperative preparation. In addition, acute changes in renal function present quite a different problem than do chronic alterations in function. Certain renal diseases require different preoperative preparation than others, but generally, renal disease of any origin presents the same preoperative problems (see also Chapters 23, 38, and 52).

RENAL DISEASE

Causes and Systemic Effects of Renal Disorders

Nephrotic syndrome may develop in patients with glomerular diseases without disturbing tubular function. The soundness of tubular function is an important consideration because tubular dysfunction with attendant uremia presents problems quite different from those presented by glomerular disease with only nephrotic syndrome. This is not to minimize the adverse effects of glomerular disease; nephrotic syndrome consists of massive proteinuria and consequent hypoalbuminemia. The resulting reduction in plasma oncotic pressure diminishes plasma volume and calls forth compensatory mechanisms that result in retention of sodium and water. As a result, a common clinical finding in nephrotic syndrome is edema. Thus, patients with nephrotic syndrome may have excess total-body water and decreased intravascular volume. In addition, diuretics are often given in an attempt to decrease edema. Although serum creatinine and creatinine clearance estimations have limitations as indices of the GFR (inulin clearance is still the gold standard), these measurements are, for now, the most readily available to the anesthesiologist. Plasma creatinine levels reflect endogenous muscle catabolism and dietary intake, as well as urinary excretion. Urinary excretion depends on both filtration and secretion by the kidney. Drugs that are commonly used in the preoperative and perioperative periods can distort this measure of glomerular filtration. Moreover, the commonly used methods for measuring creatinine have a 95% confidence limit of greater than 20% for a GFR higher than 30 mL/minute. Thus, a normal creatinine level of 1.3 mg/dL may give a measured value ranging from 1.0 to 1.5 mg/dL.

Furthermore, in patients with nephrotic syndrome in whom renal tubular function has been preserved, hypovolemia appears to be a significant cause of deteriorating tubular renal function.[322-324] No randomized study has shown that close control of intravascular volume status in these groups of patients preserves renal tubular function (or any other measure of perioperative morbidity) to a greater degree than does less rigid control.

Uremia, the end result of renal tubular failure (i.e., failure of the concentrating, diluting, acidifying, and filtering functions) manifests in many ways. Changes occur in the cardiovascular, immunologic, hematologic, neuromuscular, pulmonary, and endocrine systems, as well as in bone. These alterations are ascribed either to the toxic end products of protein metabolism or to an imbalance in functioning of the kidney. As the number of functioning nephrons diminishes, the still-functioning nephrons attempt to increase some solute and body composition preservation functions at the expense of other functions, such as excretion of phosphate. The accumulation of phosphate increases PTH levels, which in turn produce osteodystrophy. Osteodystrophy can be managed by (1) restriction of dietary phosphate, (2) the use of gels (e.g., aluminum hydroxide or carbonate) that bind with intestinal phosphate, (3) calcium supplementation, or (4) parathyroidectomy.

Certain alterations in patients with uremia, such as neuropathy, are most logically attributed to an accumulation of toxic metabolites. Peripheral neuropathy is most often sensory and involves the lower extremities, but it may also be motor; peripheral neuropathies are frequently improved with hemodialysis and can be dramatically reversed with renal transplantation. The use of depolarizing muscle relaxants in patients with peripheral neuropathy is controversial and is discussed in the section on neuropathies. Tubular function is commonly

assessed by acidifying and concentrating capabilities.[325] Although such tests are crude, these capabilities are usually readily evaluated by measuring urine pH and specific gravity. Better assessment of renal blood flow, for the purpose of improving renal blood flow and its distribution, is promised by the use of contrast-enhanced ultrasound in the operating room.[326] Along with the altered volume status and cardiac complications in uremic patients, autonomic neuropathy may contribute to hypotension during anesthesia. Atherosclerosis is often accelerated in uremic patients; hypertension, with its attendant consequences, is very common.

Cardiac failure (especially episodic failure) frequently occurs in uremic patients because of the presence of many adverse conditions: anemia with increasing myocardial work, hypertension, atherosclerosis, and altered volume status. Pericarditis can manifest by pericardial rub alone or by pain (with or without hemorrhage). Cardiac tamponade should be ruled out on the basis of clinical features and by echocardiography if this diagnosis is seriously suspected preoperatively. In addition, cardiac tamponade should be treated or planned for preoperatively.

If anemia is present, its severity generally parallels the degree of uremia; chronically uremic patients seem to adapt well to anemia. No hard data have substantiated the need to give a preoperative blood transfusion to a chronically uremic patient, even when the preoperative hematocrit is as low as 16% to 18%. Even in nonuremic patients in an ICU, a randomized trial was unable to demonstrate improved outcome with a liberal transfusion strategy,[327] and transfusions increase the risk for immune system compromise (see also Chapter 61).[328] Thus, one of the major historical reasons for not transfusing blood in patients with end-stage renal disease has been disproved by this finding: data show that the more blood transfusions a transplant recipient receives before transplantation, the greater is the chance that the transplant will function successfully.[329] In uremic patients, coagulation and platelet adhesiveness may be abnormal and factor III activity may be decreased. Even uremic patients who are not given corticosteroids or immunosuppressive drugs may demonstrate abnormal immunity, perhaps warranting increased attention regarding procedures that lessen patient cross-contamination.

Uremic patients exhibit a wide variety of metabolic and endocrinologic disorders in addition to hyperparathyroidism, including impaired carbohydrate tolerance, insulin resistance, type IV hyperlipoproteinemia, autonomic insufficiency, hyperkalemia, and anion-gap acidosis (caused by an inability of the kidneys to reabsorb filtered bicarbonate and excrete sufficient ammonium into urine). Furthermore, the excretion and pharmacokinetics of drugs are different in uremic patients than in normal patients. In addition, complications of hemodialysis include nutritional deficiencies, electrolyte and fluid imbalances, and mental disorders. Because these conditions can lead to serious perioperative morbidity, they should be evaluated preoperatively. No data, however, have substantiated the hypothesis that preoperative optimization of these metabolic and endocrinologic disorders reduces perioperative risk in uremic patients.

As with uremic patients, preoperative optimization of volume status is paramount in patients with kidney stones, and both are affected by carbohydrate intolerance.[330,331] Seventy-five percent of all kidney stones are composed of calcium oxalate. Patients with these stones frequently take diuretic drugs, consume calcium- and citrate-rich foods, and restrict salt intake. Prevention of dehydration by institution of intravenous fluid therapy along with restricted oral intake of protein may be as important for these patients as it is for patients with struvite or uric acid stones. Struvite stones often result from urinary infection. Uric acid stones can be prevented by treatment with allopurinol, by preoperative hydration, or by alkalinization of urine. Acidosis may contribute to stone formation. Again, optimal intravascular volume status is important in preventing stones and preserving renal function. More thorough discussion of renal function and physiology is provided in Chapter 23. Chapter 72 deals with the complexities of managing patients for renal surgery and other urologic procedures.

Creatinine clearance in conjunction with free water clearance appears to be the most accurate way of quantifying, for pharmacokinetic purposes, the degree of decreased renal function (see also Chapter 23).[331] For a patient with stable renal function, creatinine clearance, which is a rough estimate of GFR, can be approximated by noting the serum creatinine level: a doubling of the creatinine level represents a halving of the GFR. Thus, a patient with a stable serum creatinine level of 2 mg/dL would have a GFR of approximately 60 mL/minute. A stable serum creatinine level of 4 mg/dL would accompany a GFR of approximately 30 mL/minute, and a stable serum creatinine level of 8 mg/dL would accompany a GFR of 15 mL/minute or less. When pregnancy and considerable edema are not present and the serum creatinine level is stable, the following formulas can be used to estimate creatinine clearance and free water clearance.[331-333]

$$\text{Creatinine clearance} = \frac{(140 - \text{Age [yr]}) \times \text{Body weight (kg)}}{72 \times \text{serum creatinine}\left(\frac{\text{mg}}{\text{dL}}\right)}$$

$$\text{Free water clearance} = \text{Urine flow (mL/hour)} - \frac{\text{Urine osmolality}\left(\frac{\text{mOsm}}{\text{L}}\right) \times \text{Urine flow}\left(\frac{\text{mL}}{\text{hour}}\right)}{\text{Plasma osmolality}\left(\frac{\text{mOsm}}{\text{L}}\right)}$$

Note that renal function must be stable. Unstable renal function is often associated with changes in serum creatinine levels that lag by several days. Although knowing the serum creatinine level is more useful than knowing the BUN level, the BUN value provides some information, as discussed in the next section.

Free water clearance is a measure of renal concentrating ability, and it is normally –25 to +100 mL/hour; it becomes more positive in renal insufficiency states. It may also become more positive in patients who have a head injury or high blood alcohol levels or in those undergoing aggressive fluid infusion or administration of diuretics.[332]

Patients With Insufficient but Functioning Kidneys

One of the greatest challenges for the anesthesiologist is presented by patients with insufficient renal function whose renal function must be preserved during surgical procedures. Additionally, the presence of chronic renal failure is associated with higher rates of perioperative cardiac morbidity, which may warrant further evaluation for the presence of occult CAD.[333] The many uremic symptoms and great perioperative morbidity associated with uremia can probably be avoided by attention to detail in the preoperative and perioperative management of patients with insufficient, but still functioning kidneys.[322-324]

First, studies demonstrate that acute postoperative renal failure is associated with an extremely high mortality rate.[334] The development of perioperative renal dysfunction has multiple risk factors, the most important of which include preexisting renal disease, heart surgery involving cardiopulmonary bypass or aortic surgery involving cross-clamping of the thoracic or abdominal aorta, and ongoing sepsis.

Moreover, acute perioperative renal failure is most likely to occur in patients who have renal insufficiency before the surgical procedure, are older than 60 years, and have preoperative left ventricular dysfunction.[332,334] Proper preoperative hydration probably decreases mortality after acute renal failure induced by radiocontrast agents.[324] Clues to the presence of hypovolemia or hypervolemia should be sought from the history and physical examination (e.g., weight loss or gain, thirst, edema, orthostatic hypotension and tachycardia, flat neck veins, dry mucous membranes, decreased skin turgor). In seriously ill patients, insertion of a pulmonary artery catheter permits more precise monitoring of intravascular fluid volume. Other causes of deterioration in function in chronic renal insufficiency are low cardiac output or low renal blood flow (in prerenal azotemia, whether because of cardiac failure or fluid depletion from diuretic drugs, BUN often increases disproportionately to increases in creatinine), urinary tract infection, use of nephrotoxic drugs, hypercalcemia, and hyperuricemia. These conditions and drugs should be avoided; if any of these conditions exist, they should be treated preoperatively.

Management of patients with renal disease is discussed in Chapter 72.

Patients Undergoing Dialysis

Patients with chronic (and at times acute) renal failure require renal replacement therapy, including conventional intermittent hemodialysis, peritoneal dialysis, and continuous renal replacement therapy (CRRT). CRRT includes a wide variety of techniques whose perioperative management has been reviewed (Table 39-14).[335] Although the primary indication for CRRT is acute renal failure, it can also be used for fluid clearance, correction of electrolyte abnormalities, and management of metabolic acidosis. It can be used in surgical patients without significant hemodynamic abnormalities. These patients may return to the operating room, and their assessment and management may be complicated by the underlying disease and the use of systemic anticoagulation to prevent filter and circuit clotting. In patients undergoing intermittent treatment with hemodialysis or peritoneal dialysis, the procedure is discontinued before entering the operating room. For CRRT, the anesthesiologist must determine the appropriateness of discontinuing the therapy. With short procedures, the therapy can almost always be stopped and the arterial and venous ends of the circuit connected and run in the bypass mode. CRRT can also be used to manage fluids during the surgical procedure by changing the dialysate. If CRRT is continued, its effect on drug dosing must be recognized. In addition to effects on renal elimination of drugs, CRRT has effects resulting from changes in protein binding and volume of distribution, as well as drug removal effects from membrane permeability, membrane surface area, the ultrafiltration rate, and the dialysate flow rate.

Because a patient undergoing dialysis has already lost natural renal functioning, the emphasis in preoperative assessment shifts toward protecting other organ systems and optimally maintaining vascular access sites for cannulation. Usually, this does not require invasive monitoring. Emphasis is placed on intravascular fluid volume and electrolyte status, which can be ascertained by knowing when the patient last underwent dialysis, how much weight was normally gained or lost with dialysis, whether the fluid loss was peritoneal or intravascular, and what electrolyte composition the blood was dialyzed against. Although preoperative dialysis may benefit patients who have hyperkalemia, hypercalcemia, acidosis, neuropathy, and fluid overload, the resulting dysequilibrium between fluid and electrolytes can cause problems. Because hypovolemia induced by dialysis can lead to intraoperative hypotension, we try to avoid weight and fluid reduction in patients undergoing preoperative dialysis. In addition, hypopnea

TABLE 39-14 **CHARACTERISTICS OF RENAL REPLACEMENT THERAPY**

Renal Replacement Therapy	Blood Pump	Replacement Fluid (RF)/ Dialysate (D)	Intraoperative Use
Conventional intermittent hemodialysis	Yes	D	No
Peritoneal dialysis	No	D	No
Slow continuous ultrafiltration	Yes/ no	None	Yes
Continuous arteriovenous hemodialysis	No	D	No
Continuous arteriovenous hemodiafiltration	No	RF/D	No
Continuous venovenous hemofiltration	Yes	RF	Yes
Continuous venovenous hemodialysis	Yes	D	Yes
Continuous venovenous hemodiafiltration	Yes	RF/D	Yes

From Petroni KC, Cohen NH: Continuous renal replacement therapy: anesthetic implications, Anesth Analg *94:1288-1297, 2002.*

has been found to occur during and after dialysis when the dialysate contained acetate. Avoiding an acetate bathing solution may prevent this cause of hypoventilation.

When renal transplant recipients have subsequent surgical procedures, the status of their renal function must be determined (i.e., whether they have normal renal function, insufficient but still functioning kidneys, or end-stage renal disease requiring hemodialysis) (see also Chapter 74). Descriptions of side effects of immunosuppressive drugs should also be sought. The drugs used preoperatively and intraoperatively to prevent acute rejection themselves have serious side effects that encourage close monitoring of blood glucose and cardiovascular function.[329,336] Because renal transplantation greatly increases the risk of infection, it is very important to avoid invasive monitoring and prevent patient cross-contamination.

Drugs in Patients With Renal Failure

Patients with renal azotemia have a threefold or higher risk of having an adverse drug reaction than do patients with normal renal function.[337-339] The risk is increased by two conditions. First, excessive pharmacologic effects result from high levels of a drug or its metabolite (e.g., the metabolite of meperidine) in blood because of physiologic changes in target tissues induced by the uremic state. An example is excessive sedation in a uremic patient with standard blood levels of sedative-hypnotic drugs. Second, excessive administration of electrolytes with drugs also increases the risk of having an adverse drug reaction. Administration of standard doses of drugs that depend on renal excretion for their elimination can result in drug accumulation and enhanced pharmacologic effect. In one report, patients with end-stage renal disease required significantly higher propofol doses to achieve the clinical endpoint of hypnosis than did patients with normal renal function.[339]

INFECTIOUS DISEASE

Sepsis is a leading cause of postoperative morbidity,[324,340] probably through a decrease in systemic vascular resistance related to activation of the complement system and other mediators. Thus, attention to the effects of antibiotic drugs must be supplemented by attention to intravascular volume status.[322-324,340-342] The degree of impairment of the infected organ and its effect on anesthesia should be assessed. For instance, endocarditis merits examination of the following: intravascular volume status; antibiotic and other drug therapy and side effects[343]; myocardial function; and renal, pulmonary, neurologic, and hepatic function—organ systems that can be affected by endocarditis.

Although all surgery except emergency or essential operations is proscribed when an acute infectious disease is present, many such diseases (e.g., influenza and pneumococcal pneumonia) and even inflammatory conditions are becoming less frequent because of successful immunization recommendations and programs.[344] Furthermore, even though acute infections are less common, surgery in patients with chronic viral diseases such as hepatitis and HIV infection is more frequent. Many of these patients may also harbor opportunistic infections such as tuberculosis or may have other systemic problems. Whether anesthesia or surgery, or both, exacerbates these infections or their systemic manifestations is not clear.

ELECTROLYTE DISORDERS

Disorders of calcium, magnesium, and phosphate balance are discussed in the earlier section on diseases involving the endocrine system and disorders of nutrition (see also Chapters 38 and 60).

Hyponatremia and Hypernatremia

Electrolyte disorders are usually detected by determining the levels of electrolytes in serum. These concentrations reflect the balance between water and electrolytes. The osmolality of all body fluids is normally maintained within the narrow physiologic range of 285 to 290 mOsm/kg H_2O by integration of three key processes: thirst, release of ADH, and responsiveness of the medullary collecting ducts to ADH. Because of the permeability of biologic membranes, intracellular osmolality and extracellular osmolality are almost always equal and can be estimated by the following formula:

$$2\left[Na^{2+}\right](\text{mEq/L}) + \frac{[\text{Glucose}]\,(\text{mg/dL})}{18} + \frac{[\text{BUN}]\,(\text{mg/dL})}{2.8} = \text{mOsm/kg}$$

This formula will become easier to calculate when we convert fully to the International System of Units (SI units; metric system) because millimoles (mmol) can be substituted for mg/(factor) in the foregoing formula to read

$$2\left[Na^{2+}\right] + [\text{Glucose}] + [\text{BUN}] = \text{mOsm/kg}$$

with concentrations expressed in millimoles per liter (mmol/L). Although secretion of ADH is tightly controlled by osmotic stimuli at 285 to 290 mOsm/kg, the osmotic threshold for thirst is high (300 mOsm/kg), thus making this sign an important guide to volume deficiency.

Hyponatremia is perhaps the third most common fluid electrolyte abnormality in hospitalized patients. (Magnesium deficiency occurs in as many as 25% [see Chapter 59], and potassium deficiency, discussed later in this section, occurs in as many as 10%.) Hyponatremia can occur in isotonic, hypertonic, or hypotonic forms. For example, isotonic hyponatremia can develop in protein or liquid accumulation states such as myeloma. Hypertonic hyponatremia can be present with hyperglycemia or with infusions of glycine (as in the TURP syndrome). Hypotonic hyponatremia is the largest classification and is subdivided according to the status of the extracellular fluid into hypovolemic, isovolumic, or hypervolemic hypotonic hyponatremia. All three types require that excretion of renal water be impaired despite continued intake of dilute fluid. Common causes of hypovolemic hypotonic hyponatremia are GI losses (vomiting, diarrhea), third-space losses (diuretics or salt-wasting nephropathy), and

BOX 39-6 *Types and Causes of Hypotonic Hyponatremia**

HYPOVOLEMIC
- Gastrointestinal losses
  - Vomiting
  - Diarrhea
- Skin losses
- Third-space losses
- Lung losses
- Renal losses
  - Diuretics
  - Renal damage
  - Urinary tract obstruction
- Adrenal insufficiency

ISOVOLUMIC
- Syndrome of inappropriate secretion of antidiuretic hormone
- Renal failure
- Water intoxication
- Hypokalemia
- Dysfunctional osmostat

HYPERVOLEMIC
- Congestive heart failure
- Nephrosis
- Liver dysfunction

*Serum osmolality less than 280 mOsm/L.

adrenal insufficiency (Box 39-6). Hypervolemic hypotonic hyponatremic states complicate severe cardiac failure, cirrhosis, nephrotic syndrome, and renal failure and are characterized by retention of sodium with disproportionately larger amounts of water.

The more common isovolumic hypotonic hyponatremia is caused by retention of water without sodium. Because edema is not usually clinically apparent, such patients appear isovolumic. Edema is most often caused by SIADH, which in turn may be caused by CNS or pulmonary tumors or dysfunction. Secretion of ADH increases with age, thus rendering older adults more prone to hyponatremia. Drugs that potentiate the secretion of ADH (tricyclic antidepressants and vincristine) or its effects on the medullary collecting duct system in the kidney (nonsteroidal antiinflammatory drugs and chlorpropamide) or that have similar effects (oxytocin) may be more likely to cause hyponatremia in older adults. To establish the diagnosis of SIADH, the physician should determine that the patient is free of renal and cardiac dysfunction, has normal adrenal and thyroid function, and is normovolemic. Urine osmolality would then be found to exceed 100 mOsm/kg, serum osmolality would be low, and urine sodium excretion would be higher than 20 mEq/L (20 mOsm/L).

Disturbances in serum sodium therefore reflect alterations in glucose metabolism, renal function, or accumulation of body water. The last can be affected by disturbances in thirst, release of ADH, and renal function. Thus, hyponatremia reflects a relative excess of free water and can occur when total-body sodium increases (as in edematous disorders), when total-body sodium is normal (as in excess of free water because of SIADH), or when total-body sodium decreases (as occurs with too aggressive use of diuretic drugs). Definition of the cause defines the treatment. For instance, water restriction is the mainstay of therapy for SIADH. Administration of demeclocycline is another option that corrects SIADH by inducing a reversible nephrogenic diabetes insipidus. The anesthesiologist is faced with the question of what levels of electrolytes require treatment before anesthesia. Although slowly developing hyponatremia usually produces few symptoms, the patient may be lethargic and apathetic. Chronic hyponatremia is better tolerated than acute hyponatremia because of mechanisms regulating intracellular fluid volume that alleviate brain edema; the loss of other solutes from cells decreases the osmotic movement of water into cells. Nonetheless, severe chronic hyponatremia (i.e., serum sodium levels <123 mEq/L) can cause brain edema.

By contrast, acute hyponatremia may be manifested by severe symptoms requiring emergency treatment: profound cerebral edema with obtundation, coma, convulsions, and disordered reflexes and thermoregulatory control.[100,101,345] Depending on the cause and relative total sodium and water content, treatment can range from the administration of hypertonic saline or mannitol (with or without diuretic drugs) to restriction of fluids or administration of other drugs.[100,101,345] Because neurologic damage may develop if the serum sodium concentration is increased too rapidly, the rate of increase should not exceed 1 mEq/L/hour.[100,101,345] After the serum sodium concentration has reached 125 mEq/L, therapy may consist of water restriction; more rapid correction may result in CNS demyelination.[100,101,345] In hyponatremic patients who have excess total-body water secondary to SIADH, serum levels can be corrected by giving furosemide, 1 mg/kg, and hypertonic saline to replace the loss of electrolytes in urine.[100,101,345] The diagnosis of SIADH is discussed earlier in this chapter (see the section on pituitary abnormalities).

Neither acute nor chronic hyponatremia necessitates restoration of serum sodium to normal levels; brain swelling usually disappears at a serum sodium level of 130 mEq/L.

Hypernatremia occurs much less commonly than hyponatremia. It is often iatrogenic (e.g., it can be caused by failure to provide sufficient free water to a patient who is unconscious or who has had a recent stroke-induced deficit of the thirst mechanism) and can occur in the presence of low, normal, or excess total-body sodium. The primary symptoms of hypernatremia relate to brain cell shrinkage. Because too rapid correction of hypernatremia can lead to cerebral edema and convulsions, correction should be made gradually. Again, with no data to support this stance, we believe that all patients undergoing surgical procedures should have serum sodium concentrations of less than 150 mEq/L before anesthesia.

Hypokalemia and Hyperkalemia

Hypokalemia and hyperkalemia are also discussed in Chapters 38 and 59. The relationship between the measured potassium concentration in serum and total-body potassium stores can best be described with a scattergram. Only 2% of total-body potassium is stored in plasma (4200 mEq in cells and 60 mEq in extracellular fluid). In

normal persons, 75% of the 50 to 60 mEq/L of total-body potassium is stored in skeletal muscle, 6% in red blood cells, and 5% in the liver. Thus, a 20% to 25% change in potassium levels in plasma could represent a change in total-body potassium of 1000 mEq or more if the change were chronic or as little as 10 to 20 mEq if the change were acute.

As with serum sodium levels,[100,101,345] acute changes in serum potassium levels are less well tolerated than chronic changes. Chronic changes are relatively well tolerated because of the equilibration of serum and intracellular stores that takes place over time to return the resting membrane potential of excitable cells to nearly normal levels.

Hyperkalemia can result from the following: factitious increase of potassium administration (as in red blood cell hemolysis); excessive exogenous potassium from sources such as salt substitutes or, in large amounts, bananas; cellular shifts in potassium (as a result of metabolic acidosis, tissue and muscle damage after burns, use of depolarizing muscle relaxants, or intense catabolism of protein); and decreased renal excretion (as occurs in renal failure, renal insufficiency with trauma, and therapy with potassium-sparing diuretic drugs, especially when combined with ACE inhibitors or mineralocorticoid deficiency).[346-348] Factitious hyperkalemia can occur when a tourniquet is left on too long or even by simple fist clenching.[349]

The major danger in anesthetizing patients who have disorders of potassium balance appears to be abnormal cardiac function (i.e., both electrical disturbance[346] and poor cardiac contractility). Hyperkalemia lowers the resting membrane potential of excitable cardiac cells and decreases the duration of the myocardial action potential and upstroke velocity. This decreased rate of ventricular depolarization, in addition to the beginning of repolarization in some areas of the myocardium while other areas are still undergoing depolarization, produces a progressively widening QRS complex that merges with the T wave into a sine wave on the ECG.

At a potassium level greater than 6.7 mEq/L, the degree of hyperkalemia and the duration of the QRS complex correlate well.[346] This correlation is even better than the correlation between the serum potassium level and T-wave changes. Nevertheless, the earliest manifestations of hyperkalemia are narrowing and peaking of the T wave. Although not diagnostic of hyperkalemia, T waves are almost invariably peaked and narrow when serum potassium levels are 7 to 9 mEq/L. When serum potassium levels exceed 7 mEq/L, atrial conduction disturbances appear, as manifested by a decrease in P-wave amplitude and an increase in the PR interval. Supraventricular tachycardia, atrial fibrillation, PVCs, ventricular tachycardia, ventricular fibrillation, or sinus arrest may all occur.

The ECG and cardiac alterations associated with hyperkalemia are potentiated by low serum levels of calcium and sodium. Intravenous administration of saline, bicarbonate, glucose with insulin (1 unit/2 g glucose), and calcium can reverse these changes by shifting some extracellular potassium into the cell.

β-Adrenergic stimuli also cause redistribution of potassium into the cell. Indeed, the plasma potassium concentration measured in samples immediately before surgical procedures is usually 0.2 to 0.8 mEq/L lower than that measured during the less stressful period 1 to 3 days before surgery.[350] β-Adrenergic receptor blocking drugs can be used to prevent such an effect preoperatively. A β-adrenergic receptor stimulating agent (20 mg of nebulized albuterol for a 70-kg patient) can be used to treat hyperkalemia when it occurs; it decreases potassium levels 1.0 mEq/L within 30 minutes, and its effect lasts 2 hours.[351] Although nebulized β_2-agonists effectively lower plasma potassium concentrations by stimulating sodium- and potassium-dependent adenosine triphosphatase, this therapy should be used as an adjunct to rather than a substitute for more established measures. Kayexalate (sodium polystyrene sulfonate) enemas can be given to bind potassium in the gut in exchange for sodium. Dialysis against a hypokalemic solution also decreases serum potassium levels. However, in a hyperkalemic patient, hypoventilation can be dangerous during anesthesia because each 0.1 change in pH can produce a 0.4 to 1.5 mEq/L change in serum potassium levels in the opposite direction. For example, if pH decreases from 7.4 to 7.3, serum potassium levels could increase from 5.5 to 6.5 mEq/L.

Hypokalemia can be caused by inadequate intake of potassium, excessive GI loss (through diarrhea, vomiting, nasopharyngeal suctioning, long-term use of laxatives, or ingestion of cation exchange resins, as in certain wines), excessive renal loss (because of the use of diuretic drugs, renal tubular acidosis, chronic chloride deficiency, metabolic alkalosis, mineralocorticoid excess, excessive ingestion of licorice, use of antibiotics, ureterosigmoidostomy, and diabetic ketoacidosis), and shifts of potassium from extracellular to intracellular compartments (as occurs in alkalosis, insulin administration, administration of a β-adrenergic agonist or stress, barium poisoning, and periodic paralysis). As with hyperkalemia, knowledge of the cause of the potassium deficiency and appropriate preoperative evaluation and treatment of that cause may be as important as treatment of the deficiency itself. Also like hyperkalemia, hypokalemia may reflect small or vast changes in total-body potassium. Acute hypokalemia may be much less well tolerated than chronic hypokalemia. The major worrisome manifestations of hypokalemia pertain to the circulatory system, both the cardiac and peripheral components. In addition, chronic hypokalemia results in muscle weakness, hypoperistalsis, and nephropathy.

Cardiovascular manifestations of hypokalemia include the following: autonomic neuropathy, which results in orthostatic hypotension and decreased sympathetic reserve; impaired myocardial contractility; and electrical conduction abnormalities, which can result in sinus tachycardia, atrial and ventricular arrhythmias, and disturbances in intraventricular conduction that can progress to ventricular fibrillation. In addition to arrhythmias, the ECG shows widening of the QRS complex, ST-segment abnormalities, progressive diminution of the T-wave amplitude, and a progressive increase in the U-wave amplitude. Surawicz found these changes to be invariably present when serum potassium levels decreased to less than 2.3 mEq/L.[346] Although U waves are not specific for

hypokalemia, they are sensitive indicators of the condition. Replenishing the total-body potassium deficit for a depletion reflected by a serum deficit of 1 mEq/L (e.g., from 3.3 to 4.3 mEq/L) may require 1000 mEq of potassium. Even if this amount could be given instantaneously (and it should not be replenished at a rate exceeding 250 mEq/day), it would take 24 to 48 hours to equilibrate in all tissues. Potassium-depleted myocardium is unusually sensitive to digoxin, calcium, and most important, potassium. Rapid potassium infusion in a hypokalemic patient can produce arrhythmias as severe as those produced by hypokalemia itself.[352] One potential strategy to prevent hypokalemia from anxiety and stress includes premedication with clonidine.[353]

Thus, the decision to proceed with surgery and anesthesia in the presence of acute or chronic depletions or excesses of potassium depends on many factors.[354-359] The cause and treatment of the underlying condition creating the electrolyte imbalance and the effect of that imbalance on perioperative risk and physiologic processes must be known. The urgency of the operation, the degree of electrolyte abnormality, the medications given, the acid-base balance, and the suddenness or persistence of the electrolyte disturbance are all considerations. For example, a small study of patients undergoing vascular access procedures with preoperative potassium levels of higher than 6 mmol/L demonstrated no adverse outcomes.[357] Similarly, in a cohort study in which 38 patients had a preoperative potassium level higher than 5.5 mEq/L, no dysrhythmias or major morbidity were associated with the use of succinylcholine.[358]

Retrospective epidemiologic studies attribute significant risk to the administration of potassium (even long-term oral administration).[354] In one study, 1910 of 16,048 consecutive hospitalized patients were given oral potassium supplements. Of these 1910 patients, hyperkalemia contributed to death in 7, and the incidence of complications of potassium therapy was 1 in 250. Armed with such data, many internists do not prescribe oral potassium therapy for patients given diuretic drugs. Yet these patients frequently become moderately hypokalemic.[360] Modest hypokalemia occurs in 10% to 50% of patients given diuretic drugs. Should surgery be delayed to subject such patients to the risks of potassium therapy?

Three studies investigated whether modest hypokalemia was a problem by prospectively seeking arrhythmias on the ECGs of patients who had various preoperative levels of potassium.[355,356,359] No difference in the incidence of arrhythmias occurred in 25 normokalemic ($K^+ > 3.4$ mEq/L) patients, 25 moderately hypokalemic ($K^+ = 3$ to 3.4 mEq/L) patients, and 10 severely hypokalemic ($K^+ < 2.9$ mEq/L) patients.[355] Wahr and coauthors studied 2402 patients undergoing elective CABG and concluded that a serum potassium level less than 3.5 mmol/L was a predictor of serious perioperative arrhythmia (OR, 2.2; 95% CI, 1.2 to 4.0), intraoperative arrhythmia (OR, 2.0; 95% CI, 1.0 to 3.6), and postoperative atrial fibrillation/flutter (OR, 1.7; 95% CI, 1.0 to 2.7).[359] The inability of the eye to pick up these changes—or even the inability of Holter recordings for short periods (which seem not to have been used in this study)—points to the need for confirming studies.

Modest hypokalemia can have severe consequences.[360,361] Holland and co-workers treated 21 patients with 50 mg of hydrochlorothiazide twice a day for 4 weeks.[361] These patients had a history of becoming hypokalemic during diuretic therapy; no patients had cardiac disease or were taking other medications. Before and after diuretic therapy, 24-hour ambulatory ECGs were recorded. This study is also subject to the limitations of Holter monitoring. Ventricular ectopy, including complex ventricular ectopy (multifocal PVCs, ventricular couplets, ventricular tachycardia), developed in 7 of the 21 patients (33%). Potassium repletion decreased the number of ectopic ventricular beats per patient from 71.2 to 5.4/hour. Apparently, some patients are sensitive to even minor potassium depletion. In the Multiple Risk Factor Intervention Trial involving 361,662 patients, more than 2000 of whom were treated for hypertension with diuretics, the reduction in serum potassium after diuretic therapy was greater in patients with PVCs.[360]

GASTROINTESTINAL AND LIVER DISEASES

GASTROINTESTINAL DISEASE

Preoperative Search for Diverse Associated Disorders in Gastrointestinal Disease

Although preoperative preparation of the GI tract is usually the responsibility of the surgeon, GI disease can and often does cause derangements in many or all other systems (see also Chapter 38). Such disturbances can affect the safety of anesthesia for the patient. Preoperative preparation should include knowledge of disease processes and their effects to guide the patient smoothly through the perioperative period. The major advances of correcting fluid and electrolyte disorders and optimizing nutritional status preoperatively allow surgical procedures to be performed in patients with GI disease previously deemed to be at too great a risk and may have lessened the risk for others.[45-47,362] Nonetheless, in patients with GI disease, thorough assessment of intravascular fluid volume, electrolyte concentrations, and nutrition is essential, including an evaluation of the supervening side effects of these therapies (e.g., hypophosphatemia from parenteral nutrition, hyperkalemia or cardiac arrhythmias from too vigorous treatment of hypokalemia, and CHF from too rapid or too vigorous treatment of hypovolemia).

In addition to the vast alterations in fluids, electrolytes, and nutrition that can occur with such diverse GI diseases as neoplasms and pancreatitis, patients with GI disorders can have gastroesophageal reflux disease,[363] bowel obstruction, vomiting, or hypersecretion of acid. These effects may merit rapid induction of anesthesia with the application of cricoid pressure or endotracheal intubation with the patient unanesthetized (awake), preoperative nasogastric suctioning, or preoperative use of histamine receptor blocking drugs. Clotting abnormalities may need to be corrected because fat-soluble vitamin K (often malabsorbed) is necessary for the synthesis of factors II, VII, IX, and X in the liver (see also Chapter 62). Liver disease is often associated with GI disease and, if

severe enough, can also result in a deficiency of clotting factors synthesized by the liver.

Other factors should be remembered in the perioperative management of any patient with GI disease. First, closed spaces containing gas expand by absorbing nitrous oxide. Such expansion can lead to ischemic injury, rupture of GI viscera, or both. Second, GI surgery predisposes the patient to sepsis; sepsis and decreased peripheral vascular resistance can lead to massive fluid requirements, cardiac failure, and renal insufficiency. The surgical site infection rate has been declining. This decrease may be attributable to the use of better technique, more appropriate prophylactic timing and use of antibiotics, better nutrition, less invasive (laparoscopic and endoscopic) surgery, maintenance of normothermia, and surgical resection of even tumors.[364-368] Third, patients with GI disease may have many other associated disorders not directly related to the GI tract. For example, they may be anemic from deficiencies in iron, intrinsic factor, folate, or vitamin B_{12}. They may also manifest neurologic changes from combined-system disease. Respiration may be impaired because of heavy cigarette smoking, peritonitis, abscess, pulmonary obstruction, previous incisions, aspiration, or pulmonary embolism (as occurs with ulcerative colitis or with thrombophlebitis in bedridden patients). These patients may also have hepatitis, cholangitis, side effects from antibiotic drugs or other medications, massive bleeding with anemia and shock, or psychological derangements.

Because GI disease can be accompanied by so many diverse associated disorders, the clinician must clearly search for involvement of other systems and preoperatively assess and treat such disorders appropriately. Discussion of two specific diseases, ulcerative colitis and carcinoid tumor, highlights the importance of involvement of other systems in GI disease.

Ulcerative Colitis and Carcinoid Tumors as Examples of Gastrointestinal Disease Affecting Other Systems

Patients with ulcerative colitis often have psychological problems. They may also have the following: phlebitis; deficiencies in iron, folate, or vitamin B_{12}; anemia; or clotting disorders caused by malabsorption. They may be malnourished or dehydrated or have electrolyte abnormalities. In addition, ulcerative colitis can be accompanied by massive bleeding, bowel obstruction or perforation or toxic megacolon causing respiratory compromise, hepatitis, arthritis, iritis, spondylitis, or diabetes secondary to pancreatitis.

The site of origin of carcinoid tumors in more than 75% of patients is the GI tract. Within the GI tract, carcinoid tumors have been documented to occur from the esophagus to the rectum. The most frequent site is the appendix, but carcinoids in this location rarely, if ever, metastasize or produce carcinoid syndrome. Tumors arising in the ileocecal region have the highest incidence of metastases. Carcinoid tumors originating from sites other than the GI tract, such as the head and neck, lung, gonads, thymus, breast, and urinary tract, have also been reported. Cardiac involvement, although frequently reported, is usually limited to right-sided valvular and myocardial plaque formation.[369]

Not all patients with carcinoid tumors have symptoms attributable to secretion of hormone by the tumor. Some do, however, and unexpected carcinoid can manifest intraoperatively by hypersecretion of gastric fluid. The most comprehensive series in the literature indicates that only 7% of patients have carcinoid syndrome, which typically consists of flushing, diarrhea, and valvular heart disease. Of those patients with the syndrome, approximately 74% have cutaneous flushing, 68% have intestinal hypermotility, 41% have cardiac symptoms, and 18% have wheezing. Factors influencing symptoms include the location of the tumor and the specific hormones produced and secreted. Although it is generally believed that if patients do not exhibit carcinoid syndrome, the tumors are not producing serotonin (5-hydroxytryptamine [5-HT]), such may not be the case. Approximately 50% of patients with carcinoid tumors of the GI tract demonstrate evidence of 5-HT production as manifested by elevated urinary levels of 5-hydroxyindoleacetic acid (5-HIAA), a metabolic product of 5-HT. Carcinoid syndrome is usually associated with ileal carcinoid tumors that have metastasized to the liver. Presumably, the liver clears mediators released from the tumor. Impairment of this clearing ability by the metastatic tumor results in carcinoid syndrome.

Most patients with carcinoid tumors and increased urinary 5-HIAA levels have typical carcinoid tumors originating from the midgut (ileum or jejunum). These patients excrete only small amounts of 5-hydroxytryptophan (5-HTP). Patients with atypical carcinoid tumors that originate in the foregut (bronchus, stomach, and pancreas) excrete large amounts of 5-HT and 5-HTP, as well as moderately higher amounts of 5-HIAA.

Although it is generally agreed that 5-HT is responsible for the diarrhea experienced by patients with carcinoid tumors, other neurohumoral agents may contribute to the flushing and hypotension, including dopamine, histamine, and some of the neuropeptides such as substance P, neurotensin, vasoactive intestinal peptide, and somatostatin.

The net physiologic effect of circulating 5-HT represents a composite of both direct action (mediated by 5-HT receptors) and indirect action (mediated through modulation of adrenergic neurotransmission). The existence of several subtypes of 5-HT receptors may account for the different effects of 5-HT on various serotonin-sensitive tissue beds. Indirect actions are effected through alterations in catecholamine release and depend on the level of circulating 5-HT.

5-HT has little if any direct effect on the heart. With increased levels, however, positive chronotropic and inotropic myocardial effects may occur, mediated by the release of noradrenaline (norepinephrine). Effects of serotonin on the vasculature include both vasoconstriction and vasodilation.

Alterations in GI function attributed to 5-HT include increased motility and net intestinal secretion of water, sodium chloride, and potassium. 5-HT reportedly causes bronchoconstriction in many animals, but rarely in humans. Patients with asthma are a possible exception. Carcinoid tumors frequently manifest as diarrhea with fluid and electrolyte abnormalities. Because these tumors secrete vasoactive substances, patients can exhibit

hyspotension or hypertension along with the flush associated with release of vasoactive substances. Vasoactive substances can be released from the tumor by any number of substances, including catecholamines. Until the 1990s, management of patients with this tumor was a real challenge for the anesthesiologist. Thus, anesthesiologists of that era had to tread a fine line between avoiding substances known to release 5-HT (e.g., *d*-tubocurarine and morphine) and inducing anesthesia so light that painful stimuli activated a sympathetic stress response.[370] The anesthesiologist also needed to be ready and able to treat hypotension, decreased peripheral vascular resistance, bronchospasm, and hypertension. α-Adrenergic receptor blockade with the phenothiazines, butyrophenones, or phenoxybenzamine and β-adrenergic receptor blockade with propranolol have been advocated to prevent catecholamine-mediated release of vasoactive substances. These practices, however, can lead to hypotension. Nevertheless, the difficulty in managing carcinoid syndrome seemed to change with the availability of a somatostatin analogue. In fact, somatostatin is now such a powerful inhibitor of the release of peptides from carcinoid tumors and an inhibitor of the peptic effects on receptor cells that it is the therapy of choice for preoperative, intraoperative, and postoperative management of carcinoid symptoms and crises.[370,371] In cardiac surgical patients, mortality has declined over time, and vasopressors have been shown to be safe in conjunction with octreotide.[372] However, the ease of management of most patients[370,371,373-376] should not lull the anesthesiologist into being unprepared—in fact, somatostatin has caused problems of its own and has failed to prevent severe hypotension and bronchospasm.[377,378]

In patients with severe hypotension that is not treatable with somatostatin, the drug of choice is either angiotensin or vasopressin. (Angiotensin is not commercially available in the United States.) However, the vasoactive substances released by carcinoid tumors cause fibrosis of the heart valves that often results in pulmonic stenosis or tricuspid insufficiency. To increase cardiac output in a patient with tricuspid insufficiency, the anesthesiologist should avoid drugs or situations that increase pulmonary vascular resistance (e.g., angiotensin, vasopressin, acidosis, hypercapnia, hypothermia). In addition, the production of large amounts of 5-HT (equal to 200 mg/day of 5-HIAA) can lead to the development of niacin deficiency with pellagra (as occurs with diarrhea, dermatitis, and dementia).

Acute increase of plasma kinin activity in patients with carcinoid tumors has been the explanation for the symptoms of carcinoid syndrome. The physiologic effects of kinins are known to include vasodilation of smaller resistance vessels and stimulation of the release of histamine from mast cells. The latter action potentiates their own vasodilating properties and further reduces systolic and diastolic blood pressure. In addition, increases in vascular permeability may lead to edema. Kinins do not affect the myocardium directly.

Steroids have been effective in treating the symptoms of bronchial carcinoid tumors. Although prophylactic preoperative administration and intraoperative therapeutic use have been described, controlled studies of beneficial effects are lacking. Aprotinin, like steroids, inhibits the kallikrein cascade. This drug is capable of blocking the proteinase activity of kallikrein, and some reports have described a dramatic clinical response.

A subset of patients with symptoms of carcinoid syndrome excretes histamine at increased levels in their urine. Histamine causes vasodilation of small blood vessels, which leads to flushing and decreased total peripheral resistance. Histamine is known to cause bronchoconstriction, particularly in patients with bronchial asthma and other pulmonary diseases. Its role in carcinoid bronchospasm, if any, is uncertain. Histamine receptor blocking drugs have been used with some success in alleviating the flushing associated with carcinoid syndrome. H_2 antagonism alone was found to be just as effective as combination therapy in preventing symptoms; pure H_1 antagonism, however, was ineffective. These therapies have been relegated to a second-line defense since the use of somatostatin.

Catecholamines aggravate the symptoms of carcinoid syndrome, presumably by stimulating release of hormone by the tumor. The mechanism by which this release occurs remains obscure. Adrenergic receptors have not been demonstrated in carcinoid tumors, nor do these tumors usually have neural innervation. Perhaps adrenergic stimuli work through their mechanical effects on the gut and vessels to stimulate the release of tumor products. Treatment of patients with carcinoid tumors by means of α- and β-adrenergic antagonists has been beneficial in ameliorating flushing in some instances but ineffective in others.

The results of prospective studies on somatostatin to ameliorate the symptoms of carcinoid syndrome have been dramatic. Somatostatin appears to be a major advance in the treatment of carcinoid syndrome.

Bronchospasm with or without flushing also develops in many patients when vasoactive substances are released. Thus, a patient with carcinoid tumor may be well or may be severely incapacitated by pulmonary, neurologic, nutritional, fluid, electrolytic, or cardiovascular disturbances. Therefore, although the GI system in itself may not require extensive preoperative preparation, GI disease can cause disturbances in any or all other systems that require extensive preoperative preparation to optimize the patient's condition in addition to preoperative knowledge of physiology and the effects of diseases to guide patients through the perioperative period smoothly. In addition, the anesthesiologist's understanding of the nature of the surgical procedure probably aids in determining the system involvement caused by the GI disorder.

Another perioperative consideration is that patients with GI diseases (perhaps even more so than those with other diseases) have had to endure the psychosocial trauma of having to live with their disease for long periods or the necessity of facing such a prospect.[379] They need emotional support and holistic kindnesses as much as, if not more than, other patients without sacrificing scientific rigor in the treatment of their condition. Obtaining relevant psychological data while gathering medical information, sitting (not standing) while taking the history, and empathizing with the patient about how difficult it must be to accomplish tasks with this disease (stressing

accomplishments, we have found) legitimize the physician's interests in and support of the patient's pain and other psychosocial issues. The time spent sitting and talking with the patient also allows the anesthesiologist to discuss options for pain therapy with the patient, why systemic morphine may be avoided in a patient with a fresh bowel anastomosis,[380] and other issues that show the anesthesiologist to be both a competent physician and particularly concerned with that patient's well-being. In addition to an appreciation of the organic effects of the disease, attention to emotional support of these patients perioperatively presents opportunities to use one's full skills as a physician to bring about healing.

LIVER DISEASE

What are the risks of giving anesthesia to patients with acute liver disease who require emergency surgery? What are the risks of giving anesthesia to patients with chronic impairment of liver function? What can be done to minimize these risks? Although one may think that the experiences gained from providing anesthesia for liver transplantation would answer many of these questions, a substantial difference exists between optimizing cardiovascular function to meet the needs of a new liver (e.g., supply of nutrients) and maintaining liver function in a diseased liver. Hepatic physiology and pathology are discussed in Chapter 22.

HEMATOLOGIC DISORDERS AND ONCOLOGIC DISEASE

HEMATOLOGIC DISORDERS

Sickle Cell Anemia and Related Hemoglobinopathies

The sickle cell syndromes constitute a family of hemoglobinopathies caused by abnormal genetic transformation of amino acids in the heme portion of the hemoglobin molecule. The sickle cell syndromes arise from a mutation in the β-globin gene that changes the sixth amino acid from valine to glutamic acid. A major pathologic feature of sickle cell disease is the aggregation of irreversibly sickled cells in blood vessels. The molecular basis of sickling is the aggregation of deoxygenated hemoglobin B molecules along their longitudinal axis.[381] This abnormal aggregation distorts the cell membrane and thereby produces a sickle shape. Irreversibly sickled cells become dehydrated and rigid and can cause tissue infarcts by impeding blood flow and oxygen to tissues.[381-384] Some investigators have challenged this hypothesis, with several studies showing enhanced adhesion of sickled erythrocytes to vascular endothelium.[385] Some other abnormal hemoglobins interact with hemoglobin S to various degrees and give rise to symptomatic disease in patients heterozygous for hemoglobin S and one of the other hemoglobins such as the hemoglobin of thalassemia (hemoglobin C).

Three tenths of 1% of the African American population in the United States have sickle cell–thalassemia disease (hemoglobin SC); these patients also have end-organ disease and symptoms suggestive of organ infarction. For these patients, perioperative considerations should be similar to those for patients with sickle cell disease (hemoglobin SS).

Whereas 8% to 10% of African Americans have the sickle cell trait (hemoglobin AS), 0.2% are homozygous for sickle cell hemoglobin and have sickle cell anemia. Sickle cell trait is a heterozygous condition in which the individual has one βS globin gene and one βA globin gene, which results in the production of both hemoglobin S and hemoglobin A, with a predominance of hemoglobin A. Sickle cell trait should not be considered a disease because hemoglobin AS cells begin to sickle only when the oxygen saturation of hemoglobin is less than 20%. No difference has been found between physiologically normal persons (those with hemoglobin AA) and those with hemoglobin AS regarding survival rates or the incidence of severe disease, with one exception: patients with hemoglobin AS have a 50% increase in pulmonary infarction. However, single case reports of a perioperative death and a perioperative brain infarct in two patients with hemoglobin AS disease do exist, as does a report of death believed to be caused by aortocaval compression during general anesthesia that resulted in a sickling crisis.[386] The need for exchange transfusion before cardiac surgery has been debated.[387,388] Frequent measurement of oxygen saturation (pulse oximetry) in multiple areas of the body is recommended, including the ear and toe in pregnant patients.[386]

The pathologic end-organ damage that occurs in sickle cell states is attributable to three processes: the sickling or adhesion (or both) of cells in blood vessels, which causes infarcts and subsequent tissue destruction secondary to tissue ischemia; hemolytic crisis secondary to hemolysis; and aplastic crises that occur with bone marrow exhaustion, which can rapidly result in severe anemia. Logic dictates that patients currently in crisis not undergo surgery except for extreme emergencies, and then only after an exchange transfusion.[383,385-389]

Because sickling is increased with lowered oxygen tensions, acidosis, hypothermia, and the presence of more desaturated hemoglobin S, current therapy includes keeping the patient warm and well hydrated, giving supplemental oxygen, maintaining high cardiac output, and not creating areas of stasis with pressure or tourniquets. Meticulous attention to these practices in periods when we do not usually pay most careful attention (i.e., waiting in the preinduction area) or when gas exchange may be most unmatched to the cardiovascular-metabolic demands (early postoperative period) may be important in lessening morbidity. Even following these measures routinely, with no special emphasis placed on the periods described, succeeded in reducing mortality to 1% in several series of patients with sickle cell syndromes.[386,389,390] Retrospective review of patients' charts led the authors of those studies to conclude that, at most, a 0.5% mortality rate could be attributed to the interaction between sickle cell anemia and anesthesia.

Several investigators have advocated using partial exchange transfusions perioperatively. In children with sickle cell anemia and acute lung syndromes, partial exchange transfusion improved clinical symptoms and blood oxygenation. In addition, serum bilirubin levels

decreased in patients with acute liver injury. Clinical improvement of pneumococcal meningitis and cessation of hematuria in papillary necrosis also accompanied exchange transfusion.[382] The goal of exchange transfusion is to increase the concentration of hemoglobin A to 40% and the hematocrit to 35%. The 40% figure is an arbitrary one because no controlled studies have established a threshold ratio of hemoglobin A to hemoglobin S that would render blood unable to sickle in vivo. To achieve the 40% ratio in a 70-kg adult, approximately 4 units of washed erythrocytes would have to be exchanged; the system is inexpensive but efficient.

The possible decrease in perioperative morbidity after partial exchange transfusion has not been compared with the risks of exchange, except in 2 studies,[384,391] in which the risks of exchange were found to exceed the benefits. In the first study, a retrospective review of 82 surgical procedures performed between 1978 and 1986 in 60 patients, no advantage was noted for preoperative exchange transfusion as measured by a decrease in postoperative complications.[391] (However, only the sickest patients may have received exchange transfusions because patients were not randomly allocated to exchange or nonexchange groups.) A slight increase in postoperative atelectasis requiring treatment was seen in patients given preoperative transfusions. More than 50% of the patients given transfusions had a postoperative complication. Patients who began with a hematocrit higher than 36% had a lower rate of complications.[391] In the second study, a randomized comparison of aggressive versus conservative transfusion practices in 551 patients (604 operations), perioperative sickling complications were not different between groups, and transfusion-related complications were substantially less in the conservatively treated group.[384] A more recent retrospective review of 14 patients with sickle cell anemia who were undergoing total hip revision supports the decision to perform a simple transfusion preoperatively only if the patient's hemoglobin is significantly lower than their steady-state hemoglobin level.[392] Transfusion can be used intraoperatively according to hemoglobin level or blood loss volume. Other conditions are common in sickle cell syndromes: pulmonary dysfunction with increased shunting, renal insufficiency, gallstones, small MIs, priapism, stroke, aseptic necrosis of bones and joints, ischemic ulcers, retinal detachment as a result of neovascularization, and complications of repeated transfusions.

In thalassemia, globin structures are normal, but because of gene deletion, the rate of synthesis of either the α or β chains of hemoglobin (α- and β-thalassemia, respectively) decreases.[393-395] Two copies of the gene that codes for the α-globin chain are located on chromosome 16. Deletion of all four of these genes causes cell death in utero, and three deletions cause severe chronic hemolysis and a shortened life span. α-Thalassemia-1 (trait) occurs when two genes have been deleted and mild anemia results; α-thalassemia-2 (silent) occurs when the two genes have been deleted but no mild anemia or microcytosis results. In α-thalassemia trait, the hemoglobin A_2 level is normal. β-Thalassemia is associated with an excess of α chains, which denature developing erythrocytes, thereby leading to their premature death in marrow or to shortened survival in the circulation. An elevated hemoglobin A_2 level is the hallmark of β-thalassemia trait, a common cause of mild anemia and microcytosis. Bone marrow transplantation and pharmacologic manipulation of hemoglobin F synthesis are being tried in these hemoglobinopathies, as is direct gene replacement therapy. These therapies seem to be promising in even reversing liver failure from previous iron overload.[396] These syndromes are common in Southeast Asia, India, and the Middle East and in people of African descent.

In thalassemia, facial deformity from erythropoietin-stimulated ineffective erythropoiesis (ineffective because of a genetic inability to produce useful hemoglobin) was reported to make endotracheal intubation difficult.[393,394] This one case report has not been amplified,[394] and no reports of this complication in patients with sickle cell anemia have been published. However, the anemia associated with these syndromes often produces compensatory hyperplasia of the erythroid marrow, which in turn is associated with severe skeletal abnormalities.[393-395]

Cytoskeletal Anemias (Hereditary Spherocytosis and Elliptocytosis), Enzyme-Deficient Anemias, and Autoimmune Hemolytic Anemias

Congenital abnormalities of the erythrocyte membrane are becoming better understood. In elliptocytosis and hereditary spherocytosis, the membrane is more permeable to cations and is more susceptible to lipid loss when cell energy is depleted than is the membrane of a normal red blood cell. Both hereditary spherocytosis (present in 1 in 5000 people) and hereditary elliptocytosis are inherited as autosomal dominant traits. In both disorders, defects in the membrane are thought to result from a mutation of spectrin, a structural protein of the membrane cytoskeleton.[397] Although the therapeutic role of splenectomy in these diseases is not fully defined, in severe disease, splenectomy is known to improve the shortened life span of the red blood cell 100% (from 20 to 30 days to 40 to 70 days). Because splenectomy predisposes the patient to gram-positive septicemia (particularly pneumococcal), perhaps patients should be given pneumococcal vaccine preoperatively before predictable bacteremic events. No specific problems related to anesthesia have been reported for these disorders.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency (a gender-linked recessive trait) is also reported to occur in approximately 8% of African American men.[398] Young cells have normal activity, but older cells are grossly deficient when compared with normal cells. A deficiency in G6PD results in hemolysis of the erythrocyte and the formation of Heinz bodies. Red blood cell hemolysis can also occur with intercurrent infections or after the administration of drugs that produce substances requiring G6PD for detoxification (e.g., methemoglobin, glutathione, and hydrogen peroxide). Drugs to be avoided are sulfa drugs, quinidine, prilocaine, lidocaine, antimalarial drugs, antipyretic drugs, nonnarcotic analgesics, vitamin K analogues, and perhaps sodium nitroprusside.

The autoimmune hemolytic anemias include cold antibody anemia, warm antibody anemia (idiopathic), and drug-induced anemia.[399-401] Cold antibody hemolytic

anemias are mediated by IgM or IgG antibodies, which at room temperature and lower temperatures cause red blood cells to clump. When these patients are given blood transfusions, the cells and all fluid infusions must be warm, and body temperature must be meticulously maintained at 37° C if hemolysis is to be prevented. Warm antibody (or idiopathic) hemolytic anemia is a difficult management problem characterized by chronic anemia, the presence of antibodies active against red blood cells, a positive Coombs test, and difficulty crossmatching blood. For patients undergoing elective surgery, autologous transfusions, predeposit of blood with or without erythropoietin stimulation,[402] and blood from rare Rh-negative red blood cell donors or the patient's first-degree relatives (or both) can be used. In emergency situations, the possibility of autotransfusion, splenectomy, or corticosteroid treatment should be discussed with a hematologist knowledgeable in this area.

Drug-induced anemias have three mechanisms. In receptor-type hemolysis, a drug (e.g., penicillin) binds to the membrane of the red blood cell, and the complex stimulates the formation of an antibody against the complex. In "innocent bystander" hemolysis, a drug (e.g., quinidine, sulfonamide) binds to a plasma protein, thereby stimulating an antibody (IgM) that cross-reacts with an erythrocyte. In autoimmune hemolysis, the drug stimulates the production of an antibody (IgG) that cross-reacts with the erythrocyte. Drug-induced hemolytic anemias generally cease when therapy with the drug ends. In emergency situations, the least incompatible cells available should be used for blood transfusion.

Granulocytopenia

Granulocyte mechanisms have undergone experimental elaboration since 2000, partly because of the molecular biologic revolution: in addition to erythropoietin (discussed earlier), more than 14 hemolymphopoietic growth factors or cytokines have been characterized biochemically and cloned genetically. These growth factors interact with cell-surface receptors to produce their major actions (Table 39-15).[403] Use of the colony-stimulating factors has permitted more intense oncologic treatment. The few reports related to their perioperative effects detail the unfavorable adverse consequences that such therapies can have on gas exchange when adverse immunologic effects occur.[404]

In patients who have fewer than 500 granulocytes/mL of blood and established sepsis, the use of growth factor and granulocyte transfusion has been shown to prolong life.[405-407] Although bone marrow transplantation is being used increasingly, complications usually occur after transplantation, not on harvesting of cells (at which time the anesthesiologist who is not involved in critical care is most frequently involved). Abnormal results on pulmonary function testing before bone marrow transplantation seem to predict complications after transplantation, but not so strongly as to preclude transplantation.[408]

Platelet Disorders

Although inherited platelet disorders are rare, acquired disorders are quite common and affect at least 20% of all patients in medical and surgical ICUs, with infections and drug therapies being the leading causes (see also Chapter 61).[409] Both acquired and inherited platelet conditions cause skin and mucosal bleeding, whereas defects in plasma coagulation produce deep tissue bleeding or delayed bleeding. Perioperative treatment of inherited platelet disorders (e.g., Glanzmann thrombasthenia, Bernard-Soulier syndrome, Hermansky-Pudlak syndrome) consists of platelet transfusions. EACA has been used successfully (experimentally, 1 g/70 kg four times daily) to decrease perioperative bleeding in thrombocytopenic patients. The much more common acquired disorders may respond to one of several therapies (see Chapter 61). Immune thrombocytopenias, such as those associated with lupus erythematosus, idiopathic thrombocytopenic purpura, uremia, hemolytic-uremic syndrome, platelet transfusions, heparin, and thrombocytosis, may respond to steroids, splenectomy, plateletpheresis, eradication of *Helicobacter pylori*, or alkylating agents or may require platelet transfusions, plasma exchange, whole blood exchange, or transfusion; sometimes these disorders do not respond to anything.[185,410,411] Traditionally, splenectomy is performed when steroid therapy fails or reaches a dosage that poses unacceptable risks of toxicity. Newer agents such as anti-D immune globulin and rituximab may induce desirable remissions in idiopathic thrombocytopenic purpura without splenectomy.

Thrombotic thrombocytopenic purpura is a rare disorder of unknown cause. Despite various therapies, this disorder carries a very high mortality rate. However, the introduction of plasmapheresis has improved response rates dramatically in patients with this disease. One uncontrolled study implies that the benefit lies not only in improvement of the hematologic picture but also in prevention of ARDS, a leading cause of death in these patients.[411] In that study, early institution of plasmapheresis improved oxygenation.

By far the largest number of platelet abnormalities consists of drug-related defects in the aggregation and release of platelets. Aspirin irreversibly acetylates platelet cyclooxygenase, the enzyme that converts arachidonic acid to prostaglandin endoperoxidases. Because cyclooxygenase is not regenerated in the circulation within the life span of the platelet and because this enzyme is essential for the aggregation of platelets, one aspirin tablet may affect platelet function for a week. All other drugs that inhibit platelet function (e.g., vitamin E, indomethacin, sulfinpyrazone, dipyridamole, tricyclic antidepressant drugs, phenothiazines, furosemide, steroids) do not inhibit cyclooxygenase function irreversibly; these drugs disturb platelet function for only 24 to 48 hours. If emergency surgery is needed before the customary 8-day period for platelet regeneration after aspirin therapy or if the 2-day period for other drugs has not elapsed, administration of 2 to 5 units of platelet concentrate will return platelet function in a 70-kg adult to an adequate level and platelet-induced clotting dysfunction to normal. Only 30,000 to 50,000 normally functioning platelets per milliliter are needed for normal clotting. Because low-dose aspirin therapy (<650 mg/day) allows aspirin to be gone from the body 24 hours after the last dose and because the body makes 70,000 platelets/mL blood per day, a 48-hour

TABLE 39-15 **MAJOR EFFECTS OF HEMOLYMPHOPOIETIC GROWTH FACTORS AND CYTOKINES**

Cytokine	Other Names	Biologic Effects
Erythropoietin		Erythrocyte production
Interleukin-3 (IL-3)	Multicolony-stimulating factor Stem cell–activating factor Persisting cell-stimulating factor Hemopoietin-2	Stimulates proliferation and differentiation of granulocyte, macrophage, eosinophil, mast cell, megakaryocyte, and T- and B-cell lineage and early myeloid stem cells Interacts with erythropoietin to stimulate erythroid colony formation, stimulates proliferation of AML blasts, and stimulates histamine release by mast cells
Granulocyte colony-stimulating factor (G-CSF)	Differentiation factor MGI-2	Stimulates granulocyte lineage proliferation and differentiation Acts on early myeloid stem cells, especially in association with other factors; synergizes with IL-3 to stimulate megakaryocyte colony formation Increases neutrophil phagocytes and antibody-dependent cell-mediated cytotoxicity Releases neutrophils from bone marrow and is chemotactic for neutrophils and monocytes Enhances phagocytosis and antibody-dependent cell-mediated cytotoxicity and oxidative metabolism of neutrophils Stimulates monocyte killing of *Mycobacterium avium-intracellulare* and *Candida* species, tumoricidal activity of monocytes, antibody-dependent cell-mediated cytotoxicity, and expression of cell-surface proteins
Granulocyte-macrophage colony-stimulating factor (GM-CSF)		Stimulates granulocyte, macrophage, and megakaryocyte proliferation and differentiation, early myeloid stem cells, and—in the presence of erythropoietin—erythropoiesis Enhances the cytotoxic and phagocytic colony-stimulating factor activity of neutrophils against bacteria, yeast, parasites, and antibody-coated tumor cells Increases surface expression of neutrophil adhesion proteins and enhances eosinophil cytotoxicity, macrophage phagocytosis, and basophil histamine release Amplifies IL-2–stimulated T-cell proliferation and stimulates B-cell lines to proliferate
Colony-stimulating factor-1	Macrophage colony-stimulating factor	Stimulates predominantly macrophage-monocyte proliferation and differentiation with lesser effects on granulocytes Acts synergistically with other factors on earlier myeloid stem cells Stimulates macrophage phagocytosis, killing, migration, antitumor activity, and metabolism Stimulates secretion of plasminogen activator, G-CSF, interferon, IL-3, or tumor necrosis factor by peritoneal macrophages
Interleukin-1 (α and β)	Endogenous pyrogen Hemopoietin-1 Osteoclast-activating factor Lymphocyte-activating factor	Induces synthesis of acute-phase proteins by hepatocytes Activates resting T cells, cofactor for T- and B-cell proliferation Chemotactic for monocytes and neutrophils Induces production of growth factors, including G-CSF, GM-CSF, IL-6, CSF-1, IL-3, and interferon by many cells Radioprotective in mice
Interleukin-2	T-cell growth factor	Growth factor for T cells, activates cytotoxic T lymphocytes, promotes synthesis of other cytokines, enhances natural killer cell function
Interleukin-4	B-cell–stimulating factor-1 (BSF-1) B-cell differentiation factor (BCDF) IgG induction factor	Enhances antibody production (IgG and IgE) and up-regulates class II MHC molecules and Fc receptors on B cells Costimulant with anti-IgM antibodies for induction of DNA synthesis in resting B cells Stimulates growth of activated T cells In the presence of IL-3, enhances mast cell growth; with G-CSF, enhances granulocytes of GM colony formation; and with erythropoietin and/or IL-1, stimulates erythroid and megakaryocyte colony formation
Interleukin-5	Eosinophil differentiation factor (EDF) T-cell–replacing factor (TRF) B-cell growth factor-II (BCGF-II) B-cell differentiation factor (BCDF)	Enhances antibody production (IgA) Promotes proliferation and IgG secretion by B-cell lines and induces hapten-specific IgG secretion in vitro by in vivo–primed B cells Promotes differentiation by normal B cells Stimulates eosinophil production and differentiation (GM-CSF and IL-3 act synergistically with IL-5 to stimulate eosinophil proliferation and differentiation) Enhances synthesis of IL-2 receptors
Interleukin-6	B-cell–stimulating factor-2 (BSF-2) Interferon-β_2 T-cell activation factor Hybridoma growth factor	B-cell differentiation and IgG secretion T cells activated to cytotoxicity Synergizes with IL-3 on early marrow myeloid stem cells and stimulates proliferation and differentiation of granulocytes, macrophages, eosinophils, mast cells, and megakaryocytes, as well as platelet production (may be a thrombopoietin)

Continued

TABLE 39-15 **MAJOR EFFECTS OF HEMOLYMPHOPOIETIC GROWTH FACTORS AND CYTOKINES—cont'd**

Cytokine	Other Names	Biologic Effects
Interleukin-7	Lymphopoietin-1	Stimulates pre–B-cell production Stimulates T-cell proliferation
Interleukin-8*	Neutrophil-activating factor T-cell chemotactic factor	Inflammatory mediator; stimulates activation of neutrophils
Interleukin-9		Stimulates erythroid colony formation and proliferation of a megakaryocyte cell line
Interleukin-10	Cytokine synthesis–inhibiting factor	Inhibits cytokine production by T_H1 cells
Interleukin-11		Stimulates B-cell, megakaryocyte, and mast cell lineages
C-kit ligand	Mast cell factor Stem cell factor Hemolymphopoietic growth factor-1	Acts on relatively early stem cells synergistically with other cytokines Stimulates pre-B cells

AML, Acute myeloblastic leukemia; *IgA,* immunoglobulin A; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M; *MHC,* major histocompatibility complex; *T_H1,* first of the thymus-derived cells.
*Not considered a true growth factor but included here for completeness.
Modified from Quesenberg PJ, Schafer AI, Schreiber AD, et al: Hematology. In American College of Physicians, editor: Medical knowledge self-assessment. *Philadelphia, 1991, American College of Physicians, p 374.*

period after the last aspirin in minidose therapy should be sufficient time for platelet aggregation to become normal. This may be the period that must pass to avoid platelet transfusions and their associated risks. One platelet transfusion will increase the platelet count from 4000 to 20,000/mL blood; the platelet half-life is approximately 8 hours.

Heparin-induced thrombocytopenia can develop within hours on reexposure to heparin in a previously sensitized patient. Lepirudin and argatroban are direct thrombin inhibitors effective as therapy for heparin-induced thrombocytopenia.[412]

Major risk factors for thrombosis include factor V Leiden and prothrombin 20210A mutations, elevated plasma homocysteine, and the antiphospholipid antibody syndrome.[413,414] Clinicians facing these challenging patients may seek expert local consultation for help with management. This issue is discussed more fully in Chapter 62.

Hemophilia and Related Clotting Disorders

Abnormalities in blood coagulation as a result of defects in plasma coagulation factors are either inherited or acquired. Inherited disorders include X-linked hemophilia A (a defect in factor VIII activity), von Willebrand disease (defect in the von Willebrand component of factor VIII), hemophilia B (a sex-linked deficiency of factor IX activity), and other less common disorders. The sex-linked origin of some of these disorders means that hemophilia occurs almost exclusively in the male children of female carriers; men do not transmit the disease to their male children.

In elective surgery, levels of the deficient coagulation factor should be assayed 48 hours preoperatively and the level restored to 40% of normal before the surgical procedure. One unit of factor concentrate per kilogram of body weight normally increases the factor concentration by 2%. Thus, in an individual essentially devoid of activity, administration of 20 units/kg body weight would be required as an initial dose. Because the half-life is 6 to 10 hours for factor VIII and 8 to 16 hours for factor IX, approximately 1.5 units/hour/kg of factor VIII or 1.5 units/2 hours/kg of factor IX should be given. Additional administration of factors VIII and IX should be guided by the activity of the clotting factors for approximately 6 to 10 days postoperatively.[415-417]

These factors are available in various preparations; the newer genetically engineered von Willebrand factor, cryoprecipitate, which contains 20 units/mL, is obtained from regular donors (the risk of hepatitis being 1 in 200 for 5-mL lots) or from fresh frozen plasma (which contains 1 unit/mL). Some risk of transmitting hepatitis virus and HIV (the agent of acquired immunodeficiency syndrome [AIDS]) accompanies transfusion but, with better testing, much less than formerly.[418-421] Current screening of blood for aspartate or alanine aminotransferase levels is believed to result in a much lower risk of hepatitis C and even AIDS from transfusion. Theoretically, antigenic testing for HIV should further decrease the risk of transmission by blood products. Heat treatment is also reported to reduce the risk substantially. Factor IX, but not factor VIII, is contained in prothrombin complex concentrates; however, these concentrates may contain activated clotting factors, which can lead to disseminated intravascular coagulation (DIC) and a high risk for hepatitis. In addition, although EACA or tranexamic acid is sometimes administered as a fibrinolytic inhibitor, these substances carry with them a significant risk for DIC. Additional hazards of modern therapy include acute and chronic hepatitis, AIDS, hypersensitivity reactions, psychic trauma, chronic pain with narcotic addiction, and inhibition of factors, especially VIII.

An antibody that inactivates factor VIII or IX (fresh frozen plasma fails to increase clotting factor activity after incubation with the patient's plasma) develops in approximately 10% of patients with either hemophilia A or B. These acquired anticoagulants are usually composed of IgG, are poorly removed by plasmapheresis, and are variably responsive to immunosuppressive drugs. The use of prothrombin complex concentrates can be lifesaving but carries the risk of DIC and hepatitis.

Vitamin K deficiency is discussed in the section on liver disease. To review, vitamin K–dependent clotting factors (II, VII, IX, and X) require vitamin K for the post-synthetic addition of γ-carboxyl groups to glutamate residues; administration of vitamin K or fresh frozen plasma can correct these deficiencies.

Patients who come to the operating room after having received many units of blood (as in massive GI bleeding) may have deficient clotting. This impaired clotting is initially caused by depletion of platelets, which occurs after administration of approximately 10 to 15 units of blood and, later, by depletion of coagulation factors (see Chapter 62). Treatment of these deficiencies can be corrected with platelet concentrates—each concentrate is normally suspended in 50 mL of fresh plasma; thus, coagulation factors are also replaced.

Urokinase, streptokinase, and tissue-type plasminogen activator (t-PA) have been used to treat pulmonary embolism, deep vein thrombosis, stroke, and arterial occlusive disease. These drugs accelerate the lysis of thrombi and emboli, in contrast to heparin, which may prevent, but not dissolve a thrombus. Bleeding complications associated with these fibrinolytic agents are the result of dissolution of hemostatic plugs and can be quickly reversed by discontinuing the medication and replenishing plasma fibrinogen with cryoprecipitate or plasma. However, cryoprecipitate and plasma are seldom needed preoperatively because the fibrinolytic activity of urokinase and streptokinase usually dissipates within 1 hour of discontinuing their administration. Nonetheless, insufficient data have accumulated to prescribe the ideal preoperative preparation and intraoperative management of hemostasis in patients recently treated with urokinase, streptokinase, or t-PA. Postponing surgery for three half-lives of the drug (increases in plasmin activity in blood can be assayed for ≥4 to 8 hours) may not be possible, and meticulous observation of the operative field for hemostasis may not suffice.[422,423] The process may be even more complex in a patient with a vascular or cardiac condition who requires heparin administration intraoperatively. To correct the fibrinogen deficiency in these patients, some clinicians administer fibrinogen preoperatively and EACA at heparin administration.

DDAVP has been used in operations associated with high blood loss as a routine measure to decrease bleeding and transfusion requirements. DDAVP therapy began as treatment of platelet dysfunction in von Willebrand disease but has since expanded to routine use in patients undergoing cardiovascular surgery and to frequent use in other high–blood loss operations. A meta-analysis of cardiac surgery concluded that DDAVP was not associated with a clinically significant reduction in exposure to blood transfusion in unselected patients, and therefore the authors were unable to recommend the routine use of DDAVP in patients exposed to CPB.[424] However, DDAVP may reduce postoperative bleeding in patients who have received preoperative aspirin within 7 days of surgery, patients with CPB times in excess of 140 minutes, and patients with demonstrable platelet dysfunction. The authors suggested that DDAVP could be used selectively in these subgroups.

ONCOLOGIC DISEASE

Patients with malignant tumors may be otherwise healthy or may be desperately ill with nutritional, neurologic, metabolic, endocrinologic, electrolyte, cardiac, pulmonary, renal, hepatic, hematologic, or pharmacologic disabilities. Thus, determining the other disabilities accompanying malignant tumors requires evaluation of all systems. Abnormalities frequently accompanying such tumors include hypercalcemia either by direct bone invasion or by ectopic elaboration of PTH or other bone-dissolving substance, uric acid nephropathy, hyponatremia (especially with small cell, or oat cell, carcinoma of the lung), nausea, vomiting, anorexia and cachexia, fever, tumor-induced hypoglycemia, intracranial metastases (10% to 20% of all cancers), peripheral nerve or spinal cord disorders, meningeal carcinomatosis, toxic neuropathies secondary to anticancer therapy, and paraneoplastic neurologic syndromes (dermatomyositis, Eaton-Lambert syndrome, myopathies, and distal neuropathies).

Many patients with malignant tumors are given large doses of analgesics and should be kept comfortable during the perioperative period. Avoiding drug dependence is of no practical importance in terminally ill patients.[425] Marijuana (tetrahydrocannabinol) depresses the CNS vomiting center and may be more effective than the phenothiazines or butyrophenones in suppressing the nausea associated with cancer and its therapy; marijuana decreases anesthetic requirements 15% to 30%. Immunomodulators, stimulating factors or cytokines, gene identification,[426,427] and drugs for treating side effects (e.g., midazolam or ondansetron) have given new hope for safer, more effective therapy with fewer limiting side effects. The effect of ondansetron in preventing vomiting and the effect of midazolam in preventing memory-stimulated vomiting have been important additions. The neurokinin-1 (NK-1) antagonists have also been approved for treatment in oncologic patients.

The toxicity of cancer chemotherapy is related to the drugs used and the dose. For radiation therapy, damage occurs when the following doses are exceeded: lungs, 1500 rad; kidneys, 2400 rad; heart, 3000 rad; spinal cord, 4000 rad; intestine, 5500 rad; brain, 6000 rad; and bone, 7500 rad. The toxicities of biologic and immunomodulating therapies are related to the change in immune function that they cause. Alkylating agents cause bone marrow depression, including thrombocytopenia, as well as alopecia, hemorrhagic cystitis, nausea, and vomiting. The alkylating agents, including cyclophosphamide and mechlorethamine, can act as an anticholinesterase and prolong neuromuscular blockade.[428] The antineoplastic alkaloid vincristine produces peripheral neuropathy and SIADH, and vinblastine produces myelotoxicity. Cisplatin is also associated with peripheral neuropathy and severe nausea. Nitrosoureas can produce severe hepatic and renal damage, as well as bone marrow toxicity, myalgia, and paresthesia. Folic acid analogues such as methotrexate have been linked to bone marrow depression, ulcerative stomatitis, pulmonary interstitial infiltrates, GI toxicity, and occasionally, severe liver dysfunction. Fluorouracil

and floxuridine, both pyrimidine analogues, cause bone marrow toxicity, megaloblastic anemia, nervous system dysfunction, and hepatic and GI alterations. Purine analogues (mercaptopurine, thioguanine) have bone marrow depression as their primary toxic effect. Anthracycline antibiotics (doxorubicin, daunorubicin, mithramycin, mitomycin C, bleomycin) can all cause pulmonary infiltrates, cardiomyopathy (especially doxorubicin and daunorubicin), myelotoxicity, and GI, hepatic, and renal disturbances.

The wisdom of anesthetizing patients given bleomycin has been questioned. A retrospective study by Goldiner and coauthors reported postoperative deaths in 5 consecutive patients given bleomycin.[429] All 5 patients died of postoperative respiratory failure. Using the same anesthetic technique, Goldiner and coauthors then anesthetized 12 patients, limited the inspired oxygen concentration to 22% to 25% perioperatively, and replaced much of the blood loss with colloids rather than crystalloids.[429] None of the 12 patients died. These investigators postulated that bleomycin caused epithelial cell edema that progressed to necrosis of type I alveolar cells, leakage of fluid into the alveolar space, and the formation of hyaline membranes similar to those associated with oxygen toxicity. Goldiner and coauthors believe that this pathophysiologic similarity indicates a possible synergistic relationship between oxygen and bleomycin.[429] However, LaMantia and co-workers retrospectively analyzed the changes in 16 patients undergoing surgery after bleomycin therapy.[430] Thirteen patients were given oxygen at inspired concentrations of 37% to 45%. No instances of postoperative respiratory failure occurred. Using data from the Mayo Clinic registry, the incidence of postoperative ARDS after major surgery with general anesthesia is approximately 1.3% (95% CI, 0.6% to 2.6%).[431] The authors found a history of smoking as a major risk factor. Therefore, general anesthesia appears safe with appropriate perioperative management.

PATIENTS GIVEN DRUG THERAPY FOR CHRONIC AND ACUTE MEDICAL CONDITIONS

A steadily increasing number of potent drugs are being used to treat disease, and the average hospitalized patient receives more than 10 drugs (see also Chapter 38). Many drugs have side effects that may make anesthesia more risky or patient management more difficult. Knowing the pharmacologic properties and potential side effects of commonly used drugs helps the anesthesiologist avoid pitfalls during anesthesia and surgery.

ANTIHYPERTENSIVE DRUGS

ACE inhibitors (captopril, enalapril, lisinopril, enalaprilat, and ramipril) and angiotensin II receptor blockers are being used increasingly as first-line drugs and appear to improve the quality of life of patients taking antihypertensive drugs. One of the angiotensin II receptor blockers—valsartan—when combined with a diuretic, actually increases libido in both men and women while decreasing arterial blood pressure. However, ACE inhibitors and angiotensin II receptor blockers may be associated with more peripheral vasodilation and hypotension on induction of anesthesia than are sympatholytic agents. Added to this group are the ACE receptor blocking agents. Both ACE inhibitors and ACE receptor blocking agents are associated with such severe hypotension with standard anesthetic induction that we discontinue or at least consider discontinuing the use of these drugs preoperatively (see earlier).

Catecholamine or sympathetic receptor blocking drugs affect the three major types of catecholamine receptors: α-adrenergic, β-adrenergic, and dopaminergic. The existence of subdivisions (e.g., β_1 and β_2) suggested the possibility that some drugs would be found to affect only one set of receptors. For example, terbutaline is used more frequently than isoproterenol because terbutaline is said to exert a preferential effect on α_2 receptors (i.e., dilation of bronchial smooth muscle), thereby avoiding the cardiac stimulation produced by drugs that stimulate β_1-receptors. In fact, the selectivity is dose related. At a certain dose, a direct β_2-receptor stimulating drug affects only those receptors but, at a higher dose, stimulates both β_1 and β_2 receptors. The effect of a given dose varies with each patient. A certain dose may stimulate β_1 and β_2 receptors in one patient but neither receptor in another patient. More and more selective blocking drugs are being developed in hope of widening the margin among β_1-, β_2-, and α-adrenergic effects. Ultimately, however, even more selectivity is desired. It would be advantageous to be able to decrease the heart rate without changing myocardial contractility or to increase contractility without changing the heart rate. Such is the goal of much drug research and the development of dobutamine and fenoldopam. However, to date, all such selectivity appears to be dose related, even for dobutamine.

Metoprolol (Lopressor) and atenolol (Tenormin) (both β_1-adrenergic receptor blocking drugs) and propranolol, betaxolol, timolol, esmolol, pindolol, oxprenolol, acebutolol, carteolol, penbutolol, and nadolol are widely available β-adrenergic receptor blocking drugs used for long-term therapy in the United States. Because nadolol has poor lipid solubility, it has a long elimination half-life (17 to 24 hours) and does not cross the blood-brain barrier readily. Although selective β-adrenergic receptor blocking drugs should be more appropriate in patients with increased airway resistance or diabetes, this advantage is apparent only when low doses are used. The use of β-adrenergic receptor blocking drugs has become widespread because these drugs treat everything from angina and hypertension to priapism and stage fright. These drugs appear to decrease morbidity and mortality in patients who have initially survived MI,[432,433] and they may increase perioperative survival in selected patients.

When administration of β-adrenergic receptor blocking drugs is terminated, sympathetic stimulation often increases, as though the body had responded to the presence of these drugs by increasing sympathetic neuron activity. Thus, propranolol and nadolol (to name just two) withdrawal can be accompanied by a hyper–β-adrenergic condition that increases myocardial oxygen demands. Administering propranolol or metoprolol can cause bradycardia, CHF, fatigue, dizziness, depression, psychoses,

bronchospasm, and Peyronie disease. The POISE study emphasized the concerns that inadequate titration of these agents can lead to stroke or increased mortality.[111] Side effects of dopaminergic receptor blocking drugs are discussed later. Prazosin (Minipress), terazosin, and oxazocin are α_1-adrenergic receptor blocking drugs used to treat hypertension, ischemic cardiomyopathy, receding hairlines, and benign prostatic hypertrophy because they dilate both veins and arteries and reduce sphincter tone. These drugs are associated with vertigo, palpitations, depression, dizziness, weakness, and anticholinergic effects.

Some sympathomimetic drugs stimulate α-adrenergic receptors in the brainstem. Clonidine (Catapres), a drug with a half-life of 12 to 24 hours, guanabenz, and guanfacine (Tenex) are α_2-adrenergic receptor stimulants. Presumably, α_2-adrenergic agonists, including clonidine, guanabenz, and guanfacine, lower arterial blood pressure on a long-term basis through the central brainstem adrenergic stimulation referred to previously. They may also be used on a long-term basis to treat opiate, cocaine, food, and tobacco withdrawal. Occasionally, withdrawal from clonidine can precipitate a sudden hypertensive crisis, analogous to that occurring on withdrawal from propranolol, and it can cause a hyper–β-adrenergic condition. The degree of hypertensive crisis after clonidine withdrawal is now being debated. (Although intravenous clonidine is not available in the United States, a skin patch of clonidine is used preoperatively to ablate sympathomimetic responses perioperatively.) Tricyclic antidepressant drugs and presumably phenothiazines and the butyrophenones interfere with the action of clonidine. Although administration of a butyrophenone (e.g., droperidol) to a patient taking clonidine, guanabenz, or guanfacine on a long-term basis could theoretically precipitate a hypertensive crisis, this has not been reported. Clonidine administration can be accompanied by drowsiness, dry mouth, orthostatic hypotension, bradycardia, and impotence. Acute clonidine or dexmedetomidine administration decreases anesthetic requirements by at least 40% to 60%; long-term administration decreases requirements by 10% to 20%.[434,435] Because of the relative safety of these drugs and their ability to decrease anesthetic requirements, block narcotic-induced muscle rigidity, and provide pain relief, their popularity preoperatively, intraoperatively, and in ICU sedation is increasing dramatically.[434-438]

Three other classes of antihypertensive drugs affect the sympathetic nervous system indirectly: diuretics, arteriolar dilators, and slow-(calcium) channel blocking agents. Thiazide diuretic drugs are associated with hypochloremic alkalosis, hypokalemia, hyperglycemia, hyperuricemia, and hypercalcemia. The potassium-sparing diuretic drug spironolactone is associated with hyperkalemia, hyponatremia, gynecomastia, and impotence. All diuretic drugs can cause dehydration. The thiazide diuretics and furosemide appear to prolong neuromuscular blockade. The arteriolar dilator hydralazine can cause a lupus-like condition (usually with renal involvement), nasal congestion, headache, dizziness, CHF, angina, and GI disturbances. Such a syndrome is nonexistent with the other direct vasodilator on the U.S. market, minoxidil.

The slow-channel calcium ion antagonists (calcium channel blocking drugs) inhibit the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. Such inhibition reduces the heart rate (negative chronotropy), depresses contractility (negative inotropy), decreases conduction velocity (negative dromotropy), and dilates coronary, cerebral, and systemic arterioles (Fig. 39-7).[439] Verapamil, diltiazem, and nifedipine all

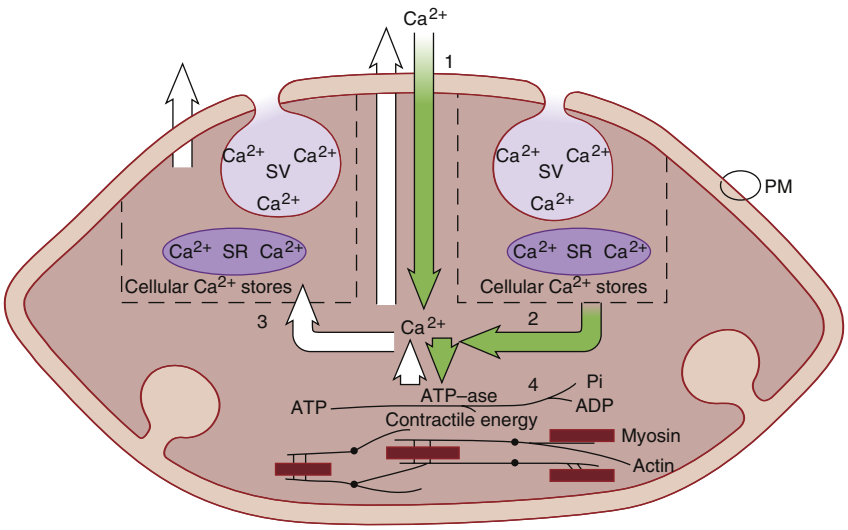


Figure 39-7. Schematic drawing of a smooth muscle cell showing calcium (Ca^{2+}) flux and possible sites of interference by halothane and nifedipine. The concentration of calcium in the cytoplasm increases *(green arrows)* because of entry through the plasma membrane (PM) and release from surface vesicles (SV) or the sacroplasmic reticulum (SR). When the concentration of cytoplasmic Ca^{2+} is sufficiently high, adenosine triphosphate (ATP) is activated. Splitting of ATP by adenosine triphosphatase (ATPase) into phosphatidylinositol (Pi) and adenosine diphosphate (ADP) provides the interaction and contraction of actin filaments and myosin particles constituting muscle fibers. The concentration of cytoplasmic Ca^{2+} decreases *(white arrows)* with the return of Ca^{2+} to cellular stores and the extracellular transport of Ca^{2+}. Both halothane and nifedipine probably (1) inhibit the entry of Ca^{2+} and (2) may also interfere with cytoplasmic Ca^{2+} flux by reducing the release of Ca^{2+} by the SR, by (3) reducing storage and reuptake, or by (4) blocking ATPase or the contractile mechanism (or both). *(Redrawn from Tosone SR, Reves JG, Kissin I, et al: Hemodynamic responses to nifedipine in dogs anesthetized with halothane,* Anesth Analg *62:903, 1983.)*

produce such effects, but to varying degrees and apparently by similar, but different mechanisms. These mechanisms relate to the three different classes of calcium channel antagonists that they represent: the phenylalkyl amines, the benzothiazepines, and the dihydropyridines, respectively. Nifedipine is the most potent of the three as a smooth muscle dilator, whereas verapamil and diltiazem have negative dromotropic and inotropic effects and vasodilating properties. Diltiazem has weak vasodilating properties when compared with nifedipine and has less of an AV conduction effect than does verapamil. Thus, verapamil and diltiazem can increase the PR interval and produce AV block. In fact, reflex activation of the sympathetic nervous system may be necessary during the administration of diltiazem, and especially during verapamil therapy, to maintain normal conduction. Clearly, verapamil and diltiazem must be titrated very carefully when a patient is already taking a β-adrenergic receptor blocking drug or when adding β-blocking drugs to a patient already taking verapamil or diltiazem.

The use of calcium channel blocking drugs has several important implications for anesthetic management.[439-441] First, the effects of inhaled and narcotic anesthetics and nifedipine in decreasing systemic vascular resistance, arterial blood pressure, and contractility may be additive. Similarly, verapamil and anesthetics (inhaled anesthetics, nitrous oxide, and narcotics) increase AV conduction times and additively decrease arterial blood pressure, systemic vascular resistance, and contractility. Second, verapamil and presumably the other calcium channel blocking drugs have been found to decrease anesthetic requirements by 25%. These drugs can produce neuromuscular blockade, potentiate both depolarizing and nondepolarizing neuromuscular blocking drugs, and, in at least one type of myopathy (Duchenne muscular dystrophy), even precipitate respiratory failure. Finally, because slow-channel activation of calcium is necessary to cause spasms of cerebral and coronary vessels, bronchoconstriction, and normal platelet aggregation, these drugs may have a role in treating ischemia of the nervous system, bronchoconstriction, and unwanted clotting disorders perioperatively. All three drugs are highly protein bound and may displace or be displaced by other drugs that are also highly protein bound (e.g., lidocaine, bupivacaine, diazepam, disopyramide, and propranolol). Adverse consequences can be minimized by titrating the inhaled or narcotic drug to the hemodynamic and anesthetic effects. Hemodynamic, but not electrophysiologic, changes can usually be reversed by administering calcium. Reversal of the electrophysiologic effects may occur if "industrial" doses of β-adrenergic agonists are given.

MOOD-ALTERING DRUGS

Mood-altering drugs are the most frequently prescribed medications in the United States.[442,443] They include MAOIs, SSRIs, phenothiazines, tricyclic antidepressant drugs, other antidepressants that do not fall into previous drug category classifications such as bupropion, and drugs of abuse such as cocaine. MAOIs, which include isocarboxazid (Marplan), phenelzine (Nardil), pargyline (Eutonyl), tranylcypromine (Parnate), and deprenyl, bind irreversibly to the enzyme MAO, thereby increasing intraneuronal levels of amine neurotransmitters (serotonin, norepinephrine, dopamine, epinephrine, octopamine). This increase is associated with an antidepressant effect, an antihypertensive effect, an antinarcoleptic effect, elevation of liver enzymes, and delayed onset of Parkinson disease (deprenyl). Because two forms of the enzyme (MAO-A and MAO-B) are selective in vitro for substrate (MAO-A is selective for serotonin, dopamine, and norepinephrine; MAO-B for tyramine and phenylethylamine), presumably MAOIs selective for MAO-A or MAO-B would have different effects.[444] This is not known for certain inasmuch as deprenyl (selegiline [Eldepryl]), an MAO-B–selective drug, improves a dopamine deficiency state, parkinsonism.

Interactions between MAOIs and a variety of foods and drugs containing indirect-acting sympathomimetic substances such as ephedrine or tyramine (found especially in aged cheeses) can occur for as long as 2 weeks after the last dose of MAOI is given. The most serious effects of this interaction are convulsions and hyperpyrexic coma (particularly after narcotics).

Anesthetic management of a patient given an MAOI can be chaotic; for this reason it is widely accepted practice to discontinue MAOIs at least 2 to 3 weeks before any planned operation.[442-448] An alternative point of view has been expressed regarding severely psychotic patients or emergency surgery.[444,449-451] Clearly, the risk of discontinuing MAOIs must be weighed against the risk of suicidal tendencies in some patients deprived of MAOIs. No reported experiences of interactions between narcotics and deprenyl have been published, so judgments about possible worsening of Parkinson disease and continuing MAOIs have no basis in data. Severe reactions have occurred when too short an interval existed between the administration of MAOIs and tricyclic antidepressants. Emergency surgery in patients given MAOIs can be punctuated by hemodynamic instability. A regional block can be attempted as treatment of postoperative pain to avoid having to give narcotics. Cases of hyperpyrexic coma after the administration of most narcotics have been reported in humans, and animal studies document a 10% to 50% incidence of hyperpyrexic coma in animals pretreated with MAOIs and then given a variety of narcotics.[442-448] These reactions appear to be treated best by therapy supporting vital functions.

Alternative drugs for the treatment of severe depression include the tricyclic antidepressant drugs: amitriptyline (Elavil, Endep), imipramine (Tofranil, Presamine), desipramine (Norpramin), doxepin (Adapin, Sinequan), nortriptyline (Aventyl), fluoxetine (Prozac), trazodone (Desyrel), and others.[442,443] Tricyclic antidepressant drugs also block the reuptake of neurotransmitters and cause their acute release. Given on a long-term basis, these drugs decrease stores of noradrenergic catecholamines. Tricyclic antidepressant drugs also produce side effects similar to those of atropine (dry mouth, tachycardia, delirium, urinary retention) and can cause changes on the ECG (changes in the T wave, prolongation of the QRS complex, bundle branch block or other conduction abnormalities, or PVCs). Although arrhythmias induced by tricyclic antidepressants have been treated

successfully with physostigmine, bradycardia has sometimes occurred.[442,443] Drug interactions with tricyclic antidepressants include those related to blockade of the reuptake of norepinephrine (e.g., interference with the action of guanethidine) and fatal arrhythmias after halothane and pancuronium.[452,453] Such interactions, although predictable for a population of patients, may not alter a patient's threshold for arrhythmias. The newer antidepressants (the SSRIs) can also have serious side effects. Fluoxetine, a tricyclic antidepressant that also has an SSRI effect, causes nausea, vomiting, headaches, nervousness, and possibly paranoia and ideas of suicide more commonly than do the other tricyclics[442,443]; however, it is less likely to cause anticholinergic effects or orthostatic hypotension. Bupropion, which is fundamentally different than the SSRIs, may cause nausea, vomiting, seizures, agitation, tremor, excitement, and increased motor activity, but it only rarely causes anticholinergic effects or orthostatic hypotension. Discontinuing drugs can cause withdrawal symptoms or precipitate recurrence of psychiatric illness. Switching among drugs for depression can cause hyperpyrexia and coma. Thus, switching drugs preoperatively should not be requested casually.[442,443]

The effectiveness of phenothiazines and butyrophenones in schizophrenia suggests a dopamine receptor blocking action. In addition, these drugs possess varying degrees of parasympathetic stimulation and ability to block α-adrenergic receptors. The phenothiazines include chlorpromazine (Thorazine, Chlor-PZ), promazine (Sparine), triflupromazine (Vesprin), fluphenazine (Prolixin), trifluoperazine, prochlorperazine (Compazine), and many others. The butyrophenones include droperidol and haloperidol (Haldol). Both the phenothiazines and butyrophenones produce sedation, depression, and antihistaminic, antiemetic, and hypothermic responses. They are also associated with cholestatic jaundice, impotence, dystonia, and photosensitivity. Other side effects associated with phenothiazines include orthostatic hypotension (partly as a result of α-adrenergic blockade) and abnormalities on the ECG such as prolongation of the QT or PR intervals, blunting of T waves, depression of the ST segment, and on rare occasion, PVCs and torsades de pointes.[442,443,452,453] Although few data are available on the antidepressant drugs selective for serotonin (the SSRIs), occasional case reports of severe hypotension and cardiac arrest with severe bradycardia have been presented in abstract form.

Several important drug interactions are noteworthy for the phenothiazine derivatives. The effects of CNS depressants (especially narcotics and barbiturates) are enhanced by the concomitant administration of phenothiazines. In addition, the CNS seizure threshold is lowered by the administration of phenothiazines, which should be avoided in patients who are epileptic or withdrawing from any drug that depresses the CNS. The antihypertensive effects of guanethidine and guanadrel are blocked by tricyclic antidepressant drugs and the phenothiazines.[454] Lithium carbonate is used to treat manic depression, but it is more effective in preventing mania than in relieving depression. In excitable cells, lithium mimics sodium and decreases the release of neurotransmitters both centrally and peripherally. Lithium prolongs neuromuscular blockade and may decrease anesthetic requirements because it blocks brainstem release of norepinephrine, epinephrine, and dopamine.

Psychoactive drugs such as the amphetamines (including methamphetamines and their smokable derivative in crystal form known as "ice") and cocaine acutely release norepinephrine, epinephrine, and dopamine and block their reuptake. Taken on a long-term basis, they deplete nerve endings of these neurotransmitters.

Drugs that appear to increase central α-adrenergic release increase anesthetic requirements, whereas drugs that appear to decrease central α-adrenergic release decrease anesthetic requirements. (This may not be the mechanism by which they alter anesthetic requirements, but it is a convenient way of remembering the alteration.) Drugs that affect only the β-adrenergic receptors do not alter anesthetic requirements.

ANTIARRHYTHMIC DRUGS

Antiarrhythmic drugs include local anesthetics (lidocaine, procaine), anticonvulsant (phenytoin) or antihypertensive (propranolol) drugs, calcium channel blocking drugs, or primary antiarrhythmic drugs (see also Chapters 67 and 68). These drugs are classified into five major categories: local anesthetics that alter phase 0 and phase 4 depolarization (quinidine, procainamide, and flecainide), local anesthetics that affect only phase 4 depolarization (lidocaine, tocainide, phenytoin, encainide), β-adrenergic receptor antagonists, antiadrenergic drugs (bretylium, disopyramide, amiodarone), and calcium entry blockers. These drugs are discussed elsewhere in this chapter. A lack of adverse reports does not indicate that all these drugs should be continued through the time of surgery; pharmacokinetic studies have not yet determined whether anesthesia (or anesthesia with specific agents) alters the volume of distribution or clearance of these drugs to an extent sufficient to warrant changing the dosage or dosage schedule in the perioperative period. The dearth of reports on this subject may reflect a lack of significant drug interaction or a lack of awareness that untoward events could be caused by such an interaction.

The pharmacologic characteristics of the various antiarrhythmic drugs can affect anesthetic management. Disopyramide is similar to quinidine and procainamide in its antiarrhythmic effectiveness. Disopyramide is excreted mainly by the kidneys, but hepatic disease increases its half-life. This drug often produces anticholinergic effects, including tachycardia, urinary retention, and psychosis. Hepatitis has also been reported to have occurred after its use.[455] Little is known of the interaction of bretylium with anesthetic agents. Because bretylium blocks the release of catecholamines, long-term therapy with this drug has been associated with hypersensitivity to vasopressors.[455] Quinidine depends on the kidneys for excretion, can produce vagolytic effects that can decrease AV block, and is associated with blood dyscrasias and GI disturbances.[455] Most of the antiarrhythmic drugs enhance nondepolarizing neuromuscular blockade. Reports have confirmed this enhancement for quinidine, phenytoin, lidocaine, procainamide, and propranolol.[456-464] No data document such an effect for depolarizing muscle relaxants. Amiodarone, an antiadrenergic drug used to treat

recurrent supraventricular and ventricular tachycardia, causes thyroid dysfunction as a result of the large amount of iodine in its structure (see the section on thyroid disorders earlier in this chapter), as well as peripheral neuropathy, and has been associated with hypertension, bradyarrhythmias, and reduced cardiac output during anesthesia.[465] The drug has a half-life of 29 days, and its pharmacologic effects persist for more than 45 days after discontinuance.[466]

ANTIBIOTICS

Many antibacterial drugs are nephrotoxic or neurotoxic, or both, and many prolong neuromuscular blockade (see also Chapters 34 and 35).[458-464] The only antibiotics devoid of neuromuscular effects appear to be penicillin G and the cephalosporins.[463] Most enzyme-inducing drugs do not increase the metabolism of enflurane or isoflurane. However, isoniazid induces the microsomal enzymes responsible for the metabolism of at least enflurane and thereby increases the possibility of fluorine-associated renal damage after enflurane administration.[467] Appropriate antibiotic prophylaxis for surgery requires a knowledge of the probability of infection for that type of surgical procedure and, if the incidence of infection warrants, the use of a drug regimen directed against the most likely infecting organisms.[468]

MEDICATIONS FOR GLAUCOMA

Medications for glaucoma include two organophosphates: echothiophate and isoflurophate (see also Chapter 84). These drugs inhibit serum cholinesterase, which is responsible for the hydrolysis and inactivation of succinylcholine and ester-type local anesthetics such as procaine, chloroprocaine, and tetracaine (see also Chapters 34 and 36).[469,470] These ester-type local anesthetics should be avoided in patients treated with eye drops containing organophosphate. Table 39-16 lists other medications related to anesthesia and their side effects (from the National Registry for Drug-Induced Ocular Side Effects,

TABLE 39-16 **COMMON OPHTHALMOLOGIC DRUGS AND THEIR ANESTHETICALLY IMPORTANT INTERACTIONS**

Drug (Trade Name)	Toxicities and Specific Treatments
Glaucoma: Primary Goal Is to Reduce IOP By Miotics and epinephrine: increase outflow of aqueous humor β-Blockade and carbonic anhydrase inhibitors: reduce production of aqueous humor Osmotic drugs: transiently decrease volume	
Miotics Parasympathomimetics Pilocarpine (Adsorbocarpine, Isopto Carpine, Pilocar, Pilocel) Carbachol	
Acetylcholinesterase Inhibitors Physostigmine Demecarium Isoflurophate (Floropryl) Echothiophate (Echodide, Phospholine)	Tox: Hypersalivation, sweating, N/V, bradycardia, hypotension, bronchospasm, CNS effects, coma, respiratory arrest, death Rx: Atropine, pralidoxime (Protopam) Ix: Succinylcholine—prolonged apnea (drugs must be discontinued 4 wk before)
Epinephrine (Epitrate, Murocoll, Mytrate, Epifrin, Glaucon, Epinal, Eppy)	Tox: (rare) Tachycardia, PVCs, HTN, headache, tremors Ix: Avoid drugs that sensitize to catecholamines (e.g., halothane)
β-Blockers Timolol (Timoptic) Betaxolol (Betoptic) Levobunolol (Betagan)	Tox: β-Blockade with bradycardia, exacerbation of asthma, CNS depression, lethargy, confusion Synergy noted with systemic drugs
Carbonic Anhydrase Inhibitors Acetazolamide (Diamox) Dichlorphenamide (Daranide, Oratrol) Ethoxzolamide (Cardrase, Ethamide) Methazolamide (Neptazane)	Tox: Anorexia, GI disturbances, "general miserable feeling" and malaise, paresthesias, diuresis, hypokalemia (transient), renal colic and calculi, hyperuricemia, thrombocytopenia, aplastic anemia, acute respiratory failure in patients with COPD
Osmotic Drugs Glycerin (Glyrol, Osmoglyn) Isosorbide (Ismotic) Urea (Urevert, Ureaphil) Mannitol (Osmitrol)	Tox: Dehydration, hyperglycemia, nonketotic hyperosmolar coma (rare); fatalities with mannitol secondary to CHF or intracranial bleeding; urea may cause thrombosis
Intraocular acetylcholine (Miochol)	Tox: Hypotension, bradycardia Rx: Atropine
Mydriatics and Cycloplegics: Provide Pupillary Dilatation and Paralysis of Accommodation Anticholinergics block muscarinic receptors; paralyzing in iris α-Adrenergics contract the dilator of the iris	

Continued

TABLE 39-16 **COMMON OPHTHALMOLOGIC DRUGS AND THEIR ANESTHETICALLY IMPORTANT INTERACTIONS—cont'd**

Drug (Trade Name)	Toxicities and Specific Treatments
Anticholinergics	Tox: Dry mouth, flushing, thirst, tachycardia, seizure, hyperactivity, transient psychosis, rare coma, and death Rx: Physostigmine
Atropine (Atropisol, Bufopto, Isopto Atropine)	
Cyclopentolate, alone (Cyclogyl) or with phenylephrine-homatropine (Cyclomydril)	
Homatropine (Homatrocel, Isopto Homatropine)	
Scopolamine (Isopto Hyoscine, Murocoll 19)	
Tropicamide (Midriacyl)	
β-Adrenergics	Tox: Tachycardia, HTN, PVCs, myocardial ischemia, agitation
Phenylephrine (Efricel, Mydfrin, Neo-Synephrine)	
Hydroxyamphetamine (Paredrine)	

Modified from the National Registry for Drug-Induced Ocular Side Effects, Portland, Ore., Oregon Health Sciences University.
CHF, Congestive heart failure; *CNS,* central nervous system; *COPD,* chronic obstructive pulmonary disease; *GI,* gastrointestinal; *HTN,* hypertension; *IOP,* intraocular pressure; *Ix,* interaction; N/V, nausea and vomiting; *PVCs,* premature ventricular contractions; *Rx,* treatment; *Tox,* toxicity.

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Complete references available online at expertconsult.com

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Chapter 40

Anesthetic Implications of Complementary and Alternative Medications

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Key Points

- Herbal medication use has increased dramatically in the overall population and particularly in preoperative patients.
- Patients might not volunteer information unless they are queried specifically about herbal medication use.
- Although many commonly used herbs have side effects that affect drug metabolism, bleeding, and neuronal function, they are not subject to regulations on purity, safety, and efficacy.
- Although discontinuing herbal medications up to 2 weeks preoperatively can eliminate many of these problems, patients often arrive for surgery without having had a preoperative visit 2 weeks before surgery. Knowledge of specific interactions and metabolism of herbs can provide practical guidelines to facilitate perioperative management.
- Other complementary therapies, including acupuncture and music therapy, have become increasingly popular, although less is known about their effectiveness.

Complementary and alternative medicine (CAM) has implications for physicians in general, but has particular importance for perioperative physicians because of specific complications associated with certain therapies often used as anesthesia adjuvants. Complementary medicine is defined as the addition of nonconventional therapies to accepted treatments; alternative medicine describes the use of nonconventional therapies in lieu of accepted treatments. They have become an important part of contemporary health care. In 2007, 38% of Americans used CAM therapies in the preceding year.[1] Visits to CAM practitioners exceed those to American primary care physicians,[2] and CAM is even more widely used in Europe, where herbal medicines are prescribed more frequently than conventional drugs are. Furthermore, patients undergoing surgery appear to use CAM more than the general population does.[3] Aside from the widespread use of CAM, perioperative physicians have a special interest in CAM therapies for several reasons. First, several commonly used herbal medications exhibit direct effects on the cardiovascular and coagulation systems. Second, some CAMs can interfere with conventional medications that are commonly given in the postoperative period. Finally, the therapeutic potential of CAM in the perioperative period is increasingly being described in the literature.

Despite the public enthusiasm for CAM, scientific knowledge in this area is still incomplete and often confusing for practitioners and patients. One recent study confirmed poor knowledge of this subject among physicians.[4] Recommendations for clinicians are often based on small clinical trials, case reports, animal studies, predictions derived from known pharmacology, and expert opinion. Research is essential because CAM therapies are often widely adopted by the public before adequate data are available to support their safety and efficacy. In 1991, Congress established the Office of Alternative Medicine, which became the National Center for Complementary and Alternative Medicine within the National Institutes of Health in 1998. In 2006, more than twice as many CAM-related English-language research articles were published compared with 1996.

Practices encompassed by CAM are heterogeneous and evolving. The most commonly used CAM were natural products (17.7%), deep breathing exercises (12.7%), meditation (9.4%), chiropractic or osteopathic manipulation

BOX 40-1 ***Five Major Categories of Complementary and Alternative Medicine***

1. Alternative medical systems (e.g., homeopathic medicine, naturopathic medicine, traditional Chinese medicine, ayurveda)
2. Mind-body interventions (e.g., meditation; prayer; art, music, or dance therapy)
3. Biologically based treatments (e.g., herbal medicines, dietary supplements)
4. Manipulative and body-based methods (e.g., chiropractic manipulation, osteopathic manipulation, massage)
5. Energy therapies (e.g., acupuncture, electromagnetic fields, reiki, qi gong)

Adapted from the National Center for Complementary and Alternative Medicine. <http://nccam.nih.gov/health/whatiscam>. (Accessed 02.06.12.)

(8.6%), massage (8.3%), and yoga (6.1%). CAM practices can be classified into five general categories (Box 40-1).[5] This chapter is not intended as a comprehensive review of CAM. Specific therapies relevant to anesthesia are discussed, and we focus primarily on herbal medicines. Nonherbal dietary supplements, acupuncture, and music are also considered because they are relevant to anesthesia practice.

HERBAL MEDICINES

Preoperative use of herbal medicines has been associated with adverse perioperative events.[6] Surveys estimate that 22% to 32% of patients undergoing surgery use herbal medications.[7-9] In a recent retrospective review, 23% of surgery patients indicated the use of natural products, and older patients preferred dietary supplements.[10]

Herbal medicines can affect the perioperative period through several classic mechanisms: direct effects (i.e., intrinsic pharmacologic effects), pharmacodynamic interactions (i.e., alteration of the action of conventional drugs at effector sites), and pharmacokinetic interactions (e.g., alteration of the absorption, distribution, metabolism, and elimination of conventional drugs). Because approximately 50% of herbal medicine users take multiple herbs concomitantly[7] and 25% of herbal medicine users take prescription drugs,[11] adverse effects are difficult to predict and attribute.

Herbal medicines are associated with unique problems not usually found with conventional drugs.[12] Many of the issues complicating the understanding of herbal medications derive from the fact that they are classified as dietary supplements under the Dietary Supplement Health and Education Act of 1994. As such, the introduction of herbal medications does not require animal studies, clinical trials, or postmarketing surveillance. Under current law, the burden is shifted to the U.S. Food and Drug Administration (FDA) to prove products unsafe before they can be withdrawn from the market. In one well-publicized action, more than 130 reports of persistent anosmia (thought to be zinc related) led to the withdrawal of intranasal Zicam (Matrixx Initiatives, Inc., Bridgewater, New Jersey), which is widely used for colds.[13] Commercial herbal medicine preparations can have unpredictable pharmacologic effects resulting from inaccurate labeling, misidentified plants, adulterants, variations in natural potency, and unstandardized processing methods. Two of the major problems confronting herbal medicine research involve quality control and added adulterants.

In a recent clinical trial to treat human H1N1 influenza, an herbal formulation containing 12 different Chinese herbal medicines including licorice (genus *Glycyrrhiza*) was used.[14] Some of the other botanicals in the formula were not accurately identified. There are three *Glycyrrhiza* species on the market, and the author did not identify the species used in the trial. The content of glycyrrhizin, a major marker compound of licorice, showed a twofold difference when the three species were compared, suggesting that the chemical composition of different *Glycyrrhiza* species varies.[15] Labeled active ingredients can vary tenfold in different commercial preparations.[16] In June 2007, the FDA issued regulations for current good manufacturing practices (GMPs) for dietary supplements.[17] This rule requires that proper controls be in place so that dietary supplements are processed in a consistent manner and meet quality standards. Especially emphasized are the identity, purity, strength, and composition of the products. Dietary product GMPs undoubtedly reduce the potential risk in the use of herbal medicines. Because this rule is somewhat similar to that for prescription drug GMPs, many supplement manufacturers believe that it is not practical for botanicals.[18]

Beyond quality control is the inclusion of biologically active pharmacologic adulterants in herbal medications and supplements. There are clinical consequences when quality control is lacking or herbal preparations are adulterated. In one popular weight-loss remedy, a manufacturing error resulted in the substitution of one herb (*Stephania tetranda*) by another with the carcinogen aristolochic acid. The substitution led to an outbreak of nephropathy and urothelial carcinoma, first noted when a renal transplant patient developed an unusual form of this cancer.[19] The effect of misidentified ingredients or adulterants can be acute. In another well-publicized event, more than 14 million capsules of Zotrex (TSN Labs, Inc., Salt Lake City, Utah), a sexual enhancement supplement, were recalled because the compound on the label did not actually exist. However, the supplement did contain an analogue of sildenafil, which has not been tested in humans.[20] In July 2011, the FDA drafted a guidance because of the popularity of dietary supplements and several egregious cases of pharmacologic adulterants in supplements.[21] The FDA's new guidance proposes to evaluate the safety of supplements on their history of use, formulation, proposed daily dose, and recommended duration of use. Although the proposal represents only a fraction of what is necessary for a new drug application, it requires some testing for tolerability in animals when products are marketed for consumption at doses substantively greater than those historically ingested. Any ingredient formulated or prepared in a novel manner is considered a new ingredient. Under the guidance, a tolerability study of even a single dose in humans is not required for approval.[21]

In this section, we discuss the preoperative assessment and management of patients who use herbal medicines

TABLE 40-1 CLINICALLY IMPORTANT EFFECTS, PERIOPERATIVE CONCERNS, AND RECOMMENDATIONS FOR PERIOPERATIVE DISCONTINUATION OF 11 COMMONLY USED HERBAL MEDICINES

Herbs (Common Names)	Pharmacologic Effects	Perioperative Concerns	Discontinue Before Surgery
Echinacea (purple coneflower root)	Activation of cell-mediated immunity	Allergic reactions Decreases effectiveness of immunosuppressants Potential for immunosuppression with long-term use	No data
Ephedra (ma huang)	Increases heart rate and blood pressure through direct and indirect sympathomimetic effects	Risk of myocardial ischemia and stroke from tachycardia and hypertension Ventricular arrhythmias with halothane Long-term use depletes endogenous catecholamines and may cause intraoperative hemodynamic instability Life-threatening interaction with MAO inhibitors	24 hours
Garlic (ajo)	Inhibits platelet aggregation (may be irreversible) Increases fibrinolysis Equivocal antihypertensive activity	May increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation	7 days
Ginger	Anti-emetic Antiplatelet aggregation	May increase risk of bleeding	No data
Ginkgo (duck-foot tree, maidenhair tree, silver apricot)	Inhibits platelet-activating factor	May increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation	36 hours
Ginseng (American ginseng, Asian ginseng, Chinese ginseng, Korean ginseng)	Lowers blood glucose Inhibits platelet aggregation (may be irreversible) Increased PT/PTT in animals	Hypoglycemia May increase risk of bleeding May decrease anticoagulant effect of warfarin	7 days
Green tea	Inhibits platelet aggregation Inhibits thromboxane A2 formation	May increase risk of bleeding May decrease anticoagulant effect of warfarin	7 days
Kava (awa, intoxicating pepper, kawa)	Sedation Anxiolysis	May increase sedative effect of anesthetics Increase in anesthetic requirements with long-term use unstudied	24 hours
Saw palmetto (dwarf palm, *Sabal*)	Inhibits 5α-reductase Inhibits cyclooxygenase	May increase risk of bleeding	No data
St. John's wort (amber, goat weed, hardhay, hypericum, Klamath weed)	Inhibits neurotransmitter reuptake MAO inhibition unlikely	Induction of cytochrome P450 enzymes; affects cyclosporine, warfarin, steroids, and protease inhibitors; may affect benzodiazepines, calcium channel blockers, and many other drugs Decreased serum digoxin levels Delayed emergence	5 days
Valerian (all heal, garden heliotrope, vandal root)	Sedation	May increase sedative effect of anesthetics Benzodiazepine-like acute withdrawal May increase anesthetic requirements with long-term use	No data

MAO, Monoamine oxidase; *PT,* prothrombin time; *PTT,* partial thromboplastin time.

and examine 11 herbal medicines that have the greatest effect on perioperative patient care: *Echinacea*, ephedra, garlic, ginger, *Ginkgo biloba*, ginseng, green tea, kava, saw palmetto, St. John's wort, and valerian (Table 40-1). These 11 medicines account for 30% of the dietary supplements sold in the United States.[22]

PREOPERATIVE ASSESSMENT AND MANAGEMENT

Preoperative assessment should address the use of herbal medicines (see Chapter 38). One study found that 90% of anesthesia providers do not routinely ask about herbal

medicine use.[23] Moreover, more than 70% of patients are not forthcoming about their herbal medicine use during routine preoperative assessment.[7] When a positive history of herbal medicine use is elicited, one in five patients is unable to properly identify the preparation being taken.[24] Asking patients to bring their herbal medicines and other dietary supplements with them at the time of the preoperative evaluation would be helpful. A positive history of herbal medicine use should alert one to the presence of undiagnosed disorders causing symptoms leading to self-medication. Patients who use herbal medicines may be more likely to avoid conventional diagnosis and therapy.[25]

In general, herbal medicines should be discontinued preoperatively. In clinical practice, patients who require nonelective surgery are not evaluated until the day of surgery or are noncompliant with instructions to discontinue herbal medications preoperatively. They may take herbal medicines until the day of surgery. In this situation, anesthesia can usually proceed safely at the discretion of the anesthesia provider, who should be familiar with commonly used herbal medicines. For example, recent use of herbal medicines that inhibit platelet function (e.g., garlic, ginseng, *Ginkgo biloba*) may warrant specific strategies for procedures with substantial intraoperative blood loss (e.g., platelet transfusion) and those that alter the risk/benefit ratio of using certain anesthetic techniques (e.g., neuraxial blockade).

Preoperative discontinuation of all herbal medicines might not eliminate complications related to their use. Withdrawal of regular medications can increase morbidity and mortality after surgery.[26] Alcoholics who abstain from drinking alcohol preoperatively may have poorer postoperative outcomes than those who continue drinking preoperatively.[27] The danger of abstinence after long-term use may be similar with herbal medicines such as valerian, which can produce acute withdrawal after long-term use.

Although the American Society of Anesthesiologists has no official standards or guidelines for the preoperative use of herbal medications, public and professional educational information released by this organization suggests that herbals be discontinued at least 2 weeks before surgery.[26] Our review of the literature favors a more targeted approach, because evaluating patients 2 to 3 weeks before elective surgery may be impossible. Moreover, some patients require nonelective surgery or are noncompliant with instructions to discontinue herbal medications preoperatively. These factors and the extensive use of herbal medicines could mean that herbal medications are taken until the time of surgery. Pharmacokinetic data on selected active constituents indicate that some herbal medications are eliminated quickly and may be discontinued closer to the time of surgery. When pharmacokinetic data for the active constituents in an herbal medication are available, the timeframe for preoperative discontinuation can be tailored. For other herbal medicines, 2 weeks is recommended.[28]

Evidence-based estimates of herbal safety in the perioperative period are limited. One study of 601 patients who used traditional Chinese herbal medications suggested an infrequent rate of potential serious complications.[29] Clinicians should be familiar with commonly used herbal medications to recognize and treat any complications that might arise. Table 40-1 summarizes the clinically important effects, perioperative concerns, and recommendations for preoperative discontinuation of the 11 herbal medications discussed in this chapter. The type of surgery and potential perioperative course should be considered in these clinical recommendations.

ECHINACEA

Three species of *Echinacea*, a member of the daisy family, are used for the prophylaxis and treatment of viral, bacterial, and fungal infections, particularly those of upper respiratory origin, although its efficacy in the latter is doubtful.[30] A recent meta-analysis showed the benefit of *Echinacea* in decreasing the incidence and duration of the common cold.[31] Its pharmacologic activity cannot be attributed to a single compound, although the lipophilic fraction, which contains alkylamides, polyacetylene, and essential oils, appears to be more active than the hydrophilic fraction. The biological activity of *Echinacea* could be immunostimulatory, immunosuppressive, or antiinflammatory depending on the portion of the plant and extraction method.[32] Although no studies have specifically addressed interactions between *Echinacea* and immunosuppressive drugs, expert opinion generally warns against the concomitant use of *Echinacea* and these drugs because of the probability of diminished effectiveness.[33,34] Therefore, patients who might require perioperative immunosuppression, such as those awaiting organ transplantation, should be counseled to avoid *Echinacea*. In contrast to its immunostimulatory effects with short-term use, long-term use of more than 8 weeks is accompanied by the potential for immunosuppression[34] and a theoretically increased risk for certain postsurgical complications, such as poor wound healing and opportunistic infections. A recent phytochemical study identified a potential immunosuppressant compound from *Echinacea*—cynarine.[35]

Echinacea can cause allergic reactions, including one reported case of anaphylaxis.[36] Therefore, *Echinacea* should be used with caution in patients with asthma, atopy, or allergic rhinitis. Concern for potential hepatoxicity has also been raised, but documented cases are lacking.[37] Although several in vitro and in vivo pharmacokinetics studies of *Echinacea* have been reported, information about its pharmacokinetics is still limited.[38] *Echinacea* significantly reduced plasma concentrations of S-warfarin, but did not significantly affect warfarin pharmacodynamics and platelet aggregation in healthy subjects.[39] However, this herb should be discontinued as far in advance of surgery as possible when compromises in hepatic function or blood flow are anticipated.[40] In the absence of definitive information, patients with preexisting liver dysfunction should be cautious in using *Echinacea*.

EPHEDRA

Ephedra, known as *ma huang* in Chinese medicine, is a shrub native to central Asia. It is used to promote weight loss, increase energy, and treat respiratory conditions

such as asthma and bronchitis. Ephedra contains alkaloids, including ephedrine, pseudoephedrine, norephedrine, methylephedrine, and norpseudoephedrine.[26] Commercial preparations can be standardized to a fixed ephedrine content. Publicity about adverse reactions to this herb prompted the FDA to bar its sale in 2004, but ephedra is still widely available via the Internet.

Ephedra causes dose-dependent increases in arterial blood pressure and heart rate. Ephedrine, the predominant active compound, is a noncatecholamine sympathomimetic that exhibits α_1, β_1, and β_2 activity directly at adrenergic receptors and indirectly by releasing endogenous norepinephrine (noradrenaline). These sympathomimetic effects have been associated with more than 1070 reported adverse events, including fatal cardiac and central nervous system complications.[41]

Although ephedrine is widely used as first-line therapy for intraoperative hypotension and bradycardia, the unsupervised preoperative use of ephedra raises certain concerns. Vasoconstriction and, in some cases, vasospasm of coronary and cerebral arteries can cause myocardial infarction and thrombotic stroke.[42] Ephedra can also affect cardiovascular function by causing hypersensitivity myocarditis, characterized by cardiomyopathy with myocardial lymphocyte and eosinophil infiltration.[43] Long-term use results in tachyphylaxis from depletion of endogenous catecholamine stores and can contribute to perioperative hemodynamic instability. In these situations, direct-acting sympathomimetics may be preferred as first-line therapy for intraoperative hypotension and bradycardia. Concomitant use of ephedra and monoamine oxidase inhibitors can result in life-threatening hyperpyrexia, hypertension, and coma. Finally, continuous ephedra is a rare cause of radiolucent kidney stones.[44]

The pharmacokinetics of ephedrine have been studied in humans.[45,46] Ephedrine has an elimination half-life of 5.2 hours, with 70% to 80% of the compound excreted unchanged in urine. Based on the pharmacokinetic data and the known cardiovascular risks associated with ephedra, including myocardial infarction, stroke, and cardiovascular collapse from catecholamine depletion, this herb should be discontinued at least 24 hours before surgery.

GARLIC

Garlic is one of the most extensively researched medicinal plants. It has the potential to modify the risk for atherosclerosis by reducing arterial blood pressure, thrombus formation, and serum lipid and cholesterol concentrations.[47] These effects are primarily attributed to its sulfur-containing compounds, particularly allicin and its transformation products. Commercial garlic preparations can be standardized to a fixed alliin and allicin content.

Garlic inhibits platelet aggregation in vivo in a concentration-dependent fashion. The effect of one of its constituents, ajoene, is irreversible and can enhance the effect of other platelet inhibitors such as prostacyclin, forskolin, indomethacin, and dipyridamole.[48] Although the effects are not consistently demonstrated in volunteers, there is one case described in an 80 year old who had a spontaneous epidural hematoma develop that was attributed to continuous garlic use.[49] Garlic has interacted with warfarin, resulting in an increased international normalized ratio (INR).[50]

In addition to bleeding concerns, garlic can decrease systemic and pulmonary vascular resistance in laboratory animals, but this effect is marginal in humans.[51] Although there are insufficient pharmacokinetic data on garlic's constituents, the potential for irreversible inhibition of platelet function may warrant discontinuation of garlic at least 7 days before surgery, especially if postoperative bleeding is a particular concern or other anticoagulants are given.

GINGER

Ginger (*Zingiber officinale*) is a popular spice with a long history of use in Chinese, Indian, Arabic, and Greco-Roman herbal medicines. Ginger has a wide range of reported health benefits for those with arthritis, rheumatism, sprains, muscular aches, pains, sore throats, cramps, constipation, indigestion, nausea, vomiting, hypertension, dementia, fever, infectious diseases, and helminthiasis.[52] Ginger contains up to 3% volatile oil, mostly monoterpenoids and sesquiterpenoids.[53] Gingerols are representative compounds in ginger.[54]

Ginger is an antiemetic and has been used to treat motion sickness and to prevent nausea after laparoscopy.[55] The number of postoperative antiemetic medications was significantly reduced after aromatherapy with essential oil of ginger.[56] In another recent trial, ginger supplementation reduced the severity of acute chemotherapy-induced nausea in adult cancer patients.[57] This response compared favorably to conventional antiemetics (see Chapter 97).

In an in vitro study, gingerols and related analogues inhibited arachidonic acid–induced human platelet serotonin release and aggregation, with a potency similar to that of aspirin.[54] In another in vitro study, the antiplatelet effects of 20 ginger constituents were evaluated. Five constituents showed antiplatelet activities at relatively low concentrations. One of the ginger compounds (8-paradol) was the most potent COX-1 inhibitor and antiplatelet aggregation drug.[58] In a case report, a ginger-phenprocoumon combination resulted in an increased INR and epistaxis.[59]

Although the sample size was relatively small, the platelet inhibition potential of ginger has been suggested in a pilot clinical study.[60] This result may warrant the discontinuation of ginger at least 2 weeks before surgery,

GINKGO

Ginkgo is derived from the leaf of *Ginkgo biloba* and has been used for cognitive disorders, peripheral vascular disease, age-related macular degeneration, vertigo, tinnitus, erectile dysfunction, and altitude sickness. Studies have suggested that ginkgo can stabilize or improve cognitive performance in patients with Alzheimer disease and multi-infarct dementia,[61] but not in healthy geriatric patients.[62] The compounds that might be responsible for its pharmacologic effects are the terpenoids and flavonoids. The two

ginkgo extracts used in clinical trials are standardized to ginkgo-flavone glycosides and terpenoids.

Ginkgo alters vasoregulation, acts as an antioxidant, modulates neurotransmitter and receptor activity, and inhibits platelet-activating factor. Of these effects, inhibition of platelet-activating factor is of primary concern for the perioperative period. Although bleeding complications have not occurred in clinical trials, four cases of spontaneous intracranial bleeding,[63-65] one case of spontaneous hyphema,[66] and one case of postoperative bleeding after laparoscopic cholecystectomy[67] have been described when ginkgo was being taken.

Terpene trilactones are highly bioavailable when administered orally. The elimination half-lives of the terpene trilactones after oral administration are between 3 and 10 hours. For ginkgolide B, a dosage of 40 mg twice daily resulted in a higher area under the curve, and a longer half-life and residence time, than after a single 80-mg dose. A once daily dose of 80 mg guaranteed a larger maximum concentration peak (T_{max}) that was reached 2 to 3 hours after administration.[68] The pharmacokinetics of terpene trilactones in three different ginkgo preparations in human plasma[69] indicate that ginkgo should be discontinued at least 2 weeks before surgery to avoid bleeding.[40]

GINSENG

Among the several species of ginseng used for their pharmacologic effects, Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*) are the most commonly described.[70] Ginseng has been labeled an "adaptogen" because it reputedly protects the body against stress and restores homeostasis.[71] Because its pharmacologic actions are attributed to the ginsenosides, a group of compounds known as *steroidal saponins,* many commercially available ginseng preparations have been standardized to ginsenoside content.[70,72]

The many heterogeneous and sometimes opposing effects of different ginsenosides[73,74] give ginseng a broad but incompletely understood pharmacologic profile including general health, fatigue, immune function, cancer, cardiovascular disease, diabetes mellitus, cognitive function, viral infections, sexual function, and athletic performance.[71] The underlying mechanism is similar to that classically described for steroid hormones. This herb decreases postprandial blood glucose in healthy patients and those with type 2 diabetes,[75] an effect that can create unintended hypoglycemia in patients who have fasted before surgery.

Ginseng can alter coagulation pathways. The antiplatelet activity of panaxynol, a constituent of ginseng, may be irreversible in humans.[76] Ginseng extract and ginsenosides inhibit platelet aggregation in vitro[77,78] and prolong thrombin time and activated partial thromboplastin time in in vivo animal models.[79,80]

The clinical evidence implicating ginseng as a cause of bleeding is weak and based on only a few case reports.[81] Although ginseng may inhibit the coagulation cascade, in one case its use was associated with a significant decrease in warfarin anticoagulation.[82] Subsequently, a study in volunteers showed that American ginseng interfered with warfarin-induced anticoagulation,[83] reducing its anticoagulant effect. When prescribing warfarin, clinicians should specifically ask about ginseng use. In another clinical trial, warfarin's clearance was moderately increased with Asian ginseng.[84] Because warfarin is often used after orthopedic or vascular procedures, this herbal drug interaction can affect perioperative management in many patients.

In rats, after an intravenous infusion of ginseng, ginsenosides Re and Rg1 were eliminated quickly from the body with elimination half-lives between 0.7 and 4 hours; ginsenosides Rb1 and Rd were eliminated slowly from the body with half-lives between 19 and 22 hours.[85] After oral administration of ginseng, ginsenoside Rb1 reached the maximum plasma concentration at approximately 4 hours with a prolonged half-life.[86,87] These data suggest that ginseng should be discontinued at least 48 hours before surgery. Because platelet inhibition by ginseng may be irreversible, ginseng use should be stopped at least 2 weeks before surgery.[40]

GREEN TEA

Tea from the *Camellia sinensis* is one of the most ancient and the second most widely consumed beverage in the world.[88,89] Tea can be classified into three types: green, oolong, and black. Green tea, which is not fermented and is derived directly from drying and steaming fresh tea leaves, contains polyphenolic compounds. Catechins in green tea account for 16% to 30% of its dry weight. Epigallocatechin-3-gallate (EGCG), the most predominant catechin in green tea, is responsible for much of the biological activity mediated by green tea.[88]

In an early in vitro and in vivo study, both green tea and EGCG significantly prolonged mouse tail bleeding time in conscious mice. They inhibited adenosine diphosphate- and collagen-induced rat platelet aggregation in a dose-dependent manner.[90] The antiplatelet activity can result from the inhibition of thromboxane A2 formation. Because adenosine triphosphate release from a dense granule is inhibited by catechins in washed platelets, thromboxane A2 formation may have been inhibited by preventing arachidonic acid liberation and thromboxane A2 synthase.[91,92] Regarding a possible adverse effect of green tea on platelets, one case report showed that after a patient consumed a weight-loss product containing green tea, thrombotic thrombocytopenic purpura developed.[93] Because green tea contains vitamin K, drinking green tea could antagonize the anticoagulant effects of warfarin.[94]

In a randomized, double-blind, placebo-controlled study, eight subjects received oral EGCG in a single dose of 50 to 1600 mg. In each dosage group, the kinetic profile revealed rapid absorption with a one-peak plasma concentration versus time course, followed by a multiphasic decrease consisting of a distribution phase and an elimination phase. The mean half-life values were observed between 1.9 and 4.6 hours.[95] In another pilot clinical study, after five healthy subjects took tea extract orally, the concentration of EGCG in plasma was determined. The half-life of EGCG was between 2.2 and 3.4 hours.[96] Based on pharmacokinetic data and possible antiplatelet activity, green tea should be discontinued at least 7 days before surgery.

KAVA

Kava is derived from the dried root of the pepper plant *Piper methysticum*. Kava has gained widespread popularity as an anxiolytic and sedative. The kavalactones appear to be the source of kava's pharmacologic activity.[97]

Because of its psychomotor effects, kava was one of the first herbal medications expected to interact with anesthetics. The kavalactones have dose-dependent effects on the central nervous system, including antiepileptic, neuroprotective, and local anesthetic properties. Kava can act as a sedative-hypnotic by potentiating inhibitory neurotransmission of γ-aminobutyric acid (GABA). The kavalactones increased barbiturate sleep time in laboratory animals.[98] This effect might explain the mechanism underlying the report of a coma attributed to an alprazolam-kava interaction.[99] Although kava has abuse potential, whether long-term use can result in addiction, tolerance, and acute withdrawal after abstinence is not known. Continuous kava use can increase γ-glutamyl transpeptidase levels, thus raising concern about hepatotoxicity.[100] With continuous use, kava produces "kava dermopathy," characterized by reversible scaly cutaneous eruptions.[101] Continuous kava use can elevate γ-glutamyl transpeptidase levels, raising concerns about hepatotoxicity.[100]

Kava use can influence coagulation and cardiovascular and hepatic functions. In an in vitro investigation, a kava compound (+)-kavain suppressed the aggregation of human platelets.[102] Kava inhibits cyclooxygenase with the potential to decrease renal blood flow and to interfere with platelet aggregation. Consumption of kava has potential cardiovascular effects that could manifest in the perioperative period.[103] The hepatotoxic effect is clinically important. Although kava has been banned in Europe since 2002, it is available in North America and many countries in the Pacific region. A concentration-based response relationship can occur with hepatotoxicity.[104] Despite safety concerns regarding liver toxicity,[105,106] even leading to numerous cases of liver transplantation, kava is still available in the United States.

Peak plasma levels occur 1.8 hours after an oral dose, and the elimination half-life of kavalactones is 9 hours.[107] Unchanged kavalactones and their metabolites undergo renal and fecal elimination.[108] Pharmacokinetic data and the possibility for enhancement of the sedative effects from anesthetics suggest that kava should be discontinued at least 24 hours before surgery. Earlier discontinuation probably should be considered when surgical procedures are expected to compromise hepatic function or blood flow.

SAW PALMETTO

Saw palmetto, which is used by more than 2 million men in the United States to treat symptoms associated with benign prostatic hypertrophy, is of questionable efficacy for this purpose.[109] The major constituents of saw palmetto are fatty acids and their glycerides (i.e., triacylglycerides and monoacylglycerides), carbohydrates, steroids, flavonoids, resin, pigment, tannin, and volatile oil. The pharmacologic activity of saw palmetto has not been attributed to a single compound.

Although the mechanism of action of saw palmetto is not known, multiple mechanisms have been proposed.[110] Saw palmetto extract, like finasteride, inhibits 5α-reductase in vitro; however, results of in vivo studies have been inconsistent.[110] Other proposed mechanisms are inhibition of estrogen and androgen receptors, binding of autonomic receptors, blocking of prolactin receptor signal transduction, interference with fibroblast proliferation, induction of apoptosis, inhibition of α_1-adrenergic receptors, and antiinflammatory effects.

In a patient undergoing craniotomy, saw palmetto was associated with excessive intraoperative bleeding that required termination of the procedure (see Chapter 70).[111] Another case of hematuria and coagulopathy in a patient who used saw palmetto was reported.[112] This complication was attributed to saw palmetto's antiinflammatory effects, specifically the inhibition of cyclooxygenase and subsequent platelet dysfunction. Because there are no pharmacokinetic or clinical data for saw palmetto, specific recommendations for preoperative discontinuation cannot be made.

ST. JOHN'S WORT

St. John's wort is the common name for *Hypericum perforatum*. A multicenter clinical trial concluded that St. John's wort is not effective in the treatment of major depression.[113] The compounds believed to be responsible for its pharmacologic activity are hypericin and hyperforin.[114] Commercial preparations are often standardized to a fixed hypericin content of 0.3%.

St. John's wort exerts its effects by inhibiting reuptake of serotonin, norepinephrine, and dopamine.[115] Concomitant use of this herb with or without serotonin reuptake inhibitors can create a syndrome of central serotonin excess.[116] Although early in vitro data implicated monoamine oxidase inhibition as a possible mechanism of action, a number of later investigations have demonstrated that monoamine oxidase inhibition is insignificant in vivo.[117]

Use of St. John's wort can significantly increase the metabolism of many concomitantly administered drugs, some of which are vital to the perioperative care of certain patients. There is induction of the cytochrome P450 3A4 isoform, with approximate doubling of its metabolic activity.[118] Interactions with substrates of the 3A4 isoform, including indinavir sulfate,[119] ethinylestradiol,[120] and cyclosporine,[121] have been documented. There are important clinical consequences of this metabolic effect, particularly in transplant patients. In two case reports of heart transplant patients, after taking St. John's wort, the patients' plasma cyclosporine concentrations became subtherapeutic and acute transplant rejection resulted. After stopping St. John's wort, plasma cyclosporine remained within the therapeutic range with no further episodes of rejection (Fig. 40-1).[122] In one series of 45 organ transplant patients, St. John's wort was associated with an average 49% decrease in blood cyclosporine levels.[123] Other P450 3A4 substrates commonly used in the perioperative period include alfentanil, midazolam, lidocaine, calcium channel

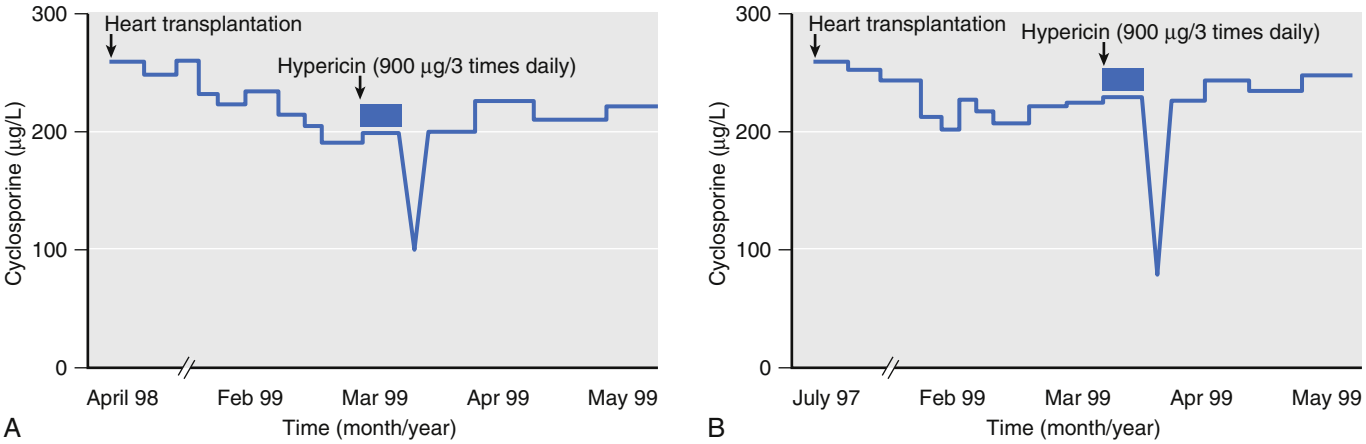


Figure 40-1. Cyclosporine concentrations in two patients (**A** and **B**) after heart transplantation. Treatment with St. John's wort extract containing 900 µg of hypericin was associated with a drop in cyclosporine values below the therapeutic range and acute transplant rejection.[122]

blockers, and 5-hydroxytryptamine receptor antagonists. In addition to the 3A4 isoform, the cytochrome P450 2C9 isoform also may be induced. The anticoagulant effect of warfarin, a substrate of the 2C9 isoform, was reduced in seven reported cases.[120] Other 2C9 substrates include the nonsteroidal antiinflammatory drugs. Furthermore, the enzyme induction caused by St. John's wort may be more pronounced when other enzyme inducers, which could include other herbal medications, are taken concomitantly. St. John's wort also affects digoxin pharmacokinetics.[117] St. John's wort markedly altered the intracellular accumulation of irinotecan and its major metabolite SN-38 in hepatocytes and glucuronidation of SN-38 in rats.[124]

The single-dose and steady-state pharmacokinetics of hypericin, pseudohypericin, and hyperforin have been determined in humans.[125,126] After oral administration, peak plasma levels of hypericin and hyperforin are achieved in 6.0 and 3.5 hours, respectively, and their median elimination half-lives are 43.1 and 9.0 hours, respectively. Long half-life and altered metabolism of many drugs make concomitant use of St. John's wort a particular risk in the perioperative setting. Pharmacokinetic data suggest that this herbal medication should be discontinued at least 5 days before surgery. Discontinuation is especially important in patients awaiting organ transplantation or in those who might require oral anticoagulation postoperatively. Moreover, these patients should be advised to avoid taking St. John's wort postoperatively.

VALERIAN

Valerian (*Valeriana officinalis*) is an herb that is native to temperate regions of the Americas, Europe, and Asia. It is used as a sedative, particularly in the treatment of insomnia, and virtually all herbal sleep aids contain valerian.[127] Valerian contains many compounds acting synergistically, but the sesquiterpenes are the primary source of valerian's pharmacologic effects. Commercially available preparations may be standardized to valerenic acid.

Valerian produces dose-dependent sedation and hypnosis.[128] These effects are probably mediated through modulation of GABA neurotransmission and receptor function.[129] Valerian increased barbiturate sleep time in experimental animals.[130] In several randomized, placebo-controlled trials in humans, there was a mild subjective improvement in sleep with valerian, especially when used for 2 weeks or more.[131,132] Objective tests have had less consistent results, with little or no improvement in sleep noted.[133] In one patient, valerian withdrawal appeared to mimic an acute benzodiazepine withdrawal syndrome characterized by delirium, cardiac complications after surgery, and attenuation of the symptoms by administration of a benzodiazepine.[134] Based on these findings, valerian should potentiate the sedative effects of anesthetics and adjuvants that act at the GABA receptor, such as midazolam (see Chapter 30).

The pharmacokinetics of valerian's constituents have not been studied, although their effects may be short-lived. Abrupt discontinuation in patients who may be physically dependent on valerian risks benzodiazepine-like withdrawal. In these individuals, this herbal medication should be gradually decreased with close medical supervision over the course of several weeks before surgery. If such tapering is not feasible, physicians can advise patients to continue taking valerian until the day of surgery. Based on the mechanism of action and a reported case of efficacy,[134] benzodiazepines can treat withdrawal symptoms should they develop in the postoperative period.

OTHER HERBAL MEDICINES

In a survey conducted in 2007,[1] the top 10 herbal medicines also included soy isoflavones, grape seed extract, and milk thistle. There are no reports of adverse effects or perioperative risks from these herbs.

Although boldo (*Peumus boldus*), Danshen (*Salvia miltiorrhiza*), Dong quai (*Angelica sinensis*), and papaya (*Carica papaya*) are encountered less frequently, it may be prudent to discontinue their use 2 weeks before surgery because they have shown antiplatelet aggregation activity and herb-drug interactions.[135]

COMMON DIETARY SUPPLEMENTS

Herbal medicines fall into the broader category of dietary supplements that also includes vitamins, minerals, amino

acids, enzymes, and animal extracts. Data on the safety of these agents in the perioperative period are scant. High-dose vitamin use, particularly of the fat-soluble vitamins (i.e., A, D, E, and K), can be associated with acute and chronic toxicity. Drug interactions for coenzyme Q_{10}, glucosamine, chondroitin, sulphate, and fish oil have been sufficiently documented to merit inclusion in this chapter.

COENZYME Q_{10}

Coenzyme Q_{10} (CoQ_{10}), or ubidecarenone, is a single-constituent antioxidant compound that is structurally related to vitamin K. It is widely promoted as an antioxidant. Endogenous CoQ_{10} can prevent the membrane transition pore from opening, because it counteracts several apoptotic events, such as DNA fragmentation, cytochrome c release, and membrane potential depolarization.[52] Of importance, this compound interacts with warfarin.

Interaction between CoQ_{10} and warfarin was investigated in rats.[136] Following oral administration of 1.5 mg/kg of racemic warfarin to rats during an 8-day oral regimen of CoQ_{10} (10 mg/kg daily), no apparent effect was observed on serum protein binding of warfarin enantiomers. Treatment with CoQ_{10} did not affect the absorption and distribution of the S- and R-enantiomers of warfarin, but it increased total serum clearance of both R- and S-warfarin. The increased clearance values are likely due to acceleration of certain metabolic pathways and renal excretion of the warfarin enantiomers.

An in vitro study using human liver microsomes led to a relatively accurate pharmacokinetic prediction of CoQ_{10} activity. A 32% and 17% increase in the total clearance of S- and R-warfarin, respectively, was predicted with coadministration of 100 mg CoQ_{10}.[137] CoQ_{10} may decrease the effects of warfarin,[138] but results were inconsistent in another controlled, clinical trial.[139] In 171 patients, coadministration of CoQ_{10} with warfarin appeared to increase the risk of bleeding.[140] Based on the clinical information regarding drug interaction and reported prolonged elimination half-life (38 to 92 hours) after a single oral dose,[141] CoQ_{10} should be discontinued at least 2 weeks before surgery.

GLUCOSAMINE AND CHONDROITIN SULFATE

Glucosamine and chondroitin sulfate are widely used for joint disorders by many patients undergoing orthopedic procedures. Standard therapies can alleviate the symptoms of osteoarthritis (OA) to some extent, but cannot prevent disease progression. A number of alternative substances are beneficial for OA. Although their mode of action may be complex, glucosamine and chondroitin sulfate have been widely accepted as supplements in the management of OA because they are the essential components of proteoglycan in normal cartilage.[142] When a large-scale trial evaluated glucosamine and chondroitin sulfate alone or in combination, pain was not reduced in a group of patients with OA of the knee. Exploratory analyses suggested that the two in combination might be effective in a subgroup of patients with moderate-to-severe knee pain.[143]

Long-term clinical data regarding the safety of glucosamine and chondroitin sulfate alone or in combination are limited. Use of chondroitin sulfate alone is well tolerated and without significant adverse drug interaction.[142] One concern regarding the use of glucosamine is its potential to cause or worsen diabetes in animal models[144]; this effect is supported by clinical studies.[145] However, in a report from the FDA MedWatch database, there were 20 cases of complications involving glucosamine or glucosamine-chondroitin sulfate use with warfarin. Coagulation was altered as manifested by increased INR or increased bleeding or bruising.[146]

When glucosamine is taken orally, 90% is absorbed. Because of extensive first-pass metabolism, only 25% bioavailability is achieved by oral administration compared with bioactivity of 96% with intravenous administration.[147] Peak plasma levels occurred 4 hours after an oral dose and declined to baseline after about 48 hours.[148] Chondroitin sulfate was absorbed slowly after oral ingestion with a plasma peak at 8.7 hours and decline to baseline at about 24 hours.[149] Considering the reported interaction between glucosamine-chondroitin and warfarin, these supplements should be discontinued 2 weeks before surgery, especially if warfarin will be given during the perioperative period.

FISH OIL

Intake of fish oil supplements containing omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) reduces the incidence of many chronic diseases that involve inflammatory processes, including cardiovascular diseases, inflammatory bowel disease, cancer, rheumatoid arthritis, and neurodegenerative illnesses.[150] In a recent study, however, omega-3 did not reduce the rate of death in patients with cardiovascular risk factors.[151] A recent meta-analysis of efficacy concluded that omega-3 polyunsaturated fatty acid (PUFA) supplementation does not decrease the risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke based on relative and absolute measures of association[152] This article included many studies of patients with complex risk factors.

Omega-3 fatty acids, however, can inhibit platelet aggregation and increase bleeding risk. In vitro experiments have demonstrated an antiplatelet aggregate effect of omega-3 fatty acids,[153] and inhibition correlated with platelet cyclic adenosine monophosphate levels.[154] In vivo studies show that omega-3 fatty acids decrease platelet aggregation but do not influence bleeding time.[155,156] In a clinical study, the inhibition of platelet aggregation by omega-3 fatty acid was gender specific.[157]

Although evidence for significant bleeding concerns is not found in clinical trials,[158,159] several case reports have illustrated a possible interaction between warfarin and omega-3 fatty acids.[160] Extremely elevated INR associated with warfarin in combination with omega-3 fatty acids was found in two cases.[161,162] These reports suggest that fish oil be discontinued 2 weeks before surgery, especially for patients taking large doses.

OTHER DIETARY SUPPLEMENTS

Other top 10 dietary supplements include flaxseed oil, fiber or psyllium, cranberry, melatonin,

methylsulfonylmethane (MSM), and lutein.[1] No special concerns have been published associated with bleeding or other perioperative risks from the use of these supplements.

SUMMARY

Commonly used herbal medications can have direct and indirect effects in the perioperative period. Although there is little direct evidence for discontinuation timing, emerging knowledge of the underlying biology of these medications and review of case reports suggest that herbal medications should be considered in the perioperative plan.

ACUPUNCTURE

MECHANISM AND GENERAL PRACTICE

Although acupuncture can reduce preoperative anxiolysis, intraoperative anesthetic requirements, postoperative ileus and support cardiovascular function, it has been most widely studied to control postoperative pain and to prevent or treat nausea and vomiting (see Chapter 97).[163]

Acupuncture is the stimulation of anatomic locations on the skin by a variety of techniques that can be classified as invasive (e.g., needles, injections) or noninvasive (e.g., transcutaneous electrical stimulation, pressure, laser). Needles inserted into the skin can be stimulated by manual manipulation, moxibustion (i.e., burning a substance to produce heat), pressure, laser, and electricity. There are Chinese, Japanese, Korean, French, and other acupuncture systems for identifying acupuncture points, but little research has compared these different systems. As a result, there are no standard or optimal acupuncture points. Practitioners consider acupuncture an art as much as a science.

The traditional theory of acupuncture is that it corrects disruptions in the flow of energy (i.e., qi) and restores the balance of dual forces (i.e., ying-yang) in the body. A scientific basis may exist for acupuncture. Acupuncture stimulates high-threshold, small-diameter nerves that activate the spinal cord, brainstem (i.e., periaqueductal gray area), and hypothalamic (i.e., arcuate) neurons, which trigger endogenous opioid mechanisms.[164] The effect of acupuncture analgesia can be reversed by administration of naloxone.[165] Other mechanisms such as modulation of immune function,[166] inhibition of the inflammatory response,[167] regulation of neuropeptide gene expression,[168] and alteration in hormonal levels[169] have been proposed. The development of neuroimaging tools, such as positron emission tomography[170] and functional magnetic resonance imaging (fMRI),[171,172] make noninvasive studies of acupuncture's effects on human brain activity possible. Studies using positron emission tomography have demonstrated that the thalamic asymmetry present in patients suffering from chronic pain was reduced after acupuncture treatment. Other studies using fMRI have pointed to relationships between particular acupoints and activation of the visual cortex.[173]

Many of the clinical acupuncture studies that have been published are of poor quality and suffer from insufficient sample size, high dropout rates, inadequate follow-up, and poorly defined illnesses, enrollment criteria, and outcome measures.[164] Acupuncture studies suffer from inherent methodologic problems, including difficulties in blinding patients and acupuncturists, using placebo or sham acupuncture, and choosing between different acupuncture techniques.

Although acupuncture was used clinically for centuries, the first trial of acupuncture for anesthesia was performed in China around 1960. Because anesthesia produced by acupuncture varies and takes too long to induce,[174] acupuncture has been used rarely as anesthesia for surgery[175] and more for pain relief afterward. Since 1970, clinical studies have been conducted on acupuncture for postoperative pain,[176] lower back pain,[177] osteoarthritis of the knee,[178] chronic headache,[179] shoulder pain,[180] and neck pain.[181] When compared with placebo, acupuncture treatment has proven efficacy for relieving pain.[182]

A review article that evaluated nine clinical trials found that auricular acupuncture to reduce postoperative pain was promising but not compelling.[183] Another review of six articles discussed the effect of acupuncture on postoperative pain.[182] Although early trials showed both equivocal[184] and negative results,[185] a later trial demonstrated short-term analgesia after acupuncture in patients who had oral surgery.[186] Such efficacy was supported by another clinical trial in 100 patients; the total amount of morphine required to control pain was significantly less in patients who received preoperative acupuncture than in patients in the control group.[176] The trial also demonstrated that acupuncture and electrical nerve stimulation at specific acupoints are valid for postoperative analgesia, and electrical stimulation increases the effect of acupuncture anesthesia.

ACUPUNCTURE FOR POSTOPERATIVE NAUSEA AND VOMITING

One of the most promising indications for acupuncture is to prevent postoperative nausea and vomiting (PONV; see Chapter 97). PONV results in patient dissatisfaction, delayed discharge, unanticipated hospital admission, and the use of resources. Drugs, the mainstay of management, have limited effectiveness, are associated with adverse effects, and can be costly. Acupuncture prevents PONV compared with placebo (e.g., sham acupuncture, no treatment).[163] In two early controlled trials, acupuncture prevented PONV in the pediatric population[187,188]; however, one review of 10 research studies of acupressure in adults concluded that it is not effective in preventing and managing PONV.[189] Other clinical studies have found that acupuncture prevents PONV and results in a greater degree of adult patient satisfaction.[190,191] For many of the trials in both adults and children, the PONV acupuncture point was P6 (i.e., Nei-guan or pericardium-6).[189,192] Intraoperative stimulation of the P6 acupuncture point reduced the incidence of PONV, and its efficacy was similar to that of antiemetic drugs.[193]

The P6 (i.e., Nei-guan or pericardium-6) acupuncture point is located between the palmaris longus and flexor

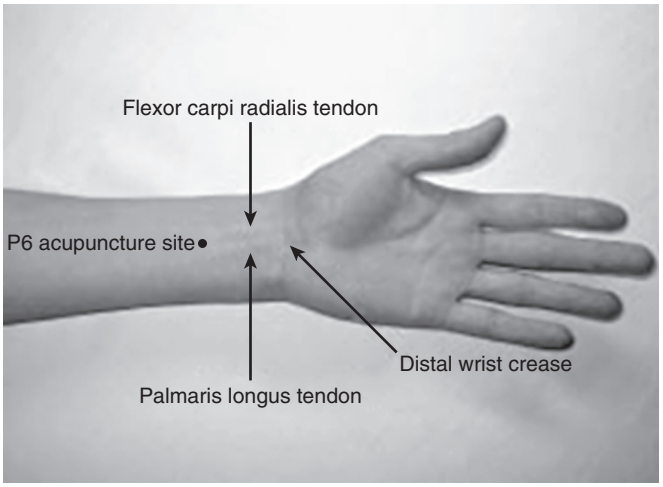


Figure 40-2. The P6 acupuncture point is located between the palmaris longus and flexor carpi radialis muscle tendons, 4 cm proximal to the distal wrist crease and 1 cm below the skin.

carpi radialis muscle tendons, 4 cm proximal to the distal wrist crease and 1 cm below the skin (Fig. 40-2). Korean hand acupuncture may be equally effective.[194] Studies often differ in acupuncture method: duration and timing of stimulation, unilateral versus bilateral stimulation, and type of stimulation (i.e., needles with or without additional stimulation, acupressure, transcutaneous electrical stimulation, cutaneous laser stimulation, injection of a 50% dextrose solution, or capsicum plaster). Data to compare the effectiveness, safety, and costs of different methods of stimulation are inadequate. Stimulation of the acupuncture point should be initiated before induction of anesthesia.[195] Postoperative stimulation may be just as or more effective.[196] In children, stimulation immediately before emergence and in the recovery room has been effective. Some anesthesiologists anecdotally report tapping a small needle cap or other piece of smooth plastic over the P6 point as an effective means of acupressure stimulation.

DEEP BREATHING

Deep breathing exercises are performed as part of a relaxation technique. With this method, a subject consciously slows breathing and focuses on taking deep breaths.[197] Deep breathing can help reduce abdominal and surgical pain.[198,199]

Studies of postoperative pain relief with breath control were reported in the 1970s.[200,201] Its efficacy against postoperative pain was reported by subsequent controlled trials in adult patients.[198,202] This intervention prevented postoperative pulmonary complications in patients who had upper abdominal surgery.[203] In a study of 50 children from 3 to 7 years of age who underwent dental treatment, deep breathing and exhalation decreased pain during treatment[199] (see Chapters 92 and 93).

Fast or forced deep breathing can also increase postoperative pain.[204] Thus, those who assist patients in postoperative pain management should encourage deep breathing exercises that are performed slowly, smoothly, and gently. Slow, deep breathing relaxation exercises have been used successfully as an adjunct to opioids for postoperative pain management in patients who had coronary bypass surgery;[205] however, after abdominal surgery, deep breathing was ineffective for pain reduction in older patients because pulmonary complications developed postoperatively.[206] Most patients who receive deep breathing education think it is useful, and the exercise was effective in increasing their feelings of rapport with staff and intention to follow their doctor's directives.[207] Results from a recent trial demonstrated that slow, deep breathing had analgesic effects with increased vagal cardiac activity.[208] Slow, deep breathing relaxation can also decrease the sensation of postoperative nausea.[209,210]

MUSIC THERAPY

Music therapy is the clinical, evidence-based use of music interventions to accomplish individualized therapeutic goals. Because music can be used for diverse applications, music therapists practice in a variety of health care and education settings.[211] Music for pain relief benefits individuals experiencing a low to moderate amount of pain more than those experiencing a high degree of pain.[212] A patient's preferred music should be considered when it is used for pain relief. The increase of endogenous opioids through music may be the reason for pain relief.[211]

Perioperatively, music can decrease preoperative anxiety, reduce intraoperative sedative and analgesic requirements, and increase patient satisfaction. Patient-selected music can reduce patient-controlled sedative requirements during spinal anesthesia and analgesic requirements during lithotripsy.[213] Music in the preoperative setting can reduce anxiety without affecting physiologic measures of stress.[214,215] Music can also increase patient satisfaction and reduce systolic blood pressure during cataract surgery after retrobulbar block.[216] Perioperative music can reduce arterial pressure, anxiety, and pain among women undergoing mastectomy for breast cancer.[217] As a noninvasive intervention, the low sensory stimulation of music reduced anxiety and increased cooperation in children undergoing induction of anesthesia.[218]

Music therapy interventions that have targeted nausea, both anticipatory or after treatment, have had conflicting results.[211] One study showed that a patient's preferred music for listening during chemotherapy infusion was effective in decreasing the onset and occasion of nausea.[219] In another study, listening to music with a personal message from the physician yielded no difference in chemotherapy-induced side effects compared with not listening to music during chemotherapy.[220] Some studies have found no effect on PONV from music therapy,[221,222] yet PONV was reduced in hospitalized transplant patients postoperatively.[223] Although the exact mechanism is not well understood, music therapy has been an alternative option to mainstream therapies in health care settings to reduce patient pain, anxiety, and perioperative stress.[224] Another use of music is in the intensive care unit. A recent clinical trial observed that among patients in the intensive care unit who received acute ventilatory support for respiratory failure, patient-directed music intervention resulted in more reduction in anxiety and sedation

TABLE 40-2 **PRINTED AND WORLD WIDE WEB SOURCES OF HERBAL MEDICINE INFORMATION**

Source	Comments
Physicians' Desk Reference for Herbal Medicines	
Encyclopedia of Dietary Supplements	
Commission E Monographs	
Textbook of Complementary and Alternative Medicine	
Center for Food Safety and Applied Nutrition, Food and Drug Administration: http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135675.htm	Clinicians should use this site to report adverse events associated with herbal medicines and other dietary supplements. Sections also contain safety, industry, and regulatory information
National Center for Complementary and Alternative Medicine, National Institutes of Health: http://nccam.nih.gov/	This site contains fact sheets about alternative therapies, consensus reports, and databases
Agricultural Research Service, U.S. Department of Agriculture: http://www.ars-grin.gov/duke	The site contains an extensive phytochemical database with search capabilities
Quackwatch: http://www.quackwatch.com	Although this site addresses all aspects of health care, there is a considerable amount of information covering complementary and herbal therapies
National Council Against Health Fraud: http://www.ncahf.org	This site focuses on health fraud with a position paper on over-the-counter herbal remedies
HerbMed: http://www.herbmed.org	This site contains information on numerous herbal medications, with evidence for activity, warnings, preparations, mixtures, and mechanisms of action. There are short summaries of important research publications with Medline links.
ConsumerLab: http://www.consumerlab.com	This site is maintained by a corporation that conducts independent laboratory investigations of dietary supplements and other health products

frequency and intensity compared with usual care.[225] In addition, music can attenuate cardiovascular variability and nociceptive effects.[226,227]

CONCLUSION

One of the fastest changing aspects of health care is the growing public and scientific interest in CAM. To manage herbal medications in the perioperative period, their possible direct and indirect effects should be recognized based on an understanding of the underlying pharmacology. Surgery and anesthesia can usually proceed safely if potential complications are anticipated and can be minimized. As CAM therapies generally gain popularity in the United States, patients are likely to accept some alternative modalities such as acupuncture, deep breathing, and musical intervention. These modalities are easy to administer, have a rapid onset of action, are cost effective, and produce minimal side effects. Based on preliminary studies, perioperative use of CAM therapies may be an adjunct for management of pain, anxiety, nausea, and vomiting. Additional large, well-designed trials are required to verify current observations on the effectiveness of CAM and to answer the concerns of possible side effects. Although medical schools are beginning to incorporate CAM into their curricula, it is important for anesthesiologists already in practice to stay informed about CAM therapies (Table 40-2).

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Chapter 41

Patient Positioning and Associated Risks

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Key Points

- Patient positioning is a major responsibility that requires the cooperation of the entire surgical team. A compromise between optimal surgical positioning and patient well-being is sometimes required.
- Many patient positions that are used for surgery result in undesirable physiologic consequences including significant cardiovascular and respiratory compromise. Anesthetic agents blunt natural compensatory mechanisms, rendering surgical patients vulnerable to positional changes.
- Peripheral nerve injuries, although rare, represent 22% of cases in the 1990-2007 American Society of Anesthesiologists (ASA) Closed Claims Project, second only to death.[1] The mechanisms of injury are stretching, compression, and ischemia. Longer procedures are a risk factor. Patient positioning is often suspected, although many times precautions have been taken and no specific cause for the injury is known.
- Brachial plexus injuries have become the most common postoperative nerve injury associated with general anesthesia in more recent closed claims data, followed by injuries to the ulnar nerve, spinal cord, and lumbosacral nerve roots.[2]
- Not all postoperative neuropathies, including ulnar neuropathy, are currently explainable and may not be entirely preventable. Many postoperative ulnar nerve deficits may not be related to intraoperative patient positioning since they appear days after surgery.
- The ASA issued a Practice Advisory in 2000 for the prevention of perioperative peripheral neuropathies that was updated in 2011. However, very few of the studies reviewed met the standard for a scientifically proven relationship between intervention and outcome.
- Postoperative visual loss is a rare but devastating complication that is associated with the prone position. It has multifactorial causes and is incompletely understood.
- Anesthetics administered outside the classic surgical unit present special challenges with regard to patient positioning because of monitoring and equipment limitations and differences in the work environment and culture.

INTRODUCTION

Positioning of patients in the operating room is a critical responsibility that requires the cooperation of the entire surgical team. Positions deemed optimal for surgery often result in undesirable physiologic changes such as hypotension from impaired venous return to the heart or oxygen desaturation as a result of ventilation-perfusion mismatching. In addition, peripheral nerve injuries during surgery remain a significant source of perioperative morbidity.[1-4] The surgeon primarily dictates the desired position; however, to maximize patient well-being and safety, anesthesiologists, surgeons, and intraoperative nurses must work together to achieve the *optimal* patient position. Vigilance regarding potential risks of position-related injuries involves foresight and monitoring, although all injuries may not be preventable.

Whenever possible, the patient's position during anesthesia care should be natural—one that would be well tolerated if the patient were awake and unsedated. Because optimal surgical exposure may require unusual positioning of the body and positions may be maintained for

long periods, preventing complications requires clinical judgment and, at times, compromise. Jewelry and hair ornaments are removed. Weight-bearing surfaces of the extremities and joints are well padded, and the curvatures of the body, including the lumbar spine, are supported. The head should ideally remain midline without substantial extension or flexion. The eyes are kept closed without external pressure. When more extreme positions cannot be avoided, their duration should be limited as much as possible. The need for tilting the surgical table during surgery should be anticipated and rehearsed before draping, and the patient should be secured accordingly. The use of safety straps and the prevention of falls from the surgical table to the floor are fundamental.

CARDIOVASCULAR CONCERNS

Complex arterial, venous, and cardiac physiologic responses have evolved to blunt the effects of positional changes on arterial blood pressure and to maintain perfusion to vital organs. Central, regional, and local mechanisms are involved. These mechanisms are particularly important for animals such as humans who maintain an upright posture, because of the vertical distance from the heart to the brain and its need for constant perfusion.

Normally, as a person reclines from an erect to a supine position, venous return to the heart increases as pooled blood from the lower extremities redistributes toward the heart. Preload, stroke volume, and cardiac output are augmented. The resultant increase in arterial blood pressure activates afferent baroreceptors from the aorta (via the vagus nerve) and within the walls of the carotid sinuses (via the glossopharyngeal nerve) to decrease sympathetic outflow and to increase parasympathetic impulses to the sinoatrial node and myocardium. The result is a compensatory decrease in heart rate and, ultimately, cardiac output. Mechanoreceptors from the atria and ventricles are also activated to decrease sympathetic outflow to muscle and splanchnic vascular beds. Lastly, atrial reflexes are activated to regulate renal sympathetic nerve activity, plasma renin, atrial natriuretic peptide, and arginine vasopressin levels.[5] As a result, during postural changes without anesthesia, systemic arterial blood pressure is normally maintained within a narrow range.

General anesthesia, muscle relaxation (paralysis), positive-pressure ventilation, and neuraxial blockade all interfere with the venous return to the heart, arterial tone, and autoregulatory mechanisms. Therefore patients receiving general and major regional anesthesia are particularly vulnerable to poorly compensated circulatory effects of changes in position. Volatile anesthetics for induction and the maintenance of anesthesia decrease venous return and systemic vascular resistance, frequently decreasing arterial blood pressure. Positive-pressure ventilation increases mean intrathoracic pressure, diminishing the venous pressure gradient from peripheral capillaries to the right atrium. Because relatively small pressure gradients are active in the venous circulation, cardiac filling, and, consequently, cardiac output may be adversely affected.[6] Positive end-expiratory pressure (PEEP) further increases mean intrathoracic pressure, as do conditions associated with low lung compliance such as airways disease, obesity, ascites, and light anesthesia (i.e., "fighting the vent"). Venous return and cardiac output may be further compromised.[7] The use of spinal or epidural anesthesia causes a significant sympathectomy across all anesthetized dermatomes, independent of the presence of general anesthesia, reducing preload and potentially blunting cardiac response. The sympathetic output to the heart is often affected even when the sensory blockade does not reach high thoracic levels.

For these reasons, arterial blood pressure is often particularly labile immediately after the start of anesthesia and during patient positioning. The anesthesia provider needs to anticipate, monitor, and treat these effects, as well as assess the safety of positional changes for each patient. Frequent blood pressure measurements should be made after the induction of anesthesia or when the neuraxial blockade is initiated. During this hemodynamic transition, adjustments to the level of anesthesia and administration of additional intravenous fluid or vasopressors may be required. Temporary use of the Trendelenburg head-down position can be helpful. At times, a delay in repositioning the patient for surgery may be necessary until the systemic blood pressure reaches an acceptable level of homeostasis. Interruptions in monitoring to facilitate positioning or turning of the surgical table should be minimized during this dynamic period. Patient positioning is always secondary to patient safety.

In addition, regional oxygen delivery to critical organs such as the brain and optic nerve may be compromised because of positional factors that limit perfusion pressure. Examples include reduced arterial pressure as a result of a position above the heart or increased venous pressure as a result of a position below the heart. In addition, patient positioning may inadvertently compress tissue or blood vessels, increasing the risk for ischemia or compartment syndrome, which is discussed in the section on the lithotomy position later in this chapter.

PULMONARY CONCERNS

Gas exchange depends largely on matching ventilation and perfusion. Anesthetized persons who are spontaneously breathing have a reduced tidal volume and functional residual capacity and an increased closing volume when compared with the nonanesthetized state. Positive-pressure ventilation with muscle relaxation may ameliorate ventilation-perfusion mismatches under general anesthesia by maintaining adequate minute ventilation and limiting atelectasis. However, the diaphragm assumes an abnormal shape because of the loss of muscle tone and is displaced less in the dependent portions of the lung.[8] These physiologic changes decrease ventilation-perfusion matching and, consequently, PaO_2 Patients undergoing neuraxial anesthesia lose abdominal and thoracic muscle function in affected dermatomes. However, diaphragmatic function may be retained if general anesthesia and muscle relaxation are not concurrently administered and if the neuraxial anesthesia is restricted to the lower dermatomes. In addition to these effects of anesthesia,

patient position has distinct effects on pulmonary function. In particular, any position that limits the movement of the diaphragm, chest wall, or abdomen may increase atelectasis and intrapulmonary shunt.

Spontaneous ventilation results from relatively small negative intrathoracic pressure shifts during inspiration because of diaphragmatic displacement and chest wall expansion. This pressure decrease also promotes venous return to the thorax by reducing the pressure in the great veins and right atrium, compared with the periphery. Normal distribution of ventilation is more complex than classically theorized, with factors including the excursion of the diaphragm, compliance of the lung, and the shape and movement of the lung and thorax.[9] When a person shifts from standing to a supine position, functional residual capacity decreases because of the cephalad displacement of the diaphragm. The relative contribution to ventilation of the chest wall, compared with the diaphragm, decreases from 30% to only 10%. With spontaneous ventilation in either position, diaphragmatic movement is greatest adjacent to the most dependent portions of the lung, helping to bring new ventilation to the zones of the lung that are preferentially perfused. Although less than previously thought, gravity affects the preferential perfusion of the dependent portions of the lung. The importance of other factors, such as pulmonary vascular length and the structure of the pulmonary vascular tree, are now increasingly appreciated as a result of newer, high-resolution imaging techniques.[8] Perfusion appears to follow a central-to-peripheral spectrum in each lobe that is maintained with changes in cardiac output.[10-12]

When patients are in the prone position, weight should be distributed to the thoracic cage and bony pelvis, allowing the abdomen to move with respiration as subsequently described. The prone position has been used to improve respiratory function in patients with adult respiratory distress syndrome (ARDS).[13,14] Under anesthesia, the prone position has advantages over the supine position with regard to lung volumes and oxygenation without adverse effects on lung mechanics,[15,16] including patients who are obese[17] (see also Chapter 71) and pediatric patients (see also Chapter 93).[18] Newer investigations using high-resolution imaging have shown the prone position to provide superior ventilation-perfusion matching in the posterior segments of the lung near the diaphragm when compared with the supine position. The aeration and ventilation of these posterior segments are better, while blood flow is maintained, despite their nondependent position.[9]

SPECIFIC POSITIONS

SUPINE

The most common position for surgery is the supine or dorsal decubitus position (Fig. 41-1). Because the entire body is close to the level of the heart, hemodynamic reserve is best maintained. However, because compensatory mechanisms are blunted by anesthesia, even a few degrees of head-down (Trendelenburg) or head-up (reverse Trendelenburg) position (Fig. 41-2) are sufficient to cause significant cardiovascular changes and are frequently used to effect temporary changes in venous return and cardiac output. Steep Trendelenburg and reverse Trendelenburg positions (up to 45 degrees) are used for some surgeries, including lengthy laparoscopic and robotic procedures with pneumoperitoneum. These positions impart associated risks, which are discussed in the section on the Trendelenburg position.

Associated Arm Position

In a supine position, one or both of the patient's arms may be abducted out to the side or adducted (tucked) alongside the body. It is recommended that upper extremity abduction be limited to less than 90 degrees to minimize the likelihood of brachial plexus injury by caudal pressure in the axilla from the head of the humerus.[19,20] The hand and forearm are either supinated or kept in a neutral position with the palm toward the body to reduce external pressure on the spiral groove of the humerus and the ulnar nerve[20-22] (Fig. 41-3). When the arms are adducted, they are usually held alongside

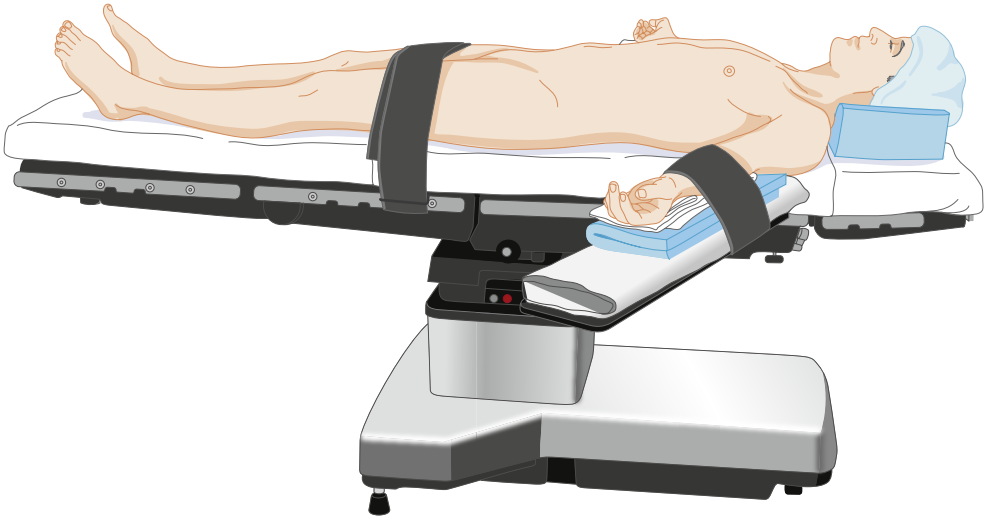


Figure 41-1. Supine position. The base of the table is asymmetrical. When positioned in the usual direction, the patient's center of gravity is over the base. Weight limits decrease when in reverse orientation to the base.

the body with a "draw sheet" that passes under the body, over the arm, and is then tucked directly under the torso (not the mattress) to ensure that the arm remains properly placed next to the body. Alternatively, in surgeries where access to the chest or abdomen is not necessary, curved arm cradles may be used. In all cases, the arms are placed in a neutral position.[20] The elbows and any protruding objects, such as intravenous fluid lines and stopcocks, are padded (Fig. 41-4).

Variations of the Supine Position

Several variations of the supine position are frequently used. The *lawn chair position* in which the hips and knees are slightly flexed (Fig. 41-5) reduces stress on the back, hips, and knees and is better tolerated by patients who are awake or undergoing monitored anesthesia care (see also Chapter 89). In addition, because the legs are slightly above the heart, venous drainage from the lower extremity is facilitated. In addition, the xiphoid-to-pubic distance is decreased, reducing the tension on the ventral abdominal musculature and easing the closure of laparotomy incisions. Proper positioning of the patient's hips at the break of the surgical table, adjusting the table back and leg sections, and using a slight tilt are required to achieve this position. Typically, the back of the bed is raised, the legs below the knees are lowered to an equivalent angle, and a slight Trendelenburg tilt is used to level the hips with the shoulders. These adjustments reduce venous pooling in the legs. The ability

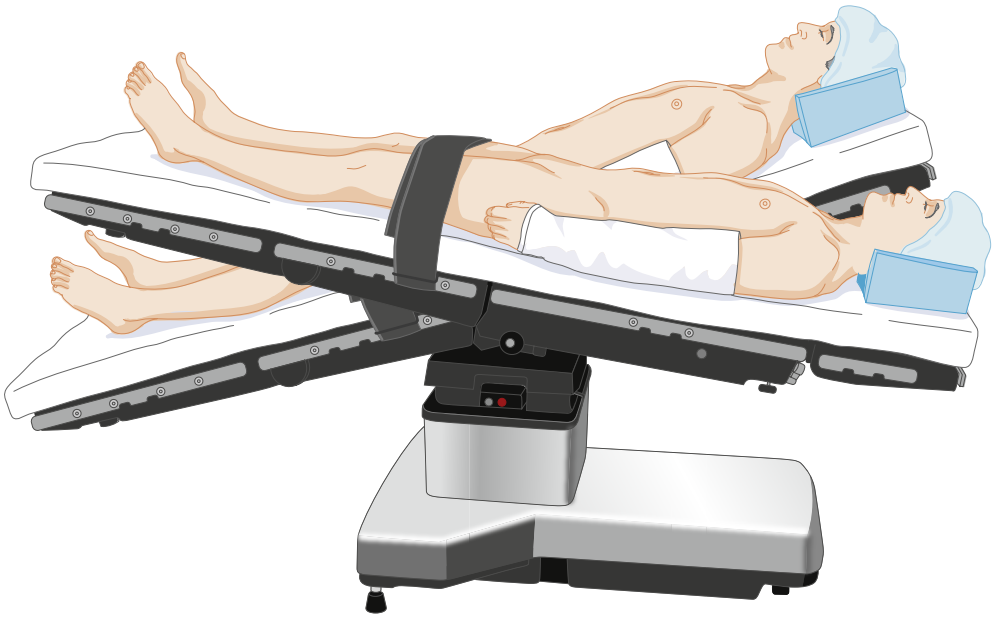


Figure 41-2. Head-down tilt (Trendelenburg) position and head-up tilt (reverse Trendelenburg) position. Shoulder braces should be avoided to prevent brachial plexus compression injuries.

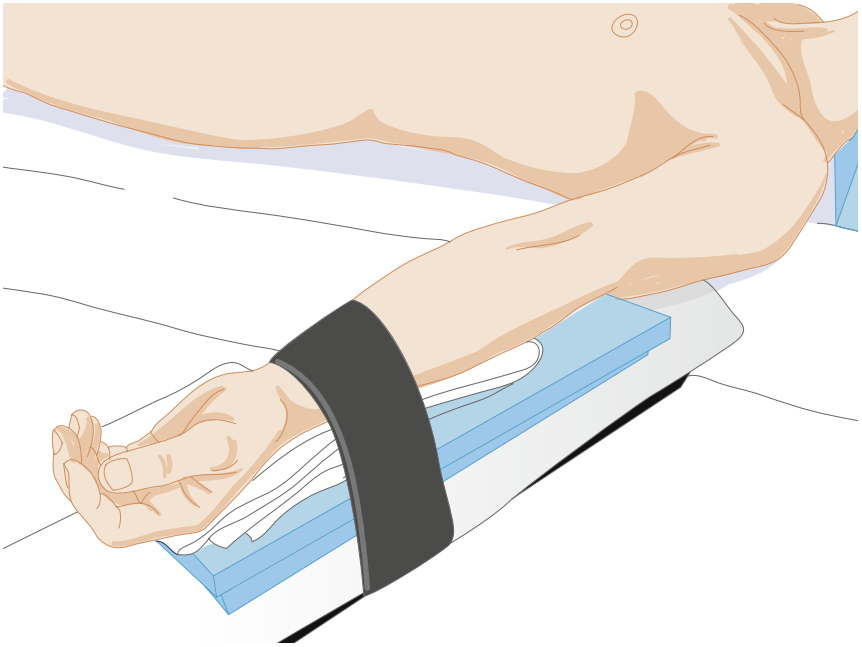


Figure 41-3. Arm position using the arm board. Abduction of the arm is limited to less than 90 degrees whenever possible. The arm is supinated, and the elbow is padded.

to use an arm board or table for upper extremity surgery is retained as the back is parallel with the floor.

The *frog-leg position*, in which the hips and knees are flexed and the hips are externally rotated with the soles of the feet facing each other, allows access to the perineum, medial thighs, genitalia, and rectum. Care must be taken to minimize stress and postoperative pain in the hips and to prevent dislocation by appropriately supporting the knees.

Tilting a supine patient head down, the *Trendelenburg position* (see Fig. 41-2), is often used to increase venous return during hypotension, to improve exposure during abdominal and laparoscopic surgery, and during central line placement to prevent air embolism and distention of the central vein. This position is linked by name to a nineteenth-century German surgeon, Friedrich Trendelenburg, who described its use for abdominal surgery.

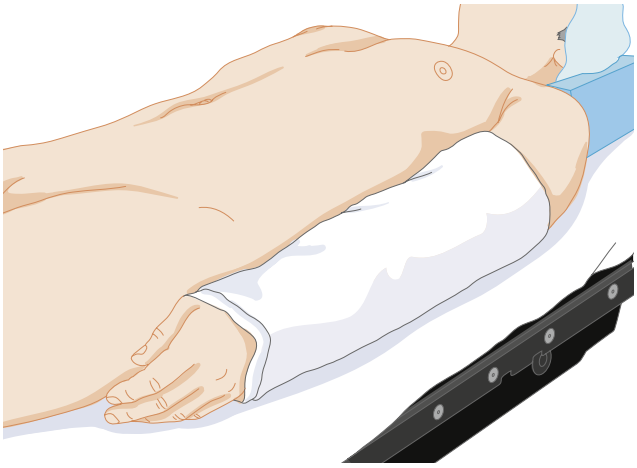


Figure 41-4. Arm tucked at patient side. The arm is in the neutral position with the palm to the hip. The elbow is padded, and the arm is well supported by the mattress.

The Trendelenburg position increases central venous, intracranial, and intraocular pressures and can have significant cardiovascular and respiratory consequences. A steep (30 to 45 degree) head-down position is now frequently used for robotic prostate and gynecologic surgeries. Robotic surgeries are often relatively long and present special challenges because once robotic instruments are set into position the table cannot be moved until the robotic portion is concluded without important consequences for the surgeon and additional procedure time. Patients undergoing robotic prostatectomies (see also Chapter 87) appeared in one study to tolerate the prolonged hemodynamic, respiratory, and neurophysiologic changes well, without evidence of harmful deviations from safe norms and cerebral perfusion pressures.[23]

Because of the augmented effects of gravity, care must be taken to prevent patients in steep head-down positions from slipping cephalad on the surgical table and to avoid compression of the brachial plexus by the torso against the shoulder girdle.[24,25] Techniques to restrain the patient from sliding include antiskid bedding, knee flexion, shoulder braces, beanbag cradling, and padded cross-torso straps.[26] Shoulder braces are not recommended because of the considerable risk of compression injury to the brachial plexus. Beanbag pads become rigid when suction is applied to set the shape, and their use in the Trendelenburg position has been associated with brachial plexus injuries.[27-29] If either shoulder braces or beanbag shoulder immobilization is used to prevent sliding, additional caution is recommended regarding abducting the arm; brachial plexus injuries on the side of the abducted arm have been reported in conjunction with beanbag shoulder immobilization and steep Trendelenburg positioning.[30] These injuries may be due to the fact that abduction of the arm stretches the upper and middle trunks of the brachial plexus as they course around the head of the humerus (Fig. 41-6).

Prolonged head-down positioning can also lead to swelling of the face, conjunctiva, larynx, and tongue with an increased potential for postoperative upper airway

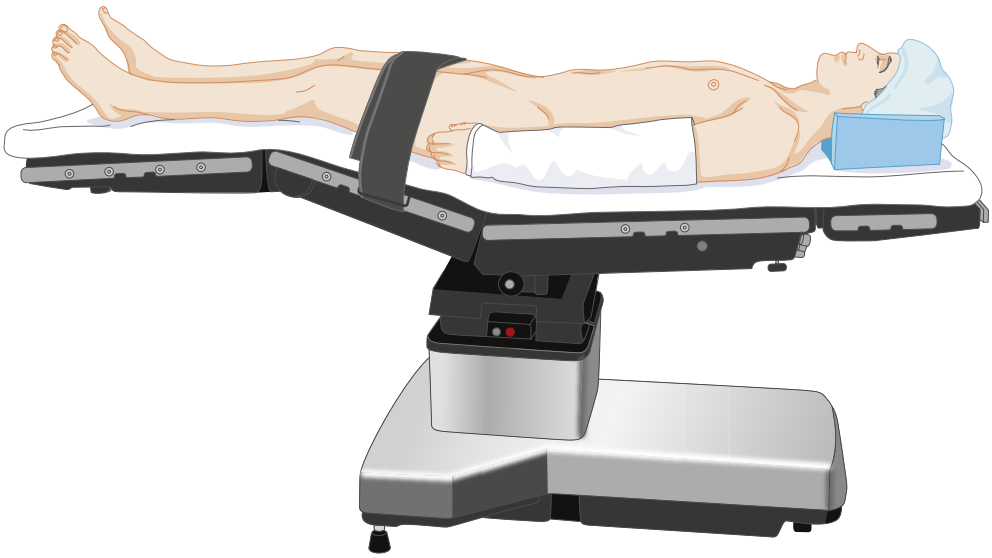


Figure 41-5. Lawn chair position. Flexion of the hips and knees decreases tension on the back.

obstruction. The cephalad movement of abdominal viscera against the diaphragm also decreases functional residual capacity and pulmonary compliance. In patients who are spontaneously ventilated, the work of breathing increases. In patients who are mechanically ventilated, airway pressures must be higher to ensure adequate ventilation. The stomach also lies above the glottis. Therefore endotracheal intubation is often preferred to protect the airway from aspiration of gastric contents related to reflux and to reduce atelectasis. Because of the risk of edema to the trachea and mucosa surrounding the airway during surgeries with patients in the Trendelenburg position for prolonged periods, verifying an air leak around the endotracheal tube or visualizing the larynx before extubation may be prudent.

The *reverse Trendelenburg position* (head-up tilt) (see Fig. 41-2) is often used to facilitate upper abdominal surgery by shifting the abdominal contents caudad. This position is increasingly popular because of the growing number of laparoscopic surgeries. Again, caution is advised to prevent patients from slipping on the table, and more frequent monitoring of arterial blood pressure may be prudent because hypotension may result from decreased venous return. In addition, the position of the head above the heart reduces perfusion pressure to the brain and should be taken into consideration when determining optimal blood pressure and the zero position of an arterial pressure transducer, when present.

In all positions in which the head is at a different level than the heart, the effect of the hydrostatic gradient on cerebral arterial and venous pressures should be considered when estimating cerebral perfusion pressure. Careful documentation of any potential arterial pressure gradients is especially prudent.

Supine Positions—Complications

Pressure alopecia, caused by ischemic hair follicles, is related to prolonged immobilization of the head with its full weight falling on a limited area, usually the occiput. Lumps such as those caused by monitoring cable connectors, should not be placed under the head; they may create focal areas of pressure. Hypothermia and hypotension during surgery, such as during cardiopulmonary bypass surgery, may increase the incidence of this complication. Consequently, ample cushioning of the head and, if possible during prolonged surgery, periodic rotation of the head, are prudent to redistribute the weight.

Backache may occur in the supine position because the normal lumbar lordotic curvature is often lost during general anesthesia with muscle relaxation or a neuraxial block due to their effects on the tone of the paraspinous muscles. Consequently, patients with extensive kyphosis, scoliosis, or a history of back pain may require extra padding of the spine or slight flexion at the hip and knee. Lastly, tissues overlying all bony prominences such as the heels and sacrum must be padded to prevent soft tissue ischemia as a result of pressure, especially during prolonged surgery.[31]

Peripheral nerve injury (discussed later in this chapter) is a complex phenomenon with multifactorial causes. The ASA published a Practice Advisory to help prevent perioperative neuropathies.[20,32] Ulnar neuropathy has historically been the most common lesion, although brachial plexus injuries have superseded ulnar neuropathies in more recent closed claims data associated with general anesthesia.[1,4] Regardless of the position of the upper extremities, maintaining the head in a relatively midline position can help minimize the risk of stretch injury to the brachial plexus.[27] Although no direct evidence suggests that positioning or padding alone can prevent

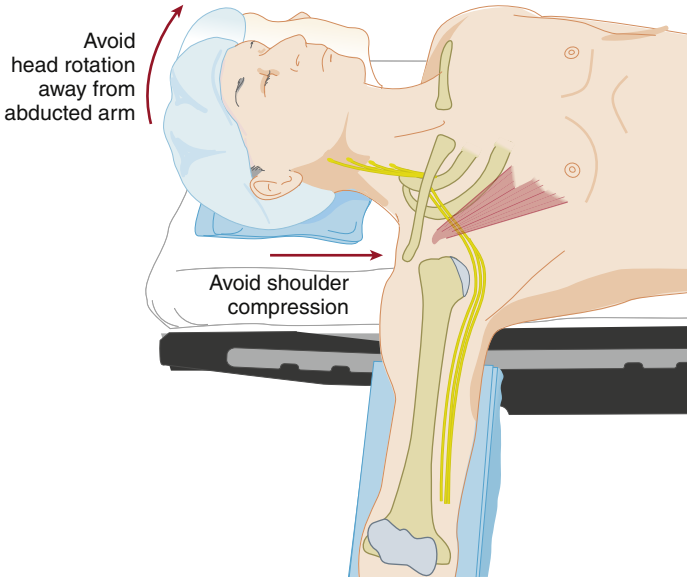


Figure 41-6. The brachial plexus, shown in yellow, is vulnerable to stretch and compression due to its long course. Arm abduction is limited to less than 90 degrees when supine because when the arm is raised the head of the humerus rotates caudad and stretches the plexus. Shoulder braces should be avoided; they may cause direct compression of the plexus medially between the clavicle and first rib or laterally below the head of the humerus. Excessive head rotation should be avoided, especially away from an abducted arm. Abduction of the arm should be avoided when in a steep head-down position if shoulder braces or a beanbag holds the shoulders.

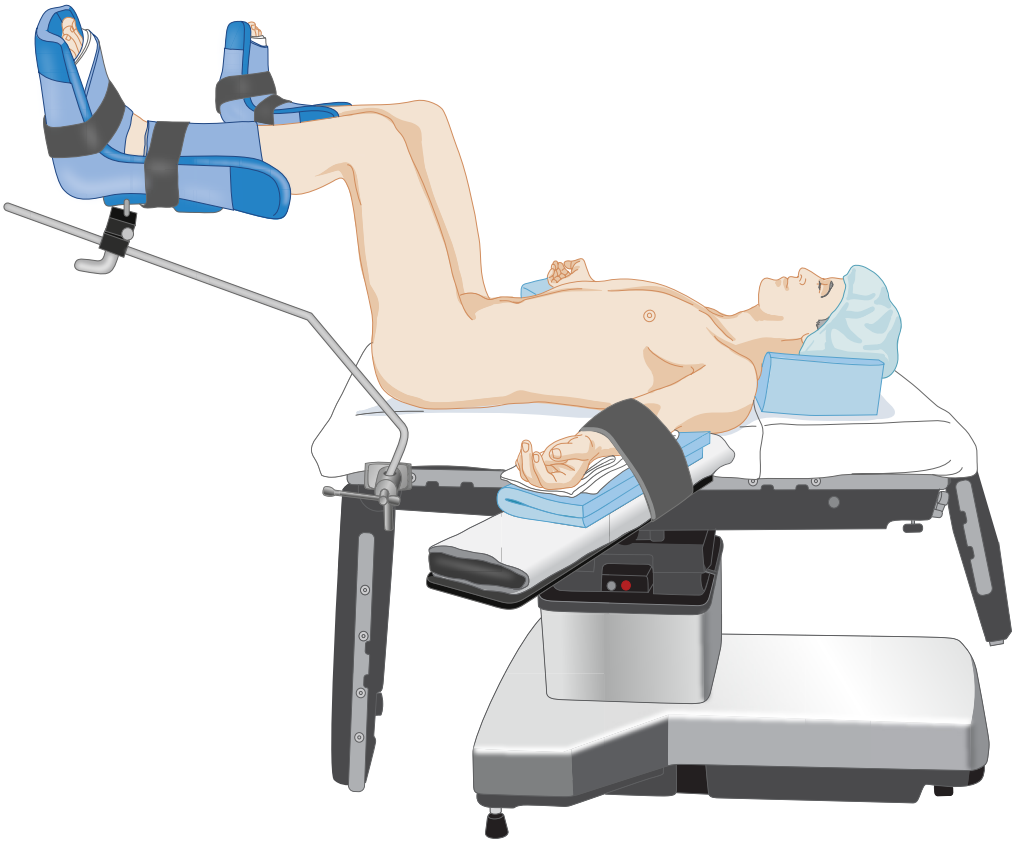


Figure 41-7. Lithotomy position. Hips are flexed 80 to 100 degrees with the lower leg parallel to the body. Pressure near the fibular head is absent. Arms are on armrests away from the hinge point of the foot section.

perioperative ulnar neuropathies, the ASA Practice Advisory recommends limiting arm abduction in the supine patient to less than 90 degrees at the shoulder with the hand and forearm either supinated or kept in a neutral position.[20]

The base of the surgical table is asymmetric, with the patient's torso generally over the base of the table (see Fig. 41-1). However, patients are often positioned with the torso over the open side of the table to improve surgical access or to permit the use of equipment such as C-arm x-ray devices. This position places the heaviest part of the body, and therefore the patient's center of gravity, opposite the weighted base of the table, with substantial leverage. When patients are heavy, caution is advised when placing them in reverse axis on the surgical table (see Chapter 71). The surgical table weight limits are significantly different when a patient is reversed, and should be strictly observed. The table can tilt and tip over if sufficient weight is placed away from the base, particularly if the leverage is increased yet further with table extensions or the Trendelenburg position.

LITHOTOMY

The classic *lithotomy position* (Figs. 41-7 to 41-9) is frequently used during gynecologic, rectal, and urologic surgeries. The hips are flexed 80 to 100 degrees from the trunk, and the legs are abducted 30 to 45 degrees from the midline. The knees are flexed until the lower legs are parallel to the torso, and supports or stirrups hold the legs, usually "candy cane," knee crutch, or calf support style. The foot section of the surgical table is lowered. If the arms are on the surgical table alongside the patient, then the hands and fingers may lie near the open edge of the lowered section of the table. When raising the foot of the table at the end of surgery, strict attention to the position of the hands must be paid to avoid a potentially disastrous crush injury to the fingers (Fig. 41-10). For this reason, when patients are in the lithotomy position, the recommended position of the arms is on armrests far from the table hinge point. If the arms must be tucked at the patient's side, then the hands need to be visualized and confirmed to be safe whenever the leg section of the surgical table is manipulated.

Initiation of the lithotomy position requires coordinated positioning of the lower extremities by two assistants to avoid torsion of the lumbar spine. Both legs should be raised together, simultaneously flexing the hips and knees. The lower extremities should be padded to prevent compression against the stirrups. After surgery, the patient must also be returned to the supine position in a coordinated manner. As previously mentioned, the hands should be positioned to prevent entrapment in any moving or articulating sections of the surgical table. The legs should be simultaneously removed from the holders, the knees brought together in the midline, and the legs slowly straightened and lowered onto the surgical table.

The lithotomy position may also cause significant physiologic changes. When the legs are elevated, venous return increases, causing a transient increase in cardiac

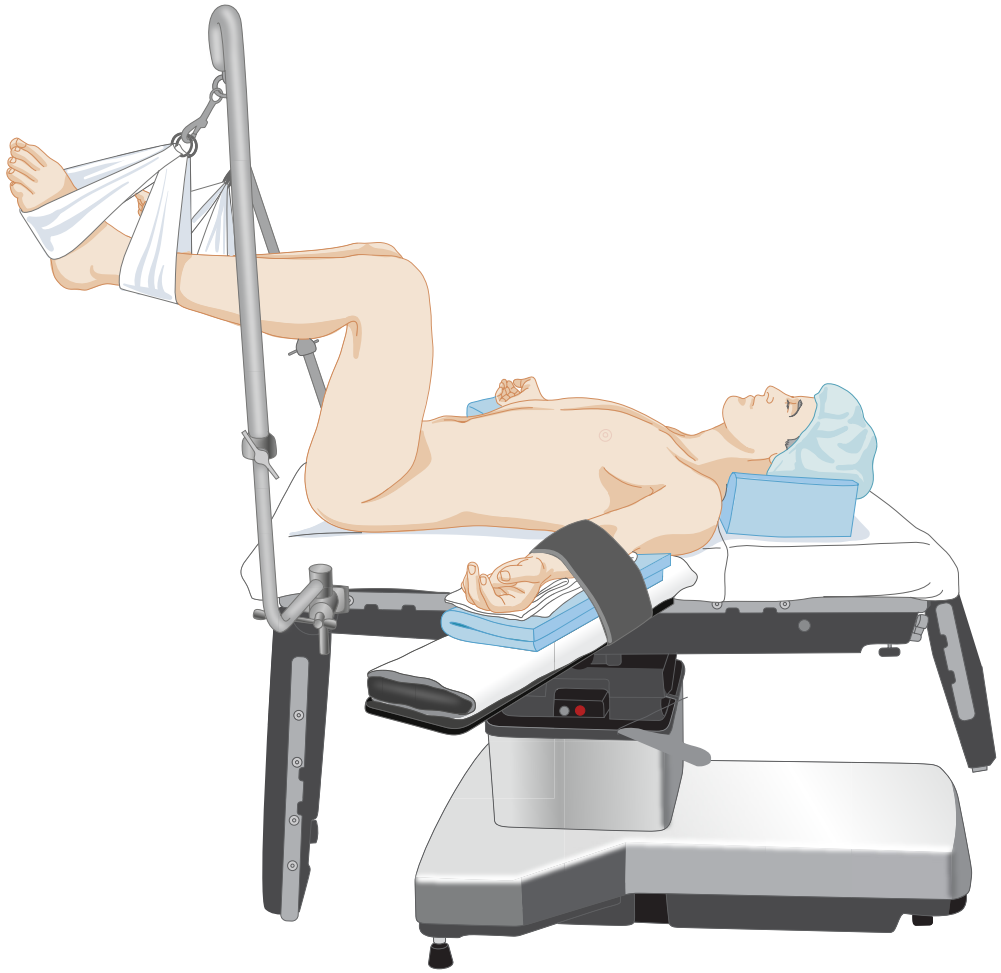


Figure 41-8. Lithotomy position with "candy cane" stirrup leg holders.

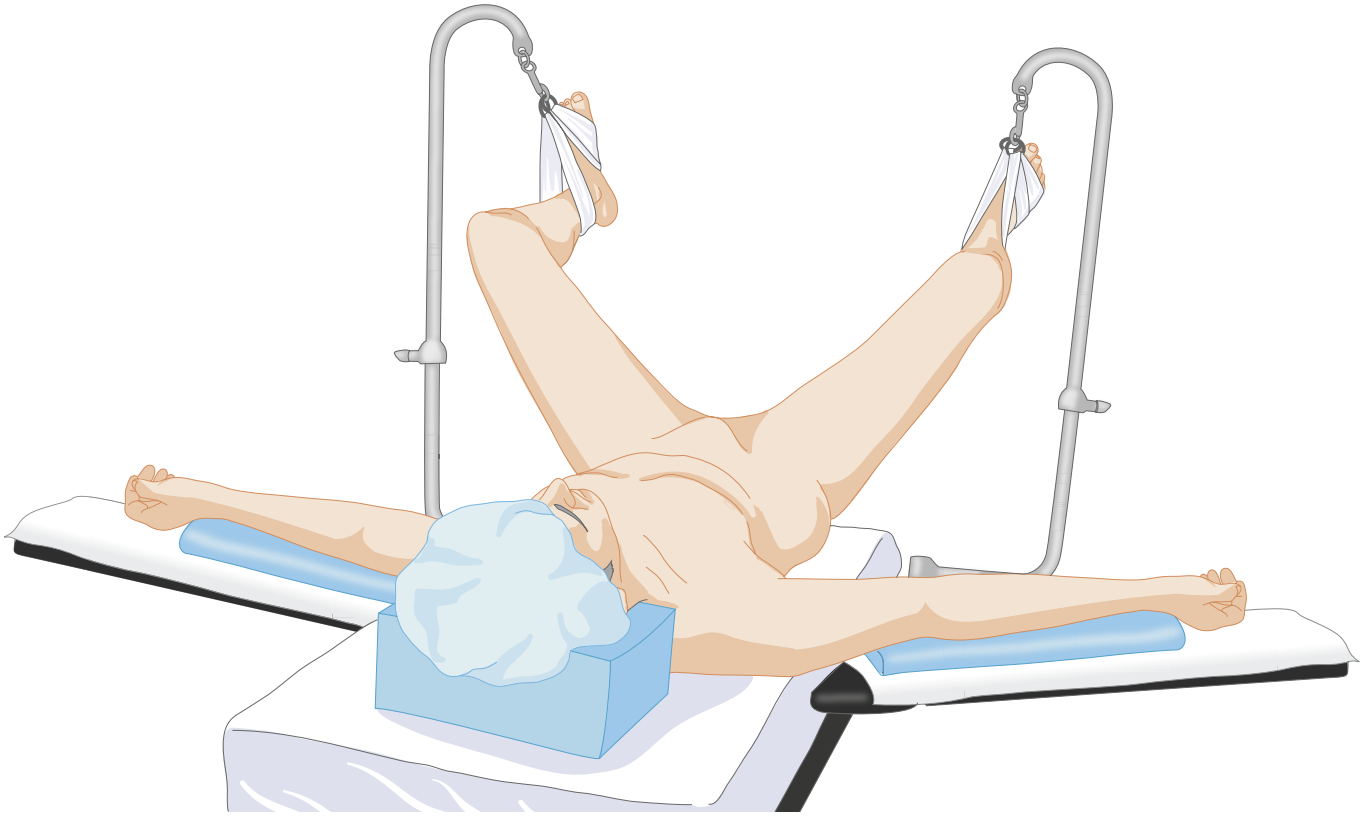


Figure 41-9. Lithotomy position. The correct position of "candy cane" supports is well away from the lateral fibular head.

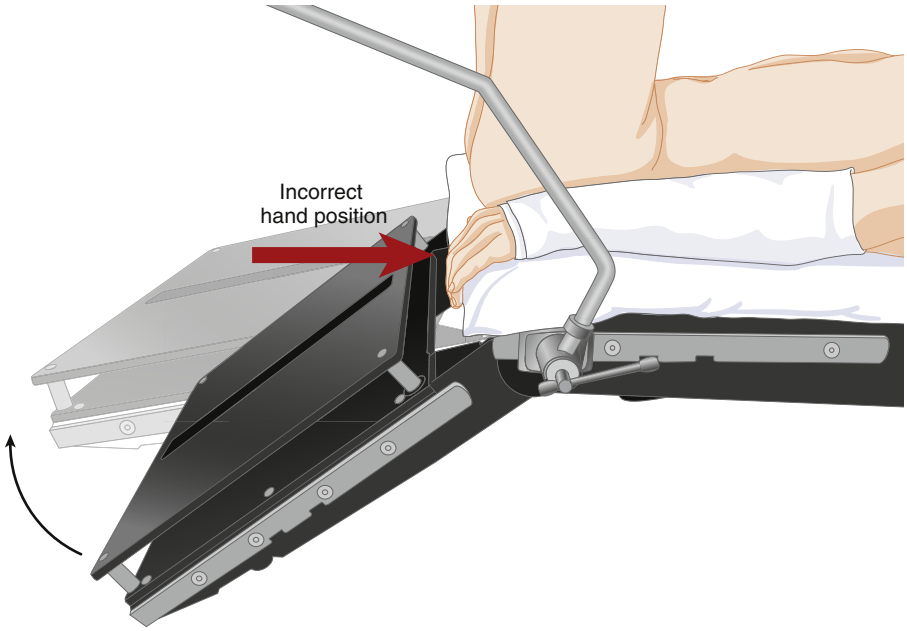


Figure 41-10. Improper position of arms in lithotomy position. The fingers are at risk for compression when the lower section of the bed is raised.

output and, to a lesser extent, cerebral venous and intracranial pressure in otherwise healthy patients. In addition, the lithotomy position causes the abdominal viscera to displace the diaphragm cephalad, reducing lung compliance and potentially resulting in a decreased tidal volume. If obesity or a large abdominal mass is present (e.g., tumor, gravid uterus), abdominal pressure may increase significantly enough to obstruct venous return to the heart. Lastly, the normal lordotic curvature of the lumbar spine is lost in the lithotomy position, potentially aggravating any previous lower back pain.[33]

In a retrospective review of 198,461 patients undergoing surgery in the lithotomy position from 1957 to 1991, injury to the common peroneal nerve was the most common lower extremity motor neuropathy, representing 78% of nerve injuries. A potential cause of the injury was the compression of the nerve between the lateral head of the fibula and the bar holding the legs. When the "candy cane" stirrups are used, special attention must be paid to avoid compression (see Fig. 41-9). The injury was more common with patients who had low body mass index, recent cigarette smoking, or prolonged duration of surgery.[34] Perhaps as a result of an increased awareness of potential injuries, no lower extremity motor neuropathies were reported in a prospective review of 991 patients undergoing surgery in the lithotomy position from 1997 to 1998. Paresthesias in the distribution of the obturator, lateral femoral cutaneous, sciatic, and peroneal nerves were reported in 1.5% of patients, and nearly all recovered. Surgical times longer than 2 hours were significantly associated with this complication.[35]

Lower extremity compartment syndrome is a rare complication caused by inadequate tissue perfusion that is associated with the lithotomy position.[36,37] Local arterial pressure decreases 0.78 mm Hg for each centimeter the leg is raised above the right atrium.[38] Leg compartment pressures initially increase in the lithotomy position for reasons that remain incompletely explained. This increase, combined with the decreased perfusion pressure in the elevated extremities, causes a vicious cycle of ischemia, edema, further ischemia, and eventually rhabdomyolysis. Reperfusion after an ischemic injury further increases edema, exacerbating the problem. Decompression fasciotomy is generally performed if tissue pressures are measured to be greater than 30 mm Hg. Irreversible muscle damage occurs with pressures over 50 mm Hg for several hours. In a large retrospective review of 572,498 surgeries, the incidence of compartment syndromes was higher in the lithotomy (1 in 8720) and lateral decubitus (1 in 9711) positions, as compared with the supine (1 in 92,441) position. Long procedure time was the only distinguishing characteristic of the surgeries during which patients developed lower extremity compartment syndromes.[36] A survey of urologists in the United Kingdom suggested that compartment syndrome after surgery in the lithotomy position is underreported and more common than appreciated. Compartment syndrome may occur in as many as 1 in 500 radical cystectomy procedures, which represented 78% of their cases. Affected patients had undergone surgeries with durations longer than 3½ hours.[39] Compartment pressures increase over time in the lithotomy position, and the legs should be periodically lowered to the level of the body if the surgery extends beyond 2 to 3 hours.[39-41] Additional risk factors include high body mass index and factors known to compromise tissue oxygenation such as blood loss, peripheral vascular disease, hypotension, and reduced cardiac output. The potential role of intermittent leg compression devices remains controversial.[38,42]

LATERAL DECUBITUS

The *lateral decubitus position* (Fig. 41-11) is most frequently used for surgery involving the thorax, retroperitoneal structures, or hip. The patient rests on the nonoperative side and is balanced with anterior and



Figure 41-11. Lateral decubitus position. The lower leg is flexed with padding between the legs, and both arms are supported and padded.



Figure 41-12. Lateral decubitus position showing placement of arms and head. Additional padding is under the headrest to ensure the alignment of the head with the spine. The headrest is kept away from the dependent eye.

posterior support, such as bedding rolls or a deflatable beanbag, and a flexed dependent leg. The arms are usually positioned in front of the patient, leading to some position-related risks to both the dependent and nondependent arms. The dependent arm rests on a padded arm board perpendicular to the torso. The nondependent arm is often supported over folded bedding or suspended with an armrest or foam cradle (Fig. 41-12). If possible, neither arm should be abducted more than 90 degrees. For some high thoracotomies, the nondependent arm may need to be elevated above the shoulder plane for exposure; however, vigilance is warranted to prevent neurovascular compromise.

The act of positioning a patient in the lateral decubitus position requires the cooperation of the entire surgical staff to prevent potential injuries. The patient's head must be kept in a neutral position to prevent excessive lateral rotation of the neck and stretch injuries to the brachial plexus. This adjustment may require additional head support (see Fig. 41-12). The dependent ear should be checked to avoid folding and undue pressure. The eyes should be securely taped closed before repositioning if the

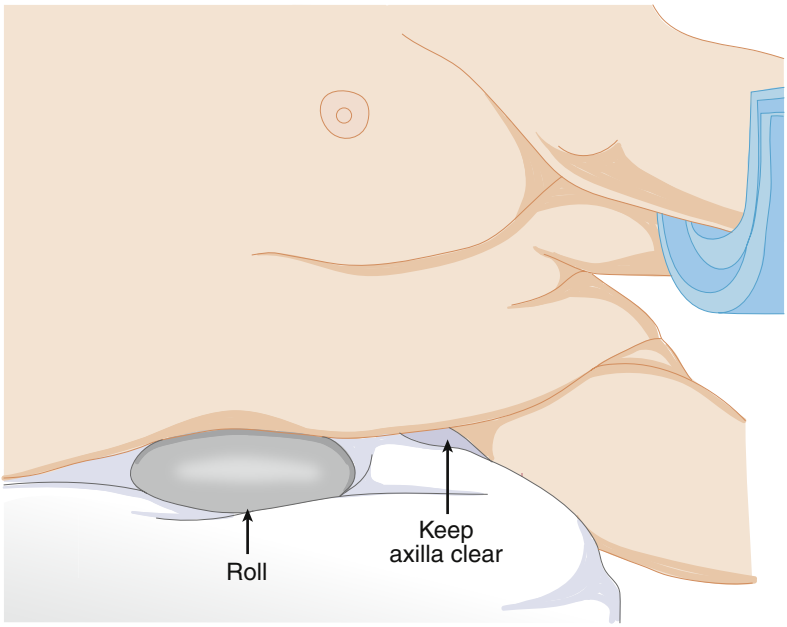


Figure 41-13. Use of chest roll in the lateral decubitus position. The roll, in this case, is a bag of intravenous fluid and is placed well away from the axilla to prevent compression of the axillary artery and brachial plexus.

patient is asleep. The dependent eye must be frequently checked for external compression.

To avoid compression to the dependent brachial plexus or blood vessels, an *axillary roll*, which is generally a bag of intravenous fluid, is frequently placed between the chest wall and the bed just caudal to the dependent axilla (Fig. 41-13). This roll should never be placed IN the axilla. The purpose of the axillary roll is to ensure that the weight of the thorax is borne by the chest wall caudad to the axilla and to avoid compression of the shoulder and axillary contents. Many practitioners do not use a roll if a deflatable beanbag is used to cradle the torso; however, the beanbag must not compress the axilla. Regardless of the technique, the pulse should be monitored in the dependent arm for early detection of compression to axillary neurovascular structures. Vascular compression and venous engorgement in the dependent arm may affect the pulse oximetry reading; a low saturation reading may be an early warning sign of compromised circulation. Hypotension measured in the dependent arm may be due to axillary arterial compression; therefore retaining the ability to measure blood pressure in both arms is useful. When a kidney rest is used, it must be properly placed under the dependent iliac crest to prevent inadvertent compression of the inferior vena cava. Lastly, a pillow or other padding is generally placed between the knees with the dependent leg flexed to minimize excessive pressure on bony prominences and stretch of lower extremity nerves.

The lateral decubitus position is also associated with pulmonary compromise.[43] In a patient who is mechanically ventilated, the combination of the lateral weight of the mediastinum and the disproportionate cephalad pressure of abdominal contents on the dependent lung favors overventilation of the nondependent lung. At the same time, the effect of gravity causes the pulmonary blood flow to the underventilated, dependent lung to increase. Consequently, ventilation-perfusion matching worsens, potentially affecting gas exchange and ventilation.

The lateral decubitus position is usually preferred during pulmonary surgery and one-lung ventilation. When the nondependent lung is collapsed, the minute ventilation is allocated to the dependent lung. This, combined with decreased compliance as a result of positioning, may further exacerbate the airway pressure required to achieve adequate ventilation. Head-down tilt in the lateral position worsens pulmonary function yet further, increasing shunt fraction.[44] Patients may be flexed while in the lateral position to spread the ribs during thoracotomies or to improve exposure of the retroperitoneum for renal surgeries. The point of flexion and the kidney rest, if raised, should lie under the iliac crest rather than the flank or ribcage to minimize compression of the dependent lung (Fig. 41-14). This position is often accompanied by a component of reverse Trendelenburg positioning, creating the potential for venous pooling in the lower body. For these reasons, the use of the flexed, lateral position is discouraged when not actively needed for surgical exposure.

PRONE

The *prone* or *ventral decubitus position* (Fig. 41-15) is primarily used for surgical access to the posterior fossa of the skull, the posterior spine, the buttocks and perirectal area, and the lower extremities. Regardless of whether the patient requires monitored anesthesia care or general anesthesia, the patient's legs should be padded and flexed slightly at the knees and hips. The head may be supported facedown with its weight borne by the bony structures or turned to the side. Both arms may be positioned to the patient's sides and tucked in the neutral position as described for the supine patient or placed next to the patient's head on arm boards—sometimes

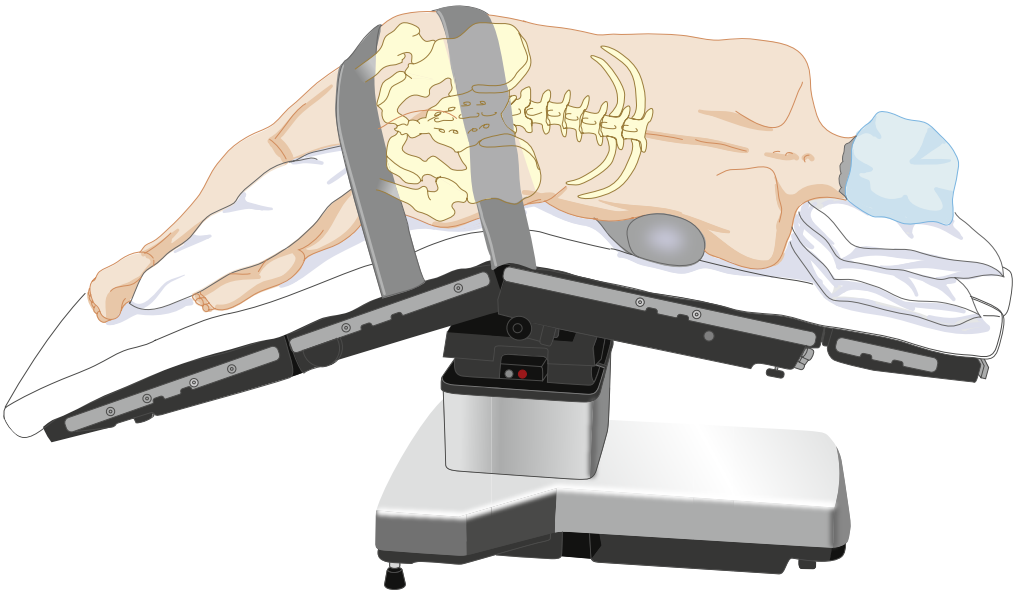


Figure 41-14. Flexed lateral decubitus position. The point of flexion should lie under the iliac crest, rather than under the flank or lower ribs to optimize ventilation of the dependent lung.



Figure 41-15. Prone position with Wilson frame. Arms are abducted less than 90 degrees whenever possible, although greater abduction may be better tolerated while prone. Pressure points are padded, and the chest and abdomen are supported away from the bed to minimize abdominal pressure and to preserve pulmonary compliance. Soft head pillow has cutouts for eyes and nose and a slot to permit endotracheal tube exit. Eyes must be checked frequently.

called the *prone superman position*. Extra padding under the elbow may be needed to prevent compression of the ulnar nerve. Again, unless necessary, the arms should not be abducted greater than 90 degrees to prevent excessive stretching of the brachial plexus, especially in patients with the head turned. Because of the effects of alterations in shoulder position on the brachial plexus, abduction of the arm greater than 90 degrees may be better tolerated in the prone position than in the supine position.[19] Finally, elastic stockings and active compression devices are used to minimize pooling of venous blood, especially with any flexion of the body.

When general anesthesia is planned, the trachea is first intubated on the stretcher, and all intravascular access is obtained as needed. The endotracheal tube is well secured to prevent dislodgement and the loosening of tape as a result of the drainage of saliva when prone. The anesthesia provider should consider using a wire-reinforced endotracheal tube to avoid kinking and obstruction as it exits the patient's mouth while in the prone position. If a head support device is used, then a corrugated extension of the endotracheal tube ensures that the anesthesia circuit Y is easily accessible, although this adds another connection in the airway circuit and a small amount of dead space ventilation. With the coordination of the entire surgical staff, the patient is then turned prone onto the surgical table, keeping the neck in line with the spine during the move. The anesthesiologist is primarily responsible for coordinating the move and for repositioning the head. An exception might be the patient in whom rigid pin fixation is used when the surgeon often holds the pin frame. Disconnecting blood pressure cuffs and arterial

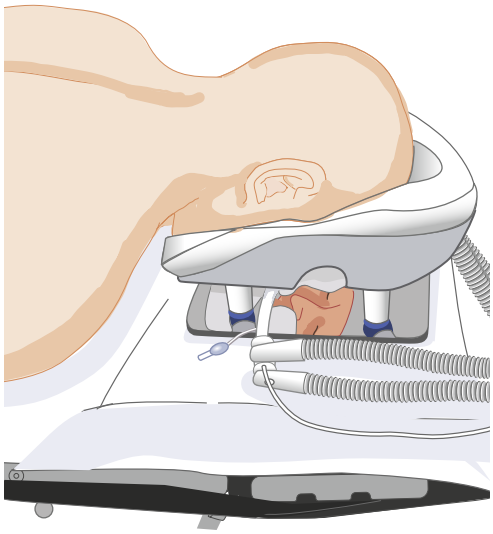


Figure 41-16. Mirror system for prone position. Bony structures of head and face are supported, and monitoring of the eyes and airway is facilitated with a plastic mirror. Although not illustrated, the eyes should be taped closed.

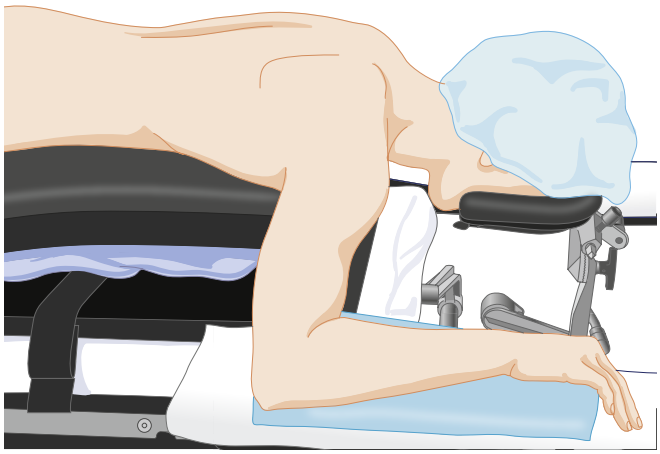


Figure 41-17. Prone position with horseshoe adapter. Head height is adjusted to position the neck in a natural position without undue extension or flexion.

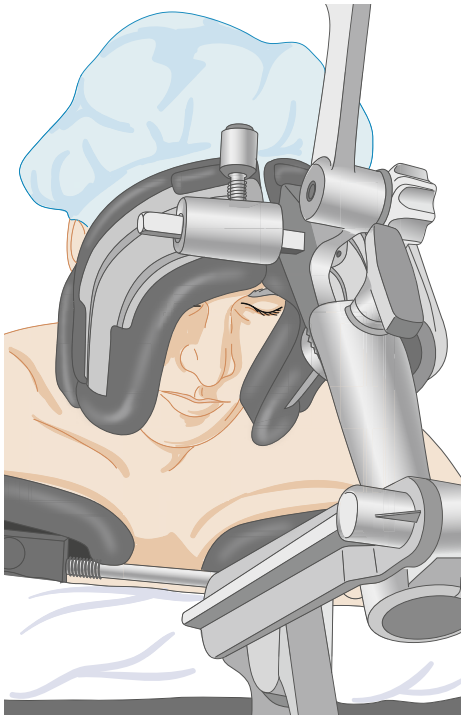


Figure 41-18. Prone position with horseshoe adapter. The face is seen from below. The horseshoe adapter permits superior access to the airway and visualization of eyes. The width may be adjusted to ensure proper support by facial bones.

and venous lines that are on the outside arm that rotates furthest is recommended to avoid dislodgment, although some prefer to disconnect all lines and monitors before moving. Pulse oximetry can usually be maintained if applied to the inside arm, and full monitoring should be reinstituted as rapidly as possible. Endotracheal tube positioning and adequate ventilation are immediately reassessed after the move.

Head position is critical. The patient's head may be turned to the side when prone if neck mobility is adequate. As in the lateral decubitus position, the dependent eye must be frequently checked for external compression. In addition, in patients with cervical arthritis or cerebrovascular disease, lateral rotation of the neck may compromise carotid or vertebral arterial blood flow or jugular venous drainage. In most cases, the head is kept in a neutral position using a surgical pillow, horseshoe headrest, or Mayfield head pins. A number of commercially available pillows are specially designed for the prone position. Most pillows, including disposable foam versions, support the forehead, malar regions, and chin, with a cutout for the eyes, nose, and mouth (see Fig. 41-15). The face is not always visible, however, making eye checks more difficult. Mirror systems are available to facilitate intermittent visual confirmation that the eyes are not impinged, although direct visualization or tactile confirmation is prudent (Fig. 41-16). The horseshoe headrest supports only the forehead and malar regions and allows excellent access to the airway; however, this headrest is rigid and therefore potentially dangerous if the head moves (Figs. 41-17 and 41-18). Mayfield rigid pins support the head without any direct pressure on the face. These pins allow access to the airway and firmly hold the head in one position that can be finely adjusted for optimal neurosurgical exposure (Fig. 41-19). Rigid pin fixation is rarely used outside cranial or cervical spine surgeries. When properly applied, the pins will cause significant periosteal stimulation. Patient movement must be prevented when the head is held in rigid pins; skidding out of pins can result in scalp lacerations or a cervical spine injury. Because horseshoe and pin headrests attach to adjustable articulating supports, any slippage or failure of this bracketing device may lead to complications if the head suddenly drops. Regardless of the head-support technique, the face must be periodically checked to ensure that the weight is borne only by the bony structures, that the airway is uncompromised, and that no pressure is placed on the eyes. Verification of proper positioning is frequently performed and noted in the anesthetic record. The face should be rechecked if any patient motion occurs during



Figure 41-19. Prone position with Mayfield head pins. Rigid fixation is provided for the cervical spine and posterior intracranial surgeries. The head position may include neck torsion or flexion that affects the depth of the endotracheal tube, and extreme head positions may increase the risk of cervical cord injury.

surgery or if the table position is significantly altered. The prone position is a risk factor for perioperative visual loss, which is discussed in a separate section later in this chapter. In addition, if motor-evoked potentials are used during spine or neurosurgery, then the position of the tongue and placement of bite blocks must be frequently checked; bite injuries are a vexing complication and can be severe if the tongue lies between the teeth.[45]

If the legs are in plane with the torso while in the prone position, then hemodynamic reserve is relatively maintained; however, if any significant lowering of the legs or tilting of the entire table occurs, then venous return may increase or decrease accordingly. The prone position does not alter the ability of pulse pressure variation to predict fluid responsiveness. However, the variation has been shown to be augmented at baseline; therefore fluid responsiveness is observed at a slightly greater level of variation than when supine.[46]

Because the abdominal wall is easily displaced, external pressure on the abdomen may elevate both intraabdominal and intrathoracic pressures. Therefore careful attention must be paid to the ability of the abdomen to hang relatively free and to move with respiration. During posterior spinal surgery, relatively low venous pressure is desirable to minimize bleeding and to facilitate surgical exposure. Abdominal pressure can transmit elevated venous pressures to the abdominal and spine vessels, including the epidural veins, which lack valves. Abdominal pressure may also impede venous return through compression of the inferior vena cava, decreasing cardiac output.

Pulmonary function may be superior to the supine and lateral decubitus positions if no significant abdominal pressure is present and if the patient is properly positioned.[47,48] External pressure on the abdomen may push the diaphragm cephalad, decreasing functional residual capacity and pulmonary compliance and increasing peak airway pressure. In one study of patients undergoing spine surgery in the prone position using the Wilson frame, pressure-controlled ventilation was found to cause less elevation of peak inspiratory pressures than volume-controlled ventilation with equal tidal volumes and end-tidal carbon dioxide concentrations.[49] In a randomized controlled trial studying patients undergoing spine surgery and ventilated with low versus high-tidal volume in the prone position, no difference in inflammatory markers or postoperative pulmonary function was exhibited.[50]

To promote low abdominal and thoracic pressures, firm rolls or bolsters placed along each side from the clavicle to the iliac crest generally support the torso. Multiple commercial rolls and bolsters are available including the Wilson frame (see Fig. 41-15), Jackson table, Relton frame, Mouradian/Simmons modification of the Relton frame, and gel bolsters. All devices serve to minimize abdominal compression by the surgical table and to maintain normal pulmonary compliance. To prevent tissue injury, pendulous structures, such as male genitalia and female breasts, should be clear of compression; the breasts should be placed medial to the gel bolsters. The lower portion of each roll or bolster must be placed under its respective iliac crest to prevent pressure injury to the genitalia and the femoral vasculature.[51] The prone position presents special risks for patients who are morbidly obese, whose respiration is already compromised, and who may be difficult to reposition quickly. At times, discussing alternate positioning options with the surgeon may be necessary to ensure patient safety.

SITTING

The sitting position, although infrequently used because of the perceived risk from venous and paradoxical air embolism, offers advantages to the surgeon in approaching the posterior cervical spine and the posterior fossa (Fig. 41-20) (see also Chapter 70). The main advantages of the sitting position over the prone position for neurosurgical and cervical spine procedures are excellent surgical



Figure 41-20. Sitting position with Mayfield head pins. The patient is typically semirecumbent rather than sitting; the legs are kept as high as possible to promote venous return. Arms must be supported to prevent shoulder traction and stretching of the brachial plexus. In a commonly used variation, the arms are placed on the abdomen and supported. The head support is preferably attached to the back section of the table to allow the back to be adjusted or lowered emergently without first detaching the head holder.

exposure, decreased blood in the operative field, and, possibly, reduced perioperative blood loss.[52] The main advantages to the anesthesiologist are superior access to the airway, reduced facial swelling, and improved ventilation, particularly in patients who are obese (see also Chapter 71).

The head may be fixed in pins for neurosurgery or taped in place with adequate support for other surgeries. Because gravity pulls the arms caudad, they must be supported to the point of slight elevation of the shoulders to avoid traction on the shoulder muscles and potential stretching of upper extremity neurovascular structures. The knees are usually slightly flexed for balance and to reduce stretching of the sciatic nerve, and the feet are supported and padded.[53]

The hemodynamic effects of placing a supine patient in the sitting position are dramatic. Because of the pooling of blood into the lower body under general anesthesia (see discussion earlier in this chapter), patients are particularly prone to hypotensive episodes. Incremental positioning and the use of intravenous fluids, vasopressors, and appropriate adjustments of anesthetic depth can reduce the degree and duration of hypotension. Elastic stockings and active leg compression devices can help maintain venous return.

The head and neck position while in the sitting position has been associated with complications during surgery to the posterior spine or skull. In a review of all cervical spinal cord injuries in the ASA Closed Claims Project database from 1970 to 2007, surgery in the sitting position was found to be associated with injury, whereas other factors often thought to be more important, such as airway management in the setting of neck trauma or cervical spine instability, were not.[54] The authors theorized that positional factors, such as sitting or hyperextension of the neck combined with unrecognized degenerative cervical spine disease, resulted in many of the cervical cord injuries in the ASA Closed Claims Project database. Excessive cervical flexion, which may occur with the head in pins, has a number of adverse consequences. It can impede both arterial and venous blood flow, causing hypoperfusion or venous congestion of the brain, and may impede normal respiratory excursion. Excessive flexion can also obstruct the endotracheal tube and place significant pressure on the tongue, leading to macroglossia. In general, maintaining at least two fingers' distance between the mandible and the sternum is recommended for a normal-sized adult, and patients should not be positioned at the extreme of their range of motion.[55] Extra caution with neck flexion is advised if transesophageal echocardiography (TEE) is used for air embolism monitoring, because the esophageal probe lies between the flexed spine and the airway and endotracheal tube, adding to the potential for compression of laryngeal structures and the tongue.

Because of the elevation of the surgical field above the heart and the inability of the dural venous sinuses to collapse because of their bony attachments, the risk of venous air embolism is a constant concern. Arrhythmia, desaturation, pulmonary hypertension, circulatory compromise, or cardiac arrest may occur if sufficient quantities are entrained. If the foramen ovale is patent, then even small amounts of venous air may result in a stroke or myocardial infarction as a result of paradoxical embolism. TEE has demonstrated some degree of venous air in a large majority of patients studied during neurosurgery in the sitting position.[56,57] Because of the risk of paradoxical embolus,



Figure 41-21. Sitting position adapted for shoulder surgery, often called the *beach chair position*. The arms must be supported to prevent stretching of the brachial plexus without pressure on the ulnar area of the elbow. As with all head-up positions, blood pressure should be regulated with the height of the brain in mind.

screening contrast echocardiography to investigate the patency of the interatrial septum is often performed before considering the sitting position for intracranial or cervical spine surgery. However, a patent foramen ovale may not always be detected.[58] Adequate hydration and early detection of entrained air with the use of TEE or precordial Doppler ultrasound may decrease the incidence and severity of venous air embolism.[56]

A variation of the sitting position, the *beach chair position* is increasingly used for shoulder surgeries, including arthroscopic procedures (Fig. 41-21). For the surgeon, its advantages versus the lateral decubitus position are superior access to the shoulder from both the anterior and posterior aspect and the potential for great mobility of the arm at the shoulder joint.[59] The beach chair position has been associated with neurologic injury, cervical neurapraxia, and hypotensive bradycardic events in association with the use of an epinephrine-containing interscalene block anesthetic.[59-62] The cause and incidence of these rare but catastrophic neurologic injuries are unknown. Theories include reduced cerebral perfusion in the beach chair position caused by reduced cardiac output, deliberate or permissive hypotension, loss of compensatory mechanisms caused by anesthesia, failure to compensate for the height of the head in the regulation of the blood pressure, dynamic vertebral artery narrowing or occlusion with the rotation of the head, and air emboli. Investigators have demonstrated positional effects on cerebral oxygen saturation,[62] as well as transient reductions in cerebral oxygen saturation associated with hypotensive periods during shoulder surgeries in the sitting position that reversed after use of ephedrine and phenylephrine to restore cerebral perfusion pressure.[62-64] Variation in the anatomy of the circle of Willis has been postulated as a cause of vulnerability to cerebral ischemia when sitting; however, causation remains unproven.[65,66] An observational study of 124 patients undergoing shoulder arthroscopy demonstrated cerebral desaturation by oximetry in 80% of those who were in the beach chair position and none in the lateral decubitus position.[67] Cerebral oxygen saturation monitoring may be helpful; however, no gold standard limits exist, and values may change along with alterations in patient position and carbon dioxide concentration. Therefore, if measured, trends in cerebral oxygen saturation are best interpreted during periods of constant ventilation and patient position.[68,69] Reasonable recommendations for patients undergoing shoulder surgery in the sitting position are to monitor blood pressure carefully in reference to the level of the brain, avoid and rapidly treat any hypotension or bradycardia, and position the head carefully to avoid extreme positions that may compromise cerebral vessels.[61] Monitoring of cerebral oxygen saturation, if available, may be useful when patients are in a steep head-up position. However, its value has not been established,[69] and the incidence of cerebral injury during shoulder surgery is estimated to be approximately 1 in 22,000.[70] The Anesthesia Patient Safety Foundation and the ASA Committee on Professional Liability in collaboration with the

ASA Closed Claims Project established the Neurologic Injury After Non-Supine Shoulder Surgery (NINS) Registry in 2010. They hope to collect a greater amount of data on such cases to clarify the details and risks associated with positioning. The NINS Registry can be accessed via the ASA Closed Claims Project web site (www.asaclosedclaims.org).

PERIPHERAL NERVE INJURY

Peripheral nerve injury remains a serious perioperative complication and a significant source of professional liability, despite the low incidence of approximately 0.11% of 81,000 anesthetics reviewed from 1987 to 1993,[71] and 0.03% of 380,680 anesthetics reviewed from 1997 to 2007.[72] Injuries occur when peripheral nerves are subjected to stretch, ischemia, or compression during surgery[73]; however, the precise mechanism of injury cannot be determined in many cases.[3] Injuries to patients under monitored anesthesia care, although infrequent, occur as well. During general or regional anesthesia, early warning symptoms of pain and the normal spontaneous repositioning that would occur are absent. Prolonged duration of surgery appears to be a risk factor.

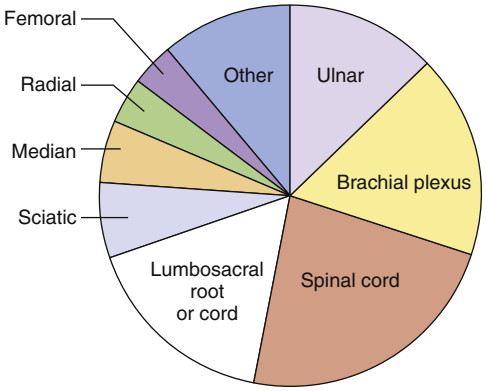
Because scientific studies regarding rare events, such as position-related injuries, are difficult to conduct, much of what is known comes from case reports and the liability insurance industry. In 1984 the ASA developed a Closed Claims Project to evaluate adverse anesthetic outcomes from the closed claims files of 35 U.S. liability insurance companies. The most common cause for claims is death, representing 22% to 41% of claims, with a decreasing fraction over time. Since the initial report in 1990, nerve injury has remained the second most frequent cause for claims. The fraction has increased, from 15% during the 1970s, to 22% in the 2000s.[1,3,74,75] However, this increase appears to track growth in the use of regional anesthesia for both surgical and obstetric patients and is unlikely to represent an increase in position-related nerve injuries.[1] Although most patients with nerve injuries recover, in the 5280 closed claims from 1990 to 2007, 23% of the injuries were permanent; 15% occurred after regional anesthesia, 5% occurred after general anesthesia, and a few cases occurred after monitored anesthesia care.[1]

The ASA Closed Claims database recorded 1564 cases of nerve injury between 1970 and 2010. Overall, injuries to the ulnar nerve represent 21% of cases, followed by the brachial plexus (20%), spinal cord (19%), and lumbosacral nerve roots or cord (17%).[2] The distribution of nerve injuries resulting in claims has changed over time, with ulnar nerve injury decreasing from 33% in the first 2 decades of the project to 14% in the second 2 decades. Over the same periods, claims filed after brachial plexus injuries decreased from 21% to 19% and claims filed after spinal cord injuries increased from 9% to 25% (Table 41-1A). Subsets of claims from 1990

TABLE 41-1A TYPES OF NERVE INJURY—FOLLOWING ALL ANESTHETIC TYPES

	Total Nerve Injuries (1970-2010)		1970-1989		1990-2010	
	Count	*% of 1564*	*Count*	*% of 570*	*Count*	*% of 994*
Ulnar nerve damage	332	21%	188	33%	144	14%
Brachial plexus nerve damage	311	20%	122	21%	189	19%
Spinal cord injury	296	19%	51	9%	245	25%
Lumbrosacral nerve root or cord	268	17%	90	16%	178	18%
Sciatic nerve damage	100	6%	35	6%	65	7%
Median nerve damage	91	6%	30	5%	61	6%
Radial nerve damage	61	4%	21	4%	40	4%
Femoral nerve damage	53	3%	17	3%	36	4%
Other nerve injuries	159	10%	36	6%	123	12%

Nerve injury claims following all anesthesia types in the American Society of Anesthesiologists (ASA) Closed Claims Database 1970-2010 ($N = 1564$ of 5436 total claims in the database). Note the change in distribution over time, particularly a decrease in the fraction of ulnar nerve injuries and an increase in the fraction of spinal cord injuries.
Data from personal communication from Posner KL for publication in Miller's Anesthesia.



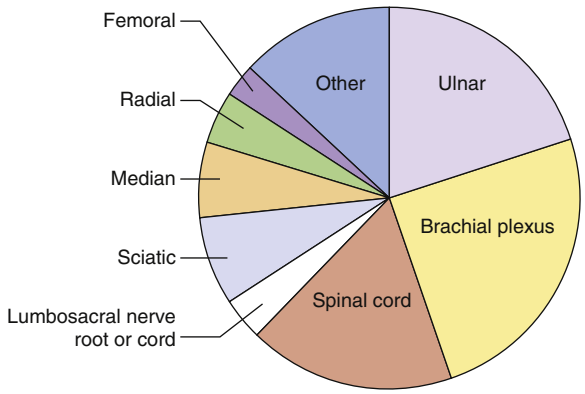
Nerve injury closed claims following all anesthesia types, 1990-2010, ($N = 994$).

to 2010 show that, after general anesthesia, the largest fractions were damage to the brachial plexus (27%) followed by the ulnar nerve (22%) and the spinal cord (19%) (Table 41-1B). For claims filed after regional anesthesia, the distribution included large fractions of injuries to the lumbosacral nerve roots (39%) and spinal cord (29%),[2] which are less likely to be related to positioning (Table 41-1C). Over the past 4 decades, the total number of claims for nerve injuries includes only 18 cases under monitored anesthesia care. In addition, 97 cases were recorded after combined general and regional anesthetics were administered, as well as a few cases for which the primary anesthetic was not recorded or no anesthetic was administered.

TABLE 41-1B TYPES OF NERVE INJURY—FOLLOWING GENERAL ANESTHESIA

	Total Nerve Injuries (1970-2010)		1970-1989		1990-2010	
	Count	*% of 886*	*Count*	*% of 346*	*Count*	*% of 540*
Ulnar nerve damage	280	32%	161	47%	119	22%
Brachial plexus nerve damage	235	27%	91	26%	144	27%
Spinal cord injury	123	14%	22	6%	101	19%
Lumbosacral nerve root or cord	30	3%	6	2%	24	4%
Sciatic nerve damage	66	7%	22	6%	44	8%
Median nerve damage	51	6%	13	4%	38	7%
Radial nerve damage	40	5%	11	3%	29	5%
Femoral nerve damage	26	3%	9	3%	17	3%
Other nerve injuries	98	11%	22	6%	76	14%

Nerve injury claims following general anesthesia in the American Society of Anesthesiologists (ASA) Closed Claims Database 1970-2010 (*N* = 886). Note that claims for brachial plexus injury outnumber those for ulnar nerve damage in the more recent data.
Personal communication from Posner KL for publication in Miller's Anesthesia.



Nerve injury closed claims following general anesthesia, 1990-2010, (*N* = 540).

TABLE 41-1C TYPES OF NERVE INJURY FOLLOWING REGIONAL ANESTHESIA

	Total Nerve Injuries (1970-2010)		1970-1989		1990-2010	
	Count	*% of 552*	*Count*	*% of 202*	*Count*	*% of 350*
Ulnar nerve damage	44	8%	23	11%	21	6%
Brachial plexus nerve damage	59	11%	29	14%	30	9%
Spinal cord injury	124	22%	23	11%	101	29%
Lumbosacral nerve root or cord	220	40%	83	41%	137	39%
Sciatic nerve damage	28	5%	11	5%	17	5%
Median nerve damage	33	6%	14	7%	19	5%
Radial nerve damage	10	2%	7	3%	3	1%
Femoral nerve damage	24	4%	8	4%	16	5%
Other nerve injuries	41	7%	11	5%	30	9%

Nerve injury claims following regional anesthesia in the American Society of Anesthesiologists (ASA) Closed Claims Database 1970-2010 (*N* = 552).
Note: Claims associated with chronic pain management excluded; claims with missing event decade excluded. The results from Tables 41-1B and 41-1C do not add up to the totals in Table 41-1A because of claims associated with monitored anesthesia care, combined anesthetic techniques, unknown primary anesthetic, or no anesthetic administered.
Personal communication from Posner KL for publication in Miller's Anesthesia.

In a detailed report published in 1999 of 670 claims related to peripheral nerve injury, the ulnar nerve was the most frequent site of injury (28%), followed by the brachial plexus (20%), lumbosacral nerve root (16%), and spinal cord (13%).[3] Data in that report showed the beginnings of a significant evolution in the distribution of nerve injuries. Ulnar neuropathy decreased from 37% of injuries in the early 1980s to 17% in the 1990s. Spinal cord injury increased from 8% of injuries in the early 1980s to 27% in the 1990s. Spinal cord injury and lumbosacral nerve root neuropathy were predominantly associated with regional anesthesia. Epidural hematoma and chemical injuries represented 29% of the known mechanisms of injury among the claims filed. The injuries were probably related to the use of neuraxial block in patients on anticoagulant therapy and the increased use of blocks to manage chronic pain.[3,76,77] In two reports on claims arising from anesthesia outside the surgical unit, nerve injuries appeared rare, making up only 4% to 7% of claims. Death represented 54% of claims in this subset, versus 24% for surgical cases. This high proportion was associated with the large fraction (58%) of monitored anesthesia care outside the surgical unit.[78] For claims after monitored anesthesia care, 40% were for patient death[79]; therefore the nonsurgical environment seems to impart additional risk of death as a cause for a claim.

In a 10-year retrospective study of 380,680 patients at a single university tertiary care institution, 112 peripheral nerve injuries were observed in the perioperative period, an incidence of 0.3%.[80] Risk factors were hypertension, diabetes, and tobacco use. General and epidural anesthesia appeared to be risk factors, compared with monitored anesthesia care, spinal anesthesia, and peripheral nerve blocks. Most injuries were sensory (60%) or combined sensory and motor (24%) with only 14% pure motor injuries. This study provides a significantly different numerator and denominator than the ASA Closed Claims Project, and its data contrast with the most recent claims data in which a greater fraction of claims were filed after the administration of regional anesthesia.

With the exception of spinal cord injuries, the mechanism of nerve injury remains incompletely explained by scientific studies. Most nerve injuries, particularly those to nerves of the upper extremity such as the ulnar nerve and brachial plexus, occurred in the presence of adequate positioning and padding. In a retrospective study of 1000 consecutive spine surgeries that used somatosensory-evoked potential (SSEP) monitoring, five arm positions were compared regarding SSEP changes in the upper extremities. A modification of arm position reversed 92% of upper extremity SSEP changes. The incidence of position-related upper extremity SSEP changes was significantly higher in the prone "superman" (7%) and lateral decubitus (7.5%) positions, compared with the supine arms out, supine arms tucked, and prone arms tucked positions (1.8% to 3.2%). Reversible SSEP changes were not associated with postoperative deficits[80] (see also Chapter 49).

Because of the significant morbidity associated with peripheral nerve injury, the ASA published a Practice Advisory for the prevention of peripheral neuropathies in 2000 that was updated in 2011.[20,32] However, the advisories were not based on scientific evidence but on the consensus of a group of expert consultants. Only 6 out of 509 studies reviewed for the original advisory "…exhibited sufficiently acceptable methods and analyses that provided a clear indication of the relationships between interventions and outcomes of interest"[32] (Box 41-1). Despite the addition of 50 new citations, the 2011 advisory stated, "No evidence linkage contained sufficient literature with well-defined experimental designs and statistical information to conduct an analysis of aggregated studies (i.e., a meta-analysis)…. In conclusion, the current literature has not been helpful in determining the efficacy of perioperative positioning techniques in reducing the occurrence of peripheral neuropathies."[20]

Because of the paucity of clear data on the causes and the prevention of peripheral injuries, individual practices vary. Good sense would avoid positions that permit stretching of the nerves and pressure to anatomic locations known to carry nerves prone to injury, such as the ulnar cubital tunnel and the peroneal nerve coursing over the fibular head (Table 41-2). Padding and support should distribute weight over as wide an area as possible; however, no padding material has been shown to be superior. Whenever possible, the patient's position should appear natural. Anesthesia and muscle relaxation increase the danger of malposition-induced injuries. Extremes of weight remain risks as well.

SPECIFIC NEUROPATHIES

ULNAR NERVE INJURY

The manner of causation of perioperative ulnar neuropathy is complex and incompletely understood. The ulnar nerve lies in a superficial position at the elbow. Although the incidence is low, the morbidity associated with ulnar neuropathy can be severe. In a prospective study among 1502 patients undergoing noncardiac surgery, 7 patients developed perioperative ulnar neuropathy, of which 3 patients had residual symptoms after 2 years.[81] The neuropathy, if permanent, results in the inability to abduct or oppose the fifth finger, diminished sensation in the fourth and fifth fingers, and eventual atrophy of the intrinsic muscle of the hands creating a clawlike hand.

Previously, the injury was thought to be associated with hyperflexion of the elbow and compression by the surgical table of the nerve at the condylar groove and the cubital tunnel against the posterior aspect of the medial epicondyle of the humerus. In a study on the effect of arm position on the ulnar nerve SSEPs in 15 healthy awake male volunteers, the supinated position was associated with the least pressure on the ulnar nerve, and the neutral position was the next most favorable. When in the neutral position on a surgical armrest, pressure decreased as the arm was abducted between 30 and 90 degrees. Interestingly, not all patients had symptoms of nerve compression when the SSEP was abnormal.[82]

BOX 41-1 ***Summary of the 2011 American Society of Anesthesiologists Practice Advisory for the Prevention of Perioperative Peripheral Neuropathies***

Preoperative Assessment

- When judged appropriate, it is helpful to ascertain that patients can comfortably tolerate the anticipated operative position.
- Body habitus, preexisting neurologic symptoms, diabetes, peripheral vascular disease, alcohol dependence, arthritis, and sex (e.g., male sex and its association with ulnar neuropathy) are risk factors for perioperative neuropathy.

Upper Extremity Positioning

- Limit arm abduction to 90 degrees in supine patients; patients who are positioned prone may tolerate arm abduction greater than 90 degrees.
- Arms should be positioned to decrease pressure on the postcondylar groove of the humerus (ulnar groove). When arms are tucked at the side, a neutral forearm position is recommended. When arms are abducted on armboards, either supination or a neutral forearm position is acceptable.
- Flexion of the elbow may increase the risk of ulnar neuropathy; however, there is no consensus on the degree of acceptable flexion.
- Prolonged pressure on the radial nerve in the spiral groove of the humerus should be avoided.
- Extension of the elbow beyond a comfortable range may stretch the median nerve.
- Periodic perioperative assessments may ensure maintenance of the desired position.

Lower Extremity Positioning

- Lithotomy positions that stretch the hamstring muscle group beyond a comfortable range may stretch the sciatic nerve.
- Extension of the hip and flexion of the knee stretch the sciatic nerve and branches. Consider the effect of both when determining the degree of hip flexion.
- Avoid prolonged pressure on the peroneal nerve at the fibular head.
- Neither extension nor flexion of the hip increases the risk of femoral neuropathy.

Protective Padding

- The risk of neuropathy may be decreased by:
  - Padded armboards.
  - The use of chest rolls in laterally positioned patients.
  - Padding at the elbow.
  - Padding at the fibular head.
- If too tight, however, padding may increase the risk of neuropathy.

Equipment

- Properly functioning and positioned automated blood pressure cuffs on the arms do not affect the risk of upper extremity neuropathies.
- Shoulder braces in steep head-down positions may increase the risk of brachial plexus neuropathies.

Postoperative Assessment

- A simple postoperative assessment of extremity nerve function may lead to early recognition of peripheral neuropathies.

Documentation

- Documentation of specific positioning actions may improve care by:
  - Helping practitioners focus attention on relevant aspects of patient positioning.
  - Providing information on positioning strategies that eventually leads to improvements in patient care.

From the Practice Advisory for the prevention of perioperative peripheral neuropathies: an updated report by the American Society of Anesthesiologists Task Force on prevention of perioperative peripheral neuropathies, Anesthesiology *114:741-754, 2011.*

TABLE 41-2 **MOST COMMON NERVE INJURIES IN THE ASA CLOSED CLAIMS DATABASE 1990-2010**[1]

Nerve Injury	Recommendations for Prevention
Ulnar nerve (14%)	• Avoid excessive pressure on the postcondylar groove of the humerus. • Keep the hand and forearm either supinated or in a neutral position.

Brachial plexus (19%)	• When utilizing a steep head-down (Trendelenburg) position:
	  ◦ Avoid the use of shoulder braces and beanbags when possible (use nonsliding mattresses).
	  ◦ Avoid abduction of the arm(s) when possible.
	• Avoid excessive lateral rotation of the head, either in the supine or prone position.
	• Limit abduction of the arm to <90 degrees in the supine position.
	• Avoid the placement of high "axillary" roll in the decubitus position— keep the chest roll out of the axilla to avoid neurovascular compression.
	• Use ultrasound to locate the internal jugular vein for central line placement.

Spinal cord (25%) and lumbosacral nerve root or cord (18%)	• Be aware that the fraction of spinal cord injuries is increasing, probably in relation to use of regional anesthesia. • Avoid severe cervical spine flexion or extension when possible. • Follow current guidelines for regional anesthesia in patients on anticoagulant therapy.*
Sciatic and peroneal nerves (7%)	• Minimize the time in the lithotomy position. • Use two assistants to coordinate simultaneous movement of both legs to and from the lithotomy position. • Avoid excessive flexion of the hips, extension of the knees, or torsion of the lumbar spine. • Avoid excessive pressure on peroneal nerve at the fibular head.

ASA, American Society of Anesthesiologists.
Data from ASA Closed Claims Project 1990-2010.
N = 994 nerve injuries. Excludes claims associated with chronic pain management. Personal communication from Posner KL.[2]
*Horlocker TT, Wedel DJ, Benzon H, et al: Regional anesthesia in the anticoagulated patient: defining the risks (The second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation), *Reg Anesth Pain Med* 28:172-197, 2003.

Current consensus is that the cause of ulnar nerve palsy is multifactorial and not always preventable.[83,84] In a large retrospective review of perioperative ulnar neuropathy lasting longer than 3 months, the onset of symptoms occurred more than 24 hours postoperatively in 57% of patients; 70% were men, and 9% experienced bilateral symptoms. Very thin or obese patients were at increased risk, as were those with prolonged postoperative bed rest. No association with intraoperative patient position or anesthetic technique was confirmed.[85] The ASA Closed Claims Project also demonstrated that perioperative ulnar neuropathy occurred predominately in men, in an older population, and with a delayed onset (median of 3 days).[3] In addition, although most ulnar damage claims were associated with general anesthesia, payment was also made for claims where the patient had been awake or sedated during regional anesthesia involving the lower extremity. Interestingly, in a prospective study of patients who did not undergo surgical procedures, 2 of 986 patients developed ulnar neuropathy.[86] The large predominance of ulnar injury in men may possibly be explained by anatomic differences. Men have a more developed and thickened flexor retinaculum with less protective adipose tissue and a larger (1.5×) tubercle of the coronoid process that can predispose this patient population to nerve compression in the cubital tunnel.[87,88] Other risk factors, including diabetes mellitus, vitamin deficiency, alcoholism, cigarette smoking, and cancer, require further studies to be substantiated. In the published ASA Closed Claims Project data, only 9% of ulnar injury claims had an explicit mechanism of injury, and in 27% of claims, the padding of the elbows were explicitly stated.[3] Postoperative ulnar nerve palsy can occur without any apparent cause, even when padding and positioning of the patient's arm were carefully managed and documented in the anesthetic record.[22]

BRACHIAL PLEXUS INJURY

The brachial plexus is susceptible to stretching because of its long superficial course from the neck to the arm via the axilla with two points of fixation—the cervical vertebrae and the axillary fascia. The nerves of the brachial plexus sling under the clavicle and the pectoralis muscles and are therefore variably stretched with many movements of the arm or head. The nerves are vulnerable to compression as they pass between the clavicle and the first rib because of the proximity and mobility of both the clavicle and the humerus (see Fig. 41-6). Among patients undergoing noncardiac surgeries, the incidence of brachial plexus injury is reported to be 0.02%.[89] After brachial plexus injury, the patient often complains of sensory deficit in the distribution of the ulnar nerve. This symptom is most commonly associated with intraoperative arm abduction greater than 90 degrees, lateral rotation of the head away from the side of the injury, asymmetric retraction of the sternum for internal mammary artery dissection during cardiac surgery, or direct trauma or compression. To avoid injury, patients should ideally be positioned with the head midline, arms kept at the sides, the elbows mildly flexed, and the forearms supinated, without pressure on the shoulders or the axilla.

Brachial plexus injury is particularly associated with the use of shoulder braces in patients undergoing surgery in the Trendelenburg position. Medial placement of the braces can compress the proximal roots, and lateral placement of the braces can stretch the plexus by displacing the shoulders against the thorax (see Fig. 41-6). The patient with injury often complains of painless motor deficit in the distribution of the radial and median nerves; however, pain may also be present. A report of three cases of upper- and middle-trunk brachial plexopathy after robotic prostatectomy highlights the potential risk of a combination of compression of the shoulder girdle against the thorax in the steep Trendelenburg position with abduction of an arm.[30] Signs of vascular compromise to the upper extremities, such as difficulty obtaining consistent blood pressure or a poor pulse oximetry signal, may be indications of compromise to the neurovascular bundle as reported in a case of bilateral injury related to shoulder braces with abduction of the arms in the Trendelenburg position.[90] Studies of the brachial plexus tension test in human volunteers and nerve strain in cadavers have demonstrated deleterious positional elements including arm abduction, rotation or flexion of the head away from the affected arm, elbow and wrist extension, and depression of the shoulder girdle.[29,91] For transaxillary robotic thyroidectomy, a recently developed approach has the arm abducted to 180 degrees. An incidence of brachial plexus injury has been reported to be 0.3%.[92] When an extreme position is used, neurophysiologic monitoring, such as motor-evoked potentials and SSEPs, has been shown to detect an evolving injury and allow for repositioning to prevent permanent damage.[93,94] Nerve function monitoring may therefore become increasingly common with newer surgical techniques that carry increased risk related to patient positioning.

In patients undergoing cardiac surgery requiring median sternotomy, brachial plexus injury has been specifically associated with the C8-T1 nerve roots. In a prospective study in which the incidence of injury was 4.9%, the authors found that 73% of the injuries occurred on the same side as the internal jugular vein cannulation; however, this study antedated the widespread use of ultrasound to guide cannulation.[95] Unilateral sternal retraction to harvest the mammary artery is associated with brachial plexus dysfunction, presumably caused by stretching the nerves. SSEP monitoring of the brachial plexus during sternal retraction has been shown to predict injury.[96]

In the 1999 ASA Closed Claims Project report, 10% of brachial plexus injuries were directly attributed to patient positioning. Of those, one half involved the use of shoulder braces in patients in the Trendelenburg position.[3] Consequently, nonsliding mattresses should be used, along with a concerted effort to avoid compression of the shoulders as much as possible.[25,26] Of the 311 brachial plexus injuries in the ASA Closed Claims Project, 59 (19%) occurred after a regional block without general anesthesia,[2] including axillary and interscalene blocks.[3] In those cases, the role of patient positioning cannot be determined.[3]

OTHER UPPER EXTREMITY NERVE INJURY

Although quite rare, the radial nerve can be injured from direct pressure as it traverses the spiral groove of the humerus in the lower one third of the arm. The injury often exhibits a wrist drop with an inability to abduct the thumb or extend the metacarpophalangeal joints. An isolated median nerve injury most often occurs during the insertion of an intravenous needle into the antecubital fossa in a patient who has been anesthetized where the nerve is adjacent to the medial cubital and basilic veins. Patients with this injury are unable to oppose the first and fifth digits and have decreased sensation over the palmar surface of the lateral three and one half fingers. Surprisingly, in an evaluation of the ASA Closed Claim database from 1970 to 2001, peripheral intravenous and arterial line insertion accounted for 2.1% of all claims filed, particularly among patients who underwent cardiac surgery where the arms were tucked and the lines were not visible for inspection.[97] Nerve injury accounted for 17% of intravenous line complications, second only to skin slough or necrosis (28%) and swelling, inflammation, and infection (17%).

LOWER EXTREMITY NERVE INJURY

Injuries to the sciatic and common peroneal nerves occur most often in the lithotomy position. Because of its fixation between the sciatic notch and the neck of the fibula, the sciatic nerve can be stretched with external rotation of the leg. The sciatic nerve and its branches cross the hip and knee joints and are stretched by hyperflexion of the hips or extension of the knees. The common peroneal nerve, a branch of the sciatic, is most often damaged from the compression between the head of the fibula and an external structure, such as the frame of a leg support. Most often, patients who suffer a peroneal nerve injury will complain of a foot drop and the inability to extend the toes in a dorsal direction or evert the foot. In a prospective study of 991 patients undergoing surgery under general anesthesia in the lithotomy position, the incidence of lower extremity neuropathies was 1.5%, with injuries to the sciatic and peroneal nerves representing 40% of the cases. Interestingly, symptoms were predominantly paresthesia with onset within 4 hours of surgery and resolution generally within 6 months. No motor deficits were noted, but in a previous retrospective study, the same authors found the incidence of severe motor disability in patients who underwent surgery in the lithotomy position to be 1 in 3608.[34,35]

Injury to the femoral or obturator nerves generally occurs from lower abdominal surgical procedures with excessive retraction. The obturator nerve can also be injured during a difficult forceps delivery or by excessive flexion of the thigh to the groin. A femoral neuropathy will exhibit decreased flexion of the hip, decreased extension of the knee, or a loss of sensation over the superior aspect of the thigh and medial or anteromedial side of the leg. An obturator neuropathy will exhibit an inability to adduct the leg with decreased sensation over the medial side of the thigh.

PERIOPERATIVE EYE INJURY AND VISUAL LOSS

Although quite rare, with an incidence of 0.056% in one retrospective review,[98] perioperative eye injuries are a source of significant morbidity and liability (see also Chapter 100). In the ASA Closed Claims database, eye complications made up 3% of all claims and were associated with greater monetary settlements as compared with nonocular injuries.[3]

Corneal abrasion continues to be the most common type of perioperative eye injury and is associated with direct trauma to the cornea from facemasks, surgical drapes, or other foreign objects. Corneal abrasion can also be associated with decreased basal tear production or swelling of the dependent eye in patients in the prone position. Patients complain of pain associated with a foreign body sensation in the eye upon awakening from surgery. This pain can also occur from a dried section of cornea. Symptoms are generally transient, and treatment is made up of supportive care and antibiotic ointment to prevent bacterial infection. In a prospective study of 671 patients undergoing nonocular surgery, 4.2% of patients reported a new onset of blurred vision lasting at least 3 days after surgery. For most patients, the symptoms resolved within 2 months without complication. However, 1% of patients required visits to eye care providers.[99] Precautionary measures to reduce the incidence of corneal abrasion include early and careful taping of the eyelids after the induction of anesthesia, an awareness of dangling objects when leaning over patients, and close observation as patients awaken. Before they are completely awake, patients often try to rub their eyes or nose with pulse oximeter probes, armboards, and intravenous lines attached, inadvertently endangering their eyes.

Postoperative visual loss is a devastating complication that has been associated with specific surgeries and patient risk factors. Chapter 100, "Postoperative Visual Loss," of this text is dedicated to this subject. Risk varies with the type of surgery. The incidence varies from a range of 1 in 60,965 to 1 in 125,234 for patients undergoing noncardiac, nonocular surgeries,[98,100] to 0.06% to 0.113% for patients undergoing cardiac surgery with cardiopulmonary bypass,[101,102] and 0.09% for patients undergoing spine surgery in the prone position.[103] Ischemic optic neuropathy (ION) and, to a lesser extent, central retinal arterial occlusion from direct retinal pressure are the conditions most cited as potential causes. Perioperative factors associated with an increased risk of ION include prolonged hypotension, long duration of surgery especially in the prone position, large blood loss, large crystalloid use, anemia or hemodilution, and increased intraocular or venous pressure from the prone position.[104,105] Intraocular pressure increases in the dependent eye in the lateral decubitus position as well.[106] In addition, steep Trendelenburg positioning for robotic prostatectomies has been shown to cause a time-dependent increase in intraocular pressure that is positively correlated with end-tidal carbon dioxide (ET_{CO_2}) concentration.[107] Patient risk factors associated with ION include hypertension, diabetes, atherosclerosis, morbid obesity, and tobacco use. However, with the exception of obvious

external compression of the eyes, the cause of perioperative visual loss appears to be multifactorial in nature with no consistent underlying mechanism.

In 1999, the ASA Committee on Professional Liability established the ASA Postoperative Visual Loss (POVL) Registry to better understand the complication. By 2005, 131 cases were reported to the registry, of which 73% of reported cases involved patients who underwent spine surgeries and 9% who underwent cardiac surgery.[108-110] Of the 93 patients with postoperative visual loss after prone spine surgery, Lee and associates reported that 89% were diagnosed with ION, predominantly posterior, and 11% with central retinal artery occlusion (CRAO). In patients who were diagnosed with ION, 66% had documented bilateral involvement, of which 42% had eventual improvement in vision, although often clinically insignificant. Compared with CRAO, patients with ION had significantly higher anesthetic duration (9.8 ± 3.1 versus 6.5 ± 2.2 hours), estimated blood loss (median 2 versus 0.75 liters) and crystalloid infusion (9.7 ± 4.7 versus 4.6 ± 1.7 liters). Patients with ION were also relatively healthy (64% ASA class I and II), and 73% were men.[110] Using a multicenter case-control design in a 2012 follow-up study, Lee and associates compared 80 patients who developed ION after spine surgery with 315 adult control patients without ION after spine fusion surgery, randomly selected from 17 institutions. After a multivariate analysis, they found that independent risk factors for ION after spine fusion surgery included obesity, male sex, Wilson frame use, longer anesthetic duration, greater estimated blood loss, and decreased percent of colloid administration.[111] However, although all of these patients were prone, the report does not include data on the tilt of the table, and cases for which multiple data fields (including table tilt) are missing, were eliminated from the POVL reports.

In 2006, the ASA issued a Practice Advisory for perioperative visual loss associated with spine surgery that was updated in 2012.[112,113] Positioning-related recommendations were the following:

- Avoid direct pressure on the eye to prevent CRAO.
- Position the high-risk patient to ensure that the head is level with or higher than the heart, when possible.
- Position the high-risk patient without significant neck flexion, extension, lateral flexion, or rotation, when possible.
- Avoid external compression of the abdomen or chest.

Although not scientifically proven, many consultants believed that the horseshoe head holder may increase intraocular pressure. No evidence suggests that facial edema or ocular compression causes anterior or posterior ION. Additional recommendations include frequent eye checks during surgery, although the required frequency has not been established; frequent checks may help prevent central retinal artery occlusion.[113] In addition, careful attention to factors related to oxygen delivery, including oxygen tension and the maintenance of adequate intravascular volume and cardiac output, is recommended.[114] The patient's vision should also be checked postoperatively when the patient is alert.[113] Unfortunately, no definite recommendations were made concerning the issue of induced hypotension, the use of vasopressors, specifically α-adrenergic agonists, or transfusion threshold because of the multifactorial nature and the low incidence of the injury.

Despite a lack of direct evidence, additional suggestions for patients at high risk for eye injury or visual loss who are undergoing complex spine surgery include the following:[112,113]

- Discuss the possibility of staging the spine surgery in consultation with the surgeon.
- Use colloids along with crystalloids to maintain intravascular volume. Consider placement of a central venous line for monitoring preload.
- For patients who are preoperatively anticipated to undergo procedures that are prolonged and have substantial blood loss (or both), consider informing the patients of a small, unpredictable risk of perioperative visual loss.

Until the causative factors of this devastating type of injury are better defined, debate regarding patient management strategies will likely continue. Intraocular pressures are increased in the dependent eye in the lateral position and in both eyes in the prone position in the absence of any external pressure. External eye pressure should be avoided at all times, time in the prone position should be limited whenever possible, and frequent eye checks should be documented when patients are in the prone position.

EVALUATION AND TREATMENT OF PERIOPERATIVE NEUROPATHIES

When a nerve injury becomes postoperatively apparent, performing and documenting a directed physical examination to correlate the extent of sensory or motor deficits with the preoperative examination and any intraoperative events is essential. Whether or not a cause is suspected, seeking consultation with a neurologist to help define the neurogenic basis, localize the site of the lesion, and determine the severity of injury is prudent to help determine the prognosis.[115,116] With proper diagnosis and management, most nerve injuries resolve; however, months to years may be required.[73] In addition, perioperative neuropathies associated with pain must be differentiated from surgically induced neuropathic pain, which is receiving increasing attention by surgeons because it postoperatively affects an estimated 10% to 40% of surgical patients postoperatively.[117]

For motor neuropathy, an electromyogram (EMG) can be performed to characterize the injury. An EMG examination involves recording the electrical activity of muscle from a needle electrode inserted within it. If present, abnormalities may point to the affected component in the motor unit, which consists of the anterior horn cell, its axon and neuromuscular junctions, and the muscle fibers that it innervates. Certain findings are suggestive of denervation, including the presence of abnormal spontaneous activity in the resting muscle (fibrillation potentials and positive sharp waves, which results from muscle irritability) and increased insertion activity. Insertion

activity increases within a few days of muscle denervation, whereas abnormal spontaneous activity takes 1 to 4 weeks to develop, depending on the distance from the nerve lesion to the muscle. From a medicolegal standpoint (see also Chapter 11), the presence of abnormal spontaneous activity in the acute setting may suggest the nerve injury was preoperatively present. In addition, depending on the pattern of abnormalities, an EMG study may distinguish between radiculopathies, plexopathies, and neuropathies. Electrodiagnostic testing will not, however, identify the cause of the neuropathy.

For anesthesiologists, nerve conduction studies may be more useful to evaluate potential peripheral nerve injuries, such as ulnar neuropathy. Nerve conduction studies permit the assessment of both motor and sensory nerves. To evaluate motor integrity, the nerve is supramaximally stimulated at two points along its course, and a recording is made of the electrical response of one of the muscles that it innervates. The size of the muscle action potential provides an estimate of the number of motor axons and muscle fibers that are activated by the stimulus. For sensory conduction studies, the nerve fiber is supramaximally stimulated at one point and the sensory nerve action potential is recorded from another point. The latency of the response can be interpreted as a reflection of the number of functioning sensory axons. Nerve conduction studies are useful for several reasons; they may reveal the presence of a subclinical polyneuropathy that made the individual nerves more susceptible to injury and help distinguish between axon loss and demyelination, which has significant implications regarding course and overall prognosis.

Most sensory neuropathies are generally transient and require only reassurance to the patient with follow-up visits, whereas most motor neuropathies include demyelination of peripheral fibers of a nerve trunk (neurapraxia) and generally take 4 to 6 weeks for recovery. Injury to the axon within an intact nerve sheath (axonotmesis) or complete nerve disruption (neurotmesis) can cause severe pain and disability. When reversible, recovery often takes 3 to 12 months. Interim physical therapy is recommended to prevent contractures and muscle atrophy.[115,116]

If a new sensory or motor deficit is found postoperatively, then electrophysiologic evaluation by a neurologist within the first week may provide useful information concerning the characteristic and temporal pattern of the injury. Another examination after 4 weeks, when enough time has elapsed for the electrophysiologic changes to evolve, will provide more definitive information about the site, nature, and severity of the nerve injury. Regardless, electrophysiologic testing must be interpreted within the clinical content for which it was obtained. No single test can define the cause of injury.

With regard to professional liability for perioperative nerve injuries, it is important for anesthesia providers to appreciate that case laws on assignment and apportionment of liability remain unsettled, largely because determining the patient's position during a procedure is not a core responsibility of the anesthesia provider.[118] In addition, injuries occur despite best practices. For perioperative ulnar neuropathy, opinion regarding its cause has evolved. Although once largely attributed to positioning in the surgical unit, the current consensus is that the cause is poorly understood, and injuries are not entirely preventable.[86,91] However, jurors and judges are not familiar with the surgical environment or practices, and the variety of "expert" opinions have contributed to a wide range of judicial outcomes with regard to the liability of anesthesiologists. Although the cooperation of the entire surgical team is required, the position for surgery is largely dictated and accepted or modified by the surgeon. National guidelines and institutional policies and procedures may help address the responsibility of team members regarding patient positioning and highlight the primary roles of the anesthesia provider, which are to protect the airway and vascular access and to promote physiologic homeostasis while the patient is in the requested position.[118]

ANESTHESIA OUTSIDE THE OPERATING ROOM

Anesthesia care providers are increasingly involved with procedures performed for gastrointestinal endoscopy, cardiac catheterization, interventional radiology, neuroradiology, magnetic resonance imaging, and computed tomography, as well as for office-based procedures (see also Chapter 90).[119] Anesthesia care may be specifically requested because an individual is not expected to tolerate the position required for the procedure because of comorbidities such as congestive heart failure, pulmonary disease, or morbid obesity. Additionally, although positions that are customarily used for procedures without anesthesia may be generally safe for patients who are awake, they may pose serious risks to those under anesthesia.

Because of the less familiar environment, relative lack of positioning equipment, and a variability in staff and nursing training with regard to patient positioning, vigilance is particularly important in settings outside the surgical unit to maintain patient safety. Many locations have not routinely had safety straps or arm supports available, for example. Diagnostic tables may not lend themselves to established intraoperative solutions to patient positioning challenges. The ability to initiate the Trendelenburg position to augment venous return and cardiac output rapidly is often lacking. When procedures are performed without securing the airway, accurate carbon dioxide monitoring is difficult. Detection of respiratory depression requires constant attention, because decreases in oxygen saturation are delayed if supplemental oxygen is being delivered. In some settings, such as magnetic resonance imaging and radiation therapy, the anesthesiologist is not in direct proximity to the patient, and vigilance is more challenging. Special monitors and video cameras are often required to supplement limited or no direct visibility of the patient or anesthesia equipment.

Currently, the number of claims in the ASA Closed Claims database for injuries during anesthesia care outside the surgical unit is extremely small (33 versus 4291 claims for intraoperative surgical anesthesia). However, 54% of these claims are associated with death, 63% with substandard care (predominantly the result of inadequate monitoring), and 58% involve monitored anesthesia

care among patients who were ASA class III to V, most of whom were at the extremes of age.[78] In such an environment, where practice patterns often evolve in the context of nonanesthetized patients, the anesthesiologist is especially important for verifying the safety of each patient's position and for implementing guidelines for patients under anesthesia.

CONCLUSION

The positioning of patients under anesthesia care is a major responsibility requiring great attention to detail and constant vigilance. Rapid positioning and optimal surgical exposure are virtues that may be instantly appreciated; however, the potential for lasting harm to patients from improper positioning and physiologic compromise must guide our actions. Each position has significant physiologic effects on ventilation and circulation. In addition, despite increased awareness, position-related complications, including peripheral nerve injuries, continue to remain a significant source of patient morbidity. As surgical techniques evolve, extreme positions sometimes permit advantages, such as smaller incisions and more effective displacement of internal organs to facilitate surgical exposure. Unfortunately, associated risks may increase with positions that would not be tolerated when patients are awake. Anesthesiologists, surgeons, and nurses must work together when each patient is positioned to promote comfort and safety in addition to the desired surgical exposure. Ideally, the final position should appear natural; that is, a position that the patient would comfortably tolerate if awake and unsedated for the anticipated duration of the procedure.

Complete references available online at expertconsult.com

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Chapter 42

Neuromuscular Disorders and Other Genetic Disorders

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Key Points

- Management of anesthesia in patients with acquired or inherited neuropathies introduces challenges for protecting the involved nerves against pressure, entrapment, or trauma associated with positioning of nerve blocks. Neurologic deficits are assessed and documented before the administration of regional anesthesia (see Chapters 56 and 57).
- Patients with autonomic dysfunction caused by conditions such as diabetes neuropathy or Guillain-Barré syndrome (GBS) are at increased risk for exaggerated hemodynamic response to anesthetics, as well as for aspiration of gastric contents from delayed gastric emptying.
- Prolonged immobility in patients who are critically ill is associated with a relative increase in immature acetylcholine receptors that can lead to insensitivity to nondepolarizing neuromuscular blocking drugs (NMBDs) or sensitivity to depolarizing neuromuscular blockers with the risk for increased potassium efflux (see also Chapter 34).
- Monitoring the neuromuscular transmission is mandatory in patients with myasthenia gravis (MG) if nondepolarizing NMBDs are to be administered. These patients may be extremely sensitive to nondepolarizing NMBDs and yet require a larger dose of succinylcholine than patients who do not have MG (see also Chapter 53).
- Lambert-Eaton myasthenic syndrome (LEMS) is caused by antibodies to the voltage-gated calcium channels on the presynaptic motoneuron terminals, with decreased acetylcholine release in the neuromuscular junction. Sensitivity to depolarizing and nondepolarizing NMBDs is increased, and the response to anticholinesterases is insufficient.
- Spinal anesthesia has been implicated in the postoperative exacerbation of multiple sclerosis (MS), but epidural application of low concentrations of local anesthetics has been successfully used in these patients.
- Because of the risk for rhabdomyolysis and hyperkalemia, succinylcholine should be avoided in patients with amyotrophic lateral sclerosis (ALS), Duchenne muscular dystrophy (DMD), and Becker muscular dystrophy (BMD) (see also Chapters 34 and 43).
- Cardiomyopathy and a progressive decline of pulmonary function are common in patients with DMD and may predispose them to perioperative pulmonary and cardiac complications. Volatile anesthetics are best avoided, and the use of total intravenous (IV) anesthesia should be considered in these patients when possible.
- Pulmonary complications caused by hypotonia, chronic aspiration of gastric contents, and central and peripheral hypoventilation are common in patients with myotonic dystrophy (DM) (see also Chapter 43). The possibility of prolonged postoperative mechanical ventilation should be considered. Cardiac manifestations of this disease include conduction abnormalities, arrhythmias, and cardiomyopathy.
- The extent of organ system involvement should be carefully assessed and documented in patients with mitochondrial disease, with particular emphasis on the degree of myopathy, endocrine and metabolic derangements, and neurologic function.

KEY POINTS—cont'd

- Evidence does not suggest that patients with hyperkalemic periodic paralysis (HyperPP) are susceptible to malignant hyperthermia (MH). Maintaining normothermia, preventing hyperkalemia, and avoiding hypoglycemia are important in these patients (see also Chapter 43).
- The genetics of mitochondrial disorders is a special case of mendelian disorders, and defects may be in mitochondrial DNA (mtDNA)–encoded or nuclear DNA (nDNA)–encoded structural or regulatory components of the mitochondrion. Recent genetic research has begun to unlock the basis for other complex diseases, which will facilitate a better understanding of perioperative implications and provide more effective and safe treatments for individual patients.

Diseases that affect peripheral nerves, neuromuscular junction, and muscles are rarely encountered in routine anesthetic practice but pose significant challenges to the perioperative management of the affected patient. Cardiovascular and respiratory systems are often involved, posing an increased risk for perioperative dysrhythmias, hypotension, or respiratory failure. Adverse reactions to neuromuscular blocking drugs (NMBDs) should be considered and may include severe hyperkalemia or prolonged paralysis. Autonomic dysreflexia, when present, increases the risk for cardiovascular instability or aspiration upon anesthesia induction. A thorough knowledge of organ system involvement is mandatory, and the choice of anesthetics and NMBDs has to be tailored to the specific needs of each patient.

In this chapter, some of the most common neuromuscular disorders and their anesthetic implications are reviewed. An overview of the genetics of the mendelian disorders and mitochondrial and complex diseases is also provided, and their implications for clinical translation and perioperative care are discussed. Lastly, because some of these disorders are related to malignant hyperthermia (MH), they are also discussed in Chapter 43. A comparison of these two conditions will provide additional points of view for the reader.

ACQUIRED AND HEREDITARY NEUROPATHIES

Lesions of peripheral nerves produce motor weakness or sensory disturbance and are accompanied by decreased muscle stretch reflexes. Mononeuropathies involve a single nerve and are commonly due to a compression associated with immobilization, entrapment, ischemia, or trauma with stretch or laceration. Carpal tunnel syndrome is the most common entrapment neuropathy caused by compression of the median nerve in the wrist, which results in pain, paresthesias of the hand and fingers, and sensory loss in the distal median nerve territory, including the thenar eminence.[1] Weakness of thumb adduction and opposition, resulting in a loss of grip strength, is a typical symptom. Comorbid conditions such as hypothyroidism and diabetes mellitus should be considered, and electromyography and nerve conduction study findings should be obtained for diagnosis and prognostication. Ulnar nerve compression and injury at the condylar groove, which lacks soft-tissue protection, is the most common perioperative peripheral neuropathy.[2] Symptoms include paresthesia of the fourth and fifth digits and weakness of the intrinsic muscles demonstrated as grip weakness and, in severe cases, clawhand. The brachial plexus with its relatively long course from the vertebral foramina to the axilla and its proximity to many mobile bony structures is particularly susceptible to injury from poor perioperative positioning.[3] Brachial plexus injuries may occur, nevertheless, despite appropriate positioning and padding during surgery. The association between hypertension and diabetes mellitus with perioperative peripheral nerve injuries[4] suggests a multifactorial etiologic origin. Over 40% of patients with diabetes are reported to develop clinical symptoms or electrophysiologic evidence of neuropathy.[5] Diabetic neuropathy includes a number of distinct clinical syndromes such as primary sensory polyneuropathy with symmetric and slowly progressive neuropathy of the feet and legs; autonomic neuropathy involving the bladder, bowel, and circulatory reflexes; and plexus neuropathy with severe hip, thigh, and knee pain, as well as weakness in the quadriceps muscles, which usually improves within weeks to months. Diabetic amyotrophy or Bruns-Garland syndrome (also known as *ischemic mononeuropathy multiplex*) is another form of plexus neuropathy with abrupt onset of asymmetric pain in the back, hips, thigh, or leg, and progressive muscle weakness.[6] Treatment is primarily expectant, although immunotherapy may be considered in severe cases. In patients who are critically ill, phrenic nerve mononeuropathy may develop as a result of prolonged systemic inflammation with immobilization during mechanical ventilation. This condition is diagnosed by electroneurography and diaphragmatic electromyographic recordings and may interfere with the ability to wean the patient from ventilator dependency and may prolong the stay in the intensive care unit (ICU).

Inherited neuropathies include Charcot-Marie-Tooth (CMT) diseases and hereditary neuropathy with liability to pressure palsies (HNPP). CMT affects approximately 1 in 2500 people and represents the most common inherited neurologic disorder.[7,8] It is not a single disease entity; rather, CMT represents a spectrum of disorders caused by mutations in myelin or axonal genes.[9]

Although traditionally classified as types 1 through 7, based on electrophysiologic, histologic, and clinical characteristics, multiple genetic subtypes[7,9] and mutations exist in more than 30 genes involving more than 40 distinct loci that give rise to the disorder.[7] The pattern of genetic inheritance is most commonly autosomal dominant, but X-linked and autosomal recessive forms also exist, as do sporadic cases as a result of new mutations.[7] In approximately two thirds of cases, demyelination as a result of mutations in genes expressed in Schwann cells causes the disorder; axonal dysfunction as a result of mutations expressed in neuronal cells cause the balance of the cases.[7,10] Demyelination, slowed motor nerve conduction velocities, and an autosomal dominant pattern of inheritance characterize CMT1, the most common type.[9] The most prevalent form of CMT1 is subtype CMT1A, which accounts for approximately 75% of CMT1 cases.[7] A 1.4 megabase (Mb) duplication in chromosome 17p11.2 causes CMT1A.[9,11] Patients with CMT typically experience progressive distal muscle weakness and wasting with hyporeflexia or areflexia. Mild sensory loss in a glove and stocking distribution, lower extremity deformity (peroneal muscle atrophy is typical), kyphoscoliosis, and neuropathic pain may also develop in some patients. Pes cavus (clawfoot) with hammer toes, footdrop, and frequent ankle sprains are not uncommon.[9] Onset generally occurs by 20 years of age; although the disorder does not compromise lifespan, it can cause significant disability. Variant forms of CMT exist, including Dejerine-Sottas neuropathy and congenital hypomyelination, which are characterized by onset in infancy and are sometimes fatal.[9]

Similar to CMT, HNPP is a slowly progressive neuropathy, but focal areas of irregular thickening of myelin sheaths (tomaculae) cause HNPP, and it demonstrates recurrent focal neuropathies caused by minor trauma.[12] HNPP typically develops during adolescence with attacks of numbness, muscle weakness, peroneal palsies, carpal tunnel syndrome, and other entrapment neuropathies. A nerve conduction study showed focal conduction block at the site of injury and generalized mild slowing, consistent with diffuse demyelinating disease. Some patients may have long-term neurologic dysfunction, but many show complete recovery after a focal neuropathy.

ANESTHETIC CONSIDERATIONS

Management of anesthesia in patients with mononeuropathies introduces challenges for protection of the involved nerve against further entrapment or trauma associated with positioning. Autonomic neuropathy may be associated with exaggerated hemodynamic response to the anesthetic as a result of involvement of the circulatory reflexes. Patients with diabetic autonomic neuropathy are also at greater risk for aspiration pneumonitis from delayed gastric emptying of food particles.[13]

Patients with CMT frequently require orthopedic surgery to correct the musculoskeletal manifestations of the disease, including foot and ankle defects, spinal deformities, and hip dysplasia.[14] Evidence regarding the anesthetic management of patients with CMT is limited and consists primarily of case reports and clinical series. Nevertheless, important concerns exist when anesthetizing patients with this condition, based on these reports and pathophysiologic considerations. Major considerations for the perioperative care of patients with CMT include the risk of adverse reactions to NMBDs, a susceptibility to MH, and the potential for respiratory weakness requiring prolonged ventilatory support. An increased sensitivity to hypnotic anesthetics has also been suggested, but intravenous and volatile anesthetics have been used in patients with CMT with no reported complications.[15] Nevertheless, multiple reports of worsening CMT symptoms have been recounted in patients exposed to nitrous oxide,[16] such that this agent should be avoided when possible. Other medications that are administered in the perioperative period that have been associated with worsening CMT include metronidazole, amiodarone, linezolid, and nitrofurantoin.[16]

The literature provides conflicting reports regarding the responses to NMBDs in patients with CMT. Pogson and associates reported an increased sensitivity to vecuronium,[17] whereas cisatracurium and mivacurium have been used with no evident prolongation of the neuromuscular blockade.[18-20] Because of the demyelination that occurs in the distal extremities, monitoring the neuromuscular blockade should preferentially occur at the facial rather than the ulnar nerve. Although succinylcholine has been successfully used in these patients,[21] clinicians are cautioned against its routine use, considering the risk of an exaggerated hyperkalemic response.[22] A single case report of MH associated with the administration of sevoflurane to a patient with CMT has been reported.[23,24] However, in the largest clinical series published to date, 77 patients with CMT were exposed to triggering anesthetics without complications.[25] No established association between CMT and MH has been established, and volatile anesthetics can be reasonably used in these patients.[24]

Regional anesthesia has been used in patients with CMT without clear evidence of associated complications.[25-28] Because of the concern for exacerbating the neurologic symptoms, however, regional anesthesia techniques are often avoided in these patients. Ultrasound-guided peripheral nerve blocks may reduce the risk of neurologic complications but should be reserved for patients with major risks for general anesthesia.[29] Neuraxial anesthesia has also been used for obstetric procedures in these patients, often with no reported exacerbation of their neurologic symptoms.[26,30] It is important that neurologic deficits are assessed and documented before administering anesthesia.[24]

As with CMT, patients with HNPP pose special concerns for their response to NMBDs, as well as the risk to exacerbate neurologic symptoms from patient positioning. The immobility associated with general anesthesia or regional block can potentially trigger pressure palsies in these patients. However, current literature provides no evidence against the use of neuraxial techniques or local anesthetics.[31] Despite the lack of evidence on the effects of surgical positioning in patients with HNPP, it is reasonable to assume that judicious positioning and thorough padding will reduce the risk of neurologic complications.

GUILLAIN-BARRÉ SYNDROME OR ACUTE INFLAMMATORY DEMYELINATING POLYRADICULOPATHY

Guillain-Barré syndrome (GBS) or acute inflammatory demyelinating polyradiculopathy (AIDP) is an acute onset of progressive peripheral neuropathy that is triggered by humoral and cell-mediated autoimmune response to a sensitizing event, such as a respiratory tract infection.[32] Its presentation is typically an ascending paralysis characterized by symmetric weakness that can vary from mild difficulty with walking to nearly complete paralysis of all extremities, facial, respiratory, and bulbar muscles. Mild variants can exhibit ataxia, ophthalmoplegia, or hyporeflexia without significant appendicular weakness. Fulminate cases can express severe ascending weakness leading to complete tetraplegia, as well as to paralysis of cranial nerves and phrenic and intercostal nerves leading to facial and respiratory muscle weakness that necessitates ventilatory support.[33] Autonomic dysfunction may occur and can cause hemodynamic instability and arrhythmias with the risk for sudden circulatory collapse and death.

Diagnosis is made based on clinical features such as areflexia and progressive motor weakness, cerebrospinal fluid (CSF) analysis with elevated protein but no pleocytosis (albuminocytologic dissociation), and electrophysiologic studies.[34] Electromyography and nerve conduction studies may be normal in the early acute period, but characteristic segmental demyelination and reduction of conduction velocity and dispersion or absence of F waves are usually observed within 1 to 2 weeks.

Management includes respiratory support, measures to prevent aspiration, and nutritional support. Early plasma exchange, typically five exchanges with 5% albumin repletion, may mitigate the course but is contraindicated in a setting of hemodynamic instability, prominent dysautonomia, and active bleeding.[35] Intravenous immunoglobulin (IVIG) is typically administered in the setting of dysautonomia or when a significant risk for catheter-related complications exist with plasmapheresis or when an exchange transfusion is performed.

ANESTHETIC CONSIDERATIONS

Cranial nerve paralysis and autonomic dysfunction predispose patients with GBS to an increased risk for aspiration. Aspiration precautions, including decompression of the stomach, should therefore be considered before the induction of anesthesia. An absence of compensatory cardiovascular responses may be associated with exaggerated hypotension at anesthesia induction or in response to hypovolemia. Conversely, laryngoscopy or noxious stimuli can be associated with an exaggerated increase in blood pressure. The hemodynamic instability is typically short-lived and self-limited, but small doses of short-acting and titratable vasoactive medications may be required.[36] Careful hemodynamic monitoring is essential, and continuous monitoring of the blood pressure with an arterial catheter is often considered. These patients may also exhibit abnormal responses to NMBDs, with a hyperkalemic response to succinylcholine *even after clinical resolution of symptoms*.[37] Nondepolarizing NMBDs can be used but are typically avoided because of the risk of prolonged muscle weakness. If these drugs are used, then the neuromuscular transmission should be closely monitored with a nerve stimulator since both resistance and sensitivity to these anesthetics have been reported.[38] Regional anesthesia is used by some practitioners,[39] but its use remains controversial because worsening neurologic symptoms have been reported.[40]

CRITICAL ILLNESS POLYNEUROPATHY AND CRITICAL ILLNESS MYOPATHY

Bolton and associates identified critical illness polyneuropathy (CIP) in 1987 and described this condition as a characteristically widespread axonal degeneration among motor and sensory fibers with subsequent extensive denervation atrophy of limb and respiratory muscle associated with polyneuropathy.[41] Although the true incidence of CIP is difficult to determine, critical illness neuropathy and critical illness myopathy (CIM) are believed to affect up to 50% of all patients remaining in the ICU for longer than 2 weeks.[42] Bolton also defined the myosin loss syndrome that is often observed in patients with CIM. This condition shows histologic signs of myosin loss, as opposed to actin, in skeletal muscle biopsies from affected muscles. The ratio of myosin to actin is typically below 1.0 with some patients showing a complete absence of myosin in skeletal muscle cells. The typical clinical manifestation consists of a profound symmetric limb weakness with reduced or absent tendon reflexes and diaphragmatic and intercostal weakness. CIM affects the lower extremities to a greater extent than the upper extremities and the distal muscle groups more severely than the proximal muscle groups. The autonomic function is not affected, and the extraocular eye movements remain intact. In CIP, no evidence of a neuromuscular junction disorder exists, and the electromyography and nerve conduction study findings are consistent with axonal motor and sensory polyneuropathy with amplitude reduction of motor and sensory action potentials and slowed conduction velocities. Serum creatine kinase levels are usually normal. Conversely, sensory nerve action potential is often normal in CIM, but compound muscle action potentials are diminished and electromyographic findings are consistent with myopathy. Serum creatine kinase levels may be elevated. No specific treatments are currently available, and management is supportive with aggressive and early rehabilitation. The use of sedation, paralytics, and corticosteroids should be limited,[43] and aggressive control of hyperglycemia can reduce the incidence of CIP by 44%.[44]

ANESTHETIC CONSIDERATIONS

Anesthetic considerations in these patients are similar to those with other acquired neuropathies (see previous text) and include protection of nerve compression sites, particularly the ulnar and peroneal nerves. Prolonged immobility in patients who are critically ill is associated with a relative increase in immature acetylcholine receptors that can lead to an insensitivity to nondepolarizing NMBDs.[45]

Conversely, the sensitivity to a depolarizing NMBD (succinylcholine) is increased, with a risk for increased potassium efflux after succinylcholine administration.[46]

MYASTHENIA GRAVIS

Myasthenia gravis (MG) is an autoimmune disorder of synaptic transmission caused by antibodies against nicotinic acetylcholine receptors (nAChRs). With an annual incidence of 1 in 200,000 to 500,000, MG has a prevalence of 0.5 to 14.2 per 100,000 in the United States and primarily affects women 20 to 30 years of age and men 60 to 80 years of age. Autoantibodies against the α-subunit of the muscle-type nAChRs destroy these receptors in the neuromuscular junction and cause transmission failure, manifested as muscle weakness and fatigue. The origin of these antibodies is not always known, but they may be associated with thymomas or thymic hyperplasia (80% of generalized MG and 30% to 50% of ocular MG). Autoantibodies against the muscle-specific tyrosine kinase (MuSK) are associated with the human leukocyte antigen (HLA)–B8 and the DRw3 antigen and are primarily identified in younger patients with MG.[47] Skeletal muscles innervated by cranial nerves are especially vulnerable, the involvement of which can lead to extraocular and facial muscle weakness or bulbar and oropharyngeal weakness. Speech and chewing may be affected, as well as the pharyngeal function and coordination of swallowing, placing the patient at an increased risk of pulmonary aspiration of gastric or oral contents. Skeletal muscle weakness in MG worsens with repetition or throughout the course of the day and, conversely, improves after rest. The clinical course may also be marked by periods of exacerbation and remission. Myocarditis, atrial fibrillation, heart block, takotsubo cardiomyopathy, and sympathetic hyperactivity with fluctuations in heart rate and blood pressure have been described in these patients.[48,49] The diagnosis of MG is made by neurologic examination and testing of the tendency to exhibit increased muscle weakness during exercise or repeated contractions. The response to edrophonium, which is administered as a 1- to 2-mg test dose followed by 8 mg intravenously, can confirm the diagnosis (Tensilon test). Improvement in the patient's preexisting weakness should be evident within 1 to 5 minutes of drug administration. Serologic studies include serum antibodies for acetylcholine receptor (present in 95% of patients), striated muscle, and MuSK (present in 65% of patients who are acetylcholine-receptor negative). Electromyography shows increased jitter, and nerve conduction studies with repetitive simulation produce decremental responses.[50] Management includes supportive care with mechanical ventilation as needed and the administration of cholinesterase inhibitors such as pyridostigmine.[51,52] Immunomodulatory drugs such as steroids and azathioprine are effective but have a delayed onset of action. Although steroids are shown to reduce the number of antibodies to the acetylcholine receptors and can significantly improve the symptoms, they may cause a transient worsening of the weakness at the initiation of therapy. IVIG and plasma exchange can be used for more rapid response in patients with severe bulbar and oropharyngeal dysfunction or those with MG crisis. Thymoma resection is helpful for paraneoplastic myasthenia, but its benefit in nonthymomatous autoimmune MG has not been conclusively established.[53]

ANESTHETIC CONSIDERATIONS

A thorough review of the neurologic symptoms and medications is of paramount importance. The ability of the patient with MG to protect and maintain a patent airway, to cough, and to clear secretions should be thoroughly assessed. These patients should be advised of the risk for worsening symptoms, which can require prolonged postoperative mechanical ventilation. Increased risk for postoperative myasthenic crisis and ventilatory support is possible if these conditions exist: prolonged duration of disease (longer than 6 years), presence of previous respiratory problems or coexisting lung disease, pyridostigmine doses of more than 750 mg/day, and preoperative forced vital capacity of less than 2.9 L have been suggested to predict increased risk for postoperative myasthenic crisis and ventilatory support.[54] The presence of bulbar symptoms, history of preoperative myasthenic crisis, preoperative serum antiacetylcholine receptor antibody level greater than 100 nmol/L, and intraoperative blood loss greater than 1000 mL have also been associated with postsurgical myasthenic crisis.[55] Elective surgeries should be performed during a stable phase of the disease and when the patient requires minimal immunomodulatory medication. Most of these medications do not interact with anesthetic agents, but azathioprine can inhibit nondepolarizing NMBDs and may extend the effect of succinylcholine. Most clinicians recommend that patients should keep taking their anticholinesterase medication on the day of surgery, but their interaction with the NMBDs should be considered.[56] A reduced number of functional acetylcholine receptors results in an increased sensitivity to nondepolarizing NMBDs.[57,58] Monitoring the neuromuscular transmission is mandatory, but clinicians should be cognizant of the possibility to overestimate the degree of neuromuscular blockade in these patients, particularly when the orbicularis oculi muscle responses are monitored. In addition, an uneven spread of muscle weakness exists; therefore, routine neuromuscular monitoring at one site (e.g., the hand) does not adequately represent the actual level of block in other muscle groups. The dose of these NMBDs should be cautiously titrated, such as by the administration of small increments corresponding to 0.1 to 0.2 times the 95% effective dose (ED_{95}) until the desired effect is achieved. Succinylcholine, on the other hand, often needs to be administered in larger-than-normal doses (ED_{95} 2.6 times the patient without MG) because of the decreased number of functional acetylcholine receptors.[59] A rapid desensitization of the myasthenic endplate receptors to succinylcholine has also been reported, indicating a susceptibility to developing phase II neuromuscular block.[60] Potent volatile anesthetics have been successfully used in patients with MG, and they commonly cause profound muscular relaxation, enough to allow most surgical procedures to be performed without the need for an NMBD.[61] Intravenous induction anesthetics and opioids have also been used

without significant adverse effects. If regional anesthesia is used, then careful monitoring of muscle function and ventilation is equally important. As ester-type local anesthetics are metabolized by the pseudocholinesterase, anticholinesterase treatment in patients with MG may potentiate their effects and lead to prolonged blockade. Although amide local anesthetics have been successfully used in patients with MG, judicious dosing is essential, as is the preparedness to manage worsening muscle weakness safely.[62,63]

LAMBERT-EATON-MYASTHENIC SYNDROME

Lambert-Eaton myasthenic syndrome (LEMS) is caused by antibodies to the voltage-gated calcium channels on the presynaptic motoneuron terminals, which lead to a decreased release of acetylcholine. This syndrome is frequently part of the paraneoplastic phenomenon (typically, a small-cell lung cancer is present in 50% to 60% of patients) but can also occur without associated cancer.[64] In more than 80% of patients with associated cancer, symptomatic onset of myasthenia precedes the diagnosis of their cancer. Symptoms are usually subacute at onset and are typically characterized by weakness in the proximal lower extremities, although upper extremity weakness, bulbar symptoms, and respiratory muscle weakness may also be present. Unlike MG, patients with LEMS are usually worse in the morning and gradually improve throughout the day. Their weakness also improves after brief exercise but can worsen with sustained physical activity. Improvement of muscle function with exercise is due to the accumulation of presynaptic calcium and subsequent improved release of acetylcholine. Autonomic dysfunction and cholinergic symptoms, including dryness of the mouth and impaired lacrimation, may be present. The diagnosis of LEMS is made by physical examination, showing proximal lower limb weakness, depressed tendon reflexes with posttetanic potentiation, and evidence of autonomic disturbances. Electromyography typically shows small compound muscle action potential (CMAP) amplitudes and a transient incremental CMAP response to rapid nerve stimulation (20 to 50 Hz) but a decremental response to slow nerve stimulation (1 to 5 Hz).[65] Autoantibodies against P/Q-type voltage-gated calcium channels are highly specific and have been detected in 85% to 90% of patients with LEMS.[66]

Cholinesterase inhibitors do not consistently produce improvement in these patients but may improve the muscle weakness or dry mouth in some. Aminopyridines (e.g., 3,4-diaminopyridine) are the first-line treatment for patients with symptomatic LEMS and improve the strength and autonomic function with minimal side effects in most patients.[67] Aggressive immunotherapy, plasma exchange, and immunoglobulin therapy result in rapid but transient improvement of symptoms.

ANESTHETIC CONSIDERATIONS

Similar to patients with MG, those with LEMS should be carefully assessed for the risk of postoperative respiratory failure and the need for prolonged mechanical ventilation. Sensitivity to depolarizing and nondepolarizing NMBDs is increased, and the response to anticholinesterases is insufficient. Autonomic dysfunction may be associated with an exaggerated response to vasodilators and anesthesia induction drugs. Close monitoring of the neuromuscular transmission is important, and in patients whose train-of-four responses are insufficient, monitoring of the tetanic stimulation and posttetanic facilitation should be considered.[68] Reversal of the neuromuscular blockade with anticholinesterase drugs may be ineffective in patients who receive aminopyridines, and a combination of oral aminopyridine and an anticholinesterase may be more effective.[69] Epidural anesthesia has been successfully used in these patients,[70] but, as with patients with MG, neuraxial anesthesia should be used with extreme caution in patients with LEMS, considering the possibility of increasing muscle weakness and respiratory failure.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a demyelinating disease of the optic nerves, cerebrum, and spinal cord where it primarily affects the corticospinal tract and posterior columns. It is considered an autoimmune disorder and is characterized by sensitization of the peripheral leukocytes to the myelin antigen and a subsequent inflammatory response, monocytic and lymphocytic perivascular cuffing and glial scars, with plaque formation within the central nervous system, especially in the periventricular white matter. Genetic predisposition and environmental factors have also been implicated in its pathophysiologic mechanisms. The disease affects mainly women between 10 to 60 years of age, with the greatest peak between ages 20 to 40 years. Exacerbations and remissions characterize its clinical course in most patients, but continuous neurologic deterioration is also reported in up to 10% of cases (primary progressive MS). Acute symptoms, which are related to the site and extent of sclerosing central nervous system plaque, commonly include visual disturbances (e.g., diplopia, blurring, field cuts), sensory abnormalities with numbness and paresthesias, and an electric shock sensation that radiates down the spine and into the limbs upon flexion of the neck (Lhermitte sign). Cranial nerve dysfunction, ataxia, and bladder and bowel disturbances are also common. A localized or, late in the course of the disease, generalized muscle weakness with the legs affected more than the arms is typical. Chronic symptoms can also include spastic paraparesis, appendicular tremor, and psychiatric disturbances such as depression or euphoria (la belle indifférence) and dementia. In severe cases, respiration may be involved with the development of hypoxemia. MS can be associated with autonomic dysfunction and, hence, an increased risk for exaggerated hemodynamic response to anesthetic induction, vasodilator, and sympathomimetic drugs.[71] A diagnosis of MS is currently based on a combination of clinical symptoms and laboratory tests, including CSF antibody analysis and radiology (detection of central nervous system plaque by magnetic resonance imaging). Diagnosing MS after

a single, acute remitting, clinically isolated syndrome is discouraged, whereas repeated attacks with increased CSF immunoglobulin G (IgG) and multifocal magnetic resonance imaging abnormalities are strongly supportive of the diagnosis.[72] Acute attacks are treated with various combinations of immunosuppression modalities including glucocorticoids, which have been shown to increase the rate of recovery but not an overall level of recovered function. Preventive therapy with interferon β1a or glatiramer acetate (a mixture of polypeptides synthesized to mimic myelin basic protein) may be used in individuals with the relapsing-remitting subtype of MS. Specific treatments aimed at chronic symptoms include baclofen and benzodiazepines for spasticity, anticonvulsants or propranolol for tremor, oxybutynin and propantheline for bladder spasticity, and selective serotonin reuptake inhibitors (SSRIs) or other antidepressive agents for mood disorders.

ANESTHETIC CONSIDERATIONS

MS symptoms may be intensified after physical and emotional stress or in the perioperative period. These patients should therefore be informed of the impact of surgical stress on the natural progression of the disease and the potential for aggravated symptoms in the postoperative period, regardless of the anesthetic approach. Increased body temperature is often cited as an offending mechanism, possibly by causing a complete block of conduction in demyelinated nerves. Body temperature should therefore be closely monitored and controlled during the perioperative period. Great care must also be exercised to minimize changes in fluid homeostasis and central hemodynamics (i.e., preload, afterload). In general, preoperative chronic immunosuppressive medications should be continued during the perioperative period. Although the literature provides no evidence to support the use of any specific inhaled or intravenous anesthetic, many clinicians believe that general anesthesia causes fewer exacerbations and is superior to neuraxial techniques in these patients. Avoiding administering depolarizing NMBDs such as succinylcholine to patients with MS is reasonable; denervation or misuse myopathy may lead to a risk for exaggerated release of muscle potassium, causing hyperkalemia and cardiac arrhythmias. Nondepolarizing NMBDs are safe to use but should be cautiously administered since both prolonged responses (increased sensitivity in patients with preexisting muscle weakness) and resistance to these NMBDs have been reported. Speculation suggests that the demyelination associated with MS renders the spinal cord susceptible to the neurotoxic effects of local anesthetics. Nevertheless, epidural application of low concentrations of local anesthetics has been successfully used in patients with MS.[73] Spinal anesthesia, on the other hand, has been implicated in postoperative exacerbations of MS symptoms. Because demyelination may also damage the blood-brain barrier, spinal anesthesia is usually not recommended for these patients. Clearly, the need for postoperative care is dependent on the preoperative symptoms, the type of surgery, and the expected complications. The need for extended postoperative care and respiratory support should be considered for those with severe preoperative weakness, respiratory compromise, and pharyngeal dysfunction.

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is a mixed upper and lower motor neuron disease with degeneration of anterior horn α-motoneurons in the spinal cord and brainstem motor nuclei and corticospinal tracts. Patients demonstrate gradually spreading focal weakness and muscle atrophy (typically of the hands), spasticity, and hyperreflexia of lower extremities. Dysarthria and dysphagia, tongue atrophy, and fasciculations may also occur. Progressive weakness can lead to respiratory failure and death. Sensory functions, including intellectual capacity and cognition, as well as bowel and bladder function, are not usually affected in ALS.

ALS has an incidence of approximately 2 in 100,000 and prevalence of 4 to 6 per 100,000. The onset of the disease usually occurs between 50 and 75 years of age, and men are more often affected than women. Most cases are sporadic, and although the pathophysiologic process remains unclear, an association with superoxide dismutase (SOD) mutations has been suggested. SOD is an important antioxidant, and its mutation can lead to decreased clearance of free radicals, increased oxidative stress, and mitochondrial dysfunction. Most familial forms are associated with the mutation of *C9ORF72* on 9p21, *TDP43*, *FUS*, and *VCP* genes. Electromyographic and electroneurographic studies and neurologic examination, which demonstrates early spastic weakness of the upper and lower extremities, typical subcutaneous muscle fasciculations, and bulbar involvement affecting pharyngeal function, speech, and the facial muscles, confirm the diagnosis. No curative treatment is currently available, and patients are therefore treated symptomatically. Riluzole, a glutamate-release inhibitor, may provide neuroprotection and extend survival in these patients.[74] Tracheostomy and gastrostomy surgeries and other supportive treatments including mechanical ventilation are often required.

ANESTHETIC CONSIDERATIONS

Patients with ALS may have an increased sensitivity to the respiratory depressant effects of sedatives and hypnotics. Bulbar involvement, in combination with respiratory muscle weakness, leads to a risk for aspiration and pulmonary complications. Sympathetic hyperreactivity and the implications of autonomic dysfunction, often displayed as orthostatic hypotension and resting tachycardia, should be considered during the perioperative management of these patients.[75] Succinylcholine should be avoided because of the risk for hyperkalemia as a result of denervation and immobilization. Nondepolarizing NMBDs may cause prolonged and pronounced neuromuscular block and hence should be used with great caution.[76] General anesthesia may be associated with exaggerated ventilatory depression. Regional anesthesia is also often avoided for fear of exacerbating disease

symptoms. However, both general and epidural anesthesia have been successfully administered to these patients without reported complications.

DUCHENNE MUSCULAR DYSTROPHY

Genetic defects in components of muscle cells, which result in progressive skeletal and smooth muscle dysfunction, are the cause of a group of disorders collectively referred to as *muscular dystrophies*. The most common and severe form of muscular dystrophy is Duchenne muscular dystrophy (DMD), which affects approximately 1 in 5000 male births.[77,78] DMD is an X-linked recessive disorder caused by mutations in the gene that encodes the protein dystrophin.[79,80] A deletion within the gene most commonly causes DMD, but duplication and point mutation have also been described.[80] Although most cases are due to inherited mutations, approximately 10% are due to spontaneous mutations, which can be explained by the large size of the dystrophin gene.[79]

The dystrophin gene is expressed in skeletal, smooth, and cardiac muscle. Although it only accounts for 0.002% of protein in striated muscle,[81] dystrophin plays an important role in sarcolemmal stability and muscle membrane integrity. A cytoskeletal protein links intracellular actin to a group of cell membrane proteins called the *dystrophin-associated protein complex*.[82] This complex, in turn, links via laminin to the extracellular matrix (Fig. 42-1).[82] In DMD, not only is dystrophin absent, but an abnormal expression of the dystrophin-associated protein complex is evident.[82] A hallmark of the disease at its early stages is increased membrane permeability and leakage of intracellular components, including creatine phosphokinase out of the cell and extracellular ions (including calcium into the cell). Traditionally, the absence of dystrophin has been thought to render the sarcolemma fragile and susceptible to rupture with contraction and that this accounts for the increased membrane permeability.[83] Recently, however, this mechanism has been called into question, and evidence has suggested that the disease alterations in channel function in the early stages lead to an increase in intracellular calcium, which activates proteases and reactive oxygen species.[79,82]

Infants with DMD are often normal. Symptoms generally emerge between 2 and 5 years of age[84]; in one population-based sample, the first signs or symptoms were noted at a mean age of 2.5 years and definitive diagnosis was made at a mean age of 4.9 years[85] (see also Chapter 93). The common signs and symptoms at presentation include proximal muscle weakness[79] that results in gait disturbance (including waddling and toe walking), difficulty climbing stairs, calf hypertrophy, and the classic Gowers sign (in which the child uses his hands to climb up their thighs to stand).[84] Creatine kinase level provides a good screening test; in children with DMD, the level is elevated (usually between 5000 and 150,000 IU/L).[84] Motor development plateaus between ages 3 and 6 years, and by 9 to 12 years of age, most patients are wheelchair bound.[84]

After children become wheelchair bound, spinal deformity generally ensues secondary to truncal weakness.[86,87] This deformity, combined with progressive respiratory muscle weakness, can compromise the pulmonary function. These patients become highly susceptible, particularly in the setting of infection, to acute respiratory failure.[84] Additionally, they are vulnerable to upper airway dysfunction and sleep apnea.[79] Cardiomyopathy occurs in nearly all patients with DMD.[88,89] Dystrophin is present in cardiac muscle cells, and the degeneration of cardiomyocytes results in fibrosis.[89] This fibrosis initially affects the posterobasal segment of the left ventricle,[89] which leads to increased myocardial wall stress and a progressive decrease in left ventricular systolic

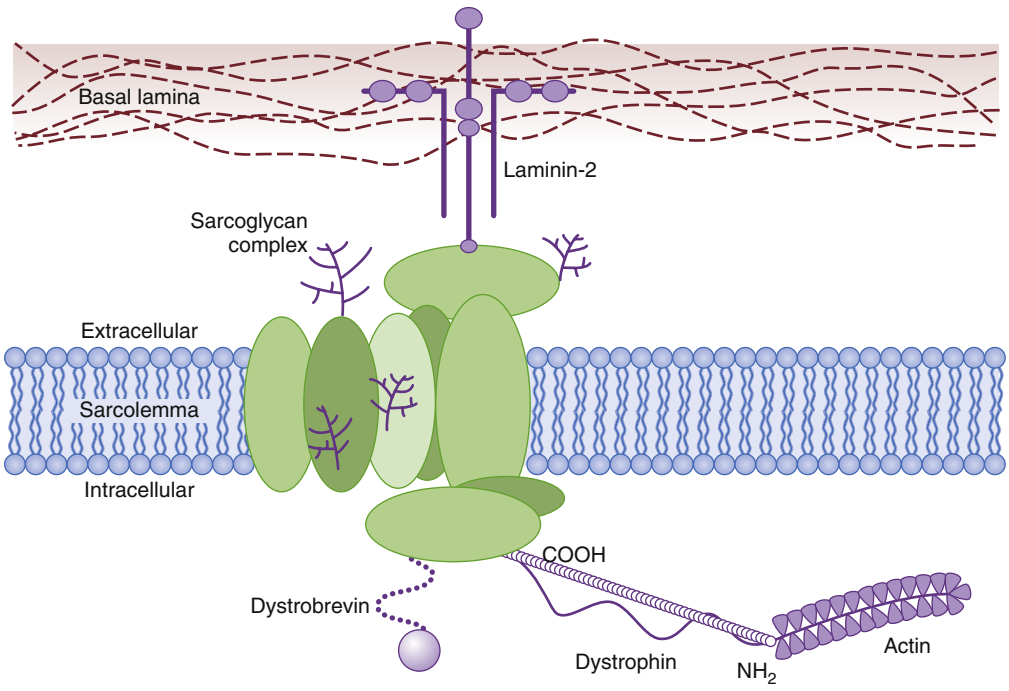


Figure 42-1. Diagram of the cell-surface and cytoskeleton protein complex. *(From Zhou J, Allen PD, Pesah IN, et al: Neuromuscular disorders and malignant hyperthermia. In Miller RD, editor:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Elsevier (Churchill Livingstone), pp 1171-1196.)*

function that eventually results in ventricular dilatation and dysfunction. These changes are evident as characteristic electrocardiographic abnormalities including tall R waves over V1; deep and narrow Q waves over I, V5, and V6; sinus tachycardia; and right axis deviation.[90] Initially, the echocardiogram will show areas of regional wall motion abnormalities at the sites of fibrosis, and, eventually, ventricular dysfunction will be apparent. Fibrosis of the posterior papillary muscle can result in significant mitral regurgitation.[91] As a consequence of the structural changes, patients with DMD are highly susceptible to a range of arrhythmias.[92]

The primary treatment for DMD is glucocorticoids. Meta-analysis of the available data suggests that treatment with glucocorticoids improves short-term muscle strength and function.[93] The most effective regimen appears to be prednisolone at 0.75 mg/kg/day.[93] Recent data suggest that the addition of bisphosphonates to steroids may be beneficial.[94] Management of the cardiomyopathy consists of angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and diuretics.[89] Pulmonary support, including continuous positive airway pressure, bilevel positive airway pressure, and full ventilatory support after a tracheostomy, is frequently required.[84] Novel molecular therapies, including gene replacement therapy, mutation suppression, and exon skipping, are being developed and hold promise for the treatment of this disease.[95] The clinical course is one of progressive decline with death, usually from respiratory or cardiac failure that generally occurs in the third decade of life.[96]

ANESTHETIC CONSIDERATIONS

Patients with DMD have a frequent need for anesthesia for procedures including muscle biopsy, spine surgery for scoliosis, release of contractures, and fractures requiring operative intervention. The principal anesthetic concerns depend on the stage of the disease. In young patients when skeletal muscle is deteriorating, anesthetic triggers can cause profound rhabdomyolysis and hyperkalemia.[79] In older patients, including adolescents and adults, respiratory and cardiac concerns predominate.[79] Irrespective of age, a careful anesthesia consultation, along with consultations from other relevant medical specialists, is required for patients with DMD who undergo nonemergent surgery.[97-99]

Because progressive pulmonary function decline is a hallmark of the disease and the majority of deaths in patients with DMD are due to pulmonary causes, preoperative pulmonary assessment is required. Experts recommend the performance of preoperative pulmonary function tests including measurement of forced vital capacity (FVC), maximum inspiratory pressure, maximum expiratory pressure (MEP), peak cough flow (PCF), and oxyhemoglobin saturation measured by pulse oximetry in room air.[98] For patients with an FVC less than 50%, consideration should be given to preoperative training in noninvasive positive pressure ventilation.[98,100] Such training may result in higher rates of successful use in the postoperative period. Patients with DMD, defined in adults by a PCF less than 270 L/min or an MEP less than 60 cm of water, are considered at high risk for respiratory complications as a result of impaired cough. For these patients, experts recommend training in manual and mechanically assisted cough.[98]

As discussed, DMD results in a progressive dilated cardiomyopathy, which predisposes the patient to both acute heart failure and arrhythmias during the perioperative period.[99,101] Preoperative assessment with an electrocardiogram and echocardiogram and consultation with a cardiologist are generally recommended to ensure that patients are optimized for surgery.[98] However, normal preoperative cardiac workup does not preclude the possibility of perioperative cardiac decompensation.[101] Optimization of preoperative nutrition is also essential. Malnutrition can occur as a consequence of increased work of breathing or an inability to eat as a result of dyspnea.[98] The introduction of appropriate ventilatory support may help with this problem. Preoperative measurement of prealbumin and albumin may be indicated to identify patients with suboptimal nutrition status who are at risk for impaired wound healing.[98]

Because DMD is a terminal illness, experts recommend clarifying with patients and guardians resuscitation parameters and, when appropriate, instituting advanced directives before major surgery.[98]

Several intraoperative considerations are important for patients with DMD. First, succinylcholine is considered contraindicated in patients with DMD. Succinylcholine can precipitate hyperkalemia via two mechanisms in these patients: (1) excess potassium release as a result of the activation of extrajunctional fetal (although its presence in patients with DMD is controversial) and adult acetylcholine receptors[102]; and (2) massive rhabdomyolysis with muscle contraction secondary to an unstable sarcolemma.[79,103] Indeed, hyperkalemic cardiac arrest after the administration of succinylcholine to young male patients with undiagnosed DMD has led to a black box warning cautioning its use in children and adolescents.[79] Second, volatile anesthetics are probably best avoided in these patients,[24,79,104] and most experts suggest the use of total intravenous anesthesia when possible. Although rare, exposure to volatile anesthetics can precipitate a life-threatening MH-like reaction characterized by profound rhabdomyolysis.[103,104] This reaction can occur at low concentrations and may even develop postoperatively, which presents an argument for the use of a clean anesthesia machine.[79,104] Although some earlier reports suggest an association between DMD and MH, a shared genetic risk for DMD and MH is thought to be unlikely—the causal mutation for DMD is on the X chromosome, and the mutations associated with MH are generally on chromosome 19.[103] Rather, the mechanism of this adverse reaction to volatile anesthetics is thought to be isolated rhabdomyolysis and hyperkalemia without the signs of hypermetabolism.[104] As such, dantrolene is unlikely to be clinically useful in these circumstances,[104] and treatment should be focused on the standard management of hyperkalemia. Some authors argue that evidence for considering volatile anesthetics as absolutely contraindicated remains insufficient[79] and have argued that brief exposure in circumstances such as a difficult airway is reasonable.[104]

DMD presents several challenges with respect to airway management. First, the incidence of difficult intubation is likely higher in these patients. In a recent series involving 232 cases of patients with DMD undergoing orthopedic surgery, the incidence of difficult direct laryngoscopy was 4%,[105] likely owing to higher rates of macroglossia, obesity, limited mouth opening, and decreased cervical spine range of motion.[105] Decreased laryngeal reflexes and slowed gastric emptying, which increase the risk for aspiration, may further complicate airway management. Sleep disordered breathing including obstructive sleep apnea and hypoventilation are common in patients with DMD.[106] It is widely recognized that sleep disordered breathing increases sensitivity to opiates in children.[107,108] Therefore, opiates should be judiciously used and titrated to effect in patients with DMD.[79]

Patients with DMD exhibit increased sensitivity to the effects of nondepolarizing NMBDs with a given dose, resulting in greater train-of-four ratio depression and a longer period of neuromuscular block.[109,110] This may be due to the decrease in muscle mass observed with DMD.[79] A delay in the onset of block has also been observed for rocuronium, which may have implications for its use in rapid sequence induction.[110]

Data are mixed regarding whether a bleeding diathesis is present in DMD. Some studies have found evidence of platelet function deficiency,[111,112] whereas other studies have not.[113,114] A relatively recent study found that patients with DMD have increased bleeding times in the setting of normal platelet function. Based on the presence of dystrophin in normal vascular smooth muscle, the authors argued that the impaired hemostasis was due to a defect in vascular smooth muscle reactivity.[114] Some experts recommend the use of aminocaproic acid in patients with DMD who are undergoing major surgery.[79]

Regional anesthesia can be safely used in patients with DMD[115] and may be preferable in some clinical circumstances, considering the problems with volatile anesthetics and NMBDs previously described. Regional anesthesia may also have particular benefits for postoperative analgesia, considering the risks for postoperative respiratory complications in these patients.

The principal concerns in the postoperative care of patients with DMD include the potential for respiratory or cardiac compromise (or both). Careful consideration should be given to the postoperative care setting, and many patients are likely to benefit from admission to an ICU. For patients with an FVC less than 50%, extubation directly to noninvasive positive pressure ventilation should be considered.[98] In some circumstances, if adequate pain control is likely to result in hypoventilation or excessive sedation, then extubation may be delayed for 1 to 2 days.[98] Additional recommendations for postoperative care of these patients include manually or mechanically assisted coughing and the use of cardiology consultants to aid in the management of postoperative fluid shifts and other cardiac issues. Given the gastrointestinal motility issues that can accompany DMD, experts recommend the use of bowel preparation and prokinetic drug regimens and gastric decompression in appropriate patients.[98] Early enteral or parenteral nutritional support is also recommended when oral intake is not possible.[98]

BECKER MUSCULAR DYSTROPHY

Becker muscular dystrophy (BMD) is a milder form of DMD with an incidence that is approximately 20% that of DMD.[116] It affects approximately 14 per 100,000 males.[117] The onset of clinical symptoms in BMD generally occurs later than in DMD, with ambulation being maintained by most affected patients into the third decade of life.[118] Life expectancy is substantially longer than what is observed in DMD, often extending into the fifth decade of life.[79]

An important feature of BMD is the frequent presence of cardiac involvement, even in the presence of benign or subclinical myopathy. In one series, 72% of patients with subclinical myopathy exhibited cardiac involvement.[119] Early right ventricular involvement and later left ventricular dilatation and a reduced ejection fraction characterize the cardiac manifestations.[119] Since skeletal muscle is less involved in BMD, patients are hypothetically able to perform strenuous exercise, which creates cardiac stress that damages the dystrophin-deficient myocardial cells.[119]

ANESTHETIC CONSIDERATIONS

Anesthetic considerations are dependent on the severity of the disease but, in general, are similar to those for DMD. These patients appear to be susceptible to the anesthetic-induced rhabdomyolysis observed in DMD. In fact, case studies report patients with previously undiagnosed BMD who experienced massive rhabdomyolysis (without hypermetabolism) and cardiac arrest upon exposure to volatile anesthetics.[120] Accordingly, as with DMD, volatile anesthetics should be generally avoided. Succinylcholine is also contraindicated for these patients. Considering the high prevalence of cardiomyopathy in patients with BMD,[119] performing a preoperative electrocardiogram and echocardiogram in patients undergoing moderate- or high-risk surgery is prudent. The manifestations of the patient's disease, particularly cardiac status, and the type of surgical procedure will dictate the type of postoperative monitoring and care.

LIMB-GIRDLE MUSCULAR DYSTROPHY

Limb-girdle muscular dystrophies are a clinical and genetically heterogeneous group of myopathies characterized by progressive weakness that begins in the proximal muscles, typically the shoulder or pelvic girdle muscles, sparing other muscle groups at early disease stages.[121,122] The age of onset can be from childhood to late adulthood, depending on the subtype. Inheritance pattern can be autosomal dominant or recessive. To date, 24 genetically distinct limb-girdle muscular dystrophies have been identified, and that number is likely to increase substantially with advances in next-generation sequencing.[122] Treatment, at present, is supportive.

ANESTHETIC CONSIDERATIONS

The literature on the anesthetic management of patients with limb-girdle muscular dystrophy is primarily limited to case reports.[123-125] The clinical manifestations of

the disease and the planned procedure should dictate the anesthetic plan. Preoperative discussion with a neuromuscular disease specialist to understand the clinical features of the patient's disease subtype is warranted. Some types of limb-girdle muscular dystrophy will have a prominent cardiac component and therefore require preoperative cardiac testing. The patients may be susceptible to the same volatile anesthetic-induced rhabdomyolysis observed in DMD and BMD[123]; therefore, avoiding these agents may be prudent. Succinylcholine should be avoided.

MYOTONIC DYSTROPHIES

Myotonic dystrophies (DMs) are autosomal dominant multisystem diseases characterized by myotonia, muscular dystrophy, cardiac conduction defects, cataracts, and endocrine disorders.[126] DMs have two major subtypes: myotonic dystrophy type 1 (DM1), classically known as Steinert disease or Batten-Gibb disease; and myotonic dystrophy type 2 (DM2). An expanded cytosine-thymine-guanine (CTG) repeat in the 3′ untranslated region on chromosome 19 encoding the dystrophia myotonica-protein kinase gene causes DM1.[126] Normal individuals generally have fewer than five of these repeats, whereas those who are affected can have repeats into the thousands.[127] In DM1 disease, onset and severity generally correlates with the number of repeats,[128] and DM1 is often divided into congenital, childhood onset, and adult onset. An expanded CTG repeat in intron 1 of the zinc finger protein 9 gene causes DM2.[126] Although both disorders share the same core clinical manifestations, in general, DM2 develops later and has a milder clinical course.[126]

Facial muscle weakness and wasting is a prominent component of DM1, resulting in a characteristic "hatchet face" appearance.[129] In addition, weakness of the neck flexors and external rotators of the arm are characteristic[130]; other muscle groups, including hands, ankles, and pharyngeal muscles, can also be involved. Proximal muscle weakness, particularly of the lower extremity is a common component of DM2 and was previously referred to as *proximal myotonic myopathy*.[131] DM has, in general, important cardiac manifestations, and these patients have a relatively high incidence of sudden cardiac death.[129] DM1 is associated with conduction abnormalities, tachyarrhythmias (particularly atrial tachyarrhythmias), cardiomyopathy, and valvular disorders.[132] Cardiomyopathy may not always be clinically apparent because of the limited capacity for exertion secondary to the myopathy.[132] In general, the cardiac manifestations are less severe in patients with DM2, compared with those with DM1.[129]

Patients with DM1 are also susceptible to respiratory complications including aspiration (as a result of pharyngeal muscle weakness) and hypoventilation (as a result of diaphragm weakness and decreased central respiratory drive).[129] Respiratory complications are less common in patients with DM2. Similarly, patients with DM1 are at risk for a number of gastrointestinal problems, including impaired esophageal peristalsis, delayed gastric emptying, and dysphagia.[129]

ANESTHETIC CONSIDERATIONS

Because of the high risk for perioperative respiratory complications, the possibility of prolonged postoperative mechanical ventilation should be considered in all patients with DM1, in particular those with severe muscular disability (as assessed by proximal muscle weakness) or those who are scheduled for upper abdominal surgery.[133] In a series of pediatric patients with DM1, the risk of postoperative respiratory complications was related to the degree of muscular impairment, the number of CTG repeats, and the duration of surgery. The use of muscle relaxants without reversal was a potentially modifiable risk factor.[134] In general, perioperative complications in patients with DM2 are less common than in DM1.[135,136]

Because of the cardiac manifestations of this disease, including conduction abnormalities, arrhythmias, and cardiomyopathy, consulting with a cardiologist may be appropriate to ensure that all of these conditions are identified and optimized before surgery. In some circumstances, an echocardiogram and even electrophysiologic studies may be necessary before surgery.[129] The potential for impaired gastrointestinal motility should also be evaluated before surgery and taken into consideration in planning the approach to airway management. Finally, these patients may show enhanced sensitivity to the respiratory depressant effects of anesthetic medications[137] and sedatives. Anesthetic and analgesic medications should therefore be carefully titrated to effect.

MYOTUBULAR OR CENTRONUCLEAR MYOPATHY

Similar to other congenital myopathies, specific structural changes in muscle fibers, early onset with hypotonia and weakness, and a genetic basis and nonprogressive course characterize myotubular myopathy (MTM) or centronuclear myopathy (CNM).[138] MTM was originally described in 1966, and early childhood weakness affecting the extraocular, facial, neck, and limb muscles characterized this disorder. MTM is now divided into three groups based on clinical and genetic features[139]: the severe X-linked recessive (myotubular) form, the autosomal (centronuclear) recessive form, and the relatively mild autosomal dominant form with late onset. The estimated frequency of the X-linked form is 1 in 50,000 male newborns.[140] The X-linked recessive MTM is the most severe form of the disease. The gene responsible for MTM has been localized to *Xq28*, which encodes myotubularin, a tyrosine phosphatase protein.[141,142] Onset is commonly in utero and may be associated with polyhydramnios and reduced fetal movement.[138] Affected male newborns typically exhibit severe floppiness at birth, feeding difficulties, and respiratory distress that requires assisted ventilation. Cardiac muscle is spared, and, in the absence of cerebral hypoxia, cognitive development is normal. Other characteristic features include birth length more than the 90th percentile, macrocephaly (+/– hydrocephalus), a narrow elongated face, and slender, long digits.[143] Serum creatine kinase levels, electromyography, and motor nerve conduction velocities are typically normal. The characteristic

histologic feature is the presence of centrally placed nuclei in muscle fibers resembling fetal myotubules.[138] The long-term prognosis is poor, although studies have reported survival of affected patients for as long as 27 years, with most patients being partially or completely ventilator dependent.[144] Liver function tests may be altered in some patients.[144]

The autosomally inherited forms of MTM or CNM are rare, both familial and sporadic forms.[138] The majority of patients with autosomal recessive CNM demonstrate the disorder in infancy or early childhood. Clinical features include hypotonia, respiratory distress, bulbar weakness, and ophthalmoplegia. The course may be slowly progressive, with development of scoliosis and a loss of ambulation by adolescence. Laboratory findings are similar to other patients with MTM. A late onset, autosomally dominant form has also been described that has a milder course than the other two forms. Autosomal recessive CNM is associated with mutations in the *BIB1* gene that encodes for amphyphysin-2,[145] whereas autosomal dominant CNM has been linked to the gene that encodes for dynamin-2.[146] Treatment is entirely supportive.

ANESTHETIC CONSIDERATIONS

A primary concern when providing anesthesia for a patient with a congenital myopathy is the risk of precipitating MH with triggering anesthetics (e.g., volatile anesthetics, succinylcholine).[147] Some of the congenital myopathies (e.g., central core disease, multiminicore myopathy, nemaline rod myopathy) are clearly linked with the risk of MH because they may all be associated with mutations in the ryanodine (*RYR1*) gene.[148] The risk of MH in MTM or CNM is likely to be low, but all reported cases have used nontriggering anesthetics, such as propofol and remifentanil.[149] However, one case study reports MH-like symptoms developing during cardiopulmonary bypass in a patient with late-onset CNM, even in the absence of administering triggering anesthetics.[150] Thus the most prudent course in patients with MTM or CNM is probably avoiding volatile anesthetics and succinylcholine. A risk of prolonged paralysis with nondepolarizing muscle relaxants exists.[151] However, avoiding the use of muscle relaxants altogether should be easy, considering the hypotonia in these patients.

DISORDERS OF MUSCLE ENERGY METABOLISM

The source of energy used by muscle for metabolism depends on several factors, most importantly the type, intensity, and duration of exercise. At rest, muscles predominantly use fatty acids. At submaximal exercise (70% to 80% of maximum oxygen consumption [VO_{2max}]) aerobic metabolism of glycogen is the most crucial source of energy. At intensities close to VO_{2max}, anaerobic glycolysis is the major source of energy.[152] Glycogen serves as a dynamic but limited reservoir of glucose, mainly stored in skeletal muscle and liver. Glycogen storage disorders (GSDs) are a group of metabolism disorders caused by enzyme deficiency or dysfunction. They reduce effective glucose storage by interfering with normal glycogen synthesis and degradation. Synthetic errors cause decreased normal glycogen, whereas degradation errors tend to block the breakdown of glycogen. Subsequently, hypoglycemia and the accumulation of glycogen in tissues could occur as a result of defective substrate use. More than 12 types of GSDs are assigned Roman numerals based on the enzyme deficiencies. Type II, acid maltase deficiency (AMD), is discussed in this text.

GLYCOGEN STORAGE DISEASE TYPE II (ACID MALTASE DEFICIENCY)

Acid maltase is a lysosomal α-glucosidase that releases glucose from maltose, oligosaccharides, and glycogen. Three clinical forms of AMD have been described. The infantile form (Pompe disease) is the most common, and symptoms are typically expressed during the first 3 months of life. The affected patients develop severe muscle weakness, cardiomegaly, hepatomegaly, and respiratory insufficiency. Cardiorespiratory failure usually causes death before 2 years of age.[153] Presentation of the childhood form of AMD is primarily a myopathy. Motor milestones are delayed, and weakness is greater in the proximal than in the distal muscles. Calf enlargement can occur, resulting in a clinical picture that simulates muscular dystrophy. The disease progresses relatively slowly; however, most patients die of respiratory failure by the second decade of life.[153] The adult form usually begins in the third or fourth decade of life but can begin as late as the seventh decade. Respiratory failure and diaphragmatic weakness are often initial manifestations, heralding progressive proximal muscle weakness. The heart and liver are not involved.[154]

The plasma creatine kinase is elevated by as much as 10-fold in the infantile and childhood forms but may be normal in adult-onset disease. Electromyography demonstrates a myopathic pattern with distinctive myotonic discharges, trains of fibrillation and positive waves, and complex repetitive discharges. The muscle biopsy in infants typically reveals vacuoles containing glycogen and the lysosomal enzyme, acid phosphatase. However, muscle biopsies in late-onset AMD may demonstrate only nonspecific anomalies.[154]

Pompe disease is inherited as an autosomal recessive mutation of the α-glucosidase gene. Enzyme replacement therapy (ERT) with intravenous recombinant human glucosidase has been shown to be beneficial in infantile-onset Pompe disease.[155] Clinical benefits in the infantile disease include reduced heart size, improved muscle function, reduced need for ventilatory support, and longer life. In late-onset cases of Pompe disease, ERT has not been associated with the dramatic response that can be seen in classic infantile Pompe disease, yet it appears to stabilize the disease process, somewhat improving motor and respiratory function.[156]

ANESTHETIC CONSIDERATIONS

Anesthesia reports in patients with AMD are rare, but paying close attention to the cardiac function in infantile Pompe disease is reasonable, considering the associated cardiomyopathy. In a series of five infants with Pompe

disease, Ing and colleagues observed that the left ventricular mass, assessed by echocardiography, was between four and five times greater than normal.[157] Isolated intraoperative cardiac arrest during halothane anesthesia in infantile AMD has been documented.[158] Despite the problem noted with halothane, enflurane and sevoflurane have been used without complications.[157] Although halothane may make the myocardium more prone to arrhythmias, meticulous attention to the hemodynamic parameters and prevention of a vicious cycle of hypotension and compromised myocardial perfusion are likely more important than the choice of a volatile anesthetic agent. Some have suggested that ketamine might be preferable to propofol or sevoflurane induction, primarily because ketamine is an indirect sympathomimetic.[159] Although ketamine is certainly a reasonable choice in these patients, its side effects, such as tachycardia and the consequent increase in myocardial oxygen consumption, need to be kept in mind.

In patients with late onset AMD, the degree of preoperative weakness and respiratory compromise should be considered to plan for the anesthetic accordingly. Epidural analgesia, used as an adjunct to general anesthesia, has been administered with success in a patient with adult-onset Pompe disease.[160] Femoral nerve blocks and caudal blocks have also been successfully used in children with Pompe disease.[161] A combined epidural-spinal technique has also been reported in the management of a pregnant woman with adult-onset Pompe disease for a cesarean section.[162]

Succinylcholine should be avoided because of the risk of hyperkalemia in a patient with myopathy. Nondepolarizing NMBDs are safe to use, provided close attention is paid to neuromuscular monitoring.[163] It should be noted that prolonged postoperative weakness has been reported even without NMBDs.[164]

MITOCHONDRIAL MYOPATHIES

The concept of disease as a result of mitochondrial dysfunction was first introduced in 1962 when Swedish investigators described a patient with severe hypermetabolism without thyroid dysfunction.[165] These investigators defined mitochondrial disease on the basis of (1) morphologic evidence of abnormal mitochondria in muscle, (2) biochemical documentation of "loose coupling" between oxidation and phosphorylation in isolated mitochondria, and (3) correlation between biochemical abnormalities and clinical features (hypermetabolism).[166] Mitochondrial diseases may be classified in terms of defects in the five main steps of mitochondrial metabolism: substrate transport, substrate utilization, the Krebs cycle, the electron transport chain, and oxidation and phosphorylation coupling.[167] The terms *mitochondrial encephalomyopathies* and *mitochondrial myopathies* are reserved for those disorders that are the result of defects in the respiratory or electron transport chain.[166] The respiratory chain is composed of five multimeric complexes (I to V) embedded in the inner mitochondrial membrane, plus two small mobile electron carriers, coenzyme Q_{10} (CoQ_{10}) and cytochrome *c*, for a total of more than 80 proteins. mtDNA encodes 13 of these proteins, and nDNA encodes all others. mtDNA is different from nDNA in several aspects: (1) mtDNA is circular and contains no intron, (2) it has a greater number of copies than nDNA and a significantly higher spontaneous mutation rate, and (3) its inheritance is maternal. Considering the dual genetic control of the respiratory chain, that is, of both mtDNA and nDNA, multiple mutations in either can give rise to mitochondrial disease.[166]

Primary mtDNA mutations may include point mutations in polypeptide, transfer RNA (tRNA), or ribosomal RNA (rRNA) encoding regions and large-scale rearrangements, duplications, or deletions. Some of the common conditions caused by point mutations include myoclonic epilepsy with ragged-red fibers (MERRF); mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS); neuropathy, ataxia, and retinitis pigmentosa (NARP); Leigh disease; and Leber hereditary optic neuropathy (LHON). Sporadic large-scale mutations may lead to Kearns-Sayre syndrome (KSS), progressive external ophthalmoplegia, and Pearson syndrome. nDNA mutations can cause deficiencies in complexes I to IV and in CoQ_{10} of the electron transport chain.[166]

Mitochondrial diseases present a diagnostic challenge as a result of their clinical heterogeneity. Since mitochondria are ubiquitous, mtDNA mutations can affect every tissue in the body. Disorders as a result of nDNA mutations follow a mendelian pattern and thus are phenotypically "all or none," whereas inheritance of mtDNA is stochastic, leading to greater variability. The overall incidence of mitochondrial myopathy is estimated to be 1 in 4000.[168] Clinically, certain symptoms or signs are "red flags" for mtDNA-related conditions because of their frequency. These include syndromic or isolated sensorineural hearing loss, short stature, progressive external ophthalmoplegia, axonal neuropathy, diabetes mellitus, and hypertrophic cardiomyopathy.[169] Pure myopathies vary considerably in the age of onset, distribution of weakness, and course, ranging from early onset severe disease with respiratory failure to adult onset with mild or even reversible weakness. In addition to fixed weakness, patients with mitochondrial myopathies complain of exercise intolerance and premature fatigue; some experience recurrent myoglobinuria.[166] The histologic hallmark of these diseases is the "ragged-red fiber" when muscle tissue is stained with the Gomori trichrome stain.[170] Common laboratory findings include a high lactate-to-pyruvate ratio (50 to 250), instead of a normal ratio (less than 25:1), increased blood levels of free carnitine, and occasionally low levels of folate (as in KSS). Computed tomography and magnetic resonance imaging of the brain may be helpful. For example, patients with MELAS demonstrate basal ganglia calcifications and strokelike patterns not confined to vascular territories.[170] Clinical features of two relatively common encephalomyopathies, MELAS and MERRF, are briefly discussed in the following text.

MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKELIKE EPISODES

MELAS is the most common mitochondrial encephalomyopathy. Onset is most commonly before age 20 years.

Seizures are common and strokelike episodes (*strokelike* because they do not conform to vascular distributions) may produce hemiparesis, hemianopia, and cortical blindness. Any patient younger than 40 years of age with a history of stroke should be assessed for MELAS. Associated findings include diabetes mellitus, hearing loss, pituitary and thyroid hypofunction, and lack of secondary sexual characteristics. In its full expression, MELAS leads to dementia, a bedridden state, and death. No specific treatment is currently available.[154]

MYOCLONIC EPILEPSY WITH RAGGED-RED FIBERS

MERRF is a multisystem disorder characterized by myoclonus, generalized epilepsy, ataxia, and ragged-red fibers on muscle biopsy. Other clinical features may include hearing loss, peripheral neuropathy, optic atrophy, dementia, short stature, and exercise intolerance.[166] Cardiomyopathy is occasionally present. Laboratory features include an increased lactate level at rest and with exercise, and a myopathic picture on an electromyogram and electroencephalogram shows generalized spike and wave discharges with background slowing. Only supportive treatment is available.

ANESTHETIC CONSIDERATIONS

The anesthesiologist may be involved in the care of patients with mitochondrial disease in multiple situations and often in the setting of obtaining a muscle biopsy in a child with an undiagnosed myopathy.[171] These patients may also have surgical procedures related to the disease (such as implantation of a permanent pacemaker in a patient with KSS),[172] for incidental medical problems, as well as in the labor and delivery suite for labor analgesia.[173] The diversity of clinical presentations encountered in the mitochondrial myopathies dictates that each patient be thoroughly evaluated and that the anesthetic plan be tailored to the patient's specific needs.

Preoperatively, the extent of organ system involvement should be carefully assessed and documented with particular emphasis on the degree of myopathy and neurologic function. Looking for evidence of cardiomyopathy or rhythm disturbances is imperative. In addition, close attention should be paid to endocrine issues because myotonic dystrophies may frequently be present together with other metabolic derangements such as electrolyte imbalances.[174] Varying degrees of respiratory compromise may be exhibited, and these patients may be at a higher risk of postoperative respiratory complications.[168] Baseline blood gases and lactate levels are helpful as well, although a normal lactate level certainly does not rule out a mitochondrial process.

Every class of anesthetics is associated with a theoretic risk of complications in patients with mitochondrial disease. Volatile anesthetics and succinylcholine raise the specter of MH. Propofol and midazolam are known to inhibit the mitochondrial respiratory chain in a dose-dependent manner.[175] Indeed, mitochondrial dysfunction has been postulated as a mechanism for the propofol-related infusion syndrome (PRIS).[176] NMBDs are associated with the risk of prolonged paralysis, and narcotics may worsen preexisting respiratory depression.[177] Even local anesthetics have been reported to cause mitochondrial toxicity.[178] Fortunately, notwithstanding the potential pitfalls previously mentioned, almost every anesthetic technique has been safely used in patients with mitochondrial disease.[174,179] The caveat, of course, is that given the rarity of the mitochondrial diseases, all anesthetic experiences reported to date take the form of individual case reports or small series that do not permit definitive conclusions.

The association of MH to patients with mitochondrial disease probably dates back to a single case described in 1985 by Ohtani and associates.[180] Another patient with a mitochondrial myopathy had a positive halothane contracture test but did not have clinical evidence of MH.[181] On the other hand, volatile anesthetics have been used on numerous occasions in this patient population without any adverse effects.[173,182] At present, evidence does not support an association between MH and mitochondrial disease. However, avoiding succinylcholine in patients with extensive myopathy to minimize the risk of hyperkalemia may be prudent, although the safe use of succinylcholine has been documented in at least one patient with KSS.[183] Similarly, propofol has been safely used in patients with MELAS, and PRIS has never been described in this group of patients. Nevertheless, propofol should not be used as an ICU sedation in patients with mitochondrial dysfunction. Although using propofol as an anesthetic-induction drug is safe, using a propofol infusion for long periods should probably be avoided.

Several studies report sensitivity to nondepolarizing muscle relaxants, including mivacurium, atracurium, vecuronium, and rocuronium, although resistance to cisatracurium in a patient with MELAS is also reported.[174] Being cautious when using muscle relaxants in patients with myopathies is important. Finally, several studies report the successful use of spinal and epidural anesthetics in patients with mitochondrial diseases.[173,184,185] Before choosing a neuraxial technique, close attention should be paid to any preexisting neurologic dysfunction.

Perhaps more important than the specific choice of anesthetics are the implications of the patient's comorbidities and metabolic status. Normothermia should be maintained during surgeries, and intravenous fluids should be warmed to body temperature. Lactated Ringer solution should probably be avoided, considering the risk of preexisting lactic acidosis, although evidence does not indicate that lactated Ringer solution has worsened acidosis when used.[174] Multiple studies have reported hyponatremia (and occasionally hyperkalemia) in these patients.[174,186,187] In such situations, adrenal insufficiency should be considered, particularly when accompanied by hypotension.[174] Finally, these patients are at increased risk of cardiac conduction abnormalities and cardiomyopathy that should be taken into consideration when formulating an anesthetic plan.

PERIODIC PARALYSES

The periodic paralyses are a group of disorders that are characterized by alterations of function in voltage-gated

ion channels; these diseases are sometimes termed *skeletal muscle channelopathies*.[188] The symptoms of the particular channelopathy depend on the specific ion channel involved and can be divided into three broad categories: (1) chloride channelopathies—myotonia without paralysis, such as myotonia congenita; (2) sodium channelopathies—myotonia with paralysis, such as hyperkalemic periodic paralysis; and (3) other cation channelopathies—paralysis without myotonia, such as hypokalemic periodic paralysis (HypoPP).[189]

HYPERKALEMIC PERIODIC PARALYSIS

Hyperkalemic periodic paralysis (HyperPP) is an autosomal dominant disease with a high penetrance that equally affects males and females. It has a prevalence of approximately 1 in 200,000.[189] The term *hyperkalemic* can be misleading because patients may have normal potassium levels during attacks. This characteristic led to the erroneous categorization of such patients as having *normokalemic periodic paralysis*. However, normokalemic periodic paralysis has now been unequivocally established as a variant of HyperPP.[190] The defining characteristic of the disease is paralysis precipitated by potassium administration.[191] Mutations at various sites on the voltage-gated sodium channel *SCN4A* gene cause HyperPP. The mutant channels, once activated by a depolarizing agent such as potassium, cannot inactivate; they flicker between open and inactivated states. This action produces persistent depolarization (causing muscle weakness) and a shift of sodium into the muscle cells and potassium to be released from the muscle cells (causing hyperkalemia). When potassium diuresis relieves the hyperkalemia, the cycle is probably terminated.[189]

Attacks of weakness begin in the first decade of life, are generally short-lived and infrequent, although they may later increase in frequency and severity. Precipitating factors include potassium-rich foods and rest after exercise. In addition, a cold environment, emotional stress, fasting, glucocorticoids, and pregnancy can provoke or worsen the attacks. In between attacks, a mild myotonia is common but does not impede activity. Laboratory studies may show elevated or normal potassium levels during attacks. Creatine kinase levels are often elevated. It is rare for serum potassium to reach cardiotoxic levels, and the electrocardiogram is usually normal. Electromyographic recordings will often show myotonic discharges during and between attacks. Muscle biopsies may show small peripheral vacuoles in the sarcoplasm. Treatment includes medication with acetazolamide (a carbonic anhydrase inhibitor) and mexiletine (an antiarrhythmic with a mechanism of action similar to lidocaine). Behavioral modification, such as avoiding potassium-containing foods, strenuous exercise, fasting, and exposure to cold, are also important.[189]

HYPOKALEMIC PERIODIC PARALYSIS

Familial hypokalemic periodic paralysis (HypoPP) is the most common form of the periodic paralyses, although its prevalence is only 1 in 100,000.[192] It is autosomal dominant with a reduced penetrance in women and affects men more commonly. Genetically, two types of HypoPP are clinically identical. Patients with type 1 HypoPP (the more common) have a mutation in the L-type calcium channel gene *CACN1AS*.[193] Type 2 HypoPP is the result of mutations in the same sodium channel gene (*SCNA4*) that causes HyperPP.[194] Although it remains unclear how defects in the same gene (*SCNA4*) give rise to pathologic characteristics with diametrically opposing clinical manifestations, it has been speculated that HyperPP is a "gain-of-function" sodium channelopathy, whereas type 2 HypoPP is a "change-of-function" channel disease.[194]

The presentation of HypoPP occurs between childhood and the third decade of life. Proximal muscles are disproportionally affected, with rare ocular and bulbar muscle involvement. Respiratory muscle weakness, although unusual, may be life threatening. Continuous physical activity and carbohydrate-rich meals may provoke the attacks. Other triggers include bacterial or viral infections, alcohol ingestion, fasting, lack of sleep, dehydration, prolonged bed rest, stress, menstruation, and pregnancy.[189] Remaining aware of the differences in the clinical features between HyperPP and HypoPP is important. HypoPP is not associated with myotonia; a spontaneous attack is associated with hypokalemia (a diagnostic criterion), potassium is a remedy, and glucose triggers an attack.[189] Treatment is centered on the identification and avoidance of triggers. Potassium administration can be useful in the treatment of an acute attack. The prophylactic medication of choice in type 1 HypoPP is acetazolamide[195]; however, acetazolamide can worsen symptoms in type 2 HypoPP.[196] Such patients may respond to potassium-sparing diuretics such as spironolactone.[197]

THYROTOXIC PERIODIC PARALYSIS

Thyrotoxic periodic paralysis (TPP) clinically resembles HypoPP. TPP occurs later in life than HypoPP, has a strong male predominance, and is significantly more common in patients of oriental descent. Loss-of-function mutations in the inward rectifying potassium channel gene (*Kir2.6*) may be involved in some cases of TPP.[198] The condition responds to antithyroid medications such as methimazole.[189]

ANESTHETIC CONSIDERATIONS

Knowledge of the pathophysiologic processes and precipitating conditions for the different types of periodic paralyses guide the anesthetic approach to patients with these disorders. Salient features are discussed in the following text.

HyperPP

If possible, all patients with HyperPP should be preoperatively admitted to allow preoperative fasting to be accompanied by the administration of a dextrose-containing, potassium-free intravenous fluid.[199] Depolarizing agents such as potassium, succinylcholine, and anticholinesterases aggravate the myotonia in HyperPP and are contraindicated.[189] Nondepolarizing NMBDs may be safely used.[199,200] Although succinylcholine can cause masseter

spasm and rigidity in HyperPP,[201,202] these are related to severe myotonic reactions and are not due to MH. No evidence suggests that patients with HyperPP are susceptible to MH.[148] The safe use of both volatile anesthetics and propofol has been documented.[199,200,203] Myotonic contractions during anesthesia may be improved with the administration of lidocaine, as chronic myotonic symptoms are improved by mexiletine.[189]

Intraoperatively, maintaining normothermia, preventing hyperkalemia, and avoiding hypoglycemia are important.[200] Both spinal and epidural techniques have been successfully used in these patients,[204,205] including the use of epidural labor analgesia.[206] Nonneuraxial regional techniques have not been extensively investigated; however, a recent report documents the use of a femoral nerve block in a single patient with HyperPP.[207]

HypoPP

Patients with HypoPP undergoing general anesthesia have been reported to exhibit weakness and respiratory distress in the postoperative period.[208,209] Important triggers to avoid include perioperative stress, glucose loading, hypothermia, and depolarizing NMBDs.[189] Although the safe use of intermediate- and short-acting nondepolarizing NMBDs such as atracurium and mivacurium has been documented,[210-212] avoiding long-acting muscle relaxants is probably prudent.[213] The use of epidural (including for labor analgesia) and spinal techniques appears to be safe,[212-214] although hypokalemia has been documented with the use of epidural techniques, both with and without epinephrine.[215] Unlike HyperPP, an association between HypoPP and MH cannot be categorically ruled out,[148] although the use of isoflurane in HypoPP has been reported.[212] A number of MH-like metabolic crises in patients with HypoPP have been reported.[216-218] Contracture-like responses to succinylcholine have also been described.[219] In one of the prior descriptions, two unrelated mutations conferring both HypoPP and sensitivity to MH in the same patient seemed likely.[218] Consequently, although the probability of MH in a given patient with HypoPP is likely to be remote, it cannot be ruled out, and the safest course might be the use of a nontriggering anesthetic. If volatile agents are used, then they should be used with extra vigilance.[148]

GENETICS OF MENDELIAN, MITOCHONDRIAL, AND COMPLEX DISEASES

With the emergence of technologies that perform genetic sequencing quickly, accurately, and inexpensively, an understanding of the genetic basis of heritable diseases has recently accelerated. The conditions discussed in this chapter generally focus on diseases that have mendelian or mitochondrial inheritance. Recent research has also begun to unlock the genetic basis for complex diseases, including coronary artery disease, diabetes, and hypertension, with which anesthesiologists interact in the course of their clinical practice. The pace of genetic discovery is expected to accelerate in the upcoming decades and become a more integral component of clinical practice. It is important for anesthesiologists to be familiar with modern approaches to genetic study; therefore, an overview of the genetics of mendelian, mitochondrial, and complex diseases is presented.

MENDELIAN DISEASES

Over the last two decades, gene discovery has led to an understanding of the causal mechanisms underlying rare, familial genetic disorders.[220] This understanding has transformed diagnosis, management, treatment, and anesthetic practice for patients with these disorders. Mendelian, or single-gene disorders, exhibit simple autosomal or sex-linked inheritance patterns with variable expressivity and penetrance. Traditionally, genes for these disorders have been identified by positional cloning, which includes linkage analysis (a measure of cosegregation of chromosomal markers with disease phenotype in families) to localize a disease gene to a subchromosomal region, and subsequent sequencing of genes and transcripts under the linkage peak in affected and unaffected family members to identify causal mutations. In the last few years, direct mutation screening using next-generation sequencing of the entire exome (protein coding region of all known genes in the genome) or entire genome in a small number of affected and unaffected family members has revolutionized gene identification for mendelian diseases.[221,222] To date, causal genes for more than 3600 common diseases have been identified, demonstrating a large extent of locus heterogeneity (in which mutations in different genes lead to the same phenotype) and allelic heterogeneity (in which different mutations in the same gene are present in patients from different families. (Visit Online Mendelian Inheritance in Man [http://www.ncbi.nlm.nih.gov/omim].)[220]

MITOCHONDRIAL DISEASES

The genetics of mitochondrial disorders is a special case of mendelian disorders because defects may be in mtDNA- or nDNA-encoded structural or regulatory components of the mitochondrion.[223] Maternal inheritance is observed in mtDNA disorders, which often exhibit a range of systemic phenotypes with varying severity, as discussed in the previous section on mitochondrial disorders. Typically, affected members from these pedigrees carry germline mutations in mtDNA, but their tissues and organs may contain both normal and mutant copies of mtDNA (heteroplasmy). Because each cell consists of hundreds to thousands of mitochondrial DNA genomes that may segregate unevenly during mitosis, the relative ratio of normal-to-mutant mitochondrial genomes in the body can influence the variability in disease phenotypes.[224] Sequencing of the 16.6 kb mtDNA molecule in affected family members, with a comparison against the background mitochondrial haplogroup as defined by lineage-specific polymorphisms, and determining the functional consequences on respiratory chain activity in vitro typically identify mutations that cause disease.[225-227] Mitochondrial disorders caused by nDNA-encoded components of the mitochondrial machinery are similar to

other mendelian disorders with variable phenotypes, and genes encoding these are increasingly being identified because of better catalogs of the mitochondrial proteome and next-generation sequencing methods.[228]

COMPLEX DISEASES

The discovery of genes for complex diseases is a powerful approach to identify important biologic pathways contributing to disease pathogenesis. Mechanistic insights gained from an understanding of these pathways can lead to new strategies for disease prevention, diagnosis, and treatment. Common diseases are complex traits influenced by multiple genes and environment, in contrast to rare diseases caused by single gene defects (mendelian traits). The heritability of a complex trait is the sum of the genetic contribution to the trait,[229,230] and the demonstration of significant heritability in twin or family studies is usually the first step in justifying gene discovery efforts. Causal genetic variation contributing to the genetic component of a trait can arise as a single nucleotide substitution (termed a *single nucleotide polymorphism* when its frequency is present in more than 1% of the population), or an insertion, duplication, or deletion ranging from one base to hundreds of kilobases in length (termed a *copy number polymorphism* when its frequency is present in more than 1% of the population). This variation can either directly alter the coding sequence of the protein encoded by the gene disrupting protein function or influence the regulatory regions of genes altering gene expression, splicing, or transcript stability. Genetic variation between humans is limited, and most variations in the genome are common.[231] Deleterious mutations in single genes causing mendelian diseases do not reach appreciable frequencies in the population because these mutations decrease reproductive fitness and are thus subjected to purifying selection. Common diseases are not subject to negative selection because they typically do not influence reproductive fitness and often have a late onset.[232] Similarly, for complex pharmacogenetic traits, drug exposures have not occurred until recently in evolutionary history; consequently, drug targets or metabolizing enzymes may not have been subjected to selective pressure.

GENETIC ARCHITECTURE OF COMPLEX TRAITS

Emerging evidence suggests that the genetic architecture of common diseases typically spans the continuum from mendelian subtypes of a common trait featuring very rare, highly deleterious mutations in a single gene, through a low-frequency range of single nucleotide or copy number variants with medium individual effect, to more common single nucleotide polymorphisms (SNPs) or copy number polymorphisms (CNPs) of modest effect segregating in the larger population.

Linkage analysis, which measures cosegregation of chromosomal markers with disease phenotypes in families, has been successful in positional cloning of genes for mendelian disease, but genetic association analysis is a study design better powered to detect the role of common genetic variation underlying complex traits.[233] Genetic association studies search for statistically significant allele frequency differences in covariate- and ethnicity-matched cases and controls to identify genetic variants altering the risk of disease. Candidate gene–association studies with the aim to validate the role of known biologic pathways identified through model organism or in vitro studies of disease physiologic processes have met with some success but have been plagued with inconsistency and irreproducibility primarily because of a lack of power in small, individual studies, insufficient accounting for population structure, technical problems with genotyping, or lack of stringent statistical thresholds for multiple testing correction.[234] Genome-wide association studies (GWASs) have been the breakthrough method that has validated candidate disease genes and revealed many more new, unsuspected genes contributing causally to common disease. GWASs typically interrogate more than 1 million common SNPs and copy number variants across the genome for statistically significant differences in allele frequency between large sets of carefully matched cases or controls. GWASs can also be used to identify genetic variants contributing to the variation in disease-related quantitative traits, highlighting roles of genes in specific disease processes. Several key advances over the last decade have made GWASs possible. These include the availability of the human genome reference sequence; catalogs of common variation, mapping of the correlation structure between variants in continental populations through the International HapMap Consortium[235]; advances in oligo array technology leading to high-throughput, cost-effective, and high-quality genotyping[236]; and analytic approaches that account for systematic biases such as population structure.[237] Although over 10 million common variants have been identified in human populations, GWASs enable testing of approximately 85% of all common variations over 5% frequency because of the phenomenon of linkage disequilibrium, in which neighboring genetic variation is inherited together in "blocks" disrupted only by ancestral recombination events that occur at hotspots (linkage disequilibrium).[231,238] Thus, SNPs in close proximity are highly correlated to each other, and one marker can serve as a surrogate for multiple variants. Common genetic variation in humans can be categorized into one of a small range of haplotypes or specific patterns of variation with populations of recent African ancestry showing the most diversity, whereas populations that arose out of Africa have fewer haplotypes and longer regions of linkage disequilibrium.[239]

Successful designs for GWASs require careful phenotype and covariate definition, sample selection and matching, high-throughput genotyping and quality control, including the removal of low-quality, cryptically related or population outlier samples and the removal of SNPs with a low-genotyping call rate or departure from Hardy-Weinberg equilibrium.[240] Population stratification, or differences in allele frequency between ethnic populations unequally apportioned between cases and controls, can be a major source of type 1 error and can be overcome by selecting a homogeneous study population or by analytic methods that adjust for genome-wide variation patterns.[237] Rigorous statistical significance

thresholds are typically set at 5×10^{-8}, correcting for the approximately 1 million common independent tests in the genome identified by simulation studies.[241] Finally, replication of significant association signals from GWASs in independent samples in a multistage design is important to distinguish true, reproducible signals from potential sources of error or bias in the original GWAS.[240]

The National Human Genome Research Institute catalogs the growing and significant GWASs reported in the literature. To date, more than 8000 associations to disease, biomarker, or behavioral traits have been identified (http://www.genome.gov/gwastudies/).[242] GWASs have led to new insights on the genetic architecture of complex traits, namely:

1. Many human traits are highly polygenic, sometimes with more than 100 loci contributing modest effects to disease risk.
2. Most individual common variant effects are modest, with an odds ratio in the range of 1.1 to 1.5; therefore, large sample sizes (1000s to 100,000s) are needed to have sufficient power to detect these effects robustly.
3. Causal SNPs and genes are challenging to pinpoint under an association peak and require intensive bioinformatic and experimental follow-up, especially since many signals are far from known genes and may represent distant regulatory elements.
4. A single gene may harbor rare alleles of strong effect and one or more common independent alleles of weak effect, contributing to disease etiologic origin.
5. Most discovered loci were not previously suspected as biologic candidates, emphasizing the fruitfulness of an unbiased genome-wide screen.
6. Most effects are observed across multiple ethnic groups, but the relative role of a genetic variant may be different across populations based on differing allele frequencies across populations.
7. Both the overlap of associations between traits (e.g., the same SNP influencing type 2 diabetes and a related trait, insulin secretion) and the unexpected pleiotropy across traits are expected.[232]

The contribution of rare variants to complex disease is being investigated, largely based on rapid advances in next-generation sequencing.[243,244] Large-scale sequencing projects (e.g., the 1000 genomes project[245] and the National Heart, Lung and Blood Institute [NHLBI]–funded Exome Sequencing Project[246]) have now sequenced tens of thousands of individuals, leading to deeper catalogs of rare variation than that queried by GWASs. These projects provide a window into querying the role of low-frequency variation (0.1% to 5% frequency) in disease, especially in protein-coding regions of all known genes in the genome (the exome) in which the impact of a protein-altering variant can be predicted in silico and is amenable to easier interpretation than regulatory variation. Recently, the exome chip, made up of approximately 240,000 validated protein-altering variants (>1:1000 frequency) has been developed.[247] This genotyping array includes novel missense, splice-site and nonsense variants, and is predicted to capture 95% of exome variation in an average individual. Even more rare variants contributing to common disease are being sought by exome or whole genome sequencing of thousands of cases and controls for many complex disease traits.[248] Since these variants are individually rare, methods to test the aggregate mutation burden or perform association analysis across gene regions have been developed.[248] Exome sequencing has proven immensely successful at identifying novel causal mutations in families with mendelian segregation of traits, including in mendelian subtypes of common disease, and is an unbiased approach that allows for combined positional cloning (using linkage) and direct-coding mutation detection.[221]

Efforts are now directed toward identifying the entire allelic spectrum of mutations for many common diseases. Even when all causal genetic variations contributing to a complex trait are defined, understanding gene-gene and gene-environment interactions will be important to explain the full genetic variance of a trait.[249] More sophisticated systems' biologic approaches, such as network medicine that integrates genetics with multiple genomic technologies, may also help understand the underlying perturbations of biologic networks that result in disease.[250]

IMPLICATIONS FOR CLINICAL TRANSLATION

Advances in complex disease gene identification should lead to clinical advances of benefit for all patients and in some scenarios to *personalized medicine*, depending on a patient's genetic risk. Identification of novel causal pathways provides new opportunities for the identification of therapeutic targets for drug development for disease treatment or prevention in all patients. Identification of causal pathways should also lead to new biomarkers to improve diagnoses, monitor disease progression, and response to therapy. Validated genetic markers are also proving to be valuable tool to determine whether relationships between existing biomarkers and disease are causal through mendelian randomization studies.[251] In certain clinical scenarios, personal disease risk prediction based on the genetic risk variant profile may lead to personalized therapy, as is now common in cancer therapeutics. However, for most diseases, such clinical use is still in the future because in the aggregate, known genetic variation explains such a small fraction of disease risk.

IMPLICATION FOR ANESTHESIOLOGISTS

The greatest clinical promise of complex trait genetics in anesthesiology is to predict and understand the response to anesthetics or the pharmacologic drugs used for pain medicine to tailor the most effective and safe treatment.[252,253] Mendelian and mitochondrial genetics have led to the identification of genes of rare diseases as presented in this chapter, and the biologic understanding of the disease has led to anesthetic considerations that maximize safety and efficacy. Pharmacogenomics is the study of genetic variation that contributes to the interindividual variability in treatment response, which is a complex trait. Although many biologic and lifestyle factors such

as age, sex, liver and kidney function, diet and exercise, smoking and alcohol use, and severity of illness may contribute to the variability in the treatment response, if variability persists after accounting for these covariates, then genetic factors may be considered.[254] Two categories of genes are recognized to harbor variants influencing drug response: pharmacokinetic (PK) and pharmacodynamic (PD) genes.

PK genes influence interindividual differences in drug metabolism including absorption, distribution, metabolism, and excretion (ADME). PK gene variability may lead to either slower or more rapid drug uptake and conversion and excretion, leading to either the elimination of the drug before the therapeutic effect is achieved or the drug remaining too long or in too high a dose in the body, thereby increasing the risk of adverse effects. Many metabolizing enzymes in the liver, including the cytochrome *P450* gene family, are important PK genes with poor or ultrarapid metabolizing alleles, such as the gene *CYP2D6*, which contributes to metabolism of up to 25% of drugs in clinical use today.[255]

PD genes are either drug-target receptors or molecular components in the signal transduction pathway targeted by the drug. Variation in PD genes is likely to be involved when the variation in drug response is dose independent and may involve synergistic, independent, or antagonistic interactions among multiple components of the signaling pathway. Thus PD effects are likely more complex than PK effects, and early pharmacogenetic studies suggest that they contribute more to the variation in treatment response than PK effects. For example, PK and PD effects are seen in warfarin anticoagulation therapy, which displays tenfold variation in treatment response among individuals. Although carriers of poor metabolizer alleles of the metabolizing enzyme *CYP2C9* (PK gene) require lower doses and have a higher risk of bleeding, genetic variation in a subunit of the warfarin target VKOR (*VKORC1*, a PD gene) is the major determinant of the amount of warfarin required to achieve a therapeutic effect.

Progress in the field of pharmacogenomics has been slow. Most pharmacogenetic discoveries have come from candidate gene studies of PK and PD genes; however, GWASs and sequencing approaches are beginning to be applied.[256,257] Importantly, several challenges remain. First, thorough phenotyping is critical to measure the variation in response precisely and to identify nongenetic factors influencing the variability that should be accounted for. Second, genetic study designs should include well-powered, large samples from a homogenous population of preferably one ancestry and analytic methods with adequate quality control for technical or population artifacts and correction for multiple testing. Studies must be relatively large because predicting how large an individual gene effect may be is not possible beforehand; *a priori* power calculations to calculate sample size are not possible. Replication in an independent sample is necessary, but finding a replication sample with the same phenotype may be difficult for some pharmacogenomic studies. Encouragingly, small early pharmacogenomic GWASs have detected genome-wide significant findings with $n = 100$ cases suggesting that effect sizes of pharmacogenomic alleles seem to be larger than those of disease susceptibility alleles and may involve fewer genes.[256] In the next few years, unbiased, whole genome genetic approaches should lead to a greater understanding of the genetic basis of PKs and PDs of anesthetics and pain drugs.

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Chapter 43

Malignant Hyperthermia and Muscle-Related Disorders

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Key Points

- Malignant hyperthermia (MH) is an anesthetic-related disorder of increased skeletal muscle metabolism. It is an inherited condition in an autosomal dominant pattern.
- Skeletal muscle accounts for approximately 40% of body weight; its increased metabolism therefore has a profound effect on whole-body metabolism.
- Signs of MH, including tachycardia, increased end-tidal carbon dioxide (CO_2), muscle rigidity, and increased temperature, are related to increased metabolism.
- The abnormal function of the skeletal muscle ryanodine receptor (RyR1) in MH-susceptible (MHS) individuals is associated with abnormal intracellular calcium handling, which is controlled by compensatory mechanisms within the cell when it is not exposed to triggering agents.
- Loss of compensatory control of intracellular calcium on exposure to triggering agents or heat stress leads to marked metabolic stimulation within the cell to provide extra adenosine triphosphate to drive the calcium pumps that restore calcium to its reservoirs (e.g., sarcoplasmic reticulum, mitochondria, extracellular fluid).
- Dantrolene significantly attenuates myoplasmic calcium (Ca^{2+}) concentrations and thereby allows restoration of normal metabolism, with a reversal of the signs of metabolic stimulation.
- MH is inherited; one RyR1 mutation accounts for all porcine MH, whereas more than 210 mutations in RyR1 and 4 mutations in $Ca_V1.1$ account for human MH.
- Evaluation of persons susceptible to MH includes contracture of a skeletal muscle biopsy specimen with halothane and caffeine and evaluation of DNA to identify mutations. Only DNA testing is needed to evaluate swine MH.
- Future MH goals include advancements of genetic evaluations in North American and European medical programs and stronger finances to support genetic studies, the identification of the mode of action of dantrolene, a determination of the immediate cause of triggering MH, and the development of effective, noninvasive tests for MHS.
- Whereas the risk for an MH mutation in patients with Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) is similar to those in the general population, the incidence of MH-like anesthetic events has been reported to be 0.002 with DMD and 0.00036 with BMD.
- Dystrophin, along with dystrophin-associated glycoproteins, is involved in sarcolemmal stability. Mutations in this gene that cause an absence or truncation of dystrophin are responsible for DMD and BMD.
- Succinylcholine is contraindicated in patients with DMD or BMD because of the risk of rhabdomyolysis and hyperkalemia as a result of their unstable sarcolemmal membrane.
- Most complications in patients with myotonic dystrophy are pulmonary related that result from hypotonia, chronic aspiration of gastric contents, and central and peripheral hypoventilation.
- There is no evidence of increased risk of MH in patients with sodium channel pathology.
- Some of these neuromuscular disorders are also discussed in Chapter 42. A comparison of both of these discussions should provide an in-depth knowledge of these rather rare but important diseases for anesthesia.

Malignant hyperthermia (MH) is one of the most devastating anesthesia-related complications. This fulminant syndrome is elicited by the administration of triggering anesthetic agents, such as a volatile anesthetic or a depolarizing neuromuscular blocking agent. MH has been and continues to be a life-threatening complication of anesthesia if the diagnosis is not promptly made and treatment is not begun in a timely fashion. Unlike other disorders described in this chapter, MH has virtually no characteristic phenotype before exposure to the triggering agent and is truly an example of the interaction of genes and the environment. Also covered in this chapter are some of the neuromuscular disorders, although rarely encountered in a routine anesthetic practice. This group of disorders challenges both perioperative management and intensive care. They affect the normal function of the peripheral nerves, the neuromuscular junction, and/or muscles. Although such diseases are thought to be rare, the number of patients that a clinician may encounter is increasing because of better medical care, increasing longevity, and possibly other unidentified factors. Neuromuscular disorders have a significant potential to interact with an improper anesthetic plan, and all affected patients require special perioperative attention for anesthetic management. In this area, the armamentarium of invasive and noninvasive diagnostic tools is being developed, especially in genetics.

MALIGNANT HYPERTHERMIA

MH is a pharmacogenetic clinical syndrome that, in its classic form, occurs during anesthesia with a volatile halogenated alkane such as halothane and/or the administration of the depolarizing muscle relaxant succinylcholine. The fulminant MH episode observed clinically produces rapidly increasing body temperature (by as much as 1° C in 5 minutes) and extreme acidosis as a result of an acute loss of control of intracellular calcium levels and compensatory uncontrolled increases in skeletal muscle metabolism that may proceed to severe rhabdomyolysis. Although MH was initially associated with a mortality rate of 60%, earlier diagnosis and the use of dantrolene have reduced the mortality to less than 1.4%.[1] Current cases of MH are restricted in severity because of diagnostic awareness, early detection through end-expired carbon dioxide (CO_2), the use of less potent anesthetic triggers, and the administration of drugs that attenuate the progression of the fulminant episode. The incidence of fulminant MH was reported to be 1 case per 62,000 anesthetics administered when triggering agents were not used, but the number of suspected cases was 1 case per 4500 anesthetics administered when triggering agents were administered.[2] The prevalence of MH events in Japan was calculated to be between 1:60,000 to 1:73,000.[3,4] However, the prevalence of MH mutations within kindred known to transmit MH-susceptibility (MHS) mutations may be as high as 1:2000.[5] Males appear to be more susceptible to developing a clinical MH episode than females.[3,6] A gender difference in MHS has also recently been demonstrated in knock-in mice expressing human MH mutation RyR1-T4825I.[7] The pediatric population accounts for 52.1% of all MH reactions.[8,9]

Between 50% and 80% of genotyped patients who have had a clinical MH syndrome and a positive muscle biopsy have had their disease linked to 1 of more than 210 mutations in the type 1 ryanodine receptor (RyR1; sarcoplasmic reticulum [SR] Ca^{2+} release channel) gene and 4 mutations in the pore subunit of the slow inactivating L-type Ca^{2+} channel $Ca_V1.1$ (dihydropyridine receptor [DHPR]).[10] The genetics of MH and the related abnormal function of RyR1, the DHPR, and associated proteins are being investigated at the molecular biologic level, with a porcine model and several new mouse models providing intricate details about the cause of the disorder. Parallel studies in humans are limited by scarce material for scientific study and are complicated by the fact that phenotypes within a genotype vary as a result of sex, age, genetic, epigenetic, and environmental modifiers.

Public education and communication in the United States are provided by Malignant Hyperthermia Association of the United States (MHAUS, 11 E. State Street, P.O. Box 1069, Sherburne, NY 13460-1069; telephone: 1-607-674-7901; fax: 1-607-674-7910; e-mail: info@mhaus.org; website: http://www.mhaus.org), and by emergency consultation with the MH Hotline (1-800-MHHYPER or 1-800-644-9737). The North American Malignant Hyperthermia Registry (NAMHR), a professional subsidiary of MHAUS, collates findings from muscle biopsy centers in Canada and the United States and provides access to specific patient data through the hotline or its director, Dr. Barbara W. Brandom (NAMHR, Room 7449, Department of Anesthesiology, Children's Hospital, University of Pittsburgh, 3705 Fifth Avenue at DeSoto St., Pittsburgh, PA 15213-2583; telephone: 1-888-274-7899; fax: 1-412-692-8658; e-mail: bwb@pitt.edu; website: https://www.mhreg.org).

HISTORY

Between 1915 and 1925, one family experienced three anesthetic-induced MH deaths with rigidity and hyperthermia and was puzzled for decades regarding the cause of these deaths.[11,12] MHS was eventually confirmed in three descendants by in vitro muscle biopsy tests.[11] In 1929, Ombrédanne described anesthesia-induced postoperative hyperthermia and pallor in children accompanied by significant mortality but did not detect any familial relationships.[13] Critical worldwide attention to MH began in 1960 when Denborough and Lovell reported a 21-year-old Australian with an open leg fracture who was more anxious about anesthesia than about surgery because 10 of his relatives died during or after anesthesia.[14] Denborough and Lovell initially anesthetized him with the then-new agent halothane, halted it when signs of MH appeared, successfully treated the symptoms, aborted the syndrome, and subsequently used spinal anesthesia. Further evaluations by George Locher in Wausau, Wisconsin, and Beverly Britt in Toronto, Canada, led to the discovery that the risk for MH was indeed familial.[15] The cause of the syndrome was also found to be the result of skeletal muscle involvement rather than central loss of temperature control by the recognition of increased muscle metabolism or muscle rigidity early in the syndrome, low-threshold contracture responses, and elevated creatine kinase (CK) values.[16]

Interestingly, a similar syndrome was discovered in swine inbred with breeding patterns designed to produce a rapid growth rate and superior muscle development (e.g., Landrace, Piétrain, Duroc, and Poland China). *Porcine stress syndrome*,[17] which is associated with increased metabolism, acidosis, rigidity, fever, and death from rapid deterioration of muscle and results in pale, soft, exudative pork,[18] can be triggered by any stress, such as separation, shipping conditions, weaning, fighting, coitus, or preparation for slaughter, and had become a significant problem for meat production. In 1966, Hall and co-workers reported that a syndrome that appeared to be identical to MH could be induced in stress-susceptible swine by the administration of halothane and succinylcholine.[19] The cause of this syndrome in pigs was discovered to be a single missense mutation in *RYR1*, and all susceptible swine have the same Arg615Cys mutation in the SR calcium release channel RyR1.[20]

In 1975, Harrison described the efficacy of dantrolene in preventing and treating porcine MH,[21] which was rapidly confirmed in humans by a multihospital evaluation of dantrolene used to treat anesthetic-induced MH episodes.[22] Today, dantrolene still remains the primary pharmacologic approach for successful MH therapy.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF EXCITATION-CONTRACTION COUPLING AND MALIGNANT HYPERTHERMIA

MH is a syndrome caused by dysregulation of excitation-contraction (EC) coupling in skeletal muscle. Normal muscle contraction is initiated by nerve impulses arriving at the neuromuscular junction (i.e., the motor end plate) that trigger the release of acetylcholine from the nerve terminal. Acetylcholine activates nicotinic acetylcholine receptors (nAChRs), nonselective cation channels located postsynaptically within the neuromuscular junction, which are essential for local depolarization of the muscle membrane and for initiating action potentials that rapidly propagate along the surface membrane of the muscle. Invaginations of the surface membrane (transverse or T tubules) act as conduits to direct action potentials rapidly and uniformly deep within the myofibrils where they transduce a conformational change in the voltage sensor integral to $Ca_V1.1$. Conformational changes in $Ca_V1.1$ are mechanically transmitted to the Ca^{2+} release channels (RyR1) residing in the junctional face of the SR. The mechanical coupling of DHPRs and RyR1 channels that occurs at specialized junctions (*triadic junctions*) is essential for linking the electrical signals arriving at the T tubules with the release of Ca^{2+} stored within the SR. Release of SR Ca^{2+} causes the free, cytoplasmic (sarcoplasmic) Ca^{2+} concentration to increase from 10^{-7} μM to approximately 10^{-5} μM. The Ca^{2+} binds to contractile proteins (troponin C and tropomyosin) in the thin filament to expose the myosin-binding sites on actin that activate the thick filament (myosin) and cause a shortening of the muscle fibers (i.e., muscle contraction). The entire process is termed *excitation-contraction (EC) coupling*. Intracellular Ca^{2+} pumps (i.e., sarcoplasmic/endoplasmic reticulum Ca^{2+}-adenosine triphosphatase [ATPase] or SERCA pumps) rapidly sequester Ca^{2+} back into the SR lumen, and muscle relaxation begins when the Ca^{2+} concentration falls below 10^{-6} μM and ends when the resting sarcoplasmic Ca^{2+} concentration is restored to 10^{-7} μM. Because both contraction and relaxation are energy-related processes that consume adenosine triphosphate (ATP), knowing the molecular events that contribute to EC coupling and the associated relaxation is essential to understanding the cause of MH (Fig. 43-1). Clinical and laboratory data from swine and humans indicate that the fulminant MH syndrome is associated with a persistent

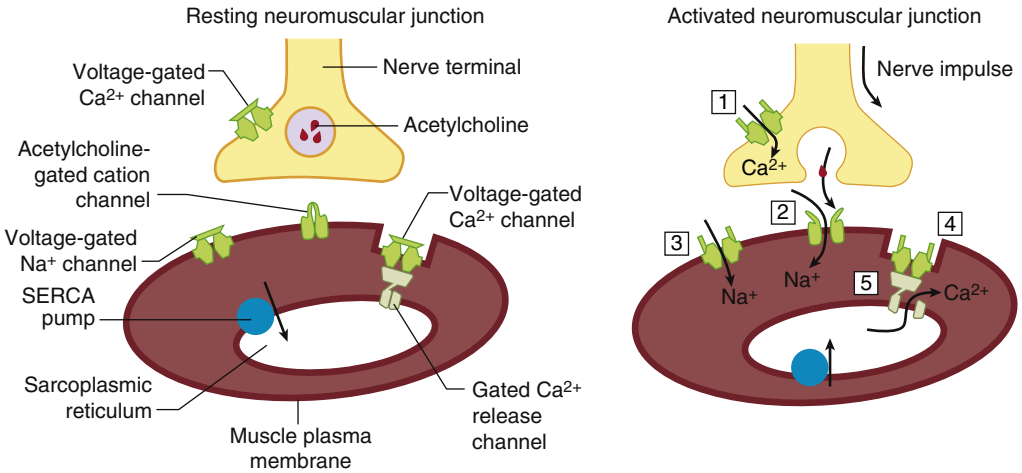


Figure 43-1. Key ion channels involved in neuromuscular transmission and excitation-contraction coupling. Nerve impulses arriving at the nerve terminal activate voltage-gated Ca^{2+} channels *(1)*. The resulting increase in cytoplasmic Ca^{2+} concentration triggers the exocytosis process of acetylcholine. Binding of acetylcholine to postsynaptic nicotinic acetylcholine receptors (nAChRs) activates an integral nonselective cation channel that depolarizes the sarcolemma *(2)*. Depolarizing the sarcolemma to threshold activates voltage-gated Na^+ channels *(3)*, which initiates action potential impulses that propagate deep into the muscle through the transverse tubule system. Within the transverse tubule system, L-type voltage-gated Ca^{2+} channels sense membrane depolarization and undergo a conformational change *(4)*. A physical link between the α1 subunit ($Ca_V1.1$) of the dihydropyridine receptor (DHPR) and the ryanodine receptor (RyR1) is the means by which the electrical signal is transferred from the T tubule to Ca^{2+} release from the SR *(5)*. *(Modified from Alberts B, Bray D, Lewis J, et al:* Molecular biology of the cell, *ed 3. New York, 1994, Garland Press.)*

increase in the concentration of sarcoplasmic Ca^{2+}.[23-26] The increased activity of pumps and exchangers trying to correct the increase in sarcoplasmic Ca^{2+} increases the need for ATP, which in turn produces heat. Thus the end result is hyperthermia. The rigidity that is frequently seen during a fulminant MH episode is the result of the inability of the Ca^{2+} pumps and transporters to reduce the unbound sarcoplasmic Ca^{2+} below the contractile threshold. Dantrolene is therapeutic because it reduces the concentration of sarcoplasmic Ca^{2+}. However, the pathway by which dantrolene lowers sarcoplasmic Ca^{2+} is complex and still not fully understood.

MALIGNANT HYPERTHERMIA IS THE RESULT OF ABNORMAL FUNCTION OF MUSCLE CALCIUM RELEASE UNITS

RYANODINE RECEPTORS

Ryanodine receptors (RyRs), which in muscle are synonymous with the junctional foot protein/SR calcium release channel, are so named because they specifically bind the toxic plant alkaloid ryanodine.[27,28] Three RyR isoforms are encoded by three genes located on human chromosomes 19q13.1,[29] 1q42.1-q43,[30] and 15q14-q15[31]—the skeletal (RyR1), cardiac (RyR2), and brain (RyR3) isoforms, respectively. Each functional RyR consists of four identical subunits (~5000 amino acids each), and each subunit binds with an accessory protein, calstabin 1 (FK506 12-kDa binding protein [FKBP12]).[32-35] The total mass of the tetramer exceeds 2 megadaltons and is one of the largest known proteins and the largest known channel in the mammalian species. Evidence of direct coupling of $Ca_V1.1$ and RyR1 has been demonstrated by expressing chimeric $Ca_V1.1/Ca_V1.2$ complementary DNA (cDNA) in dysgenic myotubes that lack constitutive expression of $Ca_V1.1$.[36,37] Such studies have provided compelling evidence that the cytoplasmic region between repeats II and III (i.e., cytosolic II-III loop) contains a stretch of 46 amino acids (L720 to Q765) that are essential for engaging bidirectional signaling with RyR1.[38]

In the past decade, understanding of EC coupling has significantly increased by identifying protein-protein interactions that regulate both the release and sequestration of Ca^{2+} within skeletal muscle. The elemental unit of function has been named the Ca^{2+} release unit (CRU), and it is localized within junctional regions of T-tubule and SR membranes.[39] The CRU is a macromolecular assembly of interacting proteins that participate in tightly regulating EC coupling. RyR1 is a high-conductance channel that regulates the release of SR Ca^{2+} and is the central component of the CRU. The functional RyR1 tetramer anchored within the SR membrane physically spans the junctional space to interact with tetrads made up of four voltage-activated $Ca_V1.1$ subunits within the T-tubule membrane. This physical interaction engages a form of bidirectional signaling that tightly regulates the function of both proteins. Moreover, the interaction of $Ca_V1.1$ and RyR1 does not occur in isolation; rather, this interaction is further subjected to regulation by a number of proteins localized within the triad junction, including Homer 1, which physically binds and functionally couples target proteins, calstabin 1, triadin, junctin, Mg29, junctophilin 1 and 2, calsequestrin, calmodulin, the catalytic and regulatory subunits of protein kinase A, and protein phosphatase 1.[40-44] It is likely that this list is not complete and that the CRU represents a tightly regulated macromolecular complex. More importantly, increasing experimental evidence suggests that mutations found in RyR1 ($_{MH}$RyR) or $Ca_V1.1$ can alter protein-protein interactions in the CRU,[45-47] as well as alter the functional fidelity of bidirectional signals.[48-52]

In the presence of certain chemical substances, MH mutations in RyR1 or DHPR cause severe dysregulation of RyR1 channel function. This dysregulation can be observed in vitro as heightened sensitivity to volatile anesthetics, 4-chloro-*m*-cresol, caffeine, ryanodine, and potassium depolarization.[53-55] Chemically induced dysfunction of the RyR1 complex appears to be the principal cause of triggering uncontrolled skeletal muscle metabolic acidosis (aerobic and glycolytic), rigidity, and hyperkalemia, but the mechanisms governing the syndrome are unclear. The relationship among exertional heat illness, exertional rhabdomyolysis, and MHS is also unclear and is an area that requires investigation and controlled clinical studies.[56]

Two essential cations greatly shape the kinetics and magnitude of Ca^{2+} release in response to depolarizing triggers: Ca^{2+} itself and magnesium (Mg^{2+}). The normal RyR1 complex responds to Ca^{2+} in a biphasic manner. First, Ca^{2+} activates the channel in a graded manner between 100 nM and 100 μM, whereas higher concentrations inhibit channel activity.[57,58] This biphasic action is thought to occur via binding of Ca^{2+} to two classes of regulatory sites on RyR1, a high-affinity stimulatory site and a low-affinity inhibitory site.[42] Mg^{2+}-induced inhibition is the second important physiologic regulator of RyR1 activity in skeletal muscle.[59,60] Mg^{2+} inhibits RyR1 in a cooperative manner ($n_H \approx 2$; 50% inhibitory concentration [IC_{50}] ≈ 650 μM). It is likely that Mg^{2+} acts by competing with Ca^{2+} at its activator sites and by binding to yet unidentified low-affinity inhibitory sites.[61,62] Possibly, MH mutations introduce allosteric instability into the RyR1 complex, which leads to a reduction of inhibition rather than directly altering the binding properties of Ca^{2+} or Mg^{2+} (or both) at the activator or inhibitor sites. Therefore hypersensitivity to pharmacologic agents is likely to be closely tied to altered responses to physiologic ligands. However, whether MHS channels are primarily hyposensitive to inhibition by Mg^{2+} or Ca^{2+} (or both),[63,64] are hypersensitive to activation by Ca^{2+}, or exhibit altered sensitivities in both directions to both ions seems to be highly dependent on the location of the MH mutation.[65,66] Studies have also pursued the *leaky channel* hypothesis by examining SR preparations from homozygous R615C MHS pigs and heterozygous R163C and C512S mice; they observed a significantly lower Ca^{2+} loading capacity (38%, 23%, and 22% lower than matched wild-type mice, respectively) primarily mediated by the presence of leaky channels that remain active even with 100 nM extravesicular Ca^{2+}.[67,68] Recent studies indicate that the expression of $Ca_V1.1$ represses the basal activity of the ryanodine-insensitive RyR1 leaky

state.[50] Importantly, MHS mutations appear to not only alter bidirectional signaling during EC coupling[51,52] and inherent regulation of RyR1 channel functions,[65,66] but they also weaken negative regulation conferred by $Ca_V1.1$ on the RyR1 Ca^{2+} leak.[48] These recent findings at the molecular and cellular level using knock-in MHS mice confirm earlier measurements made in MHS muscles, myotubes, and myoball preparations and in dyspedic myotubes expressing $_{MH}$RyR1s, all of which have been shown to have chronically elevated resting cytoplasmic $[Ca^{2+}]_i$.[47,54,69]

Some experimental evidence suggests that long-range interdomain interactions between regions of RyR1 are involved in channel regulation by stabilizing protein conformations critical for normal channel transitions.[70] A three-dimensional reconstruction of RyR1 by Samso and co-workers shows that the RyR1 architecture is designed to support long-range allosteric pathways such as coupling with $Ca_V1.1$ and binding to ligands such as calmodulin and FKBP12.[71]

VOLTAGE-GATED CALCIUM CHANNELS: ROLE OF $CA_V1.1$

Although the majority of mutations that confer MHS reside in the *RyR1* gene, recently three mutations in the *CACNA1S* gene encoding for the $Ca_V1.1$ subunit of skeletal muscle have been linked to MHS.[5,72-74] The R1086H mutation in the intracellular loop connecting homologous repeats III and IV of Ca_V represent the first MH-causing mutation so far identified in a protein other than RyR1. Physiologic characterization of the mutation further demonstrated that sensitivity of RyR1 activity is significantly enhanced by membrane depolarization or by pharmacologic activators of RyR1 (e.g., caffeine).[75] In addition, Pirone and colleagues have identified an MHS-causing Thr-to-Ser mutation at position 1354 in the S5-S6 extracellular pore-loop region of the homologous repeat IV of $Ca_V1.1$ Expression of the T1354S mutation also accelerated L-type Ca^{2+} current kinetics and also contributed to an increase in RyR1-mediated Ca^{2+} release.[74] The R174W $Ca_V1.1$ MH mutation occurs at the innermost basic residue of the IS4 voltage-sensing helix, a residue conserved among all Ca_V channels. Unlike the other $Ca_V1.1$ MHS mutations, R174W ablates the L-type current but has no influence on normal EC coupling. Nonetheless, R174W-expressing myotubes have a chronic elevation of free sarcoplasmic resting Ca^{2+} and an increased sensitivity of Ca^{2+} release to caffeine and halothane, compared with myotubes expressing wild-type $Ca_V1.1$.[48,76]

FACTORS OTHER THAN RYANODINE RECEPTOR ABNORMALITIES

Other cellular processes can affect MH episodes. It has been demonstrated that concurrent administration of nondepolarizing neuromuscular blocking drugs and triggering agents can delay or prevent the onset of clinical MH syndrome. Pretreatment of MHS pigs with sufficient nondepolarizing neuromuscular blocking agent to abolish completely the muscle twitch elicited by electrical stimulation of the nerve prevented halothane from triggering the clinical syndrome for 90 minutes, the longest time tested.[77] However, in the continued presence of halothane, when the function of the neuromuscular junction was restored by administering the cholinesterase inhibitor, neostigmine, clinical MH was immediately triggered. This result suggested a close relationship between functional neurochemical transmission within the neuromuscular junction or depolarization of the sarcolemma (or both) and the clinical syndrome.

Recently, sarcolemmal excitation-coupled Ca^{2+} entry (ECCE) has been shown to be sensitive to the conformation of the RyR1 and is enhanced by several mutations in RyR1, including MH mutations.[40,46,78] ECCE appears to be an inherent property of $Ca_V1.1$ during long or repetitive depolarization,[79] possibly mediated by shifting $Ca_V1.1$ to the mode 2–gating conformation. Nevertheless, enhanced ECCE in MHS muscle may contribute to an increased sensitivity to depolarization and appears to be one target for dantrolene's abrogation of responses to both electrical and potassium chloride depolarization.[45] In addition to ECCE, classic store-operated capacitive Ca^{2+} entry pathways similar to the store-operated Ca^{2+} entry (SOCE) observed in nonexcitable cells[80] have been shown to be present in skeletal muscle[81-83] and could be more active in MHS muscles as a response to chronic store depletion. These SOCE channels have also been suggested to be a target for dantrolene.[84] Together, these data suggest that $_{MH}$RyRs or $_{MH}Ca_V1.1$ assume a conformation that enhances Ca^{2+} entry via ECCE or SOCE (or both). This enhanced entry, when combined with decreased sensitivity of $_{MH}$RyRs to Ca^{2+} and Mg^{2+} inhibition, could provide cellular conditions that heighten sensitivity to triggering agents and perpetuate the fulminant clinical MH syndrome.

DANTROLENE

Dantrolene is the only medication that has been shown to be effective in reversing the symptoms of MH. Preadministration of dantrolene will also prevent the development of fulminant MH in homozygous pigs or heterozygous MH mice when exposed to a triggering stimulus. Dantrolene sodium is a hydantoin derivative (1-[[[5-(4-nitrophenyl)-2-furanyl]methylene]imino]-2,4-imidazolidinedione) that does not block neuromuscular transmission but causes muscle weakness by direct action on the striated muscle cell. The properties of dantrolene have been closely correlated with its ability to reduce efflux of Ca^{2+} from the SR in vitro.[85] Dantrolene (20 μM) counteracts the effect of reduced Mg^{2+} inhibition in MH-affected muscle.[86] Dantrolene (20 μM) can inhibit the enhanced sensitivity to caffeine observed in MH muscles, and both dantrolene and its water-soluble analogue, azumolene (150 μM), have been shown to reduce depolarization-induced release of Ca^{2+} in both muscle and triadic vesicles.[87] The idea that dantrolene suppresses SR Ca^{2+} release as a result of direct interactions with RyR1 is somewhat controversial. Paul-Pletzer and associates demonstrated that [^{3}H] azidodantrolene specifically labels the amino terminus of RyR1 defined by the 1400–amino acid residue N-terminal calpain digestion fragment of RyR1.[88] More detailed

analysis further localized the [^{3}H]azidodantrolene binding site to a single domain containing the core sequence corresponding to amino acid residues 590 through 609 of RyR1.[88] However, to date, no evidence suggests that dantrolene has a direct action on single RyR1 channels studied in lipid bilayers, even in the presence of FKBP12, ATP, and activating concentrations of Ca^{2+}, suggesting that dantrolene's main action is to alter key protein-protein interactions.

GENETICS

RYR1 mutations have been found in 50% to 80% of patients and relatives who are labeled MHS by positive in vitro contracture tests (IVCTs) and in almost all families with central core disease (CCD) and King-Denborough syndrome. More than 202 missense mutations and 8 deletions associated with MH have thus far been detected. Another 29 missense mutations are associated with CCD and multiminicore disease in patients with unknown MH testing status.[10] Interestingly, 40% of missense *RYR1* mutations occur at CpG dinucleotide sequences. Five other chromosomal loci (17q21-24, 1q32, 3q13, 7q21-24, and 5p) have been linked to families with positive contracture tests and an unusual response to anesthesia and have been designated MHS loci 2 through 6, respectively. However, of these five, the only gene other than *RYR1* that has been shown to be associated with MH is *CACNL1A3* in the MHS3 locus,[89] which codes for $Ca_V1.1$ (the α_{1S}-subunit of DHPR). Four causative mutations in this gene are linked to less than 1% of MHS families worldwide. In some of the other loci, all genes within the locus have been ruled out as causing MHS. Hence, for practical reasons, the *RYR1* gene remains the primary target for current clinical genetic analysis.

DISTRIBUTION OF *RYR1* MUTATIONS

The missense mutations associated with MHS, CCD, or, in some cases both, are dispersed throughout the coding region of the *RYR1* gene, and all allow transcription of a protein that is putatively functional.[10,90] Until recently, it was thought that most *RYR1* mutations were clustered in three hot spots: MH/CCD region 1—between amino acid residues 35 and 614, MH/CCD region 2—between amino acid residues 2163 and 2458 in the sarcoplasmic foot region of the protein, and MHS/CCD region 3—between amino acids 4643 and 4898 in the carboxyl-terminal transmembrane loop or pore region[91] (Fig. 43-2). It appears that the supposition that hot spots existed was simply caused by bias in the sample analysis, inasmuch as the missense mutations associated with MH or CCD (or both) are scattered over 54 of the 107 exons of *RYR1*. Approximately 41% of reported MH mutations are found in multiple families. CCD mutations are predominantly found in the C-terminal region of the gene (exons 85 to 103), and only 10 mutations (17%) have been described in more than one family: R4861H ($n = 14$), V4849I ($n = 9$), I4898T ($n = 7$), L4824P ($n = 4$), A4940T ($n = 4$), G4638D ($n = 3$), R4893W ($n = 3$), R4861C ($n = 2$), R4893Q ($n = 2$), and G4899E ($n = 2$).

The true ethnic distribution of MH and CCD is difficult to ascertain. MH and CCD have been predominantly reported in Western populations, but, more likely than not, this predominance is incorrect and the result of the manner and frequency in which cases are reported. Some mutations appear to be clustered in a given region of the world, but the distribution and frequency appear to be somewhat population specific. In the United Kingdom, 69 *RYR1* mutations have been discovered, 25 of which were found in a single family. G2434R has been found in approximately 40% of the 434 mutation-positive MH families investigated in the United Kingdom, with the

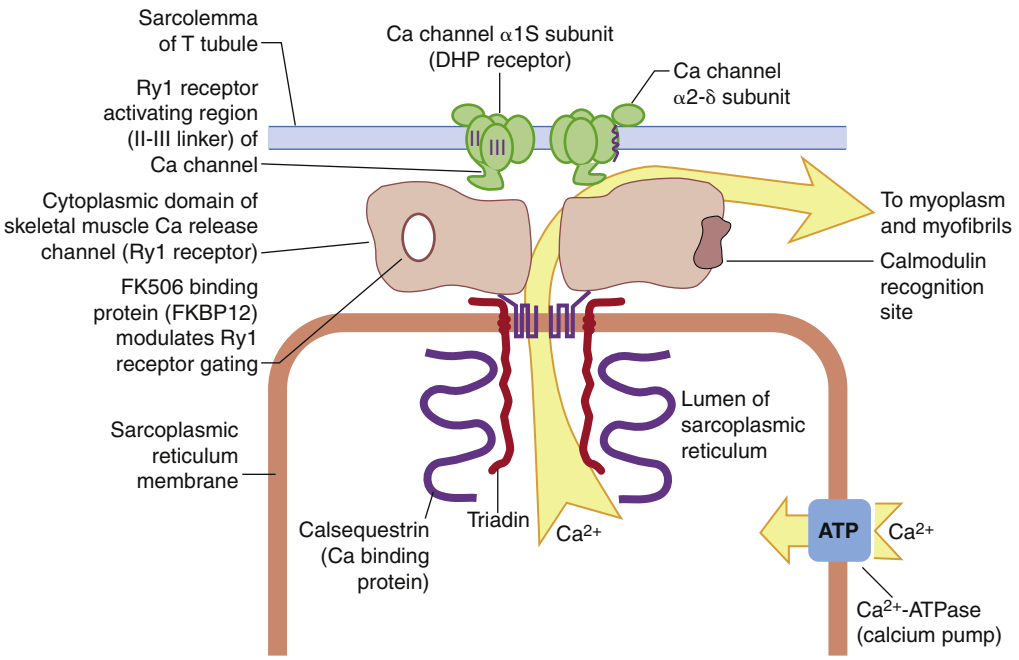


Figure 43-2. Schematic representation of the triadic junction of skeletal muscle shows the junctional foot protein (ryanodine [Ry1] receptor) and its associated proteins. In skeletal muscle, the α_{1S}-subunit of the dihydropyridine receptor (DHPR) participates in excitation-contraction coupling. These physical links transmit essential signals across the narrow gap of the triadic junction that activate the Ry1 receptor and release Ca^{2+} from the sarcoplasmic reticulum. *(Modified from Pessah IN, Lynch C III, Gronert GA: Complex pharmacology of malignant hyperthermia,* Anesthesiology *84:1275-1279, 1996.)*

next most common mutations being T2206M (10%) and G341R (8%). In Switzerland, V2168M and I2336H have been the predominant mutations,[92] and in Germany, R163C (MH and CCD), R614C (MH), T2206M (MH), G2434R (MH), and R2454H (MH) have each been detected in five or more independent cases.[93,94] G341R and R614C have been common mutations in France,[95] and R614C has also been found in several MH families from Italy[95] and Canada.[96] G341R has frequently been found in Belgium.[95] The mutation common to Europe and North America has been G2434R, which has occurred in 4% to 7% of European and 5.5% of North American families.[97] Single-family mutations have been the most common mutations reported in Japanese, Chinese, Taiwanese, Australian, and New Zealand MH families,[98-100] but likely, these findings may reflect the small number of cases investigated there. Because genetic screening in European and North American studies has predominantly targeted only regions 1 and 2 of the original hot spots in the gene, the absence of *RYR1* mutations in some of the screened population could be explained by *RYR1* mutations located outside these two regions or by involvement of other genes.

INHERITANCE AND PENETRANCE OF MALIGNANT HYPERTHERMIA

Inheritance of human MH can no longer be considered to be solely autosomal dominant with variable penetrance because more than one MH-linked mutation has been identified in some probands and families. Six nonconsanguineous families harbor at least two *RYR1* mutations that have both been linked to MHS; and in two families, one is an *RYR1* mutation and the second is a $Ca_V1.1$ mutation.[5] Although MHS homozygosity is common in affected pigs, it is rare in the human population and variable in the transgenic mouse population. The known MHS homozygous humans appear clinically normal but exhibit stronger responses to caffeine and halothane in IVCTs than heterozygous individuals do.[101-104] Homozygosity of two MH mutations in hot spot 1 leads to perinatal lethality in mice.[67,68] In humans, double heterozygous individuals do not appear to show any additive effect of the second mutation on IVCT.[5] However, recent development of the T4826I-*RYR1* knock-in mouse has revealed that an MHS mutation within the S4-S5 cytoplasmic linker of *RYR1* confers genotype- and sex-dependent susceptibility to pharmacologic and environmental stressors that trigger fulminant MH and promote myopathy.[7]

IN VITRO CONTRACTURE TEST AND CAFFEINE HALOTHANE CONTRACTURE TEST

The current gold standard for diagnosis of MH is the halothane and caffeine muscle contracture test, also known as the IVCT or the caffeine halothane contracture test (CHCT). Two protocols have been developed—the first by the European Malignant Hyperthermia Group (EMHG) and the second by the North American Malignant Hyperthermia Group (NAMHG).[9] These two protocols are similar but not identical. For the purpose of differentiation, the EMHG protocol is designated as IVCT and the NAMHG protocol as CHCT.

For the IVCT, the muscle biopsy is performed on the quadriceps (either vastus medialis or vastus lateralis).[105,106] The study consists of three parts: a static caffeine test, a static halothane test, and a dynamic halothane test.[106] For the static caffeine test, a stepwise increased concentration (0.5, 1, 1.5, 2, 3, 4, and 32 mmol/L) is applied. The lowest concentration of caffeine that produces a sustained increase of at least 0.2 g in baseline tension is reported as the caffeine threshold. Then the halothane threshold is obtained using the same method by exposing the muscle to halothane concentrations of 0.5%, 1%, 2%, and 3%. The dynamic halothane test is performed with the muscle stretched at a constant rate of 4 mm/min to achieve a force of approximately 3 g and held at the new length for 1 minute after a 3-minute exposure to halothane. For each cycle, halothane concentration will be increased from 0.5%, 1%, 2%, to 3%. The concentration of halothane that produces a sustained increase of at least 0.2 g in the muscle tension, compared with the prehalothane control, is defined as the *dynamic halothane threshold*.[106] The IVCT protocol classifies the patients into three groups: (1) MHS group with a caffeine threshold at the caffeine concentration of 2 mmol or less and a halothane threshold of 2% halothane or less; (2) MH normal (MHN) group with a caffeine threshold at the caffeine concentration of 3 mmol or more without a halothane threshold at 2% or less; and (3) MH equivocal (MHE) group with all results other than the aforementioned.[105,106]

For CHCT, a muscle biopsy can be taken from the following sites in the order of preference: (1) the vastus group, (2) the rectus abdominus, and (3) other muscle groups under special circumstances.[107] Required tests include exposure of muscle to 3% halothane alone and to incremental caffeine concentrations (0.5, 1, 2, 4, and 8.0 mmol if the response at 4 mmol is less than 1 g and 32 mmol) alone. Optional tests include exposure of muscle to a combination of both 1% halothane and incremental caffeine concentrations and to 2% halothane alone.[107] According to the CHCT protocol, an individual is MHS when either of the halothane or the caffeine test is positive and is MHN when both tests are negative.[107]

The sensitivity and specificity of IVCT was reported to be 99.0% (95% confidence interval [CI] 94.8%-100%) if the MHE group is considered susceptible and 93.6% (95% CI 89.2%-96.5%),[106] and of CHCT 97% (95% CI 84%-100%) and 78% (95% CI 69%-85%), respectively.[108] Recently, fluoroquinolones and statins, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, were found to induce significant contractures in MHS muscle bundles but not in MHN muscles.[109,110] Ondansetron and 3,4-methylenedioxymethamphetamine (MDMA) may also dose-dependently induce contracture or increase the sensitivity of the contractile apparatus to calcium in both MHS and MHN fibers.[111,112] Modifications to the IVCT protocol by adding ryanodine[113] or 4-chloro-*m*-cresol,[114,115] a ryanodine receptor–specific agonist has been reported but has not been included in the standard protocol. Furthermore, Metterlein and associates studied the possibility of replacing halothane with newer volatile agents in IVCT. At increasing concentration, except for sevoflurane, all newer volatile agents, including enflurane, isoflurane, and desflurane, induced significantly

greater contractures in MHS muscle compared with MHN bundles. However, within the MHS muscle bundles, halothane produced significantly higher contractures and was considered the strongest discriminator for MH using the IVCT protocol.[116] A direct application of high sevoflurane concentration of 8%, instead of the stepwise application, has been shown to induce significantly stronger contractures in MHS patients.[117] Nevertheless, from the retrospective analysis of the Japanese MH database, there was no evidence between the severity of MH triggered by sevoflurane and isoflurane or other agents, suggesting sevoflurane is not a weak or weaker MH-triggering agent.[118]

DISCORDANCE BETWEEN GENETIC AND CONTRACTURE MALIGNANT HYPERTHERMIA TESTING

Discordance between genetic and contracture test results has confounded linkage analysis worldwide. Examples include patients diagnosed as MHN carrying an *RYR1* mutation associated with MH and patients diagnosed as MHS who do not carry the familial *RYR1* mutation. Several explanations are possible, the most likely being that IVCT or CHCT is not clinically precise and that the thresholds for IVCT or CHCT are inexact, which would lead to errors in determining whether a patient is MHN or MHS. A second possibility is variable penetrance with possible allelic silencing,[119] and a third possibility is that individuals with discordance have mutations in other unknown genes or modifier genes that affect the function of *RYR1* and its phenotypic penetrance. The discrepancy between incidence estimates of MH events and prevalence estimates also points to possible epigenetic factors at work. Carpenter and colleagues have suggested that the severity of MHS may be related to the *RYR1* variant and mutation found within the highly conserved regions of *RYR1* gene.[72] The rarity of large kindreds with MH makes linkage analysis and understanding variability in clinical manifestations difficult. Robinson and associates demonstrated with the transmission disequilibrium test (TDT) that loci on chromosomes 5 and 7 and, to a lesser extent, loci on chromosomes 1 and 7 influence susceptibility to MH.[95]

GUIDELINES FOR GENETIC SCREENING

In 2000, the European MH group formulated guidelines for *RYR1* mutation screening with linkage data to other loci for some MH families, but all MH investigators emphasized the vital role of IVCT in the diagnosis of MH.[120] These guidelines for screening have reduced the number of relatives requiring contracture testing without increasing the risk of misdiagnosis[121,122] and include the following: (1) confirmation of MHS in a family member (preferably a proband) by IVCT before genetic testing; (2) use of 15 *RYR1* mutations characterized by in vitro functional assays for the genetic protocol; (3) confirmation of MHS and omission of IVCT if a causative mutation is detected in a first-degree relative; and (4) need for performance of IVCT before MHN is diagnosed if a familial mutation is not detected in a first-degree relative.

Only a small number of MHS families have been extensively investigated in North America by phenotyping, linkage analysis, and screening of specific genes. Collaborative protocols over the past several years between MH biopsy centers and molecular biologists have screened 209 unrelated patients diagnosed as MHS for mutations in the *RYR1*gene (see "Distribution of *RYR1* Mutations").

A recent consensus meeting agreed to the following: (1) limitations of genetic testing include low sensitivity because of the diversity of mutations and genes; (2) the *RYR1* gene is the primary focus for genetic testing, but further studies are required for a more complete understanding of the relationship between mutations and susceptibility; (3) guidelines for referral and education are needed to establish clinical testing in a Clinical Laboratories Improvement Act (CLIA)–certified laboratory; and (4) a North American MH *RYR1* Mutation Panel was not changed from the original panel set out in 2002 (Table 43-1).

Larach and co-workers reported a 34.8% morbidity rate in 181 patients with MH reported to the NAMHR between 1987 and 2006.[123] The occurrence of MH episodes was most frequent in young men (75%), and approximately one half of the patients reported having undergone two or more unremarkable general anesthetics in the past. In a more recent analysis of over 5 million nonbirth-related hospital discharges, diseases of the musculoskeletal system and connective tissue were significantly associated with MH diagnosis in children.[124]

FULMINANT MALIGNANT HYPERTHERMIA

Fulminant MH is rare. Acute episodes of MH depend on four variables: (1) a genetic predisposition, (2) the absence of inhibiting factors, (3) the presence of an anesthetic or nonanesthetic trigger, and (4) the presence of environmental factors that could potentiate the action of one or more of the other three variables.

ANESTHETIC TRIGGERING

Anesthetic drugs that trigger MH include ether, halothane, enflurane, isoflurane, desflurane, sevoflurane, and depolarizing muscle relaxants, succinylcholine being the only anesthetic drug currently used. Desflurane and sevoflurane appear to be less potent triggers than halothane and produce a more gradual onset of MH.[125,126] The onset may be explosive if succinylcholine is used. MHS swine were traditionally screened by induction with a volatile anesthetic, which led to pronounced hind limb rigidity within 5 minutes, frequently sooner.[127] Prior exercise, even an hour before induction of anesthesia, increased the severity and hastened the onset of rigidity in swine.[127] Similarly, in the new knock-in mouse models, the onset of limb rigidity after commencing exposure to volatile anesthetics was rapid. In addition, several modifying factors are more likely to be present in humans than in pigs or mice and can alter (or even prevent) the onset of clinical MH. Mild hypothermia and the preadministration of barbiturates, tranquilizers, propofol, or nondepolarizing neuromuscular blockers delay or prevent the onset of MH[25,127-129] in humans who are MHS, thus making them respond less predictably than swine or knock-in mice with MH. Many instances have occurred during

TABLE 43-1 FINDINGS OF THE NORTH AMERICAN MALIGNANT HYPERTHERMIA MUTATION PANEL, 2002

Exon	Mutation*	RyR1 Amino Acid Change	No. of Families in North America†	Estimated Incidence in Europe (%)	Phenotype
6	C487T	R163C	2	2-7	MHS, CCD
9	G742A	G248R	2 (11)	2	MHS
11	G1021A	G341R	1	6-17	MHS
17	C1840T	R614C	6 (42)	4-45	MHS
39	C6487T	R2163C	2	4	MHS
39	G6488A	R2163H	0	1	MHS, CCD
39	G6502A	V2168M	1	8	MHS, CCD
40	C6617T	T2206M	2	One family	MHS
44	Deletion	ΔG2347	2	0	MHS
44	G7048A	A2350T	1	0	MHS
45	G7303A	G2434R	9 (54)	4-10	MHS
45	G7307T	R2435H	1	2.5	MHS, CCD
46	G7361A	R2454H	4	One family	MHS
46	C7372	R2458C	0	4	MHS
46	G7373A	R2458H	0	4	MHS
101	G14582A	A4861H	0	Multiple families	CCD
102	T14693C	I4898T	0	Multiple families	MHS, CCD

CCD, Central core disease; *MHS,* malignant hyperthermia susceptibility; *RyR1,* ryanodine receptor type 1.
*Criteria for the 17 mutations: (1) they occur in more than one family in North America or Europe, and (2) previous testing of a sequence variant shows that the mutation is not a polymorphism.
†Data collaboration of the Uniformed Services University of the Health Sciences, Thomas Jefferson University, Wake Forest University, University of California, Davis, and Barrow Neurological Institute. The number in parentheses indicates those also found in Canada (e.g., for exon 45, four families with the mutation G2434R were found in Canada).

which fulminant MH has been reported in patients who previously tolerated potent triggers without difficulty.[130] The reason this occurs is unknown, but it is likely to be related to prior or concurrent administration of drugs that prevent or delay the onset of the syndrome, as described earlier, or unknown environmental influences that help provoke the positive incident. Thus the onset of the syndrome in humans is extremely variable both in initial symptoms and in the time of onset of the syndrome. Its onset is so variable that making the diagnosis in the setting of a clinical anesthetic can be quite difficult. Although not perfect, the clinical grading scale developed by Larach and colleagues[131] is a useful way for clinicians to determine retrospectively whether a patient who responds abnormally to anesthesia is in any way likely to actually have had a clinical MH episode. However, MH is most easily diagnosed prospectively by vigilance, recognizing its signs and symptoms and knowing how to treat the syndrome.

The two classic clinical manifestations of fulminant MH syndrome may start with one of the following two scenarios:

1. Rigidity after induction with succinylcholine but successful intubation, followed rapidly by the symptoms listed after scenario 2
2. Normal response to induction of anesthesia and uneventful anesthetic course until the onset of the following symptoms:
   - Unexplained sinus tachycardia or ventricular arrhythmias (or both)
   - Tachypnea, if spontaneous ventilation is present
   - Unexplained decrease in oxygen (O_2) saturation (because of a decrease in venous O_2 saturation)
   - Increase in end-tidal partial pressure of CO_2 (P_{CO_2}) with adequate ventilation and, in most cases, unchanged ventilation
   - Unexpected metabolic and respiratory acidosis
   - Central venous desaturation
   - Increase in body temperature above 38.8° C with no obvious cause

The usually muted onset of MH (scenario 2) is, in most cases, quickly detected by the development of tachycardia, increased levels of expired CO_2, and muscle rigidity. It can be delayed for several reasons and may not be overt until the patient is in the recovery room. Once initiated, the course of MH can be rapid. When clinical signs such as increased expired CO_2, muscle rigidity, tachycardia, and fever suggest MH, more than one abnormal sign must be observed before making the diagnosis, because according to a meta-analysis of many reported cases, a single adverse sign does not usually indicate MH.[131] The mechanism by which anesthetics and depolarizing muscle relaxants trigger MH is unsolved, but the facts that they are etiologic agents and that early diagnosis is critical for successful treatment cannot be ignored. A recent retrospective review of the *Adverse Metabolic/Musculoskeletal Reactions to Anesthesia* (AMRA) reports demonstrated that the onset of MH has been observed later during desflurane and isoflurane anesthesia than during exposure to sevoflurane. There has been an increased delay of MH signs to appear in the second and third hours of anesthesia than before. In MH cases with one unique first sign, the first MH signs most often encountered were hypercarbia (30.7%), masseter spasm (24.8%), and sinus tachycardia (21.1%).[131a]

NONANESTHETIC MALIGNANT HYPERTHERMIA

Fulminant MH can be easily triggered in swine subjected to environmental stress such as exercise, heat, anoxia, apprehension, and excitement (see "History" earlier in

this chapter).[9,127] Reports of MH-like episodes in humans after stressful situations or heat exposure have been reported.[132-137] Measurement of plasma catecholamine levels during exercise showed no differences between MHS and normal individuals.[138,139] Therefore it is unlikely that these responses were provoked by sympathetic overdrive or catecholamine surge.[140]

Wappler and associates reported *RYR1* mutations in 3 of the 12 unrelated patients with exercise-induced rhabdomyolysis; 10 of the same 12 patients had an abnormal contracture response with IVCT.[141] One had an equivocal response. Increased ambient temperature has been shown to trigger fulminant MH in all reported strains of MH mice.[68,69] An epidemiologic study has shown that exercise-induced symptoms, including rhabdomyolysis, occur more frequently in patients who are MHS.[141] Furthermore, an Arg401Cys *RYR1* mutation was present in three cases of exercise-induced rhabdomyolysis.[98] Other reports are largely anecdotal and relate heat stroke, sudden and unexpected death, unusual stress and fatigue, or myalgias to possible "awake" MH episodes. Stresses associated with these episodes include exercise and environmental exposure to volatile nonanesthetic vapors.[134,142,143] MHAUS has provided recommendations of adverse effects of heat and exercise in relation to MH susceptibility.[144]

MALIGNANT HYPERTHERMIA–ASSOCIATED SYNDROMES

MASSETER SPASM (HALOTHANE-SUCCINYLCHOLINE RIGIDITY)

A masseter spasm or trismus is defined as jaw muscle rigidity in association with limb muscle flaccidity after the administration of succinylcholine. The masseter and lateral pterygoid muscles contain slow tonic fibers that can respond to depolarizing neuromuscular blockers with a contracture.[145,146] This contracture is clinically manifested on exposure to succinylcholine as an increase in jaw muscle tone and defined by van der Spek and associates.[147] A spectrum of responses exists: a tight jaw that becomes a rigid jaw and then a very rigid jaw (Fig. 43-3). This jaw rigidity may occur even after pretreatment with a defasciculating dose of a nondepolarizing relaxant. If rigidity of other muscles develops in addition to trismus, then the association with MH is absolute; anesthesia should be halted as soon as possible and treatment of MH begun.

However, in more than 80% of patients with trismus but no rigidity of other muscles. It is a variant found in normal patients. If trismus occurs, then proper monitoring should include end-expired CO_2; examination for pigmenturia; and arterial or venous blood sampling for CK, acid-base status, and electrolyte levels, particularly potassium. Although scientifically unproven, it is thought that the initial tightness of the jaw and its duration may predict the gravity of the response. MHAUS recommends following CK and urine myoglobin for 36 hours with 6-hour intervals.[148] Patients with masseter spasm should be closely observed for at least 12 hours.

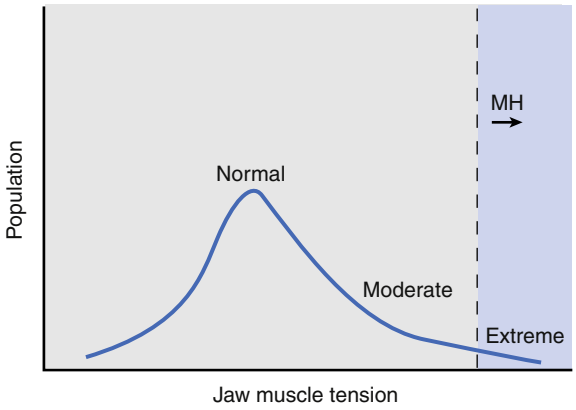


Figure 43-3. Succinylcholine usually increases jaw muscle tone slightly. In some patients, this increase is moderate; in a very few, the effect is extreme (i.e., "jaws of steel"). As many as 50% of this latter group may be susceptible to malignant hyperthermia (MH). Somewhere in the area of the declining curve is the boundary for the MH population.

CORE MYOPATHIES

CCD is a rare hereditary disease and was first reported in 1956 by Magee and Shy.[149] A recent population study in northern England revealed a prevalence of 1:250,000.[150] In1971, Engel and colleagues reported a related congenital myopathy, multicore disease (MCD).[151,152] Subsequently, various designations of the terms were reported for the variations of the disease, including minicore myopathy and multiminicore myopathy.[151] Multiminicore disease (MmD) is now the most official term for these variations sponsored by the European Neuromuscular Centre.[151]

As mentioned, most CCD cases are due to a dominant missense mutation in *RYR1*. Clinically, patients diagnosed with CCD exhibit muscle weakness of a variable degree and histologically with central cores in type I skeletal muscle fibers.[153] MmD is considered a recessively inherited myopathy with severe axial weakness, and respiratory, bulbar, and extraocular muscles are commonly affected.[153] MmD has a heterogenous genetic association with recessive mutation in *SEPN1* gene on chromosome 1p36 and in *RYR1*,[153] and in MmD, both type 1 and type 2 fibers may be affected.[151]

Serum CK levels in patients with CCD are often normal but may be elevated 6 to 14 times in rare cases. Muscle ultrasound often demonstrates increased echogenicity in the quadriceps muscle with relative sparing of the rectus muscle. A characteristic pattern of selective involvement of muscle on a magnetic resonance image has been reported in the patients with typical CCD,[151] which seems to be distinctive to conditions linked to *RYR1* locus.

The relationship between CCD and the MHS is complex. A positive IVCT has been confirmed in many patients with CCD, whereas MHS has been excluded in others. In consideration of the strong link and potential risk, considering all patients with CCD to be at risk for MH is advisable, unless the patient has a negative IVCT. Although MHS has not been reported in *SEPN1*-related myopathies, applying a nontriggering approach to patients with MmD is prudent, considering the potential

risk in *RYR1*-related MmD. Clinical MH reactions have been reported in patients with MmD.[154,155]

KING-DENBOROUGH SYNDROME

King-Denborough syndrome (KDS) features the dysmorphic facial and skeletal abnormalities similar to Noonan syndrome and congenital myopathy with proximal muscle weakness.[156] Sporadic cases have been reported in the literature.[157-166] The inheritance pattern of the disease is not clear. Elevated baseline CK appears in approximately one half of the patients with KDS. A heterozygous A97G point mutation in exon 2 of the *RYR1*, causing a substitution of lysine for glutamine at amino acid residue 33 (Lys33Glu), has been reported.[167] This substitution creates a major polarity change, from positive to negative, in a known hot spot for MH causative mutation. Dowling and associates recently identified *RYR1* mutation in three out of the four patients with KDS, which supports the hypothesis of its genetic heterogeneity.[168] Considering the strong evidence for MHS in patients with KDS, MH triggering agents should be avoided for anesthesia on patients with KDS.

DIAGNOSIS IN THE SURGICAL AND POSTANESTHESIA CARE UNITS

As stated earlier, fulminant MH is rare, and the early signs of clinical MH may be subtle (Box 43-1). These signs must be distinguished from other disorders with similar signs (Box 43-2).

When the diagnosis is obvious (i.e., fulminant MH or succinylcholine-induced rigidity with rapid metabolic changes), significant hypermetabolism and heat production occur, and little time may be left for specific therapy to prevent death or irreversible morbidity. If the syndrome begins with slowly increasing end-tidal CO_2 ($ETCO_2$), specific therapy can await a complete clinical workup before treatment. In general, MH is not expected to occur when no triggers are administered (see "Anesthesia for Susceptible Patients" later in this chapter). However, several confirmed fulminant nonanesthetic cases of MH that resulted in death have been reported (see "Nonanesthetic Malignant Hyperthermia" earlier in this chapter).[141]

When volatile anesthetics or succinylcholine are used, MH should be suspected whenever an unexpected increase in $ETCO_2$, undue tachycardia, tachypnea, arrhythmias, mottling of the skin, cyanosis, muscle rigidity, sweating, increased body temperature, or unstable blood pressure develop. If any of these occur, signs of increased metabolism, acidosis, or hyperkalemia must be pursued. The most common cause for sudden $ETCO_2$ during general anesthesia and sedation is hypoventilation. Increased minute ventilation should correct the problem.

The analysis of arterial or venous blood gases that demonstrate a mixed respiratory and metabolic acidosis can support the diagnosis of MH[169]; however, the respiratory component of acidosis may be predominate in the early stage of onset of fulminant MH. O_2 and CO_2 change more significantly in the central venous compartment than in arterial blood; therefore end-expired or venous CO_2 levels more accurately reflect whole-body stores. Venous CO_2, unless the blood drains an area of increased metabolic activity, should have P_{CO_2} levels of only approximately 5 mm Hg greater than that of expected or measured Pa_{CO_2}. In small children, particularly those without oral food or fluid for a prolonged period, the base deficit may be 5 mEq/L because of their smaller energy stores.

In North America, any patient suspected of having an MH episode should be reported to the NAMHR of MHAUS

BOX 43-1 *Clinical Signs of Malignant Hyperthermia*

Early Signs

Elevated end-tidal carbon dioxide (CO_2)
Tachypnea and/or tachycardia
Masseter spasm, if succinylcholine has been used
Generalized muscle rigidity
Mixed metabolic and respiratory acidosis
Profuse sweating
Mottling of skin
Cardiac arrhythmias
Unstable blood pressure

Late Signs

Hyperkalemia
Rapid increase of core body temperature
Elevated creatine phosphokinase levels
Gross myoglobinemia and myoglobinuria
Cardiac arrest
Disseminated intravascular coagulation

BOX 43-2 *Conditions and Disorders That May Mimic Malignant Hyperthermia*

Anaphylactic reaction
Alcohol therapy for limb arteriovenous malformation
Contrast dye injection
Cystinosis
Diabetic coma
Drug toxicity or abuse
Environmental heat gain more than loss
Equipment malfunction with increased carbon dioxide (CO_2)
Exercise hyperthermia
Freeman-Sheldon syndrome
Heat stroke
Hyperthyroidism
Hypokalemic periodic paralysis
Hypoventilation or low fresh gas flow
Increased end-tidal carbon dioxide ($ETCO_2$) from laparoscopic surgery
Insufficient anesthesia or analgesia (or both)
Intracranial free blood
Malignant neuroleptic syndrome
Muscular (Duchenne and Becker) dystrophies
Myotonias
Osteogenesis imperfecta
Pheochromocytoma
Prader-Willi syndrome
Rhabdomyolysis
Sepsis
Thyroid crisis
Ventilation problems
Wolf-Hirschhorn syndrome

via the AMRA report available from the web site at http://www.mhaus.org/registry/downloads. In addition, MHAUS has an emergency MH hotline available in the United States at 1-800-644-9737 or outside the United States at 1-209-417-3722.

TREATMENT

Acute management for MH can be summarized as follows:

1. Discontinue all anesthetic agents and hyperventilate with 100% O_2 with a fresh flow to at least 10 L/min. With increased aerobic metabolism, normal ventilation must increase. However, CO_2 production is also increased because of neutralization of fixed acid by bicarbonate; hyperventilation removes this additional CO_2.
2. Reconstitute dantrolene in sterile water (not saline), and administer rapidly (2.5 mg/kg intravenously [IV] to a total dose of 10 mg/kg IV) every 5 to 10 minutes until the initial symptoms subside.
3. Administer bicarbonate (1 to 4 mEq/kg IV) to correct the metabolic acidosis with frequent monitoring of blood gases and pH.
4. Control fever by administering iced fluids, cooling the body surface, cooling body cavities with sterile iced fluids, and, if necessary, using a heat exchanger with a pump oxygenator. Cooling should be halted when the temperature approaches 38° C to prevent inadvertent hypothermia.
5. Monitor urinary output, and establish diuresis if urine output is inadequate. Administer bicarbonate to alkalinize urine to protect the kidney from myoglobinuria-induced renal failure.
6. Blood gases, electrolytes, CK, temperature, arrhythmia, muscle tone, and urinary output guide further therapy. Hyperkalemia should be treated with bicarbonate, glucose, and insulin. Effective doses of dantrolene to reverse MH are the most effective way to lower serum potassium levels. In severe cases, calcium chloride or calcium gluconate may be used.
7. Analyze coagulation studies (e.g., international normalized ratio [INR], platelet count, prothrombin time, fibrinogen, fibrin split degradation products).

Adequate personnel support is critical to the successful management of such a crisis. Discontinuation of the trigger may be adequate therapy for acute MH if the onset is slow or if exposure was brief. Changing the breathing circuit and CO_2 absorbent can be time consuming. However, application of activated charcoal filters may rapidly reduce the volatile anesthetic concentration to an acceptable level in less than 2 minutes and should be used in the acute situation if they are readily available.[170]

Dantrolene is packaged in 20-mg bottles with sodium hydroxide for a pH of 9.5 (otherwise, it will not dissolve) and 3 g of mannitol, which converts the hypotonic solution to isotonic. The initial dose should be 2.5 mg/kg dantrolene reconstituted in sterile water and administered IV. Dantrolene must be reconstituted in sterile water rather than salt solutions or it will precipitate. Prewarming sterile water may expedite the solubilization of dantrolene, compared with water in ambient temperature.[171] In 2009, a newer, rapid soluble dantrolene became available for IV use. It reconstitutes in approximately 20 seconds, which is significantly faster than the older version.[172]

In awake, healthy volunteers, the maximum twitch depression occurs at a dantrolene dose of 2.4 mg/kg.[173] Therefore it is not surprising that at therapeutic concentrations, dantrolene may prolong the need for intubation and assisted ventilation. Brandom and associates reviewed the complications associated with the administration of dantrolene from 1987 to 2006, using the dataset in the NAMHR via the AMRA reports, and found that the most frequent complications of dantrolene were muscle weakness (21.7%), phlebitis (9%), gastrointestinal upset (4.1%), respiratory failure (3.8%), hyperkalemia (3.3%), and excessive secretions (8.2%).[174] Considering its high pH, administering dantrolene through a large-bore IV line is advisable, but its administration should not be delayed if a large-bore IV line is not already in place. Dantrolene interferes with EC coupling of murine intestinal smooth muscle cells,[175] rat gastric fundus, and colon,[176] which, in part, explains it gastrointestinal side effect. Caution should be used when ondansetron is to be used in this setting. As a serotonin antagonist, ondansetron may increase serotonin at the 5-HT_{2A} receptor in the presynaptic space. In an individual with MHS, agonism of 5-HT_{2A} receptor may precipitate MH.[177]

The clinical course will determine further therapy and studies. Dantrolene should probably be repeated at least every 10 to 15 hours, since its half-life is at least 10 hours in children and adults.[173,178] The total dose of dantrolene that can be used is up to 30 mg/kg in some patients. Recrudescence of MH can approach 50%, usually within 6½ hours.[179,180] When indicated, calcium and cardiac glycosides may be safely used and can be lifesaving during persistent hyperkalemia. Slow voltage-gated calcium channel blockers do not increase porcine survival.[181,182] Rather, a recent study by Migita and co-workers demonstrated that dihydropyridine (i.e., nifedipine), phenylalkylamine (i.e., verapamil), and benzothiazepine (i.e., diltiazem) all led to increased $[Ca^{2+}]_i$ in human skeletal muscle cells. Interestingly, the potency of such calcium release is correlated with the number of binding sites on the DHPR; that is, nifedipine > verapamil > diltiazem.[183] Clinical doses of dantrolene were only able to attenuate 20% of the nifedipine-induced $[Ca^{2+}]_i$ surge.[183] Current recommendations of MHAUS discourage the use of calcium channel blockers in the presence of dantrolene, because they can worsen the hyperkalemia, resulting in cardiac arrest.[148] The administration of magnesium sulfate could not prevent the development of MH and did not influence the clinical course.[184] Permanent neurologic sequelae, such as coma or paralysis, may occur in advanced cases, probably because of inadequate cerebral oxygenation and perfusion for the increased metabolism and because of the elevated body temperature, acidosis, hypo-osmolality with fluid shifts, and potassium release.

For patients with MH who are diagnosed in ambulatory surgical centers, guidelines have been recently proposed for transferring care to receiving hospital facilities.[185]

Although immediate treatment and onsite stabilization of the patient are preferable, several factors need to be considered before implementing a transfer plan after completing an initial dantrolene treatment, which include the capabilities of the available professionals at the initial treatment and receiving facilities, the clinical best interests of the patient, and the capabilities of the transfer team.[186]

If uncertain at any time, the physician should contact the MH Hotline (United States: 1-800-644-9737; outside the United States: 1-315-464-7079) to verify treatment and report the case to the NAMHR (1-888-274-7899). The MHAUS web site (https://medical.mhaus.org) also provides online support and resources to direct management.

ANESTHESIA FOR SUSCEPTIBLE PATIENTS

Safe anesthetics consist of nitrous oxide, barbiturates, etomidate, propofol, opiates, tranquilizers, and nondepolarizing neuromuscular blocking drugs. Volatile anesthetics and succinylcholine must be avoided at all times, even in the presence of dantrolene. Anecdotal reports suggest that some patients have experienced a hypermetabolic state, despite these precautions, but they have always responded favorably to the administration of IV dantrolene. Preoperative dantrolene is never needed, because the use of nontriggering agents is almost always associated with uneventful anesthesia. Regional anesthesia is safe and may be preferred. Amide anesthetics, such as lidocaine, were once considered dangerous in susceptible patients because they were thought to induce or worsen muscle contractures in vitro as a result of their effect of increasing calcium efflux from the SR. Porcine and human studies, however, have consistently demonstrated the lack of danger of amide anesthetics.

Before administering anesthesia for MHS patients, anesthetic machines may be "cleansed" of potent volatile agents by disconnecting or removing the vaporizers from the anesthesia workstation, renewing the CO_2 absorbent, and using a new, disposable breathing circuit and, if possible, a fresh gas hose. If a dedicated machine is not available for the patient who is MHS, flushing the anesthesia workstation to less than five parts per million (ppm) of the volatile anesthetic agents' concentration is generally accepted.[187] Flushing the workstation may take 10 to 104 minutes with different machines.[170,188-197] This preparation process also should be directed on the basis of the halogenated volatile agents that have been used. Jones and colleagues demonstrated that desflurane required longer purge time than sevoflurane on both the Datex-Ohmeda Aestiva and Aisys machines.[196] Application of activated charcoal filters have been shown to accelerate successfully the process of cleansing.[170,198-200] Such filters should be placed on both the inspiratory and the expiratory limbs of the anesthesia machine and replaced with a new set every 60 minutes.[170] MHAUS recommends flushing and preparing the anesthesia workstation according to the manufacturer's recommendations or published studies.[201] During the case, lowering the fresh gas rate after the washout period may allow the concentration of volatile anesthetic agents to reaccumulate.[192] Fresh gas flow should be kept to at least 10 L/min to avoid this rebound.

It is important to be aware that the National Institute for Occupational Safety and Health (NIOSH) issued "Criteria for a Recommended Standard. Occupational Exposure to Waste Anesthetic Gases (WAGs) and Vapors."[202] No worker is exposed to halogenated anesthetic agents at concentrations greater than 2 ppm when used alone or more than 0.5 ppm when used in combination with nitrous oxide over a sampling period not to exceed 1 hour. Anesthetic gas machines, nonrebreathing systems, and T-tube devices shall have an effective scavenging device that collects all WAGs. In addition, Occupational Safety and Health Administration (OSHA) has guidelines for workplace exposures.[203]

The anesthesiologist should confidently discuss anesthetic care with patients who are MHS and assure them that all will be done to avoid difficulties with MH and that the appropriate drugs, knowledge, and skills are immediately at hand if any problems should occur. Many of these patients have uneventfully undergone procedures, such as dental analgesia and obstetric anesthesia, before the diagnosis of susceptibility was made. The patient can enter the therapeutic environment in a reassured, relaxed, and comfortable state. Outpatient procedures are feasible in most environments; the time of discharge depends on the usual outpatient criteria.

Any anesthesia provider using MH triggers on an inpatient or outpatient basis should have dantrolene immediately available. The current recommendation by MHAUS to stock 36 vials of dantrolene is based on the quantity of dantrolene needed to treat an MH crisis on a patient weighing 70 kg.[172]

EVALUATION OF SUSCEPTIBILITY

Evaluation of susceptibility includes a history and physical examination to detect any subclinical abnormality. A genealogy with specific information about anesthetic exposure and agents can estimate the likelihood of exposure to triggering agents. Blood CK values, when determined in a resting, fasting state without recent trauma, reflect muscle membrane stability. When the CK level is elevated in a close relative of a person with known MHS, the relative may be considered to have MHS without contracture testing. If the CK level is normal on several occasions, no predictive value exists and contracture studies are necessary. The patient must travel to the test center for a surgical biopsy to ensure viability and accurate results. Muscle biopsy contracture studies, performed at approximately 30 centers around the world, involve exposure of the muscle biopsy sample to halothane, caffeine, and, in the North American test, to halothane plus caffeine.[120] Sensitivity to 4-chloro-*m*-cresol or ryanodine have also been used by some centers.[46] It is also important to note that contracture responses are sometimes positive in patients with myopathies that bear no direct relationship to MH and therefore may not indicate susceptibility. Dantrolene must be avoided before biopsy because it masks the response to contracture-producing drugs. After a patient is diagnosed as being MHS, DNA

testing for mutations should follow. When a mutation is detected, other relatives with that mutation should be considered to be MHS without the need for an invasive contracture test, and they need not travel to a testing center (see "Genetics" earlier in this chapter).

Advice should be given to susceptible patients and, if not biopsy tested, all patients with a clinical picture that suggests a high probability for MHS. Precautions are necessary regarding general anesthesia, and triggers include all potent volatile anesthetics agents and succinylcholine. Awake episodes are uncommon, and, if not experienced before diagnosis, then they are an unlikely problem. The true predictive value (i.e., percentage of positive results that are true positives) or efficiency (i.e., percentage of all results that are true, whether positive or negative) of contracture testing in determining susceptibility in the general population cannot be estimated because of the selection process that has been used to date for testing (i.e., limited to those with anesthesia reactions who do not have any other muscular pathologic disease). False-positive results from cautious interpretation or decreased specificity are masked because the patient will never be exposed to triggering agents. A promising innovative in vivo human application involves physiologic-based microdialysis infusion of caffeine or halothane into muscle of patients who are MHS to trigger exaggerated localized changes in acid-base balance.[204-208] White blood cells express *RYR1*-MH mutations and provide a substrate for a less invasive analysis for susceptibility but have the limitation that not all causative mutations are expressed in the white blood cells.[209-213] Nuclear magnetic resonance spectroscopy is promising,[214,215] but, to date, it has been difficult to standardize a stress, such as forearm ischemia, that can differentiate those who are susceptible from those who are not.

For anesthesia assessment of the pregnant patient who is non-MHS and carrying a potential MHS fetus, the patient should be treated as MHS until the fetus is delivered.[216-218] For emergencies in such patients, the use of succinylcholine, although little of the drug crosses the placenta, is controversial.[219]

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune disorder characterized by T cell–mediated autoantibodies against myelin and a subsequent inflammatory response in the central nervous system (CNS) (brain and spinal cord). Thus MS is a disorder of the myelinated part of the axon that leads to secondary nerve conduction failure. The disease mainly affects women, primarily between 20 and 40 or 45 and 60 years of age. Although the cause is unknown, speculation suggests that environmental factors, combined with a genetic predisposition, cause MS. Naturally, researchers have focused on identifying key events and the genetic origin of the disorder to provide diagnostic and possibly therapeutic tools for the management of patients with MS.

Patients with MS frequently report paresthesias, muscle weakness, and sensory disturbances. Typically, a localized or (late in the course of disease) generalized muscle weakness develops with the legs affected more than the arms. In severe cases, respiration may be involved with the development of hypoxemia. Diplopia and other cranial nerve–dependent impairments are early and frequent signs, along with sensory abnormalities and sometimes disturbed bowel and bladder function. As a rule, symptoms are closely related to the site affected within the CNS, and the amount of symptoms is related to the extent of sclerosing CNS plaque. Notably, MS can be associated with impaired autonomic function, which may lead to adverse reactions to sympathomimetic drugs.[220]

Diagnosis of MS is currently based on a combination of clinical and laboratory tests, including cerebrospinal fluid (CSF) antibody analysis and radiology (detection of CNS plaque by magnetic resonance imaging). Medication consists of various combinations of immunosuppression modalities.

Anesthetic Considerations

It has been speculated that general anesthesia and surgery may increase the risk for aggravation of MS.[221] At present, no general consensus on this matter exists, and patients should therefore be informed of the potential for aggravated symptoms in the postoperative period. In general, preoperative chronic immunosuppressive medication should be continued during the perioperative period. Patients with MS are sensitive to physical (e.g., pain, fever, infection) and emotional stress, which will more likely cause symptoms to be intensified in the perioperative period. Great care must be exercised to minimize changes in body temperature, fluid homeostasis, and central hemodynamics (preload, afterload) and to maintain respiration. Although IV agents and volatile anesthetics have been safely used, avoiding the administration of depolarizing neuromuscular blocking drugs to patients with MS is wise. MS-induced denervation or disuse myopathy may lead to a risk for succinylcholine-induced hyperkalemia, which can result in fatal cardiac arrhythmias (see also Chapter 34). Using nondepolarizing neuromuscular blockers is likely safe. Epidural anesthesia has been considered safe in patients with MS, although there is some evidence that patients with MS might benefit from lower doses of local anesthetics. Spinal anesthesia is controversial in MS and is therefore needed to proceed with caution because of potentially increased sensitivity of the spinal cord to local anesthetics due to demyelination. Notably, postpartum worsening of MS symptoms is noted in 20% of women (see also Chapter 77). The need for more extended postoperative care is dependent on the preoperative symptoms, type of surgery, and status of the patient at the end of the surgical procedure. In this context, patients with MS with severe weakness and respiratory distress, including pharyngeal dysfunction, may need extended postoperative care, such as noninvasive respiratory support and intense physiotherapy, to avoid further impairment of their pulmonary function.

MOTOR NEURON DISORDERS

Motor neuron disorders involve either the upper or the lower motor neurons of the cerebral cortex, brainstem, and spinal cord. Some forms are mixed, whereas others have predominantly upper or lower motor neuron involvement. Amyotrophic lateral sclerosis (ALS) is the

most common disease within this group and involves both upper and lower motor neurons. Other examples of motor neuron disease are Kennedy disease (spinobulbar muscular atrophy), Friedreich ataxia (mixed upper and lower motor neurons), and spinal muscular atrophy (lower motor neurons).

Progressive and variable loss of motor neurons within the cerebral cortex, medullary nuclei of cranial nerves, and nuclei of the ventral horn in the spinal cord characterize ALS (Lou Gehrig disease). Degenerative loss of these neurons leads to progressive muscle weakness, muscle atrophy, and loss of neuronal mass in these locations. Sensory functions, including intellectual capacity and cognition, as well as bowel and bladder function, are not usually affected in ALS.

ALS has an incidence of approximately 2 in 100,000 per year, and onset of the disease usually takes place around 40 to 50 years of age, with men more often affected than women. Most cases are sporadic, but rare familial forms (autosomal dominant and recessive forms) exist. The underlying mechanism or mechanisms for this selective and progressive motor neuronal death are thus far unclear, but it has recently been suggested that superoxide dismutase mutations may play a key role in the increased formation of free radicals observed in subsets of patients. The diagnosis is made by electrophysiology (electromyography [EMG] and electroneurography) and by neurologic examination, which demonstrates early spastic weakness of the upper and lower extremities, typical subcutaneous muscle fasciculations, and bulbar involvement affecting pharyngeal function, speech, and the facial muscles. No curative treatment is currently available, and patients are therefore treated symptomatically.

Anesthetic Considerations

Bulbar involvement in combination with respiratory muscle weakness leads to the risk for aspiration and pulmonary complications. Notably, these patients may have increased sensitivity to the respiratory depressant effects of sedatives and hypnotics. Sympathetic hyperreactivity and autonomic failure have been reported.[222] Succinylcholine should be avoided because of the risk for hyperkalemia as a result of denervation and immobilization. Nondepolarizing neuromuscular blocking agents may cause prolonged and pronounced neuromuscular blockade and hence should be used with great caution.[223] General anesthesia combined with epidural anesthesia has been used without complications. Careful postoperative monitoring of respiration and oxygenation are important in these patients because there might be inherent instability of respiratory control.

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome (GBS) is an acute inflammatory polyneuritis caused by an immunologic reaction. Although the cause is unknown, a timely association with a viral (influenza-like) or bacterial infection or even lymphomatous disease can be demonstrated in many patients.[224] Symmetric peripheral flaccid muscle weakness and sensory loss develop. The lower extremities are affected first, after which the disease progresses to the upper extremities and cranial nerve–innervated muscles in some patients. Importantly, patients may also have autonomic involvement that could lead to sudden fatal cardiac and circulatory collapse. The diagnosis is made after careful neurologic examination, clinical electrophysiologic testing, and CSF analysis. CSF analysis may show a typical increase in CSF protein in combination with a normal cell count, which is a classic sign of the disease. Treatment focuses on respiratory support, nutritional support, and early initiation of plasmapheresis.

Anesthetic Considerations

Succinylcholine should not be used because of the risk of hyperkalemia. Notably, case reports have described patients having clinically recovered from GBS who, after receiving succinylcholine during induction of anesthesia, rapidly developed life-threatening hyperkalemia. Nondepolarizing muscle relaxants are not contraindicated but should be avoided as a result of the increased sensitivity and risk for prolonged muscle weakness in the postoperative period. The risk for autonomic dysfunction, respiratory failure, and aspiration may require assisted or mechanical ventilation, even in the postoperative period. Great care should be taken to maintain circulatory stability, including adequate cardiac preload and afterload. Careful hemodynamic monitoring is therefore essential in these patients. General anesthesia can be used; however, the combination of general anesthesia and epidural anesthesia is more controversial.[225]

HEREDITARY MOTOR-SENSORY NEUROPATHIES, INCLUDING CHARCOT-MARIE-TOOTH DISEASE

Hereditary motor-sensory neuropathies include a spectrum of peripheral neurologic disorders, among which Charcot-Marie-Tooth (CMT) disease is often listed. These neuropathies are caused by a specific mutation in one of several myelin genes that results in defects in myelin structure, maintenance, and formation. Hereditary motor-sensory neuropathies have been classified into seven types and multiple subtypes according to the age at onset, mode of inheritance, predominantly involved muscle groups, and genotypes.[227,228] CMT types 1 and 2 are the most common hereditary peripheral neuropathies, with an estimated prevalence of 40 per 100,000.[228] Patients with CMT disease typically experience slow and progressive distal muscle weakness and wasting. Damage to sensory axons may also lead to sensory loss, resulting in frequent tripping and falls. Neuropathic pain may develop in some patients. Patients with CMT usually have normal life expectancy. CMT type 3, also known as Dejerine-Sottas neuropathy, is a very severe condition with an early onset of hypotonia during infancy. Typically, nerve conduction velocity is significantly reduced to less than 10 msec.[228] The genetic inheritance pattern for CMT disease is heterogeneous.

Anesthetic Considerations

The anesthesia experience in patients with CMT disease is limited because of the small number of cases. Major considerations include the use of hypnotic agents,

muscle relaxants, volatile agents, and neuraxial techniques. Patients with CMT type 1 have been reported to have significantly increased sensitivity to thiopental at induction that correlates with the severity of both motor and sensory defects. However, total intravenous anesthesia (TIVA) has been successfully performed in a number of patients without any reported problems.[229-231]

Because of the reduced number of acetylcholine receptors, sensitivity to nondepolarizing muscle relaxants is elevated and the response to succinylcholine is also reduced.[232] Although succinylcholine has been used without adverse effects,[233,234] the risk of an exaggerated hyperkalemic response may be sufficient to preclude it from being used in patients with suspected muscular denervation.[234] Prolonged neuromuscular block with vecuronium has been reported.[235] As a result of the large variety of disabilities in this patient group, careful baseline assessment of neuromuscular status should be conducted before the use of nondepolarizing neuromuscular relaxants. Normal response to atracurium and mivacurium has been demonstrated.[236,237] Both TIVA and volatile anesthetics have been safely used in a series of patients with CMT.[233] Neuraxial techniques for obstetric procedures have been reported to be generally successful in patients with CMT.[238-241] However, the use of regional anesthesia can be controversial, considering that the possible complications may exacerbate the neurologic symptoms.[242] Similar medicolegal concerns may apply to the surgical and anesthesia positioning of patients with CMT because of the sensory deficits and limb deformities.

DUCHENNE MUSCULAR DYSTROPHY AND BECKER MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) is the most common and severe type of muscular dystrophy with an incidence of 1 per 3500 live male births[243] and a total male prevalence of approximately 50 to 60 × 10^{-6}.[244] Becker muscular dystrophy (BMD) is relatively rare and has an incidence of approximately 1 in 18,000 live male births and a prevalence of 23.8 × 10^{-6}.[244] Both DMD and BMD are X-linked recessive diseases. The defect is located on the short arm of the X chromosome at the Xp21 region, which contains the gene for the large protein Dp427, also known as *dystrophin*. The dystrophin gene is 2500 kilobases long with more than 70 exons.[244] Dystrophin is distributed not only in skeletal, cardiac, and smooth muscle but also in the brain.[245] Because of the large size of the dystrophin gene, spontaneous new mutations are common and account for one third of new cases.[246]

The most common form of mutation is a deletion within the gene (65% to 70% of patients with DMD and more than 80% of those with BMD). Duplication and point mutations are responsible for the rest. In addition, hot spots also appear in the first 20 exons and in the central region of the gene (exons 45 to 55) where deletion and duplication are likely to occur.[244] Female patients with DMD have been reported with the 45,X and 46,XX karyotypes. The disease mechanism for the female 46,XX karyotype is thought to be preferential loss of the paternal X chromosome by postzygotic nondisjunction and manifestation of the DMD gene from the maternal X chromosome in muscle cells.[247] BMD is usually milder in severity than DMD because disruption of the translation process occurs in the relatively distal part of the gene, which leads to a reduced amount of truncated dystrophin protein.[244,248]

Dystrophin, along with dystrophin-associated glycoproteins (DAGs), is involved in sarcolemmal stability. Dystrophin is responsible for the maintenance of muscle membrane integrity, despite the fact that it accounts for only approximately 0.002% of the protein in striated muscle.[249] Dystrophin aggregates and links to actin (at its N terminus) and the DAG complex (at its C terminus) to form a stable structure that interacts with laminin in

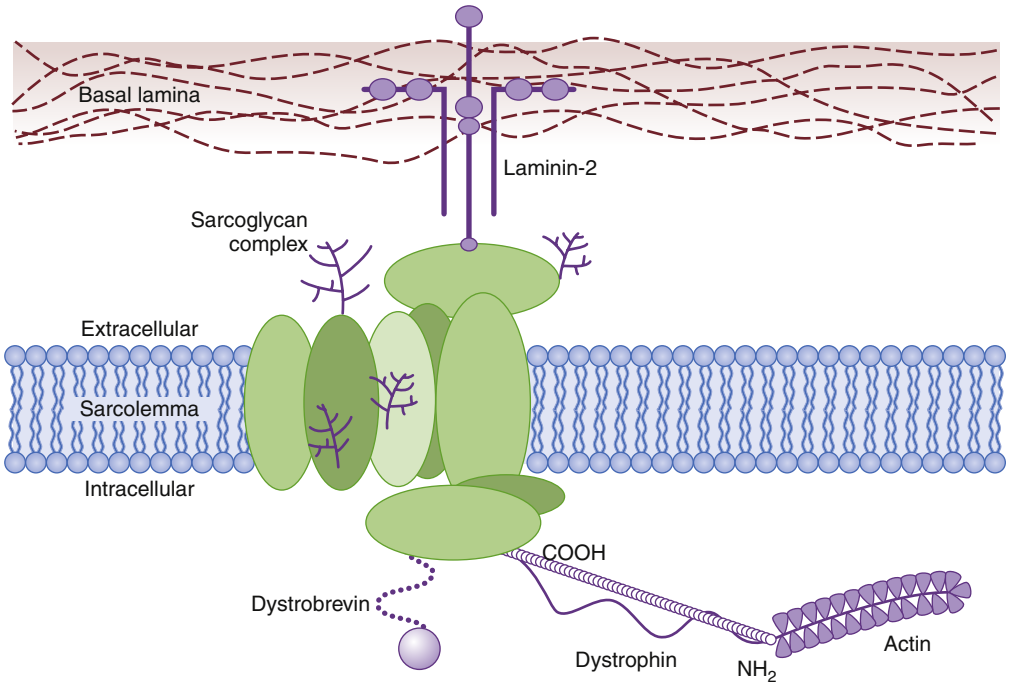


Figure 43-4. Diagram of the cellsurface and cytoskeleton protein complex.

the extracellular matrix (Fig. 43-4). Lack or dysfunction of dystrophin leads to cellular and membrane instability, with progressive leakage of intracellular components and elevation of CK levels. Eventually, damaged muscle cell units are invaded by macrophages and destroyed. A current study suggests that cytotoxic T cells are probably the culprit. Consequently, clinical pseudohypertrophy of the muscle occurs when the dead muscle shells are replaced by fibrofatty infiltrates. Loss of muscle units accounts for the weakness and contracture.[245]

Progressive weakness and wasting of predominantly the proximal musculature characterize both DMD and BMD. Pseudohypertrophy of the calves and other muscle groups is common. As the more severe of the two diseases, DMD tends to be symptomatic early in life. Of the children with DMD, 74% were found to exhibit the disease by 4 years of age.[243] Patients with DMD do not usually begin to walk until they are approximately 18 months of age or later.

The initial clinical findings include a waddling gait, frequent falling, and difficulty climbing stairs because of proximal muscle weakness in the pelvic girdle. The classic Gowers sign describes rising from a sitting to a standing position with the help of both arms. Patients may also show weakness in the shoulder girdle and trunk erectors that leads to thoracolumbar scoliosis. Earlier clinical onset of DMD has been associated with a more rapid progression of the disorder. In most cases, children with DMD are unable to walk by the age of 9 to 11 years. Proximal deep tendon reflexes in the upper extremities and patella may also disappear, despite the lack of denervation.[248] Nevertheless, the tendo Achillis reflex remains intact even in later stages of the disease. Approximately 60% of patients will have pseudohypertrophy of the calves, and 30% will have macroglossia. Some may also suffer from pain in the calves with activity.

The intellectual impairment that can be associated with the disease was thought to be related to the limitation of educational opportunities. However, with equalization of educational opportunities, psychometric studies have revealed a significantly lower average intelligence quotient in patients with DMD than in healthy groups.[250] This lower quotient implies a possible effect of dysfunctional dystrophin in the brain on learning.

Death in patients with DMD occurs in their 30s and is commonly due to cardiopulmonary compromise.[243] BMD is a mild form of DMD. The mutation that causes BMD produces dystrophin that retains partial function. The onset of symptoms occurs in the second or third decade of life. As a result, the lifespan of patients with BMD can reach the early 40s. Pneumonia is the most common cause of death (Fig. 43-5).[248]

The heart is also affected to varying degrees, depending on the stage of the disease and the type of mutation. Cardiac degeneration is due to the replacement of myocardium by connective tissue or fat, which leads to dilated cardiomyopathy.[251] Cardiac involvement starts early in the course of the disease, although clinical signs are not usually obvious in the early stage. No correlation has been established between the severity of cardiac disease and the severity of skeletal disease. Studies at necropsy have shown that the cardiomyopathy in DMD involves the posterobasal and contiguous lateral left ventricular walls as initial and primary sites of myocardial dystrophy in the absence of small vessel coronary artery disease in these areas.[252] Typical initial manifestations on the electrocardiogram (ECG) in DMD and BMD are sinus tachycardia, tall R waves in the right precordial leads, prominent left precordial Q waves, increased QT dispersion, and inverted T waves from scarring of the posterobasal portion of the left ventricle. Initially, echocardiography is normal or shows regional wall motion abnormalities in areas of fibrosis. With the spreading of fibrosis, left ventricular dysfunction can be seen, and ventricular arrhythmias frequently occur as well. In the final stages of the disease, systolic dysfunction may lead to heart failure and sudden death. Subclinical or clinical cardiac involvement is present in approximately 90% of patients with DMD or BMD but is the cause of death in only 20% of those with DMD and 50% of patients with BMD. Angiotensin-converting enzyme inhibitors are recommended in early stages of the disease, and β-blockers may be an additional option, if indicated.[251]

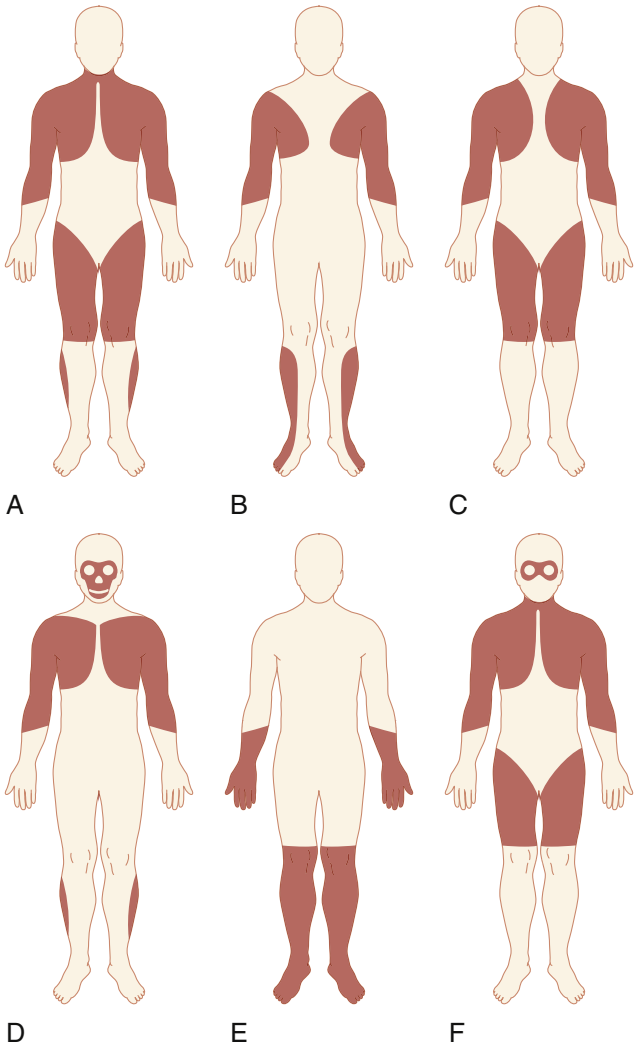


Figure 43-5. Distribution of predominant muscle weakness in different types of dystrophy: **A,** Duchenne type and Becker type; **B,** Emery-Dreifuss; **C,** limb girdle; **D,** facioscapulohumeral; **E,** distal; and **F,** oculopharyngeal. *(Redrawn from Emery AE: The muscular dystrophies,* Br Med J *317:991-995, 1998.)*

Pulmonary insufficiency is a leading cause of morbidity and mortality in DMD.[253] Usually, expiratory muscle function is affected first because of the early onset of abdominal muscle weakness. By contrast, inspiratory muscle function is relatively preserved in the first decade of life, implying sparing of the diaphragm.[254] Vital capacity (VC) increases in the first decade because of overall body growth, plateaus in early adolescence, and then dramatically declines as the diaphragmatic weakness progresses.[254] Other measured lung volumes such as inspiratory reserve volume and total lung capacity (TLC) follow the same pattern. A disproportionate loss of VC and TLC relative to the respiratory muscle dysfunction results, in part, from additional factors such as altered chest wall and lung mechanics, modifications in the distribution of surfactant, microatelectasis, and local fibrosis secondary to recurrent pneumonia.[254] Scoliosis further impairs pulmonary function. On average, for each 10 degrees of thoracic scoliosis curvature, forced vital capacity (FVC) decreases by 4%.[249] In 90% of patients, a curvature of greater than 20 degrees develops 3 to 4 years after they are wheelchair bound. Respiratory failure inevitably occurs in the second decade of life and is the most common cause of death.[255]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Chronic elevation of the serum CK level is a general indication of muscle disease. Three serum tests showing elevated CK levels obtained 1 month apart is diagnostic of muscular dystrophy. CK represents leakage of enzyme from muscle cells and does not correlate with the severity of the disease. CK could reach 50 to 300 times the normal value in early stages of the disease. The level tends to decrease with the loss of muscle mass. Elevation of the MB fraction of CK precludes its use as a marker for cardiac injury.[248] EMG can be supportive of the diagnosis; however, it can be extremely difficult to perform on children. Muscle biopsy, followed by immunostaining or Western blot analysis for dystrophin, is recommended for diagnostic testing. Multiple polymerase chain reaction is also useful in detecting more than 98% of the existing deletions.[245] The result is usually available within 24 hours, which may render muscle biopsy, the old gold standard, obsolete.

Anesthetic Considerations

Patients with DMD and BMD may require anesthesia for muscle biopsy, correction of scoliosis, release of contractures, and exploratory laparotomy for ileus,[248] as well as for dental[256] and obstetric[257] procedures. As the natural course of the disease progresses, the risk of surgery increases, concomitant with the increased comorbid conditions associated with the later phase of the disease. However, perioperative complications are not proportional to the severity of the disease. They even occur in patients who are mildly affected. Consequently, patients should undergo careful preoperative consultation and evaluation.

Of the patients with muscular dystrophy, 50% to 70% demonstrate some cardiac abnormality, although it is clinically significant in only 10%.[248] Preoperative cardiology assessment with an ECG and echocardiography is essential. Continuous cardiac Holter monitoring is necessary if an arrhythmia is captured on the ECG or if the patient describes symptoms that can be related to cardiac arrhythmias. Echocardiography will demonstrate mitral valve prolapse in 10% to 25% of patients. It may also show posterobasilar hypokinesis in a thin-walled ventricle and a slow relaxation phase with normal contraction characterizing the cardiomyopathy observed in DMD.[248] However, echocardiography may not always reflect the ability of the diseased myocardium to respond to perioperative stress. Stress echocardiography using angiotensin to detect latent heart failure and to identify inducible contraction abnormalities has been advocated.[258]

An estimated 30% of deaths in individuals with DMD are due to respiratory causes.[259] Therefore careful preoperative pulmonary assessment is important. Webster demonstrated that the manual muscle strength test has a strong statistical correlation with all of the timed functional tests. Peak expiratory flow was not only easy to perform but also statistically correlated with all timed functional tests.[260] The correlation was not significant for VC or forced expiratory volume in 1 second (FEV_1).

Intraoperatively, in terms of airway management, patients with DMD and BMD may have decreased laryngeal reflexes and prolonged gastric emptying time, which increases the risk for aspiration.[261] Decreased ability to cough up the accumulation of oral secretions predisposes patients with muscular dystrophy to postoperative respiratory tract infections.[248] Masseter spasm is also a possible complication during induction of anesthesia in these patients.[262] Preparedness for a difficult airway is necessary, especially in patients with potential airway problems.

Postoperatively, patients with DMD are at an increased risk for respiratory compromise.[263] Retrospective reviews have indicated that the incidence of prolonged postoperative ventilation (>36 hours) was greatest in patients with DMD who had a preoperative FVC of less than 40% of the predicted value.[264,265] Preoperative pulmonary function studies are valuable in determining the postoperative course. Patients with a VC greater than 30% of the predicted value can usually be extubated immediately after surgery.[248] Sleep apnea may also compound the condition and contribute to the development of pulmonary hypertension. Continuous positive airway pressure and bilevel positive airway pressure have been demonstrated to be effective in the management of postoperative respiratory depression. Delayed pulmonary insufficiency may occur up to 36 hours postoperatively, despite the apparent recovery of skeletal muscle strength.[266]

Reports have suggested a relationship between DMD or BMD and MH, but this association is not based on good rational grounds.[267] Whereas the risk for an MH mutation in patients with DMD or BMD is similar to that of the general population, the incidence of MH-like anesthetic events has been reported to be 0.002 with DMD and 0.00036 with BMD.[268] Unexplained cardiac arrest[262,269] and acute heart failure[270] have been reported in patients with DMD or BMD. Succinylcholine is contraindicated in these patients because of the potential for rhabdomyolysis and hyperkalemia as a result of their unstable sarcolemmal membrane. Succinylcholine-induced hyperkalemia during acute rhabdomyolysis is more likely to

result in cardiac arrest and unsuccessful resuscitation than is the potassium efflux resulting from the upregulation of acetylcholine receptors in patients with burns.[266] An increase in both maximal effect and duration of action usually accompanies the use of nondepolarizing muscle relaxants.[271] Narcotics can be used, but small incremental dosing and short-acting medications are recommended, given the respiratory depression associated with these medications. Recently, TIVA has become more popular[272] because of reports of inadvertent reactions to volatile anesthetics.[248] However, consideration needs to be given to the myocardial status of the patient when propofol or barbiturates are used because they may lead to profound hypotension and reduced organ perfusion.[248,273] Regional anesthesia may be used as an alternative to general anesthesia in that it avoids the risk of triggering agents and respiratory depression and enables the use of local anesthetics for postoperative analgesia. It may also facilitate postoperative chest physiotherapy.[274]

LIMB-GIRDLE MUSCULAR DYSTROPHY

Limb-girdle muscular dystrophy (LGMD) is a group of disorders with heterogeneous causes. To date, at least 18 genes have been identified as being responsible for this disease, with 7 being autosomal dominant and 11 autosomal recessive.[275] Mutations within the same gene may result in different phenotypes that sometimes are not consistent with LGMD. Proximal muscle (shoulder or pelvic) girdle weakness is the characteristic feature of this group of diseases. Considering the significant genetic heterogeneity, clinical manifestations of the disease vary. Autosomal recessive forms are approximately 10 times more common than autosomal dominant forms. Fukutin-related protein (*FKRP*) and calpain 3 (*CAPN3*) gene mutations have been associated with LGMD. In addition, a number of other disorders not strictly included under LGMD in this classification may have LGMD-like phenotypes.[275]

ANESTHETIC CONSIDERATIONS

Sporadic cases of LGMD have been reported in the anesthesia literature.[276-278] General approaches to these patients are the same as for those patients with DMD or BMD.

MYOTONIC DYSTROPHY

Myotonic dystrophy (MD) is an inherited muscular disorder characterized by progressive muscle weakness and wasting. Two types of MD result from either a mutation in the dystrophia myotonica–protein kinase (*DMPK*) gene, located on chromosome 19q13.3 (MD type 1 [MD1], also known as Steinert disease); or CysCysHisCys (CCHC)-type zinc finger, nucleic acid–binding protein (*CNBP*) gene, located on chromosome 3q21 (MD type 2 [MD2]).[279]

The incidence of MD is 1 in 8000. MD1 is by far the most common of the two types and accounts for approximately 98% of all cases. MD1 is caused by an expansion of a cytosine-thymine-guanine (CTG) trinucleotide repeat in the *DMPK* gene and is inherited in an autosomal dominant manner.[280] Typical signs and symptoms include muscle weakness and wasting (most prominent in the cranial and distal limb musculature), periodic myotonia, progressive myopathy, insulin resistance, defects in cardiac conduction, neuropsychiatric impairment, cataracts, testicular atrophy, and frontal balding in men. The typical cranial muscle weakness and wasting are exhibited not only in the facial, temporalis, masseter, and sternocleidomastoid muscles but also in the vocal cord apparatus. Mitral valve prolapse is found in 20% of patients.[266] The severity of the disease is related to the number of extra trinucleotide repeats.[86] Patients with MD1 may also have mildly elevated CK levels. Myotonic discharges can be identified on EMG, as well as an inability to relax from a handgrip. During pregnancy, the symptoms may be exacerbated. Uterine atony and retained placenta may also complicate vaginal delivery. First-degree atrioventricular heart block is a common finding on ECG before the onset of symptoms.[266]

MD2 is also called *proximal myotonic myopathy*. Intron 1 of the *CNBP* gene contains a complex repeat motif, (TG)n(TCTG)n(CCTG)n, and the expansion of the CTG repeat was determined as the cause of MD2. Patients with MD2 suffer from myotonia (90% of those affected), muscle dysfunction (82% with weakness, pain, and stiffness), and, less commonly, cardiac conduction defects, iridescent posterior subcapsular cataracts, insulin-insensitive type 2 diabetes mellitus, and testicular failure.[281]

No case report in the literature links MD to MH.[282] Lehmann-Horn and colleagues performed IVCT in 44 patients with myotonias and periodic paralyses, which revealed 4 positive results, 10 equivocal results, and 30 negative results.[283]

Anesthetic Considerations

General considerations for MD are similar to those for other muscular dystrophies. Mathieu and co-workers conducted a retrospective study on the anesthetic and surgical complications of MD. The majority of complications were found to be pulmonary related and significantly more frequent in patients undergoing an upper abdominal surgical procedure and those with severe disability as assessed by the presence of proximal limb weakness.[284] The pulmonary complications of MD are the result of hypotonia, chronic aspiration, and central and peripheral hypoventilation.[248] Smooth muscle atrophy, which leads to poor gastric motility, promotes aspiration when coupled with a diminished cough reflex.

Succinylcholine will produce contractions lasting for several minutes, thus making intubation and ventilation a challenge. These contractions are not antagonized by nondepolarizing muscle relaxants. Other agents, including methohexital, etomidate, propofol, and even neostigmine, may also induce myotonic reactions. Short-acting nondepolarizing muscle relaxants or avoidance of relaxation is therefore advised.[248] Triggering factors, such as hypothermia, shivering, and mechanical or electrical stimulation, may cause a myotonic reaction.[285] The reaction can be treated with phenytoin (4 to 6 mg/kg/day) or quinine (0.3 to 1.5 g/day).[248] Furthermore, patients with MD can be extremely sensitive to anesthetic agents, with hypersomnolence and CO_2 retention sometimes being

observed. Careful titration with relatively short-acting anesthetic agents may be beneficial. Close cardiac monitoring is required for patients with MD. Pacing equipment should be readily available because one third of those with first-degree atrioventricular blocks may not respond to atropine.[248] All patients should be treated as though they have both cardiomyopathy and conduction defects.

MYOTONIA CONGENITA

Myotonia congenita (MC) is a congenital form of muscular dystrophy characterized by uncontrolled temporary skeleton muscle excitability as a result of mutations in the muscle chloride channel gene (*CLCN1*). Two forms of MC have been described—one with autosomal dominant and the other with recessive inheritance. Type 1 is also known as Thomsen disease, and type 2 is also known as Becker myotonia. A forceful muscle contraction, particularly after rest for at least 10 minutes, usually initiates the myotonia in patients with MC. The myotonic muscle stiffness then becomes increasingly obvious after a second and third short but forceful contraction. Further contractions usually dampen the myotonia.[286]

Thomsen disease was the first myotonic disease to be described. Patients may have a hypertrophic and athletic appearance. The sign of percussion myotonia is described as an indenting-appearing myotonia triggered by tapping the muscle. Lid lag is common and muscle stretch reflexes are normal.[286] Myotonia symptoms in Becker myotonia usually start at 10 to 14 years of age or even later and are more severe than those of Thomsen disease. Becker myotonia may be associated with severe generalized stiffness, resulting in falling. It can be frequently misdiagnosed as epilepsy. Antiepileptic medications do improve the symptoms, however.[286]

Anesthetic Considerations

As with many muscle diseases, reports suggest that patients with MC are predisposed to MH, but, as is the case for almost all of them, no data exist that support this hypothesis.[287-289] However, depolarizing muscle relaxant can lead to severe masseter spasm in patients with MC. Generalized spasm involving the respiratory and skeletal muscles has been reported.[287] The findings resemble those of MH; therefore dantrolene is sometimes administered.[286] Because dantrolene is an inhibitor of calcium release from the SR, it can usually abolish the myotonia effectively.[287,288] Some believe that local anesthetics and class Ib antiarrhythmic drugs such as lidocaine should be used for myotonic reactions rather than dantrolene.[290] Because shivering in the surgical unit can trigger the myotonic reaction, patients with MC should be kept normothermic during surgery.[286]

MYOTUBULAR MYOPATHY

Myotubular myopathy (MTM) is pathologically defined by the presence of centrally placed nuclei in the majority of extrafusal muscle fibers, an appearance resembling fetal myotubes during normal muscle development. Consequently, MTM is also called *centronuclear myopathy* (CNM).[291] However, MTM now mostly refers to the X-linked form of the disease, whereas CNM is used for the autosomal form.[291]

MTM and CNM are rare. The estimated incidence of MTM is 1 in 50,000 male newborns.[291] MTM has been linked to the myotubularin (*MTM1*) gene on Xq28. Pregnancy is often complicated by polyhydramnios and reduced fetal movements. Affected male infants typically have severe floppiness and weakness and respiratory distress at birth. Cardiac muscles are not generally involved. The patient usually has a normal response to pain, but tendon reflexes are absent. The long-term prognosis for MTM is extremely poor.[291] In patients who survive the first year of life, most are either completely or partially ventilator dependent.[292] These patients often have abnormal liver function.[292] Both autosomal recessive and autosomal dominant forms have been observed in patients with CNM. Its clinical features include respiratory distress, hypotonia, bulbar weakness, ophthalmoplegia, ptosis, and facial diplegia. Although the exact genetic mechanism is not fully understood, the *MTM1*, myotubularin-related protein (*MTMR2*), and myotubularin-related phosphatase (*MTMR3*) genes have been implicated.[291] Pathologically, MTM and CNM share a similar, characteristic histologic feature: predominantly type 1 fibers with centrally placed nuclei are observed on hematoxylin-eosin staining of formalin-fixed, paraffin-embedded tissue.[291]

Anesthetic Considerations

Reports of anesthesia for patients with MTM are sparse.[293-298] Nontriggering general anesthesia has been used because of the unfounded concern of possible susceptibility to MH. Agents such as propofol, fentanyl, remifentanil, and nitrous oxide have been successfully used without adverse effects.[293-298] The possibility of a prolonged effect of nondepolarizing muscle relaxants has been suggested with mechanomyography.[293-298] However, in reality, intubation of such patients may not require any muscle relaxant because of their hypotonic state. Costi and van der Walt suspected that the defect in MTM is distal to the neuromuscular junction,[294] whereas Dorchies and co-workers suggested that muscle in MTM might be intrinsically normal, with myotubularin-deficient motor neurons involved in the development of the disease.[299]

METABOLIC MYOPATHIES

Two major energy sources for muscle exist: glycogen and fatty acid. Glycogen serves as a dynamic but limited reservoir of glucose that is mainly stored in skeletal muscle and liver. Glycogen storage disorders (GSDs) are a group of metabolism disorders caused by enzyme deficiency or dysfunction. They reduce effective glucose storage by interfering with normal glycogen synthesis and degradation. Synthetic errors cause decreased normal glycogen, whereas degradation errors tend to block the breakdown of glycogen. Subsequently, hypoglycemia and accumulation of glycogen in tissues could occur as a result of

substrate use. More than 12 types of GSD are assigned Roman numerals, based on the enzyme deficiencies. Types I and II are discussed in the following text.

GLYCOGEN STORAGE DISEASE TYPE I

The incidence of GSD type 1 (GSD I) is approximately 1 in 100,000 live newborns.[300] The incidence in non-Ashkenazi Jews from North Africa may be as high as 1 in 5420 people.[300] The defective enzyme causing the disease is glucose-6-phosphatase, which is the enzyme that converts glucose 6-phosphate (G6P) to glucose in the liver. GSD type Ia (von Gierke disease) is due to a deficiency in G6P hydrolase (catalytic subunit) activity and accounts for more than 80% of cases. GSD types Ib (G6P transporter deficiency), Ic, and Id represent allelic defects in the translocase associated with G6P. Their inheritance is autosomal recessive. The G6P gene (*G6PC*) encoding the hydrolase resides at 17q21, with the gene encoding G6P translocase (*G6PT*) located at 11q23. Mutations responsible for GSD I have been described in patients with both types Ia and Ib.[300]

Impaired glycogenolysis results in an accumulation of glycogen and G6P in the liver, kidney, intestine, skeletal muscle, and heart, producing hepatomegaly, renomegaly, proximal tubular dysfunction, and diarrhea.[301] Fasting hypoglycemia is the initial manifestation of the disease. As a result, both up-regulation of the synthesis and transport of counter-regulatory hormones, such as glucagon, cortisol, catecholamines, and growth hormone, become obvious and lead to the release of pyruvate, lactate, and free fatty acid. Lipid deposition in lean tissues such as the liver, skeletal muscle, cardiac muscle, and pancreas results in lipotoxicity and organ failure, including pulmonary hypertension, steatohepatitis, end-stage renal disease, insulin resistance, cardiac contractile dysfunction, and pancreatic beta cell failure.[300] For GSD Ib disease, specific problems such as neutropenia and neutrophil dysfunction are prominent. Patients may have recurrent infections and inflammatory bowel disease.[302]

Anesthetic Considerations

Anesthesia case reports for patients with GSD I are rare.[303,304] Patients with GSD I diseases should be given IV glucose-containing fluid preoperatively when they have fasted. Lactate-containing solutions should be avoided because these patients are not able to convert the lactic acid to glycogen.[248] Patients need to be monitored frequently to avoid hypoglycemia.

GLYCOGEN STORAGE DISEASE TYPE II (ACID MALTASE DEFICIENCY)

The incidence of acid maltase deficiency (AMD) is estimated to be 1 in every 14,000 to 40,000 births. Its inheritance is autosomal recessive with a few exceptions.[305,306] Mutations of the acid maltase gene on chromosome 17q25 cause deficiency of lysosomal acid maltase (acid α-1,4-glucosidase).[306] Cases of AMD have been arbitrarily classified into three groups—infantile, childhood, and adult—according to the age at onset or death, rate of progression, and tissue-organ involvement.[306]

Acid maltase is a lysosomal enzyme that catalyzes the one-way hydrogenation of glycogen to G6P and is found in all tissues, including skeletal and cardiac muscle.[307] Consequently, glycogen accumulates within the muscle tissues of patients who are maltase deficient. Infantile AMD, also known as Pompe disease, is usually evident within the first few months of life as rapidly progressive weakness and hypotonia and an enlargement of the tongue, heart, and liver. Massive amounts of glycogen (8% to 15% of the wet weight of the tissue) accumulate in the heart, liver, and skeletal muscle, with relatively smaller deposits in smooth muscle, eyes, kidneys, endothelial cells, lymphocytes, brain, and spinal cord. Accumulation of glycogen in cardiac muscle leads to cardiac failure in the infantile form.[306] Echocardiography demonstrates significant thickening of the interventricular septum and posterior left ventricular wall, left ventricular outflow obstruction, and trabecular hypertrophy.[306] Ventricular wall thickness may be increased to up to 25 mm.[308] Wolff-Parkinson-White syndrome has been reported.[309] The signs and symptoms of infantile AMD may resemble those of DMD. Death usually results from cardiorespiratory decompensation within several years of disease progression.[310]

Childhood AMD occurs in infancy to early childhood and exhibits clinical signs of myopathy. Respiratory muscles tend to be selectively affected. Calf enlargement can also occur. The disease progresses relatively slowly in this form, with a few patients surviving beyond the second decade of life.[306] Tongue, heart, and liver enlargement infrequently occur.[311] However, involvement of vascular smooth muscle is more severe than in the infantile form. Extensive glycogen deposition in the arterial wall, causing basilar aneurysms, has been reported.[311]

Adult AMD usually occurs after age 20 years and is characterized by slow progressive myopathy or symptoms of respiratory failure.[306] The weakness in proximal muscles is more prominent than the weakness in distal muscles. One third of adult patients with AMD suffer from respiratory failure with a restrictive pattern. Weakness in the diaphragm causes extensive atelectasis. VC may be significantly reduced.[306]

Anesthetic Considerations

Anesthesia reports in patients with AMD are rare.[312-315] Isolated intraoperative cardiac arrest during halothane anesthesia in infantile AMD has been documented.[315] Despite the problem noted with halothane, both enflurane[313] and sevoflurane[314] have been used without complications. Theoretically, TIVA with propofol may cause a reduction in afterload, leading to an increased risk for myocardial ischemia. This complication may become significant when the patient develops tachycardia.[314]

Subendocardial ischemia may occur in patients with a thickened ventricular wall and result in higher left ventricular end-diastolic pressure at lower ventricular volume.[314,316] Close cardiac monitoring is therefore necessary. A central venous or pulmonary artery catheter is not essential in patients who are normovolemic without preexisting heart failure.[314] Adequate filling pressure and normal-to-high systemic vascular resistance

(SVR) are required to ensure effective coronary perfusion.[314] Ketamine has been successfully used in a number of patients because of its ability to maintain SVR and contractility. Respiratory failure and muscle weakness are the other concerns for anesthesiologists. A spectrum of uses of muscle relaxants from none[313] to atracurium[312] or rocuronium[314] has been attempted. Low-dose rocuronium, 0.5 mg/kg, with close monitoring of neuromuscular function and the adequate use of reversal agents, has been sufficient to prevent prolonged postoperative weakness.[314] Depolarizing agents should be avoided because of the potential risk of hyperkalemia and rhabdomyolysis.[314,315]

MITOCHONDRIAL MYOPATHIES

Mitochondrial diseases refer to defects in the five main steps of mitochondrial metabolism: (1) substrate transport, (2) substrate utilization, (3) the Krebs cycle, (4) the electron transport chain, and (5) oxidation-phosphorylation coupling.[317] However, the term *mitochondrial myopathy* has been reserved for disorders caused by defects in the respiratory chain.[317] The respiratory chain is made up of five multimeric complexes (I to V) embedded in the inner mitochondrial membrane, plus two small mobile electron carriers, coenzyme Q_{10} (CoQ_{10}) and cytochrome *c*, for a total of more than 80 proteins,[317] among which 13 are encoded by mitochondrial DNA (mtDNA) and all others by nuclear DNA (nDNA). mtDNA is different from nDNA in several aspects: (1) mtDNA is circular and contains no intron, (2) it has larger numbers of copies than nDNA and a much higher spontaneous mutation rate, and (3) its inheritance is maternal. Diagnosis of mitochondrial diseases is difficult because of their clinical heterogeneity.

Primary mtDNA mutations may include point mutations in polypeptide, transfer RNA (tRNA), or ribosomal RNA (rRNA) encoding regions and large-scale rearrangements, duplications, or deletions.[318] Some of the common conditions caused by point mutations include myoclonic epilepsy with ragged-red fibers (MERRF); mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS); neuropathy, ataxia, and retinitis pigmentosa (NARP); maternally inherited Leigh disease; and Leber hereditary optic neuropathy (LHON).[317] Sporadic large-scale mutations may lead to Kearns-Sayre syndrome, progressive external ophthalmoplegia, and Pearson syndrome.[317] nDNA mutations can cause deficiencies in complexes I to IV and in CoQ_{10} of the electron transport chain.[317]

Mitochondrial myopathy is estimated to have an incidence of 1 in 4000.[319] Among all the mitochondrial functions, abnormalities in electron transport and oxidative phosphorylation are the most common causes of mitochondrial myopathies.[320] Proximal muscle weakness with increased lactic acid and positive muscle biopsy for mitochondrial cytopathy characterize mitochondrial myopathies.[321] The hallmark of mitochondrial myopathies is the *ragged-red fiber* when muscle biopsy specimens are stained with modified Gomori trichrome stain,[322] and specific defects in the activity of these enzymes have been demonstrated in patients with mitochondrial disease.[323] Fatigue and poor stamina are prominent clinical features. Movement disorders such as ataxia, dystonia, myoclonus, chorea, athetosis, and tremors have also been described as being the result of mitochondrial abnormalities.[323]

Anesthetic Considerations

Preoperative Evaluation. Considering the heterogeneous types of mitochondrial disease, patients with mitochondrial disease need a comprehensive preoperative evaluation with a particular focus on neurologic, cardiac, respiratory, musculoskeletal, endocrinopathic, and metabolic compromise (see also Chapters 38 and 39). An ECG and echocardiogram should be considered in patients with signs and symptoms of cardiomyopathy or conduction defects (or both). Although normal lactate and glucose levels cannot rule out mitochondrial diseases, laboratory studies consisting of glucose, electrolytes with anion gap, complete blood count, blood urea nitrogen, lactate, pyruvate, ammonia, CK, biotinidase, acylcarnitines, and blood and urine amino and organic acids could be used as initial investigation for suspected mitochondrial disorders.[324] Further workup should include an erythrocyte sedimentation rate, glycosylated hemoglobin (HbA_{1C}), liver and renal profiles, thyroid function tests, arterial blood gas, and urinanalysis.[319,323] Multidisciplinary consultation with special laboratory and imaging studies may be required.[323]

Induction and Maintenance of Anesthesia. Anesthesia has a significant impact on mitochondrial function. Both barbiturates and propofol inhibit complex I of the electron transport chain.[324] Local anesthetics have been demonstrated to disrupt oxidative phosphorylation and decrease the bioenergetic capacity of mitochondria.[324] Sensitivity to IV barbiturates and etomidate has been reported.[325,326] However, midazolam,[327] thiopental,[328] propofol,[329,330] remifentanil,[331] and ketamine[330] have all been safely used. Premedication should avoid respiratory depression caused by impaired respiratory responses to hypoxemia. Volatile agents such as halothane, isoflurane, and sevoflurane have been shown to inhibit complex I.[324] This direct inhibition of mitochondrial electron transport system enzymes and altered mitochondrial bioenergetics in the heart were thought to be the mechanism of cardiac preconditioning by volatile anesthetics.[332,333] Inhaled sevoflurane has been widely used for induction because of its low pungency.[321] In some cases, halothane[327] and isoflurane[327,334] have also been used. Isoflurane has been recommended as the agent of choice in patients with Kearns-Sayre syndrome because rhythm disturbances have been reported with halothane in such patients.[327,334] In addition, artificial pacing capability is recommended when dealing with this specific subset of patients.[321] With use of the bispectral index, higher sensitivity to volatile agents has been suggested in children with mitochondrial diseases, especially with dysfunction of complex I.[335] However, its methodology has been criticized.[336] A decreased minimum alveolar concentration of halothane in patients with mental retardation has also been reported.[337]

Despite no real evidence and the fact that volatile anesthetics are frequently the anesthetic of choice when

muscle relaxants are considered, several studies have expressed concern that these myopathies are associated with increased sensitivity to MH. No data support this conclusion. Increased sensitivity to nondepolarizing muscle relaxants has been documented for mivacurium,[338] atracurium,[339] and rocuronium.[339,340] In contrast, normal responses to depolarizing and nondepolarizing neuromuscular blocking drugs such as pancuronium,[341] vecuronium,[342] and atracurium[329,343] are also reported. Although muscle relaxants are not absolutely contraindicated, based on current literature, administering depolarizing or nondepolarizing neuromuscular blockers with caution to patients with mitochondrial diseases and using neuromuscular monitoring are both necessary.[319]

Nonsteroidal antiinflammatory drugs[321] and regional techniques consisting of local,[321,344] spinal,[345] and epidural administration have been reported. However, it is suggested that regional anesthesia be performed when neurologic abnormalities of the spinal cord and peripheral nerves have definitely been ruled out.[345] Importantly, coagulation function should be assessed because of the possibility of hepatic dysfunction.[321]

Opioids should be used with caution because of the increased risk for respiratory depression and their potential to induce respiratory acidosis in addition to the underlying metabolic acidosis.[321] Because patients with mitochondrial diseases have dysfunctional aerobic metabolism, any increase in the basic metabolic rate should be prevented.[323] Shivering, hypoxia, fasting, and hypotension in such patients may exacerbate the lactic acidosis and should therefore be avoided.[346] Finally, the increased postoperative infection rate in patients with mitochondrial diseases may be due to reductions in hepatic mitochondrial activity, phagocytosis by Kupffer cells, and activity of the reticuloendothelial system.[347]

MYASTHENIA GRAVIS

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction. Autoantibodies against the α-subunit of the muscle-type nAChR destroy acetylcholine receptors of the neuromuscular junction and cause classic transmission failure with muscle weakness and fatigue. Sparing of other α-subunits of neuronal-type nAChRs provides an explanation for the lack of autonomic or CNS involvement of the disease. The incidence of MG varies between geographic regions, being 1.2 per million in Japan and approximately 14 per 100,000 in some areas of the United States.[348,349] In younger age groups, females are affected more often than males, whereas in older adult age groups (>60 years), men are more frequently affected.

The association between MG and hyperplasia of the thymus is striking, with more than 70% of patients with MG having thymus hyperplasia and 10% having thymomas.[349] MG may also be observed as a part of a paraneoplastic syndrome.[349]

Typically, patients first report bulbar symptoms consisting of diplopia and ptosis. The bulbar symptoms are often followed by unevenly distributed muscle weakness and fatigue of the extremities and face. Speech and chewing may be affected, as well as pharyngeal function and coordination of swallowing, with a subsequent increased frequency of aspiration of oral contents. The muscle weakness is often exacerbated during exercise and throughout the course of the day. Apart from the patchy distribution of muscle weakness, symptoms may also vary from day to day, and periods of remission of varying duration may occur.

The diagnosis of MG is made by neurologic examination and testing of the tendency to fatigue and the tendency to exhibit increased weakness during exercise or repeated contractions. The diagnosis can be confirmed by the Tensilon test (administration of an anticholinesterase, edrophonium). Improvement is usually observed within 5 minutes after administering the drug and lasts for approximately 10 minutes. In addition, electrophysiologic evaluation is often performed and shows a classic decrement in the compound muscle action potential after repetitive nerve stimulation.

Anesthetic Considerations

Ideally, careful neurologic consultation in addition to preoperative evaluation should be performed on patients with MG with the goal of optimizing drug therapy and preparing for postoperative care. Pulmonary function tests may be indicated to determine the need for postoperative mechanical ventilation.[338] As a general rule, patients should keep taking their anticholinesterase medication and be informed about the possibility of postoperative ventilator support. Succinylcholine can be used if needed for rapid tracheal intubation. However, patients with MG might need larger than normal doses (1.5 to 2.0 mg/kg body weight) because of the decreased number of functional acetylcholine receptors.[350] On the other hand, as a result of the decrease in cholinesterase activity achieved by anticholinesterase treatment, neuromuscular blocks with succinylcholine or mivacurium are frequently prolonged.[351,352] Nondepolarizing neuromuscular blockers can be used in patients with MG but should be administered with caution because their effects are highly unpredictable and the distribution of muscle weakness is often uneven. Consequently, monitoring of neuromuscular function with a peripheral nerve stimulator is not always reliable in patients with MG, and dosing of any nondepolarizing muscle relaxant should be increased in small increments corresponding to 0.1 to 0.2 times the 95% effective dose (ED_{95}) until the desired neuromuscular blocking effect is achieved. Perioperative anticholinesterase treatment will modify the response to cholinesterase inhibitors because of the already existing acetylcholinesterase block, and recovery of neuromuscular function after the administration of a reversal agent has been reported to be prolonged in some patients.[353] Recently, multiple case reports recommend an alternative approach for the complete reversal of residual vecuronium or rocuronium neuromuscular block in patients with MG with the use of sugammadex in appropriate dosages.

Potent volatile anesthetics have been successfully used in patients with MG. Because of the impaired margin of safety at the neuromuscular junction, a volatile anesthetic usually provides adequate muscular paralysis to allow most surgical procedures to be performed without the

need for a neuromuscular blocking agent. Epidural and spinal anesthesia can be used in patients with MG, provided that muscle function and ventilation are carefully monitored perioperatively, similar to general anesthesia. (Baraka[354] and Abel and Eisenkraft[355] offer a more detailed review [see "References" at the end of this chapter].)

EATON-LAMBERT MYASTHENIC SYNDROME

Eaton-Lambert myasthenic syndrome (ELMS) is an immune-mediated channelopathy caused by a decreased release of acetylcholine as a result of autoantibodies against presynaptic voltage-gated calcium channels and other presynaptic elements.[356] Patients with ELMS have muscle weakness and fatigability, generally of the proximal limb muscles, with the lower extremities affected more often than the extraocular and bulbar muscle groups. The syndrome is frequently part of a paraneoplastic phenomenon, usually associated with small cell lung carcinoma. Unlike MG, patients with ELMS are usually worse in the morning with gradual improvement throughout the day. Improvement of muscle function with exercise is due to the accumulation of presynaptic calcium and the subsequent improved release of acetylcholine.[357] A minority of patients exhibit autonomic dysfunction. The diagnosis of ELMS is made by careful physical examination, combined with clinical electrophysiologic testing showing the typical facilitation of motor action potential with high-frequency nerve stimulation (30 Hz to 50 Hz). Anticholinesterase treatment has little effect on patients with ELMS. Plasmapheresis, immunoglobulin therapy, and 3,4-diaminopyridine (DAP) result in transient improvement.

Anesthetic Considerations

As in patients with MG, those with ELMS should be carefully evaluated for the risk of postoperative respiratory failure and the need for prolonged respiratory monitoring in the postoperative period. Sensitivity to depolarizing and nondepolarizing neuromuscular blocking agents is usually increased. In patients treated with DAP or an anticholinesterase agent, reversal of a neuromuscular blockade may be ineffective.

PERIODIC PARALYSIS (HYPERKALEMIC, HYPOKALEMIC, AND NORMOKALEMIC)

Tyler and associates first described hyperkalemic periodic paralysis (HyperPP) as an autosomal dominant disorder in 1951.[286] Attacks of flaccid weakness associated with increased serum potassium characterize HyperPP.[358] A potassium-rich meal or rest after strenuous exercise may precipitate an attack. Stressful situations may also provoke the onset of paralysis. The paralysis may last for 15 minutes to 1 hour, with decreased tendon reflexes. In the interictal state, HyperPP is usually associated with mild myotonia that does not impede voluntary movements.[286]

The pathogenetic development of HyperPP involves mutations in *SCN4A* encoding the voltage-gated sodium channel $Na_V1.4$ of mature muscle fibers. Such mutations lead to pathologically increased sodium current and an increased tendency of the muscle fiber to become depolarized.[286,358] Simultaneous efflux of potassium and hyperkalemia accompany the influx of sodium into the muscle. Mutant channels exhibit sustained sodium currents that lead to prolonged membrane depolarization, causing myotonia, followed by membrane desensitization (or inactivation) and resulting in paralysis. In patients with HyperPP, serum CK can be elevated, sometimes 5 to 10 times above the normal limit, whereas serum sodium and potassium levels are normal in the interictal state.[286] Recent studies consider normokalemic periodic paralysis as a variant of the HyperPP, not a distinct disease, because all participants exhibited clinical and laboratory features of the HyperPP.[359-361]

A decrease in potassium levels in blood characterizes hypokalemic periodic paralysis (HypoPP). Rigorous exercise, stress, high-carbohydrate or high-salt meals, pregnancy, menstruation, hypothermia, or drugs such as insulin can trigger attacks of HypoPP.[362,363] EMG does not usually show myotonia.[358] The severity of attacks is usually greater than those occurring in patients with HyperPP. HypoPP is an autosomal dominant disease with a higher penetration in males. The disease is due to a loss of function of one of the two different ion channel types: $Ca_V1.1$ and $Na_V1.4$.[358] The most common muscle groups affected are those in the arms and legs; however, the disorder can also affect swallowing and respiratory muscles, which can be fatal in severe cases.[364] The diagnosis of HypoPP is made by laboratory testing demonstrating hypokalemia during attacks and normokalemia between attacks. Mutations in the skeletal muscle voltage-gated calcium channel encoded by *CACNA1S* (HypoPP type 1) and *SCN4A* (HypoPP type 2) have been identified.[282] Theoretical association of HypoPP to MH was made because a few patients with MH were known to have mutations in the *CACNA1S*.[282] However, the risk of susceptibility of patients with HypoPP to MH is generally accepted to be similar to that of the general population. The exact mechanisms leading to hypokalemic paralysis, however, remain unclear.

Anesthetic Considerations

Potassium, cholinesterase inhibitors, and depolarizing muscle relaxants will aggravate the myotonia in patients with HyperPP.[286] Prolonged muscle weakness has been reported when succinylcholine is used.[365] Although one third of patients had no signs of myotonia,[366] masseter spasm and respiratory and skeletal muscle stiffness could still occur during intubation and ventilation.[286] Therefore neostigmine and succinylcholine should be contraindicated in patients with HyperPP. Ideally, all patients with HyperPP need to be admitted preoperatively to ensure that proper preoperative fasting is accompanied by the administration of dextrose-containing potassium-free maintenance fluid.[367] Postoperatively, patients with HyperPP may remain paralyzed for up to several hours. Preventive measures such as maintaining normal body temperature and low serum potassium levels and avoiding hypoglycemia are helpful in limiting such paralysis.[368] Although patients with a pathologic sodium channel response have

often been considered to be MHS, an increased risk for MH in these patients is not supported.[283] General anesthesia with and without nondepolarizing neuromuscular blocking drugs has been shown to have satisfactory outcomes.[365,367-370] Regional techniques may also be appropriate for this patient group.[366,369,370] Abortion of the hyperkalemic attack may be accomplished by administering glucose, insulin, epinephrine, and calcium supplements, or, alternatively, glucagon may be used. β-Adrenergic treatment with metaproterenol has also been shown to prevent attacks and facilitate recovery.[367]

Management of patients with HypoPP should focus on avoiding triggers and medications that cause a shift of potassium. General anesthesia, postoperative stress, glucose-containing IV solutions, and long-acting neuromuscular blockers are associated with postoperative paralytic events.[362] Epidural analgesia has been shown to reduce both pain-related hyperventilation and serum catecholamines, thereby minimizing changes in serum potassium levels.[362] The sympathomimetic effect of epinephrine-containing local anesthetics may also precipitate hypokalemia.[362]

SUMMARY

MH is a subclinical myopathy featuring an eerie and erratic metabolic mayhem that is unmasked on exposure to potent volatile anesthetics or succinylcholine. Skeletal muscle acutely and unexpectedly increases its sarcoplasmic Ca^{2+} concentration, thereby leading to increased O_2 consumption and lactate production and resulting in greater heat production, respiratory and metabolic acidosis, muscle rigidity, sympathetic stimulation, and increased cellular permeability. MHS skeletal muscle differs from normal muscle in that it is always closer to loss of control of Ca^{2+} concentration within the muscle fiber, and it can involve a generalized alteration in cellular or subcellular membrane permeability. This EC coupling defect is the result of an alteration in protein-protein interaction in the CRU. It is a homozygous, single-point mutation of *RYR1* in swine and a heterozygous disorder in humans, in whom a modification of *RYR1* protein function may also occur by interacting structures, membranes, or enzymes. Diagnosis rests on the acute awareness of the signs and symptoms of this syndrome, of which hyperthermia is a late sign. Specific treatment is the administration of dantrolene to lower intracellular muscle Ca^{2+} levels; symptomatic treatment consists of the reversal of the acid-base and temperature changes. Analysis of drug-induced muscle contractures (by European IVCT and North American CHCT protocols) and genetic testing of DNA samples are used to evaluate affected families. General or regional anesthesia is safe for patients susceptible to MH, provided that care is taken to specially prepare the anesthesia machine and to avoid all potent volatile anesthetics and succinylcholine if a general anesthesia technique is chosen. Research on MH has yielded insight into the physiologic progression of metabolism and into the molecular biologic makeup of genetic muscle disorders. Remaining challenges include the identification of all genetic mutations responsible for human MH, the elucidation of the mechanism that links exposure to subsequent loss of control of Ca^{2+}, the development of noninvasive and nondestructive testing for susceptibility, and the determination of the mode of action of dantrolene.

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Chapter 44

Fundamental Principles of Monitoring Instrumentation

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Key Points

- Accuracy and precision are different. Accuracy is how close a value is to the true value. Precision is how repeatable the measurements are. An inaccurate but precise monitor can be recalibrated to be accurate, but an imprecise monitor cannot be improved.
- Filtering can improve the signal display, but it can also result in smoothing and a loss of information.
- A signal can be extracted from noise by repeated measurements, because the noise is random over time but the signal is not.
- Electrical signals can be converted from analog to digital. Conversion can introduce some artifacts but can allow for greater storage and analysis capabilities.
- Invasive pressure monitors are affected by damping and resonance. Damping leads to distortion, signal loss, and lowering of peak values. Resonance can lead to amplification and overestimation of the peak value.
- Pulse oximetry combines analysis of optical plethysmography and absorption analysis with empirical data to produce an estimate of arterial oxygen saturation (Sao_2).
- Wavelength and frequency are related to the speed of the wave by the following formula: speed = wavelength × frequency. Shorter wavelengths improve the resolution of both light and ultrasound measurements.
- Flow measurements are one of the most difficult to obtain and usually involve indirect measures. (For example, a temperature change or pressure drop is measured and a flow value is derived. A small error in the initial measurement leads to a much larger error in the derived flow value.)

WHY FUNDAMENTAL PRINCIPLES ARE IMPORTANT

Patient monitoring has been a key aspect of anesthesiology since its beginnings as a medical specialty. As anesthesiology has grown more sophisticated and complex, so have the monitors and the data that they produce. The anesthesiologist's senses of sight, hearing, and touch, at first expanded with the stethoscope, sphygmomanometer, and electrocardiograph, are now supplemented by the pulse oximeter, expired gas analyzer, evoked potential monitor, and transesophageal echocardiography. The complexity of some of these devices can be intimidating, but they are an important part of clinical responsibility. Anesthesiologists must be able to understand and interpret the data from monitors but also anticipate and recognize errors associated with their use. Understanding how these devices work is a vital part of our necessary knowledge.

First, the scientific principles underlying the design and function of the most commonly used monitors are described. Some concepts of basic physics are followed by more detailed descriptions of the principles and their monitoring applications. The text and figures explain these principles predominantly in a qualitative manner. For those desiring a more quantitative explanation, the relevant physics and equations are provided in the appendixes at the end of this chapter.

BASIC PRINCIPLES

NATURE OF PHYSICS AND MEASUREMENT

Physics is the science of matter and energy and the interactions between the two; that is, physics is the study of everything in the physical universe. Physics encompasses

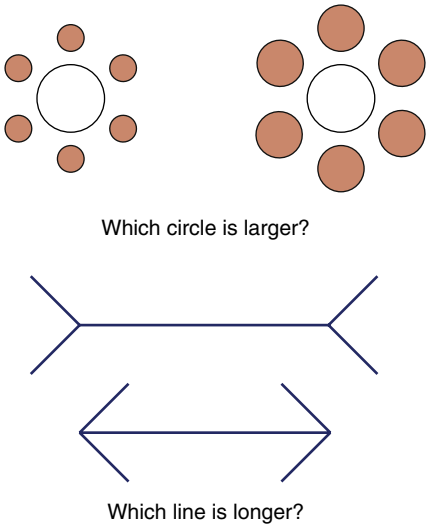


Figure 44-1. Optical illusions. We perceive the circles to be different sizes because we infer the size by relative dimension. The closeness of the smaller circles makes the inner circle appear smaller, and vice versa. The lines appear to be different sizes because we use straight-line perspective to estimate size and distance. This illusion reportedly does not work in cultures in which straight lines are not used. Therefore our internal perceptions lead us to err in estimating size and length. In the same way, the internal programming of our monitors can lead us to misinterpret results.

everything from the motions and inner workings of the atom to those of galaxies. Physics is quantitative, and mathematics is the language of physics. In fact, Isaac Newton and Gottfried Leibnitz invented *the calculus* as a mathematical tool for expressing and studying the laws of physics. Monitors are also quantitative. Before the complexity of modern anesthetic monitors can be discussed and understood, we must quantitatively define what they are attempting to measure, as well as understand the limitations of measurement.

Anesthesiologists measure and monitor mass and energy: how much of a substance is present and in what energy state does it exist. Much of what we desire to monitor is outside the range of human physical senses. Therefore, we must make measurements in this insensible realm with devices that enhance or extend our senses. Just as the senses have limitations and can be "fooled" under certain circumstances (Fig. 44-1), the design of physiologic monitors is limited and can also be fooled under some conditions. Intelligent users of these devices must understand their basic design assumptions to predict when they are likely to produce erroneous data.

ACCURACY AND PRECISION OF MEASUREMENTS

All measurements have errors. Comparing a measurement with the *gold standard* of that measure usually determines an error. Unfortunately, all measurements, even the so-called gold standards are subject to errors with respect to reproducibility. From a clinician's perspective, a physiologic measurement must be accurate to the degree required for clinical decision making. For example, arterial blood pressure can be measured in several ways, ranging from listening to Korotkoff sounds by the use of a sphygmomanometer cuff and stethoscope to continuous measurement via an intraarterial cannula. Unfortunately, each of these techniques provides slightly different arterial blood pressure values and different sources of error. The choice of method may be determined by accuracy or by the need for the frequency of the data and the ease of retrieving these data. An automatic oscillometric device is usually chosen over manual auscultatory measurements for ease of acquisition and reproducibility. Two people taking auscultatory blood pressure measurements may hear the Korotkoff sounds at slightly different points and record different arterial blood pressures. The smallest change in the measured variable that could affect a clinical decision determines the required accuracy of a clinical monitor. The requirements for *absolute accuracy* (Is the measured value correct?) may be different from the requirements for *relative accuracy* (Does the measured value follow trends?).

Consider a theoretic device that estimates hemoglobin (Hb) concentration by measuring in vivo light absorbance. This Hb concentration measured by absorbance (SpHb) of the finger is compared with the total Hb (tHb) concentration determined from in vitro laboratory analysis. SpHb is significantly dependent on the perfusion (temperature) of the finger (see Chapter 61). Yet, tHb can be associated with errors with arterial blood sampling and in vitro analysis of the sample by any method. Nevertheless, in vitro laboratory analysis is considered to be the gold standard in this comparison of methods.

The SpHb value can be compared with that of the tHb by the determination of bias and precision as recommended by Bland and Altman[1] (Fig. 44-2). Bias is the average difference between simultaneous values from the two methods, termed the *systematic error* or *offset*. If the SpHb reads an average of 5 g/dL higher than the tHb, then it has a bias of 5 g/dL and we can adjust for that systematic error by recalibrating the device. Precision is the standard deviation of the difference between the two measurements, and it quantifies the random error or *scatter*. A higher value for precision indicates a larger random error. (This statistic may be more appropriately called *imprecision*.) If the random error is too large, then the device may not be clinically useful. We can adjust for systematic error (bias) by recalibration, but no method exists to adjust for a random error. Proportional bias is yet another issue. Both the bias and the precision may vary over the range of values of clinical interest. A monitor may give accurate and precise values in the normal range but have a bias or precision error at the very range we are interested in to make a clinical decision. For example, a Hb measurement device may accurately read Hb values from 11 to 14 g/dL but have significant errors with values less than 11 g/dL (see Chapter 61), which is the range most clinically important (i.e., affecting transfusion decisions). Such a monitor may pass initial scrutiny but be clinically useless or harmful by inducing us to initiate or withhold treatment based on poor information.[2]

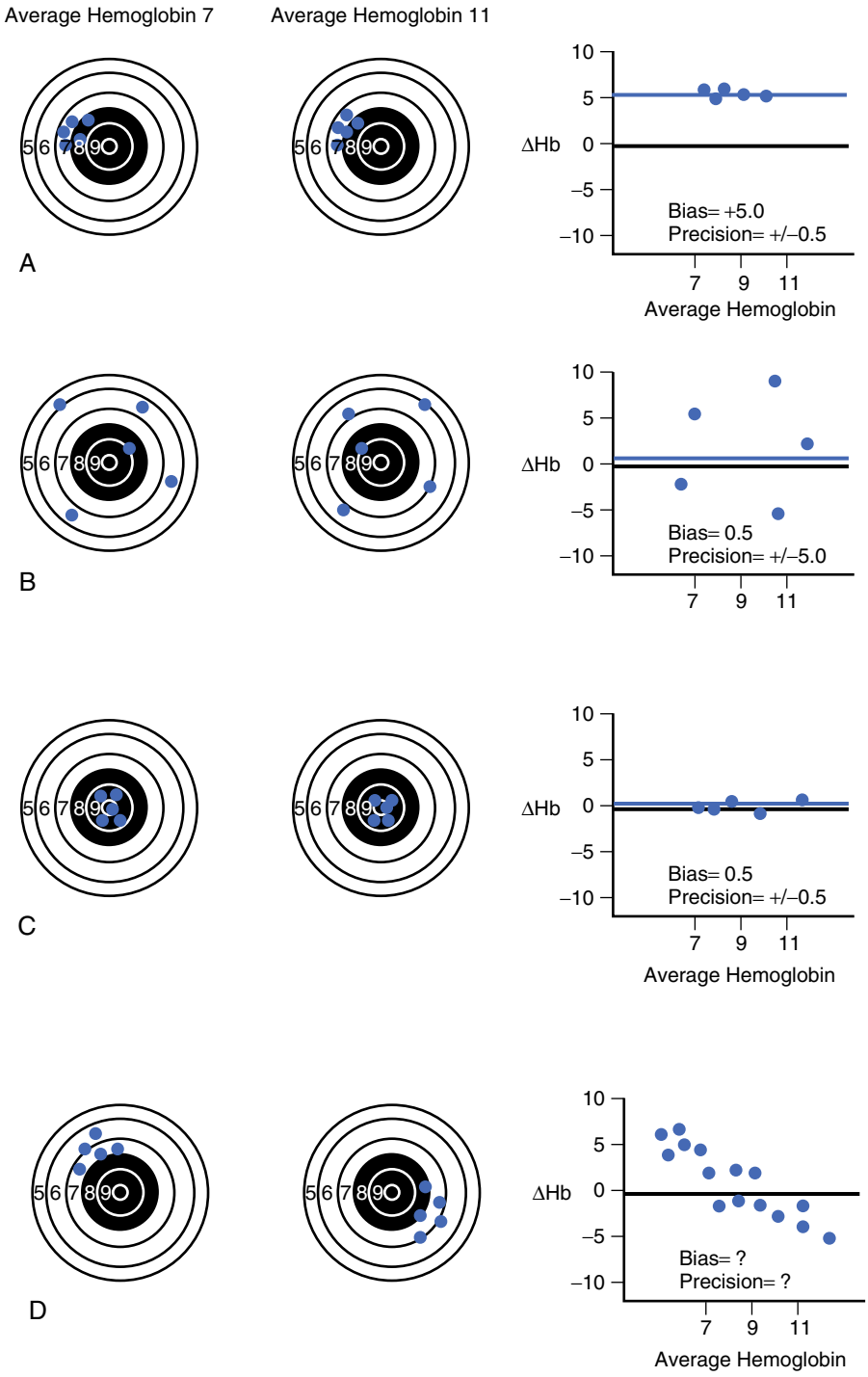


Figure 44-2. Accuracy and precision. The bias plot is a way to compare two different methods of measuring the same variable. Examples are plotted on the *right* for hemoglobin (Hb) values, blood analysis versus Hb absorbance. It is a plot of the difference between the two measurements being compared versus the average of those two measurements. **A,** If one method constantly measures slightly higher than the other by a consistent value, then the method has a positive bias. If it has only a slight variation around that bias, then the method is said to have low random error or precision, which equals the standard deviation of the differences. **B,** The values are randomly scattered, such that the average difference is near zero, but the precision value is large. This large random error makes the device unusable because calibration will not improve this random error. **C,** This is the optimal device, in that it has a bias near zero and a small precision (i.e., standard deviation of the differences) over the entire range of measurements. **D,** This device has reasonable precision at any given value, but the bias varies, depending on the value, leading to a useless device with undefined accuracy and precision over the clinical range necessary.

MEASUREMENT OF MASS

Measurement is the determination of a physical quantity. A *dimension* is a specific category or type of physical quantity; for example, mass, length, time, energy, or any of their derivatives. Units are specific ways of measuring a given dimension. Examples of units include the meter (length), second (time), kilogram (mass), ampere (current), and degree Kelvin (temperature). Describing a measurement without defining the unit is meaningless. A 30° day in Fahrenheit is literally freezing; a 30° day in Celsius is rather hot. Units can be base units or derived units. The International System of Units (SI; *Le Système International d'Unités*), which is a system used in science, has seven base units—meter, kilogram, second, ampere, degree-Kelvin, mole, and candela—from which multiple other units can be derived.

When weighing a patient, the force of gravity acting upon the patient's mass is determined. We generally mean this to be on the earth's surface, but the concept of weight is applicable to other locations. (On the surface of Jupiter, for example, a 70-kg man would weigh 12 times his earth weight, but his mass would still be 70 kg.) Since Force = mass × acceleration as a result of gravity (Newton's second law), we *balance* the force on the patient with a known

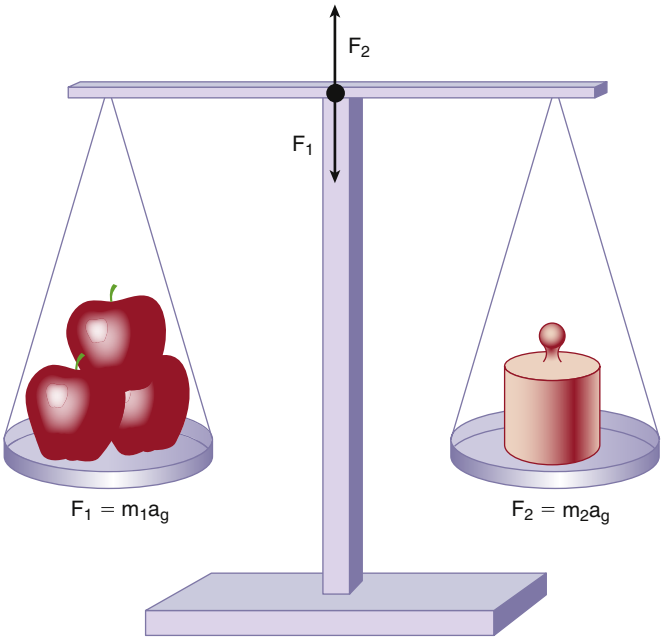


Figure 44-3. Balance. A scale is in balance when the forces are equal and in opposite directions. The force of gravity on the unknown mass of fruit is balanced by the known standard masses on the opposite side of the balance. $F_1 = F_2$, hence $m_1 a_g = m_2 a_g$; because $a_g = a_g$, m1 = m2. (a_g = acceleration due to gravity.) (See Appendix 44-1.)

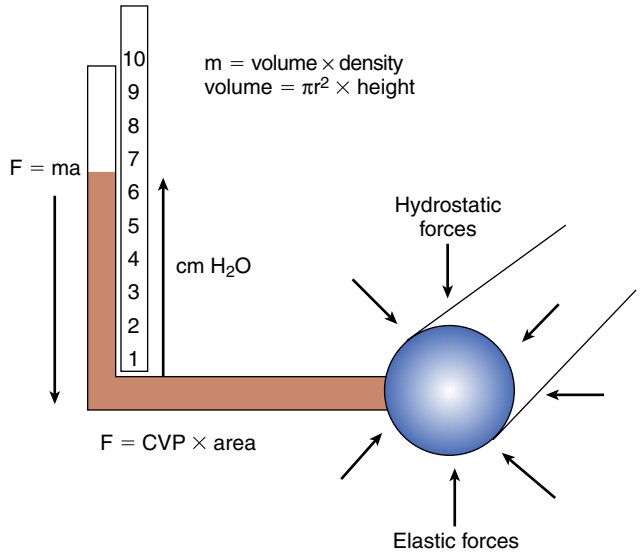


Figure 44-4. Manometer. A water manometer uses a balance of forces. In this case, the downward pressure of the fluid, as determined by its density and height, balances the upward pressure of the central venous system, caused by hydrostatic and elastic recoil forces.

mass to determine the patient's weight (the SI units of force or weight are *Newtons*) and mass (kg) (Fig. 44-3). The concept of balancing forces applies to multiple other monitoring modalities. When we measure the central venous pressure using a simple manometer, we are observing the balance of forces between the venous pressure and the force of gravity acting upon a fluid column (Fig. 44-4). When the same pressure is electronically measured, we are balancing a Wheatstone bridge (a system of resistors used to determine an unknown resistance) (Fig. 44-5).

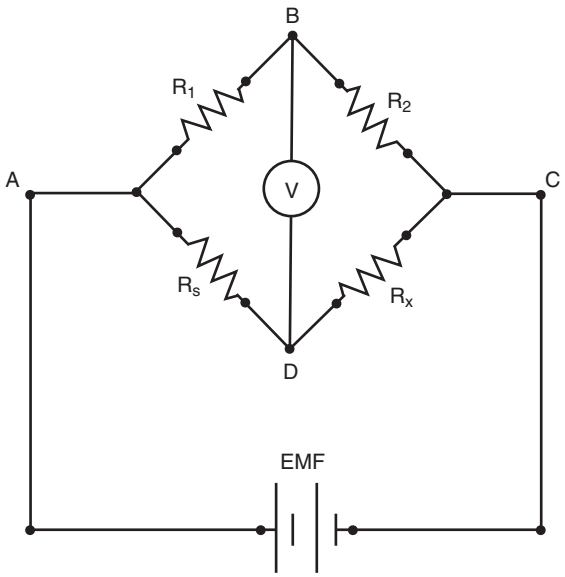


Figure 44-5. Wheatstone bridge. A Wheatstone bridge is an electronic circuit designed to enable an unknown resistance to be calculated by knowing two sets of variables: (1) the voltage drop across the bridge, and (2) the other resistances in the circuit (see Appendix 44-3).

TABLE 44-1 COMPARISON OF ENERGY LEVELS OF COMMON AND UNCOMMON EVENTS

Event	Energy
1 kg mass falling 1 meter on Earth	9.8 Joules
Heartbeat	10 J (at rest, 60 bpm, 10 watts)
Internal defibrillation for ventricular fibrillation	30 J
Maximum output of surface defibrillator	360 J
1 kilocalorie	4186 J
Car battery	1.8 MJ = 1.8×10^6 J
Kilogram of fat	3.8×10^7 J
Ton of TNT	4.2×10^9 J
Atomic bomb (Hiroshima)	15 kilotons=$15 \times 10^3 \times 4.2 \times 10^9$ J = 6.3×10^{14} J
Hydrogen bomb	1 megaton = 4.2×10^{15} J
1 kg converted completely to energy	8.987×10^{16} J
The sun (4.2×10^9 kg matter/sec)	3.8×10^{26} J/sec

Modified from Hecht E: Physics: algebra/trig. *Pacific Grove, Calif, 1994, Brooks/Cole.*

MEASUREMENT OF ENERGY

Energy can exist in many different forms. Even matter is related to energy, mathematically defined by Einstein's famous $E = mc^2$ equation. That is to say, matter and energy are different forms of the same stuff. In the absolute sense, usually reserved for thermonuclear weapons, atomic reactors, and the sun, matter can be converted into energy and vice versa (Table 44-1). The energy of motion is described as kinetic energy ($KE = \frac{1}{2} mv^2$). Temperature is a form of kinetic energy at the molecular level. Acoustic energy (sound) is a wave of pressure energy transmitted through matter. Light is a form of electromagnetic energy. Potential energy is stored energy and

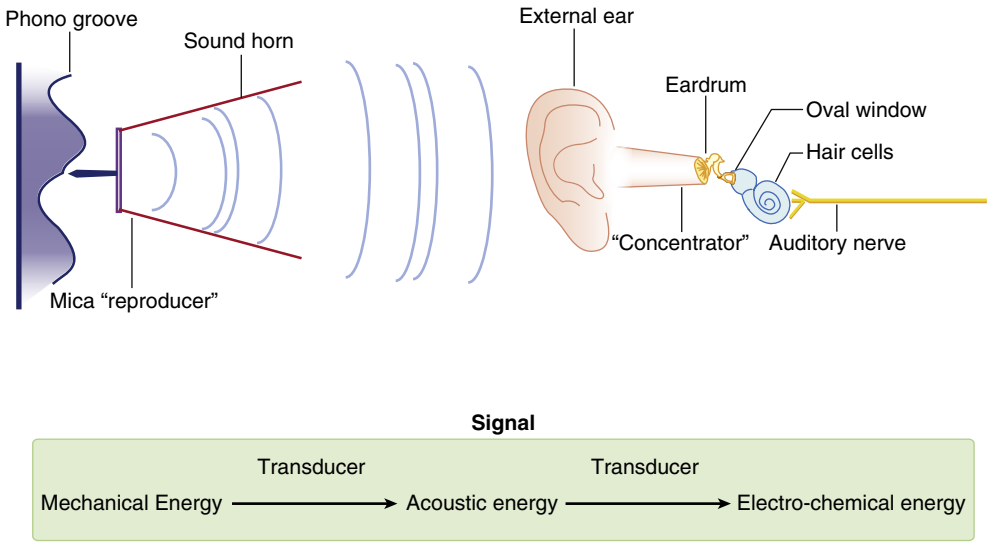


Figure 44-6. Transduction in mechanical and biologic systems. Mechanical energy of the winding mechanism causes the cylinder of the phonograph to rotate. The bumps and curves in the cylinder then move the needle, converting that energy into acoustic energy (a longitudinal wave). The mechanical vibrations are thus reproduced as longitudinal sound waves. These sound waves enter the human ear, impact the eardrum, causing it to vibrate, which moves the ossicular chain and results in an amplification of the pressure at the oval window, transmitted through the fluid of the inner ear where the appropriate hair cell resonates and generates a neural signal (transduction). A loss of hair cells leads to deafness, most commonly in the higher frequency range as one ages. This loss is analogous to a monitor lacking sensitivity in the desired range.

can be of many forms, including gravitational, chemical, pressure, and electromagnetic. The fundamental law of conservation of energy (energy and matter can neither be created nor destroyed, only changed from one form to another) is at the core of understanding many of our anesthetic monitors.

SIGNAL PROCESSING AND INFORMATION THEORY

When a quantity varies over time, it can be said to contain a *signal*. The recording of vital signs and patient data, first begun a century ago by Harvey Cushing,[3] is a primitive form of signal analysis. To quote Dr. Cushing[4]:

In all serious or questionable cases the patient's pulse and blood-pressure, their usual rate and level having been previously taken under normal ward conditions, should be followed throughout the entire procedure, and the observations recorded on a plotted chart. Only in this way can we gain any idea of physiological disturbances—whether given manipulations are leading to shock, whether there is a fall of blood-pressure from loss of blood, whether the slowed pulse is due to compression, and so on.

Often the signals (the energy or concentration of matter) we are interested in monitoring are too small for our senses to define changes adequately. Therefore we must either concentrate or amplify the signal. Often, this information is *transduced* or changed from one form to another for amplification and processing. An old style gramophone is a good example. The information stored in the shape of the record groove moves a needle attached to a mica diaphragm (the reproducer), which is then connected to a sound horn. The mechanical vibrations are thus reproduced as longitudinal sound waves. These sound waves enter the human ear, impact onto the ear drum, causing it to vibrate. This vibration moves the ossicular chain, resulting in an amplification of the pressure at the oval window transmitted through the fluid of the inner ear where the appropriate hair cell resonates and generates a neural signal transduction (Fig. 44-6). This progression is analogous to the process by which arterial pressure transducers work (Fig. 44-7).

DATA PROCESSING

When an analog signal (e.g., voltage versus time) is amplified, both the background noise and the desired signal are amplified (Fig. 44-8). Various techniques can be used to enhance the signal-to-noise ratio. For instance, most pulse oximeters assume that a pulse rate is between 30 and 300 beats per minute (bpm). Therefore the instrument filters out any pulsations that occur at frequencies below 30 or above 300 (see "Alternating current" and Fig. 44-23). Filtering can remove the noise that is outside of this frequency range, improving our ability to discern the signal of interest. Improper filtering can destroy the true signal. In some cases, a desired periodic signal can be repeated and summated, and the accompanying random noise becomes a smaller fraction of the signal. Evoked potentials are an excellent example of this process of *ensemble averaging*. The evoked-response signal for a single stimulus is actually significantly smaller than the random noise, but this signal is nearly identical after each stimulus. Therefore by summing the potentials after many stimuli, the evoked-response signal, but not the noise, is reinforced (Fig. 44-9).

Finally, the waveform of any periodic signal can be represented by a summation of sinusoidal waves, called a *Fourier series* (Fig. 44-10). The component sine waves can be described by their frequency and amplitude (or power,

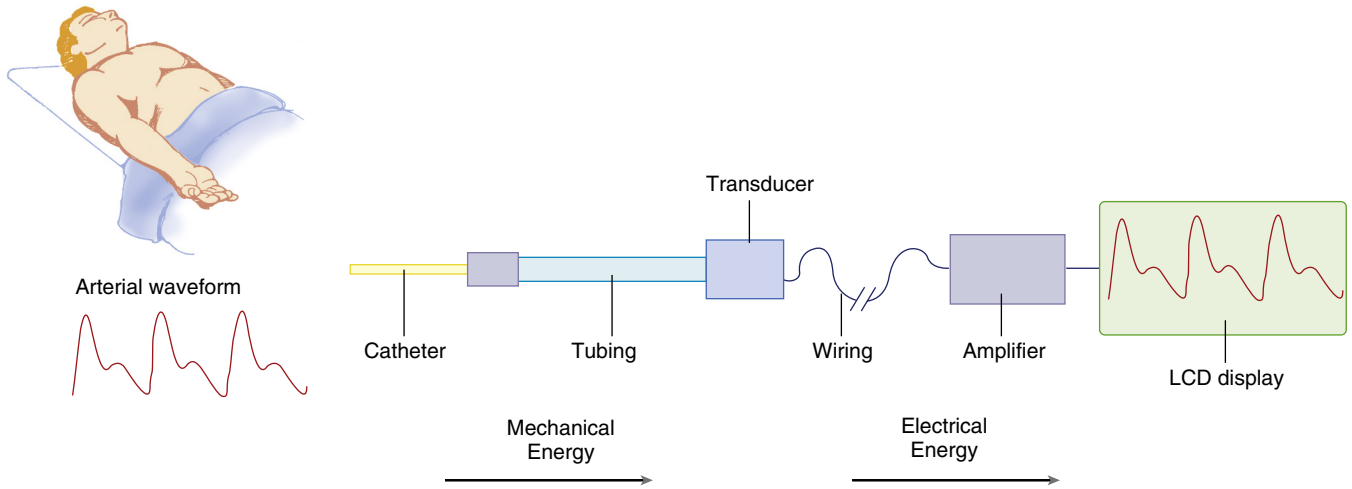


Figure 44-7. Transducer. A transducer changes a signal from one form of energy to another. A common transducer in anesthesia changes mechanical energy (e.g., an arterial pulse) into electrical energy, which is then displayed as time versus amplitude on a liquid-crystal display (LCD) or cathode ray tube (CRT) display. Microphones and speakers are also examples of transducers.

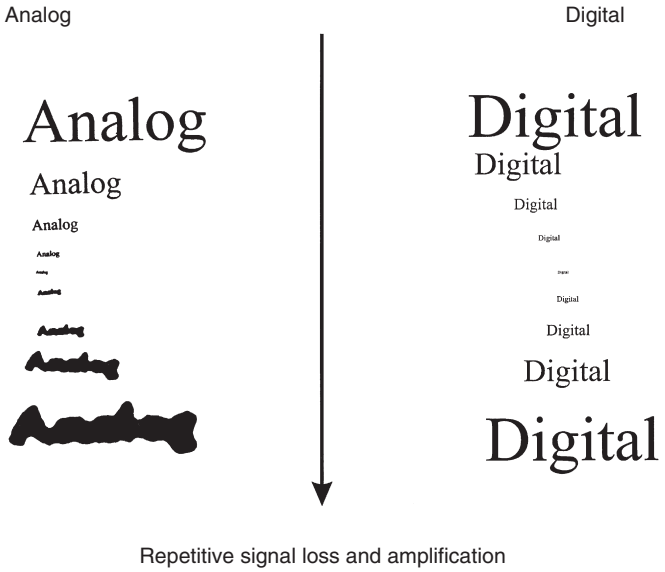


Figure 44-8. Digital and analog signal processing. The analog signal shows distortion and a loss of fidelity as it is reduced and then amplified. The digital signal shows no such loss. To create the analog example, a copying machine was used to shrink the text and then enlarge it. For the digital signal, the font size was reduced, the text copied, and the process reversed.

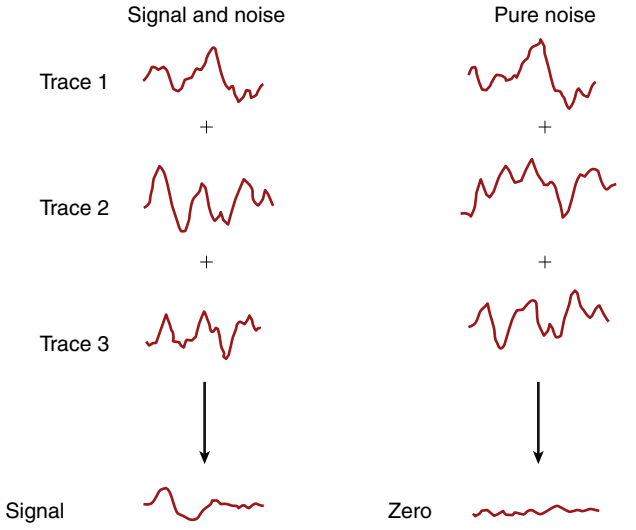


Figure 44-9. Somatosensory evoked potentials. A background signal can be separated from random noise by repeatedly adding the signals. The noise (random) is equally likely to be positive or negative; hence, adding positive and negative yields zero with multiple summations.

which is proportional to the square of the amplitude). Thus a waveform originally expressed as amplitude versus time is transformed into a plot of power versus frequency. The resulting plot, called the *power spectrum*, was a common form for displaying and interpreting some types of waveform data, such as the electroencephalogram (EEG). Most common monitors of EEG now use computer analysis to convert aspects of the power spectrum into a single, easy-to-interpret number (see Chapter 49).

ERRORS IN SIGNAL ANALYSIS

Multiple types of errors exist in signal analysis. The simplest is just missing data. Attempting to locate a 1-mm nerve using a 1-cm probe will not be successful because of a lack of spatial resolution, analogous to scanning a finely detailed print with a crude scanner, resulting in lost information. Another kind of error is *aliasing*, in which a false signal is presented. We have all seen movies where car wheels appear to be rotating backward while the car is moving forward. This is the result of temporal aliasing that occurs when the sampling frequency is too slow to capture the rapid variations of the true signal (Fig. 44-11). Aliasing can also happen with ultrasound, in which the display may show echoes from objects that do not actually exist. When dealing with nonmoving objects, spatial aliasing can occur when the resolution is too low. Figures in this book are submitted with at least a 300 dot per inch (dpi) resolution in an attempt to avoid aliasing. Figure 44-8 is an example of aliasing when the small digital signal has been reduced to "jaggies" by too low of a resolution.

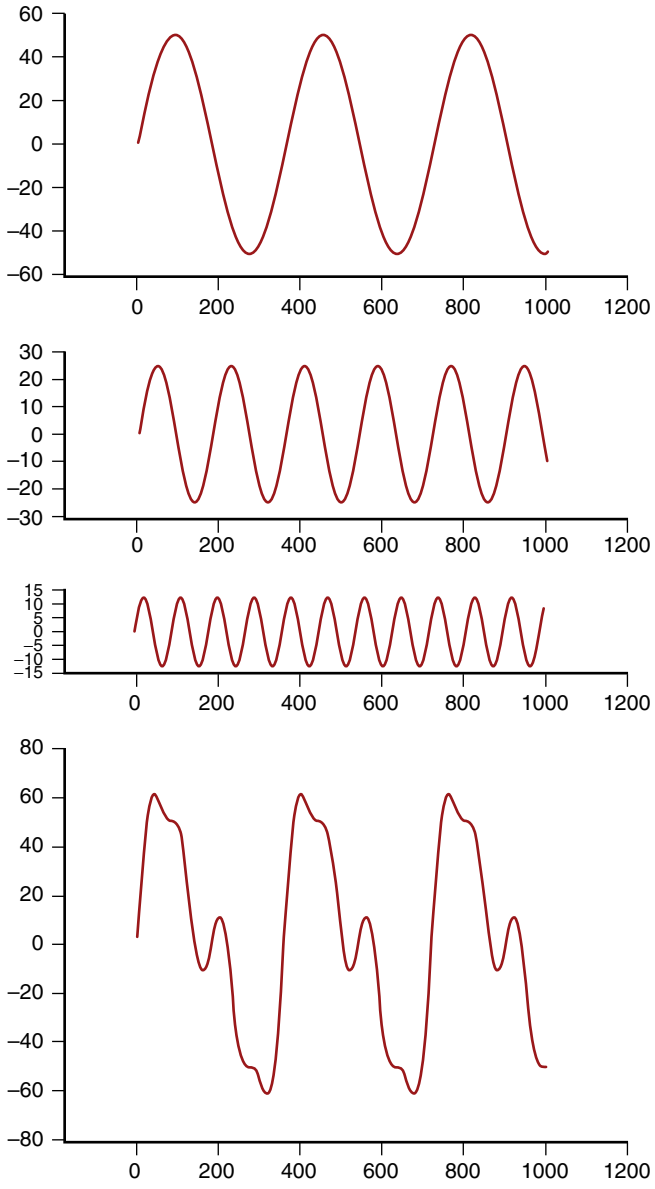


Figure 44-10. Fourier series. This pseudoarterial waveform was generated by adding the three sine waves with the following characteristics: y = 50 sinx; y = 25 sin2x; y = 12 sin4x.

In mechanical systems, such as the conventional liquid-filled tubing and pressure transducer for measuring arterial blood pressure, frictional forces can damp the signal. The signal can also be distorted by resonant amplification, in which the energy of the signal is temporarily stored in the compliance of the tubing and then released (see Appendix 44-4) (Fig. 44-12). If our display rate is too rapid, then important signals can be missed. The systolic pressure variation (SPV) (i.e., the alteration in systolic blood pressure with positive pressure ventilation)[5,6] has been used to determine volume responsiveness in hypotension. Because this change happens more slowly than the heart rate and because many displays use "auto gain", that is, the size of the display is controlled to maintain constant waveform amplitude (e.g., the plethysmographic display of most pulse oximeters), the SPV has been clinically neglected for many years.

With modern data recording and storage, Cushing's original rationale of correlating patient physiologic changes to intraoperative events can now be applied to entire populations, as well as to individuals. The original signal, whether an observed pupillary sign, palpated pulse, transduced pressure, or auscultated breath sound that was integrated, interpreted (Is this real or an artifact?), and charted (data storage) by the anesthetist, can now be automatically processed. This point is important because it introduces new possibilities in monitoring (e.g., trends, signals, feedback to user) and new pitfalls. Imagine an anesthesia record that would alert you to future potential physiologic issues from currently monitored data and predictive algorithms; in other words, an intelligent anesthesia record. New problems are introduced by such technology: security, potential loss of data (loss of not only a single chart or data point, but a loss of all the charts), and erroneous signal processing (imagine a faulty algorithm denying the very information Dr. Cushing sought to use to improve patient care).

PRESSURE MEASUREMENT

Principles of Pressure Measurement

With the basics of measurement, an example of clinical measurement will be processed. As part of a clinical examination, we can note the distention of the jugular vein. We can visualize the reflection of light off of the patient's skin, changing as the underlying structure (the jugular vein) fills and collapses; but what are the physics of this distention? If we were to insert a clear tube into the vein and hold the tube vertical with respect to gravity, then we would observe the mass of blood in the tube raised a certain distance (in centimeters) against the force of gravity by the central venous pressure (CVP) until a balance point is reached. Energy is lost in the work done in raising the fluid column, distending the tubing, and frictional losses. Therefore the actual CVP is slightly greater than we can reasonably measure. Despite these limitations, a liquid manometer is a simple and effective way to determine CVP.

The units of pressure measurement can tell us something about how the measurement is made. We commonly talk of pressure in terms of millimeters of mercury (mm Hg) or centimeters of water (cm H_2O) or pounds per square inch (psi) or atmospheres (atm). What is measured in a clear manometer tube is a pressure in centimeters of blood. Given that the content of blood in the tube can vary, more standard units than centimeters of patient blood are needed. The physics of the manometer must be understood. The density of a fluid is its mass per unit volume, which has SI units of kilograms per cubic meter (kg/m^3) or, more commonly, grams per milliliter (g/mL). The pressure exerted by a liquid column of height z and density ϱ is simply ϱgz (see Appendix 44-2 for derivation). If the manometer liquid is mercury, which has a density of 13,600 kg/m^3 (13.6 g/mL), then the manometer pressure in pascals (Pa) (the SI unit of pressure) is:

$$P\,(\text{Pa}) = 13{,}600 \times 9.8 \times z\ (\text{m}) = 1.333 \times 10^5 \times z\,(\text{m})$$

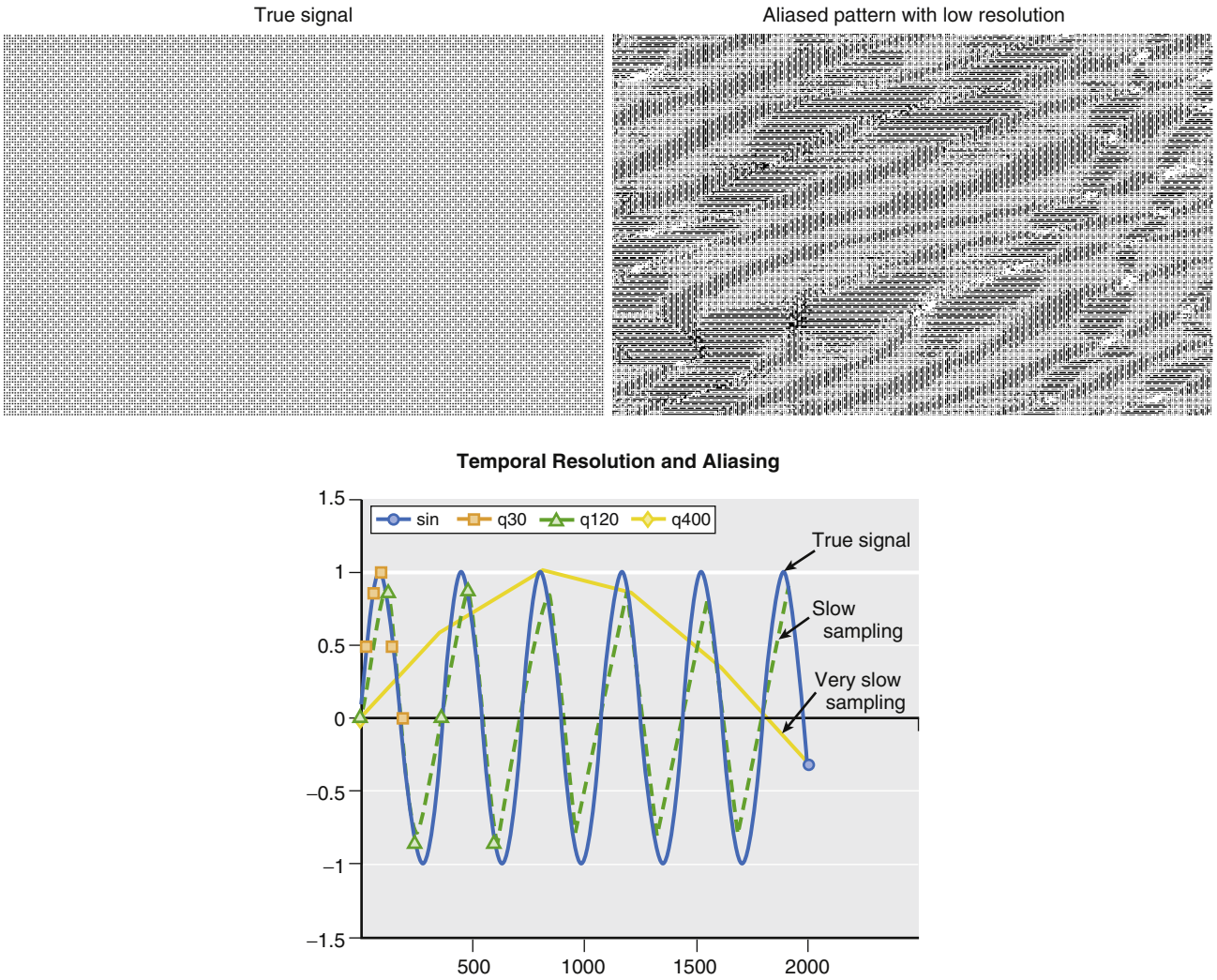


Figure 44-11. Aliasing and resolution. Spatial: Too low of a resolution results in a complete loss of information or spatial aliasing. Temporal: Improper sampling leads to an erroneous waveform. A slower sampling rate results in a change in the amplitude and wavelength.

Because these large numbers are rather awkward, P is often expressed in kilopascals (kPa) and z in mm Hg:

$$P\,(\text{kPa}) = 0.1333z\ (\text{mm Hg})$$

A useful reference for the various pressure units in use today is the pressure of the earth's atmosphere at sea level, called *one atmosphere* or 1 atm:

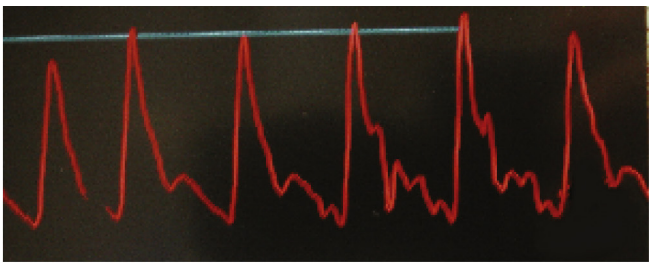
$$\begin{aligned} 1\ \text{atm} &= 101.3\ \text{kPa} \\ &= 760\ \text{mm Hg} = 29.92\ \text{inches-Hg} \\ &= 14.7\ \text{psi} \\ &= 988\ \text{cm}\ H_2O \end{aligned}$$

If a fluid-filled catheter is connected to the circulatory system of a patient, then the height of the fluid in the manometer determines the mean pressure at the tip of the catheter. If the pressure measured is CVP, then these data can be used to infer right ventricular preload. For slowly changing pressures, a water or mercury manometer is simple and dependable (see Fig. 44-4). The manometer cannot quickly respond to rapid changes in pressure because of its inertia; that is, the mass of the liquid column resists rapid changes in height.

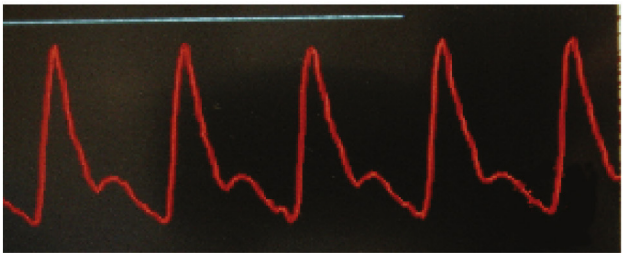
Dynamic Pressure Measurement (Transducer)

Accurate measurement of a rapidly changing pressure signal, such as arterial blood pressure, is more difficult and complex. Many characteristics of the arterial pressure–versus-time waveform (Fig. 44-13) might need to be determined. Systolic, diastolic, and mean arterial pressure is given by the maximum, minimum, and average pressure values during the cardiac cycle. In addition, the maximum upward slope of the waveform during systole, which is related to the speed of ventricular ejection, can be measured. An abnormally rapid downslope after aortic valve closure (indicated by the dicrotic notch) suggests possible aortic insufficiency. Thus the details of the pressure-time waveform, as well as its maxima and minima, are important to the clinician. Despite the display of the waveform on a vertical axis, remembering that the arterial pressure is not a transverse wave (such as a wave on the ocean) but a longitudinal wave (such as a sound wave or a pulse transmitted through a coiled spring) is important (Fig. 44-14).

A modern pressure transducer is a device that changes either electrical resistance or capacitance in response to



A



B

Figure 44-12. Arterial waveform resonance. **A,** A peaked arterial waveform indicates some resonance with an overestimation of the systolic blood pressure. **B,** The same patient is depicted when damping is added to the system.

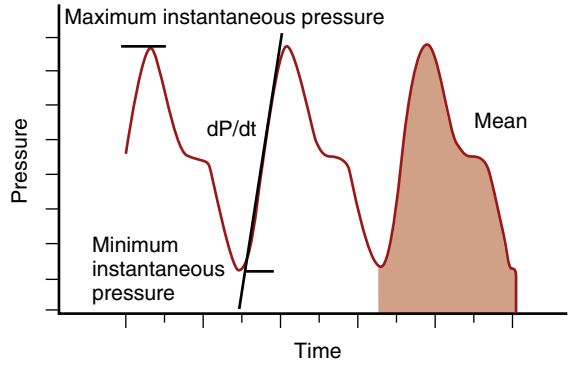


Figure 44-13. Arterial waveform. Systolic pressure is defined as the instantaneous maximal pressure; diastolic pressure is defined as the instantaneous minimum pressure; and the mean pressure is defined as the average pressure over a cycle. dP/dT refers to the upstroke of the arterial pressure (i.e., the rate of pressure generation). The mean pressure is estimated as the diastolic plus ⅓ the pulse pressure (systolic–diastolic) when only the systolic and diastolic pressures are known.

changes in pressure on a solid-state device. The variable transducer electrical resistance is placed in a circuit involving three known resistances—Wheatstone bridge (see Fig. 44-5 and Appendix 44-3)—and the change in resistance is thereby converted into electrical voltage. The moving part of the transducer, itself, is small and has little mass. This system of a fluctuating driving pressure (i.e., the arterial pressure being measured), a liquid-filled tube, and a pressure transducer is mechanically equivalent to the mass-spring harmonic oscillator (Fig. 44-15). The mass (m) represents the mass of the fluid in the tubing. The spring represents the elasticity of the tubing and transducer. The damper, shown

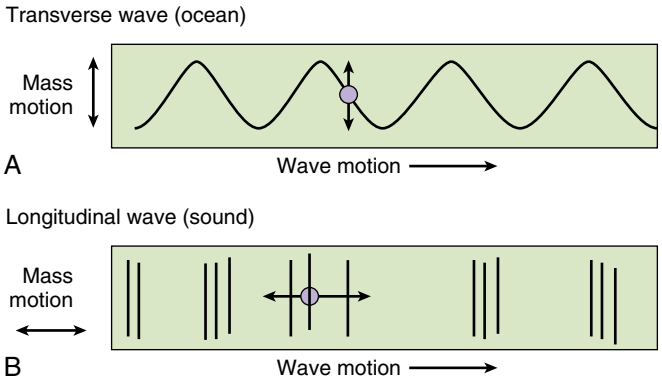


Figure 44-14. Transverse and longitudinal waves. **A,** In transverse waves (e.g., ocean waves), the particles move perpendicular to the motion of the wave. **B,** In longitudinal waves (e.g., sound waves), the particles move back and forth in the direction of the wave. The actual matter in either wave does not move much. The energy transfers without mass transfer. In arterial systems, this illustration clarifies the fact that energy transfer (blood pressure) does not mass transfer (blood flow).

schematically as a piston moving in oil, represents the friction generated by the fluid moving to and fro in the tubing.

A more commonly encountered harmonic oscillator is that of a car driving down a bumpy dirt road (see Fig. 44-15). In this case, the bumps in the road provide the oscillating driving pressure, which forces the car wheels to oscillate up and down. The car springs are analogous to the compliance of the arterial pressure tubing, and the car's shock absorbers, which oppose motion of the wheel in either direction, are analogous to the friction of the fluid moving back and forth in the fluid-filled tube. Depending on the frequency of the bumps (i.e., driving pressure frequency), the system can either suppress the bumpy road or may initiate dramatically increased oscillations. The frequency of the driving force that causes maximal amplification of the signal is called the *natural* or *resonant frequency* (Fig. 44-16). The degree of amplification is directly related to the mass and inversely related to the amount of friction present; for large amounts of friction, attenuation rather than amplification occurs (see Appendix 44-4).

To visualize this concept intuitively, hang a weight on the end of a rubber band while holding the upper end of the band in your hand. If you move your hand up and down slowly, the weight follows your hand movements almost exactly. As you increase the frequency of your hand oscillations, the weight begins to lag behind your hand, and the amplitude of the weight movement begins to increase. As you approach the natural frequency of this simple system, you will observe the phenomenon of *resonance* when the amplitude of the weight motion becomes extremely large. If you try different rubber bands and weights, you will find that stiffer bands or smaller weights yield higher natural frequencies. The same is true of our fluid-coupled pressure transducer system. Stiffer (i.e., less compliant) tubing or a shorter length of tubing (less mass) produces higher natural frequencies in this system; that is, it requires a much higher pulse rate before amplification.

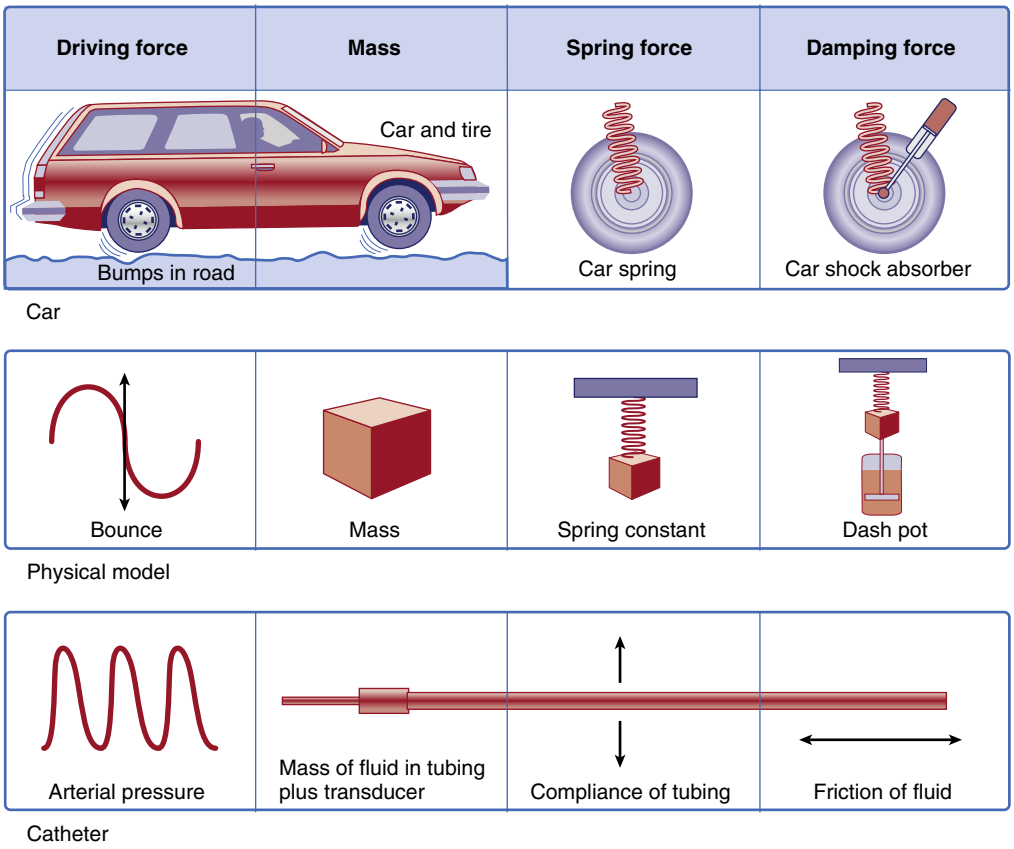


Figure 44-15. Damping and resonance. Pressure measured in an invasive arterial catheter can actually overshoot or amplify the real blood pressure. This phenomenon is referred to as the *dynamic frequency response* of the fluid-filled arterial line and transducer system. This phenomenon has a physical model, which can generate an equation to predict the output pressure response, depending on the frequency of the input pressure and several physical parameters of the system. In the physical model *(middle row)*, the driving pressure (i.e., the arterial blood pressure) acts on a mass (i.e., the fluid within the arterial pressure tubing), pushing it up and down against a spring, which stores energy (i.e., the compliant pressure tubing), and a dash pot, which opposes motion in either direction (i.e., the resistance of the fluid as it moves to and fro within the pressure tubing). Depending on the input frequency, the output may go through an amplification as it reaches a specific frequency, known as the *resonant frequency* of the system. In the *top row*, a common phenomenon is noted when a car drives along a bumpy dirt road. In this situation, the driving forces are the bumps in the road, which act on the tire. The car spring is equivalent to the compliance of the pressure tubing, and the shock absorber corresponds to the resistance of fluid moving back and forth in the arterial line. The mass of the fluid is analogous to the mass of the front of the car. You may have experienced the phenomenon in which you reach a certain speed as you are driving along a bumpy road when the front of the car starts to oscillate with increasing amplitude. If you speed up or slow down, then this phenomenon disappears. The car bounces highest when you have reached the resonant frequency of this harmonic oscillator (see Appendix 44-4 for detailed mathematical description of this process).

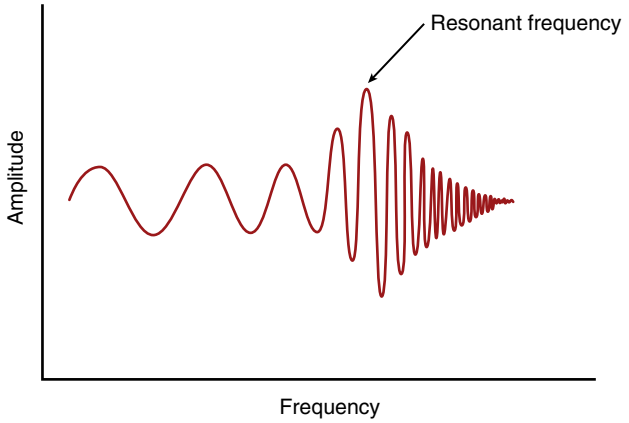


Figure 44-16. Amplitude and frequency. As the frequency increases, the amplification can increase to a maximum, and then the signal becomes attenuated. *(Modified from Sykes MK, Vickers MD, Hull CJ:* Principles of measurement and monitoring in anesthesia and intensive care, *ed 3. Oxford, 1991, Blackwell.)*

To minimize the potential of amplification of the real arterial pressure, the system should have noncompliant (i.e., stiff) tubing, and the total mass of liquid in the system should also be minimized, which can be accomplished by having small-diameter tubing and as short a length as possible. In most clinical systems, the natural resonant frequency is 10 to 15 Hz, which is significantly higher than the primary frequency of the arterial waveform (the heart rate is 60 to 120 bpm or 1 to 2 Hz). However, the arterial waveform is not a sine wave; rather, it is a more complex shape (see Figure 44-10) and made up of a summation of sine waves of frequencies that are various multiples of the heart rates—a Fourier series. The higher frequency components of the arterial waveform (higher harmonics) are those that are closer to the natural frequency of the system and are therefore amplified. This is why a *whip* is seen in the waveform when the peak systolic pressure and the initial upstroke are significantly amplified above the true systolic pressure,

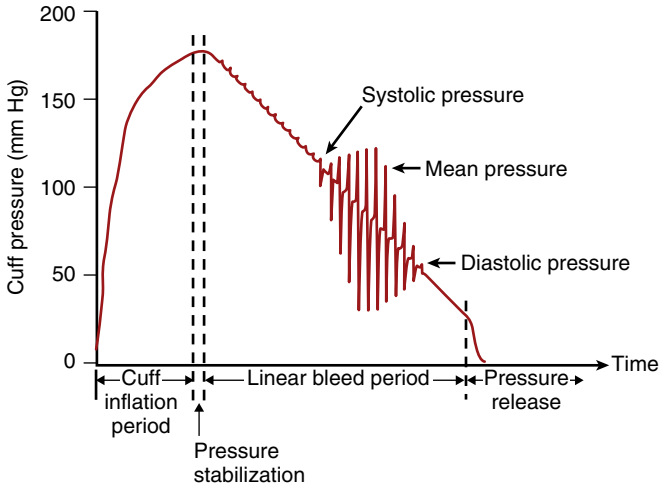


Figure 44-17. Noninvasive blood pressure measurement. Using the signal from the arterial pulse, oscillometric blood pressure measurements are obtained by determining the point at which the signal is first detected, its maximal amplitude, and the signal decay rate. *(Modified from Ehrenwerth J, Eisenkraft J:* Anesthesia equipment: principles and applications*, St Louis, 1993, Mosby.)*

although the heart rate, itself, is not near the resonant frequency. In theory, mean arterial pressure should be the same because this amplification of systolic pressure also produces a reduction in diastolic pressure (see Appendix 44-4).

Signal-Processed Pressure Measurement (Noninvasive Blood Pressure Monitor)

Systolic pressure can be estimated by noting the return of the flow pulse after occlusion of the brachial artery by a cuff. The return of flow can be detected by (1) simple palpation of the radial artery, (2) recording with a Doppler device over the radial artery, or (3) the use of a pulse oximeter. Most anesthesiologists are familiar with the loss of pulse oximeter signal when the noninvasive blood pressure monitor is cycling.

The automated noninvasive blood pressure monitoring devices in surgical units use a more sophisticated application of this principle. These devices monitor the oscillating signal generated in the cuff by the arterial pressure changes. The cuff first inflates to above systolic pressure, at which point the signal and oscillations are abolished. Then the cuff slowly deflates in a stepwise fashion. The pressure at which the oscillating pressure signal first appears is interpreted as the systolic pressure. The signal increases in amplitude as the cuff pressure decreases. The point at which the signal is at maximal amplitude is interpreted as mean arterial pressure. As cuff pressure decreases further, the oscillations rapidly drop off. Diastolic pressure is mathematically inferred from the systolic and mean values (Fig. 44-17).[7] Errors can be introduced in the same manner as for manual auscultation of Korotkoff sounds; too small or too large a cuff requires a higher or a lower pressure, respectively, to occlude arterial flow, and stiff atherosclerotic arteries are resistant to compression. External compression caused by patient motion or the surgeon leaning on the blood pressure cuff can cause pressure oscillations that are not related to arterial pressure and may result in an erroneous reading, most commonly a higher diastolic pressure.

Mercury sphygmomanometers are being phased out of use in most countries and hospitals, which leads to questions regarding the accuracy and precision of alternative devices such as the aforementioned automated noninvasive blood pressure monitors and aneroid sphygmomanometers.

MEASUREMENTS USING SOUND ENERGY (LONGITUDINAL PRESSURE WAVE)

Principles of Sound

Sound waves are small fluctuations in pressure, density, and velocity that can propagate through matter of any form—solid, liquid, or gas (see Fig. 44-14). Unlike electromagnetic waves such as light (see "Measurement Using Light Energy" later in this chapter), sound cannot propagate in a vacuum. The commonly used unit of sound, the decibel (dB), is not an SI unit but a logarithmic ratio of the sound energy referenced to 20 microPascals (μPa) (or 0.0002 millibar), the threshold of normal human hearing.

Sound has been used for many years in medical diagnosis and monitoring. It can be used as a diagnostic method in two ways: passive and active. In a passive examination, the sounds generated by the patient are studied. The basic examination of this type of examination uses the stethoscope. In an active examination, acoustic energy is transmitted into the patient, and the resulting interaction of this energy with the patient is analyzed for information. Both types of examination use the same physical principles.

In 1842, Christian Johann Doppler first described the apparent change in pitch of a sound that occurs when either the source of the sound or the listener is moving. This Doppler effect now has several applications in patient monitoring, including precordial and esophageal Doppler ultrasound monitoring of local blood velocities or cardiac output.

When a sound source is moving toward the listener, the apparent pitch increases, and vice versa. The exact amount of frequency shift depends on whether the listener or the sound source is moving (Fig. 44-18) (see Appendix 44-7). Because changes in the frequency of sine waves can be precisely measured, the Doppler principle provides an accurate method of measuring the velocities of moving sound reflectors. At the high frequencies often used (>5 MHz), objects as small as red corpuscles can scatter enough sound for detection.

PASSIVE SOUND EXAMINATION (STETHOSCOPE)

Vibrations, such as those caused by the closing and opening of heart valves or air moving through the respiratory passages, travel through the body as sound waves. Sound is better and more rapidly conducted in liquids than in gases. Thus bronchial breath sounds are better heard when the bronchi are surrounded by lung consolidation. When sound waves reach a sudden change in density,

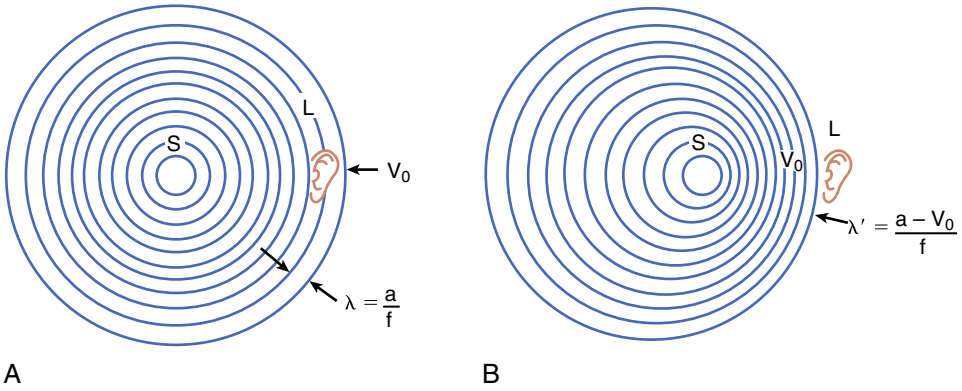


Figure 44-18. Doppler effect. **A,** When a listener is moving toward a stationary sound source, the frequency increases because the listener transverses more waves per unit time than a stationary listener. **B,** When a sound source is moving toward a stationary listener, the wavefronts "stack up," causing an apparent increased frequency.

for example a liquid-gas interface, some of the energy is reflected.

Some simple facts about sound waves can facilitate an understanding of the reflection and scattering process in the body. First, all sound waves can be represented as a summation of sinusoidal waves of various frequencies and amplitudes. (The process of Fourier or power spectral analysis is discussed earlier in this chapter.) A note from a musical instrument thus consists of a sine wave at the fundamental frequency plus many harmonics at multiples of this frequency. The fundamental frequency describes the pitch of the tone—middle C is standardized at 256 Hz, for example.

Fortunately for our ears, all of these many frequencies propagate at the same speed, the speed of sound, called *a*. For ideal gases, the speed of sound is proportional to the square root of temperature. The speed of sound in air at room temperature is 344 m/sec, or 1129 feet per second (ft/sec), or 770 miles per hour (mph). At an altitude of 13,000 m (40,000 ft), where the standard air temperature is –57° C, the speed of sound is only 295 m/sec or 661 mph. The speed of sound is significantly faster in liquids than it is in gases. For example, the speed of sound through water at 15° C is 1450 m/sec. This value also approximates the speed of sound through most of the solid parts of the human body. In other solids, the speed of sound greatly varies, with a range of 54 m/sec in rubber to 6000 m/sec in granite. Reflection of sound occurs at interfaces where the product of the density and the speed of sound ($\rho \times a$) suddenly changes. Larger changes in this acoustic impedance result in greater reflection and less transmission. In the human body, the largest changes in acoustic impedance occur at gas-tissue boundaries: the lungs and the gastrointestinal tract. Reflection of sound by the lungs thus makes it difficult to auscultate heart tones through an air-filled, emphysematous chest. For the same reason, a transthoracic echocardiograph provides less detail than the transesophageal technique; in the former case, the lungs are in the way.

The first attempts to gather information about the inside of the patient by using sound involved placing one's ear directly on the patient. Although this procedure had many limitations, it led to the development of the modern stethoscope, which is based on the physical principles of sound transmission. The stethoscope uses a large diaphragm to transmit and concentrate the sound energy. The bell acts as both an amplifier and a low-pass filter to transmit low-frequency diastolic rumbles. Rappaport and Sprague describe the physics of stethoscopy in depth.[8]

In a simple stethoscopic examination, errors are introduced by signal processing; that is, a lack of experience or appropriate knowledge on the part of the listener. Because it is a nonpowered, nontechnologic device (the energy levels come from the phenomena themselves), an esophageal or precordial stethoscope has unique value in being a continuous monitor during power outages. Physical limits to the technique include air space disease (in itself an informational finding), an inability to place the monitor appropriately, and a lack of quantifiable data.

Active Sound Examination (Percussion, Echo, Doppler)

The earliest active acoustic diagnostic technique was percussion of the chest wall. A skilled clinician can use this method to detect consolidation of the lungs, pleural effusion, and a few other chest pathologic conditions. Although based on transmission and the reflection of sound, percussion is purely qualitative and is unable to localize pathologic changes accurately. Modern ultrasound improves on percussion by using shorter-wavelength sound waves and quantitative detection of their reflections (echoes). The wavelength of the sound used limits the spatial resolution of an examination (see Fig. 44-11). Using ultrasound at frequencies in the megahertz (MHz) range (10^6 cycles/sec) allows resolution of much smaller objects. The wavelength of 1-MHz sound waves in solid tissue is approximately 1.5 mm, whereas the wavelength of a 256-Hz tone (middle C) in tissue is 5.7 m.

With the use of esophageal transducers, echocardiography has become a popular intraoperative monitoring technique. Sound waves in the 2- to 10-MHz range are transmitted toward the heart in short bursts or pulses. After each pulse, the transducer passively listens to the reflected echoes from various tissues. The ability to place the transducer in the esophagus is advantageous because sound does not then have to pass through air spaces or bone on its way to and from the heart. The speed of sound through the heart and surrounding soft tissues is a nearly constant 1540 m/sec. Thus the exact measurement of the elapsed time between transmission of the pulse and receipt of the echo provides the distance to the reflecting structure. The sound beam from the transducer

is projected in a narrow searchlight pattern; therefore the exact direction of reflecting structures is also known.

The Doppler effect is used in echocardiography to determine the presence and degree of valvular regurgitation by converting the Doppler shift of sound waves reflected from erythrocytes into a color display (see Appendix 44-7). Cardiac output can also be estimated from descending thoracic aortic blood velocity by using a Doppler technique. These devices estimate the blood flow in the descending aorta and ignore flow to the head and arms. They calibrate descending aortic flow to cardiac output by assuming a constant proportional relationship between the two flows.[9]

MEASUREMENTS USING ELECTRICAL ENERGY (TRANSVERSE WAVE)

Principles of Electricity

Most of our monitors and other anesthesiology apparatuses use the basic principles of electricity and magnetism. Nearly all transducers use some form of electrical energy as their output, and the subsequent data processing and display are entirely electrical. Some basic electromagnetic principles are reviewed in this section using examples from medical equipment. Electromagnetic waves, including light, are transverse waves, meaning that the electric and magnetic field vectors are oriented perpendicular to the direction of wave propagation. Unlike sound, these waves require no media in which to propagate.

Static Electricity

Electricity is a manifestation of a property called *charge* that is inherent in matter. The charge can be negative, positive, or neutral. Static electricity involves charges at rest; like charges repel one another, whereas opposite charges attract. Usually the meaning of the word *electricity* involves the flow of charges, or electrical current. Current flows in one direction in direct current (DC) electronic devices and alternates back and forth in alternating current (AC) devices.

The *coulomb* is the SI unit of charge , and the charge of an electron is the smallest quantum of charge (1.6×10^{-19} coulomb), which is equal but opposite to the charge of a proton. (Recently discovered subatomic particles called *quarks* actually have smaller charges, but this is beyond the scope of this chapter and not particularly relevant to medicine.) An electrostatic force is exerted between two charged objects and is directly proportional to the product of the two charges and inversely proportional to the square of the distance between them (Coulomb's law):

$$F = k \times q_1 \times q_2 / r^2 \quad (1)$$

This force is attractive when the charges are of opposite sign and repulsive when they are of the same sign. In a Nobel Prize–winning experiment, Robert Millikan determined the charge of an electron by suspending charged oil drops between two horizontal charged plates such that the electrostatic force balanced the gravitational force and the drops were held in midair (Fig. 44-19). Approximately 20 years later in 1940, his son, Glen Allen Millikan, developed one of the earliest infrared ear oximeters, the forerunner of the pulse oximeter (see "Processed Absorbance Monitors" on the pulse oximeter).

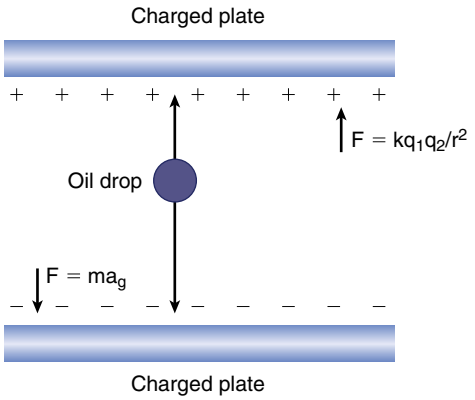


Figure 44-19. Electric force. The quantity of charge on an electron is determined by balancing the electric force on an oil drop against the gravitational force on the same drop. $F_1 = kq_1\, q_2 / r^2 = F_2 = m_1\, a_g$.

Direct Current

Just as mechanical energy may be stored as potential energy, electrical energy can be stored as a *potential difference*. A common analogy is to compare electrical potential difference with water pressure (Fig. 44-20 and Table 44-2). The potential difference between points A and B is defined as the work required to move a unit charge from A to B. The SI unit of potential difference is the volt (V); hence, the term *voltage* is often used for potential difference. Charges can easily move through conductors, but they do not move well through insulators, also called *dielectrics*. If a potential difference (V) exists between A and B and a conductor connects these two points, then charges will flow between them and produce an electrical current (I).

The SI unit of current is the coulomb per second, called the *ampere*. If an insulator separates points A and B, then no current will flow until the potential difference becomes so great that a breakdown of the insulator occurs. For example, if dry air separates A and B, then no current will flow until the potential difference reaches 3000 V/mm. At this very large potential gradient, air will ionize and become a conductor, and a current flows in the form of a visible (and audible) spark. To generate a spark between two electrodes 1 cm apart, a potential difference of 30,000 V must be created. The spark plugs in an automobile have an electrode gap of approximately 0.8 mm, thus requiring at least 2400 V from the ignition coil to generate a spark. Lightning is a larger manifestation of the same phenomenon.

A battery is a chemical cell that produces a nearly constant potential difference between two electrodes, which is called *electromotive force* (EMF). The battery can provide a continuous source of electrons, or current, to flow through any conducting circuit connected between its electrodes. Flow of electricity is opposed by resistance, analogous to resistance in water pipes. In most materials, resistance (R) is related to voltage (V) and current flow (I) in the following manner:

$$V = IR \quad (2)$$

This relationship is called Ohm's law, and the materials that follow this behavior are called *ohmic materials*.

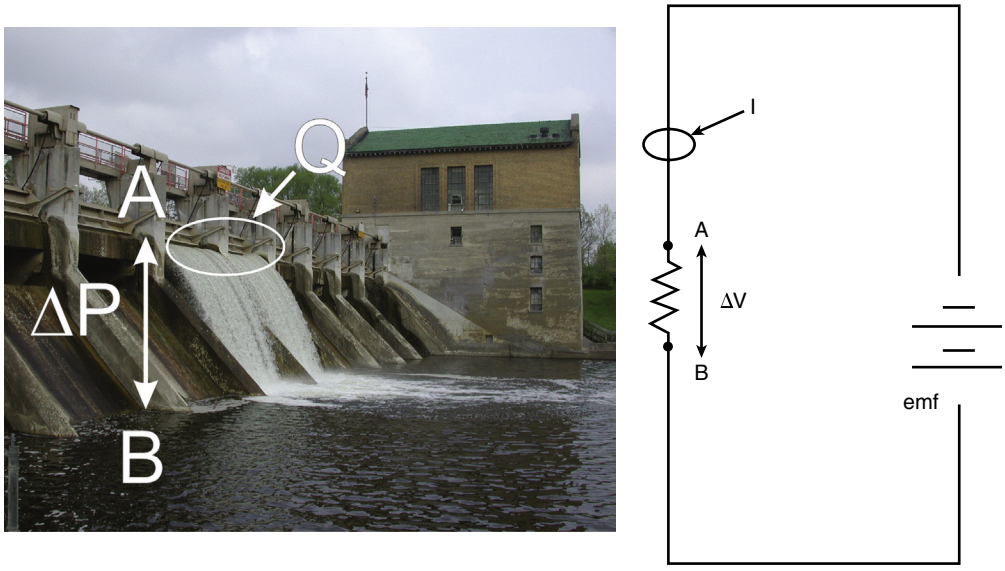


Figure 44-20. Water and electricity. The pressure drop over the dam (A to B) is analogous to the voltage drop over the resistance (A to B) (e.g., light bulb). The amount of flow (width of water) (Q) is analogous to the current (I). Both falling water and electrical potential can do work, as evidenced by the use of dams to generate electricity and electricity to pump water.

TABLE 44-2 **COMPARISON OF HYDRODYNAMIC AND ELECTRICAL ENERGY COMMONLY ENCOUNTERED**

Water	Electricity	Energy
Squirt gun	Static electric spark	High pressure, low flow, low energy
Garden hose	House current	Moderate pressure, moderate flow, moderate energy
	Car battery	Low pressure, moderate flow, moderate energy
River flood		Low pressure, huge flow, huge energy
Fire hose	High tension wires	High pressure, high flows
	Lightning	High pressure, high flow

This example is analogous to hemodynamic flow, in which the pressure drops across the systemic vasculature (mean arterial pressure – central venous pressure) (ΔP) equals cardiac output (CO) times systemic vascular resistance (SVR):

$$\Delta P = CO \times SVR \quad (3)$$

The power (i.e., rate of work) required to produce an electric current is the product of voltage and current: P = VI. By combining this formula with Ohm's law (V = IR), $P = I^2R = V^2/R$ is the result. Thus if the current is doubled through a fixed resistance (R), then four times the original power is used. This power loss in resistors is dissipated as heat, which is the reason why nearly all electrical devices become warm during use. The filament in an incandescent light bulb is merely a resistor that becomes so hot from ohmic heating that it glows or radiates light.

A capacitor is a device that stores charge (Q) in direct proportion to the potential difference (V) between its two electrodes: Q = CV. The proportionality constant (C) is called *capacitance*, which is measured in SI units of farads (1 farad = 1 coulomb/volt). When a capacitor is connected to a battery, current flows until the capacitor is charged to the point that the potential across the capacitor equals the EMF of the battery: V = Q/C = EMF (Fig. 44-21). When the charge button of a cardiac defibrillator is pushed, this kind of circuit is activated to charge a capacitor to the desired level. As shown in Figure 44-21, *B*, time is required to charge a capacitor. For a large capacitor, more time is required. Hence, it takes longer to charge a defibrillator to 200 J than to 50 J.

Alternating Current

In an AC circuit, the current and the voltage rapidly fluctuate (Fig. 44-22). Many important differences exist between AC and DC power. The voltage in common AC house power fluctuates sinusoidally at a frequency of 60 Hz (50 Hz in Europe). The amplitude of such a fluctuating voltage is characterized by its root mean square (RMS); that is, the square root of the time average of V^2. Thus for AC house power, V_{RMS} = 115 V (230 V in Europe). Current in an AC system is also constantly changing and is likewise measured as an RMS value.

AC circuits have three forms of impedance: resistance (R), capacitance (C), and inductance (L). An inductor is a circuit element whose impedance, called *inductive reactance*, increases with the frequency (f) of the current fluctuations ($R_L = 2\pi fL$). Conversely, the impedance of a capacitor, called *capacitive reactance*, decreases with increasing frequency ($R_C = {}^1/_{2\pi fC}$). Inductors thus tend to block high frequencies, whereas capacitors tend to block low frequencies (Fig. 44-23). This principle is used in stereo systems to direct the signal to either the woofer (low-frequency speaker) or the tweeter (high-frequency speaker). In medical instruments, inductance and capacitance circuits can be used to filter the signal, for example, decreasing the amount of 60-Hz interference from AC wiring.

Passive Electrical Examination (Electrocardiograph, Electroencephalograph)

With the basics of electricity discussed, the electrocardiograph (ECG) and the electroencephalograph (EEG)

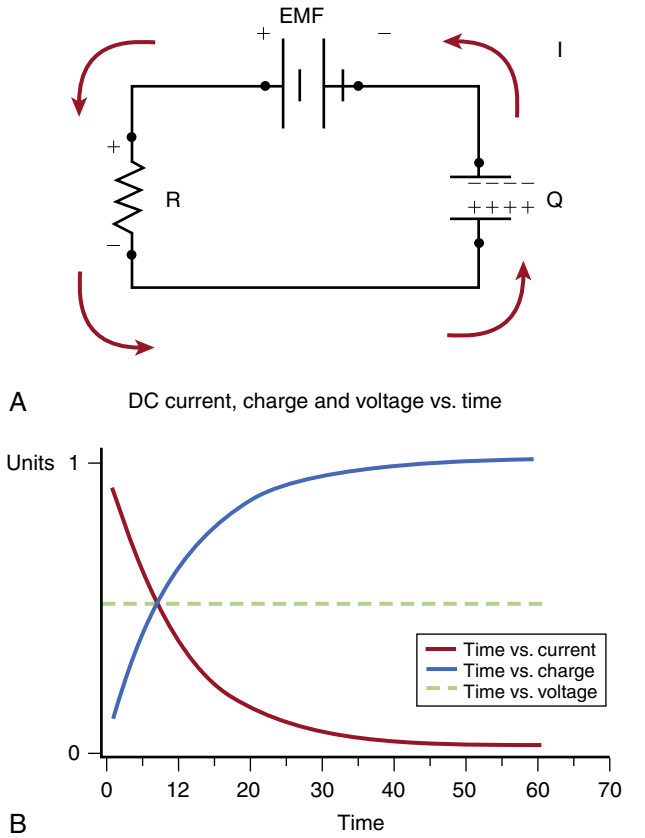


Figure 44-21. Resistance and capacitance in a direct current (DC) circuit. **A,** Under DC, the resistance impedes flow, developing a voltage drop across the resistance. The capacitor allows current to flow until the charge builds on the capacitor. **B,** Under DC, the voltage is constant over time, and the current flow decreases as the charge on the capacitor increases. This type of circuit is used to charge a defibrillator.

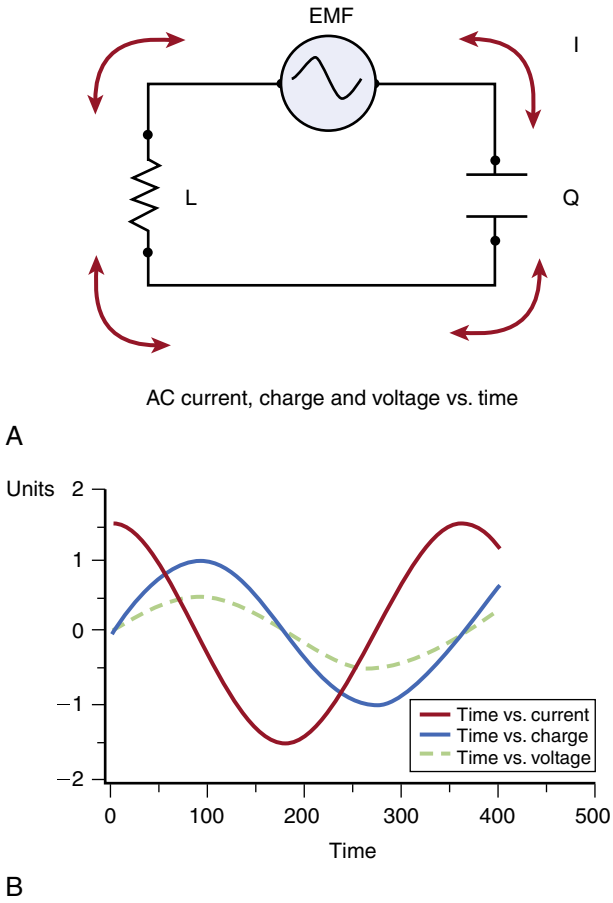


Figure 44-22. Resistance and capacitance in an alternating current (AC) circuit. **A,** In an AC circuit, unlike a DC circuit, the capacitor does not block current flow. **B,** The capacitor and resistance act to shift the phase of the AC current. Current changes lag behind voltage changes. *EMF,* Electromotive force.

are described, where the sources of the EMF are the heart and the brain, respectively (see also Chapters 47 and 49). Electrical potentials on biologic surfaces are too small to observe directly and must be amplified and processed before displaying. ECG potentials on the skin are in the 1-mV range, and EEG potentials are near 0.1 mV.

Figure 44-24 illustrates why electrical potentials on biologic surfaces are so small. The heart generates an electrical signal as a result of the synchronous depolarization and repolarization of multiple cells. The electrical potentials generated by the heart are measured between two skin electrodes, A and B. As this figure shows, multiple effective resistances and capacitances exist in the tissues between the EMF source and the measuring electrodes. These impedances lower the magnitude of the voltage signal at the skin. The shunt resistors R_3, R_4, and R_5, combined with the series resistors R_1, R_2, and R_3, form what is called a *voltage divider network*. Lower values of shunt resistance or higher values of series resistance result in smaller voltages at the skin. The capacitance of the skin (C_s) also acts to attenuate the low-frequency components and distort the waveform. Skin resistance, which may be a megaohm (10^6 ohms) for dry skin, can be reduced to a few hundred ohms by conductive gels.

If a DC voltage is applied between two body surface electrodes, then current flows through the tissues between them. Although the electrical current in metals consists entirely of electron flow, both positive and negative ions migrate in tissues. Negative ions tend to accumulate at the positive electrode (the anode), and positive ions accumulate at the negative electrode (the cathode). This collection of anions and cations near each electrode creates its own EMF, which opposes the EMF that set up the original current. The current therefore decreases and the effective impedance between the electrodes increases. This phenomenon, *called polarization of electrodes*, has two harmful effects. First, the increased impedance from polarization can attenuate the ECG signal for several seconds after defibrillation or DC cardioversion. Such attenuation could be misinterpreted as a lack of electrical activity and result in inappropriate administration of a second shock. The second consequence of prolonged application of DC voltage is the accumulation of a local concentration of toxic ions near electrode sites, a condition that can cause burns or tissue necrosis. A partial solution to the problem is the use of a nonpolarizable electrode, such as a silver and silver chloride combination. This electrode can act as a source of or *sink* for both anions and cations, thereby

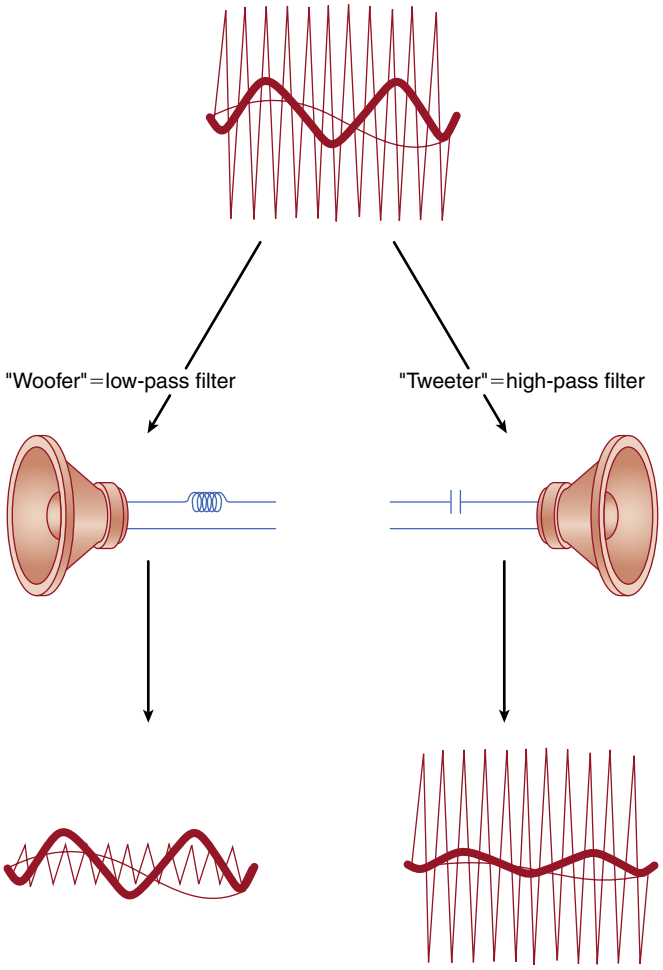


Figure 44-23. Woofer and tweeter. Stereo speakers use resistors to act as an impedance to high-frequency components of sound, allowing only the bass frequencies to pass to the woofer speaker. Capacitors are used as a high-pass filter to allow only the high frequencies to get to the tweeter speaker. A similar process can decrease 60-Hz interference from electrical appliances. *(From Hecht E:* Physics: algebra/trig. *Pacific Grove, Calif, 1994, Brooks/Cole.)*

minimizing the accumulation of ions. Most disposable ECG electrodes now use such materials. Even these electrodes, however, are nonpolarizable for only a limited time, and the application of prolonged DC voltage between any tissue electrodes must be avoided.

Similar problems complicate the measurements of the EEG; but in this case, the raw signal is one tenth the amplitude of the ECG: 100 μV versus 1 mV. The spontaneous EEG provides eight or more channels of surface voltage versus time data, which is of limited use for monitoring in the surgical unit. For rapid interpretation and diagnosis, the amplitude versus time data are usually transformed into plots of amplitude (or power) versus frequency. (This process of power spectral analysis is discussed in "Data Processing" earlier in this chapter.) The EEG power spectrum facilitates rapid diagnosis of hemisphere asymmetries and changes in frequency content that accompany either deep anesthesia or cerebral hypoxia. *Bispectral density* is another method of analyzing the raw EEG that determines the levels of correlation (or degree of phase-locking) between

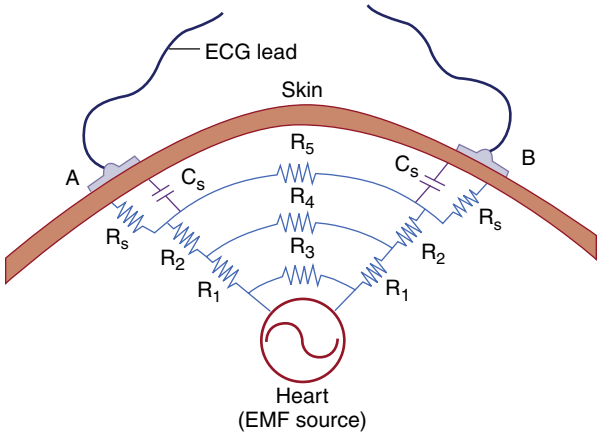


Figure 44-24. Why the electrocardiograph (ECG) is so small. Multiple resistances and capacitances in the body decrease the potential and distort the waveform before the electromotive force (EMF) reaches the surface.

various frequency components in the power spectrum. Yet another derived parameter is the *burst-suppression ratio*, which is the percentage of time during which the EEG amplitude is less than +5 microvolt (μV). Both of these last two derived quantities have been related to the depth of anesthesia in clinical studies (see Chapter 49 for a discussion on EEG monitoring).

Active Electrical Examination (Neuromuscular Block Monitor, Somatosensory Evoked Potentials)

A muscle twitch can be elicited by generating a 0.2- to 0.3-msec pulse of current to depolarize a peripheral motor nerve. This motor nerve then conducts the impulse to the muscle, where a twitch is generated. We can understand the in-use failings of this device by following the path of the signal. Clearly, we must start with an adequate power source (no power = no twitch). If the coupling of the electrodes to the patient is poor, that is, if the electrodes are dry or good skin contact is not made, then the circuit will have high resistance and little current will flow (see earlier discussion on direct current and equation 2), resulting in a diminished twitch. In summary, the simplest way to be certain that this monitor is properly functioning is to perform both a positive control (see the desired response of the thumb twitch before the chosen drug is administered) and a negative control (see the twitch disappear in response to administered drug) (see Chapters 49 and 53).

Evoked-potential (evoked-response) monitors can determine the status of multiple parts of the sensory nervous system by measuring the central nervous system response to a discrete sensory stimulus. The stimulus can be auditory, optical, or peripheral somatosensory. The amplitude of the evoked response measured at the skin can be small—less than 1 μV in the case of acoustic cortical potentials. This small signal is in a sea of spontaneous EEG signals (greater than 100-μV amplitude). We therefore resort to a signal enhancement technique called *ensemble averaging*. Rather than trying to measure the small response to a single stimulus, we average the responses from hundreds (or thousands) of stimuli.

Because we seek the evoked responses that consistently occur at the same time after the known stimulus, this averaging process reinforces the signal from the evoked response, and the random noise tends to cancel itself. In this way, we commonly measure signals whose amplitude is approximately 1% the amplitude of the background noise (see Fig. 44-9).

Whenever charged particles are moving, a magnetic field is generated in a direction perpendicular to the motion. *Paramagnetism* is a form of magnetism exhibited only in specific substances in the presence of an external magnetic field. Oxygen is a paramagnetic gas. This property is used to measure both inspired and expired oxygen concentrations; chemical methods similar to fuel cell amperometric sensors and polarographic electrodes are too slow to respond. In a fast-responding paramagnetic oxygen sensor, 100% oxygen can exert a pressure of 3 Pa in a 2.4 tesla magnetic field.

MEASUREMENT USING LIGHT ENERGY

PRINCIPLES OF LIGHT

What we commonly refer to as *light* is electromagnetic radiation in the visible range of wavelengths. Every substance with a temperature above absolute zero emits electromagnetic radiation, called *black body radiation*. This radiation is characterized by a frequency and wavelength that are related by the speed of light: frequency = speed of light ÷ wave length (c = speed of light = 3×10^8 m/sec or 186,400 miles/sec or 7.5 times around the earth's circumference in 1 second in a vacuum). High energies or temperatures are associated with high frequencies and short wavelengths, such as those of gamma rays and x-rays. As wavelength increases to the micron range, ultraviolet radiation proceeds to visible light (approximately 0.5 to 0.8 micron), and at larger wavelengths, infrared is then followed by microwaves and radio waves with wavelengths in the kilometer range.

Electromagnetic waves and sound waves have some important differences. The particles in motion in sound waves are in the same direction as the propagation (longitudinal waves), whereas in electromagnetic waves, the electric and magnetic fields are perpendicular to the direction of propagation (transverse waves). Sound waves can propagate only through matter, whereas electromagnetic waves propagate through a vacuum without attenuation. The speed of light is approximately 1 million times faster than the speed of sound in sea-level air. If an observer is moving relative to a sound source, then the measurement of the speed of sound depends on the observer's own motion, but the speed of light is the same to any observer in any frame of reference. This last statement is the basic premise of Einstein's "Special Theory of Relativity." In the high-frequency range of the electromagnetic spectrum, two forms of ionizing radiation are found: x-rays and gamma rays. These high-frequency waves are capable of knocking electrons out of their orbits and can thereby cause cell injury and death or ontogenesis. Gamma rays are commonly emitted by decaying radioactive nuclei.

Visible light and infrared light demonstrate several properties common to all electromagnetic radiation. Light represents a form of energy that, when passing through matter, may be reflected, transmitted, or absorbed. Although light itself cannot be stored, it can be converted into some other form of energy such as electricity, chemical energy, and heat. In addition, light can be generated from other forms of energy, including heat (incandescent), electrical (gas discharge), and chemical (photoluminescent) energy.

LIGHT AS A MULTIFUNCTIONAL TOOL: THE BEER-LAMBERT LAW

When light passes through matter, it is transmitted, absorbed, or reflected. The relative absorption or reflection of light at different wavelengths is used in several monitoring devices to estimate the concentrations of dissolved substances, for example, carbon dioxide (CO_2) in respiratory gas and Hb in plasma. This type of measurement is called *spectrophotometry* and is based on the Beer-Lambert law of absorption, which states that if a known intensity of light illuminates a chamber of known dimensions, then the concentration of a dissolved substance can be determined if the incident and transmitted light intensity is measured:

$$I_t = I_i e^{-dC\alpha} \quad (4)$$

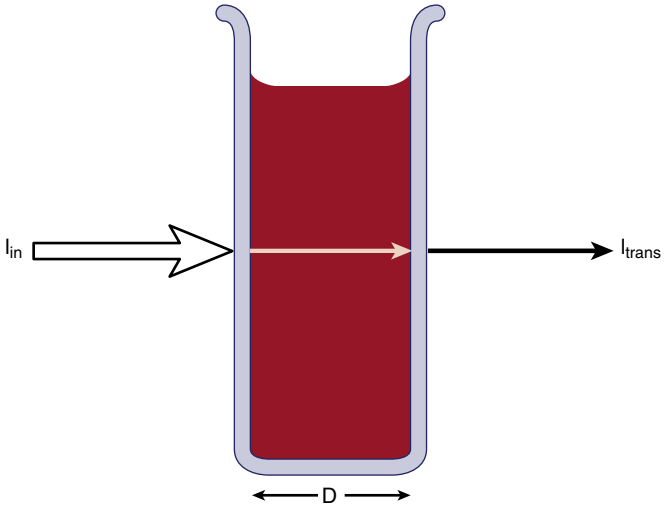
Solved for C,

$$C = (1/d\alpha) \ln [I_i/I_t] \quad (5)$$

where C is the concentration of the dissolved substance, d is the path length of the light a, and α is an absorption constant for the dissolved substance at the light wavelength used. I_i and I_t are the incident and transmitted light intensity, respectively. The unknown concentration C is thus inversely proportional to the light path length d and directly proportional to the log of the ratio of incident to transmitted light intensity (Fig. 44-25). Red and infrared light (wavelength 0.6 to 1.0 micron) are generally used because the constituents of interest to anesthesiologists (volatile anesthetics, CO_2, and Hb) absorb light within that range. Fortunately, both red and infrared light can penetrate soft tissues and may therefore be used to measure the concentrations of Hb species in vivo (see the section on "Processed Absorbance Monitors"). Small molecules absorb infrared light only if they have bonds and are asymmetric; in other words, their molecules have a dipole moment. Therefore nitrogen, oxygen, and helium cannot be measured by infrared light. Another limitation of infrared light is that ordinary glass absorbs it; therefore the measurement chambers for these devices must be made of sapphire or other infrared-permeable materials.

SIMPLE ABSORBANCE MONITORS (CAPNOMETER, ANESTHETIC ANALYZER)

Capnometers, capnographs, and anesthetic gas analyzers all use the Beer-Lambert law of absorption to analyze the constituents of the respiratory gas stream. A capnometer measures and displays only discrete values of partial



$I_{trans} = I_{in}e^{-(D \times C \times a_\lambda)}$

I_{trans} = intensity of light transmitted

I_{in} = intensity of incident light

D = distance light is transmitted through the liquid

C = concentration of solute (oxyhemoglobin)

a_λ = extinction coefficient of the solute (a constant)

Figure 44-25. Cuvette. Light entering the cuvette is reflected and absorbed. Measuring the amount of light entering and exiting the system can determine the concentration of substances absorbing and reflecting light.

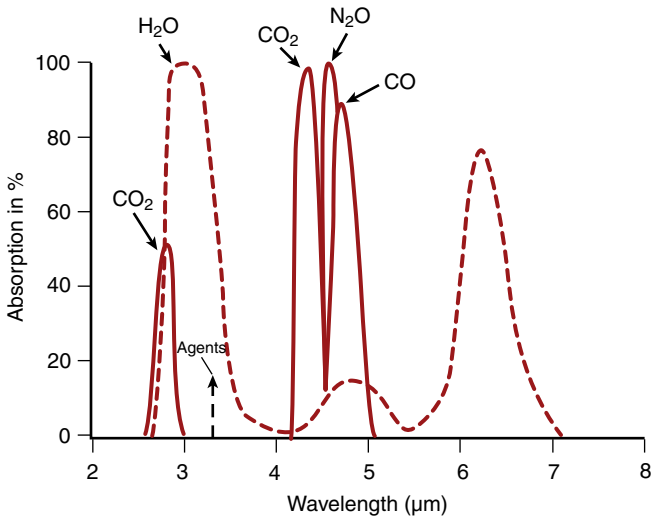


Figure 44-26. Absorption spectra. Absorption spectra of some gases and materials important to anesthesia. Note that the absorption is not constant over wavelengths. Therefore choosing the proper wavelength to measure is important. In addition, when multiple substances are present, measuring their concentrations is still possible, provided enough wavelengths are available. The solution becomes one of multiple equations with multiple unknowns. *(From Gravenstein JS, Paulus DA, Hayes TJ:* Capnography in clinical practice. *Boston, 1989, Butterworths.)*

pressure of CO_2 (P_{CO_2}), for example, the end-tidal value. A capnograph provides a continuous plot of P_{CO_2} in the airway versus time. The physical design of capnometers is divided into two categories: mainstream and sidestream. In mainstream capnometers, the light absorption chamber is placed directly in the airway and the light source shines through the chamber, with CO_2 being directly measured during inspiration and expiration. Advantages of this technique are an extremely fast response time and no problems with clogging of the sampling tubes, which is a disadvantage of sidestream capnometers. Disadvantages of the mainstream geometry include the necessity of having a potentially heavy, expensive infrared measurement device placed directly in the airway at the endotracheal tube and the unavailability of devices that can measure anesthetic agents, as well as CO_2. The most commonly used devices in the surgical unit are sidestream capnometers. A thin sampling tube is attached to the airway near the endotracheal tube, and samples are aspirated at 200 to 400 mL/min into the measurement chamber, which is located in the monitor itself. The advantages of this method are the opposite of the disadvantages of the mainstream capnometers; that is, the sampling tube is lightweight, and the device can be used to measure both CO_2 and anesthetic agents. Disadvantages of sidestream relate mostly to the delayed response time and potential clogging of the aspiration tubing.

Volatile anesthetic analyzers and capnographs function by the same physical principles but use different wavelengths of light (Fig. 44-26). The light absorbances of a mixture of gases can interfere with each other; consequently, compensations are built into current devices.

PROCESSED ABSORBANCE MONITORS (PULSE OXIMETER)

Oximeters are devices that use light absorbance measurements to determine the concentration of various species of Hb. One of the first in vivo oximeters was a noninvasive monitor used in aviation research during World War II. This device transilluminated tissue (the earlobe) with light of two wavelengths. One wavelength was sensitive to changes in oxyhemoglobin (HbO_2), and the other was not. In effect, the earlobe acted as a test tube containing the suspended Hb. For a review of the development of pulse oximetry, the reader is referred to the excellent article by Severinghaus and Astrup.[10]

One issue is the form of Hb being measured. Adult blood usually contains four species of Hb: HbO_2, reduced Hb, methemoglobin (metHb), and carboxyhemoglobin (COHb). The latter two are abnormal Hb, called *dyshemoglobins* and are normally present in only small amounts. Each of these Hb species has a different light absorption profile. Figure 44-27 illustrates the different absorption constants for each Hb species over a range of light from red to infrared. Fractional Hb saturation ($O_2Hb\%$) is defined as the *ratio of HbO_2 to total Hb*:

$$O_2Hb\% = HbO_2/(HbO_2 + Hb + metHb + COHb)$$

Measuring this quantity in the presence of metHb and COHb requires at least four wavelengths of light, which

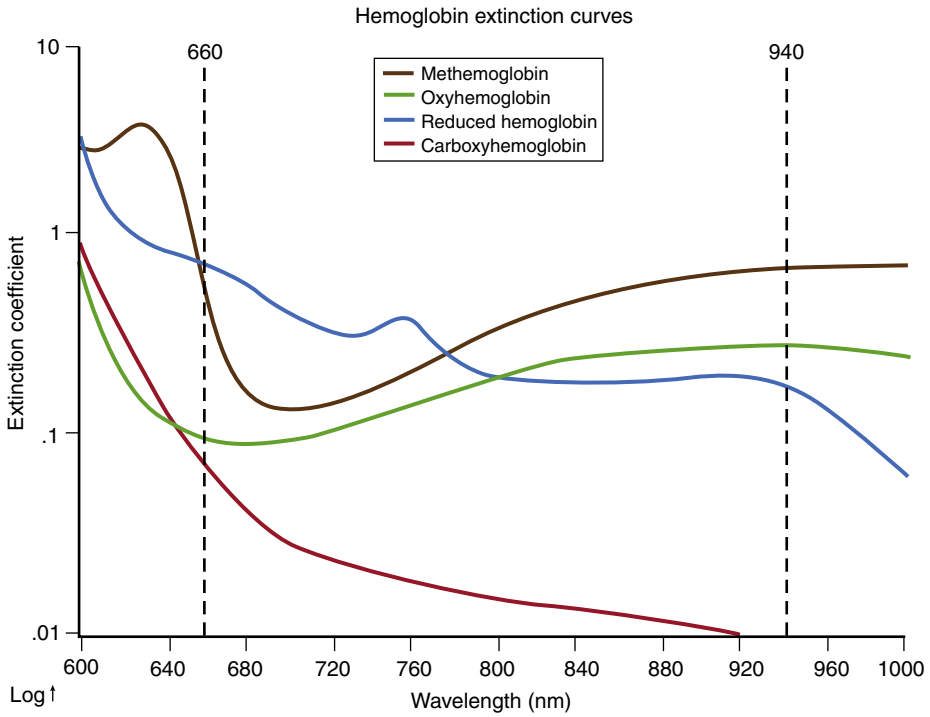


Figure 44-27. Hemoglobin extinction curves. Pulse oximetry uses the wavelengths of 660 nm and 940 nm because these wavelengths are available in solid-state emitters (not all wavelengths are able to be emitted from diodes). Unfortunately, carboxyhemoglobin (HbCO) and oxyhemoglobin (HbO_2) absorb equally at 660 nm. Therefore HbCO and HbO_2 both read as arterial oxygen saturation (Sa_{O_2}) to a conventional pulse oximeter. In addition, methemoglobin (Hbmet) and reduced hemoglobin (Hb) share absorption at 660 nm and interfere with correct Sa_{O_2} measurement. *(Courtesy Susan Manson, Boulder, Colorado, 1986, Biox/Ohmeda.)*

yield four simultaneous Beer-Lambert equations to solve for the four Hb species. Because metHb and COHb do not contribute to oxygen transport, functional saturation is defined as the ratio of HbO_2 to HbO_2 plus reduced Hb:

$$SaO_2 = HbO_2 / (HbO_2 + Hb).$$

Although functional saturation depends explicitly on only HbO_2 and Hb, four light wavelengths are still required to measure it in the presence of significant concentrations of COHb and metHb.[11] If the concentrations of both metHb and COHb are zero, then $O_2Hb\%$ and Sa_{O_2} become identical.

The pulse oximeter performs substantial signal processing of optically transduced physiologic data. Although the physical principle governing pulse oximetry is straightforward, application of this principle to produce a clinically useful device involves significant engineering problems. The remainder of this section describes the physical and physiologic problems of pulse oximeter design and the engineering solutions to these problems. The discussion is divided into basic design and management of signal artifacts.

BASIC DESIGN OF PULSE OXIMETERS

Noninvasive in vivo oximeters measure red and infrared light transmitted through and reflected by a tissue bed. Accurate estimation of Sa_{O_2} by this method entails several technical problems. First, many light absorbers other than arterial Hb are in the transmitted light path (e.g., skin, soft tissue, venous and capillary blood). The pulse oximeter accounts for the effects of absorption of light by tissue and venous blood by assuming that only arterial blood pulsates. Figure 44-28 schematically illustrates the series of absorbers in a typical sample of living

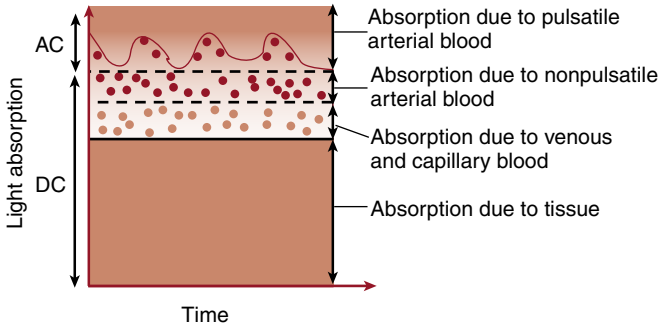


Figure 44-28. Pulse oximetry signals. A primary difficulty with pulse oximetry is that the pulsatile signal is small, compared with the total absorbance of the ear or finger being examined. Pulsatile flow is needed to determine the Sa_{O_2}. *(Modified from Ohmeda Pulse Oximeter model 3700 Service Manual.)*

tissue. At the top of the figure is the AC component, which represents absorption of light by the pulsating arterial blood. The DC (baseline) component represents absorption of light by the tissue bed, including venous, capillary, and nonpulsatile arterial blood. Pulsatile expansion of the arteriolar bed increases the light path length (see equations 4 and 5), thereby increasing absorbency. Conventional pulse oximeters (including all commercial pulse oximeters until 2005) use only two wavelengths of light, typically 660 nm (red light) and 940 nm (near-infrared light). The pulse oximeter first determines the fluctuating or AC component of absorbance at each wavelength and then divides this value by the nonfluctuating or DC component to obtain the pulse-added absorbance, which is independent of the incident light intensity. The oximeter then calculates

the ratio (R) of the two pulse-added absorbances (one for each wavelength)[11]:

$$R = (AC\ 660 / DC\ 660) / (AC\ 940/DC\ 940) \quad (6)$$

Finally, the value of R (often called the *ratio of ratios*) is related to the displayed estimate of saturation of peripheral oxygen (SpO_2) by a "look-up table" programmed into the oximeter's software. The tables used in all commercial pulse oximeters are based on experimental studies in healthy human volunteers. Although each manufacturer's exact calibration curve is proprietary, these curves are similar. For instance, when the ratio of red-to-infrared pulse-added absorbance is 1.0, the displayed SpO_2 is approximately 85%. This fact has clinical implications, which are discussed in the next section.

SIGNAL ARTIFACT MANAGEMENT

One of the most difficult engineering problems in pulse oximetry is the identification of the fluctuating absorbance pattern of arterial blood in a sea of electromagnetic and other artifacts. Artifacts have four major sources: ambient light, low perfusion (weak pulse, low AC-to-DC signal ratio), venous blood pulsations (caused by patient motion, among other things) and additional light absorbers in the blood (e.g., dyshemoglobins, intravenous dyes). All these sources of artifacts produce a low signal-to-noise ratio, resulting in either erroneous SpO_2 values or no value at all.

The photodiodes used in the sensor to detect light cannot differentiate one wavelength of light from another. Therefore the detector does not know whether the light received originates from the red (660 nm) light-emitting diode (LED), the infrared (940 nm) LED, or the room lights. This problem is solved in most pulse oximeters by alternating the red and infrared LED sources. The red LED is turned on first, and the photodiode detector produces a current resulting from the red LED plus the room lights. Next, the red LED is turned off and the infrared LED is turned on. The photodiode signal then represents the infrared LED plus the room lights. Finally, both LEDs are turned off, and the photodiode generates a signal from the room lights alone. This sequence is repeated hundreds of times per second. In this way, the oximeter attempts to eliminate light interference even in a quickly changing background of room light.[10] Some sources of fluctuating light can cause problems, despite this clever design. Simply covering the sensor with an opaque shield can minimize artifacts from ambient light.

Another engineering problem is that of a low AC-to-DC signal ratio or low perfusion. When a small pulsatile absorbance signal is detected, the conventional pulse oximeter amplifies the signal and estimates the saturation from the ratio of the amplified absorbances. In this way, the pulse oximeter can estimate saturation values of SpO_2 for a wide range of patients who generate different amplitudes for pulsatile absorbance. Unfortunately, as with a radio receiver, when a weak signal is amplified, the background noise, or static, is also amplified. At the highest amplifications (which can be up to 1 million times), some pulse oximeters may analyze this noise signal and generate an SpO_2 value from it. Because the noise is usually equal in the red and infrared signals, the ratio of the two is often near unity (1.0), which yields a displayed saturation of approximately 85%. This problem could be demonstrated in early pulse oximeters by placing a piece of paper in the sensor between the photodiode and the LED. Some early models amplified the background noise while searching for a pulse until they eventually displayed a pulse and saturation value for the piece of paper. To prevent this type of artifact, many manufacturers have now incorporated minimum values for the signal-to-noise ratio, below which the device displays no value for SpO_2. Some oximeters also display a low–signal strength error message; in addition, many display a plethysmographic wave for a visual identification of noise.

Patient motion, causing venous pulsations with a high AC-to-DC signal ratio, may be the most difficult artifact to eliminate. Engineers have tried several approaches to this problem, beginning with simply increasing the signal averaging time. If the device averages its measurements over a longer period, then the effect of an intermittent artifact is usually less. However, this longer averaging period also slows the response time to an acute change in Sao_2, and it may result in "frozen" SpO_2 values being displayed when the true saturation is rapidly changing. Most pulse oximeters now allow the user to select one of several time-averaging modes. In addition, some manufacturers use more sophisticated algorithms to identify and reject spurious signals.

One innovation aimed at reducing motion artifact is based on the premise that motion causes pulsations of venous blood within the tissue bed. Conventional pulse oximetry cannot distinguish venous pulsations from those of arterial blood; hence, large low-reading errors or loss of signal can result. In a new signal-processing algorithm developed by Masimo, Inc., the oximeter actually computes a venous *noise reference signal*, which is common to both light wavelengths. The noise reference is then subtracted from the total signal, and a *true* arterial signal is left. This is one of five "parallel engine" algorithms that Masimo SET (Signal Extraction Technology) simultaneously uses to find the most reliable SpO_2 value for the current signal conditions. Tests in human volunteers, as well as preliminary clinical studies, indicate that this new technology represents an improvement in pulse oximeter performance in low signal-to-noise ratio situations.[12,13]

More recently, the first multiwavelength pulse oximeter, the Rainbow Rad-57 Pulse CO-oximeter, has been introduced. This device uses eight light wavelengths rather than the usual two, making it capable of measuring both COHb and MetHb, in addition to the conventional SpO_2 value and pulse rate. The first human volunteer study of this instrument demonstrated that it can measure COHb with an uncertainty of ±2%, and MetHb with an uncertainty of ±0.5%.[14]

Over the past decade, other in vivo oximeters have been developed to measure light reflected by living tissue in an attempt to determine Hb saturation in specific organs. Using reflected rather than transmitted light adds complexity because the path lengths of the light through the tissue may be varied and tortuous, making calibration difficult. Nevertheless, a signal reflected from living tissue may produce useful information regarding the average

saturation of the Hb within that tissue. For example, a cerebral oximeter may be able to measure mean brain Hb saturation, which reflects the intracerebral balance among venous, arterial, and capillary blood, as well as the oxygenation of all three.

MEASUREMENT OF TEMPERATURE

PRINCIPLES OF TEMPERATURE

Moving matter contains energy. Even stationary objects are moving at the atomic level. This kinetic energy of molecules and atoms is described as temperature. When all molecular motion (translational, vibrational, and rotational) ceases, the substance is said to be at a temperature of absolute zero—the lowest possible temperature. This temperature is equivalent to –273° C and is defined as 0° Kelvin. This state provides a reference point for all temperature measurements, which in all thermodynamic calculations must be expressed in degrees Kelvin (see also Chapter 54).

Heat is a form of internal kinetic energy that can flow between two contacting bodies that are at different temperatures. The amount of heat required to raise the temperature of 1 g of a given substance by 1° C is called the *specific heat of that substance*. The *calorie*, a common heat unit, is the amount of heat required to raise the temperature of 1 g of water from 14.5° C to 15.5° C. One calorie is equivalent to 4.184 joules of energy. When we refer to calories in terms of the calories in the food that we eat or the calories that we expend while exercising, we are actually referring to kilocalories (thousands of calories and also called "kitchen calories"). Thus the total amount of heat energy in an object depends on its specific heat, its temperature, and its mass. For example, although a cup of 60° C coffee is much hotter than a 30° C swimming pool, the coffee contains significantly less total thermal energy than the pool. The same is true for potential energy stored as pressure potential or electrical potential. A small container at high pressure may have less potential energy than a larger container at lower pressure.

TEMPERATURE MONITORS (THERMOMETER, THERMISTOR, THERMOPILE, LIQUID CRYSTAL)

Three techniques are commonly used for measuring temperature: (1) those based on expansion of a material as its temperature increases, (2) those based on changes in electrical properties with temperature, and (3) those based on optical properties of a material. As heat is added to most substances (e.g., gases, liquids, solids), motion of the molecules increases, and the volume of the material increases at constant pressure. Depending on the material, this expansion can be directly calibrated to changes in temperature. Liquids are most commonly used, for example, mercury, because its effective range extends from its freezing point of –39° C to approximately 250° C. Mercury thermometers have two disadvantages. They require 2 to 3 minutes for complete thermal equilibration (mercury is a liquid metal with a high specific heat). In addition, they are enclosed in a glass tube, which may break and cause injuries. Thermometers based on the expansion of gas (Bourdon tube) or metal (bimetallic strip) are frequently used in thermostats because they also slowly respond to transient changes in temperature.

Electrical techniques for measuring temperature can be subdivided into three categories: resistance thermometers, thermistors, and thermocouples. Resistance thermometers operate on the principle that the electrical resistance of metals increases with temperature. These devices most frequently use a platinum wire as the temperature-sensitive resistor, a battery, and a galvanometer to measure current, which can be calibrated to temperature. The platinum wire is incorporated into a Wheatstone bridge circuit, which accurately measures very small changes in resistance (see Fig. 44-5).

When compared with a platinum thermometer, a thermistor is a semiconductor that displays the opposite behavior with regard to electrical resistance; that is, as the thermistor is heated, its resistance decreases. Thermistors, being solid-state devices, can be manufactured in extremely small sizes and therefore have a fast response to changes in temperature (i.e., little heat is needed to increase their temperature). Most of the temperature probes used in anesthesia, from the ones at the end of pulmonary artery catheters to esophageal probes, are thermistors. Physical problems with thermistors are few: cracked or broken wires lead to high resistance and incorrect temperature readings. More common are poor probe placement and a misinterpretation of the resulting value, for example, placing an esophageal probe in the oropharynx and measuring airway temperature rather than core temperature. Thermocouples are conductors that generate a voltage in response to a temperature gradient.

The optical properties of materials can be used to measure temperature in two ways: (1) a device known as a *thermopile* can measure the infrared *black-body emissions* of an object, and the emission is then converted to temperature; and (2) a liquid crystal matrix can be placed in direct contact with the desired zone, and an optical change in color can be observed. The most commonly encountered example of infrared temperature measurement involves the tympanic membrane temperature monitor used in recovery rooms, pediatrics, and hospital wards. The infrared detector produces an electrical signal that is proportional to the fourth power of the difference in absolute temperatures of the objects. The following formula describes this phenomenon:

$$Q_{1,2} = K\,(T_1^4 - T_2^4) \qquad (7)$$

where $Q_{1,2}$ is net heat transfer (W/cm^2), K is the Stefan-Boltzmann constant, and T_1 and T_2 are the absolute temperatures of the two objects (degrees K). In theory, this method of measuring the core temperature should be accurate. However, in practice, improper placement and lack of calibration, but not ear canal cerumen, contribute to real-world errors.[15] Additionally, the probe is rather large for intraoperative use.

Liquid crystal measures of temperature (found in "mood rings") are often used for skin temperature monitoring. Just as the molecules in a liquid crystal watch display change their optical properties with a small electric

current and become polarized and dark, the molecules in a liquid crystal temperature device change their optical properties with temperature, resulting in a rainbow of colors. The crystal matrix is sensitive to pressure and temperature. (By touching an LCD display panel, the visual rainbow of changing colors can be seen.) The reported clinical accuracy of liquid crystal devices varies.[16]

MEASUREMENT OF FLOW

PRINCIPLES OF FLOW

Although conceptually one of the easier measurements to understand as volume or mass movement over time, flow is actually not easy to measure. We must clearly distinguish between fluid flow and fluid velocity, which are often confused. Flow (Q) refers to the volume of fluid passing a particular surface area per unit of time; its SI units are cubic meters per second (m^3/sec); in medicine, however, flow is more commonly measured in milliliters per second (mL/sec) or liters per minute (L/min). Fluid velocity (U) is simply the speed of the fluid at a particular point in space, measured in meters per second (m/sec). By analogy, imagine a multilane freeway: the speed (velocity) of individual cars may vary depending on the lane; the flow is the number of cars passing a point per minute.

MASS AND VOLUME FLOWMETERS (UROMETER, VOLUMETER)

Flow can be directly measured by diverting the flow into a measuring chamber. We can measure the mass or volume of fluid flowing per unit time by catching the fluid in a container and either weighing it or measuring its volume. The common urometer for measuring urine volume is an example. The volumeter used in North American Drager anesthesia machines also measures aliquots of volume integrated over time to measure tidal and minute volumes (Fig. 44-29).[17]

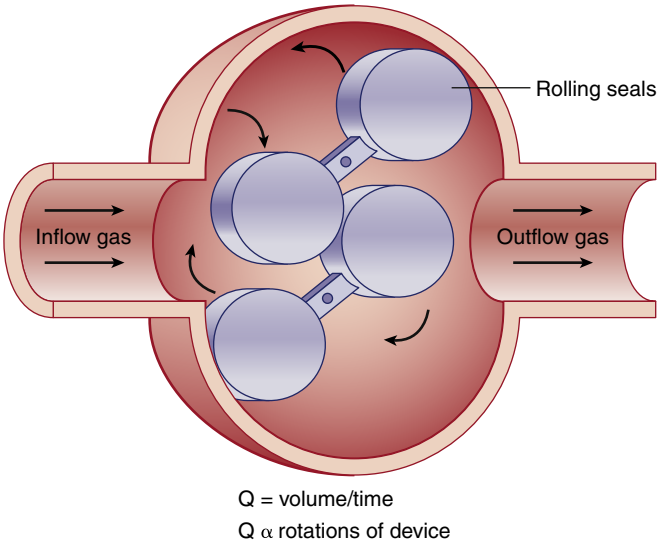


Figure 44-29. Volumeter. Flow can be described as volume over time. This design of flowmeter allows gas to pass in only little aliquots, each of which turns a counter to measure the amount flowing past. When divided by time, this results in a flow measurement. *(Modified from Ehrenwerth J, Eisenkraft J:* Anesthesia equipment: principles and applications. *St. Louis, 1993, Mosby.)*

DILUTIONAL FLOWMETERS (THERMODILUTION, FICK PRINCIPLE)

Dilutional techniques can also measure both volume and mass flow. If some measurable indicator (e.g., bolus of dye, thermal pulse, oxygen consumption, CO_2 production) is injected into a flow and its concentration is measured as a function of time at a point downstream, then the volume flow (Q) can be calculated by integration. The most common medical application is determining cardiac output by the pulmonary artery thermodilution method (see Appendix 44-6). Errors associated with these methods involve using the wrong injectate volume (too small a volume resulting in an overestimate of flow) or an error in temperature measurement (see "Measurement of Temperature" earlier in this chapter).

Continuous thermodilution cardiac output using an electric heating coil to warm the pulmonary artery blood removes errors associated with fluid injectate techniques but introduces the need to average the smaller signal over a longer time interval. Additionally, there is an upper limit to warming the blood without cellular damage; therefore signal quality is reduced in patients who are febrile. Measuring the electric current required to maintain a constant temperature at the catheter tip is a slightly different approach. Variable current is the principle behind a constant temperature hot wire anemometer (used to measure gas flows in wind tunnels and in some anesthesia machines) applied to cardiac output.

The rate of CO_2 production or oxygen consumption can be used to measure cardiac output by modifications of the Fick formula (see Appendix 44-6). When using these variables, a change in metabolic rate can lead to errors in cardiac output measurement.

VELOCITY AND PRESSURE FLOWMETERS (VENTURI, PITOT)

Flowing fluids in tubes generate both velocity and pressure, which can be used to measure the flow indirectly. As described earlier, pressure in fluids can be thought of as a form of potential energy. Kinetic energy in fluids is expressed in terms of flow, the bulk movement of fluid with a given direction and magnitude. The potential energy of pressure can be converted into the kinetic energy of flow; for example, the hydrostatic pressure generated by gravity acting on a vertical column of liquid can be transformed into flow by opening a valve at the bottom of the column. Pressure and flow can also change independently. With the human circulatory system used as an example, a healthy young trauma patient in hypovolemic shock can have relatively normal blood pressure but low blood flow with high SVR. On the other hand, a patient with sepsis can have very low blood pressure accompanied by high blood flow and low SVR (high-output septic

shock). The total mechanical energy of a moving fluid is the sum of the kinetic (flow) energy and the potential (pressure) energy (see Table 44-2).

A pressure gradient (changing pressure in a particular spatial direction) exerts a force on the fluid, and the fluid tends to accelerate in the direction of decreasing pressure. Pressure gradient is only one of the forces that commonly act on fluids; other forces include gravity (see earlier discussion in "Pressure Measurement") and viscous force or friction. If these other forces are negligible and the fluid is incompressible (i.e., a liquid with constant density), then the equation of motion (F = ma) can be integrated to yield:

$$P + {}^{1}/_{2}\rho U^2 = P_0 \qquad (8)$$

where P is pressure, ϱ is fluid density, U is the magnitude of the fluid velocity, and P_0 is a constant called the *stagnation pressure* (see Appendix 44-5). This form of the Bernoulli theorem tells us that pressure decreases as velocity increases in a frictionless flow, and vice versa. This principle dispels the common misconception that pressure always decreases in the direction of flow. For example, in the flow inside a tube (e.g., pipe, large vein) of gradually increasing diameter, fluid velocity (U) decreases in the downstream direction as the diameter and cross-sectional area of the tube increase. As U decreases, equation 8 tells us that P increases in the direction of flow. This example again shows the relationship of potential and kinetic energy in fluids: as the kinetic energy of this tube flow decreases (U^2 falls) in the flow direction, the potential energy increases (P rises) by an equal amount. The total energy remains constant because we have assumed no friction.

Measuring the average velocity of the fluid across the tube can determine flow. In laminar tube flow (Figure 44-30, *A*), the velocity profile has a parabolic shape, with the highest velocity at the centerline and the fluid at the walls being stationary. In turbulent tube flow, the velocity profile is flattened (Figure 44-30, *B*).

The Bernoulli theorem applies to a specific subset of frictionless flows, as described earlier. Many flows important to anesthesiologists do not follow the Bernoulli theorem. Most commonly, the flow that we desire to measure is not laminar but turbulent. The transition from laminar to turbulent flow depends on the type of fluid, the speed of the flow, and the shape of the flow. The fluid factors are combined in a dimensionless ratio called the *Reynolds number* (Re):

$$Re = \rho UL/\mu \qquad (9)$$

where ρ is the density of the fluid, U is the mean flow velocity, L is a characteristic dimension (length) of the flow, and μ is the viscosity of the fluid. For a given flow geometry (e.g., flow through a tube of circular cross section), transition from laminar to turbulent flow will occur at a critical value of Re. In straight, smooth, circular tubes, transition from laminar to turbulent flow occurs at Re of approximately 2100 (see Appendix 44-5).

A Venturi tube is circular tube with a gradual contraction and expansion in diameter, in contrast to the sudden contraction-expansion of an orifice flowmeter (Fig. 44-31). Because the contraction is smooth and gradual,

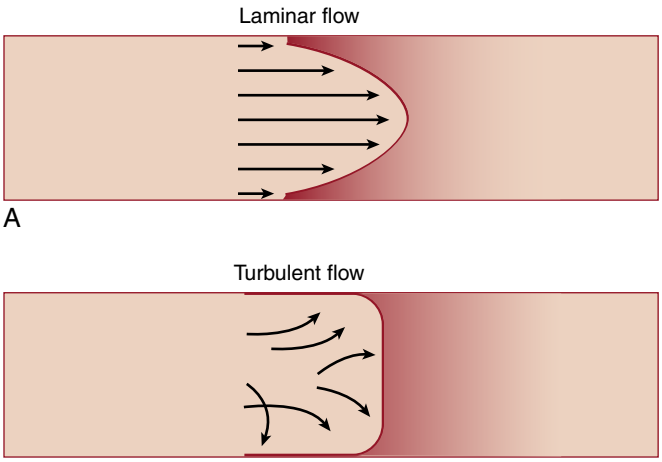


Figure 44-30. Laminar and turbulent flow. **A,** In a smooth-walled tube at low flow rates (i.e., small pressure gradients), the flow rate is laminar; that is, flow moves smoothly in concentric circles with the centermost area having the greatest flow velocity and the area nearest the wall of the tube being virtually stationary. **B,** As flow rate and pressure gradient increase, the flow transitions from laminar to turbulent. Instead of a neatly ordered flow, the velocities are more randomly distributed, energy is dissipated as heat, and the energy needed for a given flow rate increases. Many factors govern this transition, including the size of the tube, the viscosity of the fluid, and the flow rate and pressure gradient. These factors are combined in determining the Reynolds number (see Appendix 44-5).

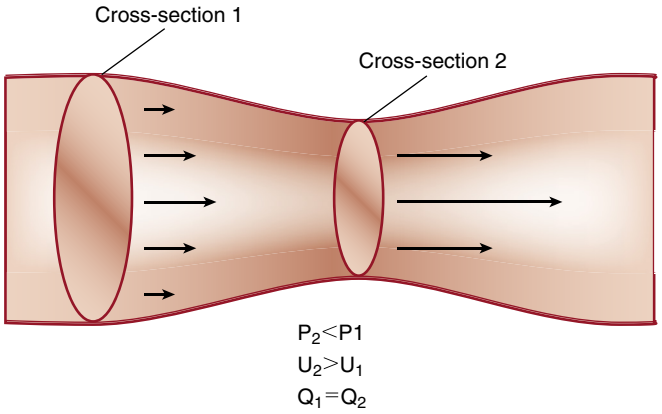


Figure 44-31. Venturi tube. By measuring the pressure difference between two points in a laminar flow, the average flow velocity can be determined because the mass flow and total energy (minus frictional losses) must be the same (see Appendix 44-5).

the Bernoulli theorem (equation 7) applies to this geometry. For conservation of mass and energy to apply, as we restrict the flow by narrowing the tube, the speed *increases*; therefore the pressure on the walls *decreases* to keep the total energy (the stagnation pressure of the Bernoulli theorem) constant. The total mass flow on both sides of the contraction must be equal (we have not created or lost any matter). If we measure the pressure difference between the widest and the narrowest parts of the Venturi tube, then we can solve the Bernoulli theorem for velocity (see Appendix 44-5). The Venturi tube derives fluid velocity (U) from the pressure difference, not volume flow (Q).

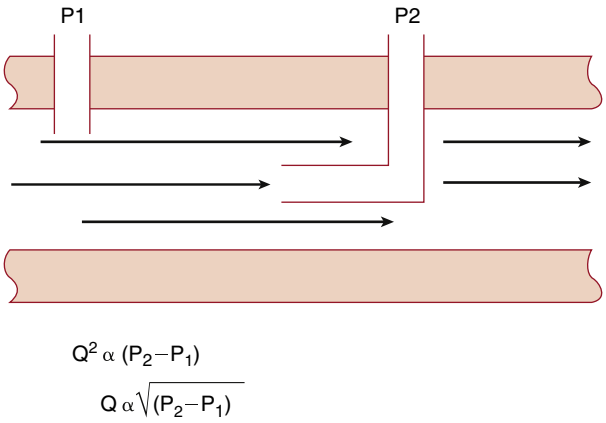


Figure 44-32. Pitot tube. As flows increase, wall pressure decreases as a result of the Bernoulli principle. The Pitot tube measures the difference in pressure from the middle of the flow to the wall and converts this to a flow measurement (see Appendix 44-5). *(Modified from Ehrenwerth J, Eisenkraft J:* Anesthesia equipment: principles and applications. *St. Louis, 1993, Mosby.)*

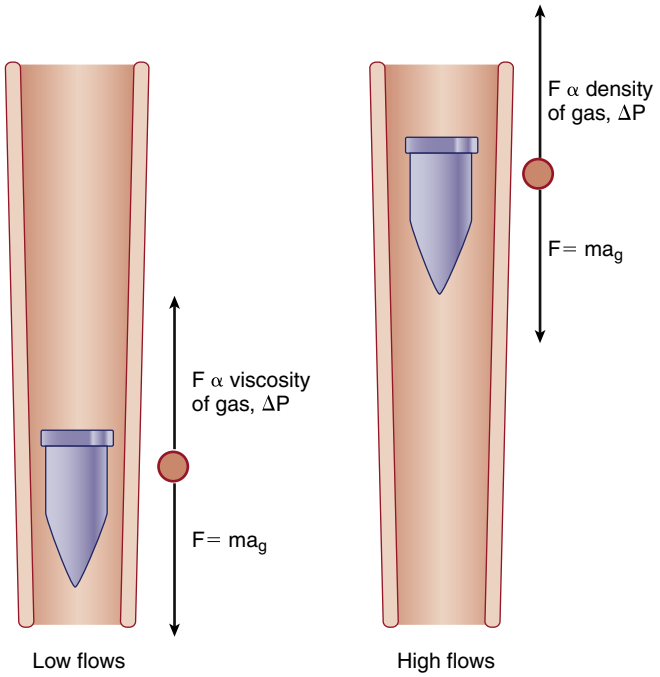


Figure 44-33. Thorpe tube flowmeter. At low flows, viscosity of gas predominates, and the flows balance when the gravitational attraction equals the pressure gradient across the equivalent orifice. At higher flows, density takes over, and the balance is the same, except for the formula determining pressure (acts like an orifice) (see Appendix 44-5).

The Venturi tube is used in many industrial applications and is also used on some aircraft to measure speed.

To ensure a measureable pressure gradient, some resistance must be present in the fluid path. The lower the rate of flow, the greater the resistance must be to generate the same pressure gradient. Therefore in respiratory applications, pediatric flowmeters have too much resistance (as a result of lower flows) to use in adults, and adult flowmeters do not generate enough resistance to give an adequate signal (pressure change) in pediatric patients. A variable resistance flowmeter has been devised (Ohmeda 7900/Aisys) in which the orifice is actually a flap that moves as the flow increases. No simple equation or relationship exists between the pressure above and below the restriction; therefore this flowmeter must be empirically calibrated and the calibration curve for each sensor electronically stored.

A Pitot tube is a cylindric tube whose open end is pointed directly into the flow, that is, *upstream* (Fig. 44-32). The pressure measured in the Pitot tube approximates the stagnation pressure given earlier in equation 7. If we independently measure the static pressure (p) (the p_1 side port in Fig. 44-32) at the same location and if we know the fluid density (ϱ), we can then easily solve equation 7 for the fluid velocity (U). Note, again, that the Pitot tube derives velocity (U), not volume flow (Q). The Pitot tube is simple and reliable and is used on most aircraft to measure speed. In anesthesia, the Pitot tube is used in Datex Ultima monitors. To measure gas flow in two directions, the Datex monitor incorporates two Pitot tubes, one facing in each direction. Additionally, the monitor samples gas composition to correct for the density and viscosity of the gas mixture.

BALANCE-OF-PRESSURE FLOWMETERS (THORPE TUBE, BOURDON TUBE)

If flow in a tube passes through a sudden restriction such as an orifice, then the volume flow (Q) is proportional to the area of the orifice and the square root of the pressure drop through the orifice. (The Bernoulli theorem does not apply to this flow geometry.) This is the principle of all orifice flowmeters, including the rotameter of an anesthesia machine (see Appendix 44-5).

The most common flowmeter used in anesthesia is the floating bobbin rotameter on the anesthesia machine (Thorpe tube, Fig. 44-33). This variable-orifice flowmeter uses a balance of forces to determine pressure change and to measure flow. When the flowmeter valve is opened, the flow of gases through the annular orifice between the bobbin and the tapered glass tube provides a force to raise the bobbin. As the bobbin rises, the area of the annular gap between the bobbin and the tube increases as a result of the taper of the tube. As the area of this gap (orifice) increases, the pressure change across the bobbin decreases; the pressure change across an orifice is inversely proportional to the square of the orifice area. The bobbin ceases its upward motion at an equilibrium point where the upward pressure force balances the downward force of gravity (weight of the bobbin). Thus the height of the bobbin in the tube is directly related to the gas flow. Although this flowmeter is simple in principle, its application becomes more complex when the flow in the tube changes from laminar to turbulent as velocity and diameter increase. (For mathematical derivations, see Appendix 44-5.)

Another flowmeter (Bourdon tube, Fig. 44-34) keeps the orifice constant and allows the pressure to vary. As flow (Q) increases, the gradient of P_1 to P_2 increases and causes the flattened metal tube to uncoil and move the pointer.

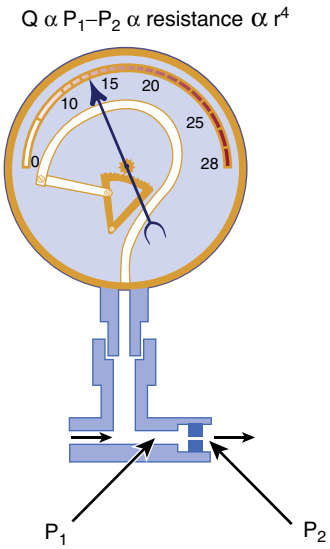


Figure 44-34. Bourdon tube flowmeter. Unlike the Thorpe tube, which has a constant pressure but a variable orifice, the Bourdon tube has a constant orifice but a variable pressure. The tube uncoils under the high backpressure. This drawback makes it unsuitable for use in low-pressure respiratory systems. However, it receives much use in portable oxygen tanks. Of note, if the orifice is increased in radius, then the flowmeter will under-read the actual flow. If the orifice is dirty (i.e., decreased radius), then the flow will be overestimated. *(From Mushin WW, Jones PL:* Physics for the anaesthetist*, ed 4. Oxford, 1987, Blackwell.)*

KINETIC ENERGY FLOWMETERS (WRIGHT SPIROMETER)

Vanes or propellers placed in a confined flow turn at a rate proportional to the volume flow if there is no friction in the propeller bearings. Various vane spirometers, such as the Wright spirometer, work by this principle (Fig. 44-35). These devices tend to be less accurate at both very high and very low flow rates because of frictional forces.

SUMMARY OF FLOW MEASUREMENT

Every method of measuring flow has its particular limitations and uncertainties. Because gases are not always pure with a known, constant density, flowmeters based on the Bernoulli theorem (equation 7) are subject to errors. Furthermore, any device inserted into a fluid flow can disturb the flow by its presence. For example, a rotating vane spirometer may reduce the gas flow at high flow rates because of internal friction. Several methods of flow or fluid velocity measurement are dependent on a pressure measurement (Pitot tube, Venturi tube, orifice

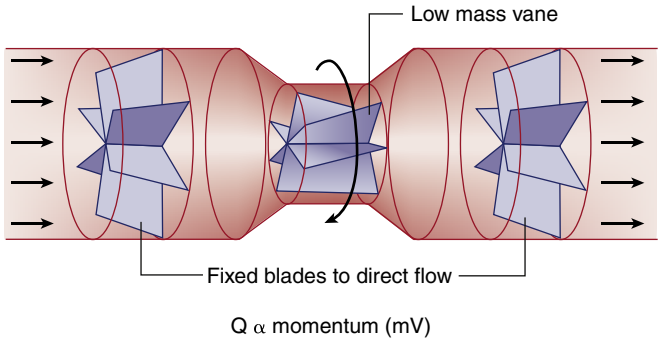


Figure 44-35. Vane spirometer. Moving gases contain kinetic energy, which can be sampled by a rotating "windmill" in the gas stream. *(Modified from Ehrenwerth J, Eisenkraft J:* Anesthesia equipment: principles and applications*. St. Louis, 1993, Mosby.)*

flowmeter); hence, the flow measurement is no more accurate than the pressure measurement.

In conclusion, new monitors are being developed almost continuously, but new physical principles are revealed only rarely. The science of physics is a constant effort to understand, simplify, and predict the behavior of our universe in quantitative terms. The terms and principles outlined in this chapter are referred to multiple times in subsequent chapters.

Complete references available online at expertconsult.com

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APPENDIX 44-1 *Distance Versus Time Under Constant Acceleration: Equivalence of Potential and Kinetic Energy*

Velocity (v) is the rate at which distance is changing; that is, it is the time derivative of distance:

$$\mathbf{v} = d\mathbf{x}/dt \quad (1)$$

The variable **v** is written in boldface type to indicate that it is a vector: it has both magnitude and direction. Distance **x** is a vector pointing from the origin to the present location of the particle or object; it is called the *position vector*. Time (t) is a scalar; it has magnitude but no direction and is therefore written in plain type.

Acceleration (**a**) is the time rate of change of velocity. Thus it is the time derivative of the velocity vector or the second derivative of distance with respect to time.

$$\mathbf{a} = d\mathbf{v}/dt = (d/dt)(d\mathbf{x}/dt) = d^2\mathbf{x}/dt^2 \quad (2)$$

If an object starts with zero velocity (**v** = 0) at time zero (t = 0) and then accelerates with constant acceleration (**a**), its velocity at time t will be simply **v** = at. To calculate the distance traveled by the object between time t = 0 and time t, we must divide the time interval 0 to t into a series of very small intervals, each of time length dt. The distance traveled during the interval dt is simply the velocity at that time multiplied by the time interval:

$$d\mathbf{x} = \mathbf{v}dt = (\mathbf{a}t)\,dt \quad (3)$$

In the second step, we have substituted the constant acceleration relationship **v** = **a**t from above. Now to compute the total distance traveled, we must sum the distance from all of the small dt time intervals that occur between 0 and t.

$$\mathbf{x} = \sum(\mathbf{a}t)dt \quad (4)$$

If we allow the length of the time interval dt to approach zero, the summation process becomes the integral with respect to time from time zero to time t.

$$x = \int v dt = \int (at)dt = \frac{1}{2}at^2 \quad (5)$$

Thus an object starting from rest at t = 0 and moving with constant acceleration (**a**) will move a distance $^1/_2$ **a**t^2 in time t. If this is a falling object (in a vacuum, where there is no air resistance), then **a** = g = 9.8 m/sec^2, and the distance formula becomes:

$$\mathbf{x} = \frac{1}{2}gt^2 = (4.9)\,t^2 \quad (6)$$

In the first second, the object falls 4.9 m; at the end of 2 seconds, it has fallen 19.6 m; after 3 seconds, 44.1 m; and so on.

The kinetic energy (KE) of a moving object is:

$$KE = \frac{1}{2}mv^2 \quad (7)$$

where m is the mass of the object and v is the magnitude of its velocity (also called *speed*). Note that v used in this sense is in plain type, not boldface. Consider, again, the falling object that started at position x = 0 at time t = 0 and falls a distance h:

$$h = \frac{1}{2}gt^2, \text{ or}$$

$$t = \sqrt{(2h/g)} \quad (8)$$

Because velocity v = at = gt, we have by substitution from equation 8

$$v = gt = g\sqrt{(2h/g)} = \sqrt{(2gh)} \quad (9)$$

The kinetic energy is given by

$$KE = \frac{1}{2}mv^2 = \frac{1}{2}m(2gh) = mgh \quad (10)$$

Now, let us consider the work required to lift the fallen object back to its original height of h. Recall that work is defined as the force exerted times the distance over which the force acts: W = Fd. The force of gravity acting on our object is F_g = mg, so the work required to lift it the distance (h) back to x = 0 is

$$W = Fd = (mg)d = mgh \quad (11)$$

Thus the work required to restore the object equals the kinetic energy possessed by the object at the bottom of its fall, KE = W = mgh. When we lift the object from x = h back to x = 0, we have increased its potential energy (PE) by the amount mgh. This PE can be converted to kinetic energy by allowing the object to fall the distance h. This type of PE is called *gravitational potential* and has a value that clearly depends on where we locate the origin of our coordinates, x = 0. However, it is the change in PE, not its absolute value, that the PE and kinetic energy balances:

$$\Delta KE = -\Delta PE \quad (12)$$

The change in kinetic energy is equal to and of opposite sign to the change in potential energy.

APPENDIX 44-2 *Physics of Hydrostatic Pressure*

A liquid manometer is a simple and reliable means of monitoring pressures that do not rapidly change. It simply uses the weight of a measured vertical column of liquid to balance the pressure exerted against the bottom of the column. We have defined weight as the force exerted by gravity on a mass (m): F_g = mg. To determine the weight of a column of liquid of known dimensions (in a manometer, see Fig. 44-4), we must first know the density (mass per unit volume) of the liquid. Density has dimensions of m/L^3, and the SI units are kilograms per cubic meter (kg/m^3). Because liquids are almost incompressible, their density is little influenced by pressure (but affected by temperature). The density of water at room temperature is 997.8 kg/m^3 or 1.0 g/cm^3.

The pressure (p) exerted by the bottom of the vertical column of liquid in a manometer (see Fig. 44-4) is determined as follows: if the cross-sectional area of the liquid cylinder is A and the height of the cylinder is z, then its volume is V = Az. If the liquid has a density of ρ, the mass of the column is:

$$m = \rho V = \rho Az \quad (1)$$

and its weight is

$$W = mg = \rho Azg \quad (2)$$

The liquid column exerts a force equal to its weight on its base, whose surface area is A, thus creating the following pressure on the surface:

$$p = \text{force/area} = \rho Azg/A = \rho gz \quad (3)$$

The pressure exerted by the manometer is therefore independent of its cross-sectional area (A); it depends only on the density of the working fluid and the vertical height of the column. If we know the liquid density, then the measurement of the column height (z) allows us to calculate the pressure (p). For example, if the working fluid is mercury (e.g., sphygmomanometers), then the density is 13,680 kg/m^3 (13.68 g/cm^3 or 13.68 times the density of water). The relationship of pressure to height of the column is then:

$$\begin{aligned} p = \rho gz &= (13{,}600\ \text{kg/m}^3)(9.8\ \text{N/kg})\,(z) \\ p[\text{N/m}^2] &= 133{,}300(z) \end{aligned} \quad (4)$$

The unit of pressure newton/meter^2 (N/m^2) is called the *pascal* (Pa). Because a Pa is a small unit of pressure, we usually use kilopascals (kPa or 10^3 Pa). If we express p in kPa and z in millimeters of mercury (rather than meters), equation 4 becomes:

$$p\ [\text{kPa}] = 0.1333\ (z)\ \ [\text{mm Hg}] \quad (5)$$

APPENDIX 44-3 *Wheatstone Bridge*

The Wheatstone bridge is a network of four resistors connected as shown in Figure 44-5, with a battery or DC voltage source (electromotive force) connected between A and C and a voltmeter (V) connected between B and D. The bridge is said to be "balanced" when the voltmeter reads zero potential difference between points B and D. From Ohm's law (V = IR), it is easy to show that balance occurs when $R_x = R_s \times (R_2/R_1)$. If R_s is an adjustable standard resistor and R_1 and R_2 are fixed known resistors, then the balanced bridge provides a very precise means of determining R_x, the unknown resistance. This principle has many applications in biomedical engineering, including strain gauge pressure transducer measurements. In this case, the transducer, itself, is the unknown resistance R_x.

APPENDIX 44-4 *Amplification Artifact of a Fluid Tube/Transducer Pressure Waveform*

The amplification artifact of a fluid tube/transducer pressure waveform can be calculated if a few properties of the system are known. The most relevant part of this solution is the response amplitude, which is plotted against the driving frequency (f) in Figure 44-16. This figure shows some important properties of fluid-coupled transducers and other harmonic oscillators. One of these properties is the existence of a resonant frequency, f_0, which is defined as follows:

$$f_0 = \frac{1}{2}\,\pi\,\sqrt{k/m} \quad (1)$$

Remember, m is the mass of the system and k is the elasticity or spring constant.

As we increase the amount of damping (i.e., friction; c is the friction constant), we observe a decrease in the peak amplitude at resonance, and the frequency at which the peak occurs decreases slightly. The damping coefficient (z) is defined as follows:

$$z = c/\sqrt{2km} \quad (2)$$

Although the arterial pressure waveform is not actually sinusoidal, Figure 44-15 shows the most important characteristics of the pressure transducer response. Any combination of catheter, tubing, and transducer can be characterized by two quantities: a resonant frequency (f_0) and a damping coefficient (z). Gardner measured these quantities for many transducer and tubing systems and found that most systems have resonant frequencies of 10 to 20 cycles/sec or hertz (Hz) and damping coefficients of 0.2 to 0.3. For clinical systems, the maximum amplification factor (the ratio of transducer output to input waveform amplitude) at resonance is near 2.5.

If the resonant frequency is 10 Hz (600 cycles/min), then one might conclude that amplification plays little role in the clinical range of pulse rates, which are 5 to 10 times smaller. However, the arterial pressure waveform is not a sine wave. It can be represented as a summation of sine waves (a Fourier series) with frequencies up to many times the pulse rate. It is these higher harmonic frequencies that are amplified most and that yield the spiked appearance of a poorly processed arterial waveform. Depending on the shape of the actual arterial pressure wave, this distortion can introduce a 20% to 40% "overshoot" error in systolic blood pressure readings. Even worse, this error is dependent on the pulse rate; therefore an error determined for a particular patient at the beginning of administration of an anesthetic may not remain constant.

From this discussion, we can easily predict how to optimize the performance of a pressure transducer system. First, the resonant frequency (f_0) should be as high as possible. Therefore the value for k in equation 1 should be large (i.e., the spring should be "stiff") and the value for m should be small (i.e., the cannula and pressure tubing should be as stiff and inelastic as possible). To minimize the mass of the moving fluid, the tubing should be short in length and small in diameter. Judging from plots of amplitude versus frequency/resonant frequency at different damping coefficients, the optimal damping coefficient would be 0.4 to 0.5. In addition, air bubbles should be carefully eliminated from the system because they add elasticity and friction, thereby lowering the resonant frequency. In a clinical system, the approximate f_0 and z of a transducer system can be determined if graphic output is available. If the high-pressure flush is turned on and then quickly off at a high chart speed (50 mm/sec), then the tracing oscillates through several cycles at a frequency near f_0. The damping coefficient can be found by determining the ratio of amplitudes of successive peaks on the tracing. This is a practical example of how fundamental principles of mechanics can be used to predict and optimize the performance of monitoring systems. These concepts of mechanics recur in later sections of this chapter.

APPENDIX 44-5 *Flowmeters, Bernoulli Principle, Laminar and Turbulent Flow*

The equations governing the motion of fluids are expressions of Newton's second law, F = ma. Forces associated with fluids fall into three major categories: (1) gravity, (2) pressure, and (3) friction. In the example using manometers, the gravitational force per unit volume of fluid is simply ϱg, acting in the vertical direction. Pressure forces are actually the result of differences in pressure from one point to another and are mathematically expressed as the negative of the pressure gradient. (A pressure gradient is a vector in the direction of the maximal rate of pressure increase, with a magnitude equal to the pressure derivative in that direction.) Friction is proportional to viscosity, the physical property of a fluid that relates shear stress to the rate of strain.

$$P_0 = p + \frac{1}{2}\rho U^2 + \rho g z \quad (1)$$

Equation 1 shows the relationship between velocity and pressure of a fluid in a flow that meets the conditions described. For flows in tubes, the manometer technique provides an easy method of measuring mean pressure. Therefore the simplest flowmeters apply a combination of these two principles to a tube of changing cross-sectional diameter. For example, the Venturi flowmeter shown in Figure 44-31 consists of a tube of varying cross-sectional area that has two ports for measurement of pressure. The Bernoulli theorem for points 1 and 2 in the figure becomes:

$$P_1 + \frac{1}{2}\rho U_1^2 = P_2 + \frac{1}{2}\rho U_2^2 \quad (2)$$

Here, the gravity terms have canceled out because the tube is horizontal, but these terms are usually negligible for gas flows in any direction.

The volume of the fluid flow (Q) (also called *flux*) at both locations must be the same because no fluid is entering or leaving through the tube walls. The dimensions and SI units for the volume of fluid flow are l^3/t and m^3/sec, respectively. This volume is determined at each cross section of the tube by multiplying the average velocity (U) by the cross-sectional area (A):

$$Q = U_1 A_1 = U_2 A_2 \quad (3)$$

Assuming that A_1, A_2, P_1, and P_2 are known, we now have two equations for the two unknowns U_1 and U_2. Solving these for the velocity U_1 produces

$$U_1 = \sqrt{\left[2(P_1 - P_2)/\rho\left(1 - A_1^2 - A_2^2\right)\right]} \quad (4)$$

To find the volume of the flow (Q), we merely multiply this result by A_1. Note that velocity is proportional to the square root of the pressure drop or that the pressure change varies as velocity squared. For a given U_1 or the magnitude of flow velocity, the pressure drop varies as the square of the ratio of the areas, or the fourth power of the ratio of the diameters. If we choose an A_2 greater than A_1, then equation 4 implies that P_2 is greater than P_1. In this case, the pressure increases in the direction of flow, a change that initially seems contrary to intuition.

The bobbin flowmeters (also called *variable-orifice flowmeters*) in anesthesia machines use a similar principle. These devices consist of a slightly tapered vertical tube and a bobbin or ball that fits inside the tube (see Fig. 44-33). The cross-sectional area of the ring-shaped gap between the bobbin and the tube wall is proportional to the height of the bobbin. Because changes in the cross-sectional area of flow are abrupt rather than gradual (see Fig. 44-31), the Bernoulli theorem does not accurately describe this type of flow. The flow above the bobbin (i.e., downstream) is highly turbulent, and turbulence is a condition that dissipates kinetic energy into heat. However, the introduction of the empirical constant C_d enables one to use the same formulation as in equation 4:

$$Q = C_d A\sqrt{[2(P_1 - P_2)]/\rho} \quad (5)$$

and

$$P_1 - P_2 = \left(\frac{1}{2}\rho Q^2\right) / \left(C_d^2 A^2\right) \quad (6)$$

where C_d is a dimensionless constant called the *discharge coefficient*. This constant varies with the shape of the orifice and with the value for another dimensionless parameter, the Reynolds number (Re). The Reynolds number, the overall ratio of inertial forces to viscous forces in a particular flow, is determined as follows:

$$Re = \rho UL/\mu \quad (7)$$

where U is mean flow velocity, L is a characteristic length for the flow (in our flowmeter, L is the diameter of the tube), and μ is the viscosity of the fluid. The dimension for viscosity is M/LT. The value for the Re is important to any fluid flow because it determines some of the most important characteristics of the flow. For example, the transition from laminar or "smooth" flow to turbulent flow is determined by the shape of the flow and the Re. Flow in a long, straight, smooth-walled tube becomes turbulent at an Re value of approximately 2100. On the other hand, flow through an abrupt orifice, such as that of the flowmeter in Figure 44-34, becomes turbulent at an Re value of less than 100.

Returning now to the function of the flowmeter, one can see that as gas flows upward through the tapered tube, the bobbin begins to rise. As the bobbin rises, the cross-sectional area of the orifice (A) increases because of the taper of the tube; therefore, the drop in pressure (P_1–P_2) decreases. The bobbin reaches an equilibrium position for a given volume of flow (Q) when the pressure lifting the bobbin is exactly equal to the weight of the bobbin. In this type of flowmeter, the pressure difference is fixed by the bobbin weight, and the area of the orifice varies with the volume of the flow, hence the name variable-orifice flowmeter. Equations 5 and 6 show that calibration of these flowmeters depends on both the density and the viscosity of the gas: density (ϱ) appears explicitly, and viscosity (μ) appears in the dependence of C_d on the Re. If we use the wrong gas in a particular flowmeter, then equations 5 and 6 and the viscosity and density of the new gas enable us to predict the change in calibration.

APPENDIX 44-6 *Measurement of Cardiac Output by the Thermal Dilution and Mass Flow Technique*

A commonly used method of measuring blood flow is dilutional calculation, that is, dye or thermal dilution. These methods are simply mass or energy balances that determine the volume of fluid that has been diluted by adding a volume of dye or a given thermal energy. If you have a bucket of water at room temperature (25° C) and you want to determine the volume of water in the bucket, then you could add a known volume of water at a known temperature. If 100 mL of water at 35° C is added to the bucket and the final temperature is 27° C, then the unknown volume can be calculated by balancing the heat energy associated with the dilutional process, assuming that no heat is lost to the environment. This dilutional process can be used to measure blood flow

by completing this same heat balance measured over time. Thermodilution cardiac output measurements can have significant error as a result of the many assumptions associated with the technique, such as rapid injection of the thermodilution injectate; accurate temperature and volume of the injected fluid; constant known heat capacity of blood, which, in reality, is a function of the hematocrit value; and little heat loss to the lung; among others.

Thermistor probes are most commonly used for clinical monitoring of patient temperature because they are inexpensive, small, and flexible. For these reasons, the thermistor probe is also used to measure cardiac output determined by the thermodilution technique. Computation of cardiac output performed in this manner is, in effect, a heat balance for the right side of the heart. (Heat balance is a method of accounting for all heat in a process or change involving the transfer of heat.) The technique consists of quick injection of a known volume of a sterile solution (usually 10 mL of 5% dextrose in water) into the right side of the heart while a sensor notes the temperature of the blood in the pulmonary artery. It is assumed that the cold injected solution thermally equilibrates with the blood as it perfuses the pulmonary artery but that the solution does not acquire heat from other tissues. The following equation is the solution of this heat balance:

$$CO = [\rho i Ci Vi\,(T_b - T_i)(60Cr)]/\left[(\rho_b C_b)\int_0^{\infty} T_b\,(t)\,dt\right] \quad (1)$$

where CO is cardiac output (L/min); ϱ_i and ϱ_b are the densities of the injectate and blood, respectively; C_i and C_b are the heat capacities of the injectate and blood, respectively; V_i is the volume of the injectate; T_b and T_i are the temperature of the blood and the injectate, respectively; Cr is a computational constant that corrects for the rising temperature of the injectate; and the integration is the area under the thermodilution curve. Because the injectate warms as it is injected through the catheter before mixing with the blood, the correction factor Cr is applied to the equation.

The same principle of balance used for temperature determination of cardiac output can be applied to oxygen (O_2) or carbon dioxide (CO_2) balance as well. Classically, O_2 balance is used as described by Fick. Measurement of O_2 consumption and content is cumbersome, and a modification of the Fick equation using CO_2 production is also used. Noninvasive cardiac output (NICO) is a new partial rebreathing method using the following equation:

$$Q = \dot{V}_{CO_2} / (C\overline{V}_{CO_2} - Ca_{CO_2}) \quad (2)$$

Cardiac output (Q) is simply the expired CO_2 divided by the arterial-venous difference in CO_2. Assuming that Q does not change, the equations for CO_2 elimination must be the same with or without rebreathing, where N indicates normal breathing and R indicates rebreathing. By rearranging the equations, cardiac output is the ratio of the change in the elimination of CO_2 divided by the change in arterial CO_2 content. Arterial CO_2 content is derived from the slope of partial pressure of end-tidal CO_2 ($Petco_2$).

$$Q = \dot{V}_{CO_{2N}} / \left(C\overline{V}_{CO_{2N}} - Ca_{CO_{2N}}\right) = \dot{V}_{CO_{2R}} / \left(C\overline{V}_{CO_{2R}} - Ca_{CO_{2R}}\right) = \frac{\Delta \dot{V}CO_2}{\Delta CaCO_2} \quad (3)$$

Therefore we can see that potential errors are induced by violations of the following assumptions: (1) change in Q during the measurement period, (2) change in metabolic rate and, hence, the production of CO_2, and (3) change in ventilation.

As a trend analysis, patients with chronic obstructive lung disease, in which the absolute value of arterial partial pressure of CO_2 ($Paco_2$) is widely different from $Petco_2$, may have an absolute error in Q determination by this method, but the relative changes should track.

APPENDIX 44-7 *Ultrasound*

The simplest sound wave to represent mathematically is a sinusoidal wave propagating in one dimension:

$$p' = p_0 \sin[(2\pi/\lambda)(x - at)] \quad (1)$$

where p′ is the pressure fluctuation, λ is the wavelength (distance between waves), x is the coordinate in the direction of propagation, and a is the speed of propagation, or the speed of sound.

The amplitude of a sound wave is measured by the root mean square value of the pressure fluctuations. This value is called the *sound pressure level* (SPL). Because the range of SPL values is often very wide, a logarithmic scale is used:

$$SPL = 20 \log (p^*/P_0) \quad (2)$$

where p* is the root mean square pressure fluctuation and P_0 is a reference pressure chosen as the lowest sound pressure detectable by the human ear. This pressure representing the threshold of hearing is 2×10^{-8} kPa at a sound frequency of 2 kHz (2000 cycles/sec). The units in this SPL scale are called *decibels* (dB). Thus a sound pressure of 2×10^{-8} kPa corresponds to an SPL of 0 dB, the lowest audible sound level [$(p^*/P_0 = 1$; log (1) = 0)]. Quiet conversation has an SPL of approximately 40 to 50 dB or a pressure 10 to 300 times that of the threshold of hearing.

When sound waves encounter a sudden change in the properties of the conducting medium, some of the sound is transmitted through the new medium and some of it is reflected or "scattered," in many directions. Although the mathematics of this process is complex, one conclusion is readily apparent: the greater the mismatch in density and compressibility between the two media, the more sound that is reflected. The quantity that best determines the degree of reflection at an interface between two media is the ratio (R) of the products of density (ϱ) and the speed of sound (a) through the two media:

$$R = (\rho_1 a_1)/(\rho_2 a_2) \quad (3)$$

We can easily see that the greatest acoustic mismatch in the body occurs between solid tissues and the lungs. Both the density and the speed of sound are much lower in the air-filled lungs than in solid tissues. Therefore ultrasonography cannot "look" through the lungs at tissues or organs on the other side. The second greatest mismatch occurs between soft tissues and bone, the latter having a much higher ϱa than the former. In 1842, Christian Johann Doppler first described the apparent change in pitch of a sound that occurred when either the source of the sound or the listener was moving. This Doppler effect now has several applications in patient monitoring, including precordial and esophageal Doppler ultrasound devices that measure local blood velocities or cardiac output. If a sound source radiating a frequency (f) is stationary and the listener is moving (see Fig. 44-18, *A*), the wavelength of the waves can be determined by the following equation:

$$\lambda = a/f \quad (4)$$

Continued on following page

APPENDIX 44-7 *Ultrasound (Continued)*

because the time between wave fronts is 1/f and the waves are moving at the speed of sound (a). If the listener moves toward the source at speed V_0, then the velocity of the listener relative to the moving wave fronts is $(a + V_0)$. The number of wave fronts that the listener encounters per unit time is therefore:

$$f' = \text{velocity/distance between waves} = (a + V_0)/\lambda \quad (5)$$

Because the sound frequency for a stationary listener is $f = a/\lambda$ (equation 4), the frequency f' heard by the moving listener becomes:

$$f' = (a + V_0)/\lambda = f + (V_0/\lambda) = f + (V_0 f/a) = f[1 + (V_0/a)] \quad (6)$$

The apparent frequency of the listener is thus increased by the factor $[1 + (V_0/a)]$. A listener moving toward the source at half the speed of sound hears a frequency 1.5 times that of a stationary listener.

Now consider a stationary listener and a source moving at speed V_0, as shown in Figure 44-18, *B*. The wave fronts are no longer concentric circles; they are more closely spaced in the direction that the source is moving. If the frequency of the sound emitted at the source is f, then the source moves a distance V_0/f during each vibration. The wavelength in the direction of motion is thus shortened by V_0/f and becomes $l = (a - V_0)/f$. The waves themselves are traveling at speed a; therefore the frequency heard by the stationary listener is:

$$f' = a/\lambda' = af/(a - V_0) = f[1/(1 - V_0/a)] \quad (7)$$

Now, if the source is moving at one half the speed of sound toward the listener, the apparent frequency doubles. Compare this situation with the preceding one in which the listener is moving and the apparent frequency increases by only 50%. Doppler ultrasound systems combine the two situations shown in Figure 44-18. The initial acoustic source is a stationary transducer, and the sound from this device is scattered from a moving target (e.g., red blood cells). The scattered sound then returns to a stationary listener—the receiving transducer. In effect, the target is a moving listener hearing a stationary source; the target then reradiates the sound as a moving source toward a stationary listener. The frequency heard by the receiving transducer is obtained by combining equations 6 and 7:

$$f' = f\left[\frac{1 + V/a}{1 - V/a}\right] \quad (8)$$

In this example, we have assumed that the target is moving toward the ultrasound transducers at speed V. If the target is moving at one half the speed of sound, then the observed frequency is increased by a factor of 3! Because changes in the frequency of sine waves can be precisely measured, the Doppler principle provides an accurate method of measuring the velocity of moving sound reflectors. At the high frequencies often used (≥5 MHz), objects as small as red corpuscles can scatter enough sound for detection.

Ultrasound imaging is exceptionally complex. For simplicity's sake, recall the submarine movies in which the sonar operator calls out "range 2000 yards, bearing 36 degrees." These two parameters are critical in describing some of the mathematics of ultrasound.

The first factor to consider is the maximal range of the ultrasound, which is described by the following relationship:

$$r_{max} = cT/2 \quad (9)$$

that is, the maximal range equals the speed of sound in tissue (≈1540 m/sec), multiplied by the time T between pulses divided by 2. A further limitation is the fact that the energy dissipates in the tissue. (You need to tap harder when percussing to detect deeper structures). For deeper penetration into tissues, higher energies and slower pulse rates are required. Wavelength and frequency are related in the following manner:

$$\lambda = c/f \quad (10)$$

where f is the frequency, λ is the wavelength, and c is the speed of sound.

Next, we need to consider both the axial resolution (Is the enemy destroyer 2000 or 2005 yards distant?) and the annular resolution (Is its bearing 36 or 38 degrees?). Sound in tissue spreads out in a bandwidth around a fundamental frequency. Therefore to determine the necessary bandwidth for an axial resolution of 2 mm, the following approximation holds:

$$B = 2c/\Delta r \quad (11)$$

where Δr is the axial resolution. Therefore we need a bandwidth of 1.54 MHz to get an axial resolution of 2 mm.

For annular resolution ($\Delta\theta$), remember that the beam spreads out the further it goes from the source. Without deriving the mathematics, two factors determine annular resolution—frequency and aperture. Aperture size is limited to a size that will fit into or onto a human. Remember that a 1-degree error at a 1-cm range will increase at a 10-cm range: circumference = $2\pi r$: $1/360 \times 2 \times \pi \times 1 = 0.17$ mm; thus, at 10 cm, circumference = 1.7 mm.

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Chapter 45

Cardiovascular Monitoring

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Key Points

- Most automated noninvasive arterial blood pressure measuring devices use an oscillometric measurement technique and rarely cause complications. Caution should be exercised in patients who cannot complain of arm pain, those with irregular rhythms that force repeated cuff inflation, and those receiving anticoagulant therapy.
- The Allen test for palmar arch collateral arterial flow is not a reliable method to predict complications from radial artery cannulation. Despite the absence of anatomic collateral flow at the elbow, brachial artery catheterization for perioperative blood pressure monitoring is a safe alternative to radial or femoral arterial catheterization.
- The accuracy of a directly recorded arterial pressure waveform is determined by the natural frequency and damping coefficient of the pressure monitoring system. Optimal dynamic response of the system will be achieved when the natural frequency is frequent, thereby allowing accurate pressure recording across a wide range of damping coefficients.
- Rather than the common placement at the midaxillary line, the preferred position for alignment (or "leveling") of external pressure transducers is approximately 5 cm posterior to the sternomanubrial junction. When using external transducers and fluid-filled monitoring systems, this transducer location will eliminate confounding hydrostatic pressure measurement artifacts.
- Because of wave reflection and other physical phenomena, the arterial blood pressure recorded from peripheral sites has a wider pulse pressure than when measured more centrally.
- Dynamic measures of cardiac preload, such as stroke volume and pulse pressure variation, are better predictors of intravascular volume responsiveness than static indicators, such as central venous pressure (CVP) and pulmonary capillary wedge pressure.
- Selecting the best site, catheter, and method for safe and effective central venous cannulation requires that the physician consider the purpose of catheterization, the patient's underlying medical condition, the intended operation, and the skill and experience of the physician performing the procedure. Right internal jugular vein cannulation is preferred due to its consistent, predictable anatomic location and its relative ease of access intraoperatively.
- Mechanical complications from central venous catheters can be decreased by the use of ultrasound vessel localization, venous pressure measurement before large catheter insertion, and radiographic confirmation that the catheter tip lies outside the pericardium and parallel to the walls of the superior vena cava.
- CVP is the result of a complex and diverse interplay among many different physiologic variables, the main ones being venous return and cardiac function. No simple relationship exists between CVP and circulating blood volume. Despite this, important pathophysiologic information can be obtained by careful assessment of the CVP waveform morphology.
- Catheter misuse and data misinterpretation are among the most common complications of central venous and pulmonary artery catheters.

KEY POINTS—cont'd

- Pulmonary artery wedge pressure is a delayed and damped reflection of left atrial pressure. The wedge pressure provides a close estimate for pulmonary capillary pressure in many cases, but it may underestimate capillary pressure when postcapillary pulmonary vascular resistance is increased, as in patients with sepsis.
- Use of central venous, pulmonary artery diastolic, or pulmonary artery wedge pressures as estimates of left ventricular preload is subject to many confounding factors, including changes in diastolic ventricular compliance and juxtacardiac pressure.
- Pulmonary artery catheter monitoring has not been shown to improve patient outcome. Reasons cited for these results include misinterpretation of catheter-derived data and failure of hemodynamic therapies that are guided by specific hemodynamic indices.
- Thermodilution cardiac output monitoring, the most widely used clinical technique, is subject to measurement errors introduced by rapid intravenous fluid administration, intracardiac shunts, and tricuspid valve regurgitation.
- Mixed venous hemoglobin oxygen saturation is a measure of the adequacy of cardiac output relative to bodily oxygen requirements. This measurement is also dependent on the arterial hemoglobin oxygen saturation and hemoglobin concentration.

INTRODUCTION TO CARDIOVASCULAR MONITORING: FOCUSED PHYSICAL EXAMINATION

Although electronic devices constitute crucially important cardiovascular monitors, the physician's senses offer an integrated, panoramic view of the patient's condition, enhanced further by an understanding of the specific clinical context. Whereas electronic instruments accurately and reliably collect massive volumes of data, the clinician plays a vital role by evaluating, and interpreting these data.[1] Just as inspection, palpation, and auscultation are the cornerstones of physical examination, they are also fundamental to perioperative cardiovascular monitoring. For example, direct palpation of a pulse can differentiate true asystole from monitoring artifact more efficiently than troubleshooting an electrocardiogram (ECG) monitor, and direct observation of a beating heart during cardiac surgery or palpation of the aorta by the surgeon provide immediate and invaluable information about the potential causes of hemodynamic instability. However, the strengths and limitations of all monitoring techniques must be understood.

Given that the cardiovascular system is responsible for the transport of substrates and by-products to and from all organ systems, end-organ function is routinely substituted for cardiovascular performance. Inspection of mucous membranes, skin color, and skin turgor often yields important information about hydration, oxygenation, and perfusion. Empiric estimation of intravascular fluid deficits and blood loss, urine output, and changes in mental status is also helpful. Unfortunately, interpretation of these clinical signs and symptoms is often confounded by anesthetic drugs and preexisting organ dysfunction.

STETHOSCOPY

Although Laennec is credited with introducing the stethoscope into general medical practice in 1818, nearly a century elapsed before Harvey Cushing proposed its routine use during surgery.[2] Stethoscopy provides a simple and reliable means of continuous monitoring of heart and breath sounds. Precordial stethoscopy consists of a heavy metal bell or accumulator attached to a length of rubber or plastic extension tubing and a custom-molded monaural plastic earpiece. The esophageal stethoscope facilitates temperature, clear breath, and heart sound monitoring, but it is only practical during general anesthesia.[3] Although generally considered very low risk, rare cases of pharyngeal or esophageal trauma or hypoxemia from tracheobronchial compression can occur.

Despite its purported value, widespread use of continuous stethoscopy has decreased in recent years, possibly related to routine use of pulse oximetry or capnography.[4-6] As a practical matter, clinicians may no longer be as adept at recognizing changes in heart or breath sounds owing to the increasing reliance on electronic monitoring devices, distraction, or operating room noise. As a result, intraoperative stethoscopy has primarily become limited to specialized clinical settings (e.g., pediatric anesthesia, remote locations).

HEART RATE MONITORING

The ability to estimate the heart rate quickly with a "finger on the pulse" is a skill as important as this expression is common, even though electronic devices are most often used to continuously monitor this crucial vital sign as an important guide to anesthetic depth and surgical stimulation. The ECG is the most common method used in the operating room, even though any device measuring the

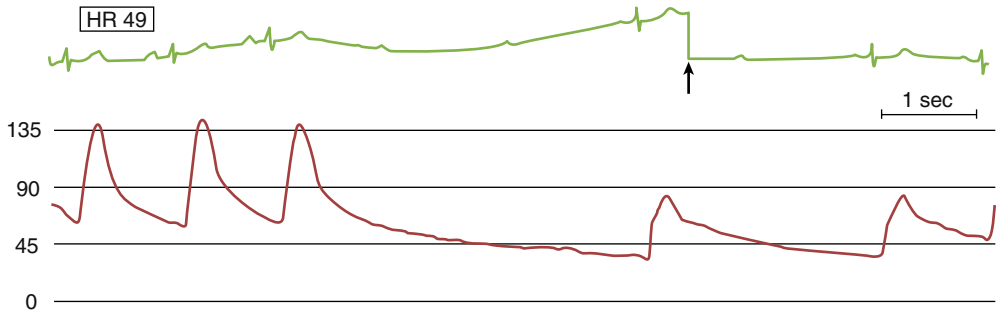


Figure 45-1. Digital heart rate (HR) displays may fail to warn of dangerous bradyarrhythmias. Direct observation of the electrocardiogram (ECG) and the arterial blood pressure traces reveals complete heart block and a 4-second period of asystole, whereas the digital display reports a HR of 49 beats/min. Note that the ECG filter (*arrow*) corrects the baseline drift so that the trace remains on the recording screen. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

period of the cardiac cycle will suffice. Accurate detection of the R wave and measurement of the R wave–R wave interval serve as the basis from which digitally displayed values are derived and periodically updated (e.g., at 5- to 15-second intervals)[7] (Fig. 45-1).

Electrical interference in the ECG trace most often arises from the electrosurgical unit but other sources may also be problematic. Power line noise appears as a 60-Hz artifact and may be eliminated by selecting narrower-bandpass ECG filters, including a 60-Hz notch filter. Problems can also be caused by random twitching and fasciculations, as well as by medical devices such as lithotripsy machines, cardiopulmonary bypass equipment, and fluid warmers.[8] High-amplitude pacing spikes may be misinterpreted as R waves and confound heart rate measurement, as can tall T waves. Decreasing the ECG gain, adjusting R-wave detection sensitivity, changing the ECG lead to one with a smaller pacing spike or T-wave amplitude, or selecting pacing detection modes may improve R-wave detection and heart rate measurement.

PULSE RATE MONITORING

The distinction between heart rate and pulse rate is the difference between electrical depolarization with systolic contraction of the heart (heart rate) and a detectable peripheral arterial pulsation (pulse rate). Pulse deficit describes the extent to which the pulse rate is less than the heart rate and may arise in conditions such as atrial fibrillation in which, intermittently, a very short R wave–to–R wave interval compromises the stroke volume to such an extent that no corresponding arterial pulse is detectable for that systolic ejection. The most extreme example of a pulse deficit is electrical-mechanical dissociation or pulseless electrical activity, seen in patients with cardiac tamponade, extreme hypovolemia, and other conditions in which cardiac contraction does not generate a palpable peripheral pulse.

Many monitors report heart rate and pulse rate separately, the former from the ECG trace and the latter from the pulse oximeter plethysmograph or arterial blood pressure monitor. In addition to indicating the pulse rate, this waveform may also provide supplementary diagnostic clues to cardiovascular function.[9,10] Although monitoring both heart rate and pulse rate may seem redundant, such redundancy is intentional, improves accuracy, and reduces measurement errors and false alarms.[11]

ARTERIAL BLOOD PRESSURE MONITORING

Like heart rate, arterial blood pressure is a fundamental cardiovascular vital sign included in the mandated standards for basic anesthetic monitoring.[12] Blood pressure is usually measured either by indirect cuff devices or direct arterial cannulation with pressure transduction. These techniques measure different physical signals and differ in their degree of invasiveness. However, both are subject to numerous confounding factors that often result in significantly discrepant results, even with simultaneous measurements.[13]

INDIRECT MEASUREMENT OF ARTERIAL BLOOD PRESSURE

Manual Intermittent Techniques

Most indirect methods of arterial blood pressure measurement use a sphygmomanometer, first described by Riva-Rocci in 1896.[14] Using an arm-encircling inflatable elastic cuff, a rubber bulb to inflate the cuff, and a mercury manometer to measure cuff pressure, the radial arterial pulse was palpated as the pressure in the cuff was increased (or later on rapid cuff deflation), identifying the systolic blood pressure (SBP). Detecting both systolic and diastolic pressure became possible with the description of the auscultatory method of blood pressure measurement by Korotkoff in 1905.[15] The Korotkoff sounds are a complex series of audible frequencies produced by turbulent flow beyond the partially occluding cuff. The pressure at which the first Korotkoff sound is heard is considered the systolic pressure (phase I). The sound character progressively changes (phases II and III), becomes muffled (phase IV), and is finally absent (phase V). Diastolic blood pressure (DBP) is recorded at phase IV or V (i.e., significant muffling or disappearance of the sounds altogether).

A fundamental shortcoming of the auscultatory method is its reliance on blood flow to generate Korotkoff sounds. Decreased peripheral blood flow from any

etiology, including shock or intense vasoconstriction, can attenuate or obscure sound generation or detection.[16] In contrast, changes in vessel or tissue compliance underlying the cuff (such as in severe edema, shivering, or calcific arteriosclerosis) require excessively high cuff-occluding pressures and may yield completely inaccurate readings.[17]

Other common sources of error during intermittent manual blood pressure measurement include selection of an inappropriate cuff size and excessively rapid cuff deflation. A well-fitted cuff has a bladder that extends to 40% of arm circumference and 80% of length of the upper arm.[17] The cuff should be applied snugly and contain no residual air, with the bladder centered over the artery. Although too large a cuff often provides acceptable results, the use of a cuff that is too small usually results in falsely high readings.[17] The cuff pressure should decrease slowly enough for the changes in Korotkoff sounds to be detected and properly interpreted. An excessively rapid deflation would cause changes in the sounds to be missed and yield a falsely low pressure reading.

Automated Intermittent Techniques

Automated noninvasive blood pressure (NIBP) devices are standard equipment in most critical care settings because they provide frequent, regular pressure measurements, free the operator to perform other vital clinical duties, provide audible alarms, and can transfer data to a computerized information system. Most NIBP devices are based on oscillometry, a technique first described by Marey in 1876.[17] In this method, small changes in cuff pressure with arterial pulsation during cuff deflation are used to estimate mean arterial blood pressure (MAP). In contrast to the auscultatory method, in this case, the maximal degree of detectable pulsation is determined to be the MAP. SBP and DBP pressures are calculated according to proprietary algorithms that vary by manufacturer; they are thus less reliable than the values for MAP.[17-19] Systolic pressure is typically identified as the pressure at which escalating pulsations reach 25% to 50% of maximum. Diastolic pressure is the most unreliable oscillometric measurement and is commonly recorded when the pulse amplitude has declined to a small fraction of its peak value. In clinical practice, oscillometric automated NIBP measurement is from the upper arm.

In general, automated NIBP measurements closely approximate directly measured arterial pressure, especially at mean pressures of 75 mm Hg and lower.[17,20] However, significant shortcomings have been identified in clinical studies and are important to recognize. Standards for performance of automated NIBP devices have been established by the Association for the Advancement of Medical Instrumentation (AAMI) and the British Hypertension Society (BHS); however, given the ethical conflict that is posed by a requirement for validation of noninvasive devices against invasive direct arterial measurements, auscultation remains the standard against which all devices are evaluated. Consequently, the minimum performance standards that all NIPB devices are required to meet are significantly affected by the fundamental nature of the auscultatory method and the specific protocols used during each validation procedure.[21] At present, in a pool of 85 subjects, new automatic devices must demonstrate average differences no more than ± 5 mm Hg, with standard deviations no greater than 8 mm Hg. This implies that some values may deviate up to 20 mm Hg from the true pressure and still achieve "acceptable performance" as defined by the AAMI.[22] However, attempts to reproduce these validation procedures in clinical situations indicate that with at least one very commonly used device, only 74% of diastolic and 60% of mean and systolic measurements were within 10% of direct measured values. Although the device did meet the minimum performance standards, (MAP ≤ 5 mm Hg difference from the standard), the variances were large.[23]

Clinical studies comparing NIPB with direct arterial pressure measurements also reflect the problematic nature of NIBP monitoring. Oscillometric methods often underestimate systolic and overestimate diastolic measurements, significantly underestimating pulse pressure calculations.[24] These devices also tend to underestimate mean values during periods of hypertension and overestimate during hypotension, potentially biasing clinical decisions in unstable patients.[25] Ankle, calf, and thigh cuffs have never been validated at all, although there is sometimes no choice but to use a cuff in such a manner. Several well-conducted studies in critically ill patients have shown that NIBP measurements show acceptable agreement when a well-fitted cuff is used on the upper arm. The devices can also be reliably used in unstable patients or in alternative locations to identify patients who are hypotensive (MAP ≤ 65 mm Hg), and to differentiate those who have responded to a therapeutic intervention from those who have not (e.g., MAP ≤ 65 mm Hg versus MAP > 65 mm Hg). However, they *cannot* be reliably used to titrate therapy outside of these variables, and averaging of several measurements is necessary for a measurement to be considered reliable.[20,26]

NIBP devices are validated against a technique that measures something slightly different—and in a fundamentally different manner. The auscultatory method measures the systolic and diastolic pressures, estimating the mean, whereas oscillometric devices measure the mean and calculate (in different ways) the systolic and diastolic. Furthermore, directly measured arterial pressure measurements use another technique altogether. It has been stated that "current protocols for validating blood pressure monitors give no guarantee of accuracy in clinical practice."[21] Perhaps expecting these techniques to yield identical or even similar values is unrealistic, especially in complex and unstable clinical situations.

Complications of Noninvasive Blood Pressure Measurement

Although automated, noninvasive blood pressure measurement is generally safe, severe complications, though rare, do occur[27] (Box 45-1). Compartment syndromes have developed after prolonged periods of frequent cuff cycling, likely related to trauma or impaired distal limb perfusion. Other contributing factors include cuff placement over a joint or other vulnerable tissue, or repeated use in the face of a significant confounding factor such as muscle tremors, significant dysrhythmias, or a kinked

BOX 45-1 *Complications of Noninvasive Blood Pressure (NIBP) Measurement*

Pain
Petechiae and ecchymoses
Limb edema
Venous stasis and thrombophlebitis
Peripheral neuropathy
Compartment syndrome

BOX 45-2 *Indications for Arterial Cannulation*

Continuous, real-time blood pressure monitoring
Planned pharmacologic or mechanical cardiovascular manipulation
Repeated blood sampling
Failure of indirect arterial blood pressure measurement
Supplementary diagnostic information from the arterial waveform

cable. Also, patients with peripheral neuropathies, arterial or venous insufficiency, severe coagulopathies, or recent use of thrombolytic therapy may be vulnerable to complications from a noninvasive blood pressure monitor.

Automated Continuous Techniques

Advances in microprocessor and servomechanical control technology have enabled noninvasive techniques to provide a reasonable representation of the arterial pressure waveform and a nearly continuous assessment of blood pressure without resorting to direct arterial cannulation. One such device measures finger blood pressure with an arterial volume-clamp method designed and first reported by Penaz in 1973.[28] Although reasonable accuracy of finger blood pressure as a surrogate for intraarterial pressure measurements are possible, many factors have precluded more widespread application of this technology.[29] Under many circumstances, finger blood pressure monitoring will not reflect brachial arterial pressure. In addition, finger arteries are prone to spasm with the potential for distal ischemia, hand position will influence pressure values, and blood sampling cannot be performed without indwelling catheters. Changes in finger physiology also influence noninvasive hemoglobin (SpHb) monitoring (also see Chapter 61).

Other automatic continuous noninvasive techniques are available to measure arterial blood pressure, using technologies based on arterial wall displacement, pulse transit time, arterial tonometry, and other methods. All techniques have limitations, including need for calibration, sensitivity to motion artifact, and limited applicability in critically ill patients.[17,30,31] It is not clear whether any noninvasive technique will reduce the need for direct arterial pressure monitoring or whether these methods will replace automated intermittent oscillometry as the standard NIBP monitoring method in anesthesia and critical care.

DIRECT MEASUREMENT OF ARTERIAL BLOOD PRESSURE

Arterial cannulation with continuous pressure transduction remains the accepted reference standard for arterial blood pressure monitoring. Despite its increased risk, cost, and need for technical expertise for placement and management, its utility in providing crucial and timely information outweighs its risks in many cases (Box 45-2). The Australian Incident Monitoring Study of 1993 confirmed the superiority of direct arterial pressure monitoring over indirect monitoring techniques for the early detection of intraoperative hypotension.[26,32]

Perhaps the most underemphasized value of direct arterial pressure monitoring is the potential for arterial pressure waveform analysis to provide diagnostic information regarding changes in the patient's condition. This was directly proposed more than a half century ago by Eather and associates, who advocated monitoring of "arterial pressure and pressure pulse contours" in anesthetized patients.[33] Some aspects are readily apparent and routinely used, such as identification of the dicrotic notch to guide proper timing for intraaortic balloon counterpulsation. Others, such as recognition of excessive variation in arterial blood pressure variables as a sign of preload reserve, have only gained significant attention more recently.[34]

Percutaneous Radial Artery Cannulation

The radial artery is the most common site for invasive blood pressure monitoring because it is technically easy to cannulate and complications are uncommon.[35,36] Slogoff and coauthors described 1700 cardiovascular surgical patients who underwent radial artery cannulation without ischemic complications despite evidence of radial artery occlusion after decannulation in more than 25% of patients.[37] Furthermore, most investigations of hand perfusion, in both the early and late postoperative periods following radial artery harvest for coronary artery bypass and flap transfer procedures, have reported no significant decrease relative to the contralateral hand.[38-43]

Before attempting radial artery cannulation, many clinicians assess the adequacy of collateral flow to the hand by performing a modified Allen test. This bedside examination is a variation on a technique originally described in 1929 to assess arterial stenosis in the hands of patients with thromboangiitis obliterans.[44] The examiner compresses both the radial and ulnar arteries and asks the patient to make a tight fist, exsanguinating the palm. The patient then opens the hand, avoiding hyperextension of the wrist or fingers. As occlusion of the ulnar artery is released, the color of the open palm is observed. Normally, the color will return to the palm within several seconds; severely reduced ulnar collateral flow is present when the palm remains pale for more than 6 to 10 seconds.

Although the Allen test is often used to identify patients at increased risk for ischemic complications from radial artery cannulation, the predictive value of this test is poor. Numerous reports of permanent ischemic sequelae note that a normal Allen test result was present before vessel cannulation.[38,45] In contrast, there are many descriptions of uncomplicated radial artery monitoring in the face of a

documented abnormal Allen test.[37,46] In recent years, the radial artery has been used safely as an access site for coronary catheterization and stenting or harvested for use in coronary bypass grafting, even in individuals who have an abnormal Allen test.[46,47] Although most patients show radial artery dominance with respect to overall hand perfusion, total radial artery occlusion does not compromise distal perfusion, perhaps as the result of collateral recruitment.[47] Overall, the diagnostic accuracy of the modified Allen test with a 5-second threshold is only 80% with 76% sensitivity and 82% specificity. It appears that the test is unable to provide a cutoff point below which perfusion can be deemed vulnerable.[48] Unfortunately, use of pulse oximetry, plethysmography, or Doppler ultrasound as adjuncts to visual inspection of the palm for return of circulation does not seem to improve its accuracy. Oximetry is able to detect blood flow at extremely low flows, leading to poor specificity, whereas no established ultrasound criteria are available by which to evaluate radial or ulnar blood flow and identify abnormalities.[38,49,50] In general, although a normal modified Allen test may be useful in identifying patients acceptable for radial artery harvest or use for coronary angiography, it does not predict clinical outcomes following cannulation for arterial blood pressure monitoring as currently practiced.[38]

In preparation for cannulation of the radial artery, the wrist and hand are immobilized and secured with the wrist resting across a soft pad. Dorsiflexion of the wrist should be mild at most to avoid attenuating the pulse by stretch or extrinsic tissue pressure. The course of the radial artery proximal to the wrist is identified by gentle palpation, the skin is prepared with an antiseptic, and a local anesthetic is injected intradermally and subcutaneously beside the artery. Arterial catheterization can be performed with a standard IV catheter or an integrated guidewire-catheter assembly designed for this purpose. A recent educational video provides great detail about this standard procedure.[50-52]

Once the catheter is fully advanced into the vessel lumen, the radial artery is occluded by applying proximal pressure, the needle is removed, the monitoring system pressure tubing is fastened to the catheter, an appropriate sterile dressing is applied, and the apparatus is taped and secured to the wrist. Although a soft arm board can be used to maintain the wrist in an anatomically neutral position during arterial pressure monitoring, extreme wrist dorsiflexion should be avoided to prevent injury to the median nerve.[53,54]

Some clinicians choose the "transfixion" technique for arterial cannulation, in which the front and back walls of the artery are punctured intentionally, the needle is removed from the catheter, the catheter is withdrawn until pulsatile blood flow appears, and then advanced into the vessel lumen either directly or over a wire using the Seldinger technique. Although it is unnecessary to place an additional hole in the back wall of the radial artery for successful cannulation, the technique *per se* is not associated with a more frequent rate of complications or failure.[55]

Other aids to arterial cannulation include the use of ultrasound imaging to guide catheter insertion, especially as a rescue method following a failed attempt.[56] Although ultrasound techniques improve first-pass cannulation success rates, improved clinical outcomes and shorter times required to place have not been documented as a justification for routine use.[57-60]

Alternative Arterial Pressure Monitoring Sites

If the radial arteries are unsuitable or unavailable, multiple alternatives exist. The ulnar artery is cannulated in a manner similar to that for the radial and has been used safely even following failed attempts to access the ipsilateral radial artery.[37,61] Similarly, the brachial artery, although lacking collateral branches to protect the hand, has a long track record of safe use. Bazaral and associates reported more than 3000 brachial artery catheters in patients undergoing cardiac surgery, with only one significant thrombotic complication and no long-term sequelae.[62] The axillary artery has the advantages of patient comfort, mobility, and access to a central arterial pressure waveform, and complications are similar in incidence to those for use of radial and femoral arteries.[36] A slightly longer catheter is preferred for the brachial or axillary sites because of their relatively deeper location and position with respect to the shoulder and elbow joints. However, the risk of cerebral embolization is significantly increased when more centrally located vessels are used.

The femoral artery is the largest vessel in common use for monitoring, but its safety appears to be comparable to those for other sites.[36] As with axillary artery pressure monitoring, the femoral artery waveform more closely resembles aortic pressure than do waveforms recorded from peripheral sites. The risk of distal ischemia may be reduced because of the large diameter of the artery, but risk of atherosclerotic plaque embolization is significant during initial vessel manipulation. Catheterization of the femoral artery is best achieved with a guidewire technique, and the point of vessel entry must be distal to the inguinal ligament to minimize the risk of arterial injury, hidden hematoma formation, or even uncontrolled hemorrhage into the pelvis or peritoneum.[63]

Less commonly used alternatives include the dorsalis pedis, posterior tibial, and superficial temporal arteries, with the pedal vessels being more popular for pediatric patients.

Complications of Direct Arterial Pressure Monitoring

Large clinical investigations confirm the infrequent incidence of long-term complications after radial arterial monitoring.[35-37] Although vascular complications from radial artery cannulation are uncommon, factors that may increase risk include vasospastic arterial disease, previous arterial injury, thrombocytosis, protracted shock, high-dose vasopressor administration, prolonged cannulation, and infection.[38,64,65] Catheter diameter and composition as well as artery size and patient gender may be associated with arterial injury.[38]

Rare complications can occur after arterial cannulation at any location (Box 45-3). In most cases, catheter placement was technically difficult or there were contributory factors such as shock or coagulopathy. In a large observational study of 2000 untoward clinical events resulting

BOX 45-3 ***Complications of Direct Arterial Pressure Monitoring***

Distal ischemia, pseudoaneurysm, arteriovenous fistula
Hemorrhage
Arterial embolization
Infection
Peripheral neuropathy
Misinterpretation of data
Misuse of equipment

from vascular access of all kinds, only 13 were related to peripheral arterial cannulation, fewer than those associated with central venous[18] or peripheral venous cannulation.[33] Of these cases, 5 involved problems with equipment; in 3 cases the arterial line was used inadvertently for drug injection, and in the remainder, the arterial line was either disrupted or kinked. In only 1 case did transient vasospasm follow radial artery cannulation.[32,66] A second report from this study noted that direct pressure monitoring was problematic in 10 cases, resulting from incorrect calibration or interpretation of the pressure display or unrecognized subclavian artery stenosis. Furthermore, the anesthesia closed claims study reported claims related to arterial pressure monitoring at any site constitute only 8% of all claims related to any vascular access (2% of total claims). Of these, almost 54% were related to radial artery use (ischemic injury, median or radial nerve injury, or retained wire fragment), less than 8% were associated with use of the brachial artery, and the remainder followed severe thrombotic or hemorrhagic complications after femoral artery monitoring.[67] Although patient physiology is important, equipment misuse, careful placement technique and catheter care, as well as improper data interpretation are primary issues in many complications related to arterial pressure monitoring.

Technical Aspects of Direct Blood Pressure Measurement

Direct measurement of arterial blood pressure requires that an accurate and appropriate pressure waveform be reproduced on the monitor. Unfortunately, several factors, including extension tubing, stopcocks, flush devices, recorders, amplifiers, and transducers, influence this process and may introduce significant error.[68]

Most invasive blood pressure monitoring systems are underdamped second-order dynamic systems modeled after mass-spring systems that demonstrate simple harmonic motion dependent on elasticity, mass, and friction.[68-70] These three properties determine the system operating characteristics (i.e., frequency response or dynamic response), which in turn are characterized by critical system parameters, natural frequency (f_n, ω) and damping coefficient (τ, Z, α, D). The natural frequency of a system determines how rapidly the system oscillates after a stimulus, whereas the damping coefficient reflects frictional forces acting on the system and determines how rapidly it returns to rest after a stimulus. Both variables may be estimated or measured at the bedside and dramatically influence the appearance of the displayed pressure waveform.

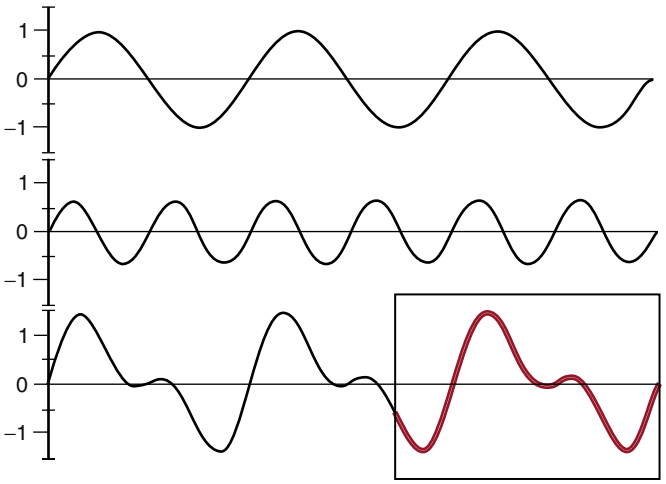


Figure 45-2. Arterial blood pressure waveform produced by summation of sine waves. The fundamental wave (*top*) added to 63% of the second harmonic wave (*middle*) results in a pressure wave (*bottom*) resembling a typical arterial blood pressure waveform (*box*). *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

Natural Frequency, Damping Coefficient, and Dynamic Response of Pressure Monitoring Systems. The displayed arterial blood pressure waveform is a periodic complex wave produced via Fourier analysis of a summation of a series of simpler but diverse propagated and reflected pressure waves. As such, it is a mathematic re-creation of the original complex pressure wave created by stroke volume ejection.[71,72] The original pressure wave is characterized by its fundamental frequency, manifested clinically as the pulse rate. Although the pulse rate is measured in beats per minute, fundamental frequency is expressed as cycles per second or Hertz (Hz).

The sine waves that sum to produce the final complex wave have frequencies that are multiples or harmonics of the fundamental frequency. A crude arterial waveform depicting a systolic upstroke and peak, dicrotic notch, and so forth can be reconstructed with reasonable accuracy from only two sine waves, the fundamental frequency and the second harmonic (Fig. 45-2). If the original arterial pressure waveform contains high-frequency components such as a steep systolic upstroke, higher-frequency sine waves (and more harmonics) are needed to provide a faithful reconstruction of the original pressure waveform. As a general rule, 6 to 10 harmonics are required to provide distortion-free reproductions of most arterial pressure waveforms.[71,73] Hence, accurate arterial blood pressure measurement in a patient with a pulse rate of 120 beats/min (2 cycles/sec or 2 Hz) requires a monitoring system dynamic response of 12 to 20 Hz (i.e., 6 to 10 waveforms × 2 Hz). The faster the heart rate and the steeper the systolic pressure upstroke, the greater the dynamic response demands on the monitoring system.

All monitoring systems have an intrinsic natural frequency and damping coefficient. If the natural frequency is too low, frequencies in the monitored pressure waveform will overlap that of the measurement system, the system will resonate, and pressure waveforms recorded on the monitor will be exaggerated or amplified versions

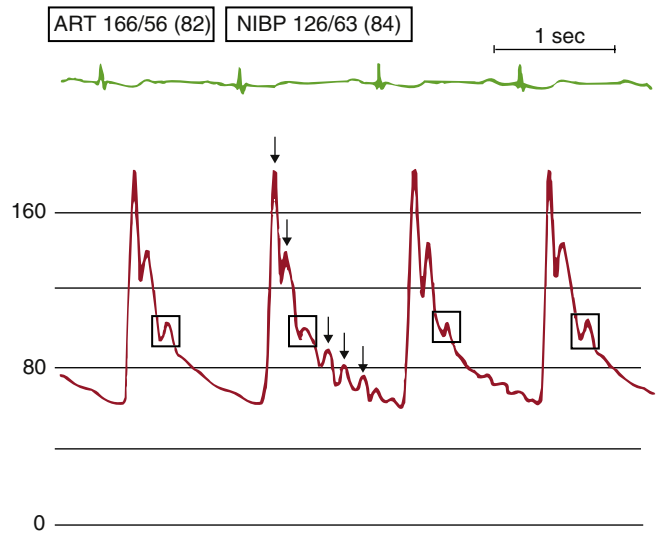


Figure 45-3. Underdamped arterial pressure waveform. Systolic pressure overshoot and additional small, nonphysiologic pressure waves (*arrows*) distort the waveform and make it hard to discern the dicrotic notch (*boxes*). Digital values displayed for direct arterial blood pressure (ART 166/56, mean 82 mm Hg) and noninvasive blood pressure (NIBP 126/63, mean 84 mm Hg) show the characteristic relationship between the two measurement techniques in the presence of an underdamped system. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

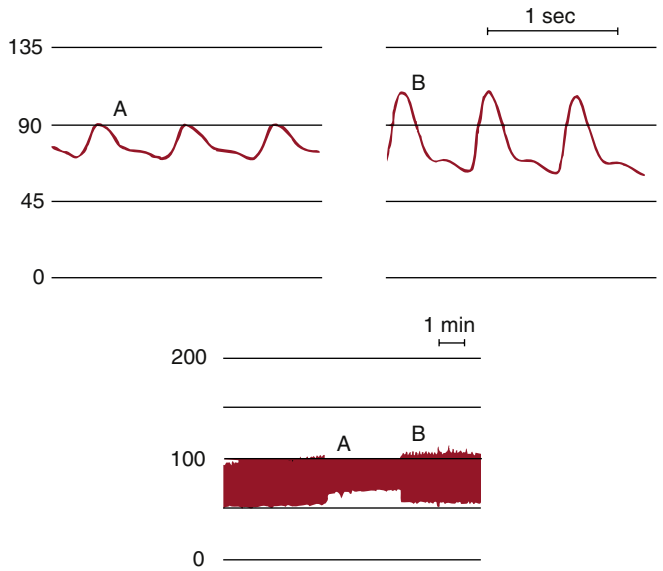


Figure 45-4. Overdamped arterial pressure waveform. The overdamped pressure waveform (**A**) shows a diminished pulse pressure compared with the normal waveform (**B**). The slow-speed recording *(bottom)* demonstrates a 3-minute period of damped arterial pressure. Note that despite the damped system, mean arterial pressure remains unchanged. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

of true intraarterial pressure. An underdamped pressure waveform displays systolic pressure overshoot and may contain elements produced by the measurement system itself rather than the original propagated pressure wave (Fig. 45-3). In contrast, an overdamped waveform is recognizable by its slurred upstroke, absent dicrotic notch, and loss of fine detail. Such waves display a falsely narrowed pulse pressure, although MAP may remain reasonably accurate (Fig. 45-4).

Catheter-tubing transducer systems in routine clinical use tend to be underdamped but have an acceptable natural frequency that exceeds 12 Hz[68] (Fig. 45-5). In general, the lower the natural frequency of the monitoring system, the more narrow the range of damping coefficients necessary to ensure faithful reproduction of the pressure wave. For example, if the monitoring system's natural frequency is 10 Hz, the damping coefficient must be between 0.45 and 0.6 for accurate pressure waveform monitoring. If the damping coefficient is too low, the monitoring system will be underdamped, resonate, and display factitiously elevated systolic blood pressure; if the damping coefficient is too high, the system will be overdamped, systolic pressure will be falsely decreased, and fine detail in the pressure trace will be lost.

For any specific system, the most rapid possible natural frequency facilitates an optimal dynamic response.[72] In theory, this is achieved best by using short lengths of stiff pressure tubing and limiting the number of stopcocks and other monitoring system appliances. Blood clots and air bubbles concealed in stopcocks and other connections have a similar impact on system dynamic response. As a general rule, adding air bubbles to a monitoring system will not improve its dynamic response because any

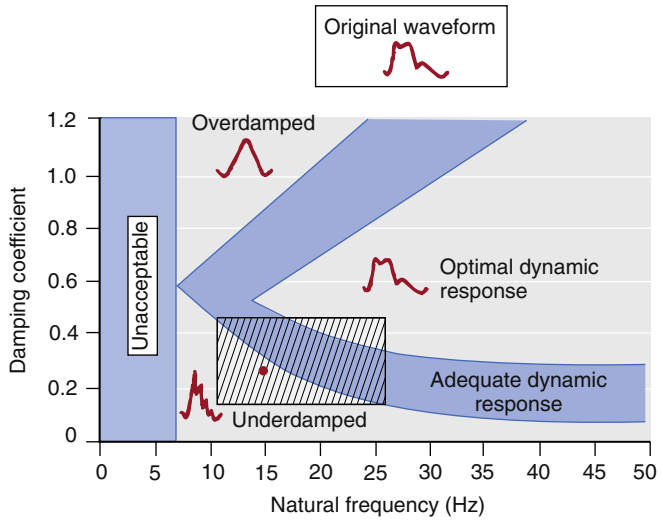


Figure 45-5. Interaction between damping coefficient and natural frequency. Depending on these two parameters, catheter tubing-transducer systems may be classified by their dynamic response range. Systems with an optimal or adequate dynamic response will record and display all or most pressure waveforms encountered in clinical practice. Overdamped and underdamped systems skew measurements in predictable ways, with those having a natural frequency <7 Hz proving unacceptable. The *rectangular crosshatched box* indicates the ranges of damping coefficients and natural frequencies commonly encountered in clinical pressure measurement systems. The *red dot* within the box marks the mean values of 30 such systems.[74] *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

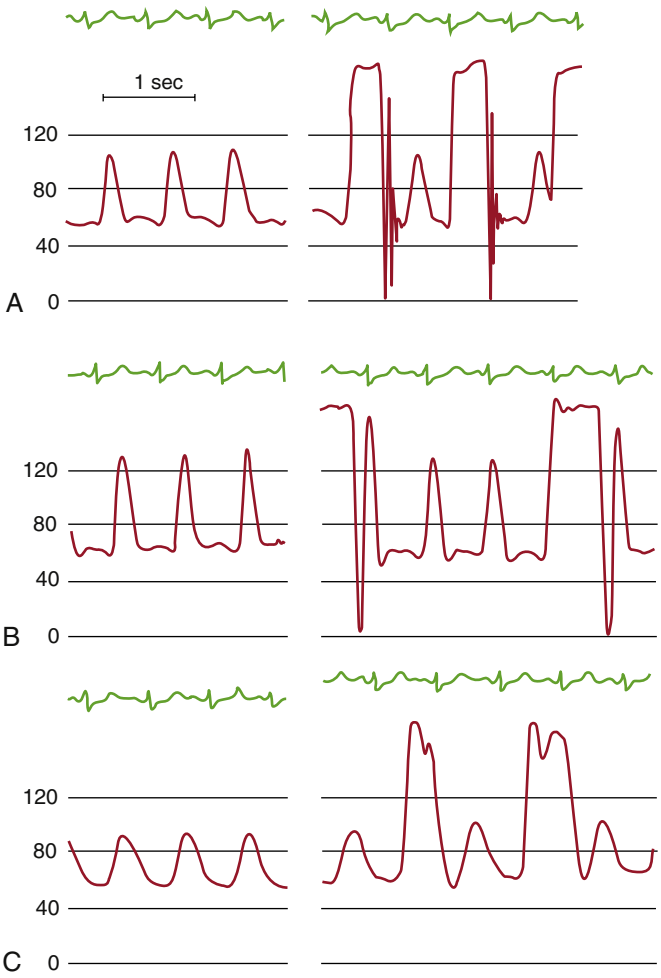


Figure 45-6. Effect of small air bubbles within arterial pressure monitoring systems. Arterial pressure waveforms are displayed, along with superimposed fast-flush square-wave artifacts. **A,** Original monitoring system has an adequate dynamic response (natural frequency 17 Hz, damping coefficient 0.2). **B,** A small 0.1-mL air bubble added to the monitoring system produces a paradoxical increase in arterial blood pressure. Note decreased natural frequency of the system. **C,** A larger 0.5-mL air bubble further degrades dynamic response and produces spurious arterial hypotension. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

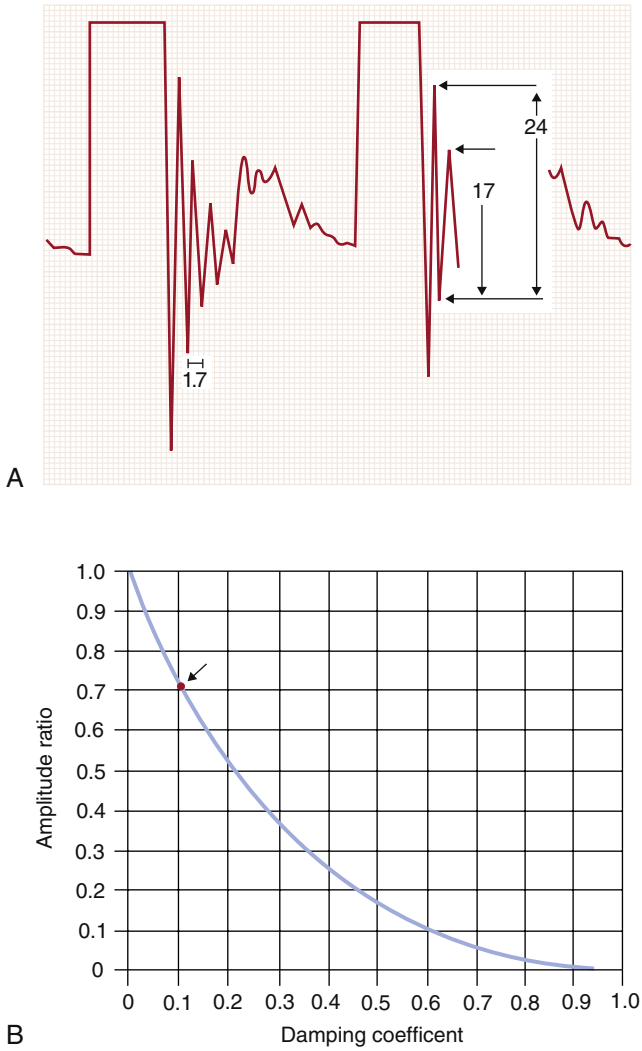


Figure 45-7. Clinical measurement of natural frequency and damping coefficient. **A,** Two square-wave fast-flush artifacts interrupt an arterial pressure waveform recorded on standard 1-mm grid paper at a speed of 25 mm/second. Natural frequency is determined by measuring the period of one cycle of adjacent oscillation peaks (1.7 mm). Damping coefficient is determined by measuring the heights of adjacent oscillation peaks (17 and 24 mm). From these measurements, a natural frequency of 14.7 Hz and an amplitude ratio of 0.71 may be calculated. **B,** Relation between amplitude ratio and damping coefficient. The amplitude ratio determined in the fast-flush test in (**A**) corresponds to a damping coefficient of 0.11. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

increase in system damping is necessarily accompanied by a decrease in natural frequency. Somewhat paradoxically, monitoring system resonance may increase and cause even greater systolic pressure overshoot (Fig. 45-6).

The fast-flush test provides a convenient bedside method for determining dynamic response of the system and assessing signal distortion.[68,70,72] The nature and duration of the flush artifact following a brief opening of the fast-flush valve are noted. Natural frequency is inversely proportional to the time between adjacent oscillation peaks, calculated as 1 cycle/1.7 mm × 25 mm/sec = 14.7 cycles/sec (14.7 Hz) (Fig. 45-7, *A*). Shorter oscillation cycles indicate a more rapid natural frequency.[72] Alternatively, the damping coefficient is related to the amplitudes of successive oscillation peaks. The amplitude ratio thus derived indicates how quickly the measuring system returns to a resting state. The damping coefficient can be calculated mathematically, but it is usually determined graphically from the amplitude ratio.[68,72] For example, the amplitudes of two successive oscillation cycles are 24 and 17 mm, giving an amplitude ratio of 17/24 or 0.71. This corresponds to a damping coefficient of 0.11 based on the graphic solution (Fig. 45-7, *B*). Note that the monitoring system illustrated has an adequate natural frequency (approximately 15 Hz) but is underdamped (damping coefficient 0.11, optimal range 0.45 to 0.6, see earlier). One would expect to find systolic pressure overshoot in such a system.

Although the technical requirements for accurate arterial blood pressure measurement are well known, these

conditions are often lacking in routine clinical practice. Examination of the frequency response of 30 radial artery catheter-transducer systems used in routine intensive care monitoring showed natural frequency (mean 14.7 ± 3.7 Hz) and damping coefficient (mean 0.24 ± 0.07) values that fell within the range of underdamped systems.[68,74] Furthermore, the range of frequency responses (10.2 to 25.3 Hz) and damping coefficients (0.15 to 0.44) measured in this setting suggests that distortion of the arterial waveform is common in clinical practice, particularly systolic arterial pressure overshoot resulting from underdamped systems (see Fig. 45-5).

Pressure Monitoring System Components. Arterial pressure monitoring systems have a number of components, beginning with the intraarterial catheter and including extension tubing, stopcocks, inline blood sampling set, pressure transducer, continuous-flush device, and electronic cable connecting the bedside monitor and waveform display screen. The stopcocks in the system provide sites for blood sampling and allow the transducer to be exposed to atmospheric pressure to establish a zero reference value. Needleless blood sampling ports and inline aspiration systems permit blood drawing without use of sharp needles and allow aspirated waste blood to be returned to the patient within a convenient closed system. Modifications such as these are intended to reduce the risk of needle injury and decrease waste of the patient's blood during sampling. However, these additional features may degrade the dynamic response of the monitoring system and further exacerbate systolic arterial pressure overshoot.

The flush device provides a continuous, slow (1 to 3 mL/hr) infusion of saline to purge the monitoring system and prevent thrombus formation within the arterial catheter. Dextrose solutions should not be used, because flush contamination of sampled blood may cause serious errors in blood glucose measurement.[75] A dilute concentration of heparin (1 to 2 units heparin/mL saline) has been added to the flush solution to reduce further the incidence of catheter thrombosis, but this practice increases the risk of heparin-induced thrombocytopenia and should be avoided. The flush device not only ensures continuous slow flushing of the line and catheter but also includes a spring-loaded valve for periodic, high-pressure flushing. This rapid flushing is used to purge the extension line of blood after an arterial sample has been taken or to restore the dynamic response characteristics of the pressure monitoring system, which otherwise slowly deteriorate over time.[76]

Transducer Setup: Zeroing and Leveling. Before use, pressure transducers must be zeroed, calibrated, and leveled to the appropriate position relative to the patient. A zero pressure reference value must be established by opening the appropriate stopcock and exposing the transducer to atmospheric pressure and executing the zero-command, a specific maneuver that may vary with each manufacturer. This underscores the fact that all pressures displayed on the monitor are referenced to local atmospheric pressure. To be precise, it is the air-fluid interface at the level of the stopcock that is the zero pressure locus. This point must be specifically positioned relative to the patient to ensure correct transducer level. When a significant or unexpected change in pressure occurs, the zero reference value can be rechecked quickly by opening the stopcock and noting that the pressure value on the bedside monitor is still zero.[72] Occasionally, a faulty transducer, cable, or monitor will cause the zero baseline to drift introducing significant error into all subsequent pressure measurements until the zero reference is reestablished.[77,78]

Historically, transducer calibration closely followed zeroing. Calibration is an adjustment in system gain to ensure accurate transducer measurement relative to a known reference. Although traditionally calibrated against a mercury manometer, current disposable pressure transducers meet accuracy standards established by the AAMI and the American National Standards Institute.[77] As such, formal bedside transducer calibration is no longer performed. However, it is good practice to routinely compare pressures obtained via a newly placed arterial catheter with a blood pressure obtained via other means as a more informal but useful calibration. On occasion, despite successful transducer zeroing, the measured blood pressure values seem erroneous, and a malfunctioning pressure transducer, cable, or monitor is identified and replaced.[78]

The final step in transducer setup is to adjust the pressure monitoring zero point to the appropriate level relative to the patient. Note that transducer zeroing and leveling are two distinct procedures. Zeroing established the zero reference point for the transducer system, whereas leveling matches this reference point to a specific point on the patient's body. That is, it determines where the value 0 will be and, hence, from where measurements will begin. Although the precise location for the zero reference level is important for accurate blood pressure monitoring, it is even more critical when the physiologic range of values is smaller, such as for cardiac filling pressures. In such cases, a small absolute error would have a large influence on the displayed pressures.

Arterial pressure transducers should be placed to best estimate aortic root pressure. Although the midchest position is often used in supine patients, several investigators have shown that cardiac filling pressures are significantly overestimated when transducers are leveled to the midchest rather than a position approximately 5 cm posterior to the sternal border.[79,80] This preferred (more anterior) transducer location obviates the confounding effect of hydrostatic pressure on cardiac filling pressure measurements.

The position of the pressure transducer relative to the patient must be considered in interpreting blood pressure measurements. In some circumstances, the clinician may choose to place the arterial transducer at a level different from the standard. In such a case, the displayed pressure is the pressure measured at that level and, important to note, is not the same at the aortic root. For example, when the arterial pressure transducer is elevated to the level of the patient's ear to approximate the location of the circle of Willis during a sitting neurosurgical procedure, arterial blood pressure at the level of the brain is being measured and displayed, and that at the aortic

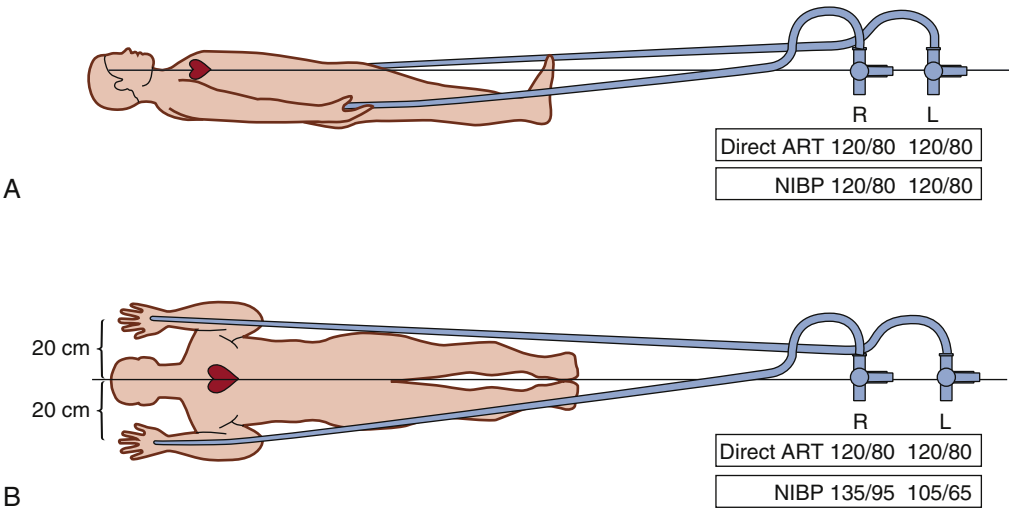


Figure 45-8. Effect of patient position on the relation between direct arterial blood pressure (ART) and indirect noninvasive blood pressure (NIBP) measurements. **A,** In the supine patient, pressures measured from the right (R) or left (L) arms by either technique will be the same. **B,** In the right lateral decubitus position, ART pressures recorded directly from the right and left radial arteries will remain unchanged so long as the respective pressure transducers remain at heart level. However, NIBP will be higher in the dependent right arm and lower in the nondependent left arm. Differences in NIBP are determined by the positions of the arms above and below the level of the heart and are equal to the hydrostatic pressure differences between the level of the heart and the respective arm. A 20-cm difference in height produces a 15-mm Hg difference in pressure. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

root is higher (by an amount equal to the vertical height difference between the two points). There is no need to re-zero the transducer when it is moved, as atmospheric pressure changes very little over the few inches of height adjustment. Errors are also common when pressure transducers are fixed to an intravenous pole and the patient's bed height is adjusted. Raising the height of the bed relative to the transducer will cause overestimation of arterial blood pressure, whereas lowering the patient below the transducer will lead to underestimation.

For proper interpretation of blood pressure measurements from a patient in the lateral decubitus position, it is helpful to differentiate zeroing and leveling pressure transducers and to appreciate the differences between noninvasive and invasive blood pressure measurement. In this position, although the aortic root remains stationary, one arm is necessarily higher than the other. However, as long as the pressure transducer remains *fixed at the level of the heart,* the location of the arms or in which vessel the catheter resides has no influence on the measured arterial pressure. On the other hand, noninvasive cuff blood pressure measurements will be different in the two arms—higher in the dependent (down) arm and lower in the nondependent (up) arm (Fig. 45-8). As a result, to check the accuracy of a cuff measurement, it may be necessary to temporarily move the pressure transducer to the level of the blood pressure cuff in question.

Normal Arterial Pressure Waveforms

In the early era of arterial pressure monitoring, significant diagnostic information was gleaned from waveform analysis.[33] Unfortunately, this practice declined, possibly because of increasing reliance on cuff sphygmomanometry, which provides "numbers which came to be linked in a simplistic way to cardiac strength (systolic pressure) and arteriolar tone (diastolic pressure). Pseudoscience had arrived with (these) numbers …"[81] With the advent of automated graphic analysis and high-resolution, multicolored displays, renewed interest in waveform analysis is attracting new attention.[34] However, full appreciation of the diagnostic clues provided by the direct arterial pressure waveform requires understanding of normal waveform components, their relationship to the cardiac cycle, and the implications of waveform variations when recorded from different arterial sites.

The systemic arterial pressure waveform results from ejection of blood from the left ventricle into the aorta during systole, followed by peripheral runoff during diastole. The systolic waveform components consist of a steep pressure upstroke, peak, and ensuing decline, and immediately follow the ECG R wave. The downslope of the arterial pressure waveform is interrupted by the dicrotic notch, continues its decline during diastole after the ECG T wave, and reaches its nadir at end-diastole (Fig. 45-9). The dicrotic notch, known as the incisura when recorded at the central aorta (from the Latin, meaning "a cutting into") is sharply defined and thought to result from aortic valve closure.[82] In contrast, more peripheral arterial waveforms generally display a later, more blunted dicrotic notch that is more dependent on properties of the arterial wall. Note that the systolic upstroke starts 120 to 180 milliseconds after beginning of the R wave (see Fig. 45-9). This interval reflects total time required for depolarization of the ventricular myocardium, isovolumic left ventricular contraction, opening of the aortic valve, left ventricular ejection, propagation of the aortic pressure wave, and finally, transmission of the signal to the pressure transducer.

The bedside monitor displays values for the peak systolic and end-diastolic nadir pressures. MAP is dependent on the algorithm used by the monitor. In simplest terms, MAP is equal to the area beneath the arterial pressure

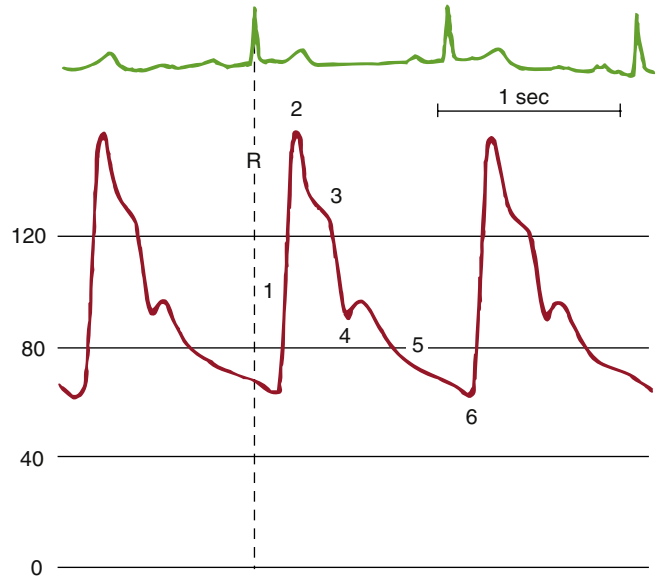


Figure 45-9. Normal arterial blood pressure waveform and its relation to the electrocardiographic R wave. (*1*) Systolic upstroke, (*2*) systolic peak pressure, (*3*) systolic decline, (*4*) dicrotic notch, (*5*) diastolic runoff, and (*6*) end-diastolic pressure. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

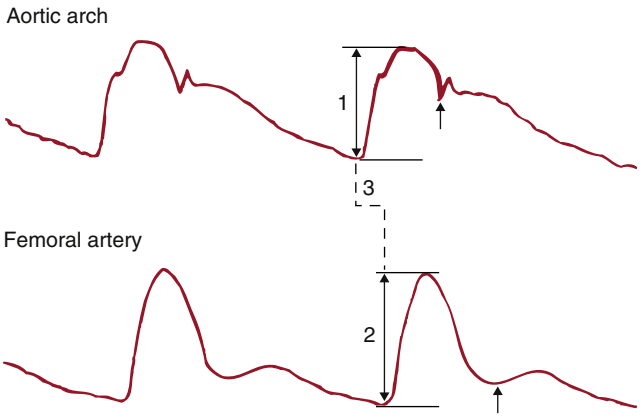


Figure 45-10. Distal pulse wave amplification of the arterial pressure waveform. Compared with pressure in the aortic arch, the more peripherally recorded femoral artery pressure waveform demonstrates a wider pulse pressure (compare *1* and *2*), a delayed start to the systolic upstroke (*3*), a delayed, slurred dicrotic notch (compare *arrows*), and a more prominent diastolic wave. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

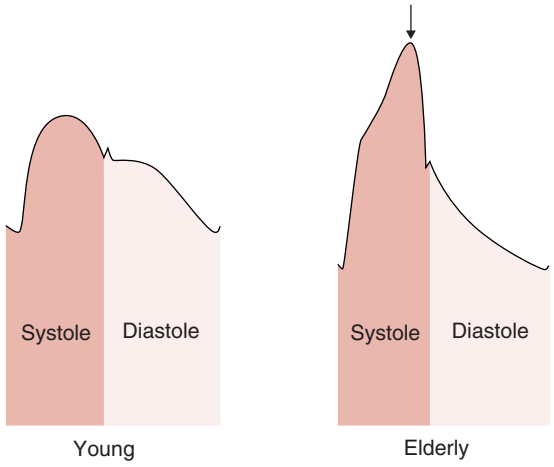


Figure 45-11. Impact of pressure wave reflection on arterial pressure waveforms. In older individuals with reduced arterial compliance, early return of peripherally reflected waves increases pulse pressure, produces a late systolic pressure peak (*arrow*), attenuates the diastolic pressure wave, and at times, distorts the smooth upstroke with an early systolic hump.

curve divided by the beat period, averaged over multiple cardiac cycles. Although MAP is often estimated as diastolic pressure plus one third times pulse pressure, this estimate is only valid at slower heart rates, because the proportion of the cardiac cycle spent in diastole decreases as the heart rate increases.[83]

An important feature of the arterial pressure waveform is distal pulse amplification. Pressure waveforms recorded simultaneously from different sites have different morphologies due to the physical characteristics of the vascular tree, namely, impedance and harmonic resonance[31,81] (Fig. 45-10). As the pressure wave travels from the central aorta to the periphery, the arterial upstroke becomes steeper, the systolic peak increases, the dicrotic notch appears later, the diastolic wave becomes more prominent, and end-diastolic pressure decreases. As a result, compared with central aortic pressure, peripheral arterial waveforms have higher systolic, lower diastolic, and wider pulse pressures. Furthermore, as the signal is delayed in arriving at the peripheral site, the systolic pressure upstroke begins approximately 60 milliseconds later in the radial artery than in the aorta. MAP in the aorta is only slightly higher than that in the periphery.

Reflection of pressure waves within the arterial tree has a great impact on changes to the arterial pressure waveform as it travels peripherally.[81] As blood flows from the aorta to the radial artery, mean pressure decreases only slightly because there is little resistance to flow in the major conducting arteries. At the arteriolar level, though, mean blood pressure decreases markedly as a result of a dramatic increase in vascular resistance. This resistance to flow diminishes pressure pulsations in smaller downstream vessels but augments upstream arterial pressure pulses by way of pressure wave reflection.[84] The summation of these antegrade and reflected waves determine the shape of the arterial pulse wave recorded from different arterial sites. For example, reduced arterial compliance causes premature return of reflected pressure waves, resulting in arterial pressure waveforms with increased pulse pressure, a late systolic pressure peak, attenuated diastolic pressure waves, and at times, an early systolic hump distorting the smooth upstroke (Fig. 45-11).

From these considerations, the morphology of the arterial waveform and the precise values of systolic and diastolic blood pressure vary throughout the arterial system under normal conditions in otherwise healthy individuals. These variations are augmented and at times greatly exaggerated by various factors, including but not limited to age, pathologic processes, and pharmacologic interventions.

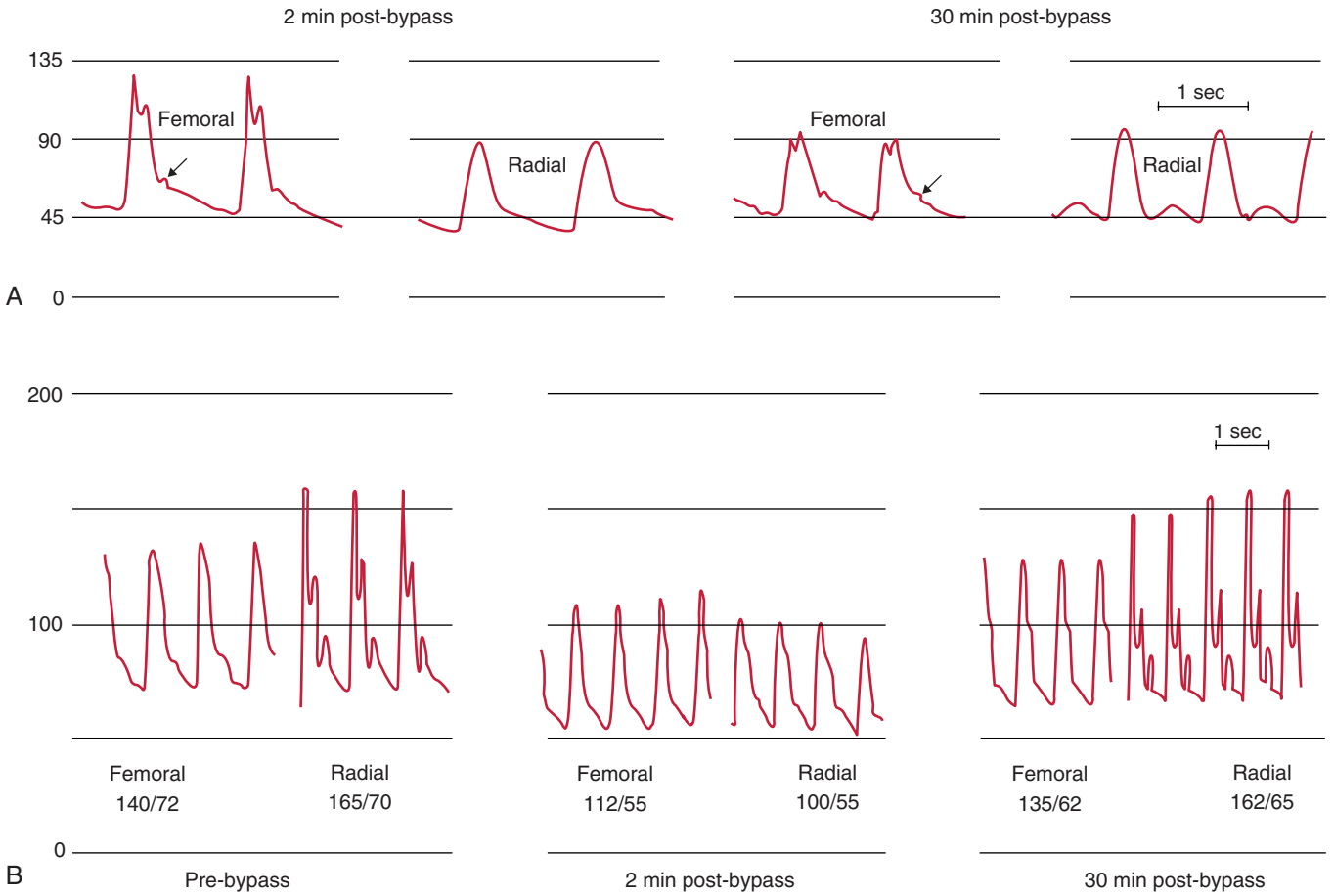


Figure 45-12. Arterial pressure gradients following cardiopulmonary bypass. **A,** Femoral and radial artery pressure traces recorded 2 minutes after bypass (2 min post-bypass), when radial artery pressure underestimates the more centrally measured femoral artery pressure and 30 minutes later (30-min post-bypass), when radial and femoral arterial pressures have equalized and radial pressure has resumed a more typical morphology. Note that dicrotic notch (*arrows*) is visible in the femoral pressure trace immediately after bypass, but is delayed in the radial pressure trace. **B,** Femoral and radial artery pressure traces recorded before cardiopulmonary bypass (pre-bypass), 2 minutes following bypass (2 min post-bypass), and 30 minutes following bypass (30 min post-bypass). Note changing relationship between femoral and radial artery pressure measurements at these different times.

Arterial Blood Pressure Gradients

A number of pathophysiologic conditions cause exaggerated arterial pressure gradients between monitoring sites, be they real, iatrogenic, or artifactual. Frank and co-workers demonstrated that 21% of patients undergoing peripheral vascular surgery had a blood pressure difference between the two arms that exceeded 20 mm Hg.[85] Clearly, monitoring blood pressure in an arm that has yielded a lower NIBP measurement or has a weaker palpable pulse will likely lead to errors in measurement and perhaps management. Atherosclerosis or pathologic conditions such as arterial dissection, stenosis, or embolism may preclude accurate pressure monitoring from affected sites. In addition, unusual patient positions during surgery may produce regional arterial compression, whereas surgical retraction can compromise perfusion and monitoring to a more localized area.[86,87]

The nature of the operative procedure is important when choosing the appropriate site for arterial pressure monitoring. Procedures requiring placement of a descending thoracic aortic cross-clamp may interrupt arterial flow to the left subclavian artery, perfusion to the left arm, and all vessels distal to the clamp unless some form of bypass is used. In such cases, blood pressure monitored in the right arm provides the best estimate of aortic root and carotid arterial pressure. Femoral artery pressure may be monitored simultaneously to estimate perfusion pressure distal to the aortic cross-clamp.

Significant physiologic disturbances, such as sepsis or shock, may produce generalized arterial pressure gradients that can affect the choice of site for arterial pressure monitoring. In patients receiving vasopressor infusions for septic shock, the femoral arterial pressure was noted to exceed the radial pressure by more than 50 mm Hg.[88] Such gradients, albeit less severe, have been noted with anesthetics, neuraxial blocks, and changes in patient temperature.[31] During hypothermia, thermoregulatory vasoconstriction causes systolic pressure in the radial artery to exceed that in the femoral artery, whereas during rewarming, vasodilation reverses the gradient.[89]

Characteristic gradients between central and peripheral sites have been described in cardiac surgery patients undergoing cardiopulmonary bypass (Fig. 45-12) (see Chapter 67). The mean radial artery pressure decreases on initiation

of bypass and remains less than mean femoral artery pressure throughout the bypass period.[90] Notably, this pattern persists in the first few minutes following separation from bypass, often by more than 20 mm Hg.[91] In most patients, this gradient resolves within the first hour, but occasionally, it remains well into the postoperative period.

Abnormal Arterial Pressure Waveforms

Detailed examination of the morphologic features of individual arterial pressure waveforms can provide important diagnostic information (Table 45-1) (Fig. 45-13, *A* to *D*). Aortic stenosis produces a fixed obstruction to ejection resulting in reduced stroke volume and a slowed rate of ejection. As a result, the waveform is small in amplitude (pulsus parvus), and has a slowly rising systolic upstroke on the arterial pressure waveform and a delayed peak in systole (pulsus tardus) (see Fig. 45-13, *B*). A distinct shoulder, termed the anacrotic notch, often distorts the pressure upstroke and even the dicrotic notch may not be discernible. These features may make the arterial pressure waveform appear overdamped.

In aortic regurgitation, the arterial pressure wave displays a sharp increase, wide pulse pressure, and decreased diastolic pressure owing to the runoff of blood into both the left ventricle and the periphery during diastole. The arterial waveform may have two systolic peaks (bisferiens pulse), with the first peak resulting from antegrade ejection and the second from a reflected wave originating in the periphery (see Fig. 45-13, *C*). In hypertrophic cardiomyopathy, the arterial pressure waveform assumes a peculiar bifid shape termed a spike-and-dome configuration. After an initial sharp blood pressure increase resulting from rapid, early systolic ejection, arterial pressure plummets as left ventricular outflow obstruction in mid-systole impedes ejection. This is finally followed by a second, late-systolic increase associated with arrival of reflected waves from the periphery (see Fig. 45-13, *D*).

Observation of how arterial waveform patterns change over time is another source of useful information. Pulsus alternans is a pattern of alternating beats of larger and

TABLE 45-1 ARTERIAL BLOOD PRESSURE WAVEFORM ABNORMALITIES

Condition	Characteristics
Aortic stenosis	Pulsus parvus (narrow pulse pressure) Pulsus tardus (delayed upstroke)
Aortic regurgitation	Bisferiens pulse (double peak) Wide pulse pressure
Hypertrophic cardiomyopathy	Spike and dome (mid-systolic obstruction)
Systolic left ventricular failure	Pulsus alternans (alternating pulse pressure amplitude)
Cardiac tamponade	Pulsus paradoxus (exaggerated decrease in systolic blood pressure during spontaneous inspiration)

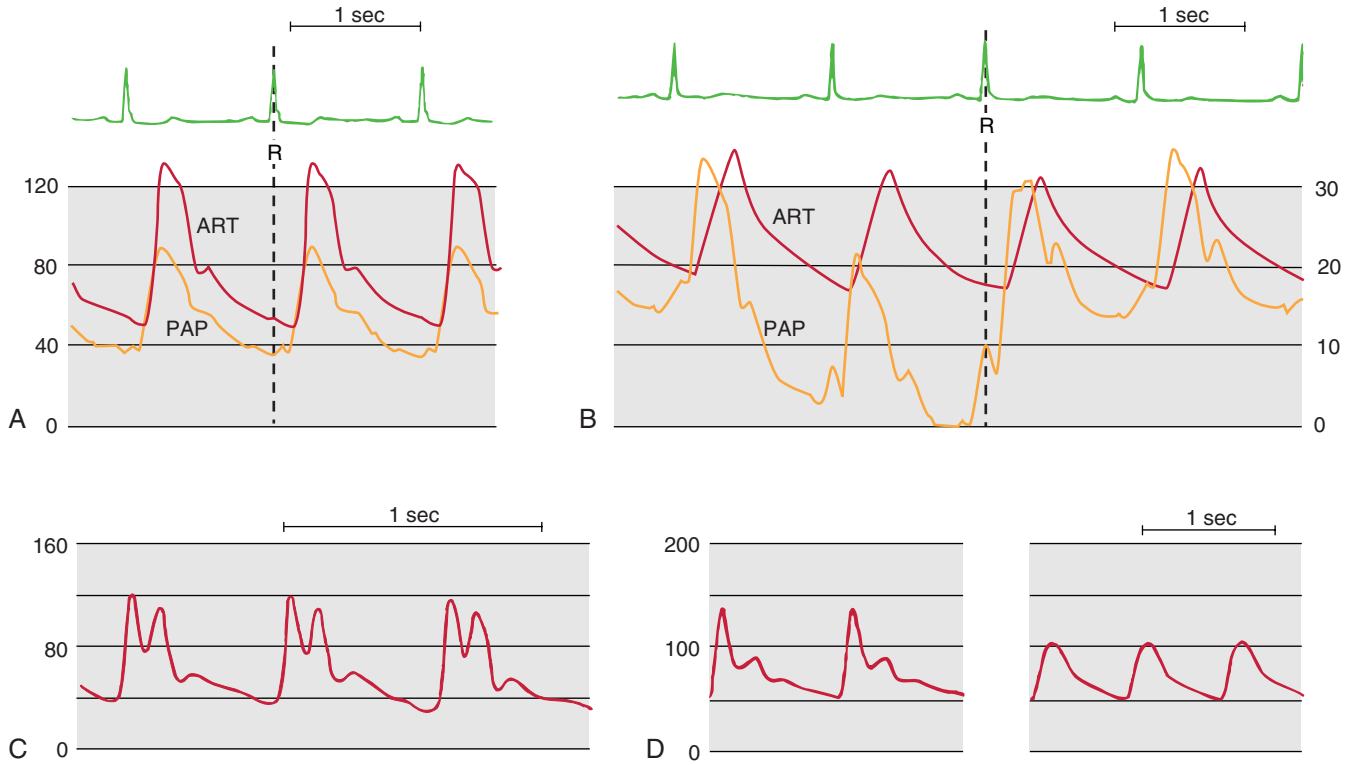


Figure 45-13. Influence of pathologic conditions on arterial pressure (ART) waveform morphology. **A,** Normal ART and pulmonary artery pressure (PAP) waveform morphologies demonstrating the similar timing of these waveforms relative to the electrocardiographic R wave. **B,** In aortic stenosis, the ART waveform is distorted with a slurred upstroke and delayed systolic peak. These changes are particularly striking in comparison with the normal PAP waveform. Note the beat-to-beat respiratory variation in the PAP waveform. For **A** and **B,** the ART scale is on the left and the PAP scale is on the right. **C,** Aortic regurgitation produces a bisferiens pulse and a wide pulse pressure. **D,** Arterial pressure waveform in hypertrophic cardiomyopathy shows a peculiar spike-and-dome configuration. The waveform assumes a more normal morphology following surgical correction of this condition. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

smaller pulse pressures that also vary with the respiratory cycle although its underlying mechanism remains poorly understood (Fig. 45-14, *A*). It may be a sign of severe left ventricular systolic dysfunction but can also be seen in patients with advanced aortic stenosis. Pulsus alternans should be distinguished from bigeminal rhythms, which are usually ventricular in origin. Although both appear as alternating pulse pressures in the arterial pressure waveform, pulsus alternans presents a regular rhythm.

Pulsus paradoxus is exaggerated variation in arterial pressure (<10 to 12 mm Hg) during quiet breathing[92,93] (Fig. 45-14, *B*). Pulsus paradoxus is not truly paradoxical, but rather an exaggeration of a normal variation in blood pressure that accompanies spontaneous ventilation. Pulsus paradoxus is highly characteristic, almost universal, in patients with cardiac tamponade but may also develop with pericardial constriction, severe airway obstruction, bronchospasm, dyspnea, or any condition that involves large swings in intrathoracic pressure. It is important to note, though, that in cases of cardiac tamponade, the pulse pressure and left ventricular stroke volume decrease during inspiration, in contrast to the arterial blood pressure changes observed in patients with forced breathing patterns and exaggerated changes in intrathoracic pressure in which pulse pressure remains constant.[94]

ARTERIAL PRESSURE MONITORING AND WAVEFORM ANALYSIS FOR PREDICTION OF INTRAVASCULAR VOLUME RESPONSIVENESSS

The starting point for hemodynamic resuscitation begins with optimizing cardiac preload, or more precisely, determining whether a specific patient has sufficient residual preload reserve. The limitations of static indicators of preload such as central venous pressure are well documented, as are the array of factors that confound their interpretation.[95] Newer dynamic markers of preload reserve and intravascular volume responsiveness have been studied for their ability to discriminate between those who would and those who would not benefit from volume expansion. Variations in arterial blood pressure observed during positive pressure ventilation, as well as a variety of derived indices, are the most widely studied of these dynamic indicators. Such changes in blood pressure may be visible on the bedside monitor in patients who are receiving direct arterial blood pressure monitoring, and they result from changes in intrathoracic pressure and lung volume that occur during the respiratory cycle.

During positive pressure ventilation, increases in lung volume compress lung tissue and displace blood contained within the pulmonary venous reservoir into the left heart chambers, thereby increasing left ventricular preload. Simultaneously, the increase in intrathoracic pressure reduces left ventricular afterload. The increase in left ventricular preload and decrease in afterload produce an increase in left ventricular stroke volume, an increase in cardiac output, and in the absence of changes in peripheral resistance, an increase in systemic arterial pressure. In most patients the preload effects are more prominent, but in patients with severe left ventricular systolic failure, the reduction in afterload plays an important role in increasing ventricular ejection. Simultaneously with increasing left heart filling during early inspiration, rising intrathoracic pressure causes a decrease in systemic venous return and right ventricular preload. The increased lung volume

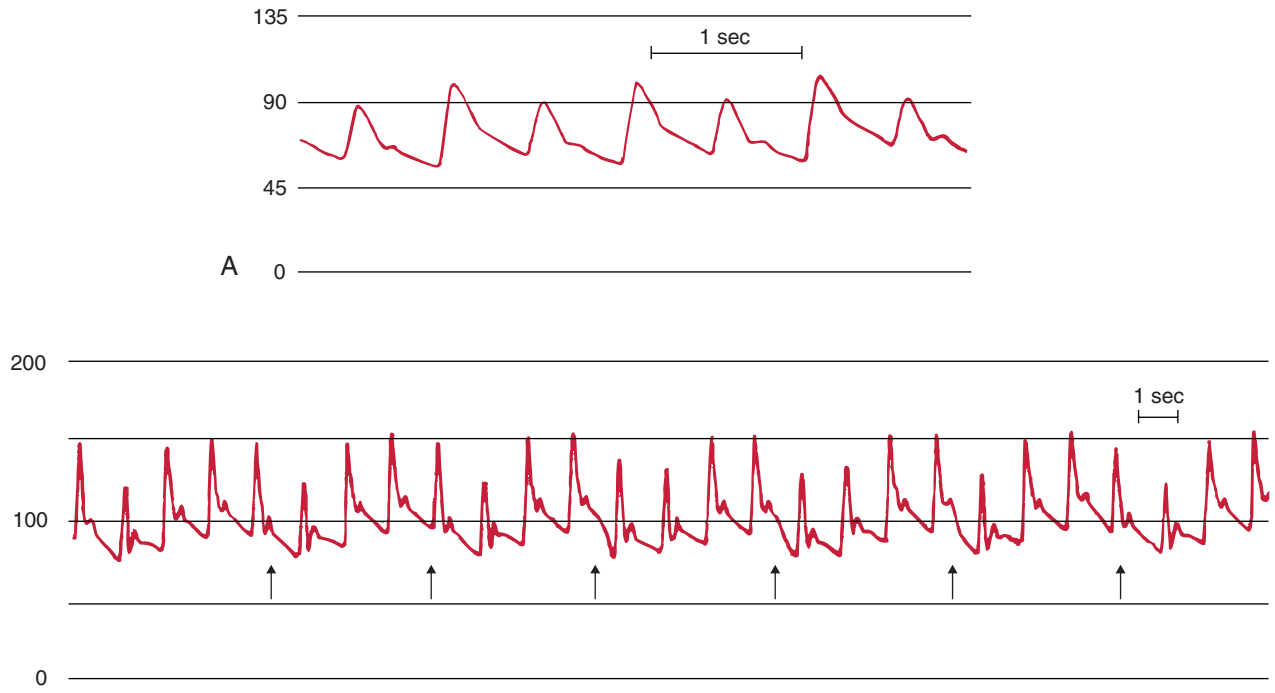


Figure 45-14. Beat-to-beat variability in arterial pressure waveform morphologies. **A,** Pulsus alternans. **B,** Pulsus paradoxus. The marked decline in both systolic blood pressure and pulse pressure during spontaneous inspiration (*arrows*) is characteristic of cardiac tamponade. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

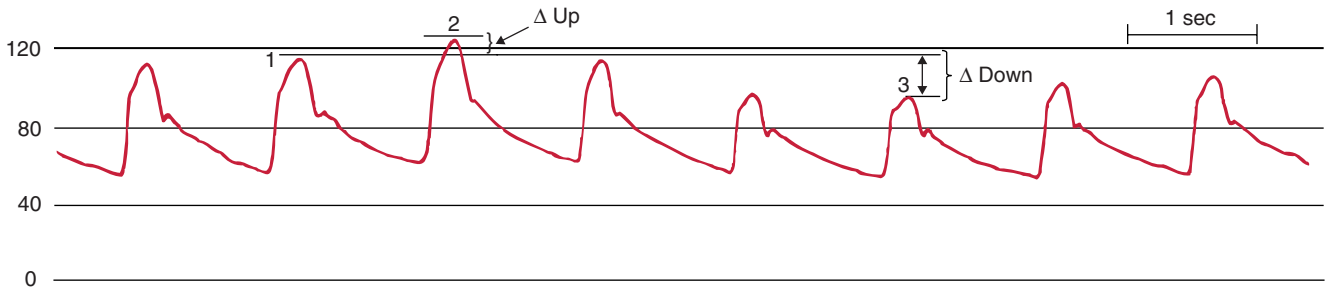


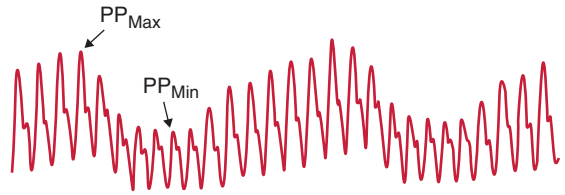
Figure 45-15. Systolic pressure variation. Compared with systolic blood pressure recorded at end expiration (*1*) a small increase occurs during positive-pressure inspiration (*2*, Δ Up) followed by a decrease (*3*, Δ Down). Normally, systolic pressure variation does not exceed 10 mm Hg. In this instance, the large Δ Down indicates hypovolemia even though systolic arterial pressure and heart rate are relatively normal. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

may also increase pulmonary vascular resistance slightly and thereby increase right ventricular afterload. These effects combine to reduce right ventricular ejection during early inspiration. During early expiration, the situation is reversed. The smaller amount of blood ejected from the right ventricle during inspiration traverses the pulmonary vascular bed and enters the left heart, resulting in reduced left ventricular filling. Left ventricular stroke volume falls, and systemic arterial blood pressure decreases. This cyclic variation in systemic arterial pressure is known as the systolic pressure variation (SPV).

SPV is often subdivided into inspiratory and expiratory components by measuring the increase (Δ Up) and decrease (Δ Down) in systolic pressure relative to the end-expiratory, apneic baseline pressure (Fig. 45-15). In a mechanically ventilated patient, normal SPV is 7 to 10 mm Hg, with Δ Up being 2 to 4 mm Hg and Δ Down being 5 to 6 mm Hg.[96] This observation has been used clinically in attempts to identify hypovolemic patients.[97] Both in experimental animals and critically ill patients, hypovolemia causes a dramatic increase in SPV, particularly the Δ Down component. However, it may be more accurate to describe the patients identified by increased SPV as having residual preload reserve. Although not identical to hypovolemia, preload reserve describes a physiologic state in which intravascular volume expansion or fluid challenge shifts the patient upward on the Frank-Starling curve, resulting in increased stroke volume, and increased cardiac output as long as systemic vascular resistance remains unchanged.

In a heterogeneous group of intensive care patients, Marik demonstrated that a large SPV (>15 mm Hg) was highly predictive of a low pulmonary artery wedge pressure (PAWP) (<10 mm Hg).[98] Using echocardiography to measure the left ventricular cross-sectional area as a surrogate for preload, Coriat and colleagues found Δ Down to be a better predictor of preload than wedge pressure.[99] Using receiver-operator curve analysis, Tavernier and coworkers showed that compared with PAWP or left ventricular end-diastolic area, Δ Down was a far better indicator of volume responsiveness.[100]

Another dynamic marker of preload reserve is pulse pressure variation (PPV). Many automated devices are now available that provide real-time PPV, and although calculated according to slightly different and proprietary algorithms, PPV should not exceed 13% to 17%[101-105]



Note: The arterial blood pressure tracing is not drawn to scale

PP_{Max} =150–70=80
PP_{Min} =120–60=60
PPV =(PP_{Max}–PP_{Min})/([PP_{Max}+PP_{Min}]/2)
PPV =80–60/([80+60]/2)=29%

Figure 45-16. Pulse pressure variation. Pulse pressure variation (PPV) is calculated as the difference between maximal (PP_{Max}) and minimal (PP_{Min}) pulse pressure values during a single mechanical respiratory cycle, divided by the average of these two values. (Note that the arterial blood pressure trace is drawn for illustrative purposes and not to scale.)

(Fig. 45-16). In addition to SPV and PPV, more sophisticated pulse contour methods for measurement of cardiac output (see later) allow online measurement of variations in stroke volume variation (SVV). As with other dynamic indicators of preload reserve, normal SVV is approximately 10% to 13%, whereas greater variability predicts a positive response to volume expansion.[104,106] Although SVV may be theoretically superior to PPV, clinical studies have not borne this out.[104]

Devices based on respiratory cycle–induced variation in the pulse plethysmogram have been developed as a less invasive but similar alternative. Measures such as photoplethysmography variation (ΔPOP) or the plethysmography variability index (PVI) appear to be useful when conditions are good, but this particular physiologic signal is even more subject to confounding influences than arterial blood pressure waveform.[103,107,108] Both numeric pulse oximetry and the photoplethysmography waveform are sensitive to sympathetic variations in regional circulation, especially in the skin and extremities in critically ill patients. Tidal volume, core and peripheral temperature, ambient light, and cardiac dysrhythmias pose significant impediments to valid and reproducible data collection and interpretation. There is no consensus regarding meaningful threshold values, and validity seems especially poor in children, under conditions of

mechanical ventilation in a sedated but not paralyzed patient, and in the setting of an open abdomen.[108] Furthermore, there are sophisticated autogaining features incorporated in most commercially available monitoring systems to optimize signal display. As such, the degree of variation visible to the naked eye may not correlate with true signal variation, resulting in erroneous clinical decisions.

Dynamic measures are significantly superior to static indices of intravascular volume and are more valuable for making informed clinical decisions, especially in critically ill patients. Both PVV and SVV are accurate following cardiac surgery (also see Chapter 67) in patients with normal and reduced ventricular function, whereas PPV was proved accurate in assessing intravascular fluid responsiveness in patients with septic shock.[109,110] Intraoperative use has also been examined with similar results.[111,112] Indeed, the ability of clinicians to "eyeball" respiratory variation in the arterial blood pressure waveform as displayed on the monitor seems reasonably accurate. Subjective estimates of such pressure variation were incorrect only 4.4% of the time, a rate that would have resulted in only 1% of treatments being erroneous.[105]

Newer automated monitors have obviated the need to interrupt mechanical ventilation and establish an apneic baseline in order to differentiate Δ Up from Δ Down and are able to continuously display PPV or SVV.[96,113,114] However, the automated nature of these monitors makes it important to recognize clinical conditions under which their use was validated. The magnitude of arterial blood pressure variation observed is influenced by positive-pressure ventilation variables, and most patients are no longer routinely ventilated in a manner similar to that in the supporting clinical studies. In general, mechanical ventilation with tidal volumes of 8 to 10 mL/kg, positive end-expiratory pressure of 5 mm Hg or greater, regular cardiac rhythm, normal intraabdominal pressure, and a closed chest are necessary to duplicate the experimental conditions. Also, effects of changes in patient position such as steep Trendelenberg or the lateral position are not clear.[104] In addition, patients with pulmonary hypertension or reduced right ventricular ejection fraction may not have reliable responses to changes in intrathoracic pressure, resulting in overhydration and worsening right heart failure.[115] Increased respiratory rates, especially when coupled with respiratory failure or significant bradycardia, may disrupt the relationship between respiratory cycle–induced changes in intrathoracic pressure and cardiac chamber volume, thus invalidating the theoretic basis for blood pressure variation analysis completely in these patients.[104]

As noted earlier, respiratory cycle–induced arterial pressure variations are not solely related to changes in left ventricular preload, but also depend in part on changes in afterload. Indeed, decreased arterial compliance and increased baseline pulse pressure seen with both normal and pathologic vascular aging results in an exaggerated PPV response to changes in stroke volume due to any stimulus. As such, PPV thresholds should be higher in such patients than in those with more elastance in their vascular tree.[116,117]

There is disagreement on precise threshold values that differentiate responders from nonresponders, and the variety of techniques, devices, and approaches have not been standardized.[103] In a recent systematic review, mean discriminatory thresholds for PVV and SVV were found to be 12.5% ± 1.6% and 11.6% ± 1.9%, respectively, with acceptable sensitivities and specificities (89%, 88% and 82%, 86%, respectively).[118] However, simply differentiating patients into responders and nonresponders does not take into account the nature of the clinical intervention at issue. Intravascular volume expansion does not result in a dichotomous outcome; it does not yield a simple positive or negative result with an equivalent range of values on each side. The asymmetric nature of the Frank-Starling curve dictates that the cost-benefit ratio of acting in one direction will be different from acting in the other. Any particular change in preload will result in a different change in stroke volume in one direction than in the other, with the differential change being dependent on how close to the peak of the curve the patient begins. Consequently, the concept of the "gray zone" has been proposed, in which two cutoffs are identified, two values between which evidence-based decision making is not possible.[119] For PPV, this zone has been described as 9% to 13%, such that those below 9% should receive intravascular volume expansion, whereas those above 13% should not. For those between the two values, the measurement is not able to provide meaningful information and the decision should be made on other criteria.[104,120]

CENTRAL VENOUS PRESSURE MONITORING

Cannulation of a central vein and direct measurement of central venous pressure (CVP) are frequently performed in hemodynamically unstable patients and those undergoing major operations. A central venous catheter may be inserted to provide secure vascular access for many reasons, including administration of vasoactive drugs or fluids, CVP monitoring, transvenous cardiac pacing, temporary hemodialysis, pulmonary artery catheterization, or aspiration of entrained air. A central venous catheter may also be inserted when no peripheral access can be obtained or when repeated blood sampling is required (Box 45-4).

CENTRAL VENOUS CANNULATION

When intraoperative cannulation is required, the decision to perform central venous cannulation before or after induction of anesthesia is guided most often by individual patient and physician preferences or institutional practice. Preoperative central venous cannulation should be terminated in any patient who becomes overly sedated or uncooperative during the procedure. The need for central venous cannulation can be reevaluated after induction of anesthesia and intubation of the trachea.

Choosing the Catheter, Site, and Method for Central Venous Cannulation

Choosing the Catheter. Central venous catheters come in a variety of lengths, diameter, composition, and lumen

BOX 45-4 ***Indications for Central Venous Cannulation***

Central venous pressure monitoring
Pulmonary artery catheterization and monitoring
Transvenous cardiac pacing
Temporary hemodialysis
Drug administration
- Concentrated vasoactive drugs
- Hyperalimentation
- Chemotherapy
- Agents irritating to peripheral veins
- Prolonged antibiotic therapy (e.g., endocarditis)

Rapid infusion of fluids (via large cannulas)
- Trauma
- Major surgery

Aspiration of air emboli
Inadequate peripheral intravenous access
Sampling site for repeated blood testing

configuration.[121,122] Different catheters are chosen according to the purpose of catheterization, whether for CVP monitoring or other therapeutic indication, and whether intended for short- or long-term use. The most commonly used catheter is a 7-Fr, 20-cm multiport catheter that allows simultaneous CVP monitoring and infusion of drugs and fluids.[123] Rapid intravascular fluid resuscitation is most efficient with short, large-bore, peripheral intravenous catheters, because central venous catheters are longer and have narrower individual lumina, significantly increasing resistance to flow. For example, according to the manufacturer's product specifications, the maximal flow rate of the 16-gauge lumen of a standard 7-Fr 20-cm central venous catheter is one quarter that of a 16-gauge, 3-cm intravenous catheter.

A popular alternative method for multilumen central venous access uses a large introducer sheath with one or two integrated ports for multiple drug infusions, combined with a single-lumen catheter inserted through the hemostasis valve for continuous CVP monitoring. Although use of these larger introducer sheaths is not free from complications, they do allow rapid placement of a pacing wire or pulmonary artery catheter should the need arise.

Choosing the Insertion Site. Selecting the best site for central venous cannulation requires consideration of the indication for catheterization (pressure monitoring versus drug or fluid administration), the patient's underlying medical condition, the clinical setting, and the skill and experience of the clinician performing the procedure. In patients with severe bleeding diatheses, a puncture site should be selected where bleeding from the vein or adjacent artery is easily detected and controlled with local compression. In such a patient, an internal or external jugular approach would be preferable to a subclavian site. Likewise, patients with severe emphysema or others who would be severely compromised by a pneumothorax would be better candidates for internal jugular than subclavian cannulation, owing to the more frequent pneumothorax risk with the latter approach. If transvenous cardiac pacing is required in an emergency situation, catheterization of the right internal jugular vein is recommended, because it provides the most direct route to the right ventricle. Trauma patients, with their necks immobilized in a hard cervical collar, are best resuscitated using a femoral or subclavian catheter; the latter may be placed even more safely if the risk of pneumothorax is obviated by prior placement of a thoracostomy tube. The physician must recognize that the length of catheter inserted to position the catheter tip properly in the superior vena cava will vary according to puncture site, being slightly (3 to 5 cm) greater when the left internal or external jugular veins are chosen, compared with the right internal jugular vein.[124] Finally, a physician's personal experience undoubtedly plays a significant role in determining the safest site for central venous cannulation, particularly when the procedure is performed under urgent or emergent circumstances.

Since its introduction into clinical practice in the late 1960s, percutaneous puncture of the right internal jugular vein has been the method preferred by anesthesiologists for central venous cannulation.[125-127] Reasons for this preference include the consistent, predictable anatomic location of the internal jugular vein, readily identifiable and palpable surface landmarks, and a short straight course to the superior vena cava. An internal jugular vein catheter is highly accessible during most surgical procedures and has a high rate of successful placement (90% to 99%).[126,128]

Left internal jugular vein cannulation may be accomplished reliably and safely, although several anatomic details make the left side less attractive than the right. The cupola of the pleura is higher on the left, theoretically increasing the risk of pneumothorax. The thoracic duct may be injured during the procedure as it enters the venous system at the junction of the left internal jugular and subclavian veins.[129] The left internal jugular vein is often smaller than the right and demonstrates a greater degree of overlap of the adjacent carotid artery.[130] Most important, any catheter inserted from the left side of the patient must traverse the innominate (left brachiocephalic) vein and enter the superior vena cava perpendicularly. As a result, the catheter tip may impinge on the right lateral wall of the superior vena cava, increasing the risk of vascular injury. This anatomic disadvantage pertains to all left-sided catheterization sites and highlights the need for radiographic confirmation of proper catheter tip location. Finally, most operators have less experience performing left internal jugular vein cannulation, which leads to more adverse events and morbidity.[131,132]

The subclavian vein is an important site for central venous cannulation and is particularly popular among surgeons and other physicians who place central venous catheters for emergency volume resuscitation and long-term intravenous therapy or dialysis, rather than for shorter-term monitoring purposes.[133,134] Advantages of subclavian venous cannulation include a less frequent risk of infection compared with femoral sites, ease of insertion in trauma patients who may be immobilized in a cervical collar, and increased patient comfort, especially for long-term intravenous therapy, such as hyperalimentation and chemotherapy.[135,136]

Both the right and left external jugular veins provide safe, albeit somewhat technically challenging, alternatives to internal jugular or subclavian vein cannulation. Because the external jugular veins are superficial, they allow central venous cannulation with essentially no risk of pneumothorax or unintended arterial puncture. In most instances, it is best to use an 18-gauge catheter rather than the thin-wall needle to introduce the guidewire (i.e., the *modified* Seldinger, as opposed to the Seldinger technique), because of the tortuous course of the external jugular vein and the frequent need to manipulate the guidewire repeatedly to guide it into the superior vena cava. A J-tip guidewire should always be used, because it may be advanced under the clavicle and into the central circulation more successfully than a straight-tip wire.[137,138] When the guidewire does not advance as desired and appears to be moving peripherally into the subclavian vein, abducting the ipsilateral shoulder beyond 90 degrees before advancing the wire may facilitate central venous passage. Alternatively, the patient's ipsilateral arm is placed at the side, and an assistant applies mild caudad traction on the shoulder to straighten the course of the external jugular vein while the wire is advanced. Essentially, the only factors that preclude use of the external jugular veins for CVP monitoring are an inability to visualize and cannulate the vessel in the neck and to advance a catheter into the central circulation. Advancing catheters and stiff dilators into the external jugular vein requires extreme caution. The catheter needs to travel around the sharp angle in the vein as it enters the subclavian vein. This may be the site for venous injury if undue force is used during insertion of the catheter. Not surprisingly, approximately 20% of the problems occur in attempted external jugular central venous catheterizations, thus limiting more widespread application of this technique.[139,140]

Femoral vein cannulation is useful when the more common jugular and subclavian sites are not accessible, as is commonly the case in patients with burns, with trauma, during surgical procedures that involve the head, neck, and upper thorax, or during cardiopulmonary resuscitation (also see Chapters 85, 66, and 108). Use of the femoral vein obviates many of the common complications of central venous catheterization, particularly pneumothorax, but it also carries the risk of injury to the femoral artery and, more rarely, the femoral nerve. Femoral venipuncture using the landmark technique is performed below the inguinal ligament just medial to the palpated femoral arterial pulse. Central venous pressure measurements may be made using longer (40 to 70 cm) catheters that reside in the inferior vena or with shorter (15 to 20 cm) catheters that terminate in the common iliac vein. Both provide CVP measurements that correlate with right atrial pressure, although the shorter more distally located catheters appear to provide wider variations in CVP values.[141,142] This holds true in both mechanically and spontaneously ventilated patients.[142,143] Disadvantages of the femoral venous route include increased risk of thromboembolic complications, as well as vascular injury that may lead to intraabdominal or retroperitoneal hemorrhage.[144] In addition, patients with femoral vascular catheters are generally unable to ambulate, which can delay and complicate postoperative recovery.

In patients with extensive, severe burn injuries, the axillary region is often spared and provides a useful site for either arterial or venous pressure monitoring.[145] Standard 20-cm CVP catheters placed in the axillary vein, approximately 1 cm medial to the palpated axillary artery, allow pressure measurement from the superior vena cava. Even more distal pressures measured from peripheral veins in the hand and forearm may provide a reasonably accurate estimate of CVP in selected surgical patients.[146] Modified volumetric infusion pumps can even measure in-line peripheral venous pressures without the need for additional transducers and monitoring equipment.[147] Although this method of measuring CVP incurs no risk beyond that associated with placing any standard peripheral intravenous catheter, it has not been validated widely and cannot replace central venous cannulation in most circumstances.

Peripherally inserted central venous catheters (PICC) have become a popular alternative to centrally inserted catheters in patients requiring long-term intravenous therapy. Advantages of the PICC include bedside placement under local anesthesia, extremely low risk of major insertion-related complications, and safe placement by non-physicians (i.e., registered nurses and physician assistants). This technique may be particularly cost-effective, because it eliminates the need for a minor operative procedure in those patients who require a Hickman or Broviac central venous catheter.[148] Venous access for a PICC is obtained through an antecubital vein, preferably the basilic vein, which is generally more successfully catheterized than the cephalic vein due to its more linear course. Early reports described only modest success with positioning PICCs in an appropriate central location as well as a considerable risk of venous thrombosis, but improvements in catheter design and insertion technique now result in successful placement with few complications in most patients.[148-150] Most PICCs are inserted for long-term therapeutic indications (chemotherapy or parenteral nutrition), using very flexible, nonthrombogenic silicone catheters. Less commonly, a standard polyurethane 40-cm intravenous catheter is inserted peripherally and advanced to a central location for short-term infusion of vasoactive drugs or monitoring CVP or PAP. Central venous pressure recorded via PICCs is slightly higher than the pressure measured using centrally inserted catheters, but this difference is clinically insignificant.[151] When these standard long venous catheters are inserted from an antecubital vein, the catheter tip may advance into the heart as the arm is abducted, thereby increasing the risk of cardiac perforation or arrhythmias.[152,153] Whenever a PICC line is in place, the clinician should cautiously place any additional central venous catheters because of the risk of shearing the PICC line within the central venous circulation.

Choosing the Central Venous Cannulation Method. A central vein may be cannulated using either a landmark technique or ultrasound guidance. Ultrasound technology is rapidly gaining acceptance, and numerous specialty groups and governmental agencies have issued practice recommendations for its use during central line placement.[154-156] See other sources for detailed descriptions

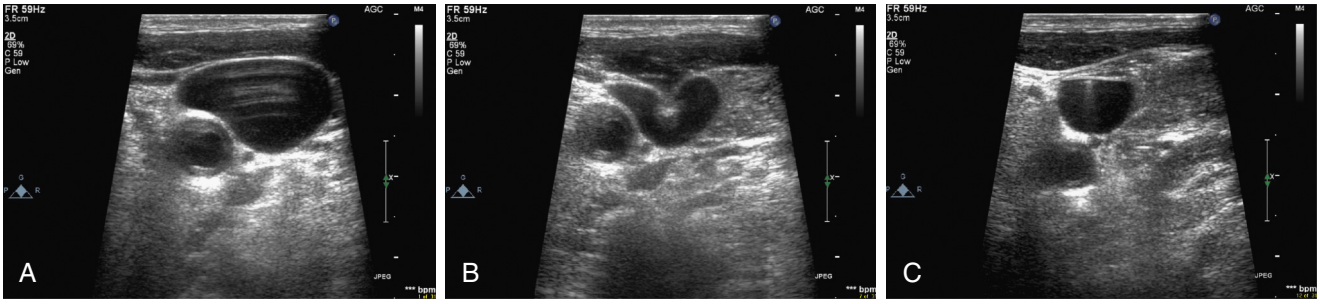


Figure 45-17. A, Transverse plane ultrasound image showing the right internal jugular vein and its typical anatomic position anterior and lateral to the right common carotid artery. **B,** Needle entering the right internal jugular vein. It is essential that the operator directly visualize the needle entering the vessel lumen, as shown here, to avoid inadvertent puncture of the posterior wall of the vein. **C,** The wire is seen as an echodense structure within the vessel lumen. Confirmation of the location of the wire should always precede the use of the vessel dilator.

and tutorials on the various insertion techniques for different access sites using surface landmarks.[123,157]

Regardless of the insertion technique used or the cannulation site chosen, certain general principles should be emphasized for all central line placements. Ideally, a protocol or checklist describing the basic procedural steps for central line insertion should be in place at every institution, and all staff members should feel empowered to speak up when they witness a protocol violation. Standardized equipment, routine use of an assistant, hand washing and maximal barrier precautions all contribute to the sterility of the procedure.[154] The use of real-time ultrasound guidance for vessel localization and venipuncture should be strongly considered, especially when the internal jugular vein site is selected. Pressure manometry or waveform measurement should be used to confirm venous placement of the catheter before use. Finally, the position of the catheter tip should be verified as soon as clinically appropriate to avoid delayed complications (see later).

Ultrasound-Guided Central Venous Cannulation

First described in 1984, ultrasound-guided central venous catheter placement has proved beneficial in most settings, including the intensive care unit and the operating room[156,158] (also see Chapter 58). Fewer needle passes are required for successful venous cannulation when real-time two-dimensional ultrasound guidance is used. In addition, ultrasound guidance reduces the time required for catheterization, increases overall success rates, and results in fewer immediate complications.[159,160] The benefits of ultrasound-guided catheterization are clear for internal jugular vein catheters, when inexperienced operators perform the procedure, and for adult rather than pediatric patients. Based on this evidence, the Agency for Healthcare Research and Quality has listed the use of real-time ultrasound guidance for central venous catheterization as one of 11 practices to improve health care.[155] It is unknown whether the additional equipment and manipulation associated with real-time ultrasound guidance may increase the rate of catheter-related infections or whether the increased dependence on this technology by trainees will prove detrimental in those clinical settings.

As an alternative to real-time ultrasound-guided catheterization, ultrasound can be used to confirm vessel location and patency, provide a clear target to mark the skin, and then allow venipuncture to proceed in the usual fashion.[154,161]

Real-time, two-dimensional ultrasound guidance for internal jugular vein cannulation requires a 7.5- to 10-MHz transducer. A rapid ultrasound scan should be performed once the patient is placed in the Trendelenburg position and before the skin is cleansed to identify the target vein location, confirm its patency, and rule out anatomic abnormalities. This simple step is aimed at avoiding futile insertion attempts when the patient has a thrombosed, narrowed, or anomalous central vein.

Once the site is prepped and draped, the operator holds the ultrasound probe protected by a sterile sheath with the nondominant hand to obtain a view of the target vessel. The vein and artery appear as two circular black structures on the ultrasound image. The vein is identified by anatomic location and by its compressibility. The artery appears mildly pulsatile, is generally smaller, and has a thicker wall (Fig. 45-17, *A*). When using ultrasound guidance, either the transverse (short axis) or longitudinal (long axis) view is adequate. In general, the transverse view is easier to learn and allows simultaneous identification of the artery and vein, whereas the longitudinal view allows visualization of the needle tip at all times, which may reduce perforation of the posterior wall of the vein.[162] After positioning the vein in the center of the ultrasound screen, the vessel is punctured under direct vision using an 18-gauge needle (see Fig. 45-17, *B*) and then proceeds as a standard Seldinger (wire through needle) or modified Seldinger (wire through catheter) technique. An additional recommended safety stop is to confirm intravenous location of the guidewire before proceeding with vessel dilation (see Fig. 45-17, *C*).

Ultrasound imaging of the subclavian vessels is more difficult and often hampered by the patient's body habitus and ultrasound probe size and shape. When using ultrasound to guide subclavian vein cannulation, the transducer is placed in the infraclavicular groove at the level of the middle or lateral third of the clavicle and the axillary vein and artery are imaged as they exit the bony canal formed by the clavicle and the first rib.[163] The artery is usually identified by its location cephalad to the vein, its noncompressibility, and its not varying size with respirations. Either a transverse or longitudinal view can be obtained and used to guide needle insertion.[164] Another

approach has been described for children in whom the probe is placed in the supraclavicular space to obtain a longitudinal view of the subclavian vein while cannulation is performed via the usual infraclavicular route[165] (also see Chapter 93).

Confirming Catheter Position

Central venous catheters placed in the operating room are commonly used for the duration of the surgical procedure without radiologic confirmation of the location of the catheter tip. Before monitoring or infusion commences, aspiration of blood should confirm intravenous location of each lumen of a multilumen catheter and remove any residual air from the catheter-tubing system. Following surgery, however, the position of the catheter tip must be confirmed radiographically. Catheter tips located within the heart or below the pericardial reflection of the superior vena cava increase the risk of cardiac perforation and fatal cardiac tamponade. Ideally, the catheter tip should lie within the superior vena cava, parallel to the vessel walls, and be positioned *below* the inferior border of the clavicles and *above* the level of the third rib, the T4 to T5 interspace, the azygos vein, the tracheal carina, or the takeoff of the right mainstem bronchus.[166,167] Using fresh human cadavers, Albrecht and colleagues confirmed that the tracheal carina was always more cephalad than the pericardial reflection on the superior vena cava, suggesting that a central venous catheter tip should always be located superior to this radiographic landmark.[168]

COMPLICATIONS OF CENTRAL VENOUS PRESSURE MONITORING

Complications of central venous cannulation are becoming increasingly recognized as major sources of morbidity, with more than 15% of patients experiencing some sort of related adverse event.[144] Although serious immediate complications are infrequent when these procedures are performed by well-trained, experienced clinicians, infectious complications are common, and use of central venous catheters continues to result in significant morbidity and mortality. Complications are often divided into mechanical, thromboembolic, and infectious etiologies (Box 45-5).

Mechanical Complications of Central Venous Catheterization

The incidence of complications depends on a number of factors, including the catheter insertion site and the patient's medical condition. Large retrospective and observational studies provide the best estimates of incidence for these types of complications.

Vascular injuries from central venous catheterization have a range of clinical consequences. The most common minor complications are localized hematoma or injury to the venous valves.[169] More serious complications include perforation into the pleural space or mediastinum, resulting in hydrothorax, hemothorax, hydromediastinum, hemomediastinum, and/or chylothorax.[129,170-173]

In general, unintended arterial puncture is the most common acute mechanical complication, with incidence ranging from 1.9% to 15%.[174] Many of these injuries result in localized hematoma formation, but in rare occasions even small-gauge needle punctures may lead to serious complications such as arterial thromboembolism.[175] If arterial puncture with a small needle occurs during central venous cannulation, the needle should be removed and external pressure applied for several minutes to prevent hematoma formation. When unintentional carotid artery cannulation with a dilator or large-bore catheter occurs, the dilator or catheter should be left in place and a vascular surgeon consulted promptly regarding removal. Immediate removal of the catheter has resulted in severe complications such as hemothorax, arteriovenous fistula, pseudoaneurysm, and cerebral infarction.[176,177] Open or endovascular repair followed by careful neurologic monitoring (and hence postponement of any elective surgical procedure) is usually required.[176]

Other catastrophic but rare vascular injuries have been reported, including aortic perforation and avulsion of the facial vein.[178,179] Delayed vascular complications following central venous catheterization are uncommon but should be considered as consequences of this procedure. A number of these have been described in the literature, including aortoatrial fistula, venobronchial fistula, carotid artery–internal jugular vein fistula, and pseudoaneurysm formation.[180-183]

The most important life-threatening vascular complication of central venous catheterization is cardiac tamponade resulting from perforation of the intrapericardial superior vena cava, right atrium, or right ventricle. These vascular injuries may cause hemopericardium or unintentional pericardial instillation of intravenous fluid leading to cardiac compression.[184] This injury was the second-most common complication related to central catheters reported in the American Society of Anesthesiologists Closed Claims Project in 2004.[185] Cardiac tamponade resulted in death in 81% of the cases in this report, and

BOX 45-5 *Complications of Central Venous Pressure Monitoring*

- Mechanical
  - Vascular injury
    - Arterial
    - Venous
    - Cardiac tamponade
  - Respiratory compromise
    - Airway compression from hematoma
    - Pneumothorax
  - Nerve injury
  - Arrhythmias
- Thromboembolic
  - Venous thrombosis
  - Pulmonary embolism
  - Arterial thrombosis and embolism
  - Catheter or guidewire embolism
- Infectious
  - Insertion site infection
  - Catheter infection
  - Bloodstream infection
  - Endocarditis
- Misinterpretation of data
- Misuse of equipment

often had a delayed presentation (1 to 5 days), indicating that this complication is related to catheter maintenance and use more often than to the vascular access procedure itself. Most reports document the avoidable nature of this catastrophic event and highlight that patients are predisposed to this complication when central venous catheter tips are malpositioned within the heart chambers or abutting the wall of the superior vena cava at a steep angle. This latter position can be recognized radiographically as a gentle curvature of the catheter tip within the superior vena cava.[186] These observations emphasize that objective confirmation of proper catheter tip location is mandatory, regardless of whether the catheter is inserted from a central or peripheral site. In fact, many early reports of catheter-related cardiovascular perforation suggested that peripheral catheters may present an unusually high risk for this complication because arm abduction may cause the catheter tip to advance into a dangerous location within the heart.[152,187] When cardiac tamponade is caused by catheter-induced cardiac perforation, symptoms develop suddenly, requiring a high index of suspicion if severe hypotension occurs in any patient with a central venous catheter in place. Cardiac arrhythmias may provide an early clue to the intracardiac location of the catheter tip.[153] Occasionally, both posteroanterior and lateral chest radiographs, as well as injection of radiopaque contrast, are required to locate the catheter tip precisely.[188]

Pneumothorax is the most common complication of subclavian vein cannulation, although unintended arterial puncture may actually be more frequent.[66,189] Mansfield and associates reported 821 patients who underwent attempted subclavian venous cannulation, with a 1.5% incidence of pneumothorax and a 3.7% incidence of arterial puncture when using the landmark technique.[189] Pneumothorax is even less frequent with the internal jugular approach. Shah and colleagues reported an incidence of pneumothorax of 0.5% in their series of nearly 6000 internal jugular catheterizations.[174] This is most likely a larger-than-expected estimate, because these patients had undergone sternotomy for cardiac surgery, a procedure that may have been responsible for the pneumothorax in many cases. Small pneumothoraces may be managed conservatively, whereas tube thoracostomy is the best treatment for larger air collections or for patients receiving positive-pressure mechanical ventilation or scheduled for major surgery. The physician must always be prepared for the possibility of tension pneumothorax and its adverse hemodynamic sequelae. In addition to pneumothorax, other respiratory tract injuries occur following central venous catheterization, including subcutaneous and mediastinal emphysema, tracheal perforation, and rupture of an endotracheal tube cuff.[190]

Nerve injury is another potential complication of central venous cannulation. Damage may occur to the brachial plexus, stellate ganglion, phrenic nerve, or vocal cords.[191,192] In addition, chronic pain syndromes have been attributed to this procedure.[193]

Thromboembolic Complications of Central Venous Catheterization

Catheter-related thrombosis varies according to the site of central venous catheterization, occurring in as many as 21.5% of patients with femoral venous catheters and 1.9% of those with subclavian venous catheters.[135] Catheters that are positioned low in the right atrium may be more prone to thrombus formation, possibly due to mechanical irritation of the right atrial endocardium by the catheter.[194] Thrombi that form at the catheter tip or adhere to the endocardium have the potential to become a nidus for infection, cause superior vena cava syndrome, or embolize into the pulmonary circulation.[195-197] Occasionally, surgical removal is required.[198]

In addition to thromboembolism, other reported embolic complications of central venous catheterization include embolism of portions of the catheter or guidewire, and air embolism.[199,200] Almost invariably, these are the result of equipment misuse, highlighting the need for proper education and training of nurses and physicians responsible for the use of these devices.

Infectious Complications of Central Venous Catheterization

By far, the most common major late complication of central venous cannulation is infection. Central line–associated bloodstream infections (CLABSI) have decreased in incidence, likely because of a focus on evidence-based best practices for catheter insertion and maintenance. Despite this, in 2009, CLABSI still represented 14% of all health care–related infections in the United States.[201] Although most of these cases occurred in non-ICU patients (inpatient wards and outpatients receiving hemodialysis), many were diagnosed in ICU patients[201-203] (also see Chapters 101 and 102).

As previously noted, the starting point for prevention of infection is meticulous attention to aseptic technique.[204] A recent review showed, in addition to a declining CLABSI rate, equal rates of infection for internal jugular, femoral, and subclavian insertion sites.[205] Multilumen catheters may create a more frequent risk of infection than single-lumen catheters, although the added clinical functionality of such catheters often mandates their use.[136,144] Catheters are made from a wide variety of materials, including silicone, polyvinyl chloride, Teflon, and polyurethane. Furthermore, catheters of the same material may be manufactured differently, which influences their surfaces and the frequency of bacterial adherence to the surface.[206] Heparin-bonded central venous catheters have been shown to reduce the incidence of catheter-related thrombosis and infection in children and adults.[207,208] The incorporation of antimicrobial treatments such as silver (this metal has broad antimicrobial activity and is nontoxic), combinations of the antiseptics chlorhexidine and silver sulfadiazine, or the antibiotics monocycline and rifampin onto the catheter surfaces reduces rates of catheter colonization and in some cases bloodstream infection.[208-210] The added expense has prevented more widespread adoption of these catheters, although an analysis has suggested their cost-effectiveness in settings in which the rate of catheter-related infections remains frequent, such as immunocompromised patients (more than 3.3/1000 catheter days).[211]

A chlorhexidine gluconate–impregnated sponge dressing reduces catheter colonization in infants and children, but it does not reduce the rate of catheter-associated

bloodstream infections[212,213] (also see Chapter 93). Current guidelines from the Centers for Disease Control and Prevention (CDC) do not support routine catheter site changes or scheduled changes over a guidewire. CDC guidelines provide other detailed recommendations for catheter management to reduce the risk of infectious complications.[136]

Other Complications of Central Venous Catheterization

Miscellaneous other adverse sequelae of central venous cannulation have been reported, and although their incidence is not clearly known, most appear to be uncommon (see Box 45-5). All physicians performing these procedures should be familiar with them, particularly since many of these complications are related to operator error.[66,214]

Use of guidewires, vessel dilators, and large-bore catheters carries certain additional risks that mandate meticulous attention to technique. The proximal tip of the guidewire must remain under the physician's control at all times to avoid inserting the wire too far into the heart, thus causing arrhythmias, or potentially losing the guidewire within the circulation.[199,215] By design, vessel dilators are stiffer than catheters and may cause significant trauma if inserted forcefully or further than necessary to dilate the subcutaneous tissue tract from skin to vein.[216] Large-bore introducer sheaths and multilumen catheters are popular because of their clinical utility, yet their size may increase the risk of cannulation-associated trauma, hemorrhage from unrecognized line disconnections, and major venous air embolism. Not only may air be entrained during initial cannulation, but improperly connected large-bore cannulas may pose an additional risk because of the large site for air entry directly into the central venous circulation.[200,217]

Although many complications of CVP monitoring relate to equipment misuse, the impact of data misinterpretation is unknown. It is extremely likely, though, that clinicians have a poor understanding of CVP monitoring and are thus more prone to misinterpretation of measured values. A similar phenomenon has been repeatedly demonstrated for pulmonary artery catheter monitoring (see discussion later). Safe and effective use of CVP monitoring requires a detailed understanding of cardiovascular physiology, normal CVP waveforms, and common pathologic abnormalities in these measurements.

PHYSIOLOGIC CONSIDERATIONS FOR CENTRAL VENOUS PRESSURE MONITORING

Cardiac filling pressures are measured directly from a number of sites in the vascular system. Central venous pressure monitoring is the least invasive method, followed by pulmonary artery and left atrial pressure monitoring. Proper interpretation of all cardiac filling pressures requires knowledge of normal values for pressures within the cardiac chambers, great vessels, and other measured and derived hemodynamic variables (Table 45-2).

CVP is the result of a complex interplay among a diverse array of physiologic variables, many of which are impossible to measure in the operating room or intensive care unit. Not surprisingly, CVP sometimes fails as a predictor of intravascular volume status or fluid responsiveness. There is, fundamentally, no simple relationship between CVP and circulating blood volume.[95,218,219] Despite this, the CVP waveform is important, so its components and potential pitfalls must be understood.

TABLE 45-2 NORMAL CARDIOVASCULAR PRESSURES

Pressures	Average (mm Hg)	Range (mm Hg)
Right Atrium		
a wave	6	2-7
v wave	5	2-7
Mean	3	1-5
Right Ventricle		
Peak systolic	25	15-30
End-diastolic	6	1-7
Pulmonary Artery		
Peak systolic	25	15-30
End-diastolic	9	4-12
Mean	15	9-19
Pulmonary Artery Wedge		
Mean	9	4-12
Left Atrium		
a wave	10	4-16
v wave	12	6-21
Mean	8	2-12
Left Ventricle		
Peak systolic	130	90-140
End-diastolic	8	5-12
Central aorta		
Peak systolic	130	90-140
End-diastolic	70	60-90
Mean	90	70-105

NORMAL CENTRAL VENOUS PRESSURE WAVEFORMS

Mechanical events during the cardiac cycle are responsible for the sequence of waves seen in a typical CVP trace. The CVP waveform consists of five phasic events: three peaks (a, c, v) and two descents (x, y) (Table 45-3) (Fig. 45-18).[220,221] The most prominent wave is the *a wave* of atrial contraction, which occurs at end-diastole following the ECG P wave. Atrial contraction increases atrial pressure and provides the atrial kick to fill the right ventricle through the open tricuspid valve. Atrial pressure decreases following the a wave, as the atrium relaxes. This smooth decline in pressure is interrupted by the *c wave*. This wave is a transient increase in atrial pressure produced by isovolumic ventricular contraction, which closes the tricuspid valve and displaces it toward the atrium. The c wave always follows the ECG R wave because it is generated during onset of ventricular systole. Note that the c wave observed in a jugular venous pressure trace might have a slightly more complex origin. This wave is due to early systolic pressure transmission from the adjacent carotid artery and may be termed a carotid impact wave. [222] Because the jugular venous pressure also reflects right atrial pressure, however, this c wave likely represents both arterial (carotid impact) and venous (tricuspid motion) origins. Atrial pressure

TABLE 45-3 CENTRAL VENOUS PRESSURE WAVEFORM COMPONENTS

Waveform Component	Phase of Cardiac Cycle	Mechanical Event
a wave	End-diastole	Atrial contraction
c wave	Early systole	Isovolumic ventricular contraction, tricuspid motion toward right atrium
v wave	Late systole	Systolic filling of atrium
h wave	Mid- to late diastole	Diastolic plateau
x descent	Mid-systole	Atrial relaxation, descent of the base, systolic collapse
y descent	Early diastole	Early ventricular filling, diastolic collapse

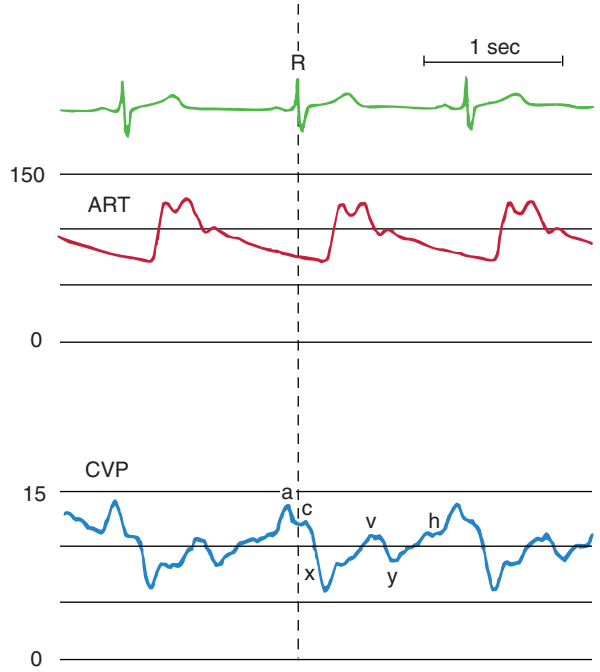


Figure 45-18. Normal central venous pressure (CVP) waveform. The diastolic components (y descent, end-diastolic a wave) and the systolic components (c wave, x descent, end-systolic v wave) are all clearly delineated. A mid-diastolic plateau wave, the h wave, is also seen because heart rate is slow. Waveform identification is aided by timing the relation between individual waveform components and the electrocardiographic R wave. Waveform timing using the arterial (ART) pressure trace is more confusing, owing to the relative delay in the systolic arterial pressure upstroke. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

continues its decline during ventricular systole, owing to continued atrial relaxation and changes in atrial geometry produced by ventricular contraction and ejection. This is the *x descent,* or systolic collapse in atrial pressure. The x descent can be divided into two portions, x and x′, corresponding to the segments before and after the c wave. The last atrial pressure peak is the *v wave*, which is caused by venous filling of the atrium during late systole while the tricuspid valve remains closed. The v wave usually peaks just after the ECG T wave. Atrial pressure then decreases, inscribing the *y descent,* or diastolic collapse, as the tricuspid valve opens and blood flows from atrium to ventricle. A final component of the CVP waveform, the *h wave,* occasionally appears as a pressure plateau in mid- to late diastole. The h wave is not normally seen unless the heart rate is slow and venous pressure is increased.[222,223] In summary, the normal venous waveform components may be remembered as follows: the a wave results from atrial contraction; the c wave results from tricuspid valve closure and isovolumic right ventricular contraction; the x descent is the systolic decrease in atrial pressure due to atrial relaxation; the v wave results from ventricular ejection, which drives venous filling of the atrium; and the y descent is the diastolic decrease in atrial pressure due to flow across the open tricuspid valve.

In relation to the cardiac cycle and ventricular mechanical actions, the CVP waveform can be considered to have three systolic components (c wave, x descent, v wave) and two diastolic components (y descent, a wave). By recalling the mechanical actions that generate the pressure peaks and troughs, these waveform components can be identified properly by aligning the CVP waveform and the ECG trace and using the ECG R wave to mark end-diastole and onset of systole. When the radial artery pressure trace is used for CVP waveform timing instead of the ECG, confusion may arise because the arterial pressure upstroke occurs nearly 200 milliseconds after the ECG R wave (see Fig. 45-18). This normal physiologic delay reflects the times required for the spread of the electrical depolarization through the ventricle (≈60 milliseconds), isovolumic left ventricular contraction (≈60 milliseconds), transmission of aortic pressure rise to the radial artery (≈50 milliseconds), and transmission of the radial artery pressure rise through fluid-filled tubing to the transducer (≈10 milliseconds).[82,224]

The normal CVP peaks are designated systolic (c, v) or diastolic (a) according to the phase of the cardiac cycle in which the wave begins. However, one generally identifies these waves not by their onset or upstroke, but rather by the location of their peaks. For instance, the a wave generally begins and peaks in end-diastole, but the peak may appear delayed to coincide with the ECG R wave, especially in a patient with a short PR interval. In this instance, a and c waves merge, and this composite wave is termed an a-c wave. Designation of the CVP v wave as a systolic event may be even more confusing. Although the ascent of the v wave begins during late systole, the peak of the v wave occurs during isovolumic ventricular relaxation, immediately before atrioventricular valve opening and the y descent. Consequently, the most precise description would be that the v wave begins in late systole, but peaks during isovolumic ventricular relaxation, the earliest portion of diastole. For clinical purposes, it is simplest to consider the v wave to be a systolic wave.

Although three distinct CVP peaks (a, c, v) and two troughs (x, y) are discernible in the normal venous pressure trace, heart rate changes and conduction abnormalities alter this pattern. A short ECG PR interval causes fusion of a and c waves, and tachycardia reduces the length of diastole and the duration of the y descent, causing v and a waves to merge. In contrast, bradycardia causes each wave to become more distinct with separate

TABLE 45-4 CENTRAL VENOUS PRESSURE WAVEFORM ABNORMALITIES

Condition	Characteristics
Atrial fibrillation	Loss of a wave Prominent c wave
Atrioventricular dissociation	Cannon a wave
Tricuspid regurgitation	Tall systolic c-v wave Loss of x descent
Tricuspid stenosis	Tall a wave Attenuation of y descent
Right ventricular ischemia	Tall a and v waves Steep x and y descents M or W configuration
Pericardial constriction	Tall a and v waves Steep x and y descents M or W configuration
Cardiac tamponade	Dominant x descent Attenuated y descent
Respiratory variation during spontaneous or positive-pressure ventilation	Measure pressures at end-expiration

x and x′ descents visible and a more prominent h wave. Although there are circumstances in which other pathologic waves may be evident in the CVP trace, one should resist the temptation to assign physiologic significance to each small pressure peak, because many will arise as artifacts of fluid-filled tubing-transducer monitoring systems. It is more useful to search for the expected waveform components, including those waveforms that are characteristic of the pathologic conditions suspected.

ABNORMAL CENTRAL VENOUS PRESSURE WAVEFORMS

Various pathophysiologic conditions may be diagnosed or confirmed by examination of the CVP waveform (Table 45-4). One of the most common applications is the rapid diagnosis of cardiac arrhythmias.[225] In atrial fibrillation, the a wave disappears and the c wave becomes more prominent because atrial volume is larger at end-diastole and onset of systole, owing to the absence of effective atrial contraction (Fig. 45-19, *A*). Occasionally, atrial fibrillation or flutter waves may be seen in the CVP trace when the ventricular rate is slow. Isorhythmic atrioventricular dissociation or junctional (nodal) rhythm alters the normal sequence of atrial contraction before ventricular contraction (see Fig. 45-19, *B*). Instead, retrograde conduction of the nodal impulse throughout the atrium causes atrial contraction to occur during ventricular systole while the tricuspid valve is closed, resulting in a tall "cannon" a wave in the CVP waveform. Absence of normal atrioventricular synchrony during ventricular pacing can be identified in a similar fashion by searching for cannon waves in the venous pressure trace (see Fig. 45-19, *C*). In these instances, the CVP helps diagnose the cause of arterial hypotension; loss of the P wave may not be as evident in the ECG trace as are the changes in the CVP waveform.

Right-sided valvular heart diseases alter the CVP waveform in different ways.[226] Tricuspid regurgitation

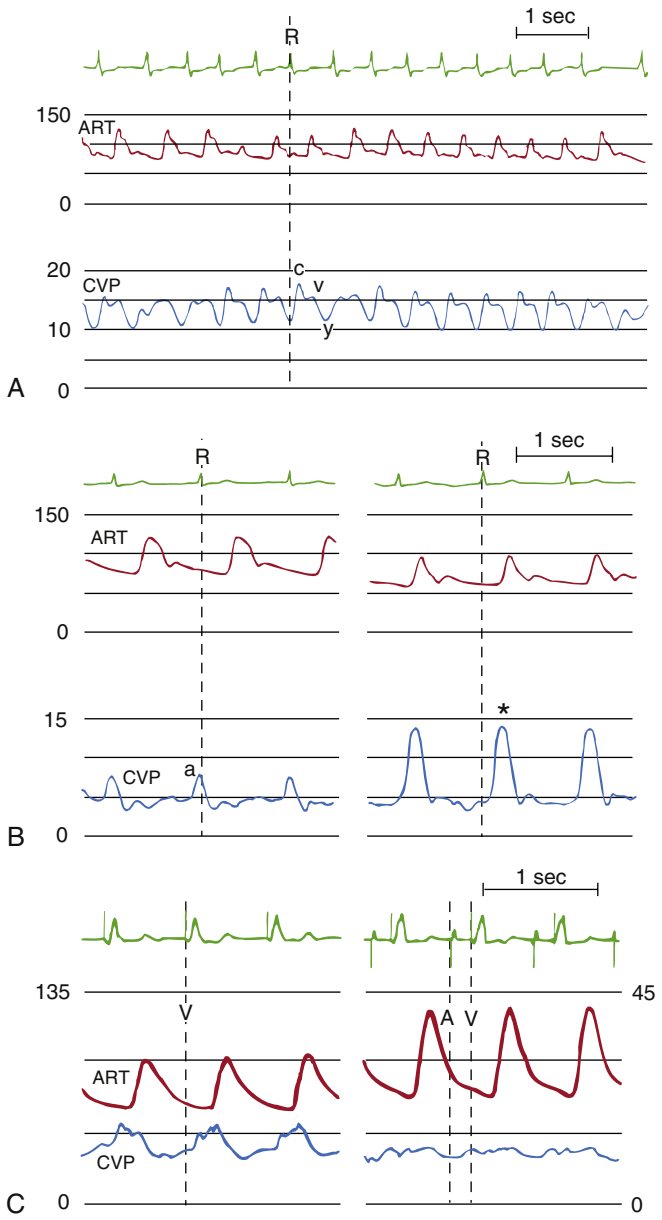


Figure 45-19. Central venous pressure (CVP) changes caused by cardiac arrhythmias. **A,** Atrial fibrillation. Note absence of the a wave, a prominent c wave, and a preserved v wave and y descent. This arrhythmia also causes variation in the electrocardiographic (ECG) R-R interval and left ventricular stroke volume, which can be seen in the ECG and arterial (ART) pressure traces. **B,** Isorhythmic atrioventricular dissociation. In contrast to the normal end-diastolic a wave in the CVP trace (*left panel*), an early systolic cannon wave is inscribed (*, *right panel*). Reduced ventricular filling accompanying this arrhythmia causes a decreased arterial blood pressure. **C,** Ventricular pacing. Systolic cannon waves are evident in the CVP trace during ventricular pacing (*left panel*). Atrioventricular sequential pacing restores the normal venous waveform and increases arterial blood pressure (*right panel*). ART scale left, CVP scale right. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

produces abnormal systolic filling of the right atrium through the incompetent valve. This results in a broad, tall systolic c-v wave, beginning in early systole and obliterating the systolic x descent in atrial pressure (Fig. 45-20, *A*). The CVP trace is said to be ventricularized, resembling

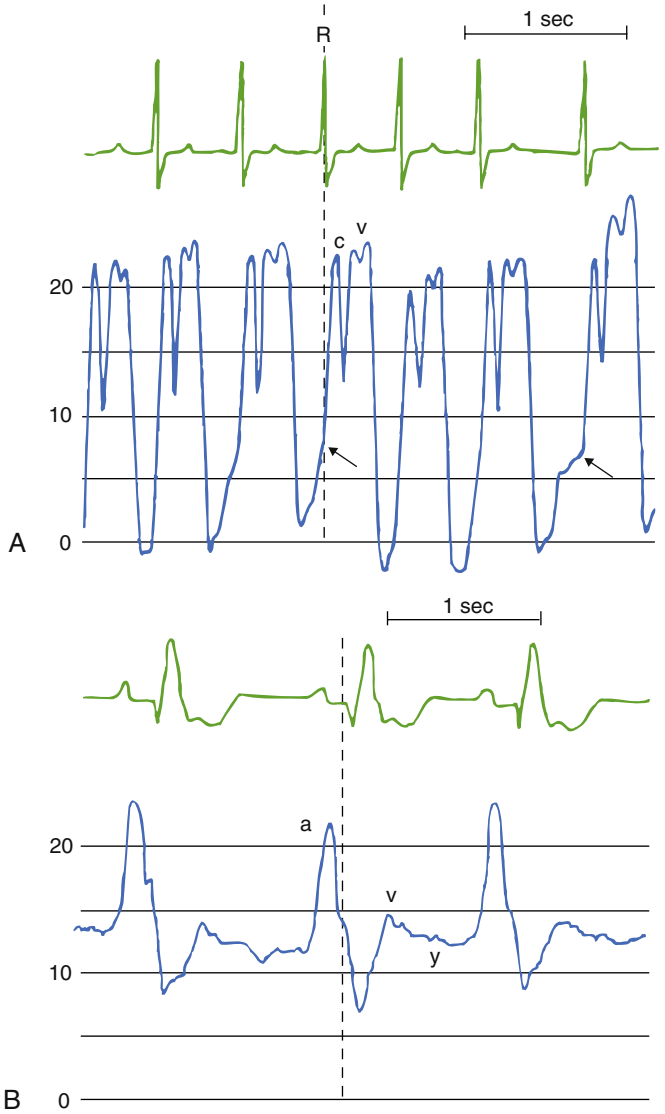


Figure 45-20. Central venous pressure (CVP) changes in tricuspid valve disease. **A,** Tricuspid regurgitation increases mean CVP, and the waveform displays a tall systolic c-v wave that obliterates the x descent. In this example, the a wave is not seen because of atrial fibrillation. Right ventricular end-diastolic pressure is estimated best at the time of the electrocardiographic R wave (*arrows*) and is lower than mean CVP. **B,** Tricuspid stenosis increases mean CVP, the diastolic y descent is attenuated, and the end-diastolic a wave is prominent. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

right ventricular pressure. Note that this regurgitant wave differs in onset, duration, and magnitude from a normal v wave caused by end-systolic atrial filling from the vena cavae. In patients with tricuspid regurgitation, right ventricular end-diastolic pressure is overestimated by the numeric display on the bedside monitor, which reports a single mean value for CVP. Instead, right ventricular end-diastolic pressure is estimated best by measuring the CVP value at the time of the ECG R wave, before the regurgitant systolic wave (see Fig. 45-20, *A*). Unlike tricuspid regurgitation, tricuspid stenosis produces a diastolic defect in atrial emptying and ventricular filling (see Fig. 45-20, *B*). Mean CVP is elevated, and a pressure gradient exists throughout diastole between right atrium and ventricle. The a wave is unusually prominent and the y descent is attenuated, owing to the impaired diastolic egress of blood from the atrium. Other conditions that reduce right ventricular compliance, such as right ventricular ischemia, pulmonary hypertension, or pulmonic valve stenosis, may produce a prominent end-diastolic a wave in the CVP trace but do not attenuate the early diastolic y descent. CVP waveform morphology changes in other characteristic ways in the presence of pericardial diseases and right ventricular infarction. These patterns are interpreted best in conjunction with pulmonary artery pressure monitoring, which is discussed later.

Perhaps the most important traditional application of CVP monitoring is to provide an estimate of the adequacy of the circulating blood volume. Several randomized trials and systematic reviews have demonstrated a very poor relationship between CVP and circulating blood volume, as well as the inability of a static CVP value to predict the hemodynamic response to a fluid challenge.[227-229] This is not surprising given the complexity of the interactions among the many variables that affect CVP. Perhaps the important clinical question with regard to intravascular volume responsiveness should be phrased in the negative—that is, whether a patient is *unlikely* to respond to an intravenous fluid challenge. The subset of patients that will suffer all the deleterious effects of fluid administration (capillary leak and tissue edema) and no benefit (increased cardiac output) is in most instances the group of clinical interest.

PULMONARY ARTERY CATHETER MONITORING

In 1970, Swan, Ganz, and colleagues introduced pulmonary artery catheterization into clinical practice for the hemodynamic assessment of patients with acute myocardial infarction.[230] These catheters allowed accurate measurement of important cardiovascular physiologic variables at the bedside, and their popularity soared. By the mid-1990s, estimated annual pulmonary artery catheter (PAC) sales in the United States approached 2 million catheters, with an estimated cost associated with their use in excess of 2 billion dollars each year.[231]

The PAC provides measurements of several hemodynamic variables that many clinicians, including experts in intensive care, cannot predict accurately from standard clinical signs and symptoms.[232] However, it remains uncertain whether PAC monitoring improves patient outcome.[233]

PULMONARY ARTERY CATHETERIZATION

The standard PAC has a 7.0- to 9.0-Fr circumference, is 110 cm in length marked at 10-cm intervals, and contains four internal lumina. The distal port at the catheter tip is used for pulmonary artery pressure monitoring, whereas the second port is 30 cm more proximal and is used for CVP monitoring. The third lumen leads to a balloon near the tip, and the fourth houses wires for a temperature thermistor, the end of which lies just proximal to the balloon.

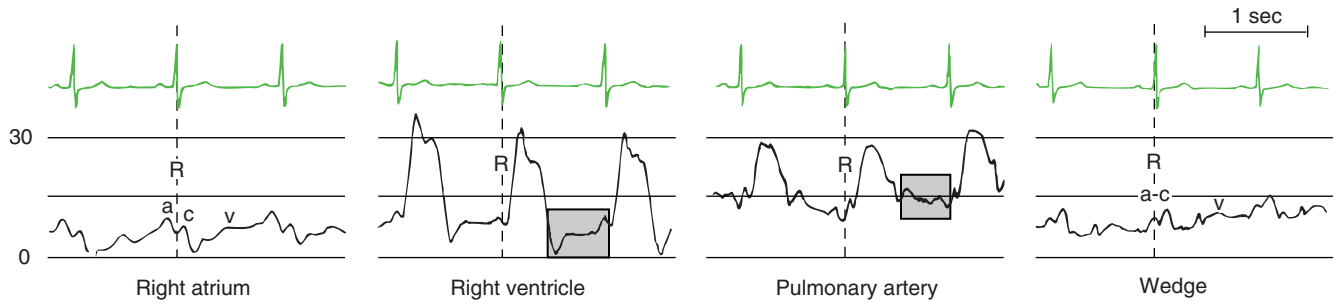


Figure 45-21. Characteristic waveforms recorded during passage of the pulmonary artery catheter. The right atrial pressure resembles a central venous pressure waveform and displays a, c, and v waves. Right ventricular pressure shows a higher systolic pressure than seen in the right atrium, although the end-diastolic pressures are equal in these two chambers. Pulmonary artery pressure shows a diastolic step-up compared with ventricular pressure. Note also that right ventricular pressure increases during diastole, whereas pulmonary artery pressure decreases during diastole (*shaded boxes*). Pulmonary artery wedge pressure has a similar morphology to right atrial pressure, although the a-c and v waves appear later in the cardiac cycle relative to the electrocardiogram. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

PACs can be inserted from any of the central venous cannulation sites described earlier, but the right internal jugular vein provides the most direct route to the right heart chambers. A large-bore introducer sheath with a hemostasis valve at its outer end is inserted in a manner similar to that for central venous cannulation. The PAC is passed through a sterile sheath to allow for later sterile manipulation of the PAC position, its distal lumen is connected to a pressure transducer, and then the catheter is inserted through the introducer's hemostatic valve to a depth of 20 cm. The gentle curvature of the PAC should be oriented to point just leftward of the sagittal plane (the 11-o'clock position, as viewed from the patient's head) to facilitate passage through the anteromedially located tricuspid valve. The balloon at the tip of the catheter is inflated with air, and the catheter is advanced into the right atrium, through the tricuspid valve, the right ventricle, the pulmonic valve, into the pulmonary artery, and finally into the wedge position. Characteristic waveforms from each of these locations confirm proper catheter passage and placement (Fig. 45-21).

After the pulmonary artery wedge pressure is measured, the balloon is deflated, and the pulmonary artery pressure waveform should reappear. Wedge pressure may be obtained as needed by reinflating the balloon and allowing the catheter to float distally until pulmonary artery occlusion again occurs.

Additional Guidelines for Pulmonary Artery Catheter Insertion

From a right internal jugular vein puncture site, the right atrium should be reached when the PAC is inserted 20 to 25 cm, the right ventricle at 30 to 35 cm, the pulmonary artery at 40 to 45 cm, and the wedge position at 45 to 55 cm. When other sites are chosen for catheter placement, additional distance is required, typically an additional 5 to 10 cm from the left internal jugular and left and right external jugular veins, 15 cm from the femoral veins, and 30 to 35 cm from the antecubital veins.[234] These distances serve only as a rough guide; waveform morphology must always be verified and catheter position confirmed with a chest radiograph as soon as practical. The tip of the PAC should be within 2 cm of the cardiac silhouette on a standard anteroposterior chest film.[235]

Use of these typical distances helps avoid complications caused by unintended catheter loops and knots within the heart. If a right ventricular waveform is not observed after inserting the catheter 40 cm, coiling in the right atrium is likely. Similarly, if a pulmonary artery waveform is not observed after inserting the catheter 50 cm, coiling in the right ventricle has probably occurred. The balloon should be deflated, the catheter withdrawn to 20 cm, and the PAC floating sequence repeated.

If repeated attempts to advance the PAC to the right ventricle prove difficult, an abnormal venous anatomy may exist. The most common abnormality of the systemic veins is persistence of the left superior vena cava (LSVC), which is present in approximately 0.1% to 0.2% of the general population and 2% to 9% of patients with other forms of congenital heart disease.[236,237] The persistent LSVC descends along the left mediastinum and empties into a dilated coronary sinus. Because of the benign nature of LSVC, virtually all cases are asymptomatic and discovered incidentally at the time of failed central venous or pulmonary artery catheterization. Because a normal right superior vena cava is present in most of these patients, the anomaly is recognized only when attempted PAC placement proceeds from a left-sided vein. More rarely, difficult PAC placement is encountered during attempted right-sided venous cannulation because the right superior vena cava is absent as well. In these cases, the right internal jugular vein joins the persistent left superior vena cava by a bridging innominate vein. A rare form of atrial septal defect, termed *unroofed coronary sinus*, may also be encountered in these patients providing coronary sinus–left atrial communication and the potential for a PAC to enter the left atrium and systemic circulation.[237] With any of these venous anomalies, PAC advancement into the coronary sinus may disclose an unexpected pressure waveform, coronary sinus pressure.

A few additional points might aid successful positioning of the PAC. The air-filled balloon tends to float to nondependent regions as it passes through the heart into the pulmonary vasculature. Consequently, positioning the patient head down will aid flotation past the tricuspid valve, and tilting the patient onto the right side and placing the head up will encourage flotation out of the right ventricle, as well as reduce the incidence of arrhythmias

during insertion.[238,239] Deep inspiration during spontaneous ventilation will increase venous return and right ventricular output transiently and may facilitate catheter flotation in a patient with low cardiac output. On occasion, a catheter may be floated to proper position when stiffened by injecting 10 to 20 mL of ice-cold solution through the distal lumen. Finally, a catheter that is initially difficult to place may be positioned easily when hemodynamic conditions change, as commonly occurs after induction of general anesthesia and initiation of positive-pressure ventilation.

COMPLICATIONS OF PULMONARY ARTERY CATHETER MONITORING

Complications of PAC use may be divided into those resulting from catheter placement, those associated with the in vivo presence of the catheter, and those resulting from catheter use and misuse. For the most part, problems encountered during catheter placement are the same for both PAC and CVP monitoring (see Box 45-5). However, catheterization of the right ventricle and pulmonary artery causes complications uniquely associated with PACs (Box 45-6).[240]

When all adverse effects from PAC use are considered, including self-limited arrhythmias observed during catheter insertion, minor complications occur in more than 50% of catheterized patients.[231] However, major morbidity specifically attributable to PAC use is uncommon.[241] In 2003, the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization emphasized that the reported incidence of complications from PAC monitoring varies widely, although serious complications occur in 0.1% to 0.5% of PAC-monitored surgical patients.[231] In 1984, Shah and colleagues reported use of PACs in 6245 patients undergoing cardiac and noncardiac operations.[174] Quite remarkably, only 10 patients (0.16%) had serious complications resulting in morbidity and only 1 patient (0.016%) died as a result of pulmonary artery catheterization. Furthermore, a 1998 European report of PAC use in 5306 patients undergoing cardiac surgery confirms this infrequent incidence of major morbidity, with injury of the right ventricle or PA occurring in only 4 patients (0.07%).[242] Finally, only 1 of 2000 adverse events reported in the Australian Incident Monitoring Study of 1993 involved use of a PAC, in contrast to 64 adverse events involving access to the arterial or venous systems.[66] However, although these large studies indicate an infrequent incidence of serious complications attributable to the use of PACs, the frequency of complications in a particular clinical setting or patient group remains unknown.

Arrhythmias are the primary complication observed during pulmonary artery catheterization. In fact, self-limited atrial or ventricular arrhythmias are so common during PAC passage through the heart that most clinicians do not consider them complications, but rather confirmation that the PAC is traversing the cardiac chambers appropriately. Shah and associates observed transient premature ventricular contractions in 68% and atrial dysrhythmias in 1.3% of their catheterized patients.[174] Of more clinical significance, persistent ventricular dysrhythmias requiring treatment occurred in only 3.1% of patients, none of whom suffered prolonged hemodynamic instability. Although the balloon-tipped PAC is less arrhythmogenic when it strikes the endocardium than a standard intravenous catheter or transvenous pacing wire, PACs have been reported to induce sustained atrial fibrillation, ventricular tachycardia, and even ventricular fibrillation.[242-244]

Prophylactic use of IV lidocaine before pulmonary artery catheterization is not effective in reducing ventricular ectopy.[245] When such problems arise, the balloon should be deflated and the catheter withdrawn to the right atrium. When hemodynamically significant dysrhythmias develop hours or even days after placement, it is unlikely that the PAC is responsible. However, the position of the catheter tip should always be checked by observation of the pressure waveform and chest radiograph to identify catheters that have migrated back into the right ventricle.

As the PAC passes through the right ventricle and strikes the interventricular septum, transient right bundle branch block occurs in up to 5% of patients.[246,247] This is important only in patients with preexisting left bundle branch block. In these patients, complete heart block may be precipitated, although this is rare. Shah and associates catheterized 113 patients with preexisting left bundle branch block; only 1 patient developing complete heart block (0.9%).[174] In a different population of 47 high-risk patients with left bundle branch block, many of whom had acute myocardial infarction or heart failure, Morris and colleagues inserted 82 PACs without a single episode of complete heart block for the initial 24 hour period. [246] However, transcutaneous pacing equipment, an external pulse generator, and a temporary transvenous pacing wire or pacing PAC should be readily available as a precaution, especially as the onset of heart block in this setting may be delayed.

Many mechanical problems have been reported with PACs or introducer sheaths. In the setting of cardiac surgery, PACs may be damaged by surgical instruments or become entrapped in sutures or bypass cannulas.[174,248-250] Whenever right heart structures are involved in surgery, free movement of the PAC should be ensured before chest closure. Sternal retraction during cardiac surgery

BOX 45-6 *Complications of Pulmonary Artery Catheter Monitoring*

- Catheterization
  - Arrhythmias, ventricular fibrillation
  - Right bundle branch block, complete heart block
- Catheter residence
  - Mechanical, catheter knots
  - Thromboembolism
  - Pulmonary infarction
  - Infection, endocarditis
  - Endocardial damage, cardiac valve injury
  - Pulmonary artery rupture
  - Pulmonary artery pseudoaneurysm
- Misinterpretation of data
- Misuse of equipment

may pose other problems, particularly when the PAC is inserted through the external jugular or subclavian route. The PAC may kink as it exits the introducer sheath and makes an acute angle between the sheath and vessel wall.[251,252] These mechanical difficulties should be suspected whenever there is a damped appearance of the monitored pressure trace or difficulty in either infusing fluids or withdrawing blood through one of the catheter lumina.

Although gross structural defects in the catheter itself should be recognized by inspection of the catheter before insertion, more subtle manufacturing problems may escape detection. Some, such as communications between the PAP, CVP, and balloon inflation lumina may be suspected only when data are contradictory or inconsistent.[253,254]

PACs may dislodge temporary transvenous pacing wires, become entangled with other cardiac catheters, or form knots within the heart.[255,256] Arnaout and colleagues reported a PAC knot around the tricuspid valve chordae tendinae, which resulted in severe tricuspid valve regurgitation following catheter removal.[255] Catheter knots should be suspected when there is difficulty withdrawing a PAC and the diagnosis may be confirmed by chest radiography. Knots may be untied by radiologists using intravascular snares and fluoroscopic guidance.[257] If the knot has already been drawn tight, surgical exploration and removal are usually required.

Although both severe tricuspid regurgitation and severe pulmonic regurgitation have been reported, these are rare complications of PAC use.[255,258,259] Using color flow Doppler echocardiography, Sherman and associates demonstrated that placement of a PAC caused a slight increase in the magnitude of tricuspid regurgitation, but in no instance did the PAC lead to severe right-sided valvular insufficiency.[260]

Although the incidence of thromboembolic complications is increased in patients who require PAC monitoring for longer periods of time, thrombi have been detected on PACs within hours of placement.[261] When administration of drugs such as aprotinin and aminocaproic acid reduce perioperative bleeding, the risk of thrombus formation on the PAC may be increased.[262,263] Although external surface heparin bonding unquestionably has reduced thrombogenicity of PACs, it does not entirely eliminate the possibility.[261,264] Fortunately, major pulmonary embolism is a rare occurrence.[265]

The incidence of PAC-related infection increases after 3 days of continuous monitoring and in patients with preexisting sepsis.[266] The most catastrophic of these infections is endocarditis, most often of the right-sided valves.[259,267] Using sophisticated microbiologic techniques in 297 critically ill patients, Mermel and colleagues demonstrated a 22% incidence of local infection of the introducer sheath, but only 0.7% incidence of bacteremia related to the PAC.[268] Changes of PACs do not reduce the risk of bloodstream infection, particularly when the catheter is changed over a guidewire.[269] However, cannulation at a new site carries a significant risk of vascular complications. The specific risks and benefits must be weighed in each patient. Although heparin-bonded PACs carry an infection risk similar to central venous catheters, non–heparin-bonded catheters have double the risk.[136]

Pulmonary artery rupture, the most deadly but also most preventable of complications, occurs in approximately 0.02% to 0.2% of catheterized patients and carries a mortality rate of 50%.[174,270] Several factors increase the risk of this catastrophic event, including hypothermia, anticoagulation, and advanced age, although many reported cases involve heart transplant procedures.[270-272] Pulmonary hypertension also may predispose patients to arterial injury during balloon inflation owing to the increased gradient between the proximal arterial and distal wedge pressures or because pulmonary hypertension distends the pulmonary vasculature and causes the PAC to wedge in a distal, less compliant vessel.[273]

Several mechanisms exist for pulmonary artery injury. These include forceful inflation of the PAC balloon and chronic erosion by the catheter tip abutting the vessel wall or eccentric balloon inflation forcing the noncushioned catheter tip through the vessel wall.[272,274] Regardless of the precise mechanism by which pulmonary arterial injury occurs, case reports highlight that this complication often results from suboptimal catheter insertion and management techniques. Procedural errors include unnecessary catheter manipulation, excessive insertion depth, unrecognized persistent wedge pressure, prolonged balloon inflation, or improper balloon inflation with liquid rather than air.[273-275] It is critical that the clinician recognize artifactual "over-wedged" pressure recordings that indicate peripheral migration of the PAC tip or impaction against the vessel wall and correct this problem immediately by withdrawing the catheter into the proximal pulmonary artery. This problem is more common during cardiopulmonary bypass, owing to the repeated cardiac manipulations and temperature changes that alter the stiffness of the catheter.[276]

The hallmark of catheter-induced pulmonary artery rupture is hemoptysis, which may cause life-threatening exsanguination or hypoxemia. Less commonly, occult hypotension or respiratory compromise may develop. If the visceral pleura fails to contain the bleeding, free rupture into the pleural space produces a large hemothorax. When time allows, a chest radiograph helps determine the diagnosis by revealing the hemothorax or a new infiltrate near the tip of a distally positioned PAC. Although its initial appearance may be confused with catheter-related pulmonary infarction, the pattern of resolution and clinical course differentiate these diagnoses. In confusing cases, the diagnosis may be confirmed by performing a wedge angiogram, in which radiopaque dye injected through the wedged PAC will extravasate into the pulmonary parenchyma to identify the site of arterial disruption.[271]

Treatment of pulmonary artery rupture focuses on resuscitation and immediate control of the hemorrhage. Specific therapeutic steps are highly individualized, depending on the setting. The first priority is ensuring adequate oxygenation and ventilation and may require endobronchial intubation with either a single- or double-lumen endotracheal tube to selectively ventilate and protect the unaffected lung. In addition, positive end-expiratory pressure applied to the affected lung may help

control hemorrhage.[277] Any anticoagulation should be reversed unless the patient must remain on cardiopulmonary bypass and bronchoscopy is performed to localize and control the site of bleeding. A bronchial blocker may be guided into the involved bronchus to tamponade the bleeding and prevent contamination of the uninvolved lung.[278] Management of the PAC itself is more controversial. Some experts recommend removing the catheter, but others suggest leaving the PAC in place to monitor pulmonary artery pressure and guide antihypertensive therapy targeted at decreasing this pressure and reducing bleeding.[279,280] The PAC balloon may be carefully reinflated and the catheter floated into the involved pulmonary artery to occlude the bleeding arterial segment as a temporizing measure.[278] Although these measures may be effective in some cases, many patients will require definitive surgical therapy, such as oversewing the involved pulmonary artery or resecting the involved segment, lobe, or lung.[271,278] In addition, angiography may be recommended to rule out pseudoaneurysm formation in those managed conservatively due to the high morbidity associated with secondary hemorrhage.[270,278,281,282]

A more insidious but possibly more common complication of PAC use is misinterpretation of data.[283,284] Although the magnitude of the problem is not clear, widespread knowledge deficits likely exist among practitioners who use PACs. In 1990, Iberti and colleagues reported the results of a 31-question multiple-choice examination given to 496 resident and staff physicians in medicine, surgery, and anesthesiology departments, who practiced in 13 North American medical centers. The authors found a poor overall level of knowledge of PACs, as evidenced by a mean score of only 67% correct answers. Although higher scores were demonstrated by individuals with more training and more experience inserting and using PACs, none of these factors ensured a high level of knowledge.[285] These results have been duplicated in a variety of other specialty care groups.[286] It is especially concerning that pulmonary artery wedge pressure measurement was performed incorrectly by 30% to 50% of the clinicians in these studies and that educational programs failed to improve performance.[287,288] Taken together, these observations highlight the fact that effective use of PACs requires a great deal of expertise and clinical experience, and even measuring the most fundamental PAC-derived variable, namely wedge pressure, is a complicated endeavor.[289]

NORMAL PULMONARY ARTERY PRESSURES AND WAVEFORMS

As the balloon-tipped PAC is floated to its proper position in the pulmonary artery, characteristic pressure waveforms are recorded (see Fig. 45-21). In the superior vena cava or right atrium, a CVP waveform with characteristic a, c, and v waves and low mean pressure should be observed. At this point, the PAC balloon is inflated, and the catheter is advanced until it crosses the tricuspid valve to record right ventricular pressure, characterized by a rapid systolic upstroke, a wide pulse pressure, and low diastolic pressure. Next, the PAC enters the right ventricular outflow tract and floats past the pulmonic valve into the main pulmonary artery. Premature ventricular beats are common during this period as the balloon-tipped catheter strikes the right ventricular infundibular wall. Entry into the pulmonary artery is heralded by a step-up in diastolic pressure and a change in waveform morphology.

On occasion, it may be difficult to distinguish right ventricular pressure from PAP, particularly if only the numeric values for these pressures are examined. However, careful observation of the pressure waveforms, focusing on the diastolic pressure contours, allows differentiation. During diastole, the PAP will fall because of interruption of flow during pulmonic valve closure, whereas the pressure in the right ventricle will increase as a result of filling from the right atrium[234] (see Fig. 45-21).

Under normal conditions, the PAP upstroke slightly precedes the radial artery pressure upstroke as a result of the longer duration of left ventricular isovolumic contraction and the time required for pressure wave propagation to a distal monitoring site. As a practical matter, though, the pulmonary and systemic arterial pressure waveforms appear to overlap on the bedside monitor (Fig. 45-22). Understanding these temporal relations is critically

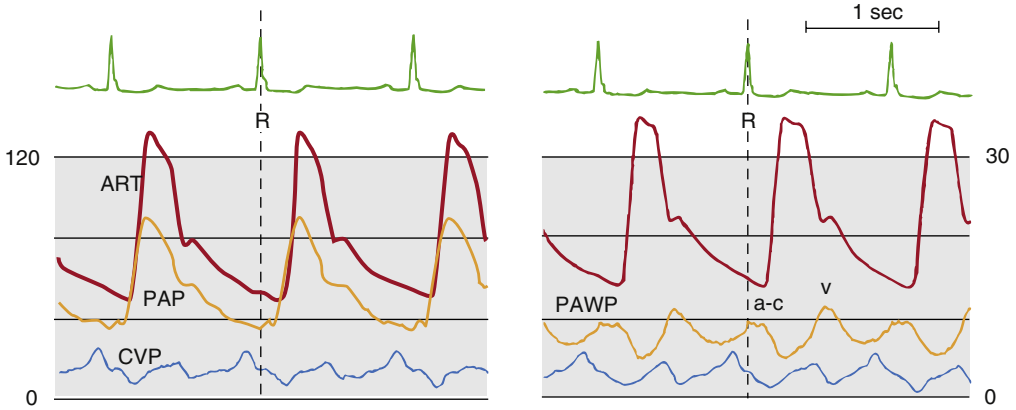


Figure 45-22. Temporal relations between normal systemic arterial pressure (ART), pulmonary artery pressure (PAP), central venous pressure (CVP), and pulmonary artery wedge pressure (PAWP). Note that the PAWP a-c and v waves appear to occur later in the cardiac cycle compared with their counterparts on the right side of the heart seen in the CVP trace. ART pressure scale on the left; PAP, CVP, and PAWP pressure scales on the right. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

important if one is to properly interpret abnormal pulmonary artery and wedge pressure waveforms, particularly when tall v waves are present (see later).

As noted earlier, the wedge pressure is an indirect measurement of pulmonary venous pressure and left atrial pressure and should therefore resemble these venous waveforms with characteristic a and v waves and x and y descents. However, owing to the pulmonary vascular bed interposed between the PAC tip and left atrium, wedge pressure is a delayed and damped representation of left atrial pressure.[290] On average, 160 milliseconds are required for the left atrial pressure pulse to traverse the pulmonary veins, capillaries, arterioles, and arteries. Additionally, atrial depolarization originates in the sinoatrial node located at the junction of the superior vena cava and the right atrium, and therefore the left-sided a wave appears slightly later than the right-sided a wave (Fig. 45-23). As a consequence of these two phenomena, the wedge pressure a wave appears to follow the ECG R wave in early ventricular systole, even though the a wave is an end-diastolic event (see Fig. 45-22). Although the a wave is the most prominent pressure peak in a normal CVP trace, the v wave is often taller than the a wave in a normal left atrial pressure waveform, suggesting that atrial contraction is stronger on the right than the left, and that the left atrium is less distensible than the right.[82] Finally, the interval between atrial and ventricular contraction is approximately 40 milliseconds longer on the right than on the left.[82] Consequently, a and c waves are seen as separate waves in a right atrial pressure trace, whereas on the left they merge into a composite a-c wave (see Fig. 45-22).

To recognize prominent a or v waves in the wedge pressure trace, it is not always necessary to inflate the PAC balloon. Because the PAWP trace reflects pressure waves transmitted in retrograde fashion from the left atrium, these waves will not normally be visible within the antegrade pulmonary artery pressure waves produced by right ventricular ejection. In the setting of prominent a or v waves, the PAP trace becomes a composite wave, reflecting both retrograde and antegrade components. Tall left atrial a or v waves will distort the normal pulmonary artery pressure waveform appearance, with the a wave inscribed at the onset of the systolic upstroke and the v wave distorting the dicrotic notch[290,291] (Fig. 45-24). Once these waves are identified by wedging the PAC and comparing the PAP and PAWP traces, it is wise to "follow" the wedge-pressure a and v waves in the unwedged PAP trace, rather than repeatedly inflating the balloon.

The terms *pulmonary artery wedge pressure* and *pulmonary artery occlusion pressure* are used interchangeably and refer to the same measurement obtained from the tip of a PAC following balloon inflation and flotation to the wedged position. However, pulmonary capillary pressure must not be confused with wedge pressure or left atrial pressure, nor should the term *pulmonary capillary wedge pressure* be used at all. The hydrostatic pressure in the pulmonary capillaries that causes edema formation according to the Starling equation is different from LAP. This is the pressure that must exceed left atrial pressure in order to maintain antegrade blood flow through the lungs. Although the magnitude of the difference between pulmonary capillary pressure and wedge pressure is generally small, it can increase markedly when resistance to flow in the pulmonary veins is elevated.[292] In most situations, the major component of pulmonary vascular resistance occurs at the precapillary, pulmonary arteriolar level. However, rare conditions like pulmonary venoocclusive disease may cause a marked increase in postcapillary resistance to flow. Similar situations arise in conditions that disproportionately increase pulmonary venous resistance, such as central nervous system injury, acute lung injury, hypovolemic shock, endotoxemia, and norepinephrine infusion.[291,293] Under these conditions, measurement of wedge pressure will underestimate pulmonary capillary pressure substantially and thereby underestimate the risk of hydrostatic pulmonary edema. Although pulmonary capillary pressure may be measured at the bedside by analyzing the decay in pulmonary artery pressure trace following PAC balloon inflation, these techniques have not been widely adopted in clinical practice.[294,295] To avoid confusion, the term *pulmonary capillary wedge pressure* should be abandoned because it is imprecise and misleading.

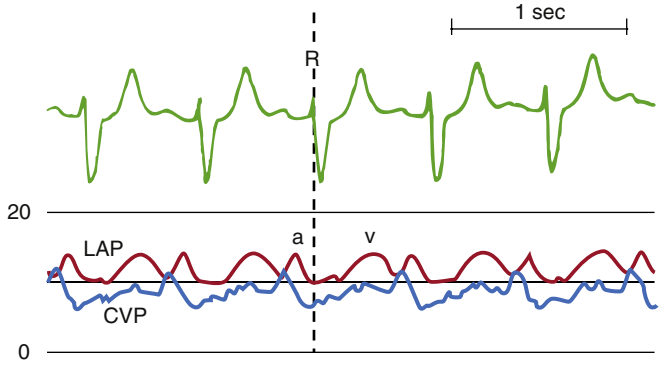


Figure 45-23. Normal temporal relations between the electrocardiographic, central venous pressure (CVP), and left atrial pressure (LAP) traces. The LAP and CVP waveforms have nearly identical morphologies, although the CVP a wave slightly precedes the LAP a wave. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

ABNORMAL PULMONARY ARTERY AND WEDGE PRESSURE WAVEFORMS

PAC monitoring is subject to the same technical artifacts inherent in all invasive pressure monitoring techniques,

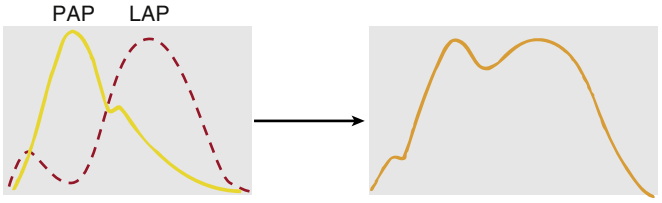


Figure 45-24. Tall left atrial pressure (LAP) a and v waves transmitted in a retrograde direction through the pulmonary vasculature distort the antegrade pulmonary artery pressure (PAP) waveform. The LAP a wave distorts the systolic upstroke, and the v wave distorts the dicrotic notch. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

as well as some additional problems unique to this method.[274,296,297] Because the PAC is longer and passes through the cardiac chambers, it is more prone to distortions from clot or air bubbles, and motion-related artifacts are more problematic. Artifactual pressure spikes may be distinguished from the underlying physiologic pressure waveform by their unique morphology and timing.

At the onset of systole, tricuspid valve closure accompanied by right ventricular contraction and ejection result in excessive catheter motion, causing the most common PAC trace artifact.[296,298] This pressure artifact is simultaneous with the CVP c wave and may produce either an artificially low pressure or a pressure peak. If the monitor detects this inappropriate pressure nadir, it may be erroneously designated as the pulmonary artery diastolic pressure (Fig. 45-25). Repositioning the PAC often solves the problem.

Another common artifact in PAC pressure measurement occurs when the balloon is overinflated and occludes the lumen orifice. This phenomenon is termed overwedging and usually is caused by distal catheter migration and eccentric balloon inflation that forces the catheter tip against the vessel wall. The catheter now records a gradually rising pressure as the continuous flush system builds up pressure against the obstructed distal opening (Fig. 45-26). For a catheter that has migrated to a more distal position, it is possible for overwedging to occur without balloon inflation. Note that the overwedged pressure is devoid of pulsatility, is higher than expected, and increases continuously because of the continuous flush pressure. This should be corrected by catheter withdrawal.

As emphasized earlier, with each PAC balloon inflation and wedge measurement, the catheter tip migrates distally. When a wedge pressure tracing appears during partial balloon inflation, it suggests that the PAC is inappropriately located in a smaller, distal branch of the pulmonary artery. The catheter should be withdrawn before overwedging results in vascular injury or pulmonary infarction.

Pathophysiologic conditions involving the left-sided cardiac chambers or valves produce characteristic changes in the pulmonary artery and wedge pressure waveforms. One of the most easily recognized patterns is the tall v wave of mitral regurgitation. Unlike a normal wedge pressure v wave produced by late systolic pulmonary venous inflow, the prominent v wave of mitral regurgitation begins in early systole. Mitral regurgitation causes fusion of c and v waves and obliteration of the systolic x descent, as the isovolumic phase of left ventricular systole is eliminated owing to the retrograde ejection of blood into the left atrium.[226] Because the prominent v wave of mitral regurgitation is generated during ventricular systole, the mean wedge pressure overestimates left ventricular end-diastolic filling pressure, which is better estimated by the pressure value before onset of the regurgitant v wave (Fig. 45-27). Although mean wedge pressure exceeds left ventricular end-diastolic pressure in patients with severe mitral regurgitation, it remains a good approximation for mean left atrial pressure and the subsequent risk of hydrostatic pulmonary edema.

When large v waves are present in the wedge pressure trace, it is critically important to recognize them and be able to distinguish the wedged from the unwedged pressure waveform. At first glance, a wedge trace with a tall

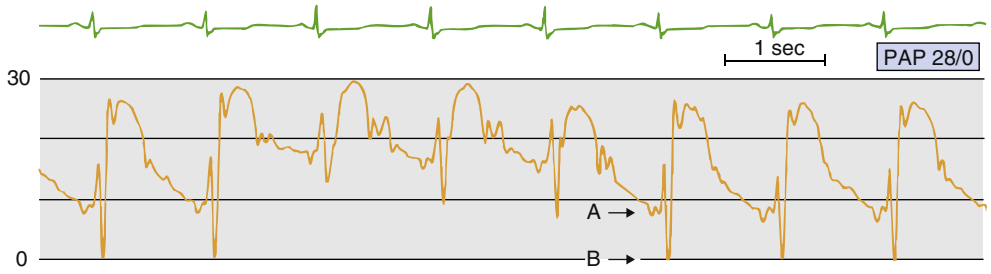


Figure 45-25. Artifactual pressure peaks and troughs in the pulmonary artery pressure (PAP) waveform caused by catheter motion. The correct value for pulmonary artery end-diastolic pressure is 8 mm Hg (A), although the monitor digital display erroneously reports the PAP as 28/0 mm Hg (B). *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

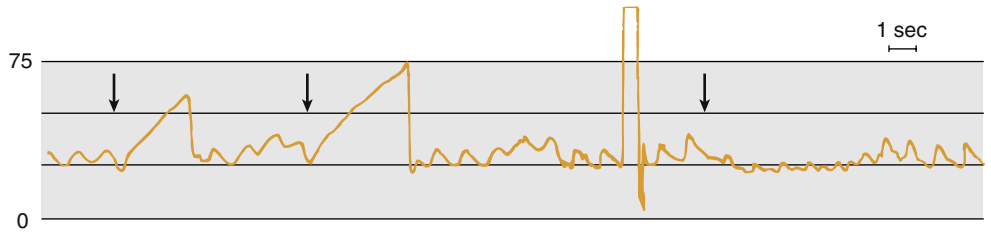


Figure 45-26. Overwedging of the pulmonary artery (PA) catheter causes artifactual waveform recordings. The first two attempts to inflate the PA catheter balloon (*first two arrows*) produce a nonpulsatile increasing pressure caused by an occluded catheter tip. After the catheter is withdrawn slightly, balloon inflation allows proper wedge pressure measurement (*third arrow*). Before the third attempt at balloon inflation, the PA pressure lumen is flushed. This restores the appropriate pulsatile nature to the PA and wedge pressure waveforms on the right side of the trace. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

systolic v wave resembles a typical unwedged pulmonary artery pressure trace, but closer observation reveals a number of discriminating details. The pulmonary artery pressure upstroke is steeper and slightly precedes the systemic arterial pressure upstroke, whereas a wedge tracing with a prominent v wave has a more gradual upstroke that begins after the radial artery pressure upstroke. Furthermore, the wedge pressure v wave reaches its peak later in the cardiac cycle, after the ECG T wave as opposed to the simultaneous peaks of the systemic and pulmonary arterial peaks[226,299] (see Fig. 45-27). Another distinguishing feature in patients with severe mitral regurgitation is the unusual morphology of the pulmonary artery waveform itself. The larger the regurgitant v wave, the more it distorts the pulmonary artery waveform, giving it a bifid appearance and obscuring the normal end-systolic dicrotic notch[291] (see Fig. 45-27).

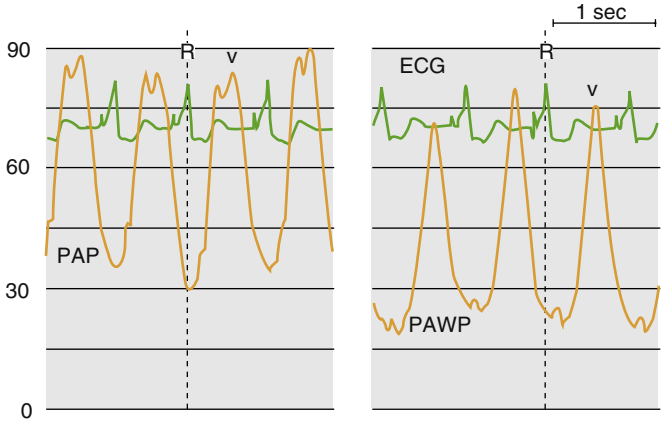


Figure 45-27. Severe mitral regurgitation. A tall systolic v wave (v) is inscribed in the pulmonary artery wedge pressure (PAWP) trace and also distorts the pulmonary artery pressure (PAP) trace, giving it a bifid appearance. The electrocardiogram (ECG) is abnormal owing to ventricular pacing. Left ventricular end-diastolic pressure is estimated best by measuring PAWP at the time of the electrocardiographic R wave, before onset of the regurgitant v wave. Note that mean PAWP exceeds left ventricular end-diastolic pressure in this condition. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

A close look at left atrial pressure-volume relations helps to explain the apparently paradoxical coexistence of severe mitral regurgitation and a normal pulmonary artery wedge pressure trace.[300,301] Three factors determine whether mitral regurgitation produces a prominent v wave in the left atrial or wedge pressure traces: left atrial volume, left atrial compliance, and regurgitant volume (Fig. 45-28). Given that the left atrial pressure-volume relation is not linear, the same volume of regurgitation will result in a variable increment in systolic pressure, depending on the preexisting atrial volume at onset of systole. Furthermore, the nature of that relationship is dependent on the compliance (i.e., stiffness) of the left atrium. Although the total regurgitant volume of blood entering the left atrium will influence the height of the v wave, this clearly is not the only determinant of v wave magnitude. This may explain why patients with acute mitral regurgitation tend to have tall wedge pressure v waves—they have smaller, stiffer left atria with poorer compliance compared with those of patients with long-standing disease. It is not surprising that wedge pressure v waves are neither sensitive nor specific indicators of mitral regurgitation severity, and the height of these waves should not be used in such a manner.[300] Prominent wedge pressure v waves may exist in the absence of mitral regurgitation when left atrial pressure is high, as might occur when the left atrium is compressed.[302] Tall v waves are also seen commonly in patients with hypervolemia, congestive heart failure, and ventricular septal defect.[300] Note that the giant v waves observed in patients with ventricular septal defect are not caused by retrograde flow, but rather by excessive antegrade systolic flow into the left atrium due to the intracardiac shunt.[303]

In contrast to mitral regurgitation, which distorts the systolic portion of the wedge pressure waveform, mitral stenosis alters its diastolic aspect. In this condition, the holodiastolic pressure gradient across the mitral valve results in an increased mean wedge pressure, a slurred early diastolic y descent, and a tall end-diastolic a wave. Similar hemodynamic abnormalities are seen in patients with left atrial myxoma or whenever mitral flow is obstructed. Diseases that increase left ventricular stiffness

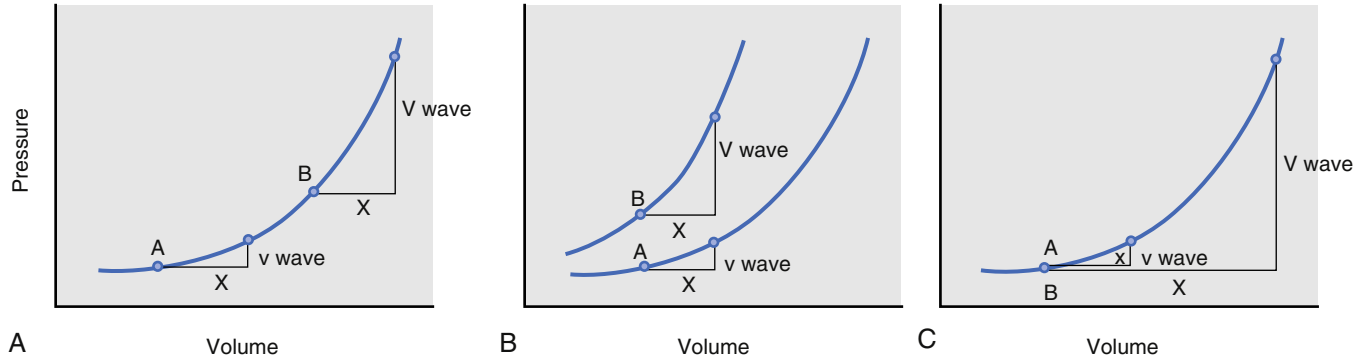


Figure 45-28. V wave height as an indicator of mitral regurgitation severity. Left atrial pressure-volume curves describe the three factors that determine v wave height. **A,** Influence of left atrial volume. For the same regurgitant volume (x), the left atrial v wave will be taller if baseline atrial volume is greater (point B versus point A). **B,** Influence of left atrial compliance. For the same regurgitant volume (x), the left atrial v wave will be taller if baseline atrial compliance is reduced (point B versus point A). **C,** Influence of regurgitant volume. Beginning at the same baseline left atrial volume (points A and B), if regurgitant volume increases (X versus x), the left atrial pressure v wave will increase (V versus v). *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

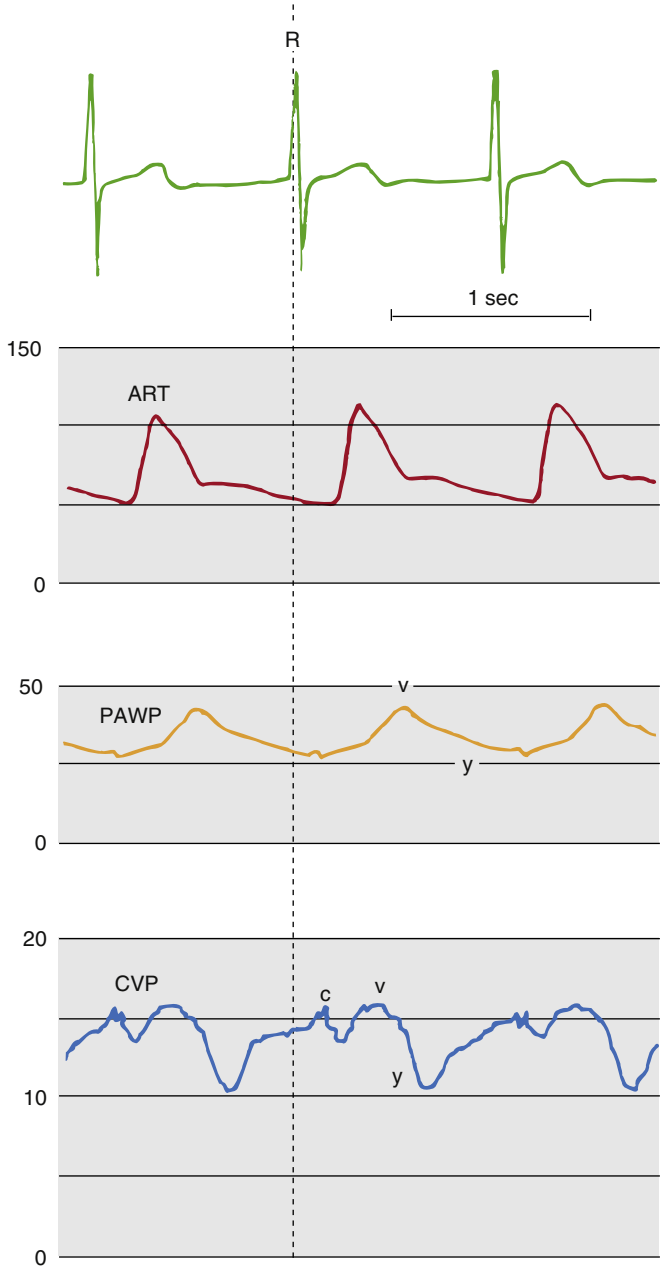


Figure 45-29. Mitral stenosis. Mean pulmonary artery wedge pressure (PAWP) is increased (35 mm Hg), and the diastolic y descent is markedly attenuated. Compare the slope of the y descent in the PAWP trace with the y descent in the central venous pressure (CVP) trace. In addition, compare this PAWP y descent with the PAWP y descent in mitral regurgitation (see Fig. 45-27); a waves are not seen in the PAWP or CVP traces, owing to atrial fibrillation. Arterial blood pressure (ART). *(From Mark JB: Atlas of cardiovascular monitoring, New York, 1998, Churchill Livingstone.)*

(e.g., left ventricular infarction, pericardial constriction, aortic stenosis, and systemic hypertension) produce changes in the wedge pressure that resemble in part those seen in mitral stenosis. In these conditions, mean wedge pressure is increased and the trace displays a prominent a wave, but the y descent remains steep, because there is no obstruction to flow across the mitral valve during diastole. Because patients with advanced mitral stenosis often have coexisting atrial fibrillation, the a wave will not be present in many of these cases[226] (Fig. 45-29).

Myocardial ischemia may be detected by PAC in several ways. Ischemia itself impairs left ventricular relaxation resulting in diastolic dysfunction, a pattern particularly characteristic of demand ischemia associated with tachycardia or induced by rapid atrial pacing.[304-306] Impaired ventricular relaxation results in a stiffer, less compliant left ventricle, resulting in an increased left ventricular end-diastolic pressure. Not only does this, in turn, increases left atrial and wedge pressures, but the morphology of these waveforms changes as well, with the phasic a and v wave components becoming more prominent as diastolic filling pressure increases.[307-309] Although myocardial ischemia will often be detectable as a rise in pulmonary artery diastolic, mean, or systolic pressures, these changes are generally less striking than the accompanying change in wedge pressure and new appearance of tall a and v waves (Fig. 45-30). In patients with left ventricular ischemia, the tall wedge pressure a wave is produced by end-diastolic atrial contraction into a stiff, incompletely relaxed left ventricle.[310] Although the diastolic dysfunction accompanying myocardial ischemia leads to an increase in left ventricular end-diastolic pressure, this pressure elevation often coexists with a decreased left ventricular end-diastolic volume or preload.[304] The dissociation between filling pressure and filling volume in this condition must be appreciated to avoid diagnostic and therapeutic errors.

Myocardial ischemia also produces a characteristic pattern of left ventricular systolic dysfunction. Systolic dysfunction is the hallmark of supply ischemia, caused by a sudden reduction or cessation of coronary blood flow to a region of the myocardium.[306,311] With severe systolic dysfunction, changes in global left ventricular contractile performance may be detected with hemodynamic monitoring. As ejection fraction falls significantly, left ventricular end-diastolic volume and pressure rise and systemic arterial hypotension and elevated pulmonary diastolic and wedge pressures develop.[312] A more common hemodynamic manifestation of myocardial ischemia occurs when left ventricular geometry is distorted or when the region of ischemic myocardium underlies a papillary muscle, resulting in acute mitral regurgitation.[313] This form of ischemic mitral regurgitation is often termed papillary muscle ischemia or functional mitral regurgitation. As noted earlier, PAC monitoring is particularly well suited to detect this event by revealing the onset of new regurgitant v waves in the pulmonary artery or wedge pressure traces (see Fig. 45-27).

Whether the PAC should be used in high-risk patients as a supplemental monitor for detection of myocardial ischemia remains controversial.[309,314-316] None of the current methods for detecting perioperative myocardial ischemia is perfectly sensitive or specific. Although patients with left ventricular ischemia are likely to have higher mean wedge pressures than those without ischemia, these differences are small and may be difficult to detect clinically.[309] Furthermore, clear quantitative threshold values for mean wedge pressure or a and v wave peak pressures that are diagnostic of ischemia have not been identified, perhaps owing to the wide variations in normal patients. Consequently, when a PAC is used to diagnose myocardial ischemia, the best approach is to integrate the PAC data with other clinical and monitored information.[317]

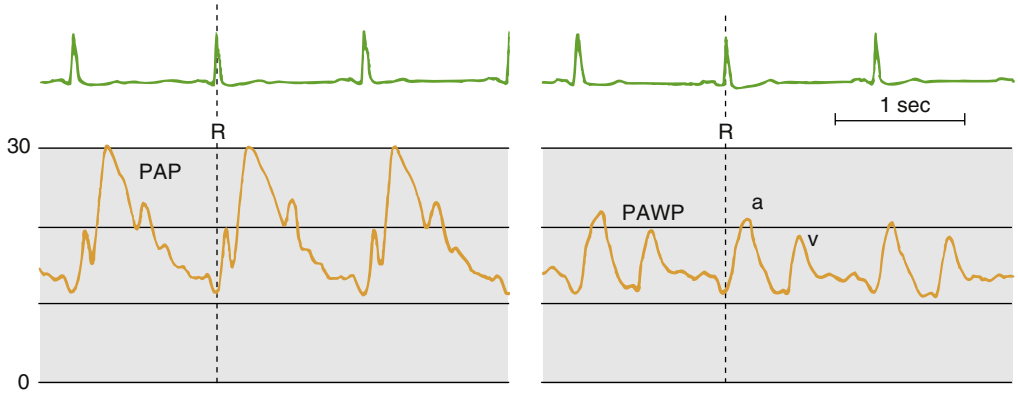


Figure 45-30. Myocardial ischemia. Pulmonary artery pressure (PAP) is relatively normal and mean pulmonary artery wedge pressure (PAWP) is only slightly elevated (15 mm Hg). However, PAWP morphology is markedly abnormal with tall a waves (21 mm Hg) resulting from the diastolic dysfunction seen in this condition. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

Right ventricular ischemia produces characteristic PAC waveform patterns that may be helpful in diagnosis and management. Just as left ventricular ischemia increases pulmonary artery wedge pressure, right ventricular ischemia increases CVP. In fact, this is one of the few situations in which CVP may be higher than wedge pressure. In addition, CVP waveforms may display a prominent a wave resulting from right ventricular diastolic dysfunction, and a prominent v wave resulting from ischemia-induced tricuspid regurgitation.[318,319] This particular CVP waveform is described as having an M or W configuration, referring to the tall a and v waves and interposed steep x and y descents. Severe pulmonary artery hypertension may also result in right ventricular ischemia and dysfunction as well as increased CVP, but this is distinguished from primary right ventricular dysfunction in that the pulmonary artery pressure and calculated pulmonary vascular resistance are normal in primary right ventricular failure.

The CVP waveform in right ventricular infarction is similar to that from a patient with restrictive cardiomyopathy or pericardial constriction, including elevated mean pressure, prominent a and v waves, and steep x and y descents.[320] The cardinal feature common to these conditions is impaired right ventricular diastolic compliance, often termed restrictive physiology. In restrictive cardiomyopathy and right ventricular infarction, diastolic dysfunction impairs ventricular relaxation and decreases chamber compliance, whereas in constrictive pericarditis cardiac filling is limited by the rigid, often calcified pericardial shell. Impaired venous return decreases end-diastolic volume, stroke volume, and cardiac output. Despite reduced cardiac volumes, cardiac filling pressures are markedly elevated and equal in all four chambers of the heart at end-diastole (Fig. 45-31). Although PAC monitoring reveals this pressure equalization, the characteristic M or W configuration is more apparent in the CVP trace, most likely because of the damping effect of the pulmonary vasculature on the left-sided filling pressures.[321-323]

Another hallmark of pericardial constriction is observed in the right and left ventricular pressure traces. These demonstrate rapid but short-lived early diastolic ventricular filling, which produces a diastolic dip-and-plateau

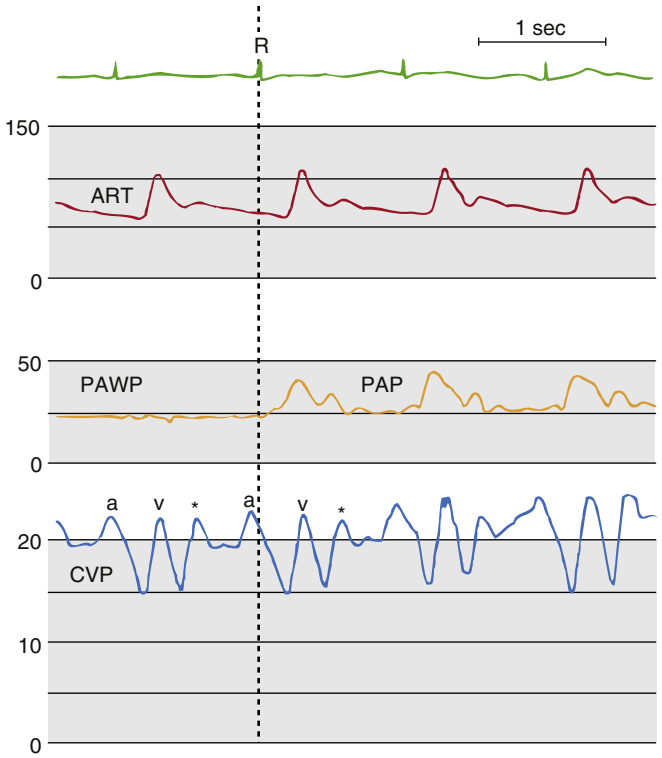


Figure 45-31. Pericardial constriction. This condition causes elevation and equalization of diastolic filling pressures in the pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), and central venous pressure (CVP) traces. The CVP waveform reveals tall a and v waves with steep x and y descents and a mid-diastolic plateau wave (*) or h wave. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

pattern or "square root sign."[93,324] In some cases, particularly when heart rate is slow, a similar waveform pattern may be noted in the CVP trace: a steep y descent (the diastolic dip) produced by rapid early diastolic flow from atrium to ventricle, followed by a mid-diastolic h wave (the plateau) from the interruption in flow imposed by the restrictive pericardial shell (see Fig. 45-31).

Like pericardial constriction, cardiac tamponade impairs cardiac filling, but in the case of tamponade, a

compressive pericardial fluid collection produces this effect. This results in a marked increase in CVP and a reduced diastolic volume, stroke volume, and cardiac output. Despite many similar hemodynamic features, tamponade and constriction may be distinguished by the different CVP waveforms seen in these two conditions. In tamponade, the venous pressure waveform appears more monophasic and is dominated by the systolic x pressure descent. The diastolic y pressure descent is attenuated or absent, because early diastolic flow from right atrium to right ventricle is impaired by the surrounding compressive pericardial fluid collection[321,325,326] (Fig. 45-32). Clearly, other clinical and hemodynamic clues help distinguish these diagnoses, such as the presence of pulsus paradoxus, an almost invariable finding in cardiac tamponade[327] (see Fig. 45-14). Coexisting abnormalities such as tachycardia, arrhythmias, and atrial contractile failure may complicate interpretation of these waveforms. On occasion, localized pericardial constriction may simulate valvular stenosis, and hypovolemia may lower cardiac filling pressures to within the normal range and confound the diagnosis.

Probably the single most important waveform abnormality or interpretive problem in PAC monitoring is discerning the correct pressure measurement in patients with large intrathoracic pressure swings like those receiving positive-pressure ventilation or those with labored spontaneous breathing. Just as in the case of CVP monitoring, all transmural cardiac filling pressures are estimated best when end-expiratory pressure values are recorded. During positive-pressure ventilation, inspiration increases pulmonary artery and wedge pressures. By measuring these pressures at end-expiration, the confounding effect of this inspiratory increase in intrathoracic pressure is minimized[328] (Fig. 45-33). Forceful inspiration during spontaneous ventilation has the opposite effect, but again, measurement of these pressures at end-expiration eliminates this confounding factor. Bedside monitors are designed with algorithms that aim to identify and report the numeric values for end-expiratory pressures but are often inaccurate.[329,330] The most reliable method for measuring central vascular pressures at end-expiration is examination of the waveforms on a calibrated monitor screen or paper recording.[330,331]

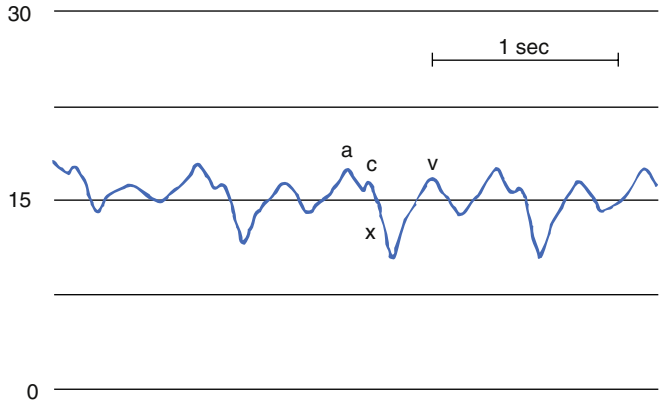


Figure 45-32. Cardiac tamponade. The central venous pressure waveform shows an increased mean pressure (16 mm Hg) and attenuation of the y descent. Compare with Figure 45-31. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

PHYSIOLOGIC CONSIDERATIONS FOR PULMONARY ARTERY CATHETER MONITORING: PREDICTION OF LEFT VENTRICULAR FILLING PRESSURE

One of the main reasons to measure pulmonary artery diastolic and wedge pressures is to be able to estimate left ventricular end-diastolic pressure, the closest surrogate to left ventricular end-diastolic volume, which is the true left ventricular preload (also see Chapter 46). When a PAC floats to the wedge position, the inflated balloon isolates the distal pressure-monitoring orifice from upstream pulmonary artery pressure. A continuous static column of blood now connects the wedged PAC tip to the junction of the pulmonary veins and left atrium. Thus, wedging the PAC, in effect, extends the catheter tip to measure the pressure at the point at which blood flow resumes on the venous side of the pulmonary circuit. Because resistance in the large pulmonary veins is negligible, pulmonary artery wedge pressure provides an indirect measurement of both pulmonary venous pressure and left atrial pressure.[71,332]

Pulmonary artery diastolic pressure (PAD) is often used as an alternative to PAWP to estimate left ventricular filling pressure. This is acceptable under normal circumstances because when pulmonary venous resistance is low, the pressure in the pulmonary artery at end of diastole will equilibrate with downstream pressure in the pulmonary veins and left atrium.[333,334] From a monitoring standpoint, PAD has the added advantage of being

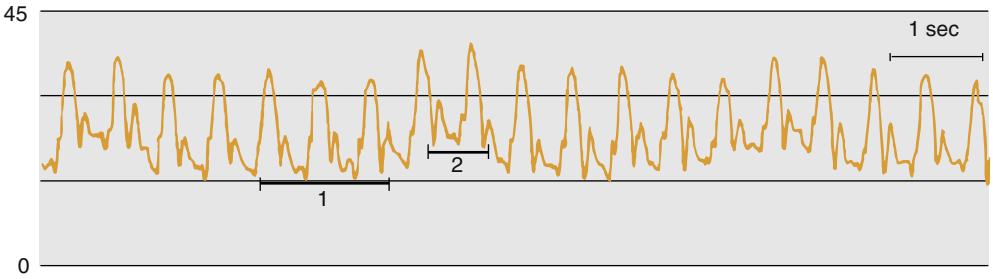


Figure 45-33. Influence of positive-pressure mechanical ventilation on pulmonary artery pressure. Pulmonary artery pressure should be measured at end expiration (*1*, 15 mm Hg) in order to obviate the artifact caused by positive-pressure inspiration (*2*, 22 mm Hg). *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

available for continuous monitoring, whereas PAWP is only measured intermittently.

For both PAD and PAWP to be valid estimates of left ventricular filling pressure, the column of blood connecting the tip of the wedged catheter and the draining pulmonary vein must be continuous and static. At the microcirculatory level, this channel consists of pulmonary capillaries that are subject to external compression by surrounding alveoli. West and associates described a three-zone model of the pulmonary vasculature based on the gravitationally determined relationships between relative pressures in the pulmonary arteries, pulmonary veins, and surrounding alveoli.[335] In West zone 1, alveolar pressure exceeds pressure in both the pulmonary artery and pulmonary veins, whereas in zone 2, it is intermediate between these two pressures (Fig. 45-34). A PAC positioned in both zone 1 and 2 will be highly susceptible to alveolar pressure, and measurements will reflect alveolar or airway pressure rather than left ventricular filling pressure. As such, the tip of the PAC must lie in zone 3 for PAWP measurements to be accurate. In most clinical settings, the supine position of the patient favors zone 3 conditions, a finding that has been confirmed by radiographic studies.[336] However, when patients are placed in the lateral or semi-upright position, zone 2 may expand significantly. In general, zones 1 and 2 become more extensive when left atrial pressure is low, when the PAC tip is located vertically above the left atrium, or when alveolar pressure is high. Clues to an incorrectly positioned catheter include absence of normal PAWP a and v waves, marked respiratory variation in PAWP, and a PAD that exceeds the PAWP measurement without excessively tall a or v waves visible on the trace.[71]

Assuming the PAC resides appropriately in West zone 3, the end-diastolic wedge pressure following atrial contraction is generally the best predictor of left ventricular end-diastolic filling pressure as measured at the Z-point. This is the point at which the slope of the left ventricular pressure upstroke changes, approximately 50 milliseconds after the ECG Q wave, and it generally coincides with the ECG R wave[82] (Fig. 45-35).

However, in many cases, the left ventricular end-diastolic pressure is either underestimated or overestimated by the PAWP and/or PAD. These situations are summarized in Figure 45-36 and Tables 45-5 and 45-6 (also see several excellent references for further discussion of this topic).[71,332,337]

USE OF CENTRAL FILLING PRESSURES TO ESTIMATE LEFT VENTRICULAR PRELOAD

A detailed understanding of the relationship between left ventricular filling pressure and preload is important for clinically meaningful interpretation of PAC-derived data. Even when surrogate pressures such as pulmonary artery diastolic pressure and wedge pressure accurately estimate left ventricular end-diastolic pressure, many factors can influence the relationship between end-diastolic pressure and end-diastolic chamber volume, which is the true preload. For example, a pulmonary artery wedge pressure of 20 mm Hg is somewhat higher than normal, but depending on its interpretation and the clinical setting, different treatments would be indicated. Proper interpretation of filling pressures requires assessment of juxtacardiac pressure and ventricular compliance. When juxtacardiac pressure and ventricular compliance are normal, a wedge pressure of 20 mm Hg is interpreted as hypervolemia, with an increased left ventricular end-diastolic volume causing the increased PAWP. However, different conclusions are reached if juxtacardiac pressure is increased, for example, as a result of cardiac tamponade, pericardial constriction, or positive-pressure ventilation. Furthermore, a wedge pressure of 20 mm Hg may mean that ventricular compliance is decreased, such as might occur with diastolic dysfunction from myocardial ischemia, hypertrophy, or

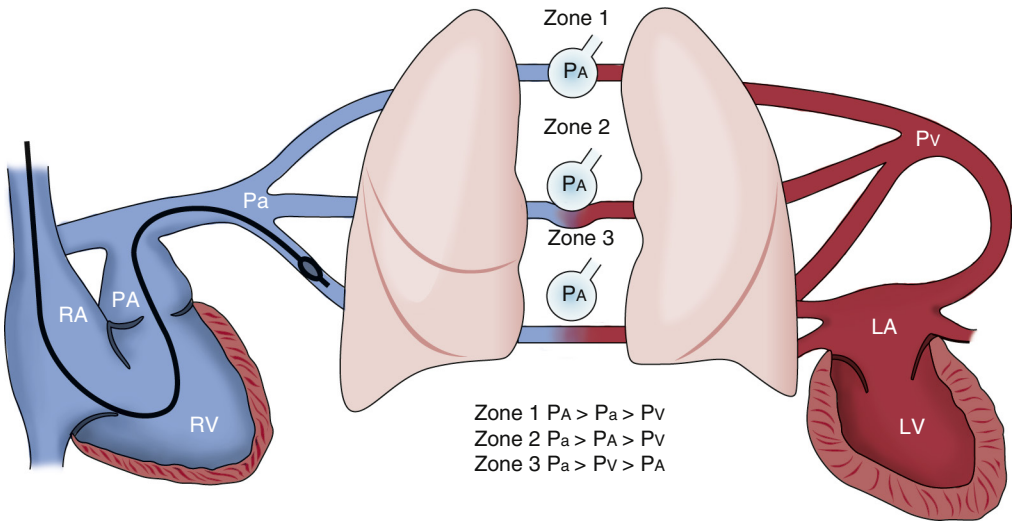


Figure 45-34. The pulmonary artery catheter tip must be wedged in lung zone 3 to provide an accurate measure of pulmonary venous (Pv) or left atrial (LA) pressure. When alveolar pressure (P_A) rises above Pv in lung zone 2, or above pulmonary arterial pressure (Pa) in lung zone 1, wedge pressure will reflect alveolar pressure rather than intravascular pressure. *LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

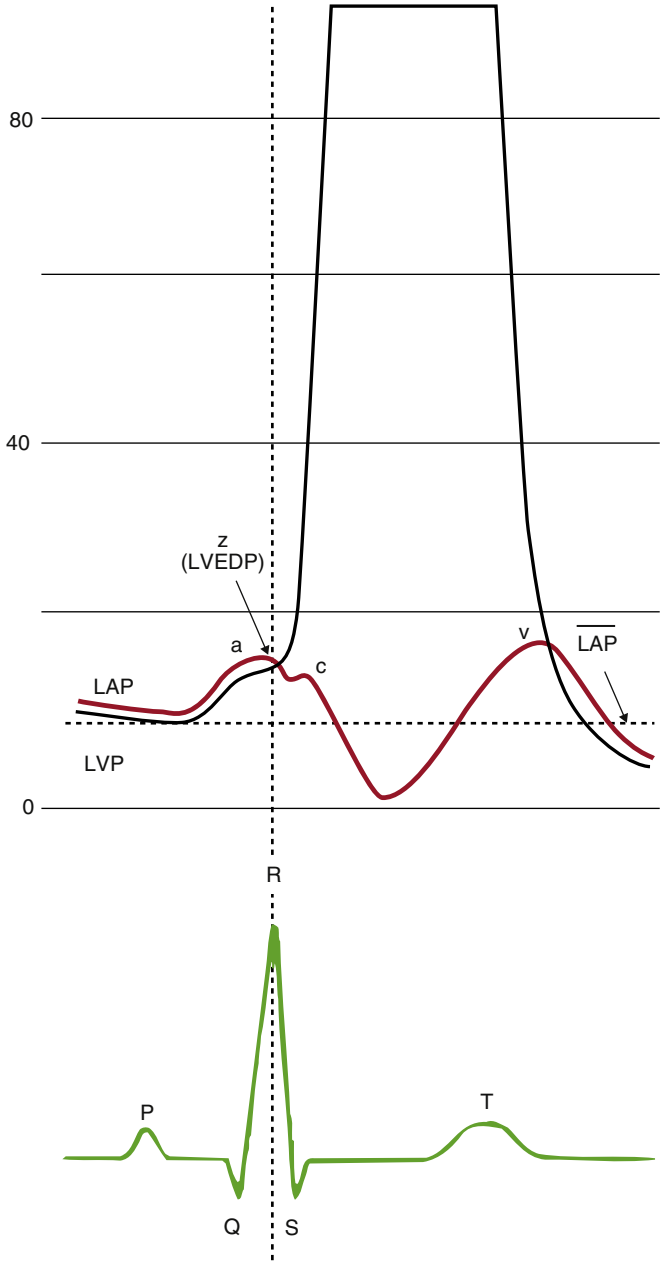


Figure 45-35. Relationship between left atrial pressure (LAP) and left ventricular end-diastolic pressure (LVEDP). LVEDP is measured at the Z-point on the left ventricular pressure (LVP) trace, at the time of the electrocardiographic R wave. Mean LAP (9 mm Hg) underestimates LVEDP (15 mm Hg), but the LAP a wave pressure peak closely estimates LVEDP.[456] *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

cardiomyopathy (Fig. 45-37). Under these two situations, a wedge pressure of 20 mm Hg can coexist with a small, hypovolemic left ventricle.

A fluid challenge may be useful in deciding whether hypovolemia exists. An intravenous bolus of crystalloid or colloid solution (250 to 500 mL) is given over 15 minutes, and the change in wedge pressure is measured. Small increases in wedge pressure following the fluid challenge (e.g., less than 3 mm Hg) suggest that the ventricle is operating on the flat portion of its diastolic filling curve, whereas large increases in wedge pressure (e.g., 7 mm Hg or greater) suggest that the steep portion of the curve has been reached and that little further increase in stroke volume and cardiac output can be achieved without a substantial risk of producing hydrostatic pulmonary edema.[71,330]

The shared septum of the left and right ventricles as well as the presence of the pericardium lead to further interpretive problems in the use of CVP for assessing ventricular preload. Ventricular interdependence and pericardial constraint couple changes in right and left ventricular function, such that a primary change in right ventricular filling may produce a secondary and opposite change in left ventricular filling by altering its diastolic pressure-volume relation.[338,339] For example, acute pulmonary artery hypertension increases right ventricular end-diastolic volume and pressure, shifts the ventricular septum leftward, and increases left ventricular end-diastolic pressure while simultaneously decreasing left ventricular end-diastolic volume, owing to a shift in the left ventricular pressure-volume relation to a steeper, stiffer curve. Conversely, primary changes on the left side can adversely affect the right heart structures in similar ways. Finally, numerous additional factors may alter the relationship between CVP and left ventricular preload[340] (see Fig. 45-37). With all these considerations in mind, both CVP and PAWP do not correlate with blood volume and do not predict the cardiac output response to an intravenous fluid challenge.[227,341]

PULMONARY ARTERY CATHETER–DERIVED HEMODYNAMIC VARIABLES

The cardiovascular system is often modeled as an electrical circuit, with the relationship between cardiac output, blood pressure, and resistance to flow related in a manner similar to Ohm's law:

$$SVR = \frac{MAP - CVP}{CO} \times 80$$

$$PVR = \frac{MPAP - PAWP}{CO} \times 80$$

where SVR = systemic vascular resistance (dyne·sec/cm^5)
PVR = pulmonary vascular resistance (dyne·sec/cm^5)
MAP = mean arterial pressure (mm Hg)
CVP = central venous pressure (mm Hg)
MPAP = mean pulmonary artery pressure (mm Hg)
PAWP = pulmonary artery wedge pressure (mm Hg)
CO = cardiac output (L/min)

Normal values for SVR and PVR are given in Table 45-7. When the numeric constant (80) in the above equations is not included, the units for SVR and PVR are termed Wood units rather than the derived metric unit values. Note that these calculations of systemic and pulmonary vascular resistance are based on a hydraulic fluid model that assumes continuous, laminar flow through a series of rigid pipes.[342] Atrial pressures are used as the downstream pressure for systemic or pulmonary flow, with CVP used for right atrial pressure in the SVR calculation and PAWP used for left atrial pressure in the PVR calculation.

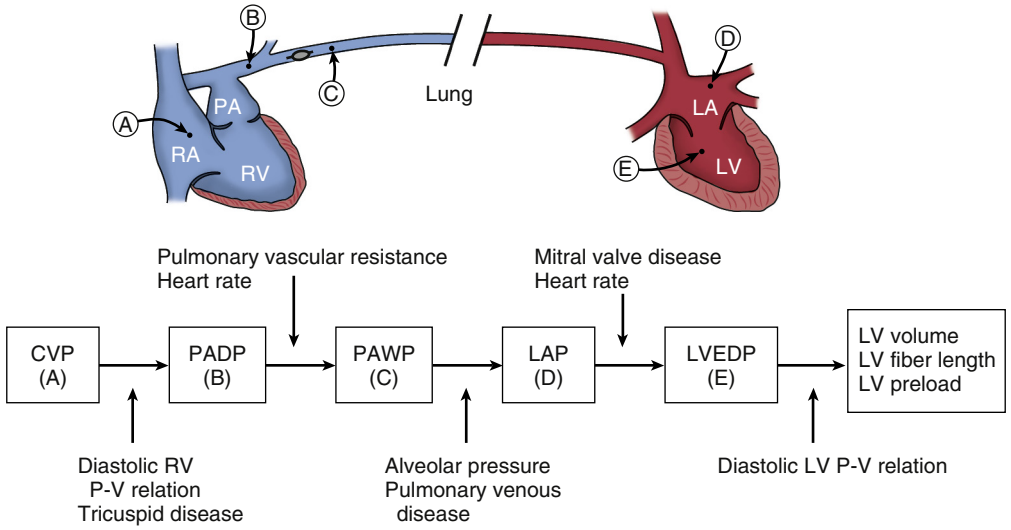


Figure 45-36. Anatomic and physiologic factors that influence the relations between various measures of left ventricular (LV) filling and true LV preload. The further upstream the filling pressure is measured, the more confounding factors may influence the relation between this measurement and LV preload. *CVP*, Central venous pressure; *LA*, left atrium; *LAP*, left atrial pressure; *LVEDP*, left ventricular end-diastolic pressure; *PA*, pulmonary artery; *PADP*, pulmonary artery diastolic pressure; *PAWP*, pulmonary artery wedge pressure; *P-V*, pressure-volume; *RA*, right atrium; *RV*, right ventricle. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

TABLE 45-5 UNDERESTIMATION OF LEFT VENTRICULAR END-DIASTOLIC PRESSURE

Condition	Site of Discrepancy	Cause of Discrepancy
Diastolic dysfunction	Mean LAP <LVEDP	Increased end-diastolic a wave
Aortic regurgitation	LAP a wave <LVEDP	Mitral valve closure before end-diastole
Pulmonic regurgitation	PADP <LVEDP	Bidirectional runoff for pulmonary artery flow
Right bundle branch block	PADP <LVEDP	Delayed pulmonic valve opening
Post-pneumonectomy	PAWP <LAP or LVEDP	Obstruction of pulmonary blood flow

Modified from Mark JB: Predicting left ventricular end-diastolic pressure. In Mark JB, editor: Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone, p 59.*
LAP, Left atrial pressure; *LVEDP*, left ventricular end-diastolic pressure; *PADP*, pulmonary artery diastolic pressure; *PAWP*, pulmonary artery wedge pressure.

TABLE 45-6 OVERESTIMATION OF LEFT VENTRICULAR END-DIASTOLIC PRESSURE

Condition	Site of Discrepancy	Cause of Discrepancy
Positive end-expiratory pressure	Mean PAWP >Mean LAP	Creation of lung zone 1 or 2, or pericardial pressure changes
Pulmonary arterial hypertension	PADP >Mean PAWP	Increased pulmonary vascular resistance
Pulmonary venoocclusive disease	Mean PAWP >Mean LAP	Obstruction to flow in large pulmonary veins
Mitral stenosis	Mean LAP >LVEDP	Obstruction to flow across mitral valve
Mitral regurgitation	Mean LAP >LVEDP	Retrograde systolic v wave raises mean atrial pressure
Ventricular septal defect	Mean LAP >LVEDP	Antegrade systolic v wave raises mean atrial pressure
Tachycardia	PADP >Mean LAP >LVEDP	Short diastole creates pulmonary vascular and mitral valve gradients

Modified from Mark JB: Predicting left ventricular end-diastolic pressure. In Mark JB, editor: Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone, p 59.*
LAP, Left atrial pressure; *LVEDP*, left ventricular end-diastolic pressure; *PADP*, pulmonary artery diastolic pressure; *PAWP*, pulmonary artery wedge pressure.

These formulas oversimplify the behavior of the cardiovascular system to a tremendous degree. A more physiologic model of the systemic circulation considers the vasculature to be a series of collapsible vessels with intrinsic tone. This model, also called the vascular waterfall, describes a critical closing pressure in the downstream end of the circuit that exceeds right atrial pressure and serves to limit flow—an effective downstream pressure that is higher than the right atrial pressure used in the SVR formula. A detailed consideration of these issues is beyond the scope of this discussion and is available in other sources.[343,344] The important point, though, for clinicians is that therapy focused on the fine adjustment of SVR may be very misleading and should be avoided.

Additional problems arise in considering the pulmonary vasculature and using the formulas as a measure of resistance to flow through the lung.[345] The pulmonary vasculature is more compliant than the systemic vasculature, and marked increases in pulmonary blood flow may not produce any significant increase in pulmonary artery

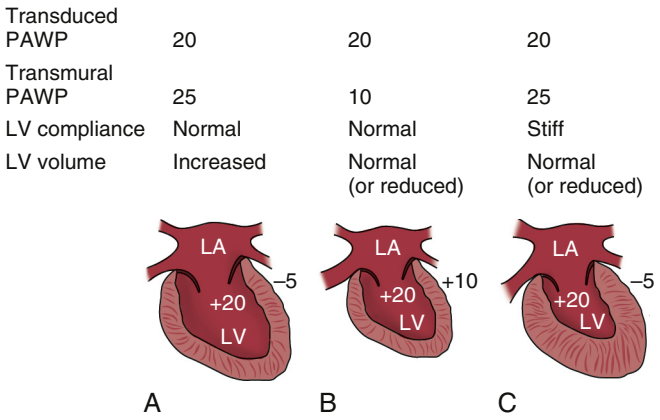


Figure 45-37. Influence of juxtacardiac pressure and ventricular compliance on left ventricular (LV) preload. Three interpretations of an increased transduced pulmonary artery wedge pressure (PAWP, 20 mm Hg) are possible. **A,** Juxtacardiac pressure (–5 mm Hg) and LV compliance are normal, transmural PAWP is increased (25 mm Hg), and LV volume is increased. **B,** Juxtacardiac pressure is increased (+10 mm Hg), LV compliance is normal, transmural PAWP is decreased (10 mm Hg), and LV volume is normal or decreased. **C,** Juxtacardiac pressure is normal, LV compliance is decreased, transmural PAWP is increased (25 mm Hg), and LV volume is normal or decreased. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

TABLE 45-7 NORMAL HEMODYNAMIC VALUES

	Average	Range
Cardiac output (L/min)	5.0	4.0-6.5
Stroke volume (mL)	75	60-90
Systemic vascular resistance (Wood units)	15	10-20
(Dynes-sec-cm^{-5})	1200	800–1600
Pulmonary vascular resistance (Wood units)	1	0.5–3
(Dynes-sec-cm^{-5})	80	40–180
Arterial oxygen content (mL/dL)	18	16-20
Mixed venous oxygen content (mL/dL)	14	13-15
Mixed venous oxygen saturation (%)	75	70-80
Arteriovenous oxygen difference (mL/dL)	4	3-4
Oxygen consumption (mL/min)	225	200-250

pressure. In addition, flow usually ceases at end-diastole in the low resistance pulmonary circuit. Thus, changes in pulmonary vascular resistance may result from intrinsic alterations in pulmonary vascular tone (constriction or dilation), vascular recruitment, or rheologic changes. For the pulmonary circuit, a better approach to evaluating the changes in pulmonary vascular resistance may be to examine the end-diastolic gradient between the pulmonary artery diastolic and wedge pressures (Fig. 45-38).

Another set of common calculations derived from standard hemodynamic variables adjusts these measurements for the patient's body surface area (BSA) in an attempt to normalize these measurements for patients of different sizes. The BSA is generally determined from a standard nomogram based on height and weight. The most

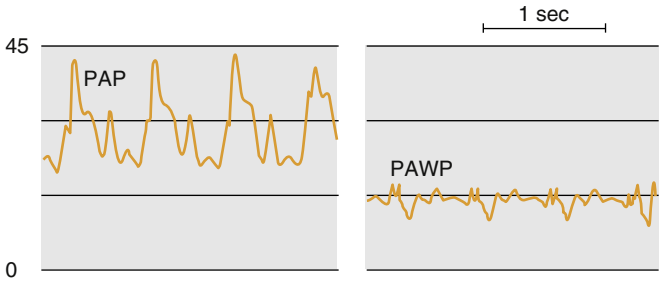


Figure 45-38. Pulmonary hypertension. The increased gradient across the pulmonary vasculature causes pulmonary artery diastolic pressure to exceed pulmonary artery wedge pressure (PAWP). *PAP,* Pulmonary artery pressure. *(From Mark JB:* Atlas of cardiovascular monitoring, *New York, 1998, Churchill Livingstone.)*

commonly indexed variables are the cardiac index (cardiac index = cardiac output/body surface area) and stroke volume index (stroke volume index = stroke volume/body surface area). On occasion, the systemic and pulmonary vascular resistances are indexed as well (systemic vascular resistance index = systemic vascular resistance × body surface area; pulmonary vascular resistance index = pulmonary vascular resistance × body surface area). In theory, normalizing hemodynamic values through "indexing" should help clinicians determine appropriate normal physiologic ranges to help guide therapy. Unfortunately, there is little evidence that these additional calculations provide valid normalizing adjustments. Body surface area is a biometric measurement with an obscure relationship to blood flow, and it does not adjust for variations between individuals based on age, sex, body habitus, or metabolic rate.[346] The patient's size and medical history is important in interpreting and treating changes in any of the measured or calculated hemodynamic variables. Therapy should not be solely directed towards achieving normal indexed values.

PULMONARY ARTERY CATHETERIZATION AND OUTCOME CONTROVERSIES

Pulmonary artery catheterization has stimulated much controversy. It is an expensive, invasive technique that is widely used but still not proven to improve patient outcome. The PAC controversy has been fueled in part by strongly worded editorials, written by prominent physicians, debating whether PAC use should be suspended pending scientific proof of its efficacy.[347-349] Although similar controversies have surrounded the use of other widely adopted, highly technical, clinical monitoring techniques such as electronic fetal monitoring,[350] physicians who use PACs should especially appreciate the uncertainties surrounding PAC monitoring and be fully informed of the evidence that must guide patient selection.[351,352]

The study published by Connors and colleagues in 1996 examining the association between PAC use during the first 24 hours of intensive care and subsequent survival marked a tipping point in the use of PACs for monitoring.[353] This prospective multicenter cohort study included 5735 patients with predicted 6-month

mortality in excess of 50%. Patients who were in the PAC-monitored group were judged to be sicker by every measurement recorded, although to the extent statistically possible, authors used case-matching analyses and applied a propensity score to adjust for these confounding medical covariates. After all adjustments, PAC-monitored patients had increased lengths of hospital stay and 20% increased mortality, and they incurred increased costs. Moreover, no subgroup of patients appeared to benefit from PAC monitoring. The publication of this study was accompanied by a strongly worded editorial calling for a moratorium on PAC use or a randomized controlled trial to define its efficacy.[347]

In the years since the study by Connors and colleagues, numerous studies have tried to determine whether patients are being helped or harmed by use of PACs. Many of these studies have been plagued by problems in study design (lack of randomization, small sample size), lack of standardization, and heterogeneity of both patients and clinical settings (medical versus surgical, cardiac surgery patients versus patients in acute congestive heart failure). In addition, little consensus exists regarding which hemodynamic variables are the most relevant to be obtained from catheter use. Furthermore, appropriate therapeutic interventions in response to specific findings are not clear.[283] Several large, randomized, adequately powered studies have been published regarding the use of the PAC in various settings: general noncardiac surgery,[233] vascular surgery,[354] CABG surgery,[338] nonsurgical patients with congestive heart failure,[355] patients with acute lung injury,[356] and critically ill patients in the intensive care unit.[357] Generally, these studies have shown no benefit to PAC use, but they also show no increase in mortality or in hospital or intensive care unit length of stay despite sometimes a more frequent incidence of adverse events, mainly infections or insertion-related events.

One common drawback to most of these large randomized studies is that they have necessarily examined the routine use of PAC and enrolled a sequential cohort of patients, most of them with a relatively moderate risk of death or complications. Also, not all of these studies have used a specific therapeutic intervention protocol.[358]

In especially high-risk patients, a clinical benefit from use of the PAC became evident. A review of 53,312 patients from the National Trauma Data Bank showed no mortality benefit to those treated with PACs in the group as a whole. However, in those with an injury severity scale greater than 25, those that arrived to the hospital in severe shock, or those older than 60 years of age, mortality was decreased significantly if PAC was used.[359] In another cohort study of 7300 mixed medical and surgical population, PAC use was associated with reduced mortality in patients with a high APACHE score (>31), but increased mortality in patients with a low APACHE score (<25).[360] Last, in a cohort of 280 older patients undergoing colon surgery, preoperative optimization with the use of PAC reduced mortality threefold in patients with a high Goldman's cardiac risk index but was not beneficial in those at a low cardiac risk (also see Chapter 80).[361]

PULMONARY ARTERY CATHETERIZATION: INDICATIONS

The most recent recommendation pertaining to the perioperative use of PACs is the American Society of Anesthesiologists practice guideline published in 2003.[231] The task force considered PAC monitoring to be appropriate in high-risk surgical patients undergoing high-risk procedures. Furthermore, the specific practice setting and the proficiency and experience of clinicians should be considered.

PAC use must be tailored to the degree of risk for the patient and the risk posed by the procedure itself. For example, a patient with advanced ischemic cardiomyopathy who needs lower extremity amputation under regional anesthesia would not warrant PAC monitoring whereas a patient with stable ischemic heart disease scheduled for extensive abdominal cancer resection may benefit from perioperative use. Furthermore, the individual practice setting must be considered.[231] Keats has termed this feature "the role of environment in the outcome of operation," by which he means important unmeasurable aspects of the clinical setting, including, but not limited to, technical skill and experience.[362] Clearly, all physicians and nurses using PAC must have the requisite knowledge and skills to use it safely and effectively.

The conclusion is that PAC use should be limited, although a moratorium on use is ill-advised. Indeed, data demonstrate a significant and continuing decrease in PAC usage.[316] Use should be reserved to centers with significant experience and expertise. PAC generally should be used to monitor and guide therapy in patients at high risk for hemodynamic instability, those who are judged more critically ill by a variety of clinical means, and those who are in shock, especially if they are older and suffer from other systemic diseases.

Much uncertainty and controversy continue to surround PAC use. Among the many measurements and calculations possible from PAC, little consensus exists regarding the most meaningful or the most useful. Obviously, PAC itself has no capacity to benefit unless it guides therapies that improve patient outcomes. Future research should focus on defining subgroups of patients who might benefit from the use of PAC, as well as defining effective therapeutic interventions based on the hemodynamic information gained from PAC.[351,358]

SPECIAL TYPES OF PULMONARY ARTERY CATHETERS

The popularity of PACs is largely due to the fact that they are multipurpose and provide a wide range of supplementary features for therapeutic and diagnostic applications. Some catheters have a third lumen, which is often used as an additional venous infusion line that opens 20 to 30 cm from the catheter tip. Specialized PACs allow temporary endocardial pacing or intracardiac ECG recording and may even have combinations of electrodes permanently implanted along its length to allow bipolar ventricular, atrial, or atrioventricular pacing.[363] These catheters can be especially useful for minimally invasive cardiac

surgery, where avoiding sternotomy hinders the placement of epicardial pacing leads.[364] Other models have a special lumen that opens into the right ventricle, through which a thin bipolar wire may be introduced for endocardial ventricular pacing, or separate atrial and ventricular lumina for passage of two pacing wires for dual-chamber sequential pacing.[365]

Specific PAC modifications were designed to allow for continuous cardiac output measurement, mixed venous oxygen saturation monitoring, or right heart function evaluation, vastly expanding the types of physiologic information available to those caring for critically ill patients.

Mixed Venous Oximetry Pulmonary Artery Catheter

Although the formal Fick cardiac output method is not widely applied in clinical practice outside the cardiac catheterization laboratory, the physiologic relations described by the Fick equation form the basis for another PAC-based monitoring technique termed *continuous mixed venous oximetry*. Rearrangement of the Fick equation reveals the four determinants of mixed venous hemoglobin saturation ($S\dot{v}O_2$):

$$S\bar{v}O_2 = SaO_2 - \frac{\dot{V}O_2}{\dot{Q} \times 1.36 \times Hgb}$$

where $S\bar{v}O_2$ = mixed venous hemoglobin saturation (%)
SaO_2 = arterial hemoglobin saturation (%)
$\dot{V}O_2$ = oxygen consumption (mL O_2/min)
$\dot{Q}$ = cardiac output (L/min)
Hgb = hemoglobin concentration (g/dL)

To the extent that arterial hemoglobin saturation, oxygen consumption, and hemoglobin concentration remain stable, mixed venous hemoglobin saturation may be used as an indirect indicator of cardiac output. For example, when cardiac output falls, tissue oxygen extraction increases and the mixed venous blood will have a lower oxygen content and lower hemoglobin oxygen saturation. However, as noted in this equation, mixed venous hemoglobin saturation also varies directly with arterial hemoglobin concentration and saturation, and varies inversely with oxygen consumption. When any of these other variables change significantly, one cannot assume that a change in mixed venous hemoglobin saturation results solely from a change in cardiac output. Although these considerations may confound the use of mixed venous hemoglobin saturation as an indicator of cardiac output, monitoring this variable provides more comprehensive information about the balance of oxygen delivery and consumption by the body—not just the cardiac output value, but also the adequacy of that cardiac output compared with tissue oxygen requirements.[366]

Although mixed venous hemoglobin saturation may be determined by intermittent blood sampling from the distal port of PAC, a specially designed PAC can provide this information reliably and continuously. Fiberoptic bundles incorporated into PAC determine the hemoglobin oxygen saturation in pulmonary artery blood based on the principles of reflectance oximetry using either a two- or three-wavelength system. A special computer connected to this PAC displays the mixed venous hemoglobin saturation continuously. The technology is typically incorporated into the standard PAC or the continuous cardiac output PAC (see later), in the latter case providing both continuous cardiac output and venous oximetry data.

Technical problems with continuous mixed venous oximetry are generally limited to improper PAC tip positioning against the vessel wall or inaccurate calibration.[367] Multi-wavelength fiberoptic technology and reflection intensity algorithms help to reduce wall artifacts caused by spurious reflections from a PAC thrombus or the pulmonary arterial walls. These catheters are calibrated at the bedside before use but may also be calibrated in vivo from a pulmonary artery blood gas sample. Recalibration every 24 hours is usually recommended because of a drift artifact. One note of caution is that a wedged PAC will read spuriously high oxygen saturation values corresponding to arterialized pulmonary blood. Most clinical trials comparing PAC-derived continuous venous oximetry values with laboratory analysis of pulmonary artery blood samples have shown good agreement between techniques.[368] Mixed venous hemoglobin saturation values reflect global, whole-body measurement. Therefore, regionally inadequate blood flow and tissue oxygen delivery (such as with limb or intestinal ischemia) can coexist with a normal or high mixed venous hemoglobin saturation.

Recently, the technology to continuously measure oxygen saturation has been incorporated into central venous catheters as well. These catheters measure central venous saturation, measured in the superior vena cava. Normally, this saturation is around 70% versus 75% in the pulmonary artery.[366] Low central venous saturation has been associated with increased complications both in trauma patients and in major surgery patients.[369,370]

The real value of measuring venous oxygen saturation lies in its ability to guide therapeutic interventions. Because one of the body's physiologic compensations for anemia is increased oxygen extraction, low venous hemoglobin saturation has been used to guide the need for blood transfusion.[371] Several studies have used venous hemoglobin saturation to guide interventions aimed at increasing cardiac output, a goal-directed approach. A recent randomized study in patients undergoing cardiac surgery has shown better outcome in patients randomized to protocol-driven interventions aimed at achieving mixed venous hemoglobin saturation above 70% (and blood lactate <2 mg/dL).[372] Similarly, optimizing the central venous oxygen saturation has been shown to improve outcome in patients with early sepsis[373] and in high-risk noncardiac and off-pump cardiac surgical patients.[374,375]

These studies have used strict protocol-driven therapeutic interventions. In contrast, a large Veterans Affairs observational trial of 3265 cardiac surgical patients noted that 49% of patients received continuous mixed venous oximetry PACs, and use of this catheter was associated with increased cost but no better outcome than the standard PAC group.[376] In this study, however, no protocol was used to guide therapeutic interventions based on monitoring results.

Right Ventricular Ejection Fraction Pulmonary Artery Catheter

Although cardiovascular monitoring has focused predominantly on left ventricular performance, in some instances right ventricular dysfunction may be the more important factor limiting circulation. Patient populations at increased risk for right ventricular dysfunction include those with chronic obstructive pulmonary disease, adult respiratory distress syndrome, pulmonary hypertension, and right ventricular ischemia and infarction.[377] Pulmonary artery catheter monitoring in patients with right ventricular infarction often reveals the characteristic hemodynamic patterns described earlier. However, accurate evaluation of right ventricular performance has proved more complicated. In patients with severe respiratory failure, for example, the confounding effects of mechanical ventilation with high levels of positive end-expiratory pressure (PEEP) have made interpretation of cardiac filling pressures difficult and, in some cases, misleading.[378]

Measurement of right ventricular ejection fraction (RVEF) with a specially designed PAC offers another method for evaluating right ventricular function. This method uses a standard PAC equipped with a rapid response thermistor that detects and quantifies the small changes in pulmonary artery blood temperature that occur with each heartbeat, in a manner somewhat analogous to a standard continuous cardiac output PAC. The cardiac output computer measures the residual fraction of thermal signal following each heart beat and derives the RVEF.[379] Clearly, all factors that confound standard thermodilution cardiac output measurement (described later) will also interfere with accurate determination of RVEF. In addition, because the temperature changes measured by the RVEF PAC are small beat-to-beat changes, the method will not work if the ECG R waves cannot be detected accurately, when the R-R interval is short owing to tachycardia, or if the cardiac rhythm is irregular.[367] Comparison of PAC-based RVEF measurements with angiographic or nuclear techniques has yielded mixed results in terms of accuracy, but this may reflect, in part, the absence of a widely accepted reference standard for this measurement.[379,380] Intraoperative use of the RVEF PAC has focused primarily on detection of right ventricular dysfunction in patients with coronary artery disease undergoing surgical revascularization. Reduced RVEF has been noted following cardiopulmonary bypass, particularly in patients with preexisting right coronary artery obstruction.[381] However, RVEF is an extremely load-dependent measurement of right ventricular performance, and the clinician must keep this fact in mind to interpret this measurement properly.[367,382] Clinical use of the RVEF PAC appears to have found its greatest application to date in critically ill patients, especially in those with respiratory failure.[382,383] In these applications, the measurement of greatest interest has been the right ventricular end-diastolic volume, which is derived mathematically from RVEF:

$$\text{RVEDV} = \frac{\text{SV}}{\text{RVEF}}$$

where RVEDV = right ventricular end-diastolic volume (mL)

SV = stroke volume (mL)

RVEF = right ventricular ejection fraction

The right ventricular end-diastolic volume appears to correlate better with volume status than standard preload measurements, such as CVP or PAWP.[383,384] These findings are not surprising given all the interpretive problems associated with cardiac filling pressure monitoring previously discussed. It should be kept in mind, however, that the better correlation between right ventricular end-diastolic volume and cardiac output may result from the mathematical coupling of measurements, because both are derivatives of stroke volume determined with PAC. Furthermore, as in the case of standard PAC monitoring, the benefit of RVEF PAC monitoring, in terms of patient outcomes, remains unproven.[231]

CARDIAC OUTPUT MONITORING

Cardiac output is the total blood flow generated by the heart, and in a normal adult at rest, it ranges from 4.0 to 6.5 L/min. Measurement of cardiac output provides a global assessment of the circulation, and in combination with other hemodynamic measurements (heart rate, arterial blood pressure, CVP, pulmonary artery pressure, and wedge pressure), it allows calculation of additional important circulatory variables, such as systemic and pulmonary vascular resistance and ventricular stroke work (see Table 45-7).

Three factors have driven efforts to measure cardiac output in clinical practice. The first is the recognition that in many critically ill patients, low cardiac output leads to significant morbidity and mortality.[385] Second, clinical assessment of cardiac output is often inaccurate; for example, seriously ill patients with decreased cardiac output might have normal systemic arterial blood pressures.[386] Finally, newer techniques for cardiac output measurement are becoming less invasive and thus might provide benefit to many patients without the attendant risks of invasive monitoring.[386,387] The advantages and disadvantages of each technique must be appreciated for proper clinical application.

THERMODILUTION CARDIAC OUTPUT MONITORING

The thermodilution technique has become the de facto clinical standard for measuring cardiac output because of its ease of implementation and the long clinical experience with its use in various settings. It is a variant of the indicator dilution method, described in more detail in Chapter 44, in which a known amount of a tracer substance is injected into the bloodstream and its concentration change is measured over time at a downstream site.[388] For thermodilution, a known volume of iced or room-temperature fluid is injected as a bolus into the proximal (right atrium) lumen of the PAC, and the resulting change in the pulmonary artery blood temperature is recorded by the thermistor at the catheter tip. As in all other forms of cardiovascular monitoring, it is important

to have a real-time display of the thermodilution curve resulting from each cardiac output measurement.[389] This allows the clinician to discern artifacts that would invalidate the cardiac output measurement, such as unstable blood temperature, recirculation, or incomplete indicator injection.

Because several groups have demonstrated equivalent accuracy in cardiac output determinations when either ice-cold or room-temperature injectates are used, it appears that room-temperature injectate is preferred for almost all clinical applications.[390] In adults, an injectate volume of 10 mL should be used, whereas in children, an injectate volume of 0.15 mL/kg is recommended.[389]

Usually, three cardiac output measurements performed in rapid succession are averaged to provide a more reliable result. When only a single injection was used to determine cardiac output, a difference between sequential cardiac output measurements of 22% was required to suggest a clinically significant change. In contrast, when three injections are averaged to determine the thermodilution measurement, a change greater than 13% indicates a clinically significant change in cardiac output.[391]

Even when carefully performed, some studies have found that thermodilution cardiac output measurements may not agree with other reference methods.[392,393] However, few complications are directly attributable to the technique itself, and following the trend in cardiac output is probably more clinically useful than emphasizing any absolute value.

Sources of Error in Thermodilution Cardiac Output Monitoring

Several important technical issues and potential sources of error must be considered to interpret thermodilution cardiac output measurements properly[388,389] (Box 45-7). The thermodilution technique measures right ventricular output. With intracardiac shunt, right ventricular and left ventricular outputs will not be equal. In patients with a left-to-right shunt, early recirculation of the thermal indicator can be seen to distort the downward slope of the thermodilution curve, and in patients with right-to-left shunt, some of the injected indicator will bypass the thermistor, resulting in overestimation of the left ventricular cardiac output.

Patients with tricuspid or pulmonic valve regurgitation pose additional problems for thermodilution cardiac output measurement owing to recirculation of the indicator across the incompetent valve. In patients with severe tricuspid regurgitation, the thermodilution curves have an abnormally prolonged decay time and the measured cardiac output is simply unreliable, either underestimated or overestimated, depending on the severity of valvular regurgitation and the magnitude of the cardiac output.[389,394]

Other technical problems with thermodilution cardiac output measurement are caused by inadequate delivery of the thermal indicator. Mishandling of an iced injectate syringe can warm the solution and reduce the signal-to-noise ratio of the thermal indicator administered. In addition, fibrin or blood clot on the PAC tip may lead to thermistor malfunction and result in spurious cardiac output values. Unrecognized fluctuation in blood temperature may also influence cardiac output measurement. In most patients, pulmonary artery blood temperature falls rapidly in the initial minutes following cardiopulmonary bypass when the rewarmed body core redistributes the heat gained at the end of bypass. Owing to this progressive decline in central core and pulmonary artery blood temperature, the thermal baseline is unstable. Thermodilution cardiac output measurements made in the minutes following bypass are notoriously unreliable, most often leading to marked underestimation of the true cardiac output.[395] Other inaccuracies in thermodilution cardiac output measurement occur when pulmonary artery blood temperature changes because of rapid fluid infusion.[396] Either overestimation or underestimation of cardiac output occurs, depending on the timing of the additional fluid bolus.

One controversy surrounding bolus thermodilution cardiac output monitoring is the proper timing of measurement in relation to the respiratory cycle, particularly in patients receiving positive-pressure mechanical ventilation, because right ventricular stroke output varies as much as 50% during the respiratory cycle. Although reproducibility of consecutive measurements improves markedly when the bolus injections are synchronized to the same phase of the respiratory cycle, an accurate measurement of average cardiac output is achieved more reliably by making multiple injections during the different phases of the respiratory cycle and then averaging the results.[389,397] Last, the measured thermodilution cardiac output can overestimate true cardiac output during low-flow states because of significant heat loss from slow injectate transit.[398]

BOX 45-7 *Factors Influencing Accuracy of Thermodilution Cardiac Output Measurement*

- Intracardiac shunts
- Tricuspid or pulmonic valve regurgitation
- Inadequate delivery of thermal indicator
  - Central venous injection site within catheter introducer sheath
  - Warming of iced injectate
- Thermistor malfunction from fibrin or clot
- Pulmonary artery blood temperature fluctuations
  - Following cardiopulmonary bypass
  - Rapid intravenous fluid administration
- Respiratory cycle influences

CONTINUOUS THERMODILUTION CARDIAC OUTPUT MONITORING

Newer technologies applied to PAC monitoring allow nearly continuous cardiac output (CCO) monitoring using a warm thermal indicator.[388,399] In brief, small quantities of heat are released from a 10-cm thermal filament incorporated into the right ventricular portion of a PAC, approximately 15 to 25 cm from the catheter tip, and the resulting thermal signal is measured by the thermistor at the tip of the catheter in the pulmonary artery. The heating filament is cycled on and off in a pseudorandom binary sequence, and the cardiac output is derived from cross correlation of the measured pulmonary artery temperature with the known sequence of heating filament activation.[399] Typically, the displayed value for cardiac

output is updated every 30 to 60 seconds and represents the average value for the cardiac output measured over the previous 3 to 6 minutes. In a laboratory investigation examining how CCO measurements responded to unstable hemodynamic conditions, such as hemorrhage and fluid resuscitation, Siegel and associates showed that CCO changes were markedly slower than changes detected by ultrasonic flow probe, blood pressure, or mixed venous oxygen saturation.[400] In view of these inherent time delays, the PAC CCO method should be considered a continual rather than a continuous real-time monitor.

In general, the CCO method has good agreement with standard bolus thermodilution cardiac output measurements or electromagnetic flow probe techniques.[388,401] The device performed well in patients with a wide range of cardiac outputs (1.6 to 10.6 L/min) and core temperatures (33.2° C to 39.8° C). Reproducibility and precision appear to be better with the CCO method compared with the standard bolus thermodilution technique, probably because the continuous method displays a time-weighted average cardiac output value, as opposed to a single instantaneous measurement.[402,403]

The CCO PAC has been widely accepted into clinical use for a number of practical reasons. Although these catheters are more expensive than standard PACs, obviating the need for bolus injections reduces nursing workload and the potential risk of fluid overload or infection. Furthermore, because the CCO PAC provides a cardiac output value that is an average derived over the previous several minutes, beat-to-beat variations in stroke volume that occur during a single respiratory cycle are all equally represented. As a result, a cardiac output measured by the CCO method may provide a more accurate measurement of global cardiac output for patients receiving positive-pressure mechanical ventilation.

However, like cold bolus thermodilution techniques, warm thermal CCO has certain methodologic pitfalls that must be recognized and avoided. The CCO computer and catheter require a significant amount of time to warm up and may work poorly in an environment with a great deal of thermal noise, such as the cardiac operating room. As already emphasized, CCO monitors have an inherent 5- to 15-minute delay in responding to abrupt changes in cardiac output, and the magnitude of this delay depends on the type of physiologic perturbation, as well as the CCO computer monitor algorithm.[400] Although modifications of CCO algorithms provide a "STAT mode" rapid response time, acute changes in cardiac output are still detected more slowly by CCO monitoring than by other methods, such as direct arterial pressure or mixed venous oximetry. In effect, the CCO technique involves a fundamental tradeoff between rapid response time and overall accuracy of measurement. The standards for these performance characteristics have not been defined, but must balance the response time against the stability of the displayed value and its immunity from thermal noise.[402]

TRANSPULMONARY THERMODILUTION CARDIAC OUTPUT

For transpulmonary thermodilution measurement, ice-cold saline is injected into a central venous line while the change in temperature is measured in a large peripheral artery (femoral, axillary, or brachial artery) via a special arterial catheter equipped with a thermistor.[404] Several studies have shown adequate agreement with standard thermodilution cardiac output.[405,406] Because the measurement lasts over several cardiac cycles, respiratory effects on stroke volume are averaged and eliminated, in contrast to standard thermodilution.[407]

Mathematic derivation from the transpulmonary thermodilution curve can produce several additional useful indices. Extravascular lung water is a measure of pulmonary edema and can be used to guide fluid therapy in patients with acute lung injury or sepsis.[408-410] Other derived indices are the global end-diastolic volume and intrathoracic blood volume. These indices are a better measure of cardiac preload than traditional measurements such as CVP or pulmonary artery wedge pressure.[411,412] However, these indices still cannot predict cardiac output response to intravenous fluid administration.[413] The last parameter derived from the transpulmonary thermodilution curve is called the cardiac function index, calculated using cardiac output and the intrathoracic blood volume. It correlates closely with echocardiography-derived left ventricular ejection fraction.[414]

LITHIUM DILUTION CARDIAC OUTPUT MONITORING

The lithium dilution technique is another cardiac output monitoring method that derives its fundamental basis from indicator dilution principles.[415] In brief, following an intravenous bolus injection of a small dose of lithium chloride, an ion-selective electrode attached to a peripheral arterial catheter measures the lithium dilution curve, from which the cardiac output is derived. This is an accurate technique compared with standard thermodilution or electromagnetic flowmetry.[416,417] The lithium indicator can be injected through a peripheral intravenous catheter with similar measurement accuracy, thus eliminating the need for a central venous line.[418] This technique can also be used in children.[419] Lithium dilution cannot be used in patients who are taking lithium or those who have just received nondepolarizing neuromuscular blockers (because these blockers also alter the lithium sensor electrode measurement).

OTHER METHODS FOR MONITORING CARDIAC OUTPUT AND PERFUSION

ESOPHAGEAL DOPPLER CARDIAC OUTPUT MONITORING

All of the ultrasound-based methods for cardiac output monitoring employ the Doppler principle (also see Chapters 44 and 46). Cardiac output can be intermittently measured by the Doppler technique during transthoracic or transesophageal echocardiography examinations (see Chapter 46). A special esophageal Doppler probe has been developed that could be positioned and left in place for continuous monitoring without the need for time-consuming measurements and calculations by the

physician or ultrasonographer. The transducer is incorporated into the tip of a probe resembling a standard esophageal stethoscope and allows continuous monitoring of cardiac output by measuring the Doppler shift of the interrogated blood flow in the descending thoracic aorta. The Doppler probe is inserted into the esophagus to a depth of approximately 35 cm from the incisor teeth and is adjusted to optimize the audible Doppler flow sound from the descending aorta. In most patients, optimal probe tip position is at the T5-T6 vertebral interspace or the third sternocostal junction, because the esophagus and the descending aorta lie in close proximity and run essentially parallel to each other at this location.[420] The ultrasound transducer is mounted at a fixed angle that is anatomically defined and known by the cardiac output computer. This angle is then used to correct the resulting Doppler shift frequency to provide an accurate velocity measurement.

Several limitations of the esophageal Doppler technique must be recognized to avoid incorrect data interpretation. This monitoring method interrogates blood flow in the descending thoracic aorta and therefore measures only a fraction of total cardiac output. To report total cardiac output, either the esophageal Doppler measurement must be "calibrated" by some alternative method, or an empirically determined correction constant of 1.4 is used.[421] This constant is accurate for most patients but does not apply universally, especially in the presence of conditions that redistribute blood flow (such as pregnancy), in aortic cross-clamping, and following cardiopulmonary bypass.[420,422] In addition, the descending thoracic aorta diameter is either measured using A-mode ultrasound or calculated from a nomogram based on the patient's age, sex, height, and weight.[423] When calculated, the aortic diameter is assumed not to change throughout the cardiac cycle.[424] In addition, the technique is likely to be inaccurate in the presence of aortic valve stenosis or regurgitation and in patients with thoracic aortic disease. It is not easily applied in nonintubated, nonsedated patients, and it cannot be used in individuals with esophageal pathology. Finally, like all ultrasound techniques, the acoustic window needed to acquire the Doppler signal may not be adequate in some individuals, thereby precluding use of this method.

Advantages of the esophageal Doppler monitoring technique include its ease of use, minimal invasiveness, and inherent safety. It appears that limited experience is needed for clinical success—as few as 10 to 12 cases for accurate application of the technique.[420] A recent review described 25 clinical trials comparing esophageal Doppler cardiac output measurement with PAC thermodilution measurements and noted that the Doppler cardiac output values correlated well with thermodilution measurements, showed minimal overall bias, and resulted in good tracking of directional changes in thermodilution cardiac output with low intra- and interobserver measurement variability.[420]

Recently, the esophageal Doppler method has seen renewed popularity.[425,426] Current devices provide a clear visual display of the spectral Doppler waveform and also calculate and display additional hemodynamic variables, including the peak blood flow velocity, flow acceleration,

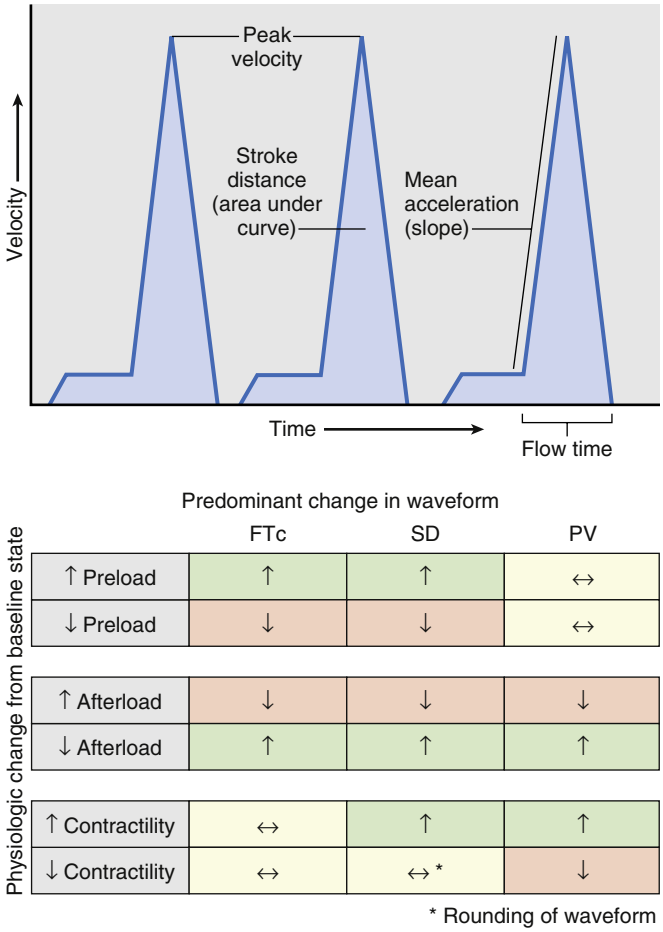


Figure 45-39. The velocity-time waveform displayed by esophageal Doppler cardiac output monitoring devices reflects alterations in contractility, preload, and afterload. Stroke distance (SD) is directly related to calculated stroke volume and provides a useful surrogate measure of cardiac output. *FTc*, Systolic flow time corrected for heart rate; *PV*, peak velocity.

and heart rate–corrected flow time (Fig. 45-39). Some studies have shown that these additional measures provide useful information about left ventricular preload, fluid responsiveness, contractility, and systemic vascular resistance.[421,427,428] One of the more important benefits of this monitor may be focusing clinical attention on optimizing stroke volume rather than total cardiac output. Indeed, in critically ill patients, complications may be better predicted by low stroke volume than by low cardiac output.[429] Several studies have shown that volume resuscitation, guided by maximizing esophageal Doppler-measured stroke volume in moderate risk surgical patients, reduces perioperative morbidity and shortens hospital stay.[425,426]

BIOIMPEDANCE CARDIAC OUTPUT MONITORING

The technique of bioimpedance cardiac output monitoring was first described by Kubicek and associates and is based on changes in electrical impedance of the thoracic cavity occurring with ejection of blood during cardiac

systole.[430] Their original formula relates these bioimpedance measurements to stroke volume:

$$SV = \rho L^2/Zo^2 \bullet VET \bullet \max\frac{dZ}{dt}$$

where SV = stroke volume
ϱ = specific resistivity of blood
L = thoracic length
Z_O = basal thoracic impedance
VET = ventricular ejection time

$\max\frac{dZ}{dt}$ = maximum rate of impedance change during systolic upstroke

For performing the measurements, disposable electrodes are applied to the skin surface along the sides of the neck and lateral aspect of the lower thorax, and a continuous small electrical current is applied across the chest. Patient height, weight, and gender are used to calculate the volume of the thoracic cavity. Bioimpedance cardiac output is computed for each cardiac cycle and continuously displayed as an average value over several heart beats.

Although the bioimpedance method is accurate in healthy volunteers, its reliability deteriorates in critically ill patients, including those with sepsis, pulmonary edema, aortic regurgitation, and cardiac pacing[431-433] (also see Chapters 47, 67, and 101). More recent changes in signal processing techniques have improved the accuracy of thoracic bioimpedance measurements and might increase its clinical acceptance.[434]

PARTIAL CO_2 REBREATHING CARDIAC OUTPUT MONITORING

Another method for cardiac output monitoring that does not require pulmonary artery catheterization is the partial CO_2 rebreathing technique.[435,436] Owing to the difficulty encountered in the standard Fick method involving measuring oxygen consumption and mixed venous hemoglobin saturation, this alternative technique is based on a restatement of the Fick equation for carbon dioxide elimination rather than oxygen uptake.

$$\dot{Q} = \dot{V}co_2/(C\bar{v}co_2 - Caco_2)$$

where $\dot{Q}$ = cardiac output
$\dot{V}co_2$ = rate of carbon dioxide elimination
$C\bar{v}co_2$ = carbon dioxide content of mixed venous blood
$Caco_2$ = carbon dioxide content of arterial blood

This method uses the change in CO_2 production and end-tidal CO_2 concentration in response to a brief, sudden change in minute ventilation. With a specially designed breathing system and monitoring computer, this measurement is easily performed in any tracheally intubated patient. Every 3 minutes, a computer-controlled pneumatic valve intermittently increases dead space for a 50-second period, thereby causing partial rebreathing of exhaled gases. Changes in end-tidal CO_2 in response to the rebreathing maneuver are used to calculate cardiac output by a differential version of the Fick equation for carbon dioxide. This method is entirely noninvasive, it can be performed every few minutes, and the brief episodes of rebreathing pose no substantial risk to most patients, with end-tidal CO_2 measurements increasing by less than 3 mm Hg. Unfortunately, accurate measurements with this technique require tracheal intubation for precise measurement of exhaled gases. Furthermore, changing patterns of ventilation may have an unpredictable influence on the measurement. As with all Fick-based techniques, the partial CO_2 rebreathing method measures pulmonary capillary blood flow as an indicator of total cardiac output and thus requires correction for pulmonary shunt.

There is good agreement between the partial rebreathing CO_2 cardiac output method and other techniques, such as thermodilution. However, the clinical trials were small (i.e., number of patients studied) and mainly focused on specific patient groups, particularly coronary artery bypass surgery patients.[437] The clinical role for this technique is mainly focused on short-term intraoperative applications or mechanically ventilated postoperative patients. Because of the mandatory increase in $Paco_2$, the technique is relatively contraindicated in patients with increased intracranial pressure.

PULSE CONTOUR CARDIAC OUTPUT MONITORING

Analysis of the arterial pulse pressure waveform is one of the most recent developments in the area of cardiac output monitoring. Basically continuous measurement of cardiac output is derived from the analysis of the arterial pulse pressure waveform. These methods, generally termed pulse contour cardiac output, determine stroke volume from computerized analysis of the area under the arterial pressure waveform recorded from an arterial catheter or even a noninvasive finger blood pressure waveform.[438-441] Pulse contour methods offer the potential for noninvasive, continuous, beat-to-beat cardiac output monitoring. Also, the change in stroke volume from beat to beat (termed *stroke volume variation*) can be used to evaluate volume status in ventilated patients.[118,442]

However, several shortcomings need to be considered.[443] First, a baseline calibration with a known cardiac output is required to account for individual differences in vascular resistance, impedance, and wave reflectance. Additionally, recalibration is required every 8 to 12 hours to account for changes in vascular characteristics over time. This need for external calibration might require the use of a more invasive technique, negating the noninvasiveness advantage of pulse contour methods. Recently, several systems were developed with the capability for an autocalibration based on patient's demographic variables. However, the accuracy of this autocalibration in various clinical situations is questionable.[444] A reasonably well-defined arterial pressure waveform with a discernible dicrotic notch is required for accurate identification of systole and diastole, a condition that might not exist under severe tachycardia or dysrhythmia, or other very low output states. Last, for a meaningful use of beat-to-beat variation in stroke volume (as well as systolic pressure or pulse pressure variation), the patient needs to be

on controlled mechanical ventilation with a tidal volume of at least 8 mL/kg body weight.[445]

Still, clinical trials in surgical patients have shown that the pulse contour cardiac output methods provide an acceptable level of accuracy with a bias of less than 0.5 L/minute compared with thermodilution cardiac output.[440,446,447] Stroke volume variation above 10% is a useful predictor of responsiveness to intravenous fluid administration.[106] Finally, goal-directed therapy based either on maximizing pulse contour–derived cardiac output or minimizing stroke volume variation results in improved perioperative outcome.[448,449]

GASTRIC TONOMETRY

Gastric tonometry aims at monitoring gastric circulation as an early indication of splanchnic hypoperfusion.[450] A balloon-tipped tube is inserted into the stomach, and the saline or air in the balloon is allowed to equilibrate with the CO_2 in the gastric lumen. Intermittently, the saline or air is aspirated and the CO_2 level is measured. With development of gastric hypoperfusion, CO_2 clearance from the gastric mucosa decreases, whereas CO_2 production increases from bicarbonate titration of acid released by anaerobic metabolism. The CO_2 from the mucosa diffuses freely to the gastric lumen and is detected by the tonometry device.

Gastric mucosal CO_2 and pH are predictors of post-trauma and perioperative complications or death.[451-453] Also, therapy guided by gastric tonometry can improve clinical outcome in critically ill or perioperative patients.[454,455] However, this somewhat cumbersome and time-consuming method for monitoring tissue perfusion has not been widely adopted.

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Chapter 46

Perioperative Echocardiography

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Key Points

- The latest guidelines for perioperative transesophageal echocardiography (TEE) recommend TEE in all patients having open heart and thoracic aortic vascular procedures and in patients with unexplained life-threatening circulatory instability unless contraindicated by esophageal pathologic abnormalities.
- The higher the ultrasound transducer frequency, the better the image quality, but the more limited the depth of penetration.
- The modified Bernoulli theorem transforms velocities measured by Doppler echocardiography into transvalvular pressure gradients. Pressure gradient = $4V^2$, where V = velocity in meters per second.
- Tissue Doppler imaging measures myocardial velocities and is the primary tool for the assessment of ventricular systolic and diastolic functions.
- Three-dimensional TEE in real time is now widely available and proving to be of significant value in perioperative patients.
- The basic TEE examination is an abbreviated version of the comprehensive examination. It is significantly faster to complete than the comprehensive examination and will identify the majority of life-threatening perioperative cardiac pathologic complications.
- The basic transthoracic echocardiography (TTE) examination is performed from three standard windows and provides cross sections comparable with those produced with TEE.
- TEE provides highly reliable and reproducible methods to assess cardiac filling and ejection.
- TEE is more sensitive than the electrocardiogram for the detection of intraoperative myocardial ischemia. It is more predictive of postoperative outcome than preoperative cardiac stress testing.
- TEE is an essential tool in the cardiac surgical unit where it plays a vital role in assessing the need for management changes, as well as guiding those changes and evaluating the effectiveness of the surgical procedure.

INTRODUCTION

Echocardiography has transformed the practice of anesthesia. Transesophageal echocardiography (TEE) is the most powerful cardiovascular diagnostic technique available in the practice of perioperative medicine today. Thousands of published reports document its vital role in the determination of hemodynamics, the detection of myocardial ischemia, cardiovascular pathologic evaluation, and the assessment of cardiac surgical plans and results. With the information provided by TEE, anesthesiologists, surgeons, and intensivists can alter therapy to decrease morbidity and increase the survival of surgical patients. No other diagnostic technique has had such an impact on the practice of anesthesia and critical care. As a result, routine intraoperative TEE is an expectation in most cardiac surgical practices, and basic TEE is a resource in many noncardiac practices. In addition, transthoracic echocardiography (TTE) has emerged as a highly portable tool for cardiac assessment in the patient whose trachea is not intubated. This chapter reviews the published literature documenting echocardiography's role in perioperative care after presenting a brief summary of its history, its underlying physical principles, and the techniques required to perform it.

HISTORY

In 1976, Dr. Leon Frazin published the results of studies using an esophageal M-mode transducer, thereby introducing the concept of TEE.[1] Subsequently, Matsumoto

and associates used M-mode TEE to study left ventricular (LV) function during cardiovascular surgery.[2] However, M-mode echocardiography provides too limited a view of spatial relationships to be practical for intraoperative monitoring or real-time decision making. In the early 1980s, Hanrath and associates introduced a two-dimensional (2-D), phased-array transducer mounted on the tip of a flexible gastroscope, and TEE's intraoperative potential became apparent.[3] However, wide adoption of TEE did not occur until the mid-1980s, when the TEE transducer design was refined and color-flow Doppler (CFD) became commercially available. With these advances, TEE could provide the high-resolution, real-time images of structure and blood flow used today on a daily basis. However, the original single-plane and subsequent biplane TEE probes limited the potential imaging planes. Multiplane TEE imaging uses a rotatable 2-D transducer within the probe tip that has substantially resolved those limitations and remains the current standard of practice.

Along with advances in probe technology, ultrasound manufacturers improved image compression algorithms, high-density digital storage, and broadband communication networks that have revolutionized the storage and processing of TEE images. Secure digital servers have replaced videotape libraries of clinical studies, resulting in vastly faster access to and fidelity of stored images. In addition, after decades of work on real-time three-dimensional (3-D) imaging, it is finally a reality. The impact of 3-D imaging on clinical practice continues to evolve but has already become a highly valuable tool in valvular pathologic assessment and repair.[4]

TRANSESOPHAGEAL ECHOCARDIOGRAPHY PRACTICE GUIDELINES

In 1992, the American Society of Echocardiography (ASE) Committee for Physician Training in Echocardiography published its guidelines for training in TEE.[5] These are based on the prior recommendations for training in TTE and are directed at training for TEE in both operative and nonoperative applications. These guidelines require the trainee to attain at least an intermediate level of training in echocardiography and to perform and interpret at least 50 supervised TEE examinations. In 1996, a joint taskforce of the American Society of Anesthesiologists (ASA) and the Society of Cardiovascular Anesthesiologists (SCA) published guidelines for perioperative TEE that defined two levels of practice: basic and advanced.[6] Anesthesiologists with basic training in perioperative TEE "should be able to use TEE for indications that lie within the customary practice of anesthesiology" and "must be able to recognize their limitations in this setting and request assistance, in a timely manner, from a physician with advanced training." Anesthesiologists with advanced training in perioperative TEE "should, in addition to the above, be able to exploit the full diagnostic potential of TEE in the perioperative period." In 2010, the ASA House of Delegates approved updated guidelines for TEE, which delineated the following three subsets of recommendations.[7]

Cardiac and thoracic aortic surgery: "For adult patients without contraindications, TEE should be used in all open heart (e.g., valvular procedures) and thoracic aortic surgical procedures and should be considered in coronary artery bypass graft surgeries to: (1) confirm and refine the preoperative diagnosis, (2) detect new or unsuspected pathology, (3) adjust the anesthetic and surgical plan accordingly, and (4) assess the results of surgical intervention. In small children, the use of TEE should be considered on a case-by-case basis because of risks unique to these patients (e.g., bronchial obstruction)" (also see Chapter 94).

Noncardiac surgery: "TEE may be used when the nature of the planned surgery or the patient's known or suspected cardiovascular pathology might result in severe hemodynamic, pulmonary, or neurologic compromise. If equipment and expertise are available, TEE should be used when unexplained life-threatening circulatory instability persists despite corrective therapy."

Critical care patients: "TEE should be used when diagnostic information that is expected to alter management cannot be obtained by transthoracic echocardiography or other modalities in a timely manner" (also see Chapter 102).

In 1999, a joint taskforce of the ASE and SCA published recommendations for a comprehensive TEE examination.[8] These recommendations described in detail the 20 TEE cross sections that make up the comprehensive examination. In addition, in 2002, a joint taskforce of the ASE and SCA used the principles and recommendations published in the aforementioned guidelines to formulate guidelines for training in perioperative TEE, including the prerequisite medical knowledge and training, echocardiographic knowledge and skills, training components and duration, training environment and supervision, and equivalence requirements for postgraduate physicians already in practice.[9] Minimum numbers of cases are delineated; however, these numbers are less important than the depth and diversity of the clinical experience and quality of training. Similar to prior published guidelines, these guidelines provide training recommendations for a basic level and an advanced level of perioperative echocardiography. Unlike prior guidelines, these guidelines do not specify the duration of training; rather, they emphasize the goals of training and the number and diversity of cases required to meet these goals (Table 46-1). The time required for perioperative training will vary significantly, depending on the patient volume and diversity of the affiliated cardiac surgical program.

The American Heart Association, the American College of Cardiology, the European Association of Echocardiography, and other professional organizations have issued other guidelines that involve TEE.[10-12] In 2011, the ASE and other societies published updated appropriateness criteria for echocardiography, including perioperative applications. More than 200 indications were classified as appropriate, uncertain, or inappropriate. Unstable coronary syndromes, decompensated heart failure, significant arrhythmias, and severe valvular diseases were listed as appropriate indications for the perioperative use of echocardiography.[13] Recent retrospective reviews performed

TABLE 46-1 RECOMMENDATIONS FOR BASIC AND ADVANCED PERIOPERATIVE ECHOCARDIOGRAPHY

	Basic*	Advanced*
Minimum number of examinations†	150	300
Minimum number of examinations personally performed‡	50	150
Program director qualifications	Advanced perioperative echocardiography training	Advanced perioperative echocardiography training plus at least 150 additional perioperative transesophageal echocardiographic examinations
Program qualifications	Wide variety of perioperative applications of echocardiography	Full spectrum of perioperative applications of echocardiography

Adapted from Cahalan MK, Abel M, Goldman M, et al: American Society of Echocardiography and Society of Cardiovascular Anesthesiologists task force guidelines for training in perioperative echocardiography, Anesth Analg *94:1384-1388, 2002.*

*Totals for basic training may be counted toward advanced training, provided the basic training was completed in an advanced training environment.

†Complete echocardiographic examinations interpreted and reported by the trainee under appropriate supervision. May include transthoracic studies recorded by qualified individuals other than the trainee.

‡Comprehensive intraoperative echocardiographic examinations personally performed, interpreted, and reported by the trainee under appropriate supervision.

on more than 2500 patients showed that echocardiography is appropriately used in 80% of the cases and inappropriately used in less than 15%.[14,15] Published audits specifically addressing perioperative echocardiography services showed that using appropriate indications leads to the identification of significant cardiac pathologic complications in 26% of the cases and significant changes 60% of the time in medical and surgical management.[16,17] The ever-expanding uses of perioperative echocardiography will require ongoing outcome-based studies and quality assessment programs. The ASE recently published recommended components of such programs.[18] When these guidelines address perioperative TEE, their recommendations are consistent with those previously noted. Finally, a section on perioperative TEE for this indication will be included in the new Guidelines on Perioperative Cardiovascular Evaluation before Noncardiac Surgery to be published in 2014.

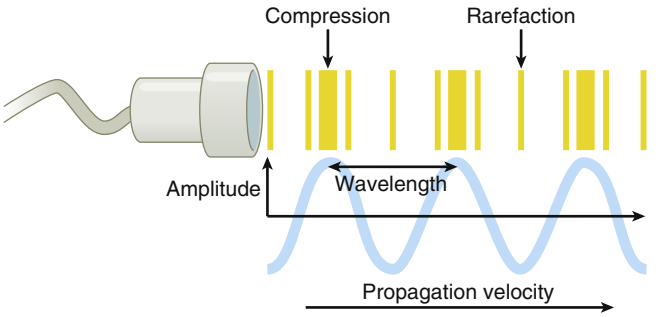


Figure 46-1. Illustration of terms used to describe ultrasound energy transmission from a transducer into adjacent tissue. As ultrasound vibrations enter surrounding tissue, particles within the tissue compress *(compression)* and then spread apart *(rarefaction)*. Sine waves are used to characterize the sequence of compression and rarefaction. The *wavelength* is the distance between two peaks of the sine wave. The *amplitude* is a measure of tissue compression. The *propagation velocity* is the speed of the ultrasound wave within tissue.

PROPERTIES OF ULTRASOUND

To noninvasively visualize structures inside the body, ultrasound machines generate an imperceptible vibration within a transducer that, when placed next to tissue surfaces, vibrates the surrounding tissue (muscle, blood, fat, or bone). During vibration, particles within the tissue compress and then spread apart. This process is called *compression* and *rarefaction*. The sequence of compression and rarefaction is described using sine waves and is characterized in terms of wavelength, frequency, amplitude, and propagation velocity (Figure 46-1).

The *wavelength* is the distance between two peaks of the sine wave. Wavelengths used in ultrasound are measured in millimeters (mm). Frequency is the number of cycles that occur in one second. One cycle per second is defined as 1 hertz (Hz). Ultrasound is sound with frequencies higher than the audible range for humans or greater than 20,000 cycles per second (20 KHz). Frequencies typically used for sonographic imaging are 2 to 10 million hertz (MHz). The wavelength is inversely related to the frequency.

The *amplitude* is a measure of tissue compression. Amplitude represents how loud an ultrasound wave is. The amplitude can vary over a large range and is described using decibels (dB). Decibels is a logarithmic transformation that allows the presentation of large amplitudes next to small amplitudes (i.e., 1000 and 0.001) on the same display. A rule of thumb is that a change of 6 dB is equivalent to a doubling or halving of the amplitude.

The *propagation velocity* describes the speed of an ultrasound wave traveling through tissue. In blood, it is 1540 meters per second (m/sec). The relationship between propagation velocity, frequency, and wavelength is described by Equation 1:

$$c = f \times \lambda \quad (1)$$

where c is the propagation velocity, f is the frequency (Hz) and λ is the wavelength (mm). Assuming the propagation velocity is constant, the wavelength for any frequency can be calculated using the relationship shown in Equations 2 and 3:

$$\lambda\,(\text{mm}) = 1,540,000\,(\text{mm/sec}) \div f\,(\text{Hz}) \quad (2)$$

or

$$\lambda\,(\text{mm}) = 1.54\,(\text{km/sec}) \div f\,(\text{MHz}) \quad (3)$$

TABLE 46-2 **RELATIONSHIP BETWEEN FREQUENCY, WAVELENGTH, AND DEPTH OF PENETRATION**

Frequency	Wavelength	Depth of Penetration (200 to 400 × Wavelength)	Approximate Resolution (2 × Wavelength)
3.5 MHz	0.44 mm	9-18 cm	0.9 mm
5.0 MHz	0.31 mm	6-12 cm	0.6 mm
6.0 MHz	0.26 mm	5-10 cm	0.5 mm
7.5 MHz	0.21 mm	4-8 cm	0.4 mm

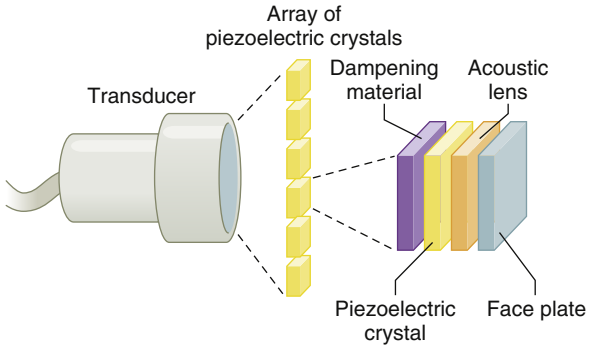


Figure 46-2. Illustration of an array of piezoelectric crystals contained within an ultrasound transducer. When pulsed with alternating current, piezoelectric crystals "ring" much like a bell. The crystal continues to vibrate after an electrical pulse has ended. To achieve a crisper pulse, a backing material is applied to the crystal to *dampen* the ring after the pulse has ended. To optimize transmission from the crystal into tissue, an *acoustic lens* focuses the ultrasound beam and an *impedance matching face plate* improves the conductance of ultrasound from the transducer into tissue.

Wavelengths associated with commonly used transducer frequencies range from 0.1 to 0.6 mm. Examples of commonly used transducer frequencies are presented in Table 46-2.

Transducers use crystals that exhibit the piezoelectric effect and are typically made out of quartz or titanate ceramic. With electricity, the crystal vibrates and emits ultrasound. The reverse also holds; when ultrasound waves strike a piezoelectric crystal and make it vibrate, the crystal generates electricity. Thus the same crystals can serve as emitters and receivers of ultrasound. The *frequency* of vibration is determined by the thickness of the piezoelectric crystal. To refine and control the emitted ultrasound beam, several layers of material are placed adjacent to the crystal (Figure 46-2).

TRANSDUCER FREQUENCY, IMAGE RESOLUTION, AND DEPTH OF PENETRATION

Echocardiography uses ultrasound waves with frequencies of 2.5 to 7.5 million cycles per second (MHz). Frequencies greater than 7.5 MHz are not used because they produce wavelengths too short for adequate penetration into tissues. Penetration is limited to between 200 and 400 times the wavelength. Frequencies less than 2.5 MHz are not used because they produce wavelengths too long for the resolution of small objects (resolution is limited to approximately twice the wavelength). Thus ultrasound transducers in the range of 2.5 to 7.5 MHz resolve objects 0.4 to 1.2 mm in size and penetrate tissues up to 24 cm.

Image resolution is characterized in terms of axial, lateral, elevational, and temporal resolution. Axial resolution is resolution along the length of an ultrasound beam. It is a function of transducer frequency and pulse width. Longer wavelengths have deeper tissue penetration but are unable to resolve objects that are close together. Shorter wavelengths do the opposite. Similarly, short-duration ultrasound pulses improve axial resolution.

Lateral resolution is resolution from side to side across a 2-D image and is a function of beam formation. The initial segment (near field) of an ultrasound beam is columnar, and the length is dependent on transducer width and wavelength (Figure 46-3, *A*). Beyond the near field, the beam diverges (far field). Divergence is also a function of transducer frequency (Figure 46-3, *B*). As the frequency goes up, the near field gets longer and the divergence angle decreases. As the width gets smaller, the angle of divergence gets larger. The lack of lateral resolution at greater depths accounts for the blurring of the image in the far field.

Another feature of ultrasound beam formation that influences lateral resolution is the grating lobes (Figure 46-4). A grating lobe is a diverging ultrasound beam that emerges from the transducer along with the main ultrasound beam. The angle of the diverging grating lobe is determined by the spacing between the crystals in the transducer array. A grating lobe is formed at the angles where the path length of an ultrasound wave between the two adjacent transducer crystals differs by one wavelength. An example of a grating lobe artifact is when a properly positioned pulmonary artery catheter appears to go through the aorta. The artifact appears as an echo-dense, archlike object that traverses structures within the heart and is at equal distance from the transducer throughout the image. In this example, a diverging ultrasound beam from a grating lobe is reflected back to the transducer. The ultrasound machine cannot differentiate between reflected ultrasound from the main beam and the grating lobe beam.

Elevational resolution refers to the thickness of the wedge-shaped ultrasound image. The thickness is typically 10 mm. Temporal resolution is the ability to locate moving structures accurately at a particular instant in time. The more images displayed per second (frame rate), the better the temporal resolution. A typical frame has 128 lines in a 90-degree 2-D image. If the depth is set at 20 cm, then the time required for sampling one line is 0.3 microseconds. To scan all 128 lines requires 33 microseconds. In one second, the sector is scanned 30 times. For cardiac applications, imaging moving structures at a frame rate of at least 30 frames per second is optimal. Decreasing the image depth will improve the temporal resolution. Ultrasound machines allow the sonographer to *zoom* in on a region of interest within the 2-D display. This function redistributes the number of scan lines used to generate a full 2-D image into a smaller region of interest, therefore improving the temporal resolution.

As ultrasound waves penetrate tissue, the signal strength is attenuated. *Attenuation* is a function of tissue *absorption* (ultrasound energy converted to heat),

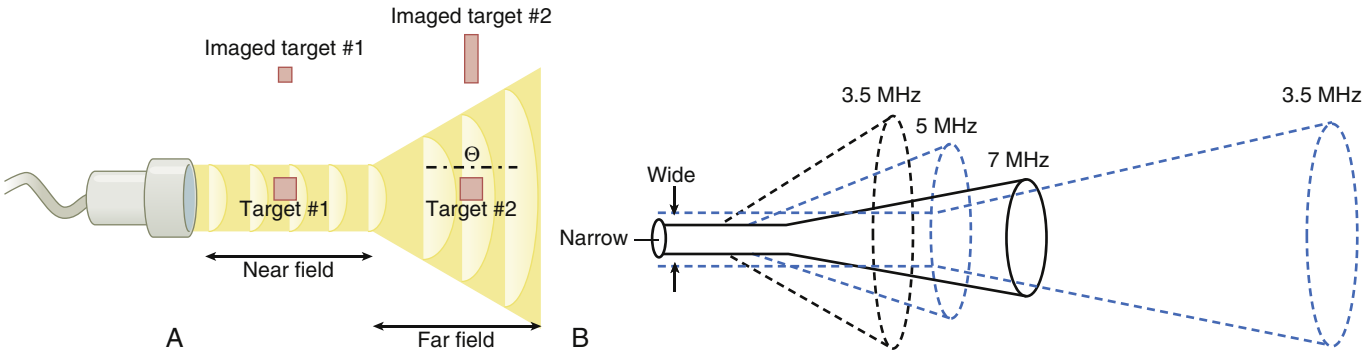


Figure 46-3. A, Near- and far-field beam formation. The near field is the columnar portion of the beam, and the far field is the diverging segment of the beam. Theta (Θ) represents the angle of divergence. Structures within the near field (Target #1) are imaged with crisp lateral resolution, whereas structures in the far field (Target #2) are imaged with blurred lateral resolution. **B,** Relationship between the near-field length and the transducer frequency and width. The length of the near field is a function of transducer width and frequency. As the frequency increases, the near field lengthens. The angle of divergence is also a function of transducer frequency. With increasing transducer frequency, the angle of divergence decreases. The *black dashed, dotted,* and *solid lines* represent the beam divergence for a 3.5-, 5.0-, and 7.0-MHz transducer, respectively. With wider transducers, the near field increases in length. The *blue dashed* lines represent the near and far field for a 3.5-MHz transducer that is twice as wide as the narrow transducer.

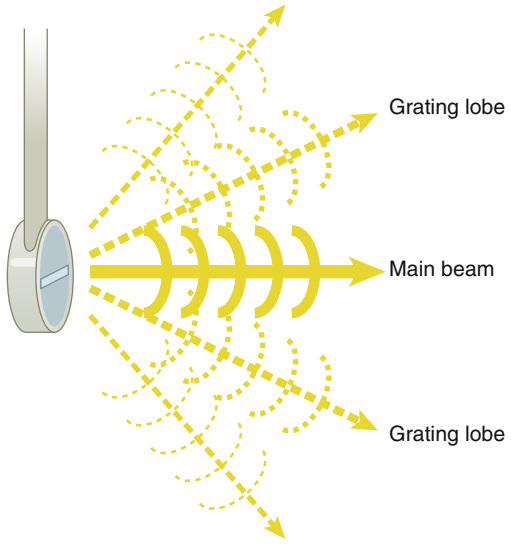


Figure 46-4. The main ultrasound beam *(solid line)* emitted from a transducer is accompanied by a series of grating lobes *(dotted lines)*. The grating lobes are a phenomenon of beam formation that is a function of the array of piezoelectric crystals within the transducer. At certain angles from the main beam, the ultrasound wave from each crystal within the array is exactly one wavelength behind the wavelength from the adjacent crystal. which generates a grating lobe. The clinical implications of grating lobes are that highly echogenic objects such as a Swan-Ganz catheter or a mitral valve prosthesis can "appear" to be locations within the heart (e.g., the aorta) that are incorrect.

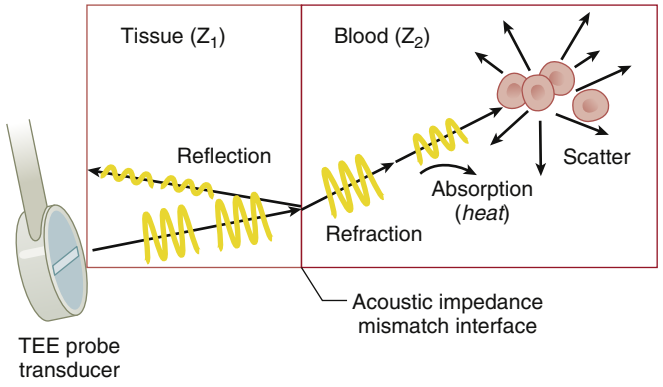


Figure 46-5. Diagram of specular reflection, refraction, absorption, scatter, and acoustic impedance. As ultrasound waves strike an interface between two different tissue types, some of it is reflected and the remainder passes through. The reflected ultrasound wave has a trajectory angle equal to the incident angle. Refraction refers to a deflection of the ultrasound beam as it travels from one tissue type to another. Scattering occurs when an ultrasound wave strikes a structure that is less than one wavelength in lateral dimension (e.g., a red blood cell). Absorption represents the amount of ultrasound energy that dissipates as heat. Acoustic impedance refers to the resistance an ultrasound wave meets when traveling through tissue. Acoustic impedance *(Z)* is defined as the product of tissue density multiplied by the propagation velocity. *TEE,* Transesophageal echocardiography.

divergence of ultrasound energy as it moves away from the transducer, *reflection*, and *scattering* (Figure 46-5). Absorption is dependent on tissue type. For example, air absorbs more ultrasound energy than bone, but bone absorbs more than blood or water. A term used to describe absorption is *half-power distance*, which is the distance required to decrease the ultrasound energy by 50%. The half-power distance for air, bone, blood, and water are 0.08, 0.8, 15, 380 cm, respectively.

As ultrasound waves strike an interface between two different tissue types, some of it is reflected and the remainder passes through (see Figure 46-5). As light is reflected from a mirror, the reflected ultrasound wave has a trajectory angle equal to the incident angle. The amplitude of reflected ultrasound waves is decreased by 40 to 60 dB (100- to 1000-fold). Ultrasound waves that pass through to the adjacent tissue are subject to refraction. *Refraction* refers to a deflection of the ultrasound beam as it travels from one tissue type to another. An example of refraction is how an image of an object can be distorted when partially submerged in a fish tank or swimming pool. Refraction can bend ultrasound beams, making objects appear to be in locations where they do not exist. Scattering occurs when an ultrasound wave strikes a structure (e.g., red blood cell) that is less than

one wavelength in lateral dimension. The scattered ultrasound energy is radiated in all directions.

Acoustic impedance refers to the resistance an ultrasound wave meets when traveling through tissue. It is a function of tissue density and is defined by Equation 4:

$$Z = \rho \times c \quad (4)$$

Z, ϱ, and c indicate the acoustic impedance, tissue density, and propagation velocity, respectively. As tissue density increases, the faster the ultrasound beam moves through the tissue. For example, ultrasound waves are significantly slower in air (330 m/sec), faster in blood (1540 m/sec), and extremely fast in bone (4080 m/sec). The extent of ultrasound beam reflection is a function of the difference in acoustic impedances between two adjacent tissues. The larger the difference in acoustic impedance, the more ultrasound energy will be reflected. Bone-soft tissue and air-soft tissue interfaces reflect most of the ultrasound beam. Imaging structures deep to these interfaces are difficult.

Mismatches in acoustic impedance and attenuation are important to consider when imaging the heart with TEE. For example, sonographers find it difficult to visualize the aortic arch from the esophagus when scanning through air-filled trachea or carina. The ultrasound energy emitted from the TEE probe is significantly attenuated as it passes through the air in the trachea. Most of the ultrasound energy that does make it to the trachea-tissue interface is reflected as a result of the large difference between the acoustic impedances between air and tissue.

BASIC PRINCIPLES OF IMAGE OPTIMIZATION: GAIN, DEPTH, AND FOCUS

Gain is used to amplify low-amplitude ultrasound waves reflected back to the transducer. Gain represents how well the ultrasound system listens. It can be used to offset the large-amplitude signals returning from proximal structures from low-amplitude signals returning from distant structures. Many ultrasound machines have a series of sliding controls that allow the sonographer to adjust the gain at a given depth called the *time gain compensation* controls. One temptation when structures are not readily visualized in the brightly lit surgical unit is to turn up the gain. Although gain increases structure brightness, it comes at the cost of amplifying background noise. A better approach is to dim the surgical unit's lights and keep the gain at normal settings.

In echocardiography, the crystals emit very short pulses of ultrasound (approximately 1 microsecond [μsec]) and receive or "listen" for the reflected ultrasound for 250 to 500 μsec. The *pulse repetition frequency* (PRF) is the number of pulses that leave and return to the transducer in a single second. The PRF can be changed by changing the depth of an image. As image depth is increased, the time required to reach the target depth and return increases. Thus the number of cycles that can be completed within 1 second is reduced. The opposite also holds true; as imaging depth decreases, the PRF increases. The PRF is also described in hertz and is audible, ranging from 1 to 10 kHz.

Early echocardiographic displays used this principal to map out the depth of structures within the heart. The first

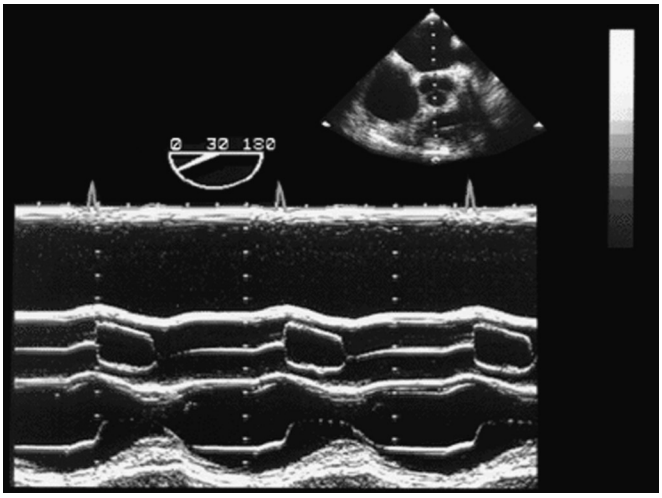


Figure 46-6. An M-mode transesophageal echocardiogram (TEE) of a normal aortic valve is shown. For reference, a single frame (stop action) of the two-dimensional cross section is shown *(top right).* The *dotted vertical line* through the 2-D TEE depicts the single line of sampling provided by the M-mode TEE over time (the horizontal axis for the lower two thirds of the figure). The TEE defines the systole and diastole. The three *tilted rectangles* are connected by the slightly *undulating line* and visualized in the middle of the M-mode image. These rectangles and lines are formed by the motion of the leaflets of the aortic valve as they open and close during the cardiac cycles shown. From top to bottom in this M-mode TEE, the structures indicated by the *white lines* are the posterior wall of the left atrium (just under the TEE), the posterior wall of the aortic annulus, the aortic valve (described above), the anterior wall of the aortic annulus, a pulmonary artery catheter, and the myocardium of the right ventricular outflow tract. *(Reproduced with permission from Cahalan MK:* Intraoperative transesophageal echocardiography. An interactive text and atlas*, New York, 1997, Churchill Livingstone.)*

echocardiograms, *motion* or *M-mode* studies, were one-dimensional views of cardiac structures produced by single crystal transducers with the results traced on moving photosensitive paper. Today, M-mode echocardiography is principally used to view rapidly moving structures, such as valve leaflets, because M-mode transducers can produce up to 1800 images per second (Figure 46-6). However, M-mode images reveal only a small portion of the heart at one time, making orientation and interpretation of spatial relationships difficult.

To generate 2-D images, ultrasound machines were configured to redirect the beam sequentially over an area or sector of interest. Transducers now contain a row of piezoelectric crystals (linear array). By introducing a small delay in the firing of adjacent crystals in the array (phased array), the ultrasound machine is now able to steer the resultant ultrasound beam. By varying the time delay between crystals, ultrasound machines are therefore able to steer the beam through a sector of interest (typically a 90-degree sector). Although 2-D techniques produce only approximately 30 images per second, the definition in 2-D images provides an enormous advantage in recognizing anatomic and pathologic landmarks (Figure 46-7). Images are displayed in *real time* on a monitor screen and digitally recorded for later review. In a similar fashion to steering the ultrasound beam, the *focal depth* of an ultrasound beam can be adjusted by triggering

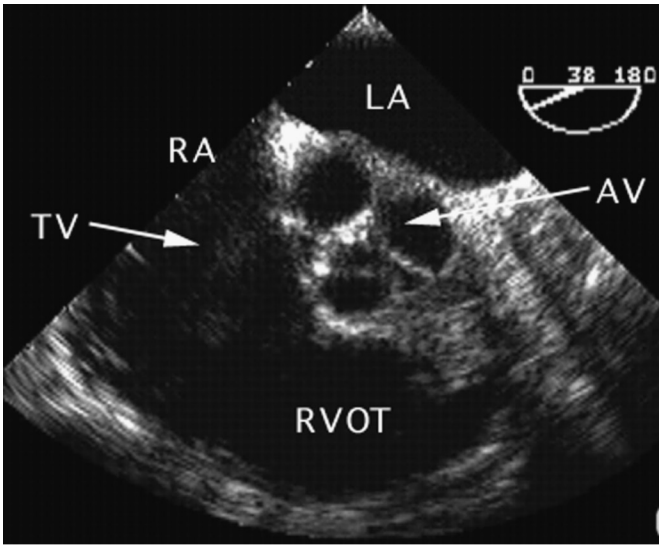


Figure 46-7. A stop-action, short-axis, two-dimensional cross section of a normal aortic valve (AV) is shown. This midesophageal short-axis view of the AV reveals the morphologic structure of the three cusps of this normal valve. *LA,* Left atrium; *RA,* right atrium; *RVOT,* right ventricular outflow tract; *TV,* tricuspid valve. *(Reproduced with permission from Cahalan MK:* Intraoperative transesophageal echocardiography. An interactive text and atlas, *New York, 1997, Churchill Livingstone.)*

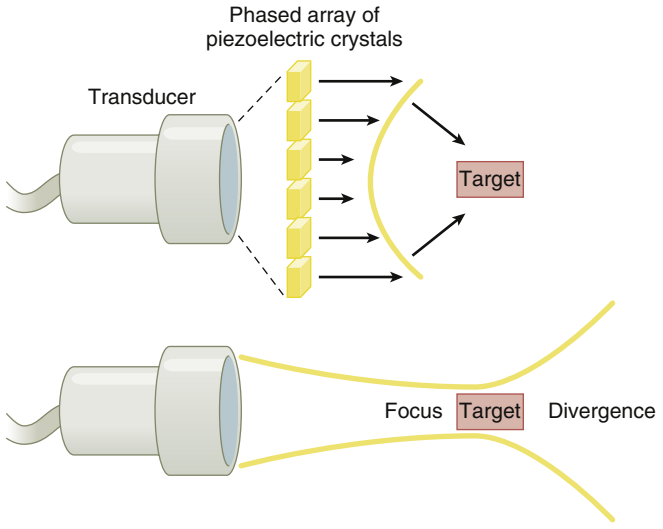


Figure 46-8. Schematic illustration depicts phasing the start of an array of piezoelectric crystals to focus an ultrasound beam. Crystals are sequentially fired from the outer edge to the middle of the array. The resultant concave wave converges at a point some distance from the transducer. The focal distance from the transducer is a function of the time delay between firing crystals from the edge to the middle of the array.

the piezoelectric crystals to concentrate the ultrasound beam at a desired depth (Figure 46-8). The focal depth is typically set at or just below the structure of interest in a 2-D image.

INTEGRATION OF FLOW AND STRUCTURE

By measuring the Doppler shift, modern ultrasonography quantifies blood-flow velocities. The Doppler shift is the shift in frequency of a wave when the source of the wave is moving (e.g., when moving red cells are reflecting the wave). When pulses of sound are used (pulsed-wave Doppler [PWD]), the operator defines a small area, termed *sample volume*, anywhere in the 2-D sector scan, and the ultrasonograph automatically converts the Doppler data in that sample volume to a display of the real-time blood-flow velocities. Thus PWD defines blood-flow velocities and their location within the heart and great vessels (Figure 46-9).

However, two important limitations apply. First, the Doppler shift is proportional to the cosine of the angle between the ultrasound beam and the direction of the blood cells. If the cells are moving directly parallel to the ultrasound beam, then the angle is zero and the cosine of zero is one. Thus at an angle of zero, Doppler echocardiography provides a true estimate of blood-flow velocity. At all other angles, the cosine is less than one, resulting in less Doppler shift and an underestimation of flow velocity. Clinically, angles of less than 15 degrees (the cosine is almost one) are insignificant to velocity estimation, whereas angles exceeding 20 degrees significantly attenuate the Doppler shift, necessitating caution in interpreting such data. This relationship is best stated in the Doppler equation:

$$V = (C \times F_d) \div (2F_0 \times \cos \theta)$$

where V is the velocity to be measured, C is the speed of sound in tissue (a constant), F_d is the Doppler shift in ultrasound frequency measured by the ultrasound machine, F_0 is the frequency of the transducer, and cos θ is the cosine of the angle between the direction of the blood flow and the ultrasound waves. Second, the maximum velocity of blood flow that can be unambiguously measured is defined by the Nyquist limit. The Nyquist limit is directly related to the ultrasound frequency and the PRF. The PRF is the number of pulses of ultrasound emitted per second. Because an emitted pulse must return before the next is emitted in PWD, an increase in the depth of the ultrasound scan decreases the PRF and the Nyquist limit. Thus the depth of the ultrasound scan is the principal determinant of the Nyquist limit under the control of the operator. If the velocity of blood flow exceeds the Nyquist limit, then sudden apparent flow reversal, or *aliasing*, will be depicted (Figure 46-10). Aliasing is analogous to the sudden apparent reversal of the direction in the stagecoach wheels visible in old Westerns when the velocity of the wheel spokes exceeded the frame rate of the movie camera. Typically, aliasing of PWD occurs at blood-flow velocities of 0.8 to1.0 m/sec. Normal flow within the heart may reach 1.4 m/sec and pathologic flows up to 6 m/sec. To measure these velocities, continuous-wave Doppler (CWD) is needed.

CONTINUOUS-WAVE DOPPLER

CWD uses two separate crystals: one to emit ultrasound continuously and one to receive ultrasound continuously. CWD is basically PWD with an infinite PRF that eliminates the problem of aliasing (Figure 46-11). However, this infinite pulse repetition rate allows insufficient time for the first pulse to return to the transducer before

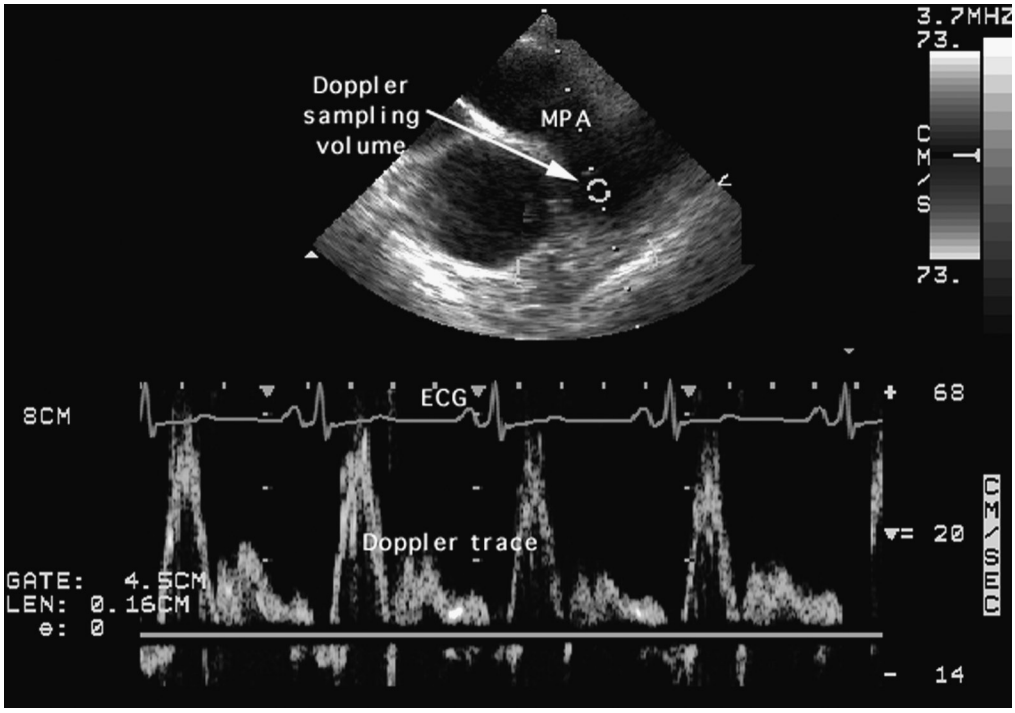


Figure 46-9. Pulsed-wave Doppler (PWD) echocardiogram of the main pulmonary artery (MPA). At the top of the echocardiogram is a still-frame image of the two-dimensional cross section used to position the Doppler sample volume *(broken white circle at the point of the arrow)*. The display *(in white)* of the instantaneous blood-flow velocities (vertical axis) versus time (horizontal axis) occurring in that sample volume is visualized on the bottom third of the figure. The electrocardiogram (ECG) provides timing, and the *bold horizontal line* is the baseline (zero flow) for the flow velocities. Flow velocities above this line are positive (i.e., toward the transducer) to a maximum of 68 cm/sec. Flow velocities below this line are negative (i.e., away from the transducer) to a maximum of –14 cm/sec. *(Reproduced with permission from Cahalan MK:* Intraoperative transesophageal echocardiography. An interactive text and atlas*, New York, 1997, Churchill Livingstone.)*

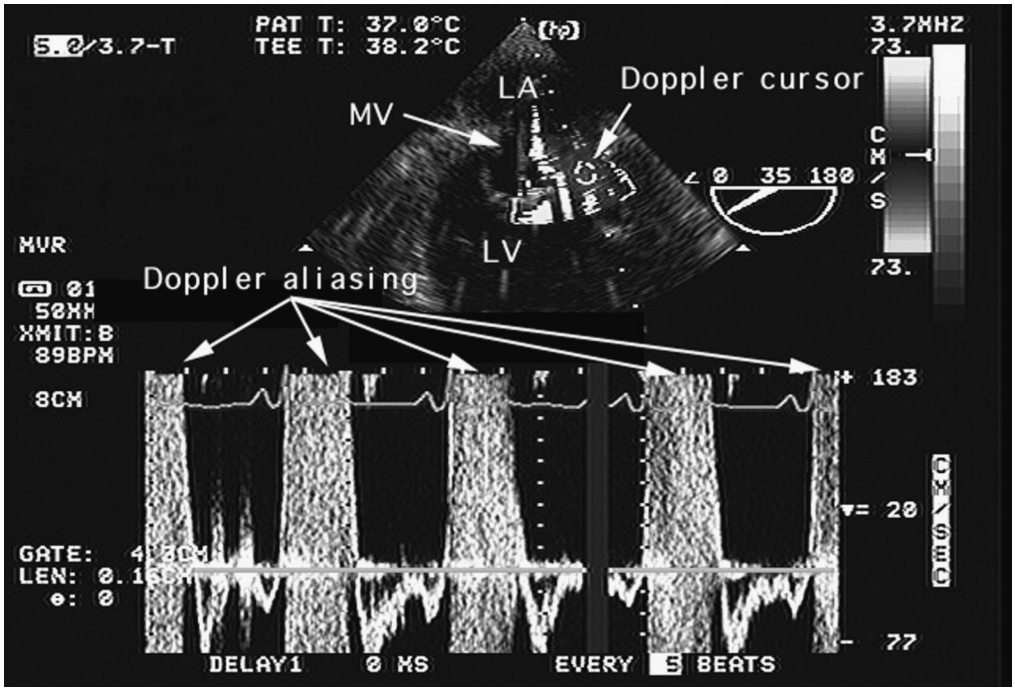


Figure 46-10. Pulsed-wave Doppler (PWD) echocardiogram with aliasing at high velocities. PWD measurement of blood-flow velocities in a mitral valve (MV) orifice during four cardiac cycles is shown. At the top of the figure is a still-frame image of the two-dimensional cross section used to position the Doppler sample volume *(broken white circle)*. The display *(in white)* of the instantaneous blood-flow velocities (vertical axis) versus time (horizontal axis) occurring in that sample volume is visualized on the bottom third of the figure. The electrocardiogram provides timing, and the *bold horizontal line* is the baseline (zero flow) for the flow velocities. Flow velocities above this line are positive (i.e., toward the transducer) to a maximum of 183 cm/sec. Flow velocities below this line are negative (i.e., away from the transducer) to a maximum of –77 cm/sec. This tracing documents significant mitral regurgitation (positive systolic velocities) but does not measure the peak velocity of regurgitated flow because it is beyond the Nyquist limit—the systolic velocities off the top of the scale are said to alias; that is, they go off scale and wrap around into the domain of negative velocities. *(Reproduced with permission from Cahalan MK:* Intraoperative transesophageal echocardiography. An interactive text and atlas*, New York, 1997, Churchill Livingstone.)*

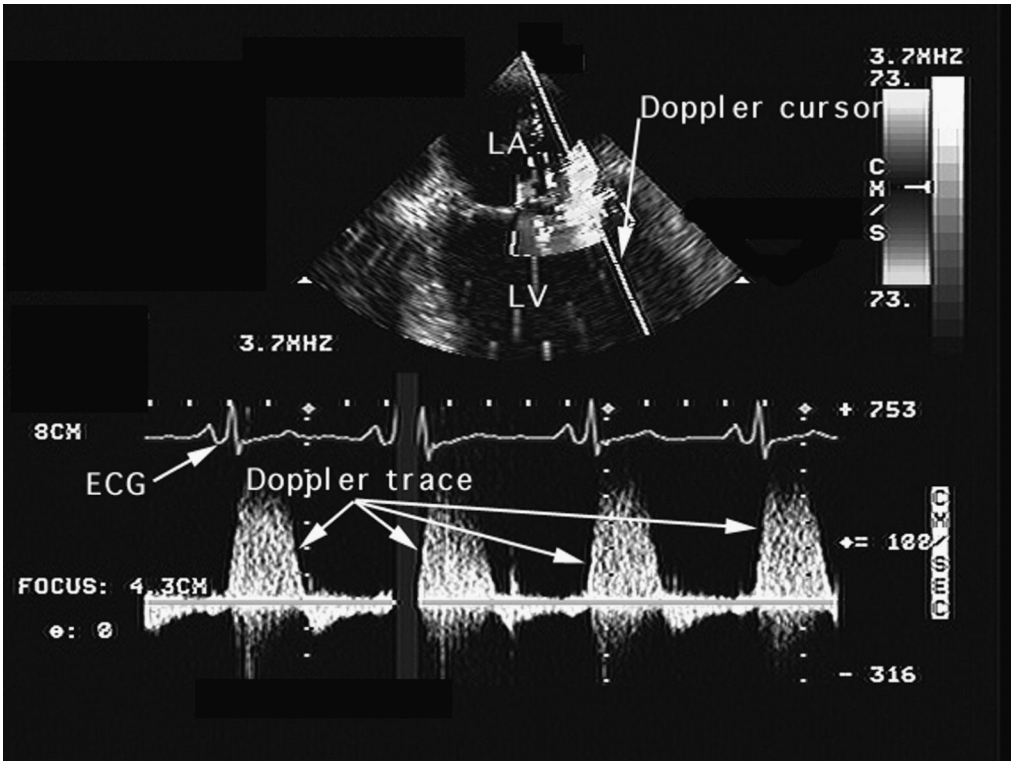


Figure 46-11. Continuous-wave Doppler (CWD) echocardiogram measures high-velocity flows without aliasing. CWD measurement of blood-flow velocities in a mitral valve orifice during four cardiac cycles is shown. At the top of the figure is a still-frame image of the two-dimensional cross section used to position the Doppler sample cursor *(diagonal white line)*. The display *(in white)* of all the instantaneous blood-flow velocities (vertical axis) versus time (horizontal axis) occurring anywhere along that cursor is visualized on the bottom third of the figure. The electrocardiogram (ECG) provides timing, and the *bold horizontal line* is the baseline (zero flow) for the flow velocities. Flow velocities above this line are positive (i.e., toward the transducer) to a maximum of 753 cm/sec. Flow velocities below this line are negative (i.e., away from the transducer) to a maximum of –316 cm/sec. This tracing documents significant mitral regurgitation (positive systolic velocities) with a peak blood-flow velocity of approximately 5 m/sec. Each white dot on the vertical axis equals 100 cm/sec or 1 m/sec). *LA,* Left atrium; *LV,* left ventricle; *(Reproduced with permission from Cahalan MK:* Intraoperative transesophageal echocardiography. An interactive text and atlas*, New York, 1997, Churchill Livingstone.)*

the next is emitted. Consequently, the ultrasonograph cannot determine which pulse of sound was frequency shifted and therefore cannot precisely define the location of the moving target. Nonetheless, the maximum velocity can prove to be vital information; by simplification of the Bernoulli equation, Hatle and colleagues[19] and Holen and colleagues[20] have proven that:

$$\Delta P = 4V^2$$

where ΔP is the peak gradient across a stenosis and V is the maximum velocity determined by CWD in m/sec.[19,20] Thus CWD defines higher blood-flow velocities than PWD but, unlike the latter, CWD cannot precisely define the location of the velocities.

COLOR DOPPLER

Point-by-point determination of blood-flow velocities by PWD is too time consuming and does not reveal the instantaneous distribution of flow velocities within the cross-sectional image that is required for many diagnostic decisions. Color Doppler imaging was developed for this purpose. In color Doppler, a form of PWD, a color code is used to depict flow toward (red) and away (blue) from the transducer; lighter and darker shades of red and blue, respectively, denote relatively faster and slower velocities. Continuous color maps of flow are superimposed on gray-scale, cross-sectional images. However, color Doppler generally is a semiquantitative technique and, similar to PWD, will alias (color reversal) when the Nyquist limit is exceeded. Two aliasing patterns are easily recognized. The first pattern is *normal* aliasing in which the area of apparent flow reversal forms one or more broad, relatively homogenous color surfaces (Figure 46-12). Blood-flow velocities within a normal heart often produce this type of aliasing because they exceed the Nyquist limit for color Doppler (0.6 to 0.8 m/sec). The second type of aliasing results from disturbed or turbulent flow within the heart (e.g., mitral regurgitation) and is never normal (Figure 46-13). When the ultrasonograph detects two different velocities within the same small sample volume as a result of disturbed flow, it displays a mixture, or mosaic, of colors. These mosaics form jetlike configurations and are called *color jets*. Because color Doppler presents the spatial relationships between structure and blood flow, it enhances the recognition of valvular abnormalities and intracardiac shunts. The clinical features of PWD, CWD, and color Doppler are compared in Table 46-3.

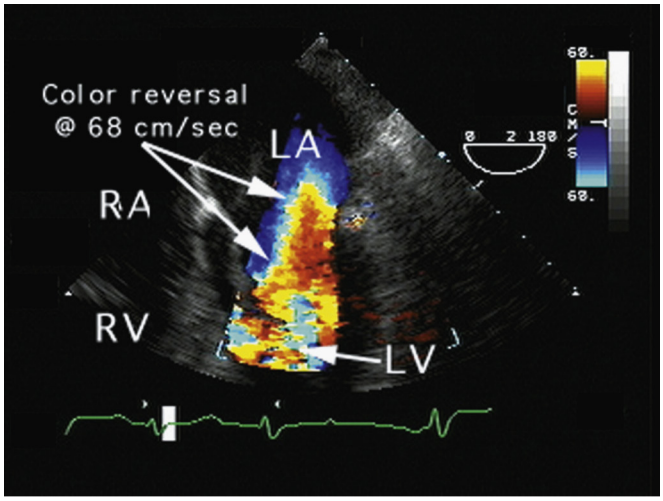


Figure 46-12. Normal color Doppler aliasing. In this echocardiogram, *normal* color Doppler aliasing is depicted because laminar flow of blood through the mitral valve and into the left ventricle (LV) exceeds the Nyquist limits (68 cm/sec, in this example; see color reference icon at the *upper right* of figure), resulting in a reversal of the color coding of flow direction. As noted in this figure, the color reversal occurs across fairly broad, regular areas but not in a random or point-by-point fashion as occurs with turbulent flows (always abnormal). In this example, the blue flow can be followed from high in the left atrium (LA) as it accelerates into the mitral orifice, and the color Doppler depicts the increasing flow velocities—the blue color becomes lighter and lighter until the Nyquist limit is reached. Then, color reversal occurs with light blue becoming yellow. At that reversal point, the velocity equals the Nyquist limit (68 cm/sec, in this example). Subsequent reversals may occur at that limit or multiples of that limit. *RA,* Right atrium; *RV,* right ventricle. *(Reproduced with permission from Cahalan MK:* Intraoperative transesophageal echocardiography. An interactive text and atlas*, New York, 1997, Churchill Livingstone.)*

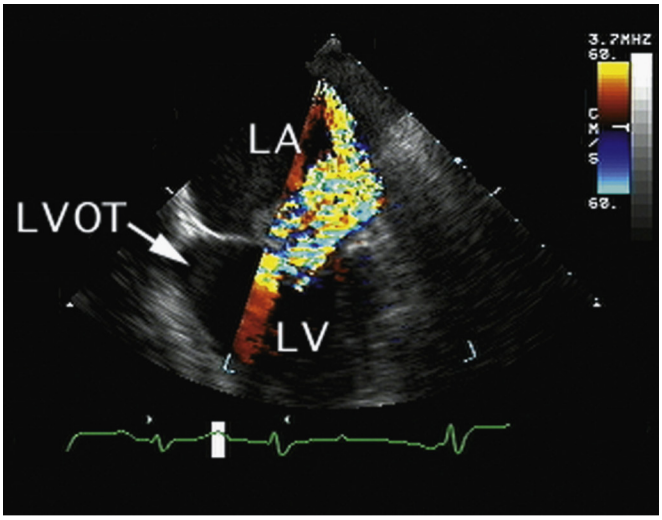


Figure 46-13. Color Doppler aliasing depicting turbulent flow. In this echocardiogram, color Doppler reveals aliasing attributable to severe mitral regurgitation. A broad-based systolic color jet emanates from the mitral valve and extends far into the left atrium (LA). This color jet is made up of a mosaic of colors mixed in a seemingly random, point-by-point fashion because the color jet results from the turbulent flow of mitral regurgitation. Turbulence is never normal in the heart, and thus mosaic color jets, such as the one shown in this figure, are highly valuable diagnostic signs of an underlying pathologic abnormality. *LV,* Left ventricle; *LVOT,* left ventricular outflow tract. *(Reproduced with permission from Cahalan MK:* Intraoperative transesophageal echocardiography. An interactive text and atlas*, New York, 1997, Churchill Livingstone.)*

TISSUE DOPPLER

Tissue Doppler imaging (TDI) is a relatively new use of PWD technology adapted to measure myocardial velocities instead of blood-flow velocities.[21] During normal LV contraction, the mitral annulus descends toward the apex of the heart. TDI measures the velocity of this descent (S_m), and S_m correlates with traditional measures of LV function including ejection fraction and the rate of increase of LV systolic pressure (dP/dt).[22,23] In addition, S_m decreases in the presence of myocardial ischemia and responds as expected with changes in inotropy.[24,25] The four-chamber cross section is best for measuring S_m; the sampling volume is placed at the lateral insertion point of the mitral valve into the left ventricle, and the cross section is aligned to ensure that the sampling cursor is directly parallel with the motion of the annulus. S_m is an easy and reproducible measurement. However, similar to measures of ejection fraction, it should be interpreted with caution when preload changes. Ama and associates tested its load dependence in 42 patients who were hemodynamically stable with normal segmental LV function after coronary surgery.[26] S_m did not significantly change in response to a 20% increase or decrease in mean arterial pressure induced by phenylephrine or nitroglycerine. However, S_m significantly increased when preload was augmented by rapid infusion of colloid. In summary, S_m is less dependent on afterload than estimates of ejection fraction but, similar to these other two measures, remains critically dependent on preload. The few measures of LV function that appear to be independent of both preload and afterload are not practical for clinical use.

TDI can also measure the diastolic function of the myocardium. An early diastolic tissue velocity (e′) and a late diastolic tissue velocity (a′) are usually present during each cardiac cycle and represent the intrinsic ability of the myocardium to relax actively during the early ventricular filling and the late atrial contraction filling. TDI use is suggested in combination with other modalities such as PWD mitral inflow velocities to assess the diastolic state and the estimation of LV filling pressure of patients.[27] (See the subsequent sections in this chapter on these topics.)

EQUIPMENT DESIGN AND OPERATION

TEE probes are a marvel of engineering. A miniaturized echocardiographic transducer (approximately 40 mm long, 13 mm wide, and 11 mm thick) is mounted on the tip of a gastroscope. Typically, the transducer is a phased-array configuration with 64 piezoelectric elements operating at 3.7 to 7.5 MHz. By sequential firing of the elements and an acoustic lens in the transducer housing, the ultrasound waves are formed into a 90-degree beam approximately 2 to 10 mm in thickness that emanates at right angles to the transducer. Similar to standard gastroscopes, two rotary knobs, or *wheel*s, control the movement of the tip

TABLE 46-3 **COMPARISON OF ADVANTAGES AND DISADVANTAGES OF DOPPLER MODALITIES**

Doppler Type	Advantages	Disadvantages	Clinical Uses
Pulse wave	Measures blood-flow velocities at selected areas of interest; 3-5 mm wide along the ultrasound scan line	Cannot measure fast blood-flow velocities (>1 m/sec) because of aliasing	Measures blood-flow velocities through pulmonary veins, mitral valve, and in low flow areas in the heart
Continuous wave	Detects blood-flow velocities up to 7 m/sec (not subject to the Nyquist limit)	Cannot identify the location of the peak velocity along the ultrasound scan line	Measures blood-flow velocities through the aorta, aortic valve, stenotic valve lesions, and regurgitant valvular jets
Color flow	Presents the spatial relationships between structure and blood flow	Similar to pulsed-wave Doppler, cannot measure fast blood-flow velocities because of aliasing	Enhances the recognition of valvular abnormalities, aortic dissections, and intracardiac shunts

of the scope. One wheel anteflexes and retroflexes the transducer (i.e., moves the transducer toward and away from the heart). The other wheel flexes the transducer rightward and leftward (Figure 46-14).

Currently, most multiplane transducers use the same transducer technology but mount the transducer on a rotating device that allows it to spin on its axis from 0 to 180 degrees within the tip of the gastroscope (transducer housing). Because cardiac structures and blood flow are not precisely aligned relative to the transducer, this design has significantly refined imaging capability. Matrix transducers accomplish the same rotation of the beam but do so electronically (i.e., without mechanically moving the transducer). The size of the probes have been decreased for pediatric applications by reducing the number of crystals and are now small enough for use in infants and neonates.

Ultrasonographs contain high-powered computers capable of initiating the ultrasound beam and processing the returning data. A series of electronic transforms (some guarded commercial secrets) produce the real-time images displayed on the video screen. All ultrasonographs share common technical aspects including gain, depth, and Doppler controls. However, the differences in technical aspects between manufacturers and even between models from the same manufacturer are sufficiently great as to prevent the formulation of any universal operating instructions. Fortunately, detailed instructions for each model are available in the operator's manual supplied with each ultrasonograph. Alternatively, cardiac sonographers are often excellent sources of instruction in the operation of these machines.

THREE-DIMENSIONAL IMAGING

Newer ultrasound machines offer the capability of producing 3-D images as recorded clips and as live 3-D images (also known as four-dimensional images with time being the fourth dimension). This technology represents a substantial jump in cardiac imaging, similar to the jump from M-mode to 2-D imaging in years past. Better visualization of heart valves, regurgitant valve lesions, cardiac chamber volumes (without geometric assumptions), regional wall motion, and 3-D stress imaging, among others, are some of the unique advantages of 3-D technology.[4]

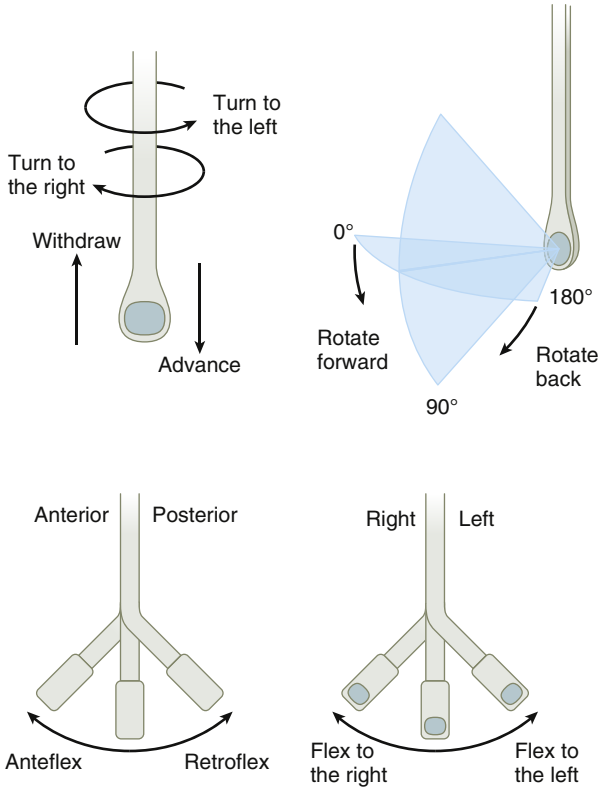


Figure 46-14. The terminology used to describe the movements of the transesophageal echocardiographic (TEE) probe is illustrated. *(Reproduced with permission from Shanewise JS, Cheung AT, Aronson S, et al: ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography,* Anesth Analg *89:870-884, 1999.)*

THREE-DIMENSIONAL TRANSDUCERS

Beyond a linear array of transducers as with a 2-D probe, a 3-D probe has a matrix array of transducers. A matrix array can have 2500 to 3000 piezoelectric crystals within one probe.[28] Significant advances in computer-processing speed, the miniaturization of the necessary electronics, and the software were required

to make this technology available. Transthoracic and transesophageal 3-D probes operate in 2 to 4 MHz and 5 to 7 MHz ranges, respectively. Imaging modes available with matrix array probes include multiplane, 3-D, and 4-D (3-D live).

MULTIPLANE IMAGING

Multiplane imaging mode simultaneously presents a set of 2-D images, typically two images. One image is a reference, whereas the second can be rotated around the first in an axial rotation or in an elevational rotation (Figure 46-15, *A-B*). CFD can be superimposed to these images. Although not a true 3-D image, this simultaneous presentation offers sonographers a depiction of a structure from multiple angles and views with CFD in real time.

THREE-DIMENSIONAL LIVE IMAGING—NARROW VOLUME MODE

Three-dimensional live imaging offers a 3-D image presented in real time (Figure 46-16, *A-B*) and interrogates a *narrow* sector pyramidal volume and is useful in diagnosing complex problems (i.e., partial rupture of mitral chordae tendineae). It consists of two narrow sector widths (i.e., 30 by 60 degrees). A disadvantage is that it is limited in the volume it can interrogate, which may not include the entire area of interest. Although this mode provides good temporal and spatial resolution, the sector widths (i.e., sides of the pyramidal volume) must remain narrow to maintain this resolution.

THREE-DIMENSIONAL LIVE IMAGING—ZOOM VOLUME MODE

Similar to 3-D live—narrow, 3-D live—zoom offers real-time interrogation of a *wide* sector pyramidal volume truncated by the zoom window with good temporal and spatial resolution (see Figure 46-16, *A-B*). This feature allows sonographers an additional option to capture real-time 3-D volumes of the cardiac structures not well visualized with narrow 3-D imaging.

THREE-DIMENSIONAL IMAGING—FULL-VOLUME MODE

Three-dimensional images—full-volume mode —are obtained using *gated* acquisition. Gated acquisition divides the acquisition volume into a set of subvolumes. To ensure that each subvolume is measured at the same time in the cardiac cycle, the R wave in the electrocardiogram (ECG) is used as a trigger. The operator determines the number of subvolumes (e.g., 3 to 8), and that number determines the number of heartbeats required to cover the entire pyramid volume. The full-volume image is *stitched* together from the subvolume images (Figure 46-17, *A-B*). Stitching artifacts may occur in patients with arrhythmias in which the R wave is difficult to track or with substantial changes in chamber size with respiration (Figure 46-18). This technique does not present images in real time.

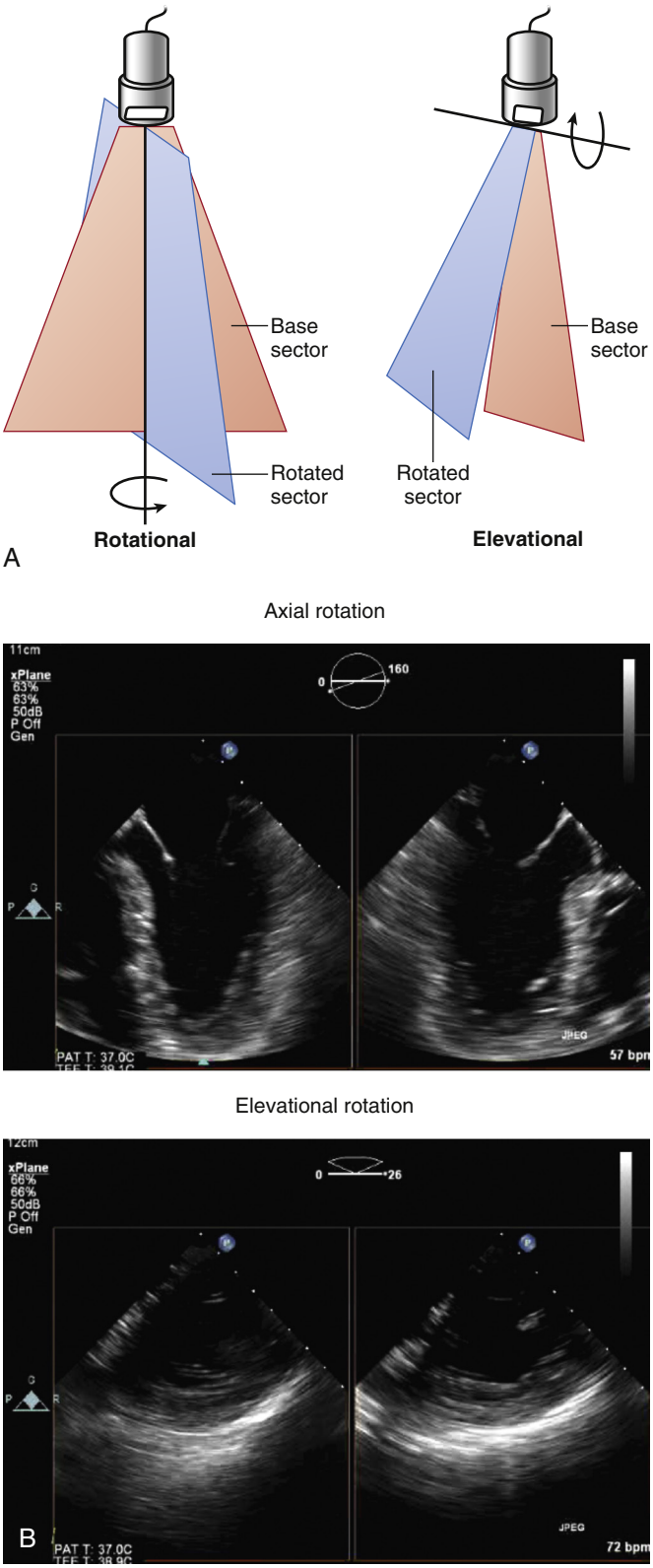
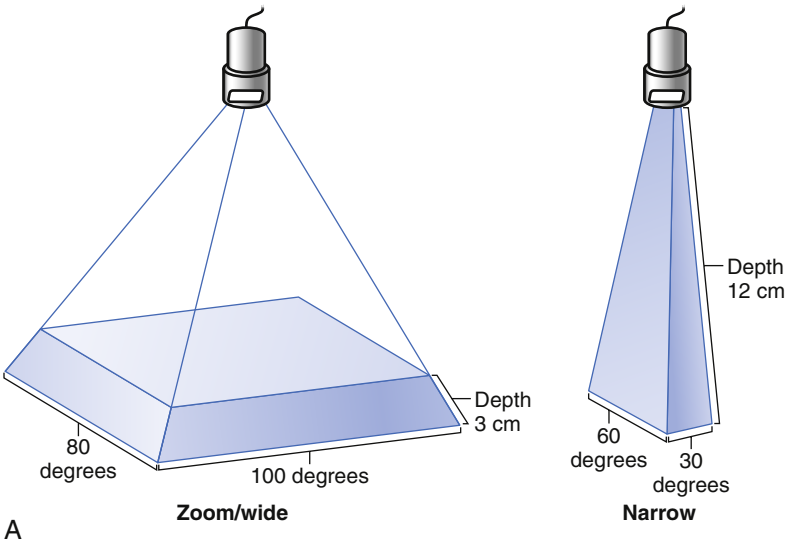


Figure 46-15. A, Rotational (*upper*) and elevational (*lower*) rotational biplane imaging are presented. *Red* and *blue* represent a schematic of the base and rotated sectors. **B,** Axial *(top)* and elevational (*bottom*) rotational biplane two-dimensional images. The base sectors *(left images)* and the rotated sectors *(right images)* are depicted. The *white dotted line* on each base sector image is the axis about which each secondary image is rotated.



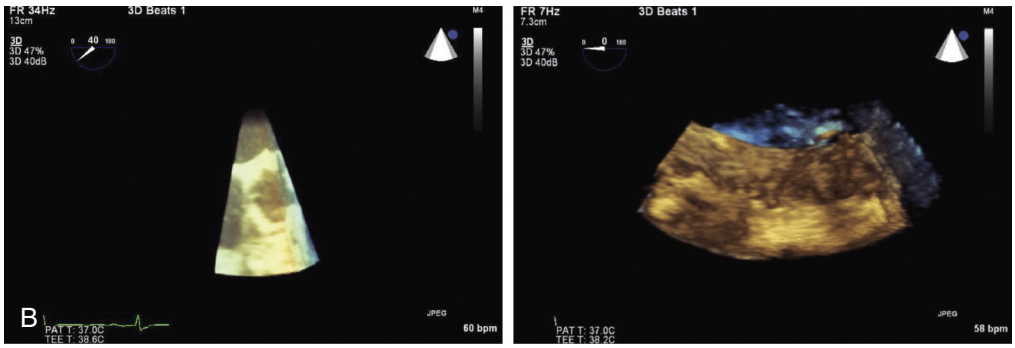


Figure 46-16. A, Three-dimensional (3-D) live images—zoom *(left)* and narrow *(right)* modes are demonstrated. A schematic of labeled sector widths and depth are each presented. **B,** 3-D live images of the mitral valve in the zoom mode and the aortic valve in the narrow mode are depicted.

COLOR-FLOW DOPPLER

As with 2-D imaging, CFD can be added to full-volume images but requires additional time to capture the Doppler information and superimpose it on the 3-D image. If using a real-time mode, then CFD may push the screen refresh frequency slower than 30 Hz, the frequency necessary for adequate temporal resolution in cardiac imaging. To minimize this limitation, pyramidal sector widths should be narrowed, depth reduced, or the zoom feature used to ensure an adequate screen refresh rate. Color Doppler can also be used in the 3-D full-volume mode. With the multiple subvolumes, the ultrasound machine will be able to display 3-D and color-flow data simultaneously. The same limitations of 3-D full-volume apply when color Doppler is added—imaging is not real time and images may suffer from the stitching artifact.

TEMPORAL VERSUS SPATIAL RESOLUTION

A major trade-off of the different 3-D imaging modes is between temporal and spatial resolution. Determinants of temporal resolution include pyramid width(s), image depth, and scan-line density. Spatial resolution is a function of the number of scan lines contained within a pyramid volume. High scan-line density, as observed with 2-D imaging, scans up to 128 lines in a 90-degree sector and provides good spatial resolution to visualize cardiac structures. When this scan-line density is implemented in three dimensions, however, large-volume imaging becomes impractical because the screen refresh rate drops well below 30 Hz, a necessary sampling rate to maintain adequate temporal resolution in cardiac imaging. Narrow and zoom (wide) modes are used in real-time 3-D imaging to maintain temporal resolution without decreasing the scan-line density and compromising spatial resolution.

Assuming the speed of ultrasound in tissue is 1540 m/sec, the influence of sector width(s) and pyramid volume, depth, and scan-line density on estimates of temporal resolution for various modes are presented in Table 46-4. Ultrasound machines use parallel processing to improve temporal resolution. This method acquires reflected ultrasound waves along multiple scan lines from a single transmission down one scan line. With this technique, ultrasound machines can achieve faster screen refresh rates. When used at extremes (i.e., the single transmission beam is far away from the receiving scan line), the signal-to-noise ratio decreases and the image quality deteriorates. Of note, the biplane mode offers the best spatial and temporal resolution yet does not offer true 3-D imaging. The trade-offs between spatial and temporal resolutions are evident between narrow and zoom versus full-volume imaging.

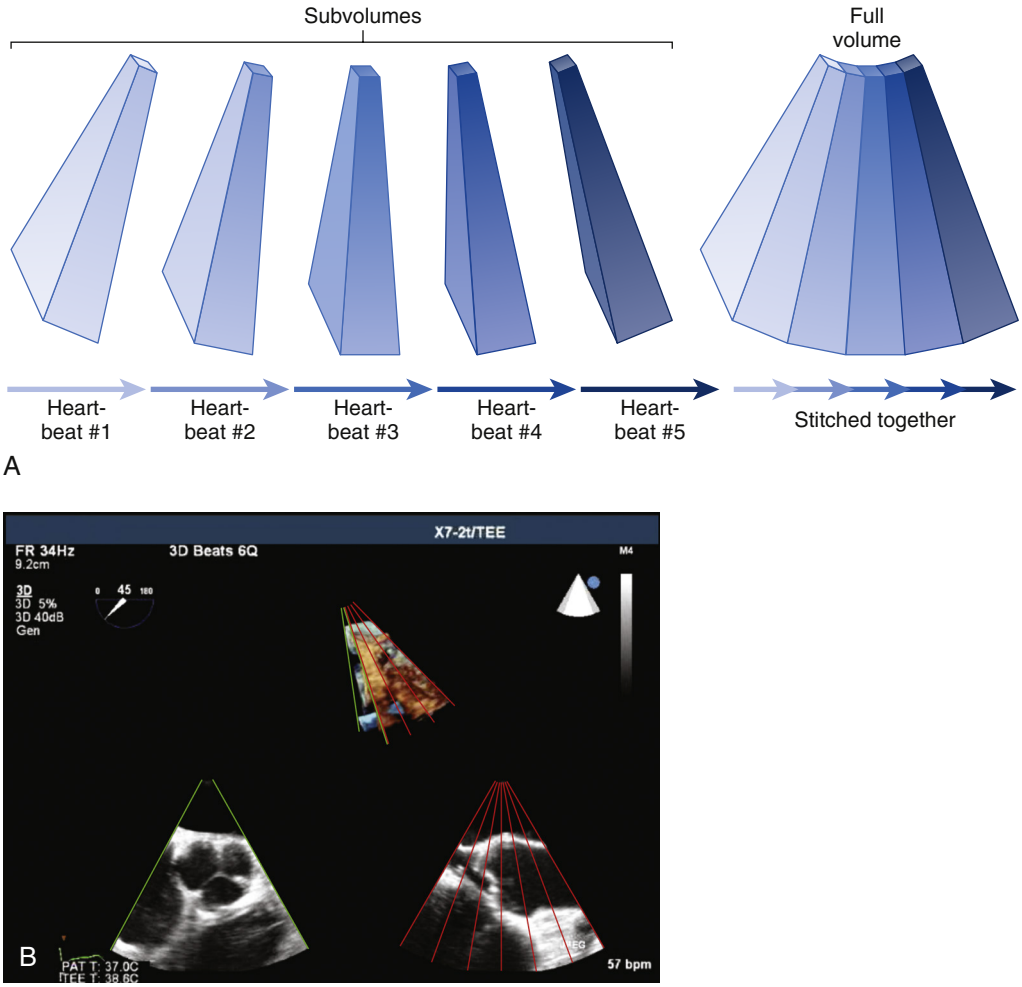


Figure 46-17. A, A schematic of a gated acquisition of a full-volume three-dimensional (3-D) image is depicted. Subvolumes are scanned in series using the R wave of the electrocardiogram as a trigger to scan each subvolume. The subvolumes are then stitched together to form the full-volume image. **B,** Subvolumes are created from a two-dimensional image by dividing up the image into seven subvolumes *(white lines)* to create a full-volume 3-D image.

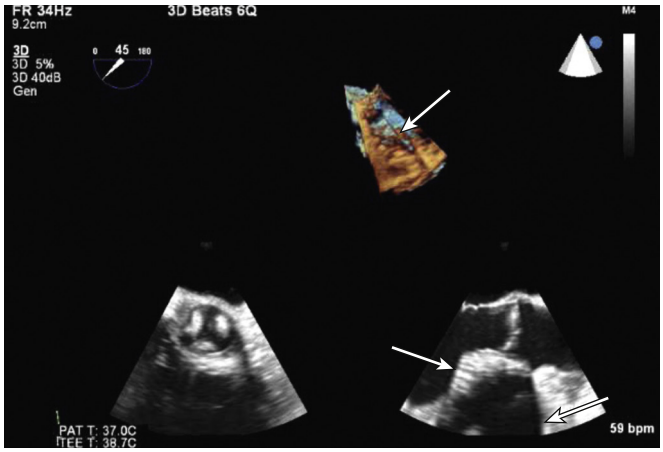


Figure 46-18. Full-volume image of the aortic valve with stitching artifact is demonstrated. Discontinuity is indicated along scan lines *(arrows)*.

THREE-DIMENSIONAL IMAGE MANIPULATION

One advantage of 3-D imaging (all modes) is that they can be rotated to visualize structures from various angles. Echocardiographers are not limited to 2-D images that may not capture an entire structure of interest at an angle best suited to interrogate it fully. A popular view is to rotate a 3-D image to visualize structures *en face*. This head-on view offers diagnostic advantages. For example, when exploring the function of a mitral valve or an aortic valve (AV) (Fig. 46-19), this feature provides visualization of spatial relationships that, in 2-D imaging, requires an often-complex spatial reconstruction in the mind of the echocardiographer. Three-dimensional images also provide a means to work through the image in a *sliced bread* fashion. Part or all of the heart can be explored in sagittal- and coronal-plane fashion.

When transitioning from 2-D to 3-D imaging, echocardiographers must conceptually move from considering the heart in various slices to a 3-D organ, much the way a surgeon does. To visualize structures deep within the

TABLE 46-4 **IMAGE REFRESH RATES FOR VARIOUS TWO-DIMENSIONAL AND THREE-DIMENSIONAL IMAGING MODES**

Mode	Depth (cm)	Scan-Line Density (Lines per Degree)	Sector Width(s) (in Degrees)	Image Refresh Rate (Hz)
Two dimension	12	High	90	50
Biplane	10	High	90 × 90	30
Three-dimension—narrow	10	Low	30 × 30	24
Three-dimension—zoom (wide)	3	Low	90 × 30	19
Full volume	12	High	90 × 90	<1
Full volume	12	Low	90 × 90	5

The values displayed are simulations and assume the speed of the ultrasound in tissue to be 1540 m/sec. Low and high scan-line densities were assumed to be 0.4 and 1.4 scan lines per degree of the scanned image.

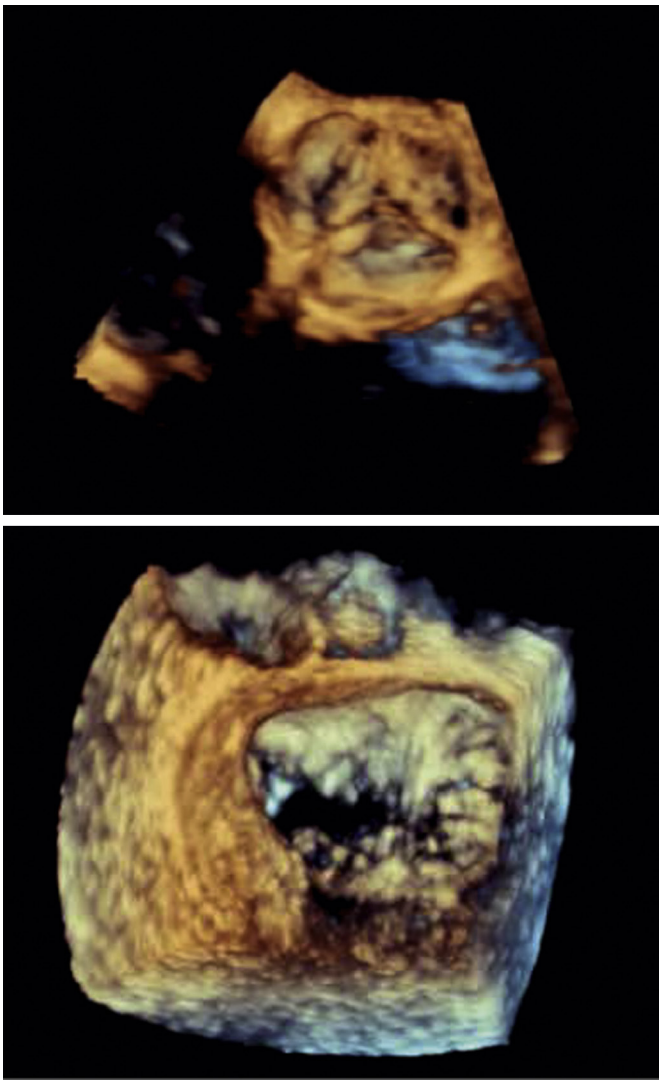


Figure 46-19. En face views of the aortic *(top)* and mitral *(bottom)* valves.

heart, more superficial structures are pealed back. Echocardiographers can cut out superficial structures to visualize internal ones by using a *cropping* tool. For example, to visualize the intraatrial septum in three dimensions, the lateral atrial walls are cropped out.

PIXEL AND VOXEL

From each scan line, reflected ultrasound is used to create an image. With 2-D, a grey scale is used to represent the amplitude of a reflected ultrasound wave from a portion of a scan line and assigned to a corresponding small space on a projected image called a *pixel*. A composite of pixels makes up the 2-D image. A similar process is used to assign small volumes according to a grey scale called a *voxel*.

BASIC TRANSESOPHAGEAL ECHOCARDIOGRAPHIC EXAMINATION

Before performing TEE, the operator must determine that the benefits of TEE outweigh the risks. Except in the presence of esophageal disease or injury, the risk is quite low. Absolute contraindications include prior esophagectomy, severe esophageal obstruction, esophageal perforation, and ongoing esophageal hemorrhage. Relative contraindications include esophageal diverticulum, varices, fistula, and prior esophageal surgery, as well as a history of a gastric surgery, mediastinal irradiation, unexplained swallowing difficulties, and other conditions that might worsen with the placement and manipulation of the TEE probe.

In some studies, TEE has been associated with an infrequent incidence of oral and pharyngeal injuries (0.1% to 0.3%), but in other studies, the incidence of postoperative gastrointestinal complaints did not significantly differ from that in comparable patients who had not undergone TEE.[29,30] The reported incidence of transient hoarseness after TEE is 0.1% to 12% in uncontrolled studies. Serious pharyngeal or esophageal injury after TEE has been reported but is rare.[31] Two case reports indicate the possibility of TEE-associated splenic injury.[32,33] Among 10,218 patients (in a multicenter European study) undergoing TEE (primarily outpatients), esophageal perforation occurred in one who subsequently died; the autopsy revealed a malignant tumor invading the esophagus.[34] Although bacteremia during TEE is uncommon, endocarditis has been reported in outpatients.[35,36] Endocarditis from intraoperative TEE has not been reported, and the risk is probably near zero because antibiotics are usually administered for the prevention of surgical wound infection. In infants, TEE has a low complication rate, but even an appropriate-sized TEE probe may obstruct the airway

distal to the endotracheal tube or compress the descending aorta[37] (also see Chapter 94).

Once the patient is anesthetized and the trachea securely intubated, the contents of the stomach should be removed by gentle suctioning. Gentle massage of the left upper quadrant of the abdomen during suctioning may help remove air that can otherwise degrade imaging. The patient's neck is extended, and the well-lubricated TEE probe is then introduced into the midline of the hypopharynx with the transducer side facing anteriorly. Usually, with minimal force, the probe will blindly pass into the esophagus, especially if the neck is extended. If the probe does not blindly pass, then a laryngoscope is used to lift the larynx anteriorly and the probe is placed into the esophagus under direct vision. During transducer insertion or withdrawal, the controls of the gastroscope must be in the neutral or relaxed position to allow the transducer to follow the natural course of the esophagus, thereby potentially minimizing the risk of injury.

Because of time constraints and relatively narrow diagnostic goals, anesthesiologists often perform a more limited intraoperative examination than described in the ASE/SCA's taskforce recommendation for a comprehensive TEE examination (see section, "Transesophageal Echocardiography Practice Guidelines" earlier in this chapter).[8,38] However, even when time is critical, the examination performed should allow at least the basic applications of TEE as outlined in the original guidelines for perioperative TEE, that is, to detect significant abnormal ventricular filling or function, extensive myocardial ischemia or infarction, large air embolism, severe valvular dysfunction, large cardiac masses or thrombi, large pericardial effusions, and major lesions of the great vessels.[6] A minimum of 8 different cross sections drawn from the 20 cross sections delineated in the comprehensive examination are required to meet these diagnostic goals. Four of the cross sections are imaged in both 2-D and color Doppler imaging to assess valvular function. The next paragraph describes the probe manipulations required to achieve these cross sections. (A review of Figure 46-14 is recommended to understand the terms used in the following description.)

After the TEE probe is safely introduced into the esophagus, it is advanced to the midesophageal (ME) level (28 to 32 cm measured at the upper incisors), and the AV is imaged in the short axis (SAX) by turning the probe, adjusting its depth in the esophagus, and rotating the multiplane transducer 25 to 45 degrees until the three cusps of the valve appear approximately equal in size and shape (Figure 46-20, *H*). Image depth is set at 10 to12 cm as required to position the AV in the center of the video screen. This cross section is ideal for the detection of aortic stenosis. This and all the subsequent cross sections are digitally recorded. Next, the probe is slightly turned to position the AV in the center of the video screen, and then the multiplane angle is rotated forward to 110 to 130 degrees to bring the long axis (LAX) of the AV in view (Figure 46-20, *I*). This cross section is best for the detection of ascending aortic abnormalities including type I aortic dissection. Color Doppler is used for the assessment of AV competence. For the detection of valvular stenosis and regurgitation, the Nyquist limit is set to 50 to 60 cm/sec.[39] Next, the Doppler is discontinued and the probe is turned rightward until the ME bicaval cross section comes into view (Figure 46-20, *L*). This cross section is usually best observed at a multiplane angle between 90 and 110 degrees and is ideal for assessing caval abnormalities, as well as compression of the right atrium from anteriorly located masses or effusions and the left atrium from posteriorly located masses or effusions. In addition, the bicaval cross section may reveal collections of air anteriorly located in the left or right atrium, as well as the structure of the interatrial septum including the foramen ovale. Next, the multiplane angle is rotated back to 60 to 80 degrees and the probe is turned leftward just past the AV to bring the ME right ventricular (RV) inflow and outflow cross section into view (Figure 46-20, *M*). Usually, an image depth of 12 to 14 cm is required to position the RV outflow track (RVOT) in the center of the video screen. This cross section reveals the contractile function of the RV, the RVOT, and the pulmonary valve function with the application of color Doppler. Next, the transducer is rotated back to 0 degrees, the probe is advanced 4 to 6 mm into the esophagus and gently retroflexed until all four cardiac chambers are visualized (ME four-chamber cross section) (Figure 46-20, *A*). Often, rotating the transducer 10 to 15 degrees enhances the view of the tricuspid annulus. Usually, an image depth of 14 to 16 cm is required to include the LV apex in the sector scan. In 2-D imaging, the free wall of the right ventricle and the lateral and septal LV wall segments are evaluated for contractile function. With color Doppler, both the mitral and tricuspid valves are assessed. Stenotic and regurgitant lesions can be accurately diagnosed. During this assessment, the image depth is decreased to 10 to 12 cm to afford a magnified view of the valves and color Doppler flow patterns. Next, color Doppler is discontinued, the left ventricle is positioned in the center of the screen, and the multiplane angle is rotated forward to 90 degrees to bring into view the ME two-chamber cross section (Figure 46-20, *B*). The image depth is returned to 14 to 16 cm. This cross section is best for revealing the function of the basal and apical segments of the anterior and inferior LV walls, as well as the anterior and inferior pericardial collections. When air emboli collect in the left ventricle, they can usually be best observed in this view as very echogenic areas located along the anterior apical endocardial surface. Then, the transducer is rotated forward to 135 degrees to reveal the ME LAX cross section, which is best for an assessment of the anteroseptal and posterior wall segments for contractile LV function (Figure 46-20, *C*). Together, the ME four-chamber, two-chamber, and LAX cross sections reveal all 17 segments of the left ventricle (Figure 46-21). However, the next and last of the basic cross sections provides a second look at the midventricular segments, as well as other benefits. To achieve this cross section, the transducer is rotated back to 0 degrees, the left ventricle is centered in the screen, and the probe is advanced 4 to 6 cm into the stomach. Then, it is gently flexed anteriorly to reveal the transgastric (TG) SAX cross section (Figure 46-20, *D*). This cross section is ideal for monitoring LV filling and contractile function. All major coronary arteries supplying the myocardium are viewed in this cross section. Moreover, changes in preload cause greater changes in the LV SAX cross section than in the LAX dimension, and

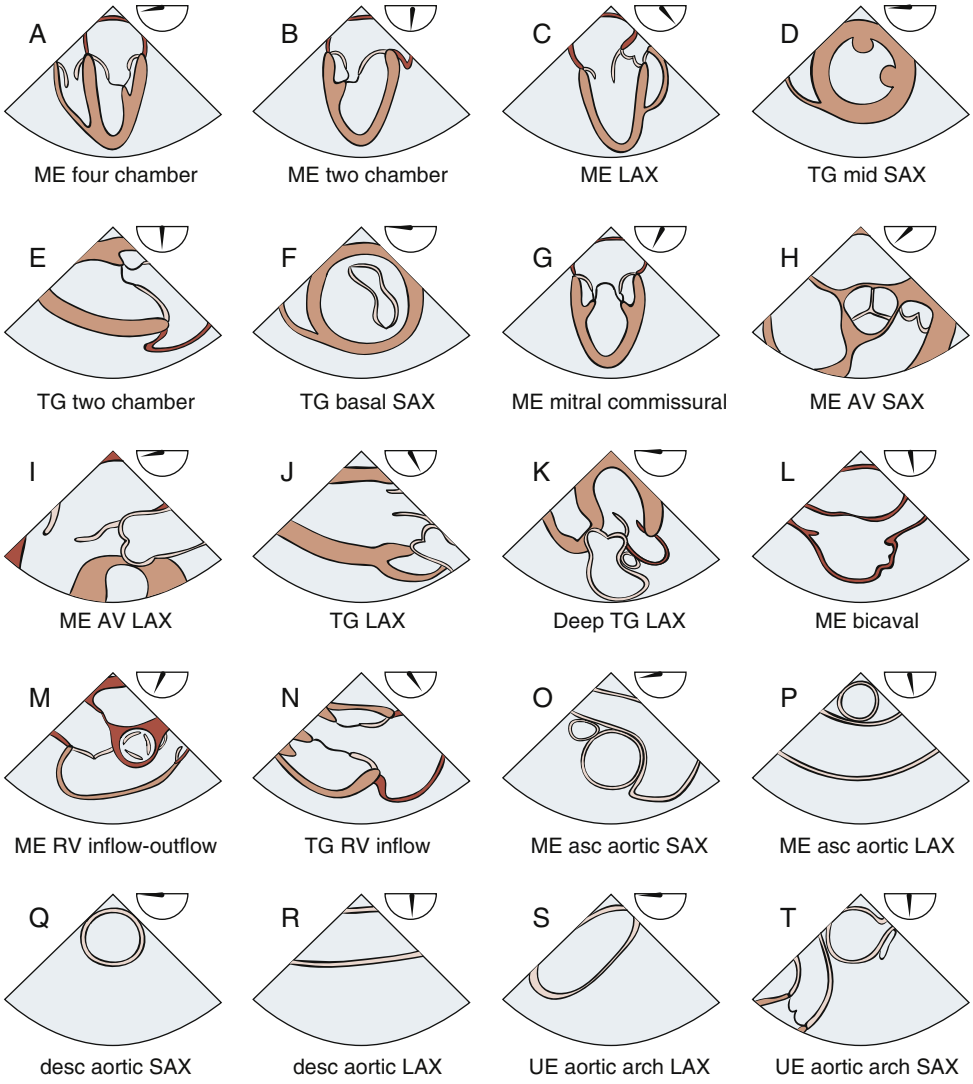


Figure 46-20. Transesophageal echocardiographic (TEE) cross sections in the comprehensive examination. Twenty standard cross sections and their abbreviated names are depicted by the line drawings. The text describes the probe manipulations required to produce each of the cross sections. *asc,* Ascending; *AV,* aortic valve; *desc,* descending; *LAX,* long axis; *ME,* midesophageal; *RV,* right ventricle; *SAX,* short axis; *TG,* transgastric; *UE,* upper esophageal. *(Reproduced with permission from Shanewise JS, Cheung AT, Aronson S. et al: ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography,* Anesth Analg *89:870-884, 1999.)*

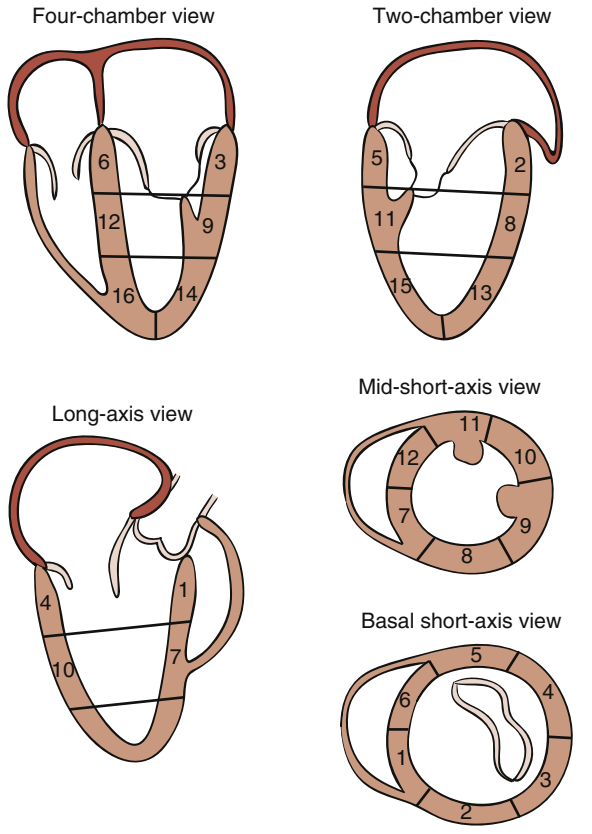
movement of the probe from this cross section is readily apparent because the papillary muscles provide prominent landmarks. Because this cross section is used to judge filling and ejection, the image depth is consistently set to 12 cm to enable the size and function of the heart to be easily judged relative to previously examined hearts.

In the authors' practice, one additional cross section is imaged in all patients as a part of the basic examination: the descending aorta in SAX (Figure 46-20, *Q*). The reason for this addition is the wealth of vital information this cross section can provide on the relative severity of atherosclerosis and the presence or absence of aortic dissection. (See the next section for a description of the technique required to image this cross section.)

COMPREHENSIVE TRANSESOPHAGEAL EXAMINATION

In addition to the 9 cross sections described in the preceding paragraph, 11 other cross sections are required to complete the comprehensive perioperative TEE examination delineated in the 1999 ASE/SCA taskforce recommendations.[8] When time permits or the diagnostic questions require, the comprehensive examination can be completed in any order deemed most appropriate by the operator. Shanewise and associates have described an examination sequence based on anatomic structures, and the reader is referred to this very detailed reference for an excellent approach.[8] However, when a single individual is responsible for anesthetic care and TEE, the comprehensive examination is completed as time permits after the basic examination has been recorded. When this is the case, the operator can use 3 of the 9 basic cross sections as take-off points for the other 11 cross sections, making the completion of the comprehensive examination a relatively easy sequence to remember and quick to perform.

With the probe positioned for the AV SAX cross section, the other six cross sections of the aorta are easily achieved. First, the probe is withdrawn slowly 1 to 3 cm, keeping the aorta in the center of the video screen to view the ascending aorta in SAX (Figure 46-20, *O*). As the probe is withdrawn, the operator views progressively more superior SAX cross sections of the aorta beginning with the sinotubular junction until the image is lost because of the interposition of the trachea between the esophagus and the aorta. Next, the multiplane angle is rotated



Basal Segments	Mid Segments	Apical Segments
1 = Basal anteroseptal	7 = Mid anteroseptal	13 = Apical anterior
2 = Basal anterior	8 = Mid anterior	14 = Apical lateral
3 = Basal lateral	9 = Mid lateral	15 = Apical inferior
4 = Basal posterior	10 = Mid posterior	16 = Apical septal
5 = Basal inferior	11 = Mid inferior	
6 = Basal septal	12 = Mid septal	

Figure 46-21. Five transesophageal echocardiographic (TEE) cross sections are presented with myocardial segments identified. A total of 16 myocardial segments are identified and named according to the standards adopted by the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. *(Reproduced with permission from Shanewise JS, Cheung AT, Aronson S, et al: ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography,* Anesth Analg *89:870-884, 1999. Since the time of this publication, a 17th segment has been added to the model, consisting of the apical tip of the left ventricle.)*

forward to 100 to 120 degrees and advanced slowly 1 to 3 cm, keeping the aorta in the center of the video screen to view the ascending aorta in LAX (Figure 46-20, *P*). These two cross sections are ideal for the pathologic assessment of the ascending aorta including type I aortic dissection and aortic atheromas. However, the most superior aspect of the aorta is rarely seen, including the take-off of the innominate artery because of the tracheal interposition previously noted. Next, the transducer is returned to 0 degrees, the image depth is decreased to 6 cm, and the probe is turned leftward past the cardiac structures to reveal the descending aorta in SAX (see Figure 46-20, *Q*). The probe is withdrawn and advanced with the aorta maintained in the center of the screen until the entire descending aorta has been examined in SAX. This maneuver is repeated with the transducer at 90 degrees to examine the descending aorta in LAX (Figure 46-20, *R*). Next, the transducer is returned to 0 degrees and the probe withdrawn until the distal (upper esophageal) aortic arch in LAX comes into view (Figure 46-20, *S*). Rotating the transducer to 90 degrees reveals the distal (upper esophageal) arch in SAX (Figure 46-20, *T*). The probe is turned leftward until the aorta just disappears from view and then is slowly turned rightward to identify the take-off of the left subclavian artery (well seen in most patients) and the left carotid artery (well seen in a minority of patients). These cross sections of the descending aorta and distal aortic arch reliably reveal dissections and atheromatous disease.

With the probe positioned for the ME four-chamber cross section, the ME mitral commissural cross section is easily achieved by positioning the coaptation point of the mitral valve in the center of the video screen and rotating the multiplane angle forward to approximately 60 degrees (Figure 46-20, *G*). This maneuver positions the ultrasound beam parallel to the closure line of the mitral leaflets and completes the LAX examination of the mitral valve. Although a detailed discussion of the mitral leaflet structure and function is beyond the scope of this chapter, Figure 46-22 summarizes an excellent approach to this challenging task.[40]

With the probe positioned for the TG mid-SAX cross section, the remaining five cross sections of the comprehensive examination are easily achieved in most patients. First, the left ventricle is centered in the video screen, and the multiplane angle is rotated forward to 90 degrees to reveal the TG two-chamber cross section (Figure 46-20, *E*). Although this cross section reveals the same structures as the ME two-chamber cross section, the viewing angle is orthogonal to the former viewing angle, and, as a result, subvalvular structures are better revealed. Next, the transducer is rotated to 100 to 120 degrees to reveal the TG LAX cross section (Figure 46-20, *J*). Again, this cross section reveals the same structures as the ME LAX dimension, but the TG LAX permits a more parallel alignment of the ultrasound beam with blood flow through the LV outflow track (LVOT) and AV. Next, the TG RV inflow cross section is achieved by returning the probe to the TG mid-SAX position, turning it rightward until the right ventricle is centered in the video screen, and then rotating the multiplane angle to 100 to 120 degrees to bring the RV apex into view (Figure 46-20, *N*). This cross section is ideal for viewing the RV inferior free wall. Next, the TG basal SAX is achieved by returning the probe to the TG mid-SAX dimension, releasing the flexion of the probe, withdrawing 1 to 2 cm, and then gently flexing the probe until the orifice of the mitral valve is seen in the SAX cross section (Figure 46-2, *F*). This cross section can prove vital in determining the precise location of mitral regurgitation.[40] Finally, the deep TG LAX cross section is achieved by returning the probe to the TG mid-SAX position, releasing the flexion of the probe, advancing it 6 to 8 cm into the stomach, fully flexing it once in the stomach, gently withdrawing it until minimal resistance is met at the gastroesophageal junction, and then slightly turning

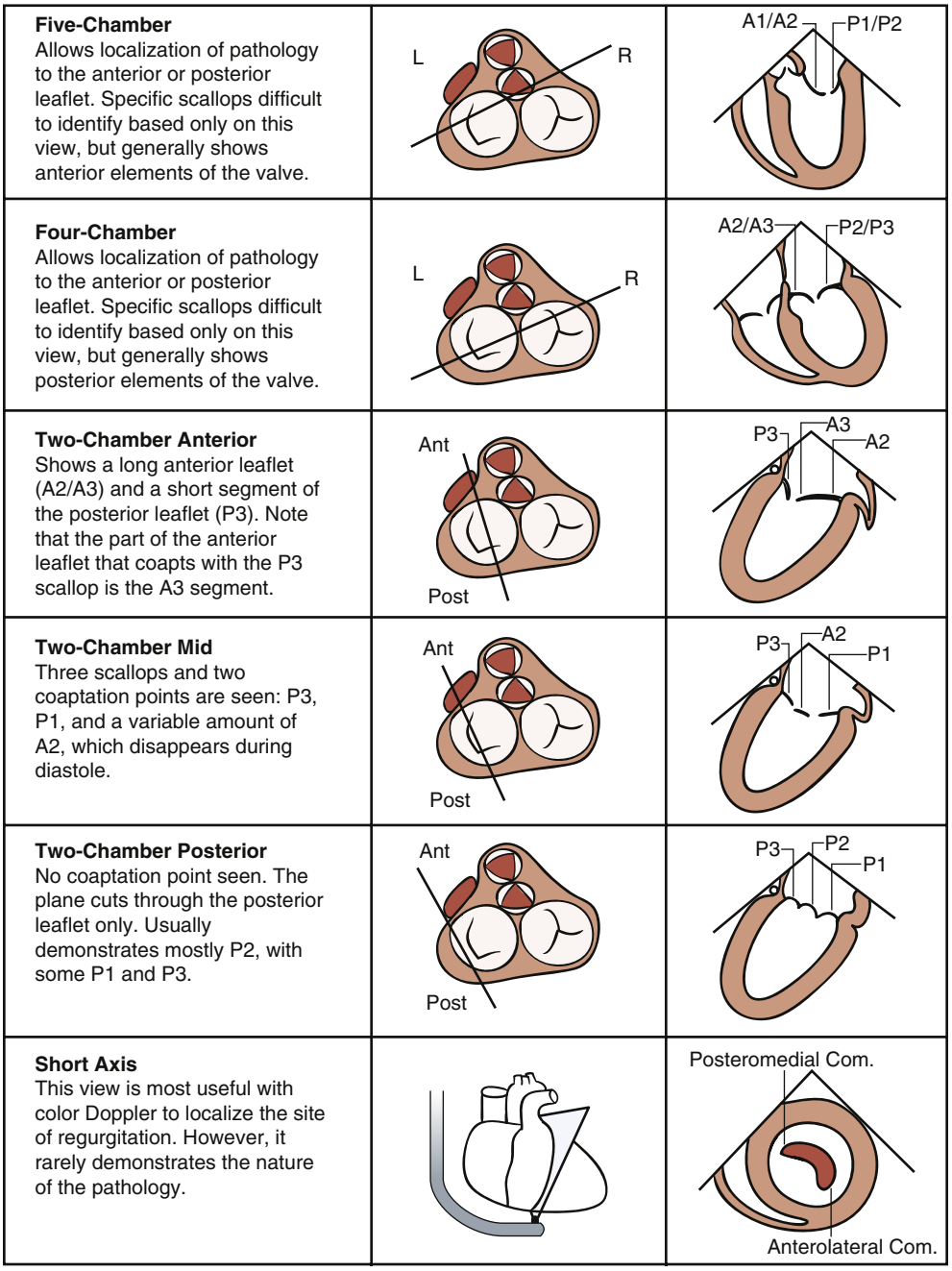


Figure 46-22. A systematic examination of the mitral valve is depicted. In this examination, the mitral valve is viewed in multiple cross sections to delineate the leaflet anatomy. The five-chamber cross section is accomplished by slightly withdrawing the probe from the standard four-chamber cross section until the left ventricular outflow track is in view. The *center column* shows the planes of the different cross sections as viewed from directly above the base of the heart. The two-chamber anterior, mid, and posterior cross sections are variations on the standard two-chamber cross section accomplished by turning the probe from the patient's right to left. P1, P2, and P3 refer to the three scallops of the posterior mitral leaflet, and A1, A2, and A3 refer to the juxtaposed segments of the anterior mitral leaflet. The *right column* shows the leaflet segments seen in the corresponding cross section. *(Reproduced with permission from Lambert AS, Miller JP, Foster E, et al: Improved evaluation of the location and mechanism of mitral valve regurgitation with a systematic transesophageal echocardiography examination,* Anesth Analg *88:1205-1212, 1999.)*

it leftward or rightward to reveal the LVOT and AV (Fig. 46-20, *K*). Usually this cross section does not resolve structures as well as the ME LAX cross section, but it does provide optimal beam alignment for Doppler interrogation of the LVOT outflow track and AV. Frequently, this cross section is the most difficult of the cross sections to achieve. If a few gentle attempts fail to accomplish it, it should be abandoned.

BASIC TRANSTHORACIC EXAMINATION

In patients with an unsecured airway, TTE is easier to perform than TEE because TTE is entirely noninvasive. TTE uses lower frequencies (1 to 3 MHz) than TEE to penetrate the greater distances inherent in the transthoracic technique, but all previously discussed modalities (M-mode, spectral Doppler, color Doppler, and TDI) can

be performed with TTE. Transthoracic cardiac probes are significantly different than the linear probes used to identify superficial vascular structures and nerve bundles. Thus, the probes used for ultrasound-guided nerve blocks and vascular access are not appropriate for TTE. TTE uses three standard *windows* (soft-tissue points that avoid boney interpositions between the transducer and heart): parasternal (PS), apical (AP), and subcostal (SC). The next paragraphs describe the probe manipulations required at these windows to achieve the TTE cross sections.

The examination begins with the patient turned halfway onto the left side with the left arm elevated alongside the head. Optimal imaging requires ultrasound gel between the probe and chest wall. Patients should be warned of the cold sensation of the gel on their skin. The PS long-axis (PS LAX) cross section is acquired first (Figure 46-23) by placing the probe on the left side of the sternum at the level of the fourth intercostal space and directing the ultrasound beam toward the patient's right shoulder. Appropriate adjustment of the image depth (15 to 18 cm), rotation, and angulation of the transducer reveals a small triangular segment of the right ventricle on the upper section of the display and the left ventricle chamber, left atrium, and aortic root in the middle section of the display. This cross section shows the same tomographic view as the ME LAX described in the TEE examination (see Figure 46-20, *C*). Similar to the ME LAX cross section, the PS LAX cross section permits an assessment of the structure and function of the AV, mitral valve, and the basal segments of the anteroseptum and posterior wall of the left ventricle. Sclerocalcific changes of the AV and reduction of the cusps excursion are demonstrated with aortic stenosis. Reduction of motion of the anterior leaflet of the mitral valve during diastole can be an indicator of mitral stenosis, LV dilation, LV dysfunction, elevated filling pressure, or any combination of these pathologic conditions. In this cross section, color Doppler allows the diagnosis of stenotic and regurgitant lesions of both atrioventricular valves. Next, the PS short-axis (PS SAX) cross section is obtained (Figure 46-24) by rotating the transducer 90 degrees clockwise and inferiorly angulating it toward the left hip until the right ventricle appears as a crescent-shaped structure at the top of the display and the left ventricle in the SAX is viewed at the bottom. This cross section shows the same tomographic view as the TG SAX described in the TEE examination (see Figure 46-20, *D*). In the absence of segmental dysfunction in the AP or basal segments of the heart, left and right ventricle sizes and contractile function can be accurately assessed from the PS SAX cross section.

The next cross sections are acquired from the AP window by placing the transducer in the fourth or fifth intercostal space lateral to the nipple line with the transducer marker (the notch or other landmark on the transducer indicating beam orientation) pointing toward the floor. Appropriate adjustment of the rotation and angulation of the transducer reveals the AP four-chamber (AP-4C) cross section (Figure 46-25) with the apex of the heart on the top of the display and the right and left atria on the bottom. This cross section shows the same tomographic view as the ME four-chamber described in the TEE examination (see Figure 46-20, *A*). The AP-4C cross section reveals the size

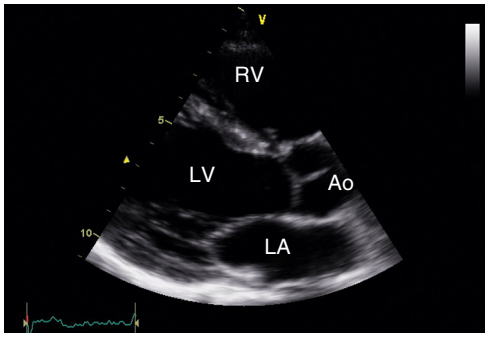


Figure 46-23. A transthoracic parasternal long-axis (PS-LAX), two-dimensional cross section of a normal heart is shown. This cross section reveals a small triangular segment of the right ventricle (RV) on the upper section of the display and the left ventricle (LV) chamber, the left atrium (LA), and the aortic (Ao) root in the middle section of the display. This cross section shows the same tomographic view as the midesophageal long-axis (ME LAX) cross section described in the transesophageal echocardiographic (TEE) examination (see Figure 46-20, *C*).

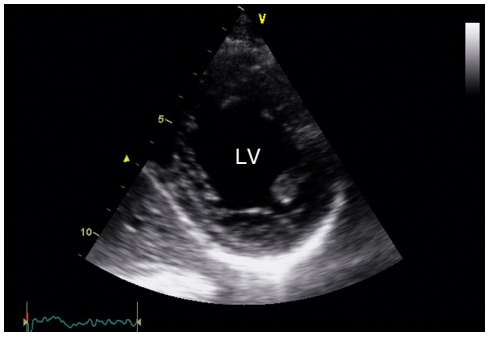


Figure 46-24. A transthoracic parasternal short-axis (PS-SAX), two-dimensional cross section of a normal heart is shown. This cross section reveals a small part of the crescent-shaped right ventricle at the top of the display and the left ventricle (LV) in the short-axis view in the rest of the image. This cross section shows the same tomographic view as the transgastric short-axis (TG SAX) view described in the transesophageal echocardiographic (TEE) examination (see Figure 46-20, *D*).

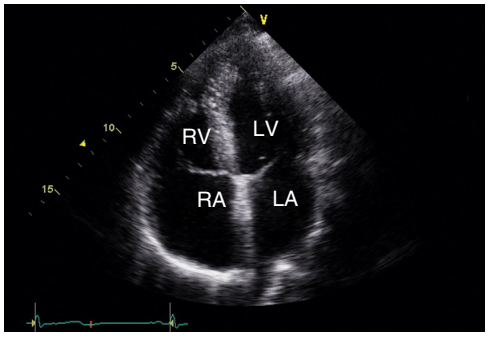


Figure 46-25. A transthoracic apical four-chamber (AP-4C), two-dimensional cross section of a normal heart is shown. This cross section reveals the apex of the heart on the top of the display and the right atrium (RA) and the left atrium (LA) on the bottom. This cross section shows the same tomographic view as the midesophageal four-chamber view described in the transesophageal echocardiographic (TEE) examination (see Figure 46-20, *A*). *LV,* Left ventricle; *RV,* right ventricle.

and global contraction of the ventricles, as well as the segmental function of their lateral walls and interventricular septum. Color Doppler of the tricuspid and mitral valves facilitates the diagnosis of valvular stenosis and regurgitation. In addition, the right upper pulmonary vein is visualized, and PWD estimates of the flow in this vein can help in fluid management (see subsequent sections on "Assessment of Ventricular Filling" and "Assessment of Ventricular Diastolic Function"). The next cross section is the AP two-chamber (AP-2C) view, which is acquired by rotating the transducer counterclockwise 60 degrees (Figure 46-26). This cross section shows the same tomographic view as the ME two-chamber described in the TEE examination and reveals segmental function of the anterior and inferior walls of the left ventricle (see Figure 46-20, *B*). The last AP cross section is the AP long-axis (AP LAX) view (Figure 46-27), which is obtained by rotating the transducer counterclockwise another 60 degrees until the LV outflow tract and AV are revealed in the bottom of the display. This cross section shows the same tomographic view as the ME LAX described in the TEE examination (see Figure 46-20, *C*). The AP-LAX provides an ideal vantage point for Doppler quantification of aortic stenosis and regurgitation because of the parallel direction of the ultrasound beam and blood flow.

The last two cross sections are acquired from the SC window with the patient in the supine position. The transducer is positioned flat under the right costal ridge next to the xiphoid appendix pointing toward the patient's left shoulder with the transducer marker pointing leftward. The SC four-chamber (SC-4C) view is seen (Figure 46-28) with the upper third of the display occupied by the liver and the heart below. RV free wall contractility and hemodynamically significant pericardial effusion are assessed best from this view. Finally, the SC inferior vena cava (SC IVC) cross section is obtained by rotating the transducer counterclockwise 90 degrees (Figure 46-29). The inferior vena cava (IVC) is demonstrated on the left side of the display as a rectangular echolucent structure inside the liver connecting to the right atrium. This view allows an assessment of the right-sided filling pressure by evaluating the size and collapsibility of the IVC in spontaneously breathing patients.[41]

When TEE is impracticable and cardiovascular status must be reliably evaluated, these basic TTE cross sections can provide most of the same information as TEE provides, thereby extending the benefits of echocardiography to many more surgical and critical care patients than when only TEE is available. The authors of this text predict that TTE will become the stethoscope of the future for anesthesiologists and other perioperative physicians who regularly care for patients who are critically ill. Already, residency programs in anesthesiology are incorporating TTE and TEE into their curriculum.[42,43] In addition, recent studies confirm the safety and value of noncardiologist physicians performing and interpreting TTE in the emergency department, during the perioperative period, and in the intensive care unit.[44-49]

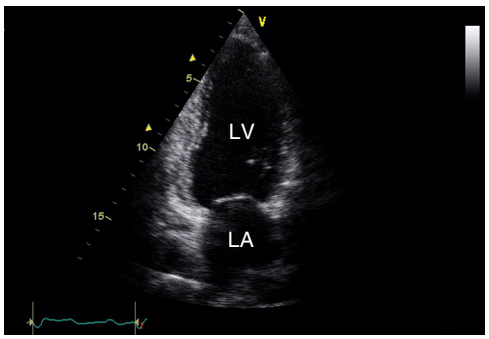


Figure 46-26. A transthoracic apical two-chamber (AP-2C), two-dimensional cross section of a normal heart is shown. This cross section reveals the left ventricle (LV) on the top (apex) and middle of the display and the left atrium (LA) on the bottom. This cross section shows the same tomographic view as the midesophageal two-chamber view described in the transesophageal echocardiographic (TEE) examination (see Figure 46-20, *B*).

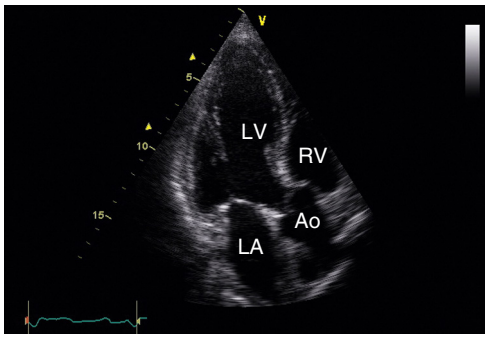


Figure 46-27. A transthoracic apical long-axis (AP-LAX), two-dimensional cross section of a normal heart is shown. This cross section reveals the left ventricle (LV) at the top (apex) and middle of the display and the left ventricular outflow tract and aortic valve (Ao) at the bottom of the display. This cross section shows the same tomographic view as the midesophageal long-axis (ME LAX) view described in the transesophageal echocardiographic (TEE) examination (see Figure 46-20, *C*). *LA,* Left atrium; *RV,* right ventricle.

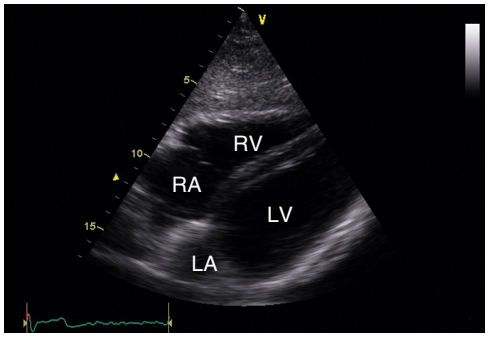


Figure 46-28. A transthoracic subcostal four-chamber (SC-4C), two-dimensional cross section of a normal heart is shown. The liver occupies the upper third of the display and the heart the lower two thirds. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

ASSESSMENT OF VENTRICULAR FILLING

TEE reveals changes in LV preload more reliably than filling pressures. In 30 patients scheduled for cardiac surgery, Cheung and associates removed 15% of each patient's blood volume in six equal aliquots before bypass surgery.[50] TEE demonstrated a significant decrease in cross-sectional area at end diastole after the removal of the first aliquot (approximately 200 mL) and a linear decrease with subsequent aliquots. The pulmonary artery occlusion

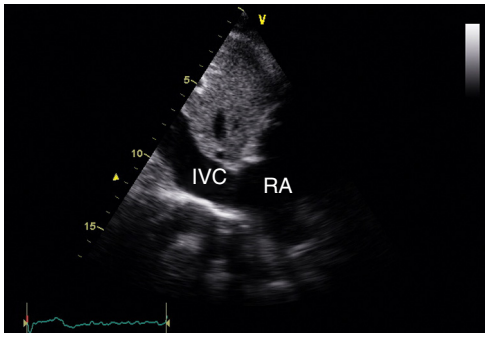


Figure 46-29. A transthoracic subcostal inferior vena cava (SC IVC), two-dimensional cross section of a normal heart is shown. The inferior vena cava (IVC) is seen on the left side of the display as a rectangular echolucent structure inside the liver connecting to the right atrium (RA).

and central venous pressures also declined but correlated poorly with the end of diastole. In most adults, an end of diastole of less than 12 cm^2 indicates hypovolemia, but values between 12 to 15 cm^2 may not because of variations in patient size and diastolic compliance. However, when a volume challenge increases the end of diastole, stroke volume also increases.[51] Although quantitative TEE measurements of ventricular preload are well validated as noted earlier, they are tedious and impractical to perform intraoperatively. Instead, clinicians assess LV filling and function subjectively with the "trained eye." This approach is a valid method to guide intravenous fluid administration. In patients with concentric hypertrophy, TEE may identify the need for higher-than-normal filling pressures to achieve optimal LV filling and function.[52]

In addition to estimating LV filling volume, TEE provides practical ways to estimate LV filling pressure. Placing the Doppler cursor at the junction of the left atrium and left superior pulmonary vein, Kuecherer and associates demonstrated that a systolic fraction of flow of less than 55% was a specific and sensitive sign of left atrial pressure greater than 15 mm Hg. This sign is easily detected as predominance of flow during diastole (Figures 46-30 and 46-31).[53] Significant mitral regurgitation, the presence of nonsinus rhythm, and extremes of cardiac output affect pulmonary venous flow and therefore limit this application of TEE. Alternative methods have been described that obviate some of these limitations.[54,55] However, the current use of TDI annular early diastolic velocity (e′) is recommended to assess the LV diastolic filling pressure.[27] As the LV diastolic relaxation and compliance deteriorate, the LV filling pressure and PW peak mitral inflow E velocity increase while the TDI e′ velocity decreases.[56] Thus the ratio of the E:e′ velocity correlates well with the LV filling pressure; a ratio under 8 is associated with normal LV filling pressures, whereas a ratio more than 15 is associated with increased filling pressures.[57] Although this method of estimating LV filling pressure is widely applicable, it is not valid in the presence of significant mitral annular calcification, mitral regurgitation or stenosis, or a prosthetic mitral valve.[27] Table 46-5 provides a summary of the echocardiographic parameters used for the estimation of LV filling pressures. Rudski and colleagues have published a summary of the echocardiographic techniques for assessment of RV filling and function.[58]

ESTIMATION OF CARDIAC OUTPUT

Real-time TEE images of LV filling and ejection permit qualitative, immediate detection of extreme changes in cardiac output. However, TEE can more precisely quantify cardiac output by measuring both the velocity and cross-sectional area of blood flow at appropriate locations in the heart or great vessels. The product of these measurements is stroke volume. Appropriately performed TEE estimates of cardiac output should fall within 0.3 to 0.8 L/min of thermodilution estimates, except in patients with severe tricuspid regurgitation when thermodilution may underestimate output.[59,60]

ASSESSMENT OF VENTRICULAR SYSTOLIC FUNCTION

Fractional shortening (FS) using M-mode measurements of the change in the midventricular SAX dimension during systole and fractional area change (FAC) using 2-D measurements of the change in the midventricular cross-sectional area during systole are commonly used measures of global LV function. They are calculated using two simple formulas:

$$FS = (EDD - ESD) \div EDD$$

and

$$FAC = (EDA - ESA) \div EDA$$

where EDD is the end-diastolic dimension, ESD the end-systolic dimension, EDA is the end-diastolic cross-sectional area, and ESA is the end-systolic cross-sectional area. Significant changes in FS and FAC are apparent by simply viewing the real-time images. Thus, severe LV depression is easy to detect with TEE. Although FS and FAC correlate reasonably well with other approximations of ventricular function, significant limitations apply. First, TEE often underestimates the LV long axis (it foreshortens the left ventricle). Second, the midventricular SAX view may be a poor guide to overall ventricular ejection, if other areas of the ventricle have significantly different function. Third, FS and FAC, similar to other traditional echocardiographic indices of systolic function, are load dependent; changes in preload and afterload significantly alter FAC without changing the intrinsic function of the ventricle.

Using echocardiographic estimates of LV end-diastolic and end-systolic volumes (EDV and ESV) to calculate the LV ejection fraction (LVEF) overcomes some of these limitations:

$$LVEF = (EDV - ESV) \div EDV$$

With 2-D images, a biplane method of disks (modified Simpson rule) is used. However, this technique is time consuming and will be effectively antiquated by modern 3-D machines that can measure LV EDV, ESV, and LVEF on a beat-by-beat basis without any assumptions about the shape of the ventricle.[4]

Measurement of RV function is more difficult than LV function because of the right ventricle's complex shape and response to changes in loading. However, severe RV dysfunction is not difficult to recognize. The hallmarks are severe hypokinesis or akinesis of the RV free wall,

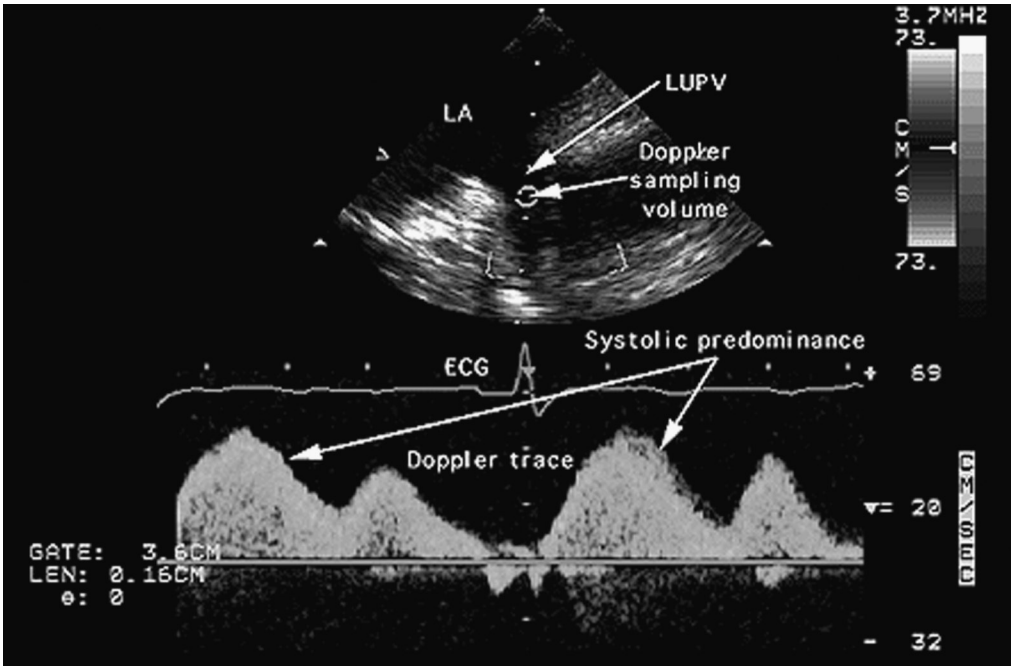


Figure 46-30. Pulsed-wave Doppler (PWD) measurement of normal blood-flow velocities in the left upper pulmonary vein (LUPV) is shown. At the top of the echocardiogram is a still-frame image of the two-dimensional cross section used to position the Doppler sample volume *(broken white circle)*. The display *(in white)* of the instantaneous blood-flow velocities (vertical axis) versus time (horizontal axis) occurring in that sample volume is visualized on the bottom third of the figure. The electrocardiogram (ECG) provides timing, and the *bold horizontal line* is the baseline (zero flow) for the flow velocities. Flow velocities above the line are positive (i.e., toward the transducer) to a maximum of 69 cm/sec. Flow below the line is negative (i.e., away from the transducer) to a maximum of –32 cm/sec. In this patient with normal left atrial pressure, systolic predominance of flow is evident; that is, more flow enters the left atrium (LA) during the period of ventricular systole than during ventricular diastole as evidenced by the greater peak and average flow velocities during systole than during diastole. *(Reproduced with permission from Cahalan MK:* Intraoperative transesophageal echocardiography. An interactive text and atlas*, New York, 1997, Churchill Livingstone.)*

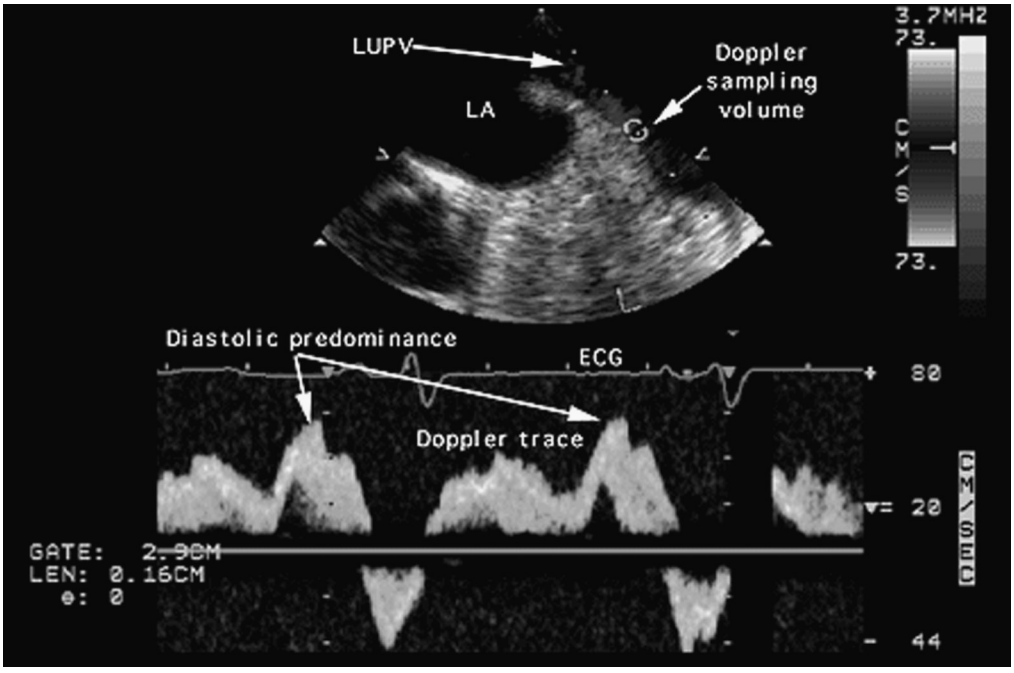


Figure 46-31. Pulsed-wave Doppler (PWD) measurement of blood-flow velocities in the left upper pulmonary vein (LUPV) is shown in a patient with abnormally high left atrial pressure. At the top of the echocardiogram is a still-frame image of the two-dimensional cross section used to position the Doppler sample volume *(broken white circle)*. The display *(in white)* of the instantaneous blood-flow velocities (vertical axis) versus time (horizontal axis) occurring in that sample volume is visualized on the bottom third of the figure. The electrocardiogram (ECG) provides timing, and the *bold horizontal line* is the baseline (zero flow) for the flow velocities. Flow velocities above the line are positive (i.e., toward the transducer) to a maximum of 80 cm/sec. Flow below the line is negative (i.e., away from the transducer) to a maximum of –44 cm/sec. In this patient with abnormally high left atrial pressure, diastolic predominance of flow is evident; that is, more flow enters the left atrium (LA) during the period of ventricular diastole than during ventricular systole as evidenced by the greater peak and average flow velocities during diastole than during systole. The negative flow velocities are due to atrial contraction pushing blood back into the pulmonary vein. *(Reproduced with permission from Cahalan MK:* Intraoperative transesophageal echocardiography. An interactive text and atlas*, New York, 1997, Churchill Livingstone.)*

TABLE 46-5 **PARAMETERS USED TO ESTIMATE LEFT VENTRICULAR FILLING PRESSURE**

Parameter	Values	Estimated Filling Pressure
Mitral inflow with Valsalva maneuver	>50% decrease in the E/A	Increased LAP
Pulmonary venous flow	Systolic fraction <40%	Decreased LA compliance and/or increased LAP
Pulmonary venous diastolic deceleration time	DT <175 ms	Increased LAP
Pulmonary venous A reversal	Ar >35 cm/sec	Increased LVEDP
	Ar – A duration >30 ms	Increased LVEDP
Color M-mode flow propagation velocity	Vp >50 cm/sec	Normal LAP
	E/Vp >2.5	Increased LAP
Tissue Doppler imaging	Septal E/e′ <8	Normal LAP
	E/e′ > 15	Increased LAP
Aortic regurgitation jet	End-diastolic peak velocity	LVEDP
	DBP – EDP gradient	
Mitral regurgitation jet	Peak MR jet velocity	LAP
	SBP – MR gradient	

A, Transmitral Doppler late-filling velocity; *Ar,* atrial systolic reversal wave; *E,* transmitral Doppler early-filling velocity; *DBP,* diastolic blood pressure; *DT,* deceleration time; *e′,* tissue Doppler early diastolic mitral annual velocity; *EDP,* end-diastolic pressure gradient measured across the aortic valve; *LA,* left atrium; *LAP,* left atrial pressure; *LVEDP,* left ventricular end-diastolic pressure; *MR,* mitral regurgitation; *SBP,* systolic blood pressure; *Vp,* velocity of left ventricular diastolic color M-mode propagation.

enlargement of the right ventricle so that it exceeds the size of the left ventricle, and a change in the shape of the right ventricle from crescent to round. When RV dysfunction is due to acute pulmonary hypertension, as occurs in pulmonary embolism, the intraventricular septum flattens or bulges leftward during systole.

However, several parameters can be used to assess the RV systolic function objectively, including myocardial performance index, tricuspid annular plane systolic excursion (TAPSE), RV FAC, 2-D RV ejection fraction (RVEF), 3-D RVEF, TDI-derived tricuspid lateral annular systolic velocity (S′), and RV longitudinal strain and strain rate.[58] TAPSE measures RV longitudinal function (decrease in the RV LAX during systole). TAPSE less than 16 mm indicates RV systolic dysfunction and has good correlation with techniques estimating RV global systolic function such as radionuclide-derived RVEF, RV FAC, and 2-D RVEF. S′ is easy to measure, reliable, and reproducible. S′ velocity less than 10 cm/sec indicates RV systolic dysfunction. The following formula defines RV FAC:

$$(\text{RV EDA} - \text{RV ESA}) = \text{RV EDA}$$

This method is good at quantitatively estimating RV systolic function with a lower reference value for normal RV systolic function of 0.35 (often expressed as 35%). RV FAC is obtained by tracing the RV endocardium both in systole and diastole from the annulus, along the free wall to the apex, and then back to the annulus, along the interventricular septum. The measurement of the RVEF is more difficult. The lower reference limit derived by pooled studies is 44%.

ASSESSMENT OF VENTRICULAR DIASTOLIC FUNCTION

Approximately one third of patients with symptomatic heart failure have normal LV systolic function. Their heart failure is due to diastolic dysfunction: abnormal diastolic relaxation and filling. TEE is an ideal tool for assessing diastolic function because of its unobstructed view of the mitral valve and pulmonary veins.[61] Normal flow across the mitral valve in diastole has an early higher velocity component generated by atrial pressure and ventricular relaxation (E wave on the Doppler echocardiogram) and a second lower velocity component generated by atrial contraction (A wave). At slower heart rates, these two waves are separated by a period of relatively little flow (diastasis). Three severities of diastolic dysfunction are diagnosed by the combination of flow patterns in the mitral valve and pulmonary veins (Fig. 46-32).[62] The least severe is *impaired relaxation,* which is characterized by a decrease in E-wave velocity, a decrease in the deceleration of early filling (demonstrated as decreased slope of the E wave and termed *deceleration time*), and an increase in the A-wave velocity to greater than the E-wave velocity, thereby reversing the E:A ratio. In impaired relaxation, left atrial pressure is normal, and therefore so is the pattern of pulmonary venous flow—the S wave is greater than the D wave. The second and more severe degree of diastolic dysfunction is termed *pseudonormal* and is characterized by the return of the normal E:A ratio because of a pathologic increase in left atrial pressure that results in abnormal pulmonary venous flow—the D wave is greater than the S wave. One simple way to confirm that the mitral flow pattern is pseudonormal and not normal is to reduce left atrial filling transiently with a Valsalva maneuver. If diastolic function is pseudonormal, then the E:A ratio will transiently reverse, with A being greater than E. If diastolic function is normal, then the normal ratio of E greater than A will persist and both waves will decrease in size. The third and most severe degree of diastolic dysfunction is termed *restrictive* and is characterized by an extremely high E-wave velocity, short deceleration time, and low A-wave velocity. In restrictive diastolic function, left atrial pressure is very high and results in an extremely small S wave and large D wave in the pulmonary veins. Patients with this pattern have a poor prognosis and suffer symptoms of congestive heart failure, regardless of their systolic function.[63]

For additional reading on this topic, the authors recommend two excellent reviews on perioperative assessment of diastolic function.[64,65]

TRANSESOPHAGEAL ECHOCARDIOGRAPHY DURING LIFE-THREATENING HYPOTENSION

Ultimately, hypotension has only two possible causes: inadequate cardiac output or inappropriately low systemic vascular resistance (Box 46-1). TEE is remarkably well suited for addressing this differential diagnosis. During severe hypotension, qualitative TEE estimates of ventricular filling and function serve as the practical guides for the

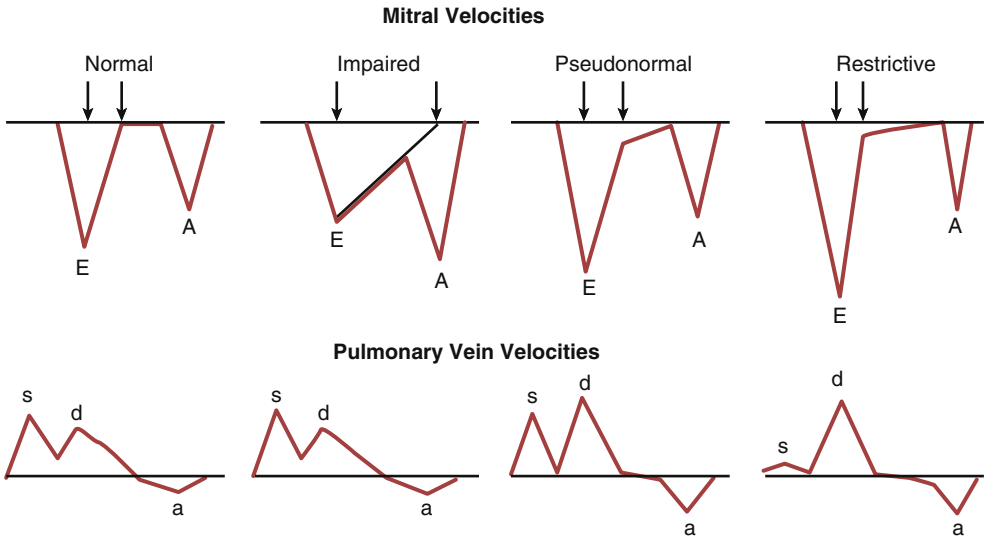


Figure 46-32. Line drawings representing simultaneous transesophageal pulsed-wave Doppler (PWD) recordings from the mitral annulus and right upper pulmonary vein are shown for normal, impaired, pseudonormal, and restrictive left ventricular diastolic function. The *solid red line* represents the slope of the E wave velocity. From the start of the line at the inflection point of the E wave until its intercept at the base line is the deceleration time. This time is depicted in each of the mitral velocity drawings by the *black arrows*. (Refer to the text for further details.)

BOX 46-1 ***Differential Diagnosis of Severe Hemodynamic Instability (Hypotension)***

Low cardiac index
- Hypovolemia
- Left ventricular systolic dysfunction
- Right ventricular systolic dysfunction
- Cardiac tamponade
- Severe valvular dysfunction
- Left ventricular outflow tract dynamic obstruction
- Pulmonary embolism

Low systemic vascular resistance

administration of fluids, inotropes, and vasopressors. An experienced observer can differentiate severe ventricular dysfunction from other life-threatening causes of hypotension. In severe LV failure, ventricular filling (as assessed by EDA) is increased and ejection is decreased, whereas in inappropriately low systemic vascular resistance, ventricular filling is usually normal or slightly decreased and ejection is significantly increased. Hypovolemia is easily recognized as a clear decrease in ventricular filling and a distinctive increase in ejection. Although inappropriately low systemic vascular resistance, severe aortic regurgitation, severe mitral regurgitation, and ventricular septal defect can demonstrate the same LV filling and ejection pattern on the TG SAX cross section, distinguishing these causes of hypotension is not difficult using other cross sections and color Doppler. LV dynamic obstruction and physiologic changes produced by tamponade are two other important possible diagnoses to consider when assessing patients with hemodynamic instability. Dynamic obstruction is observed in patients with concentric LV hypertrophy and relative hypovolemia. The hypertrophied LV muscle self-obstructs ejection of blood from the left ventricle, resulting in low cardiac output and significant eccentric mitral regurgitation. Physiologic changes produced by tamponade results when a pericardial effusion or other compression of the heart causes cardiac chamber pressures to be higher than filling pressures, resulting in the collapse of the chamber(s) and rapid deterioration of the cardiac output. Systolic atrial collapse usually precedes ventricular diastolic collapse. In general, a rapidly expanding small effusion is more detrimental to a patient's hemodynamic status than a larger and slowly accumulating effusion.

A dramatic example of the use of TEE in patients with hypotension is provided by a study of 60 consecutive patients with severe, persistent hypotension after cardiac surgery, despite intensive therapy guided by invasive monitors.[66] TEE confirmed the presumed cause of the hypotension in only 30 of these patients. In 2 patients, TEE revealed unsuspected cardiac tamponade and unsuspected hypovolemia in 6 others. In 5 patients, TEE prevented further unnecessary surgeries by proving that tamponade was not present, despite hemodynamic data suggesting the contrary. In another study, unstable patients in the cardiac operating room ($n = 57$) or the intensive care unit ($n = 83$) underwent emergent TEE.[67] Based on the TEE findings alone, 22 of these patients required urgent surgical interventions. The average time to diagnosis was 11 minutes. Still another study involving surgical patients who were critically ill proved TEE to be more cost-effective than TTE because the latter so often fails to reveal diagnostic images.[68] Moreover, TEE has prognostic value in patients who were critically ill with hypotension when it reveals nonventricular causes of hypotension (e.g., valvular or pericardial); patients are twice as likely to survive as those with other causes of hypotension.[69] Even in the setting of prolonged cardiopulmonary resuscitation, TEE may reveal crucial diagnostic information.[70]

DETECTION OF MYOCARDIAL ISCHEMIA

Within seconds after the onset of myocardial ischemia, affected segments of the heart cease to contract normally. In 50 patients undergoing cardiovascular surgery,

new intraoperative segmental wall motion abnormalities (SWMAs) diagnostic of myocardial ischemia (see next paragraph) occurred in 24 patients and ischemic ST-segment changes in only 6 patients.[71] In 3 patients who sustained intraoperative myocardial infarctions (MI), SWMAs developed in the corresponding area of the myocardium and persisted until the end of surgery, but only 1 of these 3 patients had intraoperative ischemic ST-segment changes. Subsequent studies in comparable patients confirmed these advantages of TEE over electrocardiographic monitoring.[72] In fact, new intraoperative SWMAs are more predictive of postoperative outcome than preoperative stress test–induced SWMAs.[73]

Limitations of TEE in the detection of ischemia should be recognized. When an area of the myocardium is clearly in view, segmental contraction can be difficult to evaluate if the heart significantly rotates or translates during systole or if discoordinated contraction occurs because of bundle branch block or ventricular pacing. Consequently, a valid system for assessment of SWMAs must evaluate both regional endocardial motion and myocardial thickening. A noticeable worsening of segmental wall motion and wall thickening (in the absence of similar global changes) is required to make the diagnosis of ischemia; even experts do not consistently interpret less pronounced changes. Not all SWMAs are indicative of myocardial ischemia. Myocarditis, MI, and myocardial stunning cause SWMAs. In coronary surgery, differentiating infarction, stunning, and ischemia is vitally important. When TEE reveals LV wall thickness of less than 0.6 cm, an old infarction in that thinned area is almost certain.[74] If inotropic stimulation improves the segmental motion of an SWMA, then stunning, not ischemia, is likely.[75] One other cause of SWMA is severe hypovolemia in patients with preexisting SWMAs.[76] However, with the exception of myocardial stunning and severe hypovolemia as noted earlier, a sudden, severe decrease of segmental contraction is almost certainly attributable to myocardial ischemia.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN CARDIAC SURGERY

NEW DIAGNOSES

TEE can reveal new diagnostic findings before cardiopulmonary bypass (CPB) that prompt changes in surgical management (also see Chapters 67 and 94). Skinner and associates reviewed 797 intraoperative TEEs to determine the cause of 46 unexpected new intraoperative findings; 20 were present in the preoperative echocardiographic studies but undiagnosed (reporting errors), 14 were attributable to limitations of TTE relative to TEE, 10 were due to a progression of disease, and 2 were due to interobserver variability.[77] Surgical management significantly changed in 18 out of 20 patients with reporting errors. However, the reported incidence of new intraoperative diagnoses with TEE varies widely (3.4% to 27% of cardiac cases) depending on the patient population, selected or consecutive use of TEE, and surgical practices, especially in the treatment of patent foramen ovale (PFO) and ischemic mitral regurgitation (IMR).[78-81] Recent studies help clarify the correct approach to these two variable surgical practices. First, Krasuski and associates reviewed the intraoperative TEE studies of 13,092 patients without a prior diagnosis of PFO who were undergoing cardiac surgery.[82] A new diagnosis of PFO was made intraoperatively in 2277 of these patients, and 639 of them underwent surgical closure. The patients who had PFO closure had 2.5 times greater odds of having a postoperative stroke, compared with a matched group of patients who did not have PFO closure. No long-term survival advantage resulted from PFO closure. Thus the new diagnosis of PFO during cardiac surgery should not prompt its closure without careful consideration of the additional risk of stroke. Second, Fattouch and associates randomly assigned patients with moderate IMR undergoing coronary artery bypass grafting (CABG) to receive CABG alone ($n = 54$) or CABG plus mitral valve repair (MVR) ($n = 48$).[83] Overall hospital mortality was 3% (one patient in the CABG group and two in the CABG/MVR group). Five-year survival rates were not statistically different between the groups (CABG at 88% versus CABG/MVR at 94%). However, patients in the CABG/MVR group had better postoperative exercise capacity and less cardiac distension than those in the CABG alone group. Only 40% of the patients in the CABG alone group had a decrease in their IMR, whereas 25% remained stable and 35% worsened. No patient in the CABG/MVR group had greater than mild IMR during the 5-year follow-up. A subsequent randomized multicenter trial has confirmed these findings[84]; however, neither trial is sufficiently powered (enough patients) to prove definitively the risks and benefits of adding MVR during CABG surgery in patients with mild-to-moderate mitral regurgitation.[85] Moreover, hemodynamic changes caused by general anesthesia alter the degree of mitral regurgitation (usually lessening it) thereby complicating surgical decision making. Restoring intraoperative blood pressure with phenylephrine to preoperative levels improves the concordance between preoperative and intraoperative assessment of mitral regurgitation, but discrepancies remain.[86] In patients undergoing coronary surgery, even mild mitral regurgitation identified by intraoperative TEE predicts a significantly greater likelihood of death or hospitalization for heart failure over the subsequent 3 years, compared with patients undergoing coronary surgery without mitral regurgitation.[87] Thus the decision to repair a regurgitant mitral valve during CABG surgery is complex and depends on many factors including the mechanism and degree of regurgitation, the ability of the patient to survive the additional surgery, and the skill of the surgeon.

AORTIC DISEASES

TEE may have a crucial role in surgical diseases of the aorta. The 2010 multidisciplinary guidelines on the management of thoracic aortic disease cite an 88% to 98% sensitivity and a 90% to 95% specificity for TEE in the detection of proximal aortic dissection.[88] In this true surgical emergency, speed is of the essence and TEE takes considerably less time than alternative diagnostic

techniques. To limit the time to surgery further, one center uses a regional strategy of direct admission to the operating room for patients with diagnosed or suspected acute aortic dissections.[89] TEE is performed in that facility under general anesthesia, and the decision to proceed with surgery is based on the results. In a different study, TEE reliably distinguished between subadventitial disruptions, which require emergent surgery and intimal tears, which do not.[90] Nevertheless, important TEE limitations should be noted including: TEE may miss dissections confined to the upper ascending aorta where TEE imaging is partially obstructed by the trachea, and TEE will not reveal coincident coronary lesions that should be bypassed during surgery. However, TEE can delineate the mechanisms and severity of any associated aortic regurgitation, thereby identifying patients in whom valve repair is likely to be successful.[91] Similarly, TEE-detected aortic atheromas have important implications. In 130 patients older than 65 years of age undergoing CABG, TEE detection of protruding atheroma of the ascending aorta proved to be the only independent predictor of stroke.[92] When these atheromas are detected by TEE, alteration of the aortic cannulation technique or raising the blood pressure during CPB may reduce the incidence or severity of stroke.[93,94] Although not as sensitive as epiaortic scanning for the detection of atheromas of the aortic arch, TEE is a good screening tool. If TEE reveals no significant atheromas in the ascending or descending aorta, then none are likely to be present in the arch.[95] When intraoperative TEE reveals severe atheromatous disease of the aorta, off-pump coronary surgery results in lower risk of death and stroke than on-pump surgery.[96]

In 2008, new guidelines were published on the intraoperative epiaortic ultrasonographic examination (scanning) of the aorta.[97] Epiaortic scanning avoids the limitation of TEE in assessing the ascending aorta and arch. These guidelines detail the clinical application of epiaortic scanning during heart surgery to evaluate the atherosclerotic disease burden in the ascending aorta and arch to guide proper cannulation strategies that may decrease the incidence of perioperative stroke.

VALVULAR DISEASES

TEE has profoundly affected valvular heart surgery. For example, in 205 consecutive patients undergoing posterior mitral leaflet quadrangular resection (the most common mitral repair technique) for treatment of mitral regurgitation, TEE revealed immediate failures in 24 patients (11%).[98] In 20 of these patients, TEE identified the mechanism of the failure and guided immediate further repair while 1 patient required valve replacement. In a different study, 437 patients underwent mitral valve repair by a variety of techniques.[99] During a mean follow-up period of 29 months, 41 patients (9%) required reoperation for repair failure. Successful initial repair as assessed by intraoperative TEE was the most important predictor of repair durability. Systolic anterior motion (SAM) of the mitral leaflet diagnosed with intraoperative TEE is a known complication of mitral repair surgery. In a study of 2076 patients undergoing mitral repair, TEE identified SAM in 174 patients (8.4%).[100] Four of these patients required immediate reoperation to relieve severe persistent SAM. In the others, SAM was medically managed. During a median follow-up period of 5.4 years, echocardiograms were available in 93 of these patients. SAM was present in 13 of them; in 4 patients, it was severe enough to cause partial LVOT obstruction. Thus, when TEE reveals SAM immediately after mitral repair, it can be medically managed in most patients with preload augmentation, arterial vasoconstriction, and/or beta blockade.[101] Landoni and colleagues have reported a stepwise approach to this strategy.[102] In patients with aortic regurgitation, TEE provides a highly reliable assessment of the underlying cause and is predictive of the reparability of the valve and of postoperative outcome.[103] During valve replacement surgery, TEE reliably detects periprosthetic leaks (surprisingly common). Although moderate or severe periprosthetic leaks should almost always undergo immediate repair, almost half of the small leaks resolve with the administration of protamine. However, surgically correctable prosthesis malfunction occurs in other patients and will be missed without the use of TEE. In a study of 417 patients undergoing valve replacement, immediate surgical correction was required in 15 patients (3.6%): periprosthetic leak (n = 8), immobilized leaflet (n = 4), coronary obstruction (n = 2), and xenograft incompetence (n = 1).[104] In a more recent study limited to patients undergoing elective AV replacement (n = 604), TEE revealed new information influencing surgery in 104 patients before CPB; changes regarding the mitral valve were the most frequent.[105] After CPB, TEE revealed unexpected findings requiring a second bypass in 20 patients. In the future, the incremental value of 3-D TEE in valvular heart surgery, especially mitral repair, may prove significant, but no doubt remains that properly performing and interpreting 3-D TEE requires substantial and additional operator expertise.[106]

Although a comprehensive review of valvular assessment is beyond the scope of this chapter, a brief overview of the most commonly used techniques should prepare the reader to fulfill at least the requirements for basic TEE practice, that is, to recognize gross valvular dysfunction. The degree of aortic stenosis is easily appreciated in the ME AV short-axis cross section in which the extent of leaflet opening can be visually estimated or directly measured with planimetry.[107] Severe stenosis is characterized by significant thickening of the leaflets and severely reduced leaflet motion (valve opening area of <1 cm^2). In the deep TG LAX cross section, CWD allows reliable estimation of the gradient across the AV (Figure 46-33).[108] In severe stenosis, the peak instantaneous gradient will exceed 64 mm Hg (CWD velocity exceeding 4 m/sec), provided cardiac output has not been significantly compromised. Noteworthy is the fact that the echocardiographic-derived AV gradient may be higher than the peak-to-peak gradient reported from a catheterization study because the latter does not measure the instantaneous gradient as does Doppler echocardiography. Additional information on the morphologic structure of the AV can be garnered from the ME AV LAX cross section including the dimensions of the annulus, sinotubular junction, and ascending aorta. The degree of aortic regurgitation is visualized best in this cross section. With color Doppler positioned over the leaflets and outflow track,

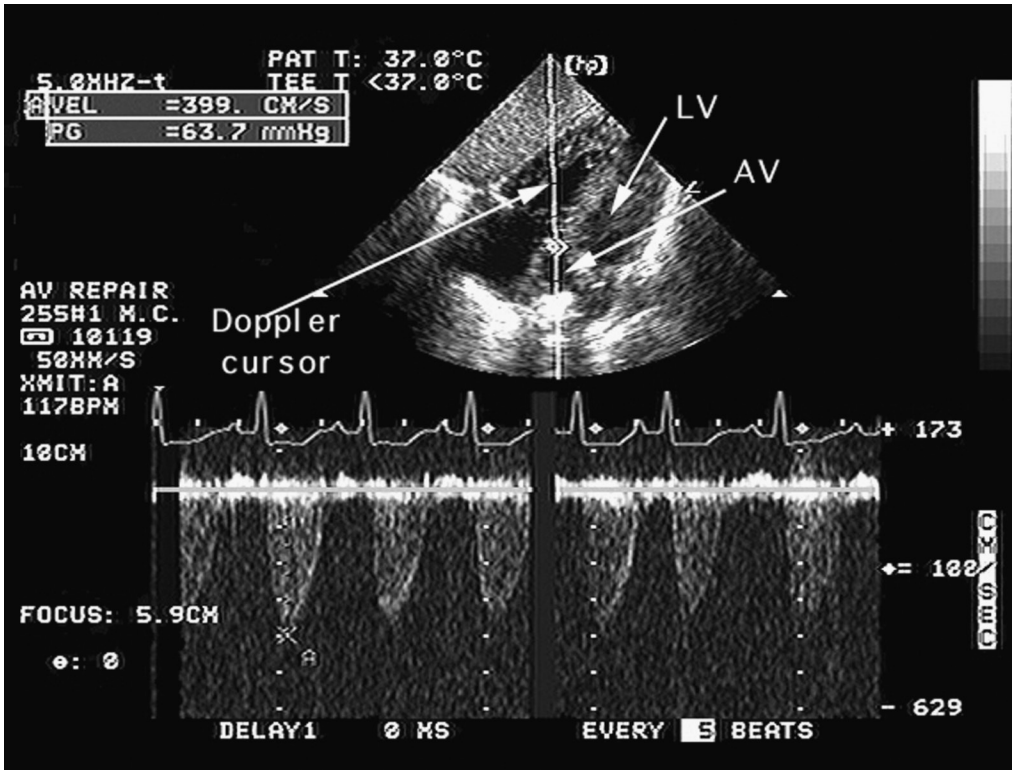


Figure 46-33. Continuous-wave Doppler (CWD) measurement of blood-flow velocities immediately above the aortic valve (AV) during seven cardiac cycles is shown. At the top of the echocardiogram is a still-frame image of the two-dimensional cross section used to position the Doppler sample cursor *(diagonal white line)*. The display *(in white)* of the instantaneous blood-flow velocities (vertical axis) versus time (horizontal axis) occurring anywhere along that cursor is visualized on the bottom third of the figure. The ECG provides timing, and the *bold horizontal line* is the baseline (zero flow) for the flow velocities. With this Doppler alignment, all flow velocities are negative (i.e., away from the transducer). The Doppler scale has been set to a maximum of –629 cm/sec, and this tracing documents significant aortic stenosis, a peak blood-flow velocity of approximately 4 m/sec (each *white dot* on the vertical axis equals 100 cm/sec or 1 m/sec) corresponding to a peak gradient across the AV of 64 mm Hg. *LV,* Left ventricle. *(Reproduced with permission from Cahalan MK:* Intraoperative transesophageal echocardiography. An interactive text and atlas*, New York, 1997, Churchill Livingstone.)*

aortic regurgitation is recognized as a color jet emanating from the valve during diastole. Even modest degrees of aortic regurgitation can be clinically significant during cardiac surgery, producing LV distention during CPB and diminishing the effectiveness of antegrade cardioplegia.[109] Mild regurgitation is characterized by a narrow-based, diastolic color jet (<2 mm at its origin in the valve) that occupies less than one third of the cross sectional area of the LVOT and extends minimally into the left ventricle (1 to 2 cm). Moderate regurgitation is a broad-based, diastolic color jet (3 to 5 mm) occupying less than two thirds of the cross-sectional area of the LVOT and extending moderately into the left ventricle (3 to 5 cm). Severe regurgitation is a broad-based, diastolic color jet (>5 mm) occupying the entire LVOT and extending well into the left ventricle (Table 46-6).

The presence and severity of mitral stenosis are easily determined with TEE using the ME four-chamber, two-chamber, commissural, and/or LAX cross sections, as well as the basal TG SAX cross section. Two-dimensional imaging reveals thickened leaflets that dome toward the left ventricle and open poorly. Color Doppler reveals laminar flow acceleration into the stenotic orifice and a turbulent jet emerging into the ventricle (Figure 46-34). PWD and CWD Doppler traces display a characteristic flow pattern with increased peak and mean velocities (Figure 46-35).

TABLE 46-6 **GRADING AORTIC INSUFFICIENCY**

Parameter	Mild	Moderate	Severe
Jet width or LVOT (%)	<25	25-60	>60
Vena contracta (mm)	<3	3-6	>6
Density of CWD jet	Faint	Moderately dense	Dense
P ½ time (msec)	>400	400-250	<250
Deceleration slope	<1.5	1.5-3	>3
Thoracic aortic flow reversal	Early diastole	Early-to-mid diastole	Holodiastolic
Regurgitant volume (mL)	<45	45-60	>60
Regurgitant fraction (%)	<30	30-55	>55
Regurgitant orifice area (cm^2)	<0.2	0.2-0.3	>0.3

CWD, Continuous-wave Doppler; *LVOT,* left ventricular outflow tract, P ½, pressure half time measured at the aortic valve; *vena contracta,* the base of the regurgitant jet at its origin.

Mathematical calculation from these traces, such as pressure half time, are the most precise methods to assess the severity of mitral stenosis; and formulas for these evaluations are built into the software of virtually every ultrasonograph.[110] In addition to the signs noted, severe mitral

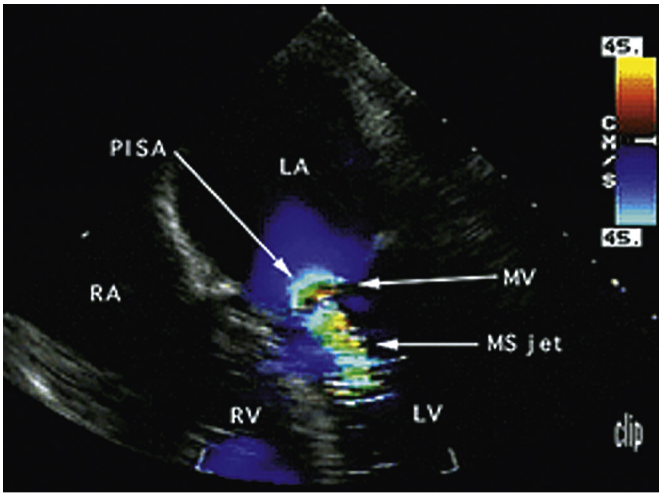


Figure 46-34. This four-chamber echocardiogram reveals a thickened and narrowed mitral valve (MV) indicating mitral stenosis (MS). Color Doppler demonstrates (1) the acceleration of blood flow into the stenotic valve (*light blue semicircular area immediately above the MV*, called the proximal isovelocity surface area [PISA]); (2) a narrow color jet across the valve itself; and (3) a 1- by 4-cm color jet extending from the under surface of the valve into the left ventricle (LV). *LA,* Left atrium; *RA,* right atrium; *RV,* right ventricle. *(Reproduced with permission from Cahalan MK:* Intraoperative transesophageal echocardiography. An interactive text and atlas*, New York, 1997, Churchill Livingstone.)*

stenosis always causes significant left atrial enlargement and left atrial spontaneous contrast. Spontaneous contrast is a swirling, smokelike appearance of 1-to 2-mm densities not attributable to exogenously administered contrast agents but to the aggregation of red cells in areas of low flow. Whenever left atrial enlargement and spontaneous contrast are noted, thrombus in the left atrium and, in particular, the left atrial appendage should be suspected and carefully examined.

The presence and severity of mitral regurgitation are evaluated from the same cross sections used for evaluation of mitral stenosis and with the same grading strategy used for aortic regurgitation (Table 46-7). Mild regurgitation is characterized by a narrow-based, systolic color jet (<2 mm at its origin in the valve) that occupies less than 25% of the left atrial cross-sectional area and extends less than one half of the distance to the posterior wall of the left atrium. Moderate regurgitation is a broad-based, systolic color jet (3 to 5 mm at its origin in the valve), occupying less than 50% of the left atrial cross-sectional area and extending 50% to 90% of the distance to the posterior wall of the left atrium. Severe regurgitation is a broad-based, systolic color jet (>5 mm), occupying most of the left atrium and extending into the pulmonary veins and left atrial appendage (Figure 46-36). Eccentrically-directed jets of mitral regurgitation that hug the wall of the atrium are generally associated with more severe valvular regurgitation than their cross-sectional area might suggest (see Figure 46-36). Moreover, eccentric-directed jets usually point away from the defective leaflet; that is, lateral-directed jets are usually associated with anterior leaflet defects and medial-directed jets are usually associated with posterior leaflet defects, provided the mechanism of regurgitation is leaflet prolapse or flail.[111] Severe mitral regurgitation is invariably associated with systolic reversal of pulmonary venous inflow (Figure 46-37).[112] The general guidelines previously listed are widely used, but many more criteria have been described for the assessment of mitral regurgitation.[39] Most importantly, the degree of regurgitation is exquisitely dependent on LV loading conditions. For practical purposes, quantitative measures of regurgitation, for example, the regurgitant orifice area based on the theory of proximal isovelocity surface area (PISA), are less often used in the operating rooms because of time restriction.

Pulmonary and tricuspid valve pathologic assessment are conducted in a fashion analogous to that described for the aortic and mitral valves (see Tables 46-6 and 46-7).

CORONARY DISEASE

In a study of 82 high-risk patients undergoing coronary artery surgery, the investigators used staged blindings of the cardiac surgeons and anesthesiologists at critical points during surgery to document the clinical impact of TEE. After these clinicians documented their planned management at each stage, the TEE results were revealed and led to at least one significant change in anesthetic management in 51% of patients and surgical management in 33% of patients including additional unplanned or revised grafts (15%) and unplanned valve procedures (20%).[113] These high-risk patients had postoperative infarction and mortality rates below predicted (1% versus 3% predicted, difference not statistically significant). In the study noted in the previous section involving 457 consecutive patients undergoing coronary artery surgery, TEE identified 71 new findings in 13% of patients. The new findings resulted in a change in surgical management in 6% of patients. After bypass, surgical management changed in 10 patients including graft evaluation or revision and mitral repair (also see Chapter 67).

CONGENITAL HEART SURGERY

Pediatric TEE probes are used in infants as small as 3 kg. Stevenson and co-workers reported that intraoperative TEE reliably detected residual cardiac defects in 17 (7%) of 230 consecutive patients undergoing congenital heart surgery.[114] These patients were immediately surgically treated for revision of the residual defects. However, a subsequent publication from the same center found that the number of residual defects missed by intraoperative TEE increased from 2% to 13% when the attending anesthesiologist, rather than a separate echocardiographer, performed TEE.[115] This study generated considerable controversy. Although this study does not resolve the issue of whether a separate echocardiographer is required to perform TEE adequately in patients undergoing congenital heart repairs, it does amply demonstrate that patients can suffer severe consequences when intraoperative TEE is not expertly performed, interpreted, and acted on. In this study, the deaths of seven patients may have been related to the delayed recognition of residual defects. With progress in pediatric congenital heart surgery, more children with palliated congenital heart disease will survive into

TABLE 46-7 **GRADING MITRAL INSUFFICIENCY**

	Trace	Mild	Moderate	Severe
Qualitative Parameters				
Angiographic grade	1+	2+	3+	4+
MV morphology	Normal	Normal or abnormal	Normal or abnormal	Abnormal (flail leaflet)
Color-flow MR jet	Small	Small and central	Intermediate	Very large central or eccentric jet to posterior LA wall
Flow-convergence zone	None	None or small	Intermediate	Large
CW signal of MR jet	Faint	Faint and parabolic	Dense and parabolic	Dense and triangular
LV and LA size and PA pressures	Normal	Normal		Usually dilated; elevated PAP
Semiquantitative Parameters				
Vena contracta width (mm)	<3	<3	3-6	≥7 (>8 for biplane)
Pulmonary vein flow	Systolic dominance	Systolic dominance	Systolic blunting	Systolic flow reversal
Mitral inflow	A wave dominance	A wave dominance	Variable	E wave dominant (>1.5 m/sec)
VTI mitral and VTI LVOT	<1	<1	Intermediate	>1.4
Quantitative Parameters				
Effective regurgitant orifice area (mm^2)	<20	<20	20-29; 30-39	≥40 ≥20
Regurgitant volume (mL)	<30	<30	30-44; 45-59	>60 >30

Modified from Lancellotti P, Moura L, Pierard LA, et al: European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease), Eur J Echocardiogr *11:307-332, 2010.*

CW, Continuous-wave Doppler; *LA,* left atrium; *LV,* left ventricle; *LVOT,* left ventricular outflow tract; *MV,* mitral valve; *MR,* mitral regurgitation; *PA,* pulmonary artery; *PAP,* pulmonary artery pressure; *VTI,* velocity time integral.

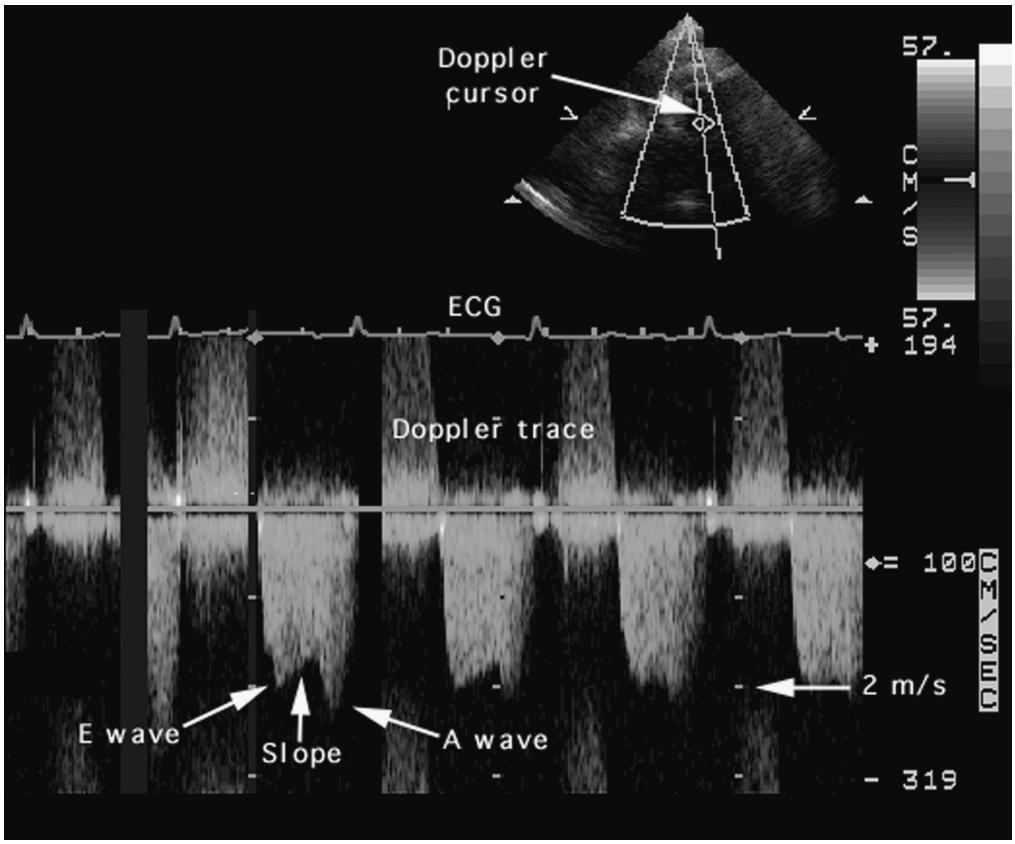


Figure 46-35. Continuous-wave Doppler (CWD) measurement of blood-flow velocities through a stenotic mitral valve is shown. At the top of the echocardiogram is a still-frame image of the four-chamber cross section used to position the Doppler cursor. The display *(in white)* of the instantaneous blood-flow velocities (vertical axis) versus time (horizontal axis) occurring anywhere along that cursor is visualized on the bottom third of the figure. The ECG is shown for timing purposes, and the *bold horizontal line* running through the Doppler tracing is the baseline (zero flow) for the flow velocities. Velocities displayed above the baseline are positive and represent flow toward the transducer. These velocities are attributable to mitral regurgitation and are so high that they exceed the scale used in this example. Velocities displayed below the baseline are negative and represent flow away from the transducer. These velocities are attributable to severe mitral stenosis and average approximately 2 m/sec, indicating a gradient across the mitral valve of 16 mm Hg. This echocardiogram also notes how slowly the flow velocity decreases after the peak of the E wave *(Slope).* The pressure half time can be calculated from this slope and is significantly increased in the presence of severe mitral stenosis. *(Reproduced with permission from Cahalan MK:* Intraoperative transesophageal echocardiography. An interactive text and atlas, *New York, 1997, Churchill Livingstone.)*

adulthood and will need cardiac and other kinds of surgery (also see Chapter 94). For excellent updates on TEE in adult and pediatric patients with congenital heart disease, the recent reviews by Russell and associates and Kamra and associates can be consulted.[116,117]

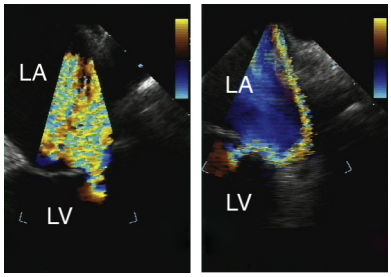


Figure 46-36. Two honed-down, stop-action, four-chamber transesophageal echocardiograms demonstrate severe mitral regurgitation. A large color jet *(left)* depicting turbulent flow emanating from the center of the mitral valve at its coaptation point is revealed. The mechanism of the regurgitation in this patient is annular dilatation. The broad base of the jet at the level of the valve leaflet and the extent of the jet's penetration into the left atrium are noted. The stop-action echocardiogram *(right)* reveals another broad-based jet with eccentric direction indicating prolapse of the anterior leaflet of the mitral valve. Wall-hugging jets such as this one have a small cross-sectional area because much of their energy is absorbed by the wall of the atrium.

OTHER DISEASES AND APPLICATIONS

TEE has a vital role in minimally invasive cardiac surgery and in the placement of cardiac support devices.[118,119] Thousands of other published reports document that TEE can reveal virtually any significant morphologic structure or pathologic function of the heart. TEE is particularly sensitive for abnormalities involving the left atrium and mitral valve including masses, thrombi, and emboli because of the proximity of left atrium and mitral to the TEE transducer. In contrast, pathologic abnormalities of the RV and LV apexes are less reliably detected. TEE is exquisitely sensitive to air embolism and, as a result, even insignificant amounts of air in the circulation can give rise to impressive densities on the video display. Currently, accurate estimation of the amount of air in the circulation is impossible using TEE. However, large amounts typically opacify the involved chambers until forming collections (i.e., very bright densities) in the most superiorly positioned parts of the chambers (i.e., anterior endocardial surface of the left ventricle in the supine patient). Pulmonary emboli may be observed with TEE if they lodge proximal to the bifurcation of the main pulmonary artery.

Anesthesiologists are asked to perform intraoperative TEE in an increasing number of procedures in the

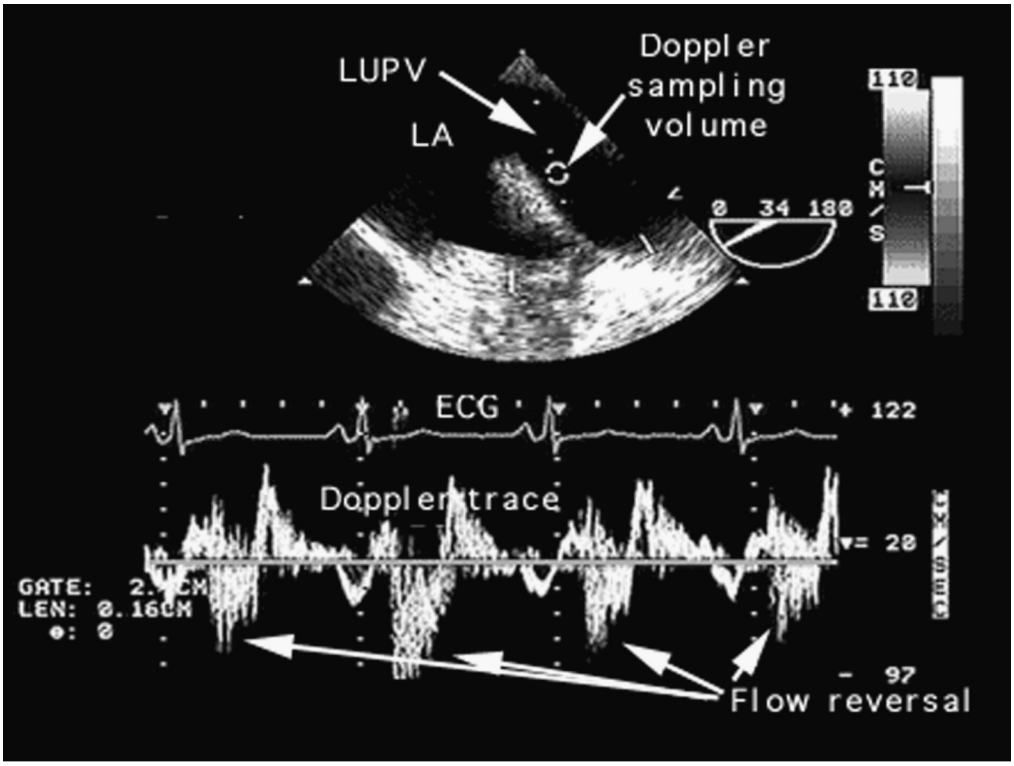


Figure 46-37. Pulsed-wave Doppler (PWD) measurement of blood-flow velocities in the left upper pulmonary vein is shown. At the top of the echocardiogram is a still-frame image of the two-dimensional cross section used to position the Doppler sampling volume *(broken white circle)*. The display of the instantaneous blood-flow velocities (vertical axis) versus time (horizontal axis) occurring in the left upper pulmonary vein is visualized on the bottom third of the figure. The ECG is shown for timing purposes and the *bold horizontal line* running through the Doppler tracing is the baseline (zero flow) for the flow velocities. Velocities displayed above the baseline are positive and represent flow toward the transducer (in this case, into the left atrium). Velocities displayed below the baseline are negative and represent flow away from the transducer (in this case, into the left upper pulmonary vein). This Doppler tracing documents systolic flow reversal (normally positive, that is, toward the left atrium in systole) and confirms the presence of severe mitral regurgitation. *(Reproduced with permission from Cahalan MK:* Intraoperative transesophageal echocardiography. An interactive text and atlas*, New York, 1997, Churchill Livingstone.)*

operating room, the catheterization laboratory, and in hybrid operating rooms. The role of imaging has evolved from complex cardiac evaluation to direct procedure guidance. TEE can be used to evaluate the correct position of central venous catheters, pulmonary artery catheters, and coronary sinus catheters. With the use of minimally invasive cardiac procedures, intraoperative TEE has become an essential tool for the safe application of these newer techniques. TEE is used to assess the correct position of venous CPB cannula in the right atrium, coronary sinus catheters, pulmonary vents, and endovascular aortic clamps. Box 46-2 lists procedures where TEE is routinely used for the direct guidance and evaluation of procedural results.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN NONCARDIAC SURGERY AND CRITICAL CARE

TEE has many of the same applications in noncardiac surgical patients and in patients who are critically ill as it does in cardiac surgical patients. Numerous case reports and case series document the effect TEE can have on patient management and outcomes. In the authors' practice, the leading indications are hemodynamic instability and massive blood loss, during which TEE has a vital role in determining the cause of the instability (see, "Transesophageal Echocardiography During Life-Threatening Hypotension") and in guiding volume resuscitation.[120,121] In the intensive care unit, TEE has similar applications, and these have been recently reviewed.[122,123]

BOX 46-2 ***Intraoperative Transesophageal Echocardiography for Guidance and Assessment of Cardiac Procedures***

- Femoral cannula placement during heart surgery (venoatrial placement)
- Coronary sinus catheter placement from the right internal jugular
- Left ventricular assist device inflow/outflow positioning
- Transmyocardial laser penetration positioning
- Left ventricular assist device positioning
- Right ventricular and pulmonary artery vent positioning
- Endovascular aortic clamp positioning
- Transcatheter aortic valve replacement assessment
- Percutaneous ventricular assist device positioning
- Intraaortic balloon pump positioning
- Atrial septal defect closure guidance and assessment
- Paravalvular leak site identification and closure guidance
- Transseptal puncture guidance
- Endovascular repair mitral regurgitation (mitral clip) assessment
- Transcatheter pulmonary valve replacement assessment
- Valvuloplasty assessments
- Pacemaker lead extraction evaluation and immediate follow-up
- Atrial fibrillation ablation guidance (three- and four-dimension applications)
- Left atrial appendage occluder positioning
- Pulmonary vein stent assessment
- Thoracic endovascular aortic repair guidance and assessment

DATA STORAGE, DOCUMENTATION, AND QUALITY ASSURANCE

Traditionally, echocardiograms were stored on videotape, and written reports of the results were placed in the patient's medical record. Currently, digital recording of individual cardiac cycles or multiple cycles is the standard. The resulting *loops* are transported via hospital networks or the Internet to secure servers where the studies can be rapidly retrieved. The SCA has published guidelines for a standardized reporting form for adult perioperative TEE (http://www.scahq.org/TEE/StandardizedReportforAdultPeriopEcho.aspx).

The ASE and SCA have published guidelines for continuous quality improvement (CQI) in perioperative echocardiography.[124] However, even relatively simple CQI interventions may produce dramatic results in the consistency of image acquisition and storage.[125] Periodic expert review of TEE interpretations is essential if practitioners are to reach and maintain their diagnostic potential. Collaboration between the departments of anesthesiology and cardiology is one approach to this review process that minimizes the duplication inherent in the formation of independent CQI programs.

CERTIFICATION

The National Board of Echocardiography (NBE) offers an examination and certification process for basic and advanced perioperative TEE (http://www.echoboards.org/content/verification-physicians-certification). At the basic level, the requirements are (1) passage of the NBE's basic perioperative echocardiography examination (basic PTeXAM), (2) current and unrestricted license to practice medicine, (3) board certification in anesthesiology, and (4) specific training in perioperative TEE. *Specific training* has two pathways, *supervised* and *practice experienced*. The practice experience pathway is the one most likely to apply to most anesthesiologists. It requires "at least 150 TEE examinations within the four (4) consecutive years immediately preceding the application with no less than 25 in any year." In addition, this pathway requires at least 40 hours of the American Medical Association (AMA) category 1 continuing medical education devoted to perioperative TEE. Of special note is the clear limitation the NBE has placed on basic TEE certification:

"The primary purpose of this certification is to provide anesthesiologists who use TEE as a monitor during general anesthesia an opportunity to demonstrate their competence with this technique. Certification in basic perioperative TEE is NOT intended to qualify an individual to use TEE as a diagnostic tool to direct or assess cardiac surgical interventions; the board certification in perioperative transesophageal echocardiography offered by the NBE since 2003 remains unchanged and still serves this purpose and from this point on will be referred to as Advanced PTE Certification.

In reality, most anesthesiologists practice somewhere between the basic and advanced levels. Regardless of the

level of practice, anesthesiologists must anticipate the need for consultation whenever the demands of anesthetic management, TEE interpretation, or both will be more than can be managed alone.

Complete references available online at expertconsult.com

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Chapter 47

Electrocardiography, Perioperative Ischemia, and Myocardial Infarction

GIORA LANDESBERG • ZAK HILLEL

Key Points

- The electrocardiogram (ECG) is an easy and important tool for diagnosing perioperative heart rate (HR) and rhythm abnormalities. Some of these abnormalities can be immediately dangerous, such as severe bradycardia, new atrioventricular (AV) blocks, and ventricular tachycardia (VT) or fibrillation, and require prompt diagnosis and treatment.
- Understanding the baseline ECG abnormalities of the patient undergoing high-risk cardiac surgery is an important part of the preoperative evaluation. Nevertheless, the ECG alone often does not provide sufficient information regarding the myocardial or valvular function and the risk of developing perioperative cardiac complications. For that purpose, some kind of stress test, either physiologic or pharmacologic, with or without cardiac imaging (nuclear or echocardiographic imaging) and/or coronary angiography is necessary.
- The ECG is an important tool for diagnosing acute myocardial ischemia, most often denoted by new or augmented ST-segment changes, such as significant ST-segment elevations or depressions.
- Myocardial ischemia is common in patients with a cardiac condition undergoing noncardiac surgery, predominantly during the early postoperative period (first 24 hours) and is almost exclusively ST-depression–type ischemia. Prolonged postoperative ST-depression–type ischemia strongly correlates with serum troponin increases, which in the first 3 postoperative days, will incrementally predict increased 30-day and long-term mortality.
- Postoperative myocardial infarction (MI) is most often a type 2 infarction; that is, it is due to prolonged myocardial oxygen supply-demand imbalance; although a type 1 infarction, which is a result of spontaneous plaque rupture and coronary thrombosis, may also occur. Therefore, therapeutic strategies to prevent and treat any potential cause of myocardial oxygen supply-demand imbalance, particularly an increase in the HR, should be applied whenever myocardial ischemia is detected or even considered. The prophylactic treatment by β-adrenergic blockers is controversial and can be hazardous in patients who are postoperatively hypotensive. Nevertheless, patients who are receiving chronic β-adrenergic blockade therapy must continue to take these drugs perioperatively unless contraindicated by their current or new hemodynamic status.

William Einthoven, who used a string galvanogram for his recordings, first invented the ECG in 1901. This time-honored and relatively simple tool remains, even today, a mainstay in clinical cardiac diagnosis and therapy. In the perioperative setting, the ECG serves two main functions: diagnosis and monitoring. In the preoperative period, standard 12-lead ECG is predominantly used for risk assessment. It provides information on the patient's baseline (chronic) cardiac status with regard to myocardial ischemia and conduction or rhythm abnormalities as part of the entire preoperative clinical assessment. Occasionally, the preoperative ECG may reveal acute or new abnormalities, especially with urgent or emergent operations, and in comparing current with previous ECGs. During and after surgery, the ECG can detect changes in rate and rhythm or myocardial ischemia. With many patients coming to surgery with pacemakers or implantable cardiac defibrillators in place, the ECG monitor enables the anesthesiologist to follow the proper function of these devices during the surgical procedure. (Perioperative management of these devices is described in Chapter 48.) During cardiac surgery, both myocardial

ischemia and arrhythmias are common, especially after separating from the cardiopulmonary bypass. The proper diagnosis and management of intraoperative ischemia and arrhythmias is especially part of the expertise of the cardiovascular anesthesiologist (see Chapters 67 and 68). A postoperative 12-lead ECG is often obtained in patients who are at high risk for developing new ischemic or rhythm changes. In all these scenarios, a good understanding of the principles of the ECG and its abnormalities is vital for the anesthesiologist. This chapter covers most aspects of ECG interpretation with a special emphasis on issues relevant to anesthesia and perioperative care.

ELECTROCARDIOGRAPHIC LEAD SYSTEMS

STANDARD RECORDING ELECTRODES AND LEADS

The small currents produced by the electrical activity of the cardiac muscle spread an electrical field throughout the body, which behaves as a volume conductor, allowing it to be recorded at various sites on the surface of the body as ECG signals. Electrodes (leads) placed at specific locations record the electrical potentials reaching the skin, and the output of these leads is amplified, filtered, and displayed. Two types of ECG leads are used: *bipolar* and *unipolar*. A bipolar lead consists of two electrodes placed at two different sites to measure the difference in potentials between these two electrodes. Unipolar leads measure the *absolute* electrical potential at one site in relation to a *reference,* or *remote* site, at which the potential is deemed to be zero. The standard clinical ECG includes recordings from 12 leads. These 12 leads include three *bipolar leads* (I, II, and III), six *unipolar precordial leads* (V_1 through V_6), and three *modified unipolar limb leads* (augmented limb leads aV_r, aV_l, and aV_f) (Table 47-1).

TABLE 47-1 LOCATION OF ELECTRODES AND LEAD CONNECTIONS FOR THE STANDARD 12-LEAD ELECTROCARDIOGRAM AND ADDITIONAL LEADS

Lead Type	Positive Input	Negative (Reference) Input
Bipolar Limb Leads		
Lead I	Left arm	Right arm
Lead II	Left leg	Right arm
Lead III	Left leg	Left arm
Augmented Unipolar Limb Leads		
aV_r	Right arm	Left arm plus left leg
aV_l	Left arm	Right arm plus left leg
aV_f	Left leg	Left arm plus left arm
Precordial Leads		
V_1	Right sternal margin, 4th intercostal space	Wilson central terminal
V_2	Left sternal margin, 4th intercostal space	Wilson central terminal
V_3	Midway between V_2 and V_4	Wilson central terminal
V_4	Left midclavicular line, 5th intercostal space	Wilson central terminal
V_5	Left anterior axillary line	Wilson central terminal
V_6	Left midaxillary line	Wilson central terminal

Modified from Zipes DP, Libby P, Bonow R, Braunwald E: Braunwald's heart disease: a textbook of cardiovascular medicine*, ed 7. Philadelphia, 2010, Churchill Livingstone.*

STANDARD ELECTROCARDIOGRAPHIC RECORDINGS

The ECG is normally recorded on special paper consisting of grids of horizontal and vertical lines. The distances between the vertical lines represent time intervals, whereas the distances between the horizontal lines represent voltages. The lines are 1 mm apart, with every fifth line intensified. The speed of the paper is standardized to 25 mm/sec. On the horizontal axis, 1 mm represents 0.04 second, and 0.5 cm represents 0.20 second. On the vertical axis, 10 mm represents 1 microvolt (mV). On every recording, a 1-cm (1-mV) calibration mark should indicate that the ECG is appropriately calibrated.

NORMAL ELECTRICAL ACTIVITY

P WAVE

Under normal circumstances, the sinoatrial (SA) node has the most rapid spontaneous depolarization rate and is therefore the dominant cardiac pacemaker. From the SA node, the impulse normally spreads to the atrioventricular (AV) node, through one left-sided and two right-sided pathways. The P wave is the result of normal depolarization of the atria, and its identification is important for the determination of normal sinus rhythm. The anatomically anterior right atrium is activated earlier, and only later does the signal shift posteriorly as activation proceeds over the left atrium. Therefore, the P wave in the right precordial leads (V_1 and, occasionally, V_2) is commonly biphasic, a positive deflection followed by a negative one, whereas in the lateral leads, the P wave is upright and reflects a right-to-left spread of the activation front.

PR INTERVAL

The PR interval is the temporal bridge between atrial and ventricular activation, during which the AV node, the bundle of His, the bundle branches, and the intraventricular conduction systems are activated (Fig. 47-1). Most of the conduction delay during this segment is due to slow conduction within the AV node. The normal PR interval measures 120 to 200 milliseconds (msec) in duration.

MYOCARDIAL ACTIVATION—THE QRS COMPLEX

The QRS complex is the manifestation of left and right ventricular muscle depolarization. Its pattern lead represents the sum of all electrical forces emanating from the wavefront propagation of ventricular electrical excitation aimed at the direction of that lead. Ventricular excitation spreads within several milliseconds from the bundle branches to the His-Purkinje fibers, which are broadly dispersed throughout the entire endocardial surfaces of both ventricles. Excitation of the Purkinje-ventricular

muscle junctions in the endocardium then proceeds by conduction from muscle cell to muscle cell to activate the entire ventricle thickness toward the epicardium. The normal pattern of activation of the ventricles starts in the interventricular septum with a vector oriented from left to right in the frontal plane and anteriorly in the horizontal plane (as determined by the anatomic position of the septum in the chest). This produces an initial small positive R wave in the right-sided leads (aV_R and V_1) and small negative waves (septal Q waves—less than 30 to 40 msec) in the left-sided leads (I, aV_L, V_5, and V_6). Subsequent QRS complex elements reflect the activation of the free walls of the left and right ventricles. However, because the right ventricular muscle mass is considerably smaller than the left ventricle, in reality, the QRS complex generally represents left ventricular (LV) activity with its main vector proceeding from right to left in the axial plane and anterior, followed by posterior vectors in the horizontal plane (R wave followed by a small S wave in the left-sided leads). The main vector of the QRS complex in the frontal plane serves to calculate the electrical axis of the heart, which is normally between –30 and +90 degrees. An axis more negative than –30 degrees is called *left axis deviation*, and an axis higher than +90 degrees is termed *right axis deviation*. The duration of the normal QRS complex is less than 120 msec (Fig. 47-2).

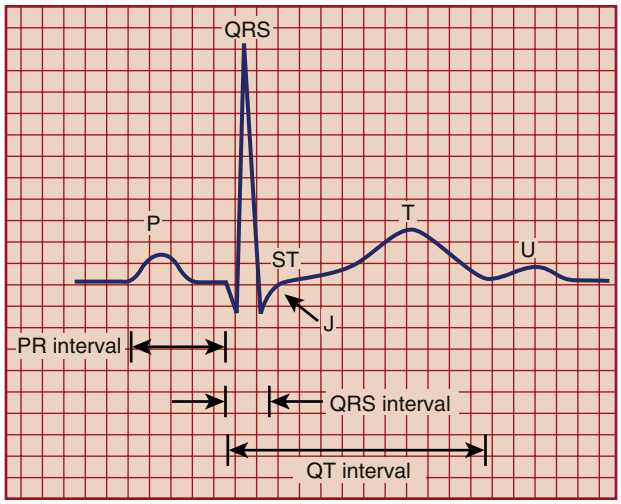


Figure 47-1. The waves and intervals of a normal electrocardiogram. *(From Goldberger AL:* Clinical electrocardiography: a simplified approach*, ed 6. St. Louis, 1999, Mosby; and from Figure 9-11 in Zipes DP, Libby P, Bonow R, Braunwald E:* Braunwald's heart disease: a textbook of cardiovascular medicine*, ed 7. Philadelphia, 2005, Saunders.)*

ST SEGMENT AND T WAVE

Repolarization of the ventricles generates the ST segment and T wave. Repolarization, similar to activation, occurs in a characteristic geometric pattern. Because the endocardial action potention lasts longer than that of its overlying epicardium, repolarization of the epicardium often starts earlier than in the endocardium. However, under normal conditions, regional differences in electrical recovery properties of the ventricles are present, and the transmural gradients predominantly determine ST-segment patterns.

Normally, concordance exists between the orientation of the QRS complex and the T wave, with both deflecting in the same direction. The junction of the QRS complex and the ST segment is called the *J junction*. The QT interval—the duration from the Q wave to the end of the T wave—is highly heart rate (HR)–dependent, and formulas have been developed to calculate the corrected QT interval (QTc), which, if prolonged, may be associated with serious ventricular arrhythmias. The T wave is sometimes followed by a small U wave, which may be associated with hypokalemia or hypomagnesemia electrolyte disturbances.

THE ABNORMAL ELECTROCARDIOGRAM

ATRIAL ABNORMALITY

The initiation of atrial electrical activation from a site other than the SA node occurs in one of two ways: (1) an escape rhythm if the normal SA nodal pacemaker slows or fails, or (2) an accelerated atrial ectopic rhythm if the automaticity of the ectopic site is associated with a rate higher than the SA. An abnormal morphologic appearance of the P wave (different from the native P) often expresses ectopic atrial activation. Most commonly, negative P waves are observed in the leads where the

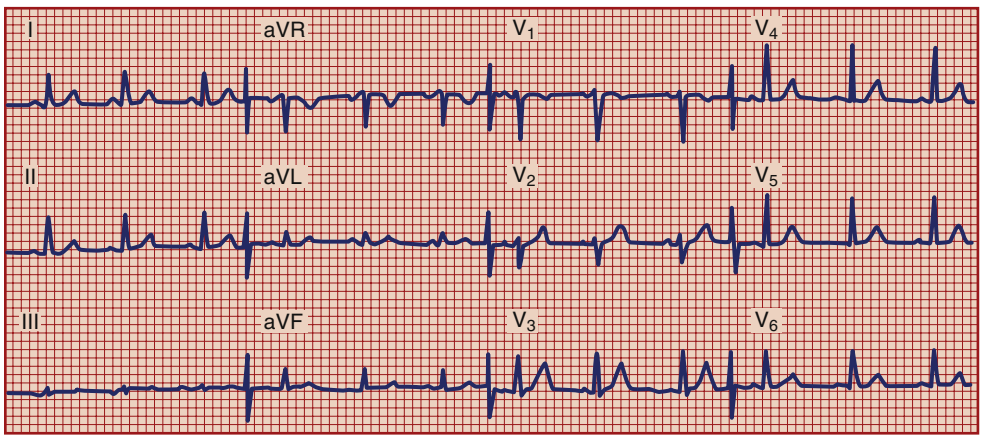


Figure 47-2. An example of a normal 12-lead electrocardiogram. *(From Figure 9-12 in Zipes DP, Libby P, Bonow R, Braunwald E:* Braunwald's heart disease: a textbook of cardiovascular medicine*, ed 7. Philadelphia, 2005, Saunders.)*

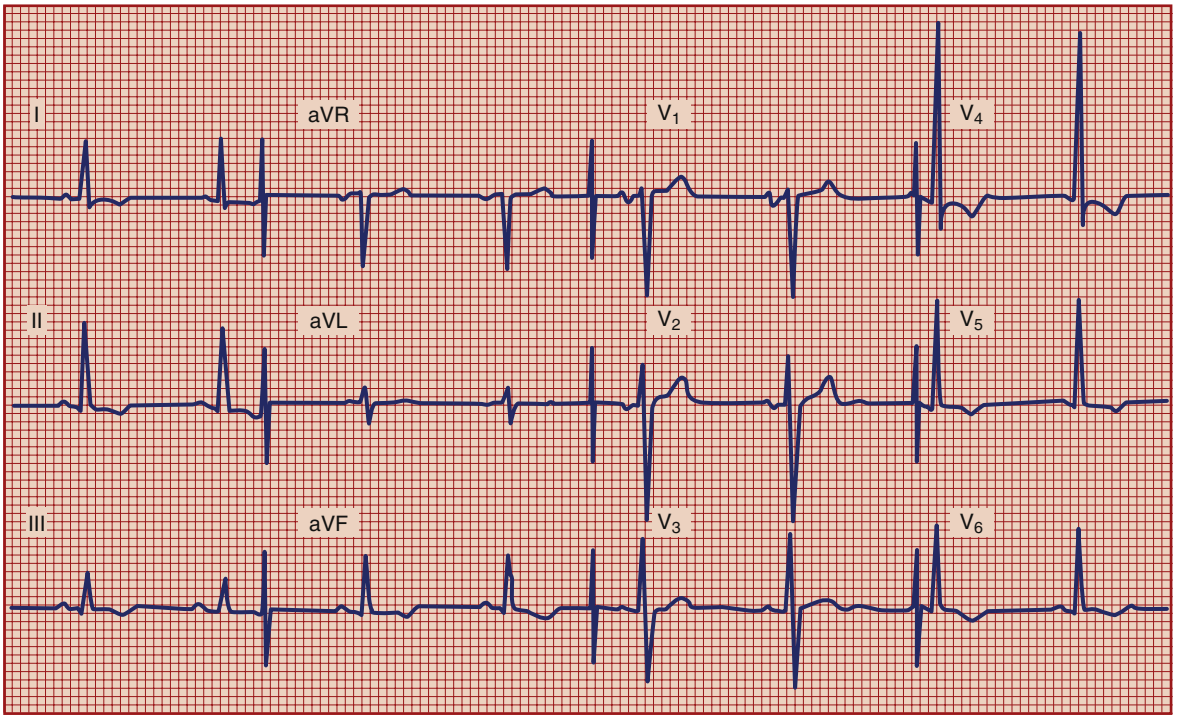


Figure 47-3. Left ventricular hypertrophy (LVH) on electrocardiography. Tall R waves on left-sided leads; and deep S waves on right-sided leads, down-sloping ST-segment depression and T-wave inversion opposite the main R-wave axis, and biphasic p wave signifying left atrial abnormality. *(From Zipes DP, Libby P, Bonow R, Braunwald E:* Braunwald's heart disease: a textbook of cardiovascular medicine*, ed 7. Philadelphia, 2005, Saunders.)*

P wave is normally upright (leads I, II, aV_f, and V_4 through V_6), with or without a shortening of the PR interval. The exact site of an ectopic atrial pacemaker is usually of little clinical significance except that left-sided atrial ectopic rhythm is more often associated with LV or left heart valvular abnormalities, whereas right-sided ectopic rhythm is more common in patients with chronic obstructive lung disease or other causes of right heart dysfunction.

VENTRICULAR HYPERTROPHY AND ENLARGEMENT

Left ventricular hypertrophy (LVH) or enlargement produces changes throughout the QRST complex. The most characteristic is increased voltage of the QRS complex: tall R waves in left-sided leads (I, aV_l, V_5, and V_6) and deep S waves in right-sided leads (V_1 and V_2). ST-segment and T-wave amplitudes can be normal or increased. ST-segment depression with downsloping from a depressed J point and inverted asymmetric T waves are common in long-standing and severe LVH. Similarly, prolonged QRS duration beyond 110 msec reflects the longer duration of activation of the thickened ventricular wall (Fig. 47-3). Diagnostic ECG criteria for LVH have been developed, although their importance in the era of echocardiography has diminished. For example, Sokolow and Lyon found the following voltage criteria to correlate best with postmortem pathologic findings of LVH: S_{V1} + (R_{V5} or R_{V6}) >3.5 mV and/or R_{aVl} >1.1 mV.

Right ventricular hypertrophy (RVH) is signified on the ECG by abnormally tall R waves in the rightward-directed leads (aV_r, V_1, and V_2), reversal of normal R-wave progression in the precordial leads, deep S waves with abnormally small R waves in left-sided leads (I, aV_l, V_5, and V_6) and obvious right axis deviation (>110 degrees) (Fig. 47-4). Chronic obstructive pulmonary disease can lead to RVH, changes in the position of the heart in the chest, and hyperinflation of the lungs. Acute right ventricular pressure overload, such as that caused by pulmonary embolism, can produce a characteristic ECG pattern: a QR or qR pattern in the right-sided leads, an $S_1Q_3T_3$ pattern, and an acute incomplete or complete right bundle branch block (RBBB). However, even the classic $S_1Q_3T_3$ pattern occurs in only approximately 10% of patients with acute pulmonary embolism.

MYOCARDIAL ISCHEMIA

The ST-T segment, representing myocardial repolarization, is the ECG component most sensitive to acute myocardial ischemia. ST elevation, with or without tall positive (hyperacute) T waves, indicates transmural ischemia and is most often the result of acute coronary artery occlusion either by coronary thrombosis or vasospasm (Prinzmetal-variant angina). Reciprocal ST-segment depression may appear in the contralateral leads. Ischemia confined to the subendocardial area is usually denoted by ST-segment depression. Subendocardial, ST-depression–type ischemia typically occurs during episodes of symptomatic or asymptomatic (*silent*) stable angina pectoris, which is characteristic of ischemia occurring during exercise, tachycardia, or pharmacologic stress test in patients with significant but stable coronary artery disease (CAD) (Fig. 47-5).

MYOCARDIAL INFARCTION

With prolonged ischemia, the risk of developing myocardial necrosis or myocardial infarction (MI) is present. The MI signature on an ECG is decreased R-wave

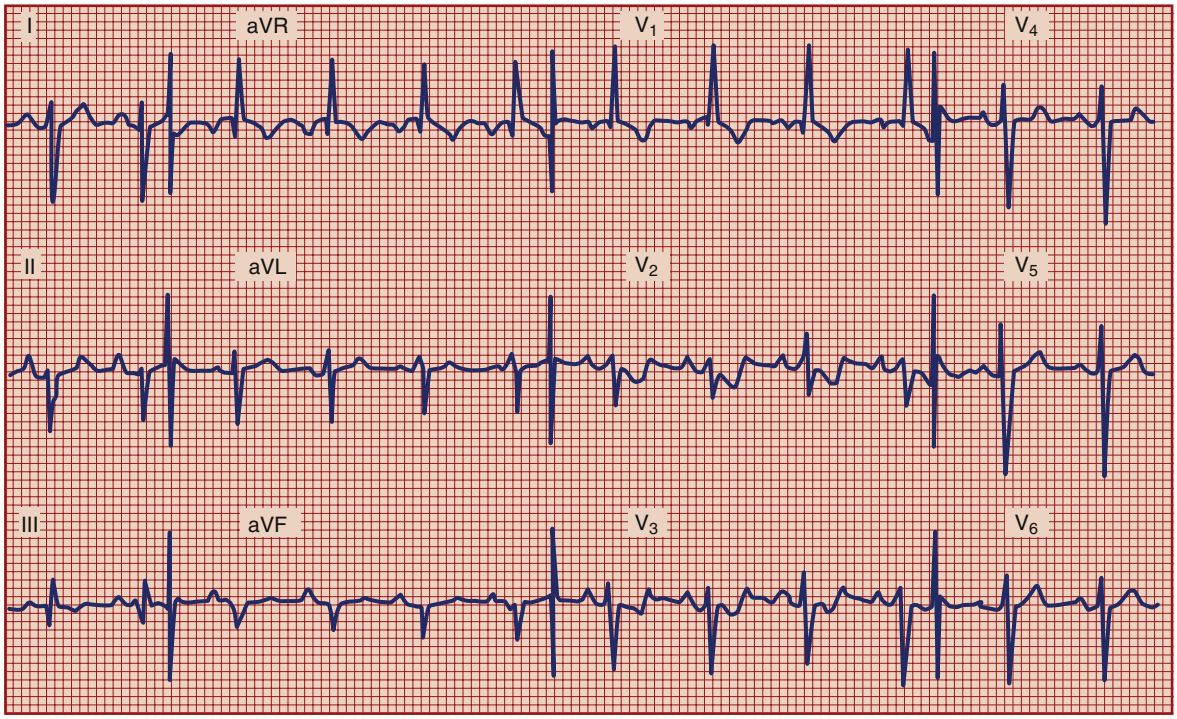


Figure 47-4. Severe right ventricular hypertrophy (RVH). Tall R waves on right-sided leads, deep S waves on left-sided leads, and T-wave inversions in right-sided leads ($S_1Q_3T_3$).

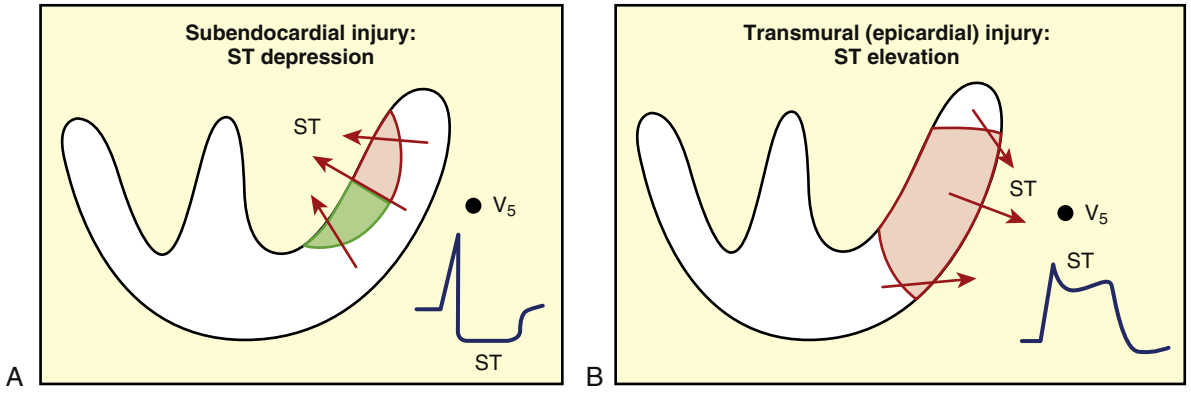


Figure 47-5. Patterns of injury currents. **A,** Acute subendocardial, ST-depression–type ischemia. **B,** Transmural, ST-elevation type ischemia. (From Zipes DP, Libby P, Bonow R, Braunwald E: *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 7, Philadelphia, 2005, Saunders.)

amplitude and pathologic Q waves, which may develop as a result of a loss of electromotive forces in the area of infarction. Transmural infarctions are more likely to culminate in abnormal Q waves, whereas subendocardial (nontransmural) infarctions are less likely to produce Q waves. However, pathologic studies have shown a wide overlap between the two entities and their ECG expression; therefore, *Q-wave* or *non–Q-wave* infarction is not synonymous with transmural or nontransmural infarction. Pathologic Q waves usually develop days after the onset of acute MI; once they develop, they seldom disappear and serve as an indicator for the location of the infarction. Persistent T-wave inversion may also be the only sign of chronic ischemia and a recent or an old MI. Pathologic Q waves, with ST-segment elevation that persists weeks or longer after an MI, strongly correlate with a severe myocardial mechanical dysfunction, akinesis, or ventricular aneurysm.

The ECG leads with ST-T changes or Q waves may help define the location and the coronary artery responsible for the ischemia or infarction. For example, precordial leads V_1 to V_3 correspond to the anteroseptal or apical walls of the left ventricle; leads V_4 to V_6 to the apical or lateral LV walls (Fig. 47-6); leads II, III, and aV_f to the inferior LV wall (Fig. 47-7); and the right-sided leads to the right ventricle. Posterior wall infarction induces ST-segment elevation or Q waves in leads placed over the left side and back (V_7 to $V_{9)}$ and reciprocal ST-segment depression or tall R waves in leads V_1 to V_3 may develop.

ELECTROLYTE ABNORMALITIES

The ECG is affected not only by structural or functional myocardial abnormalities but also by numerous metabolic and electrolyte aberrations.

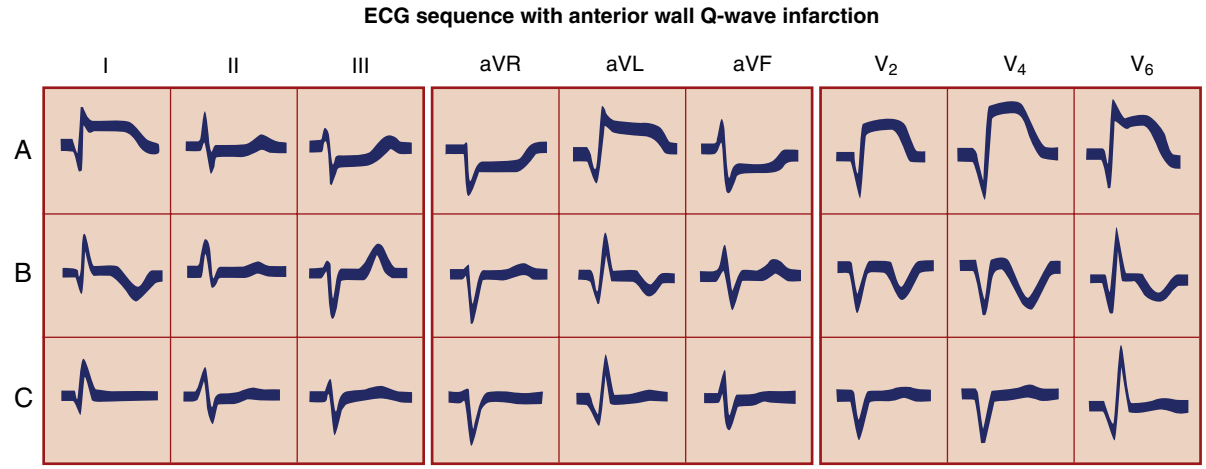


Figure 47-6. Acute ST-elevation–type anterior wall myocardial infarction. **A,** Acute phase: ST elevations and new Q waves. **B,** Evolving phase: deep T-wave inversions. **C,** Resolving phase: partial or complete regression of ST-T changes (and sometimes of Q waves). The reciprocal ST-T changes are noted in the inferior leads (II, III, and aV_F). *(From Figure 8-4 in Goldberg AL:* Clinical electrocardiography: a simplified approach*, ed 7. St. Louis, 2006, Mosby.)*

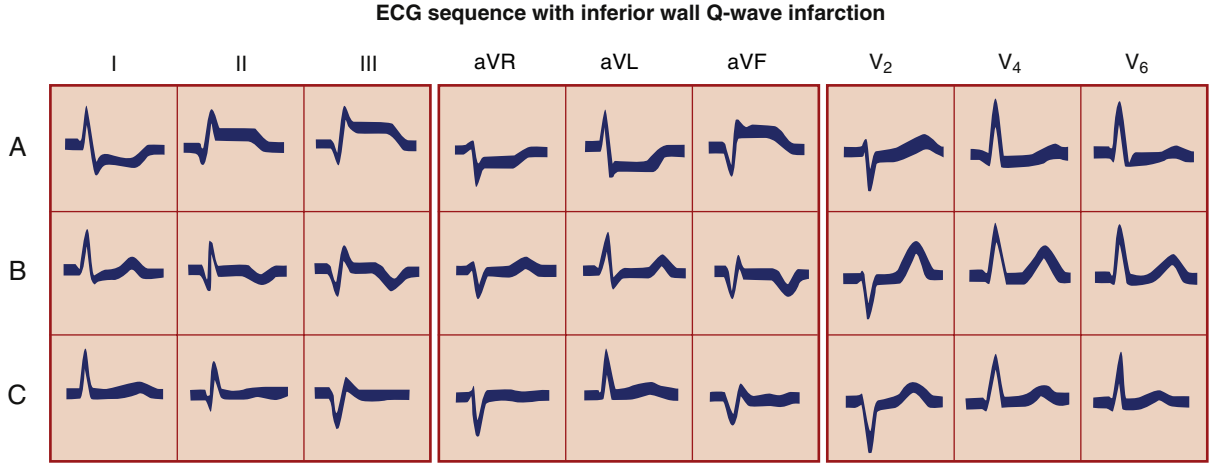


Figure 47-7. Inferior wall myocardial infarction. **A,** Acute phase: ST elevations and new Q waves. **B,** Evolving phase: deep T-wave inversions. **C,** Resolving phase: partial or complete regression of ST-T changes (and sometimes of Q waves). The reciprocal ST-T changes are noted in the anterior leads (I, aV_L, and V_2). *(From Goldberger AL:* Clinical electrocardiography: a simplified approach, *ed 7. St. Louis, 2006, Mosby.)*

Calcium. Hypercalcemia shortens and hypocalcemia prolongs the phase 2 of the action potential duration, thus leading to an abbreviation or a prolongation of the QT interval, respectively. Severe hypercalcemia (e.g., total serum Ca^{2+} >15 mg/dL) causes a decrease in T-wave amplitude or T-wave inversion, and hypercalcemia may produce a high-takeoff ST segment in leads V_1 and V_2, simulating acute ischemia.

Potassium. Hyperkalemia leads to a distinctive sequence of ECG changes, starting with a narrowing and peaking of the T wave and a shortening of QT interval. Progressive hyperkalemia causes QRS widening, low P-wave amplitude, and PR interval prolongation with the possibility of second- to third-degree AV block (Fig. 47-8). Severe hyperkalemia leads to a sine-wave ventricular flutter and eventual asystole. Hypokalemia, in contrast, may cause ST-segment depression, flattened T waves, and prominent U waves, which may sometimes exceed the amplitude of T waves. Hypokalemia prolongs repolarization and leads to long QT(U) syndrome, predisposing to a torsades de pointes–type ventricular fibrillation.

Magnesium. Mild-to-moderate hypermagnesemia or hypomagnesemia is not associated with specific ECG changes. Yet, severe hypermagnesemia can cause AV and intraventricular conduction disturbances, including complete heart block and cardiac arrest (Mg^{2+} >15 mEq/L). Hypomagnesemia is often associated with hypocalcemia or hypokalemia and may predispose to long QT(U) syndrome and torsades de pointes.

ELECTROCARDIOGRAPHIC MONITORING SYSTEMS

NOISE FILTERING

Low-Frequency Filtering

All ECG monitors use filters to narrow the signal bandwidth in an attempt to reduce environmental artifacts and to improve signal quality. Low-frequency noise, such as that produced by respiration or any other patient motion, causes the tracing to wander above and below the

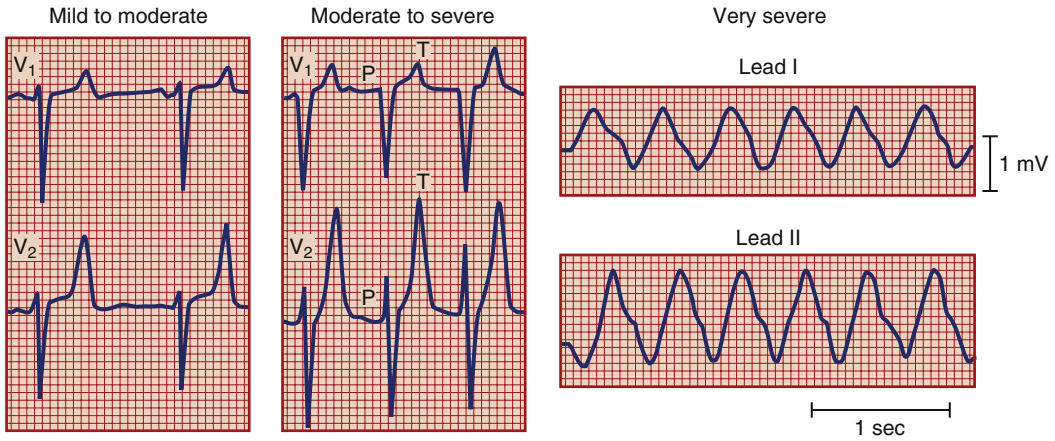


Figure 47-8. Electrocardiographic signs of hyperkalemia. The earliest change with hyperkalemia is peaking ("tenting") of the T waves. With progressive increases in the serum potassium concentration, the QRS complexes widen, the P waves decrease in amplitude and may disappear, and finally a sine-wave pattern leads to asystole unless emergency therapy is administered. *(From Goldberger AL:* Clinical electrocardiography: a simplified approach, *ed 7. St. Louis, 2006, Mosby.)*

baseline. Therefore, low-frequency filters are used in ECG monitoring. The HR in beats per minute (bpm) forms a rough lower bound for the frequency content in Hertz (Hz, cycles per second). Since HRs slower than 40 bpm (0.67 Hz) are uncommon, traditional low-frequency analog filters are used to cut off signals at frequencies below 0.5 Hz. However, such filters introduce considerable distortion into the ECG, particularly with respect to the level of the ST segment, resulting from phase nonlinearities that occur in areas of the ECG signal where frequency content and wave amplitude abruptly change, as occurs where the end of the QRS complex meets the ST segment. The 1975 American Heart Association (AHA) recommendations included a 0.05-Hz low-frequency cutoff for diagnostic ECGs. This recommendation preserves the fidelity of repolarization, but baseline drift can still be a problem. Current modern digital filtering provides more sophisticated methods for a higher cutoff for low-frequency filtration without those phase distortions observed with analog filtering. Thus, to reduce artifactual distortion of the ST segment, current AHA recommendations[1] suggest the low-frequency cutoff should be: (1) 0.05 Hz for monitors with analog filters and (2) 0.67 Hz or below for monitors and ECG recording devices with linear digital filters with zero phase distortion.

High-Frequency Filtering

High-frequency filters are needed to reduce distortions from muscle fasciculations, tremors, and electromagnetic interference from other electrical equipment. Older monitors used a 40-Hz filter to reduce electrical current interferences. However, the higher the frequencies contained in the filtered signal, the more accurate the measurement of rapid upstroke velocity, peak amplitude, and waves of short duration will be. A high-frequency cutoff of 100 Hz was considered adequate by the AHA in 1975 to maintain diagnostic accuracy during visual inspection of an ECG, although it has long been recognized that higher frequency components of the QRS complex may have clinical significance in patients with various forms of heart disease. According to current AHA recommendations, to measure routine duration and amplitudes accurately in adults, adolescents, and children, an upper frequency cutoff of at least 150 Hz is required, and an upper frequency cutoff of 250 Hz is more appropriate for infants.

Most modern ECG monitors allow the operator a choice among several bandwidths. The actual filter frequencies tend to vary among manufacturers. One manufacturer allows a choice of three different filtering modes: (1) a diagnostic mode with a bandwidth of 0.05 to 130 Hz for adults and 0.5 to 130 Hz for neonates, (2) a monitoring mode with a bandwidth of 0.5 to 40 Hz for adults and 0.5 to 60 Hz for neonates, and (3) a filter mode with a bandwidth of 0.5 to 20 Hz. Slogoff and associates evaluated the importance of bandwidth selection on the detection of perioperative myocardial ischemia and showed that the ST-segment positions with all systems using the lower filter limit (0.05 Hz) recommended by the AHA were similar.[2]

THREE-ELECTRODE ELECTROCARDIOGRAPHIC MONITORING

In contrast to the standard 12-lead ECG, in which the four limb electrodes are placed on the wrists and ankles, electrode placement for continuous cardiac monitoring is on the torso to reduce artifacts from limb movement, as well as to avoid tethering the patient. Therefore, the right arm (RA) and left arm (LA) electrodes are placed in the infraclavicular fossae close to the right and left shoulders, respectively, and the left leg (LL) electrode is placed below the rib cage on the left side of the abdomen. The ground or reference electrode (RL), if present, can be placed anywhere, but it is usually placed on the right side of the abdomen.

The three-electrode system is the simplest and most common mode of ECG monitoring in surgical units and intensive care units (ICUs). It allows monitoring three bipolar leads by recording the potential differences between each of three pairs of electrodes: lead I (positive electrode, LA; negative electrode, RA), lead II (positive electrode, LL; negative electrode, RA), lead III (positive electrode, LL; negative electrode, LA), or other

modified chest leads.[3] Three-electrode monitoring is usually adequate for tracking HR, detecting R waves for synchronized direct-current shock in cardioversion, and detecting ventricular fibrillation. However, it is inadequate for diagnosing more complex arrhythmias for which a *true* V_1 lead is necessary, such as to distinguish between right versus left bundle branch block (LBBB) or ventricular tachycardia (VT) and supraventricular tachycardia (SVT) with aberrant ventricular conduction. The three-electrode system is also inadequate for ST-segment monitoring because it does not provide multilead monitoring or precordial leads, which are often most sensitive for detecting ischemia. Modified chest leads such as CS_5 (the RA electrode is placed under the right clavicle, and the LA electrode is placed in the V_5 position) or CB_5 (the RA electrode is placed over the center of the right scapula, and the LA electrode is placed in the V_5 position) may be suitable for the detection of anterior wall myocardial ischemia; however, these modified leads are currently not recommended for monitoring myocardial ischemia.

FIVE-ELECTRODE ELECTROGRAPHIC MONITORING

In the five-electrode monitoring system, the four limb electrodes, LA, RA, LL, and RL placed at their corresponding monitoring locations allow any of the six limb leads (I, II, III, aVR, aVL, and aVF) to be obtained, and a fifth chest electrode can be placed in any of the standard V_1 through V_6 locations (Fig. 47-9). V_1 is the preferred lead for special arrhythmia monitoring, whereas the other precordial leads, especially V_3 to V_5, are the preferred leads for ischemia monitoring. The five-electrode monitoring system is currently the standard for monitoring patients with suspected perioperative myocardial ischemia. The differences in sensitivity and specificity among the different ECG leads in detecting myocardial ischemia are discussed later in this chapter.

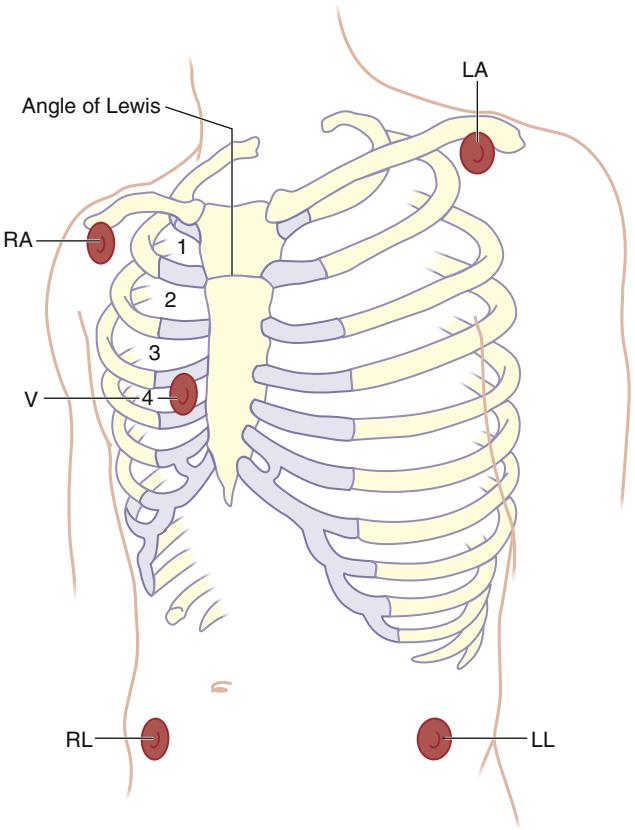


Figure 47-9. Commonly used five-electrode lead system allows the recording any of the six limb leads plus one precordial (V) lead. The lead placement for recording V_1 is shown. A limitation of this system is that only one precordial lead can be recorded. *(From Drew BJ, Califf RM, Funk M, et al: Practice standards for electrocardiographic monitoring in hospital settings: an American Heart Association Scientific Statement from the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young,* Circulation *110:2721-2746, 2004.)*

TEN-ELECTRODE, TWELVE-LEAD ELECTROCARDIOGRAPHIC MONITORING

In 1966, Mason and Likar introduced a variation on positioning the standard limb electrodes of the 12-lead ECG during exercise stress testing to minimize artifacts in the limb leads caused by movement.[4] In this design, the RA and LA electrodes are attached to the right and left infraclavicular fossae and the LL electrode is attached to the left iliac fossa. The RL electrode can be positioned anywhere but is usually placed on the right iliac fossa for symmetry. Although the limb lead QRS complexes are slightly different in amplitude and axis and the precordial leads may also vary slightly from the standard 12-lead ECG recording, studies have shown that the ST-segment measurements during exercise stress testing are only incidentally affected when the Mason-Likar 12-lead ECG system is used, as compared with the standard 12-lead ECG.[5] A major advantage of cardiac monitors using the Mason-Likar 12-lead system is that ST-segment monitoring software has been developed to analyze all 12 leads and to sound an alarm for ST-segment changes, whether or not multiple leads are being displayed on the bedside or central monitor (Fig. 47-10). Therefore, if lead II is being displayed but the patient has a transient ischemic event involving lead V_5, then an ST-segment alarm is triggered. Not all manufacturers that offer the Mason-Likar lead system perform full 12-lead ST-segment analysis nor do they store all 12 leads for printing at a later time. Another advantage of the Mason-Likar lead system is that more than one precordial lead can be displayed at the same time. The disadvantage of the system for cardiac monitoring is that 10 electrodes are required and the 6 precordial electrodes often interfere with diagnostic (e.g., echocardiograms, chest x-ray images) and emergency (defibrillation sites) procedures. In addition, the precordial sites are difficult to maintain on patients with large breasts or hirsute chests.

HOLTER MONITORING

Holter monitoring, originally a cardiologist's tool, has been used by a number of anesthesiologists to document the perioperative incidence of arrhythmias or ischemia. In Holter monitoring, ECG information from two or three bipolar leads is recorded by a miniature recorder. Up to

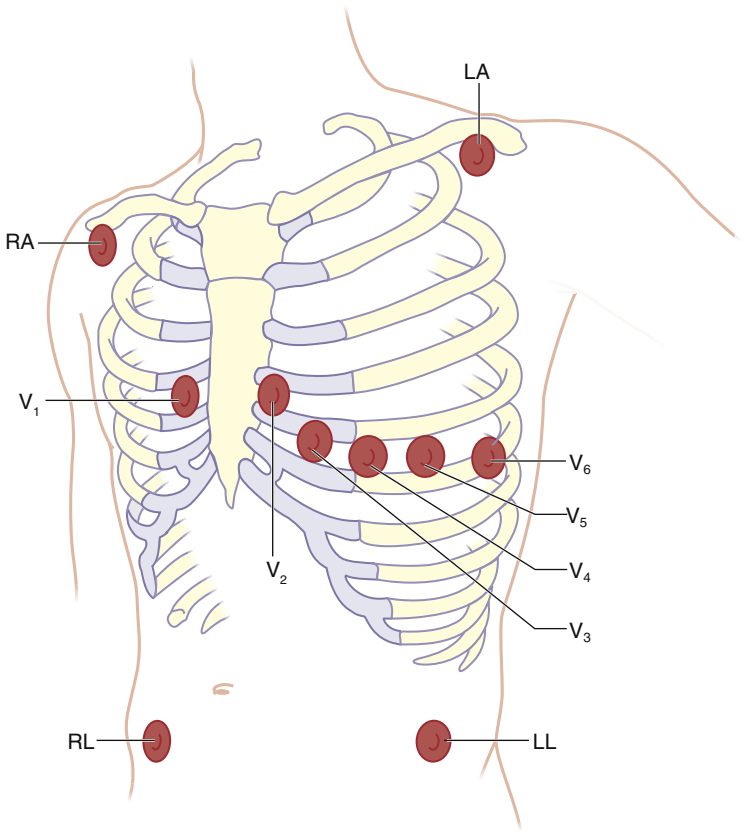


Figure 47-10. Mason-Likar 12-lead electrocardiographic (ECG) system. Anatomic locations for precordial leads are the same as for recording a standard 12-lead ECG, except that the limb leads are relocated from the standard 12-lead ECG positions on the wrists and ankles to the torso. *(From Drew BJ, Califf RM, Funk M, et al: Practice standards for electrocardiographic monitoring in hospital settings: an American Heart Association Scientific Statement from the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young,* Circulation *110:2721-2746, 2004.)*

48 hours of ECG signals can be collected. Subsequently, the data are processed using a playback system, and the ECG signals are analyzed. On most modern systems, the playback unit includes a dedicated computer for rapid analysis and automatic recognition of arrhythmias and ischemia.

A significant early obstacle to the widespread use of conventional Holter monitoring in the perioperative period was its delayed, retrospective analysis and interpretation. This limitation was, to some extent, overcome by real-time Holter monitors, which record specific ECG segments for later playback and also analyze the rhythm and ST segment in real time to alert the user to an acute event.[6,7] However, despite significant technical progress, Holter monitoring devices continue to be limited primarily to clinical investigations.

ARRHYTHMIA INTERPRETATION AND MANAGEMENT

Little doubt remains that during prolonged visual ECG monitoring, certain arrhythmias may go undetected. It has been demonstrated that coronary care unit nurses failed to detect serious ventricular arrhythmias in 84% of their patients.[8] Subsequently, computerized monitors have been designed for the automatic detection of arrhythmias in an attempt to increase the detection rate of abnormal, potentially dangerous rhythms. These monitors use proprietary sophisticated algorithms such as pattern recognition, measurements of QRS width, onset, offset, amplitude, and area calculations to classify complexes into morphologic families.[9,10] Most monitors are capable of detecting potentially fatal arrhythmias such as severe bradycardia or asystole and dangerous tachycardia such as VT or fibrillation. Yet, no study to date has evaluated the accuracy, sensitivity, and specificity of these automated, real-time arrhythmia detection monitors. However, the detection of clinically important dysrhythmias in the cardiac ICU has been shown to improve significantly if a nurse watches the monitor and pays attention to the alarms.[11] Thus today's computerized monitoring systems still have not achieved the level of accuracy sufficient to eliminate the need for human surveillance; the alarms must be recognized and the ECG interpreted and acted upon by a knowledgeable person in a timely fashion (see also Chapters 67 and 68).

DIAGNOSIS OF ARRHYTHMIAS

Arrhythmias are common during and after surgery and have numerous causes. Postoperative dysrhythmias are most likely to occur in patients with structural heart disease. The initiating factor for an arrhythmia after surgery is usually a transient insult such as hypoxemia, cardiac ischemia, catecholamine excess, or electrolyte abnormality.[12] Using perioperative Holter recordings, Mahla and colleagues[13] evaluated how anesthesia and surgery affect the course of ventricular dysrhythmias (premature ventricular beats and repetitive forms of ventricular beats—couplets and nonsustained VT) preoperatively noted in patients with structural heart disease undergoing

noncardiac surgery. They concluded that the frequency of ventricular dysrhythmias was not associated with an adverse cardiac outcome. The incidence of perioperative dysrhythmia in patients with an adverse outcome (8%) did not differ from those with a good outcome. Patients undergoing cardiac surgery have a higher incidence of cardiac dysrhythmias. The incidence of new onset atrial fibrillation alone after cardiac surgery approaches 33% and is associated with a worse outcome.[14] Several major factors contribute to the development of perioperative arrhythmias:

1. **General anesthetics.** Volatile anesthetics, such as halothane or enflurane, produce arrhythmias, probably by a reentrant mechanism.[15] Halothane also sensitizes the myocardium to endogenous and exogenous catecholamines. Drugs that block the reuptake of norepinephrine, such as cocaine and ketamine, can facilitate the development of epinephrine-induced arrhythmias (see Chapter 28). In contrast, volatile anesthetics may have an antifibrillatory effect in response to acute coronary occlusion and reperfusion, at least in a canine model.[16] Sevoflurane may cause severe bradycardia and nodal rhythm when used in high concentrations during induction in infants,[17] and desflurane may prolong QTc within the first minute of anesthesia in patients with a normal heart.[18]
2. **Local anesthetics.** Regional anesthesia by central neuraxial blockade, the goal of spinal or epidural anesthesia, may be associated with a profound, albeit transient, pharmacologic sympathectomy (also see Chapters 36 and 56). This phenomenon may cause parasympathetic nervous system dominance, leading to mild to very severe bradyarrhythmias. This result is especially true when the blockade extends to very high thoracic levels. An inadvertent intravascular injection of a large dose of local anesthetic agent may lead to asystole and cardiac arrest that are difficult to treat.[19] One proposed treatment is the administration of 20% intralipid.[20,21]
3. **Abnormal arterial blood gases or electrolyte levels.** Excessive hyperventilation, especially in the presence of low serum potassium levels, may precipitate severe cardiac arrhythmias.[22] Alterations of blood gases or electrolytes may lead to arrhythmias by producing reentrant mechanisms or by altering phase 4 depolarization of conduction fibers. Electrolyte disturbances associated with cardiopulmonary bypass can also lead to intraoperative arrhythmias (see Chapters 59 and 67).
4. **Endotracheal intubation.** This maneuver may be the most common cause of arrhythmias during surgery and is often associated with hemodynamic disturbances by eliciting autonomic reflexes (see also Chapter 55).
5. **Autonomic reflexes.** Vagal stimulation may produce sinus bradycardia and may allow ventricular escape mechanisms to occur. Vagal stimulation may also produce AV block or even asystole. These reflexes may be related to traction on the peritoneum or to direct pressure on the vagus nerve during carotid surgery (see Chapter 69). During jugular vein cannulation, stimulation of the carotid sinus by palpation of the neck can lead to bradyarrhythmias. Specific reflexes, such as the oculocardiac reflex, can also produce severe bradycardia or asystole.
6. **Central nervous system stimulation and dysfunction of the autonomic nervous system.** Many ECG abnormalities can occur in patients with intracranial disease, especially subarachnoid hemorrhage. These abnormalities are most commonly ST-T wave changes and may easily mimic myocardial ischemia and MI[23] (see Chapter 70). The mechanism of these arrhythmias appears to be related to changes in autonomic nervous system tone.
7. **Preexisting cardiac disease.** Preexisting cardiac disease is probably the most common background for arrhythmias during anesthesia and surgery.[24] Patients with a preexisting tendency for atrial or ventricular arrhythmias are more likely to exhibit them during or after surgery in response to the perioperative stresses or secondary to acute withdrawal of oral antiarrhythmic medications, most commonly β-adrenergic blockers.
8. **Central venous cannulation.** The insertion of catheters or wires into the central circulation often leads to arrhythmias (see Chapter 45).
9. **Surgical manipulation of the cardiac structures.** Arrhythmias are often observed during the insertion of atrial sutures or the placement of venous cannulae for cardiopulmonary bypass during cardiac surgery (see Chapters 67, 68, and 94). These arrhythmias are usually self-limiting and cease at the end of manipulation.
10. **Location of surgery.** Dental surgery is often associated with arrhythmias because profound stimulation of sympathetic and parasympathetic nervous systems often occurs.[25] Junctional rhythms are often observed and may be caused by stimulation of the autonomic nervous system by the fifth cranial nerve. The oculocardiac reflex leads to severe bradycardia in response to traction of the rectus muscles of the orbit. This reflex, which is mediated by the trigeminal nerve as the afferent limb and the vagus nerve as the efferent limb, is especially sensitive in neonates and children and common during strabismus operations.

After an arrhythmia is recognized, determining whether it produces a hemodynamic disturbance, what type of treatment is required, and how urgently therapy should be instituted are important. Treatment should be promptly initiated if the arrhythmia results in significant hemodynamic impairment. Prompt treatment should also be instituted if the arrhythmia is a precursor for a more severe arrhythmia (e.g., frequent multifocal ventricular premature beats [VPBs] with R-on-T phenomenon can lead to ventricular fibrillation). In addition, arrhythmias that may be detrimental on the background of a patient's underlying cardiac disease (e.g., any tachycardia in a patient with mitral valve stenosis, aortic valve stenosis, or ischemic heart disease) need immediate attention. Arrhythmias can be classified by HR or by their anatomic origin in the heart. Using HR criteria, arrhythmias can be broken down into three categories: bradyarrhythmias (HR <60 bpm), tachyarrhythmias (HR >100 bpm), and conduction blocks (at any HR). The anatomic origin of an arrhythmia can be ventricular, supraventricular,

junctional, or elsewhere. Using the following checklist can simplify the diagnosis and treatment of arrhythmias when looking at an ECG display:

1. What is the HR?
2. Is the rhythm regular?
3. Is one P wave present for each QRS complex?
4. Is the QRS complex normal?
5. Is the rhythm dangerous?
6. Does the rhythm require treatment?

The following text analyzes some common intraoperative arrhythmias.

SINUS BRADYCARDIA

Sinus bradycardia is defined when the pacemaker site is in the sinus node, but the rate is slower than normal. Etiologic factors include drug effects, acute inferior MI, hypoxia, vagal stimulation, and high sympathetic blockade. Sinus bradycardia accounts for approximately 11% of intraoperative arrhythmias. The characteristics of sinus bradycardia are as follows:

1. HR: Is slower than 60 bpm. In patients on chronic β-adrenergic blocker therapy, sinus bradycardia is defined as a HR slower than 50 bpm.
2. Rhythm: Is regular, except for occasional escape beats from other pacemaker sites.
3. P/QRS: The ratio of the P waves to the QRS complexes is 1:1.
4. QRS complex: Has a normal morphologic appearance.
5. Significance: HRs slower than 40 bpm are poorly tolerated even in healthy patients and should be evaluated on the basis of their effect on cardiac output. Treatment is recommended if hypotension, ventricular arrhythmias, or signs of poor peripheral perfusion are observed. Sinus bradycardia may be part of the sick sinus syndrome, in which sinus node dysfunction can precipitate bradycardias, heart block, tachyarrhythmias, or alternating bradyarrhythmias and tachyarrhythmias.[26]
6. Treatment: Is not usually necessary. When treatment is deemed necessary, the following progression may be considered: (1) atropine, 0.5 to 1.0 mg by intravenous (IV) bolus, repeated every 3 to 5 minutes, up to 0.04 mg/kg or approximately a 3.0-mg total dose for the average 75-kg male patient); (2) ephedrine, 5 to 25 mg by IV bolus; (3) dopamine or dobutamine (if blood pressure is adequate), 5 to 20 μg/kg/min by IV infusion; (4) epinephrine, 2 to 10 μg/min IV infusion; and (5) isoproterenol, 2 to 10 μg/min by IV infusion. Temporary transcutaneous or transvenous pacing may be necessary for severe, drug-refractory sinus bradycardia. Immediate institution of transcutaneous pacing is especially important in symptomatic patients.

SINUS TACHYCARDIA

Sinus tachycardia is defined when the pacemaker site is in the sinus node, and the rate is faster than normal. Sinus tachycardia is the most common arrhythmia in the perioperative period. It occurs with such frequency that it is not included in most arrhythmia incidence studies. Common causes include pain, inadequate anesthesia, hypovolemia, fever, hypoxia, hypercarbia, heart failure, and drug effects. The characteristics of sinus tachycardia are as follows:

1. HR: Is faster than 100 bpm in the adult patient and may be as high as 170 bpm. Patients with significant CAD may not tolerate HRs as low as 70 to 80 bpm and may develop subendocardial ischemia. Similarly, patients with severe mitral or aortic stenosis may be sensitive to even moderate increases in the HR.
2. Rhythm: Is regular.
3. P/QRS: The ratio of the P waves to the QRS complexes is 1:1.
4. QRS complex: Is normal, but ST-segment depression with severe increases in HR and resulting myocardial ischemia may be associated.
5. Significance: Prolonged tachycardias in patients with underlying heart disease can precipitate MI and congestive heart failure because of the increased myocardial work required and the decreased supply of myocardial oxygen by means of decreased diastolic coronary perfusion time. A major diagnostic problem is encountered when the HR is 150 bpm, because this rate is common for sinus tachycardia, paroxysmal atrial tachycardia, or atrial flutter with a 2:1 block. These three arrhythmias can sometimes be separated by the use of carotid sinus massage, IV administration of edrophonium, or adenosine phosphate.
6. Treatment: The underlying disorder should be treated. Hypovolemia and light anesthesia are the most common causes. In patients with ischemic heart disease who develop tachycardia, β-adrenergic blockers should be judiciously used to prevent myocardial ischemia, regardless of whether ST-segment changes occur. Hypovolemia or other causes should also be addressed in these patients.

SINUS ARRHYTHMIA

In sinus arrhythmia, the impulses arise from the SA node and a variable HR characterizes the rhythm. The PR interval is normal, as is the QRS complex. Most commonly, but not invariably, the rate increases with inspiration and decreases with expiration. This arrhythmia occurs more often in children than in adults. The characteristics of sinus arrhythmia are as follows:

1. HR: Is 60 to 100 bpm.
2. Rhythm: Is irregular.
3. P/QRS: The ratio of the P waves to the QRS complexes is 1:1.
4. QRS complex: Has normal morphologic appearance.
5. Significance: Has little clinical significance.
6. Treatment: Is considered a normal finding and requires no treatment.

ATRIAL PREMATURE BEATS

An ectopic pacemaker site in the left or the right atrium initiates the atrial premature beat (APB). The shape of the P wave is different from the usual SA node P wave and may be inverted. The PR interval may be shorter or longer than normal, depending on the site of the ectopic

focus and on the refractoriness of the AV nodal pathway. The APB spreads through the AV node and ventricular conduction system and, in retrograde fashion, reaches the SA node, resetting the sinus pacemaker. The interval from the APB to the next sinus beat is therefore a normal sinus cycle (i.e., no compensatory pause). The absence of a compensatory pause is an important distinguishing feature between APBs and VPBs. Occasionally, APBs may find part of the ventricular conduction system refractory. In these instances, they travel down an aberrant pathway and create an abnormal QRS complex. They are then called *APBs with aberrant ventricular conduction* and can easily be confused with VPBs. Because the recovery period of the right ventricular conduction system outlasts that of the left, the most common form of aberration appears as an RBBB. Helpful points in separating APBs with aberrant ventricular conduction from VPBs include (1) the presence of a preceding P wave, usually abnormally shaped; (2) an RBBB configuration of the QRS complex; (3) the presence of an rsR′ ventricular complex in V_1; and (4) the finding that the initial vector forces are identical to the preceding beat but are usually the opposite with a VPB. The characteristics of APBs are as follows:

1. HR: Is variable, depending on the frequency of the APBs.
2. Rhythm: Is irregular.
3. P/QRS: The ratio of P waves to QRS complexes is usually 1:1. The P waves have various shapes and may even be lost in the QRS or T waves. Occasionally, the P wave is so early as to find the ventricle refractory, and a nonconducted beat occurs.
4. QRS complex: Is usually normal unless ventricular aberration occurs.
5. Significance: In one study, APBs represented 10% of all intraoperative arrhythmias. They have little clinical significance, but frequent APBs may lead to other, more serious supraventricular arrhythmias or may be a sign of digitalis intoxication.
6. Treatment: Is rarely necessary.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

A rapid regular rhythm, usually with a narrow QRS complex and lacking the normal SA node P wave, characterizes paroxysmal SVT (PSVT). The inclusion of tachycardias involving the AV node (Fig. 47-11) allows a useful classification of tachycardias as caused by reentry in the AV node, by apparent or concealed accessory AV pathways or, less often, by the SA node. Ectopic atrial or ectopic nodal tachycardias are also among the less frequent SVTs. Inappropriate or persistent sinus tachycardia is another variant. PSVT rhythms are usually abrupt in onset and termination. PSVT is easily distinguished from rapid atrial fibrillation, which is an irregular rhythm, or from rapid atrial flutter, which has flutter waves. The characteristics of PSVT are as follows:

1. HR: Is between 130 and 270 bpm.
2. Rhythm: Is usually regular unless the impulse originates from multiple atrial foci.
3. P/QRS: Has a 1:1 relationship, although the P wave may often be hidden in the QRS complex or T wave.
4. QRS complex: Is generally normal, but ST-T changes indicative of ischemia may be observed. Aberration of ventricular conduction may occur, complicating the differential diagnosis with VT. SVT may also be confused with sinus tachycardia, atrial flutter, and atrial fibrillation. In differentiating these rhythms, carotid sinus massage or edrophonium (5 to 10 mg IV) was traditionally used. More recently, adenosine (6 to 12 mg by IV bolus) has been used to slow the rate by transiently enhancing the normal degree of AV block or terminate the arrhythmia.[27] Esophageal electrocardiographic leads may also be helpful to better define atrial activity.[28]
5. Significance: PSVT can be observed in 5% of normal young adults and in patients with Wolff-Parkinson-White syndrome or other preexcitation syndromes. During anesthesia, PSVT accounts for up to 2.5% of all arrhythmias, and the arrhythmia has been associated with intrinsic heart disease, systemic illness, thyrotoxicosis, digitalis toxicity, pulmonary embolism, and pregnancy. When a patient is under anesthesia, PSVT can be precipitated by changes in the tone of the autonomic nervous system, by drug effects, or by intravascular volume shifts and can produce severe hemodynamic deterioration. Sometimes the PSVT may be associated with AV block because of the fast atrial rate and slow AV conduction. PSVT with 2:1 block represents digitalis intoxication in many patients.
6. Treatment: Often, this arrhythmia must be treated because of its rapid rate and associated poor hemodynamic function. One or several of the following treatments can be undertaken:
   a. Vagal maneuvers such as carotid sinus massage should only be applied to one side.[29]
   b. Adenosine, which is the drug of choice, is given by 6-mg rapid (2 seconds) IV bolus, preferably through an antecubital or central vein. If no response is elicited, the second and third doses of 12 to 18 mg of adenosine may be administered by rapid IV bolus.[30]
   c. Verapamil (2.5 to 10 mg given IV) successfully terminates AV nodal reentry in approximately 90% of patients. This was the first drug of choice but is now the second choice.[31]
   d. Amiodarone (150-mg infusion over 10 minutes for the loading dose) is a recent addition.[32]
   e. Esmolol (1 mg/kg by bolus and 50 to 200 mg/kg/min by infusion) has been shown to be effective.[33]
   f. Edrophonium or neostigmine by IV bolus can be administered.[34]
   g. Phenylephrine (100 μg by IV bolus) is administered if the patient is hypotensive.[35]
   h. IV digitalization is performed with one of the short-acting digitalis preparations: ouabain (0.25 to 0.5 mg administered IV) or digoxin (0.5 to 1.0 mg administered IV, slow loading).[36]
   i. Rapid overdrive pacing may be performed in an effort to capture the ectopic focus.[36]
   j. Synchronized cardioversion may be performed with incremental doses of energy of 100, 200, 300, and 360 J, preferably after light sedative premedication.[37] Electrode catheter ablation using radiofrequency energy has evolved as the definitive, long-term treatment for most persistent AV reentrant or focal atrial SVTs.[38]

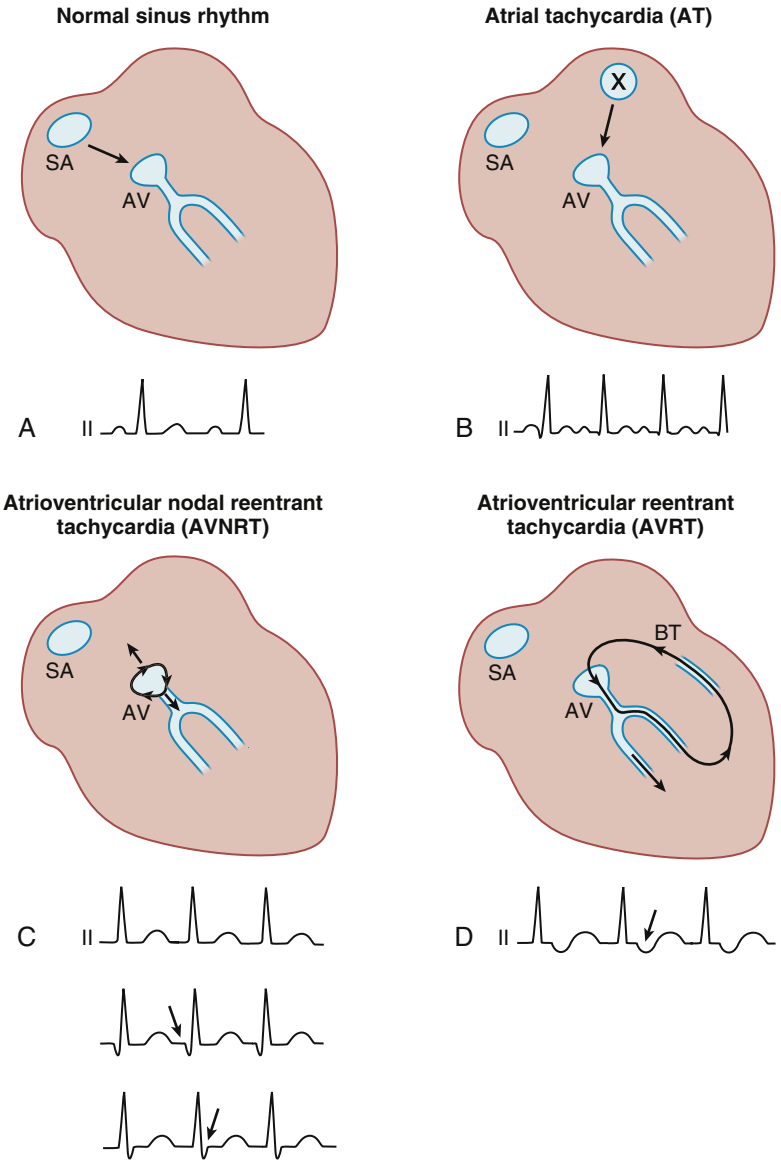


Figure 47-11. Major types of paroxysmal supraventricular tachycardia. **A,** Normal sinus rhythm. **B,** Atrial tachycardia (AT). A focus *(X)* outside the sinoatrial (SA) node automatically fires off at a rapid rate. **C,** Atrioventricular (AV) nodal reentrant tachycardia (AVNRT). The cardiac stimulus originates as a wave of excitation that spins around the AV nodal (junctional) area. As a result, retrograde P waves may be buried in the QRS complex or appear immediately before or just after the QRS complex *(arrows)* because of nearly simultaneous activation of the atria and ventricles. **D,** A similar type of reentrant (circus-movement) mechanism may occur with a bypass tract (BT) of the type found in Wolff-Parkinson-White syndrome. This mechanism is referred to as *atrioventricular reentrant tachycardia* (AVRT). The negative P wave is noted *(arrow)* in lead II, somewhat after the QRS complex. (With AVRT, the P wave in lead II may be negative or isoelectric.) *(From Goldberger AL: Clinical electrocardiography: a simplified approach, ed 7. St. Louis, 2006, Mosby.)*

ATRIAL FLUTTER

Atrial flutter most commonly represents a macro-reentrant arrhythmia that circulates in a specific manner in the right atrium (i.e., counterclockwise rotation as viewed in the angiographic left anterior oblique view). Because atrial flutter is associated with very fast HRs, it is usually accompanied by AV block. Classic sawtooth flutter waves (F waves) are usually present (Fig. 47-12). The characteristics of atrial flutter are as follows:

1. HR: The atrial HR is 250 to 350 bpm with a ventricular rate of approximately 150 bpm (2:1 or 3:1 AV conduction block).
2. Rhythm: The atrial rhythm is regular. The ventricular rhythm may be regular if a fixed AV block is present or irregular if a variable block exists.
3. P/QRS: Usually, a 2:1 block exists with an atrial rate of 300 bpm and a ventricular rate of 150 bpm, but the block may vary between 2:1 and 8:1. F waves are best observed in leads V_1 and II and in the esophageal lead.
4. QRS complex: Is normal. T waves are lost in the F waves.
5. Significance: Atrial flutter usually indicates the presence of severe heart disease. It is recognized with increased incidence in patients with CAD, mitral valve disease, pulmonary embolism, hyperthyroidism, cardiac trauma, cancers of the heart, and myocarditis.
6. Treatment: Pharmacologic or synchronized direct current (DC) cardioversion, when indicated, should be performed only after careful consideration or evaluation of a possible thromboembolic event.

   The initial treatment should be to gain control of the ventricular response rate with agents that slow AV node conduction:
   a. β-Adrenergic blockers such as IV esmolol (1 mg/kg by IV bolus) or propranolol
   b. Calcium channel blockers such as verapamil (5 to 10 mg given IV) or diltiazem[39]

      β-Adrenergic blockers and calcium channel blockers are also effective as pharmacoprophylaxis

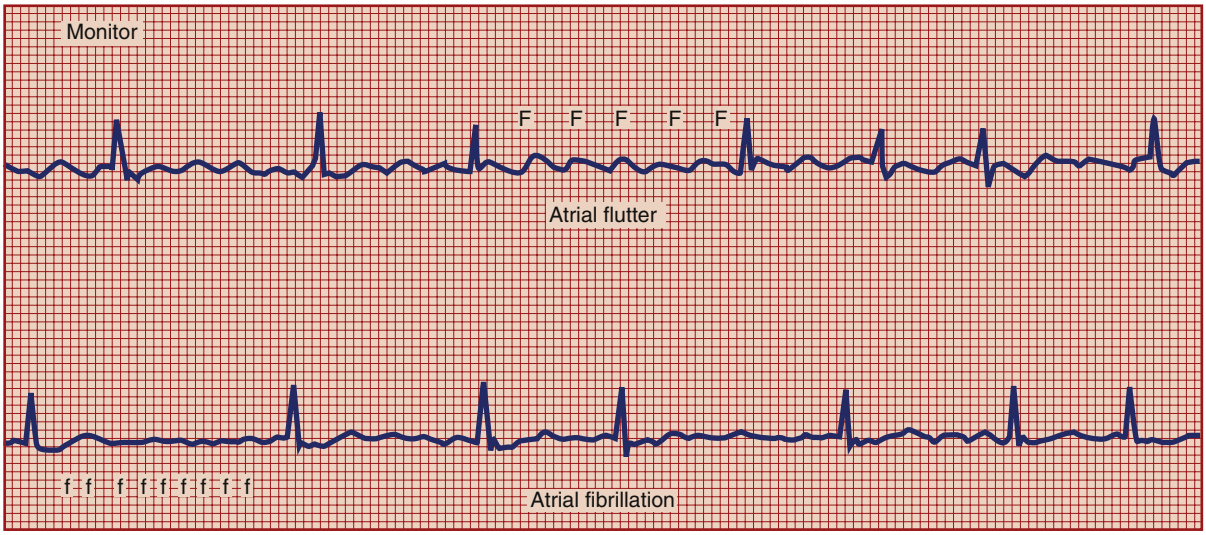


Figure 47-12. Atrial flutter and fibrillation. The "sawtooth" waves (F waves) are noted with atrial flutter and the irregular fibrillatory waves (f waves) with atrial fibrillation. *(From Goldberger AL:* Clinical electrocardiography: a simplified approach*, ed 7. St. Louis, 2006, Mosby.)*

for the prevention of postoperative atrial tachyarrhythmias after thoracic and cardiac surgery.[40]

If the ventricular response is excessively rapid or secondary hemodynamic instability is present, or both, then the following guidelines are used:

a. Synchronized DC cardioversion is indicated, starting with a relatively high energy of 100 J and gradually increasing to 360 J.
b. The class III antiarrhythmic agent ibutilide (Corvert, 1 mg in 10 mL saline, or 5% dextrose in water (D_5W), infused IV slowly over 10 minutes) has been documented to convert atrial flutter to sinus rhythm in most patients with relatively new-onset atrial flutter[41] and may be repeated once. Although it is highly effective, life-threatening torsade de pointes (discussed later in this chapter) may occur hours after ibutilide administration, making 4- to 8-hour monitoring after treatment highly desirable.
c. Procainamide (5 to 10 mg/kg for the IV loading dose, infused no faster than 0.5 mg/kg/min) may rarely be used in an attempt to restore sinus rhythm after the ventricular response has been adequately controlled.[42]

ATRIAL FIBRILLATION

Atrial fibrillation is an excessively rapid and irregular atrial focus with no P waves appearing on the ECG; instead, a fine fibrillatory activity is seen (F waves, see Fig. 47-12) and is the most irregular rhythm; it is called *irregularly irregular* and may be associated with a pulse deficit. The characteristics are as follows:

1. HR: The atrial rate is 350 to 500 bpm, and the ventricular rate is 60 to 170 bpm.
2. Rhythm: Is irregularly irregular.
3. P/QRS: The P wave is absent and replaced by F waves or no obvious atrial activity.
4. QRS complex: Is normal.
5. Significance: The causes of atrial fibrillation are similar to those of atrial flutter. This rhythm is often associated with significant cardiac disease; however, idiopathic lone paroxysmal atrial fibrillation has become increasingly recognized. The clinical significance and treatment of atrial fibrillation are also similar to those of atrial flutter, except for two important considerations. The loss of an atrial *kick* from inefficient contraction of the atria may reduce ventricular filling and may significantly compromise cardiac output. After 24 hours, atrial fibrillation may be associated with the development of atrial thrombi, with resultant pulmonary and systemic embolization.

   Atrial fibrillation is the most common postoperative arrhythmia with significant consequences on patient health. Postoperative atrial fibrillation complicates up to 8% of all noncardiac surgeries, between 3% and 30% of noncardiac thoracic surgeries, and between 16% and 46% of cardiac surgeries. It has been associated with increased morbidity; mortality; and longer, more costly hospital stays. Several epidemiologic and intraoperative factors, as well as the presence of preexisting cardiovascular and pulmonary disorders, may affect the risk of atrial fibrillation after cardiac and noncardiac surgeries. It is typically a transient, reversible phenomenon that may develop in patients who possess an electrophysiologic substrate for the arrhythmia that is present before or as a result of surgery. The efficacy of β-adrenergic blockers in postoperative atrial fibrillation prevention is well documented. Perioperative amiodarone, sotalol, nondihydropyridine calcium channel blockers, and magnesium sulfate can reduce the occurrence of atrial fibrillation.[43]
6. Treatment:
   a. Acute atrial fibrillation: The treatment of acute atrial fibrillation is similar to that for atrial flutter. More attention should be focused on ventricular response, especially with the administration of IV diltiazem or esmolol. Ibutilide may restore sinus

rhythm, but it is less effective than in the treatment of flutter. Synchronized DC cardioversion should be used in patients with pronounced hemodynamic instability. However, if fibrillation is present for longer than 48 hours, then attempts to restore sinus rhythm may be associated with a heightened risk of thromboembolism. In this setting, for a patient with normal coagulation function, adequate anticoagulation for 3 to 4 weeks should be considered before attempting to restore sinus rhythm. New developments in electrophysiologic techniques for ventricular defibrillation with biphasic current shocks have shown superiority to the conventional monophasic current techniques (discussed later in this chapter). However, data regarding biphasic shocks for conversion of atrial fibrillation are still emerging. A randomized, double-blind, multicenter trial by the BiCard Investigators[44] demonstrated that for the cardioversion of atrial fibrillation, a biphasic shock waveform has greater efficacy, requires fewer shocks and lower delivered energy, and results in less dermal injury than a monophasic shock waveform. These results mirror those observed in the ventricular fibrillation trials.

b. Long-term therapy: Long-term therapy of atrial fibrillation varies and depends on factors such as whether the arrhythmia is constant or paroxysmal, the nature of the underlying heart disease, and the state of ventricular function or hemodynamic stability or reserve. In the older individual or in the setting of specific risk factors (e.g., hypertension, diabetes mellitus, severe LV systolic dysfunction), anticoagulation with warfarin should be strongly considered. When control of ventricular response is difficult with standard drugs (e.g., β-adrenergic blockers, calcium channel blockers, digitalis), electrode catheter ablation of the AV junction and permanent pacemaker insertion are sometimes used. Another treatment option for chronic or recurrent atrial fibrillation is the Maze procedure, often performed during cardiac surgery with cardiopulmonary bypass. During this procedure, a number of incisions or scars are made by means of radiofrequency, freezing, or microwaves on the left and right atrium, resulting in a disruption of the abnormal electrical pathways from the sinus node to the AV node. The scar tissue also prevents erratic electrical signals from recurring. In the absence of CAD or significant LV systolic dysfunction, class Ic antiarrhythmic agents (e.g., flecainide, propafenone) have become the agents of choice.[45] The use of class Ia drugs (e.g., quinidine, procainamide, disopyramide) has sharply diminished because of concerns about their significant proarrhythmic function and their systemic and organ side effects. The use of antiarrhythmic drugs that block repolarizing potassium currents (e.g., sotalol,[46] amiodarone[47]) has gained popularity for the suppression of atrial fibrillation in individuals with significant structural heart disease. Sotalol, however, has a much lower efficiency of converting atrial fibrillation than the class Ic agents. New class III agents show good efficacy in converting atrial fibrillation. Ibutilide converts rapidly, can be effective in up to 50% of patients,[48] and is more effective than sotalol or procainamide. Nevertheless, all these drugs also exhibit significant proarrhythmic properties.

JUNCTIONAL RHYTHMS

The AV node itself shows no intrinsic phase 4 depolarization. Cells in the node cannot act as pacemakers. Ectopic activity, however, may be initiated from sites just above and below the AV node. Considering these arrhythmias as AV junctional in nature makes sense. The resultant P wave is abnormal and, depending on the position of the ectopic pacemaker, may be close to, buried in, or after the QRS complex. Depending on the rate of fire of the ectopic pacemaker, the resultant rhythm is nodal premature, nodal quadrigeminy, trigeminy, or bigeminy, nodal rhythm, or nodal tachycardia. The characteristics of junctional rhythms are as follows:

1. HR: Is variable, between 40 and 180 bpm (i.e., nodal bradycardia to junctional tachycardia).
2. Rhythm: Is regular.
3. P/QRS: The ratio is 1:1 but, three varieties have been identified:
   a. High-nodal rhythm: The impulse reaches the atrium before the ventricle; the P wave therefore precedes the QRS but has a shortened PR interval (0.1 second).
   b. Mid-nodal rhythm: The impulse reaches the atrium and the ventricle at the same time. The P wave is lost in the QRS complex.
   c. Low-nodal rhythm: The impulse reaches the ventricle first and then the atrium; therefore, the P wave follows the QRS complex.
4. QRS complex: Is normal, unless altered by the P wave.
5. Significance: Junctional rhythms are common in patients under anesthesia (approximately 20%) especially with volatile anesthetic agents. The junctional rhythms frequently decrease blood pressure and cardiac output by approximately 15%, but they can decrease it up to 30% in patients with heart disease.[49]
6. Treatment: Usually, no treatment is required, and the rhythm spontaneously reverts. If hypotension and poor perfusion are associated with the rhythm, then treatment is indicated. Atropine, ephedrine, or isoproterenol can increase the activity of the SA node and take over as the pacemaker. Dual-chamber electrical pacing at a rate faster than a slow nodal rhythm is another option.

VENTRICULAR PREMATURE BEATS

VPBs result from ectopic pacemaker activity arising below the AV junction. The VPB originates in and spreads through the myocardium or ventricular conducting system, resulting in a wide (>0.12 second) and bizarre QRS complex. The ST segment usually slopes in the direction opposite to that of the main deflection of the QRS complex. No P wave is associated with a VPB, but retrograde depolarization of the atria or blocked sinus beats may obscure the diagnosis.

The most important entity in the differential diagnosis is APB with aberrant ventricular conduction. The distinction should be made whenever possible.

Although an APB normally reaches the SA node and resets the sinus rhythm, such an occurrence is rare when the ectopic pacemaker is in the ventricle. A VPB often blocks the next depolarization from the SA node, but the following sinus beat occurs on time. The result is a compensatory pause, consisting of the interval from the VPB to the expected normal QRS, which is blocked at the AV node, plus a normal sinus interval.

VPBs are common during anesthesia, accounting for 15% of observed arrhythmias. They are significantly more common in anesthetized patients with preexisting cardiac disease. Other than heart disease, known etiologic factors include electrolyte and blood gas abnormalities, drug interactions, brainstem stimulation, and trauma to the heart. The characteristics of VPBs are as follows:

1. HR: Depends on the underlying sinus rate and frequency of the VPBs.
2. Rhythm: Is irregular.
3. P/QRS: No P wave is associated with VPBs.
4. QRS complex: Is wide and bizarre, with a width of more than 0.12 second. If it is of an RBBB nature, then prominent R forces are present in V_1. If it is a LBBB in appearance, then notching of the S wave and less acute downslopes are common.
5. Significance: The new onset of VPBs must be considered a potentially serious event because, in certain clinical situations, the arrhythmia may progress to VT or ventricular fibrillation. These situations include coronary artery insufficiency, MI, digitalis toxicity with hypokalemia, and hypoxemia. VPBs are more likely to lead to fibrillation if they are multiple, multifocal, or bigeminal; occur near the vulnerable period of the preceding ventricular repolarization (i.e., R-on-T phenomenon)[50]; or appear in short-long-short coupling sequences.
6. Treatment: In most patients, VPBs (occurring as single, bigeminy, or trigeminy but excluding nonsustained VT) do not need to be treated, particularly if the patient does not have an acute coronary syndrome (ACS); but the presence of symptoms attributable to VPBs usually dictates the treatment. The first step in treatment is to correct any underlying abnormalities such as decreased serum potassium or low arterial oxygen tension. If the arrhythmia is of hemodynamic significance or if it is believed to be a harbinger of worse arrhythmias, then lidocaine is usually the treatment of choice, with an initial bolus dose of 1.5 mg/kg. Recurrent VPBs can be treated with a lidocaine infusion of 1 to 4 mg/min; additional therapy can be supplied with esmolol, propranolol, procainamide, quinidine, disopyramide, atropine, verapamil, or overdrive pacing.

VENTRICULAR TACHYCARDIA

The presence of three or more sequential VPBs defines VT (Fig. 47-13). Diagnostic criteria include the presence of fusion beats, capture beats, and AV dissociation. The specific morphologic appearance of the QRS complex may also be helpful in distinguishing VT from other arrhythmias. VT is classified by its duration and morphologic appearance. In duration, nonsustained VT lasts three beats and up to 30 seconds, and sustained VT lasts 30 seconds or longer. With monomorphic form, all complexes have the same pattern, and with polymorphic form, complexes constantly change patterns. Polymorphic VT with a long QTc is also called *torsade de pointes*. The characteristics of VT are as follows:

1. HR: Is 100 to 200 bpm.
2. Rhythm: Is usually regular but may be irregular if the VT is paroxysmal.
3. P/QRS: No fixed relationship exists because the VT is a form of AV dissociation in which the P waves can be observed marching through the QRS complex.
4. QRS complex: Is wide, more than 0.12 second in width, with similar morphologic criteria in lead V_1 as for VPB.
5. Significance: Acute onset is life threatening and requires immediate treatment.
6. Treatment: If the patient is hemodynamically stable, then amiodarone, administered in one or more doses of 150 mg given IV in 100 mL saline or D_5W over 10 minutes, followed by an IV infusion of 1 mg/min for 6 hours and 0.5 mg/min thereafter, is the recommended current treatment (maximum IV dose 2.2 g/24 hr). Although amiodarone produces less hypotension, compared with bretylium, hypotension and bradycardia are its main side effects. Amiodarone's pharmacologic effects persist for longer than 45 days. Lidocaine and procainamide have been used in the past with varying degrees of success to treat VT. Synchronized cardioversion is the indicated nonpharmacologic intervention in any wide complex tachycardia, whether monomorphic VT or a wide-complex SVT. Polymorphic VT with a normal QT interval is treated with amiodarone and cardioversion. Metabolic abnormalities and drug toxicity must be considered and treated. Polymorphic VT with prolonged QT interval is a more serious rhythm disturbance, and the recommended current treatment is IV infusion of 1 g of magnesium over 2 to 3 minutes. Precipitating metabolic or toxic causes should be treated. Overdrive pacing may also be helpful in this setting.

VENTRICULAR FIBRILLATION

Ventricular fibrillation is an irregular rhythm that results from a rapid discharge of impulses from one or more ventricular foci or from multiple wandering reentrant circuits in the ventricles (Fig. 47-14). The ventricular contractions are erratic and are represented on the ECG by bizarre patterns of various sizes and configurations. P waves are not seen. Important causes of the arrhythmia include myocardial ischemia, hypoxia, hypothermia, electric shock, electrolyte imbalance, and drug effects. The characteristics of ventricular fibrillation are as follows:

1. HR: Is rapid and grossly disorganized.
2. Rhythm: Is totally irregular.
3. P/QRS: No relationship is seen.
4. QRS complex: Is not present.

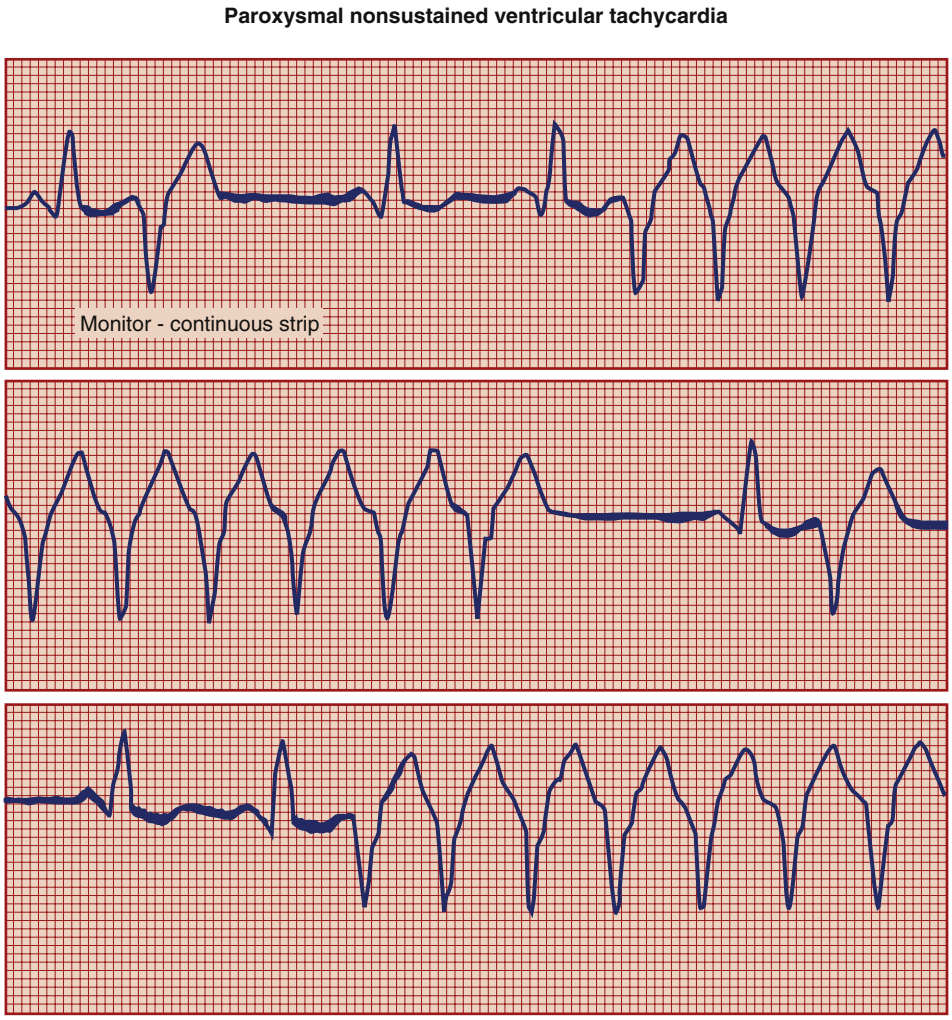


Figure 47-13. Short bursts of ventricular tachycardia. *(From Goldberger AL:* Clinical electrocardiography: a simplified approach, *ed 7. St. Louis, 2006, Mosby.)*

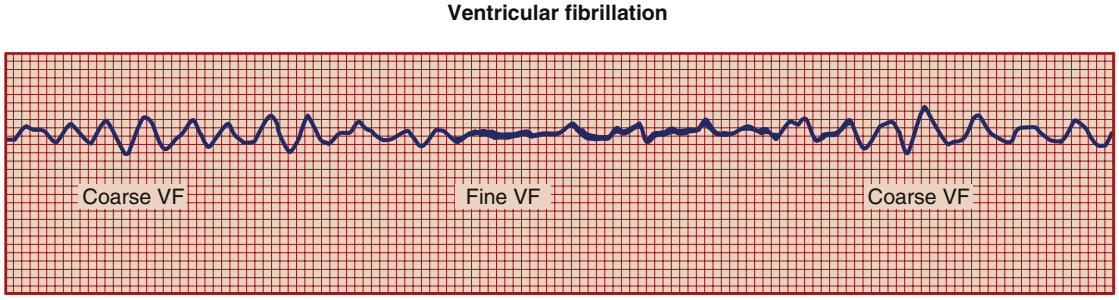


Figure 47-14. Ventricular fibrillation (VF) in the form of coarse and fine waves. *(From Goldberger AL:* Clinical electrocardiography: a simplified approach, *ed 7. St. Louis, 2006, Mosby.)*

5. Significance: No effective cardiac output exists, and artificial means, such as external cardiac massage, must be used to sustain life.
6. Treatment: Cardiopulmonary resuscitation must be immediately initiated, and then defibrillation must be performed as rapidly as possible. Asynchronous external defibrillation should be performed with a DC defibrillator, using incremental energies in the range of 200 to 360 J. The introduction of the biphasic (and rectilinear) transthoracic shocks has reduced the energy levels required and increased the efficacy of ventricular defibrillation. In a prospective, randomized, multicenter trial conducted by the ZOLL Investigators,[51,52] 120 J of biphasic current was superior to 200 J of monophasic current, especially in patients with increased chest wall impedance.

Early administration of 1 g of magnesium sulfate may facilitate defibrillation. In some instances, epinephrine has been used to coarsen the fibrillation just before and to facilitate defibrillation. Vasopressin has

been added as a drug for the treatment of ventricular fibrillation. The vasopressin dose is a single 40-unit IV bolus. If elected, subsequent administration of epinephrine should not be sooner than 5 minutes after vasopressin. Supportive pharmacologic therapy may include lidocaine, amiodarone, bretylium, procainamide, phenytoin, or esmolol.

Torsade de pointes, which may mimic ventricular fibrillation, is a life-threatening arrhythmia that occurs in the presence of disturbed repolarization; hence, its association with prolonged QT interval.[53] Discontinuation of drugs that predispose to QT-interval prolongation and correction of electrolyte abnormalities are essential in the treatment of torsades de pointes. Acute therapy may include defibrillation, 1 to 2 g of IV magnesium sulfate, IV amiodarone, IV isoproterenol, and overdrive pacing.[54]

CONDUCTION DEFECTS

Conduction defects are most often chronic, are present on the patient's preoperative ECG, and represent the patient's underlying disease state of the myocardium or conduction system. However, conduction defects may be observed for the first time during surgery and anesthesia. They can occur as a result of simple manipulation, such as the passage of a pulmonary artery catheter through the right ventricle, but they can also be a manifestation of myocardial ischemia. Because high-grade conduction defects (i.e., second- and third-degree AV blocks) often have deleterious effects on hemodynamic performance, their intraoperative recognition is important.

Three types of conduction system blocks are possible: SA block, AV heart block, and intraventricular conduction block. The bundle of His ECG used by cardiologists has greatly improved the understanding of conduction through the heart. In SA block, the block occurs at the sinus node. Because atrial excitation is not initiated, P waves are not found on the ECG. The next beat can be a normal sinus beat, a nodal escape beat, or a ventricular escape beat.

The second type of heart block is an AV heart block, or AV block, which may be incomplete or complete. First- and second-degree AV blocks are usually considered incomplete, whereas a third-degree AV block is considered to be complete heart block. First-degree AV block is often found in healthy hearts, in addition to CAD or the administration of digitalis. It is characterized by a PR interval longer than 0.21 second. All atrial impulses progress through the AV node to the Purkinje system. This form of heart block ordinarily requires no treatment. Second-degree AV block is associated with the conduction of some of the atrial impulses to the AV node and into the Purkinje system. It is further subdivided into two specific types. Mobitz type I block, or Wenckebach block, is characterized by progressive lengthening of the PR interval until an impulse is not conducted and the beat is dropped (Fig. 47-15). This form of block is relatively benign and often reversible, and it does not require a pacemaker. It may be caused by digitalis toxicity or MI and is usually transient. Mobitz type I block reflects disease of the AV node.

The other form of second-degree heart block is Mobitz type II block, which may reflect disease of the bundle of His and Purkinje tissues, especially when the QRS complex is broad. In this type, the less common and more serious form of second-degree heart block, dropped beats occur without any progressive lengthening of the PR interval (Fig. 47-16). This type of block has a serious prognosis because it frequently progresses to complete heart block and may require pacemaker insertion before major surgical procedures.

Third-degree AV block, also called *complete heart block*, occurs when all electrical activity from the atria fails to progress into the Purkinje system. The atrial and ventricular contractions have no relationship with each other,

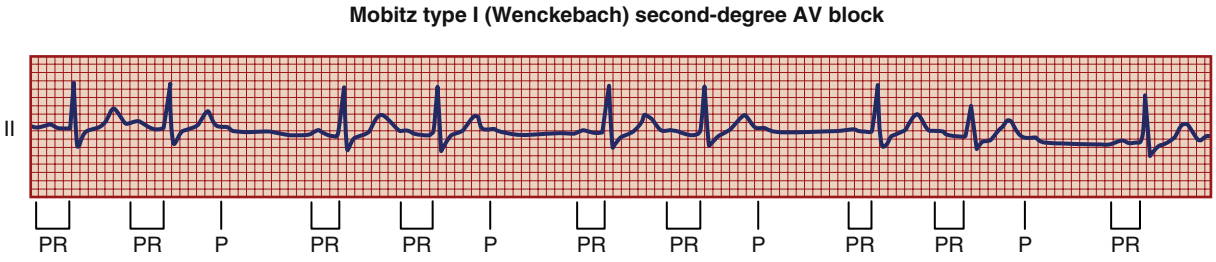


Figure 47-15. Mobitz type I (Wenckebach) block produces a characteristically syncopated rhythm with grouping of the QRS complexes (group beating). The progressive increase in PR intervals is noted with the third sinus P wave in each sequence not followed by a QRS complex. *(From Goldberger AL:* Clinical electrocardiography: a simplified approach, *ed 7. St. Louis, 2006, Mosby.)*

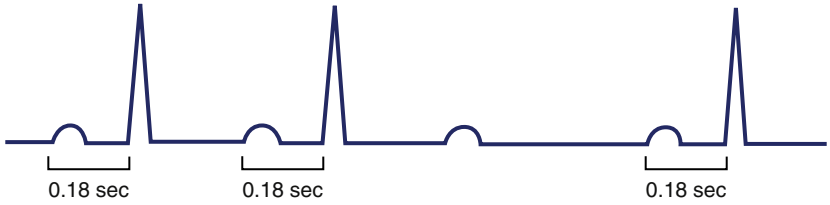


Figure 47-16. Mobitz type II atrioventricular block. The PR intervals remain constant as long as the QRS complex is not dropped, unlike in Mobitz type I. *(From Goldberger AL:* Clinical electrocardiography: a simplified approach, *ed 7. St. Louis, 2006, Mosby.)*

although each chamber regularly contracts. The ventricular rate is approximately 40 bpm. The QRS complex may be normal if the pacemaker site is in the AV node, but it is usually widened to longer than 0.12 second when the pacemaker site is located in the ventricle (Fig. 47-17). The HR is usually too slow to maintain adequate cardiac output, and syncope or Adams-Stokes syndrome may occur, as well as heart failure. These patients usually require insertion of a transvenous endocardial or epicardial pacemaker to increase their HR and cardiac output.

Intraventricular Blocks

Under normal conditions, activation of the left ventricle spreads simultaneously through both left anterior and left posterior fascicles. Blockage or even a modest delay in conduction in one of these fascicles results in a sequential rather than the simultaneous activation of the corresponding sites, producing characteristic abnormal ECG patterns (Fig. 47-18).

Left Anterior Fascicular Block. The left bundle branch of the bundle of His itself bifurcates distally into two fascicles, the anterior and the posterior. A left anterior fascicular block (LAFB) is relatively common as a result of the delicate structure of the left fascicle. It causes delayed activation of the anterosuperior LV wall and is characterized by pronounced (–45° to –90°) left axis deviation. LAFB may occur in persons without overt cardiac disease but is mainly found in patients with a wide range of myocardial and conduction system diseases, such as CAD or LVH. It has minimal and no independent prognostic significance.

Left Posterior Fascicular Block. A left posterior fascicular block (LPFB) is considerably less common than the

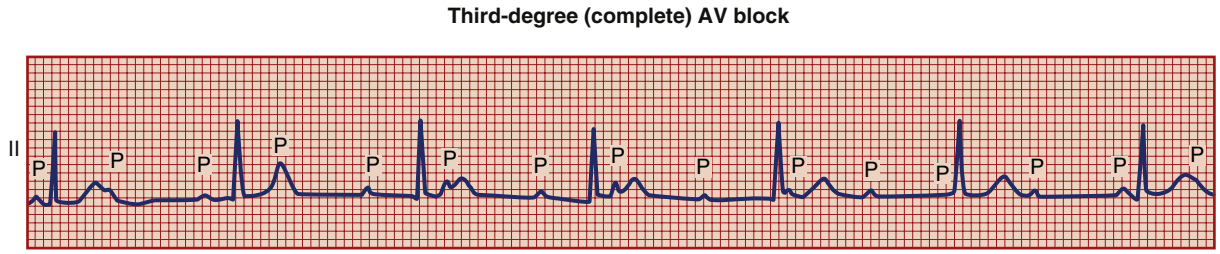


Figure 47-17. Complete heart block with underlying sinus rhythm is characterized by independent atrial (P) and ventricular (QRS complex) activity. The atrial rate is almost always faster than the ventricular rate. The PR intervals are completely variable. *(From Goldberger AL:* Clinical electrocardiography: a simplified approach, *ed 7. St. Louis, 2006, Mosby.)*

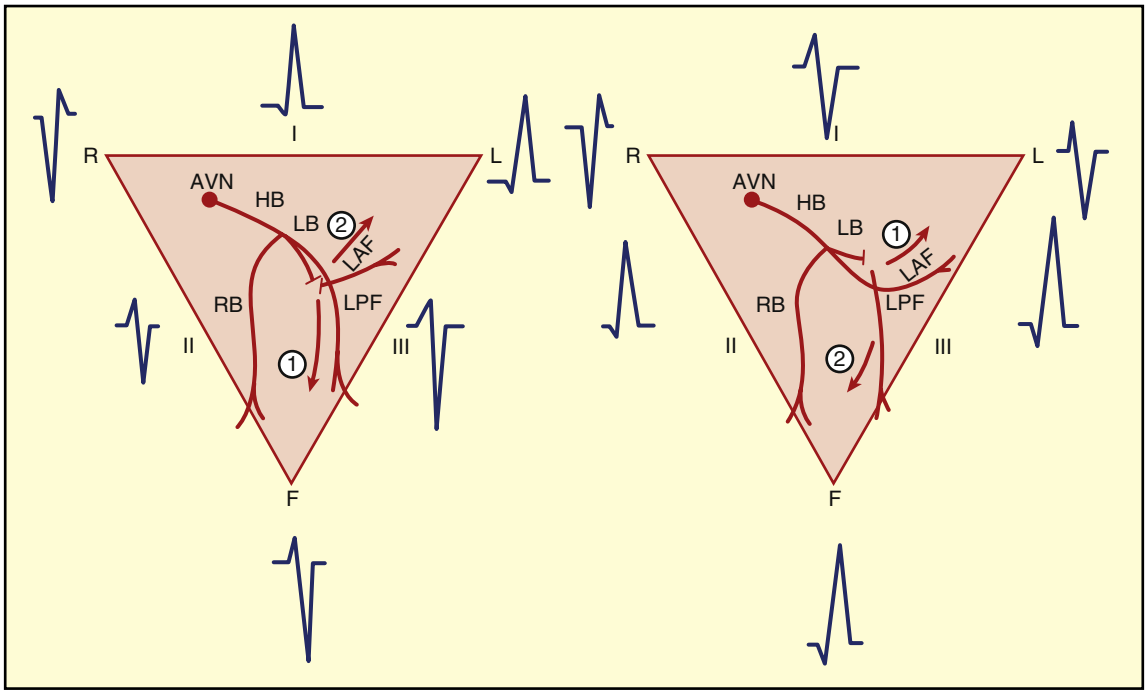


Figure 47-18. Diagrammatic representation of fascicular blocks in the left ventricle. Interruption of the left anterior fascicle (LAF) *(left)* results in an initial inferior *(1)* followed by a dominant superior *(2)* direction of activation (negative in II and positive in I and aV_L). Interruption of the left posterior fascicle (LPF) *(right)* results in an initial superior *(1)* followed by a dominant inferior *(2)* direction of activation (negative in I and positive in II and III). *AVN*, Atrioventricular node; *HB*, His bundle; *LB*, left bundle; *RB*, right bundle. *(Courtesy of Fisch C from Zipes DP, Libby P, Bonow R, Braunwald E:* Braunwald's heart disease: a textbook of cardiovascular medicine, *ed 7. Philadelphia, 2005, Saunders.)*

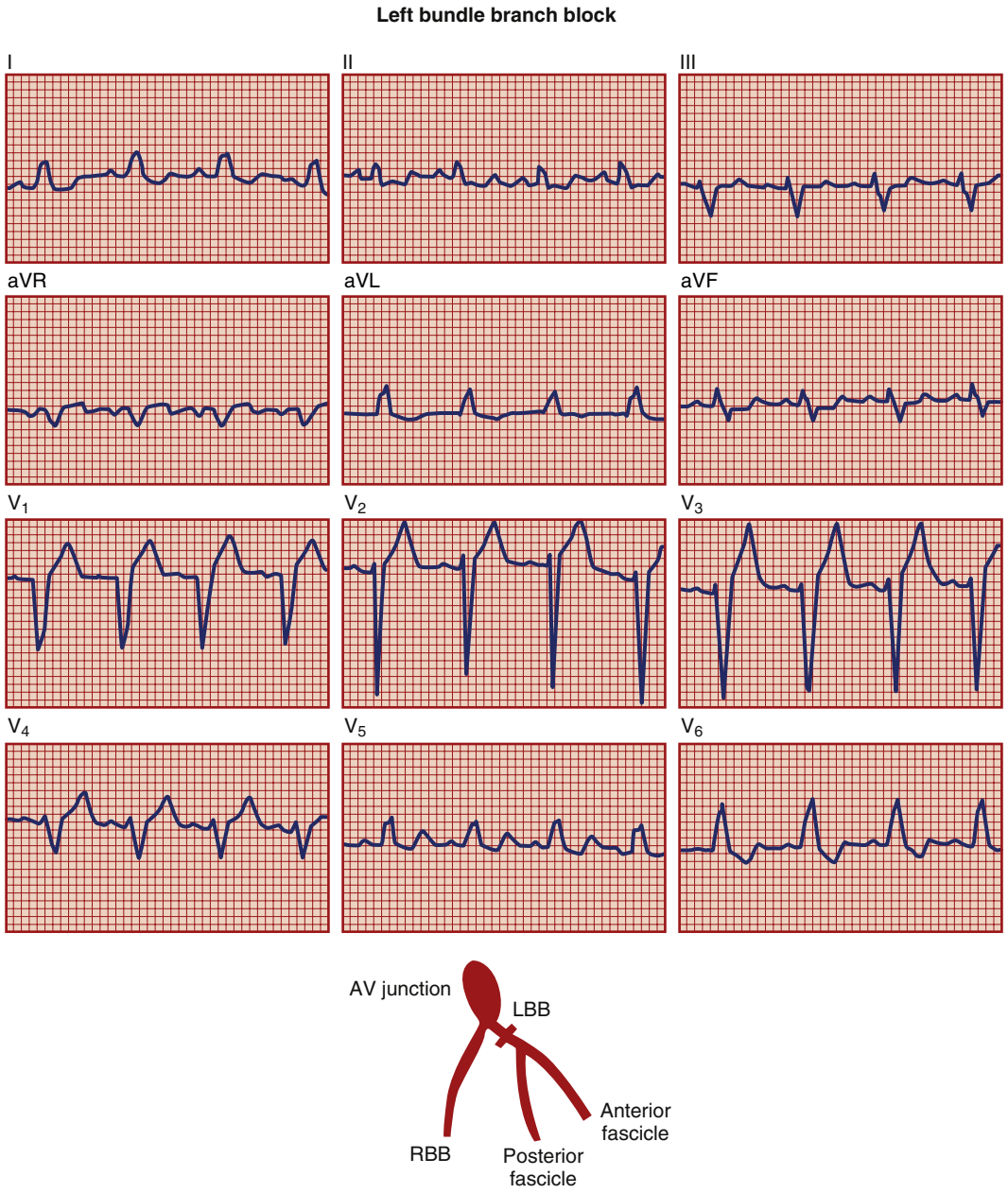


Figure 47-19. Left bundle branch block with its characteristic wide QS complex is noted in lead V_1 and the wide R wave in lead V_6 with slight notching at the peak. The inverted T waves in leads V_5 and V_6 (secondary T-wave inversions) are also characteristic of left bundle branch block. *AV*, Atrioventricular; *LBB*, left bundle branch; *RBB*, right bundle branch. *(From Goldberger AL:* Clinical electrocardiography: a simplified approach, *ed 7. St. Louis, 2006, Mosby.)*

anterior fascicular block because of the thicker structure of the right fascicle. It is also at a less vulnerable location near the LV inflow tract. LPFB results in delayed activation of the inferoposterior aspect of the left ventricle, and the ECG features of LPFB are pronounced right axis deviation (>120 degrees). LPFB can occur in patients with almost any cardiac disease but is unusual in otherwise healthy people. As in the case of LAFB, the overall QRS duration remains normal (<120 msec).

Left Bundle Branch Block. LBBB is caused by a serious delay or block of the main left bundle branch or in both of its two fascicles. This block results in a prolonged QRS duration, abnormal QRS complex, and ST-T wave abnormalities. A basic requirement is QRS duration ≥120 msec (Fig. 47-19). A broad, sometimes notched R wave is evident in the left-sided leads (I, aV_l V5, and V6) with deep S waves in the right precordial leads and absent septal Q waves. The QRS axis is highly variable. It can be normal or deviated to the left or even to the right. The ST-T waves are usually discordant with the direction of the QRS complex. LBBB is an ominous prognostic sign and has associated survival rates as low as 50%, probably reflecting the severity of the underlying cardiac disease. The QRS duration inversely correlates with LV ejection fraction and is one

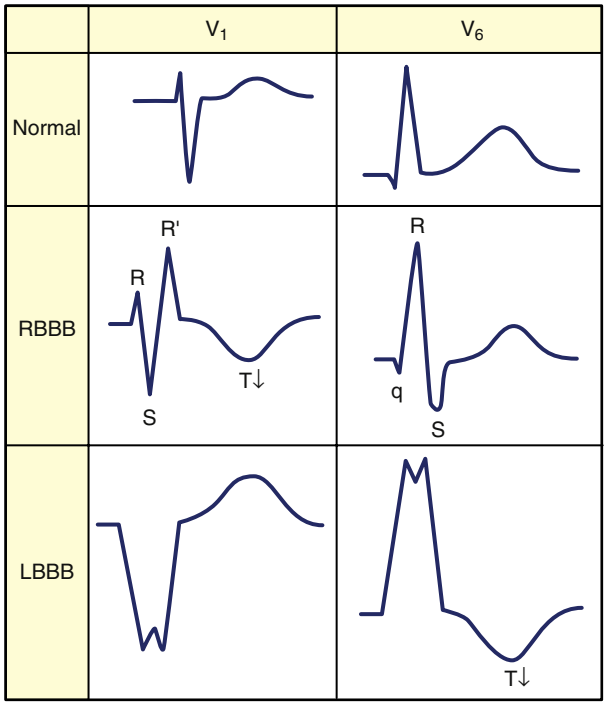


Figure 47-20. QRST changes in left bundle branch block (LBBB) are compared with the right bundle branch block (RBBB). *(From Zipes DP, Libby P, Bonow R, Braunwald E:* Braunwald's heart disease: a textbook of cardiovascular medicine, *ed 7. Philadelphia, 2005, Saunders; and from Goldberger AL:* Clinical electrocardiography: a simplified approach, *ed 7. St. Louis, 2006, Mosby.)*

of the criteria of current ventricular resynchronization therapy (biventricular pacing).

LBBB obscures or simulates other ECG patterns. In the presence of LBBB, the diagnosis of LVH, acute ischemia, or myocardial infarction may be difficult or impossible.

Right Bundle Branch Block. A conduction delay anywhere in the right-sided intraventricular conduction system causes an RBBB. The high prevalence of RBBB corresponds to the relative fragility of the right bundle branch, as suggested by the development of RBBB after minor trauma produced by right ventricular catheterization. The ECG manifestation of RBBB is prominent, and notched R waves with rsr', rsR', or rSR' on the right-sided leads and wide S waves on left-sided leads, along with QRS prolongation (≥120 msec), are evident. If the QRS duration is not prolonged, then this block is termed *incomplete RBBB*. As with LBBB, the ST-T waves are discordant with the QRS complex (Fig. 47-20).

RBBB is common in the general healthy population without clinical evidence of structural heart disease and has no prognostic significance in this group. However, in patients with organic heart disease, the new onset of RBBB predicts a higher rate of CAD, congestive heart failure, and mortality.

Trifascicular blocks usually consist of one of the foregoing bilateral bundle branch blocks (i.e., RBBB plus a LAFB or LPFB) in addition to a prolonged PR interval. Bundle of His ECGs are necessary to determine whether the AV conduction disturbance is localized in the AV node or whether it is distal, possibly representing an incomplete fascicular block in the last remaining fascicle.

REAL-TIME MYOCARDIAL ISCHEMIA MONITORING

Real-time ST-segment analysis first appeared in cardiac monitoring in the mid-1980s, and currently this feature is the standard in most ECG monitors. On some monitors, the ST-segment analysis is set up to turn on automatically when a five-electrode system is used. Unfortunately, however, anesthesiologists mainly use the five-electrode monitoring system with automatic ST-segment analysis in the surgical unit during surgery, but ST-segment monitoring is widely underused postoperatively in the postanesthesia care unit or ICU. A recent study has shown that even among coronary care units, less than 50% routinely use ST-segment monitoring for the detection of myocardial ischemia in patients admitted with ACSs.[55] Chief among the reasons for the underuse of ST-segment analysis are the frequent number of false alarms, the lack of education on how to use the technology, and the lack of knowledge of what to do in response to ST-segment alarms. In addition, no evidence exists as to whether the addition of computerized ST-segment ischemia monitoring improves patient outcomes in patients with ACSs or in patients after surgery.

Technically, the algorithm for ST-segment analysis is relatively simple. The computer determines in each ECG lead the voltage of the ST segment at 60 or 80 msec after the J point (termed as J+60 or J+80 msec) and compares it with the isoelectric point normally measured during the PR interval. One millimeter of ST-segment deviation is equivalent to a 100-mV difference. The changes in ST-segment level over time in each lead are displayed as ST-segment trends. Consequently, to overcome problems of noise and artifacts, most monitors use filters to exclude erroneous or abnormal ECG beats. Averaging processes are then used to calculate the mean ST-segment level over a period of 8 to 15 beats. Current monitors are trained to detect the J point automatically and calculate the J+60 msec ST-segment level. However, they also allow the operator to adjust manually the J-point and the ST-segment measurement point in patients with abnormal ECG patterns.

One major advantage of continuous ST-segment monitoring, compared with serial 12-lead ECGs, is that the electrodes stay in place and do not vary as standard 12-lead ECGs may do between different measuring sessions. However, for improved diagnostic accuracy of ST-segment monitoring, the following points should be recognized:

1. Changes in body position may cause ST-segment changes and lead to false ST-segment alarms. However, changes in QRS complex almost always accompany these positional ST-segment changes and therefore can be easily distinguished from true ST-segment deviations. In addition, returning the patient to the supine position may help distinguish true from positional ST-segment deviation. Changes in position of the heart in

the mediastinum have also shown to affect the ST segment. Mark and associates[56] observed that placement of a sternal retractor during cardiac surgery was associated with a reduction in V_5 R-wave amplitude. Simultaneously, V_5 S-wave amplitude and absolute ST-segment deviation were reduced. These investigators concluded that inclusion of an R-wave gain factor might improve perioperative ECG ischemia monitoring.

2. Many patients with CAD do not have perfectly isoelectric ST segments. Early repolarization (a normal variant), intraventricular conduction delays, ventricular hypertrophy, digitalis, and nonspecific ST-T wave abnormalities may cause baseline ST-segment abnormalities. Therefore, tailoring the ST-segment alarm parameters to the patient's baseline ST-segment level is important. Many current cardiac monitors with ST-segment monitoring software allow clinicians to set alarm parameters manually. If alarm parameters are set 1 to 2 mm around the isoelectric (0 mV) line rather than at the patient's baseline ST-segment level, then false alarms will frequently occur. Alarm parameters should be set 1 mm above and below the baseline ST-segment level in patients at high risk for ischemia. It should also be remembered that underlying ECG abnormalities might hinder ST-segment analysis in approximately 10% of the patients. These abnormalities include hypokalemia, digitalis, LBBB, Wolff-Parkinson-White syndrome, LVH with strain, and acute pericarditis. In these patients, other modalities for diagnosis of myocardial ischemia, such as transesophageal echocardiography, may be considered.
3. Most cardiac monitors with ST-segment monitoring software provide displays of ST-segment trends in a single lead or summated leads. Although such graphic trends are convenient for the quick identification of potential ischemic events, printing the ECG tracing in question to confirm that the ST-segment changes are the result of ischemia rather than of a transient arrhythmia (e.g., accelerated ventricular rhythm, new bundle branch block) is also of paramount importance.

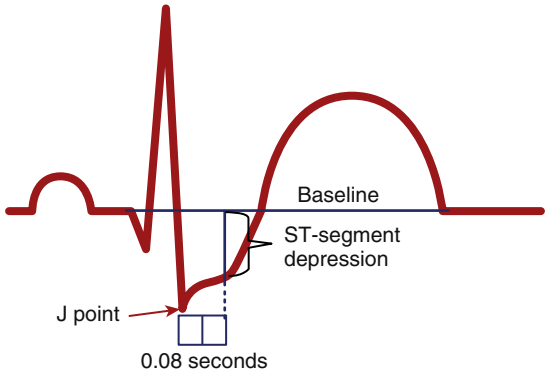


Figure 47-21. A demonstration of how the ST-segment deviation is measured at 80 msec after the J point (J+80 msec) is illustrated.

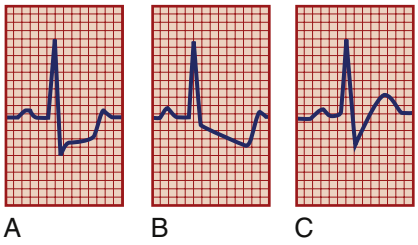


Figure 47-22. Horizontal ST depression (**A**) and down-sloping (**B**) ST depression are indicative of myocardial ischemia. Up-sloping ST depression (**C**) may be a normal finding.

ELECTROCARDIOGRAPHIC CRITERIA FOR ACUTE MYOCARDIAL ISCHEMIA

ST-DEPRESSION–TYPE ISCHEMIA

The ECG criteria most accepted for detecting myocardial ischemia on continuous ECG monitoring are those established and validated during exercise stress testing.[57] During stress testing and with acute subendocardial ischemia, the electrical forces responsible for the ST segment are deviated toward the inner layer of the heart, causing ST-segment depression (Fig. 47-21). With acute transmural (epicardial) ischemia, the electrical forces in the ischemic area are deviated toward the outer layer of the heart, causing ST-segment elevation in the overlying leads (see Fig. 47-5). As the HR increases, J-point or junctional up-sloping depression normally occurs. In patients with myocardial ischemia, however, the ST segment typically becomes horizontal (flattens) as the severity of ischemia increases. With progressive exercise or tachycardia during ischemia, the ST-segment depression may worsen; the ST segment may become down-sloping, even causing T-wave inversion in more than one ECG lead; and the patient may develop angina (Fig. 47-22). In approximately 10% of patients, especially those who are asymptomatic, ischemia may appear only in the recovery phase after exercise.

The criteria established for stress-induced ischemia are 1 mm (0.1 mV) or more of horizontal or down-sloping ST-segment depression measured 60 to 80 msec after the J point in at least three consecutive beats with a stable baseline. As previously mentioned, the ST-segment depression may be accompanied by T-wave flattening or inversion. Junctional or J-point depression is normal during exercise. In addition, a *rapidly up-sloping* ST segment (>1 mV/sec) that is also *depressed less than 0.15 mV* (1.5 mm) is considered normal. In patients with *slowly up-sloping* ST-segment depression in which the ST segment is *depressed 0.15 mV (1.5 mm) or more* at J+80 msec, the slowly up-sloping ST-segment depression may signify CAD.

Some patients have preexisting ST-segment abnormalities from a previous MI, bundle branch blocks, or LVH that make ST-segment interpretation more difficult. In these patients, additional horizontal or down-sloping ST-segment depression of 1 mm or greater from baseline is required to be considered as myocardial ischemia. Causes of ST-segment changes other than myocardial ischemia include drugs (most notably digitalis), temperature changes, hyperventilation, and position changes. The distribution of ST-depression–type ischemia correlates poorly with the specific location of CAD.

ST-SEGMENT ELEVATION–TYPE ISCHEMIA

ST-segment elevation in a non–Q-wave lead is extremely uncommon during stress testing, occurring in approximately 1% of patients with CAD, and suggests transmural myocardial ischemia caused by coronary vasospasm or a high-grade coronary narrowing. The ECG site of ST-segment elevation is relatively specific for the myocardial territory involved, in contrast to ST-depression–type ischemia. ST-segment elevation occurring during exercise testing in ECG leads with pathologic Q-waves does not indicate myocardial ischemia, but it does correlate with reduced LV function and a worse prognosis.

T-WAVE CHANGES

Body position, respiration, hyperventilation, and drug therapy, as well as myocardial ischemia or necrosis, largely influence T-wave morphologic appearance. Therefore, T-wave changes not accompanied by significant ST-segment displacement rarely signify myocardial ischemia. Pseudonormalization of T waves (i.e., inverted at rest, becoming upright during exercise) may, in rare instances, be a marker for myocardial ischemia.

In a meta-analysis that included 147 reports of patients who underwent both angiography and exercise testing, the sensitivity and specificity of the exercise ECG stress test for the detection of CAD were 68% and 77%, respectively.[58]

ELECTROCARDIOGRAPHIC LEAD SENSITIVITY FOR DETECTING PERIOPERATIVE MYOCARDIAL ISCHEMIA

During the perioperative period, ECG monitoring most commonly identifies stress-induced, ST-depression–type ischemia. Such ECG changes do not provide information about the location of the ischemic myocardial area. In contrast, ST-segment elevation indicating transmural ischemia, observed particularly during cardiac surgery, provides useful information about the myocardial segment and coronary perfusion territory responsible for the ischemic episode. Because the majority of modern patient-monitoring systems do not simultaneously monitor all 12 ECG leads, selecting which chest leads to monitor is of great importance, particularly in noncardiac surgery. During exercise stress testing, investigators have identified leads V_4 and V_5 as the most sensitive leads to detect exercise-induced ischemia (90% to 100% sensitivity).[59] London and colleagues[60] studied high-risk patients undergoing noncardiac surgery and showed that the greatest sensitivity for ischemia was obtained with lead V_5 (75%), followed by lead V_4 (61%). Combining leads V_4 and V_5 increased the sensitivity to 90%, whereas with the standard lead II and V_5 combination, the sensitivity was only 80%. They also suggested that if three leads (II, V_4, and V_5) could be simultaneously examined, the sensitivity would increase to 98%. More recently, Landesberg and associates[61] monitored continuous 12-lead ST-segment changes greater than 0.2 mV from baseline in a single lead or more than 0.1 mV in two contiguous leads at J+60 msec, lasting longer than 10 minutes in patients undergoing major vascular surgery. Troponins were used as markers for MI. They showed that, in fact, leads V_3 and V_4 were more sensitive than V_5 in detecting perioperative ischemia (87%, 79%, and 66%, respectively). Among patients who experienced an MI, V_4 was most sensitive for ischemia (83.3%), followed by V_3 and V_5 (75% each). Combined monitoring of two of these leads (V_3 and V_5) increased the sensitivity to approximately 97%.[64] The baseline, preanesthesia ST segment was above the isoelectric point in V_1 through V_3 and below the isoelectric point in V_5 through V_6. Lead V_4 was closest to the isoelectric level on the baseline ECG, rendering it most suitable for detecting ischemia. Lead V_4 also detected ischemia earlier and showed a greater ST-segment deviation. Martinez and colleagues,[62] who also used the same method to monitor postoperative ischemia in patients in the ICU after major vascular surgery, corroborated these main findings.

For patients with AVSs (i.e., those with atherosclerotic plaque disruption), monitoring limb lead III and leads V_3 and V_5 as the most sensitive combination for ischemia detection is recommended.[63] Monitoring a right-sided precordial lead (V_{4R}) may be of benefit in patients with occlusive disease of the right coronary artery,[64] as might inspection of posterior leads (V_7 to V_9) in suspected posterior ischemia.

Monitoring for intraoperative myocardial ischemia is commonly believed to be unnecessary in neonates. Whereas ECG lead systems for adults are concerned with the detection of ischemia and arrhythmias, neonatal ECG monitoring has focused on arrhythmia recognition alone. Results of some studies, however, suggest that the neonatal heart is more susceptible to ischemia than the adult heart.[65] These studies demonstrate the importance of calibrated ECG monitoring in neonates with congenital heart disease (see Chapter 94).

PERIOPERATIVE MYOCARDIAL ISCHEMIA AND INFARCTION

Perioperative myocardial ischemia monitoring in patients undergoing cardiac or noncardiac surgery started more than 20 years ago. Tinker[66] noted in 1980 the importance of intraoperative ST-segment monitoring via lead V_5 and determined that large fluctuations in systolic blood pressure, HR, or hypothermia with postoperative shivering are associated with ischemia. Coriat and colleagues[67] (1982) were pioneers in using Holter monitoring in patients undergoing major vascular surgery, showing that intraoperative ischemia on Holter monitoring was strongly associated with the severity of preoperative angina pectoris. In 1985, Slogoff and Keats[68] first demonstrated an association between intraoperative ischemia and postoperative MI. They showed that MI during coronary artery bypass graft (CABG) surgery is strongly associated with ischemia on Holter monitoring detected either before the induction of anesthesia or before the onset of cardiopulmonary bypass. During 1989, studies using perioperative Holter monitoring in patients undergoing major vascular surgery showed that early postoperative tachycardia-induced silent myocardial ischemia was frequent after surgery and associated

with postoperative clinical ischemic events.[69,70,71] In 1990, Mangano and associates[72] demonstrated that postoperative Holter-detected ischemia was most common (41%) and most predictive of adverse cardiac events, with a ninefold increase in the odds of postoperative cardiac morbidity and mortality, more than intraoperative or preoperative ischemia.

Between 1990 and 2003 a number of studies with perioperative ischemia monitoring were published.[73-87] Altogether, these studies included more than 2400 patients. Most studies included patients who underwent major vascular surgery, and most of the studies used Holter monitoring for perioperative ischemia detection (except the studies by Landesberg and colleagues who used continuous on-line 12-lead ECG monitoring). The data show that perioperative ischemia was common in these high-risk patients with an incidence between 24% and 63% and was almost exclusively ST-depression–type ischemia (97% to 100%). The average postoperative MI rate in these studies was 3.9% (range: 0.6% to 15%), the majority of which were non–Q-wave infarctions (66% to 100%). The incidence of all ischemic postoperative cardiac events was 7.3% (range: 3% to 37%), and the average mortality was 1.04% (range: 0% to 2.8%). An important observation was that postoperative ischemia duration was strongly associated with postoperative ischemic cardiac events. Patients with prolonged and often hours of postoperative ST-depression–type ischemia were likely to experience postoperative MI and serum biomarker elevation, whereas short episodes of ischemia (<30 minutes) were unlikely to culminate in MI. Perioperative ischemia was associated not only with early postoperative morbidity and mortality but also with long-term (5 years) morbidity and mortality.[90,88]

EXAMPLES OF PERIOPERATIVE ISCHEMIA AND INFARCTION

Example 1. Postoperative mortality related to HR-induced prolonged postoperative ST-depression–type ischemia. Frank and colleagues[73] published one of the first and most detailed cases of postoperative cardiac mortality related to HR-induced prolonged postoperative ST-depression–type ischemia detected on Holter monitoring. A patient who underwent lower-extremity arterial bypass surgery was observed with Holter monitoring, before, during, and after the procedure. His records showed that he had HR-related silent myocardial ischemia preoperatively that subsided intraoperatively, immediately after anesthesia was instituted, only to recur immediately as the patient woke up from the surgery. Figure 47-23 shows the ischemia progressively worsening after surgery until the patient suddenly died 10 hours after the surgery. Interestingly, the ST-depression–type ischemia of this patient occurred at a relatively low HR of 80 to 85 bpm and in the absence of significant blood pressure alterations. Two snapshots of ECG disclosure are presented at approximately 12 o'clock midnight: one at a HR of approximately 90 bpm, which showed deep ST-segment depressions and the other a short time later with a temporary slowing of the HR to approximately 60 bpm, which showed almost complete but transient resolution of the ST-segment depression. Although cardiac markers were not measured and no data were provided on myocardial function by ECG, it is suggested that the patient died as a result of prolonged, silent, HR-related, ST-depression–type ischemia, which was at least temporarily reversible by slowing his HR.

Example 2. Prolonged myocardial ischemia and infarction immediately after carotid endarterectomy surgery. A 70-year-old patient with a history of CAD and who was treated 7 years earlier with CABG now has reduced LV function, insulin-dependent diabetes mellitus, and peripheral vascular disease. On arrival to the surgical unit, the patient was connected to a continuous, 12-lead ECG monitor with on-line ST-segment analysis. During surgery, no ischemia was observed (Fig. 47-24). However, immediately after surgery and upon emergence from anesthesia, a significant ST-depression–type ischemia occurred in association with a moderate increase in HR to a maximum of 102 bpm, in accordance with vague pain in his jaw.

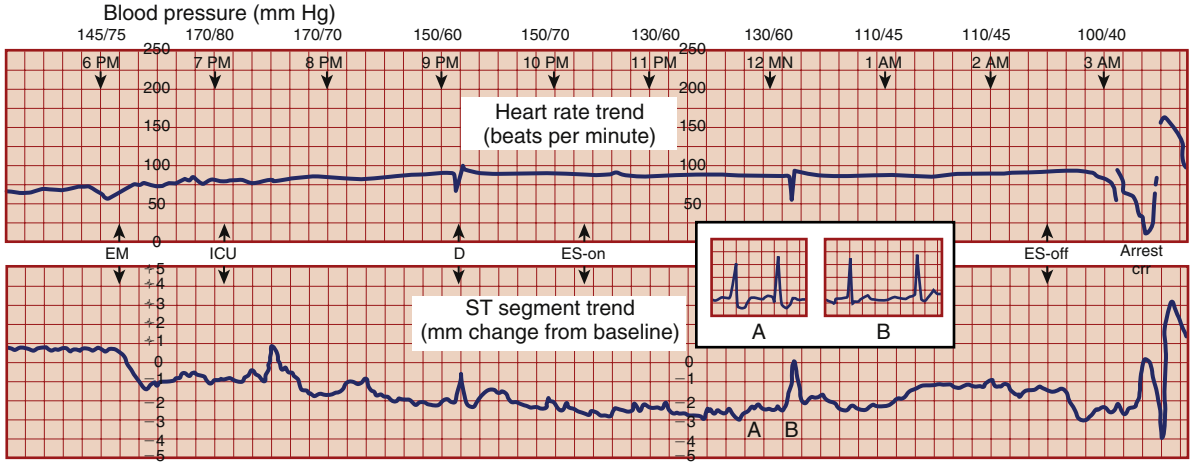


Figure 47-23. Heart rate and ST trends from emergence of anesthesia *(EM)* to cardiac arrest. *CPR*, Cardiopulmonary resuscitation; *D*, brief decrease in heart rate; *ES-off*, end of esmolol infusion; *ES-on*, start of esmolol infusion; *ICU*, intensive care unit admission. *(Modified from Frank SM, Beattie C, Christopherson R, et al: Perioperative rate-related silent myocardial ischemia and postoperative death,* J Clin Anesth *2:326-331, 1990.)*

Ischemic ST-segment changes lasted 193 minutes, after which the ECG completely reverted to its baseline. Nevertheless, an increase in troponin I to 10.2 ng/mL was measured 6 hours after surgery and up to 32.1 ng/mL on the morning after surgery (see Fig. 47-24; the figure insert depicts all 12-lead ECG complexes during peak ischemia superimposed on their baseline, preoperative pattern).[92] As demonstrated, significant ST-segment depression occurred in all the chest leads and was deepest in lead V_4 (–3.7 mm at peak ischemia). It is interesting to note the significant abnormalities—LVH, RBBB, left anterior hemiblock, and baseline ST-T changes—of this patient's baseline ECG. Despite these abnormalities, the continuous ST-trend monitoring in 12 leads combined with the significant troponin I elevation leave little doubt that the patient had prolonged (>3 hours) ischemia, which culminated in troponin elevation and, hence, MI.

Example 3. Prolonged postoperative ischemia and infarction in a patient with chronic total occlusion of one coronary artery. A 65-year-old patient was admitted for surgery because of an asymptomatic abdominal aortic aneurysm (7 cm). His medical history was only significant for hypertension, mild obesity (85 kg), and smoking until 12 years before admission. He had no clinical history of ischemic heart disease, but, because of a shortness of breath when climbing stairs, a preoperative thallium scan was performed (Fig. 47-25) that showed a moderate-to-severe, large reversible defect in the entire LV anterior wall.

On echocardiography, the size and function of both ventricles were normal with moderate mitral regurgitation. In light of the thallium scanning findings, the patient underwent preoperative coronary angiography (Fig. 47-26), which showed total ostial occlusion of the left anterior descending artery with retrograde filling through a large collateral from the right coronary artery.

Based on these findings, a decision was made not to perform preoperative coronary revascularization; instead, the patient was given bisoprolol (β_1-selective blocker) 50 mg daily for a month before he returned for surgery (aortobifemoral bypass).

As in the previous example, this patient was monitored during and after surgery by continuous 12-lead ECG with on-line ST-segment monitoring. Intraoperatively, the HR was 50 to 70 bpm, and no significant ST-segment changes were observed. However, immediately at the end of surgery and extubation, a significant ST-depression–type ischemia developed in association with an increase

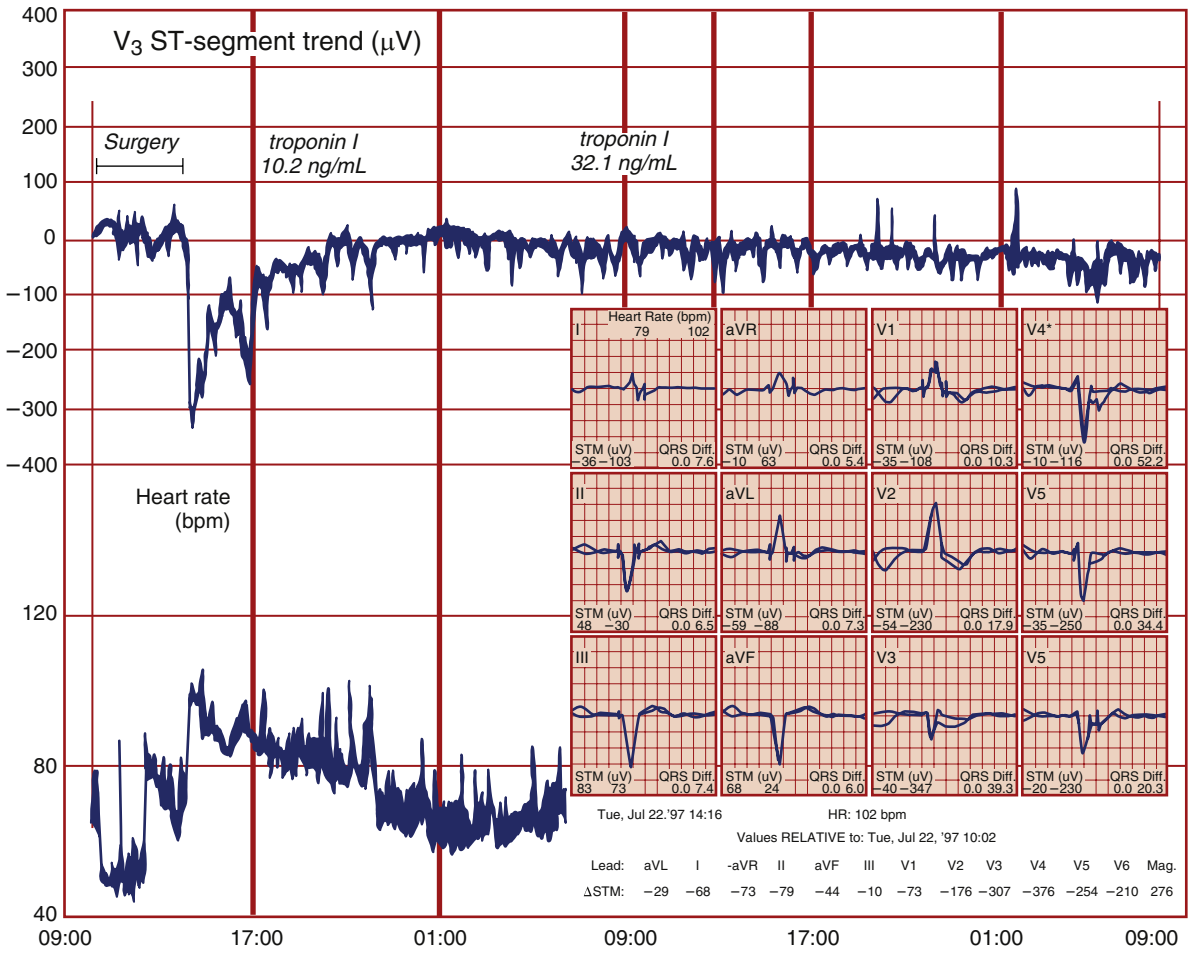


Figure 47-24. Lead V3 ST-segment and heart rate trends in a patient with prolonged (193 minutes) postoperative ST-segment depression and troponin elevation. The 12-lead ECG complexes at peak ischemia are superimposed on their baseline patterns *(insert)*.

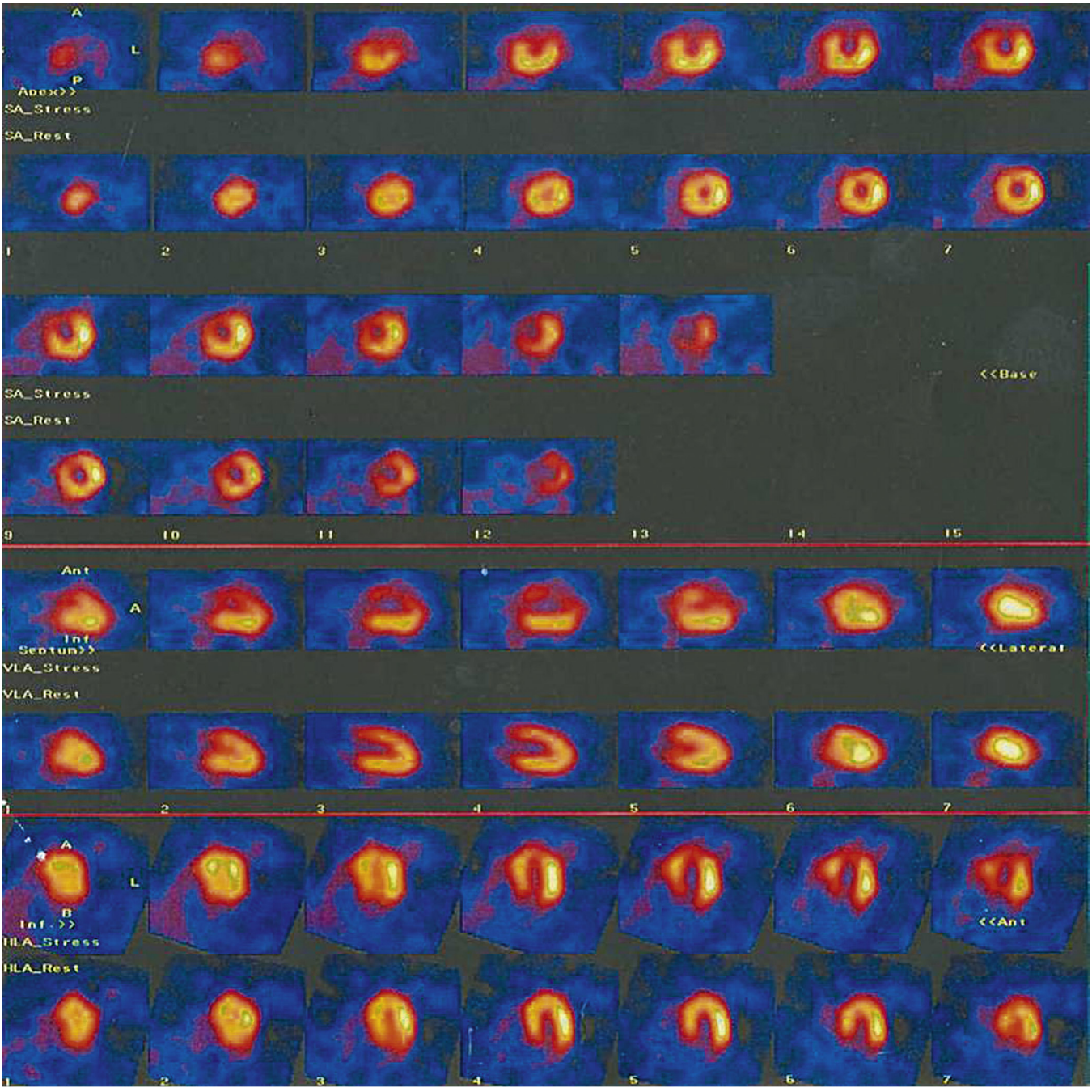


Figure 47-25. Preoperative dipyridamole-thellium single photon–emission computed tomographic scan of a patient scheduled for abdominal aortic surgery showing a moderate-to-severe reversible defect in the entire anterior wall.

in HR to a maximum of 98 bpm (Fig. 47-27) and a blood pressure of 155/86 mm Hg. IV esmolol and labetalol were immediately administered, and the ischemia subsided within 15 minutes. The patient was transferred extubated and comfortable to the ICU under continuous infusion of esmolol. In the ICU, the doses of esmolol had to be gradually escalated because of a persistent increase in HR. Postoperative pain was managed by the epidural catheter. Nevertheless, 5 hours aftter surgery, severe ST-depression–type ischemia recurred in the entire anterior wall. This time, the ischemia lasted more than 5 hours and responded poorly to β-adrenergic blocking drugs (see Fig. 47-27). The patient became delirious and developed shortness of breath. Treatment included IV diuretics and a slow infusion of packed red blood cells. Twenty-fours hours after surgery, the ischemic ECG changes regressed almost completely to normal, yet serum troponin T levels increased to 0.64 ng/mL and remained elevated for another 5 days.

This unique case demonstrates that postoperative MI may occur as a result of prolonged stress-induced ST-depression–type ischemia in the presence of stable CAD with chronic total coronary artery occlusion of even one coronary artery and without coronary plaque rupture.

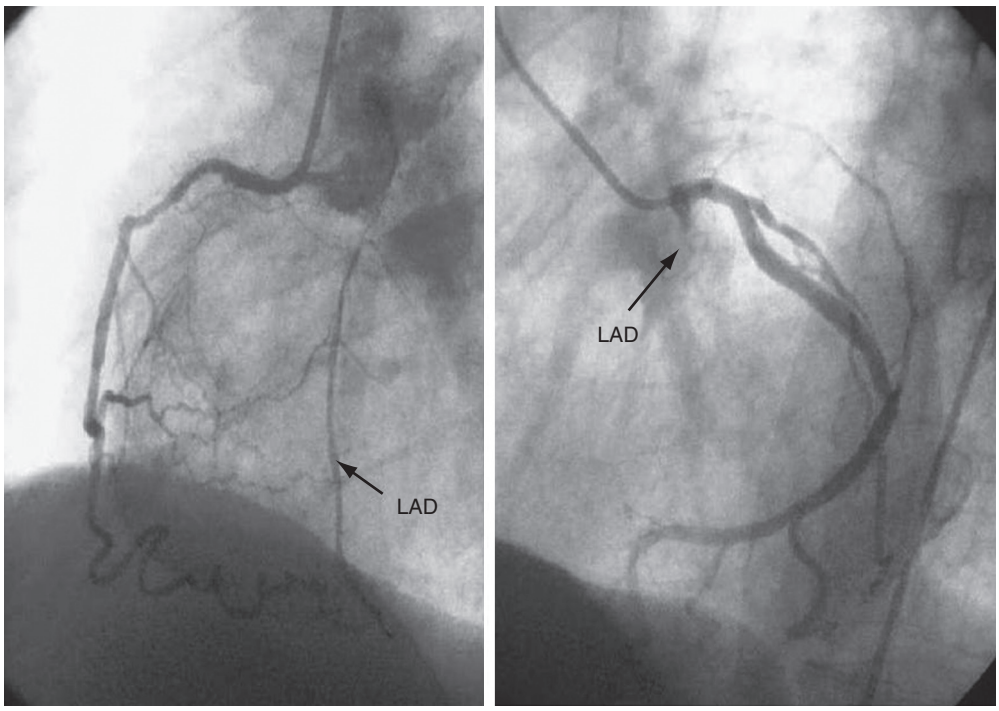


Figure 47-26. A coronary angiogram shows chronic total ostial occlusion of the left anterior descending (LAD) artery with excellent filling of the distal LAD by a collateral from the right coronary artery. A possible mild stenosis is also noted in the first marginal coronary artery.

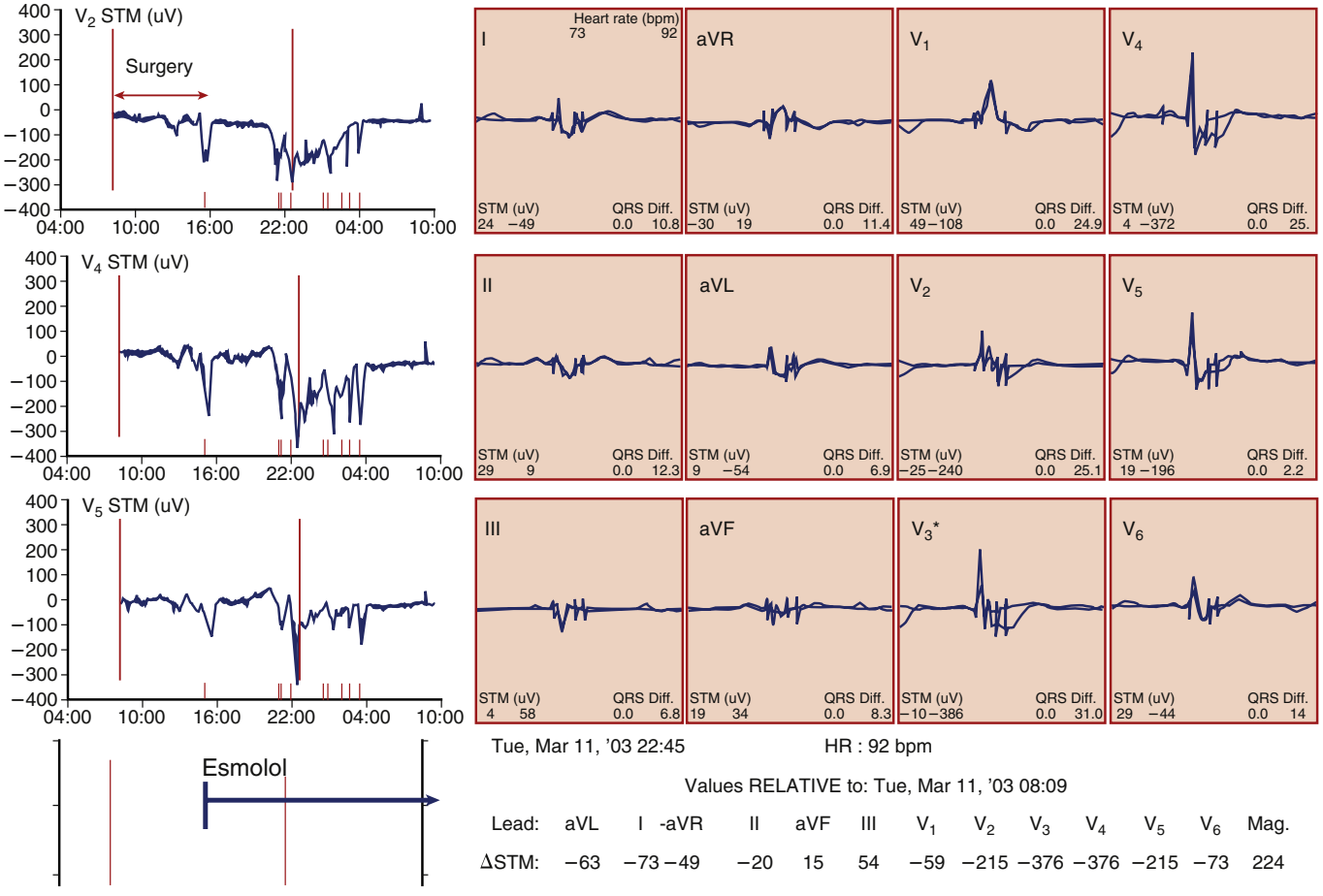


Figure 47-27. The perioperative ST-segment and heart rate trends of the patient are demonstrated on the left-sided panels. All 12-lead electrocardiographic complexes during peak ischemia, superimposed over the corresponding baseline (preoperative) complexes, are demonstrated on the right-sided panels. The ST-segment trends show two episodes of ST depression–type ischemia: a short episode of 15 minutes immediately at the end of surgery, followed by a 5-hour period of no ischemia and then another long episode of ST depression lasting longer than 5 hours. Ischemia is evident in all anterior leads but is maximal in V_3 and V_4 leads.

PATHOPHYSIOLOGIC MECHANISMS OF PERIOPERATIVE MYOCARDIAL INFARCTION

Two distinct mechanisms may lead to perioperative MI (PMI)[90]: (1) ACS and (2) prolonged, myocardial oxygen supply-demand imbalance in the presence of significant yet stable CAD. These mechanisms have been recently named type 1 and type 2 MIs by the collaborative Task Force for Universal Definition of MI.[91] A distinction between them is pivotal to therapeutic considerations (Fig. 47-28).

Acute Coronary Syndrome (Type 1 Myocardial Infarction)

The pathophysiologic processes of ACS have been extensively reviewed. Briefly, ACS occurs when an unstable or vulnerable plaque, typically one with a large lipid core, thin fibrous cap, and activated leukocytes,[92] undergoes spontaneous rupture or fissuring with subsequent exposure of thrombogenic material to the bloodstream, leading to acute coronary thrombosis, ischemia, and infarction. Clearly, plaque inflammation plays a pivotal role in spontaneous ACS.[93] In addition, however, external stimuli, such as those operating in the postsurgical setting, are believed to contribute to vulnerable plaque destabilization.

- Physiologic and emotional stresses are long known to be associated with acute MI, raising the hypothesis that sympathetic nervous system–induced hemodynamic, coronary vasoconstrictive, and prothrombotic forces promote plaque disruption and coronary thrombosis. Theoretically, the perioperative period is the perfect playground for such events. Plasma catecholamine and cortisol levels increase early after surgery[94] and may remain high for days.[95] Stress hormones increase with pain, greater surgical trauma, anemia, and hypothermia.[96,97] Plasma catecholamine levels have been shown to correlate with postoperative cardiac troponin elevations[16] and with thrombotic graft occlusion after vascular surgery.[98] However, an increased rate of plaque rupture and coronary thrombosis in the immediate postoperative period has not been confirmed when these postoperative stresses are at their peak.
- Tachycardia and hypertension, common in the perioperative period, may exert excess shear forces on

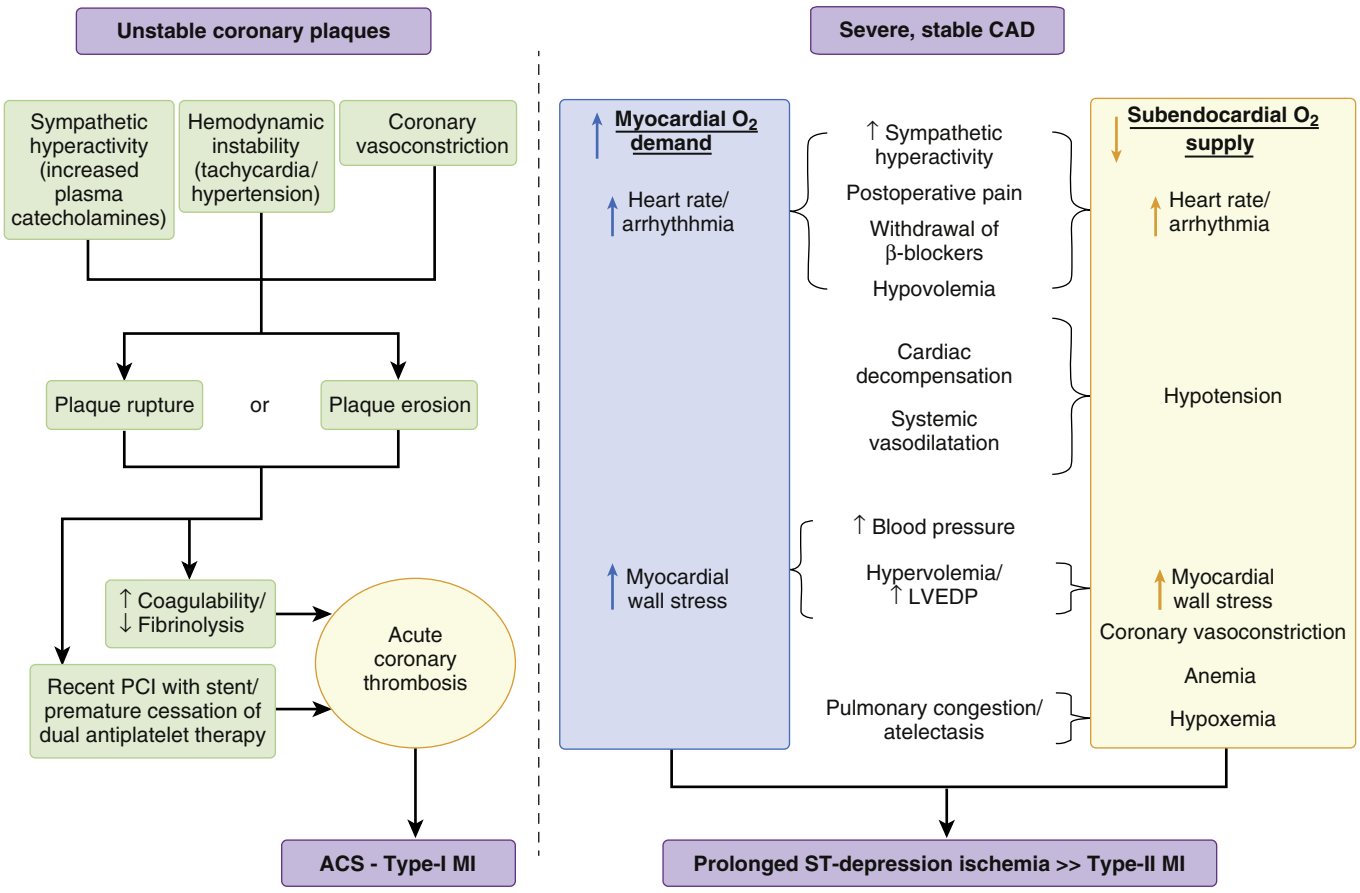


Figure 47-28. Two distinct mechanisms may lead to postoperative myocardial infarction: (1) type I—spontaneous plaque rupture or erosion and acute coronary thrombosis (acute coronary syndrome [ACS]); and type II—prolonged stress-induced myocardial oxygen supply-demand imbalance in the presence of severe yet stable coronary artery disease (CAD) (non-ACS). *LVEDP,* Left ventricular end-diastolic pressure; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention. *(Redrawn from Landesberg G, Beattie WS, Mosseri M, et al: Perioperative myocardial infarction,* Circulation *119:2936-2944, 2009.)*

vulnerable plaques with thin fibrous caps and high circumferential tensile stress or cause endothelial stripping or erosion of plaques with severe coronary stenosis, associated with high blood velocities.[99,100]

- Increased perioperative procoagulant agents (e.g., fibrinogen, factor-VIII coagulant, von Willebrand factor, α1-antitrypsin), platelet reactivity,[101] decreased endogenous anticoagulant medications (e.g., protein-C and antithrombin-III, α_2-macroglobulin),[102] and decreased fibrinolysis[103] have been reported. Postoperative hypercoagulability, however, is principally known for its venous thrombotic complications precipitated by stasis and immobilization. Reports on the association of hypercoagulability and/or decreased fibrinolysis with postoperative myocardial ischemia[104,105] or infarction[106] are rare. An association between impaired fibrinolysis and postoperative lower extremity arterial bypass thrombosis has been reported.[107] Attempts to mimic postoperative stress and hypercoagulability in healthy volunteers caused elevated tissue-plasminogen activator and protein-C activity, consistent with the inhibition of coagulation and augmented fibrinolysis and failed to cause an increase in coagulability.[108]

Myocardial Oxygen Supply-Demand Imbalance (Non–Acute Coronary Syndrome, Type 2 Myocardial Infarction)

Data obtained from studies using perioperative monitoring for myocardial ischemia in patients undergoing major, mostly vascular, surgery suggest an alternative, probably significantly more common pathophysiologic condition for PMI. Perioperative Holter monitoring for up to a week after surgery in patients at high risk for cardiac events consistently showed that silent, HR-related postoperative ischemia is common (up to 50%) postoperatively and associated with both in-hospital and long-term morbidity and mortality.[90,91] Postoperative cardiac complications, including sudden death, occur almost exclusively after prolonged (>30 minutes,[84,88] >2 hours,[81,82] or >5 hours[77,87]), silent ST-depression ischemia. These data have been corroborated by continuous perioperative 12-lead ECG monitoring with on-line ST-segment analysis after major vascular surgery and serial perioperative cardiac troponin measurements.[89,90] Troponin was elevated within hours after the onset of prolonged transient, ST-depression ischemia occurring early after the surgery, and the magnitude of troponin elevation correlated with the duration of ST-depression ischemia.[89] These findings led to the notion that prolonged, stress-induced ST-depression ischemia is a major cause of postoperative troponin elevation and myocardial infarction.

Importantly, however, sequential postoperative troponin measurements demonstrated that low-level, yet prognostically significant troponin elevations occur in patients at high risk who are undergoing major surgery with little or even no evidence of ischemia on ECGs.[90,109,110] Low-level troponin elevation (troponin T >0.03 ng/mL) occurred in as many as 24% of all patients early after major vascular surgery. Only 32% of patients had ECG evidence of ischemia. In contrast, among patients (8.7%) with conventional troponin elevations (>0.1 ng/mL), 88% had ischemia on continuous 12-lead ECG monitoring.[90] Higher troponin values were associated with longer ST-depression–type ischemia and with higher incidence of cardiac symptoms (e.g., pulmonary congestion, chest pain). Hence, prolonged postoperative ischemia, myocardial injury, and type 2 MI probably constitute a spectrum of clinical events ranging from silent, minor, myocardial injury with low-level troponin elevation and low frequency of ischemia on ECG to prolonged, overt ischemia in multiple ECG leads, associated with significant troponin elevation and PMI. Troponin elevation has an immense prognostic importance because troponin elevation measured in the first 3 postoperative days incrementally predicts both early (30 days)[111] and long-term (5 years)[90] postoperative mortality.

As opposed to coronary plaque rupture (type 1 MI) that typically occurs in relatively young and mildly occluding coronary plaques, prolonged stress-induced ST-depression–type ischemia and infarction (type 2 MI) occurs in patients with long-standing, high-grade, often multivessel yet stable CAD[93] (Fig. 47-29).

Multiple triggers may cause myocardial oxygen supply-demand imbalance in the postoperative period (see Fig. 47-28):

- Tachycardia is by far the main cause of postoperative ischemia and type 2 MI.[89,111] An increase in HR of 80 to 90 bpm in patients with significant CAD whose resting HR is 50 to 60 bpm may cause prolonged postoperative ischemia and PMI, demonstrating the low threshold for ischemia in patients after surgery.

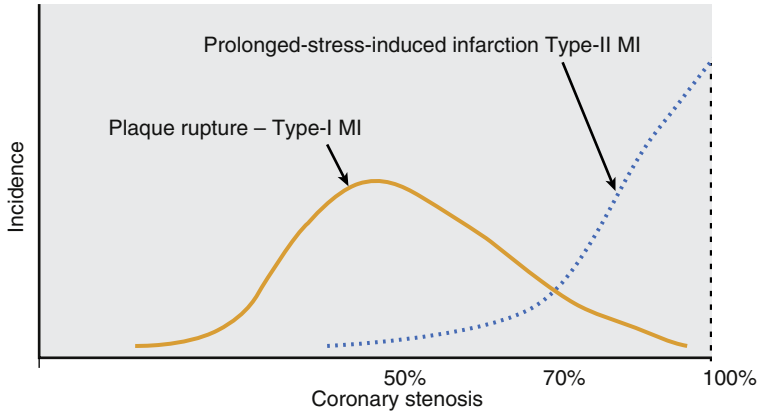


Figure 47-29. A schematic representation depicts the probability of type-I and type-II myocardial infarctions as a function of the severity of the coronary artery disease. Coronary plaque rupture mainly occurs in relatively nonoccluding coronary plaques, whereas prolonged myocardial oxygen supply-demand imbalance mainly occurs with severe, often multivessel coronary artery disease. *MI*, Myocardial infarction. *(Adapted from Landesberg G: The pathophysiology of perioperative myocardial infarction: facts and perspectives,* J Cardiothorac Vasc Anesth *17:90-100, 2003.)*

- Postoperative tachycardia is frequently associated with either hypotension, secondary to hypovolemia, bleeding, or systemic vasodilatation, or with hypertension induced by stress hormones and vasoconstriction, aggravating tachycardia-induced ischemia. The product of blood pressure and HR correlates with myocardial oxygen demand, whereas the quotient of arterial pressure divided by HR is critical for coronary perfusion, particularly in collateral-dependent myocardium.[112]
- Fluid overload in patients with reduced ventricular function may aggravate myocardial wall stress and subendocardial ischemia.
- Perioperative anemia,[113] hypoxemia, and hypercarbia are other common precipitants of myocardial ischemia in patients with significant CAD.
- Stress- and ischemia-induced coronary vasoconstriction[114,115] may further limit blood flow to areas with marginal coronary circulation.

TREATMENT AND PREVENTION OF PERIOPERATIVE ISCHEMIA AND INFARCTION

Because the majority of postoperative ischemic events and MIs are silent, the key to their prevention is a high index of suspicion and the early detection and treatment of any sign or symptom related to the heart such as chest pain, shortness of breath, hypoxemia, and ECG changes. Figure 47-30 proposes an algorithm for the prevention and treatment of perioperative ischemia and infarction. Unfortunately, however, no treatment strategy has thus far been tested by a large enough clinical trial.

The role of prophylactic perioperative β blockade remains highly controversial.[117,118] Nevertheless, the importance of preventing and treating even modest postoperative increases in the HR cannot be overemphasized. All causes of tachycardia, hypertension, hypotension, anemia, and pain should be aggressively treated. Treatment of tachycardia associated with hypotension is particularly challenging and requires an understanding of the patient's baseline and postoperative myocardial, valvular, and coronary physiologic condition. Frequently, vasopressors to maintain blood pressure and β-adrenergic blockers to slow HR while managing blood volume, postoperative pain, and respiratory function are necessary. Emergent coronary intervention, anticoagulant agents, or glycoprotein IIb/IIIa antagonists are rarely indicated in the immediate postoperative course and are hazardous because of the risk of bleeding, unless ST-segment elevation or intractable cardiogenic shock ensues.[119]

Anemia (hematocrit level <39%) independently predicts 30-day mortality, and its correction improved survival in one cohort study of patients who underwent noncardiac surgeries.[120] Blood transfusion improved survival in patients with CAD who were critically ill and hemoglobin less than 10% but not in patients without ischemia.[121] Other studies reported increased mortality and nosocomial infections with blood transfusion for hematocrit levels less

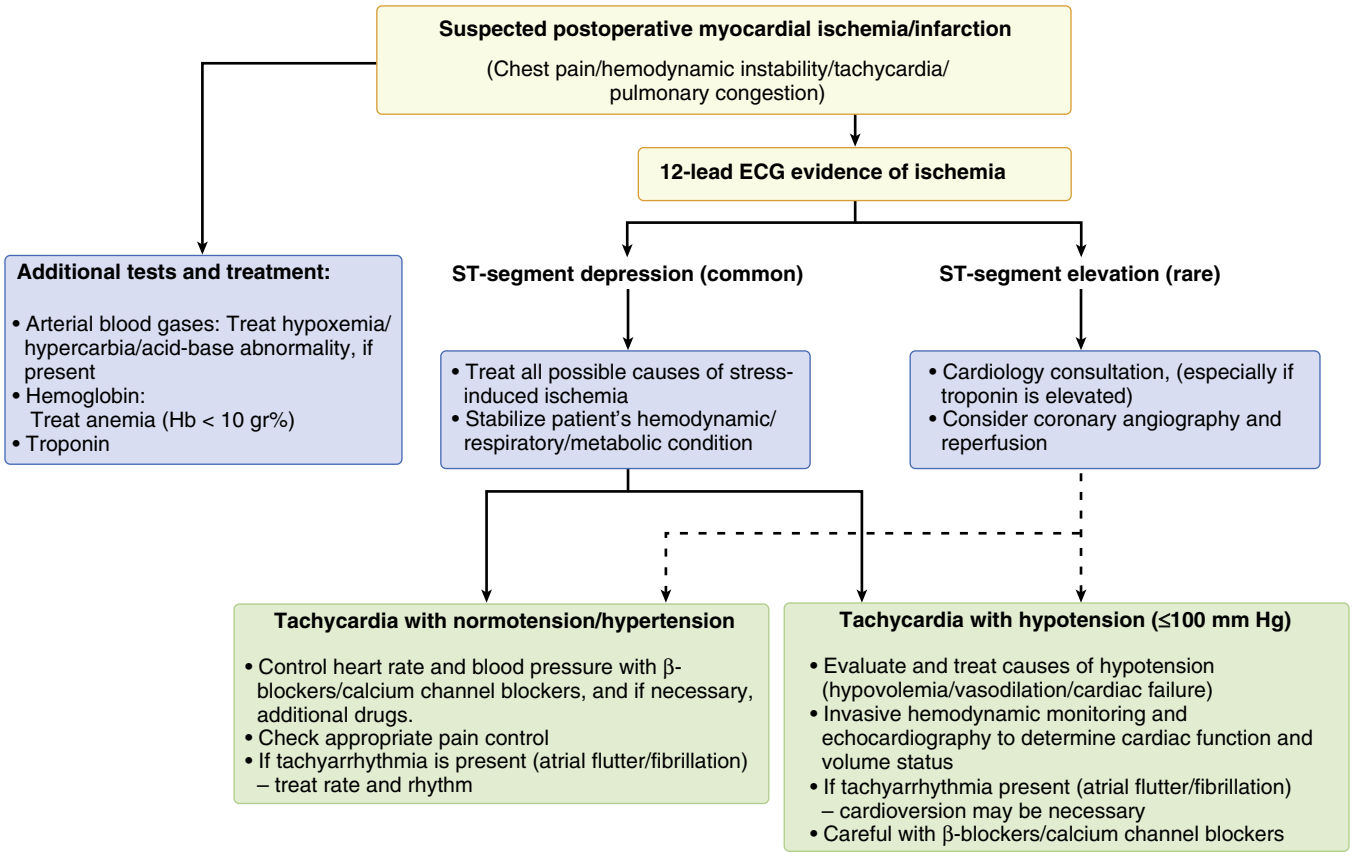


Figure 47-30. Algorithm for the prevention and treatment of perioperative ischemia and infarction. *(Redrawn from Landesberg G, Beattie WS, Mosseri M, et al: Perioperative myocardial infarction,* Circulation *119:2936-2944, 2009.)*

than 25% in stable patients with ACS,[122] in patients after cardiac surgery,[123] and in patients in the ICU.[124] Therefore, hematocrit levels between 25% and 33% is a gray zone in which transfusion must be individualized. Patients who are hemodynamically unstable postoperatively with ischemia may benefit from transfusion. Tight perioperative hemodynamic monitoring, including echocardiography, arterial line, central venous, or possibly pulmonary arterial pressure measurement, is often necessary to determine volume status and to avoid congestive failure.

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Chapter 48

Implantable Cardiac Pulse Generators: Pacemakers and Cardioverter-Defibrillators

MARC A. ROZNER

KEY POINTS*

Preoperatively

- Identify the generator manufacturer and model (pacemaker, transvenous defibrillator, subcutaneous defibrillator) of the cardiovascular implantable electronic device (CIED).
- Establish preoperative contact with the patient's CIED physician or clinic to obtain appropriate records and a perioperative prescription (Heart Rhythm Society [HRS]). Have the CIED interrogated (American Society of Anesthesiologists [ASA]) by a competent authority shortly before the anesthetic regimen.
- Obtain a copy of this interrogation. Obtain a perioperative prescription from the CIED physician (HRS). Ensure that implantable cardioverter-defibrillator (ICD) treatment settings are appropriate and that the CIED will pace the heart.
- Consider replacing any CIED near its elective replacement period in a patient scheduled to undergo either a major surgical procedure or a surgical procedure where monopolar electrosurgery will be used within 25 cm of the generator.
- Determine the patient's underlying rate and rhythm to determine the need for backup (external) pacing support.
- Ensure that all magnet behavior (pacing, suspension of shock therapy) is appropriate if magnet use is planned.
- Program minute ventilation rate responsiveness "off," if present.
- Consider disabling all rate enhancements to prevent misinterpretation of cardiac rhythm.
- Consider increasing the lower rate limit to provide optimal oxygen delivery for major procedures.
- If electromagnetic interference is likely, (1) disable antitachycardia therapy if a defibrillator is present and (2) consider asynchronous pacing for some pacing-dependent patients. Magnet application may be acceptable for some ICDs (disable antitachycardia therapy) or pacemakers (provide asynchronous pacing). Asynchronous pacing from an ICD always requires reprogramming.

Intraoperatively

- Monitor cardiac rhythm with the pulse oximeter (plethysmography) or arterial waveform analysis.
- Consider disabling the "artifact filter" on the electrocardiogram monitor. If a minute ventilation sensor is present and active, ensure that respiratory rate monitoring is disabled.
- Ask the surgeon to operate without the monopolar electrosurgical unit (ESU).
- Use a bipolar ESU if possible; if not possible, then pure "cut" electrosurgery is better than "blend" or "coag," and ESU should be applied in short bursts (<4 seconds) separated by at least 2 seconds.

*Adapted from the American Society of Anesthesiologists (ASA) *Practice Advisory* (2005, revised 2011) and the Heart Rhythm Society (HRS), formerly the North American Society of Pacing and Electrophysiology (NASPE) and ASA *Consensus Statement* (2011) *for Perioperative Management of Patients With a Pacemaker or Defibrillator.*

KEY POINTS—cont'd

- Place the ESU dispersive electrode in such a way to prevent electricity from crossing the generator-heart circuit, even if the electrode must be placed on the distal forearm and the wire covered with sterile drape.
- If the ESU causes ventricular oversensing with pacing quiescence or atrial oversensing with inappropriate ventricular pacing, limit the effect by using short ESU bursts, relocating the dispersive electrode, or placing a magnet over the pacemaker (not indicated for ICDs)

Postoperatively

- Some patients require postoperative interrogation, especially if preoperative reprogramming took place. For "low-risk cases," HRS (but not ASA) states that this interrogation can take place in an ambulatory setting up to 1 month postoperatively. Some rate enhancements can be reinitiated, and a determination of optimum heart rate and pacing parameters should be made. Any patient with disabled antitachycardia therapy must be monitored until the antitachycardia therapy is restored.

The nature of anesthesiology practice requires a wide breadth of knowledge, often encompassing situations that occur rarely throughout a career. Nowhere in medicine does this task seem more difficult than the subject of the cardiac implanted electronic device (CIED). Many factors lead to confusion regarding the behavior of a CIED and the perioperative care of a patient with a CIED. Some patients have old, technologically outdated devices that still appear to function. New developments seem to take place rapidly, and case reports, textbooks, and literature reviews sometimes present incorrect material or do not keep pace with these new developments. Proprietary features, differing magnet behaviors (even among models from the same company), confusion regarding CIED type and available therapies, and the lack of standardization make synthesis of generalizations difficult, with the potential of putting the patient at risk. Finally, preventable adverse events that can cause injury or death in patients are thought to occur "by chance" (see the later section on temporary pacing).

Battery-operated pacing devices were introduced by C.W. Lillehei (a cardiothoracic surgeon) and Earl Bakken (an electrical technician) in 1958, just 4 years after the invention of the transistor. In 1960, Wilson Greatbatch, an engineer, created the first implantable battery-powered device in his barn in Buffalo, New York.[1] The natural progression of pacemaker (PM) developments led to the invention of the implanted cardioverter-defibrillator (ICD[†]) in approximately 1980 by Michael Morchower in Baltimore. First approved by the U.S. Food and Drug Administration (FDA) in 1985, implantation of ICDs required thoracotomy, a significant operation for the patient with poor heart function. Advances in electronic miniaturization, as well as improvements in battery technology, led to the development of very small (10-mL volume), but electronically complicated, programmable pacing devices.

Technologic advances (transvenous lead placement, antitachycardia[‡] pacing [ATP] capability, continued miniaturization, advanced pacing capability, and numerous survival benefits[2,3]) led to increases in ICD implantation. Since 1997, transvenous ICDs (T-ICDs) have been approved to provide permanent antibradycardia pacing.

Sophisticated three-chamber (atrium, right ventricle, and left ventricle) pacing to provide cardiac resynchronization therapy (CRT; also called biventricular [BiV] pacing) from both PMs (CRT-P) and ICDs (CRT-D) became available in the United States in 2001. In 2009, Cameron Health (San Clemente, Calif) received a CE mark (mandatory conformity marking for certain products sold within the European Economic Area since 1985) for their subcutaneous ICD (S-ICD). Boston Scientific/Guidant Medical/CPI (BOS; Natick, Mass) purchased this company in mid-2012 and received US FDA approval for the S-ICD in September 2012.

As noted, these advances and expanding indications for implantation can create confusion when caring for patients with CIEDs. A T-ICD in a pectoral position could be mistaken, by virtue of pacing "spikes" on the surface electrocardiogram (ECG), for a (non-ICD) PM. Additionally, T-ICDs have been inappropriately called "pacemaker/defibrillators" by medical personnel, the press, and patients. Given that pacing functions in T-ICDs respond to external stimuli (magnet placement, electromagnetic interference [EMI]) differently than do PMs, this confusion could harm the patient. For example, failure to disable shock therapy in the presence of EMI, thereby leading to inappropriate shock during a perioperative experience,[4] could actually shorten a patient's life.[5] Published data suggest that significant numbers of patients actually receive an inappropriate ICD shock during hospitalization.[6] Distinguishing a conventional PM from a T-ICD can be accomplished by examining the right ventricular (RV) lead system on a

[†] Although many authors and references identify this device as an "automatic implantable cardioverter-defibrillator or AICD," the term AICD is a brand name that was originally owned by CPI (Cardiac Pacemakers, Inc.), which was acquired by Guidant Medical Corporation and is now a part of Boston Scientific (Natick, Mass). The term PCD (Programmable Cardioverter-Defibrillator) belongs to the Medtronic Corporation (Minneapolis, Minn).

[‡] The terms antibradycardia and antitachycardia are used throughout this chapter. *Antibradycardia* refers to pacing to maintain a minimum rate. Thus, conventional pacemakers are antibradycardia devices. *Antitachycardia* refers to therapy delivered in the setting of tachycardia, and this therapy is designed to reduce the underlying heart rate.

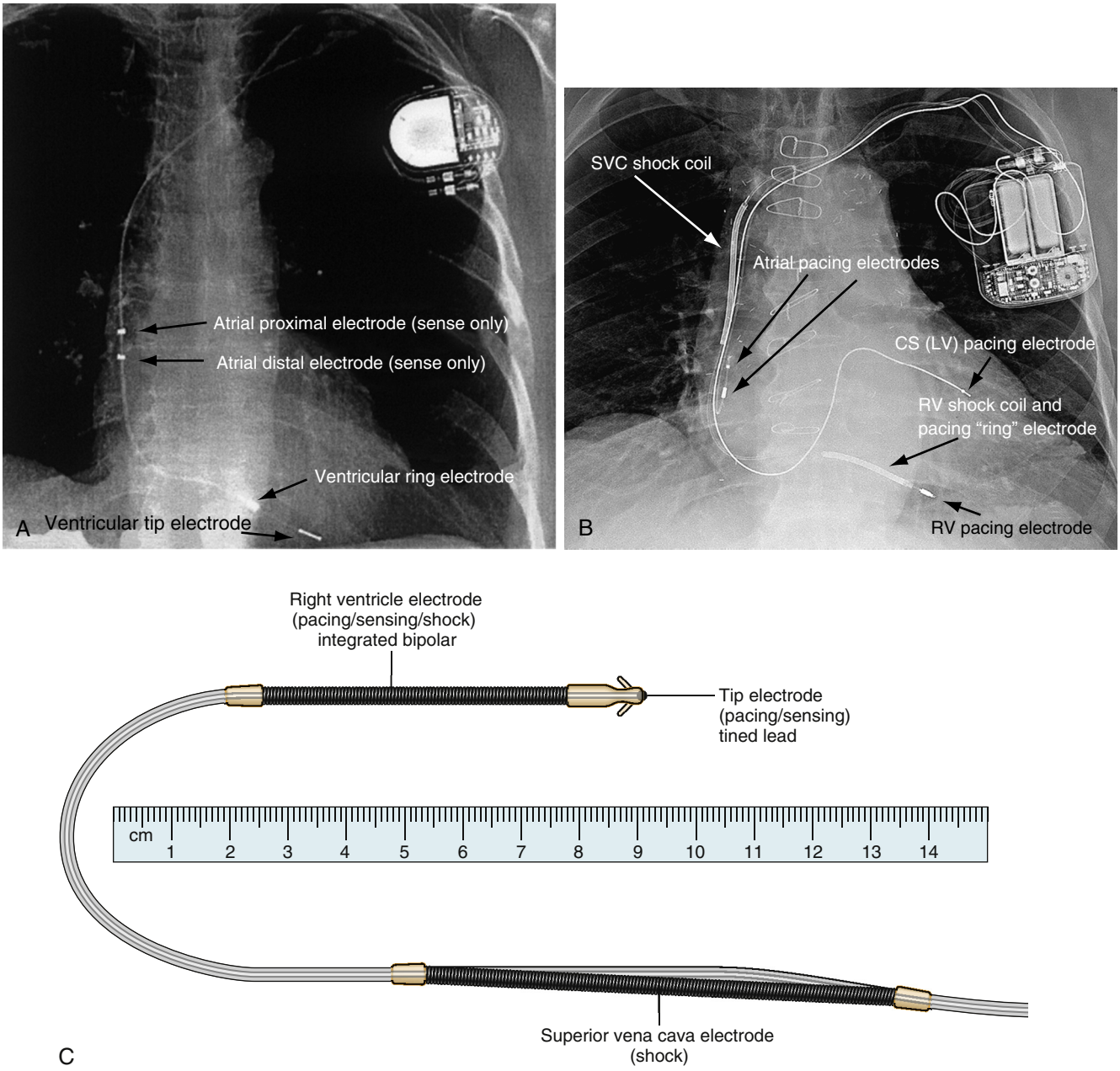


Figure 48-1. A pacemaker, an implantable cardioverter-defibrillator (ICD), and a right ventricular (RV) defibrillator lead are shown to assist in determination of the type of system using chest radiography. **A**, Conventional pacemaker with one quadripolar lead that provides atrial and ventricular sensing and ventricular pacing. This chest radiograph shows a number of features of a modern pacing system. The generator is located in the left pectoral region. The single lead enters the subclavian vein under the clavicle but superficial to the first rib (a common site for lead problems, although no problem is demonstrated here). This lead has two electrodes positioned within the right atrium to provide sensing to detect intrinsic atrial activity. The ventricular portion of the lead shows the classic bipolar pattern with a ring electrode just proximal to the tip electrode, and these electrodes can be used for sensing intrinsic ventricular activity as well as depolarizing the ventricle. This particular system is a VDD pacemaking system used to provide atrioventricular (AV) nodal activity in patients with a functioning sinoatrial node and atrium because this system cannot be used to depolarize the atrium. Because the surface electrocardiogram often demonstrates ventricular pacing that tracks the atrial activity, inspection of the surface electrocardiogram often produces an erroneous diagnosis of a dual-chamber (DDD) pacemaker. **B**, Defibrillator system with biventricular pacing capability. Note that three leads are placed: a conventional bipolar lead to the right atrium, a multipolar lead terminating in the right ventricle, and a unipolar lead to the coronary sinus (CS). The presence of a "shock" conductor in the right ventricle (called a "shock coil") distinguishes a defibrillation system from a conventional pacing system. Many ICDs have an additional shock coil in the superior vena cava (SVC). Typically, the SVC shock coil is electrically identical to the defibrillator case (called the "can"). When the defibrillation circuitry includes the ICD case, it is called "active can configuration." This particular system is designed to provide "resynchronization therapy" in the setting of dilated cardiomyopathy with a prolonged QRS complex (and frequently with a prolonged PR interval as well). The bipolar lead in the right atrium will perform both sensing and pacing function. Similarly, the tip electrode in the right ventricle along with the shock coil performs RV pacing and sensing functions. When the second RV pacing electrode is merged with the shock coil, the lead is called "integrated bipolar" because unipolar RV pacing is not permitted in an ICD system. The lead in the CS depolarizes the left ventricle (LV). Failure to depolarize one of the ventricles could result in ventricular oversensing (and inappropriate antitachycardia therapy) in an ICD. **C**, Integrated bipolar RV defibrillator lead. The tip of this lead becomes enmeshed in the RV trabeculae (called a "tined" lead), rather than engaging the myocardial wall with a screw ("active fixation"). This particular lead has an SVC shock coil as well.

chest radiograph (Fig. 48-1). A chest radiograph can also be used to identify the generator manufacturer (Fig. 48-2).

Pacemaking and defibrillation systems have a remarkable record for reliability, but they can, and do, fail. Laskey and associates analyzed FDA records for T-ICD report explantations for the period from 2003 to 2007 (459,000 T-ICDs and 256,000 CRT-Ds implanted) and found an annual explantation rate of 5.0% for T-ICD and 8.3% for CRT-D.[7] A similar study for PMs (1990 to 2002; 2.25 million implants) showed a 0.4% failure rate.[8] Thus, every patient with a cardiac generator should undergo regular in-office follow-up. For appropriately selected devices, remote (i.e., telephone) checks can be used to identify battery depletion, programming, sensing issues, arrhythmia detection (PM and ICD), and arrhythmia treatment (ICD). Some PMs and T-ICDs have automated sensing and capture testing that can report problems, but commanded iterative testing, such as pacing thresholds, cannot be performed. For "stable" PMs, Medicare coverage includes telephone evaluation every 4 to 12 weeks. The Heart Rhythm Society and European Heart Rhythm Association (HRS/EHRA) recommend evaluation (remote or in person) every 3 to 12

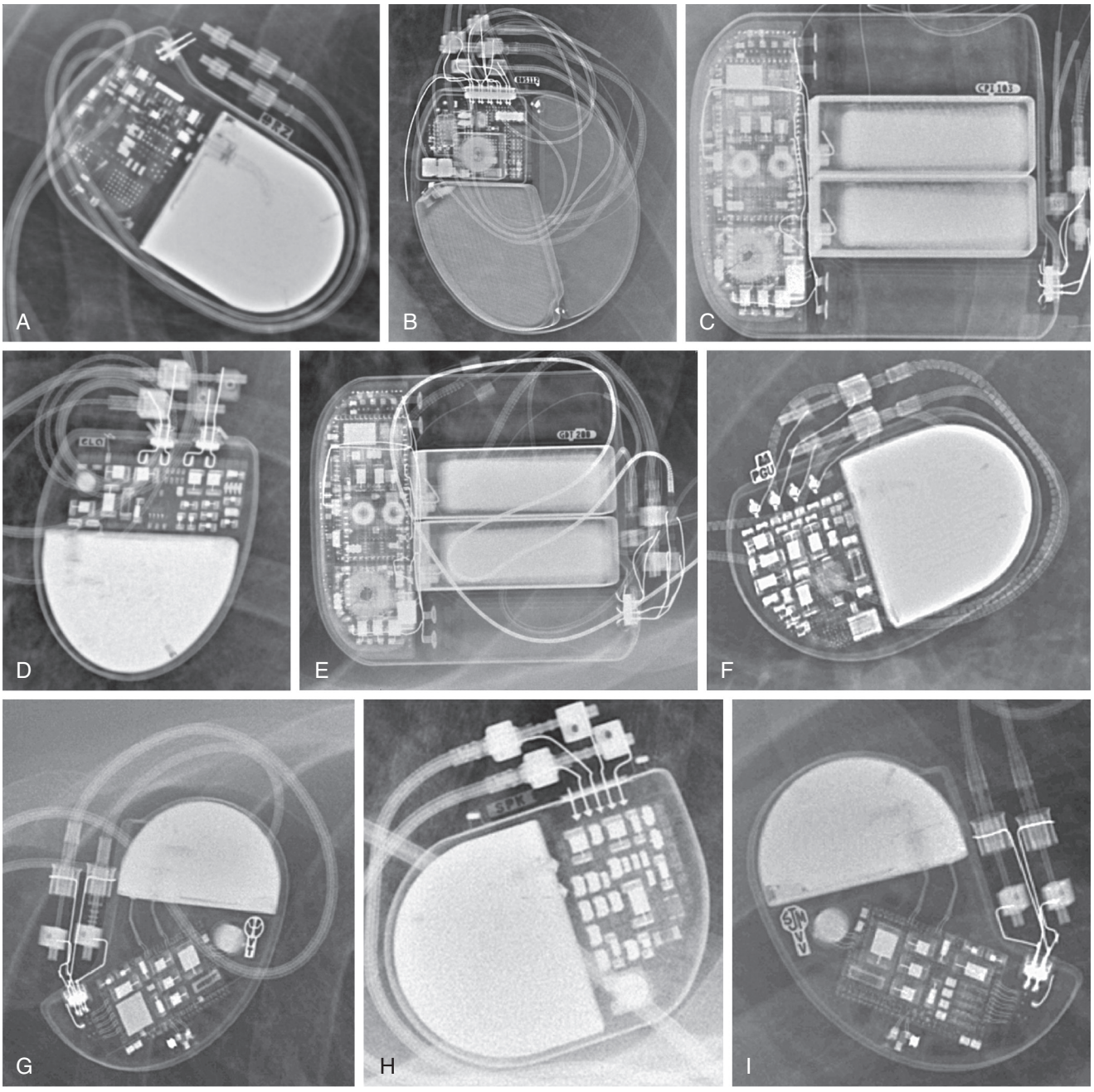


Figure 48-2. Radiographic identifiers for some generator manufacturers. Pacemaker and implantable cardioverter-defibrillator generators can be identified from operative dictations, patient cards, or some chest radiographs. Using digital x-ray equipment with postprocessing zoom capability, corporate x-ray logo identifiers from Biotronik (**A**), Boston Scientific (**B**),CPI (**C**), ELA (**D**), Guidant (**E**), Medtronic (**F**), Pacesetter (**G**), Sorin (**H**), and St. Jude Medical (**I**) are shown. For Sorin devices, all identifiers start with "SP," and the third character identifies the actual model. *Currently used logo.

months. Medicare coverage and recommendations (HRS/EHRA) include at least one in-person evaluation every year. Medicare has no coverage determination for ICD follow-up care; HRS/EHRA recommends evaluation (remote or in person) every 3 to 6 months with at least one in-person evaluation annually.[9,10]

Issues also develop leading to "notices," "product advisories," or "recalls" from the various manufacturers that may affect perioperative care. For example, BOS reported T-ICD magnet switch issues that could prevent delivery of shock. Two separate groups have been identified: (1) certain T-ICDs manufactured before 2005 (≈2000 remaining implants) whose magnet switches should be permanently disabled and (2) some T-ICDs manufactured between January 2006 and December 2007 (≈34,000 remaining implants) that must be checked for "tones/beeps" following any magnet removal. Any ICD with the magnet switch disabled will deliver a shock even with a magnet in place (Fig. 48-3).[4,11] The Medtronic (Minneapolis, Minn) Sprint Fidelis ICD lead series reports ventricular activity in the absence of true electrical systoles (oversensing), and this can result in failure to pace or the delivery of inappropriate shock (Fig. 48-4). Recommended actions included programming changes and use of telephone monitoring.[12] In December 2010, St. Jude Medical (Sylmar, Calif) reported that their Riata ICD leads (227,000 implanted) could develop insulation failures, resulting in inappropriate ICD discharge or pacing failures. They recommended in-office follow-up every 3 to 6 months.[13]

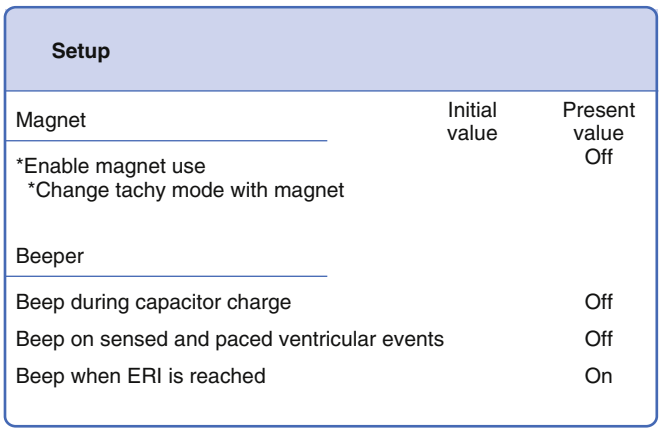


Figure 48-3. Magnet mode setup from a Guidant (now Boston Scientific) Contak Renewal 3 HE model H179. This implantable cardioverter-defibrillator (ICD) is part of an "Urgent Medical Device Safety Information and Corrective Action" letter to physicians from the Guidant Corporation on June 23, 2005, in which a magnet switch problem was announced. The corrective action was designed to disable the magnet switch permanently by programming. As a result, this ICD will not disable shock therapy in response to magnet placement. According to the notice, approximately 46,000 Guidant ICDs were affected and should have their magnet switch permanently disabled. Industry experts believe that fewer than 10,000 of these devices remained implanted and active after January 1, 2013. Note the line below the magnet switch report called "Change tachy mode with magnet." Effective with software released by Boston Scientific in October 2009, this setting was removed from all ICDs except the Contak Renewal Series. When present and enabled, this setting allows permanent deactivation of ICD function with the application of a magnet for more than 30 seconds. No Boston Scientific ICD with the "BOS" x-ray logo has this feature. *ERI,* Elective replacement indicator.

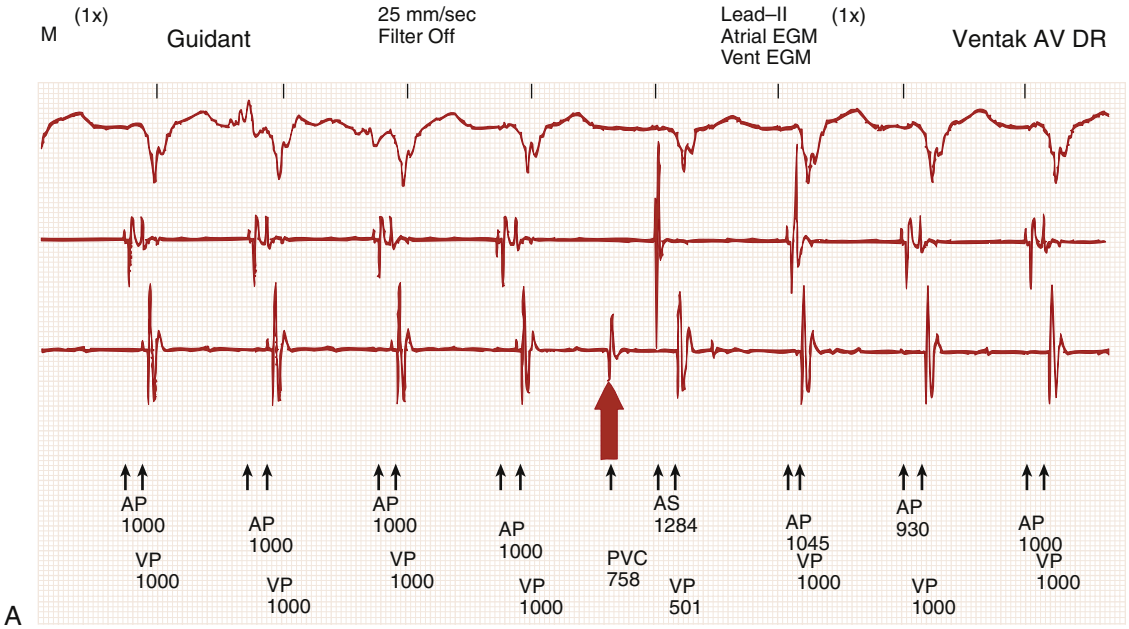
The complexity of PMs and ICDs, as well as the multitude of programmable parameters, limits the number of generalizations that can be made about the perioperative care of the patient with an implanted pulse generator (PG). Aging of the population, continued enhancements in implantable technology, new indications for implantation, and new devices continue to drive the growing numbers of implants. In 2005, the ASA published a *Perioperative Practice Advisory,* which was revised in 2011.[14] Also in 2011, the HRS and the ASA published an "Expert Consensus Statement,"[15] in which many experts from several societies tried to balance technical, economic, and safety issues in these patients. The Canadian Anesthesia Society and Canadian Cardiovascular Society (CAS/CCS) jointly published a statement in 2012,[16] and the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) published guidelines in 2006 in which the use of "surgical diathermy/electrocautery" was anticipated.[17] The MHRA document is silent on the CIED patient who is undergoing a surgical procedure without the presence of EMI. All the documents report that care of the emergency patient is more complicated than is care of the elective surgical patient (Table 48-1).

Patients with an implanted cardiac PG often have significant comorbid disease in addition to their cardiac rhythm disturbance. The ability to care for these patients requires attention to both their medical and psychological problems. Anesthesiologists also need an understanding of the patient's PG, its functions, and likely idiosyncrasies in the operating or procedure room.

Finally, not all electronic generators implanted in the chest are cardiac devices, and devices resembling cardiac PGs have been implanted for indications unrelated to cardiac issues. When implanted in the pectoral position (the usual place for current cardiac PGs), these noncardiac devices can be mistakenly identified as cardiac PGs.[18] PG implantation has been approved by the FDA for pain control, thalamic stimulation to control Parkinson disease, phrenic nerve stimulation to stimulate the diaphragm in paralyzed patients, and vagus nerve stimulation to control epilepsy and depression.[19] Vagus nerve stimulation is also under consideration to treat heart failure,[20] as well as perhaps obesity.[21] Thus, when evaluating a patient with any PG, one must now determine whether the PG will be pacing the heart, stimulating the central nervous system, stimulating the spinal cord, or stimulating the vagus nerve.

PACEMAKERS

PM manufacturers report that more than 3000 generators have been manufactured by more than 26 named entities since the 1960s. Currently, industry experts report that more than 350,000 adults and children in the United States undergo new PM placement each year, and likely 3 million patients have PMs today. Worldwide, the prevalence probably approaches 5 million patients.



A

ICD Model: Gem III VR 7231
Serial Number

Apr 26,2005 14:12:05
9971 Software Version 5.0
Copyright Medtronic, Inc. 2000

Status Report **Page 1**

Last interrogation: Apr 11, 2005 15:06:25

Battery Voltage

(ERI=2.55 V, EOL=2.40 V)
Apr 26, 2005 14:04:43
Voltage 2.97V

Last Capacitor Formation*

Dec 31, 2004 20:24:36
Charge Time 6.08 sec
Energy 0.0 – 30.0J

Last Charge

Dec. 31, 2004 20:24:36
Charge Time 6.08 sec
Energy 0.0 – 30.0J

Device Status

Charge Circuit is OK.

*Minimum Auto Cap Formation interval is 4 months

Lead Impedance

Apr 26, 2005 03:00:05
V. Pacing 444 ohms
Defibrillation (HVB) 13 ohms

Last High Voltage Therapy

May 21, 2002 09:14:00
Measured Impedance 56 ohms
Delivered Energy 20.2 J
Waveform Biphasic
Pathway AX>B

Sensing Integrity Counter

Since Apr 11, 2005 15:18:06
120–130 ms V-V intervals 875
(if>300 counts, check for sensing issues)

B

Figure 48-4. Ventricular oversensing from damaged leads. **A,** Real-time telemetry recording from a Guidant implantable cardioverter-defibrillator (ICD) with a Guidant 0154 right ventricular (RV) defibrillation lead reports a spontaneous ventricular (*red up arrow*) event that was not present on the surface electrocardiogram (ECG), termed ventricular oversensing. In this ICD, the pacing function was DDD (lower rate, 60 beats/minute; atrioventricular delay, 180 msec), and this patient depended on the ICD pacing function for his ventricular systoles. The *top tracing* is the surface ECG, the *second tracing* is the intracardiac atrial electrogram (EGM), and the *third tracing* is the intracardiac ventricular EGM. Along the *bottom* is the "marker channel," which shows the pacemaker's interpretation of events: AP is atrial pace, AS is atrial sense, VP is ventricular pace, and the inappropriate ventricular sensed event is labeled "PVC" because it occurs after a ventricular event without an intervening atrial event. This oversensing has prolonged the R-R interval between the fourth and fifth ventricular systoles because this patient depends on the pacing function for his ventricular systoles. In a pacing-dependent patient, this type of oversensing can lead to asystole. It can also provoke inappropriate antitachycardia therapy (i.e., shock) in a patient with native ventricular activity because these oversensed events can increase the apparent heart rate count to the ICD. **B,** A patient with a single-chamber Medtronic ICD and a Medtronic Sprint Fidelis RV defibrillation lead was found to have a significant ventricular oversensing issue at interrogation on April 26, 2005, before a head and neck surgical procedure. In this case the ICD is reporting 875 "short R-R intervals" (note the *arrow*) since the previous interrogation 15 days earlier (April 11, 2005). These data are consistent with a lead fracture causing intermittent "make-break" contacts. In this case, new counts began accumulating 12 minutes after the previous interrogation was complete. More than 100 counts/month is considered a problem; indications to replace the lead include ventricular oversensing in a pacing-dependent patient or a high rate of detection (frequently resulting in shock) triggered by this inappropriate oversensing. *EOL,* End of life; *ERI,* elective replacement indicator.

TABLE 48-1 BRIEF REVIEW AND COMPARISON OF PUBLISHED PERIOPERATIVE ADVISORIES FOR CARDIAC IMPLANTED ELECTRONIC DEVICES

	Preoperative Recommendation	Intraoperative Magnet Use	ESU Dispersive Electrode Placement	Postoperative Recommendation	Emergency Procedures	
					PM	ICD
ASA	"Timely interrogation" before elective surgery	Shuns magnet use in favor of reprogramming	Prevent presumed current path from crossing the chest or CIED system	Interrogation recommended; footnotes added to 2011 revision suggesting that CIED reinterrogation not needed if no monopolar ESU used	(silent)	
HRS/ASA	PM interrogation within 12 mo, ICD interrogation within 6 mo, and CRT interrogation within 3-6 mo; CIED physician must provide prescription for perioperative care	Magnet use suggested for asynchronous pacing (where needed in PM-treated patients) and disabling ICD high-energy therapy provided that patient position does not interfere with magnet access or observation	Prevent presumed current path from crossing the chest or CIED system	For most cases involving EMI (especially those inferior to umbilicus and where no preoperative reprogramming was performed), interrogation can take place within 1 mo as ambulatory procedure; for reprogrammed CIEDs, hemodynamically challenging cases, cardiothoracic surgery, RFA, and external cardioversion, interrogation before transfer from cardiac telemetry	Use 12-lead ECG to identify pacing need; presume dependence if 100% pacing Use magnet to mitigate pacing inhibition Cardiac monitoring until postoperative interrogation	Use magnet to suspend ICD tachyarrhythmia therapy
CAS/CCS	De novo interrogation likely not needed, but CIED physician must provide prescription for perioperative care	When reasonable, magnet use suggested for asynchronous pacing (as needed in PM-treated patients) and disabling ICD high-energy therapy	No mention	Clear plan for postoperative care established before elective case	Use 12-lead ECG to identify pacing need; presume dependence if 100% pacing; careful monitoring to determine magnet action; >5 second pauses if ESU interferes with CIED	
MHRA*	Preoperative contact with the PM or ICD follow-up clinic for evaluation and perioperative recommendations	Caution advised because magnet behavior can be affected by programming	"Ensure that the return electrode is anatomically positioned so that the current pathway between the diathermy electrode and return electrode is as far away from the pacemaker/defibrillator (and leads) as possible"	Follow-up clinic to prescribe postoperative follow-up	Attempt to follow routine steps; postoperative interrogation ASAP Magnet may create asynchronous pacing	Magnet may prevent inappropriate discharge

ASA, American Society of Anesthesiologists; *CAS/CCS,* Canadian Anesthesia Society and Canadian Cardiovascular Society; *CIED,* cardiac implanted electronic device; *CRT,* cardiac resynchronization therapy (any CIED that has right ventricular and left ventricular pacing capability); *ECG,* electrocardiogram; *EMI,* electromagnetic interference; *ESU,* electrosurgical unit ("Bovie"); *HRS,* Heart Rhythm Society. *ICD,* implanted cardioverter-defibrillator; MHRA, Medicines and Healthcare Products Regulatory Agency; *PM,* pacemaker; *RFA,* radiofrequency ablation.
*Recommendations appear relevant only if electromagnetic interference will be present.

TABLE 48-2 NORTH AMERICAN SOCIETY OF PACING AND ELECTROPHYSIOLOGY/BRITISH PACING AND ELECTROPHYSIOLOGY GROUP REVISED (2002) GENERIC PACEMAKER CODE (NBG)*

Position I	Position II	Position III	Position IV	Position V
Pacing Chamber(s)	**Sensing Chamber(s)**	**Response(s) to Sensing**	**Programmability**	**Multisite Pacing**
O = None **A** = Atrium **V** = Ventricle **D** = Dual (**A**+**V**)	**O** = None **A** = Atrium **V** = Ventricle **D** = Dual (**A**+**V**)	**O** = None **I** = Inhibited **T** = Triggered **D** = Dual (**T**+**I**)	**O** = None **R** = Rate modulation	**O** = None **A** = Atrium **V** = Ventricle **D** = Dual (**A**+**V**)

*The generic pacemaker code.[23] This code, initially published in 1983, was last revised in 2002 in an effort to keep current with technologic developments in the pacing field. The NBG code is a joint project from the North American Society of Pacing and Electrophysiology (NASPE: "N") and the British Pacing and Electrophysiology Group (BPEG: "B"). The "G" stands for generic.

A pacemaking system consists of an impulse generator and leads to carry the electrical impulse to the patient's heart. Leads are connected to the heart's chambers through the vena cava (transvenous leads), or they are directly sewn onto the surface of the heart (epicardial leads). Leads can be unipolar (one electrode per lead), bipolar (two electrodes per lead), or multipolar (multiple electrodes and wires contained within one lead with connections in multiple chambers) (see Fig. 48-1, *A*). Because two electrodes are required to complete a circuit, the second electrode in a unipolar configuration is the metal generator case. Use of the case as an electrode requires that the generator pocket be devoid of gas, and electrical continuity has reportedly been disrupted by the use of nitrous oxide.[22]

PMs with unipolar leads are more sensitive to the effects of EMI, and these systems produce larger "spikes" on an analog-recorded ECG. Most pacemaking systems (except older Autocapture devices from St. Jude Medical) pace in bipolar mode because bipolar pacing usually requires less energy. Bipolar sensing is more resistant to interference from muscle artifacts or stray electromagnetic fields. Often, bipolar electrodes can be identified on the chest film because they will have a ring electrode 1 to 3 cm proximal to the lead tip (see Fig. 48-1, *A*). However, generators with bipolar leads can be programmed to the unipolar mode for pacing, sensing, or both. Some PMs automatically switch to unipolar pacing or sensing on detection of a lead problem. Unipolar pacing is absolutely contraindicated in the presence of any ICD.

CODES

No discussion of PMs can take place without an understanding of the generic PM code, which was published by the HRS, formerly the North American Society of Pacing and Electrophysiology and Heart Rhythm UK, formerly the British Pacing and Electrophysiology Group. This code (NBG§) was initially published in 1983 and was last revised in February 2002.[23] It describes the basic behavior of the pacing device (Table 48-2). PMs also come with a variety of terms generally unfamiliar to the anesthesiologist, many of which are shown in the glossary at the end of this chapter.

The first two positions of this code (chamber[s] paced and chamber[s] sensed) seem relatively straightforward. Although early PMs provided only ventricular support, current models can provide pacing in the atria and ventricles, and these devices can also be programmed to determine intrinsic activity in these chambers. The code does not describe the array of diagnostic data that can be accumulated by these devices.

Probably the most confusing aspect of the NBG code is the third position (response to sensed event). Most PMs are programmed either to the DDD mode (atrial and ventricular ["dual-chamber"] pacing and sensing, both triggered and inhibited mode) or to the VVI mode (ventricular pacing in the inhibited mode). Two other modes frequently found are VDD (ventricular pacing with atrial tracking) and DDI (dual-chamber pacing and sensing, but inhibited mode only). In the United States, atrial-only PM placement (AAI mode) is unusual; however, these devices are implanted in patients with sinus node disease, but intact atrioventricular (AV) conduction, in other countries. The NBG third position describes the following behavior:

D (Dual): DDD and VDD pacing provide AV synchrony. In the DDD setting, atrial pacing takes place in the "inhibited" mode (i.e., the pacing device will emit an atrial pulse if no sensed atrial event [or intervening ventricular event, because any ventricular event will reset atrial timing] takes place within the appropriate timeframe). In DDD or VDD devices, once an atrial event has occurred (whether native or paced), the pacing device ensures that a ventricular event follows (up to the upper tracking rate [UTR; see the glossary at the end of the chapter]).

I (Inhibited): The appropriate chamber is paced unless intrinsic electrical activity is detected during the pacing interval. For the DDI mode, AV synchrony is provided only when the atrium is paced. If intrinsic atrial activity is present, then no AV synchrony is provided by the pacing function.

T (Triggered): The pacing device emits a pulse only in response to a sensed event. The triggered mode is used when the device is being tested.

The VDD and DDI modes deserve further comment. VDD pacing is used for the patient with AV nodal dysfunction but intact and appropriate sinus node behavior.

§The NBG code is a joint project of the North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG), now known as the Hearth Rhythm Society and Heart Rhythm Society UK, respectively. The "N" is NASPE, the "B" is BPEG, and the "G" stands for generic.

VDD pacing is accomplished with a single lead that incorporates atrial sensing electrodes, as well as ventricular conductors that can both pace and sense (see Fig. 48-1, *A*). A VDD device has no atrial pacing capability. As a result, in a patient who depends on atrial contraction to augment cardiac output, events that result in VVI pacing (e.g., sinus rate lower than programmed rate, battery depletion) or asynchronous ventricular pacing (e.g., magnet placement in many devices, EMI) can lead to deteriorating hemodynamics.[24,25]

DDI pacing is indicated for the patient who has a dual-chamber pacing device and also has episodes of paroxysmal atrial dysrhythmia (e.g., paroxysmal atrial fibrillation). DDI pacing prevents high ventricular rates (i.e., pacing at the UTR) that could result from attempted tracking of the atrial arrhythmia, and it provides AV synchrony only when the atrium is paced. Many DDD programs enter the DDI mode on detection of high (programmable) atrial rates (called Mode Switch, Automatic Mode Switch, or Atrial Tachy Response, depending on the manufacturer). When the mode is switched to DDI, perturbations (e.g., very high [>400/minute] atrial rates, EMI from the electrosurgical unit [ESU], or magnet placement and removal) may revert back to DDD pacing, with the resultant appearance of AV pacing or ventricular pacing at the UTR (see the section on magnets later in this discussion of pacemakers).

Rate modulation (the fourth position) also remains a poorly understood concept. Because some patients cannot increase their heart rate in response to increased oxygen demand (chronotropic incompetence), PM manufacturers have devised certain mechanisms to detect "patient exercise," such as sensors that detect vibration, respiration, and pressure (Box 48-1). As the sensor detects "exercise," it increases the pacing rate (termed-sensor indicated rate). As the exercise tapers, this sensor-indicated rate returns to the programmed lower rate. The sensitivity of these sensors to their exercise signals and the rates of change in pacing are programmable features in current generators. Activation of rate-response algorithms, resulting in an increased paced rate in the operating room, whether from vigorous chest wall skin preparation, pressure on the generator, or EMI in a minute ventilation device, has led to inappropriate treatment and harm to the patient.[26,27]

With the 2002 revision of the NBG, the fifth column describes multisite pacing functionality (it had been used to describe antitachycardia function, but this scheme has been abandoned, and a generic defibrillator code has been established). Atrial multisite pacing may prevent atrial fibrillation,[28] and ventricular multisite pacing is an acceptable treatment for pacing the patient with dilated cardiomyopathy (DCM).[29-31]

BOX 48-1 ***Rate Modulation (Activity) Sensors Available or Under Investigation****

Currently Approved in the United States

Vibration sensor
Motion sensor
Minute ventilation (bioimpedance sensor)
QT interval (Vitatron only)
Right ventricular pressure (Biotronik only)

Under Investigation

Right ventricular stroke volume
Blood pH
Blood temperature
Mixed venous oxygen sensor
Systolic time intervals
Evoked response
Intracardiac impedance

*Of the types of sensors used to detect exercise in a patient with a cardiac pacemaker, five are currently approved in the United States, although many others remain under investigation. Some devices have two sensors and can be programmed for cross-checking to prevent increases in heart rate from spurious causes. Minute ventilation sensors are very sensitive to stray electromagnetic interference, and patients have been inappropriately treated for pacemaker-driven tachycardias as a result. Perioperative experience with right ventricular pressure sensors is minimal at this time. Most pacemaker experts recommend that rate modulation be programmed to "off" in the perioperative period to prevent confusion between intrinsic tachycardia and pacemaker-induced tachycardia (e.g., see Schwartzenburg and associates[121]).

BOX 48-2 ***Pacemaker Indications****

Symptomatic diseases of impulse formation (sinus node disease)
Symptomatic diseases of impulse conduction (atrioventricular nodal disease)
Long QT syndrome
Hypertrophic obstructive cardiomyopathy†*
Dilated cardiomyopathy †*

*Indications for permanent pacing are shown. Most patients with pacemakers currently fall into the first two categories (sinus node or atrioventricular nodal disease).
†Requires 100% ventricular pacing to be effective. Thus, short atrioventricular delays (≈120-150 msec) are programmed.

INDICATIONS

Indications for permanent pacing are shown in Box 48-2 and are reviewed in detail elsewhere.[32] Classically, antibradycardia pacing treats patients with sinus node disease (improper impulse formation) and AV nodal disease (improper impulse conduction). CRT pacing for the patient with DCM requires left ventricular (LV) pacing, usually through a lead placed into the coronary sinus (CS) (see Fig. 48-1, *B*) or sewn onto the LV free wall. In patients with significant RV-to-LV activation time, loss of capture in a ventricle can lead to ventricular overcounting with resultant inappropriate antitachycardia therapy for the patient with a DCM pacing defibrillator.[33,34] Pacing continues to be explored to reduce the outflow tract obstruction in hypertrophic obstructive cardiomyopathy (HOCM) in both adults and children because paced ventricular conduction takes place in a left bundle branch pattern (the LV septum depolarizes after the other segments, rather than as the early systolic event).[35]

Pacing for HOCM and DCM requires careful attention to pacer programming. To be effective in these patients, the PM must provide the stimulus for ventricular depolarization, and AV synchrony must be preserved.[36] PM inhibition or loss of pacing (i.e., from native conduction, atrial irregularity, ventricular irregularity, development of junctional rhythm, or EMI) can lead to deteriorating hemodynamics in these patients.

CRT pacing may cause inappropriate lengthening of the QT interval in susceptible patients, and this lengthening has been reported to be associated with torsades de pointes.[37] As a result of this report, the prudent anesthesiologist should ensure adequate access to rapid defibrillation for patients with BiV pacing accomplished with a conventional PM.

MAGNETS

Despite often repeated folklore, most PM manufacturers warn that magnets were never intended to treat PM emergencies or prevent the effects of EMI. Rather, magnet-activated switches were incorporated to produce pacing behavior that demonstrates remaining battery life and, sometimes, pacing threshold safety factors.

Placement of a magnet over a generator may produce no change in pacing because *not all PMs switch to a continuous asynchronous pacing mode when a magnet is placed*. Moreover, not all models from a given company behave the same way. Possible effects of magnet placement are shown in Table 48-3.[38-40] In some devices (Biotronik [Berlin, world headquarters; Lake Oswego, Ore, U.S. headquarters], BOS, Pacesetter, St. Jude Medical, Telectronics), magnet behavior can be altered or completely eliminated by programming. For generators with programmable magnet behavior, only an interrogation with a programmer can reveal current settings.

For all generators, calling the manufacturer remains the most reliable method for determining magnet response and for using this response to predict remaining battery life (telephone numbers for the device manufacturers are shown in Appendix 48-1). As battery voltage falls, the magnet response can be used to detect the following:

Intensified follow-up interval (IFI) or elective replacement near (ERN): The device must be checked frequently (approximately every 4 weeks for most models).
Elective replacement indicator (ERI) or elective replacement time (ERT): The device is nearing the end of its useful life and should be electively replaced.
End of life (EOL): The device has insufficient battery power remaining and should be replaced immediately.

On application of a magnet, some devices perform a threshold margin test (TMT). In this test, one of more of the PM pulses is reduced in amplitude, pulse width, or both, in an attempt to gauge the safety margin for pacing voltage. Loss of capture on these TMT pulses indicates an inadequate safety margin for pacing (Fig. 48-5). Some devices from St. Jude Medical (formerly Pacesetter) with the Siemens "Vario" feature reduce the ventricular pacing energy over 16 cycles to demonstrate the pacing threshold. As a result, many pacing cycles can take place at insufficient energy for ventricular capture, and this can produce periods of asystole while the magnet is applied.[41]

Occasionally, PM-mediated tachycardia (PMT) can ensue on removal of the magnet from a dual-chamber PM (Fig. 48-6). These cases of PMT result from P waves conducted in retrograde fashion during asynchronous ventricular pacing, most commonly when the magnet rate is lower than the patient's intrinsic rate. PMT from retrograde AV nodal conduction also can occur in any DDD or VDD pacing device following EMI, premature ventricular contraction, or a noncaptured atrial pace. When present, retrograde P waves can be "tracked," typically resulting in ventricular pacing at the UTR. Each paced ventricular cycle results in another retrograde P wave, thereby producing tachycardia. Should this behavior be observed in a conventional PM, it can be treated by application, then removal, of the magnet provided the PM has asynchronous pacing with magnet application. Magnet application does not terminate PMT in an ICD.[42] Most CIED devices can be programmed to recognize these cases of PMT and periodically omit one ventricular pacing pulse, or lengthen one AV delay cycle, during UTR pacing.

In addition, as noted previously, the patient with a dual-chamber device that has detected a high atrial rate and "mode-switched" to prevent UTR pacing could have the mode switch reset on application and removal of the magnet. These patients then undergo UTR pacing until criteria are met to return to the mode-switch mode. Distinguishing PMT caused by retrograde P waves from UTR pacing resulting from high atrial rates (before mode-switch entry) can be very difficult. In general, however, mode-switch secondary to rapid atrial rates takes place within 10 to 15 seconds, and PMT from retrograde P waves is quite persistent.

PREANESTHETIC EVALUATION AND PACEMAKER REPROGRAMMING

Preanesthetic management of the patient with a PM includes evaluation and optimization of coexisting disease (see also Chapter 39). American College of Cardiology (ACC) guidelines suggest that cardiac testing (stress tests, echocardiograms) should be dictated by the patient's underlying diseases, medications, symptoms, interval from the last testing, and planned intervention.[43]

No special laboratory tests or radiographs are needed for the patient with a conventional PM. Chest radiographs rarely depict lead problems, and a standard chest radiograph may exclude the generator or its markings. Furthermore, most radiologists are unfamiliar with pacing issues.[44] However, a patient with a CRT device may need a chest radiograph to document the position of the CS lead, especially if central line placement is planned. CS leads have no fixation and may be more easily dislodged than a standard PM or ICD lead. Spontaneous LV dislodgment likely occurs in at least 4.7% of patients,[45] at a rate of 2.3% annually.[46]

Important features of the preanesthetic device evaluation are shown in Appendix 48-2. The ASA advisory recommends a recent PM interrogation; the other 3 advisories recommend contact with the patient's CIED physician and clinic. However, in abstract form, Rozner and associates reported more than 30% noncompliance with in-person follow-up guidelines in 161 consecutive preoperative patients, as well as the need to replace 5% of PMs preoperatively for battery depletion.[47] Remote evaluation provides some assurance of battery longevity, but it does not provide rigorous evaluation of the pacemaking system.

TABLE 48-3 **PACEMAKER MAGNET BEHAVIOR***

Pacemaker Company		Magnet Mode Designation	Explanation
Biotronik (except INOS and DROMOS)		AUTO	In normal operation, 10 asynchronous events at 90 beats/min, then returns to original programmed mode, without rate responsiveness. Pacing is at lowest available rate (LRL, sleep rate, or hysteresis rate). If battery at ERI, 10 asynchronous events at 80 beats/min in VOO mode, then either VDD (dual-chamber) or VVI (single-chamber) pacing at 11% lower than lowest available rate. For any dual-chamber mode (DDD, DDI, or VDD), the AV delay shortens to 100 msec while the magnet is in place.
		ASYNCH	Asynchronous pacing at 90 beats/min in normal operation. At ERI, 80 beats/min (single-step change) in VOO mode regardless of original programming. For any dual-chamber mode (DDD, DDI, or VDD), the AV delay shortens to 100 msec while the magnet is in place.
		SYNCH	In normal operation, pacing in original programmed mode, without rate responsiveness. Pacing is at lowest available rate (LRL, sleep rate, or hysteresis rate). If battery at ERI, then either VDD (dual-chamber) or VVI (single-chamber) pacing at 11% lower than lowest available rate. For any dual-chamber mode (DDD, DDI, or VDD), the AV delay shortens to 100 msec while the magnet is in place.
Boston Scientific/Guidant Medical/CPI (Cardiac Pacemakers, Inc.)		ASYNCH	Asynchronous pacing at 100 beats/min in normal operation, 85 beats/min at ERT (single-step change). Insignia and all "BOS" label devices have an intermediate step (90 beats/min) at ERN. For Triumph and Prelude models, see Medtronic pacemakers, below. Insignia and all "BOS" label devices emit a reduced 3rd pacing pulse (on ventricular lead for dual chamber devices) to demonstrate adequacy of pacing output.
		OFF	No change, magnet is ignored. OFF is the magnet mode after a "power on reset," which can occur secondary to EMI.
		EGM mode	No change in pacing. Magnet application initiates data collection.
Sorin (formerly ELA Medical)			Asynchronous pacing at 96 beats/min gradually declining to 80 beats/min at ERI. Sorin pacemakers take 8 additional asynchronous pacing cycles (the final 2 cycles are at LRL with long atrioventricular delay) on magnet removal.
Medtronic			Asynchronous pacing at 85 beats/min in normal operation, 65 SSI regardless of original programming if ERI (single-step change). Most Medtronic pacemakers emit one or more ventricular pulses during the first 3-7 asynchronous events (which may be at a rate of 100 beats/min) at a reduced pulse width or voltage to demonstrate adequacy of ventricular pacing output. A Medtronic dual-chamber pacemaker will revert to single-chamber, ventricular-only behavior on detection of ERI regardless of prior programming. Such behavior could result in hemodynamic embarrassment in a patient with sinus node disease and a bad ventricular lead.
St. Jude Medical (not including Telectronics)	"SJM" x-ray logo	Battery Test	Asynchronous pacing at 98.6 (100 for Accent/Anthem series) beats/min gradually decreasing to 86.3 or less beats/min at ERI.
		OFF	No magnet response.
		Event snapshots	No change in pacing. Magnet application causes pacemaker to collect data. Identity and Entity models lack this feature.
		Event snapshots + Battery Test	For a magnet placed 2 seconds, pacing mode and rate are unchanged, and the device stores an electrogram. If the magnet is placed ≥5 seconds, the Battery Test mode (see earlier) is activated. Identity and Entity models lack this feature.
	Pacesetter x-ray logo (ψ)	Battery Test	Asynchronous pacing and the rate depends on specific model. In general, a pacing rate of less than 90 beats/min should prompt further evaluation.
		OFF	No magnet response.
		VARIO mode (present in some models)	VARIO results in a series of 32 asynchronous pacing events. The rate of the first 16 paces reflects battery voltage, gradually declining from 100 to 85 beats/min at ERI. The next 15 paces are used to document ventricular pacing capture safety margin. The rate will be 119 beats/min with gradually declining pacing voltage. The sixteenth pace of this group is at no output. The next pace restarts the 32-event sequence. The 32-event sequence repeats as long as the magnet remains in place.

AV, Atrioventricular; *EGM,* electrogram; *EMI,* electromagnetic interference; the device should be replaced immediately; *ERI,* elective replacement indicator; the device should be replaced promptly; the FDA requires pacemakers to perform safely for at least 3 months from onset of ERI; *ERN,* elective replacement near; the device should be undergoing monthly checks (same as IFI); *ERT,* elective replacement time (same as ERI); for Boston Scientific/Guidant/CPI, at ERT rate-responsive programming is cancelled; at 3 months after ERT, only single-chamber operation continues; the device needs monthly battery checks; *LRL,* lower rate limit; the programmed lower rate, or set point, of the pacemaker; *SSI,* single-chamber, inhibited mode; if implanted for ventricular pacing, SSI = VVI; if implanted for atrial pacing, SSI = AAI.

*The effects of appropriately placing a magnet over a pacemaker are shown. Column 1 shows the pacemaker manufacturer. If the magnet response is programmable, then column 2 shows the various programmable modes available. The first mode shown for a company is the default mode. Column 3 shows the effect on pacing therapy for the magnet mode shown in column 2. Unless otherwise specified, asynchronous pacing takes place, without rate responsiveness, in the chambers originally programmed. Thus, a dual-chamber program would result in DOO pacing, and a single-chamber program would result in VOO (ventricular) or AOO (atrial) pacing, and a biventricular, dual-chamber device would be DOOOV.

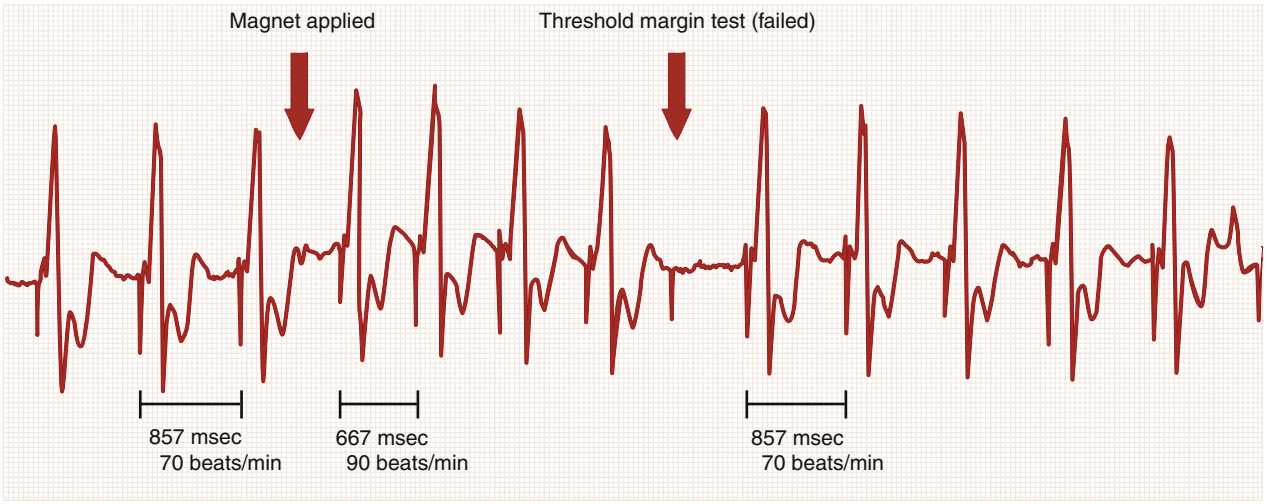


Figure 48-5. Threshold margin test (TMT) demonstrating an inadequate safety margin for pacing. Application of a magnet to some pacemakers produces asynchronous pacing in which one or more pacing stimuli are emitted with reduced ventricular pacing voltage, pulse width, or both. This sequence is used to determine, without formal pacemaker interrogation, the adequacy of pacing energy settings. In this electrocardiographic strip from an Intermedics device, the patient was being paced in the VVI mode at a rate of 70 beats/minute (equal to 857-msec intervals). On application of the magnet, this pacemaker produced four intervals (five pacing stimuli) of asynchronous pacing at a rate of 90 beats/minute (667-msec intervals), thus demonstrating adequate battery voltage for this device (pacemaker response to magnet placement depends on the manufacturer and sometimes the programming). At the fifth pacing stimulus after magnet application, the pacemaker performed a TMT by reducing the stimulus pulse width to 50% of the programmed value (equal to 50% of programmed energy). Failure of this stimulus to produce ventricular systole (i.e., failure to capture) demonstrates a dangerously low safety margin for ventricular pacing because pacing pulse width should be at least three and generally four times the threshold for capture. After these five initial stimuli, Intermedics pacemakers then pace asynchronously at the programmed lower rate (70 in this case) for 60 additional cycles. On completion of these 64 cycles (65 stimuli), Intermedics pacemakers return to programmed values and ignore the magnet.

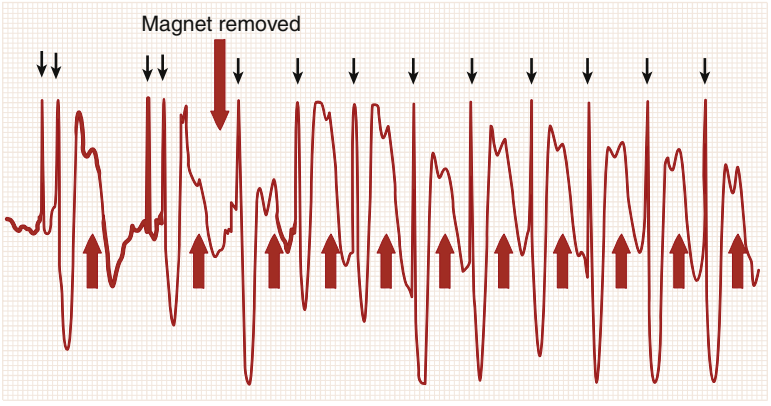


Figure 48-6. Pacemaker-mediated tachycardia (PMT) after removal of the magnet from a pacemaker. This patient had a dual-chamber pacemaker implanted for atrioventricular (AV) nodal disease, and she was pacemaker dependent for ventricular activity. She had a sinus rate of 75 beats/minute before application of the magnet with appropriate ventricular pacing (strip not shown). Her programmed AV delay was 200 msec. With magnet application, her pacemaker produced asynchronous AV sequential pacing (DOO mode) at a rate of 60 beats/minute. This strip is from an electrocardiographic recorder that enhances the pacemaker artifact indicated by *black, downward arrows*. Because the asynchronous "magnet" rate of this device was lower than her intrinsic atrial rate, many of the atrial pacing stimuli were applied during an atrial refractory period (called functional noncapture). A consequence of atrial noncapture can be retrograde AV nodal conduction with depolarization of the atria after depolarization of the ventricle or ventricles. The retrograde P waves are shown with the *red upward arrows*. While the magnet is applied, this retrograde depolarization of the atria is ignored. Shortly after the magnet was removed (shown), a paced ventricular event occurred, followed by retrograde AV nodal conduction. With the ensuing depolarization of the atria from this retrograde conduction, the pacemaker sensed an atrial event and responded by pacing the ventricle 200 msec later. Yet another retrograde P wave appears, and each ventricular pace in response to a retrograde P wave created yet another ventricular pace. The result is PMT at the upper tracking rate (programmed here to 130 beats/minute) of the pacemaker. PMT from retrograde AV nodal conduction can occur in any DDD or VDD device with magnet removal, a premature ventricular contraction, or a noncaptured atrial pace. Treatment of this PMT should be reapplication of the magnet. Some pacemakers can be programmed to eventually delay one AV cycle when pacing at the upper tracking limit to "break" PMT. Magnet application is ineffective in PMT in a patient with an ICD.

BOX 48-3 *Situations Probably Requiring Pacemaker Reprogramming**

Any rate-responsive device (see text; problems are well known,[121,122] and they have been misinterpreted, with the potential for injury to the patient[55,59,63,67]; the Food and Drug Administration has issued an alert regarding devices with minute ventilation sensors[65] [see Box 48-4])
Special pacing indication (hypertrophic obstructive cardiomyopathy, dilated cardiomyopathy, pediatric patients)
Pacing-dependent patient
Major procedure in the chest or abdomen
Rate enhancements present that should be disabled
Special procedures (see text)
- Lithotripsy
- Transurethral resection
- Hysteroscopy
- Electroconvulsive therapy
- Succinylcholine use
- Magnetic resonance imaging (generally contraindicated by device manufacturers)[123]

*In some situations and for certain patients, a cardiac implanted electronic device should be reprogrammed either to avoid potential injury to the patient or to prevent a pacemaker rhythm that could be confused with pacing system malfunction.

BOX 48-4 *Pacemakers With Minute Ventilation (Bioimpedance) Sensors**

Boston Scientific/Guidant Medical/CPI (Cardiac Pacemakers, Inc.)

Altrua
Pulsar (1172, 1272)
Pulsar Max (1170, 1171, 1270)
Pulsar Max II (1180, 1181, 1280)
Insignia Plus (1194, 1297, 1298)

Medtronic

Kappa 400 series (KDR401, KDR403, KSR401, KSR403)

Sorin (was ELA Medical)

Brio (212, 220, 222)
Chorus RM (7034, 7134)
Opus RM (4534)
Reply DR, SR
Rhapsody (2530)
Symphony (2250, 2550)
Talent (113, 133, 213, 223, 333)

Telectronics/St. Jude

Meta (1202, 1204, 1206, 1230, 1250, 1254, 1256)
Tempo (1102, 1902, 2102, 2902)

*Pacemakers with minute ventilation (bioimpedance) sensors frequently respond to electromagnetic interference (EMI) with pacing at the upper sensor rate.[63,67] These tachycardias also can be produced by connection to an operating room electrocardiographic monitor because many of these devices inject electrical signals through the electrocardiographic leads to determine respiratory rate or lead disconnection.[62,64] In 1998, the U.S. Center for Devices and Radiologic Health issued a safety alert calling for the deactivation of any minute ventilation (bioimpedance) sensor before exposing a patient to a potential source of EMI or connection to medical devices.[65]

For PMs, interrogation with a programmer remains the most reliable method for evaluating battery voltage, battery impedance, lead performance, and adequacy of current settings. Special attention should be paid to patients from countries where CIEDs may be reused, because of possibly increased malfunction rates.[48] For any PM with a battery voltage less than 2.6 volts or battery impedance (where available) greater than 3000 ohms, the company should be consulted about the possible need for elective replacement of the device preoperatively.

Appropriate reprogramming is the safest way to avoid intraoperative problems, especially for pacing-dependent patients in whom EMI (most commonly monopolar "Bovie" electrosurgery) will be present (Box 48-3). Assistance may be available from the PM manufacturers (see Appendix 48-1 for company telephone numbers). However, interrogation of any generator with or without reprogramming requires a medical prescription and supervision by an appropriately trained physician.[9,49] Hospital guidelines and policy should reflect the need for a competent physician to review and validate any care delivered by a company representative.

Reprogramming a PM to asynchronous pacing at a rate greater than the patient's underlying rate usually ensures that no oversensing during EMI will take place, thus protecting the patient. However, in one case report, a Telectronics device opened its output circuitry (i.e., no pacing stimuli were delivered) in the presence of high-voltage EMI.[50] Furthermore, at our institution, two PMs in the DOO mode dropped their rate during use of monopolar coagulation ESU, presumably because of high battery current drain.

Reprogramming a device *will not* protect the device from internal damage or reset caused by EMI. Additionally, setting a device to asynchronous mode causes the PM to ignore premature atrial or ventricular systoles, which could lead to R-on-T pacing and malignant rhythm, especially in the patient with significant structural compromise of the myocardium.[51,52]

In general, rate responsiveness and other "enhancements" (e.g., atrial fibrillation suppression, hysteresis, managed ventricular pacing, sleep rate, AV search) should be disabled by programming to prevent misinterpretation of the cardiac rhythm.[53-55] Older reports of pacing threshold changes during both intrathoracic[56] and nonchest surgical procedures,[57] as well as significant noncardiac acute disease,[58] drive the issue of postoperative pacing threshold testing in nonautomated devices.

Special attention must be given to any device with a minute ventilation (bioimpedance) sensor because inappropriate tachycardia has been observed secondary to mechanical ventilation,[27,59] monopolar "Bovie" electrosurgery,[59-61] and connection to an ECG monitor with respiratory rate monitoring[62-67] (Box 48-4). Sometimes, this PMT has led to inappropriate, unsuccessful pharmacologic treatment of the tachycardia,[27] with injury to the patient.[26]

INTRAOPERATIVE (OR PROCEDURE) MANAGEMENT OF PACEMAKERS

Although no special monitoring or anesthetic technique is required for the patient with a cardiac generator, attention must be given to several concerns (see also Chapters 45 and 67).

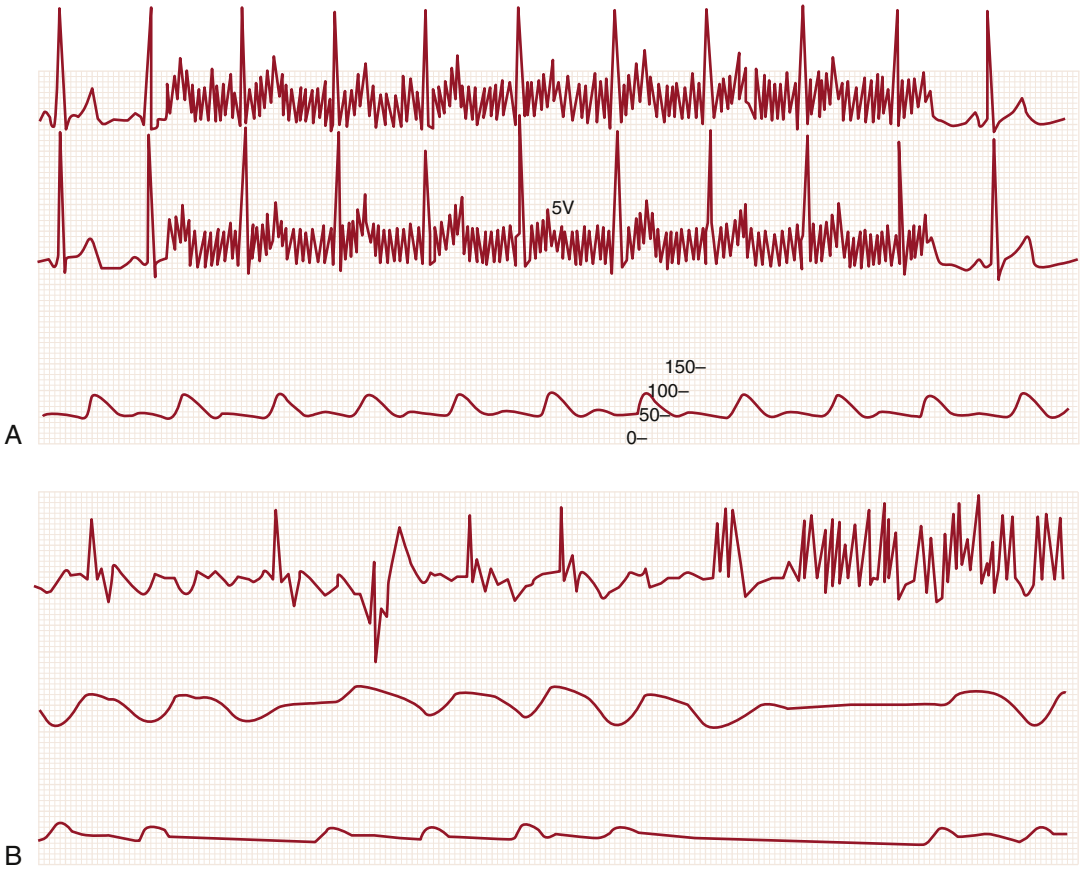


Figure 48-7. Disabling the pacemaker artifact filter on a digitally processed electrocardiographic (ECG) monitor results in the "painting" of environmental noise (electromagnetic interference [EMI]) as pacemaker artifacts. **A,** Effects of "cut" monopolar electrosurgical unit (ESU) application. Because the patient's underlying rate exceeded the pacemaker's programmed lower rate limit, no pacing took place. However, activation of the ESU in the "cut" mode produced sufficient electromagnetic noise that the monitor began "painting" pacemaker artifacts at a rate of approximately 20 Hz. The *top tracing* is the ECG lead II, the *middle tracing* is ECG lead V_5, and the *bottom tracing* is the invasive arterial pressure waveform. **B,** The effects of "Coagulation" ESU application produced ventricular oversensing with pacemaker inhibition and left this patient with compromised cardiac output. Evidence also shows inappropriate monitor "painting" of pacemaker artifacts from the EMI. The *top tracing* is ECG lead II, the *middle tracing* is the pulse oximeter plethysmogram, and the *bottom tracing* is the invasive arterial pressure waveform. *(From Rozner MA: Review of electrical interference in implanted cardiac devices,* Pacing Clin Electrophysiol *26:923-925, 2003.)*

First, ECG monitoring of the patient should include the ability to detect pacing discharges. Currently, most ECG monitors in both the operating room and the intensive care unit perform digital acquisition and analysis of ECG signals, and they are subject to considerable interference from a variety of sources.[68] In their default settings, these monitors often filter high-frequency signals, thus resulting in the exclusion of pacing artifacts. Disabling this filtering causes the monitor to "paint" pacing spikes onto the display. Even with the filtering disabled, however, pacing artifacts do not always appear because modern leads may accomplish pacing with very low-amplitude pulses. Moreover, given that many digital monitors analyze only one lead for these signals (and then "paint" on artifacts on every lead), placement of the ECG leads can markedly affect the detection axis.[¶] In practice, when a patient with known pacing is monitored, sometimes changing the "analysis" lead on the monitor results in the appearance of pacing signals. Unfortunately, when the high-frequency filter is disabled, EMI, especially from the use of the monopolar ESU, can lead to inappropriate "painting" of pacing artifacts on the monitor (Fig. 48-7).[17,69]

Second, monitoring of the patient must include the ability to ensure that paced electrical activity is converted to mechanical systoles. Mechanical systoles are best evaluated by pulse oximetry plethysmography or arterial pressure waveform display.[14,49]

Third, published perioperative experience with CRT pacing remains limited. These patients often have ejection fractions less than 30%, and they depend on pacing in both ventricles to improve their cardiac output. Loss of ventricular pacing from any cause (e.g., AV dyssynchrony [atrial fibrillation, atrial flutter, appearance of junctional rhythm], myocardial ischemia, acid-base disturbance, change in pacing threshold, ESU interference) can cause an immediate decrease in cardiac output. With the exception of transesophageal echocardiography, no beat-to-beat monitoring of cardiac output has demonstrated any utility in detecting loss of LV capture. Patients with HOCM pacing can depend on ventricular pacing to limit LV outflow tract obstruction.

¶Most monitors manufactured since 2005 have much improved capability to detect and display pacing artifacts, although they still filter these high-frequency signals in their default setup mode.

Fourth, some patients may need an increased pacing rate during the perioperative period to meet an increased oxygen demand. This subject is often not addressed. PM-treated patients reportedly have high postoperative morbidity and mortality,[70] and failure to address tissue oxygen demands and cardiac output needs could contribute to this problem.

Fifth, appropriate equipment must be on hand to provide backup pacing and defibrillation if needed. Cardiac generators, although hardy, occasionally perform some untoward maneuver or fail, even in the absence of EMI.[71] Acceptable but inappropriate behavior of a PM or ICD can create an inhospitable situation. Even a properly working, dual-chamber PM can produce R-on-T pacing and ventricular tachycardia (VT), especially in the setting of a junctional rhythm or PVCs (Fig. 48-8).

The medical team caring for the patient with an implanted cardiac PG must understand that the patient has been deemed needy of this device by a physician who is an expert in the diagnosis and management of cardiac rhythm issues. Few anesthesiologists are qualified to contradict this diagnosis, yet some persist in providing anesthesia without appropriate backup pacing and defibrillation equipment on hand.

Monopolar "Bovie" ESU use remains the principal intraoperative issue for the patient with a PM. Between 1984 and 1997, the FDA was notified of 456 adverse events with PGs, 255 from electrosurgery or external defibrillator, and a "significant number" of device failures.[72] Monopolar ESU is more likely to cause problems than bipolar ESU, and PMs with unipolar electrode configurations are more sensitive to EMI than are PMs with bipolar configurations.[73] The most common effect of ESU on pacing function is ventricular oversensing, which causes pacing inhibition (see Fig. 48-7, *B*). Sometimes, the generator detects significant EMI and begins pacing asynchronously at the programmed lower rate. This behavior is called noise or reversion mode pacing, even though the PM does not actually change modes. Noise reversion is not present in some ICDs and is programmable in others.

Magnet placement during electrosurgery may prevent aberrant PM behavior. Newer generators are believed to be relatively immune to spurious reprogramming from EMI, although they can undergo a reset condition that will likely alter the programmed settings.[49,74,75]

If monopolar ESU is to be used, then the electrosurgical dispersive electrode (often misidentified as the "grounding pad") must be placed to ensure that the ESU current path does not cross the pacemaking system. Some authors recommend placement of this electrode on the shoulder for head and neck procedures or the distal arm (with sterile draping of the wire) for breast and axillary procedures.[73,76] Procedures using only monopolar ESU or with special EMI pacing ramifications include the following:

Electroconvulsive Therapy: This treatment may require nonsensing (asynchronous) mode to prevent myopotential-induced oversensing with resultant PM inhibition.[77]

Lithotripsy: The cardiac generator must be excluded from the lithotripter field. If the lithotripter triggers its output on the sensed ECG "R" wave, atrial pacing should be disabled to prevent the lithotripter from inappropriately firing on the atrial pacing artifact (see Chapter 72).

Magnetic resonance imaging (MRI): MRI requires special expertise, including the ability to immediately reprogram a CIED. The literature reports that MRI exposure can lead to magnet switch closure (magnet mode activation), CIED reprogramming, inappropriate high-rate pacing, generator damage, myocardial injury, lead failure, or arrhythmia. Except for CIED resets to safety parameters,[75] no significant complications have been reported, even in large series.[78] On February 8, 2011, the FDA approved a Medtronic PM with MRI-conditional labeling; conditions include MRI energy limitations, a requirement for ECG and pulse oximeter plethysmography monitoring, completion of cardiac monitoring and radiology training, and peri-MRI scan reprogramming.[79] Medtronic has introduced a "second-generation" MRI-conditional PM into the U.S. market with similar conditions but with automated testing and reporting features Only PMs from Medtronic have MRI labeling in the United States at this time, but Biotronik (ICD and PM), BOS (PM), and St. Jude Medical (PM) have received MRI labeling in other countries.

Nerve stimulator testing or therapy: Nerve stimulators can cause PM oversensing, with resultant PM inhibition[80] and cardiac arrest.[81] Nerve stimulators have been used intraoperatively to inhibit undesired cardiac pacing[25] or arrest the cardiac rhythm for endovascular stent placement.[82] In patients with an ICD, inappropriate detection of neuromuscular stimulators, transcutaneous electrical nerve stimulation, and chiropractic electrical muscle stimulation as VT or VF has been reported.[83,84] Nerve stimulators can also interfere with ECG monitoring of PM artifacts.[69] As with ESU current, the electrical path for nerve stimulator current should not cross the generator system or the chest (see also Chapter 53).[85]

Radiofrequency ablation: Noncardiac radiofrequency ablation, especially when kept inferior to the umbilicus, behaves primarily like unblended "cut" monopolar ESU. Although problems seem to be rare, the HRS recommends postoperative interrogation before discharge from cardiac monitoring.[49]

Succinylcholine or etomidate use: Reports of myopotential problems on administration of succinylcholine[86] or etomidate[87] have been described (see also Chapters 30 and 34). In the succinylcholine case, muscle fasciculations may have caused ventricular oversensing with resultant PM inhibition, but the case is difficult to interpret. No ECG tracings were published, and the PM was damaged during subsequent defibrillation. Using programmers, I have witnessed succinylcholine administration to more than 50 patients with PMs or defibrillators without finding any myopotential oversensing. The etomidate issue is also questionable because the particular PM had other issues.[88] However, myopotential oversensing (in the absence of succinylcholine) has been observed to interfere with PM function[89] or cause inappropriate ICD therapy (see also Chapter 34).[90]

Transurethral resection and uterine hysteroscopy: Transurethral resection of the bladder or prostate and hysteroscopic procedures generally use monopolar ESU, and device reprogramming may be needed to



Figure 48-8. Normal dual-chamber pacemaker timing can produce R-on-T pacing. **A,** This strip demonstrates functional ventricular undersensing of a premature ventricular contraction (PVC) with resultant R-on-T pace leading to torsades de pointes in a normally functioning, appropriately programmed pacemaker (PM). This patient had a dual-chamber PM in the DDD mode with a programmed lower rate of 70 beats/minute (R-R interval of 857 msec) and atrioventricular (AV) delay of 200 msec. With these parameters, the pacemaker will pace the atrium 657 msec after any previous ventricular event. Atrial pacing is labeled A, and ventricular pacing is labeled V. The *top tracing* is electrocardiographic (ECG) lead II, the *middle tracing* is ECG lead V_5, and the *bottom tracing* is the invasive arterial blood pressure waveform. Approximately 660 msec after the first QRS complex (*1*) on the strip (which was adequately sensed by the pacemaker), an atrial stimulus was emitted. At 200 msec after this atrial pace, a ventricular stimulus was emitted and appeared to depolarize the ventricle (*2*). Approximately 660 msec later (3), the patient experienced a PVC. Because the pacemaker was preparing to emit the atrial stimulus, it had disabled its ventricular sensing element (called post atrial ventricular blanking, see also Figure 48-13) and failed to sense this PVC (termed functional undersensing). At 200 msec after the atrial stimulus, no ventricular event had been sensed, so the pacemaker emitted a ventricular stimulus on the T wave. Because the ventricle was in a refractory period from the PVC, no depolarization of the ventricle occurred (called functional noncapture). At 660 msec from this attempted V-pace, the pacemaker again paces the atrium (*4*), and it appears that the next V-pace captures the ventricle. At point *5,* a repeat of the events at point *3* occurs (i.e., the pacemaker disabled its sensing elements in preparation to pace the atrium and again failed to detect the PVC). This time, however, the V-pace on the T wave produced torsades de pointes. **B,** This strip was obtained from a Medtronic programmer during interrogation of a Kappa 700 dual-chamber pacemaker. The *top tracing* is ECG lead II, and the *bottom tracing* is the "marker channel," which shows the pacemaker's interpretation of events. This pacemaker was programmed to the DDD mode with a lower rate of 60 beats/minute. The AV delay was 200 msec. As a result, after any ventricular event, the pacemaker will emit an atrial pulse at 800 msec if no intervening atrial or ventricular event takes place. This patient had junctional rhythm at 75 beats/minute (corresponding to an R-R interval of 800 msec), so the pacemaker emitted an atrial pulse just as the junctional event occurred. Because the pacemaker disables its ventricular sensing element when emitting the atrial pulse, it failed to detect the ventricular event and emitted the ventricular pulse 200 msec later, on the T wave. This inappropriate pacing takes place every other cycle because every other junctional event is sensed approximately 600 msec after the previous ventricular pace. Decreasing the AV delay diminishes the likelihood of pacing during the vulnerable period of the ventricle. AP is an atrial pace, VP is a ventricular pace, and VS is a ventricular sensed event. The third complex deserves comment. The pacemaker sensed this ventricular event as it re-enabled its sensing element, and the pacemaker cannot tell whether the sensed event is a true ventricular depolarization or an "echo" of the atrial pace. When a signal from the ventricle is sensed within 30 to 90 msec after an atrial pace, many CIEDs immediately emit a ventricular pacing stimulus. Called a ventricular safety pace, this pacing stimulus is designed to protect the patient from inappropriate sensing of the atrial signal by the ventricular channel, which would then inhibit the ventricular output. The safety pace is emitted at 110 msec to prevent R-on-T pacing. This feature is also called nonphysiologic AV delay by some manufacturers. R-on-T pacing can be appropriate (but not ideal) behavior of a DDD or DDI pacemaker in the setting of PVCs, as well as a junctional rhythm. It can also be seen with atrial or ventricular undersensing.

prevent PM oversensing with resultant PM inhibition. A resectoscope that includes the current-return electrode on the shaft (the irrigation medium is normal saline) could limit EMI to the generator but has not been carefully tested in this environment.

PACEMAKER FAILURE

PM failure has three causes: (1) generator failure, (2) lead failure, or (3) failure of capture. Generator failure is rare in a device that has been previously evaluated and not near the end of its useful battery life, unless the generator (or leads) is struck directly by the ESU. Lead failure, also unusual but reported during patient repositioning,[91] can result in undersensing (intrinsic activity is not detected), oversensing ("detection" of events unrelated to intrinsic activity), or failure to deliver sufficient energy to the myocardium to produce a depolarization (loss of capture). Myocardial changes that lengthen the refractory period or increase the energy requirement for depolarization (failure to capture) can result from myocardial ischemia or infarction, acid-base disturbance, electrolyte abnormalities, or abnormal antiarrhythmic drug levels.

The response to PM failure depends on the clinical situation. A patient with a perfusing rhythm and stable vital signs can be observed while a plan is made to correct the problem. For a patient with inadequate perfusion, the following steps can be tried (while cardiopulmonary resuscitation is in progress when appropriate):

1. A magnet can be applied if the PM is known to revert to an asynchronous mode, which will also eliminate sensing behavior in these devices. Magnet application may add to the hemodynamic embarrassment in the setting of inadequate pacing safety margins[52] or the onset of automated TMT.[39]
2. Temporary pacing can be initiated, and it can be transthoracic (transcutaneous), transvenous, or transesophageal. Transesophageal (atrial) pacing requires a functional atrium and AV node for ventricular activation, so it is contraindicated in patients with atrial fibrillation or flutter. It is also generally contraindicated in the presence of a permanent PM (or ICD). In the setting of external pacing, the ECG can be misinterpreted because the PM artifacts are large compared with the QRS complexes (Fig. 48-9, *A*). Successful ventricular pacing has been reported with transesophageal PMs, but it remains unreliable,[92] and it produces inferior hemodynamics compared with atrial pacing (Fig. 48-9, *B*). Any external pacing may further inhibit PM output at energies that do not produce myocardial capture.[93]
3. Sympathomimetic drugs can be administered to decrease depolarization threshold or increase heart rate, or both. Epinephrine (0.5 to 1 μg/minute) or dopamine (5 to 20 μg/kg/minute) should be considered. Isoproterenol (0.5 to 10 μg/minute) is often recommended, but this drug is not widely available, and its use may produce hypotension. Atropine may be helpful.
4. Causes of myocardial ischemia should be sought and corrected. Myocardial ischemia can substantially increase the energy required for ventricular capture.[94]
5. Disturbances of electrolyte balance, antiarrhythmic drug levels, and acid-base equilibrium should be investigated and corrected. Potassium, calcium, and magnesium abnormalities, as well as amiodarone, can raise depolarization thresholds. Moreover, potassium flux, ionized calcium level, and acid-base equilibrium can be affected by hyperventilation and hypoventilation.
6. If none of the foregoing measures succeed, consideration should be given to placement of epicardial leads by the surgical staff.

POSTANESTHESIA PACEMAKER EVALUATION

A PM that was reprogrammed for the perioperative period should be reset appropriately. For nonreprogrammed devices, the performance and timing of a postoperative interrogation will depend on the nature of the case and the CIED team caring for the patient. Certainly, interrogation is warranted if any issues appear. Consideration should be given to increasing the lower paced rate in a chronotropically incompetent patient if increased cardiac output will benefit the patient during convalescence.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

The development of an implantable, battery-powered device able to deliver sufficient energy to terminate VT or ventricular fibrillation (VF) represents a major medical breakthrough for patients with a history of ventricular tachydysrhythmias. These devices reduce deaths in the setting of malignant ventricular tachydysrhythmias,[95,96] and they have been long considered superior to antiarrhythmic drug therapy.[97] Initially approved by the FDA in 1985, more than 120,000 devices will be implanted in the United States this year, and industry sources report that more than 300,000 patients have these devices today. Furthermore, results from the Sudden Cardiac Death–Heart Failure Trial (SCD-HeFT, which showed that prophylactic placement of an ICD is superior to drug therapy in any patient with an ejection fraction <0.35 and *without* evidence of arrhythmic inducibility) led to a significant increase in the number of patients for whom ICD therapy is indicated.[98]

Numerous technologic advances have been applied since the first ICD was placed, including substantial miniaturization (pectoral pocket placement with transvenous leads is the norm), as well as battery improvements that now permit permanent pacing with these devices. Thus, one could easily confuse a pectoral T-ICD with a PM.

Like PMs, ICDs have a four-place generic code (NBD[¶]) to indicate lead placement and function, as shown in Table 48-4.[99] The most robust form of identification, the label form, expands the fourth character into its component generic PM code (NBG).

[¶]The NBD code is a joint project from NASPE (the "N") and BPEG (the "B"). The "D" stands for defibrillator.

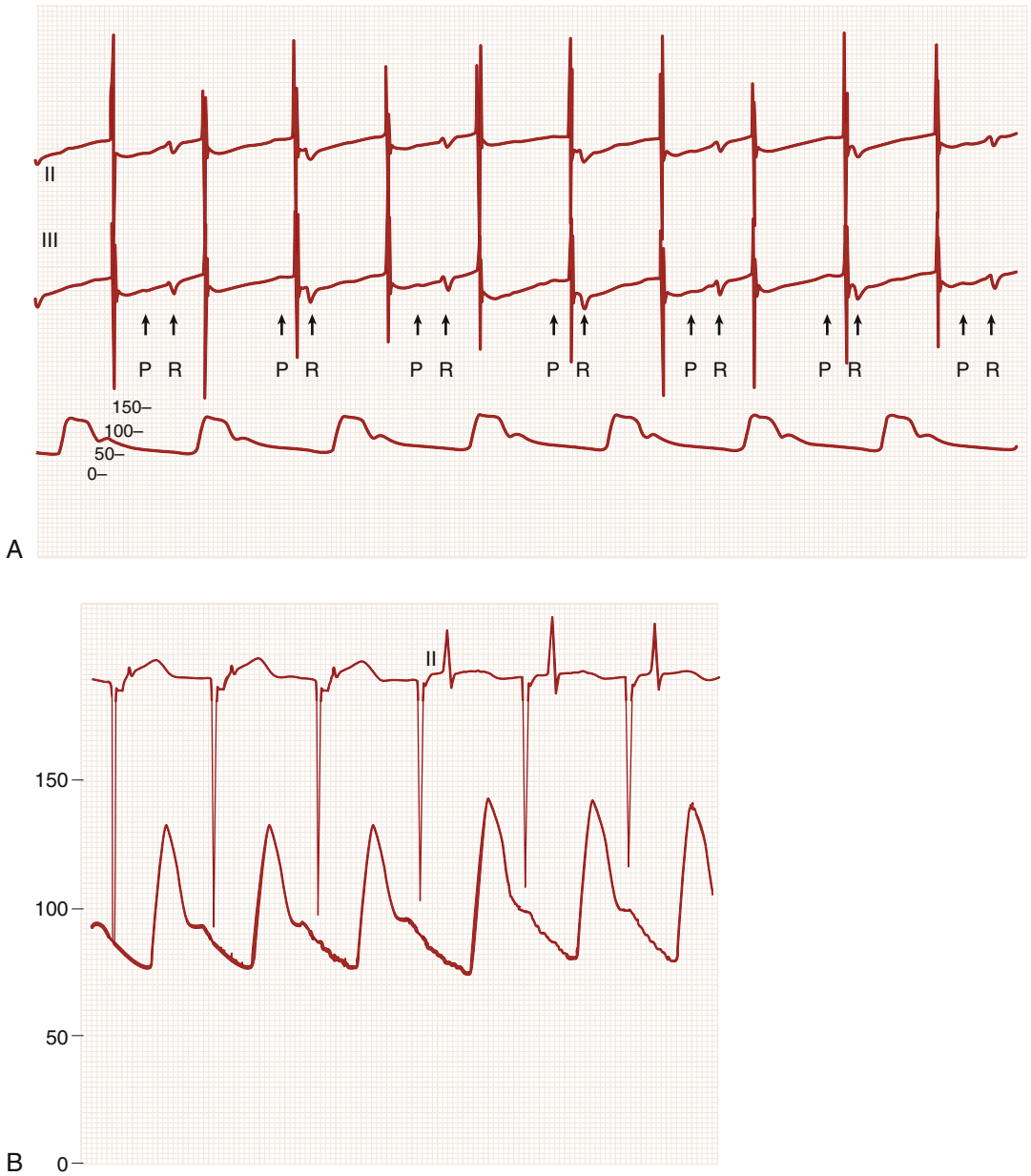


Figure 48-9. Issues with a transesophageal atrial pacemaker (TAP). **A,** Improper placement of a TAP demonstrating atrial noncapture. The *top recording* is electrocardiographic (ECG) lead II, the *middle recording* is ECG lead III, and the *bottom recording* is the invasive arterial pressure waveform. Sinus bradycardia with evidence of tissue underperfusion developed in this 72-year-old man. A TAP (CardioCommand, Tampa, Fla.) was placed, and the large ECG artifacts at 75 beats/minute were misinterpreted by personnel and by the ECG monitor as ventricular systoles (capture). This strip shows an underlying sinus rate of 50 beats/minute with a first-degree atrioventricular block (PR interval of 280 msec). The patient's native atrial (P) and ventricular (R) depolarizations are noted. The arterial pressure waveform confirms pacing noncapture. **B,** Direct ventricular activation with a transesophageal pacemaker. The *top recording* is ECG lead II, and the *bottom recording* (enhanced vertical scale) is the invasive arterial pressure waveform. This strip is from an obese 61-year-old woman with diabetes and hypertension who was undergoing transsphenoidal hypophysectomy. Shortly after induction of anesthesia, sinus bradycardia at 37 beats/minute and mild hypotension developed. A transesophageal pacemaker was placed but was advanced too far into the esophagus. This strip was recorded during "pullback." The ventricle was directly activated in the first four events, with a resultant wide-complex QRS and average blood pressure of 135/75 mm Hg. On pullback, the atrium was activated, the QRS returned to a narrow complex, and blood pressure increased to 143/80 mm Hg. Except for the bradycardia, this patient had a normal heart and did not have a permanently placed generator.

The Cameron Health–BOS S-ICD system consists of a PG implanted along the lateral chest wall with a single lead tunneled subcutaneously to the area superficial to the heart (Fig. 48-10). The principal advantage of the S-ICD implant is the ability to implant the device without gaining central venous access. The principal disadvantages include the inability to use the S-ICD to provide bradycardia support, the lack of ATP features, higher energy defibrillation thresholds (DFTs), larger size, and shorter battery life than a single-chamber T-ICD. Approximately 11.8% of all ICD patients have experienced an inappropriate shock.[100]

TABLE 48-4 NORTH AMERICAN SOCIETY OF PACING AND ELECTROPHYSIOLOGY/BRITISH PACING AND ELECTROPHYSIOLOGY GROUP GENERIC DEFIBRILLATOR CODE (NBD)*

Position I	Position II	Position III	Position IV†
Shock Chambers(s)	Antitachycardia Pacing Chamber(s)	Tachycardia Detection	Antibradycardia Pacing Chamber(s)
O = None **A** = Atrium **V** = Ventricle **D** = Dual (**A**+**V**)	**O** = None **A** = Atrium **V** = Ventricle **D** = Dual (**A**+**V**)	**E** = Electrogram **H** = Hemodynamic	**O** = None **A** = Atrium **V** = Ventricle **D** = Dual (**A**+**V**)

*The NBD code is a joint project from the North American Society of Pacing and Electrophysiology (NASPE) (the "N") and the British Pacing and Electrophysiology Group (BPEG) (the "B").[99] The "D" stands for defibrillator.
†For robust identification, position IV is expanded into its complete NBG code. For example, a defibrillator programmed to ventricular shock and antitachycardia pacing along with biventricular pacing functionality would be identified as VVE-DDDRV, assuming that the pacing section was programmed DDDRV. Currently, no hemodynamic sensors have been approved for tachycardia detection (position III).

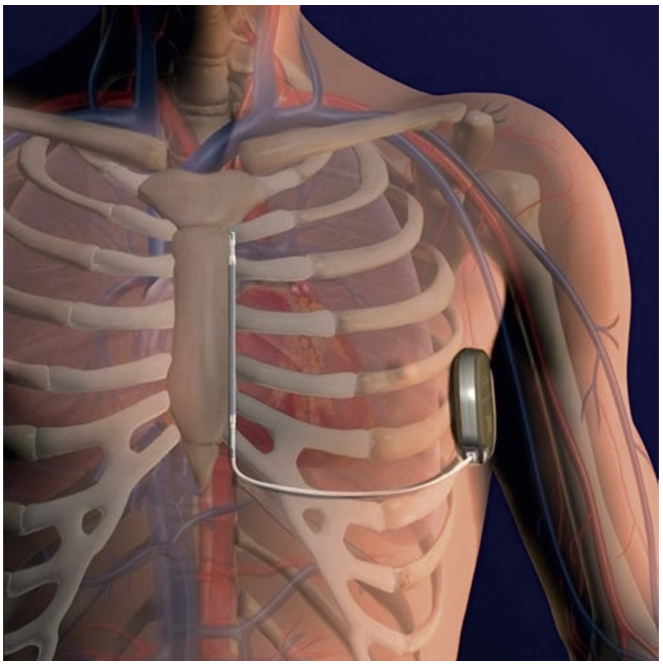


Figure 48-10. The Cameron Health–Boston Scientific subcutaneous implantable cardioverter-defibrillator. A schematic drawing of this system (CE mark 2009; U.S. Food and Drug Administration approval in 2012) is shown. This system consists of a generator implanted along the lateral chest wall with a lead tunneled into position over the heart. *(From Hauser RG: The subcutaneous implantable cardioverter-defibrillator: should patients want one?* J Am Coll Cardiol *61:20-22, 2013.)*

All T-ICDs have many programmable features to detect and treat both tachyarrhythmias and bradyarrhythmias. Essentially, these devices measure each cardiac R-R interval and categorize the rate as normal, too fast (short R-R interval), or too slow (long R-R interval). When the device detects a sufficient number of short R-R intervals within a period of time (all programmable), it begins an antitachycardia event. Depending on arrhythmia characteristics (primarily rate) and device programming, the internal computer chooses ATP (less energy use, better tolerated by patient) or shock. If the ICD chooses ATP, shock may be delayed; each cycle of ATP can delay shock 6 to 15 seconds. If shock is chosen, an internal capacitor is charged. Charging time depends on the desired output, and an additional 6 to 15 seconds may pass during a maximum shock. Charging time is lengthened by lower battery voltage, time from last charge,[#] and lower temperature.

Most ICDs are programmed to "reconfirm" VT or VF after charging to prevent inappropriate shock therapy. All T-ICDs can be programmed to begin ATP immediately on initiating a charge cycle (ATP while charging, which does not delay shock). Typically, T-ICDs deliver 6 to 18 shocks per event. Once a shock is delivered, no further ATP takes place. Despite considerable improvement in detection of ventricular dysrhythmias, more than 10% of T-ICD shocks are for rhythm other than VT or VF, and supraventricular tachycardia (SVT) remains the most common cause of inappropriate shock therapy.[6] Inappropriate ICD therapy, whether shock or ATP, has been shown to injure myocardium,[101] and it appears that any therapy, whether appropriate or inappropriate, shortens a patient's life expectancy when compared with patients not receiving therapy.[5,102] The likely results of these reports will be to delay initiation of T-ICD therapy for at least 30 to 60 seconds following onset of arrhythmia.

Programmable features in current ICDs to differentiate VT from SVT include the following[103]:

1. Onset criteria: In general, onset of VT is abrupt, whereas onset of SVT has sequentially shortening R-R intervals.
2. Stability criteria: In general, the R-R interval of VT is relatively constant, whereas the R-R interval of atrial fibrillation with rapid ventricular response is quite variable.
3. QRS width criteria: In general, the QRS complex width in SVT is narrow (<110 msec), whereas the QRS width in VT is wide (>120 msec).
4. "Intelligence" in dual-chamber devices attempts to associate atrial activity with ventricular activity.
5. Morphology waveform analysis includes comparison with stored historical templates.

When the R-R interval becomes sufficiently short for VF detection, most ICDs begin a shock sequence. As noted earlier, once the device delivers shock therapy, no further antitachycardia pacing takes place.

[#]The capacitor in an ICD "deforms" during inactivity, thus leading to increased time needed to charge the capacitor. To mitigate the effects of deformation, all ICDs perform nontherapeutic charging of their capacitor ("reforming") at a programmable periodic interval (usually 1 to 6 months).

BOX 48-5 ***Indications for Implantable Cardioverter-Defibrillators***

Ventricular tachycardia
Ventricular fibrillation
Brugada syndrome (right bundle branch block, ST-segment elevation in electrocardiographic leads V_1 to V_3)
Arrhythmogenic right ventricular dysplasia
Long QT syndrome
Hypertrophic cardiomyopathy
Prophylactic use in the patient who has CM without electrophysiologic testing to justify placement: MADIT II (EF <30%, ischemic CM)[98]; MUSTT (EF <40%, ischemic CM with nonsustained ventricular tachycardia)[97]; SCD-HeFT (EF <35%, and CM of any cause)[3]

CM, Cardiomyopathy; EF, ejection fraction, MADIT II, Multicenter Automatic Defibrillator Implantation Trial II; MUSTT, Multicenter Unsustained Tachycardia Trial; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

A T-ICD will begin pacing when the R-R interval is too long. Single-chamber T-ICDs implanted into patients with sinus rhythm typically are programmed to VVI pacing mode with a backup rate of 40 to 50 beats/minute. In July 1997, the FDA approved devices with sophisticated dual-chamber pacing modes and rate-responsive behavior for patients with T-ICD who need permanent pacing (≈20% of patients with ICDs). Because of the Dual Chamber and VVI Implantable Defibrillator (DAVID) study, which suggested that DDD pacing in a patient without a clear need for dual-chamber pacing decreased survival when compared with single-chamber device placement,[104] many electrophysiologists program long (>250 msec) AV delays in these patients to limit ventricular pacing. As noted earlier, however, long AV delays can lead to R-on-T pacing (see Fig. 48-8, *A*). In addition, many manufacturers of T-ICDs have designed algorithms to limit RV pacing. Some of these algorithms allow dropped QRS events, which can resemble second-degree Mobitz II block or pacing system malfunction.

INDICATIONS

Initially, ICDs were placed for hemodynamically significant VT or VF (Box 48-5). Additional indications associated with sudden cardiac arrest include patients awaiting heart transplantation[105] and patients with long QT syndrome,[106] Brugada syndrome (right bundle branch block, ST-segment elevation in leads V_1 to V_3), and arrhythmogenic RV dysplasia.[107,108] Studies suggest that ICDs can be placed prophylactically (i.e., used for primary prevention) to prevent sudden cardiac arrest in patients with hypertrophic cardiomyopathy,[109] as well as in patients after myocardial infarction with an ejection fraction lower than 30%,[98] but these devices are of no benefit after coronary artery bypass grafting. Three-chamber T-ICDs have been FDA approved for patients with DCM.

MAGNETS

As in PMs, magnet behavior in some ICDs can be altered by programming. Most devices suspend tachydysrhythmia detection (and therefore therapy) when a magnet is appropriately placed to activate the magnet switch (Table 48-5). Some devices from BOS, Pacesetter, and St. Jude Medical can be programmed to ignore magnet placement, and some BOS ("GDT" label) ICDs have had their magnet function permanently disabled because of a magnet switch issue (e.g., see Fig. 48-3).[11] For BOS devices, if the magnet mode is enabled and the T-ICD is enabled for antitachycardia therapy, the T-ICD will emit beeps synchronized to R waves (older BOS T-ICDs with a CPI or GDT label) or at 1 Hz (most BOS or BSC label T-ICDs) to signify adequate placement of magnet and suspension of tachyarrhythmia detection (thus disabling therapy). If any BOS T-ICD emits a constant tone when a magnet is applied, then antitachycardia therapy will remain disabled, even when the magnet is removed. Many BOS T-ICDs with the GDT label must be auscultated following magnet removal to ensure that tone emission has ceased, thus indicating that the magnet switch has returned to the open position.[11]

To ensure correct magnet placement on their devices, Medtronic marketed a device called the Smart Magnet. Manufacturing ceased in approximately 2005 because not many of these devices sold. This battery-powered instrument contains a magnet and a radiofrequency (RF) receiver. All Medtronic generators broadcast RF destined for the programmer on magnet placement, and the Smart Magnet detects this RF transmission and illuminates the "found" light when an ICD is under the magnet. Medtronic recommends that the Smart Magnet be taped onto the patient. During EMI (e.g., monopolar ESU), signal transmission from the T-ICD to the Smart Magnet can be interrupted, and the ICD "found" light often turns off. In this setting, however, the T-ICD remains disabled because the physical presence of the magnet, rather than the RF communication, disables the antitachycardia therapy.

No ICD provides asynchronous pacing with magnet placement. T-ICDs from Sorin (Milano, Italy, world headquarters; Arvada, Colo, U.S. headquarters) change their pacing rate (but not mode) to indicate battery status. Interrogating the device represents the most reliable method for determining magnet response. Contact with the CIED clinic or the manufacturer may provide additional information.

PREANESTHETIC EVALUATION AND REPROGRAMMING

In addition to evaluating and optimizing any comorbid diseases in the patient with an ICD, the ASA advisory recommends preoperative T-ICD interrogation. The other three statements recommend contact with the CIED clinic and physician. T-ICDs store considerable data on the occurrence of dysrhythmias. Because ATP is well tolerated, most patients remain unaware of this intervention. For any patient scheduled to undergo an elective procedure, the onset of new dysrhythmias likely warrants investigation of the problem before the procedure (Fig. 48-11). HRS/EHRA recommends 3- to 6-month follow-up with either in-office or remote (telephonic at this time) evaluation.[9] As with PMs, remote follow-up does not allow iterative testing of sensing or pacing thresholds. Medicare has no coverage determination for ICD follow-up.

TABLE 48-5 MAGNET BEHAVIOR OF IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS*

ICD Manufacturer		Magnet Mode Designation	Effect on Tachycardia Therapy	Effect on Bradycardia Therapy (regular pacing)	Magnet Mode Confirmation
Biotronik			Disabled	None	None
Boston Scientific (Guidant Medical, CPI)	"GDT," "CPI," "BOS 119," "BOS 203" x-ray label	ON	Disabled	None	Short beep with each detected heartbeat or constant tone†
		OFF	None	None	None
	All other "BOS" x-ray label	ON	Disabled	None	Short beep every second or constant tone†
		OFF	None	None	None
	Subcutaneous ICD		Disabled but tone for only 60 seconds	None	Short beep every second for 60 seconds, then no additional sounds (but tachyarrhythmia therapy disabled)
Medtronic	AT-500‡		Disabled	None	None§
	All others		Disabled	None	
Pacesetter and St. Jude Medical		NORMAL	Disabled	None	None
		IGNORE	None	None	
Sorin (was ELA Medical)			Disabled	Pacing rate, but not mode, changes to 96 (new device), declining to 80 beats/min, indicating elective replacement time	Pacing rate change as noted

ICD, Implantable cardioverter-defibrillator.

*The effects of appropriate magnet placement on an implantable cardioverter-defibrillator (ICD) are shown. Column 1 shows the manufacturer. Some manufacturers have multiple responses that can be determined by the x-ray identifier. If the magnet response is programmable, then column 2 shows the various magnet modes available. The first mode shown is the usual mode. A device reset from electromagnetic interference could produce some other mode (i.e., magnet mode disabled). Column 3 shows the effect on antitachycardia therapy (defibrillation and antitachycardia pacing) for the magnet mode shown in column 2. Only ICDs from Sorin Medical alter their antibradycardia pacing rate on magnet placement (column 4), and this pacing rate can be used to predict remaining battery life, provided the patient's native heart rate is less than the magnet rate. Only ICDs from Boston Scientific/Guidant/CPI produce reliable audio feedback for confirmation of magnet placement (column 5). For devices from Pacesetter and St. Jude Medical, device interrogation is required to determine the magnet mode.

†For Boston Scientific/Guidant/CPI T-ICDs, if the magnet mode is programmed to "on," appropriate magnet placement immediately disables tachycardia detection and therapy, and tachycardia therapies remain disabled for as long as the magnet remains appropriately applied. When magnet mode is enabled in these devices, the ICD will emit either a constant tone or beep to identify appropriate magnet placement. If the device emits a constant tone, then tachycardia therapy is disabled whether or not a magnet is present, and tachycardia therapy will not be present even after the magnet is removed. If any of these ICDs emit a beep (ICDs with GDT or CPI x-ray codes emit each beep with either paced or sensed R waves; most ICDs with BOS x-ray code emits a beep every second), then a properly working ICD will be enabled for tachycardia therapy on magnet removal. Any Boston Scientific/Guidant/CPI ICD that does not emit a sound when a magnet is applied should undergo immediate device interrogation.

‡The Medtronic AT-500 series defibrillators provide antitachycardia pacing in the atrium only, and usually after a delay often exceeding 1 minute from the onset of atrial tachyarrhythmia. They do not have any shock coils on any lead and are very difficult to distinguish from a conventional two-chamber pacemaker. They have no apparent magnet response. The x-ray identifier on these devices includes the Medtronic M, but the first character is I. All other Medtronic cardiac generators have the Medtronic M, with the first letter identifier P.

§Some Medtronic ICDs emit a tone for 15 to 30 seconds when a magnet is placed on the device. However, this tone is not continuous with magnet placement, and it is not interrupted with immediate magnet removal. As a result, the tone cannot be used for confirmation of appropriate magnet placement.

Determination of the need for elective replacement of an ICD resulting from battery depletion is more complicated than with PMs. Prediction of remaining ICD battery longevity obtained at interrogation is a feature available only in the newest of ICDs. For devices without battery longevity estimates, the capacitor charge time reflects battery status, and the manufacturer should be consulted when charge time exceeds 12 seconds. General statements about battery voltage in ICDs cannot be made because ICDs have different numbers of battery cells.

Most ICDs should have their antitachycardia therapy disabled before the use of any device causing EMI. The use of monopolar ESU can cause inappropriate shocks. Casavant and associates found a stored electrogram sequence in an ICD, a finding suggesting that the device had misinterpreted monopolar ESU during dermatologic facial surgery as VF.[111] Figure 48-12 shows inappropriate VT detection that occurred intraoperatively. Additionally, one report exists of a central line guidewire interacting with the RV lead, thus leading to a short-circuit shock and subsequent failure of the T-ICD.[112]

The comments in the pacing section (including Appendix 48-2 and Box 48-3) apply here for any ICD with antibradycardia pacing. Many ICDs have no noise reversion behavior, so ESU-induced ventricular oversensing may lead to nonpacing in the patient who depends on the ICD for pacing.

INTRAOPERATIVE (OR PROCEDURE) MANAGEMENT OF IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

At this time, no special monitoring (resulting from the ICD) is required for the patient with an ICD. ECG

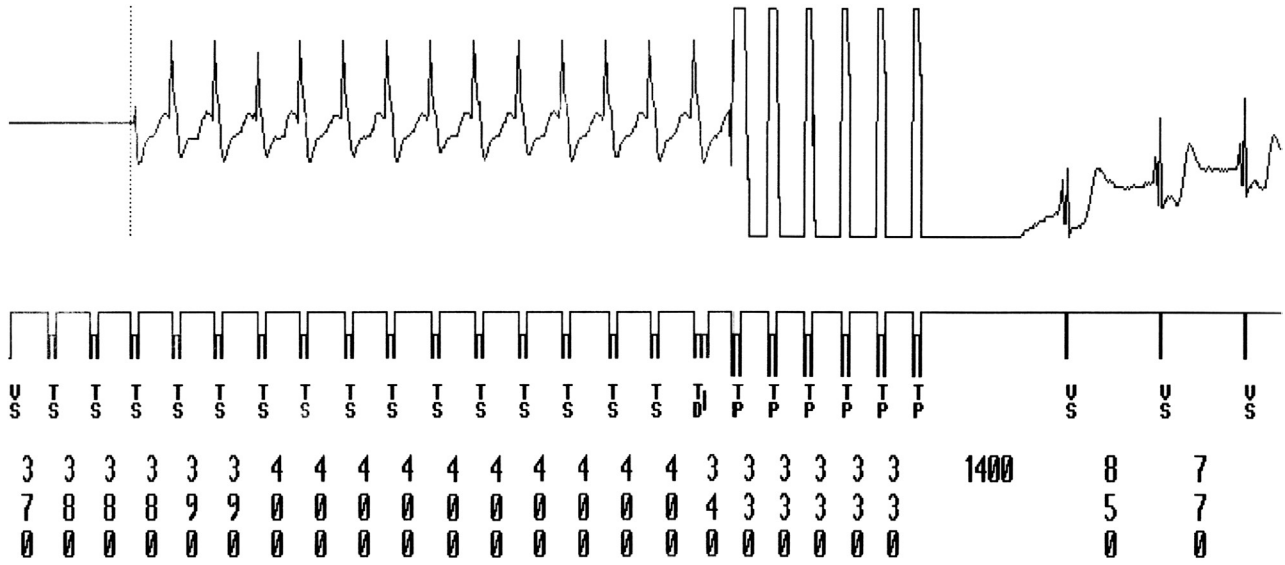


Figure 48-11. Unexpected ventricular tachycardia (VT) with antitachycardia pacing was found in this patient during her preoperative visit. A 65-year-old woman with a history of VT had undergone implantation of a Medtronic single-chamber defibrillator approximately 8 months previously. She had not had any dizziness or syncopal episodes since placement of an implantable cardioverter-defibrillator (ICD). Preoperative interrogation of her device revealed VVE-VVI programming, along with an episode of tachycardia at 150 to 162 beats/minute that was detected by the ICD as VT. The ICD delivered a six-beat burst of antitachycardia pacing at 182 beats/minute, which converted the tachycardia back to sinus rhythm. No backup pacing was needed after the VT was terminated. The *upper tracing* is a digitized ventricular electrogram that was stored in the ICD during the tachycardic event. The *lower tracing* is the "marker channel," which reports the interpretation of each event by the ICD. The numbers below the marker channel represent the interval (in milliseconds). The rate is calculated by dividing the interval into 60,000 msec/minute. TD marks the final event that starts therapy. TS represents an interval in the VT zone, TP is an antitachycardia pace event, and VS is an intrinsic ventricular depolarization with a rate that is neither too fast (short interval) nor too slow (long interval). This device was set to detect VT as 16 consecutive ventricular events with a rate between 146 and 200 beats/minute and to deliver antitachycardia pacing at 84% of the last R-R interval (the last interval was 400 msec, so antitachycardia pacing was delivered at a rate of 182 beats/minute (330 msec).

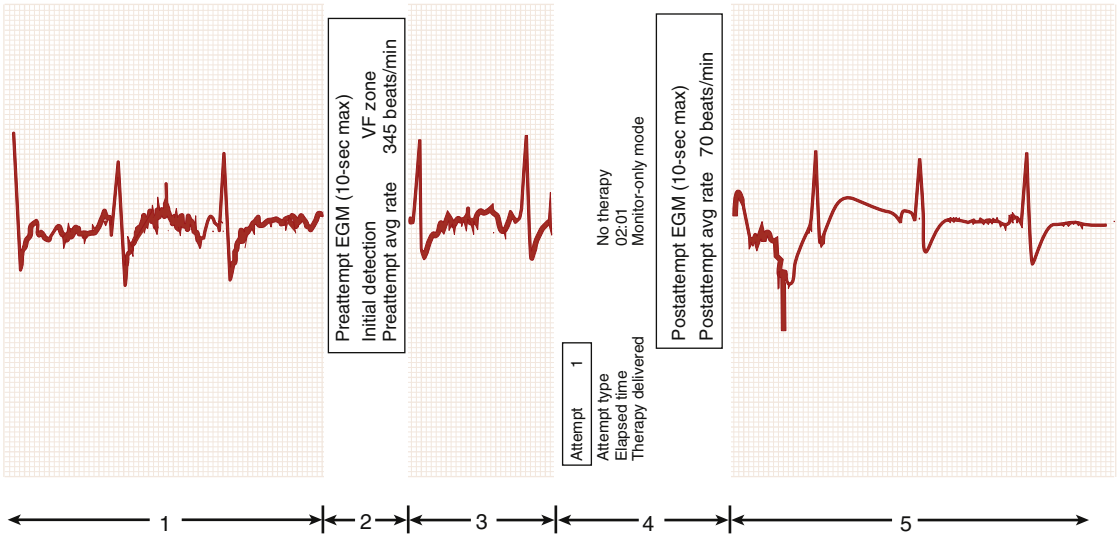


Figure 48-12. Electromagnetic interference (EMI) from the monopolar electrosurgery unit (ESU; "Bovie") caused an implantable cardioverter-defibrillator (ICD) to detect ventricular fibrillation (VF). This stored electrogram (EGM) was one of 73 found at the end of a 4-hour surgical procedure in which considerable monopolar electrosurgery was used. This patient had a Guidant Medical ICD in the VOE-VVI mode. The patient's ICD had been placed in a "monitor only" mode before surgery. As a result, the ICD recorded any instance of ventricular dysrhythmia that would have triggered therapy, but it could not actually deliver therapy. From *left to right: 1,* the EGM demonstrates a ventricular rate of 70 beats/minute, but with considerable noise on the baseline; *2,* a VF event was declared for the detected heart rate of 345 beats/minute, and the ICD charged its capacitor; *3,* the ICD was programmed to "reconfirm before shock," and the ventricular rate remained 70 beats/minute with noise on the baseline; *4,* again, the noise caused the ICD to believe that the patient remained in VF, and the ICD would have delivered a shock, except that it was programmed to "monitor only"; and *5,* because the noise is gone (the ESU had stopped), the ICD declares the event over after "successful" defibrillation.

monitoring and the ability to deliver external cardioversion or defibrillation must be present during the time of ICD disablement. Should cardioversion or defibrillation be needed, the defibrillator pads should be placed to avoid the PG to the extent possible. Nevertheless, the patient, not the ICD, is being treated. When a magnet is used to prevent ICD discharge, simple removal of a magnet may not produce immediate antiarrhythmic therapy. The actual rate of the tachycardia versus the lowest treatment zone rate, as well programmed therapy delays, could lead to lengthy treatment postponements. The recommendations in the section on intraoperative (or procedure) management of pacemakers apply here, as well, to T-ICDs (S-ICDs have no permanent pacing at this time).

No special anesthetic techniques have been championed for the patient with an ICD. Most of these patients have severely depressed systolic function, dilated ventricular cavities, and significant valvular regurgitation. Thus, the choice of anesthetic technique should be dictated by the underlying physiologic derangements that are present. Conflicting data have been published regarding the choice of anesthetic drugs and changes to DFT. In 1992, Gill and associates examined DFTs in dogs and concluded that neither halothane nor isoflurane changed DFTs in open chest defibrillation compared with a pentobarbital infusion.[113] However, Weinbroum and colleagues evaluated DFTs in humans during ICD implant and found that halothane, isoflurane, and fentanyl increased DFTs.[114] Even with these increases, however, these increased DFTs were still substantially lower than the maximum energy generally available in ICDs, and these increases would not have been noted under usual testing conditions.

POSTANESTHESIA EVALUATION

Any ICD that was reprogrammed for an intervention must be reinterrogated and re-enabled, and deaths from failure to re-enable an ICD have been reported.[115] All recorded events should be reviewed, and counters should be cleared. The pacing parameters (T-ICD only) must be checked and reprogrammed as necessary.

SPECIAL SITUATIONS: VENTRICULAR ASSIST DEVICES AND TEMPORARY PACING

Most patients with a ventricular assist device (VAD) also have a T-ICD. Although this subject exceeds the scope of this chapter, several important issues should be highlighted. First, the VAD can interfere with telemetry between the ICD and the programmer, thus resulting in the inability to modify parameters quickly[116] and possibly necessitating T-ICD replacement.[117] Several "workarounds" have been proposed, including changing the LVAD speed, covering the telemetry wand with an iron skillet, or encasing the wand and cord with metallic shielding material.[116,118] Before placement of a T-ICD in a patient with a VAD, or placement of a VAD in a patient with a preexisting CIED, compatibility issues should be investigated. Second, in many of these patients who then undergo orthotopic heart transplantation, the T-ICD is disabled by programming, and the transvenous leads are cut at the level of the superior vena cava. Unfortunately, any subsequent device reset from cosmic radiation or EMI will restore single-zone shock behavior in all T-ICDs,[49] so a patient may actually receive high-energy therapy to their superior vena cava, with likely disastrous result.

The second special situation is temporary pacing. Temporary pacing devices can be used for bradycardia unresponsive to pharmacologic therapy, bradyarrhythmias complicating myocardial infarction, heart rate support following cardiothoracic surgery, delivery of ATP to the atrium or ventricle in an attempt to treat a tachydysrhythmia, bridge to permanent PM placement, and protection for potential catastrophic failure of a CIED expected to be exposed to strong EMI in a pacing-dependent patient. Pacing can be esophageal, transcutaneous, transvenous, or epicardial. In a patient with a CIED, placement of a temporary pacing device requires CIED reprogramming for temporary pacing testing (e.g., threshold evaluation) because the energy of temporary pacing that fails to depolarize the myocardium could inhibit permanent pacing. A T-ICD must be disabled to prevent inappropriate shock during temporary pacing testing and also if central venous access is planned.[112]

Esophageal pacing requires an intact atrium and AV node. Thus, esophageal pacing remains absolutely contraindicated when a history of atrial dysrhythmia (e.g., atrial fibrillation) or significant AV block exists. This technique requires a specially adapted esophageal probe and a unique generator. Pacing is AOO only, which usually causes no problems, even when the native heart rate exceeds the programmed heart rate. The pacing artifacts typically appear as large, negative "spikes" that can produce overcounting by the ECG monitor and can be confused as QRS events (see Fig. 48-9).

Transcutaneous pacing is accomplished by placing conducting electrodes on the skin, preferably in an anteroposterior position. Device instructions should be followed. Pacing is ventricular only, and this may not produce appropriate hemodynamic support without atrial transport.

Transvenous and epicardial pacing can be atrial, ventricular, AV, or BiV, depending on the catheter or wires and the pacing generator used. Transvenous pacing requires central venous access, and complete sterile barrier technique seems indicated in any patient, especially when a preexisting CIED is present. Three different types of transvenous catheters are available at this time: a simple balloon-tipped bipolar catheter without a hemodynamic channel; a pulmonary artery catheter with one or two extra lumina for placement of bipolar wires into the atrium, right ventricle, or both; and a multielectrode pulmonary artery catheter intended for atrial-RV pacing. Both transvenous pacing and epicardial pacing require a battery-powered external generator. In any patient with only a ventricular lead (whether transvenous or epicardial), the temporary pacing generator should be programmed only to VVI pacing because the use of DDD pacing (in the absence of a functioning atrial lead) can instigate VT secondary to R-on-T pacing (Fig. 48-13).[51] The use of the DDD pacing mode

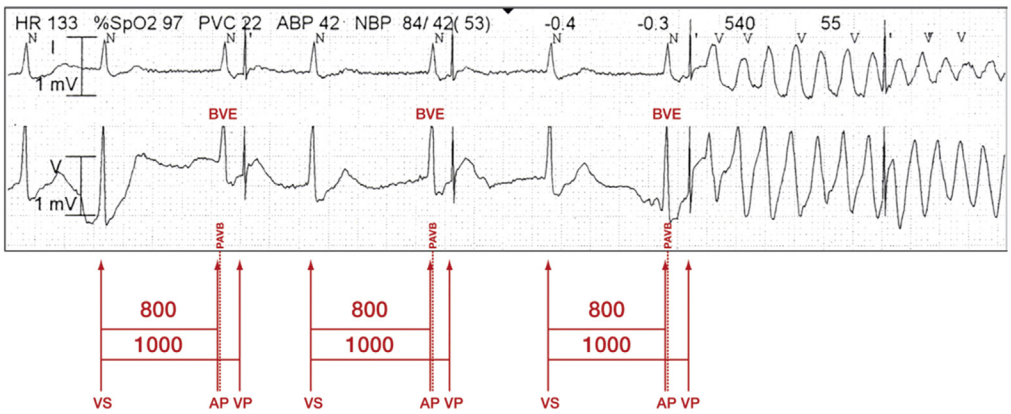


Figure 48-13. DDD pacing without atrial lead initiates ventricular tachycardia (VT) by R-on-T pacing. Temporary external dual-chamber pacing without an atrial lead produced several R-on-T paces, one of which initiated polymorphic VT. This patient had undergone elective aortic valve replacement with root repair, three-vessel coronary artery bypass grafting, and a partial Maze procedure 8 hours earlier. His underlying rhythm was atrial fibrillation. Tracings are electrocardiogram lead I (*upper*) and lead V_5 (*lower*). Pacemaker (PM) settings were DDD mode; pacing rate was 60 beats/minute; and AV delay was 200 msec, resulting in a VV cycle length of 1000 msec and a ventriculoatrial time (VA) of 800 msec. AP is presumed atrial pace, BVE is a blanked ventricular event secondary to postatrial ventricular blanking, VP is ventricular pace, and VS is presumed ventricular sense. At the expiration of the VA timer, the PM presumably emitted an AP because no atrial signal had been sensed. The PM then invoked a 20- to 36-msec postatrial ventricular blanking period to prevent any ventricular oversensing resulting from the AP. As a result, the native ventricular event was not sensed (BVE), resulting in a VP 200 msec after the AP. The VP fell on the vulnerable period of repolarization, thus initiating VT. *ABP,* Arterial blood pressure; *HR,* heart rate; *NBP,* noninvasive blood pressure; *PVC,* premature ventricular contraction; *Spo_2,* peripheral oxygen saturation. *(From Schulman PM, Stecker EC, Rozner M: R-on-T and cardiac arrest from dual-chamber pacing without an atrial lead,* Heart Rhythm *9:970-973, 2012.)*

(default mode of many temporary PMs) with only an RV lead appears to be a common practice, and this R-on-T phenomenon appears poorly understood, given that the occurrence of R-on-T–induced VT in this situation has been ascribed to "chance."[119] Some dual-chamber external pacing generators switch from VVI to DDD pacing without warning or confirmation when changing parameters other than pacing mode.[52] Temporary pacing should be discontinued as soon as possible.

SUMMARY

Electronic miniaturization has permitted the design and use of sophisticated electronics in patients who need artificial pacing and/or automated cardioversion or defibrillation of the heart. These devices are no longer confined to merely keeping the heart beating between a minimum rate (pacing function) and a maximum rate (ICD functions) because they are now used as therapy to improve the failing heart. Furthermore, the advent of sophisticated pacing algorithms that change heart rate or AV intervals, as well as permit occasional dropped QRS events, can mimic behavior that may be interpreted as "light anesthesia" (increased pacing rates) or pacing system malfunction. Inappropriate treatment of these events can lead, and has led, to injury and death in these patients.

Both the aging of the population and the ability to care for a patient with increasingly complex disease suggest that anesthesiologists will be caring for many more patients with these devices, and we must be prepared for this situation. Safe and efficient clinical management of these patients depends on an understanding of implantable systems, indications for their use, and the perioperative needs they create.

GLOSSARY

Atrial Fibrillation (AF) Suppression (formerly Dynamic Atrial Overdrive): A programmable rate enhancement for CIEDs that increases the pacing rate in response to the presence of intrinsic atrial activity. AF suppression is designed to pace the atrium at a rate just above the intrinsic rate to prevent atrial fibrillation.[120] Its presence and maximal pacing rate should be identified before an anesthetic regimen because elevated pacing rates may prompt treatment, which will not affect the heart rate but may harm the patient. Consideration should be given to disabling this feature intraoperatively, especially if monopolar ESU will be used superior to the umbilicus, where EMI would be expected.

Atrioventricular Delay: The time that a dual-chamber system waits after detecting (or initiating) an atrial event before pacing the ventricle. Some generators shorten this time as heart rate increases (termed rate-adaptive AV delay or dynamic AV delay). Some generators can be programmed to extend the AV delay to search for intrinsic conduction (search AV delay). Some generators prolong an AV delay after any atrial event in which the last ventricular event was intrinsic (AV delay hysteresis). In a patient with a conducting AV node, the sensed AV delay is slightly longer than the PR interval on the surface ECG (see Fusion Beat and Pseudofusion Beat) because the ventricular sensing element is attached to the apex of the right ventricle and detects the depolarization only after RV activation (typically >60 msec after activation of the AV node).

Automatic Rate. See Lower Rate Limit

Bipolar Lead: An electrode with two conductors. Bipolar pacing typically uses less energy than unipolar pacing, and it produces smaller artifacts on analog monitors.

Bipolar sensing is more resistant to oversensing from muscle artifact or stray electromagnetic fields. Most pacing generators (but not ICDs) can be programmed to unipolar mode (separate settings for pacing and sensing), even in the presence of bipolar electrodes.

EGM Mode (Electrogram Storage Mode): Passive acquisition and internal storage of ECG data for diagnostic purposes while pacing (or monitoring) with programmed parameters. A PM programmed to enter the EGM mode on application of a magnet will not demonstrate asynchronous pacing behavior.

Fusion Beat (FB): A PM spike delivered shortly before a native depolarization of the ventricle that alters the morphology of the QRS, often misdiagnosed as undersensing. With an FB, the pacing stimulus is delivered after the activation of the AV node but before the sensing element detects the PM-induced depolarization. It is similar to preexcitation of the ventricle seen in Lown-Ganong-Levine syndrome or Wolff-Parkinson-White syndrome. Confirmation of appropriate sensing behavior can be made by lengthening the sensing interval (i.e., lengthening the AV delay). Fusion beats suggest, but should not be used to confirm, ventricular capture. See also Pseudofusion Beat.

Generator: The device with a power source and circuitry to produce an electrical impulse designed to be conducted to the heart. Typically, cardiac generators are placed in a pectoral pocket, and leads are inserted into the right atrium, right ventricle, or both. Since 1995, ICDs have also been approved for pectoral pocket placement.

Hysteresis: If present, the amount by which the patient's intrinsic rate must fall below the programmed rate before the generator begins pacing. Some pacers periodically decrease the pacing rate to search for resumption of intrinsic activity (called search hysteresis). These functions, when present, can mimic PM malfunction.

ICD (Implantable Cardioverter-Defibrillator) Mode: The designation of chambers shocked, chambers paced for antitachycardia pacing, method of tachycardia detection, and chambers paced for antitachycardia therapy. Table 48-4 shows the NASPE/BPEG generic ICD code.

Lower Rate Limit (LRL, also Automatic Rate or Programmed Rate): The lowest sustained regular rate at which the generator will pace. Generators convert this value into the maximum allowable R-R interval and emit a pacing pulse at the expiration of this time. Dual-chamber pacing devices subtract the AV delay to determine the maximum allowable interval from a ventricular event to the expected atrial event.

Mode Switch: In dual chamber (AV) systems, a feature designed to limit ventricular pacing during high atrial rates (whether atrial fibrillation, flutter, or tachycardia) by temporarily switching to DDI(R) / VVI(R) depending upon the manufacturer. The mode switch detect rate, duration of high rate tracking (pre-mode switch) and return to dual chamber tracking mode upon termination of the atrial high rate can be manufacturer and programming dependent. Often, removal of a magnet in the setting of a high atrial rate will lead to transient ventricular pacing at the upper tracking rate until mode switch occurs. EMI can also cause inappropriate mode switch with resultant loss of atrial transport producing hemodynamic embarrassment.

Oversensing: Detection of undesired signals that are interpreted as cardiac activity. Ventricular oversensing can lead to ventricular pause (PM or ICD) or inappropriate antitachycardia therapy (ICD). Atrial oversensing can lead to inappropriately high paced ventricular rates in DDD or VDD devices; these ventricular systoles occur in the absence of true atrial systoles, and hemodynamic compromise can result.

Pacing Mode: The designation of chambers paced, chambers sensed, sensing response, rate responsiveness, and antitachyarrhythmia function for a PM system. Table 48-2 shows the NASPE/BPEG generic PM code.

Programmed Rate. See Lower Rate Limit

Pseudofusion Beat (PFB): A PM spike delivered shortly after a native depolarization without alteration of the QRS morphology. PFBs are often misdiagnosed as undersensing, and they result from the position of the sensing electrode relative to the depolarizing wavefront (see Fusion Beat). Confirmation of appropriate sensing behavior can be made by lengthening the sensing interval (i.e., decreasing the program rate [atrial FB] or lengthening the AV delay [ventricular PFB]). PFB cannot be used to confirm electronic capture.

Rate Enhancements: Features such as rate-adaptive AV delay (shortens the AV delay with increasing heart rate), AV search hysteresis (lengthens or shortens the AV delay to produce intrinsic AV conduction), AF suppression (also called dynamic atrial overdrive; increases the lower rate on appearance of native atrial depolarization, thus creating nearly constant atrial pacing but at a rate only slightly higher than the patient's intrinsic rate), rate smoothing (limits changes in ventricular paced rates resulting from changes in atrial rates; rising and falling rate limits can be programmed separately), sleep rate (see Sleep Rate), ventricular rate regulation (similar to rate smoothing but used only during atrial fibrillation), and hysteresis (see Hysteresis). Each of these enhancements can produce pacing or nonpacing that can mimic PM dysfunction, and consideration should be given to disabling these enhancements before any anesthetic regimen.

Rate Modulation: The ability of the generator to sense the need to increase heart rate in response to the patient's activity. Mechanisms include (1) a mechanical sensor in the generator to detect motion or vibration, (2) electronic detection of the QT interval (shortens during exercise), (3) transthoracic impedance to measure changes in respiration, and (4) sensors for central venous blood temperature or oxygen saturation (see Table 48-3). Some generators now incorporate multiple sensors. The pacing rate determined by the rate modulation algorithm is called sensor indicated rate.

Rest Rate: A rate lower than the programmed rate, invoked by the pacing device after some period (manufacturer specific) of patient inactivity, which is determined by the exercise sensor.

Sensor Indicated Rate: The pacing rate determined by the sensor in a PM programmed to a rate-responsive mode (fourth character of NBG = R).

Sleep Rate (also Circadian Rate): The rate (lower than the programmed rate) at which the pacing generator will pace during programmed "nighttime" hours. Travel across time zones can lead to maladaptive behavior when using this feature.

Undersensing: Failure to detect a desired event.

Unipolar Lead: An electrode with only one conductor. Some devices with bipolar leads are programmed to the unipolar lead mode. Systems with unipolar leads produce larger spikes on the ECG than bipolar leads. Systems with unipolar leads use the generator case as the second conductor. Unipolar pacing or sensing modes cannot be programmed in an ICD.

Upper Sensor Rate (USR, also Upper Activity Rate or UAR): The maximum rate to which a rate modulated CIED can drive the heart. The USR is not affected by UTR because when USR becomes active, the CIED is pacing the atrium.

Upper Tracking Rate (UTR, also called Upper Rate Limit or URL): In dual chamber (AV) systems, the maximum rate at which the ventricle can be paced regardless of the atrial rate. When the atrial rate exceeds this rate, the observed AV delay will lengthen and some QRS events can be dropped, a behavior that appears similar to Wenckebach rhythms.

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APPENDIX 48-1 *Pulse Generator Company Telephone Numbers*[*]

AM Pacemaker Corp. (Guidant Medical)	800-227-3422	Diag/Medcor (St. Jude Medical)	800-722-3774
Angeion (Sorin)	**800-352-6466**	Edwards Pacemaker Systems (Medtronic)	800-325-2518
Arco Medical (Boston Scientific)	800-227-3422	**ELA Medical** (Sorin)	800-352-6466
Biotronik	**800-547-0394**	**Intermedics (Boston Scientific)**	**800-227-3422**
Boston Scientific	**800-227-3422**	**Medtronic**	**800-505-4636**
Cardiac Control Systems	Unavailable	**Pacesetter (St. Jude Medical)**	**800-722-3774**
Cardio Pace Medical, Inc. (Novacon)	Unavailable	Siemans-Elema (St. Jude Medical)	800-722-3774
Cardiac Pacemakers, Inc.: CPI (Boston Scientific)	**800-227-3422**	**Sorin**	800-352-6466
		Telectronics Pacing (St. Jude Medical)	**800-722-3774**
Coratomic (Biocontrol Technology)	Unavailable	**Ventritex (St. Jude Medical)**	**800-722-3774**
Cordis Corporation (St. Jude Medical)	800-722-3774	Vitatron (Medtronic)	800-328-2518

*Companies in bold market both pacemakers and implantable cardioverter-defibrillators.

APPENDIX 48-2 *Preanesthetic Cardiovascular Implantable Electronic Device (Pacemaker, Implantable Cardioverter-Defibrillator) Evaluation*[*]

Determining the indication for and date of initial device placement
Identifying the type of device (pacemaker, implantable cardioverter-defibrillator) and manufacturer
Determining the patient's underlying rhythm and rate (if any)
Identifying the number and types of leads
Determining the last generator test date and battery status
Obtaining a history of generator events (if any)
Obtaining the current program information (device interrogation), including mode, rate, and rate enhancements
Ensuring that generator discharges become mechanical systoles with adequate pacing safety margins
Ensuring adequate safety margin for sensing events (if intrinsic events are present)
Ensuring that magnet detection is enabled (magnet behavior and rate should be recorded)
Determining whether the pacing parameter should be reprogrammed, which will depend on, for example, pacing dependency, surgery type and location, and need for increased heart rate

*The preanesthetic cardiovascular implantable electronic device evaluation should consist of a device interrogation. The foregoing statements can be fashioned into a request to the cardiologist or pacemaker service. For implantable cardioverter-defibrillators, the term *generator events* includes a history of antitachycardia therapy.

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Chapter 49

Neurologic Monitoring

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Key Points

- Intraoperative neurologic monitoring has four key principles:
  - The pathway at risk during the surgical procedure must be amenable to monitoring.
  - The monitor must provide reliable and reproducible data.
  - If evidence of injury to the pathway is detected, some intervention should be possible.
  - If changes in the neurologic monitor are detected, they may have prognostic value even if no intervention is possible. In this situation, the direct benefit to the patient from early detection of impending neurologic injury is minimal.
- Few randomized prospective studies have evaluated the efficacy of neurologic monitoring modalities.
- Anesthesiologists can improve the efficacy of monitoring by maintaining good physiologic homeostasis and stable levels of anesthesia during parts of the surgical procedure that place the nervous system at greatest risk.
- Based on clinical experience and nonrandomized studies, four practice patterns for use of neurologic monitoring have emerged:
  - In some procedures, monitoring is recommended and is used by most centers.
  - In certain procedures, monitoring is used frequently in some centers but not in others.
  - Some procedures have no clear clinical experience or evidence indicating that monitoring is useful at all (experimental use).
  - In certain procedures, monitoring is used selectively for patients believed to be at higher than usual risk for intraoperative neurologic injury.
- Good communication among surgeons, anesthesiologists, and neurophysiologists is essential to optimizing the utility of monitoring.

Neurologic monitoring in the context of anesthesia care for a patient spans a wide spectrum of techniques, diverse procedures, and various intraoperative or even postoperative settings. Techniques for monitoring fall into two broad categories: (1) techniques to assess metabolic integrity of the nervous system, which include either global or regional determinations of blood flow or oxygenation; or (2) techniques to assess functional integrity, which similarly may be global or focused on specific anatomic components of the nervous system.

The procedures and settings in which neurologic monitoring is typically applied all share the characteristic that changes in the monitored parameters can be corrected or minimized by either modifying the surgical approach or manipulating variables under the control of the anesthesiologist. Monitored procedures range from procedures in which monitoring dictates the surgical approach, such as localization of the motor strip during tumor operations or neurologic examination during "awake" craniotomy, to procedures that by their nature put parts of the nervous system at increased risk.

In many procedures that require neurologic monitoring, the anatomic target is also susceptible to drugs administered in the course of an anesthetic regimen. The anesthesiologist and the surgeon must be aware not only of limitations inherent in individual monitoring techniques but also of nonsurgical factors that influence the monitoring results. The monitoring approach ideally should anticipate nonsurgical factors by providing a degree of redundancy that helps distinguish localized surgical trespass from a systemic event.

For some procedures, neurologic monitoring is a marker of the quality of care and is routinely employed because outcome data support its use. Examples include correction of scoliosis and resection of vestibular schwannomas. More frequently, the approach to monitoring is

based on local conventions and surgical expectations. In this latter case, monitoring utility depends on the following: (1) a good understanding of the technique's capabilities and limitations by anesthesiologists, surgeons, and the intraoperative monitoring team; (2) good communication; and (3) mutual collaboration to allow corrective action in the presence of changing signals or to prevent false alarms that disrupt surgical procedures.

Individual monitoring modalities are initially described in isolation so that the clinician can appreciate the inherent strengths and weaknesses of each. Then this information is used to develop suitable approaches to various clinical settings that combine and integrate individual techniques to optimize neurologic outcome for patients. Finally, this chapter reviews the manner in which neurologic monitoring is currently useful and the areas where more work is needed to determine the more specific indications for monitoring in surgical patients in the future.

MONITORING MODALITIES

MONITORS OF ADEQUACY OF NERVOUS SYSTEM BLOOD FLOW

Adequacy of cerebral blood flow (CBF) can be monitored by two principal methods. The first method assesses blood flow itself, with the implicit assumption that "normal" flow provides adequately for the metabolic needs of the brain. The second approach assesses oxygen delivery either locally or globally, with the implicit assumption that "normal" values at the site of measurement reflect adequate blood supply throughout the central nervous system (CNS). However, these assumptions have limitations, as exemplified by global or hemispheric CBF in the context of a patient's disease process.

In the normal brain, values of hemispheric CBF of approximately 50 mL/100 g/minute reflect adequate oxygen delivery for maintaining structural integrity and function. Values of less than 20 to 25 mL/100 g/minute are associated first with failure of function and, on further decrease, with structural damage.[1] In neurosurgical patients, structural integrity and function may be altered by both disease processes and anesthetic drugs, which influence interpretation of measured CBF. A CBF of 40 mL/100 g/minute in a patient in barbiturate coma after resection of an arteriovenous malformation may represent hyperemia (because metabolic demand is very small), whereas the same CBF in a patient with a mass lesion may reflect a modest decrease in cerebral perfusion pressure secondary to increasing intracranial pressure. Thus, the clinical response to an abnormal value requires context and clinical judgment.

Global Blood Flow Monitoring Techniques (Noninvasive)

Intravascular Tracer Compounds. Direct measurement of CBF is possible by determining kinetics of wash-in or washout, or both, of an inert tracer compound, a method originally described by Kety and Schmidt.[2] The most widely used measurement technique involves administration of a radioactive isotope of xenon-133 (^{133}Xe), followed by measurement of the radioactivity washout with gamma detectors placed over specific areas of the brain. Depending on the number of detectors, this method can provide a spatial resolution of 4 cm. In normal brain, flow at different depths may be inferred from the early washout, which should reflect high-perfusion cortical gray matter, and late washout, from low-perfusion deeper white matter.

Drawbacks of the method are the patient's exposure to radioactive compounds and the need for externally placed and potentially cumbersome detector equipment, which may interfere with the operation itself in the case of intracranial surgical procedures. Focal areas of hypoperfusion may be missed because of underlying or overlying adequate flow, a phenomenon described as look-through.[3] Despite these shortcomings, ^{133}Xe washout has been used at a few major centers for intraoperative monitoring during operations such as carotid endarterectomy.[4-8] Modern variations of the same concept are mean transit time determinations of intravascular contrast agents during neuroimaging for determining locoregional blood flow[7,8] or a double-indicator technique for determining global CBF.[9] All these techniques share the limitation of providing a snapshot of CBF in time instead of continuous monitoring.

Transcranial Doppler Ultrasound. Transcranial Doppler (TCD) ultrasound is a technique that infers CBF from measurements of the blood flow velocity in the large conducting arteries of the brain. The TCD probe transmits pulses of sound waves through the thin temporal bone in a variation of the pulsed wave Doppler technique with which anesthesiologists may be familiar from echocardiography. When these sound waves are reflected off the red blood cells back toward the TCD probe, the velocity of the reflected sound waves is changed because the blood cells themselves are in motion toward or away from the probe. This phenomenon is known as the Doppler shift and is directly related to flow velocity and flow direction of the blood cells. Blood flow is more rapid during systole and in the center of a vessel and slower in diastole and near the vessel wall. TCD imaging records a spectrum of flow velocities whose outline resembles an arterial waveform tracing. These concepts are illustrated in Figure 49-1.

Intraoperatively, TCD measurements are usually made by continuous monitoring of the middle cerebral artery for the purpose of detecting either significant changes in flow velocity or the presence of particulate emboli. As a diagnostic study, in addition to the middle cerebral artery, the anterior cerebral, anterior communicating, posterior cerebral, and posterior communicating arteries can be examined through the temporal bone window. The basilar, ophthalmic, and internal carotid arteries also can be insonated through the foramen magnum (TCD probe at the back of the flexed neck) (basilar artery), the closed eyelid (with reduced sound energy) (ophthalmic artery and carotid syphon), and near the angle of the jaw (internal carotid artery). An important limitation of TCD ultrasound is that most of the examination is performed through the temporal bone, which may be thick enough to preclude an adequate examination in 10% to 20% of patients.[10,11]

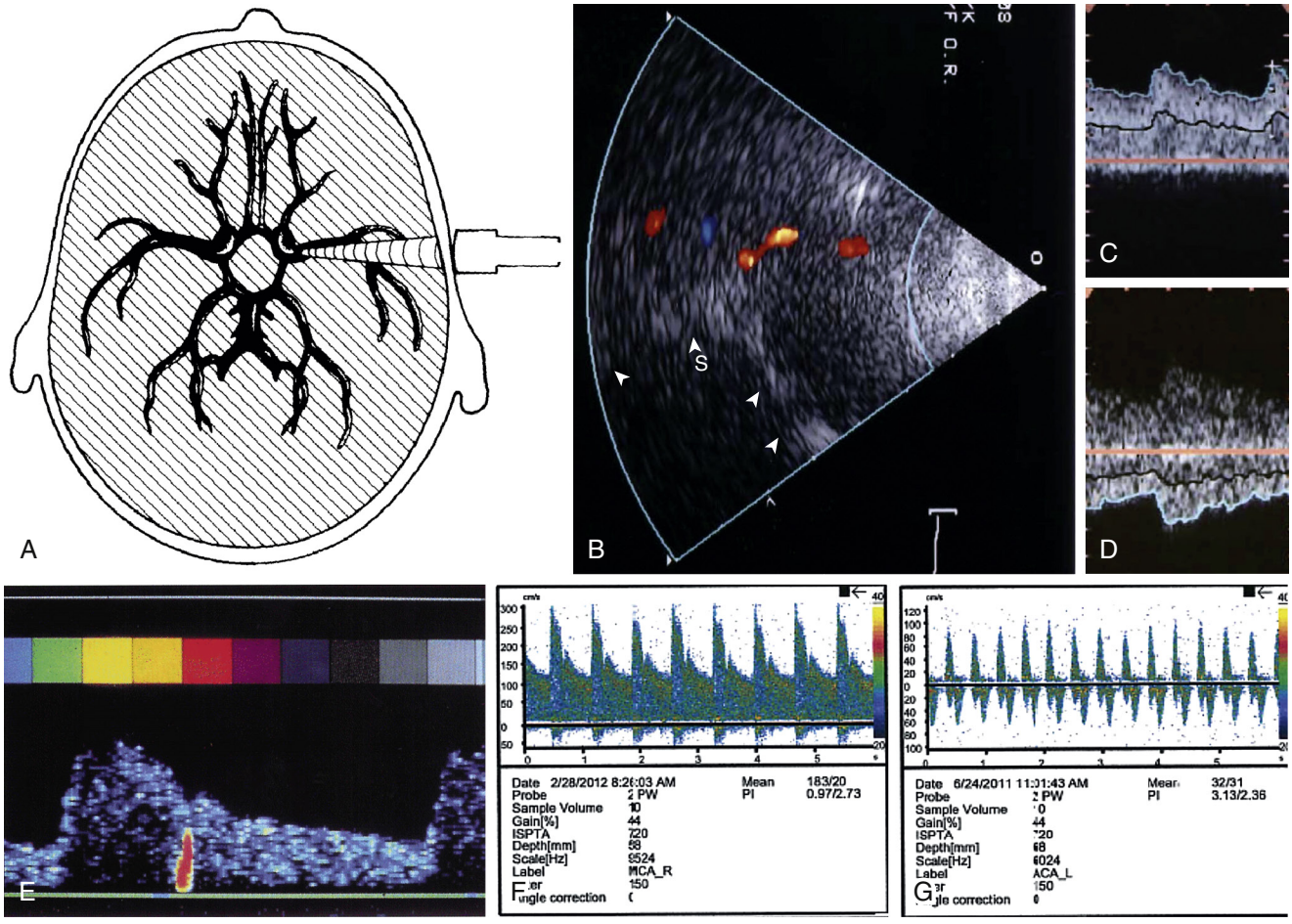


Figure 49-1. A, Transcranial Doppler monitoring is done by insonating the arteries at the base of the brain through a thin part of the temporal bone. **B,** If this procedure is performed with an imaging probe, some intracranial structures, such as the cerebral peduncles (*white triangles*) or the sella complex (*white triangle labeled "S"*), can be visualized. The captured Doppler signals originate from the right middle, right anterior, and left anterior cerebral arteries. **C,** Normal Doppler spectrum obtained from the middle cerebral artery. By convention, flow toward the probe is displayed as a waveform above the baseline. **D,** Doppler profile of the bifurcation of the terminal internal carotid artery as it branches into the middle cerebral artery (flowing toward the transducer) and the anterior cerebral artery (flowing away). This flow signal can be obtained if the transducer is focused as shown in **A. E** to **G,**Examples of three clinical applications of transcranial Doppler. **E,** Emboli are highly echogenic and appear as high-energy transient signals. On the audible output, these emboli are easily noticed as brief beeps or chirps. **F,** Doppler profile of a middle cerebral artery in a patient with severe vasospasm after an aneurysmal subarachnoid hemorrhage (compare with **C**). **G,** Transcranial Doppler examination consistent with intracranial circulatory arrest. A brief systolic inflow is followed by retrograde flow during diastole.

Two assumptions that are intuitive and plausible, but ultimately unproven, must be made for TCD-measured blood flow velocity to have a direct relationship with CBF. First, blood flow velocity is directly related to blood flow only if the diameter of the artery where the flow velocity is measured and the measurement angle of the Doppler probe remain constant. In practical terms, finding a means to affix the TCD probe in a way that prevents dislodgment or movement during monitoring is challenging. The second assumption requires that CBF in the basal arteries of the brain is directly related to cortical CBF. Because TCD monitoring is typically performed mainly using the middle cerebral artery, this assumption may be invalid if collateral blood flow by leptomeningeal collateral vessels from anterior and posterior cerebral artery territories is adequate. Although these two assumptions constrain the utility of TCD imaging as a standalone monitor of CBF, the changes in flow velocity seen in typical applications (discussed subsequently) are large enough to provide useful clinical information.

More important, TCD ultrasound is the only continuous neurologic monitoring technique that provides early warning for hyperperfusion and for the number of emboli delivered to the brain during various phases of an operation. Because of their high echogenicity, emboli show up in the TCD spectrum as high-intensity transient signals (HITSs) (see Fig. 49-1), easily identified as brief beeps or chirps within the background of the Doppler sounds.

Jugular Bulb Venous Oxygen Saturation. The degree of oxygen extraction by an organ can be monitored by measuring the oxygen saturation of the mixed venous blood that drains that organ. In the case of the brain, jugular bulb venous oxygen saturation ($Sjvo_2$) measures the degree of oxygen extraction by the brain and represents

the balance between cerebral oxygen supply and demand. To monitor $Sjvo_2$, a fiberoptic catheter is inserted in retrograde fashion into the jugular bulb through the internal jugular vein under fluoroscopic guidance. The fiberoptic bundle emits near-infrared light and records light reflected back to the catheter, a technique known as reflectance oximetry. Because near-infrared light can travel several centimeters in tissue and is mostly absorbed by hemoglobin, oxygen saturation of the surrounding tissue can be monitored (i.e., the jugular venous blood). Correct tip placement is crucial to minimize admixture of extracranial venous blood. To decrease the risk of complications, usually only one side is monitored.

Several theoretical limitations of the technique may interfere with proper interpretation of $Sjvo_2$ values and trends. Although nearly all blood from the brain drains through the jugular veins, intracranial mixing of venous blood is incomplete and may result in differences between right-sided and left-sided measurements. The dominant jugular vein (i.e., the right for most patients) drains predominantly cortical venous blood, whereas the contralateral jugular vein drains more of the subcortical regions.[12] Despite such regional differences, $Sjvo_2$ must be considered a monitor of global cerebral oxygenation because inadequate perfusion to a focal brain region may not decrease $Sjvo_2$ values less than the normal range of 55% to 75%. Because $Sjvo_2$ represents the balance between supply and demand, interpretation of the absolute value of $Sjvo_2$ must take the clinical circumstances into account.

Cerebral Oximetry. Cerebral oximetry is a noninvasive technique that, similar to $Sjvo_2$ monitoring, uses reflectance oximetry to measure the oxygen saturation of the tissues underneath the sensor. Typically, two sensors are applied to both sides of the forehead. The light passes not only through parts of the frontal brain but also through the overlying skull and scalp. Contamination of the oximetry signal by extracranial blood sources is a serious concern, although the use of two sensing diodes with different distances from the light source within one sensor patch and adjustments of the algorithm of the oximeter may minimize this problem.[13,14]

Because two thirds to four fifths of the cerebral blood volume is venous blood, cerebral oximetry determines predominantly local venous oxygen saturation.[15] It can be expected that, in the presence of cerebral ischemia, oximetry values decrease as a result of increased oxygen extraction, well before function fails or permanent neuronal damage ensues. The simplicity of its use and the familiarity with the principles of treating decreases in systemic mixed venous oxygen saturation have made cerebral oximetry a popular trend monitor in operations that potentially cause decreases in blood flow to the vessels of the head. The use of cerebral oximetry during such procedures has some significant limitations, however. First, adequacy of global cerebral perfusion is inferred from measurements over the frontopolar brain. Second, normative data on normal values or expected changes for cerebral oximetry are largely absent, but preoperative application of the sensors allows the start of a trend in conjunction with a neurologic baseline examination.

An example of how these limitations play out is provided by a study of the use of cerebral oximetry during 100 carotid endarterectomies in awake patients.[16] Cerebral oximetry was able to identify 97.4% of patients with adequate CBF as indicated by the absence of clinical symptoms. The monitor frequently indicated inadequate CBF, defined as a 20% decrease in cerebral oxygen saturation from the preclamp baseline, although the patient had no clinical symptoms of inadequate CBF. The false-positive rate of 66.7% may simply illustrate that oxygen extraction increases before function fails. The real problem is that the lower limit of acceptable regional oxygen saturation is unknown in a large population of patients.[17] The value may be different from patient to patient, and the addition of anesthetic drugs that influence cerebral metabolism may confuse the picture further.

Tissue-Level Blood Flow Monitoring Techniques (Invasive)

Tissue-level monitoring for the brain is by definition invasive. All monitors in current clinical or research use are implanted through a burr hole, extend either into the white matter or ventricular system, and typically use a bolt for stabilization. They all share a 1% to 2% risk of bleeding, infection, or ischemia related to the implantation procedure.[18] A second shared feature is their limited spatial resolution (i.e., each monitoring probe monitors only a limited area of brain surrounding the probe). When these monitors were first developed, optimal placement of the device was not clear, given such limited spatial resolution. Based on today's appreciation of the impact of secondary neurologic insults on the ultimate outcome, tissue-level monitoring is best performed in morphologically and functionally normal tissue that is part of the penumbra or vulnerable zone of interest.[19-21] Placing a blood flow monitor into the brain tissue supplied by an aneurysm-carrying artery in the setting of a subarachnoid hemorrhage maximizes, but does not ensure, the chances of early detection of vasospasm.

Of the tissue-level monitors, two have undergone sufficient refinement to be in wider clinical use. They represent the two principal modes of assessing adequate blood flow: assessing CBF through thermal diffusion monitoring and assessing oxygen delivery through tissue partial pressure of oxygen (Po_2) monitoring.

Thermal Diffusion Cerebral Blood Flow Monitoring. Thermal diffusion CBF monitoring is based on the idea that the rate at which heat dissipates in a tissue depends on the tissue's thermal conductive properties and the blood flow in that area. Because thermal conduction properties remain constant, changes in heat dissipation reflect changes in blood flow and can be expressed quantitatively in the conventional units of CBF as mL/100 g/minute. In practice, the probe consists of a thin catheter with two thermistors placed 5 mm apart (Fig. 49-2). When inserted, both thermistors are located in subcortical white matter. The proximal or passive thermistor measures brain temperature, whereas the distal or active thermistor is heated to 2° C higher than the temperature measured by the passive thermistor. The power required to sustain the

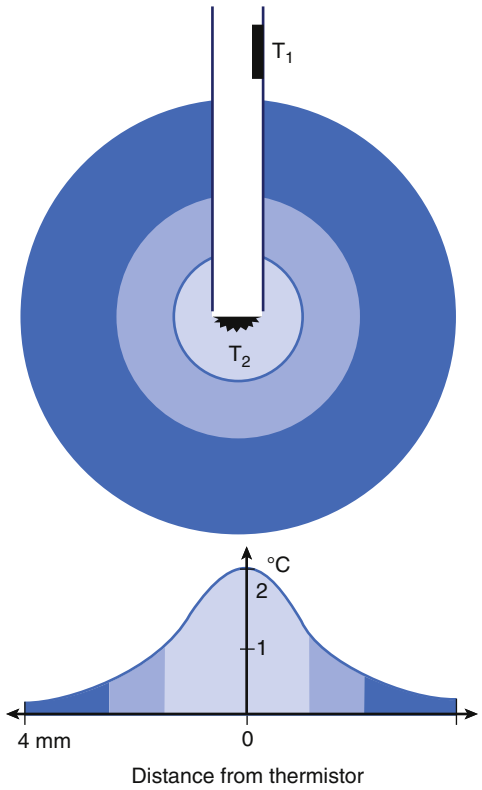


Figure 49-2. Thermal diffusion measurement of cerebral blood flow. The probe is placed in the subcortical white matter. It contains a passive thermistor (T_1) that measures brain temperature and is located outside of the area influenced by the active thermistor. The active thermistor (T_2) is heated to 2° C higher than brain temperature. The energy required to maintain that increase in temperature is proportional to cerebral blood flow.

2° C temperature difference is directly proportional to CBF. The initial rate of propagation of the thermal field is used to establish the fixed conductive component of heat transfer.

The short-term performance of this technology was validated against stable xenon computed tomography (CT) in patients with head injury, and the technology performed well across a wide range of CBF values in a sheep model of hypercarbia, hyperventilation, and cardiac arrest.[22] In continuous clinical use, the probe shows some drift and recalibrates at regular intervals.[23] To avoid thermal tissue injury, measurement is automatically suspended if the passive thermistor measures a brain temperature of 39.1° C. Because fever is a frequent complication, particularly in patients with severe brain disease, the inability to monitor during a febrile episode may constitute a true limitation of the technique.

Tissue Partial Pressure of Oxygen Monitoring. Localized monitoring of tissue Po_2 is based on an oxygen-sensitive electrode originally described by Clark.[24] The diffusion of oxygen molecules through an oxygen-permeable membrane into an electrolyte solution causes an electric current that is proportional to Po_2. Currently available catheter-based electrodes provide stable recording conditions over long periods. Similar to regional CBF probes, they are placed into the subcortical white matter.

Most of the data on brain tissue oxygen levels ($P_{Br}O_2$) come from studies in patients with head trauma. Comparison with stable xenon CT for assessment of CBF shows good correlation between $P_{Br}O_2$ and CBF.[25,26] Similarly, the time course of changes in $P_{Br}O_2$ after traumatic brain injury resembles that of CBF.[27,28] Critics of the technique argue that $P_{Br}O_2$ values are highly influenced by the partial pressure of arterial oxygen (Pao_2) and are merely an elaborate indicator of the quality of the patient's ventilation. This view is supported by the observation that increasing the fraction of inspired oxygen (Fio_2) increases $P_{Br}O_2$, but this likely represents an oversimplification.[29] Concurrent microdialysis studies have shown that increasing Fio_2 not only increases $P_{Br}O_2$ but also decreases tissue lactate levels, findings suggesting a true improvement in the metabolic milieu of the brain tissue itself.[30,31]

MONITORS OF NERVOUS SYSTEM FUNCTION

The most commonly used monitors of function are the electroencephalogram (EEG), sensory-evoked responses (SERs), motor-evoked responses, and the electromyogram (EMG). The EEG is a surface recording of the summation of excitatory and inhibitory postsynaptic potentials spontaneously generated by the pyramidal cells in the cerebral cortex. The signals are very small, and each recording electrode records only information generated directly beneath the electrode. Monitoring the EEG is usually directed toward one or more of four perioperative uses. First, the EEG is used to help identify inadequate blood flow to the cerebral cortex that is caused by either surgically induced or anesthetic-induced reduction in blood flow or retraction on cerebral tissue. Second, the EEG may be used to guide an anesthetic-induced reduction of cerebral metabolism either in anticipation of a loss of CBF or in the treatment of high intracranial pressure, when a reduction in CBF and blood volume is desired. Third, the EEG may be used to predict neurologic outcome after a brain insult. Finally, the EEG may be used to gauge the depth of the hypnotic state of the patient under general anesthesia (see Chapter 50).

EEG patterns can correlate with clinical states of the normal and diseased cerebral cortex. The electroencephalographer can accurately identify consciousness, unconsciousness, seizure activity, stages of sleep, and coma. In the absence of significant changes in anesthetic technique, the electroencephalographer also can accurately identify inadequate oxygen delivery to the brain (from either hypoxemia or ischemia). By using high-speed computerized EEG analysis and statistical methods, EEG patterns in the continuum from awake to deeply anesthetized are becoming, with few exceptions, much better understood. In addition, computer advances have made possible high-speed mathematic manipulation of the EEG signal to present the data in a manner more suitable to continuous trends for use during surgical or anesthetic monitoring.

Evoked potentials are electrical activity generated in response to either a sensory or a motor stimulus. Measurements of evoked responses may be made at multiple points along an involved nervous system pathway. The

evoked responses are generally smaller than other electrical activity generated in nearby tissue (muscle or brain) and are readily obscured by these other biologic signals. In the case of SERs, repeated sampling and sophisticated electronic summation and averaging techniques are needed to extract the desired evoked potential signal from background biologic signals. Motor-evoked responses are generally larger and commonly do not require averaging.

SERs are the most common type of evoked potentials monitored intraoperatively. Since the 1990s, much research has been done on the use of intraoperative motor-evoked potentials (MEPs). Although routine use of MEP monitoring is still not widespread, it is becoming more so. The three basic types of SERs are somatosensory-evoked potentials (SSEPs), brainstem auditory-evoked potentials (BAEPs), and visual-evoked potentials (VEPs).

The SSEP is produced by electrically stimulating a peripheral (or rarely cranial) nerve. Responses may be recorded proximally over the stimulated nerve, the spinal cord, and the cerebral cortex. The recorded responses assess the function of the peripheral nerve, the posterior and lateral aspects of the spinal cord, a small portion of the brainstem, the ventral posterolateral nucleus of the thalamus, the thalamocortical radiation, and a portion of the sensory cortex. The BAEP is usually produced by a series of rapid, loud clicks applied directly to the external auditory canal. Responses are most commonly recorded from electrodes applied to the scalp, although more invasive direct recordings from auditory structures and nerves may also be made. BAEPs assess function of the following: the auditory apparatus itself; cranial nerve VIII; the cochlear nucleus; and a small area of the rostral brainstem, the inferior colliculus, and the auditory cortex. The VEP is produced by flash stimulation of the retina. Recordings are made from cortically placed electrodes and assess visual pathways from the optic nerve to the occipital cortex.

MEP responses are generated most commonly by the application of a transcranial train of electrical stimuli, and responses are recorded at various points along the spinal column, peripheral nerve, and innervated muscle. Electrical stimuli to activate motor tracts also may be applied at the level of the spinal cord, but this method of stimulation is controversial (see later). At best, it is a mixed response and at worst primarily a sensory response. MEPs assess the integrity of the descending motor pathway through the internal capsule, the brainstem, the spinal cord, the peripheral nerve, and finally the muscle itself. The ability to record MEPs from some patients with cerebral palsy indicates that normal functional organization of the motor cortex cannot be inferred from MEPs.

Electroencephalogram

Basic Unprocessed Electroencephalogram Concepts. The EEG is produced by a summation of excitatory and inhibitory postsynaptic potentials produced in cortical gray matter. Because the EEG signal is generated only by postsynaptic potentials and is much smaller than action potentials recorded over nerves or from heart muscle, extreme care must be taken when placing electrodes to ensure proper placement and excellent contact with the skin, to avoid significant signal loss. Alternatively,

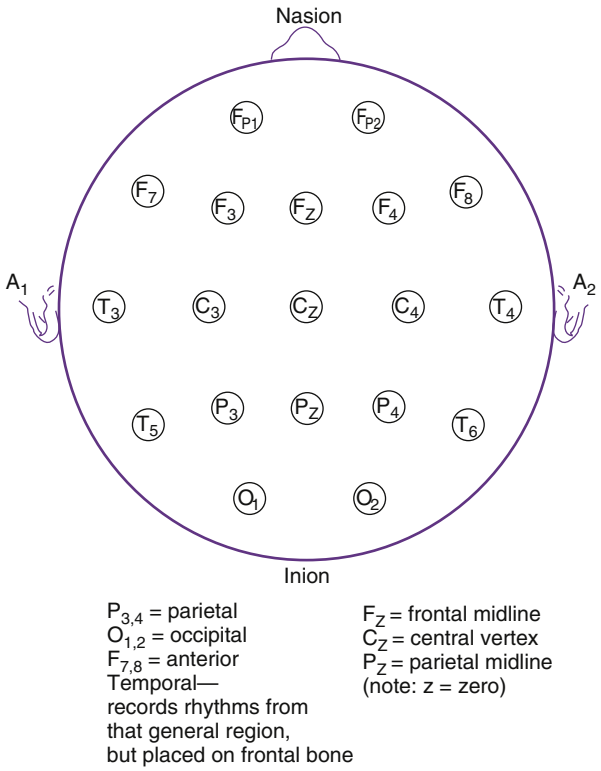


Figure 49-3. International 10-20 system of electrode placement for recording electroencephalogram and sensory-evoked responses. *(From Hughes JR:* EEG in clinical practice, *ed 2, Newton, Mass, 1994, Butterworth-Heinemann.)*

subdermal needle electrodes may be used, particularly when sterile application of an electrode close to a surgical field is necessary. When electrodes are applied directly to the surface of the brain, impedance is minimized by close electrode contact and saturation of the area with an electrolyte solution.

EEG electrodes generally are placed according to a mapping system that relates surface head anatomy to underlying brain cortical regions. The placement pattern of recording electrodes is called a montage. Use of a standard recording montage permits anatomic localization of signals produced by the brain and allows development of normative EEG patterns and comparison of EEG recordings made at different times. The standard EEG "map" is called the 10-20 system for EEG electrode placement (Fig. 49-3). This system is a symmetric array of scalp electrodes placed systematically based on the distance from the nasion to the inion and from the pretragal bony indentations associated with both temporomandibular joints. Based on 10% or 20% of these distances, recording electrodes are placed systematically over the frontal (F), parietal (P), temporal (T), and occipital (O) regions at increasing distances from the midline. Left-sided electrodes are given odd number subscripts, and right-sided electrodes are given even number subscripts. Increasing numbers indicate an increasing distance from the midline. Midline electrodes are designated with a "z" subscript. The standard diagnostic EEG uses at least 16 channels of information,[32] but intraoperative recordings have been reported using 1 to 32 discrete channels.

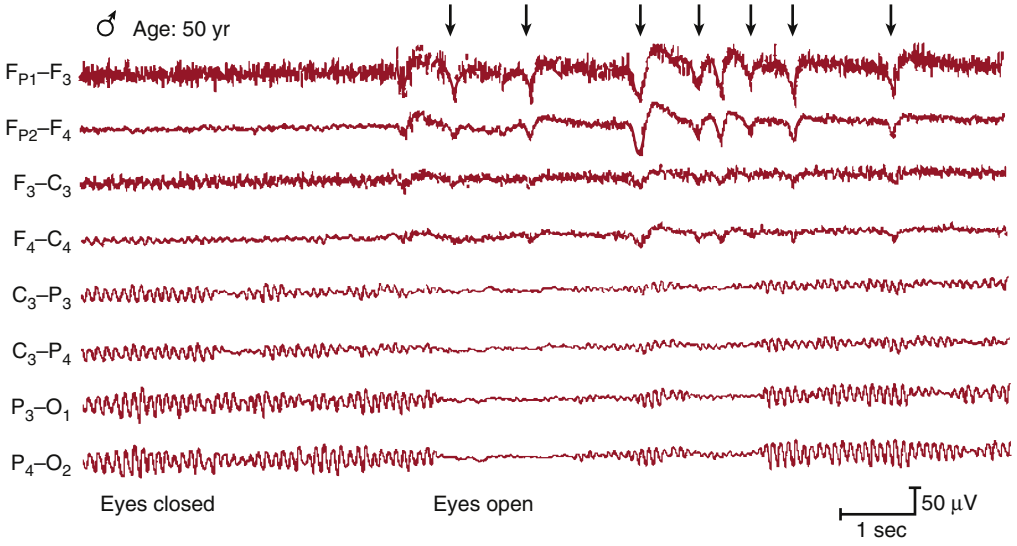


Figure 49-4. The loss and return of alpha activity as the eyes open and close can be seen. The large spikes (*arrows*) are muscle artifact from eye blinks and hence are best visible in channels that incorporate frontal electrodes (designated *F*).

The intraoperative EEG is most commonly recorded from electrodes placed on the scalp. Recordings also may be made from electrodes placed on the surface of the brain (electrocorticography) or from microelectrodes placed transcortically to record from individual neurons (e.g., during surgery for Parkinson disease).[33,34] The EEG signal is described using three basic parameters: amplitude, frequency, and time. Amplitude is the size, or voltage, of the recorded signal and ranges commonly from 5 to 500 μV (versus 1 to 2 mV for the electrocardiogram signal). Because neurons are irreversibly lost during the normal aging process, EEG amplitude decreases with age. Frequency can be thought of simply as the number of times per second the signal oscillates or crosses the zero voltage line. Time is the duration of the sampling of the signal; this is continuous and real time in the standard paper or digital EEG, but it is a sampling epoch in the processed EEG (see later).

Normal Electroencephalogram. Normal patterns seen on the EEG vary among normal individuals, but they are consistent enough to allow for accurate recognition of normal and pathologic patterns. The usual base frequency in an awake patient is the beta range (>13 Hz). This high-frequency and usually low-amplitude signal is common from an alert attentive brain and may be recorded from all regions. With eye closure, higher-amplitude signals in the alpha frequency range (8 to 13 Hz), seen best in the occipital region, appear (Fig. 49-4). This "eyes closed" resting pattern is the baseline awake pattern used when anesthetic effects on the EEG are described. When events occur that lead the brain to produce higher frequencies and larger amplitudes, the EEG is described as activated, and when slower frequencies are produced (theta = 4 to 7 Hz, and delta = <4 Hz), the EEG is said to be depressed. The EEG in a sleeping patient may contain all these frequencies at various times. The slower frequencies occur during deep natural sleep with "sleep spindles" (Fig. 49-5), but during light sleep or rapid eye movement (REM) sleep, the EEG becomes activated, and the eye muscle EMG appears on the EEG.

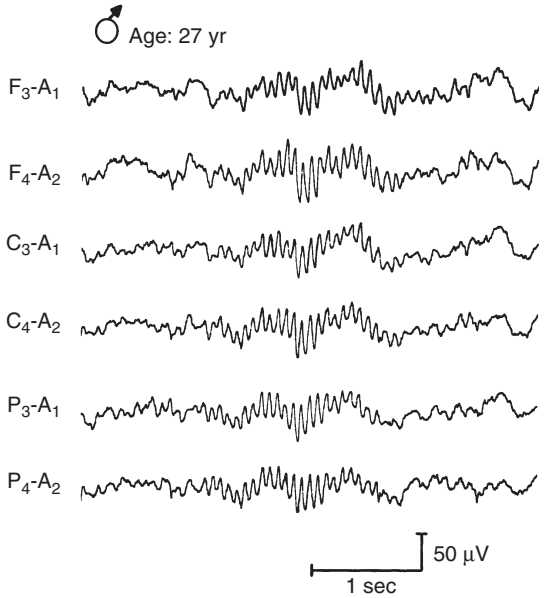


Figure 49-5. Characteristic sleep spindles in normal sleep are shown in the *center*.

In the normal EEG in awake and asleep patients, patterns recorded from corresponding electrodes on each hemisphere are symmetric in terms of frequency and amplitude, the patterns are predictable if clinical states are known, and spike (epileptic) waveforms are absent. In most cases, normal EEG patterns are associated with normal underlying brain function in awake and anesthetized patients.

Abnormal Electroencephalogram. General characteristics of the "abnormal" EEG include asymmetry with respect to frequency, amplitude, or both, recorded from corresponding electrodes on each hemisphere, and patterns of amplitude and frequency that are unpredictable or unexpected in the normal recording. These abnormal patterns reflect either anatomic or metabolic alterations

in the underlying brain. Regional asymmetry can be seen with tumors, epilepsy, and cerebral ischemia or infarction. Epilepsy may be recognized by high-voltage spike and slow waves, whereas cerebral ischemia manifests first with EEG slowing with preservation of voltage. Further slowing and loss of voltage occur as ischemia becomes more severe. Factors affecting the entire brain may produce symmetric abnormalities of the signal. Identifying pathologic abnormal patterns in the global EEG signal is very important, although sometimes quite difficult, in the clinical situation. Many of the normal global pattern changes produced by anesthetic drugs are similar to pathologic patterns produced by ischemia or hypoxemia. Control of anesthetic technique is essential when the EEG is used for clinical monitoring of the nervous system.

Processed Electroencephalogram Concepts. Interpretation of the standard raw EEG tracing is a science and an art. Until the last quarter of the twentieth century, the raw EEG was used during intraoperative monitoring, and the technologist relied on memory of the baseline and on experience to determine when significant EEG changes occurred. This qualitative approach was used simply because the waveforms could not be described mathematically in a time frame that would make such information of any practical use. Computer hardware has dramatically improved in speed and size, and real-time signal processing is now possible and commonly used.

Numerous limitations are introduced when moving from the raw EEG domain to the processed EEG domain. First, artifact is processed in many cases along with desired signal, thus leading to a perfectly believable processed EEG display that is materially incorrect. Second, the standard 16-channel EEG montage provides more information than can be practically analyzed or displayed by most processed EEG monitors and perhaps more than is needed for routine intraoperative use. Most available processed EEG devices used by anesthesiology personnel use four or fewer channels of information—translating to at most two channels per hemisphere. Processed EEG devices generally monitor less cerebral territory than a standard 16-channel EEG. Third, some intraoperative changes are unilateral (e.g., regional ischemia resulting from carotid clamping), and some are bilateral (e.g., EEG depression by bolus administration of an anesthetic drug). Display of the activity of both hemispheres is necessary to delineate unilateral from bilateral changes. An appropriate number of leads over both hemispheres is needed. Most early studies validating intraoperative EEG monitoring used continuous visual inspection of a 16- to 32-channel analog EEG by an experienced electroencephalographer; such monitoring was considered the gold standard.[35,36] Adequate studies comparing the processed EEG with fewer channels with this gold standard across multiple uses and operations have not been conducted, although limited data using processed EEG monitoring during carotid surgery suggest that 2- or 4-channel instruments would detect most significant changes,[37,38] provided the electrodes are appropriately placed over watershed areas of blood supply.

Devices. EEG processing for intraoperative monitoring is typically based on power analysis of a segment of raw EEG, referred to as an epoch (see also Chapter 50). Power analysis uses Fourier transformation to convert the digitized raw EEG signal into component sine waves of identifiable frequency and amplitude. The raw EEG data, which are a plot of voltage versus time, are converted to a plot of frequency and amplitude versus time. Many commercially available processed EEG machines display power (voltage or amplitude squared) as a function of frequency and time. These monitors display the data in two general forms, either compressed spectral array or density spectral array. In compressed spectral array, frequency is displayed along the *x*-axis, and power is displayed along the *y*-axis with height of the waveform equal to the power at that frequency. Time is displayed along the *z*-axis. Tracings overlap each other, with the most recent information in front (Fig. 49-6). Density spectral array also displays frequency along the *x*-axis; time is displayed along the *y*-axis, and power is reflected either by the density of the dots at each frequency or by a spectrum of colors. Each display format provides the same data, and choice depends on the preference of the user.

Many changes that occur during anesthesia and surgical procedures are reflected as changes in amplitude, frequency, or both. These changes can be clearly seen in these displays if adequate and appropriate channels are monitored. Power analysis has been used clinically for many years as a diagnostic tool during procedures with

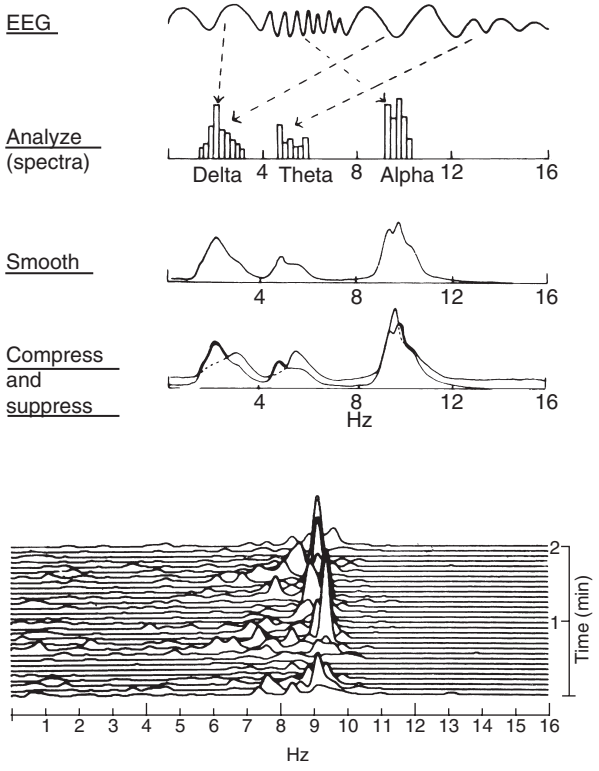


Figure 49-6. Diagram of a technique used to generate compressed spectral array. The example at the *bottom of the figure* shows compressed spectra of the alpha rhythm from a normal subject. *(From Stockard JJ, Bickford RG: The neurophysiology of anaesthesia. In Gordon E, editor:* A basis and practice of neuroanesthesia, *New York, 1981, Elsevier, p 3.)*

risk for intraoperative cerebral ischemia, such as carotid endarterectomy and cardiopulmonary bypass (CPB). Power analysis is a sensitive and reliable monitor in the hands of experienced operators using an adequate number of channels. In addition, parameters obtained from power analysis have been investigated as monitors for depth of anesthesia[39-42] (see Chapter 50).

Data Acquisition Period. An important consideration in the processed EEG is time. Raw EEG is continuous in real time. The processed EEG samples data over a given time period (epoch), processes the data, and then displays information in various formats. A relationship exists between epoch length and spectral resolution. If a long epoch length is chosen, the waveform can be described precisely, but the time required for data processing is long and not real time. If a short length of data is sampled, analysis may be done in near-real time, but the epoch chosen for analysis may not be representative of the overall waveform (i.e., the condition of the patient). Moreover, data points may be insufficient for meaningful Fourier transformation. This issue, as related to the use of intraoperative EEG for analysis of anesthetic depth, was studied by Levy.[43] A longer epoch may produce less epoch-to-epoch variability and allow more precise description of frequency and power; however, the longer epoch increases the delay before new information is processed and displayed, thereby reducing the amount and timeliness of information available for clinical decision making. In studying EEG epochs of 2 to 32 seconds, Levy concluded that 2-second epochs are appropriate during general anesthesia.[43] Many commercially available devices have used 2-second epoch lengths, updated at varying user-selected intervals. With better and faster computers, continuous monitoring of 2-second epochs and now even longer epochs is possible.

Evoked Potentials

Basic Concepts Common to All Modalities. EEG signals provide information about cortical function, but little to no information about subcortical neural pathways crucial to normal neurologic function. Intraoperative monitoring of SERs has gained increasing popularity since the 1980s because it provides the ability to monitor the functional integrity of sensory pathways in an anesthetized patient undergoing surgical procedures that place these pathways at risk. Because motor pathways are often adjacent anatomically to these sensory pathways or are supplied by the same blood vessels, or both, function of motor pathways may be inferred, albeit imperfectly, from function of these sensory pathways. Today, MEPs are ideally monitored together with SERs to provide direct information about function of motor pathways.

Sensory-Evoked Responses. SERs are electrical CNS responses to electrical, auditory, or visual stimuli. SERs are produced by stimulating a sensory system and recording the resulting electrical responses at various sites along the sensory pathway up to and including the cerebral cortex. Because of the very low amplitude of SERs (0.1 to 10 μV), it is often impossible to distinguish SERs from other background biologic signals, such as the EEG or EMG, which may be considered in this case undesirable noise. To extract the SER from the background noise, the recorded signal is digitized, and signal averaging is applied. With this technique, signal recording is time-locked to the application of the sensory stimulus. During intraoperative posterior tibial nerve SER monitoring, after nerve stimulation at the ankle, only signal information occurring less than 90 msec after the stimulus is recorded (Fig. 49-7). The SER occurs at a constant time after the stimulus application; other electrical activity, such as spontaneous EEG, occurs at random intervals after the sensory stimulus. The averaging technique improves the SER signal-to-noise ratio by eliminating random elements and enhancing the SER. This enhancing effect increases directly with the square root of the number of responses added into the averaged response.

SER recordings are of two general types, determined by the distance of the recording electrode from the neural

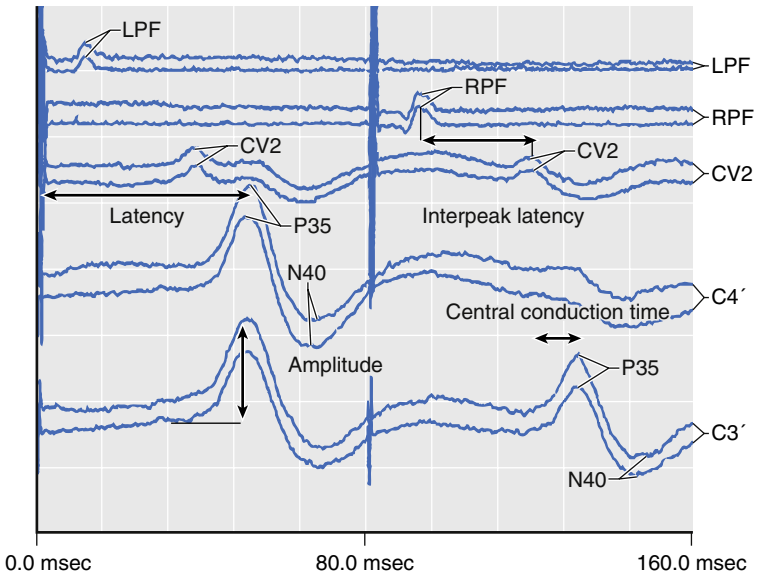


Figure 49-7. Sensory-evoked responses are described in terms of latency and amplitude. Interpeak latency is the measured time between two peaks. Interpeak latency may be measured between two peaks in the same channel or between peaks in different channels (shown in figure). The polarity of peaks is displayed contrary to standard convention (see text). The example shows a recording of posterior tibial somatosensory-evoked potentials. Each tracing is reproduced twice because reproducibility of a waveform helps distinguish signal from artifact. Left and right posterior tibial nerves are stimulated at 0 and 90 msec, respectively. The first evoked response is recorded from the left and right popliteal fossa (LPF and RPF, respectively). The peak labeled CV2 represents the brainstem response recorded at the craniocervical junction. As a far-field potential, the potential looks similar for right- and left-sided stimulation. The primary cortical responses are recorded from the contralateral hemisphere (labeled P35 and N40).

generator of the evoked response. SERs recorded from electrodes close to the neural generators (within ≈3 to 4 cm in the average adult) are termed near-field potentials.[44] Near-field potentials are recorded from electrodes placed very close to the actual signal generator site,[45] and the morphology is directly affected by electrode location.[44] Far-field potentials are recorded from electrodes located a greater distance from the neural generator and are conducted to the recording electrode through a volume conductor (brain, cerebrospinal fluid, and membranes). Because the current spreads diffusely throughout the conducting medium, it is more difficult to locate the source of the recorded signal, and the electrode position has little effect on the morphology of the recorded evoked potential (see Fig. 49-7).[44,45] As the distance between the recording electrode and the neural generator increases, the recorded SER becomes smaller. More responses must be averaged to record far-field potentials (several thousand) than near-field potentials (50 to 100).[44,45]

SERs also may be described as cortical or subcortical in origin. Cortical SERs are generated by the arrival at the cortex of the volley of action potentials generated by stimulating the sensory system. Because these SERs are recorded as near-field potentials, they are typically easy to identify by elapsed time, waveform morphology, and amplitude. Subcortical responses may arise from many different structures depending on the type of response, including peripheral nerves, spinal cord, brainstem, thalamus, cranial nerves, and others. Cortical SERs are usually recorded from scalp electrodes placed according to the standard 10-20 system for EEG recordings (see Fig. 49-3). Subcortical-evoked responses also may be recorded as far-field potentials from scalp electrodes or, as appropriate, from electrodes placed over the spinal column or peripheral nerve.

Evoked potentials of all types (sensory or motor) are described in terms of latency and amplitude (see Fig. 49-7). Latency is defined as the time measured from the application of the stimulus to the onset or peak (depending on convention used) of the response. The amplitude is simply the voltage of the recorded response. According to convention, deflections below the baseline are labeled positive (P), and deflections above the baseline are labeled negative (N). Because amplitude and latency change with recording circumstances, normal values must be established for each neurologic monitoring laboratory and may differ from values recorded in other laboratories.

SERs used for intraoperative monitoring include SSEPs, BAEPs, and, rarely, VEPs. For all these techniques, cortical recording electrodes are placed on the scalp, by using the same standard 10-20 system as for recording the EEG, whereas recordings for subcortical and peripheral signals are placed in various standardized anatomic locations. The surgical incision and the need for sterility may necessitate nonstandard electrode placements. Such deviations must be considered when interpreting baseline and subsequent SERs. In the case of MEPs, stimulating electrodes also are placed according to the 10-20 system of electrode placement, but over motor cortex instead. Recording electrodes may be placed over the spinal column, peripheral nerve, and (most commonly) innervated muscle.

Intraoperative changes in evoked responses, such as decreased amplitude, increased latency, or complete loss of the waveform, may result from surgical trespass, such as retractor placement or ischemia. They may also reflect systemic changes, such as changes in the anesthetic drugs or doses, temperature, or hypoperfusion. If these changes are clinically significant, the surgeon or anesthesiologist can make changes to relieve or lessen the insult to the monitored pathway (and presumably surrounding neural structures). Interventions by the anesthesiologist are directed at improving perfusion to the nervous tissue at risk and include increasing arterial blood pressure, especially if induced hypotension is used or if arterial blood pressure has decreased to less than the preoperative level. In addition, correction of anemia with a blood transfusion, intravascular volume expansion, augmentation of cardiac output, and ensuring that arterial blood gas tensions are adequate all must be considered. Changes in evoked potentials after retractor placement during craniotomy or after compression of the blood supply to the spinal cord from spinal column distraction promptly allow the surgeon and the anesthesiologist to make appropriate changes to the operative procedure and anesthetic management to minimize the chance of a postoperative neurologic deficit (Fig. 49-8).

Tolerance limits for degree of change in evoked response signals or duration of complete loss of waveform before permanent neurologic dysfunction occurs are not clearly defined, especially for transcranial MEPs. Such ambiguity is common among intraoperative monitors. Although we do know that increased frequency and duration of ST-segment depression during coronary bypass surgery are associated with an increased risk of perioperative infarction, exact limits for degree and duration of ST-segment depression for surgery do not exist and likely vary significantly from patient to patient. The same problem may be exhibited with neurologic monitors.

Many centers using intraoperative SER monitoring define decreases in amplitude of 50% or more from baseline associated with a less than 10% prolongation in latency as clinically significant SER changes. If not corrected, such changes are associated in clinical series and in case reports with onset of new postoperative neurologic deficits. As a result, such changes are immediately investigated. In practice, any SER changes directly associated with a surgical event are considered clinically significant, even if the magnitude of change is less than just described. Changes in SER that do not progress to complete loss of the waveform are less likely to be associated with a major new postoperative neurologic deficit. Complete loss of the SER waveform intraoperatively without recovery probably indicates a major new deficit. If the SER recovers either spontaneously or after intraoperative interventions, the likelihood of neurologic injury depends on the procedure, the duration of the SER loss, and whether the SER is mainly used to judge integrity of adjacent unmonitored structures. These problems were illustrated in one study of aortic vascular surgery in which SSEPs were monitored to predict or prevent postoperative motor deficits (i.e., paraplegia or paraparesis). Loss of the SSEP waveform for less than 15 minutes was not associated with a new permanent neurologic deficit, whereas

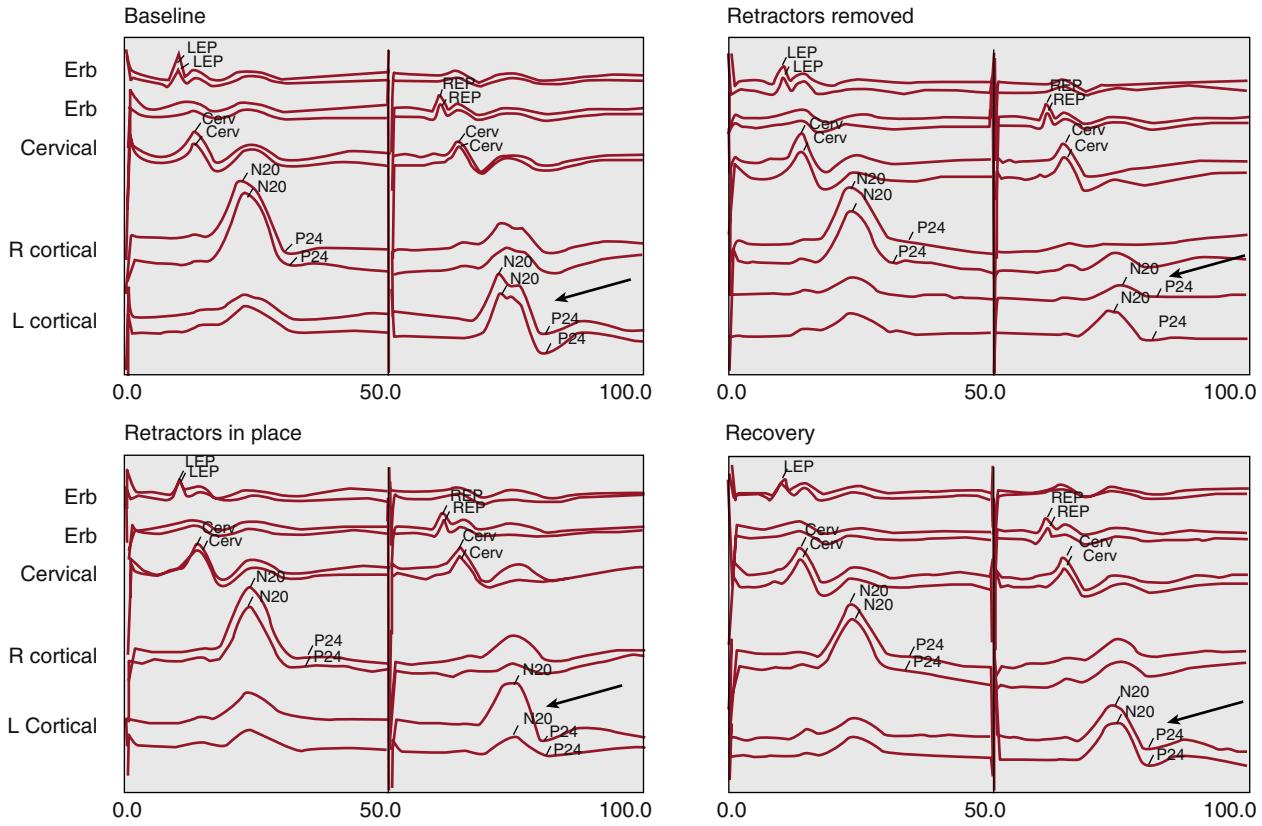


Figure 49-8. Somatosensory-evoked potentials during aneurysm clipping. Responses generated by the cortex at risk are indicated by *arrows*. Baseline, after retractor placement, after retractor removal, and recovery traces are shown. The initial evoked response change occurred 4 minutes after retractor placement. Note loss of voltage of cortical-evoked response caused by inadvertent compression of the middle cerebral artery. *Cerv,* Cervical; *LEP,* left Erb point; *REP,* right Erb point.

complete loss of the SSEP for longer periods was increasingly likely to reflect permanent neurologic injury, even if the response recovered completely to its intraoperative baseline during the surgical procedure.[46]

One of the most important principles of recording SERs intraoperatively is that reproducible, reliable tracings must be obtained at baseline before any intervention likely to cause changes in the evoked response. If good-quality tracings with identifiable waveforms cannot be recorded and reproduced at baseline, evoked response monitoring will be of little use in monitoring the integrity of the CNS intraoperatively. If significant variability exists, or waveforms are difficult to identify, it will be impossible intraoperatively to distinguish SER changes that are clinically significant from a preexisting baseline variability of waveforms. When excellent, reproducible responses cannot be recorded at baseline, monitoring should not be used for clinical decision making.

Somatosensory-Evoked Potentials. SSEPs are recorded after electrical stimulation of a peripheral mixed nerve. Stimulation is provided most commonly with surface electrodes (e.g., electrocardiogram electrodes) placed on the skin above the nerve or with fine needle electrodes. A square wave stimulus lasting 50 to 250 μsec is delivered to the peripheral nerve, and the intensity is adjusted to produce a minimal muscle contraction. Increasing the stimulus intensity beyond the sum of the motor and sensory threshold does not influence the amplitude or latency of the recorded evoked potential. On a practical basis, however, SSEP monitoring is often not initiated until after the patient is already anesthetized and paralyzed. In these cases, stimulus intensity is increased until no further increase in response size occurs at any recording site, typically constant current stimulation of 20 to 50 mA. For comparison, consider supramaximal stimulation used for the neuromuscular blockade monitor, commonly 80 mA. The rate of stimulation varies from 1 to 6 Hz. The common sites of stimulation include the median nerve at the wrist, the common peroneal nerve at the knee, and the posterior tibial nerve at the ankle[47] (see also Chapter 53).

SSEP responses consist of short-latency and long-latency waveforms. Cortical short-latency SSEPs are most commonly recorded intraoperatively because they are less influenced by changes in anesthetic depth. The pathways involved in the generation of upper extremity short-latency SSEPs include large-fiber sensory nerves with their cell bodies in the dorsal root ganglia and central processes traveling rostrally in the ipsilateral posterior column of the spinal cord and synapsing in the dorsal column nuclei at the cervicomedullary junction (first-order fibers), second-order fibers crossing and traveling to the contralateral thalamus through the medial lemniscus, and third-order fibers from the thalamus to the frontoparietal sensorimotor cortex. These primary cortical-evoked responses, which are recordable with most anesthetic

techniques, result from the earliest electrical activity generated by the cortical neurons and probably arise from the postcentral sulcus parietal neurons. The longer-latency secondary cortical waves probably arise in the association cortex. These responses have much greater variability in an awake patient,[45] habituate rapidly on repetitive stimulation,[44] and are only poorly reproducible during general anesthesia. Cortical SSEPs other than the primary cortical response are not monitored or interpreted intraoperatively because they are severely altered by general anesthesia.[44]

Upper extremity evoked potentials are likely conducted rostrally in the spinal cord through dorsal column pathways, and lower extremity SSEPs are conducted substantially by the lateral funiculus.[48] Stimulation of the posterior tibial nerve or common peroneal nerve at or higher than motor threshold activates group I fibers that synapse and travel rostrally through the dorsal spinocerebellar tract. After synapsing in nucleus Z at the spinomedullary junction, the pathway crosses and projects onto the ventral posterolateral thalamic nucleus.[49] Lower extremity SERs are conducted in all quadrants of the spinal cord, but primarily in the dorsal lateral funiculus.[50,51] This pathway difference is important because the dorsal lateral funiculus is supplied primarily by the anterior spinal artery, the artery that also supplies the descending motor pathway and neurons in the spinal cord. Manipulations, such as distraction of the spinal column to correct scoliosis, that may secondarily compress or distort radicular blood supply to the anterior spinal cord should cause changes in the SSEP in the event blood supply is reduced to critical levels. This hypothesis is verified by the very infrequent, but not zero, incidence of postoperative paraplegia on awakening without any intraoperative changes in SSEPs.

For SSEP recordings with median nerve stimulation, recording electrodes (usually electrocardiogram pads) are first placed at the Erb point, just above the midpoint of the clavicle. This point overlies the brachial plexus, and signals recorded here assure the clinician that the stimulus is actually being delivered properly to the patient. The next electrode (either an electrocardiogram pad or a gold cup electrode) is placed midline posteriorly over the neck at level of the second cervical vertebra, relatively near the dorsal column nuclei. Signals recorded here ensure proper transmission of the response from the peripheral nervous system into the spinal cord and rostral along the spinal cord to the lower medulla. The final electrodes (gold cup electrodes, corkscrew, or needle electrodes) are placed on the scalp overlying the sensory (parietal) cortex contralateral to the stimulated limb. Signals recorded here ensure the integrity of the pathway through the brainstem, thalamus, and internal capsule, and they may assess adequacy of CBF in this area of the cortex.[52-56]

To record SSEPs after posterior tibial nerve stimulation, electrodes (electrocardiogram pads) are placed first over the popliteal fossa to ensure proper stimulus delivery to the nervous system. Electrodes also may be placed over the lower lumbar spine to ensure proper transmission of the signal into the spinal cord itself, but this site is not commonly used because of the proximity of sterile surgical incisions. Cervical spine and scalp recording electrodes are placed in a similar fashion as described previously, although different locations may be used as required by the placement of the surgical incision. More invasive recording methods, such as epidural electrodes, also may be used intraoperatively.

Purported generators for short-latency SSEPs are listed in Table 49-1 and are shown in Figure 49-9.[44,47] Induction

TABLE 49-1 GENERATORS OF SOMATOSENSORY-EVOKED POTENTIALS AFTER MEDIAN NERVE STIMULATION

Peak	Generators
N9 (EP)	Brachial plexus*
N11	Posterior columns or spinal roots
N13/P13	Dorsal column nuclei*
N14, 15	Brainstem or thalamus
N19/P22	Parietal sensory cortex*

*Indicates sites commonly recorded during surgical procedures. All other waveforms indicated are not commonly monitored.

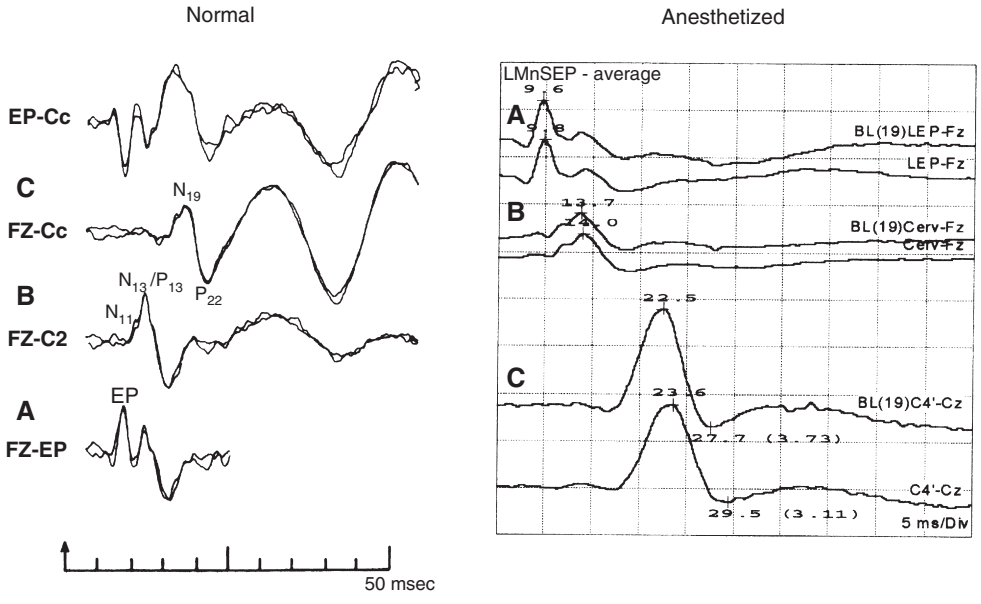


Figure 49-9. Short-latency somatosensory-evoked potentials (SEP) produced by stimulation of the left median nerve (LMn) at the wrist. The ability to identify each of the labeled peaks shown in the tracing from the awake patient is compromised by the anesthetic state and use of different recording electrode locations (*A* to *C*). Corresponding tracings are labeled with the same letter. *(From Chiappa KH, Ropper AH: Evoked potentials in clinical medicine,* N Engl J Med *306:1205, 1982.)*

of anesthesia and use of different recording electrode locations (montage), necessitated by the surgical incision, may significantly alter the appearance of the SSEP. In these cases, attribution of a particular generator to a given wave on the tracing may be quite difficult. During neurologic monitoring, such precision is not needed, and recorded waveforms are compared with tracings obtained at baseline and during earlier portions of the surgical procedure. After lower limb stimulation, absolute latencies are increased because of the greater distance the response to stimulation must travel along the peripheral sensory nerve and spinal cord. Interpeak latencies (see Fig. 49-7) also are evaluated to assess specific conduction times, such as N9 to N14 conduction time, reflecting transmission time from the brachial plexus to brainstem, or N14 to N19 conduction time, reflecting transmission time between the dorsal column nuclei and the primary sensory cortex.[57]

Brainstem Auditory-Evoked Potentials. BAEPs are produced in the diagnostic laboratory by delivering repetitive clicks or tones through headphones. Headphones are not practical for surgical monitoring of neurosurgical procedures, and click stimuli are delivered using foam ear inserts attached to stimulus transducers (Fig. 49-10). Stimulus intensity is usually set at 60 to 70 dB higher than the patient's click-hearing threshold, although, practically speaking, many intraoperative laboratories establish monitoring after induction of anesthesia and instead begin with a stimulus intensity of 90 dB nHL (normal hearing level). The duration of the click is approximately 100 μsec, and the stimulus is given usually 10 to 15 times per second. Clicks are delivered using different "polarities" (i.e., the click may cause initial movement of the tympanic membrane away from the transducer [rarefaction] or toward the transducer [condensation]). Use of these two different methods commonly produces very different waveforms, amplitudes, and latencies in individual patients, and the method that produces the largest reproducible response is chosen. If stimulus artifact is a serious problem, clicks of alternating polarity may be used to decrease the artifact, but the waveforms produced are an average of those produced by either stimulating technique alone and may be more difficult to monitor.

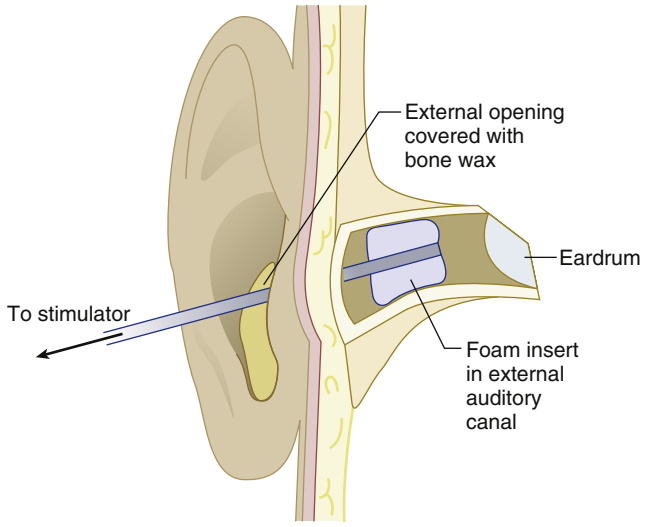


Figure 49-10. Schematic of brainstem auditory-evoked potential–stimulating apparatus. Loud click stimuli are delivered directly to the eardrum through the ear insert.

Rate and intensity of stimulus delivery affect BAEPs.[44,58] Unilateral stimulation is used because responses from the other ear, which may remain normal during surgical procedures, may obscure any abnormal responses from the monitored ear. Recording electrodes are placed on the lobe of the stimulated ear and on the top of the head (vertex).[58] White noise may be delivered to the contralateral ear to prevent bone conduction from stimulation of the monitored ear from producing an evoked response from the contralateral ear. On average, 500 to 2000 repetitions are required because BAEPs recorded from the scalp are far-field potentials and extremely small (often <0.3 μV).[44,58]

Peaks in recordings of BAEPs are labeled I through VII; the purported neural generators for these peaks and the auditory pathway are shown in Figure 49-11. The anatomic auditory pathway would predict that BAEP monitoring would be most useful for surgical procedures in the posterior fossa that risk hearing or structures in the upper medulla, pons, and midbrain. As with other SERs, amplitude, absolute latencies, and interpeak latencies are evaluated to assess integrity of the auditory system, localize the functional defect when it occurs, and assess peripheral and central conduction times. Because waves VI and VII are inconsistent and variable, they are not routinely monitored,[58] and most articles on the use of BAEP for surgical monitoring in the operating room report monitoring waves only up to wave V.[59-61]

Visual-Evoked Potentials. VEPs are recorded after monocular stimulation with recording electrodes over the occipital, parietal, and central scalp.[60] Flash stimulation of the retina using light-emitting diodes embedded in soft plastic goggles through closed eyelids or as needed by contact lenses with built-in light-emitting diodes is provided. VEPs are cortical SERs, which vary with the type of stimulus, part of the retina stimulated, degree of pupil dilation, and patient's attention level.[44] Because some of these factors change commonly and even constantly during the course of every anesthetic regimen, VEPs are highly variable during surgical procedures even when no surgical trespass on the visual system occurs. VEPs are the least commonly used evoked response monitoring technique intraoperatively. However, reproducible intraoperative VEPs have been generated using multiple red light-emitting diodes embedded in a soft silicone disk placed directly on the cornea for stimulating the retina.[62] This technique may allow for further studies that will determine the clinical utility of this modality.

Motor-Evoked Potentials. MEPs are generated most commonly by the application of a transcranial train of electrical stimuli, and responses are recorded at various points along the spinal column, peripheral nerve, and innervated muscle.

Transcranial Motor-Evoked Potentials. Monitoring of the integrity of the motor tracts within the spinal cord is

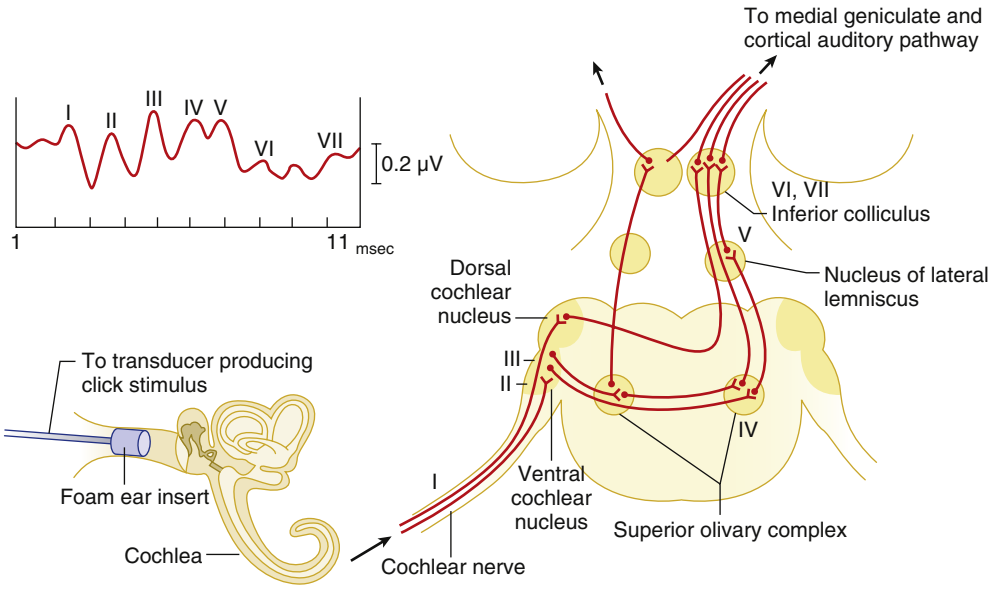


Figure 49-11. Schematic of auditory neural pathway. The brainstem auditory-evoked potential is initiated by stimulation of the cochlea with a broadband click stimulus given through an ear insert in the external auditory canal. Neural generators of the brainstem auditory-evoked potential peaks are shown.

a technique with great potential benefit, and even during the relative short history of MEP monitoring, cases of loss of MEPs with preservation of the SSEP have been reported.[63-68] This technique has potential applications in spinal surgery, in which transmission across the operative field can be assessed, and in aortic surgery, with the potential for impairment of the blood supply to the vulnerable anterior spinal cord. Relative to SER monitoring, MEP monitoring is quite invasive and, in the case of transcranial stimulation, uses much higher stimulus intensity (≥400 V).

Several variants of MEP monitoring exist. The most common method involves transcranial electrical stimulation. During transcranial electrical MEP monitoring, stimulating electrodes (usually small, metallic screw-type electrodes similar to those used in fetal monitoring) are placed into the scalp overlying the motor cortex, and a train of electrical stimuli (usually ≈400 to 500 V) is applied to the scalp. This stimulation definitely activates muscles of mastication, and bilateral bite-blocks must be placed to prevent serious damage to the tongue during stimulation. Alternatively, if the precentral gyrus or motor strip is exposed during the surgical procedure, stimulating electrodes may be placed directly onto the cortex. Because approximately 90% of the transcranial stimulus dissipates across scalp and skull, typical stimulus intensities of direct cortical stimulation are 40 to 50 V.

Both stimulating methods also activate surrounding cortical structures and subcortical white matter pathways (sensory and motor). In fact, transcranial MEPs (tcMEPs) can frequently be recorded from patients with cerebral palsy, despite the disruption of their cortical neuronal architecture. Distal antidromic propagation of the transcranially applied stimulus is blocked by synapses in all the ascending sensory pathways. The stimulus is propagated easily orthodromically through descending motor pathways. The evoked responses may be recorded over the spinal cord, the peripheral nerve, and, most commonly, the muscle itself. To enhance the MEP, these responses may be averaged in the same manner as SERs, but averaging is almost always unnecessary. Activation of the corticospinal tract well below the motor cortex may limit the utility of tcMEP to assess the adequacy of CBF to the motor cortex because activation may be distal to the site of ischemia and may be part of a different vascular bed.

Spinal Motor-Evoked Potentials. Another method of producing the MEP involves electrical stimulation of the spinal cord itself above the area of the spinal cord at risk during the surgical procedure. Responses may be recorded over the distal spinal cord, peripheral nerve, and muscle.[69-71] Responses are recorded distally, usually over the peripheral nerve, and profound surgical muscle relaxation is used to prevent gross movement intraoperatively. This type of MEP is called a neurogenic MEP. Initially, investigators believed that this response, recorded over a peripheral nerve in the lower extremity (typically the tibial nerve in the popliteal fossa), was generated by stimulation of the descending motor tracts, activation of the anterior horn cells, and propagation of the nerve action potential by the peripheral nerve. Multiple clinical trials were conducted using this technique and comparing results of MEP monitoring with the SSEP, with good results.[69-71] These responses also have the advantage that they do not show the same sensitivity to anesthetic drugs that SSEPs do and may be recorded with any anesthetic technique.

Subsequent studies in animals and humans showed that neurogenic MEPs are, at best, mixed responses with a significant component of an antidromically conducted response along the sensory pathway.[72] Stimulation of the dorsal column results in an antidromically conducted recordable signal peripherally because the somesthetic system does not synapse in the dorsal root ganglion, and fibers pass directly from the dorsal column through the cell body in the ganglion into the peripheral nerve. Because of this problem, use of neurogenic MEP monitoring has decreased significantly, replaced by the more invasive transcranial stimulation techniques, which produce responses that are exclusively produced by activation of the motor system.

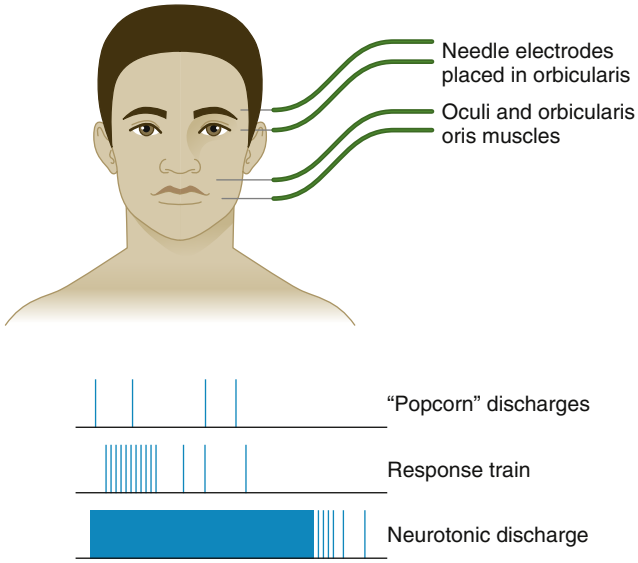


Figure 49-12. Schematic of facial nerve monitoring and typical responses seen during surgical procedures.

Electromyography. Intraoperative monitoring of EMG responses generated by cranial and peripheral motor nerves allows early detection of surgically induced nerve damage and assessment of level of nerve function intraoperatively. In these cases, the ability of a nerve to produce a response in the innervated muscle is used to assess the health of a cranial or peripheral nerve at risk during surgical procedures. Recordings are made from either surface (electrocardiogram or gold cup) electrodes or needle electrodes placed directly in the innervated muscle of interest. Sensitivity of EMG recordings is best, if recordings are made from needles within the muscle itself. Surface electrodes and, to a lesser extent, subdermal needle electrodes may completely miss neurotonic discharges that indicate damage to a nerve.[73] The most experience with this monitoring modality has been obtained during facial nerve monitoring.

EMG monitoring may be either active or passive. During active monitoring, a cranial or peripheral nerve is stimulated electrically, and the evoked EMG (compound muscle action potential) response from the muscle is recorded. Stimulation of the nerve proximal to the operative area or tumor can be used to assess functional integrity of the nerve.[74] Nerve function also may be assessed by noting the intensity of nerve stimulus needed to evoke a muscle response and by the morphology of the compound muscle action potential. Nerve function may be monitored passively during surgical procedures with continuous recording of all generated responses from innervated muscle groups. "Popcorn" EMG discharges are produced by simple, benign contact with the monitored nerve. Response trains are produced with more significant nerve irritation. Neurotonic discharges are produced by significant nerve irritation or damage, or both (Fig. 49-12).[75] When these EMG responses reach a certain voltage threshold, they are usually converted into audible signals that provide immediate feedback to the surgeon and warn of impending nerve damage in real time. Real-time feedback is key because density and frequency of neurotonic discharges may correlate with degree of postoperative nerve dysfunction, as shown by data obtained from patients undergoing resection of acoustic tumors.[74] One caveat of EMG monitoring is that sharp section of a nerve may produce no EMG discharge at all.

Intraoperative monitoring of the motor component of other cranial nerves also has been successfully performed. EMG monitoring of the trigeminal nerve can be accomplished with electrodes placed over or in the temporalis or masseter muscles. Trigeminal nerve motor monitoring has been used during nerve section for tic douloureux to ensure preservation of the motor branch of the trigeminal nerve and in combination with facial nerve monitoring during resection of large posterior fossa lesions.[75] Using recording electrodes placed in or over the trapezius or sternocleidomastoid muscles, the spinal accessory nerve has been successfully monitored during resection of large meningiomas, glomus jugulare tumors, and neck carcinomas.[75] EMG monitoring of the hypoglossal nerve with needle electrodes placed in the tongue has been infrequently used for large posterior fossa lesions and clivus tumors.[75] Although EMG monitoring of the eye muscles can be performed using tiny hook wires for recording, it is rarely used, except at a few centers.

Monitoring of peripheral motor nerves has been performed by placing needle electrodes in or over the muscles innervated by nerves that traverse the operative area and are at risk from the planned surgical procedure. Auditory feedback from EMG monitoring can warn the surgeon of unexpected surgical trespass of the nerve, help locate a nerve within the field (e.g., during untethering of the spinal cord), and localize the level of any conduction block or delay. Because radiculopathies have been reported to occur after surgical procedures of the spine, particularly because of incorrect pedicle screw placement, EMG monitoring of peripheral nerves has been used in patients undergoing spine operations, to decrease the risk of nerve root injury during the procedure.[75] During pedicle screw placement, the surgeon can stimulate the screw directly with a small amount of current. If EMG responses are produced with only a small amount of current, the screw has likely been placed outside the bony pedicle.

CLINICAL APPLICATIONS OF NEUROLOGIC MONITORING

NEUROVASCULAR SURGERY

See also Chapters 69 and 70.

Extracranial Neurovascular Surgery: Carotid Vascular Surgery (Monitors: Electroencephalogram, Somatosensory-Evoked Potentials, Transcranial Doppler, Cerebral Oximetry)

Electroencephalogram. The use of the EEG as a monitor of the adequacy of CBF during carotid endarterectomy has been established for many years. In a large series of patients undergoing carotid endarterectomy at the Mayo

Clinic in Rochester, Minn.[36] the EEG was compared with regional CBF by using the ^{133}Xe washout method. This study validated the EEG as an indicator of the adequacy of regional CBF.

Normal CBF in gray and white matter averages 50 mL/100 g/minute. With most anesthetic techniques, the EEG begins to become abnormal when CBF decreases to 20 mL/100 g/minute. The threshold for EEG changes apparently is much lower (8 to 10 mL/100 g/minute), however, when isoflurane is used.[76] Cellular survival is not threatened until CBF decreases to 12 mL/100 g/minute (lower with isoflurane). The difference in blood flow between when the EEG becomes abnormal and the blood flow at which cellular damage begins to occur provides a rational basis for monitoring the EEG during carotid surgical procedures. In many cases, prompt detection of EEG changes may allow intervention (e.g., shunting, increasing cerebral perfusion pressure) to restore CBF before onset of permanent neurologic damage. Standard hemodynamic monitoring provides no direct information about the adequacy of CBF. Blood pressure is not a specific indicator of the adequacy of CBF. Significant hypotension is not predictably associated with EEG evidence of cerebral ischemia. Severe anemia and decreases in oxygen saturation also decrease oxygen delivery. EEG activity becomes abnormal when increased blood flow cannot compensate for reduced arterial oxygen content.

Serious intraoperative decrease in cerebral oxygen supply may result from surgical factors (e.g., carotid cross-clamping) that are usually beyond the anesthesiologist's control and from factors that the anesthesiologist can correct. Reduction in CBF produced by hyperventilation, hypotension, or temporary occlusion of major blood vessels may be corrected by reducing ventilation, by restoring normal arterial blood pressure, or in the case of temporary vessel occlusion, by even increasing arterial blood pressure to higher than the normal preanesthetic value. Because the EEG may readily detect cerebral ischemia, continuous EEG monitoring can evaluate the effectiveness of therapy instituted to correct ischemia.

If monitoring of the EEG could be proved scientifically to reduce the incidence of stroke during carotid vascular surgical procedures, EEG monitoring would be established as a standard of care. Such definitive data do not exist because the incidence of stroke is too low to justify a large enough study to achieve statistical significance. So is universal use of EEG monitoring during carotid surgical procedures justified? In a large series of patients undergoing carotid endarterectomy with selective shunting who were monitored with 16-channel unprocessed EEG, no patient awakened with a new neurologic deficit that was not predicted by EEG.[77] Transient, correctable EEG changes were not associated with stroke. Persistent changes were associated with stroke. Unfortunately, this study had no comparison group (i.e., to determine the rate of stroke without EEG monitoring).

In the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial, retrospective comparison of patients receiving EEG monitoring and patients not receiving EEG monitoring failed to show a significant difference in outcome.[78,79] Because the EEG detects reductions in CBF that would not otherwise be apparent in unmonitored patients and permits intervention that may correct the problem (usually placing a shunt or increasing blood pressure), EEG monitoring should logically be useful in reducing the incidence of stroke when selective shunting is used. Data available from studies at this time bring us no closer to resolving this question, however, than we were in the 1980s. Advocates of monitoring and individuals who believe monitoring is of no value can cite multiple studies supporting each viewpoint.

Even more difficult to prove is that EEG monitoring is useful when all patients undergo shunting during carotid clamping. Such monitoring has detected correctable shunt malfunction, and investigators have described hypotension-related EEG changes in patients with critical stenoses and poor collateral circulation.[80] Advocates of selective shunting based on EEG (or other monitoring) criteria claim that inserting a shunt unnecessarily through a region of diseased vessel would surely increase embolization. A multicenter study of 1495 carotid endarterectomies provides some evidence that shunting in patients without evidence of decreased cerebral perfusion increases the incidence of stroke more than sixfold.[81] Although this study and other more recent studies advocated that selective shunting using some form of monitoring of the adequacy of CBF should improve the perioperative stroke rate,[82-84] an analysis by the Cochrane Stroke Group failed to show sufficient evidence to advocate for routine shunting, selective shunting, or even no shunting at all.[85] In addition, this review failed to demonstrate that any type of monitoring for cerebral ischemia was superior to another. Until compelling studies addressing this issue are done, it is unlikely that EEG monitoring or other forms of CNS monitoring during carotid vascular surgical procedures will become standard practice.

Processed EEG also has been used during carotid vascular surgical procedures. Two issues affect the efficacy and reliability of processed EEG as a monitor for cerebral ischemia. First, what is the minimum number of channels (or areas of the brain) to be monitored? The 16-channel unprocessed EEG is a reliable and sensitive monitor for intraoperative cerebral ischemia during carotid endarterectomy. In a series of more than 2000 patients monitored with 16-channel EEG at the Mayo Clinic, were no false-negative EEGs were found[77]; in other words, no patient had undetected intraoperative cerebral injury. However, in many operating rooms where carotid surgical procedures are performed, 16-channel EEG monitored by a dedicated technician is unavailable. Processed EEG using less than 16 channels is used much more commonly. Clinical experience and clinical investigations suggest that 4 channels (2 per side) are the minimum number of channels for adequate sensitivity and specificity.[37] When a limited number of channels were compared with 16-channel EEG monitoring, 100% sensitivity and specificity were obtained using 2 channels per hemisphere, provided those channels monitored the middle cerebral artery territory. These results were obtained with a frontoparietal channel combined with a frontotemporal channel.[37]

The second issue is the experience level of the observer monitoring the processed EEG. Is a dedicated,

experienced technician or electroencephalographer needed? In a study addressing this question, the 16-channel unprocessed EEG monitored by a dedicated technician was compared with a processed EEG reviewed by 3 anesthesiologists of differing levels of experience with processed EEG.[38] These anesthesiologists interpreted the tracings without knowledge of the case. They were presented only with the written trace with an indication of the point at which the carotid artery was clamped. In these cases, the most important interpretation pitfall to avoid is the "false-negative" pattern. If the clinician interprets the EEG as showing adequate CBF when in fact it does not, the surgeon may fail to place a shunt in an ischemic patient. A false-positive result may be less of a problem because that patient is not ischemic but is given a shunt anyway. In this case, only the risk of emboli from the "unnecessary" shunt is incurred. The positive predictive value of the anesthesiologist correctly interpreting the trace as unchanged after clamping was 91% to 98%; this finding indicates that the device can be used by novice interpreters with fair accuracy to determine the presence of cerebral ischemia at the time of carotid occlusion. In this study, the review by the anesthesiologist was not done during the course of the procedure, but rather "off line," and it did not address the issue of whether an anesthesiologist providing intraoperative anesthetic management of the patient can provide adequate monitoring of the processed EEG simultaneously.

EEG monitoring has limitations. Despite the data available from the Mayo Clinic, immediately evident postoperative strokes have been reported in patients without any evidence of EEG changes intraoperatively. In our experience, such strokes result from emboli through the lenticulostriate arteries to subcortical structures that do not generate or affect the EEG but are critically involved in the descending motor pathway. Overall, such events are rare.

Should the patient undergoing carotid endarterectomy have EEG monitoring? That question cannot be answered based on any available data. EEG monitoring provides information about CBF that would not otherwise be available. The clinician has an opportunity to intervene to increase inadequate blood flow when it occurs. Anecdotally, many clinicians have found such monitoring useful and use it routinely. Population studies do not support routine use, and it is up to the clinician to decide whether to use it.

Somatosensory-Evoked Potentials. SSEP monitoring can gauge the adequacy of CBF to the cerebral cortex and subcortical pathways during carotid vascular surgical procedures.[56,86,87] SSEPs have been found in the laboratory to have a similar but slightly lower threshold for failure compared with the EEG. SSEPs are generally intact until the cortical blood flow decreases to less than 15 mL/100 g/minute.[54] A meta-analysis of shunting during carotid vascular operations concluded that selective shunting based on SSEP monitoring results in a perioperative stroke rate similar to when EEG monitoring is used as the basis for shunting.[88] However, logic also would suggest that changes in SSEP are unlikely, for example, with ischemia involving the anterior portions of either the frontal or temporal lobe, which could readily be detected by an appropriately placed EEG electrode. Even less outcome evidence supports the use of SSEPs than the EEG during carotid surgical procedures, but we and others have found SSEPs to be useful as a simultaneous monitor with EEG to detect subcortical ischemia.

Transcranial Doppler Ultrasound. TCD monitoring during carotid vascular surgical procedures is based on measurement of two primary parameters—blood flow velocity in major conducting arteries leading to the cerebral cortex (most commonly middle cerebral artery) and the number of emboli detected in the same artery. The hypothesis justifying the use of this monitoring during carotid vascular surgical procedures has two components: blood flow velocity correlates with CBF, and increasing numbers of emboli increase the likelihood of emboli-related cerebral ischemia or stroke. The first component has not been well tested and shows variable results. An early study in a small group of patients undergoing carotid operations did not show good correlation between CBF and blood flow velocity.[89] Subsequent studies in patients with varying intracranial diseases yielded mixed results.[90-93]

The correlation between CBF and TCD-measured blood flow velocity remains good over time only when the artery being insonated does not change diameter and when cortical blood flow in the distribution of the measured artery does not have significant collateral sources of blood flow. The relationship between emboli count and stroke is better established with multiple studies conducted in the preoperative, intraoperative, and postoperative periods; these studies indicate that higher emboli counts are associated with higher stroke risk and warrant intervention.[94-100] TCD ultrasound is the only monitor able to detect dangerous hyperemia, also known as normal perfusion pressure breakthrough, after removal of severe, flow-limiting carotid stenosis. Typically, a sustained doubling of flow velocity after unclamping should prompt the anesthesiologist to consider lowering the blood pressure.

Intraoperative TCD monitoring is not often used. Good TCD signals cannot be obtained in many individuals who could benefit from monitoring. In addition, TCD probe motion during surgical procedures causes major problems with loss of signal or with angle of insonance–induced changes in the relationship between blood flow velocity and blood flow. Nonetheless, multiple series of carotid endarterectomies with TCD monitoring have had good success, with a reported critical blood flow velocity reduction of approximately 50% as indicative of inadequate CBF requiring intervention (shunt or increased arterial blood pressure, or both).[94-100] Although outcome data are lacking, emboli count and risk of stroke suggest that if technical issues with probe attachment to the patient can be overcome, TCD ultrasound may be useful as a predictor of impending stroke in the entire perioperative period.

Cerebral Oximetry (Near-Infrared Spectroscopy). Near-infrared spectroscopy (NIRS) is an attractive monitor because of its ease of application and lack of training required for interpretation. The hypothesis governing

its use is very simple: As oxygen delivery to the brain decreases, oxygen extraction from arterial blood increases, and the oxygen saturation in cerebral venous blood decreases. NIRS applied to cerebral monitoring measures the oxygen saturation in the cerebral venous blood in the prefrontal cortex and promptly detects increases in oxygen extraction resulting from decreased oxygen delivery. The use of cerebral oximetry during neurovascular surgical procedures is well documented, but several major questions surrounding use of NIRS during carotid surgical procedures remain unanswered.

What degree of decrease in oxygen saturation can be tolerated before intervention is necessary? Because most interventions involve some risk (e.g., shunt → emboli, increased BP → myocardial ischemia), the answer to this question is important; yet the answer does not exist. In awake patients, the saturation value at which any patient develops symptoms varies.[101,102] An absolute value that required shunting could not be determined. Another study showed that cerebral oxygen saturation decreased before the EEG developed changes; the investigators concluded that NIRS monitoring of the brain should be used during carotid surgery.[103] This finding should not be surprising, however, because function of the brain (in this case, electrical function) does not fail until increased extraction of oxygen no longer meets metabolic demands for the tissue. If metabolic demands are being met by increased extraction, it is unclear that intervention is needed.

Finally, a study by Friedell and colleagues compared NIRS with EEG and SSEP monitoring during carotid surgical procedures.[104] In 24 of 323 patients, significant differences were observed between NIRS and monitors of electrical function. Seventeen patients showed no changes in electrical function with significant decreases in cerebral oxygen saturation. In seven patients, no change in cerebral oxygen saturation occurred despite significant change in the EEG and SSEP. The reason for the latter finding may be that NIRS and EEG or SSEP monitor different vascular territories. These data, in combination with the data from studies in awake patients, suggest that use of NIRS alone during carotid vascular surgical procedures may be inappropriate. In addition, an aggregate of studies and case reports available in the literature suggests that no clear cutoff value of regional oxygen saturation that would mandate the use of shunting or increasing the cerebral perfusion pressure exists.

Intracranial Neurovascular Surgery (Monitors: Somatosensory-Evoked Potentials, Motor-Evoked Potentials)

Somatosensory-Evoked Potentials. SSEPs have been extensively studied during surgical repair of cerebral aneurysms. During these procedures, the surgical incision and brain retraction preclude placement of scalp or brain surface electrodes that could detect cerebral ischemia in at-risk cortex. Recording electrodes placed on the surface of the brain have been used successfully, but they are commonly considered "in the way" by neurosurgeons. Scalp electrodes may be placed easily for SSEP monitoring, although the recording montage is frequently not the same as that used in an awake patient.

For aneurysms involving the anterior cerebral circulation, SSEP monitoring has an excellent, but not perfect, record for predicting postoperative neurologic function. Most patients without surgically induced SSEP changes during the surgical procedure awaken with an unchanged neurologic examination. Patients with significant SSEP changes that do not revert to normal awaken with a new neurologic deficit. Patients with SSEP changes that return to normal after a significant intraoperative change may show at least a transient postoperative deficit, with the severity and duration increasing as the duration of the SSEP change increases. Many authors have reported significant utility of SSEP monitoring in detecting improper aneurysm clip placement (see Fig. 49-8), and in guiding intraoperative arterial blood pressure management, particularly in patients already showing, or at significant risk for, vasospasm after subarachnoid hemorrhage.[55,105-110] The same success cannot be reported, however, for posterior circulation aneurysms. In these cases, many areas of the cortex and subcortical structures are at risk for damage that cannot be monitored by somatosensory pathway function. A significant false-negative monitoring pattern exists for these patients, but changes can still be detected when a surgical insult is sufficiently severe to involve large portions of the brain.[111-114]

Some centers have begun monitoring tcMEPs in addition to SSEPs during surgical clipping of aneurysms. Inclusion of tcMEPs is motivated by the desire to evaluate the integrity of subcortical pathways in the internal capsule more effectively. Anatomically, the motor pathway runs anterior to the sensory pathway in the internal capsule and is at greater risk if the anterior choroidal artery or lenticulostriate perforator vessels are injured during dissection and clip placement. Two concerns must be addressed, if tcMEP is to be incorporated successfully in these cases. First, motion caused by stimulation needs to be minimized, to avoid interfering with the surgical procedure. Second, and more important, stimulus parameters need to be set to limit deep current spread that would activate the corticospinal tract distal to the internal capsule and obscure ischemia of the proximal pathway. The use of longer stimulus trains at intensities close to the motor threshold addresses both concerns.

Supratentorial Intracranial Nonvascular Surgery (Monitors: Awake Patient, Electroencephalogram, Somatosensory-Evoked Potentials)

During supratentorial procedures, neurologic monitoring can contribute to the precise localization of structures that need to be preserved or conversely supplement the anatomic information provided by imaging with functional data. Three techniques fall under this category: (1) awake craniotomy can be a suitable approach for the resection of tumors and seizure foci; (2) intraoperative electrocorticography (i.e., the recording from strategically placed subdural electrodes) is used to target more closely the resection of seizure foci; (3) localization of the central sulcus and, by extension, the precentral motor cortex is

sometimes helpful, if these structures have been displaced by a tumor.

The most comprehensive approach to the problem of functional localization of brain structures that need to be preserved to achieve a good outcome is to perform entire segments of supratentorial craniotomy in an awake patient who is undergoing repeated neurologic examinations targeted to assess the eloquent area at risk. Such procedures are typically divided into exposure, mapping, and resection phases and can be done with the patient entirely awake or awake only during periods when the neurologic examination must be assessed.[115] Common to all these approaches is the need for meticulous locoregional anesthesia of the scalp at the craniotomy site and the pin sites of the head holder.[116] A second requirement is a patient who is well informed about the awake parts of the procedure and is willing and able to cooperate. Dexmedetomidine, propofol, and remifentanil are the drugs most frequently incorporated into the anesthetic regimens for awake craniotomy.[117] Complications of awake craniotomy include nausea and vomiting, respiratory problems, and "tight" brain, but these complications are typically mild and occur in less than 10% of cases in experienced centers. Seizures triggered by cortical stimulation can be stopped by the application of iced saline to the exposed cortex or a small amount of barbiturate or propofol.

Seizure Focus Localization Surgery

Patients with epilepsy who have seizures that generalize from an anatomically distinct focus may benefit greatly from surgical resection of that seizure focus.[118] Precise localization of a seizure focus is important for achieving the therapeutic objective of seizure control and for minimizing complications from the resection. With sensitive magnetic resonance imaging techniques, neuronavigation, and recordings of typical seizure activity in the awake patient after placement of subdural and depth electrodes, the anatomic location and the appropriate extent of the resection frequently can be determined preoperatively.[119] These developments have diminished the role of intraoperative recordings from the epileptogenic zone with electrocorticography.[120]

Neurologic monitoring during such a resection is performed using two different techniques. First, activity of the seizure focus can be recorded through electrocorticography. Second, eloquent brain areas next to the seizure focus can be monitored during awake craniotomy as described in the previous section. Electrocorticography is done by placing a grid of subdural electrodes onto the exposed brain surface and recording spontaneous electrical activity. Electrocorticography is constrained by several limitations. The time for such recordings is limited to a few minutes; recordings are limited to interictal discharges, which may not correlate with the epileptogenic focus; and recordings need to be obtained from a brain that is under the effects of general anesthetic drugs, which alter the EEG.

To provide good conditions during the recording, the level of anesthesia is lightened (e.g., by use of a strict nitrousoxide-narcotic technique or low concentrations of volatile anesthetic drugs). Provocative techniques, such as hyperventilation or administration of a small dose of methohexital, may be useful to activate the seizure focus. Intraoperative seizure mapping requires the involvement of an expert electroencephalographer familiar with this technique.

Motor Strip Localization

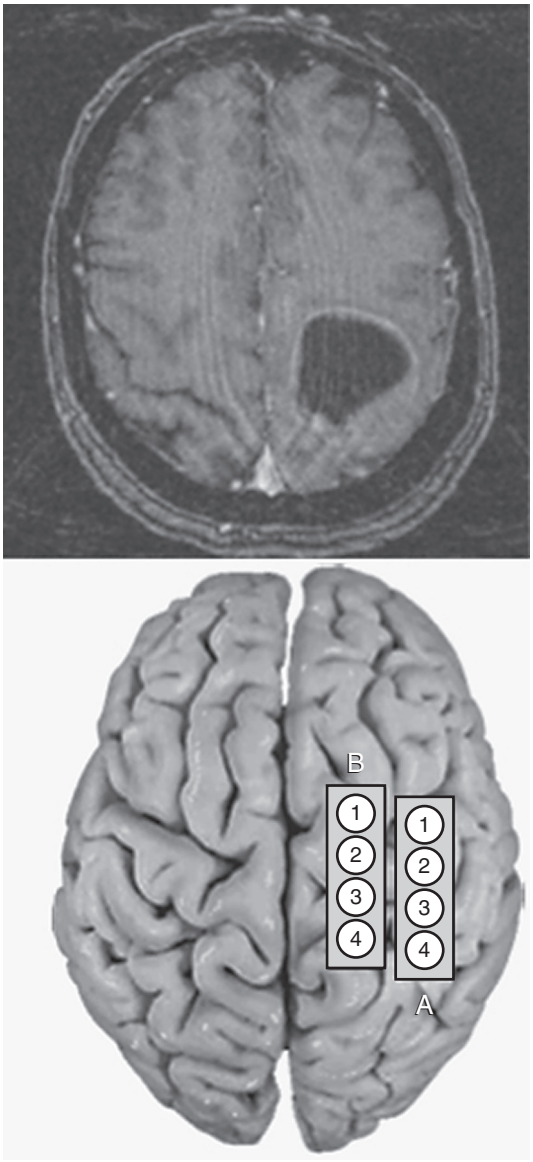
Electrophysiologic monitoring of the somatosensory system in anesthetized patients can provide a simple anatomic guide to the location of the rolandic fissure, which separates the parietal primary sensory and frontal primary motor cortex. The fissure is located by recording cortical SSEPs from a subdural strip electrode that is placed perpendicular to the presumed location of the fissure. The exact location of the fissure is characterized by a reversal in the polarity of the primary cortical response between the electrodes straddling the fissure, as illustrated in the clinical example in Figure 49-13. Subsequent placement of the electrode strip onto the primary motor area of the precentral gyrus allows subsequent monitoring of the corticospinal tract through direct cortical stimulation.

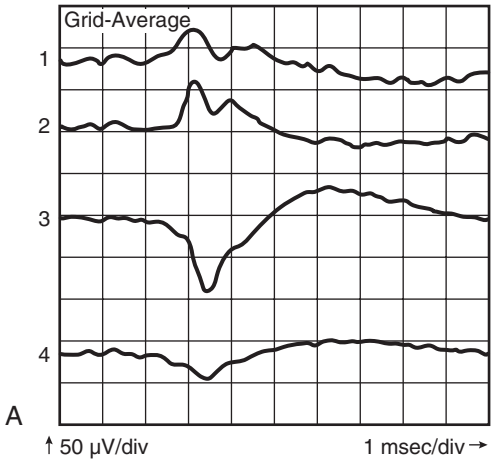
POSTERIOR FOSSA SURGERY (MONITORS: BRAINSTEM AUDITORY-EVOKED POTENTIALS, CRANIAL NERVE MONITORING, SOMATOSENSORY-EVOKED POTENTIALS, MOTOR-EVOKED POTENTIALS)

Besides the cerebellum, the posterior fossa contains within the narrow space of the brainstem many crucial neural structures, including the following: the ascending and descending sensorimotor pathways; cranial nerve nuclei; cardiorespiratory centers; the reticular activating system; and the neural networks that underlie crucial protective reflexes, such as eye blink, swallowing, gag, and cough. Surgical procedures of the posterior fossa are not undertaken lightly, and even small injuries can leave significant neurologic deficits. Although some of these neural structures, such as the sensory or auditory pathway, can be monitored consistently, intraoperative integrity of other neural structures is frequently only inferred from the well-being of neighboring structures amenable to monitoring.

Microvascular Decompression of Cranial Nerves V, VII, and IX

Microvascular decompression is performed most frequently for trigeminal neuralgia (cranial nerve V) in patients who have acceptable medical risks for posterior fossa craniotomy. More rarely, the same approach is used to treat hemifacial spasm or neurovascular compromise of lower cranial nerves. The surgical procedure entails dissecting along the intracranial portion of the nerve, identifying offending blood vessels that encroach on the nerve, and placing an insulating Teflon pad between vessel and nerve. The operation risks ischemic damage to perforating vessels coming off the offending arteries and cerebellar retraction–related damage to cranial nerves. The facial and vestibulocochlear nerves are at particular risk for stretch-induced injury caused by medial retraction of the cerebellum. Retraction-induced stretch prolongs the interpeak latency between peaks I and V of the BAEP





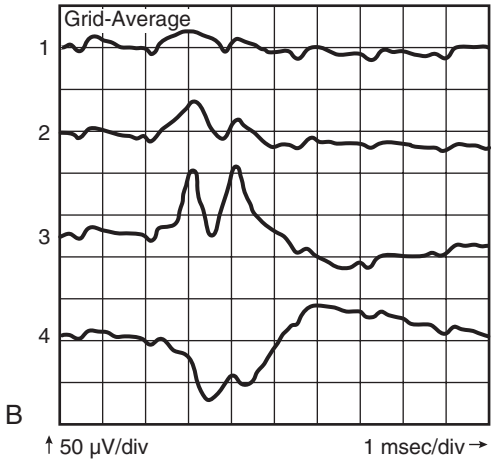


Figure 49-13. Intraoperative localization of the rolandic fissure separating the primary sensory cortex and motor cortex. The clinical example is from a patient with a large parietal tumor shown in the scan. Two of the recordings made from a four-contact subdural electrode strip are shown. The relative positions of the strip electrode are labeled *B* and *A*. In recording *A,* the primary cortical response from the electrodes anterior to the rolandic fissure shows an upward deflection, whereas the response from electrodes posterior to the fissure shows a downward deflection. Moving the strip electrode anteriorly (recording *B*) moves this "phase reversal" between electrodes 3 and 4.

waveform and ultimately leads to complete loss of all waves beyond wave I (Fig. 49-14). Failure to release retraction in a timely manner results in postoperative hearing loss. Such monitoring increases the chances for preserved hearing after microvascular decompression.[121-125]

During microvascular decompression of the facial nerve for hemifacial spasm, more recent developments using EMG monitoring have enabled some centers to document the adequacy of nerve decompression more clearly and lessen the likelihood of persistence or recurrence of hemifacial spasm postoperatively. This newer technique monitors the so-called lateral spread response (LSR) of the facial nerve. A peripheral branch of the facial nerve is stimulated. In the normal patient, this stimulation would not result in a recordable EMG response in a muscle innervated by a different branch of the facial nerve. In patients with hemifacial spasm, EMG responses can be recorded in muscles innervated by a different branch of the facial nerve (LSR) indicating abnormal crossover of electrical activity. Decompression of the facial nerve has been shown in multiple studies to result in a great decrease or elimination of this LSR, and studies have indicated that elimination of the LSR is highly predictive of immediate postoperative relief of hemifacial spasm.[126]

Vestibular Nerve Schwannoma

Vestibular nerve schwannomas are the most common tumors located in the cerebellopontine angle. Because of the common origin of the cochlear component of cranial nerve VIII and the essentially identical intracranial trajectory of the facial nerve, hearing loss and facial nerve palsy are concerns during surgical resection of these tumors.

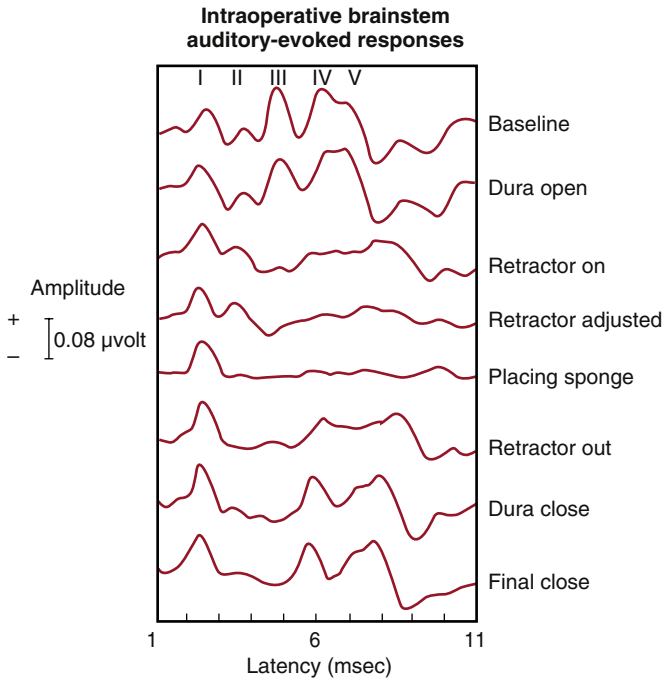


Figure 49-14. Intraoperative monitoring of brainstem auditory-evoked responses during microvascular decompression. The baseline recording shows the typical five waves of the brainstem auditory-evoked potential response. Intraoperative events are designated to the right of each trace. Placement of the retractor causes a severe increase in latency of wave V even after adjustment of retraction. During placement of the sponge, all waves subsequent to wave I, which originates in the inner ear, are nearly completely lost. Removal of the retractor causes brainstem auditory-evoked potentials to revert toward baseline.

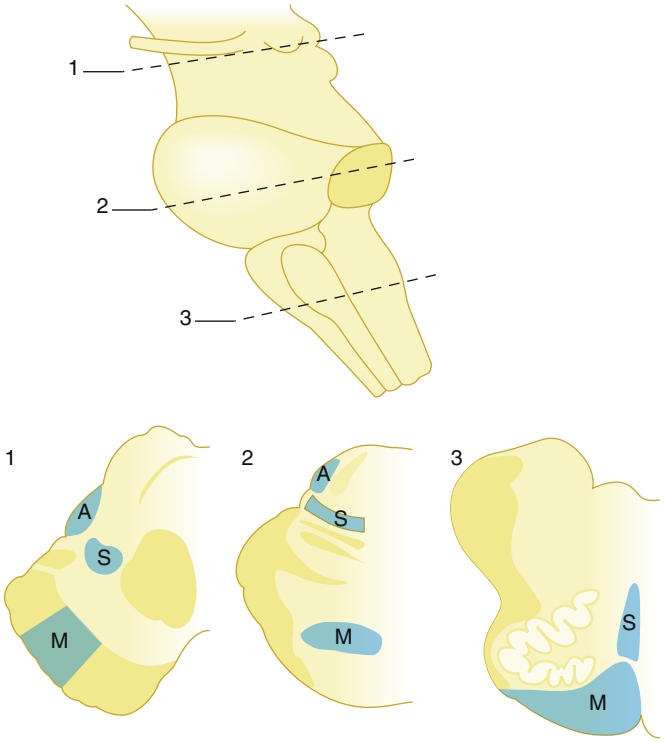


Figure 49-15. Monitoring of the brainstem with evoked potentials. Evoked potentials monitor specific tracts that encompass defined areas in the brainstem. This is shown in three transverse sections approximately at the levels indicated in the drawings. The areas directly monitored by a given modality are indicated in *blue* and are labeled M (motor), S (somatosensory), and A (auditory). Conclusions about the well-being of the remainder of the brainstem are made by inference from the monitored areas.

Size and preoperative auditory function are the best predictors of postoperative hearing.[127] For tumors up to approximately 2 to 3 cm in size, monitoring of BAEPs can increase the chances of preserving hearing.[128] In addition to BAEPs, the facial nerve is monitored through spontaneous and stimulated EMG. Prospective trials have shown a higher percentage of patients with a functional facial nerve 1 year postoperatively when facial nerve monitoring was used as previously described. Tonic discharges warn of impending damage caused by stretch or heat (Bovie procedures). Sharp section of the nerve may elicit no discharge, and neuromuscular blockade may eliminate the ability to monitor. If the course of the nerve is displaced by the tumor, the surgeon can map its course with a handheld stimulator and real-time auditory feedback.

Other Posterior Fossa Neoplasms

Monitoring for operations on other neoplasms located in the brainstem typically is individualized to each particular case or to the particular surgical approach. EMG may be recorded not only from the territory of the facial nerve, but also from the tongue to monitor the hypoglossal nerve, and from the glottis through electrodes embedded into a specialized endotracheal tube to monitor the vagus nerve. Such a setup can be used to map the floor of the fourth ventricle functionally, if it is distorted by a tumor.[129] Such monitoring may be insufficient to preserve vital reflexes because only the efferent limb of these reflexes is monitored by recording EMG from innervated muscle.

Use of neurologic monitoring for brainstem ischemia, although performed in some centers, is not well documented or supported by clinical studies. Global well-being of the brainstem may be monitored by combining multiple modalities of evoked potentials, such as BAEPs, SSEPs, and MEPs. Each modality monitors a function whose integrity would be considered important in its own right for the functional outcome of an individual patient. As illustrated in Figure 49-15, the cross-section monitored by combining all these modalities still leaves out crucial areas. Given that perfusion occurs through perforating vessels, it is easy to see that monitoring may indicate that all is well or, more likely, that a therapeutic intervention was helpful in restoring function when clinically the patient is still left with a significant deficit. This occurrence invalidates neither monitoring nor the therapeutic intervention, but it indicates only that the monitored pathway was not located in an area at risk from the surgical procedure. Because of such obligatory "false-negatives" results, few studies address the utility of such monitoring. Given that each individual monitoring modality comes with its own constraints, such an approach typically requires a dedicated neurophysiologist for interpretation and troubleshooting.

SPINAL COLUMN AND SPINAL CORD SURGERY (MONITORS: SOMATOSENSORY-EVOKED POTENTIALS, MOTOR-EVOKED POTENTIALS, ELECTROMYOGRAM)

Intraoperative monitoring of SSEPs has been used most extensively in patients undergoing surgical procedures involving the spinal column or spinal cord, or both. Extensive experience has been gained in patients who have decompressive laminectomies or who have undergone corrective procedures for scoliosis. Intraoperative changes in SSEPs have been noted in 2.5% to 65% of patients undergoing surgical procedures on the spine or spinal cord.[130-133] When these changes are promptly reversed either spontaneously or with interventions by the surgeon or anesthesiologist (e.g., lessening the degree of spine straightening in scoliosis repair or increasing arterial blood pressure), the patients most often have preserved neurologic function postoperatively. When these changes persisted, however, the patients most often awakened with worsened neurologic function.

False-negative (rare) and false-positive (common) results can occur with SSEP monitoring during spine operations. Patients with intact SSEPs throughout the procedure have awakened with a new significant neurologic deficit, but the total reported incidence of this finding is far less than 1% of all cases monitored. Patients with no postoperative neurologic deficit commonly experience significant changes in intraoperative SSEPs.[133] This monitoring pattern is most commonly caused by failure to control for other, nonpathologic factors that may alter the SSEPs. Overall, the reliability of properly performed SSEP monitoring to predict the postoperative sensory and motor function has been reported to be excellent.[44,132,134] Motor tracts are not directly monitored by SSEPs, however. In addition, the blood supply to the dorsal columns of the spinal cord, which carries all the upper extremity SSEPs and at least a portion of the lower extremity SSEPs, is derived primarily from the posterior spinal arteries. The blood supply to motor tracts and neurons is derived primarily from the anterior spinal artery. A significant motor deficit can develop postoperatively in patients with intact SSEPs throughout the operative course. Such events have been reported.[135,136]

In operations on the spinal column and after acute spinal cord injury, the sensory and motor changes generally correlate well[44]; however, in patients with neurologic dysfunction after thoracic aortic vascular surgical procedures, frequently posterior spinal cord function (proprioception, vibration, light touch) is left intact when motor and other sensory functions (pain, temperature) are impaired. This result occurred in 32% of patients with neurologic injury after aortic aneurysm repair in one series,[137] with similar results in many other series. Intraoperative SSEP monitoring in these patients carries a significant risk for false-negative results, and such monitoring therefore is not widely used.

MEP monitoring during surgical procedures on the spine or its blood supply is very useful. MEPs can decrease without changes in SSEPs. The combined use of SSEP monitoring and MEP monitoring may eliminate false-negative monitoring patterns during spine operations.[138-143] In the case of monitoring paraplegia risk during surgical repair of thoracoabdominal aneurysms, the literature shows improving support for the use of MEP monitoring. Two earlier studies suggested that MEPs may not be as effective as hoped. The first study recorded MEPs from the canine lumbar spinal cord that were produced by transcranial electrical stimulation.[137] Elmore and associates found that these spinally recorded potentials did not accurately predict postoperative motor function.[144] In a second study, Reuter and colleagues recorded MEPs at the spinal cord and the peripheral nerve level that were produced by transcranial electrical stimulation in dogs.[145] These investigators also found that the spinally recorded responses were inaccurate in predicting motor function postoperatively. The peripheral nerve responses disappeared in all animals and were not present 24 hours later regardless of whether the animal could move its lower extremities.

These studies suggest that the spinally recorded MEP likely represents a response generated by the descending corticospinal tract. This white matter pathway is resistant to ischemia compared with the more metabolically active anterior horn cells (gray matter). Recovery of this white matter–generated MEP response could occur after reperfusion of the spinal cord, whereas the gray matter may not recover. Responses recorded from the peripheral nerve would reflect postsynaptic anterior horn cell function, but lower extremity ischemia occurring after aortic cross-clamping may preclude recording this or the response from muscles during surgical procedures.

MEP monitoring during aortic vascular surgical procedures has correctly detected inadequate spinal cord blood flow and improved operative outcome. The technique has proven useful, particularly when operative strategies such as reimplantation of crucial intercostal vessels based on results of MEP monitoring, alteration of spinal cord perfusion pressure (blood pressure increase or cerebrospinal fluid drainage, or both), spinal cord cooling, and other methods are used.[146] Although this monitoring technique holds promise in aortic surgery, its validity has not been verified.

PERIPHERAL NERVE SURGERY (MONITORS: ELECTROMYOGRAM, NERVE ACTION POTENTIAL)

Neurologic monitoring for surgical procedures involving peripheral nerves can be done in two different settings. In the first, the peripheral nerve is intact but threatened by the operation. Examples include an intrinsic nerve tumor, such as a schwannoma, or an extensive soft tissue tumor, particularly if it displaces the normal anatomic course of a nerve. In the second setting there is a preexisting injury involving damage to a nerve and the objective is to explore the site of injury. Monitoring of spontaneous and stimulated muscle responses from muscle groups innervated by the nerve in question can be used to guide the resection. Spontaneous EMG discharges can be generated by stretch or compression of the nerve, by local heating from electrocautery, or from ischemia. Two caveats apply to the monitoring of spontaneous EMG: (1) the neuromuscular junction is part of the monitored pathway, and muscle relaxation decreases or abolishes the sensitivity of monitoring in a dose-dependent manner; and (2) sharp

section of the nerve may not result in a noticeable discharge. To search out the course of the nerve intraoperatively, the surgeon may stimulate the wound area with a handheld probe and listen for stimulated EMG or palpate for muscle contraction. The underlying concept should be familiar to anesthesiologists from the use of nerve stimulators in regional anesthesia.

A variation of this technique of monitoring that is in widespread use, because it is conceptually simple, is monitoring of pedicle screw placement during spinal instrumentation with the aim of avoiding nerve root injuries resulting from malpositioned pedicle screws.[147,148] The aim is to avoid malpositioned screws that weaken the construct or cause postoperative radicular pain. Typically, the pilot hole or, less desirable, the shank of an implanted pedicle screw is stimulated repetitively with increasing current to determine the threshold for eliciting a dermatomal compound muscle potential. The interpretation of responses is complicated by the anatomic relationship between pedicles and nerve roots that depends on the level of the spinal cord because the spinal cord is shorter than the bony spinal column. Thus, a medially misplaced screw in the lumbar region will come to lie next to a nerve root, whereas in the thoracic spine, a medial misplacement puts the screw next to the corticospinal tract, which cannot be activated by single stimuli. Because thresholds vary in the cervical, thoracic, and lumbar spine, as well as between healthy and diseased nerve roots, this technique has limitations but is widely thought to be useful.[149]

In patients with prolonged weakness and sensory loss after nerve injury who undergo nerve exploration monitoring, peripheral nerve activity is very useful.[150] The aim is to determine whether nerve reconstruction may improve outcome. The area of the lesion is determined by preoperative nerve conduction studies. Intraoperatively, the nerve is first stimulated proximal to the lesion, and a recording of the nerve action potential is made directly from the nerve distal to the lesion, as illustrated in Figure 49-16. If nerve conduction occurs across the lesion, lysis of scar is performed, and the incision is closed. Natural recovery by means of axonal regrowth produces the best outcome. If conduction does not occur across the lesion, resection of the damaged nerve and nerve cable grafting are performed.[151-153]

NONNEUROLOGIC SURGERY THAT RISKS DAMAGE TO THE CENTRAL NERVOUS SYSTEM (MONITORS: ELECTROENCEPHALOGRAM, TRANSCRANIAL DOPPLER, CEREBRAL OXIMETRY, JUGULAR VENOUS OXYGEN SATURATION)

Cardiopulmonary Bypass

See also Chapter 67.

Electroencephalogram. In humans, changes that occur with the institution of CPB may alter the EEG by multiple different mechanisms. Plasma and brain levels of anesthetic drugs may be altered by CPB or by anesthetics commonly given during CPB, alterations in arterial carbon dioxide tension and arterial blood pressure may occur, and hemodilution with hypothermic perfusate

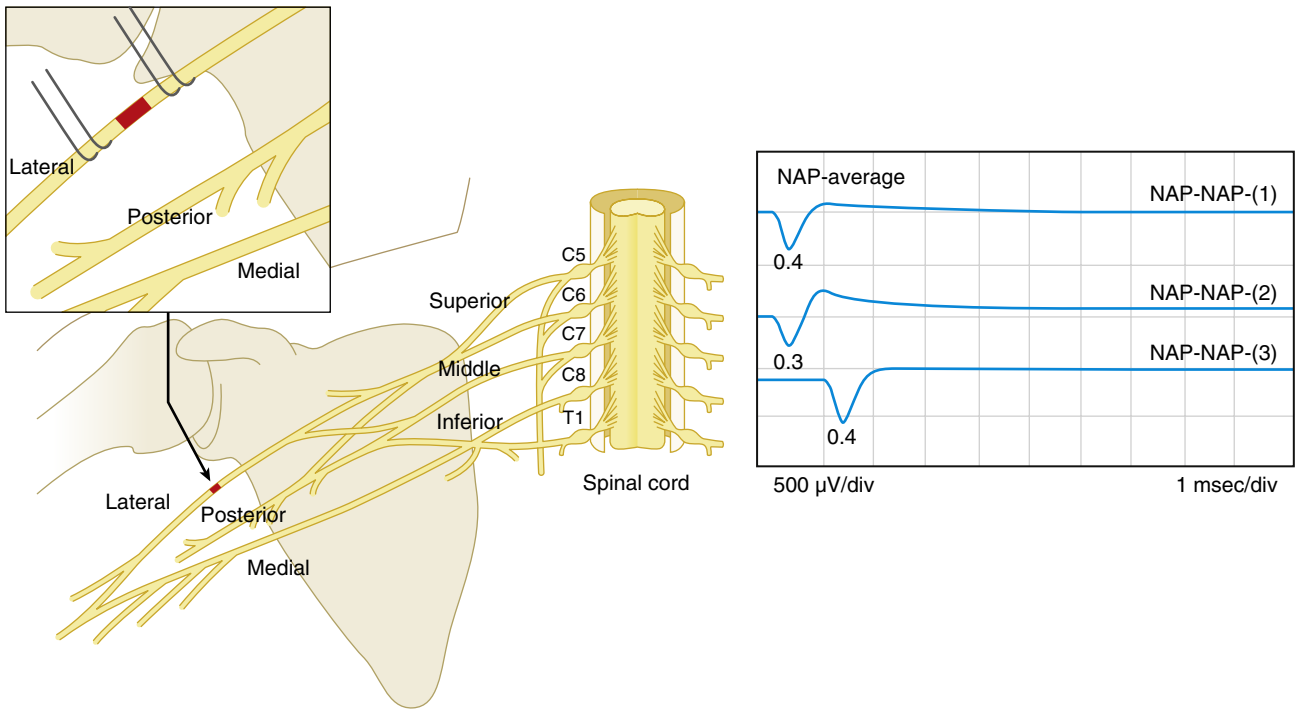


Figure 49-16. Recording a nerve action potential (NAP) during brachial plexus exploration. The site of the injury on the lateral fascicle is indicated in *red*. As shown in the *inset,* the surgeon places hook electrodes on either side of the exposed part of the nerve. If the injury is limited to an axonotmesis, proximal stimulation will result in a distal NAP similar to the ones shown in the recording to the *right.* The delay in the response in the third tracing is simply the result of a change in technical settings.

nearly always occurs. These effects, all of which may produce EEG changes similar to pathologic changes seen with ischemia, make it difficult to interpret EEG changes occurring during CPB.

Levy and others tried to distinguish the normal effects of hypothermia from other events occurring at the institution of and conclusion of CPB.[154,155] Initially, Levy concluded that only a qualitative relationship could be determined, but later, with the use of a much more sophisticated EEG analysis technique (approximate entropy), EEG changes associated with changes in temperature could be quantified.

Chabot and colleagues,[156] as well as Edmonds and colleagues,[157] attempted to use quantitative (processed, multiple-channel) EEG during CPB to detect cerebral hypoperfusion and relate these changes to postoperative neurologic function. In addition, some work has been done with intervention after detection of cerebral hypoperfusion using quantitative EEG. Although the data seem promising, only a few patients have been studied, with very few corroborating studies. In addition, this type of monitoring is extremely costly in time, personnel, and equipment. Given the lack of convincing outcome data, the cost-to-benefit ratio is unclear. Some other investigators failed to show any convincing relationship between intraoperative EEG parameters and postoperative neurologic function, especially in small infants and children[158,159] (see also Chapter 93). Whether the processed, quantitative EEG provides useful information for clinical management of patients during CPB is not clear. An evidence-based justification for routine application of this method is not apparent.

Transcranial Doppler Ultrasound. TCD ultrasound can monitor the cerebral circulation during CPB. Anecdotal reports and case series document the use of TCD for determining adequacy of CBF, detection of emboli, and detection of improper cannula placement.[160] Only very limited outcome data exist, and use of TCD ultrasound during CPB does not stand up to evidence-based examination, primarily because of lack of information. Probe placement instability and inability to obtain signals in some patients also have limited the use of this monitor intraoperatively. Finally, although the hypothesis that cerebral microemboli are at least part of the pathogenesis of postoperative cognitive decline following CPB is attractive, any relationship between CPB counts of presumed emboli and postoperative cognitive dysfunction is not convincing.[161]

Cerebral Oximetry and Jugular Venous Oxygen Saturation. As is the case with EEG monitoring during CPB, the use of NIRS or $Sjvo_2$ has been recommended as an indicator of adequate perfusion of the brain during CPB.[162,163] Incorrect placement of CPB cannulas has been detected clinically and in laboratory studies. One more recent series of patients undergoing CPB for coronary bypass surgery showed a more frequent incidence of major organ system dysfunction and longer hospital stays in patients with lower baseline and intraoperative cerebral oxygen saturation values.[164] The same questions exist for this application of NIRS, however, as do for the use of NIRS during carotid vascular surgical procedures. A systematic review of the use of NIRS during CPB showed that data are insufficient to conclude that interventions based on low cerebral oxygen saturation values prevent either stroke or postoperative cognitive dysfunction.[165] Use of NIRS during CPB does not stand up to evidence-based examination, and much more work is needed before NIRS can be recommended as a standard of care during CPB.

$Sjvo_2$ is very invasive. Although data from case reports and studies suggest that $Sjvo_2$ may have utility in detecting inadequate CBF, lack of outcome data, lack of clearly defined critical values at different temperatures during CPB, and availability of more noninvasive modalities (EEG, cerebral oximetry) have resulted in only limited use of this monitoring method during CPB. Based on current information, no neurologic monitoring techniques, either alone or in combination, are clearly useful in improving outcome during surgical procedures requiring CPB. Further research is needed before the cost in personnel and in equipment of neurologic monitoring during CPB can be justified.

INTENSIVE CARE APPLICATIONS OF NEUROLOGIC MONITORING (MONITORS: ELECTROENCEPHALOGRAM, EVOKED POTENTIALS, TRANSCRANIAL DOPPLER, JUGULAR VENOUS OXYGEN SATURATION)

Secondary injury to the CNS is a major modifiable risk factor in patients with CNS disease (see also Chapter 105). Aneurysmal subarachnoid hemorrhage, stroke, and traumatic brain injury are examples of CNS insults in which secondary injury has important implications for the ultimate functional outcome.[166-168] The same diseases frequently result in a primary insult to the CNS that severely constrains the utility of the clinical neurologic examination because of the need for mechanical ventilation and sedation. Many techniques of neurologic monitoring discussed earlier also have been used in the intensive care unit. Generally, however, techniques that require the continued presence of skilled technologists, such as monitoring of evoked potentials, are prohibitively expensive and of less practical value than techniques that can be performed as a daily examination or techniques that provide data easily integrated into the intensive care frame of mind. Along with monitoring, some of the techniques discussed previously also can provide important prognostic information in comatose patients and can guide decision making.

Cerebral Ischemia

Cerebral ischemia is an important cause of secondary injury to the CNS. It can be difficult to detect in patients who are either comatose or sedated, but it can occur even in patients with adequate cerebral perfusion pressure.[169,170] Three techniques may provide intensivists with additional information about cerebral perfusion. None of the monitors is considered "standard of care." As with all monitors, the impact of the monitor on outcome depends on the quality of the therapeutic interventions

that result from integration of the additional data into the clinical management of a given patient.

$Sjvo_2$ monitoring is used most extensively in the intensive care unit to monitor patients with traumatic brain injury. The data have been used to guide blood pressure and ventilatory management to optimize blood flow. $Sjvo_2$ monitoring has had a major effect on ventilatory management of head-injured patients and has significantly reduced the routine use of hyperventilation in neurosurgical patients.[171-175] $Sjvo_2$ values of less than 50% generally indicate cerebral ischemia. Increases in $Sjvo_2$ may occur in response to therapy, or they may be an ominous sign if the increase is caused by falling demand because of neuronal death.

Similar to $Sjvo_2$ monitoring, monitoring of $P_{Br}o_2$ and blood flow is used most frequently in patients with traumatic brain injury. $P_{Br}o_2$ performs well in clinical practice. Decreases to less than 10 to 15 mm Hg are associated with worsening outcome,[27,175] whereas $P_{Br}o_2$-targeted treatment strategies may improve outcome.[176] The data for thermal diffusion CBF are not as comprehensive, perhaps reflecting the slightly less robust technology.[177] Nonetheless, in the setting of subarachnoid hemorrhage, thermal diffusion CBF of less than 15 mL/100 g/minute showed a sensitivity of 90% and a specificity of 75% for detecting symptomatic vasospasm.[19]

TCD ultrasound is widely used in the intensive care unit to document the presence and severity of cerebral vasospasm after subarachnoid hemorrhage. As the major cerebral arteries narrow, flow velocity within the lumen must increase if blood flow is to be maintained. Such narrowing occurs 12 to 24 hours before the onset of clinical symptoms, thus allowing therapy to be initiated before the onset of clinical symptoms.[178-182] Mean flow velocities of more than 120 cm/second seem to correlate well with angiographic vasospasm,[183,184] although intracranial pressure and concurrent therapy with hypertensive hypervolemic hemodilution modify the flow velocity. The latter two factors result in characteristic changes of the TCD waveform, however, and preserve the utility of the examination.

Prognosis in Coma and Determination of Brain Death. EEG monitoring may help to assess the clinical course and the prognosis of comatose patients. Assessment of prognosis must be separated from the insult that precipitated the coma by more than 24 hours. If not, the EEG may reflect predominantly the effect of the insult and may not predict prognosis. More than 24 hours after the insult, spontaneous sustained burst suppression correlates strongly with severe irreversible brain injury.[185] Absence of EEG variability portends a high likelihood of persistent vegetative state or death,[185,186] whereas spontaneous variability, reactivity to external stimuli, and typical sleep patterns are associated with more favorable outcomes.[187-189]

A specific indication for EEG monitoring is the therapeutic induction of a coma by barbiturate administration. Because neither blood nor cerebrospinal fluid concentration of barbiturates reliably predicts burst suppression and near-maximal reduction in cerebral metabolic rate of oxygen consumption,[190] and because barbiturate administration usually requires an increase in cardiovascular support, documentation of a burst suppression pattern on EEG allows the use of the minimal effective dose of barbiturate.

Similar to EEG, evoked potential studies have a place in predicting prognosis in comatose patients. The presence of normal SSEPs bilaterally is an excellent prognostic sign, whereas the absence of any SSEP cortical response is a poor prognostic indicator. The degree of unfavorable outcome can be predicted by BAEPs. Intact and normal BAEPs with absent cortical SSEPs predict a best outcome of a chronic vegetative state. Outcome may be worse, however, because BAEPs commonly deteriorate later with rostral-to-caudal deterioration. Absent BAEP responses beyond wave I predict a high likelihood of brain death. Present but abnormal SSEPs are associated with outcomes intermediate between good to high function and a chronic vegetative state.[191-200]

TCD ultrasound also has been used in the intensive care unit as an aid to the diagnosis of brain death. As intracranial pressure increases, the pulsatility of the TCD waveform increases, accentuating the systolic peak and diminishing flow during diastole. With further increases in intracranial pressure, a characteristic to-and-fro pattern of flow is established, which is consistent with clinical brain death.[201] TCD studies are easily performed at the bedside and can minimize the need for unnecessary transports of the patient for definitive radiologic studies.

NONSURGICAL FACTORS INFLUENCING MONITORING RESULTS

ANESTHESIA AND THE ELECTROENCEPHALOGRAM

Anesthetic drugs affect the frequency and amplitude of EEG waveforms. Although each drug class and each specific drug have some specific, dose-related EEG effects (Table 49-2), some basic anesthesia-related EEG patterns may be described. Subanesthetic doses of intravenous and inhaled anesthetic drugs usually produce an increase in frontal beta activity and abolish the alpha activity normally seen in the occipital leads in an awake, relaxed patient with the eyes closed. As the patient loses consciousness with general anesthesia, the brain waves become larger in amplitude and slower in frequency. In the frontal areas, small beta activity seen in an awake patient slows to the alpha range and increases in size. In combination with the loss of the occipital alpha activity, this phenomenon produces the appearance of a "shift" of the alpha activity from the posterior cortex to the anterior cortex. Further increases in the dose of the inhaled or intravenously administered anesthetic drug produce further slowing of the EEG. Some anesthetic drugs suppress EEG activity totally (see Table 49-2). Other anesthetic drugs never produce burst suppression or an isoelectric EEG, despite increasing dose, either because they are incapable of completely suppressing the EEG (e.g., opioids, benzodiazepines) or because cardiovascular toxicity of the drug (e.g., halothane) prevents administration of a large enough dose.

TABLE 49-2 **ANESTHETIC DRUGS AND ELECTROENCEPHALOGRAM**

Drug	Effect on EEG Frequency	Effect on EEG Amplitude	Burst Suppression?
Isoflurane, Sevoflurane, Desflurane			Yes, >1.5 MAC
Subanesthetic	Loss of alpha, ↑ frontal beta		
Anesthetic	Frontal 4-13 Hz activity		
Increasing dose >1.5 MAC	Diffuse theta and delta → burst suppression → silence	↓ 0	
Nitrous oxide (Alone)	Frontal fast oscillatory activity (>30 Hz)	↓, especially with inspired concentration >50%	No
Barbiturates			Yes, with high doses
Low dose	Fast frontal ↑ beta activity	Slight	
Moderate dose	↑ Frontal alpha frequency spindles		
Increasing high dose	Diffuse delta → burst suppression → silence	↓ 0	
Etomidate			Yes, with high doses
Low dose	Fast frontal beta activity		
Moderate dose	Frontal alpha frequency spindles		
Increasing high dose	Diffuse delta → burst suppression → silence	↓ 0	
Propofol			Yes, with high doses
Low dose	Loss of alpha; frontal beta		
Moderate dose	Frontal delta; waxing/waning alpha		
Increasing high dose	Diffuse delta → burst suppression → silence	↓ 0	
Ketamine			No
Low dose	Loss of alpha, variability	↓	
Moderate dose	Frontal rhythmic delta		
High dose	Polymorphic delta; some beta	Beta is low amplitude	
Benzodiazepines			No
Low dose	Loss of alpha; increased frontal beta activity		
High dose	Frontally dominant delta and theta		
Opioids			No
Low dose	Loss of beta; alpha slows	None	
Moderate dose	Diffuse theta, some delta		
High dose	Delta, often synchronized		
Dexmedetomidine	Moderate slowing, prominent spindles		No

EEG, Electroencephalogram; *MAC,* minimum alveolar concentration.
*Delta = <4 Hz frequency; theta = 4-7 Hz frequency; alpha = 8-13 Hz frequency; beta = >13 Hz frequency.

Intravenous Anesthetic Drugs

See also Chapter 30.

Barbiturates, Propofol, and Etomidate. Despite widely varying potencies and durations of action, barbiturates, propofol, and etomidate produce similar EEG patterns (Fig. 49-17 shows EEG effects of thiopental). These drugs all follow the basic anesthesia-related EEG pattern described previously with initial EEG activation (see Fig. 49-17, *A*), followed by dose-related depression. As the patient loses consciousness, characteristic frontal spindles are seen (see Fig. 49-17, *B*), which are replaced by polymorphic 1- to 3-Hz activity (see Fig. 49-17, *C*), as the drug dose is increased. Further increases in dose result in lengthening periods of suppression interspersed with periods of activity (burst suppression). With a very high dose, EEG silence results. All these anesthetic drugs can cause epileptiform activity in humans, but epileptiform activity is clinically significant only after methohexital and etomidate when given in subhypnotic doses.

Ketamine. Ketamine does not follow the basic anesthesia-related EEG pattern. Anesthesia with ketamine is characterized by frontally dominant rhythmic, high-amplitude theta activity. Increasing doses produce intermittent polymorphic delta activity of very large amplitude interspersed with low-amplitude beta activity.[202] Electrocortical silence cannot be produced with ketamine. EEG activity may be very disorganized and variable at all doses. This disorganization of the EEG with ketamine is responsible for the failure of the bispectral index (BIS) to be useful in looking at the effect of ketamine on consciousness. Recovery of normal EEG activity even after a single bolus dose of ketamine is slow compared with barbiturates. No information is available about the relationship between emergence reactions after ketamine and the EEG. Ketamine can cause increased epileptiform activity.[202]

Benzodiazepines. Despite varying potencies and durations of action, benzodiazepines also follow the basic anesthesia-related EEG pattern. As a class, however, these drugs are incapable of producing burst suppression or an isoelectric EEG.

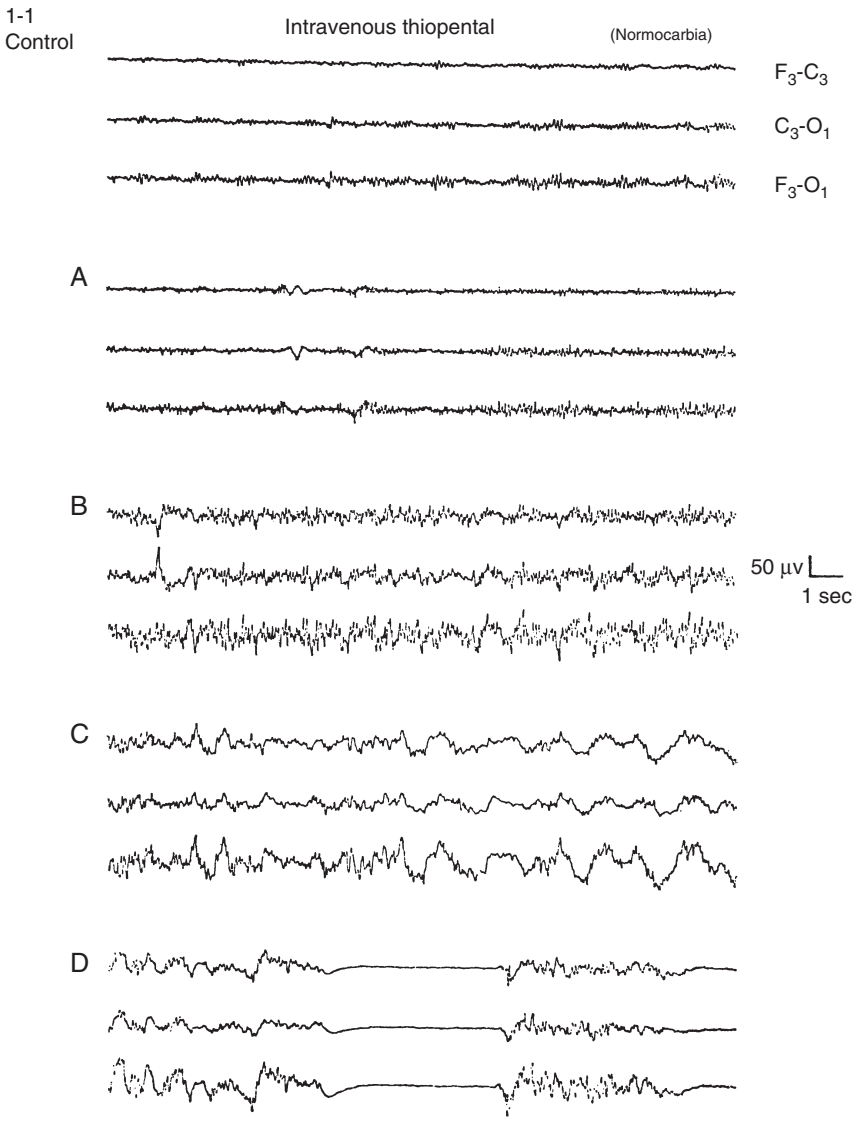


Figure 49-17. Electroencephalogram effects of intravenous administration of thiopental in humans: *A*, rapid activity; *B*, barbiturate spindles; *C*, slow waves; and *D*, burst suppression. *(From Clark DL, Rosner BS: Neurophysiologic effects of general anesthetics,* Anesthesiology *38:564, 1973.)*

Opioids. As a class, opioids do not follow the basic anesthesia-related EEG pattern. Opioids generally produce a dose-related decrease in frequency and increase in amplitude of the EEG. If no further doses of opioids are given, alpha and beta activity return as drug redistribution occurs. The rapidity of return depends on the initial dose and on the drug. Remifentanil is associated with the most rapid return to normal.[203] Complete suppression of the EEG cannot be obtained with opioids. Epileptiform activity occurs in humans and in animals receiving large to supraclinical doses of opioids. Sharp wave activity is common after induction of anesthesia with fentanyl, with 20% of patients showing this phenomenon after 30 µg/kg, 60% after 50 µg/kg, 58% after 60 µg/kg, and 80% after 70 µg/kg. Alfentanil bolus has been used clinically to activate seizure foci during surgical treatment of epilepsy.[204] This epileptiform activity is mainly noted in the frontotemporal region.[205]

Dexmedetomidine. Dexmedetomidine is being increasingly used for sedation in the operating room and in the intensive care unit, and it is also used for sedation during diagnostic EEG studies in children. EEG studies of patients undergoing sedation with dexmedetomidine alone show patterns similar to those seen in normal human sleep, with increased slow-wave activity and sleep spindles prominent.[206] Burst suppression or an isoelectric EEG pattern cannot be produced even with high doses of the drug. The level of sedation with dexmedetomidine can be effectively monitored with processed EEG parameters using BIS and entropy techniques.[207] BIS values at comparable levels of sedation are lower with dexmedetomidine than propofol.[208]

Inhaled Anesthetic Drugs

See also Chapter 25.

Nitrous Oxide. Used alone, nitrous oxide causes a decrease in amplitude and frequency of the dominant occipital alpha rhythm. With the onset of analgesia and depressed consciousness, frontally dominant fast oscillatory activity (>30 Hz) is frequently seen.[209] This activity may persist to some extent for 50 minutes after discontinuation of nitrous oxide. When nitrous oxide is used in

combination with other drugs, it increases the effects that would be associated with the drug alone clinically and with respect to the EEG pattern seen.

Isoflurane, Sevoflurane, and Desflurane. Potent inhaled anesthetic drugs, including halothane and enflurane, which are no longer available, follow the basic anesthesia-related EEG pattern. Isoflurane initially causes an activation of the EEG, followed by a slowing of the EEG activity that is more marked with increasing dose. Isoflurane begins to produce periods of EEG suppression at 1.5 minimum alveolar concentration (MAC), which become longer with increasing dose until electrical silence is produced at 2 to 2.5 MAC. Isolated epileptiform patterns sometimes can be seen during intersuppression activity at 1.5 to 2 MAC isoflurane.[210] Sevoflurane causes similar dose-dependent EEG effects. Equi-MAC concentrations of sevoflurane and isoflurane cause similar EEG changes.[211] Epileptiform activity has been induced by administration of sevoflurane in patients without epilepsy, and seizure activity on EEG, but not clinical seizure activity, has been reported in pediatric patients with a history of epilepsy during induction of anesthesia with sevoflurane.[212,213] Despite these observations, sevoflurane, similar to other inhalation drugs, is not suitable for use during electrocorticography for localization of seizure foci.[214] EEG patterns seen with enflurane are similar to the patterns seen with isoflurane, except that epileptiform activity is considerably more prominent. At 2 to 3 MAC, burst suppression is seen, but virtually all intersuppression activity consists of large spike-wave pattern discharges. Hyperventilation with high concentrations of enflurane increases the length of suppression and decreases the duration of bursts, but it increases the amplitude and main frequency component of the intersuppression epileptiform activity. Frank EEG seizures also may occur with enflurane that produce the same cerebral metabolic effects as pentylenetetrazol, a known convulsant.

Halothane also produces EEG patterns similar to those of isoflurane, but dosages of halothane that would produce burst suppression in the EEG (3 to 4 MAC) are associated with profound cardiovascular toxicity. Desflurane produces EEG changes similar to those seen with equi-MAC concentrations of isoflurane. In limited clinical studies, no evidence of epileptiform activity has been seen with desflurane, despite hyperventilation and 1.6 MAC dosage,[215] and desflurane has been used as a treatment for refractory status epilepticus.[216]

Clinical studies showed that the EEG effects of inhaled anesthetic drugs are influenced by age and baseline EEG characteristics. Older patients and patients with EEG slowing at baseline were more sensitive to the EEG effects of isoflurane and desflurane (see also Chapter 80). As anesthesia was deepened, similar EEG pattern changes occurred, but these changes occurred at lower end-tidal anesthetic concentrations.[217]

ANESTHESIA AND SENSORY-EVOKED RESPONSES

Volatile Anesthetic Drugs

Multiple drugs used in the perioperative period can influence the ability to monitor SERs accurately (Table 49-3). A more recent review provides the interested clinician with a detailed analysis of all drug effects on SERs that is beyond the scope of this chapter.[218] Table 49-3 does not quantify drug effects, but rather lists whether an individual drug is capable of producing a change in any part of an evoked response that could be mistaken for a surgically induced change. A "no" designation in this table does not mean that a given drug has no effects on SERs. The "no" designation indicates that any effects that do occur would not be called clinically significant by *clinicians experienced in intraoperative monitoring*. Several general concepts help the clinician who is trying to determine the best choice of drugs for use during monitored cases (Box 49-1).

The volatile anesthetic drugs isoflurane, sevoflurane, desflurane, enflurane, and halothane have similar effects in differing degrees on all types of SERs. VEPs are the most sensitive to the effects of volatile anesthetic drugs,

TABLE 49-3 **ABILITY OF AN INDIVIDUAL ANESTHETIC DRUG TO PRODUCE A CHANGE IN SENSORY- AND MOTOR-EVOKED POTENTIALS THAT COULD BE MISTAKEN FOR A SURGICALLY INDUCED CHANGE***

	SSEPs		BAEPs		VEPs		Transcranial MEPs	
Drug	**Lat**	**Amp**	**Lat**	**Amp**	**Lat**	**Amp**	**Lat**	**Amp**
Isoflurane	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Nitrous oxide†	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Barbiturates	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Etomidate	No	No	No	No	Yes	Yes	No	No
Propofol	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Diazepam	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Midazolam	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Ketamine	No	No	No	No	Yes	Yes	No	No
Opioids	No	No	No	No	No	No	No	No
Dexmedetomidine	No	No	No	No	No	ND	ND	No

Amp, Amplitude; *BAEPs,* brainstem auditory-evoked potentials; *Lat,* latency; *MEPs,* motor-evoked potentials; *ND,* no data available from the literature; *SSEPs,* somatosensory-evoked potentials; *VEPs,* visual-evoked potentials.

*This table is not quantitative in any way. "Yes" or "no" designations indicate whether an individual drug is capable of producing an effect on any portion of the evoked response that could be mistaken for a surgically induced change.

†Increases the anesthetic effect of the drug or drugs with which it is used.

and BAEPs are the most resistant to anesthetic-induced changes. Spinal and subcortical SSEP responses are significantly less affected than are cortical potentials.[219-221]

Because they are the most widely used intraoperative SER technique, SSEPs are the most completely studied with respect to the effects of anesthetic drugs. The effects of the currently used volatile anesthetic drugs on cortical SSEPs are dose-dependent increases in latency and conduction times and a decrease in amplitude of cortically, but not subcortically recorded signals.[219-223] When comparing the different volatile anesthetic drugs, studies are not clear.[219,221] One study suggested that halothane has a greater impact on cortical SSEPs than either isoflurane or enflurane,[221] whereas another published report supported a greater effect produced by enflurane and isoflurane than halothane.[219] None of these differences are clinically important and may be ignored by the practicing clinician. Desflurane and sevoflurane have effects on SERs that are qualitatively and quantitatively similar to those of isoflurane.[224-228] In neurologically normal patients, 0.5 to 1.0 MAC of any of the potent inhaled anesthetic drugs in the presence of nitrous oxide is compatible with monitoring of cortical SSEPs (Figs. 49-18 to 49-20).[219,223]

BOX 49-1 ***Guidelines for Choosing Anesthetic Techniques During Procedures in Which Sensory-Evoked Responses Are Monitored***

1. Intravenous drugs have significantly less effect than "equipotent" doses of inhaled anesthetics.
2. Combinations of drugs generally produce "additive" effects.
3. Subcortical (spinal or brainstem) sensory-evoked responses are very resistant to the effects of anesthetic drugs. If subcortical responses provide sufficient information for the surgical procedure, anesthetic technique is not important, and effects on cortically recorded responses may be ignored.

Neurologically impaired patients may show a significantly greater sensitivity to inhaled anesthetic drugs, even to the point of not tolerating any recordable level of inhaled anesthetic drug. Generally, better monitoring conditions are obtained, however, with narcotic-based anesthetic drugs with less than 1.0 MAC total (nitrous oxide plus potent drug) end-tidal inhaled anesthetic concentration.

The volatile anesthetic drugs result in increases in latency of BAEPs without significantly affecting the amplitude.[223,229-231] Volatile anesthetic drugs cause increases in latency and decreases in amplitude in the early (middle-latency) cortical responses after auditory stimulation,[230]

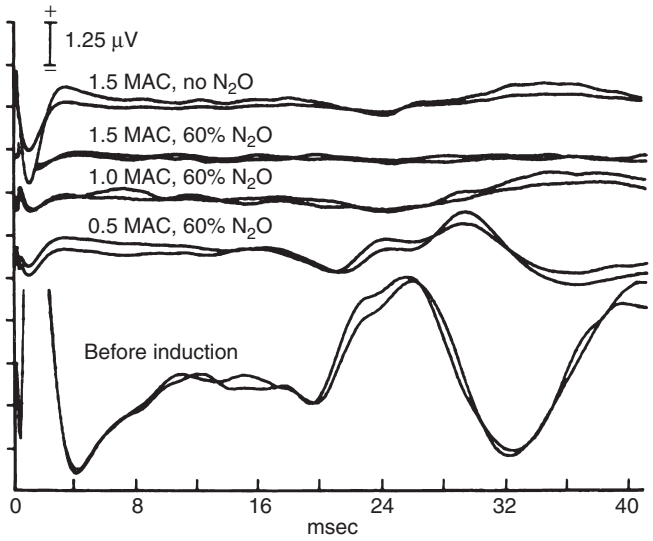


Figure 49-19. Representative somatosensory-evoked potential cortical responses (C-3, or C-4-FPz) at various minimum alveolar concentration (MAC) levels of enflurane. *(From Peterson DO, Drummond JC, Todd MM: Effects of halothane, enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials in humans,* Anesthesiology *65:35, 1986.)*

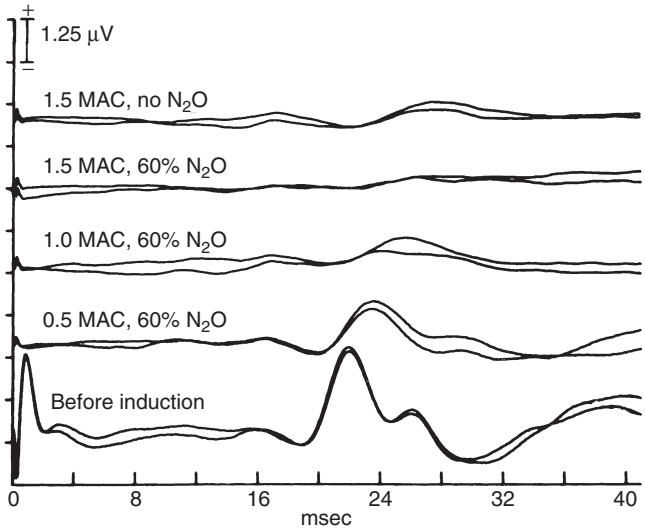


Figure 49-18. Representative somatosensory-evoked potential cortical responses (C-3, C-4-FPz) at various minimum alveolar concentration (MAC) levels of isoflurane. *(From Peterson DO, Drummond JC, Todd MM: Effects of halothane, enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials in humans,* Anesthesiology *65:35, 1986.)*

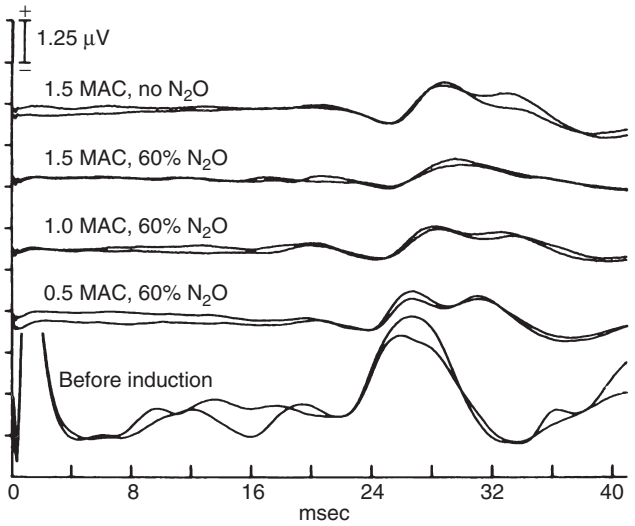


Figure 49-20. Representative somatosensory-evoked potential cortical responses (C-3, C-4-FPz) at various minimum alveolar concentration (MAC) levels of halothane. *(From Peterson DO, Drummond JC, Todd MM: Effects of halothane, enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials in humans,* Anesthesiology *65:35, 1986.)*

however, and these middle-latency responses are now used to monitor the hypnotic component of general anesthetic drugs.[32] Adequate monitoring of BAEPs is possible with any clinically useful concentrations of inhaled anesthetic drugs (with or without nitrous oxide) (Figs. 49-21 and 49-22).[223,229-232]

Use of the volatile anesthetic drugs during monitoring of VEPs results in dose-dependent increases in latency with or without changes in amplitude.[223,233-236] Isoflurane results in dose-dependent increases in latency and decreases in amplitude up to 1.8% in 100% oxygen, at which time the waveform is lost.[223,233] Enflurane, in the absence of hypocarbia, also leads to decrease in amplitude.[233] Halothane causes increases in latency without changes in amplitude.[234,235] These results are not clinically relevant because the variability of VEPs in anesthetized patients is so great that satisfactory monitoring, in the opinion of many experts, is impossible using any anesthetic technique.

Although volatile anesthetic drugs cause significant changes in the SER waveforms, adequate monitoring intraoperatively can be provided in the presence of anesthetic doses of volatile anesthetics. Doses of anesthetic drugs causing significant depression of the response to be monitored must be prevented. In our experience, end-tidal concentrations of inhaled anesthetic drugs totaling greater than 1.3 MAC have a dose-related increasing probability of obliterating cortical SSEPs, even in neurologically normal patients. Equally important, anesthetic concentrations should not be changed during the critical periods of intraoperative monitoring. Critical periods are defined as periods in which surgical interventions are most likely to result in damage to neurologic tissue and changes in the SERs. Because the volatile anesthetic-induced changes in SERs are dose dependent, increasing anesthetic dosage at a crucial point in the operative procedure can result in confusing changes in the SERs that potentially may be caused by the anesthetic drug, the surgical procedure, or both. The appropriate intervention is difficult to determine.

As with the volatile anesthetic drugs, nitrous oxide causes differing effects on the SERs, depending on the sensory system monitored. It causes decreases in amplitude without significant changes in latency in SSEPs when it is used alone or when it is added to a narcotic-based or volatile anesthetic drug.[219,220,237] The addition of nitrous oxide to a maintenance volatile anesthetic drug during the monitoring of BAEPs causes no further change.[229] Similarly, use of nitrous oxide alone causes no change in BAEPs, unless gas accumulates in the middle

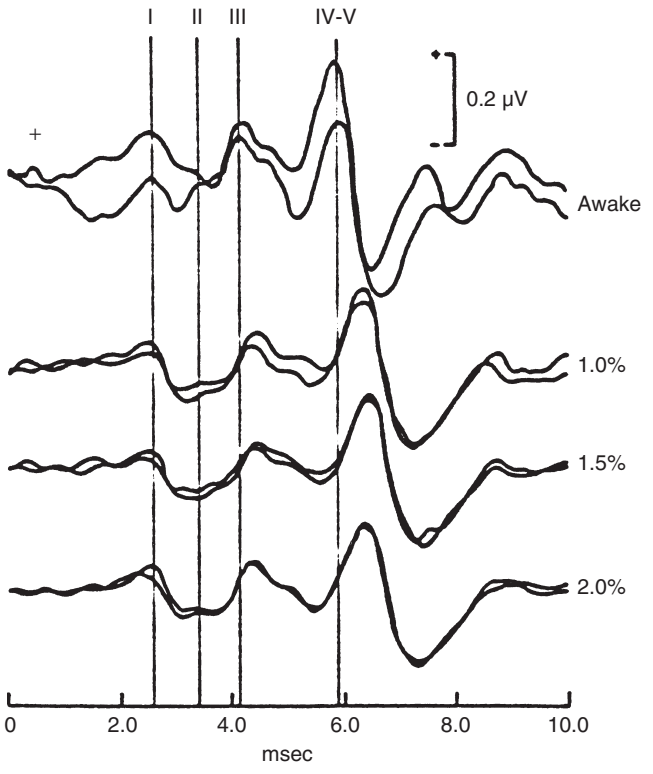


Figure 49-21. Influence of isoflurane alone on brainstem auditory-evoked potential in a typical subject. Latency of peaks III and IV to V increased at 1.0% but stabilized with increasing anesthetic depth. *(From Manninen PH, Lam AM, Nicholas JF: The effects of isoflurane–nitrous oxide anesthesia on brainstem auditory evoked potentials in humans,* Anesth Analg *64:43, 1985.)*

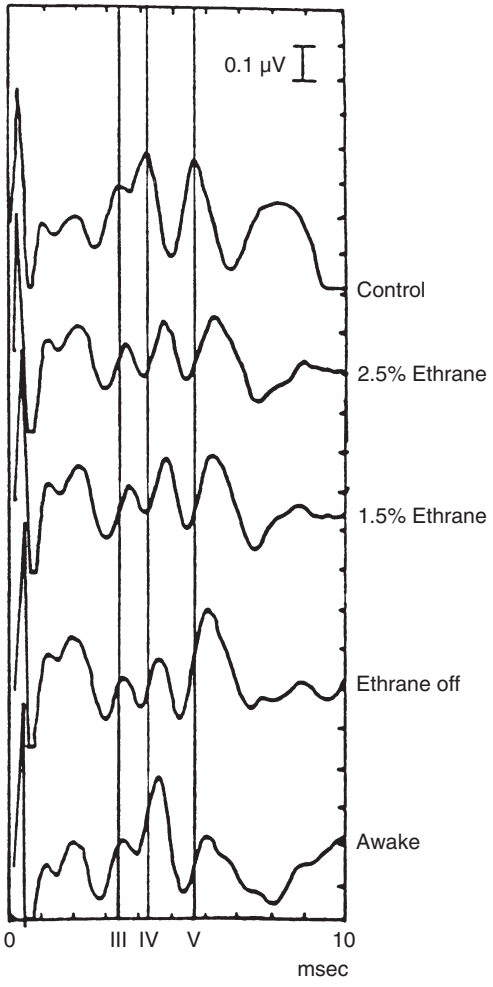


Figure 49-22. Brainstem auditory-evoked potential recording obtained in one patient at different enflurane (Ethrane)–inspired concentrations. *(From Dubois MY, Sato S, Chassy J, et al: Effects of enflurane on brainstem auditory evoked responses in humans,* Anesth Analg *61:898, 1982.)*

ear.[237] Use of nitrous oxide alone results in an increase in latency and a decrease in amplitude in VEPs, but when it is added to a volatile anesthetic technique, it causes no further changes in VEPs.[233,237]

Intravenous Anesthetics

The effects of barbiturates on SERs have been studied in animal models and in humans (see also Chapter 30). Increasing doses of thiopental in patients result in progressive dose-dependent increases in latency, decreases in amplitude of SSEPs, and progressive increases in latency of wave V in BAEPs. The changes in SSEPs are more pronounced than the changes in BAEPs, and waveforms beyond the initial primary cortical response are quickly obliterated. This finding is consistent with the theories that barbiturates affect synaptic transmission more than axonal conduction. Early waveforms in SERs result primarily from axonal transmission, and later waves depend on multisynaptic pathways in addition to axonal transmission. At doses of thiopental far larger than doses producing an isoelectric EEG, adequate monitoring of early cortical and subcortical SSEPs and BAEPs was preserved.[238] Other barbiturate compounds show similar effects. Somatosensory and auditory SERs were never obliterated even at doses larger than those causing complete suppression of spontaneous EEG activity.[239] This observation is important, especially when attempting to monitor the adequacy of CBF during cerebrovascular surgical procedures when the patient has been given large, "protective" doses of barbiturates. The EEG is isoelectric and not helpful for monitoring. The early cortical SSEP waveforms are still preserved, however, and may be very helpful in determining adequacy of CBF. Preserved ability to monitor SSEPs in head-injured patients receiving therapeutic thiopental infusions has been shown.[240] VEPs are much more sensitive to barbiturates. Low barbiturate doses obliterated all except the earliest waveforms. The early potentials persisted with increases in latency even to very high pentobarbital doses.[241] Except for VEPs, adequate perioperative monitoring of SERs is possible even in the presence of large-dose barbiturate therapy as long as the effects of the drug (increased latency with moderately decreased amplitude) are considered.

After bolus administration and intravenous infusions, etomidate causes increases in latency of all waves and prolongation of central conduction time in SSEPs. In contrast to virtually all other commonly used anesthetics, etomidate causes increases in amplitude of the cortical SSEP.[242,243] This effect may result from an alteration in the balance of inhibitory and excitatory influences or an increase in the irritability of the CNS. This effect seems to be present in the cortex, but not in the spinal cord.[243] Etomidate infusions have been used to enhance SSEP recording in patients when it was impossible to obtain reproducible responses at the beginning of intraoperative monitoring because of the patients' pathologic features (Fig. 49-23). Following baseline responses that could not be monitored, the etomidate augmentation of the SSEP allowed adequate monitoring and detection of intraoperative events leading to compromise of the spinal cord.[243] The effects of etomidate on BAEPs are dose-dependent increases in latency and decreases in amplitude that are not clinically significant.[244]

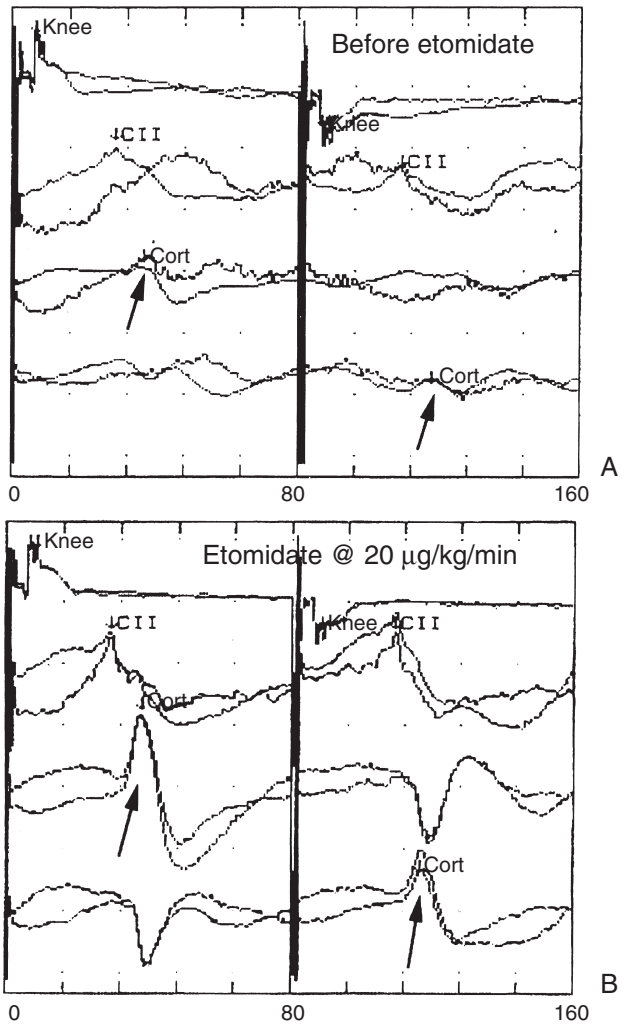


Figure 49-23. Effects of etomidate on somatosensory-evoked potential. **A,** These tracings were obtained from a mildly mentally impaired patient with severe kyphoscoliosis during the early maintenance phase of anesthesia using isoflurane and fentanyl. **B,** These tracings were obtained after discontinuing isoflurane and instituting an etomidate infusion at 20 µg/kg/minute. Note dramatically increased amplitude and clarity of the signal in the cortical (Cort) channels (marked by *arrows*), which both are recorded with the same amplification scale.

Benzodiazepines also can cause changes in SERs.[245,246] Diazepam causes increases in latency and decreases in amplitude of SSEPs, increases in latency in the cortical response after auditory stimulation, and no change in BAEPs.[245,246] Midazolam causes decreases in amplitude without changes in latency of SSEPs.[242]

Generally, opioids cause small, dose-dependent increases in latency and decreases in amplitude of SSEPs. These changes are not clinically significant. Effects on amplitude are more variable than the latency increases.[247,248] Even at large doses of fentanyl (60 µg/kg), reproducible SSEPs can be recorded.[248] Other opioids cause similar dose-dependent changes in SSEPs.[247,249] Opioids can be used even in large doses in patients requiring intraoperative SSEP monitoring without impairment of the ability to monitor neurologic function adequately. Opioid-induced changes must be taken into account, however, when evaluating the recordings. Large intravenous bolus administration of

opioids should be avoided at times of potential surgical compromise to neurologic function, to prevent confusing the interpretation of SEP changes if they develop. BAEPs were resistant to doses of fentanyl of 50 μg/kg with no changes observed in absolute latency, interpeak latency, or amplitude.[250]

Based on several case reports and small series, dexmedetomidine is compatible with all types of evoked potential monitoring, although data regarding MEPs are not entirely consistent. Once study demonstrated significant attenuation of MEPs during surgical treatment of scoliosis when dexmedetomidine was used as an adjunct to propofol and remifentanil.[251] Data are limited, and large studies are lacking. Use of dexmedetomidine currently is not a problem.

ANESTHESIA AND MOTOR-EVOKED POTENTIALS

Effects of anesthetic drugs on tcMEPs recorded from muscle are surprisingly profound (see Table 49-3).[252-257] Anesthetic techniques typically used by most anesthesiologists for surgical procedures of the spine would produce prohibitive depression of the MEP.[258,259] Intravenously administered anesthetic drugs produce significantly less depression, and techniques using any of a combination of ketamine, opioids, etomidate, and propofol have been described.[260-266] We have had excellent experience with a combination of propofol and remifentanil, which also is supported in the literature.

Anesthetic effects on MEP responses recorded at spinal levels seem to be less serious. When responses are recorded from muscle, neuromuscular blocking drugs should be monitored quantitatively, maintaining T1 twitch height at approximately 30% of control values to prevent excessive movement during the operation.[138,253] When responses are not recorded from muscle, profound relaxation is desirable because gross muscle movement produced by MEP stimulation is eliminated, facilitating the surgical procedure. More recent studies using rapid trains of stimuli with transcranial electrical and magnetic stimulus techniques have produced responses that are more resistant to the effects of anesthetic drugs, and more "traditional" techniques using inhaled anesthetic drugs and narcotics may be used.[267-269] Total intravenous anesthesia is preferred to techniques using nitrous oxide or potent inhaled anesthetic drugs, however. Precise control of the anesthetic regimen and avoidance of boluses during critical monitoring periods are more important than for SSEPs, and active cooperation of the anesthesia care team is essential for good, reproducible results. Figure 49-24 shows the dramatic effect of introduction of 0.3 MAC isoflurane to a total intravenous technique using propofol and remifentanil.

PATHOPHYSIOLOGIC EFFECTS ON THE ELECTROENCEPHALOGRAM

Hypoxia

Hypoxia may produce inadequate delivery of oxygen to the cerebral cortex generating EEG, and changes similar to those occurring with ischemia result. Initially, hypoxemia may not cause any EEG changes because the brain can increase blood flow to compensate. When the hypoxemia becomes severe enough, further increases in flow are impossible, and EEG changes occur. "Slowing" of the EEG during hypoxia is a nonspecific global effect. Fast frequencies are lost, and low frequencies dominate. Eventually, the EEG is abolished as the brain shuts down electrical activity and diverts all oxygen delivered to maintenance of cellular integrity.

Hypotension

In a normal, awake patient, significant levels of hypotension are needed to cause the earliest of CNS signs, as measured by discrimination tests such as the flicker-fusion test. This test examines the flicker rate at which the observer perceives the light to be continuous. In the early days of deliberate hypotension, this test was part of the preoperative evaluation to judge how far the pressure could be reduced during the operation. Clear signs of confusion and inability to concentrate or respond properly to simple commands generally represent very low levels of cerebral perfusion when caused by hypotension because the normal cerebral circulation has a large capacity to vasodilate and maintain normal flow in the presence of significant hypotension.

The EEG changes associated with even this level of hypotension are not dramatic, although they are clear by comparison with a previously active recording. Herein lies the problem with using intraoperative EEG to determine whether a given level of hypotension has resulted in brain ischemia. EEG changes are not very pronounced and are bilateral. These changes also are nearly identical to the changes caused by increasing doses of many anesthetic drugs. EEG changes associated with hypotension can be detected, but when the hypotension is induced slowly and is associated with changes in anesthetic drugs (e.g., use of isoflurane to reduce blood pressure), the changes are very difficult to interpret. EEG changes associated with acute, severe hypotension such as may be caused by sudden arrhythmias are easier to read. Many patients undergoing surgical procedures do not have a normal cerebral circulation, however. In these individuals, even mild hypotension may result in significant cerebral ischemia. Monitoring the EEG during planned hypotension may be helpful in these patients, provided other causes of similar EEG changes may be carefully controlled. Although not supported in the literature, when the EEG changes (e.g., during carotid surgical procedures) secondary to hypotension, cerebral ischemia is likely.

Hypothermia

During cooling on CPB, the total power and peak power frequency of the high-frequency band were highly correlated with temperature when using Fourier analysis and spectral edge data; however, significant variability was noted among subjects, especially during cooling.[270] Complete EEG suppression usually develops at 15° C to 18° C. Levy and colleagues showed an improved ability to quantify the effects of hypothermia on the EEG by using an EEG processing technique known as approximate entropy.[155]

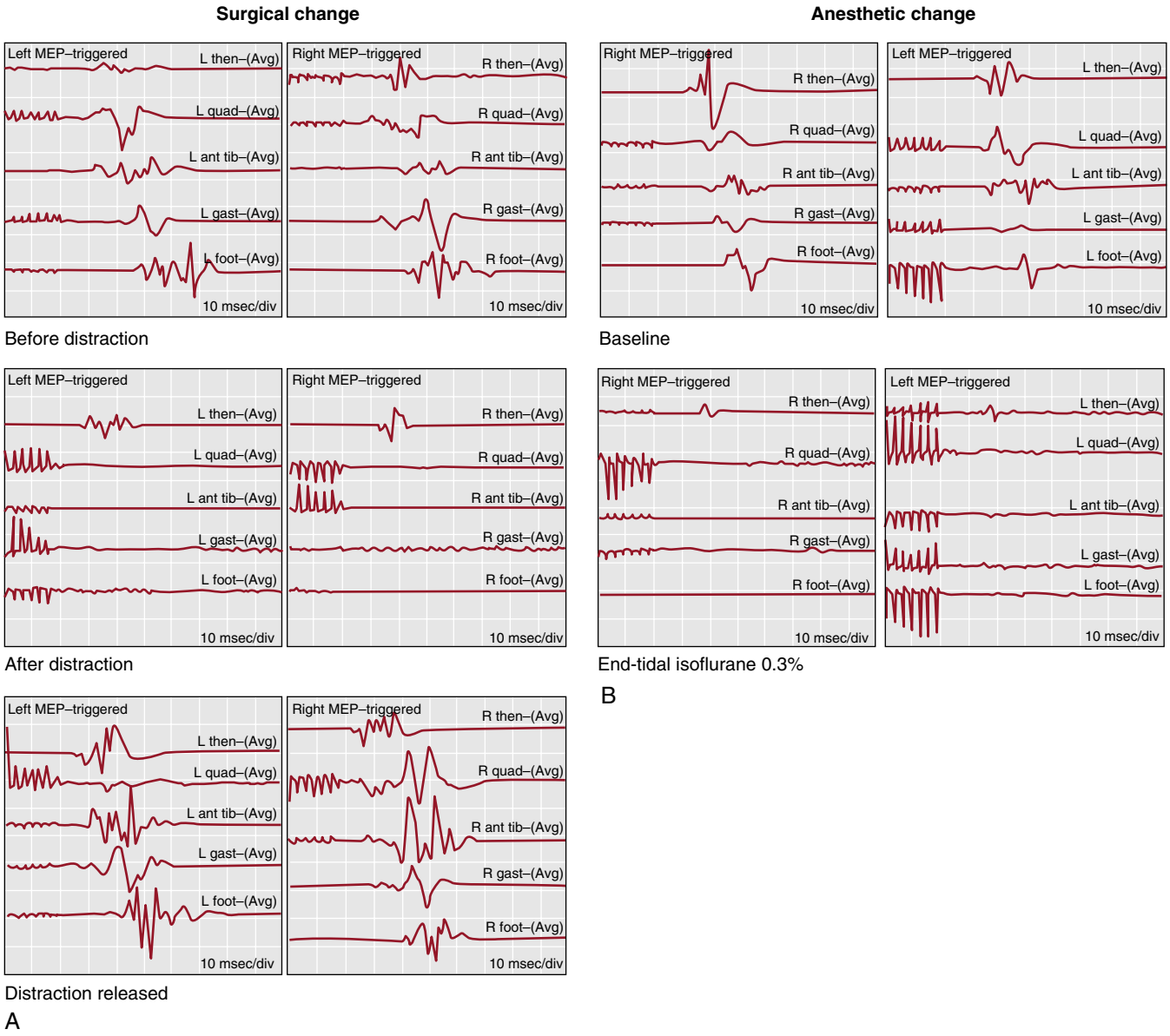


Figure 49-24. A, Transcranial electrical motor-evoked potential recording showing surgically induced change during spine surgery (scoliosis repair). **B,** Motor-evoked potential with an anesthetic-induced change. Note similarity of the change pattern, except that in the anesthetic-induced change, the responses in the upper extremity also changed. Left-sided and right-sided responses are shown on the corresponding panel. A single upper extremity response is shown (*top tracing*) in each panel. Responses from four muscle groups in each lower extremity are shown directly below them. *Ant tib,* M tibialis anterior; *gast,* m gastrocnemius; *L,* left; *quad,* m quadriceps femoris; *R,* right; *then,* thenar.

Hypercarbia and Hypocarbia

Hypocapnia is known to activate excitable seizure foci, and in rare cases it may produce EEG evidence of cerebral ischemia even in awake subjects.[271] Hypercapnia, unless severe and associated with hypoxemia, has only indirect effects secondary to increased CBF. In an anesthetized patient, hypercarbia-associated increases in CBF may have effects similar to those seen with increasing end-tidal tension of volatile anesthetic drugs.[272]

Untoward Events

One of the main reasons for monitoring the brain of an anesthetized patient is to enable detection of injuries to the nervous system that would not be otherwise apparent. Although hundreds of such case reports exist in the literature, as well as many in our experience, the cost effectiveness of such monitoring is unclear. In a more recent case at our institution, severe EEG changes occurred at the beginning of a carotid endarterectomy, before surgical incision, and were unassociated with any other vital sign changes or hypotension. Immediate angiography revealed acute carotid occlusion and completely changed the operation performed on this patient, who recovered completely. Some intraoperative events could lead to CNS insult that, if detected early, could be rapidly reversed or treated to prevent permanent injury. Given the rarity of such events, however, it is extremely unlikely that such monitoring would be shown to be beneficial in

any foreseeable randomized trial. If the "at-risk" patient could be identified preoperatively, perhaps the EEG or other types of neuromonitoring could be useful in detecting untoward CNS events during anesthesia, such as a new stroke after elective general surgical procedures.

PHYSIOLOGIC FACTORS INFLUENCING SENSORY-EVOKED RESPONSES

Numerous physiologic variables, including arterial blood pressure, temperature (local and systemic), and analysis of arterial blood gas values can influence SEP recordings. With decreases in mean arterial blood pressure to below levels of cerebral autoregulation as a result of either blood loss or vasoactive drugs, progressive changes in SERs occur. SSEP changes observed are progressive decreases in amplitude until loss of the waveform with no changes in latency.[273,274] BAEPs are resistant to even profound levels of hypotension (mean arterial pressure of 20 mm Hg in dogs).[273] Cortical (synaptic) function necessary to produce cortical SERs seems to be more sensitive to hypoperfusion than spinal cord or brainstem, nonsynaptic transmission.[274] Rapid decreases in arterial blood pressure to levels higher than the lower limit of autoregulation also have been associated with transient SSEP changes of decreased amplitude that resolve after several minutes of continued hypotension at the same level.[275] Reversible SSEP changes at systemic pressures within the normal range have been observed in patients undergoing spinal distraction during surgical treatment of scoliosis. These changes resolved with increases of arterial blood pressure to slightly higher than the patient's normal pressure; this finding suggests that the combination of surgical manipulation with levels of hypotension generally considered "safe" could result in spinal cord ischemia.[276]

Changes in temperature also affect SERs (see also Chapter 54). Hypothermia causes increases in latency and decreases in amplitude of cortical and subcortical SERs after all types of stimulation.[277-279] Hyperthermia also alters SERs, with increases in temperature leading to decreases in amplitude in SSEPs and loss of SSEPs at 42° C during induced hyperthermia.[280]

Changes in arterial blood gas tensions can alter SERs, probably in relation to changes in blood flow or oxygen delivery to neural structures.[281,282] Hypoxia produces SSEP changes (decreased amplitude) similar to the changes seen with ischemia.[282] Decreased oxygen delivery associated with anemia during isovolemic hemodilution results in progressive increases in latency of SSEPs and VEPs that become significant at hematocrit values lower than 15%. Changes in amplitude were variable until extremely low hematocrit values (≈7%) were reached, at which point the amplitude of all waveforms decreased.[283]

TABLE 49-4 CURRENT PRACTICES IN NEUROLOGIC MONITORING

Procedure	Monitors	Current Practice
Carotid endarterectomy	Awake patient neurologic examination, EEG, SSEP, TCD	NIH recommends use of one of these four available monitors
	CO	Threshold value not determined, inadequate normative population data
Scoliosis surgical treatment	SSEP	Monitoring recommended and may substitute for wake-up testing
	Wake-up test	Largely abandoned in centers using electrophysiologic monitoring; monitoring not continuous, and false-negative monitoring patterns reported
	MEP	Increased clinical use now that transcranial electrical stimulation is FDA approved; useful in combination with SSEP
Acoustic neuroma	Facial nerve monitor	Facial nerve monitoring recommended
	BAEP	BAEP showing some clinical evidence of improved outcome in some procedures
Intracranial aneurysm clipping	SSEP, EEG, tcMEP	Used routinely in some centers; limited clinical data on outcome, but appears clinically useful during anterior circulation procedures
Cranial nerve V decompression	BAEP	Used in some centers; reduces hearing loss
Cranial nerve VII decompression	BAEP, facial nerve monitor	Data from small series showing improved hearing preservation
Supratentorial mass lesions	SSEP, tcMEP	Used in some centers in selected high-risk procedures
Infratentorial mass lesions	BAEP, SSEP, tcMEP	BAEP to detect retractor-related cranial nerve VIII injury; SSEP and tcMEP in rare, high-risk lesions adjacent to ascending sensory or descending motor pathways
Decompression of spinal stenosis	SSEP, tcMEP	Used in some centers in high-risk procedures (more often cervical)
Spinal cord trauma	SSEP, MEP	Used in some centers in high-risk procedures
Cardiopulmonary bypass	EEG, TCD, $Sjvo_2$, CO	Used routinely in some centers; actively studied, but no outcome data yet
Aortic coarctation	SSEP	Used routinely in a few centers; no widespread acceptance
Aortic aneurysm repair	SSEP, MEP	Used routinely in a few centers; no widespread acceptance

BAEP, Brainstem auditory-evoked potential; *CO,* cerebral oximetry; *EEG,* electroencephalogram; *FDA,* U.S. Food and Drug Administration; *MEP,* motor-evoked potential; *NIH,* National Institutes of Health; *$Sjvo_2$,* jugular bulb venous oxygen saturation; *SSEP,* somatosensory-evoked potential; *TCD,* transcranial Doppler; *tcMEP,* transcranial motor-evoked potential.

SUMMARY

Regardless of the type of intraoperative neurologic monitor, several principles must be observed for neurologic monitoring to provide potential benefit to the patient. First, the pathway at risk during the surgical procedure must be amenable to monitoring. Second, if evidence of injury to the pathway is detected, some intervention must be possible. If changes in the neurologic monitor are detected, and no intervention is possible, although the monitor may be of prognostic value, it does not have the potential to provide direct benefit to the patient from early detection of impending neurologic injury. Third, the monitor must provide reliable and reproducible data. If the data have a high degree of variability in the absence of clinical interventions, their utility for detecting clinically significant events is limited.

This chapter reviews the most common clinically used intraoperative neurologic monitors. Ideally, clinical studies would provide outcome data on the efficacy of a neurologic monitor in a given procedure to improve neurologic outcome. Although a wealth of clinical experience exists with many of these monitoring modalities, little is available in the way of randomized prospective studies evaluating the efficacy of neurologic monitoring. Based on clinical experience with neurologic monitoring and nonrandomized clinical studies in which neurologic monitoring is used and generally compared with historical controls, practice patterns for use of neurologic monitoring have developed. In certain procedures, neurologic monitoring is recommended and used by most centers; in other procedures, monitoring is used almost routinely in some centers, but not in others; and in some procedures, no clear clinical experience or evidence indicates that monitoring is useful at all (experimental use). Finally, in some procedures, monitoring is used selectively for patients believed to be at higher than usual risk for intraoperative neurologic injury. Table 49-4 provides a summary of current clinical practice.

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Chapter 50

Monitoring Brain State During General Anesthesia and Sedation

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Key Points

- Anesthesiologists rely extensively on physiologic signals and anesthetic dosing strategies to track states of the brain and central nervous system under general anesthesia.
- Heart rate and systemic arterial blood pressure changes are the principal physiologic signals used to monitor the anesthetic state of patients receiving general anesthesia.
- Use of the neurologic examination during induction of and emergence from general anesthesia can provide information regarding loss and recovery of consciousness.
- Electroencephalogram (EEG)-based indices are used to track the level of consciousness of patients receiving general anesthesia. The most commonly used EEG-based indices are the bispectral index (BIS), the Patient Safety Index (PSI), Narcotrend, and Entropy.
- Real-time analysis of the unprocessed EEG and the spectrogram (density spectral array) is a highly informative way to monitor brain states of patients receiving general anesthesia.
- Normalized symbolic transfer entropy (NSTE) is a new approach for quantifying how changes in frontoparietal functional connectivity relate to anesthesia-induced changes in consciousness.
- In the future, closed-loop anesthetic delivery (CLAD) systems may provide highly accurate ways to control states of general anesthesia, medical coma, and sedation.
- Obtaining reliable quantitative markers of nociception is an active area of investigation.

General anesthesia is a drug-induced reversible condition composed of four behavioral and physiologic states: unconsciousness, amnesia, analgesia, immobility, and stability of the physiologic systems, including the autonomic, cardiovascular, respiratory, and thermoregulatory systems.[1,2] Continuously monitoring the status of the patient during general anesthesia is crucial for safe and proper delivery of anesthesia care. The physiologic state of the patient under general anesthesia is commonly monitored using the electrocardiogram and an arterial blood pressure cuff, or an arterial catheter, to monitor the cardiovascular system. In more complex cases, a central venous catheter can be used to monitor central venous pressures, and a pulmonary artery catheter can be placed to monitor cardiac output and pressures in the heart and pulmonary circulation. Transesophageal echocardiography can be used intermittently to gain direct visual information about the anatomy and function of the heart. The capnogram provides a continuous readout of the level of expired carbon dioxide and respiration. In intubated patients, more detailed information about the state of the lungs can be acquired from the pressure tracing on the ventilator. The pulse oximeter estimates the level of hemoglobin saturation in the arterial blood, and the thermometer tracks body temperature (see Chapter 54). Muscle relaxation, or immobility, is monitored primarily using a train-of-four stimulation device, and more grossly by observing changes in muscle tone or movement (see Chapter 53).

Monitoring the behavioral states is more challenging. During general anesthesia, amnesia is not monitored directly but implicitly by the extent to which unconsciousness is achieved. If the patient is unconscious and not simply conscious but unresponsive, the patient will also have amnesia. In this chapter, we discuss approaches

for monitoring unconsciousness and analgesia, or more accurately stated antinociception, during sedation and each of the three phases of general anesthesia: induction, maintenance, and emergence. This chapter's focus is on physiologic signs and neurologic examination findings and the electroencephalogram (EEG)-based indices used to track these states of general anesthesia.

INDUCTION OF GENERAL ANESTHESIA

Monitoring of a patient's level of consciousness begins at induction of general anesthesia. Induction is usually achieved by an intravenous bolus dose of a hypnotic drug such as propofol, a barbiturate, ketamine, or etomidate. Unconsciousness usually occurs in 10 to 30 seconds. The brain state of the patient, which in this case is the transition into unconsciousness, is tracked by monitoring the patient's physiologic signs and the EEG-based index.

PHYSIOLOGIC SIGNS OF LOSS OF CONSCIOUSNESS

When a hypnotic drug is administered to induce general anesthesia—usually as an intravenous bolus over a 5- to 10-second period—several physiologic signs are observed. If asked to count backwards from 100, the patient typically does not get beyond 85 to 90. This transition into unconsciousness can be followed easily by asking the patient to perform smooth pursuit of the anesthesiologist's finger.[2] In smooth pursuit, the patient is instructed to move his or her eyes to track the position of the anesthesiologist's finger. As loss of consciousness ensues, the lateral excursions of the eyes during smooth pursuit decrease, nystagmus may appear, blinking increases, and the eyes fix abruptly in the midline. The oculocephalic reflex and the corneal reflex are lost, but the pupillary response to light remains intact. The patient typically becomes apneic, atonic, and unresponsive at the point when the oculocephalic and corneal reflexes are lost.

The oculocephalic reflex is assessed by turning the patient's head from left to right. Before administration of the induction anesthetic, when the reflex is intact in a patient with no neurologic deficits, the eyes move in the direction opposite the motion of the head. When the reflex is lost, the eyes stay fixed in the midline.[3] The oculocephalic reflex requires the circuits of cranial nerves III, IV, and VI to be intact. The motor nuclei associated with cranial nerves III and IV are located in the midbrain, whereas the nucleus of cranial nerve VI is located in the pons. The corneal reflex has traditionally been assessed using a wisp of cotton at the corner of the eye to stroke the cornea. An easier way to assess the reflex is to allow a drop of sterile water to fall on the cornea. Using a drop of sterile water may be safer than using the wisp of cotton, because the former is less likely to cause a corneal abrasion. With either approach, the reflex is intact if the eyes blink consensually, is impaired if there is a blink in one eye and not the other, and is absent if there is no blink. The afferent component of the corneal reflex travels to the sensory nucleus of the cranial nerve V through the ophthalmic branch, whereas the efferent component arises from the motor nucleus of the cranial nerve VII. The nuclei for these nerves associated with the oculocephalic reflex and the corneal reflex lie in close proximity to the arousal centers in the midbrain, pons, hypothalamus, and basal forebrain.[3]

Loss of the oculocephalic reflex suggests that the motor nuclei required for eye movements have been affected by the anesthetic. Similarly, loss of the corneal reflex suggests that the nuclei that control sensation and motor responses to sensation on the eyes and the face have also been affected. Because the loss of the oculocephalic and corneal reflexes occur concomitantly with the loss of responsiveness, the anesthesiologists can also infer that the loss of consciousness is due at least in part to the effects of the anesthetics on the nearby arousal centers.[2-4] Apnea, which commonly occurs on induction of general anesthesia with bolus administration of a hypnotic agent, is most likely due to the inhibitory effects of the anesthetic on the dorsal and ventral respiratory groups in the medulla and pons, respectively.[5] Atonia can be due to anesthetic action at any one of multiple sites in the motor pathways between the primary motor areas and the spinal cord. The most likely brainstem sites are the pontine and medullary reticular nuclei.[2]

Loss of the oculocephalic reflex, the corneal reflex, apnea, and atonia occur concomitantly with loss of consciousness on induction of general anesthesia because the brainstem is one of the first brain sites that the hypnotic drug reaches after an intravenous bolus. Blood containing the anesthetic reaches the brainstem through the basilar artery, which arises from the fusion of the two vertebral arteries and supplies the posterior cerebral arteries that provide the posterior input to the Circle of Willis.[4] Before terminating in the posterior cerebral arteries, the basilar artery runs on the dorsal surface of the brainstem and gives off multiple penetrating arteries that perfuse the brainstem nuclei leading to the observed physiological effects.

ELECTROENCEPHALOGRAM-MARKERS OF LOSS OF CONSCIOUSNESS

Electroencephalogram-based indices are among the most commonly used methods for tracking the loss of consciousness induced by general anesthesia.[6] With induction of general anesthesia, these indices usually change from high values that indicate the awake state to lower values that indicate states of sedation and unconsciousness.

MAINTENANCE OF GENERAL ANESTHESIA: PHYSIOLOGIC SIGNS AND THE NOCICEPTIVE-MEDULLARY-AUTONOMIC PATHWAY

Despite the many advances in anesthesia care, the physiologic signs of changes in heart rate, arterial blood pressure, and movement are the measurements most commonly used to track the anesthetic during maintenance of general anesthesia.[7] When the state of general anesthesia is not adequate for the level of surgical (nociceptive) stimulation, heart rate and arterial blood pressure can increase dramatically. The changes in heart rate and arterial blood pressure that anesthetized patients show

in response to a nociceptive stimulus can be explained in terms of the nociceptive-medullary-autonomic (NMA) circuit comprised of the spinoreticular tract, the brainstem arousal circuits, and the sympathetic and parasympathetic efferent pathways (Fig. 50-1).[2,8] It is important to understand how the NMA circuit works, because it is the most used pathway for monitoring the patient's level of unconsciousness and antinociception. One example is a description of the NMA pathway in a clinical context that is commonly observed in the operating room.

Suppose that a patient is in a stable state of general anesthesia when, to gain better exposure, the surgeon moves the retractor. Suppose also that this maneuver induces an immediate increase in heart rate and arterial blood pressure. Assuming, that there are no occult hemodynamic or respiratory problems or other common issues that increase heart rate and arterial blood pressure, then these increases likely occurred because the level of general anesthesia did not maintain an adequate level of antinociception. By simultaneously monitoring the level of muscle relaxation and oxygen saturation, oxygen delivery, and EEG-based indices, the anesthesia provider can determine that these increases are due to inadequate antinociception and decide to administer more analgesic.

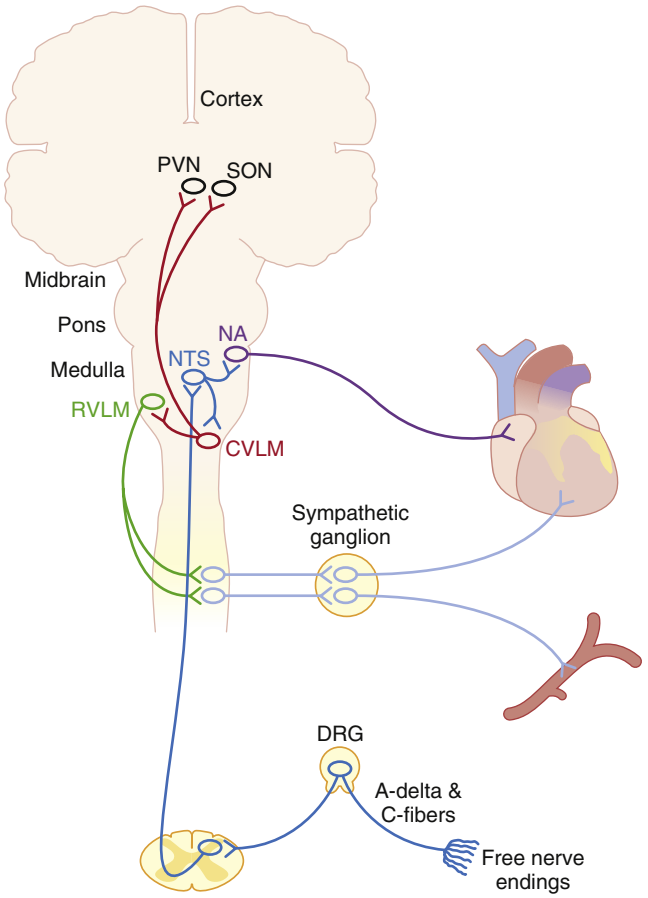


Figure 50-1. Nociceptive medullary autonomic circuit. The ascending nociceptive (pain) pathway starts with C fibers and A-delta peripheral afferent fibers that synapse on projection neurons (PN) in the dorsal horn. The PNs cross the midline, course to the brain where they synapse at several targets, including the nucleus of the tractus solitarius (NTS) in the medulla. The NTS mediates the autonomic response to a nociceptive stimulus by increasing sympathetic output through the rostral ventral lateral medulla (RVLM) and the caudal ventral lateral medulla (CVLM), which projects to the thoracolumbar sympathetic ganglia. The ganglia project to peripheral blood vessels and the heart. The nucleus ambiguous (NA) mediates the parasympathetic output to the sinoatrial node of the heart through the vagus nerve. The NTS projects also to the supraoptic nucleus (SON) and periventricular nucleus (PVN) in the hypothalamus. The NMA circuit is the reason why anesthesiologists use increases in blood pressure and heart rate as markers of increases in nociceptive stimulation and, possibly, a level of general anesthesia that is inadequate. *DRG,* Dorsal root ganglion. *(Redrawn from Brown EN, Lydic R, Schiff ND: General anesthesia, sleep, and coma.* N Engl J Med *363: 2638-2650, 2010.)*

The ascending nociceptive (pain) pathway begins with A-delta and C-fibers whose free nerve endings bring nociceptive information from the periphery to the spinal cord (see Fig. 50-1).[9] In the spinal cord, these fibers synapse in the dorsal horn on projection neurons that travel through the anterolateral fasciculus and synapse at multiple sites in the brainstem, including the nucleus of the tractus solitarius in the medulla.[2,8] The autonomic response to a nociceptive stimulus is initiated from the nucleus of the tractus solitarius, which mediates sympathetic output through the rostral ventral lateral medulla and the caudal ventral lateral medulla to the heart and peripheral blood vessels through projections to the thoracolumbar sympathetic ganglia.[2] The parasympathetic output from the nucleus of the tractus solitarius is mediated through the nucleus ambiguus, which projects through the vagus nerve to the sinoatrial node of the heart.[2] The nucleus of the tractus solitarius also projects to the periventricular nucleus and supraoptic nucleus in the hypothalamus. Thus, the nociceptive stimulus of moving the retractor initiates an increase in sympathetic output and a decrease in parasympathetic output through the NMA circuit that rapidly results in the observed increases in heart rate and arterial blood pressure.

The NMA circuit explains why increases in heart rate and arterial blood pressure are used as a rapid indicator of an inadequate level of analgesia. If unconsciousness is sufficiently well maintained, then no EEG changes will likely be observed. If no acute changes in physiology occur for other reasons, such as bleeding, hypoxemia, disconnection of the breathing circuit, or inadequate dosing of the muscle relaxant, the appropriate treatment is administration of more analgesic medication.

Activity in the NMA circuit can be observed rapidly when a patient is under general anesthesia,[10] because this pathway is a fundamental component of the fight-or-flight response.[11] This circuit is used as a sentinel for detecting nociceptive stimuli that can lead to autonomic, stress, and arousal responses. Heart rate and arterial blood pressure changes are the principal markers of activity under general anesthesia because motor responses are often blocked by muscle relaxation. Neurologists frequently test the NMA circuit with nociceptive stimuli, such as total body pinches, nail bed pinches, and sternal rubs, to evaluate the level of arousal of patients with brain injuries that affect the level of consciouness.[3,12,13]

Other signs of inadequate antinociception are perspiration, tearing, pupil dilation, and return of muscle tone and movement.[7] Changes in muscle tone and movement are not observed if the patient is receiving a muscle relaxant. The galvanic skin response has also been studied as a potentially more objective measure of antinociception;

however, it is not widely used in clinical practice.[14] If the nociceptive stimulus is sufficiently strong and dosing anesthetic is inadequate to ensure maintenance of unconsciousness, then changes in the EEG or in the EEG-based index may warn of return of consciousness.

MAINTENANCE OF GENERAL ANESTHESIA: ELECTROENCEPHALOGRAM-BASED INDICES OF LEVEL OF CONSCIOUSNESS

It is recognized that the EEG changes systematically in relation to the dose of anesthetic drug administered (Fig. 50-2).[2,6,15-17] As a consequence, the unprocessed EEG and various forms of processed EEG have been used to track the level of consciousness of patients receiving general anesthesia and sedation. Several EEG-based index systems have been studied and used in clinical practice. These systems process the EEG and provide an index value or set of values in real time or near real time that can be used to track the level consciousness. In general, the indices are designed to decrease with decreasing level of consciousness and increase as consciousness returns. In this way, the anesthesia provider can use these indices along with the physiological signs to track the patient's state of unconsciousness, and to some degree, antinociception. A summary of the EEG-based indices that have received the most use in clinical practice and clinical studies follows.

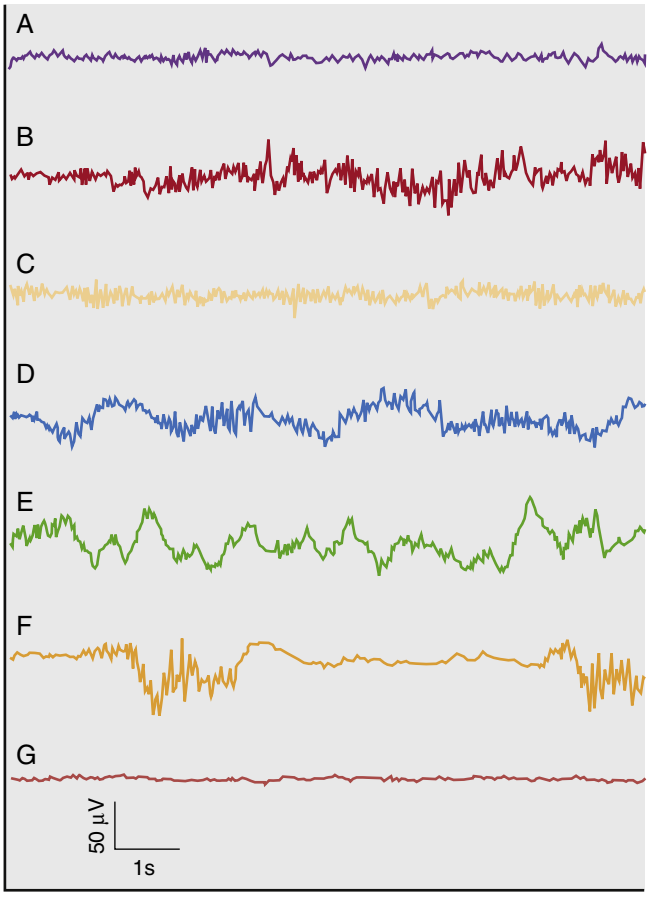


Figure 50-2. Anesthetic states and electroencephalogram signatures of propofol. **A,** Awake electroencephalogram pattern with eyes open. **B,** State of paradoxical excitation. **C,** Alpha (8 to 12 Hz) and beta (13 to 25 Hz) oscillations frequently associated with an arousable state of sedation. **D,** Slow (0.1 to 1Hz), delta (1 to 4 Hz), and alpha oscillations commonly seen during unconsciousness at surgical planes. **E,** Slow oscillations typically recorded during propofol induction and during deep dexmedetomidine sedation (see Fig. 50-8, *D*). **F,** Burst suppression, a state of profound anesthetic-induced brain inactivation, seen commonly in the elderly during normal maintenance, anesthetic induced coma, and hypothermia. **G,** Isoelectric electroencephalogram pattern commonly observed in brief periods during normal maintenance, in anesthetic-induced coma and profound hypothermia.

BISPECTRAL INDEX

The bispectral index (BIS) is an empirically derived scale that was proposed by Aspect Medical Systems (later purchased by Covidien [Boulder, Colo.]) in 1994, as a novel way to monitor level of consciousness among patients receiving general anesthesia and sedation.[18,19] The algorithm processes the EEG in near real time and computes an index value between 0 and 100 that indicates the patient's level of consciousness (Fig. 50-3).[20,21] A value of 100 corresponds to being completely awake, whereas 0 corresponds to a profound state of coma or unconsciousness that is reflected by an isoelectric or flat EEG. The BIS algorithm is proprietary, and the actual computation through which the index is derived is not public knowledge. However, it is known that BIS combines information from three EEG analyses: the spectrogram, the bispectrum, and a time domain assessment of burst suppression.[20-22] The spectrogram is a decomposition of the EEG into its power content by frequency as a function of time.[20] The bispectrum measures as a function of time the degree of nonlinear coupling between pairs of frequencies in the spectrogram.[20] The BIS algorithm works by measuring specific features of the spectrogram, the bispectrum, and the level of burst suppression and uses a predetermined weighting scheme to convert

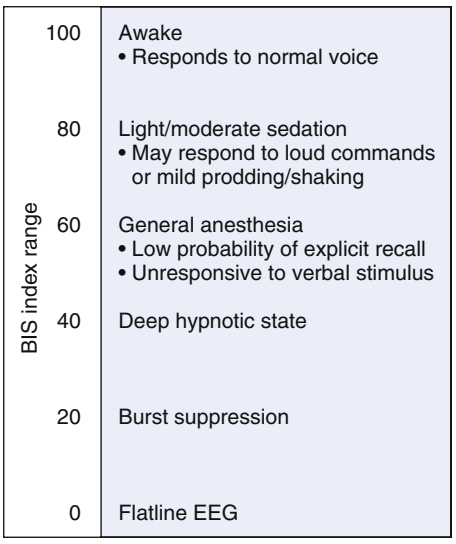


Figure 50-3. Anesthetic states and the bispectral index (BIS). The chart provides a behavioral interpretation of the values of the BIS. *EEG,* Electroencephalogram. *(Redrawn from Kelley SD:* Monitoring consciousness: using the bispectral index, *ed 2. Boulder, Colo., 2010, Covidien.)*

these features into the index value. The EEG also undergoes various artifact corrections. Along with the index value, the unprocessed EEG, the spectrogram and the level of electromyographic activity are displayed on the monitor. The production of the index is computationally intensive, so that there is a 20- to 30-second lag between the time the EEG is observed and the computation of the corresponding BIS value.[23] A patient is considered to be appropriately anesthetized (i.e., unconscious) when the value of the BIS is between 40 and 60 (Fig. 50-3).[21,24] The EEG is recorded from a four-lead frontal montage.

Since its approval by the U.S. Food and Drug Administration (FDA) in 1996, the BIS monitor has been studied extensively in clinical trials and used widely in anesthesiology practice. The changes in the index are correlated with the level of consciousness (Fig. 50-2). Primarily because, for many anesthetics, the EEG shows lower-frequency, higher-amplitude oscillations as patients achieve deeper states of unconsciousness. Three exceptions are the anesthetics ketamine (Fig. 50-6), nitrous oxide, and dexmedetomidine (Fig. 50-7). The dissociative anesthetic state produced by ketamine is associated with prominent high-frequency oscillations rather than slow wave oscillations. As a consequence, patients can be unconscious with ketamine but have unexpectedly high index values.[25] Nitrous oxide increases the amplitude of high-frequency EEG activity[26] and decreases the amplitude of low-frequency EEG activity,[27] yet it has little to no effect on the BIS index.[21,28] In the case of dexmedetomidine, slow oscillations are prominent during sedation,[29-31] (see Fig. 50-7) with BIS values that are typically in the unconscious range. However, the patient can be readily aroused by verbal commands or light shaking because dexmedetomidine does not produce profound unconsciousness. BIS values are also considered less reliable in pediatric patients.

The BIS monitor can be used as a way to prevent intraoperative awareness, which is defined as the patient having explicit recall of events that transpired during the time that he or she was under general anesthesia. Use of the BIS monitor as a way to prevent intraoperative awareness was studied in the B-Aware Trial.[32] This study compared patients at high risk for awareness who were randomly assigned to monitoring with BIS using a target range of 40 to 60 and patients monitored with the standard of care at that particular institution. The patients in the BIS group had a significantly lower incidence of awareness.

The findings from this study were called into question because of several design concerns, and for this reason the B-Unaware Trial was conducted.[33] The B-Unaware Trial was a multicenter investigation that randomly assigned patients to either BIS monitoring or monitoring of end-tidal anesthetic concentration to compare the two approaches for preventing awareness. The end-tidal anesthetic concentration criterion was maintenance of the volatile anesthetic between 0.7 and 1.3 of the age-adjusted minimum alveolar concentration (MAC) of the anesthetic administered to the patient (discussed under End-Tidal Anesthetic Criterion). As in the B-Aware Trial, the objective in the BIS-monitored group was maintenance of the BIS value between 40 and 60. This study found no significant difference in the incidence of awareness among the patients monitored with BIS compared with those monitored with the end-tidal anesthetic criterion. The authors interpreted these findings to mean that BIS monitoring was not more effective than the end-tidal anesthetic criterion in preventing awareness in patients receiving general anesthesia using volatile anesthetics. Several concerns were expressed about the findings of this study as well. The most notable were subject selection and whether the study had sufficient power to detect actual differences had they been present.[34,35]

As a follow-up to this study, the investigators in the B-Unaware Trial conducted a second trial comparing intraoperative awareness in a larger group of patients at high-risk for awareness using BIS and the end-tidal anesthetic criterion used in the first B-Unaware Trial.[36] In this trial, the investigators found that there was a statistically significant greater incidence of definite or possible awareness in the BIS group compared with the end-tidal anesthetic group. These findings suggested that monitoring of patients with BIS was less effective in reducing the likelihood of intraoperative awareness compared with patients who were monitored by the end-tidal anesthetic criterion. Because the two investigations conducted by the B-Unaware group used inhaled anesthetics as the primary anesthetic, their conclusions do not apply to cases in which the BIS is used to monitor level of consciousness in patients receiving total intravenous anesthesia.

Preventing awareness under general anesthesia is a solvable problem if strategies used to monitor the brain states of patients use markers that relate directly rather than indirectly to the mechanisms through which the anesthetics act at specific receptors and neural circuits to alter level of arousal. [2,37,38] Unlike the current EEG-based indices, these markers will most likely need to be different for the different anesthetics. (See Unprocessed EEG and the Spectrogram.)

PATIENT SAFETY INDEX

The Patient Safety Index (PSI) is like the BIS index, a proprietary algorithm that assesses level of consciousness based on the EEG for patients receiving general anesthesia or sedation. The PSI was approved by the FDA in 2000 and was originally produced by Physiometrix (North Billerica, MA), but it is now manufactured and sold by Masimo (Irvine, CA). The development of the PSI was the outgrowth of several years of research conducted by E. Roy John at the Brain Research Laboratory at the New York University School of Medicine.[39] Like the BIS index, the PSI is also scaled between 0 and 100 (see Fig. 50-4). However, the PSI range to ensure that the patient is unconscious is between 25 and 50.[40]

The original formulation of the PSI used an electrode montage that included occipital and frontal EEG leads to monitor the phenomenon of anteriorization as a marker of change in level of consciousness. Anteriorization is the forward shift of spectral power from the occipital area to the frontal area during loss of consciousness and the posterior shift of this power from the frontal areas to the occipital areas during the return of consciousness.[38,41-43] The current formulation of the PSI uses only a four-lead

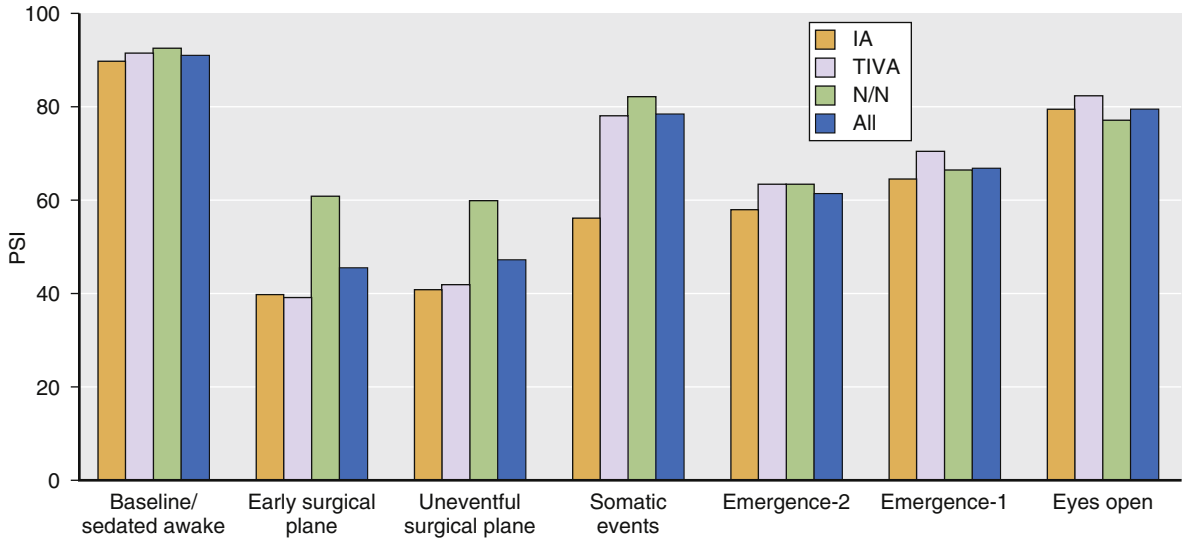


Figure 50-4. Anesthetic states and the patient safety index (PSI). The histogram provides the anesthetic state interpretation of the values of the PSI. *IA,* Inhaled anesthetics; *N/N,* nitrous narcotic; *TIVA,* total intravenous anesthesia. *(Redrawn from Drover D, Ortega HR: Patient state index,* Best Pract Res Clin Anaesthesiol *20:121-128, 2006.)*

frontal EEG montage. In addition to displaying the PSI, this monitor also shows in real time the unprocessed EEG and its spectrogram from both the left and right sides of the head, the level of electromyographic activity, an artifact index, and the suppression ratio. The suppression ratio is a number between 0 and 100 that measures the fraction of time the EEG is in burst suppression. The monitor also allows the user to change the viewing screen among various combinations of the unprocessed EEG traces, the spectrogram, and the time series of the index values.

In head-to-head comparisons, the PSI correlates strongly with the BIS readings in terms of tracking a patient's level of consciousness.[44-46] This monitor has been less frequently studied in clinical investigations and has not received the same level of clinical use as the BIS monitor. In our experience, the PSI can also give ambiguous information for ketamine, nitrous oxide, dexmedetomidine, and pediatric patients.

NARCOTREND

The Narcotrend produced by MonitorTechnik (Bad Bramstedt, Germany) is an EEG-based device designed to monitor the level of consciousness in patients receiving general anesthesia or sedation.[47] This monitor was developed at the University Medical School of Hanover, Germany, and has been approved for use in the United States for patient care by the FDA. Like the BIS and PSI, the Narcotrend uses a proprietary algorithm that converts the EEG into different states denoted as *A* to *F* (Table 50-1).[48] Stage A corresponds to the patient being wide-awake, whereas stage F corresponds to increasing burst suppression down to an isoelectric state. The newer version of the Narcotrend monitor includes a Narcotrend Index, which is scaled between 0 and 100.[48] In addition, the Narcotrend monitor displays the unprocessed EEG signal and its spectrogram. This monitor has also been validated with respect to the BIS index and separately. Its performance has been variable.[23,49,50] Narcotrend has received less clinical use than BIS and PSI.

TABLE 50-1 ANESTHETIC STATES, THE NARCOTREND STAGES, AND NARCOTREND INDEX RANGES

	Narcotrend Stage	Narcotrend Index
Awake	A	95-100
	B_0	90-94
Sedated	B_1	85-89
	B_2	80-84
Light anesthesia	C_0	75-79
	C_1	70-74
	C_2	65-69
General anesthesia	D_0	57-64
	D_1	47-56
	D_2	37-46
General anesthesia with deep hypnosis	E_0	27-36
	E_1	20-26
	E_2	13-19
General anesthesia with increasing burst supression	F_0	5-12
	F_1	1-4

From Kreuer S, Wilhelm W: The Narcotrend monitor, Best Pract Res Clin Anaesthesiol *20:111-119, 2006.*

The table provides the anesthetic state interpretation of the Narcotrend Stages and the Narcotrend Index values.

ENTROPY

The use of entropy to track the level of consciousness in patients receiving general anesthesia or sedation is a relatively new monitoring approach. The Entropy monitor was developed by Datex-Ohmeda, which is now part of GE Healthcare (Little Chalfont, UK). Entropy is a well-known concept in the physical sciences, mathematics, and information theory. Entropy measures the degree of disorder or the lack of synchrony or consistency in a system.[51] The algorithm in the GE device uses frequency domain analysis, combined with burst suppression to measure the entropy of the EEG in patients receiving anesthetic drugs. Unlike several of the other algorithms

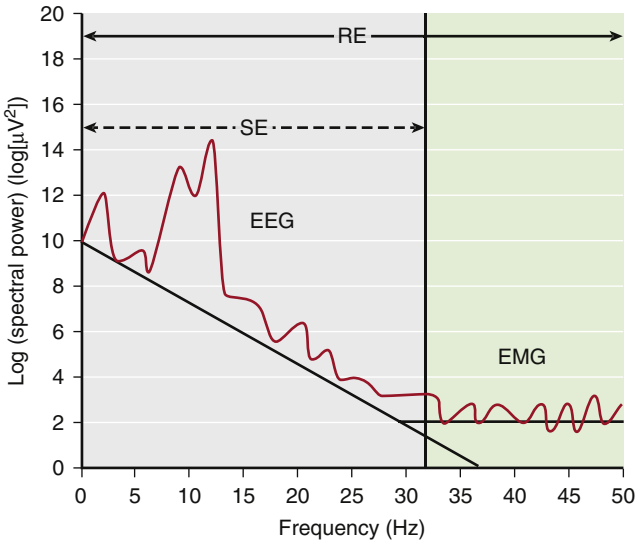


Figure 50-5. Schematic representation of the spectral entropy. The response entropy (RE) is computed from the power in the frequencies between 0 and 47 Hz. The state entropy (SE) is computed from the power in the frequencies between 0 and 32 Hz. The power between 32 and 47 Hz is assumed to represent artifacts coming from the electromyogram (EMG). The difference between the RE and SE allows the anesthesiologist to distinguish between electroencephalogram (EEG) changes related to changes in the anesthetic state and changes that are due to artifact or movement. *(Redrawn from Bein B: Entropy,* Best Pract Res Clin Anaesthesiol *20:101-109, 2006).*

we have discussed, the entropy algorithm used in the GE entropy device is publicly available.[52,53]

A readily apparent feature of the EEG, as patients proceed through deeper levels of unconsciousness induced by general anesthesia, is that the patterns become more regular and ordered (Fig. 50-2). That is, we observe an apparent decrease in the entropy of the EEG signal. The Entropy monitor reports two entropy numbers to aid in interpreting this monitor's EEG analysis (Fig. 50-5).[54] The first is the response entropy (RE) and the second is the state entropy (SE). The RE tracks the changes in the EEG power in the higher frequency range 0.8 to 47 Hz, whereas the SE tracks the changes in the EEG power in the lower frequency range of 0.8 to 32 Hz.[52] The relative changes in the RE and the SE make it possible to distinguish between real brain state changes versus those that are due to muscle activity on the electromyogram.[52] In general, electromyographic activity shows in the higher frequency range tracked by the RE. As a patient becomes more profoundly unconscious, the RE declines faster than the SE, thereby making it possible to distinguish unconsciousness from movement artifacts. Monitoring entropy is consistent with changes with the BIS.[55]

Like the BIS, PSI, and Narcotrend, the Entropy scores correlate with level of consciousness. The Entropy monitor, like BIS and the PSI, can show paradoxically high readings for ketamine and nitrous oxide. The Entropy scores can be misleading when the patient is receiving dexmedetomidine, because the highly ordered slow waves that are present commonly during deep sedation with dexmedetomidine do not necessarily indicate a profound state of unconsciousness (see Fig. 50-8, *B*).

END-TIDAL ANESTHETIC CRITERION

In 1965, Eger and colleagues[56] first introduced the concept of the MAC of inhaled anesthetic required for immobility (defined as lack of movement in response to noxious stimulation). Five years later, Eger's group also introduced the concept of MAC-awake, or the MAC of inhaled anesthetic necessary to ablate response to a verbal command.[57] The median MAC value (i.e., the MAC of inhaled anesthetic required for immobility in 50% of patients) remains the gold standard for dosing inhaled anesthetics, and some modern anesthesia machines calculate age-adjusted MAC values based on the patient's end-tidal anesthetic gas concentration. However, the ratio of MAC to MAC-awake varies widely among general anesthetics,[58] suggesting that MAC cannot be used to define or predict brain states in anesthetized patients. This has been confirmed by animal experiments demonstrating that there is no clear association between anesthetic-induced EEG patterns and immobility,[59] and that inhaled anesthetics produce immobility primarily through their actions in the spinal cord, rather than the brain.[60,61] Nevertheless, the widely accepted concept of MAC has led to the use of end-tidal anesthetic criterion as a way to monitor the level of unconsciousness induced by inhaled anesthetics.

As mentioned previously, this use of MAC has been supported by the B-Unaware Trial that reported no difference in the incidence of intraoperative awareness with an anesthetic protocol that maintained the BIS value between 40 and 60, and a protocol that maintained an end-tidal anesthetic concentration between 0.7 and 1.3 MAC[33] (see Bispectral Index). Similarly, the BAG-RECALL Trial limited enrollment to patients at high risk for intraoperative awareness. Patients with BIS-guided general anesthesia experienced a small but high and statistically significant incidence of intraoperative awareness than patients receiving general anesthesia guided by an end-tidal anesthetic criterion[36] (see Bispectral Index).

Unlike the BIS, PSI, Entropy, and Narcotrend, which provide EEG-based measures of brain activity, the end-tidal anesthetic criterion is related to brain activity through the concentration of anesthetic expired in the lungs. This assumes that the lung anesthetic concentration is in equilibrium with the brain concentration. The end-tidal anesthetic criterion is thus an indirect and less nuanced measure of level of consciousness given that the relevant effects of the anesthetics for inducing unconsciousness are in the brain and not in the lungs. That an EEG-based criterion and a lung-gas criterion are comparable for monitoring the level of consciousness under general anesthesia suggests more of a flaw in the design of the EEG-base marker rather than the superiority of the end-tidal anesthetic criterion. Because it is a more indirect measure of level of consciousness, the success of the end-tidal anesthetic criterion in preventing awareness likely comes at the expense of overdosing some patients. A key drawback of the end-tidal anesthetic criterion is that it cannot be used with total intravenous anesthesia.

OTHER STRATEGIES FOR MONITORING LEVEL OF CONSCIOUSNESS

Other strategies for monitoring level of consciousness during general anesthesia and sedation have been

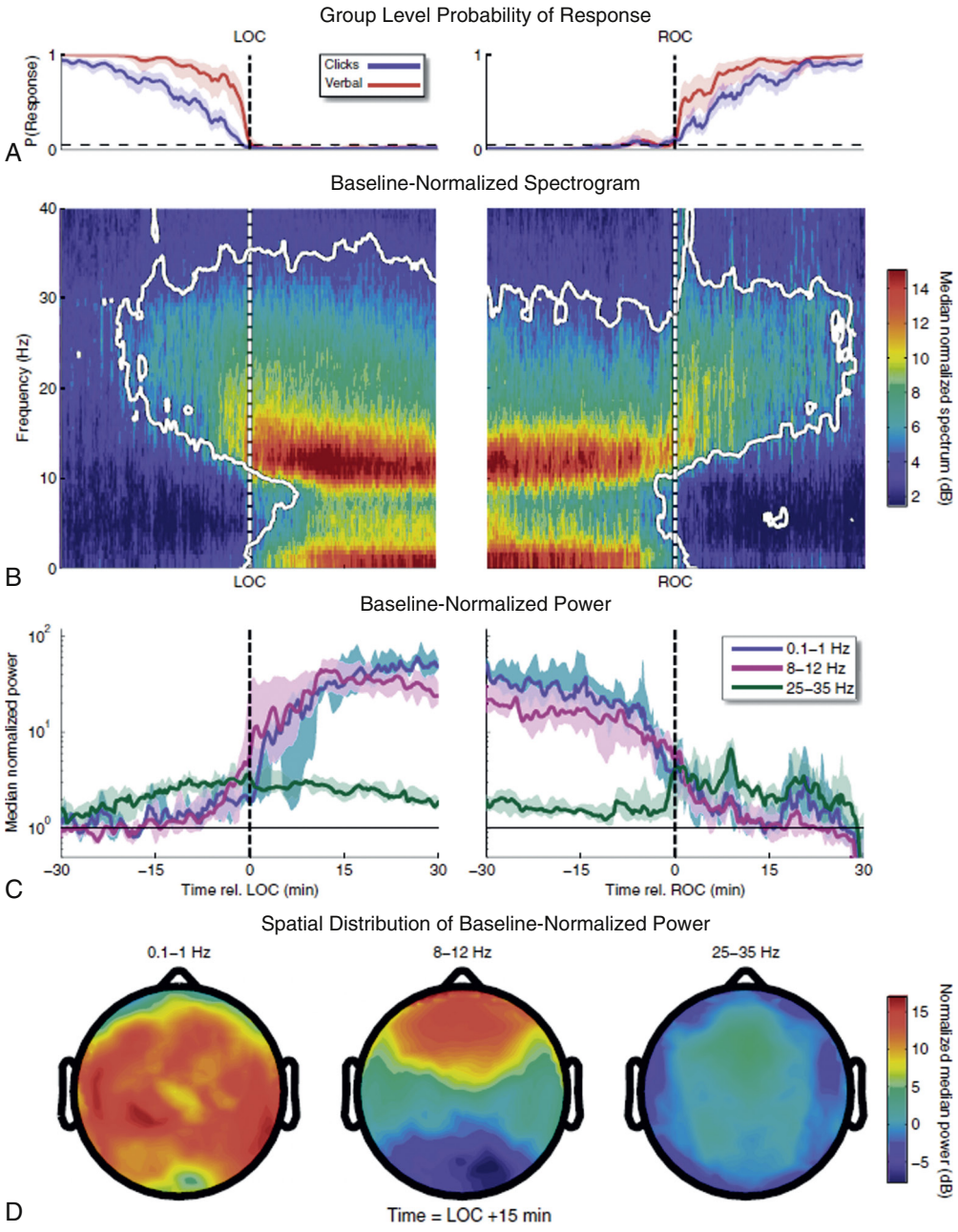


Figure 50-6. Behavioral and electroencephalogram (EEG) dynamics of loss and recovery of consciousness from propofol. **A,** Group-level (10 subjects) click or nonsalient stimulus (*blue*, P_{clicks}) and verbal or salient stimulus (*red*, P_{verbal}) response-probability curves. **B,** Group-level spectrograms computed by baseline-normalization from a frontal channel (approximately *Fz*, using nearest-neighbor Laplacian reference) aligned across subject with respect to loss of consciousness (LOC). Area enclosed within the white borders show where power is significantly different from baseline ($P < 0.05$, sign test) and shows significant power increases spanning slow (0.1-1 Hz) through gamma (25-35 Hz) bands. **C,** Time course of group-level power in slow, alpha (8-12 Hz), and gamma bands aligned with respect to LOC and recovery of consciousness (ROC). **D,** Group-level spatial distribution of slow, alpha, and gamma power during unconsciousness (LOC + 15 min). The frontal increase in alpha power is termed *anteriorization*. These analyses illustrate that changes in broad-band gamma/beta power occur with the behavioral changes before LOC and after ROC, whereas changes in slow and alpha power occur with LOC and ROC. *(From Purdon PL, Pierce ET, Mukamel EA, et al: Electroencephalogram signatures of loss and recovery of consciousness from propofol,* Proc Natl Acad Sci U S A *110:E1142-E1151, 2013.)*

studied. For example, the Cerebral State Monitor,[62] the SNAP Index,[63] and the AEP Index[64] are other EEG-based approaches that have been studied and applied in clinical practice.

EMERGENCE FROM GENERAL ANESTHESIA

ELECTROENCEPHALOGRAM-BASED INDICES AND RETURN OF CONSCIOUSNESS

As stated earlier, the EEG-based indices typically specify a range for maintenance of unconsciousness under general anesthesia (see Figs. 50-3 to Fig. 50-5 and Table 50-1). When delivery of the anesthetic drugs is decreased or terminated, the indices increase toward values that are consistent with the awake state. As the values of the indices increase, the patient is more likely to become conscious. In this way, the EEG-based indices can be used to monitor the transition from unconsciousness to return of consciousness during emergence from general anesthesia. Although the values of the indices increase during emergence, none of the indices has a value at which the patient is certain to regain consciousness. The reason for this lack of perfect correlation between the values of the EEG-based index and the return of consciousness may be due to imprecision in the definition of the indices in that many different anesthetic states are presumed to map to the same index value. Kelz and colleagues found that neural inertia can play a role with inhaled anesthetics.[65,66]

BOX 50-1 *Phases of Emergence From General Anesthesia and States of Coma Recovery*

General Anesthesia
Stable administration of anesthetic drugs
Arousal not possible, unresponsive; eyes closed, with reactive pupils
Analgesia, akinesia
Drug-controlled blood pressure and heart rate
Mechanically controlled ventilation
EEG patterns ranging from delta and alpha activity to burst suppression

Emergence, Phase 1
Cessation of anesthetic drugs
Reversal of peripheral-muscle relaxation (akinesis)
Transition from apnea to irregular breathing to regular breathing
Increased alpha and beta activity on EEG

Emergence, Phase 2
Increased heart rate and blood pressure
Return of autonomic responsiveness
Responsiveness to painful stimulation
Salivation (CN VII and IX nuclei)
Tearing (CN VII nuclei)
Grimacing (CN V and VII nuclei)
Swallowing, gagging, coughing (CN IX and X nuclei)
Return of muscle tone (spinal cord, reticulospinal tract, basal ganglia, and primary motor tracts)
Defensive posturing
Further increase in alpha and beta activity on EEG
Extubation possible

Emergence, Phase 3
Eye opening
Responses to some oral commands
Awake patterns on EEG
Extubation possible

Brain-Stem Death
No respiratory response to apneic oxygenation test
Total loss of brain-stem reflexes
Isoelectric EEG pattern

Coma
Structural brain damage to both cerebral hemispheres, with or without injuries to tegmental midbrain, rostral pons, or both
Isolated bilateral injuries to midline tegmental midbrain, rostral pons, or both
Arousal not possible, unresponsive
Functionally intact brain stem, normal arterial blood gases
EEG pattern of low-amplitude delta activity and intermittent bursts of theta and alpha activity or possibly burst suppression

Vegetative State
Spontaneous cycling of eye opening and closing
Grimacing and nonpurposeful movements
EEG pattern of high-amplitude delta and theta activity
Absence of EEG features of sleep
Usually able to ventilate without mechanical support

Minimally Conscious State
Purposeful guarding movements, eye tracking
Inconsistent communication, verbalizations
Following oral commands
Return of sleep–wake cycles
Recovery of some EEG features of normal sleep–wake architecture

From Brown EN, Lydic R, Schiff ND: General anesthesia, sleep, and coma, N Engl J Med *363:2638-2650, 2010.*
EEG, Electroencephalogram.
General anesthesia is a drug-induced, reversible coma. The physiological signs observed in the phases of emergence from general anesthesia can be related to changes in activity in specific brainstem nuclei. Emergence from general anesthesia has similarities and differences with recovery from coma due to a brain injury.

Neural inertia is the extent to which equal brain concentrations of anesthetic on induction and emergence often yield different behavioral states. In other words, the history of the brain states helps determine arousability.

PHYSIOLOGIC SIGNS AND RETURN OF CONSCIOUSNESS

The state of the patient during emergence from general anesthesia can be tracked reliably by monitoring the patient's physiologic signs and performing neurologic examinations.[2] Many of these physiologic changes relate to the return of brainstem function (Box 50-1). Therefore, by relating the physiologic signs and the findings from the neurologic examinations to the brainstem centers responsible for them, anesthesia providers can map the return of function to specific brainstem sites during emergence from general anesthesia. Once neuromuscular blockade has been reversed (see Chapter 35), the patient may breathe unassisted. As the level of carbon dioxide in the cerebral circulation becomes sufficiently high, most patients begin to breathe spontaneously. As the patient emerges from general anesthesia, the respiratory pattern can transition from one that is irregular with small tidal volumes to one that is regular with full normal tidal volumes.[2] Return of spontaneous breathing is a distinct indicator of return of function in the medulla and lower pons, as these are the locations of the dorsal and ventral respiratory groups, respectively.[5]

Over the ensuing several minutes and often concomitant with the return of spontaneous respiration, a series of other clinical signs begin to appear (see Box 50-1). These signs include swallowing, gagging, salivation, tearing, and grimacing.[2] The signs represent return of a specific center in the brainstem and their associated sensory and motor pathways. Swallowing, gagging, and coughing represent

return of the motor nuclei of the cranial nerves IX and X located in the medulla and the sensory afferent of these nerves arising from the trachea, larynx, and pharynx.[9] These physiologic signs appear because with the progressive decrease in the hypnotic and antinociceptive effects of the anesthetics, the endotracheal tube becomes a progressively more noxious stimulus. Salivation reflects the return of the inferior salivatory nucleus in the medulla and superior salivatory nucleus in the pons. Both are part of the parasympathetic nervous system. The efferent pathways from these nuclei travel in cranial nerves VII and IX, respectively.[9] Tearing also reflects the return of function in the superior salivatory nucleus. Grimacing, the use of muscles of facial expression, represents the return of function to the motor nucleus of cranial nerve VII, located in the pons.[9] Return of muscle tone to the upper and lower extremities is another important clinical sign that clearly reflects return of function in a number of circuits including the spinal cord, the reticulospinal tract, the basal ganglia, and the primary motor tracts.[2] In addition, as the endotracheal tube is perceived as more noxious and motor tone has returned, the patient may commonly exhibit defensive posturing indicated by reaching for the endotracheal tube.

These physiologic signs are often present in advance of the patient responding to any verbal commands. The patient need not respond to commands to be extubated. Tracheal extubation only requires that the patient have sufficient return of airway reflexes and motor function to ventilate and oxygenate adequately with spontaneous breathing. To meet the criteria for extubation of the trachea, a patient can be in a vegetative state as defined by the criteria used by neurologists and rehabilitation specialists to assess the brain states of patients recovering from coma (see Box 50-1).[12,13,67]

The corneal and oculocephalic reflexes typically return at the same time or after the patient begins to grimace (see Box 50-1).[2] Return of the corneal reflex reflects return of function in the sensory nucleus of cranial nerve V and the motor nucleus of cranial nerve VII.[3] The afferent pathway in the corneal reflex is the ophthalmic branch of cranial nerve V that projects to the trigeminal (cranial nerve V) nucleus, whereas the efferent pathway arises from the facial nerve (cranial nerve VII) nucleus. The consensual response in the corneal reflex indicates bilateral return of the sensory and motor components of this pathway. The trigeminal nucleus and the motor nucleus of cranial nerve VII lie in the pons. Return of the oculocephalic reflex indicates return of activity in the oculomotor (III), trochlear (IV), and abducens (VI) cranial nerves, which control movement of the eyes.[3] The cranial nerves III and IV nerve nuclei are located in the midbrain, whereas the cranial nerve VI nerve nucleus is in the pons. Return of the oculocephalic and corneal reflexes provides indirect evidence that the arousal centers in the nearby pons, midbrain, hypothalamus, and basal forebrain, may have also recovered function.[2] The pupils can remain pinpoint if the patient has received a substantial dose of narcotic. The pupillary light reflex can remain intact even when the patient is profoundly unconscious under general anesthesia[3]; therefore, the presence of the pupillary light reflex might not indicate a change in the level of consciousness while under general anesthesia.

Responding correctly to verbal commands, a criterion that is commonly used to assess the extent to which a patient has recovered from general anesthesia, and hence the patient's readiness for extubation, suggests a return of integrated function between the brainstem, the thalamus and cortex, and among cortical regions is a necessary condition.[2,68,69] Responding correctly to verbal commands means that the patient is correctly interpreting auditory information and that the cranial nerve VIII nuclei located in the pons and the auditory pathways from the pons to the cortex and the relevant effector pathways have regained substantial function. If the patient inconsistently follows motor commands, then he or she is classified as being in a minimally conscious state by the criteria neurologists use in examining patients recovering from coma (see Box 50-1).[12,13,67] With emergence, the physiologic signs and neurologic findings can be related to changes in activity in specific brainstem centers. Although the EEG shows the resumption of high-frequency activity consistent with the return of cognitive processing, normal brainstem-cortical, brainstem-thalamic, thalamocortical and intracortical communication must clearly return for full return of consciousness.[38,69-72] Current clinical monitoring approaches do not allow us to monitor these changes adequately.

Opening of the eyes is typically one of the last physiologic signs observed in patients emerging from general anesthesia. In particular, patients may respond reliably to verbal commands, have substantial return of motor functions, yet not necessarily open their eyes.[2] Generally, patients tend to keep their eyes closed even when consciousness has returned. In contrast, during coma recovery, patients can have their eyes open in a vegetative state (see Box 50-1).

EMERGING STRATEGIES FOR MONITORING THE BRAIN STATES OF GENERAL ANESTHESIA AND SEDATION

In the last several years, there has been strong growth in neuroscience of general anesthesia research. As a result, there are several reports of new approaches to monitoring the brain states under general anesthesia.

UNPROCESSED EEG AND THE SPECTROGRAM

Different anesthetics have different receptor targets[73] and neural circuit mechanisms of action.[2,37] These differences in targets and neural circuits translate into different patterns of activity in the brain that are readily visible in the unprocessed EEG or its spectrogram. The spectrum for a segment of EEG is the decomposition of the EEG signal into its power content by frequency. Power is typically expressed in decibels as the logarithm of the square of the amplitude of a given frequency component. When the spectrum is computed on successive nonoverlapping or overlapping segments of EEG data, it is termed the *spectrogram*; the *compressed spectral array* when the spectrogram is plotted in three dimensions[74]; and the *density spectral array* when it is plotted in two-dimensions.[75]

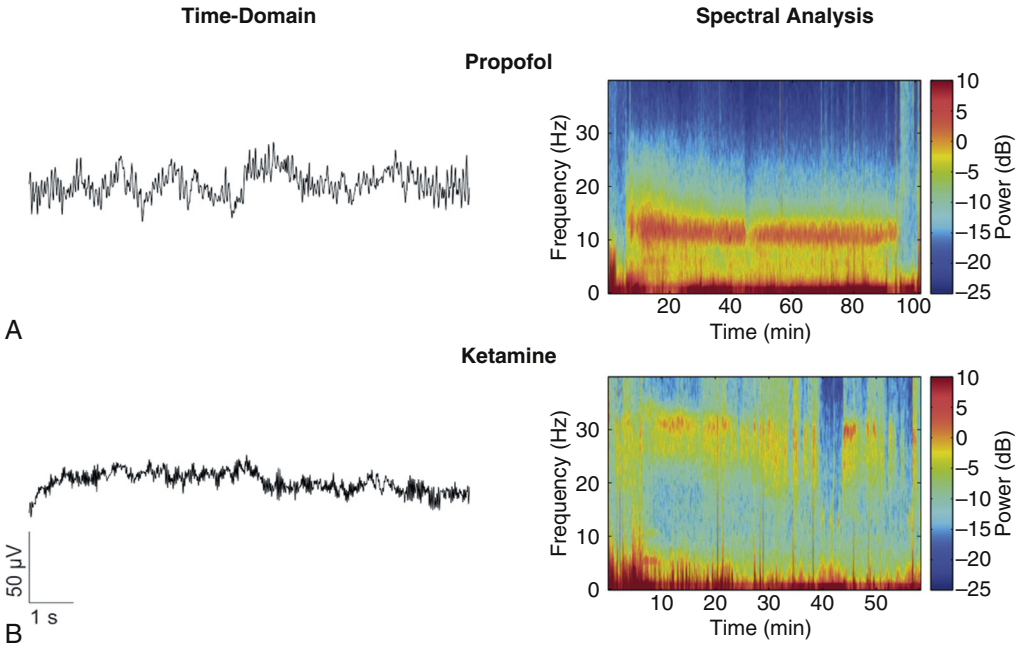


Figure 50-7. Time-domain and spectral electroencephalogram (EEG) signatures of common anesthetics. The left column shows a 10-second time-domain (unprocessed) segment of the EEG for each anesthetic. The right column shows several minutes of the spectrogram (density spectral array) computed from the EEG for each anesthetic. **A,** The spectrogram of propofol shows its characteristic alpha (8-12 Hz) and slow-delta (0.1-4 Hz) oscillation pattern. **B,** The ketamine spectrogram shows high frequency oscillations in the high beta (20-24 Hz) and low gamma (25-35 Hz) range.

The EEG patterns of propofol have been related to its neural circuit mechanisms. The brain states under propofol are readily visible in the unprocessed EEG and the spectrogram (Figs. 50-2, 50-6 and Fig. 50-7, *A*). Propofol acts primarily at $GABA_A$ receptors throughout the brain and spinal cord to enhance inhibition in neural circuits.[73,76] When patients are unconscious from propofol, the EEG shows a characteristic alpha (8 to 12 Hz) oscillation along with slow (0.1 to 1 Hz) oscillations (see Fig. 50-7, *A*).[38,43,77,78] Another phenomenon that is observed in patients who are unconscious from propofol and several other anesthetics is anteriorization, the increase in power in the alpha and beta frequency ranges during unconsciousness across the front of the scalp relative to other areas of the scalp (see Fig. 50-6, *C, D*).[38,41,43] During unconsciousness, the alpha oscillations are highly coherent across the front of the scalp, whereas the slow and gamma oscillations are not coherent.[38,43,78] Highly coherent alpha oscillations have also been identified in animal studies of inhaled anesthetics during unconsciousness.[79] The coherent structure in the alpha oscillations is most likely due to strong alpha oscillations between the thalamus and frontal cortex.[80] The slow oscillations are a marker of fragmented intracortical communication because in the presence of the slow oscillations, cortical neurons spike only in a limited phase dictated by their local slow oscillation.[78] As the slow oscillations are spatially incoherent and spiking is phase limited, communication among brain regions that are separated by more than 1 cm is greatly impeded. With return of consciousness, the alpha and slow oscillations dissipate (see Fig. 50-6, *B*). Understanding how the alpha and slow oscillations arise offers a neural circuit explanation of part of the mechanism through which propofol induces unconsciousness.

Similarly, the EEG patterns of ketamine (see Fig. 50-7, *B*)[25] and dexmedetomidine (see Fig. 50-8, *A, B*)[29,30] are distinctive and can be related to the mechanisms of actions of these drugs in the brain and central nervous system.[2,37] Ketamine acts principally by binding to *N*-methyl-D-aspartate (NMDA) receptors.[37,81] Thus, with small to moderate doses, ketamine has its primary effect by blocking excitatory glutamatergic inputs to inhibitory interneurons.[82,83] Impaired control over pyramidal neurons is why increases in cerebral metabolism, and the appearance of altered behavioral states including hallucinations, dissociative states, euphoria, and dysphoria are common with low-dose ketamine. Brain regions, such as the limbic system, cortex, and thalamus, continue to communicate but with much less regulatory control from the inhibitory interneurons; that is, information processing proceeds in the absence of proper coordination in time and space.[2,37] Increasing the dose of ketamine blocks the NMDA receptors on the excitatory glutamatergic neurons, and eventual loss of consciousness, as when ketamine is used to induce anesthesia.[84] The increased activity of pyramidal neurons throughout the brain is consistent with the high frequency (20 to 30 Hz) oscillations that are commonly observed in the EEG of patients receiving ketamine (see Fig. 50-7, *B*).[25,85] This high-frequency EEG activity helps explain why EEG-based indices often give high values in patients receiving ketamine.

Dexmedetomidine induces its sedative effects primarily by actions on presynaptic α2-adrenergic receptors on neurons that project from the locus ceruleus.[86-88] Binding of dexmedetomidine results in a decrease in the release

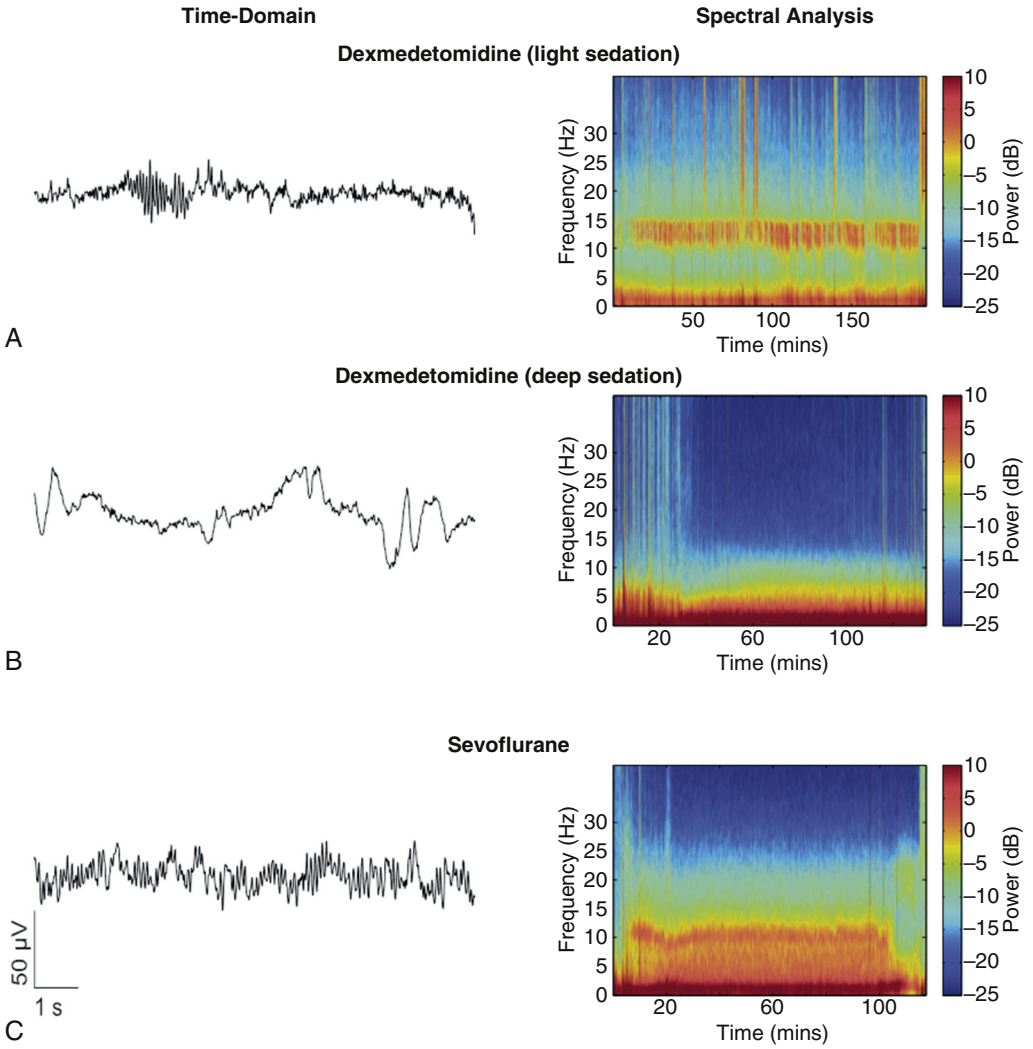


Figure 50-8. Time-domain and spectral electroencephalogram (EEG) signatures of common anesthetics. The *left column* shows a 10-second time-domain (unprocessed) segment of the EEG for each anesthetic. The *right column* shows several minutes of the spectrogram (density spectral array) computed from the EEG for each anesthetic. **A,** The dexmedetomidine spectrogram for light sedation shows spindle (9 to 15 Hz) oscillations and the slow oscillations similar to the EEG patterns observed in nonrapid eye movement (NREM) sleep stage 2. The spindle is apparent in the unprocessed EEG trace (red underscore). The spindles are intermittent and have less intensity than the alpha oscillations observed with propofol. **B,** The spectrogram for deep dexmedetomidine sedation is associated with an absence of spindles and a predominance of slow waves similar to the slow waves seen in NREM sleep stage 3, termed *slow-wave sleep*. **C,** The sevoflurane spectrogram is similar to propofol with the addition of oscillatory activity in the theta band from 4 to 8 Hz. *LOC,* Loss of consciousness; *ROC,* recovery of consciousness.

of norepinephrine from these neurons.[89-91] Loss of the norepinephrine-mediated inhibition to the preoptic area of the hypothalamus leads to activation of the preoptic area's GABAergic and galanergic inhibitory inputs to most of the principal arousal centers in the midbrain, pons, basal forebrain, and hypothalamus.[92] Activation of inhibitory inputs from the preoptic area is postulated to be an essential component of how nonrapid eye movement (NREM) sleep is initiated.[93,94] This explains why light sedation with dexmedetomidine shows spindle-intermittent bursts of 9 to 15 Hz oscillations and slow-wave patterns in the EEG that closely resemble NREM sleep stage 2 (see Fig. 50-8, *A*). In contrast, deep sedation with dexmedetomidine shows a slow-wave EEG pattern that closely resembles the patterns observed in NREM sleep stage 3 or slow-wave sleep (see Fig. 50-8, *B*).

Sevoflurane, like the other inhaled anesthetics, produces its physiologic and behavioral effects by binding at multiple targets in the brain and spinal cord. These include binding to $GABA_A$ receptors and enhancing GABAergic inhibition, and blocking glutamate release by binding to NMDA receptors, moreover, blocking two-pore potassium channels and hyperpolarization-activated cyclic nucleotide-gated channels.[73] Although debates still exist over the relative importance of these targets, sevoflurane and the other ether anesthetics have distinct EEG signatures. At doses of sevoflurane appropriate for general anesthesia, the EEG shows strong alpha and slow oscillations like propofol, in addition to a strong theta (4 to 8 Hz) oscillation (see Fig. 50-8, *C*). The presence of the theta oscillations creates a distinctive pattern of evenly distributed EEG power from the slow oscillation through the alpha oscillation range.

Although the unprocessed EEG recordings of the anesthetics can look similar, the spectrograms make clear that each anesthetic has a distinct EEG signature. These signatures can be related to the mechanisms through which the drugs act at specific receptors in specific neural circuits to alter arousal. Using the spectrogram to monitor brain function under general anesthesia and sedation is fundamentally different from using EEG-based indices that are predicated on the assumption that different anesthetics can create the same anesthetic state irrespective of mechanism. The differences in the spectral signatures between propofol (see Fig. 50-7, *A*) and ketamine (see Fig. 50-7, *B*) illustrate why the latter often gives a high index reading when clinically the patient is clearly sedated. Similarly, the predominance of the slow-wave oscillations observed during deep dexmedetomidine (see Fig. 50-8, *B*) sedation helps explain why this drug gives low index values consistent with profound unconsciousness yet the patient remains arousable.

These observations suggest that the unprocessed EEG and the spectrogram could be used to monitor the brain states of patients receiving anesthesia care (see Figs. 50-6 to 50-8). Although the spectrogram has been used on many occasions for studies of anesthetic state,[74,75,95] a strategy to use it in conjunction with the unprocessed EEG and the EEG-based indices for management of patients receiving anesthesia care has not been attempted. Furthermore, the spectrogram is easy to compute in real time. Many of the current EEG brain function monitors display both the unprocessed EEG and the spectrogram.[21,48,96] Training anesthesia providers to track brain states under general anesthesia and sedation by reading the unprocessed EEG and the spectrogram is a program being pursued currently in the Department of Critical Care and Pain Medicine of Massachusetts General Hospital (www.anesthesiaeeg.com). Use of the spectrogram to track brain states under general anesthesia and sedation can facilitate direct integration of clinical and research observations from EEG recordings into biophysically based modeling studies that can help to delineate specific, testable hypotheses about neural circuit mechanisms of anesthetic actions.[80,97-99]

NORMALIZED SYMBOLIC TRANSFER ENTROPY

A growing body of information suggests that a key marker or mechanism of unconsciousness under general anesthesia is loss of intracortical connectivity.* The loss of functional connectivity between the frontal and parietal areas is associated with unconsciousness.[84,100] By using the EEG recorded from a montage that includes both frontal and parietal electrodes, a mutual information technique termed normalized symbolic transfer entropy (NSTE) can be used to measure this loss of functional connectivity. When NSTE is used to assess functional connectivity from the parietal area to the frontal cortical area, it is termed feedforward functional connectivity, whereas when it is used to assess functional connectivity from the frontal area to the parietal area, it is termed feedback functional connectivity.

Unconsciousness induced by propofol, sevoflurane, or ketamine has been associated with loss of feedback functional connectivity (Fig. 50-9).[84,100] As a consequence, measuring NSTE to assess functional connectivity could provide a means of monitoring the level of consciousness in patients receiving general anesthesia. The loss of feedback functional connectivity is present for unconsciousness induced by all three anesthetics, suggesting that NSTE does not distinguish among the mechanisms of actions of these anesthetics.[100] Nevertheless, NSTE could still offer a way to track level of consciousness.

A partial answer regarding the mechanism of loss of the feedback functional connectivity for unconsciousness induced by propofol and the inhaled ether anesthetics may be related to anteriorization (see Fig. 50-7, *C*). The recent model by Vijayan and colleagues[99] shows that anteriorization can be explained by the differences in the electrophysiologic properties, such as the resting membrane potentials and ionic currents, in the frontal thalamocortical connections compared with the posterior thalamocortical connections. If the parietal circuits resemble their nearby occipital counterparts neurophysiologically, then the neurophysiologic dynamics that lead to anteriorization could also contribute to loss of feedback functional connectivity. Studies of functional connectivity changes during loss of consciousness due to general anesthesia using the Vijayan model may shed mechanistic light on the differences between changes in feedback connectivity and feedforward connectivity.

At present, the use of NSTE in the operating room is not tractable because it is not possible to compute these mutual information measures in real time.[84] Moreover, the use of NSTE in its current form requires an EEG montage with both frontal and parietal electrodes, unlike the montages used with most current brain function monitors, which use only frontal electrodes.

CLOSED-LOOP ANESTHETIC DELIVERY SYSTEMS

Several clinical studies have recently demonstrated the benefit of closed-loop anesthetic delivery (CLAD) systems as a means of simultaneously monitoring brain function and delivering anesthetic drugs. These studies have been summarized recently.[102,103] The CLAD systems work by using an EEG marker of anesthetic state to define a desired state for maintenance during surgery. The EEG is monitored, the marker is computed from the EEG, and a computer-controlled infusion delivering the anesthetic drug is automatically changed based on the difference between the targeted level of the EEG marker and the actual level of the marker computed from the EEG analysis. Although numerous EEG markers have been used to guide delivery of anesthetics in CLAD systems, the most widely used marker is the BIS index.[24,104] Use of the BIS requires a 20- to 30-second delay in computing updates.[23] Use of a CLAD system leads to maintenance of the desired anesthetic state while delivering significantly less anesthetic drug.[24,105-107] Although most CLAD systems have focused on maintenance of unconsciousness, a recently developed system can control maintenance of unconsciousness and antinociception.[108,109]

Recent simulation studies using rodent and human models, as well as recent experimental studies in rodents,

*References 68, 69, 78, 84, 100, 101.

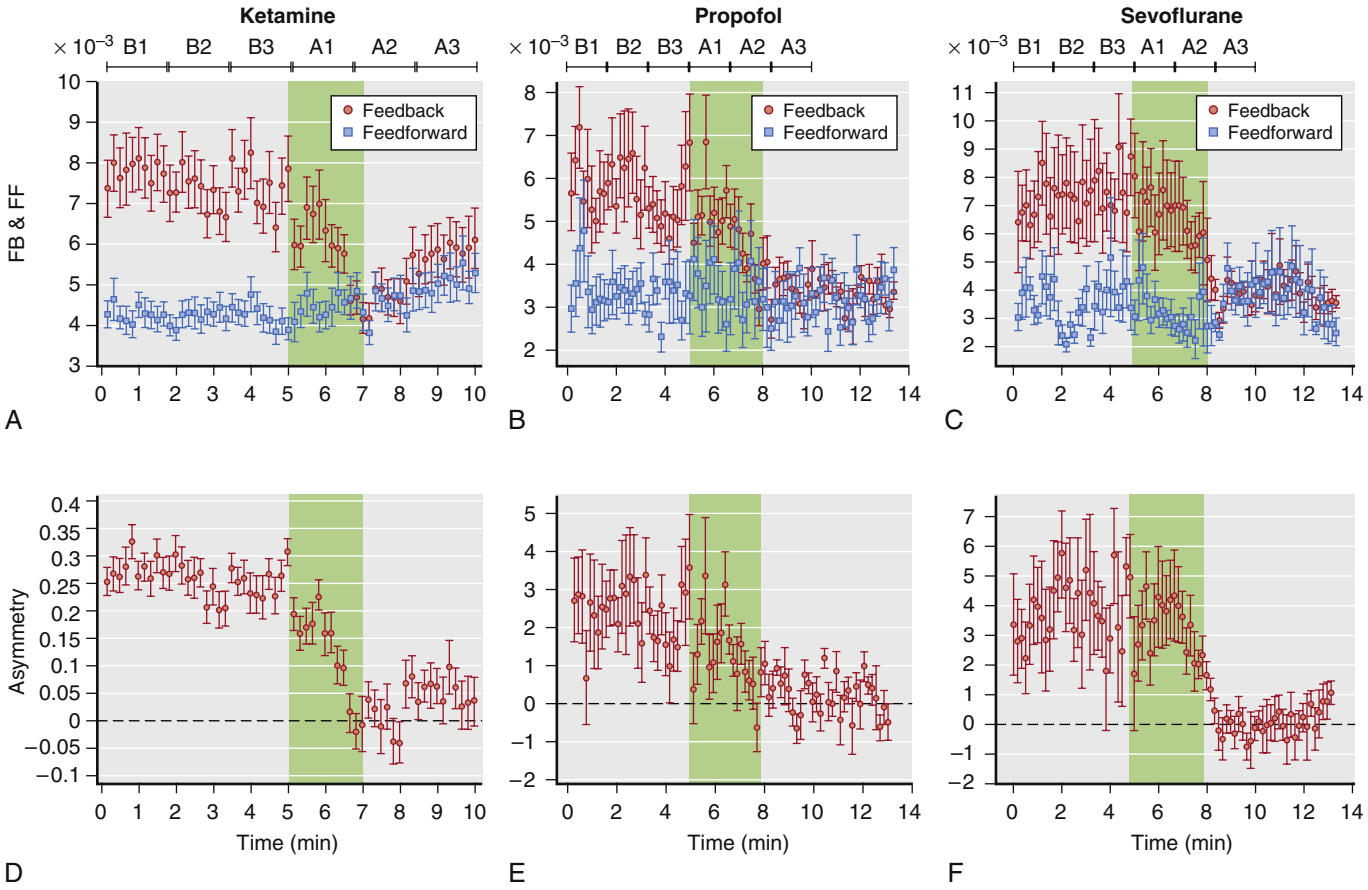


Figure 50-9. Normalized symbolic transfer entropy. An analysis of loss of consciousness induced by ketamine, propofol, and sevoflurane using normalized symbolic transfer entropy. Asymmetry in the change of feedforward (FF) and feedback (FB) connectivity is common to all three anesthetics. The FF (*blue*)/FB (*red*) connections (**A**-**C**) and their associated asymmetry (**D**-**F**) in the frontal–parietal network displayed for (**A** and **D**) ketamine, (**B** and **E**) propofol, and (**C** and **F**) sevoflurane. Green shading highlights induction of general anesthesia. *B1 to B3* define baseline substates. *A1 to A3* define anesthetized substates. There were 30, 9, and 9 subjects in the ketamine, propofol, and sevoflurane groups, respectively. All three anesthetics show a greater loss in FB frontal-parietal connectivity than FF connectivity at loss of consciousness. *(Redrawn from Lee U, Ku S, Noh G, et al: Disruption of frontal-parietal communication by ketamine, propofol, and sevoflurane,* Anesthesiology *118:1264-1275, 2013).*

have shown that highly reliable and accurate CLAD systems can be devised to maintain medical coma by using burst suppression (Fig. 50-2, F) as the control variable.[102,103] A CLAD system recently developed by Shanechi and colleagues[110] uses a stochastic control framework and, as the control variable, the burst suppression probability, which is the instantaneous probability that the brain is suppressed (Fig. 50-10).[110] The burst suppression probability is a more reliable way to track burst suppression than the suppression ratio.[111] The CLAD system precisely tracked the target level of burst suppression. If these results are successfully reproduced in human studies, the CLAD system could offer an automatic and highly efficient way to maintain medical coma in the many patients who require this therapy for multiple days to treat intractable status epilepticus or intracranial hypertension.

No CLAD system has been approved for administering general anesthesia. Many new findings and approaches will probably be reported in the near future because the study of CLAD systems is an active area of research by many investigators.

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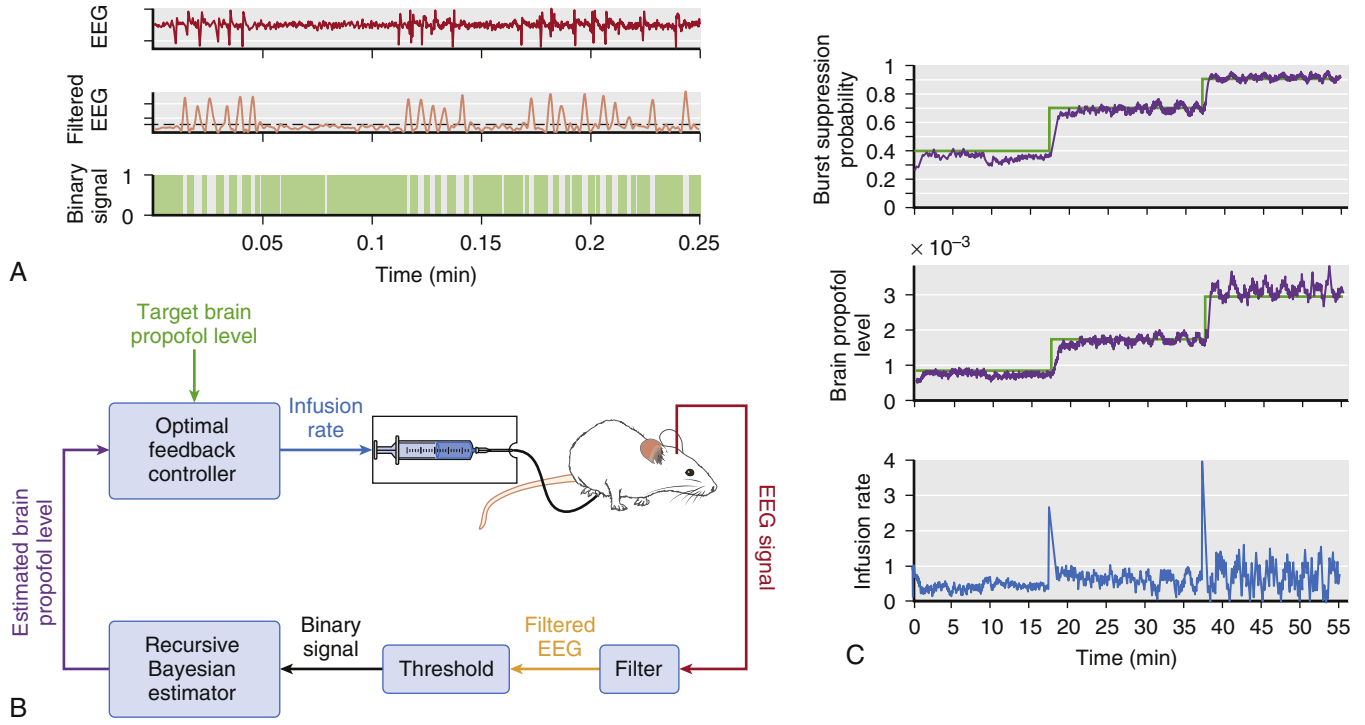


Figure 50-10. An experimental closed loop anesthetic delivery system for control of medical coma by controlling burst suppression. **A,** The electroencephalogram (EEG) of the rat in burst suppression is filtered, thresholded, and converted into binary observations (i.e., 0 for a burst and 1 for a suppression). **B,** A target brain level of propofol is set by specifying a burst suppression probability. The Bayesian estimator estimates the brain level of propofol from the EEG. The controller compares the estimated propofol level with the target level and adjusts the infusion rate every second to maintain the specified target burst suppression probability or, equivalently, the target brain propofol level. **C,** The *top panel* shows that the target burst suppression probability (*green line*) was maintained at 0.4 for 20 minutes, changed to 0.7 for 20 minutes, and then changed to 0.9 for 15 minutes. The estimated burst suppression probability (*purple curve*) tracks exactly the targeted level. The *middle panel* shows the equivalent close tracking of the target brain propofol level (*green curve*) by the estimated propofol level (*purple curve*). The *bottom panel* shows how the controller instantaneously changed the infusion rate to maintain the targeted level of burst suppression. This experimental study establishes the feasibility of real-time control of burst suppression and most likely other states of general anesthesia. *(Redrawn from Shanechi M, Chemali JJ, Liberman M, et al: A brain-machine interface for control of medically-induced coma,* PLoS Comput Biol *9:e1003284, 2013.)*

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MONITORING NOCICEPTION

The discussion of monitoring brain states under general anesthesia and sedation has focused largely on monitoring the level of consciousness. Monitoring nociception (i.e., the flow of pain information in the body during surgery) and antinociception, the ability of anesthetics or analgesics to impede nociceptive transmission, are growing areas of investigation. At present, heart rate, arterial blood pressure, and perhaps respiratory rate analyzed in the context of the patient's clinical condition are the most commonly used markers of nociception. These markers are indirect and do not tap directly into nociceptive information processing in the central nervous system. Extensions are being considered. One investigation is using multiple physiologic parameters including heart rate, heart rate variability (0.15 to 0.4 Hz band power), plethysmograph wave amplitude, skin conductance, skin conductance fluctuations, and the derivatives of these signals.[114] A second study recently investigated a measure of surgical stress in comparison to skin conductance fluctuations.[115] A recent review of nociception monitoring noted that most systems currently being studied can rapidly detect nociceptive inputs, but they are not successful in predicting the somatic or autonomic output.[116] At present, there is no approach that provides reliable and reproducible information on nociception during anesthesia care.

Complete references available online at expertconsult.com

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Chapter 51

Respiratory Monitoring

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Key Points

- Intraoperative respiratory monitoring is a fundamental component of standards for basic anesthetic monitoring (see also Chapter 44). Monitoring of oxygenation and ventilation is an absolute requirement for the safe conduct of an anesthetic regimen.
- A thorough understanding of the principles underlying respiratory monitoring is essential for appropriate clinical application.
- Most respiratory monitors in clinical use provide information at the systemic and whole-lung level from which clinical conclusions are attempted regarding the regional lung and tissue-level conditions.
- The degree of invasiveness of the monitors used should be determined by clinical requirements.
- Pulse oximetry is a noninvasive, reliable, and simple method for continuously monitoring the fractional arterial oxygen saturation and is an essential component of respiratory monitoring.
- Ventilation-perfusion mismatch, shunt, and hypoventilation are the most common causes of hypoxemia in the perioperative period. Monitoring of gas exchange can facilitate differentiation of these causes.
- Mixed venous oxygen saturation can be used to monitor the global balance between oxygen delivery and consumption, allowing for make inferences regarding gas exchange, cardiac output, and global oxygen consumption.
- Systems using infrared spectroscopy are used clinically to monitor regional tissue oxygenation. The utility of regional saturation-guided management is being established.
- Capnography is the primary quantitative method to assess ventilation in the perioperative period. Besides providing physiologic information on ventilation, pulmonary blood flow, and aerobic metabolism, capnography is important for verifying endotracheal tube positioning and determining the integrity of the breathing circuit (see also Chapter 55).
- End-tidal carbon dioxide (CO_2) is not always a reliable approximation of arterial CO_2 tension, especially in the presence of significant heterogeneity in the distribution of pulmonary ventilation and perfusion.
- Measurement of the pressures, flows, and volumes associated with ventilation is necessary to optimize mechanical ventilation, as well as to detect pathophysiologic mechanical derangements of the respiratory system (i.e., increased airway resistance or reduced lung compliance).
- Imaging techniques are emerging as important tools for respiratory monitoring. Lung ultrasonography allows for bedside assessment of pulmonary abnormalities, such as pneumothorax, edema, consolidation, and pleural effusions. Electrical impedance tomography provides information on lung aeration and recruitment.
- Current approaches to respiratory monitoring primarily assess pulmonary mechanical and global gas exchange processes. Monitoring of tissue and subcellular respiration remains a desirable goal for future innovation.

OVERVIEW OF RESPIRATORY MONITORING

Respiratory monitoring is a fundamental component of every anesthetic regimen. Its major relevance for maintenance of homeostasis and patients' safety is recognized in its position as a mandatory element in national and international standards for anesthetic monitoring.[1,2] Through the decades, advances in respiratory monitoring have reduced the incidence of anesthetic morbidity and mortality and have opened a new era of safe anesthetic practice.

Respiration is the transport of oxygen (O_2) from the environment to the body cells and the transport of carbon dioxide (CO_2) from those cells to the environment. The concept includes a component of cellular respiration, the process by which cells obtain energy in the form of adenosine triphosphate from the controlled reaction of hydrogen with O_2 to form water.[3] In its broadest sense, respiratory monitoring refers to the assessment of processes involved in the exchange of respiratory gases between the environment and the subcellular pathways where those gases are used and produced (Fig. 51-1).[3] Respiratory monitoring conceptually includes assessment of (1) convective and diffusive gas transport through the branching airway tree and alveoli, (2) equilibration of gases between alveoli and pulmonary capillary blood, (3) mass balance of the distinct regional ventilation and perfusion contributions to produce expired gases and arterial and mixed venous blood, (4) gas transport between the blood and body tissues through the microcirculation, (5) gas diffusion between tissues and mitochondria, and (6) cellular respiration with O_2 use and CO_2 production.

Significant developments in physiologic measurement have enhanced our understanding of these stages of respiratory function during anesthesia. This chapter provides an overview of current and emerging techniques of respiratory monitoring. Despite these technical advances, current instrumentation has limited ability to provide accurate and comprehensive information on respiratory function in patients. Clearly, advances in monitoring all components of respiration are needed.[4,5]

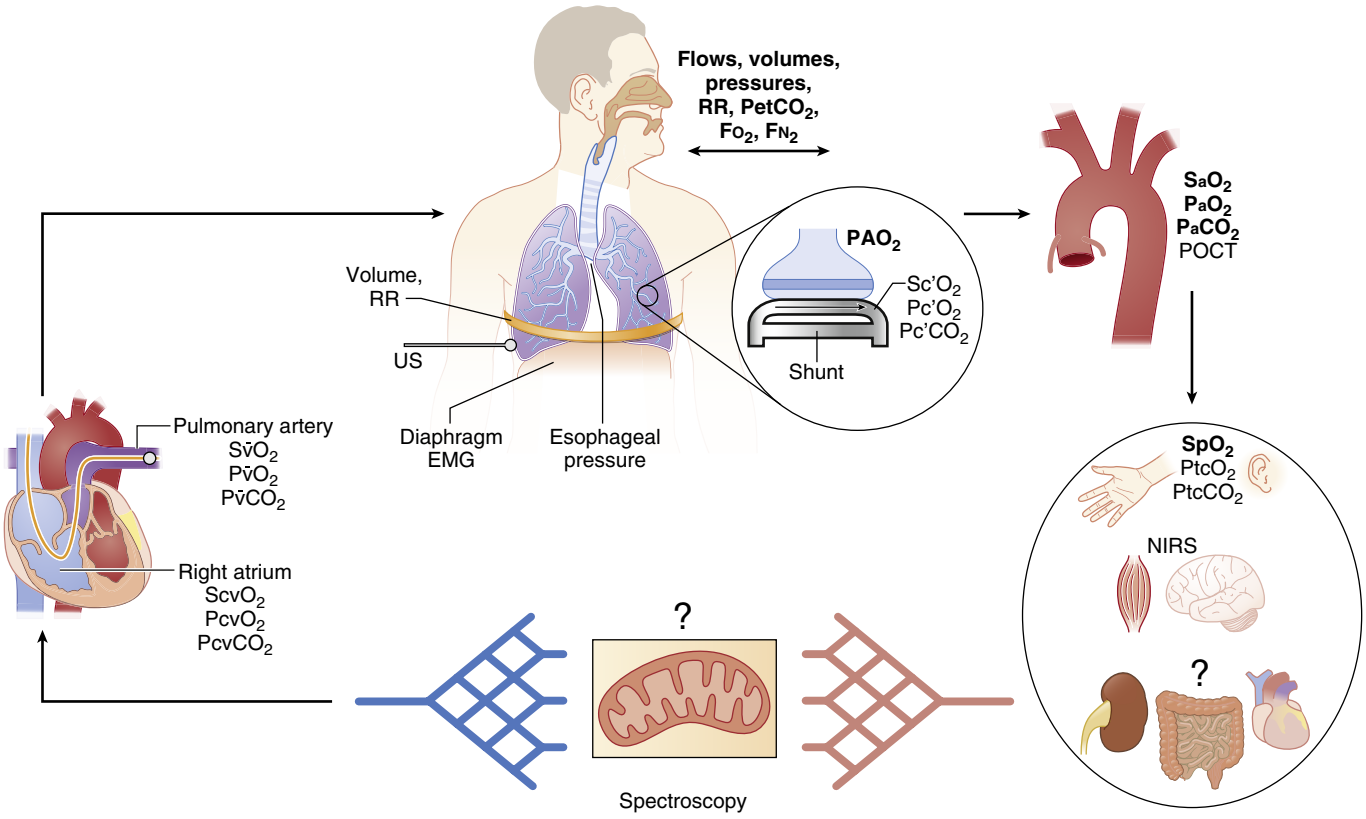


Figure 51-1. Respiratory processes and measurement sites for current respiratory monitoring techniques. Most monitored variables are derived from sites at the entrance of the airway and systemic blood (**bold**) and assess the elements of respiration related to pulmonary mechanics and gas exchange. Pulse oximetry represents a transition between systemic and local tissue oxygenation assessment. Methods for routine and reliable clinical monitoring of respiratory processes at the tissue, cellular, and subcellular levels are limited. *EMG,* Electromyography; F_{N_2}, nitrogen fraction; F_{O_2}, oxygen fraction; *NIRS,* near-infrared spectroscopy; Pa_{CO_2}, arterial partial pressure of carbon dioxide; Pa_{O_2}, arterial partial pressure of oxygen; PAO_2, alveolar partial pressure of oxygen; Pc'_{CO_2}, end-capillary partial pressure of carbon dioxide; Pc'_{O_2}, end-capillary partial pressure of oxygen; Pcv_{CO_2}, partial pressure of central venous carbon dioxide; Pcv_{O_2}, partial pressure of central venous oxygen; $PetCO_2$, partial pressure of end-tidal carbon dioxide; $P\bar{v}_{CO_2}$, partial pressure of mixed venous carbon dioxide; $P\bar{v}_{O_2}$, partial pressure of mixed venous oxygen; *POCT,* point of care testing; Pt_{CO_2}, transcutaneous partial pressure of carbon dioxide; Pt_{O_2}, transcutaneous partial pressure of oxygen; *RR,* respiratory rate; SaO_2, arterial oxygen saturation; Sc'_{O_2}, end-capillary oxygen saturation; Scv_{O_2}, central venous oxygen saturation; $S\bar{v}_{O_2}$, mixed venous oxygen saturation; SpO_2, peripheral oxygen saturation; *US,* ultrasound; *tc,* transcutaneous.

AMERICAN SOCIETY OF ANESTHESIOLOGISTS STANDARDS

The word *monitoring* is often associated with electronic instrumentation, and it is noteworthy that the current American Society of Anesthesiologists (ASA) Standards for Basic Anesthetic Monitoring states in Standard I that "Qualified anesthesia personnel shall be present in the room throughout the conduct of all general anesthetics, regional anesthetics, and monitored anesthesia care" (Box 51-1). This precedes reliance on any instrumentation (as implied in Standard II) and clearly indicates that the anesthesia provider brings essential expertise and interpretation to monitoring beyond information provided by equipment. Increased safety in our specialty lies primarily in high-quality training and environments that encourage continuing education, and not exclusively on new technology.[6] The ASA Standards for Basic Anesthetic Monitoring reflect monitoring principles during anesthesia established in the 1980s and should be systematically followed (see Box 51-1).[7] These standards represent a foundation to additional monitoring according to clinical requirements.

PHYSICAL EXAMINATION

The physical examination is still an essential component of perioperative respiratory monitoring. It provides critical information for diagnosis and treatment and may be the first indication of alterations in a patient's status that require intervention. Physical examination has limitations, but it routinely allows for detection of information relevant for a patient's management.

Respiratory monitoring starts with inspection of the patient, either when the patient is awake or during anesthesia. In elective cases, appropriate investigation of causes of abnormal presentations should be completed before surgery. In emergency situations, careful inspection may be the only source of information for timely and accurate anesthetic management. The perception of respiratory distress should be followed by a search for specific causes. Assessment of the respiratory rate provides a measure of the breathing pattern. For instance, during sepsis the respiratory rate is significantly correlated with disease severity.[8] Anatomic signs relevant to respiration include (but are not limited to) deformities of the chest wall and spine, goiter, tracheostomy scar, and tracheal deviation. Functional

BOX 51-1 ***American Society of Anesthesiologists Standards for Basic Anesthetic Monitoring Related to Respiratory Monitoring***

1. Standard I

Qualified anesthesia personnel shall be present in the room throughout the conduct of all general anesthetics, regional anesthetics, and monitored anesthesia care.

2. Standard II

During all anesthetics, the patient's oxygenation, ventilation, circulation, and temperature shall be continually evaluated.

2.1. Oxygenation

2.1.1 Objective: To ensure adequate oxygen concentration in the inspired gas and the blood during all anesthetics.

2.2. Methods

2.2.1 Inspired gas: During every administration of general anesthesia using an anesthesia machine, the concentration of oxygen in the patient breathing system shall be measured by an oxygen analyzer with a low oxygen concentration limit alarm in use.*

2.2.2 Blood oxygenation: During all anesthetics, a quantitative method of assessing oxygenation such as pulse oximetry shall be employed.* When the pulse oximeter is utilized, the variable pitch pulse tone and the low threshold alarm shall be audible to the anesthesiologist or the anesthesia care team personnel.* Adequate illumination and exposure of the patient are necessary to assess color.*

3. Ventilation

3.1. Objective

To ensure adequate ventilation of the patient during all anesthetics.

3.2. Methods

3.2.1 Every patient receiving general anesthesia shall have the adequacy of ventilation continually evaluated. Qualitative clinical signs such as chest excursion, observation of the reservoir breathing bag, and auscultation of breath sounds are useful. Continual monitoring for the presence of expired carbon dioxide shall be performed unless invalidated by the nature of the patient, procedure, or equipment. Quantitative monitoring of the volume of expired gas is strongly encouraged.*

3.2.2 When an endotracheal tube or laryngeal mask is inserted, its correct positioning must be verified by clinical assessment and by identification of carbon dioxide in the expired gas. Continual end-tidal carbon dioxide analysis, in use from the time of endotracheal tube/laryngeal mask placement, until extubation/removal or initiating transfer to a postoperative care location, shall be performed using a quantitative method such as capnography, capnometry or mass spectroscopy.* When capnography or capnometry is utilized, the end-tidal carbon dioxide alarm shall be audible to the anesthesiologist or the anesthesia care team personnel.*

3.2.3 When ventilation is controlled by a mechanical ventilator, there shall be in continuous† use a device that is capable of detecting disconnection of components of the breathing system. The device must give an audible signal when its alarm threshold is exceeded.

3.2.4 During regional anesthesia (with no sedation) or local anesthesia (with no sedation), the adequacy of ventilation shall be evaluated by continual observation of qualitative clinical signs. During moderate or deep sedation the adequacy of ventilation shall be evaluated by continual observation of qualitative clinical signs and monitoring for the presence of exhaled carbon dioxide unless precluded or invalidated by the nature of the patient, procedure, or equipment.

From American Society of Anesthesiologists: Standards for basic anesthetic monitoring, *2011.* <https://www.asahq.org/~/media/For%20Members/documents/Standards%20Guidelines%20Stmts/Basic%20Anesthetic%20Monitoring%202011.pdf>. *(Accessed 08.08.14.)*

*Under extenuating circumstances, the responsible anesthesiologist may waive the requirements marked with an asterisk (*); it is recommended that when this is done, it should be so stated (including the reasons) in a note in the patient's medical record.

†Note that "continual" is defined as "repeated regularly and frequently in steady rapid succession," whereas "continuous" means "prolonged without any interruption at any time."

elements to be noticed include the components of inspiration and expiration (diaphragmatic versus thoracic), duration and difficulty of inspiration and expiration, paradoxical chest wall motion, use of accessory muscles, central and peripheral cyanosis, pallor, wheezing, stridor, cough and sputum, aphonia, splinting, and clubbed fingers. Neck vein distention should be examined as an indicator of cardiac contribution to respiratory distress; this sign is a less reliable indicator of central venous pressure during significant dyspnea. Attention should be paid to painful respiration in trauma patients, as well as the possibility of flail chest, pericardial tamponade, hemothorax, pneumothorax, pulmonary contusion, and tension pneumothorax.

Characterization of breath sounds during anesthesia is another essential skill in physical diagnosis. Ambient noise, individual hearing limitations, and the acoustic properties of the stethoscope all influence the anesthesiologist's clinical judgment. A stethoscope of sufficient quality allows for identification of distinctive normal and abnormal breath sounds: vesicular sounds, rhonchi, wheezes, fine and coarse crackles, inspiratory stridor, and pleural friction. A clear understanding of the acoustic mechanisms of each of these sounds is essential for adequate clinical assessment.[9,10]

PULSE OXIMETRY

See also Chapter 44.

PHYSIOLOGIC FUNDAMENTALS

The primary roles of the cardiorespiratory system are the uptake and delivery of O_2 to the body. O_2 delivery (D_{O_2}) is quantified as the product of arterial O_2 content (CAO_2) and cardiac output (see Chapter 19). CAO_2 (in milliliters of O_2 per 100 mL of blood [hemoglobin—Hb], mL/100 mL) is calculated as:

$$CAO_2 = (1.34 \times SaO_2 \times Hb) + 0.0031 \times PaO_2 \qquad [1]$$

where 1.34 mL/g is the O_2 binding capacity of Hb (Hüfner constant, theoretically 1.39), which experimentally ranges between 1.31 and 1.37 mL/g, mostly because of the presence of small amounts of other Hb forms[11]; SaO_2 is the Hb O_2 saturation of the arterial blood (percent saturation/100); Hb is the concentration of Hb in the arterial blood (g/100 mL); 0.0031 is the solubility of O_2 in blood (mL O_2/100 mL blood/mm Hg); and PaO_2 is the arterial partial pressure of O_2 (mm Hg). As can be understood from the equation, SaO_2 is a major determinant of O_2 content and consequently D_{O_2}.

Four species of Hb are found in adult blood: oxygenated Hb (O_2Hb), deoxygenated Hb (deO_2Hb), carboxyhemoglobin (COHb), and methemoglobin (MetHb). Under normal circumstances, the concentrations of COHb and MetHb are small (1% to 3% and less than 1%, respectively). *Functional* O_2 saturation (SaO_2) refers to the amount of O_2Hb as a fraction of the total amount of O_2Hb and deO_2Hb and is expressed as:

$$\text{Functional } SaO_2 = \frac{O_2Hb}{O_2Hb + deO_2Hb} \times 100\% \qquad [2]$$

The O_2Hb fraction or *fractional* saturation is defined as the amount of O_2Hb as a fraction of the total amount of Hb[12]:

$$\text{Fractional } SaO_2 = \frac{O_2Hb}{O_2Hb + deO_2Hb + COHb + MetHb} \times 100\% \qquad [3]$$

SaO_2 is a function of PaO_2. The relationship between the two is described by the O_2Hb dissociation curve (Fig. 51-2). As can be appreciated by inspection of the curve, the relationship is not linear. This has important consequences. One is that a high SaO_2 cannot discriminate between normoxic and hyperoxic conditions; this can be relevant when attempting to limit O_2 exposure in neonates or in patients at risk for O_2 toxicity (see also Chapter 95). Another consequence is that a large numeric change in PaO_2 at the flat portion of the curve (PaO_2 approximately >70 mm Hg) has relatively small consequences in terms of blood O_2 content. Furthermore, changes in temperature, pH, partial pressure of CO_2 in arterial blood ($Paco_2$), and erythrocyte 2,3-diphosphoglycerate concentration can shift the curve such that the same SaO_2 can be present under a range of different O_2 partial pressures (PO_2). This is relevant given that diffusion from the microcirculation to tissue depends on PO_2 gradients.

MEASUREMENT PRINCIPLES

Oximetry

Oximetry is the measurement of the O_2 saturation of Hb. It is an application of the Beer-Lambert law (Equation 4), which relates the transmission of light through a solution

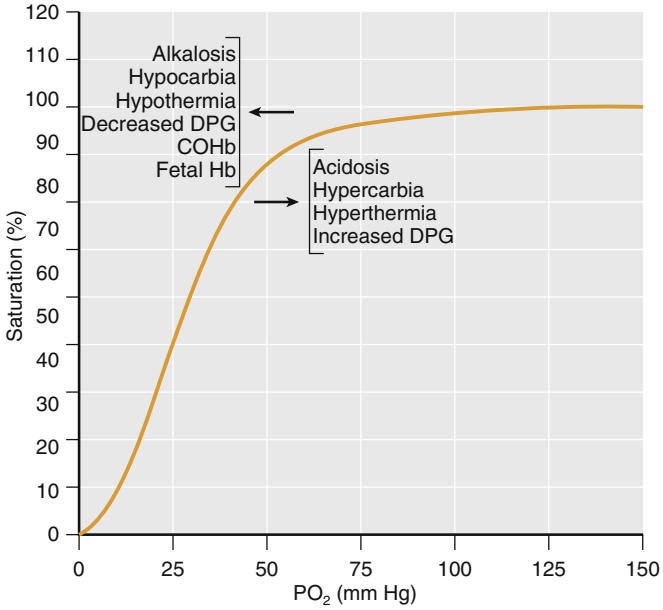


Figure 51-2. Oxyhemoglobin dissociation curve. The relationship between oxyhemoglobin saturation and the partial pressure of oxygen (PO_2) is nonlinear and affected by a number of different factors such as pH, partial pressure of carbon dioxide, and temperature. Given the nonlinear nature of the curve, it is difficult to determine the PO_2 at the higher range of oxygen saturations. *COHb,* Carboxyhemoglobin; *DPG,* 2,3-diphosphoglycerate; *Hb,* hemoglobin. *(Redrawn from Longnecker DE, Brown DL, Newman MF, Zapol WM, editors:* Anesthesiology, *ed 2, New York, 2012, McGraw-Hill.)*

to the concentration of the solute in the solution.[13] For each solute in a solution,

$$I_{trans} = I_{in} e^{-DC\varepsilon} \quad [4]$$

where I_{trans} is the intensity of transmitted light, I_{in} is the intensity of the incident light, e is base of the natural logarithm, D is the distance the light is transmitted through the solution, C is the concentration of the solute, and ε is the extinction coefficient of the solute.

The concentration of a single solute in solution can be calculated by measuring the amount of light transmitted through the solution as long as the other variables are known. For a solution containing multiple solutes, the calculation of the concentrations of the different solutes requires that light absorption be measured at a number of different wavelengths at least equal to the number of solutes. In a sample of blood in a cuvette, the absorption of a given wavelength of light passing through the blood depends on the concentrations of the four species of Hb. Figure 51-3 illustrates the extinction coefficients of the four species of Hb for wavelengths of light along the visible spectrum. To measure the concentrations of all four types of Hb in a sample of blood, light absorption of at least four different wavelengths must be measured. This measurement is typically conducted using a co-oximeter. A co-oximeter uses the principle of oximetry to measure the SaO_2 as well as the concentrations of other Hb species in a blood sample. Co-oximetry is considered the gold standard for SaO_2 measurements and is relied on when pulse oximetry readings are inaccurate or unobtainable.

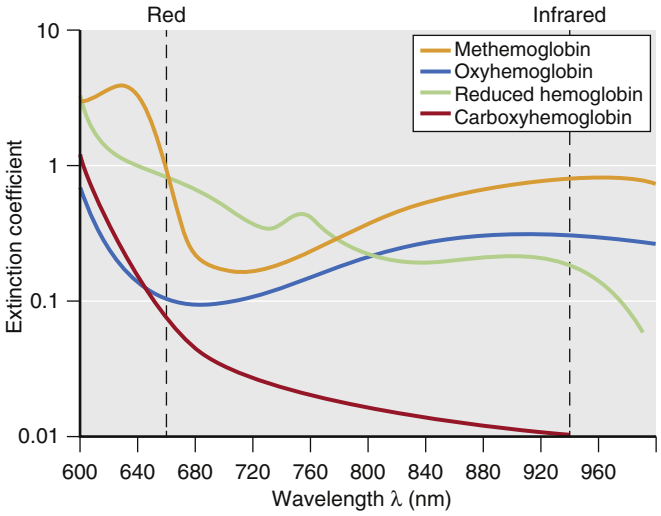


Figure 51-3. Extinction coefficients of the four species of hemoglobin for wavelengths of light across the visible spectrum. The *vertical lines* indicate the wavelengths for red and infrared light that are used in pulse oximeters. The differences in the extinction coefficients of oxyhemoglobin and reduced hemoglobin (deoxygenated hemoglobin) are pronounced at these wavelengths. The extinction coefficients of carboxyhemoglobin and methemoglobin are similar to those of oxyhemoglobin and reduced hemoglobin, respectively, at 660 nm. *(Redrawn from Tremper KK, Barker SJ: Pulse oximetry,* Anesthesiology *70:98-108, 1989.)*

Pulse Oximetry

Standard pulse oximetry aims to provide a noninvasive, in vivo, continuous assessment of functional SaO_2. Pulse oximeter readings are denoted as SpO_2. The history of the development of pulse oximetry is reviewed in detail in the literature.[14]

Pulse oximetry takes advantage of the pulsatility of arterial blood flow to provide an estimate of SaO_2 by differentiating light absorption by arterial blood from light absorption by other components. When compared with in vitro oximetry of an arterial blood sample, the challenges of obtaining SaO_2 in vivo are to ensure that the light is sampling arterial blood and to account for its absorption by other tissues. As illustrated in Figure 51-4, light absorption by tissue can be divided into a pulsatile component, historically referred to as AC, and a nonpulsatile component, referred to as DC. In a standard pulse oximeter, the ratio (R) of AC and DC light absorption at two different wavelengths is calculated. The wavelengths of light are selected to maximize the difference between the ratios of the absorbances of O_2Hb and deO_2Hb (see Fig. 51-3). Typically used wavelengths of light are 660 and 940 nm. At 660 nm, light absorption is greater by deO_2Hb than by O_2Hb. At 940 nm, light absorption is greater by O_2Hb than by deO_2Hb.

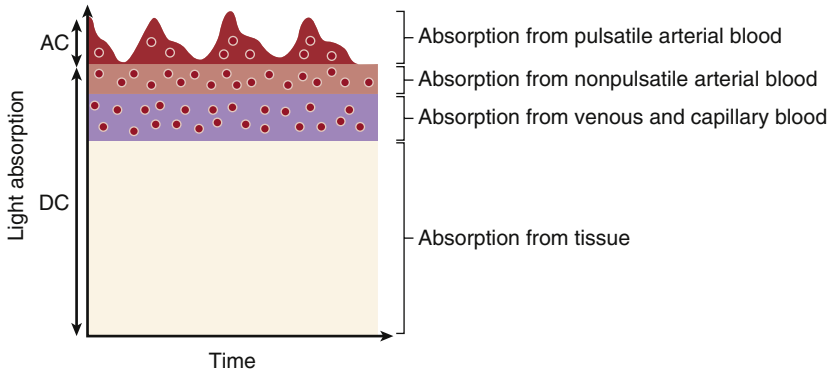


Figure 51-4. Schematic of the pulse principle. Absorption of light passing through tissue is characterized by a pulsatile component (AC) and a nonpulsatile component (DC). The pulsatile component of absorption is the result of arterial blood. The nonpulsatile component derives from arterial, venous, and capillary blood and the remainder of the tissues. *(Redrawn from Severinghaus JW: Nomenclature of oxygen saturation,* Adv Exp Med Biol *345:921-923, 1994.)*

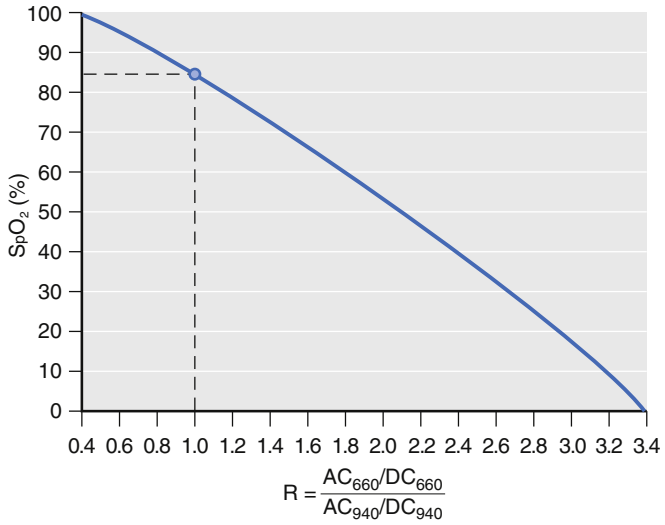


Figure 51-5. Typical pulse oximeter calibration curve relating oxygen saturation to the R value. These curves are developed using healthy volunteers and incorporated into the pulse oximeter. *SpO_2,* Peripheral oxygen saturation. See Figure 51-4 legend for explanation of AC and DC. *(Redrawn from Severinghaus JW: Nomenclature of oxygen saturation,* Adv Exp Med Biol *345:921-923, 1994.)*

$$R = \frac{AC_{660}/DC_{660}}{AC_{940}/DC_{940}} \quad [5]$$

where AC_{660}, AC_{940}, DC_{660}, and DC_{940} are the AC and DC components for the 640- and 940-nm wavelengths.

This ratio (R) is then empirically related to O_2 saturation based on a calibration curve internal to each pulse oximeter[13] (Fig. 51-5). Each manufacturer develops its own calibration curve by having volunteers breathe hypoxic gas mixtures to create a range of SaO_2 values between 70% and 100%. The international standard for pulse oximeter manufacture, ISO 80601-2-61-2011, requires an accuracy of up to a 4% error over a range of SaO_2 from 70% to 100%. Most manufacturing literature reports an accuracy of ± 2% to 3% SpO_2 over this range.[15]

A pulse oximeter probe is composed of a light emitter and a photodetector. Transmission pulse oximetry involves placement of the emitter and detector on opposite sides of the tissue being measured, usually a finger. Reflectance pulse oximetry probes have the emitters and detector arranged on the same side. They are typically placed on the forehead. In a typical pulse oximeter, two light-emitting diodes (LEDs) are used to emit light at the two wavelengths. During operation, each LED is turned on and off in sequence. The photodetector measures transmission of light from each LED. When both LEDs are turned off, the photodetector measures ambient light and subtracts it from the signals obtained throughout the remainder of the cycle.[16]

Multiwavelength pulse oximeters have been developed that use additional wavelengths of light to allow for the continuous noninvasive measurement of total Hb concentration (SpHb),[17] as well as concentrations of MetHb and COHb.[18] The accuracy of SpHb in operative and intensive care unit (ICU) settings is not clear as compared with laboratory measurements (see also Chapter 61).[19-21] However, few of the measurements reported were obtained in patients with Hb concentrations in the 6 to 10 mg/dL range used for transfusion decisions.[22] Another limitation is that SpHb readings may be absent or unreliable under conditions of low peripheral perfusion.[23] To date, noninvasive COHb measurements have not shown enough precision to replace laboratory measurements.[23,24] Pulse oximetry–based MetHb measurements with a newer device are accurate, even under conditions of hypoxia.[25]

Pulse oximetry has been an integral component of intraoperative anesthetic management since the first set of anesthetic monitoring standards was introduced in 1986.[7] It was adopted as a minimum monitoring standard by the ASA the same year and has subsequently been defined as a minimum standard for intraoperative monitoring by the World Federation of Societies of Anaesthesiologists (WFSA) and the World Health Organization (WHO).[26] The use of pulse oximetry is a part of the WHO safe surgery checklist.[27]

Universal pulse oximetry has been recommended by the U.S. Secretary of Health and Human Services to screen newborns for critical congenital heart disease.[28,29] Use of a clinical algorithm based on detection of SpO_2 lower than 95% in right upper or lower limbs or more than a 2% difference led to a sensitivity of 75% in suspected cases and 58% in cases that were not suspected. When this modality is combined with a routine anomaly scan and newborn physical examination screening, 92% of critical congenital heart disease lesions can be identified.[30,31]

Although a useful monitor for the early detection of hypoxemia, pulse oximetry has not reduced the incidence of postoperative complications.[32-34] In the largest randomized controlled trial investigating perioperative pulse oximetry (in 20,802 patients), a nineteenfold increase was noted in the incidence of diagnosed hypoxemia in the pulse oximetry group in both the operating room (OR) and the postanesthetic care unit.[33] Furthermore, the use of the oximeter was associated with a significant decrease in the rate of myocardial ischemia.[33] However, no significant difference was reported in the rate of complications, outcome, mean hospital stay, or in-hospital deaths between the two groups. Because this result was obtained in a population of primarily healthy patients, the sample size may have been insufficient to detect an effect.[35] In fact, one study indicated that early detection of deterioration of SpO_2 and heart rate with pulse oximetry led to fewer rescue events and a decreased need to escalate care (patient rescue and ICU transfers).[36]

Photoplethysmography. Along with measuring O_2 saturation, the pulse oximeter can also be used as a photoplethysmograph. Because the absorption of light is proportional to the amount of blood between the transmitter and photodetector, changes in the blood volume are reflected in the pulse oximeter trace (Fig. 51-6).[37] During anesthesia, the plethysmographic trace is affected by changes in blood volume pulsations, which depend on the distensibility of the vessel wall, as well as on the intravascular pulse pressure.[37] Variations in the amplitude of the pulse oximetry plethysmographic waveform (ΔPOP) have been shown to predict fluid responsiveness in mechanically ventilated patients.[38] An index derived from

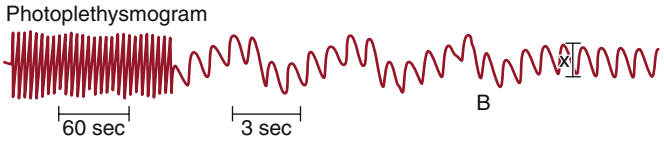


Figure 51-6. Photoplethysmograph recorded at two speeds demonstrating respiratory variation. At time point B, ventilation has been stopped, and no variation is observed. The plot illustrates the effect of intrathoracic blood volume in the pulse oximeter trace. The variation in the trace with respiration is associated with the fluid responsiveness of the patient. *(Redrawn from Dorlas JC: Photo-electric plethysmography as a monitoring device in anaesthesia,* Br J Anaesth *57:524, 1985.)*

the percentage of difference between the maximum and minimum amplitudes of the plethysmographic waveform during a respiratory cycle (PVI, Pleth Variability Index) has been incorporated into a commercially available pulse oximeter and used to quantify ΔPOP and predict fluid responsiveness.[39,40] Several small studies have shown it to be a reasonably reliable indicator of fluid responsiveness intraoperatively and in critically ill patients.[41] This index is more reliable in mechanically ventilated patients than in spontaneously breathing patients and is compromised by the presence of arrhythmias.[41] PVI-based goal-directed fluid management improves outcomes in major abdominal surgical procedures.[42]

LIMITATIONS AND SOURCES OF ERROR

SpO_2 is an estimate of SaO_2. As a consequence, it does not provide information about tissue oxygenation. SpO_2 is a measurement of functional and not fractional SaO_2, and the presence of other Hb species can significantly affect the accuracy of the measurements. Because of the nonlinearity of the Hb dissociation curve, at high saturations hyperoxia cannot be easily detected by SpO_2 measurements, whereas at low saturations such as at altitude, small changes in PaO_2 can produce large changes in SpO_2. Variability in the actual in vivo Hb dissociation curve is significant. A study in 10,079 samples showed that at a PaO_2 of 60 ± 4 mm Hg (8.0 ± 0.5 kPa), SaO_2 ranged between 69.7% and 99.4%, and at an SaO_2 of 90 ± 2%, the PaO_2 range was 29 to 137 mm Hg (3.8 to 18.3 kPa).[43] These measurements illustrate that knowledge of the individual Hb dissociation curve is important for correct interpretation of SaO_2 and PaO_2. Because of the manner in which calibration curves are obtained, SpO_2 accuracy is reduced at values lower than 70% to 75%. Changes in SpO_2 do not always reflect equal changes in SaO_2.[44,45] Pulse oximetry does not provide information about acid-base status.

Certain conditions can lead to inaccuracies in pulse oximeter readings (Table 51-1). These conditions include decreased perfusion, motion artifact, low SaO_2, variant Hb types, the presence of intravascular dyes, and the presence of nail polish.

The calibration of pulse oximeters is based on curves obtained in normal individuals under experimental conditions. As such, findings are limited in their accuracy at SaO_2 values greater than 70%. At SaO_2 levels lower than 70%, a positive or negative bias of the SpO_2 value can be observed, depending on the manufacturer of the pulse oximeter.[46] Manufacturers have developed pulse oximeters with increased accuracy at saturations as low as 60%. Preliminary data suggest that these probes may be useful in neonates with cyanotic congenital heart disease.[47]

Hypoperfusion leads to a reduction in the amplitude of the pulsatile component of the waveform, thus giving rise to lower readings. Significantly erroneous reductions in SpO_2 readings may be observed for systolic blood pressures lower than 80 mm Hg.[48] Motion artifact can produce considerable error in the pulse oximeter reading. Manufacturers have developed advanced proprietary signal processing algorithms that effectively filter out noise caused by motion.[49,50]

With continued clinical use, the performance of the LEDs in the probe may be degraded, leading to inaccuracy of the SpO_2 value outside of the range specified by the manufacturer. These inaccuracies are expected to be more pronounced at lower saturations (i.e., <90%).[15]

The presence of additional species of Hb can also generate erroneous pulse oximeter readings. As outlined earlier, the function of the pulse oximeter is predicated on the assumption that the only components present in the blood capable of absorbing light at the two wavelengths used are O_2Hb and deO_2Hb. Under normal circumstances, this assumption is valid, and the SpO_2 readings accurately reflect the SaO_2. However, the presence of significant concentrations of other Hb species or

TABLE 51-1 POTENTIAL SOURCES OF ARTIFACTS IN PULSE OXIMETRY AND THEIR EFFECTS ON MEASUREMENTS

Source of Error	Effect on SpO_2 relative to SaO_2
Hypotension	↓
Anemia	↓
Polycythemia	No significant effect
Motion	↓
Low SaO_2	Variable
Methemoglobinemia	↓/↑ (SpO_2 approaches 85%)
Carboxyhemoglobinemia	↑
Cyanmethemoglobin	No significant effect
Sulfhemoglobin	No significant effect
Hemoglobin F	No significant effect
Hemoglobin H	No significant effect
Hemoglobin K	↓
Hemoglobin S	No significant effect
Methylene blue	↓
Indigo carmine	↓
Indocyanine green	↓
Isosulfan blue	No significant effect/↓
Fluorescein	No significant effect
Nail polish	Black, dark blue, purple ↓
Acrylic fingernails	No significant effect
Henna	Red: no significant effect ↓
Skin pigmentation	At SaO_2 >80%, no significant effect At SaO_2 <80%,↑
Jaundice	No significant effect
Ambient light	No significant effect
Sensor contact	↓
IABP	↑

IABP, Intraaortic balloon pump, *SaO_2,* arterial oxygen saturation; *SpO_2,* peripheral oxygen saturation.

substances absorbing light at the used wavelengths will lead to erroneous SpO_2 readings. As illustrated in Figure 51-3, both COHb and MetHb absorb light at one or both of the wavelengths used by the pulse oximeter. Accordingly, the presence of these Hb species produces errors in SpO_2. The absorption of light at 660 nm by COHb is similar to that of O_2Hb. At 940 nm, COHb absorbs virtually no light. Thus, in a patient with carbon monoxide poisoning, the SpO_2 is falsely elevated.[51] MetHb absorbs a significant amount of light at both 660 and 940 nm. As a result, in its presence, the ratio of light absorption R (Equation 5) approaches unity. An R value of 1 represents the presence of equal concentrations of O_2Hb and deO_2Hb and corresponds to an SpO_2 of 85%. In a patient with methemoglobinemia, the SpO_2 is 80% to 85% irrespective of the SaO_2.[52]

With normal SaO_2, anemia has little effect on SpO_2.[53] However, in the presence of hypoxia, SpO_2 readings underestimate SaO_2 in anemic patients.[54] Pulse oximeters are sufficiently accurate in adult patients with sickle cell disease,[55] as well as in the presence of fetal Hb.[56] A relatively uncommon cause of reduced SpO_2 readings is the presence of congenital variants of Hb. Some variants, such as Hb Bassett, Hb Rothschild, and Hb Canabiere, have a reduced affinity for O_2, and changes in SpO_2 appropriately reflect changes in SaO_2.[57] Other variants, such as Hb Lansing, Hb Bonn, and Hb Hammersmith, have altered absorption spectra that result in low SpO_2 readings in the setting of normal SaO_2.[57]

The administration of intravenous dyes can result in inaccurate SpO_2 readings. Methylene blue leads to a transient, marked decrease in SpO_2 down to 65%. Indigo carmine and indocyanine green also artificially decrease SpO_2 measurements, although to a lesser extent than methylene blue.[58] Isosulfan blue can produce a prolonged reduction with larger doses.[58]

Although all colors of nail polish can reduce the SpO_2 reading, black, purple, and dark blue have the greatest effect. However, the error is generally within 2%.[59] Depending on the brand of pulse oximeter used, artificial acrylic nails may impair SpO_2 readings, although generally not to a clinically significant extent.[60] Under conditions of normal SaO_2, skin pigmentation has no effect on SpO_2 estimates.[61] However, increased skin pigmentation is associated with SpO_2 values that overestimate SaO_2 by as much as 8% for SaO_2 less than 80%.[46,62]

Although earlier case reports and small studies had suggested that ambient light may interfere with the accuracy of SpO_2 readings,[63,64] a larger prospective study found no significant effect on SpO_2 accuracy with exposure to five types of light sources: quartz-halogen, incandescent, fluorescent, infant bilirubin lamp, and infrared.[65] Infrared light pulses from image guidance systems used for navigational neurosurgery can interfere with pulse oximetry readings by causing decreased readings or disruptions in SpO_2 waveform detection.[66] Different pulse oximeters show variable susceptibility to such interference.[67] Shielding the probe with a single layer of aluminum foil can protect from this effect.[66,67] Misplacement of the probe can allow for direct detection of LED light by the photodetector. This optical shunt gives rise to an SpO_2 reading of 85%.[68]

In patients with intraaortic balloon pump support, SpO_2 accuracy depends on the brand of pulse oximeter used, as well as the support ratio. Accuracy is generally reduced in the setting of higher support ratios.[69] In patients with continuous-flow ventricular assist devices, pulse oximetry may not be possible because of the absence of pulsatile flow. In these cases, the use of cerebral oximetry as an adjunct is advocated.[70]

MIXED VENOUS OXYGEN SATURATION

PHYSIOLOGIC FUNDAMENTALS

Mixed venous O_2 saturation ($S\bar{v}O_2$) is the oxygen saturation of blood at the proximal pulmonary artery. It reflects the average O_2 saturation of the blood returning from the body to the right heart, weighted by the respective regional blood flows. As such, it is a measure of the balance between global DO_2 and global O_2 uptake ($\dot{V}O_2$). The factors that influence $S\bar{v}O_2$ can be illustrated through a derivation of the mixed venous O_2 content ($C\bar{v}O_2$) equation.

$\dot{V}O_2$ (mL/min) is defined as:

$$\dot{V}O_2 = 10 \times \dot{Q}_T \times (CAO_2 - C\bar{v}O_2) \quad [6]$$

where $\dot{Q}_T$ is cardiac output (L/min) and $C\bar{v}O_2$ is the O_2 content of the mixed venous blood (mL/100 mL).

Rearranging the equation to solve for $C\bar{v}O_2$ yields:

$$C\bar{v}O_2 = CAO_2 - (\dot{V}O_2/\dot{Q}_T) \quad [7]$$

The contribution of dissolved O_2 to the blood O_2 content is small. By expanding the definition of O_2 content (Equation 1) and ignoring the term for dissolved O_2, Equation 7 can be rewritten as:

$$S\bar{v}O_2 = SaO_2 - \dot{V}O_2/(1.34 \times Hb \times \dot{Q}_T) \quad [8]$$

Normal values of $S\bar{v}O_2$ range between 65% and 80%.[71,72] Values close to 40% are associated with tissue hypoxia, anaerobic metabolism, and lactate production. Although venous saturation reflects venous O_2 partial pressure ($P\bar{v}O_2$) based on the O_2Hb dissociation curve, $P\bar{v}O_2$ cannot be directly inferred from $S\bar{v}O_2$ values alone because the association is influenced by factors such as pH, PCO_2, and temperature (see Fig. 51-2). The normal value of $P\bar{v}O_2$ is 40 mm Hg.

DO_2 is defined as:

$$DO_2 = \dot{Q}_T \times CAO_2 \quad [9]$$

As is evident from Equation 8, a low $S\bar{v}O_2$ indicates a reduction in DO_2 secondary to low SaO_2, low Hb, or low $\dot{Q}_T$, or an increase in $\dot{V}O_2$. The association among $S\bar{v}O_2$, DO_2, and $\dot{V}O_2$ can be illustrated by expressing $S\bar{v}O_2$ as a function of the O_2 extraction ratio, ERO_2.

$$ERO_2 = \dot{V}O_2/DO_2 \quad [10]$$

Expanding the terms yields:

$$ERO_2 = 1 - C\bar{v}O_2/CAO_2 \quad [11]$$

which can be rewritten as follows by ignoring the dissolved O_2 term:

$$ERO_2 = 1 - S\bar{v}O_2/SaO_2 \quad [12]$$

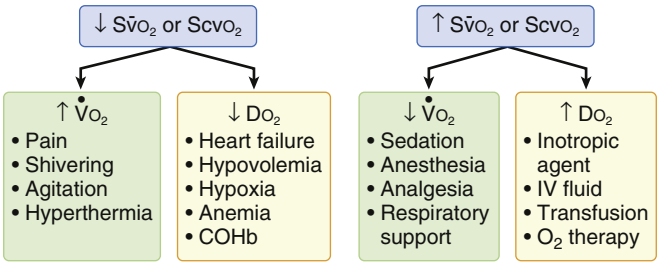


Figure 51-7. Mixed venous saturation $S\bar{v}O_2$ is a measure of the balance between global oxygen delivery and uptake. Conditions that increase oxygen uptake ($\dot{V}O_2$) or decrease oxygen delivery (DO_2) lead to a reduction in $S\bar{v}O_2$. Conversely, conditions that decrease $\dot{V}O_2$ or improve DO_2 lead to an increase in $S\bar{v}O_2$. *COHb,* Carboxyhemoglobin; *IV,* intravenous; *$ScvO_2$,* central venous oxygen saturation. *(Modified from Shepherd SJ, Pearse RM: Role of central and mixed venous oxygen saturation measurement in perioperative care,* Anesthesiology *111:649, 2009.)*

For conditions in which the arterial blood is fully saturated, the equation simplifies to:

$$ERO_2 = 1 - S\bar{v}O_2 \quad [13]$$

Solving for $S\bar{v}O_2$ yields:

$$S\bar{v}O_2 = 1 - ERO_2 \quad [14]$$

Thus, a reduction in $S\bar{v}O_2$ results from an increase in ERO_2, from either an increase in $\dot{V}O_2$ or a decrease in DO_2 (Fig. 51-7). A decrease in DO_2 occurs in conditions such as hemorrhagic or hypovolemic shock. An increase in $\dot{V}O_2$ may occur in conditions such as stress, pain, shivering, sepsis, and thyrotoxicosis. Conversely, an increase in $S\bar{v}O_2$ indicates either an elevation in O_2 supply (increased SaO_2, Hb, or $\dot{Q}_T$) or a reduction in $\dot{V}O_2$, as occurs during hypothermia.

Some subtle considerations are relevant in the interpretation of changes in $S\bar{v}O_2$. At PO_2 values typical of venous blood, small increases in the inspired fraction of O_2 (FiO_2) can cause significant increases in $S\bar{v}O_2$ because of the shape of the O_2Hb dissociation curve (see Fig. 51-2). Therefore, when $S\bar{v}O_2$ is being tracked as a measure of cardiac function, changes in FiO_2 must be taken into account when interpreting $S\bar{v}O_2$ measurements.[73] In the setting of septic shock, the impairment in O_2 extraction can produce normal $S\bar{v}O_2$ in the presence of tissue hypoxia.

The measurement of $S\bar{v}O_2$ requires the insertion of a pulmonary artery catheter, which actually increases morbidity risk. In the clinical setting, central venous catheterization is more commonly performed and has fewer risks. Thus, the use of central venous saturation can be a surrogate for mixed venous saturation. $ScvO_2$, which is the saturation of blood at the level of a central venous catheter placed in the superior vena cava, reflects the balance between O_2 supply and demand in the brain and upper extremities. Under normal physiologic conditions, $ScvO_2$ is typically 2% to 5% less than $S\bar{v}O_2$ primarily because of the higher O_2 content of splanchnic and renal venous blood.[74] However, during hemodynamic instability, as circulation is redistributed to the upper body, the relationship between $S\bar{v}O_2$ and $ScvO_2$ may reverse, and the difference between the two may increase significantly.[75-77] Although trends in $ScvO_2$ may reflect those in $S\bar{v}O_2$, the two measures cannot be used interchangeably.[77-85]

Mixed venous CO_2 has been used to compute the arteriovenous CO_2 difference ($\Delta PCO_2 = P\bar{v}CO_2 - PaCO_2$). In conditions of steady-state CO_2 production, ΔPCO_2 changes inversely and nonlinearly with cardiac output as a result of the Fick equation.[86] Accordingly, ΔPCO_2 is an indicator of the adequacy of cardiac output to provide adequate clearance of tissue CO_2. However, this measurement has not found widespread clinical use.[86]

MEASUREMENT PRINCIPLES

The measurement of venous O_2 saturation can be performed intermittently by co-oximetry of blood sampled from the distal tip of a pulmonary artery catheter ($S\bar{v}O_2$) or a central venous catheter ($ScvO_2$). Falsely increased values can occur in the presence of a wedged pulmonary artery catheter tip, mitral regurgitation, or left-to-right shunts.[87] Venous saturations can also be measured continuously by spectrophotometry using specialized fiberoptic catheters, which transmit infrared light and detect the amount of light reflected from red blood cells.[88,89] Specialized venous oximetry catheters are available for both pulmonary artery and central venous monitoring and have the advantage of providing continuous measurements of O_2 saturation. Their disadvantage is cost.

Although continuous venous oximetry catheters trend changes, their reported absolute values are not equivalent to concurrently obtained co-oximetry measurements.[90-92]

APPLICATIONS AND INTERPRETATION

In patients undergoing major abdominal as well as cardiac surgical procedures, intraoperative reductions in $S\bar{v}O_2$ and $ScvO_2$ have been associated with postoperative complications (see also Chapter 102).[93-97] Protocol-based interventions to target specific $S\bar{v}O_2$ or $ScvO_2$ values reduce the length of stay, organ dysfunction, and mortality in patients undergoing major surgical procedures and in patients presenting with sepsis.[98-100] $ScvO_2$-guided, protocol-based, goal-directed therapy is advocated for the management of sepsis, and the implementation of such protocols is associated with improvements in mortality.[101,102] The use of $ScvO_2$ as a therapeutic endpoint remains controversial for a number of reasons: $ScvO_2$ may be increased in sepsis because of impaired tissue O_2 extraction[103]; increased cost is associated with the use of $ScvO_2$-measuring catheters[104]; and other measures, such as lactate clearance, are less costly while leading to similar outcomes.[105] Furthermore, management of sepsis without an $ScvO_2$ endpoint can yield equally favorable results.[104]

TISSUE OXYGENATION

Arterial and venous O_2 saturations are measures of DO_2 and use by the whole body. Although useful, these global measures do not provide information regarding organ or tissue oxygenation, which reflects the important local balance between O_2 supply and demand. Regional O_2 balance can differ both among organs as well as within regions of the same organ. Current noninvasive methods for the assessment of microcirculatory oxygenation make

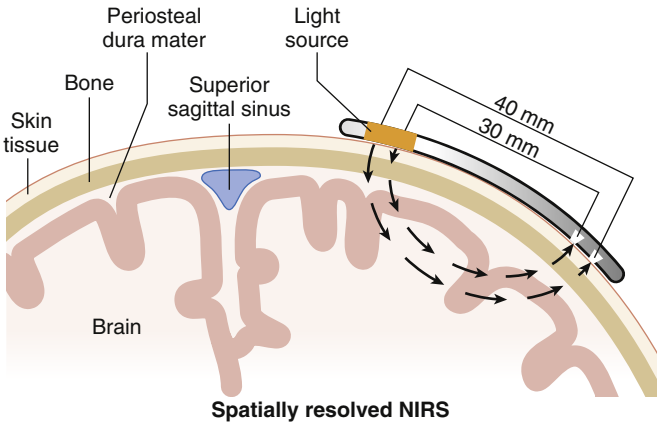


Figure 51-8. Near-infrared spectroscopy (NIRS) applied to cerebral oximetry. In this case, a reflectance oximeter is placed on the forehead. Near-infrared wavelength light is emitted from the light source and enters the underlying tissue. Light is scattered, reflected, and absorbed. Light that reaches the photodetector travels an arc-shaped path. The depth of the path is a function of the distance between the emitter and the detector. The measured value is the oxygen saturation of the tissue through which the light travels on its way to the detector. It is a primarily venous-weighted value. *(Redrawn from Casati A: New technology for noninvasive brain monitoring: continuous cerebral oximetry.* Minerva Anestesiol *72:605, 2006.)*

use of reflectance spectroscopy with light in the visible spectrum (VLS) or in the near-infrared spectrum (NIRS).

Reflectance spectroscopy probes have light emitters and receivers positioned in line (Fig. 51-8). When they are placed on a tissue surface, light transmission through the tissue is affected by reflection, absorption, and scatter. Reflection depends on the angle of incidence of the light beam and the wavelength of light, whereas scatter depends on the number and type of tissue interfaces. As previously outlined, the Beer-Lambert law relates the absorption of light by the tissue to the concentration of tissue chromophores, the extinction coefficient of each, and the path length of the light through the tissue.[106] The predominant tissue chromophore is Hb. The path length of the light is affected by both reflection and scatter, so it cannot be measured directly and must be estimated. Most of the detected photons travel in an arc between the two detectors (see Fig. 51-8). The depth of penetration of the arc into the tissue is proportional to the wavelength of light and the distance between the transmitter and the detector.[106,107]

VLS makes use of white light with wavelengths of 500 to 800 nm, whereas NIRS employs light in the range of 700 to 1100 nm.[108] In general, the depth of penetration of VLS is less than that of NIRS, thus allowing superficial measurements on the order of millimeters and making it suitable for small subsurface volumes. NIRS can penetrate tissue to a depth of several centimeters and allows sampling of a larger volume of tissue.[109] The O_2 saturation displayed is that of a volume of tissue. This volume includes arteries, capillaries, and veins and has a predominantly venous weighting.[110]

CLINICAL APPLICATIONS

Several applications have been described for VLS. Buccal microvascular Hb saturation has been associated with survival in patients with sepsis.[111] VLS has also been used for monitoring flap viability following reconstructive surgical procedures.[112] During gastrointestinal and esophageal surgical procedures, reductions in gastrointestinal tissue saturation, measured by VLS, have been associated with postoperative anastomotic complications.[113,114] Endoscopic VLS differentiates between normal and ischemic areas of the colon,[115] and it may be useful for the diagnosis of mesenteric ischemia.[116] In addition, mucosal O_2 saturation of the gastric conduit following esophagectomy is useful and explores the benefits of ischemic preconditioning.[117]

The most widespread application of NIRS is in cerebral oximetry, with probes placed on the forehead to measure frontal cortical oxygenation (rSo_2). Several NIRS systems are commercially available, and each manufacturer offers different specific technology. Because no gold standard exists for cerebral oximetry, it is difficult to compare the accuracy of the devices, and each device has its own set of "normal" values. For this reason, acquisition of baseline values for each patient at the start of the procedure is recommended.[118] Typical values of rSo_2 range from 55% to 80%. A reduction of rSo_2 to less than 20% to 25% of the baseline, or lower than an absolute value of 50%, is a recommended threshold for intervention.[119,120]

The utility of cerebral oximetry has been explored in cardiovascular, abdominal, thoracic, and orthopedic surgery. In the cardiac surgical setting, intraoperative reductions in rSo_2 have been associated with early postoperative cognitive dysfunction and prolonged ICU and hospital lengths of stay.[120-123] As a guide to therapy, interventions for rSo_2 reductions to less than 75% of baseline in patients undergoing coronary artery bypass graft surgery significantly reduce the incidence of major organ morbidity and mortality, as well as ICU length of stay.[119]

The use of rSo_2 for cerebral monitoring during carotid endarterectomy has also been investigated. Intraoperative reductions in rSo_2 correlate well with changes in transcranial Doppler variables,[124-128] electroencephalographic waveforms,[129-131] and stump pressure,[128,132] which are consistent with ischemia. Although some studies indicate that reductions in rSo_2 that are less than 20% of baseline are well tolerated, data are lacking for a clear rSo_2 threshold for carotid shunt placement (see also Chapter 69).[133,134]

In older patients undergoing major abdominal surgical procedures, protocol-based intraoperative treatment of reductions in rSo_2 results in decreases in postoperative cognitive decline and hospital length of stay.[135] In patients undergoing thoracic surgical procedures with single-lung ventilation, early postoperative cognitive dysfunction is directly related to intraoperative exposure time to rSo_2 less than 65%.[136] Patients undergoing shoulder operations in the beach chair position have a lower baseline rSo_2 and a larger number of episodes of cerebral desaturation, although the clinical implications of these findings are unclear.[137-139]

Shock is a condition in which patients may have inadequate *regional* perfusion in the setting of normal *global* perfusion parameters. In such circumstances, the use of NIRS to monitor tissue perfusion holds some promise. Values obtained by the application of an NIRS probe to

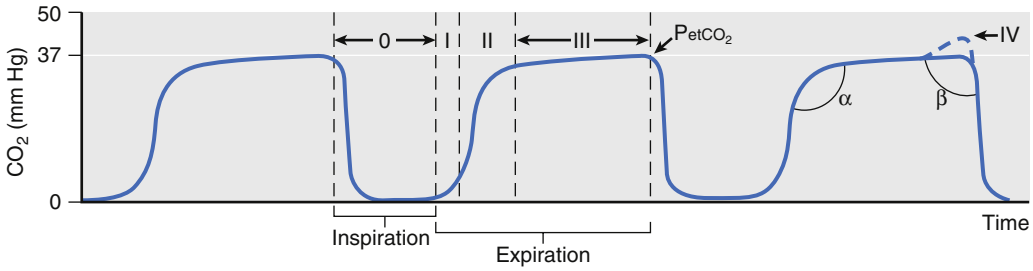


Figure 51-9. Representative time capnogram for three breaths. The expiratory segment is divided into phases I, II, III, and IV. The inspiratory segment is referred to as phase 0 in this figure. α Denotes the angle between phases II and III, whereas β denotes the angle between phase III and the descending limb of phase 0. Phase IV (*dashed line* in third breath) denotes the upstroke observed at the end of phase III in some patients. *$PetCO_2$,* Partial pressure of end-tidal carbon dioxide. *(Courtesy Respironics, Inc.)*

the thenar eminence (StO_2) discriminate between healthy volunteers and patients with shock.[140] Furthermore, in patients with major trauma who present with shock, StO_2 values can identify patients who proceed to develop multiorgan dysfunction or actually die.[141,142]

Although information to warrant clinical decision making exclusively based on NIRS measurements is limited, further investigations are improving the understanding of the measurement and its relevance for clinical management.

CAPNOMETRY AND CAPNOGRAPHY

GENERAL CONCEPTS

The presence of CO_2 in exhaled breath reflects the fundamental physiologic processes of ventilation, pulmonary blood flow, and aerobic metabolism. Its continued monitoring assures the anesthesiologist of correct placement of an endotracheal tube (ETT) or laryngeal mask airway (LMA), as well as the integrity of a breathing circuit. Exhaled CO_2 provides information primarily on ventilation. It is also used to estimate the adequacy of cardiac output. In combination with $Paco_2$, exhaled CO_2 can be used to estimate the ratio of physiologic dead space (V_D) to tidal volume (V_T) by using the Bohr equation[143]:

$$\frac{V_D}{V_T} = \left(\frac{Paco_2 - P\bar{E}co_2}{Paco_2}\right) \qquad [15]$$

where $P_{\bar{E}}CO_2$ is the mixed expired CO_2 partial pressure, such as measured in exhaled air collected in a mixing bag or chamber, or computed from a volumetric capnogram. The ability to detect and quantify CO_2 is a crucial component of respiratory monitoring in anesthesia and critical care medicine.

Considerable confusion arises from inconsistent and interchangeable terminology as applied to medical CO_2 gas analysis.[143-145] In a very general sense, *capnometry* refers to the measurement and quantification of inhaled or exhaled CO_2 concentrations at the airway opening. *Capnography*, however, refers not only to the method of CO_2 measurement, but also to its graphic display as a function of time or volume. A *capnometer* is simply a device that measures CO_2 concentrations. A capnometer may display a numeric value for inspired or exhaled CO_2. A *capnograph*, however, is a device that records and displays CO_2 concentrations, usually as a function of time. A *capnogram* refers to the graphic display that the capnograph generates. Figure 51-9 illustrates a typical CO_2 concentration profile for three breaths as a function of time.

MEASUREMENT PRINCIPLES

Various methods exist for detecting and quantifying CO_2 concentrations in respiratory gases, such as mass spectrometry, Raman spectrometry, or gas chromatography.[146,147] The most commonly used method in clinical environments relies on nondispersive infrared absorption.[148] With this technique, a beam of infrared light is passed through a gas sample, and the resulting intensity of the transmitted light is measured by a photodetector.[144] Gaseous CO_2 absorbs light over a very narrow bandwidth centered around 4.26 μm. Its presence in the sample cell decreases the amount of infrared light at this wavelength that reaches the detector in proportion to its concentration. Because the absorption spectrum for CO_2 partially overlaps with the spectra of other gaseous species commonly encountered in anesthesia (i.e., water and nitrous oxide[149]), infrared filters and compensation algorithms are used to minimize this interference and improve accuracy.[150]

Most capnometers rely on an infrared-light source that is focused on a chopper disk that rotates at approximately 60 revolutions/second. The chopper allows the beam to be alternately directed through (1) the sample cell with the gas to be analyzed and (2) a reference cell with no detectable CO_2. In addition, the light source is completely blocked at various points during the revolution of the chopper disk. The photodetector and associated circuitry process these three signals to estimate the changes in CO_2 concentration continuously in the sample cell. Alternatively, CO_2 concentration may be estimated with solid-state technology, using a beam splitter instead of a chopper wheel. The splitter allows for the measurement of infrared energy at wavelengths within and outside the absorption spectrum of CO_2.

The two general categories of capnometers are sidestream (diverting) and mainstream (nondiverting). Sidestream analyzers are more frequently used in clinical environments. Their CO_2 sensors are physically located away from the airway gases to be measured. Sidestream analyzers incorporate a pump or compressor that aspirates gases into a sample cell located at the unit's console

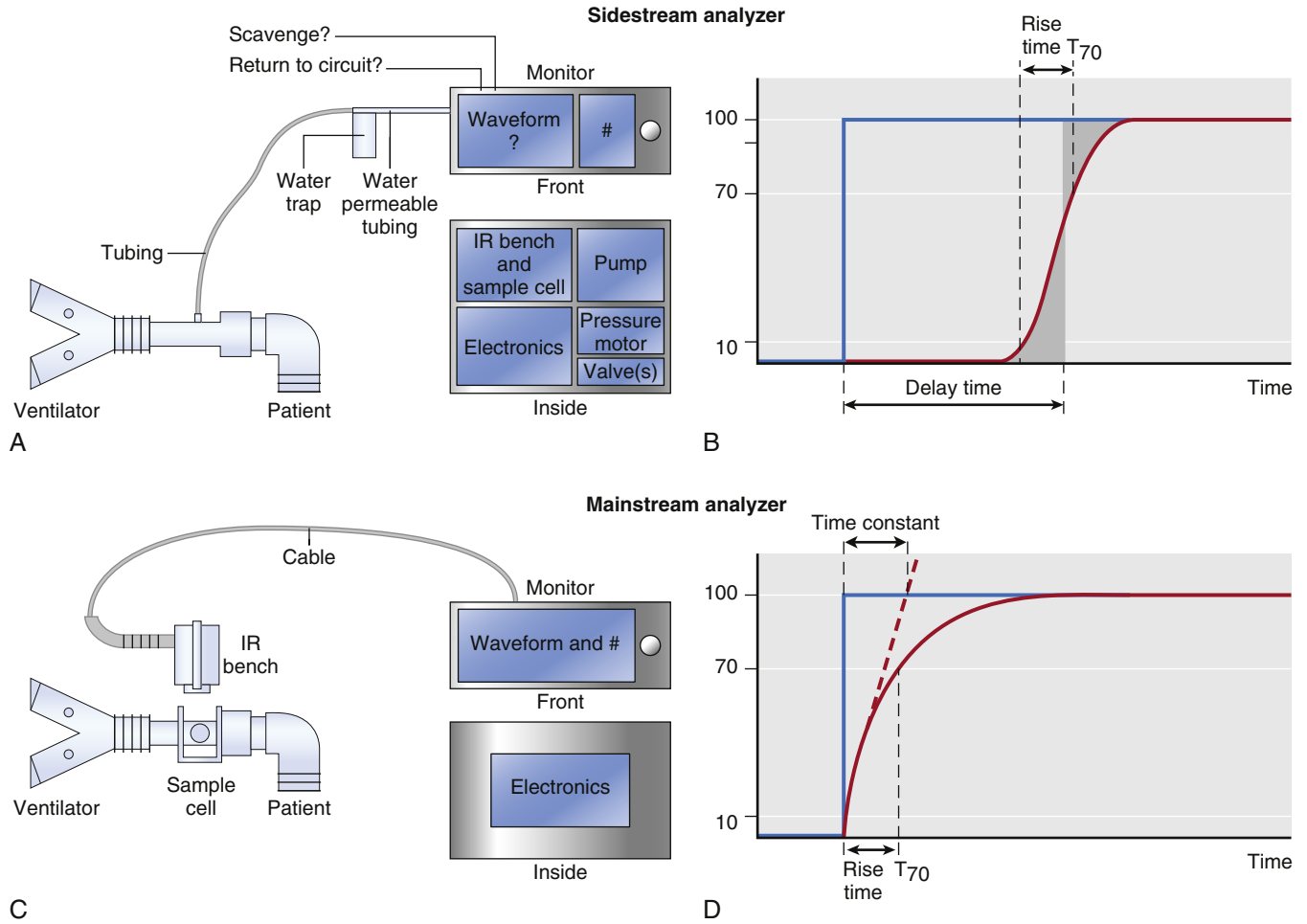


Figure 51-10. Schematics of sidestream (**A**) and mainstream (**C**) capnometry sampling methods, along with corresponding representative time capnograms (*red curves* in **B** and **D**) following a step increase in carbon dioxide concentration *(blue lines)*. Rise time (T_{70}) corresponds to the time required for either sensor to change from 10% to 70% of its final value. A delay time is observed for the sidestream analyzer, corresponding to the aspiration rate of the sampled gas and the washout of the analyzing chamber. *IR,* Infrared. *(Modified from Jaffe MB: Mainstream or sidestream capnography? Technical considerations. Wallingford, Conn, 2002, Respironics Novametric, Inc; and Brunner JX, Westenskow DR: How the rise time of carbon dioxide analysers influences the accuracy of carbon dioxide measurements,* Br J Anaesth *61: 628-638, 1988.)*

(Fig. 51-10, *A*). Typical tubing length for this aspiration may be 6 feet, and gas withdrawal rates may vary from 30 to 500 mL/minute. This lost gas volume may need to be considered during closed-circuit anesthesia or during ventilation of neonates and infants. The volume can be returned to the circuit, or it can be routed to a scavenger to prevent contamination of the environment with anesthetic or waste gases. Gases must also pass through various filters and water traps before they are presented to the sample cell.[144] Sidestream capnometers have a transport delay time corresponding to the rate at which gas is sampled and the washout of the analyzing chamber (Fig. 51-10, *B*). The capnograms generated by sidestream analyzers also have an associated rise time, defined as the time required for the analyzer to respond to a sudden change in CO_2 concentration.[151] By convention, this is usually the time interval required for the analyzer output to change from 10% to 70% of its final value.[151] Typical increase times for commercially available capnometers range from 10 to 400 msec, and they can depend on the rotation of the chopper wheel, the rate of gas aspiration, the volume of aspiration tubing and water traps, and the dynamic response of the infrared filters and other electronics.

With mainstream analyzers, the sample cell is placed directly into the patient's breathing circuit. Thus, the inspiratory or expiratory gases pass directly through the infrared light path (Fig. 51-10, *C*). An advantage of mainstream analyzers is that they have no delay time (Fig. 51-10, *D*). Moreover, their rise time is generally faster than that of sidestream analyzers.[151] A disadvantage is the potential increase in dead space, although more recent developments in solid-state electronics have made this much less of an issue.[152] In addition, the sample cell is usually heated to 40° C to minimize the condensation of water vapor, which can bias the measurement. This increase in temperature, combined with the proximity of the sensor to the patient's airway, can potentially increase the risk of facial burns.

TIME CAPNOGRAM

The simplest and most widely used form of display for exhaled CO_2 is the *time capnogram*. The time capnogram displays both inspiratory and expiratory phases.

Figure 51-9 shows a typical time capnogram for three breaths. The expiratory phase is divided into three distinct components. Phase I corresponds to the exhalation of dead space gas from the central conducting airways or any equipment distal to the sampling site, which ideally should have no detectable CO_2 (i.e., partial pressure of CO_2, P_{CO_2} ~0). During phase II, a sharp rise in P_{CO_2} to a plateau indicates the sampling of transitional gas between the airways and alveoli. The plateau region of the capnogram, phase III, corresponds to the P_{CO_2} in the alveolar compartment. For a lung with relatively homogeneous ventilation, phase III is approximately flat throughout expiration. In fact, various mechanisms contribute to the slight upsloping of CO_2 concentration versus time during phase III. Most of these mechanisms reflect a heterogeneous distribution of ventilation-perfusion ($\dot{V}/\dot{Q}$) or alveolar CO_2 partial pressure (P_{ACO_2}) throughout the lung. Well-ventilated and well-matched $\dot{V}/\dot{Q}$ regions tend to have lower P_{CO_2} and shorter time constants, and they empty earlier during the expiratory phase. Less well-ventilated and poorly matched $\dot{V}/\dot{Q}$ regions have higher CO_2 levels, and they empty later in the expiratory cycle. Respiratory disorders associated with an increase in ventilation heterogeneity, such as asthma, chronic obstructive pulmonary disease (COPD), or acute lung injury,[153] yield a steeper upslope of phase III. Interventions that improve ventilation homogeneity, such as positive end-expiratory pressure (PEEP) or bronchodilators, flatten phase III. Mechanical disturbances may also be present during phase III, thus reflecting processes such as spontaneous breathing efforts, cardiogenic oscillations, or surgical manipulation (Fig. 51-11). Following phase III, a sharp downstroke of P_{CO_2} occurs as fresh inspired gas moves past the sampling site and washes out the remaining CO_2. This is referred to as the beginning of phase 0 by some authors,[145,154] or phase IV by others.[146] Occasionally, a sharp upstroke in P_{CO_2} is observed at the very end of phase III, which is termed phase IV or IV′, depending on the author.[155] This upstroke probably results from the closure of lung units with relatively low P_{CO_2} and allows for regions of higher CO_2 to contribute a greater proportion of the exhaled gas to be sampled.[145] Additional insight into various abnormalities in ventilation or perfusion are also obtained by trending time capnograms over many breaths for long periods (Fig. 51-12).

The term "end-tidal" CO_2 ($PetCO_2$) generally refers to the final value of the exhaled P_{CO_2} curve, at the very end of the expiratory phase. The method used to determine this number is not universal and varies according to the manufacturer of the particular capnograph in use. For example, $PetCO_2$ may simply be (1) the P_{CO_2} value just before inspiration, (2) the largest P_{CO_2} value during a single exhalation cycle, or (3) the P_{CO_2} value at a specified time in the capnogram averaged across several breaths. If $PetCO_2$ is measured during a reasonably flat and undistorted phase III, it may be well correlated with Pa_{CO_2}.[150] This may not be the case if the duration of phase III is truncated or if CO_2 is measured from gas that is contaminated with room or O_2-enriched air (i.e., during spontaneous breathing with a nasal cannula or facemask). Potential causes of increased or decreased $PetCO_2$ are listed in Table 51-2. In healthy individuals with homogeneous ventilation, the difference between Pa_{CO_2} and $PetCO_2$ is usually less than 5 mm Hg, thereby expressing the equilibration between alveolar and pulmonary capillary blood. Several disease states compromise this equilibration and produce increased Pa_{CO_2} – $PetCO_2$ difference (Box 51-2). In some situations, $PetCO_2$ can be greater than Pa_{CO_2}, especially in the presence of severe ventilation heterogeneity and lung units with very low $\dot{V}/\dot{Q}$. For steady-state conditions, the $PetCO_2$ usually reflects the relative balance between CO_2 production and alveolar ventilation.

VOLUME CAPNOGRAM

Although time capnography is relatively straightforward to monitor in clinical environments, a major limitation of the technique is its lack of information regarding flow or volume.[154] The *volume capnogram* is a graphic display of CO_2 concentration or partial pressure versus exhaled volume.[146] The inspiratory phase is not defined in a volume capnogram. Similar to its temporal counterpart, it is also partitioned into three distinct phases (I, II, and III) corresponding to anatomic dead space, transitional, and alveolar gas samples (Fig. 51-13). However, it possesses several advantages over the time capnogram. First, it allows for estimation of the relative contributions of anatomic and alveolar components of V_D.[156] Second, it may be more sensitive than the time capnogram in detecting subtle changes in dead space that are caused by alterations in PEEP, pulmonary blood flow, or ventilation heterogeneity (Fig. 51-14). Finally, the numeric integral of P_{CO_2} as a function of volume allows for determination of the total mass of CO_2 exhaled during a breath and provides for estimation of $\dot{V}_{CO_2}$.

BLOOD GAS ANALYSIS

PHYSIOLOGIC FUNDAMENTALS

Arterial blood gas analysis is used to assess oxygenation, ventilation, and acid-base status. This section focuses on the use of arterial blood gases to assess oxygenation and ventilation. For a discussion of acid-base status, see Chapter 60. Oxygenation is reflected in the PaO_2, which is a function of the alveolar partial pressure of O_2 (PAO_2) and the efficiency of O_2 transfer from alveoli to the pulmonary capillary blood. In healthy adults breathing room air at sea level, PaO_2 ranges between 80 and 100 mm Hg. The normal value of PaO_2 decreases with increasing age and increasing altitude. Hypoxemia is defined as a PaO_2 less than 80 mm Hg. Hypoxemia has five physiologic causes:

1. Hypoventilation
2. $\dot{V}/\dot{Q}$ mismatching
3. Right-to-left shunt
4. Diffusion limitation
5. Diffusion-perfusion mismatch

The first three causes explain most cases of hypoxemia in the perioperative setting. Reduced inspired PO_2 (e.g., in faulty closed or partially closed anesthesia breathing circuits or at high altitude) is an additional cause of hypoxemia.

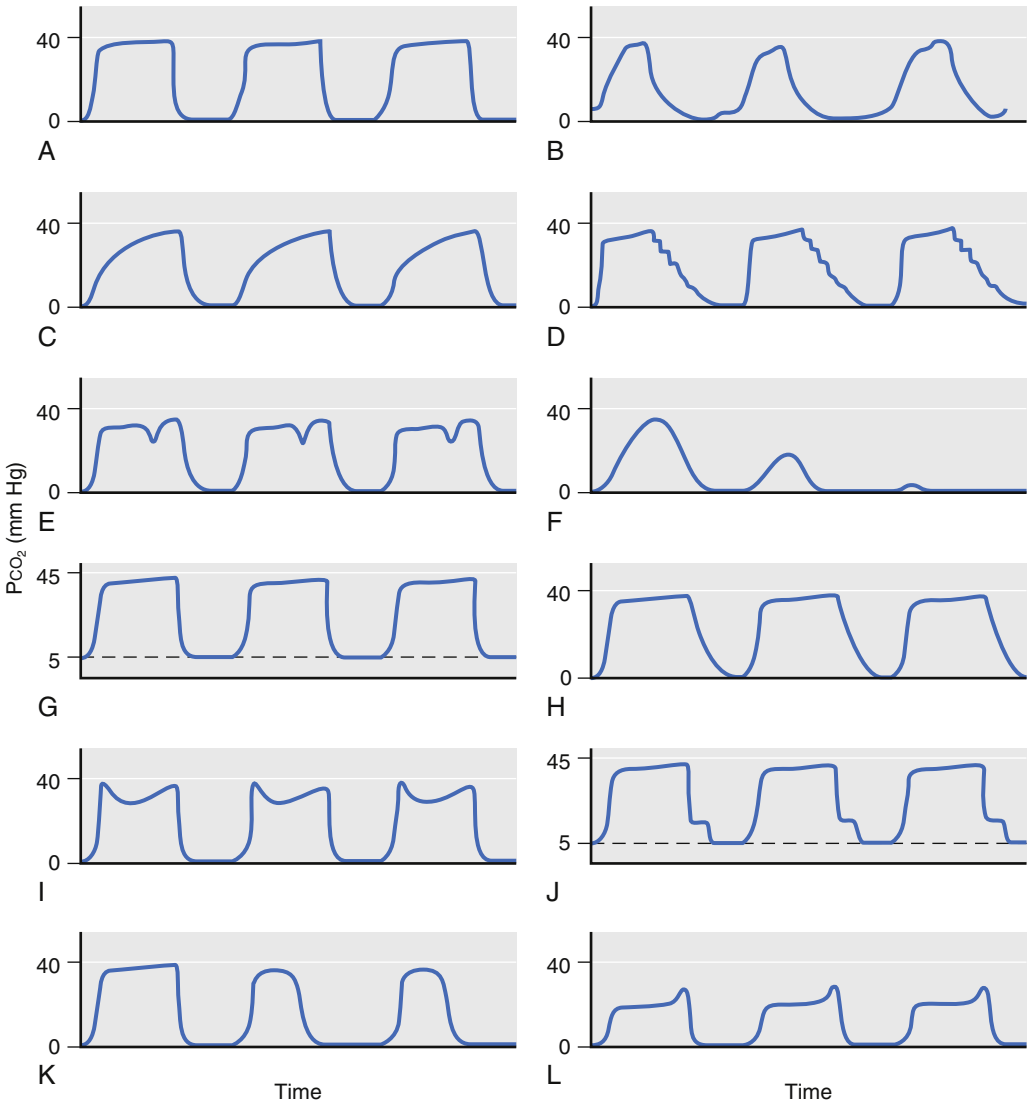


Figure 51-11. Representative time capnograms under normal and abnormal conditions. **A,** Normal capnogram during controlled mechanical ventilation. **B,** Normal capnogram during spontaneous breathing. **C,** Increased upslope of phase III, as may occur during bronchospasm (asthma, chronic obstructive pulmonary disease), or partially obstructed endotracheal tube or breathing circuit. **D,** Cardiogenic oscillations at the end of exhalation as flow decreases to zero and the beating heart causes emptying of different lung regions and back-and-forth motion between exhaled and fresh gas. **E,** Clefts during phase III that indicate spontaneous breathing efforts during controlled mechanical ventilation. **F,** Esophageal intubation. **G,** Rebreathing of carbon dioxide (CO_2), as may occur with a faulty expiratory valve or exhausted absorber system. Inspiratory CO_2 is consistently greater than zero. **H,** Faulty inspiratory valve, resulting in a slower downslope, which extends into the inhalation phase (phase 0) as CO_2 in the inspiratory limb is rebreathed. **I,** Two peaks in phase III that suggest sequential emptying of two heterogeneous compartments, as may be seen in a patient with a single-lung transplant. **J,** Faulty inspiratory valve. **K,** Sudden shortening of the duration of phase III during controlled mechanical ventilation that suggests the abrupt onset of a ruptured or leaking endotracheal tube cuff. **L,** Dual plateau in phase III that suggests the presence of a leak in a sidestream sample line. The early portion of phase III is abnormally low because of dilution of exhaled gas with ambient air. The sharp increase in CO_2 at the end of phase III reflects a diminished leak resulting from the increased circuit pressure at the onset of inspiration. P_{CO_2}, Partial pressure of CO_2. *(Modified from Hess D: Capnometry and capnography: technical aspects, physiologic aspects, and clinical applications,* Respir Care *35:557-576, 1990; Roberts WA, Maniscalco WM, Cohen AR, et al: The use of capnography for recognition of esophageal intubation in the neonatal intensive care unit,* Pediatr Pulmonol *19:262-268, 1995; and Eskaros SM, Papadakos PJ, Lachmann B: Respiratory monitoring. In Miller RD, Eriksson LI, Fleisher LA, editors:* Miller's anesthesia, *ed 7, New York, 2010, Churchill Livingstone, p 1427.)*

These factors produce hypoxemia by affecting different steps of O_2 transport from the environment to the arterial blood. A low inspired PO_2, as well as hypoventilation, reduces the PAO_2. $\dot{V}/\dot{Q}$ mismatch, right-to-left shunt, and alveolar diffusion limitation affect the efficiency of O_2 exchange. Diffusion limitation plays a role in conditions that thicken the alveolar-capillary barrier, such as interstitial lung diseases, and in hypoxemia induced by exercise or altitude.[157,158] In the clinical setting, impairment of diffusion of O_2 or CO_2 rarely occurs to a significant extent. The remainder of this section focuses on $\dot{V}/\dot{Q}$ mismatch and right-to-left shunt.

$\dot{V}/\dot{Q}$ mismatch is the most common cause of hypoxemia in the clinical setting. Ventilation and perfusion are nonuniformly distributed throughout the normal lung, with worsening mismatch in the setting of general

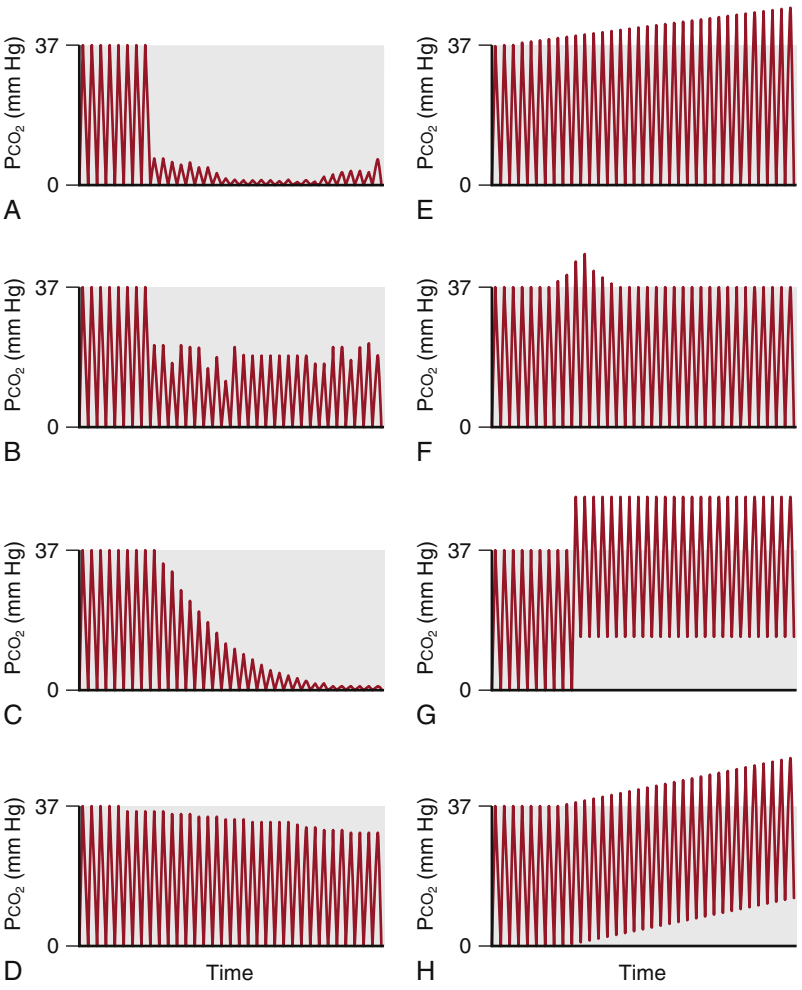


Figure 51-12. Representative time capnograms trended over many breaths that illustrate various abnormalities in ventilation or perfusion, or both. **A,** Sudden drop in carbon dioxide (CO_2) secondary to catastrophic loss of ventilation. **B,** Leak or partial obstruction in the breathing circuit. **C,** sudden interruption in pulmonary perfusion, as may occur during cardiac arrest. **D,** Gradual decrease in CO_2 resulting from hyperventilation, decreased metabolism, or decreased pulmonary perfusion. **E,** Gradual increase in CO_2 as may occur during hypoventilation, laparoscopic insufflation, increased metabolism, or increased pulmonary perfusion. **F,** Transient rise in CO_2 that indicates an acute increase in CO_2 delivery to the lungs, as may occur during release of a tourniquet or administration of a bicarbonate bolus. **G,** Rise in both the baseline and end-tidal CO_2 that is consistent with a contaminated sample cell. **H,** Gradual rise in baseline and end-tidal CO_2 that is consistent with rebreathing. P_{CO_2}, Partial pressure of CO_2. *(Modified from Swedlow DB: Capnometry and capnography: the anesthesia disaster early warning system,* Semin Anesth *5:194-205, 1986.)*

TABLE 51-2 **CAUSES OF CHANGES IN PARTIAL PRESSURE OF END-TIDAL CARBON DIOXIDE**

↑ $PetCO_2$	↓ $PetCO_2$
↑ CO_2 Production and Delivery to the Lungs	**↓ CO_2 Production and Delivery to the Lungs**
Increased metabolic rate Fever Sepsis Seizures Malignant hyperthermia Thyrotoxicosis Increased cardiac output (e.g., during CPR) Bicarbonate administration	Hypothermia Pulmonary hypoperfusion Cardiac arrest Pulmonary embolism Hemorrhage Hypotension
↓ Alveolar Ventilation	**↑ Alveolar Ventilation**
Hypoventilation Respiratory center depression Partial muscular paralysis Neuromuscular disease High spinal anesthesia COPD	Hyperventilation
Equipment Malfunction	**Equipment Malfunction**
Rebreathing Exhausted CO_2 absorber Leak in ventilator circuit Faulty inspiratory/expiratory valve	Ventilator disconnect Esophageal intubation Complete airway obstruction Poor sampling Leak around endotracheal tube cuff

Modified from Hess D: Capnometry and capnography: technical aspects, physiologic aspects, and clinical applications, Respir Care *35:557-576, 1990.*
CO_2, Carbon dioxide; *COPD,* chronic obstructive pulmonary disease; *CPR,* cardiopulmonary resuscitation; *$PetCO_2$,* partial pressure of end-tidal carbon dioxide.

BOX 51-2 ***Causes of Increased Arterial-to-End-Tidal Carbon Dioxide Pressure Difference***

Increased ventilation-perfusion heterogeneity particularly with high ventilation-perfusion regions
Pulmonary hypoperfusion
Pulmonary embolism
Cardiac arrest
Positive-pressure ventilation (especially with PEEP)
High-rate low-tidal-volume ventilation

Modified from Hess D: Capnometry and capnography: technical aspects, physiologic aspects, and clinical applications, Respir Care *35:557-576, 1990.*
PEEP, Positive end-expiratory pressure.

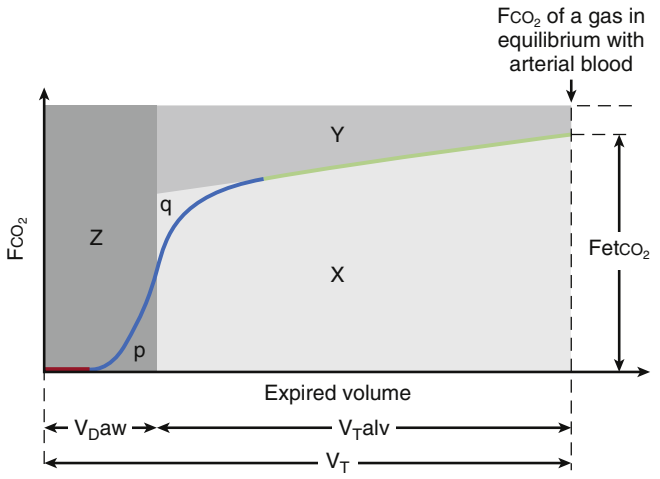


Figure 51-13. The volume capnogram is a plot of the fraction of carbon dioxide (F_{CO_2}) in exhaled gas versus exhaled volume. It is divided into three phases, which reflect the same sources of expired gas as present in the time capnograph: anatomic dead space (phase I, *red*), transitional (phase II, *blue*), and alveolar gas (phase III, *green*). The volume capnogram allows for the partition of total tidal volume (V_T) into airway dead space volume ($V_D$aw) and an effective alveolar tidal volume ($V_T$alv) by a *vertical line* through phase II, positioned such that the approximately triangular areas p and q are equal. It also provides the slope of phase III as a quantitative measure of the heterogeneity of alveolar ventilation. The total area below the *horizontal line* (denoting the F_{CO_2} of a gas in equilibrium with arterial blood) can be divided into three distinct areas: X, Y, and Z. Area X corresponds to the total volume of CO_2 exhaled over a tidal breath. This value can be used to compute the CO_2 production ($\dot{V}_{CO_2}$), and the mixed expired CO_2 fraction or partial pressure (P_{CO_2}) to be used in the Bohr equation (Equation 15) based on the division of the exhaled CO_2 volume by the exhaled tidal volume. Area Y represents wasted ventilation secondary to alveolar dead space, whereas area Z corresponds to wasted ventilation secondary to anatomic dead space ($V_D$aw). Thus, areas Y + Z represent the total physiologic dead space. The volume capnogram can also be plotted as a P_{CO_2} versus exhaled volume curve. *Fet_{CO_2},* Fraction of end-tidal CO_2. *(Modified from Fletcher R, Jonson B, Cumming G, Brew J: The concept of deadspace with special reference to the single breath test for carbon dioxide,* Br J Anaesth *53:77-88, 1981.)*

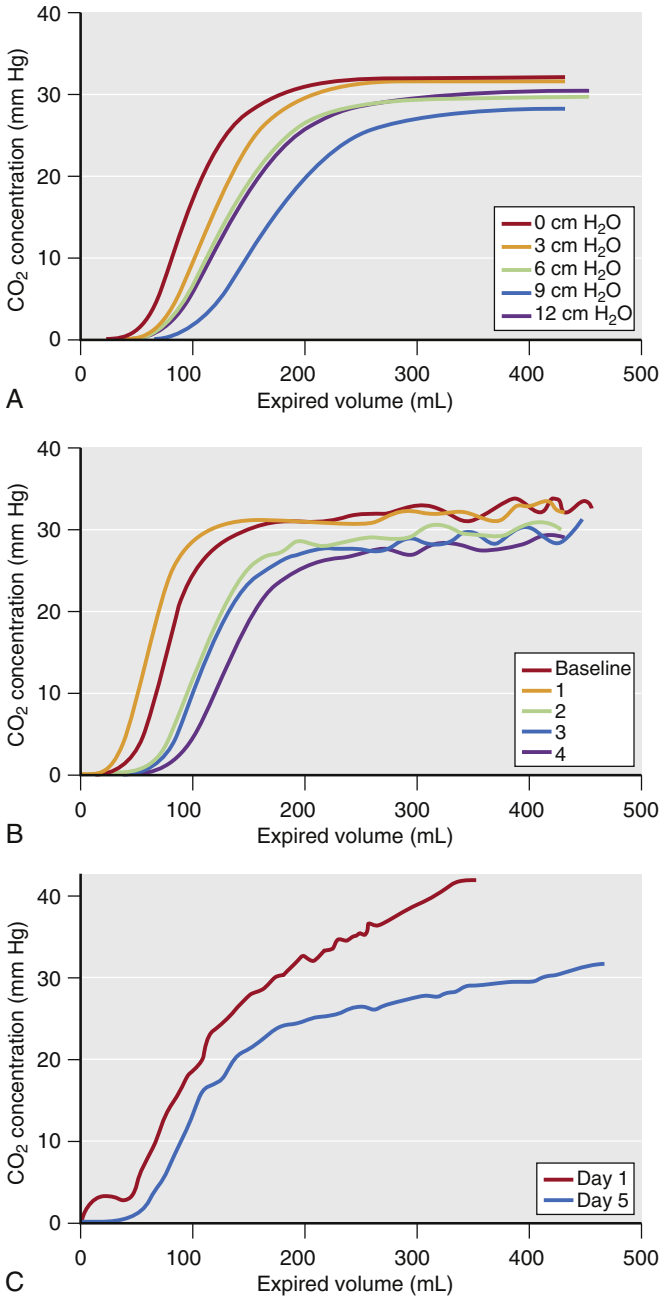


Figure 51-14. Representative single-breath volume capnograms illustrating various abnormalities in ventilation or perfusion, or both. **A,** Alterations in phases II and III with corresponding changes in PEEP (0, 3, 6, 9, and 12 cm H_2O) during positive-pressure ventilation. **B,** Alterations in phases II and III with corresponding changes in pulmonary perfusion (increasing numbers correspond to decreasing pulmonary blood flow). **C,** Pronounced positive slope of phase III during acute bronchospasm (day 1). Following resolution (day 5), a noticeable reduction in the slope of phase III occurs. *CO_2,* Carbon dioxide. *(Modified from Thompson JE, Jaffe MB: Capnographic waveforms in the mechanically ventilated patient,* Respir Care *50:100-108, 2005.)*

anesthesia, lung disease, and mechanical ventilation. Areas with low or zero $\dot{V}/\dot{Q}$ yield low end-capillary PO_2, whereas areas with normal or high $\dot{V}/\dot{Q}$ produce higher end-capillary PO_2. However, because of the plateau of the O_2Hb dissociation curve (see Fig. 51-2), the normal and high $\dot{V}/\dot{Q}$ regions are limited in the extent to which they increase the O_2 content and compensate for the low $\dot{V}/\dot{Q}$ regions (Fig. 51-15). As a consequence, $\dot{V}/\dot{Q}$ mismatch results in hypoxemia.

Right-to left shunt is the amount of blood that flows from the pulmonary artery to the systemic arterial circulation without undergoing pulmonary gas exchange.

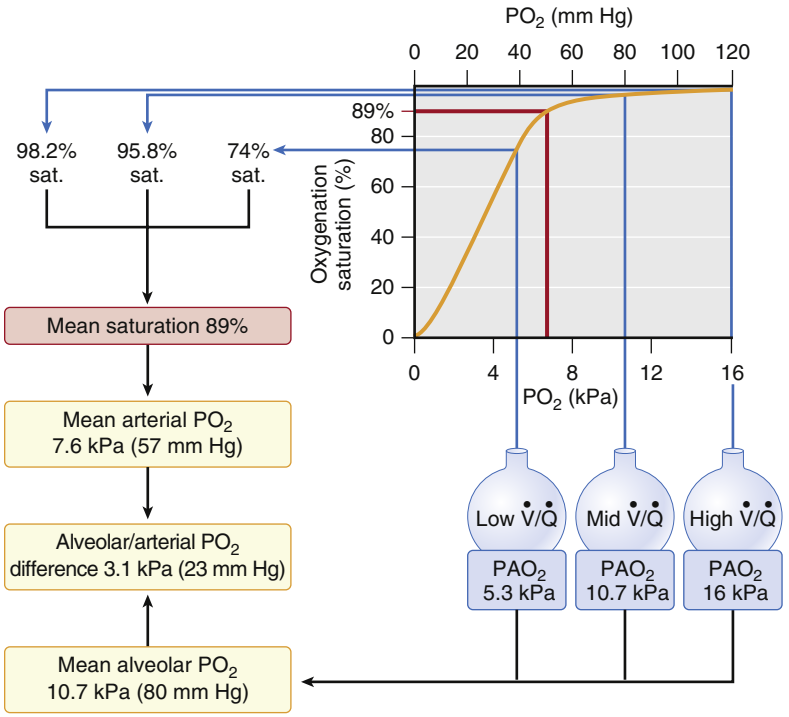


Figure 51-15. Effect of different ventilation-perfusion $\dot{V}/\dot{Q}$ regions on partial pressure of arterial oxygen (PaO_2). Because of the shape of the oxyhemoglobin dissociation curve, regions of lung with low $\dot{V}/\dot{Q}$ have a disproportionately greater effect on lowering the arterial saturation than do regions of lung with normal or higher $\dot{V}/\dot{Q}$ to increase PaO_2. Assuming equal blood flow, the average partial pressure of alveolar oxygen (PAO_2) of the $\dot{V}/\dot{Q}$ regions represented in the illustration is 10.7 kPa (80 mm Hg). Based on the oxyhemoglobin dissociation curve, however, the average saturation of the arterial blood is 89%, producing an average PaO_2 equal to 7.6 kPa (57 mm Hg). *PO_2,* Partial pressure of oxygen. *(Modified from Lumb AB:* Nunn's applied respiratory physiology, *ed 6, Philadelphia, 2005, Butterworth Heinemann.)*

It represents an extreme case of $\dot{V}/\dot{Q}$ mismatch in which the ratio equals zero and the end-capillary gas partial pressures are equal to the values found in mixed venous blood. In healthy awake spontaneously breathing subjects, intrapulmonary shunt is negligible,[159] and a small (<1% of cardiac output) extrapulmonary shunt results from drainage of the bronchial and thebesian veins into the arterial side of the circulation.[160] During general anesthesia, a right-to-left shunt can develop as a result of atelectasis.[161,162] Right-to-left shunt can also be seen in pathologic conditions such as pneumonia and acute lung injury. The effect of the shunt on PaO_2 is a function of the magnitude of the shunt, and the cardiac output (Fig. 51-16). Increases in FiO_2 have a small effect on PaO_2 in the presence of a large true right-to-left shunt (see Fig. 51-16).

The traditional method to estimate flow through shunting regions ($\dot{Q}_S$) as a fraction of the total cardiac output ($\dot{Q}_T$) is based on modeling of the lung as a three-compartment system (Fig. 51-17).[163] The three compartments represent (1) lung regions receiving both ventilation and perfusion, (2) a shunt compartment ($\dot{V}/\dot{Q}=0$), and (3) a dead space compartment with ventilation but no perfusion ($\dot{V}/\dot{Q}=$ infinity). The application of the concept of mass balance to this model yields the shunt fraction ($\dot{Q}_S/\dot{Q}_T$) expression:

$$\dot{Q}_s/\dot{Q}_T = \frac{\left(Cc'_{O_2} - CAO_2\right)}{\left(Cc'_{O_2} - C\bar{v}_{O_2}\right)} \qquad [16]$$

where $\dot{Q}_S$ is shunted blood flow, Cc'_{O_2} is end-capillary O_2 content, and $C\bar{v}_{O_2}$ mixed venous. Cc'_{O_2} is calculated using Equation 1 and assuming equilibration between the end-capillary blood and alveolar gas. The PAO_2 is calculated using the ideal alveolar gas equation:

$$PAO_2 = FiO_2 \times (P_{atm} - P_{H_2O}) - Pa_{CO_2}/R \qquad [17]$$

where FiO_2 is inspired O_2 fraction, P_{atm} is barometric pressure, P_{H_2O} is partial pressure of water vapor (47 mm Hg at 37° C). R, the respiratory quotient, is the ratio of pulmonary CO_2 elimination to $\dot{V}_{O_2}$ ($R=\dot{V}_{CO_2}/\dot{V}_{O_2}$), which equals 0.8 under normal diet and rest conditions.

The three-compartment model is a simplification of the real lung. As a result, under conditions of FiO_2 less than 100%, $\dot{Q}_S/\dot{Q}_T$ represents a combination of all factors producing hypoxemia, predominantly true right-to-left shunt and $\dot{V}/\dot{Q}$ mismatch. Under such conditions, $\dot{Q}_S/\dot{Q}_T$ is referred to as venous admixture. When FiO_2 is 100%, the effects of $\dot{V}/\dot{Q}$ heterogeneity on O_2 exchange are eliminated, and the equation exclusively yields the right-to-left shunt fraction.[164] The administration of FiO_2 of 100% can lead to the development of absorption atelectasis in compartments with very low $\dot{V}/\dot{Q}$, thus leading to an increase in the true right-to-left shunt.[164]

If the assumptions are made that end-capillary blood has an O_2 saturation of 100% and the O_2 content of blood is predominantly determined by Hb saturation, the shunt fraction equation can be simplified to:

$$\dot{Q}_s/\dot{Q}_T = \frac{(1 - SaO_2)}{(1 - S\bar{v}_{O_2})} \qquad [18]$$

where SaO_2 is arterial saturation, and $S\bar{v}_{O_2}$ is mixed venous saturation.

Other Indices of Oxygenation

The calculation of the shunt fraction is a fundamental measure of O_2 exchange impairment. However, a pulmonary artery catheter is required for the measurement of $S\bar{v}_{O_2}$. For this reason, indices of oxygenation have been developed that rely on less invasive measures. The PaO_2 certainly reflects oxygenation. However, it is limited in providing a measure of the magnitude of the O_2 exchange deficiency because of its dependence on the FiO_2 and the

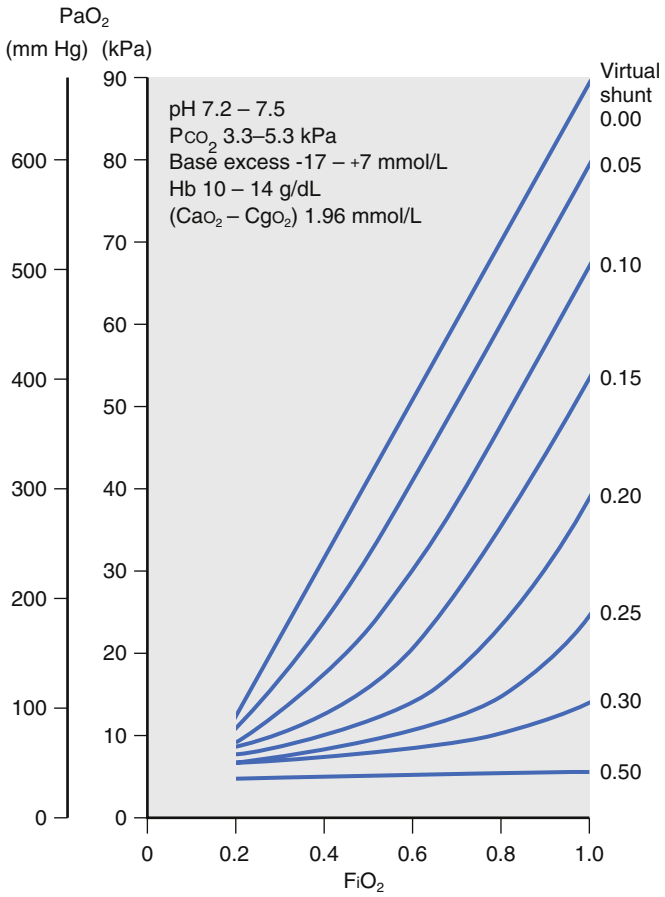


Figure 51-16. Relationship between partial pressure of arterial oxygen (PaO_2) and fraction of inspired oxygen (FiO_2) for different values of shunt fraction computed for normal values of barometric pressure, pH, partial pressure of carbon dioxide (P_{CO_2}), base excess, hemoglobin (Hb) concentration, and arterial–mixed venous oxygen content difference ($CAO_2 - C\dot{v}O_2$). Note the small increase in PaO_2 with FiO_2 in the presence of large shunt. This graph corresponds to the so-called isoshunt diagram presented in Lawler PG, Nunn JF: A reassessment of the validity of the iso-shunt graph, *Br J Anaesth* 56:1325-1335, 1984.

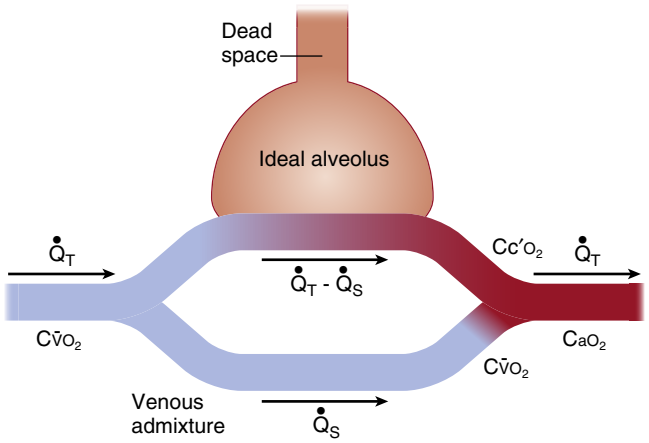


Figure 51-17. Three-compartment model of gas exchange. The lung is represented as three functional units: alveolar dead space, "ideal" alveoli, and venous admixture (shunt). The model does not differentiate between true shunt or true dead space and components of shunt and dead space that are caused by ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch. CAO_2, Arterial oxygen content; $Cc'o_2$, oxygen content of end pulmonary capillary blood; $C\bar{v}o_2$, mixed venous oxygen content; $\dot{Q}_S$, shunted blood flow; $\dot{Q}_T$, total blood flow. *(Redrawn from Lumb AB:* Nunn's applied respiratory physiology, *ed 6, Philadelphia, 2005, Butterworth Heinemann.)*

nonlinear relationship between PaO_2 and blood O_2 content.[165] As a consequence, several indices based on the PaO_2 that account for the FiO_2 or the PAO_2 have been developed: the alveolar-arterial partial pressure gradient of O_2 ($[A\text{-}a]PO_2$), the respiratory index ($[A\text{-}a]PO_2/PaO_2$), the arterial-alveolar ratio of O_2 partial pressures (PaO_2/PAO_2), and the ratio between PaO_2 and FiO_2 (PaO_2/FiO_2).[165]

The ideal index should reflect the efficiency of oxygenation, change with changes in lung function, remain constant with changes in extrapulmonary conditions (e.g., FiO_2), and provide clinically useful diagnostic and prognostic information.[165] The advantages of indices based on the PO_2 are that their calculations are fairly simple and require only arterial blood sampling. However, an important limitation is that these indices vary with the FiO_2, P_{aCO_2}, Hb, and O_2 consumption ($\dot{V}O_2$).[166,167] Consequently, changes in those variables can lead to changes in the values of the indices in the absence of any change in lung gas exchange function. Another limitation is the failure of these indices to account for changes in $\dot{V}/\dot{Q}$ matching resulting from changes in the FiO_2. Additionally, indices that use PAO_2 rely on the assumptions of the alveolar gas equation, including $P_{ACO_2} = P_{aCO_2}$, which may not hold true in pathologic conditions.

An early index developed to assess oxygenation that used only peripheral blood sampling was the $(A\text{-}a)PO_2$.[168] The $(A\text{-}a)PO_2$ helps to differentiate $\dot{V}/\dot{Q}$ mismatch, shunt, and diffusion limitation from hypoventilation and low FiO_2 as causes of hypoxemia. This is because the $(A\text{-}a)PO_2$ is unchanged under conditions of decreased FiO_2 and hypoventilation but increased with $\dot{V}/\dot{Q}$ mismatch, shunt, and diffusion limitation.

The A-a gradient is calculated as follows:

$$(A\text{-}a)PO_2 = PAO_2 - PaO_2 \qquad [19]$$

The normal value of the $(A\text{-}a)PO_2$ is less than 10 mm Hg in young adults breathing room air, and it increases with age and the administration of supplemental O_2. The change in $(A\text{-}a)PO_2$ with age can be estimated by[169]:

$$(A\text{-}a)PO_2 = 0.21 \times (age + 2.5) \qquad [20]$$

The $(A\text{-}a)PO_2$ varies significantly with the FiO_2 such that the application of supplemental O_2 can lead to an increase in the $(A\text{-}a)PO_2$ independent of pulmonary disease.[166] Like the $(A\text{-}a)PO_2$, the respiratory index $(A\text{-}a)PO_2/PaO_2$ and the PaO_2/PAO_2 are sensitive to FiO_2, particularly in the presence of a high degree of $\dot{V}/\dot{Q}$ mismatch, such as during the acute respiratory distress syndrome (ARDS), and less so in the absence of true shunt or when low $\dot{V}/\dot{Q}$ regions are minimal (e.g., in healthy lung or pulmonary embolus).[170]

Unlike the other indices based on partial pressures, the PaO_2/FiO_2 ratio does not use the PAO_2 and its associated assumptions. This index is more stable, particularly under conditions relevant to ARDS such as PaO_2 lower than 100 mm Hg in the setting of an FiO_2 greater than 0.5.[166,167] PaO_2/FiO_2 values are part of the diagnostic criteria for ARDS and have been correlated with outcomes in these

patients.[171] When repeated arterial blood sampling is not possible, the SpO_2/FiO_2 (also referred to as SF) ratio may be useful. SF ratio values have shown good correlation with PaO_2/FiO_2 values in both adults and children with respiratory failure who have SpO_2 in the range of 80% to 97%.[172,173]

Unlike PaO_2, $Paco_2$ can be maintained in the normal range in the presence of significant $\dot{V}/\dot{Q}$ mismatching. The reason is that the CO_2 content curve has no plateau. In this way, compensatory hyperventilation can be used to reduce elevations in $Paco_2$.[174] The dependence of $Paco_2$ on CO_2 elimination ($\dot{V}co_2$) and alveolar ventilation ($\dot{V}_A$) with k in the equation as a conversion factor equal to 0.863 is expressed by:

$$Paco_2 = k \times (\dot{V}co_2/\dot{V}_A) \quad [21]$$

In steady-state conditions (constant $\dot{V}co_2$), $Paco_2$ changes inversely with the alveolar ventilation. The traditional measure of ventilation inefficiency has been the fraction of dead space to tidal volume (V_D/V_T), calculated using the Bohr equation (see Equation 15) and the assumption that the arterial and alveolar partial pressures of CO_2 are equivalent ($Paco_2 = Paco_2$). The dead space fraction determined in this manner includes alveolar (i.e., nonperfused alveoli) and anatomic dead space, as well as regions of high $\dot{V}/\dot{Q}$ ratio. As with the discussion on shunt, the dead space fraction characterizes not only real anatomic dead space, but also areas of inefficient ventilation (see Fig. 51-17).

MEASUREMENT PRINCIPLES

PaO_2 is measured using a Clark electrode. The electrode consists of a cathode (electron source, platinum or gold) and an anode in an electrolyte bath, surrounded by a thin O_2-permeable membrane. The electrode is inserted into the sample, and O_2 diffuses through the membrane and is reduced by the cathode, thus generating a current. The current is proportional to the PO_2 in the sample.[175] The Pco_2 electrode measures the change in pH brought about by the equilibration of blood with a bicarbonate solution.[176]

A continuous blood gas monitor has been described using an optical PO_2 sensor; however, clinical investigations have shown inaccuracies of PaO_2 measurements under conditions of rapidly changing values. Clear clinical indications for this monitor have not been established.[177] Fluorescence quenching of O_2 technology has been shown to detect PaO_2 oscillations during mechanical ventilation in experimental studies and to bring information on cyclic derecruitment.[178,179]

Effect of Temperature

The solubility of CO_2 and O_2 in blood is affected by temperature. At lower temperatures, solubility is increased, leading to a reduction in partial pressure. Blood gas analyzers measure gas partial pressures at 37° C. As blood from a hypothermic patient is warmed to 37° C by the analyzer, CO_2 and O_2 come out of solution, leading to $Paco_2$ and PaO_2 higher than those present in the patient. Blood gas analyzers make use of algorithms to correct the reported values to the patient's actual temperature.[180] The temperature effects on blood gas analysis are most relevant during management of hypothermic patients such as during hypothermic cardiopulmonary bypass (HCPB) or deep hypothermic circulatory arrest (DHCA).

Two strategies have been developed for the management of arterial gas partial pressures under these conditions: alpha-stat and pH-stat. During alpha-stat management, blood gas measurements obtained after the analyzer warms the sample to 37° C are used for acid-base and gas exchange management. Potential benefits of alpha-stat management include the preservation of cerebral autoregulation and the maintenance of protein function.[181] During pH-stat management, measurements are corrected to the patient's temperature before they are used for acid-base and gas exchange management. Because patients are hypothermic, the PaO_2 and $Paco_2$ at the patient's temperature are lower and the pH higher than those measured in the analyzer at 37° C. CO_2 is usually added to the oxygenator to maintain the temperature-corrected $Paco_2$ and pH at normothermic values. The theoretic benefits of pH-stat management are increased cerebral vasodilation leading to more homogenous cerebral cooling.[182]

Studies have compared the two strategies with respect to outcomes, with varying results.[183-190] In general, clinical studies support the use of pH-stat management in pediatric cardiac surgical procedures during HCPB or DHCA.[185,189,191] In adult patients, the use of alpha-stat management is supported for HCPB.[192] For procedures involving DHCA in adults, use of pH-stat management has been suggested to increase the rate and uniformity of cooling and alpha-stat management during rewarming.[193]

LIMITATIONS AND SOURCES OF ERRORS

Proper handling of arterial blood gas samples is important to prevent errors. Two common sources of error are delays in sample analysis and the presence of air in the sampling syringe.[194] A delay in sample analysis by 20 minutes at room temperature or at 4° C can lead to a decline in PaO_2.[194] The decline is attributed to the metabolic activity of leukocytes and is not observed in samples placed on ice. The presence of an air bubble in the syringe can lead to a change in the measured PaO_2 toward the PO_2 of the bubble and a decline in $Paco_2$.[194]

MONITORING LUNG FLOWS, VOLUMES, AND PRESSURES

As an organ of gas exchange, the human respiratory system relies on both convective and diffusive gas transport processes for $\dot{V}o_2$ and elimination of CO_2. The transport of air to the alveoli and alveolar gas to the environment requires the creation of a pressure gradient, which will result in volume changes in the elastic components of the respiratory system, flow in the airways, velocity in moving tissues, and acceleration of air and tissues. The lung consists of a complex branching network of airway segments and viscoelastic tissues that, during the processes of breathing or ventilation, gives rise to tremendous variations in gas velocities and flow regimens. The movement of gas flow ($\dot{V}$) into and out of the lungs requires driving

pressures (P) to overcome the resistive (P_R), elastic (P_E), and at times inertial (P_I) forces offered by the airway tree, parenchymal tissues, and chest wall:

$$P = P_R + P_E + P_i \quad [22]$$

Equation 22 can be used to describe the mechanical behavior of the total respiratory system, the lungs alone, or the chest wall, depending on whether P refers to airway pressure relative to atmosphere, airway pressure relative to pleural pressure, or pleural pressure alone.[195-197]

DYNAMIC RESPIRATORY MECHANICS

As a first approximation to Equation 22, the mechanical behavior of the respiratory system during breathing or ventilation can often be described according to the simple equation of motion that encompasses its resistive (R), elastic (E), and inertial (I) properties[195,198]:

$$P = R\dot{V} + EV + I\ddot{V} + P_O \quad [23]$$

where V is volume, $\ddot{V}$ denotes volume acceleration, and P_O is the distending pressure at end expiration. The resistive properties of the respiratory system probably arise from viscous and turbulent losses associated with gas flowing through the airway tree and the deformation of parenchymal and chest wall tissues. Hence, airway resistance may reflect airway caliber.[199] Provided that variations in flow are small, resistive pressure losses are assumed to be linearly related to flow according to the first term of Equation 23. With more rapid flow rates, as with exercise or forced vital capacity maneuvers, resistive losses vary nonlinearly with flow, which may more accurately be described according to[200]:

$$P_R = K_1\dot{V} + K_2\dot{V}^2 \quad [24]$$

where K_1 and K_2 are empirically determined constants. Additional energy losses arise from the tension within the alveolar surface film,[201] friction within the pleural space, and various tissue components of the parenchyma and chest wall,[196] as well as cross-bridge cycling of contractile elements within the airway walls and lung tissues.[202,203] Such losses are collectively termed *tissue resistance*.[204,205] If these tissue resistive losses are assumed to be proportional to flow according to Equation 23, one will observe that they vary inversely with breathing frequency,[202,206] a phenomenon commonly associated with viscoelastic materials.[196] In adult patients, lung tissue resistance comprises approximately 60% of subglottal total lung resistance at typical breathing rates.[207] During volume-cycled ventilation with an end-inspiratory pause, resistance can quickly be estimated from the difference between the peak (P_{peak}) and plateau (P_{plat}) pressures (i.e., the resistive pressure loss P_R) divided by the inspiratory flow ($\dot{V}_I$) immediately before the end-inspiratory pause:

$$R = \frac{P_{peak} - P_{plat}}{\dot{V}I} = \frac{P_R}{\dot{V}I} \quad [25]$$

Thus, for a specified flow rate, alterations in P_R may reflect changes in airway caliber, as may occur during intraoperative asthma exacerbation (Fig. 51-18, *center panel*), or obstruction within the ETT or breathing circuit.

Elastic pressures arise from the recoil of the lungs and chest wall when their normal anatomic configurations are deformed, either by contraction of the diaphragm and intercostal muscles or by some external force (e.g., a ventilator).[208] Elastance is simply defined as the change in distending pressure (transrespiratory, transpulmonary, or intrapleural) for a given change in volume. Dynamic elastance refers to the change in elastic (i.e., nonresistive) distending pressure per unit volume during the process of breathing or ventilation. Elastance of the total respiratory system (E_{RS}) comprises both lung (E_L) and chest wall (E_{CW}) elastances:

$$E_{RS} = E_L + E_{CW} \quad [26]$$

In clinical settings, elastance is usually expressed as its reciprocal, compliance (i.e., change in volume per unit change in pressure). This leads to an alternate form of Equation 26, expressing the relationships of the compliant components of the total respiratory system (C_{RS}), lungs (C_L), and chest wall (C_{CW}):

$$\frac{1}{C_{RS}} = \frac{1}{C_L} + \frac{1}{C_{CW}} \quad [27]$$

Factors that reduce total respiratory or lung compliance include consolidation, pulmonary edema, pneumothorax, atelectasis, interstitial disease, pneumonectomy or surgical resection, lung overdistention, and mainstem intubation. Lung compliance generally increases in emphysema. Factors that reduce chest wall compliance are abdominal distention, abdominal compartment syndrome, chest wall edema, thoracic deformity, muscle tone, and extensive thoracic or abdominal scar (e.g., from burns); C_{CW} is reduced with muscle relaxation and flail chest.

Respiratory system elastance (E_{RS}) is most easily determined during periods of zero flow (when resistive pressures are zero) as the difference between P_{plat} and PEEP (i.e., the elastic pressure P_E) divided by the V_T:

$$E_{RS} = \frac{P_{plat} - PEEP}{V_T} = \frac{P_E}{V_T} \quad [28]$$

The corresponding C_{RS} is usually between 50 and 100 mL/cm H_2O in normal mechanically ventilated lungs. Alterations in P_E for a specified V_T may be observed during processes that alter lung or chest wall elastance, such as a pneumothorax during thoracotomy or abdominal insufflation during laparoscopic surgical procedures (see Fig. 51-18, *right panel*). In general, dynamic elastance is higher than static elastance as a result of viscoelasticity[198] and gas redistribution.[209]

Finally, inertial pressures are associated with acceleration of the gas column in the central airways, as well as the motion of the respiratory tissues.[210] Inertia is usually not a significant contributor to the work of breathing, except during sudden changes in air flow, as may occur during inspiratory step profiles or high-frequency ventilation (HFV).[211]

Equations 25 and 28 cannot be used to estimate resistive (R) and elastic (E) properties if an end-inspiratory pause is not present in the ventilator waveform. This is because one cannot easily separate the resistive and elastic pressures just by visual inspection. For example, during pressure-controlled ventilation (PCV), the airway opening is exposed to a constant inflation pressure during inspiration (Fig. 51-19). Airway flow and V_T during PCV are determined not by the

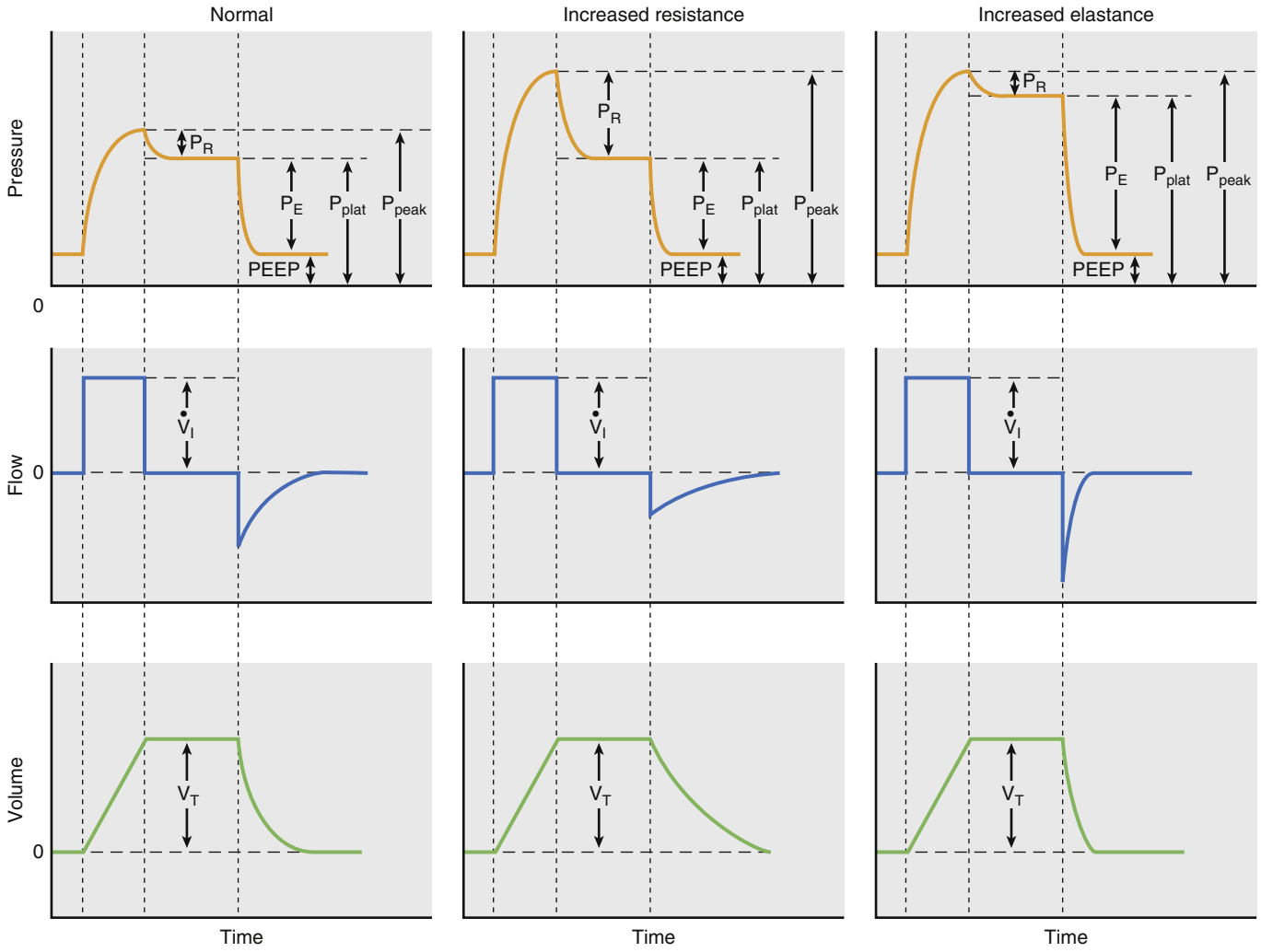


Figure 51-18. Airway pressure, flow, and volume waveforms during constant-flow volume-cycled ventilation with an end-inspiratory pause. The components of the peak inspiratory pressure (P_{peak}) and the plateau pressure (P_{plat}) are presented: resistive pressure (P_R), elastic pressure (P_E), and positive end-expiratory pressure (PEEP). The same peak flow ($\dot{V}_I$) and tidal volume (V_T) are delivered by the mechanical ventilator in each case. The *leftmost panels* represent waveforms in a healthy patient. A small P_R component is noted, with most of the peak pressure consisting of elastic pressure. Expiratory flow decreases to zero before the start of the next inspiration, this indicating an appropriate inspiratory-expiratory (I:E) ratio and the absence of slowly emptying lung regions. Volume, as the integral of flow, also returns to zero before the initiation of the next breath. The *middle panels* represent waveforms in a patient with an increase in airway resistance. A significant increase in the resistive component P_R, and consequently P_{peak}, is seen. The elastic component is unchanged, as reflected in identical P_{plat} as compared with the healthy condition. Because increased resistance slows the process of lung emptying, the expiratory phase of the flow and volume curves now takes longer to reach the zero. In several cases, zero is not reached, and a change in the I:E ratio is necessary to avoid volume trapping and auto-PEEP. The *rightmost panels* represent a subject with increased P_E, as may occur during laparoscopic insufflation or pneumothorax. The increase in P_{plat} is consistent with the increased elastance of the respiratory system and fast emptying of the lungs during exhalation.

ventilator, but rather by the gradient between airway and alveolar pressures. A more robust method of estimating respiratory R and E involves multiple linear regression of the coefficients in Equation 23 on sampled flow and pressure data.[212-214] Such numeric approaches are present in commercially available respiratory mechanics monitors, and they can be used on almost all ventilator waveforms. They are not restricted to volume- or time-cycled waveforms with an end-inspiratory pause. Moreover, one can separately estimate R and E during the inspiratory and expiratory phases, which may be different in some patients because of dynamic airway compression or derecruitment.[215,216]

Dynamic estimates of total respiratory R and E based on positive airway opening pressures are valid only during controlled modes of ventilation when the chest wall is relaxed. Although this is certainly the case during general anesthesia with neuromuscular blockade, the situation is more complicated during spontaneous breathing or assisted modes of ventilation. In such situations, the mechanics of the chest wall can be accounted for in estimates of R and E if transpulmonary pressure is estimated using esophageal manometry, as described later.

STATIC RESPIRATORY MECHANICS

As previously illustrated, elastance (or compliance) is most easily measured during periods of zero flow because

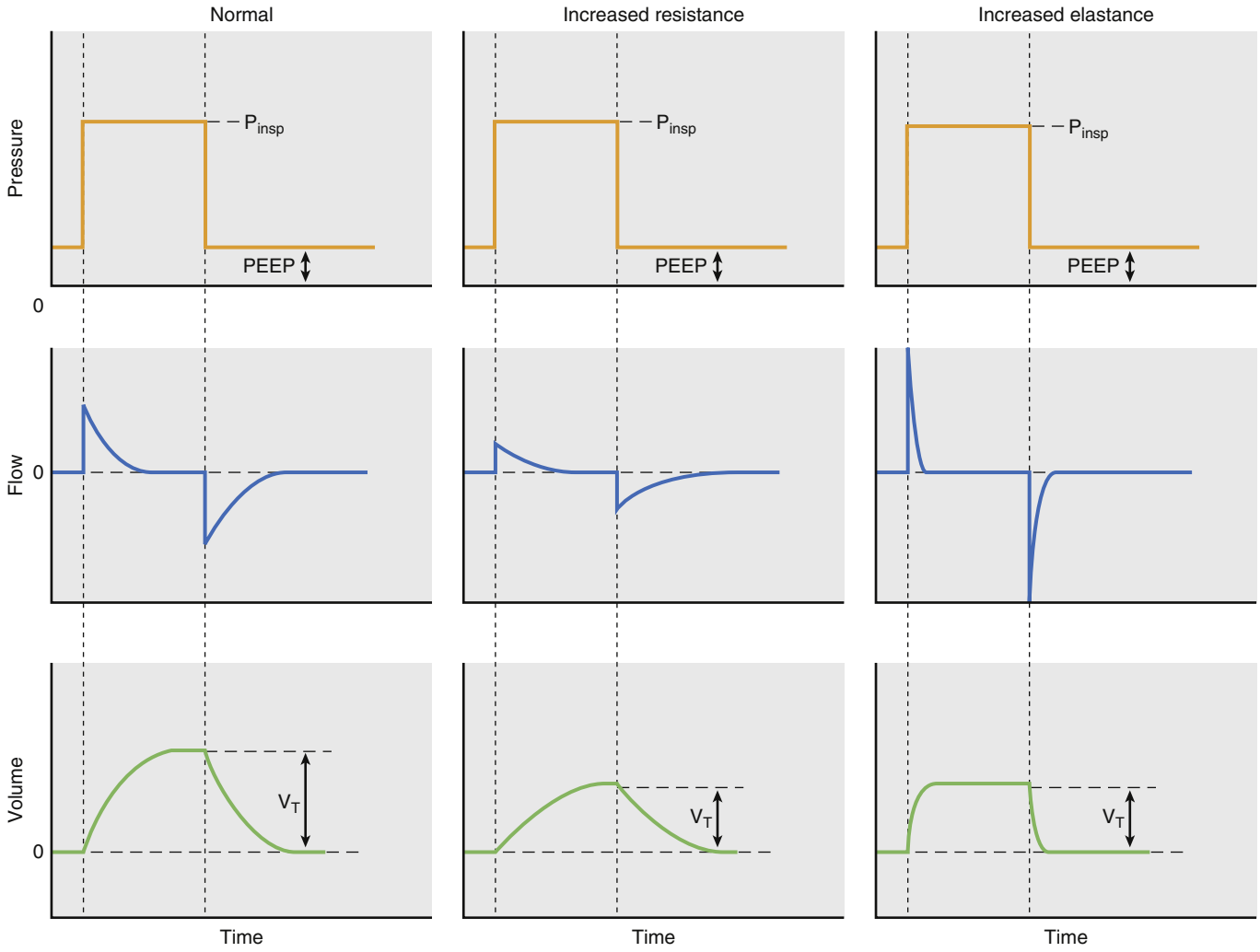


Figure 51-19. Airway pressure, flow, and volume waveforms during pressure-controlled ventilation (PCV) for the same patients depicted in Figure 51-18. In this ventilatory mode, the ventilator delivers a fixed pressure during the inspiratory phase, irrespective of the resistance and compliance. Airflow and tidal volume will consequently change with changes in those parameters. The *leftmost panels* represent waveforms in a patient with normal lungs. The *middle panels* represent waveforms in a patient with airway obstruction. Note the absence of a peak-plateau difference as compared with the volume-controlled mode, a lower tidal volume (V_T), and a prolonged time for airflow to reach zero during exhalation as compared with the normal patient. The *rightmost panels* represent a subject with increased elastance, as may occur during laparoscopic insufflation or pneumothorax. Note a reduction in V_T and a shorter time to reach zero flow, consistent with a more rigid respiratory system. *PEEP,* Positive end-expiratory pressure; P_{insp}, inspiratory pressure.

during these conditions the measured distending pressure is exclusively associated with elastic processes. However, a more comprehensive characterization of elastance can be obtained by plotting cumulative inspired or expired lung volume against the distending pressure across the lungs or total respiratory system. This quasistatic pressure-volume (PV) curve can be constructed during very slow inflations or deflations[217] (when resistive pressures are negligible), or during periodic flow occlusions.[218] For example, the expiratory limb of the PV curve can be constructed by inflating the lungs to a specified volume (usually total lung capacity) and then allowing passive deflation with flow interruptions lasting 1 to 2 seconds.

The PV curve is typically nonlinear (Fig. 51-20); that is, compliance, defined as the local slope dP/dV of the PV curve, varies with lung volume. Empirically, PV curves are usually described using single exponential[219] or sigmoidal[220] functions. When they are described using sigmoidal functions, two points are usually demarcated on such curves, incorrectly termed the upper inflection point (UIP) and lower inflection point (LIP).* The UIP is thought to represent the point at which lung overdistention occurs, as during parenchymal strain-stiffening.[196] The LIP is thought to reflect the process of maximum alveolar recruitment. During protective lung ventilation, one seeks to ventilate a patient in the most linear region of the PV curve, with enough PEEP to avoid the LIP where cyclic recruitment and derecruitment occurs, but with lower V_T to avoid the UIP and overdistention.[218] In addition, PV curves exhibit hysteresis, a phenomenon in which the

*The formal mathematical definition of an inflection point is a point on a *curve* at which its concavity (i.e., its second derivative) changes *sign* from positive to negative or vice versa.

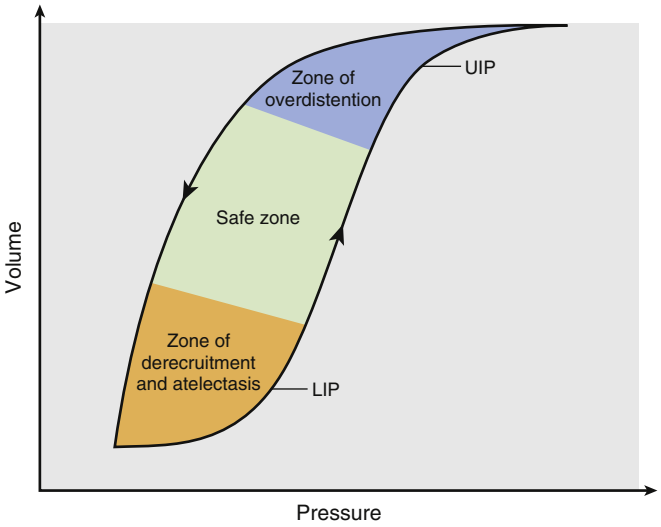


Figure 51-20. Schematic of a pressure-volume curve for the lungs or total respiratory system that demonstrates hysteresis between inspiratory and expiratory limbs. The upper inflection point (UIP) and lower inflection point (LIP) are demarcated on the inspiratory limb. During mechanical ventilation, lung regions should be in the safe zone for optimal lung protection. *(Redrawn from Froese AB: High-frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time!* Crit Care Med *25:906-908, 1997.)*

lung volume at a specified pressure depends on the direction from which the distending pressure is approached (i.e., either inspiration or expiration). The reasons that the PV curve of the lungs or total respiratory system exhibits hysteresis are numerous and complex, and include the biophysical properties of surfactant,[221] time-dependent recruitment or derecruitment,[222] as well as contact friction among various connective tissue elements.[223]

Several problems arise with managing ventilation based on PV curves. First, PV curves are constructed only during periods of zero flow or near zero flow, and they do not reflect the mechanics of the lungs or total respiratory system during the dynamic processes of breathing or mechanical ventilation. In fact, the dynamic PV relationships for the same patient may be very different. Second, the UIP and LIP are not always visually apparent. Finally, a PV curve for the lungs or total respiratory system represents the averaged static behavior of a population of many lung units, with each operating on different portions of their own individual PV curves.

WORK OF BREATHING

The work of breathing (W) represents the energy required to inflate or deflate the lungs, or chest wall, or both, by a specified volume. In its simplest form, it can be represented as the product of the applied distending pressure and resulting volume change:

$$W = PV \quad [29]$$

However when pressure and volume vary as functions of time (as during the course of a spontaneous or controlled breath), work may be expressed as the cumulative product[224]:

$$W = \int PdV \quad [30]$$

or equivalently as the integral of the pressure-flow product with respect to time[225]:

$$W = \int_0^T P(t)\dot{V}(t)dt \quad [31]$$

where T is the duration over which W is determined. For example, if T corresponds to the duration of inspiratory period and P the transpulmonary pressure, then W corresponds to the work required to overcome both the resistive and elastic forces opposing the entry of air into the lungs (Fig. 51-21). If T corresponds to the duration of an entire breath, the energy initially stored in the elastic recoil of the lung tissues will be recovered during a passive exhalation. In this case, the area of resulting PV loop represents the work performed (i.e., energy lost) overcoming purely resistive losses in the airways and tissues. In general, W is assessed during inspiration only because the respiratory musculature (or a ventilator) must overcome both elastic and resistive pressures to bring air into the lungs. For a given V_T, W varies as a function of respiratory rate and, in most cases, achieves a minimum at a specified frequency. This frequency is termed the *energetically optimum breathing frequency,*[225] because this is the rate at which energy expenditure is minimized.

MONITORING OF RESPIRATORY PRESSURES

Fundamental to any quantitative assessment of respiratory mechanics is the measurement of pressure. Such pressures include those measured in the inspiratory or expiratory limb of the anesthesia machine, at the proximal end of an ETT, or within the trachea or esophagus. Pressure allows for the inference of the forces associated with the movement of gases through the airway tree, as well as the distention of the parenchymal tissues and chest wall, according to the elements described in Equation 22. The most accessible and familiar pressure to the anesthesiologist or intensivist is the airway pressure during controlled mechanical ventilation. Ideally, this should be the pressure measured in the trachea or at the airway opening, exclusive of any distortions from airway devices or breathing circuits. However, for practical reasons, this "airway" pressure is not the actual pressure at the airway opening or within the trachea, but it is the pressure transduced at the anesthesia machine or ventilator and reflects the resistive and compliant properties of the breathing circuit and facemask or ETT, as well as the mechanical properties of the respiratory system. Although many ventilators now use computer algorithms to provide some compensation for flow and pressure losses in the breathing circuit,[226] such approaches often rely on idealized, linear models that do not truly reflect the complex processes of turbulent air flow, polytropic gas compression, or viscoelastic tubing walls.[227,228] Therefore, one must use caution when making physiologic inferences based on airway pressures and volumes reported by a ventilator.

Often airway pressure is improperly used as a surrogate for lung distention. *Transrespiratory pressure* refers to the pressure decrease across the lungs and chest wall, which during positive-pressure ventilation is usually determined by the difference between airway pressure and atmospheric pressure. Several processes that may contribute to increased transrespiratory pressure do not correspond to

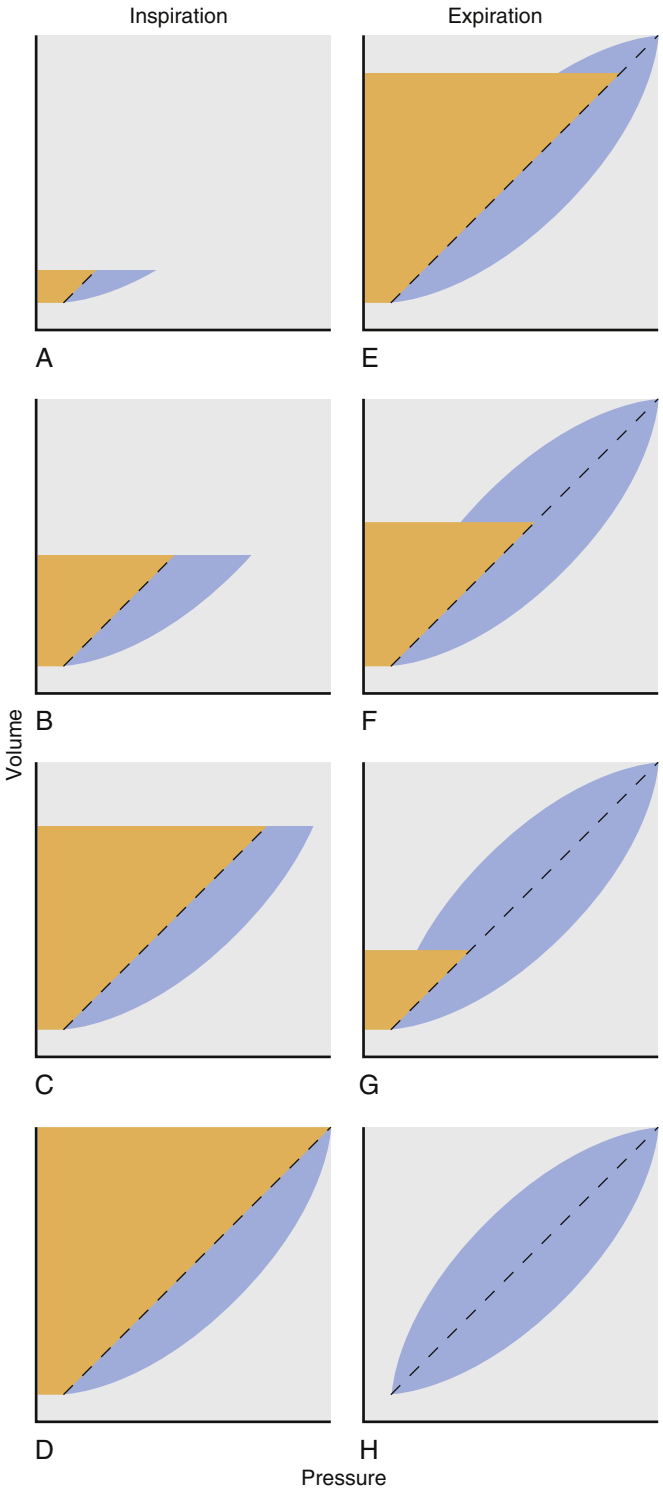


Figure 51-21. Volume plotted against transpulmonary or (transrespiratory) pressure during the course of a single breath. Plots are shown during inspiration (**A**-**D**) and expiration (**E**-**H**). The *yellow area* denotes the work of breathing related to tissue elasticity, whereas the *blue area* denotes the work of breathing related to airway and tissue resistance. Energy stored in elastic recoil at the end of inspiration is entirely recovered during expiration. However, resistive energy is always lost during both inspiration and expiration.

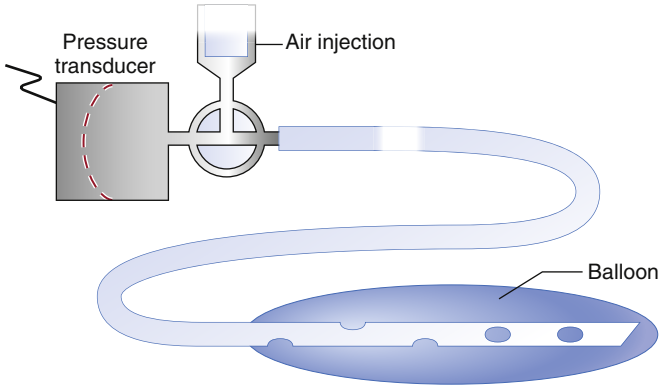


Figure 51-22. Example of an esophageal balloon catheter. The proximal end of the catheter is connected to a pressure transducer, and air is injected into the balloon through a three-way stopcock. *(Modified from Bates JHT:* Lung mechanics: an inverse modeling approach, *Cambridge, 2009, Cambridge University Press, p 220.)*

excessive lung inflation. For example, obesity, abdominal insufflation, or steep Trendelenburg position all may contribute to high airway opening pressures, but they do not necessarily indicate parenchymal overdistention (see also Chapters 41 and 71).

By contrast, *transpulmonary pressure* refers to the distending pressure across the lungs alone. Its determination requires not only measurement of airway opening pressure, but also estimates of the pressure within the pleural space. This determination can be obtained relatively noninvasively using an esophageal balloon catheter, because the pressure measured within the esophagus is relatively close to intrapleural pressure.[229] Such catheters are typically 100 cm long, with side holes in the distal tip covered by a thin-walled balloon (Fig. 51-22). The catheter can be placed through the mouth or nares and positioned in the middle-to-distal third of the esophagus. The catheter is connected to a transducer by a three-way stopcock, and a small amount of air is injected into the balloon such that its walls remain flaccid and do not contribute an additional recoil pressure to the measurement. Because the local values of pleural pressure vary depending on gravity, the balloon should be several centimeters in length to provide an average estimate of the pressure field surrounding the lungs. Estimating pleural pressure based on esophageal manometry has several limitations, including mediastinal compression of the balloon in supine patients, catheter migration, and cardiac artifact on the tracing.[230,231] Nonetheless, its use in critically ill patients may be valuable in the adjustment of appropriate levels of PEEP.[232] Peak and plateau pressures, usual in clinical practice, are obtained from the transrespiratory pressure. Accordingly, they do not characterize the pressures acting exclusively on the lungs, but rather on the whole respiratory system. Plateau pressures should range from 26 to 30 cm H_2O to minimize alveolar overdistention,[233] and they should be applied carefully.

Auto-PEEP or *intrinsic-PEEP* is the positive pressure present within the alveoli at end-exhalation and is typically observed in ventilated patients with COPD, who demonstrate dynamic airway compression and expiratory flow limitation, as well as a significant portion of patients with

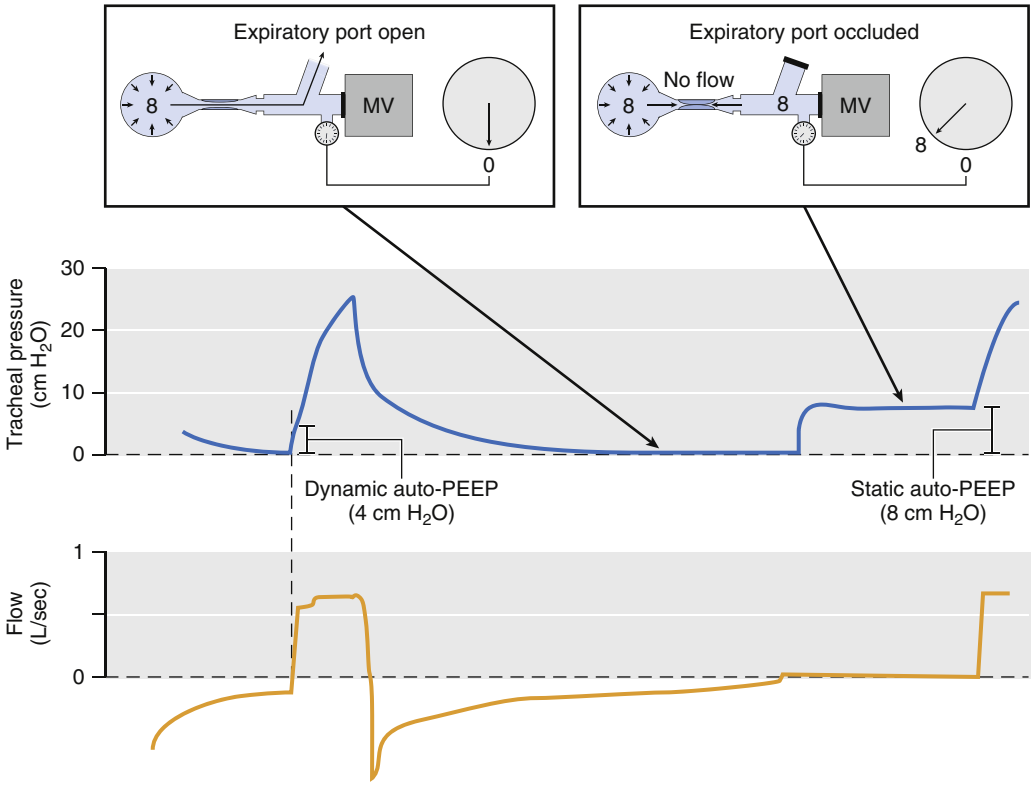


Figure 51-23. Concept of intrinsic positive end-expiratory pressure (auto-PEEP). Shown are tracheal pressure and flow waveforms during controlled mechanical ventilation. Dynamic auto-PEEP can be estimated at the beginning of inspiration as the tracheal pressure when the flow trace equals zero. Static auto-PEEP can be estimated as the tracheal pressure following prolonged expiratory occlusion. *MV,* Mechanical ventilator. *(Modified from Blanch L, Bernabé F, Lucangelo U: Measurement of air trapping, intrinsic positive end-expiratory pressure, and dynamic hyperinflation in mechanically ventilated patients,* Respir Care *50:110-123, 2005, and Moon RE, Camporesi EM: Respiratory monitoring. In Miller RD, Fleisher LA, Johns RA, editors:* Miller's anesthesia, *ed 6, New York, 2005, Churchill Livingstone, pp 1255, 1295.)*

ARDS, sepsis, and respiratory muscle weakness.[234] Auto-PEEP can promote significant respiratory and hemodynamic compromise. It is usually caused by a combination of increased airway resistance and reduced lung elastic recoil (i.e., an increase in the expiratory time constant of the respiratory system). Other factors are a decrease in expiratory time, an increase in V_T, an increase in external expiratory resistance, and persistent inspiratory muscle activity during exhalation. The amount of auto-PEEP can be estimated in mechanically ventilated patients by occluding the airway at end-exhalation and observing a rise in airway pressure during the occlusion maneuver until a plateau is visible (<4 seconds) (Fig. 51-23). Auto-PEEP is then defined as the difference between end-occlusion and preocclusion airway pressures. Other methods can be used to assess auto-PEEP under dynamic conditions, as well as in spontaneously breathing patients with use of an esophageal balloon.[234,235]

Any measurement of pressure requires pressure transducers. Most pressure transducers are differential sensors with two input channels, and they produce an electrical output that is proportional to the pressure difference between these channels (Fig. 51-24, *A*). Such transducers must have a high *common-mode rejection ratio* (CMRR), defined as the tendency of the transducer to produce zero output if both its inputs are exposed to identical pressures. Many pressure waveforms are transduced relative to atmosphere with one of the two inputs left opened

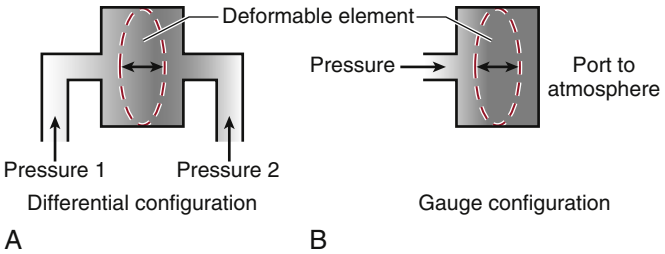


Figure 51-24. Pressure transducers arranged in differential (**A**) or gauge (**B**) configurations. *(Modified from Bates JHT:* Lung mechanics: an inverse modeling approach, *Cambridge, 2009, Cambridge University Press, p 220.)*

to ambient air (Fig. 51-24, *B*), otherwise referred to as gauge configuration. In clinical settings, pressure is most commonly measured using relatively inexpensive, piezoresistive transducers.[198] These devices rely on a pressure-sensing diaphragm whose electrical resistance changes when it is deformed in response to a differential pressure. This change in electrical resistance can be sensed with a standard Wheatstone bridge circuit, which produces an output-voltage signal appropriate for amplification and filtering. In general, piezoresistive transducers have adequate frequency responses sufficient for most respiratory applications.[236,237] However, this frequency response can be easily degraded if the transducer is connected to the pressure-sensing location with long, compliant tubing.[238]

MONITORING OF RESPIRATORY FLOWS

Ideally, any measurement of flow should indicate the exact rate at which gas is entering and leaving the patient's lungs. This can be most easily accomplished by placing the flow-measuring device as close to the patient as possible, such as between the circuit Y-connector and the proximal end of the ETT or LMA. However, for practical reasons, most ventilators and anesthesia machines measure flow close to the machine console. This flow can be considerably different from that close to the patient because of the effects of gas compression, wall distention of the breathing circuit, and changes in gas humidity.

An important clinical use of flow monitoring is the detection of nonzero end-expiratory flows. This indicates that a gradient of pressure exists between alveolar regions and the upper airway with incomplete lung emptying at end-expiration, characteristic of auto-PEEP. As a consequence, end-expiratory lung volumes would be larger than those in the absence of auto-PEEP, with risk of dynamic lung hyperinflation and reduction of venous return. Increase in expiratory time and reduction of V_T or respiratory rate should be considered to eliminate the issue.

During ventilation, airway flow can often be inferred according to time-dependent changes in delivered or inspired V_T or from the displacement waveform of a piston or cylinder arrangement or bellows.[239-241] Preferably, flow is measured using transducers designed specifically for this task. The most common method involves the measurement of a differential pressure decrease (ΔP) across a fluid resistive element. Ideally, this ΔP is linearly related to the corresponding flow through the device. Such a principle forms the basis for one of the oldest and most widely used flowmeters, the pneumotachograph. Although they provide accurate measurement of flow, pneumotachographs are very sensitive to changes in temperature, humidity, and gas composition,[242] and they require frequent calibration using various electronic or software-based techniques to ensure accurate measurements.[243,244] This sensitivity, combined with difficulties in cleaning and sterilization, limits the routine use of these instruments in clinical environments. Orifice flowmeters also have the advantage of having relatively large internal diameters that limit the formation of condensation and minimize obstruction with secretions. Given that these devices can be manufactured using inexpensive plastic injection molding techniques, many orifice flowmeters are designed to be disposable, thus making their use increasingly popular for respiratory applications in clinical environments.[245]

Most anesthesia machines use hot wire anemometers for flow measurement,[246] which rely on temperature-dependent changes in the electrical resistance of a current carrying wire. When gas flows pass the wire, the corresponding temperature drop changes the conductivity of the filament, which can be sensed with appropriate electronic circuits.[247] Because a single wire filament cannot sense the direction of flow, two different anemometers can be used in the ventilator circuit: one for the inspiratory limb, and the other for the expiratory limb. Alternatively, two wires in series must be used for sensing bidirectional flow through a single conduit,[248] with the flow direction determined according to which wire is cooled first. Generally, hot wire anemometers have a better dynamic response compared with pneumotachographs or orifice flowmeters,[249] and therefore they are ideal for flow measurement during HFV.[250]

MONITORING OF RESPIRATORY VOLUME

Similar to flow measurement, the ideal measurement of volume should be an accurate accounting of the gas quantity moving into and out of the patient. However, delivered or exhaled V_T measurement is subjected to the same limitations of flow measurement because most anesthesia machines and ventilators determine volume by electrically or numerically integrating the corresponding flow signal.[198] Care must be taken to ensure that any drifts or offsets from the flow transducer are minimized, given that their integration will result in errors in estimated volume. This may be accomplished by appropriately zeroing the transducer periodically, such as at the end of a breath. Although electronic or digital high-pass filters may be used to remove drifts and offsets in real-time, these tend to have long transient responses.

Finally, besides the pathophysiologic and monitoring applications described in this section, monitoring of pressures, volumes, and flows has been applied to monitoring, training, and education for neonatal resuscitation[251] (see also Chapter 95).

PLETHYSMOGRAPHIC MONITORING

Respiratory inductance plethysmography (RIP) is a noninvasive respiratory monitoring technique that quantifies changes in the cross-sectional area of the chest wall and the abdominal compartments. The method is used to assess V_T, respiratory rate, adequacy of high-frequency oscillatory ventilation (HFOV), lung volume changes during tracheobronchial suctioning, and thoracoabdominal synchrony.[252] RIP relies on the principle that a current applied through a loop of wire generates a magnetic field normal to the orientation of the loop (Faraday's law) and that a change in the area enclosed by the loop creates an opposing current within the loop directly proportional to the change in the area (Lenz's law). Two elastic bands containing a conductor are used: one typically placed around the patient's chest, 3 cm above the xiphoid process; and the other around the abdomen. Each of these bands produces an independent signal representative of the thoracic and abdominal cross-sectional area, and the sum of these two signals calibrated against a known gas volume yields lung volume change.

RIP has been used in several pediatric applications to monitor V_T and respiratory rate, building on the advantage that a facemask, LMA, or ETT is not required for measurements.[253] This technique could also guide lung-protective ventilation strategies by facilitating the construction of PV curves for individual patients. These can be used to optimize lung recruitment, maintain an open lung, and limit overdistention (see the section on static respiratory mechanics).

Intraoperatively, RIP may find applications in areas for which accurate monitoring of V_T are required but not possible with the usual anesthesia machine monitors. This could occur with a shared airway (e.g., laryngotracheal surgery,[254] flexible and rigid bronchoscopy) or a patient whose trachea is not intubated (e.g., monitored anesthesia care and noninvasive pressure support ventilation).

Unfortunately, RIP cannot be used during thoracic and abdominal surgical procedures, given the need for the measurement bands. Moreover, the calibration characteristics of the device are affected by changes in the pattern of breathing.

RESPIRATORY RATE MONITORING: APNEA MONITORING

Apnea and bradypnea are life-threatening events frequently observed in the intraoperative and postoperative periods of anesthesia. Prematurity, morbid obesity, age, obstructive sleep apnea, and central nervous system depressant medications have been associated with the risk of apnea or bradypnea (see also Chapters 71 and 80).[255,256] Accordingly, many different approaches have been developed for detecting those events.[257,258] Two main types of apnea are observed: central and obstructive. Central apnea is defined as apnea resulting from a failure of the central nervous system to drive respiration. Obstructive apnea is that resulting from upper airway obstruction. Current monitors assess at least one of three processes occurring during breathing to detect apnea[258]: chest wall expansion, gas flow, and gas exchange.

Chest wall expansion is usually measured as follows:

1. Changes in thoracic electrical impedance (impedance pneumography) of the chest wall. The method is based on the changes in electrical conductivity of the chest to an electrical current as air moves in and out of the lungs during breathing and blood volume changes in the same period. This is because air is a poor electrical conductor and blood is a good electrical conductor. A low electric current at high frequency is applied in two chest electrodes, corresponding changes in voltage of the chest are measured, and the impedance continuously calculated from these. The technique is implemented in several commercial systems using routine electrocardiographic leads and is also used in home monitoring of neonatal apnea.
2. Inductive plethysmography. This is described in the section "Monitoring Lung Flows, Volumes, and Pressures."
3. Abdominal and chest fiberoptic and resistive strain gauges (pressure pad placed beside the infant's rib cage, pneumatic abdominal sensors) are used.
4. Electromyographic signal of respiratory muscles is not frequently used because of the low signal-to-noise ratio.

An important drawback of techniques based on chest expansion is their inaccuracy in the presence of movement. Thus, obstructive apnea may be falsely assessed as normal respirations.[259]

Gas flow methods are based on measurements of different variables directly related to the presence of air flow in the airway:

1. Pressure gradients along the breathing circuit. This approach uses the Poiseuille principle ($\Delta P = k \cdot V$) and differential pressure transducers to detect flow.
2. Temperature of the breathed air in the nose or mouth is used.
3. Rapid response hygrometer is based on assessment of humidity in the exhaled air.

Techniques based on gas exchange focus essentially on exhaled CO_2 as routinely used in intubated patients in the OR. In nonintubated patients, use of specifically designed cannulas combining Do_2 and breathed gas sampling facilitate the monitoring of exhaled CO_2. The usual technique uses off-line or in-line infrared sensors. Respiratory rate measurements using this technique were more accurate than those obtained with thoracic impedance tomography in patients in postanesthesia care units even with supplemental O_2 at high flows.[260] Accurate end-tidal CO_2 measurements through a nasal cannula may be difficult in mouth breathers, including obese patients and those with obstructive sleep apnea. In such cases, a nasal cannula with an oral guide may improve measurement accuracy.[261]

Pulse oximetry cannot be used as the primary monitor of apnea or bradypnea because O_2 desaturation occurs only late in a well-oxygenated apneic patient (see also Chapter 44). However, pulse oximetry adds an additional level of safety combined with primary monitors of ventilation. For example, in a study using pulse oximetry and noninvasive capnography for continuous monitoring of 178 patients receiving patient-controlled analgesia, respiratory depression measured by O_2 desaturation occurred in 12% of the patients, in line with previous studies.[255] In contrast to previous estimates, episodes of bradypnea (respiratory rate <10 breaths/minute) were present in 41% of patients, far more frequently than the previously reported 1% to 2%.[262-264]

Respiratory rate monitoring is critical for infant apnea monitoring (see also Chapter 95). Combinations of transthoracic impedance and pulse oximetry may maximize the detection of true episodes of apnea in home monitors for neonatal apnea.[265] This is because pulse oximetry provides an additional level of monitoring in cases of poor performance of transthoracic impedance secondary to motion artifacts. The value of combining monitors of ventilation such as capnography with pulse oximetry to maximize detection of alveolar hypoventilation has been confirmed.[266] Capnography allowed for early detection of arterial O_2 desaturation in cases of alveolar hypoventilation in the presence of supplemental O_2.

False-positive and false-negative alarms occur during apnea monitoring. The most dangerous conditions occur when artifacts are detected as breathing, and alarms are not activated. Such artifacts include vibrations, cardiac motion, patient movement, and electromagnetic interference from other instrumentation. Impedance pneumographs are subject to cardiovascular artifacts, whereas pressure pads are subject to patient motion artifacts. A more common (yet less dangerous)

problem is when an alarm sounds in a patient without apnea. Frequent causes include inadequate sensitivity settings, malfunctioning electrodes, and movement of the patient. Motion transducers based on sensing of acceleration were used in neonates undergoing HFOV, and results showed that monitoring of regional tidal displacement may enable early recognition of deteriorating ventilation during HFOV that eventually leads to hypoxemia.[267]This study found that approximately half of the cases of hypoxemia had causes other than slowly deteriorating ventilation.[267]

Current recommendations of the Anesthesia Patient Safety Foundation for Essential Monitoring Strategies to Detect Clinically Significant Drug-Induced Respiratory Depression in the Postoperative Period [http://www.apsf.org/initiatives.php] state that continuous electronic monitoring of oxygenation and ventilation should be available and considered for all patients, not only those considered at risk for postoperative respiratory insufficiency. Clearly, respiratory depression can occur in patients without risk factors. These recommendations stress that maintaining status quo while awaiting newer technology is not acceptable, and intermittent "spot checks" of oxygenation (pulse oximetry) and ventilation (nursing assessment) are not adequate for reliably recognizing clinically significant evolving drug-induced respiratory depression. However, continuous electronic monitoring should not replace traditional intermittent nursing assessment and vigilance. Capnography or other monitoring modalities that measure ventilation and airflow are indicated when supplemental O_2 is needed to maintain acceptable O_2 saturations. The recommendations also call attention to threshold-based alarm limits on individual physiologic variables, which may result in failure to recognize early signs of progressive hypoventilation by either being insufficiently or too sensitive (excess false alarms).

IMAGING FOR RESPIRATORY MONITORING

Imaging is a monitoring technique that provides tremendous insight into pulmonary structure, function, and inflammation in both health and disease.[268-270] However, exposure to radiation and bulky devices have prevented its use at the bedside. Technologic advances have led to the introduction of newer modalities with more compact equipment for clinical use. This may herald an important shift in respiratory monitoring toward increased use of bedside imaging. Such improvements come with the advantages of less radiation exposure, noninvasiveness, and more detailed physiologic information.

CHEST RADIOGRAPHY

Chest radiography has been the traditional imaging method to assess intrathoracic conditions in the OR, postoperative anesthesia care unit, and ICUs. Accordingly, anesthesia providers should be familiar with basic radiologic findings representative of important pulmonary conditions such as interstitial infiltrates, hyperinflation, pneumothorax, pleural effusion, and consolidation. The image during chest radiography, as well as computed tomography (CT), is based on the physical principle that x-rays reaching a detector (e.g., film) depend on tissue absorption, which varies linearly with tissue density. However, radiation exposure restricts frequency of use. Furthermore, technical difficulties limit image quality. These difficulties include reduced resolution caused by movement of the patient during image acquisition and image distortion related to proximity of the x-ray beam source to the film and posterior position of the film cassette.

ULTRASONOGRAPHY

Lung ultrasonography is an emerging technique in anesthesia and critical care medicine in adults and children.[271,272] Critical and systematic approaches have proved that important clinical information can be obtained with lung ultrasonography. This adds to the advantages of practicality, low cost, and absence of radiation or other significant biologic side effects. Lung ultrasonography has been applied successfully in the assessment of pneumothorax, interstitial syndrome (i.e., cardiogenic and permeability pulmonary edema), lung consolidation, and pleural effusion. Currently available multipurpose ultrasonography probes can be used for specific portions of the pulmonary examination. For instance, the high-frequency linear array probe allows for detailed examination of the pleura and superficial changes, such as pneumothorax. This probe's limitations include its size, which impedes access to larger areas of lung tissue because of the interference of the ribs, and high frequency, which limits assessment of deeper structures. To optimize visualization of the lung, probes should have an emission frequency of 5 to 7 MHz and be small with a tip shaped so that an acoustic window on the lung parenchyma can be obtained on intercostal spaces. The 5-MHz microconvex probe is frequently favored.[271,272]

When examining the patient, a methodical approach should be used to ensure comprehensive assessment of lung structure and function. In the supine patient, each hemithorax should be assessed in at least six zones: two anterior (separated by the third intercostal space), two lateral, and two posterior zones.[273,274] Because of the significant acoustic impedance differences among air, tissue, and bone (ribs), thoracic ultrasound is based primarily on characteristic artifacts and not only on the visualization of anatomic structures.[275] The ribs are seen as hyperechoic lines producing significant ultrasonography shadow (Fig. 51-25, *A*). Approximately, 0.5 to 1.0 cm deeper and between the ribs, the pleural line is found. This is typically a bright, slightly curved line. These are major structures to be identified because many disorders of relevance to the anesthesiologist affect their observed pattern. In the normal lung, lung sliding represents the movement of the visceral on the parietal pleura during respiration and is another key sonographic finding to be appreciated. The magnitude of the movement is larger in regions closer to the diaphragm than in those near the lung apex.

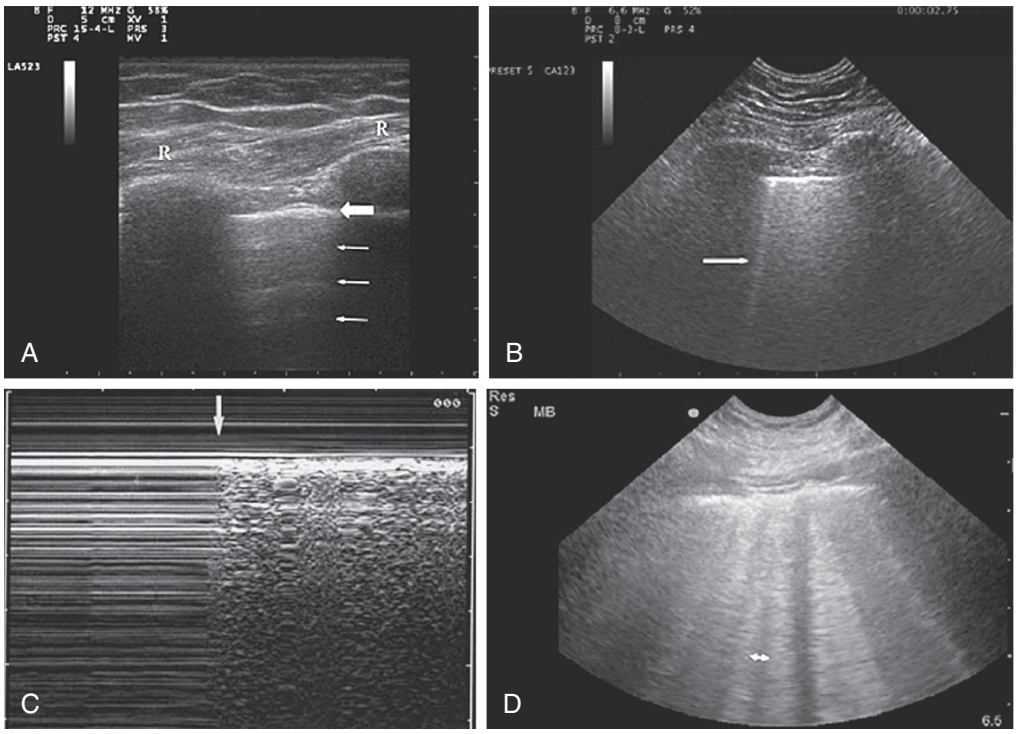


Figure 51-25. A, Typical thoracic view depicting adjacent ribs (R) producing acoustic shadowing. The white echogenic pleural line (*block arrow*) is approximately 0.5 cm below the ribs. A-line artifacts (*line arrows*) are seen at equidistant spaces below the pleural line. **B,** B-line, or comet-tail, artifact is the hyperechoic artifact extending from the pleural line to the edge of the screen and erasing the A line. A solitary B line is a usual finding in normal lungs. **C,** M-mode lung ultrasound image illustrative of the "lung point" for diagnosis of pneumothorax. The sudden inspiratory transition from a parallel line pattern indicative of absence of lung motion (pneumothorax) to a granular pattern indicative of lung tissue can be observed (*arrow*). **D,** Interstitial syndrome case showing B lines 7 mm or less apart (*arrow*). The pleural line and ribs are also appreciated. *(From Bouhemad B, Zhang M, Lu Q, Rouby JJ: Clinical review: bedside lung ultrasound in critical care practice,* Crit Care *11:205, 2007, and Turner JP, Dankoff J: Thoracic ultrasound,* Emerg Med Clin North Am *30:451, 473, ix, 2012.)*

Below the pleura, horizontal reverberation artifacts at regular distances are referred to as A lines (see Fig. 51-25, *A*). Another artifact is the B line, a discrete laser-like vertical hyperechoic reverberation artifact that arises from the pleural line (previously described as ''comet tails''), extends to the bottom of the screen without fading, moves synchronously with lung sliding, and erases A lines (Fig. 51-25, *B*). The physical and anatomic basis of the B lines is not established.[272] Solitary B lines are normal findings in the normal lung, and increased numbers are observed in disease.

Based on the recognition of such artifacts, pathologic conditions are identified.[271,272,276] Most acute disorders involve the lung surface, and this explains the utility of thoracic ultrasound in visualizing them. Ultrasonography findings for pneumothorax are the absence of lung sliding, B lines, and lung pulse, and the presence of lung points. The M-mode ultrasound scan shows parallel lines indicative of no moving structure underlying the probe. The ultrasonography finding designated as lung point is found in the presence of pneumothorax and represents imaging of the cyclic transition during breathing from the absence of any sliding or moving B lines at a physical location (i.e., air with no lung parenchyma) to the visualization of lung sliding, B lines, or altered A lines indicative of lung tissue (Fig. 51-25, *C*).[272,277] Bedside ultrasound scans can detect pneumothorax with sensitivity similar to that of a CT scan.[271,272]

An interstitial syndrome is characterized by the presence of multiple B lines. A positive region is defined by three or more B lines in a longitudinal plane between two ribs (Fig. 51-25, *D*). Lung consolidation is characterized sonographically by a subpleural echo-poor region or one with tissue-like echo texture. Lung consolidations may be caused by infection, pulmonary embolism, lung cancer and metastasis, compression atelectasis, obstructive atelectasis, and lung contusion. Additional sonographic signs that may help to determine the cause of lung consolidation include the quality of the deep margins of the consolidation, the presence of comet-tail reverberation artifacts at the far-field margin, the presence of air or fluid bronchograms, and the vascular pattern within the consolidation. Pleural effusions are characterized by a usually anechoic space between the parietal and visceral pleurae and by respiratory movement of the lung within the effusion (''sinusoid sign''). The presence of echogenic material within the effusion suggests an exudate or hemorrhage, although some exudates are anechoic. Most transudates are anechoic.

Advances in clinical research and experience in lung ultrasonography allowed for the proposal of an algorithm to assess severe dyspnea in the acute setting (Fig. 51-26). The BLUE protocol is a stepwise ultrasonographic approach to the patient with acute respiratory failure that aims at expeditious diagnosis with 90.5% accuracy.[276,278]

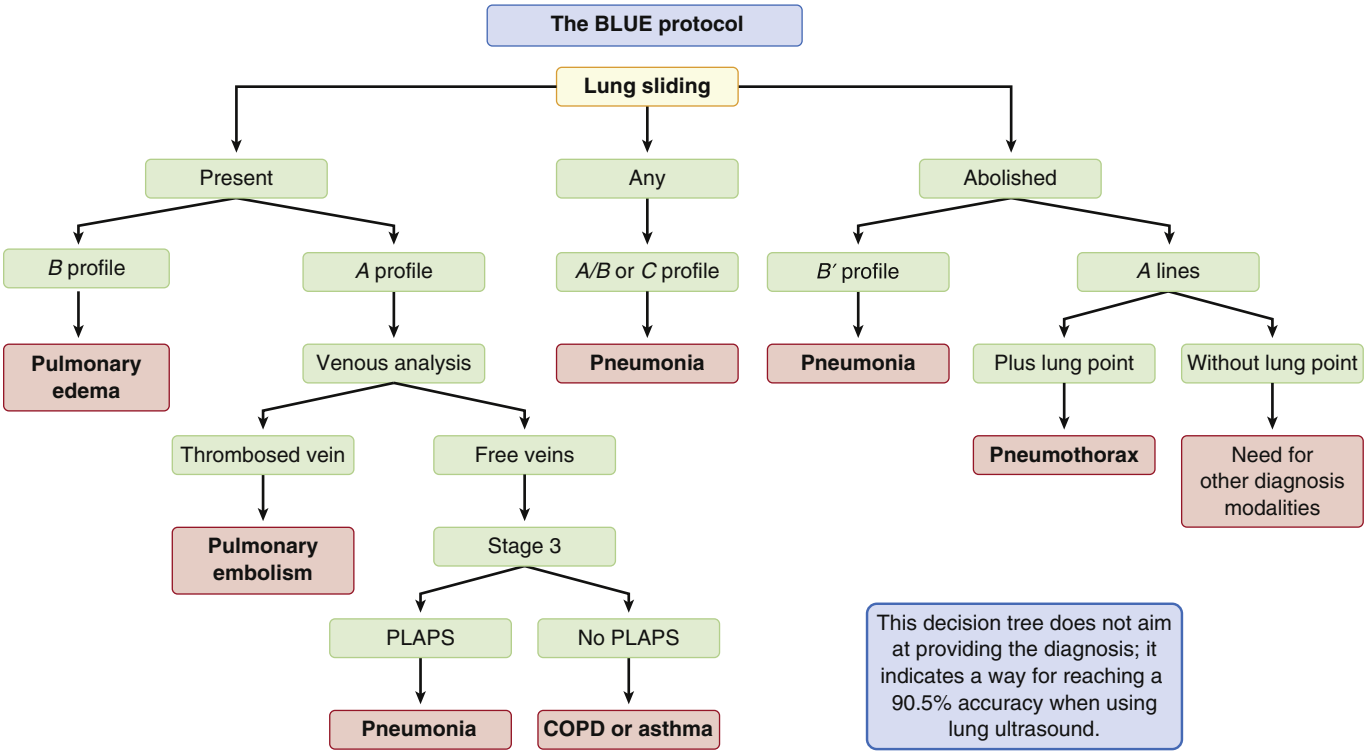


Figure 51-26. The BLUE protocol algorithm based on the particular ultrasound profile of the different kinds of respiratory failure. It uses three lung ultrasound signs with binary answers: anterior lung sliding, multiple B lines visible between two ribs in the anterior lung, and posterior and/or posterolateral alveolar and/or pleural syndrome (PLAPS). These signs are combined with venous analysis to yield 90.5% accuracy in the diagnosis of respiratory failure.[15,16] *COPD,* Chronic obstructive pulmonary disease. *(Redrawn from Lichtenstein DA, Meziere GA: Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol,* Chest *134:117-125, 2008.)*

ELECTRICAL IMPEDANCE TOMOGRAPHY

Electrical impedance tomography (EIT) is a noninvasive and radiation-free imaging modality used to assess regional lung function at the bedside. The method is clinically available and has moderate to low spatial resolution but high temporal resolution, thus allowing for assessment of regional ventilation in real-time.[270,279] Its use in estimating regional lung volume and optimizing mechanical ventilation settings brought significant attention to applications in ICUs and ORs.[270]

EIT is based on electrical impedance, a physical variable that reflects the opposition to the passage of a current through an object when a voltage is applied across it.[280] The impedance of biologic tissues depends on the tissue composition. High concentration of electrolytes, extracellular water content, large cells, and number of cell connections by gap junctions as present in blood and muscles reduce impedance. Air, fat, and bone have high electrical impedance. Pathologic changes of tissue composition influence impedance. These include extravascular lung water, (e.g., pulmonary edema), intrathoracic blood volume, fluid in cavities (pleural effusion, pericardial effusion, bronchial and alveolar fluid), foreign bodies (pleural drain), and lung fibrosis (e.g., after ARDS or as a primary disorder). During the breathing cycle, thoracic bioimpedance is influenced fundamentally by both ventilation and perfusion.

EIT relies on an array of electrodes (typically 16 to 32) around the chest region of interest. The location is chosen based on the clinical information desired, usually at the fifth intercostal space for standard lung assessment. A measurement consists of the application of a low electrical current to a pair of adjacent electrodes generating voltages measured by the other electrodes. A measurement cycle corresponds to a complete sequence of these measurements deriving from the electrode pairs encircling the chest. The surface impedance allows for the reconstruction of an image proportional to regional impedance in the studied thoracic cross section. Usually, images are presented with pixels representing relative impedance change, so called functional EIT. Because air corresponds to high impedances and fluid and tissue to low impedances, the image represents regional ventilation. Absolute EIT (a-EIT) is the modality in which the image represents the actual impedance values. Direct assessment of lung conditions can be accomplished by comparing low impedance (e.g., hemothorax, pleural effusion, atelectasis, and lung edema) with high impedance (e.g., pneumothorax, emphysema).[281] EIT has compared successfully with standard methods, including CT.[270,280,282]

Because the technique provides direct real-time assessment of changes in regional aeration, several applications related to regional lung function have been identified.[279] These include the effect of induction and tracheal intubation at the expiratory lung level and regional ventilation in children (see also Chapter 95) (Fig. 51-27),[283] perioperative monitoring of the distribution of ventilation during spontaneous and controlled breathing,[284] effects of PEEP on regional ventilation during laparoscopic surgery,[285]

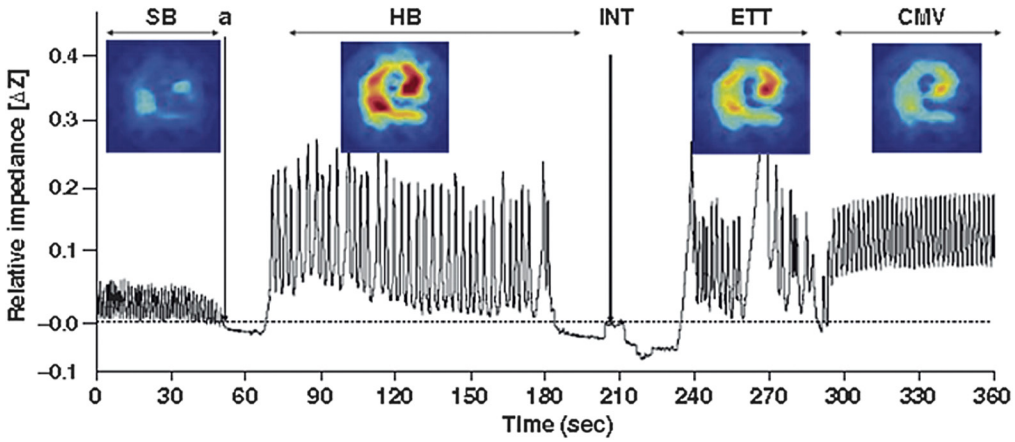


Figure 51-27. Relative impedance signal at five key stages during induction of anesthesia in children. A small impedance signal is noted during spontaneous breathing (SB) as muscle paralysis develops. Effective hand bagging (HB) produces a high-intensity signal, which is reduced to zero during tracheal intubation (INT). Distribution of regional impedances during hand bagging with the endotracheal tube (ETT) and conventional mechanical ventilation (CMV) are also visualized. *(From Humphreys S, Pham TM, Stocker C, Schibler A: The effect of induction of anesthesia and intubation on end-expiratory lung level and regional ventilation distribution in cardiac children,* Paediatr Anaesth *21:887-893, 2011.)*

assessment of ventilation distribution during mechanical ventilation,[282] bedside recruitment, PEEP titration with assessment of alveolar collapse and hyperdistention in patients with ADRS (see also Chapter 101),[286] and assessment of HFOV.[252,287] Given that optimization of lung inflation is key not only to improving gas exchange but also to minimizing ventilator-induced lung injury intraoperatively and postoperatively, EIT may be of value in patients at risk for intraoperative and postoperative respiratory complications.[288] EIT may also allow for real-time detection of pneumothorax.[289] EIT may eventually provide regional measurements of regional perfusion,[290] which could be valuable for bedside assessment of $\dot{V}/\dot{Q}$ matching during spontaneous and mechanical ventilation.

POINT-OF-CARE TESTS

Point-of-care testing (POCT) is the performance of laboratory measurements near the site of patient care. POCT technology includes portable analyzers and use of small blood samples. This implies the availability of rapid, precise, and accurate measurements in ORs and ICUs. POCT yields improvements in patient outcome through expeditious detection of physiologic deterioration and prompt treatment. Respiratory monitoring is a major element of POCT and includes analysis of arterial blood gases (PaO_2, $Paco_2$, pH), Hb, and lactate.

Blood gas measurements can be obtained with acceptable levels of accuracy and precision. For instance, three platforms for arterial blood gases and Hb were found to show a coefficient of variation of approximately 3%.[291] Mean differences among the measurements were less than 3.2 mm Hg for PaO_2 in the range of 53 to 272 mm Hg, –1.5 mm Hg for $Paco_2$ in the range of 29 to 55 mm Hg, and 0.03 for pH in the range of 6.55 to 7.50.

Hb is measured using either conductivity-based methods where hematocrit is assessed and the Hb concentration is calculated (Hb [g/dL] = hematocrit × 0.34) or with optical methods, such as using the azide-metHb reaction and photometry absorbance (see also Chapter 61).[292] Conductivity-based Hb measurements can be less than those reported by standard systems, with a clinically significant bias of –1.2 g/dL in the Hb range of 8.5 to 14.2 g/dL and a trend to underestimate the Hb value at low ranges.[291] Optical measurements have a precision of ± 1.5% compared with laboratory analysis and a correlation of 0.89.[293] The method provides precise and accurate results when used on venous blood in laboratory conditions with a coefficient of variation between 1.4% and 2.2%, only slightly higher than the precision of current hematology analyzers.[19] In patients undergoing hemorrhagic urologic surgical procedures,[19] the bias in optical-based measurements as compared with a laboratory analyzer was –0.2 ± 1.1 g/dL, and the precision was 0.7 ± 0.8 g/dL. High deviations (beyond ±1.0 g/dL) from standard laboratory analyzers occurred in 16% of those patients,[19] as well as in 1 of 78 measurements in adult patients undergoing surgical procedures of the spine.[294]

The site of blood sampling can influence POCT results. For capillary blood samples obtained from finger and ear punctures, a significant correlation exists between optical-based and automated laboratory Hb analysis, with a nonsignificant bias. Fingerstick samples may approximate standard laboratory Hb measurements better than ear lobe samples.[19] Capillary blood samples (lancet puncture to middle or ring finger and fourth drop used) in patients with gastrointestinal bleeding resulted in high deviations (>1 g/dL) in 21% of cases and very high deviations (>2 g/dL) in 4% of cases.[295] In critically ill patients, poor agreement with reference measurements is reported,[296] especially with capillary blood samples and in patients with extremity pitting edema. POCT proved relevant in the assessment of arterial blood gases during pseudohypoxemia (also called "spurious hypoxemia" and "leukocyte larceny"). This is a known cause of inaccurate blood gas measurements and occurs when PaO_2 is reduced by increased O_2 consumption as a result of markedly elevated white blood cell counts in the arterial blood sample. Measurement

error is further aggravated by delayed laboratory analysis or incorrect sampling. Pseudohypoxemia occurs not only in hyperleukocytosis but also in thrombocytosis associated with polycythemia vera.

As POCT progresses, relevant limitations will need to be addressed, including cost, accuracy, data management, and evidence for improved outcomes. Contrary to some expectations, availability of POCT in academic centers does not increase the number of tests performed.[297] Characteristics of individual institutions must be considered before implementation of POCT. For instance, POCT blood-gas analysis may offer minimal time savings and cost benefits compared with central laboratory analysis in an institution with short turnaround time.

RESPIRATORY MONITORING IN SPECIAL CONDITIONS

As methods for life support are advanced, the physiologic patterns that serve as the basis for assessment of gas exchange and respiratory mechanics can be dramatically changed. This occurs, for instance, during HFV when significant reductions in V_T are combined with large increases in respiratory rate. During rigid bronchoscopy or laryngeal interventions, the anesthesiologist is required to share management of the airway with the surgeon. This may result in intermittent loss of information regarding airway flow, volume, and pressure, as well as end-tidal gas concentration. In these situations, clinical assessment based on physical examination (i.e., inspection, auscultation) becomes paramount. Specific considerations for respiratory monitoring in special conditions are detailed later.

HIGH-FREQUENCY VENTILATION

HFV is a ventilatory mode using V_T smaller than the anatomic dead space, tenfold to fiftyfold higher respiratory frequencies, and high instantaneous flow rates. HFV is a broad term encompassing various modalities. These include high-frequency jet ventilation (HFJV) and high-frequency percussive ventilation (HFPV), both of which allow for passive exhalation, as well as HFOV, in which exhalation is actively driven by the device. The mechanisms for gas exchange during HFV are complex and include convective transport, turbulence, pendelluft, velocity profile distortion and asymmetry, Taylor dispersion, molecular diffusion, collateral ventilation, and cardiogenic mixing.[298-300] This method results in a fundamentally different relationship for CO_2 elimination ($\dot{V}_{CO_2}$) compared with conventional ventilation.[301] For example, during conventional ventilation:

$$\dot{V}_{CO_2} \propto f(V_T - V_D) \quad [32]$$

where f is the breathing frequency and V_D is dead space volume. However, during HFOV[302]:

$$\dot{V}_{CO_2} \propto f \frac{V_T^2}{V_D} \quad [33]$$

Although the use of HFOV is not uncommon for neonates in respiratory distress in whom conventional ventilation has failed is,[303-305] its use in adult patients with ARDS has been limited by its perceived lack of efficacy.[306,307] Interest has been renewed in the use of HFOV in adult patients with ARDS because HFOV could facilitate lung-protective ventilation by using high mean airway pressures and low V_T to achieve alveolar recruitment without overdistention.[308-312]

Most high-frequency oscillators use pistons to drive flow actively into and out of the airway at respiratory rates between 3 and 20 Hz.[313,314] However some oscillators, and most jet ventilators, rely on solenoid valves.[315-317] With HFOV, fresh gas and CO_2 may be removed by a continuous bias flow of warmed, humidified gas past the proximal end of the ETT, and mean airway pressure is regulated by an adjustable valve venting the bias flow and exhaled gas from the circuit. These devices may be either pressure or time cycled, and both the mean airway pressure and oscillatory pressure amplitude are displayed on the console to the clinician. However, for the frequencies used during HFV, a significant portion of the oscillatory pressure amplitude results from the inertia of the gas column contained in the breathing circuit and the patient's airways, and thus it should not be used as a surrogate for lung distention.

Clinically useful physiologic information inferred from airway flow and pressure measurements is somewhat limited during HFV. During conventional mechanical ventilation, airway pressure and flow are related according to basic mechanical properties of the respiratory system, such as airway resistance and tissue compliance. However, during HFV, airway pressure and flow reflect complex resistive and inertial gas properties in the central airways. Many investigators have assessed respiratory mechanics during HFV by transiently switching patients to conventional mechanical ventilation to obtain basic estimates of resistance and compliance,[318] or even making intermittent low-frequency oscillatory measurements to measure airway and tissue properties.[319] The pressure transmission index, defined as the ratio of the pressure measured directly in the trachea to the pressure at the proximal end of the breathing circuit (i.e., the pressure amplitude measured at the oscillator), is strongly correlated with tissue elastance.[319,320]

An important component of monitoring during any form of HFV is the assessment of mechanical function. Many important physiologic parameters, such as mean airway pressure and V_T, are not explicitly controlled by most high-frequency ventilators. Thus, the relationship between pressure transduced at the proximal end of the breathing circuit and the V_T delivered to the patient is difficult to assess. Indeed, this relationship is highly nonlinear,[303] and it depends on frequency, gas composition and inertia, and the overall mechanics of the patient's respiratory system.[211,250] Given the important role that V_T plays in CO_2 elimination during HFV (Equation 33), accurate measurement of airway flow is important for the development and standardization of clinical trials.[307] Hot wire anemometry yields the most accurate estimates of airway flow and delivered V_T during HFOV compared with other measuring devices.[211,250]

Adequacy of gas exchange is essential during HFV. Analysis of arterial blood gases should be performed within 30 minutes of any change in ventilator settings, and at least twice per day on stable settings.[308] Whereas oxygenation is usually assessed with continuous pulse oximetry, CO_2 elimination is more technically challenging to monitor. Attempts have been made to incorporate various forms of capnography into HFV circuits,[321-324] with varying degrees of success. Depending on where exhaled gases are sampled, the correlation between $PetCO_2$ and $Paco_2$ may be adequate during HFV.[323,324] The discrepancy between $PetCO_2$ and $Paco_2$ is often a reflection of the slower response time of many sidestream CO_2 analyzers.[151] The Pco_2 sampled at the airway opening may thus underestimate the true alveolar CO_2 levels.[322] The most accurate measurement of alveolar Pco_2 is obtained when it is measured at the very distal tip of the ETT,[325] although this is not always clinically feasible. Transcutaneous measurements of Pco_2 may hold considerable promise for assessment of CO_2 clearance during HFV.[326]

Although HFOV has not been shown to improve outcomes in adult patients with ARDS significantly,[301,306] this finding may reflect the variable effects of frequency, amplitude, and mean airway pressure with oscillating of a heterogeneously injured lung,[310] as well as the poorly understood phenomena of gas distribution, volume recruitment, and $\dot{V}/\dot{Q}$ matching in individual patients. Nonetheless, this ventilatory modality represents a promising approach to lung-protective ventilation. Future clinical trials will guide both therapy and technologic development of HFOV,[309] thus providing a scientific basis for the rational use of this technology in critically ill patients.

JET VENTILATION

Jet ventilation is commonly used for procedures in which the surgeon requires unobstructed access to the airway.[327] During inspiration, O_2 or an O_2-air mixture is applied under high pressure to the airway through either a specialized catheter or a rigid bronchoscope. This jet of gas, along with entrained air from the surrounding environment, leads to insufflation of the lungs. Expiration takes place through passive recoil. The entire system is open to the environment, thus leading to significant escape of respiratory gases.[316]

Oxygenation during jet ventilation can be adequately monitored using pulse oximetry. Ascertaining the presence and adequacy of ventilation, especially during HFJV, is more challenging because the composition and volume of the exhaled gases cannot be directly measured. Arterial sampling of $Paco_2$ is accurate but intermittent and invasive. Gas can be sampled at the distal end of the catheter or rigid bronchoscope through a dedicated channel. Quantitative capnography during HFJV does not accurately reflect $Paco_2$ because V_T is smaller than dead space.[328] This problem can be overcome by the intermittent suspension of HFJV or reduction in frequency to 10 breaths/minute or less. $PetCO_2$ measurements obtained in this manner accurately reflect the $Paco_2$ and allow the intermittent monitoring of ventilation.[324,329-331] The measurement of transcutaneous Pco_2 ($Ptcco_2$) is noninvasive and continuous. Although $Ptcco_2$ is not as accurate as capnometry, its use has been suggested to allow for tracking of changes in $Paco_2$.[331] The absence of V_T and continuous $PetCO_2$ monitoring precludes standard ventilator disconnect monitoring during intraoperative HFJV. RIP, which uses changes in the inductance of bands placed around the chest to monitor respirations, has been demonstrated to discriminate reliably between the presence and absence of HFJV and may be developed as a monitor to detect disconnect or the absence of adequate thoracic excursion during HFJV.[254]

INTRAHOSPITAL TRANSPORT OF PATIENTS

Intrahospital transport of critically ill patients is a frequent occurrence. Transport of adult and pediatric patients from locations with advanced monitoring to more remote locations is fraught with difficulty, ranging from simple equipment malfunction to major disasters.[332-334] Complex monitoring and numerous pieces of equipment are often required for safe transfer, especially when additional devices such as extracorporeal membrane oxygenators and ventricular assist devices are present. The lack of standardized monitoring techniques and terminology explain the wide reported discrepancies in the incidence of adverse events. Previous studies demonstrate a frequent incidence of respiratory compromise and gas exchange deterioration following transport.[333-335]

Respiratory monitoring during transport should ideally be the same as that in the OR or ICU before relocation. In practice, at least clinical signs (e.g., skin color, chest expansion, auscultation, endotracheal secretions), pulse oximetry, and respiratory rate should be monitored throughout intrahospital transport. If a transport ventilator is used, airway pressures should be readily available in numeric or graphic formats. Human factors are essential during transport, and a specialized transport team using standardized management procedures with preparatory, transfer, and posttransport stabilization phases likely limits the frequency of adverse events.[336-338] This is particularly important when high-risk patients are involved.[337] Equipment and medications needed to establish and maintain a secure airway and hemodynamics should be available during any transfer. Adequate O_2 supply with functioning low-pressure alarms should be verified during pretransport preparation. A transport ventilator can provide better oxygenation and reduce variability in pH and Pco_2 compared with manual ventilation.[335,339] The transfer phase may require several professionals under the coordination and supervision of an attending anesthesiologist.

AUTOMATED DATA SYSTEMS

Electronic anesthesia records are gaining increased use in anesthesiology (see also Chapters 1 and 5). These systems provide data from medical devices, clinical information management systems, and laboratory data. The availability of large amounts of real-time data in digital form allows for introduction of new approaches to monitoring that may have been conceptualized, but not yet clinically

implemented. In fact, although decision support research has been done for years, little progress has been made in clinical decision support for the acute management of unstable patients, a major challenge in the OR and ICU.[340]

Computerized monitoring has the potential to improve clinical monitoring.[341] However, it has limitations resulting from typical requirements not well-suited to human performance, such as monitoring graphic displays over extended periods or the execution of overt responses to low-probability events. Humans are limited in their ability to analyze large quantities of data accurately and continuously. Accordingly, computer algorithms that identify subtle but meaningful trends in physiologic data are desirable. Such tools require relevant contextualization of measurement to improve accuracy, as well as minimization of false-negative and false-positive alarms. This automated monitoring should depend not only on timely measurements, but also on prior information. Alarms should not be fixed to specified thresholds, but rather dynamically adapted to information as it becomes available. Algorithms with established clinical rules provide the opportunity to detect subtle changes in time-series data,[342] which exceed human discrimination.[343] Such automated systems minimize monitoring failures and promote timely responses, thus enhancing the performance of anesthesia delivery during long periods. Some tools of respiratory monitoring have been assessed in adult and pediatric populations.[340,344-346] Data banks have been developed for research.[347] Another potential interest in these systems is that of creating closed-loop systems, such as those currently implemented to adjust settings in commercial mechanical ventilators.[345,348]

Although these methods are not currently established for clinical use, they are expected to find increasing application as reliable monitoring algorithms are implemented and validated. Such automated systems allow for the implementation of additional levels of safety. The detection of potentially dangerous events, such as continuously low SaO_2 or the absence of $PetCO_2$ measurements for several breaths, can generate an automated alarm, a screen alert, or an automated page to the supervising clinician.[349] This type of alert system is already used in many airplanes. In a different condition (e.g., when changes in oxygenation occur over a period of minutes), improved processes should be directed to the anesthesia provider in direct contact with the patient, to initiate prompt treatment, assess artifacts, and/or call for assistance.[349]

ADDITIONAL MONITORED VARIABLES

NITROGEN WASHOUT AND END-EXPIRATORY LUNG VOLUME

A resurgence of interest has occurred in the use of nitrogen washout methods for adult[350,351] and pediatric[352] patients (see also Chapter 95). Nitrogen washout techniques are in commercial mechanical ventilators for use in ICUs (see also Chapter 101). The main parameter of interest has been the end-expiratory lung volume, a potentially valuable measurement to optimize lung expansion during mechanical ventilation and to assess ventilatory interventions such as PEEP adjustment.[351] The measurements are performed by introducing a step change in the inspired air (traditionally from room air to 100% O_2, in current systems a nitrogen washout-washin method with 10% to 20% change in FiO_2) and solving mass balance equations for the lung volume. In patients with ARDS, measurements of end-expiratory lung volume demonstrated good accuracy and reproducibility, with a coefficient of variation of less than 4%.[351] In 30 patients in ICUs who were undergoing CT for clinical reasons, the end-expiratory lung volume measured with the modified nitrogen washout-washin technique was well correlated ($r^2 = 0.89$) with CT measurements with a bias of 94 ± 143 mL (15 ± 18%; $P = .001$), within the limits of accuracy provided by the manufacturer.[350] Nitrogen washouts can also provide measures of ventilation heterogeneity.[352]

TRANSCUTANEOUS MEASUREMENTS OF PARTIAL PRESSURES OF OXYGEN AND CARBON DIOXIDE

Gas exchange is a dynamic, at times rapidly changing, process. Conventional direct measurements of arterial blood gases, although still the gold standard for PaO_2, $Paco_2$, and pH monitoring, provide only an isolated picture of that process. Expeditious assessment of circulating blood gases could facilitate faster initiation of required therapy and adjustment of implemented ventilation. A method for noninvasive continuous monitoring of PaO_2 and $Paco_2$ is a current clinical need.

Transcutaneous measurements of PO_2 ($Ptco_2$) and Pco_2 ($Ptcco_2$) are monitoring methods that aim to provide noninvasive estimates of arterial O_2 and CO_2, or at least trends associated with these variables. These indices have been useful in intensive care management of neonates and infants[353] (see also Chapter 95), as well as in the fields of wound healing and hyperbaric therapy. An advantage is that transcutaneous monitoring can be applied when expired gas sampling is limited such as during HFOV, apnea testing, and noninvasive ventilation. The measurements are based on the diffusion of O_2 and CO_2 through the skin. Because the skin is not entirely permeable to gases, warming is used to facilitate gas diffusion. Such an increase in temperature (usually 42° C to 45° C) promotes increased O_2 and CO_2 partial pressure at the skin surface resulting from changes in structure of the stratum corneum that increase diffusion and dermal hyperemia and shift the Hb dissociation curve. This process ultimately results in arterialization of the regional blood. $Ptco_2$ and $Ptcco_2$ are thus influenced not only by the arterial gas partial pressures but also by skin O_2 consumption, CO_2 production, and regional blood flow. Accordingly, $Ptco_2$ is usually lower than PaO_2, and $Ptcco_2$ is higher than $Paco_2$.

O_2 transducers are electrochemical polarographic Clark-type electrodes in which the rate of chemical reaction is related to an electrical signal proportional to the O_2 concentration. For CO_2, a transducer using a pH electrode to measure the Pco_2 (Stow-Severinghaus electrode) is used, where a change in pH is proportional to the logarithm of the Pco_2 change. For CO_2 monitors, a temperature correction factor is used to estimate $Paco_2$ from

$Ptcco_2$. In vivo correction is available in some devices based on arterial blood gases. The thin epidermal layer of infants facilitates the measurements, in contrast to the diffusion barrier introduced by the thicker adult skin. A lower electrode temperature in $Ptcco_2$-monitoring produces systematic bias of the transcutaneous electrode. However, in very preterm babies, monitoring at 40° C or 41° C to reduce the risk of burns is possible, provided a bias correction of 12% to 15% is applied.[354]

The main application of $Ptcco_2$ is in the neonatal ICU population.[353] Even in very low-birth-weight infants, the mean difference between $Ptcco_2$ and $Paco_2$ is 3.0 mm Hg (95% confidence interval, 0.2 to 6.0 mm Hg; $P < .05$).[355] In addition, $Ptcco_2$ may be used to assess the efficacy of mechanical ventilation continuously during respiratory failure. In this setting, in children 1 to 16 years old, $Ptcco_2$ was more accurate and precise than $PetCO_2$ in relation to $Paco_2$. $Ptcco_2$-$Paco_2$ differences were 2.3 ± 1.3 mm Hg in children 1 to 3.4 years old and 2.6 ± 2.0 mm Hg in children 4 to 16 years old.[353] $PetCO_2$-$Paco_2$ differences were larger (6.8 ± 5.1 mm Hg and 6.4 ± 6.3 mm Hg) for the same age ranges. When compared with $PetCO_2$, $Ptcco_2$ monitoring is equally accurate in patients with normal respiratory function. Accuracy and precision in the perioperative period of cardiac surgery for congenital heart disease in infants and children were better for $Ptcco_2$ than $PetCO_2$ in relation to $Paco_2$ with exception of patients receiving significant amounts of vasoactive medications and in low cardiac output states (see also Chapter 94).

In adults, whereas $Ptcco_2$ has not proved to be a reliable surrogate for $Paco_2$ in the general population of anesthetized and critically ill patients, $Ptcco_2$ monitoring could be suitable to some specific conditions. $Ptcco_2$ could be a more accurate estimate of $Paco_2$ than $PetCO_2$ during laparoscopic surgery with prolonged pneumoperitoneum,[356] in which even trends provided by $PetCO_2$ may be unreliable to monitor $Paco_2$.[357] During deep sedation for ambulatory hysteroscopy in healthy patients, earlobe $Ptcco_2$ agreed better with $Paco_2$ than did nasal sidestream $PetCO_2$, with lower bias (1.7 versus −7.0 mm Hg) and smaller mean differences to $Paco_2$ (3.2 ± 2.6 versus 8.0 ± 6.0 mm Hg) (see also Chapter 89).[358] The sensitivity of the $Ptcco_2$ monitor for detecting $Paco_2$ higher than 50 mm Hg was also greater than for $PetCO_2$ (66.7% versus 33.3%; $P < .01$).[358] $Ptcco_2$ is also helpful during weaning from mechanical ventilation after off-pump coronary artery bypass graft.[359] $Ptcco_2$ monitoring over 8 hours in six hemodynamically stable adult intensive care patients suggested the possibility of reaching bias and limits of agreement of 0.4 and −5.5 to 6.4 mm Hg.[360] In adults admitted to an emergency department for acute respiratory failure, agreement between $Paco_2$ and $Ptcco_2$ was 0.1 mm Hg, and the limits of agreement were from −6 to 6.2 mm Hg. None of the patients experienced adverse effects from heating of the device clipped to the earlobe. However, in patients undergoing noninvasive ventilation, unacceptably wide variability may be observed.[361]

$Ptco_2$ from normal to extremely low-birth-weight infants agreed well with PaO_2 measurements, with mean $Ptco_2$-PaO_2 difference 2.3 (−1.5 to 6.8) mm Hg, clinically acceptable in current neonatal ICUs (see also Chapter 95). $Ptco_2$ in neonates is additionally important to detect hyperoxia, which is not feasible with pulse oximetry. The use of $Ptco_2$ in adults has been focused on wound management, peripheral vascular disease, and hyperbaric medicine. Although attempts for applications in adults were promising, such as the use of $Ptco_2$ to support resuscitative efforts,[362] measurements following off-pump coronary artery surgical procedures still present very high variability.[363] The dependence of $Ptco_2$ on low-flow states has been used in conjunction with analysis of arterial blood gases to estimate adequacy of cutaneous blood flow and, by inference hemodynamic, stability.[364,365]

$Ptcco_2$ monitoring does not replace $PetCO_2$ monitoring, which remains the standard of care to demonstrate the intratracheal location of the ETT following intubation and as a disconnect alarm in the OR (details are given in the section on tissue oxygenation).

In summary, transcutaneous measurements are favorably positioned for continuous gas exchange monitoring in neonates and infants. In contrast, widespread applications of transcutaneous techniques in the perioperative settings are still hindered by limitations, such as poor cutaneous blood flow; need for frequent calibration; slow response time, and risk for skin burns with prolonged application.

LUNG WATER

Pulmonary edema is a hallmark of lung injury. It can result from increased hydrostatic pressure in the pulmonary capillaries (cardiogenic), increased permeability of the alveolar capillary membrane (noncardiogenic), and reduced lymphatic drainage from the lungs. Such mechanisms can be caused by pulmonary and extrapulmonary factors. For these reasons, interest in the development of methods to quantify extravascular lung water (EVLW) has been considerable because this may assist in the diagnosis and management of those conditions, including fluid therapy, diuretics, and mechanical ventilation. In patients, assessment of pulmonary edema is made with imaging techniques (e.g., chest radiography, ultrasonograpy, CT, and EIT) and indicator dilution methods.

Imaging Techniques

The method used primarily in clinical practice remains the bedside chest radiograph. It allows for semiquantitative assessment of EVLW, its distribution, and its possible etiology. The chest radiograph has limited diagnostic accuracy. This is because: (1) edema may not be visible until the amount of lung water increases by 30%[366]; (2) any radiolucent material that fills the air spaces (e.g., alveolar hemorrhage, pus, and bronchoalveolar carcinoma) will produce a radiographic image similar to that of pulmonary edema; (3) technical issues including rotation, inspiration, positive-pressure ventilation, patient position, and underpenetration or overpenetration can reduce sensitivity and specificity; and (4) substantial interobserver variability exists in interpretation of chest radiographs.[367,368] CT is another radiographic technique to quantify EVLW. In animal experiments, CT densitometry could detect an increase in EVLW by as little as 50%.[162] CT-based studies indicated that significant hypoxemia secondary to pulmonary edema may not

develop until the increase in EVLW approaches 200% to 300%.[163] Lack of portability and high radiation exposure limit the use of CT as a continuous intraoperative monitor. Positron emission tomography[165] and nuclear magnetic resonance[166] are imaging techniques that can assess lung water. However, they are not amenable for routine clinical use in the perioperative setting. Ultrasound and EIT are methods described previously.

Indicator Dilution Methods

Such measurements of EVLW have been expected to be superior to blood oxygenation and chest radiography. They are based on the kinetics of one or two tracers injected centrally and measured in an artery. Initial techniques were based on a double-indicator dilution method. These techniques gained renewed attention with the introduction of a clinical device to assess EVLW by using transpulmonary thermodilution technology, which facilitated bedside measurements.[369] The device uses cold saline solution as the single indicator injected in a central venous line. EVLW and additional hemodynamic parameters (i.e., cardiac output) are computed from the curve of temperature in the peripheral artery.[370] Good reproducibility and correlation can occur with gravimetric methods and can be a useful clinical and research tool. EVLW may be a predictor of mortality in patients with severe sepsis[371] and ARDS.[372,373] It is a diagnostic tool in detecting early pulmonary edema[374] and in evaluating the effect of ventilatory modes during esophagectomy.[375] The measurement has also been proposed to guide intravascular fluid therapy in ARDS[376] and subarachnoid hemorrhage,[377] as well as assess the effect of steroids during cardiac surgical procedures (see also Chapter 67).[378] EVLW was the primary outcome variable in clinical trials to study the efficacy of salbutamol to resolve pulmonary edema in patients with ARDS (the Beta-Agonist Lung Injury Trial[379]) and lung resection (see also Chapter 66).[380]

The limitations on this technique derive from the considerable and at times conflicting assumptions.[370,381] Measurement premises include that the thermal indicator reaches all lung regions and equilibrates in all of them and that the central circulation volumes between the injection and temperature measurement sites can be described as a small number of individual well-mixed compartments, each showing a monoexponential decay of temperature with time. Experimental evidence indicated that assumptions for the method do not apply to all conditions; an important factor is the changes in the regional distribution of perfusion during lung injury.[370,382,383] These changes may significantly compromise the measurement.[381] Indeed, redistribution of lung perfusion can produce measurement changes larger than those seen in the Beta-Agonist Lung Injury Trial between treatment and control groups.[379,382] Such results are also consistent with the influence of the type of lung injury on the accuracy of EVLW measurements,[384-386] as well as with the poor correlation between transpulmonary thermodilution EVLW and qualitative CT estimates of EVLW.[387] Thus, the expected reliability of transpulmonary thermodilution EVLW to follow trends[388] cannot be taken for granted, and it requires interpretation in light of potential simultaneous changes in regional perfusion. Finally, the technique requires placement of arterial and central venous catheters, thereby increasing invasiveness. The hope is that future studies and experience will determine the place of such monitors in clinical practice.

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Chapter 52

Renal Function Monitoring

KATHLEEN LIU • MARK STAFFORD-SMITH • ANDREW SHAW

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Key Points

- The incidence of perioperative acute kidney injury (AKI) (previously referred to as acute renal failure) varies, depending on the definition used.
- Although uncommon, AKI requiring dialysis is associated with extremely high morbidity and mortality rates.
- The mechanism for perioperative AKI is complex and commonly involves multiple factors including ischemia-reperfusion injury, inflammation, and toxins.
- Repeated direct perioperative assessments of renal hemodynamics or tubular function are impractical; therefore indirect assessments, such as trends of serum creatinine concentrations, are the best practical perioperative tools to assess renal function.
- Intraoperative urine formation depends on many factors and is not validated as a measure of the risk of postoperative renal dysfunction. Yet postoperatively, patients with low intraoperative urine output may develop renal dysfunction. Therefore urine output should be carefully monitored in the intraoperative setting.
- Serum chemistries and urine indices, such as blood urea nitrogen, creatinine, and fractional excretion of sodium, are generally late indicators of renal function deterioration and do not enable the clinician to delineate clearly the cause of renal failure.
- The most sensitive and specific clinical method for determining renal function is direct measurement of glomerular filtration rate (GFR). However, this measurement is limited by time and measurement restrictions.
- Early biochemical markers for kidney injury may soon become new tests that can provide prompt clinical information.
- Volume overload is a risk factor for adverse outcomes in patients with AKI and may influence concentrations of conventional markers of kidney function such as serum creatinine.

Acute kidney injury (AKI) (previously known as acute renal failure) is characterized by rapid decline in the glomerular filtration rate (GFR) and the accumulation of nitrogenous waste products (blood urea nitrogen [BUN] and creatinine). AKI occurs in approximately 5% to 25% of all hospitalized patients, depending on the precise definition used for AKI, and with more frequent rates in patients who are critically ill in the intensive care unit (ICU) (also see Chapter 101). AKI is also a serious perioperative complication for patients undergoing major surgery.[1] As the incidence of AKI varies by the definition used, the mortality of AKI ranges from 10% to 35% for mild AKI, whereas AKI in the ICU setting is associated with a 50% to 80% mortality rate (see Chapter 101). However, supportive care with dialysis has reduced mortality from AKI. Whereas the mortality rate of oliguric AKI was 91% during World War II, mortality declined to 53% during the Korean War with the provision of dialysis.[2] AKI requiring dialysis develops in 1% to 7% of patients after cardiac or major vascular surgery and is strongly associated with morbidity and mortality in this context (Fig. 52-1) (see Chapters 67 and 69).[3-8] Although mortality after cardiac surgery in those with AKI has decreased, the odds of having AKI have increased. This combination actually results in an increase in the risk of death associated with AKI.[9]

Perioperative renal failure was long defined as a requirement for postoperative dialysis. However, the thinking concerning this concept has evolved during the past several years. First, because the implications of requiring postoperative dialysis are quite different for a patient starting with a normal baseline renal function compared with one starting with advanced chronic kidney disease and because the criteria for the use of dialysis are not standardized, the usefulness of dialysis alone to

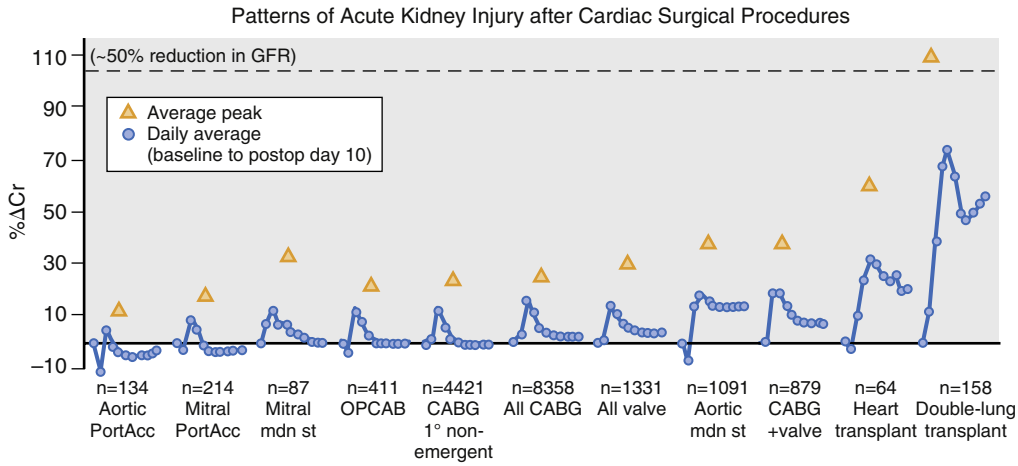


Figure 52-1. Average daily *(circles)* and unadjusted average peak *(triangles)* serum creatinine values for the first 10 days after several different cardiac surgery procedures are represented as change relative to preoperative serum creatinine. Note that for each procedure, the average peak value exceeds the highest average daily value because creatinine peaks on different days for different patients. *Aortic mdn st,* Median sternotomy aortic valve replacement; *Aortic PortAcc,* minimally invasive parasternotomy aortic valve replacement; *CABG 1° nonemergent,* coronary artery bypass surgery 1° nonemergent; *% ΔCr,* peak fractional serum creatinine rise; *GRF,* glomerular filtration rate; *Mitral mdn st,* median sternotomy mitral valve surgery; *Mitral PortAcc,* port access mitral valve surgery; *OPCAB,* off-pump coronary artery bypass surgery. *(From Stafford-Smith M, Patel U, Phillips-Bute B, et al: Acute kidney injury and chronic kidney disease after cardiac surgery,* Adv Chronic Kidney Dis *15:157-177, 2008. Used with permission.)*

define AKI has been questioned.[10-12] Second, studies are difficult to compare because of the use of nonstandard definitions for AKI. For example, in one review of 28 studies,[13] definitions for perioperative AKI varied. Third, consensus definitions that focus on small changes in serum creatinine and on changes in urine output to define AKI have received widespread adoption. This last conclusion is based on the recognition that small changes in renal function directly relate to an increased risk of death.

As a result, recent consensus criteria are being used to define AKI in both the perioperative and other medical settings. The first proposed consensus criteria were the RIFLE (**R**isk, **I**njury, **F**ailure, **L**oss, **E**nd-stage) kidney disease criteria developed by the Acute Dialysis Quality Initiative (Table 52-1).[14] These have subsequently undergone two modifications by the Acute Kidney Injury Network (AKIN) criteria[15] and in the recently published Kidney Disease: Improving Global Outcomes (KDIGO) AKI guidelines.[16] As detailed in Table 52-1, the central components of these criteria are the focus on relative and absolute changes in creatinine from a baseline value and the definition of several degrees of AKI severity. Consequently, milder AKI (e.g., KDIGO, Stage 1 disease) will be more common than Stage 3 disease and will also be associated with a lower mortality rate. These criteria have also proposed definitions for AKI based on urine output. However, using urine output criteria are not as well validated regarding their relationship to adverse outcomes including mortality because of other complexities, including a lack of correction for morbid obesity.[17]

As medical populations shift toward older and more critically ill patients undergoing increasingly high-risk procedures, patients are at an increased risk of AKI in the perioperative setting. Indeed, a recent study of dialysis after elective major surgery suggests that the incidence of dialysis-requiring AKI is rising from 0.2% in 1995 to 0.6% in 2009, with the majority of the increase occurring after vascular and cardiac surgery (see Chapters 67 and 69).[18] Although ischemic causes may be primarily responsible for perioperative AKI,[19,20] the successful development of renoprotective strategies has not occurred.[21] Furthermore, other pathophysiologic contributors to perioperative AKI may include contrast-induced nephropathy, pigment nephropathy (e.g., hemoglobin, myoglobin), cholesterol emboli (e.g., atheroembolic renal disease), aminoglycoside toxicity, norepinephrine-induced nephropathy, and sepsis, also known as systemic inflammatory response syndrome. Animal studies of such pure nephropathies treated with logical renoprotective interventions often demonstrate success; unfortunately, this success has rarely extended to equivalent renoprotection in humans. However, it is not surprising that a specific treatment for a pure nephropathy nonselectively applied to a mixture of nephropathies, variably expressed in different patients, would be unsuccessful. Protection from one type of renal failure may even add risk for another type; for example, augmenting renal blood flow (RBF) may attenuate ischemia-reperfusion injury while delivering more atheroembolic and inflammatory mediators. Postoperative AKI, rather than being a single entity, is likely a mosaic of several pure nephropathies, each of varying importance for a particular patient and procedure (Fig. 52-2).

Individualized renoprotection strategies, guided by timely point-of-care renal function monitoring, will be needed. Hence, advances in renal function monitoring are currently a major focus in the search for improved renal protection and risk stratification strategies for AKI (also see Chapter 23).

RENAL PHYSIOLOGIC FUNCTION

The kidneys are mesoderm-derived, bean-shaped retroperitoneal organs and weigh approximately 150 g each.

TABLE 52-1 COMPARISON OF THE RIFLE, AKIN, AND KDOQI CONSENSUS CRITERIA FOR AKI

	RIFLE		AKIN		KDIGO	
Class	SCr	Stage	SCr	Stage	SCr	Urine Output*
Risk	Increase in SCr to >1.5× baseline	1	Increase in SCr ≥0.3 mg/dL or to ≥1.5×-2× baseline	1	Increase in SCr ≥0.3 mg/dL within 48 hr or to ≥1.5×-2× baseline, which is known or presumed to have occurred within the past 7 days	Urine output <0.5 mg/kg/hr for >6 hr
Injury	Increase in SCr to >2× baseline	2	Increase in SCr to >2×-3× baseline	2	Increase in SCr to >2×-3× baseline	Urine output <0.5 mg/kg/hr for >12 hr
Failure	Increase in SCr to >3× baseline, or increase of ≥0.5 mg/dL to absolute value of ≥4 mg/dL	3	Increase in SCr to >3× baseline, or increase of ≥0.5 mg/dL to absolute value of ≥4 mg/dL, or need for RRT	3	Increase in SCr to >3× baseline, or increase to absolute value of ≥4 mg/dL, or need for RRT; in pediatric patients eGFR <35 mL/min/1.73 m^2	Urine output <0.3 mg/kg/hr for >12 hr or anuria for >12 hr
Loss	Need for RRT >4 wk					
End Stage	Need for RRT >3 mo					

The three consensus criteria use the same urine output criteria, but slight differences in the creatinine criteria are used to define AKI.
AKI, Acute kidney injury; *AKIN,* Acute Kidney Injury Network; *eGFR,* estimated glomerular filtration rate; *KDOGI,* Kidney Disease: Improving Global Outcomes; *RIFLE,* Risk, Injury, Failure, Loss, End-stage disease; *RRT,* renal replacement therapy; *SCr,* serum creatinine.
*Is common to all three consensus criteria.

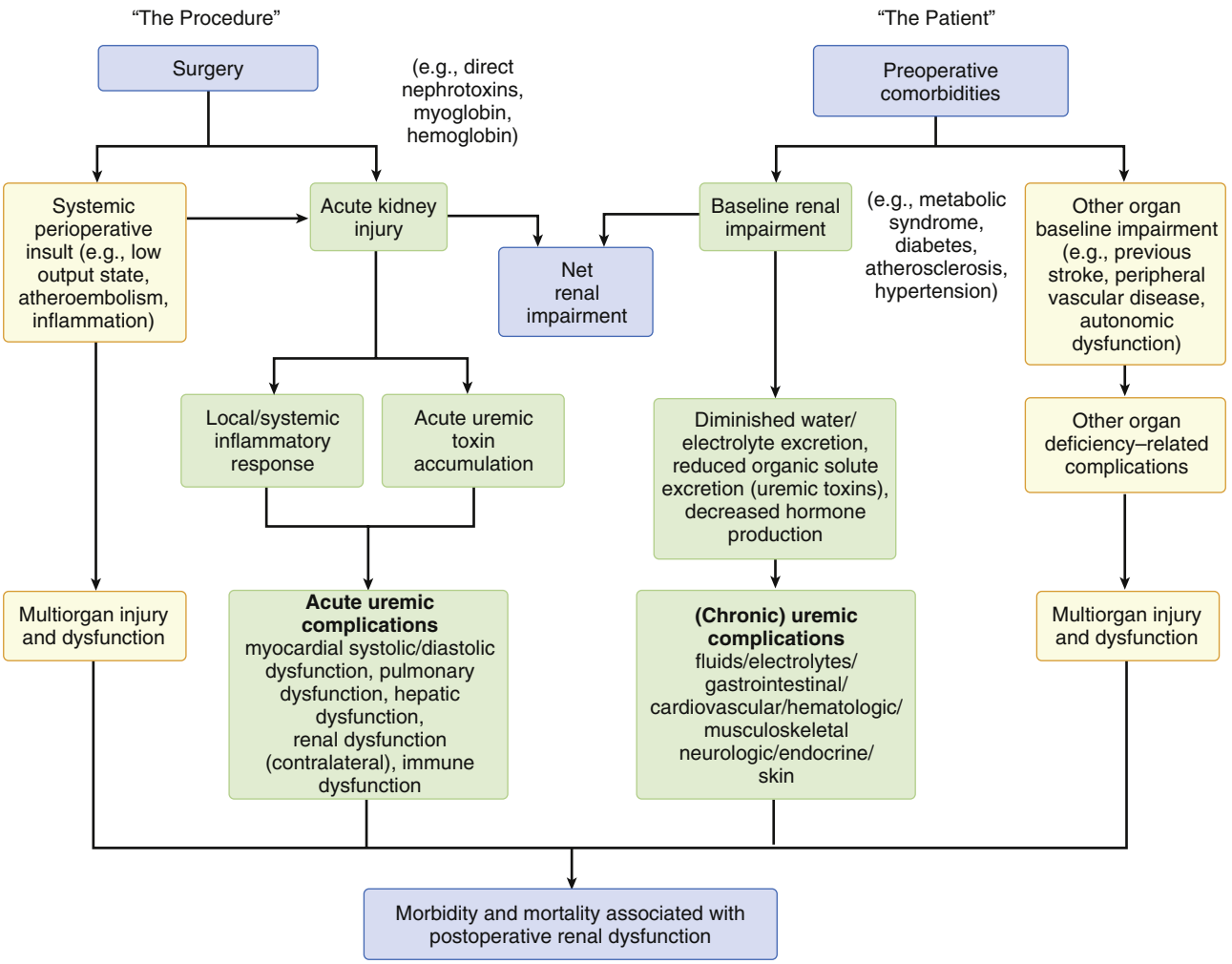


Figure 52-2. Procedural and patient factors related to surgery contributing to the risk of perioperative acute kidney injury (AKI) and postoperative morbidity and mortality. Of note, although AKI contributes to the risk of morbidity and mortality, a significant part of this association must also be attributed to other very serious conditions, such as sepsis, that can cause injury and are also major sources of adverse outcomes. *(Modified from Stafford-Smith M, Patel U, Phillips-Bute B, et al: Acute kidney injury and chronic kidney disease after cardiac surgery,* Adv Chronic Kid Dis *15:157-177, 2008. Used with permission.)*

They are the most highly perfused major organs in the body, representing only .4% of body weight but receiving an impressive 25% of cardiac output; as a comparison, at rest blood flow to the kidneys is eightfold greater per gram of tissue than blood flow to muscle during heavy exercise. Notably, RBF is not primarily linked to metabolic demand; it is this excess blood flow that allows filtration of plasma at rates as rapid as 125 to 140 mL per minute in adults. Autoregulatory reflexes do exist that regulate renal perfusion; these are myogenic and tubular-glomerular reflexes that exist to protect the glomeruli from damage attributable to excessive intravascular pressure by restricting RBF at higher pressures (e.g., >80 mm Hg).[22,23] However, significant regional differences in blood flow within the kidney and high metabolic demand paradoxically make some areas (e.g., the medulla) extremely vulnerable to ischemic injury. Cortical blood flow exceeds outer and inner medullary perfusion by 3- and 20-fold per gram of tissue, respectively.[24]

GROSS ANATOMY AND INTERNAL ARCHITECTURE

In simple terms, the internal morphologic structure of the kidney parenchyma is highly organized, including a deep medullary region and superficial cortical layer.[4] The medulla is further subdivided into inner and outer regions. Tightly packed nephrons are tubular structures that contain specialized segments including the glomerulus, proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting duct (Fig. 52-3). The collecting ducts feed urine to the renal pelvis, which empties into the ureter and goes on to the bladder. Each kidney contains approximately 1 million nephrons. The loops of Henle and collecting ducts are found in the deeper parts of the kidney (medulla). Two types of nephrons are differentiated by glomerular location into cortical (85%) and juxtamedullary (15%) types; only the latter have loops of Henle that course deep into the medulla and participate in *countercurrent exchange,* a mechanism that makes possible the formation of highly concentrated urine.

VASCULAR ANATOMY

A single renal artery enters at the kidney hilum and then divides many times, ultimately producing *arcuate arteries* that pass along the boundary between the cortex and outer medulla (see Fig. 52-3).[25] Arcuate arteries give rise to interlobular arteries that branch toward the outer kidney surface, passing through the cortex as they produce numerous afferent arterioles, which in turn supply a capillary tuft to each glomerulus. The glomerular capillary tuft is the barrier where plasma elements are filtered and pass from the vascular to the tubular space. Specialized negatively charged fenestrated capillary endothelial cells and tubular epithelial cells (podocytes) separated by a basement membrane allow approximately 25% of plasma volume to pass into the glomerulus (Bowman capsule); normally, only elements smaller than 60 to 70 kDa are small enough to be filtered. Many disease conditions cause abnormalities of this interface and allow much larger proteins and even red blood cells to pass through, which manifests as either nephrotic syndrome (proteinuria >3.5 g per 24 hours) or glomerulonephritis (proteinuria and hematuria). As the vascular tuft exits the glomerulus, capillaries merge and become the efferent arteriole. Subsequent branches of the afferent arterioles become peritubular capillaries to nourish the tubules. Peritubular capillaries receive reabsorbed fluids and solutes from tubular cells before rejoining to form venules. Peritubular vessels of juxtamedullary glomeruli are known as vasa recta and accompany the loops of Henle deep into the medulla. The venous system of the kidney runs parallel and close to the arterial vasculature, finally returning blood to the inferior vena cava through the *renal vein.* Vascular supply to the kidney is strictly segmental, and embolic arterial or venous obstruction affects renal tissue in a pizza wedge parenchymal distribution involving all cortical and medullary tubular elements of affected nephrons.

Medullary hypoxia is a key concept that refers to the low oxygen levels that exist in the renal medulla, even during normal resting conditions. Sodium and water reabsorption depend on the hypertonicity of the medullary interstitium. The countercurrent multiplier system in the loop of Henle is a critical component of the kidney's ability to excrete or conserve salt and water.

The apparent overabundance of blood flow to the cortex is designed to maximize flow-dependent functions, such as glomerular filtration and tubular reabsorption. In the medulla, blood flow and oxygen reserve are restricted by a tubulovascular anatomy specifically designed for urinary concentration. The tubules carrying blood to the medulla are arranged in a hairpin-loop pattern to allow a countercurrent exchange of solute between the ascending and descending limbs of the hairpin loop.[26] The osmotic gradient in the deeper portions of the medulla requires active transport of sodium in the thick ascending loop of Henle and limited blood flow through the medullary vessels to prevent washout of the solutes in those deeper tubules. To maintain this concentration gradient in the thick ascending limb, high-energy demand (i.e., active sodium transport) must be coupled with low-oxygen delivery.

Factors necessary to allow countercurrent exchange and to create a urea gradient conspire to make normal medullary partial pressure of oxygen ($Po_{2)}$ very low (e.g., 10 to 20 mm Hg); these include high oxygen demand from active solute transport and sluggish blood supply (5% to 10% of RBF). Average blood flow is 5 mL/g/min and .03 mL/g/min for the cortex and medulla, respectively, and the oxygen extraction ratio (i.e., oxygen consumption over oxygen delivery) is 0.18 and 0.79 for the cortex and medulla, respectively. The descending vasa recta are vasoactive arteriolar microvessels that are anatomically positioned to regulate total and regional blood flow to the outer and inner medulla.[26] Normally, the Po_2 is approximately 50 mm Hg in the cortex and 8 to 15 mm Hg in the medulla, making the thick ascending loop of Henle most vulnerable to tissue hypoxia.[27] This precarious arrangement underpins some of the specialized homeostatic abilities of the kidney, particularly the formation of concentrated urine, but it

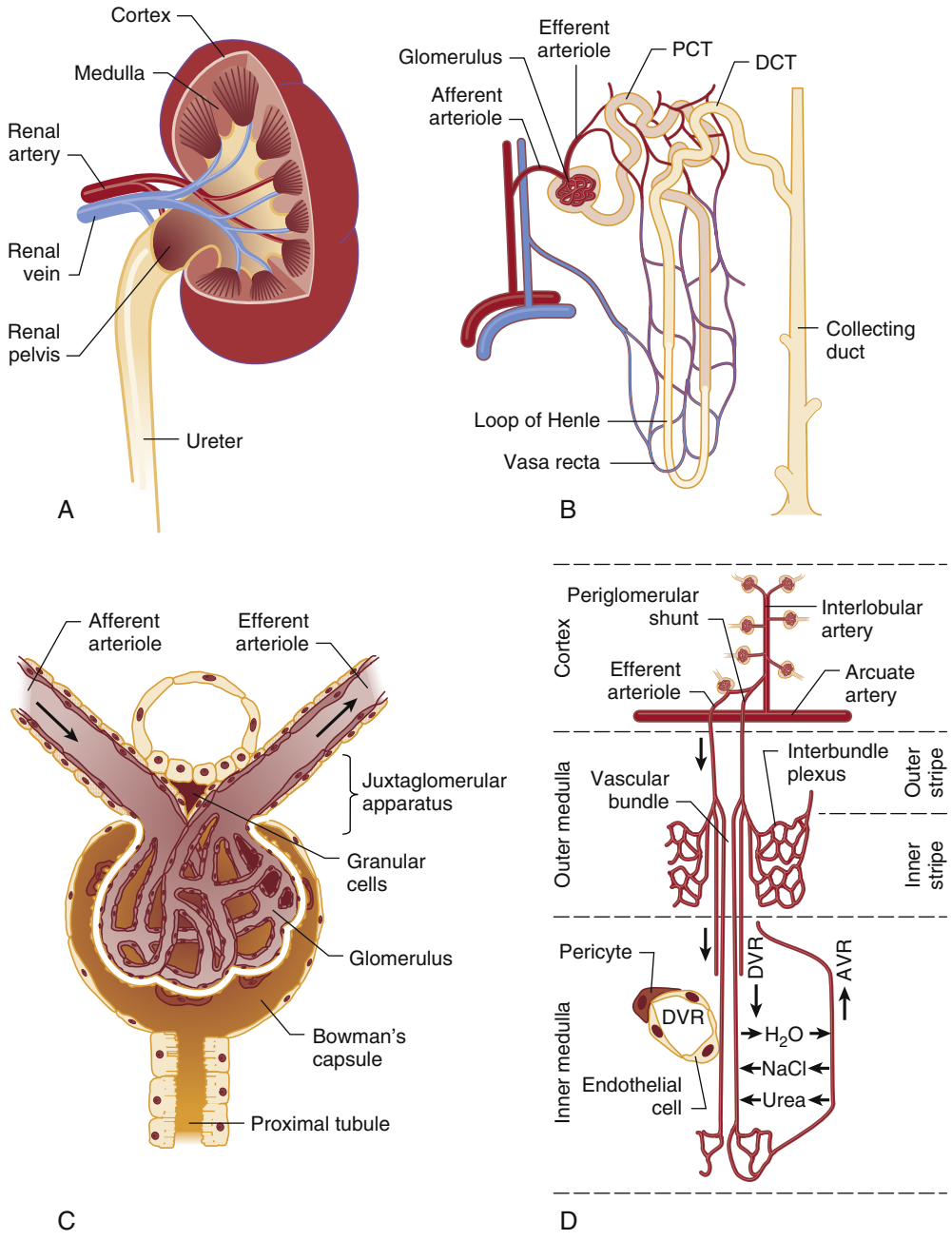


Figure 52-3. A, The internal structure of the kidney includes the vasculature, cortex and medulla regions, and urinary tract structures. **B,** The functional unit of the kidney is the nephron. **C,** The glomerulus is the site where plasma filtration occurs; approximately 20% of plasma entering the glomerulus will pass through the specialized capillary wall into the Bowman capsule and enter the tubule to be processed and to generate urine. **D,** The vascular anatomy of the kidney is highly organized, and the medullary microcirculation is part of the mechanism that permits countercurrent exchange.[41] *AVR,* Ascending vasa recta; *DCT,* distal convoluted tubule; *DVR,* descending vasa recta; *NaCl,* sodium chloride; *PCT,* proximal convoluted tubule. *(**A,** From* http://www.nida.nih.gov/consequences/kidney/ *Accessed February 17, 2008.* **B,** *From* <http://cnx.org/content/m44809/1.8/>. *(Accessed 24.02.14.)* **C,** *From* <http://www.cixip.com/index.php/page/content/id/422/>. *<Accessed 26.06.14.)* **D,** *From Pallone TL, Zhang Z, Rhinehart K: Physiology of the renal medullary microcirculation,* Am J Physiol Renal Physiol *284:F253-F266, 2003. Used with permission.)*

also underlies the extreme vulnerability of the renal medulla to ischemic injury[28]; that is, the high metabolic requirement of the thick ascending loop of Henle in a hypoxic environment makes it especially vulnerable to injury associated with an imbalance in oxygen supply and demand.[29,30]

NORMAL FUNCTION

The resting kidney continuously regulates body composition by processing plasma filtrate to keep fluid volume, osmolarity, acidity, and numerous electrolytes within narrow limits. Every 3 minutes a plasma volume equivalent to a 12-ounce soft drink is filtered, and all but 1%

(4 mL) is returned to circulation; the remnant is urine. Tightly regulated through tubular processing are extracellular solutes, including sodium, potassium, hydrogen ion, bicarbonate, and glucose. The kidney also generates ammonia and eliminates metabolic and nitrogenous wastes, including creatinine, urea, and bilirubin, as well as toxins and many classes of drugs. Finally, the kidneys generate glucose and secrete circulating hormones that influence erythrocyte generation, systemic blood pressure, and calcium homeostasis.

High concentrations of aldosterone stimulate the reabsorption of sodium and water, primarily in the distal tubule and collecting ducts. Aldosterone is produced by the adrenal cortex in response to the feedback from the renin-angiotensin-aldosterone system, simplified as follows. Reduced delivery of sodium to the macula densa causes release of renin from the granular cells of the juxtaglomerular apparatus. Renin catalyzes the release of angiotensin I from angiotensinogen. Angiotensin I is then transformed to angiotensin II in the lungs, catalyzed by angiotensin-converting enzyme. Angiotensin II stimulates the production of aldosterone.

Antidiuretic hormone (ADH, vasopressin) primarily acts on the collecting ducts to increase water reabsorption. ADH is released from the posterior pituitary gland in response to increased blood osmolarity, which stimulates osmoreceptors in the hypothalamus. ADH release is also influenced by stress and increased partial arterial pressure of carbon dioxide ($Paco_2$).[31] A high level of ADH results in the excretion of small volumes of concentrated urine. ADH is inhibited by the stimulation of atrial baroreceptors or increased atrial volume.[32]

Atrial natriuretic peptide (ANP) causes systemic vasodilation and promotes renal excretion of sodium and water by increasing glomerular filtration.[33] ANP is secreted by the cardiac atria and other organs in response to increased intravascular volume. It decreases systemic blood pressure by relaxing vascular smooth muscle, reducing sympathetic stimulation, and inhibiting the renin-angiotensin-aldosterone system. The kidney also synthesizes prostaglandins, which regulate the influence of other hormones. During hemodynamic instability and increased adrenergic stimulation, for example, prostaglandin E_2 decreases the vasoconstrictive effect of angiotensin II on the afferent arterioles and preserves RBF. Inhibition of prostaglandin synthesis during normal states of hydration, renal perfusion, and sodium balance does not affect renal function. When the kidney is confronted with a vasoconstricted state, such as hypotension and hypovolemia, however, the presence of renal prostaglandins is essential for preserving adequate RBF. Patients taking nonsteroidal antiinflammatory drugs (NSAIDs) are at risk during conditions of impaired circulatory status because these agents inhibit cyclooxygenase activity, an important enzyme in the prostaglandin synthesis pathway, thereby rendering the kidney (afferent arteriole) susceptible to the systemic vasoconstrictive effect of angiotensin II and other catecholamines normally secreted to preserve intravascular volume and perfusion pressure.

Interaction among the urinary bladder, the kidney, and the ureters influences urine production.[34] General anesthesia decreases the rate of ureteral contractility.[35] The autonomic nervous system also plays an important role in ureteral function and, consequently, in urine formation.[34] Cholinergic agonists generally increase the frequency and force of ureteral contraction. Drugs that primarily act on adrenergic receptors tend to stimulate ureteral activity, whereas agents that primarily activate adrenergic receptors tend to inhibit ureteral activity. Histamine stimulates ureteral activity. In a variety of preparations, morphine increases ureteral tone. In humans, irregular peristaltic contractions may occur with retroperitoneal inflammation resulting from appendicitis and peritonitis.[36]

A gross summary of plasma processing by the kidney involves glomerular filtration (approximately 120 mL per minute); subsequently, up to two thirds of the water and electrolytes are quickly returned to the circulation through active transport processes by the proximal convoluted tubule. Two thirds of the remaining tubular contents are more sluggishly reabsorbed in the loop of Henle and distal convoluted tubule. Finally, more water is reabsorbed from the remaining effluent in the collecting ducts (5 to 10 mL per hour) as it passes to larger urine collecting structures (1 to 2 mL per minute).

PATHOPHYSIOLOGIC PROCESSES OF ISCHEMIC ACUTE KIDNEY INJURY

In general, the causes for AKI can be divided into prerenal, intrinsic renal, and postrenal sources. In the perioperative setting, patients may be at increased risk for prerenal AKI, either attributable to volume depletion or to exacerbation of associated chronic prerenal physiologic conditions, such as congestive heart failure, which may be exacerbated by volume overload. Depending on the nature of the surgical procedure, the patient may also be at increased risk of postrenal AKI attributable to obstruction of the ureters, bladder, or urethra. However, the primary cause of perioperative AKI is *acute tubular necrosis* (ATN). Although the focus of this chapter is on renal hemodynamics, defining the cause of AKI is also critical because treatment of the underlying cause is critical for the reversal of AKI and potential renal recovery.

The two primary mechanisms of ATN are ischemia-reperfusion and nephrotoxic effects, with three sources of insult common to many surgical procedures during which postoperative AKI is prevalent: hypoperfusion, inflammation, and atheroembolism. Other sources of renal insult in selected patients may include rhabdomyolysis and specific drug-related effects. Certain classes of medications may also contribute to hypoperfusion by virtue of their hemodynamic effects (notably angiotensin-converting enzyme [ACE] inhibitor 1, angiotensin-receptor blockers [ARBs], and NSAIDs), and, consequently, the risk of ATN.

Ischemic renal failure related to shock or severe dehydration is always preceded by an early compensatory phase of normal renal adaptation (e.g., pre-prerenal failure), followed by a condition termed *prerenal azotemia* during which the kidney maximizes activities at the expense of the retention of nitrogenous end-products to preserve the internal environment through extreme retention of solutes and water (Fig. 52-4). In studies of community-acquired

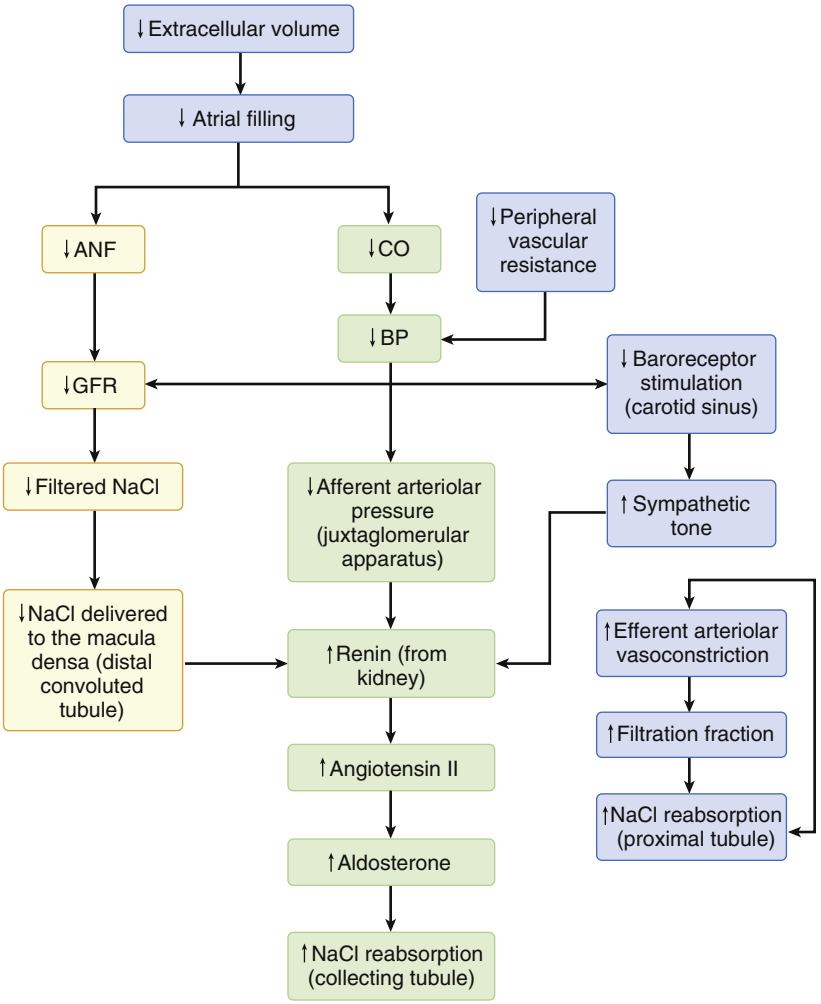


Figure 52-4. Mechanism for renal sodium and volume regulation in response to decreased extracellular volume (e.g., hypovolemia, hemorrhage). *ANF,* Atrial natriuretic factor; *BP,* blood pressure; *CO,* cardiac output; *GFR,* glomerular filtration rate; *NaCl,* sodium chloride.

AKI, the incidence of prerenal azotemia may be as frequent as 70%.[37] In contrast, in a classic study of hospital-acquired AKI, although hypoperfusion accounted for 42% of cases of AKI, only 41% of these cases of hypoperfusion were attributable to inadequate intravascular volume.[38] Although prerenal azotemia is ominous and typically accompanied by oliguria (<0.5 mL/kg/hr), it is reversible. At a critical tilting point, as conditions go beyond the compensatory mechanisms that maintain renal perfusion, ischemia leads to irreversible renal cell necrosis or ATN.[39] This represents the pure form of ischemic AKI. Other forms of ATN are due to toxins, including medications (e.g., aminoglycosides, cisplatinum), pigments (e.g., hemoglobin, myoglobin), and contrast dye. These forms of ATN do not involve the typical pattern of preceding prerenal azotemia with associated oliguria, since the insult is sudden. Importantly, most cases of perioperative AKI are the result of numerous renal insults, rather than being attributable to one pure source (Fig. 52-5). Thus patients with prerenal azotemia are likely at increased risk for toxic ATN.

Interruption of blood flow to the kidneys for more than 30 to 60 minutes results in ATN and irreversible cell damage. The kidneys receive 1000 to 1250 mL per minute of blood or 3 to 5 mL/min/g of tissue for the average adult, and this amount far exceeds what is needed to provide the kidney's intrinsic oxygen requirement. Intracortical blood flow may not be evenly distributed (see Fig. 52-3).[24] Because the renal cortex contains most of the glomeruli and depends on oxidative metabolism for energy, ischemic hypoxia injures the renal cortical structures, particularly the pars recta of the proximal tubules. As ischemia persists, the supply of glucose and substrates continues to decrease; glycogen is consumed, and the medulla, which depends to a great extent on glycolysis for its energy sources, becomes more adversely affected. Early cell changes are reversible, such as the swelling of cell organelles, especially the mitochondria. As ischemia progresses, a lack of adenosine triphosphate interferes with the sodium pump mechanism, water and sodium accumulate in the endoplasmic reticulum of tubular cells, and the cells begin to swell. Onset of tubular damage usually occurs within 25 minutes of ischemia as the microvilli of the proximal tubular cell brush borders begin to change. Within an hour, they slough off into the tubular lumen, and membrane bullae protrude into the straight portion of the proximal tubule. After a few hours, intratubular pressure rises, and tubular fluid passively backflows. Within 24 hours, obstructing casts appear in the distal tubular lumen. Even when RBF is completely restored after 60 to 120 minutes of ischemia, long-lasting vasoconstriction means that the GFR will not improve to baseline levels for a long time.[40]

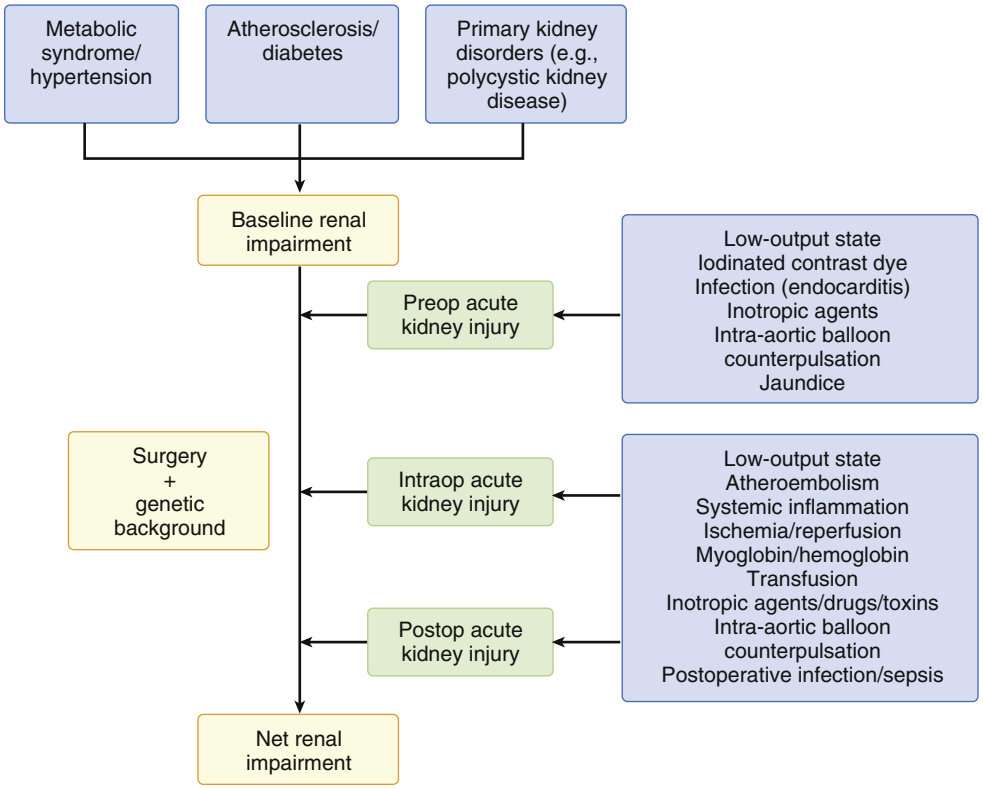


Figure 52-5. Perioperative clinical risk factors associated with postoperative kidney injury.

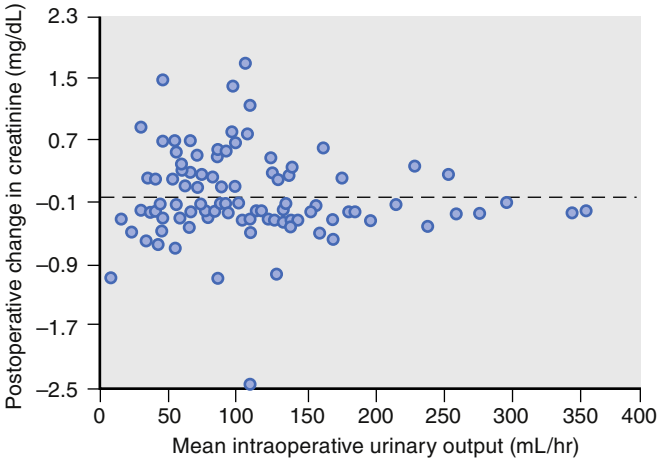


Figure 52-6. Low urine flow (<0.5 mL/kg/hr) is a marker in new diagnostic criteria for acute kidney injury (AKI) but may not be a meaningful assessment to make this diagnosis during the immediate perioperative period. In this study, intraoperative urine output does not correlate with postoperative change in serum creatinine after aortic surgery. *(From Alpert RA, Roizen MF, Hamilton WK, et al: Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization,* Surgery *95:707-711, 1984. Used with permission.)*

ANESTHESIA, SURGERY, AND NORMAL RENAL FUNCTION

Notably, the importance of oliguria (<0.5 mL/kg/hr) as a predictor of AKI is less well established in the perioperative setting than in other clinical settings (Fig. 52-6).[41,42] Anesthesia and surgery influence normal renal function primarily through changes in the GFR. Fluctuations in blood pressure have a major effect on RBF and glomerular filtration.[43-45] Anesthetic interventions, whether volatile anesthetics, intravenous drugs, or regional blocks, generally reduce arterial blood pressure and cardiac output, thereby diminishing RBF, leading to decreased glomerular filtration and urine formation.[46] Commonly used premedications can influence urine output. Narcotics and barbiturates, for example, cause a small decrease in the GFR and urine volume.

Surgical and anesthetic interventions may have autonomic consequences, such as increasing circulating catecholamines, which also reduce glomerular filtration by altering renal vascular resistance, and decreasing RBF. The normal physiologic function of the kidney includes a role of adrenergic receptors in modulating vasoconstrictor (alpha 1) and vasodilating (alpha 2) effects, respectively. Urine output may also be affected in the perioperative setting by changes in circulating ADH levels, especially during neurosurgical procedures (also see Chapter 70).

REGIONAL ANESTHESIA

Regional anesthetics and the kidneys interact in a complex manner that varies according to the underlying cardiovascular, renal, fluid, and electrolyte status of the patient (also see Chapters 56 and 57).[47] In general, epidural and spinal anesthesia reduce systemic and renal vascular sympathetic tone.[47] Spinal cord segments T4 through L1 contribute to the sympathetic innervation of the renal vasculature, which is mediated by sympathetic fibers from the celiac and renal plexus.[48,49] Autonomic blockade above the fourth thoracic level also blocks

cardioaccelerator sympathetic innervation to the heart. If neuraxial blockade reduces arterial blood pressure and cardiac output, then the RBF will be decreased with matching reductions in glomerular filtration and urine output. In studies of healthy volunteers undergoing epidural anesthesia with a T6 sensory block, Suleiman and colleagues[50] demonstrated that RBF is unchanged during the conditions of their study. Specifically, mean arterial pressure remained above 70 mm Hg, and RBF never decreased less than 6% of the baseline level.

Urine volume and free-water clearance may decrease during spinal anesthesia as a result of increased ADH secretion. Increased renal sympathomimetic activity decreases RBF through α-adrenergic mediation and increases renin release through β-adrenergic innervation directly or by interaction with the renal tubular macula densa and the baroreceptor reflex mechanism.[51] Thoracic epidural anesthesia increases RBF and urine output in animal models of endotoxic shock.[52]

Although controversial, intraoperative neuraxial blockade and postoperative epidural analgesia decrease rates of AKI. Rodgers and colleagues conducted a systematic review of 107 randomized clinical trials of intraoperative neuraxial blockade and demonstrated a 30% reduction in the odds of postoperative mortality.[53] This reduction was associated with decreases in the incidence of deep venous thrombosis, pulmonary embolism, transfusion, pneumonia, and respiratory depression, as well as renal failure, although the confidence limits for the renal failure estimates were very wide, in part due to the small number of cases of renal failure observed. Moraca and associates[54] conducted a meta-analysis and reported on the association of thoracic epidural anesthesia with improved surgical outcomes attributable, in part, to a reduction of perioperative morbidity, including blunting of stress response, attenuating infections, reduced ileus, reduced blood loss, and reduction in AKI.[54] Other studies have examined the impact of epidural anesthesia during cardiac surgery and have suggested a benefit with regards to renal failure, although the confidence intervals were wide[55] (also see Chapter 67). Unfortunately, renal failure was not an outcome of a recently published meta-analysis focused on epidural anesthesia during cardiac surgery.[56] Finally, with regards to postoperative analgesia, a recent Cochrane meta-analysis that focused on abdominal aortic surgery suggested a decreased incidence of perioperative AKI and other complications with epidural analgesia but no effect on postoperative mortality.[57]

EFFECTS OF INHALED ANESTHETICS

From an historic perspective, a nephrotoxic effect can be caused by older volatile inhaled anesthetics attributable to the liberation of inorganic fluoride when they are metabolized (also see Chapter 26).[58] Methoxyflurane (no longer clinically used) and enflurane when used for prolonged periods, lead to significant generation of inorganic fluoride.[40,58-60] Increased serum levels of inorganic fluoride were associated with polyuric renal insufficiency.[58,59] Approximately 100 published cases of renal failure and 20 renal-related deaths attest to the significance of methoxyflurane-related nephrotoxicity.[58]

Because sevoflurane metabolism is similar to enflurane in regards to the liberation of free fluoride ions,[61-63] does this anesthetic impair the ability of the kidneys to concentrate urine?[64] Methoxyflurane studies indicated that AKI was likely to occur with circulating fluoride levels more than 50 μm/L.[58] This presumed toxic threshold was extrapolated to the study of other volatile anesthetics. However, 43% of volunteers receiving sevoflurane had plasma fluoride levels that exceed 50 μm/L. Healthy patients receiving 9 minimum alveolar concentration (MAC) hours of sevoflurane anesthesia have serum fluoride levels averaging 36.6 ± 4.3 μm/L.[65] Relative to methoxyflurane, high fluoride levels with sevoflurane are short-lived, peaking 2 hours after the end of anesthesia and decreasing by 50% within 8 hours. Despite high fluoride levels with sevoflurane, volunteers have no impairment in their ability to concentrate urine in response to desmopressin, whereas 20% of volunteers receiving enflurane have transient concentrating deficits on day 1 but not day 5 after exposure.[65] To interpret these findings, investigators postulate that intrarenal production of fluoride ion may be more important for nephrotoxicity than circulating plasma fluoride levels.[63] The intrarenal metabolism of methoxyflurane is fourfold greater than that of sevoflurane.

Other explanations for the differences in the renal effects of volatile anesthetics were sought, including an evaluation of variation in nephrotoxic compounds generated when an inhaled anesthetic interacts with carbon dioxide absorbents. In breathing circuit systems at a high temperature and low flow rates, carbon dioxide absorbents degrade sevoflurane, creating fluoromethyl-2,2-difluoro-1-(trifluoroethyl) vinyl ether, also known as compound A. Metabolism of compound A occurs via conjugation in the liver with glutathione and then modification in the kidney by an enzyme (cysteine-S-conjugate β-lyase). Some compound A metabolites can cause renal injury, characterized by diuresis, glycosuria, proteinuria, and increased serum BUN and creatinine levels. AKI by this mechanism in experimental models is a function of the degree and duration of exposure to compound A,[66] with well-defined exposure thresholds in rats for injury (50 to 114 parts per million [ppm] for 3 hours) and death (331 for 3 hours, 203 for 6 hours, or 127 ppm for 12 hours).[67] However, a disparity exists between the results in rats and humans that may be due to differences in compound A processing; of the four recognized pathways for metabolism, three do not involve renal β-lyase or result in kidney toxicity. Humans have 10- to 30-fold less renal β-lyase enzyme activity compared with rats, which may account for the absence of kidney injury from sevoflurane in humans. One study[67] compared the safety of low-flow sevoflurane and isoflurane anesthesia in patients having prolonged surgeries (>6 hours). The average MAC hours in both groups was similar, and the average compound A concentration in the sevoflurane group was 20 ± 7 ppm. Markers of renal injury, including BUN, creatinine, *N*-acetyl-β-d-glucosaminidase (NAG), and alanine aminopeptidase, were similarly increased in all groups during the prolonged exposure to the volatile anesthetics.

The likely concentrations of compound A possible with sevoflurane during anesthesia have been studied

in human volunteers.[68] Fresh carbon dioxide absorbent was used, and 1.25 MAC sevoflurane was administered (without nitrous oxide) for 8 hours. Compound A levels approached 50 ppm, and 24-hour urine collections were analyzed for 3 consecutive days after exposure. Urinary glutathione S-transferase (GST) and other highly sensitive markers of tubular damage after nephrotoxic and ischemic insults were measured.[69] The investigators reported transient increases of urinary protein, albumin, glucose, α-GST, and π-GST in patients receiving sevoflurane. No such increases were observed after similar exposure to desflurane. A multicenter study[70] involving 73 elective surgical procedures lasting 2 to 8 hours compared the safety and efficacy of low flow (<2 L/min) sevoflurane to isoflurane. Fresh carbon dioxide absorbent was used for all cases, and nitrous oxide was not permitted. Sevoflurane use averaged 3.6 MAC hours, and compound A levels were as high as 223 ppm (mean 79 ± 54 ppm). No differences were found in urine albumin, glucose, protein, or osmolality between treatment groups. Moreover, within the sevoflurane group, no significant correlations were observed between compound A levels and BUN; creatinine; or urinary excretion of protein, glucose, NAG, α-GST, or π-GST.

Despite the fact that 7% to 15% of patients receiving sevoflurane may have (short-lived) circulating levels of fluoride in excess of 50 μm/L and/or significant exposure to compound A, adverse renal effects do not seem to occur.[58] Although the explanation for the apparent safety of sevoflurane in the presence of nephrotoxins is not completely understood, some have proposed that the source of methoxyflurane-related renal injury may be some other metabolic "villain" than fluoride or compound A that is unique to methoxyflurane metabolism, such as dichloroacetic acid.[71] Finally, potential benefits of sevoflurane to the kidney have been described. In a small study of patients undergoing cardiac surgery, preconditioning with sevoflurane decreased biochemical markers for renal (and myocardial) dysfunction.[72]

EFFECTS OF INTRAVENOUS ANESTHETICS

Propofol and dexmedetomidine may have antiinflammatory effects that are renoprotective. Propofol increases production of bone morphogenetic protein–7 (BMP-7), which suppresses the tumor necrosis factor (TNF) α–induced inflammatory cascade during sepsis-induced AKI,[73,74] as well as decreased injury during ischemia-reperfusion[75-77] and unilateral ureteral obstruction.[78] Similarly, in addition to altering RBF and sodium and water handling, the α_2-adrenoreceptor agonists such as dexmedetomidine may stimulate BMP-7 production. In a rat kidney renal tubular epithelial cell line exposed to lipopolysaccharide, dexmedetomidine increased the expression of BMP-7 and decreased the expression of inflammatory cytokines and histone deacetylases 2 and 5, resulting in improved cell survival.[79] In the same study, septic mice treated with dexmedetomidine had a longer survival time and a decreased incidence of AKI in a cecal-ligation and perforation model. Similar benefits have been observed in studies of ischemia-reperfusion injury in rats[80] and mice.[81] However, further studies in humans are needed to determine whether either of these anesthetics has renal benefits in the perioperative or critical care settings.

PERIOPERATIVE HEMODYNAMIC INSTABILITY AND RENAL FUNCTION

To comprehend the impact of perioperative hemodynamic instability on renal function, the complex pathogenesis of hemodynamically mediated AKI needs to be understood. Although an extreme reduction in RBF is necessary,[19] the unpredictable degree of AKI after hypotension suggests that it is not always sufficient. Even with decreased glomerular perfusion, a series of compensatory mechanisms can still preserve renal filtration.[58] Salt and water retention can restore intravascular volume and fractional tubular reabsorption. At a given level of cardiac output, intrarenal factors affect the ratio of renal-to-systemic vascular resistance, thereby influencing the fraction of cardiac output received by the kidneys. At the glomerular capillary, plasma is separated into a protein-free ultrafiltrate and a nonfiltered portion. Normally, the filtration fraction (i.e., relationship of glomerular filtration to renal plasma flow) is approximately 0.2. Initially, the filtration fraction is maintained by efferent arteriolar constriction. However, if unabated, the mechanisms that influence efferent arteriolar vasoconstriction may ultimately influence afferent arteriolar vasoconstriction. The resulting decrease in filtration fraction is the hallmark of postischemic AKI.[58] Ischemic tubular damage may be further exacerbated by an imbalance between oxygen supply and demand. Most vulnerable to the imbalance are the thick ascending tubular cells of the loop of Henle in the medulla.[30]

Cortical blood flow decreases in ischemic models of AKI.[82] Because 85% to 90% of RBF is normally distributed to cortical glomeruli, the finding of cortical pallor and RBF redistribution away from cortex suggests that redistribution may contribute to the functional lesions of AKI. In some cases, the return of perfusion to the cortex has correlated with a return of renal function.[82] The theory that intrarenal distribution of blood flow away from the outer cortex to the inner medulla decreases oxygen supply while increased tubular reabsorption of solute increases oxygen demand is further supported by studies of renal energetics during AKI.[83,84] A decrease in the glomerular filtration, and consequently in the energy requirement for tubular reabsorption, may be a mechanism by which the kidney reduces energy demands before energy supply is critically limited.

OTHER PERIOPERATIVE PERTURBATIONS AND RENAL FUNCTION

Several surgical interventions can affect RBF and, consequently, renal function. Whereas aortic cross-clamping above the renal arteries has obvious influence on glomerular filtration, infrarenal aortic cross-clamping and unclamping also have significant indirect effects on glomerular filtration and urine formation through changes in myocardial function, sympathetic activity, neuronal and hormonal activity (e.g., renin and angiotensin

production), intravascular volume, and systemic vascular resistance[85](also see Chapter 69). During standard cardiopulmonary bypass (CPB) surgery, cardiorenal relationships are approximately as expected; RBF decreases to 12% to 13% of total pump flow and is predicted by flow rate and perfusion pressure; however, only mean pressure correlates with urine output.[43,44] The intactness of myogenic and tubular-glomerular autoregulatory feedback has not been evaluated during CPB[22,23] (also see Chapter 67).

AKI after aortocoronary bypass surgery continues to be a devastating complication that is associated with multiorgan dysfunction, increased resource utilization, high cost, and increased mortality (see Chapters 67 and 69). Annually, approximately 800,000 patients worldwide undergo coronary artery bypass graft (CABG) surgery. In a recent multicenter observational study focused on AKI after cardiac surgery, 5% of participants developed AKI as defined by the need for acute dialysis or a doubling of serum creatinine from baseline.[4] The mechanism of perioperative AKI during cardiac surgery is multifactorial. Significant risk factors for AKI include underlying patient characteristics, such as age older than 75 years, history of diabetes, hypertension, pulse pressure, ventricular dysfunction, myocardial infarction, renal disease (also see Chapters 39 and 80), perioperative medication exposures (e.g., aprotinin, hetastarch), and surgical characteristics such as intraoperative use of multiple inotropes, insertion of intraaortic balloon pump, and extended duration of the CPB surgery.[86-90] Preoperative pulse pressure (systolic minus diastolic) more than 40 mm Hg has a clear relationship with renal risk—an odds ratio of 1.49 (confidence interval [CI], 1.17 to 1.89; $P = .001$) was added for every additional 20 mm Hg increment in pulse pressure.[86]

The role of CPB surgery in postoperative AKI remains controversial. In their comprehensive guidelines on AKI, KDIGO reviewed the literature on postoperative AKI between patients undergoing off-pump and on-pump coronary revascularization surgeries and ultimately recommended that "off-pump CABG surgery not be selected solely for the purpose of reducing perioperative AKI or need for RRT [renal replacement therapy]."[16] However, patients with chronic kidney disease, who are at the highest risk for AKI after CPB surgery, have often been excluded from randomized clinical trials of off-pump versus on-pump CABG. For example, in the Randomized On/Off Bypass (ROOBY) trial, in which 2303 patients were randomized to off-pump versus on-pump CABG, approximately 7.5% of patients had a preoperative serum creatinine level ≥1.5 mg/dL.[91]

However, a large observational study of 742,909 nonemergent, isolated CABG cases (including 158,561 off-pump cases) from the Society of Thoracic Surgery Database suggests a benefit to off-pump CABG in those with chronic kidney disease.[92] Propensity methods were used to adjust for patient- and center-level imbalances. The primary endpoint was death or dialysis. In those with lower estimated GFR (eGFR), the risk difference (i.e., number of patients with the outcome per 100 patients in those who underwent CPB minus the number with the outcome in those who underwent off-pump CABG) for the primary endpoint was 0.66 (95% CI, 0.45 to 0.87) for eGFR 30 to 59 mL/min/1.73 m^2 and 3.66 (95% CI, 2.14 to 5.18) for eGFR 15 to 29 mL/min/1.73 m^2. Both component endpoints followed the same trend. Highlighting the importance of chronic kidney disease as a risk factor for AKI after cardiac surgery, whereas slightly less than 1% of the overall cohort received dialysis after cardiac surgery, 2% of those with eGFR 30 to 59 mL/min/1.73m^2 and 12.5% of those with eGFR 15 to 29 mL/min/1.73m^2 required dialysis. The risk difference for dialysis alone in the same groups was 0.47 (95% CI, 0.31 to 0.62) and 2.79 (95% CI, 1.37 to 4.20) with on-pump versus off-pump CABG, respectively (Fig. 52-7). Thus, this study suggests that in those with advanced chronic kidney disease, there may be a benefit to off-pump surgery, but further studies are needed.

Finally, several genetic polymorphisms known to affect inflammation and vasoconstriction demonstrate strong associations with AKI after cardiac surgery.[93] Polymorphisms identified as relevant include the interleukin (IL)–6 572C and angiotensinogen 842C polymorphisms as a predictor of an approximately fourfold greater than the average peak creatinine rise after coronary revascularization. Such polymorphisms may have potential as a preoperative screening tool if validated in other populations and highlight the potential feasibility of such an approach. Thus in the future, the underlying genetic risk may also be assessed as a measure of the risk of perioperative AKI.

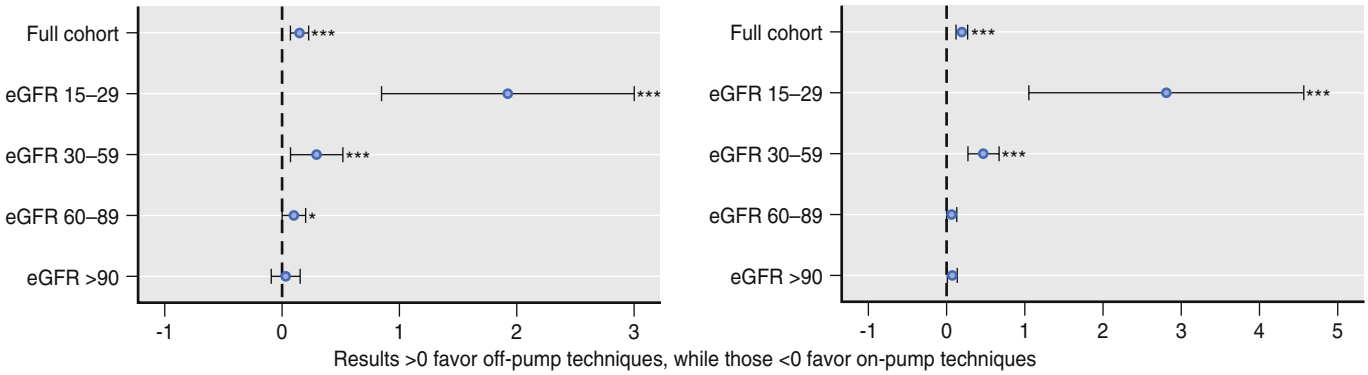


Figure 52-7. Estimates of adverse outcomes associated with on-pump versus off-pump coronary artery bypass grafting (CABG) by baseline estimated glomerular filtration rate (eGFR). For both mortality *(left panel)* and renal replacement therapy (RRT) *(right panel)*, off-pump CABG techniques appear to confer a benefit in those with lower eGFR. *P <0.05, **P <0.01, ***P <0.001. *(Redrawn from Chawla LS, Zhao Y, Lough FC, et al: Off-pump versus on-pump coronary artery bypass grafting outcomes stratified by preoperative renal function,* J Am Soc Nephrol *23:1389-1397, 2012.)*

MONITORS OF RENAL FUNCTION

In patients with perioperative AKI, one of the major challenges to optimal perioperative management and early intervention has been the inability to detect early onset, subtle AKI. Monitoring tools for traditional renal failure are typically insensitive until less than 40% of normal functioning nephrons remain (Fig. 52-8), which leaves only a small margin of renal function before symptoms are apparent.[39] Furthermore, late recognition of AKI allows little opportunity for the treatment of AKI.

Consensus criteria to define AKI are typically used in most studies of perioperative AKI. However, large blood volume loss and fluid shifts, which may artificially dilute serum creatinine, make these criteria sometimes questionable. Furthermore, the use of consensus urine output criteria in this context is unknown. Unlike the postoperative or critical care setting where renal monitoring can involve periodic evaluation of kidney function under relatively stable conditions, intraoperative renal monitoring involves a more brief unstable period, often involving significant blood loss, major fluid shifts, wide hemodynamic fluctuations, and even direct compromise to renal artery blood flow.

Therefore the anesthesia provider is likely the first monitor (i.e., in a sense) required for preserving renal function by recognizing and treating factors that may contribute to or exacerbate AKI; for example, the toxic effects of aminoglycosides and iodinated contrast materials are exacerbated by intravascular volume depletion. Furthermore, the anesthesia provider often relies on indirect variables, such as urine volume, to assess renal perfusion. Unfortunately, urine output does not reliably reflect glomerular filtration and renal function under intraoperative conditions. Even knowledge of RBF is not, in and of itself, particularly informative because increased flow mandates increased filtration and active transport demands, as well as increased oxygen delivery. A monitor of balanced supply and demand of regional renal perfusion, particularly in the renal medulla, would be an ideal, although currently unavailable, direct monitoring tool.

The best tools currently available intraoperatively are indirect hemodynamic monitors that can assist in optimizing conditions consistent with kidney well-being, such as ensuring adequate intravascular volume (i.e., preload), cardiac performance, and systemic perfusion. Serum chemistries and urinary indices may enable the assessment of adequate distribution of cardiac output to the kidneys themselves.

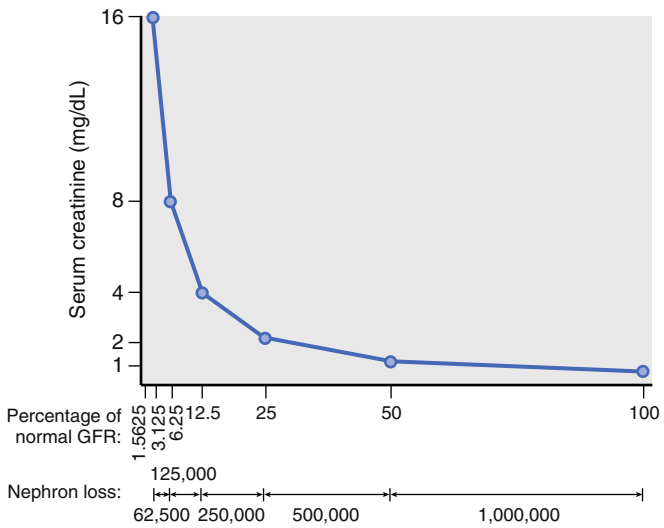


Figure 52-8. The inverse logarithmic relationship between serum creatinine concentration (*y* axis) and relative reductions in glomerular filtration rate (GFR) and approximate nephron loss (*x* axis) is shown. The nonlinear relationship means that the serum creatinine level is not significantly increased until a 75% reduction in GFR (e.g., 120 to 30 mL/min) occurs. *(Modified from Faber MD, Kupin WL, Krishna G, et al: The differential diagnosis of ARF. In Lazarus JM, Brenner BM, editors:* Acute renal failure*, ed 3. New York, 1993, Churchill Livingstone, p 133.)*

INDIRECT MARKERS OF OPTIMAL RENAL PERFUSION AND FUNCTION

Intravascular volume depletion, which commonly occurs in fasting patients undergoing surgery, is a risk factor for AKI. For example, the combination of diabetes mellitus and intravascular volume depletion increases the chance of developing AKI by 100-fold.[94] The most practical preoperative methods to assess volume status are with preoperative patient history and physical examination and by assessing changes in arterial blood pressure in response to changing conditions and dynamic maneuvers. For example, an awake patient normally does not have significant orthostatic changes in arterial blood pressure unless an autonomic or intravascular volume deficit exists. During anesthesia, a similarly dehydrated patient may demonstrate paradoxical arterial pulse changes with positive-pressure inspiration.

OXYGEN DELIVERY: BLOOD GAS, ACID-BASE BALANCE, AND HEMATOCRIT

Severe arterial hypoxemia to a partial arterial pressure of oxygen (Pao_2) value of less than 40 mm Hg is associated with decreased RBF and renal vasoconstriction.[95,96] Capnometry may be a useful monitor because hypercarbia has been associated with decreased RBF in patients requiring mechanical ventilation.[97] Inequalities in oxygen supply demand are exaggerated and medullary hypoxia is extreme during CPB, effects that last well beyond separation from circulatory support[69] (also see Chapter 67).

The effects of anemia on the kidney have been studied mostly in the context of CPB management. When crystalloid and colloid solutions are used to prime an extracorporeal circuit, the initiation of CPB surgery obligates an acute decrease of approximately 30% in oxygen-carrying capacity. Animal studies endorse moderate hemodilution (hematocrit 20% to 30%) as renoprotective during CPB surgery through a reduction of blood viscosity and improved regional blood flow.[98] However, although hematocrit values less than 20% during CPB surgery are commonly accepted clinically (extreme hemodilution), very low hematocrit values are linked with adverse outcomes, including AKI.[99-103] The solution may not be as simple as transfusion because blood transfusions themselves have

been linked to AKI. In a systematic review, Karkouti found 22 studies that examined the association between blood transfusions and AKI postcardiac surgery.[104] An independent association between transfusions and AKI was found in 18 of the 22 studies. The association of perioperative anemia with AKI was further examined in 14 studies, and 9 of the studies found an independent association of perioperative anemia with AKI. Proposed mechanisms for transfusion-associated AKI include exacerbation of inflammation and oxidative stress, which occur during the CPB surgery. The age of stored blood probably increases the risk of AKI (also see Chapter 61). Old blood may result in higher circulating levels of free hemoglobin and free iron. Finally, anemia might increase the risk of AKI and other organ injury by increasing the risk of tissue hypoxia and oxidative stress, as well as impaired iron metabolism. The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists guidelines suggest that transfusion triggers (also see Chapter 61) should be lower during CPB surgery and that a transfusion trigger of 6 g/dL is reasonable, except in those at risk for end-organ ischemia, in whom a higher trigger may be reasonable.[105] However, many clinicians may not wish to wait for a hemoglobin level of 6 g/dL before giving a blood transfusion, especially intraoperatively.

SYSTEMIC PERFUSION: SYSTOLIC ARTERIAL AND PULSE PRESSURE

Large multicenter epidemiologic studies have identified a relationship between markers of abnormal central aortic compliance, such as preoperative isolated systolic hypertension (>160 mm Hg) and wide pulse pressure hypertension (>40 mm Hg),[86,106] and postoperative AKI and dialysis, in particular in patients undergoing cardiac surgery (also see Chapter 67). The systolic component of the arterial blood pressure number is determined by stroke volume and the rate of ventricular ejection, whereas the pulsatile component of arterial blood pressure is governed by the relationships among stroke volume, ventricular ejection, viscoelastic properties of large arteries, and peripheral vascular resistance. Pulse pressure is an index of the effects of large artery stiffness and the rate of pressure on propagation and reflection within the arterial tree. Early return of reflected arterial waves during late systolic rather than early diastolic pressure (from increased propagation velocity in stiff vessels) increases systolic blood pressure (i.e., afterload) and decreases diastolic blood pressure (i.e., perfusion pressure). Perfusion pressure and the risk of perioperative renal dysfunction are linked by the preexisting capacity of the vasculature to compensate for low pressure as it determines flow. Those with a predisposition to low flow attributable to abnormal central aortic compliance may represent patients who require higher pressure to maintain adequate flow and minimize renal risk compared with normotensive patients.

RBF during CPB is not autoregulated and varies with pump flow rates and arterial blood pressure.[44] However, CPB hypotension is not equivalent to hypotension with hemorrhagic shock or low cardiac output states, because a low pressure during CPB surgery is rarely associated with low flow. CPB flow rates and perfusion pressures were compared in a case-control analysis of three groups of patients with normal baseline renal function who postoperatively required dialysis (n = 44), sustained a renal injury without requiring dialysis (n = 51), or had no renal impairment (n = 48).[107] Usually, renal injury was associated with long bypass durations, low flows, and long periods with CPB pressure less than 60 mm Hg. A serious limitation of this study is the potential for confounding CPB variables and known renal risk factors. In contrast, several studies that accounted for known risk factors in evaluating perfusion management did not link low CPB blood pressure (with maintained flow) with postoperative AKI.[108-110]

RBF is affected by renal artery stenosis. In a retrospective study of 798 patients undergoing aortocoronary bypass whose cardiac catheterization procedures routinely included renal angiogram, Conlon and colleagues found that 18.7% of patients had at least 50% stenosis of one renal artery (nine patients had >95% renal artery stenosis bilaterally).[111] However, in a multivariable logistic regression analysis, no association of the presence or severity of renal artery stenosis was observed with postoperative AKI.

INTRAVASCULAR VOLUME STATUS: CENTRAL VENOUS PRESSURE, PULMONARY CAPILLARY WEDGE PRESSURE, LEFT ATRIAL PRESSURE, AND LEFT VENTRICULAR END-DIASTOLIC AREA

The decision to use any monitor should depend on the patient's functional cardiac reserve status and the extent of the proposed surgical insult. Although maintaining adequate cardiac output is necessary for maintaining adequate RBF, adequate flow may still not occur. Intravascular volume monitoring techniques must include caution to identify physiologic conditions that influence their validity as a reflection of preload in a particular patient (see Chapters 20, 23, and 44). Monitoring central venous pressure to assess preload involves assumptions about normal left and right ventricular function, pulmonary vascular resistance, and mitral, pulmonary, and tricuspid valve function. Similarly, monitoring pulmonary artery pressure or pulmonary capillary wedge pressure assumes normal left ventricular compliance, mitral valve function, and normal airway pressure.

Direct measurements of left atrial pressure may offer insight into the kidney pressure-flow relationship because left atrial hypotension is a powerful stimulus for renal vasoconstriction. Despite equivalent reductions in cardiac output and arterial blood pressure, RBF decreases significantly more when left atrial pressure is decreased (e.g., hemorrhagic shock), compared with left atrial pressure when it is increased (e.g., cardiogenic shock).[112] Left atrial pressure receptors modulate renal vasoconstriction through the release of ANP, a hormone secreted by the cardiac atria in response to intravascular volume expansion.[113] ANP acts on the arterial and venous systems, the adrenal glands, and the kidneys to reduce intravascular volume and decrease blood pressure.[33] Within the kidney, the hormone increases hydraulic pressure in the glomerular capillaries through afferent arteriolar dilation and efferent arteriolar vasoconstriction. ANP reduces arterial

blood pressure by relaxing smooth muscle and reducing sympathetic vascular stimulation and also inhibits renin and aldosterone secretion, causing renal vasodilation, natriuresis, and diuresis.[5]

Despite the direct relationship of left atrial pressure and renal vasoconstriction, static monitors of intravascular volume status are gradually being replaced by echocardiographic and dynamic monitors of intravascular volume status (see the next section on guided fluid optimization). Intraoperatively, one of the most direct ways to monitor intravascular volume may be by direct assessment of the left ventricular end-diastolic area with transesophageal echocardiography. Monitoring with invasive devices, such as pulmonary artery catheters, arterial cannulas, and transesophageal echocardiography, has not been demonstrated to reduce the incidence of AKI.

BLOOD FLOW: CARDIAC OUTPUT AND ESOPHAGEAL DOPPLER ULTRASONOGRAPHY–GUIDED FLUID OPTIMIZATION

The phrase *guided fluid optimization* has recently garnered significant interest as a step beyond traditional, somewhat unreliable guides to fluid administration (e.g., central venous pressure). The principle behind fluid optimization is to maximize tissue-oxygen delivery by achieving a maximum stroke volume. Intravascular fluid management is typically guided by the physiologic response to dynamic measures; proposed measures include systolic pressure variation, pulse pressure variation, continuous cardiac output monitoring, and esophageal Doppler ultrasonography fluid boluses.[114-117] Some maneuvers to assess fluid responsiveness may be feasible in the critical care setting but not in the perioperative setting (e.g., passive leg raise). Considering the improved outcomes in patients who are critically ill with the acute respiratory distress syndrome and are treated with a restrictive fluid management strategy, fluid restriction in the perioperative setting has gained attention. Yet, a meta-analysis of seven randomized clinical trials in the setting of intraabdominal surgery suggested a restrictive fluid strategy offered no benefit; however, there was also no evidence of harm, including AKI.[118] In some studies, excessive fluid restriction was associated with harm, including an increased risk of anastomotic breakdown and sepsis, and should clearly be avoided.[119] Although a systematic review of over 80 perioperative fluid management randomized trials concluded that the optimal amount of fluid to be administered for fluid replacement in elective surgical procedures is not clear, it recommended strict avoidance of fluid overload[120] (also see Chapter 59).

Others have described the disastrous and unpredictable occurrence of acute pulmonary edema related to postoperative fluid retention.[121] Thus evidence on which to base judgments of the importance of fluid management strategies on perioperative renal function is insufficient at present. However, balanced electrolyte solutions may be beneficial over hyperchloremic intravenous fluids.[122] Physiologically, hyperchloremia leads to renal vasoconstriction and a decrease in GFR, although the precise mechanism of this effect remains unknown.[123]

AUTOREGULATION AND DISTRIBUTION OF CARDIAC OUTPUT TO THE KIDNEYS

The fraction of cardiac output perfusing the kidneys depends on the ratio of renal vascular resistance to systemic vascular resistance.[39] In general, the response to renal hypoperfusion involves three major regulatory mechanisms that support renal function: (1) afferent arteriolar dilation increases the proportion of cardiac output that perfuses the kidney; (2) efferent arteriolar resistance increases the filtration fraction; and (3) hormonal and neural responses improve renal perfusion by increasing intravascular volume, thereby indirectly increasing cardiac output. The afferent arterioles react to reductions in perfusion pressure by relaxing their smooth muscle elements to decrease renal vascular resistance. Decreased solute delivery to the macula densa in the cortical portion of the thick ascending loop of Henle results in the relaxation of the juxtaposed afferent arteriolar smooth muscle cells, improving glomerular perfusion and filtration (also see Chapter 23).

The kidney produces vasodilator prostaglandins to counteract the effects of systemic vasoconstrictor hormones such as angiotensin II. In a state of low cardiac output when systemic blood pressure is preserved by the action of systemic vasopressors, RBF is not depressed because the effect of the vasopressors is blunted within the kidney.

A selective increase in efferent arteriolar resistance decreases glomerular plasma flow, thereby preserving GFR. Glomerular filtration is augmented because capillary pressure upstream from the site of vasoconstriction tends to rise. This mechanism enables the kidney to offer high organ vascular resistance to contribute to the maintenance of systemic blood pressure without compromising its function of filtration. Studies using specific inhibitors of angiotensin II have shown that efferent arteriolar resistance largely results from the action of angiotensin II.[124] At low concentrations, norepinephrine has a vasoconstricting effect on efferent arterioles, indicating that the adrenergic system may also be important for maintaining the renal compensatory response.[125]

Reductions in cardiac output are accompanied by the release of vasopressin and by increased activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system. These regulatory mechanisms to preserve RBF conserve salt and water. The control of blood delivery to the kidney, the fraction of plasma filtered, and the amount of volume returned to the systemic circulation are determined by regulatory mechanisms within the kidney that attempt to preserve filtration function during compromised circulation.

One study reported the normal response to hemorrhage in otherwise healthy patients, describing a 30% reduction in RBF with a decrease in mean perfusion pressure from 80 to 60 mm Hg.[126] Changes known to occur at the initiation of CPB surgery include greater reduction in renal perfusion than systemic perfusion, loss of RBF autoregulation, and stress hormone and inflammatory responses known to be harmful to the kidney.[44,127] These effects may explain why the duration of CPB surgery independently predicts postcardiac surgery renal impairment. During experimental CPB surgery, medullary Po_2 decreases from typically low levels to unmeasurable levels.[69]

EXCESSIVE INTRAVASCULAR VOLUME AND THE ABDOMINAL COMPARTMENT SYNDROME

The abdominal compartment syndrome was first defined in 1985; since then, it has been progressively recognized as a common contributor to renal dysfunction in the setting of excessive intravascular volume.[128,129] Not surprisingly, excessive intravascular volume and mechanical ventilation with high airway pressures are significant contributors to the abdominal compartment syndrome. Abdominal compartment syndrome is defined as a sustained increase in intraabdominal pressures to greater than 20 mm Hg that causes organ dysfunction; in contrast, intraabdominal hypertension is typically defined as intraabdominal pressures ≥12 mm Hg without organ dysfunction. This increase in intraabdominal pressure decreases abdominal perfusion pressure (which is mean arterial pressure – intraabdominal pressure), and results in a functional prerenal state attributable to reduced renal perfusion.

The intraabdominal pressure can easily be measured using an indwelling Foley catheter and the same pressure tubing setup used for arterial line blood pressure monitoring.[130] The Foley catheter is clamped distal to the instillation port, and up to 25 mL of saline is instilled into the bladder. The transduced should be zeroed at the midaxillary line, and the pressure should be measured at end-expiration approximately 30 to 60 seconds after fluid is instilled into the bladder to allow for detrusor muscle relaxation. Of note, intraabdominal pressure may be chronically elevated to as high as 12 mm Hg in the obese adult but is not associated with end-organ dysfunction in this context (also see Chapter 71).[131] Prompt recognition of the abdominal compartment syndrome and treatment via decompression in the appropriate clinical context is critical.

LABORATORY TESTS OF SERUM AND URINE AS MARKERS OF RENAL FUNCTION

An ideal monitor for perioperative AKI recognition would be accurate, point-of-care, simple, brief, and inexpensive; in addition, it should have confirmed links with AKI-related outcomes (e.g., mortality). Because no such test currently exists, trends in repeated serum creatinine determinations (relative or absolute changes), alone or integrated into eGFR, are the clinical tools most often used for this purpose.[132] Although traditional tests are useful in identifying kidney failure, an inherent limitation of almost all currently available tools is the obligate delay between the *onset* of AKI and the *diagnosis* of AKI. One striking difference between the management of AKI and acute myocardial infarction (AMI) is the lack of early biomarkers for AKI to guide prompt recognition and intervention when tissue is threatened (i.e., AMI—troponin, creatine kinase–MB [CK-MB]). Thus significant ongoing efforts are testing the value of early AKI biomarkers. The following discussion is categorized into traditional diagnostic tools and the currently expanding field of early biomarkers for AKI.

TRADITIONAL BIOMARKERS OF ACUTE KIDNEY INJURY

Biomarkers are those used to estimate renal function (serum creatinine and GFR estimating equations and creatinine and urea clearance), those biomarkers used to recognize AKI (urine volume, serum BUN, and creatinine), and those used to distinguish the different causes of AKI (urine-specific gravity, urine osmolality, urine sodium level, fractional excretion of sodium (Fe_{Na}) and urea, and urinalysis). Because AKI represents a change in renal function, some of the estimates of renal function are also used to recognize AKI (e.g., serum creatinine). Another test frequently used to distinguish the causes of AKI is ultrasonography of the kidneys and urinary tract to rule out obstruction as a cause of AKI, noting that in individuals with two functioning kidneys, both kidneys must be obstructed for AKI to occur. Because ultrasonography is not a functional test *per se*, its use is not discussed further in this text. Although not routinely used in clinical practice, other functional measures include measured GFR using exogenous markers such as inulin, as well as RBF (Box 52-1). Finally, interest in cystatin C and other novel markers of GFR is increasing; therefore these are introduced in the section that discusses novel (early) biomarkers of AKI later in this chapter.

BOX 52-1 *Markers of Kidney Function*

- Serum creatinine
  - Analysis tools
    - Baseline-to-peak postoperative fractional change
    - Peak in-hospital postoperative
    - Baseline-to-peak maximum change
    - AKI definitions
    - STS definition
    - AKIN criteria
    - RIFLE criteria
    - KDIGO criteria
    - Modified contrast nephropathy criteria
- Creatinine clearance
  - Cockcroft-Gault estimating formula
    - 24-hour urine collection
    - Shorter (e.g., 2- or 4-hour) urine collection
- Glomerular filtration rate
  - Estimated glomerular filtration rate
    - MDRD equation
    - CKD-EPI equation
  - Direct measures
    - Insulin clearance
    - Iohexol clearance
- Urine volume
  - RIFLE, AKIN, KDIGO criteria
- Blood urea nitrogen
- Urine specific gravity
- Urine osmolality
- Urinary sodium
- Fractional excretion of sodium
- Renal blood flow

AKI, Acute kidney injury; *AKIN,* Acute Kidney Injury Network; *CKD-EPI,* Chronic Kidney Disease Epidemiology Collaboration; *KDIGO,* Kidney Disease: Improving Global Outcomes; *MDRD,* Modification of Diet in Renal Disease; *RIFLE,* Risk, Injury, Failure, Loss, End-stage kidney disease; *STS,* Society of Thoracic Surgeons.

Functional measures of kidney health such as serum creatinine are essentially surrogates for glomerular filtration, which is governed by the following equation:

$$GFR = K_f \times (P_{GC} - P_{BC} - P_{PO})$$

where GFR is the rate at which fluid is filtered through the glomerular capillaries into the Bowman capsule, K_f is the glomerular filtration coefficient or the factor that considers the permeability and surface area of the glomerular basement membrane, P_{GC} is the glomerular capillary pressure, P_{BC} is the pressure in the Bowman capsule, and P_{PO} is the plasma oncotic pressure.

Acute changes in GFR and, consequently, in urine formation are commonly caused by changes in glomerular capillary pressure. For example, events that reduce plasma flow rates reduce the hydraulic pressure of glomerular capillaries and favor decreased ultrafiltration, whereas events that increase plasma flow rate have the opposite effect. In theory, varying concentrations of plasma proteins may influence oncotic pressure and influence GFR, with smaller plasma protein concentrations decreasing oncotic pressure and increasing GFR. The glomerular filtration coefficient is the product of glomerular capillary hydraulic permeability and total surface area available for filtration. Hydrostatic pressures are normally maintained higher in glomerular capillaries than in other capillary beds by a delicate balance of preglomerular and postglomerular vascular tone in arterioles. The permeability of the glomerular capillary wall is equal for substances with molecular masses up to 5000 to 6000 daltons (Da) and decreases to almost zero at 60,000 to 70,000 Da.[133] Metabolic wastes and essential nutrients are filtered freely, and larger proteins, such as albumin and immunoglobulin G (IgG), are filtered in trace amounts or not at all. The hope is that real-time GFR measurements will be possible in the future in the perioperative and critical care settings; such technology is being developed and tested in small and large animal models.[134-136]

Serum Creatinine Concentration

Despite all of its limitations, the serum creatinine concentration remains the most used clinical tool to assess renal function and to diagnose AKI. Serum creatinine is a cyclic anhydride of creatine, which is a small molecule (113 Da) that is continuously released during skeletal muscle protein catabolism. Muscle mass, which is smaller in women and declines with age, directly predicts creatinine release. Creatinine levels in body fluids (e.g., plasma, serum, urine) are also easy and inexpensive to measure. These properties have made serum creatinine a mainstay as a marker of steady-state changes in renal filtration.

However, because of its nonlinear relationship with changes in renal function (see Fig. 52-8), variability among individuals, and susceptibility to changes unrelated to changes in GFR (e.g., cimetidine, trimethoprim, N-acetylcysteine),[132,137,138] an increase of serum creatinine concentration is only somewhat reliable as a sign of renal dysfunction. GFR may be reduced by as much as 75% before increases reach abnormal levels attributable to the kinetics of creatinine accumulation.[139,140] Often the magnitude of the changes in serum creatinine may be more important than the absolute value. Because creatinine production is proportional to muscle mass, many chronically ill, malnourished, older patients have serum creatinine values in the normal range, despite reduced renal concentrating ability and GFR. Conversely, many critically ill patients at risk for developing AKI may have high metabolic rates because of hyperalimentation, sepsis, or posttraumatic states. Nonetheless, the serum creatinine concentration remains a useful; inexpensive; and, so far, unsurpassed clinical tool to reflect particularly *trends* of change in renal filtration function and to predict outcome, even during the perioperative period.

An inverse logarithmic relationship exists between GFR and serum creatinine concentration (see Fig. 52-8); that is, as GFR decreases, creatinine increases. Within the normal ranges, changes relative to baseline can represent significant changes in renal function. For example, a patient with a baseline serum creatinine level of 0.6 mg/dL who develops contrast nephropathy sufficient to reduce the GFR to 50% of baseline would have a serum creatinine level of approximately1.2 mg/dL, still in the normal range. Thus a trend in serum creatinine values is always more useful than a single serum creatinine measurement to evaluate renal function reserve, particularly when changes are anticipated.

Nephrologists and critical care physicians have focused on developing consensus criteria for AKI. Although the cardiac surgery literature has commonly defined AKI using the Society of Thoracic Surgeons' definition of at least a twofold creatinine rise to a value exceeding 2 mg/dL or new dialysis or both[141] and the contrast nephropathy literature has focused on creatinine rises exceeding 25% or 0.5 mg/dL (44 μmol/L), [a] major push to define AKI using the same criteria across all study types now exists (Table 52-1).

Additional methodologic concerns with the use of creatinine as a measure of renal function include the fact that creatinine distributes into total body water; when patients become volume overloaded, creatinine may become diluted, and AKI may be masked. AKI recognition may be delayed or entirely missed in the setting of excessive intravascular volume.[142,143] Furthermore, outcomes in those with AKI that is masked by excessive intravascular volume have very poor outcomes, with mortality rates similar to those with conventional AKI. In addition, creatinine generation rates may change under conditions of acute illness.[144,145] Despite these limitations, considering the low cost of the test and the ability to obtain frequent measurements, serum creatinine remains the best test of renal function currently available.

Creatinine and Urea Clearance

When monitoring renal function, the measure of interest is the GFR, which is slightly overestimated by creatinine clearance, since creatinine is partially secreted in the renal tubule. Since gold standard measurements of GFR including inulin and iothalamate clearance are expensive and cumbersome, these measurements are not routinely used in clinical practice. Creatinine clearance can be either estimated when creatinine is at steady state or directly measured. When creatinine is at steady state, the Cockcroft-Gault equation can be used to estimate creatinine

clearance based on patient gender, age (years), weight (kg), and serum creatinine (Cr) (mg/dL)[146]:

$$\text{Cockcroft – Gault eGFR (mL/min)} = [140\ (\text{age}) \times \text{weight (kg)}] \div (\text{Cr} \times 72) \times .85\ (\text{for females})$$

However, as described in the next section, under conditions where serum creatinine is at steady state, the Cockcroft-Gault equation has largely been superseded by more modern GFR estimating equations.

Precise measurements of creatinine clearance require the collection of timed urine samples using the following formula:

$$\text{GRR} - (\text{UV} \div \text{P})$$

where U is the urinary concentration of creatinine (mg/dL), V is the volume of urine (mL/min), and P is the plasma concentration (mg/dL). The major limitation in determining creatinine clearance is the necessity of accurately collecting urine. Although reasonable correlation between short-timed creatinine clearance measurements (as short as 2 hours) and 24-hour creatinine clearance has been reported for patients in ICUs[147] (Fig. 52-9), in general, the longer the urine collection period, the more accurate is the measurement. Nonetheless, short-timed clearance measurements may be useful to identify AKI before changes in serum creatinine[148] and as an assessment to guide therapy, including discontinuation of dialysis[149] and medication dosing. However, changing hydration of the patient and failing to record urine volume accurately may make such short-timed collections inaccurate.[150] The error in calculation of creatinine clearance can vary significantly, depending on the accuracy of urine collection, body weight, surface area, and normal day-to-day variations. Regardless, these direct measurements can be extremely useful for patients in whom a concern exists that eGFR equations may overestimate renal function. These individuals include older and critically ill patients who may have limited muscle mass, as well as those who are under conditions of acute stress and critical illness, during which emerging data have suggested that changes in creatinine generation may occur. Because creatinine is excreted by glomerular filtration and tubular secretion, as the GFR decreases the tubular secretion becomes a progressively more important fraction of creatinine excretion, such that creatinine clearance overestimates the GFR by 50% to 100% if the true GFR is less than 15 mL/min.

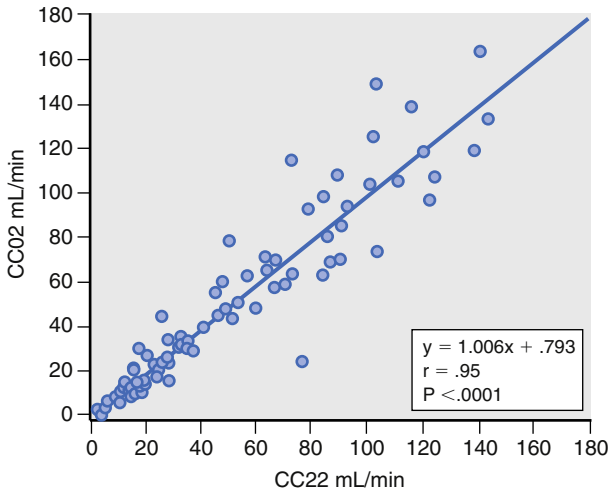


Figure 52-9. Correlation between the 2-hour creatinine clearance (CC02) and the 22-hour creatinine clearance (CC22). *(Modified from Sladen RN, Endo E, Harrison T: Two-hour versus 22-hour creatinine clearance in critically ill patients,* Anesthesiology *67:1013-1016, 1987.)*

Although urea is freely filtered at the glomerulus, it is also reabsorbed, and, as a result, measuring timed urea clearance underestimates GFR. Consequently, timed urea clearance measurements are not used with one exception: when GFR is low (less than 20 mL/min/1.73 m^2), the average of the timed urea and creatinine clearances is often used to estimate GFR, since the timed urea clearance underestimates clearance and the timed creatinine clearance overestimates clearance.

Glomerular Filtration Rate Estimating Equations Using Steady-State Creatinine

The Modification of Diet in Renal Disease (MDRD) GFR estimating formula uses several clinical variables to obtain estimates of GFR in a population with chronic kidney disease.[151] Several forms of this equation are available, but the one in widespread clinical use incorporates serum creatinine, age, gender, and race:

$$\text{GFR} = 186 \times [\text{serum Cr (mg/dL)}]^{-1.154} \times (\text{age})^{-0.203} \times 0.742\ (\text{for females}) \times 1.210\ (\text{for blacks})$$

This equation has been adopted by many clinical laboratories. However, two important caveats must be kept in mind when interpreting these results. First, interpretation of eGFR assumes that creatinine is at steady state; during an episode of AKI when the serum creatinine is rising, the eGFR will be inaccurate. In addition, because the equation was derived in a group of patients with chronic kidney disease, the equation is inaccurate when eGFR exceeds 60 mL/min/1.73 m^2 and is often reported out as >60 mL/min/1.73 m^2 rather than as an exact number.

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is a more recent eGFR equation derived in both normal populations and those with chronic kidney disease[152]; this equation uses splines to allow for precise eGFR across a large range of values. This equation will likely replace the MDRD equation in the clinical laboratory setting over the next 5 to 10 years. Again, this equation cannot be used when serum creatinine is not at steady state.

Urine Volume

Although consistently recorded, intraoperative urine output remains a controversial perioperative marker of renal function. Whereas the presence of urine (regardless of amount) confirms blood flow to the kidney, many nonrenal factors directly and profoundly influence urine production. During surgery, patients are often hemodynamically unstable; decreased blood volume or cardiac output, fluctuating hormone levels (e.g., aldosterone, renin, ADH), nervous system reflexes, and increased

catecholamine concentrations added to the effects of general anesthesia can alter GFR. Although intraoperative urine output has been associated with subsequent AKI in some studies,[153] whether it is a reliable intraoperative sign of pending renal dysfunction is not clear, with several studies suggesting that intravascular volume resuscitation in the surgical setting may not improve urine output or affect rates of AKI.[41,154] For example, Alpert and colleagues observed patients who underwent oliguric aortic surgery (urine flow <0.125 mL/kg/hr) and were given additional crystalloid solution, intravenous mannitol, furosemide, or no intervention[41]; no correlation was found between intraoperative mean or the smallest hourly urine output and subsequent AKI (see Fig. 52-7).

In contrast to the intraoperative setting, significant prolonged preoperative or postoperative oliguria has been proposed as a diagnostic criterion for AKI, with urine output (<0.5 mL/kg/hr for longer than 6 hours) forming the basis for RIFLE, Stage R, and AKIN and KDIGO, Stage 1, AKI.[14-16] The kidney concentrates the ultrafiltrate so that at maximal concentration, a minimum of 400 to 500 mL of urine is required to clear the daily obligatory nitrogenous wastes. However, the urine output criteria for AKI have not been well validated in the clinical literature and remain controversial.[17] Furthermore, the lack of correlation of immediate perioperative oliguria with AKI has not been incorporated into these recent consensus statements, primarily developed by nephrologists and critical care physicians.[14-16]

Blood Urea Nitrogen

BUN is often measured as part of the assessment of renal function but is inherently problematic as a measure of renal function on its own. BUN is a protein degradation product and is consequently increased by high protein intake, blood in the gastrointestinal tract, and accelerated catabolism in traumatized or septic patients. Because urea is synthesized in the liver, hepatic dysfunction decreases urea production and therefore BUN concentration. It had been proposed that BUN/creatinine ratios could suggest whether AKI was due to prerenal causes or ATN, with BUN/creatinine ratios >20 consistent with prerenal azotemia; however, this criterion is nonspecific.

Urine Specific Gravity and Osmolality

Once AKI is diagnosed, a number of tests can be used to try to distinguish the cause of AKI. The distinction between prerenal azotemia and ATN is emphasized in this discussion. This distinction has clinical relevance since a patient with prerenal azotemia in the perioperative setting may require intravascular fluid administration, whereas avoiding excessive intravascular volumes may be important in the patient with established ATN. Nonetheless, an important caveat to this discussion is the fact that prerenal azotemia and ATN likely represent a spectrum of disease, rather than two distinct entities. Consequently, rigorous attempts to distinguish one disease from the other have been unsuccessful; perhaps, as a result, this distinction should not be made.[155] The tests proposed to distinguish prerenal azotemia from ATN have mostly been urine based and are more comprehensively reviewed by Perazella and Coca.[156]

Urine specific gravity reflects the mass of 1 mL of urine compared with 1 mL of distilled water. Normal values range between 1.001 and 1.035. In settings of poor perfusion or prerenal azotemia, urine specific gravity is high (e.g., 1.030), reflecting the kidney's ability to conserve sodium and water. With a loss of concentrating ability attributable to ATN, urine specific gravity resembles plasma osmolarity (e.g., 1.010). Unfortunately, when interfering substances that raise urine specific gravity (e.g., glucose, protein, contrast dye) are present in large amounts (Box 52-2), high urine specific gravity can provide misleading reassurance that the renal concentrating ability is preserved; depending on the nature of these agents, some will affect urine osmolality as well. Of note, the ability of the kidneys to concentrate urine is impaired in many older patients and many with chronic kidney disease.

Urine specific gravity is a surrogate for osmolality (normal range, 50 to 1000 mOsm/kg), a measure of the number of osmotically active particles in solution in the solvent phase. Theoretically, urine osmolality is physiologically superior to urine specific gravity as a test of renal function; however, the same substances and conditions that render urine specific gravity a nonspecific test can also affect the reliability of urine osmolality (see Box 52-2). Similar to urine-specific gravity, the sensitivity and specificity of urine osmolality as a test for predicting or distinguishing ATN from prerenal azotemia are clinically inadequate.[157]

Urinary Sodium Concentration

With decreasing perfusion, the normally functioning kidney conserves sodium and water. It is traditionally suggested that a urinary sodium level of less than 20 mEq is consistent with prerenal azotemia (since the normal kidney, under conditions of hypoperfusion, retains sodium) and that a level greater than 40 mEq indicates ATN.[157] However, the factors affecting urine sodium are numerous and include heterogeneity of nephrons, secretion of aldosterone, secretion of ADH, diuretic therapy, saline content of intravenous infusion solutions, sympathetic neural tone, and sodium-avid states (e.g., congestive heart failure, cirrhosis). Therefore urine sodium in isolation cannot be used to distinguish prerenal azotemia and ATN reliably.

Fractional Excretion of Sodium

Failure of avid sodium reuptake by the kidney in the setting of dehydration exhibits increased urine sodium

BOX 52-2 ***Substances and Conditions Affecting Urine-Specific Gravity and Urine Osmolality***

Proteins
Glucose
Mannitol
Dextran
Diuretic drugs
Extremes of age
Radiographic contrast media
Antibiotics (e.g., carbenicillin)
Hormonal imbalances (e.g., diabetes insipidus)

and is the principle underpinning the utility of Fe_{Na} as a diagnostic tool. A sodium excretion value of less than 1%, compared with greater than 1%, suggests differentiation between prerenal azotemia and ATN, particularly in the presence of oliguria. The Fe_{Na} was first described by Espinel[158]; it represents the fraction of sodium excreted versus that filtered by the kidneys. Fe_{Na} is calculated as follows:

$$FE_{Na} = \frac{\text{Excreted Na}}{\text{Filtered Na} \times 100} = \frac{U_{Na}P_{Cr}}{(U_{Cr}P_{Na} \times 100)}$$

where P_{Cr} is the plasma creatinine level, P_{Na} is the plasma sodium level, U_{Cr} is the urinary creatinine level, and U_{Na} is the urinary sodium level. However, under conditions of normal GFR, Fe_{Na} is low, and generally the Fe_{Na} is useful only when oliguria is already present.[159] Fe_{Na} is affected by other factors, including, in particular, diuretic therapy. Some have proposed that the fractional excretion of urea can be useful in this context, with a fractional excretion of urea of <35% being consistent with prerenal azotemia, even in the setting of diuretic use.[159-161] However, a number of studies have not shown FE_{Urea} to be useful in distinguishing prerenal azotemia from ATN or transient versus persistent AKI.[162-164] Finally, Fe_{Na} may be low in the context of contrast nephropathy; therefore caution must be used when interpreting Fe_{Na} in this context.[165]

Urinalysis

Cells and cellular elements in the urine can provide important indications as to the cause of AKI. For example, dysmorphic red blood cells and red blood cell casts suggest a glomerulonephritis, whereas white blood cells and white blood cell casts suggest an interstitial nephritis. However, one must also consider nonglomerular causes for hematuria (urinary tract pathologic conditions including trauma or tumor) and pyuria (urinary tract infection, including pyelonephritis), if present. A urine test result that is positive for blood in the absence of red blood cells suggests the presence of free hemoglobin or myoglobin in the urine.

In contrast to hematuria and pyuria, the presence of renal tubular epithelial cells and granular or muddy brown casts are most suggestive of ATN, whereas hyaline casts may be consistent with a prerenal state or early ATN. Indeed, a simple scoring system that quantitates the number of renal tubular epithelial cells and granular casts has been proposed to differentiate ATN from prerenal azotemia with 76% sensitivity and 86% specificity.[166] Important caveats to this study include the fact that this was a single-institution study and all study participants underwent renal consultation and evaluation of urine microscopy by subspecialty consultants. Although additional studies are needed to validate the utility of such scoring systems for the diagnosis of AKI, these studies underscore the importance of the urine sediment in assessing the cause of AKI.

The presence of proteinuria on a routine dipstick examination may be normal, or it may suggest severe renal disease. In a concentrated urine sample, trace or 1+ proteinuria is a nonspecific finding, whereas 3+ or 4+ proteinuria suggests glomerular disease. The existence of glucosuria without hyperglycemia suggests proximal tubular damage.

Timed Clearance Measurements: Inulin, Iothalamate, and Others

Inulin, a polymer of fructose with a molecular mass of 5200 Da found in Jerusalem artichokes, dahlias, and chicory, has been used to measure GFR because it is filtered freely in the glomerulus, not reabsorbed or secreted, and is excreted in the urine. To assess inulin clearance, the clinician intravenously administers a priming dose of inulin, followed by a continuous infusion calculated to maintain constant blood concentrations. After an equilibration period (usually 1 hour), clearance measurements are obtained. Urine is collected (typically with a Foley catheter), and venous blood samples are obtained at the midpoint of each clearance period. The longer the clearance period, the less likely is the introduction of error from incomplete voiding. The standard formula for calculation of clearance is as follows:

$$C_I = (U_I V) \div P_I$$

where U_I and P_I are the urine and plasma concentrations of inulin, respectively, C_I is the rate of inulin clearance, and V is the urine flow rate. Other exogenously administered clearance markers include iohexol, iothalamate, and radiolabeled ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA); a detailed discussion of these markers and the pros and cons of measured and eGFR can be found in a recent review by Stevens and Levey.[132]

Renal Blood Flow

Although an extended period of renal artery clamping (e.g., 30 to 40 minutes) sufficient to cause blood flow to cease is also sufficient to cause ischemic AKI, it is simplistic to assume that moderate increases and decreases in RBF are good and bad for the kidney, respectively. Regional variations in perfusion result in a precarious balance between oxygen supply and demand in some renal tissues, particularly in the inner renal medulla. Notably, high levels of RBF also oblige high levels of oxygen demand to facilitate active transport of sodium and other solutes back into the circulation. Consequently, RBF is a very poor indicator of the adequacy of regional medullary perfusion and oxygen delivery. Furthermore, hypovolemia and AKI affect the distribution of RBF with renal arteriographic and xenon washout studies in patients with AKI showing a selected, profound reduction in RBF.[167] Thus clinically useful techniques to measure RBF must measure total RBF and the distribution of RBF; techniques include the clearance of para-aminohippurate, indicator dilution, renocortical tissue Po_2, radiolabeled tracers, Doppler ultrasonography, and external gas-washout techniques.[168] Owing to the risks and limitations associated with these techniques and the lack of clear utility of the diagnostic information, their clinical use has been limited.

However, if clinical utility could be demonstrated with the use of RBF measurements, then many noninvasive measures, including two-dimensional transesophageal echocardiography and renal arterial Doppler waveform images, primarily of the left kidney, could assess RBF to describe

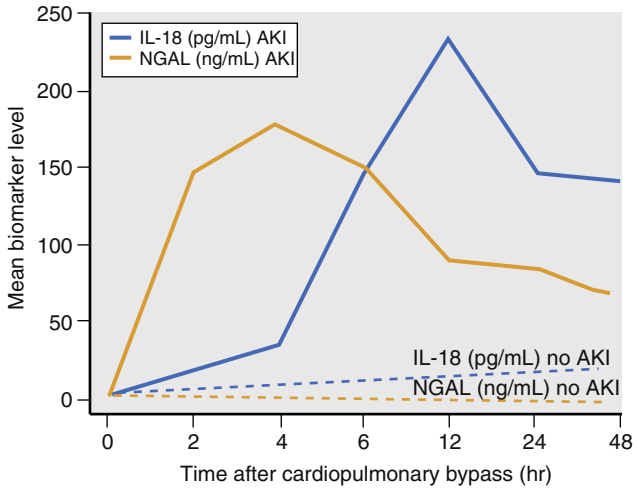


Figure 52-10. Pattern of early biomarkers for urinary interleukin (IL)-18 and neutrophil gelatinase–associated lipocalin (NGAL) after cardiopulmonary bypass (CPB) surgery in 55 patients with and without criteria for acute kidney injury (AKI) diagnosed 48 to 72 hours postoperatively (defined as a peak rise in serum creatinine concentration to >150% of baseline). *(From Parikh CR, Mishra J, Thiessen-Philbrook H, et al: Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery,* Kidney Int *70:199-203, 2006. Used with permission.)*

RBF changes qualitatively over time,[121] as well as contrast ultrasonography using sonicated microbubbles.[169] Finally, scintigraphic functional magnetic resonance imaging can characterize kidney physiologic abnormalities, including GFR, tubular concentration, transit, blood volume, perfusion, inflammation, and even tissue hypoxia, although this is likely to be impractical in the perioperative setting.[170,171]

NOVEL (EARLY) BIOMARKERS OF ACUTE KIDNEY INJURY

Limited progress in the care for AKI has fueled an enormous interest in new early biomarkers.[172-174] Although a few of the new tools represent attempts to find a substitute *ideal* creatinine-like substance to use in estimates of renal filtration (e.g., cystatin C), most markers take advantage of one of the three early consequences of AKI: (1) tubular cell damage, (2) tubular cell dysfunction, and (3) adaptive stress response of the kidney. The hope is that prompt biomarker information will allow timely AKI risk identification, surveillance (i.e., recognition of pre-AKI states such as prerenal azotemia), diagnosis, and prognosis. Some of the more promising biomarkers are presented in this text, including classes reflecting impaired renal filtration, tubular cell damage, tubular cell dysfunction, and adaptive responses of the kidney to stress (Box 52-3).

NEW FILTRATION-BASED MARKERS OF RENAL DYSFUNCTION

Of the most novel filtration-based markers of renal dysfunction, the most advanced is cystatin C, a member of the cystatin *superfamily* of cysteine-proteinase inhibitors that is produced by all nucleated cells at a constant rate. Cystatin C has been clinically available for longer than 15 years and can be rapidly determined. Similar to creatinine, cystatin C accumulates in the circulation with renal impairment and can be used as a marker of glomerular filtration. Urinary cystatin C has also been proposed as a marker of renal dysfunction; rather than as a marker of GFR, urinary cystatin C is due to proximal tubular injury and impaired metabolism. Serum cystatin C has theoretical advantages over creatinine, particularly as an indicator of mild chronic kidney disease and its sequelae.[175] Several GFR estimating equations have been proposed, based on cystatin C alone or cystatin C and creatinine,[176,177] but these are not in widespread use at present.

Although cystatin C outperformed creatinine in detecting AKI after cardiac surgery in some small studies,[178] this sensitivity has not consistently been the case (also see Chapter 67). Indeed, a recent large multicenter prospective observational study of AKI after cardiac surgery suggested that serum cystatin C was less, not more, sensitive for the detection of AKI. This study, conducted by the Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI) Consortium, prospectively enrolled more than 1200 adults undergoing cardiac surgery and has rapidly advanced the field of novel biomarkers in this context. Of note, the subset of patients who

BOX 52-3 ***Early Biomarkers* of Acute Kidney Injury***

Filtration-Based Markers of Renal Dysfunction
Cystatin C
Beta-trace protein
Beta-2 microglobulin

Biomarkers Reflecting Renal Tubular Cell Damage (Tubular Enzymuria)
α-Glutathione S-transferase
π-Glutathione S-transferase
β-*N*-Acetyl-β-D-glucosaminidase
γ-Glutamyl transpeptidase
Alkaline phosphatase
Ala-(Leu-Gly)-aminopeptidase
Sodium hydrogen exchanger isoform 3

Biomarkers Reflecting Renal Tubular Cell Dysfunction (Tubular Proteinuria)
α_1-Microglobulin
β_2-Microglobulin
Albumin
Retinol-binding protein
Immunoglobulin G
Transferrin
Ceruloplasmin
Lambda and kappa light chains
Total protein

Biomarkers Reflecting Renal Tubular Cell Response to Stress
Neutrophil gelatinase–associated lipocalin
Urinary interleukin-18
Kidney injury molecule-1
Liver fatty acid–binding protein
Insulinlike growth factor binding protein 7
Tissue inhibitor of metallo-proteinase 2

*New early biomarkers are being developed to provide information promptly to improve risk stratification, surveillance, diagnosis, and prognostic information concerning acute kidney injury.

had AKI by cystatin C and creatinine had more frequent risk of dialysis and death than those who had AKI by creatinine alone.[179] Conditions such as malignancy, human immunodeficiency viral infection, or corticosteroidal or thyroid hormone therapy are associated with increased serum levels without changes in renal function. Other novel markers of filtration include beta-trace protein and beta-2-microglobulin; these markers may be novel markers of mortality in the general population, compared with creatinine-based eGFR.[180] However, the additional utility of these markers in estimating GFR above and beyond creatinine and cystatin C is unknown.

BIOMARKERS REFLECTING RENAL TUBULAR CELL DAMAGE (TUBULAR ENZYMURIA)

Renal tubular cells contain enzymes that are highly specific to their location within the kidney and even tubule region. Under conditions of cellular stress, these enzymes are shed into the urine, making these potentially appealing markers of kidney dysfunction. These markers include α and π isomers of GST, which are cytosolic enzymes from proximal and distal tubular cells, respectively, and NAG, a proximal tubule lysosomal enzyme. General brush border injury is reflected by other markers including γ-glutamyl transpeptidase (γ-GT), alkaline phosphatase, and Ala-(Leu-Gly)-aminopeptidase. Of note, although enhanced urinary excretion of tubular enzymes can signal damaged tubular cells, it can also reflect an increased turnover of tubular cells or some other metabolic disturbance; thus the signals of early, irreversible disease may not always be distinguished from the noise of biologic variability, and the use of these markers should be applied with appropriate caution.

BIOMARKERS REFLECTING RENAL TUBULAR CELL DYSFUNCTION (TUBULAR PROTEINURIA)

When small proteins are filtered by the glomerulus, binding and endocytic reuptake in the proximal tubule normally returns these substances to the body through a megalin-mediated transport system. So-called tubular proteinuria results from functional impairment of this process and the escape of small proteins into the urine. Endogenous low–molecular-weight (LMW) proteins that are normally taken up in this way include β_2- and α_1-microglobulin, albumin, adenosine deaminase–binding protein, renal tubular epithelial antigen-1, retinol-binding protein, lysozyme, ribonuclease, IgG, transferrin, ceruloplasmin, lambda (λ) and kappa (κ) light chains, and urinary total protein. Appearance of any of these substances in the urine heralds abnormal proximal nephron function consistent with AKI. However, enthusiasm for LMW protein markers as perioperative tools to diagnose AKI has been reduced, particularly with cardiac surgery, by the confusion that can occur when an antifibrinolytic drug is used[181,182] (also see Chapter 67). Lysine and its analog (e.g., ε-aminocaproic acid, tranexamic acid) specifically block renal-binding sites, causing a profound but reversible inhibition of LMW protein reuptake[183] that is transient and apparently benign.

BIOMARKERS REFLECTING RENAL TUBULAR CELL RESPONSE TO STRESS

Examples of markers that assess the response of the kidney to stress include neutrophil gelatinase–associated lipocalin (NGAL), urinary IL-18, kidney injury molecule–1 (KIM-1), and liver fatty acid–binding protein (L-FABP). These have each been extensively reviewed in detail in recent literature.[172-174] Two markers of G1-cell cycle arrest have been shown to be upregulated in AKI.[184]

NGAL is a protein with a critical role in iron scavenging. A transcriptome-wide interrogation for genes induced very early after renal ischemia identified NGAL as a protein generated by ischemic renal tubular cells.[185] Administration of exogenous NGAL in animal models attenuates renal injury.[186] Enthusiasm for NGAL as a biomarker of AKI was fueled by a study in pediatric patients who underwent cardiac surgery, suggesting that plasma and urinary NGAL could predict AKI before elevations in serum creatinine[187] (Fig. 52-10). Although increased NGAL levels are associated with adverse outcomes,[188] studies in the adult perioperative literature have not consistently shown NGAL to predict AKI before elevations in serum creatinine. In a large biomarker study in the cardiac surgery field, the TRIBE-AKI consortium showed that plasma NGAL, not urinary NGAL, improved the prediction of a combined endpoint of dialysis and death over clinical risk factors, although the final model had only good discrimination, with an area under the receiver operating characteristic (ROC) curve of 0.75.[4] In the same study, plasma NGAL, not urinary NGAL, was also associated with subsequent AKI progression.[189]

Inflammation is a central aspect of the pathophysiologic processes of AKI. Cytokines and adhesion molecules mediate injury in the kidney, and levels of urinary cytokines such as IL-18 and platelet-activating factor have been assessed as early biomarkers of AKI. IL-18 is an inflammatory mediator of ischemic AKI in animals.[190] In human studies, a cross-sectional study comparing a variety of renal conditions with AKI found an increased urinary IL-18 level to be a good discriminator between patients with AKI and those with prerenal azotemia, urinary tract infections, chronic renal insufficiency, and nephrotic syndrome.[191] Similar to plasma NGAL, urinary IL-18 improved the prediction of adverse outcomes in the TRIBE-AKI study, with a modest improvement in the area under the ROC curve to 0.76, as well as AKI progression.[4,189] Other plasma and urinary cytokines, such as IL-6, are predictive of AKI, but not well developed.[192-194]

KIM-1 is a transmembrane protein expressed at low levels in a normal kidney that is significantly upregulated in proximal renal tubular cells in response to ischemic or nephrotoxic AKI.[195] In studies conducted by the Predictive Testing Safety Consortium, an academic-industrial partnership that has worked closely with the U.S. Food and Drug Administration (FDA) to develop novel biomarkers of kidney injury for use in the preclinical setting (in particular, as markers of drug toxicity), KIM-1 outperformed a number of traditional markers of kidney injury in a variety of preclinical models.[196] KIM-1 has also been associated with AKI in the TRIBE-AKI study.[196]

L-FABP is an intracellular protein that is shed by proximal tubule cells into the urine under conditions of cellular stress and has been proposed as a novel biomarker for both AKI and chronic kidney disease.[197] Studies in patients who are critically ill[198,199] and patients undergoing cardiac surgery[200,201] have suggested an association of L-FABP with AKI in both of these contexts; although, as for other biomarkers, it remains unclear how L-FABP will be clinically used to identify AKI before changes in serum creatinine are observed. One potential strategy may be to use a combination of clinical and biologic measures to identify patients at very high risk of AKI in the perioperative period, but more studies are needed.

Finally, cell cycle arrest has been implicated in models of AKI[202]; more recently, two proteins that induce cell cycle arrest, insulin-like growth factor–binding protein 7 and tissue inhibitor of metalloproteinases-2, have both been shown in a multicenter study to predict the development of KDIGO Stage 2 and 3 AKI in critically ill patients. In a validation cohort, these biomarkers had an impressive area under the ROC curve of 0.80 for subsequent AKI.[184] These two biomarkers are being actively developed for use in the clinical setting, although further studies are needed to confirm these findings and to determine the utility of these biomarkers in larger groups of patients at risk for AKI.

PREOPERATIVE EVALUATION OF RENAL FUNCTION

The greater the magnitude and duration of the surgical insult and the number of acute and chronic risk factors, the greater the likelihood of perioperative renal compromise and the need for preoperative identification of high-risk individuals (see Chapters 38 and 39). Common risk factors for AKI include intravascular volume depletion, aminoglycoside use, radiocontrast dye exposure, use of NSAIDs, septic shock, and pigmenturia. ACE inhibitors and ARBs, respectively, may contribute to intraoperative hypotension and may exacerbate AKI in the setting of impaired hemodynamics (volume depletion, NSAID use). Patients with preexisting renal insufficiency are clearly at increased risk for AKI and should be identified in the perioperative evaluation (also see Chapter 38). Chronic kidney disease affects more than 10% of the United States population. Common risk factors for chronic kidney disease include advanced age, diabetes, and hypertension. The potential value of understanding the genetic makeup of patients has yet to be fully explored and is likely to be important (see earlier discussion). Additional key determinants of postoperative renal function include maintenance of appropriate intravascular volume and normal myocardial function.[13]

Urinalysis provides qualitative information that must be cautiously interpreted (see "Laboratory Tests of Serum and Urine as Markers of Renal Function"). In particular, urinalysis can identify patients with chronic kidney disease with relatively preserved GFR but with significant proteinuria. Other urinary indices, if abnormal, may indicate urinary tract infection, urinary tract pathologic abnormality, or intrinsic kidney disease and must be interpreted in the clinical context of a given patient.

Serum creatinine levels offer rapid eGFR. The incidence and severity of AKI are usually more frequent when the preoperative serum creatinine level is more than 2 mg/dL[38]; however, an isolated serum creatinine measurement is an unreliable indicator of GFR when renal function is changing. The measurement of creatinine clearance may constitute the best overall indicator of GFR, although this index also has its limitations.

SUMMARY

In patients with or at risk for developing AKI, perioperative management continues to be challenging. Numerous factors contribute to the heterogeneous condition referred to as perioperative *AKI*, but insults collectively combine through ischemic and toxic mechanisms. The recent research efforts directed to the investigation of AKI will likely lead to rapid developments in the field of renal function monitoring, including early biomarker tests or panels of tests that aid in predicting risk factors, identifying patients with conditions that precede AKI, such as prerenal azotemia, and determining the diagnosis and prognosis of AKI. The major hope is that improvements in monitoring will translate into better prevention, treatment, and outcome from AKI, something that has been absent over the past half century since the problem of perioperative AKI was first described. Meanwhile, serum creatinine continues to be the mainstay of most renal function monitoring strategies.

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Chapter 53

Neuromuscular Monitoring

JØRGEN VIBY-MOGENSEN • CASPER CLAUDIUS

Key Points

- Good evidence-based practice dictates that clinicians always quantitate the extent of neuromuscular block by objective monitoring.
- The neuromuscular block should be adjusted to ensure optimal surgical conditions. In most procedures, one or two responses to train-of-four (TOF) stimulation will suffice.
- Adequate recovery of postoperative neuromuscular function cannot be guaranteed without objective neuromuscular monitoring.
- Objective neuromuscular monitoring is essential for management of neuromuscular blockade intraoperatively and its reversal for postoperative care. Muscle relaxants should not be given in the intensive care unit (see Chapters 34, 35, and 101) without proper monitoring.
- It is impossible to exclude with certainty clinically significant residual neuromuscular block by clinical evaluation of recovery of neuromuscular function.
- Residual postoperative neuromuscular block causes decreased chemoreceptor sensitivity to hypoxia, functional impairment of the pharyngeal and upper esophageal muscles, impaired ability to maintain an open upper airway, and an increased risk of hypoxemic events, as well as the development of postoperative pulmonary complications.
- Absence of tactile fade in the response to TOF stimulation, tetanic stimulation, and double-burst stimulation does not exclude significant residual block.
- To exclude clinically significant residual neuromuscular block, the TOF ratio must exceed 0.9 when measured mechanically or electromyographically and 1.0 when measured acceleromyographically.
- Antagonism of the neuromuscular block with a cholinesterase inhibitor should not be initiated before at least two to four responses to TOF stimulation are observed.
- Antagonism of the neuromuscular block achieved by rocuronium and vecuronium can be initiated at all levels of block with the selective relaxant binding agent, sugammadex.
- If sufficient recovery (TOF ≥ 0.9-1.0) has not been documented objectively at the end of the surgical procedure, the neuromuscular block should be antagonized with neostigmine or sugammadex. Minority opinion is that even with a TOF greater than 0.9, neostigmine or sugammadex should still be given.

Clinically significant residual neuromuscular block (i.e., paralysis) cannot be excluded using clinical criteria only and can persist postoperatively.[1,2] Objective monitoring of the degree of neuromuscular block during and after anesthesia reduces the incidence of residual neuromuscular block and should be part of standard monitoring equipment.[3-9]

In awake patients, muscle power can be evaluated by tests of voluntary muscle strength, but this is impossible during anesthesia and recovery from anesthesia. Instead, the clinician must use clinical tests to assess muscle power directly and to estimate neuromuscular function indirectly (muscle tone; feel of the anesthesia bag as an indirect measure of pulmonary compliance, tidal volume, and inspiratory force). All these tests, however, are influenced by factors other than the degree of neuromuscular block; therefore, whenever more precise information regarding the status of neuromuscular functioning is desired, the response of muscle to nerve stimulation should be assessed. This procedure also takes into account the considerable variation in individual response and sensitivity to muscle relaxants.

This chapter reviews the basic principles of neuromuscular monitoring and the requirements for effective use of nerve stimulators for peripheral nerve stimulation. It also describes the response to nerve stimulation

during depolarizing (phase I and phase II) and nondepolarizing neuromuscular block. Finally, methods of evaluating evoked neuromuscular responses with and without the availability of recording equipment are discussed.

TYPES OF PERIPHERAL NERVE STIMULATION

Neuromuscular function is monitored by evaluating the muscular response to supramaximal stimulation of a peripheral motor nerve. Two types of stimulation can be used: electrical and magnetic. Electrical nerve stimulation is by far the most commonly used method in clinical practice, and it is described in detail in this chapter. In theory, magnetic nerve stimulation has several advantages over electrical nerve stimulation.[10,11] It is less painful and does not require physical contact with the body; however, the equipment required is bulky and heavy, it cannot be used for train-of-four (TOF) stimulation, and it is difficult to achieve supramaximal stimulation with this method. As a result, magnetic nerve stimulation is seldom used in clinical anesthesia.

PRINCIPLES OF PERIPHERAL NERVE STIMULATION

Whatever method is used for neuromuscular monitoring, the clinician must be familiar with the two terms, supramaximal stimulation and calibration.

SUPRAMAXIMAL STIMULATION

The reaction of a single muscle fiber to a stimulus follows an all-or-none pattern. In contrast, the response (the force of contraction) of the whole muscle depends on the number of muscle fibers activated. If a nerve is stimulated with sufficient intensity, all fibers supplied by the nerve will react, and the maximum response will be triggered. After administration of a neuromuscular blocking drug, the response of the muscle decreases in parallel with the number of fibers blocked. The reduction in response during constant stimulation reflects the degree of neuromuscular block.

For the preceding principles to be in effect, the stimulus must be truly maximal throughout the period of monitoring; therefore, the electrical stimulus applied is usually at least 15% to 20% greater than that necessary for a maximal response. For this reason, the stimulus is said to be supramaximal; however, supramaximal electrical stimulation can be painful, which is not a concern during anesthesia, but during recovery the patient may be awake enough to experience the discomfort of nerve stimulation. Therefore, some researchers advocate stimulation with submaximal current during recovery. Although several investigations indicate that testing of neuromuscular function can be reliably performed postoperatively with submaximal stimulation,[12,13] the accuracy of such monitoring is unacceptable with low current.[14]

CALIBRATION

A device used for objective monitoring of the neuromuscular function should be calibrated before the neuromuscular blocking drug is administered. Calibration adjusts the gain of the device to ensure that the observed response to supramaximal stimulation is within the measurement window of the device and as close as possible to the "100% control response." The calibration procedure varies with the type of device used, but most often it is done with 1.0 Hz single-twitch stimulation. It is especially important to calibrate when the onset and recovery of the neuromuscular block is established with single-twitch stimulation.

In the TOF mode of nerve stimulation, calibration is considered less important because all four responses are amplified equally. Consequently, the TOF ratio is rarely influenced by calibration; however, in patients with very weak or strong responses to nerve stimulation, one or more responses to TOF stimulation might be out of the recording window, and the displayed TOF response might be incorrect. In some devices, supramaximal stimulation is established concurrently with the calibration procedure.

PATTERNS OF NERVE STIMULATION

For evaluation of neuromuscular function, the most commonly used patterns of electrical nerve stimulation are single-twitch, TOF, and tetanic. Other patterns, such as posttetanic count (PTC) and double-burst stimulation (DBS) can be valuable in certain clinical situations that are described later.

SINGLE-TWITCH STIMULATION

In the single-twitch mode of stimulation, single supramaximal electrical stimuli are applied to a peripheral motor nerve at frequencies ranging from 1.0 Hz (once every second) to 0.1 Hz (once every 10 seconds; Fig. 53-1). The response to single-twitch stimulation depends on the frequency at which the individual stimuli are applied. If the rate of delivery is increased to greater than 0.15 Hz, the evoked response will gradually decrease and stabilize at a lower level. As a result, a frequency of 0.1 Hz is generally used. Because 1-Hz stimulation shortens the time necessary to determine supramaximal stimulation, this frequency is sometimes used during induction of anesthesia; however, the apparent time of onset and length of neuromuscular block depend on the pattern and duration of stimulation. Therefore, results obtained with 1-Hz single-twitch stimulation cannot be compared with results obtained using, for example, 0.1-Hz single-twitch stimulation or TOF stimulation.[15]

TRAIN-OF-FOUR STIMULATION

Train-of-four nerve stimulation pattern, as introduced by Ali and associates[16,17] during the early 1970s, consists of four supramaximal stimuli given every 0.5 seconds (2 Hz; Fig. 53-2). When used continuously, each set (train) of

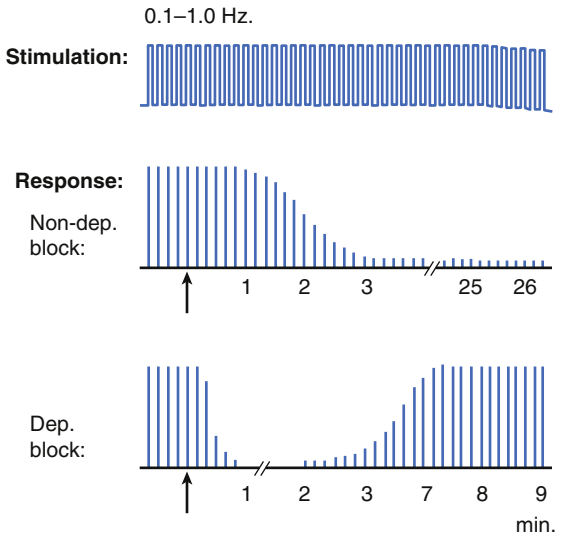


Figure 53-1. Pattern of electrical stimulation and evoked muscle responses to single-twitch nerve stimulation (at frequencies of 0.1 to 1.0 Hz) after injection of nondepolarizing (Non-dep.) and depolarizing (Dep.) neuromuscular blocking drugs (*arrows*). Note that except for the difference in time factors, no differences in the strength of the evoked responses exist between the two types of block.

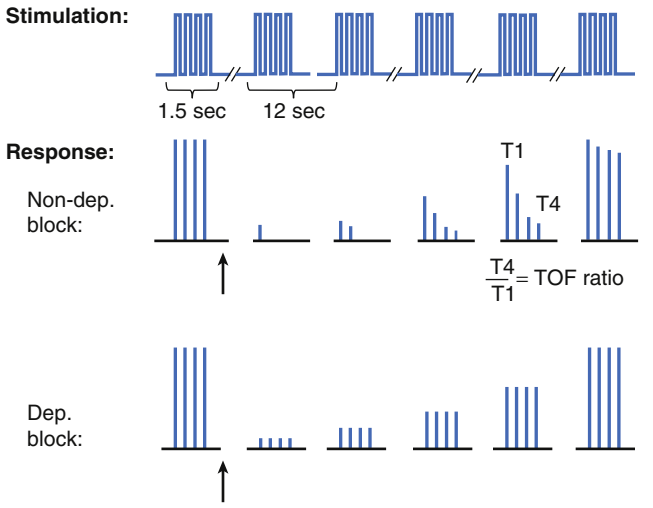


Figure 53-2. Pattern of electrical stimulation and evoked muscle responses to train-of-four (TOF) nerve stimulation before and after injection of nondepolarizing (Non-dep.) and depolarizing (Dep.) neuromuscular blocking drugs (*arrows*).

four stimuli is typically repeated every tenth to twentieth second. Each stimulus in the train causes the muscle to contract, and the "fade" in the train of responses provides the basis for evaluation; that is, dividing the amplitude of the fourth response by the amplitude of the first response provides the TOF ratio. In the control response (the response obtained before the administration of a muscle relaxant), all four responses are ideally the same: the TOF ratio is 1.0. During a partial nondepolarizing block, the ratio decreases (fades) and is inversely proportional to the degree of block. During a partial depolarizing block, no fade occurs in the TOF response; ideally, the TOF ratio is approximately 1.0. Fade in the TOF response after injection of succinylcholine signifies the development of a phase II block (discussed later in the section on depolarizing neuromuscular block).

The advantages of TOF stimulation are most apparent during a nondepolarizing neuromuscular block because the degree of block can be read directly from the TOF response even though a preoperative value is lacking. In addition, TOF stimulation has some advantages over double-burst stimulation and tetanic stimulation; it is less painful and, unlike tetanic stimulation, does not generally influence subsequent monitoring of the degree of neuromuscular block.

TETANIC STIMULATION

Tetanic stimulation consists of high-frequency delivery of electrical stimuli (e.g., 30, 50, or 100 Hz). The most commonly used pattern in clinical practice is 50-Hz stimulation given for 5 seconds, although some investigators have advocated the use of 50-, 100-, and even 200-Hz stimulation for 1 second. In normal neuromuscular transmission or during a depolarizing block, the muscle response to 50-Hz tetanic stimulation for 5 seconds is

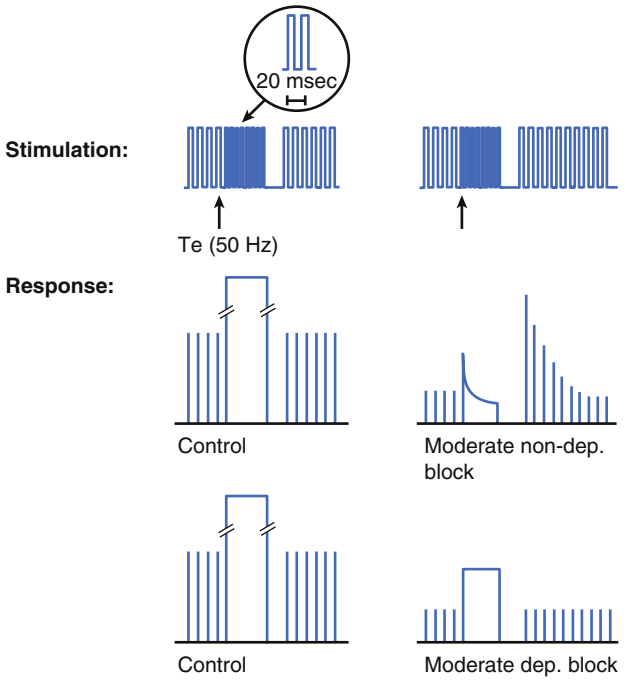


Figure 53-3. Pattern of stimulation and evoked muscle responses to tetanic (50 Hz) nerve stimulation for 5 seconds (Te) and posttetanic twitch stimulation (1.0 Hz; *arrows*). Stimulation was applied before the injection of neuromuscular blocking drugs and during moderate nondepolarizing (non-dep.) and depolarizing (dep.) blocks. Note the fade in the response to tetanic stimulation, plus the posttetanic facilitation of transmission during nondepolarizing block. During depolarizing block, the tetanic response is well sustained, and no posttetanic facilitation of transmission occurs.

sustained. On the other hand, during a nondepolarizing block and a phase II block after the injection of succinylcholine, the response is not sustained (i.e., fade occurs; Fig. 53-3).

Fade in response to tetanic stimulation is normally considered a presynaptic event (see Chapter 18); the traditional explanation is that at the start of tetanic

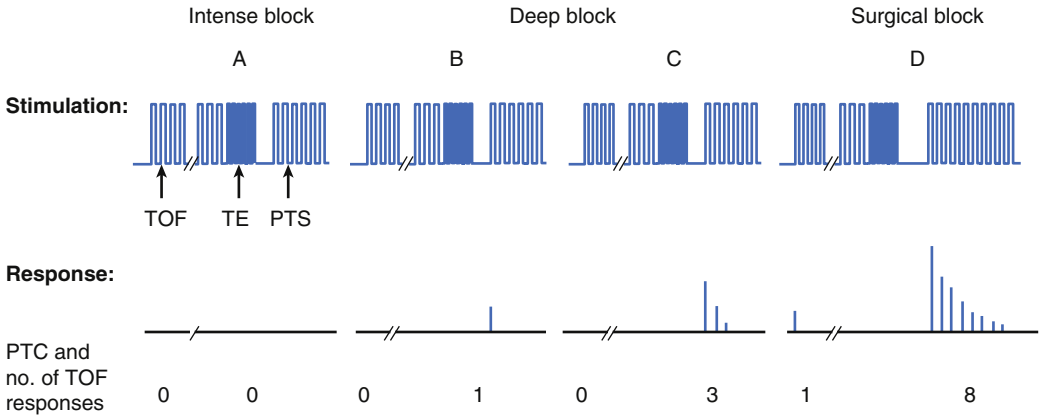


Figure 53-4. Pattern of electrical stimulation and evoked muscle responses to train-of-four (TOF) nerve stimulation, 50-Hz tetanic nerve stimulation for 5 seconds (TE), and 1.0-Hz posttetanic twitch stimulation (PTS) during four different levels of nondepolarizing neuromuscular block. During intense block of peripheral muscles (**A**), no response to any of the forms of stimulation occurs. During less pronounced block (deep block, **B** and **C**), there is still no response to TOF stimulation, but posttetanic facilitation of transmission is present. During surgical block (**D**), the first response to TOF appears and posttetanic facilitation increases further. The posttetanic count (see text) is 1 during very deep block (**B**), 3 during less deep block (**C**), and 8 during surgical (or moderate) block (**D**).

stimulation, large amounts of acetylcholine are released from immediately available stores in the nerve terminal. As these stores become depleted, the rate of acetylcholine release decreases until equilibrium between mobilization and synthesis of acetylcholine is achieved. Despite this equilibrium, the muscle response to tetanic nerve stimulation is maintained (given normal neuromuscular transmission) because the acetylcholine released is many times greater than the amount necessary to evoke a response. When the "margin of safety"[18] at the postsynaptic membrane (i.e., the number of free cholinergic receptors) is reduced by nondepolarizing neuromuscular blocking drugs, a typical reduction in twitch height is seen with a fade during, for example, repetitive stimulation. In addition to this postsynaptic block, nondepolarizing neuromuscular blocking drugs can also block presynaptic neuronal subtype acetylcholine receptors, thereby leading to impaired mobilization of acetylcholine within the nerve terminal (see Chapter 18).[19] This effect substantially contributes to fade in the response to tetanic (and TOF) stimulation. Although the degree of fade depends primarily on the degree of neuromuscular block, fade also depends on the frequency (Hz), the length (seconds) of stimulation, and on how often tetanic stimuli are applied. Unless these variables are kept constant, results from different studies using tetanic stimulation cannot be compared.

During partial nondepolarizing block, tetanic nerve stimulation is followed by a posttetanic, slight increase in twitch tension called *posttetanic facilitation* (see Fig. 53-3). This event occurs because the increase in mobilization and synthesis of acetylcholine caused by tetanic stimulation continues for some time after discontinuation of stimulation. The degree and duration of posttetanic facilitation depend on the degree of neuromuscular block, with posttetanic facilitation usually disappearing within 60 seconds of tetanic stimulation. Posttetanic facilitation is evident in electromyographic, kinemyographic, acceleromyographic, and mechanomyographic recordings during partial nondepolarizing neuromuscular block. In contrast, posttetanic twitch potentiation, which sometimes occurs in mechanical recordings before any neuromuscular blocking drug has been given, is a muscular phenomenon that is not accompanied by an increase in the compound muscle action potential.

Tetanic stimulation is extremely painful, which limits its use in unanesthetized patients. Furthermore, especially in the late phase of neuromuscular recovery, tetanic stimulation can produce lasting antagonism of neuromuscular block in the stimulated muscle such that the response of the tested site may no longer be representative of other muscle groups.[20] Traditionally, tetanic stimulation is used to evaluate residual neuromuscular block. Except in connection with the technique of PTC, tetanic stimulation has little use in everyday clinical anesthesia. If the response to nerve stimulation is recorded, all the information required can be obtained from the response to TOF nerve stimulation. In contrast, if the response to nerve stimulation is evaluated only visually or by tactile evaluation,[21,22] even experienced observers are unable to judge the response of tetanic stimulation with sufficient certainty to exclude residual neuromuscular block.

POSTTETANIC COUNT STIMULATION

Injection of a nondepolarizing neuromuscular blocking drug in a dose sufficient to ensure smooth tracheal intubation causes intense neuromuscular block of peripheral muscles. Because there is no response to TOF and single-twitch stimulation under these conditions, these modes of stimulation cannot be used to determine the degree of block. However, an intense neuromuscular block of the peripheral muscles can be monitored by applying tetanic stimulation (50 Hz for 5 seconds) and observing the posttetanic response to single-twitch stimulation given at 1 Hz starting 3 seconds after the end of tetanic stimulation.[23] During intense block, there is no response to either tetanic or posttetanic stimulation (Fig. 53-4). As the period of very intense

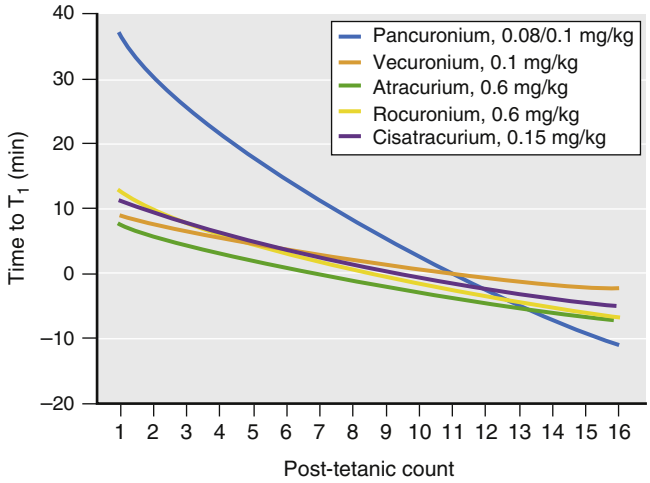


Figure 53-5. Relationship between the posttetanic count and time when onset of train-of-four (T_1) is likely to be elicited for various neuromuscular blocking agents. *(From El-Orbany MI, Joseph JN, Salem MR: The relationship of post-tetanic count and train-of-four responses during recovery from intense cisatracurium-induced neuromuscular block,* Anesth Analg *97:80, 2003.)*

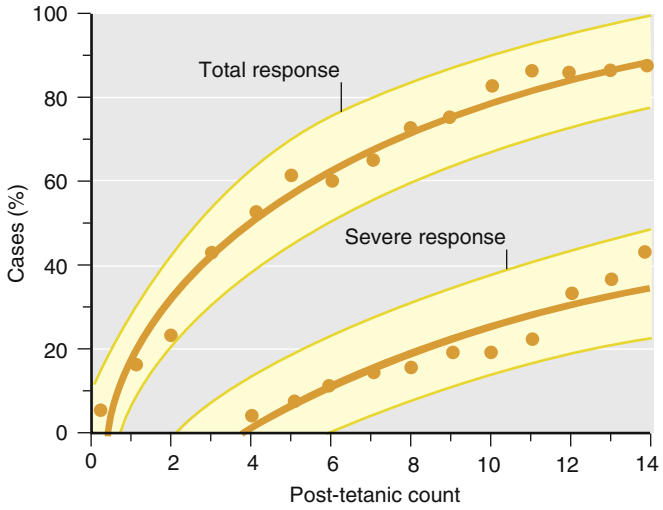


Figure 53-6. Relationship between the rate of muscle response to stimulation of the tracheal carina and the degree of neuromuscular block of peripheral muscles, as evaluated by posttetanic count (PTC). The subjects were 25 patients who were anesthetized with thiopental, nitrous oxide, and fentanyl and given vecuronium (0.1 mg/kg) for tracheal intubation. For comparison, the first response to train-of-four stimulation usually occurs when the PTC is approximately 10 (range, 6 to 16). The carina was stimulated with a soft sterile rubber suction catheter introduced via the endotracheal tube. The total response consisted of mild responses plus severe responses. A mild response was said to occur if stimulation of the carina induced only slight bucking that did not interfere with surgery. A severe response was said to occur if stimulation elicited bucking that interfered with surgery and required intervention. Elimination of severe responses requires an intense neuromuscular block; PTC must be less than 2 to 3, and elimination of all reactions requires that PTC be 0. *(From Fernando PUE, et al: Relationship between post-tetanic count and response to carinal stimulation during vecuronium-induced neuromuscular block.* Acta Anaesthesiol Scand *31:593, 1987. Copyright 1987, Munksgaard International Publishers, Ltd. Copenhagen, Denmark.)*

neuromuscular block dissipates, the first response to posttetanic twitch stimulation occurs and is followed by a gradual return of posttetanic twitches until the first response to TOF stimulation reappears. For a given neuromuscular blocking drug, the time until return of the first response to TOF stimulation is related to the number of posttetanic twitch responses present at a given time (i.e., the PTC; Fig. 53-5).[23-27]

The PTC method is mainly used to assess the degree of neuromuscular block when there is no reaction to single-twitch or TOF nerve stimulation. However, PTC can also be used whenever sudden movements must be eliminated (e.g., during surgery in the airways or ophthalmic surgery). A specific clinical example of the value of PTC occurs in ophthalmic surgery (see Chapter 84). The necessary level of block at the adductor pollicis muscle to ensure paralysis of the diaphragm depends on the type of anesthesia. To ensure elimination of any bucking or coughing in response to tracheobronchial stimulation, a neuromuscular block must be intense (i.e., no response to TOF or PTC stimulation) (Fig. 53-6).[24-28]

When using the new selective relaxant binding drug, sugammadex for reversing a rocuronium-induced or vecuronium-induced deep or intense block (discussed later), the necessary dose of sugammadex depends on the level of block (see Chapter 35). In this situation, PTC can be used to quantitate the degree of block.

The response to PTC stimulation depends primarily on the degree of neuromuscular block. It also depends on the frequency and duration of tetanic stimulation, the length of time between the end of tetanic stimulation and the first posttetanic stimulus, the frequency of the single-twitch stimulation, and probably the duration of single-twitch stimulation before tetanic stimulation. When the PTC method is used, these variables should be kept constant. In addition, because of interference between PTC stimulation and the actual neuromuscular block within the monitored hand, tetanic stimulation should ideally not be performed more often than every 6 minutes.[23]

DOUBLE-BURST STIMULATION

DBS consists of two short bursts of 50-Hz tetanic stimulation separated by 750 msec, with a 0.2-msec duration of each square wave impulse in the burst (Fig. 53-7). Although the number of impulses in each burst can vary, DBS with three impulses in each of the two tetanic bursts ($DBS_{3,3}$) is most commonly used.[29-31]

In nonparalyzed muscle, the response to $DBS_{3,3}$ is two short muscle contractions of equal strength. In a partially paralyzed muscle, the second response is weaker than the first and corresponds to the typical TOF fade (see Fig 53-7). When measured mechanically, the TOF ratio correlates closely with the $DBS_{3,3}$ ratio. DBS was developed with the specific aim of improving manual (tactile) detection of residual block under clinical conditions,[30] or during recovery and immediately after surgery; tactile evaluation of the response to $DBS_{3,3}$ is superior to tactile evaluation of the response to TOF stimulation.[31,32] However, as shown in Figure 53-8, absence of fade in the manually evaluated response to $DBS_{3,3}$ (and TOF) does

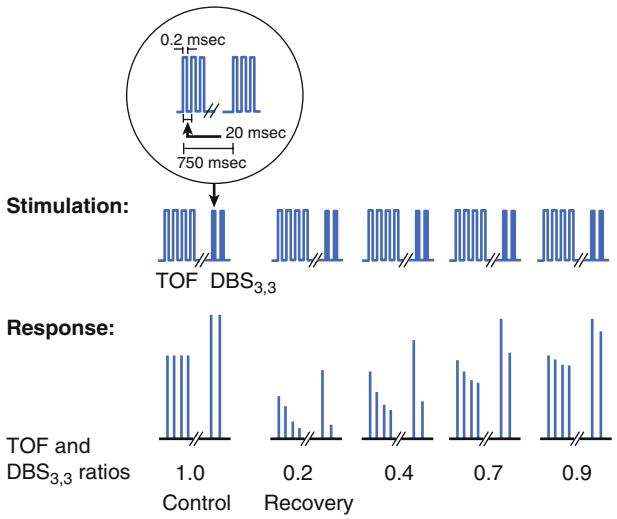


Figure 53-7. Pattern of electrical stimulation and evoked muscle responses to train-of-four (TOF) nerve stimulation and double-burst nerve stimulation (i.e., three impulses in each of two tetanic bursts, $DBS_{3,3}$) before injection of muscle relaxants (control) and during recovery from nondepolarizing neuromuscular block. The TOF ratio is the amplitude of the fourth response to TOF divided by the amplitude of the first response. The $DBS_{3,3}$ ratio is the amplitude of the second response to $DBS_{3,3}$ divided by the amplitude of the first response. (See text for further explanation.)

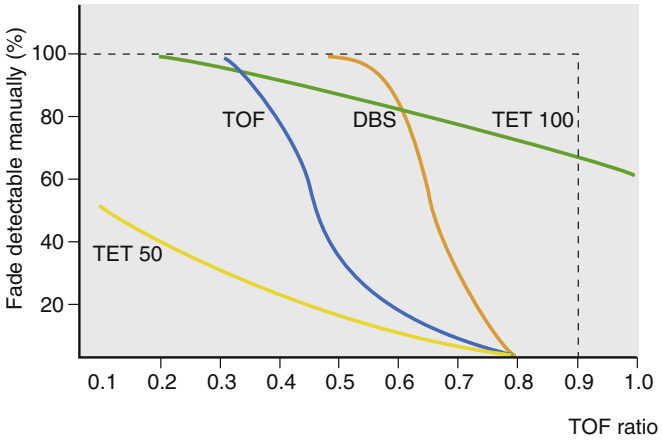


Figure 53-8. Fade detectable by feel in the response to train-of-four (TOF), double-burst stimulation ($DBS_{3,3}$), and 50- and 100-Hz tetanic stimulation (TET 50 and TET 100) in relation to the true TOF ratio, as measured mechanically. The axis indicates the percentage of instances in which fade can be detected at a given TOF ratio.[22,29,31] It appears that it is not possible to exclude residual neuromuscular block by any of the methods. (See text for further explanation.)

not exclude residual neuromuscular block.[33] Accordingly, $DBS_{3,3}$ cannot replace objective monitoring. On the other hand, when objective monitoring is not possible, residual neuromuscular block corresponding to a TOF less than 0.6 or lower can be detected using this method.

THE NERVE STIMULATOR

Although many nerve stimulators are commercially available, not all meet the basic requirements for clinical use. The stimulus should produce a monophasic and rectangular waveform, and the length of the pulse should not exceed 0.2 to 0.3 msec. A pulse exceeding 0.5 msec may stimulate the muscle directly or cause repetitive firing. Stimulation at a constant current is preferable to stimulation at a constant voltage because current is the determinant of nerve stimulation. Furthermore, for safety reasons, the nerve stimulator should be battery operated, include a battery check, and be able to generate 60 to 70 mA, but not more than 80 mA. Many commercially available stimulators can deliver just 25 to 50 mA and provide a constant current only when skin resistance ranges from 0 to 2.5 kΩ. These limitations are a disadvantage; during cooling, skin resistance can increase to approximately 5 kΩ, which can cause the current delivered to the nerve to decrease below the supramaximal level and lead to a decrease in the response to stimulation and possible misjudgment in the degree of block used. Ideally, the nerve stimulator should have a built-in warning system or a current level display that alerts the user when the selected current is not delivered to the nerve. The polarity of the electrodes should be indicated, and the apparatus should be capable of delivering the following modes of stimulation: TOF (as both a single train and in a repetitive mode, with TOF stimulation being given every 10 to 20 seconds), single-twitch stimulation at 0.1 and 1.0 Hz, and tetanic stimulation at 50 Hz. In addition, the stimulator should have a built-in time constant system to facilitate PTC. The tetanic stimulus should last 5 seconds and be followed 3 seconds later by the first posttetanic stimulus. If the nerve stimulator does not allow objective measurement of the response to TOF stimulation, at least one DBS mode should be available, preferably $DBS_{3,3}$. Single-twitch, 1-Hz stimulation is particularly useful in assessing the level of supramaximal stimulation. Tetanus at 100 or 200 Hz is rarely indicated because 50-Hz tetanic stimulation is similar to maximal voluntary muscle contraction. Furthermore, in contrast to 100- and 200-Hz stimulation, 50-Hz tetanic stimulation does not cause fatigue (fade) in nonparalyzed muscle.

STIMULATING ELECTRODES

Electrical impulses are transmitted from stimulator to nerve by means of surface or needle electrodes, the former being the more commonly used in clinical anesthesia. Normally, disposable pregelled silver or silver chloride surface electrodes are used. The actual conducting area should be small, approximately 7 to 11 mm in diameter (Fig. 53-9). Otherwise, the current produced in the underlying nerve may not be adequate.[34] The skin should always be cleansed properly and preferably rubbed with an abrasive before application of the electrodes. When a supramaximal response cannot be obtained with surface electrodes, needle electrodes can be used in a few exceptional cases. Although specially coated needle electrodes are commercially available, ordinary steel injection needles often suffice. A sterile technique should be used, and the needles should be placed subcutaneously to avoid direct injury to the underlying nerve.

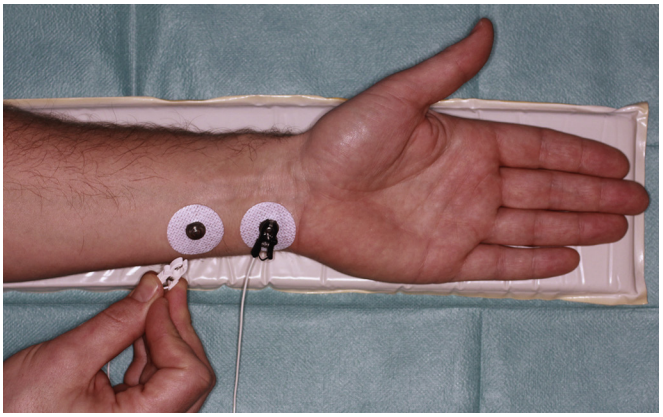


Figure 53-9. Stimulating electrodes with the appropriate contact area in the correct position over the ulnar nerve of the left forearm.

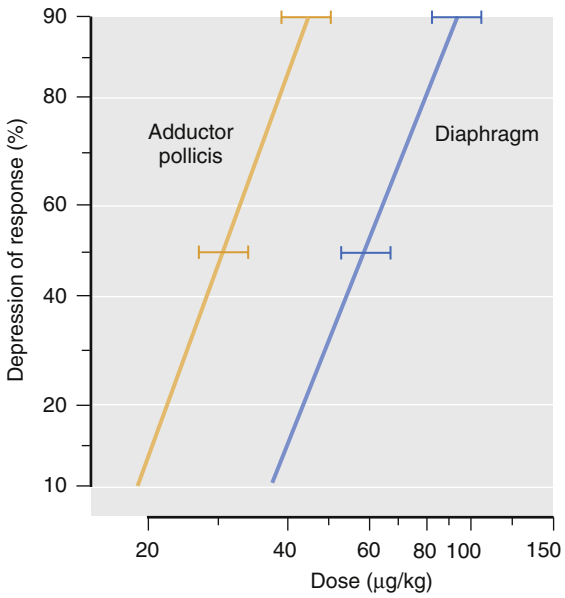


Figure 53-10. The mean cumulative dose-response curve for pancuronium in two muscles shows that the diaphragm requires approximately twice as much pancuronium as the adductor pollicis muscle for the same amount of neuromuscular block. The depression in muscle response to the first stimulus in train-of-four nerve stimulation (probit scale) was plotted against dose (log scale). The force of contraction of the adductor pollicis was measured on a force-displacement transducer; response of the diaphragm was measured electromyographically. *(From Donati F, Antzaka C, Bevan DR: Potency of pancuronium at the diaphragm and the adductor pollicis muscle in humans,* Anesthesiology *65:1, 1986.)*

SITES OF NERVE STIMULATION AND DIFFERENT MUSCLE RESPONSES

In principle, any superficially located peripheral motor nerve can be stimulated. In clinical anesthesia, the ulnar nerve is the most popular site; the median, posterior tibial, common peroneal, and facial nerves are also sometimes used. For stimulation of the ulnar nerve, the electrodes are best applied to the volar side of the wrist (see Fig. 53-9). The distal electrode should be placed approximately 1 cm proximal to the point at which the proximal flexion crease of the wrist crosses the radial side of the tendon to the flexor carpi ulnaris muscle. The proximal electrode should preferably be placed so that the distance between the centers of the two electrodes is 3 to 6 cm (see Fig. 53-9). With this placement of the electrodes, electrical stimulation normally elicits only finger flexion and thumb adduction. If one electrode is placed over the ulnar groove at the elbow, thumb adduction is often pronounced because of stimulation of the flexor carpi ulnaris muscle. When this latter placement of electrodes (sometimes preferred in small children) is used, the active negative electrode should be at the wrist to ensure maximal response. Polarity of the electrodes is less crucial when both electrodes are close to each other at the volar side of the wrist; however, placement of the negative electrode distally normally elicits the greatest neuromuscular response.[35] When the temporal branch of the facial nerve is stimulated, the negative electrode should be placed over the nerve, and the positive electrode should be placed somewhere else over the forehead.

Because different muscle groups have different sensitivities to neuromuscular blocking drugs, results obtained for one muscle cannot be automatically extrapolated to other muscles. The diaphragm is among the most resistant of all muscles to both depolarizing[36] and nondepolarizing neuromuscular blocking drugs.[37] In general, the diaphragm requires 1.4- to 2.0-fold as much muscle relaxant as the adductor pollicis muscle for an identical degree of block (Fig. 53-10).[37] Also of clinical significance is that onset time is normally shorter for the diaphragm than for the adductor pollicis muscle, and the diaphragm recovers from paralysis more quickly than the peripheral muscles (Fig. 53-11).[38] The other respiratory muscles are less resistant than the diaphragm, as are the larynx and the corrugator supercilii muscles.[39-41] Most sensitive are the abdominal muscles, the orbicularis oculi muscle, the peripheral muscles of the limbs, and the geniohyoid, masseter, and upper airway muscles.[42-45] From a clinical point of view, the response of the corrugator supercilii to facial nerve stimulation reflects the extent of neuromuscular block of the laryngeal adductor muscles and abdominal muscles better than the response of the adductor pollicis to ulnar nerve stimulation.[41,46] Furthermore, the upper airway muscles seem to be more sensitive than the peripheral muscles.[42,43] Although some investigations using acceleromyography have indicated small differences in the response to TOF nerve stimulation in the hand (adductor pollicis muscle) compared to the leg (flexor hallucis brevis muscle), these differences are probably of little clinical significance.[47,48] When comparing different sites of stimulation, there might be large differences between contralateral limbs (e.g., arm-to-arm variation of ± 20%).[49,50]

Although the precise source of these differences is unknown, possible explanations may be variations in acetylcholine receptor density, acetylcholine release, acetylcholinesterase activity, fiber composition, innervation ratio (number of neuromuscular junctions), blood flow, and muscle temperature.

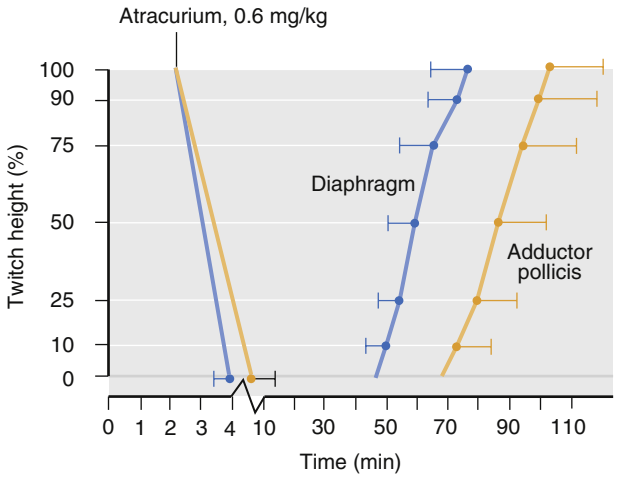


Figure 53-11. Evolution of twitch height (mean ± SD) of the diaphragm (*blue circles*) and the adductor pollicis muscle (*yellow circles*) in 10 anesthetized patients after the administration of atracurium (0.6 mg/kg). *(From Pansard J-L, Chauvin M, Lebrault C, et al: Effect of an intubating dose of succinylcholine and atracurium on the diaphragm and the adductor pollicis muscle in humans,* Anesthesiology *67:326, 1987.)*

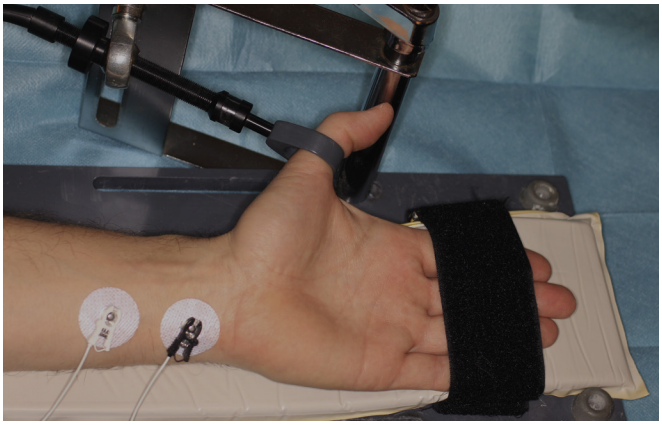


Figure 53-12. The setup for mechanomyography. The response to nerve stimulation is measured using a force transducer (TD-100; Biometer, Odense, Denmark) placed at the proximal phalanx of the thumb.

RECORDING OF EVOKED RESPONSES

Five methods are available for clinical monitoring of neuromuscular function: evoked mechanical response of the muscle (mechanomyography [MMG]), evoked electrical response of the muscle (electromyography [EMG]), acceleration of the muscle response (acceleromyography [AMG]), evoked electrical response in a piezoelectric film sensor attached to the muscle (kinemyography [KMG]) and measurement of low-frequency sounds evoked by the muscle contraction (phonomyography [PMG]). The five methods are described below. For further information on recording evoked responses, the reader is referred to guidelines for good clinical research practice in pharmacodynamic studies of neuromuscular blocking drugs.[34] The only objective monitors currently available are based on AMG, EMG, and KMG. The use of computer-guided administration of neuromuscular blocking drugs and "closed loop control" systems has been suggested, but no systems are commercially available.[51,52]

MECHANOMYOGRAPHY

For correct and reproducible measurement of evoked tension, the muscle contraction needs to be isometric. In clinical anesthesia, this condition is most easily achieved by measuring the force of contraction of the thumb after the application of a resting tension of 200 to 300 g (a preload) to the thumb. When the ulnar nerve is stimulated, the thumb (the adductor pollicis muscle) acts on a force-displacement transducer (Fig. 53-12). The force of contraction is then converted into an electrical signal, which is amplified, displayed, and recorded. The arm and hand should be rigidly fixed, and care should be taken to prevent overloading of the transducer. In addition, the transducer should be placed in correct relation to the thumb (i.e., the thumb should always apply tension along the length of the transducer). It is important to remember that the response to nerve stimulation depends on the frequency with which the individual stimuli are applied and that the time used to achieve a stable control response may influence subsequent determination of the onset time and duration of block.[34] Generally, the reaction to supramaximal stimulation increases during the first 8 to 12 minutes after commencement of the stimulation (staircase phenomenon). Therefore, in clinical studies, recording of the control response (before injection of muscle relaxant) should not be made until the response has stabilized for 8 to 12 minutes or a 2- or 5-second 50-Hz tetanic stimulation has been given.[53] Even then, twitch response often recovers to 110% to 150% of the control response after paralysis with succinylcholine. This increase in response, possibly caused by a change in the contractile response of the muscle, normally disappears within 15 to 25 minutes.

Although there are numerous methods for mechanical recording of evoked mechanical responses, not all meet the criteria outlined. Mechanomyography is recognized as the gold standard of neuromuscular monitoring.[34] Despite this status, there is no commercially available neuromuscular monitor for daily clinical use based on this principle.

ELECTROMYOGRAPHY

Evoked EMG records the compound action potentials produced by stimulation of a peripheral nerve. The compound action potential is a high-speed event that for many years could be detected only by means of a preamplifier and a storage oscilloscope. Modern neuromuscular transmission analyzers are able to make online electronic analyses and graphic presentations of the EMG response.

The evoked EMG response is most often obtained from muscles innervated by the ulnar or the median nerves. Stimulating electrodes are applied as in force measurements. Although both surface and needle electrodes can be used for recording, no advantage is obtained by using the latter. Most often, the evoked EMG response is obtained from the thenar or hypothenar eminence of the hand or from the first dorsal interosseous muscle of the hand, preferably with the active electrode over the motor

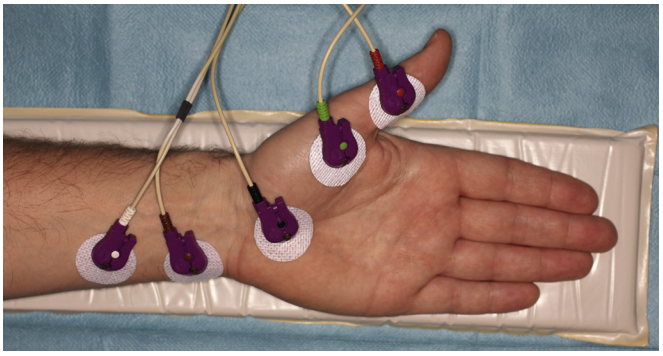


Figure 53-13. The setup for electromyography (NMT ElectroSensor, Datex-Ohmeda, Helsinki, Finland) for recording the compound action potential from the adductor pollicis muscle.

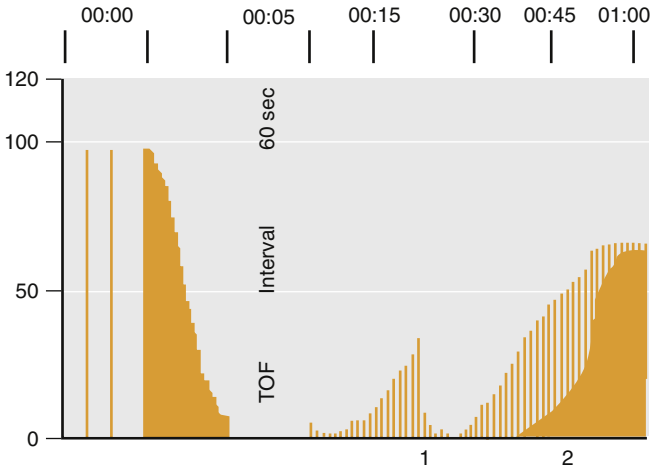


Figure 53-14. Evoked electromyographic printout from a Relaxograph (Datex-Ohmeda, Helsinki, Finland). Initially, single-twitch stimulation was given at 0.1 Hz, and vecuronium (70 μg/kg) was administered intravenously for tracheal intubation. After approximately 5 minutes, the mode of stimulation was changed to train-of-four (TOF) stimulation every 60 seconds. At a twitch height (first twitch in the TOF response) of approximately 30% of control (marker 1), 1 mg of vecuronium was given intravenously. At marker 2, 1 mg of neostigmine was given intravenously, preceded by 2 mg of glycopyrrolate. The printout also illustrates the common problem of failure of the electromyographic response to return to the control level. *(Courtesy Datex-Ohmeda, Helsinki, Finland.)*

point of the muscle (Fig. 53-13). The signal picked up by the analyzer is processed by an amplifier, a rectifier, and an electronic integrator. The results are displayed either as a percentage of control or as a TOF ratio.

Two new sites for recording the EMG response have been introduced: the larynx and the diaphragm.[54,55] Using a noninvasive disposable laryngeal electrode attached to the tracheal tube and placed between the vocal cords, it is possible to monitor the onset of neuromuscular block in the laryngeal muscles. However, the method is mainly of interest in clinical research when investigating onset times of the laryngeal muscles. In paravertebral surface diaphragmatic EMG, the recording electrodes are placed on the right of vertebrae T12/L1 or L1/L2 for monitoring the response of the right diaphragmatic crux to transcutaneous stimulation of the right phrenic nerve at the neck.[54-57] As is the case with surface laryngeal EMG, surface diaphragmatic EMG is mainly of interest in clinical research.

Evoked electrical and mechanical responses represent different physiologic events. Evoked EMG records changes in the electrical activity of one or more muscles, whereas evoked MMG records changes associated with excitation-contraction coupling and contraction of the muscle as well. For these reasons, the results obtained with these methods may differ.[57,58] Although evoked EMG responses generally correlate well with evoked mechanical responses,[30] marked differences can occur, especially in the response to succinylcholine and in the TOF ratio during recovery from a nondepolarizing block.[30,57,59]

In theory, recording of evoked EMG responses has several advantages over recording of evoked mechanical responses. Equipment for measuring-evoked EMG responses is easier to set up, the response reflects only factors influencing neuromuscular transmission, and the response can be obtained from muscles not accessible to mechanical recording. However, evoked EMG does entail some difficulties. Although high-quality recordings are possible in most patients, the results are not always reliable. For one thing, improper placement of electrodes can result in inadequate pickup of the compound EMG signal. If the neuromuscular transmission analyzer does not allow observation of the actual waveform of the compound EMG, determining optimal placement of the electrodes is difficult. Another source of unreliable results may be that fixation of the hand with a preload on the thumb might be more important than is generally appreciated,[30] inasmuch as changes in the position of the electrodes in relation to the muscle can affect the EMG response. In addition, direct muscle stimulation sometimes occurs. If muscles close to the stimulating electrodes are stimulated directly, the recording electrodes can pick up an electrical signal even though neuromuscular transmission is completely blocked. Another difficulty is that the EMG response often does not return to the control value. Whether this situation is the result of technical problems, inadequate fixation of the hand, or changes in temperature is unknown (Fig. 53-14). Finally, the evoked EMG response is highly sensitive to electrical interference, such as that caused by diathermy.

ACCELEROMYOGRAPHY

The technique of AMG is based on Newton's second law: Force = Mass × Acceleration.[60] If mass is constant, acceleration is directly proportional to force. Accordingly, after nerve stimulation, one can measure not only the evoked force but also acceleration of the thumb.

AMG uses a piezoelectric ceramic wafer with electrodes on both sides. Exposure of the electrode to a force generates an electrical voltage proportional to acceleration of the electrode. Consequently, when an accelerometer is fixed to the thumb and the ulnar nerve is stimulated, an electrical signal is produced whenever the thumb moves. This signal can be analyzed in a specially designed analyzer[61] or displayed on a recording system. At least two detached monitors are commercially available, based on the same transducer: the TOF-Watch (Biometer, Odense, Denmark) and the Infinity Trident NMT SmartPod (Dräger, Lübeck, Germany; Fig. 53-15).

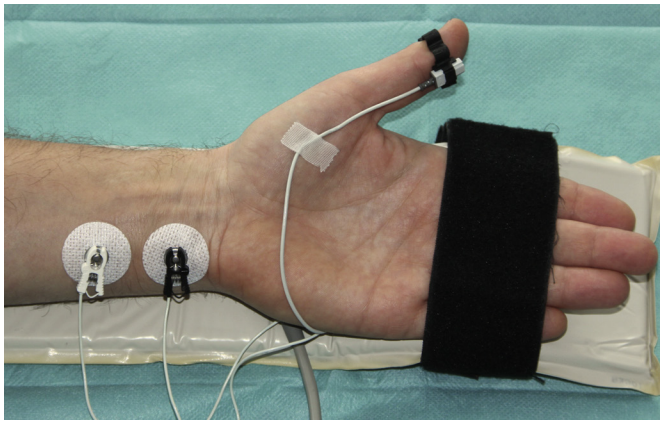


Figure 53-15. The setup of acceleromyography without preload (TOF Watch, Biometer, Odense, Denmark). The response to nerve stimulation is measured with a small piezoelectric acceleration transducer placed distally on the volar site of the thumb.

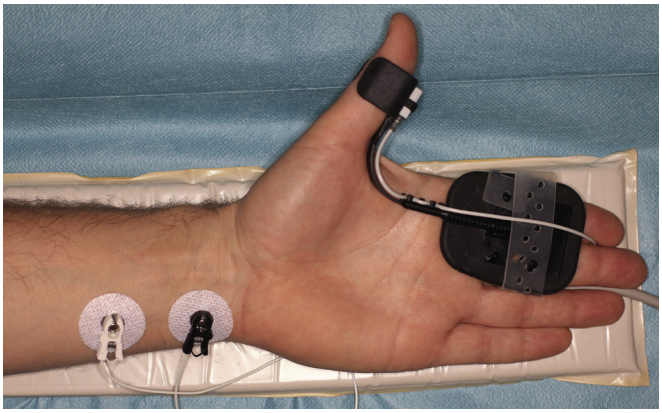


Figure 53-16. The setup of acceleromyography with preload (TOF Watch with Hand Adapter, Biometer, Odense, Denmark). The piezoelectric acceleration transducer is placed in the Hand Adapter. The stretching wing ensures that the thumb does not touch the palm of the hand.

AMG is a simple method of analyzing neuromuscular function, both in the operating room and in the intensive care unit. Although good correlation exists between the TOF ratio measured by this method and the TOF ratio measured with a force-displacement transducer or EMG,[60,62,63] measurements made via AMG are not directly comparable with results obtained by the other two methods.[63-69] When AMG is used with a free-moving thumb, as originally suggested,[60] wide limits of agreements in twitch height (T1) and TOF ratio and differences in the onset and recovery course of block between AMG and MMG have been found. Moreover, the AMG control TOF ratio is consistently higher than when measured with a force-displacement transducer. In accordance with this, several studies have indicated that when using AMG, the TOF ratio indicative of sufficient postoperative neuromuscular recovery is 1.0 rather than 0.90, as when measured by MMG or EMG in the adductor pollicis muscle.[2,22,68,70,71] In contrast to MMG and EMG, the control baseline TOF value before administration of a neuromuscular blocking drug is most often 1.1 to 1.2 when measured with AMG, and in some patients is as high as 1.4. A high control baseline value probably indicates that the TOF ratio necessary for excluding residual curarization is equally higher. For instance, in a patient with a high control baseline value (e.g., TOF = 1.2), it is to be expected that a higher TOF ratio during recovery is necessary to exclude residual block compared with a patient with a low control baseline value (e.g., TOF = 0.95). It is generally accepted that the TOF ratio should be at least 0.90 to exclude clinically significant residual paralysis; using the preceding example, a TOF ratio of 1.08 (90% of 1.2) would represent safe recovery in the first patient, whereas a TOF ratio of 0.86 (90% of 0.95) would suffice in the other patient. To overcome such problems, it has been suggested to refer the actually obtained TOF ratios during recovery to the baseline control TOF ratio (normalization).[22,67,72-75] Currently, no commercially available monitors can "normalize" the TOF ratio automatically. Intuitively, for excluding residual block using AMG, a TOF ratio of at least 1.0 should be targeted to exclude residual block.[22,67,68,73]

One reason for the wide limits of agreement between AMG and MMG is probably and paradoxically connected with one of the originally claimed advantages of the method, that fixation of the hand could be reduced to a minimum as long as the thumb could move freely.[60] In clinical practice, it is often not possible to ensure that the thumb can move freely and that the position of the hand does not change during the surgical procedure. The evoked response can therefore vary considerably. Several solutions have been proposed, but the use of an elastic preload on the thumb improves the precision without compromising the agreement between results obtained with AMG and MMG (Fig. 53-16).[67,68] Several studies have indicated that objective monitoring with AMG reduces and almost eliminates the problem of postoperative residual neuromuscular block.[67,76-80]

When the thumb is not available for monitoring during surgery, some clinicians prefer to monitor the AMG response of the orbicularis oculi or the corrugator supercilii in response to facial nerve stimulation.[46] However, neuromuscular monitoring of both sites with AMG is subject to large uncertainty regarding the extent of paralysis, and it cannot be recommended for routine monitoring. It provides only a rough estimate of the degree of block of the peripheral muscles.[81,82]

PIEZOELECTRIC NEUROMUSCULAR MONITORS

The technique of the piezoelectric monitor is based on the principle that stretching or bending a flexible piezoelectric film (e.g., one attached to the thumb) in response to nerve stimulation generates a voltage that is proportional to the amount of stretching or bending.[83,84] At least one device based on this principle is available commercially in two sizes (adult and pediatric): the NMT MechanoSensor (Datex-Ohmeda, Helsinki, Finland; Fig. 53-17).

Few studies have evaluated the function of these monitors.[83-85] Limited data indicate not only a good relationship between results obtained with PZEMG, AMG, and MMG, but also wide limits of agreement between

the methods. Therefore, although PZEMG may be a valuable clinical tool, the values obtained in an individual patient with this method can vary from those obtained with MMG or AMG.

PHONOMYOGRAPHY

Phonomyography (acoustic myography) is an interesting new method of monitoring neuromuscular function, but it is not yet commercially available.[49,86-91] Contraction of skeletal muscles generates intrinsic low-frequency sounds, which can be recorded with special microphones. This method has been evaluated for clinical and research purposes. Several reports indicate good correlation between evoked acoustic responses and those obtained with more traditional methods of recording, such as MMG, EMG, and AMG. However, it is uncertain whether PMG will ever be used for monitoring neuromuscular block during routine anesthesia. What does make PMG interesting, however, is that in theory the method can be applied not only to the adductor pollicis muscle, but also to other muscles of interest such as the diaphragm, larynx, and eye muscles. In addition, the ease of application is attractive.

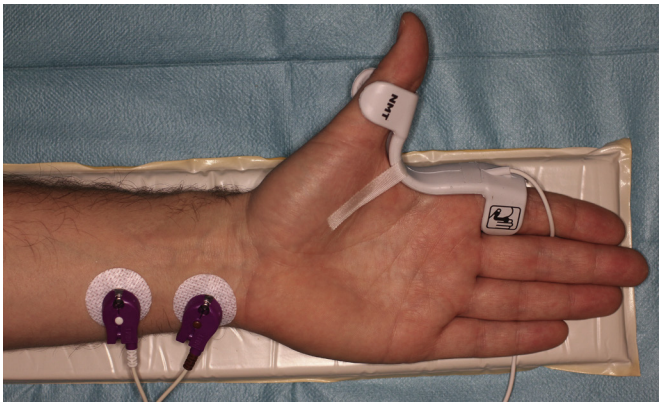


Figure 53-17. The setup of kinemyography (NMT MechanoSensor, Datex-Ohmeda, Helsinki, Finland). The response to nerve stimulation is measured by the bending of a small piezoelectric sensor positioned between the index finger and the thumb.

EVALUATION OF RECORDED EVOKED RESPONSES

Nerve stimulation in clinical anesthesia is usually synonymous with TOF nerve stimulation. Therefore, the recorded response to this form of stimulation is used to explain how to evaluate the degree of neuromuscular block during clinical anesthesia.

NONDEPOLARIZING NEUROMUSCULAR BLOCK

After injection of a nondepolarizing neuromuscular blocking drug in a dose sufficient for smooth tracheal intubation, TOF recording demonstrates four phases, or levels, of neuromuscular block: intense block, deep block, moderate or surgical block, and recovery (Fig. 53-18).

Intense Neuromuscular Block

Intense or profound neuromuscular block occurs within 3 to 6 minutes of injection of an intubating dose of a nondepolarizing muscle relaxant, depending on the drug and the dose given. This phase is also called the "period of no response" because no response to any pattern of nerve stimulation occurs. The length of this period varies, again depending primarily on the duration of action of the muscle relaxant and the dose given. The sensitivity of the patient to the drug also affects the period of no response. An intense block cannot be antagonized with a cholinesterase inhibitor (e.g., neostigmine), and only a high dose of sugammadex (16 mg/kg) can antagonize an intense block caused by rocuronium or vecuronium.[92,93]

Deep Neuromuscular Block

Intense neuromuscular block is followed by a period of deep neuromuscular block, characterized by absence of

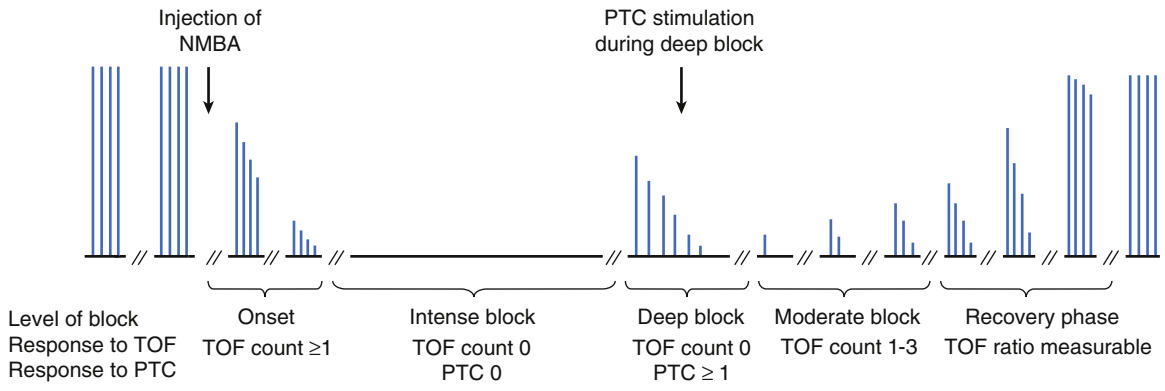


Figure 53-18. Levels of block after a normal intubating dose of a nondepolarizing neuromuscular blocking agent (NMBA) as classified by posttetanic count (PTC) and train-of-four (TOF) stimulation. During intense (profound) block, there are no responses to either TOF or PTC stimulation. During deep block, there is response to PTC but not to TOF stimulation. Intense (profound) block and deep block together constitute the "period of no response to TOF stimulation." Reappearance of the response to TOF stimulation heralds the start of moderate block. Finally, when all four responses to TOF stimulation are present and a TOF ratio can be measured, the recovery period has started. *(From Fuchs-Buder T, et al: Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: The Stockholm revision,* Acta Anaesthesiol *Scand 51:789, 2007.)*

response to TOF stimulation, but with the presence of posttetanic twitches (i.e., PTC ≥ 1; compare with Figure 53-4). Although prediction of the duration of a deep neuromuscular block is difficult, correlation usually exists between PTC stimulation and the time until reappearance of the first response to TOF stimulation (see Fig. 53-5). Attempts to reverse a deep neuromuscular block with neostigmine is usually impossible (see Chapter 35). However, a deep neuromuscular block caused by rocuronium or vecuronium can be antagonized completely within a few minutes using a dose of sugammadex of 4 mg/kg.[94-96]

Moderate or Surgical Neuromuscular Block

Moderate or surgical neuromuscular block begins when the first response to TOF stimulation appears. This phase is characterized by a gradual return of the four responses to TOF stimulation. Furthermore, good correlation exists between the degree of neuromuscular block and the number of responses to TOF stimulation. When only one response is detectable, the degree of neuromuscular block (the depression in twitch tension) is 90% to 95%. When the fourth response reappears, neuromuscular block is usually 60% to 85%.[97,98] The presence of one or two responses in the TOF pattern normally indicates sufficient relaxation for most surgical procedures. During light anesthesia, however, patients may move, buck, or cough; therefore, a deeper block (or a deeper level of anesthesia) may be necessary when elimination of sudden movements or facilitation of surgery is necessary. The deep neuromuscular block can then be evaluated with PTC (see Fig. 53-6).[23]

Antagonism of neuromuscular block with neostigmine should usually not be attempted when the block is intense or deep. Even if some reversal occurs, it will often be inadequate, regardless of the dose of neostigmine administered.[99] Furthermore, after the administration of large doses of muscle relaxants, reversal of the block with neostigmine to clinically normal activity is not always possible if only one TOF response is present. In general, antagonism with neostigmine should not be initiated before at least two to four responses are observed. Even then, sufficient recovery cannot be guaranteed unless documented using objective monitoring (see Chapter 35).[100,101]

Antagonism of moderate block induced by rocuronium and vecuronium can be achieved with a small dose of sugammadex (2 mg/kg) within a few minutes.[102-104] However, the reappearance of neuromuscular blockade has been reported by anesthesiologists from Japan[105] when the 2 mg/kg dose has been used. They did not monitor the degree of neuromuscular blockade. Did the reappearance of neuromuscular blockade occur because of inadequate monitoring or too small a dose of sugammadex? Even with proper monitoring, these results suggest that a dose larger than 2 mg/kg should be used.[106] Although the antagonism of neuromuscular block from sugammadex seems to be fast and predictable, objective monitoring should still be used until the TOF ratio is 0.9 to 1.0.

Recovery from Neuromuscular Block

Return of the fourth response in the TOF heralds the recovery phase. During neuromuscular recovery, a reasonably good correlation exists between the actual TOF ratio and clinical observation, but the relationship between the TOF ratio and signs and symptoms of residual block varies greatly among patients.[80,99] When the TOF ratio is 0.4 or less, the patient is generally unable to lift the head or arm. Tidal volume may be normal, but vital capacity and inspiratory force is reduced. When the ratio is 0.6, most patients are able to lift their head for 3 seconds, open their eyes widely, and stick out their tongue, but vital capacity and inspiratory force are often still reduced. At a TOF ratio of 0.7 to 0.75, the patient can normally cough sufficiently and lift the head for at least 5 seconds, but grip strength may still be as low as about 60% of control.[107] When the ratio is 0.8 and higher, vital capacity and inspiratory force are normal.[17,108-110] The patient may, however, still have diplopia, blurred vision, and facial weakness (Table 53-1).[80,107]

The TOF ratio must exceed 0.90 when recorded with MMG or EMG, and 1.0 when using AMG to exclude clinically important residual neuromuscular block.[30,44,67,68,70,111-116] Moderate degrees of neuromuscular block can impair carotid body chemosensitivity to hypoxia with absent ventilatory response to arterial desaturation.[111,112,114,116] Moreover, residual block (TOF < 0.90) is associated with functional impairment of the pharyngeal and upper esophageal muscles, which most probably predisposes to regurgitation and aspiration of gastric contents.[44] Eikermann and colleagues[117] have documented that partial neuromuscular block, even to a degree that does not evoke dyspnea or oxygen desaturation, can decrease inspiratory upper airway volume and can evoke partial inspiratory airway collapse.[117] Also, residual block (TOF < 0.70) caused by the long-acting muscle relaxant pancuronium is a significant risk factor for the development of postoperative pulmonary complications (Table 53-2 and Fig. 53-19).[113] Intraoperative neuromuscular monitoring reduces the risk of residual neuromuscular block and results in fewer patients with hypoxemic events or airway obstruction in the postanesthesia care unit.[79] Even in volunteers without sedation or impaired consciousness, a TOF ratio of 0.90 or less

TABLE 53-1 CLINICAL SIGNS AND SYMPTOMS OF RESIDUAL PARALYSIS IN AWAKE VOLUNTEERS AFTER MIVACURIUM-INDUCED NEUROMUSCULAR BLOCK

Train-of-Four Ratio	Signs and Symptoms
0.70-0.75	Diplopia and visual disturbances Decreased handgrip strength Inability to maintain apposition of the incisor teeth "Tongue depressor test" negative Inability to sit up without assistance Severe facial weakness Speaking a major effort Overall weakness and tiredness
0.85-0.90	Diplopia and visual disturbances Generalized fatigue

From Kopman AF, Yee PS, Neuman GG: Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers, Anesthesiology *86:765, 1997.*

TABLE 53-2 **RELATIONSHIP BETWEEN TRAIN-OF-FOUR RATIO AT THE FIRST POSTOPERATIVE RECORDING AND POSTOPERATIVE PULMONARY COMPLICATIONS***

	Pancuronium (*n* = 226)			Atracurium or Vecuronium (*n* = 450)		
		Patients with POPC			Patients with POPC	
	No. of patients	n	%	No. of Patients	n	%
TOF ≥ 0.70	167	8	4.8	426	23	5.4
TOF < 0.70	59	10	16.9†	24	1	4.2

*Results from a prospective, randomized, and blinded study of postoperative pulmonary complications (POPC) in a total of 691 adult patients undergoing abdominal, gynecologic, or orthopedic surgery and receiving either pancuronium, atracurium, or vecuronium.[82] In 4 of the 46 patients with POPC (1 in the pancuronium group and 3 in the atracurium and vecuronium groups), the train-of-four (TOF) ratio was not available. Because there were no significant differences in the two groups of patients given the intermediate-acting muscle relaxants, the data from these groups are pooled.
†$p < 0.02$ versus patients in the same group with a train-of-four ratio of 0.70 or greater.

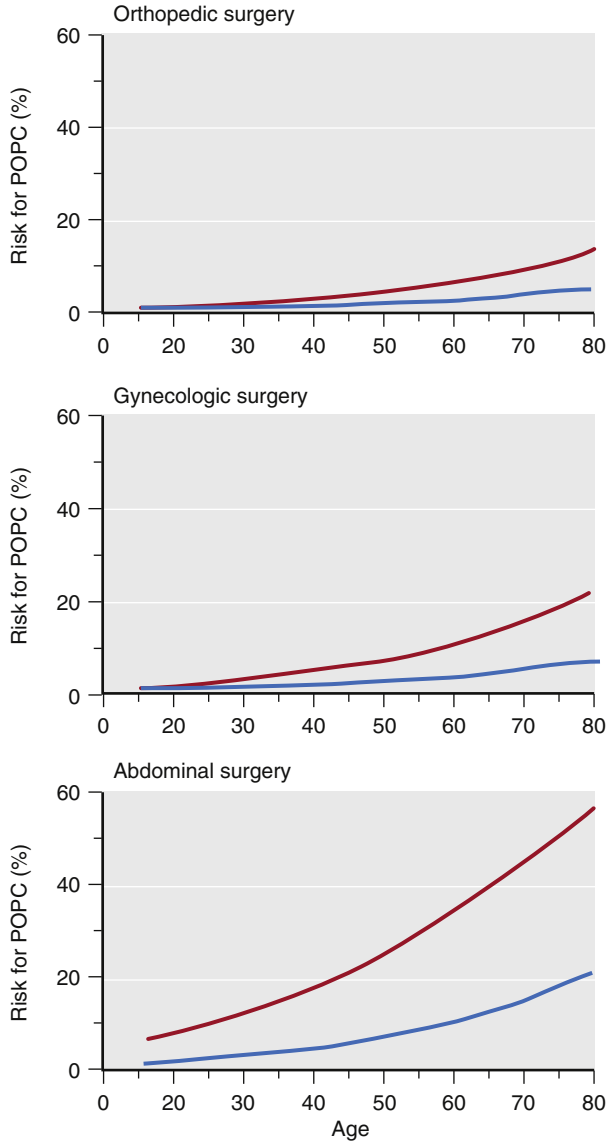


Figure 53-19. Predicted probabilities of a postoperative pulmonary complication (POPC) in different age groups in orthopedic, gynecologic, and major abdominal surgery with duration of anesthesia of less than 200 minutes. The *red lines* represent patients with residual neuromuscular block (train-of-four [TOF] < 0.70) after the administration of pancuronium; the *blue lines* represent patients with a TOF of 0.70 or greater after the administration of pancuronium, as well as all patients after the administration of atracurium and vecuronium, independent of the TOF ratio at the end of anesthesia.[113]

can impair the ability to maintain the airway.[76,107,118] Even small degrees of residual block are unpleasant for patients causing symptoms, such as general weakness and blurred vision.[80] In summary, adequate recovery of neuromuscular function requires the return of an MMG or EMG TOF ratio to at least 0.90, and an AMG TOF ratio to at least 1.0 (or normalized to 0.90),[74] which cannot be guaranteed without objective neuromuscular monitoring.[77,78,80,119-122]

DEPOLARIZING NEUROMUSCULAR BLOCK (PHASE I AND II BLOCKS)

Patients with normal plasma cholinesterase activity who are given a moderate dose of succinylcholine (0.5 to 1.5 mg/kg) undergo a typical depolarizing neuromuscular block (phase I block; i.e., the response to TOF or tetanic stimulation does not fade, and no posttetanic facilitation of transmission occurs). In contrast, some patients with genetically determined abnormal plasma cholinesterase activity who are given the same dose of succinylcholine undergo a nondepolarizing-like block characterized by fade in the response to TOF and tetanic stimulation and the occurrence of posttetanic facilitation of transmission (Fig. 53-20). This type of block is called a *phase II block* (dual, mixed, or desensitizing block). In addition, phase II blocks sometimes occur in genetically normal patients after repetitive bolus doses or a prolonged infusion of succinylcholine.

From a therapeutic point of view, a phase II block in normal patients must be differentiated from a phase II block in patients with abnormal cholinesterase activity. In healthy patients, a phase II block can be antagonized by administering a cholinesterase inhibitor a few minutes after discontinuation of succinylcholine. In patients with abnormal genotypes, however, the effect of intravenous injection of a cholinesterase inhibitor (e.g., neostigmine) is unpredictable because it inhibits acetylcholinesterase and plasma-cholinesterase. For example, neostigmine can potentiate the block dramatically, temporarily improve neuromuscular transmission, and then potentiate the block or partially reverse the block, all depending on the time elapsed since administration of succinylcholine and the dose of neostigmine given. Therefore, unless the cholinesterase genotype is known to be normal, antagonism of a phase II block with a cholinesterase inhibitor should be undertaken with extreme caution. Even if

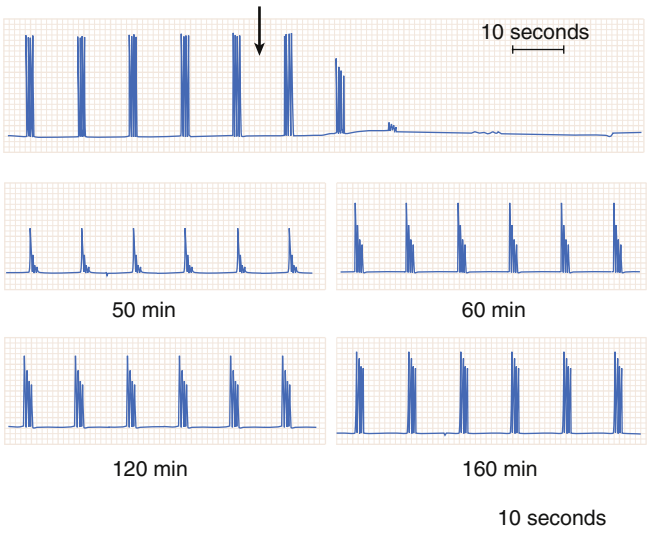


Figure 53-20. Typical recording of the mechanical response to train-of-four ulnar nerve stimulation after injection of 1 mg/kg of succinylcholine (*arrow*) in a patient with genetically determined abnormal plasma cholinesterase activity. The prolonged duration of action and the pronounced fade in the response indicate a phase II block.

neuromuscular function improves promptly, patient surveillance should continue for at least 1 hour.

USE OF NERVE STIMULATORS IN DAILY CLINICAL PRACTICE

Whenever a neuromuscular blocking drug is administered to a patient, objective monitoring of the evoked response using recording equipment is the best way to evaluate the neuromuscular block. However, tactile or visual evaluation are still the most common forms of clinical neuromuscular monitoring, not least when recording equipment is not available or considered unreliable. The following is a description of how to use nerve stimulators with or without recording equipment (objective monitoring).

PREPARATIONS BEFORE INDUCTION OF ANESTHESIA AND ADMINISTRATION OF THE NEUROMUSCULAR BLOCKING AGENT

First, for supramaximal stimulation, careful cleansing of the skin and proper placement and fixation of electrodes are essential. When the ulnar nerve is used for nerve stimulation, one should take advantage of the fact that the nerve follows the artery by placing the electrodes above the pulse. This placement gives the best response (see Fig. 53-9). Second, every effort should be taken to prevent central cooling, as well as cooling of the extremity being evaluated. Both central and local surface cooling of the adductor pollicis muscle can reduce twitch tension and the TOF ratio.[123-125] Peripheral cooling can affect nerve conduction, decrease the rate of release of acetylcholine and muscle contractility, increase skin impedance, and reduce blood flow to the muscles, thus decreasing the rate of removal of muscle relaxant from the neuromuscular junction. These factors might account for the occasional and pronounced difference in muscle response between a cold extremity and the contralateral warm extremity.[126]

USE OF A NERVE STIMULATOR DURING INDUCTION OF ANESTHESIA

The nerve stimulator should be attached to the patient before induction of anesthesia, but should not be turned on until after the patient is unconscious.

Single-twitch stimulation at 1 Hz can be used initially when seeking supramaximal stimulation. However, after supramaximal stimulation has been ensured and before the muscle relaxant is injected, the recording equipment (when using objective monitoring) should be calibrated to ensure that the response is in the measurement window and the response to 1 Hz stimulation is set to 100%. Currently, all commercially available devices have an automatic calibration modus. Without calibration, the recorded response to nerve stimulation might differ significantly from the visual or tactile response throughout all levels of neuromuscular block; therefore, the mode of stimulation should be changed to TOF (or 0.1-Hz twitch stimulation). When the response to this stimulation is observed (the control response), the neuromuscular blocking drug is injected. Although the trachea is often intubated when the response to TOF stimulation disappears, postponement of this procedure for 30 to 90 seconds, depending on the muscle relaxant used, usually produces better conditions.

When possible, the response to nerve stimulation should be evaluated at the thumb (rather than at the fifth finger). Direct stimulation of the muscle often causes subtle movement of the fifth finger when no response is present at the thumb. Finally, the different sensitivities of various muscle groups to neuromuscular blocking drugs should always be kept in mind.

USE OF A NERVE STIMULATOR DURING SURGERY

If tracheal intubation is facilitated by the administration of succinylcholine, no more muscle relaxant should be given until the response to nerve stimulation reappears or the patient shows other signs of returning neuromuscular function. If plasma cholinesterase activity is normal, the muscle response to TOF nerve stimulation reappears within 4 to 8 minutes.

When a nondepolarizing neuromuscular drug is used for tracheal intubation, a longer-lasting period of intense block usually follows. During this period of no response to TOF and single-twitch stimulation, the time until the return of response to TOF stimulation can be evaluated by PTC (see Fig. 53-5 and Fig. 53-21).

For most surgical procedures requiring muscle relaxation, it is not necessary to have an intense block, provided that the patient is adequately anesthetized. If a nondepolarizing relaxant is used, a moderate level of neuromuscular block with one or two of the responses to TOF stimulation is sufficient. However, because the respiratory muscles (including the diaphragm) are less sensitive to neuromuscular blocking drugs than the peripheral

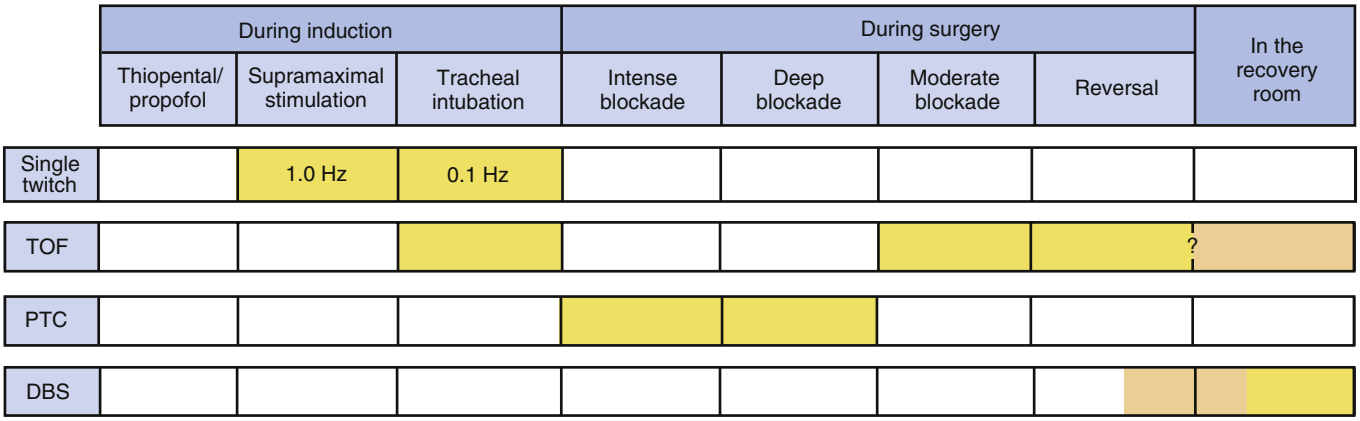


Figure 53-21. Diagram showing when the different modes of electrical nerve stimulation can be used during clinical anesthesia. *Dark areas* indicate appropriate use and *light areas*, less effective use. Modes of nerve stimulation are train-of-four (TOF) stimulation; posttetanic count (PTC); double-burst stimulation (DBS); and the question mark (?), indicating that TOF is less useful in the recovery room unless measured with mechanomyography, electromyography, or acceleromyography. (See text for further explanation.)

muscles are, the patient may breathe, hiccup, or even cough at this depth of block. Moreover, tonus of the diaphragm might impede the surgical conditions. To ensure paralysis of the diaphragm, neuromuscular block of the peripheral muscles must be so intense that the PTC is zero at the thumb.

The disadvantages of sustaining a deep or intense neuromuscular block is that the risk of awareness most probably is increased (see Chapters 13 and 50). When muscles are completely paralyzed, the patient cannot signal awareness with voluntary or involuntary movements. Another disadvantage of a deep or intense block is that the neuromuscular block cannot readily be reversed by neostigmine. Only sugammadex can reverse a deep or intense neuromuscular block (if caused by rocuronium or vecuronium; see Chapter 35).

USE OF A NERVE STIMULATOR DURING REVERSAL OF NEUROMUSCULAR BLOCK

Antagonism of nondepolarizing neuromuscular block is most often facilitated with a cholinesterase inhibitor, such as neostigmine, or with the selective relaxant binding agent sugammadex when the neuromuscular block is achieved using rocuronium or vecuronium.

Antagonism with neostigmine should not be initiated before at least two to four responses to TOF stimulation are present or before there are obvious clinical signs of returning neuromuscular function. Reversal of neuromuscular block will not be hastened and can possibly be delayed by giving neostigmine when no response to peripheral nerve stimulation is present. Moreover, even when there are two to four responses to TOF stimulation, the reversal is slow and insufficient in some patients. With a large dose of neostigmine (e.g., 5 mg/70 kg) the median time to achieve a TOF ratio of 0.90 is 15 to 20 minutes, and it will take approximately 90 to 120 minutes to achieve a TOF ratio of 0.90 in 95% of the patients after an intermediate-acting neuromuscular blocking drug (e.g., rocuronium). Conversely, a large dose of neostigmine after full recovery might give a paradoxical block with decreasing TOF ratio.[127-131]

When rocuronium or vecuronium is used, the selective relaxant binding drug, sugammadex can be used for reversal[102,103] (see Chapter 35). Sugammadex encapsulates rocuronium and vecuronium with a high affinity, thereby antagonizing the neuromuscular blocking effect. Three different doses of sugammadex are recommended according to the level of block. A large dose (16 mg/kg) is given during intense block (no response to PTC stimulation),[92,93] a medium dose (4 mg/kg) during deep block (two or more responses to PTC),[94-96] and a low dose (2 mg/kg) during moderate block (two or more responses to TOF stimulation).[102-104] In most patients, all levels of neuromuscular block are reversed within 2 to 5 minutes. However, residual neuromuscular block can be excluded only with objective monitoring (TOF ratio, 0.9 to 1.0).[132]

As previously described, a recent observational study from Japan also placed emphasis on the relative relationship between a dose of sugammadex and monitoring of neuromuscular blockade.[105] Basically, Kotake and colleagues[105] observed reappearance of neuromuscular block after administration of an average dose of 2.7 mg/kg of sugammadex. The accompanying editorial by Naguib and colleagues[106] placed prime importance on the lack of monitoring as the problem. They also lamented the frequent incidence of not using neuromuscular monitoring during anesthesia. The emphasis on monitoring is important and correct, but incomplete. In this editor's (R. D. Miller) opinion, a larger dose of sugammadex should be given. However, Naguib and colleagues[106] state that this recommendation would double the cost of the reversal drug. Should we not give a proper dose of sugammadex in the interest of decreasing the incidence of residual neuromuscular block? The fact that these two publications are being referenced twice within this chapter indicates their importance.

During recovery of neuromuscular function, when all four responses to TOF stimulation can be felt, an estimation of the TOF ratio can be attempted. However, manual (tactile) evaluation of the response to TOF stimulation (see Fig. 53-8) is not sensitive enough to exclude the possibility of residual neuromuscular block.[22,29,119,133] Greater sensitivity is achieved with $DBS_{3,3}$, but even absence of manual

BOX 53-1 *Clinical Tests of Postoperative Neuromuscular Recovery*

Unreliable

- Sustained eye opening
- Protrusion of the tongue
- Arm lift to the opposite shoulder
- Normal tidal volume
- Normal or nearly normal vital capacity
- Maximum inspiratory pressure less than 40 to 50 cm H_2O

More reliable, but still not excluding residual neuromuscular block

- Sustained head lift for 5 seconds
- Sustained leg lift for 5 seconds
- Sustained handgrip for 5 seconds
- Sustained "tongue depressor test"
- Maximum inspiratory pressure 40 to 50 cm H_2O or greater

fade in the $DBS_{3,3}$ response does not exclude clinically significant residual block.[22,32] Moreover, some patients might suffer from residual block, even after recovery to a TOF ratio of 0.9 to 1.0.[76,80] Therefore, manual evaluation of responses to nerve stimulation should always be considered in relation to reliable clinical signs and symptoms of residual neuromuscular block (Box 53-1).

WHEN TO USE A PERIPHERAL NERVE STIMULATOR

In clinical practice, significant residual block can be excluded with certainty only if an objective method of neuromuscular monitoring is used.[77,78] Therefore, good evidence-based practice dictates that clinicians should always quantitate the extent of neuromuscular recovery by objective monitoring.[3-9] Only a TOF ratio of 0.90 to 1.00 that is measured by objective monitoring ensures a low risk of clinically significant residual block.

However, in many departments clinicians do not have access to equipment for measuring the degree of block.[134] How then to evaluate and, as far as possible, exclude a clinically significant postoperative block? First, long-acting neuromuscular blocking drugs should not be used. Second, the tactile response to TOF nerve stimulation should be evaluated during surgery. Third, if possible, total twitch suppression should be avoided. The neuromuscular block should be managed so that there are always one or two tactile TOF responses. Fourth, the block should be antagonized at the end of the procedure, preferably with sugammadex if rocuronium or vecuronium have been used. When using neostigmine, reversal should not be initiated before at least two to four responses to TOF stimulation are present. Fifth, during recovery, tactile evaluation of the response to DBS is preferable to tactile evaluation of the response to TOF stimulation because it is easier to manually assess fade in the DBS than in the TOF response. Sixth, the clinician should recognize that the absence of tactile fade in both the TOF and DBS responses does not exclude significant residual block. Finally, reliable clinical signs and symptoms of residual block (see Box 53-1) should be considered in relation to the response to nerve stimulation. Figure 53-22 shows how to minimize the risk of residual block with or without objective monitoring.[135]

In view of the uncertainty connected with the use of clinical tests of postoperative neuromuscular recovery and tactile evaluation of the response to nerve stimulation, all patients receiving neuromuscular blocking drugs should be monitored with an objective monitor (also see Chapter 35). Whether the functioning of such a neuromuscular transmission analyzer is based on EMG, MMG, AMG, PZEMG, or PMG is not crucial, as long as the apparatus is used appropriately.

Complete references available online at expertconsult.com

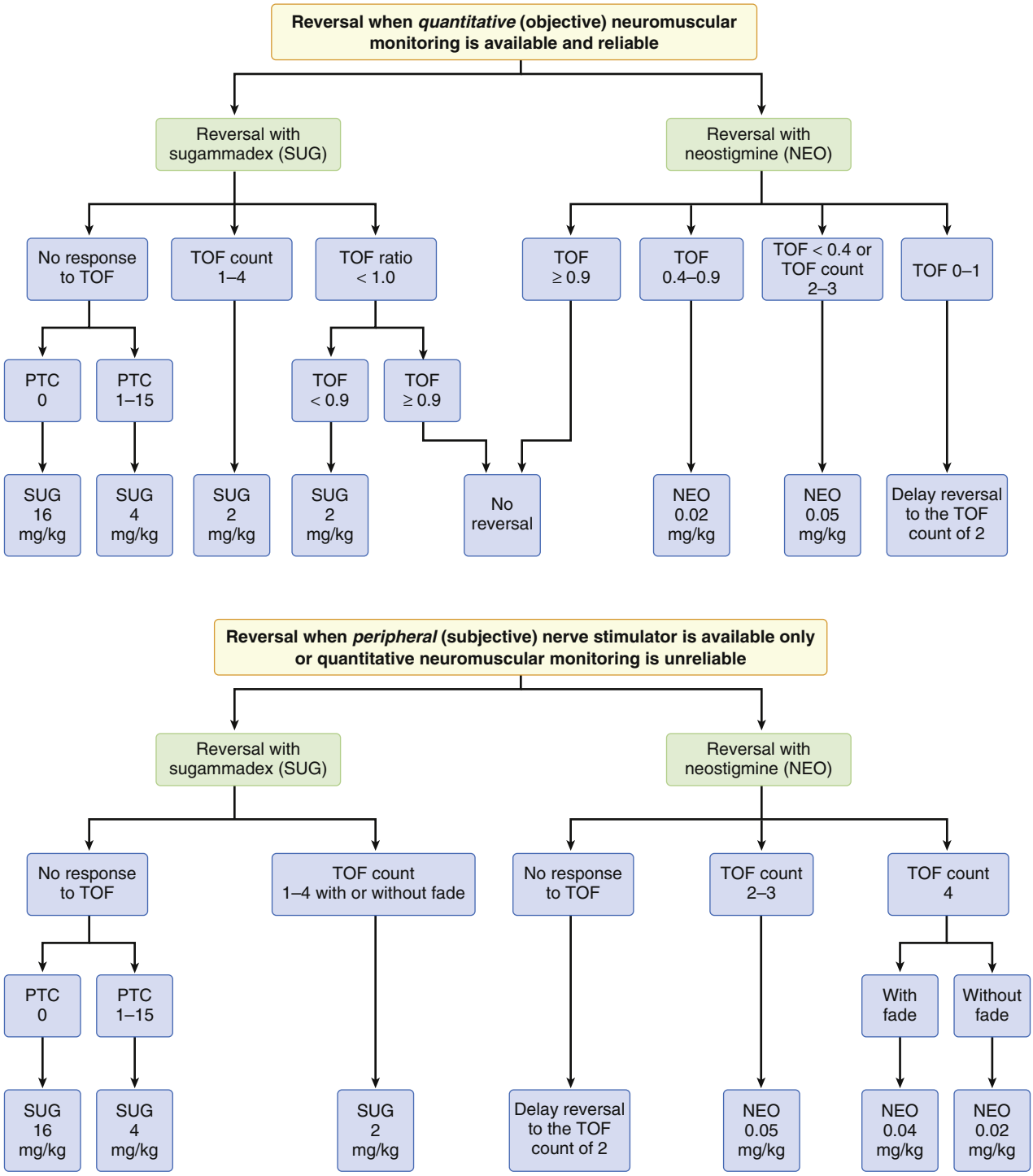


Figure 53-22. Suggestion to diminish the incidence of residual curarization by neostigmine or sugammadex according to the level of block, determined with a nerve stimulator (quantitative or peripheral). Note that only a quantitative measured TOF ratio of 0.90 to 1.00 ensures low risk of clinically significant residual block. *PTC,* Posttetanic count; *TOF,* train-of-four. *(Modified from Kopman AF, Eikermann M: Antagonism of non-depolarising neuromuscular block: current practice,* Anaesthesia *64[Suppl 1]:22-30, 2009.)*

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Chapter 54

Temperature Regulation and Monitoring

DANIEL I. SESSLER

KEY POINTS

- General anesthetics decrease the thresholds (triggering core temperatures) for vasoconstriction and shivering by 2° C to 3° C.
- Anesthetic-induced impairment of thermoregulatory control, combined with a cool operating room environment, makes most patients hypothermic.
- The major initial cause of hypothermia in most patients is core-to-peripheral redistribution of body heat.
- Neuraxial anesthesia impairs both central and peripheral thermoregulatory control and is associated with substantial hypothermia.
- Large randomized trials have proved that even mild hypothermia (i.e., 1.5° C to 2.0° C) causes adverse outcomes, including a threefold increase in morbid myocardial outcomes, a threefold increase in wound infection risk, coagulopathy and need for allogeneic transfusion, prolonged recovery, and prolonged hospitalization.
- Body temperature should be monitored in patients having surgery lasting more than 30 minutes, and core temperature should be maintained at 36° C or higher whenever possible. Forced-air warming currently offers the best combination of high efficacy, low cost, and remarkable safety.

Mammals and birds are homeothermic, requiring a nearly constant internal body temperature. When internal temperature deviates significantly from normal, metabolic functions usually deteriorate, and death may result. The thermoregulatory system usually maintains core body temperature within a few tenths of a degree centigrade of "normal," which is approximately 37° C in humans. Anesthetic-induced inhibition of thermoregulation combines with exposure to a cold operating room environment to make most unwarmed patients hypothermic.

Major outcome studies have shown that mild hypothermia (≈1° C to 2° C) (1) triples the incidence of morbid cardiac outcomes, (2) triples the incidence of surgical wound infections, (3) increases surgical blood loss and the need for allogeneic transfusions by approximately 20%, and (4) prolongs postanesthesia recovery and the duration of hospitalization. An understanding of normal and anesthetic-influenced thermoregulation will facilitate prevention and management of these and numerous other temperature-related complications.

NORMAL THERMOREGULATION

Thermoregulation is similar to many other physiologic control systems in that the brain uses negative and positive feedback to minimize perturbations from preset, "normal" values. Since 1912, animals have been known to regulate body temperature poorly when the hypothalamus is destroyed. The importance of thermal input from the skin surface was recognized in the late 1950s, when investigators observed that mice placed in a cold environment shivered *before* decreasing their hypothalamic temperatures.

In the early 1960s, physiologists reported active thermoregulation in response to isolated warming and cooling at sites other than the hypothalamus or skin surface, including extrahypothalamic portions of the brain, deep abdominal tissues, and the spinal cord. Thus, thermoregulation is based on multiple, redundant signals from nearly every type of tissue. The processing of thermoregulatory information occurs in three phases: *afferent thermal sensing*, *central regulation*, and *efferent responses*.

AFFERENT INPUT

Temperature information is obtained from thermally sensitive cells throughout the body. Cold-sensitive cells are anatomically and physiologically distinct from those that detect warmth. Warm receptors increase their firing rates when temperature increases, whereas cold receptors do so when temperature decreases. Cutaneous warm receptors rarely depolarize at normal skin temperatures and probably are important only during heat stress. The actual sensors appear to be a class of transient receptor potential (TRP) protein receptors.[1]

Cold signals travel primarily via Aδ nerve fibers and warm information by unmyelinated C fibers, although some overlap occurs.[2] The C fibers also detect and convey pain sensation, and that is why intense heat cannot be distinguished from sharp pain. Most ascending thermal information traverses the spinothalamic tracts in the anterior spinal cord, but no single spinal tract is critical for conveying thermal information. Consequently, the entire anterior cord must be destroyed to ablate thermoregulatory responses.

The hypothalamus, other parts of the brain, the spinal cord, the deep abdominal and thoracic tissues, and the skin surface each contribute roughly 20% of the total thermal input to the central regulatory system.[3]

CENTRAL CONTROL

Temperature is regulated by central structures (primarily the hypothalamus) that compare integrated thermal inputs from the skin surface, neuraxis, and deep tissues with *threshold* temperatures for each thermoregulatory response. Although integrated by the hypothalamus, most thermal information is "preprocessed" in the spinal cord and other parts of the central nervous system. This hierarchic arrangement presumably developed when the evolving thermoregulatory control system co-opted previously existing mechanisms (e.g., shivering from muscles previously used for posture and locomotion). It is likely that some thermoregulatory responses can be mounted by the spinal cord alone.[4] For example, animals and patients with high spinal cord transections regulate temperature better than would be expected.

The slope of response intensity versus core temperature defines the *gain* of a thermoregulatory response. Response intensity no longer increasing with further deviation in core temperature identifies the *maximum intensity*. This system of thresholds and gains is a model for a thermoregulatory system that is further complicated by interactions between other regulatory responses (i.e., vascular volume control) and time-dependent effects.

How the body determines absolute threshold temperatures is unknown, but the mechanism appears to be mediated by norepinephrine, dopamine, 5-hydroxytryptamine, acetylcholine, prostaglandin E_1, and neuropeptides. The thresholds vary daily in both sexes (circadian rhythm) and monthly in women by approximately 0.5° C. Exercise, food intake, infection, hypothyroidism and hyperthyroidism, anesthetic and other drugs (including alcohol, sedatives, and nicotine), and cold and warm adaptation alter threshold temperatures.

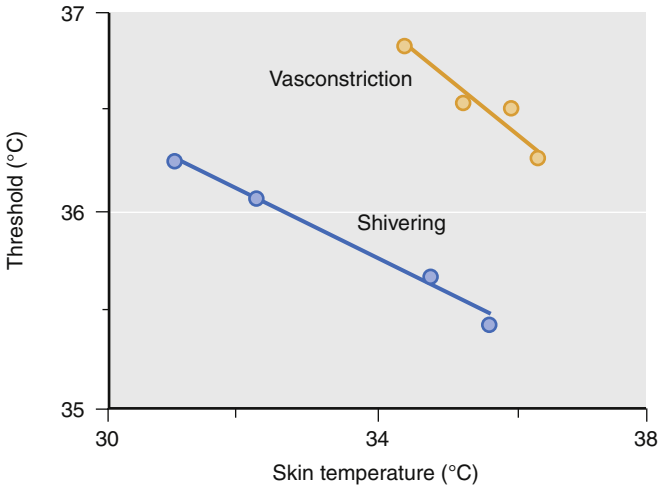


Figure 54-1. A linear relationship exists between mean skin temperature and the core temperature triggering vasoconstriction and shivering. Skin temperature contributes approximately 20% to control of each thermoregulatory defense. *(From Cheng C, Matsukawa T, Sessler DI, et al: Increasing mean skin temperature linearly reduces the core-temperature thresholds for vasoconstriction and shivering in humans,* Anesthesiology *82:1160-1168, 1995.)*

Control of autonomic responses is approximately 80% determined by thermal input from core structures (Fig. 54-1).[5,6] In contrast, a large fraction of the input controlling behavioral responses is derived from the skin surface. The *interthreshold range* (core temperatures *not* triggering autonomic thermoregulatory responses) is a few tenths of a degree centigrade.[7] This range is bounded by the sweating threshold at its upper end and by vasoconstriction at the lower end. Because energy cost and nutrients are conserved without excessive autonomic control within this range, some animals such as camels and desert rats use this strategy extensively, thus allowing core temperature changes up to 10° C each day. However, most mammals—including humans—normally regulate core temperature tightly.

Both sweating and vasoconstriction thresholds are 0.3° C to 0.5° C higher in women than in men, even during the follicular phase of the monthly cycle (first 10 days).[8] Differences are even greater during the luteal phase.[9] Although central thermoregulatory control is apparently intact even in premature infants,[10] thermoregulatory control may be impaired in older adults.[11]

EFFERENT RESPONSES

The body responds to thermal perturbations (body temperatures differing from the appropriate threshold) via effector mechanisms that increase metabolic heat production or alter environmental heat loss. Each thermoregulatory effector has its own threshold and gain, so an orderly progression of responses and response intensities occurs in proportion to need. In general, energy-efficient effectors such as vasoconstriction are maximized before metabolically costly responses such as shivering are initiated. Figure 54-2 shows the normal values for the major autonomic response thresholds.

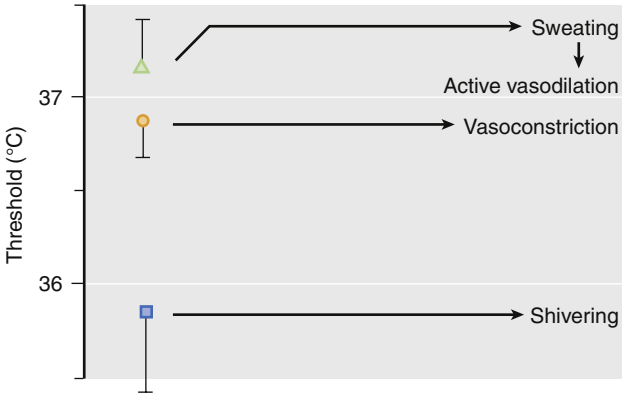


Figure 54-2. A core temperature lower than the thresholds for response to cold provokes vasoconstriction, nonshivering thermogenesis, and shivering. Core temperature exceeding the hyperthermic thresholds produces active vasodilation and sweating. No thermoregulatory responses are initiated when core temperature is between the sweating and vasoconstriction thresholds; these temperatures identify the interthreshold range. The interthreshold range in humans is usually only approximately 0.2° C. *(Threshold data from Lopez M, Sessler DI, Walter K, et al: Rate and gender dependence of the sweating, vasoconstriction, and shivering thresholds in humans,* Anesthesiology *80:780-788, 1994.)*

Effectors determine the ambient temperature range that the body will tolerate while maintaining a normal core temperature. When specific effector mechanisms are inhibited (e.g., when shivering is prevented by administration of muscle relaxants), the tolerable range is decreased. Still, temperature will remain normal unless other effectors cannot compensate for the imposed stress. Quantitatively, *behavioral regulation* is the most important effector mechanism. Behavioral compensations include dressing appropriately, modifying environmental temperature, assuming positions that appose skin surfaces, and moving voluntarily.

Infants regulate their temperatures remarkably well. In contrast, advanced age, infirmity, or medications can diminish the efficacy of thermoregulatory responses and increase the risk of hypothermia. For example, decreased muscle mass, neuromuscular diseases, and muscle relaxants all inhibit shivering and thereby increase the minimum tolerable ambient temperature. Similarly, anticholinergic drugs inhibit sweating,[12] and this decreases the maximum tolerable temperature.

Cutaneous vasoconstriction is the most consistently used autonomic effector mechanism. Metabolic heat is lost primarily via convection and radiation from the skin surface, and vasoconstriction reduces this loss. Total digital skin blood flow is divided into nutritional (mostly capillary) and thermoregulatory (mostly arteriovenous shunt) components.[13] The arteriovenous shunts are anatomically and functionally distinct from the capillaries supplying nutritional blood to the skin (hence vasoconstriction does not compromise the needs of peripheral tissues). Shunts are typically 100 μm in diameter, which means that one shunt can convey 10,000-fold as much blood as a comparable length of capillary 10 μm in diameter.

Control of blood flow through the arteriovenous shunts tends to be "on" or "off." In other words, the gain of this response is high with digital flow increasing from trivial to maximal levels over core temperature changes of only a few tenths of a degree centigrade. Local α-adrenergic sympathetic nerves mediate constriction in the thermoregulatory arteriovenous shunts, and flow is minimally affected by *circulating* catecholamines. Roughly 10% of cardiac output traverses arteriovenous shunts; consequently, shunt vasoconstriction increases mean arterial pressure approximately 15 mm Hg.[14]

Nonshivering thermogenesis increases metabolic heat production (measured as whole-body oxygen consumption) without producing mechanical work. It doubles heat production in infants,[15] but increases it only slightly in adults.[16] The intensity of nonshivering thermogenesis increases in linear proportion to the difference between mean body temperature and its threshold. Skeletal muscle and brown fat tissue are the major sources of nonshivering heat in adults. The metabolic rate in both tissues is controlled primarily by norepinephrine release from adrenergic nerve terminals and is further mediated locally by an uncoupling protein.[17]

Sustained shivering augments metabolic heat production by 50% to 100% in adults. This increase is small compared with that produced by exercise (which can, at least briefly, increase metabolism by 500%) and is thus surprisingly ineffective. Shivering does not occur in newborn infants and probably is not fully effective until children are several years old. The rapid tremor (≤250 Hz) and unsynchronized muscular activity of thermogenic shivering suggest no central oscillator. However, superimposed on the fast activity is usually a slow (four to eight cycles/minute), synchronous "waxing-and-waning" pattern that presumably is centrally mediated.[18]

Sweating is mediated by postganglionic, cholinergic nerves.[19] It thus is an active process that is prevented by nerve block or atropine administration.[20] Even untrained individuals can sweat up to 1 L/hour, and athletes can sweat at twice that rate. Sweating is the only mechanism by which the body can dissipate heat in an environment exceeding core temperature. Fortunately, the process is remarkably effective, dissipating 0.58 kcal/g of evaporated sweat.

Active vasodilation is apparently mediated by nitric oxide.[21,22] Because active vasodilation requires intact sweat gland function, it also is largely inhibited by nerve block. During extreme heat stress, blood flow through the top millimeter of skin can reach 7.5 L/minute—equaling the entire resting cardiac output.[23] The threshold for active vasodilation usually is similar to the sweating threshold, but the gain may be less. Consequently, maximum cutaneous vasodilation usually is delayed until core temperature is clearly higher than that provoking maximum sweating intensity.

THERMOREGULATION DURING GENERAL ANESTHESIA

Behavioral regulation is not relevant during general anesthesia because patients are unconscious and frequently paralyzed. All general anesthetics tested thus far markedly impair normal autonomic thermoregulatory control. Anesthetic-induced impairment has a specific form: warm-response thresholds are elevated slightly, whereas cold-response

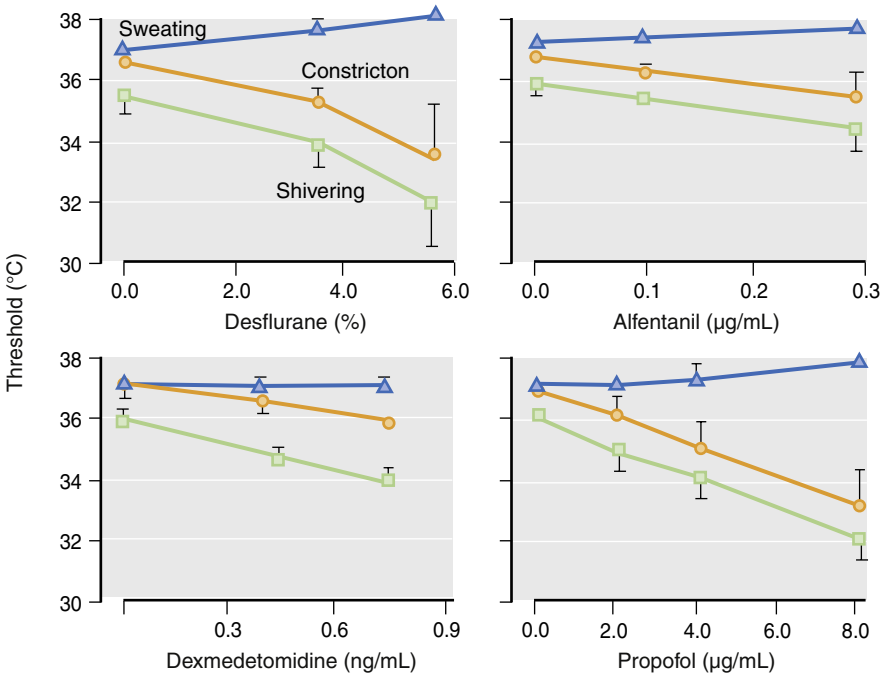


Figure 54-3. The major autonomic thermoregulatory response thresholds in volunteers given desflurane, alfentanil, dexmedetomidine, or propofol. All the anesthetics slightly increase the sweating threshold (triggering core temperature) while markedly and synchronously decreasing the vasoconstriction and shivering thresholds. Standard deviation bars smaller than the data markers have been deleted. *(Data from references 24 to 27.)*

thresholds are markedly reduced. Consequently, the interthreshold range is increased from its normal values near 0.3° C to approximately 2° C to 4° C.[24-28] The gain and maximum intensity of some responses remain normal, [8] whereas other responses are reduced by general anesthesia.[29,30]

RESPONSE THRESHOLDS

Propofol,[24] alfentanil,[25] and dexmedetomidine[26] all produce a slight, linear increase in the sweating threshold combined with a marked and linear decrease in the vasoconstriction and shivering thresholds. Isoflurane[28] and desflurane[27] also slightly increase the sweating threshold; however, they decrease the cold-response thresholds nonlinearly. Consequently, the volatile anesthetics inhibit vasoconstriction and shivering less than propofol at low concentrations, but more than propofol at typical anesthetic doses. In all cases (except after meperidine[31] and nefopam[32] administration), vasoconstriction and shivering decrease synchronously and maintain their normal approximate 1° C difference.

The dose-dependent response thresholds for four anesthetic drugs are shown in Figure 54-3. The combination of increased sweating thresholds and reduced vasoconstriction thresholds increases the interthreshold range approximately 20-fold, from its normal value near 0.2° C to approximately 2° C to 4° C. Temperatures within this range do *not* trigger thermoregulatory defenses; by definition, patients are poikilothermic within this temperature range.

Isoflurane,[28] desflurane,[27,29] enflurane,[33] halothane,[34] and the combination of nitrous oxide and fentanyl[35] decrease the vasoconstriction threshold 2° C to 4° C from its normal value near approximately 37° C. The dose dependence is nonlinear (i.e., greater concentrations produce disproportionate threshold reductions). The shivering thresholds decrease synchronously. In contrast, these drugs increase the sweating threshold only slightly.

Clonidine synchronously decreases cold-response thresholds,[36] while slightly increasing the sweating threshold.[37] Nitrous oxide decreases the vasoconstriction[38] and shivering[39] thresholds less than equipotent concentrations of volatile anesthetics. In contrast, midazolam only slightly impairs thermoregulatory control.[40,41] Painful stimulation slightly increases vasoconstriction thresholds[33]; consequently, thresholds are somewhat lower when surgical pain is prevented by simultaneous local or regional anesthesia.

RESPONSES IN INFANTS AND OLDER ADULTS

Thermoregulatory vasoconstriction is comparably impaired in infants, children, and adults given isoflurane[42] or halothane[43] (Fig. 54-4). In contrast, the vasoconstriction threshold is approximately 1° C less in patients 60 to 80 years old than in those between 30 and 50 years old (Fig. 54-5).[44,45]

Nonshivering thermogenesis does not occur in anesthetized adults.[46] This finding is unsurprising because this response is not particularly important in unanesthetized adults.[16] In contrast to adult humans, nonshivering thermogenesis is an important thermoregulatory response in animals and human infants. However, nonshivering thermogenesis in animals is inhibited by volatile anesthetics,[47] and it fails to increase the metabolic rate in infants anesthetized with propofol (Fig. 54-6).[48]

GAIN AND MAXIMUM RESPONSE INTENSITY

Both the gain and maximum intensity of sweating remain normal during isoflurane[8] and enflurane anesthesia.[49] However, the gain of arteriovenous shunt vasoconstriction is reduced threefold during desflurane anesthesia

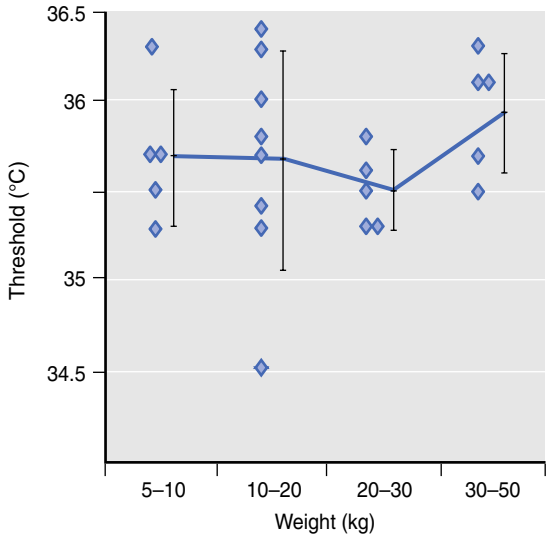


Figure 54-4. The core thermoregulatory threshold in 23 healthy children and infants undergoing abdominal surgery with halothane anesthesia. Differences among the groups are not statistically significant. Results are presented as means ± SDs. *(From Bissonnette B, Sessler DI: Thermoregulatory thresholds for vasoconstriction in pediatric patients anesthetized with halothane or halothane and caudal bupivacaine,* Anesthesiology *76:387-392, 1992.)*

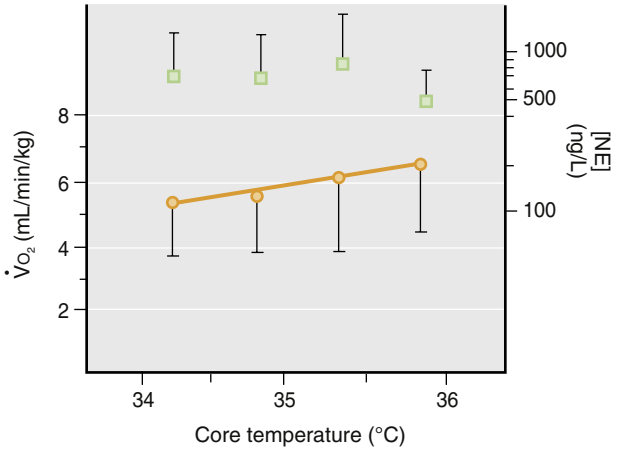


Figure 54-6. Progressive reduction in core temperature did not trigger an increase in oxygen consumption ($\dot{V}O_2$) that may indicate nonshivering thermogenesis. Instead, hypothermia decreased systemic VO_2: $\dot{V}O_2$ = 0.83 (Core Temperature) – 23.3; r^2 = 0.92. Intraoperative plasma norepinephrine (NE) concentrations were variable, but they did not change significantly as a function of core temperature (squares). Data are presented as means ± SD. *(From Plattner O, Semsroth M, Sessler DI, et al: Lack of nonshivering thermogenesis in infants anesthetized with fentanyl and propofol,* Anesthesiology *86: 772-777, 1997.)*

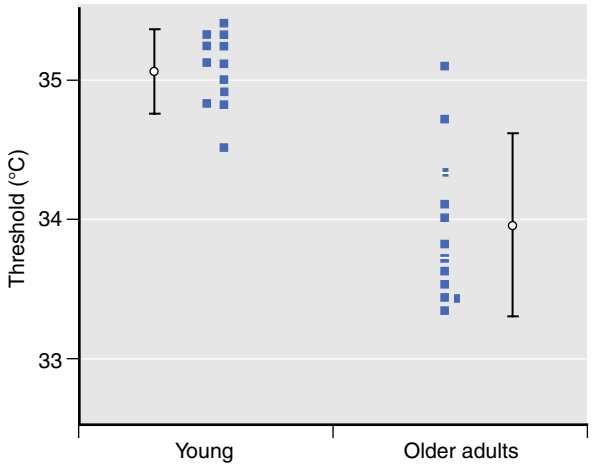


Figure 54-5. The vasoconstriction threshold was significantly less in the older adults (33.9 ± 0.6° C) than in younger patients (35.1 ± 0.3° C) during 60% nitrous oxide and isoflurane (0.75% end-tidal concentration). *Filled squares* indicate the vasoconstriction threshold in each patient; *open circles* show the mean and standard deviation in each group. *(From Kurz A, Plattner O, Sessler DI, et al: The threshold for thermoregulatory vasoconstriction during nitrous oxide/isoflurane anesthesia is lower in elderly than young patients,* Anesthesiology *79:465-469, 1993.)*

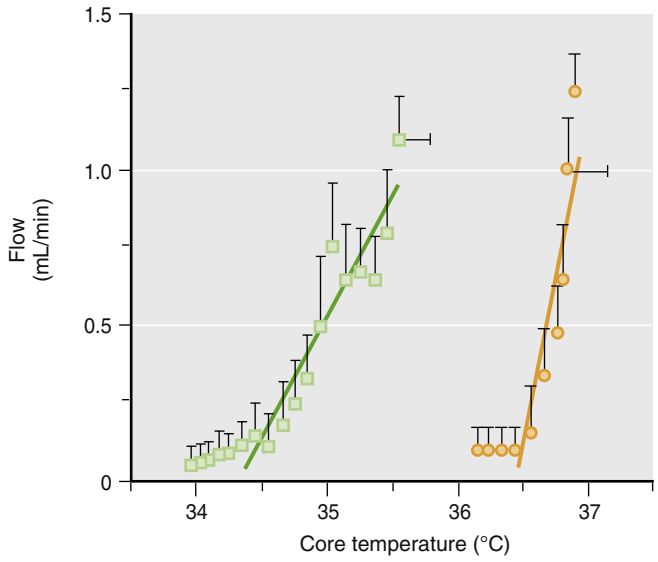


Figure 54-7. Finger blood flow without (*circles*) and with (*squares*) desflurane administration. Values were computed relative to the thresholds (finger flow = 1.0 mL/min) in each subject. Flows of exactly 1.0 mL/min are not shown because flows in each individual were averaged over 0.1° C or 0.05° C increments; each data point thus includes both higher and lower flows. The horizontal standard deviation bars indicate variability in the thresholds among the volunteers; although errors bars are shown only at a flow near 1.0 mL/min, the same temperature variability applies to each data point. The slopes of the flow versus core temperature relationships (1.0 to ≈0.15 mL/min) were determined using linear regression. These slopes defined the gain of vasoconstriction with and without desflurane anesthesia. Gain was reduced by a factor of three, from 2.4 to 0.8 mL/min/°C^{-1} ($P < 0.01$). *(From Kurz A, Xiong J, Sessler DI, et al: Desflurane reduces the gain of thermoregulatory arterio-venous shunt vasoconstriction in humans,* Anesthesiology *83:1212-1219, 1995.)*

(Fig. 54-7),[29] even though the maximum vasoconstriction intensity remains normal.[50]

Shivering is rare during surgical doses of general anesthesia. This finding is consistent with the shivering threshold being roughly 1° C less than the vasoconstriction threshold.[24-28] (Vasoconstriction usually prevents additional hypothermia,[51] so even unwarmed patients rarely become cold enough to shiver.) Nonetheless, shivering can be induced by sufficient active cooling.

Gain and maximum shivering intensity remain normal during both meperidine and alfentanil administration.[52]

Gain also remains nearly intact during nitrous oxide administration, although maximum intensity is reduced.[53] Isoflurane changes the macroscopic pattern of shivering to such an extent that it is no longer possible to determine gain easily. The drug does, however, reduce maximum shivering intensity.[30]

Sweating is the best preserved major thermoregulatory defense during anesthesia. Not only is the threshold only slightly increased, but the gain and maximum intensity remain normal. In contrast, the thresholds for vasoconstriction and shivering are markedly reduced, and furthermore, the efficacy of these responses is diminished even after being activated.

DEVELOPMENT OF HYPOTHERMIA DURING GENERAL ANESTHESIA

Inadvertent hypothermia is by far the most common perioperative thermal disturbance during anesthesia. Hypothermia results from a combination of anesthetic-impaired thermoregulation and exposure to a cold operating room environment. Of these two causes, however, impaired thermoregulation is much more important.

HEAT TRANSFER

Heat can be transferred from a patient to the environment four ways: (1) radiation, (2) conduction, (3) convection, and (4) evaporation. Among these, radiation and convection contribute most to perioperative heat loss.

All surfaces with a temperature higher than absolute zero radiate heat; similarly, all surfaces absorb radiative heat from surrounding surfaces. Heat transfer via this mechanism is proportional to the difference of the fourth power of the absolute temperature difference between the surfaces. It is likely that radiation is the major type of heat loss in most surgical patients.[54]

Conductive heat loss is proportional to the temperature difference between two adjacent surfaces and the strength of the thermal insulation separating them. In general, conductive losses are negligible during surgery because patients usually directly contact only the foam pad (an excellent thermal insulator) covering most operating room tables.

Conductive loss of heat directly to air molecules is limited by development of a layer of still air adjacent to the skin that serves as an insulator. When this layer is disturbed by air currents, the insulative properties diminish substantially, thereby increasing heat loss. This increase is termed convection and is proportional to the square root of air speed; this is the basis of the familiar "wind chill" factor. Air speed in operating rooms—even those with high rates of air turnover—typically is only approximately 20 cm/second, which only slightly increases loss compared with still air. Nonetheless, convective loss usually is the second most important mechanism by which heat is transferred from patients to the environment. Presumably, convective loss increases substantially in operating rooms equipped to provide laminar flow. However, the actual augmentation has not been quantified and may be less than expected from the increase in air speed because surgical draping provides considerable thermal insulation.

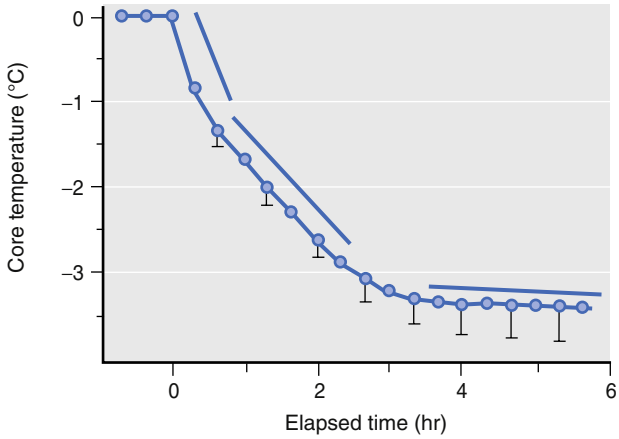


Figure 54-8. Hypothermia during general anesthesia develops with a characteristic pattern. An initial rapid decrease in core temperature results from a core-to-peripheral redistribution of body heat. This is followed by a slow, linear reduction in core temperature that results simply from heat loss exceeding heat production. Finally, core temperature stabilizes and subsequently remains virtually unchanged. This plateau phase may be a passive thermal steady state, or it may result when sufficient hypothermia triggers thermoregulatory vasoconstriction. Results are presented as means ± SDs.

Sweating increases cutaneous evaporative loss immensely, but is rare during anesthesia. In the absence of sweating, evaporative loss from the skin surface is less than 10% of metabolic heat production in adults. In contrast, infants lose a higher fraction of their metabolic heat from transpiration of water through thin skin. The problem becomes especially acute in premature infants, who may lose one fifth of their metabolic heat production via transcutaneous evaporation.[55] Simple thermodynamic calculations and clinical measurements indicate that only trivial amounts of heat are lost from the respiratory system.[56] Evaporation inside surgical wounds may contribute substantially to total heat loss,[57] but this has never been quantified in humans.

PATTERNS OF INTRAOPERATIVE HYPOTHERMIA

Hypothermia during general anesthesia develops with a characteristic pattern. An initial rapid decrease in core temperature is followed by a slow, linear reduction in core temperature. Finally, core temperature stabilizes and subsequently remains virtually unchanged (Fig. 54-8). Each section of this typical pattern has a different etiology.

Volatile anesthetics cause vasodilation via a direct peripheral action.[58] More importantly, they also inhibit tonic thermoregulatory vasoconstriction, resulting in arteriovenous shunt dilation.[24-28] Nonetheless, anesthetic-induced vasodilation increases cutaneous heat loss only slightly.[59] Anesthetics reduce the metabolic rate 20% to 30%.[60] However, even the combination of increased heat loss and reduced heat production is insufficient to explain the 0.5° C to 1.5° C decrease in core temperature usually observed during the first hour of anesthesia.

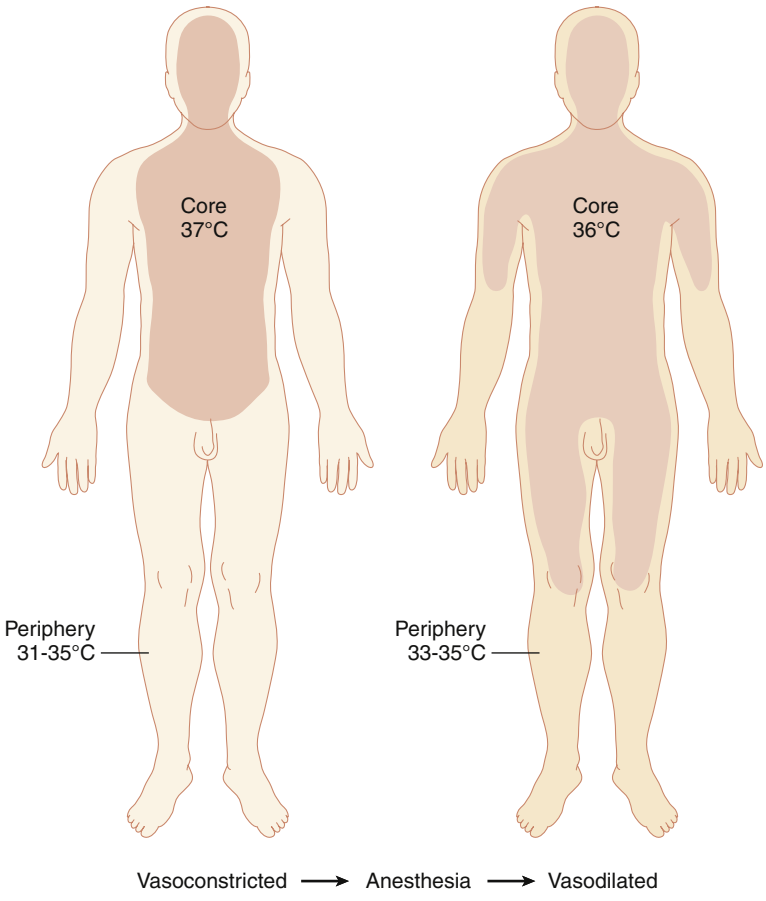


Figure 54-9. A drawing illustrating internal redistribution of body heat following induction of general anesthesia. Hypothermia following induction of spinal or epidural anesthesia results similarly, but redistribution is restricted to the legs.

The key to understanding the initial decrease in core temperature is to appreciate that body heat is not normally evenly distributed. Core temperature represents only approximately half the body mass (mostly the trunk and head); the remaining mass is typically 2° C to 4° C cooler than the core. This core-to-peripheral tissue temperature gradient is normally maintained by tonic thermoregulatory vasoconstriction. Anesthetic-induced vasodilation, however, allows core heat to flow peripherally. This flow warms the arms and legs, but it does so at the expense of the core (Figs. 54-9 and 54-10).[61] The extent to which redistribution reduces core temperature depends on the core-to-peripheral tissue temperature gradient at the time of induction. This gradient, in turn, depends on the patient's prior thermal environment and thermoregulatory status, both of which are difficult to determine clinically.

Following initial redistribution hypothermia, core temperature usually decreases in a slow, linear fashion for 2 to 4 hours. This reduction results simply from heat loss exceeding metabolic heat production,[62] and the rate at which core temperature decreases depends on the difference and size of the patient. After 3 to 4 hours of anesthesia, core temperature usually reaches a plateau and remains virtually constant for the duration of surgery.[35] The core temperature plateau may simply represent a thermal steady state (heat production equaling heat loss) in patients who remain relatively warm.[63] In others, however, the plateau phase is associated with peripheral thermoregulatory vasoconstriction triggered by core temperatures of 33° C to 35° C.[64]

Thermoregulatory vasoconstriction during anesthesia decreases cutaneous heat loss,[50] but this decrease alone is usually insufficient to produce a thermal steady state. Furthermore, neither adults[46] nor infants[48] appear able to increase intraoperative heat production in response to hypothermia. An additional mechanism must therefore contribute to the core temperature plateau. Evidence suggests that a primary factor is constraint of metabolic heat to the core thermal compartment. In this situation, distribution of metabolic heat (which largely is produced centrally) is restricted to the core compartment, thus maintaining its temperature. Peripheral tissue temperature, in contrast, continues to decrease because it is no longer being supplied with sufficient heat from the core.[51] A core temperature plateau resulting from thermoregulatory vasoconstriction is not a thermal steady state, and body heat content continues to decrease even though core temperature remains nearly constant.

NEURAXIAL ANESTHESIA

Autonomic thermoregulation is impaired during regional anesthesia, and the result typically is intraoperative core hypothermia. This hypothermia often is not consciously perceived by patients, but nonetheless triggers shivering.

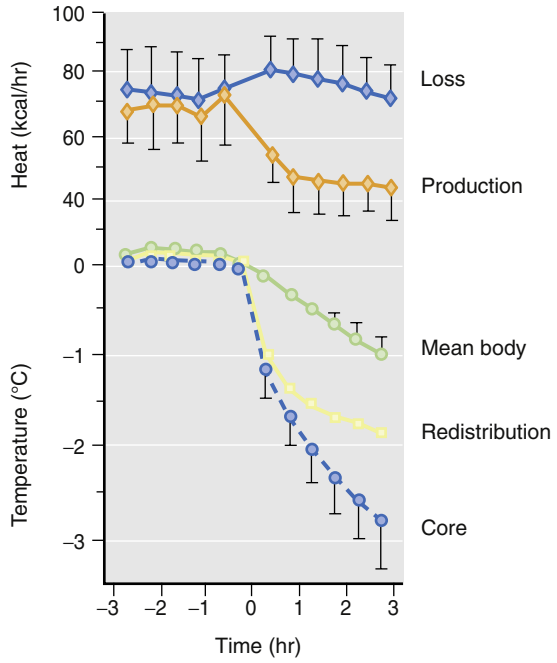


Figure 54-10. Changes in body heat content and distribution of heat within the body during induction of general anesthesia (at elapsed time zero). The change in mean body temperature was subtracted from the change in core (tympanic membrane) temperature, thereby leaving the core hypothermia specifically resulting from redistribution. Redistribution hypothermia was thus not a measured value; instead, it is defined by the decrease in core temperature not explained by the relatively small decrease in systemic heat content. After 1 hour of anesthesia, core temperature had decreased 1.6 ± 0.3° C, with redistribution contributing 81% to the decrease. Even after 3 hours of anesthesia, redistribution contributed 65% to the entire 2.8 ± 0.5° C decrease in core temperature. Results are presented as means ± SD. *(Modified from Matsukawa T, Sessler DI, Sessler AM, et al: Heat flow and distribution during induction of general anesthesia,* Anesthesiology *82:662-673, 1995.)*

The result, frequently, is a potentially dangerous clinical paradox: a hypothermic patient who denies feeling cold.

THERMOREGULATION

Epidural[65,66] and spinal[66,67] anesthesia each decrease the thresholds triggering vasoconstriction and shivering (above the level of the block) approximately 0.6° C (Fig. 54-11). Presumably, this decrease does not result from recirculation of neuraxially administered local anesthetic because impairment is similar during epidural and spinal anesthesia,[65-67] although the amount and location of administered local anesthetic differ substantially. Furthermore, lidocaine administered intravenously in doses producing plasma concentrations similar to those occurring during epidural anesthesia has no thermoregulatory effect.[68] Finally, neuraxial administration of 2-chloroprocaine, a local anesthetic with a plasma half-life of only approximately 20 seconds, also impairs thermoregulatory control.[69]

The vasoconstriction and shivering thresholds are comparably decreased during regional anesthesia,[67] a finding suggesting an alteration in central, rather than peripheral, control. The mechanism by which peripheral administration of local anesthesia impairs centrally

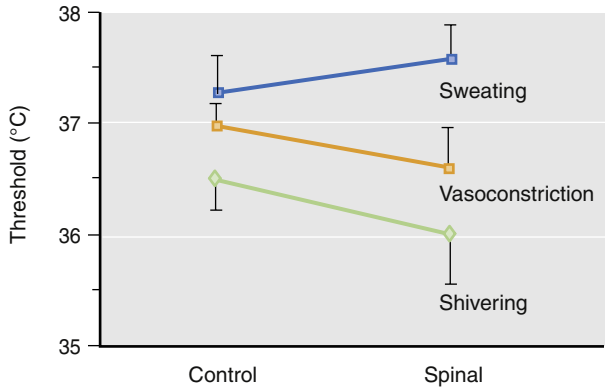


Figure 54-11. Spinal anesthesia increased the sweating threshold but reduced the thresholds for vasoconstriction and shivering. Consequently, the interthreshold range increased substantially. The vasoconstriction-to-shivering range, however, remained normal during spinal anesthesia. Results are presented as means ± SDs. *(From Kurz A, Sessler DI, Schroeder M, Kurz M: Thermoregulatory response thresholds during spinal anesthesia,* Anesth Analg *77:721-726, 1993.)*

mediated thermoregulation may involve alteration of afferent thermal input from the legs. The key factor here is that tonic cold signals dominate thermal input at leg skin temperatures in typical operating room environments.[2,70] Regional anesthesia blocks all thermal input from blocked regions, which in the typical case is primarily cold information. The brain may then interpret decreased cold information as relative leg warming. This appears to be an unconscious process because perceived temperature does not increase.[71] Given that skin temperature is an important input to the thermoregulatory control system, leg warming proportionately reduces the vasoconstriction and shivering thresholds. Consistent with this theory, a leg skin temperature near 38° C is required to produce the reduction in cold-response thresholds in an unanesthetized subject that is produced by regional anesthesia.[72] Furthermore, reduction in the thresholds is proportional to the number of spinal segments blocked (Fig. 54-12). [73] Major conduction anesthesia may thus reduce the vasoconstriction and shivering thresholds by producing an abnormal elevation of *apparent* (as opposed to actual) leg temperature. However, this explanation remains speculative.

Because neuraxial anesthesia prevents vasoconstriction and shivering in blocked regions, it is not surprising that epidural anesthesia decreases the maximum intensity of shivering. However, epidural anesthesia also reduces the gain of shivering, a finding that suggests that the regulatory system is unable to compensate for lower body paralysis (Fig. 54-13).[30] Thermoregulatory defenses, once triggered, are thus less effective than usual during regional anesthesia.

Neuraxial anesthesia is frequently supplemented with sedative and analgesic medications. Most of these drugs significantly impair thermoregulatory control.[25,31,74] Such inhibition may be severe when combined with the intrinsic impairment produced by regional anesthesia and other factors, including advanced age or preexisting illness.[11] Core hypothermia during regional anesthesia may not trigger a perception of cold.[65,75] The reason is

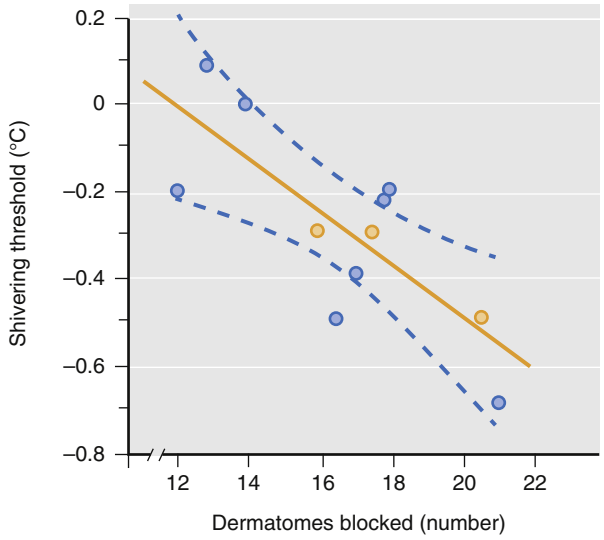


Figure 54-12. The number of dermatomes blocked (sacral segments = 5; lumbar segments = 5; thoracic segments = 12) versus reduction in the shivering threshold (difference between the control shivering threshold and spinal shivering threshold). The shivering threshold was reduced more by extensive spinal blocks than by less extensive ones (Δ threshold = 0.74 − 0.06 (dermatomes blocked); r^2 = 0.58, P <.006). The *dashed lines* indicate the 95% confidence intervals for the slope. *(From Leslie K, Sessler DI: Reduction in the shivering threshold is proportional to spinal block height,* Anesthesiology *84:1327-1331, 1996.)*

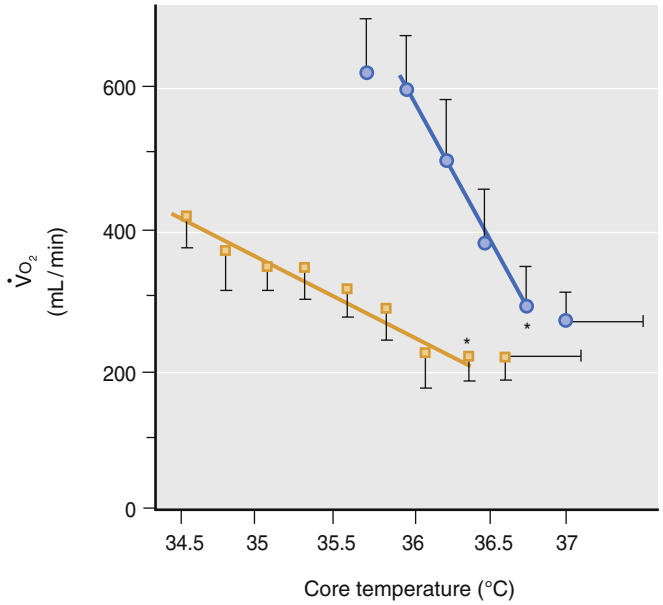


Figure 54-13. Systemic oxygen consumption ($\dot{V}_{O_2}$) without (*circles*) and with (*squares*) epidural anesthesia. The horizontal standard deviation bars indicate variability in the thresholds among the volunteers; although errors bars are shown only once in each series, the same temperature variability applies to each data point. The slopes of the $\dot{V}_{O_2}$ versus core temperature relationships (*solid lines*) were determined using linear regression. These slopes defined the gain of shivering with and without epidural anesthesia. Gain was reduced 3.7-fold, from −412 mL/min/°C (r^2 = 0.99) to −112 mL/min/°C (r^2 = 0.96). *(From Kim J-S, Ikeda T, Sessler D, et al: Epidural anesthesia reduces the gain and maximum intensity of shivering,* Anesthesiology *88:851-857, 1998.)*

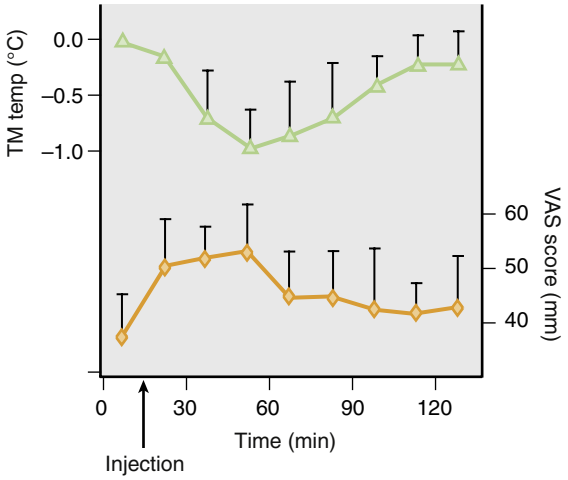


Figure 54-14. Induction of epidural anesthesia at elapsed time 15 minutes decreased core temperature and increased thermal comfort as determined by a 100–mm visual analog scale (VAS). However, maximal thermal comfort coincided with *minimum* core temperature. Results are presented as means ± SDs. *TM,* Tympanic membrane. *(Modified from Sessler DI, Ponte J: Shivering during epidural anesthesia,* Anesthesiology *72:816-821, 1990.)*

that thermal perception (behavioral regulation) is largely determined by skin temperature, rather than core temperature. During regional anesthesia, core hypothermia is accompanied by a real increase in skin temperature. The result typically is a perception of continued or increased warmth accompanied by autonomic thermoregulatory responses including shivering (Fig. 54-14).[65,75] Taken together, these data indicate that neuraxial anesthesia inhibits numerous aspects of thermoregulatory control. The vasoconstriction and shivering thresholds are reduced by regional anesthesia,[65-67,72,73] and they are further reduced by adjuvant drugs[25,40] and advanced age.[11] Even once triggered, the gain and maximum response intensity of shivering are approximately half normal.[76] Finally, behavioral thermoregulation is impaired.[75] The result is that cold defenses are triggered at a lower temperature than normal during regional anesthesia, defenses are less effective once triggered, and patients frequently do not recognize that they are hypothermic. Because core temperature monitoring remains rare during regional anesthesia, substantial hypothermia often goes undetected in these patients.[77]

HEAT BALANCE

Hypothermia is common during regional anesthesia and may be nearly as severe as during general anesthesia.[78] Core temperature typically decreases 0.5° C to 1.0° C shortly after induction of anesthesia. However, vasodilation induced by regional anesthesia only slightly increases cutaneous heat loss. Furthermore, metabolic heat production remains constant or increases because of shivering thermogenesis. This rapid decrease in core temperature, similar to the one that follows induction of general anesthesia, also results from an internal core-to-peripheral redistribution of body heat.[79] As during general anesthesia,[80,81] redistribution hypothermia

during regional anesthesia can be minimized by cutaneous warming before induction.[82]

Subsequent hypothermia results simply from heat loss exceeding metabolic heat production. Unlike patients given general anesthesia, however, core temperature does not necessarily plateau after several hours of surgery. Not only is the vasoconstriction threshold centrally impaired by regional anesthesia,[66,67] but more importantly, vasoconstriction in the legs is directly prevented by nerve block.[83,84] Because the legs constitute the bulk of the peripheral thermal compartment, an effective plateau cannot develop without vasoconstriction in the legs and the resulting decrease in cutaneous heat loss and constraint of metabolic heat to the core.

The importance of intraoperative leg vasoconstriction is illustrated during combined regional and general anesthesia. Consistent with the impairment of thermoregulatory responses with regional anesthesia alone,[66,67] vasoconstriction during combined regional and general anesthesia is triggered at a core temperature approximately 1° C less than during general anesthesia alone. Furthermore, vasoconstriction, once triggered, produces a core temperature plateau during general anesthesia alone but not during combined regional and general anesthesia. The result is that core temperature during combined regional and general anesthesia continues to decrease throughout surgery.[85] Consequently, core temperature monitoring and thermal management are especially important in patients given simultaneous regional and general anesthesia.

SHIVERING

Shivering-like tremor, so typical in neuraxial anesthesia, is preceded by core hypothermia and vasoconstriction (above the level of the block).[65] Furthermore, electromyographic analysis indicates that the tremor has the waxing-and-waning pattern of four to eight cycles/minute that characterizes normal shivering.[69] The tremor thus apparently is normal thermoregulatory shivering, triggered when redistribution hypothermia decreases core temperature.

Spinal thermal receptors have been detected in every mammal and bird tested. Experimental stimulation of these receptors reliably produces shivering in animals. Stimulation in humans of these putative receptors by epidural anesthetic injection theoretically could initiate thermoregulatory responses, including shivering. However, epidural administration of large amounts of ice-cold saline does not trigger shivering in volunteers.[86] Furthermore, the incidence of shivering is comparable in volunteers[65] and patients[87] given warm or cold epidural anesthetic injections. These data indicate that temperature of injected local anesthetic does not influence the incidence of shivering during major conduction anesthesia.

The risk of shivering during neuraxial anesthesia is markedly diminished by maintaining strict normothermia.[65] However, a distinct incidence of low-intensity, shivering-like tremor occurs in normothermic patients and is not thermoregulatory.[88] The cause of this muscular activity remains unknown. However, it is associated with pain,[89] and it may thus result from sympathetic nervous system activation (Fig. 54-15).

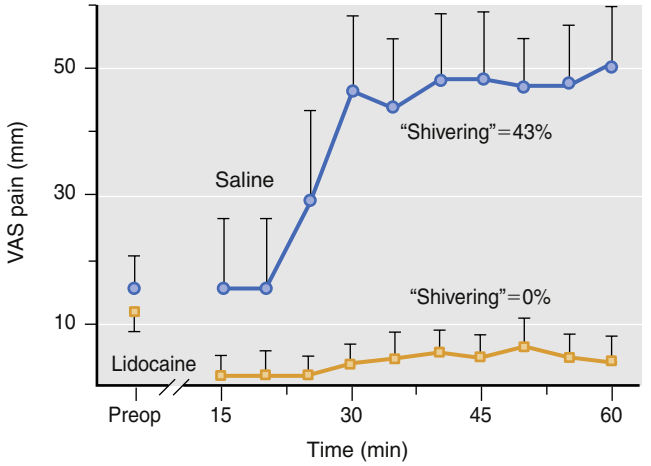


Figure 54-15. Visual analog pain scores (VAS) in normothermic patients given intraarticular lidocaine or saline after knee surgery. Pain was assessed postoperatively by an investigator blinded to the group assignment. Time zero indicates discontinuation of anesthesia. Data are presented as mean ± SD. Patients receiving a local anesthetic block (lidocaine) had significantly less postoperative pain than did those given saline; all values after 10 elapsed minutes differed significantly in the two groups. Shivering-like tremor was observed in 43% more of the patients given saline than those given lidocaine, a finding indicating that the tremor is related to pain. *(From Horn E-P, Schroeder F, Wilhelm S, et al: Postoperative pain facilitates non-thermoregulatory tremor,* Anesthesiology *91:979-984, 1999.)*

Shivering during neuraxial anesthesia can sometimes be treated by warming sentient skin. This approach augments cutaneous thermal input to the central regulatory system and thus increases the degree of tolerated core hypothermia.[90] Because the entire skin surface contributes 20% to thermoregulatory control,[5] and the lower body contributes approximately 10%,[72] sentient skin warming is likely to compensate for only small reductions in core temperature. The same drugs that are effective for postanesthetic tremor also are useful for shivering during regional anesthesia: these include meperidine (25 mg intravenously [IV] or epidurally),[91] clonidine (75 μg IV),[92] dexmedetomine,[93] ketanserin (10 mg IV),[92] and magnesium sulfate (30 mg/kg IV).[94]

CONSEQUENCES OF MILD INTRAOPERATIVE HYPOTHERMIA

Perianesthetic hypothermia produces potentially severe complications, as well as distinct benefits. Thermal management thus deserves the same thoughtful analysis of potential risks and benefits as other therapeutic decisions.

BENEFITS

Substantial protection against cerebral ischemia and hypoxia is provided by just 1° C to 3° C of hypothermia in animals.[95,96] Protection initially was thought to result from the approximate 8%/°C linear reduction in tissue metabolic rate. However, the efficacy of mild hypothermia far exceeds that of treatments such as high-dose isoflurane or barbiturate coma, which comparably reduce the metabolic rate.[97]

These data suggest that other actions (e.g., decreased release of excitatory amino acids) explain the protective action of hypothermia.[98] As such, no reason exists to expect protection to decrease linearly with temperature, and in animals, it appears that much of the total benefit from moderate hypothermia occurs within the first couple of degrees.

As could be expected from in vitro and animal studies, therapeutic hypothermia has twice been shown to improve outcomes from out-of-hospital cardiac arrest.[99,100] Rapid induction of hypothermia is thus becoming routine for patients after recovery from cardiac arrest. The other situation in which therapeutic hypothermia appears beneficial is in asphyxiated neonates.[101-103]

The potential protection afforded by mild hypothermia is so great that reduced core temperature (i.e., ≈34° C) is sometimes used during neurosurgery and other procedures in which tissue ischemia can be anticipated. The difficulty is that few outcome data are available to substantiate extrapolation from animal data to clinical practice. Furthermore, the appropriate target temperature for therapeutic hypothermia has yet to be established.

The Brain

Hypothermia for brain trauma was initially claimed to be therapeutic based on a post hoc subgroup analysis of a study that overall showed no benefit.[104] A subsequent large randomized trial was unable to demonstrate any benefit overall or in subgroups, although interpretation of the study was limited by violations in the fluid administration protocol in some patients.[105] More recently, hypothermia was shown to be beneficial in a nonrandomized study in which patients with brain trauma who had elevated intracranial pressure refractory to conventional treatment were assigned to therapeutic hypothermia. Despite being sicker than the comparison patients (who had low intracranial pressure), the hypothermic patients demonstrated improved outcome.[106] Small nonrandomized series suggested that mild hypothermia could improve the outcome from stroke.[107] A small feasibility trial for treatment of stroke with hypothermia has been published,[108] but no large trial is currently even in progress. Although initial feasibility trials were encouraging,[108,109] a subsequent large outcome trial failed to demonstrate any improvement caused by therapeutic hypothermia in patients having surgery for subarachnoid hemorrhage.[110] This result was especially disappointing because surgery is one of the few circumstances in humans when hypothermia can be instituted before the onset of ischemia.

The Heart and Other Organs

Hypothermic protection against ischemia may extend to other organs. For example, mild hypothermia markedly reduced infarct size in experimental acute myocardial infarction in human-sized pigs,[111] and a preliminary study in patients was encouraging.[112] However, a subsequent major outcome trial in humans failed to demonstrate convincing benefit (unpublished).

Acute malignant hyperthermia is more difficult to trigger in mildly hypothermic swine than in those kept normothermic. Furthermore, once triggered, the syndrome is less severe.[113,114] These data suggest that active warming should be avoided in patients known to be susceptible to malignant hyperthermia; instead, these patients should be allowed to become slightly hypothermic during surgery.

Limitations of most therapeutic hypothermia studies are that cooling began well after the ischemic insult, and patients typically took many hours to cool. It thus remains possible that benefit will yet be identified in future studies that initiate hypothermia earlier and use more recently developed systems to cool patients faster. Table 54-1 lists selected major studies that evaluated the potential benefits of mild perioperative hypothermia.

TABLE 54-1 POTENTIAL BENEFITS OF MILD PERIOPERATIVE HYPOTHERMIA IN HUMANS*

Consequence	First Author	Yr	*N*	ΔT_{core} (° C)	Normothermic	Hypothermic	*P*
Mortality after brain trauma	Clifton[105]	2001	392	4.2	27%	28%	NS
Favorable Glasgow outcome score at 3 mo after brain trauma	Shiozaki[256]	2001	91	4	59%	47%	NS
Glasgow outcome score at 12 mo after brain trauma (1-3/4-5)	Marion[104]	1997	81	≈4	62%/38%	39%/61%	NS
Neurologic outcome after cardiac arrest (good)	Bernard[99]	2002	77	≈4	26%	49%	.01
Neurologic outcome 6 mo after cardiac arrest (good recovery or moderate disability)	Hypothermia Group[100]	2002	273	≈4.5	55%	39%	.009
Mortality at 6 mo	Hypothermia Group[100]	2002	273	≈4.5	55%	41%	.02
Neurologic outcome of neonatal hypoxia (death or moderate-severe disability)	Gluckman[101]	2005	218	≈2	66%	59%	.1
Neurologic outcome of neonatal hypoxia (death or moderate-severe disability)	Shankaran[102]	2005	208	3.8	62%	44%	.01
Good neurologic outcome after intracranial aneurysm surgery	Todd[110]	2005	1,001	3.5	63	66	NS

*Only prospective, randomized human trials are included; subjective responses were evaluated by observers blinded to treatment group and core temperature. Different outcomes of some studies are shown in separate rows. Results are presented as means ± SDs or median (interquartile range) unless otherwise specified. For the effects of mild hypothermia on neonatal asphyxia, see the Cochrane meta-analysis by Jacobs and associates.[257]

ΔT_{core}, Difference in core temperature between the treatment groups; *N,* total number of subjects; *NS,* not significant.

ADVERSE EFFECTS OF HYPOTHERMIA

Coagulation is impaired by mild hypothermia. The most important factor appears to be a cold-induced defect in platelet function.[115] The defect in platelet function is related to local temperature, not core temperature.[116] Wound temperature, however, is largely determined by core temperature and is distinctly higher in normothermic patients. Perhaps as importantly, hypothermia directly impairs enzymes of the coagulation cascade. This is not apparent during routine coagulation screening because the tests are performed at 37° C. When these tests are performed at hypothermic temperatures, however, the defect becomes apparent.[117]

Consistent with these in vitro defects, nearly all randomized trials indicate that mild hypothermia increases blood loss during hip arthroplasty and increases allogeneic transfusion requirements.[118-131] Similarly, nearly all randomized trials report an increased transfusion requirement in hypothermic patients.[118-120,122-125,130-132] Meta-analyses indicate that both blood loss (Fig. 54-16) and transfusion requirement (Fig. 54-17) are significantly

Study	Sample size (*N*) N:H	Normothermic (N) mean (SD)	Hypothermic (H) mean (SD)	Outcome (N/H) mean (95%CI)
Schmied	30:30	1670 (32)	2150 (550)	0.79 (0.70, 0.88)
Winkler	75:75	1531 (1055,1746)	1678 (1366,1965)	0.90 (0.82, 1.00)
Widman	22:24	923 (410)	1068 (482)	0.87 (0.68, 1.11)
Persson	29:30	186 (145)	308 (257)	0.62 (0.43, 0.89)
Hofer	29:29	1497 (497)	2300 (788)	0.65 (0.55, 0.77)
Bock	20:20	635 (507)	1070 (803)	0.58 (0.38, 0.89)
Johansson	25:25	1047 (413)	1066 (441)	0.99 (0.80, 1.23)
Smith	31:30	423 (562)	159 (268)	3.14 (1.82, 5.42)
Frank	142:158	390 (834)	520 (754)	0.56 (0.43, 0.73)
Mason	32:32	111 (40)	157 (73)	0.73 (0.60, 0.89)
Casati	25:25	470 (170)	442 (216)	1.11 (0.89, 1.40)
Murat	26:25	160 (61)	161 (100)	1.09 (0.84, 1.43)
Hohn	43:73	660 (230,1870)	956 (340,5480)	0.69 (0.36, 1.34)
Nathan	73:71	569 (356)	666 (405)	0.85 (0.70, 1.02)
Summary				**0.84 (0.74, 0.96)** **Treatment effect *P* = 0.009**

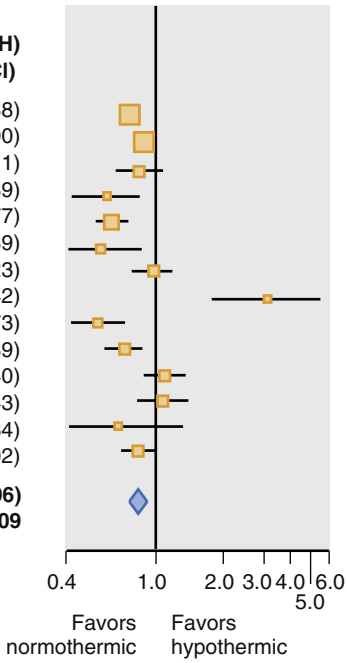


Figure 54-16. Total blood loss meta-analysis and forest plot. Treatment effect expressed as ratio of geometric means of blood loss for normothermic (N) versus hypothermic (H) patients. Results indicate an estimated 16% (95% confidence interval [CI], 4%, 26%) lower average blood loss in normothermic versus hypothermic ($P = .009$). *(From Rajagopalan S, Mascha E, Na J, Sessler DI: The effects of mild perioperative hypothermia on blood loss and transfusion requirement: a meta-analysis,* Anesthesiology *108:71-77, 2008.)*

Study	Normothermic *n/N* (%)	Hypothermic *n/N* (%)	Outcome (N/H) mean (95%CI)
Schmied	1/30 (3%)	7/30 (23%)	0.14 (0.02, 1.09)
Winkler	29/75 (39%)	40/75 (53%)	0.73 (0.51, 1.03)
Widman	9/22 (41%)	11/24 (46%)	0.89 (0.46, 1.73)
Hofer	5/29 (17%)	11/29 (38%)	0.45 (0.18, 1.14)
Johansson	15/25 (60%)	13/25 (52%)	1.15 (0.7, 1.89)
Kurz	23/104 (22%)	34/96 (35%)	0.62 (0.4, 0.98)
Bock	3/20 (15%)	9/20 (45%)	0.33 (0.11, 1.05)
Hohn	17/43 (40%)	18/43 (42%)	0.94 (0.57, 1.57)
Nathan	23/73 (32%)	24/71 (34%)	0.93 (0.58, 1.49)
Smith	2/31 (6%)	1/30 (3%)	1.94 (0.19, 200.24)
Summary			**0.78 (0.63, 0.97)** **Treatment effect *P* = 0.027**

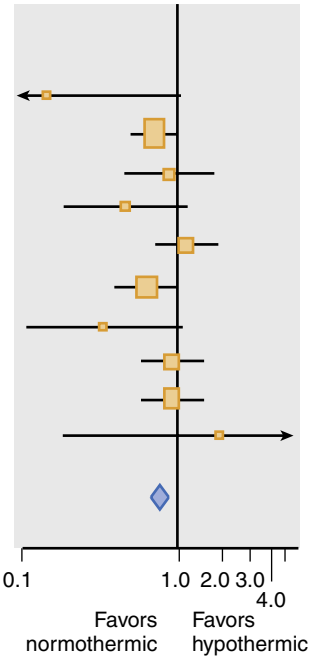


Figure 54-17. Transfusion meta-analysis and forest plot. Treatment effect expressed as the relative risk of transfusion in normothermic versus hypothermic patients. Normothermia is associated with 22% less risk of transfusion than hypothermia (95% confidence interval [CI], 3%, 37%; $P = .027$). *(From Rajagopalan S, Mascha E, Na J, Sessler DI: The effects of mild perioperative hypothermia on blood loss and transfusion requirement: a meta-analysis,* Anesthesiology *108:71-77, 2008.)*

increased by hypothermia.[133] The treatment effect is substantial with just 1° C of core hypothermia increasing each complication by approximately 20%.

Drug metabolism is markedly decreased by perioperative hypothermia. The duration of action of vecuronium is more than doubled by a 2° C reduction in core temperature (Fig. 54-18), and the prolongation is a pharmacokinetic effect, not a pharmacodynamic one.[134] Atracurium duration is less dependent on core temperature: a 3° C reduction in core temperature increases the duration of muscle relaxation only by 60%.[135] With each drug, the recovery index (time for 25% to 75% twitch recovery) remains normal during hypothermia. Core hypothermia per se decreases twitch strength 10% to 15%, even without muscle relaxants.[136] The efficacy of neostigmine as an antagonist of vecuronium-induced neuromuscular block is not altered by mild hypothermia, although onset time is approximately 20% longer.[137] The effects of temperature on muscle relaxants and antagonism of neuromuscular blocks was reviewed by Heier and Caldwell.[138]

During a constant infusion of propofol, plasma concentration is approximately 30% greater than normal when individuals are 3° C hypothermic.[135] The effects of mild hypothermia on the metabolism and pharmacodynamics of most other drugs has yet to be reported. However, the results for muscle relaxants and propofol suggest that the effects are substantial. Hypothermia also alters the pharmacodynamics of the volatile anesthetics, thus reducing minimum alveolar concentration (MAC) approximately 5%/°C.[139] Consequently, no anesthesia whatsoever is required to prevent movement in response to skin incision at core temperatures lower than 20° C.[140] As could be expected from the pharmacokinetic and pharmacodynamic effects of hypothermia, the duration of postanesthetic recovery is significantly prolonged—even when temperature is not a discharge criterion. When "fitness for discharge" and a core temperature exceeding 36° C are required (as in many postanesthesia care units), recovery duration is prolonged by several hours.[141]

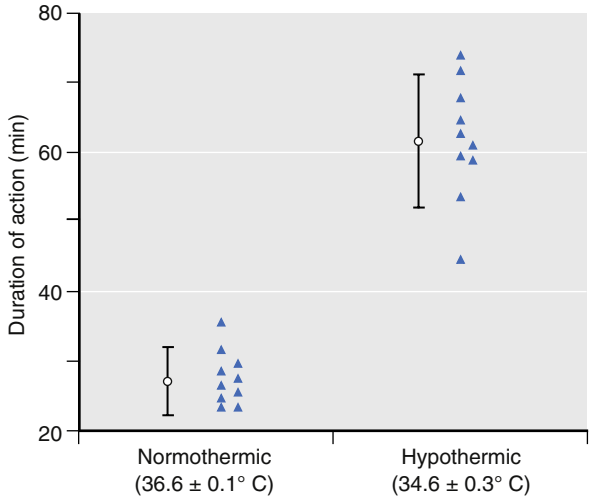


Figure 54-18. Just 2° C reduction in core temperature more than doubled the duration of action of vecuronium. *(From Heier T, Caldwell JE, Sessler DI, Miller RD: Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans,* Anesthesiology *74:815-819, 1991.)*

Wound infections are among the most common serious complications of anesthesia and surgery, and they probably cause more morbidity than all other anesthetic complications combined.[142] Hypothermia can contribute to wound infections both by directly impairing immune function[143] and by triggering thermoregulatory vasoconstriction that, in turn, decreases wound oxygen delivery.[144] It is well established that fever is protective and that infections are aggravated when naturally occurring fever is prevented.[145] Similarly, mild hypothermia, maintained only during anesthesia, impairs subsequent resistance to both *Escherichia coli* and *Staphylococcus aureus* dermal infections in guinea pigs.[146,147] As could be expected from these in vitro and animal data, a prospective, randomized clinical trial indicated that mild intraoperative hypothermia tripled the incidence of surgical wound infection in patients undergoing colon surgery. Furthermore, hypothermia delayed wound healing and prolonged the duration of hospitalization 20% even in patients without infection.[132] Consistent with poor wound healing, urinary nitrogen excretion remains elevated for several postoperative days in patients allowed to become hypothermic during surgery.[148]

Thermal comfort is markedly impaired by postoperative hypothermia; this feeling persists for several hours in patients who are several degrees centigrade hypothermic at the beginning of recovery (Fig. 54-19).[149] Patients, asked years after surgery, often identify feeling cold in the immediate postoperative period as the worst part of their hospitalization—sometimes rating it worse than surgical pain. Postoperative thermal discomfort is also physiologically stressful, by elevating blood pressure, heart rate, and plasma catecholamine concentrations.[150,151] These factors presumably contribute to what may be the

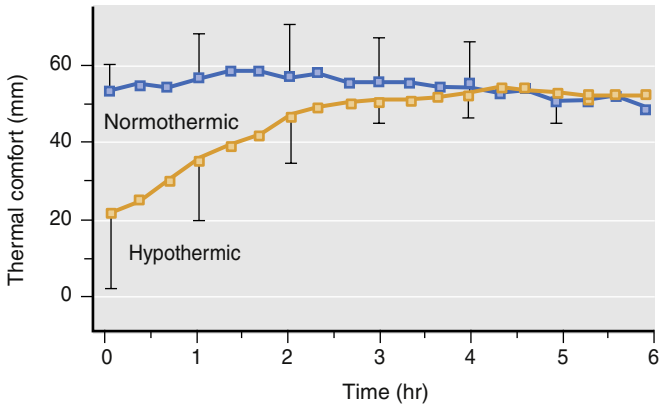


Figure 54-19. Patients who started recovery approximately 2° C hypothermic reported feeling unpleasantly cold, and the sensation persisted for more than 2 hours. Only a few of the warmed patients shivered at any time during the recovery period. In contrast, most of the hypothermic patients demonstrated grades 2 or 3 tremor during the first postoperative hour. By the end of the first elapsed hour, however, shivering was rare, even in the hypothermic patients. Error bars indicate standard deviations. Thermal comfort is shown on a 100-mm visual analog scale where 0 mm is the worst possible cold sensation, 50 mm is neutral, and 100 mm is extreme heat. *(From Kurz A, Sessler DI, Narzt E, et al: Postoperative hemodynamic and thermoregulatory consequences of intraoperative core hypothermia,* J Clin Anesth *7:359-366, 1995.)*

most important consequence of mild perioperative hypothermia: a threefold increase in morbid myocardial outcomes.[126] Given that myocardial ischemia is among the leading causes of unanticipated perioperative death, the results of this prospective randomized trial must be taken extremely seriously.

Table 54-2 lists the major studies that evaluated complications caused by mild perioperative hypothermia.

POSTANESTHETIC SHIVERING

The incidence of postoperative shivering-like tremor reportedly is approximately 40%, but it now appears to be less as more patients are kept normothermic and opioids are administered more frequently and in larger doses than in the past. This potentially serious complication increases oxygen consumption roughly 100%, in proportion to intraoperative heat loss.[152] However, myocardial ischemia is poorly correlated with shivering, a finding suggesting that increased metabolic rate is not the primary etiology of this complication.[126] In addition to increasing intraocular and intracranial pressures, postoperative shivering possibly aggravates wound pain by stretching incisions. The most important determinants of shivering risk are young age and core temperature.[153]

Over the years, postanesthetic tremor has been attributed to uninhibited spinal reflexes, pain, decreased sympathetic activity, pyrogen release, adrenal suppression, respiratory alkalosis, and, most commonly, simple thermoregulatory shivering in response to intraoperative hypothermia. Unfortunately, the etiologies of postanesthetic, shivering-like tremor remain unclear. Certainly, much postoperative tremor is simply normal shivering. As early as 1972, however, investigators recognized the existence of at least two distinct tremor patterns.[154] That perceptive observation subsequently was confirmed in a study that used electromyography to demonstrate that postoperative tremor has the following patterns: (1) a tonic pattern resembling normal shivering, typically having a waxing-and-waning component of four to eight cycles/minute; and (2) a phasic, 5- to 7-Hz bursting pattern resembling pathologic clonus.[155] The clonic pattern was consistent with the previous observation that pathologic spinal cord responses, including clonus, nystagmus, and exaggerated deep tendon reflexes, were common during recovery from general anesthesia.[156]

Not until 1991 did a triple crossover study in volunteers establish that the tonic and clonic patterns were both thermoregulatory (i.e., always preceded by core hypothermia and arteriovenous shunt vasoconstriction).[157] The tonic pattern consistently demonstrated the waxing-and-waning pattern of four to eight cycles/minute that characterizes normal shivering,[18] and apparently it is a simple thermoregulatory response to intraoperative hypothermia. In contrast, the clonic pattern is not a normal component of thermoregulatory shivering and appears specific to recovery from volatile anesthetics. Although the precise etiology of this tremor pattern remains unknown, the cause may be anesthetic-induced disinhibition of normal descending control over spinal reflexes. More recent data in surgical patients, however, belies the simple conclusion from the volunteer study[157] that all postanesthetic tremor is thermoregulatory. Instead, there appears to be a distinct incidence of nonthermoregulatory tremor in normothermic postoperative patients.[158] A similar nonthermoregulatory tremor has been observed in women during labor.[88] The etiology of this tremor and the reason that volunteers and patients should respond differently remain unknown; however, surgical pain appears to be a key factor.[89]

Postanesthetic shivering can be treated by skin surface warming because the regulatory system tolerates more core hypothermia when cutaneous warm input is augmented.[90] However, the skin surface contributes only 20% to control of shivering,[5,6] and available skin surface warmers increase mean skin temperature only a few degrees

TABLE 54-2 MAJOR COMPLICATIONS OF MILD PERIOPERATIVE HYPOTHERMIA IN HUMANS*

Consequence	First Author	Yr	*N*	ΔT_{core} (° C)	Normothermic	Hypothermic	*P*
Surgical wound infection	Kurz[132]	1996	200	1.9	6%	19%	<.01
Duration of hospitalization	Kurz[132]	1996	200	1.9	12.1 ± 4.4 days	14.7 ± 6.5 days	<.01
Duration of hospitalization	Frank[126]	1997	300	1.3	8 (5-13, range)	8 (5-11)	NS
Postoperative troponin I	Nesher[253]	2003	60	1.0	22 ± 9 ng/mL	8 ± 5 ng/mL	<.001
Morbid cardiac events	Frank[126]	1997	300	1.3	1%	6%	<.05
Myocardial damage	Nesher[253]	2003	60	1.0	8 ± 5 ng/mL	22 ± 9 ng/mL	<.01
Urinary excretion of nitrogen	Carli[148]	1989	12	1.5	982 mmol/day	1,798 mmol/day	<.05
Duration of vecuronium	Heier[134]	1991	20	2.0	28 ± 4 min	62 ± 8 min	<.001
Duration of atracurium	Leslie[135]	1995	6	3.0	44 ± 4 min	68 ± 7 min	<.05
Postoperative shivering	Just[254]	1992	14	2.3	141 ± 9 mL/min/m^2	269 ± 60 mL/min/m^2	<.001
Duration of postanesthetic recovery	Lenhardt[141]	1997	150	1.9	53 ± 36 min	94 ± 65 min	<.001
Adrenergic activation	Frank[151]	1995	74	1.5	330 ± 30 pg/mL	480 ± 70 pg/mL	<.05
Thermal discomfort	Kurz[149]	1995	74	2.6	50 ± 10 mm VAS	18 ± 9 mm VAS	<.001
Mortality after major trauma	Gentillo[255]	1997	57	≈1.5	2 / 29 (7%)	12 / 28 (43%)	<.05

*Only prospective, randomized human trials are included; subjective responses were evaluated by observers blinded to treatment group and core temperature. Different outcomes of some studies are shown in separate rows. The study by Just et al is but one of dozens of studies showing that hypothermia provokes shivering. Results are presented as means ± SDs or median (interquartile range) unless otherwise specified. For the effects of hypothermia on perioperative blood loss and transfusion requirement, see the meta-analysis by Rajagopalan and colleagues.[133]

ΔT_{core}, Difference in core temperature between the treatment groups; *N*, total number of subjects; *NS*, not significant; *VAS*, a 100-mm visual analog scale (0 mm, intense cold; 100 mm, intense heat).

centigrade.[159,160] Consequently, cutaneous warming compensates for only small amounts of core hypothermia and does not usually prove effective in most patients with core temperatures much lower than 35° C.[161]

Postanesthetic shivering also can be treated using a variety of drugs, including clonidine (75 μg IV),[92] ketanserin (10 mg IV),[92] tramadol,[162] physostigmine (0.04 mg/kg IV),[163] nefopam (0.15 mg/kg),[164] dexmedetomidine, and magnesium sulfate (30 mg/kg IV).[94] The specific mechanisms by which ketanserin, tramadol, physostigmine, and magnesium sulfate stop shivering remain unknown. Similarly, how clonidine arrests shivering also remains unknown. However, clonidine[36] and dexmedetomidine[26] comparably reduce the vasoconstriction and shivering thresholds, a finding suggesting that they act on the central thermoregulatory system, rather than preventing shivering peripherally. Postoperative shivering has been reviewed in detail,[165] and treatment options have been subjected to a systematic review.[166]

Alfentanil, a pure μ-receptor agonist, significantly impairs thermoregulatory control.[25] However, meperidine is considerably more effective in treating shivering than are equianalgesic doses of other μ agonists.[167] Clinically, this efficacy is manifested as a shivering threshold that is reduced twice as much as the vasoconstriction threshold,[31] without a decrease in the gain or maximum intensity of shivering.[52] The efficacy of meperidine is at least partially preserved during administration of moderate doses of naloxone (0.5 μg/kg/minute) but is virtually obliterated by larger doses (5.0 μg/kg/minute).[168] These data suggest that action of this drug is in part mediated by non–μ opioid receptors. Meperidine possesses considerable κ activity,[169] and it also has central anticholinergic activity, although neither mechanism appears to mediate the special antishivering activity of meperidine.[12] Instead, it may result from agonist activity at central α adrenoceptors.[170] Whatever the mechanism, however, meperidine appears to be a considerably more effective treatment for postoperative shivering than the other opioids.

PERIOPERATIVE THERMAL MANIPULATIONS

Intraoperative thermoregulatory vasoconstriction, once triggered, is remarkably effective in preventing further core hypothermia.[43,51] Nonetheless, most patients are poikilothermic during surgery because they do not become sufficiently hypothermic to trigger thermoregulatory responses.[24,25,27,28] Therefore, intraoperative hypothermia can be minimized by any technique that limits cutaneous heat loss to the environment resulting from cold operating rooms, evaporation from surgical incisions, or conductive cooling produced by administration of cold intravenous fluids. The efficacy of various approaches differs enormously, however.

Mean body temperature decreases when heat loss to the environment exceeds metabolic heat production. Heat production during anesthesia is approximately 0.8 kcal/kg/hour. Because the specific heat of the human body is approximately 0.83 kcal/kg,[171] body temperature decreases approximately 1° C/hour when heat lost to the environment is twice metabolic production. Normally, approximately 90% of metabolic heat is lost through the skin surface. During anesthesia, additional heat is also lost directly from surgical incisions and by administration of cold intravenous fluids.

EFFECTS OF VASOMOTOR TONE ON HEAT TRANSFER

Thermoregulatory vasodilation causes the initial core-to-peripheral redistribution of body heat[61]; similarly, reemergence of vasoconstriction in patients becoming sufficiently hypothermic produces a core temperature plateau.[51] It is thus evident that vasomotor tone alters intercompartmental heat transfer. In addition to thermoregulatory arteriovenous shunt status, arteriolar tone is directly modulated by anesthetics per se.[58] Both factors potentially influence the speed with which peripherally applied heat reaches the core thermal compartment.

Thermoregulatory vasoconstriction slightly impairs induction of therapeutic hypothermia during neurosurgery.[172] However, arteriovenous shunt tone has little effect on intraoperative cooling[173] or heating.[174] Intraoperative vasoconstriction thus only slightly impedes peripheral-to-core transfer of cutaneous heating and cooling. Little clinical effect presumably results because intraoperative thermoregulatory vasoconstriction is opposed by direct anesthetic-induced peripheral vasodilation.

During postanesthetic recovery, however, the situation differs markedly. Here, anesthetic-induced peripheral dilation[58,175] dissipates, leaving unopposed thermoregulatory vasoconstriction. As could be expected, this vasoconstriction then becomes an important factor and significantly impairs transfer of peripherally applied heat to the core thermal compartment. Patients having a residual spinal anesthetic block thus warm considerably faster than do those recovering from general anesthesia alone (Fig. 54-20).[176] Heat balance studies indicate that core warming is slowed because vasoconstriction constrains up to 30 kcal in peripheral tissues.[177]

Because postoperative thermoregulatory vasoconstriction decreases peripheral-to-core transfer of heat, applied warming is most effective during surgery when patients are vasodilated. From a practical perspective, this means that it is easier to maintain intraoperative normothermia (when most patients are vasodilated) than to rewarm them postoperatively (when virtually all hypothermic patients are vasoconstricted). In addition to being more effective, intraoperative warming is more appropriate than postoperative treatment of hypothermia because it prevents the complications resulting from hypothermia.[118,126,132] Patients who unavoidably become hypothermic during surgery nonetheless should be actively heated postoperatively to increase thermal comfort, decrease shivering, and hasten rewarming.

PREVENTING REDISTRIBUTION HYPOTHERMIA

The initial 0.5° C to 1.5° C reduction in core temperature is difficult to prevent because it results from redistribution of heat from the central thermal compartment to cooler

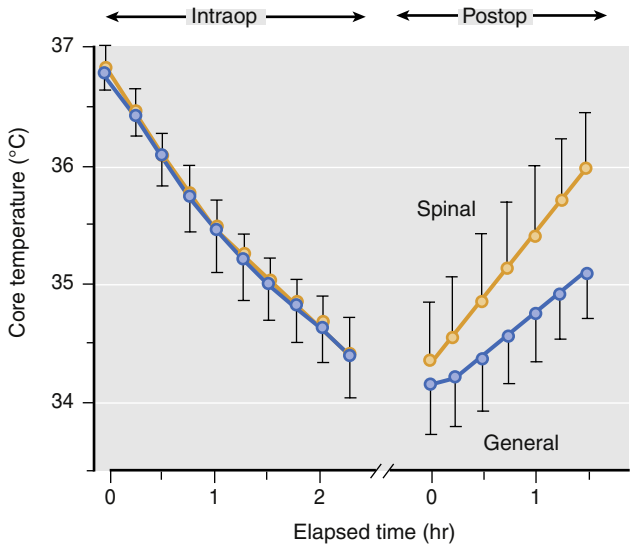


Figure 54-20. Intraoperative and postoperative core temperatures in patients assigned to general anesthesia ($n = 20$) and spinal anesthesia ($n = 20$). All patients were warmed with forced air during the postoperative period. Core temperature did not differ significantly during surgery, but it increased significantly faster postoperatively in patients given spinal anesthesia (1.2 ± 0.1° C/hour versus 0.7 ± 0.2° C/hour; means ± SDs). *(From Szmuk P, Ezri T, Sessler DI, et al: Spinal anesthesia only minimally increases the efficacy of postoperative forced-air rewarming,* Anesthesiology *87:1050-1054, 1997.)*

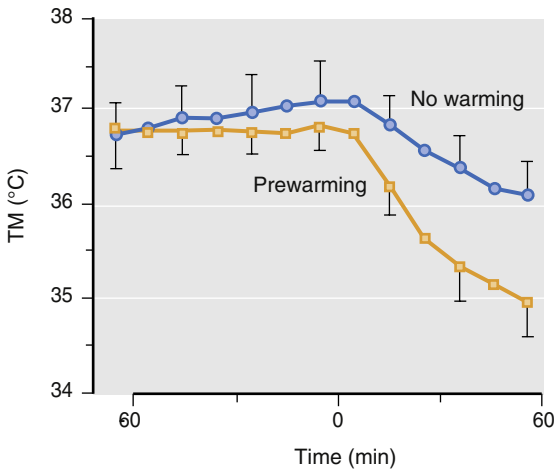


Figure 54-21. During the preinduction period (–120 to 0 minutes), volunteers were either actively warmed or passively cooled (no warming). At induction of anesthesia (time = 0 minutes), active warming was discontinued, and volunteers were exposed to the ambient environment. Initial tympanic membrane (TM) temperatures were similar before each preinduction treatment. During the 60 minutes following induction of anesthesia, core temperature decreased less when volunteers were prewarmed: (ΔT = –1.1 ± 0.3° C) compared with when the same volunteers were not warmed (ΔT = –1.9 ± 0.3° C). Data are presented as means ± SDs. *(From Hynson JM, Sessler DI, Moayeri A, et al: The effects of pre-induction warming on temperature and blood pressure during propofol/nitrous oxide anesthesia,* Anesthesiology *79:219-228, 1993.)*

peripheral tissues.[61] Consequently, surface warming usually fails to prevent hypothermia during the first hour of anesthesia.[62,132] Lack of efficacy during this period results both because the central-to-peripheral flow of heat is massive and because transfer of applied cutaneous heat to the core requires nearly an hour, even in vasodilated patients.

Although redistribution is difficult to treat,[62,132] it can be prevented. Redistribution results when anesthetic-induced vasodilation allows heat to flow peripherally down the normal temperature gradient. Skin surface warming before induction of anesthesia does not much increase core temperature (which remains well regulated), but it does increase body heat content. Most of the increase is in the legs, the most important component of the peripheral thermal compartment. When peripheral tissue temperature is sufficiently increased, subsequent inhibition of normal tonic thermoregulatory vasoconstriction produces little redistribution hypothermia because heat can flow only down a temperature gradient (Fig. 54-21).[80,81] Although substantial amounts of heat must be transferred across the skin surface, active prewarming for as little as 30 minutes likely prevents considerable redistribution.[178]

The "afterdrop" associated with discontinuation of cardiopulmonary bypass is a type of redistribution hypothermia that results from a substantial core-to-peripheral tissue temperature gradient. As could be expected, it is more impressive after bypass at 17° C[179] than at 27° C to 31° C.[180] Cutaneous warming during and after bypass reduces core temperature afterdrop by 60%. However, heat balance data indicate that this reduction results primarily because cutaneous warming prevents the typical decrease in body heat content after discontinuation of bypass, rather than by reducing redistribution.[181]

AIRWAY HEATING AND HUMIDIFICATION

Simple thermodynamic calculations indicate that less than 10% of metabolic heat production is lost via the respiratory tract. The loss results both from heating and humidifying inspiratory gases, but humidification requires two thirds of the heat.[56] Because little heat is lost via respiration, even active airway heating and humidification minimally influence core temperature.[62,182] The *apparent* clinical efficacy of these methods probably results from artifactual warming of proximally positioned esophageal stethoscopes.[183] Because respiratory heat loss remains virtually constant during anesthesia, the fraction of total heat lost via the respiratory tract decreases dramatically during large operations in which substantial heat is lost from evaporation within surgical incisions.[57] Consequently, airway heating and humidification are even less effective than usual in patients most in need of effective warming. Cutaneous warming maintains normothermia so much better than does respiratory gas conditioning that intraoperative active airway heating and humidification are rarely, if ever, indicated.

Airway heating and humidification are more effective in infants and children than in adults.[184] However, cutaneous warming also is more effective in these patients and transfers more than 10 times as much heat. Hygroscopic condenser humidifiers and heat-and-moisture exchanging filters ("artificial noses") retain substantial amounts of moisture and heat within the respiratory system. In terms of preventing heat loss, these passive devices are approximately half as good as active systems,[184] but they cost only a fraction as much. Heat retention is comparable in all clinically available heat-and-moisture exchangers.[56]

INTRAVENOUS FLUIDS

It is not possible to warm patients by administering heated fluids because the fluids cannot greatly exceed body temperature. Conversely, heat loss resulting from cold intravenous fluids becomes substantial when large amounts of crystalloid solution or blood are administered. One unit of refrigerated blood or 1 L of crystalloid solution administered at room temperature each decreases mean body temperature approximately 0.25° C. (The blood is twice as cold, but it has only half the volume.) Fluid warmers minimize these losses and should be used when large amounts of intravenous fluid or blood are administered. In smaller cases, however, they contribute little.

For routine cases, no clinically important differences are noted among the available fluid warmers. Although most warmers allow fluid to cool in the tubing between the heater and the patient, this cooling is of little consequence in adults. At high flows, little cooling occurs, and at low flows, the amount of fluid given is trivial.[185] Special high-volume systems with powerful heaters and little resistance to flow facilitate care of trauma victims and are useful in other cases in which large amounts of fluid must be administered quickly.

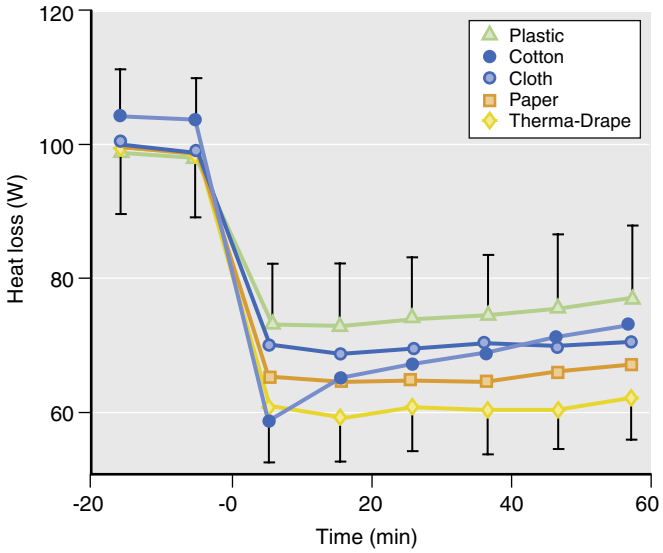


Figure 54-22. Insulators readily available in most operating rooms include cotton blankets, surgical drapes, plastic sheeting, and reflective composites ("space blankets"). A single layer of each reduces total cutaneous heat loss approximately 30%, and no clinically important differences exist among the insulation types. Data are presented as means ± SDs. *(From Sessler DI, McGuire J, Sessler AM: Perioperative thermal insulation,* Anesthesiology *74:875-879, 1991.)*

CUTANEOUS WARMING

Operating room temperature is the most critical factor influencing heat loss because it determines the rate at which metabolic heat is lost by radiation and convection from the skin and by evaporation from within surgical incisions. Consequently, increasing room temperature is one way to minimize heat loss. However, room temperatures exceeding 23° C are generally required to maintain normothermia in patients undergoing all but the smallest procedures.[186] Most operating room personnel find such temperatures uncomfortably warm. Infants may require ambient temperatures exceeding 26° C to maintain normothermia. Such temperatures are sufficiently high to impair performance of operating room personnel and decrease their vigilance.

The easiest method of decreasing cutaneous heat loss is to apply passive insulation to the skin surface. Insulators readily available in most operating rooms include cotton blankets, surgical drapes, plastic sheeting, and reflective composites ("space blankets"). A single layer of each reduces heat loss approximately 30%, and no clinically important differences exist among insulation types (Fig. 54-22).[187] Insulators therefore should be chosen strictly based on cost; paying a premium to purchase reflective composites, for example, is not justified.

The reduction in heat loss from all the commonly used passive insulators is similar because most of the insulation is provided by the layer of still air trapped beneath the covering. Consequently, adding additional layers of insulation further reduces heat loss only slightly. For example, one cotton blanket reduces heat loss by approximately 30%, but three cotton blankets reduce heat loss only by 50%. Furthermore, warming the cotton blankets provides little benefit, and the benefit is short-lived.[188] These data indicate that simply adding additional layers of passive insulation, or warming the insulation before application, usually will be insufficient in patients who become hypothermic while covered with a single layer of insulation.

Cutaneous heat loss is roughly proportional to surface area throughout the body.[189] (The popular perception that a large fraction of metabolic heat is lost from the head is false in adults. Loss from the head can be substantial in small infants,[190] but loss is high mostly because the head represents a large fraction of the total surface area.) Consequently, the amount of skin covered is more important than which surfaces are insulated. It does not make sense, for example, to cover the head and leave the arms exposed because the arms have more surface area than the head and account for more heat loss.

Passive insulation alone rarely is sufficient to maintain normothermia in patients undergoing large operations; active warming is required in those cases. Because approximately 90% of metabolic heat is lost via the skin surface, only cutaneous warming will transfer sufficient heat to prevent hypothermia. Consequently, for intraoperative use, circulating water and forced air are the two major systems requiring consideration.

Studies consistently report that circulating-water mattresses are nearly ineffective.[191] Presumably, they are unable to maintain normothermia because little heat is lost from the back into the 5 cm of foam insulation covering most operating room tables. Furthermore, the combination of heat and decreased local perfusion (resulting when the patient's weight reduces capillary blood flow) increases the propensity for pressure and heat necrosis ("burns"). Such tissue injury can occur even when water temperature does not exceed 40° C.[192] Circulating water is more effective—and safer—when it is placed *over* patients rather than *under* them and, in that position, can almost completely eliminate metabolic heat loss.[159]

Metabolic heat production increases mean body temperature approximately 1° C/hour when cutaneous heat loss is eliminated. Circulating-water garments transfer large amounts of heat by increasing the warmed surface area or by using materials that facilitate conduction.[193,194]

The most common perianesthetic warming system is forced air. The best forced-air systems completely eliminate heat loss from the skin surface.[159,160] Forced air usually maintains normothermia even during the largest operations,[62,132] and it is superior to circulating-water mattresses.[195] It is also remarkably safe, with few if any injuries reported with proper use. The hospital cost of forced-air warming in the United States is now only approximately $10, and it is justifiably by far the most common warming method.

INDUCTION OF MILD THERAPEUTIC HYPOTHERMIA

A paucity of evidence supports the application of therapeutic hypothermia for indications other than out-of-hospital cardiac arrest and asphyxiated neonates. Nonetheless, hypothermia is occasionally used during neurosurgery or acute myocardial infarction. Typically, target core temperatures are 32° C to 34° C, and it is thought to be important to reach the target temperature quickly.

Passive cooling is far too slow for induction of therapeutic hypothermia. Immersion in cold water is the quickest noninvasive method of actively cooling patients. However, immersion is difficult under clinical conditions and poses a substantial electrical safety risk. Administration of refrigerated intravenous fluids also is effective and reduces mean body temperature 0.5° C/L.[196] However, this method may be impractical in neurosurgical patients in whom fluids must be restricted.

Forced-air cooling is easy to implement, but it is relatively slow, taking approximately 2.5 hours to cool neurosurgical patients to 33° C.[172] Conventional circulating-water mattresses are unlikely to be efficient because relatively little skin surface contacts the mattress, and the patient's own body weight reduces bloodborne convection of heat to the back (i.e., circulating water probably does not cool well, for the same reason it heats poorly).[159] Newer circulating-water systems include garment-like covers or "energy exchange pads" that cover far more skin surface and transfer large amounts of heat and are fairly effective.[197,198]

The best way to induce therapeutic hypothermia rapidly is probably endovascular cooling. These systems consist of a heat-exchanging catheter, usually inserted into the inferior vena cava via the femoral artery, and a servocontroller. They can decrease core temperatures at rates approaching 4° C/hour (Fig. 54-23).[199]

Inducing therapeutic hypothermia during surgery is relatively easy because anesthetics profoundly impair thermoregulatory responses. In contrast, unanesthetized patients—even those who have suffered a stroke—vigorously defend core temperature by vasoconstricting and shivering.[200] It is thus necessary to induce tolerance to hypothermia pharmacologically. The best method so far identified is the combination of buspirone and meperidine, drugs that synergistically reduce the shivering threshold to approximately 34° C without provoking excessive sedation or respiratory toxicity.[201] The combination of dexmedetomidine and meperidine may also be helpful, although the interaction is simply additive in this case.[93] In contrast, ondansetron,[202] doxapram,[203] and magnesium sulfate[204] only slightly reduce the shivering threshold in humans. Although initially reported to be effective,[205] neither arm warming nor face warming reduces the shivering threshold by clinically important amounts.[206]

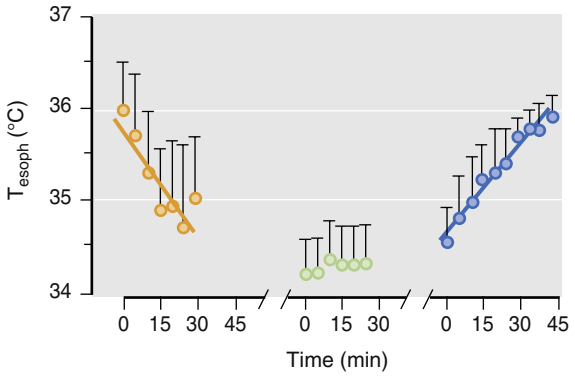


Figure 54-23. Average (± SDs) intraoperative esophageal temperatures (T_{esoph}) during the cooling (*yellow circles*), temperature maintenance (*green circles*), and rewarming (*blue circles*) periods in eight neurosurgical patients who were cooled with endovascular heat-exchanging catheters in the vena cava. Time zero identified the beginning of each thermal management period; the duration of these periods differed in individual patients depending on the duration of surgery and other factors. The regression lines are shown for the cooling *(yellow line)* and rewarming *(blue line)* periods. *(From Doufas AG, Akça O, Barry A, et al: Initial experience with a novel heat-exchanging catheter in neurosurgical patients,* Anesth Analg *95:1752-1756, 2002.)*

DELIBERATE SEVERE INTRAOPERATIVE HYPOTHERMIA

Severe hypothermia may be induced deliberately to confer protection against tissue ischemia, specifically during cardiac surgery and, occasionally, neurosurgery. Drugs such as barbiturates and volatile anesthetics provide considerably less protection than even mild hypothermia.[97] Because many organs compensate poorly for hypothermia, temperatures as low as those deliberately induced are usually lethal when unintentional. Deliberate hypothermia is safe only because anesthesiologists understand and treat the physiologic changes caused by core temperatures 10° C to 15° C lower than normal.

Although deep hypothermia (i.e., 28° C) has been used to facilitate cardiopulmonary bypass for decades, more recent evidence suggests that this degree of hypothermia is either unhelpful or simply harmful. For example, hypothermia may be associated with prolonged ventricular dysfunction,[207] and it does not limit cognitive impairment after bypass.[208] Furthermore, normothermia appears to improve major outcomes after bypass surgery.[209] Consequently, cardiac surgery is increasingly performed at either "tepid" temperatures (i.e., 33° C) or normothermia. Increasing evidence indicates that outcomes of bypass

surgery, whether on or off pump, are improved by maintaining normothermia or near normothermia.[210,211] Deep hypothermia (i.e., 18° C) remains routine for cases of intentional circulatory arrest.[179]

ORGAN FUNCTION

Ischemia damages tissues because oxygen deprivation forces cells to obtain energy anaerobically. Given that this mechanism is inefficient, it may not provide adequate energy. Anaerobic metabolism also produces more toxic metabolic waste products (e.g., lactate and superoxide radicals) than does the Krebs cycle; this is particularly serious when these waste products are not removed by circulating blood.

Hypothermia decreases whole-body metabolic rate by approximately 8%/°C,[46] to approximately half the normal rate at 28° C.[212] Whole-body oxygen demand diminishes, and oxygen consumption in tissues that have higher than normal metabolic rates, such as the brain, is especially reduced. Brain oxygenation is thus improved by hypothermia.[213] Low metabolic rates allow aerobic metabolism to continue during periods of compromised oxygen supply; toxic waste production declines in proportion to the metabolic rate. Although decreased metabolic rate certainly contributes to the observed protection against tissue ischemia, other effects of hypothermia, including "membrane stabilization" and decreased release of toxic metabolites and excitatory amino acids, appear to be most important.[98]

Cerebral blood flow also decreases in proportion to metabolic rate during hypothermia because of an autoregulatory increase in cerebrovascular resistance.[98] The arteriovenous oxygen tension (Pao_2–Pvo_2) difference thus remains constant, and venous lactate concentration does not increase. Cerebral function is well maintained until core temperatures reach approximately 33° C, but consciousness is lost at temperatures lower than 28° C. Primitive reflexes such as gag, pupillary constriction, and monosynaptic spinal reflexes remain intact until approximately 25° C. Nerve conduction decreases, but peripheral muscle tone increases, resulting in rigidity and myoclonus at temperatures near 26° C. Somatosensory- and auditory-evoked potentials are temperature dependent, but they are not significantly modified at core temperatures of 33° C or higher.

Hypothermic effects on the heart include a decrease in heart rate, increased contractility, and well-maintained stroke volume.[214] Cardiac output and blood pressure both decrease. At temperatures lower than 28° C, sinoatrial pacing becomes erratic, and ventricular irritability increases. Fibrillation usually occurs between 25° C and 30° C, and electrical defibrillation is usually ineffective at these temperatures. Because coronary artery blood flow decreases in proportion to cardiac work, hypothermia per se does not cause myocardial ischemia. However, even mild hypothermia decreases tissue damage in response to experimental cardiac ischemia.[111]

Hypothermia decreases blood flow to the kidneys by increasing renovascular resistance. Inhibition of tubular absorption maintains normal urinary volume. As temperature decreases, reabsorption of sodium and potassium is progressively inhibited, causing antidiuretic hormone–mediated "cold diuresis." Despite increased excretion of these ions, plasma electrolyte concentrations usually remain normal. Kidney functions return to normal when patients are rewarmed. Respiratory strength is diminished at core temperatures less than 33° C, but the ventilatory CO_2 response is minimally affected. Hepatic blood flow and function also decrease, thus significantly inhibiting metabolism of some drugs.

ACID-BASE CHANGES

The pH of neutral water ($[OH^-] = [H^+]$) increases 0.017 units for each 1° C reduction in temperature.[215] The pH of blood in a closed system (e.g., test tube or artery) changes similarly. Cold-blooded animals allow pH to vary with body temperature as it would in vitro (i.e., blood becomes more alkalotic as temperature decreases); in contrast, homeotherms, which decrease body temperature during hibernation, maintain a pH_a near 7.4 that is known as pH-stat management. Interpretation of arterial pH in hypothermic humans is difficult because it is unclear which strategy is optimal.[216]

To mimic the compensatory mechanisms used by hibernating homeotherms, blood pH (which is measured by electrodes at 37° C) traditionally has been "corrected" to the patient's actual body temperature. Without correction, tissue oxygen availability decreases because hemoglobin's affinity for oxygen increases approximately 1.7%/°C. This effect is small compared with the 5.7%/°C increase in oxyhemoglobin affinity caused by hypothermia itself. Fortunately, the combined increases in affinity are offset by the 8%/°C reduction in metabolic rate caused by hypothermia. Tissue hypoxia is thus unlikely, with or without correction, and it has not been demonstrated experimentally.

Ectothermic strategy also is known as alpha stat because the dissociation constant of the α-imidazole group in histidine changes parallel to those of water. Maintaining constant imidazole ionization results in optimal enzyme function as temperature changes. In contrast, homeothermic dynamics significantly decrease metabolic function, and animals are essentially anesthetized by cold. Constant relative alkalinity also maintains a stable intracellular-to-extracellular gradient that promotes removal of acidic products of intracellular metabolism, a process that may be salutary.[217]

Both alpha-stat and pH-stat management strategies appear to work well, and physiologic differences between them appear to be subtle. However, increasing evidence indicates that pH-stat management better preserves neurons in the context of ischemic stress.[218-220] Furthermore, clinical outcomes appear to be improved by pH-stat management[221]—or at least not worsened.[222] Nonetheless, alpha-stat management remains common, and no consensus indicates that either strategy markedly influences the outcome of cardiac surgery.

HYPERTHERMIA AND FEVER

Hypothermia is by far the most common perianesthetic thermal perturbation. However, hyperthermia is probably

more dangerous than a comparable degree of hypothermia, and hyperthermia is certainly more dangerous when perturbations exceed a few degrees centigrade. *Hyperthermia* is a generic term simply indicating a core body temperature exceeding normal values. In contrast, *fever* is a regulated increase in the core temperature targeted by the thermoregulatory system. Hyperthermia can result from a variety of causes and usually indicates a problem of sufficient severity that intervention by the physician is required.

PASSIVE HYPERTHERMIA AND MALIGNANT HYPERTHERMIA

Passive intraoperative hyperthermia results from excessive patient heating and is most common in infants and children. It is especially frequent when effective active warming is used without adequate core temperature monitoring. Passive hyperthermia, by definition, does not result from thermoregulatory intervention. Consequently, it can easily be treated by discontinuing active warming and removing excessive insulation.

The increase in body temperature during malignant hyperthermia results from an enormous increase in metabolic heat produced by both internal organs and skeletal muscles.[223] Central thermoregulation presumably remains intact during acute crises, but efferent heat loss mechanisms may be compromised by intense peripheral vasoconstriction resulting from circulating catecholamine concentrations 20 times normal.[224] For comprehensive information on malignant hyperthermia, see Chapter 43.

FEVER

Normal body temperature is neither set nor maintained by circulating factors. In contrast, fever results when endogenous pyrogens increase the thermoregulatory target temperature ("setpoint"). Identified endogenous pyrogens include interleukin-1, tumor necrosis factor, interferon-α, and macrophage inflammatory protein-1.[225] Although it was initially believed that these factors acted directly on hypothalamic thermoregulatory centers,[226] increasing evidence indicates a more complicated system involving vagal afferents.[227] Most endogenous pyrogens have peripheral actions (e.g., immune system activation) in addition to their central generating capabilities.

Fever is relatively rare during general anesthesia, considering how often febrile stimuli are likely to be present. It is rare because volatile anesthetics per se inhibit expression of fever (Fig. 54-24),[228] as do opioids.[229] Infection is by far the most common cause of fever. Such fevers may reflect preexisting infection or may result, for example, from urologic manipulations. However, perioperative fever also occurs in response to mismatched blood transfusions, blood in the fourth cerebral ventricle, and allergic reactions. Some degree of fever is also typical after surgery.[230] The causes of fever are sufficiently diverse—and potentially serious—that a search for a specific etiology usually is warranted.

Treatment of hyperthermia depends on the etiology, with the critical distinction being between fever and the other causes of hyperthermia. (In general, patients with fever and increasing core temperature have constricted fingertips whereas those with other types of hyperthermia are vasodilated.) It is always appropriate to treat underlying causes, but nonfebrile hyperthermia also improves with cooling.

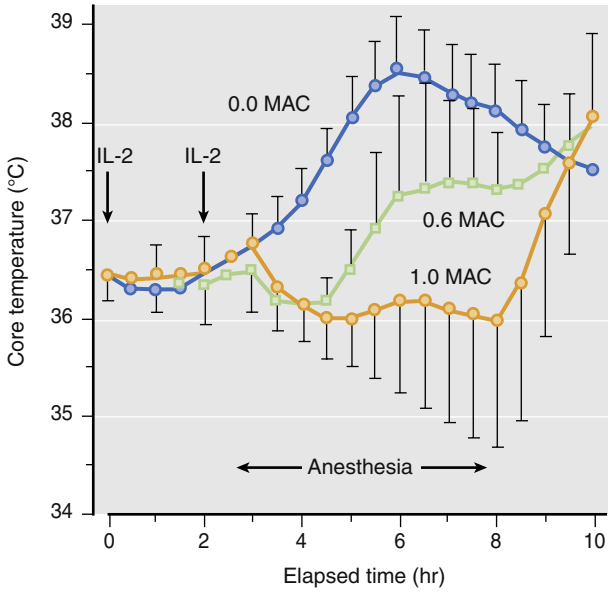


Figure 54-24. Change in core temperature after administration of 50,000 IU/kg of interleukin-2 (IL-2) followed by a second dose of 100,000 IU/kg 2 hours later. The first dose of IL-2 defined elapsed time zero; anesthesia was started after 3 elapsed hours and continued for 5 hours. Data are presented as means ± SDs. *MAC,* Minimum alveolar concentration. *(From Negishi C, Lenhardt R, Sessler DI, et al: Desflurane reduces the febrile response to interleukin-2 administration,* Anesthesiology *88:1162-1169, 1998.)*

The first- and second-line treatments for fever are amelioration of the underlying cause and administration of antipyretic medications. The first treatment strategy often fails because the etiology of fever remains unknown; alternatively, the source may be known but unresponsive. The second strategy also often fails or is only partially effective, perhaps because some fever is mediated by mechanisms that bypass conventional antipyretics.[225] In these patients, third-line treatment is most likely to be implemented: active cooling (Table 54-3). Active cooling of febrile patients is intuitive. However, it often fails to reduce core temperature while simultaneously worsening the situation by triggering thermoregulatory defenses, including intense discomfort, shivering, and autonomic nervous system activation.[231] Active cooling of febrile patients should thus be instituted with considerable care, to be sure that the putative benefits outweigh the stress induced by activation of thermoregulatory defenses.

HYPERTHERMIA DURING EPIDURAL ANALGESIA

Hyperthermia frequently complicates epidural analgesia for labor and delivery,[232] as well as in nonpregnant postoperative patients.[233] This is especially the case when labor is long, more than 8 hours. A clinical consequence of this hyperthermia is that women given epidural analgesia

TABLE 54-3 ACTIVE CUTANEOUS COOLING AS A TREATMENT FOR FEVER*

	Control	Cooling	Warming
Integrated core temperature (°C/hr)	6.0 ± 1.6	5.7 ± 2.2	6.4 ± 1.2
Oxygen consumption (mL/min)	330 ± 50	430 ± 40†	310 ± 30
Duration of shivering (min)	33 ±11	229 ± 35	20 ± 0
Mean arterial pressure (mm Hg)	90 ± 4	98 ± 6†	86 ± 6‡
Mean norepinephrine (nM)	1.0 ± 0.4	1.4 ± 0.7†	1.1 ± 0.5‡
Baseline epinephrine (nM)	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
Mean epinephrine during treatment (nM)	0.3 ± 0.1	0.5 ± 0.1†	0.4 ± 0.1
Severe cold sensation (% of time)	27	89†	11

*Volunteers were given 30,000 IU/kg of interleukin-2 (IL-2), followed 2 hours later by an additional dose of 70,000 IU/kg. The first dose of IL-2 defined elapsed time zero; thermal management started after 3 elapsed hours and continued for 5 hours. Each volunteer participated on 3 separate days: no warming or cooling, active cooling, and active warming. Mean and integrated values are presented over the treatment period, from 3 to 8 elapsed hours. Times are presented in terms of hours elapsed since the first injection of IL-2. Data are presented as means ± SDs.
†Statistically significant differences from control.
‡Statistically significant differences from the cooling day.
Modified from Lenhardt R, Negishi C, Sessler DI, et al: The effects of physical treatment on induced fever in humans, *Am J Med* 106:550-555, 1999.

are more often given antibiotics than are women treated conventionally, and their infants are more commonly treated for sepsis.[234]

Because passive hyperthermia and excessive heat production are unlikely etiologies, elevated body temperature in laboring and postoperative patients is presumably true fever (i.e., a regulated increase in core temperature) resulting from infection or inflammation.[235] For example, Dashe and co-workers concluded: "Epidural analgesia is associated with intrapartum fever, but only in the presence of placental inflammation. This suggests that the fever reported with epidural analgesia is due to infection rather than the analgesia itself."

The conventional assumption is that hyperthermia is *caused* by the technique, although no convincing mechanism has been proposed. It is worth remembering, however, that pain in "control" patients is usually treated with opioids—which themselves attenuate fever.[229] Fever associated with infection or tissue injury could then be suppressed by low doses of opioids, which are usually given to "control" patients, while being expressed normally in patients given epidural analgesia (Fig. 54-25).[236] The extent to which this mechanism contributes remains to be determined and has been disputed,[237] but no convincing alternative explanation has been advanced.

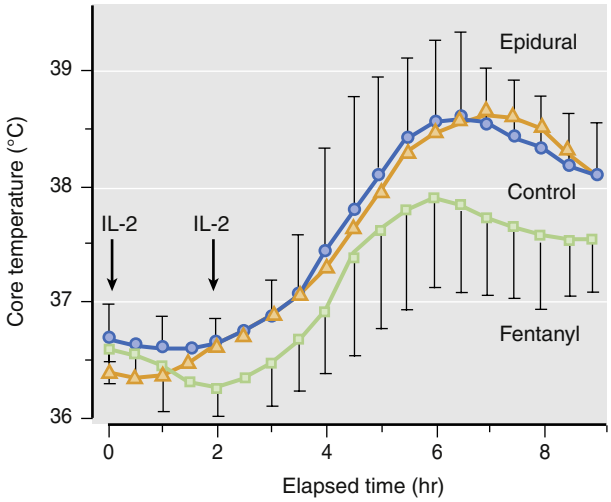


Figure 54-25. Core temperatures after administration of 50 IU/g of interleukin-2 (IL-2) followed by a second dose of 100 IU/g 2 hours later. The first dose of IL-2 defined elapsed time zero. Data are presented as means ± SDs. Error bars for the epidural days are omitted for clarity, but they were similar to those shown for control and intravenous fentanyl. *(From Negishi C, Lenhardt R, Ozaki M, et al: Opioids inhibit febrile responses in humans, whereas epidural analgesia does not: an explanation for hyperthermia during epidural analgesia,* Anesthesiology *94:218-222, 2001.)*

TEMPERATURE MONITORING

Core temperature measurements (e.g., tympanic membrane as measured with a thermocouple, pulmonary artery, distal esophagus, and nasopharynx) are used to monitor intraoperative hypothermia, prevent overheating, and facilitate detection of malignant hyperthermia. Muscle or skin surface temperatures may be used to evaluate vasomotion,[238] as well as to ensure the validity of peripheral neuromuscular monitoring.[239]

Both core and skin surface temperature measurements are required to determine the thermoregulatory effects of different anesthetic drugs. The combination of core and mean skin temperature can be used to estimate mean body temperature, and therefore body heat content, with remarkable accuracy.[240] Temperatures are not uniform within the body; consequently, temperatures measured at each site have different physiologic and practical significance.

THERMOMETERS

Mercury-in-glass thermometers are slow and cumbersome and thus have universally been replaced with electronic systems. The most common electronic thermometers are thermistors and thermocouples. Both devices are sufficiently accurate for clinical use and inexpensive enough to be disposable. Also sufficiently accurate for clinical use are "deep tissue" thermometers that are based on actively reducing cutaneous heat flux to zero[241]. Infrared monitors that extrapolate tympanic membrane temperature from outer ear temperature are

unreliable,[242] as are infrared systems that scan forehead skin.[243]

TEMPERATURE MONITORING SITES

The core thermal compartment is composed of highly perfused tissues whose temperature is uniform and high compared with the rest of the body. Temperature in this compartment can be evaluated in the pulmonary artery, distal esophagus, tympanic membrane, or nasopharynx.[244,245] Temperature probes incorporated into esophageal stethoscopes must be positioned at the point of maximal heart sounds, or even more distally, to provide accurate readings. Even during rapid thermal perturbations, such as cardiopulmonary bypass, these temperature-monitoring sites remain reliable. Core temperature can be estimated with reasonable accuracy using oral, axillary, rectal, and bladder temperatures, except during extreme thermal perturbations.[244,245]

Skin surface temperatures are considerably lower than core temperature. Skin surface temperatures—when adjusted with an appropriate offset—nonetheless reflect core temperature reasonably well.[246] However, skin temperatures fail to confirm the clinical signs of malignant hyperthermia (tachycardia and hypercarbia) reliably in swine,[247] and they have not been evaluated for this purpose in humans (Fig. 54-26). Rectal temperature also normally correlates well with core temperature,[244,245] but it fails to increase appropriately during malignant hyperthermia crises[247] and under other documented situations.[248] Consequently, rectal and skin surface temperatures must be used with considerable caution.

Even during cardiopulmonary bypass, the core temperature monitoring sites (e.g., tympanic membrane, nasopharynx, pulmonary artery, and esophagus) remain useful. In contrast, rectal temperatures lag behind those measured in core sites. Consequently, rectal temperature is considered an "intermediate" temperature in deliberately cooled patients. During cardiac surgery, bladder temperature is equal to rectal temperature (and therefore intermediate) when urine flow is low, but it is equal to pulmonary artery temperature (and thus core) when flow is high.[249] Because bladder temperature is strongly influenced by urine flow, it may be difficult to interpret in these patients. The adequacy of rewarming is best evaluated by considering both "core" and "intermediate" temperatures.

WHEN TEMPERATURE MONITORING IS REQUIRED

Core temperature monitoring is appropriate during most general anesthetic cases both to facilitate detection of malignant hyperthermia and to quantify hyperthermia and hypothermia. Malignant hyperthermia is best detected by tachycardia and an increase in end-tidal CO_2 tension (P_{CO_2}) out of proportion to minute ventilation.[250] Although increasing core temperature is not the first sign of acute malignant hyperthermia, it certainly helps confirm the diagnosis. More common than malignant hyperthermia is intraoperative hyperthermia, which has other causes, including excessive warming, infectious fever, blood in the fourth cerebral ventricle, and mismatched blood transfusions. By far the most common perioperative thermal disturbance is inadvertent hypothermia. Core temperature usually decreases 0.5° C to 1.5° C in the first 30 minutes following induction of anesthesia. Hypothermia results from internal redistribution of heat and a variety of other factors whose importance in individual patients is difficult to predict.[61,79] Core temperature perturbations during the first 30 minutes of anesthesia thus are difficult to interpret, and measurement is not usually required. Body temperature should, however, be monitored in patients undergoing general anesthesia exceeding 30 minutes in duration and in all patients whose surgery lasts longer than 1 hour.

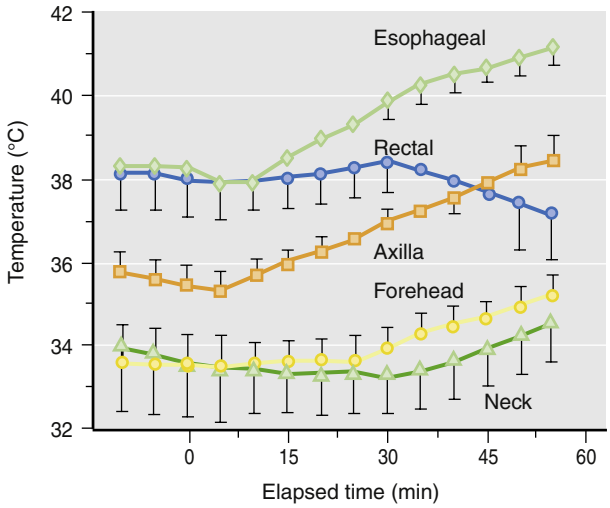


Figure 54-26. Axillary and esophageal temperatures correlated well during acute malignant hyperthermia in swine, but forehead and neck skin temperatures did not. Rectal temperature also failed to identify the onset of malignant hyperthermia promptly. Elapsed time zero indicates an end-tidal P_{CO_2} of 70 mm Hg. These data indicate that forehead and neck skin surface temperatures do not adequately confirm other clinical signs of malignant hyperthermia. Valid core temperature monitoring sites include the distal esophagus, pulmonary artery, nasopharynx, and tympanic membrane. Except during cardiopulmonary bypass, body temperature also can be measured in the mouth, axilla, and bladder. Data are presented as means ± SDs. *(Modified from Iaizzo PA, Kehler CH, Zink RS, et al: Thermal response in acute porcine malignant hyperthermia,* Anesth Analg *82:803-809, 1996.)*

Local anesthetics (including amides), which are used to produce regional blocks, and sedatives, which are used during monitored anesthesia care, do not trigger malignant hyperthermia.[251] Nonetheless, core hypothermia is as common during epidural and spinal anesthesia as during general anesthesia, and it can be nearly as severe.[77] Therefore, core temperature should be measured during regional anesthesia in patients likely to become hypothermic, which at the very least includes those undergoing body cavity surgery.

TEMPERATURE MONITORING AND THERMAL MANAGEMENT GUIDELINES

The objectives of temperature monitoring and perioperative thermal management are to detect thermal disturbances

and to maintain appropriate body temperature during anesthesia. Available data suggest the following guidelines:

1. Core body temperature should be measured in most patients given general anesthesia for longer than 30 minutes.
2. Temperature should also be measured during regional anesthesia when changes in body temperature are intended, anticipated, or suspected.
3. Unless hypothermia is specifically indicated (e.g., for protection against ischemia), efforts should be made to maintain intraoperative core temperature higher than 36° C.

Various organizations have also proposed temperature monitoring and thermal management strategies. The American Society of Anesthesiologists (ASA) standards require only that "every patient receiving anesthesia shall have temperature monitored when clinically significant changes in body temperature are intended, anticipated or suspected." For office-based sedation, regional anesthesia, or general anesthesia, the ASA also requires that "the body temperature of pediatric patient shall be measured continuously."

The State of New Jersey has stronger requirements, specifically that the body temperature of each patient under general or regional anesthesia shall be continuously monitored. Italy probably has one of the strongest local standards, which require, among other things, that (1) core temperature is measured in adults undergoing general anesthesia for more than 30 minutes (and all children), (2) ambient operating room temperature exceeds 21° C, (3) patients are kept normothermic, and (4) patients who become hypothermic remain in the postanesthesia care unit until normothermia is restored.

In 2007, the American College of Cardiology and American Heart Association published guidelines for the care of patients undergoing noncardiac surgery. They include a class 1 recommendation that "maintenance of body temperature in a normothermic range is recommended for most procedures other than during periods in which mild hypothermia is intended to provide organ protection (e.g., during high aortic cross-clamping)."[252] Based on overwhelming evidence of hypothermia-induced complications, maintaining perioperative normothermia became one of the first anesthetic "pay-for-performance" measures.

SUMMARY

Body temperature normally is controlled by a negative-feedback system in the hypothalamus, which integrates thermal information from most tissues. Approximately 80% of this thermal input is derived from core body temperature, which can be measured using distal esophageal, nasopharyngeal, or tympanic membrane thermometer probes. The hypothalamus coordinates increases in heat production (nonshivering thermogenesis and shivering), increases in environmental heat loss (sweating), and/or decreases in heat loss (vasoconstriction) as needed to maintain normothermia.

Thermal steady state requires that heat loss to the environment equals metabolic heat production; hypothermia occurs when heat loss exceeds production. Mild core hypothermia is common during surgery and anesthesia. It results initially from redistribution of body heat from the core to peripheral tissues and subsequently from heat loss exceeding metabolic heat production. Clinical doses of general anesthetics decrease the threshold for response to hypothermia from approximately 37° C (normal) to 33° C to 35° C. Anesthetized patients whose core temperatures exceed these values usually are poikilothermic and do not actively respond to thermal perturbations. Patients who become sufficiently hypothermic do trigger thermoregulatory vasoconstriction, and the vasoconstriction is remarkably effective in minimizing further core hypothermia.

Mild intraoperative hypothermia provides significant protection against tissue ischemia and hypoxia in animals. However, the only situations in which improved outcome has been demonstrated with therapeutic hypothermia in humans are out-of-hospital cardiac arrest and neonatal asphyxia. Hypothermia also decreases triggering of malignant hyperthermia, and it reduces the severity of the syndrome, once triggered. However, most consequences of inadvertent hypothermia are harmful. Major adverse effects include morbid myocardial outcomes, reduced resistance to surgical wound infections, increased blood loss and transfusion requirement, prolonged duration of drug action, shivering, and decreased postoperative thermal comfort.

Little metabolic heat is lost via the respiratory tract. Consequently, even active airway heating and humidification are of little benefit. Administration of sufficient volumes of cold intravenous fluid can produce substantial hypothermia. Fluids therefore should be warmed in patients requiring intravenous administration of more than several liters per hour; however, fluid warming should always be secondary to active cutaneous warming. Among the clinically available active systems, forced air offers the best combination of efficacy, safety, and price. Forced air can usually maintain normothermia even during the largest operations.

Regional anesthesia produces both peripheral and central inhibition of thermoregulatory control. Peripheral inhibition results when local anesthetics block nerves that are required for thermoregulatory defenses. Hypothermia during neuraxial anesthesia results initially from core-to-peripheral redistribution of body heat and subsequently from heat loss exceeding heat production. Hypothermia during major conduction anesthesia may be as severe as that during general anesthesia.

Increased core temperature can result from augmented thermogenesis (malignant hyperthermia), excessive heating (passive hyperthermia), or a specific increase in the thermoregulatory target temperature (fever). Because the causes of hyperthermia are varied and often serious, the etiology of observed increases in core temperature should be sought and appropriate treatments instituted.

A reasonable strategy for detecting and preventing thermal disturbances is to monitor core temperature in patients having general anesthesia lasting longer than 30 minutes and in those undergoing major surgery with regional anesthesia. Unless hypothermia is specifically indicated (i.e., for protection against cerebral ischemia), core temperature should be maintained higher than 36° C.

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Chapter 55

Airway Management in the Adult

CARIN A. HAGBERG • CARLOS A. ARTIME

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Key Points

- One of the fundamental responsibilities of the anesthesiologist is to mitigate the adverse effects of anesthesia on the respiratory system by maintaining airway patency and ensuring adequate ventilation and oxygenation. The term *airway management* refers to this practice and is a cornerstone of anesthesia.
- Successful airway management requires a range of knowledge and skill sets—specifically, the ability to predict difficulty with airway management and to formulate an airway management plan, as well as have the skills necessary to execute that plan using the wide array of airway devices available.
- The American Society of Anesthesiologists' *Practice Guidelines for Management of the Difficult Airway* and the accompanying "Difficult Airway Algorithm" provide guidelines for the evaluation of the airway and preparation for difficult airway management and can guide clinical decision making when an anesthesiologist is faced with a known or potentially difficult airway.
- A detailed understanding of airway anatomy is essential for the anesthesia provider.
- A complete evaluation of the airway and knowledge of difficult airway predictors can alert the anesthesiologist to the potential for difficulty with airway management and allow for appropriate planning.
- To facilitate airway management, some form of anesthesia is usually required to provide comfort for the patient, to blunt airway reflexes, and to blunt the hemodynamic response to airway instrumentation, which may be accomplished with the induction of general anesthesia or by the application of local anesthesia to the airway.
- Over the past 25 years, the laryngeal mask airway (LMA) has emerged as one of the most important developments in airway devices.
- Endotracheal intubation establishes a definitive airway, provides maximal protection against the aspiration of gastric contents, and allows for positive-pressure ventilation with higher airway pressures than via a facemask or supraglottic airway.
- Flexible scope intubation of the trachea in an awake, spontaneously ventilating patient is the *gold standard* for the management of the difficult airway.
- Percutaneous (invasive) airways are indicated as a rescue technique when attempts at establishing a noninvasive airway fail. The anesthesia practitioner should become proficient with techniques for transtracheal jet ventilation and cricothyrotomy.
- Extubation is a critical component of airway management with the potential for significant complications. The plan for an extubation of the trachea must be preemptively formulated and includes a strategy for reintubation of the trachea should the patient be unable to maintain an adequate airway after extubation.

INTRODUCTION

General anesthesia is associated with various effects on the respiratory system, including the loss of airway patency, loss of protective airway reflexes, and hypoventilation or apnea. Therefore one of the fundamental responsibilities of the anesthesiologist is to establish airway patency and to ensure adequate ventilation and oxygenation. The term *airway management* refers to the practice of establishing and securing a patent airway and is a cornerstone of anesthetic practice. Traditionally, ventilation via a mask and endotracheal intubation has been the foundation of airway management; in the past 25 years, however, the laryngeal mask airway (LMA) has emerged as one of the most important developments in airway devices.

Because failure to secure a patent airway can result in hypoxic brain injury or death in only a few minutes, difficulty with airway management has potentially grave implications. Analysis of the American Society of Anesthesiologists (ASA) "Closed Claims Project" database has shown that the development of an airway emergency increases the odds of death or brain damage by 15-fold.[1] Although the proportion of claims attributable to airway-related complications has decreased over the past 3 decades, airway complications are still the second-most common cause of claims.[2] In 1993, the ASA published the first *Practice Guidelines for Management of the Difficult Airway*, which was written with the intent to "facilitate the management of the difficult airway and to reduce the likelihood of adverse outcomes."[3] The most recent update to this report, published in 2013, defines the difficult airway as "the clinical situation in which a conventionally trained anesthesiologist experiences difficulty with ventilation of the upper airway via a mask, difficulty with tracheal intubation, or both" and provides guidelines for the evaluation of the airway and preparation for difficult airway management, including a "Difficult Airway Algorithm" intended to guide clinical decision making when an anesthesiologist is faced with a known or potential difficult airway (Figure 55-1).[4]

Successful airway management requires a range of knowledge and skill sets—specifically, the ability to predict difficulty with airway management, to formulate an airway management plan, and to have the skills necessary to execute that plan using the wide array of available airway devices.[5] Development of these skills should be an ongoing endeavor for all anesthesiologists. As with any manual skill, continued practice improves performance and may reduce the likelihood of complications. New airway devices are continually being introduced into the clinical arena, each with unique properties that may be advantageous in certain situations. Becoming familiar with new devices under controlled conditions is important for the anesthesia practitioner—the difficult airway is not an appropriate setting during which to experiment with a new technique.

FUNCTIONAL AIRWAY ANATOMY

A detailed understanding of airway anatomy is essential for the anesthesiologist. Various aspects of airway management depend on a working knowledge of the anatomy involved, including airway assessment, preparation of the airway for awake intubation, and the proper use of airway devices. Knowledge of normal anatomy and anatomic variations that may render airway management more difficult helps with the formulation of an airway management plan. Because some critical anatomic structures may be obscured during airway management, the anesthesiologist must be familiar with the interrelationship between different airway structures.

The airway can be divided into the upper airway, which includes the nasal cavity, the oral cavity, the pharynx, and the larynx; and the lower airway, which consists of the tracheobronchial tree.

NASAL CAVITY

The airway begins functionally at the naris (*pl.* nares), the external opening of the nasal passages. The nasal cavity is divided into the right and left nasal passages (or fossae) by the nasal septum, which forms the medial wall of each passage. The septum is formed by the septal cartilage anteriorly and by two bones posteriorly—the ethmoid (superiorly) and the vomer (inferiorly). Nasal septal deviation is common in the adult population[6]; therefore the more patent side should be determined before passing instrumentation through the nasal passages. The lateral wall of the nasal passages is characterized by the presence of three turbinates (or conchae) that divide the nasal passage into three scroll-shaped meatuses (Figure 55-2). The inferior meatus, between the inferior turbinate and the floor of the nasal cavity, is the preferred pathway for passage of nasal airway devices[7]; improper placement of objects in the nose can result in avulsion of a turbinate.[8,9] The roof of the nasal cavity is formed by the cribriform plate, part of the ethmoid bone. This fragile structure, if fractured, can result in communication between the nasal and intracranial cavities and a resultant leakage of cerebrospinal fluid. Because the mucosal lining of the nasal cavity is highly vascular, vasoconstrictor should be applied, usually topically, before instrumentation of the nose to avoid epistaxis. The posterior openings of the nasal passages are the choanae, which lead into the nasopharynx.

ORAL CAVITY

Because of the relatively small size of the nasal passages and the significant risk of trauma, the mouth is often used as a conduit for airway devices. Many airway procedures require adequate mouth opening, which is accomplished by rotation within the temporomandibular joint (TMJ) and subsequent opening by sliding (also known as *protrusion* or *subluxation*) of the condyles of the mandible within the TMJ.[10]

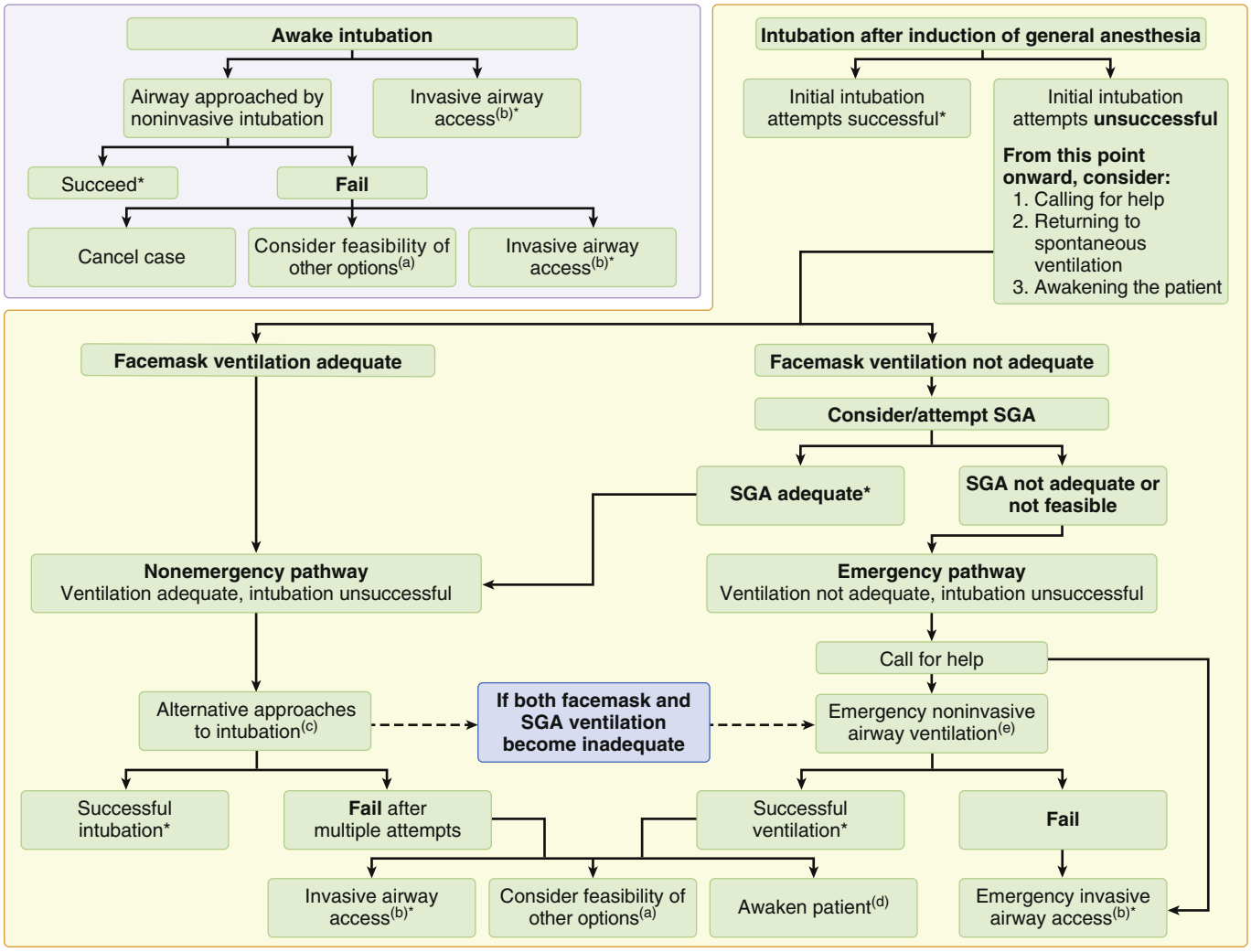
The oral cavity leads to the oropharynx and is inferiorly bounded by the tongue and superiorly by the hard and soft palates. The hard palate, formed by parts of the maxilla and the palatine bone, makes up the anterior two thirds of the roof of the mouth; the soft palate (velum palatinum), a fibromuscular fold of tissue attached to the hard palate, forms the posterior one third of the roof of

1. Assess the likelihood and clinical impact of basic management problems:
   - Difficulty with patient cooperation or consent
   - Difficult mask ventilation
   - Difficult supraglottic airway placement
   - Difficult laryngoscopy
   - Difficult intubation
   - Difficult surgical airway access

2. Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management.

3. Consider the relative merits and feasibility of basic management choices:
   - Awake intubation *vs.* intubation after induction of general anesthesia
   - Noninvasive technique *vs.* invasive techniques for the initial approach to intubation
   - Video-assisted laryngoscopy as an initial approach to intubation
   - Preservation *vs.* ablation of spontaneous ventilation

4. Develop primary and alternative strategies:



***Confirm ventilation, tracheal intubation, or SGA placement with exhaled CO_2.**

a. Other options include (but are not limited to): surgery using facemask or supraglottic airway (SGA) anesthesia (e.g., LMA, ILMA, laryngeal tube), local anesthesia infiltration, or regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore these options may be of limited value if this step in the algorithm has been reached via the Emergency Pathway.
b. Invasive airway access includes surgical or percutaneous airway, jet ventilation, and retrograde intubation.
c. Alternative difficult intubation approaches include (but are not limited to): video-assisted laryngoscopy, alternative laryngoscope blades, SGA (e.g., LMA or ILMA) as an intubation conduit (with or without fiberoptic guidance), fiberoptic intubation, intubating stylet or tube changer, light wand, and blind oral or nasal intubation.
d. Consider re-preparation of the patient for awake intubation or cancelling surgery.
e. Emergency noninvasive airway ventilation consists of a SGA.

Figure 55-1. The American Society of Anesthesiologists' "Difficult Airway Algorithm." *(From Apfelbaum JL, Hagberg CA, Caplan RA, et al: Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway,* Anesthesiology *118:251-270, 2013.)*

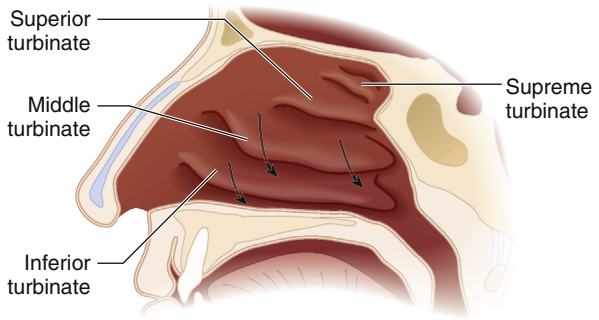


Figure 55-2. Lateral wall of the nasal cavity. *(From Redden RJ: Anatomic considerations in anesthesia. In Hagberg CA, editor:* Handbook of difficult airway management*, Philadelphia, 2000, Churchill Livingstone, p. 3, Figure 1-2.)*

the mouth. The tongue is anchored to various structures by its extrinsic musculature; of these, the most clinically relevant to the anesthesiologist is the genioglossus, which connects the tongue to the mandible. The jaw-thrust maneuver uses the sliding component of the TMJ to move the mandible and the attached tongue anteriorly, thereby relieving airway obstruction caused by the posterior displacement of the tongue into the oropharynx.[10] Beneath the tongue, the mylohyoid muscles separate the floor of the mouth into the sublingual space superiorly and the submental space inferiorly. Cellulitis (Ludwig angina) or hematoma formation in these spaces can cause elevation and posterior displacement of the tongue and resultant airway obstruction.[11]

PHARYNX

The pharynx is a muscular tube that extends from the base of the skull down to the level of the cricoid cartilage and connects the nasal and oral cavities with the larynx and esophagus. The posterior wall of the pharynx is made up of the buccopharyngeal fascia, which separates the pharynx from the retropharyngeal space. Improper placement of a gastric or tracheal tube can result in laceration of this fascia and the formation of a retropharyngeal dissection.[12,13] The pharyngeal musculature in the awake patient helps maintain airway patency; loss of pharyngeal muscle tone is one of the primary causes of upper airway obstruction during anesthesia.[14,15] A chin lift with mouth closure increases longitudinal tension in the pharyngeal muscles, counteracting the tendency of the pharyngeal airway to collapse.[16]

The pharynx can be divided into the nasopharynx, the oropharynx, and the hypopharynx (Figure 55-3). Along the superior and posterior walls of the nasopharynx are the adenoid tonsils, which can cause chronic nasal obstruction and, when enlarged, can cause difficulty passaging airway devices. The nasopharynx ends at the soft palate; this region is termed the *velopharynx* and is a common site of airway obstruction in both awake and anesthetized patients.[14] The oropharynx begins at the soft palate and inferiorly extends to the level of the epiglottis. The lateral walls contain the palatoglossal folds and the palatopharyngeal folds, also termed the *anterior* and *posterior faucial* (tonsillar) *pillars*, respectively; these

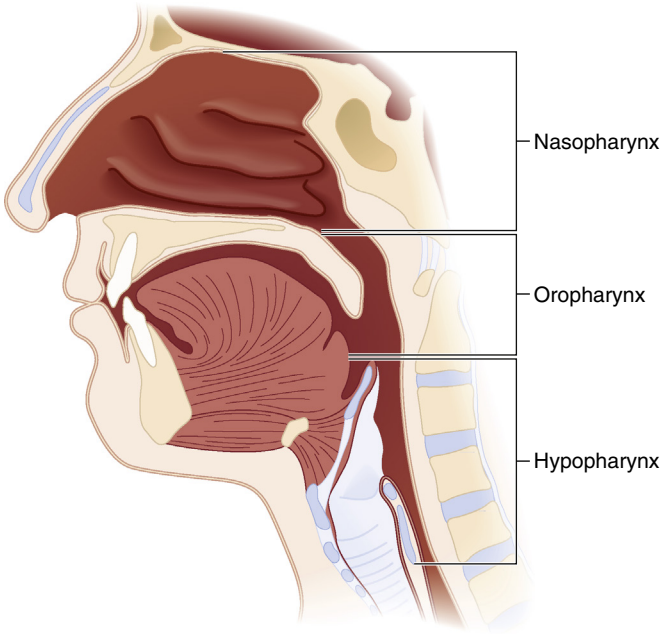


Figure 55-3. Sagittal section through the head and neck showing the subdivisions of the pharynx. *(From Redden RJ: Anatomic considerations in anesthesia. In Hagberg CA, editor:* Handbook of difficult airway management*, Philadelphia, 2000, Churchill Livingstone, p. 7, Figure 1-6.)*

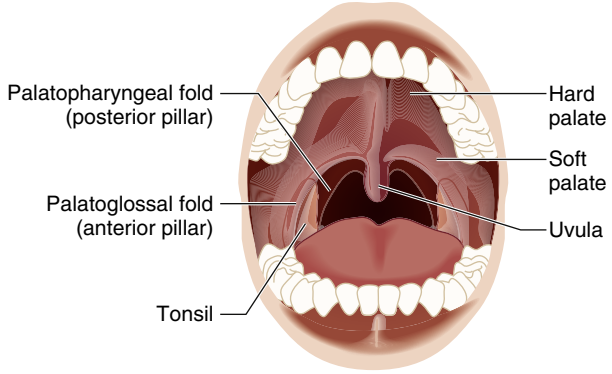


Figure 55-4. Oral cavity and oropharynx. *(From Redden RJ: Anatomic considerations in anesthesia. In Hagberg CA, editor:* Handbook of difficult airway management*, Philadelphia, 2000, Churchill Livingstone, p. 8, Figure 1-7.)*

folds contain the palatine tonsils, which can hypertrophy and cause airway obstruction (Figure 55-4). The base of the tongue lies in the anterior aspect of the oropharynx, connected to the epiglottis by the glossoepiglottic folds, which bound paired spaces known as the *valleculae* (although these are frequently referred to as a single space called the *vallecula*). The hypopharynx begins at the level of the epiglottis and terminates at the level of the cricoid cartilage, where it is continuous with the esophagus. The larynx protrudes into the hypopharynx, creating two piriform recesses on either side (Figure 55-5).

LARYNX

The larynx is a complex structure of cartilage, muscles, and ligaments that serves as the inlet to the trachea and

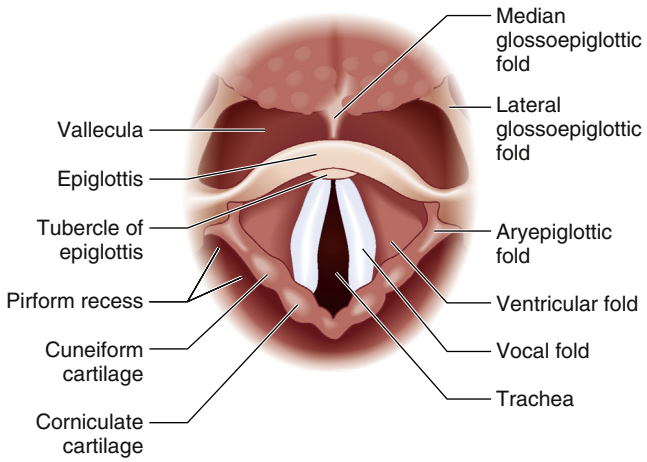


Figure 55-5. Larynx as visualized from the hypopharynx. *(From Redden RJ: Anatomic considerations in anesthesia. In Hagberg CA, editor:* Handbook of difficult airway management*, Philadelphia, 2000, Churchill Livingstone, p. 8, Figure 1-8.)*

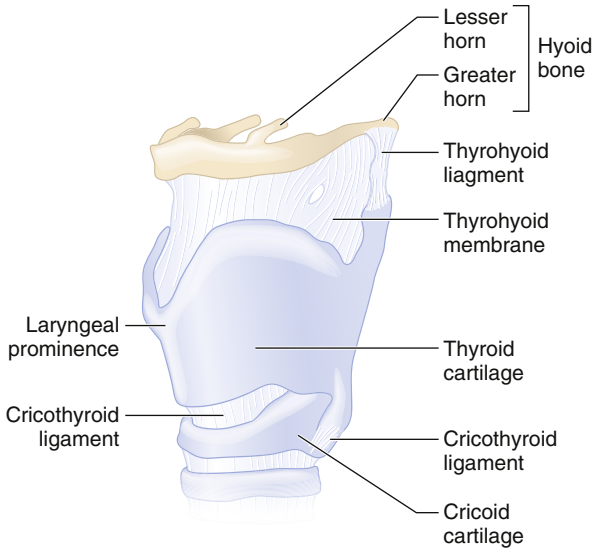


Figure 55-6. Cartilaginous and membranous components of the larynx. *(From Redden RJ: Anatomic considerations in anesthesia. In Hagberg CA, editor:* Handbook of difficult airway management*, Philadelphia, 2000, Churchill Livingstone, p. 10, Figure 1-9.)*

performs various functions, including phonation and airway protection. The cartilaginous framework of the larynx is made up of nine separate cartilages: the thyroid and cricoid cartilages; the paired arytenoid, corniculate, and cuneiform cartilages; and the epiglottis. They are joined by ligaments, membranes, and synovial joints, and are suspended by the hyoid bone via the thyrohyoid ligaments and membrane (Figure 55-6).

The thyroid cartilage is the largest of these cartilages and supports most of the soft tissues of the larynx. The superior thyroid notch and the associated laryngeal prominence *(Adam's apple)* are appreciable from the anterior neck and serve as important landmarks for percutaneous airway techniques and laryngeal nerve blocks. The cricoid cartilage, at the level of the sixth cervical vertebra, is the inferior limit of the larynx and is anteriorly connected to the thyroid cartilage by the cricothyroid membrane (CTM). It is the only complete cartilaginous ring in the airway. The arytenoid cartilages articulate with the posterior cricoid and are the posterior attachments for the vocal cords.

When viewed from the pharynx, as during direct laryngoscopy (DL), the larynx begins at the epiglottis, which is a cartilaginous flap that serves as the anterior border of the laryngeal inlet. It functions to divert food away from the larynx during the act of swallowing, although its role in this regard is not essential to prevent tracheal aspiration.[17] The anterior surface of the epiglottis is attached to the upper border of the hyoid bone by the hyoepiglottic ligament. The laryngeal inlet is bound laterally by the aryepiglottic folds, and posteriorly by the corniculate cartilages and the interarytenoid notch (see Figure 55-5).

The space inferior to the laryngeal inlet down to the inferior border of the cricoid cartilage is the laryngeal cavity. The ventricular folds (also referred to as the *vestibular folds* or *false vocal cords*) are the most superior structure within the laryngeal cavity. Beneath these are the true vocal cords, which attach to the arytenoids posteriorly and the thyroid cartilage anteriorly, where they join together to form the anterior commissure. The space between the vocal cords is termed the *glottis*; the portion of the laryngeal cavity above the glottis is known as the *vestibule*, and the portion inferior to the vocal cords is known as the *subglottis*.

TRACHEA AND BRONCHI

The trachea begins at the level of the cricoid cartilage and extends to the carina at the level of the fifth thoracic vertebra; this length is 10 to 15 cm in the adult. It consists of 16 to 20 C-shaped cartilaginous rings that open posteriorly and are joined by fibroelastic tissue; the trachealis muscle forms the posterior wall of the trachea. At the carina, the trachea bifurcates into the right and left mainstem bronchi. In the adult, the right mainstem bronchus branches off at a more vertical angle than the left mainstem bronchus, resulting in a greater likelihood of foreign bodies and endotracheal tubes (ETTs) entering the right bronchial lumen.[18]

AIRWAY ASSESSMENT

Although the anesthesia provider should always be prepared for potential difficulty with airway management, the ability to predict the difficult airway in advance is obviously desirable. Certain physical findings or details from the patient's history can be prognostic of difficulty with mask ventilation, supraglottic airway placement, laryngoscopy, endotracheal intubation, or the performance of a surgical airway. No single test has been devised to predict a difficult airway accurately 100% of the time; however, a complete evaluation of the airway and knowledge of the difficult airway predictors can alert the anesthesiologist to the potential for difficulty and allow for appropriate planning.

Airway assessment should begin with a directed patient history whenever possible.[4] One of the most

BOX 55-1 ***Components of the Physical Examination of the Airway***

- Visual inspection of the face and neck
- Assessment of mouth opening
- Evaluation of oropharyngeal anatomy and dentition
- Assessment of neck range of motion (ability of the patient to assume the sniffing position)
- Assessment of the submandibular space
- Assessment of the patient's ability to slide the mandible anteriorly (test of mandibular prognathism)

predictive factors for difficult intubation is a history of previous difficulty with intubation.[19] On the other hand, a history of a previously easy airway does not rule out the possibility of difficulty with ventilation or intubation. In either case, the patient interview should specifically address changes in weight, symptomatology, and pathologic conditions since the last induction of an anesthetic (if there was one), and attempts should be made at obtaining prior anesthetic records; they may yield useful information concerning airway management. The presence of pathologic states that increase the risk of a difficult airway should be elicited by performing a medical history. A focused review of systems can alert the anesthesiologist to other potential factors that may predict difficult airway management; for example, a history of snoring has been shown to be predictive of difficult mask ventilation.[20,21]

A physical examination of the airway should be preoperatively performed, when possible, to detect any physical characteristics that may suggest a difficult airway.[4] The specific characteristics that should be evaluated in this examination are listed in Box 55-1.

The visual inspection of the face and neck should focus on any physical characteristics that may indicate the potential for difficulty with airway management. These include obvious facial deformities, neoplasms involving the face or neck, facial burns, a large goiter, a short or thick neck, or a receding mandible. The presence of a beard has been shown to be associated with difficult ventilation attributable to the difficulty in obtaining a mask seal.[20,21] Cervical collars or cervical traction devices can interfere with both mask ventilation and DL. A neck circumference greater than 43 cm (17 inches) is associated with difficulty with tracheal intubation[22] (also see Chapter 71); Brodsky showed that a large neck circumference is, in fact, more predictive of difficulty with endotracheal intubation than a high body mass index (BMI).[23]

Assessment of the mouth opening and inspection of the oropharyngeal anatomy is achieved by instructing the patient to open his or her mouth as wide as possible. An interincisor distance of less than 3 cm (or two fingerbreadths), as measured from the upper to the lower incisors with maximal mouth opening, can suggest the possibility of difficult intubation[24]; some studies have used 4 or 4.5 cm as the cutoff.[25] A thorough inspection of the oropharynx can help identify pathologic characteristics that may result in difficulty with intubation, such as neoplasm, a high arched palate, or macroglossia. In

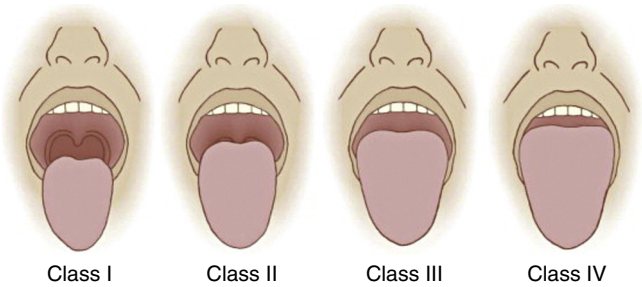


Figure 55-7. Modified Mallampati classification as described by Samsoon and Young. Classes are differentiated on the basis of the structures visualized: class I—soft palate, fauces, uvula, tonsillar pillars; class II—soft palate, fauces, uvula; class III—soft palate, base of the uvula; class IV—soft palate not visible. *(From Mallampati SR: Recognition of the difficult airway. In Benumof JL, editor:* Airway management principles and practice*, St Louis, 1996, Mosby, p. 132.)*

1983, Mallampati and associates described a clinical sign to predict difficult tracheal intubation based on the size of the base of the tongue.[26] A Mallampati classification of I to III is assigned, based on the visibility of the faucial pillars, uvula, and soft palate when the patient is seated upright with the head neutral, the mouth open, the tongue protruded, and no phonation.[27] Higher scores on the Mallampati classification indicate poor visibility of the oropharyngeal structures attributable to a large tongue relative to the size of the oropharyngeal space, and, subsequently, a more difficult laryngoscopy. The modified Mallampati classification described by Samsoon and Young,[28] which adds a fourth classification, is the most commonly used airway assessment test in current anesthesia practice and is defined as follows (Figure 55-7):

- Class I: Faucial pillars, uvula, and soft palate are visualized.
- Class II: Base of the uvula and soft palate are visualized.
- Class III: Soft palate only is visualized.
- Class IV: Hard palate only is visualized.

As a stand-alone test, the modified Mallampati classification is insufficient for accurate prediction of difficult intubation; however, it may have clinical utility in combination with other difficult airway predictors.[29] Some studies support obtaining a Mallampati score with the head in full extension to improve the predictive value of the test.[27,30] A Mallampati *zero* classification has been proposed when the epiglottis can be visualized during examination of the oropharynx; this finding is usually associated with easy laryngoscopy,[31,32] although difficulty with airway management attributable to a large, floppy epiglottis in patients with a Mallampati zero classification can occur.[33,34]

An examination of dentition should be performed when the oropharyngeal anatomy is being evaluated.[24] Relatively long upper incisors can impair DL. Poor dentition and loose teeth increase the risk of dental trauma and present a risk of tooth dislodgment with subsequent aspiration; very loose teeth should be removed before laryngoscopy. Cosmetic dental work, such as veneers, caps, crowns, and bridges, are particularly susceptible to

damage during airway management. Edentulousness is predictive of easy tracheal intubation but potentially difficult mask ventilation.[35]

The ideal positioning for DL is achieved by cervical flexion and atlantooccipital extension and is most commonly referred to as the *sniffing position*[36] (see Preparation and Positioning). Assessment of a patient's ability to assume this position should be included in the airway examination; an inability to extend the neck at the atlantooccipital joint is associated with difficult laryngoscopy.[37] Head and neck mobility can also be quantitatively assessed by measuring the sternomental distance between the sternal notch and the point of the chin with the head in full extension and the mouth closed. Distances less than 12.5 cm are associated with difficult intubation.[38] An assessment of overall neck range of motion can be performed by measuring the angle created by the forehead when the neck is fully flexed and then fully extended; a measurement of less than 80 degrees is predictive of difficult intubation.[39]

During DL, the tongue is displaced into the submandibular space; glottic visualization may be inadequate if this space is diminished because of a small mandible. This scenario is frequently referred to as an *anterior larynx*. A thyromental distance of less than 6.5 cm (three fingerbreadths), as measured from the thyroid notch to the lower border of the mentum, is indicative of reduced mandibular space and may predict difficulty with intubation.[25,38] Compliance of this space should also be assessed; a lack of compliance or the presence of a mass is a nonreassuring finding.[24]

Tests of the ability for mandibular protrusion (prognathism) have predictive value and should be included in the airway assessment. The inability to extend the lower incisors beyond the upper incisors may be indicative of difficult laryngoscopy.[40] A similar evaluation, the upper lip bite test (ULBT) described by Khan and colleagues, has been shown to predict difficult laryngoscopy with higher specificity and less interobserver variability than the Mallampati classification; an inability of the lower incisors to bite the upper lip is associated with more difficult laryngoscopy.[41,42]

Although individual airway tests are limited by low sensitivity and positive predictive value, multivariable assessments have been shown to have higher predictive power. The Mallampati score has been shown to have improved predictive value when combined with thyromental, sternomental, and/or interincisor distances.[38,43] Models that use several risk factors, such as the Wilson risk sum score (weight, head and neck movement, jaw movement, receding mandible, and buck teeth) and the El-Ganzouri risk index (mouth opening, thyromental distance, Mallampati class, neck movement, prognathism, weight, and history of difficult intubation) have been developed in an attempt to improve the predictive value of airway assessment.[39,44] Langeron and associates developed a computer-assisted model that uses complex interactions among several risk factors (BMI, mouth opening, thyromental distance, Mallampati class, and receding mandible) to predict difficult intubation more accurately than other models based on simpler statistical analyses.[45]

PHYSIOLOGIC CONCEPTS FOR AIRWAY MANAGEMENT

PREOXYGENATION

With the induction of anesthesia, hypoxemia can quickly develop as a result of hypoventilation or apnea in combination with decreases in functional residual capacity (FRC) attributable to the supine position, muscle paralysis, and the direct effects of the anesthetic agents themselves. Preoxygenation, the process of replacing nitrogen in the lungs with oxygen, provides an increased length of time before hemoglobin desaturation occurs in a patient with apnea. This lengthened *apnea time* provides an improved margin of safety while the anesthesiologist secures the airway and resumes ventilation. Adequate preoxygenation is essential when mask ventilation after the induction of anesthesia is contraindicated or anticipated to be difficult, when intubation is anticipated to be difficult, and in patients with a smaller FRC (i.e., patients who are obese or pregnant)[46] (also see Chapters 71 and 77). Because difficulty with airway management can unexpectedly occur, routine preoxygenation before induction of general anesthesia is recommended.[47]

Preoxygenation is typically performed via a facemask attached to either the anesthesia machine or a Mapleson circuit. To ensure adequate preoxygenation, 100% oxygen must be provided at a flow rate high enough to prevent rebreathing (10 to 12 L/min), and no leaks around the facemask must be present. An end-tidal concentration of oxygen greater than 90% is considered to maximize apnea time. Two primary methods are used to accomplish preoxygenation. The first method uses tidal volume ventilation through the facemask for 3 minutes, which allows the exchange of 95% of the gas in the lungs.[46] The second method uses vital capacity breaths to achieve adequate preoxygenation more rapidly. Four breaths over 30 seconds is not as effective as the tidal volume method but may be acceptable in certain clinical situations; eight breaths over 60 seconds has been shown to be more effective.[46] Head-up positioning has been shown to improve the quality of preoxygenation in both obese[48] and nonobese patients.[49] The use of noninvasive positive-pressure ventilation (PPV) for preoxygenation also prolongs apnea time.[50,51]

PULMONARY ASPIRATION OF GASTRIC CONTENTS

In 1946, Mendelson was the first to describe aspiration pneumonitis attributable to the pulmonary aspiration of acidic gastric secretions in pregnant women undergoing anesthesia.[52] This potentially fatal complication, occasionally referred to as Mendelson syndrome, has since been the intense focus of preventive efforts among the anesthesia community. Prevention of aspiration of gastric contents is primarily accomplished by adherence to established preoperative fasting guidelines, premedication with drugs that may decrease the risk of aspiration pneumonitis, and specialized induction techniques, which are discussed later in this chapter (also see Chapter 77).

Traditionally, patients who were scheduled for elective procedures requiring sedation, regional anesthesia, or general anesthesia were instructed to remain NPO (Latin for *nulla per os* or *nothing by mouth*) after midnight to ensure an empty stomach to decrease the risk of regurgitation. Based on evidence that allowing ingestion of clear liquids 2 to 4 hours before surgery resulted in lower gastric volumes and higher gastric pH, the ASA published *Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration* in 1999 that liberalized the traditional NPO policy and allowed clear liquids up to 2 hours before beginning elective procedures requiring anesthesia. The guidelines, updated in 2011, recommend 4 hours of fasting from breast milk and 6 hours of fasting from solid foods, infant formula, and nonhuman milk. Fried or fatty foods may require longer fasting times (e.g., 8 hours or more).[53] Although the ASA guidelines do not specifically address chewing gum, hard candies, or smoking, guidelines published by the European Society of Anaesthesiology on the topic do not recommend delaying the start of anesthesia if a patient has consumed any of these immediately before the induction of anesthesia.[54]

The routine use of drugs as prophylaxis against aspiration pneumonitis is not recommended by the ASA guidelines[53] but may be beneficial in patients with specific risk factors for aspiration, such as a full stomach, symptomatic gastroesophageal reflux disease (GERD), hiatal hernia, presence of a nasogastric tube, morbid obesity, diabetic gastroparesis, or pregnancy. The goal of aspiration prophylaxis is twofold: to decrease gastric volume and to increase gastric fluid pH. Commonly used agents include nonparticulate antacids (e.g., Bicitra), promotility drugs (e.g., metoclopramide), and H_2-receptor antagonists. These drugs may be used alone or in combination.[55]

AIRWAY REFLEXES AND THE PHYSIOLOGIC RESPONSE TO INTUBATION OF THE TRACHEA

One of the most important teleologic functions of the larynx is that of airway protection, which is primarily provided by the glottic closure reflex. This reflex is triggered by sensory receptors in the glottic and subglottic mucosa and results in strong adduction of the vocal cords.[56] An exaggerated, maladaptive manifestation of this reflex, referred to as *laryngospasm*, is a potential complication of airway management. Laryngospasm is usually provoked by glossopharyngeal or vagal stimulation attributable to airway instrumentation or vocal cord irritation (e.g., from blood or vomitus) in the setting of a light plane of anesthesia (stage II of the Guedel classification), but it can also be precipitated by other noxious stimuli and can persist well after the removal of the stimulus. Treatment of laryngospasm includes removal of airway irritants, deepening of the anesthetic, and the administration of a rapid-onset neuromuscular blocking drug (NMBD), such as succinylcholine.[57] Continuous positive airway pressure with 100% oxygen is commonly cited as a therapeutic maneuver, although the pressure may push the aryepiglottic folds closer together and may actually promote laryngospasm by acting as a mechanical stimulus.[58,59] Bilateral pressure at the *laryngospasm notch* between the condyle of the mandible and the mastoid process can be effective at treating laryngospasm by causing an intense, painful stimulus, which may function to terminate laryngospasm by arousing a semiconscious patient or by activating autonomic pathways.[57]

The tracheobronchial tree also possesses reflexes to protect the lungs from noxious substances. Irritation of the lower airway by a foreign substance activates a vagal reflex–mediated constriction of bronchial smooth muscle, resulting in bronchospasm. Untreated bronchospasm can result in an inability to ventilate because of an extremely elevated airway resistance. Treatment includes a deepening of anesthetic with propofol or a volatile agent and the administration of inhaled β_2-agonist or anticholinergic medications. Administration of intravenous (IV) lidocaine has been studied, but the evidence does not support its use for treatment of bronchospasm.[60]

Endotracheal intubation, as well as laryngoscopy and other airway instrumentation, provides an intense noxious stimulus via vagal and glossopharyngeal afferents that results in a reflex autonomic activation, which is usually manifested as hypertension and tachycardia in adults and adolescents; in infants and small children, autonomic activation may result in bradycardia. Hypertension and tachycardia are usually of short duration; however, they may have consequences in patients with significant cardiac disease. Central nervous system activation as a result of airway management results in increases in electroencephalographic (EEG) activity, cerebral metabolic rate, and cerebral blood flow, which may result in an increase in intracranial pressure in patients with decreased intracranial compliance.[60]

ANESTHESIA FOR AIRWAY MANAGEMENT

To facilitate airway management, some form of anesthesia is usually required to provide comfort for the patient, to blunt airway reflexes, and to blunt the hemodynamic response to airway instrumentation. Most commonly, airway management is performed after induction of general anesthesia. Alternatively, an *awake* technique, which means establishing an airway (including endotracheal intubation) by using local anesthesia of the airway and/or sedation, can be used to meet these goals when clinically indicated. In emergency scenarios where the patient is obtunded or comatose, such as in the event of acute respiratory or cardiac arrest, anesthetic drugs may not be required.

AIRWAY MANAGEMENT AFTER THE INDUCTION OF GENERAL ANESTHESIA

Airway management is usually performed after the induction of general anesthesia if the anesthesiologist determines that it is safe to do so. Several pharmacologic techniques are used for the induction of anesthesia, each with its own implications for airway management. The decision of which induction technique to use should be made with careful consideration of the specific clinical circumstances at hand.

Standard Intravenous Induction With Neuromuscular Blockade

The most common technique for induction of general anesthesia is the standard IV induction, which entails the administration of a rapid-acting IV anesthetic, followed by a NMBD. Muscle relaxation achieved by the administration of NMBDs improves intubating conditions by facilitating laryngoscopy, preventing both reflex laryngeal closure and coughing after intubation.[10,61]

Propofol is the most frequently used IV anesthetic drug; other options include etomidate, ketamine, thiopental, and midazolam (also see Chapter 30). The choice of drug depends on a variety of factors including the patient's hemodynamic status, comorbidities, and allergies, as well as drug pharmacokinetics, side effects, physician preference, and availability.[62] Whether the choice of an anesthetic drug has any effect on the quality of intubating conditions when NMBDs are also administered is not well-established. Studies comparing propofol, etomidate, and thiopental in combination with NMBDs showed no difference in intubating conditions between the different anesthetics.[63,64] On the other hand, one study, during which patients received cisatracurium, showed that larger doses of propofol were associated with improved intubating conditions, as compared with smaller doses.[65]

For many years, succinylcholine was the most frequently used NMBD for routine IV induction[62]; recently, however, nondepolarizing NMBDs have gained greater popularity attributable to the risk of adverse effects from succinylcholine administration, including bradycardia, myalgia, hyperkalemia, increased intracranial pressure, and increased intragastric pressure[66] (also see Chapter 34). Succinylcholine, the only depolarizing NMBD in clinical use, has the benefit of a rapid onset, combined with a short duration of action, and it is currently used most often when those properties are desired. Most notably, succinylcholine is still commonly used in the setting of a suspected difficult airway; its short duration of action theoretically allows for the resumption of spontaneous ventilation before severe hypoxia develops in a preoxygenated patient, although evidence suggests that this may not predictably occur *in vivo*.[67]

Nondepolarizing NMBDs are the more frequently used relaxants for routine IV induction of anesthesia.[66] The most commonly used nondepolarizing NMBDs in current practice—rocuronium, vecuronium, and cisatracurium—are notable for having a favorable safety profile with relatively few side effects. The primary limitation of these drugs is a significantly longer duration of action; once administered, a functional airway must be established within minutes to avoid life-threatening hypoxia. Sugammadex is a selective relaxant-binding agent for rocuronium that has the ability to reverse profound neuromuscular blockade rapidly in a time comparable with spontaneous recovery from succinylcholine.[68] The introduction of sugammadex, which is currently unavailable in the United States, may result in a further reduction in the use of succinylcholine for routine induction of general anesthesia (also see Chapter 35).

Traditional teaching has advocated withholding NMBDs until the ability to mask ventilate has been established. If ventilation via a mask cannot be achieved, a patient who has been breathing oxygen can then resume spontaneous ventilation or be awakened before the onset of hypoxia.[69] This practice has been increasingly questioned in the literature due, in part, to a number of studies demonstrating that ventilation via a mask is *not* rendered more difficult by muscle relaxation[70,71]; rather, mask ventilation is, in fact, facilitated by muscle relaxation.[72] One issue with the traditional paradigm is that the theoretic advantage of the practice—the ability to awaken the patient if ventilation via a mask fails—is rarely used.[73] The desire to preserve that ability may, in fact, result in giving an inadequate dose of anesthetic during induction, resulting in a difficult mask ventilation situation when one would not have otherwise occurred.[73] Delaying the administration of NMBDs can result in the onset of hypoxia before spontaneous recovery (with succinylcholine) or reversal (with rocuronium and sugammadex) is possible.

Proponents of traditional teaching point to the fact that the effect of muscle relaxation on the ability to ventilate via a mask has only been studied in patients with normal airways. In patients with predicted or known difficult airways, checking the ability to mask ventilate allows for the formulation of the best airway management plan. In the authors' opinions, in patients with normal airways in whom difficulty with mask ventilation is often a result of glottic closure attributable to opioid-mediated rigidity or airway irritation, withholding an NMBD is not likely to be of benefit. In patients with a potentially difficult airway, the ability to ventilate via a mask should be confirmed before administering long-acting NMBDs when the ability to reverse quickly with sugammadex is not an option.

Rapid-Sequence Induction of Anesthesia and Intubation of the Trachea

Rapid-sequence induction of anesthesia and intubation (RSII) of the trachea (frequently referred to as simply *rapid sequence induction* [RSI] in the anesthesia literature) is a specialized method of IV induction commonly used when a frequent risk for gastric regurgitation and pulmonary aspiration of gastric contents is present. After adequate preoxygenation and while cricoid pressure is applied, an induction dose of IV anesthetic is rapidly followed by 1 to 1.5 mg/kg of IV succinylcholine, and the trachea is intubated without attempts at PPV, all while cricoid pressure is applied. The goal is to achieve optimal intubating conditions rapidly to minimize the length of time between the loss of consciousness (LOC) and securing of the airway with a cuffed ETT. Cricoid pressure, eponymously referred to as the Sellick maneuver after the physician who first described it, involves the application of pressure at the cricoid ring to occlude the upper esophagus, thereby preventing the regurgitation of gastric contents into the pharynx.[74] The recommended force to be applied is 10 Newtons (N) while the patient is awake, increased to 30 N after LOC. These values are based on esophageal manometry on patients undergoing induction of anesthesia and cadaver studies of safe amounts of pressure.[75] RSII is widely practiced and approaches a standard of care in patients with a full stomach (i.e., when NPO guidelines have not been observed) and in the setting of bowel obstruction.[76,77] RSII has historically been

recommended for patients who are pregnant, starting in the second trimester,[78] but this dogma has recently been called into question[79,80] (also see Chapter 77). Other clinical situations for which RSII may be considered due to a higher than normal risk for aspiration of gastric contents, include poorly controlled GERD, presence of a nasogastric tube, morbid obesity, and diabetic gastroparesis. RSII is also a useful induction technique when ventilation via a mask is predicted to be difficult, but intubation is not, such as with an edentulous, bearded patient with an otherwise reassuring airway examination.

Some common variations to RSII have developed from the technique first described in 1970.[81] When succinylcholine is contraindicated or its side effects are undesired, RSII can be accomplished using nondepolarizing NMBDs (rocuronium 1.0 to 1.2 mg/kg or vecuronium 0.3 mg/kg); these doses provide adequate intubating conditions in less than 90 seconds.[82,83] The primary disadvantage with these drugs is the prolonged duration of neuromuscular blockade; however, the introduction of sugammadex may result in their increased use (also see Chapters 34 and 35). Although traditional RSII calls for induction with a fixed dose of thiopental, the use of other anesthetics such as propofol, etomidate, or ketamine is common. Some advocate for the titration of the chosen anesthetic agent to LOC rather than the delivery of a fixed, predetermined dose.[77]

The application of cricoid pressure is the most controversial aspect of RSII.[77] Opponents point to studies showing that cricoid pressure results in a decrease in lower esophageal sphincter tone, potentially increasing the risk for regurgitation,[84] and to magnetic resonance imaging (MRI) studies showing that cricoid pressure does not, in fact, result in compression of the esophagus, but rather a lateral displacement.[85] Cricoid pressure also worsens laryngeal visualization during DL, potentially lengthening the time to intubation and increasing the risk of pulmonary aspiration, and can result in occlusion of the subglottic airway, resulting in difficulty with intubation of the trachea or ventilation via a mask.[86] On the other hand, advocates argue that properly applied cricoid pressure is effective in reducing the risk of aspiration and that reports of problems are due to incorrect application. The authors of a recent MRI study of cricoid pressure argue that the position of the esophagus is irrelevant because the effectiveness of cricoid pressure is due to occlusion of the hypopharynx.[87] In general, because of the relatively infrequent risk of application of cricoid pressure, its use is encouraged for RSII unless glottic visualization proves difficult, in which case it can be easily released.

The term *modified RSII* is frequently used, but no standardized definition exists. A survey of anesthesia residents and attending anesthesiologists in the United States showed that the term was most commonly used to refer to the use of mask ventilation in conjunction with cricoid pressure.[88] Indications for this technique include patients at risk for rapid development of hypoxemia (e.g., patients who are obese, pregnant, or critically ill; pediatric patients) in emergent situations during which preoxygenation cannot be satisfactorily completed or when a longer time to acceptable intubating conditions is required because of the use of standard doses of nondepolarizing NMBDs. Although the effect of PPV with cricoid pressure applied in terms of gastric insufflation of air is not definitively known, gentle PPV (inspiratory pressure <20 cm water [H_2O]) in conjunction with cricoid pressure may be acceptable in these clinical scenarios.[89]

Inhalational Induction of Anesthesia

Another option for the induction of general anesthesia is an inhaled induction with volatile anesthetic. This technique is commonly used in pediatric anesthesia to provide a painless, needle-free experience for the child (also see Chapter 93). In adults, an inhaled induction of anesthesia is used when IV access is not available or when the specific advantages of the technique are desirable. Advantages of an inhaled induction of anesthesia are the maintenance of spontaneous ventilation and the potential for gradual changes in the depth of anesthesia and associated respiratory and cardiovascular effects.[10] Inhaled induction of anesthesia has also been used for RSII, with a rapid-onset NMBD administered at LOC[90] (also see Chapter 34).

Sevoflurane is currently the most commonly used volatile anesthetic for inhalational induction because of its lack of pungency and low blood:gas solubility (see Chapter 21), allowing for a smooth induction of anesthesia that can provide suitable conditions for airway management with or without adjuvant drugs such as NMBDs or opioids.[91] The two principal techniques for sevoflurane induction of anesthesia are a *tidal volume induction*, in which patients are instructed to breathe normally through the facemask, and a *vital capacity induction*, in which patients are instructed to exhale to residual volume and then take a vital capacity breath from the facemask. High delivered concentrations of sevoflurane (8%) are used for vital capacity induction, whereas tidal volume inductions may start with lower sevoflurane concentrations before the concentration is increased. Nitrous oxide (N_2O) can be used with either method to speed induction via the second-gas effect (also see Chapter 21).[92] Both methods are effective and can be used for either LMA placement or endotracheal intubation.[91] Deep levels of anesthesia are required to achieve satisfactory intubating conditions when using sevoflurane as a sole induction agent, increasing the risk of adverse effects, such as hypotension. The administration of propofol,[93] fast-acting opioids,[94,95] NMBDs,[96] and ketamine[97] have all been shown to improve intubating conditions and allow for lower end-tidal concentrations of sevoflurane.

Halothane, which is still commonly used in developing countries, can also be used for an inhaled induction of anesthesia.[98] One main disadvantage of halothane is its high blood:gas coefficient, which leads to relatively long induction times. It also can produce cardiac dysrhythmias, myocardial depression, and halothane-induced hepatitis. Because of the inability to achieve deep levels of anesthesia with halothane as a result of its side effects, the use of NMBDs, opioids, or both, is often required.[91] The use of desflurane for inhaled induction of anesthesia is limited by its tendency to cause airway irritation, although reports of its use for induction in combination with opioids has been reported.[99,100]

Intravenous Induction Without Neuromuscular Blocking Drugs

IV induction of general anesthesia without the use of NMBDs is commonly used for LMA placement but can be used to achieve satisfactory intubating conditions as well. This technique is useful when the use of succinylcholine is contraindicated and the prolonged recovery time from nondepolarizing NMBDs is undesirable. Of the commonly available IV anesthetics, propofol is the best suited for induction without muscle relaxation because of its unique ability to suppress airway reflexes and to produce apnea.[101,102] Larger doses are required, however, when propofol is used as a sole anesthetic, increasing the risk of significant hypotension. Improvement of intubating conditions and smaller doses of propofol are possible when rapid-onset opioids (e.g., alfentanil, remifentanil) or IV magnesium are administered.[103,104] Remifentanil is more effective than comparable doses of alfentanil[103]; in combination with propofol 2 mg/kg, remifentanil 4 to 5 μg/kg can reliably provide good-to-excellent intubating conditions.[105] When combined with cricoid pressure and an avoidance of mask ventilation, this induction technique can be used for RSII.[106]

Disadvantages of this technique include a potentially more frequent incidence of difficult intubation[107] and an increased risk for laryngeal morbidity.[61,108] This technique also introduces the risk of opioid-induced muscle rigidity resulting in difficulty with mask ventilation. Although this risk is commonly attributed to chest wall rigidity, studies in intubated patients and patients with tracheostomies have shown that decreases in pulmonary compliance due to chest wall rigidity are not sufficient to explain an inability to mask ventilate after a large dose of an opioid.[109,110] Examination of the vocal cords during induction with opioids has shown that vocal cord closure is the primary cause of difficult ventilation after opioid-induced anesthesia.[111,112] Treatment with small doses of NMBD or topical lidocaine (laryngotracheal anesthesia) can be effective in relaxing the vocal cords to allow for mask ventilation and/or intubation.[111,113]

AIRWAY MANAGEMENT IN AN AWAKE (NONANESTHETIZED) PATIENT

In the ASA "Difficult Airway Algorithm," a consideration of whether the airway should be secured before or after induction of general anesthesia is one of the basic management choices that should be considered when an airway management plan is being devised.[24] The benefits of awake airway management include the preservation of pharyngeal muscle tone and patency of the upper airway, the maintenance of spontaneous ventilation, an ability to obtain a quick neurologic examination, and a safeguard against aspiration attributable to the preservation of protective airway reflexes.[114] In general, when difficult mask ventilation and difficult intubation are expected, the safest approach to airway management is to secure the airway while the patient remains awake.[24] Other indications for awake airway management include the risk of severe aspiration of gastric contents, facial or airway trauma, severe hemodynamic instability, and cervical spine pathologic instability.[115]

Because of the nature of these indications, endotracheal intubation is most often chosen as the goal of awake airway management; however, awake placement of an LMA for diagnostic bronchoscopy has been described. The most useful technique for awake intubation is the flexible scope intubation (FSI),[114] although other techniques have been successfully used, including video laryngoscopes (VLs),[116] optical stylets,[117] lighted nonoptical stylets,[118] intubating LMAs,[119] and retrograde intubation (RI).[120]

Topicalization of the airway with local anesthetics should, in most cases, be the primary anesthetic for awake airway management.[114] Lidocaine is the most commonly used local anesthetic for awake airway management because of its rapid onset, high therapeutic index, and availability in a wide variety of preparations and concentrations.[121,122] Benzocaine and Cetacaine (a topical application spray containing benzocaine, tetracaine, and butamben; Cetylite Industries, Pennsauken, NJ) provide excellent topical anesthesia of the airway, but their use is limited by the risk of methemoglobinemia, which can occur with as little as 1 to 2 seconds of spraying.[123] Topical cocaine is primarily used for anesthesia and vasoconstriction of the nasal mucosa during awake nasotracheal intubation.[124] A mixture of lidocaine 3% and phenylephrine 0.25%, which can be made by combining lidocaine 4% and phenylephrine 1% in a 3:1 ratio, has similar anesthetic and vasoconstrictive properties as topical cocaine and can be used as a substitute.[125]

Topicalization should primarily be focused on the base of the tongue (pressure receptors here act as the afferent component of the gag reflex), the oropharynx, the hypopharynx, and the laryngeal structures; anesthesia of the oral cavity is unnecessary. If a nasotracheal intubation is planned, then the nasal cavity should also be topicalized. Before airway topicalization, an anticholinergic should be administered to aid in the drying of secretions, which helps improve both the effectiveness of the topical local anesthetics and visualization during laryngoscopy. Glycopyrrolate is usually preferred because it has less vagolytic effects than atropine at doses that inhibit secretions and does not cross the blood-brain barrier. It should be administered as early as possible to maximize its effectiveness.

Direct application of topical cocaine, lidocaine 4% with epinephrine, or lidocaine 3%/phenylephrine 0.25% solution via cotton swabs or cotton pledgets is effective for anesthesia of the nasal mucosa. Oropharyngeal anesthesia can be achieved by the direct application of local anesthetic or by the use of an atomizer or nebulizer. Topicalization of the larynx can be achieved by aspiration of a local anesthetic or by the *spray-as-you-go* (SAYGO) method, which involves intermittently injecting local anesthetics through the suction port or working channel of a flexible intubation scope (FIS) or optical stylet, as it is advanced toward the trachea.

Topicalization of the airway mucosa using one or more of these methods is often sufficient. If supplemental anesthesia is required, then a variety of nerve blocks may be used. Three of the most useful are the glossopharyngeal nerve block, superior laryngeal nerve block, and translaryngeal block.

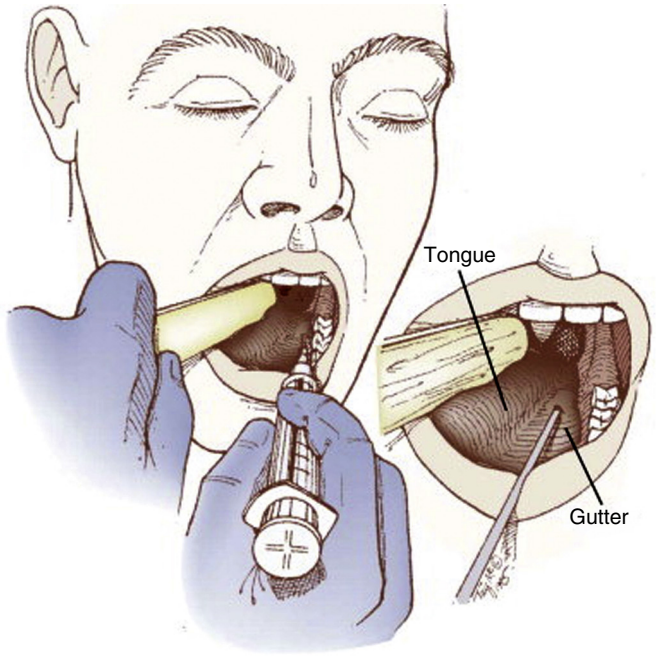


Figure 55-8. Left glossopharyngeal nerve block. *(Reprinted from Artime CA, Sanchez A: Preparation of the patient for awake intubation. In Hagberg CA, editor:* Benumof and Hagberg's airway management*, ed 3, Philadelphia, 2013, Saunders, p. 258. From* Difficult airway teaching aids*, Irvine, University of California, Department of Anesthesia.)*

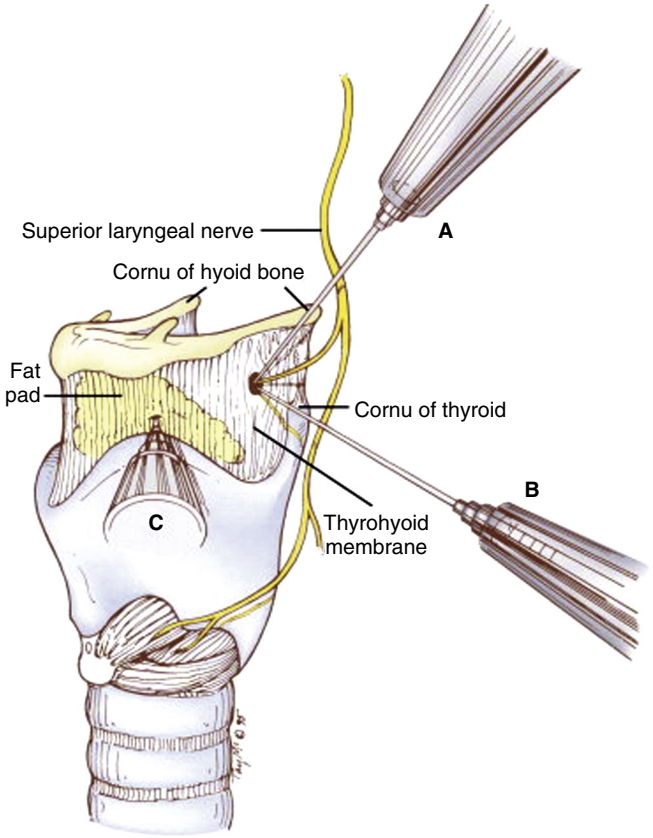


Figure 55-9. Superior laryngeal nerve block, external approach using as a landmark the greater cornu of the hyoid bone (A), the superior cornu of the thyroid cartilage (B), or the thyroid notch (C). *(Reprinted from Artime CA, Sanchez A: Preparation of the patient for awake intubation. In Hagberg CA, editor:* Benumof and Hagberg's airway management*, ed 3, Philadelphia, 2013, Saunders, p. 259. From* Difficult airway teaching aids*, Irvine, University of California, Department of Anesthesia.)*

The glossopharyngeal nerve supplies sensory innervation to the posterior third of the tongue, vallecula, the anterior surface of the epiglottis, and the posterior and lateral walls of the pharynx and is the afferent pathway of the gag reflex. To block this nerve, the tongue is displaced medially, forming a gutter (glossogingival groove). A 25-gauge spinal needle is inserted at the base of the anterior tonsillar pillar, just lateral to the base of the tongue, to a depth of 0.5 cm (Figure 55-8). After negative aspiration for blood or air, 2 mL of 2% lidocaine is injected. The process is then repeated on the contralateral side.[114]

The superior laryngeal nerve, a branch of the vagus nerve, provides sensory input from the lower pharynx and the upper part of the larynx, including the glottic surface of the epiglottis and the aryepiglottic folds. A block of this nerve may be achieved using one of three landmarks (Figure 55-9). Using either the superior cornu of the hyoid or the superior cornu of the thyroid cartilage, a 25-gauge spinal needle is walked off the cornu anteriorly toward the thyrohyoid ligament. Resistance is felt as the needle is advanced through the ligament, usually at a depth of 1 to 2 cm. After negative aspiration for blood and air, 1.5 to 2 mL of 2% lidocaine is injected and then repeated on the opposite side.[121] The third landmark for the superior laryngeal nerve block is particularly useful in patients who are obese, in whom palpation of the hyoid or the superior cornu of the thyroid cartilage may be difficult or uncomfortable for the patient. In this approach, the needle is inserted 2 cm lateral to the superior notch of the thyroid cartilage and directed in a posterior and cephalad direction to 1 to 1.5 cm depth, where 2 mL of 2% lidocaine is infiltrated and, again, repeated on the contralateral side.[126]

Translaryngeal (or transtracheal) block provides anesthesia of the trachea and vocal cords. This block may be particularly useful in situations where a neurologic examination is needed after intubation; it makes the presence of the ETT in the trachea more comfortable. The CTM is identified, and a 20- to 22-gauge needle attached to 5-mL syringe is directly advanced posteriorly and slightly caudally until air is aspirated, at which point 4 mL of either 2% or 4% lidocaine is quickly injected. This causes the patient to cough, anesthetizing the vocal cords and the trachea. To minimize the risk of trauma, a catheter may first be placed over the needle and the local anesthetic then injected through the catheter (Figure 55-10).[121]

These techniques may be used in various different combinations as long as the maximum dose of local anesthetic is not exceeded. The maximum dose of lidocaine for application to the airway is not well-established; different sources suggest total doses in the range of 4 to 9 mg/kg.[121,127,128] Monitoring for signs and symptoms of lidocaine toxicity, including tinnitus, perioral tingling, metallic taste, lightheadedness, dizziness, and sedation is important. Severe lidocaine overdose can cause hypertension, tachycardia, seizures, and cardiovascular collapse.[129]

Depending on the clinical circumstance, IV sedation may facilitate airway management in an awake patient

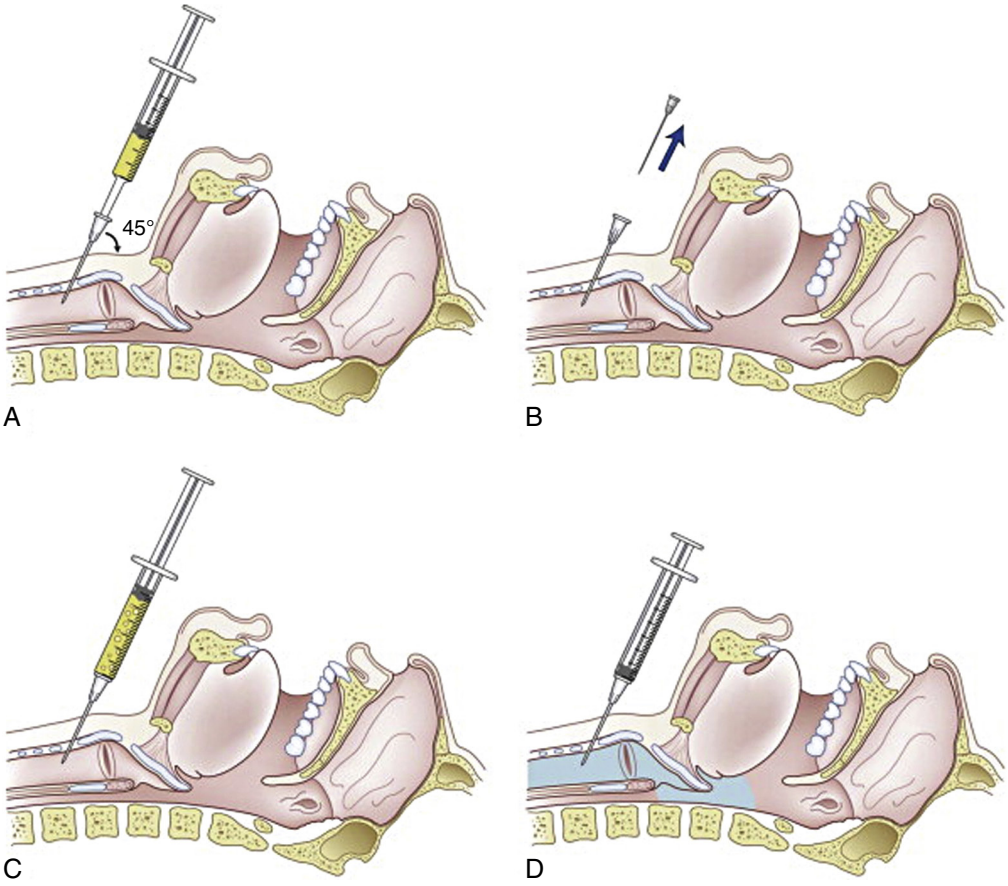


Figure 55-10. Translaryngeal anesthesia, angiocatheter technique (midsagittal view of the head and neck). **A,** The angiocatheter is inserted at the cricothyroid membrane, aimed caudally. An aspiration test is performed to verify the position of the tip of the needle in the tracheal lumen. **B,** The needle is removed from the angiocatheter. **C,** The syringe containing local anesthetic is attached, and the aspiration test is repeated. **D,** Local anesthetic is injected, resulting in coughing and nebulization of the local anesthetic *(shaded blue area). (Reprinted from Artime CA, Sanchez A: Preparation of the patient for awake intubation. In Hagberg CA, editor:* Benumof and Hagberg's airway management*, ed 3, Philadelphia, 2013, Saunders, p. 259. From* Difficult airway teaching aids*, Irvine, University of California, Department of Anesthesia.)*

by providing anxiolysis, amnesia, and analgesia. Benzodiazepines, opioids, IV hypnotics, α_2 agonists, and neuroleptics can be used alone or in combination. A summary of common medications used for sedation can be found in Table 55-1. These drugs should be carefully titrated to effect; oversedation can render a patient uncooperative and make awake intubation more difficult. Spontaneous ventilation should always be maintained. Care should be taken in situations with critical airway obstruction, because awake muscle tone is sometimes necessary in these patients to maintain airway patency. Avoiding oversedation is also important in the patient at high risk for aspiration of gastric contents, because an awake patient can protect his or her own airway if regurgitation should occur.[130]

VENTILATION VIA A MASK

Mask ventilation is a straightforward, noninvasive technique for airway management that can be used as a primary mode of ventilation for an anesthetic of short duration or as a bridge to establishing of a more definitive airway. Administration of oxygen via a facemask is common for "preoxygenation", and inhaled induction of anesthesia and as a means to provide oxygen and anesthetic gases to both a spontaneous ventilating patient and an anesthetized patient with apnea via PPV. Mask ventilation is not only used to ventilate and oxygenate before conditions for tracheal intubation have been achieved, but it is also a valuable rescue technique when tracheal intubation proves difficult. For this reason, mask ventilation is an important part of the ASA "Difficult Airway Algorithm" and an essential skill for the anesthesia practitioner.[24]

Mask ventilation is relatively contraindicated when the risk for regurgitation is increased; no protection from pulmonary aspiration of gastric contents exists. Mask ventilation should also be performed with caution in patients with severe facial trauma and in patients in whom head and neck manipulation must be avoided (e.g., those with an unstable cervical spine fracture).

Anesthesia facemasks are designed to form a seal around the patient's nose and mouth, allowing for PPV and the administration of anesthetic gases; they should not be confused with oxygen facemasks, which are designed only to administer supplemental oxygen. Early anesthesia facemasks were reusable and made of black rubber. These have been almost entirely replaced in clinical use

TABLE 55-1 **SEDATIVE DRUGS FOR AWAKE AIRWAY MANAGEMENT**

Drug	Class	Sedative Dose	Notes
Midazolam	Benzodiazepine	1-2 mg IV, repeated prn (0.025-0.1 mg/kg)	Frequently used in combination with fentanyl.
Fentanyl	Opioid	25-200 μg IV (0.5-2 μg/kg)	Usually used in combination with other agents (e.g., midazolam, propofol).
Alfentanil	Opioid	500-1500 μg IV (10-30 μg/kg)	Has faster onset, shorter duration than fentanyl.
Remifentanil	Opioid	Bolus 0.5 μg/kg IV, followed by an infusion of 0.1 μg/kg/min	Infusion can be subsequently titrated by 0.025-0.05 μg/kg/min in 5-minute intervals to achieve adequate sedation.
Propofol	Hypnotic	0.25 mg/kg IV in intermittent boluses or Continuous IV infusion of 25-75 μg/kg/min, titrated to effect	Can also be used in combination with remifentanil (decrease dose of both drugs).
Ketamine	Hypnotic	0.2-0.8 mg/kg IV	Pretreat with antisialagogue. Consider administration of midazolam to attenuate undesirable psychologic effects.
Dexmedetomidine	α_2 Agonist	Bolus 1 μg/kg IV over 10 minutes, followed by an infusion of 0.2-0.7 μg/kg/hr	Reduce dose in older adults and in patients with depressed cardiac function.

IV, Intravenous; *prn,* as needed, *pro re nata* (Latin).

by disposable, clear plastic masks, which are less frightening for patients and have the added benefit of allowing for better visualization of cyanosis and the need for oral suctioning. Facemasks are available in various styles and sizes but share a basic design: main body, seal, and connector. The seal is the portion of the mask that comes in contact with the face, and in clear plastic masks is comprised of a plastic, air-filled, high-volume, low-pressure cushion that conforms to the facial anatomy while minimizing the chance for pressure ischemia; some models have a valve on the cushion to allow changing the volume of the air within. The connector is a standard 22-mm female adapter that allows a connection to a standard anesthesia circuit or a bag-valve device; pediatric masks usually have a 15-mm male adapter that allows the same connections.

The technique for mask ventilation is dependent on two key elements: (1) maintenance of a seal between the facemask and the patient's face and (2) an unobstructed upper airway.[10] The mask is usually held with the left hand, with the thumb and index finger forming a C around the collar of the connector, the third and fourth digits on the ramus of the mandible, and the fifth digit on the angle of the mandible (Figure 55-11). The thumb and index finger are used to produce downward pressure to ensure a tight mask seal, while the remaining digits provide upward displacement of the mandible (jaw thrust) to aid with airway patency. The right hand is free to provide manual ventilation. Ensuring that pressure is placed on the bony ridge of the mandible and not the soft tissue is important—compression of the submandibular space can cause obstruction of the airway and difficulty with mask ventilation. Many facemasks have hooks around the collar for use with mask straps that can facilitate formation of a seal.

The one-handed technique is occasionally ineffective, especially in patients who are obese or edentulous, attributable to the failure to maintain a seal and/or a patent upper airway. In these situations, a two-handed technique

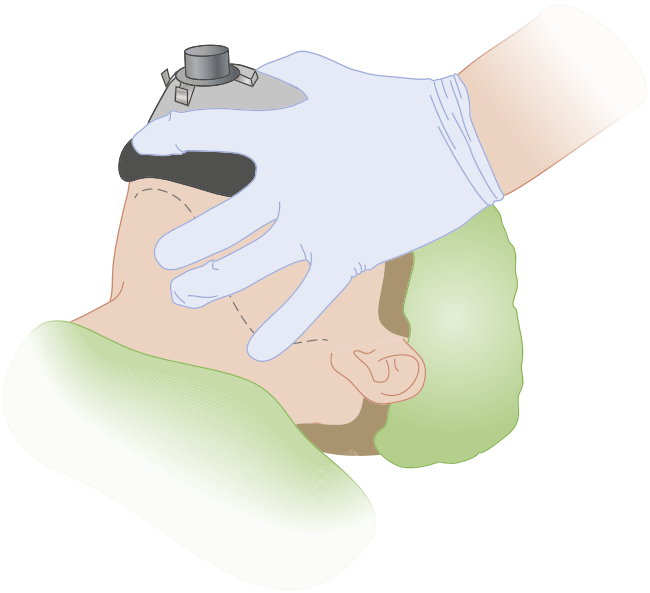


Figure 55-11. Standard one-handed facemask ventilation technique. The position of the fifth digit is at the angle of the jaw. *(From Matioc AA: The adult ergonomic face mask: historical and theoretical perspectives,* J Clin Anesth *21:300-304, 2009.)*

can be more successful. Two-handed techniques depend on either an assistant or the use of pressure-control ventilation (PCV) with the anesthesia machine to provide PPV. The use of PCV for mask ventilation results in lower peak airway pressures and reduced inspiratory flow rates when compared with manual ventilation, providing an additional measure of safety against gastric insufflation.[131] In one approach to the two-handed technique, the left hand is positioned as in the one-handed technique and the right hand is placed on the other side of the mask in an identical conformation. A more effective approach involves using the second and third digits to perform a jaw

thrust while the mask is held in place with the thumbs. A study in anesthetized patients showed that this technique improved upper airway patency, compared with the traditional one-handed technique, as measured by greater tidal volumes during PCV.[132] Additional techniques to improve the mask seal in difficult scenarios include leaving dentures in place in edentulous patients and placing an adhesive plastic dressing over facial hair.

Once a seal is established between the facemask and the patient's face, ventilation is achieved by either spontaneous ventilation or PPV. The effectiveness of mask ventilation should be ascertained by observing for chest rise, exhaled tidal volumes, pulse oximetry, and capnography. During controlled ventilation in patients with normal lungs and a patent airway, adequate tidal volumes should be achieved with peak inspiratory pressures less than 20 cm H_2O; higher pressures should be avoided to prevent gastric insufflation.[133] If PPV is inadequate at acceptable inspiratory pressures, then airway patency and pulmonary compliance should be assessed.

Because of a reduction in muscle tone as a result of general anesthesia, tissues fall backward under the influence of gravity in a supine patient and can obstruct the upper airway. Upper airway obstruction most commonly takes place at the level of the soft palate (velopharynx), epiglottis, and tongue.[10,14] To maximize airway patency, mask ventilation should be performed with maximal atlantooccipital extension in combination with the forward displacement of the mandible (jaw thrust) involved in the mask-holding techniques.[134] The addition of cervical flexion to head extension (i.e., placing the patient in the sniffing position) improves pharyngeal patency.[135] If the sniffing position and jaw thrust fail to relieve airway obstruction, then oropharyngeal or nasopharyngeal airways may be used to facilitate airway patency.

Oropharyngeal airways are the most commonly used. They follow the curvature of the tongue, pulling it away from the posterior pharynx (Figure 55-12). Because they place pressure on the base of the tongue and may come in contact with the epiglottis, oropharyngeal airways can precipitate coughing, retching, or laryngospasm if laryngeal and pharyngeal reflexes are not sufficiently blunted; therefore they are not appropriate for use in conscious patients. The oropharyngeal airway is sized by measuring from the corner of a patient's mouth to the angle of the jaw or the earlobe. Inappropriately sized oropharyngeal airways can actually worsen airway obstruction; therefore proper size selection is important. Proper placement is accomplished by inserting the oropharyngeal airway with the curvature facing posteriorly and then rotating 180 degrees; alternatively, a tongue depressor can be used to displace the tongue anteriorly as the oropharyngeal airway is inserted with the curvature facing anteriorly. Complications from oropharyngeal airways include lingual nerve palsy and damage to the teeth.[136,137] Once in place, nasopharyngeal airways are less stimulating than oropharyngeal airways and thus are more appropriate for conscious patients (Figure 55-13). Nasopharyngeal airways should be well lubricated before insertion and inserted with the bevel facing the nasal septum. To avoid epistaxis, force should never be used during insertion of a nasopharyngeal airway.

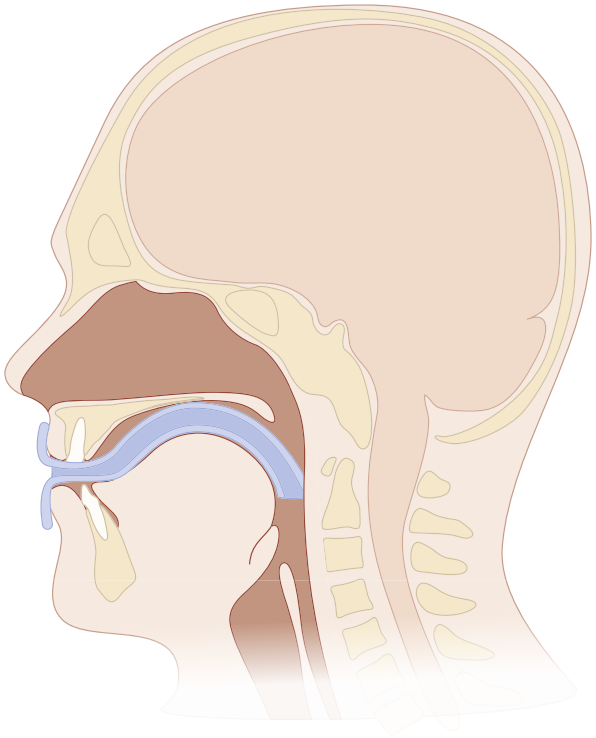


Figure 55-12. Oropharyngeal airway in place. The airway follows the curvature of the tongue. It pulls the tongue and the epiglottis away from the posterior pharyngeal wall and provides a channel for the passage of air. *(Adapted from Dorsch JA, Dorsch SE:* Understanding anesthesia equipment*, ed 4, Baltimore, 1999, Williams & Wilkins.)*

Difficult mask ventilation occurs when ventilating via the facemask is not possible because of an inadequate mask seal, excessive gas leak, and/or excessive resistance to the ingress or egress of gas.[24] Predictors for difficult mask ventilation that can be identified during the preoperative airway assessment are listed in Box 55-2.

SUPRAGLOTTIC AIRWAY

The term *supraglottic airway* (SGA) or *extraglottic airway* refers to a diverse family of medical devices that are blindly inserted into the pharynx to provide a patent conduit for ventilation, oxygenation, and delivery of anesthetic gases without the need for tracheal intubation. SGAs have the advantage of being less invasive than endotracheal intubation while providing a more definitive airway than a facemask, and can be used for either spontaneous ventilation or PPV. One of the first SGAs, the LMA, was described in 1983 by Dr. Archie Brain and introduced into clinical practice in 1988.[138] Since that time, the LMA has proved to be one of the single most important developments in both routine and difficult airway management and is a pivotal component of the ASA "Difficult Airway Algorithm." Various different designs of SGAs are now available and are widely used in current anesthesia practice as a primary airway management device, a rescue airway device, and a conduit for endotracheal intubation.

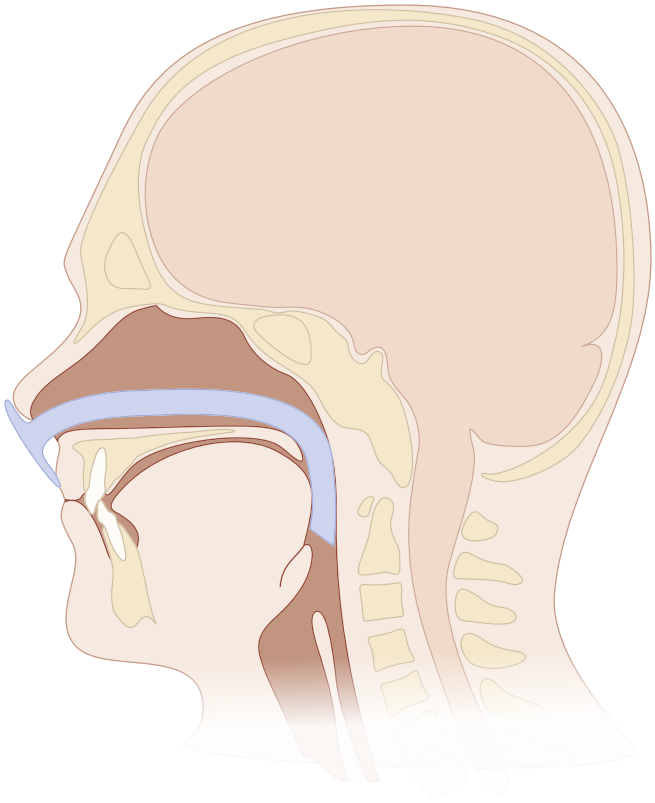


Figure 55-13. Nasopharyngeal airway in place. The airway passes through the nose and ends at a point just above the epiglottis. *(Adapted from Dorsch JA, Dorsch SE:* Understanding anesthesia equipment*, ed 4, Baltimore, 1999, Williams & Wilkins.)*



Figure 55-14. LMA Classic. *(Image provided courtesy of LMA North America, San Diego, CA.)*

BOX 55-2 ***Predictors of Difficult Mask Ventilation***

- Obstructive sleep apnea or history of snoring
- Age older than 55 years
- Male gender
- Body mass index of 30 kg/m^2 or greater
- Mallampati classification III or IV
- Presence of a beard
- Edentulousness

The specific advantages of SGAs include the ease and speed of placement, improved hemodynamic stability, reduced anesthetic requirements, lack of a need for muscle relaxation, and an avoidance of the risks of tracheal intubation (e.g., trauma to the teeth and airway structures, sore throat, coughing on emergence, bronchospasm).[139,140] The primary disadvantages are that SGAs have comparatively smaller seal pressures than ETTs, which can lead to ineffective ventilation when higher airway pressures are required, and they provide no protection from laryngospasm. First-generation SGAs also provide little protection from gastric regurgitation and aspiration, although newer devices have incorporated design elements to minimize this risk.

SGAs have many applications. They are considered the first choice for airway management for diagnostic and minor surgical procedures.[141] No standardized classification system exists for the different designs of SGAs, although several have been proposed. This chapter uses the terminology described by Donald Miller: perilaryngeal sealers; cuffless, anatomically preshaped sealers; and cuffed pharyngeal sealers.[142] Second-generation SGAs are differentiated from first-generation SGAs in that they incorporate features designed to reduce the incidence of aspiration.[143]

LARYNGEAL MASK AIRWAY

LMA Classic

The LMA (LMA North America, San Diego, CA) is the most widely used, well-studied SGA and is the archetype of the perilaryngeal sealer. The original version, the LMA Classic (cLMA), consists of an oval-shaped, silicone mask with an inflatable cuff that sits in the hypopharynx and forms a seal around the periglottic tissues (Figure 55-14). An airway tube attached to the mask exits the mouth and has a standard 15-mm connector for attachment to an anesthesia circuit or to a bag-valve device. The seal around the laryngeal inlet allows for the delivery of oxygen and inhaled anesthetics during spontaneous ventilation and permits PPV at pressures up to 20 cm H_2O. The cLMA is reusable up to 40 times and is available in a variety of sizes from size 1 (neonate) to size 6 (large adult, >100 kg).

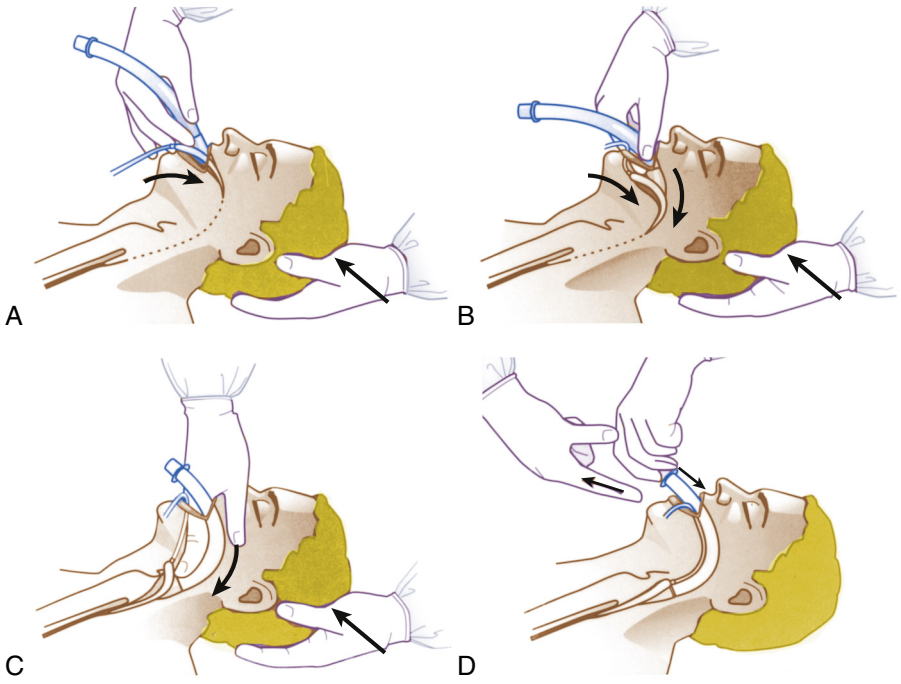


Figure 55-15. Insertion of a laryngeal mask airway (LMA). **A,** The tip of the cuff is pressed upward against the hard palate by the index finger while the middle finger opens the mouth. **B,** The LMA is pressed backward in a smooth movement. The nondominant hand is used to extend the head. **C,** The LMA is advanced until definite resistance is felt. **D,** Before the index finger is removed, the nondominant hand presses down on the LMA to prevent dislodgment during removal of the index finger. The cuff is subsequently inflated. *(Courtesy of LMA North America, San Diego, CA.)*

The LMA Classic Excel is an updated version that incorporates design features to facilitate endotracheal intubation through the device, including an epiglottic-elevating bar, a wider-bore airway tube, and a removable connector. A disposable, single-use version of the cLMA, the LMA Unique, is made from polyvinyl chloride (PVC) and has gained popularity because of its lower costs and maintenance, as well as concerns over the perceived risk of cross-contamination and the transmission of infection (e.g., human immunodeficiency virus [HIV], hepatitis C, prion-based diseases) with reusable medical devices. The LMA Flexible, available in reusable and single-use models, has a flexible, kink-resistant airway tube that can be positioned away from the surgical field for head and neck procedures.

To achieve a proper fit, the manufacturer of the LMA suggests placing the largest size LMA possible; an airtight seal is achieved more frequently with a size 5 LMA in the average adult man and a size 4 LMA in the average adult woman.[144] Using too small of an LMA can result in overinflation of the cuff to achieve a seal, which can predispose the patient to oropharyngolaryngeal morbidity and nerve damage.[145] Larger sizes, however, may be associated with a more frequent incidence of sore throat; therefore a smaller size may be appropriate when spontaneous ventilation through the LMA is planned.[146]

The manufacturer's instructions for the placement of the cLMA are summarized in Figure 55-15. Adequate depth of anesthesia for LMA insertion can be achieved with propofol or sevoflurane[147]; short-acting opioids such as fentanyl, alfentanil, and remifentanil may be coadministered to facilitate placement and to decrease the incidence of coughing, gagging, and laryngospasm.[148,149] Before insertion, the LMA cuff should be deflated and the posterior aspect of the mask should be lubricated with a water-based lubricant. Once positioned (see Figure 55-15), the cuff should be inflated with the minimum effective volume of air, with a target cuff pressure of 40 to 60 cm H_2O.[144] To allow the LMA to position itself correctly, the device should not be secured or attached to the anesthesia circuit until the cuff has been inflated. Confirmation of proper placement is performed by attempting gentle PPV while checking capnography and auscultation and by quantifying the inspiratory pressure at which a leak is audible, which should be 18 to 20 cm H_2O. Once proper positioning is confirmed, a roll of gauze is inserted as a bite block and the LMA is secured in place with tape. Several modifications to the recommended insertion technique have been described, including a *thumb insertion method* by the manufacturer, although these modifications are not detailed in this chapter.[150,151] Cuff pressure should be periodically monitored if N_2O is being used; cuff pressures may increase above the recommended threshold of 60 cm H_2O as a result of diffusion of N_2O into the cuff.

Initial difficulty with ventilation after the placement of an LMA may be due to a down-folded epiglottis. The *up-down maneuver* described by Dr. Brain may help correct this problem; the LMA is withdrawn 2 to 4 cm and reinserted without deflating the cuff. Head extension and LMA repositioning may also improve ineffective ventilation. If these actions do not correct the problem, then a different size may be needed. Insufficient depth of anesthesia, resulting in laryngospasm or bronchospasm, may make ventilation through an LMA impossible; the administration of topical, inhaled or IV anesthesia can help to correct this. Although not necessary, DL can also facilitate proper LMA placement.

Serious complications from LMA use are relatively rare. More commonly, minor oral, pharyngeal, or laryngeal injury occurs, expressed as complaints of a dry or sore throat.[152] The incidence of sore throat is approximately 10% to 20%,[140,153] and has been linked to higher cuff pressures and larger LMA sizes.[146,154] More serious cases of oropharyngolaryngeal injury have been described, such

as trauma to the uvula and pharyngeal necrosis.[155,156] Injury to the lingual, hypoglossal, and recurrent laryngeal nerves has also been reported; these usually spontaneously resolve over a period of weeks to months.[145] Predisposing factors include high cuff pressures (often attributable to the use of N_2O), using too small of an LMA, and nonsupine positions.[145]

LMA ProSeal

The LMA ProSeal (pLMA, LMA North America, San Diego, CA) is a reusable second-generation SGA that incorporates a posterior cuff, improving the perilaryngeal seal and allowing for PPV at pressures up to 30 cm H_2O. It also incorporates a gastric drainage tube that allows for gastric access with an orogastric tube and channels any regurgitated gastric contents away from the airway, effectively isolating the respiratory and gastrointestinal tracts.[157] Additional features include an incorporated bite block and a softer cuff.

The insertion technique is similar to the cLMA but requires deeper anesthetic levels.[157,158] An optional introducer can be used to facilitate insertion. As with the cLMA, cuff pressure should not exceed 60 cm H_2O. Once inserted, assessment of proper placement is accomplished by providing PPV; adequate tidal volumes should be accomplished with reasonable peak inspiratory pressures, leak pressure should be above 20 cm H_2O, and the capnography waveform should appear normal.[10] An additional test to confirm proper placement and separation of the airway and gastrointestinal tract is performed by placing a small layer (<5 mm) of water-based lubricant over the drainage tube orifice; PPV and suprasternal notch palpation should result in a small up-down movement of the gel meniscus. Easy passage of an orogastric tube through the gastric drainage tube confirms proper positioning.

LMA Supreme

The LMA Supreme (sLMA) is a single-use, second-generation SGA based on the pLMA design. Similar to the pLMA, the sLMA has an improved cuff design that produces higher airway leak pressures, a drainage tube that allows for gastric access, and an integrated bite block (Figure 55-16). A fixation tab allows for insertion without inserting the fingers in the mouth and provides a visual guide for determining proper sizing.

Although not clinically proven, evidence suggests that second-generation SGAs, such as the pLMA and the sLMA, reduce the risk of aspiration of gastric contents. This property, along with the improved airway seal and higher leak pressures, have enabled SGA devices to be used in various applications where the cLMA is potentially unsuitable, such as in nonsupine positions (e.g., lateral, prone),[159] in laparoscopic surgery (e.g., cholecystectomy, gynecologic surgery),[160,161] and in patients who are obese.[162] The successful, routine use of the sLMA in fasted, nonobese patients for cesarean section has also been reported.[163]

OTHER PERILARYNGEAL SEALERS

Over the past 10 years, a multitude of manufacturers have produced SGAs that incorporate the basic perilaryngeal sealing design of the cLMA. Because the term *LMA* is a protected trademark, these devices are referred to as *laryngeal masks* (LMs). Each has its own unique characteristics that may afford it specific advantages over other designs. Although an exhaustive description of every available LM is outside the scope of this chapter, some unique features merit mentioning.

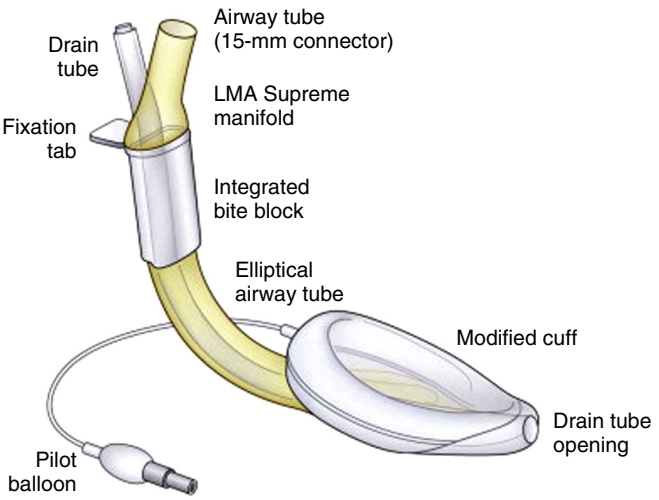


Figure 55-16. The LMA Supreme has a modified cuff design, a drainage tube that allows for gastric access, and an integrated bite block. *(From Verghese C, Mena G, Ferson DZ, Brain AIJ: Laryngeal mask airway. In Hagberg CA, editor:* Benumof and Hagberg's airway management, *ed 3, Philadelphia, 2013, Saunders, p. 459.)*

Some design features address the issue of high cuff pressures, which can lead to oropharyngolaryngeal morbidity, nerve palsies, and improper device positioning. The line of LMs manufactured by AES, Inc. (Black Diamond, WA) incorporates a cuff pilot valve (CPV) that allows constant cuff pressure monitoring. Color-coded indicator bands on the CPV alert the clinician to changes in cuff pressure attributable to temperature, N_2O, and movement within the airway, allowing the clinician to maintain the recommended cuff pressure of 60 cm H_2O. The air-Q SP (Cookgas LLC, St. Louis, MO; distributed by Mercury Medical, Clearwater, FL) has a self-pressurizing cuff that uses the positive pressure that ventilates the patient to also pressurize the cuff, obviating the need for an inflation line and eliminating the possibility of cuff overinflation. On exhalation, the mask cuff deflates to the level of positive end-expiratory pressure (PEEP), decreasing the total mucosal pressure over the course of an anesthetic, thereby potentially reducing the incidence of cuff pressure–related complications.

Other LMs incorporate design features that facilitate endotracheal intubation, such as removable connectors or wider bore airway lumina to allow intubation with standard-sized ETTs (see "Tracheal Intubation Through a Supraglottic Airway Device")

CUFFLESS ANATOMICALLY PRESHAPED SEALERS

Cuffless anatomically preshaped sealers do not have a cuff; rather, they provide an airway seal by their anatomically preshaped design. Advantages include simplicity of insertion and positioning and the lack of a need to inflate

a cuff. The first of these devices, the SLIPA (Curveair, London, UK), contains a hollow chamber that can trap regurgitated liquid and prevent aspiration. Newer cuffless devices such as the i-gel (Intersurgical Inc., Wokingham, Berkshire, UK) and the Baska Mask (Strathfield, NSW, Australia) can also be included in this classification.

CUFFED PHARYNGEAL SEALERS

Cuffed pharyngeal sealers have an airway with a pharyngeal cuff that seals at the level of the base of the tongue and can be subclassified as to whether they also possess an esophageal sealing cuff.[142] SGAs with only a pharyngeal cuff include the Cobra Perilaryngeal Airway (Cobra-PLA; Engineered Medical Systems, Indianapolis, IN) and the Tulip Airway (Marshall Medical, Bath, UK); they are not detailed in this chapter. The following devices all have an esophageal sealing cuff.

The esophageal-tracheal combitube (ETC) (Covidien, Mansfield, MA) is a uniquely designed SGA with both a pharyngeal and esophageal sealing cuff and two lumina. The ETC is primarily designed for emergency intubation and is mostly used in the prehospital setting, although it has occasionally been used during general anesthesia as both a primary airway and as a rescue airway device.[164,165] It is inserted blindly through the mouth in a curved, downward motion until the printed ring marks lie between the teeth. Both the proximal, oropharyngeal cuff and the distal esophageal-tracheal cuff are inflated. Greater than 90% of the time, esophageal placement of the device occurs, in which ventilation should be performed via the longer, blue, #1 (esophageal) lumen.[166] This lumen has a closed distal end with eight small perforations located between the two cuffs, which allow oxygenation and ventilation. When the device is placed into the trachea, ventilation should occur via the shorter, clear, #2 (tracheal) lumen, which is open at its distal end. When the ETC is placed in the esophagus, an orogastric tube may be passed through the tracheal lumen to empty the stomach. Use of the ETC as a primary airway is limited by a higher risk of complications, compared with the LMA or tracheal intubation, including hoarseness, dysphagia, and bleeding.[167] Because the oropharyngeal cuff of the ETC contains latex, this device should not be used in latex-sensitive individuals.

The Rüsch EasyTube (Teleflex Medical, Research Triangle Park, NC) is a double-lumen SGA that is similar to the ETC. The primary differences are its nonlatex construction and a proximal lumen that ends just below the oropharyngeal balloon, allowing for the passage of a tube exchanger or FIS. The insertion technique and risks are similar to the ETC; a comparative study showed shorter insertion times with the EasyTube.[168] The King LT series of SGAs (King Systems Corporation, Noblesville, IN) are similar in design to the ETC and EasyTube, with a ventilation port between the pharyngeal and esophageal cuffs. The King LT and the King LT-D (reusable and disposable, respectively) are single-lumen devices with a tapered distal tip that allows easy passage into the esophagus. The distal (esophageal) portion of the tube is occluded. The King LTS and the disposable King LTS-D, on the other hand, have an open distal tip with a secondary channel to allow suctioning of gastric contents. Although tracheal placement of a King LT device has not be reported, if it should occur, then the device should be removed and reinserted.

ENDOTRACHEAL INTUBATION

Endotracheal intubation is the gold standard for airway management. It establishes a definitive airway, provides maximal protection against the aspiration of gastric contents, and allows for PPV with higher airway pressures than with a facemask or an SGA. Endotracheal intubation is usually facilitated by DL; however, a wide variety of alternative intubation devices and techniques have been developed to circumvent the problems encountered when conventional DL is difficult.

In the fasted patient undergoing elective surgery with general anesthesia, an SGA is many times suitable. Certain conditions or clinical situations, however, favor endotracheal intubation, although the advent of second-generation SGAs has somewhat narrowed this list. Absolute indications for endotracheal intubation include patients with a full stomach or who are otherwise at high risk for aspiration of gastric secretions or blood, patients who are critically ill, patients with significant lung abnormalities (e.g., low lung compliance, high airway resistance, impaired oxygenation), patients requiring lung isolation, patients undergoing otorhinolaryngologic surgery during which an SGA would interfere with surgical access, patients who will likely need postoperative ventilatory support, and patients in whom SGA placement has failed. Other indications for intubation include a surgical requirement for NMBDs, patient positioning that would preclude rapid tracheal intubation (e.g., prone or turned away from the anesthesia provider), a predicted difficult airway, and prolonged procedures.[10]

ENDOTRACHEAL TUBES

The modern, standard ETT is a disposable, single-use, cuffed, plastic tube that is designed to be inserted through the nose or mouth and sit with its distal end in the midtrachea, providing a patent airway to allow for ventilation of the lungs. A variety of different types of ETTs are available for use in specialized situations. Several features are commonplace among the different styles, however, including a universal 15-mm adapter that allows the attachment of the proximal end to different ventilating circuits and devices; a high-volume, low-pressure cuff; a beveled tip to facilitate passage through the vocal cords; and an additional distal opening in the side wall of the ETT known as a *Murphy eye*, which serves to provide an additional portal for ventilation should the distal end of the lumen become obstructed by either soft tissue or secretions.

Cuffed ETTs are routinely used for endotracheal intubation in most patients; cuffless ETTs are used in neonates and infants. The high-volume, low-pressure cuff is inflated with air to provide a seal against the tracheal wall to protect the lungs from pulmonary aspiration and to ensure that the tidal volume delivered ventilates the lungs rather than escapes into the upper airway.[10] A pilot balloon with a one-way valve allows for the inflation of

the cuff and an assessment of the cuff pressure. The cuff should be inflated to the minimum volume at which no air leak is present with positive pressure inspiration; the cuff pressure should be less than 25 cm H_2O.[169] Excessive cuff pressure may result in tracheal mucosal injury, vocal cord dysfunction from recurrent laryngeal nerve palsy, and sore throat. Monitoring the cuff pressure with a pressure gauge is recommended. When N_2O is used as part of the anesthetic, cuff pressure should be periodically measured throughout the surgery; N_2O diffusion into the cuff can result in increases in cuff pressure to potentially dangerous levels.

ETT size is normally described in terms of its internal diameter (ID); the relationship of the ID to the external diameter varies between different designs and manufacturers. Selection of the ETT size depends on the reason for placement and patient-specific factors such as gender and airway pathologic conditions. Smaller ETTs result in increased airway resistance and work of breathing, and ETTs with a smaller than 8-mm ID preclude therapeutic fiberoptic bronchoscopy. Larger ETTs are more likely to be associated with laryngeal or tracheal mucosal trauma and have a higher incidence of sore throat after general anesthesia. Generally, in patients intubated only for the purposes of a general anesthetic, a smaller ETT may be used than on the patient who will remain intubated in the medium to long term as a result of respiratory failure; typically a 7-mm ETT is used for women and an 8-mm ETT is used for men.

A variety of specialized tracheal tubes are available for use in specific clinical situations. Preformed tubes, such as the nasal and oral Ring-Adair-Elwin (RAE) tubes, have a specific contour to maintain a low profile and to avoid surgical interference. Armored (reinforced) tubes have an embedded coil that minimizes kinking of the tube when it is subjected to angulation. Microlaryngeal tubes, which have small IDs with a longer length tube, are useful in laryngeal surgery or for specific applications, such as intubation through a cLMA. Other specialized tubes include laser-resistant tubes and both single- and double-lumen tubes that allow for one-lung ventilation.

OROTRACHEAL VERSUS NASOTRACHEAL INTUBATION

Endotracheal intubation can proceed via the orotracheal or nasotracheal route—this decision should be made before deciding which airway management technique will be used. Nasotracheal intubation is generally indicated when the orotracheal route is not possible (e.g., when the mouth opening is severely limited) or when the need for surgical access precludes an orotracheal route. In addition, certain intubation techniques, such as blind intubation, awake intubation, and FSI, are significantly easier when performed through the nose.

When the nasotracheal route is not specifically indicated, however, the orotracheal route is usually preferred for several advantages. The orotracheal route is potentially less traumatic and presents a lower risk of bleeding, it usually allows for the placement of a larger ETT, and it provides for more options in terms of airway management techniques. The major disadvantages include the potential for damage to the teeth and stimulation of the gag reflex during awake intubation, requiring denser airway anesthesia and potentially being less comfortable for the patient. Nasotracheal intubation, on the other hand, bypasses the gag reflex and is usually more easily tolerated by the awake patient. However, the risks of epistaxis, trauma to the nasal turbinates, and submucosal tunneling in the nasopharynx must be taken into account.[114] Nasotracheal intubation is relatively contraindicated in the setting of maxillary or skull base fractures.

DIRECT LARYNGOSCOPY

The most commonly used technique for endotracheal intubation is DL, which involves direct visualization of the glottis with the assistance of a laryngoscope. The ETT is inserted through the glottic opening into the trachea under continuous observation.

Preparation and Positioning

Preparation for DL includes proper patient positioning, adequate preoxygenation, and ensuring the availability and proper functioning of all necessary equipment—laryngoscopes, tracheal tubes, tube stylets, an empty syringe for inflating the tracheal tube cuff, a suction apparatus, and the essential equipment for mask ventilation, including an oxygen source. A skilled assistant should be present to help with external laryngeal manipulation and stylet removal, among other tasks. Adequate preparation is of the utmost importance; as with any airway procedure, the first attempt should be the best attempt.

For DL to be successful, a line of sight from the mouth to the larynx must be achieved. The classical model used to describe the anatomic relationships necessary to achieve this was proposed in 1944 by Bannister and Macbeth and involves the alignment of three anatomic axes—oral, pharyngeal, and laryngeal.[170] Positioning the patient in the sniffing position approximates this alignment. Cervical flexion aligns the pharyngeal and laryngeal axes, and maximal head extension at the atlantooccipital joint brings the oral axis closer into alignment (Figure 55-17). The accuracy of this model has been questioned,[171] and various alternative models to explain the anatomic advantage of the sniffing position have been proposed.[172,173] Regardless of the explanatory model, however, the evidence in the literature supports the assertion that the sniffing position is the optimal position for DL.[36,174]

Proper positioning in the sniffing position involves approximately 35 degrees of cervical flexion, which is accomplished by a 7- to 9-cm elevation of the head on a firm cushion; patients with shorter necks may require less head elevation.[36,175] Patients who are obese often require elevation of the shoulders and upper back to achieve adequate cervical flexion, which can be accomplished by placing the patient in the *ramped* position using either a specialized device, such as the Troop Elevation Pillow (Mercury Medical, Clearwater, FL) or folded blankets. Confirming horizontal alignment of the external auditory meatus with the sternal notch is useful for ensuring optimal head elevation in both obese and nonobese patients.[176] Adequate cervical flexion also facilitates maximal atlantooccipital extension, which provides optimal

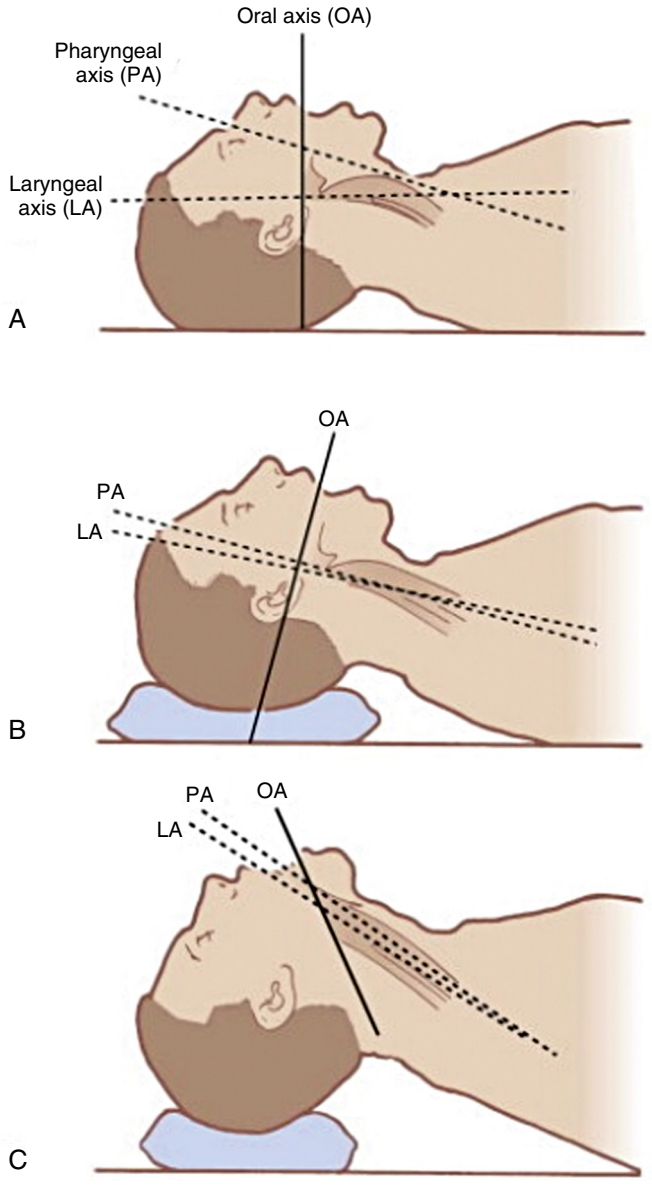


Figure 55-17. Visual axis diagram. **A,** The head is in the neutral position. None of the three visual axes align. **B,** Elevation of the head produces cervical flexion, which aligns the laryngeal axis (LA) and the pharyngeal axis (PA). **C,** Extension at the atlantooccipital joint brings the visual axis of the mouth into better alignment with those of the larynx and pharynx. *(From Stone DJ, Gal TJ: Airway management. In Miller RJ, editor:* Anesthesia*, ed 6, Philadelphia, 2005, Churchill Livingstone.)*

alignment of the oral and pharyngeal axes (the primary determinant for quality of laryngeal view) and enhanced mouth opening.[177]

Technique

The laryngoscope is a handheld instrument consisting of a blade attached to a handle containing a light source. Most are reusable and made of steel, although disposable, plastic versions are available. The curved blade and the straight blade are the two basic types of laryngoscope blades available for DL; multiple variations of both styles exist. The Macintosh is the most commonly used curved

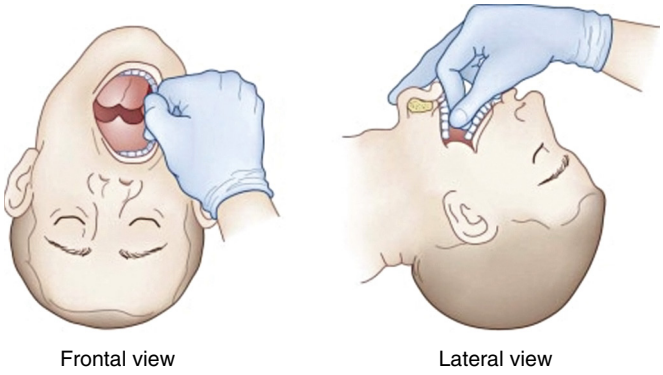


Figure 55-18. The *scissors* technique for mouth opening. The thumb of the right hand is pressed on the right, lower molars in a caudad direction while the index or third finger of the right hand presses on the right, upper molars in a cephalad direction. *(From Berry JM, Harvey S: Laryngoscopic orotracheal and nasotracheal intubation. In Hagberg CA, editor:* Benumof and Hagberg's airway management*, ed 3, Philadelphia, 2013, Saunders, p. 351.)*

blade, whereas the Miller is the most commonly used straight blade. Both are designed to be held in the left hand, and both have a flange on the left side that is used to retract the tongue laterally. Each type of blade has its benefits and drawbacks and is associated with its own technique for use.

The technique for laryngoscopy consists of the opening of the mouth, inserting the laryngoscope blade, positioning of the laryngoscope blade tip, applying a lifting force exposing the glottis, and inserting a tracheal tube through the vocal cords into the trachea. Mouth opening is best achieved using the *scissors* technique; the right thumb pushes caudally on the right lower molars while the index or third finger of the right hand pushes on the right upper molars in the opposite direction (Figure 55-18).

The decision of whether to use a Macintosh or a Miller blade is multifactorial; however, the personal preferences and experience of the laryngoscopist is a significant consideration. In general, the Macintosh is most commonly used for adults, whereas the straight blades are typically used in pediatric patients.[178] Curved blades provide greater room for passage of an ETT through the oropharynx, attributable to their larger flange, and are generally considered less likely to cause dental damage.[179] Straight blades are preferred in patients with a short thyromental distance and usually provide a better view of the glottis in patients with a long, floppy epiglottis. Often, when one style of laryngoscope does not provide an adequate view of the glottis, the other may be more effective. For most adults, a Macintosh size 3 or a Miller size 2 blade is usually the proper size; in larger patients or patients with a very long thyromental distance, a larger blade may be more appropriate.

The Macintosh blade is inserted in the right side of the mouth, and the flange is used to sweep the tongue to the left. Once the laryngoscope has been inserted in the mouth, the right hand can be used to ensure that the upper lip is not impinged between the laryngoscope and the upper incisors. The blade is advanced along the base of the tongue until the epiglottis is visualized; the tip of

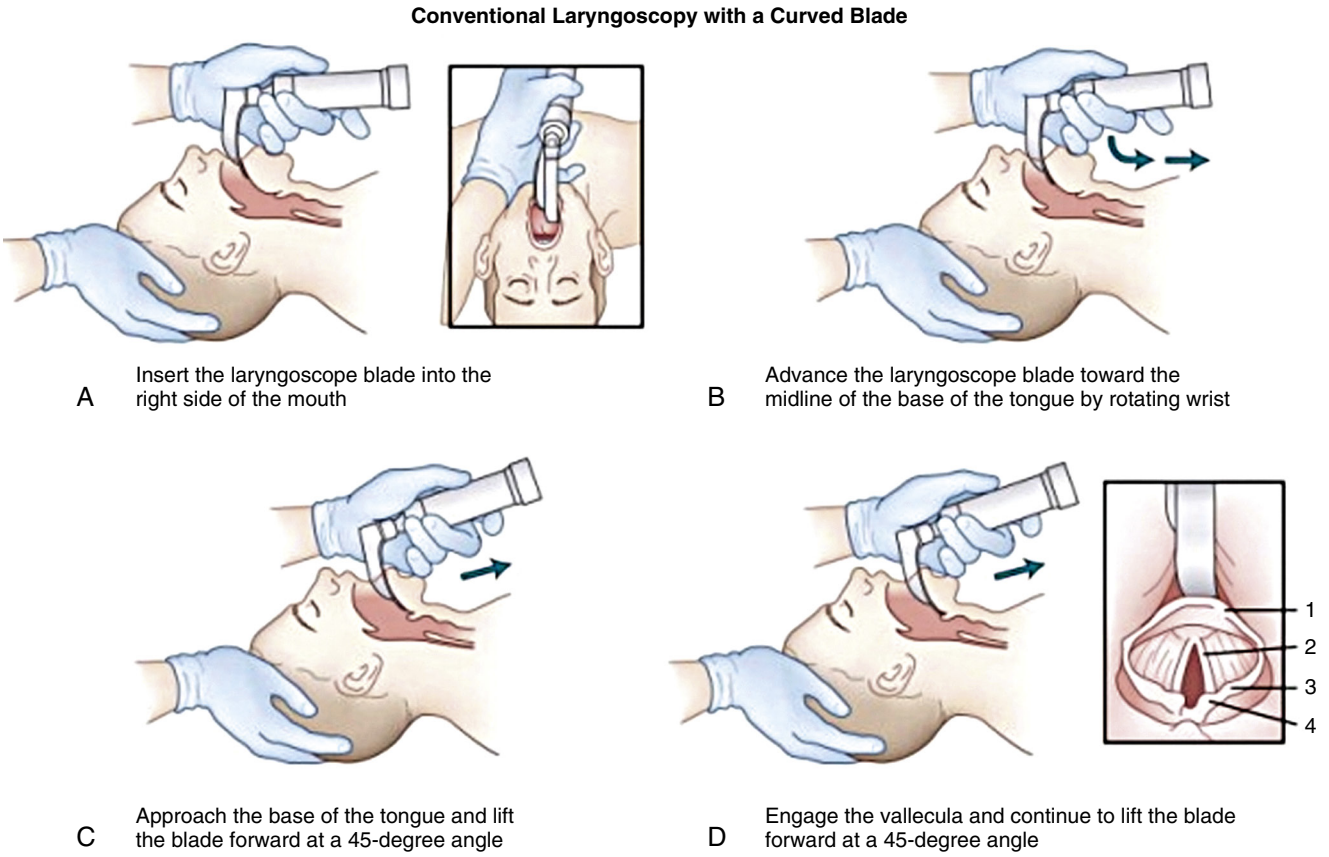


Figure 55-19. Conventional laryngoscopy with a Macintosh (curved) blade. **A,** The laryngoscope blade is inserted into the right side of the mouth, sweeping the tongue to the left of the flange. **B,** The blade is advanced toward the midline of the base of the tongue by rotating the wrist so that the laryngoscope handle becomes more vertical *(arrows)*. **C,** The laryngoscope is lifted at a 45-degree angle *(arrow)* as the tip of the blade is placed in the vallecula. **D,** Continued lifting of the laryngoscope handle at a 45-degree angle results in exposure of the laryngeal aperture. The epiglottis *(1)*, vocal cords *(2)*, cuneiform cartilage *(3)*, and corniculate cartilage *(4)* are identified. *(From Berry JM, Harvey S: Laryngoscopic orotracheal and nasotracheal intubation. In Hagberg CA, editor:* Benumof and Hagberg's airway management*, ed 3, Philadelphia, 2013, Saunders, p. 350.)*

the blade is then advanced further and positioned in the vallecula. A force oriented at a 45-degree angle up and away from the laryngoscopist indirectly lifts the epiglottis by placing tension on the hyoepiglottic ligament, exposing the glottic structures (Figure 55-19). The tip of the blade should not be lifted by using the laryngoscope as a lever, rocking back on the upper incisors, which can damage the teeth and provides an inferior view of the glottis. A properly oriented vector of force is achieved by using the anterior deltoid and triceps, not by radial flexion of the wrist. Once a complete view of the glottis is achieved, the ETT is grasped similar to a pencil with the right hand and guided through the vocal cords into the trachea. Passage of the ETT is facilitated by an anterior angulation of the tip, which can be accomplished by shaping the ETT with a malleable stylet into a *hockey stick* shape, with approximately a 60-degree angle formed 4 to 5 cm from the distal end, or by accentuating the natural anterior curvature of the ETT by inserting the tip into the 15-mm connector, forming a circle, for several minutes before performing DL.

The Miller laryngoscope blade is inserted using the paraglossal technique described by Henderson.[10] This method provides maximal tongue control and avoids contact of the laryngoscope with the maxillary incisors. The laryngoscope is inserted lateral to the tongue and carefully advanced along the paraglossal gutter between the tongue and tonsil. Application of continued moderate lifting force to the laryngoscope handle helps maintain lateral displacement of the tongue and reduces contact with the maxillary teeth. As the laryngoscope is advanced, the epiglottis comes into view and the tip of the laryngoscope is passed posterior to the epiglottis. The optimal position of the tip of the straight laryngoscope is in the midline of the posterior surface of the epiglottis, close to the anterior commissure of the vocal cords (Figure 55-20).[10] This position achieves good control of the epiglottis and facilitates the passage of the tracheal tube. The direction of force applied to the handle is the same as when using the Macintosh blade.

The use of external laryngeal manipulation can improve the laryngeal view. Backward, upward, rightward pressure (the BURP maneuver) on the thyroid cartilage is most commonly used. Optimal external laryngeal manipulation (OELM) is achieved when the laryngoscopist uses his or her right hand to guide the position and pressure is exerted by an assistant's hand on the larynx (Figure 55-21).

Difficulty with endotracheal intubation by DL is primarily a function of an inadequate view of the glottis.

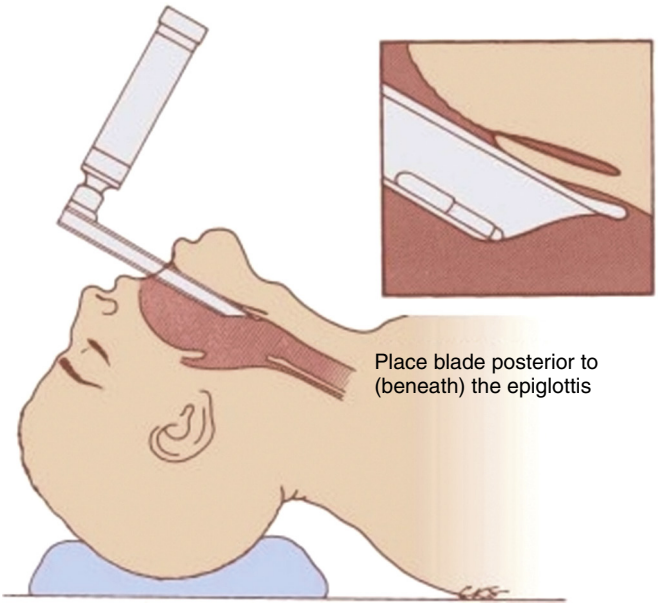


Figure 55-20. Conventional laryngoscopy with a Miller (straight) blade. The tip of the blade should be placed beneath the epiglottis and a 45-degree lifting force applied to expose the glottic aperture. *(From Berry JM, Harvey S: Laryngoscopic orotracheal and nasotracheal intubation. In Hagberg CA, editor:* Benumof and Hagberg's airway management*, ed 3, Philadelphia, 2013, Saunders, p. 352.)*

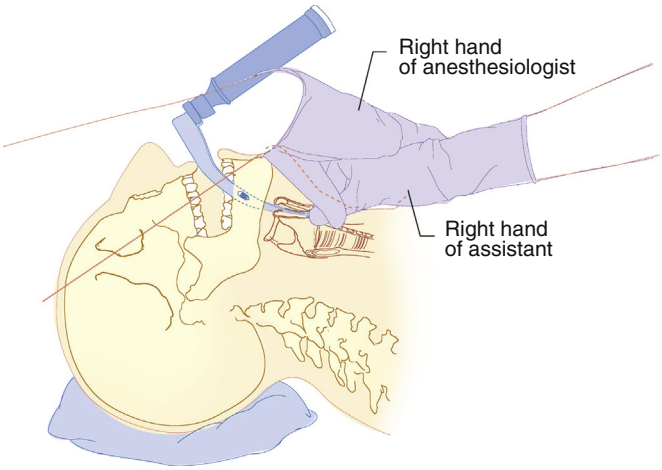


Figure 55-21. Optimal external laryngeal manipulation (OELM). The laryngoscopist guides the position, and pressure is exerted by the assistant's hand on the larynx to maximize the view of the vocal cords. The left hand of the laryngoscopist, which holds the laryngoscope handle, is omitted. *(From Henderson J: Airway management. In Miller RJ, editor:* Anesthesia*, ed 7, Philadelphia, 2009, Churchill Livingstone.)*

Predictors for difficult laryngoscopy that can be identified during the preoperative airway assessment are listed in Box 55-3. Cormack and Lehane developed a grading scale in 1984 to describe laryngoscopic views.[180] The grades range from I to IV, beginning with grade I (the best view), in which the epiglottis and vocal cords are in complete view, and culminating with grade IV (the most difficult view), in which the epiglottis or larynx is not visualized (Figure 55-22). A modified classification scheme with five different grades based on the Cormack-Lehane scoring

BOX 55-3 ***Predictors of Difficult Laryngoscopy***

- Long upper incisors
- Prominent overbite
- Inability to protrude mandible
- Small mouth opening
- Mallampati classification III or IV
- High, arched palate
- Short thyromental distance
- Short, thick neck
- Limited cervical mobility

Modified from Apfelbaum JL, Hagberg CA, Caplan RA, et al: Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway, Anesthesiology *118:251-270, 2013.*

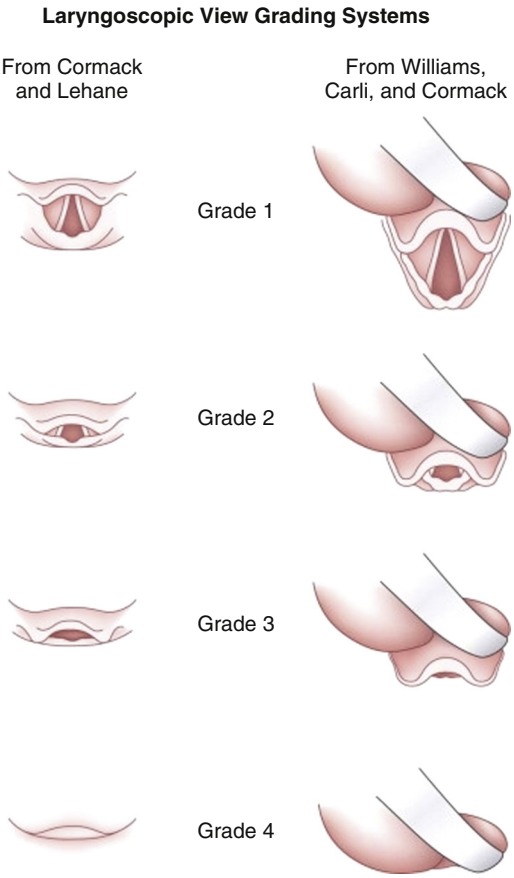


Figure 55-22. The Cormack-Lehane grading system for laryngoscopic view. Grade 1 is visualization of the entire laryngeal aperture; grade 2 is visualization of only the posterior portion of the laryngeal aperture; grade 3 is visualization of only the epiglottis; and grade 4 is no visualization of the epiglottis or larynx. *(Modified from Cormack RS, Lehane J: Difficult tracheal intubation in obstetrics,* Anaesthesia *39:1105, 1984; and Williams KN, Carli F, Cormack RS: Unexpected difficult laryngoscopy: a prospective survey in routine general surgery,* Br J Anaesth *66:38, 1991.)*

system is described by Yentis, who proposed that grade II be differentiated into IIA (partial view of the glottis) and IIB (arytenoids or posterior vocal cords only are visible).[181] Intubation is rarely difficult when a grade I or IIA view is achieved; grades IIB and III are associated

with a significantly higher incidence of failed intubation. A Grade IV laryngoscopic view requires an alternate method of intubation. An alternate method of rating laryngoscopic view is the percentage of glottic opening (POGO) scale, which is determined by the percentage of the vocal cords from the anterior commissure to the arytenoid notch that can be visualized during laryngoscopy. This scale has been shown to have a higher interobserver reliability than the Cormack-Lehane scoring system and is potentially more useful for research studies in direct and indirect laryngoscopy.[182]

When the laryngeal view is inadequate, the laryngoscopist should verify that the patient is in an optimal position, that OELM is being provided, and that the laryngoscope has not been inserted too deeply. Whether a larger laryngoscope or an alternate style of blade would be beneficial should be considered. When the ETT cannot be passed into the trachea under direct visualization, the options include the following: (1) attempts at blind passage of the ETT, which risks laryngeal trauma, bleeding, and airway obstruction; (2) the use of an intubating stylet (see Intubating Introducers and Stylets); and (3) alternative approaches to intubation as per the ASA "Difficult Airway Algorithm."

When the glottic view is adequate, the ETT should be inserted into the right corner of the mouth and advanced such that it intercepts the long axis of the laryngoscope blade at the glottis, rather than inserted midline and parallel to the long axis of the laryngoscope blade, which ensures that the view of the glottis is not obscured. The tip of the ETT is passed through the glottic inlet and advanced until the proximal portion of the cuff is approximately 2 cm past the vocal cords. If a stylet is being used, then the stylet should be removed when the tip of the ETT is right at the level of the vocal cords while the ETT is firmly held stationary; this technique helps limit trauma to the tracheal mucosa from the semirigid stylet.

Nasotracheal Intubation Technique

Before nasotracheal intubation, the more patent nostril should be selected. This selection can be accomplished by separately occluding each nostril and having the patient inhale—the patient will usually be able to inhale more effectively through one of the nares. To reduce the risk of epistaxis, a nasal mucosal vasoconstrictor (e.g., cocaine, phenylephrine, oxymetazoline) should be administered. The nasal ETT should be lubricated and inserted into the naris with the bevel facing away from the midline, which decreases the risk of avulsion of a turbinate. Cephalad traction should be applied as the ETT is advanced through the nasal passage to ensure a trajectory along the floor of the nose, beneath the inferior turbinate.

Once the ETT enters the oropharynx (typically at a depth of 14 to 16 cm), standard DL is performed. The ETT can be guided into the laryngeal inlet by repositioning the head as the ETT is advanced or with the aid of Magill forceps (Figure 55-23). Care should be taken to grasp the ETT proximal to the cuff to prevent cuff damage. Other techniques for nasotracheal intubation include blind nasal intubation, video laryngoscopy, and FSI.

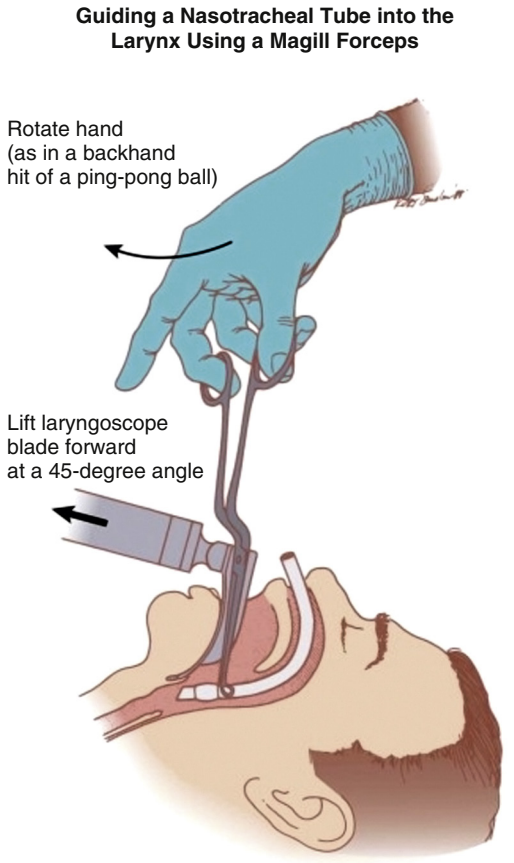


Figure 55-23. Guiding a nasal endotracheal tube (ETT) into the larynx with Magill forceps. *(From Berry JM, Harvey S: Laryngoscopic orotracheal and nasotracheal intubation. In Hagberg CA, editor:* Benumof and Hagberg's airway management*, ed 3, Philadelphia, 2013, Saunders, p. 357.)*

Confirmation of Endotracheal Tube Placement

Once the ETT is in place, the laryngoscope is removed from the mouth, the ETT cuff is appropriately inflated, and the patient is manually ventilated while the ETT is manually held in place. Immediate verification of endotracheal placement of the ETT is necessary; esophageal or endobronchial intubation is a significant source of avoidable anesthetic-related morbidity and mortality. Endotracheal placement can be determined by confirmation of chest rise, visible condensation in the ETT, equal breath sounds bilaterally over the chest wall, lack of breath sounds over the epigastrium, large exhaled tidal volumes, and appropriate compliance of the reservoir bag during manual ventilation.[179] The most important and objective indicator of endotracheal intubation, however, is the presence of a normal capnogram (carbon dioxide [CO_2] waveform) for the presence of at least three breaths. Severe bronchospasm, equipment malfunction, cardiac arrest, or hemodynamic collapse may prevent the appearance of a capnogram tracing, despite proper ETT placement. If doubt remains, then fiberoptic bronchoscopy, although not routinely used, is very reliable at confirming ETT placement.

Hypoxemia, increased airway pressures, asymmetric chest expansion, and the absence of breath sounds over one lung, generally the left, are indicative of endobronchial intubation; pneumothorax can also produce this picture. Fiberoptic bronchoscopy or chest radiography can be used if the clinical picture is unclear.

Securing the Endotracheal Tube

Once the proper depth of the ETT has been determined, the tube should be secured in place to prevent movement and inadvertent endobronchial intubation or extubation. The most common method is to tape the ETT to the skin of the face. Because it is less mobile, the skin of the maxilla is preferred. When tape cannot be used, such as in the case of a severe tape allergy, extensive facial burns, or epidermolysis bullosa, a surgical mask may be tied around the back of the head to secure the ETT. Other methods that may be used for intraoral or facial surgery include wire fixation to a tooth or suturing the ETT to the skin of the cheek.

INDIRECT LARYNGOSCOPY

Conventional DL requires wide mouth opening, cervical flexion, and atlantooccipital extension to create a direct line of vision from the mouth to the larynx. In certain conditions, this positioning is impossible or contraindicated. Other times, attributable to anatomic variations in the airway (e.g., redundant soft tissue, protruding incisors, anterior larynx), DL cannot be achieved, despite optimal positioning and technique. Indirect laryngoscopy entails the indirect visualization of the glottis by way of optical aids, such as fiberoptic bundles, video cameras, mirrors, prisms, or lenses. Various different devices that use indirect laryngoscopy are available, including FISs, VLs, and intubating optical stylets. They are indispensable tools for the management of the known or predicted difficult airway. Because no direct line of sight is needed, visualization of the larynx can occur without tissue distortion; consequently, these techniques can be readily used with topical anesthesia in an awake patient.[10]

Flexible Scope Intubation of the Trachea

The flexible fiberoptic bronchoscope (FOB) is the most widely-used, versatile, indirect laryngoscopy device. Since the first use of fiberoptics for airway management in 1967, FISs, including the FOB, have become invaluable tools for endotracheal intubation in both awake and anesthetized patients. There are various clinical scenarios within which FSI provides a superior technique for airway management, as compared with DL or alternative airway devices. FSI of the awake, spontaneously ventilating patient is well-accepted as the *gold standard* for the management of the difficult airway.[183]

The standard FOB (Figure 55-24) consists of thousands of flexible glass fibers approximately 8 to 10 μm in diameter that are capable of transmitting reflected light along their length. Light is transmitted from an external light source to the distal end of the FOB; the light reflecting off the object to be viewed is transmitted back along the length of the FOB to an eyepiece or video camera at the proximal end of the scope. In recent years, FOBs have been replaced by modern FISs that use video chip and light-emitting diode (LED) technology instead of fiberoptics. An example is the Storz Five Scope, which is a highly portable video bronchoscope for use with the C-MAC VL system.

Indications for FSI essentially include any indication for endotracheal intubation. However, FSI may be the airway management technique of choice in any one of the following clinical scenarios[183]:

- Known or anticipated difficult airway (i.e., cannot intubate or cannot ventilate [CICV])
- Undesirable extension of the neck (e.g., unstable cervical fracture, severe cervical stenosis, vertebral artery insufficiency, Chiari malformation)
- Increased Risk of dental damage (e.g., poor dentition, fragile dental work)
- Limited mouth opening (e.g., TMJ disease, mandibular-maxillary fixation, severe facial burns)

No specific contraindications exist for FSI; however, in certain clinical situations, successful FSI is unlikely. Severe airway bleeding can obscure anatomic landmarks and soil the tip of the FIS with blood, making visualization of the larynx extremely difficult. Obstruction or severe stenosis of the airway, resulting in the inability to pass a FIS can also make FSI impossible.

FSI provides several advantages over DL[183]:

- Allows for a more complete visual examination of the airway before intubation.
- Provides confirmation of tube placement, avoiding esophageal and endobronchial intubation.
- Eliminates the need for three-axis alignment; therefore FSI is among the techniques least likely to result in cervical spine movement.
- Is well-tolerated in awake patients; results in less tachycardia and hypertension.
- Has less of a potential for airway and dental trauma.
- Can be performed in multiple positions.

FSI can be performed in the awake or anesthetized patient. Indications for an awake FSI are generally those situations during which ventilation via a mask is anticipated to be difficult, when a postintubation neurologic examination is needed, or when induction of general anesthesia could cause adverse hemodynamic or respiratory consequences. The major technical disadvantage to performing FSI under general anesthesia is the loss of pharyngeal muscle tone, which can lead to upper airway collapse and difficult fiberoptic laryngoscopy.[183]

Before its use, the anesthesia practitioner or skilled assistant must ensure that the FIS, light source, and video monitor are in proper working condition and that all components have been fully prepared for use. This preparation includes focusing the image if using a FOB, ensuring proper view orientation if using a video camera, lubricating the distal third of the flexible insertion cord, applying antifogging solution to the tip of the scope, and connecting a suction line or oxygen source to the suction port. The ETT should be prepared by placing it in a warm water bath, which softens the plastic, easing passage into the trachea and minimizing airway trauma.

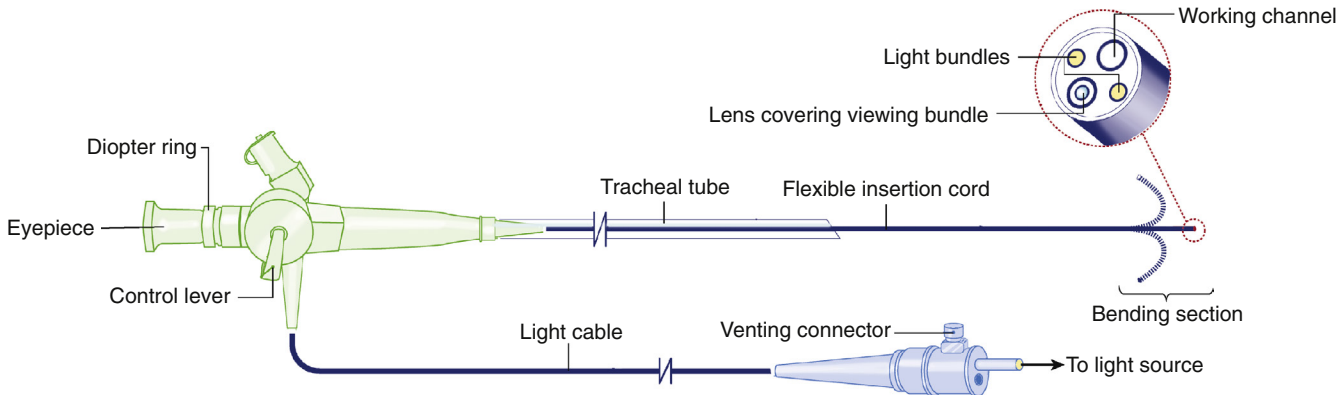


Figure 55-24. Flexible fiberoptic bronchoscope (FOB). *(From Henderson J: Airway management. In Miller RJ, editor:* Anesthesia*, ed 7, Philadelphia, 2009, Churchill Livingstone.)*

FSI is usually performed in the supine or sitting (i.e., beach-chair) position, although emergency FSI in the lateral decubitus or prone position has also been described.[184] When performing FSI in the supine position, the anesthesia provider stands at the head of the patient. Advantages to this position are that the laryngeal view through the FIS is in the same orientation as during DL, and the patient and physician are already in the optimal position to perform mask ventilation or other airway maneuvers, if necessary. When performing FSI with the patient in the sitting or beach-chair position, the practitioner should stand facing the patient at the patient's side. This position may be the position of choice in awake FSI as a result of improved ventilation and greater patient comfort. In addition, the sitting position optimizes airway anatomy and prevents airway collapse in patients who are obese, in patients with obstructive sleep apnea, and in patients with anterior extrinsic airway obstruction.[185]

Before FSI, unless contraindicated, an antisialagogue, such as glycopyrrolate 0.2 mg IV, should be administered to dry airway secretions. Both the orotracheal and nasotracheal routes can be used for FSI. While weighing the advantages and disadvantages, the clinician should determine which approach is best-suited for the clinical situation. Whichever route is chosen, however, essentially two steps to FSI must be taken[183]:

1. Indirect laryngoscopy and endoscopy are performed, obtaining a view of the glottis with the FIS and maneuvering the FIS through the vocal cords into the trachea.
2. The ETT is advanced over the FIS into its proper position in the trachea, and the FIS is removed.

When performing orotracheal FSI navigating the FIS around the base of the tongue to achieve a satisfactory view of the larynx is one of the major challenges. The FIS has a tendency to stray off the midline, and, frequently, little to no airspace is found between the tongue and the palate through which to navigate the FIS. To mitigate this issue, several devices or techniques can be used. Specialized intubating oral airways can be used to protect the FIS from damage by biting, to prevent the tongue from falling back into the pharynx and obstructing the airspace, and to keep the FIS midline while it is guided to the larynx. Several types of intubating oral airways are available, each with unique design differences, and include the Ovassapian, Berman, and Williams airways. A disadvantage of these devices is that they place pressure on the base of the tongue, potentially causing gagging in awake patients. In both awake patients and those under general anesthesia, gentle traction on the tongue anteriorly is helpful in preventing the tongue from falling back into the pharynx if an intubating airway is not used. This traction can be easily accomplished by hand with the help of 4 × 4-inch gauze pads for traction or with Magill forceps. Care should be taken to not injure the tongue on the bottom teeth. As previously described, LMAs and intubating LMAs can also be used as conduits for oral FSI. Obtaining a laryngeal view during nasal FSI is often easier, as compared with the oral approach, which is due to the fact that the FIS stays midline and the tip of the FIS is usually directed at the glottis as it enters the oropharynx.

Once the FIS has been successfully positioned in the oropharynx, the epiglottis and vocal cords can usually be visualized with a slight anterior deflection of the tip of the FIS The FIS is aimed toward the anterior commissure of the vocal cords and posteriorly flexed to enter into the trachea. The trachea is easily identifiable by the presence of the cartilaginous tracheal rings. The FIS is advanced distally until a point just above the carina, and the ETT is advanced over the FIS while continually visualizing the trachea through the FIS, which provides confirmation that the FIS and ETT have not been accidentally dislodged into the oropharynx or esophagus. Frequently, especially with orotracheal intubation, resistance is met as the tip of ETT reaches the glottic inlet. Often, this resistance has been shown to be attributable to the bevel of the ETT impinging on the right arytenoid.[186] A slight withdrawal of the ETT and a counterclockwise 90-degree turn, orienting the bevel posteriorly, usually resolves this issue. For nasotracheal intubation, a clockwise 90-degree turn, ensuring that the bevel is oriented anteriorly, can prevent the tip of the ETT from impinging on the epiglottis.

Alternatively, the Parker Flex-Tip ETT (Parker Medical, Englewood, CO), which has a bull-nosed tip directed toward the center of the distal lumen, can be used. This ETT has been shown to have a high first-pass success rate when being advanced over a FIS.[187]

After the successful passage of the ETT, proper depth (2 to 3 cm from the carina) is confirmed during the withdrawal of the FIS. On rare occasions, the FIS may prove difficult to remove from the ETT, which may be attributable to the FIS having passed through the Murphy eye rather than the distal lumen or a result of inadequate lubrication of the FIS. In these situations, forceful removal may damage the device; therefore the FIS and ETT should be removed as a unit and the procedure repeated.

Rigid Indirect Laryngoscopes

The first indirect laryngoscopes for intubation were based on modifications of the standard direct laryngoscope and used mirrors or prisms to project an image at an angle from the horizontal, facilitating visualization of the larynx. Modern indirect laryngoscopes based on the direct laryngoscope design that uses optical lenses to project a refracted image of the glottis include the Viewmax (Rüsch, Duluth, GA) and the TruView EVO2 (Truphatek, Netanya, Israel).

One of the most well-studied rigid indirect laryngoscopes is the Bullard Elite (Gyrus ACMI, Southborough, MA). This device features an anatomic L-shape, an attachable metal stylet, and a 3.7-mm working channel that can be used for oxygen insufflation, suction, or instillation of local anesthetic. The Bullard laryngoscope has been shown to be especially useful in patients with limited cervical spine mobility or cervical spine injury.[188,189] The blade's 6.4-mm thickness allows its use in patients with minimal mouth opening. The device is rotated over the base of the tongue from the oropharynx into the laryngopharynx. Once the tip of the Bullard is in the appropriate position in relation to the epiglottis, a lifting force is applied to elevate the epiglottis. Visualization of the larynx is optimized by adjusting the lifting force and the position of the tip of the device.[10]

The Airtraq SP (Prodol Meditec S.A., Guecho, Spain) is a disposable, portable, anatomically shaped, optical laryngoscope that provides a magnified view of the glottis without alignment of the oral, pharyngeal, and laryngeal axes. It includes a guiding channel to hold the ETT and direct it toward the vocal cords. It can be used for a variety of applications, including the known or predicted difficult airway, as well as for awake intubation. The Airtraq laryngoscope has been shown to result in more rapid endotracheal intubation with a reduced incidence of esophageal intubation when compared to DL, especially when used by novices.[190] It is available in two adult and two pediatric sizes, as well as in specific designs for nasotracheal intubation and double-lumen tube placement. The Airtraq Avant is a newer model that features a reusable optic piece that is used in combination with disposable blades.

Lighted Optical Stylets

Lighted optical stylets are rigid or semirigid fiberoptic devices that incorporate the optical and light-transmitting components into a tubular, stainless steel sheath over which the ETT is loaded. A substantial body of evidence supports the use of these optical stylets in patients with limited neck mobility,[191] small mouth opening,[192] abnormal airway anatomy,[193] or anticipated difficult laryngoscopy.

The Bonfils retromolar intubation fiberscope (Karl Storz Endoscopy, Tuttlingen, Germany) is a 40-cm long, rigid optical stylet with a fixed anterior tip curvature of 40 degrees.[194] The proximal eyepiece can be used with the naked eye or connected to a video monitor. It is available with a working channel that can be used for suction, SAYGO local anesthesia,[195] or oxygen insufflation (oxygen flow rates should be limited to 3 L/min to avoid barotrauma).[196] The Shikani optical stylet (Clarus Medical, Minneapolis, MN) is a similar device to the Bonfils fiberscope but with a malleable shaft. The Levitan FPS stylet (Clarus Medical, Minneapolis, MN) is a shorter version of the Shikani stylet intended for use in combination with DL, although usable on its own.[197] The Clarus Video System (Clarus Medical, Minneapolis, MN) is a newer version of the Shikani fiberscope that incorporates a liquid crystal display (LCD) screen.

These optical stylets can be used on their own or in combination with DL or video laryngoscopy.[198] The ETT is mounted on the optical stylet and advanced under direct vision via a midline or right paraglossal route until it passes under the tongue. After indirect visualization of the tip of the stylet passing through the vocal cords (via the eyepiece or video monitor), the ETT is advanced over the stylet into the trachea. When these are not used in conjunction with DL or video laryngoscopy, the left hand of the operator should lift the patient's jaw by gently grasping the mandible and displacing it anteriorly. This maneuver helps create more airspace in the oropharynx and lifts the epiglottis. Optical stylets can be used for awake intubation and have also been used for the transillumination technique (see Lighted stylets).[194,199]

The SensaScope (Acutronic, Hirzel, Switzerland) is a new *hybrid* rigid optical stylet that uses video chip technology. It has an S-shaped curvature and a 3-cm long steerable tip.[200] Visualization is achieved by a connection to a video monitor. The SensaScope is designed to be used in combination with DL and has been successfully used for awake intubation in patients with a predicted difficult airway.[201] The Video RIFL (AI Medical Devices, Williamston, MI) is a similar device with a rigid shaft and a flexible, steerable tip. This device features an LCD monitor attached to the handle that displays the video image.

VIDEO LARYNGOSCOPY

As with flexible bronchoscopes, video chip technology has begun to largely replace fiberoptic technology in rigid indirect laryngoscopes because of the advantages of a higher quality image, increased durability, and reduced maintenance costs. Over the past 10 years, VLs have revolutionized the practice of airway management, and their use may become standard not only for difficult airways, but also for routine airways as well. In fact, video

laryngoscopy is now included in the ASA "Difficult Airway Algorithm" as an alternative approach to intubation and should be considered for patients with a known or predicted difficult airway.[4] A VL is also listed as a suggested piece of equipment on a portable difficult airway cart.[4]

VLs have been shown to result in improved glottic visualization, compared with DL, in both routine airway management and in the predicted difficult airway.[4,202] Although this improved visualization does not necessarily translate into increased success with intubation (particularly in the normal airway), studies have shown improved intubation success with video laryngoscopy in patients with predicted difficult airways .[203,204] VLs are also useful in the unexpected difficult airway; intubation success rates of 94% and 99% have been reported for video laryngoscopy as a rescue modality after failed DL.[205,206] These devices have also been successfully used for awake intubation.[207,208]

Various different VLs have been introduced, each with its own design and specific features. Generally, VLs can be divided into three groups: (1) those whose design is based on the Macintosh blade, (2) those who incorporate highly curved or distally angulated blades, and (3) those that incorporate an ETT-guiding channel.[209] Although no single design has been shown to be superior, there are certain clinical circumstances where one style may be preferable to another. Other features that vary among different VLs include the degree of portability and the size of the video monitor. Many VLs are available in both reusable and single-use models.

VLs based on the Macintosh blade design include the C-MAC laryngoscope (Karl Storz, Tuttlingen, Germany), the McGrath MAC laryngoscope (Aircraft Medical, Edinburgh, UK), and the GlideScope Direct intubation trainer (Verathon, Bothell, WA). These devices can be used for both DL and video laryngoscopy, making them particularly useful for teaching the DL technique. The C-MAC laryngoscope is the most extensively studied of these and is associated with shorter intubation times and greater ease of use, compared with other VLs,[210,211] which is possibly due to laryngoscopists' familiarity with the use of a Macintosh-style blade (Figure 55-25). The technique for using the C-MAC laryngoscope is identical to that of DL with a Macintosh blade; the tip of the VL can be used to lift the epiglottis directly.[212] In contrast to other VLs, most intubations with the C-MAC laryngoscope can be performed without the use of a stylet[213,214]; the use of an oral RAE ETT can facilitate endotracheal intubation.[215]

VLs with a distally angulated or highly curved blade permit a "look around the corner," providing an improved laryngoscopic view without requiring manipulation of the cervical spine. These devices are therefore of particular utility in patients with cervical immobilization, micrognathia, or limited mouth opening.[209] The GlideScope (Verathon, Bothell, WA) is the prototype for this subset of devices. It possesses a 60-degree blade angulation, an antifogging mechanism, a 7-inch LCD monitor, and is available in reusable and single-use models. The McGrath Series 5 laryngoscope is a similar device in that it possesses a distally angulated blade; its primary difference is its greater portability and a disarticulating handle that can be useful in patients with limited mouth opening and limited movement of the head and neck.



Figure 55-25. C-MAC video laryngoscope. *(From Cavus E, Dörges V: Video laryngoscopes. In Hagberg CA, editor:* Benumof and Hagberg's airway management*, ed 3, Philadelphia, 2013, Saunders, p. 544.)*

The D-Blade (Karl Storz, Tuttlingen, Germany) is a highly curved VL blade for use with the C-MAC system. These devices are typically inserted in the mouth midline, without sweeping the tongue from right to left as in DL. Because of the high degree of angulation of the blade, an ETT stylet is almost always necessary; malleable stylets with a 60- to 90-degree bend, articulating stylets, and the GlideRite stylet (a rigid stylet with a 90-degree curve specifically designed for use with the GlideScope) have all been successfully used with these VLs.[216,217] The VL and the styletted ETT should be inserted into the oral cavity under direct vision to avoid oropharyngeal trauma.[218]

Some VLs with highly curved blades have integrated tube-guiding channels to facilitate intubation without the use of a stylet, similar to the Airtraq. The King Vision (King Systems, Noblesville, IN) and the Pentax Airway Scope (AWS; Pentax Medical, distributed by Ambu Inc., Glen Burnie, MD) fall into this category. This type of VL has been shown to be useful in patients with cervical immobilization and has been successfully used for awake intubation.[219,220] The VividTrac (Vivid Medical, Palo Alto, CA) is a new single-use, channeled VL with a Universal Serial Bus (USB) interface that works with any monitor.

INTUBATING INTRODUCERS AND STYLETS

Intubating stylets are generally long, slender devices used to assist in guiding an ETT through the glottis. Malleable ETT stylets are frequently used to create an anterior *hockey stick* curvature to an ETT to facilitate tracheal intubation. ETT introducers can be used to perform a blind intubation when the glottic opening cannot be visualized during laryngoscopy (i.e., a Cormack-Lehane Grade III laryngeal view). Lighted stylets are used to blindly intubate the trachea using the transillumination technique.

Endotracheal Tube Introducers

The original ETT guide was the Eschmann introducer, developed by Venn in 1973.[221] This device, also known

as the *gum elastic bougie*, is long enough to allow advancement of an ETT over its distal end after being placed through the vocal cords. It also possesses an anterior angulation at the distal end (coudé tip) to facilitate maneuvering underneath the epiglottis toward the glottic opening, even when the glottic structures are not visualized. A variety of similar introducers with different sizes and features are available; some are hollow to allow for ventilation if the need arises.

Coudé-tip introducers are particularly useful when only a portion of the laryngeal structures, such as only the tip of the epiglottis, can be visualized. Proper placement of the stylet is indicated by the perception of *tracheal clicks* as the coudé tip passes along the tracheal rings and by a *distal hold-up* as it reaches the small bronchi. An ETT is subsequently advanced over the introducer into the correct position.[222]

Lighted Stylets

Lighted stylets make use of the transillumination technique to blindly intubate the trachea and have been described in the literature as an alternative or aid to DL, particularly in the predicted difficult airway. Lighted stylets may be particularly helpful when the presence of blood or heavy secretions limits visualization of the airway. However, because lighted stylet insertion is a blind technique, it is contraindicated in certain clinical situations, such as neoplasm of the airway or airway trauma. Because increased soft tissue leads to difficulty with transillumination, this technique is less useful in the patient who is morbidly obese.[222]

To perform the transillumination technique, an ETT is preloaded onto the stylet. The left hand of the operator lifts the supine patient's jaw by gently grasping the mandible and displacing it anteriorly to facilitate the insertion of the stylet under the tongue. The stylet should be inserted using a retromolar approach. Once inserted, the stylet should be kept midline and advanced under the tongue. A well-circumscribed *glow* (approximately the size of a half dollar) should appear in the midline of the patient's neck at the level of the cricoid cartilage (Figure 55-26), which indicates correct positioning of the stylet within the trachea. Subsequently, the ETT can be advanced over the stylet into proper position.[222]

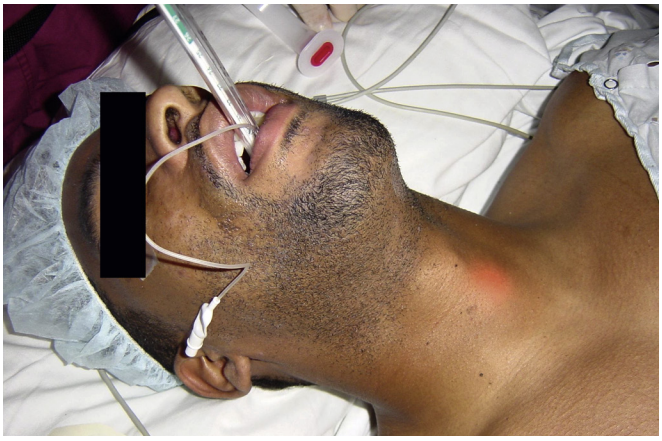


Figure 55-26. When the tip of a lighted stylet is placed at the glottic opening, a well-circumscribed glow can be seen in the anterior neck just below the thyroid prominence.

TRACHEAL INTUBATION THROUGH A SUPRAGLOTTIC AIRWAY DEVICE

The intubating LMA (ILMA), known as the LMA Fastrach (LMA North America, San Diego, CA), was first described by Dr. Archie Brain in 1997; it became available for commercial use in the United States shortly thereafter. The ILMA was designed as a conduit for tracheal intubation to facilitate ventilation between attempts at tracheal intubation. The rigid handle and airway tube enable a rapid and precise control of mask position. An epiglottic elevating bar is designed to elevate the epiglottis as the tube is advanced into the bowl. A disposable, single-use version is available, in addition to the original reusable model. Specialized reusable or single-use tracheal tubes are designed to facilitate atraumatic blind intubation through the ILMA. The tubes are straight, wire-reinforced, and have a soft molded tip designed to prevent impingement on laryngeal structures.

The technique of inserting the ILMA differs in many respects from the insertion of the cLMA, and the learning curve is significant. A *neutral* head position (nonextended head on a support) is recommended. The ILMA handle is used to rotate the mask into the pharynx. Oxygenation, ventilation, and anesthesia are stabilized after insertion. If resistance to ventilation is encountered, then the position of the ILMA is adjusted. The *Chandy maneuver* consists of two separate maneuvers: (1) the ILMA is rotated in the sagittal plane until resistance to bag ventilation is minimal; and then (2) the ILMA is gently lifted from the posterior pharyngeal wall just before passage of the tracheal tube (Figure 55-27). The original, reusable ILMA should be removed soon after tracheal intubation has been verified because its rigidity results in high pressure on adjacent tissues. Although the blind technique has a high rate of success, intubation under vision with a FIS through the ILMA achieves higher first-attempt a overall success rates.

Other SGAs can be used to facilitate endotracheal intubation. The cLMA, although not designed for intubation, can be an effective conduit if used in conjunction with a FIS. Because of the long and narrow airway tube, a microlaryngeal tube should be used. Alternatively, a cLMA can be exchanged for an ETT by using a FIS in conjunction with the Aintree intubation catheter (Cook Critical Care, Bloomington, IN), which is a hollow airway exchange catheter designed to fit over a standard intubating FIS (Figure 55-28). The airQ intubating laryngeal airway (Cookgas, Mercury Medical, Clearwater, FL) is a unique SGA designed for use in both blind and FIS-guided intubation.

RETROGRADE INTUBATION

RI is a well-described technique for orotracheal or nasotracheal intubation that involves guiding an ETT into the trachea with a narrow, flexible guide that has been percutaneously placed through the CTM into the trachea and passed retrograde through the larynx and pharynx,

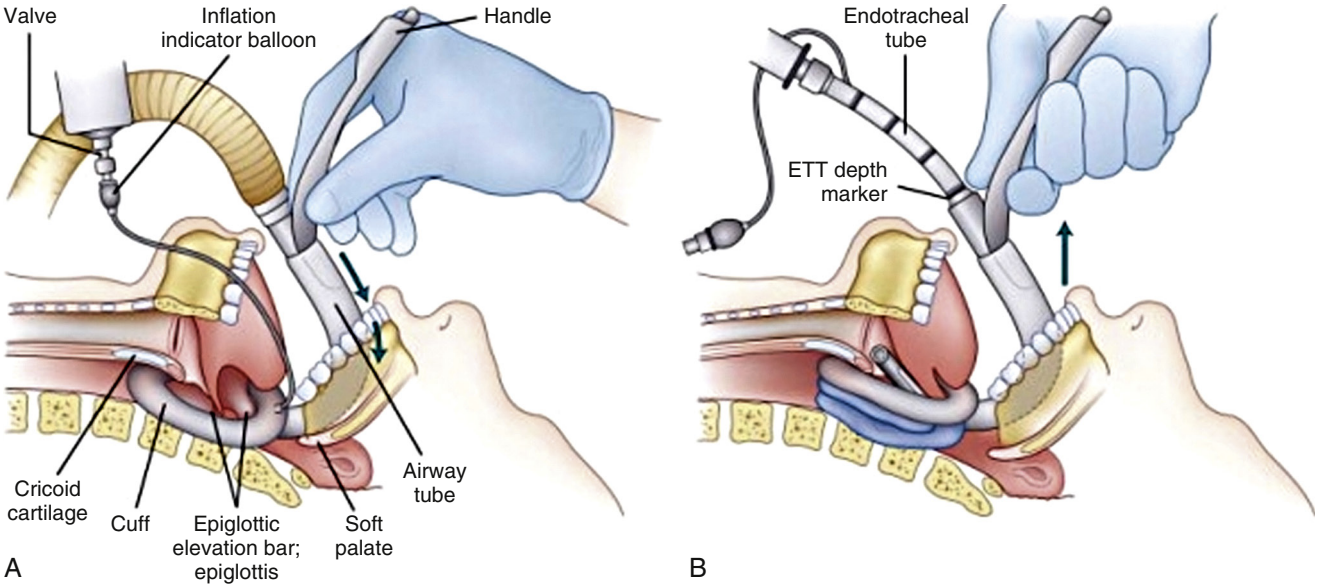


Figure 55-27. The Chandy maneuver consists of two steps. **A,** The first step is important for establishing optimal ventilation. The intubating laryngeal mask airway (ILMA) is slightly rotated in the sagittal plane using the handle until the least resistance to bag ventilation is achieved. **B,** The second step is performed just before blind intubation. The handle is used to lift (but not tilt) the ILMA slightly away from the posterior pharyngeal wall, which facilitates the smooth passage of the endotracheal tube (ETT) into the trachea. *(From Verghese C, Mena G, Ferson DZ, Brain AIJ: Laryngeal mask airway. In Hagberg CA, editor:* Benumof and Hagberg's airway management*, ed 3, Philadelphia, 2013, Saunders, p. 457.)*

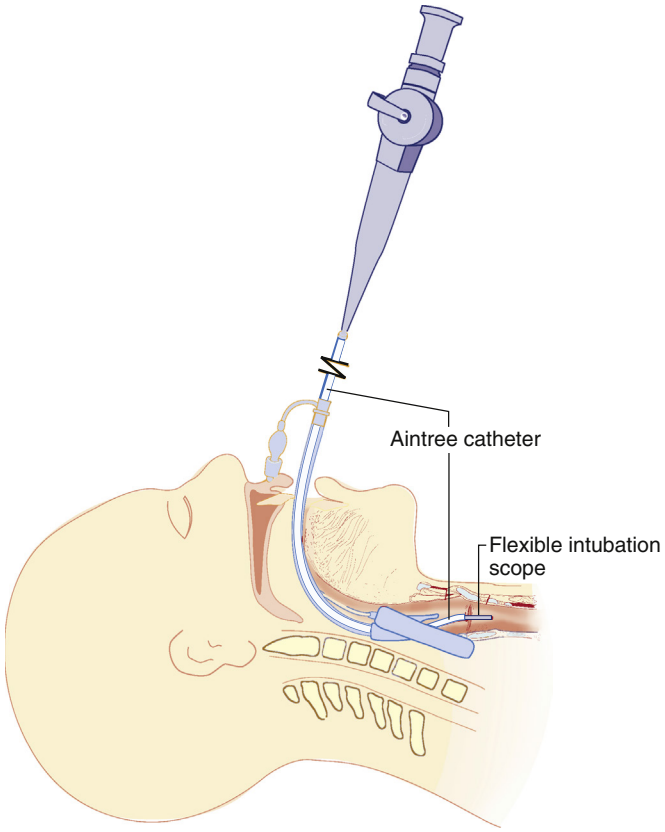


Figure 55-28. Aintree intubating catheter within a flexible intubation scope, inserted through a laryngeal mask airway. *(From Henderson J: Airway management. In Miller RJ, editor:* Anesthesia*, ed 7, Philadelphia, 2009, Churchill Livingstone.)*

exiting the mouth or nose. The guide is typically a steel guidewire, although an epidural catheter can be used. This technique has several modifications, each with its own benefits and disadvantages, and can be successfully used in awake, sedated, obtunded, or apneic patients who have either an anticipated or unanticipated difficult airway.[223] Indications include failure of DL; obstruction of the view of the vocal cords by blood, secretions, or anatomic derangement; and difficult intubation scenarios such as unstable cervical spine, ankylosing spondylitis, maxillofacial trauma, or trismus. RI is also an alternative to FSI in developing countries where the availability of FISs is limited.[223]

The ASA "Difficult Airway Algorithm" describes RI as an alternative approach to difficult intubation in the nonemergent pathway, when intubation is unsuccessful but mask ventilation is adequate. It is suggested that equipment for RI be included in a portable storage unit for difficult airway management. RI can take several minutes to accomplish; therefore this technique is contraindicated in an emergent CICV scenario.[223] Other contraindications are generally relative and include anatomic abnormalities (e.g., malignancy, goiter) that preclude access to the CTM, tracheal stenosis at the level of the CTM, coagulopathy, and local infection.

The ideal position for RI is supine with the neck in extension, allowing easy palpation of the cricoid cartilage and surrounding structures. If this position is not possible, then RI can also be performed with the patient in the sitting position or with the neck in a neutral position. If landmarks are difficult to identify, then ultrasound guidance may be used. The anterior neck should be cleansed before puncture, and aseptic technique should be used. The translaryngeal puncture site can be performed superior or inferior to the cricoid

cartilage. The CTM (superior to the cricoid cartilage) has the advantage of being relatively avascular; however, a puncture at this site allows only 1 cm of space below the level of the vocal cords for the tip of the ETT. A puncture site inferior to the cricoid cartilage, at the cricotracheal ligament, allows the ETT to travel in a straight path with a long length of the ETT below the vocal cords; however, this site is associated with a greater potential for bleeding.[223]

The classic technique for RI involves using a Tuohy needle to puncture the CTM and an epidural catheter as the guide. More commonly, an IV catheter and a steel guidewire are used. The diameter of the guidewire should be small enough to fit through the IV catheter and should be at least twice as long as the ETT to be used; a guidewire with a .038″ diameter (which passes through an 18-gauge IV catheter) and a length of 110 cm is commonly used. Commercial kits are available that include all necessary equipment. Performing a RI with a J-tip, steel guidewire rather than an epidural catheter provides the following advantages: the J-tip of a guidewire is less traumatic to airway; the guidewire has a lower tendency to coil or kink retrieval of the guidewire from the oral or nasal cavity is easier; and the technique is quicker.[223]

Once the patient has been positioned, the operator's nondominant hand stabilizes the trachea by placing the thumb and third digit on either side of the cricoid cartilage. The index finger is used to identify the midline of the CTM and the upper border of the cricoid cartilage. A syringe half-filled with saline is attached to an 18-gauge angiocatheter and advanced at a 90-degree angle to the CTM with the bevel facing cephalad, aspirating for air bubbles to confirm the position inside the trachea. The angle of insertion is slightly lowered, and the needle is removed. At this stage, reconfirmation of a position within the trachea and instillation of a local anesthetic can be performed with a second syringe filled with 2 to 4 mL of 2% or 4% lidocaine. This transtracheal block can provide additional comfort to a patient who is awake or sedated and undergoing RI, or it can reduce the incidence of sympathetic stimulation and laryngospasm in a patient under general anesthesia.

The guidewire is then advanced through the angiocatheter until it exits the mouth or nose. DL can be used to facilitate the wire exiting the mouth, if necessary. The guidewire is clamped with a hemostat at the level of the skin of the neck to prevent migration. Although the ETT can then be directly advanced over the guidewire, a tapered guide catheter (e.g., Arndt airway exchange catheter) is useful to reduce the discrepancy in diameter between the guide-wire and the ETT, which can predispose the ETT to catch on the arytenoids or vocal cords rather than smoothly slide into the trachea. The guide catheter is placed over the portion of the wire exiting the mouth or nose and advanced until it contacts the CTM. The wire is then removed, and an ETT is advanced over the guide catheter (Figure 55-29). Potential complications include bleeding (usually minimal), subcutaneous emphysema, pneumomediastinum, pneumothorax, and injury to the posterior trachea or esophagus.[223]

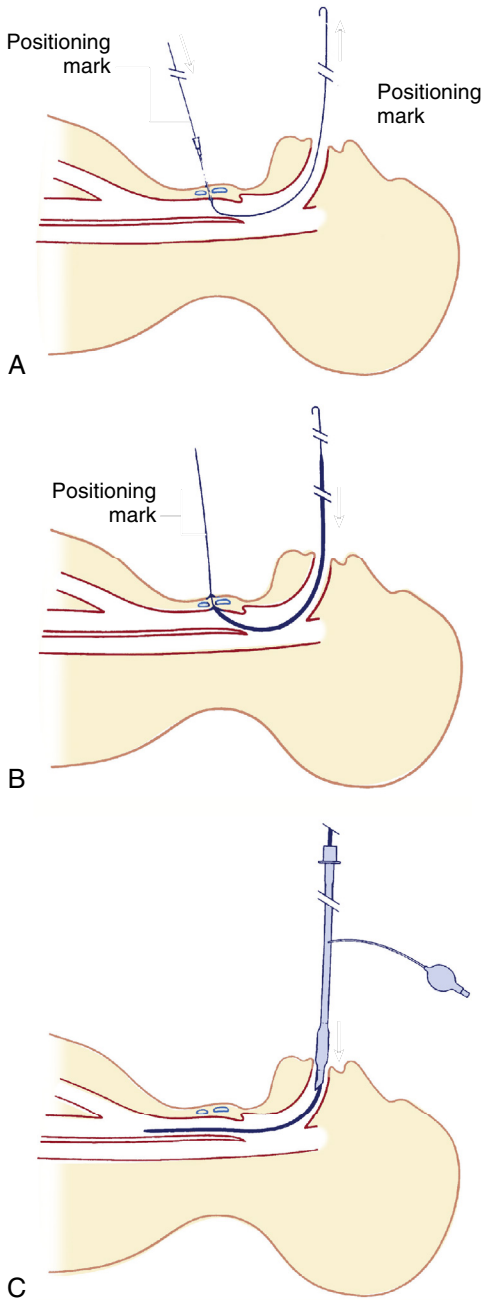


Figure 55-29. The guidewire technique for retrograde intubation. **A,** After the placement of an 18-gauge angiocatheter through the cricothyroid membrane (CTM), the J-tip of the guidewire is inserted in a cephalad direction until it exits the mouth or nose. **B,** The guide catheter is threaded over the guidewire until it contacts the laryngeal access site. The guidewire is then removed from above. **C,** After advancing the guide catheter 2 to 3 cm, the endotracheal tube is advanced into the trachea. *(Courtesy of Cook Critical Care, Bloomington, IN.)*

DOUBLE-LUMEN TUBES AND BRONCHIAL BLOCKERS

Single-lung ventilation is required for certain clinical circumstances, including protective lung isolation from infection or hemorrhage, attaining adequate exposure for surgical procedures (e.g., video-assisted thoracoscopy), and for controlling the distribution of ventilation in the

setting of major bronchial surgery, trauma, or fistula. Double-lumen tubes (DLTs) and bronchial blockers are two options that allow for ventilation of only one lung (also see Chapter 66).

DLTs have a bronchial lumen and a tracheal lumen. They are designated as left sided or right sided, depending on whether the bronchial lumen goes to the left or right main bronchus. Most commonly, a left-sided DLT is used to avoid blockage of the right upper lobe bronchus. DLTs are placed in a similar fashion to the standard ETT, although placement is usually more difficult attributable to their size and stiffness. Video laryngoscopy can facilitate DLT placement.[224] After placing the DLT into the trachea, verification of the location of the bronchial port with a FIS should be determined. The blue bronchial cuff should be positioned just below the carina in the appropriate bronchus. Inflation of the blue bronchial balloon under direct visualization helps verify proper placement. Care should be taken to ensure that the bronchial cuff does not herniate over the carina. Once the DLT is properly placed, isolating a lung is possible by inflating the bronchial cuff and clamping either the tracheal or bronchial connector.

Bronchial blockers are essentially hollow, balloon-tipped catheters that are endobronchially placed to isolate and deflate one lung. In some clinical situations, lung isolation is required, but the use of a DLT is not practical, because of a difficult airway, decreased size of the tracheal lumen, or the need for postoperative mechanical ventilation. In these instances, the use of a modified single-lumen tube with an integrated bronchial blocker (e.g., the Univent [Fuji Systems, Tokyo, Japan]) or the use of a bronchial blocker in conjunction with a standard ETT is appropriate.

PERCUTANEOUS AIRWAYS

Percutaneous (invasive) airways are indicated as a rescue technique when attempts at establishing a noninvasive airway fail. They may also be used as a primary airway in some difficult airway situations when attempts at securing a noninvasive airway are likely to fail, such as a patient with a laryngeal neoplasm and critical airway obstruction. Options for invasive airway access include transtracheal jet ventilation (TTJV), cricothyrotomy, and tracheostomy. Whereas tracheostomy is usually performed by a surgeon, the anesthesia practitioner should become proficient with the techniques for TTJV and cricothyrotomy; the situation will inevitably arise in which an invasive airway will become necessary. An emergent situation is not the time to become familiar with a new technique.

TRANSTRACHEAL JET VENTILATION

Percutaneous TTJV is a relatively quick and effective but invasive method of oxygenation and ventilation in the CICV scenario when more conservative measures fail. The ASA "Difficult Airway Algorithm" lists TTJV as an emergent invasive technique to be used in patients who cannot be conventionally ventilated or intubated.[4] TTJV is widely regarded as a life-saving procedure that can provide adequate, temporary oxygenation and ventilation with less training and complications than a surgical airway, a last resort for obtaining an airway in the algorithm.[225] Nonetheless, TTJV is an invasive technique, and its primary use is as an emergency airway. Occasionally, it is used on an elective basis for laryngeal surgery.

Inspiration during TTJV is achieved by insufflation of pressurized oxygen through a cannula placed by needle cricothyrotomy. Expiration is passive as a result of the elastic recoil of the lungs and the chest wall. Allowing sufficient time for passive expiration to avoid barotrauma from breath stacking is imperative. Expiration occurs through the glottis and depends on a nonobstructed upper airway, which is imperative to avoid barotrauma and resulting pneumothorax. The egress of air through the glottic aperture can also provide bubbles to facilitate the placement of an ETT. In fact, several case reports have demonstrated that after the initiation of TTJV in an airway with little or no visualization of the glottis, successful intubation occurred because of the opening of the glottis and guidance from the bubbles with jet ventilation.[225]

TTJV should not be performed in patients who have sustained direct damage to the cricoid cartilage or larynx or in patients with complete upper airway obstruction. Other relative contraindications to TTJV include coagulopathy, obstructive pulmonary disease, and distorted anatomy in which catheter placement might be difficult.

Typically, a 12- to 16-gauge kink-resistant catheter is used for TTJV. A coil-reinforced 6 Fr catheter (Cook Critical Care, Bloomington, IN) is specifically designed for TTJV to prevent kinking, and its Teflon coating facilitates its passage through the CTM into the trachea. The technique for placement is similar to the technique for RI, with the exception that the needle is inserted with the bevel facing caudally. Confirmation of proper intratracheal placement of the catheter by testing for aspiration of air is imperative before initiating jet ventilation.

The minimum pressure required to drive a jet ventilator is 15 psi. The pipeline pressure for oxygen in hospitals in the United States is approximately 55 psi. Commercially available jet ventilators generally contain pressure regulators to lower the pipeline pressure to provide successful jet ventilation while avoiding higher pressures that might result in barotrauma. In most instances in the operating room, adequate pressure for jet ventilation can be achieved by connecting straight to the pipeline supply. Difficulty usually arises in locations outside of the surgical unit where TTJV may be needed but adequate driving pressure is not available.[225]

A major complication of TTJV is barotrauma with resulting pneumothorax from the use of high-pressure oxygen. To prevent this complication, ensuring that a path for air egress exists and that adequate time for passive expiration is available is an absolute necessity. The lowest possible pressure that will provide adequate oxygenation and ventilation should be used. Other complications associated with TTJV include subcutaneous or mediastinal emphysema, hemorrhage, aspiration, and perforation of the posterior wall of the trachea or esophagus.[225]

CRICOTHYROTOMY

Cricothyrotomy is an invasive technique that provides access to the airway in situations when either noninvasive maneuvers have failed or when it is clinically indicated as a primary plan to secure the airway.[226] Cricothyrotomy is included in the ASA "Difficult Airway Algorithm" as an emergent invasive technique after other rescue maneuvers have failed or are not feasible. Cricothyrotomy equipment should be included in all emergency airway storage units and readily available. Cricothyrotomy is not considered a permanent airway, and, after placement, plans should be made for either the removal of the cricothyrotomy catheter or conversion to a formal tracheostomy.[226]

In children younger than 6 years of age (also see Chapter 93), the cricoid cartilage is the narrowest portion of the airway and the isthmus of the thyroid gland typically reaches the level of the CTM; therefore cricothyrotomy is contraindicated. Needle cricothyrotomy with TTJV is indicated in this pediatric population. Other contraindications to cricothyrotomy include laryngeal fractures, laryngeal neoplasm, subglottic stenosis, coagulopathy, and distorted or unidentifiable neck anatomy.

The two most common techniques for performing a cricothyrotomy are the percutaneous dilational cricothyrotomy and the surgical cricothyrotomy. For the anesthesiologist, the percutaneous technique is usually preferred because the technique is less complicated compared with a surgical cricothyrotomy, and because of the familiarity of using the Seldinger technique for other procedures (e.g., central venous catheterization). Because of the location of the cricothyroid artery and the proximity of the CTM to the vocal folds, puncture or incision of the CTM should be made in the lower third of the membrane and directed posteriorly (Figure 55-30).[226]

A number of commercially available cricothyrotomy kits use the percutaneous dilational technique. The basis for this procedure is the insertion of an airway catheter over a dilator that has been inserted over a guidewire. The patient's neck is extended, and the cricothyroid groove is identified. If landmarks are difficult to identify, then ultrasound guidance may be used. A 1- to 1.5-cm vertical incision is made through the skin overlying the CTM. An 18-gauge needle-catheter attached to a fluid-filled syringe is passed through the incision at a 45-degree angle in the caudal direction with continuous aspiration. Aspiration of free air confirms passage through the CTM. The catheter is advanced over the needle into the trachea. The needle is removed, and the catheter is left in place. The guidewire is inserted caudally to a depth of approximately 2 to 3 cm. The catheter is removed, and the curved dilator with the airway cannula is threaded over the guidewire. The dilator and cannula unit is advanced through the CTM while maintaining control of the guidewire. The dilator and guidewire are removed together while the cannula remains in place. The cuff is inflated, and ventilation is attempted. Proper placement is confirmed by capnography, and the airway cannula is secured in place.[226]

Surgical cricothyrotomy is performed using the technique outlined in Box 55-4. A No. 20 scalpel is preferred because its width is sufficient for inserting a narrow tube without the need for extending the incision, and its length is such that damage to the posterior wall of the trachea is unlikely. This technique is the most rapid and should be used when equipment for the less invasive techniques is unavailable and speed is particularly important.[10]

Complications include hemorrhage, injury to the posterior tracheal wall or esophagus, vocal cord injury, laceration of the thyroid gland, and improper insertion of the cannula. Placement of the airway cannula in the subcutaneous tissue can result in subcutaneous or mediastinal emphysema. Late complications from cricothyrotomy include swallowing dysfunction, infection, voice changes, and tracheal stenosis. Tracheal stenosis has an incidence of approximately 2% to 8% in adults and is more likely if preexisting trauma or infection is present.

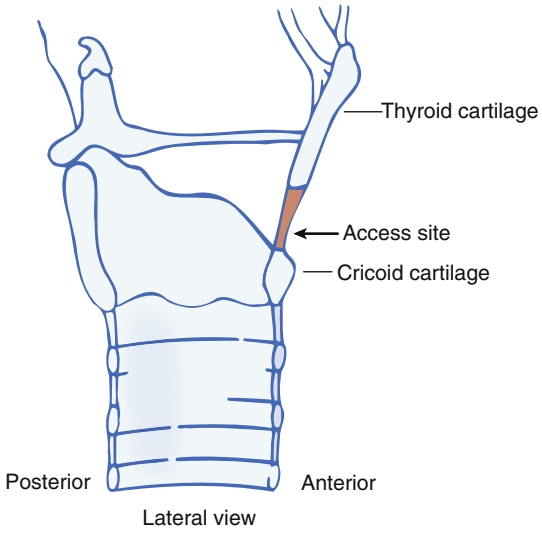


Figure 55-30. Midsagittal anatomy of the larynx and trachea. The access point for percutaneous cricothyrotomy is in the lower third of the cricothyroid membrane. *(Courtesy of Cook Critical Care; Bloomington, IN.)*

BOX 55-4 *Surgical Cricothyrotomy*

EQUIPMENT

- No. 20 scalpel
- Cuffed tracheostomy tube or endotracheal tube (ETT) with a 6- or 7-mm internal diameter

TECHNIQUE

- Step 1: Extend the head and neck, and identify and immobilize the cricothyroid membrane. (Make an initial vertical incision if identification is not possible.)
- Step 2: Make a horizontal stab incision through the skin and cricothyroid membrane. Leave the blade in place until the tracheal hook is in position (step 3).
- Step 3: Apply caudal and outward traction on the cricoid cartilage with the tracheal hook; remove the scalpel.
- Step 4: Insert the tube, and inflate the cuff.
- Step 5: Ventilate with a low-pressure source.
- Step 6: Confirm pulmonary ventilation.

Modified from Henderson J: Airway management. In Miller RJ, editor: Anesthesia*, ed 7, Philadelphia, 2009, Churchill Livingstone.*

BOX 55-5 ***Complications Associated With Extubation***

- Laryngospasm and bronchospasm
- Upper airway obstruction
- Hypoventilation
- Hemodynamic changes (hypertension, tachycardia)
- Coughing and straining, leading to surgical wound dehiscence
- Laryngeal or airway edema
- Negative-pressure pulmonary edema
- Paradoxical vocal cord motion
- Arytenoid dislocation
- Aspiration

EXTUBATION OF THE TRACHEA

A critical component of airway management is the process of extubation. Although considerable emphasis is placed on the problems that can arise during induction and intubation, the risk for complications can potentially be more frequent during extubation of the trachea.[227] Analysis of the ASA Closed Claims database has shown that although the number of claims for death and brain damage during intubation have decreased since the adoption of the ASA *Practice Guidelines for Management of the Difficult Airway*, the number of claims arising from injury at extubation and during recovery have not decreased.[1] In response to these trends and in the absence of any well-established strategies for the management of tracheal extubation, the Difficult Airway Society (DAS) established a set of guidelines in 2012 to "discuss the problems arising during extubation and recovery" and to "promote a strategic, stepwise approach to extubation."[228]

A number of complications can arise during extubation (Box 55-5); although some of these complications are minor with no long-term sequelae, others can lead to a failed extubation. Failed extubation can result from the failure of oxygenation, failure of ventilation, inadequate clearance of pulmonary secretions, or loss of airway patency.[229] If an airway is not quickly reestablished, then serious complications, including death, may result. As such, the anesthesia practitioner needs to stratify the extubation risk preemptively and establish an extubation plan before attempting extubation. Per the DAS guidelines, risk stratification can be accomplished by considering the following: (1) whether the airway was normal and uncomplicated at induction; (2) whether the airway has become difficult to manage as a result of surgical changes, trauma, or nonsurgical factors; and (3) whether the patient has general risk factors for an unsuccessful extubation.[228]

GENERAL CONSIDERATIONS FOR EXTUBATION OF THE TRACHEA

For both routine and difficult extubation scenarios, an extubation plan must be preemptively formulated, including a plan for reintubation that can be implemented should the patient be unable to maintain an adequate airway after extubation.[4] The decision of whether to extubate the trachea when the patient is fully awake versus a *deep* extubation before the return of consciousness should be made based on the risks and benefits of each technique. The awake patient can more easily maintain a patent airway, attributable to the recovery of awake pharyngeal muscle tone and airway reflexes. Deep extubation avoids coughing and adverse hemodynamic effects but risks upper airway obstruction and hypoventilation. An alternative extubation technique, known as the Bailey maneuver, involves exchanging an ETT for an SGA while the patient is under deep anesthesia.[230] Extubation during a light plane of anesthesia (stage II) can increase the risk for laryngospasm and other airway complications and should be avoided.

General preparations for extubation should include ensuring adequate reversal or recovery from neuromuscular blockade, hemodynamic stability, normothermia, and adequate analgesia. Patients should be preoxygenated with a 100% fraction of inspired oxygen concentration (Fio_2), and alveolar recruitment maneuvers should be considered if appropriate. Suctioning of the pharynx (and the trachea, if indicated), the removal of throat packs, and the placement of a bite block should be performed while the patient is under deep anesthesia.[10] Bite blocks are essential for an awake intubation to prevent biting of the tube during emergence, which can result in airway obstruction and the development of negative-pressure pulmonary edema. Oropharyngeal airways are not recommended for use as a bite block because they can result in dental damage; rather, taped, rolled gauze securely inserted between the molars should be used.[231]

Gastric insufflation with air can increase the risk of pulmonary aspiration after extubation and can impede ventilation. Patients in whom mask ventilation with high pressures is necessary should have an orogastric tube placed and suctioned before extubation.

The sniffing position is the standard position for extubation; its major advantage is that the patient is optimally positioned for airway management, if necessary. Patients who are morbidly obese and other patients at risk for hypoventilation and airway obstruction can benefit from extubation in the head-up position. The lateral decubitus position may be the preferred option when the risk for pulmonary aspiration is high.[10]

Application of positive pressure immediately before cuff deflation may help expel secretions that have collected above the ETT cuff. Inspection of the pilot balloon to ensure complete cuff deflation before extubation is essential; extubation with an inflated cuff can cause vocal cord injury or arytenoid dislocation.

EXTUBATION OF THE DIFFICULT AIRWAY

Many surgical and anesthetic factors can increase extubation risk; a summary of the most pertinent factors is listed in Box 55-6. Although several techniques can be used to manage extubation of the difficult airway, including the Bailey maneuver and remifentanil infusion,[228] the use of an airway exchange catheter (AEC) is most common and recommended by the ASA's Task Force on Management of the Difficult Airway. This hollow reintubation guide is passed through the ETT before extubation and kept in situ until the possible need for reintubation has passed. AECs have the additional capability of maintaining

BOX 55-6 ***Factors Associated With Increased Extubation Risk***

Airway Risk Factors

- Known difficult airway
- Airway deterioration (bleeding, edema, trauma)
- Restricted airway access
- Obesity and obstructive sleep apnea
- Aspiration risk

General Risk Factors

- Cardiovascular disease
- Respiratory disease
- Neuromuscular disease
- Metabolic derangements
- Special surgical requirements

Modified from Popat M, Mitchell V, Dravid R, et al: Difficult Airway Society Guidelines for the management of tracheal extubation, Anaesthesia *67:318-340, 2012.*

oxygenation or monitoring respiration by connection to a capnograph. Smaller AECs (11 Fr) are generally well-tolerated by awake patients, who can breathe, talk, and cough around them. They should be secured with tape in place to prevent accidental dislodgement and labeled to distinguish them from traditional feeding tubes, which can have a similar appearance. Reintubation over an AEC, if necessary, can be facilitated by gentle DL to retract the tongue and oropharyngeal soft tissue.

SUMMARY

Airway management is at the core of safe anesthetic practice. The anesthesia practitioner must have a fundamental knowledge of airway anatomy, physiology, and pharmacology, and well-developed skills in the use of a wide variety of airway devices. Although most airways are straightforward, management of the difficult airway remains one of the most relevant and challenging tasks for anesthesia care providers. Prediction and anticipation of the difficult airway and the formulation of an airway management plan are essential. Many airway problems can be solved with relatively simple devices and techniques; however, experience and good clinical judgment are necessary for their successful application. Newer airway devices with the potential to improve patient outcomes are continually being developed. Anesthesia providers must concurrently develop their skills and learn new techniques to be prepared when difficulty presents itself. Competency-based training with routine assessment of clinical ability with airway techniques is likely in the future for all practitioners involved in airway management. Expertise comes from dedicated practice and a commitment from the practitioner for career-long learning.

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Chapter 56

Spinal, Epidural, and Caudal Anesthesia

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Key Points

- The distal termination of the spinal cord varies from L3 in infants to the lower border of L1 in adults.
- The speed of neural blockade depends on the size, surface area, and degree of myelination of the nerve fibers exposed to the local anesthetic.
- Blockade of the peripheral (T1-L2) and cardiac (T1-T4) sympathetic fibers is responsible for the decrease in arterial blood pressure (cardiac output and systemic vascular resistance) associated with neuraxial techniques.
- Cerebrospinal fluid volume and local anesthetic baricity are the most important determinants for the spread (i.e., block height) of spinal anesthesia.
- The use of smaller-gauge spinal needles decreases the incidence of post–dural puncture headache.
- Serious neurologic complications associated with neuraxial blockade are rare.
- The use of low-molecular-weight heparin and potent platelet inhibitors increases the risk of epidural hematoma from neuraxial blockade.
- Epidural blood patches are greater than 90% effective in relieving post–dural puncture headache.
- Local anesthetic systemic toxicity results from unintentional administration of the drug into an epidural vein.
- Use of neuraxial blockade can reduce perioperative morbidity and mortality.

PRINCIPLES

Spinal, epidural, and caudal neuraxial blocks result in one or a combination of sympathetic blockade, sensory blockade, or motor blockade depending on the dose, concentration, or volume of local anesthetic administered. Despite these similarities, there are significant technical, physiologic, and pharmacologic differences. Spinal anesthesia requires a small mass (i.e., volume) of drug that is almost devoid of systemic pharmacologic effects to produce rapid (<5 minutes), profound, reproducible sensory analgesia. In contrast, epidural and caudal anesthesia progress more slowly (>20 minutes) after a large mass of local anesthetic that produces pharmacologically active systemic blood levels, which may be associated with side effects and complications unknown to spinal anesthesia. The introduction of combined spinal and epidural techniques blurs some of these differences, but also adds flexibility to clinical care.

PRACTICE

Neuraxial blockade has a wide range of clinical applications for surgery, obstetrics, acute postoperative pain management, and chronic pain relief. Single-injection spinal or epidural anesthesia with local anesthetic is most commonly used for surgery to the lower abdomen, pelvic organs (e.g., prostate), and lower limbs, and for cesarean deliveries. Continuous catheter-based epidural infusions of dilute local anesthetics and opioids are used for obstetric labor analgesia and postoperative pain relief after major surgery (e.g., thoracic, abdominal, lower limb) to provide analgesia for days. Evidence demonstrating that epidural analgesia can reduce cardiovascular and pulmonary morbidity and mortality in high-risk patients undergoing major thoracic and abdominal surgery served to propel the practice of epidural analgesia at the beginning of the millennium.[1] More recently, however, the goals of epidural analgesia have shifted from reduction of morbidity and mortality in high-risk patients to facilitation of fast-track

recovery in otherwise healthy patients undergoing various types of elective inpatient surgical procedures. Caudal blocks are mostly performed for surgical anesthesia and analgesia in children, and for therapeutic analgesia in adults with chronic pain. Indwelling spinal catheters can be applied long term (from months to years) for the treatment of chronic malignant and nonmalignant pain.

HISTORICAL PERSPECTIVES

The first case of spinal anesthesia in humans was performed by August Bier in 1898 using the local anesthetic cocaine.[2] Subsequently, spinal anesthesia was successfully performed using procaine by Braun in 1905, tetracaine by Sise in 1935, lidocaine by Gordh in 1949, chloroprocaine by Foldes and McNall in 1952, mepivacaine by Dhunér and Sternberg in 1961, and bupivacaine by Emblem in 1966. Spinal anesthesia using ropivacaine and levobupivacaine was introduced in the 1980s. The year 1901 marked the first reported use of intrathecal morphine described by Racoviceanu-Pitesti, as well as the first description of caudal anesthesia reported by Cathleen. Lumbar epidural anesthesia in humans was first described by Pagés in 1921, the loss-of-resistance technique by Dogliotti in the 1930s, continuous caudal for obstetrics by Hingson in 1941, and lumbar epidural catheterization for surgery by Curbelo in 1947.[3] The use of epidural morphine analgesia was first reported by Behar in 1979.

Despite the extensive experience using neuraxial techniques throughout the past century, several events caused major setbacks along the way, including the Woolley and Roe case detailing paraplegia after spinal anesthesia in 1954,[4] the reports of persistent neurologic deficits and adhesive arachnoiditis with spinal chloroprocaine in the early 1980s, and cauda equina syndrome with continuous spinal lidocaine anesthesia in the early 1990s.[5] More recently, the potential for catastrophic epidural hematoma with newer potent anticoagulants (e.g., low-molecular-weight heparin [LMWH]) and antiplatelet agents (e.g., clopidogrel) has caused concern.[6]

ANATOMY

The spinal cord is continuous with the brainstem proximally and terminates distally in the conus medullaris as the filum terminale (fibrous extension) and the cauda equina (neural extension). This distal termination varies from L3 in infants to the lower border of L1 in adults because of differential growth rates between the bony vertebral canal and the central nervous system.

Surrounding the spinal cord in the bony vertebral column are three membranes (from innermost to outermost): the pia mater, the arachnoid mater, and the dura mater (Fig. 56-1). The cerebrospinal fluid (CSF) resides in the space between the pia mater and the arachnoid mater, termed the *subarachnoid* (or *intrathecal*) *space*. The pia mater is a highly vascular membrane that closely invests the spinal cord and brain. Approximately 500 mL of CSF is formed daily by the choroid plexuses of the cerebral ventricles, with 30 to 80 mL occupying the subarachnoid

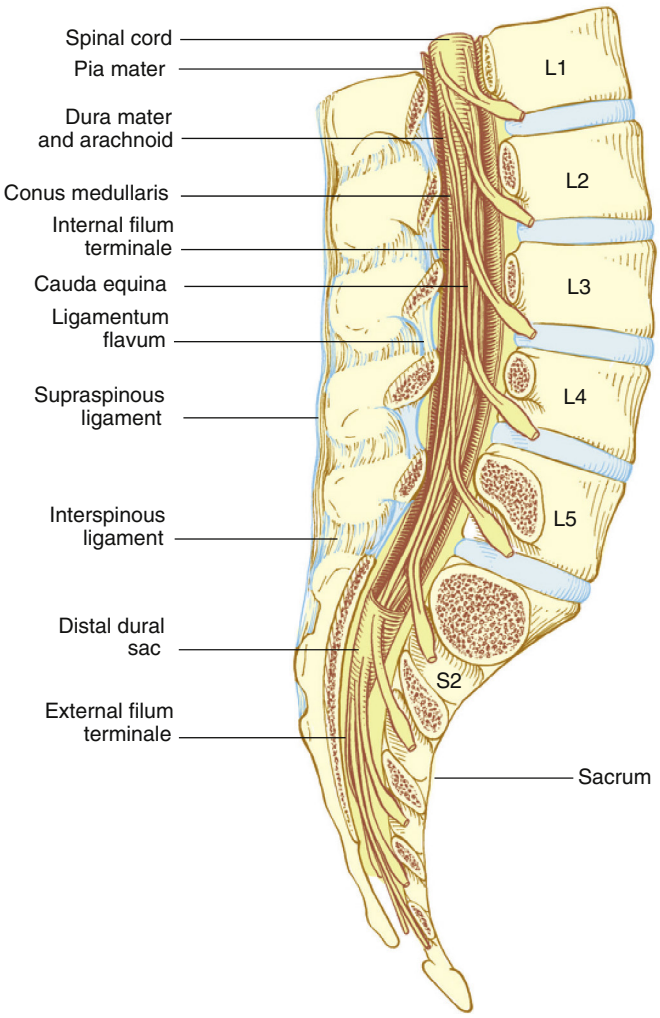


Figure 56-1. Spinal cord anatomy. Notice the termination of the spinal cord (i.e., conus medullaris) at L1-L2 and termination of the dural sac at S2.

space from T11-T12 downward. The arachnoid mater is a delicate, nonvascular membrane that functions as the principal barrier to drugs crossing into (and out of) the CSF and is estimated to account for 90% of the resistance to drug migration.[7] As Liu and McDonald[8] and Bernards[9] emphasize, the functional proof of the arachnoid's role as the primary barrier to flow is the observation that spinal CSF resides in the subarachnoid, and not the subdural, space. The outermost layer is the dura.

Surrounding the dura mater is the epidural space, which extends from the foramen magnum to the sacral hiatus and surrounds the dura mater anteriorly, laterally, and posteriorly. The epidural space is bound anteriorly by the posterior longitudinal ligaments, laterally by the pedicles and intervertebral foramina, and posteriorly by the ligamentum flavum. Contents of the epidural space include the nerve roots and fat, areolar tissue, lymphatics, and blood vessels including the well-organized Batson venous plexus.

Posterior to the epidural space is the ligamentum flavum (the so-called yellow ligament), which also extends from the foramen magnum to the sacral hiatus. Although classically portrayed as a single ligament, it is actually

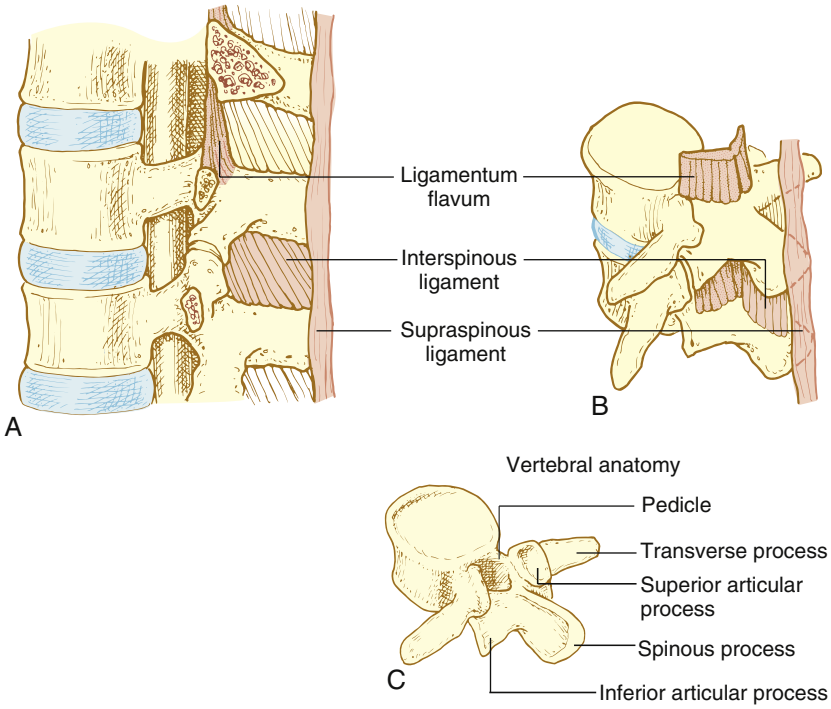


Figure 56-2. Vertebral anatomy. **A,** Sagittal view. **B,** Oblique view of the lumbar vertebrae showing the ligamentum flavum thickening in the caudad extent of the intervertebral space and in the midline. **C,** Oblique view of a single lumbar vertebra.

comprised of two ligamenta flava—the right and the left—which join in the middle and form an acute angle with a ventral opening (Fig. 56-2).[10,11] The ligamentum flavum is not uniform from skull to sacrum, nor even within an intervertebral space. Ligament thickness, distance to the dura, and skin-to-dura distance vary with the area of the vertebral canal. The vertebral canal is triangular and largest in area at the lumbar levels, and it is circular and smallest in area at the thoracic levels. The two ligamenta flava are variably joined (fused) in the midline, and this fusion or lack of fusion of the ligamenta flava even occurs at different vertebral levels in individual patients.[10] Immediately posterior to the ligamentum flavum are the lamina and spinous processes of vertebral bodies or the interspinous ligaments. Extending from the external occipital protuberance to the coccyx posterior to these structures is the supraspinous ligament, which joins the vertebral spines (see Fig. 56-2).

There are 12 thoracic vertebrae, 5 lumbar vertebrae, and a sacrum. The vertebral arch, spinous process, pedicles, and laminae form the posterior elements of the vertebra, and the vertebral body forms the anterior element. The vertebrae are joined together anteriorly by the fibrocartilaginous joints with the central disks containing the nucleus pulposus, and posteriorly by the zygapophyseal (facet) joints. The thoracic spinous process is angulated steeply caudad as opposed to the almost horizontal angulation of the lumbar spinous process. This is a clinically important distinction for needle insertion and advancement in the thoracic versus lumbar levels.

The sacral canal contains the terminal portion of the dural sac, which typically ends at S2. Variation is found in this feature as well, with the termination of the dural sac being lower in children. In addition to the dural sac, the sacral canal contains a venous plexus, which is part of the valveless internal vertebral venous plexus. The volume of the caudal canal in adults, excluding the foramina and dural sac, is about 10 to 27 mL. Perhaps this wide variability in volume accounts for some of the variation in block height with caudal anesthesia (Fig. 56-3).[12]

BLOOD SUPPLY

Blood is supplied to the spinal cord from one anterior spinal artery (originating from the vertebral artery), two posterior spinal arteries (originating from the inferior cerebellar artery), and the segmental spinal arteries (originating from the intercostal and lumbar arteries).[13] The spinal arteries enter the spinal canal at each intervertebral foramen and give off branches to both the nerve roots and the medullary branches to the spinal cord; one of the major branches is the artery of Adamkiewicz, variably entering between T7 and L4 on the left, which supplies the lower thoracic and upper lumbar regions. The anterior two thirds of the spinal cord is supplied by the anterior arterial branches and the posterior one third by the posterior branches. The anterior and deep portion of the cord (gray matter) is most prone to ischemia (leading to anterior horn motor neuron injury, or anterior spinal syndrome) because there are fewer anterior medullary feeder vessels than posterior feeder vessels. Likewise, the midthoracic part of the spinal cord (from T3 to T9) is most at risk where segmental medullary feeder vessels are rare. Venous drainage of the spinal cord follows a similar distribution as the spinal arteries. There are three longitudinal anterior spinal veins and three posterior spinal veins that communicate with the segmental anterior and posterior radicular veins before draining into the internal vertebral venous plexus in the medial and lateral components of the epidural space. There are no veins in the posterior epidural space except those caudal to the L5-S1 disk.

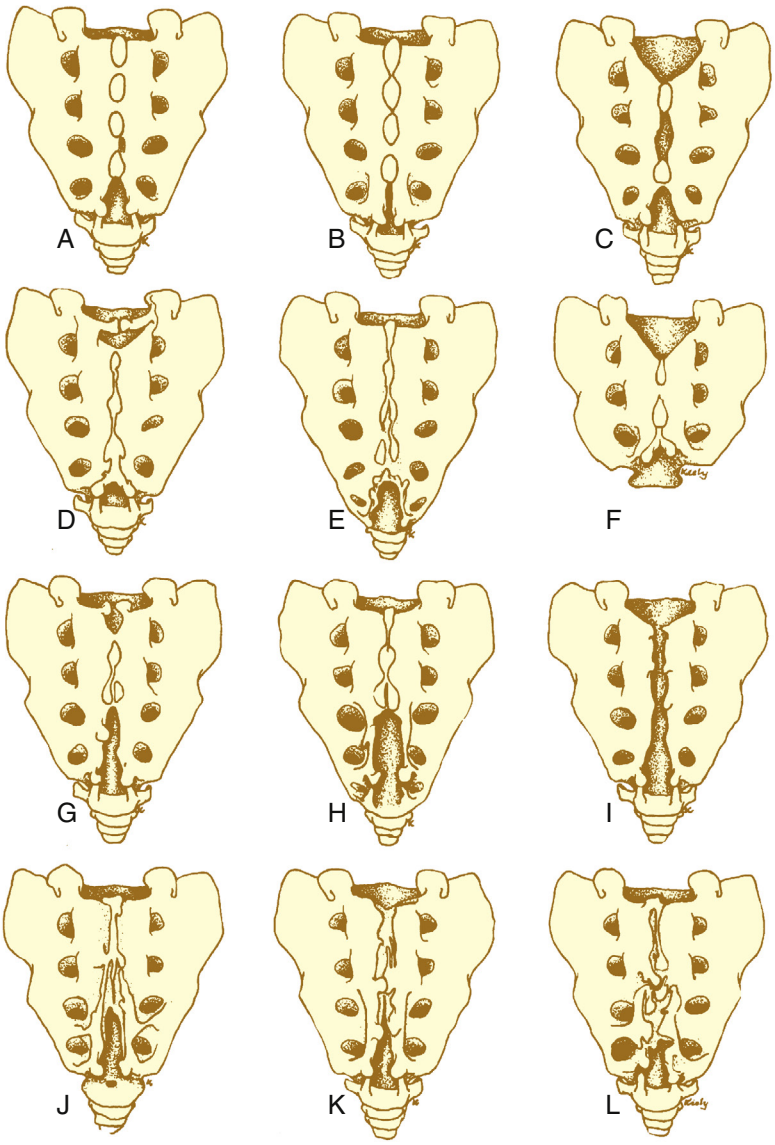


Figure 56-3. Anatomic variants of the sacrum and sacral hiatus. **A,** Normal. **B,** Longitudinal slitlike hiatus. **C,** Second midline hiatus. **D,** Transverse hiatus. **E,** Large hiatus with absent cornua. **F,** Transverse hiatus with absent coccyx, two prominent cornua, and two proximal "decoy hiatuses lateral to the cornua." **G-I,** Large midline defects contiguous with the sacral hiatus. **J-L,** Enlarged longitudinal hiatuses, each with an overlying decoy hiatus. *(From Willis RJ: Caudal epidural block. In Cousins MN, Bridenbaugh PO, editors:* Neural blockade in clinical anesthesia and management of pain*, ed 2, Philadelphia, 1988, JB Lippincott, p 365.)*

ANATOMIC VARIATIONS

NERVE ROOTS

The spinal nerve roots are not uniform in size and structure. Specifically, Hogan and Toth[14,15] have shown that there is considerable interindividual variability in nerve root size. These differences may help to explain the interpatient differences in neuraxial block quality when equivalent techniques are used on seemingly similar patients. Another anatomic relationship may affect neuraxial blocks; although generally larger than the ventral (motor) roots, the dorsal (sensory) roots are often blocked more easily. This apparent paradox is explained by organization of the dorsal roots into component bundles, which creates a much larger surface area on which the local anesthetics act, possibly explaining why larger sensory nerves are blocked more easily than smaller motor nerves.[8]

CEREBROSPINAL FLUID

Lumbosacral CSF has a constant pressure of approximately 15 cm H_2O, but its volume varies by patient, in part because of differences in body habitus and weight.[16] It is estimated that CSF volume accounts for 80% of the variability in peak block height and regression of sensory and motor blockade. Nevertheless, except for body weight (less CSF in subjects with high body mass index [BMI]), the volume of CSF does not correlate with other anthropomorphic measurements available clinically.[17] (see Factors Affecting Block Height, later in the chapter)

EPIDURAL SPACE

Hogan's[10] study of frozen cryomicrotome cadaver sections suggests that the epidural space is more segmented and less uniform than previously believed from indirect anatomic analysis. Another study by Hogan[18] has also

shown in cadavers that the spread of solution after epidural injection into the tissues of the epidural space is nonuniform, and he postulated that this accounts for the clinical unpredictability of epidural drug spread. This lack of uniformity also extends to age-related differences. There is evidence that adipose tissue in the epidural space diminishes with age,[19] and this decrease in epidural space adipose tissue may dominate the age-related changes in epidural dose requirements (see Chapter 80).

MECHANISM OF ACTION

Local anesthetic binding to nerve tissue disrupts nerve transmission, resulting in neural blockade. For spinal and epidural anesthesia, the target binding sites are located within the spinal cord (superficial and deep portions) and on the spinal nerve roots in the subarachnoid and epidural spaces. The spinal nerve roots and dorsal root ganglia are considered the most important sites of action. Nerves in the subarachnoid space are highly accessible and easily anesthetized, even with a small dose of local anesthetic, compared with the extradural nerves, which are often ensheathed by dura mater (the "dural sleeve"). The speed of neural blockade depends on the size, surface area, and degree of myelination of the nerve fibers exposed to the local anesthetic. Anatomic studies show that the S1 and L5 posterior roots are the largest and thus most resistant to blockade during epidural anesthesia.[15] Smaller nerves are more sensitive to the effects of local anesthetics because of their relatively high membrane surface area to axon unit volume ratio. For example, the small preganglionic sympathetic fibers (B fibers, 1 to 3 μm, minimally myelinated) are most sensitive to local anesthetic blockade. Among the sensory nerves, the C fibers (0.3 to 1 μm, unmyelinated), which conduct cold temperature sensation, are blocked more readily or earlier than the A-delta fibers (1 to 4 μm, myelinated), which conduct pinprick sensation. The A-beta fibers (5 to 12 μm, myelinated), which conduct touch sensation, are the last to be affected among the sensory fibers. The larger A-alpha motor fibers (12 to 20 μm, myelinated) are more resistant than any of the sensory fibers. Regression of blockade ("recovery") follows in the reverse order: motor function followed first by touch, then pinprick, and finally cold sensation.[20] Another manifestation of relative sensitivity or susceptibility to the effects of local anesthetics is the observed differences in the peak block height (highest or most cephalad level of anesthesia) according to each sensory modality, which is termed *differential sensory block*. For example, the level of anesthesia to cold sensation (also an approximate level of sympathetic blockade) is most cephalad and is on average one to two spinal segments higher than the level of pinprick anesthesia, which in turn is one to two segments higher than the level of touch anesthesia.[21]

DRUG UPTAKE

When local anesthetic is injected directly into the subarachnoid space during spinal anesthesia, it diffuses through the pia mater and penetrates through the spaces of Virchow-Robin (extensions of the subarachnoid space accompanying the blood vessels that invaginate the spinal cord from the pia mater) to reach the deeper dorsal root ganglia.[22] Furthermore, a portion of the subarachnoid drug diffuses outward through the arachnoid and dura mater to enter the epidural space,[23] whereas some is taken up by the blood vessels of the pia and dura maters.[24]

Drug penetration and uptake is directly proportionate to the drug mass, CSF drug concentration, contact surface area, lipid content (high in spinal cord and myelinated nerves), and local tissue vascular supply, but is inversely related to nerve root size. The concentration of local anesthetic in the CSF is highest at the site of subarachnoid injection in the case of spinal anesthesia (generally L2-L4 levels).

For epidural anesthesia, drug uptake is more complex. Some of the injected local anesthetic will move from the epidural space through the meninges into the CSF to exert its neural blocking effect, whereas some will be lost through vascular absorption into the capillary vessels and into the systemic circulation and uptake into epidural fat. The bioavailability of local anesthetics found in the CSF after epidural administration is low (<20%).

DRUG DISTRIBUTION

Diffusion is the primary mechanism of local anesthetic distribution in the CSF from areas of high concentration (i.e., at the site of injection) toward other segments of the spinal cord with low drug concentration.[25] Rostral spread after the administration of a small local anesthetic dose, often evident within 10 to 20 minutes, is related to the CSF circulation time. Longitudinal oscillations generated by the pulsations of the arteries in the skull are believed to be responsible for CSF bulk flow. This likely facilitates the cephalad distribution of local anesthetic from the lumbar subarachnoid space to the basal cisterns within 1 hour of injection.

Drug distribution in the epidural space is more complex, with possible contributions from one, some, or all of the following mechanisms: (1) crossing the dura mater into the subarachnoid space, (2) rostral and caudal (longitudinal) spread within the epidural space, (3) circumferential spread within the epidural space, (4) exit of the epidural space through the intervertebral foramina, (5) binding to epidural fat, and (6) vascular absorption into the epidural vessels. Longitudinal spread of local anesthetic by bulk flow within the epidural space may occur after the administration of a larger dose (i.e., volume). Factors that may enhance the distribution of local anesthetic within the epidural space are small caliber (greater spread in the thoracic space), increased epidural space compliance, decreased epidural fat content, decreased local anesthetic leakage through the intervertebral foramina (e.g., elderly and spinal stenosis), and increased epidural pressure (e.g., pregnancy).[26] Drug is also preferentially distributed from areas of high to low concentration. Finally, the direction of drug spread varies with the vertebral level—that is, epidural spread is mostly cephalad in the lumbar region, caudad after a high thoracic injection, and mostly cephalad spread after a low thoracic injection.[26]

DRUG ELIMINATION

Regression of neural blockade results from a decline in the CSF drug concentration, which in turn is caused by nonneural tissue uptake and, most importantly, vascular absorption. Time for block regression is also inversely correlated with CSF volume.[27] Drug is absorbed by the vessels in the pia mater or the epidural vessels through back diffusion before entering the systemic circulation. No drug metabolism takes place in the CSF. The rate of elimination is also dependent on the distribution of local anesthetic; greater spread will expose the drug to a larger area for vascular absorption and thus a shorter duration of action. Lipid-soluble local anesthetics (e.g., bupivacaine) bind to epidural fat to form a depot that can slow vascular absorption.

PHYSIOLOGIC EFFECTS

Safe conduct of spinal, epidural, and caudal anesthesia requires an appreciation of their physiologic effects. Neuraxial anesthesia evokes blockade of the sympathetic and somatic (sensory and motor) nervous systems, along with compensatory reflexes and unopposed parasympathetic activity.[28] The physiologic effects of epidural anesthesia are similar to those of spinal anesthesia, with the exception that local anesthetic blood levels reach concentrations sufficient enough to produce systemic effects on their own.

CARDIOVASCULAR

The effects of neuraxial blocks on blood pressure are similar in some ways to the combined use of intravenous α_1- and β-adrenergic blockers on cardiac output: decreased stroke volume and heart rate (see Chapter 20) caused by blockade of the peripheral (T1-L2) and cardiac (T1-T4) sympathetic fibers as well as adrenal medullary secretion. The decrease in arterial blood pressure is believed to be more gradual and of less magnitude with epidural than with spinal anesthesia of comparable levels. However, when tetracaine (10 mg) spinal anesthesia was compared with lidocaine (20 to 25 mL of a 1.5% solution) epidural anesthesia, there was a larger decrease in arterial blood pressure (approximately 10%) with the epidural technique than with the spinal anesthetic.[29] Of prime importance, the extent to which arterial blood pressure decreases with either technique depends on multiple factors, including patient age and intravascular volume status.

Stroke Volume

Sympathectomy usually decreases stroke volume. Venous and arterial vasodilation reduces preload (venous return) and afterload (systemic vascular resistance), respectively. Because of the large amount of blood that resides in the venous system (approximately 75% of the total blood volume), the venodilation effect predominates, owing to the limited amount of smooth muscle in venules; in contrast, the vascular smooth muscle on the arterial side of the circulation retains a considerable degree of autonomous tone. Cardiac output is thought to be either maintained or slightly decreased during the onset of spinal anesthesia. Yet a biphasic response, characterized by an early transient increase followed by an eventual decrease in cardiac output,[30] has been observed. This initial increase is caused by a greater magnitude of decline in the systemic vascular resistance than by venous return, especially in elderly patients with preexisting hypertension and high baseline systemic vascular resistance (also see Chapter 80).

The vasodilatory changes after neuraxial blockade that can affect cardiac output depend on each patient's baseline sympathetic tone (i.e., higher sympathetic tone in the elderly equates to a greater hemodynamic change) and the extent of the sympathectomy (i.e., the height of the block). The extent of the sympathectomy is typically described as extending for two to six dermatomes above the sensory block level with spinal anesthesia and at the same level with epidural anesthesia.[31] If normal cardiac output is maintained, systemic vascular resistance should decrease only 15% to 18% after neuraxial blockade in healthy normovolemic patients, even with nearly total sympathectomy. In elderly patients with cardiac disease, systemic vascular resistance may decrease almost 25% after spinal anesthesia, whereas cardiac output decreases only 10%.[32] Determination of baseline autonomic nervous system activity (e.g., blood pressure variability signaled by low-frequency band power and near-infrared spectroscopy reduction) has been found to predict the risk of hypotension in the elderly.[30]

Heart Rate

Heart rate may decrease during a high neuraxial block as a result of blockade of the cardioaccelerator fibers arising from T1-T4.

Heart rate may also decrease in the presence of extensive peripheral sympathectomy (T5-L2), with venous pooling in the lower extremity and the abdominal and pelvic viscera. Although hypotension will trigger a compensatory baroreceptor sympathetic response (vasoconstriction and increased heart rate) above the level of blockade, the reduction in venous return and right atrial filling causes a decrease in signal output from intrinsic chronotropic stretch receptors located in the right atrium and great veins,[31] leading to a marked increase in parasympathetic activity (vagal tone). The two opposing responses are usually in check with a minimal change in heart rate (or a slight reduction). However, when neuraxial anesthesia is extended to the T1 level, blockade of the cardioaccelerator fibers in addition to a marked reduction in venous return may result in severe bradycardia and even asystole because of unopposed parasympathetic activity. However rare, the likelihood of cardiac arrest appears to be more likely in young, healthy, and conscious patients.[33] The Bezold-Jarisch reflex may be a possible cause of profound bradycardia and circulatory collapse after spinal anesthesia, especially in the presence of hypovolemia, when a small end-systolic left ventricular volume may trigger a mechanoreceptor-mediated bradycardia.[34]

Coronary Blood Flow

When coronary artery blood flow and myocardial metabolism were determined in humans during spinal anesthesia

to T4 in hypertensive and normotensive patients, decreases in coronary blood flow (153 to 74 mL/100 g per minute) paralleled the decrease in mean arterial blood pressure (119 to 62 mm Hg), and the percent extraction of myocardial oxygen was unchanged (75% to 72%). Extraction of oxygen was unchanged because myocardial work, as expressed by myocardial use of oxygen, paralleled the decrease in mean arterial blood pressure and coronary blood flow (16 to 7.5 mL/100 g per minute).[35] A high thoracic block in patients with ischemic heart disease can be beneficial, with improvement in global and regional myocardial function and reversal of ischemic changes likely a result of reduced myocardial oxygen demand and left ventricular afterload.[36] Both infarction size and ischemia-induced arrhythmias improved in coronary occlusion experiments in animals, with no apparent vasodilatory effect on the coronary vessels.[37] These data support the observations by Stanley and co-workers[38] but still do not provide a patient-by-patient indication of the organ most at risk for flow-related ischemia.

Treatment

The clinical question of what level of decrease in arterial blood pressure after a neuraxial block is acceptable without a significant decrease in organ perfusion (e.g., brain, liver, gut) remains to be answered, although some human and animal data are available (see respective sections). Once arterial blood pressure decreases to a level at which treatment is believed to be necessary, ephedrine, a mixed adrenergic agonist, provides more appropriate therapy for the noncardiac circulatory sequelae of neuraxial block than does a pure α-adrenergic agonist (see Chapters 16 and 20), unless the patient has a specific and defined arterial blood pressure requirement.[39] That the decrease in arterial blood pressure after neuraxial block can be minimized by the administration of crystalloids intravenously is probably not a valid concept. Specifically, 250- to 2000-mL preblock hydration regimens may temporarily increase preload and cardiac output but do not consistently increase arterial blood pressure or prevent hypotension.[8] Useful techniques to prevent hypotension include the repeated low-dose local anesthetic boluses through a continuous spinal catheter,[40] small-dose unilateral spinal anesthesia, and selective small-dose spinal anesthesia.

CENTRAL NERVOUS SYSTEM

Spinal anesthesia–induced hypotension may decrease regional cerebral blood flow (CBF) in elderly patients and those with preexisting hypertension. In a study of elderly patients who had hypotension during bupivacaine spinal anesthesia, Minville and colleagues demonstrated a significant but transient decrease of middle cerebral artery blood flow velocity and an increase in cerebral vascular resistance, both of which suggest a decrease in cerebral perfusion.[41] There was no change in cognitive function after surgery in any of these patients. Both CBF and velocity decline as a result of changes in the cerebral vasculature, especially in the elderly. Whether cerebral autoregulation is impaired in the elderly is still debatable (see Chapter 80).

Kety and colleagues[42] demonstrated that producing spinal anesthesia to the midthoracic levels with procaine, even in patients with essential hypertension, results in a decrease in mean arterial blood pressure of 26% (155 to 115 mm Hg) accompanied by a 12% (52 to 46 mL/100 g per minute) decrease in CBF. When the level of spinal anesthesia was purposely increased to produce higher levels of block (T4) in normotensive and hypertensive patients, CBF was unchanged in the normotensive group (45 to 46 mL/100 g per minute), whereas a 19% decrease occurred in the apparently untreated hypertensive patients (46.5 to 37.5 mL/100 g per minute).[43]

RESPIRATORY

Alterations in pulmonary variables in healthy and even in elderly patients during neuraxial block are usually of little clinical consequence.[44] A decrease in vital capacity follows a reduction in expiratory reserve volume related to paralysis of the abdominal muscles necessary for forced exhalation rather than a decrease in phrenic or diaphragmatic function.[45] Blockade of the intercostal and abdominal muscles during neuraxial anesthesia is adequately compensated by unaltered function of the diaphragm and other accessory respiratory muscles (e.g., sternomastoid, scalenes), especially for forceful inspiration and expiration.[46] Nonetheless, neuraxial block should be used cautiously in the setting of severe respiratory disease because paralysis of the intercostal and abdominal muscles is common. However rare, respiratory arrest associated with spinal anesthesia is often unrelated to phrenic or inspiratory dysfunction but rather to hypoperfusion of the respiratory centers in the brainstem. Supportive evidence for this concept is observed after resuscitation, when apnea almost always disappears as soon as pharmacologic and intravascular fluid therapies have restored cardiac output and arterial blood pressure.

Pregnancy

In young healthy pregnant women undergoing cesarean delivery, spinal bupivacaine, ropivacaine, and levobupivacaine affect pulmonary function minimally (a reduction of 3% to 6% for forced vital capacity [FVC] and 6% to 13% for peak expiratory flow rate [PEFR]), irrespective of the peak sensory block level.[47] However, in overweight pregnant women, vital capacity declines even more (24% vs 11%) and recovers more slowly compared with normal-weight pregnant women after hyperbaric spinal bupivacaine administration (see also Chapter 77).[48]

Obesity (Also see Chapter 71)

The impact of spinal anesthesia on lung volume variables is significantly reduced compared with general anesthesia[49] but is significantly more in overweight patients than in normal-weight patients.[48] The magnitude of decline in vital capacity is proportional to the BMI value (vital capacity –19% for BMI 30 to 40 kg/m^2 versus –33% for BMI >40 kg/m^2).[50] Importantly, however, for obese patients undergoing laparotomy surgery, thoracic epidural anesthesia lessens the extent of decline in postoperative vital capacity and hastens recovery when compared with parenterally administered opioids.[49]

GASTROINTESTINAL

Neuraxial blockade from T6 to L1 disrupts splanchnic sympathetic innervation to the gastrointestinal tract, resulting in a contracted gut and hyperperistalsis. Nausea and vomiting may be associated with neuraxial block in as much as 20% of patients and they are primarily related to gastrointestinal hyperperistalsis caused by unopposed parasympathetic (vagal) activity.[51] Atropine is effective in treating nausea associated with high (T5) subarachnoid anesthesia.[52]

Thoracic epidural anesthesia (TEA) has a direct blood pressure–dependent effect on intestinal perfusion.[53] TEA improves anastomotic mucosal blood flow in patients undergoing esophagectomy when mean arterial blood pressure is minimally altered but worsens local perfusion when arterial blood pressure is decreased by about 50%. In colorectal surgery, TEA decreases anastomotic blood flow but improves gastric and transverse colonic blood flow.[54] Correction of systemic hypotension by vasopressor therapy (e.g., norepinephrine) has been found to reverse impaired colonic perfusion. TEA may also reduce the rate of anastomotic leak after emergency laparotomy, esophageal surgery,[55] and other gastrointestinal interventions.[56]

A reduction in hepatic blood flow parallels the reduction in mean systemic arterial pressure in the setting of spinal anesthesia.[57] Although lumbar epidural anesthesia also results in a decline in hepatic perfusion despite colloid preloading in young and elderly patients, hepatic perfusion can increase, though mildly (<10%), with TEA after major abdominal surgery.[57]

RENAL

Despite a predictable decrease in renal blood flow accompanying neuraxial blockade, this decrease is of little physiologic importance.[58,59] One aspect of genitourinary function of clinical importance is the belief that neuraxial blocks are a frequent cause of urinary retention, which delays discharge of outpatients and necessitates bladder catheterization in inpatients (see Complications–Urinary Retention, later in the chapter). However, this belief is questionable. For example, in orthopedic patients undergoing hip replacement, bladder catheterization was no more frequent after spinal or epidural anesthesia than it was after general anesthesia and opioid analgesics. In any case, excessive volumes of intravenous crystalloid solutions should not be given to patients undergoing spinal anesthesia. The requirement for voiding before discharge in low-risk ambulatory surgery patients after short-acting spinal or epidural anesthetics should be encouraged.[60]

INDICATIONS

At the most basic level, neuraxial blockade is indicated when the surgical procedure can be accomplished with a spinal level of anesthesia that does not produce adverse patient outcomes. The level of anesthesia or analgesia required is of prime importance because the physiologic effects of a high-level block may be untenable.

NEURAXIAL ANESTHESIA

When considering neuraxial anesthesia, the nature and duration of surgery, patient comorbidities, the ease of spinal insertion (i.e., positioning and spinal pathology), and the relative benefits and risks to the individual are important. Spinal anesthesia is most commonly used for patients who require surgical anesthesia for procedures of known duration that involve the lower extremities, perineum, pelvic girdle, or lower abdomen. Descriptions of spinal anesthesia as the primary surgical anesthetic have more recently expanded to include lumbar spine surgery,[61] as well as upper abdominal procedures, such as laparoscopic cholecystectomy.[62] Spinal anesthesia may be useful when patients wish to remain conscious or when comorbidities such as severe respiratory disease or a difficult airway increase the risks of using general anesthesia. Epidural anesthesia can also be used for the lower extremities, perineum, pelvic girdle, or lower abdomen, but by virtue of intermittent or continuous catheter-based local anesthetic delivery, the duration of surgical anesthesia is not necessarily finite as it is with single-injection spinal anesthesia. Continuous catheter-based spinal anesthesia is arguably less conventional than either single-shot spinal anesthesia or catheter-based epidural anesthesia, but may be especially useful when insertion of an epidural catheter is challenging[63] or in the setting of severe cardiac disease when the reliability of a single-shot spinal anesthetic must be combined with more hemodynamically stable incremental dosing.

NEURAXIAL ANALGESIA

Local anesthetics (as well as other additives, discussed later) applied to the neuraxis in subanesthetic doses can provide potent, long-lasting analgesia for a variety of indications, including intraoperative analgesia, acute postsurgical pain,[64] and severe chronic pain associated with malignancy. The use of intrathecal and/or epidural opioids either alone or in combination with local anesthetics can provide excellent quality pain relief[65,66] and are an analgesic mainstay in labor and delivery,[67,68] during and after hip[69] or knee replacement,[70] in laparotomy,[71] in thoracotomy,[72] and increasingly even in cardiac surgery.[73,74] Some of the most important benefits of epidural analgesia are realized in patients with preexisting respiratory disease undergoing abdominal surgery.[75] Neuraxial analgesia may have other beneficial outcomes beyond analgesia and these are reviewed later.

CONTRAINDICATIONS

ABSOLUTE

There are few absolute contraindications to neuraxial blockade. Some of the most important include patient refusal, localized sepsis, and an allergy to any of the drugs planned for administration. A patient's inability to maintain stillness during needle puncture, which can expose the neural structures to traumatic injury,[76] as well as raised intracranial pressure, which may theoretically predispose

to brainstem herniation,[77] should also be considered absolute contraindications to a neuraxial technique.

RELATIVE

Relative contraindications must be weighed against the potential benefits of neuraxial blockade. Relative contraindications can be approached by system.

Neurologic

Myelopathy or Peripheral Neuropathy. The proof that neuraxial anesthesia or analgesia in the setting of preexisting neurologic deficit can worsen the extent of injury (so-called double-crush phenomenon) is absent.[78-80] Chronic low back pain without neurologic deficit is not a contraindication to neuraxial blockade. The association between neuraxial techniques and the exacerbation of back pain symptoms is not documented.

Spinal Stenosis. Patients with spinal stenosis may be at increased risk of neurologic complications after neuraxial blockade,[81] but the relative contribution of surgical factors and natural history of the spinal pathology itself is unknown.

Spine Surgery. Previous spine surgery does not predispose patients to an increased risk of neurologic complications after neuraxial blockade.[81,82] However, depending on postsurgical anatomy and the presence of scar tissue, adhesions, hardware, and/or bone grafts, needle access to the CSF, or epidural space and/or epidural catheter insertion may be challenging or impossible. In addition, the resultant spread of local anesthetic in the CSF or epidural space can be unpredictable and incomplete.

Multiple Sclerosis. Patients with multiple sclerosis (MS) may be more sensitive to neuraxial local anesthetics and thus exhibit a prolonged duration of motor and sensory blockade; however, any association between neuraxial anesthesia and exacerbation of MS symptoms is not based in evidence.[83,84]

Spina Bifida. Depending on the severity of the neural tube defect, patients with spina bifida may have a tethered cord and the ligamentum flavum may be absent, thereby increasing the potential for traumatic needle injury to the spinal cord. The spread of local anesthetic in the CSF and epidural space (if present) can be highly variable.

If a neuraxial technique is undertaken in any of these circumstances, a careful evaluation of neurologic status must first be undertaken and noted along with documentation of the discussion of the risks and benefits.

Cardiac (Also see Chapter 67)

Aortic Stenosis or Fixed Cardiac Output. The unpredictable speed and extent to which systemic vascular resistance is reduced after spinal anesthesia may cause many providers to avoid spinal anesthesia in preload-dependent patients and try to prevent a dangerous decrease in coronary perfusion. This concern is borne of theoretic risk and a great deal of caution rather than evidence.[85] Clinical practice mandates that neuraxial anesthesia be considered individually for each patient with aortic stenosis in the context of their own disease severity, left ventricular function, and case urgency. A catheter-based neuraxial anesthetic, whether it is an epidural or intrathecal catheter, allows for the repeated administration of small doses of local anesthetic, with potentially more control over hemodynamic changes, and may be a logical alternative choice.

Hypovolemia. An extension of patients who are preload-dependent, hypovolemic patients may exhibit an exaggerated hypotensive response to the vasodilatory effects of neuraxial blockade.

Hematologic

Thromboprophylaxis. Borne of the catastrophic cases of spinal hematoma causing paralysis associated with the introduction and use of LMWH in the United States (U.S. FDA public health advisory: reports of epidural or spinal hematomas with the concurrent use of low molecular weight heparin and spinal/epidural anesthesia or spinal puncture. U.S. Department of Health and Human Resources, 1997), the American Society of Regional Anesthesia and Pain Medicine (ASRA) first published a practice advisory to guide the provision of neuraxial techniques in patients receiving antithrombotic or thrombolytic therapy in 2004. Now in its third iteration and addressing a myriad of novel potent oral anticoagulants, the ASRA practice advisory[6] is an invaluable resource for providers performing neuraxial techniques in this challenging and ever-growing patient population. A summary of the ASRA guidelines, along with those of other professional societies is reproduced in Table 56-1.

Inherited Coagulopathy. The safety of neuraxial techniques in patients with common bleeding diatheses is not well documented. Hemorrhagic complications after neuraxial techniques in patients with known hemophilia, von Willebrand disease, or idiopathic thrombocytopenic purpura appear infrequently when factor levels are more than 0.5 IU/mL for factor VIII, von Willebrand factor, and ristocetin cofactor activity, or when the platelet count is greater than $50 \times 10^9/L^1$ before block performance.[86] The minimum safe factor levels and platelet count for neuraxial blockade remain undefined in both the obstetric and general populations.[86]

Infection

Theoretic concerns based on animal data and laboratory and case reports in humans[87-89] suggest iatrogenic seeding of the neuraxis in the setting of a systemic infection. Some providers avoid neuraxial techniques in febrile patients. A definitive causative relationship between existing systemic infection and meningitis or epidural abscess after a neuraxial technique has never been shown. In fact, a lumbar puncture is a critical component of the investigation of fever of unknown origin, yet there are no definitive data linking lumbar puncture to increased risk of neuraxial infection in this setting.[90] Although the profound vasodilation may be sufficient reason to avoid neuraxial techniques in patients with profound bacteremia or septic shock, the theoretic risk of seeding the

TABLE 56-1 NEURAXIAL* ANESTHESIA IN THE PATIENT RECEIVING THROMBOPROPHYLAXIS

		Unfractionated Heparin		
	Antiplatelet Medications	Subcutaneous	Intravenous	LMWH
German Society for Anaesthesiology and Intensive-Care Medicine[†]	NSAIDs: no contraindication Hold LMWH, fondaparinux 36-42 hours; thienopyridines and GP IIb/IIIa are contraindicated	Needle placement 4 hours after heparin; heparin 1 hour after needle placement or catheter removal	Needle placement and catheter removal 4 hours after discontinuing heparin, heparinize 1 hour after neuraxial technique; delay bypass surgery 12 hours if traumatic	Neuraxial technique 10-12 hours after LMWH; next dose 4 hours after needle or catheter placement; delay block for 24 hours after therapeutic dose
Belgian Association for Regional Anesthesia[‡]	NSAIDs: no contraindication Discontinue ticlopidine 14 days, clopidogrel 7 days; GP IIb/IIIa inhibitors 8-48 hours in advance	Not discussed	Heparinize 1 hour after neuraxial technique; remove catheter during normal aPTT; reheparinize 1 hour later	Neuraxial technique 10-12 hours after LMWH; next dose 4 hours after needle or catheter placement; delay block for 24 hours after therapeutic dose
American Society of Regional Anesthesia and Pain Medicine	NSAIDs: no contraindication Discontinue ticlopidine 14 days, clopidogrel 7 days, GP IIb/IIIa inhibitors 8-48 hours in advance	No contraindication with twice-daily dosing and total daily dose <10,000 U, consider delay heparin until after block if technical difficulty anticipated; the safety of neuraxial blockade in patients receiving doses >10,000 U of UFH daily, or more than twice daily dosing of UFH has not been established	Heparinize 1 hour after neuraxial technique, remove catheter 24 hours after last heparin dose; no mandatory delay if traumatic	Twice-daily dosing: LMWH 24 hours after surgery, regardless of technique; remove neuraxial catheter 2 hours before first LMWH dose Single-daily dosing: according to European statements but with no additional hemostasis-altering drugs Therapeutic dose: delay block for 24 hours
American College of Chest Physicians[§]	NSAIDs: no contraindication Discontinue clopidogrel 7 days before neuraxial block	Needle placement 8-12 hours after dose; subsequent dose 2 hours after block or catheter withdrawal	Needle placement delayed until anticoagulant effect is minimal	Needle placement 8-12 hours after dose; subsequent dose 2 hours after block or catheter withdrawal Indwelling catheter safe with twice-daily dosing Therapeutic dose: delay block for 18+ hours

Data adapted from Horlocker TT, Wedel DJ, Rowlingson JC, et al: Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy. American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition), Reg Anesth Pain Med *35:64-101, 2010.*

aPTT, Activated partial thromboplastin time; *GP,* glycoprotein; *LMWH,* low-molecular-weight heparin; *NSAID,* nonsteroidal antiinflammatory drug; *UFH,* unfractionated heparin.

*For patients undergoing deep plexus or peripheral block, follow ASRA recommendations for neuraxial techniques.

[†]Adapted from the German Society of Anaesthesiology and Intensive Care Medicine Consensus guidelines.

[‡]Adapted from the Belgian Association for Regional Anesthesia. Working Party on Anticoagulants and Central Nerve Blocks.

[§]Adapted from the American College of Chest Physicians.

intrathecal or epidural spaces by performing neuraxial techniques in patients with untreated systemic infection further supports using another technique. Yet patients with evidence of systematic infection may safely undergo neuraxial anesthesia once antibiotic therapy has been initiated and the patient has demonstrated a response to the antibiotics.[90]

TABLE 56-2 DERMATOMAL LEVEL REQUIRED FOR VARIOUS COMMON SURGICAL PROCEDURES

Type of surgery	Dermatomal Level
Upper abdominal surgery	T4
Ceserean delivery	T4
Transurethral resection of prostate	T10
Hip surgery	T10
Foot and ankle surgery	L2

SPINAL ANESTHESIA

FACTORS AFFECTING BLOCK HEIGHT

The dermatomal level required for various surgical procedures is outlined in Table 56-2. The provider must recall that intraabdominal structures such as the peritoneum (T4), bladder (T10), and uterus (T10) have a spinal segment innervation that may be much more cephalad compared with that of the corresponding skin incision used to operate on these structures.

TABLE 56-3 **FACTORS AFFECTING LOCAL ANESTHETIC DISTRIBUTION AND BLOCK HEIGHT**

	More Important	Less Important	Not Important
Drug factors	Dose Baricity	Volume Concentration Temperature of injection Viscosity	Additives other than opioids
Patient factors	CSF volume Advanced age Pregnancy	Weight Height Spinal anatomy Intraabdominal pressure	Menopause Gender
Procedure factors	Patient position Epidural injection post spinal	Level of injection (hypobaric more than hyperbaric) Fluid currents Needle orifice direction Needle type	

Adapted from Greene NM: Distribution of local anesthetic solutions within the subarachnoid space. Anesth Analg *1985;64(7):715–730.*
CSF, Cerebrospinal fluid.

Drug, patient, and procedural factors can all affect the distribution of local anesthetic spread within the intrathecal space, some of which are more clinically relevant than others.[25,91] Many of these factors are not controllable by the anesthesiologist, leading to significant interpatient variability (Table 56-3).

Drug Factors

The adjustable factors for any given local anesthetic solution are dose, volume, concentration, temperature, and baricity. Baricity and dose are most important.

Baricity. Baricity is the ratio of the density of a local anesthetic solution to the density of CSF. Density is defined as the mass per unit volume of solution (g/mL) at a specific temperature. Density may be compared between different substances by calculating the specific gravity, which is the ratio of the density of a solution to the density of water. Because density varies inversely with temperature, the baricity of a local anesthetic solution is conventionally defined at 37° C. The density of CSF is 1.00059 g/L.[92] Local anesthetic solutions that have the same density as CSF are termed *isobaric*, those that have a higher density than CSF are termed *hyperbaric*, and those with a lower density than CSF are termed *hypobaric*. The spread of hyperbaric solutions is more predictable,[93] with less interpatient variability.[94] To make a drug hyperbaric to CSF, it must be denser than CSF, with a baricity appreciably more than 1.0000 or a density appreciably more than 1.00059. The reverse is true for making a drug hypobaric to the CSF. Dextrose and sterile water are commonly added to render local anesthetic solutions either hyperbaric or hypobaric, respectively. The clinical importance of baricity is the ability to influence the distribution of local anesthetic spread based on gravity. Hyperbaric solutions will preferentially spread to the dependent regions of the spinal canal, whereas hypobaric solutions will spread to nondependent regions. Isobaric solutions tend not to be influenced by gravitational forces.[95] Anesthesiologists can capitalize on this phenomenon by altering the position of the patient. For example, the administration of hyperbaric local anesthetic to patients in the lateral decubitus position will result in a preferential anesthetic effect on the dependent side, whereas the opposite is true for the administration of a hypobaric solution. A thoughtful understanding of the natural curvatures of the vertebral column can help predict local anesthetic spread in patients placed in the horizontal supine position immediately after intrathecal administration. Hyperbaric local anesthetics injected, while sitting, at the L3-4 or L4-5 interspace will spread with gravity from the height of the lumbar lordosis down toward the trough of the thoracic kyphosis in the horizontal supine position, resulting in a higher level of anesthetic effect than isobaric or hypobaric solutions.[91] Hyperbaric solutions are also useful in small doses for a saddle block and to achieve unilateral anesthesia. CSF and local anesthetic density change with temperature. Plain bupivacaine 0.5%, for example, may be isobaric at 24° C but is slightly hypobaric at 37° C. A small volume of drug at room temperature injected intrathecally quickly equilibrates after injection and increases to the temperature of the CSF. Nevertheless, increasing temperature decreases density of a solution and warming of local anesthetic solution to body temperature, therefore making it more hypobaric, increases the block height in patients who remain seated for several minutes after injection.[96]

Dose, Volume, and Concentration. The dose, volume, and concentration are inextricably linked (Volume × Concentration = Dose), but dose is the most reliable determinant of local anesthetic spread (and thus block height) when compared with either volume or concentration for isobaric and hypobaric local anesthetic solutions.[97,98] Hyperbaric local anesthetic injections are primarily influenced by baricity.

The choice of local anesthetic itself does not influence spread if all other factors are controlled. Additive drugs, other than opioids, also do not affect spread. However, opioids do seem to increase mean spread,[91,99] possibly as a result of pharmacologic enhancement at the extremes of the spread where the local anesthetic block alone would have been subclinical.[100,101]

Patient Factors

Patient characteristics that may influence block height include patient height, weight, age, sex, pregnancy, anatomic configuration of the spine, and the CSF properties

(volume and composition). Within the range of "normal-sized" adults, patient height does not seem to affect the spread of spinal anesthesia. This is likely because the length of the lower limb bones rather than the vertebral column contributes most to adult height. A correlation has been found between the vertebral column length and local anesthetic spread[102] and, at extremes of height, consideration should be given to altering the dose accordingly.

The CSF volume is an important patient-related factor that significantly influences peak block height and regression of sensory and motor blockade.[17] Lumbosacral CSF has a fairly constant pressure of approximately 15 cm H_2O but its volume varies from patient to patient, in part because of differences in body habitus and weight.[16] In a small sample of patients, block height varied indirectly with CSF volume.[17] Unfortunately, CSF volume does not correlate well with anthropomorphic measurements available clinically other than body weight.[17] In theory, the increased abdominal mass in obese patients, and possible increased epidural fat, may decrease the CSF volume and therefore increase the spread of local anesthetic and block height. This has indeed been demonstrated using hypobaric solutions,[103,104] which are characterized by more variable spread anyway, but not hyperbaric solutions[103,105] (see Chapter 71).

CSF density can also vary between and within individuals depending on sex, menopausal status, and pregnancy[92] (see Chapter 77). The density of CSF is lower in women compared with men, premenopausal compared with postmenopausal women, and pregnant compared with nonpregnant women. Although this may affect relative baricity of local anesthetics, the clinical variation in spread is probably unimportant.

Advanced age is associated with increased block height[106,107] (see Chapter 80). In older patients, CSF volume decreases, whereas its specific gravity increases. Further, the nerve roots appear more sensitive to local anesthetic in the aged population.

Gender can theoretically affect block height by several mechanisms. CSF density is higher in males, thereby reducing the baricity of local anesthetic solution and possibly limiting the extent of cephalad spread. In the lateral position, the broader shoulders of males relative to their hips make the lateral position slightly more head-up. The reverse is true in females who have a slightly head-down tilt in the lateral position compared with males. Despite this, there is little objective data that males have a slightly less cephalad spread than females in the lateral position.

Variations of the spine may be an important contributor to block height. Scoliosis, although it possibly makes insertion of the needle more difficult, will have little effect on local anesthetic spread if the patient is turned supine. Kyphosis, however, in a supine patient may affect the spread of a hyperbaric solution. Spread of local anesthetic is enhanced by changes in the lumbar lordosis during pregnancy, as well as by the volume and density of CSF, by twin pregnancies compared with singletons, by intraabdominal pressure increases (possibly), and by a progesterone-mediated increase in neuronal sensitivity.

Procedure Factors

Patient position, needle type and alignment, and the level of injection are each procedure-related factors that can affect block height. Combined with the baricity and local anesthetic dose, patient position is the most important factor in determining the block height. Position should not affect the spread of a truly isobaric solution.[95] Intrathecal local anesthetic appears to stop spreading 20 to 25 minutes after injection, thus positioning of the patient is most important during this time period, but particularly in the initial few minutes. However, marked changes in patient posture up to two hours after injection can still result in significant changes in the block level, probably because of bulk movement of CSF.[108,109] Although a 10-degree head-up tilt can reduce the spread of hyperbaric solutions without hemodynamic compromise,[110] a head-down tilt does not always increase the spread of hyperbaric bupivacaine.[111] Flexion of the hips in combination with the Trendelenburg position flattens the lumbar lordosis and has been shown to increase cephalad spread of hyperbaric solutions.[112] A "saddle block" where only the sacral nerve roots are anesthetized can be achieved by using a small dose of hyperbaric local anesthetic while the patient remains in the sitting position for up to 30 minutes. When larger hyperbaric doses are administered, however, the block can still extend cephalad despite maintaining the sitting position for a prolonged period of time.[113] The reverse holds true for hypobaric solutions, where block height is greater (than hyperbaric solutions) if they are administered in a sitting position.[114]

The specific needle type and orientation of the orifice may affect block quality. With hypobaric solutions, cephalad alignment of the orifice of Whitacre, but not Sprotte, needles produces greater spread.[115-117] The orientation of the needle orifice does not appear to affect the spread of hyperbaric solutions. When directing the needle orifice to one side (and using hyperbaric anesthetic), a more marked unilateral block is achieved again when using a Whitacre, rather than a Quincke, needle.[118]

The level of injection affects block height. Most studies have demonstrated that, even when the difference is only one interspace more cephalad, the block height is greater[119-122] when using isobaric bupivacaine. The level of injection does not appear to influence the spread of hyperbaric solutions.[123,124] Injection rate and barbotage (repeated aspiration and reinjection of CSF) of isobaric and hyperbaric solutions have not consistently been shown to affect block height.[91] A slower injection may actually increase spread, and this is perhaps also safer because forceful injection may cause the syringe to disconnect from the needle. Other maneuvers that do not appear to affect block height are coughing and straining after local anesthetic injection. This is related to the physics of injecting drugs into a closed column of CSF, which instantaneously transmits pressure changes throughout the CSF column, such as those that occur with coughing or straining.[25] The injection of local anesthetic or even saline into the epidural space after a spinal anesthetic increases the block height. This is discussed separately in the combined spinal-epidural section.

DURATION

The duration of a spinal anesthetic depends on how this variable is defined. For example, the duration of surgical anesthesia is less than the time for complete block resolution. In addition, surgical anesthesia depends on the surgical site because anesthesia is more prolonged at the lower lumbar and sacral levels than at those more cephalad from where the block regresses first. Duration is affected primarily by the dose,[97,125] the intrinsic properties of the local anesthetic (which affect elimination from the subarachnoid space), and the use of additives (if applicable). The latter two are described later. Hyperbaric solutions have a shorter duration of action than isobaric solutions.[125]

PHARMACOLOGY

The clinical effects of intrathecal local anesthetics are mediated by drug uptake and distribution within the CSF and elimination. These in turn are dictated in part by the p*K*a, lipid solubility, and protein binding of the local anesthetic solution. Rather than their pharmacologic structure (i.e., amide or ester), it is the duration of action—short-acting (i.e., procaine, chloroprocaine, articaine), intermediate-acting (i.e., lidocaine, prilocaine, mepivacaine), and long-acting (i.e., tetracaine, bupivacaine, levobupivacaine, ropivacaine)—that is most often used to classify local anesthetics in the clinical setting. The choice and dose of local anesthetic depend on both the expected duration and the nature (location, ambulatory) of surgery. Table 56-4 shows a range of local anesthetics used for spinal anesthesia with corresponding doses, onset times, and durations of action.

Short- and Intermediate-Acting Local Anesthetics

Procaine. Procaine is a short-acting ester local anesthetic and one of the oldest spinal anesthetics, having originally replaced cocaine as the drug of choice for spinal anesthesia in the early twentieth century. Procaine itself was then replaced by lidocaine, but with concerns about lidocaine and transient neurologic symptoms (TNS), procaine has recently been reexamined as an alternative fast-acting local anesthetic. However, it is not commonly used because of a more frequent failure rate than lidocaine, significantly more nausea, and a slower time to recovery.[135] If used, it is often administered as a hyperbaric drug in a dose ranging between 50 and 200 mg in a 10% concentration.

Chloroprocaine. Chloroprocaine is an ultra–short-acting ester local anesthetic that was introduced in the 1950s. Its initial popularity stemmed from its rapid metabolism by pseudocholinesterase, which translated into minimal systemic or fetal effects in the setting of epidural labor analgesia. However, its reputation as a spinal anesthetic has been tarnished because of reports of neurologic injury associated with the preservative once used in older preparations of the drug[136-139] (see Complications, discussed later). Recently, interest in chloroprocaine has increased for use in spinal anesthesia for ambulatory surgery (see Chapter 89). Modern, preservative-free preparations of chloroprocaine administered in small doses (30 to 60 mg) produce reliable, short-duration spinal anesthesia,[126] with a faster recovery time than procaine, lidocaine, and bupivacaine.[140-144] TNS can occur with modern chloroprocaine preparations, albeit at a considerably lesser rate (0.6%) than lidocaine (14%).[145-147]

Articaine. Articaine is a relatively novel amide local anesthetic that also has an ester linkage. The ester linkage allows for metabolism by nonspecific cholinesterases. It has been widely used since 1973 for dental nerve blocks with a good safety profile. Intrathecal articaine has not been extensively investigated, but studies do suggest that doses of 50 to 80 mg with or without glucose appear to

TABLE 56-4 **DOSE, BLOCK HEIGHT, ONSET TIMES, AND DURATION OF COMMONLY USED SPINAL ANESTHETICS**

Local Anesthetic Mixture	Dose (mg)		Duration (min)		Onset (min)
	To T10	*To T4*	*Plain*	*Epinephrine (0.2 mg)*	
Lidocaine 5% (with/without dextrose)*	40-75	75-100	60-150†	20%-50%	3-5
Mepivacaine 1.5% (no dextrose)	30-45‡	60-80§	120-180¶	—	2-4
Chloroprocaine 3% (with/without dextrose)	30-40	40-60	40-90‖	N/R	2-4
Bupivacaine 0.5%-0.75% (no dextrose)	10-15	12-20	130-230#	20%-50%	4-8
Levobupivacaine 0.5% (no dextrose) (ref B)	10-15	12-20	140-230#	—	4-8
Ropivacaine 0.5%-1% (with/without dextrose)	12-18	18-25	80-210**	—	3-8

N/R Not recommended.
Note that duration depends on how the regression of the block is measured, which varies widely between studies.
*Lidocaine is not commonly used now.
†Regression to T12.[126-134]
‡Note peak with these doses was T12, and not in all cases.
§Median peak block height in this study with 60 mg was T5, not T4.
¶Regression to S1 for block duration.
‖Regression to L1.
#Regression to L2.
**Regression to S2.

provide rapid-onset spinal anesthesia for about 1 hour, with a recovery profile faster than bupivacaine.[148,149]

Lidocaine. Lidocaine is a hydrophilic, relatively poorly protein-bound amide local anesthetic. It has a rapid onset and intermediate duration and is used in doses of 50 to 100 mg for shorter procedures that can be completed in 1.5 hours or less. It was traditionally prepared as a 5% solution in 7.5% dextrose; this preparation has been associated with both permanent nerve injury and transient neurologic symptoms (TNS, see Complications, discussed later). Despite efforts to reduce the concentration of both the drug and dextrose,[150,151] the use of intrathecal lidocaine declined and has not yet recovered.

Prilocaine. Prilocaine is an amide local anesthetic based on the structure of lidocaine. Prilocaine was introduced in 1965 and has an intermediate duration of action that may lend itself to use in the ambulatory surgery setting.[152] A dose of 40 to 60 mg of 2% hyperbaric prilocaine can provide a block to T10 for 100 to 130 minutes, whereas as little as 20 mg combined with fentanyl has been successfully used for ambulatory arthroscopic knee surgery.[153] Prilocaine is rarely associated with TNS.[152,154,155] In large doses (>600 mg), prilocaine can result in methemoglobinemia. This should not be an issue with doses used for spinal anesthesia, but it has been reported after epidural infusions.[156]

Mepivacaine. Mepivacaine is another short-acting amide local anesthetic. It was first introduced for spinal anesthesia in 1962 and was initially prepared as a hyperbaric solution. The use of spinal mepivacaine has declined because the incidence of TNS after hyperbaric mepivacaine was similar to that of lidocaine,[147] although TNS was less frequent with the isobaric preparation of mepivacaine.[157-159] Doses of 30 to 80 mg with and without additives have been used (see Table 56-4) and, when compared with lidocaine, mepivacaine has a slightly longer duration of action.[160]

Long-Acting Local Anesthetics

Tetracaine. Tetracaine is an ester local anesthetic with a rate of metabolism one tenth that of chloroprocaine. It is packaged either as niphanoid crystals (20 mg) or as an isobaric 1% solution (2 mL, 20 mg). When niphanoid crystals are used, a 1% solution is obtained by adding 2 mL of preservative-free sterile water to the crystals. Mixing 1% solution with 10% dextrose produces a 0.5% hyperbaric preparation that may be used for perineal and abdominal surgery in doses of 5 and 15 mg, respectively. Tetracaine is usually combined with a vasoconstrictor additive because the duration of tetracaine alone can be unreliable. Although such combinations can provide up to 5 hours of anesthesia,[161-164] the addition of phenylephrine in particular has been associated with TNS.[165]

Bupivacaine. Bupivacaine was introduced in 1963 and is a highly protein-bound amide local anesthetic with a slow onset because of its relatively high p*K*a. It is appropriate for procedures lasting up to 2.5 to 3 hours (see Table 56-4).[166,167] Bupivacaine is available as 0.25%, 0.5%, and 0.75% clear isobaric solutions and also as a hyperbaric 0.5% (in Europe) and 0.75% solution containing 80 mg/mL glucose. At room temperature, plain bupivacaine is actually slightly hypobaric compared with CSF. Recovery profiles using small doses appear to be similar to that of lidocaine[168-170] and thus low-dose bupivacaine is used in ambulatory procedures. A recent systematic review[171] concluded that 4 to 5 mg of hyperbaric bupivacaine combined with unilateral positioning was adequate for short knee arthroscopy procedures. Bupivacaine is rarely associated with TNS.

Levobupivacaine. Levobupivacaine is the pure S (–) enantiomer of racemic bupivacaine. Although it is used in similar doses to bupivacaine and has a similar onset and duration, levobupivacaine potency appears to be slightly less than bupivacaine.[129] Nevertheless, the majority of clinical studies using identical doses of levobupivacaine and bupivacaine have found no significant difference in clinical efficacy for spinal anesthesia.[129,172-174] The main advantage of levobupivacaine is that it is less cardiotoxic than bupivacaine,[175,176] which is more of a theoretic than a real risk in the setting of spinal anesthesia.

Ropivacaine. Ropivacaine was introduced in 1996 and is another highly protein-bound amide local anesthetic. It is structurally related to bupivacaine, with the same p*K*a (8.1) and so it is also characterized by slow onset and a long duration of action. Compared to bupivacaine, the proposed advantages of spinal ropivacaine were less cardiotoxicity and greater motor-sensory block differentiation, resulting in less motor block. Subsequently, the potency of ropivacaine was found to be 0.6 that of bupivacaine.[179-181] When ropivacaine is given in an equivalent dose to bupivacaine, there is slightly less motor block and earlier recovery with ropivacaine.[8,182-184]

Spinal Additives

Whether administered into the CSF in conjunction with a local anesthetic or alone, a variety of medications may exert a direct analgesic effect on the spinal cord and nerve roots, or prolong the duration of sensory and motor blockade. As such, the coadministration of these agents often allows for a reduction in the required dose of local anesthetic, with the advantage of motor block sparing and faster recovery while still producing the same degree of analgesia.

Opioids. The effects of opioids within the CSF are complex, because of a combination of direct spinal cord dorsal horn opioid receptor activation, cerebral opioid receptor activation after CSF transport, and peripheral and central systemic effects after vascular uptake. The effect at each of these sites depends on both the dose administered and the physicochemical properties of the opioid, particularly lipid solubility. Highly lipid-soluble drugs such as fentanyl and sufentanil have a more rapid onset and shorter duration of action than more hydrophilic opioids. In addition to increasing uptake into neural tissue, greater lipid solubility results in rapid uptake into both blood vessels (with a resultant systemic effect) and fatty tissue. The spread of lipophilic opioids within the CSF is there-

fore more limited than hydrophilic opioids such as morphine, which demonstrate greater spread as a result of slower uptake and elimination from the CSF. As a result, hydrophilic opioids have a greater risk of late respiratory depression, which is one of the rare but most serious consequences of intrathecal opioid administration. The extent of neural tissue and vascular uptake also affects the potency of intrathecal opioids. For example, the relative intrathecal to intravenous potency of morphine is 200 to 300 to 1, whereas for fentanyl and sufentanil it is only 10 to 20 to 1.[185] In addition to respiratory depression, intrathecal opioids have other side effects including nausea and vomiting, pruritus, and urinary retention. These are discussed later in the Complications section.

Hydrophilic Opioids. Preservative-free morphine is the most widely used hydrophilic opioid in spinal anesthesia. It has a slow onset but provides analgesia for up to 24 hours.[186] Adequate analgesia is achieved with 100 μg, with minimal side effects for cesarean deliveries, whereas the most efficacious dose for major orthopedic surgery is less clear.[187] For hip or knee replacement surgery, side effects tend to increase without a corresponding improvement in analgesia with intrathecal morphine doses of 300 μg or more. Doses as high as 500 μg may be used for major abdominal surgery or thoracotomies, where it is becoming increasingly common to administer spinal opioids alone as a simple alternative to epidural local anesthetic–based analgesia. The magnitude of the analgesic response and the optimal dose remain unclear. Overall, the beneficial effects of intrathecal morphine seem most marked in abdominal surgery, and within the first 24 hours in particular.[186,188]

Diamorphine is available for use in the United Kingdom only. It is a lipid-soluble prodrug that crosses the dura faster than morphine and is cleared from the CSF more quickly than morphine. Once in the dorsal horn of the spinal cord, it is converted to morphine and 6-monoacetyl morphine, both of which are μ-agonists with a relatively long duration of action. It is recommended for use in doses of 0.3 to 0.4 mg for cesarean delivery[189] and is widely used instead of morphine in the United Kingdom.

There are only limited data related to the use of hydromorphone for spinal analgesia. It is more commonly used epidurally, as discussed later. Limited data suggest that intrathecal hydromorphone 50 to 100 μg provides comparable analgesia with similar side effects to 100 to 200 μg of morphine, with a similar duration of action. However, it has not undergone full neurotoxicity screening and does not provide any advantage compared with morphine.[190]

Meperidine is an opioid of intermediate lipid solubility, but it also has some local anesthetic properties and has been used as the sole intrathecal agent (doses ranging from 0.5 to 1.8 mg/kg) in both obstetric and general surgery.[191,192] Smaller doses are used in combination with local anesthetics. Both 10 mg and 20 mg improve analgesia compared with placebo after cesarean delivery,[193] although side effects were more frequent with the larger dose. However, this drug is used infrequently because of the availability of other opioids and its unknown neurotoxicity profile.

Lipophilic Opioids. Fentanyl and sufentanil are used frequently in obstetrics for labor analgesia and cesarean delivery as discussed elsewhere (also w 77). Sufentanil 2 to 10 μg and fentanyl 25 μg provide comparable analgesia in early labor.[194-197] In transurethral prostatectomy surgery, when combined with low-dose bupivacaine, sufentanil 5 μg provides superior analgesia compared with fentanyl 25 μg.[198] Fentanyl in doses of 10 to 30 μg is commonly used in ambulatory surgery because of its rapid onset time of 10 to 20 minutes and relatively short duration of 4 to 6 hours. Although the local anesthetic dose can be reduced and analgesia prolonged,[199] the addition of fentanyl to bupivacaine may increase side effects and delay discharge.[171]

Vasoconstrictors. Vasoconstrictors, such as epinephrine and phenylephrine, prolong the duration of sensory and motor blockade when added to local anesthetics. The mechanism of action is reduced systemic local anesthetic uptake caused by an α_1-mediated vasoconstriction. Epinephrine may also enhance analgesia via a direct α_2-mediated effect. Traditionally, epinephrine 0.1 to 0.6 mg, was thought to prolong tetracaine spinal anesthesia, but not bupivacaine or lidocaine spinal anesthesia.[22] This theory was postulated because of differences in the vasodilatory action of the local anesthetic drugs; plain lidocaine and bupivacaine cause vasodilation, whereas plain tetracaine does not. However, lidocaine spinal anesthesia can be prolonged by epinephrine when measured by both two-dermatome regression in the lower thoracic dermatomes and by occurrence of pain at the operative site for procedures carried out at the level of the lumbosacral dermatomes.[200,201] Similarly, bupivacaine spinal duration may be increased, but because of the already long duration, epinephrine is not generally added to bupivacaine. There is a concern that potent vasoconstrictive action places the blood supply of the spinal cord at risk. However, there are no human data supporting this theory, and in animal studies,[164,202-204] administering either subarachnoid epinephrine (0.2 mg) or phenylephrine (5 mg) does not decrease spinal cord blood flow. Phenylephrine 2 to 5 mg prolongs both lidocaine and tetracaine spinal anesthesia to a similar extent as epinephrine.[201,205] Bupivacaine spinal anesthesia is not prolonged by phenylephrine.[206,207] Concepcion and co-workers[208] compared epinephrine (0.2 and 0.3 mg) and phenylephrine (1 and 2 mg) added to tetracaine and did not find any differences in duration between the two vasoconstrictors. Caldwell and associates[163] used larger doses of vasoconstrictors, epinephrine at 0.5 mg and phenylephrine at 5 mg, and showed that phenylephrine prolonged tetracaine spinal anesthesia significantly more than did epinephrine. The addition of phenylephrine has declined in popularity because of its association with TNS.[165,209]

α_2-Agonists. Clonidine, dexmedetomidine, and epinephrine all act on prejunctional and postjunctional α_2 receptors in the dorsal horn of the spinal cord. Activation of presynaptic receptors reduces neurotransmitter release, whereas postjunctional receptor activation results in hyperpolarization and reduction of pulse transmission.[210] In doses of 15 to 225 μg, clonidine prolongs the duration of sensory and motor blockade by

approximately 1 hour and improves analgesia, reducing morphine consumption by up to 40%.[211-215] It appears to cause less urinary retention than morphine but, as with intravenous clonidine administration, spinal clonidine can also cause hypotension. A systematic review concluded that the hypotension associated with spinal clonidine was not dose-related and that the risk of bradycardia with clonidine was not increased.[216] Sedation can also occur with spinal clonidine, peaking within 1 to 2 hours and lasting up to 8 hours.[210] Dexmedetomidine is approximately 10-fold more α_2-selective than clonidine is.[217] As little as 3 μg of dexmedetomidine can prolong motor and sensory block without hemodynamic compromise.[218,219]

Other Drugs. Neostigmine in doses of 10 to 50 μg has analgesic effects after intrathecal administration.[220,221] Intrathecal neostigmine has been shown to prolong motor and sensory blockade and reduce postoperative analgesic requirements. Neostigmine inhibits the breakdown of acetylcholine, therefore increasing acetylcholine concentration, which itself is antinociceptive. It also appears to stimulate the release of nitric oxide in the spinal cord. Its benefits, however, are limited by nausea, vomiting, bradycardia, and, in higher doses, lower extremity weakness,[222,223] and is therefore not in widespread use.[224] Midazolam is a γ-aminobutyric acid receptor agonist that in doses of 1 to 2 mg appears to increase sensory and motor block and decrease analgesic requirements postoperatively, without the adverse effects observed with α_2 agonists or opioids. Early work raised concerns of spinal cord toxicity, but more recent studies suggest that it is safe.[225] Ketamine, adenosine, tramadol, magnesium, and nonsteroidal antiinflammatory drugs have also all been administered intrathecally, but further work is required to establish whether these drugs have any clinical value.

Technique

Technique should be classified into a series of steps (i.e., the four Ps): preparation, position, projection, and puncture.

Preparation. Informed consent must be obtained, with adequate documentation of the discussion of risk (see Complications, discussed later). Resuscitation equipment must always be readily available whenever a spinal anesthetic procedure is performed. The patient should have adequate intravenous access and be monitored with pulse oximetry, noninvasive arterial blood pressure, and electrocardiogram. Pre-prepared packs are now commonly used and often contain fenestrated drapes, swabs and towels, syringes, needles, filters, spinal needles, sterilizing solution, and local anesthetic for skin infiltration. When the local anesthetic for subarachnoid injection is chosen, the duration of block should be matched with both the surgical procedure and patient variables (see Table 56-4).

The most important characteristics of a spinal needle are the shape of the tip and the needle diameter. Needle tip shapes fall into two main categories: those that cut the dura and those with a conical, pencil-point tip. The former include the Pitkin and the Quincke-Babcock needle,

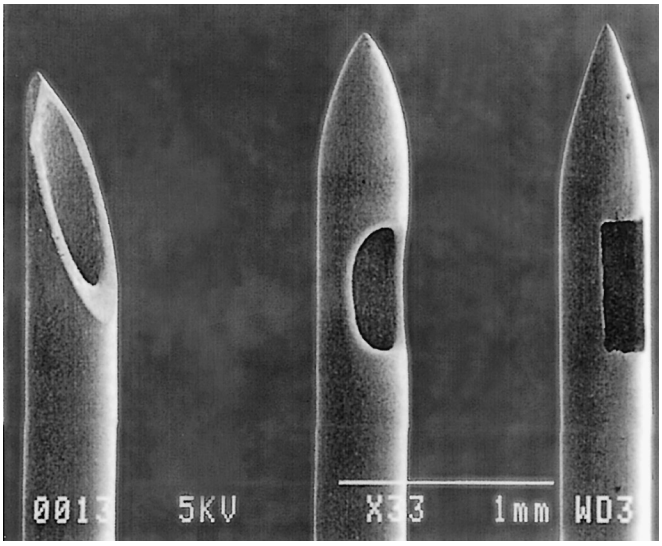


Figure 56-4. Scanning electron micrographs of spinal needle tip designs: Quincke (*left*), Sprotte (*middle*), and Whitacre (*right*). *(Adapted from Puolakka R, Andersson LC, Rosenberg PH: Microscopic analysis of three different spinal needle tips after experimental subarachnoid puncture,* Reg Anesth Pain Med *25:163, 2000.)*

and the Whitacre and Sprotte needles belong to the latter group (Fig. 56-4). The orifice of the Whitacre needle is smaller. If a continuous spinal technique is chosen, use of a Tuohy or other thin-walled needle can facilitate passage of the catheter. The use of small needles reduces the incidence of post–dural puncture headache from 40% with a 22-G needle to less than 2% with a 29-G needle. The use of larger needles, however, improves the tactile sense of needle placement, and so although 29-G needles result in a very low rate of post–dural puncture headache, the failure rate is increased.[226,227] Pencil-point needles provide better tactile sensation of the different layers encountered during needle insertion but, more importantly, they reduce the incidence of post–dural puncture headache. Pencil-point needles of 25, 26, and 27 G probably represent the optimal needle choice. An introducer needle can assist with guidance of smaller-gauge spinal needles in particular. Special Luer lock needles and syringes for spinal kits are now also available. These have been designed to prevent inadvertent intrathecal injection but still rely on the correct drug being drawn up into the "special" connector syringe (Fig. 56-4).

Sterility is an issue of utmost importance. One of the most common organisms responsible for postspinal bacterial meningitis is *Streptococcus viridans,* which is an oral commensal, emphasizing the purpose of wearing a mask as part of a full aseptic technique. Hands and forearms must be washed and all jewelry removed. A variety of solutions may be used to clean the back, such as chlorhexidine or alcohol (alone or in combination), or iodine solutions. Chlorhexidine and alcohol together have been concluded to be most effective.[229-231] If chlorhexidine is used, it is important that the solution is allowed to dry completely before skin puncture because chlorhexidine is neurotoxic.

Position (Also see Chapter 41). The three primary patient positions include the lateral decubitus, sitting, and prone

positions, each of which has advantages in specific situations. The superiority of any one particular position is unclear. In the obstetric population, there have been small studies demonstrating that block operator performance was faster in the sitting position, albeit this benefit was offset by a slower onset time compared with the lateral decubitus position[232] (see Chapter 77). Current consensus guidelines state that neuraxial blocks should be undertaken with the patient awake,[76] except in those circumstances where the physician and patient conclude that benefit outweighs the risk. General anesthesia or heavy sedation can prevent a patient from recognizing warning signs of pain or paresthesia if the needle is in close proximity to nervous tissue.

A patient in the lateral decubitus position facilitates the administration of sedative medication if required, is less dependent on a well-trained assistant than for a patient in the sitting position, and is arguably more comfortable. Patients are placed with their back parallel to the edge of the operating table nearest the anesthesiologist, thighs flexed onto the abdomen, with the neck flexed to allow the forehead to be as close as possible to the knees in an attempt to "open up" the vertebral spaces. The assistant may still be invaluable during this positioning by encouraging and assisting the patient in assuming the ideal lateral decubitus position. Because of the differing proportional sizes of hips and shoulders, the spine may slope down toward the head in females, with the opposite occurring in males. The patient should be positioned so that spread of hypobaric, isobaric, or hyperbaric solution to the operative site is optimized.

Identification of the midline may be easier when the patient is placed in the sitting position, especially when obesity or scoliosis renders midline anatomy difficult to examine. When placing patients in this position, a stool can be provided as a footrest and a pillow placed in the lap, or a specially designed stand may be used. The assistant helps to maintain the patient in a vertical plane while flexing the patient's neck and arms over the pillow, relaxing the shoulders, and asking the patient to "push out" the lower back to open up the lumbar vertebral spaces. Care must be taken not to oversedate a patient in this position. Hypotension may also be more common for a person in the sitting position.

The prone position is rarely used but may be chosen when the patient is to be maintained in that position (often with the jack-knife modification) during the surgical procedure. Such cases may include rectal, perineal, or lumbar procedures. The anesthesiologist may have to aspirate for CSF because CSF pressure is minimized when insertion of the lumbar needle is carried out in this position.

Projection and Puncture. The midline approach relies on the ability of patients and assistants to minimize lumbar lordosis and allow access to the subarachnoid space between adjacent spinous processes, usually at the L2-L3, L3-L4, or the L4-L5 space. The spinal cord ends at the level of L1-L2 and so needle insertion above this level should be avoided. The intercristal line is the line drawn between the two iliac crests and traditionally corresponds to the level of the L4 vertebral body or the L4-L5 interspace, but the reliability of this landmark is questionable as demonstrated by recent ultrasonography studies.[233] Once the appropriate space has been selected, a subcutaneous skin wheal of local anesthetic is developed over this space, and the introducer is inserted at a slight cephalad angle of 10 to 15 degrees through skin, subcutaneous tissue, and supraspinous ligament to reach the substance of the interspinous ligament. The introducer is grasped with the palpating fingers and steadied while the other hand is used to hold the spinal needle like a dart, and the fifth finger is used as a tripod against the patient's back to prevent patient movement and unintentional insertion to a level deeper than intended. The needle, with its bevel parallel to the midline, is advanced slowly to heighten the sense of tissue planes traversed and to prevent skewing of nerve roots, until the characteristic change in resistance is noted as the needle passes through the ligamentum flavum and dura. On passing through the dura, there is often a slight "click" or "pop" sensation. The stylet is then removed, and CSF should appear at the needle hub. The smaller the needle diameter, the longer the wait for CSF flow, particularly if the patient is not in the sitting position. If the CSF does not flow, the needle might be obstructed and rotation in 90-degree increments can be undertaken until CSF appears. If CSF does not appear in any quadrant, the needle should be advanced a few millimeters and rechecked in all four quadrants. If CSF still has not appeared and the needle is at a depth appropriate for the patient, the needle and introducer should be withdrawn and the insertion steps should be repeated. A common reason for failure is insertion of the needle off the midline (Fig. 56-5).

After CSF is freely obtained, the dorsum of the anesthesiologist's nondominant hand steadies the spinal needle against the patient's back while the syringe containing the therapeutic dose is attached to the needle. CSF is again freely aspirated into the syringe, and the anesthetic dose is injected at a rate of approximately 0.2 mL/sec. After completion of the injection, 0.2 mL of CSF can be aspirated into the syringe and reinjected into the subarachnoid space to reconfirm location and clear the needle of the remaining local anesthetic.

The paramedian approach exploits the larger "subarachnoid target" that exists if a needle is inserted slightly lateral to the midline (Fig. 56-6). The paramedian approach may be especially useful in the setting of diffuse calcification of the interspinous ligament. The most common error when using the paramedian technique is that the needle entry site is placed too far off midline, which makes the vertebral laminae barriers to insertion of the needle. In the paramedian approach, a skin wheal is raised 1 cm lateral and 1 cm caudad to the corresponding spinous process. A longer needle (e.g., 3 to 5 cm) is then used to infiltrate deeper tissues in a cephalomedial plane. The spinal introducer and needle are next inserted 10 to 15 degrees off the sagittal plane in a cephalomedial plane (see Fig. 56-6). Similar to the midline approach, the most common error is to angle the needle too far cephalad on initial insertion. Nevertheless, if the needle contacts bone, it is redirected slightly in a cephalad direction. If bone is again contacted, but at a deeper level, the slight cephalad angulation is continued because it is likely that

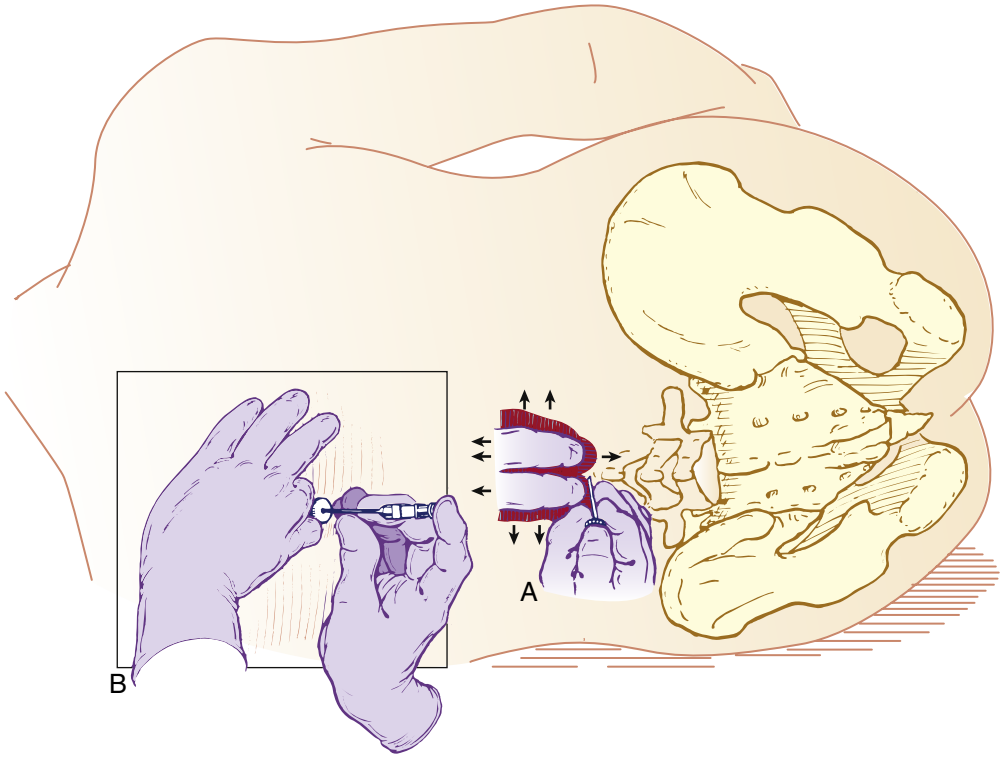


Figure 56-5. Insertion of the spinal needle. **A,** The palpating fingers are "rolled" in a side-to-side and a cephalad-to-caudad direction to identify the interspinous space. **B,** During needle insertion, the needle should be stabilized in a tripod fashion while placed in the hand, similar to a dart being thrown.

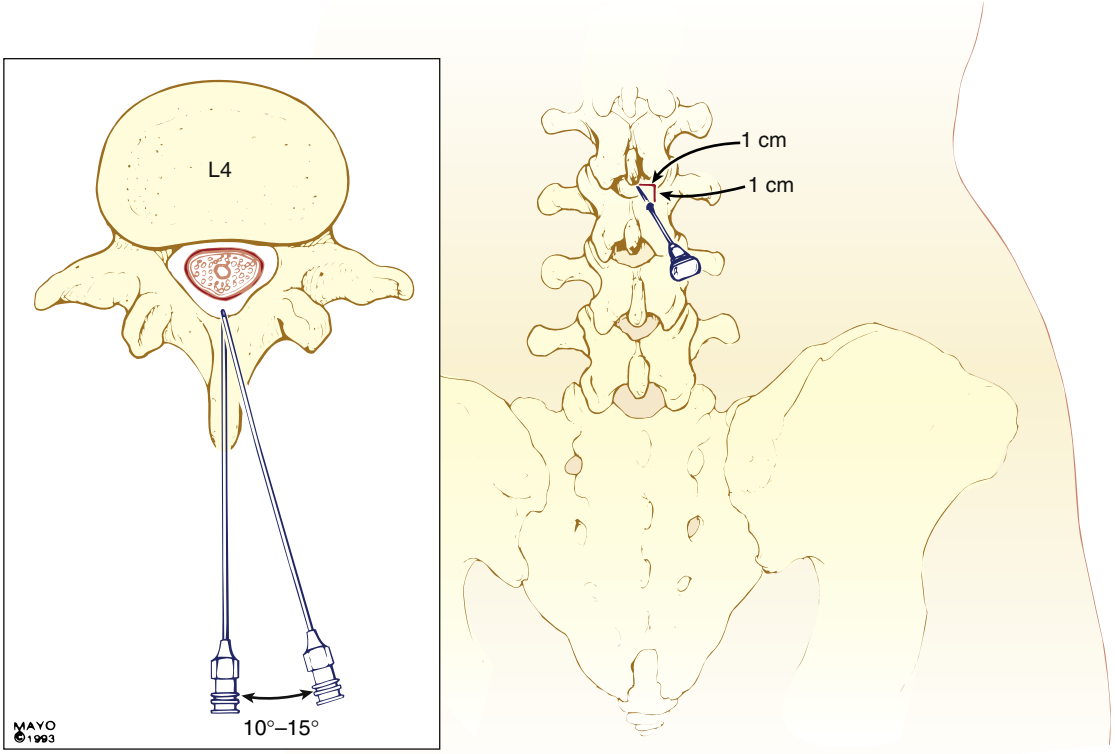


Figure 56-6. Vertebral anatomy of the midline and paramedian approaches to centroneuraxis blocks. The midline approach highlighted in the *inset* requires anatomic projection in only two planes: sagittal and horizontal. The paramedian approach shown in the *inset* and in the posterior view requires an additional oblique plane to be considered, although the technique may be easier in patients who are unable to cooperate in minimizing their lumbar lordosis. The paramedian needle is inserted 1 cm lateral and 1 cm caudad to the caudad edge of the more superior vertebral spinous process. The paramedian needle is inserted approximately 15 degrees off the sagittal plane, as shown in the inset. *(Courtesy of the Mayo Foundation, Rochester, Minn.)*

the needle is being "walked up" the lamina. As in the midline approach, the characteristic feel of the ligaments and dura is possible, but only once the ligamentum flavum is reached because the needle is this time not passing through the supraspinous and interspinous ligaments. After CSF is obtained, the block is carried out in a manner similar to that described for the midline approach.

SPECIAL SPINAL TECHNIQUES

Continuous Spinal Anesthesia

Continuous spinal anesthesia allows incremental dosing of local anesthetic and therefore predictable titration of the block to an appropriate level, with better hemodynamic stability than a single-shot spinal.[40] It is useful in controlling arterial blood pressure in such patients with severe aortic stenosis or pregnant women with complex cardiac disease. In obstetrics, it may also be used in patients with morbid obesity and where previous spinal surgery may hinder epidural spread. Spinal catheters also serve as an alternative to the combined spinal-epidural (CSE) technique for prolonged cases and have been used in selected patients for laparotomies where general anesthesia may be too great a risk.[234] If a continuous spinal anesthetic is undertaken, a needle with a laterally facing opening may be used to perform the lumbar puncture (Fig. 56-7). A midline or paramedian approach may be used, with some experts suggesting that use of the paramedian approach facilitates insertion of the catheter.[235] The catheter should be threaded 2 to 3 cm into the subarachnoid space and the needle withdrawn over the catheter. The catheter must never be withdrawn back into the needle shaft in case a piece of the catheter is sheared off and left in the subarachnoid space. Care must also be taken to ensure that the catheter is not inserted more deeply into the subarachnoid space when the needle is withdrawn over the catheter. Spinal microcatheters exist, but these have been associated with cauda equina syndrome,[5] probably because of lumbosacral pooling of local anesthetic. Catheter-over-the-needle devices are also available for use with continuous spinal anesthesia, with the advantage of minimizing leakage of CSF around the catheter,[236] but these may be more difficult to insert.[236] Finally, epidural doses of local anesthetic should not be infused or "bloused" into spinal catheters, and strict attention must also be paid to sterile technique.

Unilateral Spinal Anesthesia and Selective Spinal Anesthesia

The terms *unilateral spinal anesthesia* and *selective spinal anesthesia* overlap slightly, but both refer to small-dose techniques that capitalize on baricity and patient positioning to hasten recovery. A recent systematic review found that a dose of 4 to 5 mg of hyperbaric bupivacaine with unilateral positioning was adequate for knee arthroscopy.[171] This technique has also been used for unilateral inguinal hernia repair with a dose of 8 mg bupivacaine. In selective spinal anesthesia, minimal local anesthetic doses are used with the goal of anesthetizing only the sensory fibers to a specific area.[237,238] These doses are discussed in more detail in the chapter on anesthesia for ambulatory surgery (see Chapter 89).

BLOCK MONITORING

Once the spinal anesthetic has been administered, the onset, extent, and quality of the sensory and motor blocks must be assessed while heart rate and arterial blood pressure are also being monitored for any resultant sympathetic blockade. There are many methods of assessing sensory block, but cold sensation and pinprick representing C- and A-delta fibers, respectively, are used more

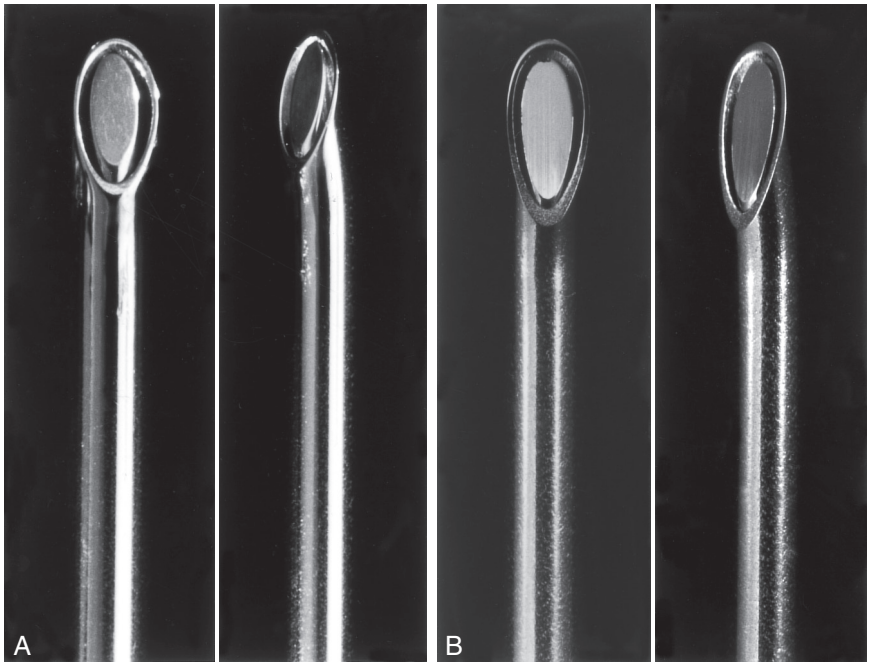


Figure 56-7. Examples of continuous spinal needles, including a disposable, 18-G Hustead **(A)** and a 17-G Tuohy **(B)** needle. Both have distal tips designed to direct the catheters inserted through the needles along the course of the bevel opening; 20-G epidural catheters are used with these particular needle sizes.

often than mechanical stimuli such as touch, pressure, and von Frey hairs, which reflect the A-beta nerves. Loss of sensation to cold usually occurs first, verified using an ethyl chloride spray, ice, or alcohol, followed by the loss of sensation to pinprick, verified using a needle that does not pierce the skin.[20] Finally, loss of sensation to touch occurs. Dermatomal block height also varies with the method of assessment, but in general, peak height is measured most cephalad using loss of cold, and is measured lower with pinprick, and lowest with touch.[239] Assessing dermatomal block height assumes that absence of sensation to these stimuli equates to blockade of the nociceptive fibers, but this is not necessarily the case.[240] Other electrical and experimental chemical methods of assessing pain have been used but gentle pinprick remains the simplest.[91,241] Motor block may also be measured in a variety of ways. The modified Bromage scale (Box 56-1) is most commonly used, although this represents only lumbosacral motor fibers.[242] Electromyography and pulmonary function tests have been used to measure abdominal and thoracic motor function, but these are neither practical nor specific.

In practice, the combination of sympathetic block with an adequate sensory level and motor block (inability to straight-leg raise ensures at least that lumbar nerves are blocked) are used to confirm spinal efficacy. Ensuring that the level of block using cold or pinprick is two to three segments above the expected level of surgical stimulus is commonly considered adequate.

EPIDURAL ANESTHESIA

FACTORS AFFECTING EPIDURAL BLOCK HEIGHT

The epidural space is a collapsible, distensible reservoir through which drugs spread and are removed by diffusion, vascular transport, and leakage. Spread of anesthetic within the epidural space, and subsequent block height, is related to a variety of factors, not all of which can be manipulated by the anesthesiologist (Table 56-5).[26]

BOX 56-1 *Modified Bromage Scale*

- 0: No motor block
- 1: Inability to raise extended leg; able to move knees and feet
- 2: Inability to raise extended leg and move knee; able to move feet
- 3: Complete block of motor limb

Drug Factors

The volume and total mass of injectate are the most important drug-related factors that affect block height after the administration of local anesthetic in the epidural space. As a general principle, 1 to 2 mL of solution should be injected per segment to be blocked. Although additives such as bicarbonate, epinephrine, and opioids influence onset, quality, and duration of analgesia and anesthesia, these do not affect spread.

Patient Factors

Age can influence epidural block height.[26] There appears to be a stronger correlation with age and block height in thoracic epidurals, with one study suggesting that 40% less volume is required in the elderly (see Chapter 80).[243] Possible reasons include decreased leakage of local anesthetic through intervertebral foramina, decreased compliance of the epidural space in the elderly resulting in greater spread, or an increased sensitivity of the nerves in the elderly. As with spinal anesthesia, it appears that only the extremes of patient height influence local anesthetic spread in the epidural space. Weight is not well correlated with block height in the settings of either lumbar or thoracic epidural anesthesia.[244] Less local anesthetic is required to produce the same epidural spread of anesthesia in pregnant patients. Although this may be in part a result of engorgement of epidural veins secondary to increased abdominal pressure, the effect also occurs in early pregnancy.[245]Also, continuous positive airway pressure increases the height of a thoracic epidural block.[246,247]

Procedure Factors

The level of injection is the most important procedural-related factor that affects epidural block height. In the upper cervical region, spread of injectate is mostly caudal, in the midthoracic region spread is equally cephalad and caudal, and in the low thoracic region spread is primarily cephalad.[248] After a lumbar epidural, spread is more cephalad than caudal. Some studies suggest that the total number of segments blocked is less in the lumbar region compared with thoracic levels for a given volume of injectate. Patient position has been shown to affect spread of lumbar epidural injections, with preferential spread and faster onset to the dependent side in

TABLE 56-5 **FACTORS AFFECTING EPIDURAL LOCAL ANESTHETIC DISTRIBUTION AND BLOCK HEIGHT**

	More Important	Less Important	Not Important
Drug Factors	Volume Dose	Concentration	Additives
Patient Factors	Elderly age Pregnancy	Weight Height Pressure in adjacent body cavities	
Procedure Factors	Level of injection	Patient position	Speed of injection Needle orifice direction

Adapted from Visser WA, Lee RA, Gielen MJM: Factors affecting the distribution of neural blockade by local anesthetics in epidural anesthesia and a comparison of lumbar versus thoracic epidural anesthesia, Anesth Analg *2008;107:708-721.*

the lateral decubitus position.[249] The sitting and supine positions do not affect epidural block height. However, the head-down tilt position does increase spread in obstetric patients.[250] Needle bevel direction and speed of injection also do not appear to influence the spread of a bolus injection.

PHARMACOLOGY

Local anesthetics for epidural use may be classified into short-, intermediate-, and long-acting drugs. A single bolus dose of local anesthetic in the epidural space can provide surgical anesthesia ranging from 45 minutes up to 4 hours depending on the type of local anesthetic administered and the use of any additives (Table 56-6). Most commonly, an epidural catheter is left in situ so that local anesthetic–based anesthesia or regular analgesia can be extended indefinitely.

Short-Acting and Intermediate-Acting Local Anesthetics

Procaine. Similar to spinal anesthesia, procaine is not commonly used for epidural anesthesia. Five-percent procaine has a slow onset and the resultant block can be unreliable and of poor quality.

Chloroprocaine. Chloroprocaine is available preservative free in 2% and 3% concentrations for epidural injection, with the latter preferable for surgical anesthesia because the former may not produce muscle relaxation. The 3% preparation has an onset time of 10 to 15 minutes and a duration of up to 60 minutes. Adding epinephrine prolongs the block for up to 90 minutes. Before the development of preservative-free preparations, large volumes (>25 mL) of chloroprocaine had been associated with deep, aching, burning lumbar back pain.[251] This was thought to be secondary to the ethylenediaminetetraacetic acid that chelated calcium and caused a localized hypocalcemia. In addition, chloroprocaine can antagonize the effects of epidural morphine.[242] This may be a result of opioid receptor antagonism by either the chloroprocaine or a metabolite. Antagonism of an intracellular messenger and decreased morphine availability caused by a reduction in perineural pH are also proposed mechanisms. However, morphine and chloroprocaine seem like an illogical combination because the beneficial ultra-short duration of action of chloroprocaine is offset by the addition of morphine.

Articaine. Articaine is not widely used for epidural anesthesia and has not been studied extensively. When 2% articaine was compared with epidural lidocaine in one study, it had a similar latency, spread, duration, and motor block.[252] It has also been used for obstetric epidural analgesia.[148]

Lidocaine. Lidocaine is available in 1% and 2% solutions; it has an onset time of 10 to 15 minutes and a duration of up to 120 minutes, which can be extended to 180 minutes with the addition of epinephrine. Unlike spinal anesthesia, TNS is not commonly associated with epidural lidocaine.[253]

Prilocaine. Prilocaine is available in 2% and 3% solutions. The 2% solution produces a sensory block with minimal motor block. Onset time is approximately 15 minutes, with a duration of approximately 100 minutes. When compared with lidocaine, prilocaine has a more marked sensory blockade and a longer duration (different from Cousins).[242] In large doses, prilocaine is associated with methemoglobinemia.[156,254]

Mepivacaine. Mepivacaine is available as 1%, 1.5%, and 2% preservative-free solutions. The 2% preparation has an onset time similar to lidocaine of approximately 15 minutes, but a slightly longer duration (up to 200 minutes with epinephrine), making it a preferred option by some centers for surgery of an intermediate duration.

Long-Acting Local Anesthetics

Tetracaine. Tetracaine is not widely used for epidural anesthesia because of unreliable block height and, in larger doses, systemic toxicity.

Bupivacaine. Bupivacaine is available in 0.25%, 0.5%, or 0.75% preservative-free solutions. The onset time is around 20 minutes with a duration of up to 225 minutes, which is prolonged only slightly by the addition of epinephrine (to 240 minutes). More dilute concentrations such as 0.125% to 0.25% can be used for analgesia. However, disadvantages include cardiac and central nervous system toxicity and the potential for motor block

TABLE 56-6 **COMPARATIVE ONSET TIMES AND ANALGESIC DURATIONS OF LOCAL ANESTHETICS ADMINISTERED EPIDURALLY IN 20- TO 30-ML VOLUMES**

Drug	Concentration (%)	Onset (min)	Duration (min)	
			Plain	1:200,000 Epinephrine
2-Chloroprocaine	3	10-15	45-60	60-90
Lidocaine	2	15	80-120	120-180
Mepivacaine	2	15	90-140	140-200
Bupivacaine	0.5-0.75	20	165-225	180-240
Etidocaine	1	15	120-200	150-225
Ropivacaine	0.75-1.0	15-20	140-180	150-200
Levobupivacaine	0.5-0.75	15-20	150-225	150-240

Data from Cousins MJ, Bromage PR: Epidural neural blockade. In Cousins MJ, Bridenbaugh PO, editors: Neural blockade in clinical anesthesia and management of pain. *Philadelphia, 1988, JB Lippincott, pp 255.*

from larger doses. Solutions of 0.5% and 0.75% are used to provide surgical anesthesia. Liposomal bupivacaine is currently under investigation for epidural use. An epidural bolus of liposomal 0.5% bupivacaine provided similar onset but longer-lasting analgesia to boluses of plain bupivacaine.[255] It does not appear to be more toxic than plain bupivacaine or to have a differing cardiac safety profile. The benefit, as with extended-release morphine (discussed later), is the lack of need for an epidural catheter. Conversely, such extended-release boluses are less titratable if for any reason the epidural needs to be terminated early.

Levobupivacaine. Levobupivacaine can be used as an epidural local anesthetic in 0.5% to 0.75% concentrations for surgical anesthesia, whereas analgesia can be achieved with concentrations of 0.125% to 0.25%. Levobupivacaine administered epidurally has the same clinical characteristics as bupivacaine.[129,256,257] The advantage of levobupivacaine is that it is less cardiotoxic compared with bupivacaine.[175,258]

Ropivacaine. Ropivacaine is available in 0.2%, 0.5%, 0.75%, and 1.0% preservative-free preparations. For surgical anesthesia, 0.5% to 1.0% is used, whereas 0.1% to 0.2 % is used for analgesia. Ropivacaine is associated with a superior safety profile compared with bupivacaine.[259,260] Data from animal models suggest that bupivacaine has a 1.5 to 2.5 lower seizure threshold than ropivacaine. Ropivacaine is also less cardiotoxic. When compared with bupivacaine and levobupivacaine, ropivacaine at equivalent concentrations has a relatively similar clinical profile. Ropivacaine has a slightly shorter duration of action and less motor block, although the reduced motor block may in fact reflect different potencies of the drugs rather than a true motor-sparing effect of ropivacaine. Epidurally administered ropivacaine is 40% less potent than bupivacaine.[179,180,261]

Epidural Additives

Vasoconstrictors. Epinephrine reduces vascular absorption of local anesthetics in the epidural space. The local anesthetics vary in their responsiveness to epinephrine. The effect is the most with lidocaine,[262] mepivacaine, and chloroprocaine (up to 50% prolongation), with a lesser effect with bupivacaine, levobupivacaine, and etidocaine, and a limited effect with ropivacaine, which already has intrinsic vasoconstrictive properties (see Table 56-6). Epinephrine itself may also have some analgesic benefits because it is absorbed into the CSF, where it can act on dorsal horn α_2 receptors.[263] Phenylephrine has been used in epidural anesthesia less widely than in spinal anesthesia, perhaps because it does not reduce peak blood levels of local anesthetic as effectively as epinephrine does during epidural use.[264]

Opioids. Opioids synergistically enhance the analgesic effects of epidural local anesthetics, without prolonging motor block. A combination of local anesthetic and opioid reduces the dose-related adverse effects of each drug independently. The analgesic benefits of neuraxial opioids must be balanced against the dose-dependent side effects. As with intrathecal opioids, there appears to be a therapeutic ceiling effect above which only side effects increase. Opioids may also be used alone, particularly when there are concerns regarding hemodynamic instability. Epidural opioids work by crossing the dura and arachnoid membrane to reach the CSF and spinal cord dorsal horn. Lipophilic opioids, such as fentanyl and sufentanil, partition into epidural fat and therefore are found in lower concentrations in CSF than hydrophilic opioids, such as morphine and hydromorphone. Fentanyl and sufentanil are also readily absorbed into the systemic circulation, and several studies suggest that this is the principal analgesic mechanism.[265,266]

Epidural morphine is administered as a bolus of 1 to 5 mg, with an onset time of 30 to 60 minutes and duration of up to 24 hours. The optimal dose that balances analgesia while minimizing side effects is 2.5 to 3.75 mg.[267] Alternatively, morphine can be administered continuously in doses of 0.1 to 0.4 mg/hr through an epidural catheter. Hydromorphone is more hydrophilic than fentanyl but more lipophilic than morphine. It can be administered as a bolus of 0.4 to 1.5 mg, with onset at 15 to 30 minutes and a duration of 18 hours. Hydromorphone used as an infusion is delivered at rates between 5 and 20 μg/hr. The onset of epidural fentanyl and sufentanil is 5 to 15 minutes and lasts only 2 to 3 hours. Bolus doses of 10 to 100 μg may be used to provide analgesia. Diamorphine is available in the United Kingdom and used in doses of 2 to 3 mg as epidural boluses, or approximately 0.05 mg/mL in an infusion.

Depodur is an extended-release liposomal formulation of morphine used as a single-shot lumbar epidural dose, thereby avoiding issues and side effects of a continuous local anesthetic infusion and indwelling catheters, particularly in patients receiving anticoagulants. When administered before surgery (or after clamping of the cord in cesarean deliveries), Depodur can provide up to 48 hours of pain relief.[268,269] A dose of 10 to 15 mg is recommended for lower abdominal surgery, and 15 mg is recommended for major lower limb orthopedic surgery.

α_2-Agonists. Epidural clonidine can prolong sensory block to a greater extent than motor block. The mechanism appears to be mediated by the opening of potassium channels and subsequent membrane hyperpolarization[270] rather than an α_2-agonist effect. The addition of clonidine reduces both epidural local anesthetic and opioid requirements.[271-273] Other benefits of clonidine may include a reduced immune stress and cytokine response.[274] Epidural clonidine does have a variety of side effects including hypotension, bradycardia, dry mouth, and sedation. The cardiovascular effects may be greatest when clonidine is administered in the epidural space at the thoracic level.[275] In preliminary studies, epidural dexmedetomidine has also been shown to reduce intraoperative anesthetic requirements, improve postoperative analgesia, and prolong both sensory and motor block.[276]

Other Drugs. Conflicting reports exist regarding the benefit of epidural ketamine and whether it is neurotoxic.[277-279] Epidural neostigmine provides labor analgesia before local anesthetic infusion without causing respiratory depression,

hypotension, or motor impairment.[280] Midazolam, tramadol, dexamethasone, and droperidol have also been studied but are not commonly used.

Carbonation and Bicarbonate. Many local anesthetic preparations have a pH between 3.5 and 5.5 for chemical stability and bacteriostasis. At these low pHs, a higher proportion of the drug is in the ionized form and is therefore unable to cross nerve membranes to reach the internal binding site on sodium channels. Both carbonation of the solution and adding bicarbonate have been used in an attempt to increase the solution pH, and therefore the non-ionized free-base proportion of local anesthetic. Although carbonation may theoretically increase the speed of onset and quality of the block by producing more rapid intraneural diffusion and more rapid penetration of connective tissue surrounding the nerve trunk,[281,282] available data suggest that there are no clinical advantages for carbonated solutions.[235,283]

EPIDURAL TECHNIQUE

Preparation

Patient preparation as previously described for spinal anesthesia must equally be applied to epidural anesthesia, namely consent, monitoring, and resuscitation equipment, intravenous access, and choosing the patient and drugs appropriately depending on comorbidities and the nature of surgery. Sterility is arguably even more important than spinal anesthesia because a catheter is often left in situ. The extent of the surgical field must be understood so that the epidural may be inserted at the appropriate level—that is, the lumbar, low-, mid-, or high-thoracic, or less commonly, cervical.[26] A variety of epidural needles have been used for epidural anesthesia, but Tuohy needles are most common (Fig. 56-8). These needles are usually 16 to 18 g in size and have a 15- to 30-degree curved, blunt "Huber" tip designed to both reduce the risk of

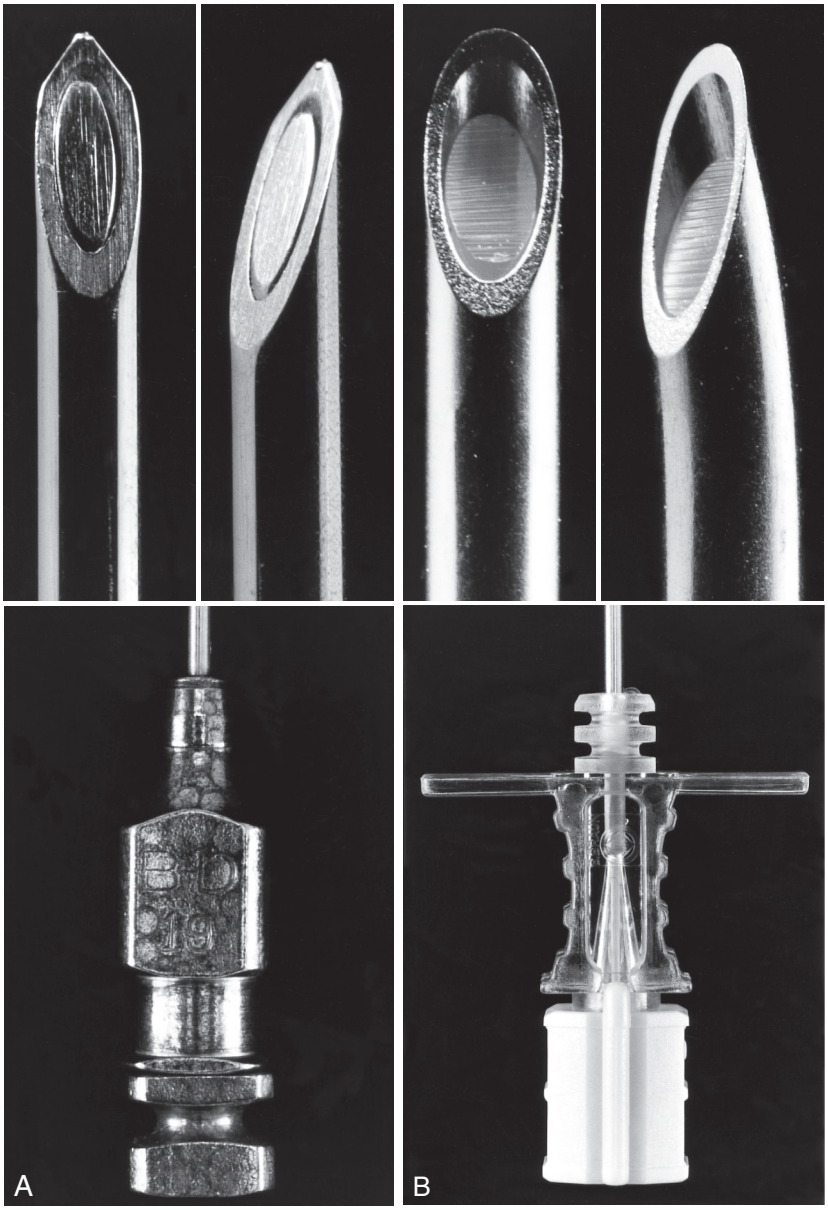


Figure 56-8. Epidural needles with catheter assortment. **A,** A 19-G reusable Crawford epidural needle. **B,** A 19-G disposable Tuohy needle.

Continued

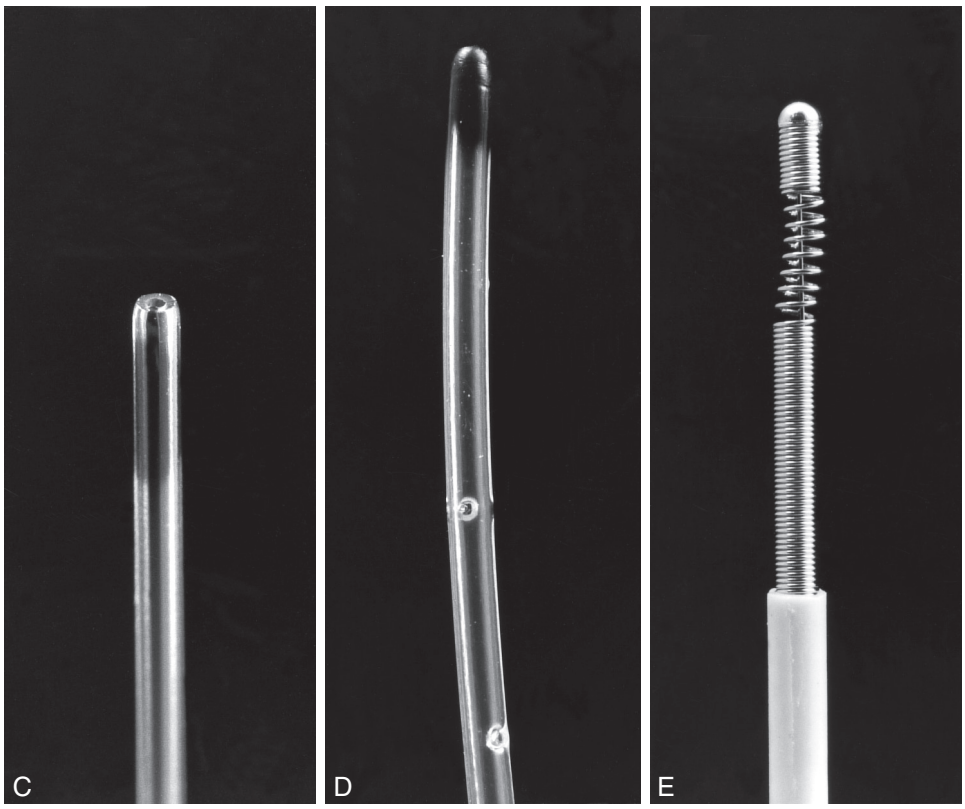


Figure 56-8, cont'd. C, Single–end-hole epidural catheter. **D,** Closed-tip, multiple–side-hole catheter. **E,** Spring wire–reinforced, polymer-coated epidural catheter.

accidental dural puncture and guide the catheter cephalad. The needle shaft is marked in 1-cm intervals so that depth of insertion can be identified. The catheter is made of a flexible, calibrated, durable, radiopaque plastic with either a single end hole or multiple side orifices near the tip. Several investigators have found that multiple-orifice catheters are superior, with a reduced incidence of inadequate analgesia.[284-286] However, the use of multiorifice catheters in pregnant women resulted in a more frequent incidence of epidural vein cannulation.[287]

The method of identifying the epidural space must also be predetermined. Most practitioners use a loss-of-resistance technique to either air or saline, rather than the hanging drop technique, both of which are described later. If a loss-of-resistance technique is used, an additional decision about the type of syringe (i.e., glass versus low-resistance plastic and Luer-Lok versus friction hub) is required.

Position

The sitting and lateral decubitus positions necessary for epidural puncture are the same as those for spinal anesthesia (see also Chapter 77). As before, inadequate positioning of the patient can complicate an otherwise meticulous technique. Shorter insertion times occur in the sitting position for thoracic epidurals compared with the lateral decubitus position, but ultimately, success rates are comparable.[288] As with spinal anesthesia, epidurals are performed with the patient awake.[76]

TABLE 56-7 **SUGGESTED EPIDURAL INSERTION SITES FOR COMMON SURGICAL PROCEDURES**

Nature of Surgery	Suggested Level of Insertion	Remarks
Hip surgery Lower extremity Obstetric analgesia	Lumbar L2-L5	
Colectomy, Anterior resection Upper abdominal surgery	Lower thoracic T6-T8	Spread more cranial than caudal
Thoracic	T2-T6	Midpoint of surgical incision

Modified from Visser WA, Lee RA, Gielen MJM: Factors affecting the distribution of neural blockade by local anesthetics in epidural anesthesia and a comparison of lumbar versus thoracic epidural anesthesia, Anesth Analg *107:708-721, 2008.*

Projection and Puncture

The level of needle insertion depends on the location of surgery (Table 56-7). Important surface landmarks include the intercristal line (corresponding to the L4-L5 interspace), the inferior angle of the scapula (corresponding to the T7 vertebral body), the root of the scapular spine (T3), and the vertebra prominens (C7). Ultrasonography may be useful to identify the correct thoracic space[233]; it is less commonly used for thoracic

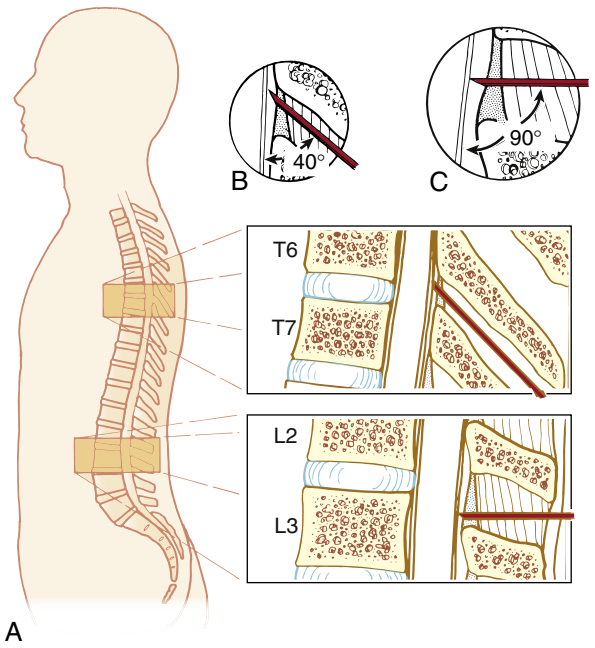


Figure 56-9. A, Lumbar and thoracic epidural technique. The increased angle of needle insertion during thoracic epidural cannulation may provide a slightly longer distance of "needle travel" before entering the subarachnoid space. In contrast to lumbar epidural cannulation **(B),** the distance traveled is modified by a more perpendicular angle of needle insertion **(C).**

epidural insertion, however, because the acoustic shadows make visualization of landmarks such as the ligamentum flavum and intrathecal space more difficult.[289] A variety of different needle approaches exist: midline, paramedian, modified paramedian (Taylor approach), and caudal.

A midline approach is commonly chosen for lumbar and low thoracic approaches. After local anesthetic infiltration of the skin, the nondominant hand can be rested on the back of the patient, with the thumb and index finger holding the needle hub or wing. The angle of approach should be only slightly cephalad in the lumbar and low-thoracic regions, whereas in the midthoracic region, the approach should be more cephalad because of the significant downward angulation of the spinous processes (Fig. 56-9). In a controlled fashion, the needle should be advanced with the stylet in place through the supraspinous ligament and into the interspinous ligament, at which point the stylet can be removed and the syringe attached. If it is in the correct location, the needle should rest firmly in the tissues. Some advocate needle placement in the ligamentum flavum for both the loss-of-resistance and hanging-drop methods before attaching the syringe, but this may be difficult, particularly for novices; however, this may allow an improved appreciation of epidural anatomy for the operator. If the needle is merely inserted into the supraspinous ligament and then loss-of-resistance or hanging-drop insertion is begun, there is an increased chance of false loss-of-resistance, possibly because of defects in the interspinous ligament.[290] Such false-positive rates can be as high as 30%.

Air or saline are the two most common noncompressible media used to detect a loss-of-resistance when identifying the epidural space. Each involves intermittent (for air) or constant (for saline) gentle pressure applied to the bulb of the syringe with the dominant thumb while the needle is advanced with the nondominant hand. A combination of air and saline may also be used, incorporating 2 mL of saline and a small (0.25 mL) air bubble. Usually the ligamentum flavum is identified as a tougher structure with increased resistance, and when the epidural space is subsequently entered, the pressure applied to the syringe plunger allows the solution to flow without resistance into the epidural space. There are reports that air is less reliable in identifying the epidural space, results in a higher chance of incomplete block, and may also cause both pneumocephalus (which can result in headaches) and venous air embolism in rare cases. If air is chosen, the amount of air injected after loss-of-resistance should therefore be minimized. A recent meta-analysis suggested that there was no difference in adverse outcome in the obstetric population when air or saline was used.[291] Another meta-analysis found that fluid inserted through the epidural needle before catheter insertion reduces the risk of epidural vein cannulation by the catheter.[287] One proposed disadvantage of using saline is that it may be more difficult to readily detect an accidental dural puncture.

An alternative method of identifying the epidural space is the hanging-drop technique. After the needle is placed into the ligamentum flavum, a drop of solution such as saline is placed within the hub of the needle. When the needle is advanced into the epidural space, the solution should be "sucked in." The theory behind this maneuver has traditionally been attributed to subatmospheric pressure in the epidural space, although recent experimental evidence in the cervical region suggests that using negative-pressure methods are poorly reliable and only useful in the sitting position.[292] The subatmospheric pressure has been related to expansion of the epidural space as the needle pushes the dura away from the ligamentum flavum.[293] The negative intrathoracic pressure may influence the pressure in the epidural space in the thoracic region and should be maximal during inspiration. Timing needle advancement to coincide with inspiration may be difficult, however.

When a lumbar midline approach is used, the depth from skin to the ligamentum flavum commonly reaches 4 cm, with the depth in most (80%) patients being between 3.5 and 6 cm; it can be longer or shorter in obese or very thin patients, respectively. Ultrasonography may be useful to predict the depth before needle insertion.[233] In the lumbar region, the ligamentum flavum is 5 to 6 mm thick in the midline. When a thoracic approach is chosen, needle control is of equal or greater importance because injury to the spinal cord is possible if the needle is advanced too far, although there are no data to suggest that approaching the epidural space at the lumbar level is any more or less safe than at the thoracic level. This may be partly because those using the thoracic technique are most often anesthesiologists with considerable experience in lumbar epidural anesthesia.[294] In addition, the increased angle of needle insertion in the thoracic region

may theoretically provide an element of safety in that the more acute angle necessary to gain access to the epidural space provides some margin of safety (see Fig. 56-9).

When the epidural space is identified, the depth of the needle at the skin should be noted. The syringe can then be removed and a catheter gently threaded to approximately the 15- to 18-cm mark to ensure a sufficient length has entered the epidural space. The needle can then be carefully withdrawn, and the catheter is withdrawn to leave 4 to 6 cm in the space. Catheter space less than 4 cm in length in the epidural space may increase the risk of catheter dislodgement and inadequate analgesia, whereas threading more catheter may increase the likelihood of catheter malposition or complications.[295-298]

As described earlier, a false loss-of-resistance can occur and is one of the causes of a failed block. The Tsui test may be used to confirm the epidural catheter position.[299] This test stimulates the spinal nerve roots with a low electrical current conducted through normal saline in the epidural space and an electrically conducting catheter. A metal-containing catheter must be used, with the cathode lead of the nerve stimulator connected to the catheter via an electrode adapter, whereas the anode lead is connected to an electrode on the patient's skin. At currents of approximately 1 to 10 mA, corresponding muscle twitches (i.e., intercostal or abdominal wall muscles for thoracic epidural catheters) can be used to identify catheter tip location. Subarachnoid and subdurally positioned epidural catheters elicit motor responses at a much lower threshold current (<1 mA), because the stimulating catheter is in very close or direct contact with highly conductive CSF.[300,301]

When the catheter is positioned at the desired depth, it must be secured to the skin. Commercial fixation devices exist, and some are superior to tape alone.[302] Tunneling can reduce catheter migration and improve lasting block success.[303] However, tunneling has not been compared with noninvasive catheter fixation devices in a well-designed study.

Paramedian Approach

The paramedian approach is particularly useful in the mid- to high thoracic region, where the angulation of the spine and the narrow spaces render the midline approach problematic. The needle should be inserted 1 to 2 cm lateral to the inferior tip of the spinous process corresponding to the vertebra above the desired interspace. The needle is then advanced horizontally until the lamina is reached and then redirected medially and cephalad to enter the epidural space. The Taylor approach is a modified paramedian approach via the L5-S1 interspace, which may be useful in trauma patients who cannot tolerate or are not able to maintain a sitting position. The needle is inserted 1 cm medial and 1 cm inferior to the posterior superior iliac spine and is angled medially and cephalad at a 45- to 55-degree angle.

Before initiating an epidural local anesthetic infusion, a test dose may be administered. The purpose of this is to exclude intrathecal or intravascular catheter placement. A small volume of lidocaine 1.5% with epinephrine is traditionally used for this purpose. A recent systematic review found reasonable evidence that 10 to 15 μg of epinephrine alone in nonpregnant adult patients was the best pharmacologic method of detecting intravascular placement, using endpoints of an increase in systolic blood pressure more than 15 mm Hg or an increase in heart rate more than 10 beats/min. The optimal method of detecting intrathecal or subdural placement, however, could not be ascertained.[304]

COMBINED SPINAL-EPIDURAL

Combined spinal-epidural anesthesia was first described in 1937 but has subsequently been modified over the past 30 years[305-310] and the CSE technique is now seeing increasing popularity. A CSE allows flexibility in a number of clinical settings because the more rapid onset of spinal block compared with epidural anesthesia allows the operative procedure to begin earlier, whereas the epidural catheter still provides both effective postoperative analgesia and allows anesthesia to be extended as the spinal resolves. This is particularly useful during labor, where opioid and a small dose of local anesthetic may be injected through a small spinal needle to provide rapid analgesia, whereas the epidural catheter can be used thereafter for both analgesia and surgical anesthesia if an operative delivery becomes necessary. Another significant advantage of CSE in general is the ability to use a low dose of intrathecal local anesthetic, with the knowledge that the epidural catheter may be used to extend the block if necessary. The addition of either local anesthetic or saline alone to the epidural space via the catheter compresses the dural sac and increases the block height. This latter technique is called epidural volume extension (EVE) and has been shown in cesarean delivery to provide a comparable sensory block to larger doses of intrathecal local anesthetic (with no epidural volume extension) but with significantly faster motor recovery.[311] The principle of using a lower dose of spinal anesthetic and titrating the epidural dose after the spinal anesthetic to reach the appropriate block height is a reduction in side effects,[312] with faster recovery, which can in turn potentially hasten discharge. This sequential technique also provides greater hemodynamic stability for high-risk patients using a lower initial mass of drug for spinal anesthetic, with subsequent gradual extension of the block if necessary using the epidural.

TECHNIQUE

The CSE technique most commonly involves placement of the epidural needle first, followed by either a "needle through needle" technique to reach the subarachnoid space or an altogether separate spinal needle insertion at either the same or different interspace. Some but not all studies have demonstrated greater success and lower failure rates with the separate needle insertion technique.[313-316] This method has the potential advantage of being able to confirm that the epidural catheter is functional before spinal anesthesia is administered, which, although it is time consuming, may be advantageous if the epidural catheter is to be relied upon for anesthesia when the spinal component resolves. Conversely, this method theoretically risks shearing the epidural catheter

that is already in situ. If a needle-through-needle technique is chosen, special CSE kits are available with long spinal needles, some of which can be locked in place for the subarachnoid injection.

CAUDAL ANESTHESIA

Caudal anesthesia is popular in pediatric anesthesia (see Chapter 93), but the technique also can be used in adults, although it is unpredictable when upper abdominal or thoracic spread is required. Its indications in adults therefore are essentially the same as those for lumbar epidural anesthesia, although it may be particularly useful when sacral anesthetic spread is desired (e.g., perineal, anal, rectal procedures), where a spinal surgery scar may prevent a lumbar anesthetic technique and, more commonly, in chronic pain and cancer pain management (see Chapter 64). The use of fluoroscopic guidance and, more recently, ultrasonography can help guide correct needle placement and reduce the rate of a failed block.[317] Ultrasonography is of even greater benefit in children because the lack of bony ossification allows visualization of both local anesthetic spread and the position of caudal epidural catheters.[318,319]

PHARMACOLOGY

The local anesthetics used are similar to those described for epidural anesthesia and analgesia. However, in adults approximately twice the lumbar epidural dose is required to achieve a similar block with the caudal approach. The spread is also variable, making this technique in adults unreliable for procedures above the umbilicus.

TECHNIQUE

Patient preparation as described before for spinal and epidural anesthesia must be equally applied to caudal anesthesia, namely consent, monitoring and resuscitation equipment, intravenous access, and the same asepsis precautions. Caudal anesthesia requires identification of the sacral hiatus. The sacrococcygeal ligament (i.e., extension of ligamentum flavum) overlies the sacral hiatus between the two sacral cornua. To facilitate locating the cornua, the posterior superior iliac spines should be located and, by using the line between them as one side of an equilateral triangle, the location of the sacral hiatus should be approximated (Fig. 56-10). Ultrasonography can also be used to identify these landmarks,[317-319] as can fluoroscopy. Three positions (see Chapter 41) are available for caudal anesthesia, with the prone position most often chosen in adults, the lateral decubitus position most chosen in children, and the knee-chest position the most infrequently used. The lateral decubitus position is used in children because it is easier to maintain a patent airway in this position than in the prone position, and the landmarks are more easily palpable than they are in adults (see Chapter 92). This consideration is valuable because caudal anesthesia is often combined with general anesthesia in pediatric patients to decrease the amount of volatile agent used intraoperatively or to provide postoperative analgesia. In contrast, a caudal block is often administered during preoperative sedation in adults and when the prone position is applicable. When placing a patient in the prone position, a pillow should be inserted beneath the iliac crests to rotate the pelvis and make cannulation of the caudal canal easier. An additional aid is to spread the lower extremities about 20 degrees with the heels rotated laterally, which minimizes gluteal muscle contraction and eases needle insertion.

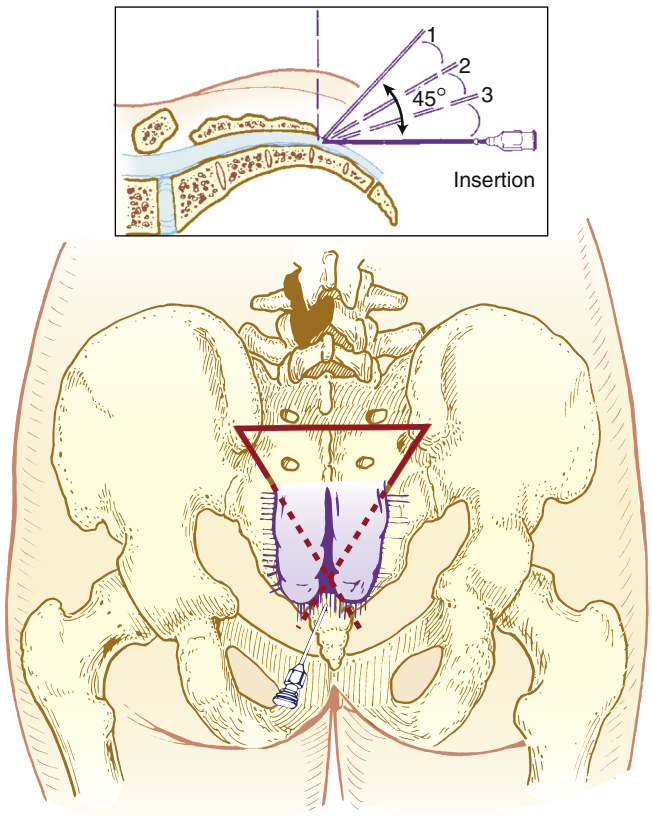


Figure 56-10. Caudal technique. Palpating fingers locate the sacral cornua by using the equilateral triangle. Needle insertion is completed by insertion and withdrawal in a stepwise fashion (*inset,* so-called 1-2-3 insertion) until the needle can be advanced into the caudal canal and the solution can be injected easily (without creation of a subcutaneous "lump" of fluid).

After the sacral hiatus is identified, the index and middle fingers of the palpating hand are placed on the sacral cornua, and after local infiltration, the caudal needle (or Tuohy needle if a catheter is to be placed) is inserted at an angle of approximately 45 degrees to the sacrum. While the needle is advanced, a decrease in resistance to needle insertion should be appreciated as the needle enters the caudal canal. The needle is advanced until bone (i.e., the dorsal aspect of the ventral plate of the sacrum) is contacted and then is slightly withdrawn, and the needle is redirected so that the angle of insertion relative to the skin surface is decreased. In male patients, this angle is almost parallel to the coronal plane; in female patients, a slightly steeper angle (15 degrees) is necessary. During redirection of the needle, loss-of-resistance is sought to confirm entry into the epidural space, and the needle advanced no more than approximately 1 to 2 cm into the caudal canal. In adults, the tip should never be advanced

beyond the S2 level (approximately 1 cm inferior to the posterior superior iliac spine), which is the level to which the dural sac extends. Additional advancement of the needle increases the risk of dural puncture, and unintentional intravascular cannulation becomes more likely. One method of increasing the likelihood of correct caudal needle placement is to inject 5 mL of saline rapidly through the caudal needle while palpating the skin overlying the sacrum. If no midline bulge is detected, the needle is probably positioned correctly. In contrast, if a midline bulge is detected during saline injection, the needle is positioned incorrectly.

After ensuring correct needle position and before injection of the therapeutic dose of caudal anesthetic, aspiration should be performed and a test dose administered because, as in lumbar epidural anesthesia, a vein or the subarachnoid space can be entered unintentionally.

COMPLICATIONS

The physiologic effects of neuraxial blocks may be misinterpreted as complications; however, clear distinction should be made between the physiologic effects of the neuraxial technique and complications, which imply some harm to the patient.[320] The material risks associated with neuraxial anesthesia must be intimately understood and respected because catastrophic injury is not unknown and serves to remind us that a person's nervous system is at the other end of the needle.[321]

NEUROLOGIC

Serious neurologic complications associated with neuraxial anesthesia are rare. As such, prohibitively large numbers of patients are required for study to estimate the frequency of these events. The true incidence of most neurologic injury after neuraxial anesthesia is unknown.

Paraplegia

The frequency of paraplegia related to neuraxial anesthesia is reported to be approximately 0.1 per 10,000,[322,323] and the mechanism of such a severe injury is likely multifactorial and difficult to identify for certain.[324] Although injury resulting from direct needle trauma to the spinal cord[325-329] may be self-evident, historical cases highlight the fundamental danger that accompanies the injection of a foreign substance into the CSF. The highly publicized cases of Woolley and Roe, two healthy, middle-aged men who became paraplegic after spinal anesthesia by the same anesthesiologist using the same drug on the same day for minor surgery at the same hospital in the United Kingdom in 1947, arguably set back the practice of spinal anesthesia for decades despite evidence that contamination by the descaling liquid used to cleanse the procedure tray had most likely been responsible.[4] Another example of catastrophic injury related to intrathecal injectate was the chloroprocaine neurotoxicity experience in the early 1980s, during which several patients developed adhesive arachnoiditis, cauda equina syndrome, or permanent paresis thought to be related to a combination of low pH and the antioxidant sodium bisulfite preservative used in early (and discontinued) preparations of the short-acting ester local anesthetic chloroprocaine.[136-139,330]

Profound hypotension or ischemia of the spinal cord can be important contributing factors in cases of paraplegia associated with neuraxial anesthesia. Anterior spinal artery syndrome, characterized by painless loss of motor and sensory function, is associated with anterior cord ischemia or infarction with sparing of proprioception, which is carried by the posterior column. The anterior cord is believed to be especially vulnerable to ischemic insult because of its single and tenuous source of arterial blood supply (the artery of Adamkiewicz). Ischemia caused by any one or a combination of profound hypotension, mechanical obstruction, vasculopathy, or hemorrhage can contribute to irreversible anterior cord damage.[331-333]

Cauda Equina Syndrome

The rate of cauda equina syndrome is approximately 0.1 per 10,000 and invariably results in permanent neurologic deficit.[322] The lumbosacral roots of the spinal cord may be particularly vulnerable to direct exposure of large doses of local anesthetic, whether it is administered as a single injection of relatively highly concentrated local anesthetic (e.g., 5% lidocaine)[334] or prolonged exposure to a local anesthetic through a continuous catheter.[5,335,336] The U.S. Food and Drug Administration withdrew approval for spinal catheters smaller than 24 G in size in 1992 because of concerns about a perceived association between the small-bore catheters and the development of cauda equina syndrome.[337] Although small-bore catheters can reduce the risk of headache, they can predispose to pooling of local anesthetic around the lumbosacral nerve roots, possibly because of slow injectate flow through the fine-bore catheter, thereby exposing them to high concentrations of local anesthetic. However, small-bore spinal catheters are being used effectively in Europe, and they are beginning to reappear in the United States, although it has taken nearly 15 years for them to emerge from the regulatory cloud of the early 1990s.[338]

Epidural Hematoma

Bleeding within the vertebral canal can cause ischemic compression of the spinal cord and lead to permanent neurologic deficit if not recognized and evacuated expeditiously. Many risk factors have been associated with the development of an epidural hematoma, including difficult or traumatic needle or catheter insertion,[339] coagulopathy, elderly age, and female gender.[340] Radicular back pain, prolonged blockade longer than the expected duration of the neuraxial technique, and bladder or bowel dysfunction are features commonly associated with a space-occupying lesion within the vertebral canal and should prompt magnetic resonance imaging on an urgent basis. Before the recently published United Kingdom National Health Service (NHS) audit, the largest contemporary studies report rates of epidural hematoma of less than 0.06 per 10,000 after spinal anesthesia, whereas the rates of epidural hematoma after epidural blockade may be as much as tenfold higher.[294,341-345] The United Kingdom NHS audit arguably provides the most accurate rates of neurologic complications associated with neuraxial anesthesia in contemporary practice. This unique prospective nationwide audit found five cases of epidural hematoma among 707,455 neuraxial

techniques (0.07 per 10,000), all of which occurred among 97,925 perioperative epidural techniques (0.5 per 10,000) performed over the course of 1 year.[323]

Nerve Injury

In 1955, Vandam and Dripps[346] were the first to capture data prospectively on nerve injury from more than 10,000 patients who underwent spinal anesthesia. No severe neurologic injuries occurred in this population. In 1969, Dawkins[347] published the classic review of neurologic complications after 32,718 epidural anesthetics and reported the frequency of transient and permanent nerve injury to be 0.1% and 0.02%, respectively. Despite interim advances in practice and research methodology, some of the largest contemporary studies available[341,344,348-350] suggest that the rate of neurologic injury related to neuraxial anesthesia is mostly unchanged compared with that reported nearly a half century ago. Most notable from these contemporary data are that epidural (including CSE) anesthesia is likely associated with a more frequent rate of radiculopathy or peripheral neuropathy compared with spinal anesthesia,[322] and that neuraxial anesthesia performed in adults for the purposes of perioperative anesthesia or analgesia is apparently associated with a higher likelihood of neurologic complications compared with that performed in the obstetric, pediatric, and chronic pain settings.[323,341,342,351,352] The rate of permanent nerve injury after neuraxial blockade is even more difficult to determine because methods of investigation and diagnosis, determination of causation, and reporting of outcomes are highly variable within the literature.[353] The United Kingdom NHS audit found the overall rate of permanent nerve injury to be 7 in 707,455 or 0.1 per 10,000,[323] which is remarkably similar to studies published a half century earlier by Dawkins. Three cases of nerve injury occurred among 293,050 epidurals (0.1 per 10,000), 3 among 324,950 spinal anesthetics (0.1 per 10,000), and 1 among 41,875 CSEs (0.2 per 10,000), mostly in young, healthy patients. Procedure-related risk factors traditionally associated with nerve injury after neuraxial anesthesia in the perioperative setting include radicular pain or paresthesia occurring during the procedure.[321,344,354,355]

Post–Dural Puncture Headache

A relatively common complication of neuraxial anesthesia is post–dural puncture headache. As the name implies, post–dural puncture headache is believed to result from unintentional or intentional puncture of the dura membrane in the setting of neuraxial anesthesia or after myelography and diagnostic lumbar puncture. There are two possible explanations for the cause of the headache, neither of which has ever been proven. First, the loss of CSF through the dura is proposed to cause traction on pain-sensitive intracranial structures as the brain loses support and sags. Alternatively, the loss of CSF initiates compensatory yet painful intracerebral vasodilation to offset the reduction in intracranial pressure.[356] The characteristic feature of a post–dural puncture headache is a frontal or occipital headache that worsens with the upright or seated posture and is relieved by lying supine. Associated symptoms can include nausea, vomiting, neck pain, dizziness, tinnitus, diplopia, hearing loss, cortical blindness, cranial nerve palsies, and even seizures. In more than 90% of cases, the onset of characteristic post–dural puncture headache symptoms will begin within 3 days of the procedure,[357] and 66% start within the first 48 hours.[358] Spontaneous resolution usually occurs within 7 days in the majority (72%) of cases, whereas 87% of cases resolve by 6 months.[359]

Post–dural puncture headache can occur in the setting of either spinal or epidural anesthesia, the former associated with certain modifiable risk factors during intentional dural puncture and the latter associated with unintentional puncture of the dura by advancing the Tuohy needle. Orienting a needle bevel parallel with the axis of the spine, such that the longitudinal fibers of the dura would more likely be separated than cut, results in a lower incidence of postspinal puncture headache.[360] This clinical observation has been supported by laboratory investigations[361] showing that simulated spinal puncture with cone-shaped (pencil-point) spinal needle tips produces slower transdural loss of fluid than a similar puncture with cutting tipped needles does. Indeed a meta-analysis has shown that noncutting needle tip designs have a lower frequency of post–dural puncture headache than do cutting spinal needle tip designs.[362] Other studies suggest that the collagen layers of the dura are oriented in a multidirectional fashion, not always in a cephalocaudad direction, and are variable in thickness, leading to the suggestion that damage to the longitudinal cells of the arachnoid membrane is more likely to be influenced by the type of bevel and may even be the predominant factor affecting post–dural puncture headache.[9] Reports vary as to whether the incidence of post–dural puncture headache is increased with the combined spinal-epidural technique compared with epidural alone.[363,364]

Aside from the type of needle tip (cutting versus pencil-point) and the bevel direction, there are additional risk factors common to the performance of both spinal and epidural anesthesia that contribute to the likelihood of developing a post–dural puncture headache. These risk factors are listed in Box 56-2.[365]

Conservative management for post–dural puncture headache includes supine positioning, hydration, caffeine, and oral analgesics. Sumatriptan has also been used with varying effect but is not without side effects.[366,367]

BOX 56-2 ***Relationships Among Variables and Post–Spinal Puncture Headache***

Factors That Can Increase the Incidence of Headache After Spinal Puncture

- Age: Younger, more frequent
- Sex: Females > males
- Needle size: Larger > smaller
- Needle bevel: Less when the needle bevel is placed in the long axis of the neuraxis
- Pregnancy: More when pregnant
- Dural punctures: More with multiple punctures

Factors That Do Not Increase the Incidence of Headache After Spinal Puncture

- Insertion and use of catheters for continuous spinal anesthesia
- Timing of ambulation

Epidural blood patch is the definitive therapy for postdural puncture headache.[368] This therapy was introduced by Gormley[369]; its safety and efficacy have been well-documented, and contemporary practice has validated that a single epidural blood patch continues to have a greater than 90% initial improvement rate[370] and persistent resolution of symptoms in 61% to 75% of cases.[371]

Epidural blood patch is ideally performed 24 hours after dural puncture and after the development of classic post–dural puncture headache symptoms. The efficacy of prophylactic epidural blood patching is not supported by evidence.[372,373] By injecting radionuclide-labeled red blood cells epidurally, Szeinfeld and co-workers[374] demonstrated that approximately 15 mL of blood will spread over a mean distance of nine spinal segments, and that the direction of spread was preferentially cephalad relative to the level of blood injection. As a result, these authors recommend inserting the blood patch needle at or caudad to the level of the previous culprit dural puncture. These findings have since been validated by magnetic resonance imaging of epidural blood patch spread.[375] A recent multinational, multicenter, randomized, blinded trial suggested that 20 mL of blood is a reasonable starting target volume.[376] A second epidural blood patch may be performed 24 to 48 hours after the first in the case of ineffective or incomplete relief of symptoms.

Transient Neurologic Symptoms

Traditionally associated with lidocaine, TNS have been described after intrathecal administration of every local anesthetic used for spinal anesthesia. TNS, previously known as transient radicular irritation,[377] is usually characterized by bilateral or unilateral pain in the buttocks radiating to the legs or, less commonly, isolated buttock or leg pain. Symptoms occur within 24 hours of the resolution of an otherwise uneventful spinal anesthetic and are not associated with any neurologic deficits or laboratory abnormalities.[378] The pain can range from mild to severe and typically resolves spontaneously in 1 week or less.[379] The likelihood of TNS is highest after intrathecal lidocaine and mepivacaine and is far less frequent with bupivacaine.[147,159,380] The phenomenon is related to the concentration of lidocaine,[147] the addition of dextrose or epinephrine, or solution osmolarity. The type of needle can influence the likelihood of TNS, with the rate reduced by a double-orifice needle,[381] possibly because single-orifice needles increase the risk of injecting anesthetic caudally in the thecal sac. TNS is not commonly associated with epidural procedures but has occurred with epidural lidocaine and other local anesthetics.[253,382] Finally, TNS occurs more commonly in patients who are placed in the lithotomy position for surgery. Nonsteroidal antiinflammatory drugs are the first line of treatment, but pain can be severe and may even require opioids.

CARDIOVASCULAR

Hypotension

Hypotension may be considered a complication of neuraxial blockade if the patient faces harm. In the setting of spinal anesthesia, hypotension (defined as systolic blood pressure <90 mm Hg) is more likely to occur with a variety of factors including peak block height greater than or equal to T5, age older than or equal to 40 years, baseline systolic blood pressure less than 120 mm Hg, combined spinal and general anesthesia, spinal puncture at or above the L2-L3 interspace, and the addition of phenylephrine to the local anesthetic.[51] Hypotension (defined as a reduction in mean arterial blood pressure >30%) is independently associated with chronic alcohol consumption, history of hypertension, BMI, and the urgency of surgery.[383] Nausea is a common symptom of hypotension in the setting of neuraxial anesthesia, as are vomiting, dizziness, and dyspnea. Although prevention of hypotension caused by vasodilatation by a prophylactic ("preloading") infusion of colloid or crystalloid during the performance of the neuraxial block ("coloading") has been reported,[384] this is no longer recommended as a routine practice.[384]

Bradycardia

The development of severe bradycardia after spinal anesthesia has long been recognized as an important risk of spinal anesthesia.[385,386] Bradycardia stems from blockade of the thoracic sympathetic fibers (preganglionic cardiac accelerator fibers originating at T1-T5), as well as reflexive slowing of the heart rate as vasodilation reduces the venous return to the right atrium where stretch receptors respond by a compensatory slowing of the heart rate. Factors that may increase the likelihood of exaggerated bradycardia (40 to 50 beats/min) include baseline heart rate less than 60 beats/min, age younger than 37 years, male gender, nonemergency status, β-adrenergic blockade, and prolonged case duration. Severe bradycardia (<40 beats/min) is associated with a baseline heart rate less than 60 beats/min and male gender.[387]

Cardiac Arrest (Also see Chapter 108)

In a review of closed insurance claims, Caplan and associates[388] identified 14 cases of sudden cardiac arrest in healthy patients receiving spinal anesthesia. The etiology of sudden cardiac arrest after spinal anesthesia is not understood. Whether these catastrophic events represented lack of vigilant monitoring and treatment as opposed to some mysterious physiologic explanation is not known.[389] The latter notwithstanding, it is clear that hypoxemia and oversedation are complicit in the severe bradycardia and asystole that can occur suddenly during well-conducted spinal anesthesia.[390,391] Curiously, these rare events seem to be preferentially associated with spinal anesthesia rather than epidural techniques. In their inaugural survey of French anesthesiologists, Auroy and colleagues reported the rate of cardiac arrest to be 6.4 per 10,000 after spinal anesthesia compared with 1 per 10,000 for all other neuraxial and peripheral regional anesthesia techniques combined.[344] In their larger follow-up survey of all anesthesiologists in France, Auroy and colleagues[350] reported 10 cases of cardiac arrest after 35,439 spinal anesthetics (2.5 per 10,000) and none after 5,561 epidural techniques. Most recently, Cook and colleagues uncovered three cases of cardiovascular collapse among 707,425 neuraxial blocks (0.04 per 10,000) during their nationwide audit, two of

which were during spinal anesthesia and one in the setting of CSE.[323]

RESPIRATORY

Neuraxial opioids are commonly added to local anesthetic solutions to improve the quality and duration of neuraxial anesthesia and analgesia. The risk of respiratory depression associated with neuraxial opioids is dose-dependent, with a reported frequency that approaches 3% after the administration of 0.8 mg of intrathecal morphine.[392] Respiratory depression may stem from rostral spread of opioids within the CSF to the chemosensitive respiratory centers in the brainstem.[65] With lipophilic anesthetics, respiratory depression is generally an early phenomenon occurring within the first 30 minutes; respiratory depression has never been described more than 2 hours after the administration of intrathecal fentanyl or sufentanil.[225] With intrathecal morphine, there is a risk of late respiratory depression, occurring as much as 24 hours after injection. Respiratory monitoring for the first 24 hours after the administration of intrathecal morphine is therefore advisable. Patients with sleep apnea can be especially sensitive to the potent respiratory-depressant effects of opioid medications and although definitive safety data evidence is lacking, the decision to administer neuraxial opioids to these patients is made with considerable caution.[393,394] Older patients also have a higher risk of respiratory depression, and the dose of neuraxial opioids should be reduced in this population (see Chapter 80). Coadministration of systemic sedatives also increases this risk.

INFECTION

Bacterial meningitis and epidural abscess are rare, but potentially catastrophic, infectious complications of all neuraxial techniques. Sources of infection in neuraxial procedures include the equipment, the patient, or the practitioner. Staphylococcal infections arising from the patient's skin are one of the most common epidural-related infections, whereas oral bacteria such as *Streptococcus viridans* are a common cause of infection after spinal anesthesia, underscoring the need for the clinician to wear a facemask when performing neuraxial procedures. Other factors that may increase the likelihood of infection include the presence of a concomitant systemic infection, diabetes, immunocompromised states,[90] and prolonged maintenance of an epidural (or spinal) catheter. Large contemporary studies estimate the rate of serious neuraxial infection to be less than 0.3 per 10,000[341,348,350] for spinal anesthesia, whereas infectious complications after epidural techniques may be at least twice as common.[341,348,350,395,396,397] Obstetric patients are less likely to develop deep infections related to epidural analgesia. The recent United Kingdom NHS audit reported no cases of meningitis and eight cases of epidural abscess after 707,455 neuraxial techniques, five of which occurred among 293,050 epidural techniques, two among 324,950 spinal anesthetics, and one among 47,550 caudal blocks.[323] In 2004, ASRA published practice guidelines regarding the prevention of infectious complications associated with regional anesthesia, specifically addressing (1) the importance and implications of aseptic techniques during regional anesthesia,[229] (2) regional anesthesia in the febrile or infected patient,[90] (3) regional anesthesia in the immunocompromised patient,[398] and (4) infectious risk of chronic pain treatments.[399] These guidelines concluded that chlorhexidine in an alcohol base is the most effective antiseptic for the purposes of neuraxial techniques.[229] Concerns regarding neurotoxicity associated with the routine use of chlorhexidine have not been confirmed.[230,231]

Aseptic meningitis occurred mostly in the early twentieth century, likely secondary to chemical contamination and detergents, which are no longer present in modern preservative-free preparations.

BACKACHE

Back injury is perhaps the most feared complication of neuraxial anesthesia among patients.[400] Nonetheless, approximately 25% of all surgical patients undergoing anesthesia, regardless of anesthetic technique, experience backache, the incidence of which increases to 50% when surgery lasts 4 to 5 hours.[401] There is no association between epidural analgesia and new-onset back pain up to 6 months postpartum.[402,403] Moreover, in a randomized, controlled trial comparing epidural versus systemic analgesia for pain relief during labor, the rates of postpartum back pain were identical between groups, suggesting that the neuraxial techniques do not play a role in the development of back pain after delivery.

NAUSEA AND VOMITING

There are multiple possible mechanisms that contribute to nausea and vomiting in the setting of neuraxial anesthesia, including direct exposure of the chemoreceptive trigger zone in the brain to emetogenic drugs (e.g., opioids), as well as hypotension associated with generalized vasodilation and gastrointestinal hyperperistalsis secondary to unopposed parasympathetic activity (see also Chapter 97).[404] Although regional anesthesia is often recommended as an alternative to general anesthesia for patients at risk for postoperative nausea and vomiting, there are few studies that have primarily investigated the effects of neuraxial anesthesia on postoperative nausea and vomiting with sufficient statistical power. Factors associated with developing nausea or vomiting after spinal anesthesia include the addition of phenylephrine or epinephrine to the local anesthetic, peak block height greater than or equal to T5, baseline heart rate greater than 60 beats/min, use of procaine, history of motion sickness, and the development of hypotension during spinal anesthesia. Among the opioids commonly added to intrathecal or epidural local anesthetics, morphine administration has the most frequent risk of nausea or vomiting, whereas fentanyl and sufentanil carry the least frequent risk.[404] Neuraxial opioid-related nausea and vomiting appears to be dose-dependent. Using less than 0.1 mg morphine reduces the risk of nausea and vomiting, without compromising the analgesic effect.[225]

URINARY RETENTION

Urinary retention can occur in as much as one third of patients after neuraxial anesthesia. Local anesthetic blockade of the S2, S3, and S4 nerve roots inhibits urinary function as the detrusor muscle is weakened. Neuraxial opioids can further complicate urinary function by suppressing detrusor contractility and reducing the sensation of urge.[405] Spontaneous return of normal bladder function is expected once the sensory level decreases to below S2-3.[406] Although male gender and age have been (albeit inconsistently) linked to urinary retention after neuraxial anesthesia, the administration of intrathecal morphine is strongly associated with this complication.[405,407,408]

PRURITUS

Pruritus can be distressing to the patient. It is the most common side effect related to the intrathecal administration of opioids, with rates between 30% and 100%.[225] Pruritus actually occurs more commonly after intrathecal opioid administration than after intravenous opioid administration and is not dependent on the type or dose of opioid administered. Reducing the dose of intrathecal sufentanil from 5 μg to as little as 1.5 μg can reduce the likelihood of pruritus without compromising analgesia when added to hyperbaric bupivacaine for cesarean delivery (see Chapter 77).[409] The mechanism of pruritus is unclear but is likely related to the central opioid receptor activation rather than histamine release because naloxone, naltrexone or the partial agonist nalbuphine can be used for treatment. Ondansetron and propofol are also useful therapies.

SHIVERING

The rate of shivering related to neuraxial anesthesia is as frequent as 55%.[410] The intensity of shivering is likely related more to epidural anesthesia than spinal.[411] Although there are multiple possible explanations for the difference in shivering intensity, this observation may simply be related to the inability to shiver because of the profound motor block associated with spinal anesthesia compared with epidural techniques. Another explanation may be the relatively cold temperature of the epidural injectate, which can affect the thermosensitive basal sinuses.[410] The addition of neuraxial opioids, specifically fentanyl and meperidine, reduces the likelihood of shivering.[410] Recommended strategies to prevent shivering after neuraxial anesthesia include prewarming the patient with a forced air warmer for at least 15 minutes and avoiding the administration of cold epidural and intravenous fluids.

COMPLICATIONS UNIQUE TO EPIDURAL ANESTHESIA

Intravascular Injection

Epidural anesthesia can produce local anesthetic–induced systemic toxicity (see Chapter 36), primarily through the unintentional administration of drug into an epidural vein. The frequency of vascular puncture with the needle or cannulation with the catheter can reportedly approach 10%, with the highest rates seen in the obstetric population, where these vessels are relatively dilated and more vulnerable to entry.[287,412] The rate of seizures related to epidural anesthesia may be as frequent as 1%.[294,344,350] In obstetrics (see also Chapter 77), the likelihood of intravascular injection is decreased by placing the patient in the lateral (as opposed to the sitting) position during needle and catheter insertion, administering fluid through the epidural needle before catheter insertion, using a single-orifice rather than multi-orifice catheter or a wire-embedded polyurethane compared with polyamide epidural catheter, and advancing the catheter less than 6 cm into the epidural space. The paramedian as opposed to the midline needle approach, and the use of a smaller-gauge epidural needle or catheter, does not reduce the risk of epidural vein cannulation.[287]

One of the most controversial issues related to epidural anesthesia has been the use of an epinephrine-containing test dose.[413] Epinephrine (15 μg) in 3 mL of local anesthetic remains the best pharmacologic method of detecting intravascular placement in nonpregnant adult patients.[304] However, controversy surrounds the use of epinephrine in obstetric patients, in whom uterine blood flow may be decreased by the intravascular injection, thereby putting the fetus at risk, and where the cardiovascular changes occurring in active labor may represent a false-positive response to epinephrine. Although epinephrine may place the fetus at risk in theory,[414] no such case has been described. The epidural epinephrine test dose can be unreliable in patients receiving β-adrenergic blockers[415] or if the test dose is administered during general anesthesia.[416] Because there is no fail-safe method of guaranteeing an extravascular location of an epidural local anesthetic, prevention of systemic toxicity should also involve aspiration of the catheter and incremental administration of the local anesthetic. The onset of block, quality of the block, and block height are unaffected by administration of the epidural drug in 5-mL fractions.[417]

Subdural Injection

Blomberg[418] used a fiberoptic technique to demonstrate that the subdural extra-arachnoid space is easily entered in 66% of autopsy attempts in humans. Despite this being an infrequent clinical problem with epidural anesthesia (<1%), it does allow a visual understanding of the subdural complications of epidural anesthesia.[419] This space, unlike the epidural space, also extends intracranially. When an epidural block is performed and a higher-than-expected block develops, but only after a delay of 15 to 30 minutes (unlike a total spinal), subdural placement of local anesthetic must be considered. With a subdural block, the motor block will be modest compared to the extent of the sensory block, and the sympathetic block may be exaggerated. The treatment is symptomatic.

COMPLICATIONS UNIQUE TO COMBINED SPINAL-EPIDURALS

The risk of metal toxicity from abraded spinal needle particles using the needle-through-needle technique has not been confirmed.[420]

OUTCOMES

Although the benefit of properly applied epidural anesthesia and analgesia as an excellent pain relief modality is unquestionable, its effect on postoperative morbidity and mortality is less clear. Several recent meta-analyses showed a relative risk reduction in overall mortality in patients receiving neuraxial blockade, by as much as 30% in patients undergoing all types of surgery[421] to 11% in patients undergoing intermediate- to high-risk noncardiac surgery.[422] For cardiac surgery, recent meta-analyses showed a reduced risk of mortality and myocardial infarction (composite endpoint), a reduced risk for acute renal failure, pulmonary complications, and supraventricular arrhythmia; and reduced duration of postoperative controlled ventilation in patients who received combined intraoperative general anesthesia and thoracic epidural anesthesia.[74,423] For major thoracic and abdominal surgery, thoracic epidural analgesia reduced mortality, respiratory complications, and opioid consumption and improved cough and time to ambulation.[424,425] However, the effect of epidural analgesia on postoperative outcomes is not consistent, and it may be procedure-specific (particularly advantageous for thoracic surgery) and technique-specific (i.e., thoracic epidural is more advantageous than lumbar epidural, and epidural local anesthetic is more advantageous than epidural opioid).

Mortality and morbidity aside, there are other advantages of neuraxial blockade. For bilateral total knee arthroplasty, neuraxial anesthesia decreases the rate of blood transfusion.[426] In patients undergoing major vascular and abdominal surgery, thoracic epidural local anesthetic infusion can reverse postoperative paralytic ileus associated with pain-induced sympathetic overactivity and systemic opioid.[427] Lumbar epidural infusion or thoracic epidural opioid infusion alone does not speed intestinal function recovery. For fast-track laparoscopic colon resection, thoracic epidural analgesia provides superior pain relief but fails to speed intestinal function recovery or hospital discharge time.

What are the potential effects of neuraxial anesthesia on stress response, the immune system, and cancer recurrence?[428-430] Functional cell-mediated immunity is required for monitoring and eradicating cancer cell growth. Lymphocytes, such as the natural killer (NK) cells and the cytotoxic T lymphocytes, can lyse the cancer cell through the perforin and granzyme pathway or through secretion of cytokines (e.g., interferons) to induce cancer cell apoptosis. In addition, the helper T cells control tumor angiogenesis through interferons, inhibit oncogenic signaling, and stimulate tumor destruction by engaging macrophages and granulocytes through interleukin production. There is an inverse relationship between NK cell activity at the time of surgery and the development of metastatic disease. Systemic cancer cell seeding happens during surgical dissection and manipulation. Unfortunately, this happens at a time of significant immunosuppression. Surgically induced stress hormone (e.g., corticosteroids), as well as inhaled volatile anesthetics and systemic opioids (morphine and fentanyl), can diminish NK cell function. Morphine also has proangiogenic properties that may promote dissemination of angiogenesis-dependent tumors. Thoracic epidural anesthesia and analgesia may be beneficial by virtue of its opioid and general anesthetic sparing and surgical stress–alleviating properties. Some encouraging data indicate a reduction of cancer recurrence associated with the use of perioperative epidural anesthesia and analgesia in patients undergoing retropubic prostatectomy,[431,432] rectal cancer,[433] and ovarian cancer resection.[434,435]

RECENT ADVANCES

ULTRASOUND

There is a growing interest in ultrasound imaging to guide neuraxial blockade, because it can accurately identify the intervertebral levels, the midline spinous process, the midline interspinous window, and the paramedian interlaminar window (see also Chapter 58).[233] Bone does not permit ultrasound beam transmission, thus casting a hypoechoic (dark) shadow on the image. Conversely, passage of the ultrasound beam through the interspinous and interlaminar windows allows visualization of the hyperechoic dura (a bright line), the subarachnoid space, and the posterior aspect of the vertebral body.[436] Visualization of the ligamentum flavum and epidural space is often more difficult. Successful transverse or longitudinal scan facilitates identification of the optimal location for proper needle insertion during neuraxial block and an estimation of the skin-to-dura distance. This is particularly useful in patients with difficult surface anatomic landmarks (e.g., obesity), spine pathology (e.g., scoliosis), and previous spine surgery (e.g., laminectomy).[437]

Ultrasound-facilitated neuraxial block involves preprocedure scanning of the spine to determine the best possible intervertebral level and window for needle insertion without actual real-time guidance (a highly challenging technique). Imaging of the lumbar spine is significantly easier than that of the thoracic spine, which has narrow interspinous and interlaminar windows, especially at T5-T8 levels.[438] Ultrasonography in the pediatric population is impressive because the vertebral column with limited ossification not only permits visualization of the spinal canal sonoanatomy, but the inserted needle and catheter tip, dural displacement, and the extent of cranial spread can be visualized during a fluid bolus injection in young infants and children (also see Chapter 93).[439,440] Several outcome studies have confirmed the utility of ultrasonography when neuraxial block is performed by the novice and in patients with difficult anatomic landmarks.[441]

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Chapter 57

Peripheral Nerve Blocks

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Key Points

- Regional anesthesia is only successful when local anesthetic is inserted in close proximity to the targeted nerves. From the inception of regional anesthesia over a century ago, there have been several techniques designed and available to facilitate the correct placement of local anesthetic, including paresthesia-seeking, peripheral nerve stimulator, and most recently ultrasound guidance.
- Continuously administered peripheral nerve block improves outcome and rehabilitation after major surgery to the extremities, including surgery to the knee, hip, and shoulder.
- Total local anesthetic dosage should be determined and kept within acceptable limits. Accumulation may occur with continuous techniques.
- The frequency of neurologic complications after peripheral blockade is less than that associated with neuraxial techniques. Neurotoxicity and direct needle trauma are the major causes of neurologic complications.
- There are no data to support the superiority of one nerve localization technique—paresthesia, nerve stimulation, ultrasound—over another with regard to reducing the risk of nerve injury.
- A lipid infusion improves success of resuscitation from cardiac arrest because of local anesthetic toxicity if given immediately after a local anesthetic overdose (see Chapter 36)

The techniques of peripheral neural blockade were developed early in the history of anesthesia. The American surgeons Halsted and Hall[1,2] described the injection of cocaine into peripheral sites, including the ulnar, musculocutaneous, supratrochlear, and infraorbital nerves, for minor surgical procedures in the 1880s. James Leonard Corning[3] recommended the use of an Esmarch bandage in 1885 to arrest local circulation, prolonging the cocaine-induced block and decreasing the uptake of that local anesthetic from the tissues. This concept was furthered by Heinrich F.W. Braun,[4] who substituted epinephrine, a "chemical tourniquet," in 1903. Braun[5] also introduced the term *conduction anesthesia* in his 1905 textbook on local anesthesia, which described techniques for every region of the body. In 1920, the French surgeon Gaston Labat was invited by Charles Mayo to teach innovative methods of regional anesthesia at the Mayo Clinic. During his appointment there, Labat authored *Regional Anesthesia: Its Technic and Application*.[6] The book was considered the definitive text on regional anesthesia for at least 30 years after its publication. Labat's textbook focused on the intraoperative management of patients undergoing intraabdominal, head, neck, and extremity procedures using infiltration, peripheral, plexus, and splanchnic blockade. Neuraxial techniques were not widely applied at the time.

The use of peripheral nerve blockade has grown in popularity because it decreases pain as assessed by visual analog scale scores postoperatively, decreases the need for postoperative analgesics, decreases the incidence of nausea, shortens postanesthesia care unit time, and increases patient satisfaction.[7] Peripheral nerve blocks can be customized and used for anesthesia, postoperative analgesia, and diagnosis and treatment of chronic pain disorders (see Chapters 64 and 98). The regional technique chosen depends on the surgical site, the anticipated length of the procedure, ambulation requirements, and the desired duration of postoperative pain control. Detailed anatomic knowledge enables the anesthesia provider to choose the appropriate technique for the intended surgical procedure and to salvage inadequate nerve blocks with local anesthetic supplementation. In addition, important side effects and complications of peripheral regional techniques must be understood. With appropriate selection

and sedation, these techniques can be used in all age groups. Skillful application of peripheral neural blockade broadens the anesthesia provider's range of options in providing optimal anesthetic care.

TECHNIQUES FOR LOCALIZING NEURAL STRUCTURES

PARESTHESIA TECHNIQUES

The paresthesia-seeking technique has a long, successful history as a simple technique that requires little specialized equipment. A paresthesia is elicited when a needle makes direct contact with a nerve. Paresthesia-seeking techniques are reliant on patient cooperation and participation to guide the local anesthetic injection accurately; therefore, only small doses of sedation medication are recommended. Paresthesia techniques have been criticized for causing patient discomfort, although clinical studies have not shown a significant increase in neurologic complications with this technique.[8] Caution should be used when initiating the injection of local anesthetic to ensure that the needle is not intraneural. There is controversy in the literature regarding the use of B-bevel (blunt bevel or short bevel) needles versus sharp needles regarding the incidence and severity of nerve injury if the needle inadvertently contacts the nerve. Because B-bevel needles have a blunt tip, which is likely to push the nerve aside, they are much less likely to penetrate the nerve; however, when an injury does occur, it appears to be more severe.[9] In contrast, sharp needles are more likely to penetrate the nerve, but the injury appears to be less destructive.[10] Success with the paresthesia technique is highly dependent on the skill of the practitioner and requires a thorough understanding of anatomy. This technique was slowly replaced by many in the 1980s when peripheral nerve stimulation was introduced. Currently, no single technique has been shown to be superior with respect to success rate or incidence of complications.

PERIPHERAL NERVE STIMULATION

Peripheral nerve stimulators transmit a small electric current to the end of a stimulating needle that will cause depolarization and muscle contraction when the tip of the needle is in close proximity to a neural structure. This technique allows for localization of a specific peripheral nerve without requiring the elicitation of a paresthesia, thus allowing patients to be more heavily sedated during block placement. A thorough understanding of anatomy is a prerequisite to this technique and all techniques of peripheral nerve blockade. It is necessary to attach the cathode (negative terminal) to the stimulating needle and the anode (positive terminal) to the surface of the patient because depolarization occurs as the cathode allows current to flow from the needle to the adjacent nerve. Current flows away from the needle causing hyperpolarization if the terminals are reversed. Most current-stimulating needles are coated with a thin layer of insulation along the needle with the exception of the tip. This allows for a more discrete field of stimulation only at the tip of the needle. Higher current output (>1.5 mA) is more likely to stimulate neural structures through tissue or fascial planes and can be associated with painful, vigorous muscle contractions. After localization of the correct motor response, the current is gradually decreased to a current of 0.5 mA or less. A motor response at a current of approximately 0.5 mA is appropriate when used to facilitate the location of the injection of local anesthetic or catheter placement.

ULTRASOUND-GUIDED REGIONAL ANESTHESIA

Ultrasound-guided regional anesthesia is an exciting and rapidly developing technique used to visualize and localize nerve structures (see Chapter 58). Ultrasound allows visualization of the nerve target, the approaching needle, and the deposition of local anesthetic around the nerve. Superficial nerve structures (e.g., brachial plexus) are easily imaged in most patients and therefore are most suited for ultrasound guidance. Practitioners must become familiar with the fundamentals of ultrasound equipment, as well as sonoanatomy, to become proficient in ultrasound-guided regional anesthesia.[11]

CERVICAL PLEXUS BLOCK

The cervical plexus is derived from the C1, C2, C3, and C4 spinal nerves and supplies branches to the prevertebral muscles, strap muscles of the neck, and phrenic nerve. The deep cervical plexus supplies the musculature of the neck segmentally and the cutaneous sensation of the skin between the trigeminally innervated face and the T2 dermatome of the trunk. Blockade of the superficial cervical plexus results in anesthesia of only the cutaneous nerves.

Clinical Applications

Blocks of the cervical plexus are easy to perform and provide anesthesia for surgical procedures in the distribution of C2 to C4, including lymph node dissections, plastic repairs, and carotid endarterectomy. The ability to monitor the awake patient's neurologic status continuously is an advantage of this anesthetic technique for the latter procedure and has resulted in an upsurge in the popularity of this technique.[12] Bilateral blocks can be used for tracheostomy and thyroidectomy.

Technique

Superficial Cervical Plexus. The superficial cervical plexus is blocked at the midpoint of the posterior border of the sternocleidomastoid muscle. A skin wheal is made at this point, and a 22-gauge, 4-cm needle is advanced, injecting 5 mL of solution along the posterior border and medial surface of the sternocleidomastoid muscle (Fig. 57-1). It is possible to block the accessory nerve with this injection, resulting in temporary ipsilateral trapezius muscle paralysis.

Deep Cervical Plexus. The deep cervical plexus block is a paravertebral block of the C2 to C4 spinal nerves as they emerge from their foramina in the cervical vertebrae (Fig. 57-2). The traditional approach uses three

separate injections at C2, C3, and C4. The patient lies supine with the neck slightly extended and the head turned away from the side to be blocked. A line is drawn connecting the tip of the mastoid process and the Chassaignac tubercle (the transverse process of C6); a second line is drawn 1 cm posterior to this first line. The C2 transverse process lies 1 to 2 cm caudad to the mastoid process, where it can usually be palpated. The C3 and C4 transverse processes lie at 1.5-cm intervals along the second line. After skin wheals are raised over the transverse processes of C2, C3, and C4, three 22-gauge, 5-cm needles are advanced perpendicular to the skin entry site with a slight caudad angulation. The transverse process is contacted at a depth of 1.5 to 3 cm. If a paresthesia is obtained, 3 to 4 mL of solution is injected after careful aspiration for blood and cerebrospinal fluid. If no paresthesia is elicited initially, the needle is walked along the transverse process in the anteroposterior plane until a paresthesia is obtained.

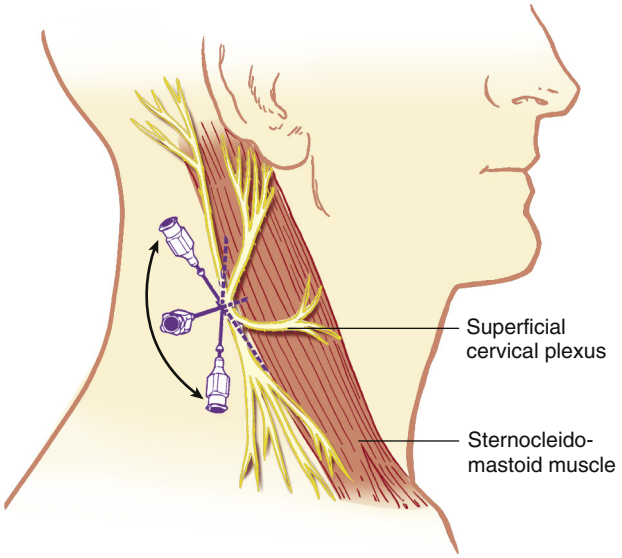


Figure 57-1. Anatomic landmarks and method of needle placement for a superficial cervical plexus block.

This block can also be performed with a single injection of 10 to 12 mL at the C4 transverse process.[13] Cephalad spread of the local anesthetic usually anesthetizes the C2 and C3 nerves. Cervical plexus anesthesia can also be observed after injection at the interscalene level for brachial plexus blockade. Maintenance of distal pressure and a horizontal or slightly head-down position can facilitate the onset of cervical plexus blockade using the interscalene technique.

Side Effects and Complications

Although these blocks are technically straightforward, needle placement for the deep cervical block allows local anesthetic injection in close proximity to a variety of neural and vascular structures. Complications and side effects include intravascular injection, blockade of the phrenic and superior laryngeal nerve, and spread of local anesthetic solution into the epidural and subarachnoid spaces.

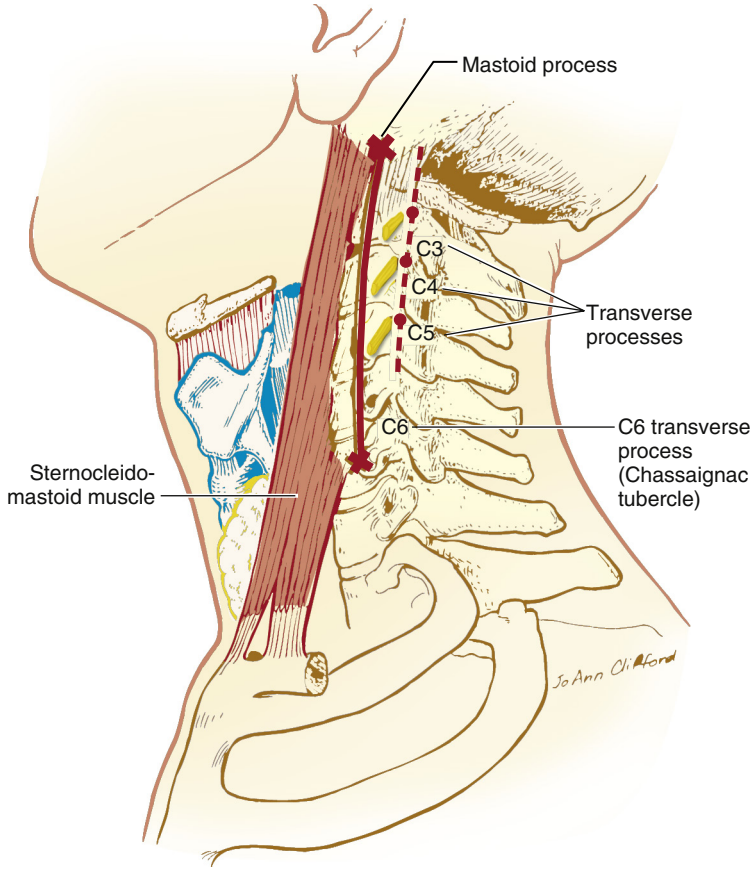


Figure 57-2. Anatomic landmarks and method of needle placement for deep cervical plexus blocks at C2, C3, and C4.

ACCESSORY NERVE BLOCK

The accessory nerve (cranial nerve XI) is occasionally blocked to supplement the interscalene brachial plexus approach for shoulder procedures. A blockade of the accessory nerve results in motor paralysis of the trapezius muscle, ensuring a lack of patient movement during the surgical procedure. The nerve traverses the posterior triangle of the neck (bordered by the posterior border of the sternocleidomastoid muscle, middle third of the clavicle, and anterior border of the trapezius muscle) in a superficial position after emerging from the substance of the sternocleidomastoid muscle at the junction of the superior and middle thirds of that muscle's posterior border. It can be blocked easily at that site by an injection of 6 to 10 mL of local anesthetic. This nerve is often unintentionally anesthetized when a superficial cervical plexus block is performed.

UPPER EXTREMITY BLOCKS

Blockade of the brachial plexus (C5-T1) at several locations from the roots to the terminal branches will allow for surgical anesthesia of the upper extremity and shoulder. Successful regional anesthesia of the upper extremity requires knowledge of brachial plexus anatomy from its origin, where the nerves emerge from the intervertebral foramina, to its termination in the peripheral nerves.

ANATOMY

The brachial plexus is derived from the anterior primary rami of the fifth, sixth, seventh, and eighth cervical nerves and the first thoracic nerve, with variable contributions from the fourth cervical and second thoracic nerves. After leaving their intervertebral foramina, these nerves course anterolaterally and inferiorly to lie between the anterior and middle scalene muscles, which arise from the anterior and posterior tubercles of the cervical vertebra, respectively. The anterior scalene muscle passes caudad and laterally to insert into the scalene tubercle of the first rib; the middle scalene muscle inserts on the first rib posterior to the subclavian artery, which passes between these two scalene muscles along the subclavian groove. The prevertebral fascia invests the anterior and middle scalene muscles, fusing laterally to enclose the brachial plexus in a fascial sheath.

Between the scalene muscles, these nerve roots unite to form three trunks, which emerge from the interscalene space to lie cephaloposterior to the subclavian artery as it courses along the upper surface of the first rib. The superior (C5 and C6), middle (C7), and inferior (C8 and T1) trunks are arranged accordingly and are not in a strict horizontal formation, as often depicted. At the lateral edge of the first rib, each trunk forms anterior and posterior divisions that pass posterior to the midportion of the clavicle to enter the axilla. Within the axilla, these divisions form the lateral, posterior, and medial cords, named for their relationship with the second part of the axillary artery. The superior divisions from the superior and middle trunks form the lateral cord, the inferior divisions from all three trunks form the posterior cord, and the anterior division of the inferior trunk continues as the medial cord.

At the lateral border of the pectoralis minor, the three cords divide into the peripheral nerves of the upper extremity. The lateral cord gives rise to the lateral head of the median nerve and the musculocutaneous nerve; the medial cord gives rise to the medial head of the median nerve, as well as the ulnar, the medial antebrachial, and the medial brachial cutaneous nerves; and the posterior cord divides into the axillary and radial nerves (Fig. 57-3).

Aside from the branches from the cords that form the peripheral nerves as described, several branches arise from the roots of the brachial plexus providing motor innervation to the rhomboid muscles (C5), the subclavian muscles (C5 and C6), and the serratus anterior muscle

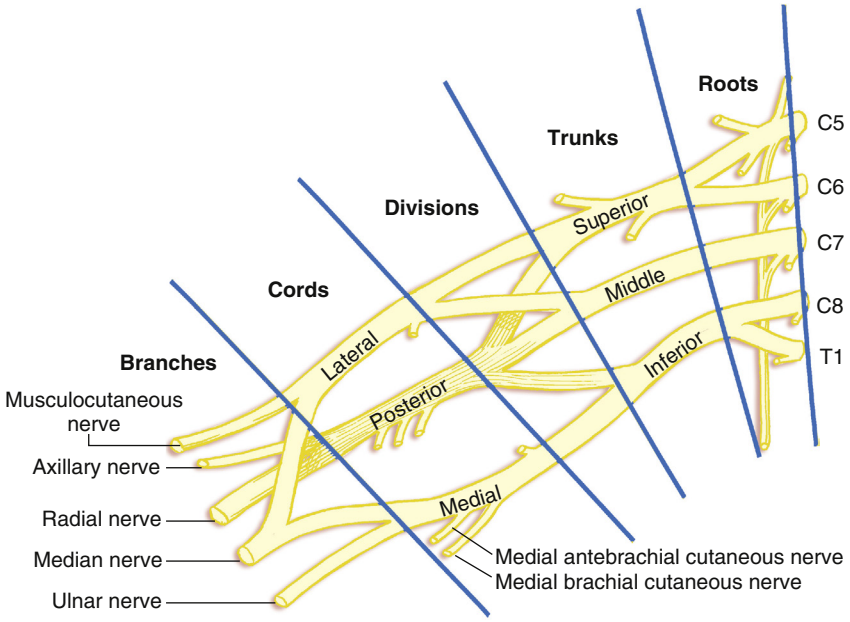


Figure 57-3. Roots, trunks, divisions, cords, and branches of the brachial plexus.

(C5, C6, and C7). The suprascapular nerve arises from C5 and C6, supplies the muscles of the dorsal aspect of the scapula, and makes a significant contribution to the sensory supply of the shoulder joint.

Branches arising from the cervical roots are usually blocked only with the interscalene approach to the brachial plexus. Sensory distributions of the cervical roots and the peripheral nerves are shown in Figure 57-4.

INTERSCALENE BLOCK

Clinical Applications

The principal indication for interscalene block is surgery on the shoulder. Blockade occurs at the level of the superior and middle trunks. Although this approach can be used for forearm and hand surgery, blockade of the inferior trunk (C8 through T1) is often incomplete and requires supplementation of the ulnar nerve for adequate surgical anesthesia in that distribution.[14]

Technique

Peripheral Nerve Stimulation or Paresthesia. The brachial plexus shares a close physical relationship with several structures that serve as important landmarks for the performance of interscalene block. In its course between the anterior and middle scalene muscles, the plexus is superior and posterior to the second and third parts of the subclavian artery. The dome of the pleura lies anteromedial to the inferior trunk.

This technique can be performed with the patient's arm in any position and is technically simple because of easy identification of necessary landmarks.[13] The patient should be in the supine position, with the head turned away from the side to be blocked. The posterior border of the sternocleidomastoid muscle is readily palpated by having the patient briefly lift the head. The interscalene groove can be palpated by rolling the fingers posterolaterally from this border over the belly of the anterior scalene muscle into the groove. A line is extended laterally from the cricoid cartilage to intersect the interscalene groove, indicating the level of the transverse process of C6. Although the external jugular vein often overlies this point of intersection, it is not a constant or reliable landmark.

After injection of a skin wheal, a 22- to 25-gauge, 4-cm needle is inserted perpendicular to the skin with a 45-degree caudad and slightly posterior angle (Fig. 57-5). The needle is then advanced until a paresthesia or nerve stimulator response is elicited. This usually occurs at a superficial level. Paresthesia or motor response of the arm or shoulder is equally efficacious as a distal response.[15] If a blunt needle is used, a "click" may be detected as the needle passes through the prevertebral fascia. If bone is encountered within 2 cm of the skin, it is likely to be a transverse process, and the needle can be "walked" across

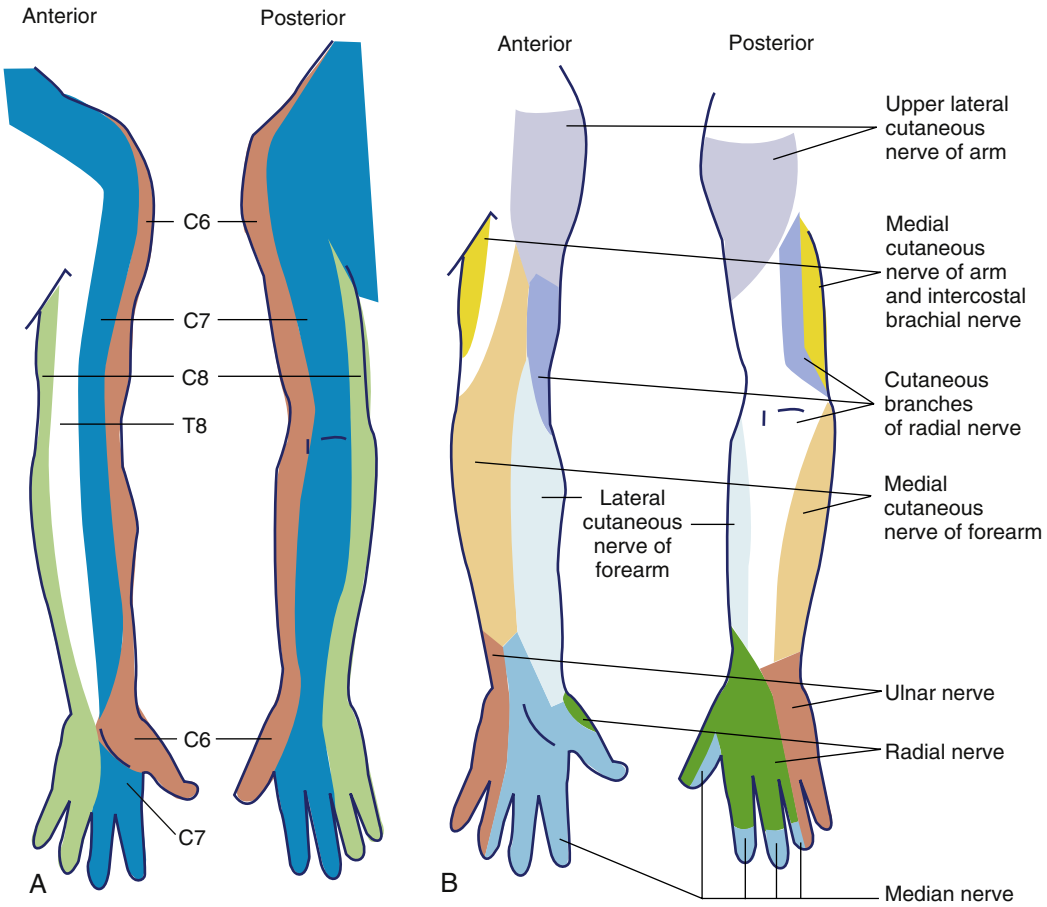


Figure 57-4. A, Cutaneous distribution of the cervical roots. **B,** Cutaneous distribution of the peripheral nerves.

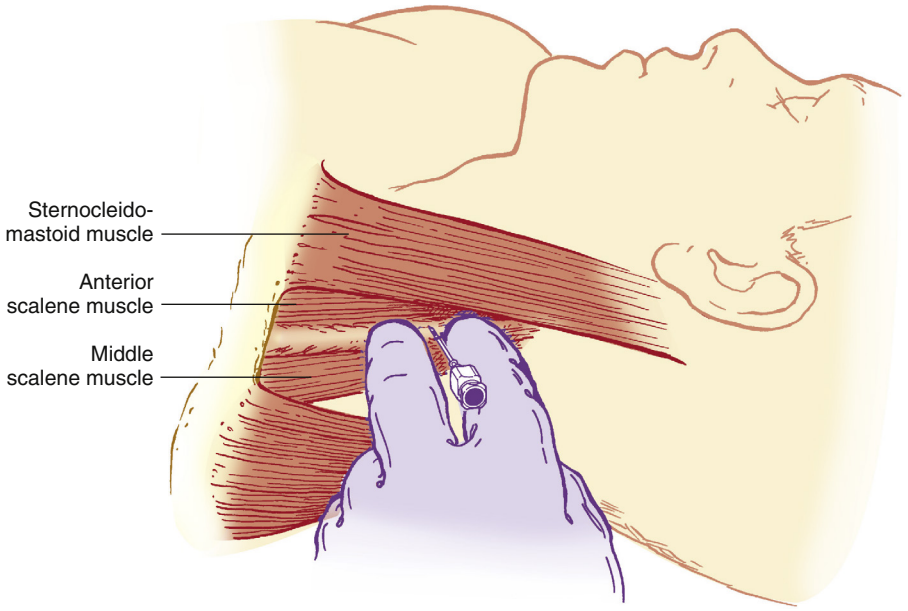


Figure 57-5. Interscalene block. The fingers palpate the interscalene groove, and the needle is inserted with a caudad and slightly posterior angle.

this structure to locate the nerve. Contraction of the diaphragm indicates phrenic nerve stimulation and anterior needle placement; the needle should be redirected posteriorly to locate the brachial plexus.

After the appropriate paresthesia or motor response is obtained, and after negative aspiration, 10 to 30 mL of solution is injected incrementally, depending on the desired extent of blockade. Radiographic studies suggest a volume-to-anesthesia relationship, with 40 mL of solution associated with complete cervical and brachial plexus block.[13] Clinical studies, however, indicate variable blockade of the lower trunk (i.e., ulnar nerve), even with large volumes of solution.[14]

Ultrasound Guided. This block is well suited to the use of ultrasound guidance. It is often easiest to obtain a supraclavicular view of the subclavian artery and brachial plexus and then trace the plexus up the neck with the ultrasound probe until the plexus trunks are visualized as hypoechoic structures between the anterior and medial scalene muscles (Fig. 57-6). The needle can then be advanced in an out-of-plane, or an in-plane approach. After negative aspiration, a small test dose is administered, and local anesthetic spread around the brachial plexus confirms appropriate placement of the needle. Volumes as little as 5 mL may be successful and associated with a decreased frequency of diaphragmatic paresis.[16]

Side Effects and Complications

At the conventional level (C6) of blockade, ipsilateral phrenic nerve block resulting in diaphragmatic paresis occurs in 100% of patients undergoing interscalene blockade,[17] even with dilute solutions of local anesthetics, and is associated with a 25% reduction in pulmonary function.[18,19] This effect probably results from anterior spread of the solution over the anterior scalene muscle and may cause subjective symptoms of dyspnea. Although rare, respiratory compromise can occur in patients with severe respiratory disease. Techniques to decrease blockade of the phrenic nerve include using very small volumes of local anesthetic and localizing the brachial plexus at a lower level in the neck.[20]

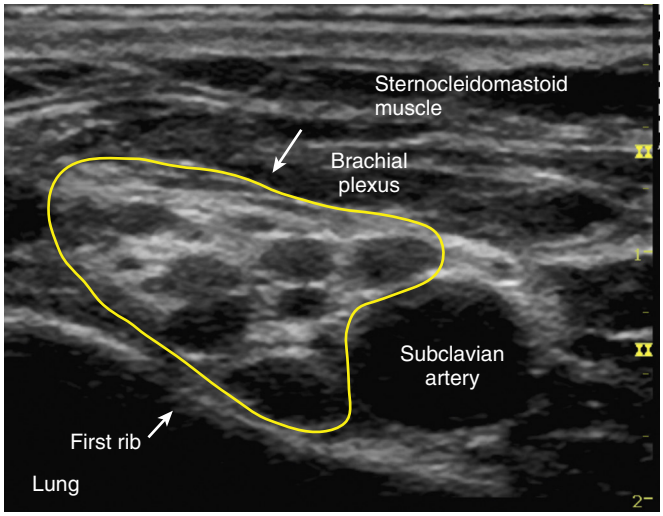


Figure 57-6. Ultrasound image of the brachial plexus at the level of interscalene block.

Involvement of the vagus, recurrent laryngeal, and cervical sympathetic nerves is rarely significant, but the patient experiencing symptoms related to these side effects may require reassurance. The risk of pneumothorax is small when the needle is correctly placed at the C5 or C6 level because of the distance from the dome of the pleura.

Severe hypotension and bradycardia (i.e., Bezold-Jarisch reflex) can occur in awake, sitting patients undergoing shoulder surgery under an interscalene block. The cause is presumed to be stimulation of intracardiac mechanoreceptors by decreased venous return, producing an abrupt withdrawal of sympathetic tone and enhanced parasympathetic output. This effect results in bradycardia, hypotension, and syncope. The frequency is decreased when prophylactic β-adrenergic blockers are administered.[21]

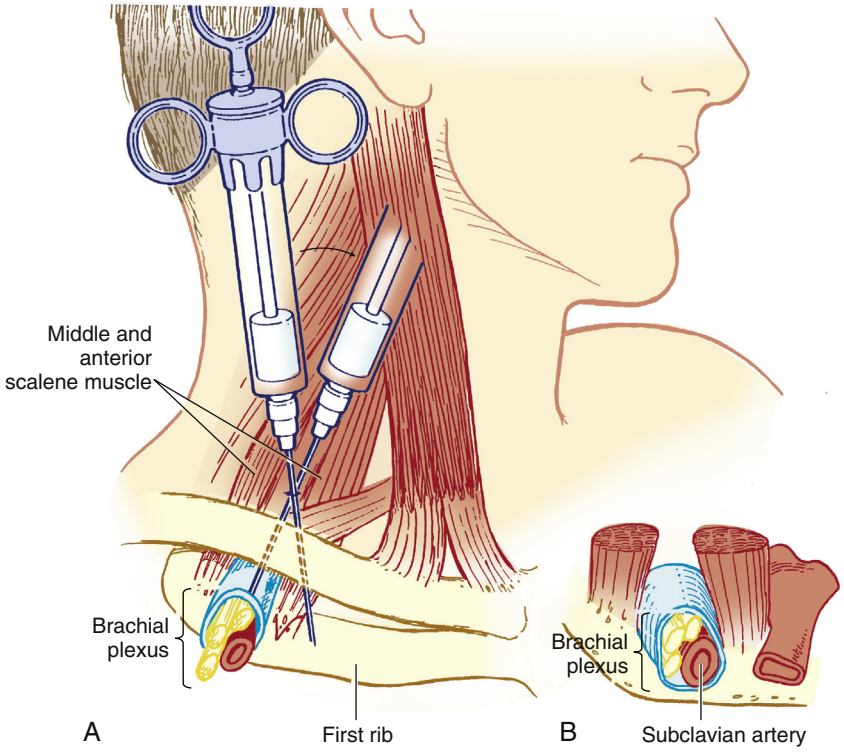


Figure 57-7. A, Supraclavicular block. The needle is systematically walked anteriorly and posteriorly along the rib until the plexus is located. **B,** The three trunks are compactly arranged at the level of the first rib.

Some surgical approaches to the shoulder, such as total shoulder arthroplasty, are associated with neurologic risk to the brachial plexus. In such cases, an interscalene block can be placed postoperatively after the surgical service has ascertained and documented that no neurologic damage has occurred. Epidural and intrathecal injections can occur with this block, a finding emphasizing the importance of inserting the needle in a caudad direction.[22] The proximity of significant neurovascular structures can increase the risk of serious neurologic complications when interscalene block is performed in heavily sedated or anesthetized patients.[23] Accordingly, an interscalene block should be placed with the patient awake or under light sedation.[24]

SUPRACLAVICULAR BLOCK

Clinical Applications

Indications for supraclavicular block are operations on the elbow, forearm, and hand. Blockade occurs at the distal trunk-proximal division level. At this point, the brachial plexus is compact, and a small volume of local anesthetic produces rapid onset of reliable blockade of the brachial plexus. An additional advantage is that the block can also be performed with the patient's arm in any position.

Technique

Peripheral Nerve Stimulation or Paresthesia. Several anatomic points are important in the performance of the supraclavicular approach. The three trunks are clustered vertically over the first rib cephaloposterior to the subclavian artery, which can often be palpated in a slender, relaxed patient. The neurovascular bundle lies inferior to the clavicle at about its midpoint. The first rib acts as a medial barrier to the needle's reaching the pleural dome and is short, broad, and flat, with an anteroposterior orientation at the site of the plexus.

The patient is placed in a supine position, with the head turned away from the side to be blocked. The arm to be anesthetized should be adducted, and the hand should be extended along the side. In the classic technique, the midpoint of the clavicle should be identified and marked. The posterior border of the sternocleidomastoid can be easily palpated when the patient raises the head slightly. The palpating fingers can then roll over the belly of the anterior scalene muscle into the interscalene groove, where a mark should be made approximately 1.5 to 2.0 cm posterior to the midpoint of the clavicle. Palpation of the subclavian artery at this point confirms the landmark.

After injection of a skin wheal, the anesthesiologist stands at the side of the patient facing the patient's head. A 22-gauge, 4-cm needle is directed in a caudad, slightly medial, and posterior direction until a paresthesia or motor response is elicited or the first rib is encountered. If a syringe is attached, this orientation causes the needle shaft and syringe to lie almost parallel to a line joining the skin entry and the patient's ear. If the first rib is encountered without elicitation of a paresthesia, the needle can be systematically walked anteriorly and posteriorly along the rib until the plexus or the subclavian artery is located (Fig. 57-7). Location of the artery provides a useful landmark. The needle can be withdrawn and reinserted in a more posterolateral direction that usually results in a paresthesia or motor response. After localization of the brachial plexus, aspiration for blood should be performed before incremental injections of a total volume of 20 to 30 mL of local anesthetic.

The rib usually is contacted at a needle depth of 3 to 4 cm; however, in an obese patient or in the presence of tissue distortion resulting from hematoma or injection of solution, the depth may exceed the needle length. Nonetheless, before the needle is advanced further, gentle probing in the anterior and posterior directions should be done at the 2- to 3-cm depth if paresthesias are not obtained. Multiple injections can improve the quality or shorten the onset of blockade.

Ultrasound Guided. The use of ultrasound for the supraclavicular block allows the practitioner to see the brachial plexus structures, as well as the subclavian artery and pleura, just below the first rib. The inherent safety of this technique requires continuous visualization of the needle tip during needle advancement (see Chapter 58).

Side Effects and Complications

Although the block is more difficult in obese patients (see Chapter 71), an increased risk of complications has not been documented.[25] The prevalence of pneumothorax after supraclavicular block is 0.5% to 6% and diminishes with increased experience. Importantly, although the use of ultrasound has perhaps decreased the incidence of pneumothorax, the risk has not been eliminated.[26] The onset of symptoms is usually delayed, and it can take up to 24 hours. Thus, routine chest radiography after the block is not justified. The supraclavicular approach is best avoided when the patient is uncooperative or cannot tolerate any degree of respiratory compromise. Other complications include frequent phrenic nerve block (40% to 60%), Horner's syndrome, and neuropathy. The presence of phrenic or cervical sympathetic nerve block usually requires only reassurance. Although nerve damage can occur, it is uncommon and usually is self-limited.

INFRACLAVICULAR BLOCK

Clinical Applications

Infraclavicular block provides anesthesia to the arm and hand. Blockade occurs at the level of the cords and offers the theoretical advantages of avoiding pneumothorax while affording block of the musculocutaneous and axillary nerves. No special arm positioning is required. A nerve stimulator ultrasound visualization is required because there are no palpable vascular landmarks to aid in directing the needle.

Technique

Peripheral Nerve Stimulation or Paresthesia. The needle is inserted 2 cm below the midpoint of the inferior clavicular border and is advanced laterally, using a nerve stimulator to identify the plexus.[27] Marking a line between the C6 tubercle and the axillary artery with the arm abducted is helpful in visualizing the course of the plexus. An incremental injection of 20 to 30 mL of solution is sufficient after the needle is correctly placed. Success rate is improved with a distal motor response.[28] A coracoid technique, with needle insertion site 2 cm medial and 2 cm caudal to the coracoid process, has also been described.[29] However, the more lateral insertion site can result in the absence of blockade of the musculocutaneous nerve, removing the major advantage of this approach over the simpler axillary block.

Ultrasound Guided. Ultrasound guidance is frequently used to visualize the neurovascular bundle and ideally, local anesthetic spread should be visualized around the axillary artery (see Chapter 58).

Side Effects and Complications

Because of the blind approach to the plexus, the risk of intravascular injection may be increased. Exaggerated medial needle direction may result in pneumothorax.

AXILLARY BLOCK

Clinical Applications

The axillary approach to the brachial plexus is popular because of its ease, reliability, and safety.[30] Blockade occurs at the level of the terminal nerves. Although blockade of the musculocutaneous nerve is not always produced with this approach, it can be supplemented at the level of the axilla or at the elbow. Indications for axillary block include surgery to the forearm and hand. Elbow procedures are also performed successfully using the axillary approach.[31] This block is ideally suited for outpatients and is easily adapted to the pediatric population[32] (see Chapter 92). However, axillary block is unsuitable for surgical procedures on the upper arm or shoulder, and the patient must be able to abduct the arm to perform the block.

Anatomic concepts that should be considered before an axillary block include the following:

1. The neurovascular bundle is multicompartmental.[33]
2. The axillary artery is the most important landmark
3. Although anatomic variations exist, typically, the median nerve is found superior to the artery, the ulnar nerve is inferior, and the radial nerve is posterior and somewhat lateral (Fig. 57-8).
4. At this level, the musculocutaneous nerve has already left the sheath and lies with the coracobrachialis muscle.
5. The intercostobrachial nerve, a branch of the T2 intercostal nerve, is usually blocked by the skin wheal overlying the artery; however, adequate anesthesia for the tourniquet can be ensured by extending the wheal 1 to 2 cm caudad and cephalad.

Technique

Peripheral Nerve Stimulation, Paresthesia, or Sheath. The patient should be in the supine position with the arm to be blocked placed at a right angle to the body and the elbow flexed to 90 degrees. The dorsum of the hand rests on the bed or pillow; hyperabduction of the arm with placement of the hand beneath the patient's head is not recommended, because this position frequently obliterates the pulse.

The axillary artery is palpated, and a line is drawn tracing its course from the lower axilla as far proximally as possible. The artery is then fixed against the patient's

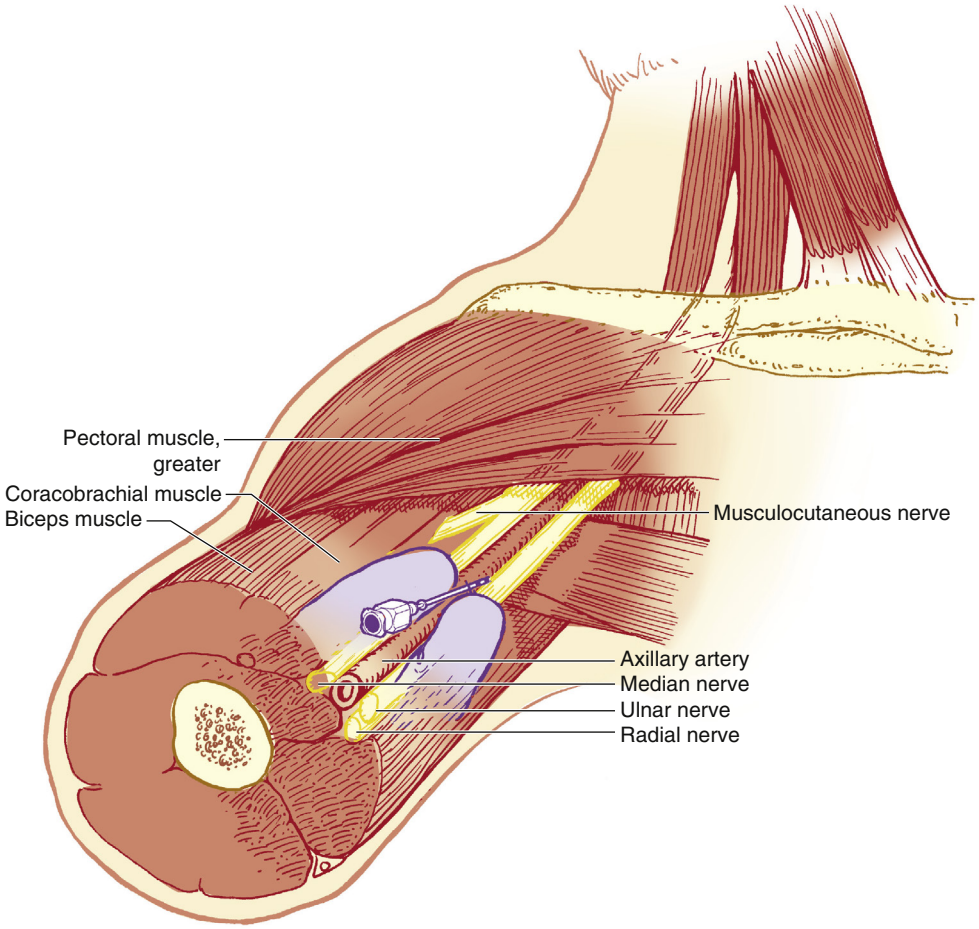


Figure 57-8. Axillary block. The arm is abducted at right angles to the body. Distal digital pressure is maintained during needle placement and injection of the local anesthetic.

humerus by the index and middle fingers of the left hand, and a skin wheal is raised directly over the artery at a point in the axilla approximating the skin crease. Proximal needle placement and maintenance of distal pressure facilitate proximal spread of the solution.

Several methods of identifying the axillary sheath have been described, all with reportedly good results. Overall, paresthesias are unnecessary; however, multiple injections can shorten the onset and improve the reliability of blockade.

1. Paresthesias can be sought with a 25-gauge, 2-cm needle, beginning deeply (i.e., radial nerve) or with the nerves supplying the surgical site. Needles longer than 2 cm are rarely needed to reach the neurovascular bundle. Smaller needles and a short needle bevel may be associated with a less frequent risk of nerve damage.[9] Each paresthesia is injected with 10 mL of local anesthetic.
2. A nerve stimulator can also be used with an insulated needle to locate the nerves. Stimulation with a low current threshold (0.5 mA) decreases onset time, but increases block performance time compared with higher-threshold stimulation (1.0 mA).[34]
3. A short-bevel needle can be advanced until the axillary sheath is entered, as evidenced by a fascial click, whereupon 40 to 50 mL of solution is injected after negative aspiration.
4. A transarterial technique can be used, whereby the needle pierces the artery and 40 to 50 mL of solution is injected posterior to the artery. Alternatively, half of the solution is injected posterior and half is injected anterior to the artery. Great care must be taken to avoid intravascular injection with this technique, particularly because the pressure of injection within the compartments of the axillary sheath may move anatomic structures in relation to the immobile needle.
5. Ultrasound guidance with visualization of local anesthetic spread around the four nerves (with and without motor stimulation) decreases block onset time and can reduce the number of needle redirections; however, the rates of success and complications are similar to other approaches.[35,36] Ultrasound can also help with the success with smaller volumes of local anesthetic, although the overall duration of sensory and motor block will be markedly decreased.[37]

Classically, upon completion of the injection, the arm should be adducted and returned to the patient's side to prevent the humeral head from obstructing proximal flow of the local anesthetic solution. However, maintaining the arm in abduction decreases onset time and prolongs both sensory and motor block.[38] If the musculocutaneous nerve is not blocked by the axillary approach, it can be blocked by injection within the body of the coracobrachialis muscle or at the elbow superficially at the lateral

aspect of the antecubital fossa just above the interepicondylar line.

Success Rate With Axillary Block Techniques

The success rate for an axillary block depends on the definition of a successful block (i.e., surgical anesthesia versus blockade of all four terminal nerves of the upper extremity), the technique used to localize the brachial plexus, and the number of injections. Success rates with single-injection techniques can vary.[39] Thompson and Rorie[33] concluded that the presence of multiple compartments limits diffusion of the local anesthetic (and the success of single injection compared to multiple injection techniques). Although Partridge and coworkers[40] confirmed the presence of these compartments, they concluded that the "septa" dividing them were incomplete based on injections of methylene blue and latex solutions into cadavers. The controversy surrounding single- versus multiple-injection techniques remains unresolved.

Eliciting a paresthesia is as efficacious as peripheral nerve stimulation (with a motor response of 0.5 to 1.0 mA). Most studies suggest that two-injection transarterial techniques are equivalent to single-paresthesia or single-nerve stimulation approaches. In general, the efficacy of paresthesia and peripheral nerve stimulator techniques increases when multiple injections are used. Conversely, success rates with perivascular or fascial click approaches are variously reliable.[41]

Side Effects and Complications

Nerve injury and systemic toxicity are the most significant complications associated with the axillary approach. The assertion that neuropathies are more common with the paresthesia technique is not supported by the available data. Even when paresthesias are not sought, they often occur unintentionally.[8] Injection of large volumes of local anesthetic, particularly with the transarterial approach, increases the risk of intravascular injection and systemic toxicity of local anesthetics. Hematoma and infection are rare complications.

PERIPHERAL BLOCKS AT THE MIDHUMERAL LEVEL, ELBOW, AND WRIST

Clinical Applications

As techniques for brachial plexus blockade have gained popularity, indications for peripheral nerve blockade at the wrist and elbow have diminished. However, these techniques can be useful when limited anesthesia is required, when contraindications to brachial plexus block (e.g., infection, bilateral surgery, coagulation abnormalities, bleeding diathesis, difficult anatomy) exist, or when brachial plexus blockade is incomplete. Only the midhumeral approach provides anesthesia for the use of a tourniquet. Peripheral blocks performed at the level of the elbow and wrist are typically performed as "field" blocks without neural localization. However, ultrasound imaging or peripheral nerve stimulation can be used.

Midhumeral Block

Midhumeral block involves blocking each of the four nerves of the brachial plexus separately in the humeral canal at the level of the proximal one third and distal two thirds of the humerus. At this level, the median and ulnar nerves are located on the lateral and medial aspects of the brachial artery, respectively. The musculocutaneous nerve is identified within the body of the biceps muscle, and the radial nerve lies adjacent to the humerus. A volume of 8 to 10 mL of local anesthetic is injected after localization of each nerve with a nerve stimulator (or ultrasound). Midhumeral block has been reported to have a higher success rate than traditional (defined as stimulation of two nerves) axillary brachial plexus block.[42] In this study, time to complete the block was not different between the two techniques; however, the onset of complete sensory block was shorter in the axillary approach, whereas the success rate of blockade of all four major nerves was higher in the midhumeral group.

Median Nerve Block

Block of the median nerve provides anesthesia of the palmar aspects of the thumb and index finger, the middle finger and radial half of the ring finger, and the nail beds of the same digits. Motor block includes the muscles of the thenar eminence, lumbrical muscles of the first and second digits, and in the case of the block at the elbow, median-innervated wrist flexor muscles of the forearm.

Technique at the Elbow. With the patient's arm placed in the anatomic position (palm up), a line is drawn connecting the medial and lateral epicondyles of the humerus. The major landmark for this technique is the brachial artery, which is found medial to the biceps tendon at the intercondylar line. The median nerve lies medial to the artery (Fig. 57-9) and can be blocked with 3 to 5 mL of solution after eliciting a paresthesia. If no paresthesia is

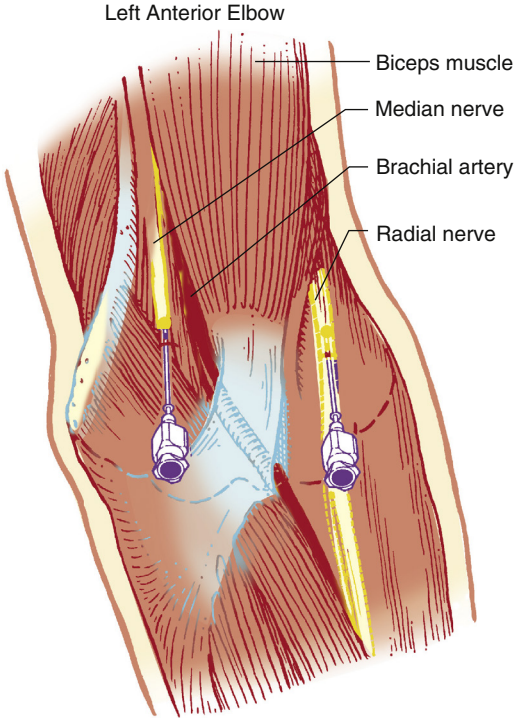


Figure 57-9. Anatomic landmarks for median and radial nerve blocks at the elbow.

obtained, the local anesthetic can be injected in a fanlike pattern medial to the palpated artery.

Technique at the Wrist. The median nerve is located between the flexor carpi radialis and palmaris longus tendons and can be blocked at a point 2 to 3 cm proximal to the wrist crease (Fig. 57-10). (The palmaris longus tendon is congenitally or postsurgically absent from some patients.) A loss of resistance is felt as the needle passes through the flexor retinaculum, at which point 2 to 4 mL of solution should be injected. A superficial palmar branch supplying the skin of the thenar eminence can be blocked by injecting 0.5 to 1 mL of local anesthetic subcutaneously above the retinaculum. Paresthesias should not be sought because of the confinement of this nerve within the carpal tunnel.

Radial Nerve Block

Block of the radial nerve provides anesthesia to the lateral aspect of the dorsum of the hand (i.e., thumb side) and the proximal portion of the thumb, index, middle, and lateral half of the ring fingers.

Technique at the Elbow. The radial nerve can be blocked at the elbow as it passes over the anterior aspect of the lateral epicondyle. The intercondylar line and lateral edge of the biceps tendon are marked. A 22-gauge, 3- to 4-cm needle is inserted at a point 2 cm lateral to the biceps tendon and is advanced until bone is encountered (see Fig. 57-9). A fanlike injection is made using 3 to 5 mL of local anesthetic.

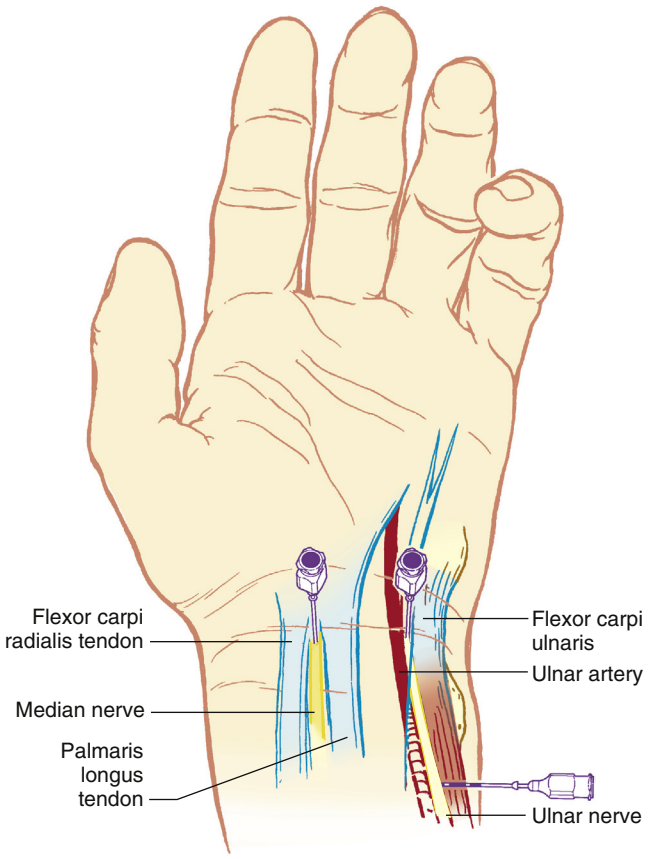


Figure 57-10. Anatomic landmarks for median and ulnar nerve blocks at the wrist. An alternative method for ulnar nerve block, from the ulnar side of the wrist, is shown.

Technique at the Wrist. The radial nerve block at the wrist is a field block of the multiple peripheral branches descending along the dorsum and radial side of the wrist. The extensor pollicis longus tendon can be identified when the patient extends the thumb. The needle insertion is over this tendon at the base of the first metacarpal; the injection is superficial to the tendon. A volume of 2 mL of local anesthetic is injected proximally along the tendon, and an additional 1 mL is injected as the needle passes at a right angle across the anatomic snuffbox (Fig. 57-11).

Ulnar Nerve Block

Blockade of the ulnar nerve provides anesthesia of the ulnar side of the hand, the little finger, and the ring finger and all the small muscles of the hand, except those of the thenar eminence and the first and second lumbrical muscles.

Technique at the Elbow. Although the ulnar nerve is easily accessible at its subcutaneous position posterior to the medial epicondyle, blockade at this site is associated with a high incidence of nerve injury. The nerve is surrounded by fibrous tissue at this point, requiring an intraneural injection for successful blockade. Use of a very fine needle with a small volume of local anesthetic (1 mL) diminishes the risk; however, the nerve can be blocked satisfactorily with 5 to 10 mL of local anesthetic at a site 3 to 5 cm proximal to the elbow. The local anesthetic should be injected in a fanlike fashion without elicitation of a paresthesia.

Technique at the Wrist. At the wrist, the ulnar nerve lies beneath the flexor carpi ulnaris tendon between the ulnar artery and the pisiform bone. At this point, it has already given off its palmar cutaneous and dorsal branches. The nerve can be approached by directing the needle medially from the radial side of the tendon or, alternatively, by directing the needle radially from the ulnar side of the tendon (see Fig. 57-10). After eliciting a paresthesia, 3 to 5 mL of anesthetic solution is injected or spread in a fanlike fashion.

Musculocutaneous Nerve Block

The musculocutaneous nerve terminates as the lateral cutaneous nerve of the forearm. This nerve provides

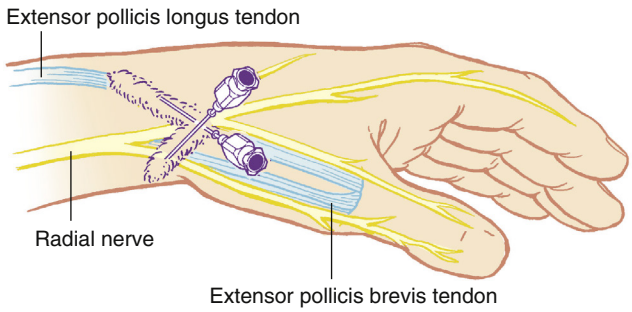


Figure 57-11. Anatomic landmarks and method of needle insertion for a radial nerve block at the wrist.

sensory innervation to the skin on the radial side of the forearm up to the radiocarpal joint. This block is usually performed to supplement the axillary approach to brachial plexus anesthesia.

Technique at the Elbow. The lateral cutaneous nerve of the forearm can be blocked 1 cm proximal to the intercondylar line immediately lateral to the biceps tendon. Fanlike infiltration of 3 to 5 mL of local anesthetic subcutaneously at this site provides excellent anesthesia of this nerve.

Peripheral Blockade at the Elbow Versus the Wrist

The forearm cutaneous nerves arise in the upper arm, and they are not anesthetized by block of the peripheral nerves at the elbow. There is no advantage of a block of the peripheral nerves of the upper extremity when comparing elbow with wrist techniques; both provide sensory anesthesia of the hand.

Side Effects and Complications

In general, distal peripheral blocks have a less frequent risk of complications. However, intravascular injection can occur, and the usual precautions of incremental injection after aspiration are recommended. The risk of nerve injury is more frequent when more distal peripheral blocks are performed, possibly because of superficial nerve placement between bony and ligamentous structures, thereby offering ready access to the probing needle point.

INTRAVENOUS REGIONAL BLOCKS

Intravenous regional blocks were first described by a German surgeon, August Bier, in 1908.[43] Early methods involved two tourniquets and the first synthetic local anesthetic, procaine. The technique lost popularity as reliable methods of blocking the brachial plexus evolved.

Clinical Applications

The Bier block has multiple advantages, including ease of administration, rapidity of recovery, rapid onset, muscular relaxation, and controllable extent of anesthesia. It is an excellent technique for short (<90 minutes) open surgical procedures and for closed reductions of bony fractures.

Technique

An intravenous cannula is placed in the upper extremity to be blocked as distally as possible; the patient should also have an intravenous cannula in the nonoperative upper extremity for administration of fluids and other drugs. Traditionally, a double tourniquet is placed on the operative side; both cuffs should have secure closures and reliable pressure gauges. After exsanguination of the arm, the proximal cuff is inflated to approximately 150 mm Hg greater than the systolic pressure, and absence of a radial pulse confirms adequate tourniquet pressure. The total dose of local anesthetic is based on the patient's weight, and it is injected slowly (3 mg/kg of 0.5% prilocaine or lidocaine, without epinephrine). The use of bupivacaine for intravenous regional anesthesia has been associated with local anesthetic toxicity and death[44] and is not recommended (see Chapter 36). However, dilute solutions (0.125% levobupivacaine) of long-acting amides and the addition of adjuvants (tramadol, ketorolac, clonidine) have been used to prolong sensory block and analgesia after tourniquet deflation.[45]

The onset of anesthesia is usually within 5 minutes. When the patient complains of tourniquet pain, the distal tourniquet, which overlies anesthetized skin, is inflated, and the proximal tourniquet is released. Use of a single, wide cuff allows use of smaller inflation pressures during intravenous regional anesthesia. The postulated advantage is that the smaller pressures will decrease the incidence of neurologic complications related to high inflation pressures with the narrow double cuffs.[46] The tourniquet can be released safely after 25 minutes, but the patient should be closely observed for local anesthetic toxicity for several minutes after the tourniquet release. Slow injection of local anesthetic solutions at a distal site decreases the risk of toxicity.[47]

Side Effects and Complications

Technical problems with this block include tourniquet discomfort, rapidity of recovery leading to postoperative pain, difficulty in providing a bloodless field, and the necessity of exsanguination in the case of a painful injury. Accidental or early deflation of the tourniquet or use of excessive doses of local anesthetics can result in toxic reactions. Injection of the drug as distally as possible at a slow rate decreases blood levels and theoretically may increase safety.[47] Cyclic deflation of the tourniquet at 10-second intervals increases the time to peak arterial lidocaine levels that can decrease potential toxicity.[48] Other rare complications associated with this technique include phlebitis (with 2-chloroprocaine), development of compartment syndrome, and loss of a limb.

BLOCKS OF THE THORAX AND ABDOMEN

PARAVERTEBRAL BLOCK

Anatomic landmarks of the wedge-shaped paravertebral space include the parietal pleura anteriorly; the vertebral body, intervertebral disk, and foramen medially; and the posterior intercostal membrane laterally and the superior costotransverse ligament posteriorly. The neural structures within the paravertebral space include the intercostal nerve, the dorsal rami and communications, and the sympathetic chain. The intercostal nerve itself is fragmented within the paravertebral space and is blocked easily with local anesthetics. Awareness of the spinous processes, transverse processes, ribs, and costotransverse ligaments are essential while performing the block.

Clinical Applications

The paravertebral block can be used to provide anesthesia or analgesia to patients undergoing intrathoracic, abdominal, or pelvic procedures or surgery to the breast.[49,50] Bilateral and continuous applications have been described.[51,52] In patients undergoing thoracotomy,

thoracic paravertebral block provides analgesia comparable to epidural techniques, but with fewer side effects and complications.[53,54] Paravertebral block can be useful in the diagnosis and treatment of certain chronic pain disorders, including postthoracotomy and postmastectomy pain.

Technique

Thoracic Paravertebral Block. Thoracic paravertebral blockade occurs as the spinal nerves emerge from the vertebral foramina. This results in somatic and sympathetic block of multiple contiguous thoracic dermatomes above and below the injection site.

Neural Localization. Peripheral nerve stimulation has been used to signify entry into the paravertebral space and guard against pleural puncture. The peripheral nerve stimulator will elicit a motor response on the intercostal muscles before the needle enters the pleura. Caution needs to be taken during a multilevel block, because local anesthetic injected at one level can spread to the contiguous levels and either modify or abolish the intercostal motor response. Ultrasound measurements of the depth from skin to the transverse process and from skin to the parietal pleura have been found to correlate closely to the actual needle depth. Theoretically, knowing the maximal insertion depth could minimize the risk of pneumothorax.

Thoracic paravertebral block can be performed with the patient in the sitting, lateral, or prone position; the sitting position allows easy identification of landmarks. Typically, the thoracic spinous processes are identified, and the needle is inserted 2.5 to 3 cm lateral to the most cephalad aspect of the spinous process and advanced perpendicular to the skin in all planes to contact the transverse process of the vertebra below, typically at a depth of 2 to 4 cm. After the transverse process is identified, traditionally, the needle is redirected cephalad and gradually advanced until a loss of resistance is felt 1 to 1.5 cm past the superior edge. However, walking the needle caudad can decrease the risk of pneumothorax.[51] The safety of this procedure relies on the proceduralist not advancing the needle farther than 1 to 1.5 cm past the skin-transverse process distance.

Although spread of local anesthetic is variable, a single injection of 15 mL produces unilateral somatic blockade over four or five dermatomes; there is a tendency for caudal (compared with cephalad) spread.[51] To achieve greater spread, 3 to 4 mL of a local anesthetic may be injected at each segment.[55]

Lumbar Paravertebral Block. Lumbar nerves exit the vertebral foramina inferior to the caudad edge of the transverse process. Each nerve divides into anterior and posterior branches; the anterior branches of L1 through L4 (with a contribution from T12) form the lumbar plexus.

The patient is placed in the prone position as described for intercostal blockade. Lines are drawn across the cephalad edges of the lumbar vertebral spinous processes. These lines lie opposite the caudad edges of the homologous transverse processes (Fig. 57-12, *A*). A skin wheal is raised 3 cm lateral to the midline, and a 20-gauge, 10-cm needle is advanced perpendicularly until it contacts the transverse process at a depth of 3 to 5 cm. The needle is then redirected to walk off the caudad edge of the transverse process. At 1 to 2 cm (the thickness of the transverse process) beyond this point, 6 to 10 mL of local anesthetic is injected (see Fig. 57-12, *B*). Elicitation of a paresthesia or use of a nerve stimulator is helpful in confirming correct needle placement.

Side Effects and Complications

Because of the proximity of the neuraxis, epidural or subarachnoid injection of local anesthetic is a risk.[49] Intravascular injection through the lumbar vessels, vena cava, or aorta is possible. Pleural puncture and pneumothorax have occurred with frequencies of 1.1% and 0.5%, respectively.[51]

INTERCOSTAL NERVE BLOCK AND INTERPLEURAL CATHETER PLACEMENT

The intercostal nerves are the primary rami of T1 through T11. T12 is technically a subcostal nerve, and it supplies branches to the ilioinguinal and iliohypogastric nerves. Fibers from T1 contribute to the brachial plexus; T2 and T3 provide a few fibers to the formation of the intercostobrachial nerve, which supplies the skin of the medial aspect of the upper arm. Each intercostal nerve has four branches: the gray ramus communicans, which passes anteriorly to the sympathetic ganglion; the posterior cutaneous branch, supplying skin and muscle in the para vertebral area; the lateral cutaneous branch, arising just anterior to the midaxillary line and sending subcutaneous branches anteriorly and posteriorly; and the anterior cutaneous branch, which is the termination of the nerve.

Medial to the posterior angles of the ribs, the intercostal nerves lie between the pleura and the internal intercostal fascia. At the posterior angle of the rib, the nerve lies in the costal groove accompanied by the intercostal vein and artery.

Clinical Applications

Few surgical procedures can be performed with an intercostal block alone, and the application of these blocks in combination with other techniques has largely been supplanted by epidural blockade. However, in patients with contraindications to neuraxial blockade, these techniques can be used alone or combined with celiac plexus blocks and light general anesthesia to provide excellent surgical conditions for intraabdominal procedures. In a similar fashion, intrathoracic surgery can be accomplished using intercostal and stellate ganglion blocks with endotracheal sedation. Although surgical applications are possible, the majority of indications are for postoperative analgesia.

Interpleural catheter placement for management of postoperative pain was first described by Reiestad and Stromskag in 1986.[56] Because the mechanism of action is poorly understood, and reports of efficacy have varied, the use of this technique has varied in frequency over time. Overall, the results with cholecystectomy have been most favorable. The advantages of interpleural analgesia are more difficult to prove in patients undergoing thoracotomy, perhaps because of technical problems relating to blood in the pleural space and chest tube drainage. Recent applications include analgesia after minimally invasive cardiopulmonary bypass surgery.[57]

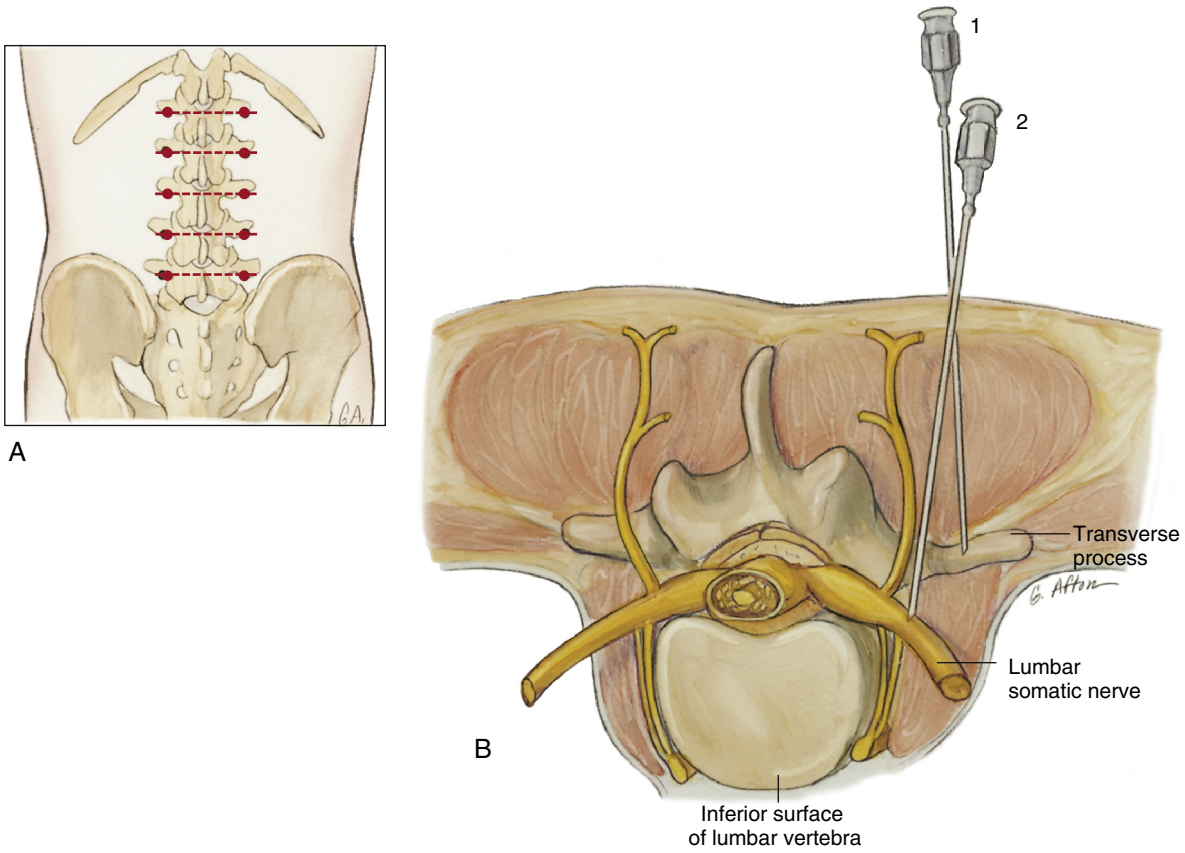


Figure 57-12. A, Patient positioning and surface landmarks for a lumbar paravertebral nerve block. **B,** For a paravertebral nerve block, the needle is advanced perpendicularly until it contacts the transverse process. It is redirected to walk off the caudad edge of the transverse process and advanced 1 to 2 cm.

Technique

Intercostal Block. The intercostal nerve can be readily blocked at the angle of the rib just lateral to the sacrospinalis muscle group. The patient is placed in the prone position with a pillow placed under the abdomen to reduce the lumbar curve (Fig. 57-13, *A*). A line is drawn along the posterior vertebral spines. Nearly parallel lines are drawn along the posterior angles of the rib, which can be palpated 6 to 8 cm from the midline. These lines angle medially at the upper levels to prevent overlying of the scapula. The inferior edge of each rib is palpated and is marked on the line intersecting the posterior angle of the rib. After appropriate skin preparation, skin wheals are injected at each of these points. A 22-gauge, short-bevel, 4-cm needle is attached to a 10-mL syringe. Beginning at the lowest rib, the index finger of the left hand displaces the skin up over the patient's rib. The needle is inserted at the tip of the finger until it rests on the rib. The fingers of the left hand are shifted to grasp the needle hub firmly. The left hand then walks the needle 3 to 5 mm off the lower rib edge, where 3 to 5 mL of local anesthetic are injected (see Fig. 57-13, *B, C*). This process is repeated at each rib. Appropriate intravenous sedation providing analgesia and some degree of amnesia is desirable for the patient's comfort. Ultrasound imaging of the intercostal nerves has been reported, but the visibility is highly variable.

Alternatively, intercostal block can be performed in the supine patient at the midaxillary line. Theoretically, the lateral cutaneous branch of the nerve can be missed, but computed tomography studies show that injected solutions spread several centimeters along the costal groove. Further injection of 1 to 2 mL of local anesthetic as the needle is withdrawn blocks the subcutaneous branches.

Interpleural Catheter. The technique for interpleural catheter placement is simple and can be performed with the patient in a lateral (and slightly oblique) or sitting position. The sixth or seventh intercostal space is identified. Needle insertion is performed approximately 10 cm lateral from the posterior midline, and an epidural needle tip is advanced until it rests on the cephalad edge of the rib below the intercostal space to be entered. A glass syringe filled with saline or air is then attached to the needle, and the unit is advanced slowly over the superior edge of the rib. When the tip of the needle enters the parietal pleura, the solution in the syringe is drawn into the chest cavity because of the negative intrathoracic pressure. This effect can be observed in mechanically and spontaneously ventilating patients, but it is accentuated in the latter group.

The catheter is then inserted approximately 5 to 8 cm into the interpleural space and is secured on the chest

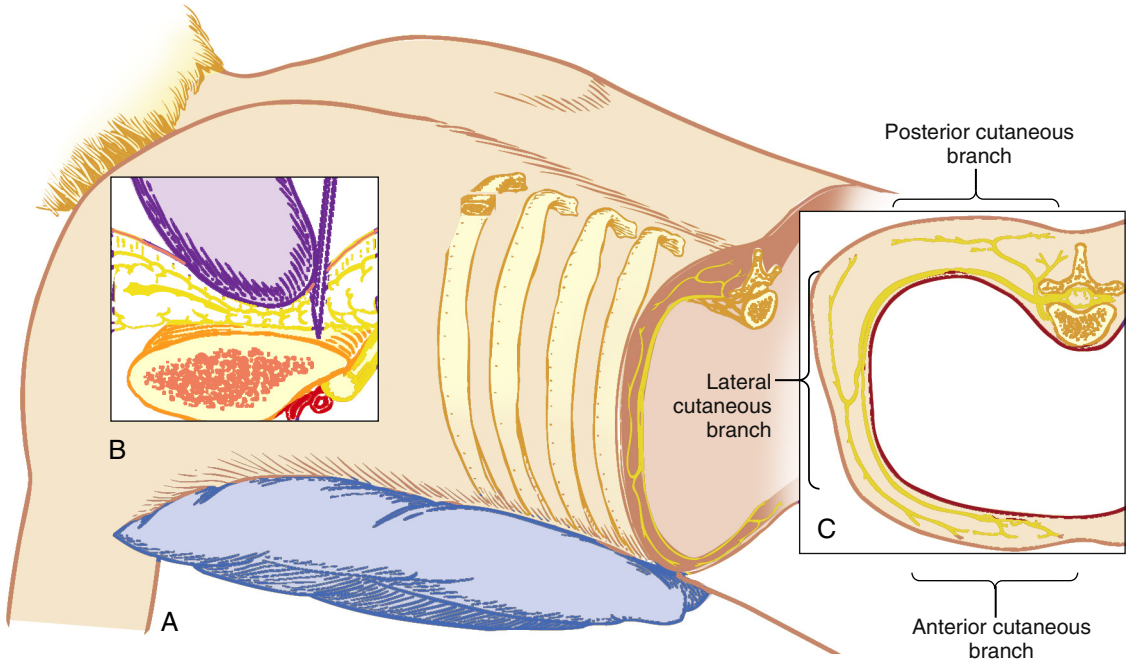


Figure 57-13. A, Patient positioning for an intercostal nerve block. **B,** The index finger displaces the skin up over the rib. The needle is inserted at the tip of the finger and rests on the rib. The needle is walked off the lower rib edge and inserted 3 to 5 mm. **C,** An intercostal nerve and its branches.

wall. During needle positioning and catheter placement, care must be taken to minimize entrainment of air through the needle. Lung parenchymal damage can occur with loss-of-resistance techniques or insertion of excessive lengths of catheter.

Side Effects and Complications

The major complication feared with intercostal blockade is pneumothorax. The actual incidence, however, was as low as 0.07% in a large series performed by anesthesiologists at all levels of training. Routine postoperative chest radiographs showed an incidence of nonsymptomatic pneumothorax of 0.42%.[58] If this unusual complication occurs, treatment is usually limited to observation, administration of oxygen, or needle aspiration. Rarely, chest tube drainage is required when these treatments are unsuccessful.

The risk of systemic local anesthetic toxicity is present with multiple intercostal blocks because of the large volumes and rapid absorption of the solutions. Use of epinephrine has been shown to decrease blood levels. Patients should be monitored and observed carefully during the block and for at least 20 to 30 minutes afterward. Interpleural block should not be performed in patients with pleural fibrosis or inflammation, pleural effusion, lung parenchymal disease associated with pleural disease, or bleeding diathesis. Pleural disease can result in poor spread of local anesthetic solutions or rapid uptake in the case of inflammation. Patients with severe pulmonary disease who rely on their intercostal muscles can exhibit respiratory decompensation after bilateral intercostal blockade.

TRANSVERSUS ABDOMINUS PLANE BLOCK

The lateral abdominal wall consists of subcutaneous tissue, the external oblique muscle, the internal oblique muscle, and the transversus abdominis muscle progressing from superficial to deep. The fascial sheath that lies deep to the internal oblique muscle and superficial to the transversus abdominis muscle is the target for the transversus abdominus plane (TAP) block. The nerves that exit the thoracolumbar spinal column pass laterally through the fascial layer to innervate the abdominal wall.

The landmarks for the TAP block are referred to as the *triangle of Petit*, and they consist of the iliac crest, the latissimus dorsi muscle, and the external oblique muscle. The triangle of Petit is located along the midaxillary line inferior to the lower costal margin and superior to the iliac crest.

Indications

TAP blocks are indicated for any lower abdominal surgery, including hernia repair, appendectomy, caesarian delivery, abdominal hysterectomy, laparoscopic surgery, renal transplantation, and prostatectomy.[59-61] Bilateral blocks can be used for midline incisions or laparoscopic procedures. It is reasonable to expect analgesia between T10 and L1 with a single injection.

Technique

Loss of Resistance (Blind Injection). The point of entry for the blind TAP block is the lumbar triangle of petit. This is situated between the lower costal margin and iliac crest. It is bound anteriorly by the external oblique muscle and posteriorly by the latissimus dorsi. This technique relies on feeling double "pops" as the needle traverses the external oblique and internal oblique muscles. A blunt needle will make the loss of resistance more significant.

Ultrasound-Guided. The patient is positioned supine. Using sterile technique the ultrasound probe is placed

firmly several centimeters superior and parallel to the iliac crest. A 21-gauge, 10-cm insulted needle is inserted several centimeters medial to the probe using an in-plane approach. Bowel peristalsis can often be seen just deep to the transversus abdominis muscle layer. After negative aspiration, 15 to 20 mL of local anesthetic is incrementally injected under ultrasound visualization (see Chapter 58).

Side Effects and Complications

Peritoneal puncture is possible (even with ultrasound guidance),[62] and there has been one reported case of a liver hematoma following a blind TAP block technique.[63]

ILIOINGUINAL AND ILIOHYPOGASTRIC BLOCKS

The ilioinguinal and iliohypogastric nerves arise from the first lumbar spinal root. They pierce the transversus abdominus cephalad and medial to the anterior superior iliac spine and lie between the transversus abdominus and internal oblique muscles. After traveling a short distance caudal and medially, their ventral rami pierce the internal oblique muscle before giving off branches, which then pierce the external oblique and provide sensory fibers to the skin. The ilioinguinal nerve courses anterior and inferiorly to the inguinal ring, where it exits to supply the skin on the proximal, medial portion of the thigh. The iliohypogastric nerve supplies the skin in the inguinal region.

Indications

Ilioinguinal and iliohypogastric blocks are used for analgesia following inguinal hernia repair and for lower abdominal procedures utilizing a Pfannenstiel incision. These blocks have been shown to reduce pain associated with herniorrhaphy significantly, although they do not provide visceral analgesia, and they cannot be used as the sole anesthetic during surgery. Despite the relatively simple technique, a failure rate as frequent as 10% to 25% has been reported.

The ilioinguinal and iliohypogastric nerves arise from the first lumbar spinal root. They pierce the transversus abdominus cephalad and medial to the anterior superior iliac spine and lie between the transversus abdominus and internal oblique muscles. After traveling a short distance caudal and medially, their ventral rami pierce the internal oblique muscle before giving off branches, which then pierce the external oblique and provide sensory fibers to the skin. The ilioinguinal nerve courses anterior and inferiorly to the inguinal ring, where it exits to supply the skin on the proximal, medial portion of the thigh. The iliohypogastric nerve supplies the skin in the inguinal region.

Technique

Landmark Technique. These blocks are performed using a loss-of-resistance technique. The local anesthetic should be inserted between the transversus abdominus and the internal oblique and between the internal and external oblique muscles.

The anterior superior iliac spine is located and a mark is made 2 cm cephalad and 2 cm medial. A blunt needle is inserted perpendicular to the skin through a small puncture site. Increased resistance is noted as the needle passes into the external oblique muscle. A loss of resistance is then observed as the needle passes through the external oblique muscle to lie between it and the internal oblique muscle. After negative aspiration, 2 mL of local anesthetic is injected. The needle is then inserted farther until another loss of resistance is noted as the needle passes out of the internal oblique to lie between it and the transversus abdominus muscle where another 2 mL of local anesthetic is injected. The needle is withdrawn, and the same procedure is repeated two more times in a fanlike distribution between the internal and external oblique and then the internal oblique and the transversus abdominus muscle. A total of approximately 12 mL of local anesthetic is used.

It is often difficult to appreciate the loss of resistance. Given the potential complications of advancing the needle too far, ultrasound guidance is often used for these blocks (see Chapter 58).

Side Effects and Complications

Blind injection can result in inadvertent injury to the intestine or blood vessels. Perforation of the large and small bowel and pelvic hematoma have been reported. Lower extremity weakness owing to local anesthetic spread and subsequent femoral nerve blockade can occur.

LOWER EXTREMITY BLOCKS

Knowledge of the anatomy of the lumbosacral plexus and peripheral nerves of the lower extremity enables anesthesiologists to provide comprehensive anesthetic care. These blocks are safe and have certain advantages, such as postoperative pain relief and lack of complete sympathectomy, which make them ideal for selected patients.

Historically, lower extremity blocks were less popular than blocks used routinely for surgical procedures of the upper extremity, in part because of the widespread acceptance and safety of spinal and epidural anesthesia. Unlike the brachial plexus, the nerves supplying the lower extremity are not anatomically clustered where they can be blocked easily with a relatively superficial injection of local anesthetic. Because of the anatomic considerations, lower extremity blocks are technically more difficult and require more training and practice before expertise is acquired. Many of these blocks were classically performed using paresthesia, loss of resistance, or field block technique, and success rates varied. Advances in needles, catheters, nerve stimulator technology, and ultrasound imaging have facilitated localization of neural structures and improved success rate.[64] Recent applications have focused on postoperative analgesia (rather than intraoperative anesthesia) to improve patient comfort and to assist in rehabilitation and hospital dismissal.

ANATOMY

The nerve supply to the lower extremity is derived from the lumbar and sacral plexuses. The lumbar plexus

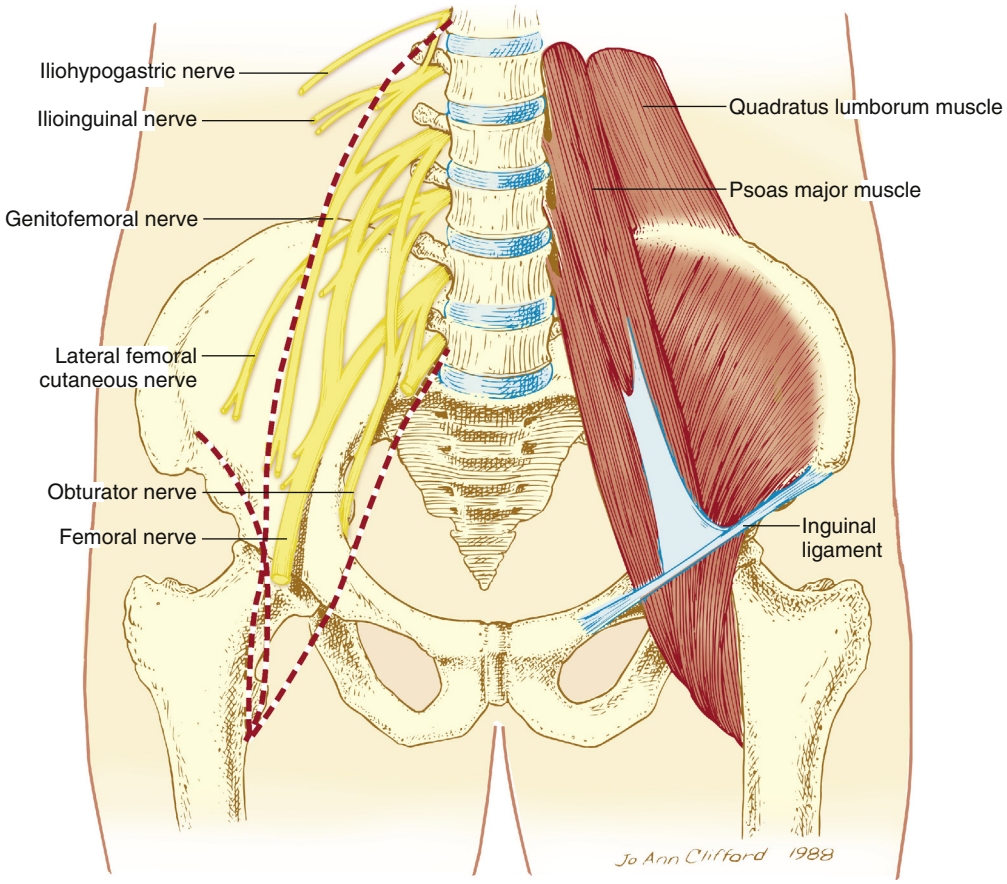


Figure 57-14. The lumbar plexus lies in the psoas compartment between the psoas major and quadratus lumborum muscles.

is formed by the anterior rami of the first four lumbar nerves, frequently including a branch from T12 and occasionally from L5 (Fig. 57-14). The plexus lies between the psoas major and quadratus lumborum muscles in the so-called psoas compartment. The lower components of the plexus, L2, L3, and L4, primarily innervate the anterior and medial thigh. The anterior divisions of L2, L3, and L4 form the obturator nerve; the posterior divisions of the same components form the femoral nerve; and the lateral femoral cutaneous nerve is formed from posterior divisions of L2 and L3.

The sacral plexus gives off two nerves that are important for lower extremity surgery: the posterior cutaneous nerve of the thigh and the sciatic nerve. The posterior cutaneous nerve of the thigh and the sciatic nerve are derived from the first, second, and third sacral nerves plus branches from the anterior rami of L4 and L5, respectively. These nerves pass through the pelvis together, and the greater sciatic foramen and are blocked by the same technique. The sciatic nerve is a combination of two major nerve trunks, the tibial (i.e., ventral branches of the anterior rami of L4, L5, S1, S2, and S3) and the common peroneal (i.e., dorsal branches of the anterior rami of L4, L5, S1, S2, and S3), which form the sciatic nerve. The trunks separate at or above the popliteal fossa, with the tibial nerve passing medially and the common peroneal laterally. The cutaneous distributions of the lumbosacral and peripheral nerves are shown in Figure 57-15.

PSOAS COMPARTMENT BLOCK (POSTERIOR APPROACH TO THE LUMBAR PLEXUS)

The psoas compartment block uses a technique in which a needle is placed into the space between the psoas major and quadratus lumborum muscles. The block was initially performed using a loss-of-resistance technique and a large volume of injected solution to provide anesthesia to the hip and anterolateral thigh.[65]

Clinical Applications

The psoas compartment block provides blockade of the three main components of the lumbar plexus with a single injection.[66] The technique must be combined with a sciatic block for anesthesia of the entire lower extremity. Psoas compartment block is often used to provide postoperative analgesia for patients undergoing major knee and hip surgery.[67,68]

Technique

Although loss-of-resistance or paresthesia techniques are feasible,[69] most practitioners use nerve stimulation to confirm the location of the lumbar plexus.[64] With the classic technique, the patient is placed in the lateral position, with hips flexed and operative extremity uppermost. A line is drawn to connect the iliac crests (i.e., intercristal line), identifying the fourth lumbar spine. A skin wheal is raised 3 cm caudad and 5 cm lateral to

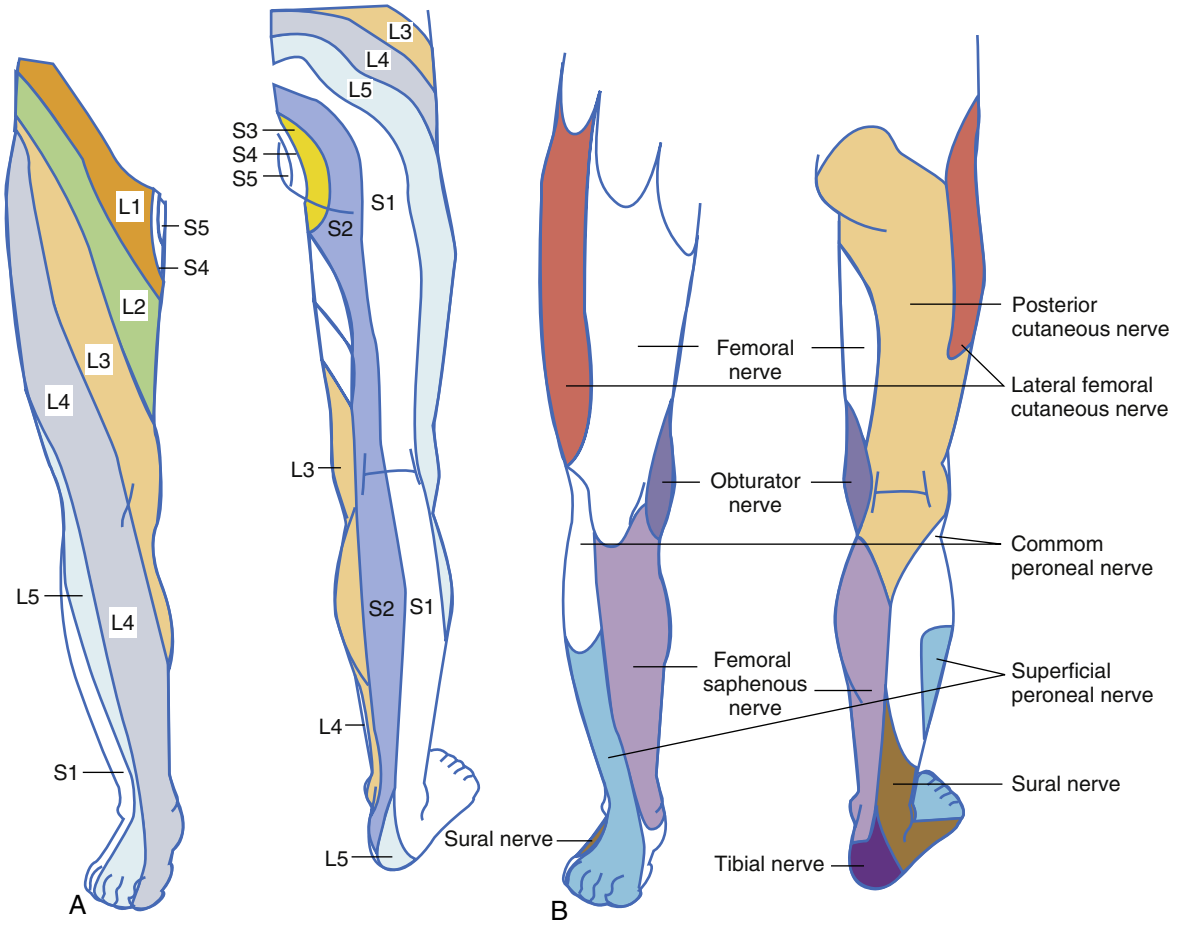


Figure 57-15. A, Cutaneous distribution of the lumbosacral nerves. **B,** Cutaneous distribution of the peripheral nerves of the lower extremity.

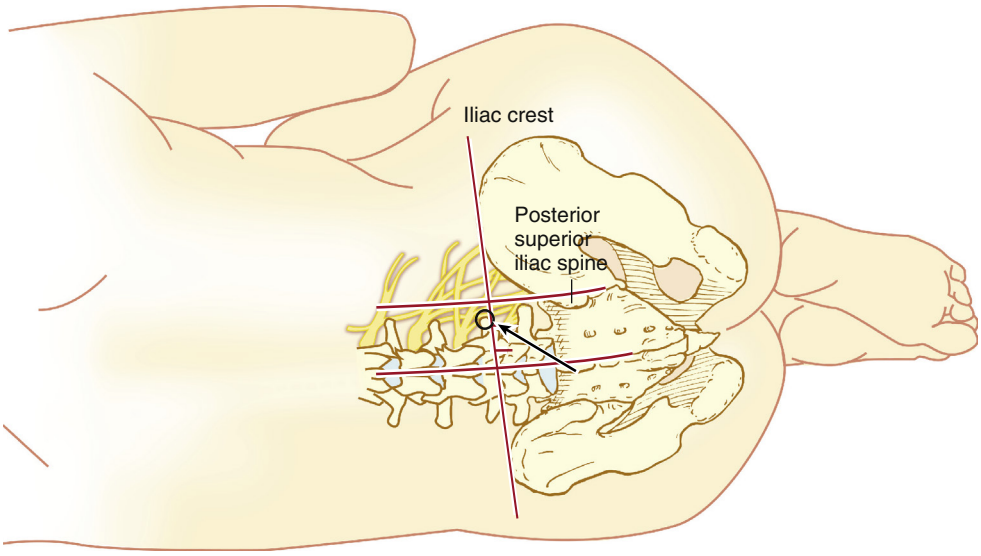


Figure 57-16. Psoas compartment block**.** Needle entry is marked 1 cm cephalad to the intercristal line, two thirds the distance from the midline to the posterior superior iliac spine line. The lumbar plexus is identified between the transverse processes of L4 and L5. Dural sleeves extend 3 to 5 cm laterally. The cross is the site of needle insertion.

the midline on the side to be blocked. A 21-gauge, 10-cm stimulating needle is then advanced perpendicular to the skin entry site until it contacts the fifth lumbar transverse process. The needle is redirected cephalad until it slides off the transverse process. The lumbar plexus is identified by elicitation of a quadriceps motor response, and after negative aspiration, 30 mL of local anesthetic is incrementally injected.

Based on anatomic imaging studies, Capdevila and colleagues[70] modified the classic psoas technique (Fig. 57-16). Needle insertion site is the junction of the lateral third and medial two thirds of a line between the spinous

process of L4 and a line parallel to the spinal column passing through the posterior superior iliac spine. (The spinous process of L4 was estimated to be approximately 1 cm cephalad to the upper edge of the iliac crests.) The needle is advanced perpendicularly to the skin until contact with the transverse process of L4 is obtained and is then advanced under the transverse process until quadriceps femoris muscle twitches are elicited. Despite a difference between men and women in the depth of the lumbar plexus, the distance from the L4 transverse process to the lumbar plexus was comparable (median value, 2 cm) in both sexes (see Fig. 57-12). It is crucial to achieve contact with the L4 transverse process to establish appropriate needle depth and position. A more recent study using ultrasound imaging demonstrated that the intersection of the middle and lateral thirds of the intercrestal line between the midline, and a parallel line through the posterosuperior iliac spine was too lateral to permit needle–transverse process contact in 50% of patients.[71]

Ultrasound-Guided Psoas Compartment Block

Despite the recent popularity of ultrasound guidance in regional anesthesia, there has been limited interest in using ultrasound for lumbar plexus blockade (see Chapter 58). This is likely due to the deep nature of the block; the increasing number of obese patients (also see Chapter 71); and the need for specialized curved-array, low-frequency transducers. Although images of the lumbar plexus have been obtained in volunteers and cadavers, the actual clinical experience for using ultrasound guidance to facilitate the placement of lumbar plexus blocks has not been well described.

Side Effects and Complications

Unlike the relatively minor complications associated with other lower extremity nerve blocks, the risks associated with a posterior lumbar plexus block can be quite severe.[72] Because of the proximity of the neuraxis, intrathecal or epidural local anesthetic or catheter placement is a potential complication. Epidural spread of local anesthetic is the most common complication with an incidence ranging from 1.8% to 16%.[64,66,67,70] Factors that contribute to epidural spread are a medially directed needle, large volumes of local anesthetic, and the presence of a spinal deformity (scoliosis). Less commonly, intrathecal or subarachnoid injection or catheter placement can lead to risk of widespread spinal anesthesia.

Because the psoas compartment block results in injection of local anesthetic into large, richly vascularized muscles (e.g., psoas, quadratus lumborum), the early plasma concentrations are significantly higher than levels obtained during a femoral block. Patients must be monitored for signs of local anesthetic toxicity when given large boluses of local anesthetics. Because of the same rich vascular supply, severe retroperitoneal or renal capsular hematomas have occurred in patients who have undergone a psoas compartment block while anticoagulated, or who received anticoagulation medication shortly after block placement or in the presence of a continuous psoas catheter. Although larger studies are needed, the American Society of Regional Anesthesia conservatively recommends that patients having a lumbar plexus block be managed in much the same way as those undergoing neuraxial blockade when thromboprophylaxis is ordered.[73]

PERIVASCULAR THREE-IN-ONE (FEMORAL) NERVE BLOCK

The femoral nerve is formed within the psoas major muscle by posterior divisions of the second, third, and fourth lumbar nerves. It emerges from the lateral border of the psoas muscle to descend in the groove between the psoas and iliacus muscles and enters the thigh by passing beneath the inguinal ligament lateral to the femoral artery. At this point, the nerve divides into multiple terminal branches, which have been classified as anterior and posterior. The anterior branches are primarily cutaneous, and the deep branches are chiefly motor.The femoral nerve supplies the anterior compartment muscles of the thigh (i.e., quadriceps, sartorius) and the skin of the anterior thigh from the inguinal ligament to the knee. Its terminal branch is the *saphenous nerve*, which supplies an area of skin along the medial side of the leg from the knee to the big toe.

Clinical Applications

The perivascular approach (i.e., three-in-one block) to the lumbar plexus is based on the premise that injection of a large volume of local anesthetic within the femoral canal while maintaining distal pressure will result in proximal spread of the solution into the psoas compartment and subsequent lumbar plexus block.[74] However, imaging studies suggest that blockade occurs through lateral (lateral femoral cutaneous nerve) and medial (obturator nerve) spread of injected local anesthetic.[75]

Indications for femoral nerve block include anesthesia for knee arthroscopy in combination with intraarticular local anesthesia and analgesia for femoral shaft fractures, anterior cruciate ligament reconstruction, and total knee arthroplasty as a part of multimodal regimens. Their use in complex knee operations is associated with smaller pain scores and fewer hospital admissions following same-day surgery.[64,67]

Technique

Femoral Block

Peripheral Nerve Stimulation or Paresthesia. The patient is placed in the supine position. A line is drawn between the anterior superior iliac spine and the pubic tubercle, identifying the inguinal ligament. The femoral artery is marked. A 22-gauge, 4-cm needle is advanced lateral to this line (Fig. 57-17, *A*). Elicitation of a motor response (or paresthesia) verifies correct needle position. Commonly, the anterior branch of the femoral nerve is identified first. Stimulation of this branch leads to contraction of the sartorius muscle and should not be accepted. The needle should be redirected slightly laterally and with a deeper direction to encounter the posterior branch of the femoral nerve. Stimulation of this branch is identified by patellar ascension as the quadriceps contract. A total of 20 to 40 mL of local anesthetic is injected incrementally after negative aspiration. Reliable anesthesia of the femoral and lateral

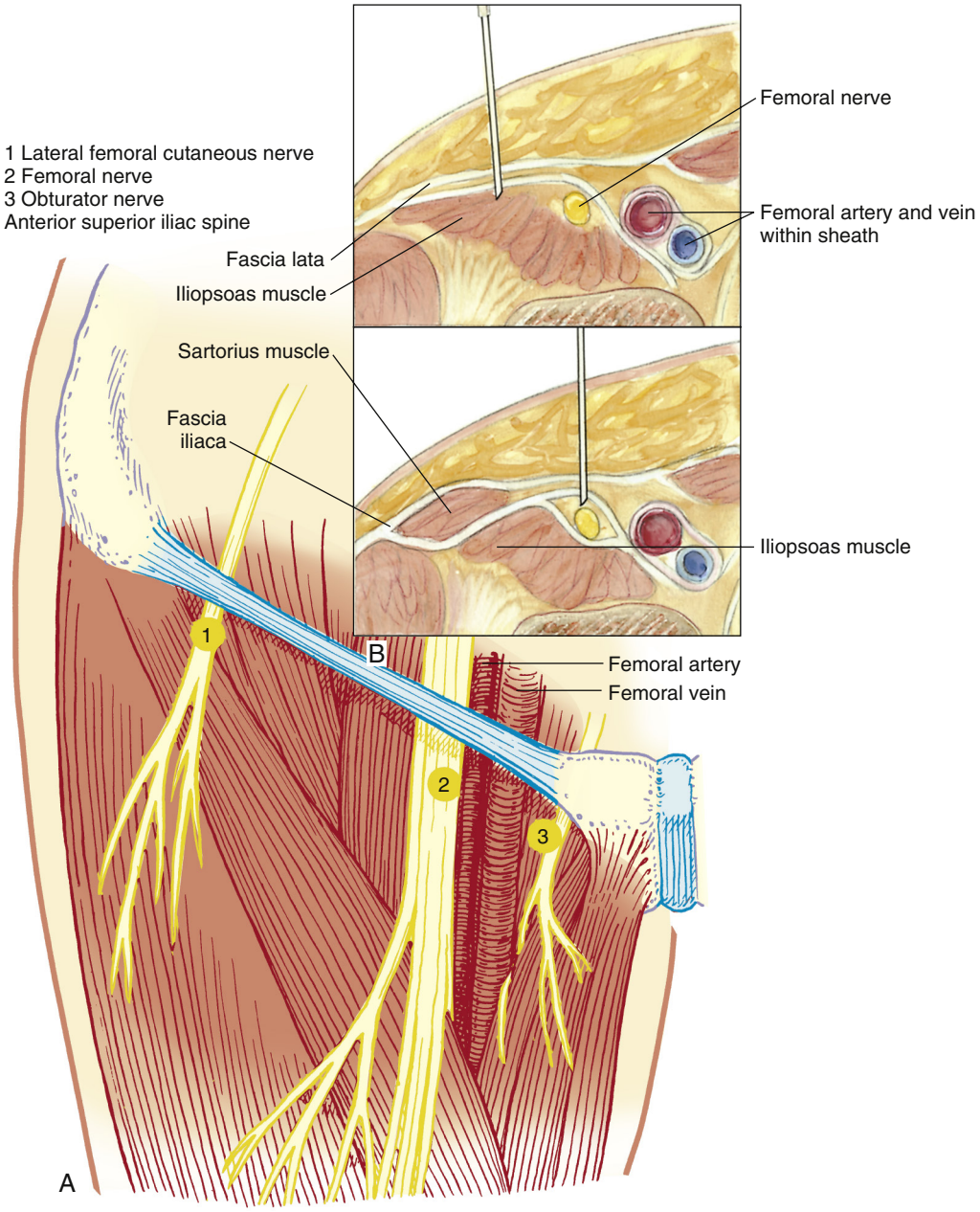


Figure 57-17. A, Anatomic landmarks for lateral femoral cutaneous, femoral, and obturator nerve blocks. **B,** For an obturator nerve block, the needle is walked off the inferior pubic ramus in a medial and cephalad direction until it passes into the obturator canal.

femoral cutaneous nerves can be predicted with 20 mL; however, obturator nerve block might not occur even with volumes greater than 30 mL.

Ultrasound Guided. The use of ultrasound can be useful in patients in whom it is difficult to palpate a femoral pulse, because of weight, anatomic variability, or changes to the needle insertion site (before radiation or surgery). The femoral nerve can be identified lateral to the artery as a triangular shaped structure.

Technique

Fascia Iliaca Nerve (Modified Femoral) Block. The fascia iliaca block was originally described in children (see Chapter 92). The clinical applications for its use are the same as those for femoral nerve block.[64,76] The simplicity of the double pop technique has been emphasized. The *double pop* refers to the sensation felt as the needle traverses the fascia lata then the fascia iliaca. Penetration of both layers of fascia is important for successful fascia iliaca blockade (see Fig. 57-17). To facilitate the appreciation of the "clicks" or "pops," the use of a short bevel or bullet-tipped needle has been advocated to provide more tactile feedback than cutting needles. The needle entry site for the fascia iliaca block is determined by drawing a line between the pubic tubercle and the anterior superior iliac crest and dividing this line into thirds. The needle entry point is one centimeter caudal to the intersection of the medial

two thirds and lateral one third along this line. This site is well away from the femoral artery, which is useful for patients in whom femoral artery puncture is contraindicated. Ultrasound can also be used to visualize the two fascial layers and spread of local anesthetic behind the fascia iliaca.

Side Effects and Complications

Intravascular injection and hematoma are possible because of the proximity of the femoral artery. Anatomically, the nerve and artery are located in separate sheaths approximately 1 cm apart. In most patients with normal anatomy, the femoral artery can be easily palpated, allowing correct, safe needle positioning lateral to the pulsation. The presence of femoral vascular grafts is a relative contraindication to these techniques. Nerve damage is rare.

LATERAL FEMORAL CUTANEOUS NERVE BLOCK

The lateral femoral cutaneous nerve (L2 and L3) emerges at the lateral border of the psoas muscle immediately caudad to the ilioinguinal nerve. It descends under the iliac fascia to enter the thigh deep to the inguinal ligament 1 to 2 cm medial to the anterior superior iliac spine. The nerve emerges from the fascia lata 7 to 10 cm below the spine and divides into anterior and posterior branches. The skin of the lateral portion of the thigh from the hip to midthigh is supplied by the posterior branch; the anterior branch supplies the anterolateral thigh to the knee.

Clinical Applications

The lateral femoral cutaneous nerve block is useful for skin graft harvesting and can be used in concert with other peripheral nerve blocks for complete anesthesia of the lower extremity.

Technique

A point is marked 2 cm medial and 2 cm caudad to the anterior superior iliac spine. A 22-gauge, 4-cm needle is advanced perpendicular to the skin entry site until a sudden release indicates passage through the fascia lata. As the needle is moved in a fanlike pattern laterally and medially, 10 to 15 mL of solution is injected, depositing local anesthetic above and below the fascia (see Fig. 57-17, *A*). Although a sensory nerve, the lateral femoral cutaneous nerve can be localized using a nerve stimulator technique by seeking pulsatile tingling in the distribution of the nerve.[77]

Side Effects and Complications

There is an infrequent risk of associated complications because there are no large blood vessels near this nerve. In addition, the likelihood of rapid uptake or intravascular injection is low.

SAPHENOUS NERVE BLOCK

Indications

The saphenous nerve provides innervation to the medial aspect of the lower extremity from the knee to the medial malleolus. Saphenous nerve blocks are commonly combined with popliteal and ankle blockade. Several approaches to the saphenous nerve block have been described using both a transsartorial (above the knee) and paravenous (below the knee) approach.[78] Ultrasound guidance can be used for both techniques. The saphenous nerve can also be blocked at the level of the ankle and will be described as part of the ankle block.

Anatomy

The saphenous nerve is a cutaneous sensory branch off the posterior division of the femoral nerve. It runs in the adductor canal along the posterior border of the sartorius muscle. The nerve emerges and divides at the level of the knee before continuing distally along the medial border of the tibia, posterior to the great saphenous vein. The saphenous nerve is located approximately 1 cm medial and 1 cm posterior to the saphenous vein at the level of the tibial tuberosity.

Technique

The saphenous nerve is purely sensory; therefore, a field block technique is most common. Ultrasound guidance can also be used to identify the neural and vascular structures.

Paravenous Approach. At the level of the tibial tuberosity, approximately 5 to 10 mL of local anesthetic is infiltrated deep to the great saphenous vein.

Localized Field Block. Approximately 5 to 10 mL of local anesthetic may be infiltrated from the medial condyle of the tibia anteriorly to the tibial tuberosity and posteriorly to the medial head of the gastrocnemius muscle. Success rates for this technique range from 33% to 65%.

Transsartorial Approach. The sartorius muscle is palpated on the medial side of the leg, just cephalad to the patella. At the upper pole of the patella, a 22-gauge, 5-cm needle is advanced 45 degrees from the coronal plane, through the muscle belly of the sartorius until a fascial pop is noted. Approximately 5 to 10 mL of local anesthetic is injected. Success rates for this technique range from 70% to 80%.

Ultrasound Guided. Ultrasound-guided saphenous nerve block can be performed either above or below the knee. For the transsartorial technique, the nerve can be found lying medial to the vastus medialis muscle within the fascia.

Side Effects and Complications

The risks of complications with this block are low, although the same theoretical risks all regional anesthetic techniques apply to this block. Given that the great saphenous vein is used as a landmark for the field block technique, minor hematoma formation is not uncommon.

OBTURATOR NERVE BLOCK

The obturator nerve is derived primarily from the third and fourth lumbar nerves, with an occasional minor

contribution from L2. The nerve lies deep in the obturator canal, having descended from the medial border of the psoas muscle. As the nerve leaves the obturator canal, it divides into anterior and posterior branches. The anterior branch supplies an articular branch to the hip and the anterior adductor muscles and a variable cutaneous branch to the lower medial thigh. The posterior branch innervates the deep adductor muscles and may send an articular branch to the knee.

Clinical Applications

The obturator nerve usually is blocked as part of regional anesthesia for knee surgery.[67] Because it is primarily a motor nerve, it is rarely blocked on its own; however, obturator nerve block can be useful in treating or diagnosing the extent of adductor spasm in patients with cerebral palsy and other muscle or neurologic diseases affecting the lower extremities before surgical intervention (e.g., adductor tenotomy).

Technique

The patient is placed in the supine position, and a mark is made 1 to 2 cm lateral and 1 to 2 cm caudad to the pubic tubercle. A skin wheal is raised, and a 22-gauge, 8- to 10-cm needle is advanced perpendicular to the skin entry site with a slight medial direction. The inferior pubic ramus is encountered at a depth of 2 to 4 cm, and the needle is walked in a lateral and caudad direction until it passes into the obturator canal. The obturator nerve is located 2 to 3 cm past the initial point of contact with the pubic ramus (see Fig. 57-17, *B*). After negative aspiration, 10 to 15 mL of local anesthetic is injected. A nerve stimulator is helpful in locating the obturator nerve, and correct needle position is evidenced by contraction of the adductor muscles of the medial thigh.

The classic approach to obturator nerve block involves painful periosteal contact and multiple needle redirections. An alternate interadductor approach was described by Wasseff.[79] In this technique, the needle is inserted behind the adductor tendon, near its pubic insertion, and is directed laterally toward a mark on the skin 1 to 2 cm medial to the femoral artery and immediately below the inguinal ligament representing the obturator canal. The nerve is identified by a motor response to peripheral nerve stimulation in the adductor muscle. An inguinal approach, with needle insertion in the inguinal crease at the midpoint of a line drawn between the inner border of the adductor longus tendon and the femoral arterial pulse has been recently described.[80]

Side Effects and Complications

Complications are rare, but this block is technically more difficult than other lower extremity blocks. The obturator canal contains vascular and neural structures, and there is a theoretical risk of intravascular injection, hematoma, and nerve damage.

PARASACRAL BLOCK

Parasacral block will consistently block both components of the sciatic nerve and the posterior cutaneous nerve of the thigh. Spread of local anesthetic may also anesthetize other branches of the sacral plexus including the superior and inferior gluteal and pudendal nerves. The pelvic splanchnic nerves (S2-S4), the terminal portion of the sympathetic trunk, the inferior hypogastric plexus, and the obturator nerve all lie in close proximity to the elements of the sacral plexus and can all be anesthetized with this approach.[81]

Clinical Applications

For procedures about the knee, the parasacral block can provide an advantage over more distal approaches to the sciatic nerve because of the block of both the sciatic and posterior cutaneous nerves, particularly if a tourniquet is used. For procedures below the knee, the adductor weakness from the obturator and superior gluteal nerve block may actually be disadvantageous for mobilization of the patient. This technique is also useful when immediate access to the individual nerves of the sacral plexus is not possible, such as owing to trauma or infection.

Technique

This approach is based on the bony relationship of the posterior superior iliac spine and the ischial tuberosity. The patient is positioned laterally with the side to be blocked uppermost. The most prominent aspects of the posterior superior iliac spine and the ischial tuberosity are identified, and a line is drawn joining these two points. Along the line, a mark is made at 6 cm inferior to the posterior superior iliac spine, defining the needle insertion site (Fig. 57-18). A 21-gauge, 10-cm, insulated needle is advanced in a sagittal plane until an evoked motor response is elicited, typically at a depth of 5 to 7 cm from the skin. Once the needle is placed properly, 20 to 30 mL of local anesthetic is injected slowly and incrementally. Plantar flexion of the foot (tibial nerve component) or dorsiflexion (common peroneal nerve) is an acceptable motor response. Because of the proximal nature of the block, a hamstring motor response also is acceptable.

Complications

Because the sacral nerves represent the parasympathetic portion of the autonomic nervous system, sympathetic blockade and its potential for hypotension are not seen with transsacral block unless excessive volumes of solution spread proximally to the lumbar sympathetic fibers. Loss of parasympathetic function to bowel, bladder, and sphincters can occur.[82] Injection of local anesthetic through misdirected needles into the subarachnoid or vascular compartments is a remote risk. Classically, the dural sac terminates at the lower border of S2; however, there are clinical reports of subarachnoid puncture with a 6- to 7-cm caudal needle to suggest individual variations below this "classic" location. Finally, an appreciation of the pelvic contents, especially colon, rectum, and bladder, is important. Should a deeply inserted needle enter the colon or rectum and not be noticed, it can result in contamination of the sacral canal.

SCIATIC NERVE BLOCK

The sciatic nerve (L4 and L5, S1 through S3) is the largest of the four peripheral nerves of the lower extremity,

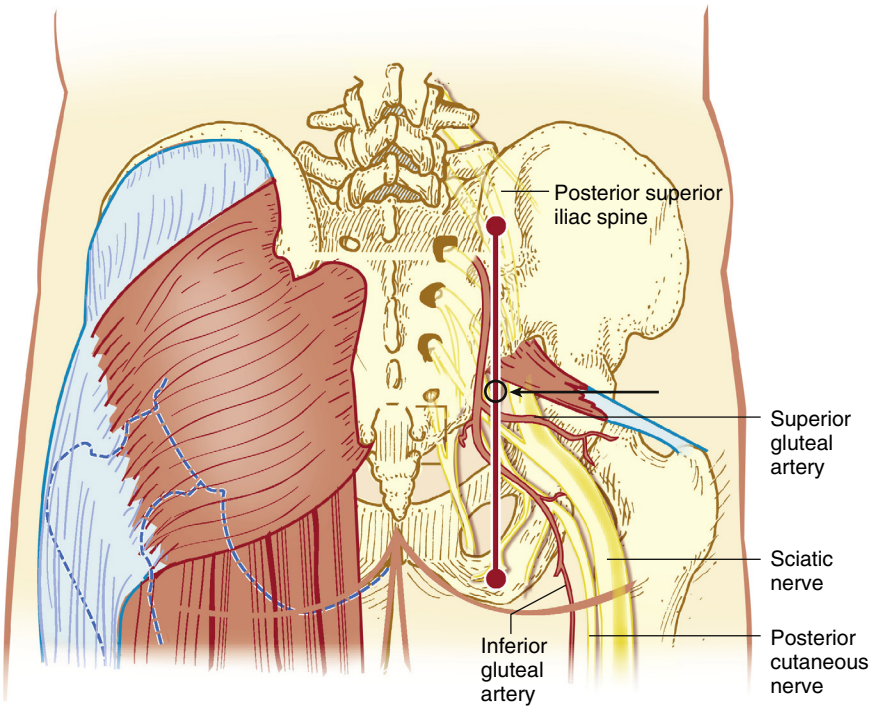


Figure 57-18. Parasacral block. This is the most proximal approach to the sciatic nerve, and it results in block of the posterior femoral cutaneous nerve. The most prominent aspects of the posterior superior iliac spine and the ischial tuberosity are identified, and a line is drawn joining these two points. Needle insertion site is along the line, 6 cm inferior to the posterior superior iliac spine.

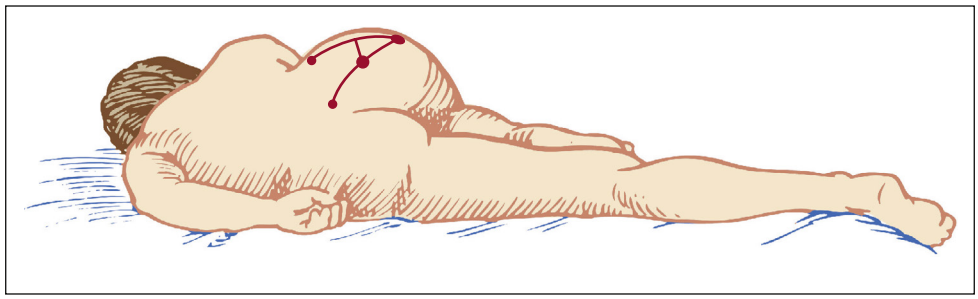


Figure 57-19. Patient positioning for the posterior approach to the sciatic nerve.

with a width of 2 cm as it leaves the pelvis with the posterior cutaneous nerve of the thigh. The sciatic nerve is composed of two nerves bound by a common sheath of connective tissue; the tibial component is medial and anterior, and the common peroneal component is lateral and slightly posterior. After passing through the sacrosciatic foramen beneath the piriformis muscle, it lies between the greater trochanter of the femur and the ischial tuberosity. The nerve becomes superficial at the lower border of the gluteus maximus muscle, where it begins its descent down the posterior aspect of the thigh to the popliteal fossa. The nerve supplies cutaneous innervation to the posterior aspect of the thigh and the entire leg and foot below the knee, except a thin medial strip supplied by the saphenous nerve.

Clinical Applications

Because of its wide sensory distribution, the sciatic nerve block can be used, together with a saphenous or femoral nerve block, for any surgical procedure below the knee that does not require a thigh tourniquet. It can also be combined with other peripheral nerve blocks to provide anesthesia for surgical procedures involving the thigh and knee. This form of anesthesia avoids the sympathectomy associated with neuraxial blocks and therefore may be advantageous when any shift in hemodynamics could be deleterious, such as in patients with severe aortic stenosis.

Technique

Classic (Posterior) Approach of Labat. For the classic (posterior) approach of Labat, the patient is positioned laterally, with the leg to be blocked rolled forward onto the flexed knee as the heel rests on the knee of the dependent nonoperative leg (modified Sims position; Fig. 57-19).[6] A line is drawn to connect the posterior superior iliac spine to the greater trochanter of the femur. A perpendicular line is drawn bisecting the first line and extending 5 cm caudad. A second line is drawn from the greater trochanter to the sacral hiatus. The intersection of this line with the perpendicular line indicates the point of needle entry and falls 3 to 5 cm along the line. A 22-gauge, 10- to 12-cm needle is advanced until a motor response (or paresthesia) is elicited or bone is contacted (Fig. 57-20). Stimulation

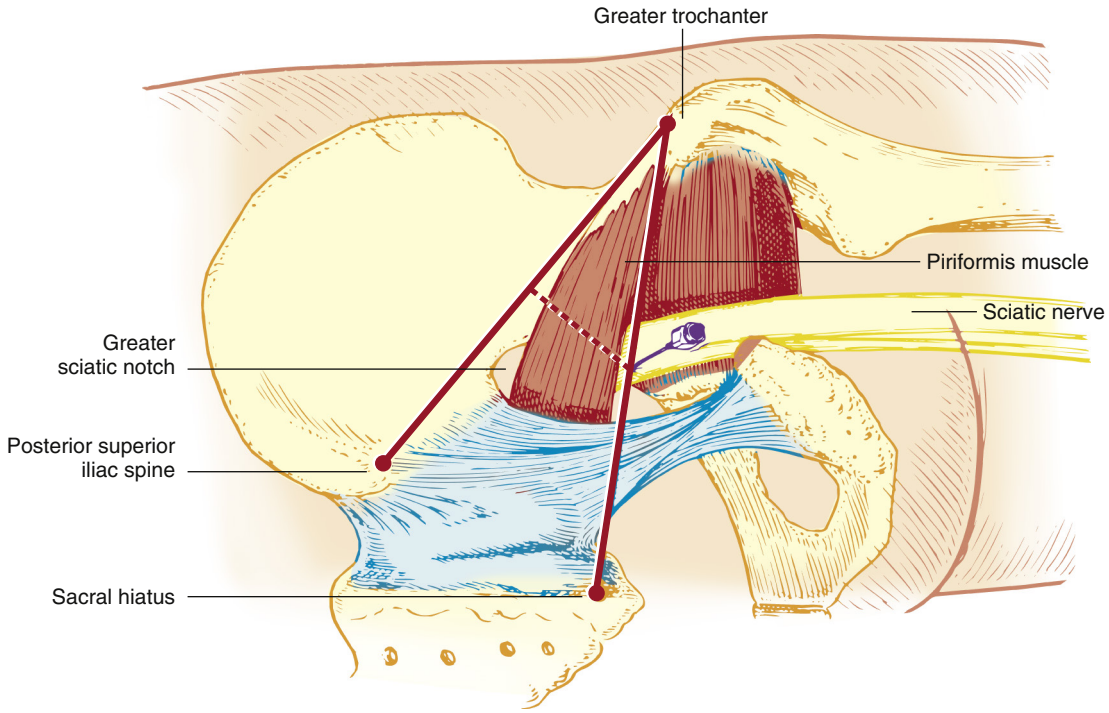


Figure 57-20. Anatomic landmarks for the classic posterior approach of Labat for sciatic nerve block.

of the tibial nerve component produces plantar flexion and inversion of the foot, and common peroneal nerve stimulation produces dorsiflexion and eversion. If bone is encountered, the needle is redirected medially; if blood is apirated (superior gluteal artery), the needle is redirected laterally. After the needle is placed properly, a total of 20 to 30 mL of local anesthetic is injected.

Subgluteal Approach. With this approach, the patient is positioned laterally in a modified Sims position; the leg to be blocked is rolled forward onto the flexed knee as the heel rests on the knee of the dependent (nonoperative) leg. This approach is based on the bony relationship to the greater trochanter and the ischial tuberosity. The most prominent aspects of the greater trochanter and the ischial tuberosity are identified by palpation, and a line is drawn joining these two points. A perpendicular line is drawn bisecting this line and extending 4 to 6 cm caudad. The second line approximates the location of the sciatic nerve. The site of the needle insertion can be at the intersection of the two lines or as far as 6 cm distally along the second line. A 21-gauge, 10- to 12-cm needle is inserted perpendicularly and advanced until a tibial or peroneal motor response (or paresthesia) in the ankle or foot is elicited, and 20 to 30 mL of local anesthetic is injected incrementally (Fig. 57-21). If no response is elicited, the needle can be redirected 1 to 2 cm medially or laterally to the original direction of the needle. It may be helpful to palpate or visualize the groove on the posterior aspect of the thigh. If bony contact is made, the needle is withdrawn and redirected medially.

Ultrasound Guided. A curvilinear probe is placed just distal to the gluteal cleft and scanned lateral to medial. The sciatic nerve can be identified as a flat hyperechoic structure medial to the greater trochanter and lateral to the hyperechoic border of the ischial tuberosity. The needle is advanced in an out-of-plane approach towards the sciatic nerve (see also Chapter 58).

Anterior Approach. The anterior approach is useful when the patient cannot be positioned for the classic posterior approach because of pain.[83] With the patient in the supine position, a line drawn along the inguinal ligament from the anterior superior iliac crest to the pubic tubercle is trisected. A second line parallel to the inguinal ligament is drawn, beginning at the tuberosity of the greater trochanter. The intersection of this second line with the more medial of the perpendicular lines represents the point of needle entry. A 22-gauge, 10.5- to 12-cm needle is inserted perpendicularly with a slightly lateral angulation at the point where the line representing the juncture of the middle and medial thirds crosses the second line. The needle is advanced until it contacts bone, the lesser trochanter of the femur (Fig. 57-22). The needle is redirected medially past the femur, and a paresthesia or nerve stimulator response is sought at a depth of about 5 cm past the bone. A total of 20 to 25 mL of solution is injected incrementally after careful aspiration.

Other Approaches. The sciatic nerve can also be blocked with the patient in the lateral[84] and lithotomy positions,[85] although these are rarely used clinically.

Side Effects and Complications

Serious complications of sciatic nerve block are rare; however, theoretical concerns regarding muscle trauma and puncture of a variety of vascular structures, must be considered. Sciatic nerve block is primarily a somatic nerve block. It does carry some sympathetic fibers to the extremity,

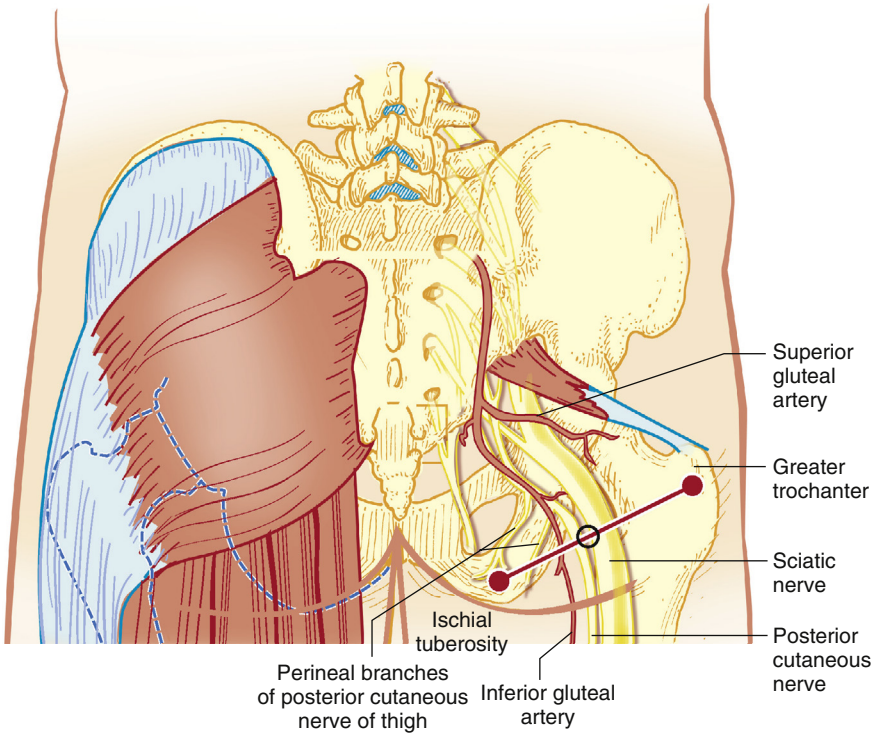


Figure 57-21. Sciatic nerve block (subgluteal approach). The sciatic nerve is relatively superficial at this level. Needle insertion is near the gluteal crease, between the hamstring muscles.

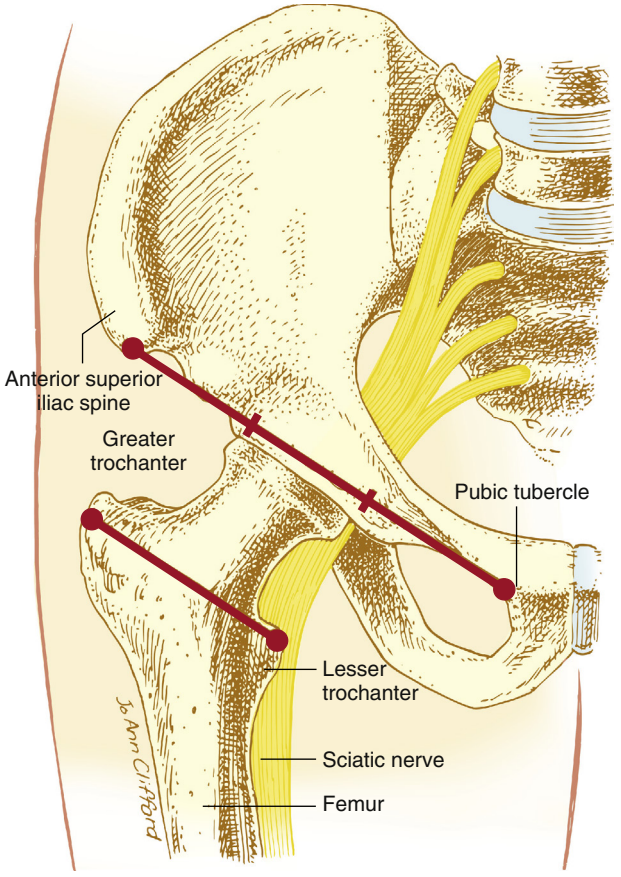


Figure 57-22. Anatomic landmarks for the anterior approach to a sciatic nerve block.

however, and may therefore allow pooling of small quantities of blood that is usually insufficient to cause significant hypotension. On some occasions, such as limb reimplantations and sympathetically mediated pain conditions, this sympathetic block may be advantageous. Residual dysesthesias for periods of 1 to 3 days are not uncommon, but usually resolve within several months.[72,86] Importantly, many orthopedic surgical procedures (including total hip and knee replacement) are associated with neuropraxia to one or both components of the sciatic nerve. Thus, thoughtful application of this technique is required to optimize neurologic outcome for patients considered to be at high risk of perioperative nerve injury from surgery or preexisting neurologic dysfunction.

POPLITEAL FOSSA BLOCK

The posterior muscles of the thigh are the biceps femoris, the semimembranosus, semitendinosus, and the posterior portion of the adductor magnus. As these muscles are traced distally from their origin on the ischial tuberosity, they separate into medial (semimembranosus, semitendinosus) and lateral (biceps) musculature, and they form the upper border of the popliteal fossa. The lower border of the popliteal fossa is defined by the two heads of the gastrocnemius. In the upper part of the popliteal fossa, the sciatic nerve lies posterolateral to the popliteal vessels. The popliteal vein is medial to the nerve, and the popliteal artery is most anterior, lying on the popliteal surface of the femur. Near the upper border of the popliteal fossa, the two components of the sciatic nerve separate. The peroneal nerve diverges laterally, and the larger tibial branch descends almost straight down through the fossa. The tibial nerve and popliteal vessels then disappear deep to the converging heads of the gastrocnemius muscle.

Clinical Applications

This block is chiefly used for foot and ankle surgery. Popliteal fossa block is preferable to ankle block for surgical procedures requiring the use of a calf tourniquet. The components of the sciatic nerve may be blocked at the level of the popliteal fossa through posterior or lateral approaches. Supplemental block of the saphenous nerve is required for surgical procedures to the medial aspect of the leg or when a calf tourniquet or Esmarch bandage are used.

Technique

Posterior Approach: Peripheral Nerve Stimulation or Paresthesia. The classic approach to the popliteal fossa is posteriorly, with the patient positioned prone. However, access can also occur with the patient in the lateral position (operative side nondependent) or supine position (with leg flexed at the hip and knee).

The borders of the popliteal fossa are identified by flexing the knee joint. A triangle is constructed, with the base consisting of the skin crease behind the knee, and the two sides composed of the semimembranosus (medially) and the biceps (laterally). A bisecting line is drawn from the apex to the base of the triangle, and a 5-cm needle is inserted at a site 5 to 10 cm above the skin fold and 0.5 to 1 cm lateral to the bisecting line (Fig. 57-23, *A*). Classically, the 5-cm distance was described; however, in an attempt to block the sciatic nerve before its division, a 7- to 10-cm distance has been recommended.[87] The needle is advanced at a 45-degree angle until a motor response (or paresthesia) is elicited. With a nerve stimulator technique, inversion is the motor response that best predicts complete neural block of the foot.[88] Injection of approximately 30 mL of local anesthetic solution is sufficient.

The success rate is typically 90% to 95%.[88] No formal comparison between paresthesia and nerve stimulator techniques has been performed to assess efficacy and complications. It is believed that incomplete block is the result of poor diffusion (because of the size of the sciatic nerve), the separate fascial coverings of the tibial and peroneal nerves, or blockade of only a single component of the sciatic nerve. Identification of the tibial and peroneal components decreases onset time and improves the success rate.[89]

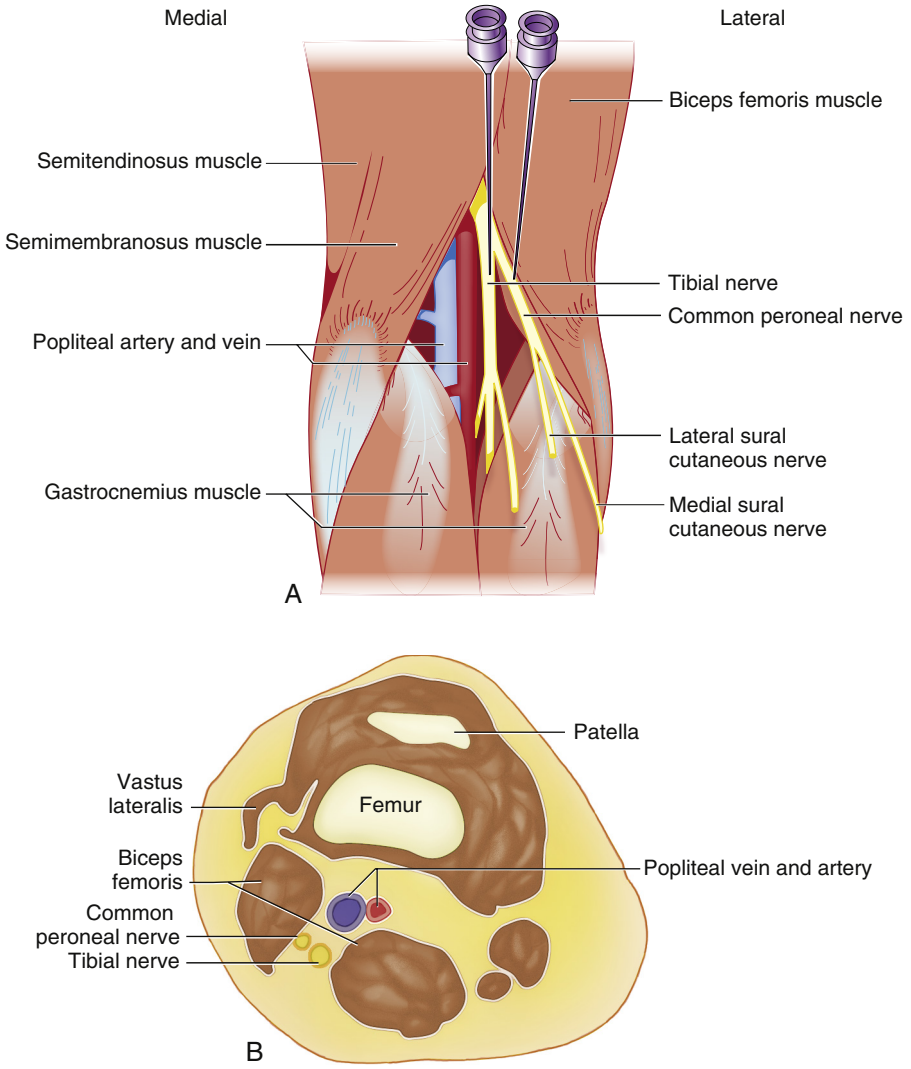


Figure 57-23. A, Anatomic landmarks for the posterior approach to the sciatic nerve in the popliteal fossa. **B,** Anatomic landmarks for the lateral approach to the sciatic nerve in the popliteal fossa.

Ultrasound Guided. The use of ultrasound can help identify the point of divergence of the sciatic nerve into the peroneal and tibial branches. Blockade at this level allows for a single (rather than a double) injection with comparable success[90] (see Figs. 57-23 and 57-24)

Lateral Approach. A lateral approach to blockade of the sciatic nerve in the popliteal fossa has been described.[91] Although block time is somewhat longer, onset and quality of block are similar to the posterior approach.[92] The lateral approach allows the patient to be positioned supine and eliminates the need for repositioning. The patient's leg is extended, with the long axis of the foot at a 90-degree angle to the table. The site of insertion is the intersection of the vertical line drawn from the upper edge of the patella and the groove between the lateral border of the biceps femoris and vastus lateralis. A 10-cm needle is advanced at a 30-degree angle posterior to the horizontal plane (see Fig. 57-23, *B*). Because the common peroneal nerve is located lateral to the tibial nerve, the stimulating needle often encounters the common peroneal nerve first with the lateral approach. As with the classic posterior approach, a tibial response is sought.[93] If a response associated with common peroneal nerve stimulation (e.g., eversion) is elicited, the needle is redirected more posteriorly.

Side Effects and Complications

Intravascular injection can occur because of the presence of vascular structures within the popliteal fossa. Performance of popliteal fossa block in patients with previous total knee arthroplasty or vascular bypass (femoral-popliteal) obviously should be performed extremely carefully. However, there have been no cases of graft disruption or joint infections related to needle placement in these patients.

NERVE BLOCKS AT THE ANKLE

Four of the five individual nerves that can be blocked at the ankle to provide anesthesia of the foot are terminal branches of the sciatic nerve: the posterior tibial, sural, superficial peroneal, and deep peroneal branches. The sciatic nerve divides at or above the apex of the popliteal fossa to form the common peroneal and tibial nerves. The common peroneal nerve descends laterally around the head of the fibula, where it divides into the superficial and deep peroneal nerves.

The tibial nerve divides into the posterior tibial and sural nerves in the lower leg. The posterior tibial nerve becomes superficial at the medial border of the Achilles tendon near the artery of the same name, and the sural nerve emerges laterally to the Achilles tendon.

Clinical Applications

Ankle blocks are simple to perform and offer adequate anesthesia for surgical procedures of the foot not requiring a tourniquet above the ankle.

Technique

Posterior Tibial Nerve. The posterior tibial nerve can be blocked with the patient in either the prone or the supine positions. The posterior tibial artery is palpated, and a 25-gauge, 3-cm needle is inserted posterolateral to the artery at the level of the medial malleolus (see Fig. 57-24, *A, B*). A paresthesia is often elicited; however, it is not necessary for a successful block. If a paresthesia is obtained,

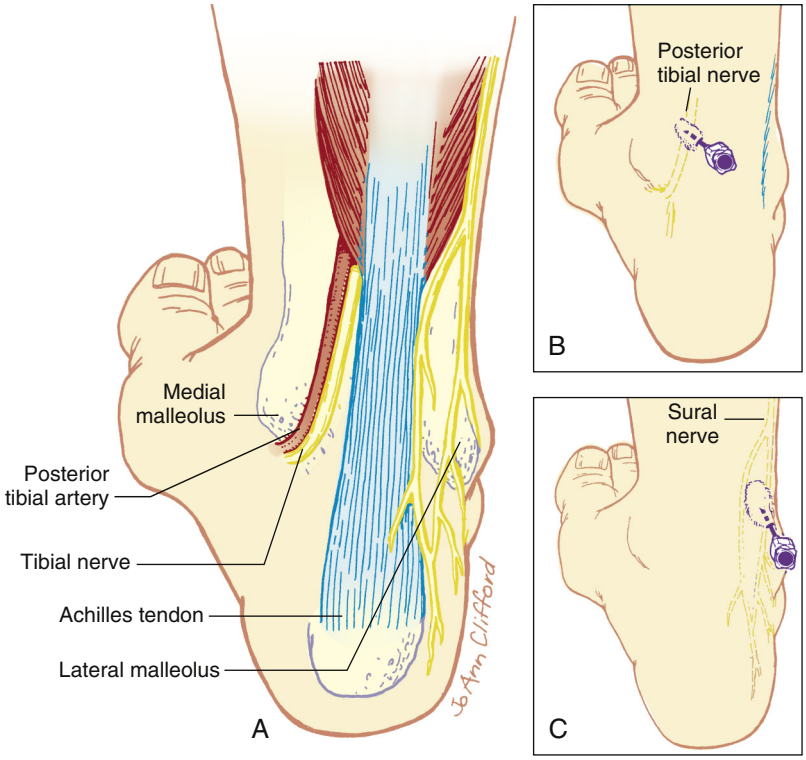


Figure 57-24. A, Anatomic landmarks for a block of the posterior tibial and sural nerves at the ankle. **B,** Posterior tibial nerve and method of needle placement for a block at the ankle. **C,** Sural nerve and method of needle placement for a block at the ankle.

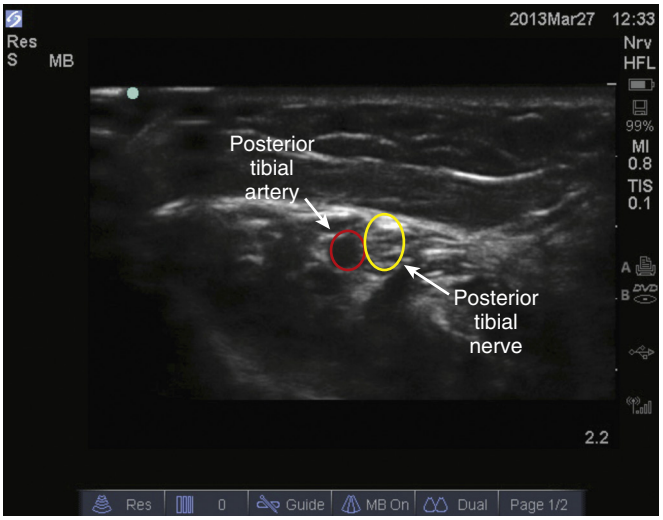


Figure 57-25. Ultrasound image of the medial aspect of the ankle showing the posterior tibial artery *(red)* and the posterior tibial nerve *(yellow)*.

3 to 5 mL of local anesthetic should be injected. Otherwise, 7 to 10 mL of local anesthetic should be injected as the needle is slowly withdrawn back from the posterior aspect of the tibia. Blockade of the posterior tibial nerve provides anesthesia of the heel, plantar portion of the toes, and the sole of the foot, as well as some motor branches in the same area. Ultrasound imaging of the posterior tibial nerve can shorten onset time[94] (Fig. 57-25).

Sural Nerve. The sural nerve is located superficially between the lateral malleolus and the Achilles tendon. A 25-gauge, 3-cm needle is inserted lateral to the tendon and is directed toward the malleolus as 5 to 10 mL of solution is injected subcutaneously (Fig. 57-26, *A, C*). This block provides anesthesia of the lateral foot and the lateral aspects of the proximal sole of the foot.

Deep Peroneal, Superficial Peroneal, and Saphenous Nerves. The deep peroneal, superficial peroneal, and saphenous nerves can be blocked through a single needle entry site (see Fig. 57-26). A line is drawn across the dorsum of the foot connecting the malleoli. The extensor hallucis longus tendon is identified by having the patient dorsiflex the big toe. The anterior tibial artery lies between this structure and the tendon of the extensor digitorum longus muscle and is palpable at this level. A skin wheal is raised just lateral to the pulsation between the two tendons on the intermalleolar line. A 25-gauge, 3-cm needle is advanced perpendicular to skin entry site, and 3 to 5 mL of local anesthetic is injected deep to the extensor retinaculum to block the deep peroneal nerve. This technique anesthetizes the skin between the first and second toes and the short extensors of the toes.

The needle is directed laterally through the same skin wheal while injecting 3 to 5 mL of local anesthetic subcutaneously, blocking the superficial peroneal nerve and resulting in anesthesia of the dorsum of the foot, excluding the first interdigital cleft. The same maneuver can be performed in the medial direction, thereby anesthetizing the saphenous nerve, a terminal branch of the femoral

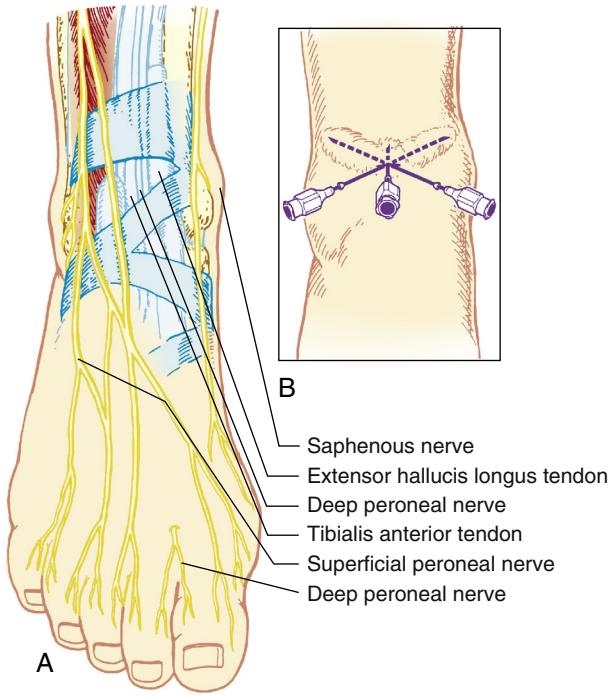


Figure 57-26. A, Anatomic landmarks for a block of the deep peroneal, superficial peroneal, and saphenous nerves at the ankle. **B,** Method of needle placement for a block of the deep peroneal, superficial peroneal, and saphenous nerves through a single needle entry site.

nerve that supplies a strip along the medial aspect of the foot.

Side Effects and Complications

Multiple injections are required for some techniques, resulting in discomfort for the patient. Persisting paresthesias can occur, but they are self-limited. The presence of edema or induration in the area of the ankle block can make palpation of landmarks difficult. Intravascular injection is possible but unlikely if aspiration for blood is negative. The volume of local anesthetic used is small, thereby decreasing the risk of local anesthetic toxicity.

CONTINUOUS CATHETER TECHNIQUES

The advantages cited for continuous nerve blockade include prolongation of surgical anesthesia, decreased risk of toxicity because of lower incremental doses, and postoperative pain relief and sympathectomy. Catheter placement using over-needle and through-needle methods have been described. Advances in equipment technology, including the development of stimulating needles and catheters and portable pumps allowing local anesthetic infusion after hospital dismissal, have increased the success rate and popularity of continuous peripheral blockade (Fig. 57-27).[95] Although concern regarding accurate catheter placement and maintenance still exists, the use of stimulating catheters and radiographic confirmation may further improve the functionality.[96] Overall, continuous peripheral nerve block provides superior analgesia compared with conventional opioid therapy. Minor technical problems such as catheter kinking, displacement

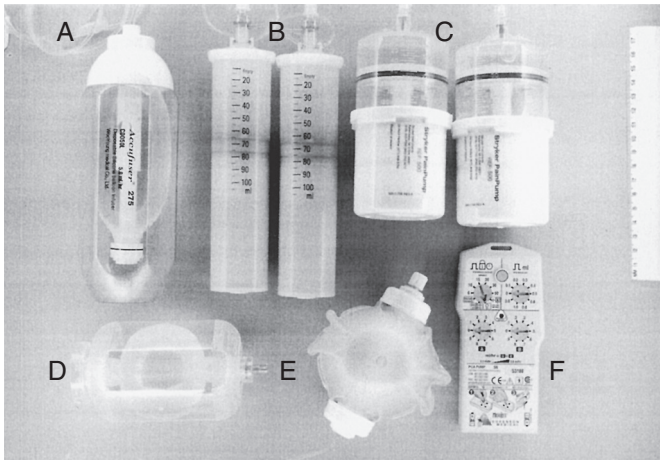


Figure 57-27. Portable infusion pumps. **A,** Accufuser (McKinley Medical, Wheat Ridge, Colo.). **B,** Sgarlato (Sgarlato Labs, Los Gatos, Calif.). **C,** Stryker PainPump (Stryker Instruments, Kalamazoo, Mich.). **D,** MedFlo II (MPS Acacia, Brea, Calif.). **E,** C-Bloc (I-Flow, Lake Forest, Calif.). **F,** Microject PCA (Sorenson Medical, West Jordan, Utah). *(From Ilfeld BM, Morey TE, Enneking FK: The delivery rate accuracy of portable infusion pumps used for continuous regional analgesia,* Anesth Analg *95:1331-1336, 2002.)*

or leakage, and bacterial colonization are frequent, with no adverse clinical consequences in the large majority of cases. However, major neurologic and infectious adverse events are rare.[97]

Methods of providing continuous brachial plexus anesthesia have been described since at least the 1940s. These methods frequently offer ingenious solutions for the placing and securing of the needle or catheter. This technique is especially applicable to patients with upper extremity or digit replantation, total shoulder or elbow arthroplasty, or reflex sympathetic dystrophies, for which prolonged pain relief and sympathectomy are advantageous.[95]

Continuous lower extremity techniques were also described decades ago, but remained underused compared with continuous upper extremity and neuraxial approaches until recently. Reliable, improved success rates and the risk of spinal hematoma after neuraxial techniques led clinicians to reconsider continuous lower extremity blocks. Contemporary applications for continuous psoas compartment, sciatic, femoral, and popliteal fossa blockade have been reported. Compared with conventional systemic and neuraxial analgesic methods, continuous lower extremity blocks provide superior analgesia with fewer side effects, improve perioperative outcomes, and accelerate hospital dismissal after major joint replacement.[95,98]

CHOICE OF LOCAL ANESTHETIC

The choice of local anesthetic for a peripheral nerve block obviously depends to some degree on the duration of the surgical procedure, although other factors are also important (see Chapter 36). Prolonged blockade for up to 24 hours often occurs with long-acting local anesthetics such as bupivacaine or ropivacaine. Although this feature results in superb postoperative pain relief for the inpatient, it may be undesirable for the ambulatory patient because of the possible risk of nerve or tissue injury in a partially blocked limb. A short- or medium-acting local anesthetic, such as lidocaine or mepivacaine, may be more appropriate in the outpatient setting (see Chapter 89). Whatever drug is chosen, the total dosage should be calculated for each patient and should be kept within safe limits (see Chapter 36 for details).

The highest concentrations of local anesthetic drugs are not appropriate for peripheral neural blockade; therefore, 0.75% bupivacaine or ropivacaine, 2% lidocaine, 2% mepivacaine, and 3% 2-chloroprocaine *are not recommended*. The lowest concentrations of the same local anesthetics (i.e., 0.25% bupivacaine or ropivacaine and 0.5% mepivacaine or lidocaine) might not provide complete motor blockade.

Vasoconstrictors, usually epinephrine, can be added to the chosen local anesthetic to improve onset of action, to decrease drug uptake, and to prolong action. A concentration of 1:200,000 epinephrine is usually recommended. Ideally, the epinephrine should be added to the local anesthetic at the time the block is to be performed. Commercially prepared solutions with epinephrine have a lower pH than those in which it is freshly added, resulting in a higher percentage of ionized drug molecules. These ionized molecules do not readily cross the neural membrane, delaying the onset of drug action after injection. Epinephrine should not be added to the local anesthetic for blocks of the digits or penis because tissue ischemia can result. Various other additives, including clonidine, opioids, and ketamine, have been reported to enhance or prolong local anesthetic peripheral nerve blockade.[41,64]

COMPLICATIONS

Nerve injury is a recognized complication of peripheral regional techniques (Box 57-1). In a combined series involving more than 250,000 regional anesthetics, the frequency of neurologic complications after peripheral blockade was less than that associated with neuraxial techniques and was associated with pain on needle placement or injection of local anesthetic.[72,99] Risk factors contributing to neurologic deficit after regional anesthesia include neural ischemia, traumatic injury to the nerves during needle or catheter placement, infection, and choice of local anesthetic solution. However, postoperative neurologic injury due to pressure from improper patient positioning, tightly applied casts or surgical dressings, and surgical trauma is often attributed to the regional anesthetic. Patient factors such as body habitus or a preexisting neurologic dysfunction can also contribute.

Although needle gauge, type (i.e., short versus long bevel), and bevel configuration can influence the degree of nerve injury after peripheral nerve block, the findings are conflicting, and there are no confirmatory human studies. Theoretically, localization of neural structures with a nerve stimulator or ultasound imaging would allow a high success rate without increasing the risk of neurologic complications, but this has not been established.[11]

BOX 57-1 ***Recommendations for Limiting Peripheral Nerve Injury***

- The superiority of one nerve localization technique—paresthesia, nerve stimulation, ultrasound—over another concerning reducing the likelihood of nerve injury is not clear.
- Animal data have linked high injection pressures to subsequent fascicular injury, but the effectiveness of injection pressure monitoring for limiting nerve injury has not been confirmed in humans.
- The superiority of one local anesthetic or additive over another concerning reducing the likelihood of neurotoxicity has not been confirmed in humans.
- Patients with diseased or previously injured nerves (e.g., diabetes mellitus, severe peripheral vascular disease, or chemotherapy) may theoretically be at increased risk for block-related nerve injury. Although isolated case reports have described new or progressive neurologic deficits after regional anesthetic techniques in patients with multiple sclerosis or previous exposure to chemotherapy, clinical experience can neither refute nor confirm these concerns. Based on limited animal data, consideration may be given to avoiding potent local anesthetics, reducing local anesthetic doses or concentration, and avoiding or limiting vasoconstrictive additives in these patients.
- If damage to protective tissue barriers, such as the perineurium, is suspected from an abnormally painful paresthesia or pain on injection of local anesthetic, further injection should be terminated immediately, and the needle repositioned. Consideration may be given to aborting the block procedure to avoid further deposition of local anesthetic and vasoconstrictive additives.

From Neal JM, Bernards CM, Hadzic A, Hebl JR, et al: Asra practice advisory on neurologic complications in regional anesthesia and pain medicine, Reg Anesth Pain Med *33:404, 2008.*

Likewise, prolonged exposure, high dose, or high concentrations of local anesthetic solutions can also result in permanent neurologic deficits. In laboratory models, the addition of epinephrine increases the neurotoxicity of local anesthetic solutions and decreases nerve blood flow; however, the clinical relevance of these findings in humans remains unclear. Nerve damage caused by traumatic needle placement, local anesthetic neurotoxicity, and neural ischemia during the performance of a regional anesthetic can worsen neurologic outcome in the presence of an additional patient factor or surgical injury.[100]

Hemorrhagic complications have been described with nearly every peripheral technique and range from localized bruising and tenderness to severe hematomas or hemorrhagic complications. Patients who are receiving hemostasis-altering medications (e.g., low-molecular-weight heparin, warfarin, antiplatelet or antithrombotic medications) are at the highest risk. The risk of hematoma in anticoagulated patients undergoing peripheral nerve blockade is less clear than the risk of spinal hematoma in anticoagulated patients undergoing neuraxial blockade. The placement of peripheral nerve blocks in patients with a coagulopathy should be performed with caution, especially in a deep, noncompressible site where an expanding hematoma could go unnoticed (lumbar plexus) or in a location where a hematoma could compress the airway (interscalene).[73]

Infectious complications can be caused by exogenous (contaminated medication or equipment) or endogenous sources.[101] Infection at the site of needle placement is an absolute contraindication to peripheral nerve blockade, although caution should be used in patients with nearby cellulitis or systemic blood infections (bacteremia or sepsis). Although bacterial colonization of peripheral nerve catheters is not uncommon, cellulitis, abscess, or bacteremia are extremely rare.[97]

Prevention of neurologic complications begins during the preoperative visit with a careful evaluation of the patient's medical history and appropriate preoperative discussion of the risks and benefits of the available anesthetic techniques. It is imperative that all preoperative neurologic deficits are documented to allow early diagnosis of new or worsening neurologic dysfunction postoperatively. Postoperative sensory or motor deficits must also be distinguished from residual (prolonged) local anesthetic effect. Imaging techniques, such as computed tomography and magnetic resonance imaging, are useful in identifying infectious processes and expanding hematomas. Although most neurologic complications resolve completely within several days or weeks, significant neural injuries necessitate neurologic consultation to document the degree of involvement and coordinate further workup. Neurophysiologic testing, such as nerve conduction studies, evoked potentials, and electromyography, are often useful in establishing a diagnosis and prognosis.

Several large studies have established that severe systemic toxicity (seizures with or without cardiac arrest) occur on the order of 1:1000 for peripheral nerve blocks, depending on the type of block.[99] Therefore, practitioners of regional anesthesia must be familiar with the immediate detection and treatment of systemic local anesthetic toxicity. Systemic local anesthetic toxicity can occur immediately from an intravascular injection or it may be delayed because of rapid or excessive systemic absorption of local anesthetic. In addition to frequent aspiration during injection of local anesthetic, the addition of epinephrine will help alert the practitioner to potential intravascular injection. Attaching intravenous tubing to the needle allows immobility of the needle during injection. Typically, an assistant will aspirate with the syringe after each 5 mL injection of local anesthetic. Recent studies indicate that a lipid infusion improves success of resuscitation from cardiac arrest due to local anesthetic toxicity if given immediately after a local anesthetic overdose.[102]

SUMMARY

It is possible to perform all surgical procedures while the patient is under general anesthesia, but the addition of peripheral nerve block techniques adds flexibility and skills that benefit the patient intraoperatively and postoperatively. Successfully mastering these techniques and applying them to the appropriate clinical situations add valuable options to the anesthetic care. Knowledge of regional anesthesia is also essential for the diagnosis and treatment of acute and chronic pain syndromes (see Chapters 64 and 98).

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Chapter 58

Ultrasound Guidance for Regional Anesthesia

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Key Points

- Ultrasound is a highly useful tool for discovery, particularly enlightening and revealing to those who practiced regional anesthesia before the advent of direct nerve imaging. Ultrasound imaging can elucidate the structure of peripheral nerves and adjacent anatomic structures for regional block. Anatomic variation in nerve position and course, which is a potential source of block failure, can be directly visualized.
- Peripheral nerves have a characteristic *honeycomb* echotexture formed by their connective tissue and nerve fibers.
- Ultrasound provides real-time imaging for needle tip placement and drug injection. Successful local anesthetic injections clarify the border of the nerve and track along the nerve path and its branches.
- Ultrasound guidance results in more consistent procedure times for peripheral nerve blocks[1] and can be applied to many regional anesthesia procedures.[2]

INTRODUCTION

The last decade of clinical practice has witnessed a revolution in how regional anesthesia is performed. Ultrasound imaging allows direct visualization of peripheral nerves, the block needle tip, and local anesthetic distribution.[3] This imaging modality has proven highly useful for guiding targeted drug injections and catheter placement. This chapter describes the general principles of ultrasound imaging for regional blocks and gives specific examples of peripheral nerve block procedures.

FUNDAMENTAL ASSUMPTIONS AND ARTIFACTS IN ULTRASOUND IMAGING

Ultrasound is sound with a frequency above the audible range (greater than 20,000 cycles per second). The frequencies used in clinical imaging are within the range of 1 to 20 megahertz (MHz). High-frequency ultrasound beams are well collimated and therefore can provide high resolution. For most regional blocks, the highest frequency is selected that adequately penetrates the depth of field. Sound waves reflected at the interface of two tissues with different acoustic impedances generate echoes. Ambient lighting has a large effect on visual discrimination; therefore, dim lighting without glare is especially useful for imaging low-contrast targets such as peripheral nerves.

Ultrasound imaging is predicated on several common assumptions.[4] First, the speed of sound through soft tissue is 1540 m/sec, meaning 13 microseconds elapse for each centimeter of soft tissue traversed back and forth for the total fly-back time of received echoes. This assumption allows interconversion of time and distance for echo-ranging. Local heterogeneities in soft tissue can cause artifactual bending of the block needle on ultrasound scans, the so-called *bayonet artifact*[5,6] (Fig. 58-1). Bayonet artifacts are commonly observed during the lateral in-plane approach to popliteal block (see "Sciatic Nerve Blocks in the Popliteal Fossa") because more adipose tissue is present over the nerves near the posterior midline of the leg. (Adipose tissue has a slower speed of sound than the adjacent muscle.) The speed of sound artifacts relate both to time-of-flight considerations and to refraction that occurs at the interface of tissues with different speeds of sound.

Second, ultrasound waves are assumed to take a straight path to and from tissue. When this does not occur, reverberation artifacts are displayed deep to the reflector. Reverberation artifacts are commonly observed from the block needle shaft at shallow angles of insertion because sound waves bounce back and forth between the walls of the needle before returning to the transducer (Fig. 58-2). Comet tail artifact is another type of reverberation artifact and helps identify strong reflectors such as the pleura during supraclavicular and intercostal blocks. At low receiver gain, the comet tail is seen as a tapering series of discrete echo bands just deep to a strongly reflecting structure. The spacing between the bands represents the distance between the anterior and posterior walls of the object.[7] Internal reverberations (arising from within the object) cause the comet tail artifact, most intensely observed when the anatomic object is perpendicular to the beam. Comet-tail artifact

from the pleura relates to lung water content, because small collections of lung water lined by the strongly reflecting pleura can allow the sound beam to enter and then return at varying times to the transducer (Fig. 58-3).

Third, all reflectors are assumed to be on the central ray of the transducer beam. When this assumption is not true, out-of-plane artifacts are observed (slice thickness artifacts). Definitive proof of out-of-plane artifacts requires multiple views, which are recommended when such ambiguities arise.

Unlike adjacent soft tissue, most biologic fluids do not significantly attenuate the sound beam and therefore cause acoustic enhancement (sometimes referred to as *posterior acoustic enhancement* or *increased through-transmission*). Acoustic enhancement artifacts deep to blood vessels can be erroneously interpreted as peripheral nerves (Fig. 58-4). For example, acoustic enhancement deep to the second part of the axillary artery in the axilla can be mistaken for the radial nerve.

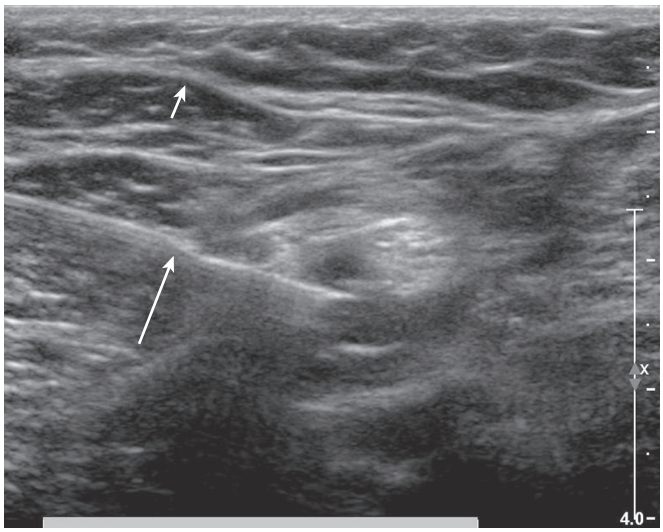


Figure 58-1. Bayonet artifact is observed during popliteal block of the sciatic nerve. In this sonogram, the block needle appears to bend as it approaches the sciatic nerve in the popliteal fossa *(long arrow)*. The slower speed of sound in the overlying adipose tissue, compared with the adjacent muscle *(short arrow)*, produces this artifact.

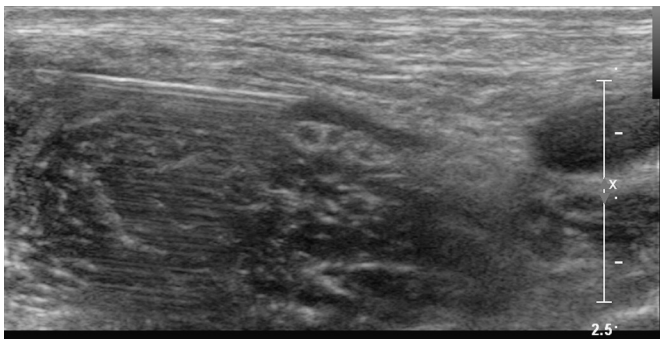


Figure 58-2. Reverberation artifact is observed during femoral nerve block. Sound waves reverberate back and forth between the walls of the needle and then return later to the transducer. Because the sound waves return at a later time, they are displayed deep within the field of imaging. No reverberation artifact is observed from the needle tip because the bevel opening does not have opposing walls.

In the infraclavicular region, acoustic enhancement deep to the axillary artery can be mistaken for the posterior cord of the brachial plexus (similarly, for the femoral artery and the femoral nerve in the inguinal region).

Acoustic shadowing occurs deep to strong reflecting structures, such as the cortical surface of mature bone (Fig. 58-5). Acoustic shadows from refraction (refractile shadowing or lateral edge shadowing) are often observed deep to the edges of blood vessels when the vessels are imaged in the short-axis view. Refractive edge shadows can be seen from the carotid artery during stellate ganglion block or from the second part of the axillary artery during infraclavicular block. Refraction artifacts (e.g., refractile shadowing) are less apparent when spatial compound imaging (refer to the discussion later in this chapter) is used to reduce angle-dependent artifacts.

TRANSDUCER SELECTION, MANIPULATION, AND MODES OF IMAGING

Ultrasound transducers consist of piezoelectric crystals that emit and receive high-frequency sound waves by interconverting electrical and mechanical energy. Transducer selection is important to the success of ultrasound-guided

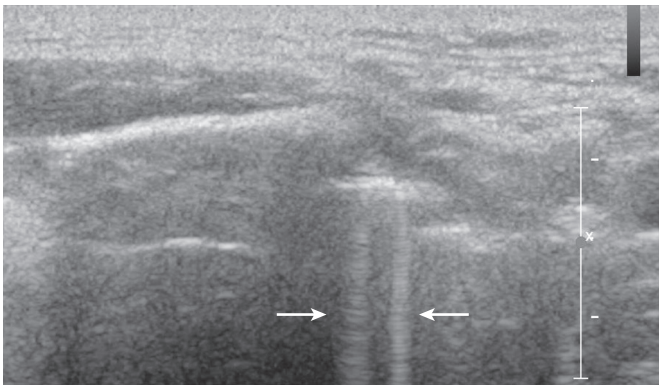


Figure 58-3. Comet-tail artifact is observed during the scanning of the upper airway *(arrows)*. Small collections of water near the air interface, which also are seen during scanning of the pleura, generate this artifact.

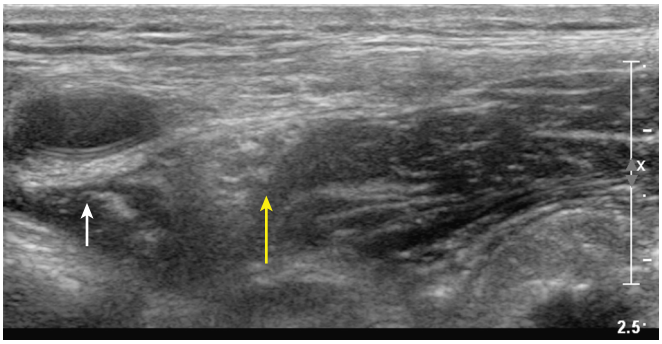


Figure 58-4. Posterior acoustic enhancement artifact is observed during femoral nerve block. The echoes deep to the femoral artery are enhanced *(white arrow)* and may be incorrectly identified as the femoral nerve *(yellow arrow)*.

regional anesthesia procedures. High-frequency sound waves provide the best resolution but will not penetrate far into tissue. The frequency range is therefore chosen to be the highest that will allow adequate insonation of the entire depth of field. A low-frequency transducer can be used to image large nerves that lie deep, such as the cords of the brachial plexus that surround the second part of the axillary artery or the proximal sciatic nerve in the gluteal region.

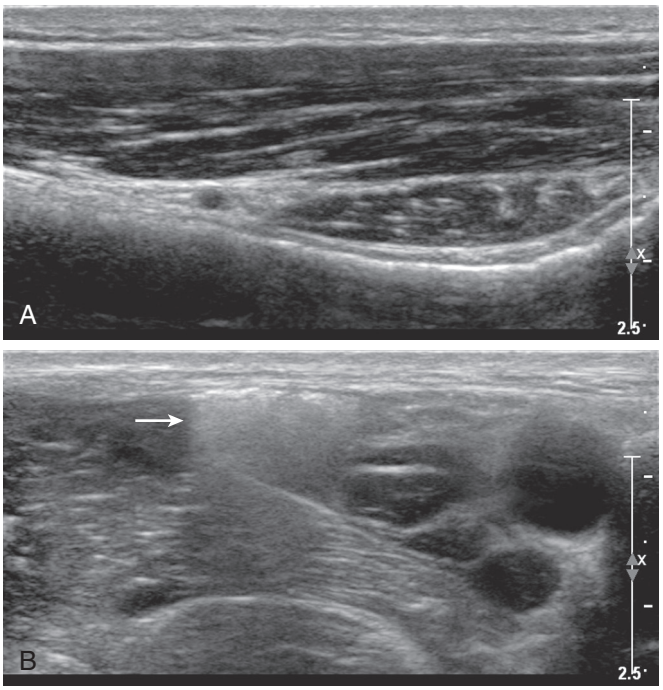


Figure 58-5. Acoustic shadowing occurs during regional blocks. **A,** During block of the axillary nerve in the proximal arm, the cortical surface of the humerus reflects and absorbs sound waves, thereby producing acoustic shadowing deep to the bone surface. **B,** During femoral nerve block, air inadvertently injected into the field layers to produce strong reflection and acoustic shadowing *(arrow)*.

The footprint size (i.e., the length of the active face transducer that contacts the skin) is chosen to provide a broad enough view of the structures of interest. As a general rule, the footprint should be at least as large as the anticipated depth of field. A square or landscape view is better than a keyhole view (depth greater than footprint) for guidance. For in-plane technique (see "Approaches to Regional Block With Ultrasound"), the millimeter of the footprint is approximately the millimeter of guidance.

Linear-array transducers generally have a higher scan line density than curved arrays and therefore produce the best image quality. Images from linear arrays are usually displayed in a rectangular format. When a linear transducer is needed but space at the site of block is limited by anatomic structures such as adjacent bone, a compact linear (*hockey stick*) transducer that has a smaller footprint can be very useful. Curved arrays provide a broad field of view for a given footprint size and are generally used when space is limited (e.g., infraclavicular region). Curved probes are easier to rock (see "Infraclavicular Blocks") and produce images in sector format.

Universal precautions should be used when handling dirty equipment. External surface probes require disinfection between every use and after extended periods of nonuse, per instructions of the manufacturer. Do NOT drop any ultrasound transducer, because the active face of the transducer is especially sensitive to contact with hard surfaces.

One of the essential skills to acquire for regional block with ultrasound is transducer manipulation (Fig. 58-6). Standardized nomenclature has been established[8]:

- Sliding (moving contact) the transducer along the known course of the nerve using a short-axis view often helps with nerve identification.

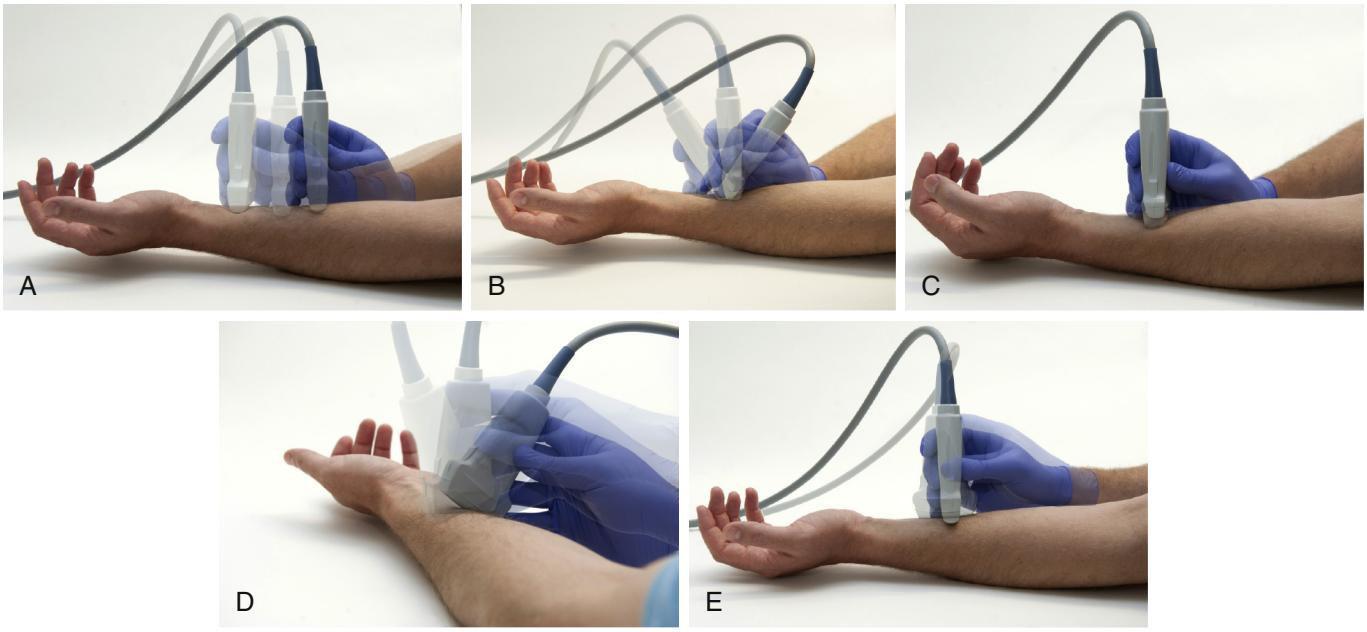


Figure 58-6. Transducer manipulation. Sliding (**A**), tilting (**B**), compression (**C**), rocking (**D**), and rotation (**E**) of the transducer are shown.

- Tilting (cross-plane, side-to-side) will vary the echobrightness of peripheral nerves. Optimizing this angle is critical to promote nerve visibility.
- Compression is often used to confirm venous structures. To improve imaging, compression not only provides better contact, but it also brings the structures closer to the surface of the transducer. Soft tissue is subject to compression; therefore, estimates of tissue distances will vary.
- Rocking (in-plane, toward or away from the indicator) is often necessary to improve visibility of the needle and anatomic structures when the working room is limited.
- Rotation of the probe will produce true short-axis views rather than oblique or long-axis views.

Anisotropy is the change in echogenicity with inclination of the transducer. In general, when objects are obliquely imaged, they appear less echogenic (Fig. 58-7). This relationship is most pronounced for tendons but also occurs for muscle and nerves.[9] Although the term *anisotropy* was first used to describe changes in received echoes when rocking the transducer with structures viewed in long axis, it has also been used for short-axis views when tilting the transducer. With experience, operators learn to rock and tilt the transducer naturally to fill in the received echoes from peripheral nerves. Sliding and rotating the transducer achieves needle tip localization after optimizing peripheral nerve echoes by tilting.

Spatial compound imaging steers ultrasound beams in different, predetermined angles, typically within approximately 20 degrees from the perpendicular (Fig. 58-8). These multiple lines of insonation are then combined to produce a single composite image. Spatial compound imaging appears to reduce angle-dependent artifacts, anisotropic effects, and acoustic shadows. Another advantage for regional block is that the definition of tissue planes and the detection of nerve borders can be improved. In the systems that have been tested, spatial compound imaging improves needle tip visibility over a limited range of needle insertion angles (less than 30 degrees). The stray lines of sight (i.e., those that travel off the field underneath the transducer) can be used to form a wider field of view in a trapezoidal format.

A Doppler shift occurs when a wave source and receiver are moving relative to each other, which produces a change in frequency such that the frequencies of the transmitted and reflected sound waves are not the same. When a wave source and receiver are moving toward each other, the observed frequency is greater than the source frequency; and when moving away from each other, the observed frequency is lower. The change in frequency is related to the velocity of moving reflectors and the angle of insonation. Red blood cells are the primary reflectors that produce Doppler shifts in clinical medicine.

Doppler ultrasound imaging has different modes (Fig. 58-9). Traditional color Doppler encodes mean-frequency shifts to provide directional velocity information; that is, conventional blue color indicates flow away from the transducer, whereas red color indicates flow toward the transducer. More recently, a more sensitive Doppler technology has been developed that encodes color based on the integration of the Doppler power spectrum.[10] Power Doppler is less angle dependent and not subject to aliasing. The disadvantages are that no directional information is provided and motion sensitivity (flash artifact) is high. Power Doppler is especially useful for detecting small arteries that accompany nerves (Box 58-1 and Table 58-1). Power Doppler can detect these small arteries and better delineate the course of tortuous vessels that have unfavorable angles to the ultrasound beam.

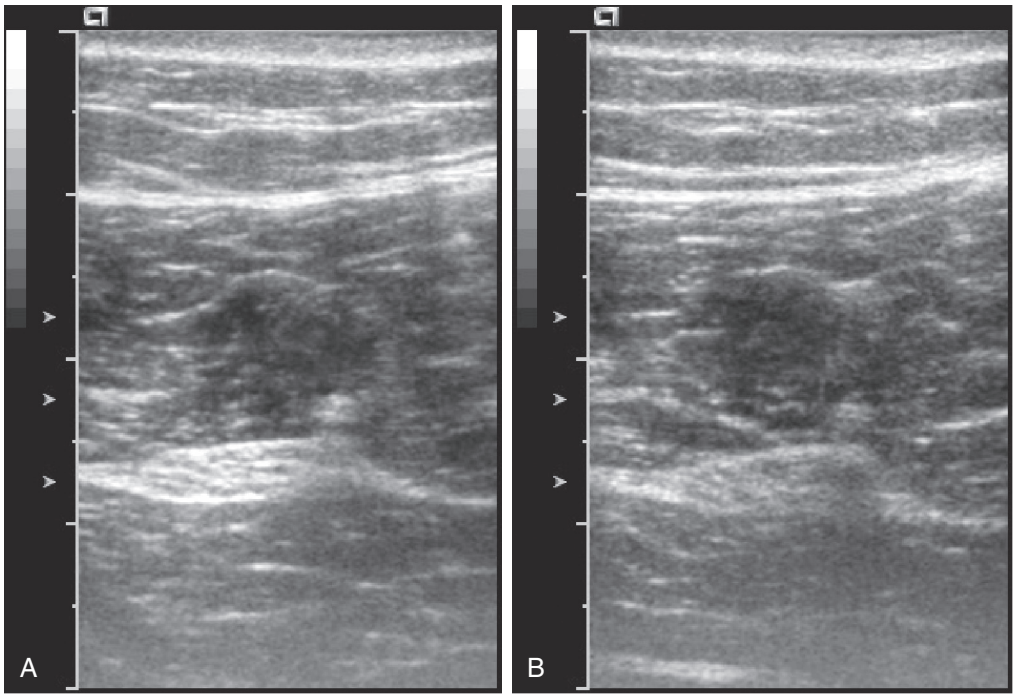


Figure 58-7. A, Sciatic nerve imaging in the subgluteal region. **B,** The amplitude of the received echoes diminishes when the angle of insonation is changed away from perpendicular to the nerve path, thereby demonstrating anisotropy.

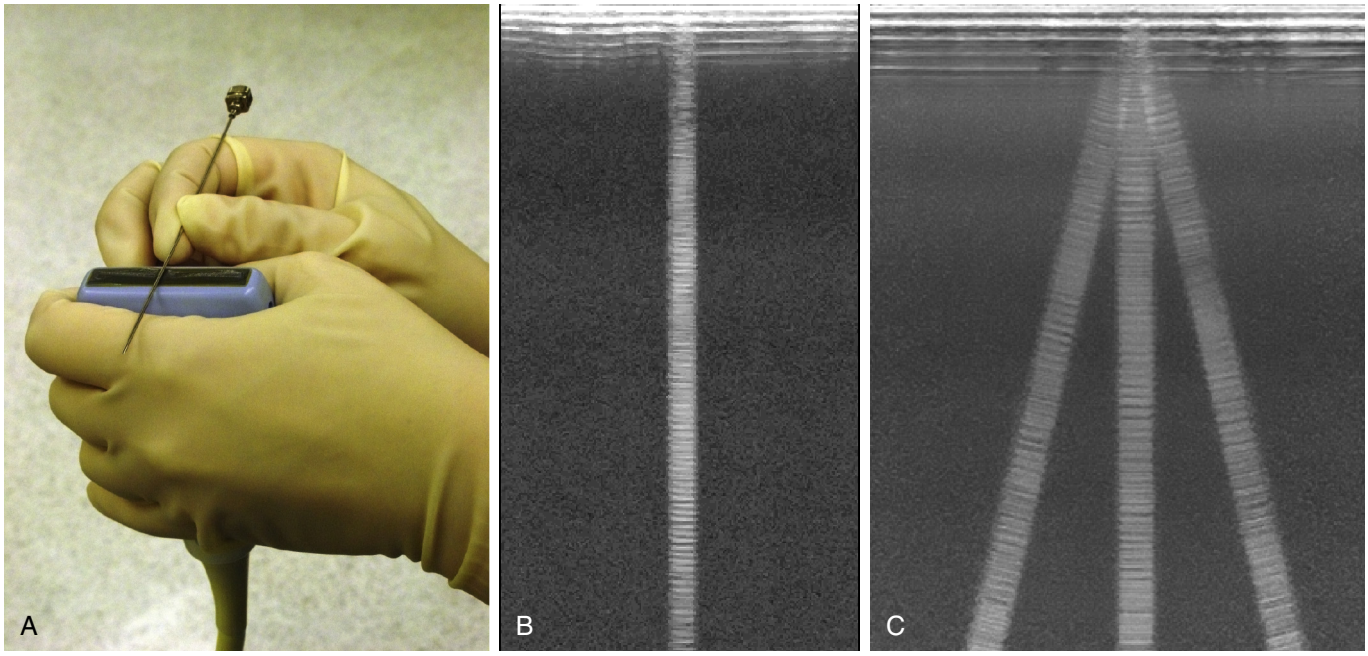


Figure 58-8. Spatial compound imaging. Some forms of ultrasound imaging use multiple lines of sight by electronically steering the beam to different angles. These sonograms were obtained by placing a linear array test tool (the solid metal stylet of a 17-gauge epidural needle) over the active face of the transducer to isolate a single element. **A,** External photograph demonstrates the linear array test tool applied to the active face of the ultrasound transducer. **B,** Single-beam imaging is demonstrated. **C,** Three lines of sight are used to form a compound image. The test tool images do not display the beam itself, but rather the transmit and receive apertures.

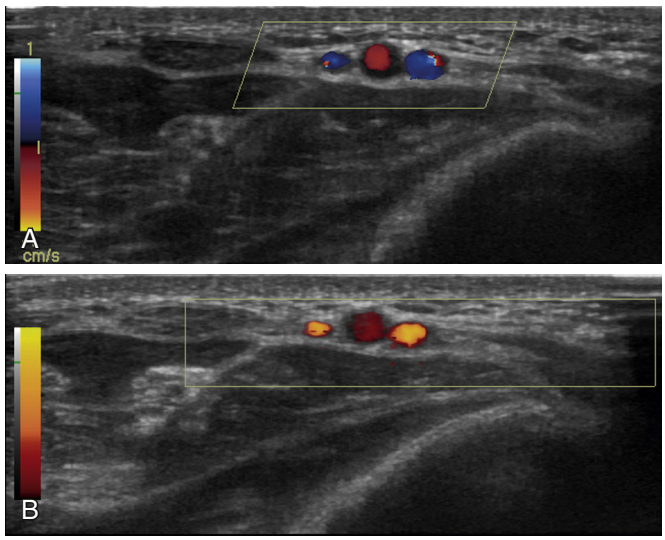


Figure 58-9. Duplex sonograms illustrate the Doppler shift. **A,** In color Doppler, color encoding is based on the mean frequency shift. **B,** In power Doppler, color encoding is based on the power spectrum.

NEEDLE TIP VISIBILITY

A large number of factors influence needle tip visibility in clinical practice. Metal needles are hyperechoic and can cause reverberation artifact. Needle tip visibility is best when the needle path is parallel to the active face of the transducer. Under this condition, the needle is perpendicular to the sound beam; therefore, strong specular reflections will be produced; that is, mirror-like reflections will be produced from a smooth surface.

BOX 58-1 *Respective Advantages of Color and Power Doppler Imaging Modalities*

Color Doppler

- Directional information
- Velocity estimates
- Less motion artifact (flash artifact)

Power Doppler

- More sensitive to detect the presence of flow (by a factor of 3 to 5 in some cases)
- Less angle dependent
- No aliasing

TABLE 58-1 **EXAMPLES OF ACCOMPANYING ARTERIES FREQUENTLY IMAGED DURING REGIONAL BLOCKS***

Regional Block	Adjacent Artery
Mandibular nerve	Maxillary artery
Cervical root	Radicular artery
Stellate ganglion	Vertebral artery
	Inferior thyroid artery
Suprascapular nerve	Suprascapular artery
Intercostal nerve	Intercostal artery
Transversus abdominis plane	Subcostal artery
Ilioinguinal nerve	Deep circumflex iliac artery
Rectus sheath	Epigastric artery
Proximal fascia iliaca	Deep circumflex iliac artery
Obturator nerve	Obturator artery
Parasacral sciatic nerve	Superior gluteal artery

*These small arteries can be used as sonographic landmarks to help identify adjacent peripheral nerves.

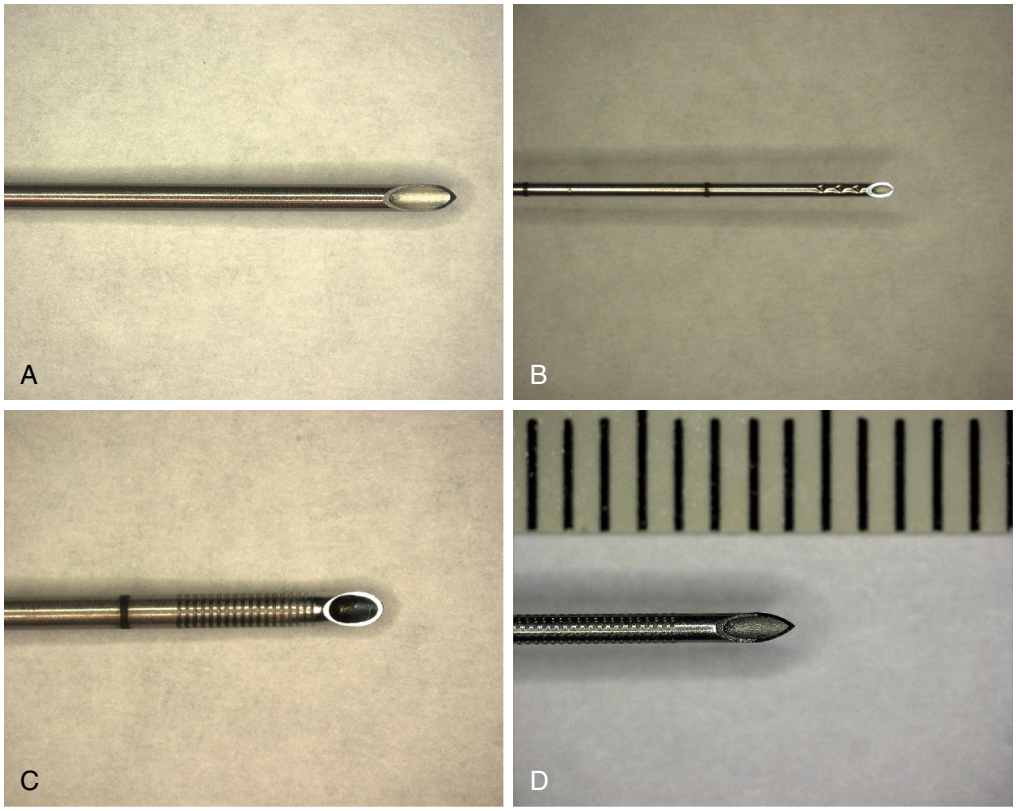


Figure 58-10. Photomicrographs of needles are used for regional block. A plain conventional needle (**A**) and echogenic designs (**B, C, D**) are shown. A smooth needle may not generate a recordable echo because its rounded shaft reflects most incident sound away from the source. A variety of textured surfaces are manufactured and marketed to improve needle tip detection on acquired sonograms. *(Modified from Gray AT:* Atlas of ultrasound-guided regional anesthesia*, ed 2. Philadelphia, 2012, Saunders.)*

As the angle of incidence is increased, the mean brightness will decrease.[11] In this same study, the bevel angles were ground from 10 to 70 degrees but were found to have no effect on the needle tip echo. However, bevel orientation does influence the needle tip echo; visibility is best with the bevel either directly facing or averting the transducer.[12] Because needle diameters are smaller than the scan plane thickness, larger needles are more echogenic than finer ones.

Visualization of needles in echogenic tissue is difficult, particularly in bright adipose tissue. A number of strategies have been proposed to improve needle tip visibility.[13,14] A low-receiver gain can improve the detection of the needle tip echo. Spatial compound imaging can help identify the needle tip when the needle path is at an angle with respect to the transducer. However, one limitation of this strategy is that only a small triangular section of the field of imaging receives all the lines of sight and is therefore fully compounded. In addition, the range of angles for spatial compound imaging is limited and is usually exceeded by the desired needle insertion path. Rocking back the transducer can improve the angle between the ultrasound beam and needle during in-plane technique (see "Approaches to Regional Block with Ultrasound"). Most practitioners orient the needle so that the needle bevel faces the transducer.

Among needles originally developed for use in regional anesthesia, Hustead bevels tended to be more visible than side port needles that lack cutting bevels. Needles with echogenic modifications are now commercially marketed for peripheral nerve blocks. One engineering strategy has been to texture the needle surface so that echoes return to the transducer source, regardless of the angle of insonation (Fig. 58-10). One potential limitation of these needle designs is the finite size of the needle texturing. Low-frequency transducers produce longer wavelengths that may be too large to reflect strongly back from the textured surface of the needle.

APPROACHES TO REGIONAL BLOCK WITH ULTRASOUND

Peripheral nerves can be directly detected with high-resolution ultrasound imaging.[15] The fascicular echotexture is the most distinguishing feature of nerves (*honeycomb* architecture) (Fig. 58-11). More central nerves, such as the cervical ventral rami, have fewer fascicles and can appear monofascicular on ultrasound scans. Ultrasound frequencies of 10 MHz or higher are required to distinguish tendons from nerves based on echotexture alone. One of the most powerful techniques to identify nerve fascicles is to slide a broad linear transducer over the known course of a peripheral nerve with the nerve viewed in short axis (transverse cross section).

Nerves can be round, oval, or triangular. Although nerve shape can change along the nerve path, the cross-sectional nerve area is relatively constant in the absence of major branching[16] (Fig. 58-12). Peripheral nerves are pathologically enlarged either by entrapment or in certain neuromuscular disorders, such as Charcot-Marie-Tooth, type 1A, disorder (Fig. 58-13). Some evidence suggests that patients with diabetic neuropathy also have enlarged peripheral nerves.

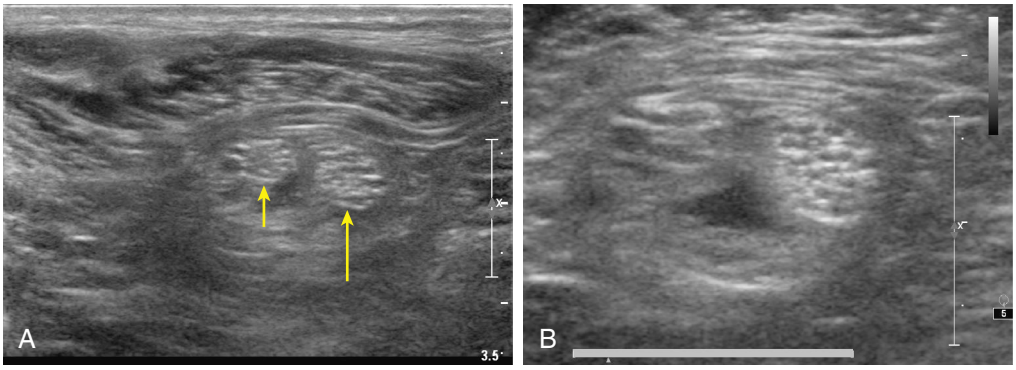


Figure 58-11. Nerve echotexture. **A,** Fascicles of the common peroneal *(short yellow arrow)* and tibial *(long yellow arrow)* nerves are visualized in the popliteal fossa. In this sonogram the *honeycomb* appearance of a polyfascicular peripheral nerve is observed. **B,** Close-up view shows detailed echotexture of the two nerves.

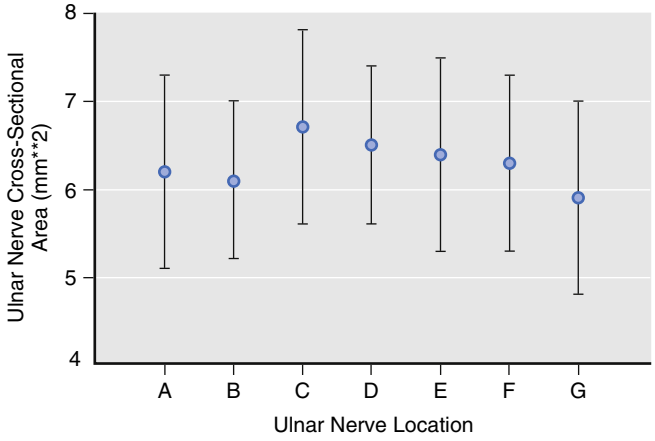


Figure 58-12. Cross-sectional area of a peripheral nerve as a function of nerve path length. In this figure the cross-sectional area of the ulnar nerve is shown at various points in the upper extremity. Axilla *(A)*; midhumerus *(B)*; 2 cm proximal to medial epicondyle *(C)*; medial epicondyle *(D)*; 2 cm distal to medial epicondyle *(E)*; arterial split *(F)*; and wrist crease *(G)*. Data are shown as mean values with standard deviations. Despite changes in shape that can occur, the cross-sectional area of nerves is relatively constant along the nerve path in the absence of major branching. *(Modified from Cartwright MS, Shin HW, Passmore LV, Walker FO: Ultrasonographic findings of the normal ulnar nerve in adults,* Arch Phys Med Rehabil *288(3): 394-396, 2007.)*

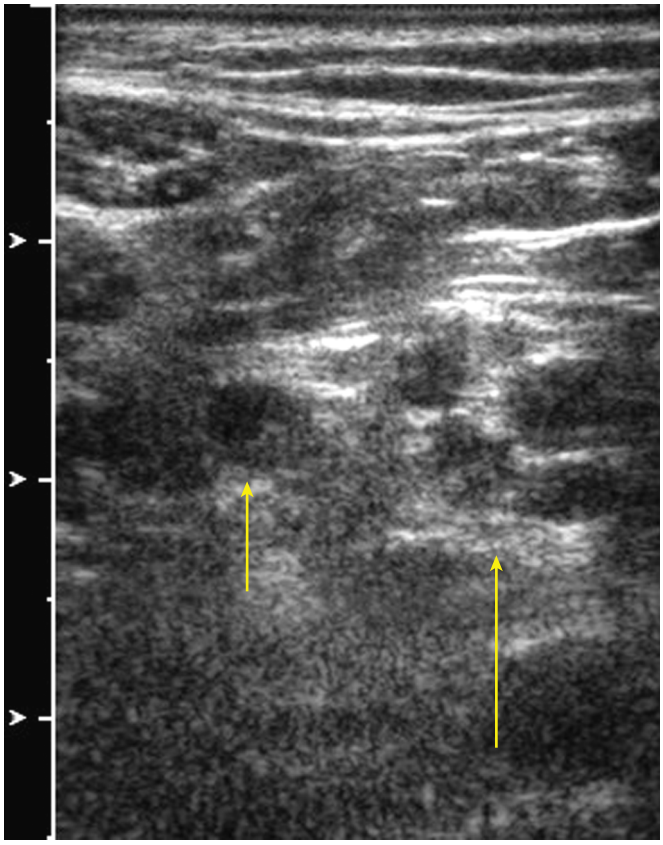


Figure 58-13. Sonogram demonstrates the popliteal fossa of a patient with Charcot-Marie-Tooth, type 1A, disorder. The peripheral nerves are significantly enlarged because of the large fascicles *(yellow arrows)*. Nerves of the symptomatic and asymptomatic sides can appear similar in these patients. Large tick marks are 10 mm apart.

Although direct nerve imaging has led to a phenomenal increase in ultrasound-guided regional anesthesia, the identification of other nearby anatomic structures, such as the fascia and other connective tissue), is also critical in this endeavor. These layers permit favorable distribution of local anesthetic, making nerve contact with the block needle unnecessary.

Many approaches to regional blocks with ultrasound are available (Table 58-2). Peripheral nerves are usually viewed in short axis rather than long axis. The needle can approach within the plane of imaging (in-plane technique) or cross the plane of imaging as an echogenic dot (out-of-plane technique). For some regional blocks, offline markings (skin markings before needle insertion) are used instead of online imaging (i.e., imaging during needle insertion and injection). Most studies have suggested that adequate visualization and correct identification of the relevant structures (e.g., peripheral nerve, needle tip, local anesthetic, adjacent anatomic structures) is more important than the approach, per se, for outcomes after regional blocks. Nevertheless, consistent practice patterns are developing among institutions and illustrate the underlying principles.

Successful injection for peripheral nerve block has several characteristics (Fig. 58-14). Injections should distribute around the nerve (clarifying the nerve border), travel along the nerve path and branches, and separate the nerve from common anatomic structures such as adjacent arteries that are wrapped together

in common fascia and connective tissue. Because anechoic fluid is typically injected, echoes received from the peripheral nerve will also be enhanced by increased through transmission (but not necessarily a sign of block success).

TABLE 58-2 **EXAMPLES OF APPROACHES TO REGIONAL BLOCKS WITH ULTRASOUND GUIDANCE**

Approach	Examples of Regional Block
Short axis view, in-plane	Almost any peripheral nerve block Almost any peripheral catheter placement
Short axis view, out-of-plane	Shallow blocks Interscalene catheter Lateral femoral cutaneous nerve block Femoral nerve catheter placement
Long axis view, in-plane	Proximal fascia iliaca block Proximal obturator block Anterior sciatic block
Long axis view, out-of-plane	Epidural placement (longitudinal paramedian view during midline approach) Transtracheal anesthesia

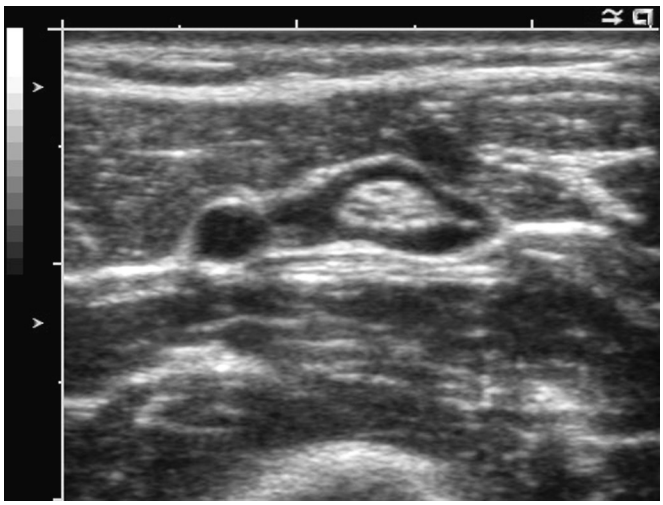


Figure 58-14. Local anesthetic injection for successful peripheral nerve block. The ulnar nerve and ulnar artery are viewed in short axis in the forearm in this sonogram. The nerve is surrounded with anechoic local anesthetic.

EXAMPLES OF COMMON REGIONAL BLOCKS

SUPRACLAVICULAR BLOCKS

Ultrasound-guided blocks were first described in the supraclavicular region.[17] The advantages of the supraclavicular block are that the brachial plexus is compact, the nerve visibility is extremely good, and the structures are shallow (20- to 30-mm field). In the supraclavicular region, sonography will image the divisions of the brachial plexus. Excellent block characteristics have been reported from ultrasound-guided supraclavicular blocks. The principal concerns are the risk of vascular puncture in an area that is difficult to compress and the risk of pneumothorax.

An in-plane approach from medial to lateral to ensure that the needle will pass over the subclavian artery can be used to reach the brachial plexus (Fig. 58-15). One current technique is to place the patient in a semi-sitting position with the head turned to the opposite side and the arms flush with the body. The operator either stands at the head of the bed or at the patient's side, depending on the side of the block and the handedness of the operator. Proximity to the phrenic nerve occurs if the block location is too cephalad. A compact linear transducer (20- to 30- mm footprint) is used for the procedure[18] to provide working room and to allow rocking of the transducer. Some authors have also recommended a specialized compact linear *hockey stick* transducer for supraclavicular blocks. The C5 ventral ramus (and other contributions to the brachial plexus) can pass over or through the anterior scalene muscle rather than between the scalene muscles. When this condition is identified, the block is usually performed at a more caudal position in the neck to avoid incomplete brachial plexus anesthesia.[19] The medial-to-lateral and the lateral-to-medial in-plane approaches to supraclavicular block both have excellent efficacy and safety profiles.

INFRACLAVICULAR BLOCKS

The advantages of the infraclavicular block are that it usually results in complete brachial plexus anesthesia,

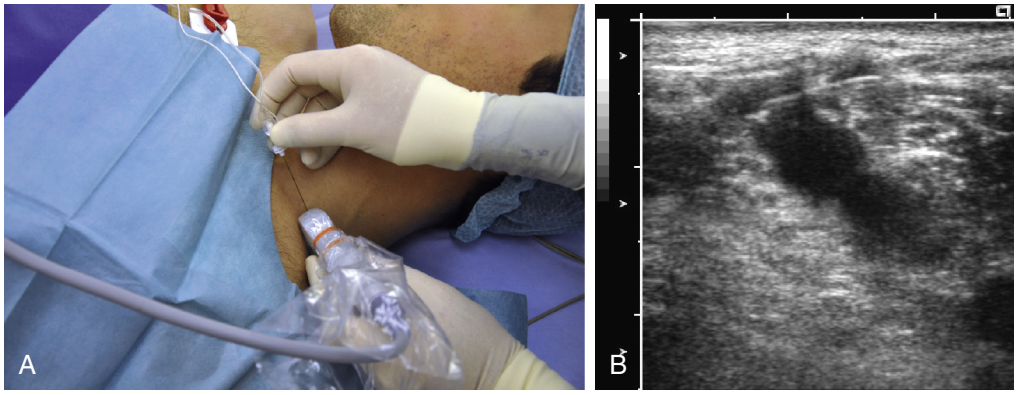


Figure 58-15. Supraclavicular block with ultrasound imaging. **A**, In this external photograph of ultrasound-guided supraclavicular block, the needle approaches the brachial plexus from medial to lateral. **B,** Sonogram of supraclavicular block with ultrasound guidance. The block needle approaches from medial to lateral within the plane of imaging for this procedure. Local anesthetic is observed to distribute around the compact brachial plexus.

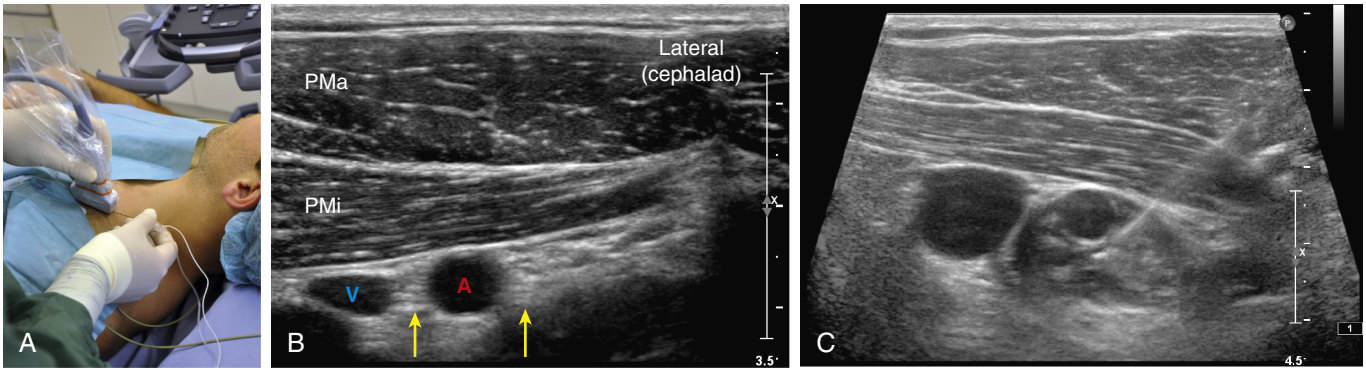


Figure 58-16. Infraclavicular block with ultrasound imaging. **A,** External photograph of the setup for infraclavicular block shows the arm has been abducted in this case. **B,** Sonogram of the cords of the brachial plexus *(yellow arrows)* are adjacent to the axillary artery *(A)* and vein *(V)*. The neurovascular bundle lies deep to the pectoralis major *(PMa)* and pectoralis minor *(PMi)* muscles in this anatomic region. **C,** Needle tip is in position for infraclavicular block and the resulting local anesthetic distribution.

TABLE 58-3 EXAMPLES OF SONOGRAPHIC LANDMARKS FOR INFRACLAVICULAR BLOCK*

Proximal	Optimal Location	Distal
Cephalic vein	Pectoralis minor muscle (midportion)	Subscapular artery
Thoracoacromial artery	Brachial plexus cords surround axillary artery	Coracobrachialis muscle
Chest wall and pleura	Posterior (or medial) cord underneath axillary artery	Anterior circumflex artery Posterior circumflex artery

* Infraclavicular block is usually performed at the level of the second part of the axillary artery (deep to the pectoralis minor muscle). Proximal and distal landmarks along the course of the axillary artery are listed.

BOX 58-2 ***Sonographic Signs Indicating Infraclavicular Block Success***

- U-shaped distribution underneath the axillary artery
- Separation of cords from axillary artery
- *White wall* appearance to the axillary artery
- Reduction in axillary artery diameter
- *Dark streak* underneath the axillary artery in the long axis view

Several studies of clinical block characteristics have validated the high predictive value of local anesthetic distribution underneath the axillary artery for three-cord anesthesia.

TABLE 58-4 COMPARISON OF THE INFRACLAVICULAR AND AXILLARY APPROACHES TO BRACHIAL PLEXUS BLOCK

	Infraclavicular Block	Axillary Block
Depth	Deep (two muscles)	Shallow
Onset	Slower	Faster
Tourniquet tolerance	Better	Good
Catheter success	High	Low

it is a stable place for a catheter, and no manipulation of the arm is necessary. The disadvantages are that the infraclavicular block is a deeper block; therefore, needle or probe manipulations are necessary, along with steep angles of needle insertion that result in needle tip visibility issues. Although the arm can remain at the side of the patient, the block is easier when the arm is abducted to straighten the neurovascular bundle. The three arterial wall-hugging cords are named with respect to the second part of the axillary artery; therefore, the expected positions are medial, lateral, and posterior. The artery is visualized in short-axis view deep to the pectoralis major and minor muscles (Fig. 58-16). Most practitioners use an in-plane approach from the head of the table or side of the table. The ideal place for local anesthetic distribution to achieve complete infraclavicular block of the brachial plexus is posterior to the axillary artery for single-shot or catheter placement. Substantial evidence suggests that local anesthetic distribution posterior to the axillary artery produces complete brachial plexus block in the infraclavicular region (Table 58-3 and Box 58-2). The cords of the brachial plexus do not need to be directly visualized for successful block. Duplication of the axillary vein is one of the few anatomic variations in the infraclavicular region. The clinical problem is that the accessory vein lies adjacent to the lateral cord of the brachial plexus and near the usual desired position of the needle tip.

AXILLARY BLOCKS

The axillary block is a versatile block for upper extremity anesthesia. Although relatively safe and effective with classical approaches, the cardinal weakness has been the failure to block the musculocutaneous nerve. With the advent of ultrasound imaging, this limitation can be overcome by directly visualizing the musculocutaneous nerve.

The axillary block provides surgical anesthesia of the elbow and more distal upper extremity. The shallow depth of the neurovascular bundle (a 20-mm field is typical) and the large amount of working room make this block relatively easy with ultrasound guidance (Table 58-4). Usually, three arterial wall-hugging branches (median, ulnar, and radial) and one branch with a characteristic medial-to-lateral course in the axilla (musculocutaneous) are

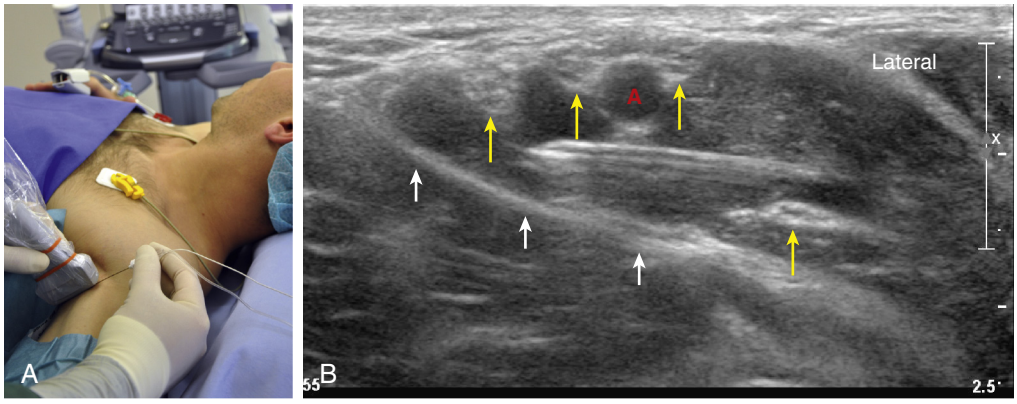


Figure 58-17. Axillary block with ultrasound guidance. **A,** External photograph demonstrates the in-plane approach. **B,** Sonogram of the neurovascular bundle in the short axis view shows the needle tip in-plane after injection of the local anesthetic. The probe compression is just sufficient to coapt the walls of the satellite veins. The block is performed at the level of the conjoint tendon of the latissimus dorsi and teres major *(white arrows)*, which lies under the neurovascular structures. The third part of the axillary artery *(A)* and nerves of the brachial plexus—radial, ulnar, median, and musculocutaneous—in order from medial to lateral *(yellow arrows)* are shown.

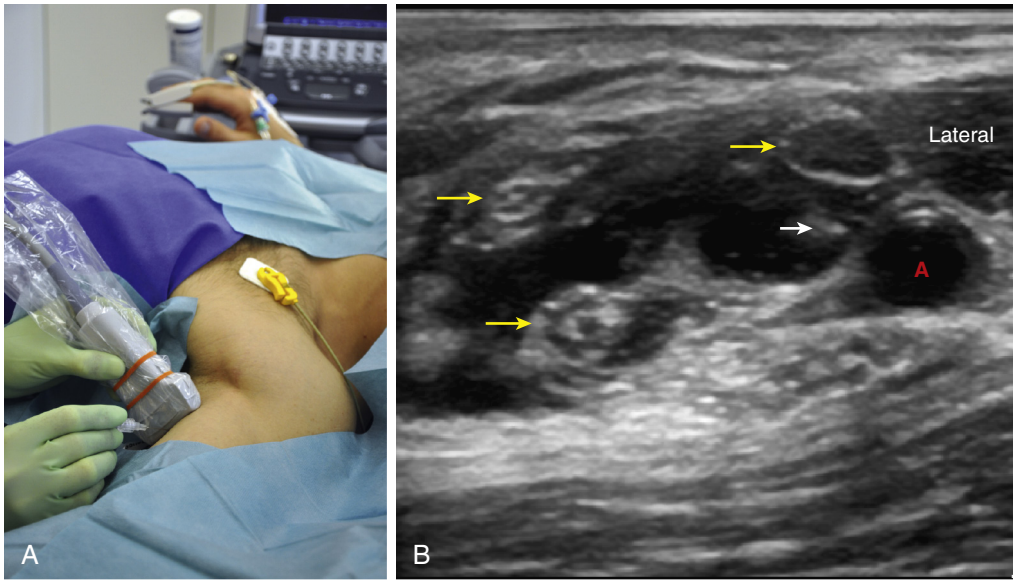


Figure 58-18. Axillary block with ultrasound guidance. **A,** External photograph demonstrates the out-of-plane approach. **B,** Sonogram of the neurovascular bundle in the short axis view shows the needle tip *(white arrow)* crossing the plane of imaging. The probe compression is just sufficient to coapt the walls of the satellite veins. The third part of the axillary artery *(A)* and nerves of the brachial plexus *(yellow arrows)* are shown.

visualized. In addition, the musculocutaneous nerve has a characteristic change in shape as it moves from adjacent to the artery (round) to within the coracobrachialis muscle (flat) and then exiting the muscle (triangular).

Both in-plane (with needle approaching from the lateral side of the arm) and out-of-plane (with needle approaching from distal to proximal) techniques can be used (Figs. 58-17 and 58-18). The block is performed in the proximal axilla, with the transducer gently pressed against the chest wall to visualize the conjoint tendon of the latissimus dorsi and teres major. A high-frequency linear probe with a small footprint (25 to 50 mm) with sterile cover can be used for axillary block. The ideal location for local anesthetic injection is between the nerves and the artery so that separation between the two structures occurs to ensure distribution within the neurovascular bundle. These injections result in excellent clinical blocks. The musculocutaneous nerve is usually blocked within the coracobrachialis, where its flat shape gives a large amount of surface area for rapid block. Duplication of the axillary artery and musculocutaneous-median nerve fusion (low-lying lateral cord) are common anatomic variations in the axilla.

TRANSVERSUS ABDOMINIS PLANE AND ILIOINGUINAL NERVE BLOCKS

Four peripheral nerves, the subcostal, ilioinguinal, iliohypogastric, and genitofemoral, primarily innervate the lower abdominal wall.[20] The extended course of the first three nerves through the abdominal wall within the layer between the transversus abdominis and the internal oblique muscles makes this the desired anatomic location for regional block. For ultrasound-guided transversus abdominis plane (TAP) block, the patient is usually in the supine position (Fig. 58-19). The transducer is placed between the iliac crest and costal margin in the midaxillary line. In this location, the muscle layers of the lateral abdominal wall (external oblique, internal oblique, and transversus abdominis) are well defined.

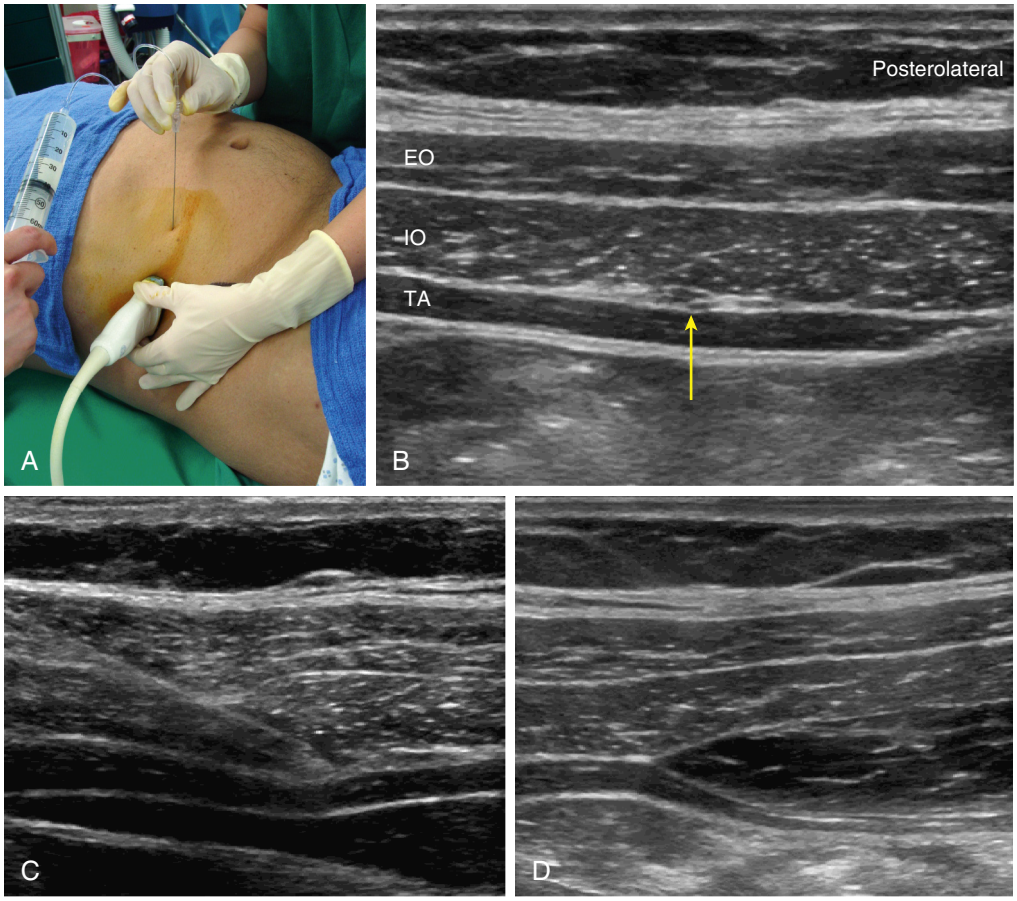


Figure 58-19. Transversus abdominis plane (TAP) block with ultrasound guidance. **A,** Abdominal wall image demonstrates the approach for TAP block. **B,** In this sonogram the external oblique *(EO),* internal oblique *(IO),* and transversus abdominis *(TA)* muscles are identified (the *three layer cake* appearance). Nerves *(yellow arrow)* are seen entering the plane between the IO and TA muscles. **C,** The needle approaches in-plane and is directed toward the posterolateral edge of the TA muscles. **D,** The *kayak* sign demonstrates successful TAP injection. The fascia between the IO and TA muscles is split apart in the shape resembling a kayak.

Injection is in the fascial layer that separates the internal oblique and the transversus abdominis muscles. Direct visualization and proximity to the nerves is not critical if 15 to 20 mL of dilute local anesthetic is injected in this layer. The needle approach is in-plane from the anterior side and directed toward the posterolateral corner of the transversus abdominis muscle. The respiratory motion of the peritoneal cavity and influence of muscle contraction makes general anesthesia an appealing option for performing this block. The transversus abdominis muscle is relatively thin; therefore, careful placement of the needle tip is necessary. Ilioinguinal nerve blocks (Fig. 58-20) can be performed in a similar fashion above the iliac crest.[21]

FEMORAL NERVE BLOCKS

The advantages of using ultrasound to guide femoral nerve block include a more complete block, local anesthetic volume sparing, and fewer vascular punctures.[22] The femoral nerve usually lies lateral to the femoral artery in the groove formed by the iliacus and psoas muscles. The nerve can be oval or triangular in cross-sectional shape with an anteroposterior diameter of approximately 3 mm and a mediolateral diameter of 10 mm. The best depiction of the femoral nerve is from 10 cm proximal to 5 cm distal to the inguinal ligament. According to the pelvic inclination, some tilting of the ultrasound probe is necessary for the sound beam to meet the nerve perpendicularly for optimal scanning. In addition, the femoral nerve has a slight medial-to-lateral course; therefore, some rotation of the probe is also necessary for the best view of the nerve. Because the femoral nerve is covered by echobright adipose tissue and fascia, the echogenic outer sheath of the nerve is difficult to establish. In some patients, the psoas tendon can appear similar to the femoral nerve. However, the psoas tendon lies deep within the muscle. If the profunda femoris artery (i.e., the deep branch of the femoral artery) is visualized, then the transducer is usually too distal for complete femoral nerve block. The femoral nerve is often identified as a slight indentation in the surface of the iliacus and psoas muscles.

For femoral nerve block, a broad (35- to 50-mm footprint) linear transducer is used (Fig. 58-21). Both in-plane (from lateral to medial) and out-of-plane (from distal to proximal) approaches can be used. The advantage of in-plane approach is visualization of the approaching needle. The disadvantages are the longer needle path and a tendency of the needle to skim over the fascia iliaca by deforming it rather than puncturing it. The out-of-plane approach is often used for catheter placement.

For either approach, the needle tip is positioned between the fascia iliaca and the iliopsoas muscle near the lateral corner of the femoral nerve to avoid the femoral vessels, similar to the method for fascia iliaca block. The fascia iliaca has a characteristic mediolateral slant. The desired distribution is local anesthetic layering under or completely around the femoral nerve. When layering of local anesthetic is restricted over the nerve, the concern is that the fascia iliaca is intact and that block failure will result. For patients who are obese, femoral nerve imaging



Figure 58-20. Ilioinguinal nerve block with ultrasound imaging. The transducer is rotated and placed near the iliac crest for ilioinguinal nerve block.

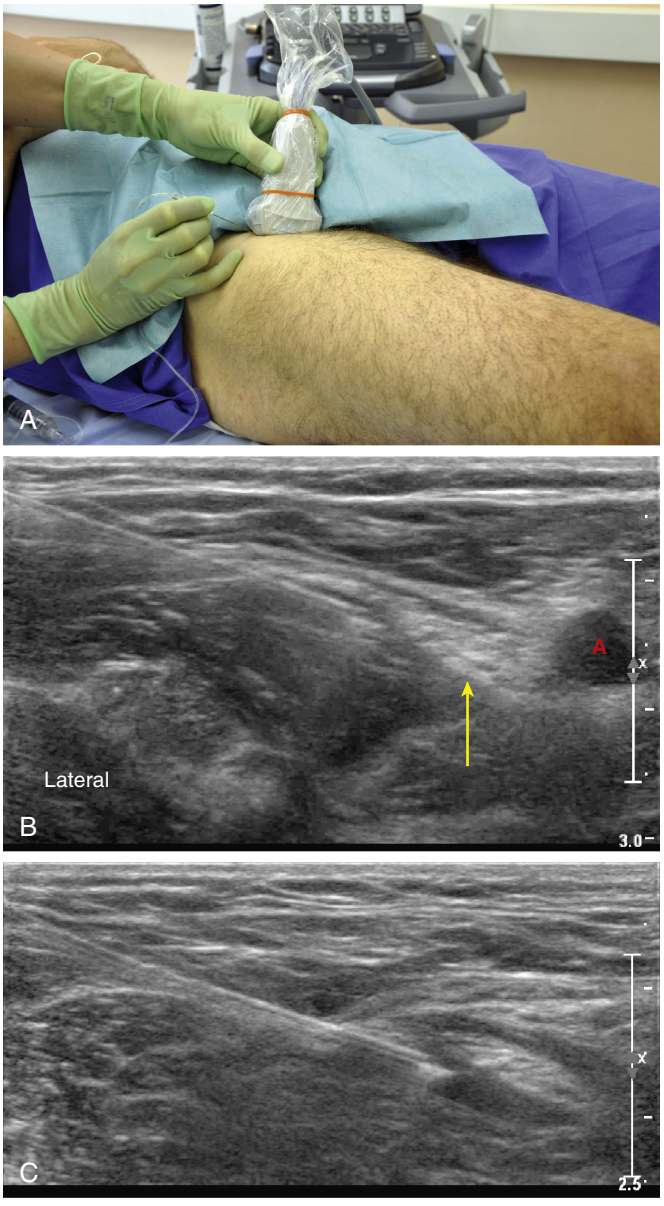


Figure 58-21. Femoral nerve block with ultrasound imaging (in-plane approach). **A,** External photograph shows the setup for femoral nerve block. **B,** The needle tip is in position before injecting adjacent to the femoral nerve *(yellow arrow)*. The femoral nerve lies lateral to the femoral artery *(A)*. **C,** Local anesthetic surrounds the femoral nerve after injection. *(Modified from Gray AT:* Atlas of ultrasound-guided regional anesthesia*, ed 2, Philadelphia, 2012, Saunders.)*

is challenging. Ultrasound can be combined with nerve stimulation for successful block in these patients. After successful injection of a local anesthetic, distal branches of the femoral nerve can be appreciated by sliding the transducer along the known course of the nerve.

The saphenous branch of the femoral nerve can be blocked in the midthigh, deep to the sartorius muscle using ultrasound guidance (Fig. 58-22). This approach has the advantage that the quadriceps motor block is reduced.[23]

SCIATIC NERVE BLOCKS IN THE POPLITEAL FOSSA

The sciatic nerve can be blocked anywhere along its course from the gluteal region to the popliteal fossa.[24-26] Many approaches have been described, including those from the anterior aspect of the thigh.[27] One of the most common approaches is to block the sciatic nerve in the popliteal fossa using a lateral approach in supine position with the leg elevated.[28] In this anatomic location, the block can be performed close to the skin surface. The division of the sciatic nerve provides a broad target with large surface area to promote clinical block characteristics. For this technique, the needle tip is positioned between the tibial and common peroneal components of the sciatic nerve near the division so that a single injection distributes to both nerves (Fig. 58-23). By sliding the transducer along the known course of the sciatic nerve, its characteristic division in the popliteal fossa can be identified. This method of sliding assessment is also important to verify the local anesthetic distribution after injection. The tibial nerve has a straighter course than the common peroneal nerve and has approximately twice the cross-sectional area. The tibial nerve lies posterior to the popliteal artery and vein at the popliteal crease, and this location can be a

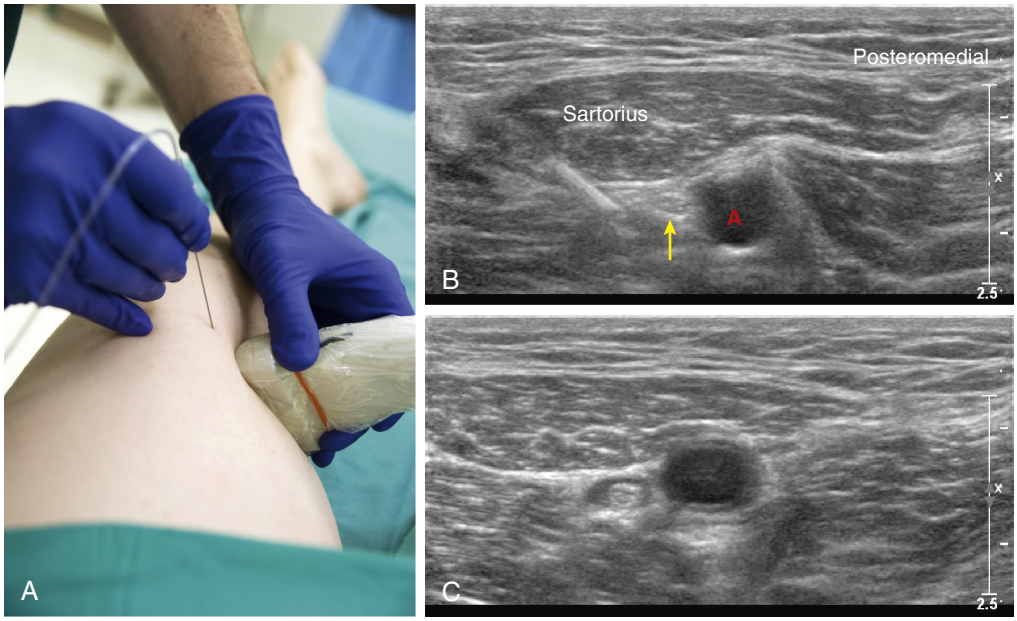


Figure 58-22. Saphenous nerve block in the middle thigh with ultrasound imaging (in-plane approach). **A,** External photograph shows the setup for saphenous nerve block. **B,** The needle tip has been placed through the sartorius muscle adjacent to the saphenous nerve *(yellow arrow)* and superficial femoral artery *(A)* before injection. **C,** Local anesthetic surrounds the saphenous nerve after injection deep to the sartorius muscle. *(Modified from Gray AT:* Atlas of ultrasound-guided regional anesthesia, *ed 2, Philadelphia, 2012, Saunders.)*

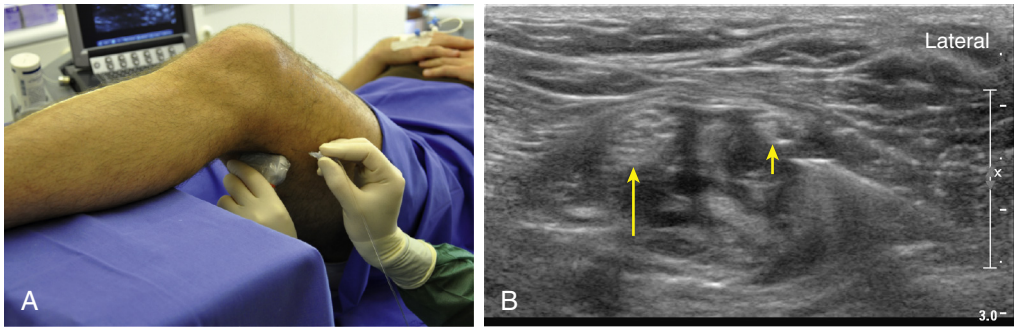


Figure 58-23. Popliteal block with ultrasound imaging (in-plane approach). **A,** External photograph shows the setup for popliteal nerve block in the supine position. The leg is elevated, and the transducer is applied to the posterior surface of the leg. **B,** The needle approaches the bifurcation of the sciatic nerve in the plane of imaging from the lateral aspect of the leg. The needle tip is positioned between the tibial *(long yellow arrow)* and common peroneal *(short yellow arrow)* nerves.

useful starting point when imaging is difficult. When the foot is moved, the nerves of the popliteal fossa have characteristic motions that can be helpful for nerve identification in some patients. The advantages of this approach are the convenient position, the transducer position is remote from the site of needle entry, and the parallel in-plane approach of the block needle results in optimal needle tip visibility. After injection, following the local anesthetic distribution around and along the nerve path (Fig. 58-24) is relatively easy.

TRAINING AND SAFETY

Interventional sonography is not without risks. Many studies have now demonstrated efficacy of ultrasound-guided regional blockade. Ultrasound has the potential to prevent and detect two important adverse events during peripheral nerve blocks: intravascular injection and intraneural injection of a local anesthetic.[29,30] The characteristic contrast from dissolved gas that is distributed within the vessel lumen can identify intravascular injection. The hallmark sign of intraneural injection is nerve expansion during injection (Fig. 58-25). Although ultrasound has tremendous promise in improving the safety of regional blockade, confirmatory studies of clinical practice are in progress. Many of these adverse events have only been recognized in retrospect by the review of recorded sonograms, which is a valuable training practice.

One of the original techniques developed for training novices in ultrasound-guided interventions was use of a tissue-equivalent phantom.[31] The phantom consisted of simulated tissue for needle placement practice (Fig. 58-26). To be realistic, the speed of sound must be similar as in soft tissue. In the first prototype, the phantom and container were clear; as a result, visual confirmation was possible. Several phantoms are now marketed for regional anesthesia purposes, and biologic tissue models that simulate nerve blocks have been developed.

A number of other effective teaching tools are being used. Cadavers have the advantage of realistic regional

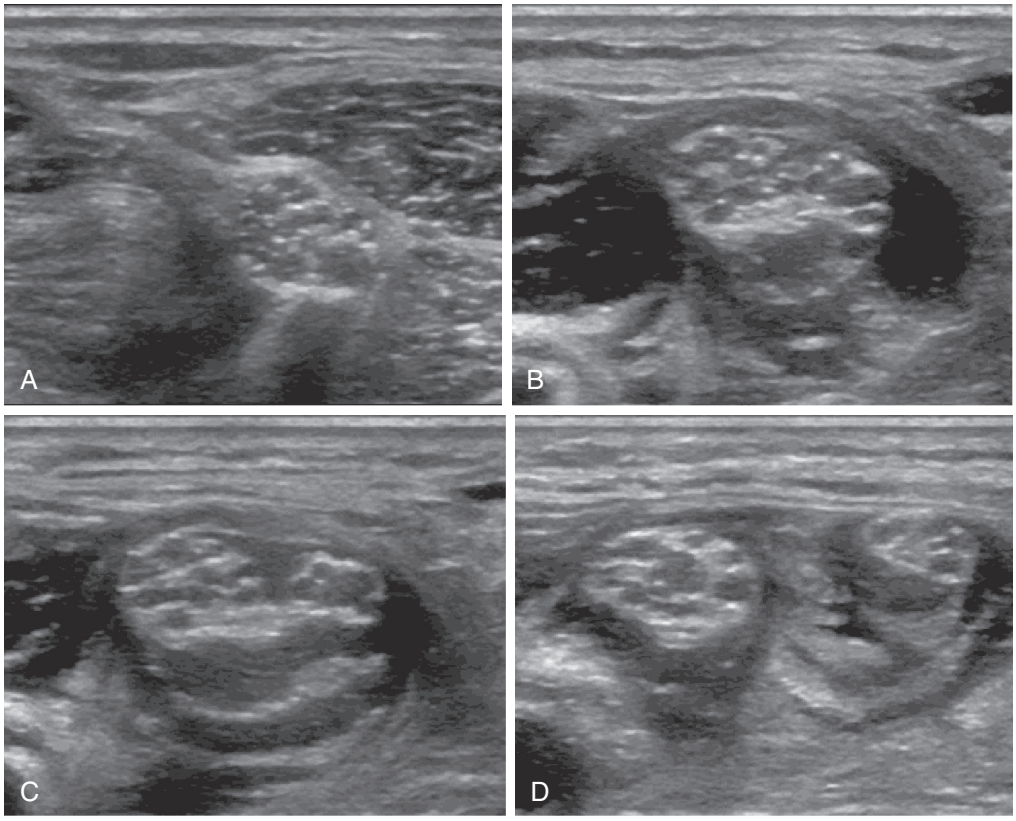


Figure 58-24. Sciatic nerve imaging in the popliteal fossa before (**A**), during (**B** and **C**), and after (**D**) division into the tibial and common peroneal nerves. Local anesthetic tracks with both individual nerves, thereby confirming a successful block.

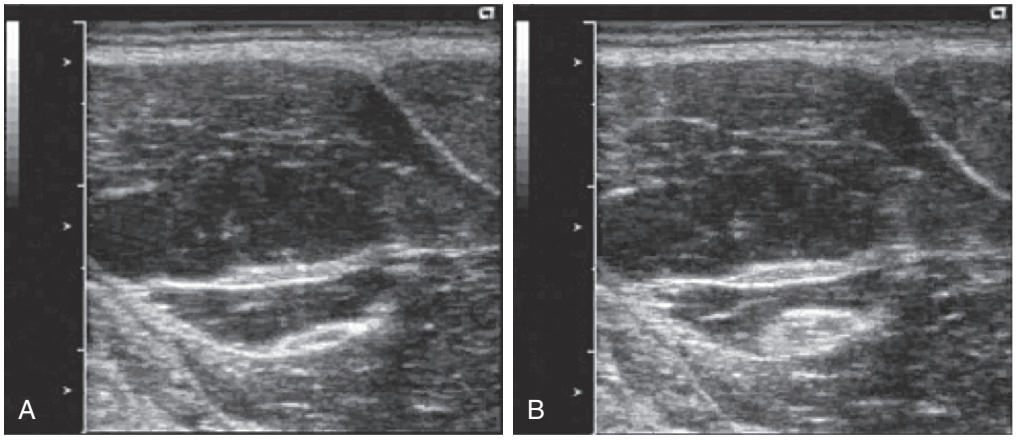


Figure 58-25. Ultrasound image reveals intraneural injection. These sonograms were obtained in the axilla before (**A**) and after (**B**) injection in the musculocutaneous nerve. Nerve expansion is detected but with preservation of the overall integrity of the nerve borders. No paresthesias were observed during or after the procedure. Neurologic outcome was favorable after this low-volume, low-pressure injection.

anatomic structures and can be used for simulated interventions.[32] The cost and use of specialized embalming methods that preserve nerve imaging and cadaver flexibility have limited this approach to a few specialized institutions. Most training studies have concluded that skills for ultrasound-guided procedures can be rapidly acquired.

One training study has identified common errors of novices while learning ultrasound-guided regional blocks.[33] These errors included advancing the needle when it was not visualized and unintentional probe movement. Novices often advance the needle even when it is not visualized, presumably because the natural inclination is to assume the needle has not reached the field of view. The potentially quality-compromising behaviors were largely eliminated by the end of the study period, which ranged from 66 to 114 blocks per training participant.

CONCLUSIONS

Ultrasound is a guidance tool that many people are electing to choose for regional anesthesia blocks. Once proficiency is established for a particular procedure, starting to use ultrasound for other interventional applications is relatively easy. Ultrasound imaging can prevent and



Figure 58-26. Tissue equivalent phantom for training in ultrasound-guided interventions.

detect critical events such as intravascular or intraneural injection that may improve safety during regional anesthesia procedures.[34] However, if safety outcomes are to improve, then education and training play key roles in reducing these relatively uncommon adverse events.

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Chapter 59

Perioperative Fluid and Electrolyte Therapy

MARK R. EDWARDS • MICHAEL P.W. GROCOTT

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Key Points

- Intravenous fluid therapy is a core part of perioperative practice, with the potential to influence patient outcomes.
- Water makes up approximately 60% of total body weight, varying widely with age and body composition. The ratio between the water volume within the intracellular and functional extracellular compartments is approximately 2:1.
- The endothelial glycocalyx forms a protein-poor intravascular fluid layer at the vessel perimeter; it has been integrated into a revised version of the Starling equation and updated model of capillary fluid movement.
- Sodium is the dominant extracellular cation and is responsible for much of extracellular fluid osmolality; dysnatremia is typically associated with disturbed extracellular fluid volume.
- Potassium is the dominant intracellular cation with a key role in the maintenance of transmembrane potentials; dyskalemia may be accompanied by impaired function of excitable tissues.
- Calcium is a key intracellular second messenger with roles in neuromuscular function, cell division, and oxidative pathways.
- Magnesium has a diverse range of physiologic effects, underlined by the increasing range of therapeutic applications of supplemental magnesium in the perioperative setting.
- Acid-base balance is relevant to fluid therapy because fluids containing supraphysiologic levels of chloride may cause an iatrogenic acidosis; the clinical relevance of this acidosis is debated.
- Intravenous fluids have a range of physiologic effects and should be considered to be drugs with indications, dose ranges, cautions, and side effects.
- The physiologic insult of the perioperative period may lead to a wide variety of disturbances in fluid and electrolyte balance.
- Clinical evidence to guide perioperative fluid therapy is lacking in many areas, and cannot be directly extrapolated from general critical care trials.
- A balance must be found between inadequate fluid administration—allowing tissue hypoperfusion—and the adverse effects of excess intravenous fluids and toxicities related to fluid constituents.
- Goal-directed fluid therapy (GDT) may help in finding this balance for an individual patient in the perioperative setting, with evidence of reduced postoperative morbidity supporting its use in many surgical settings.
- No clear consensus exists on which intravenously administered fluid is associated with the best clinical outcomes in the perioperative setting. Comparisons of "balanced" with "unbalanced" and "crystalloid" with "colloid" fluids are being studied in many clinical settings; definitive conclusions are often lacking.
- The approach to fluid and electrolyte management may need adapting to numerous patient and surgical factors.

The administration of intravenous (IV) fluid is a core expertise for anesthesia providers and an area in which we have an important role in advising clinical colleagues. Alongside the traditional triad of maintenance of unconsciousness, pain relief, and neuromuscular relaxation, IV fluid therapy is a core element of the perioperative practice of anesthesia. The aims of perioperative fluid administration should be to avoid dehydration, maintain an effective circulating volume, and prevent inadequate tissue perfusion during a period when the patient is unable to achieve these goals through normal oral fluid intake.

Knowledge of the clinical effects of different fluids has increased substantially in recent years. The choice of fluid type in a variety of clinical situations can be rationally guided by an understanding of the physicochemical and biologic properties of the various crystalloid and colloid solutions available in combination with the available clinical trial data. Each clinical decision about fluid therapy has two key elements: which fluid to use and how much fluid to give. Recently, several clinical studies have changed our concepts regarding both of these questions. However, we should be cautious about overinterpreting data from nonperioperative contexts. Despite recent high-quality "mega-trials" involving thousands of critically ill patients, key questions remain unresolved in the perioperative setting. Goal-directed fluid therapy (GDT) is a good example of an intervention that is effective in the perioperative phase, but ineffective in established critical illness, and this should alert us to other possible such distinctions.

This chapter reviews the physiology and pharmacology of IV fluid therapy in humans before discussing the clinical practice of fluid and electrolyte management and the impact of alternative approaches on clinical outcomes.

PHYSIOLOGY

FLUID COMPARTMENTS

Water makes up approximately 60% of total body weight in the average adult, varying with age, gender, and body composition. Adipose tissue contains little water compared with other tissues, leading to marked variability in total body water (TBW) proportion between lean (75%) and obese (45%) individuals. Variation in adipose tissue also contributes to differences in TBW between adult males and females; these differences are reduced in old age as adipose tissue is reduced. The variations in body composition with age lead to a wide variation in TBW (Table 59-1). TBW is divided between anatomic and functional fluid compartments within the body, with the major division between intracellular fluid (ICF) and extracellular fluid (ECF). The size of these compartments and their widely differing composition are shown in Figure 59-1 and Table 59-2. The extracellular fluid can be subdivided into the following compartments:

- Interstitial fluid (ISF): Lymphatic fluid and protein-poor fluid occupying cell spaces.
- Intravascular fluid: Plasma volume, including a proportion contained within the subglycocalyx (see later discussion).

TABLE 59-1 AGE-RELATED VARIATION IN TOTAL BODY WATER AND EXTRACELLULAR FLUID AS PERCENT OF BODY WEIGHT (MULTIPLY BY 10 FOR mL/kg)*

Age	TBW (%)	ECF (%)	Blood Volume (%)
Neonate	80	45	9
6 mo	70	35	
1 yr	60	28	
5 yr	65	25	8
Young adult (male)	60	22	7
Young adult (female)	50	20	7
Elderly	50	20	

Data from references 226 to 229.
ECF, Extracellular fluid; *TBW,* total body water.
*In pregnancy, blood and plasma volumes increase by 45% and 50% respectively by term.

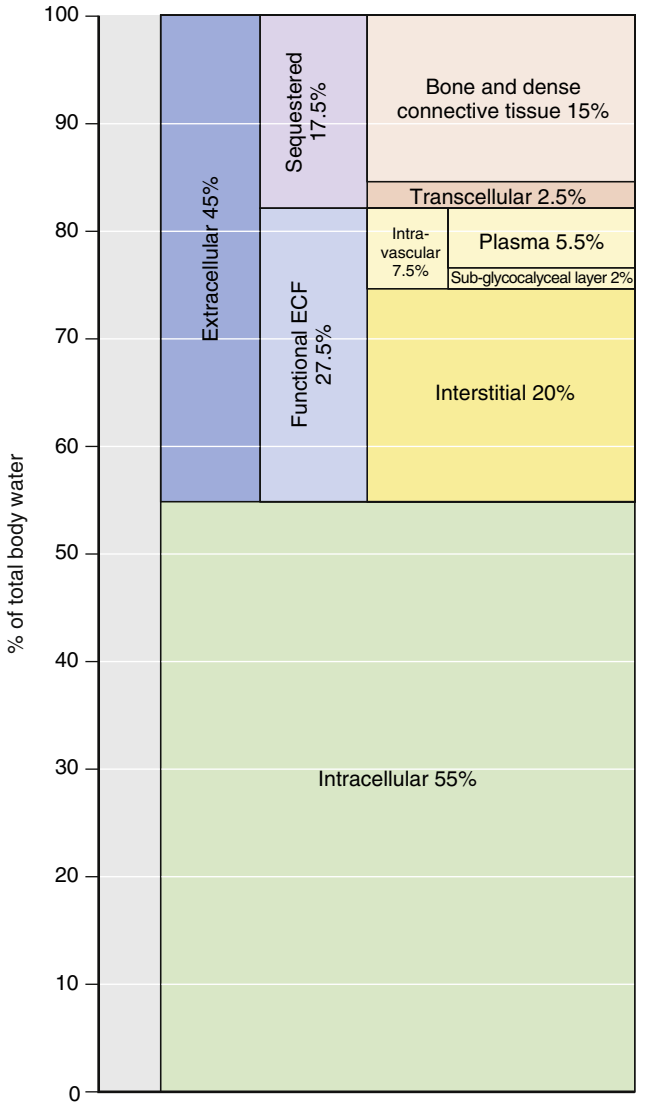


Figure 59-1. Distribution of total body water between fluid compartments. "Sequestered" extracellular fluid (ECF) refers to water associated with bone and dense connective tissue or within the transcellular compartment and therefore not immediately available for equilibration with the other fluid compartments.

- Transcellular fluid: Includes gastrointestinal (GI) tract fluid, bile, urine, cerebrospinal fluid, aqueous humor, joint fluid, and pleural, peritoneal, and pericardial fluid. These are functionally important fluids of widely varying composition contained within epithelia-lined spaces and regulated by active cellular transport (Table 59-3).
- Water in bone and dense connective tissue: Constitutes a substantial proportion of TBW but not part of the functional ECF because of slow kinetics of water distribution between this and other compartments.[1]

Total blood volume comprises extracellular (plasma and subglycocalyx compartments) and intracellular (blood cells) elements. With the nonfunctional ECF compartment (bone and connective tissue) excluded, the ratio between ICF and functional ECF is approximately 2:1 (ICF 55% of body weight to ECF 27.5% of body weight).

TABLE 59-2 COMPOSITION OF INTRACELLULAR AND EXTRACELLULAR FLUID COMPARTMENTS (IN mOsm/L WATER)

	Intracellular	Extracellular	
		Intravascular	Interstitial
Cations			
Na^+	10	142	145
K^+	157	4	4
Ca^{2+}	0.5*	2.5	2.5
Mg^{2+}	20	0.8	0.7
Anions			
Cl^-	10	103	117
HCO_3^-	7	25	27
$HPO_4^{2-}/H_2PO_4^-$	11	2	2
SO_4^{2-}	1	0.5	0.5
Organic acids		6	6
Protein	4	1.2	0.2

Data from references 230 to 232.

*Total intracellular Ca^{2+} concentration may be as high as extracellular levels; however, this is largely sequestered or buffered, such that the cytoplasmic ionized Ca^{2+} concentration is approximately 1000 times lower than extracellular fluid (0.3 to 2.6 μEq/L).[124] The intracellular content of anions such as PO_4^{3-} has been difficult to establish for similar reasons.

Physicochemical Laws Governing Fluid and Electrolyte Movement

The movement of water and solutes is governed by a variety of physicochemical and biologic processes, discussed in the following section.

Diffusion. Diffusion is the process by which solute particles fill the available solvent volume by motion from areas of high to low concentration. The speed of this equilibration is proportional to the square of the diffusion distance. Diffusion also may occur across permeable membranes, according to Fick's law of diffusion:

$$J = -DA\left(\frac{\Delta c}{\Delta x}\right) \quad (1)$$

where J is the net rate of diffusion, D is the diffusion coefficient, A is the cross-sectional area available for diffusion, and $\Delta c/\Delta x$ is the concentration (chemical) gradient.

Diffusion also may be driven by the tendency of charged solutes to move down electrical gradients.

Osmosis. If a semipermeable membrane (one that is permeable to water but not a solute) separates pure water from water in which solute is dissolved, water molecules will diffuse across the membrane into the region of higher solute concentration. The hydrostatic pressure required to resist the movement of solvent molecules in this way is osmotic pressure. This is one of the fundamental colligative properties of a solution—that is, it depends on the number rather than the type of osmotically active particles in a solution, which may be complete molecules or dissociated ions. Osmotic pressure in an ideal solution is affected by temperature and volume:

$$P = \frac{nRT}{V} \quad (2)$$

where P is the osmotic pressure, n is the number of particles, R is the gas constant, T the absolute temperature, and V the volume. n can be calculated by multiplying (mass of solute/molecular weight of solute) by the number of particles into which the solute dissociates.

However, body fluids are not ideal solutions, because interionic interactions reduce the number of particles free

TABLE 59-3 COMPOSITION OF TRANSCELLULAR FLUIDS (mEq/L UNLESS STATED)

	Daily Volume (L)	Cations				Anions		pH
Fluid		Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	HCO_3^-	
Gastrointestinal tract								
Saliva	1-1.5	30-90	20-40	2.5	0.6	15-35	10-40	6-7
Gastric	1.5-2.5	20-60	10-20			20-160	0	1-3.5
Bile	0.7-1.2	130-150	5-12	10-50		25-100	10-45	7-8
Pancreatic	1-1.5	125-150	5-10			30-110	40-115	8-8.3
Small bowel (concentrations from proximal to distal)	1.8	140-125	5-9			110-60	100-75	7-8
Large bowel	0.2 (lost in feces)	20-40	30-90			0-15	40	7-8
Sweat	0.1-0.5	45-60	5-10			45-60	0	5.2
Cerebrospinal fluid		140	2.8	2.1	1.7	120		7.33

Data from references 233 to 235.

to exert an osmotic effect. The total osmotic pressure of plasma is approximately 5545 mm Hg.

Osmolality. Molality is the number of moles (each containing 6×10^{23} particles of a specific substance) present in 1 kg of solvent. Osmolality may be used to describe solutions containing many different types of particles and is the number of osmoles (each containing 6×10^{23} of any type of particle present) present in 1 kg of solvent. Normal body osmolality is 285 to 290 mOsm/kg and is the same in intracellular and extracellular compartments because of the free movement of water between compartments that consequently prevents the development of any osmotic gradients. The largest contribution to plasma osmolality is made by sodium and its related anions chloride and bicarbonate. It can be estimated by:

$$\textit{Serum osmolality} = \begin{pmatrix} (2 \times Na) + (glucose \div 18) \\ + (urea \div 2.8) \end{pmatrix} \quad (3)$$

where *Na* is the serum sodium concentration (mEq/L), *glucose* is the serum glucose concentration (mg/dL), *urea* is the blood urea nitrogen concentration (mg/dL), and the (2 × Na) component reflects both Na and its associated anions (predominantly Cl^- and HCO_3^-). Alternatively, osmolality can be measured by depression of plasma freezing point. *Osmolarity* is the number of osmoles of solute per liter of solution; unlike osmolality, this may be affected by temperature changes as a result of the volume-expanding effect of increasing temperature.

Tonicity. This is the *effective osmolality* of a solution with respect to a particular semipermeable membrane and takes into account solutes that do not exert an in vivo osmotic effect. For example, Na^+ and Cl^- do not cross cell membranes freely and therefore exert an effective osmotic force across these membranes, whereas urea freely diffuses across cell membranes and therefore does not exert an osmotic effect here. Similarly, glucose is normally taken into cells by insulin-stimulated facilitated diffusion, so it is an ineffective osmole. Tonicity is important in determining in vivo distribution of fluids across a cell membrane and is sensed by the hypothalamic osmoreceptors. It can be estimated by subtracting urea and glucose concentrations from measured osmolality.

Oncotic Pressure. Oncotic pressure is the component of total osmotic pressure that is due to the colloids—that is, large-molecular-weight particles, predominantly proteins (albumin, globulins, fibrinogen). Of the total plasma osmotic pressure of 5545 mm Hg, 25 to 28 mm Hg is due to plasma oncotic pressure. The negative charge on proteins has the net effect of retaining a small excess of Na^+ ions within the plasma (the Gibbs-Donnan effect), which effectively increases the oncotic pressure above what would be predicted by calculations based purely on protein concentration. As the most abundant plasma protein, albumin is responsible for 65% to 75% of plasma oncotic pressure.

Fluid Compartment Barriers and Distribution

The volume and composition of each fluid compartment depends on the barriers separating it from neighboring compartments.

Cell Membrane. The cell membrane separates the intracellular and extracellular compartments and as a lipid bilayer is impermeable to large hydrophilic molecules and charged particles such as free ions. Other than by passive diffusion of certain molecules, solutes may cross cell membranes in several ways.

Carrier Proteins

Primary Active Transport. Solute transport against a concentration gradient requires energy and is therefore directly coupled to adenosine triphosphate (ATP) hydrolysis—for example, by Na^+/K^+–adenosine triphosphatases (ATPases). This is the fundamental mechanism by which ionic concentration gradients are maintained, which in turn drive a variety of biologic processes, including water and solute movement and electrical impulse transmission in excitable tissues.

Secondary Active Transport. The process of secondary active transport uses concentration gradients set up by ATPases to transport a solute driven by an ion moving down its concentration gradient, typically Na^+. This process is termed cotransport when the solute is also moving down its concentration gradient or countertransport when the solute is being moved against its concentration gradient.

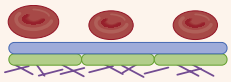
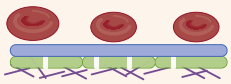
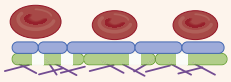
Solute Channels. The solute channels allow much faster transport of solutes than by ATPases or transmembrane diffusion. Examples include voltage-gated Na^+ channels and the glucose transporter GLUT1, which when inserted into the plasma membrane allows glucose to travel down its concentration gradient. This process is termed facilitated diffusion.

Endocytosis and Exocytosis. The processes of endocytosis and exocytosis are involved in the transport of large proteins and polypeptides across cell membranes.

Vascular Endothelium. The barrier function of the vascular endothelium is particularly relevant perioperatively because of its key role in maintaining intravascular fluid volume. Surgical tissue trauma typically leads to loss of intravascular volume through surgical blood loss or inflammation-related shifts to other tissue compartments. The physiologic effect of IV fluid administered to overcome these losses and maintain adequate tissue oxygen delivery is highly dependent on fluid handling at the capillary level. Our understanding of this area has been refined by experimental physiologic models and techniques.

Capillary Structure. As shown in Table 59-4, the structure of capillaries varies depending on the underlying organ function. The most common capillary type is the nonfenestrated capillary, comprising continuous basement membrane and a single layer of endothelial cells joined by junctions that are punctuated by breaks. These intercellular clefts are the primary channel for transcapillary fluid flow. The intravascular aspect of the endothelial cells is covered by a continuous network

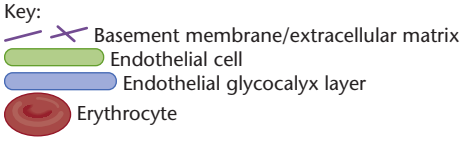
TABLE 59-4 **CAPILLARY CHARACTERISTICS**

Capillary Type	Site	Large Pores	Basement Membrane	Glycocalyx Layer	Notes on Function
Nonfenestrated (continuous) 	Muscle, connective tissue, lung, nervous tissue	None	Continuous	Continuous	Intercellular clefts are the main route for fluid filtration. These are partly occluded by junctional strands with multiple breaks. In the blood-brain barrier these breaks are small (1 nm) and infrequent (zona occludens tight junctions), permitting passage of only the smallest non–lipid soluble molecules. In other tissues the breaks are larger (5-8 nm) and more frequent (macula occludens loose junctions).
Fenestrated 	Endocrine, gut mucosa, choroid plexus, lymph nodes	Pores within endothelial cells with covering diaphragm 6-12 nm size	Continuous	Continuous	Fenestrations allow capillary reabsorption of fluid from ISF, in contrast to other capillary types.
	Glomeruli	Endothelial pore size up to 65 nm	Continuous	Discontinuous over pores, reducing *effective* pore size	Numerous pores allow large-volume filtration at the glomerulus. The effective pore size is reduced further to 6 nm by podocytes; thus, proteins not usually filtered.
Sinusoidal 	Liver, spleen, bone marrow	Large intercellular gaps up to 120 nm	Discontinuous	No effective layer because of endothelial uptake of hyaluronic acid	Large fenestrations allow macromolecules (lipoproteins, chylomicrons) to pass between plasma and ISF; the result is no COP to oppose filtration, and the ISF in these tissues is effectively part of the plasma volume. Large volume filtration to the ISF here cannot be accommodated by tissue expansion because of fibrous capsules and is returned via lymphatics (e.g., liver lymph production accounts for 50% of total body lymph production)

Modified from Woodcock TE, Woodcock TM: Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy, Br J Anaesth *108:384, 2012.*

COP, Colloid oncotic pressure; *ISF,* interstitial fluid.

Key:



of glycosaminoglycan (GAG) chains, including syndecan-1, hyaluronic acid, and glypican, associated with membrane-bound proteoglycans; and glycoproteins, together forming the endothelial glycocalyx layer (EGL). The EGL covers fenestrations and intercellular clefts and has a thickness of up to 1 μm. In addition to its functions in preventing platelet and leukocyte adhesion, it has emerged as an important semipermeable layer contributing to endothelial barrier function.[2] Water and electrolytes can move freely across the vascular endothelial barrier through the EGL and then intercellular clefts or through fenestrations in the more specialized capillaries. Proteins were previously thought to be excluded from the ISF at the level of endothelial cells; however, it now appears that this occurs at the level of the glycocalyx. The subglycocalyceal layer (SGL) therefore contains protein-poor fluid; slower protein transport into the ISF may occur across the endothelial cells by endocytosis and exocytosis and by transport through a small number of large pores, forming a gradient in protein concentration from SGL to ISF compartments. The volume of the SGL may be as much as 700 to 1000 mL; this

volume therefore forms part of the intravascular volume and has an electrolyte composition in equilibrium with the plasma but a much lower protein concentration because of the effective exclusion of larger molecules by the glycocalyx.

Capillary Function. The movement of fluid across the capillary membrane was initially described by Starling and then further refined. A hydrostatic pressure gradient at the arteriolar end of the capillary, greater than the inward oncotic pressure gradient, leads to net filtration of water into the ISF. Much of this water was previously thought to be reabsorbed into the vascular space toward the venular end of the capillary, where the outward hydrostatic pressure is less and the inward oncotic pressure gradient is increased by exclusion of proteins from the capillary filtrate by the capillary endothelium. The water not reabsorbed by the capillary is removed from the ISF by the lymphatics.

More recent experimental and modeling techniques have integrated the role of the glycocalyx into a revised Starling equation and updated model of capillary fluid movement:

$$J_v = K_f([P_c - P_i] - \sigma[\pi_c - \pi_{sg}]) \quad (4)$$

where J_v is the transcapillary flow, K_f is the filtration coefficient, P_c is capillary hydrostatic pressure, P_i is the interstitial hydrostatic pressure, σ is the reflection coefficient (the degree to which the tendency of a macromolecule to cross the endothelial barrier is resisted), π_c is the capillary oncotic pressure, and π_{sg} is the subglycocalyx oncotic pressure.

The key differences and their clinical relevance are as follows[3]:

- At steady state, continuous capillaries *do not* exhibit fluid reabsorption toward the venous end of the capillary (the "no-absorption" rule). However, overall measured capillary filtration (J_v) is much less than predicted by the Starling principle, consistent with the larger colloid oncotic pressure (COP) gradient between SGL and capillary (opposing filtration) than between ISF and capillary. The smaller volume of filtrate is returned to the circulation by lymphatics.
- Plasma-SGL COP difference, not plasma-ISF COP difference affects J_v. However, the no-absorption rule means that artificially raising COP (e.g., by albumin infusion) may reduce J_v but will not lead to reabsorption of fluid from the ISF into the plasma.
- An exception to the no-absorption rule occurs in acutely subnormal capillary pressures; a transient period of autotransfusion may occur, limited to approximately 500 mL. If subnormal pressures persist beyond this, J_v will approach zero, but ongoing reabsorption does not occur. Infusion of colloid in this setting will expand plasma volume, whereas infusion of crystalloid will expand total intravascular volume (plasma and EGL); J_v will remain close to zero in both cases until capillary pressure rises to normal or supranormal levels.
- At supranormal capillary pressures, COP difference is maintained and J_v is proportional to the hydrostatic pressure difference. In this setting, colloid infusion will maintain plasma COP but raise capillary pressure further and increase J_v. Crystalloid infusion will also increase capillary pressure, but reduce plasma COP and therefore increase J_v to a greater extent than colloids.

The revised EGL model of fluid distribution, including the proposal that the intravascular volume effects of crystalloids and colloids are partly dependent on the preexisting capillary pressures (context sensitivity) helps explain some of the apparently conflicting findings in clinical fluid research.

Crystalloid Versus Colloid Intravascular Volume Effects. Infused crystalloid has been thought to distribute evenly throughout the extracellular compartments as a result of capillary filtration (J_v), leaving approximately one fourth or one fifth of the original volume within the circulating blood volume, whereas colloids were presumed to initially remain largely within the intravascular volume. However, many studies of the effects of fluids on blood volume are based on red blood cell (RBC) dilution and changes in the hematocrit and do not take into account the influence of the SGL volume, from which RBCs are excluded. Colloids are also excluded from the SGL; by remaining in the plasma volume they will have a diluting effect on the hematocrit and appear to remain within the circulating volume. Crystalloids initially distribute throughout the plasma and SGL volumes. As a result, their RBC dilutional effects are less than those of colloids. This has previously been interpreted as crystalloid leaving the circulating compartment and entering the ISF; however, a proportion of the infused crystalloid will remain in the blood volume within the SGL. Furthermore, context sensitivity is responsible for the observation that clearance of crystalloid from its central compartment (the intravascular volume) is slower under anesthesia than in awake subjects.[4] It may also help to explain why the amount of isotonic crystalloid required to give early intravascular volume effects similar to those from isotonic colloid in low capillary pressure situations such as resuscitation is in the ratio 1.5:1 rather than the predicted 4:1.[5-7] The value of this ratio in the perioperative context is less clear and has been inferred from large clinical trials in critically ill patients. However, it is likely to be closer to the measured values in critical illness than the theoretic values traditionally used.

Failure to Reduce Edema by Increasing Capillary Colloid Oncotic Pressure. Hypoalbuminemia is well recognized as a marker of disease severity in critical illness. However, administering exogenous albumin or other colloids to increase capillary COP does not reduce peripheral or pulmonary edema, nor improve overall outcomes in sepsis. The no-absorption rule can provide a partial explanation; even increasing COP gradient across the capillary wall by administration of albumin or synthetic plasma substitutes will not lead to reabsorption of fluid from edematous tissues. Again, previous studies showing apparent shifts of fluid from the interstitial to the intravascular compartment based on a reduced hematocrit after albumin infusion do not account for the potential role of compaction of the glycocalyx layer and transfer of fluid from the SGL to the plasma volume in reducing the hematocrit.

Finally, the importance of the endothelial glycocalyx is highlighted by studies showing that its degradation significantly impairs endothelial barrier function.[8] A range of physiologic insults may lead to glycocalyx injury and shedding, with the subsequent appearance of free heparin, chondroitin, and hyaluronic acid in the plasma. These include natriuretic peptides (which may be released in acute excessive intravascular volume),[9] hyperglycemia, and inflammatory mediators released during surgery, trauma, and sepsis, such as C-reactive protein, bradykinin, and tumor necrosis factor (TNF).[10] Glycocalyx degradation may make an important contribution to the already well-characterized endothelial dysfunction seen in inflammation, in which phenotypic changes in endothelial cells. Here, an increase in the number of large pores, and a reduction in interstitial hydrostatic pressure favor J_v, with an increase in edema in compliant tissues such as the lung, muscles, and loose connective tissue. Impaired glycocalyx function will further favor J_v and lead to endothelial platelet aggregation and leukocyte adhesion. Maintenance of glycocalyx integrity is therefore gaining interest as a therapeutic target in perioperative fluid management.[11]

Physiologic Control of Overall Fluid Balance

In health, 60% of daily water loss is through urinary excretion, although this proportion is less when sweating and insensible losses are increased. Integrated cardiovascular and renal neuroendocrine mechanisms attempt to maintain fluid volume homeostasis in response to perioperative challenges, such as reduced oral fluid intake, increased lower GI tract loss as a result of bowel preparation, blood loss, and IV infusion of fluids.

TBW volume is controlled by a system of sensors, central control, and effectors. The sensors are the hypothalamic osmoreceptors, responding to changes in ECF tonicity, low-pressure baroreceptors in the large veins and right atrium that sense central venous pressure, and high-pressure baroreceptors in the carotid sinus and aortic arch. The latter are important if changes in intravascular volume are sufficient to affect arterial blood pressure. The sensory inputs are integrated within the hypothalamus, which then triggers the effector mechanisms to either increase water intake from thirst or modulate output via antidiuretic hormone (ADH, arginine vasopressin) secretion. Thirst and ADH release may be triggered by increased plasma tonicity, hypovolemia, hypotension, and angiotensin II. ADH release also may be stimulated by stress (including surgery and trauma) and certain drugs (e.g., barbiturates). Water intake does not usually depend on thirst because of social drinking behavior; thirst acts as a backup mechanism when the normal intake is inadequate. ADH, produced in the hypothalamus and released from the posterior pituitary, acts on the principal cells of the renal collecting ducts, which in the absence of ADH are relatively impermeable to water. ADH combines with the vasopressin 2 (V2) receptors on the basolateral membrane of the cells, triggering cyclic adenosine monophosphate (cAMP)-mediated insertion of aquaporin 2 water channels into the apical membrane. This results in water reabsorption down its osmotic gradient and formation of low volumes of concentrated urine.

Acute Disturbances in Circulating Volume. Acute variation in the intravascular volume leads to compensatory mechanisms over minutes to hours in an attempt to correct the acute abnormality. The homeostatic processes occurring in response to rapid blood loss are aimed at minimizing the change in effective blood volume (venoconstriction and mobilization of venous reservoirs, limited autotransfusion from ISF to plasma, reduced urine production) and maintenance of cardiac output and arterial pressure (tachycardia, increased inotropy, and vasoconstriction). The sensor organs for the acute change are the low-pressure and high-pressure baroreceptors, and initial changes are mediated through increased sympathetic outflow. Renal vasoconstriction leads to a reduced volume of filtrate, and activates the renin-angiotensin-aldosterone (RAA) axis. Renin is released from the juxtaglomerular cells and cleaves angiotensinogen to form angiotensin I, which is rapidly converted to angiotensin II. This induces further sympathetic activity and vasoconstriction, aldosterone release from the adrenal cortex, and hypothalamic ADH production. The overall result is increased renal salt and water retention, increased peripheral vascular resistance, and increased cardiac output. In the absence of ongoing loss, the delayed responses to major blood loss restore plasma volume within 12 to 72 hours, increase hepatic plasma protein synthesis, and restore RBC levels by erythropoiesis within 4 to 8 weeks.

Conversely, the rapid infusion of fluid to a normovolemic healthy adult leads to an initial rise in venous and arterial pressure and cardiac output. Several mechanisms act rapidly to bring these cardiovascular parameters toward normal, including pressure receptor–mediated venodilatation and venous blood pooling and reduction in systemic vascular resistance. At a tissue level, autoregulatory responses lead to arteriolar vasoconstriction to maintain constant blood flow in the face of increased perfusion pressure. Multiple mechanisms then act to return circulating volume toward normal. A proportion of the infused fluid will be lost as a result of capillary filtration, particularly if the infused fluid reduces COP. Low-pressure baroreceptor stimulation leads to a decrease in pituitary ADH secretion, allowing diuresis, and atrial stretch leads to atrial natriuretic peptide (ANP) release, favoring natriuresis. Further ADH-independent renal mechanisms include glomerulotubular imbalance resulting from the marginal reduction in plasma COP; this rapidly increases the glomerular filtration rate (GFR) and reduces proximal tubule water and Na^+ reabsorption, increasing urine volume. Finally, increased arterial blood pressure promotes the excretion of excess water and salt (i.e., pressure natriuresis and pressure diuresis). This is the pressure-volume control mechanism, one of the key mechanisms for the long-term maintenance of normal blood volume. However, arterial blood pressure is only slowly restored by cardiovascular reflexes after acute hypervolemia. It may take several days for a 20 mL/kg dose of isotonic salt solution to be fully excreted. Excretion of excess Na^+ and water depends more on these passive processes and suppression of the RAA axis than on natriuretic peptide activity.[12] The contrast between this inefficiency and the rapid, effective mechanisms for dealing with reduced fluid volume and Na^+ content reflects

the evolution of physiology in an environment with a paucity of salt and variable water availability; excess Na^+ intake is a feature of modern diets.

Long-Term Control of Circulating Intravascular Volume. The Guyton-Coleman model is the archetypal representation of the circulation. Despite calls to refine the mathematic modeling of the long-term control of arterial blood pressure, it remains the most widely used model to explain the chronic control of blood volume and arterial pressure.[13-15] In health, short-term variations in blood volume are very small and the cardiovascular system behaves as a closed system with arterial pressure a product of peripheral resistance, vascular compliance, and the Starling curve.[16] In the chronic setting or in acute alterations in blood volume, as described earlier, the circulating volume will vary and equality of input and output must be restored to avoid chronic fluid retention or dehydration; thus the circulation acts as an open system. The kidneys are the primary organ regulating this equilibrium, largely through pressure natriuresis and diuresis. Indeed, in the chronic setting, arterial pressure subserves the renal requirement to excrete ingested Na^+ and water rather than simply being a product of cardiac output, vascular compliance, and resistance. A recent interpretation integrates the Guyton-Coleman model with experimental observations (Fig. 59-2).[16] In health, the pressure-natriuresis curve is relatively flat, and excess intake of salt and water can be excreted without long-term rises in circulating volume or blood pressure. In many models of chronic hypertension, the renal excretion mechanism is reset such that natriuresis occurs only at higher arterial pressures and excessive exogenous water and salt results in higher blood pressure.

Electrolyte Physiology

Sodium Physiology. Na^+ is the dominant extracellular cation, and along with its associated anions accounts for nearly all of the osmotically active solute in plasma and interstitial fluid. The relatively free movement of water throughout the fluid compartments means that Na^+ is therefore the prime determinant of ECF volume. Total body Na^+ content is approximately 4000 mmol, of which only 10% is intracellular. The concentration gradient between the intracellular and extracellular compartments (ratio 1:15) is maintained by ATPases and is vital for the function of excitable tissues, including action potentials and membrane potential, and for the handling of renal solute.

Na^+ intake is typically far in excess of minimum daily requirements, which are 2 to 3 mEq/kg/day at birth and decrease to 1 to 1.5 mEq/kg/day in adulthood.[17,18] Na^+ is actively absorbed from the small intestine and colon under the influence of aldosterone and the presence of glucose in the gut lumen. Loss is predominantly by the renal route, with minor contributions from feces, sweat, and skin (10 mEq/day each). Na^+ is freely filtered at the glomerulus, of which 99.5% is reabsorbed, mainly at the proximal convoluted tubule. Serum Na^+ concentrations are maintained within a tight range (138 to 142 mEq/L) despite wide variation in water intake by the systems

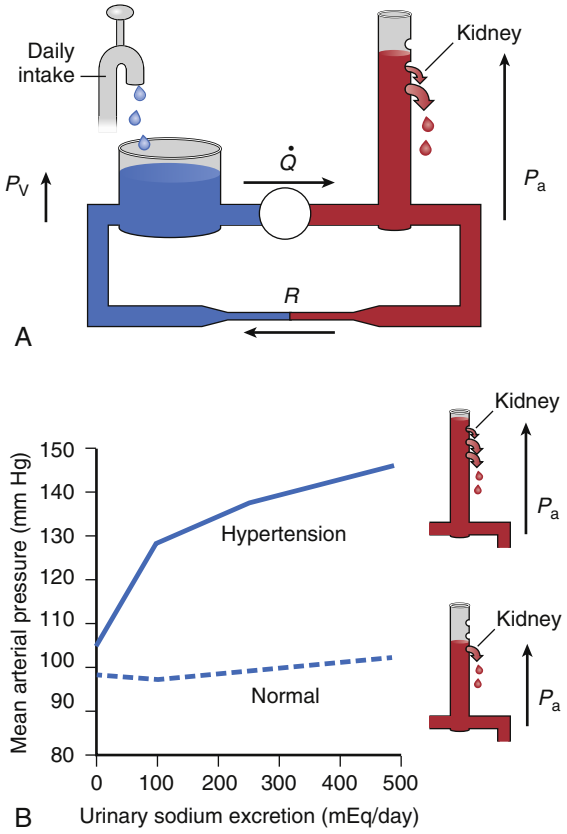


Figure 59-2. Long-term control of blood volume in health and hypertension. **A,** Representation of the open circulation model. In the chronic setting arterial pressure (*Pa*) depends on daily water and sodium intake (*dripping tap*) and the renal pressure-natriuresis relationship (*represented by the height of the holes in the arterial column*) rather than cardiac output ($\dot{Q}$) and peripheral resistance (*R*). **B,** Experimental models of hypertension (e.g., long-term angiotensin II infusion) with controlled sodium intake (and therefore excretion) demonstrate a reset pressure-natriuresis curve in hypertension. This may be represented by kidney *holes* positioned further up the arterial column. Natriuresis occurs to a degree similar to that in normotension, so as to maintain a stable body water volume, but requires a higher arterial pressure to do so. *Pv*, Venous pressure. *(**A,** Redrawn from Dorrington KL, Pandit JJ: The obligatory role of the kidney in long-term arterial blood pressure control: extending Guyton's model of the circulation,* Anaesthesia *64:1218, 2009; and **B,** Data from Hall JE: The kidney, hypertension, and obesity,* Hypertension *41:625, 2003.)*

involved in the control of circulating volume outlined previously, as follows:

- Hypothalamic osmoreception: ADH release
- Atrial volume sensing: ANP release
- Juxtaglomerular apparatus (renal arteriolar baroreception and filtrate NaCl content sensing): RAA activation

The excretion of total body excess Na^+ relies on inefficient passive mechanisms, particularly the pressure-volume effect. Long-term ingestion of excess salt combined with low potassium ingestion contributes to hypertension, a condition not seen in populations with daily salt intake less than 50 mmol. The mechanism involves renal salt retention and initial extracellular volume expansion (later mitigated by pressure natriuresis), with release of an

endogenous digitalis-like factor and stimulation of renal Na^+ pumps, furthering renal Na^+ retention. Low K^+ combined with the chronic action of digitalis-like factor inhibits vascular smooth muscle cell Na^+/K^+ATPases, resulting in excess intracellular Na^+ content and reduced intracellular K^+, smooth muscle contraction, and increased peripheral vascular resistance.[19]

Potassium Physiology. K^+ is the dominant intracellular cation in the body, with a total body content of approximately 4000 mmol, 98% of which is intracellular, particularly in muscle, liver, and RBCs. The ratio of ICF to ECF K^+ balance is vital in the maintenance of cellular resting membrane potential, and K^+ therefore has a key role in the behavior of all excitable tissues. Daily requirements reflect age and growth, with more K^+ required in higher metabolic rates. Term infants require 2 to 3 mEq/kg/day and adults 1 to 1.5 mEq/kg/day. Nearly all ingested K^+ is absorbed by the intestine, and minimal amounts are excreted in feces; the acute and chronic handling of K^+ must therefore maintain a stable plasma K^+ concentration and resting membrane potential in the face of a daily K^+ intake of a similar magnitude to the entire ECF K^+ content. Transmembrane potentials particularly depend on K^+ permeability, with K^+ egress occurring through ion channels down its concentration gradient. This leaves behind intracellular anions, with a resultant negative transmembrane potential. The resting value of this potential is achieved when the tendency of K^+ to move extracellularly as a result of its concentration gradient is matched by the tendency of K^+ to move intracellularly because of the electrical gradient.

Acute K^+ distribution involves shifts in K^+ between the ECF and ICF, performed by ion transport systems under the influence of insulin, catecholamines, and ECF pH. The cell membrane Na^+/K^+ATPase exports three Na^+ for every two K^+ imported and is the means by which the gradients of these ions are maintained. Insulin, released after ingestion of K^+-containing food, stimulates the Na^+/H^+ antiporter, increasing intracellular Na^+, which is then removed by Na^+/K^+ATPase with the net cellular uptake of K^+. Conversely, in the presence of hypokalemia, skeletal muscle expression of Na^+/K^+ATPase is reduced, allowing a "leak" of K^+ from the ICF to ECF.[20] Catecholamines activate β_2-adrenoceptors, which ultimately stimulate Na^+/K^+ATPase activity, leading to increases in ICF K^+, a mechanism that counteracts the release of K^+ from muscle cells during exercise.[21] ECF pH also has a bearing on K^+ handling. The presence of mineral organic acids (where the acid anion is unable to diffuse into the cell) leads to increased cellular H^+ uptake in exchange for K^+ ions with consequent increases in ECF K^+. Organic acids (e.g., lactic acid and ketone bodies) are more able to diffuse across cellular membranes and H^+/K^+ exchange is much less. Hyperkalemia may be observed in the setting of organic acidemia resulting from alternative mechanisms, such as insulin deficiency and osmotic drag in diabetic ketoacidosis or a failure of ATP production for Na^+/K^+ATPase in situations typified by anaerobic metabolism and lactic acidosis. Other factors that may influence ECF to ICF K^+ balance include aldosterone (which at high levels may induce intracellular K^+ shift, beyond its renal effects), hyperosmolar states (solvent drag of K^+ along with water efflux), and digoxin (inactivates Na^+/K^+ATPase and may cause hyperkalemia).

Chronic K^+ distribution involves renal mechanisms. K^+ is freely filtered at the glomerulus, then undergoes extensive unregulated reabsorption along the proximal tubule, with only 10% to 15% reaching the distal nephron, where its reabsorption or secretion is tightly controlled. This occurs predominantly in two cell types found in the collecting ducts.

Principal Cells. The principal cells have the ability to secrete K^+ under the electrochemical gradients set up by basal Na^+/K^+ATPases, which maintain low intracellular Na^+ concentrations (aiding Na^+ reabsorption from the tubule via Na^+ channels) and high intracellular K^+ concentrations (favoring K^+ secretion into the tubule via K^+ channels). Principal cell behavior is influenced by the following:

- Aldosterone, synthesized and released by the adrenal glands in response to raised K^+ concentrations. This mineralocorticoid increases the synthesis and activity of both basal Na^+/K^+ATPases and luminal K^+ channels to drive urinary K^+ secretion.
- Tubular Na^+ delivery. Increased distal tubular Na^+ content leads to a steeper Na^+ concentration gradient and increased principal cell reabsorption of Na^+. To maintain electroneutrality of the tubular fluid, K^+ efflux into the tubule increases; this is partly responsible for the hypokalemia associated with diuretics that increase delivery of Na^+ to the cortical collecting ducts (thiazides and loop diuretics). In contrast, amiloride blocks the principal cell luminal Na^+ channel and therefore does not affect K^+ efflux here.

Intercalated cells. In addition to basal Na^+/K^+ATPases, these cells have luminal H^+/K^+ATPases that excrete one hydrogen into the tubule for every K^+ reabsorbed. Low K^+ settings lead to up-regulation of this luminal antiporter, reabsorbing more K^+ at the expense of renal acid loss.

In addition to mechanisms involving aldosterone in a feedback loop, it is likely that feed-forward mechanisms also exist to rapidly modulate renal K^+ handling when K^+ is sensed in the GI system, even before plasma K^+ levels rise.[20]

Calcium Physiology. Beyond its role in bone structure, where 98% of body Ca^{2+} is stored, Ca^{2+} is one of the body's most important intracellular second messengers, playing a key role in muscular contraction, neuromuscular transmission, cell division and movement, and oxidative pathways. Intracellular Ca^{2+} entry may have direct effects—for example, leading to neurotransmitter release or inducing further large-scale release of Ca^{2+} from intracellular stores (Ca^{2+}-induced Ca^{2+} release), in cardiac and skeletal muscle contraction. A large ECF-to-ICF gradient of ionized Ca^{2+} is maintained by ATPases, and cytoplasmic free Ca^{2+} levels are kept low by pumping into the sarcoplasmic reticulum. Increases in cytoplasmic free Ca^{2+} concentration occurring as a result of cellular energetic failure and impaired Ca^{2+} transport are a key mediator of cell death pathways.[22] Ca^{2+} also plays a key role in coagulation by linking coagulation factors to the negatively

charged plasma membrane of activated platelets (see also Chapter 62).

Homeostatic mechanisms maintain serum Ca^{2+} concentrations between 4.5 and 5 mEq/L (8.5 to 10.5 mg/dL), largely under the influence of vitamin D and parathyroid hormone (PTH). Ionized Ca^{2+} is sensed by the extracellular domain of a G-coupled receptor expressed on parathyroid cells (the Ca^{2+}/Mg^{2+}-sensing receptor), inhibiting PTH release.[23] When ionized Ca^{2+} levels decrease, PTH is rapidly released with the following actions:

- Stimulates osteoclast bone resorption, releasing Ca^{2+} into the ECF
- Stimulates distal tubule calcium reabsorption
- Stimulates the renal conversion of 25-(OH)-vitamin D to 1,25-$(OH)_2$-vitamin D (calcitriol, the most active vitamin D metabolite)

The manufacture of active vitamin D involves cholecalciferol formation in the skin during exposure to ultraviolet light, which then undergoes hepatic hydroxylation to 25-hydroxy-calciferol, then renal hydroxylation under the influence of PTH to 1,25-dihydroxycalciferol (calcitriol). As with PTH, this stimulates osteoclastic bone resorption and additionally stimulates absorption of Ca^{2+} from the GI tract. Other hormones, such as calcitonin[24] and stanniocalcin,[25] have Ca^{2+}-lowering effects that are not necessary for normal long-term maintenance of normal ECF Ca^{2+} content. For example, Ca^{2+} levels remain normal after loss of the calcitonin-secreting parafollicular (C-) cells during thyroidectomy.

Ca^{2+} homeostasis is interlinked with that of other anions. In particular, magnesium is also able to modulate PTH levels, and hypocalcemia and hypomagnesemia frequently coexist. The homeostasis of PO_4^{3-} is effectively the converse of Ca^{2+} (e.g., renal hydroxylation of vitamin D is inhibited by hyperphosphatemia), and in health the (calcium × phosphate) product is kept relatively stable. An increase in the (calcium × phosphate) product may be seen in advanced chronic kidney disease and is associated with ectopic bone deposition.

Approximately 50% of circulating Ca^{2+} is in the biologically active ionized form (normal range 2 to 2.5 mEq/L), 40% bound to proteins, predominantly albumin and globulins, and 10% complexed to anions such as HCO_3^-, citrate, sulfate, PO_4^{3-}, and lactate. Hypoalbuminemia decreases the total serum Ca^{2+} but has less effect on the biologically important ionized form. To calculate the corrected total Ca^{2+} concentration, 0.8 mg/dL is added per 1 g/dL decrease in albumin concentration below 4 g/dL. The degree of albumin-protein binding is affected by pH, with acidemia reducing protein binding and increasing the ionized fraction. Ionized Ca^{2+} rises by approximately 0.1 mEq/L per 0.1 decrease in pH.[26] Given the approximate nature of estimates of corrected total Ca^{2+}, biologically active ionized Ca^{2+} should be measured when possible, by using ion-specific electrodes. Specimens should ideally be taken without tourniquet (uncuffed), because local acidosis increases the ionized fraction.

Magnesium Physiology. Mg^{2+} has a diverse range of cellular actions, including modulation of ion channel activity and as an essential component of ATP production and hydrolysis. It is primarily an intracellular anion, although most is sequestered within organelles, bound to phospholipids, proteins, and nucleic acids. Free ionized Mg^{2+} levels within the cytoplasm and ECF are therefore low (0.8 to 1.2 mM), and chemical concentration gradients are much less than for other anions. Of total body Mg^{2+}, 50% is within bone, 20% within muscle, and the rest in liver, heart, and other tissues. Only 1% is within the ECF, and normal plasma levels may be maintained in the face of total body Mg^{2+} depletion. Within the plasma, total Mg^{2+} concentration is 1.5 to 2.1 mEq/L, of which approximately 25% is protein (mostly albumin) bound, 65% is in the biologically active ionized form, and the remainder is complexed to phosphates, citrates, and other anions.[27] Measurement of ionized Mg^{2+} can be performed, although correction is required for interference from Ca^{2+} ions.[28] The key roles of Mg^{2+} (Table 59-5) are underlined by its diverse range of clinical applications when administered exogenously and stem from the following three main cellular actions:

1. Energy metabolism: Mg^{2+} is required for ATP phosphorylation reactions, interacting with the outer two PO_4^{3-} groups of ATP. Intracellular Mg^{2+} deficiency therefore impairs any enzyme systems using high-energy PO_4^{3-} bonds, such as glucose metabolism.[27]
2. Nucleotide and protein production: Mg^{2+} acts as a cofactor in every step of DNA transcription and replication and translation of messenger RNA (mRNA).
3. Ion transport: By supporting the activity of ion-pumping ATPases, Mg^{2+} helps maintain normal transmembrane electrochemical gradients, effectively stabilizing cell membranes and organelles. In addition, effects on ion channels underlie one of the core functions of Mg^{2+}, namely physiologic competitive antagonism of Ca^{2+}. This is mediated through inhibition of L-type Ca^{2+} channels and extracellular local modification of membrane potential, preventing the intracytoplasmic influx of Ca^{2+} from both the ECF and within intracellular sarcoplasmic reticulum stores. Mg^{2+} also effectively antagonizes *N*-methyl-D-aspartate (NMDA) receptors within the central nervous system, reducing Ca^{2+} entry by specific ion channels. These effects result in inhibition of a diverse array of excitable tissue cellular actions, including neurotransmitter release, muscular contraction, cardiac pacemaker and action potential activity, and pain signal transmission.

Mg^{2+} is absorbed from the GI tract by a saturable transport system and passive diffusion, in quantities inversely proportional to the amount ingested. Excretion is via the GI tract (~60% of the ingested amount) and kidneys. Seventy-five percent is freely filtered at the glomerulus, and proximal tubule reabsorption is minimal, with 60% to 70% being reabsorbed at the thick ascending loop of Henle and 10% reabsorbed under regulation in the distal tubule. The regulation of total body Mg^{2+} levels by GI uptake and control of renal excretion is not under the control of a well-defined hormonal feedback loop. Although many factors can influence Mg^{2+} reabsorption (particularly PTH but also calcitonin, glucagon, acid-base

TABLE 59-5 PHYSIOLOGIC ROLES OF MAGNESIUM

System	Effect	Mechanism and Clinical Relevance
Neurologic	Reduction in pain transmission	NMDA antagonism. Mg^{2+} treatment provides effective perioperative analgesia.[236]
	Reduces neuromuscular transmission	Inhibition of neuronal Ca^{2+} influx reduces neuromuscular junction ACh release (and motor end-plate sensitivity to ACh). Hypermagnesemia potentiates the effects of neuromuscular blockade.
	Sympatholysis	Inhibition of neuronal Ca^{2+} influx reduces catecholamine release from adrenal medulla and adrenergic nerve endings. Pharmacologic use of Mg^{2+} in obtunding pressor response to intubation or during surgery for pheochromocytoma.
	Anticonvulsant	Mechanism may relate to NMDA antagonism or cerebral arteriolar vasodilation, possible mechanisms for its efficacy in eclampsia, in which vasospasm has been observed.[29]
	Cortical depression at high levels	
Cardiovascular	Vasodilation	Predominantly arteriolar, because of inhibition of Ca^{2+} influx–mediated vascular smooth muscle contraction. Mg^{2+} administration typically leads to a minor reflex increase in inotropy despite the direct action of Mg^{2+} on reducing cardiac contractility.[237]
	Antiarrhythmic effects	Mixed class IV (Ca^{2+} channel inhibition) and weak class I (Na^{+} channel inhibition) effects. Increases atrioventricular nodal conduction time and refractory periods, suppresses accessory pathway transmission, and inhibits early and delayed afterdepolarizations. Clinical use is in supraventricular tachycardias, atrial fibrillation rate control and postoperative prophylaxis, and tachyarrhythmias associated with dyskalemia, digoxin, bupivacaine, or amitriptyline.[29]
	Improved myocardial O_2 supply-to-demand ratio	Coronary vasodilation in combination with reductions in heart rate and contractility; however, no clear evidence of benefit in the setting of acute myocardial infarction.
Respiratory	Bronchodilation	Smooth muscle relaxation. Pharmacologic use of Mg^{2+} is in acute bronchospasm.
Renal	Renal vasodilation and diuresis	Ca^{2+} antagonism–related smooth muscle relaxation
Immune	Antiinflammatory	Pharmacologic doses of magnesium sulfate reduce monocyte inflammatory cytokine production.[238]
	Adaptive immunity	Mg^{2+} is required as a second messenger during T-lymphocyte activation.[239]
Obstetric	Tocolysis	May be due to smooth muscle relaxation

ACh, Acetylcholine; *NMDA, N*-methyl-D-aspartate.

balance, Ca^{2+} and K^{+} levels), the main determinant is the plasma Mg^{2+} concentration, sensed by Ca^{2+}/Mg^{2+}-sensor receptors present on the basal aspect of thick ascending loop cells. Other influences may alter the intracellular-extracellular balance of magnesium distribution. Catecholamines, acting by both α-adrenoreceptors and β-adrenoreceptors, and glucagon lead to extrusion of magnesium from intracellular stores. Although experimental models have shown that adrenergic stimulation may increase serum Mg^{2+} concentrations, decreases in serum Mg^{2+} concentrations actually occur after stressors such as cardiac, orthopedic, and abdominal surgery, trauma, burns, and sepsis.[27, 29] This may be due to a later phase of catecholamine-driven cellular uptake after the initial Mg^{2+} efflux.[30]

Phosphate Physiology. PO_4^{3-} is the most abundant intracellular anion and helps form some of the most important biologic molecules, including ATP, DNA, and RNA, membrane phospholipids, 2,3-diphosphoglycerate (2,3-DPG), and hydroxyapatite in bone. PO_4^{3-} is therefore required for energy metabolism, cellular signaling through phosphorylation reactions, cellular replication and protein synthesis, membrane integrity, and O_2 delivery. In addition, the PO_4^{3-} buffer system is one of the key intracellular buffers. Of total body phosphorus, 80% to 90% is stored in bone, with the remainder in the intracellular (soft tissues and erythrocytes) and extracellular fluid compartments.[31] Normal plasma inorganic phosphates are maintained at 3 to 5 mg/dL, and at normal pH 80% exists in the divalent (HPO_4^{2-}) rather than monovalent ($H_2PO_4^{-}$) form. Plasma phosphates also include lipid phosphates and organic ester phosphates. Most intracellular PO_4^{3-} is organic.[18]

The typical daily intake of PO_4^{3-} (~1 g) outweighs metabolic requirements, yet 70% is absorbed, leading to postprandial increases in serum PO_4^{3-} levels that are rapidly dealt with by increased renal excretion. GI uptake occurs predominantly by paracellular diffusion and is unregulated unless PO_4^{3-} ingestion is reduced, when vitamin D and PTH-stimulated active transport intervene.[32,33] Plasma inorganic PO_4^{3-} is freely filtered at the glomerulus, 80% of which is reabsorbed in the proximal tubule and a smaller amount in the distal tubule. Proximal tubule reabsorption is via Na^{+}-dependent cotransporters, the expression and activity of which are under the influence of PTH and PO_4^{3-} intake.

The regulation of normal PO_4^{3-} levels is mediated primarily by the PTH and vitamin D systems. Low plasma PO_4^{3-} levels stimulate 1-hydroxylase activity, with the formation of active vitamin D (1,25-dihydroxycalciferol), which increases GI and renal PO_4^{3-} absorption. Conversely, PTH release (stimulated by reduced plasma Ca^{2+}) reduces renal PO_4^{3-} reabsorption. PO_4^{3-} plasma levels also may be reduced in the short term by cellular uptake in response to dopamine and adrenergic activity and alkalosis and intestinal factors (phosphatonins) released in response to increased intestinal luminal PO_4^{3-}.[31]

Chloride Physiology. As the second most abundant electrolyte in the extracellular compartment, Cl^{-} has a

key role in the maintenance of plasma osmolality, preservation of electrical neutrality, and acid-base status (explained by the Stewart model, see later discussion). Normal plasma values are 97 to 107 mEq/L; Cl^- is therefore responsible for nearly a third of plasma osmolality and two thirds of plasma negative charge.[34] Most Cl^- intake is derived from dietary NaCl, and the GI tract absorbs and secretes large amounts of Cl^-, primarily as gastric hydrochloric acid, but also throughout the intestinal lumen. This cellular Cl^- secretion leads to paracellular movement of Na^+ into the lumen, with water moving down its osmotic gradient to form GI secretions. Cl^- excretion is primarily renal, largely in the proximal tubule by passive reabsorption or cotransport. More regulated control of Cl^- excretion is performed in the intercalated cells of the distal nephron under the influence of plasma acid-base balance—for example, by exchange of HCO_3^- for Cl^-.

Acid-Base Disturbances and Fluid Therapy

Acid-base balance in general is discussed in Chapter 60; however, the two key areas in which intravascular fluid therapy may affect acid-base balance are iatrogenic acidosis caused by the administration of Cl^--rich fluids and administration of sodium bicarbonate to correct acidosis. In summary, the interpretation of acid-base balance can be viewed in three main ways: by the Henderson-Hasselbach equation, by anion gap, or by Stewart's strong ion model. The Henderson-Hasselbach equation represents the HCO_3^- buffer system and has plasma HCO_3^- concentration as an independent determinant of plasma pH (see Chapter 60). The anion gap model is consistent with the Henderson-Hasselbach equation, because it places changes in plasma HCO_3^- at the core of plasma acid-base balance. It represents a simple method for differentiating causes of metabolic acidosis and is defined as the difference between the most abundant measured cation and anion concentrations in the plasma ($[Na^+] + [K^+]$) – ($[Cl^-] + [HCO_3^-]$). The normal anion gap is 4 to 11 mEq/L, and this difference is represented by "unmeasured" anions (PO_4^{3-}, sulfate, and anionic proteins). In the presence of excess organic acids (e.g., lactic acid or ketoacid), the accumulation of unmeasured anions is accompanied by a reduction in HCO_3^- to buffer the excess H^+ ions, leading to an increase in the anion gap. In cases in which Cl^- is administered, even if HCO_3^- falls, the anion gap will remain normal.[35]

Stewart's model of acid-base balance has a different approach and proposes that plasma pH is dependent on the following three independent variables:

1. P_{CO_2} (the plasma CO_2 tension)
2. A_{tot}, the total plasma concentration of all nonvolatile buffers (albumin, globulins, and PO_4^{3-})
3. Strong ion difference (SID), the difference between the total charge of plasma strong cations (Na^+, K^+, Mg^{2+}, and Ca^{2+}) and strong anions (Cl^-, lactate, sulfate, and others). In a more simplified approach, apparent SID is defined as ($[Na^+] + [K^+]$) – ($[Cl^-]$ + [lactate]). Normal plasma SID is approximately 42 mEq/L, and reductions in SID will lead to a fall in plasma pH.

The Stewart model has caused some controversy by representing HCO_3^- as a dependent variable,[36] but it has utility in explaining acid-base disturbances caused by fluid administration.[37]

Hyperchloremic Acidosis. Administration of fluid with a Cl^- concentration higher than that of plasma will in sufficient quantities (e.g., 30 mL/kg/hr of 0.9% saline) cause a metabolic acidosis because of the Cl^- content.[38] This hyperchloremic acidosis may be explained by the Henderson-Hasselbach model of acidosis, in which saline infusion causes dilution of HCO_3^- and a resultant base deficit, or by the Stewart model. Here, the increasing plasma Cl^- concentration reduces apparent SID and therefore reduces plasma pH. The SID of completely ionized saline is zero; therefore, its infusion progressively dilutes the normal plasma SID. Similar changes are not seen with solutions containing other anions, which are metabolized after infusion, such as lactated Ringer solution. Although in vitro as an electroneutral solution, it also has a SID of zero; after administration the lactate undergoes metabolism in patients with intact hepatic function, giving it an effective in vivo SID of approximately 29 mEq/L. This is slightly less than the plasma SID and is enough to counteract any alkalosis caused by dilution of A_{tot}.

Saline-induced hyperchloremic acidosis is recognized to have a variety of potentially deleterious physiologic effects. These include renal vasoconstriction, reduced GFR, reduced renin activity (shown in animal models[39-41]), and reduced renal cortical perfusion (in healthy volunteers[42]). Coagulopathy and GI dysfunction also have been suggested.[43] However, it is not clear that acidosis purely attributable to iatrogenic hyperchloremia leads to clinically important morbidity. A meta-analysis of studies comparing saline with balanced perioperative fluid regimens confirmed the presence of hyperchloremia and acidosis postoperatively in the saline groups, but typically these biochemical abnormalities had cleared by the first or second postoperative day.[38] No overall differences in markers of kidney injury or need for renal replacement therapy were found, nor in other morbidities such as clinically important coagulopathy or GI symptoms. However, the available trials were relatively small, and higher risk surgical groups (those with preexisting impairment of acid-base status or emergency and major surgery) were underrepresented. Interestingly, in one trial of patients undergoing renal transplant, saline administration was associated with significant hyperkalemia, presumably caused by cellular K^+ extrusion resulting from extracellular acidosis.[44] It is therefore possible that the acidosis observed as a result of saline administration has a greater clinical effect on a selected high-risk group; further focused large-scale clinical trials are required.

Bicarbonate Administration. The administration of IV $NaHCO_3$ to treat metabolic acidosis should be reserved for the emergency treatment of select conditions, including severe hyperkalemia and arrhythmias associated with tricyclic antidepressant overdose. In many other situations, clinical benefit is not apparent, a finding that highlights an important pathophysiologic concept. Acidosis

in itself may not be physiologically deleterious; indeed it is a normal event during strenuous exercise, in which it may aid O_2 offloading to tissues. Rather, perhaps acidosis serves as a marker for the severity of underlying disease processes, such as hypoxia, ischemia, or mitochondrial dysfunction, which cause morbidity without adequate correction.[43] HCO_3^- administration also has the following negative effects[18]:

1. Carbon dioxide production. Most of the HCO_3^- administered is converted to CO_2, with two important consequences. First, excess CO_2 requires excretion by hyperventilation. Converted HCO_3^- of 100 mEq represents an excess of 2.24 L of CO_2 to be exhaled, which may present a significant physiologic challenge to critically ill patients with preexisting ventilatory impairment. Second, the excess CO_2 may diffuse into the intracellular space, aggravating intracellular acidosis, although this is disputed.[18]
2. IV HCO_3^- brings a significant Na^+ content and therefore osmotic load. This may lead to hyperosmolar hypernatremia, ECF expansion, and volume overload.
3. If renal HCO_3^- distribution is impaired, there may be an "overshoot" toward metabolic alkalosis once the underlying disease process causing the initial acidosis is resolved.

In situations in which HCO_3^- administration is required, the total dose required to correct the base deficit can be calculated using the equation:

$$\text{Dose (mEq)} = 0.3 \times \text{weight (kg)} \times \text{base deficit (mEq/L)} \qquad (5)$$

although half this dose is usually given, because of the problems outlined before, and treatment should stop once the pH rises above 7.2.

FLUID PHARMACOLOGY

Given the diverse range of physiologic effects of administered fluids, and the potentially large volumes that can be administered perioperatively, they should be considered as drugs with specific indications, cautions, dose ranges, and side effects. Many of the fluids available currently were developed several decades ago and entered clinical practice without rigorous analysis of their clinical benefits or knowledge of their effects at an organ or cellular level. Newer colloid solutions have been approved by regulatory authorities and entered widespread clinical usage based on relatively small trials of efficacy. In some cases, safety concerns such as the impact of colloid-related renal dysfunction have been highlighted only by much later adequately powered trials.[45] Furthermore, lack of knowledge of fluid composition is common among the clinicians who are most often responsible for postoperative fluid administration, which may be linked to poor prescribing practices and increased postoperative morbidity.[46-48] The composition of available fluids is shown in Table 59-6, although not all fluids are available in all countries. This table includes an example of renal dialysate fluid, which in special circumstances may be suitable for IV infusion.

Crystalloids

Crystalloids are solutions of electrolytes in water. They may be classified by their tonicity after infusion or their overall composition; crystalloids containing a range of electrolytes also found in plasma and a buffer such as lactate or acetate may be referred to as balanced solutions. Crystalloids are indicated for replacement of free water and electrolytes but also may be used for volume expansion. Conventional concepts of fluid compartments dictate that infused electrolytes will distribute freely throughout the ECF, that water will follow down osmotic gradients, and that the net result is a distribution of infused crystalloids throughout the entire ECF, with only 20% remaining in the intravascular compartment. This is challenged by large clinical trials and current knowledge of microvascular fluid handling (see section on vascular endothelium), which suggest that isotonic crystalloids may have a larger intravascular volume expanding effect than this, particularly in patients with low capillary hydrostatic pressures. The study of volume kinetics has quantified the redistribution of crystalloids from the central (intravascular) volume to the larger peripheral (total extracellular) volume. Perhaps up to 70% of a crystalloid infusion remains in the intravascular compartment at the end of a 20-minute continuous infusion, decreasing to 50% after 30 minutes.[4] Nevertheless, more fluid will ultimately be filtered out of the capillary with crystalloids than with colloids, owing to colloids' effects on oncotic pressure, and patients resuscitated with crystalloids have a more positive fluid balance for the same volume expansion effect.[49] Tissue edema may increase in compliant tissues such as the lung, gut, and soft tissues, particularly when crystalloid solutions are infused into normovolemic subjects. Large-volume crystalloid infusion also may be associated with a hypercoagulable state caused by dilution of circulating anticoagulant factors; the clinical significance of this is not currently known.[50]

Saline Solutions

0.9% Sodium Chloride. One of the most commonly administered crystalloids is 0.9% NaCl solution, yet it is not clear historically how it entered routine clinical practice. Although many of the crystalloids being examined for in vivo clinical usage during the 1800s had a composition much closer to that of plasma, Hamburger ascertained using in vitro red cell lysis experiments that 0.9% was the NaCl concentration that was isotonic with human plasma. Therefore, 0.9% saline was not initially developed with the aim of in vivo administration, yet has entered widespread clinical use despite having a Na^+ and Cl^- concentration far in excess of that of plasma.[51] Its osmolarity, calculated as the sum of the solutes present, is slightly higher than that of plasma, although the osmolality (measured by freezing point depression) is 285 mOsm/kg, very similar to that of plasma. This discrepancy reflects the nonideal behavior of solutions. Both ions present remain in the ECF after infusion, and it can be said to be isotonic—that is, of a similar *effective osmolarity* to that of plasma with respect to the cell membrane.

A 2-L infusion of 0.9% NaCl leads to an increase in ECF volume, dilutional decrease in hematocrit and albumin, increase in Cl^- and K^+ concentrations, and decrease in

TABLE 59-6 **COMPOSITION OF FLUIDS AVAILABLE FOR INTRAVENOUS ADMINISTRATION***

Fluid	Sodium	Potassium	Chloride	Calcium	Magnesium	Bicarbonate	Lactate
Plasma	140	5	100	4.4	2	24	1
0.9% NaCl	154	—	154	—	—	—	—
1.8% NaCl	308	—	308	—	—	—	—
0.45% NaCl	77	—	77	—	—	—	—
5% dextrose	—	—	—	—	—	—	—
5% dextrose/0.45% NaCl	77	—	77	—	—	—	—
4% dextrose/0.18% NaCl	33	—	33	—	—	—	—
Lactated Ringer solution (U.S. composition)	130	4	109	3	—	—	28
5% dextrose in lactated Ringer solution	130	4	109	3	—	—	28
Hartmann solution/compound Na^+ lactate	131	5	111	4	—	—	29
Plasma-Lyte 148/Normosol-R	140	5	98	—	3	—	—
Plasma-Lyte 56 and 5% dextrose/ Normosol M with 5% dextrose	40	13	40	—	3	—	—
Plasma-Lyte A pH 7.4	140	5	98	—	3	—	—
Sterofundin	140	4	127	5	2	—	—
Plasma-Lyte R	140	10	103	5	3	—	8
Hemosol	140	—	109.5	3.5	1	32	3
4%-5% albumin	†	—	†	—	—	—	—
20% albumin	†	—	†	—	—	—	—
Plasmanate: Plasma protein fraction (human) 5%	145	0.25	100	—	—	—	—
Gelofusine (4%)	154	—	125	—	—	—	—
Plasmion/Geloplasma (3%)	150	5	100	—	3	—	30
Isoplex (4%)	145	4	105	—	1.8	—	25
Gelaspan (4%)	151	4	103	2	2	—	—
Haemaccel (polygeline)	145	5.1	145	12.5	—	—	—
Voluven: Waxy maize HES 6% (130/0.4)	154	—	154	—	—	—	—
Venofundin: Potato HES 6% (130/0.42)	154	—	154	—	—	—	—
Hetastarch: Waxy maize HES 6% (670/0.75)	154	—	154	—	—	—	—
Hextend: Waxy maize HES 6% (670/0.75)	143	3	124	5	1	—	28
Pentaspan: Pentastarch 10%	154	—	154	—	—	—	—
Volulyte: Waxy maize HES 6% (130/0.4)	137	4	110	—	3	—	—
Plasma volume: Potato HES 6% (130/0.42)	130	5.4	112	1.8	2	—	—
Tetraspan: Potato HES 6% (130/0.42)	140	4	118	5	2	—	—
10% Dextran 40	—	—	—	—	—	—	—

HES, Hydroxyethyl starch; *kDa,* kilodaltons; *MWw,* weight-averaged mean molecular weight. Plasma-Lyte, PlasmaVolume, Baxter International, Deerfield, Ill; Gelofusine, Gelaspan, Venofundin, Sterofundin, and Tetraspan, B Braun (Melsungen, Germany); Plasmion, Geloplasma, Voluven, and Volulyte, Fresenius-Kabi, Bad Homburg, Germany; Hextend, BioTime, Berkeley, Calif; Pentaspan from Bristol-Myers Squibb, Canada; Hemosol, Hosptal, Rugby, U.K.; Isoplex Beacon, Kent, U.K.; Normosol, Hospira, Lake Forest, Ill.

*Presented as mEq/L, except where stated.

†The NaCl content and osmolarity of albumin solutions varies dependent on formulation. Osmolarity values are calculated in vitro.

plasma HCO_3^-.[42] The expansion of the ECF is more persistent than with balanced crystalloid solutions; although both fluids induce diuresis, this has a later onset and is less extensive with isotonic saline (see section on acute disturbances in circulating volume), and the excess salt and water load may take multiple days for even a healthy subject to excrete.[12]

Infusion of saline leads to a hyperchloremic metabolic acidosis and reduced renal perfusion. Although important differences in clinical outcomes in the surgical populations are not clear,[38] in the wider critical care population an increased incidence of kidney injury and requirement for renal replacement therapy are seen when compared with the use of lower Cl^- solutions.[52] In healthy volunteers, the large-volume (50 mL/kg) infusion of 0.9% NaCl led to abdominal discomfort, nausea, and vomiting.

These side effects mean that the volume of saline administered perioperatively should be limited, unless there are compelling indications such as the following:

- Situations in which increased plasma Na^+ may be beneficial, such as in the presence of cerebral edema.
- Preexisting Na^+ or Cl^- total body depletion, such as gastric outlet obstruction (see later discussion). However, 0.9% NaCl is not suitable for the treatment of acute severe hyponatremia, because it has little effect on plasma Na^+ levels in this situation.

Hypertonic Saline. Solutions of 1.8%, 3%, and 7.5% NaCl are available. Their uses include the following:

- Plasma volume expansion: The hypertonic nature of these solutions draws water out of the intracellular

Acetate	Gluconate	Glucose (g/L)$^{-1}$	Other	Osmolarity	Notes	pH (in vitro)
—	—	—	—	285	SID 42	7.4
—	—	—	—	308	SID 0	6.0
—	—	—	—	616		
—	—	—		154		
—	—	50		252		4.5
—	—	50		406		4.0
—	—	40		283		
—	—	—		273		6.5
—	—	50		525		5.0
—	—	—		275	In vivo SID 27	6.5
27	23	—	—	294		4-6.5
16	—	50		389 / 363		3.5-6
27	23	—	NaOH for pH	294		7.4
24	—	—	Maleate 5	309		5.1-5.9
47	—	—		312		
—	—	—			In vivo SID 33	
—	—	—	Stabilizer: octanoate (caprylate)	†		7.4
—	—	—	Stabilizer: octanoate (caprylate)	†		
—	—	—	88% human albumin, 12% α-/β-globulins		COP 20 mm Hg	7.4
—	—	—	MWw 30 kDa		Succinylated gelatin	
—	—	—	MWw 30 kDa		Succinylated gelatin	
—	—	—	MWw 30 kDa		Succinylated gelatin	
24	—	—	MWw 30 kDa			
—	—	—	MWw 35 kDa			
—	—	—		308		
—	—	—				
—	—	—		309		5.5
—	—	—				
—	—	—	MWw 264 kDa	326		5.0
34	—	—		287		
27	—	—				
24	5	—				
—	—	50		255		4.0

compartment and into the extracellular (including plasma) volume and may therefore achieve plasma volume expansion while minimizing the volume of fluid administered. Although it has not been studied extensively in the perioperative phase, use of hypertonic saline for trauma resuscitation, particularly in the prehospital phase, has been considered, with no convincing benefit. In fact, one large trial showed no improvement in outcome and was stopped early.[53]

- Correction of hypoosmolar hyponatremia (see later discussion).
- Treatment of increased intracranial pressure (see also Chapter 70). The increased plasma osmolality reduced cerebral edema and increased intracranial pressure. Hypertonic saline may be superior to mannitol in this regard.[54] However, as with its use in hypovolemic trauma, hypertonic saline used early in traumatic brain injury without knowledge of intracranial pressure is not beneficial in clinical trials.[55]

At NaCl concentration greater than 7.5%, these solutions may cause endothelial damage; indeed 11.7% NaCl may be used as a sclerosant agent and should therefore be administered into a central vein.

Balanced Crystalloid Solutions. Intravenous crystalloid solutions were initially used clinically for the management of cholera in 1832 by O'Shaughnessy and Latta and then further developed by others. Interestingly, Latta's early solutions were more closely matched to physiologic plasma composition than NaCl solutions, containing 134 mEq/L Na^+, 118 mEq/L Cl^-, and 16 mEq/L HCO_3^-.[51] However,

clinical interest in more balanced solutions waned until Hartmann used a lactated modification of Ringer solution for pediatric patients with acidosis associated with hypovolemia and liver and renal failure in 1932.[56] By this time, NaCl solutions were already in use for resuscitation from hemorrhage and trauma.[51]

Currently available balanced crystalloid solutions have lower overall osmolarity than 0.9% NaCl, with a lower Na^+ concentration and much lower Cl^- concentration (see Table 59-6). The reduction in anionic content is compensated for by the addition of stable organic anionic buffers such as lactate, gluconate, or acetate. The measured osmolality of balanced solutions (265 mOsm/kg) is slightly lower than that of plasma, and they are therefore mildly hypotonic. Fluid compartment distribution of balanced solutions is similar to that of other crystalloids. After administration, the buffer is metabolized to produce HCO_3^- in equimolar quantities by entry into the citric acid cycle. Lactate undergoes predominantly hepatic oxidation or gluconeogenesis to yield HCO_3^- at a maximum rate of approximately 200 mmol/hr.[57] Acetate is normally present in trace quantities in the plasma (0.2 mM), being rapidly oxidized by liver, muscle, and heart to yield HCO_3^- at a maximum turnover of 300 mmol/hr, beyond which zero-order kinetics intervene.[58] A small proportion may be converted to the ketone body acetoacetate. The metabolism of gluconate is less well characterized in terms of location and kinetics, but it is converted to glucose with subsequent entry into the citric acid cycle.[59] Although balanced crystalloids can be constituted with HCO_3^- as a main anion, this is limited by two factors. First, HCO_3^- reacts with water to form CO_2, which is able to diffuse out of most packaging materials. This has been addressed by some products, although availability is limited.[60,61] Second, the pH shift induced by the presence of HCO_3^- can lead to precipitation of Ca^{2+} (and Mg^{2+}) if present.

The excretion of the excess water and electrolyte load with balanced crystalloids is more rapid than with isotonic saline.[62] This is due to the transient decrease in plasma tonicity after infusion, which suppresses ADH secretion and allows diuresis in response to the increased intravascular circulating volume. Balanced crystalloids do not reduce plasma SID to the same degree as NaCl solutions and therefore do not cause an acidosis; HCO_3^- concentration is maintained or slightly elevated.

Some potential negative effects have been identified with balanced crystalloid solutions. Lactated Ringer solutions contain racemic (D- and L-) lactate, although D-lactate is only found in trace quantities in vivo. Concerns that large doses of D-lactate may be associated with encephalopathy and cardiac toxicity in patients with renal failure[63,64] have not been confirmed in human studies at plasma levels achievable by the use of racemic lactated Ringer solution; the metabolism of D-lactate appears to be nearly as rapid as that of L-lactate.[65] The reliance on hepatic metabolism of most of the infused lactate means that lactated solutions should be avoided in severe liver failure. Concerns over the effects of excess exogenous acetate have been raised by the well-recognized syndrome of acetate intolerance experienced by patients undergoing hemodialysis with acetate-based dialysate. The proinflammatory, myocardial depressant, vasodilatory, and hypoxemia-promoting effects of high acetate levels manifest as nausea, vomiting, headaches, and cardiovascular instability and have led to the removal of acetate from contemporary dialysis fluids.[58,66-70] Acetate turnover is limited in patients with end-stage kidney disease and by the presence of other substrates for oxidation—for example, during lactic acidosis or proteolysis. It is therefore possible that critically ill patients or those with advanced kidney disease may exhibit biochemical acetate intolerance, although this possibility has not been explored in patients receiving acetate-based balanced crystalloids. Unlike acetate, much less is known about the effects of increased gluconate levels, which occurs with the infusion of fluids containing this as an anion.[71] Indeed, this area requires investigation at a cellular, organ, and whole organism level, particularly because data in animal studies suggest poorer outcome and late increases in lactate in a hemorrhage model when acetate/gluconate-containing crystalloids are compared to lactated Ringer solution or isotonic saline for resuscitation.[72]

Dextrose Solutions. Dextrose solutions have the following two main indications in the perioperative setting:

1. As a source of free water: An infusion of 5% dextrose effectively represents administration of free water. In vitro osmolality is similar to that of plasma so that infusion does not lead to hemolysis, but soon after infusion the dextrose is taken up into cells in the presence of insulin, leaving free water. These solutions are therefore hypotonic with respect to the cell membrane and in excess can dilute plasma electrolytes and osmolality. They should therefore be used with care in the postoperative period, during which the relative syndrome of inappropriate secretion of antidiuretic hormone (SIADH) leads to water retention, increasing the risk for hyponatremia (see later discussion). Nevertheless, in carefully controlled volumes and with regular monitoring of serum electrolytes they are a useful source of free water for maintenance requirements postoperatively, particularly if combined with a low concentration of NaCl. Dextrose solutions are less suitable for intravascular plasma volume expansion, because water is able to move between all fluid compartments and a very small volume therefore remains in the intravascular space.
2. Source of metabolic substrate: Although the caloric content of 5% dextrose is inadequate to maintain nutritional requirements, higher concentrations are adequate as a metabolic substrate, such as 4000 kCal/L for 50% glucose. Glucose solutions also may be coadministered with IV insulin to patients with diabetes to reduce the risk for hypoglycemia, such as 10% dextrose at 75 mL/hr.

Colloids

Colloid is defined as large molecules or ultramicroscopic particles of a homogeneous noncrystalline substance dispersed in a second substance, typically isotonic saline, or a balanced crystalloid (see also Chapter 61). These particles cannot be separated out by filtration or centrifugation. Although not all solutions are available in all countries, those in production include semisynthetic colloids and

human plasma derivatives. Semisynthetic colloids have a range of molecular sizes (polydispersed) in contrast to human albumin solution, which contains more than 95% albumin molecules of a uniform size (monodispersed). Colloid molecules above 70 kDa are too large to pass through the endothelial glycocalyx and are excluded from the subglycocalyx layer, with their initial volume of distribution as the plasma (rather than the entire intravascular) volume (see discussion of vascular endothelium). In contrast to pure electrolyte solutions, colloids have a higher COP and minimize transcapillary filtration, particularly at low capillary hydrostatic pressures. This maximizes their potential intravascular plasma volume expansion effect. However, at normal or supranormal capillary pressures, hydrostatic pressure will be increased and transcapillary filtration will occur.[3] In addition, colloid molecules may be lost from circulation in several ways—by filtration across capillaries whose barrier function is impaired by glycocalyx shedding, endothelial cell pore formation in inflammation or other stressors, or both; by renal filtration of smaller colloid molecules; or by removal from the circulation by metabolism. Therefore, colloids have variable effective plasma half-lives, as outlined later. Colloids alter blood rheology, typically improving blood flow by hemodilution effects, reductions in plasma viscosity, and red cell aggregation effects.[50] In contrast to their beneficial effects, the introduction of a large dose of semisynthetic molecules (typically 40 to 60 g/L) to a complex physiologic system may bring a variety of undesired effects on the immune, coagulation, and renal systems. In an attempt to limit these toxicities, maximum recommend doses are produced for most colloids, but adverse effects may still occur with smaller administered doses. As the potential clinical relevance of toxicity is highlighted by large clinical trials, the use of colloids, at least in critical care, is increasingly cautious.[73] Whether these trials in critical care can be applied to the entire perioperative period is not established (also see Chapter 61).

Semisynthetic Colloids

Gelatins. Gelatins are derived from the hydrolysis of bovine collagen, with subsequent modification by succinylation (Gelofusine, B Braun, Bethlehem, Pa; Geloplasma, Fresenius, Waltham, Mass) or urea-linkage to form polygeline (Haemaccel, Piramal, Orchard Park, NY). These forms have a similar molecular weight (MW), but the succinylated version undergoes conformational change as a result of increased negative charges, such that it is a larger molecule. The wide range of MWs present means that much of an infused gelatin bolus will rapidly leave the circulation, predominantly by renal filtration. Despite this, a recent study suggests that 60 minutes after the end of infusion, 50% of the infused fluid volume remains in the intravascular space, similar to larger MW colloids.[74] Excretion is primarily by the renal route. In terms of negative effects, the gelatins have the least impact on clinically relevant hemostasis of all the semisynthetic colloids despite reductions in von Willebrand factor (vWF), factor VIIIc, and ex vivo clot strength,[75] but the highest estimated incidence of severe anaphylactic and anaphylactoid reactions (<0.35%).[50] The high Ca^{2+} content of Haemaccel is a contraindication to coadministration of citrated blood products in the same infusion set. No known cases of variant Creutzfeldt-Jakob disease transmission have occurred involving pharmaceutical gelatin preparations. Gelatins are commonly used in perioperative practice in Europe but are not approved by the U.S. Food and Drug Administration.

Hydroxyethyl Starches. Hydroxyethyl starches (HESs) are modified natural polymers of amylopectin derived from maize or potato (see also Chapter 61). Substitution of hydroxyethyl radicals onto glucose units prevents rapid in vivo hydrolysis by amylase, and the degree of substitution both in terms of hydroxyethyl substitutions per glucose unit (maximum three) and total number of glucose units with substitutions is a determinant of HES kinetics of elimination. The degree of substitution (DS) is expressed as the number of substituted glucose molecules present divided by the total number of glucose molecules present. An alternative measure of substitution is the molar substitution (MS) ratio, calculated as the total number of hydroxyethyl groups present divided by the quantity of glucose molecules. MS is used to define starches as hetastarches (MS 0.7), hexastarches (MS 0.6), pentastarches (MS 0.5), or tetrastarches (MS 0.4). The pattern of substitution may vary because hydroxyethylation can occur at carbon positions 2, 3, or 6 of the glucose unit. The substitution type is defined by the C2/C6 hydroxyethylation ratio, and a higher ratio leads to slower starch metabolism. Starches are also classified by in vitro MW into high MW (450 to 480 kDa), medium MW (200 kDa), and low MW (70 kDa). However, HES solutions are very polydispersed and the MW quoted is an average. Although the size of starch molecule is responsible for both the therapeutic volume effects and adverse side effects, this changes when infused; smaller HES molecules (<50 to 60 kDa) are rapidly excreted and larger molecules are hydrolyzed to form a greater number of smaller molecules at a rate depending on the degree of substitution and C2/C6 hydroxyethylation ratio. The in vivo MW is therefore smaller and has a narrower distribution.[76] Ongoing renal excretion accounts for the elimination of smaller HES molecules, with medium-sized molecules being excreted in the bile and feces. A proportion of larger molecules, particularly those resistant to hydrolysis, is taken up by the mononuclear phagocyte (reticuloendothelial) system, where they may persist for several weeks or more.[77] The prolonged metabolism of HES means that their plasma volume effects typically last longer than those of gelatins or crystalloids, with larger MW starches increasing intravascular volume by approximately 70% to 80% of the infused dose at 90 minutes.[78] Smaller MW starches with a low MS may have even larger volume effects as a result of the rapid initial metabolism with the formation of a large number of oncotically active molecules.[79] Yet studies in healthy human volunteer experiments suggest a similar volume effect to that of gelatins.[74] Also, starch-related side effects may be associated with adverse outcomes in critical illness (see also Chapter 61). Problems such as coagulopathy, accumulation, and renal dysfunction initially appeared to be related to larger MW starches, but now smaller tetrastarches are a concern as well. Despite this, study populations with critical illness, particularly sepsis, cannot be compared directly with elective perioperative patients. These trials should be interpreted with

caution when considering the relevance of HES to surgical patients. Nevertheless, the official recommendations against the use of HES are clearly negative.

Coagulation. As with other synthetic colloids, HES products affect coagulation through dilutional effects in the circulation and MW-dependent reductions in vWF, factor VIII, and clot strength. The effect is most likely to occur with larger MW or slowly degraded medium MW (200 kDa/MS 0.62 or 200 kDa/MS 0.5/C2:C6 13) HES preparations and larger amounts of perioperative blood loss. This clinical effect is less marked with more rapidly degraded medium and small MW starches.[50] In patients with sepsis, even lower MW HES is associated with an increased risk of bleeding and blood transfusion, but it is unclear whether this also occurs in the perioperative setting.[80,81]

Accumulation. The accumulation of HES molecules in the mononuclear phagocyte system and skin, liver, muscle, and gut is a dose-dependent effect that gradually decreases over time. However, the accumulation may persist for several years, and a larger degree of tissue deposition is associated with pruritus.[77]

Anaphylactoid Reactions. The estimated incidence of severe anaphylactoid or anaphylactic reactions with HES products is less than with other colloids (<0.06%).[50]

Renal Dysfunction. HES products with medium to high MW are associated with oliguria, increased creatinine, and acute kidney injury in critically ill patients with preexisting renal impairment.[6,82] Although newer solutions with low MW (130 kDa/MS 0.4) were initially thought to be safer in this respect, recent large-scale trials have shown a similar effect on the need for renal replacement therapy in severe sepsis, particularly when compared with balanced crystalloids.[80,81] A recent large trial in a mixed critical care population comparing HES with isotonic saline also reported an increase in renal replacement therapy with the starch solution. This study is more difficult to interpret given the potential renal effects of saline, and, as with previous studies, the possibility that patients were given study fluids after partial resuscitation had already been achieved.[49] Currently no similar data are available from large-scale studies on the intraoperative use of HES solutions, and a recent meta-analysis examining perioperative use of 6% HES concluded that although no increase in mortality or kidney injury was seen, the available evidence lacked statistical power to definitively answer this question.[83] Meanwhile, the use of starch-based colloids has been restricted or even completely suspended by regulatory authorities in both the United States and Europe (see also Chapter 61).

Dextrans. Dextrans are highly branched polysaccharide molecules produced by the bacterium *Leuconostoc mesenteroides* after conversion of sucrose in the growth medium by bacterial dextran sucrase (see also Chapter 61). The large MW dextrans produced undergo acid hydrolysis to yield smaller MW molecules, which are then separated by fractionation to produce a solution with a restricted range of MWs. Available dextrans have an average MW of 40 kDa or 70 kDa. As with other colloids, the polydispersal nature of dextran solutions means that a proportion of smaller MW molecules are present that are rapidly filtered at the glomerulus; 70% of a dextran dose is renally excreted within 24 hours. Higher MW molecules are excreted into the GI tract or taken up into the mononuclear phagocyte system, where they are degraded by endogenous dextranases.[50] Dextrans have a plasma volume effect similar to that of starches, with a duration of 6 to 12 hours. In addition to their use in volume expansion, dextran 40 may be used in microvascular surgery, where its dilutional effects on blood viscosity and anticoagulant effects (see later discussion) favor flow in the microcirculation. Overall, the use of dextrans is limited by their range of toxicities, as follows:

- Antithrombotic effect: This is particularly marked in lower MW dextrans and is mediated through a range of mechanisms, including red cell coating and inhibition of aggregation, factor VIIIc and vWF reductions, and impaired activity of factor VIII. Platelet aggregation is also inhibited. The result is clinically impaired hemostasis and increased perioperative blood loss.[75]
- Blood cross-matching: Dextrans coat the erythrocyte cell membrane and may interfere with blood type cross-matching.
- Anaphylactoid reactions: Dextrans have an intermediate risk for serious anaphylactic and anaphylactoid reactions (<0.28%). Preemptive treatment with dextran 1, a hapten inhibitor, may reduce this incidence to less than 0.0015%.[50]
- Renal dysfunction: Renal dysfunction resulting from osmotic nephrosis is recognized after low-MW dextran infusion,[84] although the true incidence of this phenomenon in perioperative patients is difficult to estimate because of the limited use of dextrans in contemporary practice.

Human Plasma Derivatives. The human plasma derivatives include human albumin solutions, plasma protein fractions, fresh frozen plasma, and immunoglobulin solution. Preparation techniques result in relatively purified solutions with the elimination of infective agents, although the theoretic risk for transmission of variant Creutzfeldt-Jakob disease remains, associated with bovine spongiform encephalopathy. One U.K. case of presumed prion transmission has been described in association with factor VIII transfusion, although without clinical manifestation.[85] The ongoing transmission risk has been mitigated by sourcing many plasma derivatives from non-U.K. sources. Solutions such as 5% albumin have a near-physiologic COP of 20 mm Hg and are used for volume expansion. Despite the association of hypoalbuminemia with worse outcomes from critical illness, the administration of exogenous albumin does not improve outcome in these situations. Early concerns that resuscitation with albumin may actually increase mortality in critical illness were not confirmed by a large controlled trial that found no difference in outcomes whether albumin or isotonic saline was used for resuscitation.[5] In this heterogeneous population, the albumin group required less fluid to attain similar endpoints (ratio 1:1.4), although in the subgroup of patients with trauma, and particularly brain injury, albumin may be associated with an increased incidence of mortality.[5,86] Conversely, in a subgroup analysis

of patients with sepsis, albumin administration trended toward a decreased frequency of mortality that was supported by a subsequent meta-analysis.[87]

CLINICAL FLUID AND ELECTROLYTE MANAGEMENT

Pathophysiologic Fluid Alterations in the Perioperative Phase

Before recommending practical approaches to administering fluid in the perioperative phase, it is important to consider the pathophysiologic processes that may occur perioperatively and affect not just the body's requirement for exogenous fluid and electrolytes but also the manner by which those fluids are distributed by the body. The patient may enter the perioperative phase with abnormalities of intravascular fluid volume and distribution. Subsequent trauma (including surgery) induces a range of evolutionarily conserved neurohumoral and inflammatory changes, termed the *stress response*, which may have a significant impact on fluid and electrolyte responses and distribution. When the stress response is of an appropriate magnitude and duration, it can be a beneficial process for recovery from trauma; however, it could become pathologic if it is either exaggerated or prolonged or presents a physiologic burden to patients with limited baseline physiologic reserves.

Preoperative. Patients may enter the perioperative phase with established derangements of fluid and electrolyte balance. Hepatic, renal, and cardiac dysfunction are all associated with disordered Na^+ distribution (see later discussion), which has profound secondary effects on ECF volume. Patients with oligoanuric end-stage renal disease depend on dialysis for fluid removal, and the timing of dialysis relative to surgery is critical. Chronic treatment with diuretics may also lead to electrolyte depletion. Depending on treatment, hypertensive patients may have a volume-contracted circulation, making them prone to marked intraoperative relative hypovolemia (see Chapter 39).

The effects of preoperative fasting also should be considered, although its influence on fluid balance has perhaps been overstated. Modern perioperative practice mandates cessation of oral fluids only 2 hours before elective surgery, and even overnight fasting results in a normal blood volume when measured using robust experimental techniques.[88] Conversely, bowel preparation can cause a weight loss of 1.5 to 1.7 kg[89,90] with a high water and K^+ content. The potentially deleterious effects of this should be limited by restricting bowel preparations when possible and compensating for fluid loss with the simultaneous IV infusion of 1 to 2 L of crystalloid with K^+ supplementation. This intervention improves hemodynamics and lowers serum creatinine.[90]

More severe disturbances of fluid and electrolyte balance can occur in patients presenting with acute disease requiring surgical intervention. This may be influenced by one or more of the following:

- Direct intravascular depletion resulting from bleeding.
- Loss of fluid from the GI tract. This results in ECF depletion and loss of electrolytes, depending on the site of loss. Excess gastric loss because of obstruction, vomiting, or excess nasogastric suction results in loss of Na^+, K^+, Cl^-, and acid. Loss of small bowel secretions results in high losses of Na^+, Cl^-, and HCO_3^- with lesser K^+ losses. Large bowel losses, such as in diarrhea, deplete large quantities of K^+ with lesser losses of Na^+ and HCO_3^-. Pathologic fluid sequestration within the bowel lumen may have similar effects without external signs of fluid loss.
- Inflammation-related redistribution from the intravascular to the extracellular compartment (see later discussion).
- Fluid sequestration in the physiologic third space, with edema, pleural effusions, and ascites.

Intraoperative. Many factors influence intraoperative fluid balance, such as the following:

- Altered distribution of intravascular volume. Vasodilation caused by anesthetics affects both the venous and arterial systems and may reduce cardiac preload and afterload. This reduction may be exacerbated by sympathetic blockade caused by central neuraxial blockade, and cardiac output also may be decreased by the negative inotropic effect of anesthetic drugs. The distribution of blood within the vascular system is also influenced by the differential blunting of autoregulatory responses within organ beds caused by anesthesia. Microcirculatory dysfunction related to the effects of anesthesia and the inflammatory response to surgery may result in impaired functional matching of local O_2 delivery with tissue O_2 requirements, which may not be responsive to intravascular fluid therapy.
- Direct loss of intravascular volume as a result of bleeding. The clinical manifestation of surgical blood loss may vary greatly depending on the volume and time course of the blood loss.
- Insensible losses. The opening of anatomic compartments leads to evaporative fluid loss from mucosal surfaces, although estimating the extent of this loss may be difficult. Humidity chamber studies indicate that the loss may be as little as 1 mL/kg/hr even during a major laparotomy with extensive bowel exposure.[91]
- Inflammation-related redistribution. Major surgery induces an inflammatory response that favors redistribution of fluid from the intravascular to the extracellular compartment. This typically manifests in the postoperative phase (see later discussion), although it may become clinically apparent intraoperatively during surgery of sufficient magnitude and duration.
- Renal output. The suppression of renal urine production is related to perioperative ADH secretion and may also be influenced by the effects of positive-pressure ventilation. Increased intrathoracic pressure reduces venous return and cardiac output, which combine with a variety of neurohumoral responses such as sympathetic activation and suppression of ANP release to decrease GFR and urine output.[92] As a result, intraoperative urine output may be small regardless of the volume of IV fluid administered.[93]

The early phase of the stress response is triggered during major surgery. Absolute or relative (redistributive) hypovolemia during the intraoperative phase invokes a range of conservative responses—described in the section on acute disturbances in circulating volume—that are aimed at redistributing blood away from the periphery and toward vital organs, and maintaining circulating volume by retaining salt and water. The tissue trauma of surgery also triggers a well-described inflammatory and immune response, and together these changes may persist into the postoperative phase. The inflammatory response elicited by tissue trauma may be aggravated by periods of hypotension and tissue hypoperfusion, as described in the following discussion.

Postoperative. As a result of the preoperative and intraoperative factors outlined previously, patients may start the postoperative phase with significant derangements of intravascular volume and fluid compartment distribution. The stress response triggered by surgery may have an ongoing influence on postoperative fluid balance.

Inflammation and Immune Response. Tissue injury leads to local vasodilation, increased endothelial permeability, and influx of leukocytes to the damaged area, with consequent production of proinflammatory cytokines for up to 72 hours, particularly interleukin-1 (IL-1), TNF-α, and IL-6. Cardiopulmonary bypass, extensive tissue trauma, or surgery in areas with subclinical preoperative inflammation, such as tumor or infection, may lead to a postoperative systemic inflammatory response syndrome (SIRS). An alternative trigger for SIRS is GI hypoperfusion. The physiologic response to hypovolemia is preservation of cardiac and brain perfusion at the expense of kidney, gut, and peripheral perfusion. The intestinal villi have a countercurrent blood supply that shunts blood away from the mucosa in this situation, leading to mucosal necrosis and further impairment of gut barrier function by luminal digestive enzymes and bacteria. This allows gut bacterial endotoxin to translocate into the systemic circulation, acting as a potent trigger for systemic inflammation.[94,95] The reactive O_2 species released on reperfusion of compromised bowel further aggravate the inflammatory cascade.

Systemic inflammation impairs endothelial barrier function through changes in endothelial cell phenotype, increases in endothelial large pores, and degradation of the endothelial glycocalyx.[2] Hypervolemia caused by excessive fluid infusion leads to the release of cardiac natriuretic peptides, which may further degrade the endothelial glycocalyx.[9,96] In severe cases, inflammation-related endothelial dysfunction leads to a capillary leak syndrome, with loss of water, electrolytes, and proteins into the interstitial space causing edema in the lungs, bowel, and connective tissue. Reduced plasma oncotic pressure facilitates ongoing capillary fluid filtration into the extravascular space and consequent hypovolemia.

Catabolic Metabolism. The response to tissue injury requires an increase in energy substrate delivery, particularly to leukocytes involved in the acute inflammatory and immune reaction. This metabolic shift is mediated by catecholamine and cortisol release and involves muscle protein catabolism, with associated hepatic gluconeogenesis, acute phase protein production, and increased substrate delivery to damaged tissues. An increase in basal metabolic rate and adequate circulating volume are required to meet the needs of increased fuel mobilization, processing, and delivery.

Regulation of Salt and Water Balance. As described in the section on physiologic control of overall fluid balance, ADH release is induced during surgery, leading to postoperative retention of water. This may be a direct result of the acute stress response, and IL-6 has been proposed as a key mediator.[97] In addition, periods of hypovolemia and hypotension further stimulate ADH release and activate the RAA system with further water and salt retention and amplified ADH production. This may lead to a temporary period of oliguria despite a restored circulating volume and the risk for postoperative fluid overload and hyponatremia or Na^+ overload depending on ongoing fluid infusions. Na^+ retention postoperatively is more pronounced in the hypercatabolic state after major surgery, as excess nitrogen competes with Na^+ for renal excretion.

In addition to these processes, fluid may be lost from the circulating volume as a result of rapid reaccumulation into third spaces drained intraoperatively (ascites or pleural effusions), by sequestration into the bowel lumen or through vomiting, nasogastric drainage, or stoma losses. Intravascular fluid distribution is also a dynamic situation postoperatively because of changes in vascular tone caused by rewarming, evolving epidural sympathetic blockade, or systemic inflammation.

Assessment and Treatment of Perioperative Fluid and Electrolyte Imbalance

Intravascular Volume. As a key variable influencing cardiac output (preload), and therefore tissue O_2 delivery, intravascular volume is at the core of adequate tissue perfusion. Although the assessment of intravascular volume is an important part of perioperative fluid therapy, it may be challenging. Clinical history suggesting abnormal volume status should be sought (see earlier discussion) and accompanied by frequent clinical examinations, although many of the conventional markers of volume status are not reliable when taken in isolation. Obvious hypovolemia may manifest with tachycardia, reduced pulse pressure, hypotension, and increased capillary refill time, but the abnormalities of these individual physiologic variables may have numerous causes in the perioperative phase. Conversely, loss of up to 25% of blood volume may not be accompanied by significant hemodynamic alterations in healthy patients.[98] Urine output, frequently taken as a measure of adequate end-organ perfusion, may also be reduced postoperatively, even in the presence of normal circulating volume, as a result of ADH and RAA activation. More invasive measures of intravascular volume also have limitations. Central venous pressure (CVP) is used as a marker of central venous volume, yet is clearly also influenced by venous compliance; CVP may be normal or high in venoconstricted states even when the absolute vascular volume is reduced (see also Chapter 45). Furthermore, the relationship between right-heart and left-heart filling pressures is not reliable in the presence of cardiopulmonary pathologic processes. Trends in CVP values over time may be a more useful marker, because static CVP readings are poorly predictive

of subsequent responses to intravascular fluid challenges.[99] Stroke volume (SV) and cardiac output may be measured using a variety of techniques (see also Chapter 45), and targeting these variables has been widely investigated in perioperative fluid management, as described later. Alternatively, the adequacy of tissue perfusion may be assessed at a whole organism level using blood lactate concentrations (which may also be elevated during reperfusion of ischemic tissue or in advanced liver failure), or mixed venous O_2 saturation, which identifies a mismatch between global O_2 delivery (DO_2) and O_2 usage (VO_2). Techniques used to assess the perfusion of individual organs have the potential to detect clinically occult hypovolemia affecting those tissue beds or surgical sites most at risk for hypoperfusion, such as the gut. These include near-infrared spectroscopy,[100] microdialysis,[101] and GI CO_2 and pH measurement. The latter technique is gastric tonometry and is based on the association between inadequate gut perfusion and mucosal hypercarbia and acidosis.[102] It may detect hypovolemia of a magnitude not detectable by changes in systemic blood lactate, SV, or other cardiovascular parameters[98] that is nevertheless associated with increased postoperative morbidity.[103] Despite some encouraging findings in early research studies, none of these monitors is currently in routine use for guiding perioperative hemodynamic therapy.

Both excessive and inadequate intravascular volume can have a range of adverse physiologic effects, and achieving the fine balance between the two is a key goal of perioperative fluid administration. Modest hypovolemia, through its effects on gut perfusion and stimulation of protective neurohumoral reflexes, may exacerbate the inflammatory and antidiuretic aspects of the surgical stress response. More severe hypovolemia reduces preload, cardiac output, and therefore DO_2. The result may be inadequate DO_2 to meet metabolic demands, with an increase in O_2 extraction ratio (reflected in reduced mixed venous O_2 saturation), progressing to inefficient anaerobic ATP production, if there is inadequate O_2 delivery to sustain mitochondrial oxidative phosphorylation. This situation may be aggravated by insufficient compensatory increases in cardiac output, impaired microvascular blood flow, or failure of cellular O_2 usage. Lactate is a byproduct of anaerobic metabolism and accumulates with a consequent metabolic acidosis. At its most extreme, ATP production to support normal cell functions in those tissues with the worst perfusion may be inadequate, leading to cell death and organ dysfunction. Inadequate global O_2 delivery has been associated with a range of postoperative morbidities and increased mortality and has been the target of numerous clinical trials. At an individual organ level, particular areas that have been manipulated surgically, such as tissue flaps and bowel anastomoses, may be susceptible to poor healing and failure when local perfusion is insufficient.

Hypervolemia also has adverse effects and is often an iatrogenic problem in the perioperative setting. Crystalloids or colloids administered when capillary hydrostatic pressures are normal or increased lead to increased capillary filtration of fluid into the interstitial space. If this exceeds the capacity of the lymphatics to return the excess fluid to the circulation, edema will develop in compliant tissues such as the lungs, muscle, and bowel. The effect is more pronounced if inflammation or deterioration of the glycocalyx reduces the endothelial barrier function opposing the passage of large molecules into the interstitium. The correction of salt and water overload is a slow process because of inefficient renal handling of excess Na^+ loads, and the effects of postoperative ADH secretion. Clinically significant edema contributes to postoperative GI dysfunction, although this is not well defined by small clinical trials.[104,105] Further potential effects of excessive intravascular fluid include reduced tissue oxygenation with impaired healing, pulmonary congestion predisposing to pulmonary infection, and increased myocardial work resulting from ventricular filling beyond the optimum portion of the Starling curve.[106] Side effects may occur that are attributable to the volume of a particular fluid given, such as hypercoagulability or hypocoagulability, hyperchloremic acidosis, or renal dysfunction. A positive fluid balance and weight gain in the early perioperative period increases postoperative morbidity.[107,108]

Electrolyte Imbalance

Sodium Disorders

Hyponatremia. Hyponatremia may be present preoperatively, develop as a consequence of perioperative events, or both. It is classified as mild (130 to 134 mEq/L), moderate (120 to 130 mEq/L), or severe (<120 mEq/L). Moderate-to-severe hyponatremia, particularly of acute onset, is associated with significant perioperative morbidity.

Causes. Assessment of serum osmolality, TBW status, and urinary Na^+ concentration is vital for the accurate diagnosis of the underlying cause of hyponatremia.[109,110] A diagnostic algorithm with common causes is shown in Figure 59-3. Na^+ is normally the key determinant of serum osmolality, and hyponatremia is usually observed in conjunction with reduced osmolality. In some situations, however, osmolality is normal or raised by the presence of solutes that induce cellular dehydration and translocation of water from cells to the ECF. These include glucose in the absence of adequate insulin, mannitol, maltose, and glycine. Alternatively, hyponatremia may be artifactual (pseudohyponatremia), caused by the presence of high lipid concentrations. In hypoosmolar hyponatremia, imbalanced gains or losses of TBW and Na^+ occur such that serum Na^+ concentration is reduced.

Preoperative Hyponatremia. Hyponatremia may be an incidental finding during preoperative assessment, with the underlying pathologic mechanisms identified in Figure 59-3. Even mild preoperative hyponatremia is associated with increased 30-day mortality, major cardiac events, wound infection, and pneumonia.[111] Whether hyponatremia is a direct causal mechanism in postoperative adverse events or a marker of underlying overt or subclinical pathologic processes, such as cardiac failure, is not clear, although excess risk is seen even in American Society of Anesthesiologists (ASA) class 1 and 2 patients undergoing elective surgery. However, correcting preoperative hyponatremia does not clearly improve outcomes. Pragmatically, the finding of preoperative hyponatremia should prompt a search for, and optimization of, potential

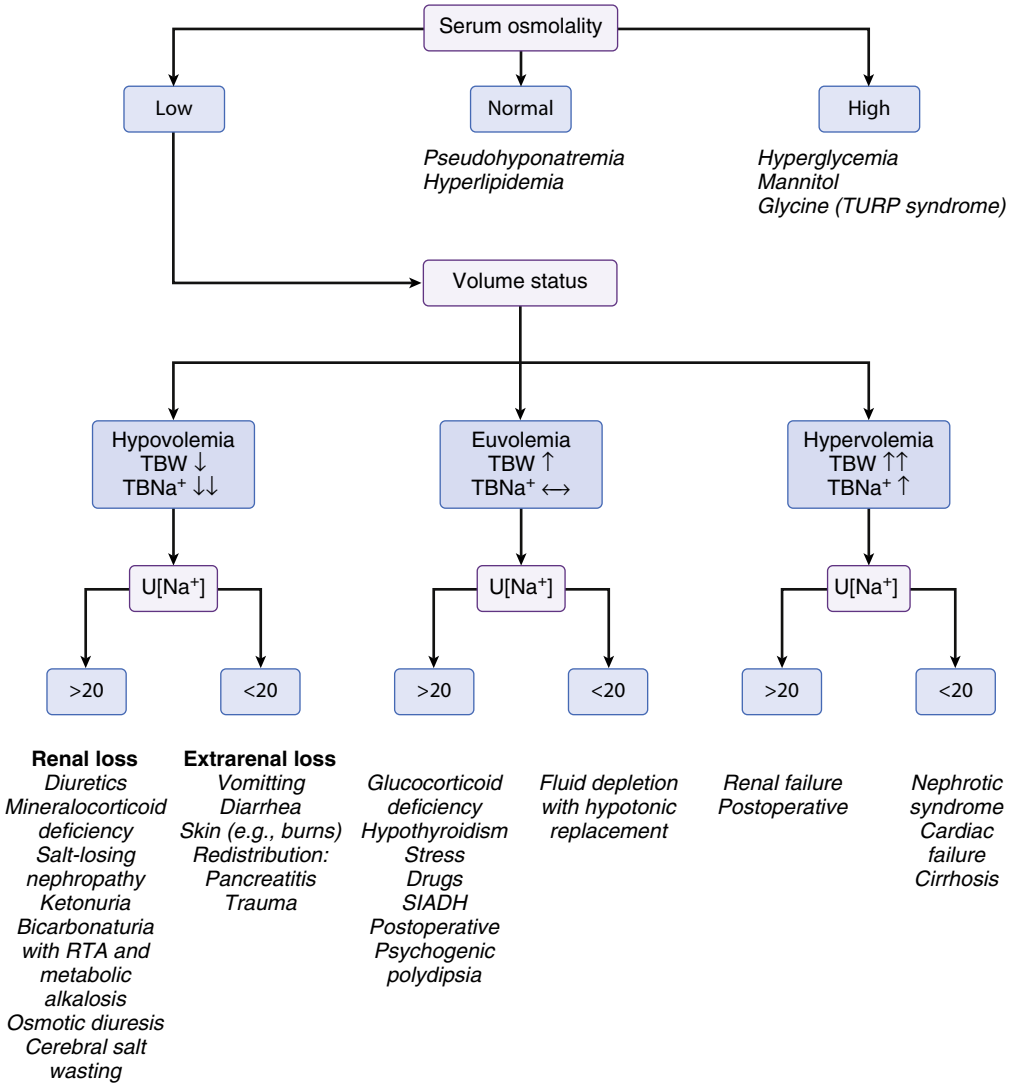


Figure 59-3. Causes and diagnostic algorithm for hyponatremia. The diagnostic criteria for the syndrome of inappropriate secretion of antidiuretic hormone (*SIADH*) include exclusion of adrenal, thyroid, and renal disease or diuretic usage, serum hypoosmolality (<270 mOsmol/kg), clinical euvolemia, increased urinary [Na^+] despite normal water and salt intake and inappropriate urinary concentration (>100 mOsmol/kg). A characteristic response to water restriction occurs, with a 2- to 3-kg fall in weight accompanied by a reduction in salt wasting and hyponatremia over 2 to 3 days. *RTA,* renal tubular acidosis; *TBW,* total body water; *TURP,* tranurethral resection of the prostate; *U[Na^+],* urinary sodium concentration in mEq/L. *(Modified from Kumar S, Berl T: Sodium,* Lancet *352:220, 1998; and Tisdall M, Crocker M, Watkiss J, et al: Disturbances of sodium in critically ill adult neurologic patients: a clinical review,* J Neurosurg Anesthesiol *18:57, 2006.)*

underlying diseases. In moderate-to-severe hyponatremia, nonurgent surgery should probably be postponed to allow the carefully monitored, gradual correction of hyponatremia (see later discussion).

Postoperative Hyponatremia. As previously discussed, the surgical stress response, aggravated by periods of hypotension and pain-related or physiologic stress–related sympathetic activity, can lead to a state of Na^+ and water retention similar to SIADH. Avid water retention puts postoperative patients at risk for hyponatremia, particularly when administration of free water from IV dextrose-containing or other hypotonic solutions is ongoing. The incidence of postoperative hyponatremia is 1% to 5%, with children and premenopausal females at particularly high risk for neurologic symptoms. In these groups, symptoms and neurologic sequelae may occur at Na^+ levels as high as 128 mEq/L, whereas elderly women typically do not become symptomatic above 120 mEq/L unless the decrease is particularly rapid. The potential impact of postoperative hyponatremia is considerable; 8% of hyponatremic patients may develop encephalopathy, of whom 52% suffer permanent neurologic sequelae or death.[112] Failure to recognize hyponatremia as a cause of postoperative symptoms (see later discussion) or inadequate treatment based on fears of causing osmotic demyelination may contribute to these poor outcomes.[113] Prevention of postoperative hyponatremia should be a key goal of postoperative fluid therapy, based on limiting free water administration to pure maintenance requirements (1 to 1.2 mL/kg/hr), replacing losses of Na^+-containing fluids (e.g., GI) with an appropriate isotonic salt solution, stopping IV therapy as soon as the oral route can be used, and daily (or more frequent in high-risk groups) checking of serum electrolytes. The treatment of hyponatremia is outlined later.

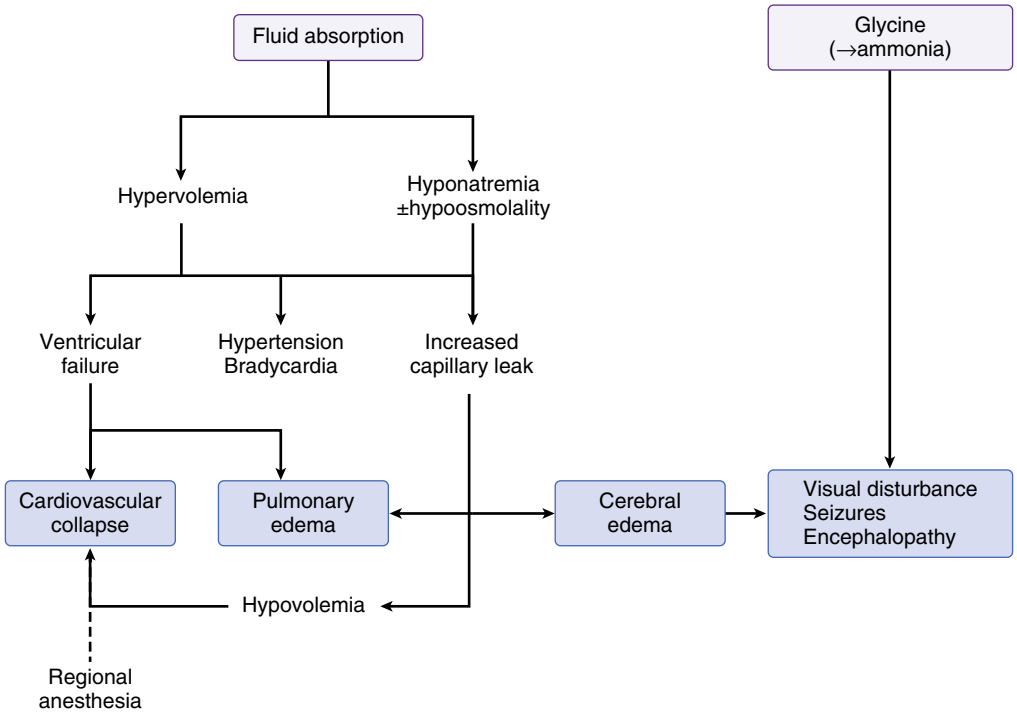


Figure 59-4. The transurethral resection of the prostate (TURP) syndrome. Early hypervolemia-related hypertension may be followed by profound hypotension as a result of increased capillary filtration with hypovolemia, depressed cardiac function, and sympathetic blockade. Glycine itself may lead to seizures through allosteric activation of the *N*-methyl-D-aspartate receptor and is thought to cause the visual disturbance of the TURP syndrome. The hepatic deamination of glycine yields ammonia, which can further contribute to encephalopathy. *(Modified from Gravenstein D: Transurethral resection of the prostate [TURP] syndrome: a review of the pathophysiology and management,* Anesth Analg *84:438, 1997.)*

Transurethral Resection of the Prostate Syndrome. The transurethral resection of the prostate (TURP) syndrome describes symptomatic hyponatremia, excessive intravascular volume, and edema resulting from IV absorption of hypotonic nonconductive (electrolyte-free) irrigation fluid during TURP or, rarely, transurethral resection of the bladder[114] or during ureteroscopic or hysteroscopic procedures (see also Chapters 72 and 87). The syndrome may complicate 10% to 15% of TURP procedures, with onset between 15 minutes and 24 hours after the onset of resection.[115] Risk factors include increased intravesical pressure, prolonged resection, hypotonic irrigants, and open prostatic sinuses. The clinical features (Fig. 59-4) are related to intravascular volume changes, hyponatremia, and absorption of irrigant solutes; the use of distilled water as an irrigant has largely been replaced by solutions of glycine, sorbitol, or mannitol because of the incidence of massive hemolysis. Hyponatremia resulting from free water absorption may lead to hypoosmolality, although the presence of glycine or other osmotically active solutes may maintain osmolality in the normal range. The following measures may help prevent the TURP syndrome:

- The use of conducting (isotonic saline) irrigant with bipolar diathermy.[116]
- Monitoring fluid absorption by comparing the amount instilled with the amount removed. Surgery should be halted if 750 mL (for females) or 1000 mL (for males) has been absorbed and the patient's Na^+ levels and neurologic status (if awake) assessed. Surgery should be terminated if 1000 to 1500 mL (for females) or more than 2000 mL (for males) has been absorbed. If saline irrigant is used, surgery should be terminated after 2500 mL has been absorbed; although the risk for hypoosmolar hyponatremia is removed, the risk for excessive intravascular volume remains.[117,118]
- Limiting the duration of irrigation; irrigation should continue only for longer than 1 hour after careful assessment of the patient for possible TURP syndrome.
- Limiting intravesical pressure to less than 15 to 25 mm Hg or 70 mm Hg for endometrial procedures.
- Monitoring the patient's neurologic status by using regional anesthetic techniques. Symptoms in the awake patient include nausea and vomiting, visual disturbance, reduced level of consciousness, agitation, confusion, and seizures.

Treatment of the TURP syndrome should take into account the patient's intravascular volume status, Na^+ level, and osmolality, but typically involves cessation of irrigation solutions, and water restriction, and, if excessive intravascular volume is present, a loop diuretic should be given to promote free water excretion. In severe hypoosmolar hyponatremia with neurologic symptoms, hypertonic saline may be used. Conversely, when osmolality is normal or marginally decreased, hemodialysis is preferred.[119] Mg^{2+} can be given for seizures, because its negative control of NMDA receptors counteracts dilutional hypomagnesemia and the excitatory effects of glycine.[115]

Presentation and Treatment of Hyponatremia. The symptoms of hyponatremia are related to cerebral edema

and increased intracranial pressure, and are highly dependent on how rapidly hyponatremia occurred. In acute onset, symptoms typically occur when Na^+ concentrations are as low as 120 to 125 mEq/L (higher in children and premenopausal females) with headache, confusion, agitation, vomiting, and lethargy. At Na^+ concentrations less than 110 mEq/L, symptoms progress to seizures and coma. In the chronic setting, clinical features may be absent even at concentrations less than 120 mEq/L. In all cases of hyponatremia, potential underlying causes such as steroid deficiency, renal disease, and cardiac disease should be identified and treated. Treatment should be tailored to the patient's intravascular volume status, the chronicity of onset, and the presence of symptoms. Chronic hyponatremia (>48 hours or of unknown duration) should be treated cautiously because of cerebral compensation for the hypoosmolar state; sudden increases in osmolality lead to cerebral water loss and osmotic demyelination (e.g., central pontine myelinolysis).

- Hypovolemic hyponatremia: Symptoms are unusual because osmotic shifts in the brain are limited by the loss of both Na^+ and water. ECF volume should be restored with isotonic saline, which will also reduce ongoing ADH release.
- Hypervolemic hyponatremia: In chronic cases this should focus on restriction of water intake and optimization of the underlying disease state, such as improving cardiac output with angiotensin-converting enzyme (ACE) inhibitors to reduce the neurohumoral influence on water retention in cardiac failure, and possibly using loop diuretics (rather than thiazides, which impair urinary dilution) to excrete free water once a negative Na^+ balance has been achieved.
- Chronic, asymptomatic hyponatremia: No immediate correction of hyponatremia is required, and the underlying cause should be treated. Fluid restriction, ADH antagonists (lithium, demeclocycline), and loop diuretics may be used.
- Symptomatic hyponatremia (typically euvolemic or hypervolemic): In patients with moderate symptoms (confusion, lethargy, nausea, and vomiting), hypertonic 3% saline may be used at an initial rate of 1 mL/kg/hr with the goal of increasing $[Na^+]$ by 1 mEq/L/hr for 3 to 4 hours, after which electrolytes should be rechecked. The infusion rate should be modified to ensure that $[Na^+]$ is increased by no more than 10 mEq/L in the first 24 hours of treatment. Severely symptomatic hyponatremia (coma, seizures, often with $[Na^+]$ <120 mEq/L) is typically of acute onset and the risks of undertreating are more than those of osmotic demyelination. A bolus of 100 mL of 3% saline should initially be given with the aim of acutely increasing $[Na^+]$ by 2 to 3 mEq/L. If no improvement in neurologic status occurs, this approach may be repeated once or twice at 10-minute intervals. After this, treatment should continue as for moderately symptomatic patients, with a similar goal of increasing $[Na^+]$ by no more than 10 mEq/L in the first 24 hours.[120] Electrolytes and osmolality should be rechecked every few hours, fluid input and output should be carefully monitored, and patients reassessed regularly.

Hypernatremia. Hypernatremia ([Na] > 145 mEq/L) is less common than hyponatremia, but may affect up to 10% of critically ill patients. If severe ([Na] > 160 mEq/L), a 75% mortality may occur depending on the severity of the underlying disease process.[109,110] (Fig. 59-5). The major mechanisms are excessive water loss with inadequate compensatory intake, lack of ADH, or administration of exogenous sodium. Diabetes insipidus (DI) is caused by a lack of ADH action as a result of impaired production or release (central DI) or reduced renal sensitivity to ADH (nephrogenic DI) with consequent failure to concentrate urine and excretion of large quantities of inappropriately dilute urine. If the patient is unable to accept compensatory fluid orally (e.g., because of coma or in the elderly with impaired thirst reflexes), they may rapidly become hypovolemic. Central DI is seen after pituitary surgery, subarachnoid hemorrhage, traumatic brain injury (particularly skull base fractures), and brainstem death. Nephrogenic DI may be due to renal disease, electrolyte disorders, or drugs (lithium, foscarnet, amphotericin B, demeclocycline).

Clinical features of hypernatremia include altered mental status, lethargy, irritability, seizures, hyperreflexia, and spasticity. Diagnosis is based on assessment of intravascular volume status and urinary osmolality and Na^+ concentration. In patients with persistent urine output of more than 100 mL/hr and hypernatremia, DI should be considered. Diagnostic criteria include an inappropriately dilute urine (<300 mOsm/kg) in combination with hypernatremia and high serum osmolality (>305 mOsm/kg). Urine specific gravity (SG) may provide a rapid guide to urine osmolality where urgent treatment is being considered; urine SG less than 1.005 in the context of hypernatremia and a potential underlying cause is consistent with DI.

Treatment is tailored to the intravascular volume status, but as with hyponatremia, correction of the Na^+ concentration should be no more rapid than 10 mEq/L/day unless the onset has been very acute.

- Hypovolemic hypernatremia: Correction of the intravascular volume deficit with isotonic saline and correction of the underlying cause (e.g., insulin to reduce hyperglycemia), then correction of the water deficit with 0.45% saline, 5% dextrose or enteral water to cover the deficit and ongoing losses.
- Euvolemic hypernatremia: Use of 0.45% saline, 5% dextrose, or enteral water to replace the deficit and ongoing losses. In central DI, in which urine output is greater than 250 mL/hr and risk exists for hypovolemia, titrated intravenous doses of desmopressin acetate 0.4 to 1 μg (1-deamino-8-D-arginine vasopressin [DDAVP], an ADH analogue) should be given to reduce the urine output. Higher acute doses may have a prolonged effect with the risk for water intoxication.[109,110]
- Hypervolemic hypernatremia: Stop administration of exogenous Na^+, give furosemide with 5% dextrose or enteral water. Dialysis may be indicated in the presence of renal failure.

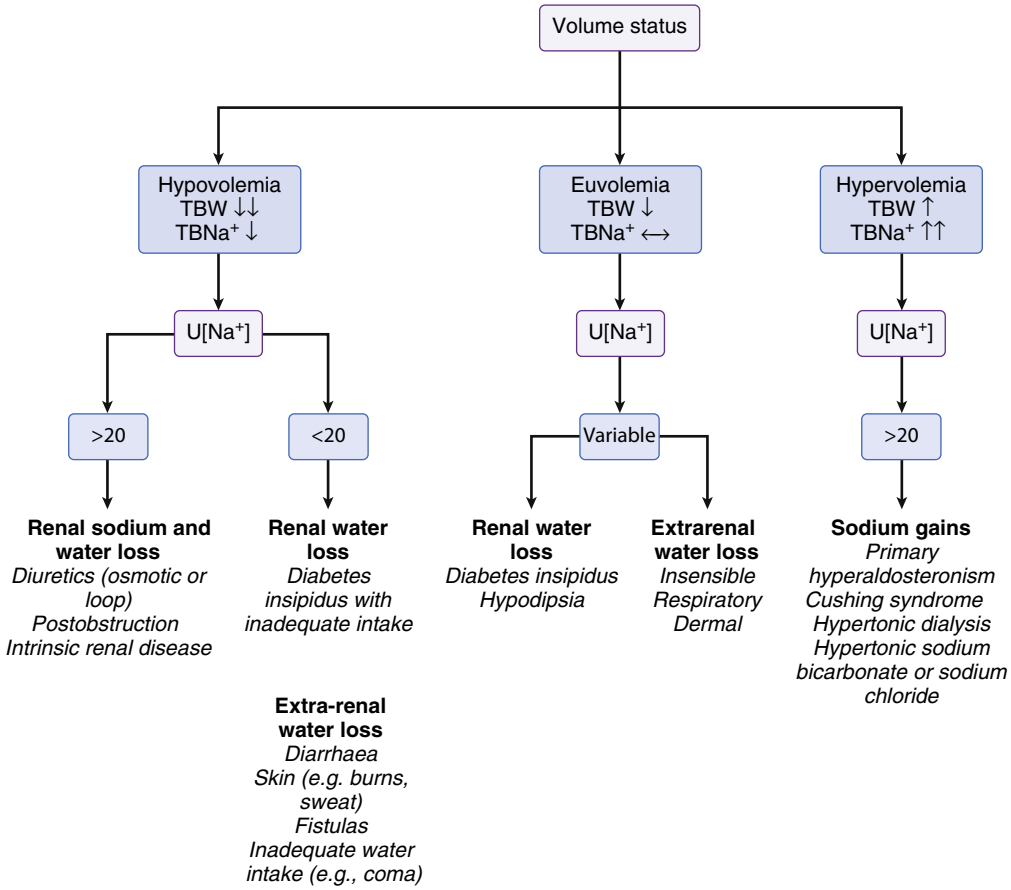


Figure 59-5. Causes and diagnostic algorithm for hypernatremia. *TBW,* Total body water; *U[Na⁺],* urinary sodium concentration in mEq.L^{-1}. *(Modified from Kumar S, Berl T: Sodium,* Lancet *352:220, 1998.)*

Potassium Disorders. Because of the key role of K^+ on excitable tissue resting membrane potential, dyskalemia can lead to life-threatening cardiac arrhythmias in the perioperative period. The normally predominant intracellular distribution of K^+ means that abnormal plasma K^+ levels may reflect abnormal ECF to ICF distribution, derangements of total body K^+ content, or both. Sampling artifacts may be introduced into laboratory tests of K^+; anticoagulated samples typically give results 0.4 to 0.5 mEq/L less than those from clotted samples because of erythrocyte K^+ release during clotting. Hemolysis also artificially increases K^+ levels and may be introduced by poor sampling technique or delayed processing of samples.

Hypokalemia. Hypokalemia (<3.5 mEq/L) may be caused by the conditions outlined in Table 59-7. Moderate-to-severe hypokalemia (2 to 2.5 mEq/L) leads to muscle weakness, electrocardiogram (ECG) abnormalities (ST segment depression, T wave depression, U wave elevation), and arrhythmias (atrial fibrillation and ventricular extrasystoles). All logic dictates that hypokalemia (e.g., as low as 2.6 mEq/L) should be associated with an increased rate of perioperative morbidity or mortality; however, no data support this conclusion.[18] Hypokalemia should be pragmatically corrected in the perioperative phase to optimize neuromuscular function and reduce cardiac irritability. Such treatment is of prime importance when acute arrhythmias exist, and K^+ should be maintained at greater than 4 to 4.5 mEq/L. The speed of the infusion should be slow enough to allow equilibration throughout the entire ECF, typically no faster than 0.5 mEq/kg/hr. K^+ solutions of concentration more than 40 mEq/L may be an irritant to veins and should be administered via a central venous catheter.

Hyperkalemia. Hyperkalemia (>5.5 mEq/L) may result from excess intake, failure of excretion, or shift from the intracellular to extracellular compartment (Table 59-8). Failure of renal secretion is mediated through impaired principal cell function in the cortical collecting duct, which depends on aldosterone-stimulated Na^+/K^+ exchange via basal Na^+/K^+ATPases and luminal Na^+ and K^+ channels. The features of hyperkalemia include muscle weakness, paralysis, and altered cardiac conduction (increased automaticity and enhanced repolarization) with consequent ECG changes as K^+ levels increase[121]:

- 5.5 to 6.5 mEq/L: Tall, peaked T waves
- 6.5 to 7.5 mEq/L: Prolonged PR interval
- Greater than 7.5 mEq/L: Widened QRS
- Greater than 9.0 mEq/L: Sine wave pattern, bradycardia, ventricular tachycardia, increased risk for cardiac arrest

Chronically induced hyperkalemia, (e.g., chronic renal failure), is better tolerated than acute increases in blood K^+ concentrations. Ratios between intracellular and extracellular K^+ concentrations may be very abnormal with acute hyperkalemia. With chronic hyperkalemia, these ratios

TABLE 59-7 CAUSES AND MECHANISMS OF HYPOKALEMIA

Mechanism	Cause	Notes
Inadequate intake	Anorexia nervosa	
	Alcoholism	
	Malnutrition	
Gastrointestinal loss	Vomiting	
	Diarrhea	Especially secretory diarrhea
	Fistulas	
Excess renal loss	Mineralocorticoid excess	Primary and secondary hyperaldosteronism
	Glucocorticoid excess	High concentration of cortisol overwhelms mineralocorticoid receptor despite lower affinity
	Diuretics	Loop or thiazide diuretics deliver increased Na^+ load to principal cells
	Osmotic substances	Glucose, urea, and mannitol also lead to increased collecting duct Na^+ delivery
	Hypomagnesemia	Impairs thick ascending limb Na^+ reabsorption; therefore, increased distal N^+ delivery and K^+ loss via principal cells
	Renal tubular acidosis	Failure of principal cell H^+/K^+ exchange
	Bartter and Gitelman syndromes	Tubule ion transporter mutations mimicking loop or thiazide diuretic effect, respectively
Intracellular K^+ shift	β_2-Agonists	Also seen in sympathetic activity
	Insulin therapy	
	Acute alkalosis	
	Lithium overdose	
	Hypokalemic periodic paralysis	
	Vitamin B_{12} therapy	

Modified from Kaye AD, Riopelle JM: Intravascular fluid and electrolyte physiology. In Miller RD, Eriksson LI, Fleisher LA, et al, editors: Miller's anesthesia, *ed 7. New York, Churchill Livingstone, 2009, p. 1705.*

TABLE 59-8 CAUSES AND MECHANISMS OF HYPERKALEMIA

Mechanism	Cause	Notes
Increased intake	Excessive K^+ treatment	
	Blood transfusion	Typically in patients who also have impaired excretion (i.e., severe chronic kidney disease)
	Antibiotics containing K^+ salts	
Failure of renal secretion	Mineralocorticoid deficiency	Hypoaldosteronism
		Hyporeninemic, hypoaldosteronemic state (diabetic nephropathy, tubulointerstitial disease)
	Drugs causing mineralocorticoid blockade	Spironolactone (blocks mineralocorticoid receptor)
		ACE-I and ARBs (reduce aldosterone production)
		Heparin (selective hypoaldosteronism)
	Collecting duct Na^+ channel blockade	Amiloride
		Trimethoprim
		Triamterene
		Pentamidine
	Tubulointerstitial nephritis	Cause damage or destruction of the cortical collecting duct
	Renal obstruction	
Extracellular K^+ shift	Suxamethonium	
	Reperfusion of ischemic tissues	Cellular ischemia reduces ATP production with failure of Na^+/K^+ATPase activity and K^+ "leak" to the ECF. Cell lysis further releases K^+. On reperfusion, excess ECF K^+ is rapidly delivered to the systemic circulation. During solid organ transplantation this may be combined with residual perfusing solution used for ex vivo organ preservation, which contains a high K^+ content
	Insulin deficiency	
	Acute acidosis	
	Malignant hyperpyrexia	

ACE-I, Angiotensin-converting enzyme inhibitor; *ARBs,* angiotensin II receptor blockers; *ATP,* adenosine triphosphate; *ECF,* extracellular fluid.

have probably been restored to normal. Acute hyperkalemia sufficient to induce electrocardiographic changes is a medical emergency that requires rapid treatment. The acute treatment of hyperkalemia involves shifting K^+ from the ECF to ICF, antagonizing its cardiac toxicity with Ca^{2+}, and increasing renal excretion. Elimination by GI resin exchange also may be used in more chronic cases (Table 59-9). Hyperkalemia greater than 6.5 mEq/L, in the context of anuric renal failure, is an indication for acute renal replacement therapy.

TABLE 59-9 TREATMENTS FOR HYPERKALEMIA

Mechanism	Treatment	Indication	Notes
Antagonize cardiac toxicity	$CaCl_2$ 10% (10 mL) or Calcium gluconate	K^+ >6.5 mEq/L, particularly with ECG changes	Onset of action within a few min, duration 30-60 min
Intracellular potassium shift	Insulin 10-20 units (administered in 50 mL 50% glucose to avoid hypoglycemia)	K^+ >6.0 mEq/L	Onset within 10-20 min, duration 4-6 hr
	β_2-Agonists (e.g., nebulized salbutamol 2.5 mg)		
	Hyperventilation		Induce K^+ uptake by increasing extracellular pH
	$NaHCO_3$ 1 mEq/kg	K^+ >6.5 mEq/L	
Increase renal excretion	Furosemide 20-40 mg IV	Moderate-to-severe hyperkalemia	Increases Na^+ delivery to cortical collecting duct and exchange with K^+
	Volume expansion with isotonic saline		
	Fludrocortisone		Mineralocorticoid effect
Other routes of K^+ elimination	Gastrointestinal resin exchange: Ca^{2+} resonium 15-30 g or sodium polystyrene sulfonate (Kayexalate) 15-30 g PO or per rectum	Any sustained hyperkalemia	
	Hemodialysis	Moderate-to-severe hyperkalemia with oliguria	

Hyperkalemia can be defined as mild (5.5-5.9 mEq/L), moderate (6.0-6.4 mEq.L) or severe (>6.5 mEq/L), with or without ECG changes.[240]
ECG, Electrocardiogram.

TABLE 59-10 CAUSES AND MECHANISMS OF HYPOCALCEMIA

Mechanism	Cause	Notes
Reduced regulatory hormones	Hypoparathyroidism	Postparathyroid or thyroid surgery. May be acute effect of reduced PTH or more long-term hypocalcemia during remineralization of bone after surgery for hyperparathyroidism ("hungry bone syndrome")
		Hypomagnesemia (suppresses PTH secretion)
	Pseudohypoparathyroidism	Reduced receptor response to PTH
	Reduced vitamin D activity	Hyperphosphatemia (inhibits hydroxylation—e.g., in chronic kidney disease)
		Dietary/sunlight deficiency
		Anticonvulsants (increased turnover into inactive forms)
Ca^{2+} chelation	Massive transfusion	Caused by citrate in stored red blood cell solutions
	Cell lysis	Phosphate release as a result of tumor lysis syndrome, trauma, or rhabdomyolysis
	Pancreatitis	Intraperitoneal free fatty acids formed by the action of released pancreatic lipase, which chelate Ca^{2+} salts; further contributions from coexistent hypomagnesemia and hypoalbuminemia
Increased bone deposition	Prostate, breast cancer	Increased osteoclastic activity
Reduced ionized fraction	Alkalosis	For example, acute intraoperative hyperventilation
Reduced bound Ca^{2+}	Hypoalbuminemia	Critical illness (where ionized Ca^{2+} may be normal, and Ca^{2+} replacement not required), poor nutrition
Unknown mechanism	Endotoxemic shock	

PTH, Parathyroid hormone.

Calcium Disorders

Hypocalcemia. The causes of hypocalcemia are related to reduced PTH and/or vitamin D activity, increased bone deposition, Ca^{2+} chelation, or changes in binding protein concentration or ionized fraction (Table 59-10). The following are characteristic symptoms, some of which will be absent in the anesthetized patient:

- Neuromuscular irritability
  - Circumoral and peripheral paresthesia
  - Chvostek sign (facial twitching induced by tapping on the facial nerve)
  - Trousseau sign (forearm muscular spasm induced by inflating a pressure cuff)
  - Muscle cramps
  - Laryngospasm
  - Tetany
  - Seizures
- Cardiac
  - Impaired inotropy
  - Prolonged QT
  - Ventricular fibrillation
  - Heart block

After a rapid large-volume transfusion of citrate-stored blood (>1.5 mL/kg/minute) or fresh frozen plasma, ionized hypocalcemia may occur as a result of citrate chelation. This may be particularly severe and prolonged in patients

TABLE 59-11 **CAUSES AND MECHANISMS OF HYPERCALCEMIA**

Mechanism	Cause	Notes
Increased PTH	Primary hyperparathyroidism	The most common cause, typically manifests with mild hypercalcemia resulting from an isolated parathyroid adenoma
	Secondary and tertiary hyperparathyroidism	The hypocalcemia of kidney disease–related hyperparathyroidism may progress to hypercalcemia with prolonged disease
Malignancy	PTH-related peptide secretion	PTH-rP may be secreted by most solid tumors; mimics PTH effects
	Osteolytic metastases	Breast, lung, lymphoma, thyroid, kidney, prostate, and multiple myeloma
	Calcitriol production	Typical in lymphoma
Excess vitamin D	Ectopic production	Granulomatous disease (e.g., sarcoid), malignancy
	Excess intake	
Decreased renal excretion	Thiazide diuretics	
Increased bone turnover	Hyperthyroidism	
	Immobilization	
Increased Ca^{2+} intake	Milk-alkali syndrome	

PTH, Parathyroid hormone; *PTH-rP,* parathyroid hormone–related peptide.

with hepatic impairment, in whom citrate metabolism is reduced.[122] Citrate intoxication has been described for many years, but is rarely a clinical problem (see also Chapter 61). Although Ca^{2+} plays an important role in coagulation, coagulopathy specifically attributable to hypocalcemia only occurs at ionized Ca^{2+} concentrations less than 1.2 mEq/L; rather, supplemental Ca^{2+} should be given in this situation to support cardiac inotropy and neuromuscular function, aiming for ionized Ca^{2+} more than 1.8 mEq/L.[123] Ca^{2+} also may be given during other situations in which myocardial contractility is impaired, such as during cardiac surgery, to optimize ventricular function (see also Chapter 67). After parathyroidectomy, Ca^{2+} levels should be checked frequently until they have stabilized, because Ca^{2+} and vitamin D supplementation may be required in both the short and long term. In critical illness, total Ca^{2+} levels may be reduced because of hypoalbuminemia; however, Ca^{2+} supplementation should be required only if the ionized levels are low. Ca^{2+} may be given intravenously as 10% (weight/volume) calcium gluconate or 10% (weight/volume) $CaCl_2$. Although in these formulations calcium gluconate contains less elemental Ca^{2+} (0.45 mEq/mL versus 1.36 mEq/mL for $CaCl_2$), they are equally efficacious as long as the total Ca content given is equal. Calcium gluconate may be preferable for peripheral administration because the tissue injury from inadvertent extravasation is less severe than with $CaCl_2$. Mg^{2+} levels are often low during hypocalcemia and should also be corrected, particularly when hypocalcemia has been caused by infusion of isotonic saline or colloids in large volumes.

Hypercalcemia. Hypercalcemia occurs when ECF Ca^{2+} influx from the GI tract, bone, or both outweighs efflux to bone or via the kidneys (Table 59-11). The symptoms are related to the severity and speed of onset of the abnormality, so mild chronic hypercalcemia is usually asymptomatic. More severe hypercalcemia manifests with neurologic symptoms (drowsiness, weakness, depression, lethargy, coma), GI symptoms (constipation, nausea, vomiting, anorexia, peptic ulcers), renal manifestations (nephrogenic diabetes insipidus—which may further aggravate hypercalcemia through dehydration—and renal stones), electrocardiographic abnormalities (shortened QT interval, prolonged PR interval), and potentiation of digoxin toxicity. Treatment should address the underlying cause, including surgical parathyroidectomy in cases of severe hyperparathyroidism, or cessation of thiazide diuretics. In addition, the treatment of symptomatic hypercalcemia should aim to increase renal Ca^{2+} excretion by volume expansion with isotonic saline and possibly loop diuretics. This combination may reduce Ca^{2+} by 0.5 to 1.5 mEq/L in 1 to 2 days.[26] Bisphosphonates enhance osteoclastic bone deposition and are given if the hypercalcemia is severe or in milder cases in which response to hydration has been inadequate. A single IV dose of pamidronate 60 mg (moderate hypercalcemia, up to 13.5 mg/dL) or 90 mg (severe hypercalcemia) should return Ca^{2+} levels to normal within 7 days, and the effect may persist for up to 1 month. Zoledronic acid is a newer bisphosphonate that may be even more effective and is given intravenously at a dose of 4 mg.[124] Bisphosphonates should only be given when any clinical dehydration has been treated to avoid calcium bisphosphonate precipitation and nephrotoxicity. Glucocorticoids may also be given for hypercalcemia associated with lymphoproliferative disease or ectopic vitamin D production.[125] Calcitonin increases renal Ca^{2+} excretion and reduces bone resorption for up to 48 hours when given intramuscularly or intravenously and may contribute to a mild reduction in Ca^{2+} levels during the rehydration phase.

Magnesium disorders

Hypomagnesemia. Serum Mg^{2+} concentration may be a poor indicator of total body content because of its large distribution in the intracellular compartment and slow equilibration with bone stores (see also Chapter 77). Intraerythrocyte or intralymphocyte Mg^{2+} levels may give a better approximation of total body and tissue stores, but are more complex to process.[126,127] Chronic Mg^{2+} deficiency and acute hypomagnesemia increase cardiovascular morbidity[29] and are particularly prevalent in diverse hospital populations (12% of general inpatients, 19% of preoperative cardiac surgery patients, 65% of critical care patients) (see also Chapters 67 and 101). The causes are related to reduced Mg^{2+} intake from the GI tract or increased renal losses (Table 59-12), although relative depletion may occur in times of increased cell turnover and protein production (pregnancy, athletes, cold acclimatization). The clinical presentation of hypomagnesemia may be nonspecific; rather symptoms

TABLE 59-12 CAUSES AND MECHANISMS OF HYPOMAGNESEMIA

Mechanism	Cause
Inadequate gastrointestinal uptake	Malnutrition
	Prolonged vomiting or diarrhea
	Intestinal fistula
	Pancreatitis
	Prolonged nasogastric suction
	Malabsorption syndromes
	Small bowel syndrome
	Primary intestinal hypomagnesemia
Increased renal losses	Chronic parenteral fluid therapy
	Hypercalcemia and hypercalciuria
	Osmotic diuresis
	Drugs: Alcohol, loop and thiazide diuretics, aminoglycosides, cisplatin, amphotericin, cyclosporin, foscarnet
	Phosphate depletion
	Hungry bone syndrome
	Postobstructive nephropathy
	Renal transplantation
	Polyuric phase of acute kidney injury
	Primary hyperparathyroidism
	Bartter and Gitelman syndromes

often relate to common coexisting hypocalcemia or hypokalaemia[32]:

- Neuromuscular: Trousseau and Chvostek signs, vertigo, seizures, weakness
- Metabolic: Carbohydrate intolerance, hyperinsulinemia, atherosclerosis
- Cardiovascular: Wide QRS, prolonged PR, T-wave inversion, ventricular arrhythmias
- Musculoskeletal: Osteoporosis and osteomalacia

Treatment should be tailored to the severity of symptoms and degree of hypomagnesemia. Asymptomatic patients with moderate-to-severe hypomagnesemia should receive oral supplementation as acute IV infusions will stimulate the renal Ca^{2+}/Mg^{2+}-sensing receptor, reducing Mg^{2+} reabsorption and leading to the renal excretion of much of the acute dose. In the presence of symptoms or Mg^{2+} concentration of less than 0.8 mEq/L, IV Mg^{2+} should be administered (50 mEq/day, plus an initial dose of 8 to 16 mEq over 5 to 10 minutes in the presence of seizures or acute arrhythmias).[32] Coexistent hypocalcemia, hypokalemia, or both should also be treated, although are unlikely to improve without replenishment of Mg^{2+}. Mg^{2+} has many other therapeutic indications, even in the absence of hypomagnesemia, as outlined earlier. A few of these patients are likely to have total body Mg^{2+} depletion that has not been detected by serum Mg^{2+} levels.

Hypermagnesemia. Limited GI absorption and efficient renal excretion mean that hypermagnesemia is typically iatrogenic. Symptoms reflect the effect of Mg^{2+} on neurologic and cardiac function and relate to the serum concentration[18]:

- 5 to 7 mg/dL: Therapeutic levels in the treatment of preeclampsia (see also Chapter 77)
- 5 to 10 mg/dL: Impaired cardiac conduction (widened QRS, long PR), nausea
- 20 to 34 mg/dL: Sedation, reduced neuromuscular transmission with hypoventilation, reduced tendon reflexes, and muscle weakness (see also Chapter 18)
- 24 to 48 mg/dL: Diffuse vasodilation with hypotension, bradycardia
- 48 to 72 mg/dL: Areflexia, coma, respiratory paralysis

Mg^{2+} administration should therefore be performed with several important cautions. First, serum Mg^{2+} levels should be monitored closely during therapeutic administration. Second, because excretion is renal, doses should be decreased for patients with kidney disease. Third, it should be used with extreme caution in patients with a background impairment of neuromuscular transmission (myasthenia gravis, Lambert-Eaton myasthenic syndrome). Fourth, coadministration of neuromuscular blockers during anesthesia should be performed in reduced doses titrated to neuromuscular monitoring, because Mg^{2+} potentiates the effects of both depolarizing and nondepolarizing neuromuscular blockers (see also Chapters 34 and 35). Treatment of acute hypermagnesemia includes promoting renal excretion by administration of fluids intravenously and diuresis. IV Ca^{2+} is given to temporarily antagonize Mg^{2+} and avoid diuretic-induced hypocalcemia. Definitive treatment, particularly in the presence of kidney disease, may require dialysis.

Phosphate Disorders

Hypophosphatemia. Hypophosphatemia may be related to impaired enteral uptake, increased renal excretion, or shifts to the cellular compartment or bone (Table 59-13). Symptoms of hypophosphatemia may be precipitated by hyperventilation in patients with chronic depletion. Refeeding syndrome may be observed on commencement of enteral or parenteral nutrition after a period of prolonged starvation and may manifest postoperatively. Insulin secretion is decreased during starvation. The consequent fat and protein catabolism results in intracellular electrolyte depletion despite normal plasma levels, particularly phosphate. On refeeding, a switch back occurs to carbohydrate metabolism, increased insulin secretion, and an increased cellular uptake of PO_4^{3-}, which may lead to profound hypophosphatemia. In the most severe forms (<1.5 mg/dL), features may include rhabdomyolysis, leukocyte dysfunction, cardiac and respiratory failure, seizures, hypotension, and coma. IV PO_4^{3-} replacement carries a risk for precipitating severe hypocalcemia so should be reserved for moderate (<2.2 mg/dL) to severe or symptomatic cases and avoided in cases of ongoing hypocalcemia. Replacement protocols should be based on patient weight and serum PO_4^{3-}.[128]

Hyperphosphatemia. The causes of hyperphosphatemia are shown in Table 59-13. The most common cause in clinical practice is renal failure, in which filtered PO_4^{3-} load is reduced. This may be partly compensated for in mild chronic kidney disease by increased PTH secretion and inhibition of tubular PO_4^{3-} reabsorption, but in more severe kidney disease hyperphosphatemia must be controlled by oral PO_4^{3-} binders. The features of hyperphosphatemia may be related to symptomatic hypocalcemia caused by an acute elevation in PO_4^{3-} levels; hypocalcemia

TABLE 59-13 CAUSES AND MECHANISMS OF PHOSPHATE ABNORMALITIES

Hypophosphatemia		Hyperphosphatemia	
Mechanism	**Cause**	**Mechanism**	**Cause**
Internal redistribution	Respiratory alkalosis	Increased endogenous load	Tumor lysis syndrome
	Refeeding		Rhabdomyolysis
	Hormones (insulin, glucagon, epinephrine, cortisol)		Bowel infarction
	Sepsis		Malignant hyperthermia
	Hungry bone syndrome		Hemolysis
Increased urinary excretion	Hyperparathyroidism		Acidoses
	Disorders of vitamin D metabolism	Increased exogenous load	Intravenous infusion
	Renal transplant		Oral supplementation
	Volume expansion		Vitamin D intoxication
	Malabsorption	Reduced urinary excretion	Renal failure
	Renal tubular defects		Hypoparathyroidism
	Alcoholism		Acromegaly
	Metabolic or respiratory acidosis		Tumor calcinosis
Decreased intestinal absorption	Dietary restriction		Bisphosphonate therapy
	Excess antacids		Magnesium deficiency
	Vitamin D deficiency	Pseudohyperphosphatemia	Multiple myeloma
	Chronic diarrhea		In vitro hemolysis
			Hypertriglyceridemia

Data from Weisinger JR, Bellorín-Font E: Magnesium and phosphorus, Lancet *352:391, 1998.*

TABLE 59-14 CAUSES AND MECHANISMS OF CHLORIDE ABNORMALITIES

Hypochloremia		Hyperchloremia	
Mechanism	**Cause**	**Mechanism**	**Cause**
Cl^- loss	Diuretics	Cl^- infusion	Cl^--rich fluids
	Gastric drainage		Parenteral nutrition
	Vomiting	Water loss	Skin
	Chronic respiratory acidosis		Fever
			Renal losses
Water balance in excess of Cl^-	Congestive cardiac failure		Diabetes insipidus
	Syndrome of inappropriate secretion of antidiuretic hormone	Water loss exceeding Cl^- loss (extrarenal)	Diarrhea
	Infusion of hypotonic fluids		Burns
		Water loss exceeding Cl^- loss (renal)	Osmotic diuresis
			Postobstructive diuresis
			Intrinsic renal disease
		Increased tubular chloride reabsorption	Renal tubular acidosis
			Recovery from diabetic ketoacidosis
			Early renal failure
			Acetazolamide
			Ureteral diversion
			Posthypocapnia

Data from Yunos NM, Bellomo R, Story D, et al: Bench-to-bedside review: chloride in critical illness, Crit Care *14:226, 2010.*

is mediated via Ca^+ deposition in soft tissues when the calcium × phosphate product is elevated, and by inhibition of renal 1α-hydroxylase.[32]

Chloride Disorders. Disorders of Cl^- have the potential to affect acid-base balance, although this depends on the other constituents of the SID. As described, exogenous Cl^- administration from isotonic saline will increase the plasma Cl^- concentration with a lesser effect on Na^+ concentration, thus reducing the plasma SID and therefore pH. Conversely, disease states typified by both hyperchloremia and hypernatremia or by hypochloremia and hyponatremia will not affect the SID and therefore not alter pH. Many of the causes of Cl^- abnormalities (Table 59-14) are pathologic processes that also affect Na^+ levels. Investigation and treatment of these "matched" electrolyte imbalances should initially target the dysnatremia. In very rare cases it may be necessary to supplement Cl^- ions using 0.1 M hydrochloric acid administered via a central venous catheter. The required Cl^- dose can be estimated as follows:

$$Chloride\ dose = (Cl_{desired} - Cl_{measured}) \times 0.2 \times weight\,(kg) \quad (6)$$

Practical Management of Perioperative Fluid Therapy

At each stage in the perioperative journey, the physician must decide how much and what type of IV fluid is required. Unfortunately, a robust evidence base with answers to these questions is not always available, so a pragmatic approach based on sound physiologic knowledge and the best available evidence is required. To make the process more complicated, fluid and electrolyte requirements are a dynamic situation with great interindividual variability. Different fluid requirements are encountered in the preoperative, intraoperative, and postoperative phases, and these vary depending on patient factors, including weight and comorbidity, and on surgical factors, such as the magnitude and site of surgery (see later discussion). Furthermore, the goals of fluid therapy vary depending on the severity of surgery and its associated morbidity. In "low-risk" minor surgery, fluid strategies may influence the incidence of relatively minor morbidity such as nausea and vomiting[129,130] (also see Chapter 97), whereas in major surgery the focus is on the potential for fluid administration to affect major postoperative morbidity, postoperative length of stay, and possibly postoperative mortality.[107,131,132]

The goals of fluid therapy for major surgery are as follows:

- To ensure adequate circulating volume to support cellular O_2 delivery and avoid the deleterious effects of hypoperfusion on cellular function and survival, inflammation, and neurohumoral responses. This may involve manipulation of not just circulating volume but also of cardiac output and vascular resistance.
- To avoid the iatrogenic side effects of fluid administration; excessive intravascular volume (which may not be readily apparent clinically), edema, excess Na^+ or Cl^- load, toxicities related to synthetic compounds, or unphysiologic quantities of anions (lactate, acetate, gluconate).

Many approaches have been explored in an effort to determine the optimum quantity and type of fluid that should be given to achieve these goals in perioperative care.

Quantity of Fluid. IV fluid quantities may be given in two main ways: by estimating the requirements based on patient weight, the phase of surgery, and nature of losses to estimate the required dose, or by direct measurement of an individual's physiologic variables, and administering fluid in sufficient quantities to achieve an improvement in these physiologic variables, so-called goal-directed therapy.

Targeting Overall Fluid Balance. Traditional approaches to perioperative fluid administration are based on historical estimates of fluid requirements during fasting (e.g., using the "4-2-1" calculation) (Table 59-15[133]) and during episodes of excess loss, such as when body cavities are open or bleeding occurs.

The fluid volumes prescribed are then based on perceived knowledge of the movement of fluids between compartments—for example, crystalloid being used to replace blood loss in a 3:1 ratio to account for crystalloid movement into the extravascular compartment.[18]

TABLE 59-15 THE 4-2-1 ESTIMATION OF MAINTENANCE WATER REQUIREMENTS

Weight	Fluid Prescription
First 10 kg	4 mL/kg/hr
Second 10 kg	2 mL/kg/hr
All subsequent kilograms	1 mL/kg/hr

Worked example: A 25-kg patient would require (4 × 10) + (2 × 10) + (1 × 5) = 65 mL/hr "maintenance" water.

Data from Holliday MA, Segar WE: The maintenance need for water in parenteral fluid therapy, Pediatrics *19:823, 1957.*

However, much of the physiologic basis of this management approach has been questioned recently.[3,11]

An extension of the milliliter-per-kilogram approach to fluid administration has been to examine whether higher (e.g., 12 to 18 mL/kg/hr of intraoperative crystalloid) or lower (5 to 7 mL/kg/hr) fluid doses in the immediate perioperative phase are associated with benefit after major surgery. Unfortunately, this work has been hampered by widely varying definitions of "restrictive/conservative," "standard," and "liberal," differing fluid types (colloids/crystalloids) examined, and different time courses over which the fluid strategy is applied. Despite these differences, a common theme is that when fluid is given based on a milliliter-per-kilogram protocol and on clinical assessment rather than to target defined physiologic endpoints, the administration of more than 3500 to 5000 mL of crystalloid solution in the immediate perioperative period is associated with increased postoperative morbidity in contrast to administration of smaller fluid volumes. This may be reflected in increased weight gain, cardiopulmonary dysfunction, impaired wound healing,[107,129] delayed GI function, and increased hospital length of stay.[134,135] One study gives apparently conflicting results,[136] although this may be partly accounted for by methodologic differences with the other studies here. Very few studies have robustly examined the specific effects of postoperatively administered fluid volumes; of those tackling this area, one showed an earlier return to gut function and hospital discharge when postoperative infusions were limited to 2000 mL of water and less than 100 mEq Na^+/24 hr,[104] whereas another showed no difference.[137] These represent very small studies with methodologic differences.

Although it seems likely that there exists an optimum fluid volume to be given to maximize perfusion while avoiding excessive intravascular volumes (a U-shaped curve when volume is plotted against morbidity), the position of this curve is likely to vary widely across patients and in response to different insults. This is the rationale behind individualization of fluid therapy, whereby objective variables are measured and targeted with fluid therapy.

Goal-Directed Therapy. The practice of goal-directed therapy (GDT) is based on measuring key physiologic variables related to cardiac output or global O_2 delivery and administering fluids, and possibly inotropes, vasopressors, vasodilators, and RBCs as appropriate, to manipulate these variables toward levels associated with improved tissue perfusion and clinical outcome. This approach to fluid administration is a continuous dynamic

process that targets defined physiologic endpoints rather than giving fluids without objective assessments of fluid status. GDT, used both in the perioperative and critical care setting, originated from observations that survivors of high-risk surgery achieved a particular elevation in global O_2 delivery and utilization in the perioperative period.[138] Subsequent trials used hemodynamic manipulation in an effort to replicate these supranormal "survivor values" in patients undergoing major surgery (cardiac index > 4.5 L/min/m, O_2 delivery index (DO_2I)> 600 mL/min/m, O_2 consumption index (VO_2I)> 170 mL/min/m).[139,140] The GDT approach has been studied in a wide variety of surgical settings, and at various time points, including during preoperative optimization, intraoperative management, and the immediate postoperative period. Various tools to measure the physiologic targets of GDT have been studied and are becoming increasingly noninvasive (see also Chapter 45). Most of the evidence in perioperative GDT is based on measurements from two devices, as follows:

- Pulmonary artery catheter (PAC) (see also Chapter 45). Considered to be the gold standard hemodynamic monitor, providing measured and derived values for left-heart and right-heart filling pressures, mixed and central venous saturations, cardiac output, DO_2, and VO_2 while allowing access to the central circulation. This was the tool used in the earlier GDT trials targeting increases in cardiac index and DO_2I, but its use is declining because of concerns about catheter-associated morbidity, reduced expertise in insertion and data interpretation, and the availability of less invasive tools. In countries such as the United Kingdom, its use is typically restricted to cardiac, major liver, and transplant surgery.
- Esophageal Doppler monitor (EDM) (see also Chapter 46). This device uses transesophageal ultrasound measurement of descending aorta blood velocity, integrating this with estimated aortic cross-sectional area to derive SV. Other measurements include peak velocity, used as an indicator of ventricular contractility, and corrected flow time (FTc), the duration of systolic aortic blood flow corrected for heart rate. FTc may be reduced (<330 ms) by increased systemic vascular resistance (SVR), reduced SV, or both. SVR may be calculated by inputting CVP and mean arterial pressure (MAP), helping to identify whether a low FTc is due to inadequate preload or excessive afterload. Variation in SV with positive-pressure ventilation (SV variation [SVV]) is also measured by the latest EDM models. Perioperative GDT trials have targeted increases in SV and FTc, typically aiming to preemptively optimize these values with colloid boluses rather than responding to evidence of overt hypovolemia. Multiple algorithms for EDM-guided GDT have been studied. Some incorporate FTc and SV (Fig. 59-6),[141,142] whereas more simple algorithms rely on repeated fluid boluses until SV does not increase further, presumably corresponding with the peak of the Starling curve.[143]

Other targets for goal-directed therapy are as follows:

- Arterial blood pressure and waveform analysis: These monitors analyze the invasive arterial blood pressure or plethysmograph trace to yield two types of measurement. First, an estimate of SV (and therefore cardiac output and index) based on the principle that pulse pressure is proportional to SV when arterial compliance is constant. Interpatient variation in arterial compliance may be accounted for by regular calibration steps using lithium dilution (LiDCO Plus, LiDCO, Lake Villa, Ill) or thermodilution (PiCCO, Phillips, Andover, Mass) or ignored in uncalibrated monitors (LiDCO Rapid, LiDCO; Vigileo, Edwards, Washington, DC), the latter representing SV trends rather than absolute estimates. Second, SVV, a predictor of fluid responsiveness based on systolic pressure variation with intermittent positive-pressure ventilation, can be measured.
- Thoracic bioimpedance: This has been underexplored in perioperative GDT and outcomes.
- CVP: Despite one study that demonstrated improved outcomes from hip fracture surgery when CVP response to intravascular fluid challenges was compared to unmonitored control,[144] CVP readings are clearly poorly predictive of intravascular blood volume and fluid responsiveness.[145]
- Echocardiography (also see Chapter 46): This advanced technique is used for guiding fluid therapy and yielding information on cardiac performance and filling, but requiring operator expertise and a transesophageal approach in the intraoperative setting.
- Lactate: A reduction in increased blood lactate concentrations is used clinically as a marker of successful resuscitation, and is used as a therapeutic target in very few studies.[146]
- O_2 extraction and venous O_2 saturation (SvO_2) or central venous saturation ($ScvO_2$): Inadequate tissue O_2 delivery may be signaled by increased O_2 extraction and the resultant mixed or central venous O_2 desaturation. Low $ScvO_2$ is associated with poor outcomes after high-risk surgery,[147] although it has been targeted in only one interventional study in major noncardiac surgery.[148]

Recent meta-analyses have highlighted the potential benefits of the GDT process. One meta-analysis with the most tightly defined patient group (surgery but not trauma or sepsis) and all time points (preoperative, intraoperative, and postoperative GDT) and GDT tools (PAC, EDM, and arterial waveform analysis), showed GDT to be associated with a reduction in postoperative morbidity and hospital length of stay.[132] Specifically, GDT leads to a reduction in the number of patients with postoperative renal impairment, respiratory failure, and postoperative wound infection. Many of the individual studies were not powered to detect a mortality difference; however, when analyzed rigorously in this Cochrane systematic review, excluding poorly controlled studies, hospital or 28-day mortality was also reduced by GDT.[132] In another meta-analysis, subgroup analysis of studies using the EDM as the GDT tool was performed, albeit in a more diverse patient group including those with multiple trauma. EDM-guided GDT, even when fluids and not inotropes or vasopressors were used, was again found to reduce postoperative morbidity, but not mortality.[149]

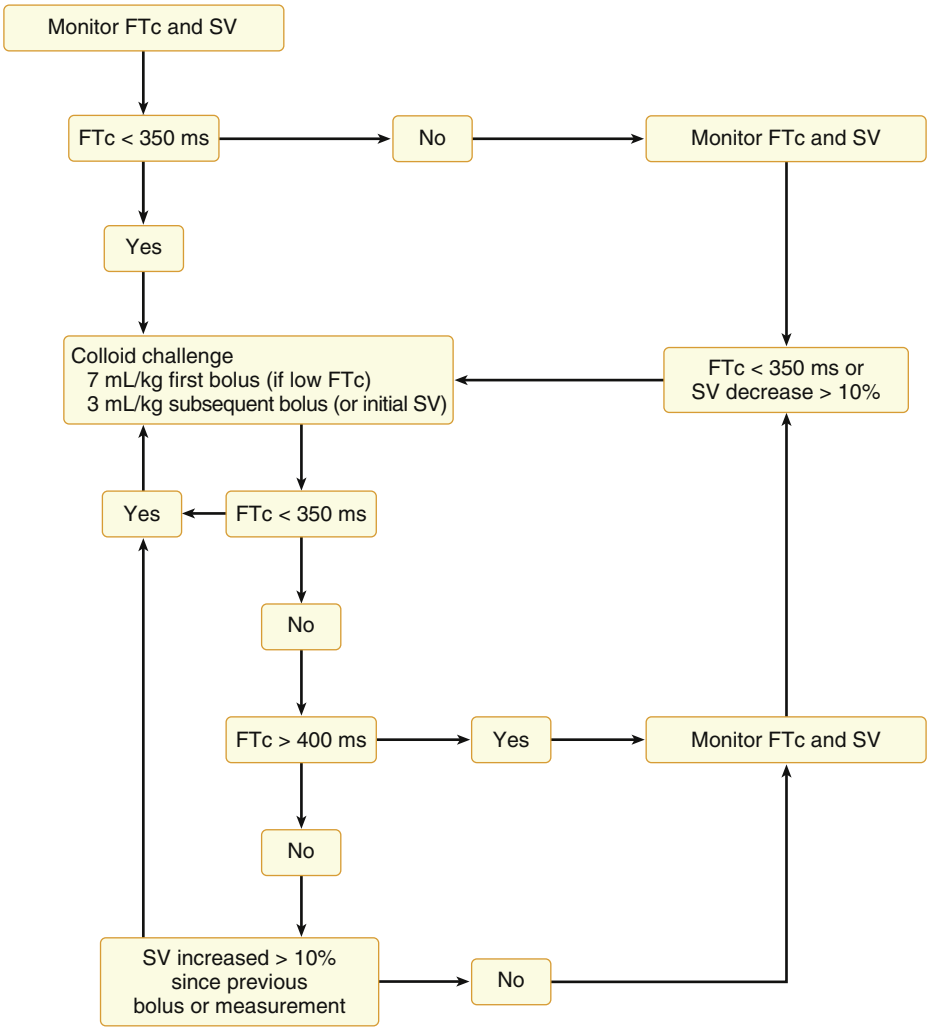


Figure 59-6. Protocol for ODM-based intraoperative goal-directed fluid therapy. *FTc,* Heart rate-corrected descending aorta flow time; *SV,* stroke volume. *(Redrawn from Noblett SE, Snowden CP, Shenton BK, et al: Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection,* Br J Surg *93:1069, 2006.)*

A frequent finding in GDT studies is that the intervention group receives more fluid, typically an extra 500 mL of colloid, a finding that has raised questions, as follows:

1. This fluid excess may seem to be at odds with the potential benefits of a conservative fluid strategy. However, it should be noted that the fluid excess in the liberal groups of fluid balance studies is typically of greater magnitude and different type (~1500 mL of excess crystalloid overall) and is indiscriminate, in comparison to the targeted administration to some patients based on specific physiologic variables in GDT. This difference may be partly responsible for the finding that overall outcomes in "liberal" groups are worse than those in GDT groups in their respective trials.[108]
2. The potential benefit of the GDT process is underlined by a failure to replicate the improved outcomes when these fluid balance differences are used as therapeutic targets. This was shown in a study in which the intervention group subjects were uniformly administered an extra 500 mL of colloid compared with the control group, with no improvement in postoperative outcomes.[150] This suggests that it is the individualization of therapy supported by monitored variables that may bring the clinical benefit.
3. Even in GDT trials with few overall differences in intravascular fluid balance between the control and intervention groups, the individualization of patient fluid requirements may be reflected in the timing of intraoperative fluid administration. In one study, early intraoperative EDM-guided fluid administration in the first quarter of surgery increased cardiac output above that of the control group, a difference that was sustained until the end of surgery and reduced postoperative morbidity.[142]

Despite the apparent benefit of GDT in the studies performed so far, further research is still required in large-scale multicenter trials to address the following:

- Although most of the GDT studies have used boluses of a variety of colloids, it is not clear if one colloid is superior or whether crystalloids could be used for boluses instead. This is particularly relevant given the cost and potential toxicities of colloids when

examined in sufficiently powered studies in critical care populations[49,81,151] (see also Chapter 61).
- The benefits of GDT need to be reappraised in the context of current perioperative and surgical practices that have developed since the advent of GDT, including enhanced recovery programs,[136,152] increasing use of laparoscopic surgery, regional anesthesia for orthopedic surgery, and declining control group postoperative mortality.[149]
- Inadequate numbers of certain surgical populations have been studied, in particular those in emergency surgery; meanwhile findings in one subpopulation should not be freely generalized to others undergoing fundamentally different physiologic insults.
- Hemodynamic monitors are currently under rapid ongoing development, and newer devices should be compared with existing ones for their utility in guiding GDT. Ultimately, as newer technologies are evaluated, the potential benefits of GDT may relate to the process of administering fluids based on rational physiologic endpoints rather than to the specific GDT tool used. As previous evaluations of monitoring devices have shown, no benefit is gained from using a device per se, but rather from the therapeutic intervention that the device allows.[153]

Appropriate Fluid Selection

Crystalloids or Colloids for Intravascular Plasma Volume Expansion. Although crystalloids are the most rational choice of fluid for replacement of evaporative losses, maintenance fluid requirements, and expansion of the entire extracellular fluid volume, the choice of crystalloid or colloid for plasma volume replacement in the perioperative phase is not clear. This underlines the lack of adequately powered perioperative studies directly comparing the two fluid types when administered in a similar fashion. Although the majority of GDT studies use colloid for their intravascular volume expansion, these studies are also comparisons of fluid administration guided by physiologic endpoints with nonguided therapy. Whether the same level of benefit can be achieved by crystalloid-based GDT merits further investigation. Crystalloid may be effective in plasma volume expansion (PVE) at amounts less than previously reported, although typically 40% to 50% more crystalloid than colloid must be administered to obtain the same clinical volume effect.[3] When combined with the increased propensity of crystalloid to filter across the capillary membrane, more extravascular volume expansion occurs, potentially causing tissue edema. When compared with colloids, crystalloids may lead to increased GI mucosal edema,[154] with the potential for delayed postoperative GI function and bacterial translocation. The differential effect of crystalloids when compared to colloids on tissue O_2 tension has no clear consensus.[50] The limited data comparing colloid with crystalloid for perioperative PVE may lead clinicians to extrapolate findings from studies in critical care. A Cochrane review highlighted the lack of improvement in all-cause mortality when colloids were used for intravascular volume expansion in unselected critical care populations.[155] In studies specific to patients with sepsis, starch-based colloids, including smaller MW versions, are associated with an increased requirement for renal replacement therapy, blood transfusion, and an increase in severe adverse events.[80] Although these findings may not be directly related to patients undergoing surgery, starch colloids should be avoided in perioperative patients with severe sepsis or at increased risk for renal failure pending the necessary large-scale trials assessing their safety in the perioperative setting (see also Chapter 61). This is reflected in license restrictions for these fluids in the United States, and in the United Kingdom the use of starches has been suspended in all settings. The potential toxicities of colloids must be weighed against the potential for excessive intravascular volume effects of PVE using crystalloids until more data are available informing the debate on crystalloids versus colloids for perioperative PVE.

Saline-Based or Balanced Solutions. Although its clinical relevance has been debated,[43] evidence demonstrates that intraoperative fluid administration based on isotonic saline causes a postoperative hyperchloremic acidosis and increase in spontaneous ventilation for respiratory compensation.[38] The excess NaCl and water load associated with isotonic saline is also excreted more slowly than that associated with balanced crystalloids. More focused trials in groups at risk for renal injury and postoperative respiratory failure will help to determine whether these adverse physiologic effects translate into worse clinical outcomes, as has been found in the general critical care population.[52] More practical problems may include the inappropriate administration of fluid boluses as the result of the finding of a base deficit incorrectly ascribed to tissue hypoperfusion. It is reasonable to restrict isotonic saline solution to the indications outlined in the section on preoperative fluid and electrolyte management and to use balanced crystalloids when required, until further data are available. Very limited data exist on the impact of colloids administered in either saline or balanced crystalloid solutions.

Typical Practical Approach. The following guidance represents an assimilation of the physiology, fluid pharmacology, and available evidence presented in this chapter. However, in many areas of perioperative fluid management the lack of robust evidence means that the choice of fluid and method of administration remains a clinician's choice informed by the balance of risks and benefits. The following overall themes in prescribing fluids in moderate-to-major surgery are important:

- Fluids administered should be individualized. This may be as simple as dosing postoperative maintenance fluids on a milliliter-per-kilogram basis or titrating intraoperative plasma volume expansion to objectively measured physiologic variables.
- Fluid status changes constantly throughout the perioperative period and should be frequently reassessed.
- The approach should be adapted to the patient and surgical factors outlined later.

Preoperative. In preparing for elective surgery, oral clear fluid intake should continue until 2 hours preoperatively and longer fasting discouraged. The use of preoperative bowel preparation should be restricted to carefully selected cases, and in these cases an infusion of 1 to 2 L of

balanced crystalloid with K^+ supplementation should be given in the preoperative period. Chronic comorbidities should be assessed for their influence on fluid and electrolyte balance, as outlined later.

Emergency surgery patients are likely to have acute disturbances of fluid compartments. They require timely resuscitation guided by rational physiologic endpoints such as trends in blood pressure and heart rate, lactate, urine output, and mixed or central venous O_2 saturations. Although preoperative fluid administration using cardiac output monitoring makes clinical sense, often logistical implications are involved with this approach and in some cases (ongoing blood loss or early surgical control of sepsis) surgery should not be delayed. A pragmatic approach is required to provide ongoing fluid resuscitation without compromising early surgical intervention. Upper GI losses should be quantified and replaced with isotonic saline, and lower GI losses (fistula, ileus, or obstruction) with balanced crystalloid. K^+ should be supplemented as appropriate.

Intraoperative. A background infusion of balanced crystalloid should be used to replace the ongoing water and electrolyte losses experienced during surgery. Hypotension caused by general or regional anesthesia is related primarily to vasodilation and reduced inotropy, and, unless the patient is hypovolemic because of preoperative factors, it is more rational to treat this with small doses of vasopressors, inotropes, or both.[11] Fluid therapy in patients considered to be at higher risk should be guided by invasive pressure monitoring to allow early recognition of overt hypovolemia and markers of global tissue perfusion, including lactate and acid-base status. Although no universally accepted definitions of a high-risk case exist,[156] major elective or emergency surgery should be included, especially in patients with advancing age (see also Chapter 80), comorbidities (see Chapter 39), and poor exercise tolerance, whose overall postoperative mortality risk is estimated to be more frequent than 5%. In these cases and particularly in certain orthopedic and intraabdominal operations about which the evidence base is strongest, cardiac output should be optimized by titrating boluses of a suitable colloid to a measured variable such as SV and FTc, cardiac output and O_2 delivery, or SVV, depending on the monitor used. Blood loss should be replaced with colloid or blood and blood products depending on the volume lost and variables suggesting inadequate tissue O_2 delivery (see also Chapter 61). Crystalloid may be used as an alternative for intravascular plasma volume expansion, but the increased volume required and potential for extravascular volume expansion should be considered. Overall the goal should be to achieve euvolemia by the end of surgery or the early postoperative period.

Postoperative. High-risk surgical patients may benefit from an ongoing period of GDT targeting O_2 delivery in the early postoperative period.[157] In all other patients after major surgery, an assessment of fluid status should be made based on clinical examination and supporting physiologic measurements such as lactate, central or mixed venous saturations, and cardiac output variables, if available. If patients are euvolemic and able to return to oral fluid intake, this is the best way of avoiding the iatrogenic effects of postoperative fluid administration. Early oral intake is typically well tolerated and safe, and early oral nutrition may reduce the incidence of postoperative complications.[158]

The following should be done in patients requiring ongoing IV therapy:

1. Electrolytes should be checked at least daily to monitor for hyponatremia and other electrolyte derangements.
2. Fluid requirements should be strictly divided into three categories for their ongoing assessment and treatment:
   a. "Pure" maintenance requirements should be salt-poor and contain a modest volume of free water to account for the postoperative state of salt and water retention. Infusions should therefore consist of the following[159]:
      - 1500 to 2500 mL in 24 hours, depending on weight, or 1 to 1.2 mL/kg/hr. Given the relative reduction in TBW in obesity (see previous discussions on crystalloids, fluid compartments), consideration should be given to dosing this fluid requirement based on ideal body weight in this setting.
      - 50 to 100 mEq Na^+ should be given in 24 hours.
      - 40 to 80 mEq K^+ should be given in 24 hours.
      - It is likely that part of this minimal maintenance volume should comprise hypotonic fluids such as 5% dextrose or 0.18% saline with 4% dextrose. Because of the risk for postoperative hyponatremia, this maintenance intravascular fluid volume should not be increased if suspicion for hypovolemia exists. Rather, the source of the ongoing loss should be identified and treated separately. As oral fluid intake increases, this maintenance fluid should be reduced proportionately.
   b. Replacement of ongoing losses. This fluid requirement requires frequent reassessment to appropriately titrate replacement fluids, if indeed any are needed. Volumes given should reflect measured amounts lost and an assessment of intravascular volume status and adequacy of organ perfusion (mental state, lactate, hemodynamic trends). Losses from the GI tract (vomiting, nasogastric aspirates, stoma) should be replaced with an equal volume of isotonic saline or balanced crystalloid with K^+ as appropriate. Losses to third spaces, such as reaccumulation of ascites, should be treated with a mixture of colloid and crystalloid, and blood loss replaced with colloid, blood, or blood products, as well as definitive intervention, if appropriate.
   c. New requirements (resuscitation). New requirements may relate to the development of postoperative complications such as hemorrhage (absolute hypovolemia) or acute sepsis (relative or absolute hypovolaemia).

Postoperative oliguria should be interpreted cautiously, particularly in the first postoperative 24 hours. The patient should be carefully assessed for corroborative evidence of impaired end-organ perfusion and alternative causes of oliguria, including catheter obstruction and intraabdominal hypertension, considered. In the absence of markers indicating hypovolemia and inadequate tissue perfusion, large volumes of fluid challenge

are inappropriate and may aggravate postoperative positive fluid and Na^+ balance in the face of a normal surgical stress response.

Special Considerations

Patient Factors

Heart Failure. The diverse pathophysiologic effects of heart failure and their treatment may make perioperative fluid management particularly challenging. The hemodynamic effects of chronic heart failure are typified by systolic and diastolic dysfunction of the left, right, or both ventricles with secondary maladaptive neurohumoral responses. These include persistent activation of the RAA axis, with consequent salt and water retention, and chronic sympathetic nervous system (SNS) activation, with persistent tachycardia and vasoconstriction. Undertreated patients may therefore present with edema in both lungs and peripheral tissues and increased central blood volume in the face of poor myocardial function.

Treatments for heart failure attempt to correct many of the neurohumoral responses, and many have been shown to improve long-term prognosis in heart failure. In the perioperative phase they may bring challenges to fluid management, including chronic volume depletion, blunting of normal sympathetic responses, and electrolyte disturbances. They include β-adrenoreceptor antagonists, diuretics, digoxin, and antagonists of aldosterone and angiotensin.

Perioperative fluid therapy in patients with heart failure has two goals. The first is to preserve cardiac output, bearing in mind the influence of preload, contractility, and afterload. The ventricles are typically poorly compliant and require adequate preload, which may be reflected in a relatively high CVP and adequate diastolic filling time to maintain good cardiac output. However, the flattened Starling curve of the failing heart means that excessive intravascular volume infusion and preload may lead to impaired contractility and worsening cardiac output. This leads to "forward failure," manifested as inadequate organ perfusion, and "backward failure," manifested as pulmonary and peripheral edema, particularly in the presence of aberrant salt and water excretion. The second goal is to minimize the cardiac work to avoid a vicious cycle of increased cardiac O_2 demand, inadequate O_2 supply, and worsening myocardial function. In particular, tachycardia triggered by hypovolemia and other stimuli should be avoided. Striking a balance between hypovolemia and hypervolemia is particularly important in patients with heart failure, but it may be difficult to assess clinically.

The practical approach to patients with heart failure involves careful preoperative assessment of fluid status and electrolytes and optimization of heart failure treatments when time allows. The complex cardiovascular situation mandates invasive hemodynamic monitoring for moderate or major surgery with consideration of cardiac output monitoring using modalities such as transesophageal echocardiography or pulmonary artery catheterization,[160] although less invasive modalities may be used. Measurement of cardiac filling and contractility is particularly important because the sources of intraoperative hypotension (reduced preload, contractility, or afterload) require different treatments and, particularly in this group, should not be blindly treated with fluid boluses. Infusion of large volumes of any fluid, including blood and products, should be undertaken only with objective evidence of intravascular volume loss.

The effects of heart failure therapies should be taken into account in the perioperative phase. Diuretics may leave patients in a chronically volume-contracted state that worsens anesthesia-related hypotension. Loop diuretics frequently cause hypokalemia and hypomagnesemia, whereas aldosterone antagonists cause hyperkalemia, which may be severe when combined with ACE-inhibitor treatment or chronic kidney disease. Normalization of electrolytes is particularly important in patients taking digoxin, in whom hypokalemia may potentiate digoxin toxicity. ACE-inhibitors or angiotensin receptor antagonists themselves lead to a blunted sympathetic and angiotensin response to anesthesia-related vasodilation. The hypotension caused by these should be treated appropriately by small doses of inotropes or vasopressors, which may include vasopressin analogues.[160]

Kidney Disease. Patients with dialysis-dependent chronic kidney disease have multiple pathologic features that must be taken into account in perioperative fluid therapy (see also Chapter 75). Overall fluid balance may be disturbed by reduced or absent native urine production, with reliance on dialysis to achieve the target "dry" weight, representing estimated euvolemia. Organ O_2 delivery may be impaired by various factors, including chronic anemia, endothelial dysfunction, and microvascular perfusion abnormalities. The frequent coexistence of heart failure and systemic or pulmonary hypertension and the bleeding tendency caused by platelet dysfunction further increase the perioperative challenge.[161]

Preoperative assessment should focus on the adequacy of chronic dialysis in attaining euvolemia, and estimating the normal volume of native urine output. Comorbidities should be assessed and optimized. Surgery should be undertaken in a facility where preoperative and postoperative dialysis or hemofiltration can be offered, in case of intraoperative fluid overload or hyperkalemia that is not responsive to conservative measures. In elective surgery, preoperative dialysis should be timed such that the patient enters the intraoperative phase with a normal blood volume. Surgery in the presence of hypervolemia increases the risk for pulmonary and peripheral edema, hypertension, and poor wound healing, whereas hypovolemia brings a risk for anesthesia-related hypotension and inadequate tissue perfusion. Practically, this means performing dialysis the day before surgery to allow equilibration of fluid and electrolyte compartments and time for dialysis anticoagulants to be metabolized. Electrolytes should be checked on the morning of surgery; sampling too soon after dialysis, before equilibration, may give an artificially low K^+ result leading to unnecessary exogenous supplementation. Conversely, fasting may actually favor a hyperkalemic state as a result of the reduced presence of insulin; the ideal K^+ value after dialysis is in the low-to-normal range. In emergency surgery, sufficient time to safely dialyze patients preoperatively may not be available. In this case, electrolyte abnormalities must be managed conservatively, with particular care paid to intraoperative fluid balance.

As with other major comorbidities with a critical impact on fluid and electrolyte balance, the importance of avoiding both hypovolemia and hypervolemia and the predisposition to inadequate tissue perfusion mean that detailed monitoring of hemodynamic variables, including invasive central venous and arterial pressure and cardiac output should be considered for moderate-to-major surgery. The amount of fluid administered intraoperatively should be titrated to objective physiologic measurements, although the type of fluid given is open to debate. Large volumes of isotonic saline should be avoided, because the acidosis induced favors extrusion of K^+ from cells. In contrast, K^+-containing balanced crystalloids do not cause hyperkalemia in clinical trials.[44,162] An alternative crystalloid is a K^+-free HCO_3^--buffered dialysis solution such as Hemosol. Colloids may be used for intravascular volume replacement, although owing to their predominantly renal excretion, the volume effect and potential toxicities may be exaggerated in these patients. Liaising with the nephrologist is important before considering blood transfusion; if the patient is awaiting renal transplantation, human leukocyte antigen–matched blood may be required to minimize antibody formation and future difficulties with blood and tissue matching.

Upper Gastrointestinal Loss. Large-volume gastric fluid loss may be caused by congenital or acquired gastric outlet obstruction and causes a distinct pattern of fluid and acid-base abnormalities. Dehydration occurs as a result of water loss, reduced total body Cl^- content, and alkalosis caused by proton loss, with raised serum HCO_3^-. The initial renal response is formation of urine with low Cl^- and high HCO_3^- content. However, progressive dehydration leads to increased aldosterone secretion, aimed at retaining Na^+ and water. Na^+ is retained at the expense of K^+ and H^+ ions, leading to hypokalemia, and worsening metabolic alkalosis with a paradoxically acid urine. The alkalosis also reduces the circulating ionized fraction of Ca^{2+}.

Correction should include gradual rehydration with isotonic saline and K^+ supplementation, changing to dextrose-containing saline solutions depending on electrolyte analysis. Any surgery required to treat gastric outlet obstruction should be scheduled after correction of the volume and acid-base status.

Sepsis and Acute Lung Injury. Patients with infection and sepsis syndromes may be encountered early in their presentations, because surgical source control of infection (drainage of abscesses, debridement of necrotic tissues, removal of infected devices) forms a key part of early sepsis therapy (see also Chapter 101).[163] Cardiovascular instability may be a particular problem, contributed to by endothelial dysfunction and intravascular fluid loss, vasodilation with fluid maldistribution, sympathetic redistribution of blood volume away from the peripheral circulation, and impairment of cardiac function. Fluid resuscitation, with the goal of maintaining adequate end-organ perfusion is therefore a key part of the first 6 hours of sepsis treatment, which may represent the perioperative period for some patients. The following pragmatic targets are suggested for patients with sepsis who have tissue hypoperfusion, defined by blood lactate concentration at or more than 4 mmol/L or hypotension persisting after initial IV fluid challenge[163]:

- CVP 8 to 12 mm Hg (12 to 15 mm Hg in patients on ventilation)
- MAP 65 mm Hg or greater
- Urine output 0.5 mL/kg/hr or greater
- $Scvo_2$ greater than 70% (or mixed venous O_2 saturation > 65%)

Some have criticized the use of fixed CVP targets to guide early sepsis therapy because of their limited value in predicting fluid responsiveness and tissue hypoxia; alternative suggested targets include stroke volume, pulse pressure variation, and echocardiographic assessment of cardiac function.[164] Given the apparent nonsuperiority of colloids for resuscitation in this patient group and concerns about trends toward kidney injury when starches are administered in sepsis, current recommendations are to use 30 mL/kg of crystalloid in a protocolized fashion to achieve the described targets. In patients requiring further fluid, albumin should be considered, along with vasopressors, inotropes, and RBC transfusion to attain these goals. Further fluid challenges may be guided by dynamic measurements of fluid responsiveness, such as SV or pulse pressure variation. In established sepsis, fluid management becomes even more challenging as a result of the frequent presence of microvascular dysfunction, extravascular fluid overload, and disturbed neurohumoral responses to variations in intravascular volume.[165] A disruption occurs in the O_2 delivery and usage relationship as a result of cellular inability to use O_2 (cytopathic hypoxia),[166,167] with the result that strategies to elevate global O_2 delivery may be of little benefit while exposing patients to potential side effects of excessive fluid and catecholamines.[168,169] At this stage a less positive overall fluid balance is associated with improved outcomes.[170]

Patients with established acute respiratory distress syndrome (ARDS) may also present for surgical procedures. Here the focus of fluid therapy is the fine balance between avoiding an increase in lung edema while maintaining adequate tissue perfusion. ARDS is typified by increased pulmonary endothelial permeability, with extravasation of water and protein. The consequences are interstitial and alveolar edema, atelectasis, reduced pulmonary compliance, increased pulmonary artery pressures, and hypoxemia. Meanwhile, organ perfusion may be impaired by increased intrathoracic pressures and a reduction in cardiac filling pressures. Observational studies have highlighted an association between overall positive fluid balance and mortality in ARDS,[171] backed by a large randomized controlled trial demonstrating a reduction in ventilator and intensive therapy unit days in patients treated with a conservative fluid administration strategy.[172] Findings were similar in a subgroup of this trial who had undergone surgery, without any increase in kidney injury in patients treated with lower fluid volumes.[173] Extravascular lung water (EVLW) seems to be important in mediating the worse outcomes associated with a more positive fluid balance, with thermodilution studies showing excess EVLW to have reasonable sensitivity and specificity in predicting intensive therapy unit mortality in

patients with ARDS.[174] Assuming global organ perfusion appears adequate, as demonstrated by normal lactate levels, intraoperative losses should be replaced but otherwise be conservative in the volumes of fluid given to patients with ARDS intraoperatively. There is a lack of adequately powered studies on the choice of colloid or crystalloid for intravascular volume replacement in patients with ARDS.

Burns. Extensive burns create a situation of copious fluid loss from the circulation combined with particular sensitivity to the effects of excess fluid administration. Thermal injury creates an area of necrotic tissue with surrounding ischemic areas. The combination of dead tissue with areas undergoing ischemia and subsequent reperfusion causes localized and systemic inflammatory reactions through histamine, prostaglandin, reactive O_2 species, and cytokine release. Local impairment of endothelial barrier function leads to the loss of oncotically active plasma constituents, increased capillary filtration into the interstitial compartment, and evaporative transcutaneous fluid loss as a result of loss of skin integrity. Through similar mechanisms, extensive burns may lead to the systemic inflammatory response syndrome, with its well-recognized effects on fluid compartments outlined previously. The deleterious role of this inflammatory response is underlined by the reduction in mortality seen with early burn excision compared with conservative care.[175] IV fluid therapy is generally instituted for burns of greater than 15% total body surface area in adults and 10% total body surface area in children.[176] However, increasing uncertainty exists about the volume and type of fluid that should be given to patients with burns. Fluid administration is largely still based on formulas such as the Parkland formula (Box 59-1) or the Muir and Barclay versions. Although these have given a starting point for resuscitation volumes based on patient weight and extent of burn, myriad other patient and pathologic factors put such a recipe-based approach at odds with modern perioperative fluid therapy based on objective physiologic goals. Although the approaches based on these formulas advocate down-titration of administered fluid volumes if urine output is adequate (0.5 to 1 mL/kg/hr),[177] in reality this appears not to be practiced. Indeed, large studies have shown that the majority of burn patients receive fluid volumes in excess of those predicted by the Parkland formula, with a mean of 6 mL/kg/% burn compared with 4 mL/kg/% burn in 24 hours predicted by the formula.[178] Conversely, patients with inhaled and other nonburn injuries, electrical burns, or delayed resuscitation are considered to need increased resuscitation intravascular volumes, yet this is not taken into account by the formula approaches.

BOX 59-1 ***Parkland Burn Fluid Resuscitation Formula***

First 8 hours: 2 mL/kg × % TBSA (lactated Ringer solution)
Next 16 hours: 2 mL/kg × %TBSA (lactated Ringer solution)
Next 24 hours: 0.8 mL/kg × %TBSA (5% dextrose) + 0.015 mL/kg × %TBSA (5% albumin)

Data from Baxter CR: Problems and complications of burn shock resuscitation, Surg Clin North Am *58:1313, 1978.*
%TBSA, Burn size as % of total body surface area. Time periods refer to the time since the burn occurred.

Excessive fluid administration in burned patients ("fluid creep") is not benign. As in all conditions typified by systemic inflammation, excess administered fluid will collect in compliant compartments. Pulmonary edema requiring ventilatory support, fasciotomies in nonburned muscle compartments, raised intraocular pressure, and conversion of superficial to deep burns have been observed and attributed to fluid resuscitation.[176] Intraabdominal hypertension and compartment syndrome are correlated to the volume of fluid administered, with a particular rise when more than 300 mL/kg is administered in 24 hours.[179] These concerns have led to renewed efforts to find the optimum regimen for burn resuscitation in terms of crystalloid versus colloid, newer formulas using lower volumes such as the Haifa formula, and targeting objective physiologic parameters such as SV or intrathoracic blood volume. Pending a consensus from this ongoing work, burn resuscitation should be commenced with one of the currently accepted formulas, but actively down-titrated if a urine output of 0.5 to 1 mL/kg/hr is obtained, and consideration given to using a combination of crystalloids and colloids to reduce the total fluid volume administered.[180] Intraabdominal pressure should be monitored and consideration given to assessing resuscitation endpoints, such as lactate and cardiac output, in addition to urine output.

Pediatrics. Perioperative fluid therapy in pediatric patients has for many years been based on traditional approaches that are increasingly being reexamined (see also Chapter 93). Holliday and Segar[133] proposed a quantity and composition of maintenance fluid in hospitalized children in 1957 based on water requirements to sustain average metabolic activity and the electrolyte composition of milk. This developed into the 4-2-1 volume calculation for maintenance fluid requirements aimed at replacing insensible and urinary losses with hypotonic crystalloids containing glucose to maintain isoosmolality. These concepts were translated into the perioperative phase; glucose-based solutions were administered intraoperatively to reduce the apparently high risk for preoperative hypoglycemia after prolonged fasting,[181] and postoperative maintenance fluids were prescribed based on the 4-2-1 calculation using hypotonic crystalloids. Furthermore, the pediatric population was thought to be at risk for clinically significant preoperative dehydration by fasting, as a result of limited urinary concentrating ability and ongoing insensible losses because of the relatively large body surface area. Intraoperative replenishment of these volumes using 25 mL/kg of isotonic salt solution for those 3 years of age and younger or 15 mL/kg for those 4 years of age and older has been recommended.[182]

Multiple factors have led to a reevaluation of this approach. First, the modern approach to preoperative fasting, such that children may take clear—and potentially carbohydrate-containing—fluids up to 2 hours before surgery, reduces the risk for hemodynamically significant preoperative dehydration. It should therefore be necessary only to replace preoperative deficits using the amounts given previously when fasting has been excessive or preoperative pathologic processes reducing circulating volume intervene.[183] Second, the incidence of preoperative hypoglycemia is infrequent (<2.5%) and

related to inappropriately prolonged fasting or other risk factors, such as premature infants, neonates who are small for gestational age, or those with poor nutritional status.[184,185] Surgery itself increases blood glucose concentration, and administering glucose-containing solutions intraoperatively may cause hyperglycemia,[186] with the potential for osmotic diuresis and electrolyte abnormalities, or even adverse neurologic outcomes in the event of an ischemic or hypoxic event.[185] Glucose-free balanced crystalloid solutions should therefore be used intraoperatively, except in those at particularly high risk for hypoglycemia. Third, increasing awareness of the incidence and potentially disastrous neurologic outcomes from postoperative hyponatremia in pediatric populations has led to a reappraisal of postoperative hypotonic crystalloid maintenance fluids in 4-2-1 volumes. The effective SIADH induced by surgical stress and aggravated by the presence of pain and hypovolemia causes water retention and the risk for hypoosmolar hyponatremia if hypotonic solutions continue to be infused in significant volumes. Proposed strategies to avoid this include using half to two thirds of the calculated 4-2-1 formula maintenance fluids,[183] avoiding the most hypotonic fluids (4% dextrose with 0.18% NaCl),[185] and general measures that should be applied to all patients, as follows:

- Returning to oral fluids as early as possible
- Ensuring euvolemia to minimize the ADH response[187]
- Not confusing *maintenance* requirements with the variable amounts of fluid required because of *ongoing losses* (e.g., GI or blood), which should typically be replaced by isotonic crystalloids, colloids, or blood
- Checking electrolytes at least daily in those still receiving IV fluids

Although isotonic saline has been advocated as a "safer" fluid for postoperative maintenance, this brings the risk for Na^+ overload and hyperchloremic acidosis.

More recent developments in perioperative fluid management remain underexplored in pediatric populations. In particular, there is a dearth of data on whether colloid volume expansion is beneficial or harmful in pediatrics or whether goal-directed fluid therapy may confer the advantages that have been seen in adult populations. These areas require urgent investigation.

Hepatic Failure. Progressive liver disease and cirrhosis cause a distinctive pattern of abnormal fluid balance (see also Chapters 73 and 74). The combination of peripheral vasodilation and relative intravascular depletion can mimic a decrease in intravascular volume. Yet, total body Na^+ and water are retained with ascites and edema.[188]

The widely accepted pathophysiologic mechanisms are that progressive disruption of liver architecture combines with decreased hepatic nitric oxide (NO) bioavailability and increased vasoconstrictor production, leading to sinusoidal hypertension. Compensatory vasodilatory mechanisms, including NO overproduction, lead to splanchnic and systemic vasodilation, relative hypovolemia, and reduced systemic arterial pressure. This triggers baroreceptor-mediated activation of the RAA, SNS, and ADH release. Although cardiac output increases, reduced systemic vascular resistance persists despite these compensatory mechanisms. The state of hyperaldosteronism causes salt and water retention, frequently combined with hyponatremia resulting from a relative excess of water retention. Splanchnic vasodilation and vascular permeability combine with decreased lymphatic drainage to favor the formation of ascites. The neurohumoral response also induces renal artery vasoconstriction, reducing renal blood flow and increasing the risk for hepatorenal syndrome. A range of therapies centered around reduction of total body salt and water may maintain patients in a compensated state. These include dietary fluid and salt restriction, diuretics (particularly the aldosterone antagonist spironolactone and loop diuretics), and intermittent or continuous drainage of ascites. However, the perioperative period presents considerable potential for disturbance of this fine balance. Excessive administration of isotonic saline will aggravate the preexisting salt and water overload, potentially leading to further ascites and edema formation. Conversely, periods of hypovolemia are poorly tolerated, leading to a significant deficit in organ perfusion, further stimulation of the RAA, SNS, and ADH axes, and risk for kidney injury. The approach should therefore be to assess volume status carefully, possibly assisted by cardiac output monitoring, to replace losses with appropriate volumes of isotonic crystalloid, colloid, or blood but to avoid salt and water overload with excessive volumes of saline without clear clinical indication. In instances of large-volume (>6 L) ascites drainage, hemodynamic instability is a risk. Albumin appears to be a more effective prophylactic treatment for this than saline, abrogating the stimulated increase in plasma renin activity and maintaining more stable hemodynamics.[189] Lactate and other buffered fluids may be used in hepatic failure, although their metabolism may be slowed in advanced liver disease.

In decompensated liver disease with encephalopathy, raised intracranial pressure may be present and osmotherapy, such as hypertonic saline, should be used to bring plasma Na^+ into the high-normal range.[190] This is in contrast to chronic compensated liver disease, in which a degree of hyponatremia is well tolerated and does not require acute correction unless it is severe or symptomatic (see earlier discussion).

Obstetrics: Preeclampsia. Preeclampsia is a multisystem disease of pregnancy characterized by hypertension, proteinuria, and multiorgan involvement that may affect the kidneys, liver, pulmonary, and central nervous systems (see also Chapter 77). In contrast to the usual volume-expanded status in pregnancy, patients with preeclampsia have reduced plasma volume, combined with endothelial dysfunction and hypoalbuminemia. Previously IV volume expansion was thought to be beneficial in treating hypertension in preeclampsia. However, this has not been borne out by later studies.[191,192] Furthermore, a clear association exists between positive fluid balance and the incidence of pulmonary edema in this condition.[193] Acute pulmonary edema occurs in between 5% and 30% of cases of preeclampsia, is associated with increased hospital length of stay, and is a leading cause of death in preeclampsia. Most cases present in the postpartum period, perhaps reflecting the autotransfusion into a vasoconstricted circulation that occurs after delivery. Low COP also contributes.

Patients with preeclampsia should receive restricted volumes of IV crystalloid (80 mL/hr, including that received as drug diluents[194]), and fluid balance should be observed carefully. Oliguria should not be treated by administration of large volumes of fluids in the presence of normal renal function. This conservative strategy has not been associated with an increase in kidney injury.[195] Any blood loss in the peripartum or perioperative period should be replaced with an appropriate volume of crystalloid, colloid, or blood, depending on magnitude. Invasive monitoring should be used to direct fluid therapy in cases of severe preeclampsia.

Surgical Factors

Neurosurgery. Multiple physiologic factors mean that fluid and electrolyte therapy are a key component in the perioperative management of intracranial pathology (see also Chapter 70). This management may be complicated by disturbances of water and Na^+ balance caused by neurosurgical diseases themselves. Much of the current fluid management in this area is based on knowledge of this physiology, experimental models, and gradual evolution of interventions investigated in small trials rather than large randomized studies.

The intact blood-brain barrier (BBB) excludes electrolytes and large molecules but allows passage of water. Extravascular brain water is therefore related to plasma osmolality, with cerebral edema a feature of hypoosmolar hyponatremic conditions. Intracranial diseases may compromise the integrity of the BBB, increasing the predisposition to edema. Cerebral perfusion also may be impaired if systemic blood pressure is inadequate in the face of increased intracranial pressure, particularly in pathologic conditions in which autoregulation is impaired. Rational management of fluids in neurosurgical patients should start with maintaining baseline blood volume and cerebral perfusion and avoiding significant decreases in serum Na^+, osmolality, and oncotic pressure. Several situations may require more specific management, as follows:

1. Increased intracranial pressure: Increasing serum osmolality may reduce total brain water and therefore intracranial pressure by creating brain-blood osmotic gradients. Mannitol and hypertonic saline given by bolus have been the pharmacologic mainstays in this area. The osmotic action of these drugs may be reduced to variable degrees by dysfunction of the BBB, frequently seen in brain injury. However, they likely have therapeutic effects beyond simple osmotic effects.[196] Meta-analysis of the small studies available suggests that hypertonic saline may be superior to mannitol in reducing intracranial hypertension, but large-scale controlled studies are required to confirm this.[54] Conversely, using hypertonic saline in all patients with early traumatic brain injury without intracranial pressure monitoring has not been shown to improve outcomes.[55] Similarly, continuous infusion of hypertonic saline to induce persistent hypernatremia in the presence of cerebral edema also lacks evidence of benefit.[197] Restrictive fluid strategies have been advocated to minimize intracranial hypertension in severe traumatic brain injury. Although retrospective data analysis suggests that positive fluid balance is not associated with refractory intracranial hypertension, an association between hypervolemia and pulmonary edema was observed.[198]
2. Cerebral vasospasm: Manipulation of hemodynamics and hematocrit is traditionally used in the treatment of vasospasm after subarachnoid hemorrhage. This "triple-H" therapy (hypervolemia, hemodilution, hypertension) has entered practice based on small trials of efficacy rather than randomized studies.[199,200] Some workers, using extensive animal models, have advocated a hematocrit no lower than 30%, below which the benefits of reducing blood viscosity are outweighed by a reduction in O_2 delivery. They also caution against hypervolemia, both for its potentially injurious effects in the presence of a dysfunctional BBB and for the extracranial effects, particularly pulmonary edema.[201]
3. An intracranial pathologic condition may itself be a cause of disturbances of both water and Na^+ balance through diabetes insipidus, cerebral salt wasting, or SIADH. This should be assessed and treated as described in the section on electrolyte imbalance.

Clear comparisons of crystalloid and colloid in a variety of neurosurgical settings are lacking. Of the available evidence, albumin is associated with an increase in mortality in traumatic brain injury compared with isotonic saline.[5] In the absence of more robust evidence, a mixture of isotonic crystalloids and colloids is advocated in other neurosurgical settings.[200,202]

Trauma. In patients with evidence of major traumatic hemorrhage the key goals are to avoid clot disruption until definitive control of bleeding, to treat the acute coagulopathy of trauma, to maximize tissue O_2 delivery by the early use of packed red cell transfusion, and to avoid hypothermia and acidosis (see also Chapter 81). In the prehospital setting, restrictive fluid therapy may improve outcomes, particularly in penetrating trauma.[203] The approach should initially be one of permissive hypovolemia, with fluid administered to achieve cerebration rather than normotension in awake patients, systolic blood pressure of 70 to 80 mm Hg in penetrating trauma, or 90 mm Hg in blunt trauma.[204] The duration of organ hypoperfusion that may be involved with this approach should be minimized by rapid transfer for damage control intervention to stop bleeding, whether radiologic or surgical. Large volumes of IV crystalloids or colloids in early resuscitation will cause hemodilution and dilute clotting factors, and saline-based fluids may aggravate the acidosis associated with major blood loss. Rather, packed RBCs (PBRCs), clotting factors (e.g., fresh frozen plasma [FFP]) and platelets should be replaced early. Limited evidence, particularly from military populations and retrospective analyses, suggests "high" ratios of FFP to PRBC (e.g., 1:1 to 1:2) are associated with the best outcomes in massive transfusion compared with lower ratios (e.g., 1:9)[204,205] (see also Chapter 61). Active patient and fluid warming should be used and clot stability improved with tranexamic acid.[206] Once hemostasis has been achieved, restoration of normal circulating volume and tissue perfusion is the goal, with ongoing blood, clotting factors, platelet, and fluid infusions targeting normalization of

cardiac output and O_2 delivery, lactate levels, and blood clotting (best checked using near-patient whole-blood tests of clotting, such as thromboelastography). A small number of trials support the practice of GDT in the immediate perioperative trauma setting, but larger controlled trials are required. After surgery and initial resuscitation, much of the evidence for ongoing fluid approaches is derived from unselected critical care populations. As outlined previously, the evidence suggests that in established critical illness, aggressive GDT may be harmful.[203]

Patients with traumatic brain injury in addition to major hemorrhage present a dilemma because the raised cerebral perfusion pressure required for adequate cerebral blood flow in the face of raised intracranial pressure is at odds with the hypotensive resuscitation approach. In isolated head injuries, using fluids and vasopressors to achieve a mean arterial pressure above 90 mm Hg is recommended, with avoidance of hyponatremia and hypoosmolality to minimize cerebral edema.[196,207] Little evidence exists to inform resuscitation treatment in patients with mixed intracranial and extracranial trauma, so the strategy should be a clinically judged compromise prioritizing the requirements of the most severe injuries. Rapid hemorrhage control is particularly important to allow subsequent normalization of systemic blood pressure to meet the need for adequate cerebral perfusion. Even in general trauma, much of the evidence supporting current resuscitation approaches is derived from animal models and limited randomized trials, predominantly in young otherwise healthy subjects in the prehospital setting.[204] The needs of individual patients should therefore be taken into account, particularly because older patients with comorbidities may tolerate periods of hypoperfusion very poorly.

Free Tissue Flap Surgery. Free tissue flaps are frequently used during oncoplastic surgery, typically for breast reconstruction or after resection of head and neck tumors and involve the autologous transplantation of tissue to fill a defect, complete with arterial supply and venous drainage. Transplanted vessels are denervated and lack intrinsic sympathetic tone, but the feeding vessels are not; vasoconstriction in these feeding vessels related to cold and excessive doses of vasopressor must be avoided because it may threaten the perfusion of the flap. Flap blood flow depends on systemic blood pressure and blood viscosity, and hypervolemic hemodilution has traditionally been used to address these requirements. However, given the reduction in O_2 carrying capacity and potential for flap edema that this entails, a more conservative fluid strategy should be used, which may improve flap outcome.[208] The use of dextrans to improve blood flow is not currently favored, because no benefit has been demonstrated and the risks for medical complications is relatively high.[209] Free tissue flaps have disrupted lymphatics, which take several weeks to reconnect, making them particularly prone to interstitial edema. Large volumes of crystalloid—favoring increased capillary filtration—should be avoided and colloids used for blood volume expansion.[210]

Intrathoracic Procedures. Any procedure within the thorax, including upper GI and thoracic surgery, can lead to postoperative respiratory problems, including ARDS and acute lung injury (ALI) (see also Chapter 66). The development of ARDS and ALI is partly due to the proinflammatory nature of one-lung ventilation,[211,212] modified by a host of other patient and surgical risk factors. In esophagogastrectomy, retrospective studies and case series have suggested reduced pulmonary complications with restrictive fluid strategies.[213-216] One retrospective observational study of esophagectomy patients found a cumulative fluid balance greater than 1900 mL from surgery to the second postoperative day to be an independent risk factor for other adverse outcomes, including death.[217] The use of diuretics to actively target fluid balance, degree of cardiovascular support, and presence or absence of epidurals is not explored in this study, and controlled trials of fluid balance approaches are therefore required in this population. However, the potential benefit of conservative fluid administration in this group is consistent with the large randomized study of patients with ARDS demonstrating improved pulmonary outcomes in those treated with a restrictive rather than liberal fluid regimen.[172] While maintaining adequate tissue perfusion, a cautious approach to fluid administration is recommended, both to minimize pulmonary complications and to avoid anastomotic edema.

Hepatic Resection. Blood loss during liver parenchymal resection, a risk factor for worse outcomes, is associated with high venous pressure and backflow of blood through the valveless hepatic veins (see also Chapter 73). One study has shown that a CVP of 5 cm H_2O or lower is associated with significantly lower blood loss and transfusion requirements.[218] Several techniques are used to maintain a low CVP, including conservative fluid management, at least until the hepatic resection is completed. Despite evidence that using a low CVP technique does not have adverse effects on renal or liver function,[219] a pragmatic compromise must be sought for each patient; inducing hypovolemia during liver resection risks hemodynamic instability and end-organ hypoperfusion, particularly in those with preexisting cardiorespiratory morbidity, increases the risk for air embolism, and reduces the physiologic reserve should massive blood loss occur. Once liver resection is finished, a more generous fluid approach can be taken to ensure adequate circulating volume. This may be guided by invasive hemodynamic monitoring and minimally invasive cardiac output monitoring to provide a rational endpoint to fluid therapy in this phase.

Major Intraabdominal Surgery. Major intraabdominal operations, particularly those involving multiple organ resections for tumor require careful perioperative fluid management. Major gynecologic operations such as pelvic exenteration or ovarian debulking and urologic procedures including cystectomy, radical nephrectomy, and major retroperitoneal lymph node dissection can involve dramatic fluid shifts in the perioperative period. Fluid losses during surgery are caused by prolonged peritoneal exposure, significant blood loss, and acute drainage of tumor-related ascites. The total volume lost is difficult to quantify, so cardiac output monitoring is valuable when combined with CVP and arterial pressure monitoring and serial blood gas analysis.[220, 221] Intraoperative drainage of ascites is followed by fluid shift from the vascular space as this reaccumulates postoperatively and may require

large volumes to replace the ongoing loss. Another consequence of fluid redistribution is electrolyte abnormalities; hypokalemia and hypomagnesemia are frequently seen.

Renal Transplant. The key goals of fluid therapy in the perioperative management of renal transplant are to ensure adequate renal perfusion to support early graft function and avoid fluid therapy side effects to which patients with impaired renal function may be susceptible (see also Chapter 74). Traditionally, CVP-guided intraoperative fluid therapy has been advocated, using large volumes of crystalloid (up to 60 to 100 mL/kg) to achieve a CVP of 10 to 12 mm Hg or higher before reperfusion.[222] Recently, more conservative goals have been advocated, limiting crystalloid infusion to 15 mL/kg/hr, aiming for a CVP of 7 to 9 mm Hg[223] with no apparent increase in graft failure. The role of alternative tools such as esophageal Doppler or pulse contour analysis to supplement or replace CVP-guided fluid therapy in this area also has been suggested.[224] Patients with renal failure may develop acidosis-related hyperkalemia when isotonic saline is infused during transplant,[44] so balanced crystalloid solutions, or even K^+-free, buffered dialysate solutions, should be used. The role of colloids in this population requires further study, although concerns over renal toxicity of starches may limit their use.[224] Postoperative fluid therapy should take into account the baseline maintenance requirements and the ongoing losses resulting from urine production.

Liver Transplant. Liver transplantation involves a series of major physiologic disruptions that have direct relevance to fluid and electrolyte management (see Chapter 74).[225] Therapy should be guided by data from invasive monitoring, possibly including pulmonary artery catheterization. During phase I (preanhepatic), large-volume blood loss and further fluid shift resulting from drainage of ascites may occur. During phase II (anhepatic) a major reduction in venous return and therefore cardiac output may occur if (depending on surgical technique) the inferior vena cava, portal vein, and hepatic artery are cross-clamped. Crystalloid and colloid infusion may be required with vasopressors to maintain arterial pressure during this phase, although excessive volume administration risks right heart failure after later unclamping. Absent citrate and lactate metabolism during this phase contributes to acidosis, hypocalcemia, and hypomagnesemia. On reperfusion and unclamping, cold, acidotic, hyperkalemic fluid is released into the circulation. Preparation for this must include normalizing pH and maintaining plasma K^+ in the low-normal range during phase II. This may require Ca^+, insulin-dextrose, hyperventilation, and even $NaHCO_3$ treatment. Phase III (reperfusion) leads to an acute rise in CVP, possibly with hepatic congestion and right heart strain. Systemic vasodilation and cardiac suppression may occur, leading to hypotension requiring vasopressor or inotrope support. If not given already, a bolus of $CaCl_2$ should be used to prevent hyperkalemia-related arrhythmias. Subsequent uptake of K^+ by a working graft may then require aggressive replacement. Ongoing infusion of fluids, red cells, and blood products should be guided by clinical blood loss, maintaining a hematocrit of 26% to 32% and addressing coagulopathy as guided by near-patient tests of clotting.

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Chapter 60

Perioperative Acid-Base Balance

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KEY POINTS

- The presence of a significant acid-base abnormality often signals a sinister underlying problem.
- All acid-base abnormalities result from alterations in the dissociation of water.
- Only three factors independently affect acid-base balance—the partial pressure of carbon dioxide in the arterial blood (Pa_{CO_2}), the strong ion difference (SID), and the total concentration of weak acids (A_{TOT}).
- Respiratory acidosis and alkalosis are caused by hypercarbia and hypocarbia, respectively.
- Metabolic acidosis is caused by decreased SID or increased A_{TOT}. Decreased SID results from accumulation of metabolic anions (shock, ketoacidosis, and renal failure), hyperchloremia, and free water excess. Increased A_{TOT} results from hyperphosphatemia.
- Metabolic alkalosis is caused by increased SID or decreased A_{TOT}. SID increases in response to sodium gain, chloride loss, or free water deficit. A_{TOT} decreases in hypoalbuminemia and hypophosphatemia. This is particularly common in critical illness.
- Most acid-base disorders are treated by elimination of the cause.

WHY IS ACID-BASE BALANCE IMPORTANT?

The human body is composed principally of water, partitioned into intracellular and extracellular compartments. The electrolyte composition of each of these spaces is tightly controlled to maintain homeostasis. Alterations in the relative concentrations of electrolytes and of carbon dioxide (CO_2) affect the tendency of water to autoionize into its component parts: hydrogen and hydroxyl ions. The hydrogen ion concentration is conventionally measured as pH, the negative logarithmic value of its concentration. Deviations in extracellular pH away from the resting value of 7.4 have long been associated with acute and critical illness. Such deviations are known as acid-base abnormalities.[1-3] The detection, interpretation, and treatment of acid-base abnormalities have become a core element of clinical care.[4]

All acid-base abnormalities result from changes in the local concentration of strong ions, weak acids, and CO_2.

This chapter first looks at the basic chemistry behind acid-base balance. From there, we explain the various acid-base abnormalities encountered in clinical practice. Subsequently, we explore several different, although interconnected, approaches to acid-base abnormalities that are in widespread use. These approaches can be roughly described as descriptive, based on changes associated with the Henderson-Hasselbalch equation; semiquantitative, based on calculations; and quantitative, based on physical chemistry. Finally, we address acid-base abnormities specific to the practice of anesthesiology in the perioperative and critical care setting.

WHAT ARE ACIDS AND BASES?

The concept of acids and bases is relatively new. In the early part of the twentieth century, it was known that the CO_2 content of the blood decreased in critically ill patients. As early as 1831, O'Shaughnessy identified loss of "carbonate of soda" from the blood as a fundamental disturbance in patients dying of cholera. L.J. Henderson, in 1909, coined the term "acid-base balance."[5] He was able to define this process in terms of carbonic acid equilibrium. Henderson's work was later refined by Hasselbalch in 1916.[6] Their method described acid-base balance in terms of the hydration equation for CO_2.[7]

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

$$pH = pK_a + \log\ [HCO_3^-] / [H_2CO_3]$$

$$\text{Total } CO_2 = [HCO_3^-] + [\text{Dissolved } CO_2] + [\text{Carbamino } CO_2] + [H_2CO_3]$$

$$\approx P_{CO_2} \times 0.03 \text{ mmol } CO_2/\text{L/mm Hg}$$

So, substituting into the foregoing equation:

$$pH = 6.1 + \log [HCO_3^-] / P_{CO_2} \times 0.03$$

This is the Henderson-Hasselbalch equation.

Because the human body contains a large quantity of water, the physical properties of water have enormous implications for maintenance of homeostasis. Water is a simple triatomic molecule. Its chemical formula is H_2O, and its structural formula is H-O-H. The charge distribution of each covalent bond is unequal, and the molecule has a polar conformation and an H-O-H bond angle of 105 degrees. Water molecules attract, and form hydrogen bonds, with one another. Consequently, water has a high surface tension, a low vapor pressure, a high specific heat capacity, a high heat of vaporization, and a high boiling point.

Water molecules are in continual motion. Occasionally a collision generates sufficient energy to transfer a proton from one water molecule to another. Thus, water is always slightly dissociated into a negatively charged hydroxyl (OH^-) ion and a positively charged hydronium (H_3O^+) ion. Conventionally, this self-ionization of water is written as follows:

$$H_2O \leftrightarrow H^+ + OH^-$$

The symbol H^+ is convenient because, although protons dissociating from water have many aliases (such as H_3O^+ and $H_9O_4^+$), most physicians and chemists refer to them as hydrogen ions.

The self-ionization of water is miniscule. In pure water at 25° C, the $[H^+]$ and $[OH^-]$ are 1.0×10^{-7}mmol/L. The tendency for water to dissociate into its component parts is represented by the following expression:

$$K_{eq}H_2O = [H^+][OH^-]$$

The molarity of water is extremely high—55.5M ("there is a lot of water in water"). Because the concentration of water and the K_{eq} are constants, the ion-product dissociation constant for water can be expressed as follows:

$$K_{eq}H_2O = K_{eq}(55.5) = K_w = [H^+][OH^-]$$

The implication is that the product of the concentrations of hydroxyl and hydrogen is constant, so when the concentration of hydrogen ions increases, a concomitant decrease occurs in the concentration of hydroxyl ions, and vice versa.

Pure water is considered neutral because the relative concentrations of hydrogen and hydroxyl are equal at 1.0×10^{-7}mmol/L. A solution is considered *acidic* if the concentration of hydrogen ions exceeds that of hydroxyl ions ($[H^+] > 1.0 \times 10^{-7}$mmol/L, $[OH^-] < 1.0 \times 10^{-7}$mmol/L). A solution is considered *alkaline* if the hydroxyl ion concentration exceeds the hydrogen ion concentration.

Svante Arrhenius (1859 to 1927) established the foundations of acid-base chemistry in 1903. In an aqueous solution, an Arrhenius acid is any substance that delivers a hydrogen ion into the solution.[1] A base is any substance that delivers a hydroxyl ion into the solution. Because of its high dielectric constant, water is a highly ionizing solution. Substances with polar bonds will dissociate into their component parts (dissolve) in water. Brønsted and Lowry (BL) independently advanced this concept using slightly different terminology: an acid is a proton donor, a base a proton acceptor. Water itself is amphoteric, and it can act as either an acid or as a base. Thus, when hydrochloric acid (HCl) is dissolved in water, chloride (Cl^-), the acid, donates a proton to water, the base. Similarly, when potassium hydroxide (KOH) is dissolved in water, potassium (K^+), the base, receives a hydrogen ion from water, the acid or proton donor.

The degree of dissociation of substances in water determines whether they are strong acids or strong bases. Lactic acid, which has an ion dissociation constant (pK_a) of 3.4, is completely dissociated at physiologic pH, and is a strong acid. Conversely, carbonic acid, which has a pK_a of 6.4, is incompletely dissociated, and is a weak acid. Similarly, ions, such as sodium (Na^+), potassium (K^+), and Cl^-, which do not easily bind other molecules, are considered strong ions—they exist free in solution. As each Na^+ delivers a hydroxyl moiety into extracellular fluid (ECF), it is functionally a base because are all cations. As each Cl^- delivers a hydrogen moiety into ECF, it is functionally an acid because are all anions. The hydrogen and hydroxyl ions delivered in this way bind to one another, forming water molecules, and relatively few free hydrogen or hydroxyl ions remain free in solution.

$$HCl + H_2O \rightarrow H_3O^+ + Cl^-$$

In this reaction, HCl acts as a BL acid and water as a BL base.

$$NaOH + H_2O \rightarrow H_2O + OH^- + Na^+$$

In this reaction, water acts as a BL acid and Na^+ as a BL base.

$$OH^- + Na^+ + H_3O^+ + Cl^- = Na^+ + Cl^- + H_2O$$

Because of electrical neutrality, the hydrogen and hydroxyl ions delivered by Cl^- and Na^+ become water.

In summary, all acid-base reactions in the human body relate to the presence of charged particles within an aqueous environment. In the following section, we discuss how the components of ECF influence the acid-base status of the body, as measured by clinicians. We subsequently explain different acid-base abnormalities and the tools used to identify them. These approaches are neither distinct from one another nor scientifically incompatible.

WHAT DETERMINES THE ACIDITY OR ALKALINITY OF A SOLUTION?

Because all acid-base reactions are based on the principles of physical chemistry, three simple rules must be followed[8]:

1. *Electrical neutrality*: In aqueous solutions, in any compartment, the sum of all the positively charged ions must equal the sum of all the negatively charged ions.

2. *Dissociation equilibriums*: The dissociation equilibriums of all incompletely dissociated substances, as derived from the law of mass action, must be satisfied at all times.
3. *Mass conservation*: The amount of a substance in a given compartment remains constant unless it is added, removed, generated, or destroyed. The total concentration of an incompletely dissociated substance is the sum of concentrations of its dissociated and undissociated forms.

To determine the acid-base status of a fluid, all substances to which these rules could be applied must be accounted for. Fundamentally this involves counting up all the charges (and hence hydrogen and hydroxyl ions) delivered by strong cations (bases) and strong anions (acids), weak acid buffers, and CO_2.[9] A discussion of key groups follows.

STRONG IONS

The first group of ions, the strong ions, dissociates completely. The most abundant strong ions in the extracellular space are Na^+ and Cl^-. Other important strong ions include K^+, sulfate (SO_4^{2-}), magnesium (Mg^{2+}), and calcium (Ca^{2+}). In a solution containing strong ions, created, for example, using specified concentrations of NaOH and HCl, the hydrogen ion concentration can be calculated by solving for electric neutrality:

$$([Na^+] - [Cl^-]) + ([H^+] - [OH^-]) = 0$$

This creates two separate simultaneous equations:

$$[H^+] = \sqrt{K_w + ([Na^+] - [Cl^-])^2/4} - ([Na^+] - [Cl^-])/2$$

and

$$[OH^-] = \sqrt{K_w + ([Na^+] - [Cl^-])^2/4} - ([Na^+] - [Cl^-])/2$$

These equations tell us that hydrogen and hydroxyl concentrations are determined by K_w (water dissociation constant), and the difference in charge between Na^+ and Cl^-. Because the former is constant, in this system ($[Na^+] - [Cl^-]$) must determine $[H^+]$ and $[OH^-]$. Given that the concentrations of both Na^+ and Cl^- are known, the net positive charge minus net negative charge can be quantified. It is the strong ion difference (SID).[3] Logically, in any solution, the sum total of the charges imparted by strong cations minus the charges from strong anions will represent the SID. SID independently influences hydrogen ion concentration (Fig. 60-1). SID is always positive in human ECF.

$$SID = \left([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]\right) - ([Cl^-] + [A^-])$$
$$= 40\text{–}44 \text{mEq/L}$$

Hydroxyl ions almost always exceed hydrogen ions quantitatively in solution. The relationship between SID and $[H^+]$ is nonlinear in these conditions. Any change in SID will change both $[H^+]$ and $[OH^-]$ concentrations. Because of the K_w, this relationship is inverse: as $[H^+]$ increases, $[OH^-]$ decreases (see Fig. 60-1). SID is an independent variable, and $[H^+]$ and $[OH^-]$ are dependent, meaning that the addition of hydrogen ions alone (without strong corresponding anions) cannot influence the pH of the solution.

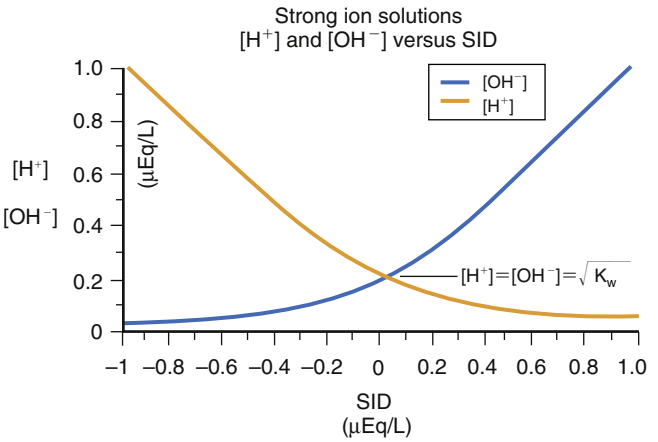


Figure 60-1. Effect of changes in the strong ion gap (SID) on hydrogen and hydroxyl ion concentration. *(Modified from Stewart PA: Modern quantitative acid-base chemistry,* Can J Physiol Pharmacol *61:1444-1461, 1983.)*

WEAK ACID "BUFFER" SOLUTIONS

The degree of water dissociation, and the hydrogen ion concentration, is also influenced by charges derived from weak acids. These acids are partially dissociated compounds whose degree of dissociation is determined by the prevailing temperature and pH. The predominant molecules in this group are albumin and phosphate. Stewart used the term A_{TOT} to represent the total concentration of weak anions or acids that influence acid-base balance.[8]

The acid HA only partly dissociates, represented by the equilibrium:

$$[HA] = K_A [H^+][A^-]$$

K_A is the weak acid dissociation constant. If we assume that HA and A^- play no further part in this reaction (the law of mass conservation), the amount of A^- present in the solution must equal the amount initially present, so:

$$[HA][A^-] = [A_{TOT}]$$

where $[A_{TOT}]$ is the total weak acid concentration.

To calculate the effect of weak acid dissociation on $[H^+]$, we must take into account water dissociation and electrical neutrality:

$$[H^+][OH^-] = K'_w \text{ (water dissociation)}$$
$$[SID] + [H^+] - [A^-] - [OH^-] = 0 \text{ (electrical neutrality)}$$

These four simultaneous equations determine the $[H^+]$ in this solution containing strong ions and weak acids. SID and A_{TOT} are independent variables, whose concentration

was determined during the production of the system. K_w and K_A are constants. Consequently, the other variables [HA], [H^+], [OH^-], and [A^-] must adjust to satisfy the foregoing equations. They are dependent variables.

CARBON DIOXIDE

Along with strong ions and weak bases, ECF contains CO_2. The concentration of CO_2 in ECF is determined by tissue production and alveolar ventilation. CO_2, when in solution, exists in four forms: CO_2 [denoted CO_2(d)], carbonic acid (H_2CO_3), bicarbonate ions (HCO_3^-), and carbonate ions (CO_3^{2-}).

The concentration of CO_2(d) is determined by the solubility coefficient of CO_2 (S_{CO_2}), which depends on body temperature, P_{CO_2}, and other factors. Several equilibrium equations can be derived from the hydration of CO_2:

$$[CO_2\,(d)] = [S_{CO_2}] \times P_{CO_2}$$

The tendency for CO_2 to hydrate to H_2CO_3, and subsequently dissociate to H^+ and HCO_3^-, is reflected by this equation:

$$[CO_2\,(d)] \times [OH^-] = K_1 \times [HCO_3^-]$$

These equations can be combined together and with water equilibrium to the following:

$$[H^+] \times [HCO_3^-] = K_C \times P_{CO_2}$$

HCO_3^- also dissociates to release hydrogen ions and carbonate, the equilibrium reaction for which is represented by this equation:

$$[H^+] \times [CO_3^{2-}] = K_3\,[HCO_3^-]$$

Factors Independently Influencing Water Dissociation

Now that we have looked at the different factors that may influence the concentration of hydrogen ions in a solution, strong ions, weak acids, and CO_2, we can combine the derived equations to solve for [H^+]:

1. Water dissociation equilibrium: $[H^+] \times [OH^-] = K_w$
2. Weak acid dissociation equilibrium: $[H^+] \times [A^-] = K_A \times [HA]$
3. Conservation of mass for weak acids: $[HA] + [A^-] = [A_{TOT}]$
4. HCO_3^- formation equilibrium: $[H^+] \times [HCO_3^-] = K_C \times P_{CO_2}$
5. Carbonate ion formation equilibrium: $[H^+] \times [CO_3^{2-}] = K_3 \times [HCO_3^-]$
6. Electrical neutrality: $[SID] + [H^+] - [HCO_3^-] - [A^-] - [CO_3^{2-}] - [OH^-] = 0$

There are six independent simultaneous equations, and just six unknown, dependent variables determined by them: [HA], [A^-], [HCO_3^-], [CO_3^{2-}], [OH^-], and [H^+]. The three known independent variables are [SID], [A_{TOT}], and P_{CO_2}.

Solving the equations for [H^+]:

$$[SID] + [H^+ - K_C \times P_{CO_2} / [H^+] - K_A \times [A_{TOT}] / (K_A + [H^+]) - K_3 \times K_C P_C / [H^+]^2 - K_w' / [H^+] = 0$$

In other words, [H^+] is a function of SID, A_{TOT}, P_{CO_2}, and several constants. All other variables, most notably [H^+], [OH^-], and [HCO_3^-], are dependent and cannot independently influence acid-base balance.

ACID-BASE ABNORMALITIES

The value of the physical chemistry approach (Stewart approach) is that it allows us to use a simple model for understanding acid-base disturbances because all abnormalities can be explained in terms of SID, A_{TOT}, or P_{CO_2}.[8] Traditionally, acid-base disturbances have been classified as resulting from either alterations in arterial carbon dioxide (Pa_{CO_2}) tension (respiratory acidosis or alkalosis) or alterations in blood chemistry (metabolic acidosis or alkalosis).[10] This classification remains useful, although respiratory or metabolic abnormalities rarely occur independently of one another.

RESPIRATORY ACID-BASE ABNORMALITIES

Respiratory Alkalosis

Respiratory alkalosis occurs when an acute decrease in Pa_{CO_2} results from hyperventilation. The patient presents with symptoms and signs of vasoconstriction: lightheadedness, visual disturbances, dizziness, and perhaps hypocalcemia from increased binding of calcium to albumin. The hypocalcemia is caused by an increase in the available negative charge on albumin in alkaline states. Acute hypocalcemia is associated with parasthesias and tetany.

Respiratory Acidosis

Respiratory acidosis occurs in the presence of an acute increase in Pa_{CO_2}, usually associated with respiratory failure. This may result from problems with the following':

- Central ventilator control—such as toxicity from anesthetic drugs, benzodiazepines, or opioids, stroke, spinal cord injury
- Peripheral ventilator control—such as myasthenia gravis, poliomyelitis, polymyopathy, or neuromuscular blockade
- Ventilation-perfusion mismatch—associated with pneumothorax, pleural effusion, atelectasis, pneumonia, or pulmonary edema

Clinically, patients have signs of CO_2 retention: cyanosis, vasodilatation, and narcosis.

Respiratory acidosis causes a rapid increase in [H^+]. Compensation for hypercarbia is slow, requiring increased urinary excretion of Cl^-,[8] and pH falls rapidly. A concomitant increase in the serum HCO_3^- occurs and reflects a higher total CO_2 load. The acuity of respiratory failure can be deduced by looking at the relative ratio of CO_2 to HCO_3^- (Table 60-1). Many investigators have suggested that respiratory acidosis may not necessarily be harmful. There has been extensive clinical experience

TABLE 60-1 CHANGES IN $Paco_2$ AND $[HCO_3^-]$ IN RESPONSE TO ACUTE AND CHRONIC ACID-BASE DISTURBANCES*

Disturbance	$[HCO_3^-]$ versus $Paco_2$
Acute respiratory acidosis	$\Delta HCO_3^- = 0.2\ \Delta Paco_2$
Acute respiratory alkalosis	$\Delta HCO_3^- = 0.2\ \Delta Paco_2$
Chronic respiratory acidosis	$\Delta HCO_3^- = 0.5\ \Delta Paco_2$
Metabolic acidosis	$\Delta Paco_2 = 1.3\ \Delta HCO_3^-$
Metabolic alkalosis	$\Delta Paco_2 = 0.75\ \Delta HCO_3^-$

Modified from Narins RB, Emmett M: Simple and mixed acid-base disorders: a practical approach, Medicine (Baltimore) *59:161-187, 1980.*

Δ, Change in value; *$[HCO_3^-]$*, concentration of bicarbonate ion; *$Paco_2$*, partial pressure of arterial carbon dioxide.

* HCO_3^- is measured in mEq/L or mmol/L and $Paco_2$ is measured in mm Hg.

with "permissive hypercapnia" for acute respiratory failure, which appears to be well tolerated,[11,12] and it may indeed be beneficial.[13]

METABOLIC ACID-BASE ABNORMALITIES

Metabolic acid-base abnormalities are caused by alterations in the SID or A_{TOT}, or both. An increase in the SID causes alkalemia; a decrease in the SID causes acidemia. The alteration may be caused by a change in the total or relative concentration of strong ions. For example, a decrease in the SID (i.e., more anions relative to cations) causes acidosis; this may occur because of a net increase in anions (e.g., hyperchloremia, lactatemia) or an increase in the volume of distribution of the same quantity of ions (e.g., dilutional acidosis) (Table 60-2).

Metabolic acidosis is of clinical significance for two reasons: disorders arising from the acidosis itself and disorders arising from the cause of the acidosis. Acidosis is associated with alterations in transcellular ion pumps and increased ionized calcium. The results are vasodilation, diminished muscular performance (particularly myocardial), and arrhythmias. The oxyhemoglobin dissociation curve shifts rightward to increase oxygen offload into the tissues (see also Chapter 61). Rapid-onset metabolic acidosis may be associated with profound hypotension, cardiac arrhythmias, and death. The malignancy of the acidosis is strongly related to the underlying disease process; lactic acidosis caused by circulatory shock is more malevolent than is hyperchloremic acidosis resulting from excessive administration of 0.9% saline solution.[13] The body is hyperresponsive to acidosis. Increasing hydrogen ion content in cerebrospinal fluid activates the respiratory center to stimulate respiration. Alveolar ventilation increases, thus reducing both arterial CO_2 content and total-body $[H^+]$. HCO_3^- concentration simultaneously decreases secondary to buffering activity and to the reduction in total CO_2. As a result, the blood pH falls less in metabolic acidosis than in respiratory acidosis.

Metabolic alkalosis rarely occurs as a result of acute illness. Symptoms and signs of metabolic alkalosis include widespread vasoconstriction, lightheadedness, tetany, and paresthesia. The main compensatory mechanism is hypoventilation, which may delay weaning from mechanical ventilation in critically ill patients.

In normal ECF, the SID is 44 mEq, and this positive charge is balanced principally by weak acids. Anything

TABLE 60-2 CLASSIFICATION OF PRIMARY ACID-BASE ABNORMALITIES

Abnormality	Acidosis	Alkalosis
Respiratory	Increased P_{CO_2}	Decreased P_{CO_2}
Metabolic		
Abnormal SID		
Caused by water excess or deficit	Water excess = dilutional ↓ SID + ↓ $[Na^+]$	Water deficit = contraction ↑ SID ↑ $[Na^+]$
Caused by electrolytes	Chloride excess	Chloride deficit
Chloride (measured)	↓ SID ↑ $[Cl^-]$	↑ SID + ↓ $[Cl^-]$
Other (unmeasured) anions, such as lactate and keto acids	↓ SID ↑ $[UMA^-]$	—
Abnormal A_{TOT}		
Albumin [Alb]	↑ [Alb] (rare)	↓ [Alb]
Phosphate [Pi]	↑ [Pi]	

Modified from Fencl V, Jabor A, Kazda A, Figge J: Diagnosis of metabolic acid-base disturbances in critically ill patients, Am J Respir Crit Care Med *162:2246-2251, 2000.*

[Alb], Concentration of serum albumin; *A_{TOT}*, the total concentration of weak ions; *$[Cl^-]$*, concentration of chloride ions; *$[Na^+]$*, concentration of sodium ions; *P_{CO_2}*, partial pressure of carbon dioxide; *[Pi]*, concentration of inorganic phosphate; *SID*, strong ion difference; *$[UMA^-]$*, unmeasured anions; *↑*, increased; *↓*, decreased.

that increases the SID will increase the relative concentration of cations to anions and alkalinize the solution. Anything that decreases the SID will decrease the relative concentration of cations to anions and will acidify the solution. If the extracellular compartment volume is expanded with free water (no electrolytes), the components of the system are diluted, with relatively more dilution of more abundant moieties (Na^+ rather than Cl^-); the results are a reduction in SID and *dilutional acidosis*. This condition rarely occurs in the presence of normally functioning kidneys. Conversely, if free water is removed from the ECF (e.g., from increased evaporative losses), the relative concentration of charged moieties increases, and this concentration affects more abundant ions and compounds (Na^+ rather than Cl^-). The SID increases, and *contraction alkalosis* occurs (see Table 60-2).

In perioperative medicine, "normal saline" (NaCl 0.9%), containing 154 mEq of Na^+ and 154 mEq of Cl^-, is commonly used. The SID of this solution is 0. Functionally, however, each liter of normal saline delivers approximately 50 mmol of hydrochloric acid into ECF. The effects are a net reduction in the relative concentration of Na^+ to Cl^-, a reduction in SID, and *hyperchloremic acidosis*.[14]

Any process that removes Cl^- without Na^+, such as aggressive nasogastric suctioning with a loss of HCl, causes metabolic alkalosis (hypochloremic alkalosis) because of an increase in SID. The alkalosis is caused by Cl^- loss, which obeys the law of conservation of mass (i.e., a finite quantity is available in the ECF), and not by hydrogen ions, whose source, water, is unlimited. Severe diarrhea, which is associated with loss of both K^+ and Na^+, reduces the SID and is associated with metabolic acidosis. Aggressive use of diuretics causes a net loss of free water over Na^+ and Cl^- and leads to contraction alkalosis.

The most significant form of metabolic acidosis is associated with a net gain of "unmeasured" anions (i.e., electrolytes not conventionally measured on serum chemistry analysis) and, consequently, a decreased SID:

1. In dysoxia and states of severe stress, lactate is produced, thus reducing the SID and causing acidosis.
2. In out of control diabetes (ketoacidosis) or during starvation, β-hydroxybutyrate and acetoacetate are produced, thereby reducing the SID and causing acidosis (see also Chapter 39).
3. In severe renal failure, SO_4^{2-} and phosphate (PO_4^{3-}) ("fixed renal acids") are not excreted, with resulting acidosis (see also Chapter 74).

The total weak acid pool, principally serum albumin and phosphate, is also an important determinant of acid-base status. Hyperphosphatemia is associated with the acidosis of renal failure. Hypoalbuminemia is common in critical care (see also Chapter 101). Hypoalbuminemia decreases A_{TOT} and is associated with metabolic alkalosis.[15,16] A strong association exists between hypoalbuminemia and severity of critical illness. Albumin deficits result from four different homeostatic changes: (1) reprioritization of hepatic protein production favoring production of acute phase reactants and limiting albumin synthesis, (2) capillary leak with loss of albumin into the interstitium, (3) breakdown of preexisting albumin so that its constituent amino acids can be used for protein synthesis, and (4) replacement of plasma with protein-free fluids.

The impact of hypoalbuminemia on acid-base balance is important. Stewart's original theory was subsequently modified by Fencl and Figge.[17] The serum albumin concentration is the core negative charge offsetting the net positive charge of the SID.[15] Consequently, the presence of hypoalbuminemia may mask the detection of acidosis[18] that is caused, for example, by unmeasured anions (UMAs), when using conventional tools of acid-base chemistry: pH, HCO_3^-, base deficit, and the anion gap.[19] The presence of hypoalbuminemia has significant implications, not least for its association with adverse outcomes.[20] Hyperalbuminemia is very unusual; in cholera, when associated with hemoconcentration, it is linked with acidosis.[21]

REGULATION OF ACID-BASE BALANCE

Extracellular hydrogen ion concentration appears to be tightly controlled by the body. In all probability this regulation reflects a need to prevent rapid changes in extracellular electrochemical balance from interfering with the function of transcellular ion pumps. To prevent fluctuation, various intracellular and extracellular buffering systems have evolved. A *buffer* is a solution of two or more chemicals that minimizes changes in pH in response to the addition of an acid or base. Ideally, a buffer has a pK_a that is equal to the pH, and an ideal body buffer has a pK_a between 6.8 and 7.2. Most biologically salient buffers are weak acids.

The control of hydrogen ion concentration should be viewed in terms of volatile and metabolic acids. The major source of acid in the body is the volatile acid CO_2, which produces 12,500 mEq of H^+ a day, most excreted by the lungs. In contrast, only 20 to 70 mEq of hydrogen ion–promoting anions are excreted daily through the kidney. Volatile acid is principally buffered by hemoglobin. Deoxygenated hemoglobin is a strong base, and there would be a huge rise in the pH of venous blood if hemoglobin did not bind the hydrogen ions produced in oxidative metabolism.

CO_2 easily passes through cell membranes. Within the erythrocyte, CO_2 combines with H_2O, under the influence of the enzyme carbonic anhydrase, to form H_2CO_3, which ionizes to hydrogen and HCO_3^-. Hydrogen ions bind to histidine residues on deoxyhemoglobin, and HCO_3^- is actively pumped out of the cell. Cl^- moves inward to maintain electroneutrality (the Cl^- shift) and to ensure the continued production of carbonic acid. CO_2 is also buffered directly by hemoglobin (carbaminohemoglobin) and by plasma proteins (carbamino proteins). Venous blood contains 1.68 mmol/L of extra CO_2 over arterial blood: 65% as HCO_3^- and H^+ bound to hemoglobin, 27% as carbaminohemoglobin (CO_2 bound to hemoglobin), and 8% dissolved.

When respiratory failure occurs, the principal CO_2 buffering system, hemoglobin, becomes overwhelmed, leading to the rapid development of acidosis (see also Chapter 103). In response, the kidney excretes an increased Cl^- load, using ammonium (NH_4^+), a weak cation, for electrochemical balance. ECF osmolality is maintained. This process is conventionally referred to as metabolic compensation. Chronic respiratory acidosis increases total-body CO_2 content, reflected principally by an increase in serum HCO_3^-. Hypercapnia increases cerebrospinal fluid HCO_3^-, thus reflecting an overall increase in total CO_2 load. Compensation for this hypercarbia is a reduction in cerebrospinal fluid Cl^-,[22] as well as an increase in cerebrospinal fluid SID.[23-25] This is probably controlled by active transport mechanisms across the blood-brain barrier or at the level of the choroid plexus and can be blocked by furosemide and acetazolamide.[26-29] The result is a rightward shift in the P_{CO_2} response curve: the respiratory center responds to hypercarbia by increasing respiratory drive at a higher P_{CO_2} level than under normal conditions. Mathematically,

$$\Delta HCO_3^- = 0.5\,\Delta Pa_{CO_2} \text{ in mm Hg}$$ [30]

HCO_3^- is a dependent variable that increases or decreases with P_{CO_2}. The rate of conversion of CO_2 to HCO_3^- depends on carbonic anhydrase activity and occurs slowly. It is possible mathematically to determine whether an increase in Pa_{CO_2} is acute or long-standing (see Table 60-1). In acute respiratory acidosis,

$$\Delta HCO_3^- = 0.2\,\Delta Pa_{CO_2}$$

Metabolic acid is buffered principally by increased alveolar ventilation, thus producing respiratory alkalosis, and extracellular weak acids. These weak acids include plasma proteins, phosphate, and HCO_3^-. The HCO_3^- buffering system (92% of plasma buffering and 13% overall) is probably the most important extracellular buffer.

The pK_a of HCO_3^- is relatively low (6.1), but the system derives its importance from the enormous quantity of CO_2 present in the body. The coupling of HCO_3^- and H_2O produces CO_2, which is then excreted through the lungs and increases alveolar ventilation. Physicians must be aware of the importance of this compensatory mechanism. For example, anesthetized or critically ill patients receiving controlled mechanical ventilation lose the capacity to regulate their own P_{CO_2}. Consequently, the combination of acute metabolic and respiratory acidosis can cause a devastating reduction in pH.

The major effect of the kidney on acid-base balance relates to renal handling of Na^+ and Cl^- ions. Because dietary intake of Na^+ and Cl^- is roughly equal, the kidney excretes a net Cl^- load, using NH_4^+, a weak cation, to neutralize urinary chloride electrochemically.[2]

In metabolic acidosis, the kidneys preferentially excrete Cl^-. In metabolic alkalosis, Cl^- is retained, and Na^+ and K^+ are excreted. The presence of HCO_3^- in the urine reflects the need to maintain electrical neutrality. Abnormalities in the renal handling of Cl^- may be responsible for several inherited acid-base disturbances. In renal tubular acidosis, patients are unable to excrete Cl^- in proportion to Na^+.[31] The diagnosis can be made by observing hyperchloremic metabolic acidosis with inappropriately low levels of Cl^- in the urine. The urinary SID is positive. If the urinary SID is negative, the process is not of renal origin. Similarly, pseudohypoaldosteronism appears to result from high reabsorption of chloride.[32] Bartter syndrome is caused by a mutation in the gene encoding the Cl^- channel—*CLCNKB*—that regulates the Na-K-2Cl cotransporter (NKCC2).[33]

The other causes of hyperchloremic metabolic acidosis are gastrointestinal losses (diarrhea, small bowel or pancreatic drainage), parenteral nutrition, excessive administration of saline, and the use of carbonic anhydrase inhibitors.

ANALYTIC TOOLS USED IN ACID-BASE CHEMISTRY

Acid-base balance is a core component of the clinical evaluation of acutely and critically ill patients. Arterial blood gas analysis provides immediate information on the status of the patient's respiratory system and ascertains whether or not a state of acidosis or alkalosis is present. By applying a variety of empiric "rules," the information contained in arterial blood gas analysis is often sufficient to identify the presence, cause, and progression of a disease (see also Chapters 44 and 51). The diagnostic sensitivity of arterial blood gas analysis is augmented when a serum chemistry panel, glucose and lactate determinations, and urinary ketone measurements are added.

Several different approaches to acid-base balance are in widespread use.[34] These can be described as follows: descriptive, based on changes in the Henderson-Hasselbalch equation; semiquantitative, based on calculations and nomograms; or quantitative, based on physical chemistry. The descriptive approach uses the interrelationship between P_{CO_2} and $[HCO_3^-]$ to detect and diagnose acid-base abnormalities. An extension of this is the anion gap. The semiquantitative approach includes the buffer-base concept, the standardized base deficit-excess, and the base-deficit gap. The quantitative approach uses SID and A_{TOT} and is quantified using the strong ion gap (SIG).

DESCRIPTIVE APPROACH: CARBON DIOXIDE–BICARBONATE (BOSTON APPROACH)

Schwartz and colleagues at Tufts University in Boston developed a descriptive approach to acid-base chemistry. Their formulation uses acid-base maps and the mathematic relationship between CO_2 tension and serum HCO_3^- (or total CO_2), derived from the Henderson-Hasselbalch equation to classify acid-base disturbances in terms of two independent variables: P_{aCO_2} and $[HCO_3^-]$.[35,36] To validate this approach, patients with known acid-base disturbances, at steady states of compensation, were evaluated. The degree of compensation, relative to what was considered normal, was measured for each disease state. The investigators described six primary states of acid-base imbalance by using linear equations or maps, relating hydrogen ion concentration to P_{CO_2} for respiratory disturbances, and P_{CO_2} to HCO_3^- concentration for metabolic disturbances (Fig. 60-2). For any given acid-base disturbance, an expected HCO_3^- concentration was determined. These maps and equations were then compiled into a series of mathematic rules (Box 60-1). For most simple disturbances, this is a reasonable approach. For example, in acute respiratory acidosis, the $[HCO_3^-]$ will increase by 1 mEq/L for every 10 mm Hg elevation in P_{aCO_2} greater than 40 mm Hg. In chronic respiratory acidosis, the $[HCO_3^-]$ will increase by 4 mEq/L for every

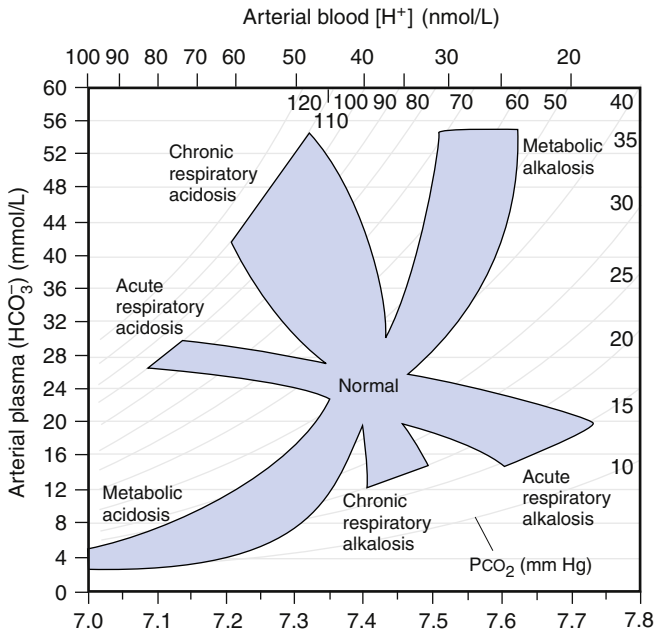


Figure 60-2. Acid-base nomogram using the Boston approach. Different acid-base disturbances can be distinguished based on the relative values of P_{CO_2} and HCO_3^-. *(Modified from Brenner BM, Rector FC:* The kidney, *ed 3. Philadelphia, 1986, Saunders, p 473.)*

BOX 60-1 ***The Descriptive (CO_2-HCO_3^-) Approach to Acid-Base Disorders***

RESPIRATORY DISORDERS

Acute Respiratory Acidosis

$$\text{Expected } [HCO_3^-] = 24 + [(\text{Measured } Paco_2 - 40)/10]$$

Chronic Respiratory Acidosis

$$\text{Expected } [HCO_3^-] = 24 + 4\ [(\text{Measured } Paco_2 - 40)/10]$$

Acute Respiratory Alkalosis

$$\text{Expected } [HCO_3^-] = 24 - 2\ [(40 - \text{Measured } Paco_2)/10]$$

Chronic Respiratory Alkalosis

$$\text{Expected } [HCO_3^-] = 24 - 5\ [(40 - \text{Measured } Paco_2)/10]\ (\text{range: } \pm 2)$$

METABOLIC DISORDERS

Metabolic Acidosis

$$\text{Expected } Paco_2 = 1.5 \times [HCO_3^-] + 8\ (\text{range: } \pm 2)$$

Metabolic Alkalosis

$$\text{Expected } Paco_2 = 0.7 \times [HCO_3^-] + 20\ (\text{range: } \pm 5)$$

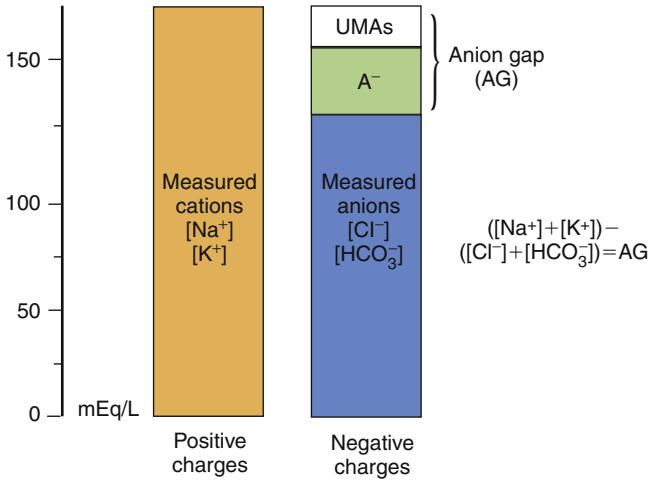


Figure 60-3. The anion gap. The anion gap represents the difference in charge between measured cations and measured anions. The missing negative charge is made up of weak acids (A^-), such as albumin and phosphate, and strong unmeasured anions (UMAs), such as lactate.

10 mm Hg elevation in $Paco_2$ greater than 40 mm Hg. In acute metabolic acidosis, the $Paco_2$ follows the 1.5 × $[HCO_3^-]$ plus 8 rule. In metabolic alkalosis, the expected $Paco_2$ follows the 0.7 × $[HCO_3^-]$ plus 20 rule.

Using these maps and equations and rules, physicians can determine the nature of most respiratory and metabolic acid-base disturbances and in a manner that is usually accurate. Although a mathematic relationship is in place, alterations in $[H^+]$ and $[HCO_3^-]$ do not reflect cause and effect. For example, chronic hypoventilation is associated with an increase in Pco_2 and $[HCO_3^-]$. Many physicians have incorrectly assigned the increase in $[HCO_3^-]$ as compensation for raised Pco_2. It is not. The increased HCO_3^- concentration reflects increased total CO_2 in the body.

Although the Pco_2-HCO_3^- approach is relatively accurate for most disturbances and is particularly useful for respiratory problems, it has several inherent pitfalls, particularly in relation to the metabolic component. First, the approach is not as simple as it seems. It requires the clinician to refer to confusing maps or to learn formulas and perform mental arithmetic. Second, the system neither explains nor accounts for many of the complex acid-base abnormalities seen in perioperative and critically ill patients, such as patients with acute acidosis in the setting of hypoalbuminemia, hyperchloremic acidosis, or dilutional acidosis or patients with lactic acidosis in the setting of chronic respiratory acidosis.

ANION GAP APPROACH

The most widely used tool for investigating metabolic acidosis is the anion gap, developed by Emmet and Narins in 1975.[37] It is based on the law of electrical neutrality. It is entirely consistent with the physical chemistry approach, described later, and is usually used alongside the Boston approach to acid-base balance. The system is based on data that were not easily available or known at the time of publication: the contribution to electrical neutrality ascribed to weak acids (phosphate and albumin) and UMAs. The sum of the difference in charge of the common extracellular ions reveals an unaccounted for "gap" of –10 to –12 mEq/L. Three variants of the anion gap are widely used (Fig. 60-3), and they depend on whether or not K^+ and lactate are included:

$$\text{Anion gap (simple)} = \left([Na^+] - ([Cl^-] + [HCO_3^-])\right)$$
$$= 12 \text{ to } 14 \text{ mEq/L}$$

$$\text{Anion gap (conventional)} = \left([Na^+] + [K^+] - ([Cl^-] + [HCO_3^-])\right)$$
$$= 14 \text{ to } 18 \text{ mEq/L}$$

$$\text{Anion gap (modern)} = \left([Na^+] + [K^+] - ([Cl^-] + [HCO_3^-] + [\text{Lactate}^-])\right)$$
$$= 14 \text{ to } 18 \text{ mEq/L}$$

If the patient develops metabolic acidosis, and the gap "widens" to, for example, more than 20 mEq/L, then the acidosis is caused by UMAs: renal acids or ketones. If the gap does not widen, then the anions are being measured, and the acidosis has been caused by hyperchloremia (HCO_3^- cannot independently influence acid-base status) or lactate (if used). Although this is a useful tool, it is weakened by the assumption of what is or is not a "normal gap."[38] The anion gap frequently underestimates the extent of the metabolic disturbance.[18] Most critically ill patients are hypoalbuminemic, and many are also hypophosphatemic.[39] Consequently, the gap may be normal in the presence of UMAs. This was extensively studied by Fencl and Figge, who provided a variant known as the corrected anion gap[19]:

$$\text{Anion gap corrected (for albumin)} = \text{Calculated anion gap} + 2.5 \times (\text{Normal albumin g/dL} - \text{Observed albumin g/dL})$$

In this corrected form, the anion gap accurately quantifies metabolic acidosis, and it is useful for discriminating acidosis caused by UMAs from acidosis reflecting hyperchloremia in a previously healthy patient (e.g., in acute trauma). Moviat and colleagues demonstrated that the anion gap corrected for albumin accurately detects complex acid-base abnormalities in intensive care.[40]

Another version of the anion gap is the delta anion gap (Box 60-2), an approach that has successfully predicted adverse outcomes in critical illness.[41] Simply, if the anion gap is normal, or unchanged, and the HCO_3^- level falls, then the delta ratio will be less than 0.4, and hyperchloremic acidosis is present. A delta ratio between 1 and 2 is what one would expect from metabolic acidosis caused by UMAs or lactate. If the ratio is greater than 2, mixed acid-base abnormalities are present. Although, on the surface, this process is relatively simple, it assumes that the clinician knows the normal anion gap and HCO_3^- for that particular patient. In addition, it does not result in a clear diagnosis other than hyperchloremia. Figure 60-4 is a decision tree that uses this descriptive approach to acid-base balance.

BOX 60-2 *The Delta Anion Gap (Delta Ratio)*

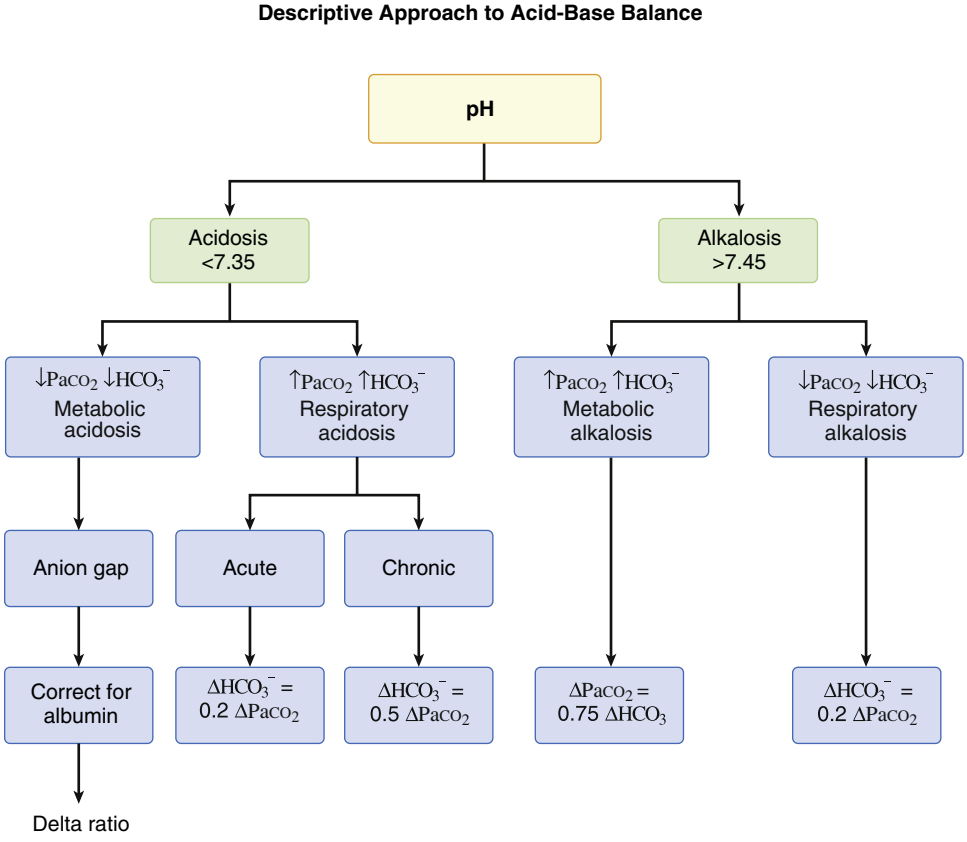
$$\text{Delta ratio} = \Delta \text{ Anion gap} / \Delta [HCO_3^-] \text{ or } \uparrow \text{Anion gap} / \downarrow [HCO_3^-]$$

$$= \frac{\text{Measured anion gap} - \text{Normal anion gap}}{\text{Normal } [HCO_3^-] - \text{Measured } [HCO_3^-]}$$

$$= \frac{(\text{Anion gap} - 12)}{(24 - [HCO_3^-])}$$

SEMIQUANTITATIVE APPROACH: BASE DEFICIT OR EXCESS (COPENHAGEN)

In metabolic acidosis, the addition of routinely UMAs to the ECF results in a net gain of one hydrogen ion for each anion. This is "buffered" principally by HCO_3^-, such that each anion gained results in a fall in the HCO_3^-



Delta ratio	Clinical assessment
<0.4	Hyperchloremic normal AG acidosis
<1	High AG and normal AG acidosis
1 to 2	Pure anion gap acidosis Lactic acidosis: average value 1.6 DKA more likely to have a ratio closer to 1 because of urine ketone loss
>2	High AG acidosis and concurrent metabolic alkalosis or preexisting compensated respiratory acidosis

Figure 60-4. The descriptive ("Boston") approach to acid-base balance. *AG,* Anion gap; *DKA,* diabetic ketoacidosis.

concentration. The change in the HCO_3^- concentration from baseline should reflect the total quantity of net anions gained. Adherents to the descriptive approach to acid-base balance refer to this as the "delta" HCO_3^-. However, this is problematic because it does not separate the effect of CO_2 metabolism on the $[HCO_3^-]$.

In 1948, Singer and Hastings proposed that changes in the whole-blood buffer base could be used to quantify the metabolic component independent of the Henderson-Hasselbalch equation.[42] The buffer base represented the sum of the HCO_3^- and the nonvolatile buffer ions (essentially the serum albumin, phosphate, and hemoglobin). Applying the law of electrical neutrality, the buffer base was forced to equal the electrical charge difference between strong (fully dissociated) ions. Normally buffer base = $[Na^+] + [K^+] - [Cl^-]$. Alterations in buffer base represented changes in strong ion concentrations (which could not be easily measured in 1948). The buffer base increases in metabolic alkalosis and decreases in metabolic acidosis. The major drawback of buffer base measurements is the potential for changes in buffering capacity associated with alterations in hemoglobin concentration.

In 1957, Astrup and colleagues developed the standard HCO_3^-—the HCO_3^- concentration at 37° C and at a $Paco_2$ of 40 mm Hg. Building on this work, Astrup and Siggard-Andersen recognized that Pco_2 and $[HCO_3^-]$ were not independent variables.[43] As a result, they derived the base deficit excess (BDE) approach as a measure that could differentiate respiratory from metabolic acid-base disturbances. As defined, the BDE is the amount of strong acid or base required to return the pH to 7.4, assuming that Pco_2 is constant at 40 mm Hg and that the temperature is 37° C. As in the Boston group, the Siggard-Andersen data were derived from observations on a large population of patients. The investigators carefully titrated known amounts of acid or base to blood maintained by tonometry at various $Paco_2$ values and a wide range of hemoglobin concentration at 37° C. These studies led to the development of an alignment nomogram (Fig. 60-5 and Table 60-3), which allowed for the determination of BDE from a single measurement of pH, $Paco_2$, and hemoglobin concentration at 37° C. Current algorithms for computing the BDE are derived from the Van Slyke equation published in 1977.[44]

$$BDE = (HCO_3 - 24.4 + [2.3 \times Hb + 7.7] \times [pH - 7.4]) \times (1 - 0.023 \times Hb)$$

A very high level of agreement exists between this calculation and the empiric data that were used to construct the original nomogram. The calculation is accurate in vitro, but not in vivo, because of the dynamic buffering activity of hemoglobin within the acid-base paradigm of gas and electrolyte exchange. This approach was modified to use only anemic blood (hemoglobin 5 g/dL), which more accurately reflects whole-body base excess in vivo: the calculation became the *standard* base excess (SBE):

$$SBE = 0.93 \times (HCO_3 - 24.4 + 14.83] \times [pH - 7.4]$$

The BDE approach to acid-base chemistry was successfully validated by Schlichtig[45] and Morgan.[46] The major weakness of this equation is the assumption of a normal quantity of weak acids (A_{TOT}), which is rarely the case in critical illness. Wooten corrected SBE for weak acids (albumin and phosphate) and produced an accurate multicompartment model (SBEc)[47]:

$$SBEc = (HCO_3 - 24.4) + ([8.3 \times Albumin\ g/dL \times 0.15] + [0.29 \times Phosphate\ mg/dL \times 0.32] \times [pH - 7.4]$$

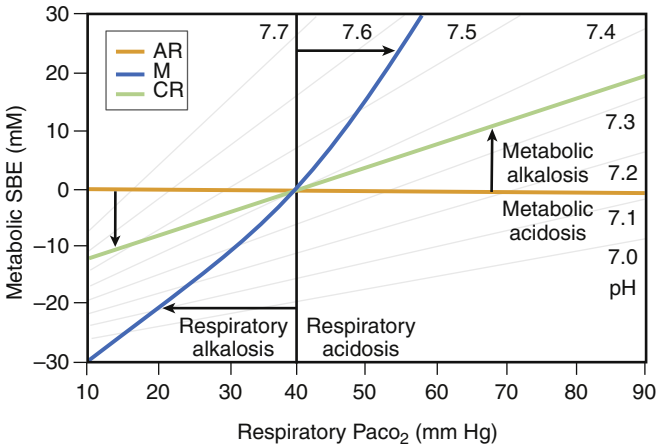


Figure 60-5. Acid-base nomogram using the Copenhagen approach as revised by Schlichtig. The various acid-base disturbances can be distinguished based on Pco_2 and base deficit or excess, here referred to as standard base excess (SBE). *Arrows* represent changes as the body compensates for acute acidosis or alkalosis. *AR,* Acute respiratory acidosis or alkalosis; *CR,* chronic respiratory acidosis or alkalosis; *M,* metabolic acidosis or alkalosis. *(From Schlichtig R, Grogono AW, Severinghaus JW: Human $Paco_2$ and standard base excess compensation for acid-base imbalance,* Crit Care Med *26:1173-1179, 1998.).*

TABLE 60-3 CHANGES IN STANDARD BASE DEFICIT OR EXCESS IN RESPONSE TO ACUTE AND CHRONIC ACID-BASE DISTURBANCES

Disturbance	SBDE versus $Paco_2$
Acute respiratory acidosis	$\Delta BDE = 0$
Acute respiratory alkalosis	$\Delta BDE = 0$
Chronic respiratory acidosis	$\Delta BDE = 0.4\ \Delta Paco_2$
Metabolic acidosis	$\Delta Paco_2 = \Delta BDE$
Metabolic alkalosis	$\Delta Paco_2 = 0.6\ \Delta BDE$

Modified from Narins RB, Emmett M: Simple and mixed acid-base disorders: a practical approach, Medicine (Baltimore) *59:161-187, 1980.*

Δ, Change in value; *BDE,* base deficit or excess; *$Paco_2$,* partial pressure of arterial oxygen; *SBDE,* standard base deficit or excess.

BOX 60-3 ***Calculation of Base Deficit or Excess of Sodium, Chloride, and Free Water and Albumin****

$$BDE_{NaCl} = ([Na^+] - [Cl^-]) - 38$$

$$BDE_{Alb} = 0.25\ (42 - Albumin\ g/L)$$

$$BDE_{NaCl} - BDE_{Alb} = BDE_{calc}$$

$$BDE - BDE_{calc} = BDE\ gap = The\ effect\ of\ unmeasured\ anions\ or\ cations$$

* This approach involves calculating the base deficit or excess (BDE) for sodium, chloride, and free water (BDE_{NaCl}) and that for albumin (BDE_{Alb}). The result is the calculated BDE (BDE_{calc}). This is subtracted from the measured BDE to find the BDE gap.

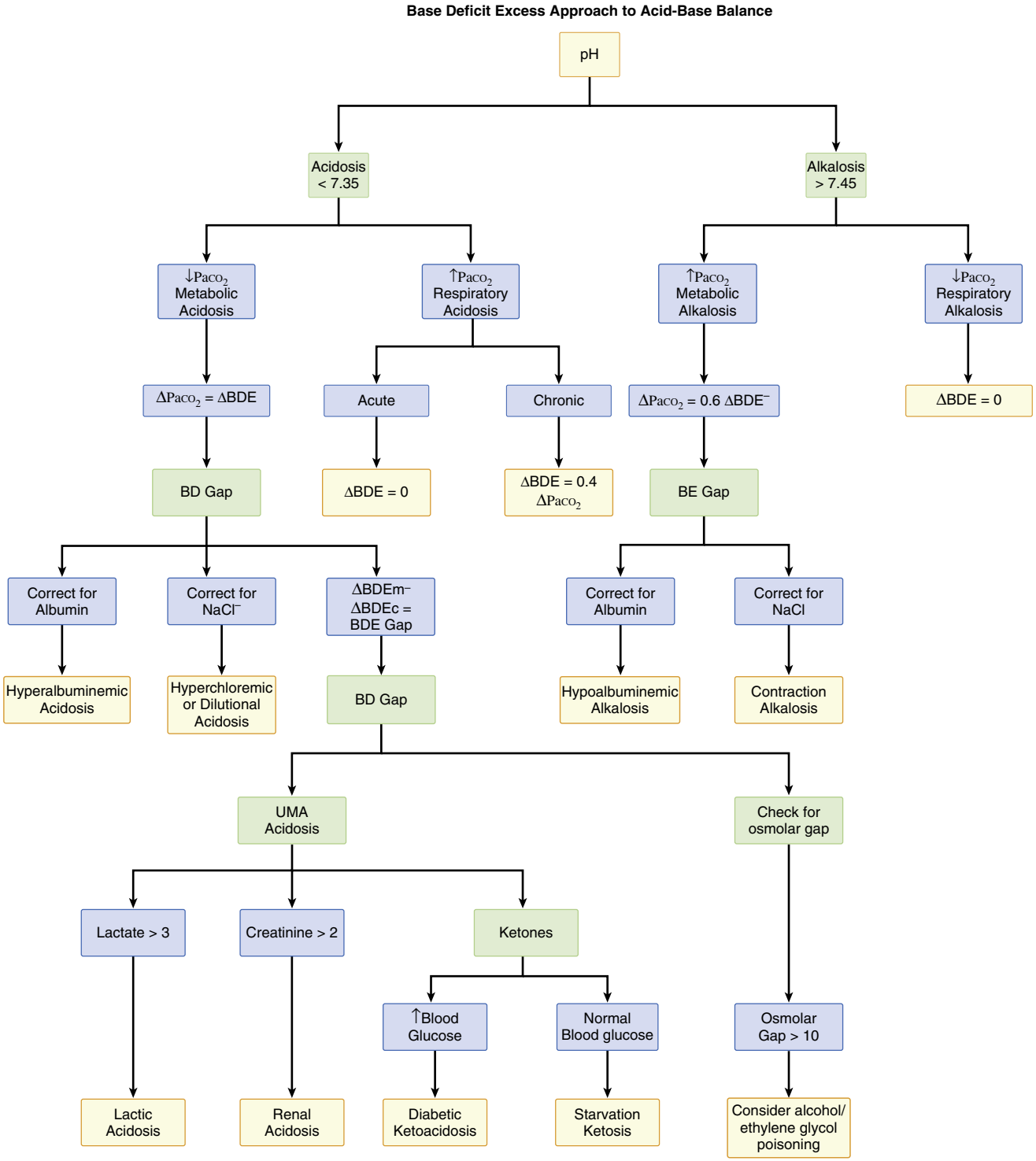


Figure 60-6. The semiquantitative ("Copenhagen") approach to acid-base balance. *BD,* Base deficit; *BE,* base excess; *BDEm,* measured base deficit or excess; *BDEc,* base deficit or excess corrected for albumin, sodium, chloride, and free water (see Box 60-3); *UMA,* unmeasured anion; lactate in mmol/L, creatinine in mg/dL, osmolar gap in mOsm.

Using Wooten's multicompartment model,[47] it can be seen that the SBE is the quantity of strong anion or strong cation required to bring SID back to normal, with the pH corrected to 7.4 and the P_{CO_2} at 40 mm Hg.

Application of simple mathematic rules allows for use of the BDE in each of the common acid-base disturbances (Box 60-3 and Fig. 60-6). For example, in acute respiratory acidosis or alkalosis, BDE does not change. Conversely, in acute metabolic acidosis, the magnitude of change of the P_{CO_2} (in millimeters of mercury) is the same as that of the BDE (in milliequivalents per liter).

Considerable discussion has arisen since the 1980s about the merits and demerits of the BDE, as compared with the CO_2-HCO_3^- system. In reality, little difference

exists between the two; both equations and nomograms were derived from patient data and abstracted backward. Calculations use HCO_3^- as measured on a blood gas analyzer. Consequently, for most patients, either approach is relatively accurate, but calculations may be misleading because they do not allow the clinician to distinguish between, for example, acidosis caused by lactate or Cl^- and alkalosis resulting from dehydration or hypoalbuminemia. These measures may miss the presence of an acid-base disturbance entirely; for example a hypoalbuminemic (metabolic alkalosis) critically ill patient with lactic acidosis (metabolic acidosis) may have a pH, HCO_3^-, and base excess in the normal range. This lack of precision may lead to inappropriate or inadequate therapy.

A complementary approach, used by Gilfix and colleagues,[48] and subsequently by Balasubramanyan and associates[49] and Story and associates,[50] is to calculate the BDE gap. This allows recalculation of BDE using strong ions, free water, and albumin. The resulting BDE gap should mirror the SIG, and the anion gap should be corrected.

We find the simplified calculation of Story and associates to be most useful (see Box 60-3).[50] These investigators used two equations to calculate the BDE for Na^+, Cl^-, and free water (BDE_{NaCl}) and for albumin (see Box 60-3).

STEWART-FENCL APPROACH

A more accurate reflection of true acid-base status can be derived using the Stewart-Fencl or physical chemistry approach.[1,3] This approach is based on the concept of electrical neutrality, a small advance from the anion gap. Plasma has an apparent SIDa $[(Na + Mg^{2+} + Ca^{2+} + K^+) - (Cl^- + A^-)]$ of 40 to 44 mEq/L, balanced by the negative charge on HCO_3^- and A_{TOT} (the buffer base, effective SID [SIDe]). A small difference between SIDa and buffer base (SIDe) represents a SIG and quantifies the amount of UMA present (Fig. 60-7).

$$SIDa = \left([Na^+] + [K^+] + [Mg^{2+}] + [Ca^{2+}]\right) - [Cl^-]$$

$$SIDe = [HCO_3^-] + [\text{Charge on albumin}] + [\text{Charge on Pi}] \quad (\text{in mmol/L})$$

The degree of ionization of weak acids is pH dependent, so one must calculate for this:

$$[Alb^-] = [\text{Alb g/L}] \times (0.123 \times pH - 0.631)$$
$$[Pi] \quad (\text{in mg/dL}) = [Pi]/10 \times pH - 0.47$$
$$SIG = SIDa - SIDe$$

Unfortunately, the SIG may not represent unmeasured strong anions, but only all anions that are unmeasured. For example, if resuscitated with gelatin, a patient's SIG will increase. Further, SID changes quantitatively in absolute and relative terms when changes in plasma water concentration occur. Fencl and Leith addressed this by correcting the Cl^- concentration for free water (Cl^-corr) with the following equation[1]:

$$[Cl^-]\,corr = [Cl^-]\,\text{observed} \times ([Na^+]\,\text{normal}/[Na^+]\,\text{observed})$$

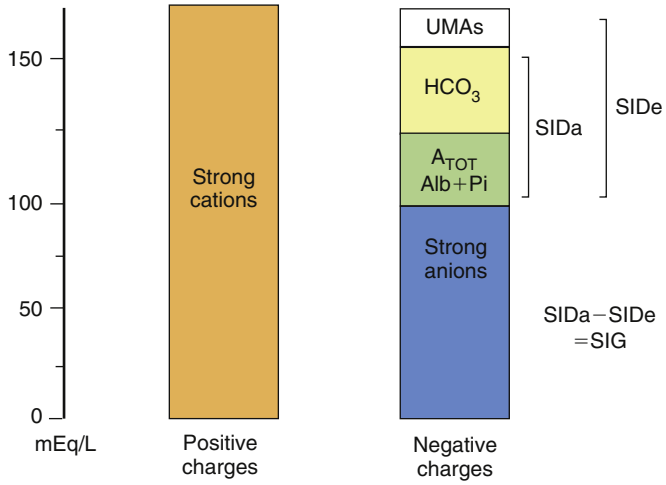


Figure 60-7. The strong ion gap (SIG). SID apparent (SIDa) is the sum of total concentration of weak acids (A_{TOT}) plus concentration of bicarbonate ion (HCO_3^-). SID effective (SIDe) is the real SID. The difference between the two is made up of unmeasured anions (UMAs). *Alb,* Albumin; *Pi,* phosphate.

This corrected Cl^- concentration may then be inserted into the SIDa equation. Similarly, the derived value for UMAs can also be corrected for free water by substituting UMAs for Cl^- in the previous equation.[18] In a series of nine normal subjects, Fencl and colleagues estimated the "normal" SIG as 8 ± 2 mEq/L.[18]

Calculation of SIG is cumbersome. The data required are more extensive and expensive than other approaches, and much confusion exists about the normal range of SIG. It is unclear, in standard clinical practice, that SIG has any advantage over the corrected anion gap (which is SIG without calcium, magnesium, and phosphate—which usually cancel out each other's charges).

No single number can make sense of complex acid-base disturbances. Fencl and associates suggested that anion gap or BDE should be replaced by viewing each blood gas in terms of all alkalinizing and acidifying effects: respiratory acidosis or alkalosis, the presence or absence of abnormal SID (from water excess or deficit, measured electrolytes or unmeasured electrolytes), and abnormal A_{TOT}.[18] Consider the following patient, described by Fencl and colleagues[18] (data in mEq/L unless otherwise stated):

Na, 117; Cl, 92; Ca, 3.0; albumin, 6.0 g/L; K, 3.9; Mg, 1.4; Pi, 0.6 mmol/L; arterial blood gases: pH, 7.33; P_{CO_2}, 30 mm Hg; HCO_3^-,15

Derived values would be as follows:

Anion gap, 13; corrected anion gap, 23; BE, −10; SID, 18; corrected Cl, 112; corrected UMA, 18

Using traditional methods, one would describe this as nongap metabolic acidosis and look for causes of HCO_3^- wasting, such as renal tubular acidosis or gastrointestinal losses. The degree of respiratory alkalosis is appropriate for the degree of acidosis ($\Delta BD = \Delta P_{CO_2}$). The Fencl-Stewart approach reveals a much more complex situation. SID is reduced to 18 mEq/L—caused by free water excess, UMAs, and surprisingly, hyperchloremia (see the corrected Cl^-). The degree of acidosis does not mirror the metabolic disturbance because of the alkalinizing force of hypoalbuminemia. The corrected anion gap mirrors the change in

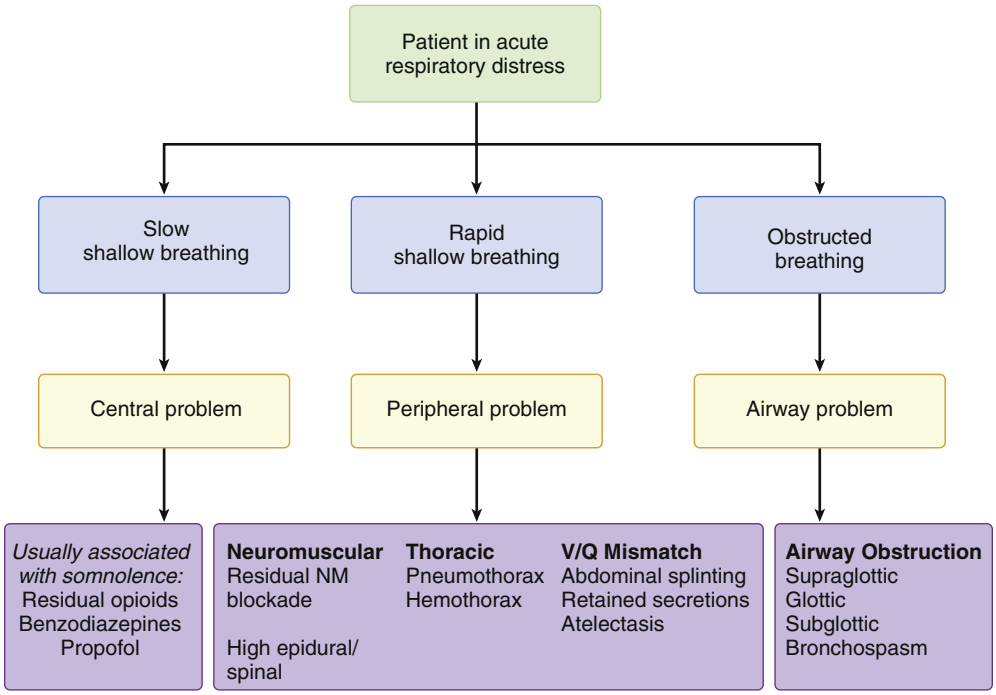


Figure 60-8. Using the breathing pattern to determine the cause of acute respiratory distress and respiratory acidosis. *NM,* Neuromuscular; *V/Q,* ventilation-perfusion.

SID, but this alteration is grossly underestimated by the base deficit. This patient has dilutional acidosis, hyperchloremic acidosis, and lactic acidosis.

In conclusion, for most patients presenting to the emergency room or operating suite who have been previously healthy, the use of tools such as the base deficit or anion gap to assess metabolic disturbances remains reasonable, particularly if it is corrected for albumin. For critically ill patients, the most effective method of interpreting acid-base conundrums involves unraveling simultaneous acidifying and alkalinizing processes and using calculations to distinguish among the various forces at play. Unfortunately, a clinician's ability to interpret such information depends on the amount of available data. A simple blood gas analysis alone may camouflage a significant acid-base disturbance.

In the next section, we look at the causes of many commonly seen acid-base disturbances in different clinical settings.

ACID-BASE PROBLEMS IN DIFFERENT CLINICAL SETTINGS

ACID-BASE DISTURBANCES IN THE EMERGENCY SETTING

Acid-base disturbances are an important part of laboratory investigation of acutely ill patients (see also Chapter 101). The most common disturbances are acute respiratory acidosis or alkalosis and acute metabolic acidosis. Acute metabolic alkalosis is unusual. Mixed respiratory and metabolic acidosis is seen in the severely injured or infected patient.

Acute respiratory acidosis results from hypoventilation or increased dead space ventilation. Assessment begins with an examination of the patient's breathing pattern (Fig. 60-8): slow, shallow breathing indicates impaired respiratory drive; rapid, shallow breathing suggests chest wall or lung disease; and obstructed breathing signifies airway obstruction.

Respiratory acidosis complicates a wide variety of pathologic processes. These include neurologic injury (stroke, spinal cord injury, botulism, tetanus), toxic suppression of the respiratory center (opioids, barbiturates, benzodiazepines), neuromuscular disorders (Guillain-Barré syndrome, myasthenia gravis), abdominal hypertension, flail chest, hydrohemopneumothorax, pulmonary edema, and pneumonia. It also complicates anesthesia with excessive sedation, partial neuromuscular blockade, and intraoperative hypoventilation. Frequently, mechanical ventilation is required to reverse the acidosis.

Acute respiratory alkalosis is caused by hyperventilation, in response to anxiety or pain, central respiratory stimulation (as occurs early in salicylate poisoning), or excessive artificial ventilation. Acute respiratory alkalosis usually accompanies acute metabolic acidosis, in which case the reduction in P_{CO_2} from baseline (usually 40 mm Hg) is equal to the magnitude of the base deficit (see Table 60-3). For example, in a patient with lactic acidosis whose lactate concentration is 10 mEq/L, the base deficit should be –10 and the P_{CO_2} 30 mm Hg. If the P_{CO_2} is higher than expected, then a concomitant problem exists with the respiratory apparatus. An example is the multitrauma patient in whom massive blood loss leads to lactic acidosis and a flail chest causes respiratory acidosis.

Acute metabolic acidosis is caused by an alteration in SID or A_{TOT}. SID is changed by an alteration in the relative quantity of strong anions to strong cations. Anions can be gained, as occurs with lactic acidosis, renal acidosis, ketoacidosis, and hyperchloremic acidosis, or cations can be lost, as occurs with severe diarrhea or renal tubular

BOX 60-4 ***Evaluation of a Patient With Metabolic Acidosis***

1. Is acidosis being caused by measured or unmeasured anions (i.e., chloride)?

Look at blood chemistry
- Calculate anion gap: Na + K – Cl = 10-12
- If gap is normal, too much chloride is present because of excessive administration, excess loss of sodium (diarrhea, ileostomy), or renal tubular acidosis
- If gap is wide (>16), other unmeasured anions are present, causing acidosis

Check serum lactate—if >2, probably lactic acidosis
- If high lactate is explained by circulatory insufficiency (shock, hypovolemia, oliguria, underresuscitation, anemia, carbon monoxide poisoning, seizures), then "type A" lactic acidosis
- If not, think about "type B (rare)" causes—biguanides, fructose, sorbitol, nitroprusside, ethylene glycol, cancer, liver disease

Look at creatinine and urine output
- If patient is in acute renal failure, these may be renal acids

Look at blood glucose and urinary ketones
- If patient is hyperglycemic and ketotic, this is diabetic ketoacidosis
- If patient is ketotic (unmeasured anion) and normoglycemic, this is either alcoholic (check blood alcohol) or starvation ketosis
- Check for presence of chronic alcohol abuse—high mean corpuscular volume, increased γ-glutamyl transferase on liver panel

2. If all these test results are negative, think of intoxication
- Send toxicology laboratory tests (particularly salicylates) and serum osmolality, and calculate osmolality using the formula: 2(Na + K) + Glucose / 18 + BUN / 2.8
- Look for unmeasured source of osmoles: if gap between measured and calculated serum osmolality >12, think of alcohol, particularly ethylene glycol, isopropyl alcohol, and methanol

acidosis. Acidosis also can result from an increase in free water relative to strong ions—the dilutional acidosis that accompanies excessive hypotonic fluid intake and certain poisonings with alcohol such as methanol, ethylene glycol, or isopropyl alcohol.

To investigate acute metabolic acidosis in previously healthy patients, simple observational and mathematic tools, such as the anion gap and base deficit, are useful (see Fig. 60-4; Box 60-4). The base deficit merely demonstrates the presence of an acid-base anomaly. The anion gap differentiates acidosis caused by hyperchloremia (renal tubular acidosis or excessive administration of "normal saline") or lactate from that caused by UMAs (ketones or renal acids) and dilution. When a patient presents with acute metabolic upset, such as trauma, exsanguination, loss of consciousness, or tachypnea, the tests needed to evaluate the patient completely include blood gas analysis, an electrolyte panel, serum osmolality testing, and urinalysis.

In acute metabolic acidosis, three diagnoses should be immediately investigated: (1) lactic acidosis (send for a serum lactate determination—it should mirror the magnitude of base deficit); (2) ketoacidosis secondary to diabetes (the patient should be hyperglycemic and have positive urinary ketones); or (3) starvation and acute renal failure, as demonstrated by high serum urea and creatinine levels and low total CO_2. Starvation and renal failure are diagnoses of exclusion. The presence of a low serum Na^+ concentration (<135 mEq/dL) or a very wide anion/base deficit/SIG should alert the clinician to the unusual possibility of dilutional acidosis, such as that caused by alcohol poisoning. Alcohols such as ethanol, methanol, isopropyl alcohol, and ethylene glycol are osmotically active molecules that expand extracellular water. Alcohol poisoning should be suspected in the patient with an osmolar gap: a difference between the measured and calculated serum osmolality of greater than 12 mOsm demonstrates the presence of unmeasured osmoles. Toxicology analysis can reveal the presence of various alcohols.

Renal acidosis is caused by accumulation of strong ion products of metabolism excreted exclusively by the kidney. Examples include sulfate and formate. In addition, accumulation of phosphate, a weak acid, is caused by relative deficiency of vitamin D. Diabetic ketoacidosis is treated with volume resuscitation and insulin. Starvation ketosis is treated by administration of glucose and then protein. Renal acidosis is treated with dialysis.

The use of $NaHCO_3$ boluses or infusions to treat metabolic acidosis is controversial. Little evidence supports the use of this agent in lactic acidosis or ketoacidosis. $NaHCO_3$ will indeed reverse the acidosis by increasing SID, but in general the acidosis is a reflection of a greater underlying problem. Nevertheless, $NaHCO_3$ (8.4%) is a hypertonic solution and should have a plasma-expanding effect similar to that of hypertonic saline, albeit at the cost of increasing $Paco_2$. This property likely explains the perceived hemodynamic benefit in shock. $NaHCO_3$ infusions have been used to increase SID to reduce patients' symptoms and prevent hyperkalemia in patients awaiting dialysis.

Methanol is metabolized to formaldehyde and formate by alcohol dehydrogenase. These metabolites are highly toxic, causing blindness, cardiovascular instability, and death. Treatment strategies include the use of ethanol to compete for binding on alcohol dehydrogenase and fomepizole to inhibit the enzyme. Ethylene glycol poisoning causes central nervous system depression, lactic acidosis, and formation of calcium oxalate urinary crystals. The resultant hypocalcemia can lead to renal failure, cardiovascular depression, and death. Treatment includes administration of fomepizole with or without hemodialysis.

Lactic Acidosis

Lactic acidosis occurs when the production of lactate in the body is greater than the liver's capacity to clear it. The problem is overproduction or inadequate clearance.

Lactic acid is produced physiologically as a degradation product of glucose metabolism. Its formation from pyruvate is catalyzed by lactate dehydrogenase. Under normal conditions, the ratio of lactate to pyruvate is less than 20:1. In anaerobic conditions, for example following vigorous exercise, lactate levels increase dramatically. In addition, lactate can be produced under aerobic conditions. Activation of β-adrenergic receptors in skeletal muscle by stress (increased circulating catecholamines) or exogenous infusion (epinephrine or norepinephrine

infusions) increases lactate, with resulting aerobic glycolysis. Lactate can be converted to CO_2 and H_2O by the liver; the lactate in Ringer lactate solution is functionally HCO_3^-.

Serum lactate and arterial pH should be measured early in any critically ill patient. A lactate concentration of more than 2 mEq/L is clinically significant, and a level of 5 mEq/L in the presence of metabolic acidosis is severe.[51] Isolated hyperlactatemia in the absence of acidosis is of unclear clinical significance.[52]

Two types of lactic acidosis are recognized. Type A (global inadequate oxygen delivery) is seen in hypovolemic or hemorrhagic shock, whereas type B occurs despite normal global oxygen delivery and tissue perfusion. Lactic acidosis may also develop in situations of significant regional hypoperfusion. Examples include bowel ischemia, in which lactate is produced in large quantity as a result of glycolysis despite global oxygen delivery that is normal. Type B lactic acidosis is associated with any state characterized by excess circulating catecholamines (endogenous or exogenous). Examples include simple exercise and the hyperinflammatory state of trauma or sepsis. Type B lactic acidosis may also be seen in cyanide poisoning (associated with sodium nitroprusside), with biguanides (metformin), and in hypercatabolic diseases, such as lymphoma, leukemia, acquired immunodeficiency syndrome (AIDS), or diabetic ketoacidosis (also see Chapter 39).

Lactic acidosis is a sensitive marker of disease severity,[53] and failure to clear the acidosis is a strong predictor of adverse outcomes.[54-56] The presence of a low mixed venous oxygen saturation (SvO_2) with a high lactate concentration, coupled with an elevated lactate-to-pyruvate ratio (>20:1), is indicative of type A (hypoxia associated) acidosis (Fig. 60-9).

The presence of normal systemic indices of perfusion does not exclude significant regional hypoperfusion or mitochondrial failure.[57,58] Clinicians frequently misinterpret high serum lactate levels as indicative of tissue hypoperfusion and as a result may institute inappropriate therapy.[58,59] Dynamic measurements of lactate over time are better predictors of outcome than are static measures.[60] Lactate clearance has been proposed as an end point of resuscitation in sepsis,[61,62] because lactate concentration should decrease with adequate resuscitation.[62] Rapid clearance of lactate has been associated with improved outcomes.[63,64] A failure of lactate clearance in response to resuscitation suggests that global perfusion is not the underlying problem and should prompt a search for a more sinister etiology (see also Chapter 108).

PERIOPERATIVE ACID-BASE DISTURBANCES

In addition to the acid-base disturbances seen in emergency situations, several acid-base conundrums are peculiar to the perioperative and critically ill patient (Table 60-4; see also Chapters 81, 82, and 101). These include the respiratory acidosis and alkalosis associated with mechanical ventilation, acidosis secondary to hyperchloremia or contraction, and alkalosis resulting from Na^+ gain or Cl^- loss.

Perioperative respiratory acidosis is most often the result of a poor mechanical ventilation strategy, narcosis, or incomplete reversal of neuromuscular blockade. Respiratory alkalosis is likely caused by hyperventilation from secondary pain or anxiety.

Metabolic acid-base disturbances are relatively common perioperatively. Pathologic causes involve lactic acidosis, ketoacidosis, and renal acidosis, as previously described. Iatrogenic causes reflect manipulation of SID by administration of electrolyte or osmotically imbalanced solutions.

Hyperchloremic acidosis is frequently seen in the perioperative period. This abnormality usually follows administration of large volumes of 0.9% (normal) saline solution, which contains 154 mEq of both Na^+ and Cl^- and has an SID of 0. Each liter of normal saline is associated with a reduction in the ECF SID, and it produces hyperchloremic acidosis.

Is hyperchloremic acidosis clinically significant? As a cause of acidosis, hyperchloremia is less sinister than other causes: in a study of critically ill patients with various acid-base disorders, mortality was highest for lactic acidosis (56%); for SIG acidosis it was 39%, and for hyperchloremic acidosis it was 29% ($P < .001$),[65] findings consistent with other data.[66,67] Nevertheless, hyperchloremia may result in clinically significant organ dysfunction. An observational study of 31,000 surgical patients[68] comparing intravenous saline with intravenous balanced salt solutions demonstrated significant outcome differences favoring balanced salt solutions. Complications enhanced by the use of normal saline included postoperative infections, blood transfusions, and kidney injury requiring dialysis. Patients with perioperative metabolic acidosis have a prolonged duration of hospital stay.[69]

A hyperchloremic state may be associated with nephrotoxicity: saline infusion has been associated with reduced renal blood flow,[70] renal vasoconstricton,[71,72] reduced glomerular filtration,[73] splanchnic hypoperfusion,[74] and perhaps an increased risk of contrast nephropathy.[74,75] Critically ill patients with sepsis frequently develop hyperchloremic acidosis that appears to be associated with worse outcomes.[76] In a relatively large before and after cohort study of patients treated in an Australian intensive care unit, the use of Cl^--rich fluids was associated with a 3.7% absolute increase in the risk for need of renal replacement therapy relative to balanced salt solution.[77]

The presence of a significant base deficit and low pH in a patient with diabetic ketoacidosis or lactic acidosis usually prompts continued fluid resuscitation. However, this strategy may be inappropriate if the cause of acidosis is hyperchloremia (see Table 60-4). International guidelines recommending the use of 0.9% $NaHCO_3$ (normal saline) for fluid resuscitation in diabetic ketoacidosis are based on scant evidence. This practice developed as a result of concern that the K^+ content of balanced salt solutions could become problematic if renal insufficiency was the underlying cause of acidosis. However, a study of anephric patients undergoing renal transplantation demonstrated that patients treated with normal saline were more acidotic and hyperkalemic than were patients treated with lactated Ringer solution.[78] Further, a small study that compared normal saline with Plasma-Lyte 148 (a balanced salt solution) reported that patients receiving the balanced salt solution instead of normal saline

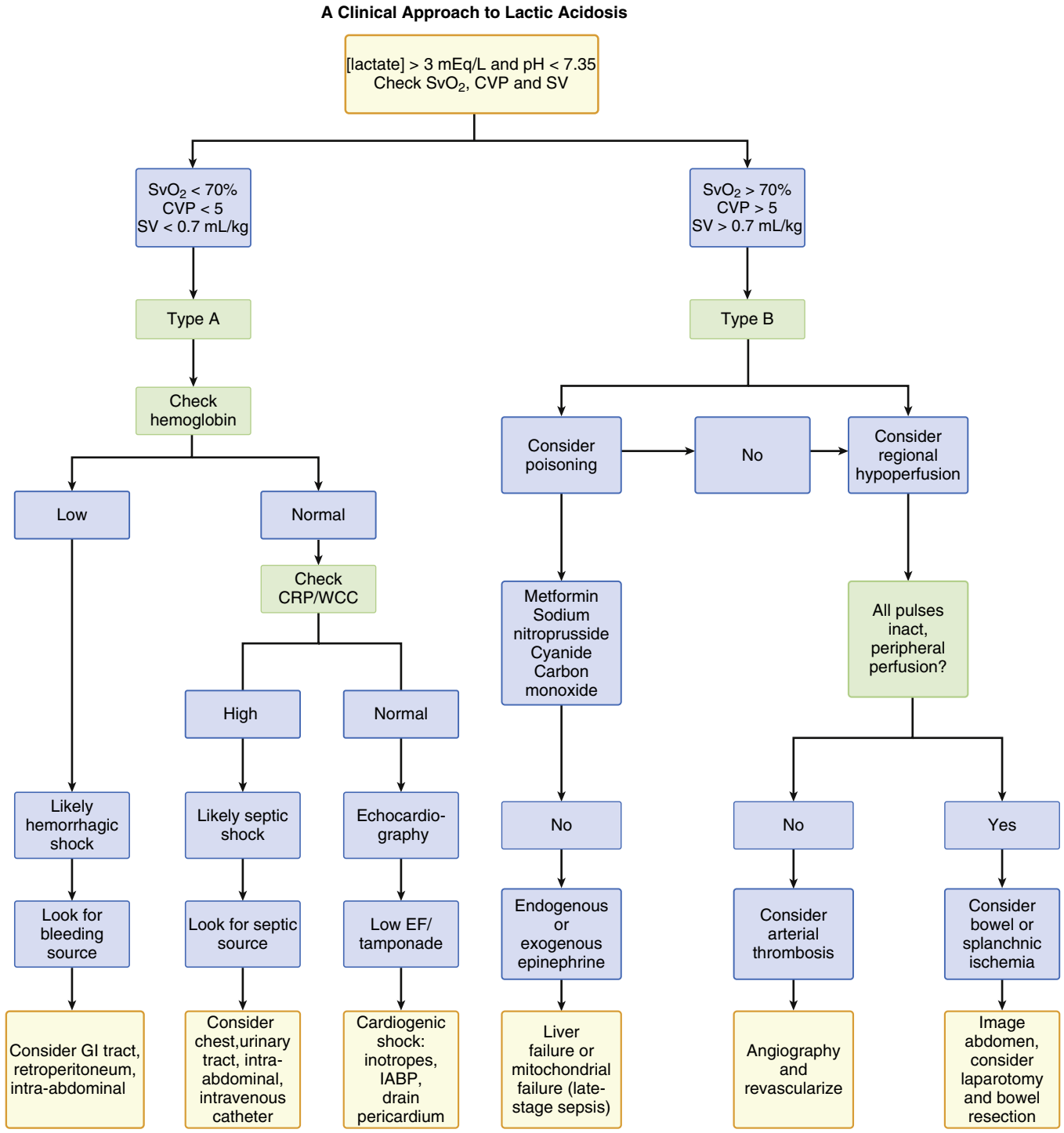


Figure 60-9. Evaluation of a patient with lactic acidosis. *CRP,* C-reactive protein; *CVP,* central venous pressure; *EF,* ejection fraction; *GI,* gastrointestinal; *IABP,* intraaortic balloon counterpulsation; *SV,* stroke volume; *SvO_2,* mixed venous oxygen saturation; *WCC,* white cell count.

had more rapid resolution of metabolic acidosis, less hyperchloremia, an improved blood pressure profile, and greater urinary output.[79]

Mahler and colleagues conducted a study comparing normal saline with lactated Ringer solution in diabetic ketoacidosis: hyperchloremic acidosis was significantly more common in the group receiving normal saline.[80] A similar study comparing normal saline with lactated Ringer solution failed to demonstrate a benefit with lactated Ringer solution; the time to normalization of blood glucose was longer with lactated Ringer solution than with normal saline.[81]

Until more data are available, 0.9% $NaHCO_3$ is not the resuscitation fluid of choice in critically ill patients, in particular those at risk for development of acute kidney injury (see also Chapter 108).

Perioperative metabolic alkalosis is usually of iatrogenic origin. Overventilation of patients with chronic

respiratory failure results in acute metabolic alkalosis because the presence of chronic compensatory alkalosis associated with Cl^- loss in urine has not been taken into account (Fig. 60-10). More frequently, metabolic alkalosis is associated with increased SID secondary to Na^+ gain. This abnormality results from the administration of fluids in which Na^+ is "buffered" by weak ions, such as citrate (in blood products), acetate (in parenteral nutrition), and HCO_3^-. Buffer ions such as citrate, acetate, gluconate, and lactate, under normal conditions, are rapidly cleared by the liver and do not contribute to acid-base balance. Na^+ and Cl^- obey the law of conservation of mass. Na^+ gain is Cl^--sensitive alkalosis, treated by administration of net loads of Cl^-—0.9% $NaHCO_3$, KCl, CaCl, and, occasionally HCl. It is important to correct Cl^--sensitive alkalosis because the normal compensatory measure is hypoventilation, thus increasing $Paco_2$, which may lead to CO_2 narcosis and failure to liberate from mechanical ventilation.

Another cause of metabolic alkalosis in perioperative patients stems from the loss of Cl^--rich fluids from the gastrointestinal tract. Gastric juice contains HCl, which, when lost as a result of continuous suctioning or vomiting, obeys the law of conservation of mass and leads to alkalosis. The loss of hydrogen ions is not the cause of the alkalosis because the ability to produce hydrogen ion is virtually unlimited.

It is important to understand the effects of fluids on acid-base disturbances. For patients receiving 1 or 2 L of fluid perioperatively, little difference exists among the choices of fluids. If larger-volume crystalloid resuscitation is expected, then balanced buffered solutions, which mirror the electrolyte content of ECF, such as lactated Ringer solution, Normosol, or Plasma-Lyte, are recommended. If the patient has been undergoing continuous nasogastric suctioning, then normal saline should be administered intravenously until the base deficit returns to 0; balanced buffered solutions should be used thereafter. Similarly, if large volumes of blood or plasma are administered intravenously, then normal saline should be given. Care must be taken to avoid hypokalemia, hypocalcemia, hypomagnesemia, and hypophosphatemia. Patients who have received purgatives for bowel surgery should be treated with balanced salt solutions.

TABLE 60-4 ACID-BASE DISTURBANCES COMMONLY SEEN PERIOPERATIVELY

Disorder	Cause
Respiratory acidosis	Hypoventilation: narcosis, incomplete reversal of neuromuscular blockade
Respiratory alkalosis	Hyperventilation: anxiety, pain
Metabolic acidosis from unmeasured anions (widened gap acidosis)	Hypoperfusion—lactic acidosis; diabetic ketoacidosis; renal failure
Metabolic acidosis from measured anions (nongap hyperchloremic acidosis)	Hyperchloremia—"normal" saline and saline containing fluids; renal tubular acidosis; bladder reconstructions
Metabolic acidosis from free water excess (hyponatremia, dilution acidosis)	Hypotonic fluid administration; sodium loss—diarrhea; administration of hyperosmolar fluids—mannitol, alcohol: hyperproteinemia
Metabolic alkalosis	Hyperventilation of patient with a history of CO_2 retention (COPD); sodium gain (sodium bicarbonate, massive blood transfusion); chloride loss—nasogastric suctioning

COPD, Chronic obstructive pulmonary disease.

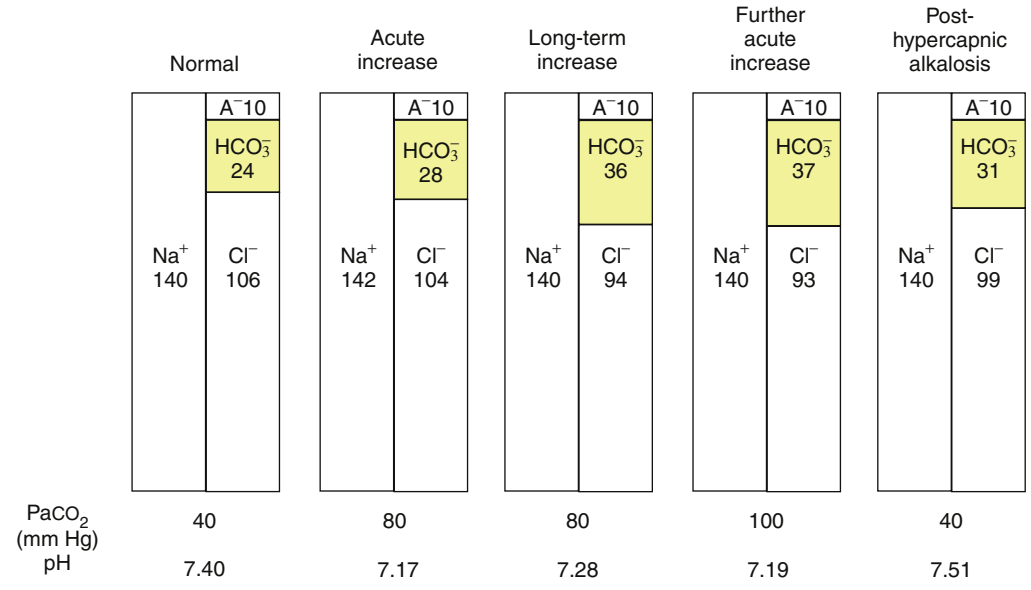


Figure 60-10. Changes in acid-base and electrolyte composition in patients with respiratory acidosis. *Left to right,* the panels depict normal acid-base status; adaptation to an acute rise in the partial pressure of arterial carbon dioxide ($Paco_2$) to 80 mm Hg; adaptation to a long-term rise in $Paco_2$ to 80 mm Hg; superimposition of an acute further increment in $Paco_2$ (to a level of 100 mm Hg) in the same patient; and posthypercapnic alkalosis resulting from an abrupt reduction in $Paco_2$ to the level of 40 mm Hg in the same patient. A^- denotes unmeasured plasma anions, and the numbers within the bars give ion concentrations in millimoles per liter. *(Modified from Androgue H, Madias N: Management of life-threatening acid-base disorders: first of two parts,* N Engl J Med *338:26–34, 1998.)*

ACID-BASE DISTURBANCES IN CRITICAL ILLNESS

Critically ill patients may have many confounding acid-base disturbances that are not evident when only a single quantitative measure, such as base deficit, is employed (see also Chapter 101). Patients frequently have perturbations of P_{CO_2}, SID, and A_{TOT}, and significant disturbances may be overlooked because of apparently normal blood gas results.[82]

The most common single disturbance in acid-base chemistry in critically ill patients is hypoalbuminemia.[17] This abnormality is ubiquitous and causes metabolic alkalosis of unpredictable magnitude. Hypoalbuminemia may mask significant alterations in SID, such as lactic acidosis. Therefore, when the anion gap is used in critically ill patients, it should be corrected for albumin.[19] Similarly, the use of base deficit to predict lactate is unreliable in critical illness, particularly in patients undergoing secondary deterioration.[18] Prolonged respiratory failure, with associated hypercarbia, leads to additional metabolic alkalosis resulting from Cl^- loss in urine.[83] Kidney injury is associated with accumulation of metabolic by-products, phosphate, renal anions, Cl^-, and other UMAs. Polyuric renal failure may be associated with significant contraction alkalosis in response to loss of Na^+, K^+, and free water.

Critically ill patients are vulnerable to significant changes in SID and free water. Nasogastric suctioning causes Cl^- loss, and diarrhea leads to Na^+ and K^+ deficits. Surgical drains placed in tissue beds may remove fluids with varying electrolyte concentrations (e.g., the pancreatic bed secretes fluid rich in Na^+). Fever, sweating, evaporation from denuded tissue, and inadequately humidified ventilator circuits all can lead to large volume insensible loss and contraction alkalosis.

Infusions administered to patients may be responsible for unrecognized alterations in serum chemistry. Many antibiotics, such as piperacillin-tazobactam, are diluted in Na^+-rich solutions. Others, such as vancomycin, are administered in large volumes of free water (5% dextrose). Lorazepam is diluted in propylene glycol, large volumes of which will cause metabolic acidosis similar to that seen with ethylene glycol.[84]

Continuous renal replacement therapy is used in critical illness for hemofiltration and hemodialysis in patients who are hemodynamically unstable. Rocktaeschel and colleagues demonstrated that continuous renal replacement therapy resolved the acidosis of acute renal failure by removing strong ions and phosphate.[85,86] However, in the presence of hypoalbuminemia, use of dialysis to correct metabolic acidosis may unmask metabolic alkalosis caused by hypoalbuminemia. Continuous renal replacement therapy is not an effective treatment for either type A or type B lactic acidosis.

Other, seemingly innocuous therapies may cause significant disturbances to acid-base balance. Loop diuretics, such as furosemide, are often administered to critically ill patients. These agents preferentially excrete water over electrolytes and provoke contraction alkalosis. Carbonic anhydrase inhibitors, such as acetazolamide, may be used to treat patients with hypochloremic metabolic alkalosis or respiratory alkalosis by decreasing the serum SID. This effect is completely explained by the increased renal excretion ratio of Na^+ to Cl^- that results in an elevation in serum chloride.[87] No treatment for hypoalbuminemic metabolic alkalosis exists except recovery. Contraction alkalosis is treated by correcting the free water deficit using the following formula:

$$\text{Free water deficit} = 0.6 \times \text{Patient's weight in kilograms} \times (\text{Patient's } Na^+/140 - 1)$$

Hypochloremic alkalosis should be treated by correcting the Cl^- deficit with normal saline.

Neurosurgical patients are vulnerable to a variety of acid-base disturbances as a result of osmotherapy or from disturbances caused by brain injury (see also Chapter 70). Mannitol is administered to reduce intracranial pressure and causes brief dilutional acidosis. Moreover, these patients are routinely treated with normal saline solution, which causes acidosis. Diabetes insipidus is a frequent complication of severe head injury, particularly when the patient is progressing toward brain death. Diabetes insipidus is caused by damage to the pituitary and/or the hypothalamus and results in a loss of antidiuretic hormone (ADH) secretion. Absent ADH, the kidney is unable to concentrate the urine, and massive diuresis follows. The disorder is characterized by an increase in plasma osmolality in the presence of low urinary osmolality. Diabetes insipidus typically manifests as contraction alkalosis. The treatment is hormonal replacement with either vasopressin or desmopressin.

TREATING ACID-BASE DISTURBANCES

Therapeutic treatment of acid-base disturbances is controversial. Many experts regard it as "window dressing," rather than addressing the cause. This refers particularly to the use of $NaHCO_3$ in the treatment of lactic acidosis.[88] Therapeutic use of $NaHCO_3$ has three effects: (1) intravascular volume expansion because the 7.5% solution is hypertonic (hence the often marked improvement in cardiovascular performance), (2) increased SID resulting from the administration of Na^+ without accompanying strong anion,[89] and (3) increased CO_2 generation. No evidence indicates that $NaHCO_3$ administration improves outcomes in circulatory shock.[88] Much discussion has focused on induction of intracellular acidosis by HCO_3^-,[90] but this is probably clinically insignificant.[88,91] Lactic acidosis is treated with intravascular volume resuscitation and source control. Diabetic ketoacidosis is treated with intravascular volume resuscitation and insulin.

Hyperchloremic or dilutional acidosis is treated by increasing the SID of infused fluids (e.g., by infusing Na^+ without Cl^-). Although no such fluid is available commercially, such a fluid can be constructed by using $NaHCO_3$ or sodium acetate.

Renal acidosis is treated with dialysis, which removes fixed acids. However, alteration in SID with $NaHCO_3$ or sodium acetate can be used, for the patient's comfort, as a bridge to dialysis.

Significant interest in hypercapnic acidosis has been shown since the 1990s, following the introduction of "permissive hypercapnia" in patients with acute respiratory distress syndrome (ARDS), to prevent ventilator-associated lung injury[11] (see also Chapter 101). Accumulating evidence indicates that hypercapnia has a lung-protective effect and that reversing the acidosis may have adverse effects.[92] Nevertheless, in patients with hypercapnic acidosis and associated cardiovascular instability, we recommend the use of *t*ris-*h*ydroxymethyl-*a*mino-*m*ethane (THAM).[93] THAM titrates hydrogen ions (e.g., lactic acid or CO_2) according to the following reaction:

$$R-NH_2 + HA \leftrightarrow R-NH_3^+ + A^-$$

THAM is a proton acceptor that generates NH_3^+/HCO_3^- without generating CO_2, and the protonated R-NH_3^+ is eliminated by the kidneys, along with Cl^-. THAM has the significant advantage of buffering acidosis without increasing serum Na^+ or generating more CO_2.

SUMMARY

Much of the confusion regarding acid-base chemistry relates to the attempt to apply observational approaches, such as that of Henderson-Hasselbalch and Schwartz and Brackett, to the entire spectrum of pathophysiologic processes. The use of physical chemistry principles has permitted an easier explanation of acid-base balance and provides tools to apply to a wide variety of clinical situations. This does not suggest that the "traditional" approach is incorrect, merely that it looks at a mirror image of that proposed by Stewart, Fencl, and others. All acid-base disorders can be explained in terms of SID, A_{TOT}, and P_{CO_2}. This is important to anesthesiologists, who may significantly affect acid-base balance with our choice of fluids and mechanical ventilation strategy.

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Chapter 61

Patient Blood Management: Transfusion Therapy

RONALD D. MILLER

Key Points

- The blood supply is safer now than at any other time in history. Advances in donor screening, improved testing, automated data systems, and changes in transfusion medicine practices account for these increases in safety (see 2012 U.S. Food and Drug Administration Fatalities Report).
- Although the overall condition of the patient is of prime importance, hemoglobin (Hb) values remain a primary component for transfusion decisions with the use of either a restrictive or liberal strategy. Generally, a transfusion trigger of an Hb level of 6 to 8 g/dL or less (restrictive strategy) can be tolerated by relatively healthy, younger patients. Those who are older, critically ill, or have severe cardiorespiratory disease may require a transfusion trigger of 9 to 10 g/dL (liberal strategy).
- Preoperative anemia is an independent risk factor for postoperative morbidity and mortality.
- The term *patient blood management* (see also Chapter 63) has become synonymous with appropriate transfusion strategy, especially with the initial unit of blood given. The indications for more than 1 unit of blood are addressed in this chapter.
- The addition of plasma and sometimes platelets to packed red blood cells (PRBCs) is described by the term *transfusion ratios.* For example, 2 units of plasma with 1 unit of platelets with 1 unit of PRBCs would be 2:1:1.
- Infectivity of blood is no longer a major cause of transfusion-related morbidity and mortality. Transfusion-related acute lung injury is the leading cause of transfusion-related mortality.
- Fresh whole blood has been reemphasized as an excellent choice in patients who are in a dire clinical situation, especially with major blood loss and a related coagulopathy (see also Chapters 62 and 63).
- The quality and effectiveness of blood transfusion is directly related to the length of time blood has been stored. In certain patients in critical clinical situations, blood that has been stored for 14 days or less may be considered.

EVOLUTION AND RECENT HISTORY OF BLOOD TRANSFUSION THERAPY

SOURCE OF DONORS AND HISTORY

Eighty percent of the world's population has access to only 20% of the world's "safe" blood—that is, blood that is properly collected and tested. Only 30% of the world's countries have a nationwide transfusion service and an appropriate donor pool.[1] Another issue in some parts of the world is incentivized donors. The policy of the World Health Organization (WHO) has been that a safe and reliable blood supply should use nonremunerated blood donation. More recently, the WHO suggested that offering economic rewards to donors should be seriously considered.[2] Yet the WHO's Coordinator for Blood Transfusion Safety, Neelam Dhingra, strongly defends the voluntary nonremunerated blood donation as a vehicle to a safer blood supply and increased donor participation.[3] The conclusions presented in this chapter assume the use of contemporary concepts and technology by organized transfusion services with voluntary nonremunerated blood donors.

THE 1960s

Transfusion medicine has undergone enormous changes in the last 50 years and especially since the writing of

this chapter for the 7th edition of *Miller's Anesthesia*. Although many changes have occurred, especially regarding the infectivity of blood, the consensus of whether to use whole blood, its components, or both has vacillated every decade or so. In the l960s, most blood given was in the form of whole blood. Fresh frozen plasma (FFP) was available for the treatment of coagulopathies. In addition, fresh whole blood (usually <24 hours of storage) was given for treatment of severe coagulopathies.[4,5]

THE 1970s THROUGH THE 1980s

Transfusion therapy was characterized in this 10- to 15-year period by "giving the patient only that component of blood that was needed." This philosophy led to component therapy rather than whole blood as the standard of care. For example, if the patient was anemic, only packed red blood cells (PRBCs) would be given instead of whole blood. If thrombocytopenia existed, only platelet concentrates would be given. Overall, caution regarding administration of blood transfusions increased from 1970 to l990 in part because of a major valid concern regarding the infectivity of blood (e.g., hepatitis and immunodeficiency syndrome [AIDS]). These and other health risks appropriately caused clinicians to be extremely cautious when giving blood. Furthermore, individual clinical decisions regarding blood transfusions were and continue to be monitored by local hospital transfusion committees (as required by regulatory agencies of various countries including the United States), which have the responsibility of monitoring the appropriateness of individual and institutional transfusion practices. One outcome of this increased scrutiny was to place prime attention on what the transfusion trigger should be.[6] Specifically, a transfusion trigger defines what the hemoglobin (Hb) value should be to trigger a blood transfusion, as discussed later in this chapter.

1990 TO 2005

In the period from 1990 to 2005, the strategy of specific component therapy was still prominent but not practical for urgent medical and surgical situations. Led by trauma hospitals and the military, the concept of reconstituted whole blood was introduced. Basically, FFP and platelets were added to PRBCs, resulting in the concept of transfusion ratios, which are reviewed in a separate section in this chapter. The addition of plasma and platelets to PRBCs results in a transfusion that is similar to that with whole blood.[7,8] Accordingly, the use of reconstituted whole blood logically rouses the opinion that perhaps we should go back to the previous practice of using whole blood more often instead of PRBCs. Today, even the concept of giving fresh blood has been reintroduced[9] and is emphasized in modern transfusion practice.[10,11]

2005 TO THE PRESENT

The aforesaid issues and the marked decrease in the infectivity of blood transfusions have resulted in multiple transfusion guidelines published by several societies and specialties based on many outcome studies.[12-14] As a result, more fundamental changes in transfusion medicine have occurred in the last 5 years than had taken place since 1970. Also, the term *patient blood management* has become synonymous with appropriate transfusion medicine.[15-17] This term is described as "the appropriate use of blood and blood components with a goal of minimizing their use."[18] Patient blood management tends to emphasize transfusion practice in a nonbleeding state. The clinical importance of preoperative anemia is also receiving significant attention. Clinicians will need to decide whether they wish to practice a liberal versus restrictive transfusion strategy. The anesthesia provider should be an expert on the implications and complications associated with blood transfusions and should be a leader of acute transfusion medicine in the hospital setting. Such experts must understand the changes in transfusion therapy and how patient blood management fits into their clinical situation (see also Chapter 63). Patient blood management in many countries has been facilitated by computerized data systems[19] and supply guidelines.[20] Specifically, transfusion therapy includes all forms and purposes of blood transfusion. Once again, even frozen blood products are being resurrected for use in remote and military locations.[21] A limitation of most of the patient blood management publications is that they describe mostly nonbleeding anemic patients and the initial transfusion. Very little information addresses what guidelines should be used for repetitive transfusions. This chapter focuses on transfusion medicine in the perioperative period, including the indications for both the initial and subsequent blood transfusions.

The decreased incidence of infectivity from blood transfusions has led to the term *noninfectious serious hazards of transfusions (NISHOTs)*.[22] These hazards are numerous and widely based and are described in this chapter.

INDICATIONS FOR TRANSFUSION

ALLOGENEIC (HOMOLOGOUS) BLOOD

Blood transfusions are given to increase oxygen-carrying capacity and intravascular volume. Theoretically, increasing intravascular volume is not an indication for blood transfusion because volume can be augmented with administration of intravascular fluids that are not derived from human blood (e.g., crystalloids or some colloids). For my entire career, Hb values were only one of many variables in a transfusion decision. To add emphasis, it was often stated that an Hb value should not be the sole basis for a transfusion decision; it should be the overall status of the patient. Although the overall status of the patient is of prime importance, I have been surprised at how important the Hb value has become as the basis for many transfusion strategies. In fact, it is the prime criterion for defining restrictive versus liberal transfusion strategies, as described later.

When a patient is hemorrhaging, the goals should be to restore intravascular volume, cardiac output, and

TABLE 61-1 **AMERICAN COLLEGE OF SURGEONS CLASSES OF ACUTE HEMORRHAGE**

Factors	Class I	Class II	Class III	Class IV
Blood loss (mL)	750	750-1500	1500-2000	2000 or more
Blood loss (% blood volume)	15	15-30	30-40	40 or more
Pulse (beats/min)	100	100	120	140 or higher
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal or increased	Decreased	Decreased	Decreased
Capillary refill test	Normal	Positive	Positive	Positive
Respirations per minute	14-20	20-30	30-40	35
Urine output (mL/hr)	30	20-30	5-10	Negligible
Central nervous system: Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Fluid replacement (3-1 rule)	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

organ perfusion to normal levels. By using crystalloids, colloids, or both to treat hypovolemia, normovolemic dilutional anemia may be created. Increasing cardiac output enhances O_2 delivery to the tissues to a limited extent. In fact, using normovolemic anemia clinically, Mathru and colleagues[23] found inadequate splanchnic and preportal O_2 delivery and consumption when the Hb level decreased to 5.9 g/dL.[23] Although the current patient blood management emphasis is on fewer or even avoidance of blood transfusions, clearly an Hb value exists below which a blood transfusion should be given, as discussed later. Additional O_2 delivery to organs and tissues can only be enhanced by RBCs via whole blood or PRBCs. Thus, increasing O_2-carrying capacity is the only real indication for blood transfusions.

The basis for using the Hb or hematocrit (Hct) value as the initial consideration for defining transfusion requirements followed a 1988 National Institutes of Health (NIH) Consensus Conference[7] that concluded that otherwise healthy patients with Hb value more than 10 g/dL rarely require perioperative blood transfusions, whereas patients with acute anemia (as in intraoperative blood loss) of less than 7 g/dL frequently require blood transfusions. They also recognized that patients with chronic anemia (as in renal failure) might tolerate an Hb concentration of less than 6 to 7 g/L. Amazingly, and despite many studies, publications, and debates, the fundamental guidelines have not changed substantially in the 25 plus years since this conference.

An excellent editorial by Manach and associates[24] outlines key questions that should be considered regarding transfusion triggers, including what we need to learn and the role of databases. Of prime importance is identifying the variables that are predictive for erythrocyte transfusion and the approach that can most accurately estimate the impact of transfusions. Many studies use death rate as their main indicator. Although clearly an important indicator, there are additional obvious factors in between the extremes of life and death, including vital signs, key laboratory values, and other indicators used in critical care units (see also Chapter 101). The ultimate determination of the Hb or Hct value at which blood should be given is a clinical judgment based on many factors, such as cardiovascular status, age, anticipated additional blood loss, arterial oxygenation, mixed venous O_2 tension, cardiac output, and intravascular blood volume (Table 61-1). The O_2 extraction ratio has been recommended as an indicator for transfusions[9]; however, this technique requires invasive monitoring. Even so, the results by this indicator were not dramatic between groups who were or were not transfused.

ADDITIONAL BLOOD TRANSFUSIONS

After the initial administration of blood, what should be the indications for administering additional units of blood? Of major importance is the overall condition of the patient. Generally, most clinical situations should be combined with key information that, at a minimum, should be used to guide the need for additional transfusions. The following key information is required:

1. Overall condition of the patient, including measurement of vital signs
2. Assessment of anticipated blood loss
3. Measurement of blood loss
4. Quantitation of intravenous fluids given overall
5. Determination of Hb concentration

Overall Condition

Of prime importance in effective clinical care is the overall analysis of the patient (see list item 1). Although all five of these variables are clearly important, items 3 and 5 require additional clarification, especially in a chapter focused on blood transfusion.

Measurement of Blood Loss

Measuring blood loss is obviously important when assessing the need for both the initial and subsequent blood transfusions (see Table 61-1). However, the accuracy of these measurements is not uniformly accurate. The overall clinical condition of the patient is explained and illustrated in Table 61-1. With regard to measurement of blood loss, clinical investigators at Duke University emphasized that "interpretation of intermittent measurements of hemoglobin levels is often complicated by fluid shifts, intravenous volume infusions, and actual

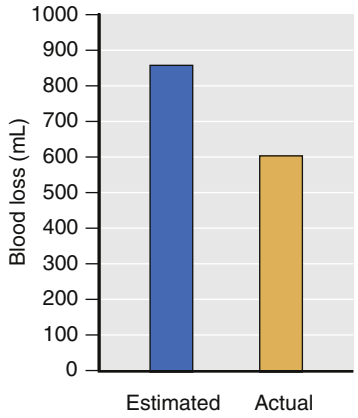


Figure 61-1. Discrepancy between estimated and actual blood loss. *(From Stovener J: Anesthesiologists vastly overstate bleeding,* Anesthesiol News *May 14, 2012.)*

transfusions."[25] A standard approach includes a combination of visualization and gravimetric measurements based on weight differences between dry and blood-soaked gauze pads. A study in patients undergoing spine surgery found that the anesthesiologists' estimate of blood loss was as much as 40% too large (Fig. 61-1). Basically, they collected the blood into heparinized saline to prevent clotting and then measured the volume of blood lost. Their findings were disturbing because overestimation of blood loss could lead to larger amounts of stored blood being given. Another study used an optical scanner for Apple's iPad tablet computer.[26] The scanner tended to underestimate blood loss, compared with the standard gravimetric calculations. Measuring intraoperative blood loss is extremely important and hopefully will be a more frequent topic of investigation.

Quantitation

The indications for administering additional units of blood are clear and logical. However, the five components of the key information (listed earlier) needed for making the decision to give more blood are often not very precise. As indicated previously and in Figure 61-1, intraoperative blood loss is even difficult to adequately quantify. Yet we need to make these decisions.

Determination of Hemoglobin Concentration

Transfusion decisions depend on many clinical factors and the blood Hb value, as indicated earlier. Clearly, these values are critical to decision making regarding blood transfusion and patient blood management decisions. Continuous blood Hb monitoring has become available on a noninvasive basis using spectrophotometric finger technology (Masimo SpHb, Masimo, Irvine, Calif). Numerous studies have been performed in a variety of clinical situations with emphasis on assessment of blood loss and/or the need for transfusions. Although measurement is frequently accurate (i.e., SpHb-Hb < 1.0 to 1.5 g/dL), the appearance of inaccurate values is not uncommon.[27,28]

Accuracy depends on both sensory factors and the physiology of the finger. If blood flow and temperature are increased, so is accuracy. For example, a digital nerve block decreases the number of inaccurate values and increases the number of accurate values.[29] The monitor displays many values, which can be helpful in assessing the accuracy of the SpHb value. Of prime importance is the perfusion index (PI). The accuracy of SpHb can be improved with a PI greater than 4% to 5%. This can be consistently achieved with a bupivacaine digital nerve block for several hours.[30] Although not specifically studied, warming the finger should increase the PI and, therefore, the accuracy of SpHb. This type of thinking was required in the early days of pulse oximetry; perhaps SpHb will evolve into being accurate even when the physiology of the finger is not optimal.

Can SpHb monitoring still be valuable even though its accuracy is not consistent? For example, Giraud and colleagues[31] concluded that SpHb is less invasive and less accurate than other measurements but provides valuable data on a continuous basis. They then concluded that none of the results would have led to transfusion errors as identified by the American Society of Anesthesiologists (ASA) Task Force on Perioperative Blood Transfusion and Adjuvant Therapies' updated practice guidelines published in 2006. Unfortunately, that outline is out of date, and a new one will appear in 2015. Observation of the trend is often recommended. Specifically, if the SpHb value suddenly changes 1 or 2 g/dL, the reasons for this change should be explored even if the absolute value is satisfactory. For example, if the SpHb reading is 11 g/dL, but rapidly decreases to 9.5 g/dL, the clinical situation has changed and needs to be reassessed. Although an attractive concept and possibly accurate, it is largely speculative.

HemoCue (HCue) (AB Leo Diagnostics, Helsinborg, Sweden) can be an accurate point-of-care Hb value. Hb values can be determined at the bedside or operating room in 5 to15 minutes. If the person performing the test is properly trained, both Giraud and colleagues[31] and Miller and colleagues[28] concluded that HCue measurements are extremely accurate. Yet, although HCue is probably more accurate than SpHb, the continuous manner of SpHb may identify some Hb changes more rapidly than HCue. In other words, an Hb value automatically occurs with SpHb whereas with HCue the clinician must make a decision that an Hb value is needed.

My opinion is that SpHb technology will consistently improve, as was the case with pulse oximetry. If so, SpHb could become very valuable with transfusion decision making in the future.

Preoperative Anemia

Preoperative anemia (i.e., low Hb value in women <12 g/dL; in men <13 g/dL) is an independent risk factor for increases in perioperative morbidity and mortality,[17] such as postoperative acute kidney injury (AKI).[32] Ideally, the patient's Hb value is known 2 to 4 weeks preoperatively. This provides sufficient time for the patient to undergo iron therapy, to correct nutritional deficiencies, or both. In a recent review of pharmacologic therapies in patient blood management, Goodnough and Shander[33] emphasized erythropoiesis-stimulating agents, especially intravenously administrated iron therapy, for treatment

of preoperative anemia. The concept of treating anemia preoperatively as a vehicle for decreasing the need for intraoperative transfusions is widely accepted. This concept has been demonstrated in other clinical situations. For example, intravascular iron therapy has eliminated the need for blood transfusions in gynecologic cancer.[34] If limited preoperative time is available, Karkouti and associates[35] seriously suggested that prophylactic erythrocyte transfusion should be used to reduce perioperative anemia. This suggestion met with controversy in the form of editorials and letters to the editor that were written supporting[33] (Karkouti) and condemning[36] such an approach.

Liberal Versus Restrictive Transfusion Strategy

The terminology of liberal versus restrictive has become completely indoctrinated into the transfusion therapy vocabulary. Several medical and surgical organizations have provided documents regarding their own definition of liberal and restrictive approaches. Some of these organizations include the American Association of Blood Banks,[37] International Conference on Transfusion Outcomes Group,[7] and Surgical Hip Fracture Repair (FOCUS).[38,39] Anesthesia providers need to understand exactly what the "strategies" are and their limitations.

Liberal versus restrictive transfusion strategy is based on the Hb value when a transfusion decision is made. A restrictive policy would be giving a blood transfusion only when the Hb value is 7 to 8 g/dL or less. In contrast, a liberal policy would be giving a blood transfusion when the Hb value is 9 to 10 g/dL or greater. Many studies have been performed in multiple clinical situations, with varying patient conditions, and ASA physical status values. One conclusion is that if no clinical advantages are associated with the liberal transfusion policy, perhaps the restrictive approach should be used. Certainly, fewer transfusion reactions would be expected with the restrictive approach.[38] In fact, many of these studies were supported by the NIH, which is an indication of how important this topic is for patient care. As indicated before, I find it amazing how important one laboratory test (Hb) has become regarding transfusion policies and patient blood management. One of many examples is the study by Kotze and colleagues.[40] One of their conclusions is that preoperative Hb values predict markers of hip or knee arthroplasty outcome. Kotze's group is one of many recommending a systemic approach to correcting Hb mass preoperatively. More recently, a meta-analysis was performed on all randomized trials of the liberal versus restrictive transfusion approaches to transfusion medicine.[41] Not surprisingly, they concluded, "restrictive strategies may decrease the incidence of health care–associated infections." Their restrictive Hb values were 6.4 to 9.7 g/dL and liberal 9.0 to 11.3 g/dL (some overlap). Although a meta-analysis contains no original data, Carson[42] provided a cautious editorial regarding Hb values. In my opinion, Hb values are important, but the overall condition of the patient is of prime importance. Accordingly, the American College of Surgeons attempted to categorize patient characteristics and blood loss as a basis for transfusion decisions (see Table 61-1).

The liberal versus restrictive strategy associated with patient blood management has some limitations. This strategy primarily addresses the indications for administering an initial unit of blood.[43] Most of this strategy is directed toward anemia in stable patients who are not actively bleeding. It does not describe what the indications for administration of repetitive units of blood should be. The need for repetitive transfusions in a bleeding patient is not addressed in the liberal versus restrictive discussion. Yet it is a very important topic for anesthesia providers and is discussed later in this chapter. The other considerations include status of the patient, vital signs, and blood loss. The transfusion trigger probably should be different in older patients with coexisting conditions who have abnormal cardiovascular status. Clearly, patients with active bleeding, especially those with cardiovascular disease, should be subjected to a more liberal transfusion strategy.[44]

General Conclusions

The emphasis on Hb levels for transfusion decisions needs some caution. The limitation of such values is based on a potential extreme variability from one patient to another regarding the need for increased O_2-carrying capacity via blood transfusions. For example, young healthy patients with normal cardiorespiratory function may easily compensate for anemia (i.e., chronic or acutely induced by hemorrhage), whereas at an identical Hct value, older patients with cardiac disease may have serious problems with surgery and anesthesia (see also Chapter 80). An individual patient's Hb level may vary markedly in the perioperative period independent of and in addition to transfusions of RBCs. For example, in the process of acute bleeding, Hb values are only slightly decreased initially even if the intravascular volume is markedly depleted.[44] Despite this caution, Hb levels are of principal importance in transfusion decisions.

AUTOLOGOUS BLOOD

Autologous blood (see also Chapter 63) is assumed to be much safer than allogeneic blood, mainly because of the decreased risk for infection. Because of a marked decrease in infectivity from allogeneic blood (see section on infectivity of blood), the difference in safety compared with that with autologous blood is much less. Not surprisingly, the proportion of autologous blood collected has significantly decreased since the peak in 1992. In fact, autologous blood may not be safer than allogeneic blood. Furthermore, autologous blood does have risks. Complications associated with autologous blood transfusions include the following:

- Anemia
- Preoperative myocardial ischemia from anemia induced by preoperative donation
- Autologous units given to the wrong patient
- Need for more frequent blood transfusions

In fact, transfusion-related bacterial sepsis may be more frequent with use of autologous blood because of the underlying medical condition of the donor and less stringent donor selection. Also, autologous blood must be tested the same as allogeneic blood.

TABLE 61-2 **PROPERTIES OF WHOLE BLOOD AND PACKED RED CELL CONCENTRATES STORED IN CPDA-1**

	Days of Storage		
Variable	**0**	**35 (Whole Blood)**	**35 (Packed Cells)**
pH	7.55	6.73	6.71
Plasma hemoglobin (mg/dL)	0.50	46.00	246.00
Plasma potassium (mEq/L)	4.20	17.20	76.00
Plasma sodium (mEq/L)	169.00	153.00	122.00
Blood dextrose (mg/dL)	440.00	282.00	84.00
2,3-Diphosphoglycerate (μM/mL)	13.20	1.00	1.00
Percent survival*	—	79.00	71.00

CPDA-1, Citrate phosphate dextrose adenine-1.
*Percent recovery of O_R-tagged red blood cells at 24 hours.

The testing and screening of blood donors is by no means perfect. Ask yourself a question: If given a choice, would you want your own blood or allogeneic blood?[45]

CHANGES DURING STORAGE OF BLOOD

BIOCHEMICAL CHANGES IN STORED BLOOD

Units of blood collected from donors are usually separated into components, such as RBCs, plasma, cryoprecipitate, and platelets. PRBCs or whole blood can be stored for up to 42 days. The storage bags allow separation of blood into components. Citrate phosphate dextrose adenine-1 (CPDA-1) is an anticoagulant preservative in which blood is stored at 1° to 6° C. Citrate is an anticoagulant, phosphate serves as a buffer, and dextrose is a red cell energy source. The addition of adenine to citrate phosphate dextrose (CPD) solution allows RBCs to resynthesize adenosine triphosphate (ATP), which extends the storage time from 21 to 35 days. As a result, RBCs or whole blood can be stored for 35 days when stored in CPDA-1.[46] The shelf life can be extended to 42 days when AS-1 (Adsol), AS-3 (Nutricel), or AS-5 (Optisol) is used.[47,48] Adsol contains adenine, glucose, mannitol, and sodium chloride. Nutricel contains glucose, adenine, citrate, phosphate, and NaCl. Optisol contains only dextrose, adenine, NaCl, and mannitol. At the University of California, San Francisco (UCSF), 90% of RBCs are stored in AS-1. On a national level, 85% of RBCs are collected in AS-1. The Hct of PRBCs stored in AS-1 is approximately 60%. This duration of storage has been set by U.S. federal regulation and is determined by the requirement that at least 70% of the transfused RBCs remain in circulation for 24 hours after infusion. RBCs that survive 24 hours after transfusion disappear from the circulation at a normal rate. The RBCs that do not survive are subsequently removed from circulation by the blood recipient.

That blood can be stored for 42 days is a mixed blessing. The obvious advantage is the increased availability of blood. However, an increasing number of authors think blood stored for long periods is less effective than fresher blood in critically ill patients, possibly because of a leftward shift in the O_2-dissociation curve (see section on changes in oxygen transport).[49] An increased incidence of postoperative pneumonia in cardiac patients has been associated with the use of older blood.[50]

The citrate ion prevents clotting by binding Ca^{2+}; dextrose allows the RBCs to continue glycolysis and maintain sufficient concentrations of high-energy nucleotides (ATP) to ensure continued RBC metabolism and subsequent viability during storage. Storage at 1° to 6° C assists preservation by slowing the rate of glycolysis approximately 40 times the rate at body temperature. The addition of adenine prolongs storage time by increasing RBC survival, allowing them to resynthesize the ATP needed to fuel metabolic reactions. Without adenine, RBCs gradually lose their ATP and their ability to survive after transfusion.

During storage of whole blood and PRBCs, a series of biochemical reactions occur that alter the biochemical makeup of blood and account for some of the complications that are discussed later. During storage, RBCs metabolize glucose to lactate, hydrogen ions accumulate, and plasma pH decreases. The storage temperatures of 1° to 6° C stimulate the sodium-potassium pump, and RBCs lose K^+ and gain Na. The osmotic fragility of RBCs increases during storage, and some cells undergo lysis, resulting in increased plasma Hb levels. Progressive decreases in RBC concentrations of ATP and 2,3-diphosphoglycerate (2,3-DPG) occur during storage.

PRBCs have a slightly shorter survival time than whole blood (Table 61-2), although values for Hb and K^+ concentrations may appear somewhat high in 35-day stored RBC concentrates. However, the total plasma volume in the concentrates is only 70 mL. Specifically, when CPDA is the anticoagulant used, the Hct is approximately 65%. Because most of the plasma is removed, the resulting volume is approximately 250 mL. When CPDA-1 is used, the storage time is increased from 35 to 42 days. The plasma is removed and 100 mL of storage solution is added, resulting in an Hct of 40% and volume of 310 mL.[51]

CLINICAL IMPLICATIONS: DURATION OF BLOOD STORAGE

Several groups working with patients in intensive care units (ICUs) have attempted to define the point at which blood transfusions should be given by measures of tissue oxygenation and hemodynamics (e.g., increase in O_2 consumption in response to added O_2 content).[52-54] No

specific measure can consistently predict when a patient will benefit from a blood transfusion. However, the quality (e.g., age) of the blood and its increased O_2 capacity (e.g., Hb level > 10 g/dL) may benefit very sick patients. Purdy and colleagues[55] found that patients who received 17-day-old blood (range, 5 to 35 days) versus 25-day-old blood (range, 9 to 36 days) had a more frequent survival rate. In 1999, the length of storage of banked blood was related to the development of postoperative pneumonia after cardiac surgery.[50] (Yet, in contrast, in 2003 prolonged storage of blood was not associated with increased morbidity after cardiac surgery.)[49]

As stated in the 7th edition of this book, "Yet the saga continues," which also applies to this 8th edition. In 2006, Weiskopf and associates[56] performed studies in healthy volunteers who were evaluated by a standard computerized neuropsychological test 2 days and 1 week after acute isovolemic anemia was induced.[56] When correcting the anemia, they concluded that erythrocytes stored for 3 weeks are as efficacious as those stored for 3.5 hours. Spahn[57] wrote an accompanying editorial agreeing with Weiskopf and associates[57] and, furthermore, postulated that 2,3-DPG levels may not be the key factor in determining the delivery of O_2 (i.e., 2,3-DPG levels are reduced in older blood, but the blood still delivers O_2).

Two years later, different conclusions were published. Koch and colleagues[58] concluded that giving erythrocytes (PRBCs) older than 14 days was associated with an increased risk for postoperative complications along with reduced short-term and long-term survival in patients undergoing coronary artery bypass surgery. This article also had an accompanying editorial that concluded, "to the extent possible, newer blood might be used in clinical situations that seem to call for it."[59] Rather than continuing the ongoing saga and debate regarding the influence of the age of blood transfused, all of the available studies that probably relate to the underlying health of the patient and the specific condition that requires blood transfusions need to be analyzed together. Thus, the debate regarding the effectiveness of a blood transfusion and its duration of storage continues. Because the quality of blood decreases with length of storage, an association with morbidity could be expected. Several other studies have sought resolution regarding the impact of storage time on blood.

In 2007, Bennett-Guerrero and associates[60] described the biochemical changes in RBCs in great detail. Yet the most current opinions and data do not answer the questions. A meta-analysis concluded that older stored blood is associated with an increased risk for death.[61] However, Spinella and associates[62] did not arrive at a clear conclusion and recommended more studies. Cata and associates[63] also concluded that no change in outcome occurred in patients undergoing radical prostatectomy and receiving older blood. Saager and colleagues[64] also found no relationship between duration of blood storage and mortality in nearly 7000 patients undergoing noncardiac surgery. This study was a retrospective analysis with mortality as its end point. Yet Frank and associates[65] studied the blood of patients undergoing posterior spinal fusion surgery and found that duration of blood storage was associated with RBC deformity, which was not "readily" reversible after transfusion. They speculated that these deformed cells may be defective in delivering O_2 to the cells. On a broader basis, they concluded that both the "age of blood storage" (i.e., because of the changes in rheology of older blood) and "amount" of blood given should be considered when giving blood.

Although conclusions cannot be definitive, logic dictates that blood less than 14 days of storage should be better than older storage. Yet we still do not have a complete answer for the possible importance of duration of storage on clinical outcomes. Furthermore, the measures of outcome may be insufficiently sensitive to detect clinical outcomes. Many studies use mortality as their outcome measure. Although this is obviously a crucial outcome, it may not be sensitive enough to detect the importance of how long the storage of blood transfused has been. However, other clinical outcomes should be better (e.g., duration of hospitalization, cardiovascular changes). Certainly, many adverse clinical outcomes could occur without a change in mortality per se. Also, many of the studies rely on retrospective analysis, which is significantly dependent on the thoroughness of the database content that records the patient's past clinical course and outcomes. Of course, mortality is a definitive outcome and easily validated, but the less dramatic outcomes need to be analyzed. Two national studies are underway in the United States, including Age of Blood Evaluation (ABLE) and Red Cell Storage Study (RECESS), which will hopefully provide some decisive conclusions regarding the influence of the duration of blood storage.

The development of more sensitive indicators of tissue oxygenation (e.g., intramucosal pH) may provide indicators for transfusion. In the 1990s, several investigative efforts could not relate postoperative Hb levels to specific outcomes. Furthermore, Weiskopf and co-workers[66] found that decreases in Hb concentration to 5.0 g/dL did not produce any evidence of inadequate oxygenation in healthy patients. However, these patients were not subjected to the stresses of recovery from surgery and anesthesia. Still, Weiskopf and co-workers[66] found that these patients compensated for their low Hb levels with increased heart rates and stroke volumes. It is tempting to argue that patients who have a more rapid than expected heart rate or who cannot increase their cardiac output should receive a transfusion at a higher Hb level than 10 g/dL. Unfortunately, precise conclusions cannot be derived from these suggestive data. The following paragraph and list of guidelines was published in the 7th edition of *Miller's Anesthesia* and still applies.

To arrive at some conclusions in the presence of incomplete data, two complementary recommendations are given. The ASA's 2006 updated practice guidelines offer these recommendations[67]:

1. Transfusion is rarely indicated when the Hb concentration is more than 10 g/dL and is almost always indicated when it is less than 6 g/dL, especially when the anemia is acute.
2. The determination of whether intermediate Hb concentrations (6 to 10 g/dL) justify or require RBC transfusion should be based on the patient's risk for complications of inadequate oxygenation.

3. The use of a single Hb trigger for all patients and other approaches that fail to consider all important physiologic and surgical factors affecting oxygenation is not recommended.
4. When appropriate, preoperative autologous blood donation, intraoperative and postoperative blood recovery, acute normovolemic hemodilution, and measures to decrease blood loss (i.e., deliberate hypotension and pharmacologic drugs) may be beneficial. The pharmacologic approach is discussed later in this chapter.
5. The indications for transfusion of autologous RBCs may be more liberal than those for allogeneic RBCs because of less frequent (but still significant) risks associated with the former.

As previously mentioned, the 2006 ASA updated practice guidelines will be updated again in 2015. The following indications were recommended in the 6th edition of *Miller's Anesthesia* and are still useful, with the rule of thumb that administration of 1 unit of PRBCs increases the Hct value by 3% to 5%:

1. Blood loss greater than 20% of blood volume when more than 100 mL
2. Hb level less than 8 g/dL
3. Hb level less than 9 to 10 g/dL with major disease (e.g., emphysema, ischemic heart disease)
4. Hb level of less than 10 g/dL with autologous blood
5. Hb level less than 11 to 12 g/dL and ventilator dependent

Although these recommendations are current, the elusive transfusion trigger remains in a prominent part of the debates in anesthesia specifically and in medicine in general. Both lists of recommendations[67] agree that a transfusion trigger of 8.0 g/dL or less can be tolerated by patients who are not critically ill or do not have severe cardiorespiratory disease. That conclusion is still valid.

How liberal should the transfusion trigger be in critically ill patients? Some critical care physicians have suggested that administration of blood transfusions is related to the incidence of ventilator-assisted pneumonia[68] and nosocomial infections[69]; although this possibility cannot be excluded, these are complicated problems with many variables. Despite the difficulty with identifying a specific transfusion trigger, Ely and Bernard[70] have generally confirmed the conclusions listed earlier in the 6th edition of *Miller's Anesthesia*. Subsequent efforts and editorials lean toward a lower transfusion trigger for even critically ill patients.[71,72] Better outcomes have not consistently occurred with transfusion-induced Hb levels more than 8.0 g/dL (i.e., 9.0 to 10.0 g/dL).[73,74] Yet Vincent and associates,[75] using a multicenter observational study, found that "blood transfusions may no longer be associated with increased mortality rates and may be associated with improved survival." Although these multicenter studies have statistical challenges,[76] a more liberal transfusion trigger is suggested. Perhaps the margin of safety should be increased by increasing the Hb in critically ill patients, including those with cardiorespiratory disease. Some concern even exists about the underuse of blood transfusion therapy.[77] However, blood is a valuable resource that sometimes is in short supply. Perhaps with the availability of erythropoietin and synthetic RBCs, a more liberal Hb concentration can be used. As concluded by Weiskopf,[78] "We merely await advances in technology that will enable us to measure directly the value of concern and thereby free us from arguments over which surrogate (e.g., hemoglobin) to measure and what value indicates the need for augmented oxygen delivery." Although Weiskopf wrote this opinion in l998, surrogate indicators, such as the blood Hb values, are still used for transfusion decisions.

COMPATIBILITY TESTING

GENERAL PRINCIPLES

The ABO-Rh type, crossmatch, and antibody screen are frequently referred to as compatibility tests. These tests were designed to demonstrate harmful antigen-antibody interactions in vitro so that harmful in vivo antigen-antibody interactions could be prevented. Donor blood used for emergency transfusion of group-specific blood must be screened for hemolytic anti-A or anti-B antibodies, or both. All donor blood must be tested for the correct ABO and Rh type and screened for unexpected antibodies. Similarly, recipient blood must also undergo ABO-Rh typing, as well as testing for unexpected antibodies. Once this has been completed, proper selection of donor blood requires a test for compatibility between recipient blood and donor blood; this test is known as a crossmatch (Fig. 61-2).

All approved blood banks have redundant processes in place to ensure that the patient receives the correct unit of blood. For example, in 2012, UCSF's Blood Bank reported 88 incidents of near misses, which infers that some part of the process was not sufficiently precise. Four near misses occurred when the wrong blood was in the tube that was given to the blood bank; five other tubes had wrong patient information on the tube. These incidences emphasize the advantage of and need for a confirmatory specimen drawn at a separate time from the type and screen. At the risk for being redundant, a patient must not receive the wrong unit of blood. A hemolytic blood transfusion reaction usually occurs when the wrong unit of blood is given. This type of reaction is described later in the chapter.

ABO-RH TYPING

Determination of the patient's correct blood type is exceedingly important because the most serious and tragic reactions are usually caused by accidental transfusion of ABO-incompatible blood. These reactions result from naturally occurring antibodies (i.e., anti-A and anti-B), which activate complement and lead to rapid intravenous hemolysis. Anti-A or anti-B antibodies, or both, are formed whenever the individual lacks either or both of the A and B antigens. In essence, antibodies are directed against those antigens that are lacking in the individual's own cells. ABO typing is performed by testing RBCs for the A and B antigens and the serum for the A and B antibodies before transfusion (Table 61-3).

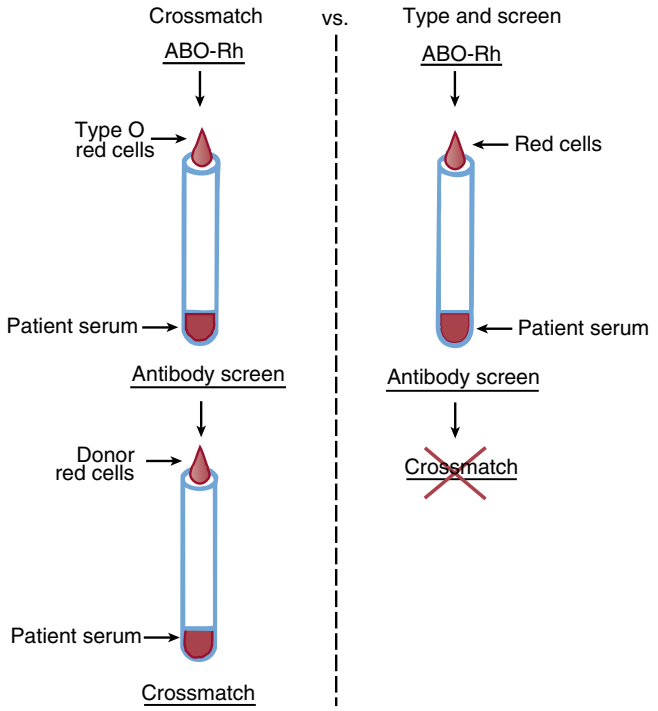


Figure 61-2. Outline of the tests used for a crossmatch. The X over the word *crossmatch* means that the crossmatch is not included in the type and screen.

The only additional required testing is that for the Rh(D) antigen. Antigen D is a very common one and, except for the A and B antigens, the one most likely to produce immunization. Of Rh(D)-negative recipients, 60% to 70% are immunized (produce anti-D) if they are given blood transfusions with Rh(D)-positive blood. Approximately 85% of individuals possess the D antigen and are classified as Rh(D) positive; the remaining 15%, who lack the D antigen, are classified as Rh(D) negative. Because anesthesiologists and surgeons often have difficulty understanding the blood grouping system, Table 61-4 is included to facilitate identification of donor blood groups whose blood patients can receive.

CROSSMATCHING

A crossmatch is essentially a trial transfusion within a test tube in which donor RBCs are mixed with recipient serum to detect a potential for serious transfusion reaction. The crossmatch can be completed in 45 to 60 minutes and is performed in three phases: an immediate phase, an incubation phase, and an antiglobulin phase.

The first, or immediate, phase (RT) is conducted at room temperature and is a check against errors in ABO typing. It detects ABO incompatibilities and those caused by naturally occurring antibodies in the MN, P, and Lewis systems. This takes 1 to 5 minutes to complete.

The second, or incubation, phase involves incubation of the first-phase reactions at 37° C in albumin or low–ionic strength salt solution. The addition of albumin and low–ionic strength salt solution aids in the detection of incomplete antibodies or antibodies able to attach to a specific antigen (i.e., sensitization) but are unable to cause agglutination in a saline suspension of RBCs. This phase primarily detects antibodies in the Rh system. An incubation period of 30 to 45 minutes in albumin and of 10 to 20 minutes in low–ionic strength salt solution in this phase is of sufficient duration to allow antibody uptake sensitization by cells so that incomplete antibodies missed in this phase can be detected in the subsequent antiglobulin phase.

The third, or antiglobulin, phase of the crossmatch, the indirect antiglobulin test, involves the addition of antiglobulin sera to the incubated test tubes. With this addition, antihuman antibodies present in the sera become attached to the antibody globulin on the RBCs, causing agglutination. This antiglobulin phase detects most incomplete antibodies in the blood group systems, including the Rh, Kell, Kidd, and Duffy blood group systems.

Although all three phases of the crossmatch are important, the first two are of prime importance in preventing serious hemolytic transfusion reactions (see section on type and screen). The incubation and antiglobulin phases are especially important because the antibodies appearing in these phases are capable of causing serious hemolytic reactions. Except for hemolytic reactions involving anti-A and anti-B, reactions caused by antibodies appearing in the immediate phase are frequently less severe. This is because many of the antibodies appearing in this phase are naturally occurring antibodies present in a low titer and are not reactive at physiologic temperatures.

ANTIBODY SCREENING

The antibody screen is also carried out in three phases and is similar in length to the crossmatch. The screen, however, is a trial transfusion between the recipient's serum and commercially supplied RBCs that are specifically selected to contain optimal numbers of RBC antigens or antigens that will react with antibodies that are commonly implicated in hemolytic transfusion reactions.

TABLE 61-3 ABO COMPATIBILITY TESTING

	Red Cells Tested With		Serum Tested With	
Blood Group	Anti-A	Anti-B	A Cells	B Cells
A	+	–	–	+
B	–	+	+	–
AB	+	+	–	–
O	–	–	+	+

TABLE 61-4 DONOR BLOOD GROUPS THAT PATIENTS CAN RECEIVE

Donor	Recipient
O	O, A, B, AB
A	A, AB
B	B, AB
AB	AB

The screen for unexpected antibodies is also used on donor serum and is performed shortly after withdrawal of blood from the donor. It is necessary to screen donor serum for unexpected antibodies to prevent their introduction into the recipient serum. This screen is performed primarily to prevent reactions between transfused donor units.

APPROACHES REQUIRING LESS THAN A COMPLETE CROSSMATCH

TYPE AND SCREEN

The term *type and screen* refers to elimination of the crossmatch in which blood is set aside with only the ABO-Rh type having been determined and antibody screening having been performed. The type and screen without crossmatch determines the ABO-Rh of the patient and the presence of the most commonly found unexpected antibodies. Specifically, the patient's serum is screened for the presence of unexpected antibodies by incubating it with selected reagent RBCs (i.e., screen cells).[79] These cells contain all antigens capable of inducing clinically significant RBC antibody reactions.

Complete transfusion testing for compatibility between donor and recipient blood ensures optimal safety and therapeutic effect of transfused blood. In some cases, however, the crossmatch is eliminated and blood can be set aside in which only the ABO-Rh type and antibody screen are performed (i.e., type and screen). For those few patients in whom the antibody screen reveals the presence of unexpected antibody, the antibody is subsequently identified in the blood bank and units of blood lacking the corresponding antigen are set aside for surgery. If an emergency transfusion is required after type and screen alone, an immediate-phase crossmatch is performed before transfusion to eliminate reactions that may result from human errors in ABO-Rh typing. Blood given in this manner is more than 99% effective in preventing incompatible transfusion reactions caused by unexpected antibodies.[80] The type and screen without the complete crossmatch does not protect against reactions caused by antibodies reactive against lower incidence antigens—that is, those not represented on the screening cells but present on the donor RBCs. Generally, antibodies that are not detected in the type and screen are weakly reactive antibodies that do not result in serious hemolytic transfusion reactions. In a study of 13,950 patients, Oberman and associates[81] discovered only eight "clinically significant" antibodies after complete crossmatch that were not detected during the antibody screening. The antibodies were all in lower titer and were believed by Oberman and associates to be unlikely to cause serious hemolytic reactions.

Most recently, Dexter and associates[82] established that using the estimated blood loss located in an anesthesia information system is more efficacious than that based on estimated blood loss and incidences of transfusions. An editorial by Reich and associates[83] emphasizes that this approach to type and screen decisions is an example of medicine's increasing dependence on information systems as described in the Preface of this book.

Type and screen should not be confused with the term *type and hold.* This term refers to a sample of blood from a potential blood recipient received by the blood bank in which the blood type but no crossmatch has been ordered. This term is misleading because it does not denote how long the blood should be held or whether an antibody screen has been performed on the sample. However, in most cases in which a type and hold has been ordered, an antibody screen is performed on that sample. Because of the confusion that has arisen with type and screen, the type and hold terminology and method of ordering blood have been abandoned by most blood banks.

MAXIMAL SURGICAL BLOOD ORDER SCHEDULE

The following paragraph is the same one that appeared in the 7th edition of *Miller's Anesthesia* and still applies in hospitals without contemporary information technology systems in place: Routine preoperative crossmatching of blood for surgical cases means that crossmatched blood is unavailable for others for 24 to 48 hours. During this time, 1 to 2 days is lost and the chance for outdating increases. A second aspect relates to the growing realization that, for certain elective surgical procedures, the number of crossmatched units ordered frequently far exceeds the number actually transfused. To quantify this problem better, the crossmatch-to-transfusion (C/T) ratio has been used. If the C/T ratio is high, the blood bank is burdened with keeping a large blood inventory, using excessive personnel time, and having a high incidence of outdated units. Sarma[84] recommended that for surgical procedures in which the average number of units transfused per case is less than 0.5, determination of the ABO-Rh type and a screen of the patient serum for unexpected antibodies (type and screen) should be used. This would be in lieu of a complete type and crossmatch for patients with negative antibody screens. For those with a positive antibody screen, the blood bank must provide compatible units that lack the corresponding antigen. Blood banks attempt to maintain C/T ratios of 2.1 to 2.7.[84] To increase the rate of use and lower the C/T ratio, blood banks attempt to decrease the emphasis on crossmatching of blood through such means as the type and screen and such programs as the maximal surgical blood order schedule (MSBOS).[85] This schedule consists of a list of surgical procedures and the maximal number of units of blood that the blood bank will crossmatch for each procedure. This schedule is based on the blood transfusion experience for surgical cases in hospitals in which the schedule is employed. Each hospital's MSBOS is developed by the suppliers and the users of blood in that hospital, such as blood bank staffers, anesthesiologists, and surgeons.

In the past several years, many blood banks have implemented information technology systems and revised procedures. Although information systems may vary among some institutions, some common pathways exist. Instead of the blood bank examining the next day's surgical schedule and allocating blood as described in the previous paragraph, now information technology systems have the capability of displaying the surgical schedule along with the MSBOS's recommendation regarding

blood for each surgical procedure. For institutions with information technology systems in place, the process is more as follows. The night before, the blood bank examines the surgical schedule and MSBOS recommendations to see what blood samples are missing and whether blood is needed. A communication to the preoperative team on what samples are needed (e.g., is any type and screen and ABO confirmation missing) and what tests have already been performed is disseminated. Then the preoperative team checks this communication and sends appropriate blood samples. The blood bank uses the MSBOS information to see if additional testing should be performed. If the MSBOS says that a type and screen is not needed, testing will not occur.*

IS THE CROSSMATCH REALLY NEEDED?

In previously transfused or pregnant patients, only approximately 1 patient in 100 may have an irregular antibody other than the anti-A and anti-B antibodies. However, some of these irregular antibodies are reactive only at temperatures below 30° C and therefore are insignificant in most transfusions. Others that are reactive at approximately 30° C can produce serious reactions if the transfused cells contain appropriate antigen. In order of probable significance, anti-Rh(D), Kell, C, E, and Kidd are the most common of clinically significant antibodies. After anti-A and anti-B, anti-Rh(D) is the most common significant antibody. If the correct ABO and Rh blood type is given, the possibility of transfusing incompatible blood is less than 1 chance in 1000. Put in other terms, ABO-Rh typing alone results in a 99.8% chance of a compatible transfusion, the addition of an antibody screen increases the safety to 99.94%, and a crossmatch increases this to 99.95%.[86]

The blood bank can reduce the chance of incompatibility by performing an antibody screen. The chance of this screening test missing an antibody that is potentially dangerous has been estimated to be no more than 1 in 10,000.

EMERGENCY TRANSFUSION

Blood transfusions constitute a part of the overall care of a patient with a serious and urgent clinical situation (see also Chapters 81 to 83). In the past few years, terminology has been added to our clinical vocabulary to characterize these situations. The "lethal triad" consists of hypothermia, acidosis, and a coagulopathy, the combination of which is well known to contribute to morbidity and mortality in severely injured or hemorrhaging patients. These factors add many biochemical and physiologic factors that contribute to persistent hemorrhage and clinical decline in patient welfare. The approach of damage control resuscitation has evolved. This approach includes use of permissive hypotension, damage control surgical techniques, and cautious administration of crystalloids. Topical hemostatic agents may include topical application of hemostatic dressings. There are even "walking blood banks" of prescreened donors available for urgent transfusion needs.[87]

In many situations, urgent need for blood occurs before completion of compatibility testing (ABO-Rh, antibody screen, and crossmatch; see also Chapter 81), which describes transfusion challenges in patients who require surgery and anesthesia after injury from trauma. In essence, for those situations that do not allow time for complete testing, an abbreviated format for testing can be used, such as described in the following paragraphs.

TYPE-SPECIFIC, PARTIALLY CROSSMATCHED BLOOD

When using uncrossmatched blood, it is best to obtain at least an ABO-Rh typing and an immediate-phase crossmatch. This incomplete crossmatch is accomplished by adding the patient's serum to donor RBCs at room temperature, centrifuging it, and then reading it for macroscopic agglutination. This takes 1 to 5 minutes and eliminates serious hemolytic reactions resulting from errors that may occur in ABO typing. Only a few unexpected antibodies outside the ABO systems are detected, such as those directed against antigens in the MN, P, and Lewis systems, most of which are not clinically significant.

TYPE-SPECIFIC, UNCROSSMATCHED BLOOD

For proper use of type-specific blood, the ABO-Rh type must be determined during the patient's hospitalization. Blood types from historical records, relatives, ambulance drivers, and other hospitals are frequently inaccurate. For those who have never been exposed to foreign RBCs, most ABO type-specific transfusions are successful. Caution should be used for patients who have previously received transfusions or have had pregnancies. In my experience in the military, type-specific uncrossmatched blood was frequently used in emergencies with no serious consequence. In the civilian setting, using 1 year's experience with 56 patients, uncrossmatched, type-specific blood for emergency transfusion produced no adverse effects, even though complete serologic testing had not been performed.[88] These investigators concluded that although the use of uncrossmatched blood is usually safe, the potential for serious reaction still exists, and they cautioned against its indiscriminate use. Approximately 1 in 1000 patients has an unexpected antibody detected in crossmatch. For those who have previously been exposed to RBC antigens, transfusion of the ABO-Rh type-specific, uncrossmatched blood may be more hazardous. For every 100 of these individuals, 1 has an antibody detected by the crossmatch.

TYPE O RH-NEGATIVE (UNIVERSAL DONOR), UNCROSSMATCHED BLOOD

Type O blood lacks the A and B antigens and consequently cannot be hemolyzed by anti-A or anti-B antibodies in the recipient's blood (see Tables 61-3 and 61-4). Because of this, people with type O blood have been

*This author acknowledges the help of Morvarid Moayeri, MD, PhD, Associate Director of the UCSF Blood Bank, for his help with this paragraph.

called universal donors and their blood can be used in emergency transfusions when typing or crossmatching is not available. However, some type O donors produce high titers of hemolytic immunoglobulin G (IgG), IgM, anti-A, and anti-B antibodies. High titers of these hemolysins in donor units are capable of causing destruction of A or B RBCs of a non–type O recipient. Type O Rh-negative, uncrossmatched PRBCs should be used in preference to type O Rh-negative whole blood because packed erythrocytes have smaller volumes of plasma and are almost free of hemolytic anti-A and anti-B antibodies. If type O Rh-negative whole blood is to be used, the blood bank must supply type O blood that is free of hemolytic anti-A and anti-B antibodies.

In addition to trauma units, anesthesia and surgical teams often struggle with how much and how the crossmatch process can be attenuated in emergency situations. At the risk for being repetitive, a brief situation is described. Some hospitals have an emergency-release RBC pack, which is uncrossmatched RBCs that are O negative. If clinicians think the situation is urgent, this blood usually can be provided in approximately 5 minutes. Also available in concept in some hospitals is a massive transfusion protocol (MTP), which includes 4 units uncrossmatched O negative RBCs, 4 units thawed AB plasma, and 1 unit of platelet concentrates. A physician must directly order this blood, and that decision is reviewed after analysis of the emergency situation. The complete crossmatch (i.e., electronic, immediate spin, or Coombs or antihuman globulin) is only eliminated in a well-defined emergency and with only O-negative blood.

This process is usually with PRBCs and not whole blood. Although uncrossmatched blood appropriately causes great concern, the risks for complication "appear" to be quite infrequent.[†]

During emergency transfusion of more than 2 units of type O Rh-negative, uncrossmatched whole blood, the patient probably cannot be switched to his or her blood type (A, B, or AB) as soon as the blood bank determines the correct blood type. Switching could cause major intravascular hemolysis of donor RBCs by increasing titers of transfused anti-A and anti-B. Continued use of O Rh-negative whole blood results only in minor hemolysis of recipient RBCs, with hyperbilirubinemia as the only complication. The patient must not be transfused with his or her correct blood type until the blood bank determines that the transfused anti-A and anti-B has decreased to levels that permit safe transfusion of type-specific blood.

FRESH WHOLE BLOOD

The definition of fresh whole blood is based on storage time, which varies from 1 hour to 5 days[89] before it is administered to patients. This definition takes into account that whole blood stored for 1 hour is much different from that stored for 5 days. For example, Kor and associates[90] concluded that there was no difference in pulmonary function or coagulation status when comparing fresh blood with standard-unit blood transfusion. However, this rather liberal definition of fresh blood is based on being stored for less than 5 days. Was this really fresh blood? For example, blood stored for less than 24 hours is much different than that stored for 4 days. The degree to which fresh blood regains its various functions is directly related to the length of storage and whether it has been cooled. The longer blood is stored, the less effective it becomes, especially regarding coagulation. Even 1 unit of whole blood stored for 24 hours at 4° C has less hemostatic effects than 1 unit of fresh blood stored for less than 6 hours because of decreased platelet aggregability.[91] Whole blood that has been typed and crossmatched, but not cooled retains most of the factors in normal in vivo blood. Spinella and colleagues[92] define fresh blood as having a shelf life of 24 hours and that is stored at 1° to 6° C within 8 hours after collection. Some institutions define it as fresh if it has been stored less than 48 hours at 2° to 5° C. The difference between 1 hour and 2 days of storage is tremendous, especially as it relates to platelet activity.

Numerous articles appear in the literature regarding the use of fresh whole blood. Part of the explanation of variability among studies is related to the duration of storage and use of hypothermia during the storage of fresh whole blood. Nevertheless, whole blood has been a component of transfusion for over 70 years, including during World War II.[11] The military and trauma hospitals have promoted and fine-tuned its use. My experience in Vietnam verified that typed and crossmatched warm whole blood was extremely effective in treating the coagulopathy from massive transfusions, especially in the absence of sepsis.[4,5] The use of unrefrigerated fresh whole blood is well known to be clinically very effective.[93] Many different protocols have complicated variations to the concept of simple administration of fresh whole blood as very effective, as described in the next paragraph.

The current literature is not consistent partly because of the variety of clinical situations. Even the ratio concept has been used for platelets. A transfusion ratio of 1:1:1 (RBCs to frozen plasma to platelets) was compared with a standard MTP based on laboratory values.[94] No difference between the two groups was found. However, the fixed ratio was associated with increased plasma wastage. Cotton and colleagues[95] compared whole blood versus component therapy. Unfortunately, each group automatically received platelets, making any conclusions regarding platelets impossible. Not surprisingly, fresh whole blood is effective in treating unresponsive life-threatening hemorrhage. A study of human volunteers who were given fresh and stored autologous blood came to the conclusion that blood stored for more than 21 days is not more injurious than fresh whole blood.[15] Yet using autologous blood is probably not an appropriate model to answer this question.

Basically, administration of older stored blood, colloids, and crystalloids dilute the platelets resulting in dilutional thrombocytopenia. After 15 to 20 units of blood have been given, the thrombocytopenia will cause a coagulopathy on a dilutional basis. If any additional cause of the coagulopathy exists (e.g., sepsis, massive

[†]This author acknowledges the help of Morvarid Moayeri, MD, PhD, Associate Director of the UCSF Blood Bank, with this section.)

consumption), the clinical coagulopathy will appear with fewer than 15 to 20 units of blood given. A more current rule of thumb is to transfuse 1 apheresis pack (6 units) of platelets in anticipation of a platelet count of 50 to 75,000/μL.[96]

One additional consideration is the best source of platelets—fresh blood or apheresis platelets. This question was studied in the armed forces when given to massively transfused military patients. No difference was found in adverse effects and mortality between patient groups receiving platelets.[97] In an atmosphere of limited resources, fresh whole blood is an excellent source of platelets.

SPECIFIC RECOMMENDED PROTOCOLS

In view of the aforementioned considerations, recommended protocols exist for the care of patients who are in urgent clinical situations potentially including hypovolemia and the possible requirement for blood transfusions. Of course, administration of blood products is only one part of a comprehensive approach to such urgent clinical challenges (see also Chapters 81 through 83). The following recommendations are brief and general, with the details of these further discussed in other sections of this chapter or in other chapters of this edition.

1. Infuse colloids, or crystalloids, or both. This topic was addressed by Myberg and associates.[98] Colloids are discussed in this chapter's section on synthetic colloid solution therapy, and the section on crystalloids in Chapter 59. The Myberg article "Resuscitation Fluids" states, "Although albumin has been determined to be safe for use as a resuscitation fluid in most critically ill patients and may have a role in early sepsis, its use is associated with increased mortality among patients with acute brain injury (also see Chapter 70). The use of hydroxyethyl starch (HES) solutions is associated with increased rates of renal-replacement therapy and adverse events among patients in ICUs. There is no evidence to recommend the use of other semisynthetic colloid solutions." In essence, crystalloids and blood (assuming blood loss and/or anemia) are the main fluids for resuscitation in acutely ill patients.
2. Draw a blood sample for typing and crossmatching.
3. If crossmatched blood is not ready to give, use type-specific or type O Rh-negative RBCs or type O-positive RBCs for males or postmenopausal females without a history of transfusions; type-specific, partially crossmatched blood; or type-specific, crossmatched blood.
4. In certain severe cases, the problems of massive transfusion should be anticipated. As indicated in this chapter, fresh whole blood should be considered if available.

Innovative methods of storing blood are being developed. For example, storing blood in an electrostatic field of 500 to 3000 V decreases hemolysis and attenuates the decrease in pH associated with prolonged storage.[99]

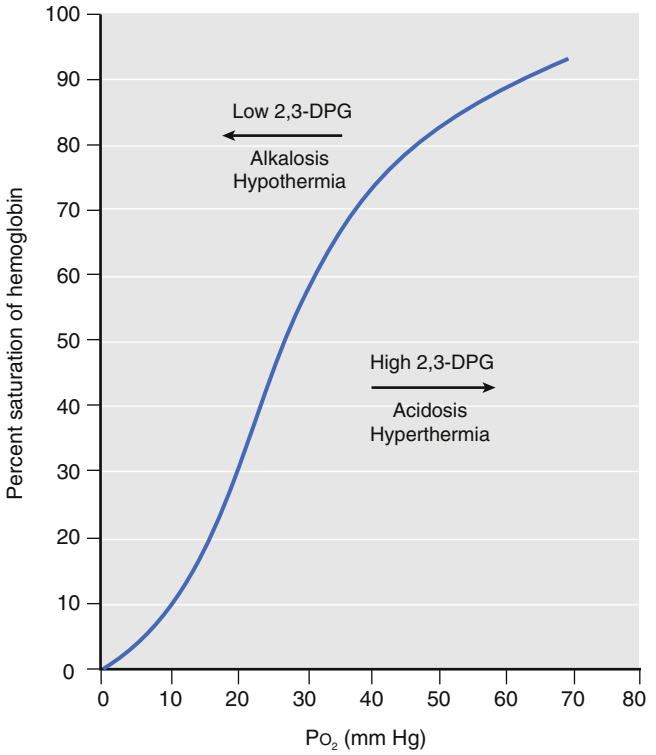


Figure 61-3. Factors that shift the oxygen dissociation curve. *2,3-DPG,* 2,3-Diphosphoglycerate. *(From Miller RD: The oxygen dissociation curve and multiple transfusions of ACD blood. In Howland WS, Schweizer O, editors:* Management of patients for radical cancer surgery: clinical anesthesia series, *vol 9, Philadelphia, 1972, FA Davis, p 43.)*

COMPLICATIONS

CHANGES IN OXYGEN TRANSPORT

RBCs are transfused primarily to increase transport of O_2 to tissues. An increase in the circulating red cell mass produces an increase in O_2 uptake in the lungs and a corresponding probable increase in O_2 delivery to tissues. The respiratory function of RBCs may be impaired during preservation, making it difficult for them to release O_2 to the tissues immediately after transfusion.

REVIEW OF THE OXYGEN DISSOCIATION CURVE

The O_2 dissociation curve is determined by plotting the partial pressure of O_2 (Po_2) in blood against the percentage of Hb saturated with O_2 (Fig. 61-3). As Hb becomes more saturated, the affinity of Hb for O_2 also increases. This is reflected in the sigmoid shape of the curve, which indicates that a decrease in Pao_2 makes considerably more O_2 available to the tissues. The sigmoid shape of the curve implies greater efficiency of blood transportation of O_2 from the lungs to tissues.

Shifts in the O_2 dissociation curve are quantitated by the P_{50}, which is the partial pressure of O_2 at which Hb is half saturated with O_2 at 37° C and pH 7.4. A low P_{50} indicates a left shift in the O_2-dissociation curve and an increased affinity of Hb for O_2; in other words, the left

shift of the curve indicates that a lower-than-normal O_2 tension saturates Hb in the lung and the subsequent release of O_2 to the tissues occurs at a lower than normal capillary O_2 tension. An increased affinity may be enough to ensure that O_2 is released to the tissues unless the tissue P_{O_2} is in the hypoxic range. The clinical evidence supporting the accuracy of this hypothesis during infusion is discussed in the following section.

CLINICAL EVIDENCE

The clinical evidence is not consistent, reflecting the difficulty of conducting a systematic study of seriously ill patients in varied clinical settings. For 40 years, various clinicians in a variety of clinical settings have tried to establish a firm relationship between the 2,3-DPG levels associated with stored blood and patient welfare (e.g., organ function). In 1993, Marik and Sibbald[100] found that the administration of blood that had been stored for more than 15 days actually decreased intramucosal pH, suggesting that splanchnic ischemia had occurred. In the past 10 years, numerous studies have tried to prove that older blood (and therefore decreased O_2 delivery) is not as beneficial as fresher blood in critically ill patients. Although a definitive conclusion cannot be made, I think that blood with less than 15 days of storage should be used in very ill patients.

COAGULATION IN GENERAL

Unless a patient has a preoperative coagulopathy (e.g., aspirin, antiplatelet drugs, hemophilia), major trauma or blood loss will initiate a cascade of coagulation abnormalities, including a consumptive coagulopathy from tissue hypoperfusion as manifested by increased protein C levels.[101] The addition of a large amount of blood (e.g., 6 to 10 units of PRBCs) only augments this coagulopathy. Various protocols have been developed for approaches to massive blood transfusion administration (Fig. 61-4). This coagulopathy is caused by a combination of factors, of which the most important are the volume of blood given and the duration of hypotension or hypoperfusion. Patients who are well perfused and are not hypotensive for a long period (e.g., 1 hour) can tolerate multiple units of blood without developing a coagulopathy. The patient who is hypotensive and has received many units of blood probably has a coagulopathy from a condition that resembles disseminated intravascular coagulation (DIC) and dilution of coagulation factors from stored bank blood. When such bleeding occurs, the differential diagnosis for a patient who did not have a pretransfusion coagulopathy (e.g., hemophilia) is dilutional thrombocytopenia, low factors V and VIII, a DIC-like syndrome, or hemolytic transfusion reaction. Clinical manifestations include oozing into the surgical field, hematuria, gingival bleeding, petechial bleeding from venipuncture sites, and ecchymosis.

THROMBOCYTOPENIA

Thrombocytopenia is defined as a platelet count less than 150,000/mm^3 or more than 50% over the previous measurement. Clinical bleeding usually does not occur until less than 50,000/mm^3 for surgical bleeding and even less for spontaneous bleeding.[96] Thrombocytopenia can be a cause of a hemorrhagic diathesis in a patient who has received multiple units of bank blood. Independent of whether whole blood or PRBCs are given, few viable platelets exist in a unit of blood stored for more than 24 hours. For whole blood at a storage temperature of 4° C, platelets are damaged sufficiently to be readily trapped and absorbed by the reticuloendothelial system soon after infusion. Even platelets that are not immediately stored have a reduced survival time. Considering survival time and viability, total platelet activity is only 50% to 70% of the original in vivo activity after 6 hours of storage in bank blood at 4° C. After 24 or 48 hours of storage, platelet activity is only approximately 10% or 5% of normal, respectively. Infusion of bank blood stored for longer than 24 hours dilutes the available platelet pool. Platelet counts decreased to less than 100,000/mm^3 when 10 to 15 units of blood were given to acutely wounded, previously healthy soldiers.[101] The platelet count in smaller, older patients may decrease to 100,000/mm^3 after being given fewer units of blood because these patients have a smaller blood volume and possibly a lower preoperative platelet count than soldiers. Over 40 years ago, my colleagues and I defined the importance of the platelet count because when it is approximately 75,000/mm^3 or less, a hemorrhagic diathesis is likely to occur (Table 61-5). One trauma group even suggested that a normal platelet count may not be high enough in severely injured trauma patients.[13] The general principle of using the platelet count as one of the indicators of clinical bleeding still applies even when thromboelastography (TEG) is used as a monitor.[102] Also, as indicated in Chapter 62, TEG and other devices are increasingly being used instead of specific blood levels of coagulation factors (e.g., platelet count, partial thromboplastin time [PTT]).

The preceding paragraph places emphasis on dilutional thrombocytopenia being the major cause of clinical bleeding in patients receiving multiple units of blood. In this situation, the clinician can dependably predict what the platelet count will be.[11] However, a concomitant medical condition can alter these relationships. Other authors emphasize that platelet counts cannot be predicted.[96] Certainly, if the patient has other medical issues (e.g., DIC, sepsis), thrombocytopenia will happen more rapidly. Routine monitoring of coagulation (see later discussion) should be a standard approach when hemorrhage occurs.[96] As discussed earlier in this chapter, the military and trauma hospitals tend not to follow this approach because they give blood in combinations of transfusion ratios.

Although major emphasis had been placed on monitoring the platelet count, several investigators[103,104] have questioned the role of dilutional thrombocytopenia in the coagulopathy of massively transfused patients. They correctly point out that the platelet count rarely decreases to as low a level as would be predicted from dilution alone (Fig. 61-5). This is probably because platelets are released into the circulation from the spleen and bone marrow and because of the presence of nonfunctional platelets. Reed and associates[104] found no benefit to prophylactic

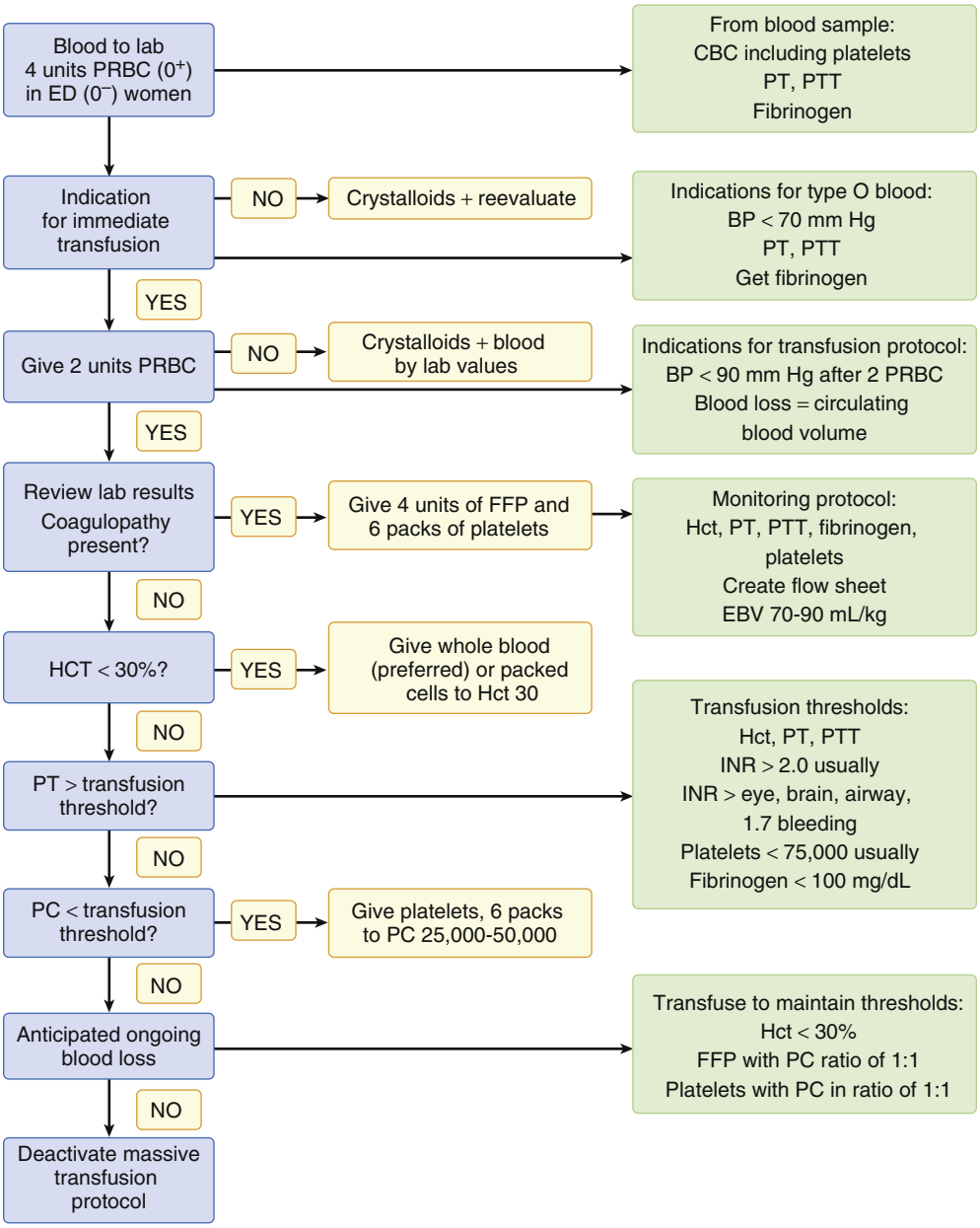


Figure 61-4. This algorithm for diagnosing and treating a massive transfusion was modified from the massive transfusion protocol used at the San Francisco General Hospital. There are many other similar approaches (e.g., Fig. 61-8 provides an algorithm for a pure coagulation). This protocol suggests how to approach a patient with major blood loss but does not include the use of recombinant activated factor VII, which may be possible in the future. (Kleinman)[168] *BP,* Blood pressure; *CBC,* complete blood cell count; *EBV,* effective blood volume; *ED,* emergency department; *FFP,* fresh frozen plasma; *Hct,* hematocrit; *INR,* international normalized ratio; *PC,* platelet count; *PRBCs,* packed red blood cells; *PT,* prothrombin time; *PTT,* partial thromboplastin time.

TABLE 61-5 CORRELATION BETWEEN PLATELET COUNT AND INCIDENCE OF BLEEDING

Platelet Count (cells/mm³)	Total No. Patients	No. Patients with Bleeding
>100,000	21	0
75,000-100,000	14	3
50,000-75,000	11	7
<50,000	5	5

Data from Miller RD, Robbins TO, Tong MJ, et al: Coagulation defects associated with massive blood transfusions, Ann Surg *174:794, 1971.*

platelet administration during massive transfusion. Platelets should not be given to treat laboratory evidence of thrombocytopenia unless clinical coagulopathy is also present. Treating laboratory numbers without correlation with the clinical status is fundamentally contrary to good medical practice; transfusion medicine is no exception. When the platelet count is less than 50,000 to 75,000/mm³, a bleeding problem is likely and is probably a combination of dilutional thrombocytopenia and DIC. Platelet therapy would be appropriate in this situation (see later section on platelet concentrates). Evaluation of

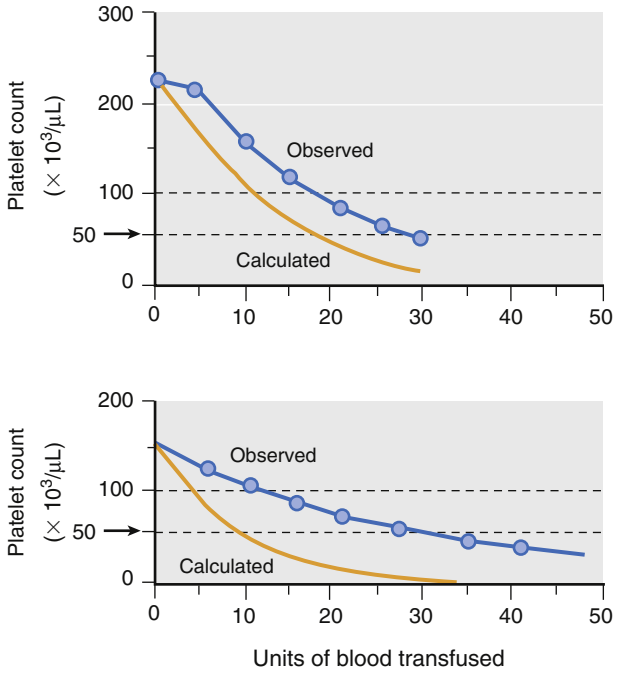


Figure 61-5. Mean platelet counts after massive transfusions in relation to number of units of blood transfused. Observed versus predicted values calculated on the basis of blood exchange model. *(From Myllylä G: New transfusion practice and haemostasis,* Acta Anaesthesiol Scand Suppl *89:76, 1988.)*

the literature with regard to the benefit of some blood-related therapy is difficult. Basically, sicker patients often need more blood. Yet, are these patients better off because of the blood? Patients who receive platelets during liver transplantation have an increased mortality rate in one study.[105] The unanswered question is whether the increased mortality rate is because the patients who received platelets were more critically ill before platelets were given. This is just one of the reasons why efficacy of blood product administration is often difficult to assess.

To place such emphasis on the platelet count as a guide is appropriate, as defended previously, with some exceptions. For example, patients with chronic thrombocytopenia or leukemia are commonly known to survive and not have a hemorrhagic diathesis with a platelet count lower than 15,000 cells/mm^3. However, this does not negate the general guideline that patients with a platelet count of less than 75,000 cells/mm^3 are likely to bleed. For unexplained reasons, patients with an acutely induced thrombocytopenia (e.g., from blood transfusions) develop a hemorrhagic diathesis at a much higher platelet count than patients with a chronically induced thrombocytopenia (e.g., idiopathic thrombocytopenic purpura). A higher platelet count is required to maintain adequate hemostasis with a surgical incision or trauma because damaged capillaries require platelets to plug the holes. The chapter on transfusion therapy in the 7th edition of this book resolved that the platelet count was a reasonably accurate guide as to when patients will develop a bleeding problem from dilutional thrombocytopenia (see Table 61-5). Although that conclusion is still correct, increasingly it is not practically useful because of the growing use of point-of-care thromboelastometry (ROTEM) to guide hemostatic therapy.[106]

LOW LEVELS OF FIBRINOGEN AND FACTORS V AND VIII

In the past few years considerable attention has been brought to the decreases in blood fibrinogen concentrations that occur during blood loss and blood replacement, probably because of the availability in some countries of a lyophilized fibrinogen concentrate for clinical use. Previously, fibrinogen supplementation was primarily received from administration of FFP and cryoprecipitate. Levy and colleagues[107] provided an excellent scholarly review of fibrinogen and hemostasis. As indicated earlier, more precise monitoring with thromboelastometry has allowed much more information to become available regarding fibrinogen. Levy and colleagues had two major conclusions. First, "fibrinogen is critical for effective clot formation, and its monitoring and guided supplementation as the treatment of major bleeding increasingly recognized." Second, their last sentence is typical of such reviews: "The prospective study of fibrinogen supplementation in acquired bleeding is needed to accurately assess the range of clinical settings in which this management strategy is appropriate, the most effective method of supplementation, and a comprehensive safety profile of fibrinogen concentrate used for such an approach." Indeed, such studies are beginning to appear. An examination of the Cochrane Database concluded that fibrinogen administration probably does reduce transfusion requirements.[108] Another group concluded that current recommendations for fibrinogen replacement are too conservative.[109] Yet another group[110] amazingly concluded that the clinical effectiveness of FFP was not apparent in trauma patients, but administration of fibrinogen concentrate generally improved outcome. I find the conclusion about FFP unbelievable, but we have an obligation to report the entire literature. However, fibrinogen increased fibrin-based clot firmness after aortic surgery.[111] Furthermore, a dilutional coagulopathy from colloid administration was better treated with a combination of factor XIII concentrates and fibrinogen rather than fibrinogen alone[112]—not a surprising result. Finally, a quote from Weiskopf[113] probably provides the best summary—"clinical trials with fibrinogen offer the exciting possibility of testing our understanding of static coagulation as it applies to the dynamics of surgery."

Historically, factors V and VIII and not fibrinogen have received prime attention.[114] These factors gradually decrease to 15% and 50% of normal, respectively, in whole blood after 21 days of storage. PRBCs even have fewer coagulation factors. Consequently, administration of FFP, which contains all the factors except platelets, has been recommended on a therapeutic or a prophylactic basis. However, this practice is of questionable benefit because only 5% to 20% of factor V and 30% of factor VIII are needed for adequate hemostasis during surgery. In other words, in spite of a patient receiving massive blood transfusion, factors V and VIII rarely decrease below those levels required for hemostasis. My colleagues and I examined this problem by giving 500 to 1000 mL of FFP to

TABLE 61-6 LABORATORY FINDINGS IN VARIOUS PLATELET AND COAGULATION DISORDERS IN THE INTENSIVE CARE UNIT

Condition	Prothrombin Time	Activated Partial Thromboplastin	Fibrinogen Level	D-Dimer Level	Bleeding Time	Platelet Count	Findings on Blood Smear
Vitamin K deficiency or use or use of vitamin K antagonist	Prolonged	Normal or mildly prolonged	Normal	Unaffected	Unaffected	Unaffected	
Aspirin or thienopyridines	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Unaffected	
Liver failure							
Early stage	Prolonged	Unaffected	Unaffected	Unaffected	Unaffected	Unaffected	
End stage	Prolonged	Prolonged	Low	Increased	Prolonged	Decreased	
Uremia	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Unaffected	
DIC	Prolonged	Prolonged	Low	Increased	Prolonged	Decreased	Fragmented red cells
TTP	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Very low	Fragmented red cells
Hyperfibrinolysis	Prolonged	Prolonged	Low	Very high	Possibly prolonged	Unaffected	

From Hunt BJ: Bleeding and coagulopathies in critical care, N Engl J Med *370;847-859, 2014.*
DIC, Disseminated intravascular coagulation; *TTP,* thrombotic thrombocytopenic purpura.

five patients who had received more than 15 units of bank blood and who had a clinically significant hemorrhagic diathesis. Despite the PTTs (which measure all factors except VII and XIII) and platelets having returned to normal, bleeding persisted in every patient. Only when platelets in the form of fresh blood were administered did bleeding cease. Although low factors I, V, and VIII are likely not the primary cause of bleeding during massive blood transfusion, such deficiencies may intensify bleeding from other causes, usually dilutional thrombocytopenia in the case of blood transfusion.

In 1985, the NIH conducted a consensus conference on this issue.[115] The conference concluded that little or no scientific evidence exists for the administration of FFP as part of the therapy for coagulopathy induced by multiple blood transfusions. Despite the fact that this conference and its recommendations are over 25 years old, the following criteria are still relevant even though they did not have the advantage of ROTEM:

1. Generalized bleeding that cannot be controlled with surgical sutures or cautery
2. PTT time at least 1.5 times normal
3. Platelet count greater than 70,000/mm^3 (to ensure that thrombocytopenia is not the cause of bleeding)

DISSEMINATED INTRAVASCULAR COAGULATION–LIKE SYNDROME

The coagulation system consists of clotting and fibrinolytic mechanisms. The function of the former is to prevent excessive blood loss, and that of the latter is to ensure circulation within the vasculature. With this DIC-like syndrome, the clotting system is deranged and this leads to disseminated fibrin deposition, which renders the fluid blood unclottable. The deposited fibrin may severely alter the microcirculation and lead to ischemic necrosis in various organs, particularly the kidney. The unclottable blood or circulating serum may induce a severe hemorrhagic diathesis. Although Table 61-6 centers around platelet disorders that have an impact on the coagulation system overall, it also displays the interchange between various medical conditions and their impact on various measures of the coagulation system, which is well described in this reference.[116]

The specific reasons for the development of DIC syndrome are usually not apparent. However, hypoxic acidotic tissues with stagnant blood flow probably release tissue thromboplastin directly or through liberation of some toxin as possibly modulated through the protein C pathway.[101] The release of tissue plasminogen activator from damaged tissue may cause fibrinolysis. In sepsis and eventual organ failure, the pathogenesis of this DIC syndrome is more apparent. The extrinsic route of coagulation is activated by tumor necrosis factor and endotoxins. Presumably, tumor necrosis factor induces tissue factor expression on the surface of activated monocytes and possibly by exposure to subendothelially localized tissue factor in blood[117] (see Chapter 62 for more details). Although the intrinsic system does not induce DIC, it may contribute to hypotension. This triggers the coagulation process, resulting in consumption of factors I, II, V, and VIII and platelets. Supposedly, thrombi and fibrin are deposited in the microcirculation of vital organs, interrupting their blood flow.

In an attempt to counteract the hypercoagulable state, the fibrinolytic system is activated to lyse the excessive fibrin almost simultaneously; this is called secondary fibrinolysis (see also Chapter 62). DIC should not be considered a distinct disease entity but rather a sign of another disease. DIC has been associated with almost all life-threatening diseases. Any condition in which tissue

damage is sufficient to release tissue products or toxins into the circulation can be associated with DIC. If enough thromboplastin lodges in the circulating blood, the result is massive focal necrosis or more generalized activation of the coagulation system.

HEMOLYTIC TRANSFUSION REACTION

The appearance of a hemorrhagic diathesis after blood transfusion should signal the possibility of a hemolytic transfusion. This entity is discussed later in this chapter.

DIAGNOSIS AND TREATMENT OF A HEMORRHAGIC DIATHESIS AFTER WHOLE BLOOD TRANSFUSIONS

Although treatment is more likely to be successful when the cause of the bleeding problem has been identified, precise diagnosis is often difficult. In addition to clinical examination of the patient, various coagulation laboratory tests have been used for years. One traditional approach has been to obtain a blood specimen on which the following tests can be performed: platelet count, PTT, and plasma fibrinogen level; observation of a clot for size, stability, and lysis; and observation of the plasma for evidence of hemolysis. Provided the PTT is 1.5 times normal or more and other tests are normal, the bleeding is probably a result of very low levels of factors V and VIII. This can be treated with FFP, which contains all the coagulation factors except platelets, or with cryoprecipitate. Although the preceding situation is a nice textbook description, I have never observed a clinical situation involving blood transfusions in which the PTT was increased without the presence of thrombocytopenia.

Point-of-care diagnosis of perioperative clinical coagulopathies is being increasingly facilitated by TEG and ROTEM, as reviewed by Srivastava and Kelleher.[118] Specifically, point-of-care ROTEM (viscoelastic and rotational) is being used to diagnose intraoperative coagulopathies.[119-123] All varieties of major surgeries and types of patients are being monitored with one of these devices, including liver transplantation[124] and postpartum hemorrhage.[102] Data are available within 10 to 20 minutes and are increasingly used to guide hemostatic therapy in trauma patients and, more recently, in other clinical situations. The theoretic advantages are assessment of clot formation in the context of whole blood, including contributions from platelets and RBCs and analysis of multiple stages of the clotting process from fibrin formation through fibrinolysis‡ (see also Chapter 62 for further details).

Dilutional thrombocytopenia in association with DIC, and hypoperfusion is the most likely cause of bleeding from blood transfusion.[114] When the platelet count is less than 100,000/mm^3, a bleeding problem is likely to develop (see Table 61-5); therefore, platelets are ordered. The rule of thumb is based on the fact that a bleeding diathesis probably will develop after infusion of 20 units of stored blood in healthy patients and after lesser amounts in debilitated or small patients (Fig. 61-6).

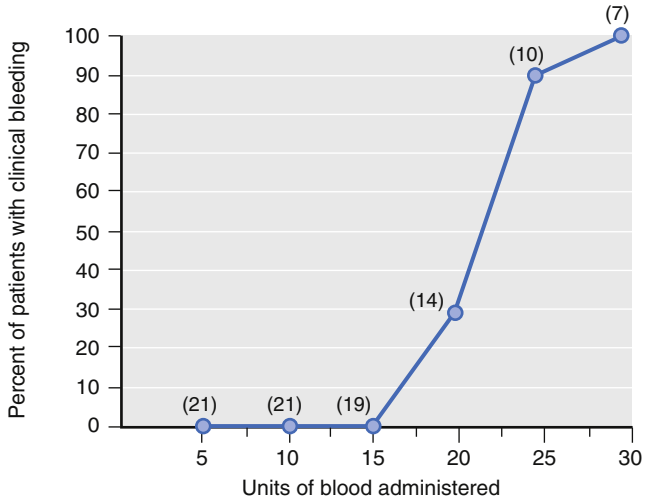


Figure 61-6. Correlation between units of blood administered and percent of patients who had a hemorrhagic diathesis. The numbers in parentheses represent the number of patients at each data point. (*From Miller RD: Transfusion therapy and associated problems,* Reg Refresher Courses Anesthesiol *1:101, 1973.)*

Whether platelets are administered in the form of fresh blood, platelet-rich plasma, or platelet concentrates depends on intravascular volume replacement requirements, personal preference, and availability of laboratory personnel. Fresh blood (<6 hours old) supplies the largest number of platelets per donation. More than 80% of the platelets can be given by platelet-rich plasma, which has half of the volume of a unit of blood. However, because most blood banks advocate giving patients only components that are necessary, platelet concentrates are frequently recommended. The remainder of the unit of blood, such as RBCs, plasma, and albumin, can be saved for other patients. Platelet concentrates are contained in a 50-mL unit and provide approximately 70% of the platelets in a unit of blood. In a 70-kg person, approximately 10 units of platelet concentrates are required to increase the platelet count by 100,000/mm^3.

Although logistically difficult to obtain, fresh blood is extremely effective in treating transfusion-induced coagulopathies. My personal and subjective observations in Vietnam indicated that fresh blood (i.e., ≤6 hours and unrefrigerated blood) had a dramatic effect in patients with extensive hemorrhage. Approximately 20 years later, Lavee and associates[125] found that 1 unit of fresh whole blood was as effective as, if not superior to, 8 to 10 platelet units. In 1996, Erber and colleagues,[93] used fresh unrefrigerated whole blood in surgical patients with ongoing extensive bleeding despite adequate component replacement therapy and adequate surgical hemostasis. An accompanying editorial expressed caution and described the unfortunate problems with conducting a larger trial with fresh blood.[126] I think that fresh blood also contains unidentified factors that make it far more effective than blood components.

Determining the plasma fibrinogen level is useful because this coagulation factor does not decrease in

‡Thank you to Brian M. Gilliss, MD, MS, for his help in facilitating my understanding of this process.

bank blood. If the in vivo plasma fibrinogen level is low (<150 mg/dL), it is not a result of a dilutional coagulopathy and strongly suggests DIC or a DIC-like syndrome. DIC is likely with thrombocytopenia, hypofibrinogenemia, and lysis of a clot within 2 hours.[114] Unfortunately, fibrinogen levels in PRBCs decrease with increasing storage time. As a result, hypofibrinogenemia occurs on a dilutional basis when multiple units of PRBCs are given.[127]

ε-Aminocaproic acid (EACA) inhibits the formation of plasmin and attenuates fibrinolysis. EACA should not be used in the treatment of DIC. Blocking the fibrinolytic system and having the coagulation system activated have resulted in disseminated thrombosis. Because primary fibrinolysis is rare other than in prostatectomy and liver transplantation[128] (see also Chapter 75), EACA should probably not be given unless the preceding diagnosis is clearly established after expert consultation. Despite the previous recommendations, bleeding from a transfusion-associated coagulopathy occasionally persists. A new approach has been described. Administration of recombinant activated coagulation factor VII (rfVIIa, Novo Nordisk Pharmaceuticals, Plantation, Fla) has produced successful treatment of such coagulopathies intraoperatively. Most of these patients also had other conditions, such as necrotizing pancreatitis, cirrhosis, or severe trauma. This exciting product is extremely expensive and should be viewed as a rescue therapy until approval by the U.S. Food and Drug Administration (FDA) is more broadly based[129] (see Chapter 62 for details).

DIAGNOSIS AND TREATMENT OF HEMORRHAGIC DIATHESIS AFTER PACKED RED BLOOD CELL TRANSFUSIONS

With much less plasma, dilution of certain coagulation values may be more profound with the use of PRBCs rather than whole blood. Murray and co-workers[127] specifically examined the question of using PRBCs for major blood loss. In general, the direction of coagulation changes was similar to that seen with whole blood, with one major exception. With use of PRBCs, fibrinogen levels decreased significantly in contrast to use of whole blood, in which fibrinogen levels remained unchanged unless DIC was present (Fig. 61-7). Although all the coagulation factors decreased, the decrease was less than expected from dilution. The researchers thought that factors such as factor VIII are probably stored in endothelial cells and released from the endothelium during surgical stress. When PRBCs are used to replace major blood loss, the clinician may be tempted to give FFP prophylactically. However, Murray and co-workers[127] specifically recommended not following the policy; they stated that FFP was needed only when prothrombin time (PT) and PTT were at least 1.5 times normal and fibrinogen levels were less than 75 mg/dL. These recommendations are similar to those stated in the section on FFP. Leslie and Toy[130] provided more specific guidelines when PRBCs are used for massive transfusions. They believed that when 12 or more units of PRBCs or cell-saver blood had been given, coagulation factors (i.e., FFP) were necessary. Patients who received 20 or more units often required platelet therapy, a finding identical to that of patients given whole blood.

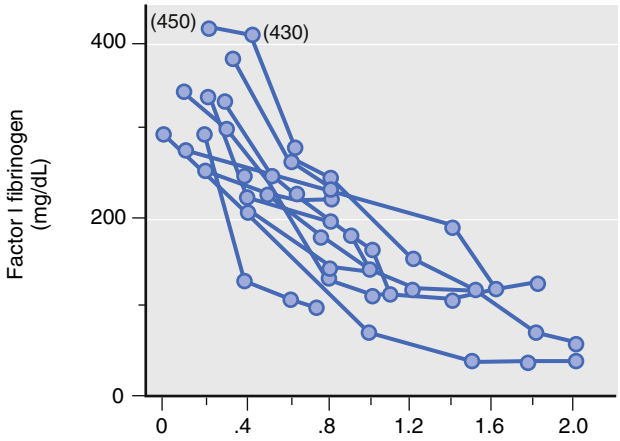


Figure 61-7. Decreases in fibrinogen level as blood volume is replaced with Adsol-packed red blood cells and crystalloid solutions. Each patient is represented by a *solid line. (From Murray DJ, Olson J, Strauss R, et al: Coagulation changes during packed red cell replacement of major blood loss,* Anesthesiology *69:839, 1988.)*

An algorithm for the evaluation and initial therapy of a patient with a suspected coagulopathy is given in Figure 61-8 (see also the section on blood transfusions, pharmacology, and hemostasis).

TRANSFUSION RATIOS

The transition from administration of whole blood to component therapy in the l970s created new challenges in transfusion medicine, especially in patients undergoing trauma or any type of surgery associated with significant blood loss. As indicated previously, administration of whole blood (1960s to mid-l970s) usually did not require FFP. Significant thrombocytopenia usually occurred after 15 to 20 units of blood.[5] The decision to give FFP or platelet concentrates was usually based on laboratory results, such as a platelet count and a PTT.

With the change from whole blood to PRBCs, the incidence of coagulopathies increased, especially with medical units responsible for trauma patients. Rather than basing treatment of transfusion or clinically induced coagulopathies on clinical judgment or laboratory tests, the concept of developing ratios of FFP and/or platelet concentrates with PRBCs evolved. For example, a 1:1:1 ratio would be transfusion of plasma and platelets to RBCs on a one-to-one basis. A 1:1 ratio frequently appears in the literature, which could be the combination of either FFP or platelets with RBCs.

Can an analysis of the literature specifically identify what the ratio should be? The most aggressive recommendation was that both a high-dose FFP (1.5 RBC to 1 FFP) and platelets (1 platelet to 6 RBCs) decreases mortality.[131] Some clinicians give FFP automatically to massively transfused patients even without a demonstrated coagulopathy with improved mortality rates.[132] Holcomb and associates[133] also concluded that increased platelet (i.e., instead of FFP) ratios were associated with improved survival after massive blood transfusions. However, these aggressive uses of FFP, platelets, and other blood products should only be given in response to coagulopathies from massive blood transfusions. For example, aggressive

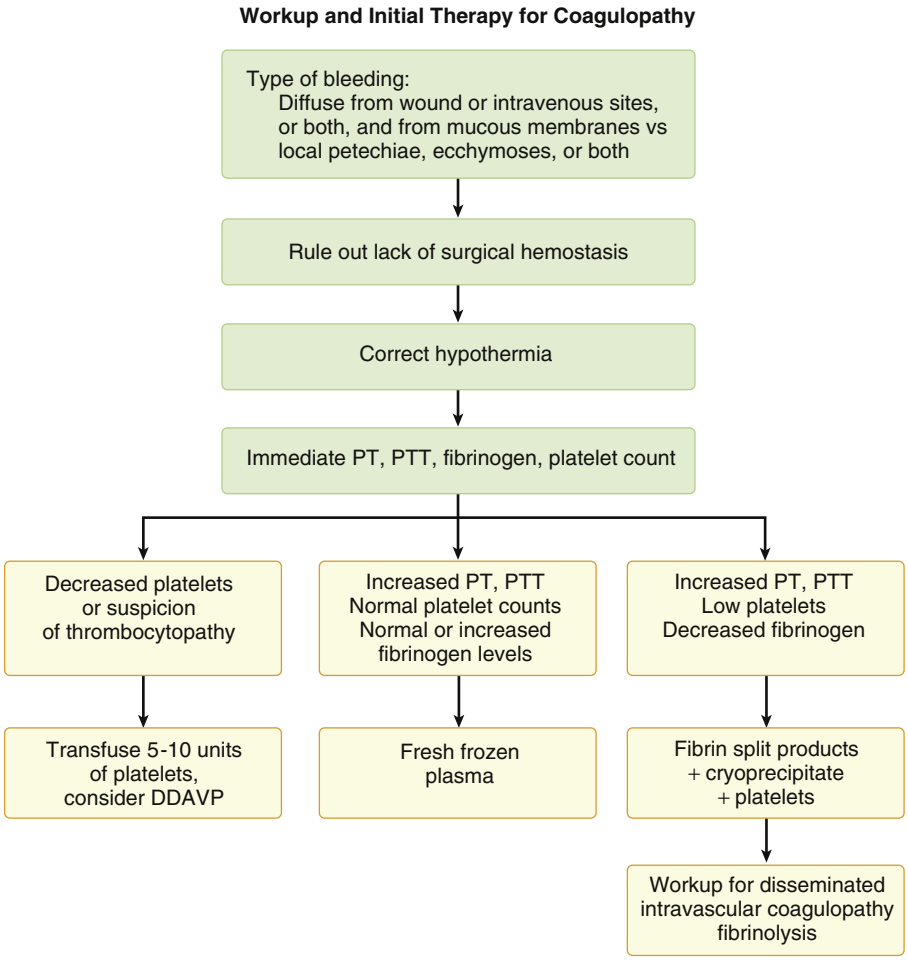


Figure 61-8. Algorithm of the evaluation and initial therapy of a patient with suspected perioperative coagulopathy. The evaluation is based on the clinical scenario and is affected by the type and location of injury, the amount of fluid administered, and the age and body temperature of the patient. *DDAVP,* 1-Deamino-8-D-arginine vasopressin, a vasopressin analogue also known as desmopressin acetate; *PT,* prothrombin time; *PTT,* partial thromboplastin time. *(Modified from Habibi S, Corrsin DB, McDermott JC, et al: Trauma and massive hemorrhage. In Muravchick S, Miller RD, editors:* Atlas of anesthesia: subspecialty care, *New York, 1998, Churchill Livingstone.)*

plasma administration to nonmassively transfused patients was associated with an increased rate of serious complications, including acute respiratory distress syndrome (ARDS) and organ dysfunction.[134]

Mortality was less frequent when patients with traumatic brain injury were given blood products with a high ratio of FFP to PRBCs.[135] A retrospective study showed that a higher FFP/PRBC ratio was associated with the need for advanced interventional procedures in patients with postpartum hemorrhage.[136] Yet an analysis of 26 studies concluded, "Without randomized controlled trials controlling for survivor bias, the current available evidence supporting higher plasma-to-erythrocyte resuscitation is inconclusive." Even more recently, the results of the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study were reported with a commentary by Maier.[137] The sources of the data were 10 U.S. level-I trauma centers. The conclusion of the study[138] was that "higher plasma and platelet ratios early in resuscitation were associated with decreased mortality in patients who received transfusions of at least 3 units of blood products during the first 24 hours after admission.[138] Among survivors at 24 hours, the subsequent risk for death by day 30 was not associated with plasma or platelet ratios." Yet a review by a group in the military divided their data according to the Injury Severity Score. A survival benefit was seen in ratios with high plasma to RBC resuscitation. However, no additional benefit of 1:1 over 1:2 ratios was identified.[139]

To me, an interesting philosophic problem has evolved. Approximately 30 to 40 years ago, whole blood was primarily given. Then in the 1970s, the concept of giving patients only the specific blood component they needed was the basis for dividing blood into separate components. However, in the last 10 years, military and trauma units have been using a concept they described as "reconstruction of deconstructed blood for trauma"—that is, components are added to PRBCs to make it more like whole blood, but it is called reconstituted whole blood. In summary, we had primarily whole blood 30 to 40 years ago and returned to that concept by approximately 2005. This is a rather strange and ironic pathway for blood transfusion medicine to follow.

BLOOD TRANSFUSIONS, PHARMACOLOGY, AND HEMOSTASIS

An extensive review of pharmacologic therapies in patient blood management has been made by Goodnough and Shander.[33] Iron therapy and erythropoiesis-stimulating agents are described earlier in this chapter. Drugs used for hemostasis are categorized into three groups: (1) antifibrinolytics, (2) serine protease inhibitors, and (3) analogues of the antidiuretic hormone.

The first group, antifibrinolytics, includes EACA and tranexamic acid, which are plasminogen inhibitors. Two studies found a decreased blood loss from total knee arthroplasty. Presumably, release of the pneumatic tourniquet releases fibrinolytic material, which is inhibited by tranexamic acid.

The second group is the serine protease inhibitors, including aprotinin, nafamostat, and ecallantide. Aprotinin inhibits fibrinolysis and improves platelet function. It has been used to decrease blood loss in multiple surgical procedures, including cardiopulmonary bypass. However, its ultimate place in the treatment of coagulopathies has not been established.

The third group is synthetic analogues of the antidiuretic hormone vasopressin. Three other drugs (i.e., desmopressin, recombinant factor VIIa, and prothrombin complex concentrates) have been recommended for perioperative coagulation problems.[140] Two of those drugs have received special attention. The first is desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]), a synthetic analogue of the antidiuretic hormone vasopressin and a procoagulant drug. It increases the levels of factor VIII and von Willebrand factor and is a well-established therapy for hemophilia and von Willebrand disease. It also reduces blood loss and transfusion requirements in patients with normal preoperative coagulation status who are undergoing spinal or cardiac surgery. However, the ultimate role of desmopressin remains to be determined.[140] It can cause hypotension, hyponatremia, and increased platelet adhesion. As indicated before, recombinant factor VIIa and prothrombin complex concentrates are also in this category.

Other vehicles for producing hemostasis include fibrin sealant, collagen, thrombin, and gelatin sponges. A large meta-analysis using perioperative blood transfusion as the outcome in cardiac surgery concluded that aprotinin and tranexamic acid, but not desmopressin, decreased the exposure of patients to allogeneic blood transfusion perioperatively.[141] The ultimate use of these drugs is evolving.

CITRATE INTOXICATION AND HYPERKALEMIA

Citrate intoxication is not caused by the citrate ion per se; it occurs because citrate binds Ca^{2+}. The signs of citrate intoxication are those of hypocalcemia—hypotension, narrow pulse pressure, and increased intraventricular enddiastolic pressure and central venous pressure. However, citrate intoxication is very rare. Having hypothermia, liver disease, liver transplantation, or hyperventilation or being a pediatric patient[142] increases the possibility of citrate intoxication. The appearance of severe hypocalcemia during liver transplantation is well documented (see also Chapter 74). The combination of infusion of large amounts of citrate (i.e., through blood transfusions) and of reduced metabolism from absent or reduced liver blood flow (i.e., in the anhepatic phases of liver transplantation) leads to citrate intoxication. As a result, Ca^{2+} infusions are common during liver transplantation. The rate of citrate metabolism is decreased by 50% when body temperature is decreased from 37° to 31° C. Excluding these conditions, infusion of more than 1 unit of blood every 10 minutes is necessary for ionized Ca^{2+} levels to begin to decrease. Even at these rates of infusion, ionized Ca^{2+} levels do not decrease enough to cause bleeding. As indicated previously, if a hemorrhagic diathesis starts after administration of blood, low Ca^{2+} levels are not part of the differential diagnosis.

As evidenced from the preceding discussion, citrate intoxication is rare. As described by Kleinman and associates,[51] serum K^+ levels may be as high as 19 to 50 mEq/L in blood stored for 21 days. This would be approximately 90 mEq/L units of PRBCs. However, when the loss of K^+ via blood loss is compared with administration of blood, the net gain of K^+ is approximately 10 mEq/L. The change in serum K^+ is usually minor because excess K^+ either moves into the cell or is excreted via the urine. Although hyperkalemia is occasionally reported,[142,143] large amounts of blood must be given. For significant hyperkalemia to occur clinically, bank blood must be given at a rate of 120 mL/minute or more. The fact that such rapid infusion rates of blood are required for the production of hyperkalemia suggests that the K^+ ion must leave the intravascular spaces by diffusion into extravascular spaces, by reuptake into RBCs, or through the kidneys. Although rare, hyperkalemia can occur in patients with severe trauma, impaired renal function, or both[144] (also infants and newborns, see also Chapters 94 and 95).

As with citrate intoxication, hyperkalemia is rare and this also rules against the routine administration of Ca^{2+}. Ca^{2+} may cause cardiac arrhythmias. Ca^{2+} administration should be based on diagnostic signs of hyperkalemia (i.e., peak T wave). Although irritating to veins, 10% calcium chloride provides three times more Ca^{2+} than an equal volume of 10% calcium gluconate because chloride has a molecular mass of 147 and gluconate has a molecular mass of 448. Finally, even though hyperkalemia is rare, it still occurs. Recently, Lee and associates[145] described nine cases of pediatric patients who had cardiac arrest during massive blood transfusions. The mean blood K^+ level was 9.2 ± 1.8 mmol/L. Risk factors were several, including the administration of older (i.e., longer storage) blood.

TEMPERATURE

Administration of unwarmed blood that has been stored at 4° C can decrease the recipient's temperature. If the temperature decreases to less than 30° C, ventricular irritability and even cardiac arrest may occur. This can be prevented by warming the blood to body temperature before transfusion. More subtle reasons exist for warming all blood, even in patients receiving only 1 to 2 units intraoperatively. Because of the cool temperature of the operating room, body temperature often decreases, particularly in patients undergoing extensive abdominal surgery; administration of cold blood further decreases temperature. Maintaining a patient's normal temperature is considered to be increasingly important (see also Chapter 54).

Perhaps the safest and most common method of warming blood is to pass it through plastic coils or plastic cassettes

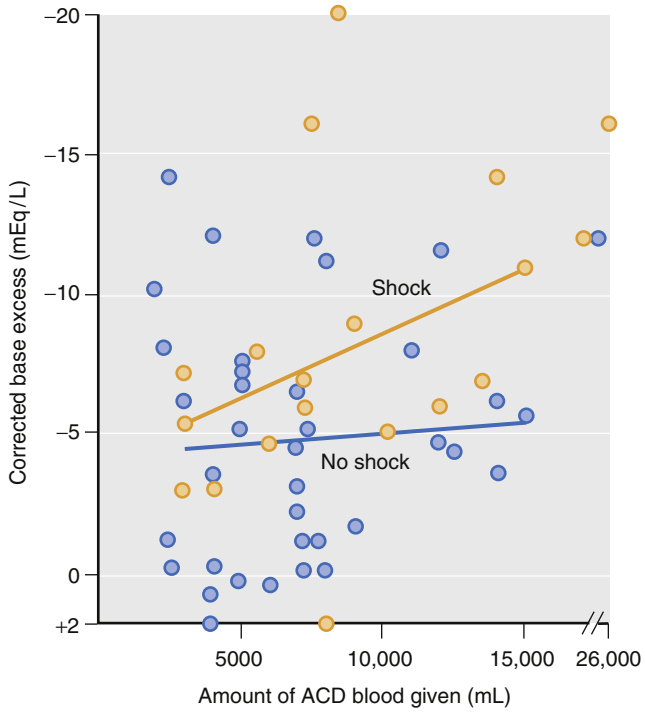


Figure 61-9. Correlation between the amount of blood administered (milliliters) and corrected base excess intraoperatively. *ACD,* Acid citrate dextrose. *(From Miller RD, Tong MJ, Robbins TO: Effects of massive transfusion of blood on acid-base balance,* JAMA *216:1762, 1971.)*

in a warm water (37° to 38° C) bath or warming plates. These heat exchangers should have upper (e.g., 43° C) and lower (e.g., 33° C) temperature limits (see also Chapter 54).

ACID-BASE ABNORMALITIES

The pH of most storage media is very acidotic (e.g., 5.5 for CPD). When this solution is added to a unit of freshly drawn blood, the pH of the blood immediately decreases from 7.0 to 7.1. As a result of accumulation of lactic and pyruvic acids by RBC metabolism and glycolysis, the pH of bank blood continues to decrease to approximately 6.9 after 21 days of storage. A large portion of the acidosis can be accounted for by the P_{CO_2} of 150 to 220 mm Hg. The P_{CO_2} is high mainly because the plastic container of blood does not provide an escape mechanism for carbon dioxide. With adequate ventilation in the recipient, the high P_{CO_2} should be of little consequence. Even when the P_{CO_2} is returned to 40 mm Hg, metabolic acidosis is still present in blood (see Table 61-2). Still, the empirical administration of sodium bicarbonate is not indicated, but it actually may also be unwise without concomitant analysis of arterial blood gases and pHs.[146] Miller and colleagues[147] found that the metabolic acid-base response to blood transfusion was variable (Fig. 61-9). Blood transfusions provide a substrate, namely, citrate, in large quantities for the endogenous generation of bicarbonate, and this accounts for the significant incidence of metabolic alkalosis after blood transfusions.[146] Little logic exists in the empirical administration of bicarbonate for prophylactic treatment of an unpredictable acid-base abnormality.

TABLE 61-7 FREQUENCY AND SIGNS AND SYMPTOMS OF HEMOLYTIC TRANSFUSION REACTIONS IN 40 PATIENTS

Sign or Symptom	No. Patients
Fever	19
Fever and chills	16
Chest pain	6
Hypotension	6
Nausea	2
Flushing	2
Dyspnea	2
Hemoglobinuria	1

TRANSFUSION REACTIONS

HEMOLYTIC TRANSFUSION REACTION

From 2008 to 2012, transfusion-related acute lung injury (TRALI) was the common cause of transfusion-related fatalities (Table 61-7).[148] First, a hemolytic transfusion reaction will be discussed because this is frequently the result of the wrong unit of blood being given. A discussion of TRALI will follow. Since 1975, the FDA has required that all fatal reactions occurring in blood recipients or donors be reported within 24 hours by telephone or within 7 days in writing by all FDA-registered transfusion services. From 1976 to 1985, 328 deaths were reported and analyzed.[149] Of these deaths, 159 were acute from hemolytic reactions and 23 from delayed reactions. In 2011, the incidence of an acute hemolytic transfusion reaction resulting from ABO incompatibility was 1:1200 to 1:190,000.[150] (*Anesthesiology News*[151] reported an incidence of 1:606,978). Of the 159 deaths from acute hemolytic reaction, 137 were caused by errors involving ABO incompatibility. More than half of these mistakes occurred after the blood had been issued by the blood bank and were committed by nurses and physicians in the operating room, emergency department, or ward. The incidence of hemolytic transfusion reactions is sufficient enough that The Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations)[152] requires peer-review programs to reduce transfusion errors and complications. Specifically, two patient identifiers are required before a blood product can be given (see discussion on compatibility testing). New technologies are being used to facilitate a decreased incidence of transfusion-related errors. However, when delayed hemolytic reactions (discussed later) are included, the incidence of ABO-incompatible RBC transfusions is more frequent.[153] One of the most catastrophic transfusion reactions is that arising from intravascular hemolysis. Intravascular hemolysis occurs when there is a direct attack on transfused donor cells by recipient antibody and complement. Such a reaction can occur from infusion of as little as 10 mL of blood.[154] If properly treated, death is rare.[152] However, prevention of kidney failure and a coagulopathy (DIC) is crucial. Hemolytic transfusion reactions involving extravascular RBC destruction are generally less serious than those of the intravascular variety. In these cases, recipient antibody coats but does not immediately hemolyze the transfused RBCs. Destruction occurs primarily in the reticuloendothelial system.

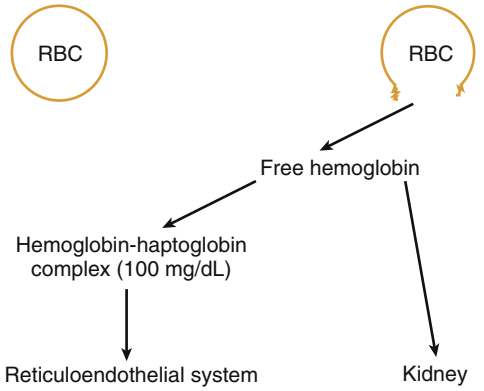


Figure 61-10. Schematic representation of what happens to hemolyzed erythrocytes (*RBC*) as a result of the administration of incompatible blood.

Signs and Symptoms

The clinical consequences of incompatible blood transfusions are very serious but quite variable. Factors include volume of transfused blood, number of antigenic sites on the red cell membrane, and activity of the reticuloendothelial system. The properties of the antibody, including concentration and ability to activate complement, are also important.

The classic signs and symptoms (see Table 61-7) of a hemolytic transfusion reaction—chills, fever, chest and flank pain, and nausea—are masked by anesthesia. Under general anesthesia, the only signs may be hemoglobinuria, bleeding diathesis, or hypotension. The presenting sign is usually hemoglobinuria. As little as 50 mL of incompatible blood may exceed the binding capacity of haptoglobin, which is a protein that can bind approximately 100 mg of Hb/100 mL of plasma. When Hb not exceeding this amount is injected or liberated into the bloodstream, the Hb circulates as a complex with haptoglobin, which is cleared by the reticuloendothelial system (Fig. 61-10). A sample of plasma that contains 2 mg/dL of Hb is faintly pink or light brown. When the level of Hb reaches 100 mg/dL, the plasma is red. When the level of plasma Hb reaches 150 mg/dL, hemoglobinuria occurs. In general, the quantity of the free Hb in the plasma correlates with the volume of incompatible blood transfused. Also, complement activation causes release of various substances, including histamines and vasoactive amines. The symptoms can be so alarming that cessation of blood is indicated, even if Hb is not seen in plasma. Laboratory tests that should be performed if hemolytic transfusion reaction is suspected include serum haptoglobin, plasma and urine Hb, bilirubin, and direct antiglobulin determinations. The direct antiglobulin test can confirm the presence of hemolytic transfusion reaction because it shows that antibody is attached to transfused donor RBCs.

Treatment

If a hemolytic reaction is suspected, blood and urine samples should be sent to the laboratory for examination. The blood bank should check all paperwork to ensure that the correct blood component was transfused to the patient. Laboratory tests should be performed to determine the presence of hemoglobinemia: a direct antiglobulin test, repeat compatibility testing, repeat other serologic tests (i.e., ABO and Rh), and analysis of urine for hemoglobinuria.

Although several consequences of intravascular hemolysis are possible, mainly the renal and coagulation systems are affected. The cause of acute renal failure from intravascular hemolysis is likely that Hb in the form of acid hematin precipitates in the distal tubule and causes mechanical tubular blockage. The magnitude of the precipitation probably is inversely related to the volume of urine flow and its pH. The primary emphasis of therapy should be directed toward maintaining urinary output in excess of 75 mL/hr by generous administration of intravenous fluids and diuretics. One approach is summarized in Box 61-1 and includes the administration of crystalloids to maintain the central venous pressure between 10 and 15 cm H_2O while initially administering 12.5 to 50 g of mannitol. If this is ineffective, the dose of mannitol may be increased or the use of more potent diuretics, such as furosemide, which increases blood flow to the renal cortex, may be required to maintain adequate urinary output. Alkalinization of the urine to prevent precipitation of acid hematin in the distal tubules is of questionable value but is easy and therefore recommended. DIC commonly occurs with hemolytic transfusion reactions, probably because RBC stroma is severed, releasing erythrocytin, which activates the intrinsic system of coagulation. This activated coagulation leads to fibrin formation. Subsequently, platelets and factors I, II, V, and VII are consumed. As soon as a hemolytic transfusion reaction is recognized, platelet count, PT, and PTT should be determined to provide baseline values with which subsequent laboratory values can be compared. Hypotension during a hemolytic transfusion reaction may result from activation of the kallikrein system.[155] After a series of reactions, plasma kininogen is converted to bradykinin, a potent vasodilator that can cause hypotension.

Another approach to treatment of a severe hemolytic transfusion reaction has been proposed by Seager and co-workers,[156] who postulated that the kidneys might be spared from exposure to massive amounts of hemolyzed red cells by removing all blood from a patient and replacing it with compatible blood. This was accomplished in a patient who had received 3000 mL of incompatible blood by hemodilution by use of an extracorporeal circuit. Because the patient had rapid recovery of urinary function, this method shows much promise.

In summary, hemoglobinuria or hemolysis should be assumed to be a hemolytic transfusion reaction until proved otherwise. The steps outlined in Box 61-1 should be taken when the diagnosis is suspected or confirmed.

TRANSFUSION-RELATED ACUTE LUNG INJURY

From 2008 to 2012, TRALI was the common cause of transfusion-related fatalities (Table 61-8). ARDS and acute lung injury (ALI) refer to life-threatening respiratory failure from several causes (see also Chapter 101).[157] Sepsis, pneumonia, and blood transfusions are among the most common causes. TRALI is now the leading cause of transfusion-related mortality (see Table 61-7), although it

BOX 61-1 ***Steps in the Treatment of a Hemolytic Transfusion Reaction***

1. STOP THE TRANSFUSION.
2. Maintain the urine output at a minimum of 75 to 100 mL/hr by the following methods:
   a. Generously administer fluids intravenously and possibly mannitol 12.5 to 50 g, given over 5 to 15 minutes.
   b. If intravenously administered fluids and mannitol are ineffective, administer furosemide (20 to 40 mg) intravenously.
3. Alkalinize the urine; because bicarbonate is preferentially excreted in the urine, only 40 to 70 mEq of sodium bicarbonate per 70 kg of body weight is usually required to raise the urine pH to 8, whereupon repeat urine pH determinations indicate the need for additional bicarbonate.
4. Assay urine and plasma hemoglobin concentrations.
5. Determine platelet count, partial thromboplastin time, and serum fibrinogen level.
6. Return unused blood to blood bank for repeat crossmatch.
7. Send patient's blood and urine sample to blood bank for examination.
8. Prevent hypotension to ensure adequate renal blood flow.

TABLE 61-8 **TRANSFUSION-RELATED FATALITIES IN THE UNITED STATES, 2008 THROUGH 2012**

Cause of Fatality	2008 to 2012	2012
TRALI	74	17
Other reactions (non-ABO hemolytic therapy, anaphylaxis)	53	8
Bacterial contamination	21	3
ABO hemolytic transfusion therapy	22	3
Transfusion not ruled out	99	27

From Fatalities Reported to FDA following blood collection and transfusion: annual summary for fiscal year 2012. These reports are available online. at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/ucm346639.htm
TRALI, Transfusion-related acute lung injury.

probably is underdiagnosed and underreported.[158-160] This injury manifests as noncardiogenic pulmonary edema. Specifically, TRALI occurs in the absence of excessive intravascular volume and cardiac failure.[161] Clinically, symptoms and signs appear 1 to 2 hours after transfusion and are in force within 6 hours. Fever, dyspnea, fluid in the endotracheal tube, and severe hypoxia are typical. During anesthesia, a persistent decrease in blood O_2 saturation can be the manifesting sign. Although the chest radiograph is characteristic of pulmonary edema, excessive circulatory volume (i.e., left atrial hypertension) is not present. All blood components, especially FFP, are implicated as caustic factors. The only specific therapy is stopping the transfusion and instituting critical care supportive measures. However, the transfusion should be immediately stopped and the blood bank notified for a different donor and quarantining all units from that donor. All records should be reexamined, and the results of the patient's human leukocyte antigen (HLA) testing should be evaluated if possible. Most patients recover within 96 hours, although TRALI remains the leading cause of transfusion-related death.

Recently, an intense analysis of the risk factors associated with TRALI have been reported.[162] Risk factors include higher interleukin-8 (IL-8) levels, liver surgery, chronic alcohol abuse, shock, higher peak airway pressures while being mechanically ventilated, smoking, and positive fluid-balance. As far as transfusions are concerned, receipt of plasma or whole blood from female donors was identified and subsequently markedly reduced. The decreased use of plasma from female donors reduced the incidence of TRALI. A related finding is that transfusion of PRBCs in the ICU to patients who already have ALI was not associated with 90-day mortality.[18]

DELAYED HEMOLYTIC TRANSFUSION REACTION (IMMUNE EXTRAVASCULAR REACTION)

An immediate hemolytic transfusion reaction often is a dramatic event because the concentration of the antibody is high enough to cause immediate and appreciable RBC destruction. In many cases of hemolytic transfusion reaction, the transfused donor cells may survive well initially, but after a variable delay (2 to 21 days) they are hemolyzed.[163] This type of reaction occurs mainly in recipients sensitized to RBC antigens by previous blood transfusions or pregnancy. As a result, this type of delayed reaction is more common in females who have a known disposition of alloimmunization. These reactions are delayed hemolytic transfusion reactions and are those in which the level of antibody at the time of transfusion is too low to be detected or cause RBC destruction. RBC destruction occurs only when the level of antibody is increased after a secondary stimulus (i.e., anamnestic response). These delayed reactions are often manifested only by a decrease in the posttransfusion Hct value. However, jaundice and hemoglobinuria can occur in these patients and can cause some impairment in renal function, but only rarely do they lead to death. Unlike immediate reactions, antibodies most commonly involved in delayed hemolytic reactions are those in the Rh and Kidd systems rather than the ABO system. Although improved blood-banking procedures have decreased the incidence of immediate hemolytic transfusion reactions, the delayed hemolytic reaction may not be preventable, because pretransfusion testing is unable to detect very low levels of antibody present in potential blood recipients.

Although impairment of renal function is uncommon, the surgical team should include in their differential diagnosis a delayed hemolytic transfusion reaction in any patient who has an unexplained decrease in Hct 2 to 21 days after a transfusion, even without obvious manifestation of hemolysis. This is especially important in a postoperative patient when the decrease in Hct value is thought to be from blood loss and may be an important criterion as to whether additional surgery is necessary.

NONHEMOLYTIC TRANSFUSION REACTIONS

Nonhemolytic reactions to blood transfusions usually are not serious and are febrile or allergic. Specific infectious

causes of febrile reactions are discussed in the section on other options to reduce infectivity. Occasionally, fever may be the first sign of a hemolytic reaction or of bacterial contamination.

The most common adverse reactions to blood transfusions are the less serious febrile reactions. The symptoms consist of chills, fever, headache, myalgia, nausea, and nonproductive cough occurring shortly after blood transfusion, caused by pyrogenic cytokines and intracellular contents released by donor leukocytes. Use of leukoreduced blood lowered the incidence of febrile reactions.[164] Less frequently, the patient may have hypotension, chest pain, vomiting, and dyspnea. Even pulmonary infiltrations with radiographic evidence of prehilar nodule formation and lower lung infiltrates along with overt pulmonary edema have been reported.[164] Because febrile reactions obviously involve fever, they can be easily confused with a hemolytic transfusion reaction. A direct antiglobulin test readily differentiates a hemolytic reaction from a febrile reaction because this test rules out the attachment of an RBC antibody to transfused donor RBCs. More serious complications need to be ruled out (hemolytic and septic reactions), which may also be associated with fever and chills. No clear consensus exists on whether the transfusion should be terminated when a febrile reaction occurs.[165,166]

Allergic reactions can be minor, anaphylactoid, or anaphylactic. An anaphylactoid reaction is clinically similar to anaphylaxis, but it is not mediated by IgE. Most allergic transfusion reactions are minor and caused by the presence of foreign protein in the transfused blood. The most common symptom is urticaria associated with itching. Occasionally, the patient has facial swelling. When these reactions are clearly not a serious hemolytic reaction, the transfusion does not need to be discontinued. Antihistamines are used to relieve the symptoms of the allergic reaction. Infrequently, a more severe form of allergic reaction involving anaphylaxis occurs in which the patient has dyspnea, hypotension, laryngeal edema, chest pain, and shock. These are anaphylactic reactions caused by the transfusion of IgA to patients who are IgA deficient and have formed anti-IgA. This type of reaction does not involve red cell destruction and occurs very rapidly, usually after the transfusion of only a few milliliters of blood or plasma. Patients who experience these anaphylactic reactions can be given transfusions with washed RBCs from which all traces of donor IgA have been removed or with blood lacking the IgA protein. Several investigators have reviewed many other rare transfusion reactions.[149,154,167,168]

OTHER NONINFECTIOUS RISKS OF BLOOD TRANSFUSIONS

Although hemolytic transfusion reactions and TRALI have received an appropriate amount of prime attention in this chapter, the noninfectious risks of blood transfusions are also problematic and of significant concern (Table 61-9). Some of these risks were discussed previously, including febrile, allergic, and anaphylactoid reactions. In fact, the noninfectious hazards or risks have gained attention partly because of the decrease in risk for infectious complications such as hepatitis and human immunodeficiency virus (HIV) infection. In fact, The United Kingdom has a system-wide reporting scheme (SHOT) that requires reporting of transfusion-related adverse outcomes. In the past few years, several review articles have appeared in the literature.[169,170] Their labels were slightly different in that Hendrickson and Hillyer added the word *serious* to their title (i.e., "Noninfectious Serious Hazards of Transfusion"). Nevertheless, they are generally discussing the same risks.

Table 61-9 lists most of the hazards associated with noninfectious risk issues. TRALI and hemolytic transfusion reactions are discussed separately in other sections of this chapter. The term *NISHOT* includes all noninfectious complications. The following are some of the less common risks.

1. Transfusion-associated circulatory overload (TACO): Unlike TRALI, TACO simply refers to an excessive administration of blood. Patients with cardiopulmonary disease, renal failure, and extremes of age (i.e., especially infants; see also Chapter 93) are especially vulnerable. Other than decreasing the rate of infusion, administration of diuretics may be helpful.
2. Transfusion-related immunomodulation (TRIM): Blood transfusions can suppress the immune system because of circulating lymphocytes. The effects of blood transfusion transplant outcomes are consistent with this hypothesis, which confirms the concept of TRIM; the effects on malignancy and infection are not clear (see also the section on transfusion-related immunomodulation).
3. Microchimerism: Chimerism refers to more than one cell line in an individual organism. Specifically, donor lymphocytes may persist in a patient. It is associated with pregnancy, transplant, and trauma. The outcome of patients with microchimerism is not known.
4. Posttransfusion purpura: This refers to recipient alloantibodies attacking donor platelet antigens and is treated with intravenous immunoglobulin.
5. Hypotensive transfusion reactions: Activation of the coagulation pathway activates production of bradykinin and allergic reactions.
6. Transfusion-associated graft-versus-host disease (GVHD): Superficially, this refers to transfusion into an immunocompromised host. This is an extremely serious and often fatal problem (see Reference 22 for more details; see section on transfusion-associated GVHD).
7. Transfusion-related AKI.
8. Alloimmunization: Only 2% to 8% of recipients who are chronically transfused develop RBC alloantibodies (see Hendrickson and Hillyer, reference 22, for more details).
9. HLA alloimmunization and human platelet antigen (HPA) alloimmunization: HLA alloimmunization refers to patients whose platelets become refractory because of antibodies directed against HLA class I antibodies. HPA alloimmunization is platelet refractoriness from antibodies against platelet antigens (HPA antibodies).
10. Undertransfusion and overtransfusion: This complication is listed only for the sake of completeness,

TABLE 61-9 **NONINFECTIOUS HAZARDS OF TRANSFUSION**

Transfusion Reaction	Incidence (per 10^5 Transfusions)	Etiology	Therapy	Prevention
Febrile	All components: 70-6800	Storage-generated proinflammatory cytokines Patient antileukocyte antibodies bind to donor leukocytes	Stop transfusing Give antipyretics Supportive care	Prestorage leukoreduction
TACO	All components: 16.8-8000 Practice-dependent	Circulatory overload Patients with cardiac or renal disease, infants, and the critically ill are at increased risk	Stop transfusing Give diuretics Oxygen	Identify patients at high risk Transfuse slowly
TRALI	Erythrocytes: 10-20 Platelets/plasma: 50-100	Passive transfusion of donor antibodies Storage-generated toxic lipids	Supportive care	Remove high-risk donors from the donor pool
Allergic	All components: 3000 mild, 2 anaphylactic	Mild reactions: Transfusion of soluble antigens in donor plasma Anaphylaxis: IgA deficiency or other recipient protein deficiency	Stop transfusing ASA monitors Large-bore IV access Epinephrine Antihistamines Supportive care	Pretransfusion antihistamine use remains common practice despite limited evidence
Hemolytic	Erythrocytes: 1.1-9.0	Donor antibodies bind to patient erythrocytes Patient antibodies bind to donor erythrocytes	Stop transfusing Repeat matching Supportive care Treat DIC	Standard operating procedures
TRIM	Unknown	The mechanism is unknown but may depend on the presence of donor leukocytes	Treat complications (e.g., infection, malignancy)	Prestorage leukocyte reduction may be beneficial, but this approach is controversial
Microchimerism	All components: 5000-10,000 massive transfusion	Permanent residence of donor cells in recipient	Unknown	Unknown
Posttransfusion purpura	All components: 2	Recipient alloantibodies attack donor platelet antigens	IVIG	Avoid units positive for implicated HPA antigens in patients with a history of PTP
Hypotensive	Unknown	Production of kinins by the activation of the contact system Patients on ACE inhibitors are at increased risk	Stop transfusing ASA monitors Large-bore IV access Supportive care	Avoid the use of negatively charged leukocyte reduction filters
Graft-versus-host	Varies by patient population	Transfusion into immunocompromised host Transfusion of donor cells closely matching HLA type	No consensus exists Consider bone marrow transplant	Gamma irradiation of cellular products

Reprinted from Hillyer CD, Silberstein LE, Ness PM, et al: Blood banking and transfusion medicine: basic principles and practice, *ed 2, Philadelphia, 2007, Elsevier, pp 678-679.*

ACE, Angiotensin converting enzyme; *ASA,* American Society of Anesthesiologists; *DIC,* disseminated intravascular coagulation; *HLA,* human leukocyte antigen; *HPA,* human platelet alloantigen; *IgA,* immunoglobulin A; *IV,* intravenous; *IVIG,* intravenous immunoglobulin; *PTP,* posttransfusion purpura; *TACO,* transfusion associated circulatory overload; *TRALI,* transfusion-related acute lung injury; *TRIM,* transfusion-related immunomodulation.

because this topic is adequately reviewed in several previous sections of this chapter.

11. Iron overload: This complication usually does not involve anesthesia because it is the result of chronic transfusion therapy. Iron then begins to deposit into vital organs. In the absence of adequate chelation of iron, fatal liver or heart dysfunction, or both, can occur.

Hendrickson and Hillyer[170] correctly indicated that the list is lengthy. Their recommendations were general and not surprising and included the liberal versus restrictive

TABLE 61-10 PERCENTAGE RISK OF TRANSFUSION-TRANSMITTED INFECTION WITH A UNIT OF SCREENED BLOOD IN THE UNITED STATES*

Infection	Risk	Window Period (Days)
Human immunodeficiency virus-1 and -2	1:1,476,000	5-6
Human T-lymphotropic virus (HTLV-II)	1:2,993,000	51
Cytomegalovirus (CMV)	Infrequent with leukocyte-reduced components	
Hepatitis C virus (HCV)	1:1,149,000	3-4
Hepatitis B virus (HBV)	1: 280,000	24
Hepatitis A virus (HAV00)	1:1,000,000	
Bacteria red blood cells	1:1,000 with septic reaction in 1:500,000	
Pheresis platelets (with early aerobic culture)		
Parasites: Babesia and malaria	<1:4,000,000	7-14
West Nile virus (WNV)	1/1,100,000	?
Acute hemolytic transfusion reactions	1:38,000-1:70,000	

**Data from AABB:* AABB technical manual, ed *17, 2011, AABB; and Fiebig ER, Busch MP: Infectious risks of transfusions. In Spiess BD, Spence RK, Shander A, editors:* Perioperative transfusion medicine, *Philadelphia, 2006, Lippincott Williams & Wilkins.*

BOX 61-2 ***Infectious Disease Testing for Blood Transfusions: 1998***

1. Discontinue serum alanine aminotransferase testing
2. Hepatitis C antibody testing
3. Antibody to hepatitis B core antigen
4. Human immunodeficiency virus (HIV) type 1
5. HIV-2
6. HIV Ag (p24 antigen)
7. Human T-cell lymphotropic virus (HTLV) types 1 and 2
8. Serologic test for syphilis

Modified from National Institutes of Health, Consensus Development Panel on Infectious Disease Testing for Blood Transfusions: Infectious disease testing for blood transfusions, JAMA *274:1374-1379, 1995.*

indications for blood transfusion as well as the possible length of storage issue, both of which are extensively covered in this chapter. Gilliss and colleagues[169] stated that evidence-based transfusion should be followed. They also stated that the FDA has provided guidelines rather than mandates; their concern was that a diversity of transfusion medicine would evolve. They conclude that "avoidance of unnecessary transfusions will be the most effective way to reduce complications of blood transfusions." Although their recommendation is inherently obvious, the challenge is defining the word *necessary* or *unnecessary*. No clinician would knowingly administer an unnecessary transfusion. What is the difference between necessary and unnecessary? Accordingly, this chapter (see the section on indications for transfusion) has devoted an entire section to discussion of all of the variables that need to be considered when making a decision to give a unit of blood.

The use of more sensitive screening tests and changes in transfusion medicine practices has made these infectious risks quite rare. Historically, the FDA has published a table on the risks for infectivity, as displayed in Table 61-10 for the year 2011. Because the rates of infectivity are so infrequent, the FDA may not publish such tables in the future. Finally, rarely, anaphylaxis can occur.

Non–donor-transmitted issues have become dominant concerns (see the section on transfusion reactions; see Table 61-7). The summary of Fiebig and Busch[171] provides definitive information on this topic.

Several blood-safety changes made from 1982 to 2008 have made the risk for disease transmission by allogenic blood so small that even the demand for autologous blood has decreased because of the safety of allogeneic blood. Perhaps the West Nile virus story illustrates how rapidly our blood banks can respond. In 2002, West Nile virus caused the largest outbreak of arboviral encephalitis ever recorded in the United States (i.e., ~4200 patients). Twenty-three cases of transfusion-transmitted infections resulted in seven deaths. In 2003, testing was available that now makes that infection very rare (see Table 61-10).

Yet many questions arise—for example, regarding variant Creutzfeldt-Jakob disease. Three probable transfusion-transmitted cases occurred in Great Britain. How strict should testing be? As described recently,[172] "the sheer number of potential pathogens that have threatened the blood supply[173,174] since 1995 renders it impractical to keep adding expensive safety measures" for each new agent. Surveillance needs to be added to all these tests as a safety measure.

The changes in blood transfusion testing can be appreciated when comparing tests used in 1998 (Box 61-2) with those used in 2008 (Table 61-11). The use of nucleic acid technology has decreased the window of infectivity (i.e., time from being infected to a positive test result), which is a major reason for the decrease in infectivity with hepatitis, HIV, and West Nile virus.

HEPATITIS B

When blood transfusions became a reality in the 1940s, viral hepatitis was recognized as a major complication. The concern is mainly with hepatitis B, C, and, rarely, D, which are parenterally transmitted viruses. Before 1985, the overall incidence of posttransfusion hepatitis ranged from a low of 3% to a high of 19%, depending on the institution and the location (e.g., donors from large cities have a more frequent incidence of the hepatitis virus). In most areas, the incidence of hepatitis has ranged from 3% to 10%. Ninety percent of posttransfusion hepatitis is caused by the hepatitis C virus. Fewer than a third of these patients develop jaundice.[175] To determine their ultimate fate, Tong and colleagues[175] monitored 131 patients with chronic posttransfusion hepatitis C for several years and

TABLE 61-11 TESTS USED FOR DETECTING INFECTIOUS AGENTS IN ALL UNITS OF BLOOD: 2008

Virus	RNA Minipool	Antibody To
Human immunodeficiency virus (HIV)	Nucleic acid technology	HIV-1, HIV-2
Hepatitis C virus (HCV)	Nucleic acid technology	HCV
Hepatitis B virus (HBV)		HCV
Human T-cell lymphotropic, virus (HTLV)		HTLV-1, HTLV-2
West Nile virus	Nucleic acid technology	

TABLE 61-12 INFECTIOUS DISEASES THEORETICALLY TRANSMISSIBLE BY BLOOD TRANSFUSION FOR WHICH NO TEST IS AVAILABLE: 2004

Disease	Risk
Malaria	<1 million in the United States
Chagas disease	<1 million
Severe acute respiratory syndrome (SARS)	?
Variant Creutzfeldt-Jakob disease	Three cases (?) in the United Kingdom

found the following incidence of signs, symptoms, and conditions:

- Fatigue (67%)
- Hepatomegaly (67%)
- Chronic hepatitis (23%)
- Chronic active hepatitis (51%)
- Hepatocellular carcinoma (11%)

It was found that 20 patients had died of the following:

- Complications of cirrhosis (8 patients)
- Hepatocellular carcinoma (11 patients)
- Chronic active hepatitis-pneumonia (1 patient)

Even in 2013, patients are having ramifications from hepatitis C, from which they apparently recovered in the late 1960s and early 1970s. Several decades later, they can get carcinoma of the liver. Although I do not know the incidence, I have had three close friends who have had this outcome. The Centers for Disease Control and Prevention (CDC) reports that of every 100 people infected with the hepatitis C virus, about 75 to 85 will develop chronic hepatitis C virus infection; of those, 60 to 70 will go on to develop chronic liver disease, 5 to 20 will develop cirrhosis over a period of 20 to 30 years, and 1 to 5 people will die from cirrhosis or liver cancer. (Centers for Disease Control, Hepatitis C FAQs for the Public. Available at http://www.cdc.gov/hepatitis/c/cfaq.htm. Accessed July 8, 2014.)

CYTOMEGALOVIRUS

Asymptomatic chronic infection with cytomegalovirus (CMV) is so common in healthy adults that this agent can almost be viewed as normal flora. CMV survives best within cells and is thought to exist in latent form in the monocytes of many people with antibodies indicative of earlier infection. Fortunately, the primary concern is recipients who are at risk because of pregnancy (multiple), immaturity, or immunosuppression. CMV seroconversion usually occurs in subsets of patients receiving multiple transfusions. CMV causes a heterophil antibody-negative response that closely resembles infectious mononucleosis in many respects. An infectious mononucleosis–like syndrome that can occur 1 to 2 months after open-heart surgery is known as the postperfusion syndrome or posttransfusion mononucleosis.[176]

The evidence for transmission of CMV is most convincing when the recipient changes from a seronegative state before transfusion to a seropositive state accompanied by the mononucleosis-like illness several weeks after transfusion.

Transfusion-transmitted CMV can cause significant clinical problems in certain patient populations, such as premature neonates, allograft recipients, and patients who have had their spleen removed.[177] To prevent infection in high-risk populations, use of leukocyte-depleted blood, use of frozen deglycerolized RBCs, and screening of donors for the absence of antibody to CMV have been sometimes recommended (see the section on leukoreduction and irradiation of blood transfusions). The risk for seroconversion is approximately 0.14% overall, or 0.38% per unit of seropositive donor blood. Wilhelm and associates[178] concluded that it is not necessary to provide blood products from CMV-seronegative donors for most patients who receive blood transfusions. They continue to use CMV-seronegative blood to prevent CMV infection in preterm and newborn infants.

Plasma components, such as FFP and cryoprecipitate, components from seronegative donors, and leukoreduced components are considered to be CMV safe.

OTHER TRANSFUSION-ASSOCIATED INFECTIOUS DISEASES

Although many other infectious diseases can theoretically be transmitted by blood transfusion, only a few are of real concern. They include *Yersinia enterocolitica* infection, syphilis, malaria, Chagas disease, variant Creutzfeldt-Jakob disease, parvovirus B19, and severe acute respiratory syndrome (SARS) (Table 61-12).

During the late 1980s, Tripple and colleagues[179] described seven cases of fatal transfusion-associated *Y. enterocolitica* sepsis. These investigators also reviewed the literature and found 26 cases of gram-negative bacterial sepsis with whole blood or PRBCs. *Y. enterocolitica* is a bacterium that can cause mostly mild gastrointestinal problems. However, in severe cases, sepsis and death can occur. Unfortunately, storage of blood at 4° C in phosphate buffer enhances its growth.

Posttransfusion syphilis is unlikely because the infective agent cannot survive during storage at 1° to 6° C. The only blood products that have the potential to transmit syphilis are those stored at room temperature. Platelet concentrates are the blood component most likely to be implicated because they commonly are stored at room temperature.

TABLE 61-13 **COMPARISON OF WHOLE BLOOD AND PACKED RED BLOOD CELLS**

Value	Whole Blood	Packed Red Blood Cells
Volume (mL)	517	300
Erythrocyte mass (mL)	200	200
Hematocrit (%)	40	70
Albumin (g)	12.5	4
Globulin (g)	6.25	2
Total protein (g)	48.8	36
Plasma sodium (mEq)	45	15
Plasma potassium (mEq)	15	4
Plasma acid (citric-lactic)	80	25 (mEq)
Donor-to-recipient ratio	1 unit per patient	1 unit per 4-6 patients

From Landers DF, Hill GE, Wong KC, et al: Blood transfusion-induced immunomodulation. Anesth Analg *82:187, 1996.*

Posttransfusion malaria has never been a significant cause of blood recipient morbidity. Nevertheless, malaria can occur, especially if blood donors at risk for harboring parasites are not excluded. Consequently, blood banks thoroughly question donors for history of travel or migration from areas where malaria is endemic.

Several other diseases have been reported to be transmitted by blood transfusion, including herpesvirus infections, infectious mononucleosis (i.e., Epstein-Barr virus), toxoplasmosis, trypanosomiasis, leishmaniasis, brucellosis, typhus, filariasis, measles, salmonellosis, and Colorado tick fever.

Like malaria, several infectious agents are feared as possibly transmitting disease to patients through blood transfusions for which there are no blood testing methods (Table 61-13). Without a specific test, donor screening with increasingly restrictive criteria are used. For example, in 2003 in the United States, donors with suspected SARS or who traveled to certain countries in Southeast Asia would not be accepted. Even though there are no cases of variant Creutzfeldt-Jakob disease from blood transfusions, the virus can be transmitted by blood in animal models and stringent donor policies based on travel and residence in England or other countries in Europe are in place. Do these increasingly restrictive donor policies increase the risk for an inadequate blood supply[180] (see the section on synthetic O_2-carrying substances).

OTHER ADVERSE EFFECTS OF BLOOD TRANSFUSION

TRANSFUSION-ASSOCIATED GRAFT-VERSUS-HOST DISEASE

Transfusion-associated GVHD is caused by engraftment of donor lymphocytes from transfused blood products, initiating an immune reaction against recipient tissues. Severely immunocompromised patients are at risk. Also, directed donations from first- or second-degree relatives are at risk because transfused lymphocytes with shared HLA haplotypes cannot be recognized and eliminated.[181] A generalized rash, leukopenia, and thrombocytopenia occur. Sepsis and death usually result. Irradiation of blood can prevent transfusion-associated GVHD from occurring, although one case reported it occurring despite leukocyte filtering.[182]

ADVERSE OCULAR REACTION

In 1997, 112 cases of bilateral conjunctival erythema occurred within 24 hours of transfusion. The Centers for Disease Control and Prevention studied 49 other cases in 1997 and 1998 and concluded that they were toxic reactions to a chemical or material used in the blood collection filtration system, most likely a leukocyte-reducing filter system.[183]

TRANSFUSION-RELATED IMMUNOMODULATION

Homologous (allogeneic) blood transfusion exerts a nonspecific immunosuppressive action on the recipient. More than 150 clinical studies have tried to relate allogeneic blood transfusions to recurrence of resected cancers, postoperative infections, and virus activation, with the conclusion that adverse effects may be caused by TRIM. Although the conclusions of these studies are contradictory and inconclusive, universal leukocyte reduction of RBCs is moving forward (see the following section).[184]

LEUKOREDUCTION AND IRRADIATION OF BLOOD TRANSFUSIONS

GENERAL CONSIDERATIONS

Several complications of PRBCs are likely due to leukocytes. These include HLA alloimmunization against class I antigens, febrile reactions, and transfusion-transmitted CMV infections. The universal use of leukoreduced PRBCs internationally includes Western Europe, the United Kingdom, and Canada. Most of the PRBCs given in the United States are leukoreduced. What is the logic on which the use of leukoreduced blood is based?

Clear indications exist for leukoreduced blood. The chances of a febrile reaction can be reduced, especially in patients who are already alloimmunized from pregnancy. The risk for HLA alloimmunization from blood transfusions can be reduced, which would be especially helpful in minimizing refractoriness to platelet transfusions, and the risk for CMV can be reduced by using leukoreduced blood. More specifically, these include chronically transfused patients, potential transplant recipients, patients with transplants, patients with previous febrile nonhemolytic transfusion reactions, and CMV-seronegative at-risk patients for whom seronegative components are not available. Identification of these specific patients groups is from Kleinman.[51]

Universal leukoreduction has been seriously considered or implemented because of some anticipated benefits, including decreased transmission of variant Creutzfeldt-Jakob disease, leukocyte-induced immunomodulation, and even decreased postoperative mortality. In 2001, the case for and against universal leukoreduction was debated.[185,186] As of 2004, these anticipated benefits were not confirmed, despite numerous studies attempting to do so.[187] As nicely summarized by Corwin

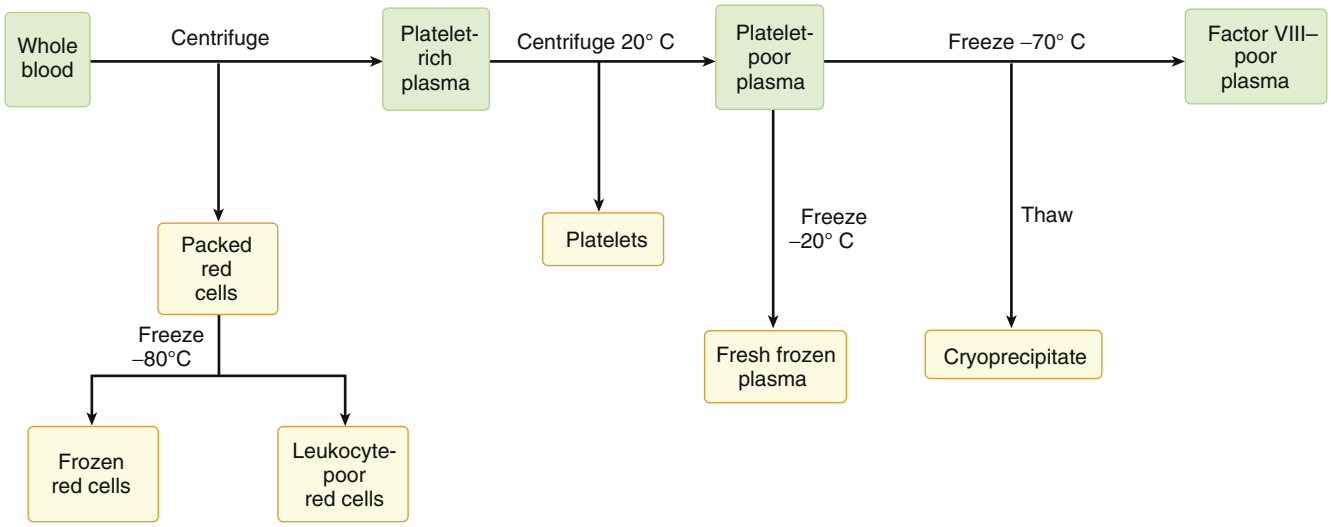


Figure 61-11. Scheme for separation of whole blood for component therapy.

and AuBuchon,[185] a "may help, won't hurt" approach has been used to justify universal leukoreduction. Yet bacterial contamination of platelets, TRALI, and acute hemolytic reactions cause more morbidity and mortality that would not be significantly helped by leukoreduction (see Table 61-7). Nevertheless, universal leukoreduction is the direction in which transfusion medicine has gone.

IRRADIATED BLOOD PRODUCTS

Irradiated blood components include only cellular products (RBCs, platelets, and granulocytes), but not noncellular products (thawed frozen plasma and cryoprecipitate). Indications for irradiation include intrauterine transfusions, neonates younger than 4 months of age, neonates, and pediatric patients undergoing transfusions (for ICU protocols only) (see also Chapters 93 to 95), infants younger than 1 year of age undergoing extracorporeal membrane oxygenation/extracorporeal cardiac life support, adult hematology or oncology patients, and those with immunodeficiency syndrome–directed donations from relatives before release from the blood bank. Irradiation will not be done for patients undergoing routine nonmyeloablative chemotherapy for solid tumors and solid organ transplant patients receiving routine postttransplant immunosuppressive therapy.

BLOOD COMPONENT THERAPY

A major advance in the field of blood banking has been the development of blood component therapy. It is beyond the scope of this chapter to describe the various separation steps in detail, but a superficial outline of the scheme by which various blood components are derived is shown in Figure 61-11. The basic philosophy is based on the concept that patients are best treated by administration of the specific fraction of blood that they lack. This concept has presented problems to the surgical team, who often desire whole blood.

TABLE 61-14 COMPATIBILITY OF BLOOD WITH INTRAVENOUS SOLUTIONS

Blood to Intravenous Solution (1:1 Ratio)	Hemolysis at 30 Minutes	
	Room Temperature	37° C
5% Dextrose in water	1+	4+
Plasmanate*	1+	3+
5% Dextrose in 0.2% saline	0	3+
5% Dextrose in 0.4% saline	0	0
5% Dextrose in 0.9% saline	0	0
0.9% Saline	0	0
Normosol-R, pH 7.4†	0	0
Lactated Ringer solution	0 (clotted)	0 (clotted)

*Cutter Laboratories, Berkeley, Calif.
†Abbott Laboratories, Chicago, Ill.

PACKED RED BLOOD CELLS

PRBCs contain the same amount of Hb as whole blood, but much of the plasma has been removed. The Hct value is 40% in whole blood and 70% in packed erythrocytes (see Table 61-13). Philosophically, whole blood provides O_2-carrying capacity and intravascular blood volume expansion. Other than severe hemorrhage, most indications for RBCs can be effectively treated with PRBCs, retaining the plasma and the components thereof for other patients (see Fig. 61-11). Many blood banks have conscientiously followed this principle, and whole blood cannot be obtained in the operating rooms except by special request. In essence, blood bank practice is that except for a rare situation (e.g., hypovolemic shock), whole blood is not necessary.

The administration of PRBCs is facilitated by reconstituting them with a crystalloid or colloid; however, not all crystalloids are suitable. If the solution contains Ca^{2+}, clotting occurs. Lactated Ringer solution is not recommended for use as a diluent for PRBCs (Table 61-14). Conversely, using flow rates and clot formation, Cull and colleagues[188] found lactated Ringer solution and normal saline to be equally acceptable. A more important factor

may be whether the diluent is hypotonic with respect to plasma. If so, the RBCs will swell and eventually lyse. Solutions that cause hemolysis are listed in Table 61-14. Clinicians who fear that the crystalloid-reconstituted RBCs may cause low serum concentrations may be tempted to use a plasma derivative, such as Plasmanate. However, these solutions also can cause hemolysis. The osmolality of Plasmanate is only 180 mOsm/kg. Solutions recommended for reconstituted packed erythrocytes are 5% dextrose in 0.4% saline, 5% dextrose in 0.9% saline, 0.9% saline, and Normosol-R with a pH of 7.4.

PLATELET CONCENTRATES

Platelet concentrates are obtained either as pooled concentrates from 4 to 6 whole-blood donations or as apheresis concentrates obtained from one donor[189] Platelet concentrates are prepared by differential centrifugation from freshly drawn units of blood or from donors who specifically donate large amounts of platelets by plateletpheresis techniques. If platelets are stored at room temperature, they are satisfactory to use 7 days after collection with constant and gentle agitation. Platelet concentrates present unique conflicts in medicine. First, bacterial contamination, mainly from platelet concentrates, is the third leading cause of transfusion-related deaths (see Table 61-7). They are primarily effective at room temperature, which enhances bacterial growth. Furthermore, this has been a problem for more than 20 years. In the report of 10 septic platelet transfusions between 1982 and 1985, half were platelets stored for 5 days or more. A prospective analysis from 1987 to 1990 resulted in seven cases of sepsis in patients receiving platelets for thrombocytopenia secondary to bone marrow failure.[190] Because use of multidonor platelet products stored for 5 days results in an incidence of sepsis five times higher than use of those stored for 4 days, shorter storage times are being emphasized. The incidence of platelet-related sepsis was approximately 1 case in 12,000 people.[191] The estimated incidence of bacterial contamination of platelets was approximately 1 case in 2000.[192]

The increased risk for bacterial overgrowth is related to the storage temperature of 20° to 24° C. For any patient who develops a fever within 6 hours after receiving platelets, sepsis from platelets should be considered. The evaluation of storing platelets for increased efficacy, but yet needing additional testing, actually makes the platelets available to the clinician for only approximately 3 days (Table 61-15). More recently, allowing platelets to be stored for 7 days minus 2 days for testing makes them available for 5 days, which enhances overall use of a valuable product and improves platelet inventory management. At present, platelet concentrates are routinely tested for bacteria and are the only blood product stored at room temperature.[193] The rate of bacteria in platelets was 1/5000 before and 1/50,000 after routine bacteria culturing.[193] Data in 2007 indicated 186 positive cultures in 1,004,206 units, of which 20 were septic reactions. Thirteen of these occurred 5 days after collection and resulted in three fatalities.[194]

Indications for the use of platelets are somewhat difficult to define. In the July 1989 *FDA Drug Bulletin* it was stated that platelets should not be given to patients with immune thrombocytopenic purpura (unless there is life-threatening bleeding), prophylactically with massive blood transfusion, or prophylactically after cardiopulmonary bypass. ASA Task Force[67] provided the following recommendations:

1. Prophylactic platelet transfusion is ineffective and rarely indicated when thrombocytopenia is due to increased platelet destruction (e.g., idiopathic thrombocytic purpura).
2. Prophylactic platelet transfusion is rarely indicated in surgical patients with thrombocytopenia because of decreased platelet production when the platelet count is greater than 100×10^9/L and is usually indicated when the platelet count is less than 50×10^9/L. The determination of whether patients with intermediate platelet counts (50 to 100×10^9/L) require therapy should be based on the patient's risk for bleeding.
3. Surgical and obstetric patients with microvascular bleeding usually require platelet transfusion if the platelet count is less than 50×10^9/L and rarely require therapy if it is greater than 100×10^9/L. With intermediate platelet counts (50 to 100×10^9/L), the determination should be based on the patient's risk for more significant bleeding.
4. Vaginal deliveries or operative procedures ordinarily associated with insignificant blood loss may be undertaken in patients with platelet counts less than 50×10^9/L.
5. Platelet transfusion may be indicated despite an apparently adequate platelet count if there is known platelet dysfunction and microvascular bleeding.

The ASA will be publishing new guidelines in 2015.

Some institutions (e.g., UCSF) have charts that outline the minimum platelet count needed for the categories of (1) prophylaxis, (2) periprocedure, and (3) active bleeding. In the first category, a required platelet count may be 20,000/μL in patients receiving chemotherapy. In the second category, bone marrow biopsy or lumbar puncture should be 20,000 and 30,000/μL. For neurosurgery a platelet count of 100,000/μL may be needed. In the third category, platelet counts as listed before may be at least 100,000/μL. It is likely that all major medical center blood banks have a chart, as superficially described here. A clinician's local blood bank will likely have precise platelet recommendations for most procedures, which should be followed.

TABLE 61-15 **HISTORY OF PLATELET CONCENTRATES SHELF LIFE IN RELATIONSHIP TO KEY EVENTS**

Year	Shelf Life	Practical Shelf Life*
1984-1986	7 days	6-7 days†
1986-1999	5 days	3 days‡
1999-2004	5 days	3 days§
2004-present	5 days	2.5 to 3 days

*Days that platelet concentrates are actually available to clinicians.
†Reports of bacterial contamination.
‡Nucleic acid technology testing, centralized blood donor testing.
§Bacterial detection implemented.

Patients with severe thrombocytopenia (<20,000 cells/mm^3) and clinical signs of bleeding usually require platelet transfusion. However, patients may have very low platelet counts (much less than 20,000 cells/mm^3) and not have clinical bleeding. Patients such as these probably do not need platelet transfusions. Individuals who have undergone trauma or require surgery need higher platelet counts, probably 100,000 cells/mm^3, to maintain adequate hemostasis (see Table 61-5). Laboratory determinations and clinical evaluations must be taken into account before a decision to transfuse platelets is made.

When possible, ABO-compatible platelets should be used. The need to use them, however, is not well documented. Specific testing is difficult. Aggregation, the end point of RBC crossmatch, cannot be used because platelets cause clumping. The platelet membrane has immunoglobulins. Any additional deposit of recipient antibodies is difficult to detect. Despite the fact that platelets can be destroyed by antibodies directed against class I HLA proteins on their membranes and, to a lesser extent, by antibodies against ABO, platelets chosen for transfusion probably will continue to be chosen without regard to antigen systems.[134] ABO-incompatible platelets produce very adequate hemostasis.

The effectiveness of platelet transfusions is difficult to monitor (see also Chapters 62 and 81). Under ideal circumstances, one platelet concentrate usually produces an increase of approximately 7000 to 10,000 platelets/mm^3 at 1 hour after transfusion to the 70-kg adult. Ten units of platelet concentrates are required to increase the platelet count by 100,000 cells/mm^3. However, many factors, including splenomegaly, previous sensitization, fever, sepsis, and active bleeding, may lead to decreased survivals and decreased recovery of transfused platelets.

Various different types of platelet concentrates have been proposed, including apheresis (i.e., collecting more platelets from one donor to avoid pooling of platelets from multiple donors), leukocyte-depleted platelets, and ultraviolet B–irradiated platelets. The use of these products is reviewed by Kruskall.[192]

FRESH FROZEN PLASMA

FFP is the most frequently used plasma product and is prepared at the time blood is obtained from a donor. It contains all the plasma proteins, particularly factors V and VIII, which gradually decline during the storage of blood. The use of FFP carries with it certain inherent risks that are observed with the use of essentially any blood product, such as sensitization to foreign proteins. To increase overall usage of blood products, many variations on the production of FFP exist. For example, variation is seen in how long FFP is viable after thawing from 24 hours to 5 days. Also, plasma frozen 24 hours after phlebotomy (FP24) is comparable to FFP except for an approximately 25% decrease in factor VIII.[195] Of course, plasma is a vital part of the transfusion ratios concept.

The 2006 ASA Task Force concluded that little scientific evidence supports increasing the use of FFP in clinical medicine. A more recent ASA Task Force will publish their summary about FFP and other blood products in 2015. Although FFP is a reliable solution for intravascular volume replacement in cases of acute blood loss, alternative therapies are equally satisfactory and considerably safer. No documentation exists that FFP has a beneficial effect when used as part of transfusion management of patients with massive hemorrhage. Not surprisingly, the risks of FFP administration include TRALI, transfusion-associated circulatory overload, and allergic or anaphylactic reactions. Other uncommon risks exist as well.[196]

In 2012, guidelines for plasma administration were published in an ASA publication.[197] Comparison of the 2006 and 2012 guidelines reflect the changes in thinking of the ASA, as follows:

1. Replacement of inherited single coagulation factor deficiencies for which no virus-safe products exists
2. Replacement of multiple coagulation factor deficiencies with associated bleeding, DIC, or both
3. As a component of plasma exchange in patients with thrombotic thrombocytopenic purpura
4. Reversal of warfarin anticoagulation when severe bleeding is present and prothrombin complex concentrations are not available
5. Prevention of dilutional coagulopathy in patients with major trauma and/or massive hemorrhage

FFP or plasma is often given to critical care patients before insertion of an intravascular catheter. Hall and associates[198] studied 1923 patients admitted to 29 ICUs in the United Kingdom who underwent intravascular catheterization. They compared patients who did and did not receive FFP. Chronic liver disease and more abnormal coagulation tests increased the frequency of patients receiving FFP. Yet the severity of PT alone was not a factor. Whether prophylactic FFP should be given in this situation is not well defined.

In an effort to "expedite" the availability of plasma for patients who require massive transfusions, some trauma centers keep thawed plasma readily available. In one study, patients with severe trauma who had already received 1 unit of RBCs and plasma were then divided into two groups, one of which immediately received 4 units of thawed plasma. The patients who received the plasma had a reduction in overall blood product use and 30-day mortality.[199] To me, the improvement in outcome was impressive. It makes one wonder if any other reasons accounted for improvement in care independent of blood administration.

OTHER PLASMA PRODUCTS

Several plasma products should be briefly described. This topic was well reviewed by Tanaka and Kor[197] in a publication from the ASA. Plasma frozen within 24 hours of collection is labeled PF24. Other products are labeled prothrombin complex concentrates. In Europe, prothrombin complex concentrates are available that are sterile lyophilized concentrates of vitamin K–dependent factors. Other preparations are available. In the United States, three-factor prothrombin complex concentrate products are available. Indications approved by the FDA are very restrictive.

CRYOPRECIPITATE

Cryoprecipitate is prepared in such a way that it contains significant levels of factor VIII and fibrinogen. It also contains von Willebrand factor and fibronectin. All other plasma proteins are present in only trace amounts in cryoprecipitate. The use of cryoprecipitate in the treatment of factor VIII deficiency or hemophilia A has been outlined by Brown and co-workers.[200] Cryoprecipitate contains factor VIII:C (i.e., procoagulant activity), factor VIII:vWF (i.e., von Willebrand factor), fibrinogen, factor XIII, and fibronectin, which is a glycoprotein that may play a role in reticuloendothelial clearance of foreign particles and bacteria from the blood.

Cryoprecipitate is frequently administered as ABO compatible; however, this probably is not very important because the concentration of antibodies in cryoprecipitate is extremely low. Cryoprecipitate may contain RBC fragments, and cryoprecipitate prepared from Rh-positive individuals can possibly sensitize Rh-negative individuals to the Rh O antigen.

Cryoprecipitate should be administered through a filter and as rapidly as possible. The rate of administration should be at least 200 mL/hr and infusion should be completed within 6 hours of thawing.

Commercial concentrates of factor VIII have been the standard therapy for hemophilia. Although heat inactivation of factor VIII concentrate reduces infectivity, such a risk is still present. Recombinant DNA techniques have been used to develop factor VIII, which is free of disease transmission.[201] Mild cases of hemophilia may be treated without blood products by administration of desmopressin. Appropriate therapy is difficult to ascertain for patients who have inhibitors (i.e., alloantibodies) to factor VIII.

Fibrin glue is used occasionally by surgeons to create local hemostasis. It is prepared in a manner similar to that of cryoprecipitate. When FFP is thawed, the precipitate contains large amounts of fibrinogen. When centrifuged, approximately 4 mL of concentrated precipitate results. With added thrombin, it is applied locally, the efficacy of which is difficult to determine.

PROTHROMBIN COMPLEX

Factor IX can be recovered from plasma or plasma fractions by absorption with ion exchanges or inorganic chemicals. These products are all complexes of factors II, VII, IX, and X. Two commercial preparations are Konyne (Cutter Laboratories, Berkeley, Calif) and Proplex (Hyland Division of Travenol Laboratories, Costa Mesa, Calif). Other products include AlphaNine SD (BDI Pharma, Columbia, SC), BeneFix (Wyeth Pharmaceuticals, New York), Mononine (CSL Behring, King of Prussia, Pa), and Profilnine SD (Grifols, Los Angeles, Calif). Bebulin VH (Baxter, Deerfield, Ill) is a vapor-heated concentrate of vitamin K–dependent factors in a much smaller volume than is achievable with FFP.

The main indication for these products is treatment of factor IX deficiency, or hemophilia B (i.e., Christmas disease). This hemorrhagic disorder is distinguishable from hemophilia A only by laboratory tests. Factor IX or prothrombin complex also has been used for the treatment of acquired hypoprothrombinemic bleeding disorders, principally sodium warfarin overdose; however, its use is limited because of the risk for hepatitis.

FIBRINOGEN CONCENTRATES

Fibrinogen concentrate is derived from human plasma and does not contain relevant levels of other coagulation factors. It also does not have the complications associated with blood transfusions. Accordingly, administration of fibrinogen can reduce the required need for allogeneic blood components. Quite often, the efficacy of fibrinogen administration has been clinically documented by fibrin-based ROTEM briefly described in this chapter and Chapter 62.[202] This randomized controlled trial strongly suggested that fibrinogen concentrate could be a first-line therapy to reduce transfusion requirements. In an accompanying editorial, Faraday[203] stated that "The administration of fibrinogen concentrates demonstrates clear potential to improve hemostasis more rapidly and at lower risk for immunologic reactions, infection, and (intravascular) volume overload than conventional allogeneic blood products." Also, Tanaka and colleagues[204] concluded that a single dose of 4 g of fibrinogen would achieve a blood level approximately 200 mg/dL and reduce the incidence of platelet administration and number of donor exposures. Yet a systematic review of five randomized trials and 15 nonrandomized studies concluded that that prothrombin complex and fibrinogen concentrations were not superior to conventional blood components for the treatment of perioperative coagulopathy in bleeding patients.[205]

SINGLE-DONOR PLASMA

Single-donor plasma is plasma that has been removed from stored blood without any effort being made to preserve coagulation factors. Single-donor plasma is very effective as a volume expander. All the precautions outlined for the administration of FFP should be followed when single-donor plasma is administered. It obviously cannot be used to correct deficiencies in coagulation factors.

ALBUMIN AND PLASMA PROTEIN PREPARATIONS

Several commercial products containing albumin are available for use to increase intravascular volume. Albumin is available as a 5% or a 25% solution in isotonic saline. Plasma protein fractions containing albumin and α and β globulins are available. These solutions are prepared commercially from albumin fractions from large pools of plasma reconstituted in isotonic electrolyte solutions. Such solutions can be given without regard to ABO blood type and without crossmatch and should be used primarily as volume expanders. They are very expensive and in short supply. Bacterial sepsis has been associated with albumin administration.[206] For much of 1997, there was a shortage of 5% albumin because of the concern

about contamination with variant Creutzfeldt-Jakob disease. If available, albumin should be administered within 4 hours of initiation of the infusion because of the potential for contamination after opening the bottle. In 2003, Vincent and associates[207] analyzed all adverse reports on the 10 major suppliers of human albumin worldwide from 1998 to 2000. Although cases were possibly underreported, the investigators concluded that adverse events were rare with human albumin administration. It appears to be quite safe, but the indications for its use are controversial.

Administration of the plasma protein fraction of 5% serum albumin solutions should be restricted for the treatment of documented hypoproteinemia or conditions such as burns and peritonitis, in which hypoproteinemia is likely. These solutions expand the vascular space for a longer period than do balanced electrolyte solutions. However, albumin's osmotic ability draws fluid into the vascular space from other extracellular fluid compartments. In most states of hypovolemia and dehydration, the entire extracellular fluid space is already depleted. Fluids such as 0.9% saline or lactated Ringer solution, which expand the entire extracellular fluid space, should be given.

SYNTHETIC COLLOID SOLUTION THERAPY

The crystalloid-versus-colloid conflict has been debated for many years. The University Hospital Consortium developed guidelines for the use of albumin, nonprotein colloid, and colloid solutions.[208] Unfortunately, no anesthesiologists were represented in the consensus exercise. No doubt exists that colloids expand intravascular volume more than crystalloids (i.e., a smaller amount of colloid is required for adequate intravascular resuscitation).[209] However, outcomes (e.g., mortality) do not provide convincing evidence that one fluid replacement strategy is better than others.

SYNTHETIC HYDROXYETHYL STARCH

Various starch preparations have been used to enlarge intravascular volume for many years. An excellent review by Van Der Linden and colleagues[210] stated that the understanding "the pharmacokinetics and pharmacodynamics of the hydroxyethyl starches has evolved so that we now appreciate that both properties vary depending on the starch source and on their chemical composition: degree of substitution, molecular location of the substitution, average molecular weight and molecular weight distribution." The most commonly used preparation was 6% hydroxyethyl starch (HES, Hespan). Although an effective intravascular expander, it has not gained widespread popularity, probably because of its effects on coagulation, particularly with regard to increased bleeding and platelet function. The molecular mass plays some role in the adverse coagulation effects (i.e., smaller molecular mass has less effect on coagulation). Two other HES preparations have been developed to decrease coagulation effects. Hextend has been studied extensively. It is 6% HES but also contains a physiologically balanced medium of electrolytes, glucose, and lactate. It has a pharmacokinetic and pharmacodynamic profile similar to those of other starch preparations with fewer effects on coagulation.[211] Gelatin also has been used, but it has not been as widely studied as HES.[212]

Van Der Linden and associates[211] could not find evidence that tetrastarches signaled any adverse safety issues. However, Zarychanski and co-workers[213] concluded that these starches should not be used because of serious safety concerns, especially increased risk for mortality and AKI. They also took into account research misconduct by one investigator who had published many articles regarding the clinical use of HES-like compounds. In an accompanying editorial,[214] the conclusions with HES-like compounds were outlined, including the extensive unethical research that has been described as data fabrication and scientific misconduct. Accordingly, Antonelli and Sandroni[214] concluded that HES most likely should not be used for acute intravascular volume resuscitation of critically ill patients. It remains to be seen whether more clinical research will be conducted.

In 2013, the FDA Safety Information and Adverse Event Reporting Program published via their MedWatch program a "Boxed Warning on Increased Mortality and Severe Renal Injury and Risk of Bleeding." Specifically, they recommended that HES solutions not be administered to patients with sepsis who are in the ICU, those with preexisting renal function issues, and those undergoing cardiopulmonary bypass. Also if HES is being given, it should be stopped at the first sign of a coagulopathy and/or renal dysfunction.

Since 2012, various forms of caution regarding the use of HES have been steadily appearing, which puts the future of colloids for clinical care in question. Yet in late 2013, an editorial by Seymour and Angus[215] states that whether patients with hypovolemic shock should be resuscitated with colloids or crystalloids (i.e., normal saline or lactated Ringer solution) is one of the oldest debates in medicine. Their editorial was in response to another study[216] regarding colloids versus crystalloids in patients with hypovolemic shock. Although there was a slightly better outcome with colloids regarding 90-day mortality, the overall conclusion leaned toward no difference between the use of colloids versus crystalloids (the Colloids versus Crystalloids for the Resuscitation of the Critically Ill [CRISTAL] trial). They point out that numerous clinical trials have been conducted, including Saline versus Albumin Fluid Evaluation (SAFE), Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP), Scandinavian Starch for Severe Sepsis/Septic Shock (6S), Crystalloid versus Hydroxyethyl Starch Trial (CHEST), and the aforementioned CRISTAL trials. The conclusion is that there may be no definitive answer to the question of whether patients with hypovolemic shock should preferentially receive colloids or crystalloids.

The preceding paragraph indicates that the colloid versus crystalloids topic has been extensively studied, with no definitive answer. Nearly all of these groups have conducted their studies in acutely ill patients, frequently located in ICUs, except for one report. HES may be more effective for treating anaphylaxis associated with anesthesia.[217] Yet although many of the conclusions can

apply to intraoperative care, none of the studies were conducted during surgery and anesthesia. In summary, the justification and benefit for the use of colloids (which are expensive) (i.e., instead of crystalloids) are often not clear. Although many studies have been conducted, they frequently conclude that further study is required. My opinion is different. If the use of colloids is similar to that of crystalloids, perhaps the correct answer is that little or no difference exists, not that more studies are needed. If colloids (especially HES) are used, the anesthesia provider should be able to justify this decision based on the most recent available clinical evidence. Moral and associates[218] ask the question as to whether tetrastarch solutions are definitely dead? The editorial by Nolan and colleagues[219] goes further to say, "hydroxyethyl starch: here today, gone tomorrow."

DEXTRANS

Dextran 70 (Macrodex), with a molecular mass of approximately 70,000 Daltons, is an effective volume expander. However, after infusion of more than 20 mL/kg in 24 hours, dextran 70 may interfere with normal blood clotting, causing a deficiency with crossmatching procedures and possibly a bleeding diathesis. These clotting defects reflect reduced platelet adhesiveness resulting from an antithrombin effect. The incidence of severe anaphylactoid or anaphylactic reactions is a concern. These reactions are mediated by dextran-reactive antibodies that are IgG immunoglobulins. Dextran-reactive antibodies are formed in response to dextran polysaccharides. This process can be prevented if the potentially reactive sites on the dextran-reactive antibody are blocked before the antibody is given. By prior administration of a hapten, a substance capable of combining with immunoglobulins but not producing a reaction, the reactive sites are occupied and unable to react to the antigen. Prior administration of dextran I (Promit, molecular mass of 1000 D) proved effective as a hapten and decreases, but does not eliminate, the incidence of severe reactions.[220] Dextran 70 exerts a higher colloid osmotic pressure than blood. Dextran 70 and albumin may deplete the extracellular fluid space of water, as does albumin.

Dextran 40 (Rheomacrodex), with a molecular mass of 40,000 Daltons, has been used primarily to reduce blood viscosity and cellular aggregation and improve microcirculation during low-flow states. It is often given prophylactically to decrease the incidence of postoperative thromboembolism. Blood viscosity may be increased by trauma, blood loss, burns, and endotoxin shock. Although viscosity can be decreased by dextran 40, the presumed improvement in flow through the microcirculation has not been well documented.

HYPERTONIC SALINE, POSSIBLY WITH DEXTRAN

The Na concentration of hypertonic saline solutions is 250 to 1200 mEq/L. The theoretical advantage is that the greater the Na concentration, the less total volume is required for adequate resuscitation. The lower infusion volume probably reflects the osmotically related movement of intracellular water into the extracellular space. Other mechanisms include a direct inotropic effect on the myocardium and a direct peripheral vasodilator effect. The main problem is severe hypernatremia, which can cause brain dehydration and can be fatal.

Various hyperosmotic-hyperoncotic solutions have been used for resuscitation of hypovolemic patients. The most common combination is hypertonic saline and 6% dextran 70. In animals, these fluids restore gut and kidney microcirculation more effectively than normal saline.[221,222] The addition of dextran increases the intravascular volume effect of hypertonic saline but does not extend the duration of effect in a clinically significant manner.[221] Clinical practice will be required to ascertain the ultimate role, if any, of these fluids.

SYNTHETIC OXYGEN-CARRYING SUBSTANCES

OTHER THAN HUMAN RED BLOOD CELLS (BLOOD)

Various other substances that carry or facilitate the transport of O_2 have been made. Two attempts have been made using the concept of synthetic blood. The first approach uses linear binding kinetics, unlike the nonlinear binding of Hb. The most notable is the perfluorochemical emulsion called Fluosol-DA. However, it had little use because it carries O_2 (i.e., a small amount) only when the Pa_{O_2} is more than 300 mm Hg.[222] A newer perfluoro compound, perfluorooctyl bromide, carries three to four times more O_2 and has a longer half-life and presumably fewer problems than are associated with Fluosol-DA. Other related products are Oxygent (Alliance), Oxycyte (synthetic blood), and several other perfluorocarbon emulsions.

The remaining synthetic blood (a term this author uses but not one officially accepted by industry and the FDA) or O_2 therapeutics are labeled as Hb-based O_2 carriers (HBOCs). These products modify the Hb molecule from humans, animals, or recombinant technology. Original efforts required Hb to be stroma free to prevent nephrotoxicity. The stroma-free Hb needed to be modified to have a favorable O_2 affinity and to extend its relatively short intravascular half-life. Only three products have been undergoing clinical trials. Two products are from outdated human RBCs and the third from bovine RBCs. However, these solutions are not without complications. The most serious are kidney toxicity, an increase in affinity for O_2 (i.e., left shift in the O_2 dissociation curve), and arteriolar vasoconstriction from nitric oxide scavenged by the infused Hb. As described at the end of this section, this vasoconstriction may prove to be their ultimate downfall. A variety of approaches are being used, including crosslinking, pyridoxylation and polymerization, and conjugation and encapsulation, to decrease O_2 affinity, to increase deposition in the reticuloendothelial system, and to increase half-life.

Genetic engineering has provided hope for blood products. Initially, recombinant erythropoietin was developed for treatment of anemias and facilitation of autologous blood donation (see also Chapter 63). In 1992, a human

TABLE 61-16 COMPARISON OF SYNTHETIC BLOOD IN GENERAL WITH ALLOGENEIC BLOOD

Parameter	Synthetic	Allogeneic
Oxygen delivery	Rapid and consistent	Dependent on 2,3-DPG
Risk for disease transmission	None	See Table 61-11
Storage	Room temperature Stable efficacy	Refrigeration Loss of efficacy
Shelf life	1-3 yr	42 days
Preparation	Ready to use	Crossmatch
Compatibility	Universal	Type specific
Duration of action	1-3 days	60-90 days

2,3-DPG, 2,3-Diphosphoglycerate.

recombinant Hb (rHb 1.1) was designed as a blood substitute.[223] With the use of genetic engineering techniques, it was made from *Escherichia coli*. It functions as normal Hb in terms of O_2-carrying capacity, but it does not require crossmatching, transmit disease, or become rapidly outdated. How much recombinant material can be tolerated by humans remains to be determined. Unfortunately, this caused arteriolar vasoconstriction from NO scavenging. Although arterial blood pressure was sustained, it was at the expense of severe vasoconstriction of microvascular structures, which is not beneficial for organ perfusion. Recently, rHbg 2.0, which minimizes NO scavenging, caused little arteriolar vasoconstriction when compared with rHbg 1.1 and diaspirin crosslinked Hb.[224,225] It is hoped that studies of these newer Hb solutions will lead to new synthetic blood products in humans.

An example of a product that appears to be the initial one possibly approved for routine clinical practice is Hemopure.[226] It is from ultrapurified bovine RBCs that have been glutaraldehyde polymerized. It has a higher P_{50} (i.e., 43 instead of 26 mm Hg), which means that it should deliver O_2 to the tissues at least as well, if not better, than human RBCs.[226] It has the added advantage of not requiring type and crossmatch and not transmitting infectious agents such as HIV and hepatitis virus.[225,226] These, of course, are typical characteristics of most synthetic blood products (Table 61-16). Many clinical trials have been safely conducted with a few possibly minor complications, the significance of which are not clear. Complications include a slight increase in mean arterial blood pressure and a decrease in cardiac index, which presumably may be from NO. Most of the clinical trials have shown a decreased use of allogeneic blood transfusions.[227]

However, the most recent information regarding HBOCs is not encouraging. Natanson and colleagues[228] performed a cumulative meta-analysis on 16 trials involving five different products and 3711 patients. They concluded that there was a significant increased risk for myocardial infarction and death when HBOCs were given. An accompanying editorial concluded that a 30% increased risk for death and a three-fold increase in the risk for myocardial infarction should preclude any additional studies.[229] Furthermore, a consistency of harm was found among all the technologies (e.g., cross-linked, polymerized, or conjugated). In essence, investigators must demonstrate that HBOCs are at least as effective in reducing mortality or serious morbidity as the current standards of care. I have reluctantly concluded that use of synthetic blood (HBOCs) is not likely with the current technologic approaches.

Despite the negative conclusion regarding the future of HBOCs, attempts to find useful roles for them occasionally occur.

For example, organ function and systemic oxygenation could be sustained in rats by using perfluorocarbon emulsion (an HBOC) during extreme anemia.[230] The proposal is that perhaps HBOC could be used until blood transfusions were available. Accordingly, a human polymerized hemoglobin, PolyHeme, can provide "life-sustaining" capability in the presence of hemorrhage in trauma patients while waiting for blood products.[231] Olofsson and colleagues[232] used an oxygenated polyethylene glycol–modified Hb to decrease the hypotensive episodes during total hip arthroplasty. Although this was successful, a higher risk for adverse effects was found. These results led Levy[36] to conclude that "it is unlikely that we will have a NO-scavenging agent to treat hypotension or shock until the molecule is sufficiently safe for any benefits provided." Although this possibility seems unlikely, other possible uses of HBOC solutions will likely be proposed.

INFORMED CONSENT

Before any transfusion is given, informed consent should be obtained from the patient or guardian (see also Chapter 11). What constitutes consent varies across the United States and is still changing. If a patient is damaged by a transfusion administered without a valid consent, damages may be recovered even though the defendant did everything properly.[228] Many years ago, the *Paul Gann Blood Safety Act* was passed in California. This law mandates that patients be informed of the risks of blood transfusions and of any alternatives. The changes in transfusion medicine probably dictate an intense, ongoing educational process for clinicians who administer blood products to ensure they are compliant with current laws and regulations. Local hospital transfusion medicine committees can likely provide clinicians with such information.

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Chapter 62

Patient Blood Management: Coagulation

THOMAS F. SLAUGHTER

Key Points

- Under normal physiologic conditions, clot formation requires participation of vascular endothelium, platelets, and plasma-mediated hemostasis.
- Tissue factor (extrinsic pathway) initiates plasma-mediated hemostasis, whereas factor XI (intrinsic pathway) amplifies the response.
- Thrombin generation proves the key regulatory enzymatic step in hemostasis.
- Platelets participate in clot formation as (1) anchoring sites for coagulation factor activation complexes, (2) delivery "vehicles" releasing hemostatically active proteins, and (3) major structural components of the clot.
- A carefully obtained history of bleeding remains the most effective means for identifying bleeding and thrombotic tendencies.
- Thrombosis is potentiated by stasis, vascular endothelial injury, and underlying hypercoagulable conditions.
- Heparin-induced thrombocytopenia comprises a heparin-mediated autoimmune response potentiating platelet activation and venous and arterial thromboses.

NORMAL HEMOSTASIS

Hemostasis comprises cellular and biochemical processes that limit blood loss resulting from injury, maintain intravascular blood fluidity, and promote revascularization of thrombosed vessels after injury. Normal physiologic hemostasis necessitates a delicate balance between procoagulant pathways responsible for generation of a stable localized hemostatic "plug" and counterregulatory mechanisms inhibiting thrombus formation beyond the injury site. Vascular endothelium, platelets, and plasma coagulation proteins play equally important roles in this process. Failure to maintain balance commonly leads to excessive bleeding or pathologic thrombus formation.

Vascular endothelial injury—mechanical or biochemical—leads to platelet deposition at the injury site, a process often referred to as primary hemostasis. Although primary hemostasis may prove adequate for a minor injury, control of more significant bleeding necessitates stable clot formation incorporating crosslinked fibrin—a process mediated by activation of plasma clotting factors and often referred to as secondary hemostasis. Although the terms primary and secondary hemostasis remain relevant for descriptive and diagnostic purposes, advances in understanding cellular and molecular processes underlying hemostasis suggest a far more complex interplay between vascular endothelium, platelets, and plasma-mediated hemostasis than is reflected in this model.

VASCULAR ENDOTHELIAL ROLE IN HEMOSTASIS

Under normal conditions, vascular endothelium provides a nonthrombogenic surface to promote blood fluidity. Healthy endothelial cells possess antiplatelet, anticoagulant, and profibrinolytic effects to inhibit clot formation.[1] Negatively charged vascular endothelium repels platelets and produces prostacyclin and nitric oxide (NO), which are potent platelet inhibitors.[2] Adenosine diphosphatase synthesized by vascular endothelial cells degrades adenosine diphosphate (ADP), another potent platelet activator. Given these endogenous antiplatelet effects, nonactivated platelets do not adhere to healthy vascular endothelial cells. Vascular endothelium further expresses several inhibitors of plasma-mediated hemostasis, including thrombomodulin (an indirect thrombin inhibitor), heparin-like glycosaminoglycans, and tissue factor pathway inhibitor (TFPI).[3] Finally, vascular endothelium synthesizes tissue plasminogen activator (t-PA), which is responsible for activating fibrinolysis—a primary counterregulatory mechanism limiting clot propagation.

Despite these natural defense mechanisms to inhibit thrombus generation, a variety of mechanical and chemical stimuli may shift the balance such that the endothelium promotes clot formation. Damage to vascular endothelial cells exposes the underlying extracellular matrix (ECM), including collagen, von Willebrand factor (vWF), and other platelet-adhesive glycoproteins.[4,5] Platelets bind to and are activated by exposure to ECM components. Exposure of tissue factor, constitutively expressed by fibroblasts in the ECM, activates plasma-mediated coagulation pathways to generate thrombin and, ultimately, fibrin clot. Certain cytokines (i.e., interleukin-1, tumor necrosis factor, and γ-interferon) and hormones (i.e., desmopressin acetate or endotoxin) induce prothrombotic changes in vascular endothelial cells, including synthesis and expression of vWF, tissue factor, plasminogen activator inhibitor–1 (PAI-1, an inhibitor of fibrinolysis), and down-regulate normal antithrombotic cellular and biochemical pathways.[6,7] Thrombin, hypoxia, and high fluid shear stress induce prothrombotic vascular endothelial changes. Increased vascular endothelial synthesis of PAI-1 and associated inhibition of fibrinolysis have been implicated in the prothrombotic state and high incidence of venous thrombosis after surgery.[8,9]

PLATELETS AND HEMOSTASIS

Platelets contribute a critical role in hemostasis. Derived from bone marrow megakaryocytes, nonactivated platelets circulate as discoid anuclear cells.[10] The platelet membrane is characterized by numerous receptors and a surface-connected open canalicular system serving to increase platelet membrane surface area and provide rapid communication between the platelet interior and external environment.[11] Under normal circumstances, platelets do not bind vascular endothelium; however, when injury exposes ECM, platelets undergo a series of biochemical and physical alterations characterized by three major phases: adhesion, activation, and aggregation.

Exposure of subendothelial matrix proteins (i.e., collagen, vWF, fibronectin) allows for platelet adhesion to the vascular wall. vWF proves particularly important as a bridging molecule between ECM and platelet glycoprotein Ib/factor IX/factor V receptor complexes.[12] Absence of either vWF (von Willebrand disease) or glycoprotein Ib/factor IX/factor V receptors (Bernard-Soulier syndrome) results in a clinically significant bleeding disorder.

As platelets adhere along the ECM, a series of physical and biochemical changes occur termed platelet activation. Platelets contain two specific types of storage granules: α granules and dense bodies.[11] Alpha granules contain numerous proteins essential to hemostasis and wound repair, including fibrinogen, coagulation factors V and VIII, vWF, platelet-derived growth factor, and others. Dense bodies contain the adenine nucleotides ADP and adenosine triphosphate, as well as calcium, serotonin, histamine, and epinephrine. During the activation phase, platelets release granular contents, resulting in recruitment and activation of additional platelets and propagation of plasma-mediated coagulation.[13] During activation, platelets undergo structural changes to develop pseudopod-like membrane extensions and to release physiologically active microparticles, with both mechanisms serving to increase dramatically platelet membrane surface area. Redistribution of platelet membrane phospholipids during activation exposes newly activated glycoprotein platelet surface receptors and phospholipid binding sites for calcium and coagulation factor activation complexes, which is critical to propagation of plasma-mediated hemostasis.[14]

During the final phase of platelet aggregation, activators released during the activation phase serve to recruit additional platelets to the site of injury. Newly active glycoprotein IIb/IIIa receptors on the platelet surface bind fibrinogen to provide for cross-linking with adjacent platelets (platelet aggregation).[15] The importance of these receptors is reflected by the bleeding disorder associated with their hereditary deficiency, Glanzmann thrombasthenia.

PLASMA-MEDIATED HEMOSTASIS

Plasma-mediated hemostasis, the coagulation cascade, might best be summarized as an amplification system to accelerate thrombin generation from an inactive precursor (i.e., prothrombin). Trace plasma proteins, activated by exposure to tissue factor or foreign surfaces, initiate a cascading series of reactions culminating in conversion of soluble fibrinogen to insoluble fibrin clot.[16] Thrombin generation, the "thrombin burst," represents the key regulatory step in this hemostatic process. Thrombin not only generates fibrin but also activates platelets and mediates a host of additional processes affecting inflammation, mitogenesis, and even down-regulation of hemostasis.[17]

Traditionally, the coagulation cascade describing plasma-mediated hemostasis has been depicted as intrinsic and extrinsic pathways, both of which culminate in a common pathway in which fibrin generation occurs.[18] Although this cascade model has proved an oversimplification, it remains a useful descriptive tool for organizing discussions of plasma-mediated hemostasis (Fig. 62-1). Coagulation factors are, for the most part, synthesized hepatically and circulate as inactive proteins termed zymogens. The somewhat confusing nomenclature of the classic coagulation cascade derives from the fact that inactive zymogens were identified using Roman numerals assigned in order of discovery. As the zymogen is converted to an active enzyme, a lower-case letter "a" is added to the Roman numeral identifier. For example, inactive prothrombin is referred to as factor II and active thrombin is identified as factor IIa. Some numerals were subsequently withdrawn or renamed as our understanding of the biochemistry underlying hemostasis evolved.The coagulation cascade characterizes a series of enzymatic reactions in which inactive precursors—zymogens—undergo activation to amplify the overall reaction. Each stage of the cascade requires assembly of membrane-bound activation complexes, each composed of an enzyme (activated coagulation factor), substrate (inactive precursor zymogen), cofactor (accelerator or catalyst), and calcium.[19] Assembly of these activation complexes occurs on phospholipid membranes (most often platelet or microparticle membranes) that localize and concentrate reactants. In the absence of phospholipid membrane anchoring sites,

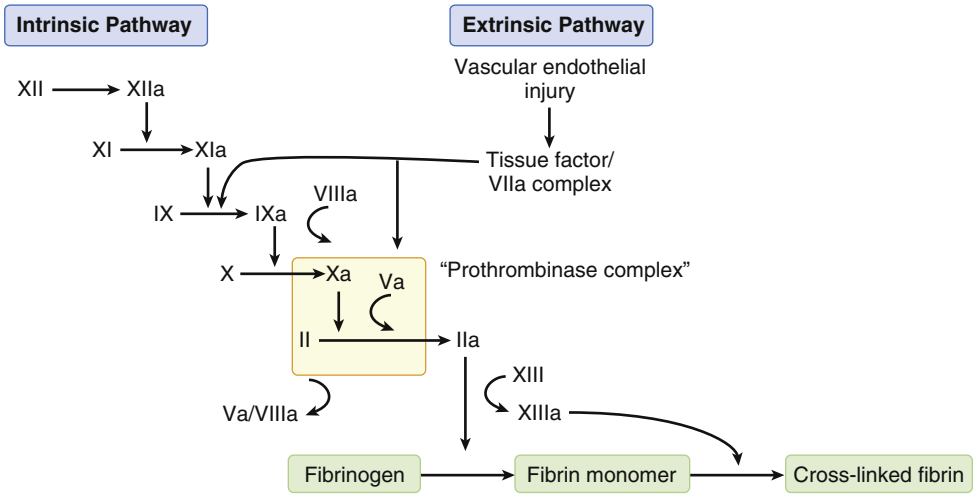


Figure 62-1. Depiction of the classic coagulation cascade incorporating extrinsic and intrinsic pathways of coagulation. *(From Slaughter TF: The coagulation system and cardiac surgery. In Estafanous FG, Barasch PG, Reves JG, editors:* Cardiac anesthesia: principles and clinical practice, *ed 2, Philadelphia, Lippincott Williams & Wilkins, 2001, p. 320, with permission.)*

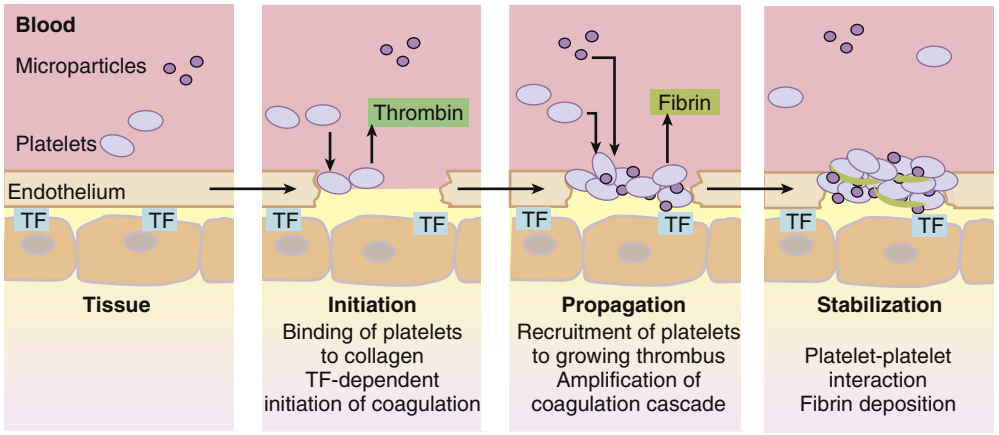


Figure 62-2. Clot formation at vascular injury site. Vascular injury exposes subendothelial tissue factor (*TF*) initiating plasma-mediated hemostasis via the extrinsic pathway. The intrinsic pathway further amplifies thrombin and fibrin generation. Platelets adhere to exposed collagen to undergo activation, resulting in recruitment and aggregation of additional platelets. *(From Mackman N, Tilley RE, Key NS: Role of extrinsic pathway of blood coagulation in hemostasis and thrombosis,* Arterioscleros Thromb Vasc Biol *27:1688, 2007, with permission.)*

activation of coagulation factors slows dramatically, further localizing clot generation to injury sites.

EXTRINSIC PATHWAY OF COAGULATION

The extrinsic pathway of coagulation, widely recognized as the initiating step in plasma-mediated hemostasis, begins with exposure of blood plasma to tissue factor.[20] Tissue factor is prevalent in subendothelial tissues surrounding vasculature; however, under normal conditions the vascular endothelium minimizes contact between tissue factor and plasma coagulation factors. After vascular injury, small concentrations of factor VIIa circulating in plasma form phospholipid-bound activation complexes with tissue factor, factor X, and calcium to promote conversion of factor X to Xa.[21] Recently, the tissue factor/factor VIIa complex has been demonstrated to activate factor IX of the intrinsic pathway, further demonstrating the key role of tissue factor in initiating hemostasis.[22]

INTRINSIC PATHWAY OF COAGULATION

Classically, the intrinsic or contact activation system was described as a parallel pathway for thrombin generation by way of factor XII. However, the rarity of bleeding disorders resulting from contact activation factor deficiencies led to our current understanding of the intrinsic pathway as an amplification system to propagate thrombin generation initiated by the extrinsic pathway.[22] Recent cell-based models of coagulation suggest that thrombin generation by way of the extrinsic pathway is limited by a natural inhibitor, TFPI.[23] However, small quantities of thrombin generated before neutralization of the extrinsic pathway activate factor XI and the intrinsic pathway. The intrinsic pathway subsequently amplifies and propagates the hemostatic response to maximize thrombin generation (Fig. 62-2). Although factor XII may be activated by foreign surfaces (i.e., cardiopulmonary bypass circuits or glass vials), the intrinsic pathway appears to play a minor role in initiation of hemostasis. Proteins of the intrinsic pathway may, however, contribute to inflammatory processes, complement activation, fibrinolysis, kinin generation, and angiogenesis.[22,24]

Common Pathway of Coagulation

The final pathway, common to both extrinsic and intrinsic coagulation cascades, depicts thrombin generation and subsequent fibrin formation. Signal amplification through both extrinsic and intrinsic pathways culminates in formation of prothrombinase complexes (phospholipid membrane–bound activation complexes) comprising factor Xa, factor II (prothrombin), factor Va (cofactor), and calcium ions.[25] Prothrombinase complexes mediate the thrombin burst—a surge in thrombin generation from the

inactive precursor prothrombin. Thrombin proteolytically cleaves fibrinopeptides A and B from fibrinogen molecules to generate fibrin monomers, which polymerize into fibrin strands (i.e., fibrin clot).[25] Finally, factor XIIIa, a transglutaminase activated by thrombin, covalently crosslinks fibrin strands to produce an insoluble fibrin clot resistant to fibrinolytic degradation. Both fibrinogen and factor XIII have been implicated in acquired bleeding disorders. Reduced concentrations of either protein may promote excess postoperative hemorrhage and transfusion requirements. Recent availability of plasma concentrates for both fibrinogen and factor XIII suggest potential for randomized controlled trials to determine efficacy of these biologics in treatment of acquired coagulopathies.[26] Regardless, thrombin generation remains the key enzymatic step regulating hemostasis.[27] Not only does thrombin activity mediate conversion of fibrinogen to fibrin, it also activates platelets and factor XIII, converts inactive cofactors V and VIII to active conformations, activates factor XI and the intrinsic pathway of coagulation, up-regulates cellular expression of tissue factor, and stimulates vascular endothelial expression of PAI-1 to down-regulate fibrinolytic activity.[17,27]

Intrinsic Anticoagulant Mechanisms

Once activated, regulation of hemostasis proves essential to limit clot propagation beyond the injury site. One simple, yet important, anticoagulant mechanism derives from flowing blood and hemodilution. The early platelet and fibrin clot proves highly susceptible to disruption by shear forces within flowing blood. Blood flow further limits localization and concentration of both platelets and coagulation factors such that a critical mass of hemostatic components may fail to coalesce.[25,28] However, later in the clotting process more robust counterregulatory mechanisms are necessary to limit clot propagation. Four major counterregulatory pathways have been identified that appear particularly crucial for down-regulating hemostasis: fibrinolysis, TFPI, the protein C system, and serine protease inhibitors.

The fibrinolytic system comprises a cascade of amplifying reactions culminating in plasmin generation and proteolytic degradation of fibrin and fibrinogen. As with the plasma-mediated coagulation cascade, inactive precursor proteins are converted to active enzymes, necessitating a balanced system of regulatory controls to prevent excessive bleeding or thrombosis (Fig. 62-3). The principal enzymatic mediator of fibrinolysis, plasmin, is generated from an inactive precursor, plasminogen.[29] In vivo, plasmin generation most often is initiated by release of t-PA or urokinase from vascular endothelium. Thrombin provides a potent stimulus for t-PA synthesis.[27] Factor XIIa and kallikrein of the intrinsic pathway activate fibrinolysis after exposure to foreign surfaces. The presence of fibrin accelerates plasmin generation.[30] Rapid inhibition of free plasmin also limits spread of fibrinolytic activity. In addition to enzymatic degradation of fibrin and fibrinogen, plasmin inhibits hemostasis by degrading essential cofactors V and VIII and reducing platelet glycoprotein surface receptors essential to adhesion and aggregation.[31] Fibrin degradation products also possess mild anticoagulant properties.TFPI inhibits the tissue factor/factor VIIa complex and thereby the extrinsic coagulation pathway, which is responsible for initiation of hemostasis. TFPI and factor

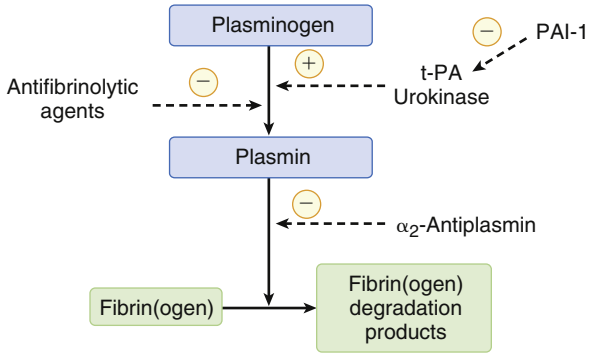


Figure 62-3. Principal mediators of fibrinolysis. *Dashed lines* depict sites of action for promoters and inhibitors of fibrinolysis. *PAI,* Plasminogen activator inhibitor; *tPA,* tissue plasminogen activator. *(From Slaughter TF: The coagulation system and cardiac surgery. In: Estafanous FG, Barasch PG, Reves JG, editors:* Cardiac anesthesia: principles and clinical practice, *ed 2, Philadelphia, Lippincott Williams & Wilkins, 2001, p. 320, with permission.)*

Xa form phospholipid membrane–bound complexes that incorporate and inhibit tissue factor/factor VIIa complexes.[3] Most TFPI is bound to vascular endothelium but may be released into circulation by heparin administration. Heparin further catalyzes TFPI inhibitory activity.[32] As TFPI rapidly extinguishes tissue factor/VIIa activity, the critical role of the intrinsic pathway to continued thrombin and fibrin generation becomes apparent.[22]

The protein C system proves particularly important in down-regulating hemostasis because it inhibits thrombin and the essential cofactors Va and VIIIa. Thrombin initiates this inhibitory pathway by binding a membrane-associated protein, thrombomodulin, to activate protein C.[33] Protein C, complexed with the cofactor protein S degrades both cofactors Va and VIIIa. Loss of these critical cofactors limits formation of tenase and prothrombinase activation complexes essential to formation of factor X and thrombin, respectively. Thrombin, once bound to thrombomodulin, is inactivated and removed from circulation, providing another mechanism by which protein C down-regulates hemostasis.[33]

The most significant serine protease inhibitors regulating hemostasis include antithrombin and heparin cofactor II. Antithrombin binds to and inhibits thrombin and factors IXa, Xa, XIa, and XIIa. Heparin cofactor II inhibits thrombin alone. Although the precise physiologic role for heparin cofactor II remains unclear, antithrombin plays a major role in down-regulating hemostasis.[34] Heparin, a catalyst accelerator, binds antithrombin to promote inhibition of targeted enzymes.[35] Heparin-like glycosaminoglycans, located on vascular endothelial cells, provide inhibitory sites for thrombin and factor Xa in vivo.

DISORDERS OF HEMOSTASIS

EVALUATION OF BLEEDING DISORDERS

Few would argue the importance of assessing bleeding risk preoperatively; however, appropriate methods for ascertaining this risk remain subject to debate. Although

routine coagulation testing of all surgical patients preoperatively intuitively may be appealing, this approach lacks predictive value for bleeding disorders and certainly lacks cost effectiveness.[36] A carefully performed history of bleeding remains the single most effective predictor for perioperative bleeding.

A thorough history should focus on prior bleeding episodes.[37] Does the patient have a history of excessive bleeding in association with trauma or prior surgery? Were blood transfusions or reoperation required to control the bleeding? A history suggestive of a bleeding disorder might include frequent epistaxis of a severity necessitating packing the nasal passage or surgical intervention. Oral surgery and dental extractions prove a particularly good test of hemostasis because of high concentrations of fibrinolytic activity in the oral cavity. Von Willebrand disease not infrequently manifests as menorrhagia, and postpartum hemorrhage commonly occurs in women with underlying disorders of hemostasis.[38] A history of spontaneous hemorrhage (nontraumatic) proves particularly concerning when associated with joints (hemarthroses) or deep muscles. Identification of a bleeding disorder at an early age or in family members suggests an inherited, as opposed to acquired, condition.[39] A careful medication history including direct questions relating to consumption of aspirin-containing nonprescription drugs, herbs, and fish oil may prove noteworthy. Finally, inquiries regarding coexisting diseases should be included (i.e., renal, hepatic, thyroid, and bone marrow disorders and malignancy).

For most patients, a thoughtfully conducted bleeding history will eliminate need for preoperative laboratory-based coagulation testing. Regardless, several valid reasons remain for preoperative coagulation testing. Should the preoperative history or physical examination reveal signs or symptoms suggestive of a bleeding disorder, further laboratory-based assessment of coagulation would be indicated. Preoperative screening tests of coagulation may be indicated, despite a negative history, in cases in which major surgery commonly associated with significant bleeding is planned (i.e., cardiopulmonary bypass). Finally, preoperative testing may prove justified in settings in which the patient is unable to provide a bleeding history preoperatively. Should evidence of a bleeding disorder be detected preoperatively, underlying mechanisms must be ascertained if possible before proceeding with surgery.

INHERITED BLEEDING DISORDERS

Although inherited disorders of hemostasis may involve platelet function, plasma-mediated hemostasis, or fibrinolytic pathways, von Willebrand disease characterized by quantitative or qualitative deficiencies of vWF proves the most common of inherited bleeding disorders.[38] Variants include types I and III with varying quantitative vWF deficiencies and type II comprising a collection of qualitative defects affecting vWF function. Under normal conditions, vWF plays a critical role in platelet adhesion to ECM. vWF further acts as a carrier molecule preventing proteolytic degradation of factor VIII in free plasma.[40] Classically, patients with von Willebrand disease describe a history of easy bruising, recurrent epistaxis, and menorrhagia, all characteristic of defects in primary (i.e., platelet mediated) hemostasis. In more severe cases (i.e., type III vWD), concomitant reductions in factor VIII may lead to serious spontaneous hemorrhage, including hemarthroses, which is common in hemophilia. Laboratory testing often demonstrates mild-to-moderate prolongation of the activated partial thromboplastin time (aPTT), prolonged bleeding time, decreased immunoreactive vWF concentrations, and reduced platelet aggregation in response to ristocetin.[38,41] Increasingly, the PFA-100 and similar ex-vivo platelet function tests have replaced bleeding times in assessing for vWD.[42] Measurable reductions in factor VIII activity may occur in severe cases. Mild cases of vWD often respond to desmopressin acetate (DDAVP); however, given a significant bleeding history, specific replacement of vWF and factor VIII with select factor VIII concentrates (i.e., Humate-P (CSL Behring, King of Prussia, Pa.) may be indicated.[43,44]

Although relatively uncommon, the hemophilias merit consideration given their diverse clinical presentation. Hemophilia A, characterized by variable degrees of factor VIII deficiency, is an X-linked inherited bleeding disorder most frequently presenting in childhood as spontaneous hemorrhage involving joints, deep muscles, or both. Hemophilia A occurs with an incidence of 1:5000 males; however, nearly one third of cases represent new mutations with no family history.[45] In mild cases, patients with hemophilia may not be identified until later in life, often after unexplained bleeding with surgery or trauma. Classically, laboratory testing in patients with hemophilia reveals prolongation of the aPTT, whereas the prothrombin time (PT) and bleeding time remain within normal limits. Specific measurement of factor VIII:C is required to confirm the diagnosis and to clarify the severity of factor VIII deficiency. Mild cases of hemophilia A may be treated with desmopressin; however, in most cases, perioperative management of these patients necessitates consultation with a hematologist and administration of recombinant or purified factor VIII concentrates.[43,46] An increasingly common complication of hemophilia, particularly in the case of hemophilia A, has been development of alloantibodies directed against the factor VIII protein. In cases of high-titer antibodies, administration of factor VIII concentrates may fail to control bleeding. Several approaches have reduced bleeding in these patients, including substitution of porcine factor VIII, administration of activated or nonactivated prothrombin complex concentrates, or treatment with recombinant factor VIIa (NovoSeven, Novo Nordisk Inc., Bagsvaerd, Denmark) (see also Chapter 63).[44,47] Also inherited as an X-linked disorder, hemophilia B (i.e., Christmas disease) occurs in approximately 1:40,000 and necessitates blood component replacement with factor IX concentrates.

ACQUIRED BLEEDING DISORDERS

A detailed account of acquired hemostatic disorders is beyond the scope of this discussion; however, given that a limited number of drugs and coexisting medical conditions account for the majority of acquired bleeding disorders, these conditions merit consideration. Heparin,

warfarin, and fibrinolytic drugs historically accounted for most serious drug-induced bleeding complications (Table 62-1).[48,49] More recently, antiplatelet drug therapy further has complicated perioperative management (Table 62-2).[49-52] Unfractionated heparin comprises a heterogeneous mixture of membrane-associated glycosaminoglycans derived from either bovine or porcine mucosal tissues. Specificity and potency of unfractionated heparin varies by molecular weight, which ranges between 5000 and 30,000 daltons.[35] Heparin derives its anticoagulant effect by interacting with plasma antithrombin, which in turn inhibits serine proteases participating in plasma-mediated hemostasis.[34] The half-life of heparin is 1 to 2 hours and varies directly with total dose. Heparin is cleared from the circulation both renally and hepatically. Most often, heparin's anticoagulant effect is monitored using the aPTT with a target prolongation of 1.5 to 2 times control, commonly used for treatment of venous thrombosis.[53] At heparin concentrations exceeding measurement limits of the aPTT, such as during cardiopulmonary bypass or interventional cardiovascular procedures, the activated clotting time (ACT) provides an alternative, albeit less sensitive, measure of heparin anticoagulation.[54] Heparin's anticoagulant effect is rapidly reversible by protamine administration.[55]

More recently, low-molecular-weight heparins (LMWHs) have gained favor as a result of reduced dosing frequency and the lack of need for monitoring. Owing to shorter saccharide chain lengths, LMWHs exhibit reduced inhibitory activity toward thrombin while retaining factor Xa inhibitory activity.[56] Theoretically, LMWHs may be associated with reduced bleeding tendencies. Regardless, LMWHs have a more predictable pharmacokinetic response, fewer effects on platelet function, and a reduced risk for heparin-induced thrombocytopenia (HIT). Although monitoring of LMWHs is not performed routinely, the PT and aPTT most often are unaffected, necessitating measurement of anti–factor Xa activity. Furthermore, should rapid

TABLE 62-1 ANTICOAGULANT AGENTS

Drug	Site of Action	Route	Plasma Half-life	Excretion	Antidote	Stop Before Procedure	Prolongation of PT/aPTT
Unfractionated heparin	IIa/Xa	IV/subcutaneous	1.5 hr	Hepatic	Protamine	6 hr	No/Yes
LMWH	Xa	Subcutaneous	4.5 hr	Renal	Protamine (partial reversal)	12-24 hr	No/No
Streptokinase	Plg	IV	23 min	Hepatic	Antifibrinolytics	3 hr	Yes/Yes
t-PA	Plg	IV	<5 min	Hepatic	Antifibrinolytics	1 hr	Yes/Yes
Coumarin	Vitamin K–dependent factors	Oral	2-4 days	Hepatic	Vitamin K rfVIIa PCCs Plasma	2-4 days	Yes/No
Fondaparinux	Xa	SC	14-17 hr	Renal	None	3 days*	No/No
Bivalirudin	IIa	IV	25 min	Hepatic	None	3 hr	Yes/Yes
Argatroban	IIa	IV	45 min	Hepatic	None	4-6 hr	†Yes/Yes
Lepirudin/ Desirudin	IIa	IV	1.5 hr	Renal	PMMA, dialysis	8-10 hr*	†Yes/Yes
Rivaroxaban	Xa	Oral	9-13 hr	Renal	None	24-48 hr*	Yes/Yes
Apixaban	Xa	Oral	9-14 hr	Hepatic	None	26-30+ hr*	Yes/Yes
Dabigatran	IIa	Oral	14-17 hr	Renal	None	±5* days	Yes/Yes

Data from Roberts HR, Monroe DM, Escobar MA: Current concepts of hemostasis: implications for therapy, *Anesthesiology* 100:722-730, 2004, with permission.
HIT, Heparin-induced thrombocytopenia; *IIa,* thrombin; *IV,* intravenous; *LMWH,* low-molecular-weight heparin; *PCCs,* prothrombin complex concentrates; *Plg,* plasminogen; *PMMA,* polymethyl methylacrylate; *rFVIIa,* recombinant factor VIIa; *t-PA,* tissue plasminogen activator.
*Limited data regarding safe interval (assumes prophylactic dosage regimen).
†Argatroban and hirudins may increase the prothrombin time by several seconds.

TABLE 62-2 ANTIPLATELET AGENTS

Drug	Site of Action	Route	Plasma Half-life	Metabolism	Antidote	Stop Before Procedure	Prolongation of PT/aPTT
Aspirin	COX 1-2	Oral	20 min	Hepatic	None	7 days	No/No
Dipyridamole	Adenosine	Oral	40 min	Hepatic	None	24 hr	No/No
Clopidogrel	ADP	Oral	7 hr	Hepatic	None	7 days	No/No
Prasugrel	ADP	Oral	7 hr	Serum/hepatic	None	7-10 days	No/No
Ticlopidine	ADP	Oral	4 days	Hepatic	None	12-14 days	No/No
Abciximab	GPIIb-IIIa	IV	30 min	Renal	None	48-72 hr	No/No
Eptifibatide	GPIIb-IIIa	IV	2.5 hr	Renal	None	24 hr	No/No
Tirofiban	GPIIb-IIIa	IV	2 hr	Renal	Hemodialysis	24 hr	No/No

Data from Roberts HR, Monroe DM, Escobar MA: Current concepts of hemostasis: implications for therapy, *Anesthesiology* 100:722-730, 2004, with permission.
ADP, Adenosine diphosphate; *COX,* cyclooxygenase diphosphate; *IV,* intravenous; *GP,* glycoprotein.

reversal of LMWH prove necessary, protamine is only partially effective.[57]

Oral anticoagulant therapy in the form of coumarin derivatives, interferes with hepatic synthesis of vitamin K–dependent coagulation factors—factors II, VII, IX, X, protein C, and protein S.[58] Specifically, coumarin inhibits carboxylation of glutamic acid residues essential for anchoring coagulation factor activation complexes to phospholipid membranes. Coumarin therapy is monitored using the international normalized ratio (INR) system derived from the PT. Generally, an INR of 2 to 3 is considered reflective of adequate anticoagulation.[53] In most cases, excessive coumarin anticoagulation is managed by withholding drug administration. However, given a half-life of 2 to 4 days, more rapid reversal in perioperative settings may be needed. Vitamin K administered orally or parentally in doses of 1 to 2 mg reverses coumarin anticoagulation.[58] More rapid reversal may be achieved by administration of plasma or prothrombin complex concentrates.[59] Recombinant factor VIIa also has proved effective at reversing coumarin-associated bleeding.

Despite relatively short half-lives and increasing fibrin specificity, fibrinolytic drug administration continues to be associated with significant bleeding potential. Bleeding after fibrinolytic drugs proves multifactorial resulting from proteolytic degradation of fibrin and fibrinogen, proteolysis of cofactors V and VIII, and digestion of platelet glycoprotein surface receptors.[29] In addition, both fibrin and fibrinogen degradation fragments impair platelet function and inhibit assembly of fibrin monomers into strands. Once the fibrinolytic agent is cleared from plasma, antifibrinolytic drugs prove of limited benefit. Therapy must rely on selective repletion of platelet and plasma protein constituents. In many cases, cryoprecipitate or fibrinogen concentrate will be administered to replace fibrinogen and platelet infusions will be needed to compensate for qualitative platelet dysfunction. Plasma infusions may be required to replete plasma coagulation factors, particularly cofactors V and VIII.

Liver Disease

Hemostatic defects associated with hepatic failure prove complex and multifactorial. Severe liver disease impairs synthesis of coagulation factors, impedes clearance of activated clotting and fibrinolytic proteins, and produces quantitative and qualitative platelet dysfunction. Laboratory findings commonly associated with liver disease include a prolonged PT, possible prolongation of the aPTT, and thrombocytopenia.[60] Prolongation of bleeding time reflects qualitative defects in platelet adhesion and aggregation. Treatment of bleeding in the setting of liver disease most often is based on laboratory abnormalities. Plasma and platelets frequently are administered for acute bleeding. Low fibrinogen concentrations may necessitate administration of cryoprecipitate or fibrinogen concentrate. In addition, low-grade fibrinolysis may benefit from antifibrinolytic drug administration in select settings.

Renal Disease

Platelet dysfunction commonly occurs in association with chronic renal failure, as reflected by a prolonged bleeding time and propensity for bleeding associated with surgery or trauma. Underlying mechanisms appear multifactorial and may include accumulation of guanidinosuccinic acid and NO in uremic plasma.[61] In addition, red blood cell (RBC) concentration has been speculated to play a role as correction of anemia results in shortened bleeding times, presumably related to the role of RBCs in causing platelet margination along the vessel wall under laminar flow conditions.[28] Both dialysis and correction of anemia have been reported to shorten bleeding times in patients with chronic renal failure. Traditionally, cryoprecipitate administration occurs in this setting; however, desmopressin 0.3 μg/kg and conjugated estrogens similarly may shorten bleeding times.[43] Risks associated with these therapies, and the predictive value of bleeding time for subsequent hemorrhage, remain unclear.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) comprises a pathophysiologic hemostatic response to tissue factor/factor VIIa complex exposure and activation of the extrinsic pathway of coagulation. Numerous underlying disorders may precipitate DIC, including trauma, amniotic fluid embolus, malignancy, sepsis, or incompatible blood transfusions.[62] Most often, DIC presents clinically as a diffuse bleeding disorder associated with consumption of coagulation factors and platelets during widespread microvascular thrombotic activity. Underlying fibrinolysis, providing a counterregulatory mechanism to maintain vascular integrity, proves common as well. Laboratory findings typical of DIC include reductions in platelet count; prolongation of the PT, aPTT, and thrombin time (TT); and elevated concentrations of soluble fibrin and fibrin(ogen) degradation products. Chronic DIC states have been identified with relatively normal screening tests of coagulation accompanied by elevated concentrations of soluble fibrin and fibrin(ogen) degradation products.[63] Management of DIC requires alleviating the underlying condition precipitating hemostatic activation. Otherwise, treatment includes selective blood component transfusions to replete coagulation factors and platelets consumed in the process. Antifibrinolytic therapy generally is contraindicated in DIC owing to potential for catastrophic thrombotic complications.

PROTHROMBOTIC STATES

Thrombophilia, a propensity for thrombotic events, most often manifests clinically in the form of venous thrombosis (frequently deep venous thrombosis of the lower extremity).[64] As with bleeding disorders, thrombophilia may result from inherited or acquired conditions (Box 62-1). In the majority of cases, a precipitating event may be identified.[65] For example, thrombotic complications often occur after surgery, during pregnancy, and in association with obesity or underlying malignancy.[66] Random screening of asymptomatic patients for thrombotic risk has not proved cost effective or clinically efficacious.[67,68] As with bleeding disorders, a careful history focusing on prior thrombotic events, family history of thrombosis, and concurrent drug therapy offers greater predictive value than random screening.

BOX 62-1 ***Hypercoagulable States and Risk for Perioperative Thrombosis***

High Risk

Heparin-induced thrombocytopenia
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Antiphospholipid antibody syndrome

Moderate Risk

Factor V Leiden genetic polymorphism
Prothrombin G20210A genetic polymorphism
Hyperhomocysteinemia
Dysfibrinogenemia
Postoperative prothrombotic state
Malignancy
Immobilization

Common Inherited Thrombotic Disorders

Although understanding of thrombotic disorders from a biochemical and molecular level remains limited at present, careful testing may identify an underlying heritable thrombotic predisposition in as many as 50% of patients with venous thromboembolism.[69] Relatively common inherited conditions underlying prothrombotic tendencies include single point mutations in genes for factor V (factor V Leiden) or prothrombin (prothrombin G20210A). In the case of the factor V Leiden mutation, the essential cofactor Va acquires resistance to degradation by protein C.[70] This simple alteration in balance between hemostasis and the protein C counterregulatory system induces a prothrombotic tendency present in approximately 5% of the population. In the case of the prothrombin gene mutation, increased prothrombin concentrations in plasma again generate a hypercoagulable state. Less common inherited forms of thrombophilia include deficiencies of antithrombin, protein C, and protein S.[34] Inherited forms of thrombophilia are characterized by highly variable penetrance affected by blood type, sex, and other confounding variables. In the absence of coexisting precipitating conditions, absolute thrombotic risk secondary to a heritable thrombophilia proves limited.[71] In the presence of a family history or test abnormality suggesting thrombophilia with no history of thrombosis, risks associated with long-term preventive anticoagulation may outweigh potential benefits. After a thrombotic complication, however, these patients most often are managed with life-long anticoagulation.

COMMON ACQUIRED THROMBOTIC DISORDERS

Antiphospholipid Syndrome

Antiphospholipid syndrome describes an acquired autoimmune disorder characterized by venous or arterial thromboses, or both, and recurrent pregnancy loss. This syndrome may occur secondarily to autoimmune disorders such as systemic lupus erythematosus or rheumatoid arthritis, or it may occur in isolation. Characteristically, antiphospholipid syndrome results in mild prolongation of the aPTT and positive testing for lupus anticoagulant or anticardiolipin antibodies.[72] Despite the prolonged aPTT, antiphospholipid syndrome poses no increased bleeding risk but rather increases the potential for thrombosis. Antibodies associated with antiphospholipid syndrome interfere with phospholipids common to many laboratory-based tests of coagulation. Isolated prolongation of an aPTT in a preoperative patient merits consideration of the diagnosis of antiphospholipid syndrome. Patients with this syndrome who have experienced a thrombotic complication are at increased risk for recurrent thrombosis and most often are managed by life-long anticoagulation.[73]

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia describes an autoimmune-mediated drug reaction occurring in as many as 5% of patients receiving heparin therapy. As opposed to other drug-induced thrombocytopenias, HIT results in platelet activation and potential for venous and arterial thromboses.[74,75] Evidence suggests that HIT is mediated by immune complexes (composed of immunoglobulin G [IgG] antibody, platelet factor 4 [PF4], and heparin) that bind platelet Fcγ receptors to activate platelets. Anti-PF4/heparin antibodies may "activate" vascular endothelium, monocytes, and macrophages by up-regulating tissue factor expression (Fig. 62-4). Patients developing HIT during heparin therapy experience substantially increased risk for thrombosis (odds ratio 20:40, absolute risk 30% to 75%).[74,75]

In most cases, HIT manifests clinically as thrombocytopenia occurring 5 to 14 days after initiating heparin therapy. However, with prior heparin exposure, thrombocytopenia or thrombosis may occur within 1 day. In some reported cases, thrombosis occurred simultaneously with thrombocytopenia, providing no warning. Although HIT remains a clinical diagnosis, laboratory testing provides confirmatory evidence. Both functional (i.e., serotonin platelet release assays or heparin-induced platelet aggregation) and quantitative (i.e., solid-phase enzyme-linked immunosorbent assays [ELISA]) tests for PF4/heparin immune complexes prove beneficial.[75] Recent evidence suggests that PF4/heparin antibodies alone, in the absence of thrombocytopenia or thrombosis, may predict adverse outcomes.[76,77]

A diagnosis of HIT should be entertained for any patient experiencing thrombosis or thrombocytopenia (absolute or relative [≥50% reduction in platelet count]) during or after heparin administration. In cases in which HIT is suspected, heparin must be discontinued immediately (i.e., including unfractionated heparin, heparin-bonded catheters, heparin flushes, LMWH). Alternative nonheparin anticoagulation must be administered concurrently. In most cases, a direct thrombin inhibitor (i.e., bivalirudin, lepirudin, argatroban) is substituted for heparin until adequate prolongation of the INR can be achieved with warfarin.[78,79] Typically, PF4/heparin immune complexes clear from the circulation within 3 months. If possible, patients experiencing HIT should avoid future exposure to unfractionated heparin; however, several reports describe subsequent limited perioperative reexposure to

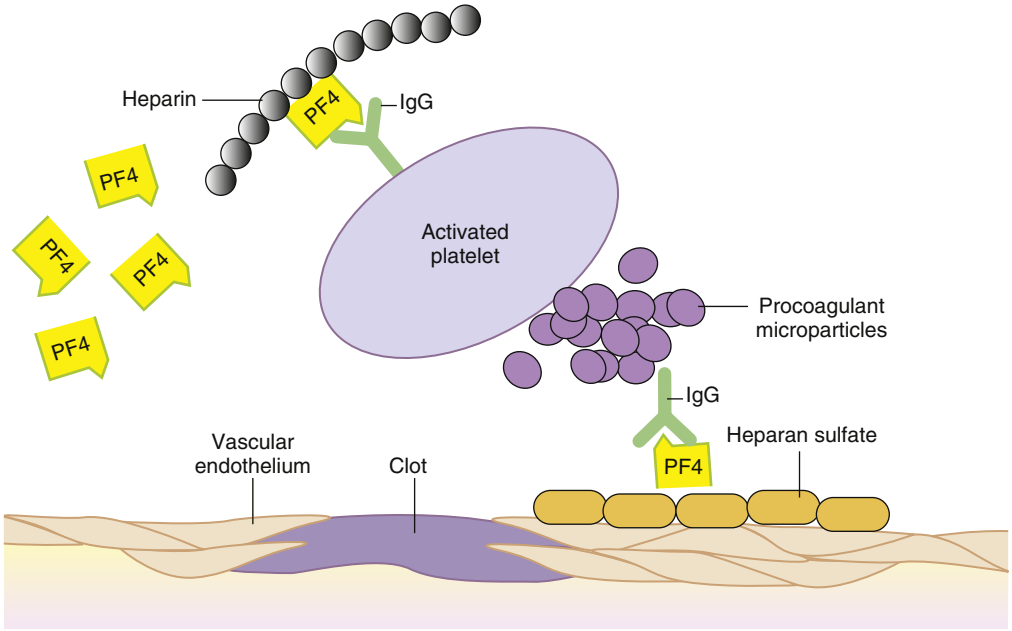


Figure 62-4. Mechanisms underlying thrombosis in heparin-induced thrombocytopenia (HIT). Immune complexes composed of heparin, platelet factor 4 (*PF4*), and antibodies bind to platelet surface Fcγ receptors to activate platelets. PF4/heparin immune complexes further activate vascular endothelium, monocytes, and macrophages to increase tissue factor expression. *IgG,* Immunoglobulin G. *(From Slaughter TF, Greenberg CS: Heparin-associated thrombocytopenia and thrombosis: Implications for perioperative management,* Anesthesiology *87:669, 1997, with permission.)*

unfractionated heparin after laboratory testing to ensure absence of PF4/heparin immune complexes.

MONITORING COAGULATION

Traditionally, perioperative coagulation monitoring has focused on (1) preoperative testing to identify patients at increased risk for perioperative bleeding and (2) intraoperative monitoring of heparin therapy during cardiac and vascular surgery. As discussed previously, routine preoperative coagulation testing lacks either predictive value or cost efficacy.[80] However, in patients with a history suggestive of a bleeding disorder or whose surgery may be associated with a high incidence of bleeding or coagulopathy, baseline preoperative coagulation testing may be advisable.

Given the widely acknowledged pharmacokinetic and pharmacodynamic response to heparin, monitoring anticoagulation during cardiac and vascular surgery remains necessary. Patient-specific factors affecting response to heparin include age, weight, intravascular volume, and plasma and membrane concentrations of antithrombin, heparin cofactor II, PF4, and other heparin-binding proteins. Therefore, patients experience widely divergent anticoagulant responses to identical weight-based doses of heparin. Regardless, monitoring of heparin anticoagulation must be performed if only to prevent the rare, but potentially lethal, complication resulting from inadvertent failure to administer heparin before cardiopulmonary bypass or vascular surgery.

The ideal test of perioperative coagulation would prove simple to perform, accurate, reproducible, diagnostically specific, and cost effective. No current coagulation monitor meets these expectations; however, integrating results from multiple forms of monitoring may provide valuable diagnostic insight into perioperative coagulopathies.

COMMON LABORATORY-BASED MEASURES OF COAGULATION

Activated Partial Thromboplastin Time

The aPTT assesses integrity of the intrinsic and common pathways of plasma-mediated hemostasis. It measures the time required in seconds for clot formation to occur after mixing a sample of patient plasma with phospholipid, calcium, and an activator of the intrinsic pathway of coagulation (i.e., celite, kaolin, silica, or ellagic acid). In most cases, coagulation factor deficiencies are detectable at factor concentrations below 30% to 40% of normal; however, aPTT reagents vary in sensitivity to factor concentrations, necessitating institutional specific determination of "normal" ranges.[81] Prolongation of the aPTT is evaluated further with mixing studies to determine whether delayed clot formation is attributable to a coagulation factor deficiency or an inhibitor (i.e., heparin, antiphospholipid antibody, fibrin split products). The mixing study is performed by mixing the patient's plasma sample with "normal" donor plasma. In the case of a coagulation factor deficiency, time to clot formation will correct and sequential assays for specific coagulation factor concentrations allow for identification of the deficiency. A common means of confirming heparin prolongation of the aPTT is to perform a thrombin clotting time (TCT) test. In this test, the patient's citrate-containing plasma sample is mixed with thrombin and time to clot formation is measured in seconds.[39] The most common mechanism underlying prolongation of the TCT is presence of heparin or a direct thrombin inhibitor anticoagulant; however, dysfibrinogenemia or fibrin(ogen) degradation products also may impair clot formation in this setting.

Prothrombin Time

The PT assesses integrity of the extrinsic and common pathways of plasma-mediated hemostasis. It measures

time required in seconds for clot formation to occur after mixing a sample of patient plasma with tissue factor (thromboplastin) and calcium. As with the aPTT, thromboplastin test reagents vary in sensitivity, limiting the ability to compare results between laboratories. Given the importance of monitoring PT results for patients on long-term warfarin therapy, the INR was introduced as a means of normalizing PT results among different laboratories.[81] Thromboplastin reagents are tested against an international recombinant standard and assigned an international sensitivity index (ISI) based on results. The INR subsequently is calculated as INR = (patient PT/standard PT)ISI, in which the standard PT represents the geometric mean of multiple normal samples from the testing laboratory. Institution of the INR substantially reduced interlaboratory variations in the PT. As with the aPTT, prolongation of the PT is assessed further with mixing studies.

Platelet Count and Bleeding Time

The platelet count remains a standard component in screening for coagulation abnormalities. Automated platelet counts are performed in bulk using either optical-based or impedance-based measurements. Recommendations regarding optimal platelet counts prove somewhat arbitrary; however, platelet counts exceeding 100,000/μL commonly are associated with normal hemostasis. Abnormally low platelet counts merit further assessment, including a visual platelet count using a blood smear. Sample hemodilution and platelet clumping are common causes for false low platelet counts. Ethylenediaminetetraacetic acid (EDTA)-induced platelet clumping, a common artifact underlying thrombocytopenia, may be identified by manually counting platelets or by substituting a citrate anticoagulant (as opposed to EDTA).

With growth in point-of-care platelet function monitors the bleeding time has declined in popularity; however, under controlled conditions the bleeding time may provide useful information regarding primary hemostasis. Employing a commercial template cutting device and a sphygmomanometer adjusted to 40 mm Hg venous pressure, bleeding times of 2 to 10 minutes on the anterior forearm are considered normal. Limitations of the bleeding time include poor reproducibility, time needed to perform the test, and potential for scarring. Furthermore, the bleeding time is affected by numerous confounding variables, including skin temperature, skin thickness, age, ethnicity, anatomic test location, and a host of other factors.[82] In general, the bleeding time has not proved predictive of bleeding and for that reason its use as a preoperative screening test to assess bleeding risk is not recommended.

COMMON POINT-OF-CARE MEASURES OF COAGULATION

Although laboratory-based measures of coagulation remain the mainstay of preoperative coagulation testing, increasing availability of sensitive and specific point-of-care coagulation monitoring may soon offer opportunities to direct blood component and hemostatic drug therapy more specifically without delays inherent to standard laboratory testing. Commercially available point-of-care monitors applicable in the perioperative setting may be considered in four broad categories: (1) functional measures of coagulation or assays that measure the intrinsic ability of blood to generate clot, (2) heparin concentration monitors, (3) viscoelastic measures of coagulation, and (4) platelet function monitors.

Functional Measures of Coagulation

The ACT, described by Hattersley in 1966 as a variation of the Lee-White whole blood clotting time, employs a contact activation initiator, typically celite (diatomaceous earth) or kaolin, to accelerate clot formation and reduce time for assay completion. Kaolin is recommended for use in patients receiving the antifibrinolytic drug aprotinin because celite ACTs in this setting are subject to artifactual prolongation.[83] Failure to appreciate this drug-mediated effect may result in inadequate heparin administration if using celite ACT measurements with aprotinin. Whether high plasma concentrations of aprotinin affect the kaolin ACT remains unclear.

Current commercial ACT monitors automate clot detection. One of the more widely available ACT monitors uses a glass test tube containing a small magnet (Hemochron Response Whole Blood Coagulation System, ITC, Edison, NJ). After adding sample blood, the tube is placed into the analyzer and the tube is rotated slowly at 37° C, allowing the magnet to maintain contact with a proximity detection switch. As fibrin clot forms, the magnet becomes entrapped and dislodged from the detection switch, thereby triggering an alarm to signal completion of the ACT. Another ACT device uses a "plumb bob" flag assembly that is raised and released repeatedly to settle in the sample vial containing blood and contact activator (Hepcon HMS Plus, Medtronic, Minneapolis, Minn.). With clot formation, the descent rate of the flag through the blood sample slows, triggers an optical detector, and sets off an alarm to signal completion of the ACT.

The ACT in normal individuals is 107 ± 13 seconds (mean ± SD). However, the time at which a patient's baseline ACT is measured influences the result.[83] After surgical incision, baseline ACT may decrease. Because the ACT measures clot formation by way of intrinsic and common pathways, heparin and other anticoagulants prolong time to clot formation. The ACT proves somewhat resistant to platelet dysfunction and thrombocytopenia.

ACT testing remains a popular perioperative coagulation monitor because of its simplicity, low cost, and linear operating response at high heparin concentrations. Limitations of ACT monitoring include lack of sensitivity at low heparin concentrations and poor reproducibility.[83] ACT testing performed with and without added heparinase improves sensitivity for detecting low heparin concentrations. Further limitations of the ACT include artifactual prolongation of results with hemodilution or hypothermia and the fact that ACT values beyond 600 seconds exceed the linear response range for the assay. Duplicate measurements improve results; however, newer electrochemically based ACT analyzers (i-STAT, Abbott, Princeton, NJ) improve reproducibility such that single ACT determinations may prove adequate.

The high-dose thrombin time (HiTT) (ITC) provides an alternative functional measure of heparin anticoagulation. Primarily employed in cardiac surgical settings, the HiTT assay contains high thrombin concentrations to cleave fibrinogen directly and generate fibrin clot.[84] Given excess thrombin concentrations, clot formation occurs independently of plasma coagulation factors other than fibrinogen. As a result, HiTT is prolonged by heparin (or other thrombin inhibitors), extreme degrees of hypofibrinogenemia or dysfibrinogenemia, and high concentrations of fibrin split products (as occur with fibrinolysis). During most surgical procedures requiring heparin administration, HiTT prolongation will correlate with heparin anticoagulant effect.

Heparin Concentration Measurement

Protamine titration remains the most popular point-of-care method for determining heparin concentration in perioperative settings. Protamine, a strongly basic polycationic protein, directly inhibits heparin in a stoichiometric manner. In other words, 1 mg of protamine will inhibit 1 mg (~100 units) of heparin, thereby forming the basis for protamine titration as a measure of heparin concentration. As increasing concentrations of protamine are added to a sample of heparin-containing blood, time to clot formation decreases until the point at which the protamine concentration exceeds heparin concentration to delay clot formation. If a series of blood samples with incremental doses of protamine are analyzed, the sample in which the protamine and heparin concentrations are most closely matched will clot first. In this manner, protamine titration methodology allows for heparin concentration estimation. Assuming that the heparin-protamine titration curve for an individual patient remains constant throughout the operative period, protamine titration methods may estimate heparin doses required to achieve a desired plasma heparin concentration or the protamine dose needed to reverse a given heparin concentration in blood.[54] Current point-of-care heparin concentration monitoring employs automated measurement techniques (Hepcon HMS Plus, Medtronic). Advantages of heparin concentration measurement include sensitivity for low heparin concentrations as well as relative insensitivity to hemodilution and hypothermia. In addition, heparin concentration measures are unaffected by aprotinin.

A major limitation of heparin concentration monitoring is failure to assess directly for an anticoagulant effect. To use an extreme example, consider a patient with a homozygous deficiency of antithrombin; in this setting, heparin concentration determination alone would fail to identify the lack of anticoagulant effect after heparin administration.

Viscoelastic Measures of Coagulation

Initially developed in the 1940s, viscoelastic measures of coagulation have undergone a resurgence in popularity. The unique aspect of viscoelastic monitors lies in their ability to measure in whole blood the entire spectrum of clot formation from early fibrin strand generation through clot retraction and eventual fibrinolysis. The early thromboelastograph (TEG) developed by Hartert in 1948 has evolved into two independent viscoelastic monitors: the modern TEG, or TEG 5000 Thromboelastograph Hemostasis Analyzer System (Haemoscope, Braintree, Mass.) and rotational thromboelastometry (ROTEM) (TEM Systems, Durham, NC). In the case of the thromboelastograph (TEG 5000), a small (0.35-mL) sample of whole blood is placed into a disposable cuvette within the instrument. The cuvette is maintained at a temperature of 37° C and continuously rotates around an axis of approximately 5 degrees. A sensor "piston" attached by a torsion wire to an electronic recorder is lowered into the blood within the cuvette. Addition of an activator, most often kaolin or celite, initiates clot formation. As the fibrin-platelet plug evolves, the piston becomes enmeshed within the clot, transferring rotation of the cuvette to the piston, torsion wire, and electronic recorder.[85]

Although variables derived from the TEG tracing do not coincide directly with laboratory-based tests of coagulation, the TEG depicts characteristic abnormalities in clot formation and fibrinolysis. Various parameters describing clot formation and lysis are identified and measured by the TEG. For example, the R value (reaction time) measures time to initial clot formation (normal, 7.5 to 15 minutes). Comparable to the whole blood clotting time, addition of a contact activator (i.e., celite or kaolin) to the sample cuvette reduces time to results. The R value may be prolonged by a deficiency of one or more plasma coagulation factors or inhibitors such as heparin. Maximum amplitude (MA) provides a measure of clot strength and may be decreased by either qualitative or quantitative platelet dysfunction or decreased fibrinogen concentration. Normal MA is 50 to 60 mm. The α angle and K (BiKoatugulierung or coagulation) values measure rate of clot formation and may be prolonged by any variable slowing clot generation such as a plasma coagulation factor deficiency or heparin anticoagulation. Modification of clotting activators may be incorporated to assess platelet or fibrin contributions to clot strength.[86] In a somewhat analogous manner, ROTEM measures viscoelastic changes in a sample of whole blood subjected to activation of coagulation. Specific activators differ from that of the TEG 5000 with resulting quantitative measures termed (1) coagulation time (CT; seconds), (2) α angle (clot formation time; seconds), (3) maximal clot firmness (MCF; millimeter), and (4) lysis time (LT; second).

The Sonoclot Analyzer (Sienco, Arvada, Colo.) provides an alternative viscoelastic measure of coagulation. In contrast to thromboelastography and ROTEM, the Sonoclot Analyzer immerses a rapidly vibrating probe into a 0.4-mL sample of blood. As clot formation proceeds, impedance to probe movement through the blood increases to generate an electrical signal and characteristic clot signature. The analyzer signature may be used to derive the ACT and to provide information regarding clot strength and presence of fibrinolysis.

Viscoelastic monitors generate characteristic diagrams by translating mechanical resistance to sensor movement within a sample of whole blood to an electronic waveform subject to quantitative analysis. One of the more common applications for viscoelastic monitoring has been real-time detection of excess fibrinolysis during liver transplantation or cardiac surgery. Evidence suggests that viscoelastic monitoring may prove beneficial in

differentiating surgically related bleeding from that due to a coagulopathy. When used as one component of a diagnostic algorithm, both thromboelastography and ROTEM have been demonstrated to reduce blood administration. More widespread application of viscoelastic monitoring has been hindered by lack of specificity associated with abnormal findings and qualitative assay interpretation.[86] Digital automation of these instruments has simplified interpretation and improved reproducibility.

PLATELET FUNCTION MONITORS

Assessment of platelet function has proved challenging for several reasons. Historically, tests of platelet function have proved costly, time consuming, and technically demanding. Platelet dysfunction may occur as a result of diverse inherited or acquired disorders affecting surface receptors involved in adhesion or aggregation, storage granules, internal activation pathways, phospholipid membranes, or other mechanisms.[51] Lack of standardized quality controls necessitates use of local donor blood to establish normal control ranges. Furthermore, even established tests such as platelet aggregation lack performance standardization, resulting in widely varying results across laboratories. Complicating assessment further is the fact that platelets are highly susceptible to activation or desensitization during sample collection, transport, storage, and processing.

Although viscoelastic measures of coagulation (i.e., TEG 5000 or ROTEM) may detect platelet dysfunction, sensitivity and specificity prove limited. Incorporation of a platelet mapping assay into thromboelastography provides a method for viscoelastic measurement of drug-induced platelet inhibition with reasonable correlation to optical aggregometry.[85] The standard laboratory-based method for identifying qualitative platelet dysfunction remains optical aggregometry performed using specific platelet agonists and samples of platelet-rich plasma. Flow cytometry employing fluorescent-labeled antibodies provides another sensitive method for quantitating platelet activation, responsiveness, and surface receptor availability.[87] Despite representing standards of care, these measures remain technically challenging, costly, and time-consuming laboratory-based assays.

Fortunately, an increasing array of platelet function assays specifically designed as point-of-care instruments are available.[88,89] As a measure of primary hemostasis, the PFA-100 (Platelet Function Analyzer, Siemens, Tarrytown, NY) increasingly has replaced the bleeding time in assessment of primary hemostasis. Unique among both laboratory-based and point-of-care platelet function monitors, the PFA-100 incorporates high-shear conditions to simulate small vessel injury in the presence of either ADP or epinephrine, both potent platelet activators.[90] Time to clot–mediated aperture occlusion is reported as closure time. The PFA-100 has proved effective in detecting von Willebrand disease and aspirin-mediated platelet dysfunction. This instrument, as a component of a standardized screening protocol, reduces time to identify and classify platelet dysfunction. Limitations of the PFA-100 include interference by thrombocytopenia and hemodilution.

The HemoSTATUS (Medtronic) platelet function test exploits the ability of platelet activating factor (PAF) to accelerate clot formation of the kaolin-activated ACT. HemoSTATUS testing is performed on the Medtronic HMS Plus coagulation analyzer employing a six-channel kaolin ACT cartridge preloaded with serially increasing concentrations of PAF. A clot ratio is determined for each individual patient assay based on the ratio of the PAF-accelerated ACT to the standard ACT. An individual patient's clot ratio is compared with a maximal clot ratio derived from normal volunteers to provide a relative measure of platelet function. In the presence of platelet dysfunction, higher concentrations of PAF are required to achieve a comparable PAF-activated ACT. In cardiac surgery, investigators demonstrated a relationship between platelet dysfunction and postoperative bleeding.[83] Furthermore, the maximal clot ratio as determined by HemoSTATUS improved after desmopressin or platelet administration. Other investigators, however, failed to identify a relationship between platelet dysfunction as measured by HemoSTATUS and postoperative bleeding.

The VerifyNow System (formerly known as the Ultegra Rapid Platelet Function Analyzer, Accumetrics, San Diego, Calif.) is an automated turbidimetric whole blood platelet function assay that assesses ability of activated platelets to bind fibrinogen-coated polystyrene beads. On addition of the whole blood test sample, thrombin receptor activating peptide directly activates platelets within the sample to stimulate glycoprotein IIb/IIIa platelet surface receptor expression. As activated platelets bind and aggregate fibrinogen-coated beads, light transmission through the sample increases to generate a signal. Although the VerifyNow System is simple to operate and provides a rapid bedside measure of platelet function, a baseline reference measurement is suggested for each patient to calculate the extent of subsequent changes in platelet function.[88] Potential applications for this methodology in the perioperative setting remain unclear.

Plateletworks (Helena Laboratories, Beaumont, Tex.) employs a hemocytometer to perform automated platelet counts on whole blood samples collected in the presence and absence of platelet-stimulating agonists such as collagen or ADP. The difference in platelet counts before and after agonist addition provides a direct measure of platelet aggregation (i.e., platelet responsiveness) and is reported as "% aggregation." Preliminary investigations demonstrated reasonable correlations between platelet counts attained with the Plateletworks monitor and laboratory-based instruments.[88] In addition, the Plateletworks assay proved effective in identifying platelet dysfunction in the setting of glycoprotein IIb/IIIa antagonists and appeared to correlate relatively well with laboratory-based measures of platelet aggregation.

Employing a sample of whole blood, the Hemostasis Analysis System (Hemodyne, Bethesda, Md.) measures platelet contractile force, the force produced by platelets during clot retraction, and clot elastic modulus, a measure of clot rigidity. In preliminary investigations, platelet contractile force was reduced after cardiopulmonary bypass and modestly correlated with perioperative blood loss.

Advances in our understanding of hemostasis and thrombosis at the molecular level have contributed directly to recent biotechnologic innovations in

point-of-care testing. Further advances in point-of-care coagulation monitoring offer the opportunity for clinicians to make informed decisions about transfusion therapy and hemostatic drug administration to minimize perioperative bleeding. In considering any point-of-care coagulation testing, it must be recognized that results will not necessarily mirror those reported from laboratory-based testing. Reagent sensitivities vary across manufacturers and even one lot of reagent to another. In addition, point-of-care testing typically relies on whole blood samples for testing as opposed to laboratory-based testing using plasma or processed platelets. A final consideration for which point-of-care platelet function testing provides a particularly relevant example is that monitors from different manufacturers measure differing aspects of platelet-mediated or plasma-mediated hemostasis. In the case of platelet function monitors, a dozen instruments purport to measure platelet function. However, using different instruments results may vary from "severe" platelet dysfunction to "no platelet dysfunction" in a single sample of blood. Before adopting any point-of-care monitoring, an understanding of the quality assurance requirements, test methodology, and concomitant strengths and weaknesses will prove essential to inform patient care.

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Chapter 63

Patient Blood Management: Autologous Blood Procurement, Recombinant Factor VIIa Therapy, and Blood Utilization

LAWRENCE T. GOODNOUGH • TERRI G. MONK

Key Points

- The two primary reasons for employing autologous transfusion are avoidance of complications associated with allogeneic transfusion and conservation of blood resources.
- The three types of autologous blood transfusion are preoperative autologous donation (PAD), acute normovolemic hemodilution (ANH), and intraoperative and postoperative blood recovery (salvage).
- PAD became accepted as a standard practice in certain elective surgical settings such as total joint replacement surgery, so that by 1992 more than 6% of the blood transfused in the United States was autologous. Subsequently, substantial improvements in blood safety were accompanied by a decline in PAD as well as an interest in ANH as an alternative, lower-cost strategy. The criteria for autologous donors are different from those for allogeneic donors. Transfusion service policies, implemented under the auspices of hospital transfusion committees, differ regarding collection and use of autologous blood with positive viral markers. It is common practice to exclude autologous blood reactive for hepatitis B surface antigen and hepatitis C and human immunodeficiency viruses because of patients' safety concerns related to wrong blood unit transfused to wrong patient (mistransfusion). Contraindications to autologous blood donation include evidence of infection and risk of bacteremia, scheduled surgery for correction of aortic stenosis, and unstable angina.
- The costs associated with PAD are higher than those associated with the collection of allogeneic blood.
- ANH is the removal of whole blood from a patient while restoring the circulating blood volume with an acellular fluid shortly before an anticipated significant surgical blood loss. The chief benefit of ANH is the reduction of red blood cell losses when whole blood is shed perioperatively at the lower hematocrit levels associated with ANH.
- The term *intraoperative blood collection* or *recovery* describes the technique of collecting and reinfusing blood lost by a patient during surgery. The oxygen transport properties of recovered red blood cells are equivalent to those of stored allogeneic red blood cells. The survival of recovered blood cells appears to be at least comparable to that of transfused allogeneic red blood cells.
- Postoperative blood collection denotes the recovery of blood from surgical drains followed by reinfusion, with or without processing. Postoperative autologous blood salvage and reinfusion are practiced widely but not uniformly.
- Recombinant factor VIIa (rfVIIa) has been approved for treatment of bleeding in patients with hemophilia and inhibitors to factors VIII or IX. Pharmacologic doses of rfVIIa enhance the thrombin generation on activated platelets and therefore may also be of benefit in providing hemostasis in other situations such as those characterized by consumptive coagulopathies or platelet conditions with impaired thrombin generation.
- Level I evidence and guidelines support restrictive transfusion practices. However, no one hemoglobin level should be used as a transfusion trigger, and transfusion decisions should be made for individual patients (see also Chapter 61).
- Bloodless medicine and surgery use a multidisciplinary team approach that incorporates anemia management, controlled hemostasis, autologous blood procurement, and pharmacologic alternatives to blood transfusion.

Blood management has been defined as "the appropriate use of blood and blood components, with a goal of minimizing their use."[1] This goal has been motivated historically by (1) known blood risks, (2) unknown blood risks, (3) preservation of the national blood inventory, and (4) constraints from escalating costs. Known risks of blood include transmissible infectious disease, transfusion reactions, and potential effects of immunomodulation (e.g., postoperative infection or tumor progression). Unknown risks include emerging pathogens transmissible by blood (e.g., new variant Creutzfeldt-Jakob disease and West Nile virus).[2,3] Several studies have linked allogeneic blood transfusions with unfavorable outcomes, including increased risk of mortality and various morbidities.[4] Blood management has been 1 of the 10 key advances in transfusion medicine since the 1960s.[5]

Patient blood management encompasses an evidence-based medical and surgical approach that is multidisciplinary (transfusion medicine specialists, surgeons, anesthesiologists, and critical care specialists) and multiprofessional (physicians, nurses, pump technologists, and pharmacists).[6] Preventive strategies are emphasized: to identify, evaluate, and manage anemia[7-9] (e.g., pharmacologic therapy[10] and reduced iatrogenic blood losses from diagnostic testing)[11]; to optimize hemostasis (e.g., pharmacologic therapy[12] and point-of-care testing[13]); and to establish decision thresholds (e.g., guidelines) for the appropriate administration of blood therapy.[14,15]

In the United States, The Joint Commission developed patient blood management performance measures and submitted these to the National Quality Forum for endorsement. The National Quality Forum did not endorse these submitted performance measures because of a lack of data on the outcomes proposed; as a result, these measures currently do not carry consequences if not met. Because these performance measures were process based rather than outcomes based, data on proposed outcomes are difficult to retrieve. The Joint Commission has placed these performance measures in their Topic Library, where they are to be used as additional patient safety activities and/or quality improvement projects by provider institutions as accreditation goals.[15] The principles of these performance indicators are summarized in Box 63-1.

BOX 63-1 *Patient Blood Management*

TJC Performance Measures	Principles
1. Preoperative Anemia Screening	A. Formulate a plan of proactive management for avoiding and controlling blood loss tailored to the clinical management of individual patients, including anticipated procedures.
2. Preoperative Blood Type and Antibody Screen (Blood Compatibility Testing)	B. Employ a multidisciplinary treatment approach to blood management using a combination of interventions (e.g., pharmacologic, therapy, point-of-care testing).
3. Transfusion Consent	C. Promptly investigate and treat anemia.
4. Blood Administration	D. Exercising clinical judgment, be prepared to modify routine practices (e.g., transfusion triggers) when appropriate.
5. RBC Transfusion Indication	E. Restrict blood drawing for unnecessary laboratory tests.
6. Plasma Transfusion Indication	F. Decrease or avoid the perioperative use of anticoagulants and antiplatelet agents.
7. Platelet Transfusion Indication	

RBC, Red blood cell; *TJC,* The Joint Commission.

AUTOLOGOUS BLOOD PROCUREMENT

The three types of autologous blood transfusion are preoperative autologous donation (PAD), acute normovolemic hemodilution (ANH), and intraoperative and postoperative blood recovery (blood salvage). The advantages, disadvantages, applications, and complications vary with the techniques used.

The two primary reasons for employing autologous transfusion are avoidance of complications associated with allogeneic transfusion and conservation of the national blood inventory. Patients with rare blood phenotypes or alloantibodies can also benefit from autologous transfusion because compatible allogeneic blood may not always be available.[16] Potential complications of allogeneic transfusion that can be eliminated or minimized when autologous blood is administered include acute and delayed hemolytic reactions, alloimmunization, allergic and febrile reactions, and transfusion-transmitted infectious diseases. Intraoperative blood recovery may be the only option for providing a sufficient volume of compatible blood when severe, rapid blood loss occurs. ANH provides the only practical source of fresh whole blood.

The role of autologous blood procurement in surgery is evolving, based on improved blood safety, increased blood costs, and emerging pharmacologic alternatives to blood transfusion.[17-19] PAD became accepted as a standard practice in certain elective surgical settings such as total joint replacement surgery; by 1992 more than 6% of the blood transfused in the United States was autologous.[20] Subsequently, substantial improvements in blood safety were accompanied by a decline in PAD, as well as an interest in ANH as an alternative strategy.[21] Nevertheless, public perception of blood safety and the reluctance to accept allogeneic blood transfusion in the elective transfusion setting,[22] along with possible future blood inventory shortages and the potential for new, emerging blood pathogens, continue to give autologous blood procurement strategies an important role in the surgical arena.

PREOPERATIVE BLOOD DONATION

Patient Selection

The criteria for autologous donors are not as stringent as are those for allogeneic donors. The AABB (formerly,

the American Association of Blood Banks) standards for blood banks and transfusion services require that the donor patient's hemoglobin be no less than 11 g/dL or the hematocrit be no less than 33% before each donation.[23] No age or weight limits exist, and patients may donate 10.5 mL/kg, in addition to testing samples. Donations may be scheduled more than once a week, but the last donation should occur no less than 72 hours before surgery, to allow time for restoration of intravascular volume and for transport and testing of the donated blood.

Transfusion service policies, implemented under the auspices of hospital transfusion committees, differ regarding collection and use of autologous blood with positive viral markers. Some hospitals exclude use of autologous blood reactive for hepatitis B surface antigen, hepatitis C virus, or human immunodeficiency virus (HIV) because of concerns for patients' safety related to a wrong blood unit transfused to the wrong patient (mistransfusion). Other hospitals accept and transfuse autologous blood with any positive viral markers because denying patients infected with HIV the opportunity to receive their own blood may have implications related to the Americans with Disabilities Act.[24]

Candidates for preoperative blood collection are patients scheduled for elective surgical procedures in which blood transfusion is likely. The most common surgical procedures for which autologous blood is predonated are total joint replacements.[25] For procedures that are unlikely to require transfusion (i.e., a maximal surgical blood ordering schedule [MSBOS] suggests that crossmatched blood should not be ordered),[26] the use of preoperative blood collection is not recommended. Autologous blood should not be collected for procedures that seldom (<10% of cases) require transfusion, such as cholecystectomy, herniorrhaphy, vaginal hysterectomy, and uncomplicated obstetric delivery.[27]

In special circumstances, preoperative autologous blood collection can be performed for patients who would not ordinarily be considered for autologous donation. Availability of medical support is important in assessing a patient's suitability. With appropriate volume modification, parental cooperation, and attention to preparation and reassurance, pediatric patients can participate in preoperative blood collection programs.[28] Patients with significant cardiac disease are considered poor risks for autologous blood donation. Despite reports of safety in small numbers of such patients who underwent autologous blood donation,[29] the risks associated with autologous blood donation[30] in these patients are greater than current estimated risks of allogeneic transfusion.[2,3] Box 63-2 summarizes the medical contraindications to a patient's participation in an autologous blood donation program.[31] The collection of autologous blood from women during routine pregnancy is unwarranted,[32] because blood is so seldom needed. PAD can be considered for women with alloantibodies to multiple or high-incidence antigens or with placenta previa or other conditions placing them at high risk for antepartum or intrapartum hemorrhage.[27] AABB standards no longer permit allogeneic transfusion of unused autologous units ("crossover") because autologous donors are not, in the strictest sense, volunteer donors.[23]

BOX 63-2 ***Contraindications to Participation in Autologous Blood Donation Programs***

1. Evidence of infection and risk of bacteremia
2. Scheduled surgery to correct aortic stenosis
3. Unstable angina
4. Active seizure disorder
5. Myocardial infarction or cerebrovascular accident within 6 months of donation
6. Significant cardiac or pulmonary disease in patients who have not yet been cleared for surgery by their treating physician
7. High-grade left main coronary artery disease
8. Cyanotic heart disease
9. Uncontrolled hypertension

Attempts to stratify patients into groups at high and low risk for needing transfusion based on the baseline level of hemoglobin and on the type of procedure show some promise. In a Canadian study using a point score system, 80% of patients undergoing orthopedic procedures were identified to be at low risk (<10%) for transfusion, and therefore autologous blood procurement for these patients would not be recommended.[33] However, one problem with algorithms that consider the estimated blood loss and preoperative hematocrit is that blood losses are difficult to measure[34] or predict because specific surgical procedures performed even by the same surgeon can be accompanied by a wide range of blood loss. Although autologous blood donation programs are popular with patients, the costs associated with autologous blood collection are higher than are those associated with allogeneic blood. The reduced risk of allogeneic blood transfusions has made PAD poorly cost effective.[35,36]

The Role of Aggressive Phlebotomy and the Use of Erythropoiesis-Stimulating Agents

The efficacy of PAD depends on the degree to which the patient's compensatory erythropoiesis increases the production of red blood cells (RBCs).[37] The endogenous erythropoietin response and compensatory erythropoiesis are suboptimal under "standard" conditions of 1 unit of blood donated weekly.[38] As shown in Table 63-1, weekly PAD is accompanied by an expansion in RBC volume of 11% (with no oral iron supplementation) to 19% (with oral iron supplementation), which is not sufficient to prevent increasing anemia in patients undergoing PAD. If the erythropoietic response to autologous blood phlebotomy does not maintain the patient's hematocrit level during the donation interval, the donation of autologous blood actually may be harmful by causing perioperative anemia and an increased likelihood of any blood transfusion.[37,38] A mathematic model has been published to demonstrate the relationships among anticipated surgical blood losses, the desired hematocrit, and the need for autologous blood donation.[39]

In contrast to autologous blood donation under "standard" conditions, studies of "aggressive" autologous blood phlebotomy (twice weekly for 3 weeks, beginning 25 to 35 days before surgery) have demonstrated that endogenous erythropoietin levels do increase,

TABLE 63-1 ENDOGENOUS ERYTHROPOIETIN-MEDIATED ERYTHROPOIESIS IN AUTOLOGOUS BLOOD DONORS*

		RBC (mL)		Net RBC		
	Patients (*n*)	Removed (Donated)	Produced	Expansion (%)	Iron Therapy	Reference
Standard phlebotomy	108	522	351	19	PO	Goodnough et al, 1989[40]
	22	590	220	11	None	Messmer et al, 1986[47]
	45	621	331	17	PO	Messmer et al, 1986[47]
	41	603	315	16	PO, IV	Messmer et al, 1986[47]
Aggressive phlebotomy	30	540	397	19	None	Brecher and Rosenfeld, 1994[48]
	30	558	473	23	PO	Brecher and Rosenfeld, 1994[48]
	30	522	436	21	IV	Brecher and Rosenfeld, 1994[48]
	24	683	568	26	PO	Weiskopf, 1995[51] and Petry et al, 1994[52]
	23	757	440	19	PO	Monk et al, 1999[53]

From Goodnough LT, Skikne B, Brugnara C: Erythropoietin, iron, and erythropoiesis, Blood *96:823-833, 2000.*
IV, Intravenous; *PO,* oral; *RBC,* red blood cell.
*Data are expressed as means.

TABLE 63-2 ADVANTAGES AND DISADVANTAGES OF AUTOLOGOUS BLOOD DONATION

Advantages	Disadvantages
Prevents transfusion-transmitted disease	Does not affect risk of bacterial contamination
Prevents red cell alloimmunization	Does not affect risk of ABO incompatibility error
Supplements the blood supply	Is more costly than allogeneic blood
Provides compatible blood for patients	Results in wastage of blood not transfused with alloantibodies
Prevents some adverse transfusion reactions	Has an increased incidence of adverse reactions to autologous donation
Provides reassurance to patients concerned about blood risks	Subjects patient to perioperative anemia and increased likelihood of transfusion

along with enhanced erythropoiesis representing RBC volume expansion of 19% to 26% (see Table 63-1). The use of erythropoiesis-stimulating agents to stimulate erythropoiesis further (≤50% RBC volume expansion)[40-42] during autologous donation has been approved in the European Union, Canada, and Japan, but not in the United States.[43] Perisurgical erythropoietin therapy is also approved in the United States and Canada for anemic (hematocrit < 39%) patients who are scheduled for noncardiac, nonvascular surgical procedures.

Transfusion Trigger

Advantages and disadvantages of autologous blood transfusion are summarized in Table 63-2. Disagreement exists about the proper hemoglobin and hematocrit levels ("transfusion trigger") at which autologous blood should be given (see Chapter 61).[44] In general, autologous and allogeneic blood transfusion triggers should be similar because the risks from administrative errors associated with both autologous and allogeneic blood are higher than are risks related to the transfusion of allogeneic blood.[45]

ACUTE NORMOVOLEMIC HEMODILUTION

ANH is the removal of whole blood from a patient while restoring the circulating blood volume with an acellular fluid shortly before an anticipated significant surgical blood loss. To minimize the manual labor associated with hemodilution, the blood should be collected in standard blood bags containing anticoagulant on a tilt-rocker with automatic cutoff through volume sensors. The blood is then stored at room temperature and reinfused during surgery after major blood loss has ceased, or sooner if indicated. Simultaneous infusions of crystalloid (3 mL crystalloid for each 1 mL of blood withdrawn) and colloid (dextrans, starches, gelatin, albumin [1 mL for each 1 mL of blood withdrawn]) have been recommended.[46] Blood units are reinfused in the reverse order of collection because the first unit collected and therefore the last to be infused will have the highest hematocrit and concentration of coagulation factors and platelets.

Reduction of Red Blood Cell Losses

The chief benefit of ANH is the reduction of RBC losses when whole blood is shed perioperatively at lower hematocrit levels associated with ANH.[47] Mathematic modeling suggests that severe ANH to preoperative hematocrit levels of less than 20%, accompanied by substantial blood losses, would be required before the RBC volume "saved" by ANH would become clinically important.[48] A clinical analysis of patients who had undergone "minimal" ANH (representing ≤15% of patients' blood volume) estimated that only 100 mL of RBCs (the equivalent of 0.5 unit of blood)[49] was "saved" under these conditions.[50] With moderate hemodilution (target hematocrit levels of 28%), the "savings" become more substantial. The removal of 3 blood units in a patient who subsequently underwent a blood loss of 2600 mL resulted in surgical RBC losses

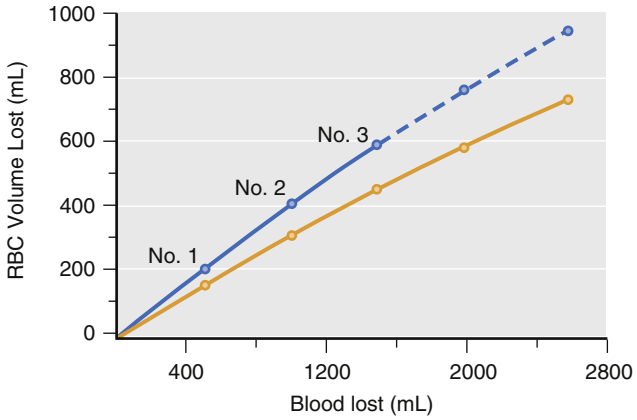


Figure 63-1. The relationship between whole blood volume (mL) lost (*abscissa*) and red blood cell (RBC) volume lost (*ordinate*) in a 100-kg patient undergoing hemodilution: RBC volume lost with 2800 mL whole blood lost intraoperatively after hemodilution of 1500 mL whole blood (*solid blue line*); RBC volume lost with 2800 mL whole blood lost during hemodilution at each of three 500 mL volumes (*solid orange line*); cumulative RBC volume lost intraoperatively, derived for 2800 mL whole blood lost if hemodilution had not been performed (*blue dashed line*). A net of 215 mL reduction in RBC volume lost with hemodilution is illustrated by the divergence of the two curves. *(From Goodnough LT, Grishaber JE, Monk TG, et al: Acute normovolemic hemodilution in patients undergoing radical suprapubic prostatectomy: a case study analysis,* Anesth Analg *78:932-937, 1994, with permission.)*

"saved" by hemodilution of 215 mL, or the equivalent of 1 unit of allogeneic blood (Fig. 63-1).[50] This RBC volume approaches the RBC volume expansion generated by autologous blood predonation under standard phlebotomy conditions.

The benefit of ANH has been determined in a mathematic model[46]. An adult with an estimated 5-L blood volume and an initial hematocrit of 40%, with surgical blood losses of up to 3000 mL, would have a hematocrit level that would remain 25% postoperatively without an autologous blood intervention. This level is generally considered safe for patients without known risk factors. In this model, the performance of ANH with initial hematocrit levels of 40% to 45% would allow up to 2500 to 3500 mL of surgical blood loss, yet the nadir level of hematocrit could be maintained at 28%.

Improved Oxygenation

Withdrawal of whole blood and replacement with crystalloid or colloid solution decrease arterial oxygen content, but compensatory hemodynamic mechanisms and the existence of surplus oxygen delivery capacity make ANH safe. A sudden decrease in RBC concentration reduces blood viscosity, thereby decreasing peripheral resistance and increasing cardiac output. If cardiac output can effectively compensate, oxygen delivery to the tissues at a hematocrit of 25% to 30% is as good as, but no better than, oxygen delivery at a hematocrit of 30% to 35%.[51]

Preservation of Hemostasis

Because blood collected by ANH is stored at room temperature and is usually returned to the patient within 8 hours of collection, deterioration of platelets or coagulation factors is minimal. The hemostatic value of blood collected by ANH is questionable for orthopedic or urologic surgery because plasma and platelets are rarely indicated in this setting. Its value in protecting plasma and platelets from the acquired coagulopathy of extracorporeal circulation in cardiac surgery (known as "blood pooling") is better established.[52]

Clinical Studies

Prospective randomized studies in patients undergoing radical prostatectomy,[53] knee replacement,[54] and hip replacement[55] suggested that ANH can be considered equivalent to PAD as a method of autologous blood procurement. Selected clinical trials of ANH are summarized in Table 63-3.[56-72] Commentaries on the relative merits of ANH have been published.[73-75] When ANH and reinfusion are accomplished in the operating room by on-site personnel, the procurement and administration costs are minimized. Blood obtained during ANH does not require the commitment of the patient's time, transportation, costs, and loss of work time that can be associated with PAD. The wastage of PAD units (approximately 50% of units collected)[27] also is eliminated with ANH. Additionally, autologous blood units procured by ANH require no inventory or testing costs. Because the blood never leaves the patient's room, ANH minimizes the possibility of an administrative or clerical error that could lead to an ABO-incompatible blood transfusion and death, as well as bacterial contamination associated with prolonged storage at 4° C.

An ANH program has some important practical considerations. Decisions about ANH should be based on the surgical procedure and on the patient's preoperative blood volume and hematocrit, target hemodilution hematocrit, and other physiologic variables. The institution's policy and procedures and the mechanisms for educating staff should be established and periodically reviewed.

The patient's circulating volume and perfusion status should be carefully monitored during the procedure. Blood must be collected in an aseptic manner, ordinarily into standard blood collection bags with citrate anticoagulant. Units must be properly labeled and stored. The label must contain, at a minimum, the patient's full name, medical record number, date and time of collection, and the statement "For Autologous Use Only." Room temperature storage should not exceed 8 hours. If more time elapses between collection and transfusion, the blood should be stored in a monitored refrigerator. Suggested criteria for patient selection are listed in Box 63-3.

Cost-Effective Analysis of Acute Normovolemic Hemodilution Versus Preoperative Autologous Donation

Most clinical trials compared ANH to PAD as the "standard of care." Medicolegal concerns may also prevent the inclusion of a treatment arm consisting of only allogeneic blood transfusion because blood safety acts in several states mandate that physicians offer autologous blood options before elective surgical procedures.[18] These studies found ANH to be similar to PAD in eliminating

TABLE 63-3 SELECTED CLINICAL TRIALS OF ACUTE NORMOVOLEMIC HEMODILUTION

	Estimated Blood Loss (mL)			Postoperative Hematocrit (%)			Allogeneic RBC-Containing Units or Liters ( ) Transfused			
Type of Surgery	Control	ANH	*P* Value	Control	ANH	*P* Value	Control	ANH	*P* Value	Reference
Colectomy	NR	NR	NR	37.0	35.0	NR	2.4	0	NR	Semkiw et al, 1989[56]
Spinal fusion	5490	1700	< .005	NR	28.7	NR	8.6	<1	<0.001	Eng et al, 1990[57]
Hip arthroplasty	1800	2000	NS	38.4	32.4	NS	(2.1)	(0.9)	NR	Roberts et al, 1991[58]
Prostate	1246	1106	NS	35.5	31.8	< .001	0.16	0	NS	Martin et al, 1992[59]
Liver resection	1479	1284	NS	37.9	33.8	< .01	3.8	(0.4)	<0.001	Ward et al, 1993[60]
Prostate	1717	1710	NS	29.5	27.9	< .5	0.30	(0.13)	NS	Umlas et al, 1994[61]
Vascular	2250	2458	NS	NR	33.0	NR	6.0	2.6	<0.01	De Haan et al, 1995[62]
Hepatic resection	890	750	NS	31	32	NS	NR	NR	NR	Matot et al, 2002[63]
Hepatic resection	700	800	NS	29	32	NS	47	28	0.06	Jarnagin et al, 2008[64]
Pancreaticoduodenectomy	500	700	NS	30	29	NS	12	11	NS	Fischer et al, 2010[65]

Modified from Brecher ME, Rosenfeld M: Mathematical and computer modeling of acute normovolemic hemodilution, Transfusion *34:176-179, 1994.*
ANH, Acute normovolemic hemodilution; *NR,* not reported; *NS,* not significant; *RBC,* red blood cell.

BOX 63-3 ***Criteria for Selection of Patients for Acute Normovolemic Hemodilution***

1. Likelihood of transfusion exceeding 10% (i.e., blood requested for crossmatch according to a maximum surgical blood order schedule)
2. Preoperative hemoglobin level of at least 12 g/dL
3. Absence of clinically significant coronary, pulmonary, renal, or liver disease
4. Absence of severe hypertension
5. Absence of infection and risk of bacteremia

the need for allogeneic blood transfusions during elective surgery.[76] Other outcomes including anesthesia and surgery times, intraoperative hemodynamic values, and length of hospital stays were also equivalent in PAD and ANH. Even though only a few studies included economic evaluations comparing the cost of autologous blood techniques, all these studies demonstrated that ANH is much less costly than PAD.[76] Therefore, ANH can be considered a cost-minimizing technique for autologous blood procurement for elective surgery.

INTRAOPERATIVE CELL SALVAGE

The term *intraoperative blood collection* or *recovery* or *cell salvage* describes the technique of collecting and reinfusing blood lost by a patient during surgery. The oxygen transport properties of recovered RBCs are equivalent to those of stored allogeneic RBCs. The survival of recovered RBCs appears to be at least comparable to that of transfused allogeneic RBCs.[77] Intraoperative collection is contraindicated when certain procoagulant materials (e.g., topical collagen) are applied to the surgical field because systemic activation of coagulation may result. Microaggregate filters (40 μm) are most often used because recovered blood may contain tissue debris, small blood clots, or bone fragments.

Cell washing devices can provide the equivalent of 12 units/hour of banked blood to a massively bleeding patient.[77] Data on adverse events of reinfusion of recovered blood have been published.[78] Air embolus is a potentially serious problem. Three fatalities from air embolus were reported over a 5-year interval to the New York State Department of Public Health, for an overall fatality risk of 1 in 30,000.[35] Hemolysis of recovered blood can occur during suctioning from the surface instead of from deep pools of shed blood. For this reason, manufacturers' guidelines recommend a maximum vacuum setting of no more than 150 mm Hg; one study found that vacuum settings as high as 300 mm Hg could be used, when necessary, without causing excessive hemolysis.[79] Patients exhibit a level of plasma free hemoglobin that is usually higher than after allogeneic transfusion. The clinical importance of free hemoglobin in the concentrations usually seen has not been established, although excessive free hemoglobin may indicate inadequate washing. Positive bacterial cultures from recovered blood are sometimes observed; however, clinical infection is rare.[80] Most programs use machines that collect shed blood, wash it, and concentrate the RBCs. This process typically results in 225-mL units of saline-suspended RBCs with a hematocrit of 50% to 60%.

Clinical Studies

As with PAD and ANH, collection and recovery of intraoperative autologous blood should undergo scrutiny with regard to both safety and efficacy.[81] A controlled study in cardiothoracic surgery demonstrated a lack of efficacy when transfusion requirements and clinical outcomes were followed.[80] A second study found that only a minority of patients undergoing major orthopedic and cardiac surgery achieved cost equivalence with intraoperative blood recovery using semiautomated instruments compared with banked blood.[82] Although the collection of a minimum of one blood unit equivalent is possible for less expensive (with unwashed blood) methods, at least two blood unit equivalents must be recovered using a cell recovery instrument (with washed blood) to achieve cost effectiveness.[83] The value of intraoperative blood collection is apparent for vascular surgical procedures with large blood losses, such as aortic aneurysm repair and liver transplantation.[84] However, a prospective, randomized trial of intraoperative recovery and reinfusion in patients undergoing aortic aneurysm repair showed no benefit in a reduction of allogeneic blood exposure.[83] The value of this technology may be in cost savings and blood inventory considerations in patients with substantial blood losses.[85]

Collection devices that neither concentrate nor wash shed blood before reinfusion increase the risk of adverse effects. Shed blood has undergone varying degrees of coagulation or fibrinolysis and hemolysis, and infusion of large volumes of washed or unwashed blood has been described in association with disseminated intravascular coagulation (DIC).[84] In general, blood collected at low flow rates or during slow bleeding from patients who are not systemically anticoagulated will have undergone coagulation and fibrinolysis and will not contribute to hemostasis on reinfusion. The high suction pressure and surface skimming during aspiration and the turbulence or mechanical compression that occurs in roller pumps and plastic tubing make some degree of hemolysis inevitable. High concentrations of free hemoglobin may be nephrotoxic to patients with impaired renal function. Many programs limit the quantity of recovered blood that may be reinfused without processing. To minimize hemolysis, the vacuum level should ordinarily not exceed 150 mm Hg, although higher levels of suction may occasionally be needed during periods of rapid bleeding.

An alternative approach is to collect blood in a canister system designed for direct reinfusion and then to concentrate and wash the recovered RBCs in a blood bank cell washer. Intraoperatively collected and recovered blood must be handled in the transfusion service laboratory similarly to any other autologous unit. The unit should be reinfused through a filter.

Some practical considerations for cell recovery programs are listed in Box 63-4. If collected under aseptic conditions with a saline-wash device and if properly labeled, blood may be stored at room temperature for up to 4 hours or at 1° C to 6° C for up to 24 hours, provided storage at 1° C to 6° C is begun within 4 hours of ending the collection.[23] The allowable interval of room temperature storage is shorter for recovered blood (4 hours) than for ANH blood (8 hours). Storage times are the same for recovered blood whether unwashed or washed.

BOX 63-4 ***Practical Considerations for Intraoperative Cell Recovery, Storage, and Reinfusion***

1. If not transfused immediately, units collected from a sterile operating field and processed with a device for intraoperative blood collection that washes with 0.9% saline, USP, shall be stored under one of the following conditions before initiation of transfusion:
   a. At room temperature for up to 4 hours after terminating collection
   b. At 1° C to 6° C for up to 24 hours, provided storage at 1° C to 6° C is begun within 4 hours of ending the collection
2. Transfusion of blood collected intraoperatively by other means shall begin within 6 hours of initiating the collection.
3. Each unit collected intraoperatively shall be labeled with the patient's first name, last name, and hospital identification number; the date and time of initiation of collection and of expiration; and the statement "For Autologous Use Only."
4. If stored in the blood bank, the unit shall be handled like any other autologous unit.
5. The transfusion of shed blood collected under postoperative or posttraumatic conditions shall begin within 6 hours of initiating the collection.

POSTOPERATIVE CELL SALVAGE

Postoperative blood collection denotes the recovery of blood from surgical drains followed by reinfusion, with or without processing.[62] In some programs, postoperative shed blood is collected into sterile canisters and reinfused, without processing, through a microaggregate filter. Recovered blood is dilute, is partially hemolyzed and defibrinated, and may contain high concentrations of cytokines. For these reasons, most programs set an upper limit on the volume (e.g., 1400 mL) of unprocessed blood that can be reinfused. If transfusion of blood has not begun within 6 hours of initiating the collection, the blood must be discarded.

Clinical Studies

The evolution of cardiac surgery has been accompanied by broad experience in postoperative conservation of blood. Postoperative autologous blood transfusion is practiced widely but not uniformly. Prospective and controlled trials have disagreed over the efficacy of postoperative blood recovery in cardiac surgical patients; at least three such studies demonstrated lack of efficacy,[58,60] whereas at least two studies showed benefit.[57] The disparity of results in these studies may be explained, in part, by differences in transfusion practices. Modification of physicians' transfusion practices may have been an uncredited intervention in these blood conservation studies.

In the postoperative orthopedic surgical setting, several reports have similarly described the successful recovery and reinfusion of washed[56] and unwashed[59] wound drainage blood from patients undergoing arthroplasty. The volume of reinfused drainage blood

has been reported to be as great as 3000 mL and averages more than 1100 mL in patients undergoing cementless knee replacement.[59] Because the RBC content of the fluid collected is low (hematocrit levels of 20%) the volume of RBCs reinfused is often small.[61] A prospective, randomized study of postoperative salvage and reinfusion in patients undergoing total knee or hip replacement found no differences in perioperative hemoglobin levels or allogeneic blood transfusions between patients who had joint drainage devices and those who did not.[86]

The safety of reinfused unwashed orthopedic wound drainage has been controversial. Theoretic concerns have been expressed regarding infusion of potentially harmful materials in recovered blood, including free hemoglobin, RBC stroma, marrow fat, toxic irritants, tissue or methacrylate debris, fibrin degradation products, activated coagulation factors, and complement. Although two small studies reported complications,[87,88] several larger studies reported no serious adverse effects when the drainage was passed through a standard 40-μm blood filter.[56,59,89]

The potential for decreasing exposure to allogeneic blood among orthopedic patients undergoing postoperative blood collection, whether the blood is washed or unwashed, is greatest for cementless bilateral total knee replacement, revision hip or knee replacement, and long-segment spinal fusion. As in the case of intraoperative recovery, blood loss must be sufficient to warrant the additional cost of processing technology.[90] One study demonstrated comparable costs between postoperative cell salvage and allogeneic transfusion for patients undergoing total knee arthroplasty, but the investigators found that cell salvage represented a significant savings in patients undergoing total hip arthroplasty.[91] As in the selection of patients who can benefit from PAD and ANH, the prospective identification of patients who can benefit from intraoperative and postoperative autologous blood recovery is possible if patients' preoperative hemoglobin level, anticipated surgical blood loss, and perioperative "transfusion trigger" are taken into account.

RECOMBINANT FACTOR VIIa

Recombinant factor VIIa (rfVIIa) has been approved for treatment of bleeding in patients with hemophilia who have inhibitors, patients with congenital factor VII deficiency, and patients with inherited qualitative platelet defects. Pharmacologic doses of rfVIIa enhance the thrombin generation on platelets and therefore may also likely be of benefit in providing hemostasis in clinical settings characterized by profuse bleeding and impaired thrombin generation,[92] such as in patients with thrombocytopenia and in those with functional platelet defects.[93,94] Additionally, it has been used successfully in a variety of less well-characterized surgical bleeding situations in patients with dilutional or consumptive coagulopathies and in patients with impaired liver function.[95-97] Policies for the approval of rfVIIa therapy in nonapproved settings should therefore undergo periodic review and revision as relevant new information and data are generated.[98] Because of the trends in rfVIIa usage in nonapproved settings, significant concerns about the safety, efficacy, and costs of rfVIIa have arisen. Additionally, dosing of rfVIIa for these potentially broad clinical applications is not standardized.

COMPLEX SURGERY AND TRAUMA RESULTING IN PROFUSE BLEEDING

A hemostatic effect has been demonstrated after the administration of rfVIIa in a limited number of patients after trauma and bleeding (see also Chapters 61 and 62).[95,96] Seven trauma patients treated with rfVIIa after failure of conventional measures to achieve hemostasis reported cessation of diffuse bleeding and correction of abnormal coagulation assays; three of the seven patients died of reasons other than bleeding or thromboembolism.[96]

Anecdotal case reports have been published that describe the successful use of rfVIIa in patients with substantial perisurgical bleeding. The experience of rfVIIa use in trauma with excessive bleeding, as well as in profuse postoperative bleeding, based largely on case reports, has indicated a hemostatic effect of rfVIIa given in doses ranging from 20 to 120 μg/kg. The issue of preemptive, preoperative rfVIIa (40 to 90 μg/kg) was studied in nine patients with coagulopathy and urgent neurosurgical intervention.[99] Post-rfVIIa coagulation parameters normalized as early as 20 minutes after infusion, with no noted procedural or operative complications. No associated thromboembolic complications were observed. Subsequently, a prospective, randomized study of rfVIIa (20 or 40 μg/kg) versus placebo perioperatively in 36 patients undergoing radical retropubic prostatectomy found that the cohorts receiving rfVIIa had substantially less median operative blood loss compared with placebo (1235 mL, 1089 mL, and 2688 mL, respectively).[100] This study was not powered to demonstrate reductions in blood transfusions.

In single-center series, 51 patients undergoing rfVIIa therapy for intractable blood loss after cardiac surgery were compared with 51 matched controls.[101] The investigators found that bleeding 1 hour after therapy was reduced in the treated cohort, compared with the control cohort. No differences in serious adverse events were noted. A subsequent review from the same institution of 114 cardiac surgical patients who received rfVIIa compared with 541 concurrent patients who did not receive rfVIIa concluded that rfVIIa is not associated with increased risk of adverse events, and early treatment may be associated with better outcomes.[102] A second series of rfVIIa in 53 patients during cardiac surgery found a significant decrease in doses of all blood products.[103] However, a third series of 24 patients treated with rfVIIa for refractory bleeding after cardiac surgery, compared with 24 matched controls, found no differences in RBC or plasma units transfused over a 24-hour period.[104]

A pilot study of 20 patients undergoing complex noncoronary cardiac surgery who were randomized to receive either placebo or rfVIIa (90 μg/kg) prophylactically after completion of cardiopulmonary bypass and

reversal of heparin found a significantly reduced need for allogeneic transfusion in the cohort who received rfVIIa.[105] However, a pediatric study of 76 pediatric patients undergoing surgery for congenital heart disease found no benefit of rfVIIa (40 μg/kg) prophylaxis as determined by chest closure time after cardiopulmonary bypass[106] (see also Chapter 94).

Two randomized placebo-controlled trials of rfVIIa as adjunctive therapy for control of bleeding in trauma patients were published.[107] In an analysis of 143 patients with blunt trauma, the percentage of patients alive at 48 hours after receiving more than 20 units of RBCs was reduced from 33% to 14% ($P = .03$). For 143 patients with penetrating trauma, the reduction from 19% to 7% was not significant ($P = .08$). No differences in serious adverse events between the rfVIIa-treated and placebo cohorts were observed (see also Chapters 62 and 81).

DOSE

A retrospective review of 40 patients with coagulopathic bleeding in a variety of medical and surgical settings from 13 hospitals in an Internet-based database (excluding history of coagulopathy and trauma patients) who received rfVIIa (15 to 180 μg/kg, with 38 patients receiving fewer than 5 doses) found that 32 patients (80%) achieved complete ($n = 18$) or partial ($n = 14$) cessation of bleeding.[108] Responses occurred in all dose ranges, without any evidence of a dose-response effect; the percentages of complete, partial, or absent responses were not different at doses of less than 70 μg/kg, 70 to 90 μg/kg, or more than 90 μg/kg. Significantly fewer blood products were administered after rfVIIa therapy. Twenty-three (58%) patients died, thus reflecting the unstable clinical status of the patients at the decision point for considering rfVIIa therapy. On the basis of this study, one recommended dosage strategy is for a 4.8-mg vial administered to an adult patient weighing 50 to 100 kg, which represents a 100 to 50 μg/kg dose.[98]

PATIENTS RECEIVING ORAL ANTICOAGULANT THERAPY

One report described the use of rfVIIa in seven adult patients with a prolonged international normalized ratio (INR); three of these patients required surgery. The doses administered ranged from 20 to 90 μg/kg, and all patients were reported to have a positive outcome.[109] These observations indicate that rfVIIa may be used to reverse the effect of warfarin (Coumadin) or other vitamin K–antagonist therapy when the administration of vitamin K alone has been found to be insufficient. Two published reports of a total of 15 patients treated with rfVIIa for reversal of excessive anticoagulation with warfarin supported a dosage of 20 μg/kg, or 1.2 mg for an adult patient.[110,111] A review of 12 patients with acute warfarin-associated intracranial hemorrhage over this same time period at one institution (all these patients received rfVIIa [30 to 135 μg/kg] as well as vitamin K [10 mg/day for 3 days] and fresh frozen plasma [1307 ± 652 mL] for treatment) found that treatment was associated with rapid correction of the INR, and single doses appeared safe in this high-risk population.[112] However, more recent guidelines from several medical societies have discouraged the off-label use of rfVIIa in this setting[12] (see also Chapter 62).

PATIENTS WITH IMPAIRED LIVER FUNCTION

A multicenter trial studied 71 patients with advanced liver disease who were undergoing laparoscopic liver biopsy.[115] The patients were randomized to receive 1 of 4 doses of rfVIIa (5, 20, 80, or 120 μg/kg); 48 (74%) of 65 patients achieved hemostasis within 10 minutes. One thrombotic event and a single case of DIC were reported, and they were not believed to be related to rfVIIa therapy. Despite these complications, the authors concluded that laparoscopic liver biopsy can be performed safely and reliably by using rfVIIa in patients in whom the standard procedure may be contraindicated because of coagulopathy.

The safety and efficacy of rfVIIa in patients with cirrhosis and upper gastrointestinal hemorrhage were studied in a randomized study of 245 patients with a composite primary end point including failure to control bleeding within 24 hours after first dose, failure to prevent rebleeding within 24 hours to 5 days, or death within 5 days.[116] No significant differences were found between the placebo compared with the rfVIIa (8 doses at 100 mg/kg over 30 hours) cohorts: failures on composite end point were 16% and 14%, respectively ($P = .72$). Similarly, a randomized controlled study of patients with cirrhosis who underwent partial hepatectomy found no benefit to rfVIIa compared with placebo when the volume of blood products administered, or the percentage of patients transfused, was analyzed.[115] Finally, no value for peri-adjuvant rfVIIa was found in patients undergoing liver transplantation, when compared with placebo[114] (see also Chapter 62).

PATIENTS WITH NORMAL HEPATIC FUNCTION

A prospective, randomized, double-blind multicenter study evaluated the efficacy of two different doses of rfVIIa compared with placebo on RBC transfusions for adult patients without cirrhosis who were undergoing partial hepatectomy.[117] Mean RBC volume transfused was 1024, 1354, and 1036 mL for placebo, 20 μg/kg rfVIIa, and 80 μg/kg rfVIIa, respectively ($P > .05$). Similarly, no differences were noted in the percentage of patients transfused and in intraoperative blood losses. Serious adverse event rates were not different.

PATIENTS WITH HEMORRHAGIC STROKE

A prospective, randomized, double-blind placebo-controlled trial of three doses of rfVIIa compared with placebo was reported in patients presenting with acute (<4 hours) hemorrhagic stroke.[118] At 24 hours after treatment, the percentage of patients showing expansion was 28%, 16%, 14%, and 11% for the placebo, 40 μg/kg, 80 μg/kg, and 160 μg/kg, respectively ($P < .05$ treatment cohorts versus placebo). The percentage

of patients who died was 29%, 18%, 18%, and 19%, respectively ($P < .05$, treatment cohorts versus placebo). Impairment scored at 90 days was also improved in the treatment cohorts compared with placebo. However, a follow-up, clinical trial (placebo, 40 μg/kg, and 80 μg/kg) failed to show a mortality benefit for rfVIIa compared with placebo.[119]

SAFETY

Of the more than 170,000 standard doses of rfVIIa given after its approval (almost all to patients with hemophilia and inhibitors), only rare (<1 in 11,300) thrombotic events have been reported.[92] Thrombotic complications have also been reported with rfVIIa therapy in patients without inhibitors to factor VIII or IX. An acute cerebrovascular accident and death occurred in a clinical trial of rfVIIa (90 μg/kg) before and after minor surgery or dental procedures in patients with factor XII deficiency.[120] The last of 10 patients enrolled in an open-label, dose-escalation trial to prevent rebleeding after subarachnoid hemorrhage developed middle cerebral artery thrombosis after receiving rfVIIa.[121] In a high-risk trauma population, 3 of 40 (7.5%) patients who were deemed at high risk for thrombosis developed thrombotic complications after receiving rfVIIa.[122]

Although significant adverse events and thrombotic events were distributed evenly among treatment and placebo cohorts in several large randomized clinical trials of patients undergoing radical prostatectomy,[100] trauma,[109] upper gastrointestinal bleeding,[114] or partial hepatectomy,[120] an uneven distribution of thromboembolic events was found in the clinical trial of patients with hemorrhagic stroke.[120] Total events in this last trial were 2 (2%), 7 (6%), 4 (5%), and 10 (10%) for the placebo, 40, 80, and 160 μg/kg cohorts, respectively. Most of these events were arterial, including thrombotic stroke and myocardial infarction. Whether these serious adverse events can be attributed to rfVIIa or to a population at risk for these events will need to be determined in a follow-up clinical trial.

A summary of thromboembolic events reported to the U.S. Food and Drug Administration (FDA) from March 1999 to December 2004 indicated a total of 151 events in settings with unlabeled indications for rfVIIa.[123] These events included deep vein thrombosis (42), cerebrovascular accident (39), acute myocardial infarction (34), pulmonary thromboembolus (32), arterial thrombosis (26), and clotted devices (10). Thirty-eight percent of cases had concomitant use of other hemostatic agents. In 36 (72%) of 50 reported deaths, rfVIIa was listed as the probable cause. The authors concluded that randomized clinical trials are necessary to demonstrate the safety and efficacy of rfVIIa in nonapproved settings. A subsequent report analyzed safety data from 13 clinical trials in patients treated with rfVIIa for cirrhosis, trauma, or reversal of anticoagulant therapy.[124] The authors reported thrombotic adverse events in 5.3% of patients who received placebo, compared with 6.0% in patients who received rfVIIa ($P = .57$).

In cardiac surgical patients, cohort-matched studies[100,101] and a systematic review found no differences in serious adverse events in patients treated with rfVIIa[125] (see also Chapter 62). We reported a patient who had fatal thrombosis after administration of activated prothrombin complex concentrate (PCC) and who had also received two doses of rfVIIa more than 6 hours earlier, while supported by extracorporeal membrane oxygenation.[126] Because of this experience, we recommend that patients should not receive combination therapy with both activated PCC and rfVIIa.

In summary, the safety profile of rfVIIa in controlled trials in patients with spontaneous *intracerebral hemorrhage* suggests that an increased risk of thrombotic arterial events may be underreported by treating physicians.[127] Thromboembolic events associated with rfVIIa were reported to the FDA in approximately 2% of treated patients in clinical trials, but sufficient data were not available to identify the incidence in patients who received rfVIIa for warfarin reversal.[123] A careful case review of 285 trauma patients revealed that 27 (9.4%) had thromboembolic complications after administration of rfVIIa, including 3 patients who were treated for warfarin reversal.[128] Levi and colleagues analyzed 35 randomized trials with 4468 subjects and found that 11.1% had thromboembolic events. Rates of venous thromboembolic events were similar for subjects who received rfVIIa compared with placebo (5.3% and 5.7%, respectively); arterial events, however, were significantly higher (5.5% versus 3.2%, $P < .003$) in subjects receiving rfVIIa compared with placebo, particularly for older patients (>75 years of age) and/or higher doses.[129]

Dose, timing, and safety of rfVIIa have yet to be defined in this diverse patient population, and formal prospective trials are needed. Consensus-based recommendations on the use of rfVIIa in nonapproved settings have been developed.[130] The decisions on when and where to use rfVIIa for patients with uncontrolled bleeding must be made by individual physicians, assisted by their hospital pharmacotherapeutic or transfusion committees.[98,131]

BLOOD UTILIZATION

Of the estimated 39 million discharges in the United States in 2004, 5.8% (2.3 million) were associated with blood transfusion.[132] Blood transfusion occurred in more than 10% of all hospital stays that included a procedure and was the most frequently performed procedure in 2009. The rate of blood transfusion more than doubled from 1997 to 2009.[133] Increased provider awareness of the costs associated with blood transfusion[134] and recognition of the potential negative outcomes have stimulated multidisciplinary, multiprofessional, and institution-based approaches to patient blood management (see also Chapter 61).

Guidelines for blood transfusion attest to the inadequacy of discrete hemoglobin levels as "triggers" for transfusion, and in addition to recommending transfusion of one blood unit each treatment event, they also acknowledge the necessity of considering other more physiologic criteria.[14] It is generally agreed that transfusion is not of benefit when hemoglobin levels are greater than 10 g/dL and is beneficial when hemoglobin levels are lower than 6 g/dL.[15,135] The variability in transfusion

outcomes in patients undergoing cardiothoracic surgery continues to persist even after adjusting for patient- and institution-related factors.[136,137] Moreover, prospective randomized trials in patients undergoing cardiac[138] and noncardiac[139,140] surgery demonstrated that such patients can tolerate perioperative anemia without transfusion to hemoglobin levels between 7 and 8 g/dL, and these patients have equivalent clinical outcomes comparable to transfusions to hemoglobin levels greater than 10 g/dL. The FOCUS trial found that older (mean > 80 years of age) high-risk (factors for coronary artery disease) patients who underwent hip fracture surgery tolerated a hemoglobin trigger as low as 8 g/dL (or higher if symptomatic).[140]

A Cochrane meta-analysis of prospective randomized trials comparing "high" and "low" hemoglobin thresholds in more than 3700 patients found that (1) "low" hemoglobin thresholds were well tolerated, (2) RBC transfusions were reduced (≈37%) significantly in patients randomized to the "low" hemoglobin cohorts, (3) infections were reduced by 34% in patients in the "low" hemoglobin cohorts, and (4) a hemoglobin of 7 g/dL was sufficient for most patients.[141] More recently, a randomized controlled trial of 2016 older patients with history or risk factors of cardiovascular disease who underwent hip surgery demonstrated that mortality rates, inability to walk independently, and in-hospital morbidity rates were similar in patients transfused according to liberal criteria and in patients transfused according to restrictive guidelines despite significantly fewer transfusions in the restrictive group.[140] On the basis of this study, the AABB guidelines recommend the use of a restrictive transfusion approach (hemoglobin 7 to 8 g/dL) in stable patients who do not have cardiovascular risk factors.[142]

Data from the most recent National Blood Collection and Utilization Survey show a progressive annual decrease in the number of patients and the percentage of hospitals who have canceled elective surgical procedures because of blood inventory constraint.[143] Current initiatives in research for blood transfusions are reflected in the growing literature on adverse effects of blood storage and their possible implications for oxygen delivery by blood transfusion.[144]

INDICATIONS FOR PLASMA TRANSFUSION

In an evidence-based review, the Transfusion Practices Committee of the AABB recommended plasma therapy for only a few clinical indications, based on the available evidence in the literature (which was assessed to be of "weak quality"[145]): trauma patients with substantial hemorrhage, patients undergoing complex cardiovascular surgery, and patients with intracranial hemorrhage requiring emergency reversal of warfarin-associated coagulopathy[146] (see also Chapter 62). Patients with mild prolongations of the INR (< 1.7) are not at risk of bleeding and do not need plasma therapy for minor procedures.[147] Therefore, for most clinical settings, ample evidence indicates that plasma transfusions are inappropriate. However, logistic or technical barriers that prevent effective and timely plasma therapy (possibly resulting in plasma therapies that are "too little, too late") have probably contributed to the paucity of evidence demonstrating any benefit for plasma therapy.[12]

Lack of enthusiasm and logistic or technical barriers in this and other settings have led to approaches for plasma therapy that are perhaps too little, too late. First, transfusion services must identify the patient's blood group type before issuing blood type–compatible plasma; for patients unknown to the institution and/or without a historic blood type in the patient record within the past year, considerable time (up to 60 minutes) can elapse from presentation until a blood type can be ordered, drawn, and determined by the transfusion service. Second, because plasma is stored frozen at −18° C, further time (30 to 45 minutes) may be required to thaw and issue plasma. Third, the volume for each plasma unit infused (≈200 to 250 mL) represents a challenge regarding volume overload, which occurs commonly in an older population who may have preexisting comorbidities such as atrial fibrillation or other cardiovascular disease. The dosing of plasma needed to correct the coagulopathy has often been underestimated and therefore may be subtherapeutic in some clinical practices; plasma therapy of 15 to 30 mL/kg is necessary to restore hemostatic clotting factor levels to 30% to 50% of normal in acute reversal of warfarin toxicity.[12]

In the coagulopathy of liver disease, plasma therapy may not represent appropriate management.[148] In liver disease, the extent of coagulopathy as measured by the prothrombin time or INR is not predictive of bleeding complications.[149-151] Thrombin-generation assays,[152,153] which measure platelet procoagulant activity, have found that patients with cirrhosis have primary hemostasis through cell-mediated pathways that are not measured by traditional laboratory assays such as prothrombin time and partial thromboplastin time. Increasing evidence indicates that these patients can undergo major hemostatic challenges such as liver biopsies and surgical procedures without plasma therapy and without bleeding complications.[154] Moreover, normalization of laboratory tests in this setting is rarely achieved by plasma therapy.[155] The most clinically relevant bleeding problems are a consequence of local vascular abnormalities and increased venous pressures.[151,156] Thus, a more conservative plasma therapy approach would be to avoid volume and fluid overload that paradoxically favors hemorrhage, such as portal hypertension and endothelial damage.[157] Alternative therapies to plasma infusion have been proposed to improve hemostasis in patients with liver disease, including the infusion of low-volume PCCs or antifibrinolytic agents, which lack the side effects of volume overload.[148]

One of the largest prospective studies of plasma transfusions and their effect on INR and bleeding included both medical and surgical patients with pretransfusion INR of between 1.1 and 1.85.[158] The authors reported that less than 1% of patients had normalization of their INR and only 15% had at least 50% correction. The median dose of plasma was 2 units (only 5 to 7 mL/kg), and no correlation was found between plasma dose and change in INR. This study had many of the limitations common to other reports[154] in this clinical arena: lack of control groups, only modest prolongation in coagulation tests, poorly defined clinical end points (e.g., change in hemoglobin or need for transfusion), and/or an inadequate dose of plasma therapy. Point-of-care testing, coupled with algorithms for targeted plasma therapy

TABLE 63-4 CURRENTLY APPROVED PROTHROMBIN COMPLEX CONCENTRATE PRODUCTS

Product (Manufacturer)	Factor Levels (International Units/mL)* II	VII	IX	X
I. Available in the USA:				
A. Four factor				
KCentra (CSL Behring)	17-40	10-25	20-31	25-51
B. PCCs, three factor (II, IX, X)				
1. Profilnine SD (Grifols)‡	≤150	≤35	≤100	≤100
2. Bebulin VH (Baxter, Deerfield, Ill.)‡	24-38	<5	24-38	24-38
II. Available outside the USA:				
A. PCCs, four factor (II, VII, IX, X)				
1. Beriplex (CSL Behring, King of Prussia, Pa.)§	20-48	10-25	20-31	22-60
2. Octaplex (Octapharma, Lachen, Switzerland)‖	14-38	9-24	25	18-30
3. Cofact (Sanquin, Amsterdam)¶	14-35	7-20	25	14-35
4. Prothromplex T (Baxter)#	30	25	30	30
5. Proplex T (Baxter)**	20	20	20	20
B. PCCs, three factor (II,IX,X)				
1. Prothromplex HT (Baxter)††	30	—	30	130
2. Prothrombinex VF†† (CSL Bioplasma, Broadmeadows, Australia)	100	—	100	100
III. Activated PCC				
FEIBA (Baxter)‡‡	32 ± 8	38 ± 5	35 ± 2.5	28 ± 5

Modified from Goodnough LT, Shander AS: How I treat warfarin-associated coagulopathy in patients with intracerebral hemorrhage, Blood *117:6091-6099, 2011.*

PCC, Prothrombin complex concentrate.

*The values given for factor contents are the number of units (International Units/mL) present per 100 factor IX units in each vial.

‡Product insert specifies: "Indicated for replacement of factor IX in patient with hemophilia B. Not indicated for treatment of factor VII deficiency."

§United Kingdon and European Union.

‖United Kingdom, Canada, and European Union.

¶European Union.

#Austria.

**Japan.

††Australia.

‡‡Factor VIII inhibitor bypass activity calculated for 25 U/mL vial. NB product insert specifies FEIBA is contraindicated for treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to factors VIII or IX.

in settings such as cardiothoracic surgery, liver transplantation, and trauma surgery, shows promise in improving blood utilization and patient outcomes[159] (see also Chapter 61).

The paucity of evidence for benefit of plasma transfusion therapy is accompanied by growing evidence that risks of plasma have been underrecognized. In a prospective study, 6% of transfused patients developed transfusion-associated excessive cardiac volume,[160] a percentage that is much higher than previously reported rates in retrospective studies.[161,162] Transfusion-related acute lung injury is a significant cause of morbidity and mortality from blood transfusions.[163] The incidence of this complication has declined with use of plasma from male donors or from female donors who have no history of pregnancy.[164]

PROTHROMBIN COMPLEX CONCENTRATES

PCCs are either activated (i.e., to allow for bypassing inhibitors to factor VIII or factor IX in the treatment of patients with hemophilia A or B) or nonactivated. The nonactivated PCC products currently available worldwide are listed in Table 63-4,[12] and they are further categorized based on the presence (four factor) or absence (three factor) of sufficient levels of factor VII.[165] PCCs that contain all four (including factor VII) of the vitamin K–dependent clotting factors are approved in the European Union,[166] as well as in various other countries such as Canada and Australia, and are now approved in the United States for emergency reversal of warfarin coagulopathy in patients with major bleeding[167,168] and also for perioperative management of patients receiving warfarin therapy.[169] Three-factor PCCs are approved in the United States only for the replacement of factor IX. Use of these three-factor PCCs for reversal of warfarin is controversial; although these agents can be demonstrated to normalize INR,[170] one report showed a suboptimal effect in correcting INR because of minimal increments in levels of factor VII.[165] A review of the role of PCCs and other options for reversing warfarin-associated coagulopathy has been published.[12]

Guidelines for acute reversal of warfarin coagulopathy have been published by several medical societies (Table 63-5).[171-177] One review of emergency reversal of anticoagulation therapy in neurosurgical patients recommended the concomitant administration of a three-factor concentrate (4000 International Units) and rfVIIa (1.0 mg) for patients treated at one trauma center in the United States.[178] Another review of PCCs for reversal of warfarin concluded that "PCC should be compared directly in randomized controlled trials [with] other

TABLE 63-5 PUBLISHED GUIDELINES FOR REVERSAL OF WARFARIN ANTICOAGULATION IN PATIENTS WITH INTRACEREBRAL HEMORRHAGE

Society (Year)	Vitamin K	Plasma (mL/kg)		PCC (units/kg)	rfVII
Australian (2004)	IV (5-10 mg)	Yes (NS)	AND	Yes (NS)*	NS
EU Stroke (2006)	IV (5-10 mg)	Yes (10-40)	OR	Yes (10-50)	NS
ACCP (2012)	IV (5-10 mg)	No (NS)	OR	Preferred (NS)	Yes†
AHA (2010)	IV (NS)	Yes (10-15)	OR	Yes (NS)	No
French (2010)	Oral or IV (10 mg)	Yes (NS)‡	OR	Preferred (25-50)	No
British Standards (2011)	IV (5 mg)	No		Yes (NS)	No

ACCP, American College of Chest Physicians; *AHA,* American Heart Association; *EU,* European Union; *IV,* intravenous; *NS,* not specified; *PCC,* prothrombin complex concentrate; *rfVIIa,* recombinant human activated factor VII.
*If a three-factor PCC is administered, fresh frozen plasma is also recommended as a source of factor VII.
†Use of PCCs or rfVIIa may vary depending on availability.
‡Use of plasma only when PCCs not available.

treatment strategies including fresh frozen plasma and rfVIIa, evaluating effect on patient outcomes."[179] Normalization of the INR is just a surrogate end point.[180] The role of PCC therapy relative to plasma therapy is in evolution, in part related to the following: the variability in PCC contents and clotting factor levels[165,181]; their regulatory approval status in different countries; their uncertain availability among hospital formularies, particularly in community hospitals; and their potential risks of thrombogenicity.

Product information for activated PCCs such as FEIBA VH Immuno and Autoplex-T (Baxter, Deerfield, Ill.) states, under warnings, that these agents "must be used only for patients with circulating inhibitors to one or more coagulation factors and should not be used for the treatment of bleeding episodes resulting from coagulation factor deficiencies."[182,183] Additionally, the presence of DIC is a stated contraindication to PCC use in the package inserts.

The safety of PCCs in the setting of emergency reversal of warfarin anticoagulation remains a subject of debate. One prospective study of 173 patients treated with PCC found that 4.6% of patients had a thrombotic event, but the investigators attributed these adverse events to cessation of anticoagulant therapy for underlying and ongoing risks of thrombosis.[184] A study in a pig model of coagulopathy with blunt liver injury found that although 35 International Units/kg PCC improved coagulation and attenuated blood loss, increased doses (50 International Units/kg) of PCC therapy appeared to increase the risk of thromboembolism and DIC.[185] Thrombogenicity has been a recognized problem for patients,[186,187] in part related to the presence of activated clotting factors (for which heparin and antithrombin III have been added to some preparations) and in part because of the presence of other preexisting thromboembolic risk factors that resulted in initiation of warfarin therapy in these patients (e.g., venous thrombosis, atrial fibrillation) or new, concurrent risk factors (e.g., trauma, head injury).

We previously reported a patient who was initially successfully treated with rfVIIa for refractory, massive hemorrhage while on extracorporeal membrane oxygenation (ECMO) after cardiothoracic surgery but who suffered massive thrombosis after subsequently receiving an activated PCC.[126] Another case of fatal intracardiac thrombosis following rapid administration of activated PCC for urgent warfarin coagulation reversal was also reported.[188] The reported incidence of thromboembolic events published between 1998 and 2008 ranged from 0% to 7% (overall weighted mean, 2.3%), with higher and repeated dosing potentially associated with higher risk.[179] Multinational trials of patients receiving a four-factor PCC product at various infusion speeds for urgent vitamin K antagonist reversal supported the safety and efficacy of rapid infusion of PCC in these patients.[189,190] However, the recommendation that "whenever possible, patients receiving PCCs should be under low dose heparin prophylaxis"[181] underscores that the use of PCCs in this setting is accompanied by risks of thrombosis. One review of eight clinical studies identified a thromboembolic event rate of 0.9% associated with PCC therapy.[191] Studies of optimal dosing strategies for PCC, including fixed versus variable (weight-based) dosage, provide a basis for future research.[192]

As pooled blood product derivatives, PCCs also have potential risks of transmitting infectious agents.[193] Various processing methods such as nanofiltration, solvent detergent treatment, and vapor heating have been used to inactivate pathogens in commercially available PCCs and pooled plasma products.[194] The cost effectiveness of such products with pathogen reduction technology is an area of current debate.[195,196] Potential risks and limitations of PCC therapy compared with plasma therapy are summarized in Table 63-6.

INDICATIONS FOR PLATELET TRANSFUSION

The Joint Commission developed a performance indicator for prophylactic platelet transfusions in patients with malignant hematologic diseases or in patients who undergo stem cell transplantation, in which a platelet count threshold of $10{,}000/mm^3$ is appropriate for prophylactic platelet transfusions.[197]

Current guidelines from the European Union and United States recommend a transfusion trigger of 10×10^9/L for platelets transfused prophylactically.[158,198] These guidelines are based on outcomes from four randomized clinical trials that compared prophylactic triggers of 10×10^9/L versus 20×10^9/L in patients with acute leukemia and in autologous and allogeneic hematopoietic stem cell transplant recipients.[197,199-202] Two additional prospective studies also demonstrated safety with the lower threshold

of 10 × 10^9/L for prophylactic platelet transfusions.[203,204] The impact of these thresholds on numbers of platelet and blood transfusions is variable; however, one study demonstrated a 36% and 16% reduction in platelet and blood transfusions, respectively,[204] whereas another showed no differences.[203]

Another trial demonstrated that "low-dose" prophylactic platelet transfusions are as effective as "standard-dose" or "high-dose" transfusions.[205] For therapeutic platelet transfusions, algorithms based on point-of-care testing have demonstrated promise in patients who have platelet-derived bleeding, such as in cardiothoracic surgery[13,206] and in trauma.[207] As for the evidence-based literature for plasma therapy, additional studies in platelet transfusion are needed (see also Chapter 61).[208]

TABLE 63-6 POTENTIAL RISKS AND LIMITATIONS OF PLASMA AND PROTHROMBIN COMPLEX CONCENTRATE THERAPY

Product	Risks and Limitations
I. Single-donor plasma	1. Longer time to administer 2. Volume constraints 3. Transmissible disease, known/unknown 4. Allergic reactions 5. Transfusion-related acute lung injury (TRALI)
II. Prothrombin complex concentrates	1. Limited availability 2. Some preparations lack factor VII 3. Donor pools: 3,000 to 20,000 4. Transmissible disease, known or unknown (for nonenveloped pathogens) 5. Thrombogenicity

From Goodnough LT: A reappraisal of plasma, prothrombin complex concentrates, and recombinant factor VIIa in patient blood management, Crit Care Clin *28:413, 2012 with permission.*

BLOODLESS MEDICINE

Some patients object to receiving blood or blood products as part of their medical treatment. Many of these individuals are Jehovah's Witnesses and refuse the transfusion of another person's blood based on strict interpretations of both Old and New Testament texts that refer to the sanctity of blood.[209] This religious group currently has more than 6 million active and 14 million associated followers worldwide, and its publications are translated into more than 200 different languages. In the 1980s, bloodless medicine programs were started at the request of Jehovah's Witness patients who wanted hospitals where they could receive the best medical care and have their desire to avoid allogeneic blood transfusions respected.[209]

Many people in the United States, regardless of their religious background, have voiced concern about the safety of blood transfusions. A telephone survey found that only 61% of the respondents believed the blood supply in the United States to be safe, and 33% said that they would refuse blood transfusions if hospitalized.[22] Since 2000, public concerns about problems with the blood supply and shortages in the availability of volunteer blood donors have also led to the development of bloodless medicine centers.

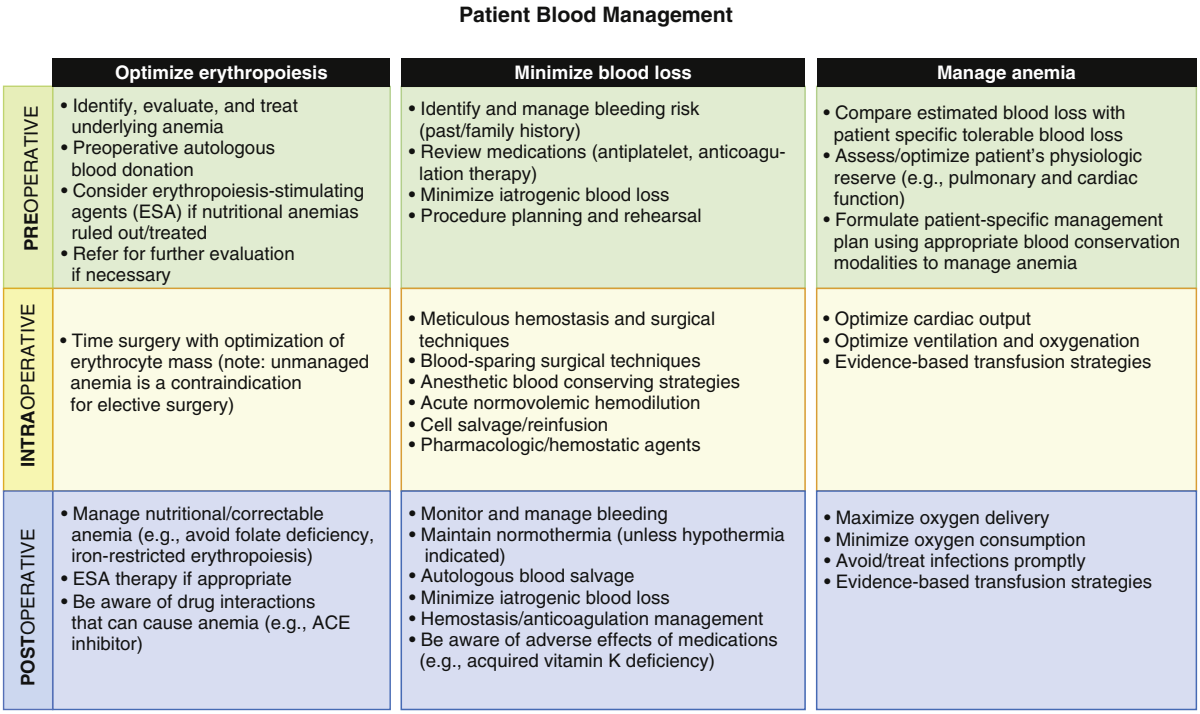


Figure 63-2. Patient blood management. These principles applied in the perisurgical period enable treating physicians to have the time and tools to provide patient-centered evidenced-based patient blood mangement to minimize allogeneic blood transfusions. *(From Goodnough LT, Shander A: Patient blood management,* Anesthesiology *116:1367-1376, 2012.)*

Bloodless medicine and surgery are defined as a team approach "that reduces blood loss and uses the best available alternatives to allogeneic transfusion therapy while focusing on the provision of the best possible medical care to all patients."[16] The objectives of a bloodless medicine program should include "providing leadership within an institution for bloodless medicine and being the advocate for patients not accepting transfusion."[210] All clinicians should realize that a philosophy of blood management that incorporates avoidance of unnecessary blood transfusions in all patients is appropriate even if a bloodless medicine center does not exist at their institutions.[16] The principles of patient blood management can serve to achieve a goal of minimizing allogeneic blood transfusions, not only for Jehovah's Witness patients, but also for all patients (Fig. 63-2).[6]

CONCLUSION

Blood transfusions carry risks, they are costly, and the supply of blood is limited (see also Chapter 61). Blood transfusion outcomes are therefore undergoing renewed scrutiny by health care institutions to reduce blood use. In addition to accreditation organizations, professional societies are also well positioned to incorporate blood transfusion outcomes as quality indicators in their own guidelines and recommendations.[211]

The foundations of patient blood management in the perisurgical period are illustrated in Figure 63-2: (1) optimize erythropoiesis, (2) minimize blood loss, and (3) manage anemia. Strategies begin with preoperative preadmission testing and extend throughout the intraoperative and postoperative intervals, thus enabling treating physicians to minimize allogeneic blood transfusions while delivering safe and effective health care. Physicians and hospital quality or clinical effectiveness departments should incorporate the principles of patient blood management into hospital-based process improvement initiatives that enhance patient safety and clinical outcomes.

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Chapter 64

Anesthesia and Treatment of Chronic Pain

CHRISTOPH STEIN • ANDREAS KOPF

Key Points

- The normal physiology of neuronal function, receptors, and ion channels, is altered by persistent pain.
- Because of the large number of sources and manifestation of chronic pain, classification must include cancer-related, neuropathic, inflammatory, arthritis, and musculoskeletal pain.
- Interdisciplinary management of chronic pain must include specialists in psychology, physical therapy, occupational therapy, neurology, and anesthesiology.
- Drugs used for chronic pain are multiple and include opioids, nonsteroidal antiinflammatory drugs and antipyretic analgesics, serotonin receptor ligands, antiepileptics, antidepressants, topical analgesics (e.g., nonsteroidal antiinflammatory drugs, capsaicin, local anesthetics, opioids), and adjuvants such as local anesthetics, α_2-agonists, baclofen, botulinum toxin, antiemetics, laxatives, novel drugs such as cannabinoids, and ion channel blockers.
- Interventional management of chronic pain includes the use of diagnostic blocks, therapeutic blocks, continuous catheter techniques (peripheral, epidural, intrathecal), and stimulation techniques such as acupuncture, transcutaneous electrical nerve stimulation, and spinal cord stimulation.
- Perioperative management of patients with chronic pain involves the following: the use of opioid and nonopioid analgesics; evaluation for dependence, addiction, and pseudoaddiction; and practical considerations.

PHYSIOLOGIC CHANGES IN PERSISTENT PAIN

EXCITATORY MECHANISMS

Pain may be roughly divided into two broad categories: physiologic and pathologic pain. Physiologic (acute, nociceptive) pain is an essential early warning sign that usually elicits reflex withdrawal and thereby promotes survival by protecting the organism from further injury. In contrast, pathologic (e.g., neuropathic) pain is an expression of the maladaptive operation of the nervous system; it is pain as a disease.[1] Physiologic pain is mediated by a sensory system consisting of primary afferent neurons, spinal interneurons and ascending tracts, and several supraspinal areas. Trigeminal and dorsal root ganglia (DRGs) give rise to high-threshold Aδ and C fibers innervating peripheral tissues (skin, muscles, joints, viscera). These specialized primary afferent neurons, also called nociceptors, transduce noxious stimuli into action potentials and conduct them to the dorsal horn of the spinal cord (Fig. 64-1). When peripheral tissue is damaged, primary afferent neurons are sensitized or directly activated, or both, by a variety of thermal, mechanical, and/or chemical stimuli. Examples are protons, sympathetic amines, adenosine triphosphate (ATP), glutamate, neuropeptides (calcitonin gene–related peptide, substance P), nerve growth factor, prostanoids, bradykinin, proinflammatory cytokines, and chemokines.[2,3] Many of these agents lead to opening (gating) of cation channels in the neuronal membrane. Such channels include the capsaicin-, proton-, and heat-sensitive transient receptor potential vanilloid 1 (TRPV1), or the ATP-gated purinergic $P2X_3$ receptor. Gating produces an inward current of sodium (Na^+) and calcium (Ca^{2+}) ions into the peripheral nociceptor terminal. If this depolarizing current is sufficient to activate voltage-gated Na^+ channels (e.g., $Na_v1.8$), they too will open, further depolarizing the membrane and initiating a burst of action potentials that are then conducted along the sensory axon to the dorsal horn of the spinal cord.[3,4] Thereafter, these impulses are transmitted to spinal neurons, brainstem, thalamus, and cortex.[5,6]

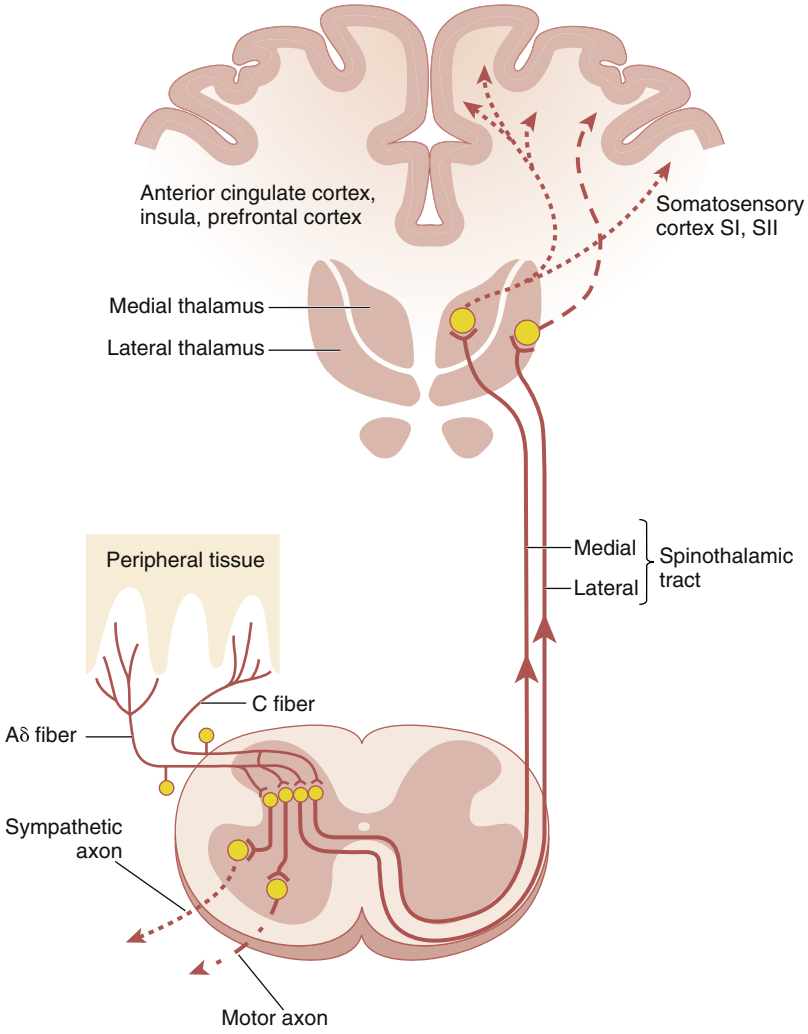


Figure 64-1. Nociceptive pathways. For details see text. *(Modified from Brack A, Stein C, Schaible HG: Periphere und zentrale Mechanismen des Entzündungsschmerzes. In Straub RH, editor:* Lehrbuch der klinischen Pathophysiologie komplexer chronischer Erkrankungen, *vol 1, Göttingen, Germany, 2006, Vandenhoeck & Ruprecht, pp 183-192.)*

Transmission of input from nociceptors to spinal neurons that project to the brain is mediated by direct monosynaptic contact or through multiple excitatory or inhibitory interneurons. The central terminals of nociceptors contain excitatory transmitters such as glutamate, substance P, and neurotrophic factors that activate postsynaptic *N*-methyl-D-aspartate (NMDA), neurokinin (NK_1), and tyrosine kinase receptors, respectively. Repeated nociceptor stimulation can sensitize both peripheral and central neurons (activity-dependent plasticity). In spinal neurons, such a progressive increase of output in response to persistent nociceptor excitation has been termed wind-up. Later, sensitization can be sustained by transcriptional changes in the expression of genes coding for various neuropeptides, transmitters, ion channels, receptors, and signaling molecules (transcription-dependent plasticity) in both nociceptors and spinal neurons. Important examples include the NMDA receptor, cyclooxygenase-2 (COX-2), Ca^{2+} and Na^{+} channels, cytokines, and chemokines expressed by neurons and/or glial cells.[7,8] In addition, physical rearrangement of neuronal circuits by apoptosis, nerve growth, and sprouting occurs in the peripheral and central nervous systems.[1,5]

INHIBITORY MECHANISMS

Concurrent with the events just described, powerful endogenous mechanisms counteracting pain unfold both in the periphery and in the central nervous system. In injured tissue, this process results from interactions between leukocyte-derived opioid peptides and peripheral nociceptor terminals carrying opioid receptors[9,10] and/or by antiinflammatory cytokines.[2] Inflammation of peripheral tissue leads to increased expression, axonal transport, and enhanced G-protein coupling of opioid receptors in DRG neurons as well as enhanced permeability of the perineurium. These phenomena depend on sensory neuron electrical activity, the production of proinflammatory cytokines, and the presence of nerve growth factor within the inflamed tissue. In parallel, opioid peptide–containing immune cells extravasate and accumulate in the inflamed tissue.[10] These cells up-regulate the gene expression of opioid precursors and the enzymatic machinery for their processing into functionally active peptides.[11,12] In response to stress, catecholamines, corticotropin-releasing factor, cytokines, chemokines, or bacteria, leukocytes secrete opioids. The latter activate peripheral opioid receptors and produce analgesia by inhibiting the excitability

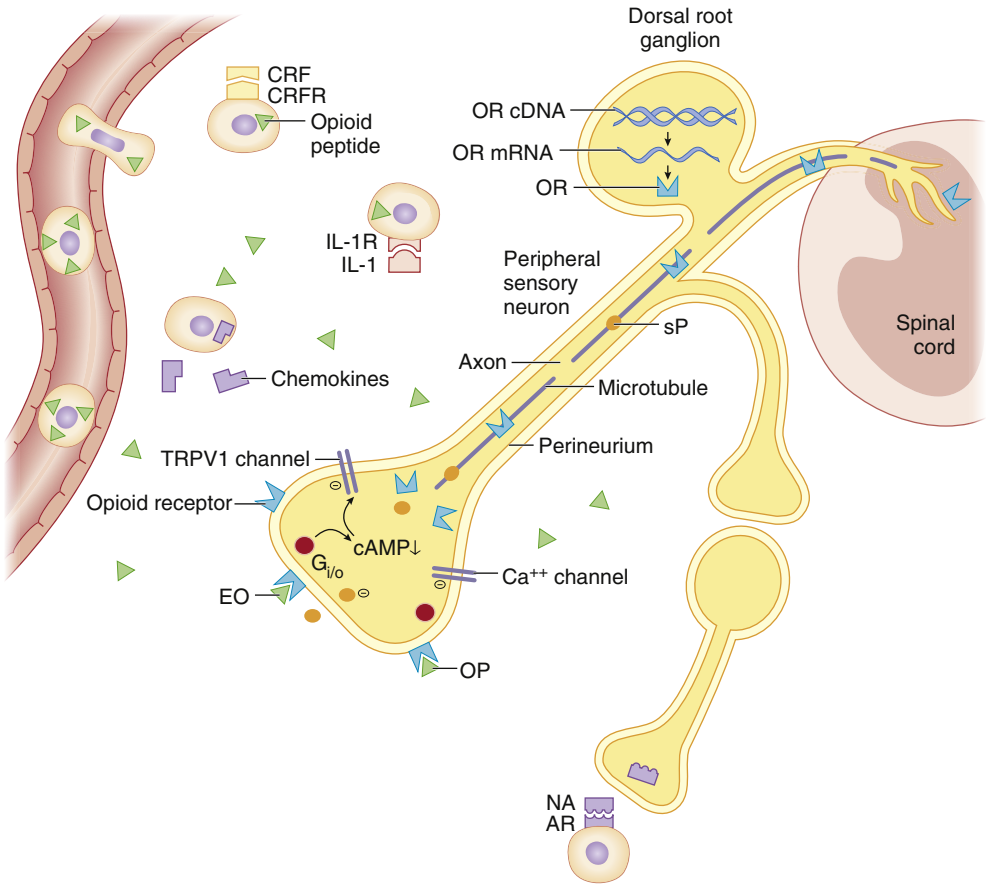


Figure 64-2. Endogenous antinociceptive mechanisms within peripheral injured tissue. Opioid peptide-containing circulating leukocytes extravasate upon activation of adhesion molecules and chemotaxis by chemokines. Subsequently, these leukocytes are stimulated by stress or releasing agents to secrete opioid peptides. For example, corticotropin-releasing factor (CRF), interleukin-1β (IL-1) and norepinephrine (noradrenaline [NA], released from postganglionic sympathetic neurons) can elicit opioid release by activating their respective CRF receptors (CRFR), IL-1 receptors (IL-1R), and adrenergic receptors (AR) on leukocytes. Exogenous opioids (EO) or endogenous opioid peptides (OP, *green triangles*) bind to opioid receptors (OR) that are synthesized in dorsal root ganglia and are transported along intraaxonal microtubules to peripheral (and central) terminals of sensory neurons. The subsequent inhibition of ion channels (e.g., TRPV1, Ca^{2+}) (see Fig. 64-3 and text) and of substance P (sP) release results in antinociceptive effects. *cAMP,* Cyclic adenosine monophosphate. *(Modified from Stein C, Machelska H: Modulation of peripheral sensory neurons by the immune system: implications for pain therapy,* Pharmacol Rev *63:860-881, 2011.)*

of nociceptors, the release of excitatory neuropeptides, or both[10,13] (Fig. 64-2). The clinical relevance of these mechanisms was shown in studies demonstrating that patients with knee joint inflammation expressed opioid peptides in immune cells and opioid receptors on sensory nerve terminals within synovial tissue.[14] After knee surgery, pain and analgesic consumption were enhanced by blocking the interaction between the endogenous opioids and their receptors with intraarticular naloxone[15] and diminished by stimulating opioid secretion.[16]

In the spinal cord, inhibition is mediated by the release of opioids, γ-aminobutyric acid (GABA), or glycine from interneurons, which activate presynaptic opioid or GABA receptors, or both, on central nociceptor terminals to reduce excitatory transmitter release. In addition, the opening of postsynaptic potassium (K^+) or chloride (Cl^-) channels by opioids or GABA, respectively, evokes hyperpolarizing inhibitory potentials in dorsal horn neurons. During ongoing nociceptive stimulation, spinal interneurons up-regulate gene expression and the production of opioid peptides.[17,18] Powerful descending inhibitory pathways from the brainstem also become active by operating mostly through noradrenergic, serotonergic, and opioid systems. A key region is the periaqueductal gray, which projects to the rostral ventromedial medulla, which then projects along the dorsolateral funiculus to the dorsal horn.[19] The integration of signals from excitatory and inhibitory neurotransmitters with cognitive, emotional, and environmental factors (see later) eventually results in the central perception of pain. When the intricate balance of biologic, psychological, and social factors becomes disturbed, chronic pain can develop.

TRANSLATION OF BASIC RESEARCH

Basic research on pain continues at a rapid pace, but translation into clinical applications has been difficult.[20] Animal studies are indispensable. However, for ethical reasons these studies are restricted to days or weeks, whereas human chronic pain can last for months or years. Therefore, animal models do not mirror the truly chronic clinical situation and should be more cautiously termed

reflections of persistent pain.[21,22] Brain imaging is an area of intense research, and numerous studies have investigated changes in patients with various pain syndromes. However, such studies have not yet provided reproducible findings specific for a disease or a pathophysiologic basis for individual syndromes.[21] Neuroimaging can detect only alterations associated with nociceptive processes, whereas clinical pain encompasses a much more complex subjective experience that critically relies on self-evaluation. Thus, imaging cannot provide an objective proxy, biomarker, or predictor for pain[23] (see also the next section). Similarly, although basic research has produced some evidence for genetic control of pain, such findings are not expected to serve as a guide to individualized (personalized) clinical pain therapy any time soon.[21,24]

CLINICAL DEFINITIONS, PREVALENCE, AND CLASSIFICATION OF CHRONIC PAIN

DEFINITIONS

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[25,26] This classification further states that pain is always subjective and that it is a sensation in parts of the body. At the same time, pain is unpleasant and therefore also has an emotional component. Aside from malignant disease, many people report pain in the absence of tissue damage or any likely pathophysiologic cause. Usually, no way exists to distinguish their experience from a condition resulting from tissue damage. If patients regard their experience as pain or if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to a stimulus. *Nociception* is neurophysiologic activity in peripheral sensory neurons (nociceptors) and higher nociceptive pathways and is defined by the IASP as the "neural process of encoding noxious stimuli." Nociception is not synonymous with pain. Pain is always a psychological state, even though it often has a proximate physical cause. *Chronic pain* is defined by the American Society of Anesthesiologists as "extending in duration beyond the expected temporal boundary of tissue injury and normal healing, and adversely affecting the function or well-being of the individual."[27] The IASP subcommittee on taxonomy defined it in 1986 as "pain without apparent biological value that has persisted beyond the normal tissue healing time usually taken to be three months." The presence or extent of chronic pain often does not correlate with the documented tissue disorder.

PREVALENCE

Beyond these general definitions, no common understanding exists about the characteristics of the patient with chronic pain. This may be one reason that estimates of pain prevalence differ greatly from one publication to another. Heterogeneous populations, the occurrence of undetected comorbidity, different definitions of chronic pain, and different approaches to data collection have resulted in estimates of 20% to 60%. Some surveys indicate a more frequent prevalence among women and older adults. Chronic pain has enormous socioeconomic costs. In the United States alone, annual expenditures amount to more than $600 billion for health care, disability compensation, lost work days, and related expenses. Similar figures have been reported by other countries.[28,29]

CLASSIFICATION

Traditionally, a distinction is made between malignant (related to cancer and its treatment) and nonmalignant (e.g., neuropathic, musculoskeletal, inflammatory) chronic pain. To separate somatic and psychological mechanisms is probably not warranted. Patients with cancer tend to have more serious health restrictions than do patients with chronic nonmalignant pain. Patients with nonmalignant pain may report higher pain scores and expect more pain relief than do patients with cancer.[30] Nonmalignant chronic pain is frequently classified into inflammatory pain (e.g., arthritic), musculoskeletal pain (e.g., low back pain), headaches, and neuropathic pain (e.g., postherpetic neuralgia, phantom pain, complex regional pain syndrome, diabetic neuropathy, human immunodeficiency virus–associated neuropathy). Frequent symptoms of neuropathic pain include the following: spontaneous lancinating, shooting, or burning pain; hyperalgesia; and allodynia; or any combination of such pain.[31] Cancer pain can originate from invasion of the tumor into tissues innervated by primary afferent neurons (e.g., pleura, peritoneum) or directly into a peripheral nerve plexus. In the latter situation, neuropathic symptoms may be predominant. A problem in the treatment of cancer pain is the lack of correlation between the patient's self-reporting and the assessment of clinical staff. Pain may be underestimated by medical staff and family members, thus resulting in poor pain control.[29] Many treatments for cancer are associated with severe pain. For example, cytoreductive radiation therapy or chemotherapy frequently causes painful oral mucositis, especially in patients undergoing bone marrow transplantation.[32]

BIOPSYCHOSOCIAL CONCEPT OF CHRONIC PAIN

Patients with chronic pain who have cancer or nonmalignant diseases have in common the complex influences of biologic (tissue damage), cognitive (memory, expectations), emotional (anxiety, depression), and environmental factors (reinforcement, conditioning). Many patients present with limited mobility, lack of motivation, depression, anger, anxiety, and fear of reinjury, all of which hamper the return to normal work or recreational activities. Such patients may become preoccupied with pain and somatic processes, which may disrupt sleep, cause irritability, and social withdrawal. Other cognitive factors such as patients' expectations or beliefs (e.g., perceived inability to control the pain) influence psychosocial and physical functioning. Pain behavior such as limping, medication intake, or avoidance of activity is subject to operant conditioning; that is, it responds to reward and punishment. For example, pain behavior may be positively reinforced by attention from a spouse or health

care provider (e.g., by inadequate use of nerve blocks or medications). Conversely, such behavior can be extinguished when it is disregarded and incremental activity is reinforced by social attention and praise.[33] Respondent learning mechanisms (i.e., classic conditioning) may also contribute to chronicity.[34] Other issues often coexist, such as substance abuse problems, family dysfunction, and conflicts with legal or insurance systems. Consequently, care seeking is an integral feature of the pain experience, and excessive use of the health care system ensues. The interplay among these biologic, psychological, and social factors results in the persistence of pain and illness behaviors.[33,34] Treating only one aspect of this complex syndrome is obviously insufficient. Therefore, a biopsychosocial concept of pain has been adopted. This concept was first described by Engel in 1959,[35] but its implementation into daily practice has been tardy, especially concerning patients with chronic pain.[36,37] This concept helps us understand why chronic pain may exist without obvious physical cause or why pathologic somatic findings may remain unnoticed by the patient. The experience and regulation of social and physical pain may share a common neuroanatomic basis.[38] In a multimodal approach, pain management addresses physical, psychological, and social skills and underscores the patients' active responsibility to regain control over life by improving function and well-being.[34,39]

INTERDISCIPLINARY MANAGEMENT OF CHRONIC PAIN

The anesthesiologist John J. Bonica was the first to appreciate the need for a multidisciplinary approach to chronic pain. His early experiences in and after World War II convinced Bonica that complex pain problems could be more effectively treated when different disciplines contributed their specialized knowledge and skills to the common goal of making a correct diagnosis and developing the most effective therapeutic strategy. The first multidisciplinary facility was put into practice at the Tacoma General Hospital in the state of Washington, followed by the University of Washington in 1960. From 1970 through 1990, the number of pain management facilities continued to increase in North America and Europe, and they were mostly directed by anesthesiologists. Such comprehensive pain centers should have personnel and facilities to evaluate and treat the biomedical, psychosocial, and occupational aspects of chronic pain and to educate and teach medical students, residents, and fellows. Guidelines for characteristics of pain treatment facilities have been published by the IASP.[40] Multidisciplinary and multimodal management results in increased physical and psychosocial function, reduced health care use, and vocational rehabilitation. A meta-analysis found that such programs offer the most efficacious and cost-effective, evidence-based treatment of chronic nonmalignant pain.[37] Treatment of chronic pain without an interdisciplinary approach is inadequate and may lead to misdiagnoses. For example, overlooking psychological processes in a patient with presumed discogenic back pain or overlooking a somatic etiology in a presumed "psychogenic" pain disorder may lead to the wrong conclusion.[41] Moreover, conventional monomodal approaches such as pharmacotherapy alone only perpetuate the expensive, futile, and endless search for medical solutions.[37,39]

The core team usually comprises a pain management physician (anesthesiologist with subspecialty training), a psychologist, a physical therapist, and an occupational therapist. Other medical specialties, such as neurology, may be involved. Depending on the local circumstances, administrators, nurse specialists, and/or pharmacists can also be involved. The initial screening of the patient by members of the core team determines what other specialists will be needed for a complete assessment. After this evaluation, the patient is presented to the entire core team, and a comprehensive treatment plan is developed. This plan is tailored to the patient's needs, abilities, and expectations, with a focus on achieving measurable treatment goals established with the patient. For some patients, education and medical management may suffice, whereas for others, an intensive full-day rehabilitation program over several weeks may be needed. Early stratification of the management according to the patient's prognosis (low, medium, or high risk for persistent disability because of pain) results in significantly higher clinical and cost effectiveness.[42] To foster patient compliance, an open discussion of treatment goals with regard to the patient's anticipations is essential. Many patients expect complete resolution of pain and return to full function, a goal that may not be achievable. In many cases, realistic options are as follows: reduction of pain; improvement of physical function, mood, and sleep; development of active coping skills; and return to work. Thus, rehabilitation rather than cure is the most appropriate therapeutic option.[37]

PSYCHOLOGY

The role of the psychologist includes the initial assessment and treatment approaches such as education, cognitive-behavioral therapy, and relaxation training. Assessment of the patient addresses the sensory, affective, cognitive, behavioral, and occupational dimensions of the pain problem. The assessment includes an extensive biographic history and behavioral analysis, along with the obligatory use of questionnaires. Most questionnaires include scoring systems for pain intensity (e.g., numeric or visual analog scales), pain behavior (e.g., West-Haven-Yale Multidimensional Pain Inventory), multidimensional pain quality, cognitive coping, fear (e.g., State-Trait-Anxiety-Inventory), depression, and other associated symptoms. Indications for psychological pain management are relevant somatization, depressive disorders, inadequate coping, drug abuse, and high levels of pain behavior reinforced by the environment (e.g., family members). Patients with some types of pain syndromes, such as chronic headache, inflammatory rheumatic pain, or unspecific back pain, may specifically benefit from behavioral therapy.[34,37] This usually means a complete change of approach for the patient, from a purely passive recipient of curative treatment to an active, self-reliant participant in functional restoration, vocational rehabilitation, and reduced health care use despite pain. Thus, pain reduction alone is no longer the focus of therapy.[37]

PHYSICAL THERAPY

The role of the physical therapist includes initial evaluation of the musculoskeletal system, assessment of the patient's work place and home, education in active physical coping skills, and management of the physical rehabilitation process. An intensive exercise program emphasizing the patient's responsibility for self-management is an integral part of comprehensive programs for chronic nonmalignant pain.[37,43] Improving fitness, mobility, and posture counteracts the effects of disuse and complements behavioral treatment. The physical therapist encourages the adoption of regular exercise into daily life, facilitates repeated exposure to movement as much as possible despite pain, and reinforces education in the biopsychosocial model of pain management. Different techniques of exercise such as muscle conditioning and aerobics are efficacious in improving function, pain, disability, and fear avoidance behavior.[44,45] In contrast, passive treatments such as massage or chiropractic interventions are not beneficial.[46] The regimen of graded exercise follows the original concept of Fordyce.[33] Patients are instructed to find a baseline tolerance level for each exercise. Next, a program of improvement is negotiated and agreed upon. Patients note improvements on a daily basis and are required to complete the exercise plan regardless of how they feel. Thus, the control over exercise behavior is contingent upon plan rather than pain because exercise and pain are disconnected. Individual motivation is an important factor in determining how well patients learn to manage pain.[47]

OCCUPATIONAL THERAPY

The occupational therapist teaches the patient to achieve life goals despite pain and to overcome the limitations imposed by pain. Occupational therapy assessment includes a history of working life and place, family life, and daily activities, as well as a physical examination to determine range of motion and the presence of movement disorders or deformities that could hinder performance. The primary therapeutic objectives are reduction of pain and associated disability, promotion of optimal function in everyday life, and the encouragement of meaningful family, social, and work relationships.[48] An important target is supporting the patient's return to work, including specific work conditioning.[49] The chance of returning to work after a period of sick leave from low back pain, for example, apparently decreases over time, thereby generating enormous costs to society through wage compensation, social support, and loss of production.[29] Barriers to return to work include job dissatisfaction and perceptions of the impact of work on the cause of pain. Together with the patient, the occupational therapist should develop a program to increase self-esteem, restore self-efficacy, and promote optimal occupational and recreational function despite pain.

ANESTHESIOLOGY

The role of the anesthesiologist in the treatment of chronic pain has changed considerably over the last decades. "Nerve block practices" have been replaced by interdisciplinary pain management centers. In this context the anesthesiologist acts as both a physician-educator and a technical expert. The challenge is to complement regional anesthesia skills and pharmacologic knowledge optimally with the psychosocial components of chronic pain to render more comprehensive pain management services. Anesthesiologists must use their expertise in pharmacotherapy, nerve blocks, and skilled techniques within the broad-based biopsychosocial approach. The focus is not only on reducing pain but also on decreasing disability, improving quality of life, and increasing function. The conventional way of administering medication "as needed" or the use of nerve blocks for short-term pain relief may risk reinforcement of pain behavior and the patient's belief in an underlying physical abnormality that is best managed by biomedical procedures.[39] Moreover, false expectations are maintained; for example, the patient cannot be the passive recipient, but rather must be an active participant in the process. Patients may believe that pain is the primary problem in their lives. This belief neglects psychosocial factors, perpetuates the expensive and futile search for unidimensional biomedical solutions, and promotes iatrogenic somatization, medicalization, and high health care use by patients with chronic pain.[39]

The role of the anesthesiologist within the interdisciplinary team differs depending on the type of patient being treated. Management of cancer pain and of acute pain demands the full range of the anesthesiologist's technical skills and pharmacologic knowledge. In chronic nonmalignant pain, the anesthesiologist's abilities as an educator, coach, and motivator are far more important. As a member of the interdisciplinary team, the anesthesiologist must reinforce and maintain the biopsychosocial focus, respond appropriately to somatic concerns, and manage medications. In concert with the other members of the team, the anesthesiologist uses motivational strategies to encourage the patient to attain self-managed reactivation goals in physical, psychosocial, recreational, and vocational domains. At the same time, the anesthesiologist's presence provides "white coat credibility" and is essential to avoid the patient's pejorative conclusion that the pain is "all in my head." The anesthesiologist monitors the patient's physical status, potential development of new medical problems, and medications. In addition, the anesthesiologist provides real-time reassurance and education regarding the absence of relevant abnormalities, discusses the minimal role of surgery, and conveys medical information to make informed choices. The anesthesiologist plays a crucial role within the multidisciplinary team to direct the patient toward a multimodal pain treatment plan. This role is reflected in the fact that most pain therapists worldwide are anesthesiologists. In the described clinical setting, anesthesiologists work closely with other health care professionals and thereby gain added recognition outside the operating room.[39]

DRUGS USED FOR CHRONIC PAIN

Analgesic drugs interfere with the generation or transmission, or both, of impulses following noxious stimulation in the nervous system (nociception). This action can

TABLE 64-1 ANALGESIC DRUGS, TARGETS, MECHANISMS, AND SIDE EFFECTS

Drugs	Targets	Mechanisms	Functional Consequences	Side Effects
Opioids	G-protein coupled μ, δ, κ receptors	↓ cAMP ↓ Ca^{2+} currents ↑ K^+ currents	↓ Excitability of peripheral and central neurons ↓ Release of excitatory neurotransmitters	μ, δ: Sedation, nausea, euphoria/reward, respiratory depression, constipation κ: Dysphoria/aversion, diuresis, sedation
NSAIDs	Cyclooxygenases (COX-1, COX-2)	↓ Prostaglandins ↓ Thromboxanes	↓ Sensitization of sensory neurons ↑ Inhibition of spinal neurons	Nonselective: gastrointestinal ulcers, perforation, bleeding, renal impairment COX-2: thrombosis, myocardial infarction, stroke
Serotonin agonists	G-protein coupled 5-HT receptors 5-HT_3: ion channels	↓ cAMP (5-HT_1) ↑ cAMP ($5\text{-HT}_{4\text{-}7}$) ↑ PLC (5-HT_2)	↓ Release of excitatory neuropeptides ↓ Neurogenic inflammation ↑ Vasoconstriction	Myocardial infarction, stroke, peripheral vascular occlusion
Antiepileptics	Na^+, Ca^{2+} channels GABA receptors	↓ Na^+ currents ↓ Ca^{2+} currents ↑ GABA receptor activity	↓ Excitability of peripheral and central neurons ↓ Release of excitatory neurotransmitters	Sedation, dizziness, cognitive impairment, ataxia, hepatotoxicity, thrombocytopenia
Antidepressants	Norepinephrine/5-HT transporters Na^+, K^+ channels	↓ Norepinephrine/5-HT reuptake ↓ Na^+ currents ↑ K^+ currents	↓ Excitability of peripheral and central neurons	Cardiac arrhythmia, myocardial infarction, sedation, nausea, dry mouth, constipation, dizziness, sleep disturbance, blurred vision

Ca^{2+}, Calcium; *cAMP,* cyclic adenosine monophosphate; *GABA,* γ-aminobutyric acid; *5-HT,* 5-hydroxytryptamine (serotonin); *K^+*, potassium; *Na^+*, sodium; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PLC,* phospholipase C.

occur at both the peripheral and central levels of the neuraxis. The therapeutic aim is to diminish the perception of pain. Analgesics aim at modulating either the formation of noxious chemicals (e.g., prostaglandins) or the activation of neuronal receptors or ion channels transducing or transmitting noxious stimuli (e.g., peptide, kinin, monoamine receptors, Na^+ channels). Drugs currently used in chronic pain include opioids, nonsteroidal antiinflammatory drugs (NSAIDs), serotonergic compounds, antiepileptics, and antidepressants (Table 64-1). Other classes, such as adrenergic receptor agonists, excitatory amino acid receptor (e.g., NMDA) antagonists, neurotrophin antagonists, neuropeptide (e.g., calcitonin gene–related peptide) receptor antagonists, kinin receptor antagonists, prostaglandin E receptor (EP) antagonists, cannabinoids, and ion channel (e.g., TRP, P2X) blockers are under investigation. Local anesthetics are used for local and regional anesthetic techniques. Mixed drugs combine different mechanisms, for example, norepinephrine reuptake inhibition and opioid agonist effects (tramadol, tapentadol), or opioid agonist and NMDA antagonist effects (ketamine). Various routes of drug administration (e.g., oral, intravenous, subcutaneous, intrathecal, epidural, topical, intraarticular, transmucosal) can be used, depending on the clinical circumstances. In addition, placebo treatments have shown impressive analgesic effects, mediated by opioid and nonopioid mechanisms.[50] Chronic pain requires a multidisciplinary approach encompassing various pharmacologic and nonpharmacologic (psychological, physiotherapeutic) treatment strategies (see the previous section on the interdisciplinary management of chronic pain).

OPIOIDS

Opioids act on heptahelical G-protein–coupled receptors (see also Chapter 31). Three types of opioid receptors (μ, δ, κ) have been cloned. Several subtypes (e.g., μ_1, μ_2, δ_1, δ_2), possibly resulting from gene polymorphisms, splice variants, or alternative processing, have been proposed. Opioid receptors are localized and can be activated along all levels of the neuraxis, including peripheral and central processes of primary sensory neurons (nociceptors), spinal cord (interneurons, projection neurons), brainstem, midbrain, and cortex. All opioid receptors couple to G proteins (mainly G_i/G_o) and subsequently inhibit adenylyl cyclase, decrease the conductance of voltage-gated Ca^{2+} channels, or open rectifying K^+ channels, or any combination of these effects (Fig. 64-3, *top*). These effects ultimately result in decreased neuronal activity. The prevention of Ca^{2+} influx inhibits the release of excitatory (pronociceptive) neurotransmitters. A prominent example is the suppression of substance P release from primary sensory neurons, both within the spinal cord and from their peripheral terminals within injured tissue. At the postsynaptic membrane, opioids produce hyperpolarization by opening K^+ channels, thereby preventing excitation or propagation of action potentials in second order projection neurons. In addition, opioids inhibit sensory neuron-specific tetrodotoxin-resistant Na^+ channels, TRPV1 channels, and excitatory postsynaptic currents evoked by glutamate receptors (e.g., NMDA) in the spinal cord. The results are decreased transmission of nociceptive stimuli at all levels of the neuraxis and profoundly reduced perceptions of pain. Endogenous opioid receptor ligands are derived from the precursors proopiomelanocortin

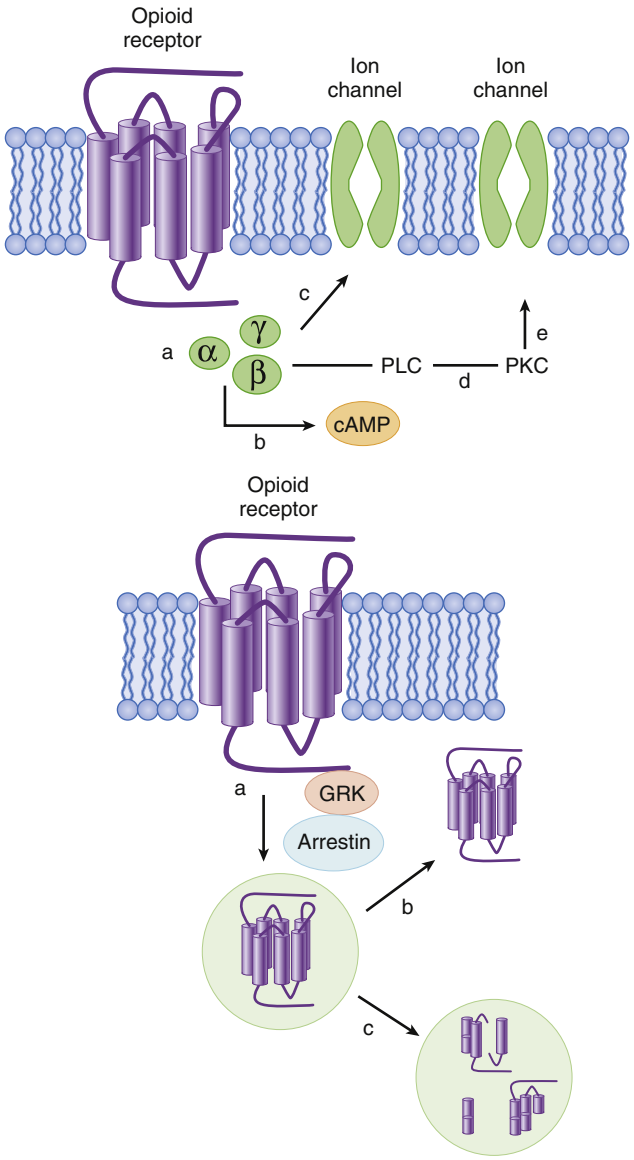


Figure 64-3. Opioid receptor signaling and recycling. *Upper panel:* Opioid ligands induce a conformational change at the receptor that allows coupling of G-proteins to the receptor. The heterotrimeric G-protein dissociates into active Gα and Gβγ subunits *(a),* which can inhibit adenylyl cyclase and reduce cyclic adenosine monophosphate (cAMP) *(b),* decrease the conductance of voltage-gated calcium (Ca^{2+}) channels, or open rectifying potassium (K^+) channels *(c).* In addition, the phospholipase C (PLC)/phosphokinase C (PKC) pathways can be activated *(d)* to modulate Ca^{2+} channel activity in the plasma membrane *(e). Lower panel:* Opioid receptor desensitization and trafficking is activated by G-protein–coupled receptor kinases (GRK). After arrestin binding, the receptor is in a desensitized state at the plasma membrane *(a).* Arrestin-bound receptors can then be internalized via a clathrin-dependent pathway and can either be recycled to the cell surface *(b)* or degraded in lysosomes *(c). (Modified from Zöllner C, Stein C: Opioids,* Handb Exp Pharmacol *177:31-63, 2007.)*

(encoding β-endorphin), proenkephalin (encoding Met-enkephalin and Leu-enkephalin), and prodynorphin (encoding dynorphins). These peptides contain the common Tyr-Gly-Gly-Phe-Met/Leu sequence at their amino terminals, known as the opioid motif. β-Endorphin and the enkephalins are potent antinociceptive agents acting at μ and δ receptors. Dynorphins can elicit both pronociceptive and antinociceptive effects through NMDA receptors and κ opioid receptors, respectively. A fourth group of tetrapeptides (endomorphins) with yet unknown precursors does not contain the pan-opioid motif but binds to μ receptors with high selectivity. Opioid peptides and receptors are expressed throughout the central and peripheral nervous systems, in neuroendocrine tissues, and in immune cells.[10,51] Extracellular opioid peptides are susceptible to rapid enzymatic inactivation by aminopeptidase N and neutral endopeptidase. Both peptidases are expressed in the central nervous system, peripheral nerves, and leukocytes; among opioids, enkephalins are considered their preferred substrates. Preventing the extracellular degradation of endogenous opioid peptides by peptidase inhibitors, both in central and peripheral compartments, has been shown to produce potent analgesic effects in many animal models and in some small human trials.[52,53]

The commonly available opioid drugs (morphine, codeine, methadone, and fentanyl and its derivatives) are μ agonists. Naloxone is a nonselective antagonist at all three receptors. Partial agonists must occupy a greater fraction of the available pool of functional receptors than full agonists to induce a response of equivalent magnitude. Mixed agonist-antagonists (buprenorphine, butorphanol, nalbuphine, and pentazocine) may act as agonists at low doses and as antagonists (at the same or a different receptor type) at higher doses. Such compounds typically exhibit ceiling effects for analgesia, and they may elicit an acute withdrawal syndrome when administered together with a pure agonist. All three receptors (μ, δ, κ) mediate analgesia but have differing side effects. μ Receptors mediate respiratory depression, sedation, reward and euphoria, nausea, urinary retention, biliary spasm, and constipation.[54] κ Receptors mediate dysphoric, aversive, sedative, and diuretic effects. δ Receptors mediate reward and euphoria, respiratory depression, and constipation.[51] Immunosuppressive effects of opioids were frequently proposed in experimental trials but have not been verified in clinical studies.[55] Tolerance and physical dependence may occur with prolonged administration of pure agonists, and abrupt discontinuation or antagonist administration can result in a withdrawal syndrome (see also the later section on perioperative management of patients with chronic pain).

Tolerance describes the phenomenon that the magnitude of a given drug effect decreases with repeated administration of the same dose, or that increasing doses are needed to produce the same effect. Tolerance is not synonymous with dependence (see the later section on perioperative management of patients with chronic pain). All opioid effects (e.g., analgesia, nausea, respiratory depression, sedation, constipation) can be subject to tolerance development, albeit to different degrees. For example, tolerance to respiratory depression, sedation, and nausea often develops faster than does tolerance to constipation or miosis[54-57] (see also the later section on other analgesics and adjuvants). Incomplete cross-tolerance among opioids or genetic differences may explain clinical observations that switching drugs ("opioid rotation") is occasionally useful in patients with inadequate pain relief or intolerable side effects.[58] Opioid-induced adaptations occur at multiple levels in the nervous and other organ

systems, beginning with direct modulation of opioid receptor signaling and extending to complex neuronal networks including learned behavior. Proposed mechanisms in pharmacodynamic tolerance include opioid receptor–G-protein uncoupling, decreased receptor internalization and recycling, and increased sensitivity of the NMDA receptor[51,59] (see Fig. 64-3, *bottom*). In addition, pharmacokinetic (e.g., altered distribution or metabolism of the opioid) and learned tolerance (e.g., compensatory skills developed during mild intoxication), as well as increased nociceptive stimulation by tumor growth, inflammation, or neuroma formation, may be possible reasons for increased dose requirements.[56,60] Carefully controlled studies that unequivocally demonstrate pharmacodynamic tolerance to opioid analgesia (i.e., reduction of clinical pain) in patients are lacking.[61]

Whether opioids may paradoxically induce hyperalgesia continues to be debated. However, most studies have, in fact, shown withdrawal-induced hyperalgesia, a well-known phenomenon following the abrupt cessation of opioids (see also the later section on perioperative management of patients with chronic pain).[62,63] At ultralarge doses, occasionally encountered in patients with extreme cancer pain, singular cases of allodynia have been observed and attributed to neuroexcitatory effects of opioid metabolites.[64] No conclusive evidence indicates that hyperalgesia occurs during perioperative or long-term administration of regular opioid doses in patients.[62]

Opioids are effective in the periphery (e.g., topical or intraarticular administration, particularly in inflamed tissue), at the neuraxis (intrathecal, epidural, or intracerebroventricular administration), and systemically (intravenous, oral, subcutaneous, sublingual, or transdermal administration).[51,65] The clinical choice of a particular compound or its formulation is based on pharmacokinetic considerations (route of administration, desired onset or duration, lipophilicity) and on side effects associated with the respective route of drug delivery.[65] Dosages depend on patients' characteristics, the type of pain, and the route of administration. Systemically and spinally administered opioids can produce similar side effects, depending on dosage and rostral or systemic redistribution. For intrathecal application, lipophilic drugs are preferred because they are trapped in the spinal cord and are less likely to migrate to the brain within the cerebrospinal fluid. Adverse side effects can be minimized by careful dose titration and close patient monitoring, or these effects can be treated by comedication (antiemetics, laxatives) or opioid receptor antagonists (e.g., naloxone). No significant side effects have been reported for the peripheral (e.g., topical) application of small, systemically inactive doses of opioids. Current research pursues the development of systemically applicable peptidase inhibitors and opioids aiming at the selective activation of peripheral but not central opioid receptors.[10,52,53,66,67]

Opioids are considered the most effective analgesics for severe acute and cancer-related chronic pain. However, the long-term use of opioids in chronic noncancer (e.g., neuropathic, musculoskeletal) pain is highly controversial. Randomized controlled trials (RCTs) have been conducted only for a maximum period of 3 months. In meta-analyses, the reduction in pain scores was clinically insignificant, and epidemiologic data suggest that quality of life and functional capacity are not improved.[68,69] Adverse side effects (e.g., nausea, sedation, constipation, dizziness) and lack of analgesic efficacy led to the dropout of high numbers of subjects, both in RCTs and in uncontrolled observational studies beyond 3 months.[69,70] Psychosocial outcome variables were rarely investigated and showed only modest improvement. Thus, consistent with the multifactorial nature of chronic pain, opioids alone probably cannot produce an analgesic response. Examples would be the presence of a major affective component or a situation in which learned pain behavior is the main problem; clearly, the entire patient must be evaluated, not just the pain.[71] The target of intervention is not only the source of nociception (if at all identifiable) but suffering, dysfunction, psychosocial factors, and dependence on the health care system. In addition, addiction has been reported in up to 50% of patients treated with opioids for chronic pain,[72,73] and overdoses, death rates, and abuse of prescription opioids have become public health problems.[74,75] Thus, the use of opioids as a sole treatment modality in chronic nonmalignant pain is not recommended.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS AND ANTIPYRETIC ANALGESICS

The acidic NSAIDs and the nonacidic antipyretic analgesics (e.g., acetaminophen, phenazones) inhibit COX, the enzyme that catalyzes the transformation of arachidonic acid (a ubiquitous cell component generated from phospholipids) to prostaglandins and thromboxanes (see also Chapter 32).[76] Two isoforms, COX-1 and COX-2, are constitutively expressed in peripheral tissues and in the central nervous system. In response to injury and inflammatory mediators (e.g., cytokines, growth factors), both isoforms can be up-regulated, resulting in increased concentrations of prostanoids. In the periphery, prostanoids (mainly prostaglandin E_2 [PGE_2]) sensitize nociceptors by phosphorylation of ion channels (e.g., Na^+, TRPV1) through EP receptor activation. As a result, nociceptors become more responsive to noxious mechanical (e.g., pressure, hollow organ distention), chemical (e.g., acidosis, bradykinin, neurotrophic factors), or thermal stimuli. In the spinal cord PGE_2 blocks glycinergic neuronal inhibition, enhances excitatory amino acid release, and depolarizes ascending neurons. These mechanisms facilitate the generation of impulses within nociceptors and their transmission through the spinal cord to higher brain areas. By blocking COX, prostanoid formation diminishes. Subsequently, nociceptors become less responsive to noxious stimuli, and spinal neurotransmission is attenuated.

Less severe pain states (e.g., early arthritis, headache) are commonly treated with nonselective NSAIDs (e.g., aspirin, ibuprofen, indomethacin, diclofenac) or antipyretic analgesics (e.g., acetaminophen), mostly used orally. Some analgesic drugs are available for parenteral, rectal, or topical application. Over-the-counter availability and self-medication have led to frequent abuse and toxicity.[77] Adverse side effects are attributed to COX-1–induced blockade of thromboxane production and impairment of platelet function (gastrointestinal and other bleeding disorders), decrease of tissue-protective prostanoids

(gastrointestinal ulcers, perforation), decrease of renal vasodilatory prostanoids (nephrotoxicity), and formation of highly reactive metabolites (acetaminophen hepatotoxicity). The development of selective COX-2 inhibitors was driven by the assumptions that COX-2 expression is selectively induced in inflamed tissue and that the constitutive tissue-protective COX-1 would be spared. It has now become clear that COX-2 expression is constitutive in many tissues (e.g., gastrointestinal epithelium, vascular endothelium, spinal cord), and COX-2 inhibition may exacerbate inflammation, impair ulcer healing, and decrease formation of vasoprotective prostacyclin. COX inhibitors confer an increased risk of thrombosis, myocardial infarction, renal impairment, hypertension, stroke, and liver toxicity, and they can cause rare anaphylactic reactions. Acetaminophen (paracetamol) has relatively weak antiinflammatory and antiplatelet activity and is used for osteoarthritis, headache, and fever.[76,78]

SEROTONERGIC DRUGS

Serotonin (5-hydroxytryptamine [5-HT]) is a monoamine neurotransmitter found in the sympathetic nervous system, in the gastrointestinal tract, and in platelets. It acts on 5-HT receptors expressed at all levels of the neuraxis and on blood vessels. Within the dorsal horn of the spinal cord, serotoninergic neurons contribute to endogenous pain inhibition. With the exception of 5-HT_3 (a ligand-gated ion channel), 5-HT receptors are G-protein–coupled receptors. 5-$HT_{1B/1D}$ agonists (triptans) have been studied extensively and are effective against neurovascular (migraine, cluster) headaches. Migraine is thought to be related to the release of neuropeptides (e.g., calcitonin gene–related peptide) from trigeminal sensory neurons innervating meningeal and intracranial blood vessels. This process leads to vasodilation, an inflammatory reaction, and subsequent pain. Triptans inhibit neurogenic inflammation through 5-HT_{1D} receptors on trigeminal afferents, with possible additional sites of action on thalamic neurons and in the periaqueductal gray. The activation of vascular 5-HT_{1B} receptors constricts meningeal (and coronary) vessels. These last effects have stimulated a search for nonvasoconstrictor approaches such as highly selective $5HT_{1D}$ and $5HT_{1F}$ agonists. However, none has demonstrated clinical antimigraine effects so far.

Triptans can be applied orally, subcutaneously, or transnasally, and these drugs have been used in the treatment of migraine. All triptans narrow coronary arteries through 5-HT_{1B} receptors by up to 20% at clinical doses and should not be administered to patients with risk factors for coronary, cerebrovascular, or peripheral vascular disease. Some triptans have the potential for significant drug-drug interactions (e.g., with monoamine oxidase inhibitors, propranolol, cimetidine, hepatic cytochrome P450–metabolized medications, or p-glycoprotein pump inhibitors). Rational use of triptans should be restricted to patients with disability associated with migraine.[79]

ANTIEPILEPTIC DRUGS

Antiepileptics are used in neuropathic pain resulting from lesions to the peripheral (e.g., diabetes, herpes) or central nervous system (e.g., stroke) and for migraine prophylaxis. Neuropathic syndromes have been attributed to ectopic activity in sensitized nociceptors from regenerating nerve sprouts, recruitment of previously "silent" nociceptors, or spontaneous neuronal activity (or any combination of these processes). These events may result in sensitization of primary afferents and subsequent sensitization of second- and third-order ascending neurons. Among the best studied mechanisms are the increased expression and trafficking of ion channels (e.g., Na^+, Ca^{2+}, TRP) and increased activity at glutamate (NMDA) receptor sites. The mechanisms of action of antiepileptics include neuronal membrane stabilization by blockage of pathologically active voltage-sensitive Na^+ channels (carbamazepine, phenytoin, lamotrigine, topiramate), blockage of voltage-dependent Ca^{2+} channels (gabapentin, pregabalin), inhibition of presynaptic release of excitatory neurotransmitters (gabapentin, lamotrigine), and enhanced activity of GABA receptors (topiramate).[80,81]

The most common adverse effects are impairments in mental status (somnolence, dizziness, cognitive impairment, fatigue) and motor function (ataxia), which limit clinical use, particularly in older patients. Serious side effects have been reported, including hepatotoxicity, thrombocytopenia, and life-threatening dermatologic and hematologic reactions. Plasma drug concentrations should be monitored.[79] Antiepileptics are frequently coadministered with antidepressants.

ANTIDEPRESSANTS

Antidepressants are used in the treatment of neuropathic pain, headache, and other conditions. They are divided into nonselective norepinephrine–5-HT reuptake inhibitors (amitriptyline, imipramine, clomipramine, duloxetine, venlafaxine), preferential norepinephrine reuptake inhibitors (desipramine, nortriptyline), and selective 5-HT reuptake inhibitors (citalopram, paroxetine, fluoxetine). The reuptake block leads to a stimulation of endogenous monoaminergic pain inhibition in the spinal cord and brain. Tricyclic antidepressants also have NMDA receptor antagonist, endogenous opioid enhancing, Na^+ channel blocking, and K^+ channel opening effects, which can suppress peripheral and central sensitization. Block of cardiac ion channels by tricyclic antidepressants can lead to arrhythmias. The selective 5-HT transporter inhibitors have a different side effect profile and are safer in cases of overdose. Tricyclic antidepressants require monitoring of plasma drug concentrations to achieve optimal effect and avoid toxicity, unless sufficient pain relief is obtained with low doses. Patients with ischemic heart disease may have an increased risk of sudden arrhythmia, and in patients with recent myocardial infarction, arrhythmia, or cardiac decompensation, tricyclic antidepressants should not be used at all. Tricyclic antidepressants also block histamine, cholinergic, and adrenergic receptor sites. Adverse events of antidepressants include sedation, nausea, dry mouth, constipation, dizziness, sleep disturbance, and blurred vision.[82,83]

TOPICAL ANALGESICS

The topical application of various analgesics is an area of considerable interest because many chronic pain syndromes depend to some degree on the peripheral activation of primary afferent neurons. The localized administration

can potentially optimize drug concentrations at the site of pain generation while avoiding high plasma levels, systemic side effects, drug interactions, and the need to titrate doses into a therapeutic range. RCTs have demonstrated effectiveness for topical NSAIDs, tricyclic antidepressants, capsaicin, local anesthetics, and opioids.[79,84,85]

Topical NSAIDs are typical over-the-counter medications, widely advertised and used for acute and chronic pain. Many formulations (cream, gel, ointment) are commercially available, with varying drug delivery to the skin and subcutaneous tissues. Meta-analyses concluded that topical NSAIDs are effective in osteoarthritis.[77] Local adverse effects include rash and pruritus. A topical tricyclic (doxepin) showed efficacy in a mixed group of patients with neuropathic pain and, as a mouthwash, in patients with chemotherapy-induced oral mucositis. Side effects included burning discomfort.[84]

Capsaicin is the active pungent ingredient in chili peppers. Topically applied capsaicin interacts with nociceptive neurons through the vanilloid receptor (TRPV1). It causes an initial activation of these neurons with release of substance P. This action is perceived as a burning or itching sensation with a flare response and occurs in a high number (≤80%) of patients. After repeated application desensitization occurs, probably secondary to depleting sensory neurons of substance P. Another potential mechanism is a direct neurotoxic effect resulting in the degeneration of small-diameter sensory nerve fibers.[84] Topical capsaicin was shown to provide pain relief in postherpetic neuralgia, postmastectomy syndrome, osteoarthritis, and a variety of neuropathic syndromes. Systematic reviews revealed moderate to poor effectiveness, with numbers needed to treat between 5.7 and 12.[86,87] Thus, topical capsaicin may be a supplement for the treatment of neuropathic pain in a limited number of patients unresponsive to or intolerant of other therapeutic approaches.

Topical formulations of local anesthetics block Na^+ channels in primary afferent neurons. Blockade of Na^+ channels reduces impulse generation both in normal and in damaged sensory neurons. Such neurons exhibit spontaneous and ectopic firing, possibly contributing to certain conditions of chronic neuropathic pain. Under these conditions the altered expression, distribution, and function of ion channels along axons is associated with increased sensitivity to local anesthetics. Thus, pain relief can be achieved with local anesthetic concentrations lower than those that totally block impulse conduction.[88] Controlled studies using lidocaine patches and gels showed reduction of allodynia in postherpetic neuralgia.[79,89] In addition, patients with painful diabetic polyneuropathy, complex regional pain syndrome, postmastectomy syndrome, or postthoracotomy syndrome have been shown to experience pain relief. Except for skin irritation, no reports of serious side effects have been published. Gel formulations of lidocaine were also beneficial in diabetic neuropathy and oral mucositis.[90,91]

Topically applied or locally injected opioids produce analgesia by activating opioid receptors on primary afferent neurons. This action leads to inhibition of Ca^{2+}, Na^+, and TRPV1 currents, which are activated by inflammatory agents.[10,92] Subsequently, the excitability of nociceptors, the propagation of action potentials, and the release of proinflammatory neuropeptides (substance P) from sensory nerve endings are inhibited. All these mechanisms result in analgesia or antiinflammatory effects, or both.[9,10,67] Other mechanisms accounting for the particular efficacy of peripheral opioids in pain associated with inflammation include up-regulation[93] and accelerated centrifugal transport of opioid receptors in sensory neurons,[94] enhanced G-protein coupling of peripheral opioid receptors,[95] and disruption of the perineural barrier facilitating access of opioid agonists to their receptors.[96,97] Consistently, the perineural application of opioids along uninjured nerves (e.g., axillary plexus) does not reliably produce analgesic effects.[98] In addition, the production and secretion of endogenous opioid peptides from immune cells within inflamed tissue[2,14] appear to produce additive-synergistic interactions,[99] rather than tolerance at peripheral opioid receptors.[100] Peripheral opioid administration is regularly used and well documented in the case of perioperative intraarticular morphine.[101-103] Intraarticular morphine also produces analgesia in chronic rheumatoid and osteoarthritis. In these diseases, the potency of its effect was shown to be similar to that of standard intraarticular steroids and long lasting (≤7 days), possibly because of morphine's antiinflammatory activity.[10,67] In numerous small studies, locally applied opioids (e.g., in gels) have shown analgesic efficacy in the treatment of skin ulcers, cystitis, cancer-related oral mucositis, corneal abrasion, and bone injury. No significant adverse effects have been reported.[84,85]

OTHER ANALGESICS AND ADJUVANTS

Local anesthetics have been used topically, orally, intravenously, in trigger point injections, and in regional anesthetic techniques for selected chronic pain syndromes (see the later section on interventional methods used in chronic pain and also Chapters 30, 36, 56, and 57). The systemic application of local anesthetics (e.g., oral mexiletine) exhibited mixed success in various neuropathies. Evidence supports mexiletine as a third-line drug in selected patients with diabetic neuropathy.[79] Meta-analyses indicated that intravenous local anesthetics produce moderate analgesic effects of questionable clinical significance in neuropathic pain.[104,105] Severe side effects including arrhythmias, dizziness, nausea, and fatigue limit the systemic application of local anesthetics.

α_2-Adrenergic receptors are G-protein coupled. Similar to opioids, α_2-agonists (clonidine) lead to opening of K^+ channels, inhibition of presynaptic Ca^{2+} channels, and inhibition of adenylyl cyclase. Thus, like opioids, α_2-agonists reduce neurotransmitter release and decrease postsynaptic transmission, resulting in an overall inhibitory effect.[106] Epidural or systemic clonidine is analgesic in patients with complex regional pain syndrome and in neuropathic and cancer pain. However, its use is limited by a frequent incidence of sedation, hypotension, and bradycardia.[79] Flupirtine is used in musculoskeletal pain, but its mechanism of action is unknown. Initial studies postulated involvement of descending adrenergic pathways, indirect actions at NMDA receptors, and activation of G-protein–regulated K^+ channels.[107]

Cannabinoids have been studied extensively in the past decade. Animal and in vitro models have shown that derivatives of tetrahydrocannabinol produce

antinociceptive effects and that cannabinoid receptors and their endogenous ligands are expressed in pain processing areas of the brain, spinal cord, and periphery.[10,108] Peripheral cannabinoid receptors likely play a prominent role in pain inhibition.[10] Meta-analyses of human studies concluded that the analgesic effects of cannabinoids are modest, not superior to those of other analgesics, and of questionable clinical significance. Psychotropic side effects, sedation, dizziness, cognitive impairment, nausea, dry mouth, and motor deficits are limiting factors in clinical practice.[109]

Drugs reducing muscle spasm (e.g., benzodiazepines) are often used in musculoskeletal pain. However, the available evidence does not indicate lasting beneficial effects, and drowsiness and dizziness are frequently encountered[110] (see also Chapter 30). Baclofen activates $GABA_B$ receptors presynaptically and postsynaptically, thereby leading to a decrease in excitatory and an increase in inhibitory neurotransmission. In some reports, baclofen was found to exhibit analgesic effects in trigeminal neuralgia and central neuropathic pain. The most common side effects are drowsiness, dizziness, and gastrointestinal distress.[111] Botulinum toxin inhibits acetylcholine release at the neuromuscular junction and may alleviate muscle spasticity. The use of botulinum toxin injections has produced inconsistent results in headaches,[112] and it was not effective in myofascial trigger points, orofacial, or neck pain.[113-115] Side effects include pain and erythema at the injection site and unintended paralysis of adjacent muscles.[116]

The synthetic peptide ziconotide blocks N-type voltage-sensitive Ca^{2+} channels and thereby inhibits release of excitatory neurotransmitters from central terminals of primary afferent neurons in the spinal cord. Ziconotide has been approved for intrathecal application. However, it produces substantial side effects (dizziness, confusion, abnormal gait, memory impairment, nystagmus, hallucinations, vertigo, delirium, apnea, hypotension) and thus is suitable for only a small subset of patients with otherwise intractable (e.g., neuropathic) pain.[117] Under the assumption of antiinflammatory activity, steroid injections are frequently used epidurally or perineurally, albeit without convincing evidence for effectiveness (see the later section on therapeutic nerve blocks).

Antiemetics are used to treat nausea, a frequent side effect of analgesics (particularly opioids) and a frequent complaint in patients with cancer (see Chapters 96 and 97). Recommendations for the treatment of postoperative nausea and vomiting cannot readily be extrapolated to the patient with chronic pain. For example, in patients with cancer, causes other than opioids must be considered, such as radiation therapy and chemotherapy, uremia, hypercalcemia, bowel obstruction, and increased intracranial pressure. In addition, pain itself, as well as anxiety, can cause nausea. Opioid-related nausea usually diminishes by tolerance within a few days (see also Chapter 31). Management guidelines for the treatment of nausea and vomiting are available, and the selection of antiemetics should be mechanism based[54,118] (see also Chapters 96 and 97). The medullary chemoreceptor trigger zone, gastrointestinal stimulation or failure, and vestibular and cortical mechanisms, as well as alterations of taste and smell, may contribute to nausea and vomiting, particularly in patients with cancer. Most recommendations for the choice of antiemetic medication include gastrointestinal prokinetics (metoclopramide), phenothiazines (e.g., levomepromazine), dopamine receptor antagonists (e.g., haloperidol), serotonin antagonists (e.g., ondansetron), and antihistamines (e.g., cyclizine). In addition, the use of dexamethasone (unknown mechanism), anticholinergics (e.g., scopolamine), and neurokinin-1 receptor antagonists has been reported. Combinations of antiemetics with different modes of action can be used. Many of these drugs cause undesirable side effects by themselves (e.g., sedation, drowsiness, confusion, and extrapyramidal symptoms).[54,118] The efficacy of cannabinoids and benzodiazepines is considered comparatively low, and these drugs are not recommended as first-line treatment.[118,119]

Laxatives are indicated when bowel movements are less frequent than three per week and are associated with difficulty or discomfort. Risk factors for constipation include opioid medication, older age, advanced cancer, hypokalemia, and immobilization, as well as therapy with tricyclic antidepressants, phenothiazines, anticonvulsants, diuretics, and iron supplements. Opioid-related constipation is mediated through intestinal and (partially) through central μ receptors.[51,120] It is the most commonly occurring side effect of opioid medication in patients with cancer and frequently does not exhibit tolerance. Ample fluid intake, fiber-rich nutrition, and mobilization are nonpharmacologic approaches to prophylaxis. Laxatives include the following: bulk-forming, osmotic, and hyperosmolar agents; substances for colonic lavage; prokinetic drugs; and opioid antagonists. Recommendations usually include lactulose, senna, or polyethylene glycol as a first choice.[54] However, lactulose should be avoided in patients with impaired fluid intake, such as older adults and patients with advanced cancer. If this approach is insufficient, the drugs of first choice may be combined with paraffin or anthraglycosides (bisacodyl). Rectal sorbitol and contrast medium are the choices for the next more intensified step. Prokinetic drugs, such as metoclopramide, are sometimes added for refractory constipation. Possible alternatives in opioid-related constipation are opioid antagonists. To avoid central effects that reduce analgesia or produce withdrawal, oral naloxone and the peripherally restricted antagonists methylnaltrexone and alvimopan were developed. The use of these drugs in clinical practice is limited by relatively low response rates, adverse effects, and high costs.[120,121] In malignant bowel obstructions, different algorithms must be followed.[122]

DEVELOPMENT OF NOVEL ANALGESICS

Areas of intense research and examples emerging as potential drug targets include opioid receptors, cannabinoid receptors, bradykinin receptors, Na^+ channels expressed in peripheral nociceptive neurons ($Na_v1.8$, $Na_v1.7$), voltage-gated Ca^{2+} channels (e.g., $Ca_v2.2$), K^+ channels, the capsaicin receptor TRPV1, and the P2X receptors[123] (see also Chapter 32). Increasing attention is paid to novel enzyme inhibitors that prevent the degradation of endogenous opioids and cannabinoids, with a focus on the activation of peripheral receptors to avoid central side effects,[52,53] as well as to nanomaterials for drug delivery.[124] However, failures

in clinical phases of analgesic drug development are common and have been attributed to inappropriate animal models or nociceptive tests, species differences, publication bias, lack of mechanistic understanding, and shortcomings in experimental design, randomization, blinding, and statistical analysis.[20,22]

INTERVENTIONAL METHODS USED FOR CHRONIC PAIN

The popularity of interventional methods has decreased over time. Although early pain therapists (e.g., Leriche) were generally using "blocks" to treat pain, the biopsychosocial concept of chronic pain led to a much more cautious and judicial use of such techniques (see the earlier section on interdisciplinary management of chronic pain), particularly because most of these methods are not evidence based. Block therapy alone is usually not curative, but it can facilitate participation in rehabilitation and therefore does have a role in the management of chronic pain. Regardless of which procedure is considered, a consensus decision on its use must be reached within the interdisciplinary team.[40]

DIAGNOSTIC NERVE BLOCKS

Neural blockade is thought to be a useful tool to understand the mechanisms underlying pain in an individual patient better and to provide a prognosis for planned neuroablative procedures, particularly in cancer pain (see also Chapters 57 and 58). Differential blockade aims to block either single peripheral nerves selectively, to identify an anatomic pain source, or to block only one type of nerve fiber selectively (autonomic versus somatic).[125] Often active and nonactive compounds are injected sequentially to differentiate drug-related from placebo responses. Differential neural blockade can be performed at the peripheral and central (neuraxial) level. A popular protocol is the sequential intrathecal application of short- and long-acting local anesthetics (or opioids), or increasing concentrations of a local anesthetic. Diagnostic neural blockade is used in low back pain, headache, neuropathic pain, and complex regional pain syndrome. Examples include zygapophyseal (facet) joint injections and medial branch blocks,[126] sacroiliac joint injections,[127] trigger point injections, spinal nerve blocks, occipital nerve blocks, and sympathetic blocks.[125] Sympathetic blocks may be achieved by local anesthetic injections at the sympathetic chain (e.g., stellate ganglion) or by intravenous regional infusions of sympatholytic drugs (e.g., phentolamine). However, an extensive review of the experimental and clinical literature concluded that none of these procedures has unequivocally proved clinical usefulness in controlled studies.[125] This finding was confirmed in systematic reviews.[126,127] In particular, the validity of diagnostic nerve blocks is limited by the complexity of factors determining pain perception (see the earlier sections on biopsychosocial concept of pain and interdisciplinary management of chronic pain). Furthermore, the assumption that local anesthetics can selectively produce conduction block of only one fiber type in a nerve is probably false.[125] Nevertheless, experienced and observant clinicians have found that such procedures may occasionally provide information that is helpful in guiding subsequent therapy even though systematic reviews have methodologic limitations.[128,129] Provided the clinician takes great care in carrying out the technique, interpreting the results, and integrating them into interdisciplinary decisions, nerve blockade may still play a role in the comprehensive diagnostic workup of patients with chronic pain.[125]

THERAPEUTIC NERVE BLOCKS

Cancer Pain

Therapeutic nerve blocks are used for only a minority of patients in the management of cancer-related pain. In these cases, interventional treatment represents the fourth step in the World Health Organization analgesic ladder.[130] Approximately 90% to 95% of patients usually obtain adequate pain relief from pharmacologic management.[131] A comprehensive biopsychosocial approach to pain management and careful balancing of the risks against the benefits in individual patients are prerequisites for successful use of interventional techniques.[132] Therapeutic nerve blocks extend the treatment range when conservative methods fail to achieve tolerable pain or side effect levels, or both. For example, neuropathic pain and incidental (breakthrough) pain are sometimes poorly controlled by systemic analgesics and may be indications for invasive therapy. Well-evaluated interventional techniques such as celiac plexus block, hypogastric plexus block, and saddle blocks should not be withheld from patients with cancer in the context of palliative symptom control.[133]

In patients with unresectable pancreatic cancer, neurolysis of the celiac plexus may be used for pain treatment (Fig. 64-4). Patients with other upper abdominal

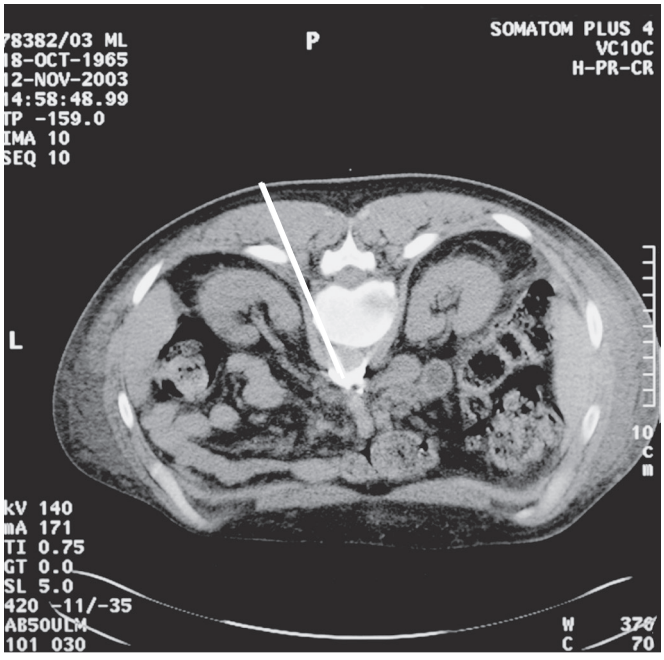


Figure 64-4. Transaortic approach for neurolysis of the celiac plexus with typical dye distribution ventral to the aorta. For details see text.

malignancies, such as hepatic or gastric cancer, may also benefit from this intervention. This technique is based on the assumption that nociceptive stimulation is transmitted along primary afferent fibers that travel with the sympathetic fibers of the splanchnic nerves arising from T5-T12 and with the parasympathetic efferent fibers that together form the celiac plexus. The ganglia are situated in the retroperitoneal space adjacent to the L1 vertebral body. Anatomic landmarks can be identified with the help of computed tomography, fluoroscopy, and ultrasound,[134] and they are particularly recommended for celiac plexus blocks.[135,136] The most common dorsal techniques include the bilateral transcrural and unilateral transaortic approaches using alcohol (50% to 100%) or phenol (7% to 12 %).[131] In patients undergoing laparotomy, intraoperative neurolysis of the celiac plexus can also be used.[137] Most centers advocate a diagnostic local anesthetic block to predict analgesic and side effects (mostly diarrhea and hypotension).[138] Systematic reviews of RCTs comparing neurolytic celiac plexus blockade with standard treatment (oral NSAIDs and morphine) plus sham blockade, or sham blockade alone, concluded that celiac plexus neurolysis was associated with lower pain scores, decreased morphine use, and reduced constipation, albeit with minimal clinical significance.[133,139]

Less common sites for neurolyses are intercostal nerves (e.g., in rib metastasis), the superior hypogastric ganglion, the ganglion impar, and the lumbar sympathetic ganglia (e.g., for pelvic tumors). In perineal pain secondary to local infiltration of rectal cancer, intrathecal neurolysis may be considered if bladder and sphincter function is not of concern.[133,140] An indication for thoracic intrathecal or epidural neurolysis may be advanced lung cancer.[141] As a neurolytic agent, alcohol may be preferred because of its perceived higher success rate and longer duration of pain relief (3 to 6 months) compared with phenol (2 to 3 months), although no studies directly comparing these two agents are available. Depending on the patient's survival prognosis, the duration of pain relief provided by alcohol may be sufficient.

A diagnostic local anesthetic block to predict analgesic and side effects is advocated. Because alcohol is hypobaric and phenol is hyperbaric, the patient must be positioned accordingly during administration of intrathecal neurolysis. In many cases, pain relief is incomplete, but intake and side effects of opioids decrease. The limited period of pain reduction and the limited possibility of repeat injections are reasons that neurolysis is mostly used in patients with short life expectancies.[142]

Non–Cancer-Associated Pain

Both the complexity of factors contributing to pain perception and perpetuation (see the earlier sections on the biopsychosocial concept of pain and interdisciplinary management of chronic pain) and the detrimental long-term effects of nerve destruction (neuropathic pain caused by spontaneous ectopic neuronal discharges, up-regulation of neuronal ion channels, and excitatory amino acid receptors (see the earlier sections on the physiologic changes in persistent pain and antiepileptic drugs) caution against neuroablative procedures in the patient who does not have cancer. Nonetheless, many practitioners advocate radiofrequency ablations or cryoneurolysis at facet joints and sacroiliac joints, as well as several other destructive procedures.[143,144] However, such interventions did not provide long-term pain relief in RCTs,[145,146] or in systematic reviews,[147] except for the use of pulsed radiofrequency in cervical radicular pain.[148]

Nondestructive procedures include trigger point, epidural, perineural, and intraarticular injections of local anesthetics or steroids, or both. Steroids are used under the assumption of antiinflammatory activity. For example, in chronic back or neck pain (the most common patient complaints), injections into facet or zygapophyseal joints or along the medial branch from the posterior ramus of the spinal nerve root are frequently performed, although without convincing documented long-term results.[146,147] Similarly, injections into sacroiliac joints, trigger points, or occipital nerve blocks show no consistent long-lasting effects.[128,149,150] Epidural steroids are also used extensively for low back and neck pain,[151] but they provided questionable long-term pain relief in RCTs,[152] and these injections are recommended only after careful individual patient selection.[153] The same applies to lumbar transforaminal epidural steroid injections.[154] Although it has been asserted that transforaminal steroid injections are more efficacious than interlaminar injections, supporting evidence is limited. In summary, epidural steroids may provide short-term relief for radicular symptoms, but only limited long-term effects for relief of back pain.[155] Further, no evidence indicates that the addition of other agents such as hyaluronic acid produces better results.[146,152] Neither preoperative nor postoperative nerve blocks provide consistent improvement of phantom limb pain.[156] Some RCTs indicate that epidural or intrathecal steroids with local anesthetics can be effective in herpes zoster and postherpetic neuralgia.[157] In addition, local infiltration of herpes zoster lesions provides inconsistent relief of pain.

Sympathetic nerve blocks with local anesthetics, often carried out as a series, such as in herpes zoster–associated pain and complex regional pain syndrome, are commonly used, but evidence from RCTs is lacking. Especially in adolescents and children, the role of sympathetic and other nerve blocks has been questioned.[158] Some studies were able to demonstrate short-term effects, but no clear reduction of the risk to develop postherpetic neuralgia.[157,159] Similarly, the long-term effectiveness of sympathetic blockade in complex regional pain syndrome was not demonstrated in RCTs.[160,161] Anecdotal reports have described sympathetic blocks for ischemic pain, such as in peripheral vascular or Raynaud disease.

In contrast to the lack of evidence for long-term effects, interventional techniques can produce short-term pain relief. In the context of interdisciplinary management, such techniques can be effectively used to facilitate initial physical therapy in chronic nonmalignant pain.[143,162]

CONTINUOUS CATHETER TECHNIQUES

Continuous drug delivery to the intrathecal or epidural space can be accomplished by using programmable implanted pumps, implanted accessible reservoir systems, and tunnelled exteriorized catheters. The principal benefit

appears to be the reduction of systemic side effects. As with nerve blocks, the evidence of effectiveness of these approaches is stronger for cancer pain than for chronic nonmalignant pain.

Cancer Pain

Only a few patients with cancer require neuraxial drug delivery because of intolerable side effects, but in patients refractory to systemic analgesics, such methods may be underused.[163,164] The preponderance of evidence supporting this mode of drug delivery is derived from nonrandomized, uncontrolled studies.[134,165] The advantage of the epidural technique is its ubiquitous availability in most anesthesia departments, but its disadvantages are the chance of inhomogeneous distribution of the analgesics, high drug volume requirements and possible systemic absorption, and limited duration of therapy as a result of local granuloma formation and technical failures.[134] The intrathecal approach allows homogeneous distribution of the analgesics, low-volume injections, control of catheter positioning with cerebrospinal fluid aspiration, and long-term therapy with minimal infection rates, although case reports on catheter tip inflammatory granulomas have occurred. Usually, morphine (1 to 5 mg, depending on the preceding systemic dosage) or hydromorphone is recommended as a drug of first choice. For refractory pain, combinations with bupivacaine, clonidine, ziconotide, and other compounds have been used.[165] This approach should be used only if the treatment facility has the capacity for emergency in-house treatment, 24-hour emergency calls, and adequate home care service with stringent protocols to avoid infections. To transfer the patient from high-dose systemic analgesia to intraspinal analgesia, 24-hour monitoring is required. The initial intrathecal morphine dose is approximately 1% of the oral morphine equivalent. Thereafter, the systemic opioid dose is reduced by 50% and then is slowly tapered by 10% daily to avoid withdrawal, at the same time allowing usual systemic opioid doses as rescue medication.

Non–Cancer-Associated Pain

No RCTs are available, but observational reports described continuous catheter techniques for chronic noncancer pain.[134,166] Most of these studies used intrathecal morphine, and some used hydromorphone, baclofen, or ziconotide in patients with chronic low back pain. On average, these patients exhibited increasing daily morphine doses over time and a high incidence (≤25%) of complications, such as catheter obstruction, catheter-tip granuloma formation, pruritus, urinary retention, and infection. Effectiveness of these techniques in relieving pain or improving function compared with placebo, natural history, or other treatments either has not been shown[134,166] or is limited.[167]

STIMULATION TECHNIQUES

Stimulation techniques frequently used in pain management include acupuncture, spinal cord (or dorsal column) stimulation (SCS), and transcutaneous electrical nerve stimulation (TENS). Acupuncture has long been popular among patients and lately has also generated interest within the conventional medical community. Systematic reviews of sham-controlled studies in migraine prophylaxis and arthritic pain showed that treatments using traditional Chinese concepts of meridians and specified classic points are as effective as the selection of acupuncture points at random.[168,169] The conclusion was that acupuncture has no specific effect compared with standard medical migraine prophylaxis.[168] In osteoarthritis, adequately blinded studies yielded inconclusive results.[169,170] In rheumatoid arthritis, acupuncture was not recommended.[171] In chronic low back pain, several reviews concluded that, in the long term, acupuncture is not more effective than other treatments.[172-174] With respect to pain relief in patients with cancer, available data do not support the effectiveness of acupuncture, either.[175]

The idea of modulating neural transmission by electrical stimulation dates back to ancient Rome, with the observation that gout pain was alleviated through accidental contact with a torpedo fish. The gate control theory of pain in the 1960s proposed that pain perception was influenced by the balance of firing between large and small nerve fibers, and that retrograde nonpainful stimulation of large fibers would "close the gate" by adjusting the level of voltage.[134] This theory prompted the development of TENS, SCS, and various techniques of brain stimulation that have been applied in patients with refractory complex regional pain syndrome or neuropathic, low back, and ischemic pain. None of these methods have been validated by adequately powered and blinded RCTs for chronic pain.[176,177] Unblinded studies suggest that selected patients with complex regional pain syndrome or back pain, especially with failed back surgery syndrome, may benefit from SCS, but controlled trials are needed.[178] Complications include electrode displacement, infection, and battery failure.[177,179] Because it is noninvasive and easy to administer, TENS is used widely. However, systematic reviews of its application for chronic low back pain[180] and painful rheumatoid arthritis or osteoarthritis[181,182] have not yielded conclusive evidence of its effectiveness.

PERIOPERATIVE MANAGEMENT OF PATIENTS WITH CHRONIC PAIN

CHARACTERISTICS OF PATIENTS WITH CHRONIC PAIN IN THE PERIOPERATIVE PERIOD

The patient with chronic pain has certain distinctive features important for perioperative management (see also Chapter 98). Enhanced central sensitization or reduced endogenous inhibition may result in increased and prolonged pain after surgery.[183] Moreover, altered opioid sensitivity secondary to long-term exposure to opioid medications must be considered.[184] Patients with chronic pain also frequently exhibit higher preoperative expectations of pain, anxiety, depression, or hypervigilance.[185,186] It may be difficult to distinguish normal from maladaptive anxiety, but patients with cancer pain are more likely to be anxious than are patients with cancer who do not have pain. In addition, the patient with chronic pain, including the patient with cancer, is not as

BOX 64-1 ***Risk Factors in the Perioperative Management of the Patient With Chronic Pain***

- Conventional perioperative analgesia regimens do not meet the needs of the patient with chronic pain.
- Unrelieved postoperative pain resulting from undermedication may provoke withdrawal.
- Patients tend to underreport their medication.
- With uncontrolled anxiety or fear of pain, patients tend to overestimate the effect of painful stimuli.
- Epidural and intravenous opioid (including PCA) requirements can be two to four times higher in opioid-consuming than in opioid-naïve patients.
- Expect prolonged recovery and the need for postoperative analgesia.
- Anxiety and insufficient coping result in poor compliance with analgesic strategies.
- Individual variations in response to opioids may necessitate selection of the optimal drug and dosing by sequential trials.
- Individual titration of doses is required to find the optimal balance between analgesia and adverse effects.
- Adjuvant medication may interfere with anesthesia and postoperative analgesia.

Modified from Kopf A, Banzhaf A, Stein C: Perioperative management of the chronic pain patient, Best Pract Res Clin Anaesthesiol *19:59-76, 2005.*
PCA, Patient-controlled analgesia.

confident of recovery as are other patients with chronic diseases.[187] Thus, difficult perioperative pain control and, possibly, an increased risk of chronic pain development after surgery must be expected. However, patients with chronic pain, with or without long-term opioid medication, opioid abuse, or opioid misuse, require and must receive adequate pain control.

The preanesthetic visit should therefore include questions regarding chronic pain and regular use of analgesics and adjuvant medication (see also Chapter 38). Although some characteristics, including increased opioid demand, underreporting of pain, and noncompliance, are known, only few specific recommendations are available, such as adequate increase of opioid dose for analgesia, continuation of preoperative analgesics to prevent withdrawal, and intensive education to strengthen the patient's coping potential. No differences among specific techniques for postoperative analgesia (e.g., systemic patient-controlled, or regional analgesia) have been demonstrated so far. Furthermore, preoperative intensity of pain alone, independent of the use of analgesics, correlates positively with postoperative pain.[188] Patients with chronic pain often suffer from prolonged inactivity or neurologic deficits, or both, that increase the risk for adverse events during the perioperative period. Some key issues are summarized in Box 64-1.

LONG-TERM USE OF ANALGESICS AND ADJUVANT DRUGS

Patients with chronic pain are often pretreated with opioids, COX inhibitors, and antidepressants or anticonvulsants, or both. Tolerance, drug interactions, and side effects may occur. In addition, inappropriate or excessive medication is commonly observed.[74,75,189] Patients with chronic pain tend to underestimate and underreport their medication use.[190] Thus, undertreatment in the perioperative period may be unnoticed and may induce a neuroexcitatory withdrawal syndrome with associated cardiopulmonary strain.

Long-term opioid medication has been discussed thoroughly in the literature (see the earlier section on opioids). Together with aggressive marketing, this information has gradually led to decreasing reservations among practitioners toward the use of these drugs. As a result, opioids are used more frequently in patients with cancer pain and noncancer pain, and most patients with noncancer pain are now prescribed opioid medication.[74,75,190] Although this approach this seems justified in cancer pain and certain chronic destructive diseases, indications for the use of opioids in patients with chronic noncancer pain are less convincing (see the earlier section on opioids). Nevertheless, anesthesia providers are increasingly confronted with patients receiving long-term opioid treatment. Such pretreatment can result in a severalfold increased and prolonged requirement for systemic and epidural analgesics in the perioperative period compared with opioid-naïve patients.[57,61,191,192] Patients with chronic pain and prior opioid consumption may also exhibit higher postoperative pain scores.[192] The increased postoperative analgesic demands may result from lower pain thresholds or a need for higher drug concentrations. In addition, opioid requirements can be influenced by gender, genetic predisposition, age, type of surgery, and preoperative pain levels.[58,188] Conversely, opioid-related side effects (e.g., nausea and pruritus) may be less dominant. Physicians and nurses may overestimate tolerance, addiction, and sedation but underestimate dependence. A paramount concern is the maintenance of adequate perioperative opioid dosing to prevent withdrawal[61,192] (see Box 64-1).

COX inhibitors are the most commonly used nonopioid analgesics. Unlike opioids, they are not associated with tolerance and physical dependence, but they produce serious side effects, mainly in the gastrointestinal tract, kidneys, and cardiovascular and coagulation systems (see the earlier section on drugs used for chronic pain). Major concerns for the anesthesiologist are coagulation disturbances and the increased risk for hematoma formation associated with spinal and epidural anesthesia. Practice guidelines do not differentiate between selective COX-2 and nonselective COX inhibitors. European and American societies disagree in their recommendations. Before neuraxial anesthesia, a 24- to 72-hour (in case of aspirin) drug-free interval is recommended by the German Society of Anesthesiology and Intensive Care Medicine and by the Spanish Consensus Forum, whereas the American Society of Regional Anesthesia and Pain Medicine does not believe that these drugs pose any added significant risk. This discrepancy likely arises from the findings that the development of a spinal or epidural hematoma is a rare event (≈1 in 220,000 spinal and 1 in 150,000 epidural anesthetics) and that none of the studies to date has a large enough patient population to predict the risk of hematoma formation when COX inhibitors are continued preoperatively.[193]

Antiepileptic drugs can interfere with anesthesia in different ways. Sedation produced by anticonvulsant drugs may have additive effects with anesthetics, whereas drug-induced enzyme induction could alter responses to or contribute to the organ toxicity of anesthetics. Gabapentin has a favorable side effect profile, and its relative absence of drug interactions allows continuation and rapid titration in the perioperative period.[194] Phenytoin and carbamazepine accelerate recovery from nondepolarizing muscle relaxants, but the mechanism is unclear. Preoperative exclusion of toxic serum levels of phenytoin is recommended, to reduce the risk of atrioventricular conduction block. States of disorientation, nystagmus, ataxia, and diplopia may be manifestations of excessive plasma concentrations. Carbamazepine may produce sedation, ataxia, nausea, and (rarely) bone marrow depression or hepatorenal dysfunction. Plasma sodium levels must be monitored perioperatively to avoid hyponatremia. Oral valproic acid is commonly used for prophylaxis of migraine, and intravenous valproic acid may be used to control episodic headaches.[195] This drug may inhibit activity of hepatic microsomal enzymes and interfere with platelet aggregation.[196] To avoid central nervous system hyperexcitability, antiepileptics should never be discontinued abruptly. Stable dosages must be maintained throughout the perioperative period.

Antidepressants are frequently used for neuropathic pain and for associated depression. Adverse effects are numerous and include sedation, anticholinergic effects, and cardiovascular changes. Electrocardiographic changes can occur, such as prolongation of the PR interval and widening of the QRS complex, but previous suggestions of increased risk of perioperative cardiac dysrhythmias have not been substantiated in the absence of drug overdose.[197] Therefore, antidepressants need not be discontinued before anesthesia, but increased anesthetic requirements may be expected because of enzyme induction. Postoperatively, the likelihood of delirium and confusion may be increased as a result of additive anticholinergic effects. Selective serotonin reuptake inhibitors and atypical antidepressants such as mirtazapine or venlafaxine are less likely to interfere with anesthesia.

Ketamine is a mixed opioid agonist–NMDA antagonist that can produce analgesia at subanesthetic doses in selected patients with neuropathic pain[198,199] (see also Chapter 32). Very rarely, patients taking oral ketamine medication on a long-term basis are encountered. In these cases, perioperative administration of ketamine should be discontinued because correct conversion from oral to intravenous ketamine is difficult.[200] Within analgesic dose ranges, the risk of a withdrawal syndrome is small.[199,201]

Benzodiazepines are not analgesic and are rarely used in chronic pain, with the exception of palliative care situations.[110,202] Nevertheless, chronic pain is a predictor of increased benzodiazepine use.[203] Side effects relevant to anesthesia include sedation and skeletal muscle weakness. Because of the long half-life of these drugs, delayed withdrawal should be anticipated and avoided by maintaining stable perioperative dosage. Neuroleptics are also inappropriate, but they are sometimes used in chronic pain.[79] In the perioperative period, patients treated with antipsychotic drugs can develop a neuroleptic malignant syndrome. Hyperthermia, hypertonicity of skeletal muscles, fluctuating levels of consciousness, and autonomic nervous system instability are typical symptoms (see also Chapter 43).

DEPENDENCE, ADDICTION, AND PSEUDOADDICTION

Physical dependence is defined as a state of adaptation that is manifested by a drug class–specific withdrawal syndrome that can be elicited by abrupt cessation, rapid dose reduction, decreased blood level of the drug, or administration of an antagonist (see also Chapter 110).[204] Dependence is not synonymous with tolerance (see the earlier section on opioids). All opioids, benzodiazepines, and anticonvulsants produce clinically relevant physical dependence when administered for a prolonged period of time, but sometimes physical dependence can develop within hours of agonist exposure.[205] Thus, all patients with continuous preoperative opioid intake should be considered at risk for withdrawal syndrome if adequate substitution of opioids in the perioperative period is withheld. Opioid and benzodiazepine withdrawal syndromes, especially tachycardia and hypertension, may be detrimental for the high-risk cardiac patient. Rapid withdrawal from anticonvulsant drugs may trigger seizures, anxiety, and depression.

Addiction is a behavioral syndrome characterized by evidence of psychological dependence (craving), uncontrolled or compulsive drug use despite harmful side effects, and other drug-related aberrant behavior (e.g., altering prescriptions, manipulating health care providers, drug hoarding or sales, unsanctioned dose escalation).[72,204] The prevalence of opioid addiction is as high as 50% in patients with chronic nonmalignant pain and up to 8% in patients with cancer pain.[72,73] Many issues regarding patients with chronic pain who consume opioids also apply to patients who abuse or are addicted to opioids. The daily dose of opioids in abusing or addicted patients is typically larger, such patients often have coexisting psychiatric diseases (depression, anxiety, psychosis). In addition, the known history of abuse may lead to tempered use of opioids by health care providers, a practice that makes these patients particularly vulnerable to inadequate postoperative pain control.[61] Further special considerations in the management of the drug-addicted patient are discussed in the literature.[61,192,206]

Pseudoaddiction describes a situation in which medical personnel do not provide a sufficient dosage of medication, thereby provoking repetitive demands from the patient for analgesics. This may be interpreted as "drug-seeking behavior." Pseudoaddiction can be avoided with adequate algorithms and regular education of health care providers.[56]

MANAGEMENT AND PRACTICAL RECOMMENDATIONS

Perioperative management must address the risk of opioid withdrawal, the altered pain sensitivity, and the psychological alterations typical in the population

of patients with chronic pain. Most of the following recommendations must be considered "expert views" only.[192,207,208]

Preoperative Evaluation

Preanesthesia evaluation is necessary to educate patients, to organize resources for preoperative improvement of the patient's physical function, to choose optimal anesthetic techniques, and to formulate plans for postoperative recovery, including perioperative pain management[61] (see also Chapter 38). Misconceptions about the surgical procedure, the role of the anesthesiologist in perioperative care, and postoperative pain treatment are common among patients.[209] A thorough history must be obtained to identify all preoperative medications, including opioids, other analgesics, and adjuvants, as well as signs of psychiatric comorbidity and aberrant drug-related behavior. Patients with spinal cord stimulators should be instructed to turn off their devices.[210] Screening tools and thorough education of the patient are recommended.[186,211] Consultation of a pain specialist should always be considered. Pertinent issues and practical recommendations are summarized in Boxes 64-1 and 64-2.

BOX 64-2 ***Preoperative Considerations and Recommendations in Patients With Chronic Pain***

- Take a thorough history to identify all analgesic and adjuvant medications, risk factors, and comorbidity.
- Educate the patient about the perioperative procedures, the potential for aggravated pain, and increased opioid requirements.
- Communicate plans among the designated anesthesiologist in the operating room, the postanesthesia care unit, and the surgical and nursing personnel on the ward.
- Differentiate among addiction, pseudoaddiction, and physical dependence in patients receiving long-term opioid medication.
- Expect physical dependence in patients receiving long-term opioid medication.
- Continue previous long-acting opioid analgesics for short procedures.
- For major surgery, calculate and order the background infusion of an equianalgesic opioid dose to be started in the operating room for patients with NPO status for more than 8 hours.
- Order regular opioid medication on the morning of surgery.
- Maintain anticonvulsant drugs and benzodiazepines at preoperative doses.
- Discontinue all other adjuvants if NPO status lasts longer than 24 hours.
- Identify an untreated depressive disorder with screening questions for disturbed sleep, lowered mood, and reduced concentration, self-confidence, and motivation.
- Identify an untreated anxiety disorder with screening questions for restlessness, irritability, difficulties in controlling anxiousness, and worrying.
- Consider referral to a pain specialist for evaluation.
- Choose regional or general anesthesia based on individual considerations.

Data from Farrell C, McConaghy P: Perioperative management of patients taking treatment for chronic pain, BMJ *345:e4148, 2012; and Kopf A, Banzhaf A, Stein C: Perioperative management of the chronic pain patient,* Best Pract Res Clin Anaesthesiol *19:59-76, 2005.*
NPO, Nothing by mouth.

Perioperative Management

To avoid opioid withdrawal, the preoperative systemic dosage should be continued throughout the perioperative period, and mixed agonist-antagonists (buprenorphine, nalbuphine) must be avoided (see also Chapters 38 and 40). If a neuraxial catheter with opioid medication is used, the flow and concentration of the opioid should be continued throughout the perioperative period as background analgesia.[212] For minor surgery and for surgical procedures between minor and major surgery, oral slow-release opioid medication may be continued at its regular intervals. For major surgery with postoperative restriction of enteral intake, oral opioids should be discontinued and replaced by equivalent doses of intravenous opioids, which must be continued for the entire perioperative period. This applies to general and regional anesthesia. The anesthesia technique should be selected on an individual basis, considering the patient's expectations, because no data are available favoring general, regional, or combined anesthesia for this patient population.[208] The frequency and extent of monitoring techniques should be adapted to the patient's risk of instability.

Pain should be periodically assessed during emergence and recovery.[213] For thorough evaluation of pain relief, functional criteria (ability to cough, breathe deeply, perform physical therapy, ambulate) should be used in conjunction with patient-generated pain ratings to determine the end points for analgesic therapy. Pain acts as an antagonist to central nervous system depressants, and in particular to the respiratory depressant effects of opioids. Thus, any surgical procedure that removes a major nociceptive stimulus (e.g., an infiltrating tumor) may lead to unopposed opioid-mediated respiratory depression or somnolence in the postoperative period.

For patients without chronic pain, RCTs suggest that adequate postoperative analgesia by a multimodal approach may facilitate the return of gastrointestinal function, be cardioprotective, reduce pulmonary complications, and shorten the length of stay in the intensive care unit and the hospital.[214] Whether these findings are applicable to patients with chronic pain is unknown. Individually adapted regimens are usually superior to "conventional" analgesia, regardless of the specific analgesia technique used.[215] In minor surgery and in surgical procedures between minor and major surgery, an opioid-NSAID combination should always be considered to enhance opioid effects. Because pregabalin and gabapentin can reduce postoperative pain and opioid consumption[216] and have anxiolytic effects,[217] the patient with chronic pain and anxiety may benefit. A dose range for pregabalin of 150 mg twice daily until the second or third postoperative day has been recommended.[207] Ketamine may also be applied as an adjunctive therapy,[199] but no data encourage its routine use in the perioperative period for the patient with chronic pain. Support from a multimodal pain treatment facility should be requested. Apart from the choice of analgesia technique and adequate opioid medication, optimization of organizational structures is a key factor for improving perioperative analgesia.[218] If addiction is suspected, the patient should be reevaluated for weaning or rehabilitation only after recovery from surgery and

postoperative pain.[219] Specific risk factors in patients with chronic pain are summarized in Box 64-1.

Postoperative Regional Anesthesia

Although no strong evidence indicates the superiority of particular anesthetic techniques for postoperative analgesia in patients with chronic pain, individual considerations may favor regional anesthesia, particularly because these patients are prone to intensified postoperative pain experiences (see also Chapter 98). Patients who have been consuming opioids on a long-term basis need their daily systemic dosage by the intravenous or oral route to prevent withdrawal.[61] In addition, postoperative analgesia with an epidural or plexus catheter may be accomplished with a combination of local anesthetics and opioids, similar to patients without chronic pain (see Chapters 56 and 98). However, higher doses of epidural opioids are recommended because cross-tolerance between orally and epidurally administered opioids has been described. Epidural lipophilic opioids (fentanyl, sufentanil) may provide better postoperative pain relief than epidural morphine in patients who have been consuming opioids on a long-term basis; this effect has been attributed to the need for a lower receptor occupancy or incomplete cross-tolerance between morphine and sufentanil.[220]

Postoperative Intravenous Opioids

The total required opioid dose consists of the daily dose taken before and the dose made necessary by surgical stimulation (see also Chapter 98). A continuous perioperative intravenous opioid infusion equivalent to the regular daily dosage is recommended if the oral route is unavailable.[61,215] Additional bolus doses of opioid or nonopioid analgesics, or both, must be titrated to individual needs to achieve adequate pain control in the postanesthesia care unit. Depending on the local circumstances, this may be patient, nurse, or physician controlled. The bolus size should be equal to the hourly dose of the background infusion. Once the patient demands less than four extra bolus doses per day, the background infusion may be reduced in daily steps of approximately 20% to 30%. For calculation of opioid dose equivalents, the relative potency, half-life, bioavailability, and route of administration must be considered.[221] As soon as possible, oral medication should be resumed. Intravenous doses during the first 24 to 48 hours after surgery should be converted to oral dose equivalents. Half the total dosage may be delivered as long-acting and half as short-acting breakthrough medication.[61]

Perioperative Transdermal Opioids

Transdermal fentanyl patches are relatively reliable in administering controlled amounts of the drug to the circulation over long periods. However, during surgery the amount of drug delivered to the patient may significantly shift. Changes in intravascular volume, body temperature, and volatile anesthetics alter skin permeability and perfusion, thus resulting in relatively large fluctuations in transdermal fentanyl passage. In addition, forced-air warming blankets and heat packs applied onto the patch itself can lead to severalfold increases in fentanyl permeation through the skin.[57] Thus, in major surgery, removal of transdermal systems is advisable to avoid unforeseen decreases and increases of systemic opioid uptake. The transdermal opioid dose should be converted to intravenous morphine to be administered as a continuous background infusion.[221] Pertinent issues and practical recommendations are summarized in Box 64-3.

BOX 64-3 ***Intraoperative and Postoperative Management Issues and Practical Recommendations in Patients With Chronic Pain***

- Start the background opioid infusion immediately when the patient arrives in the operating room.
- Remove an opioid-patch when major surgery is planned; in minor surgery, a patch may be continued without a background infusion.
- Every patient with chronic pain must be seen postoperatively three times daily to evaluate pain at rest, pain with exercise (e.g., coughing), nausea, sedation, mobilization, and sleep quality.
- Monitor closely for signs of respiratory depression and of withdrawal (e.g., unexplained tachycardia, restlessness, sweating, confusion, hypertension).
- Integrate the patient into the acute pain service protocol if available.
- Titrate a short-acting opioid for acute pain with two to four times the usual starting dose needed for an opioid-naïve patient.
- Add COX inhibitors, anticonvulsants, and other adjuvants as needed.
- Evaluate the demand-delivery ratio of PCA frequently, and adapt the demand dose in relation to the background infusion (the demand dose equals the hourly dose of background infusion).
- Increase the background infusion in PCA in relation to the cumulative daily opioid demand dose (add 50% to 75% of the daily demand dose to background infusion).
- Change the technique of postoperative analgesia if inadequate use persists in spite of repeated patient education.
- In case of insufficient epidural analgesia with morphine, use epidural fentanyl or sufentanil.
- In case of IV opioid dose escalation, consider spinal or epidural opioid application or switch to an IV agonist.
- Reduce daily opioid doses after the second postoperative day stepwise to the preexisting dose.
- Switch back to an oral or transdermal medication as early as possible: use 50% to 75% of the last daily IV opioid dose as slow release oral or transdermal delivery plus the rest as a demand dose.
- When switching back to the transdermal route, consider 12- to 16-hour delayed effects, and supply the patient for this period with sufficient on-demand analgesia.
- Do not attempt to solve a chronic pain problem in the immediate postoperative period.
- Use nonpharmacologic techniques (distraction, relaxation) when appropriate, and offer counseling in the pain unit after postoperative recovery.

Data from Farrell C, McConaghy P: Perioperative management of patients taking treatment for chronic pain, BMJ *345:e4148, 2012; and Kopf A, Banzhaf A, Stein C: Perioperative management of the chronic pain patient,* Best Pract Res Clin Anaesthesiol *19:59-76, 2005.*

COX, Cyclooxygenase; *IV,* intravenous; *PCA,* patient-controlled analgesia

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Chapter 65

Palliative Medicine

SARAH GEBAUER

Key Points

- Palliative care is an interdisciplinary approach to symptom management and decision making in treating serious illnesses that are appropriate for patients with a wide range of illnesses and is not limited to patients who are imminently expected to die.
- Palliative care teams reduce costs and decrease the burden of symptoms for patients with serious illnesses.
- Physicians receive little training in discussing difficult topics and tend to focus on details and use medical jargon.
- Patients and families want physicians to be truthful and empathetic and to participate in shared decision making.
- Physicians have difficulty prognosticating the future for an individual patient. Patients and families understand and accept this reality.
- Opioids administered in small doses do not hasten death in patients receiving palliative care and are effective in treating dyspnea.
- Patients with perioperative limitations on treatment should prompt a thorough discussion of a perioperative plan with the patient and surgical team.

WHAT IS PALLIATIVE MEDICINE?

DEFINITION

The World Health Organization (WHO) defines palliative care as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."[1] Illness has many facets, and symptom management, family support, and aid in decision making are common areas of focus for palliative care teams[2] (Fig. 65-1). Palliative care refers to the work of an interdisciplinary team, whereas palliative medicine refers to the medical subspecialty focused on providing symptom relief and decision-making support for patients with serious illnesses.

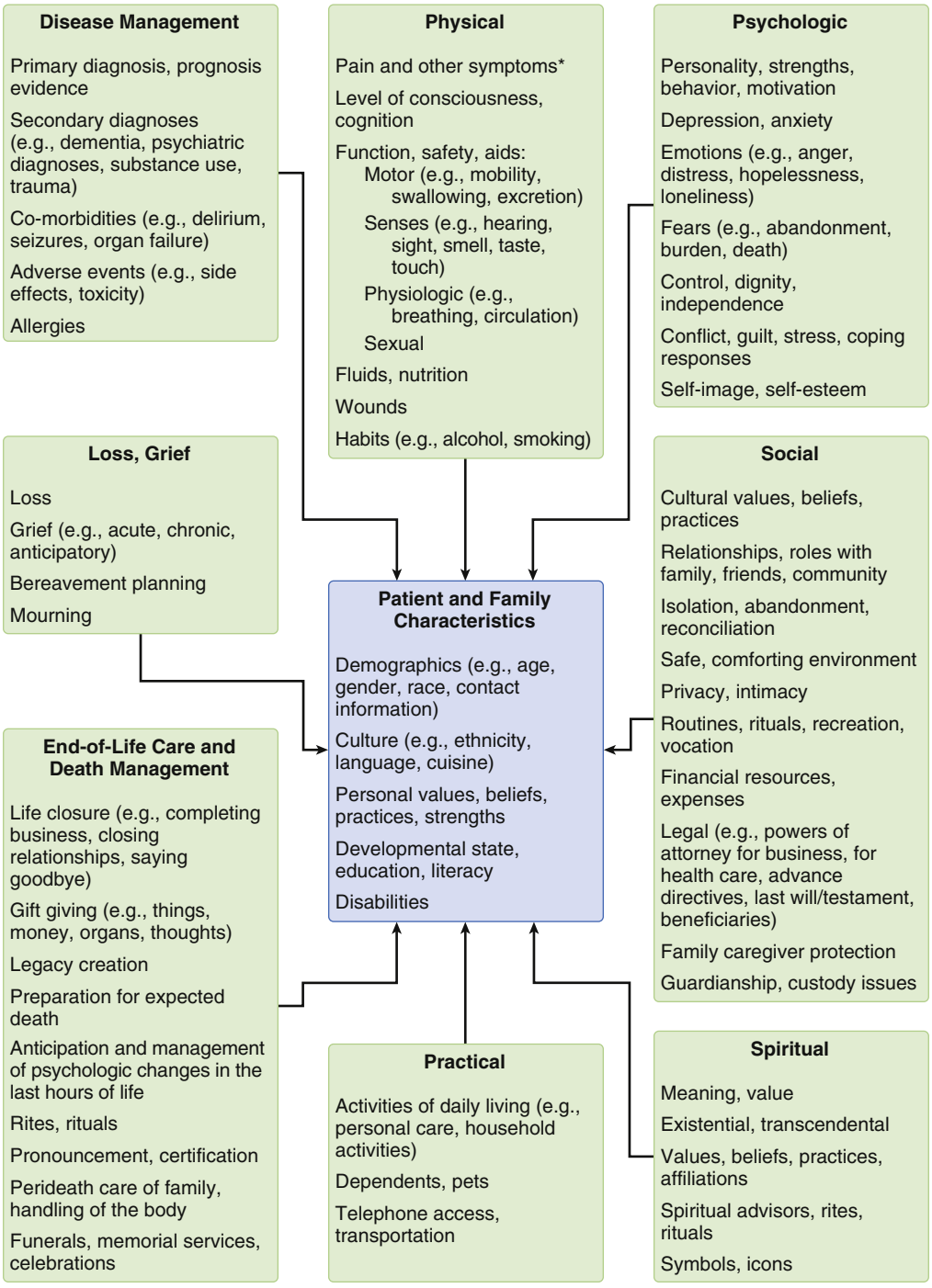
PRIMARY VERSUS SPECIALIST PALLIATIVE MEDICINE

A distinction has been made among the levels of palliative care. This distinction facilitates the differentiation among the skills expected from all physicians and from those more suitable to a specialist service. Examples of primary palliative medicine include basic pain and symptom management, as well as discussions about prognosis, goals of treatment, and resuscitation status.[3] Specialty palliative medicine includes the management of refractory or complex symptoms, as well as the facilitation of conflict resolution among families, staff members, and treatment teams related to the goals of care.[4]

HISTORY OF PALLIATIVE MEDICINE

The word *palliative* comes from the Latin word *to clothe* and refers to the "covering up" of symptoms such as pain. Modern palliative medicine grew out of the hospice movement that was started by Dr. Cicely Saunders in the late 1960s.[5] Since that time, the field has broadened from a focus on patients at the end of life to include patients with serious illnesses, with the growing recognition that many hospice principles, such as the relief from suffering, also apply to patients regardless of prognosis[6] (Fig. 65-2). After its introduction to the United States in the 1970s, several academic medical centers developed palliative care teams in the 1990s to meet this growing need.[6]

Inpatient palliative care teams have rapidly grown over the past decade,[7] and currently 85% of hospitals with more than 300 beds and 63% of hospitals with 50 or more beds have palliative care teams.[8] Hospice and palliative medicine became a recognized subspecialty in 2006, with the first board examinations offered in 2008. Physicians from 10 medical specialties, including anesthesiology, are eligible to complete a fellowship and to take the board examination.[9] Currently, 129 anesthesiologists are board-certified or eligible to practice in hospice and palliative medicine, which represents 3% of the estimated 4400 hospice and palliative medicine physicians in the United States.[10]



* Other common symptoms include, but are not limited to:
Cardiorespiratory: breathlessness, cough, edema, hiccups, apnea, agonal breathing patterns
Gastrointestinal: nausea, vomiting, constipation, obstipation, bowel obstruction, diarrhea, bloating, dysphagia, dyspepsia
Oral conditions: dry mouth, mucositis
Skin conditions: dry skin, nodules, pruritus, rashes
General: agitation, anorexia, cachexia, fatigue, weakness, bleeding, drowsiness, effusions (pleural, peritoneal), fever/chills, incontinence, insomnia, lymphedema, myoclonus, odor, prolapse, sweats, syncope, vertigo

Figure 65-1. Aspects of illness. *(Modified from Ferris FD, Balfour HM, Bowen K, et al: A model to guide patient and family care: based on nationally accepted principles and norms of practice,* J Pain Symptom Manage *24:106-123, 2002.)*

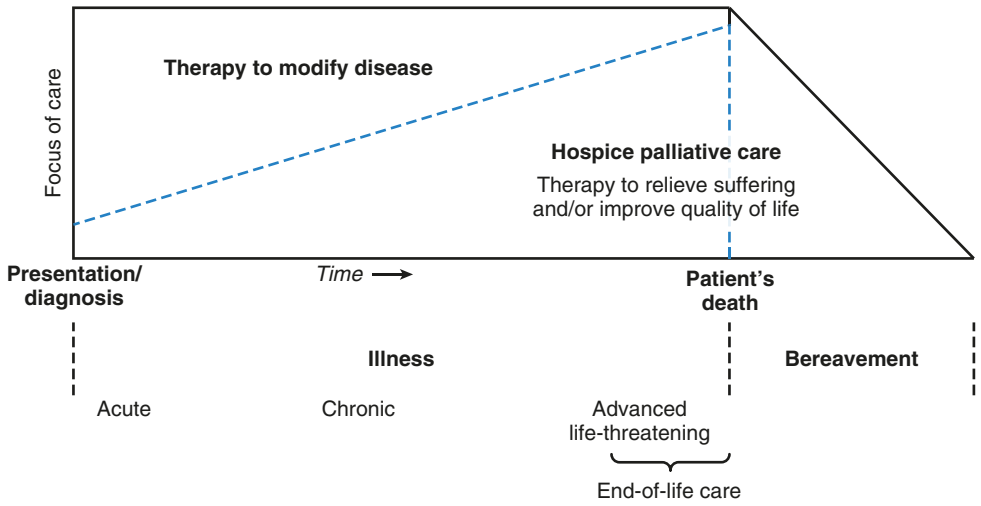


Figure 65-2. Schematic illustration depicting the role of hospice care and palliative care during illness and bereavement. *(From Ferris FD, Balfour HM, Bowen K, et al: A model to guide patient and family care: based on nationally accepted principles and norms of practice,* J Pain Symptom Manage *24:106-123, 2002.)*

WHY IS PALLIATIVE MEDICINE NEEDED?

The combination of an aging population and medical advancement has contributed to a growth in the number of patients with chronic illnesses. In the United States in 2011, Medicare spent $549 billion, with 55% of Medicare expenses going to the most expensive 10% of patients in 2008.[11] Many of these patients have multiple comorbidities, repeated or prolonged hospitalizations, or a life expectancy of less than 1 year, and many patients may be appropriate for hospice or palliative care services.[12]

Patients with serious illnesses have a significant symptom burden, most often involving pain, dyspnea, anxiety, and depression, and their family members report similar concerns.[13] Although the quality of pain control during a life-limiting illness is often a major concern of patients and their families, several surveys have found that they are often dissatisfied with the quality of pain control.[13,14] Patients and families also describe poor communication with health professionals, particularly in the setting of conversations regarding prognosis.[15] Palliative care, with its emphasis on symptom management and goal setting, attempts to address these concerns.

WHY IS PALLIATIVE MEDICINE IMPORTANT TO ANESTHESIOLOGISTS?

As patients who are older and more seriously ill undergo surgery,[16] anesthesiologists should develop an understanding of the concepts of palliative medicine. Anesthesiologists have specific skills in symptom management that may benefit the patient, and they have a unique perspective on the surgical process that can provide insight to palliative medicine and surgery teams.[17] As more patients and families interact with palliative care teams, anesthesiologists should be able to discuss related concerns and to develop an anesthetic plan that includes palliative concepts, including goals of care discussions and symptom management. Additionally, many pain and critical care anesthesiologists regularly care for patients who are seriously ill and have specific expertise to offer.

GLOBAL PALLIATIVE CARE

Approximately one half of the countries in the world have at least one hospice or palliative care service, although most exist in larger and more developed countries. The variation in availability is vast, from 1 physician for every 1000 inhabitants in the tiny country of Niue near New Zealand to 1 per 8.5 million inhabitants in China and 1 per 90 million in Pakistan.[18] In addition to the variation in physician availability, the access to appropriate medications is often restricted. An estimated 80% of people with pain worldwide are unable to access opioids, often attributable to concerns about addiction or restrictive national opioid policies.[19] The WHO has implemented a "Public Health Strategy for Palliative Care" that incorporates aspects of policy, drug availability, and education to customize and integrate palliative care throughout the globe.[20]

PALLIATIVE CARE TEAM

Guidelines suggest that professionals with skills to meet the patient and family's physical, psychological, social, and spiritual needs participate in the creation of a specialized care plan. Ideally, teams are interdisciplinary and include a nurse, physician, social worker, and chaplain, as well as other professionals, depending on the need.[21] Many professional disciplines have developed specialized certification or training in palliative care (Table 65-1).

WHERE IS PALLIATIVE CARE DELIVERED?

In the United States, palliative care is often a consult service in hospitals or in an inpatient unit.[6] Approximately two thirds of U.S. hospitals and 85% of middle-to-large hospitals have palliative teams, although access varies, depending on the geography and type of hospital.[22] Geography is an important factor in the availability of services. Seventy-three percent of Northeastern U.S. hospitals with 50 or more beds have palliative teams, whereas 51% of

TABLE 65-1 MEMBERS AND ROLES IN A PALLIATIVE CARE TEAM

Physician	• Diagnoses, treats, and manages a wide variety of medical issues for patients. • Provides expert symptom management and consultation. • Provides expert skills and consultation in communication with patients who are seriously ill, their families, and other providers.
Nurse	• Participates in the diagnosis, treatment, and management of acute and chronic serious illnesses within his or her scope of practice. • Assesses the patient's psychosocial and spiritual needs in the setting of a serious illness. • Participates in symptom management within his or her scope of practice. • Uses unique skillsets to communicate with the patient, family, health care team, and community.
Social worker	• Addresses the psychosocial needs of patients and their families affected by serious illness. • Participates in meetings with the medical team, patients, and families. • Assists in complex discharge needs, and communicates with community resources.
Spiritual advocate	• Assists patients and families in identifying and addressing spiritual distress related to serious illness. • Provides or facilitates appropriate spiritual or religious rituals. • Provides liaison services to community spiritual resources.
Additional professionals who provide expertise to the palliative care team	• Anesthesia pain experts • Pharmacists • Rehabilitation therapists • Psychiatrists

Data from the following resources:
National Association of Social Workers. The certified hospice and palliative social worker. Accessed June 20, 2013. <http://www.socialworkers.org/credentials/credentials/chpsw.asp>
Hospice and Palliative Nurses Association. Accessed June 20, 2013. <http://www.hpna.org/DisplayPage.aspx?Title=Position Statements>
Board of chaplaincy certification. Palliative care specialty certfication competencies. Accessed June 20, 2013. <http://bcci.professionalchaplains.org/content.asp?admin=Y&pl=45&sl=42&contentid=49>
Center to Advance Palliative Care. Accessed June 20, 2013. <http://www.capc.org>
Note: Roles and competencies may vary by region and training.

Southern U.S. hospitals have palliative teams.[8] Patients admitted to the hospital are actively dying or often have symptoms that are difficult to manage, although only 20% to 26% of U.S. cancer centers offer dedicated palliative care inpatient beds.[6,23] Palliative care clinics are increasingly available, although home palliative care for patients who do not meet hospice eligibility criteria is rare in the United States, likely attributable to the reimbursement model.[6] Methods and locations of palliative care delivery are widely variable throughout the world, depending on the country's infrastructure.

INPATIENT PALLIATIVE CARE TEAMS

Outcomes With Palliative Care Teams

Inpatient palliative care teams reduce hospital costs. A retrospective study of six hospitals with well-established palliative care teams showed a decrease of $1700 per admission for patients discharged alive and $5000 for patients who died.[7] A study of Medicaid beneficiaries showed hospital costs decreased by an average of $6900 during an admission once palliative care teams became involved, with a reduced length of stay in the intensive care unit (ICU)[24] and fewer deaths in the ICU[25] (also see Chapters 101 and102). Making decisions about hospital length of stay is not clearcut.[24,26] Inpatient palliative care teams increase patient quality of life[27] and patient and caregiver satisfaction.[27] Data on symptom improvement is sparse but suggests improvement in some areas.[28,29] Importantly, palliative care teams do not increase in-hospital mortality.[24,30] This fact may be important for families and patients who incorrectly view palliative care as hastening death.

When to Consult Palliative Care Teams

A variety of indicators have been developed to help physicians decide when a palliative care assessment should be performed. Patients' palliative care needs can be assessed by the treating physician, and a consultation with a palliative medicine specialist should be made on the basis of that assessment. The first screening criterion is generally considered to be whether a patient has a condition that is potentially life-limiting or life-threatening.[31] These terms, although open to interpretation, are not meant to include patients who routinely return to their baseline status, such as a previously healthy patient with community-acquired pneumonia.[31] Rather, these terms are meant to describe patients with a condition known to be life-threatening (e.g., metastatic cancer, cirrhosis, chronic renal failure)[31] or with conditions that have a high likelihood of leading to death (e.g., multiorgan failure, major trauma, sepsis).[31] Additionally, the patient should fit at least one additional criterion, including frequent hospital admissions for the same condition, functional decline, and an ICU stay of 7 days or longer. In general, consultation is often requested for assistance with symptoms that are difficult to control, complex decision making, and provider or family support.

Palliative Care in the Surgical Intensive Care Unit

The two main models of palliative care integration in the ICU are the consultative model and the integrative model.[32] In the consultative model, a specialist palliative care team makes recommendations to the primary physician regarding the care of the patient; in the integrative model, the surgeon or intensivist identifies and addresses

issues related to palliative care without specialist input. The most effective model is not clear at this point and is often determined by hospital resources and culture (also see Chapters 101 and 102).

Although initial palliative care efforts and research have focused on medical intensive care units (MICUs), increased attention is being focused on providing palliative care to appropriate patients in the surgical intensive care unit (SICU) to improve symptom management, to communicate the goals of treatment, and to provide family support.[32] One study of patients in a trauma ICU showed early assessment of patient and family preferences and interdisciplinary meetings led to unchanged mortality, do not resuscitate (DNR) orders, and the withdrawal of life support; however, the DNR and withdrawal orders were completed early in the hospital stay, and the ICU length of stay decreased in patients who died.[26]

Trigger Criteria in the Surgical Intensive Care Unit

Identifying appropriate palliative care consultations early in the hospital course is increasingly the focus. Trigger criteria, in which a predefined list of patient factors results in automatic notification of a member of the critical care or palliative care team, are sometimes used to identify ICU consultations earlier and have shown encouraging results.[24] However, the most effective trigger criteria for surgical ICUs have not been defined.[32] Many proposals include some combination of the lengths of stay in the ICU, the lack of improvement during the ICU stay, patient age, and the patient's illness.[32] One study, specifically in the SICU, used 10 triggers based on expert opinion; these included multiorgan system failure, SICU stay longer than 1 month, greater than three SICU admissions during one hospitalization, and death expected during a current SICU admission, among other triggers.[33] This study showed no benefit with palliative care, but its applicability may have been limited. Only 6% of the patients in this study met the trigger criteria, and although the attending physician was notified when a patient met the criteria, a palliative care consultation was left to the judgment of the attending physician.[33] A more inclusive screening process or a mandated palliative care referral, as observed in some of the successful medical ICU studies,[24] may have altered these results.

OUTPATIENT PALLIATIVE CARE

Increasingly, palliative care clinics exist that can follow patients after discharge or see patients for outpatient symptom management and psychosocial support.[34] The providers, availability, and focus vary widely.[34] A landmark study by Temel in 2010 randomized 151 patients with metastatic non–small-cell lung cancer to early outpatient palliative care plus the standard oncologic care or standard oncologic care alone. Patients in the palliative care group had higher quality-of-life scores, as well as fewer symptoms of depression.[35] Perhaps most surprisingly to some, the patients in the palliative care group lived a median of 2.7 months longer than those with standard care, despite receiving less aggressive care.[35] These results and others have led to a recommendation by the American College of Chest Physicians that palliative care be introduced early in the course of disease for patients with stage IV lung cancer or a high symptom burden.[36] Smaller studies have shown positive but variable improvement in symptoms.[37,38]

Palliative Care and Hospice Care

Continuous Features

- Multidisciplinary team
- Symptom management: pain, dyspnea, psychosocial
- Focus on quality-oriented care
- Family support
- Attempts to minimize suffering

Early Palliative Care	Hospice Care
• Appropriate at any stage of serious illness	• Prognosis <6 months (can be renewed every 60 days)
• Often provided in hospitals or outpatient clinics	• Focus on home-based care
• Can be used in conjunction with "aggressive" care	• Patient usually agrees to focus on comfort rather than life-prolonging treatments
• Free-for-service model	• Throuh Medicare, billed on a per-diem rate

Figure 65-3. Features of palliative care and hospice care in the United States.

DIFFERENCES BETWEEN HOSPICE CARE AND PALLIATIVE CARE

In contrast to palliative care, the definition of hospice care varies among countries as it applies to the type of patient, the involvement of the medical team, and the setting.[39] In some countries, such as the United States, hospice care refers to a benefit provided by the governmental health care system, whereas in other countries, hospice care and palliative care are interchangeably used. In general, hospice services tend to focus on later-stage illnesses. Despite the logistic differences, the philosophy of hospice care generally focuses on reducing suffering, enhancing the quality of life, and supporting the patient and family. The available services, as well as the concerns for the patients, caregivers, and physicians, may be different, depending on the country's health care framework and culture. In the United States, palliative services are provided on a continuum, whereas hospice care is only available to patients with a life expectancy of less than 6 months (Fig. 65-3).

HOSPICE CARE IN THE UNITED STATES

In the United States, hospice is a per-diem capitated payment system for a defined set of services for patients with a life expectancy of 6 months or less, as agreed on by two physicians.[40] Medicare pays for approximately 80% of hospice care in the United States, and many private insurers have established similar guidelines. These services include visits to a patient's residence by a nurse (the main provider of clinical care[41]), aide, social worker, and chaplain.[40] Family members are also eligible to receive a year of bereavement counseling.[40] Continuous care and short-term hospital admission are available for patients with uncontrolled symptoms. A core set of requirements for the hospice benefit exists (Fig. 65-4). However, beyond these requirements, each hospice unit can decide which

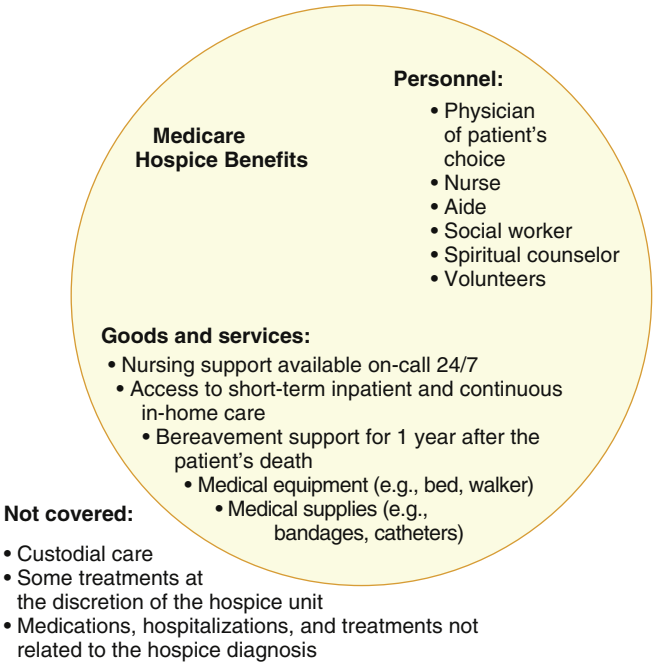


Figure 65-4. Aspects of the Medicare hospice benefits.

treatments to cover, and this coverage can vary widely. For example, some hospice organizations may cover palliative radiation treatments, whereas others may not. Patients who outlive their 6-month prognoses may have their benefits extended in 60-day increments after a face-to-face visit with a physician, recertifying that the patient continues to meet hospice criteria.

Who Is Eligible for Hospice Care?

To qualify for hospice, an attending physician and a hospice medical director must certify that the patient's prognosis is less than 6 months if the disease runs its normal course.[40] Medicare has created guidelines that describe eligibility criteria for hospice services, although the opportunity for interpretation does exist. For example, the criteria for a patient with chronic lung disease include disabling dyspnea at rest, poor response to bronchodilators, hypoxemia at rest, and repeated hospitalizations for emergency department visits.[41] As a result of the subjectivity of some of the guidelines, some hospices may accept patients that other hospices deem ineligible. Patients are not required to have a DNR order to be enrolled in hospice.

Recipients of Hospice Care

Although patients with cancer were previously the primary recipients of hospice care, the proportion of patients receiving hospice care with noncancerous diagnoses such as dementia, chronic obstructive pulmonary disease (COPD), and congestive heart failure (CHF) has increased from 16% in 1990 to 69% in 2010.[42] During this same period, the percentage of patients with Medicare who died while receiving hospice care increased from 5.5% to 44%.[42] This increase is particularly problematic, considering the lack of good prognostic criteria for a 6-month life expectancy in these disorders, which can complicate hospice referral timing.[43] The median length of stay in hospice was 18 days in 2010,[42] and approximately one third of all hospice patients live for less than 1 week after admission to hospice care.[41] This trend toward late admission suggests that many patients are referred to hospice well after they are eligible.

Outcomes with Hospice Care

Hospice care decreases patient symptom burden[44] and increases caregiver satisfaction, with 98% of family members recommending hospice care to others.[41] A survey of over 1500 bereaved family members showed that 70% of respondents whose family member received hospice services considered the care "excellent" with less than 50% of those with decedents in hospitals, nursing homes, or home with home health services considering the care received at the same level.[45] Studies related to cost-effectiveness vary in their conclusions. Yet, a few studies suggest that the length of hospice use is correlated with cost savings.[44,46] A 2007 study by Taylor suggested cost savings only with a hospice stay of 53 to 107 days,[46] whereas a 2013 study by Kelley showed cost savings with shorter hospice stays as well.[44]

HOSPICE CARE AND ANESTHESIOLOGISTS

Surgical anesthesiologists, as well as pain and critical care medicine anesthesiologists, are likely to interact with patients who are enrolled in hospice care. Awareness of the goals of care in the hospice setting and what services are provided will help the anesthesiologist develop an appropriate plan based on the individual patient's goals. Pain medicine physicians (also see Chapters 64 and 98) may be providing care as part of a hospice benefit. Critical care anesthesiologists are often called on to aid in the determination of hospice eligibility and to help families discuss care plans that may involve hospice (also see Chapters 101 and 102).

PEDIATRIC HOSPICE CARE AND PALLIATIVE CARE

Pediatric palliative care is appropriate for many children with chronic serious illnesses, and the WHO states that pediatric palliative care can be successfully delivered even in resource-limited settings.[1] Pediatric hospice and palliative care are similar to their adult counterparts, but the patient's development stage is incorporated into the pediatric care plan. Explanations of illness and death depend on the child's developmental stage; a child younger than 2 years of age has no concept of death, whereas a 10-year-old child may be interested in the details of the death process[47] (also see Chapters 93 and 95).

Characteristics of the Pediatric Palliative Care Population

The variety of diagnoses for patients in pediatric palliative care are wider than those for adults[48] with the most common disorders being congenital and neuromuscular in origin.[48] In the largest observational study to date, over one third of pediatric patients referred for palliative care consultation services were 1 to 9 years of age, one third were 10 to 18 years old, and less than 20% were

younger than 1 year of age.[48] Children often have prolonged survival after the initial palliative care consultation, compared with adults.[48] Some disorders, including chromosomal or severe developmental abnormalities, are rarely seen by adult palliative care physicians and pose additional difficulties for adult palliative care teams. The decision to forgo treatment with curative intent is generally difficult for families, and prognostication is similarly difficult for providers.[47] Moreover, multiple legal issues related to declining medical treatment exist that differ from the regulations that concern adults.[49]

Symptom Management in Pediatric Palliative Care

Historically, symptoms in children with serious illnesses have been poorly managed. In a retrospective survey of parents of deceased children in 2000, parents noted that their children suffered "a lot" or "a great deal," mostly from pain, fatigue, and dyspnea.[49] In contrast to most studies of adults near the end of life, a 2011 study noted neurologic symptoms being more prevalent than pain in children,[48] suggesting a need for a better understanding and treatment of these symptoms in the pediatric population. Regional anesthesia has been reported as being of benefit to pediatric patients with pain that is difficult to manage with systemic treatment.[50] Data on specific therapies for children are limited, and many practitioners use medications based on adult studies.

PALLIATIVE SURGERY

Palliative surgery has been defined as "the deliberate use of a procedure in a patient with an incurable disease with the intention of relieving symptoms, minimizing patient distress, and improving the quality of life."[51] Although a diagnosis may not be specifically cancer, the few studies on palliative surgery focus on oncology patients. Palliative surgery for patients with cancer is most often for bowel obstruction, with wound management also common.[52] A 2004 study of over 1000 patients with advanced cancer showed a 30-day morbidity of 29% and mortality of 11%, with 80% of patients experiencing improved symptoms at 30 days. A similar study by the same author in 2011 of 227 patients showed a morbidity of 20% and mortality of 4%, with 90% experiencing symptom resolution, a significant improvement from the similar study in 2004.[51,53] The study authors attribute at least some of this change to better patient selection through shared decision making with patients and families.[51] Poor functional status was associated with decreased survival in both studies.

COMMUNICATION

ADVANCE CARE PLANNING

The Patient Self-Determination Act took effect in 1991 in the United States and requires health care providers and institutions to advise patients of their right to an advance directive and to develop institutional policies and education regarding advance directives.[54] However, since the introduction of advance directives, multiple issues have been identified, such as changing preferences as the illness changes and the inherent difficulty in predicting future desires as circumstances change.[55-57] Because the outcomes of studies on advance directives have been disappointing, many experts believe a patient discussing preferences with and naming a surrogate decision maker may be the most crucial part of the process,[58,59] although the decisions made by the surrogate may not always be in accordance with the patient's wishes.[60] Understanding a patient's goals requires open communication with the patient and physician and sometimes repeated conversations to clarify and update the goals of treatment as the patient's condition changes. More information on advance directives and decision-making surrogates can be found in Chapter 10.

OUTCOMES OF ADVANCE CARE PLANNING

The landmark 1995 Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) was a 2-year prospective observational study, followed by a 2-year randomized trial of 9105 patients in five U.S. teaching hospitals, with the goal of improving end-of-life decision making.[14] The study enrolled patients with advanced stages of nine illnesses and a 6-month mortality of 45% to 48%; patients with trauma were notably excluded.[14] The observation period showed that 49% of patients who did not want cardiopulmonary resuscitation (CPR) did not have a written DNR order, and that the physicians were often not aware of the patients' wishes.[14] In the intervention, prognostic data were made available to physicians, and a nurse was available to facilitate information sharing, advance care planning, and pain assessment. In the intervention phase, no differences in physician communication, pain, use of hospital resources, or other measured outcomes were documented[21] (also see Chapter 102).

Based on the data from the SUPPORT trial, a study that examined the rates of advance directive completion showed that although more advance directives were documented, only 14% of the patients spoke with a physician when completing their advance directive, and only approximately 25% of the physicians were aware of their patients' advance directives a week after hospital admission.[61] Similar studies did not demonstrate that advance directives influenced the types of care or the resources used.[62,63]

PHYSICIAN COMMUNICATION SKILLS TRAINING

How physicians communicate about difficult issues can affect how patients and families perceive illness, death, and treatment options. Many of these skills have not traditionally been taught as part of the medical school curriculum, and most physicians are less comfortable discussing code status than they are with other topics, such as consent for procedures[64]; between 40% and 75% of physicians, depending on their level of training, assess their own knowledge of delivering "bad news" as inadequate.[65] In one survey of surgical residents, only 9% believed they "received adequate training in palliation"

during residency,[66] and as many as 90% of internal medicine residents expressed a desire for additional training in discussing topics such as DNR orders.[67] Despite this lack of training, residents often talk about these issues with patients,[68] highlighting the importance of education in this area.

PHYSICIAN COMMUNICATION SKILLS

Physicians often favorably rate themselves in terms of patient communication, but surveys of other practitioners and of patients suggest that physicians may not be able to self-assess accurately. One study in an ICU showed 90% of surgeons were satisfied with their communication skill concerning prognosis, but only 23% of intensivists and 3% of nurses rated it as such.[69] Similarly, patients' perceptions of their cancer stage and prognosis were often incorrect in one study, although oncologists thought they were clear in their explanations of the illness.[70] Recordings of physician discussions with patients and families show that physicians focus on technical detail, avoid emotional topics, and tend to dominate the conversations,[71] despite increased family satisfaction when the family spoke more and physicians exhibited more supportive behaviors.[71] Even when a conversation takes place between a physician and patient, the physician and patient may not agree on the outcome. One study of patients with metastatic cancer showed that physicians misunderstood their patients' preferences for CPR 30% of the time.[72] Currently, no comparable studies regarding anesthesiologists have been conducted. These findings highlight the importance of the anesthesiologist's role in assessing a patient's understanding of his or her disease process before a procedure is performed or during an ICU stay.

WHAT DO FAMILIES CONSIDER IMPORTANT IN END-OF-LIFE COMMUNICATION?

A majority of family members consider trust in the treating physician and truthful communication about the patient's illness as two of the most important factors in receiving quality end-of-life care.[73] In addition, families have greater satisfaction when a higher level of decision making is shared.[74] Family satisfaction increases with the number of empathetic statements made by a physician during a meeting.[75] A variety of patient and family preferences are available that address how much information is desired and how to receive it. A combination of personal, cultural, and family reasons influence these preferences, and physicians should not assume a preference based on a patient's race or ethnicity.[76] Many practitioners use a question such as, "How much would you like to know?"[77] although no studies of patient perceptions of that approach have been conducted. One study of patients with cancer indicated that some patients' preferences for involvement in decision making changed over the course of the illness.[78] A few studies have noted that caregivers wanted more information than the patients.[79] Some patients may indicate that they do not want to know about their condition and name a surrogate decision maker instead (also see Chapter 10). Sometimes these interactions do not work out well. Another type of conflict was nationally illustrated in Oakland, California, early in 2014. A patient in her teens had a postoperative hemorrhage after a tonsillectomy. She was resuscitated, but she did not have a return of brain function. The disagreement between the parents and the medical establishment was substantial and has never been publically resolved.

SPIRITUALITY AT THE END OF LIFE

Serious illness and the prospect of death can bring a number of spiritual issues to the foreground for patients and families, from questioning the meaning of one's life to a religion's teaching on specific medical interventions.[80] Patients typically want physicians to ask about their spiritual preferences[81] but often describe their spiritual needs as frequently not being met.[82] A simple screening question such as, "Is religion or spirituality important in your life?" has been proposed and may help identify patients in whom a spiritual need remains unmet. Asking about religion and spirituality may provide a context for the health care team, since many patients and families make decisions based on their religious and spiritual beliefs.[83] Physician understanding of the reasoning behind their patients' decisions is likely to improve end-of-life care. A spiritual counselor or chaplain can help patients and families with issues of spiritual suffering,[84] as well as identify and facilitate specific rituals related to illness or burial.

COMMUNICATION FRAMEWORKS

The aforementioned studies, which demonstrate frequent misunderstandings and poor communication, emphasize the need for an understanding of the importance of effective communication among physicians, patients, and families.[85] A number of frameworks have been developed to aid physicians in discussions with patients and families.[86-88] No study has compared their relative effectiveness on patient or family outcomes, and very few are assessing the effect of a specific communication framework on patient or family outcomes.[77] Commonalities in the approaches include active listening, validating patient concerns, and assessing understanding.

Family Meetings

Family conferences in the ICU have increasingly been used to facilitate information sharing between families and providers. In the ICU setting, meetings held within 72 hours of admission have shown decreased lengths of stay without increased mortality.[89] One of the few studies that evaluated a standardized communication approach was a single-site study of families of patients who were seriously ill and randomized to either a standardized communication template with a bereavement brochure or the standard care.[87] The communication intervention emphasized empathy, understanding of the patient as a person, and allowed family members to ask questions with the mnemonic of VALUE (value, acknowledge, listen, understand, elicit questions).[87] Family members in the study arm had decreased symptoms of psychological distress in a survey 3 months later[87] (Box 65-1).

BOX 65-1 ***VALUE: Framework for End-of-Life Conferences***

Value: Value and appreciate what the family member says. "Thank you for helping me understand how your husband's condition has changed over the past year."

Acknowledge: Acknowledge emotions. "This is often a sad time for families."

Listen: Actively listen. Remember to be silent and to give the family member time to speak.

Understand: Gain an understanding of the patient. Ask who the patient is as a person. "Can you tell me about your father, what kind of person he is and what's important to him?"

Elicit questions: Ask family members if they have questions. "We have discussed a lot of information. Do you have any questions?"

Data from Lautrette A, Darmon M, Megarbane B, et al: A communication strategy and brochure for relatives of patients dying in the ICU, N Engl J Med *356:469-478, 2007.*

BOX 65-2 ***SPIKES: Framework for Breaking Bad News***

Setting: Arrange for a quiet, private space large enough for all participants.

Perception: Assess the participants' understanding. "What have the doctors told you about your wife's illness?"

Invitation: Ask how much information is desired. "Some people like all the details, others just like the big picture. What would you like?"

Knowledge: Tell the participants what is known, using language that is easy to understand and avoiding the use of complex medical phrases.

Empathy: Acknowledge emotions. "I wish things were different."

Sequelae: Agree on the next steps. "Let's meet tomorrow afternoon so I can update you on her condition."

Data from Baile WF, Buckman R, Lenzi R, et al: SPIKES–A six-step protocol for delivering bad news: application to the patient with cancer, Oncologist *5:302-311, 2000.*

BOX 65-3 ***NURSE: Framework for Dealing With Emotion***

Name: State the emotion you believe the patient or caregiver is exhibiting. "It seems like you are angry."

Understand: Empathize with and legitimize the emotion. "I can't imagine how hard this must be for you."

Respect: Praise the patient or caregiver for his or her strength. "You've done so much for your mother during this difficult time."

Support: Show support. "I want to help."

Explore: Ask the patient or caregiver to elaborate on the emotion. "Can you help me understand what was so frustrating today?"

Data from Back AL, Arnold RM, Baile WF, et al: Approaching difficult communication tasks in oncology, CA Cancer J Clin *55:164-177, 2005.*

Many physicians struggle with how to begin family meetings. Although no study specifically addresses this concern, common approaches include introducing the family and team members; a brief summary is given by the physician that explains why he or she is holding the meeting; and the physician asks the family members to tell him or her what they understand. For example, "What have you been told about what's going on with your dad?"

Breaking Bad News

The six-step SPIKES (setting, perception, invitation, knowledge, empathy, sequelae) protocol is a framework for breaking bad news. Several of the elements, such as finding a quiet meeting space, asking what the patient or family understands, and making a plan for the future, apply in many situations[86] (Box 65-2).

Responding to Emotion

The NURSE (name, understand, respect, support, explore) protocol is a framework for responding to emotion, including anger. Patient and family anger directed toward health care providers is common in the setting of serious illness.[90] Crucial concepts in responding to anger include not becoming defensive or personalizing the anger, respectfully listening, and setting appropriate boundaries for safety.[90] Although difficult to accomplish in the moment, viewing anger as a coping mechanism in the grieving process is often helpful[91] (Box 65-3).

Requests for Nondisclosure

Family members may ask physicians to withhold a diagnosis from the patient. The cultural norms for disclosing a patient's diagnosis may vary widely among cultures and countries. In the United States, the culture of disclosure has rapidly changed, and now most physicians expect to disclose the prognosis to the patient.[92] No evidence is available that recommends how to deal with requests for nondisclosure, but expert opinions recommend empathetically responding to the family member, trying to understand the family's concerns about disclosing the prognosis, and asking the patient how and if he wants to be involved. For example, "Some people want to be told about any health issues and make their own decisions, and yet others prefer for a family member to be told the medical information and to make the decisions. What would you like?"[93]

Time-Limited Trials

In cases where the benefit of a clinical intervention is unclear for a specific patient, such as mechanical ventilation for ischemic encephalopathy, a time-limited trial, in which the physician and patient or family agree to reevaluate the benefit after a specified period, may be helpful.[94] Time-limited trials give families a sense of when the health care team expects to know whether an intervention is helping and creates the expectation that the issue will be readdressed.

RESUSCITATION STATUS

Outcomes of Cardiopulmonary Resuscitation

Resuscitation status is another conversation that some providers consider challenging[64] and that anesthesiologists may have with patients in the ICU or in the

perioperative period. CPR was introduced around 1960, initially as a treatment for intraoperative events[95] and then introduced outside the surgical unit. Outcomes of CPR have improved, with over one half of patients surviving the initial resuscitation and nearly one quarter surviving to discharge.[96] In surgical patients, approximately 85% of cardiac arrests occur postoperatively, and surgical patients may have a higher likelihood of survival than other groups of patients.[97,98] In one large study of older patients who survived to discharge after in-hospital CPR, approximately one half had moderate-to-severe neurologic defects[99] and 60% were alive 1 year later[99] (also see Chapters 101 and 102).

Resuscitation Status Discussions

Few studies examine the best way to approach discussions regarding resuscitation.[95] Ideally, the discussion about code status takes place in the context of a conversation about the patient's overall condition and goals. For example, one patient might decide on life prolongation as a goal, in which case a physician might recommend resuscitation attempts even if unlikely to succeed, whereas another patient with the same illness might prioritize physical independence as a goal, in which case the physician might recommend a DNR order to decrease the likelihood of prolonged ICU time or an unacceptable physical status. Some physicians advocate for making a recommendation about resuscitation status based on the patient's goals. The impact of this approach is unknown; a small simulated study that played a standardized video of a code status discussion to patients with cancer showed no difference between asking the patient his or her desired resuscitation status or making a suggestion for DNR order.[100]

Perioperative Limitations on Treatment

The American Society of Anesthesiologists (ASA) has published guidelines related to orders for the limitation of treatment in the perioperative setting.[101] The ethics of perioperative DNR orders are discussed in Chapter 10.

WITHDRAWAL OF LIFE SUPPORT

Some patients or family members may wish to discontinue ventilation or other forms of life support. Withdrawal of life support is ethically acceptable and respects patient autonomy (also see Chapter 10). Anesthesiologists can add expert skills in medication titration and the management of pain and anxiety to the withdrawal of ventilation. Multiple protocols for withdrawal of ventilatory support are available in the ICU, most using a narcotic for pain or dyspnea and a benzodiazepine for agitation or anxiety that are rapidly titrated to patient comfort.[102] Studies of the protocol use for the withdrawal of life support have not demonstrated an improvement in provider perception of the quality of death.[103,104] Specific concerns include making arrangements for rituals and family support, preparing the family, and discontinuing unnecessary tubes, treatments, and monitors.[102] Involving a spiritual advisor may be appropriate for some families.

Outcomes of Withdrawal of Life Support

One study of 74 medical patients in an ICU who were expected to die shortly after extubation showed a mean morphine dose of 5.3 mg/hr in the last hour of mechanical ventilation, followed by 10.6 mg/hr during the hour before death.[105] The average time to death was 153 minutes after extubation, with a range of 4 to 934 minutes. Somewhat surprisingly, each 1 mg/hr increase of morphine corresponded to an 8-minute delay in death.[105] This response is similar to an earlier study that showed a 13-minute increase in the time to death with each 1 mg/hr increase of benzodiazepine.[106]

Paralytic Drugs in the Withdrawal of Life Support

As noted in Chapter 10, patients should not be paralyzed before extubation of the trachea; it obscures symptom assessment and may lead to patient suffering. Patients already on paralytic medications should await the return of neuromuscular function before extubation unless doing so causes undue burden on the patient.[107]

PROGNOSIS

Multiple studies have examined the ability of physicians to prognosticate survival for a given patient. In a meta-analysis of eight studies in patients with a median survival of 4 weeks, physicians overestimated the prognosis by approximately 30%, with predictions more accurate in patients with poorer performance status.[108] In a prospective cohort study of 365 physicians and 504 patients receiving hospice care, the physicians overestimated survival by a factor of five, and 63% of their predictions were overestimates.[109] The longer a physician knew a patient, the more difficult it was for that physician to prognosticate.[109] Physicians in the ICU tend to be overly pessimistic; in a study of 851 patients on ventilation, only 71% of patients for whom a physician estimated a likelihood of survival of less than 10% at some point during their stay in the ICU died in the ICU.[110] A meta-analysis suggested that physicians are more accurate than algorithmic scoring systems (described in the Prognostic Tools section) in the first 24 hours after ICU admission; however, neither physicians nor scoring systems are reliably accurate for individual patients.[111] Overall, physician estimates do correlate with survival.[112] However, a study of 521 patients in a medical ICU found that physicians and nurses were unable to predict satisfaction with the quality of life 6 months after admission. In general, nurses tended to be more pessimistic than physicians and suggested withdrawal of therapy more often in patients who ultimately survived[113] (Figs. 65-5 and 65-6).

Difficulty with prognostication has led some physicians to avoid giving any kind of timeframe to eliminate the possibility of being wrong.[114,115] However, 87% of 179 surrogate decision makers wanted the physician to give a prognosis, even if it was uncertain.[116] Most understood the inherent unpredictability of prognostication and preferred that physicians make the prognostic uncertainty clear during the discussion.[116] Prognosis, even in the face of uncertainty, can help families prepare for bereavement

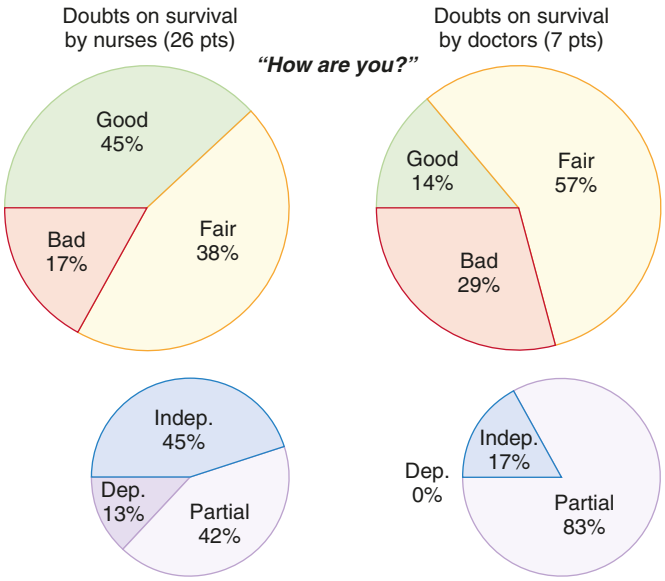


Figure 65-5. Answers of survivors 6 months after being discharged from the intensive care unit for whom treatment had been considered futile or questionable by nurses or physicians to improve survival. *Dep.,* Dependent; *Indep.,* independent. *(From Frick S, Uehlinger DE, Zuercher Zenklusen RM: Medical futility: predicting outcome of intensive care unit patients by nurses and doctors—a prospective comparative study,* Crit Care Med *31:456-461, 2003.)*

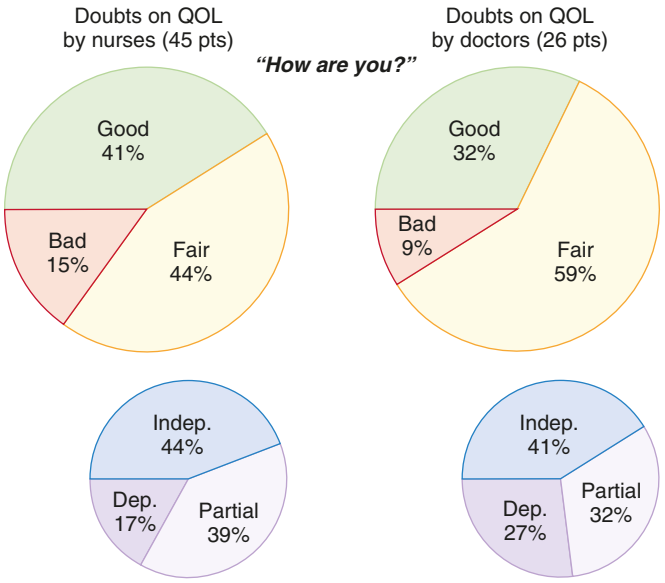


Figure 65-6. Answers of survivors 6 months after being discharged from the intensive care unit for whom treatment had been considered futile or questionable by nurses or physicians to improve the quality of life (QOL). *Dep.,* Dependent; *Indep.,* independent. *(From Frick S, Uehlinger DE, Zuercher Zenklusen RM: Medical futility: predicting outcome of intensive care unit patients by nurses and doctors—a prospective comparative study,* Crit Care Med *31:456-461, 2003.)*

and make important decisions about coordinating work, visitors, and finances.[116] Good data suggesting how to present prognoses to patients are not available. One approach to prognostication involves giving ranges such as hours to days, days to weeks, weeks to months, and months to years, with those categories roughly tracking with functional status. These ranges, along with an explanation from the physician about the difficulty of prognosticating, can often give families sufficient guidance with which to make important decisions. However, interpretation of a given prognosis may vary with the patient and family. One study that gave surrogate decision makers in the ICU hypothetical physician statements about prognosis and asked them to interpret them showed that surrogates tended to be optimistic, especially with worse prognoses.[117] These findings are similar to a study of patients with cancer in phase I and II clinical trials.[118]

DISEASE TRAJECTORIES

Multiple disease trajectories exist, although most can be included in one of the following functional categories: sudden extreme disability or near death; a period of good functionality, followed by a rapid, steady decline; a waxing and waning course with periods of decompensation followed by improvements; and a slow decline, starting at a low functional level[119] (Fig. 65-7). These frameworks can be useful when discussing prognoses with patients, particularly in talking to patients with conditions that are difficult to predict such as COPD and CHF.

PROGNOSTIC TOOLS

Cancer

Multiple Web-based cancer prognostic tools exist but none that are useful for every type of cancer. An important consideration is that the type of cancer is less important than a variety of patient factors, such as functional status and laboratory values as the disease becomes more advanced[120] (Fig. 65-8). In general, a patient with cancer who spends more than one half of the day in bed has a median survival of 6 months[121] (Box 65-4).

Intensive Care Unit

Multiple tools have been proposed to help the clinician predict mortality in the ICU, which are covered in depth in Chapter 101.

Other Selected Conditions

Many conditions have courses that are difficult to predict. The tables give characteristics associated with patients with a median survival of 6 months or less,[122] although it should be noted that the prognostic accuracy of these factors is not known. Table 65-2 offers a general sense of where the patient might be in the illness trajectory.

Congestive Heart Failure. CHF often has a waxing and waning course. The Seattle Heart Failure Model estimates mean 1- to 3-year survival but does not appear to be able to predict whether individual patients are in the last year of life.[123] Factors associated with a poor prognosis include hospitalization, tachycardia, hypotension, decreased ejection fraction, and increased creatinine level.[124] In patients hospitalized for acute decompensation of heart failure, older age and COPD were associated with decreased 1-year survival.[125]

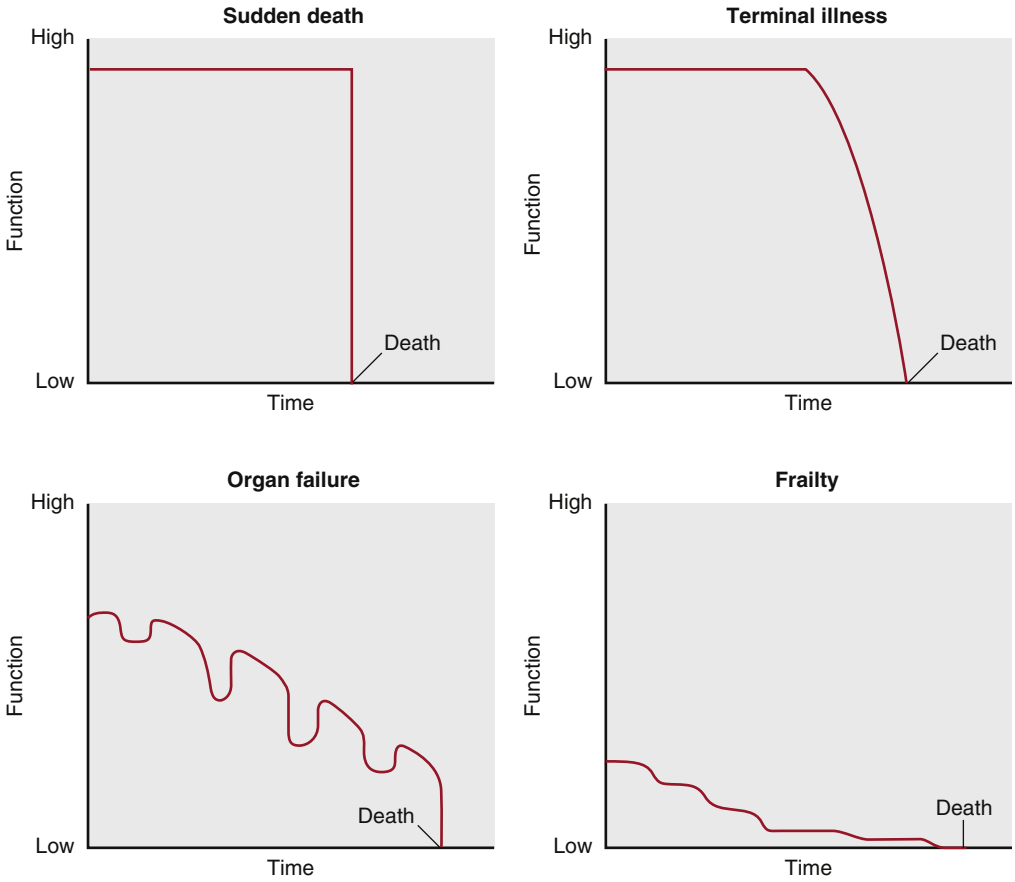


Figure 65-7. Trajectories of dying. *(From Lunney JR, Lynn J, Hogan C: Profiles of older Medicare decedents,* J Am Geriatr Soc *50:1108-1112, 2002.)*

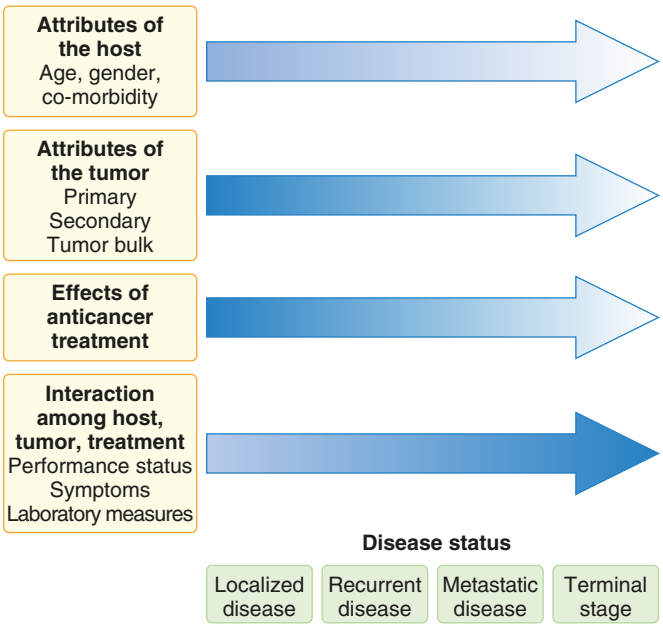


Figure 65-8. Factors associated with the length of survival in patients with cancer. Depth of shading represents relative importance of the factor as a predictor of subsequent survival. *(From Hauser CA, Stockler MR, Tattersall MH: Prognostic factors in patients with recently diagnosed incurable cancer: a systematic review,* Support Care Cancer *14:999-1011, 2006.)*

BOX 65-4 *Cancer Presentations With a Median Survival of 6 Months or Less*

Solid Cancers in General

Any locally advanced or metastatic solid cancer with one or more of the following presentations:

- Patient spends more than one half of the day in bed
- Serum calcium >11.2 mg/dL
- Episode of extremity venous thromboembolism or pulmonary embolism
- Two or more brain metastases plus intracranial metastases
- Spinal cord compression with decreased ability to walk
- Malignant pericardial effusion

Carcinoma of Unknown Primary Origin

Any metastatic adenocarcinoma or undifferentiated carcinoma of unknown primary origin with one or more of the following presentations:

- Patient is ambulatory and can care for him or herself but cannot work
- Hepatic, bone, or adrenal metastases
- Recurrence of disease after chemotherapy
- Serum albumin <3.5 mg/dL or weight loss of ≥10% in 6 months

Modified from Salpeter SR, Malter DS, Luo EJ, et al: Systematic review of cancer presentations with a median survival of six months or less, J Palliat Med *15:175-185, 2012.*

TABLE 65-2 **PRESENTATIONS OF NONCANCER DIAGNOSES WITH A MEDIAN SURVIVAL OF 6 MONTHS OR LESS**

Diagnosis	Presentation
Heart failure	
Hospitalization for moderate-to-severe symptomatic heart failure, NYHA Class III or IV, with three or more of the presentations listed.	• Age >70 years • LVEF ≤20% • Serum BNP >950 pg/mL • Cardiac troponin I >0.4 ng/mL • CRP >3.5 mg/L • Fourth hospitalization for heart failure or repeat hospitalization within 2 months • Dependency for two or more activities of daily living or need for home care after hospital discharge • Weight loss ≥2.3 kg within 2 months, or serum albumin <2.5 g/dL • History of cardiogenic shock, ventricular or supraventricular arrhythmia, cardiac arrest, CPR, or mechanical ventilation • Systolic blood pressure <110 mm Hg • Serum creatinine >2 mg/dL or BUN >40 mg/dL • Serum sodium <135 mEq/L • Peripheral vascular disease or cerebrovascular disease • Other comorbid illness, such as diabetes mellitus, dementia, COPD, cirrhosis, and cancer, among others
Dementia	
Advanced dementia with dependency in all activities of daily living, bedbound status, urinary and bowel incontinence, decreased ability to communicate verbally, and admission to a hospital or skilled nursing facility with one or more of the presentations listed.	• BMI <18.5 kg/m^2, decreased oral intake, or significant weight loss • Presence of at least one pressure ulcer • Evidence of at least one comorbid illness • Male sex plus >90 years of age • Placement of a feeding tube attributable to inability to eat or history of aspiration
Hepatic cirrhosis	
Decompensated hepatic cirrhosis and one or more of the presentations listed.	• MELD score ≥21
Decompensated hepatic cirrhosis with hospitalization for an acute illness related to liver disease and one or more of the presentations listed.	• MELD score ≥18 • Hospitalization in an intensive care unit related to severe decompensation of liver disease with hypotension requiring the use of pressors, serum creatinine >1.5 mg/dL, or evidence of jaundice • Evidence of hepatopulmonary syndrome or rapidly progressive hepatorenal syndrome
Chronic obstructive pulmonary disease	
Hospitalization for a severe COPD exacerbation, with Pao_2 ≤55 mm Hg, $Paco_2$ ≥50 mm Hg, and supplemental oxygen dependence, with three or more of the presentations listed.	• Age >70 years • Evidence of right-sided heart failure • Repeat hospitalization for COPD within 2 months • History of intubation and mechanical ventilation • Required considerable assistance and frequent medical care and/or dependence for three or more activities of daily living before hospitalization • Need for home care after hospital discharge • Malnutrition (weight loss of ≥2.3 kg, serum albumin <2.5 g/dL or BMI <18 kg/m^2 • Serum creatinine >2 mg/dL

Modified from Salpeter SR, Luo EJ, Malter DS, Stuart B: Systematic review of noncancer presentations with a median survival of 6 months or less, Am J Med *125:512 e1-6, 2012.*

BMI, Body mass index; *BNP,* brain natriuretic peptide; *BUN*, blood urea nitrogen; *COPD,* chronic obstructive pulmonary disease; *CPR*, cardiopulmonary resuscitation; *CRP,* C-reactive protein; *LVEF,* left ventricular ejection fraction; *MELD,* Model for End-Stage Liver Disease; *NYHA,* New York Heart Association; *$Paco_2$*, partial arterial pressure of carbon dioxide; *Pao_2,* partial arterial pressure of oxygen.

Dementia. The course of dementia is difficult to predict, and a patient's 6-month mortality is higher once the patient develops the common problems of infection and an inability to eat.[126] Probability of death within 6 months increases with advancing age, shortness of breath, immobility, and insufficient oral intake, among other presentations.[127]

Chronic Obstructive Pulmonary Disease. The BODE Index measures **b**ody mass index (BMI), airflow **o**bstruction, **d**yspnea, and **e**xercise capacity and is used to predict the risk of death in COPD,[128] although its use of a 6-minute exercise capacity test makes it impractical for the bedside anesthesiologist. More than 3 days of mechanical ventilation and an inability to extubate the trachea successfully suggest a poor prognosis.[129]

Liver Disease. In decompensated liver disease, the Model for End-Stage Liver Disease (MELD) score (see Chapter 101)

is often used to predict a prognosis.[130] Hepatic encephalopathy and hepatorenal syndrome are also predictors of a poor prognosis.[130,131]

Renal Disease. Patients with stage 5 chronic kidney disease (CKD; patients on dialysis) will live 16% to 33% as long as age- and sex-matched patients who are not on dialysis.[132] For patients on dialysis who are older than 65 years of age, their probability of survival at 10 years is 3.1%.[132] Poor functional and nutritional status, as well as comorbid conditions, suggest a poor prognosis.[132] Withdrawal of dialysis makes up 20% of deaths in patients on dialysis each year, and the average patient lives 8 to 12 days after dialysis withdrawal.[133]

DYING PROCESS

Most physicians have observed people die but may not have witnessed the dying process. Over 500,000 people die in the ICU every year in the United States alone, and more die after an ICU stay.[134] Understanding the dying process is important because family members may ask physicians what the dying process will be like for the patient; anesthesiologists need to be able to recognize the signs that a patient is imminently dying. The individual variation in the timing with which a patient develops many symptoms is substantial, with 84% of patients being drowsy or comatose 24 hours before death, and acrocyanosis and the loss of a radial pulse occurring a median of 1 hour before death[135] (Table 65-3).

SYMPTOM MANAGEMENT

Alternative Routes of Drug Delivery

Many patients near the end of life may be unable to swallow oral medications as a result of oral lesions, nausea, the dying process, or other reasons. Many patients in palliative and hospice care have difficult intravenous access as a result of frequent medical care, dehydration, or other issues. To avoid multiple attempts at intravenous cannulation, many palliative medicine practitioners and most hospices use subcutaneous infusions for the delivery of medications, especially opioids.[136,137] An assumption of safety is based, in part, on studies showing that many intramuscular injections are actually administered into the subcutaneous tissue,[138] although often off-label use. The subcutaneous administration of opioids is safe, although the optimal conversion ratio from one route to another is a subject of debate.[139] Opioids can be subcutaneously given as boluses or continuous infusions. Notably, methadone can cause skin irritation when administered via this route.[140] Other studies support the transmucosal, sublingual, and rectal administration of opioids,[139] with emerging literature supporting transnasal application. This method of delivery has been used for other medications, including ketorolac, as well as ketamine and lidocaine infusions.[141,142] Of note, other types of drugs such as benzodiazepines, some antiemetic medications, antibiotics, neuroleptics, and even fluids are subcutaneously administered in the palliative care setting.[136,137,143]

Pain

Management of pain in patients who are seriously ill can be quite different from other patients with pain. Some of these patients have pain that is best managed by a pain expert (also see Chapter 64), and some patients will need adjuvant medications (Table 65-4). Major differences in the care of patients with life-limiting diseases are discussed in this text.

Of those patients with cancer, 15% to 90% with solid tumors have pain, depending on the type and stage of cancer, as well as the age, race, and sex of the patient.[144] Most cancer pain is due to the cancer itself, whereas approximately one fifth of patients develop pain related to the cancer treatment.[145] The majority of cancer pain can be managed with the WHO "Cancer Pain Stepladder."[146] Zech published a prospective study of 2118 patients with cancer in 1995 during which 76% of the patients received pain relief[146] with minimal side effects with this approach. Psychological issues may also contribute to pain in this population.[147] Palliative chemotherapy is a treatment that is not expected to cure the patient, but it may improve symptoms, especially pain related to tumor burden; sometimes palliative chemotherapy may prolong life and may be a useful option for pain control in carefully selected patients.

Bone Pain

Breast, lung, kidney, and prostate cancers frequently metastasize to the bones.[148] These metastases may have osteolytic or osteoblastic components, and many patients have both osteoblastic and osteolytic bony lesions.[149] Multiple targets for bone pain are possible, but no clear consensus has been reached on the best treatment methods.[150] Sometimes the pain is extremely intense. Hormonal therapy is effective in breast, prostate, and endometrial cancers. Interventional techniques such as intrathecal catheters may be appropriate in some patients[151] (also see Chapter 64). Palliative radiotherapy can be helpful for patients with bone metastases, although pain relief may take several weeks.[152] According to guidelines from the American Society for Radiation Oncology, pain relief from single-fraction radiotherapy for bone metastases is as effective as multifraction radiation and has the benefit of decreased visits for the patient. However, the retreatment rate is 20% for single-fraction radiation versus 8% for multifraction dosing.[153] Dexamethasone orally, subcutaneously, or intravenously is commonly recommended for bone pain by expert consensus, although only a few, small studies support its use.[154] Bone-modifying agents, such as zoledronic acid or pamidronate have shown benefit for bony pain in some cancers and should be initiated when pain begins or when appropriate from an oncology standpoint.[148,155] Nonsteroidal antiinflammatory drugs (NSAIDs) are helpful in alleviating cancer pain, although their advantage when combined with opioids is less clear.[156] More advanced interventions such as vertebroplasty or surgery may be indicated in some bony metastases.

TABLE 65-3 **CHANGES DURING THE DYING PROCESS**

Changes	Exhibited Signs
Fatigue, weakness	Decreasing function
	Decreasing attention to hygiene
	Inability to move around the bed
	Inability to lift head off the pillow
Cutaneous ischemia	Erythema over bony prominences
	Skin breakdown
	Wounds
Pain	Facial grimacing
	Tension in forehead and between eyebrows
Decreasing food intake, wasting	Anorexia
	Poor intake
	Aspiration, asphyxiation
	Weight loss, muscle and fat loss notable in temples
Loss of ability to close eyes	Eyelids not closed
	Whites of eyes show (with or without pupils visible)
Decreasing fluid intake, dehydration	Poor intake
	Aspiration
	Peripheral edema attributable to hypoalbuminemia
	Dehydration, dry mucous membranes or conjunctivae
Cardiac dysfunction, renal failure	Tachycardia
	Hypertension followed by hypotension
	Peripheral cooling
	Peripheral and central cyanosis (bluing of extremities)
	Mottling of the skin (livedo reticularis)
	Venous pooling along dependent skin surfaces
	Dark urine
	Oliguria, anuria
Neurologic dysfunction, including:	
Decreased level of consciousness	Increased drowsiness
	Difficulty awakening
	Nonresponsive to verbal or tactile stimuli
Decreased ability to communicate	Difficulty finding words
	Monosyllabic words, short sentences
	Delayed or inappropriate responses
	Not verbally responsive
Respiratory dysfunction	Change in ventilatory rate—increasing first, then slowing
	Decreasing tidal volume
	Abnormal breathing patterns—apnea, Cheyne-Stokes respirations, agonal breaths
	Loss of ability to swallow
	Dysphagia
	Coughing, choking
	Loss of gag reflex
	Buildup of oral and tracheal secretions
	Gurgling
Loss of sphincter control	Incontinence of urine or bowels
	Maceration of skin
	Perineal candidiasis
	Terminal delirium
	Early signs of cognitive failure, (e.g., day-night reversal)
	Agitation, restlessness
	Purposeless, repetitious movements
	Moaning, groaning
Rare, unexpected events	Bursts of energy just before death occurs, the "golden glow"
	Aspiration, asphyxiation

From Ferris FD: Last hours of living, Clin Geriatr Med *20:641-667, vi, 2004.*

TABLE 65-4 **ADJUVANT ANALGESICS IN THE MANAGEMENT OF CANCER PAIN**

	Examples	Comment
Multipurpose analgesics		
Glucocorticoids	Dexamethasone, prednisone	Are used for bone pain, neuropathic pain, lymphedema pain, headache, and bowel obstruction.
Antidepressants		
TCAs	Desipramine, amitriptyline	Are used for opioid-refractory neuropathic pain; often used with comorbid depression; secondary amine compounds (e.g., desipramine) have fewer side effects and might be preferred.
SNRIs	Duloxetine, milnacipran	Good evidence exists for their use in some conditions but are overall less effective than TCAs; better side-effect profile than TCAs and are often tried first.
SSRIs	Paroxetine, citalopram	Evidence for their use is scarce; if pain is the target, then other subclasses are preferred.
Other	Bupropion	Little evidence exists for its effectiveness but less sedating than other antidepressants; is often tried early when fatigue or somnolence is a problem.
α_2-Adrenergic agonists	Tizanidine, clonidine	Are seldom used systemically because of side effects, but tizanidine is preferred for a trial; clonidine is used in neuraxial analgesia.
Cannabinoid	THC/cannabidiol, nabilone, THC	Good evidence exists for THC/cannabidiol when used in cancer pain; evidence is scarce for other commercially available compounds.
Topical agents		
Anesthetic	Lidocaine patch, local anesthetic creams	Sometimes used in localized pain.
Capsaicin	8% patch; 0.25%-0.75% creams	High concentration patch is indicated for postherpetic neuralgia.
NSAIDs	Diclofenac and others	Evidence exists for their use in focal musculoskeletal pains.
TCA	Doxepin cream	Is used in treating itching; can be tried for pain.
Others		Compounding creams with various drugs have been empirically tried, but no evidence exists for effectiveness.
Used for neuropathic pain		
Multipurpose drugs	As above	As above
Anticonvulsants		
Gabapentinoids	Gabapentin, pregabalin	Are used first for opioid-refractory neuropathic pain unless comorbid depression; may have multipurpose uses in view of the evidence in postsurgical pain; both drugs act as N-type calcium channel blockers in the CNS, but individuals vary in response to one or the other.
Others	Oxcarbazepine, lamotrigine, topiramate, lacosamide, valproate, carbamazepine, phenytoin	Evidence is scarce for all drugs listed; newer drugs are preferred because of reduced side-effect liability, but individual variation is great; all drugs are considered for opioid-refractory neuropathic pain if antidepressants and gabapentinoids are ineffective.
Sodium-channel drugs		
Sodium-channel blockers	Mexiletine, intravenous lidocaine	Good evidence exists for intravenous lidocaine.
Sodium-channel modulator	Lacosamide	New anticonvulsant with very scarce evidence of analgesic effects.
GABA agonists		
$GABA_A$ agonist	Clonazepam	Evidence is scarce but used for neuropathic pain with anxiety.
$GABA_B$ agonist	Baclofen	Evidence for the treatment of trigeminal neuralgia is the basis for trials in other types of neuropathic pain.
N-methyl-D-aspartate inhibitors	Ketamine, memantine, and others	Evidence is scarce for ketamine, but experience is positive with intravenous use in advanced illness or pain crisis; little evidence exists for oral drugs.
Used for bone pain		
Bisphosphonates	Pamidronate, ibandronate, clodronate	Good evidence exists for its use; similar to NSAIDs or glucocorticoids, usually considered first-line treatment; also reduces other adverse skeletal-related events; concern about osteonecrosis of the jaw and renal insuffciency might restrict its use.
Calcitonin		Evidence is scarce but is usually well tolerated.
Radiopharmaceuticals	Strontium-89, samarium-153	Evidence is good, but its use is restricted because of bone-marrow effects and the need for expertise.
Used for bowel obstruction		
Anticholinergic drugs	Hyoscine compounds, glycopyrronium	Along with a glucocorticoid, are considered first-line adjuvant treatments for nonsurgical bowel obstruction.
Somatostatin analog	Octreotide	Along with a glucocorticoid, is considered a first-line adjuvant treatment for nonsurgical bowel obstruction.

Modified from Portenoy RK: Treatment of cancer pain, Lancet *377:2236-2247, 2011.*

CNS, Central nervous system; *GABA,* gamma-aminobutyric acid; *NSAID,* nonsteroidal antiinflammatory drug; *SNRIs,* selective noradrenaline reuptake inhibitors; *SSRIs,* selective serotonin reuptake inhibitors; *TCAs,* tricyclic antidepressants; *THC,* tetrahydrocannabinol.

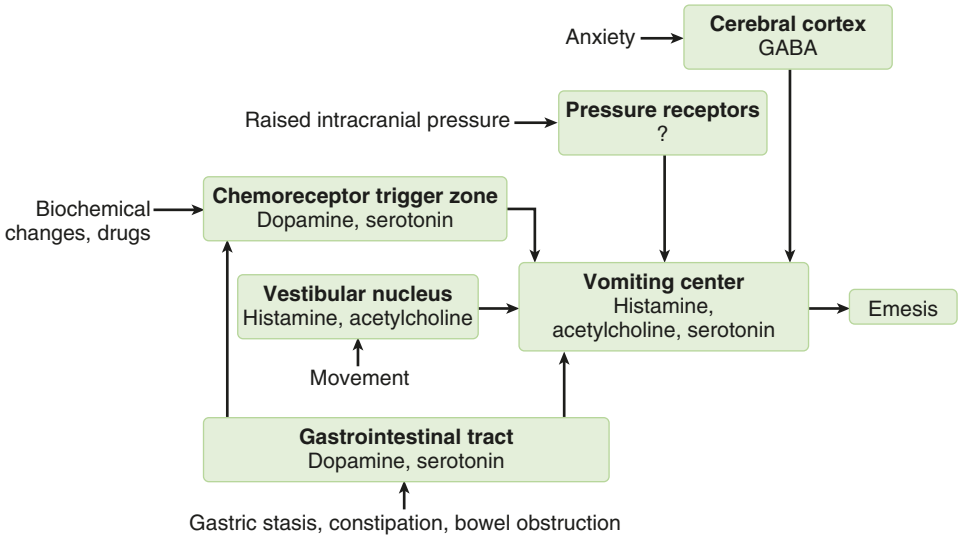


Figure 65-9. Causes of nausea and vomiting. *GABA,* Gamma-aminobutyric acid. *(From Gupta M, Davis M, LeGrand S, et al: Nausea and vomiting in advanced cancer: the Cleveland Clinic protocol,* J Support Oncol *11:8-13, 2013.)*

Neuropathic Pain

Between 17% and 28% of patients with advanced cancer have neuropathic pain.[157] More information on neuropathic pain, the use of lidocaine and ketamine, and other adjuvant medications is available in Chapters 32 and 64. As always, a patient's life expectancy should be considered; some medications may be difficult to titrate in a short period. More information on neurolytic techniques is available in Chapter 64.

Pain in the Intensive Care Unit

In the ICU, pain is also common and attributable to many factors such as surgical or traumatic wounds, placement of invasive monitoring devices, and immobility.[158] In addition, pain can be difficult to assess because the trachea is intubated or otherwise the patient is unable to speak. The Behavioral Pain Scale[159] and the Critical Care Pain Observation Tool[160] are validated methods of assessing pain in the ICU population.[161] Commonalities among the tools include assessment of facial expression, body movement, and compliance with ventilation. In the SUPPORT trial, pain was also poorly controlled among those who died in the hospital, with one half of the surrogates indicating that their family member had moderate-to-severe pain for at least one half of the time in the 3 days before death.[14] However, a more recent study has demonstrated improvement in pain assessment and treatment in the ICU[162] (also see Chapter 101).

OPIOID USE

Opioid use at the end of life is common, although consumption dramatically varies throughout the world.[19] In a 2012 study of 1068 patients at six U.S. medical centers, 70% of patients received an opioid in the last week of life, and 47% received opioids in the last 24 hours.[163] Some physicians are hesitant to use opioids at the end of life for fear of hastening a patient's death. A study by Morita in 2001 retrospectively analyzed opioid and sedative consumption of 209 patients in the 48 hours before death and found no difference in survival based on opiate or sedative dose.[164] A small study on the rate of increase of opioids found no correlation with time to death, although total morphine doses were relatively low.[165] A larger study by Portenoy in 2006 showed a weak association with absolute narcotic dose and time to death, but this association appeared to account for less than 10% of the variance even when combined with other variables.[166] Narcotics should be titrated based on the clinician's assessment of the pain. Most experts believe that appropriately administered opiates do not hasten death, can be safely used, and generally do not require invoking the doctrine of double effect[167] (also see Chapter 10). Some authors have urged caution with the use of opioids in patients with cancer and uncertain prognoses to decrease the risk of narcotic dependence and abuse in patients with the possibility of a long life after treatment.[168]

NAUSEA AND VOMITING

Nausea and vomiting are common complaints in the palliative care and hospice populations and cause significant distress for patients and families.[169] Many techniques and medications used in the treatment of nausea and vomiting in the patient who is seriously ill are similar to those used in the patient after surgery. As with every patient, the first step in treating nausea and vomiting is a thorough evaluation of possible causes (Fig. 65-9). This section highlights issues specific to patients with life-limiting diseases (also see Chapter 97).

Nausea and Vomiting Related to Chemotherapy and Radiation Therapy

Many patients undergoing chemotherapy experience anticipatory nausea and vomiting, and the 2011 American Society of Clinical Oncology Practice Guidelines for chemotherapy and radiation therapy include the prescription of a 5-hydroxytryptamine-3 antagonist, such as ondansetron, often with dexamethasone, and the

addition of a neurokinin-1 antagonist, such as aprepitant, for the most emetogenic chemotherapy regimens.[170] For nonchemotherapy-related or radiation therapy–related nausea and vomiting, no Level 1a or 1b evidence is currently available to guide decisions on the choice of an antiemetic agent in the palliative care population.

BOWEL OBSTRUCTION

Some patients with abdominal tumors may develop partial or complete bowel obstruction. First-line therapy consists of medical management, often with steroids and octreotide.[171] Surgical outcomes for patients with bowel obstruction and a life expectancy of less than 2 months are poor,[172] and gastrointestinal stents should be considered. Placement of a nasogastric tube should be considered for immediate relief while other options are sought. A venting gastrostomy tube is an option in patients who are refractory to treatment and can allow the patients to enjoy the taste of food while allowing the stomach contents to be drained.

ARTIFICIAL HYDRATION AND NUTRITION

Many patients receiving palliative care are unable to take in food or fluids because of nausea, dysphagia, or obstruction. The decision of whether to administer artificial hydration and nutrition is often a difficult one for patients and physicians. Both parties may hold strong cultural or religious views, and many describe a fear of "starving" the patient.[173] Symptoms of hunger are less common in advanced disease, and thirst can be treated with ice chips or mouth swabs.[174] The administration of artificial hydration and nutrition is associated with risks of fluid overload leading to choking or edema, as well as diarrhea and nausea.[175] Additional risks associated with the gastrostomy tube, such as dislodgement and the increased need for restraints attributable to agitation, are present.[175] The administration of enteral or parenteral nutrition and hydration is considered a medical intervention, and, as such, the risks and benefits should be discussed with patients and families.[173] The benefit of artificial hydration and nutrition has been established for patients in a persistent vegetative state or those with acute stroke or head injury, short-term critical illness, oropharyngeal cancers, and possibly bulbar amyotrophic lateral sclerosis.[176] Additionally, artificial hydration may improve symptoms of delirium in patients with cancer, although it does not influence survival in most advanced cancers.[177] The use of percutaneous feeding tubes in patients with advanced dementia does not prevent pneumonia or improve survival and is not recommended.[178,179] For some patients, a time-limited trial of artificial hydration or nutrition may be appropriate to evaluate for benefit, such as improvement in delirium, while monitoring for side effects, such as dyspnea from pulmonary edema.

DYSPNEA

Dyspnea is "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity,"[180] as differentiated from breathing that appears labored or fast to an observer. Dyspnea in patients receiving palliative care has many causes, including dyspnea of physical and psychological origins.[181] Dyspnea is common in patients with a high risk of death[182,183] and was identified as the most distressing symptom by patients who could self-report in the ICU, regardless of their mechanical ventilation status.[184] Dyspnea increases closer to the time of death, even in patients without known cardiopulmonary disease.[185] Treatment is either aimed at reversing the cause of dyspnea, for example with a thoracentesis for an effusion, or at symptomatic management. Nonpharmacologic therapy such as a fan or pulmonary rehabilitation may be helpful.[186] Studies of low-dose opioids in refractory dyspnea in this population support their safety and efficacy.[187,188] In a randomized, double-blind, crossover study of 48 mostly older patients with COPD who were taking 20 mg of sustained-release morphine daily, a significant improvement in dyspnea was observed with minimal side effects.[189] Studies of the effect of benzodiazepines with and without opioids for dyspnea are small and mixed, with a trend toward possible benefit as a second- or third-line treatment.[190-192] Forced air through a nasal cannula generally gives the same benefit as oxygen unless the patient is hypoxic.[193]

NOISY BREATHING AT THE END OF LIFE

Approximately one half of patients experience noisy breathing, sometimes referred to as the *death rattle*, usually 1 to 2 days before death.[194,195] Terminal secretions are thought be secretions from the airway or oropharynx that cannot be cleared because of the inability to cough or swallow.[195] Despite widespread clinical use of antimuscarinic drugs for terminal secretions, strikingly few studies support this practice. A large study comparing atropine, hyoscine butylbromide, and scopolamine infusions showed improvement in symptoms and no difference among those agents, but this study lacked a placebo arm. A study of a one-time dose of sublingual atropine versus placebo showed no difference.[196] Of note, many of these earlier, small studies have multiple methodologic limitations. Family members differ in their interpretations of the sound, with some but not all finding it unsettling.[197] Many clinicians believe the noisy breathing, itself, is not bothersome to patients because most are generally unconscious, although evidence to support this view is lacking.

DEPRESSION AND ANXIETY IN THE PATIENT RECEIVING PALLIATIVE CARE

Depression and anxiety are common at the end of life, with estimates ranging from 5% to 30% and 7% to 13%, respectively.[198] Many factors contribute to psychological distress, including social, economic, spiritual, and physical stressors associated with serious illness.[199] A screening test for depression consisting of two parts, "Are you depressed?" and "Have you experienced a loss of interest in things or activities you would normally enjoy?" has a sensitivity of 91% and a specificity of 68% and has been validated in the palliative care

TABLE 65-5 DISTINGUISHING CHARACTERISTICS OF GRIEF AND DEPRESSION IN PATIENTS WHO ARE TERMINALLY ILL

Characteristic	Normal Grief	Depression
Nature of response	Adaptive	Maladaptive
Focus of distress	In response to a particular loss; not affecting all aspects of life	Pervasive; affecting all aspects of life
Symptom fluctuations	Symptoms coming in waves, generally improving with time	Constant
Mood	Sadness and dysphoria	Protracted and constant depression or flat affect
Interests and capacity for pleasure	Interests and capacity for pleasure remaining intact; diminishing engagement in activities because of functional decline	Anhedonia with significant diminished interest or pleasure in all activities
Hope	Episodic and focal loss of hope; hopes possibly changing over time; giving positive orientation toward the future	Persistent and pervasive hopelessness
Self-worth	Maintaining self-worth, although with feelings of helplessness	Worthlessness with the belief that one's life has no value
Guilt	Regrets and guilt over specific events	Excessive feelings of guilt
Suicidal ideation	Passive and fleeting desire for a hastened death	Preoccupation with a desire to die

From Widera EW, Block SD: Managing grief and depression at the end of life, Am Fam Physician *86:259-264, 2012.*

population.[200] Referral should be made to a psychiatrist or other experienced provider for patients who screen positive or for patients who have suicidal or homicidal ideations. Depression must be distinguished from delirium and normal grief, which can be a difficult distinction[200,201] (Table 65-5). For the anesthesiologist, recognizing depression and making appropriate referrals is important; depression may affect pain management, quality of life, and treatment decisions. Treatments for depression vary by life expectancy. Selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) may be appropriate for patients with a longer life expectancy; the time to onset of action is 1 to 2 months. For patients with a life expectancy of weeks to a few months, methylphenidate has been well studied in the cancer population. The onset of action is 1 to 3 days and is generally effective and well-tolerated for depression and fatigue.[202,203]

DELIRIUM AT THE END OF LIFE

Delirium is covered in depth in Chapter 80. It affects 28% to 88% of patients who are terminally ill, with incidence increasing closer to the time of death.[204,205] The Confusion Assessment Method has been validated in the palliative care population[206,207] (also see Chapter 80). Some patients may have more than one possible cause of delirium (Box 65-5). Delirium can have a major impact on a patient's ability to make a well-informed decision about treatment options, including surgery, which may have ethical and legal implications. Most patients who recover remember being delirious, and those who do find it very distressing.[208]

As much as one half of delirium near the end of life may be reversible.[205] Knowing which cases of delirium could be reversible can be difficult, although a younger age, less severe impairment, and lack of organ failure appear to correspond to a greater likelihood of reversibility.[209] Patients with true terminal delirium have a very short life expectancy.[204] The pursuit of the workup should be based on the patient's goals of care (Box 65-6). For example, the family of a patient with cancer who develops delirium but previously had an acceptable quality of life may desire a workup for potential causes

BOX 65-5 *Causes of Delirium*

- Metabolic disturbance
  - Hypercalcemia
  - Hyponatremia
  - Hypernatremia
  - Dehydration
  - Glycemic derangements
- Organ failure
  - Renal failure
  - Liver failure
  - Respiratory failure
- Medications
  - Opioids
  - Benzodiazepines
  - Anticholinergic agents
  - Steroids
- Sepsis
  - Pneumonia
  - Urinary tract infection
- Brain pathologic conditions
  - Tumor
  - Metastases
  - Leptomeningeal disease
  - Nonconvulsive status epilepticus
- Hypoxia
- Withdrawal
  - Alcohol
  - Benzodiazepines
- Hematologic conditions
  - Disseminated intravascular coagulation
  - Anemia

From LeGrand SB: Delirium in palliative medicine: a review, J Pain Symptom Manage *44:583-594, 2012.*

including a urinalysis and chest x-ray study, whereas the family of a patient who had previously been nearly comatose and expected to die in hours to days may not want to subject their family member to a bladder catheterization for a urinalysis.

Although delirium is often associated with agitation, hypoactive delirium, during which a patient may have decreased interaction with the environment and exhibit inattention, is likely more common than most clinicians appreciate.[210] Hypoactive delirium is considered disturbing by patients who experience it, but no consensus has been reached on whether or how to treat hypoactive delirium.[211]

BOX 65-6 *Evaluation of Delirium*

- Determining the goals of care
- Reviewing medications
- Considering the possibility of withdrawal
- Identifying any hematologic or metabolic abnormalities or organ failure
  - Complete metabolic panel
  - Complete blood count
- Evaluating oxygen levels
  - Oxygen saturation
- Identifying infections
  - Urine culture
  - Blood cultures
  - Chest x-ray imaging
- Performing specialized testing, if appropriate
  - Electroencephalogram
  - Arterial blood gas
  - Tests for disseminated intravascular coagulation
  - Test for thyroid-stimulating hormone
  - Computed tomography scan or magnetic resonance imaging scan of the brain
  - Lumbar puncture

From LeGrand SB: Delirium in palliative medicine: a review, J Pain Symptom Manage *44:583-594, 2012.*

BLEEDING IN THE PATIENT RECEIVING PALLIATIVE CARE

Bleeding can be caused by a number of pathologic conditions, including coagulation disorders and cancers. In addition to dressings and radiation therapy, fibrinolytic inhibitors such as tranexamic acid, interventional radiologic procedures such as embolization, and surgery have been suggested for patients with compatible goals and life expectancy.[212] Exsanguination in patients receiving palliative care is uncommon but can be upsetting to patients, families, and providers. No randomized trials of best treatments have been conducted. Some practical suggestions include the use of dark towels, suction, using pressure, and staying with the patient. Medications are frequently suggested during exsanguination to provide sedation and amnesia. The use of medications varies, but often benzodiazepines, opioids, and sometimes ketamine are used, with midazolam 5 to 10 mg being the most common[213] (also see Chapter 62).

ANESTHETIC CONCERNS IN THE PATIENT RECEIVING PALLIATIVE CARE

PREOPERATIVE CONSIDERATIONS

A patient's decisional capacity may change during hospitalization or over time and should be assessed before seeking consent from the patient for anesthesia. As noted in Chapter 10, patients awaiting surgery with a standing DNR order should prompt a discussion of the patient's goals and the creation of a plan for intraoperative and postoperative management that meets a patient's goals. In the case of the reversal of a DNR order, a plan for when that order would be reinstituted should be developed.[101] The anesthesiologist should also discuss the patient's preferences with the surgeon and nurse as appropriate.

TABLE 65-6 **ANESTHETIC DRUGS AND HOST DEFENSES**

Drug	Potential Effect on Antitumor Host Defenses
Ketamine	Reduces natural killer (NK) cell activity and the number in animal models.
Thiopental	Reduces NK cell activity and the number in animal models.
Propofol	Reduces NK cell number in animal models.
Volatile agents	Inhibits interferon stimulation of NK cell cytotoxicity in animal models. Reduces NK cell number in humans; is associated with worse outcomes when compared with local anesthesia for melanoma excision.
Nitrous oxide	Associated with acceleration in the development of lung and liver metastases in animal models. No effect on cancer outcomes after surgery for colorectal carcinoma in humans. Inhibits the formation of hematopoietic cells that may be important for tumor cells.
Local anesthetic drugs	Lidocaine inhibits epidermal growth factor (EGF) receptor and tumor cell proliferation *in vitro*; ropivacaine inhibits growth of cancer cells.
Morphine	Inhibits cellular immunity including NK cell activity in animal models Inhibits NK cell activity in humans.
Fentanyl	Inhibits NK cell activity in humans.
Tramadol	Stimulates NK cell activity in animal models. Stimulates NK cell activity in humans.
Cyclooxygenase-2 (COX-2) inhibitors	Display antiangiogenesis and antitumor effects in animal models

From Snyder GL, Greenberg S: Effect of anaesthetic technique and other perioperative factors on cancer recurrence, Br J Anaesth *105:106-115, 2010.*

BOX 65-7 *Perioperative Considerations in the Patient in Palliative Care*

Preoperative Considerations

Review the chart for advance directive or documentation of code status.

If a Do Not Resuscitate (DNR) order or other limits on treatment are listed, then clarify the patient's desires based on the American Society of Anesthesiologists (ASA) guidelines.[101]

- Full attempt at resuscitation is defined.
- Limited attempt at resuscitation is defined with regard to specific procedures.
  - Patient or surrogate decision maker should be informed about which procedures are essential to providing anesthesia (e.g., endotracheal tube) and which are not (e.g., chest compressions).
  - Example: Patient with extensive rib metastases declines chest compressions but desires other medications and procedures as appropriate
- Limited attempt at resuscitation is defined with regard to the patient's goals and values.
  - Patient or surrogate decision maker allows the medical team to decide which procedures are appropriate.
  - Example: Patient wants to have treatments that seem easily reversible (e.g., respiratory depression in the postanesthesia care unit [PACU] after accidental narcotic overdose) but does not want treatment that may to lead to neurologic compromise (e.g., prolonged cardiopulmonary resuscitation [CPR])
- Clearly document any changes in treatment limitation in the chart.
  - Include the people present during the discussion.
  - Document when the original advance directive will be reinstated.
  - Per ASA guidelines, "…when the patient leaves the postanesthesia care unit or when the patient has recovered from the acute effects of anesthesia and surgery."
- Discuss any changes in treatment limitation with the surgeon, nurse, or other appropriate health care providers.
- Ensure that the patient preoperatively receives any scheduled pain medications.
- Consider involving spiritual care to perform appropriate rituals if the risk of death is high.
- Review past medications for agents such as adriamycin and bleomycin.
- Review records for sites of metastases including the lung or brain that may affect the physiologic mechanisms.
- Assess decision-making ability of the patient with brain metastases or suspected cognitive impairment.
- Consider preoperative epidural placement for the appropriate patient.
- Assess baseline functional status and general prognosis.

Intraoperative Considerations

- Take special care in positioning patients with cachexia and those with poor skin integrity.
- Consider postoperative nausea and vomiting (PONV) prophylaxis for at-risk patients.
- Communicate any limitations in treatment to on-coming providers.

Postoperative Considerations

- Consider possibly increased postoperative pain requirements in the context of baseline opioid use.
- Ensure the availability of a rescue antiemetic therapy for at-risk patients.
- Communicate any limitations in treatment to PACU providers.

Data from Ethical Guidelines for the Anesthesia Care of Patients with Do-Not-Resuscitate Orders or Other Directives that Limit Treatment, 2008. Accessed June 20, 2013. <http://www.asahq.org/For-Members/Standards-Guidelines-and-Statements.aspx>

A thorough preoperative evaluation of the patient's disease should also take place with attention to the patient's cognitive status, recent medications (including chemotherapy), presence of metastases, and wounds. Knowledge of the patient's preoperative functional status and prognosis may impact the anesthetic plan, in addition to giving the patient an accurate assessment of risks and benefits. Details on special considerations in specific disease states such as cancer, COPD, and others are included in Chapter 39. Considering the number of patients receiving palliative care who will be given be given pain medication perioperatively, anesthesiologists are advised to follow the guidelines in Chapter 64 regarding perioperative pain management.

INTRAOPERATIVE CONCERNS

Resuscitation status should be communicated to any providers caring for the patient intraoperatively or postoperatively. Consideration should be given to postoperative nausea and vomiting (PONV) prophylaxis (also see Chapter 97), and the care of fragile skin in this population.

ANESTHETIC CHOICE AND CANCER

Recent studies have attempted to clarify the role of anesthesia in cancer progression and recurrence. Studies of the effect of regional anesthesia on those with cancer are mixed but suggest a possible benefit; additional discussion is available in Chapter 56. Studies that examine the choice of specific systemic anesthetics on cancer are mostly in vivo or in vitro but also suggest differences in responses to tumor cells among the different drugs[214] (Table 65-6).

POSTOPERATIVE COURSE

Standard postoperative care is sufficient for most patients in palliative care. Risks for postoperative pain, delirium, and nausea and vomiting may be increased, depending on the individual patient. Some patients may need increased dosages of pain medication, depending on baseline use. Providers should communicate any limitations in care and when limitations revert to their preoperative status (Box 65-7).

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Chapter 66

Anesthesia for Thoracic Surgery

PETER D. SLINGER • JAVIER H. CAMPOS

Key Points

- Patients undergoing pulmonary resection should have a preoperative assessment (see Chapter 38) of their respiratory function in three areas: lung mechanical function, pulmonary parenchymal function, and cardiopulmonary reserve (the "three-legged stool" of respiratory assessment).
- Patients with underlying lung disease have a decreased risk of respiratory complications when pulmonary resections are performed with video-assisted thoracoscopic surgery (VATS).
- After lung resection surgery and proper weaning, the trachea can usually be extubated in patients who had adequate predicted postoperative respiratory function in the operating room. In addition, they must be "AWaC" (alert, warm, and comfortable).
- Interventions that decrease the incidence of respiratory complications in high-risk patients undergoing thoracic surgery include cessation of smoking, physiotherapy, and thoracic epidural analgesia.
- Geriatric patients (see Chapter 80) are at high risk for cardiac complications, particularly cardiac arrhythmias (see Chapter 47), after large pulmonary resections. Preoperative exercise capacity is the best predictor of post thoracotomy outcome in the elderly.
- The ability to perform fiberoptic bronchoscopy and a detailed knowledge of bronchial anatomy are required for providing reliable lung isolation.
- The use of double-lumen endobronchial tubes (DLTs) is the standard method for providing lung isolation in adults. Bronchial blockers are a reasonable alternative for lung isolation in patients with abnormal upper or lower airways.
- With the use of intravenous anesthetic techniques or volatile anesthetics at less than or equal to 1-MAC doses, hypoxemia usually does not occur during one-lung ventilation (OLV). The use of continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP) as treatment for hypoxemia during OLV should be guided by the individual patient's lung mechanics.
- The use of large tidal volumes during OLV (e.g., 10 mL/kg) can contribute to acute lung injury, particularly in patients at increased respiratory risk, such as after pneumonectomy.
- The underlying principle of management of a patient with a bronchopleural fistula is to secure lung isolation before positive pressure ventilation or to reposition the patient for surgery.
- Anesthetic management of a patient with an anterior or superior mediastinal mass should be guided by the patient's symptoms, the preoperative computed tomography (CT) scan, and the echocardiography findings. The fundamental principle of anesthetic management for these patients is *noli ponti ignii consumere* ("don't burn your bridges").
- Continuous paravertebral local anesthetic blockade combined with multimodal analgesia is a reasonable alternative to epidural analgesia for thoracic surgery, with fewer side effects.

Thoracic anesthesia encompasses a wide variety of diagnostic and therapeutic procedures involving the lungs, airways, and other intrathoracic structures. As the patient population presenting for noncardiac thoracic surgery has evolved, so have the anesthetic techniques to manage these patients. At the beginning of the last century, thoracic surgery was primarily done to treat infectious indications (e.g., lung abscess, bronchiectasis, empyema). Although these cases still present for surgery in the post-antibiotic era, now the most common indications are related to malignancies (i.e., pulmonary, esophageal, and mediastinal). In addition, the past 2 decades have seen the beginning of surgical therapy for end-stage lung diseases with procedures such as lung transplantation and lung volume reduction. Fundamental to anesthetic management for the majority of thoracic procedures are two techniques: (1) lung isolation to facilitate surgical access within the thorax and (2) management of one-lung anesthesia. In this chapter, we initially discuss preanesthetic assessment for thoracic surgery, outline intraoperative management principles common to most thoracic surgical procedures, discuss specific anesthetic considerations in common and less common surgical operations, and we finally finish with a description of postoperative management issues in thoracic surgical patients.

PREOPERATIVE EVALUATION OF THE THORACIC SURGERY PATIENT
(See Chapter 38)

Preoperative anesthetic assessment before chest surgery is a continually evolving science and art. Recent advances in anesthetic management, surgical techniques, and perioperative care have expanded the realm of patients now considered to be "operable."[1] This discussion focuses primarily on preanesthetic assessment for pulmonary resection surgery in cancer patients. However, the basic principles described apply to all other types of nonmalignant pulmonary resections and to other chest surgeries.

Although 87% of patients with lung cancer will die of their disease, the 13% cure rate represents approximately 26,000 survivors per year in North America. Surgical resection is responsible for essentially all of these cures. A patient with "resectable" lung cancer has a disease that is still local or locoregional in scope and can be encompassed in a plausible surgical procedure. An operable patient is someone who can tolerate the proposed resection with acceptable risk.

The patient is commonly assessed initially as an outpatient, often not by anesthesia personnel. Yet it is necessary to organize and standardize the approach to preoperative evaluation for these patients into two temporally disjointed phases: the initial (clinic) assessment and the final (day of admission) assessment. Elements vital to each assessment are described.

Increasingly, thoracic surgeons are performing lung-sparing resections such as sleeve-lobectomies or segmentectomies, and resections with minimally invasive techniques such as video-assisted thoracoscopic surgery (VATS) or robotic surgery. The postoperative preservation of respiratory function is proportional to the amount of functioning lung parenchyma preserved. To assess patients with limited pulmonary function, these newer surgical options need to be understood in addition to the conventional open lobectomy or pneumonectomy.

Preoperative assessment should identify patients at increased risk and that risk assessment should stratify the perioperative management and focus resources on the high-risk patients to improve their outcome. This is the primary function of the preanesthetic assessment. There are occasions when the anesthesiologist should contribute his or her opinion about whether a specific high-risk patient will tolerate a specific surgical procedure. This may occur preoperatively but also occurs intraoperatively when the surgical findings suggest that a planned procedure, such as a lobectomy, may require a larger resection, such as a pneumonectomy. For these reasons, it is necessary that the anesthesiologist have a complete preoperative knowledge of the patient's medical status and the pathophysiology of lung resection surgery, which are needed for a proper anesthetic to be given. Prethoracotomy assessment naturally involves all of the factors of a complete anesthetic assessment: past history, allergies, medications, upper airway, and so on. This section concentrates on the additional information, beyond a standard anesthetic assessment, that the anesthesiologist needs to manage a patient undergoing a pulmonary resection.

PERIOPERATIVE COMPLICATIONS

The major cause of perioperative morbidity and mortality in the thoracic surgical population is respiratory complications. Major respiratory complications—atelectasis, pneumonia, and respiratory failure—occur in 15% to 20% of patients and account for the majority of the expected 3% to 4% mortality rate.[2] For other types of surgery, cardiac and vascular complications are the leading cause of early perioperative morbidity and mortality. Cardiac complications such as arrhythmia and ischemia occur in 10% to 15% of the thoracic population.

ASSESSMENT OF RESPIRATORY FUNCTION
(See Chapter 19)

The best assessment of respiratory function comes from a detailed history of the patient's quality of life. All patients undergoing a pulmonary resection should have baseline simple spirometry done preoperatively.[3] Objective measures of pulmonary function are required to guide anesthetic management and to have this information in a format that can be easily transmitted between members of the health care team. Respiratory function can be divided into three related but somewhat independent areas: respiratory mechanics, gas exchange, and cardiorespiratory interaction. The basic functional units of extracellular respiration are to move the oxygen: (1) into the alveoli, (2) into the blood, and (3) into the tissues (the process is reversed for carbon dioxide removal).

Respiratory Mechanics

Many tests of respiratory mechanics and volumes show correlation with postthoracotomy outcome: forced

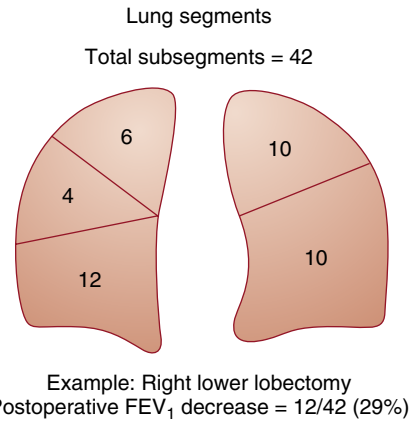


Figure 66-1. The number of subsegments of each lobe is used to calculate the predicted postoperative (ppo) pulmonary function (e.g., after a right lower lobectomy, a patient with a preoperative FEV_1 [or D_Lco] 70% of normal would be expected to have a $ppoFEV_1$ of 70% × (1 – 29/100) = 50%. *(Reproduced with permission from Slinger P:* Principles and practice of anesthesia for thoracic surgery. *New York, Springer, 2011.)*

expiratory volume in one second (FEV_1), forced vital capacity (FVC), maximal voluntary ventilation (MVV), residual volume/total lung capacity ratio (RV/TLC), and so on (see Chapter 19 on pulmonary function testing). It is useful to express these as a percent of predicted volumes corrected for age, sex, and height (e.g., FEV_1 %). Of these, the most valid single test for postthoracotomy respiratory complications is the predicted postoperative FEV_1 ($ppoFEV_1$ %),[4] which is calculated as:

$$ppoFEV_1\,\% = \text{preoperative } FEV_1\,\% \times (1 - \%\ \text{functional lung tissue removed}/100)$$

One method of estimating the percent of functional lung tissue is based on a calculation of the number of functioning subsegments of the lung removed (Fig. 66-1). Patients with a $ppoFEV_1$ greater than 40% are at low risk for postresection respiratory complications. The risk of major respiratory complications is increased in the subgroup with a $ppoFEV_1$ less than 40% (although not all patients in this subgroup develop respiratory complications), and patients with a $ppoFEV_1$ less than 30% are at high risk.

Lung Parenchymal Function

As important to the process of respiration as the mechanical delivery of air to the distal airways is the subsequent ability of the lung to exchange oxygen and carbon dioxide between the pulmonary vascular bed and the alveoli. Traditionally, arterial blood gas data such as partial pressure of oxygen in the blood (PaO_2) less than 60 mm Hg or partial pressure of carbon dioxide in the blood ($Paco_2$) greater than 45 mm Hg have been used as cutoff values for pulmonary resection. Cancer resections have now been successfully performed singly or even combined with volume reduction in patients who do not meet these criteria, although they remain useful as warning indicators of increased risk. The most useful test of the gas exchange capacity of the lung is the diffusing capacity for carbon monoxide (D_Lco). The D_Lco correlates with the total functioning surface area of alveolar-capillary interface. The corrected D_Lco can be used to calculate a postresection (ppo) value using the same calculation as for the FEV_1 (see Fig. 66-1). A $ppoD_Lco$ less than 40% predicted correlates with both increased respiratory and cardiac complications and is usually independent of the FEV_1.[5] The D_Lco, but not the FEV_1, is negatively affected by preoperative chemotherapy and may be the most important predictor of complications in this subgroup of patients. Some authors feel a higher cutoff risk-threshold for $ppoD_Lco$ of less than 50% may be more appropriate.[6] The National Emphysema Treatment Trial has shown that patients with a preoperative FEV_1 or D_Lco less than 20% had an unacceptably frequent perioperative mortality rate.[7] These can be considered as the absolute minimal values compatible with a successful outcome.

Cardiopulmonary Interaction

The final and perhaps most important assessment of respiratory function is an assessment of the cardiopulmonary interaction. Formal laboratory exercise testing is currently the gold standard for assessment of cardiopulmonary function,[8] and the maximal oxygen consumption (VO_{2max}) is the most useful predictor of postthoracotomy outcome. The risk of morbidity and mortality is increased if the preoperative VO_{2max} is less than 15 mL/kg/min and is considered very high if it is less than 10 mL/kg/min.[9] Few patients with a VO_{2max} greater than 20 mL/kg/min have respiratory complications (for comparison, the highest VO_{2max} recorded is 85 mL/kg/min by the American cyclist Lance Armstrong in 2005[10]). Complete laboratory exercise testing is expensive. Several alternatives have been demonstrated to be valid surrogate tests for prethoracotomy assessment.

The distance that a patient with chronic obstructive pulmonary disease (COPD) can walk during a 6-minute test shows an excellent correlation with VO_{2max} and requires little or no laboratory equipment.[11] VO_{2max} can be estimated from the 6-minute walk test distance in meters divided by 30 (i.e., 6-minute walk text of 450 m: estimated VO_{2max} = 450/30 = 15 mL/kg/min). Patients with a decrease of oxygen saturation (SpO_2) greater than 4% during exercise[12] are also at increased risk. The traditional exercise test in ambulatory patients is stair climbing. The ability to climb five flights of stairs correlates with a VO_{2max} more than 20 mL/kg/min, and climbing two flights corresponds to a VO_{2max} of 12 mL/kg/min.

After pulmonary resection, right ventricular dysfunction appears to be in proportion to the amount of functioning pulmonary vascular bed that has been removed. The exact etiology and duration of this dysfunction remains unknown. Clinical evidence of this hemodynamic problem is minimal when the patient is at rest but is dramatic when the patient exercises, leading to elevation of pulmonary vascular pressures, limitation of cardiac output, and absence of the normal decrease in pulmonary vascular resistance usually seen with exertion.[13]

Ventilation-Perfusion Scintigraphy

Prediction of postresection pulmonary function can be further refined by assessment of the preoperative contribution of the lung or lobe to be resected using ventilation-perfusion ($\dot{V}/\dot{Q}$) lung scanning. If the lung region to be

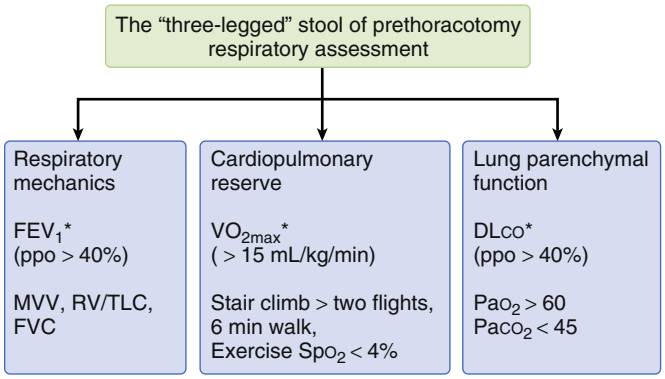


Figure 66-2. The "3-legged" stool of prethoracotomy respiratory assessment. *Most valid test (see text). *(Reproduced with permission from Slinger P:* Principles and practice of anesthesia for thoracic surgery, *New York, Springer, 2011.)*

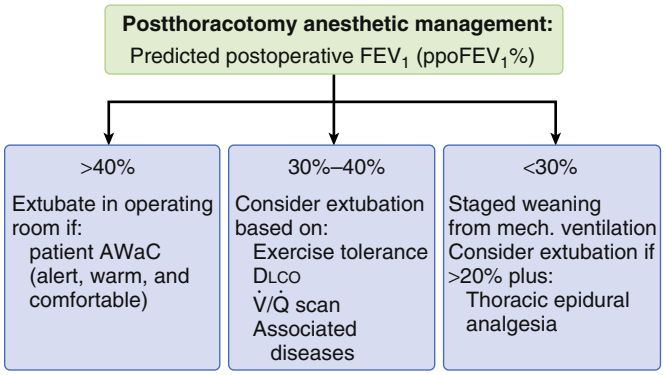


Figure 66-3. Anesthetic management guided by preoperative assessment and the amount of functioning lung tissue removed during surgery. *(Reproduced with permission from Slinger P:* Principles and practice of anesthesia for thoracic surgery, *New York, Springer, 2011.)*

resected is nonfunctioning or minimally functioning, the prediction of postoperative function can be modified accordingly. This is particularly useful in pneumonectomy patients[14] and $\dot{V}/\dot{Q}$ scanning should be considered for any pneumonectomy patient who has a preoperative FEV_1 and/or D_Lco less than 80%. However, $\dot{V}/\dot{Q}$ scanning is of limited usefulness to predict postlobectomy function.

Combination of Tests

No single test of respiratory function has shown adequate validity as a sole preoperative assessment. Before surgery, an estimate of respiratory function in all three areas—lung mechanics, parenchymal function, and cardiopulmonary interaction—should be made for each patient. These three aspects of pulmonary function form the "three-legged stool" that is the foundation of prethoracotomy respiratory assessment (Fig. 66-2) that can be used to plan intraoperative and postoperative management (Fig. 66-3). These plans and intraoperative surgical factors sometimes necessitate that a resection becomes more extensive than was foreseen. If a patient has a $ppoFEV_1$ greater than 40%, the trachea usually can be extubated in the operating room at the conclusion of surgery assuming the patient is alert, warm, and comfortable ("AWaC"). If the $ppoFEV_1$ is greater than 30% and exercise tolerance and lung parenchymal function exceed the increased-risk thresholds, then tracheal extubation can be done in the operating room depending on the status of associated medical conditions. Patients in this subgroup who do not meet the minimal criteria for cardiopulmonary and parenchymal function should be considered for staged weaning from mechanical ventilation postoperatively (see Chapter 103). Patients with a $ppoFEV_1$ of 20% to 30% and favorable predicted cardiorespiratory and parenchymal function can be considered for early tracheal extubation if thoracic epidural analgesia is used or if the resection is performed with VATS. In the increased-risk group, the presence of several associated factors and diseases should be documented during the preoperative assessment (see Chapter 3) and will enter into the consideration for postoperative management (discussed later).

CONCOMITANT MEDICAL CONDITIONS

CARDIAC DISEASE (See Chapter 39)

Cardiac complications are the second most common cause of perioperative morbidity and mortality in the thoracic surgical population.

Ischemia

Because the majority of pulmonary resection patients have a smoking history, they already have one risk factor for coronary artery disease. Elective pulmonary resection surgery is regarded as an intermediate-risk procedure in terms of perioperative cardiac ischemia.[15] The overall documented incidence of postthoracotomy ischemia is 5% and peaks on days 2 to 3 postoperatively. Beyond the standard history, physical, and electrocardiogram, routine screening testing for cardiac disease does not appear to be cost-effective for all prethoracotomy patients. Noninvasive testing is indicated in patients with major (i.e., unstable ischemia, recent infarction, severe valvular disease, significant arrhythmia) or intermediate (i.e., stable angina, remote infarction, previous congestive failure, diabetes) clinical predictors of myocardial risk. Therapeutic options to be considered in patients with significant coronary artery disease are optimization of medical therapy, coronary angioplasty, or coronary artery bypass, either before or at the time of lung resection. Timing of lung resection surgery after a myocardial infarction is always a difficult decision to make. Limiting the delay to 4 to 6 weeks in a medically stable and fully investigated and optimized patient seems acceptable after myocardial infarction. The appropriate delay after coronary stenting is conventionally 4 to 6 weeks after bare metal stents and 12 months after drug-eluting stents.[16] Surgery should be delayed until it is safe to temporarily discontinue major antiplatelet drugs (except aspirin). A recent study upholds the 6-week delay after bare metal stents but suggests that the risks after drug-eluting stents are minimal after 6 months (Fig. 66-4).[17]

Arrhythmia

Dysrhythmias (see Chapter 47) are a common complication of pulmonary resection surgery, and it occurs is 30% to 50% of patients within the first week postoperatively,

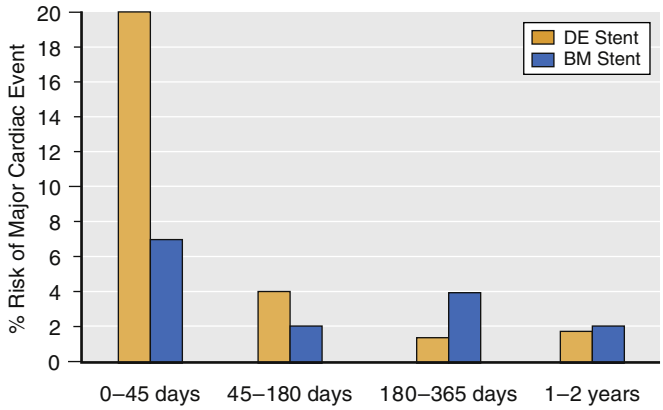


Figure 66-4. Risk of major 30-day postoperative cardiac event after elective noncardiac surgery in more than 2000 patients after coronary artery stents. *DE*, drug eluting; *BM*, bare metal. The risks after stent become minimal after 6 weeks for BM stents and after 6 months for DE stents. *(Based on data from Wijeysundera ND, Wijeysundera HC, Wasowicz M, et al: Risk of elective major non-cardiac surgery after coronary stent insertion,* Anesth Analg *113:s62, 2012).*

when Holter monitoring is used.[18] Of these arrhythmias, 60% to 70% are atrial fibrillation. Several factors correlate with an increased incidence of arrhythmias, including extent of lung resection (pneumonectomy 60% versus lobectomy 40% versus nonresection thoracotomy 30%), intrapericardial dissection, intraoperative blood loss, and age of the patient. Extrapleural pneumonectomy patients are a particularly high-risk group.[19]

Two factors in the early postthoracotomy period interact to produce atrial arrythmias: (1) increased flow resistance through the pulmonary vascular bed because of permanent (lung resection) or transient (atelectasis, hypoxemia) causes, with attendant strain on the right side of the heart; and (2) increased sympathetic stimuli and oxygen requirements, which are maximal on the second postoperative day as patients become more mobile.

In some patients undergoing a pneumonectomy, the right heart may not be able to increase its output adequately to meet the usual postoperative stress. Transthoracic echocardiographic studies have shown that pneumonectomy patients develop an increase in right ventricular systolic pressure as measured by the tricuspid regurgitation jet on postoperative day 2 but not on postoperative day 1. An increase in tricuspid regurgitation jet velocity is associated with postthoracotomy supraventricular tachyarrhythmias.[20] Preoperative exercise testing, which assesses the cardiopulmonary interaction, can predict postthoracotomy arrhythmias. Patients with COPD are more resistant to pharmacologic-induced heart rate control when they develop postthoracotomy atrial fibrillation and often require multiple drugs.[21]

Many antiarrhythmics are used to decrease the incidence of atrial arrhythmias after lung surgery, of which digoxin preparations are the most common. Digoxin does not prevent arrhythmias after pneumonectomy or other intrathoracic procedures. Other antiarrhythmics that have been used to prevent postthoracotomy arrhythmias include β-adrenergic blockers, verapamil, and amiodarone. Although all of these drugs decrease arrhythmias in thoracic patients, their side effects preclude their widespread application in this surgical population. At present, diltiazem is the most useful drug for postthoracotomy arrhythmia prophylaxis.[19] It seems that atrial arrhythmias are a sign of a dysfunctional right heart, for which prevention does not solve the underlying problem.

AGE-RELATED FACTORS (See Chapter 80)

There is no maximum age that is a cutoff for pulmonary resection.[4] The operative mortality in a group of patients 80 to 92 years of age was 3%, a very respectable figure, in one series.[22] However, the rate of respiratory complications (40%) was double that expected in a younger population, and the rate of cardiac complications (40%), particularly arrhythmias, was nearly triple that which would be seen in younger patients. In older patients, thoracotomy should be considered a high-risk procedure for cardiac complications, and cardiopulmonary function is the most important part of the preoperative assessment. An algorithm for the cardiac assessment of the older patient for thoracic surgery is presented in Figure 66-5. Although the mortality resulting from lobectomy among the older patients is acceptable, the mortality from pneumonectomy, particularly right pneumonectomy, is excessive.[23] Quality of life after pneumonectomy is significantly worse than it is after lesser pulmonary resections.[24] For these reasons, lung-sparing pulmonary resections are performed whenever possible. As a proportion of all lung cancer resections, pneumonectomy has decreased to approximately one third of its share of 15 years ago.[25] Exercise tolerance seems to be the primary determinant of outcome in older patients (see Chapter 80). Older patients should have, as a minimum cardiac investigation, a transthoracic echocardiogram to rule out pulmonary hypertension.

RENAL DYSFUNCTION

Renal dysfunction after pulmonary resection surgery was previously associated with a high mortality rate. Gollege and Goldstraw[26] reported a perioperative mortality of 19% (6/31) in patients in whom a significant elevation of serum creatinine developed in the postthoracotomy period, compared with 0% (0/99) in those who did not show any renal dysfunction. More recently, postthoracotomy renal dysfunction, as assessed by significant increases in serum creatinine levels, has been found to be associated with prolonged length of stay but not increased mortality.[27] Predictive factors for renal dysfunction include preoperative hypertension, angiotensin II receptor blockers, use of hydroxyethel starch, and open thoracotomies.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The most common concurrent illness in the thoracic surgical population is COPD, which incorporates three disorders: emphysema, peripheral airways disease, and chronic bronchitis (see Chapter 39). Any individual patient may have one or all of these conditions, but the dominant clinical feature is impairment of expiratory airflow.[28] Assessment of the severity of COPD is made on the basis of the FEV_1% of predicted values. The American Thoracic

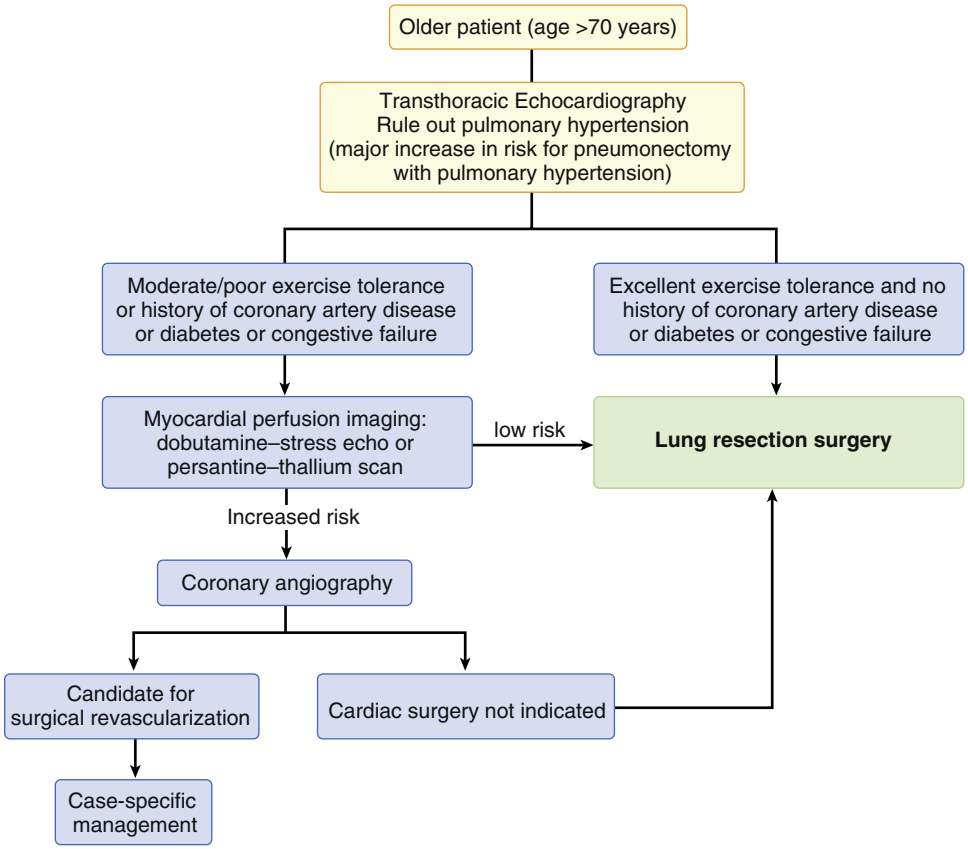


Figure 66-5. Algorithm for the preoperative cardiac assessment of older patients for thoracic (noncardiac) surgery.

Society categorizes stage I as greater than 50% predicted, stage II as 35% to 50%, and stage III as less than 35%. Stage I patients should not have significant dyspnea, hypoxemia, or hypercarbia, and other causes should be considered if these are present.

Respiratory Drive

Many patients with stage II or III COPD have an elevated $Paco_2$ at rest. It is not possible to differentiate these "CO_2 retainers" from nonretainers on the basis of history, physical examination, or spirometric pulmonary function testing.[29] CO_2 retention is related more to an inability to maintain the increased work of respiration required to keep the $Paco_2$ normal in patients with mechanically inefficient pulmonary function and not primarily resulting from an alteration of respiratory control mechanisms. It was previously thought that chronically hypoxemic/hypercapnic patients relied on a hypoxic stimulus for ventilatory drive and became insensitive to $Paco_2$. This explained the clinical observation that COPD patients in incipient respiratory failure could be put into a hypercapnic coma by the administration of a high concentration of oxygen (FiO_2). In actuality, only a minor fraction of the increase in $Paco_2$ in such patients is caused by a diminished respiratory drive, because minute ventilation is basically unchanged.[30] The $Paco_2$ rises because a high FiO_2 causes a relative decrease in alveolar ventilation and an increase in alveolar dead space and shunt by the redistribution of perfusion away from lung areas of relatively normal $\dot{V}/\dot{Q}$ matching to areas of very low $\dot{V}/\dot{Q}$ ratio because regional hypoxic pulmonary vasoconstriction (HPV) is decreased[31] and also as a result of the Haldane effect.[32] However, supplemental oxygen must be administered to these patients postoperatively to prevent hypoxemia associated with the unavoidable fall in functional residual capacity (FRC). The attendant rise in $Paco_2$ should be anticipated and monitored. To identify these patients preoperatively, all stage II and III COPD patients need an arterial blood gas analysis.

Nocturnal Hypoxemia

COPD patients have decreases in blood oxygen saturation more frequently and severely than normal patients during sleep.[33] This is because of the rapid/shallow breathing pattern that occurs in all patients during rapid-eye-movement sleep. In COPD patients breathing air, this causes a significant increase in the respiratory dead space/tidal volume (V_D/V_T) ratio and a fall in alveolar oxygen tension (PAO_2) and PaO_2. This is not the sleep apnea–hypoventilation syndrome (SAHS). There is no increased incidence of SAHS in COPD.

Right Ventricular Dysfunction

Right ventricular (RV) dysfunction occurs in as many as 50% of COPD patients. The dysfunctional right ventricle is poorly tolerant of sudden increases in afterload,[34] such as the change from spontaneous to controlled ventilation.[35] RV function becomes critical in maintaining cardiac output as the pulmonary artery pressure rises. The RV ejection fraction does not increase with exercise in COPD patients as it does in normal patients. Chronic recurrent hypoxemia is the cause of the RV dysfunction and the subsequent progression to cor pulmonale. Patients who have

episodic hypoxemia in spite of normal lungs (e.g., central alveolar hypoventilation, SAHS)[36] develop the same secondary cardiac problems as COPD patients. The only therapy that improves long-term survival and decreases right-sided heart strain in COPD is administration of increasing concentrations of oxygen. COPD patients who have a resting PaO_2 less than 55 mm Hg, as well as those who have decreases to less than 44 mm Hg with exercise, should receive supplemental oxygen at home. The goal of supplemental oxygen is to maintain a PaO_2 of 60 to 65 mm Hg. Compared with patients with chronic bronchitis, emphysematous COPD patients tend to have a decreased cardiac output and mixed venous oxygen tension while maintaining lower pulmonary artery pressures.

Bullae

Many patients with moderate or severe COPD develop cystic air spaces in the lung parenchyma known as *bullae*. These bullae are often asymptomatic unless they occupy more than 50% of the hemithorax, in which case the patient presents with findings of restrictive respiratory disease in addition to their obstructive disease. A bulla is a localized area of loss of structural support tissue in the lung with elastic recoil of surrounding parenchyma (Fig. 66-6). The pressure in a bulla is actually the mean pressure in the surrounding alveoli averaged over the respiratory cycle. This means that during normal spontaneous ventilation, the intrabulla pressure is actually slightly negative in comparison with the surrounding parenchyma.[37] However, whenever positive-pressure ventilation is used, the pressure in a bulla becomes positive in relation to the adjacent lung tissue, and the bulla expands with the attendant risk of rupture, tension pneumothorax, and bronchopleural fistula. Positive-pressure ventilation can be used safely in patients with bullae provided the airway pressures are kept low and there is adequate expertise and equipment immediately available to insert a chest drain and obtain lung isolation if necessary. Management of patients for bullectomy is discussed later.

Flow Limitation

Patients with severe COPD are often "flow-limited" even during tidal volume expiration at rest.[38] Flow limitation is present in normal patients only during a forced expiratory maneuver. Flow limitation occurs when an equal pressure point develops in the intrathoracic airways during expiration. During quiet expiration in the normal patient, the pressure in the lumen of the airways always exceeds the intrapleural pressure because of the upstream elastic recoil pressure that is transmitted from the alveoli. The effect of this elastic recoil pressure diminishes as air flows downstream in the airway. With a forced expiration, the intrapleural pressure may equal the intraluminal pressure at a certain point, the equal pressure point, which then limits the expiratory flow. Then, any increase in expiratory effort will not produce an increase in flow at that given lung volume.[39]

Flow limitation occurs particularly in emphysematous patients who primarily have a problem with loss of lung elastic recoil and have marked dyspnea on exertion. Flow limitation causes dyspnea because of stimulation of mechanoreceptors in the muscles of respiration, the thoracic cage, and the airway distal to the equal pressure point. Any increase in the work of respiration leads to increased dyspnea. This variable mechanical compression of airways by overinflated alveoli is the primary cause of the airflow obstruction in emphysema.

Severely flow-limited patients are at risk for hemodynamic collapse with the application of positive-pressure ventilation because of dynamic hyperinflation of the lungs. Even the modest positive airway pressures associated with manual ventilation with a bag/mask at induction can lead to hypotension because these patients have no increased resistance to inspiration but a marked obstruction of expiration. In some of these patients, this has contributed to the "Lazarus" syndrome, in which patients have recovered from a cardiac arrest only after resuscitation and positive-pressure ventilation were discontinued.[40]

Auto-PEEP

Patients with severe COPD often breathe in a pattern that interrupts expiration before the alveolar pressure has fallen to atmospheric pressure. This incomplete expiration is caused by a combination of factors that include flow limitation, increased work of respiration, and increased airway resistance. This interruption leads to an elevation of the end-expiratory lung volume above

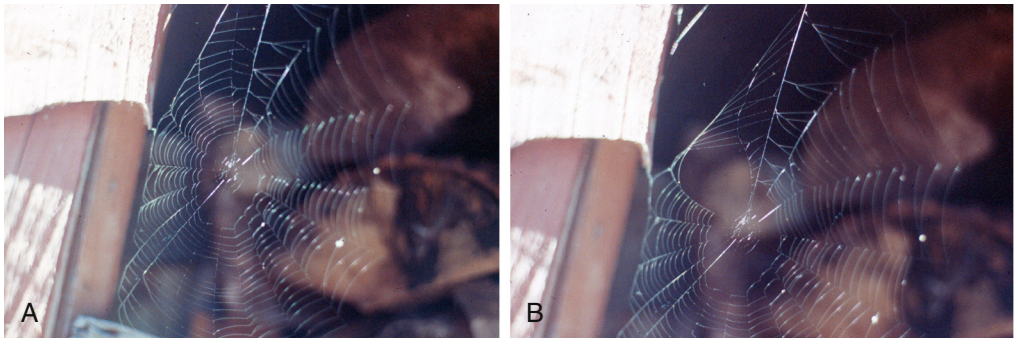


Figure 66-6. A, A spider's web as a lung model to demonstrate the pathophysiology of bullae. **B,** Breaking one septum of the spider's web causes a bulla to appear as elastic recoil pulls the web away from the area where structural support has been lost. Although the cells surrounding the bulla appear compressed, this is only because of redistribution of elastic forces. It is not positive pressure inside the bulla that causes this appearance of surrounding compression. *(Reproduced with permission from Slinger P:* Principles and practice of anesthesia for thoracic surgery, *New York, Springer, 2011.)*

the FRC. This positive end-expiratory pressure (PEEP) in the alveoli at rest has been termed auto-PEEP or intrinsic PEEP. During spontaneous respiration, the intrapleural pressure has to be decreased to a level that counteracts auto-PEEP before inspiratory flow can begin. Thus COPD patients can have an increased inspiratory load added to their already increased expiratory load.

Auto-PEEP becomes even more important during mechanical ventilation. It is directly proportional to tidal volume and inversely proportional to expiratory time. The presence of auto-PEEP is not detected by the manometer of standard anesthesia ventilators. It can be measured by end-expiratory flow interruption, a feature available on most intensive care ventilators. Auto-PEEP has been found to develop in most COPD patients during one-lung anesthesia.[41]

PREOPERATIVE THERAPY OF COPD

There are four treatable complications of COPD that must be actively sought and therapy begun at the time of the initial prethoracotomy assessment: atelectasis, bronchospasm, respiratory tract infections, and pulmonary edema (Table 66-1). Atelectasis impairs local lung lymphocyte and macrophage function, predisposing to infection. Pulmonary edema can be very difficult to diagnose by auscultation in the presence of COPD and may present very abnormal radiologic distributions (e.g., unilateral, upper lobes). Bronchial hyperreactivity may be a symptom of congestive failure or may represent an exacerbation of reversible airways obstruction. All COPD patients should receive maximal bronchodilator therapy as guided by their symptoms. Only 20% to 25% of COPD patients respond to corticosteroids. In a patient who is poorly controlled on sympathomimetic and anticholinergic bronchodilators, a trial of corticosteroids may be beneficial.

PHYSIOTHERAPY

Patients with COPD have fewer postoperative pulmonary complications when a perioperative program of intensive chest physiotherapy is initiated preoperatively.[42] Among the different modalities available (cough and deep breathing, incentive spirometry, PEEP, continuous positive airway pressure [CPAP]), there is no clearly proven superior method. Family members or nonphysiotherapy hospital staff can easily be trained to perform effective preoperative chest physiotherapy, and this should be arranged at the time of the initial preoperative assessment. Even in patients with the most severe COPD, exercise tolerance with a physiotherapy program will improve. Little improvement is seen before 1 month. Among COPD patients, those with excessive sputum benefit the most from chest physiotherapy.

A comprehensive program of pulmonary rehabilitation involving physiotherapy, exercise, nutrition, and education can improve functional capacity for patients with severe COPD.[43] These programs are usually of several months duration and are generally not an option in resections for malignancy, although for nonmalignant resections in severe COPD patients, rehabilitation should be considered. The benefits of short-duration rehabilitation programs before malignancy resection have not been fully assessed.

TABLE 66-1 **CONCURRENT PROBLEMS THAT SHOULD BE TREATED PRIOR TO ANESTHESIA IN COPD PATIENTS**

Problem	Method of Diagnosis
Bronchospasm	Auscultation
Atelectasis	Chest radiograph
Infection	History, sputum analysis
Pulmonary edema	Auscultation, chest radiograph

SMOKING

Pulmonary complications are decreased in thoracic surgical patients who cease smoking for more than 4 weeks before surgery.[44] Carboxyhemoglobin concentrations decrease if smoking is stopped more than 12 hours.[45] It is extremely important for patients to avoid smoking postoperatively. Smoking leads to a prolonged period of tissue hypoxemia. Wound tissue oxygen tension correlates with wound healing and resistance to infection. There is no rebound increase in pulmonary complications if patients stop for shorter (<8 weeks) periods before surgery.[46] Intensive smoking-cessation interventions are the most successful.[47]

PRIMARY THORACIC TUMORS

The majority of patients presenting for major pulmonary surgery will have some type of malignancy. Because the different types of thoracic malignancies have varying implications for both surgery and anesthesia, it is important for the anesthesiologist to have some knowledge of the presentation and biology of these cancers. By far the most common tumor is lung cancer. There are more than 200,000 new cases of lung cancer diagnosed per year in North America and more than 1.2 million diagnosed in the world. Lung cancer is currently the leading cause of cancer deaths in both genders in North America subsequent to the peak incidence of smoking in the period 1940 to 1970.[48] Worldwide, lung cancer incidence is more than double in men than in women (rate ratio 2.5:1.0).[49]

Lung cancer is broadly divided into small-cell lung cancer (SCLC) and non–small-cell lung cancer (NSCLC), with approximately 75% to 80% of these tumors diagnosed as NSCLC. Other less common and less aggressive tumors of the lung include the carcinoid tumors (typical and atypical) and adenoid cystic carcinoma. Compared with lung cancer, primary pleural tumors are rare. They include the localized fibrous tumors of pleura (previously referred to as *benign mesotheliomas*) and malignant pleural mesothelioma. Asbestos exposure is implicated in as many as 80% of malignant pleural mesotheliomas. A dose-response relationship is not always apparent, and even brief exposures can lead to the disease. An exposure history is often difficult to obtain because the latent period before clinical manifestation of the tumor may be as long as 40 to 50 years.

Tobacco smoke is responsible for approximately 90% of all lung cancers, and the epidemiology of lung cancer follows the epidemiology of cigarette smoking with approximately a 3-decade lag time.[50] Other environmental causes include asbestos and radon gas (a decay product of naturally occurring uranium), which act as co-carcinogens with tobacco smoke. For a pack-a-day cigarette smoker, the lifetime risk of lung cancer is approximately 1 in 14. Assuming that current mortality patterns continue, cancer will pass heart disease as the leading cause of death in North America in this decade.

Non–Small-Cell Lung Cancer

This pathologically heterogeneous group of tumors includes squamous cell, adenocarcinoma, and large-cell carcinoma. Overall 5-year survival with surgery approaches 40%. This seemingly low figure must be viewed in the light of an estimated 5-year survival without surgery of less than 10%. Although it is not always possible to be certain of the pathology of a given lung tumor preoperatively, many patients will have a known tissue diagnosis at the time of preanesthetic assessment based on prior cytology, bronchoscopy, mediastinoscopy, or transthoracic needle aspiration. This is useful information for the anesthesiologist to obtain preoperatively. Specific anesthetic implications of the different types of lung cancer are listed in Table 66-2.

Squamous Cell Carcinoma

This subgroup of NSCLC is strongly linked to cigarette smoking. The tumors tend to grow to a large size and metastasize later than others. They tend to cause symptoms related to local effects of a large tumor mass with a dominant endobronchial component, such as cavitation, hemoptysis, obstructive pneumonia, superior vena cava syndrome, and involvement of mainstem bronchus, trachea, carina, and main pulmonary arteries. Hypocalcemia may be associated with this cell type because of elaboration of a parathyroid-like factor and not as a result of bone metastases.

TABLE 66-2 ANESTHETIC CONSIDERATIONS FOR DIFFERENT TYPES OF LUNG CANCER

Type	Considerations
Squamous cell	Central lesions (predominantly) Often with endobronchial tumor Mass effects: obstruction, cavitation Hypercalcemia
Adenocarcinoma	Peripheral lesions Extrapulmonary invasion common Most Pancoast tumors Growth hormone, corticotropin Hypertrophic osteoarthropathy
Large cell	Large, cavitating peripheral tumors Similar to adenocarcinoma
Small cell	Central lesions (predominantly) Surgery usually not indicated Paraneoplastic syndromes Lambert-Eaton syndrome Fast growth rate Early metastases
Carcinoid	Proximal, endobronchial Bronchial obstruction with distal pneumonia Highly vascular Benign (predominantly) No association with smoking Carcinoid syndrome (rarely)

Adenocarcinoma

Adenocarinoma is currently the most common NSCLC in both sexes. These tumors tend to be peripheral and often metastasize early in their course, particularly to brain, bones, liver, and adrenals. They often invade extrapulmonary structures, including the chest wall, diaphragm, and pericardium. Almost all Pancoast tumors are adenocarcinomas. A variety of paraneoplastic metabolic factors can be secreted by adenocarcinomas, such as growth hormone and corticotropin. Hypertrophic pulmonary osteoarthropathy is particularly associated with adenocarcinoma.

Bronchioloalveolar carcinoma is a subtype of adenocarcinoma that is not related to cigarette smoking. In its early stages, it lines the alveolar membrane with a thin layer of tumor cells without destroying the alveolar architecture. Because of its low potential to spread outside of the lungs, multifocal bronchioloalveolar carcinoma can be treated by lung transplantation.[51]

Large-Cell Undifferentiated Carcinoma

This is the least common of the NSCLCs. It tends to present as a large, often cavitating peripheral tumor. The rapid growth rate may lead to widespread metastases, similar to adenocarcinoma.

Small-Cell Lung Cancer

This tumor of neuroendocrine origin is considered metastatic on presentation and is usually regarded as a medical, not a surgical, disease. Surgery is only very rarely indicated. The staging system differs from NSCLC and is divided simply into a limited stage and an extensive stage. Treatment of limited-stage SCLC with combination chemotherapy (etoposide/cisplatin or cyclophosphamide/doxorubicin/vincristine) gives objective response rates in more than 80% of patients. In addition, these patients typically receive aggressive radiotherapy to the primary lung tumor and prophylactic cranial irradiation. Despite this initial response, the tumor invariably recurs and is quite resistant to further treatment. The overall survival rate is no more than 10%. Extensive-stage disease is treated with chemotherapy and palliative radiation as needed.

SCLC causes a variety of paraneoplastic syndromes owing to the production of peptide hormones and antibodies. The most common of these is hyponatremia, usually as a result of an inappropriate production of antidiuretic hormone. Cushing syndrome and hypercortisolism through ectopic production of adrenocorticotropic hormone are also commonly seen.

A rare neurologic paraneoplastic syndrome associated with small-cell lung tumors is the Lambert-Eaton (also called Eaton-Lambert) myasthenic syndrome caused by impaired release of acetylcholine from nerve terminals. This typically presents as proximal lower limb weakness and fatigability that may temporarily improve with exercise.

The diagnosis is confirmed by electromyography showing increasing amplitude of unusual action potentials with high-frequency stimulation. Similar to those with true myasthenia gravis, paitents with myasthenic syndrome are extremely sensitive to nondepolarizing muscle relaxants (see Chapter 18). However, they respond poorly to acetylcholinesterase inhibitors such as neostigmine.[52] Of clinical importance, subclinical involvement of the diaphragm and muscles of respiration may exist. Thoracic epidural analgesia has been used after thoracotomy in these patients without complication. Neuromuscular function may improve after resection of the lung cancer.

Carcinoid Tumors

These are part of a continuum of neuroendocrine tumors that form a spectrum of diseases from SCLC as the most malignant to typical carcinoid as the most benign. Five-year survival after resection for typical carcinoid exceeds 90%. Systemic metastasis is rare, as is the carcinoid syndrome, which is caused by the ectopic synthesis of vasoactive mediators, and is usually seen with carcinoid tumors of gut origin that have metastasized to the liver. Atypical carcinoid tumors are more aggressive and may metastasize. Carcinoid tumors can precipitate an intraoperative hemodynamic crisis or coronary artery spasm, even during bronchoscopic resection.[53] The anesthesiologist should be prepared to deal with severe hypotension that may not respond to the usual vasoconstrictors and will require the use of the specific antagonists octreotide or somatostatin.[54]

Pleural Tumors

Localized fibrous tumors of the pleura are usually large, space-occupying masses that are attached to visceral or parietal pleura. They can be either benign or malignant.

Malignant pleural mesotheliomas are strongly associated with exposure to asbestos fibers. Their incidence in Canada has almost doubled in the past 15 years. With the phasing out of asbestos-containing products and the long latent period between exposure and diagnosis, the peak incidence is not predicted for another 10 years. The tumor initially proliferates within the visceral and parietal pleura, typically forming a bloody effusion. Most patients present with shortness of breath or dyspnea on exertion from this pleural effusion. Thoracentesis often relieves the symptoms but rarely provides a diagnosis. Pleural biopsy by VATS is the most efficient method to secure a diagnosis, and talc pleurodesis is performed during the same anesthetic period to treat the effusion.

Malignant pleural mesotheliomas respond poorly to therapy, and the median survival is less than 1 year. In patients with early disease, extrapleural pneumonectomy may be considered but it is difficult to know whether survival is improved. Recently, several groups have reported improved results with combinations of radiation, chemotherapy, and surgery. Extrapleural pneumonectomy is an extensive procedure that is rife with potential complications, both intraoperative and postoperative.[55] Blood loss from the denuded chest wall or major vascular structures is always a risk. Complications related to resection of the diaphragm and pericardium are additional risks to those of pneumonectomy.

ASSESSMENT OF THE PATIENT WITH LUNG CANCER (See Chapter 38)

At the time of initial assessment, cancer patients should be assessed for the "4 Ms" associated with malignancy (Box 66-1): **m**ass effects, **m**etabolic abnormalities, **m**etastases, and **m**edications. The prior use of medications that can exacerbate oxygen-induced pulmonary toxicity, such as bleomycin, should be considered.[56] Bleomycin is not used to treat primary lung cancers, but patients presenting for excision of lung metastases from germ-cell tumors often have received prior bleomycin therapy. Although the association between previous bleomycin therapy and pulmonary toxicity from high inspired oxygen concentrations is well documented, none of the details of the association are understood (i.e., safe doses of oxygen or safe period after bleomycin exposure). The safest anesthetic management is to use the lowest FiO_2 consistent with patient safety and to closely monitor oximetry in any patient who has received bleomycin. We have seen lung cancer patients who received preoperative chemotherapy with cisplatin and then developed an elevation of serum creatinine when they received nonsteroidal antiinflammatory drugs (NSAIDs) postoperatively. For this reason, we do not routinely administer NSAIDs to patients who have been treated recently with cisplatin.

PLANNING POSTOPERATIVE ANALGESIA

The strategy for postoperative analgesia (see Chapter 98) should be developed and discussed with the patient during the initial preoperative assessment. A discussion of postoperative analgesia is presented at the end of this chapter. Many techniques are superior to the use of on-demand parenteral (intramuscular or intravenous) opioids alone in terms of pain control. These include the addition of neuraxial blockade, paravertebral blocks, and antiinflammatories to narcotic-based analgesia. However, only epidural techniques can decrease postthoracotomy respiratory complications in high-risk patients.[2] As well, continuous paravertebral blockade may offer comparable analgesia with a less frequent rate of block failure and fewer side effects.[57]

At the time of initial preanesthetic assessment, the risks and benefits of the various forms of postthoracotomy analgesia should be explained to the patient. Potential contraindications to specific methods of analgesia should

BOX 66-1 *Anesthetic Considerations in Lung Cancer Patients (the "4 Ms")*

1. **M**ass effects: Obstructive pneumonia, lung abscess, SVC syndrome, tracheobronchial distortion, Pancoast syndrome, recurrent laryngeal nerve or phrenic nerve paresis, chest wall or mediastinal extension
2. **M**etabolic effects: Lambert-Eaton syndrome, hypercalcemia, hyponatremia, Cushing syndrome
3. **M**etastases: Particularly to brain, bone, liver, adrenal
4. **M**edications: Chemotherapy agents, pulmonary toxicity (bleomycin, mitomycin), cardiac toxicity (doxorubicin), renal toxicity (cisplatin)

be determined, such as coagulation problems, sepsis, or neurologic disorders. If the patient is to receive prophylactic anticoagulants and it has been elected to use epidural analgesia, appropriate timing of anticoagulant administration and neuraxial catheter placement need to be arranged. American Society of Regional Anesthesia guidelines suggest an interval of 2 to 4 hours before or 1 hour after catheter placement for prophylactic heparin administration.[58] Low-molecular-weight heparin (LMWH) recommendations and precautions are: (1) a minimal interval of 12 hours after low-dose LMWH and (2) 24 hours after higher-dose LMWH before catheter placement.

PREMEDICATION

We do not routinely order preoperative sedation or analgesia for pulmonary resection patients. Mild sedation such as an intravenous short-acting benzodiazepine is often given immediately before placement of invasive monitoring lines and catheters. In patients with copious secretions, an antisialogogue (e.g., glycopyrrolate) is useful to facilitate fiberoptic bronchoscopy for positioning of a double-lumen endobronchial tube (DLT) or bronchial blocker. To avoid an intramuscular injection, this can be given orally or intravenously immediately after placement of the intravenous catheter. It is a common practice to use short-term intravenous antibacterial prophylaxis such as a cephalosporin in thoracic surgical patients. If it is the local practice to administer these drugs before admission to the operating room, they will have to be ordered preoperatively. Consideration for patients allergic to cephalosporins or penicillin should be made at the time of the initial preoperative visit.

SUMMARY OF THE INITIAL PREOPERATIVE ASSESSMENT

The anesthetic considerations that should be addressed at the time of the initial preoperative assessment are summarized in Box 66-2. Patients need to be specifically assessed for risk factors associated with respiratory complications, which are the major cause of morbidity and mortality afte thoracic surgery.

FINAL PREOPERATIVE ASSESSMENT

The final preoperative anesthetic assessment for the majority of thoracic surgical patients is carried out immediately before admission of the patient to the operating room. At this time, it is important to review the data from the initial prethoracotomy assessment and the results of tests ordered at that time. In addition, two other specific areas affecting thoracic anesthesia need to be assessed: (1) the potential for difficult lung isolation and (2) the risk of desaturation during one-lung ventilation (OLV) (Box 66-3).

BOX 66-2 *Initial Preanesthetic Assessment for Thoracic Surgery*

1. All patients: Assess exercise tolerance, estimate ppoFEV_1%, discuss postoperative analgesia, discontinue smoking
2. Patients with ppoFEV_1 < 40%: $D_L$co, $\dot{V}/\dot{Q}$ scan, VO_{2max}
3. Cancer patients: consider the four *M*s: mass effects, metabolic effects, metastases, medications
4. COPD patients: arterial blood gas, physiotherapy, bronchodilators
5. Increased renal risk: measure creatinine and blood urea nitrogen levels

DIFFICULT ENDOBRONCHIAL INTUBATION

The most useful predictor of difficult endobronchial intubation is the plain chest radiograph (Fig. 66-7).

The anesthesiologist should view the chest imaging before induction of anesthesia because neither the radiologist's nor the surgeon's report of the imaging is made with the specific consideration of lung isolation in mind. Distal airway problems not detectable on the plain chest film can sometimes be visualized on the computed tomography (CT) scan: a side-to-side compression of the distal trachea, the so-called saber-sheath trachea

BOX 66-3 *Final Preanesthetic Assessment for Thoracic Surgery*

1. Review initial assessment and test results
2. Assess difficulty of lung isolation: examine chest radiograph and computed tomographic scan
3. Assess risk of hypoxemia during one-lung ventilation

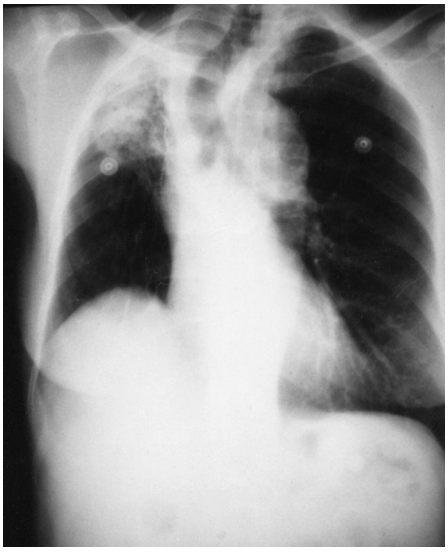


Figure 66-7. Preoperative chest radiograph of a 50-year-old woman with a history of previous tuberculosis, right upper lobectomy, and recent hemoptysis presenting for right thoracotomy and possible completion pneumonectomy. The potential problems positioning a left-sided double-lumen tube (DLT) in this patient are easily appreciated by viewing the radiograph but are not mentioned in the radiologist's report. The anesthesiologist must solely examine the chest imaging preoperatively to anticipate problems in lung isolation. *(Reproduced with permission from Slinger P:* Principles and practice of anesthesia for thoracic surgery, *New York, Springer, 2011.)*

can cause obstruction of the tracheal lumen of a left-sided DLT during ventilation of the dependent lung for a left thoracotomy.[59] Similarly, extrinsic compression or intraluminal obstruction of a mainstem bronchus that can interfere with endobronchial tube placement may only be evident on the CT scan. The major factors in successful lower airway management are anticipation and preparation based on the preoperative assessment. Management of lung isolation in patients with difficult upper and lower airways is discussed later in this chapter.

PREDICTION OF DESATURATION DURING ONE-LUNG VENTILATION

In the vast majority of cases, it is possible to determine the patients who are most at risk of desaturation during OLV for thoracic surgery. The factors that correlate with desaturation during OLV are listed in Box 66-4. In patients at high-risk of desaturation, prophylactic measures can be used during OLV to decrease this risk. The most useful prophylactic measures are the use of CPAP (2 to 5 cm H_2O of oxygen) to the nonventilated lung or PEEP to the dependent lung (see Treatment of Hypoxemia During OLV) (also see Chapter 19 regarding more detailed physiology.).

The most important predictor of PaO_2 during OLV is the PaO_2 during two-lung ventilation (TLV), specifically the intraoperative PaO_2 during TLV in the lateral position before OLV.[60] The proportion of perfusion or ventilation to the nonoperated lung on preoperative $\dot{V}/\dot{Q}$ scans also correlates with the PaO_2 during OLV.[61] If the operative lung has little perfusion preoperatively because of unilateral disease, the patient is unlikely to desaturate during OLV. The side of the thoracotomy has an effect on PaO_2 during OLV. Because the left lung is 10% smaller than the right lung, there is less shunt when the left lung is collapsed. In a series of patients, the mean PaO_2 during left thoracotomy was approximately 70 mm Hg higher than during right thoracotomy.[62] Finally, the degree of obstructive lung disease correlates in an inverse fashion with PaO_2 during OLV. Other factors being equal, patients with more severe airflow limitation on preoperative spirometry tend to have a better PaO_2 during OLV than patients with normal spirometry (this is discussed later in Anesthetic Management).[63]

BOX 66-4 ***Factors That Correlate with an Increased Risk of Desaturation During One-Lung Ventilation***

1. High percentage of ventilation or perfusion to the operative lung on preoperative $\dot{V}/\dot{Q}$ scan
2. Poor PaO_2 during two-lung ventilation, particularly in the lateral position intraoperatively
3. Right-sided thoracotomy
4. Normal preoperative spirometry (FEV_1 or FVC) or restrictive lung disease
5. Supine position during one-lung ventilation

ASSESSMENT FOR REPEAT THORACIC SURGERY

Patients who survive lung cancer surgery form a high-risk cohort to have a recurrence of the original tumor or to develop a second primary tumor. The incidence of developing second primary lung tumors is estimated at 2% per year. The use of routine screening low-dose spiral CT scans probably increases the rate of early detection.[64] Patients who present for repeat thoracotomy should be assessed using the same framework as those who present for surgery the first time. Predicted values for postoperative respiratory function based on the preoperative lung mechanics, parenchymal function, exercise tolerance, and the amount of functioning lung tissue resected should be calculated and used to identify patients at increased risk.

INTRAOPERATIVE MONITORING
(See Chapters 44 and 51)

A few points specific to intraoperative monitoring of the thoracic surgical patient should be emphasized. The majority of these operations are major procedures of moderate duration (2 to 4 hours) and are performed with the patient in the lateral position and the hemithorax open. Thus consideration for monitoring and maintenance of body temperature and fluid volume should be given to all of these cases. Because surgery is usually performed with the patient in the lateral position, monitors are initially placed with the patient in the supine position and have to be rechecked and repositioned after the patient is turned. It is difficult to add additional monitoring, particularly invasive vascular monitoring, after the case is started if complications arise. Thus, the risk-benefit ratio often tends to favor being overly invasive at the outset. Choice of monitoring should be guided by a knowledge of which complications are likely to occur (Table 66-3).

OXYGENATION

Significant desaturation (SpO_2 <90%) during OLV occurs in 1% to 10% of the surgical population despite a high

TABLE 66-3 **INTRAOPERATIVE COMPLICATIONS THAT OCCUR WITH INCREASED FREQUENCY DURING THORACOTOMY**

Complication	Etiology
Hypoxemia	Intrapulmonary shunt during one-lung ventilation
Sudden severe hypotension	Surgical compression of the heart or great vessels
Sudden changes in ventilating pressure or volume	Movement of endobronchial tube/blocker, air leak
Arrhythmias	Direct mechanical irritation of the heart
Bronchospasm	Direct airway stimulation, increased frequency of reactive airways disease
Massive hemorrhage	Surgical blood loss from great vessels or inflamed pleura
Hypothermia	Heat loss from the open hemithorax

FiO_2 (1.0) (see Management of OLV later in the chapter). Pulse oximetry (SpO_2) has not negated the need for direct measurement of arterial PaO_2 via intermittent blood gases in the majority of thoracotomy patients. The PaO_2 value offers a more useful estimate of the margin of safety above desaturation than the SpO_2. A patient with a TLV PaO_2 greater than 400 mm Hg with an FiO_2 of 1.0 (or an equivalent PaO_2/FiO_2 ratio) is unlikely to desaturate during OLV, whereas a patient with a PaO_2 of 200 mm Hg is prone to desaturate during OLV, although both may have SpO_2 values of 99% to 100%.

CAPNOMETRY

The end-tidal CO_2 ($PetCO_2$) is a less reliable indicator of the $Paco_2$ during OLV than during TLV, and the $Paco_2$-$PetCO_2$ gradient tends to increase during OLV. Although the $PetCO_2$ is less directly correlated with alveolar minute ventilation during OLV, because the $PetCO_2$ also reflects lung perfusion and cardiac output, it gives an indication of the relative changes in perfusion of the two lungs independently during position changes and during OLV.[65] As the patient is turned to the lateral position, the $PetCO_2$ of the nondependent lung will fall relative to the dependent lung, reflecting increased perfusion of the dependent lung and increased dead space of the nondependent lung. However, the fractional excretion of CO_2 will be higher from the nondependent lung in most patients because of the increased fractional ventilation of this lung. At the onset of OLV, the $PetCO_2$ of the dependent lung will usually fall transiently as all of the minute ventilation is transferred to this lung. The $PetCO_2$ will then rise as the fractional perfusion is increased to this dependent lung by collapse and pulmonary vasoconstriction of the nonventilated lung. If there is no correction of minute ventilation, the net result will be both an increased baseline $Paco_2$ and $PetCO_2$ with an increased gradient. Severe (>5 mm Hg) or prolonged decreases in $PetCO_2$ can indicate a maldistribution of perfusion between ventilated and nonventilated lungs and may be an early warning sign of a patient who will subsequently desaturate during OLV.

INVASIVE HEMODYNAMIC MONITORING
(See Chapter 45)

ARTERIAL LINE

Transient severe hypotension from surgical compression of the heart or great vessels can occur during intrathoracic procedures. For this reason, in addition to the utility of intermittent arterial blood gas sampling, it is useful to have beat-to-beat assessment of systemic blood pressure during the majority of thoracic surgery cases. Naturally, exceptions occur during limited procedures, such as thoracoscopic resections in younger and healthier patients. For most thoracotomies, placement of a radial artery catheter can be in either the dependent or nondependent arm.

CENTRAL VENOUS PRESSURES

It is a common impression that central venous pressure (CVP) readings in the lateral position with the chest open are not reliable as a monitor of volume status. The CVP may be a useful monitor postoperatively, particularly for cases in which fluid management is critical (e.g., pneumonectomies). A CVP may be required in some cases for vascular access or for vasopressor/inotrope infusions. It is our practice to routinely place CVP lines in pneumonectomy cases, complex procedures, or redo thoracotomies, but not for lesser resections unless there is significant other concurrent illness. Our choice is to use the right internal jugular vein to minimize the risk of pneumothorax for CVP access unless there is a contraindication. Internal jugular CVP data are not reliable in patients with superior vena cava obstruction.

PULMONARY ARTERY CATHETERS

Similar to CVP data, intraoperative pulmonary artery pressure may be a less accurate indicator of true left-heart preload in the lateral position with the chest open than in other clinical situations. This is partly because it is often initially not known whether the catheter tip lies in the dependent or nondependent lung. In addition, it is possible that thermodilution cardiac output data may be unreliable if there are significant transient unilateral differences in perfusion between the lungs, as can occur during OLV. There is no consensus on the reliability of thermodilution cardiac output data during OLV.[66]

FIBEROPTIC BRONCHOSCOPY

Placement of DLTs and bronchial blockers is discussed later in the section "Lung Isolation." Significant malpositions of DLTs and blockers that can lead to desaturation during OLV are often not detected by auscultation or other traditional methods of confirming placement.[67] Placement of DLTs or blockers should be performed with fiberoptic bronchoscopic guidance and should be reconfirmed after placing the patient in the surgical position, because a large number of these tubes/blockers migrate during repositioning of the patient.[68]

CONTINUOUS SPIROMETRY

The development of side-stream spirometry has made it possible to continuously monitor inspiratory and expiratory volumes, pressures, and flow interactions during one-lung anesthesia. This monitoring is particularly useful during pulmonary resection surgery. The breath-by-breath monitoring of inspired and expired tidal volumes gives early warning of accidental changes in the intraoperative position of a DLT, with loss of lung isolation if the expired volume suddenly decreases (there is normally a 20- to 30-mL/breath difference caused in part by the uptake of inspired oxygen). The development of a persistent end-expiratory flow during OLV, which correlates with the development of auto-PEEP, can be seen on the flow-volume loop.[69] Also the ability to accurately measure differences in inspiratory and expiratory tidal volumes is extremely useful in assessing and managing air leaks during and after pulmonary resections.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Transesophageal echocardiography (TEE) allows the anesthesiologist to view a continuous real-time monitor of myocardial function and cardiac preload (see Chapter 46). This information is difficult to estimate intraoperatively in the lateral position from other hemodynamic monitors.[70] Potential indications for intraoperative TEE that apply to thoracic surgery include hemodynamic instability (Fig. 66-8), pericardial effusions, cardiac involvement by tumor, air emboli, pulmonary thromboendarterectomy, thoracic trauma, lung transplantation, and pleuropulmonary disease. A rare cause of hypoxemia associated with thoracic surgery is reversal of shunt flow through an undiagnosed patient foramen ovale. When PEEP (to 15 cm H_2O) was applied during controlled ventilation for nonthoracic surgery, 9% of the patients developed a right-to-left intracardiac shunt.[71] TEE should be capable of detecting situations in patients who might intraoperatively develop a right-to-left interatrial shunt during or after thoracic surgery.

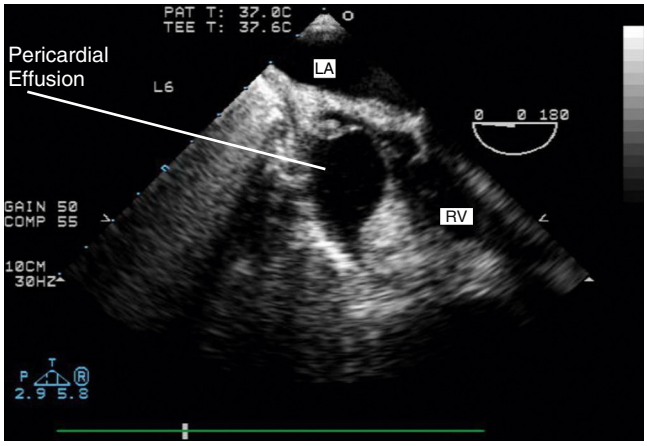


Figure 66-8. Midesophageal TEE view of a patient with metastatic breast cancer who had a hemodynamic collapse after induction of general anesthesia for video-assisted thoracoscopic drainage of a left pleural effusion. TEE was performed for diagnosis of hemodynamic instability and revealed a previously undiagnosed large pericardial effusion. The "Pericardial Effusion" label shows complete collapse of the right atrium during systole as a result of the effusion, consistent with tamponade. The procedure was modified to include creation of a pericardial window. *LA*, Left atrium; *RV*, right ventricle.

OTHER NEW MONITORING TECHNOLOGY

Cerebral oximetry ($SctO_2$) has been reported for intraoperative monitoring during OLV.[72] Older, debilitated patients are more likely to have falls in $SctO_2$ during OLV, and these are associated with decreases in SpO_2 and postoperative cognitive dysfunction. However, it has not been shown whether any treatment for decreases in $SctO_2$ affects outcomes. Goal-directed fluid therapy using indirect monitors of cardiac output or venous oxygen saturation seems to improve fluid management in abdominal surgery.[73] This is currently a much needed area of research in thoracic anesthesia.

LUNG ISOLATION

Lung isolation techniques are primarily designed to facilitate OLV in patients undergoing cardiac, thoracic, mediastinal, vascular, esophageal, or orthopedic procedures involving the chest cavity.[74] Lung isolation is also used to protect the lung from soiling by the contralateral lung in such cases as bronchopleural fistula, pulmonary hemorrhage, and whole-lung lavage. In addition, lung isolation can be used to provide differential patterns of ventilation in cases of unilateral reperfusion injury (after lung transplantation or pulmonary thromboendarterectomy) or in unilateral lung trauma.

Lung isolation can be achieved by three different methods: DLTs, bronchial blockers, or single-lumen tubes (SLTs) (Table 66-4). The most common technique is with a DLT. The DLT is a bifurcated tube with both an endotracheal and an endobronchial lumen and can be used to achieve isolation of either the right or the left lung. The second method involves blockade of a mainstem bronchus to allow lung collapse distal to the occlusion. These bronchial blockers can be used with a standard endotracheal tube or contained within a separate channel inside a modified SLT such as the Univent tube (LMA North America, San Diego, Calif). The final option for lung isolation is to use either an SLT or an endobronchial tube that is advanced into the contralateral mainstem bronchus, protecting this lung while allowing collapse of the lung on the side of surgery (Fig. 66-9). This technique is rarely used today in adult practice (except in some cases of difficult airways, carinal resection, or after a pneumonectomy), owing to the limited access to the nonventilated lung and the difficulty in positioning a standard SLT in the bronchus. This technique is still used when needed in infants and small children: an uncuffed uncut pediatric-size endotracheal tube is advanced into the mainstem bronchus under direct guidance with an infant bronchoscope.

DOUBLE-LUMEN ENDOTRACHEAL TUBES

The design of the Carlens DLT for lung surgery in 1950 was a landmark in the development of thoracic anesthesia because it allowed anesthesiologists to obtain reliable lung isolation in a majority of patients using only laryngoscopy and auscultation. However, the Carlens tube had a high flow resistance owing to the narrow lumina and the carinal hook was difficult to pass through the glottis in some patients. In the 1960s, Robertshaw introduced design modifications for separate left- and right-sided DLTs, removing the carinal hook and using larger lumina. In the 1980s, manufacturers introduced disposable DLTs made of polyvinyl chloride based on the design of the Robertshaw DLT. Among other subsequent improvements is the inclusion of radiographic markers near the endotracheal and endobronchial cuffs and a radiographic marker surrounding the ventilation slot for the right upper lobe bronchus for the right-sided DLT version. Bright blue, low-volume, low-pressure endobronchial cuffs are incorporated for easier visualization during fiberoptic bronchoscopy. Table 66-5 lists the sizes of DLTs, the

TABLE 66-4 **OPTIONS FOR LUNG ISOLATION**

Options	Advantages	Disadvantages
Double-lumen tube	Easy to place successfully	Size selection more difficult
1. Direct laryngoscopy	Repositioning rarely required	Difficult to place in patients with difficult airways or abnormal tracheas
2. Via tube exchanger	Bronchoscopy to isolated lung	
3. Fiberoptically	Suction to isolated lung	Not optimal for postoperative ventilation
	CPAP easily added	Potential laryngeal trauma
	Can alternate one-lung ventilation to either lung easily	Potential bronchial trauma
	Placement still possible if bronchoscopy not available	
	Best device for absolute lung isolation	
Bronchial blockers (BB)	Size selection rarely an issue	More time needed for positioning
1. Arndt	Easily added to regular ETT	Repositioning needed more often
2. Cohen	Allows ventilation during placement	Bronchoscope essential for positioning
3. Fuji	Easier placement in patients with difficult airways	Limited right lung isolation due to RUL anatomy
4. EZ Blocker	and in children	Bronchoscopy to isolated lung impossible
	Postoperative two-lung ventilation by withdrawing blocker	Minimal suction to isolated lung
		Difficult to alternate one-lung ventilation to either lung
	Selective lobar lung isolation possible	
	CPAP to isolated lung possible	
Univent tube	Same as BBs	Same as for BBs
	Less repositioning compared with BBs	ETT portion has higher air flow resistance than regular ETT
	Rarely used	ETT portion has larger diameter than regular ETT
Endobronchial tube	Like regular ETTs, easier placement in patients with difficult airways	Bronchoscopy necessary for placement
		Does not allow for bronchoscopy, suctioning, or CPAP to isolated lung
	Longer than regular ETT	
	Short cuff designed for lung isolation	Difficult one-lung ventilation (right lung)
Endotracheal tube advanced into bronchus	Easier placement in patients with difficult airways	Does not allow for bronchoscopy, suctioning, or CPAP to isolated lung
		Cuff not designed for lung isolation
		Extremely difficult right one-lung ventilation

CPAP, continuous positive airway pressure; *ETT*, endotracheal tube; *RUL*, right upper lobe.

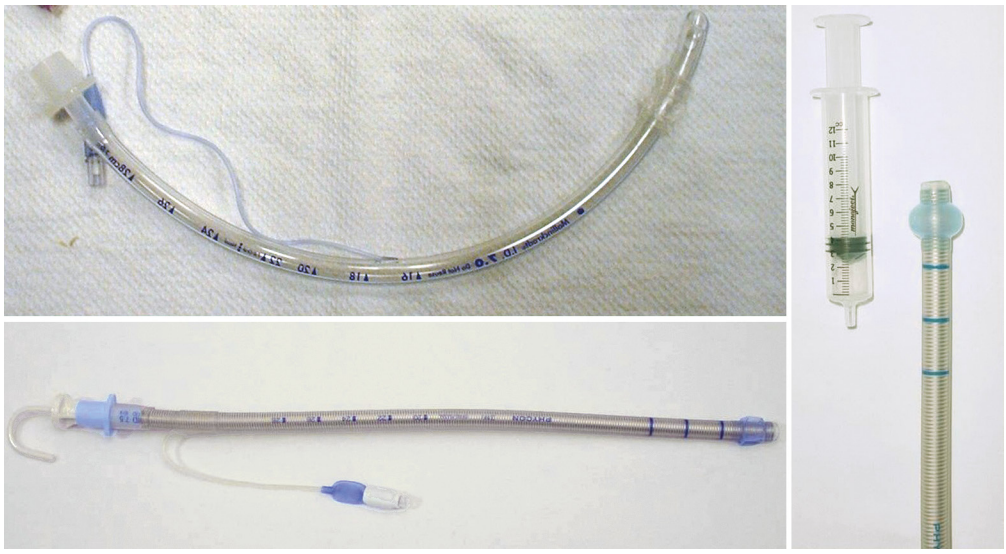


Figure 66-9. Photographs of a standard single-lumen endotracheal tube (SLT) *(upper left)* and a specifically designed SLT *(lower left and right)*. The endobronchial tube is longer and has a shorter cuff. It can be used as an endotracheal tube and advanced into a mainstem bronchus with fiberoptic guidance when needed for lung isolation. *(Courtesy Phycon, Fuji Systems, Tokyo, Japan.)*

appropriate fiberoptic bronchoscope sizes to be used, and the comparable diameters of SLTs.

Size Selection

A properly sized, left-sided DLT should have a bronchial tip 1 to 2 mm smaller than the patient's left bronchus diameter to allow for the space occupied by the deflated bronchial cuff. A study by Eberle and associates[75] used a three-dimensional image reconstruction of tracheobronchial anatomy from the spiral CT scans combined with superimposed transparencies of DLTs to predict proper size for a right- or left-sided DLT. Chest radiographs and CT scans are valuable tools for selection of proper DLT size in addition to their proven value in assessment of abnormal tracheobronchial anatomy and should be reviewed before the placement of the DLT (Fig. 66-10).

TABLE 66-5 COMPARATIVE DIAMETERS OF SINGLE- AND DOUBLE-LUMEN TUBES

Single-Lumen Tubes		Double-Lumen Tubes			
ID (mm)	ED (mm)	French Size (Fr)	Double-Lumen ED (mm)	Bronchial Lumen ID (mm)	FOB size (mm)
6.5	8.9	26	8.7	3.2	2.4
7.0	9.5	28	9.3	3.4	2.4
8.0	10.8	32	10.7	3.5	2.4
8.5	11.4	35	11.7	4.3	≥3.5
9.0	12.1	37	12.3	4.5	≥3.5
9.5	12.8	39	13.0	4.9	≥3.5
10.0	13.5	41	13.7	5.4	≥3.5

ED, external diameter; *FOB,* fiberoptic bronchoscope; *ID,* internal diameter.
Double-lumen ED is equal to the approximate external diameter of the double-lumen portion of the tube. FOB size is equal to the maximal diameter of fiberoptic bronchoscope that will pass through both lumina of a given size of double-lumen tube.

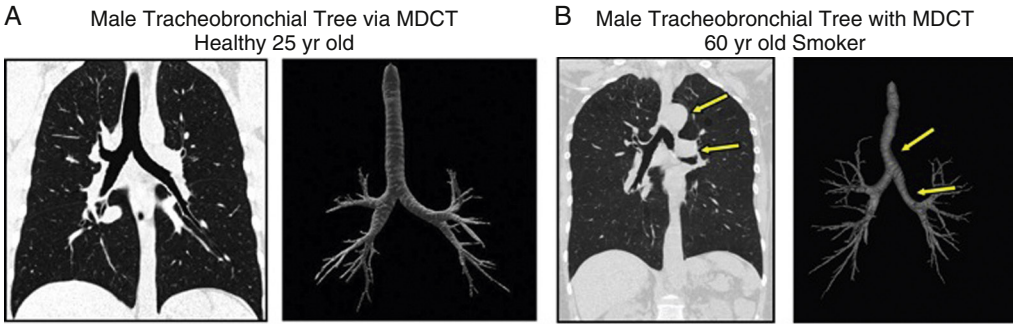


Figure 66-10. A, The multidetector CT scan and also three-dimensional view of tracheobronchial anatomy in a healthy volunteer. **B,** Abnormal tracheobronchial anatomy in a 60-year-old smoker. The *arrows* show enlarged aorta *(left)* and the deviation of the trachea to the right caused by the enlarged aorta *(right).*

TABLE 66-6 SELECTION OF DOUBLE-LUMEN TUBE SIZE BASED ON ADULT PATIENT'S SEX AND HEIGHT

Sex	Height (cm)	Size of Double-Lumen Tube (Fr)
Female	<160 (63 in)*	35
Female	>160	37
Male	<170 (67 in)†	39
Male	>170	41

*For females of short stature (<152 cm or 60 in), examine the bronchial diameter on computed tomographic scan, consider 32-Fr double-lumen tube.
†For males of short stature (<160 cm) consider 37-Fr double-lumen tube.

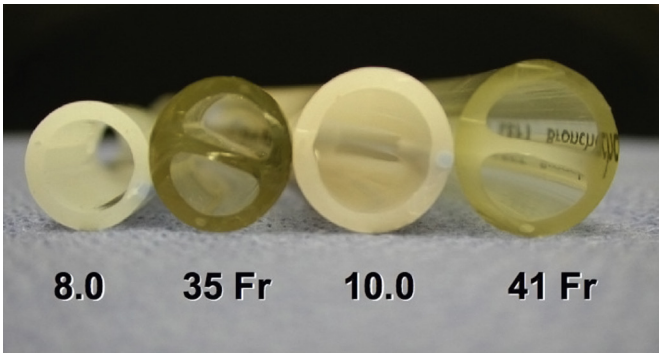


Figure 66-11. Photograph of the cut cross sections of several SLTs and DLTs. The external diameter of a 35-Fr DLT is larger than that of an 8.0-mm (internal diameter) SLT, and a 41-Fr DLT is larger than a 10-mm SLT. *(Courtesy Dr. J. Klafta.)*

A multidetector CT scan (MDCT) of the chest allows appreciation of any abnormal tracheobronchial anatomy before placement of a DLT. A simplified method of selection of DLT size is given in Table 66-6. It is important to appreciate that compared with SLTs, DLTs have a large external diameter (Fig. 66-11) and they should not be advanced against significant resistance.

Methods of Insertion

Two techniques are commonly used when inserting and placing a DLT. One is the blind technique: the DLT is passed by direct laryngoscopy and then turned 90 degrees counterclockwise (for a left-sided DLT placement) after the endobronchial cuff has passed beyond the vocal cords. The DLT should pass the glottis without any resistance. Seymour[76] showed that the mean diameter of the cricoid ring is approximately the same as that of the left mainstem bronchus. The optimal depth of insertion for a left-sided DLT is correlated with the patient's height in average-sized adults. In adults, depth, measured at the teeth for a properly positioned DLT, will be approximately 12 + (patient height/10) cm.[77] In patients of Asian

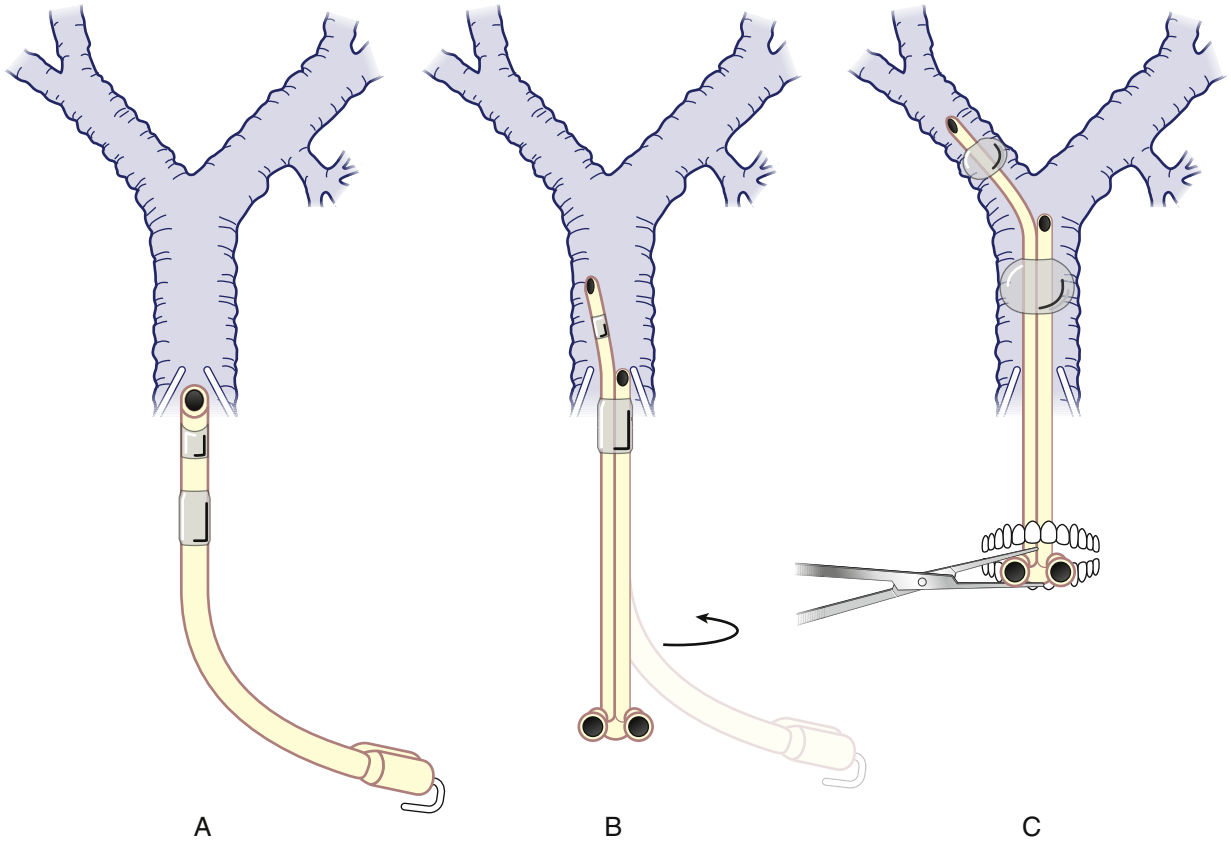


Figure 66-12. Blind method for placement of a left-sided DLT. **A,** The DLT is passed with direct laryngoscopy beyond the vocal cords. **B,** The DLT is rotated 90 degrees to the left (counter-clockwise). **C,** The DLT is advanced to an appropriate depth (in general 27-29 cm marking at the level of the teeth). *(Reproduced with permission from Slinger P:* Principles and practice of anesthesia for thoracic surgery, *New York, Springer, 2011.)*

descent, many of whom are of shorter stature (<155 cm), patient height is not a good predictor of depth of insertion of a DLT.[78] An inadvertently deep insertion of a DLT can lead to serious complications, including rupture of the left mainstem bronchus. Figure 66-12 depicts the blind method technique for insertion of a left-sided DLT.

The direct vision technique uses bronchoscopic guidance, in which the tip of the endobronchial lumen is guided into the correct bronchus after the DLT passes the vocal cords using direct vision with a flexible fiberoptic bronchoscope. A study by Boucek and associates[79] comparing the blind technique versus fiberoptic bronchoscopy-guided technique showed that of the 32 patients who underwent the blind technique approach, primary success occurred in 27 patients and eventual success occurred in 30 patients. In contrast, in the 27 patients using the bronchoscopy-guided technique, primary success was achieved only in 21 patients and eventual success in 25 patients. Although both methods resulted in successful left mainstem bronchus placement in all patients, more time was required when the fiberoptic bronchoscopy guidance technique was used (181 versus 88 seconds).

RIGHT-SIDED DOUBLE-LUMEN ENDOBRONCHIAL TUBES

Although a left-sided DLT is used more commonly for most elective thoracic procedures,[80] there are specific clinical situations in which the use of a right-sided DLT is indicated (Box 66-5). The anatomic differences between the right and the left mainstem bronchus are reflected in the fundamentally different designs of the right-sided and left-sided DLTs. Because the right mainstem bronchus is shorter than the left bronchus, and because the right upper lobe bronchus originates at a distance of 1.5 to 2 cm from the carina, techniques using right endobronchial intubation must take into account the location and potential for obstruction of the orifice of the right upper

BOX 66-5 ***Indications for a Right-Sided Double-Lumen Tube****

- Distorted anatomy of the entrance of left mainstem bronchus
  - External or intraluminal tumor compression
  - Descending thoracic aortic aneurysm
- Site of surgery involving the left mainstem bronchus
  - Left lung transplantation
  - Left-sided tracheobronchial disruption
  - Left-sided pneumonectomy†
  - Left-sided sleeve resection

*This is a common clinical practice pattern for using right-sided double-lumen tubes (DLTs) and assumes normal tracheobronchial anatomy, specifically a normal position of the orifice of the right upper lobe; however, some clinicians prefer to use right DLTs for all left-sided surgeries.

†It is possible to manage a left pneumonectomy with a left-sided DLT or bronchial blocker; however, the DLT or blocker will have to be withdrawn before stapling the left mainstem bronchus.

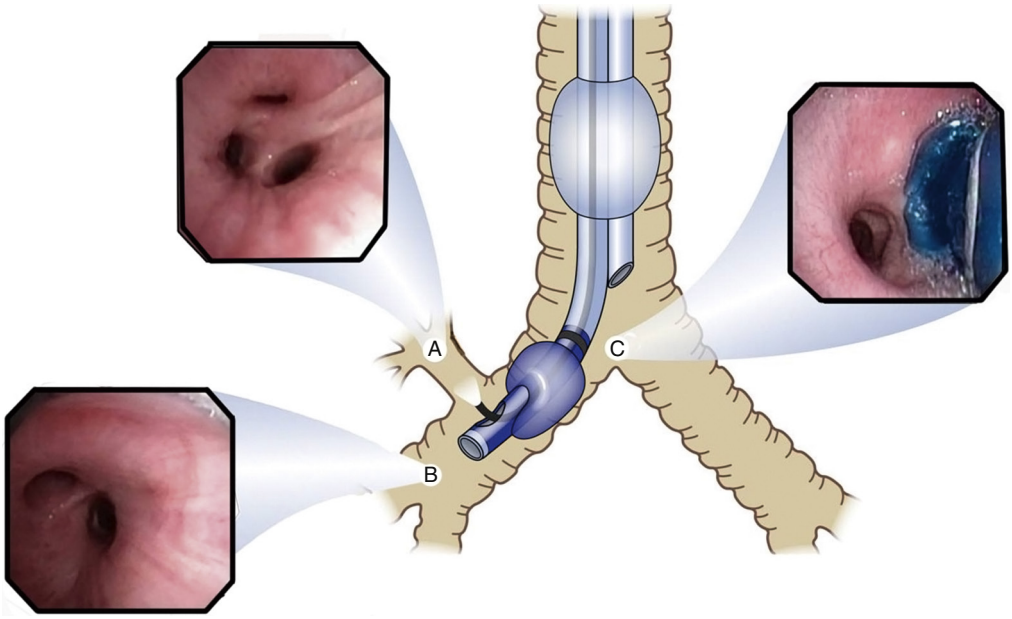


Figure 66-13. Fiberoptic bronchoscopic examination of a Rusch right-sided DLT. **A,** Slot of the bronchial lumen properly aligned within the entrance of the right upper lobe bronchus. **B,** Part of the bronchus intermedius when the bronchoscope is advanced through the distal portion of the bronchial lumen. **C,** The edge of the bronchial cuff at the entrance of the right mainstem bronchus when the bronchoscope is passed through the tracheal lumen. *(Reproduced with permission from Slinger P:* Principles and practice of anesthesia for thoracic surgery, *New York, Springer, 2011.)*

lobe bronchus. The right-sided DLT incorporates a modified cuff and slot on the endobronchial lumen that allows ventilation for the right upper lobe (Fig. 66-13).[81]

Positioning of Double-Lumen Tubes

Auscultation alone is unreliable for confirmation of proper DLT placement. Auscultation (Fig. 66-14) and bronchoscopy should both be used each time a DLT is placed and again when the patient is repositioned. Fiberoptic bronchoscopy is performed first through the tracheal lumen to ensure that the endobronchial portion of the DLT is in the left bronchus and that there is no bronchial cuff herniation over the carina after inflation. Through the tracheal view, the blue endobronchial cuff ideally should be seen approximately 5 mm below the tracheal carina in the left bronchus. It is crucial to identify the takeoff of the right upper lobe bronchus through the tracheal view. Going inside this right upper lobe with the bronchoscope should reveal three orifices (apical, anterior, posterior). This is the only structure in the tracheobronchial tree that has three orifices. In the supine patient, the takeoff of the right upper lobe is normally on the lateral wall of the right mainstem bronchus at the 3- to 4-o'clock position in relation to the main carina. Broncho-Cath tubes from Mallinckrodt (St. Louis, Mo) have a radiopaque line encircling the tube. This line is proximal to the bronchial cuff and can be useful while positioning a left-sided DLT. The radiopaque marker is 4 cm from the distal tip of the endobronchial lumen. This marker reflects white during fiberoptic visualization and, when positioned slightly above the tracheal carina, should provide the necessary margin of safety for positioning into the left mainstem bronchus.[82] The next observation with the fiberoptic bronchoscope is made through the endobronchial lumen to check for patency of the tube and determination of the margin of safety. The orifices of both the left upper and lower lobes must be identified to avoid distal impaction in the left lower lobe and occlusion of the left upper lobe (Fig. 66-15). Figure 66-16 displays the tracheobronchial anatomy along with fiberoptic bronchoscopy findings from the endotracheal or endobronchial lumen for a left-sided DLT.

Problems Related to Double-Lumen Tubes

The most common problems and complications associated with the use of a DLT are malpositioning and airway trauma. A malpositioned DLT will fail to allow collapse of the lung, causing gas trapping during positive-pressure ventilation, or it may partially collapse the ventilated or dependent lung, producing hypoxemia. A common cause of malpositioning is dislodgment of the endobronchial cuff because of overinflation, surgical manipulation of the bronchus, or extension of the head and neck during or after patient positioning. Fiberoptic bronchoscopy is the recommended method to diagnose and correct intraoperative malpositioning of DLTs, along with proper recognition of tracheobronchial anatomy. If a DLT is malpositioned with the patient in the supine or lateral decubitus position, there is a greater likelihood of hypoxemia during OLV. If a DLT is in the optimal position, but lung deflation is not completely achieved, a suction catheter should be passed to the side where lung collapse is supposed to occur. This suction will expedite lung deflation. The suction catheter must then be removed to avoid including it in a suture line.

Airway trauma and rupture of the membranous part of the trachea or the bronchus is a potential complication with the use of DLTs.[83] Airway trauma can occur from an oversized DLT or when an undersized DLT migrates distally into the lobar bronchus and the main (i.e., tracheal) body of the DLT comes into the bronchus, producing lacerations or rupture of the airway. Airway damage during the use of DLTs can present an unexpected air leak,

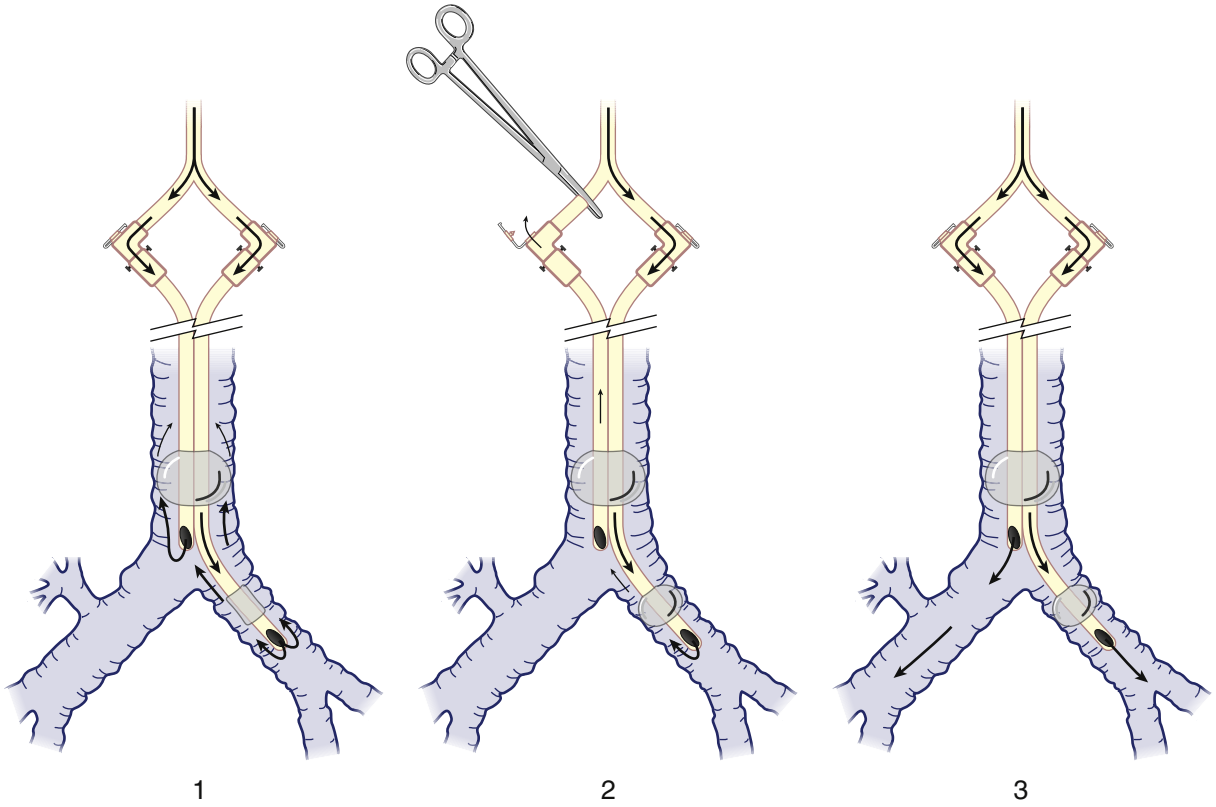


Figure 66-14. A "3-step" method to confirm position of a left DLT by auscultation. *Step 1,* During bilateral ventilation, the tracheal cuff is inflated to the minimal volume that seals the air leak at the glottis. Auscultate to confirm bilateral ventilation. *Step 2,* The tracheal lumen of the DLT is clamped proximally ("clamp the short side short") and the port distal to the clamp is opened. During ventilation via the bronchial lumen, the bronchial cuff is inflated to the minimal volume that seals the air leak from the open tracheal lumen port. Auscultate to confirm correct unilateral ventilation. *Step 3,* The tracheal lumen clamp is released and the port is closed. Auscultate to confirm resumption of bilateral breath sounds. *(From Youngberg, JA:* Cardiac, vascular, and thoracic anesthesia. *Philadelphia, Churchill Livingstone, 2000.)*

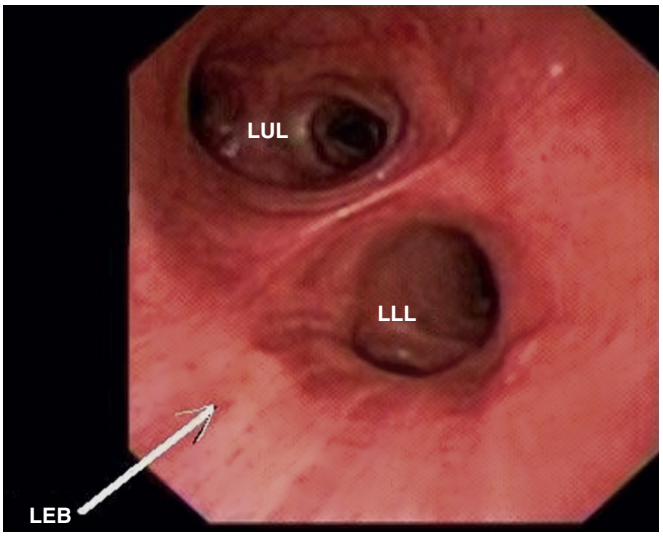


Figure 66-15. The view from the distal bronchial lumen of a well-positioned left-sided DLT. Both the orifices of the left upper lobe (LUL) and left lower lobe (LLL) can be identified. Note the longitudinal elastic bundles (LEB, *arrow*). These extend down the posterior membranous walls of the trachea and mainstem bronchi. They are useful landmarks to orient the bronchoscopist to anterior-posterior directions. In the left mainstem bronchus, they extend into the left lower lobe and are a useful landmark to distinguish the lower from the upper lobe.

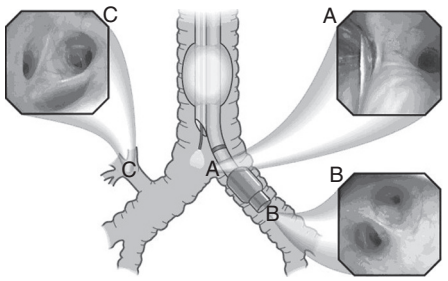


Figure 66-16. Fiberoptic bronchoscopic examination of a Mallinckrodt left-sided DLT. **A,** The edge of the endobronchial cuff around the entrance of the left mainstem bronchus when the bronchoscope is passed through the tracheal lumen. A white line marker is seen above the tracheal carina. **B,** A clear view of the bronchial bifurcation (left upper and left lower bronchi) when the left-sided DLT is in the optimal position and the fiberoptic bronchoscope is being advanced through the endobronchial lumen. **C,** Clear view of the right upper lobe bronchus and its three orifices: apical, anterior, and posterior segments. *(Reproduced with permission from Slinger P:* Principles and practice of anesthesia for thoracic surgery, *New York, Springer, 2011.)*

subcutaneous emphysema, massive airway bleeding into the lumen of the DLT, or protrusion of the endotracheal or endobronchial cuffs into the surgical field, with visualization of this by the surgeon. If any of the aforementioned problems occur, a bronchoscopic examination and surgical repair should be performed. Another potential problem is the development of a tension pneumothorax in the dependent, ventilated lung during OLV.[84]

BRONCHIAL BLOCKERS

An alternative method to achieve lung separation involves blockade of a mainstem bronchus to allow lung collapse distal to the occlusion (Fig. 66-17). Bronchial blockers also can be used selectively to achieve lobar collapse if necessary. Currently, there are several different bronchial blockers available to facilitate lung separation. These devices are either within a modified SLT as an enclosed bronchial blocker (Torque Control Blocker Univent; Vitaid, Lewinston, N.Y.) or are used independently with a conventional SLT, the Arndt wire-guided endobronchial blocker (Cook Critical Care, Bloomington, Ind), the Cohen tip-deflecting endobronchial blocker (Cook Critical Care), the Fuji Uniblocker (Vitaid), or the EZ Blocker (Teleflex, Dresden, Germany).

There are specific conditions in which a bronchial blocker may be preferred to a DLT, such as patients with previous oral or neck surgery who present with a challenging airway and require lung separation for intrathoracic surgery. In these cases, the use of an SLT during an awake nasotracheal or orotracheal intubation or via tracheostomy secures the airway, and thereafter an independent bronchial blocker can be placed to achieve lung separation. Another group of patients who may benefit from the use of bronchial blockers are cancer patients who have undergone a previous contralateral pulmonary resection. In such cases, selective lobar blockade with a bronchial blocker in the ipsilateral side improves oxygenation and facilitates surgical exposure. Blockers can be advanced over a guidewire placed with a fiberoptic bronchoscope into the required lobar bronchus. Bronchial blockers are most commonly used intraluminally (coaxially) with the SLT. The Cohen and Fuji Uniblockers can also be placed separately through the glottis or tracheostomy exterior to the SLT. This allows the use of a smaller SLT and is often an option in pediatrics. Another advantage of the bronchial blockers is when postoperative mechanical ventilation is being considered after prolonged thoracic or esophageal surgery. In many instances, these patients have an edematous upper airway at the end of the procedure. If a bronchial blocker is used, there is no need to change the SLT and there is no compromise of the airway if mechanical ventilation is needed in the postoperative period. Table 66-7 describes the characteristics of current

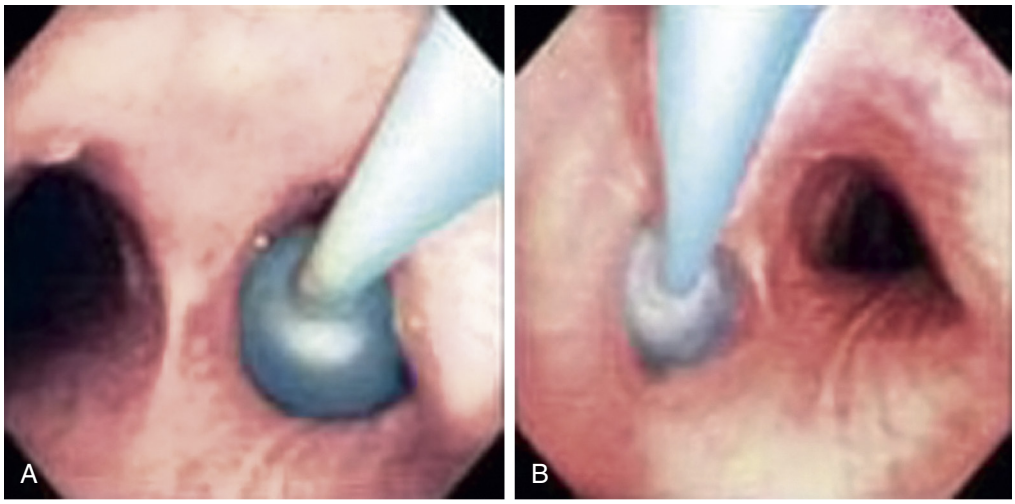


Figure 66-17. Placement of a bronchial blocker. Correct positioning of a blocker in the right **(A)** and left **(B)** mainstem bronchi as seen through a fiberoptic bronchoscope just above the carina in the trachea. *(Reproduced with permission from Slinger P: Principles and practice of anesthesia for thoracic surgery, New York, Springer, 2011.)*

TABLE 66-7 **CHARACTERISTICS OF THE COHEN, ARNDT, FUJI, AND EZ BRONCHIAL BLOCKERS**

	Cohen Blocker	Arndt Blocker	Fuji Uniblocker	EZ Blocker
Size	9 Fr	5 Fr, 7 Fr, 9 Fr	5 Fr, 9 Fr	7 Fr
Balloon shape	Spherical	Spherical or elliptical	Spherical	Spherical × 2
Guidance mechanism	Wheel device to deflect the tip	Nylon wire loop that is coupled with the fiberoptic bronchoscope	None, preshaped tip	None
Smallest recommended ETT for coaxial use	9 Fr (8.0 ETT)	5 Fr (4.5 ETT), 7 Fr (7.0 ETT), 9 Fr (8.0 ETT)	9 Fr (8.0 ETT)	7.5
Murphy eye	Present	Present in 9 Fr	Not present	No
Center channel	1.6 mm ID	1.4 mm ID	2.0 mm ID	1.4 mm ID

ETT, endotracheal tube; ID, internal diameter.
Modified with permission from Campos JH: Which device should be considered the best for lung isolation: double-lumen endotracheal tube versus bronchial blockers, Curr Opin Anaesthesiol *20:30,2007.*

bronchial blockers. The smallest internal diameter (ID) of an endotracheal tube that will allow passage of both a bronchial blocker and a fiberoptic bronchoscope depends on the diameters of the bronchoscope and blocker. For standard adult 9-Fr blockers, an endotracheal tube greater than or equal to 7.0 mm ID can be used with a bronchoscope less than 4.0 mm in diameter. Larger bronchoscopes will require an endotracheal tube greater than 7.5 mm ID. All blockers need to be well lubricated before placement.

Wire-Guided Endobronchial Blocker (Arndt Blocker)

Figure 66-18, *A*, displays the Arndt blockers. The Arndt blocker has a retractable loop that is placed over the fiberoptic bronchoscope, which is then used to guide the blocker into place. The Arndt blockers usually advance easily into the right mainstem bronchus without the loop. The original Arndt design was an elliptical blocker, but a spherical blocker is now available that may function better in the short, right mainstem bronchus.

Cohen Endobronchial Blocker

The Cohen blocker (see Fig. 66-18, *B*, *left*) uses a wheel located in the most proximal part of the unit that deflects the tip of the distal part of the blocker into the desired bronchus. This blocker has been preangled at the distal tip to facilitate insertion into a target bronchus. On the distal shaft above the balloon, there is an arrow that, when seen with the fiberoptic bronchoscope, indicates in which direction the tip deflects. To position the Cohen blocker, the arrow is aligned with the bronchus to be intubated, the proximal wheel is turned to deflect the tip toward the desired side, and then the blocker is advanced with fiberoptic guidance.

Fuji Uniblocker

The Fuji Uniblocker (see Fig. 66-18, *B*, *right*) is an independent blocker that is made of silicone material and has a simple, fixed distal hockey-stick (ice hockey) angulation to facilitate insertion. The blocker is simply rotated to the left or right as needed under fiberoptic bronchoscope guidance for placement in the required bronchus.

EZ Blocker

The EZ blocker is a recently introduced 7-Fr, 4-lumen catheter with a Y-shaped bifurcation. Each distal end has a balloon that can be guided into the right and left main bronchus. This device comes with its own multiport adapter and is used through an 8.0 SLT. The end of the Y sits in the tracheal carina. Each distal end is positioned into the right and left bronchus, and the bronchial balloon is inflated in the operative side for lung isolation.

Complications Related to the Bronchial Blockers

Failure to achieve lung separation because of abnormal anatomy or lack of a seal within the bronchus has been reported.[85] Inclusion of the bronchial blocker or the distal wire loop of an Arndt blocker into the stapling line has been reported during a lobectomy[86] and required surgical reexploration after unsuccessful removal of the bronchial blocker after extubation. To avoid these mishaps, communication with the surgical team regarding the presence of a bronchial blocker in the surgical side is crucial. Clearly, the bronchial blocker needs to be withdrawn a few centimeters before stapling.

Another potentially dangerous complication with all bronchial blockers is that the inflated balloon can move and lodge above the carina or be accidentally inflated in the trachea. This leads to an inability to ventilate and possibly the development of hypoxia and potentially cardiorespiratory arrest unless quickly recognized and the blocker deflated.[87] There is a report of more malpositions with the use of bronchial blockers when compared with DLTs.[88]

DIFFICULT AIRWAYS AND ONE-LUNG VENTILATION

Some patients requiring OLV are identified during preoperative evaluation to have a potentially difficult airway. Others present with unexpected difficulty to intubate after induction of anesthesia. Between 5% and 8% of patients with primary lung carcinoma also have a carcinoma of the pharynx, usually in the epiglottic area.[89]

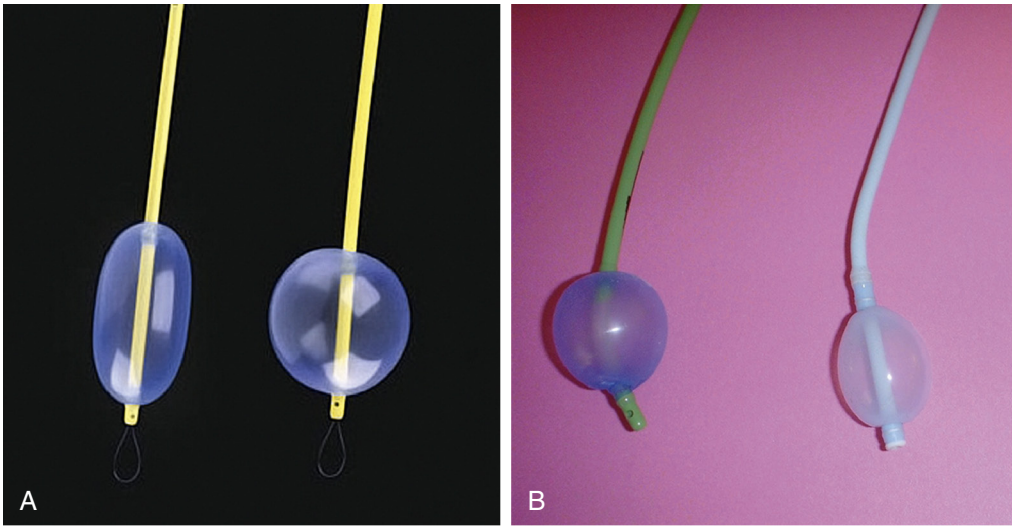


Figure 66-18. A, The original elliptical *(left)* and the newer spherical *(right)* Arndt designs of bronchial blocker (Cook Critical Care, Bloomington, Ind) (see text for details). **B,** The Cohen *(left)* (Cook Critical Care) and Fuji Uniblocker *(right)* (Vitaid, Lewinston, NY) bronchial blockers.

Many of these patients have had previous radiation therapy on the neck or previous airway surgery, such as hemimandibulectomy or hemiglossectomy, making intubation and achievement of OLV difficult because of distorted upper airway anatomy. In addition, a patient who requires OLV may have distorted anatomy at or beyond the tracheal carina, such as a descending thoracic aortic aneurysm compressing the entrance of the left mainstem bronchus or an intraluminal or extraluminal tumor near the tracheobronchial bifurcation that makes the insertion of a left-sided DLT relatively difficult or impossible. Such anomalies can be detected by reviewing the chest radiographs and CT scans of the chest. A flexible fiberoptic bronchoscopic examination is necessary to assess a distorted area of the airway before selection of a specific tube or blocker to achieve OLV.

In patients who require OLV and present with a difficult airway, the primary goal is to establish an airway with an SLT placed orally with the aid of a flexible fiberoptic bronchoscope, after appropriate airway anesthesia is achieved. In selected patients who seem easy to ventilate, this may be performed after induction of anesthesia with a bronchoscope or with a videolaryngoscope.[90] Once the SLT is in place, an independent bronchial blocker can be passed. If the patient requires OLV and cannot be intubated orally, an awake nasotracheal intubation can be performed with an SLT and, once the airway is established, then a bronchial blocker can be used.

An alternative to achieve OLV in a patient with a difficult airway is to intubate the patient's trachea with an SLT; then a DLT-SLT tube-exchange catheter can be used to replace the existing SLT with a DLT after general anesthesia is induced. For a DLT, the exchange catheter should be at least 83 cm. A 14-Fr exchange catheter can be used for 41-Fr and 39-Fr DLTs; for 37-Fr or 35-Fr DLTs, an 11-Fr exchange catheter is used. Specially designed exchange catheters for DLTs are available with a softer distal tip to try to decrease the risk of distal airway trauma (e.g., Cook Exchange Catheter, Cook Critical Care).

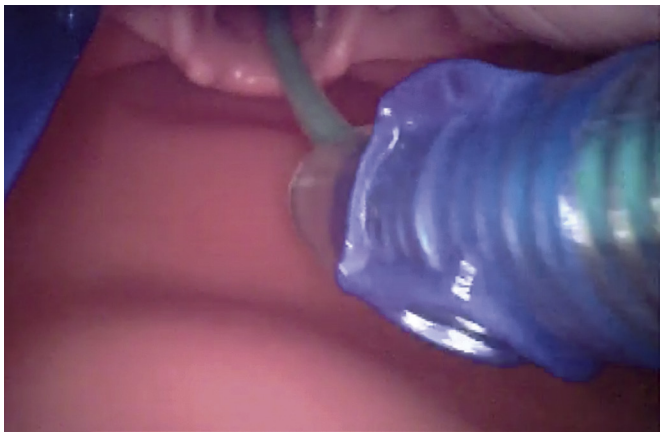


Figure 66-19. A DLT is placed over a tube-exchange catheter using a video laryngoscope for guidance. The green SLT-DLT tube-exchange catheter (Cook Critical Care, Bloomington, Ind) was passed initially through the SLT, which has been withdrawn (before the photo was taken) and the catheter then passed retrograde through the bronchial lumen of a DLT, which is advanced under direct vision through the glottis. The DLT in this picture (Fuji, Phycon, Vitaid, Lewinston, NY) has a bevel on the distal bronchial orifice and a flexible bronchial lumen that facilitates this procedure.

The exchange catheter, SLT, and the DLT combination should be tested in vitro before the exchange. A sniffing position facilitates tube exchange. After the exchange catheter is lubricated, it is advanced through the SLT. The catheter should not be inserted deeper than 24 cm at the lips to avoid accidental rupture or laceration of the trachea or bronchi. After cuff deflation, the SLT is withdrawn. Then the endobronchial lumen of the DLT is advanced over the exchange catheter. It is optimal to use a videolaryngoscope during the tube exchange to guide the DLT through the glottis under direct vision (Fig. 66-19). If a videolaryngoscope is not available, having an assistant perform standard laryngoscopy during tube exchange partially straightens out the alignment of the oropharynx and glottis and facilitates the exchange. Proper final position of the DLT is then achieved with auscultation and bronchoscopy.

LUNG ISOLATION TECHNIQUES IN PATIENTS WITH A TRACHEOSTOMY IN PLACE

Placement of a DLT through a tracheostomy stoma may be prone to malpositioning because the upper airway has been shortened and the conventional DLT may be too long. Before placing any lung isolation devices through a tracheostomy stoma, it is important to consider whether it is a fresh stoma (i.e., a few days old, when the airway can be lost immediately on decannulation) versus a chronic tracheostomy. The alternatives to achieve OLV in a tracheostomized patient include (1) insertion of an SLT followed by an independent bronchial blocker passed coaxially or external to the SLT[91]; (2) the use of a disposable cuffed tracheostomy cannula with an independent bronchial blocker; (3) replacement of the tracheostomy cannula with a specially designed short DLT such as the Naruke DLT, which is made for use in tracheostomized patients[92]; (4) placement of a small DLT through the tracheostomy stoma; or (5) if possible, oral access to the airway for standard placement of a DLT or blocker (this is occasionally an option in patients on prolonged mechanical ventilation for respiratory failure or postoperative complications).

In summary, the optimal method of lung isolation depends on a number of factors, including the patient's airway anatomy, the indication for lung isolation, the available equipment, and the training of the anesthesiologist. Suggested methods for lung isolation in specific clinical situations are listed in Table 66-8. Whichever method of lung isolation is used, the "ABCs" of lung isolation are:

Anatomy: Know the tracheobronchial anatomy. One of the major problems that many anesthesiologists have in achieving satisfactory lung isolation is a lack of familiarity with distal airway anatomy (Fig. 66-20).

Bronchoscopy: Whenever possible, use a fiberoptic bronchoscope to position endobronchial tubes and blockers. The ability to perform fiberoptic bronchoscopy is now a fundamental skill needed by all anesthesiologists

TABLE 66-8 SUGGESTED METHODS OF LUNG ISOLATION FOR SPECIFIC INDICATIONS

Indication for Lung Isolation	Preferred Methods	Possible Alternatives
Pulmonary resection right side	Left DLT	BB/Left EBT
Pulmonary resection left side		
Pneumonectomy unlikely	Left DLT	BB/Right DLT
Pneumonectomy	Right DLT	Left DLT/BB
Thoracoscopy (either side)	Left DLT	BB/Right DLT
Pulmonary hemorrhage	Left DLT	BB/contralateral EBT
Bronchopleural fistula		
Left mainstem bronchus	Right DLT	EBT
All other sites	Left DLT	Right DLT/BB/EBT
Purulent secretions (e.g., abscess, cyst)	Left DLT	Right DLT/BB/EBT
Bullae, blebs	Left DLT	Right DLT/BB
Nonpulmonary surgery (e.g., thoracic aorta, esophagus)	Left DLT/ BB	Right DLT/EBT
Bronchial surgery (e.g., tumor, trauma)		
Left side	Right DLT	EBT
Right side	Left DLT	EBT
Upper airway abnormalities	BB	Left DLT/EBT
Lung transplantation		
Bilateral	Left DLT	BB/EBT
Single right lung	Left DLT	BB/EBT
Single left lung	Right DLT	BB/Left DLT/EBT
Whole lung lavage	Left DLT	—
Independent lung ventilation	Left DLT	Right DLT

DLT, Double-lumen tube; *BB*, ipsilateral bronchial blocker; *EBT*, contralateral single-lumen endobronchial tube.

providing anesthesia for thoracic surgery. An online bronchoscopy simulator has been developed to help train anesthesiologists in positioning DLTs and blockers. This simulator, which uses real-time video, is available without cost at www.thoracicanesthesia.com.

Chest imaging: The anesthesiologist should always consult the chest imaging before placement of a DLT or blocker. Abnormalities of the lower airway can often be identified in advance, and this will affect the selection of the optimal method of lung isolation for a specific case (see Figs. 66-7 and 66-10).

POSITIONING

The majority of thoracic procedures are performed in the lateral position, most often the lateral decubitus position, but depending on the surgical technique, a supine, semisupine, or semiprone lateral position may be used. These lateral positions have specific implications for the anesthesiologist.

Position Change (See Chapter 41)

It is awkward to induce anesthesia with the patient in the lateral position. Thus monitors will be placed and anesthesia will usually be induced in the supine position and the anesthetized patient will then be repositioned for surgery. It is possible to induce anesthesia in the lateral position, and this may rarely be indicated with unilateral lung diseases such as bronchiectasis or hemoptysis until lung isolation can be achieved. However, even these patients will then have to be repositioned and the diseased lung turned to the nondependent side.

Because of the loss of venous vascular tone in the anesthetized patient, it is not uncommon to observe hypotension in the patient when turning them to or from the

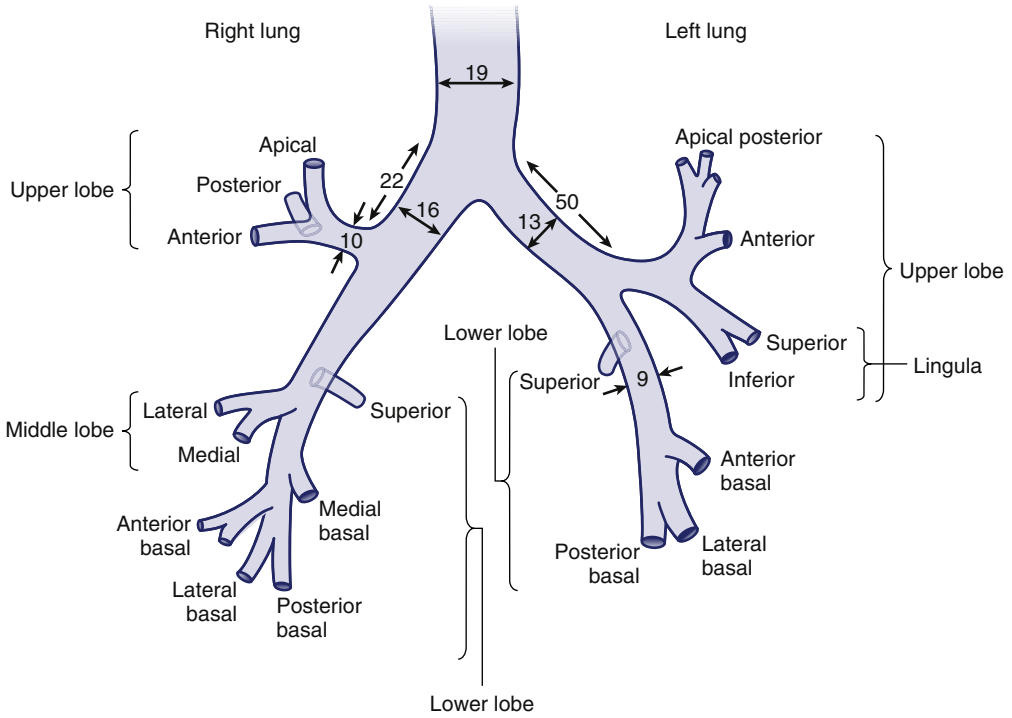


Figure 66-20. Diagram of the tracheobronchial tree. Mean lengths and diameters are shown in millimeters. Note that the right middle lobe bronchus exits directly anteriorly and the superior segments (some authors refer to these as the "apical" segments) of the lower lobes exit directly posteriorly. Using the apical designation, on the right side the segmental bronchi in a rostral to caudal sequence give the mnemonic "A PALM A MAPL." *(From Youngberg, JA:* Cardiac, vascular, and thoracic anesthesia. *Philadelphia, Churchill Livingstone, 2000.)*

lateral position. All lines and monitors will have to be secured during positioning changes and their function reassessed after repositioning. The anesthesiologist should take responsibility for the head, neck, and airway during position changes and must be in charge of the operating team to direct repositioning. It is useful to make an initial "head-to-toe" survey of the patient after induction and intubation to check oxygenation, ventilation, hemodynamics, lines, monitors, and potential nerve injuries. This survey then must be repeated after repositioning. It is nearly impossible to avoid some movement of a DLT or bronchial blocker during repositioning. Certainly the patient's head, neck, and endobronchial tube should be turned "en-bloc" with the patient's thoracolumbar spine. However, the margin of error in positioning endobronchial tubes or blockers is often so narrow that even very small movements can have significant clinical implications. The carina and mediastinum may shift independently with repositioning and this can lead to proximal misplacement of a previously well-positioned tube. Endobronchial tube/blocker position and the adequacy of ventilation must be rechecked by auscultation and fiberoptic bronchoscopy after patient repositioning.

Neurovascular Complications

There are a specific set of nerve and vascular injuries related to the lateral position that must be appreciated. The brachial plexus is the site of the majority of intraoperative nerve injuries related to the lateral position.[93] These are basically of two varieties: the majority are compression injuries of the brachial plexus of the dependent arm, but there is also a significant risk of stretch injuries to the brachial plexus of the nondependent arm. The brachial plexus is fixed at two points: proximally by the transverse process of the cervical vertebrae and distally by the axillary fascia. This two-point fixation, plus the extreme mobility of neighboring skeletal and muscular structures, makes the brachial plexus extremely liable to injury (Box 66-6). The patient should be positioned with padding under the dependent thorax (Fig. 66-21) to keep the weight of the upper body off the dependent arm brachial plexus. However, this padding will exacerbate the pressure on the brachial plexus if it migrates superiorly into the axilla.

BOX 66-6 ***Factors That Contribute to Brachial Plexus Injury in the Lateral Position***

- Dependent arm (compression injuries)
  - Arm directly under thorax
  - Pressure on clavicle into retroclavicular space
  - Cervical rib
  - Cranial migration of thorax padding into the axilla*
- Nondependent arm (stretch injuries)
  - Lateral flexion of cervical spine
  - Excessive abduction of arm (>90 degrees)
  - Semiprone or semisupine repositioning after arm fixed to a support

*Unfortunately, this padding under the thorax is misnamed an "axillary roll" in some institutions. This padding absolutely should *not* be placed in the axilla.

The arms should not be abducted beyond 90 degrees and should not be extended posteriorly beyond the neutral position nor flexed anteriorly more than 90 degrees. Fortunately, the majority of these nerve injuries resolve spontaneously over a period of months. Anterior flexion of the arm at the shoulder (circumduction) across the chest or lateral flexion of the neck toward the opposite side can cause a traction injury of the suprascapular nerve.[94] This causes a deep, poorly circumscribed pain of posterior and lateral aspects of the shoulder and may be responsible for some cases of postthoracotomy shoulder pain.

It is very easy, after repositioning the patient in the lateral decubitus position, to cause excessive lateral flexion of the cervical spine because of improper positioning of the patient's head. This malpositioning, which exacerbates brachial plexus traction, can cause a "whiplash" syndrome and can be difficult to appreciate from the head of the operating table, particularly after the surgical drapes have been placed. It is useful for the anesthesiologist to survey the patient from the side of the table immediately after turning to ensure that the entire vertebral column is aligned properly.

The dependent leg should be slightly flexed with padding under the knee to protect the peroneal nerve lateral to the proximal head of the fibula. The nondependent leg is placed in a neutral extended position and padding placed between it and the dependent leg. The dependent leg must be observed for vascular compression. Excessively tight strapping at the hip level can compress the sciatic nerve of the nondependent leg. Other sites particularly liable for neurovascular injury in the lateral position are the dependent ear pinna and eye. A head-to-toe protocol to monitor for possible neurovascular injuries related to the lateral decubitus position is presented in Box 66-7.



Figure 66-21. Typical positioning of a patient in the lateral decubitus position for thoracotomy seen from the side. It is useful for the anesthesiologist to survey the anesthetized patient from this perspective before draping to ensure that there is no lateral flexion of the cervical spine, which can be very difficult to appreciate from the head of the operating table. Note also the padding of the dependent thorax and the nondependent leg. *(From Youngberg, JA:* Cardiac, vascular, and thoracic anesthesia. *Philadelphia, Churchill Livingstone, 2000.)*

Physiologic Changes in the Lateral Position (See Chapter 41)

Ventilation. Significant changes in ventilation develop between the lungs when the patient is placed in the lateral position.[95] The compliance curves of the two lungs are different because of their difference in sizes. The lateral position, anesthesia, paralysis, and opening of the thorax all combine to magnify these differences between the lungs (Fig. 66-22). The compliance curve (change in volume versus change in pressure) of a lung depends on the balance of two "springs": the chest wall (normally distending the lung) and the elastic recoil of the lung itself. Any factor that changes the mechanics of either of these springs places the lung on a different compliance curve.[96]

In a healthy, conscious, spontaneously breathing patient, the ventilation of the dependent lung increases approximately 10% when the patient is turned to the lateral position. Once the patient is anesthetized and paralyzed, the ventilation of the dependent lung then decreases by 15%. Although the ventilation does not change significantly once the nondependent hemithorax is open, the FRC of this nondependent lung tends to increase by approximately 10%. These changes depend on the method used for ventilation in the individual patient. When the chest is open, because of disruption of the chest wall, both lungs tend to collapse to a minimal lung volume if expiration is prolonged. Thus the end-expiratory volume of each lung is directly a function of the time allowed for expiration. The compliance of the entire respiratory system increases significantly once the nondependent hemithorax is open.

Because of the fall in FRC and compliance of the nondependent lung in the lateral position, application of PEEP selectively to this lung only (using a DLT and two anesthetic circuits) will improve gas exchange.[97] This is different from the effect of nonselectively applying PEEP to both lungs in the lateral position, where PEEP tends to preferentially distribute to the most compliant lung regions and will tend to hyperinflate the nondependent lung without causing any improvement in gas exchange.[98]

Atelectasis will develop in an average of 6% of the lung parenchyma after induction of anesthesia in the supine position. This atelectasis will be evenly distributed in the dependent portions of both lungs.[99] By turning the patient to the lateral position, there will be a slight decrease of total atelectasis to 5% of lung volume, but this will now be concentrated totally in the dependent lung.

Perfusion. Gravity has some effect on distribution of pulmonary blood flow. In the lateral position, the blood flow to the dependent lung is generally thought to be increased by 10% compared with the same lung in the supine position.[100] However, the distribution of pulmonary blood flow in various positions may be related more to inherent pulmonary vascular anatomy than to gravity (Fig. 66-23).[101] The matching of ventilation and perfusion will usually be decreased in the lateral position compared with the supine position during anesthesia. Pulmonary arteriovenous shunt during general anesthesia will usually increase from approximately 5% in the supine position to 10% to 15% in the lateral position.[102]

BOX 66-7 ***Neurovascular Injuries Specific to the Lateral Position: Routine "Head-to-Toe" Survey***

- Dependent eye
- Dependent ear pinna
- Cervical spine in line with thoracic spine
- Dependent arm: (a) brachial plexus, (b) circulation
- Nondependent arm: (a) brachial plexus, (b) circulation*
- Dependent and nondependent suprascapular nerves
- Nondependent leg sciatic nerve
- Dependent leg: (a) peroneal nerve, (b) circulation

*Neurovascular injuries of the nondependent arm are more likely to occur if the arm is suspended or held in an independently positioned arm rest.

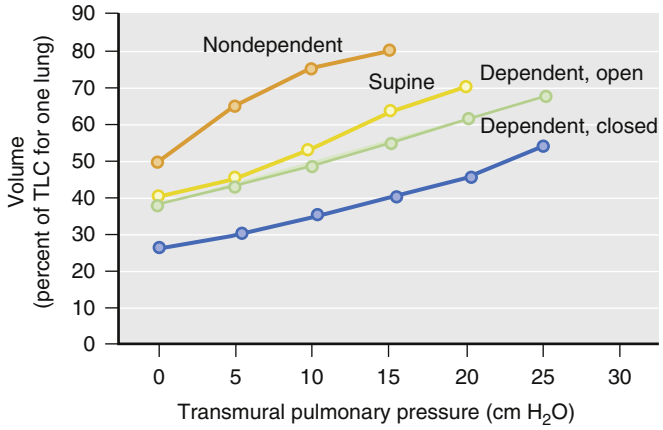


Figure 66-22. Changes in the compliance of a single lung during position changes in an anesthetized, paralyzed patient during controlled mechanical ventilation. These compliance changes are responsible for the resulting differences in ventilation between the lungs that occur in the lateral position. The compliance of the dependent lung is increased when the nondependent hemithorax is open versus closed.

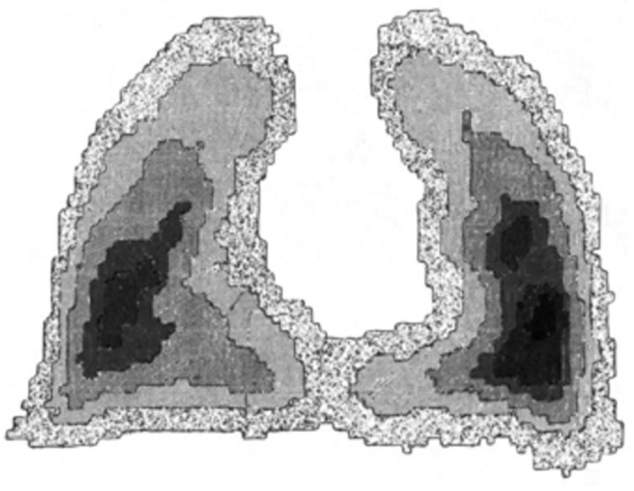


Figure 66-23. In vivo perfusion lung scanning in the upright position demonstrates a predominant central to peripheral distribution of pulmonary blood flow in addition to a gravitational effect that also increases the blood flow in dependent lung regions. *(From Youngberg, JA:* Cardiac, vascular, and thoracic anesthesia. *Philadelphia, Churchill Livingstone, 2000.)*

ANESTHETIC MANAGEMENT

The development of thoracic anesthesia and thoracic surgery was delayed more than 50 years after the introduction of ether because anesthesiologists could not manage patients during mask anesthesia with spontaneous ventilation and an open chest. These patients developed what was originally called the "pneumothorax syndrome."[103] The respiratory systems of mammals do not function adequately with an open hemithorax because of two physiologic problems. The first is paradoxical ventilation (also called *pendelluft*), in which gas moves into the open-chest lung from the intact lung during expiration and then reverses flow during inspiration. This leads to hypercapnia and hypoxemia. The second is caused by the swinging motion of the mediastinum between the hemithoraces during the respiratory cycle, which interferes with cardiac preload and causes hemodynamic instability. In the early 1900s, several pioneers, such as the New Orleans surgeon Matas, advocated positive-pressure ventilation and a primitive form of endotracheal ventilation, which had been demonstrated to be safe in animal experiments, for thoracic anesthesia. Modern methods incorporating OLV have evolved from this. Essentially, any anesthetic technique that provides safe and stable general anesthesia for major surgery can and has been used for lung resection.

FLUID MANAGEMENT

Because of hydrostatic effects, excessive administration of intravenous fluids can cause increased shunting and subsequently lead to pulmonary edema of the dependent lung, particularly during prolonged surgery.[104] Because the dependent lung is the lung that must carry on gas exchange during OLV, it is best to be as judicious as possible with fluid administration. Intravenous fluids are administered to replace volume deficits and for maintenance only during lung resection anesthesia. No volume is given for "third space" losses (Box 66-8). It is possible that there is no "third space."[105]

TEMPERATURE (See Chapter 54)

Maintenance of body temperature can be a problem during thoracic surgery because of heat loss from the open hemithorax. This is particularly a problem at the extremes of the age spectrum. Most of the body's physiologic functions, including HPV, are inhibited during hypothermia. Increasing the ambient room temperature, fluid warmers and the use of lower and/or upper body forced-air patient warmers are the best methods to prevent inadvertent intraoperative hypothermia.

BOX 66-8 ***Fluid Management for Pulmonary Resection Surgery***

- Total positive fluid balance in the first 24-hour perioperative period should not exceed 20 mL/kg.
- For an average adult patient, crystalloid administration should be limited to less than 3 L in the first 24 hours.
- No fluid administration for third-space fluid losses during pulmonary resection
- Urine output greater than 0.5 mL/kg/h is unnecessary.
- If increased tissue perfusion is needed postoperatively, it is preferable to use invasive monitoring and inotropes rather than to cause fluid overload.

PREVENTION OF BRONCHOSPASM

Because of the frequent incidence of coexisting reactive airways disease in the thoracic surgical population, an anesthetic technique that decreases bronchial irritability should be chosen. This is particularly important because the added airway manipulation caused by placement of a DLT or bronchial blocker is a potent trigger for bronchoconstriction. The principles of anesthetic management are the same as they are for any asthmatic patient: avoid manipulation of the airway in a lightly anesthetized patient, use bronchodilating anesthetics, and avoid drugs that release histamine. For intravenous induction of anesthesia, either propofol or ketamine can be expected to diminish bronchospasm. This benefit will not be seen with barbiturate, opioid, benzodiazepine, or etomidate intravenous induction of anesthesia. For maintenance of anesthesia, propofol and/or any of the volatile anesthetics will diminish bronchial reactivity. Sevoflurane may be the most potent bronchodilator of the volatile anesthetics.[106]

CORONARY ARTERY DISEASE (See Chapter 47)

Because the lung resection population is largely elderly and/or smokers, there is a high coincidence of coronary artery disease. This consideration will be a major factor in the choice of the anesthetic technique for most thoracic patients. The anesthetic technique should optimize the myocardial oxygen supply/demand ratio by maintaining arterial oxygenation and diastolic blood pressure while avoiding unnecessary increases in cardiac output and heart rate. Thoracic epidural anesthesia/analgesia may aid in this (see Postoperative Analgesia later in this chapter).

The ability to provide effective regional anesthesia with thoracic epidural blockade has opened the possibility of performing some thoracic surgical procedures in awake patients. A wide variety of thoracic operations have been reported using this technique, including thoracoscopy, thoracotomy, and sternotomy.[107] Epidural block is often combined with ipsilateral stellate ganglion block to decrease the cough reflex from stimulation of the hilum. The specific indications to use these techniques do not arise commonly but may occur in severely compromised patients with airway management issues.[108] Obviously the original concerns with the pneumothorax syndrome apply to prolonged surgery with these techniques. However, during VATS, the operative hemithorax is effectively closed and gas exchange is usually adequate during spontaneous ventilation with supplemental oxygen.

MANAGEMENT OF ONE-LUNG VENTILATION

During OLV, the anesthesiologist has the unique and often conflicting goals of trying to maximize atelectasis in the nonventilated lung to improve surgical access while

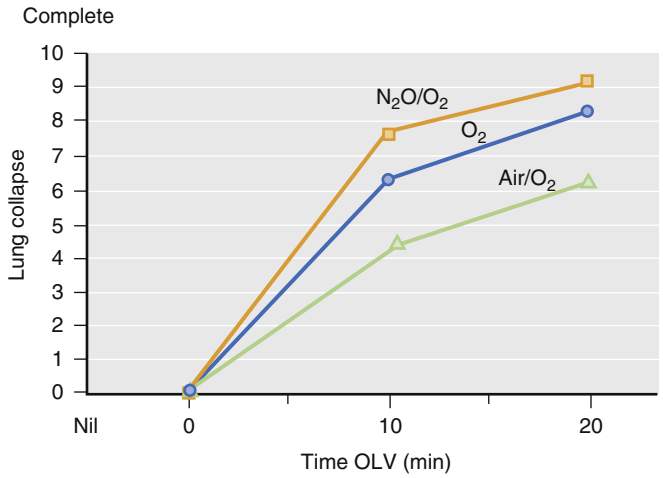


Figure 66-24. The effects of the gas mixture used during two-lung ventilation (TLV), immediately before one-lung ventilation (OLV), on the speed of collapse of the nonventilated lung during OLV. O_2 = FiO_2 1.0; N_2O/O_2 = nitrous oxide/oxygen 60/40; air/O_2 = air/oxygen FiO_2 0.4. All patients were ventilated with an FiO_2 of 1.0 during OLV. The poorly soluble nitrogen in the air/oxygen mixture delays collapse of the nonventilated lung. *(Based on data from Unzueta C, Tusman G, Suarez-Sipman F, et al: Alveolar recruitment improves ventilation during thoracic surgery: a randomized controlled trial,* Br J Anaesth *108: 517, 2012.)*

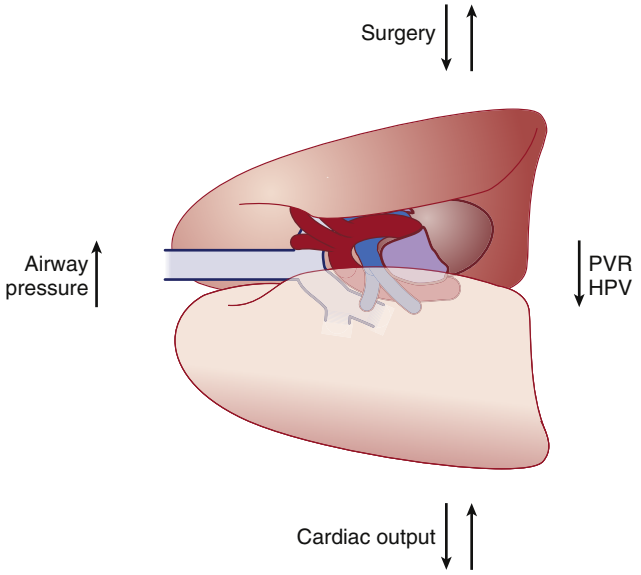


Figure 66-25. Factors affecting the distribution of pulmonary blood flow during OLV. Hypoxic pulmonary vasoconstriction (HPV) and the collapse of the nonventilated lung, which increases pulmonary vascular resistance (PVR), tend to distribute blood flow toward the ventilated lung. The airway pressure gradient between the ventilated and nonventilated thoraces tends to encourage blood flow to the nonventilated lung. Surgery and cardiac output can have variable effects, either increasing or decreasing the proportional flow to the ventilated lung.

trying to avoid atelectasis in the ventilated lung (usually the dependent lung) to optimize gas exchange. The gas mixture in the nonventilated lung immediately before OLV has a significant effect on the speed of collapse of this lung. Because of its low blood-gas solubility, nitrogen (or an air-oxygen mixture) will delay collapse of this lung (Fig. 66-24).[109] This is particularly a problem at the start of VATS surgery when surgical visualization in the operative hemithorax is limited, and in patients with emphysema who have delayed collapse of the nonventilated lung because of decreased lung elastic recoil. It is important to thoroughly de-nitrogenate the operative lung, by ventilating with oxygen, immediately before it is allowed to collapse. Although nitrous oxide is even more effective than oxygen in speeding lung collapse, for the reasons just cited it is not commonly used in thoracic anesthesia because many patients may have blebs or bullae.

Also, during the period of two-lung anesthesia before the start of OLV, atelectasis will develop in the dependent lung. It is useful to perform a recruitment maneuver to the dependent lung (similar to a Valsalva maneuver, holding the lung at an end-inspiratory pressure of 20 cm H_2O for 15 to 20 seconds) immediately after the start of OLV to decrease this atelectasis. Recruitment is important to maintain PaO_2 levels during subsequent OLV.[110]

HYPOXEMIA

A major concern that influences anesthetic management for thoracic surgery is the occurrence of hypoxemia during OLV. There is no universally acceptable figure for the safest lower limit of oxygen saturation during OLV. A saturation greater than or equal to 90% (PaO_2 >60 mm Hg) is commonly accepted, and for brief periods a saturation in the high 80s may be acceptable in patients without significant comorbidity. However, the lowest acceptable saturation will be higher in patients with organs at risk of hypoxia because of limited regional blood flow (e.g., coronary or cerebrovascular disease) and in patients with limited oxygen transport (e.g., anemia or decreased cardiopulmonary reserve). It has been shown that during OLV, patients with COPD desaturate more quickly during isovolemic hemodilution than normal patients.[111]

Previously, hypoxemia occurred frequently during OLV. Reports for the period between 1950 and 1980 describe an incidence of hypoxemia (arterial saturation <90%) of 20% to 25%.[112] Current reports describe an incidence of less than 5%.[113] This improvement is most likely a result of several factors: improved lung isolation techniques such as routine fiberoscopy to prevent lobar obstruction from DLTs, improved anesthetic agents that cause less inhibition of HPV, and better understanding of the pathophysiology of OLV. The pathophysiology of OLV involves the body's ability to redistribute pulmonary blood flow to the ventilated lung. Several factors aid and impede this redistribution and these are under the control of the anesthesiologist to a variable degree. These factors are illustrated in Figure 66-25. The anesthesiologist's goal during OLV is to maximize pulmonary vascular resistance (PVR) in the nonventilated lung while minimizing PVR in the ventilated lung. The key to understanding this physiology is the appreciation that PVR is correlated with lung volume in a hyperbolic fashion (Fig. 66-26). PVR is lowest at FRC and increases as lung volume rises or falls above or below FRC.[114] The anesthesiologist's aim, to optimize pulmonary blood flow redistribution during OLV, is to maintain the ventilated lung as close as possible to its FRC while facilitating collapse of the nonventilated lung to increase its PVR.

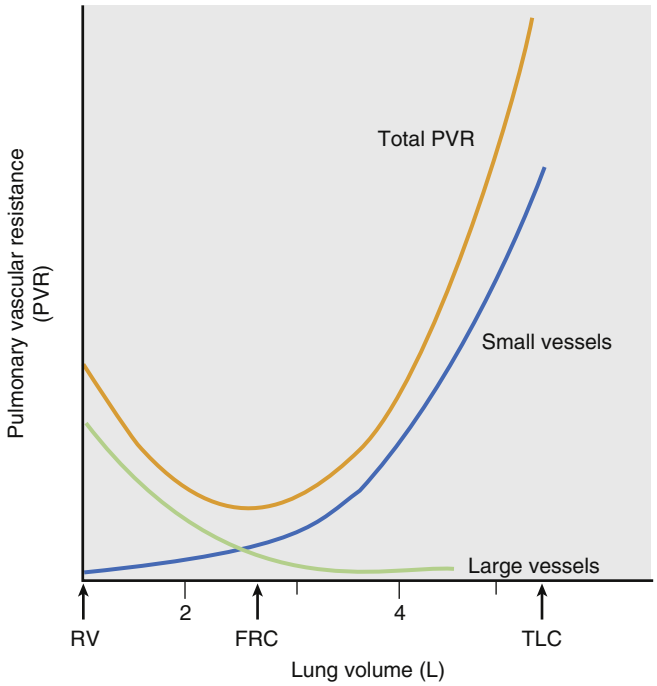


Figure 66-26. The relationship between PVR and lung volume. PVR is lowest at functional residual capacity (FRC) and increases as the lung volume decreases toward residual volume (RV), caused primarily by an increase in the resistance of large pulmonary vessels. PVR also increases as lung volume increases above FRC toward total lung capacity (TLC) as a result of an increase in the resistance of small interalveolar lung vessels.

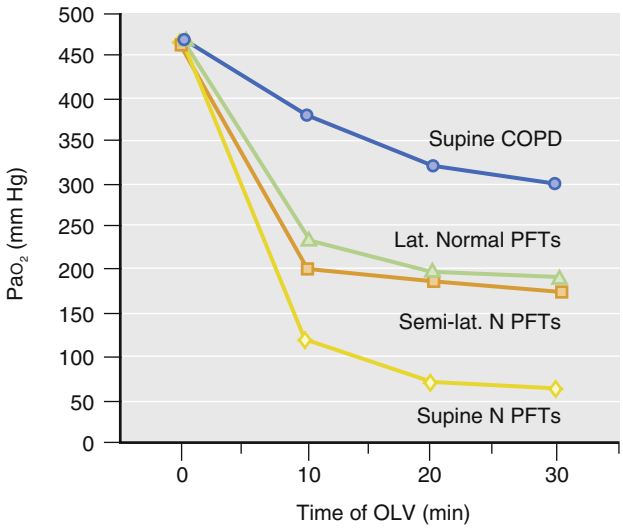


Figure 66-27. Mean PaO_2 in groups of patients versus time of OLV. Supine COPD = patients with COPD having OLV in the supine position. Lat. Normal PFTs = patients with normal pulmonary function having OLV in the lateral position. Semi-lat. N PFTs = patients with normal pulmonary function having OLV in the semilateral position. Supine N PFTs = patients with normal pulmonary function having OLV in the supine position. Patients with normal pulmonary function having OLV in the supine position are the most likely to desaturate. *(Based on data from Bardoczky GI, Szegedi LL, d'Hollander AA, et al: Two-lung and one-lung ventilation in patients with chronic lung disease: the effects of position and FiO2,* Anesth Analg *90:35, 2000; Eisenkraft JB: Effects of anaesthetics on the pulmonary circulation,* Brit J Anaesth *65:63, 1990.)*

INTRAOPERATIVE POSITION
(See Chapter 41)

Most thoracic surgery is performed with patients in the lateral position. Patients having OLV in the lateral position have significantly better PaO_2 levels than patients during OLV in the supine position.[115] This applies both to patients with normal lung function and to those with COPD (Fig. 66-27).[116]

HYPOXIC PULMONARY VASOCONSTRICTION

HPV is thought to be able to decrease the blood flow to the nonventilated lung by 50%.[117] The stimulus for HPV is primarily the alveolar oxygen tension (PAO_2), which stimulates precapillary vasoconstriction, redistributing pulmonary blood flow away from hypoxemic lung regions via a pathway involving nitric oxide and/or cyclooxygenase synthesis inhibition.[118] The mixed venous PO_2 (PVo_2) is also a stimulus, although considerably weaker than PAO_2. HPV has a biphasic temporal response to alveolar hypoxia. The rapid-onset phase begins immediately and reaches a plateau by 20 to 30 minutes. The second (delayed) phase begins after 40 minutes and plateaus after 2 hours (Fig. 66-28).[119] The offset of HPV is also biphasic, and pulmonary vascular resistance may not return to baseline for several hours after a prolonged period of OLV. This may contribute to increased desaturation during the collapse of the second lung during bilateral

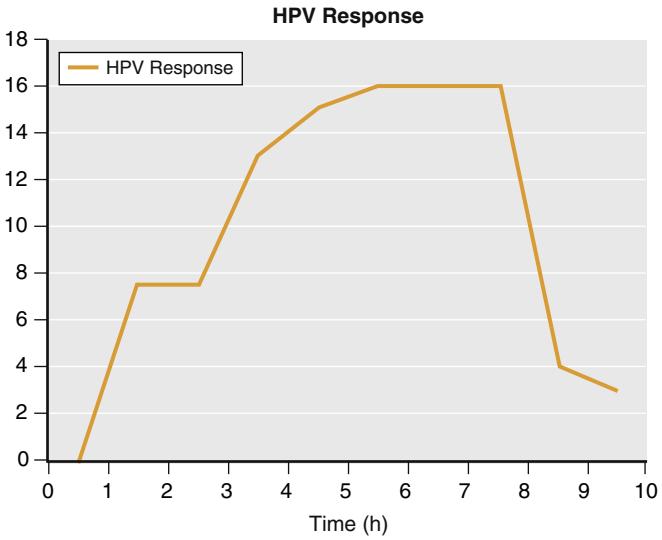


Figure 66-28. The relationship between hypoxic pulmonary vasoconstriction (HPV) (vertical axis) and time in hours (h) (horizontal axis) in humans exposed to isocapnic hypoxia (approximate inspired PO_2 60 mm Hg) beginning at baseline with a return to normoxia at 8 hours. HPV response was measured as the increase in echocardiographic right ventricular systolic pressure. Note the two-phase, rapid and slow, onset of HPV. Also note that after prolonged HPV, the pulmonary pressures do not return to baseline for several hours. *(Based on data from Van Der Spek AFL, Spargo PM, Norton ML: The physics of lasers and implications for their use during airway surgery,* Br J Anaesth *60: 709, 1988.)*

thoracic procedures. HPV is also a reflex that has a preconditioning effect, and the response to a second hypoxic challenge will be greater than to the first challenge.[120]

The surgical trauma to the lung can affect pulmonary blood flow redistribution. Surgery may oppose HPV by release of vasoactive metabolites locally in the lung. Conversely, surgery can dramatically decrease blood flow to the nonventilated lung by deliberately or accidentally mechanically interfering with either the unilateral pulmonary arterial or venous blood flow.[121] Ventilation increases blood flow through a hypoxic lung more than in a normoxic lung, which is generally not of clinical relevance but does complicate studies of HPV. HPV is decreased by vasodilators such as nitroglycerin and nitroprusside. In general, vasodilators can be expected to cause deterioration in PaO_2 during OLV. Thoracic epidural sympathetic blockade probably has little or no direct effect on HPV, which is a localized chemical response in the lung.[122] However, thoracic epidural anesthesia can have an indirect effect on oxygenation during OLV if it is allowed to cause hypotension and a fall in cardiac output (see Cardiac Output later in this chapter).

CHOICE OF ANESTHETIC

All of the volatile anesthetics inhibit HPV in a dose-dependent fashion with halothane > enflurane > isoflurane.[123] The older anesthetics were potent inhibitors of HPV and this may have contributed to the high incidence of hypoxemia reported during OLV in the 1960s and 1970s (see earlier); many of these studies used 2- to 3-MAC doses of halothane.

In doses of less than or equal to 1 MAC, the modern volatile anesthetics (isoflurane, sevoflurane,[124] and desflurane[125]) are weak, and equipotent, inhibitors of HPV. The inhibition of the HPV response by 1 MAC of a volatile anesthetic such as isoflurane is approximately 20% of the total HPV response, and this could account for only a net 4% increase in total arteriovenous shunt during OLV, which is a difference too small to be detected in most clinical studies.[126] In addition, volatile anesthetics cause less inhibition of HPV when delivered to the active site of vasoconstriction via the pulmonary arterial blood than via the alveolus. This pattern is similar to the HPV stimulus characteristics of oxygen. During established OLV, the volatile agent only reaches the hypoxic lung pulmonary capillaries via the mixed venous blood. No clinical benefit in oxygenation during OLV has been shown for total intravenous anesthesia above that seen with 1 MAC of the modern volatile anesthetics.[127]

The use of nitrous oxide/oxygen (N_2O/O_2) mixtures is associated with a higher incidence of postthoracotomy radiographic atelectasis (51%) in the dependent lung than when air/oxygen mixtures are used (24%). Nitrous oxide also tends to increase pulmonary artery pressures in patients who have pulmonary hypertension, and N_2O inhibits HPV. For these reasons, N_2O is usually avoided during thoracic anesthesia.

CARDIAC OUTPUT

The effects of alterations of cardiac output during OLV are complex (Fig. 66-29). Increasing cardiac output tends to cause increased pulmonary artery pressures and passive dilation of the pulmonary vascular bed, which in turn opposes HPV and has been shown to be associated with increased arteriovenous shunt ($\dot{Q}s/\dot{Q}t$) during OLV.[128] However, in patients with a relatively fixed oxygen consumption, as is seen during stable anesthesia, the effect of an increase in cardiac output is to increase the mixed venous oxygen saturation (SvO_2). Thus increasing cardiac output during OLV tends to increase both shunt and SvO_2, which have opposing effects on PaO_2. There is a ceiling effect to the amount that SvO_2 can be increased. Increasing the cardiac output to supranormal levels by administering inotropes such as dopamine tends to have an overall negative effect on PaO_2.[129] Conversely, allowing the cardiac output to fall will lead to decreases in both shunt and SvO_2, with a net effect of decreasing PaO_2. Because even with optimal anesthetic management there is usually a shunt of 20% to 30% during OLV, it is very important to maintain cardiac output.

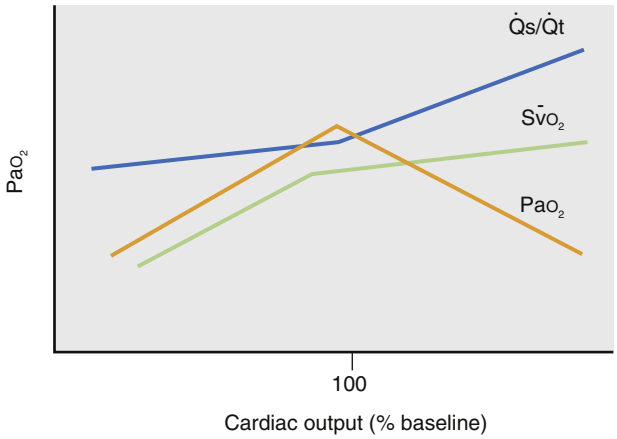


Figure 66-29. The relationship between PaO_2 and cardiac output during OLV. As cardiac output falls below baseline, arteriovenous shunt ($\dot{Q}s/\dot{Q}t$) falls, but the mixed venous oxygen saturation (SvO_2) also decreases, resulting in a net fall in PaO_2. Conversely, raising cardiac output above baseline tends to increase SvO_2 but also increase $\dot{Q}s/\dot{Q}t$ and the net result again is a decrease in PaO_2. *(Based on data from Russell WJ, James MF: The effects on arterial haemoglobin oxygen saturation and on shunt of increasing cardiac output with dopamine or dobutamine during one-lung ventilation,* Anaesth Intensive Care *32:644, 2004; Kim SH, Jung KT, AN TH: Effects of tidal volume and PEEP on arterial blood gases and pulmonary mechanics during one-lung ventilation,* J Anesth *26:568, 2012.)*

VENTILATION STRATEGIES DURING ONE-LUNG VENTILATION

The strategy used to manage the ventilated lung during OLV plays an important part in the distribution of pulmonary blood flow between the lungs. It has been the practice of many anesthesiologists to use the same large tidal volume (e.g., 10 mL/kg ideal body weight) during OLV as during TLV. This strategy probably decreases hypoxemia by recurrently recruiting atelectatic regions in the dependent lung and may result in higher PaO_2 values during OLV compared with smaller

tidal volumes.[130] However, there is a trend to use smaller tidal volumes with PEEP during OLV for several reasons. First, the incidence of hypoxemia during OLV is much lower than it was 20 to 30 years ago. Second, there is a risk of causing acute injury to the ventilated lung with prolonged use of large tidal volumes. And finally, third, a ventilation pattern that allows recurrent atelectasis and recruitment of lung parenchyma seems to be injurious.[131] The ventilation technique needs to be individualized depending on the patient's underlying lung mechanics.

RESPIRATORY ACID-BASE STATUS
(See Chapter 60)

The efficacy of HPV in a hypoxic lung region is increased in the presence of respiratory acidosis and is inhibited by respiratory alkalosis. However, there is no net benefit to gas exchange during OLV from hypoventilation because the respiratory acidosis preferentially increases the pulmonary vascular tone of the well-oxygenated lung, and this opposes any clinically useful pulmonary blood flow redistribution.[132] Overall, the effects of hyperventilation will usually tend to decrease pulmonary vascular pressures.

POSITIVE END-EXPIRATORY PRESSURE

Resistance to blood flow through the lung is related to lung volume in a biphasic pattern and is lowest when the lung is at its FRC (see Fig. 66-26). Keeping the ventilated lung as close as possible to its normal FRC favorably encourages pulmonary blood flow to this lung. Several intraoperative factors known to alter FRC tend to cause the FRC of the ventilated lung to fall below its normal level; these include lateral position, paralysis, and opening the nondependent hemithorax, which allows the weight of the mediastinum to compress the dependent lung. Attempts to measure FRC in human patients during OLV have been complicated by the presence of a persistent end-expiratory airflow in patients with COPD.[133] Many patients do not actually reach their end-expiratory equilibrium FRC lung volume as they try to exhale a relatively large tidal volume through one lumen of a DLT. These patients develop dynamic hyperinflation and an occult positive end-expiratory pressure (auto-PEEP).[41]

AUTO-PEEP

Auto-PEEP occurs in patients with decreased lung elastic recoil, such as in older patients or those with emphysema.[134] Auto-PEEP increases as the inspiratory/expiratory (I:E) ratio increases (i.e., as the time of expiration decreases). This auto-PEEP, which averages 4 to 6 cm H_2O in most series of lung cancer patients studied, opposes the previously mentioned factors which tend to diminish dependent-lung FRC during OLV. The effects of applying external PEEP through the ventilator circuit to the lung in the presence of auto-PEEP are complex (Fig. 66-30). Patients with a very low auto-PEEP (<2 cm H_2O) will have a greater increase in total PEEP from a moderate (5 cm H_2O) external PEEP than those with a high level of auto PEEP (>10 cm H_2O). Whether the application of PEEP during OLV will improve a patient's gas exchange depends on the individual's lung mechanics. If the application of PEEP tends to shift the expiratory equilibration position on the compliance curve toward the lower inflection point of the curve (i.e., toward the FRC), then external PEEP is of benefit (Fig. 66-31). However, if the application of PEEP raises the equilibration point such that it is further from the lower inflection point, then gas exchange deteriorates.

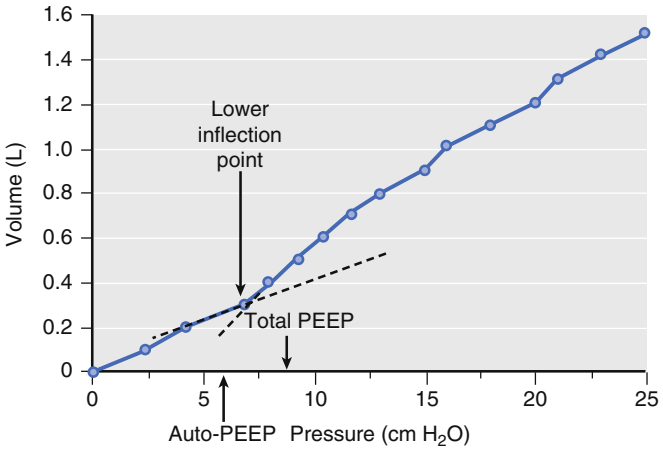


Figure 66-30. The static compliance curve of the ventilated (dependent) lung in a typical lung cancer patient with mild COPD. The Lower Inflection Point is thought to represent FRC. This patient had 6 cm H_2O of auto-PEEP during OLV. Adding 5 cm H_2O PEEP to the ventilator resulted in a total PEEP in the circuit of 9 cm H_2O. This patient had a decrease in PaO_2 with the addition of PEEP. *(Based on data from Slinger P, Kruger M, McRae K, et al: Relation of the static compliance curve and positive end-expiratory pressure to oxygenation during one-lung ventilation,* Anesthesiology *95:1096, 2001.)*

Auto-PEEP is difficult to detect and measure using currently available anesthetic ventilators. To detect auto-PEEP, the respiratory circuit must be held closed at the end of a normal expiration until an equilibrium appears in the airway pressure.[135] Most current intensive care ventilators can be used to measure auto-PEEP.

TIDAL VOLUME

There will be an optimal combination of tidal volume, respiratory rate, I:E ratio, or pressure- or volume-control ventilation for each individual patient during OLV. However, to try to assess each of these parameters while still providing anesthesia with the available anesthetic ventilators is not practical, and the clinician must initially rely on a simplified strategy (Table 66-9). The results of alterations in tidal volume are unpredictable. This may be caused partly by the interaction of tidal volume with auto-PEEP. The use of 5 to 6 mL/kg ideal body weight tidal volumes plus 5 cm H_2O PEEP initially for most patients (except those with COPD) seems a logical starting point during OLV. Tidal volume should be managed so that peak airway pressures do not exceed 35 cm H_2O. This will correspond to a plateau airway pressure of approximately 25 cm H_2O.[136] Peak airway pressures exceeding 40 cm

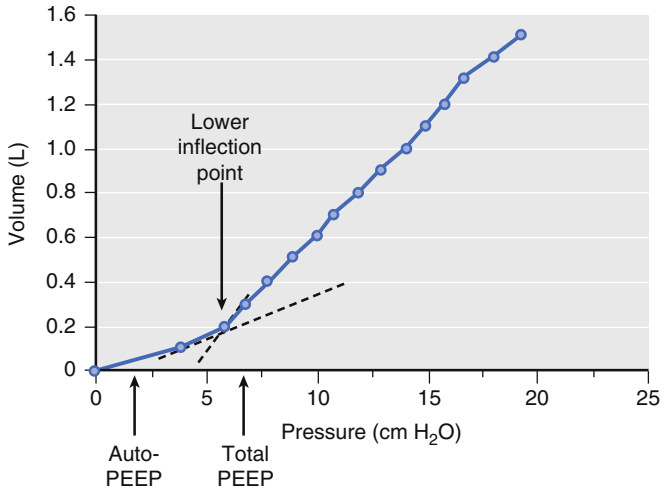


Figure 66-31. Static compliance curve of a young patient with normal pulmonary function during OLV (in this case for removal of a mediastinal tumor). The lower inflection point of the curve (FRC) was at 6 cm H_2O. The patient had 2 cm H_2O auto-PEEP during OLV. Adding 5 cm H_2O PEEP to the ventilator raised the total PEEP to 7 cm H_2O and improved PaO_2. Young patients and patients with increased lung elastic recoil (such as caused by restrictive lung diseases) have an increase in PaO_2 from PEEP during OLV. *(Based on data from Slinger P, Kruger M, McRae K, et al: Relation of the static compliance curve and positive end-expiratory pressure to oxygenation during one-lung ventilation,* Anesthesiology *95:1096, 2001.)*

TABLE 66-9 SUGGESTED VENTILATION PARAMETERS FOR ONE-LUNG VENTILATION

Parameter	Suggested	Guidelines/Exceptions
Tidal volume	5-6 mL/kg	Maintain: Peak airway pressure <35 cm H_2O Plateau airway pressure <25 cm H_2O
Positive end-expiratory pressure	5 cm H_2O	Patients with COPD, no added PEEP
Respiratory rate	12 breaths/min	Maintain normal $Paco_2$, Pa-etCO_2 will usually increase 1-3 mm Hg during one-lung ventilation
Mode	Volume or pressure controlled	Pressure control for patients at risk of lung injury (e.g., bullae, pneumonectomy, post lung transplantation)

H_2O may contribute to hyperinflation injury of the ventilated lung during OLV.[137]

Turning the patient to the lateral position will increase respiratory dead space and the arterial to end-tidal CO_2 tension gradient (Pa-etCO_2). This will usually require a 20% increase in minute ventilation to maintain the same $PaCO_2$. Individual variations in Pa-$ETCO_2$ gradient can become much larger, and $PetCO_2$ is less reliable as a monitor of $Paco_2$ during OLV. This effect is possibly because there are individual differences in the excretion of CO_2 between the dependent and nondependent lungs.

VOLUME-CONTROLLED VERSUS PRESSURE-CONTROLLED VENTILATION

Traditionally, volume-controlled ventilation has been used in the operating room for all types of surgery. The recent availability of anesthesia ventilators with pressure-control modes has made it possible to study and use this form of ventilation during thoracic surgery. Pressure-control ventilation has not been shown to improve oxygenation versus volume-controlled ventilation for most patients, although the peak airway pressures are lower.[138] The decrease in peak pressure with pressure control ventilation may be largely in the anesthetic circuit and not at the distal airway.[139] Pressure-control ventilation will avoid sudden increases in peak airway pressures that may result from surgical manipulation in the chest. This will be of benefit in patients at increased risk for lung injury from high volumes or pressures such as after lung transplantation or during a pneumonectomy.[140] Because of the rapid changes of lung compliance that occur during pulmonary surgery, when pressure-control ventilation is used, the delivered tidal volume needs to be closely monitored because it may change suddenly.

PREDICTION OF HYPOXEMIA DURING ONE-LUNG VENTILATION

The problem of hypoxemia during OLV has prompted much research in thoracic anesthesia. Hypoxemia during OLV is predictable (see Box 66-4), preventable, and treatable in the vast majority of cases.[141]

PREOPERATIVE VENTILATION-PERFUSION SCAN

The shunt and PaO_2 during intraoperative OLV are highly correlated with the fractional perfusion of the ventilated lung as determined by a preoperative ventilation perfusion scan.[142] Patients with long-standing unilateral disease on the operative side develop a unilateral decrease of ventilation and perfusion and tolerate OLV very well. Similarly, patients who intraoperatively have a higher proportion of gas exchange in the dependent lung during OLV tend to have better oxygenation during OLV.

SIDE OF OPERATION

Patients having right-sided thoracotomies tend to have a larger shunt and lower PaO_2 during OLV because the right lung is larger and normally 10% better perfused than the left. The overall mean PaO_2 difference between left and right thoracotomies during stable OLV is approximately 100 mm Hg.[143]

TWO-LUNG OXYGENATION

Patients who have better PaO_2 levels during TLV in the lateral position tend to have better oxygenation during OLV. These patients may have better abilities to match ventilation and perfusion (individual variability of HPV response) and/or they may have less atelectasis in the

dependent lung. This is a particularly relevant consideration in trauma patients who may require a thoracotomy but have a contusion of the dependent lung.

PREOPERATIVE SPIROMETRY

Studies consistently show that when the previous factors are controlled, patients with better spirometric lung function preoperatively are more likely to desaturate and have lower PaO_2 values during OLV. Clinically this is evident because emphysematous lung volume reduction patients generally tolerate OLV very well. The explanation is not clear but may be related to maintenance of a more favorable FRC in patients with obstructive airways disease during OLV with an open hemithorax because of the development of auto-PEEP.[54]

TREATMENT OF HYPOXEMIA DURING ONE-LUNG VENTILATION

During OLV there will be a fall in arterial oxygenation that usually reaches its nadir 20 to 30 minutes after the initiation of OLV, and then the saturation will stabilize or may rise slightly as HPV increases over the next 2 hours. The majority of patients who desaturate do so quickly and within the first 10 minutes of OLV. Hypoxemia during OLV responds readily to treatment in the vast majority of cases. Potential therapies are outlined in Box 66-9.

1. *Resume two-lung ventilation.* Reinflate the nonventilated lung and deflate the bronchial cuff of the DLT or the bronchial blocker. This will necessitate interruption of surgery but is necessary in case of severe or precipitate desaturation. After an adequate level of oxygenation is obtained, the diagnosis of the cause of desaturation can be made and prophylactic measures instituted (see later) before another trial of OLV is attempted.
2. *Increase FiO_2.* Ensure that the delivered FiO_2 is 1.0. This is an option in essentially all patients except those who have received bleomycin or similar therapies that potentiate pulmonary oxygen toxicity.
3. *Recheck the position of the DLT or bronchial blocker.* Ensure that there is no lobar obstruction in the ventilated lung.
4. *Check to be sure there has been no decrease in cardiac output.* The surgeon can accidentally compress the inferior vena cava during pulmonary resections, which decreases arterial blood pressure and cardiac output that leads to a rapid desaturation during OLV. Treat the decrease in cardiac output as indicated (e.g., inotropes/vasopressors if caused by thoracic epidural sympathetic blockade). Stop administration of vasodilators, decrease the MAC of volatile anesthetics to less than or equal to 1 MAC.
5. *Perform a recruitment maneuver of the ventilated lung.* To eliminate any atelectasis, inflate the lung to 20 cm H_2O or more for 15 to 20 seconds. This may cause transient hypotension and will also cause a transient further fall in the PaO_2 as the blood flow is temporarily redistributed to the nonventilated lung.
6. *Apply PEEP to the ventilated lung.* It is necessary to perform a recruitment maneuver before applying PEEP to get the maximal benefit. PEEP will raise the end-expiratory volume of the ventilated lung toward the FRC in patients with normal lung mechanics and in those with increased elastic recoil caused by restrictive disease. It is not possible to predict the optimal PEEP for individual patients; a level of 5 cm H_2O is a useful starting point. PEEP will increase the end-expiratory lung volume of patients with significant levels of auto-PEEP (e.g., emphysema patients). Unlike CPAP, application of PEEP does not require reinflation of the nonventilated lung and interruption of surgery. PEEP has been shown to be as effective for increasing PaO_2 levels during OLV in patients with normal lung function as CPAP (Fig. 66-32).[144] For patients with normal pulmonary function, it is logical to routinely apply a recruitment maneuver and PEEP from the start of OLV.
7. *Continuous positive airway pressure (CPAP) with oxygen to the nonventilated lung is the next line of therapy after application of PEEP.*[145] There is an important caveat to be observed when CPAP is applied to the nonventilated lung, and that is that CPAP must be applied to an inflated (recruited) lung to be completely effective. The opening pressure of atelectatic lung regions is greater than 20 cm H_2O[146] and these units will not be recruited by simple application of CPAP levels of 5 to 10 cm H_2O. Even a period as short as 5 minutes of collapse before CPAP application can have deleterious effects on oxygenation during OLV.[147] When CPAP is applied to a fully inflated lung, levels of CPAP as low as 1 to 2 cm H_2O can be used.[148] Because the normal transpulmonary pressure of the lung at FRC is approximately 5 cm H_2O, levels of 5 to 10 cm H_2O CPAP applied to a fully recruited lung result in a large-volume lung that impedes surgery, particularly during minimally invasive procedures.

BOX 66-9 ***Therapies for Desaturation during One-Lung Ventilation***

- Severe or precipitous desaturation: resume two-lung ventilation (if possible).
- Gradual desaturation
  - Ensure that delivered FiO_2 is 1.0.
  - Check position of double-lumen tube or blocker with fiberoptic bronchoscopy.
  - Ensure that cardiac output is optimal; decrease volatile anesthetics to <1 MAC.
  - Apply a recruitment maneuver to the ventilated lung (this will transiently make the hypoxemia worse).
  - Apply PEEP 5 cm H_2O to the ventilated lung (except in patients with emphysematous pathology).
  - Apply CPAP 1-2 cm H_2O to the nonventilated lung (apply a recruitment maneuver to this lung immediately before CPAP).
  - Use intermittent reinflation of the nonventilated lung.
  - Partial ventilation techniques of the nonventilated lung:
    - Lung oxygen insufflation
    - Lobar insufflation
  - Lobar collapse (using a bronchial blocker)
  - Use mechanical restriction of the blood flow to the nonventilated lung

PEEP, positive end-expiratory pressure; *CPAP,* continuous positive airway pressure.

CPAP levels less than 10 cm H_2O do not interfere with hemodynamics. The beneficial effects of low levels of CPAP are primarily caused by oxygen uptake from the nonventilated lung and not because of blood flow diversion to the ventilated lung. CPAP is most effective when oxygen (FiO_2 1.0) is applied to the nonventilated lung. Lower FiO_2 levels of CPAP are of clinical benefit and can be used along with decreased FiO_2 to the ventilated lung in patients at risk of oxygen toxicity.

Numerous anesthetic systems to apply CPAP to the nonventilated lung have been described. Essentially all that is required is a CPAP (or PEEP) valve and an oxygen source. Ideally the circuit should permit variation of the CPAP level and include a reservoir bag to allow easy reinflation of the nonventilated lung and a manometer to measure the actual CPAP supplied. Such circuits are commercially available (Fig. 66-33) or can be readily constructed from standard anesthetic equipment. CPAP can be applied with either a DLT or through the suction channel of a bronchial blocker.

CPAP, even when properly administered, is not completely reliable to improve oxygenation during OLV. When the bronchus of the operative lung is obstructed, or open to atmosphere (as in a bronchopleural fistula or during endobronchial surgery), CPAP will not improve oxygenation. Also in certain situations, particularly during thoracoscopic surgery where access to the operative hemithorax is limited, CPAP can significantly interfere with surgery.[149]

PHARMACOLOGIC MANIPULATIONS

Eliminating known potent vasodilators such as nitroglycerin and halothane and large doses of other volatile anesthetics will improve oxygenation during OLV.[150] The selective administration of the vasodilator prostaglandin E_1 to the ventilated lung[151] or a NO synthase inhibitor (L-NAME)[152] to a hypoxic lobe results in improved redistribution of pulmonary blood flow in animal models. This is not currently applicable in humans. Selective administration of NO alone to the ventilated lung was not shown to be of benefit in humans.[153] The combination of NO (20 ppm) to the nonventilated lung and an intravenous infusion of almitrene, which enhances HPV, has been shown to restore PaO_2 values during OLV in humans to essentially the same levels as during TLV. However, this may have been primarily a result of the augmentation of HPV by almitrene.[154] It is unlikely that almitrene, which was previously available in North America as a respiratory stimulant, will be reintroduced to this market because of side effects such as hepatic enzyme changes and lactic acidosis. However, the combination of NO and other pulmonary vasoconstrictors such as phenylephrine has been shown to improve oxygenation in ventilated intensive care unit patients with adult respiratory distress syndrome,[155] and this may have applications in OLV.

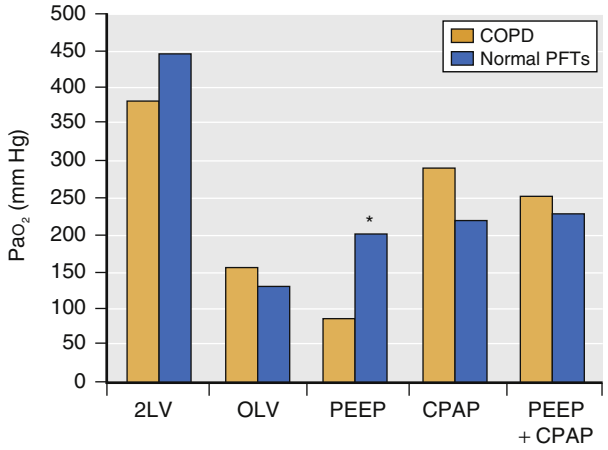


Figure 66-32. A comparison of the effects of positive end-expiratory pressure (PEEP) to the ventilated lung and continuous positive airway pressure (CPAP) to the nonventilated lung on mean PaO_2 levels during OLV. *2LV*, two-lung ventilation; *COPD*, a group of lung cancer surgery patients; *Normal PFTs*, a group of esophageal surgery patients with normal preoperative pulmonary function tests. *Significance of $P < .05$ versus OLV. *(Based on data from Capan LM, Turndorf H, Patel C, et al: Optimization of arterial oxygenation during one-lung anesthesia,* Anesth Analg *59:847, 1980; Rothen HU, Sporrc B, Engberg G et al: Re-expansion of atelectasis during general anesthesia: a computed tomographic study,* Br J Anaesth *71:788, 1993.)*

INTERMITTENT REINFLATION OF THE NONVENTILATED LUNG

HPV becomes more effective during repeated hypoxic exposure. Often after reinflation, the oxygen saturation will be more acceptable during a second period of lung collapse. Reexpansion can be performed by regular reexpansion of the operative lung via an attached CPAP circuit.

PARTIAL VENTILATION METHODS

Several alternative methods of OLV, all involving partial ventilation of the nonventilated lung, have been described and improve oxygenation during OLV. These techniques are useful in patients who are particularly at risk of desaturation, such as those who have had previous

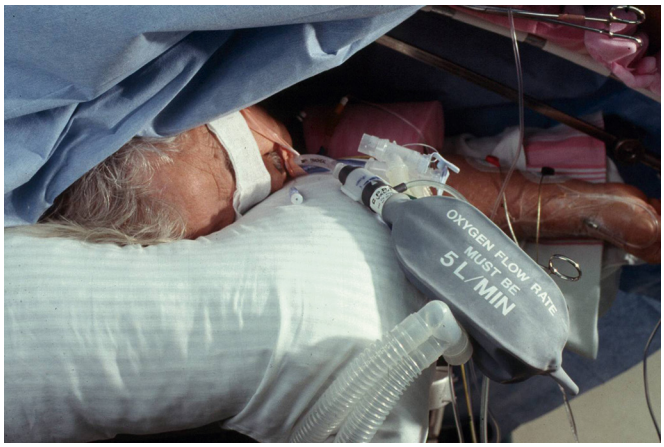


Figure 66-33. Photograph of a commercial (Mallinckrodt, St. Louis, Mo) disposable CPAP circuit applied to the nonventilated lung during a left thoracotomy (in this case applied to the tracheal lumen of a right-sided DLT). This circuit has an adjustable exhaust valve that allows titration of CPAP between 1 and 10 cm H_2O. *CPAP,* continuous positive airway pressure; *DLT,* double-lumen endobronchial tube.

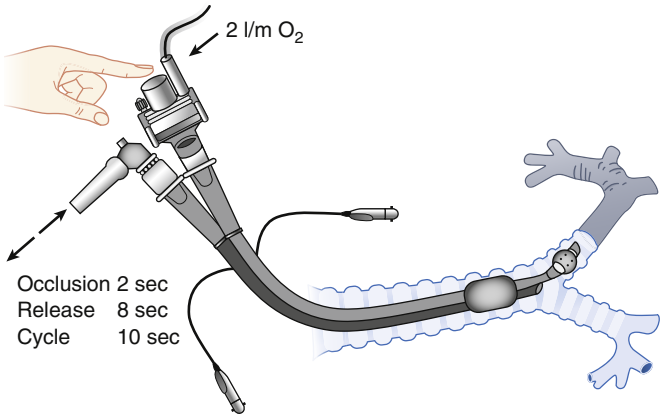


Figure 66-34. A simple device to provide intermittent positive airway pressure to the nonventilated lung. A standard bacteriostatic filter is attached to the lumen of the DLT to the nonventilated lung and an oxygen source is connected to the CO_2 sampling port of the filter. Intermittent manual occlusion of the open filter end improves oxygenation with minimal impact on surgical exposure (see text for details). *(Reproduced with permission from Slinger P:* Principles and practice of anesthesia for thoracic surgery, *New York, Springer, 2011.)*

pulmonary resections of the contralateral lung. These alternatives include:

1. *Intermittent positive airway pressure to the nonventilated lung.* This can be performed by a variety of methods. Russell described attaching a standard bacteriostatic filter to the nonventilated lumen of the DLT with a 2-L oxygen inflow attached to the CO_2 port of the filter (Fig. 66-34).[156] Manual occlusion of the filter for 2 seconds gives an insufflation of approximately 66 mL of oxygen to the nonventilated lung. This could be repeated at 10-second intervals with minimal interference with surgical exposure.
2. *Selective insufflation of oxygen to recruit lung segments on the side of surgery but remote from the site of surgery* (Fig. 66-35).[157] A useful technique in minimally invasive surgery is intermittent insufflation of oxygen using a fiberoptic bronchoscope. A 5-L oxygen flow is attached to the suction port of a fiberoptic bronchoscope that is passed under direct vision into a segment of the lung remote from the site of surgery, which is then reinflated by triggering the suction on the fiberoptic bronchoscope. The surgeon aids this technique by

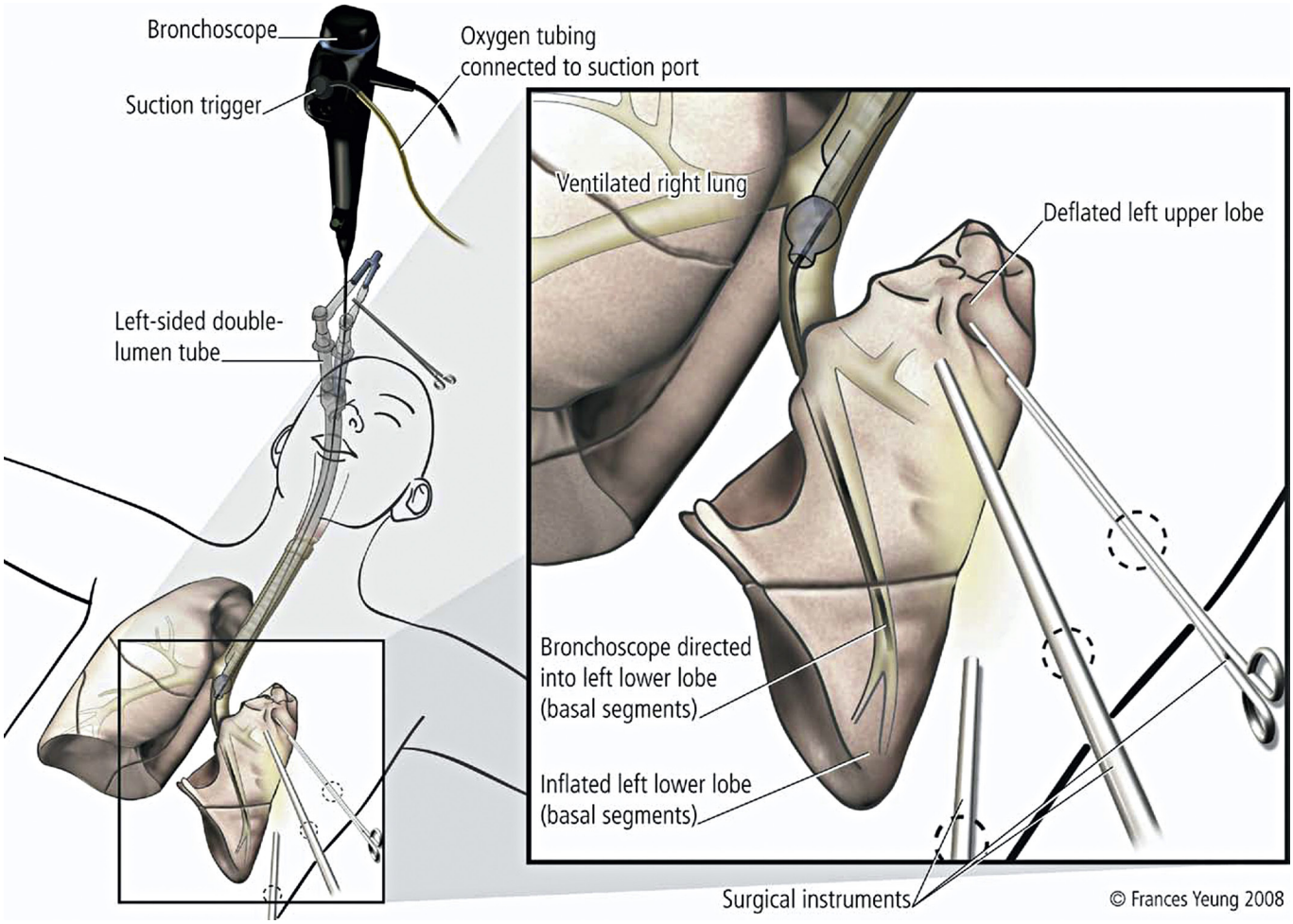


Figure 66-35. Intermittent oxygen insufflation during thoracoscopic surgery to segments of the nonventilated lung on the side of surgery using a fiberoptic bronchoscope (see text for details). *(Reproduced with permission from Slinger P:* Principles and practice of anesthesia for thoracic surgery, *New York, Springer, 2011.)*

observing the lung inflation with the videoscope to avoid overdistention of the recruited segment(s).

3. *Selective lobar collapse of only the operative lobe in the open hemithorax.*[158] This is accomplished by placement of a blocker in the appropriate lobar bronchus of the ipsilateral operative lung.

MECHANICAL RESTRICTION OF PULMONARY BLOOD FLOW

It is possible for the surgeon to directly compress or clamp the blood flow to the nonventilated lung.[159] This can be done temporarily in emergency desaturation situations or definitively in cases of pneumonectomy or lung transplantation. Another technique of mechanical limitation of blood flow to the nonventilated lung is the inflation of a pulmonary artery catheter balloon in the main pulmonary artery of the operative lung. The pulmonary artery catheter can be positioned at induction with fluoroscopic guidance and inflated as needed intraoperatively. This has been shown to be a useful technique for resection of large pulmonary arteriovenous fistulas.[160]

HYPOXEMIA PROPHYLAXIS

Most treatments outlined as therapies for hypoxemia can be used prophylactically to prevent hypoxemia in patients who are at high risk of desaturation during OLV. The advantage of prophylactic therapy of hypoxemia, in addition to the obvious patient safety benefit, is that maneuvers involving CPAP or alternative ventilation patterns of the operative lung can be instituted at the onset of OLV in a controlled fashion and will not require interruption of surgery and emergent reinflation of the nonventilated lung at a time that may be extremely disadvantageous.

BILATERAL PULMONARY SURGERY

Because of mechanical trauma to the operative lung, the gas exchange in this lung will always be temporarily impaired after OLV. Also HPV offset may be delayed after reinflation of the first lung collapsed. Desaturation during bilateral lung procedures is particularly a problem during the second period of OLV (i.e., during OLV of the lung that has already had surgery).[161] Thus, for bilateral procedures it is advisable to operate first on the lung that has better gas exchange and less propensity to desaturate during OLV. For the majority of patients, this means operating on the right side first.

ANESTHETIC MANAGEMENT FOR COMMON SURGICAL PROCEDURES

FLEXIBLE FIBEROPTIC BRONCHOSCOPY

Flexible fiberoptic bronchoscopy is a diagnostic and therapeutic procedure of great value in the clinical practice of thoracic surgery and anesthesia. In many centers, it is common practice to perform flexible fiberoptic bronchoscopy before lung resections to reconfirm the diagnosis (if a tumor compresses the airway) or to determine the invasion and obstruction of the distal airway (in relation to the extension of the bronchial resection).

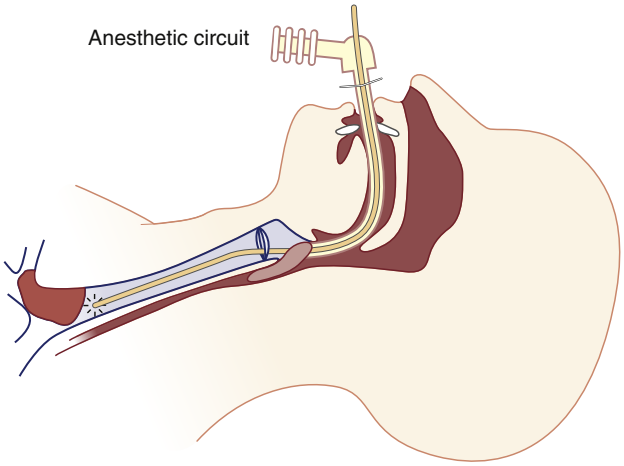


Figure 66-36. Diagram of fiberoptic bronchoscopy performed via a laryngeal mask airway (LMA) during general anesthesia in a spontaneously breathing patient with a carinal tumor, in this case for diagnosis and Nd:YAG laser tumor excision. The LMA permits visualization of the vocal cords and subglottic structures with the bronchoscope, which is not possible when fiberoptic bronchoscopy is performed via an endotracheal tube.

Anesthetic Management

There are multiple techniques for flexible fiberoptic bronchoscopy. Options include awake versus general anesthesia and oral versus nasal approaches. Options for local anesthesia include: topical anesthesia via a nebulizer, handheld aerosol, or soaked pledgets; nerve blocks (laryngeal and/or glossopharyngeal nerves); and direct administration of local anesthetic through the bronchoscope (spray-as-you-go technique)[162] with/without sedation/opioid or antisialogogues. Options during general anesthesia include spontaneous versus positive-pressure ventilation with/without muscle relaxation. Airway management during general anesthesia can be done with an endotracheal tube or a laryngeal mask airway (LMA). A Portex swivel connector (Smiths Medical, Ashford, Kent, UK) with a self-sealing valve is used to facilitate the ventilation and manipulation of the bronchoscope; at the same time inhalation and/or intravenous agents can be used for anesthesia. Patients who have copious secretions in the preoperative period should receive anticholinergic medication to ensure a dry field, which provides optimal visualization with the use of a flexible bronchoscope.

The advantages of an LMA technique include visualization of the vocal cords and subglottic structures as well as a lower airway resistance versus an ETT when the bronchoscope is inserted (Fig. 66-36). This is particularly useful in a patient with a difficult airway, when maintaining spontaneous respiration may be the safest method of anesthetic management.[163] Self-expanding flexometallic tracheal and bronchial stents can be placed with fiberoptic or rigid bronchoscopy (Fig. 66-37). However, silastic airway stents require rigid bronchoscopy for placement.

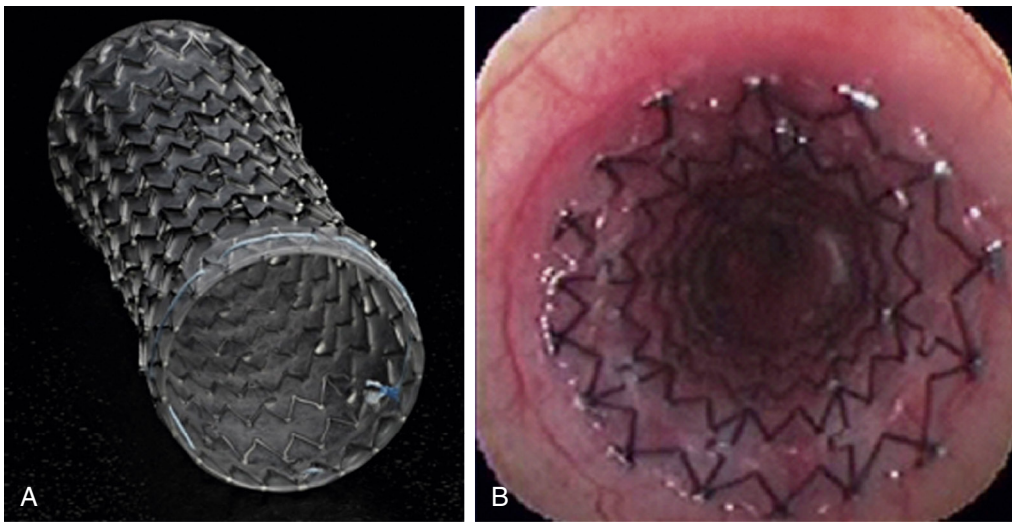


Figure 66-37. A, A self-expanding flexometallic airway stent. **B,** Fiberoptic bronchoscopic view of the proximal end of a flexometallic tracheal stent.

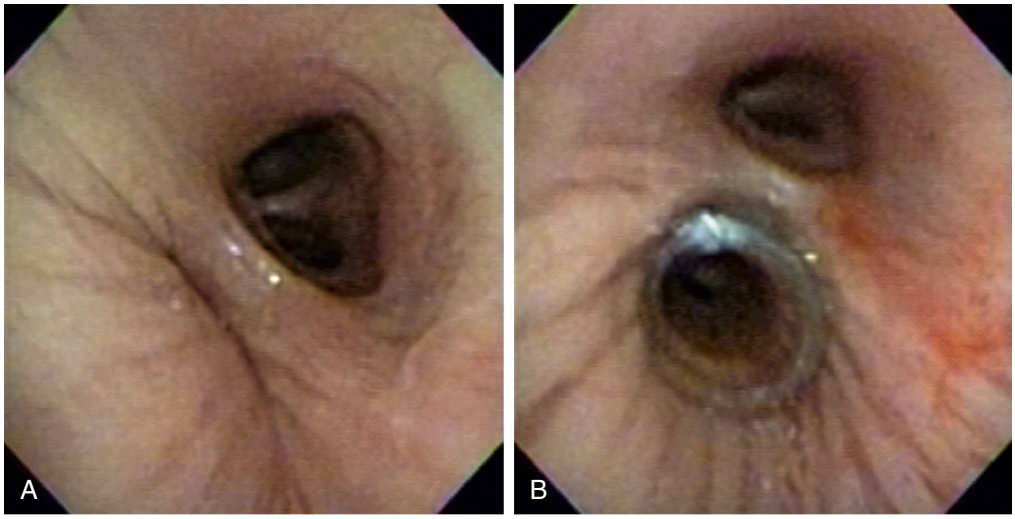


Figure 66-38. A, Photograph of a patient with a collapse of the left lower lobe bronchus post lung transplantation. **B,** A silastic stent has been placed in the left lower lobe bronchus with rigid bronchoscopy.

RIGID BRONCHOSCOPY

Rigid bronchoscopy has traditionally been considered the technique of choice for the preoperative diagnostic assessment of an airway obstruction involving the trachea and in the therapy of massive hemoptysis and foreign bodies in the airway. The role of interventional bronchoscopy with laser, bronchial dilation, or stent insertion is well established for the treatment of malignant and benign central airway and endobronchial lesions (Fig. 66-38).[164] Rigid bronchoscopy is the procedure of choice for operative procedures such as dilation of tracheal stenosis.

Anesthetic Management

Patients undergoing rigid bronchoscopy should have a complete preoperative evaluation including radiologic studies. Chest radiographs and chest CT scans should be reviewed in the preoperative evaluation. If time permits, it is recommended that patients with severe stridor receive pharmacologic interventions for temporary stabilization of the condition. Treatments may include inspired cool saline mist, nebulized racemic epinephrine, and the use of systemic steroids.[165]

There are four basic methods of ventilation management for rigid bronchoscopy:

1. *Spontaneous ventilation.* The addition of topical anesthesia or nerve blocks to the airway decreases the tendency to breath-hold and cough when volatile anesthetics are used.
2. *Apneic oxygenation (with/without insufflation of oxygen).* This requires thorough preoxygenation, and the anesthesiologist will have to interrupt surgery to ventilate the patient before desaturation occurs. This should allow the surgeon working intervals of 3 minutes or longer depending on the underlying condition of the patient.
3. *Positive-pressure ventilation via a ventilating bronchoscope* (Fig. 66-39). This allows the use of a standard anesthetic circuit but may cause significant air leaks if there is a discrepancy between the size of a smaller bronchoscope and a larger airway.
4. *Jet ventilation.* This can be performed with a handheld injector such as the Sanders injector (Sulz, Germany)[166] or with a high-frequency ventilator. These techniques

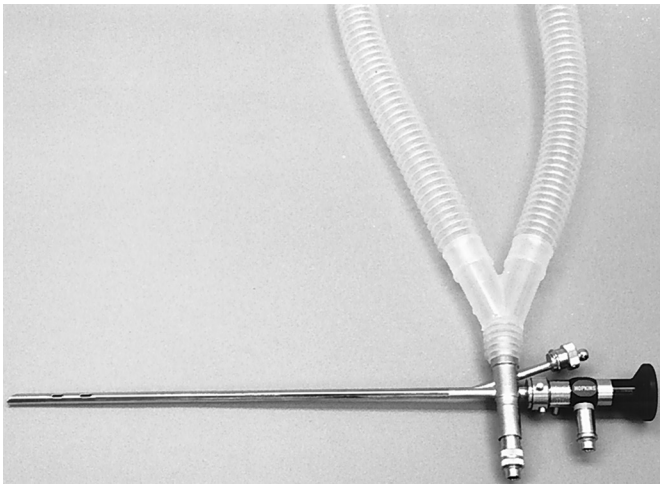


Figure 66-39. Photograph of a ventilating rigid bronchoscope with an anesthetic circuit attached to the side arm. This photograph also shows a telescopic lens sealing the proximal end of the bronchoscope. *(From Kaplan J, Slinger P, editors:* Thoracic anesthesia, *ed 3, Philadelphia, 2003, Churchill Livingstone.)*

are most useful with intravenous anesthesia because they entrain gas from either the room air or an attached anesthetic circuit, and the dose of any volatile agent delivered will be very uncertain.

The use of anticholinergic agents (e.g., 0.2 mg intravenous [IV] glycopyrrolate) before manipulation of the airway will decrease secretions during the bronchoscopic examination. For a patient undergoing rigid bronchoscopy, the surgeon must be at the bedside for the induction of anesthesia and be prepared to establish airway control with the rigid bronchoscope. Anesthesia in children for rigid bronchoscopy is most commonly done with spontaneous ventilation and a volatile anesthetic. In adults, IV anesthesia and the use of muscle relaxants is more common.

In cases for which the use of neuromuscular blocking drugs is not contraindicated, succinylcholine can be used initially to facilitate intubation with either a small SLT or the rigid bronchoscope. Nondepolarizing neuromuscular blocking drugs (see Chapter 34) may be needed for prolonged procedures such as stent placement or tumor resection. Mouthguards should be used to protect the upper and lower teeth and gums from the pressure of the bronchoscope. Remifentanil and propofol infusions can be administered if an IV regimen is the planned anesthetic.[167] This is a useful technique if the surgeon needs repeated access (for suction or instrumentation) to the open airway because it maintains the level of anesthesia and avoids contaminating the operating room with exhaled anesthetic vapors.

For cases in which a neodymium-doped yttrium aluminium garnet (Nd:YAG) laser is used, the inspired fraction of oxygen should be maintained in the lowest acceptable range (i.e., <30% if possible) according to patient oxygen saturation, to avoid the potential for fire in the airway. Because any common material (including porcelain and metal) can be perforated by the Nd:YAG laser, it is best to avoid any potentially combustible substance in the airway when the Nd:YAG laser is used.[168] Because of its high energy and short wavelength, the Nd:YAG laser has several advantages for distal airway surgery over the CO_2 laser, which is used in upper airway surgery. The Nd:YAG laser penetrates tissue more deeply so it causes more coagulation in vascular tumors, and it can be refracted and passed in fibers through a flexible or rigid bronchoscope. However, there is a higher potential for accidental reflected laser strikes and there is more delayed airway edema.

Rigid bronchoscopes have different sizes, commonly from 3.5- to 9-mm diameters, with a ventilating side port to facilitate ventilation when the bronchoscope is placed into the airway. If excessive leak of tidal volume occurs around the bronchoscope with positive-pressure ventilation, it may be necessary to place throat packs to facilitate ventilation. Continuous communication with the surgeon or pulmonologist is necessary in case desaturation occurs. If desaturation does occur, it must be corrected by stopping surgery and allowing the anesthesiologist to ventilate and oxygenate the patient, either via the rigid bronchoscope or by removing the bronchoscope and ventilating with a mask, LMA, or ETT.

Pulse oximetry is vital during rigid bronchoscopy because there is a high risk of desaturation. There is no simple way to monitor end-tidal CO_2 or volatile anesthetics because the airway remains essentially open to atmosphere. For prolonged procedures, it is useful to perform repeated arterial blood gas analysis to confirm the adequacy of ventilation. An alternative is to interrupt surgery and ventilate the patient with a standard circuit and a mask or ETT to assess the end-tidal CO_2.

Unlike during fiberoptic bronchoscopy via an ETT, with rigid the bronchoscopy the airway is never completely secure and there is always the potential for aspiration in patients at increased risk, such as those with a full stomach, hiatal hernia, morbid obesity, and so on. It is always best to defer rigid bronchoscopy to decrease the aspiration risk if possible in these patients. When there is no benefit to be gained by deferring and/or the airway risk is acute (e.g., aspiration of an obstructing foreign body), there is no simple solution and each case will need to be managed on an individual basis depending on the context and weighing the competing risks.

Other uses of the rigid bronchoscope that require anesthesia include dilation for benign airway stenosis, coring-out of malignant lesions in the trachea, laser ablation of endobronchial and carinal tumors, and therapeutic bronchoscopic interventions before surgical resection of lung cancer. In addition, interventional bronchoscopy is often used for the management of airway complications after lung transplantation.

Complications of rigid bronchoscopy include airway perforation, mucosal damage, hemorrhage, postmanipulation airway edema, and potential airway loss at the end of the procedure. In some situations, it may be necessary to keep the patient intubated with a small (i.e., 6.0-mm ID) SLT after a rigid bronchoscopy if an edematous airway is suspected or if the patient is not able to be extubated. These patients may require the use of steroids, nebulized racemic epinephrine, or helium-oxygen mixtures to treat stridor in the postoperative period.

MEDIASTINOSCOPY

Mediastinoscopy is the standard method for the evaluation of mediastinal lymph nodes in the staging of NSCLC. In addition, mediastinoscopy is used to aid in the diagnosis of anterior/superior mediastinal masses.[169] The most common mediastinal diagnostic procedure is a cervical mediastinoscopy, in which a small transverse incision (2 to 3 cm) is made in the midline of the lower neck in the suprasternal notch. The pretracheal fascial plane is dissected bluntly and the mediastinoscope inserted toward the carina. An alternative procedure is a parasternal (or anterior) mediastinoscopy with a small incision made through the interchondral space or the space of the excised second costal cartilage.

Morbidity related to mediastinoscopy ranges from 2% to 8%. The most severe complication of mediastinoscopy is major hemorrhage, which may require emergent thoracotomy. Other potential complications include airway obstruction, compression of the innominate artery, pneumothorax, paresis of the recurrent laryngeal, phrenic nerve injury, esophageal injury, chylothorax, and air embolism.[170]

Anesthetic Management

For patients undergoing cervical mediastinoscopy, the chest radiograph and CT scan should be reviewed for the presence of a mass that might obstruct the airway during the preoperative evaluation. It is possible to perform mediastinoscopy (particularly anterior mediastinoscopy) with local anesthesia. This may be an option with an anterior mediastinal mass in a cooperative adult with a compromised airway. However, patient coughing or movement could result in surgical complications. The majority of these patients require general anesthesia with placement of an SLT. An arterial line is not necessarily used in these cases. However, it is mandatory to monitor the pulse in the right arm (pulse oximeter on the right hand, arterial line, or anesthesiologist's finger) because compression of the innominate artery by the mediastinoscope may occur and the surgeon usually is not aware that this is happening. The innominate artery supplies blood not only to the right arm but also to the right common carotid. Patients who do not have good cerebral collateral circulation (it is generally not possible to predict who these patients are) are at risk for cerebrovascular ischemia with innominate compression. A noninvasive blood pressure cuff is placed on the left arm to confirm the correct systolic pressure in case of suspected innominate compression.

Mild mediastinal hemorrhage may respond to conservative measures: the patient can be placed in the head-up position, the systolic pressure kept in the 90s, and tamponading the wound with surgical sponges. However, massive hemorrhage requires an emergent sternotomy or thoracotomy to stop the bleeding (Box 66-10). A bronchial blocker can be passed through the lumen of the existing lung isolation device if lung isolation is required because it is often difficult to change to a DLT while the surgeon is tamponading the wound. An arterial line should be placed (if it was not placed previously) to measure arterial blood pressure. If hemorrhage originates from a tear in the superior vena cava, volume replacement and drug treatment may be lost into the surgical field unless they are administered through a peripheral IV catheter placed in the lower extremity.

BOX 66-10 *Anesthetic Management of Mediastinoscopy Hemorrhage*

1. Stop surgery and pack the wound. There is a serious risk that the patient will approach the point of hemodynamic collapse if the surgery-anesthesia team does not realize soon enough that there is a problem.
2. Begin the resuscitation and call for help, both anesthetic and surgical.
3. Obtain large-bore vascular access in the lower limbs.
4. Place an arterial line (if not placed at induction).
5. Prepare for massive hemorrhage with blood warmers and rapid infusers.
6. Obtain cross-matched blood in the operating room.
7. Place a double-lumen tube or bronchial blocker if the surgeon believes that thoracotomy is a possibility.
8. Once the patient is stabilized and all preparations are made, the surgeon can reexplore the cervical incision.
9. Convert to sternotomy or thoracotomy if indicated.

Pneumothorax is an infrequent complication of mediastinoscopy. Pneumothorax that occurs intraoperatively (as evidenced by increased peak inspiratory pressure, tracheal shift, distant breath sounds, hypotension, and cyanosis) requires immediate treatment by chest tube decompression. All patients must have a chest radiograph taken in the postanesthesia care unit after mediastinoscopy to rule out pneumothorax.

When mediastinoscopy causes injury to the recurrent laryngeal nerve, it can be permanent in approximately 50% of the cases. If injury to the recurrent laryngeal nerve is suspected, the vocal cords should be visualized while the patient is spontaneously breathing. If the vocal cords do not move or are in a midline position, consideration has to be given to the problem of postoperative laryngeal obstruction.

During mediastinoscopy, the tip of the mediastinoscope is located intrathoracically and therefore it is directly exposed to pleural pressure. A venous air embolus can occur if venous bleeding occurs and patients are breathing spontaneously because of the development of negative intrathoracic pressure during inspiration. Autonomic reflexes may result from compression or stretching of the trachea, vagus nerve, or great vessels. With an uncomplicated mediastinoscopy, the patient can be extubated in the operating room and discharged home the same day.

ENDOBRONCHIAL ULTRASOUND–GUIDED BIOPSY

Various alternative techniques are available for obtaining pathology specimens from the mediastinal lymph nodes. These include CT-guided percutaneous needle aspiration, conventional bronchoscopy with transbronchial needle aspiration, and endobronchial ultrasound–guided biopsy. Endobronchial ultrasonography (EBUS) using a radial probe through a working channel of the flexible fiberoptic bronchoscope can be used to identify mediastinal and hilar lymph nodes.[171] Under direct EBUS

TABLE 66-10 COMPARISON OF SURGICAL APPROACHES FOR PULMONARY RESECTIONS

Incision	Pro	Con
Posterolateral thoracotomy	Excellent exposure to entire operative hemithorax	Postoperative pain with or without respiratory dysfunction (short and long term)
Lateral muscle-sparing thoracotomy	Decreased postoperative pain	Increased incidence wound seromas
Anterolateral thoracotomy	Better access for laparotomy, resuscitation, or contralateral thoracotomy, especially in trauma	Limited access to posterior thorax
Axillary thoracotomy	Decreased pain Adequate access for first rib resection, sympathectomy, apical blebs, or bullae	Limited exposure
Sternotomy	Decreased pain Bilateral access	Decreased exposure of left lower lobe and posterior thoracic structures
Transsternal bilateral thoracotomy ("clamshell")	Good exposure for bilateral lung transplantation	Postoperative pain and chest wall dysfunction
Video-assisted thoracoscopic surgery or robotic surgery	Less postoperative pain and respiratory dysfunction	Technically difficult with central tumors and chest wall adhesions

guidance with fine-needle aspiration for mediastinal staging, an ultrasound puncture bronchoscope can be used to assist with the safe and accurate diagnostic interventional bronchoscopy of the mediastinal and hilar lymph nodes. Management of these patients is often done at a satellite location, either in the bronchoscopy facility or a CT suite. In general, these patients are managed with topical anesthesia (aerosolized lidocaine) and conscious sedation (e.g., fentanyl and/or midazolam). EBUS may replace mediastinoscopy as the standard method of staging lung cancer before resection.

PULMONARY SURGERY

Any given pulmonary resection can be accomplished by a variety of different surgical approaches. The approach used in an individual case will depend on the interaction of several factors that include the site and pathology of the lesion(s) and the training and experience of the surgical team. Common thoracic surgical approaches and their generally accepted advantages and disadvantages are listed in Table 66-10.

MINIMALLY INVASIVE THORACOSCOPIC SURGERY

VATS is the procedure of choice for the diagnosis and management of diseases of the pleura, nondiagnosed peripheral pulmonary nodules, and interstitial lung disease. Since the start of the modern era of thoracoscopic surgery in the early 1990s, VATS has been proposed as a less invasive approach than open procedures. Today it is a well-accepted and established procedure and has become the first-choice technique for lung biopsies, pleurectomies, sympathectomies, and other various pulmonary disorders.[172]

In addition, VATS may be used in a variety of other surgical procedures. Some centers routinely perform the majority of lobectomies under VATS. The outcomes for VATS lobectomy in patients with limited respiratory reserve seem superior to that for open thoracotomy. The spirometry threshold for increased risk for VATS seems to be a ppoFEV_1 of 30% versus 40% for open thoracotomy (Fig. 66-40); however, it was not possible to define a threshold for ppo$D_L$co.[173] Other surgeries, such as spinal fusion and scoliosis, have been performed with VATS. The advantage of VATS, when compared with open thoracotomy, include: (1) reduced hospital length of stay, (2) less blood loss if no mishaps occur, (3) less pain, (4) improvement in pulmonary function when compared with open thoracotomy,[174] (5) early patient mobilization with early recovery and rapid return to work and daily activities, and (6) less inflammatory reaction, as measured by cytokine response in patients undergoing VATS lobectomy compared with open thoracotomy.[175]

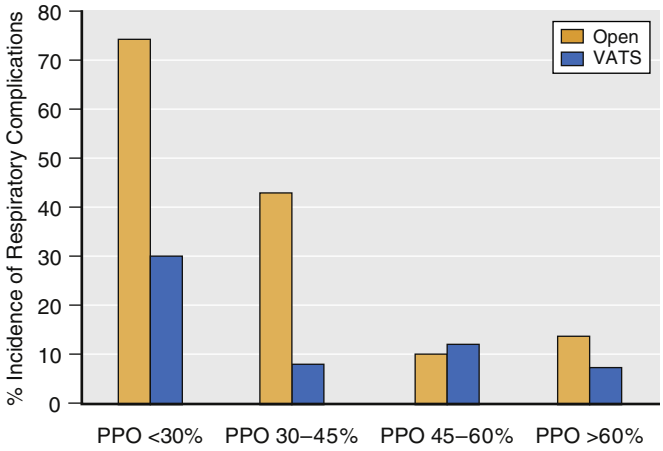


Figure 66-40. Incidence of major postoperative respiratory complications after lobectomy compared with the predicted postoperative (ppo) FEV_1% for open thoracotomy versus VATS. The threshold for increased risk appears to be increased only if the ppoFEV_1 is <30% for VATS. *(Based on data from Kaseda S, Aoki T, Hangai N, et al. Better pulmonary function and prognosis with video-assisted thoracic surgery than with thoracotomy,* Ann Thorac Surg *70:1644, 2000.)*

VATS lobectomy has been demonstrated to be a safe and effective procedure to treat early-stage NSCLC.[176] Thoracoscopic lobectomy is performed with a limited number of ports (1-3) and an access incision of approximately 5 cm in length.[177] The advantage of the VATS



Figure 66-41. Robotic surgery. The operating surgeon is on the far left, seated at the robot console. Note the limited access to the patient for the anesthesiologist after the robot has been docked.

BOX 66-11 *Anesthetic Considerations for Robotic Thoracic Surgery*

- A protocol for rapid emergency undocking (<60 s) of the robot must be developed and practiced in advance.
- Limit access to the patient. The position of lung isolation device needs to be confirmed before docking the robot.
- Extensions to monitoring lines and anesthesia circuit may be required.
- There is an increased need for intrathoracic CO_2 insufflation with possible venous return and hemodynamic compromise.
- Take precautions so that the operating room table cannot be moved while the robot is docked.
- Potentially prolonged procedures therefore increase risk of positional neuropathies; fluid restriction advisable.

technique is that the ribs are not spread open. VATS procedures are commonly performed in the lateral decubitus position; however, bilateral VATS procedures, such as bilateral wedge resections or lung volume reduction, can be performed in the supine position.

Robotic thoracic surgery has been suggested as the logical advancement of VATS because of the perceived better three-dimensional vision and increased range of motion in the chest for the surgeon with robotic techniques (Fig. 66-41).[178] Important points in anesthetic management are outlined in Box 66-11.

ANESTHETIC TECHNIQUE

Thoracoscopic surgery can be performed under local, regional, or general anesthesia with OLV or TLV.[179] For minor diagnostic procedures, VATS can be done in the awake patient. Intercostal nerve blocks performed at the level of the incision and two interspaces above and below provide adequate analgesia. Partial collapse of the lung on the side of surgery occurs when air enters the pleural cavity. When using local anesthesia with the patient awake, it is hazardous to insufflate gases under pressure into the hemithorax in an attempt to increase visualization of the pleural space. Although many patients suffer from advanced pulmonary disease, changes in PaO_2, $PaCO_2$, and cardiac rhythm are usually minimal during the procedure when it is performed under local anesthesia and the patient is breathing spontaneously.[180] However, it is recommended that a high FiO_2 is delivered via a facemask to overcome the shunt because of the loss in lung volume caused by the unavoidable pneumothorax.

For most invasive procedures, VATS is performed under general anesthesia with a DLT or a bronchial blocker to achieve OLV. If the procedure is short in duration and the lung needs to be deflated for only a brief period, blood gases are not routinely monitored during the procedure. However, for patients undergoing prolonged VATS procedures such as lobectomy or for patients with marginal pulmonary status, an arterial line and measurement of arterial blood gases is required. Paravertebral blocks have been used with a single dose of local anesthetic and have been shown to reduce pain after thoracoscopic surgery for 6 hours.[181]

Anesthetic complications are rare during this procedure, although it is possible that any structure that the surgeon has to manipulate may be damaged. The anesthesiologist needs to be aware of the potential for conversion to open thoracotomy if massive bleeding ensues or if the surgeon is unable to localize the lung nodule to be biopsied. The majority of thoracoscopic surgery requires placement of a chest tube postoperatively. It is important to have a functional chest tube with underwater seal drainage so that extubation can be performed safely.

LOBECTOMY

Lobectomy is the standard operation for the management of lung cancer because local recurrence of the tumor is reduced compared with lesser resections. Lobectomy is commonly performed via open thoracotomy or VATS. Sometimes, if the clinical staging of the lung cancer is advanced, an elective lobectomy is converted to a bilobectomy (right lung) or pneumonectomy during the operation. Although a posterolateral thoracotomy is the classic incision for lobectomies, anterolateral and muscle-sparing lateral incisions have also been used.

Postoperative analgesia is commonly performed with TEA or paravertebral analgesia (see Postoperative Analgesia later in the chapter). An arterial line for management of arterial blood gases and measurement of systemic blood pressure is used in all patients requiring an open thoracotomy or major VATS surgery. In addition, a large-bore IV catheter should be placed to facilitate rapid transfusion if necessary. Patients undergoing a lobectomy must be kept normothermic and normotensive and have an acceptable PaO_2 and oxygen saturation, particularly during OLV. Patients should have a thermal blanket covering the lower extremities to prevent hypothermia and its deleterious effects during HPV. After the lobe and blood vessels have been dissected, a test maneuver is performed with the surgeon clamping the surgical bronchus to confirm that the specific lobe is extirpated. This maneuver is accomplished by unclamping the limb of the DLT connector of the respective side, or in the case of a bronchial blocker, by deflating the blocker balloon, and reexpanding the lung with manual ventilation. During

VATS lobectomy, because of the interference to the surgical field caused by reinflating the residual lobe, the anesthesiologist may be asked to fiberoptically inspect the bronchial tree to confirm patency of the bronchus of the noninvolved lobe(s). Once the lobectomy has been performed, the bronchial stump is usually tested with 30 cm H_2O positive pressure in the anesthetic circuit to detect the presence of air leaks. A patient undergoing an uncomplicated lobectomy can usually be extubated in the operating room provided preoperative respiratory function is adequate (see Preoperative Assessment earlier in the chapter) and the patient is alert, warm, and comfortable ("AWaC").

Pancoast tumors are carcinomas of the superior sulcus of the lung and can invade and compress local structures including the lower brachial plexus, subclavian blood vessels, stellate ganglion (causing Horner syndrome), and vertebrae. Lobectomy may require a two-stage procedure with an initial operation for posterior instrumentation/stabilization of the spine. During lobectomy, extensive chest wall resection may be required and massive transfusion is a possibility. Peripheral lines and monitoring should be in the contralateral arm to accommodate the frequent compression of the ipsilateral vessels during surgery.

SLEEVE LOBECTOMY

Bronchial sleeve resections are performed for neoplasms or benign strictures. Bronchogenic carcinoma is the most frequent indication for a sleeve lobectomy, followed by carcinoid tumors, endobronchial metastases, primary airway tumors, and bronchial adenomas. Sleeve lobectomy involving parenchyma-sparing techniques in patients with a limited pulmonary reserve, is an alternative procedure for patients who cannot tolerate a pneumonectomy. The sleeve technique involves mainstem bronchial resection without parenchymal involvement and possibly resection of pulmonary arteries to avoid pneumonectomy (Fig. 66-42).

Patients undergoing sleeve lobectomy require lung isolation with a contralateral DLT or endobronchial tube (i.e., use a right-sided DLT for a left sleeve lobectomy). High-frequency jet ventilation can be used for resections done close to the tracheal carina. For a sleeve lobectomy involving resectioning of vessels, heparinization is necessary. In these cases, thoracic epidural catheters should not be manipulated for 24 hours after heparin administration. During pulmonary arterioplasty, uncontrollable bleeding may occur. For this reason, large-bore intravenous catheters should be used. Patients undergoing sleeve lobectomy are usually extubated in the operating room before transfer to the postanesthesia recovery room. Immediate and long-term survival is better after sleeve lobectomy compared with right pneumonectomy for comparable stages of right upper lobe cancer.[182]

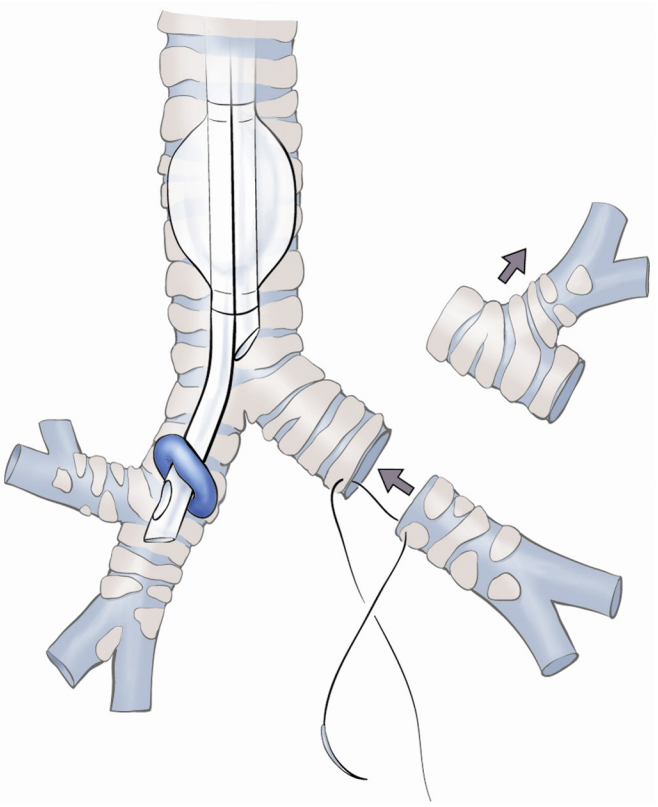


Figure 66-42. Diagram of the surgical procedure for a left upper sleeve lobectomy. Airway management is done with a right-sided double-lumen endobronchial tube. It will not be possible to position an endobronchial tube or bronchial blocker in the ipsilateral mainstem bronchus during this procedure.

PNEUMONECTOMY

Complete removal of the lung is required when a lobectomy or its modifications is not adequate to remove the local disease and/or ipsilateral lymph node metastases. Atelectasis and pneumonia occur after pneumonectomy as they do after lobectomy, but they may be less of a problem because of the absence of residual parenchymal dysfunction on the operative side. However, the mortality rate after pneumonectomy exceeds that for lobectomy because of postoperative cardiac complications and acute lung injury. The overall operative mortality for the first 30 days after pneumonectomy ranges from 5% to 13% and correlates inversely with the surgical case volume.[183] The risk of complications increases fivefold in patients aged 65 and older.[184]

Thoracotomy for pneumonectomy is usually performed through a standard posterolateral incision. After all vessels are stapled, stapling of the bronchus occurs and the entire lung is taken from the chest. A test for air leaks is generally performed at this point and reconstruction of the bronchial stump is completed. The bronchial stump should be as short as possible to prevent a pocket for the collection of secretions.

There is no consensus among thoracic surgeons on the best method of management of the postpneumonectomy space. If suction is applied to an empty hemithorax or a chest drain is connected to a standard underwater-seal system, it may cause a mediastinal shift with hemodynamic collapse. Some thoracic surgeons do not place a chest drain after a pneumonectomy; some thoracic surgeons prefer to use a temporary drainage catheter to add or remove air. The removal of air, ranging from 0.75 to

1.5 L, is necessary to empty the chest and to keep the mediastinum and the trachea in the midline ("balanced"). Some surgeons place a specifically designed postpneumonectomy chest drainage system with both high- and low-pressure underwater relief valves to balance the mediastinum.[185] A chest radiograph is mandatory after the patient arrives in the postanesthesia care unit or in the surgical intensive care unit to assess the mediastinal shift.

The patient scheduled to undergo a pneumonectomy is considered at high risk for perioperative morbidity and mortality. The placement of large-bore intravenous lines is necessary in case blood products need to be administered. An invasive arterial line is placed for measurement of beat-to-beat blood pressure and to monitor arterial blood gases. A CVP catheter is recommended to help guide intravascular fluid management and to administer vasopressors if needed, specifically in the postoperative period.

A major lung resection, such as pneumonectomy, decreases ventilatory function and has significant effects on right ventricular function.[186] Immediately after pneumonectomy, the right ventricle may dilate and the right ventricular function decreases. Increased right ventricular afterload is caused by an increase in pulmonary artery pressure and pulmonary vascular resistance. This is considered to be one of the main causes of right ventricular dysfunction after a major lung resection.

Management of lung isolation in a pneumonectomy patient can be achieved with a DLT, bronchial blocker, or SLT. When using a DLT for a pneumonectomy patient, it is optimal to use a device that does not interfere with the ipsilateral airway (i.e., for a right pneumonectomy use a left-sided DLT). If a left-sided DLT or bronchial blocker is used for a left pneumonectomy, it must be withdrawn before stapling the bronchus to avoid accidental inclusion into the suture line.

Specific areas of concern in the management of the patient undergoing pneumonectomy include: (1) fluid management, (2) intraoperative tidal volume, and (3) acute lung injury post surgery. Fluid administration after major lung resection continues to be an issue. In a retrospective report by Zeldin and associates,[187] the risk factors that were identified for the development of acute lung injury ("postpneumonectomy pulmonary edema") were a right-sided pneumonectomy, increased perioperative IV fluid administration, and increased urine output in the postoperative period. A more recent study by Licker and colleagues has shown that the excessive administration of intravenous fluids in thoracic surgical patients (more than 3 L in the first 24 hours) is an independent risk related to an acute lung injury.[188] There is reasonable clinical evidence that excessive fluid administration is associated with the development of an acute lung injury, which has a high mortality rate after pneumonectomy. Consequently, pneumonectomy patients should have restricted intraoperative fluid administration while preserving renal function. Some cases may require the use of inotropes/vasopressors to maintain hemodynamic stability while restricting fluids (see Box 66-8).

Respiratory failure is a leading cause of postoperative morbidity and mortality in patients undergoing pneumonectomy. A retrospective report[189] involving 170 pneumonectomy patients showed that patients who received median tidal volumes greater than 8 mL/kg had a greater risk of respiratory failure in the postoperative period after pneumonectomy. In contrast, patients who received tidal volumes less than 6 mL/kg were at lower risk for respiratory failure. Schilling and colleagues[190] have shown that a tidal volume of 5 mL/kg during OLV significantly reduces the inflammatory response to alveolar cytokines. Considering these factors, it is prudent to use lower tidal volumes (i.e., 5-6 mL/kg ideal body weight) in the pneumonectomy patient and limit peak and plateau inspiratory pressures (i.e., <35 and 25 cm H_2O, respectively) during OLV.

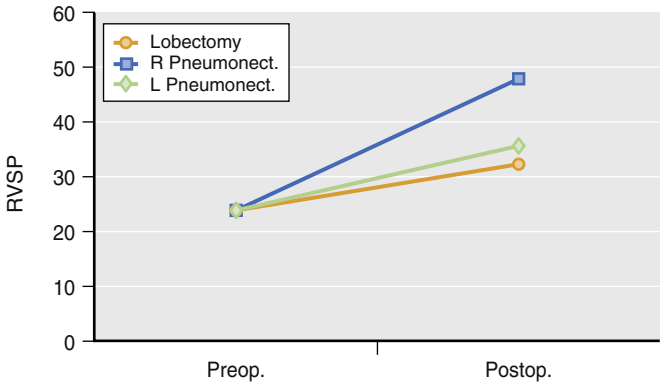


Figure 66-43. Comparison of right ventricular systolic pressure (RVSP) measured by echocardiography in patients before (Preop.) and at 6 months after (Postop.) pulmonary resections. *L Pneumonect.*, left pneumonectomy; *R Pneumonect.*, right pneumonectomy. Note the elevated RVSP, and therefore pulmonary artery pressure, after a right pneumonectomy. *(Based on data from Iglesias M, Martinez E, Badia JR, Macchiarini P: Extrapulmonary ventilation for unresponsive severe acute respiratory distress syndrome after pulmonary resection,* Ann Thorac Surg *85: 237, 2008.)*

The incidence of acute lung injury (postpneumonectomy pulmonary edema) after pneumonectomy is only 4%. However, the mortality rate is 30% to 50%. The etiology seems multifactorial. One study[190] has identified four independent risk factors for acute lung injury after pulmonary resection: (1) pneumonectomy; (2) excessive administration of fluids in the intraoperative period; (3) high intraoperative ventilatory pressure index (combined airway pressure and time); and (4) preoperative alcohol abuse. The incidence of an acute lung injury is greater for a right- versus a left-sided pneumonectomy. This may be related to the higher postoperative pulmonary artery pressures after a right versus a left pneumonectomy (Fig. 66-43).[191] Currently, only symptomatic management is appropriate for this lung injury. This includes fluid restrictions, diuretic administration, low ventilatory pressures and tidal volumes (if mechanical ventilation is used), and measures to decrease the pulmonary artery pressure. Extracorporeal techniques of ventilatory assist may be useful in managing this complication.[192]

EXTRAPLEURAL PNEUMONECTOMY

Extrapleural pneumonectomy is a therapeutic option for selected patients with malignant pleural mesothelioma.[193]

Significant improvement in survival has been achieved in patients who have an advanced malignant pleural mesothelioma with extrapleural pneumonectomy and high-dose radiotherapy in the postoperative period. Extrapleural pneumonectomy involves an extensive resection that may include lymph nodes, pericardium, diaphragm, parietal pleura, and the chest wall. The anesthetic management of the extrapleural pneumonectomy patient is characterized by significant loss of blood caused by chest wall vessel involvement. In these patients, it is recommended that a CVP catheter be used to guide intravascular fluid administration and ensure large-bore IV access. During tumor dissection, venous return to the heart may be compromised owing to multiple factors including blood loss, compression effect by the tumor in superior vena cava, or surgical causes. If there is an excessive loss of blood, it must be replaced to maintain an acceptable hematocrit level and the coagulation profile kept within normal limits. Because of extensive tumor resection and the potential for a pericardial resection in right-sided surgery, cardiac herniation or hemodynamic instability can appear postoperatively after the patient is turned from the lateral decubitus to the supine position. It is common to ventilate these patients for a short period postoperatively because of the extended duration of the surgery and the large fluid shifts. If a DLT is used intraoperatively, the DLT is usually replaced at the end of the case with an SLT.

SLEEVE PNEUMONECTOMY

Tumors involving the most proximal portions of the mainstem bronchus and the carina may require a sleeve pneumonectomy. These are most commonly performed for right-sided tumors and can usually be performed without cardiopulmonary bypass via a right thoracotomy. A long SLT can be advanced across into the left mainstem bronchus during the period of tracheo-bronchial anastomosis. High-frequency positive-pressure ventilation (HFPPV) has also been used for this procedure and the combined use of HFPPV and a DLT has been described.[194] Because the carina is surgically more accessible from the right side, left sleeve pneumonectomies are commonly performed as a two-stage operation. First is a left thoracotomy and pneumonectomy, and a right thoracotomy for the carinal excision follows. The complication and mortality rates are higher, and the 5-year survival (20%) is significantly lower than for other pulmonary resections. Postpneumonectomy pulmonary edema is particularly a problem after right sleeve pneumonectomy.

LIMITED PULMONARY RESECTIONS: SEGMENTECTOMY AND WEDGE RESECTION

A limited pulmonary resection is one in which less than a complete lobe is removed. The two procedures fitting this definition are *segmentectomy* and *wedge resection*. Segmentectomy is an anatomic pulmonary resection of the pulmonary artery, vein, bronchus, and parenchyma of a particular segment of the lung. Segmentectomy is usually performed as surgical therapy for patients with primary lung cancer and limited cardiorespiratory reserves. In contrast, a wedge resection is a nonanatomic removal of a portion of the lung parenchyma with a 1.5- to 2.0-cm margin and can be accomplished by open thoracotomy or VATS. Wedge resections are most commonly performed for diagnosis of lung lesions with unknown histology or for palliation in patients with metastatic lesions in the lungs from distant primary tumors. Lung cancers that are considered for limited resection are usually smaller than 3 cm and are located in the periphery of the lung with regional lymph nodes free of metastatic cancer.

A group of patients considered for limited pulmonary resection are those who develop a new primary lesion after a previous lobectomy or pneumonectomy. The patient with compromised lung function presents a greater risk in the intraoperative period (hypoxemia during OLV or prolonged intubation after surgery). Cerfolio and associates[195] reported that lung cancer patients with compromised pulmonary function can safely undergo limited pulmonary resection if selected appropriately. Segmentectomies and wedge resections can be performed with any of the standard thoracotomy or VATS incisions. Segments that are most commonly resected are in the upper lobes or the superior segments of the lower lobes.

Anesthetic technique and monitoring are essentially the same as for larger pulmonary resections. To facilitate surgical exposure and achieve OLV, it is necessary to use either a DLT or a bronchial blocker. If the patient had a previous contralateral lobectomy or a pneumonectomy, selective lobar collapse with the use of a bronchial blocker will facilitate surgical exposure while maintaining oxygenation. In selected cases, the combined use of a DLT and a bronchial blocker will allow selective lobar collapse/ventilation in the ipsilateral lung.[196] It is very important to use low tidal volumes (i.e., 3-5 mL/kg) during selective lobar ventilation, particularly in patients with previous pneumonectomy to prevent overinflation in the remaining lobes.

Segmentectomy plays a significant role in the management of patients with a second primary lung cancer. Many of these patients have previously undergone thoracic surgery, including previous lobectomy or pneumonectomy; therefore the potential for increased intraoperative bleeding is always a risk. In addition, because many of these patients have compromised lung function, early extubation may not be feasible. A common complication after surgery is an air leak. Chest tubes are placed to maximize postoperative expansion and minimize space complications. Suction and underwater-seal chest drainage is used in the postoperative period.

ANESTHETIC MANAGEMENT FOR SPECIFIC SURGICAL PROCEDURES

ESOPHAGEAL SURGERY

Esophageal surgery is performed for both malignant and benign disease and may be curative or palliative. General

considerations that apply to almost all esophageal surgery patients include an increased risk of aspiration caused by esophageal dysfunction and the possibility of malnutrition.

Esophagectomy

Esophagectomy is a palliative and potentially curative treatment for esophageal cancer and may occasionally be required for some benign obstructive lesions that do not respond to conservative therapy. It is a major surgical procedure and is associated with high morbidity and mortality rates (10%-15%). There is an inverse correlation between perioperative mortality and surgical volume, and the cure rate of esophageal cancer with esophagectomy is between 10% and 50%. There are multiple surgical procedures for esophageal cancer (Table 66-11) that combine some or all of three fundamental approaches: (1) a transthoracic approach, (2) a transhiatal approach, and (3) minimally invasive surgery (laparoscopic/thoracoscopic or robotic esophagectomy).[197] The incidence of respiratory complications has been reported to be between 18% and 26% for both the transthoracic and transhiatal esophagectomy approaches.[198] One study showed that the development of acute respiratory distress syndrome occurred in 14.5% of patients and acute lung injury occurred in 24%.[199] Complications associated with the gastroesophageal anastomosis are: anastomotic leakage/dehiscence (5%-26%) and stenosis (12%-40%). Outcomes are improved with a multimodal anesthetic management protocol using fluid restriction, early extubation, thoracic epidural analgesia, and vasopressor/inotrope infusions to support blood pressure.[200] Hypotension decreases the blood flow to the esophagogastric anastomosis. The use of vasopressors or inotropes, in normovolemic patients, restores the systemic pressure and the anastomotic blood flow.[201] Fluid management for esophageal surgery is essentially the same as for pulmonary resection surgery.

Transthoracic Approach. Transthoracic esophagectomy is commonly a two-phase procedure. The first phase involves a laparotomy performed with the patient in the supine position and the creation of a neoesophagus tube using the stomach. The second phase involves a right-sided thoracotomy in the left lateral position and esophageal reconstruction through the thoracic route. Some surgeons may perform this procedure through an extended left thoracoabdominal incision.

The anesthetic management for these patients includes the use of standard monitors, an invasive arterial line, and a CVP catheter to accommodate the large fluid shifts. Access to the right internal jugular is not a problem, but there is always the possibility of a surgical esophageal anastomosis in the left neck contraindicating access to the left internal jugular. A thoracic epidural catheter is usually placed to provide postoperative analgesia. Because of the wide number of dermatomes that must be covered for both incisions by the epidural infusion, it is best to use hydrophilic opioids (such as hydromorphone) in combination with local anesthetics in preference to lipophilic opioids. Most patients with an esophageal carcinoma have gastric reflux; for this reason, precautions (including a rapid-sequence induction with cricoid pressure) should be taken to protect the airway against aspiration.

During the second phase (right thoracotomy), a left-sided DLT or a right-sided bronchial blocker is required to facilitate lung collapse. Because esophagectomy requires a prolonged period of OLV, this procedure is marked by an important inflammatory response. Michelet and colleagues[202] have shown that the use of protective ventilatory strategies during OLV decreases the proinflammatory systemic response. This decreased response can be achieved by delivering 5 mL/kg of tidal volume and a PEEP of 5 cm H_2O to the dependent lung, instead of the 9 mL/kg of tidal volume that is conventionally used during esophagectomy.

TABLE 66-11 **SURGICAL APPROACHES FOR ESOPHAGECTOMY AND ESOPHAGOGASTRECTOMY**

Surgery	Incisions	Anesthetic Considerations
Laparotomy and right thoracotomy ("Ivor Lewis")	Two incisions: upper abdominal midline, right thoracotomy at ≈5th or 6th intercostal space	One-lung ventilation necessary Repositioning of patient intraoperatively from supine to right lateral
Transhiatal ("Orringer") (lower-third lesions; may be used for mid-third in some centers)	Two incisions: upper abdominal midline and left neck	Hemodynamic instability from cardiac compression during blunt intrathoracic dissection Possibility of occult perforation of tracheobronchial tree during blunt dissection (leave endotracheal tube uncut in case of need to advance into bronchus) No vascular access in left neck
Left thoracoabdominal (lower esophageal lesions only)	One incision: left lateral thoracotomy extended to left upper lateral abdominal	One-lung ventilation desirable
Combined chest, abdominal, and neck ("three hole"; upper and mid esophageal lesions)	Three incisions: right thoracotomy, laparotomy, left neck	One-lung ventilation necessary Repositioning lateral to supine intraoperatively No vascular access in left neck
Thoracoscopy plus laparotomy or laparoscopy	One or two incisions plus video port access Thoracoscopy to avoid blunt dissection in chest; neck incision at end	One-lung ventilation necessary Potentially prolonged surgery

Manipulation of the esophagus during thoracotomy may compromise venous return, which can cause hypotensive episodes. Early extubation in the operating room is encouraged if the patient meets the standard criteria for extubation. If extubation is not possible, the DLT should be replaced with an SLT and mechanical ventilation used in the postoperative period.

Transhiatal Approach. Airway management is done with an SLT. Apart from this, anesthetic management is essentially the same as for a transthoracic approach. Of special concern is that the blunt/blind manual dissection of the thoracic esophagus by the surgeon through the hiatus during this approach is often associated with cardiac compression and sudden severe hypotension. In addition, this blind dissection can cause vascular or distal airway injuries if the tumor is adherent.[203] It is good practice to not cut the endotracheal tube for this procedure in case of surgical perforation of the trachea or bronchus necessitating advancement of the endotracheal tube into a mainstem bronchus for emergent OLV.

Minimally Invasive Approach. Minimally invasive esophagectomy involves the use of laparoscopic, thoracoscopic, or robotic surgical approaches. For a laparoscopic approach, distention of the peritoneum may produce hemodynamic changes because of the intragastric pressure generated by carbon dioxide insufflation. In these cases, it is important to adjust ventilatory parameters to achieve an optimal $Paco_2$. For the thoracoscopic approach, a left-sided DLT or a bronchial blocker is required. During robotic surgery, the use of a lung isolation device is required to achieve OLV. Special considerations for robotic surgery include protecting the patients against any injury related to the robot and not moving the operating room table while the robot is being used. The thoracoscopic-assisted esophagectomy has several advantages including less blood loss, less pain, and a shorter length of hospitalization. This method does, however, require a prolonged duration of surgery.

All patients undergoing esophagectomy require a nasogastric tube, which must be well-secured at the end of the operation. Respiratory complications, including the development of an acute lung injury, may be present after an esophagectomy. Intrathoracic anastomotic leakage is a feared major complication after esophageal surgery and carries a high mortality rate of 4% to 30%.[204] To treat this potential complication, nasogastric decompression and nutritional support should be used. Severe leakage usually occurs in the early postoperative period as a consequence of gastric necrosis, and it may present with respiratory symptoms and signs of shock. Even though there is a very high mortality rate, prompt surgical intervention is recommended. Patients older than 80 years have an increased risk of mortality after esophagectomy, independent of comorbidity.[205]

Esophageal Surgery for Benign Disease

Hiatal Hernia. Although most patients with gastroesophageal reflux have a hiatal hernia, most patients with a hiatal hernia do not have significant reflux.[206] Patients with heartburn have a lowered barrier pressure and may be at increased risk for regurgitation of gastric contents. Two types of hiatal hernia have been described. Type I hernias, also called "sliding hernias," make up approximately 90% of esophageal hiatal hernias. In this type, the esophagogastric junction and fundus of the stomach have herniated axially through the esophageal hiatus into the thorax (Fig. 66-44). The term *sliding* refers to the presence of a sac of parietal peritoneum. The lower esophageal sphincter is cephalad to the diaphragm and may not respond appropriately to increased abdominal pressure. Thus a reduced barrier pressure during coughing or breathing leads to regurgitation. The type II or "paraesophageal hiatal hernia," is characterized by portions of the stomach herniating into the thorax next to the esophagus. In the presence of a type II hernia, the esophagogastric junction is still located in the abdomen. The most common complications from type II hernias are blood loss, anemia, and gastric volvulus.

The goal of surgical repair of a sliding hernia is to obtain competence of the gastroesophageal junction. Because restoration of the normal anatomy is not always successful in preventing subsequent reflux, several antireflux operations have been developed, such as the Nissen fundoplication. Repair of a hiatal hernia can be performed via a thoracotomy or laparotomy, or minimally invasively.

Benign Esophageal Stricture. Chronic reflux of acidic gastric contents can lead to ulceration, inflammation, and eventually stricture of the esophagus. The pathologic

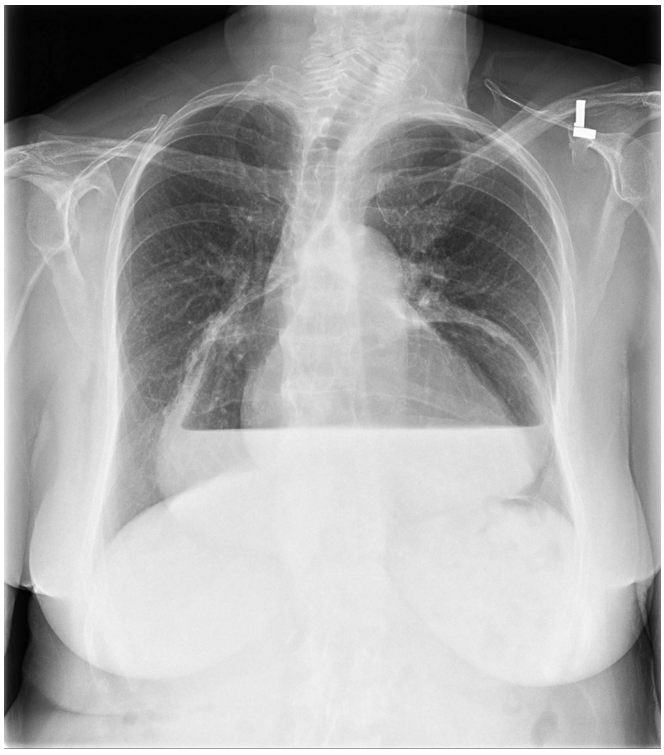


Figure 66-44. Chest radiograph of a patient with a hiatal hernia and a dilated intrathoracic stomach, scheduled for hiatal hernia repair via a left thoracotomy. An air-fluid level can be seen in the stomach behind the heart. These patients are at high risk for aspiration on induction of anesthesia.

changes are reversible if the acidic gastric contents cease their contact with the esophageal mucosa. Surgery may be necessary if medical treatment and dilatations are inadequate. There are two types of surgical repair, both of which are usually approached via a left thoracoabdominal incision. Gastroplasty after esophageal dilatation interposes the fundus of the stomach between the esophageal mucosa and the acidic milieu of the stomach. The remaining fundus may be sewn to the lower esophagus to create a valvelike effect. The second type of repair is resection of the stricture and the creation of a thoracic end-to-side esophagogastrostomy. Vagotomy and antrectomy are performed to eliminate stomach acidity, and a Roux-en-Y gastric drainage procedure is performed to prevent alkaline intestinal reflux.

Esophageal Perforation and Rupture. There are multiple causes of esophageal perforation, including foreign bodies, endoscopy, bougienage, traumatic tracheal intubation, gastric tubes, and oropharyngeal suctioning. Iatrogenic causes are the most common, with upper gastrointestinal endoscopy being the most frequent cause. A rupture is a burst injury often caused by uncoordinated vomiting, straining associated with weight-lifting, childbirth, defecation, and crush injuries to the chest and abdomen. The rupture is usually located within 2 cm of the gastroesophageal junction on the left side. Rupture is the result of a sudden increase in abdominal pressure with a relaxed lower esophageal sphincter and an obstructed esophageal inlet. In contrast to a perforation, in the presence of a rupture, the stomach contents enter the mediastinum under high pressure and the patient becomes symptomatic much more abruptly.

In addition to chest and/or back pain, patients with intrathoracic esophageal perforation or rupture may develop hypotension, diaphoresis, tachypnea, cyanosis, emphysema, and hydrothorax or hydropneumothorax.[207] Radiologic studies may reveal subcutaneous emphysema, pneumomediastinum, widening of the mediastinum, pleural effusion, and pneumoperitoneium. Minor perforations can in some cases be managed conservatively. Major injuries will rapidly develop mediastinitis and sepsis if not treated surgically, so repair and drainage is an emergency procedure usually performed via a left or right thoracotomy.

Achalasia. Achalasia is a disorder in which there is a lack of peristalsis of the esophagus and a failure of the lower esophageal sphincter to relax in response to swallowing. Clinically, the patients have esophageal distention that may lead to chronic regurgitation and aspiration. The goal of treatment is to alleviate the distal obstruction. This can be done by either esophageal dilatation or by surgery. Dilatation, which carries with it the risk of perforation, can be achieved by mechanical, hydrostatic, or pneumatic means. The surgical repair consists of a Heller myotomy, which is an incision through the circular muscle of the esophagogastric junction. The myotomy is often combined with a hiatal hernia repair to prevent subsequent reflux. This can be performed via thoracotomy, laparotomy, or laparoscopy.[208] The Dor operation is a modification of the Heller procedure in which a stent is inserted into the muscular defect created by the myotomy to prevent muscular reapposition and thus recurrent dysphagia.[209]

Esophagorespiratory Tract Fistula. Esophagorespiratory tract fistula in an adult is most often a result of malignancy. Sometimes the fistula is benign and may be caused by injury from a tracheal tube, trauma, or inflammation. Of the malignant fistulas, approximately 85% are secondary to esophageal cancer. In contrast to the pediatric patient with esophagorespiratory tract fistula, which usually connects the distal esophagus to the posterior tracheal wall, these fistulas may connect to any part of the respiratory tract.[210] In most cases, the fistula can be seen on esophagoscopy or bronchoscopy. In malignant cases, the goal of surgery is usually palliation. The technique of lung isolation will depend on the location of the fistula. One option in adults with a distal tracheal fistula is the use of bilateral small (5-6 mm ID) endobronchial tubes.[211]

Zenker Diverticulum. Zenker diverticulum is actually a diverticulum of the lower pharynx that arises from a weakness at the junction of the thyropharyngeus and cricopharyngeus muscles just proximal to the esophagus. It is commonly considered an esophageal lesion because of its proximity to the upper esophagus and because the underlying cause may be a failure of relaxation of the upper esophageal sphincter during swallowing. Early symptoms may be nonspecific such as dysphagia or complaints of food being stuck in the throat. As the diverticulum enlarges, patients describe noisy swallowing, regurgitation of undigested food, and coughing spells while supine. Recurrent aspiration and pneumonia may develop.

The major concern for anesthesia is the possibility of aspiration on induction of general anesthesia for excision of the diverticulum.[212] Even prolonged fasting does not ensure that the diverticulum will be empty. The best method to empty the diverticulum is to have the patient express and regurgitate the contents immediately before induction. Many of these patients will be used to doing this on a regular basis at home. Because the diverticulum orifice is almost always above the level of the cricoid cartilage, cricoid pressure during a rapid-sequence induction does not prevent aspiration and may contribute to aspiration by causing the sac to empty into the pharynx. Surgical excision is usually done through a lower left neck incision.

The safest method of managing the airway for these patients may be awake fiberoptic intubation. However, intubation has been managed without incident using a modified rapid-sequence induction without cricoid pressure and with the patient supine and in a head-up position of 20 to 30 degrees. Other considerations in these patients include the possibility of perforation of the diverticulum when passing an orogastric or nasogastic tube or an esophageal bougie.

ANESTHESIA FOR TRACHEAL RESECTION

Tracheal resection and reconstruction is indicated in patients who have a tracheal obstruction as a result of a tracheal tumor, previous tracheal trauma (most

commonly because of postintubation stenosis), congenital anomalies, vascular lesions, and tracheomalacia. For patients who have operable tumors, approximately 80% undergo segmental resection with primary anastomosis, 10% undergo segmental resection with prosthetic reconstruction, and the remaining 10% undergo placement of a T-tube stent.

Diagnostic studies are reviewed as part of the preoperative evaluation. The CT scan is a useful diagnostic tool to evaluate the degree, level, and length of the lesion. Bronchoscopy is one of the definitive diagnostic tests for tracheal obstruction. Bronchoscopy for a patient with tracheal stenosis should be carried out in the operating room where the surgical and anesthesia teams are present and ready to intervene should loss of airway occur. An advantage of rigid bronchoscopy over flexible bronchoscopy is that it can bypass the obstruction and provide a ventilation pathway if complete obstruction occurs. During surgery, all patients should have an invasive arterial catheter placed to facilitate measurement of arterial blood gases, as well as to measure arterial blood pressure. CVP catheters are only used if the patient requires cardiopulmonary bypass (CPB).

A variety of methods for providing adequate oxygenation and elimination of CO_2 have been used during tracheal resection. The different alternatives include (1) standard orotracheal intubation, (2) insertion of a sterile SLT into the opened trachea or bronchus distal to the area of resection, (3) high-frequency jet ventilation (HFJV) through the stenotic area, (4) high-frequency positive-pressure ventilation (HFPPV), and (5) the use of CPB.

Induction of anesthesia in patients with a compromised airway requires good communication between the surgical team and the anesthesiologist. The surgeon should always be in the operating room during induction and available to manage a surgical airway if this becomes necessary.[213] A rigid bronchoscope must be immediately available. The patient should be thoroughly preoxygenated with 100% oxygen before induction. The airways of patients with congenital or acquired tracheal stenosis are unlikely to collapse during induction of anesthesia. However, intratracheal masses may lead to airway obstruction with induction of anesthesia and should be managed similarly to anterior mediastinal masses (discussed later). One airway management technique is to begin the case with rigid bronchoscopy and tracheal dilation and then to pass an SLT through the stenosis. This tube is withdrawn into the proximal trachea once the distal trachea is opened and a second sterile SLT is placed into the distal trachea by the surgeon. Ventilation is done via a sterile anesthetic circuit passed across the drapes into the surgical field. With a low tracheal lesion, a right thoracotomy provides the optimal surgical exposure. A sterile SLT is used to provide ventilation to the lung distal to the resection. After the posterior anastomosis is completed, the endobronchial tube is removed and the original SLT is advanced past the site of resection (Fig. 66-45). This technique can also be used for carinal resection.

A third technique for airway management during tracheal resection includes HFJV through a small-bore endotracheal tube or catheter.[214] With this technique, a small-bore uncuffed catheter is placed through the stenotic area, and ventilation is accomplished by intermittently exposing the lung to a high flow of fresh gas through the catheter. Other techniques that have been used for oxygenation during distal airway resections include HFPPV, helium-oxygen mixtures, and CPB.

After the tracheal resection is completed, most patients are kept in a position of neck flexion to reduce tension on the suture line. Replacement of the SLT by an LMA for emergence facilitates bronchoscopy if required. A thick chin-sternum suture may be placed for several days to maintain neck flexion, or a cervical splint may be used.[215] A T-tube with the upper limb 0.5 to 1 cm above the vocal cords may be inserted at the end of surgery in cases where glottic edema is a concern, or for patients requiring

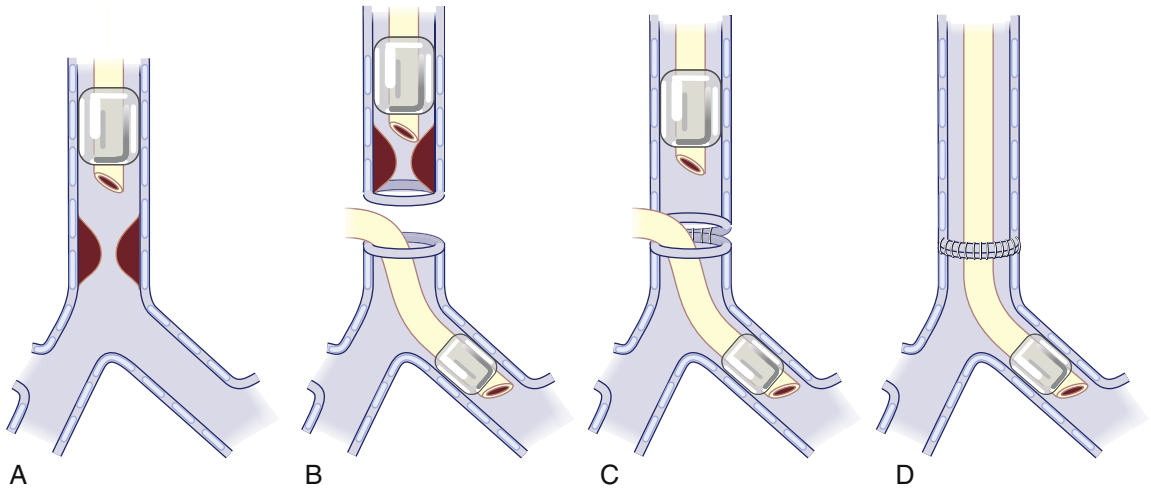


Figure 66-45. Airway management and surgical procedure for resection of a low tracheal lesion. **A,** Initial intubation above the lesion. **B,** Left endobronchial intubation distal to the lesion after the trachea has been opened. **C,** Placement of sutures for the posterior anastomosis. **D,** The endobronchial tube has been removed, and the original endotracheal tube has been advanced distal to the anterior anastomosis into an endobronchial position. *(Modified from Geffin B, Bland J, Grillo HC: Anesthetic management of tracheal resection and reconstruction,* Anesth Analg *48:884, 1969.)*

ventilatory support. If a tracheostomy is performed, it will be done distal to the anastomosis. Early extubation is highly desirable. If a patient requires reintubation, it should be performed with a flexible fiberoptic bronchoscope by advancing an SLT under direct vision over the bronchoscope and then placing it in the patient's trachea. The patient is kept in a head-up position to diminish swelling. Steroids may be useful in these cases to decrease airway edema.

One of the complications in the postoperative period is tetraplegia, with hyperflexion of the neck having been implicated as a potential cause. In these cases, it is necessary to cut the chin stitch. An infusion of propofol and remifentanil, with fiberoptic bronchoscopy guidance and full patient cooperation, can aid extubation.[216]

BRONCHIECTASIS/LUNG ABSCESS/ EMPYEMA

Bronchiectasis is a disease that causes localized, irreversible dilatation of part of the bronchial tree. Involved bronchi are inflamed and easily collapsible, resulting in airflow obstruction and impaired clearance of secretions. Bronchiectasis is associated with a wide range of disorders, but it usually results from necrotizing bacterial infections. Bronchiectasis may require surgery if it causes hemoptysis or recurrent pneumonia. An abscess is a nonanatomic area of liquefactive necrosis of the lung, often distal to an obstruction or after a bout of pneumonia (Fig. 66-46). An empyema is a collection of pus between the visceral and parietal pleural layers, often a complication of pneumonia or surgery. Empyema complicating lung resections occurs in 2% to 16% of cases and with a 40% increase in the associated perioperative mortality rate. Mortality further increases when the empyema is associated with a bronchopleural fistula. Surgical interventions for patients with empyema include: decortication (the method of choice when the underlying lung is unable to expand because of a thick inflammatory coat) or open-window thoracostomy (the ideal method for drainage of the pleural cavity to control septic symptoms in patients with postpulmonary resection empyema).[217] In less severe cases, tube drainage, antibiotic irrigation, and debridement may be sufficient.

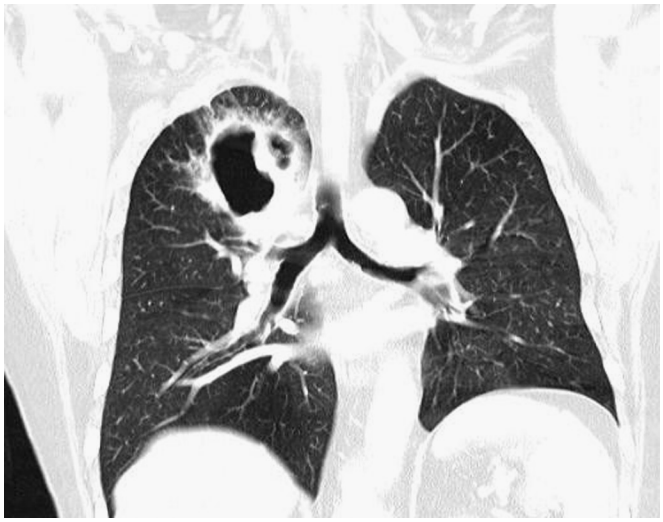


Figure 66-46. Computed tomographic scan of a patient with a lung abscess distal to an obstructing carcinoma of the right upper lobe. The diagnostic thick wall of the abscess and the air-fluid level can be appreciated in the right upper thorax. These patients are at risk for soiling of uncontaminated lung regions during repositioning for surgery from pus in the abscess. The optimal method of lung isolation is with a double-lumen endobronchial tube.

All of these infective indications for thoracic surgery are less common in the developed world since the introduction of antibiotics. Anesthetic considerations during surgery for these infective indications include the need for lung isolation to protect uninvolved lung regions from soiling by pus in the infected areas. The risk of soiling occurs if the patient is repositioned for surgery after induction of anesthesia before the lung is adequately isolated. Because of the inflammation, surgery is technically more difficult and there is a greater risk of massive hemorrhage.

Anesthetic Management

Some of these patients may present with sepsis at the time of surgery. In these patients, the placement of a thoracic epidural catheter is not recommended. They require lung isolation, preferably with a DLT. The DLT facilitates suctioning of debris and copious secretions that are present in the tracheobronchial tree. Patients undergoing a decortication may have massive blood loss. If the lung has been chronically collapsed, expansion should be done gradually to avoid the development of pulmonary edema upon reexpansion. Extubation in the operating room is encouraged if the patient meets the standard criteria for extubation.

BRONCHOPLEURAL FISTULA

A bronchopleural fistula may be caused by (1) rupture of a lung abscess, bronchus, bulla, cyst, or parenchymal tissue into the pleural space; (2) the erosion of a bronchus by carcinoma or chronic inflammatory disease; or (3) stump dehiscence of a bronchial suture line after pulmonary resection. Pneumonectomy patients have an incidence of bronchopleural fistula ranging from 2% to 11%,[218] with a mortality ranging from 5% to 70%.

The diagnosis of bronchopleural fistula is usually made clinically. After pneumonectomy, the diagnosis is based on the sudden onset of dyspnea, subcutaneous emphysema, contralateral deviation of the trachea, and a decrease of fluid level on serial radiographs of the chest (Fig. 66-47). In lobectomy patients, persistent air leak, purulent drainage, and expectoration of purulent material are usually diagnostic indicators of a bronchopleural fistula. When the fistula appears after removal of a chest tube, the diagnosis of bronchopleural fistula is made on the basis of fever, purulent sputum, and a new air-fluid level in the pleural cavity on the chest radiograph.

The diagnosis is confirmed by bronchoscopic examination. In addition, bronchography and sinograms of the fistula may be used to confirm the diagnosis. Other diagnostic methods include the injection of an indicator, such as methylene blue, into the pleural space and subsequent recovery of the indicator from sputum.

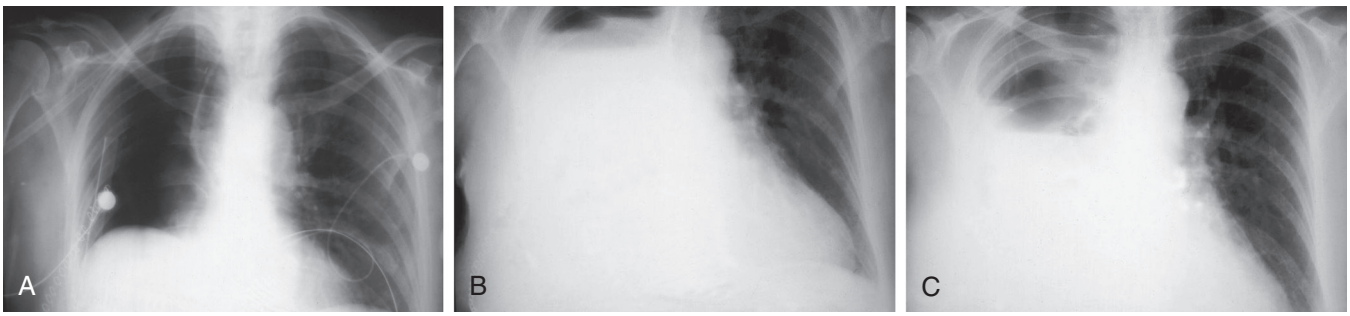


Figure 66-47. A, Chest radiograph of a patient immediately postoperatively after a right pneumonectomy. **B,** The same patient on postoperative day 6. This is a normal postpneumonectomy film. The right hemithorax is gradually filling with serous fluid. **C,** The same patient on postoperative day 7. The patient had the sudden onset of severe dyspnea, desaturation, and coughing. The chest radiograph reveals a decrease in the fluid level in the right hemithorax. This is diagnostic of a bronchopleural fistula caused by the dehiscence of the bronchial stump.

Accumulation of radionuclide in the pleural space after inhalation of xenon or a mixture of O_2 and N_2O to detect the presence of a bronchopleural fistula can also be used as indicators.[219]

If the disruption occurs early in postpneumonectomy patients it can be life threatening and it is possible to resuture the stump. Late or chronic postpneumonectomy bronchial disruption is managed with drainage or with the Clagett procedure, which includes open pleural drainage and the use of a muscle flap to reinforce the bronchial stump. In nonpneumonectomy cases, if the lung expands to fill the thoracic cavity, the air leak can usually be controlled with chest tube drainage alone. However, if the fistula is large and a significant leak through a large persistent pleural space occurs, it is unlikely that the fistula will close, and surgical resection is necessary

Anesthetic Management

The patient with a bronchopleural fistula presents several intraoperative challenges for the anesthesiologist, including: (1) the need for lung isolation to protect healthy lung regions, (2) the possibility of tension pneumothorax with positive-pressure ventilation, and (3) the possibility of inadequate ventilation caused by air-leak from the fistula.

Preoperatively, it is useful to estimate the loss of tidal volume through the bronchopleural fistula, which may be done in two ways. First, one should determine whether air bubbles flow intermittently or continuously through the chest tube. If air bubbles flow intermittently, then the fistula is small. In contrast, when a patient has a large bronchopleural fistula or bronchial rupture, air will bubble continuously through the water-seal chamber of the chest tube drainage system. Second, the size of the bronchopleural fistula may be quantified by the difference between inhaled and exhaled tidal volumes. In a nonintubated patient, this may be determined with a tight-fitting mask and a fast-responding spirometer. In an intubated patient, it is determined by direct attachment of the spirometer to the endotracheal tube. The larger the air leak, the greater the need to isolate the bronchopleural fistula with the use of a lung isolation device (a DLT or an independent bronchial blocker).

Several nonsurgical approaches (i.e., the use of various mechanical ventilation–chest tube drainage systems) have been used for the treatment of patients with a bronchopleural fistula. These approaches consist of OLV and differential lung ventilation, including HFV, PEEP to the pleural cavity equal to intrathoracic PEEP, and unidirectional chest tube values. One-way endobronchial valves have been used successfully in patients with bronchopleural fistula who were considered unfit for surgery.[220]

For patients undergoing operative repair, the ability to adequately deliver positive-pressure ventilation intraoperatively must be carefully considered before surgery. A chest drain should be placed before induction to avoid the possibility of tension pneumothorax with positive-pressure ventilation. A DLT is the best choice for delivering positive-pressure ventilation. The DLT can provide positive-pressure ventilation to the normal lung without loss of minute ventilation through the fistula and prevent the hazard of contamination of the uninfected lung with infected material when the patient is turned to the lateral decubitus position.

The safest method of obtaining lung isolation is awake fiberoptic intubation with a DLT.[221] However, this requires a cooperative patient and excellent topical anesthesia and is often not an option. Another option is to maintain spontaneous ventilation during induction and intubation until lung isolation is secured. This avoids the possibility of inadequate positive-pressure ventilation because of air-leak but is not well tolerated in older patients with significant comorbidity. If the patient has a postpneumonectomy fistula, the DLT or SLT must be guided under direct vision with the assistance fiberoptic bronchoscopy, and the tip of the endobronchial lumen should be placed in the noninvolved lung (i.e., for right-sided fistula, use a left-sided tube). Whatever anesthetic technique is used, the principle of anesthetic management for a bronchopleural fistula is: lung isolation before positive-pressure ventilation or repositioning the patient.

One option to avoid instrumentation of the airway in patients with bronchopleural fistula after pneumonectomy is the use of thoracic epidural anesthesia with intravenous sedation during minimally invasive surgery.[222] An alternative method of ventilating patients with multiple bronchopleural fistulas is the use of high-frequency oscillatory ventilation with permissive hypercapnia. This avoids barotrauma to the nonoperative lung, decreases bronchopleural fistula air-leak, and optimizes the operative outcome.[223] The advantage of high-frequency oscillatory ventilation over conventional mechanical ventilation is that it uses lower peak airway pressure and

higher minimum airway pressure and may decrease the air-leak across the fistula. Early extubation in the operating room should be considered in all patients undergoing fistula repair to avoid barotrauma to the surgical stump from positive-pressure ventilation in the postoperative period.

BLEBS, BULLAE, CYSTS, AND PNEUMATOCELES

BLEBS

A bleb is a subpleural collection of air under the visceral pleura caused by a ruptured alveolus. The air dissects through the pulmonary parenchyma and enlarges to form a bubble on the surface of the lung. Blebs most commonly occur at the apices of the lung and can rupture into the interpleural space, causing a pneumothorax. A single episode of spontaneous pneumothorax is usually treated conservatively with chest tube drainage until the air-leak has stopped. Resection of blebs is commonly indicated for recurrent pneumothoraces, bilateral pneumothoraces, or prolonged chest tube drainage. Resection of blebs after a single pneumothorax may be indicated if the patient's occupation exposes them to significant rapid fluctuations in atmospheric pressure (e.g., flight crews or scuba divers). Resection is most commonly combined with a procedure to obliterate the pleural space by partial pleurectomy or pleural abrasion. Resection of blebs is most often performed by VATS. Although VATS procedures per se are generally associated with a limited need for postoperative analgesia, pleurectomy or abrasion is very painful.

BULLAE

Bullae are thin-walled, air-filled intraparenchymal lung spaces caused by the loss of alveolar structural tissue (Fig. 66-48). These are usually associated with emphysema but their exact cause is unclear. Although there is some confusion over terminology in this area, bullous-like lesions of the lung associated with congenital malformations or secondary to trauma or infection are more correctly termed *pneumatoceles* or *cysts*. There are no universally accepted surgical indications for resection of lung bullae. A patient with symptomatic dyspnea and a giant bulla (or bullae) that occupies more than 30% of a hemithorax and in whom radiography and CT scans suggest that reasonably functional lung tissue can be restored to a more anatomically favorable position should be considered for bullectomy. Factors that support the effect of the bullae as a cause of a patient's dyspnea are a restrictive pattern of spirometry (proportional decrease of both FEV_1 and FVC) and a discrepancy in lung volume studies in which the FRC measured by plethysmography exceeds the FRC measured by helium dilution by more than 2 liters.

In the usual tidal volume range, bullae are more compliant than normal lung and fill preferentially during spontaneous ventilation. However, beyond the normal tidal volume range, bullae become much less compliant and the intrabulla pressure rises acutely as airway pressure increases. Measurement of in vivo intrabullae pressures in patients using fine needles both before and during anesthesia showed no evidence of a valve mechanism.[37] All bullae studied communicated with the central airways, although some did this very slowly. The typical compression pattern seen on radiographs or CT scans is most likely caused by secondary elastic recoil of normal lung regions (see Fig. 66-6). Intrabulla pressure at FRC corresponds with the mean airway pressure averaged over the respiratory cycle. Thus during spontaneous ventilation, the intrabulla pressure will be negative with respect to the surrounding lung tissue. However, whenever positive pressure is used, the intrabulla pressure will rise in relation to surrounding lung regions. There is a risk of hyperinflation and rupture whenever positive pressure is used. The complications of bulla rupture can be life threatening because of hemodynamic collapse from tension pneumothorax or inadequate ventilation owing to resultant bronchopleural fistula.

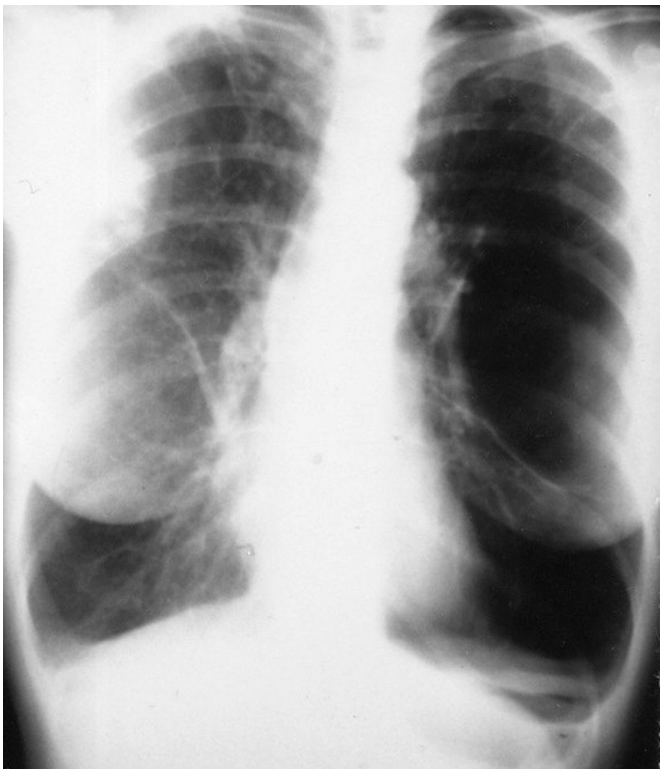


Figure 66-48. Chest radiograph of a patient with severe emphysema and multiple bullae including giant bullae of the left upper and lower lobes.

Relief of dyspnea symptoms and improved pulmonary function are well documented in patients after resection of giant bullae, with most patients showing an increase in FEV_1 of more than 0.3 L and excellent short-term improvement in quality of life, but with a decrease in improvement by 3 years.[224] Hypercapnia is not a contraindication for bulla resection. Lung infection must be meticulously treated preoperatively. Outcome depends on patient age, smoking history, and cardiac status. In the postoperative period, lung air-leaks are the major complication.

The surgical approach can be by traditional sternotomy or by VATS. Laser resection may decrease the incidence of air-leaks. Various nonsurgical thoracoscopic

and bronchoscopic procedures such as the subsegmental injections of fibrin glue have been used to deal with these air-leaks.

The anesthetic considerations for bullectomy are similar to those for a patient with a bronchopleural fistula, with the exception that it is best to not place a chest drain prophylactically because this may enter the bulla and create a fistula, and there is not the risk of soiling healthy lung regions from extrapleural fluid that there is with fistulas. For induction of anesthesia, it is optimal to maintain spontaneous ventilation until the lung or lobe with the bulla or bleb is isolated.[225] When there is a risk of aspiration or it is felt that the patient's gas exchange or hemodynamics may not permit spontaneous ventilation for induction, the anesthesiologist will have to use small tidal volumes and low airway pressures during positive-pressure ventilation until the airway is isolated.

CYSTS

Congenital bronchogenic cysts are products of abnormalities in the tracheobronchial budding process of lung organogenesis. They may occur peripherally within the lung parenchyma (70%) or centrally attached to the mediastinum or hilum. Bronchogenic cysts become problematic if they become enlarged, exerting a mass effect on functional lung or mediastinal structures; if they rupture and create a pneumothorax; or if they become infected. Small cysts without communication to a bronchus are asymptomatic and may be incidentally noted as round, clearly demarcated lesions on chest radiographs. Communicating cysts often produce air-fluid levels, are prone to recurrent infection, and may trap air by a ball-valve mechanism, risking rapid expansion or rupture. Infected cysts may be obscured by surrounding pneumonia, or they may be difficult to differentiate from an empyema. CT scans help differentiate cystic from solid lesions. Conservative surgical excision of bronchogenic cysts is generally recommended, regardless of whether a bronchial communication is evident.

Pulmonary hydatid cysts are watery, parasitic cysts containing larvae of the dog tapeworm *Echinococcus granulosus*.[226] *E. granulosus* is a relatively common cause of pulmonary cysts in endemic areas (e.g., Australia, New Zealand, South America, and some third-world regions). Hydatid cysts may grow in diameter by as much as 5 cm per year and become medically problematic in several ways. By mass effect, they may exert pressure on adjacent structures (e.g., bronchus, great vessels, esophagus). Spontaneous or traumatic rupture may occur, sending fluid, parasites, or laminated debris into adjacent tissue, bronchus, pleura, or the circulation (i.e., systemic emboli). Hypersensitivity reactions, bronchospasm, and anaphylaxis can result. Drainage into the bronchi may cause dramatic expulsion of fluid with respiratory distress or asphyxiation, depending on the amount of fluid involved. Rupture into the pleural space may result in a large hydropneumothorax, severe dyspnea, shock, suffocation, or anaphylaxis. Rupture becomes more dangerous and more likely as cysts become larger. It is recommended that any cyst larger than 7 cm should be removed.

Small, intact peripheral cysts are often easily enucleated without loss of lung parenchyma. Segmentectomy or lobectomy is indicated when single or multiple cysts occupy most of the segment or lobe. Patients with suppurative cysts should be prepared for surgery with postural drainage and antibiotics. Lung isolation and/or reduced airway pressure during dissection may be helpful in preventing herniation of the cyst. Increased airway pressure at the time of delivery may aid in removal of the cyst. The multiple bronchial openings in the residual cavity must then be identified and closed. Multiple "leak tests" with saline poured into the residual opening may be required to locate all bronchial openings. An alternative surgical strategy is to inject hypertonic saline into the cyst to sterilize it, followed by aspiration of the contents and removal of the evacuated cyst.

PNEUMATOCELE

Pneumatoceles are thin-walled, air-filled spaces generated by pulmonary infections or trauma. They usually appear in the first week of pneumonia and resolve spontaneously within 6 weeks. As with other lung cysts, potential complications of pneumatoceles include secondary infection and enlargement as a result of air entrapment, with possible rupture or displacement and compression of normal lung. Adverse hemodynamic consequences may result either from a tension pneumothorax or a tension pneumatocele. The latter is unusual and is presumed to result from a one-way valve mechanism, usually in the setting of positive-pressure mechanical ventilation.[227] Sometimes surgical decompression is required and is performed by percutaneous needle aspiration, catheter drainage, or chest tube drainage under CT or fluoroscopic guidance. Rarely is thoracoscopic or open surgical drainage or excision required.

LUNG TRANSPLANTATION

End-stage pulmonary disease is one of the most common causes of death. Lung transplantation is a definitive treatment for these patients. Indications and contraindications to lung transplantation are summarized in Box 66-12. Approximately 1500 lung transplants are performed annually worldwide; the number is limited by the supply of donor organs. Recipients fall into four major categories (by frequency of indication):

1. COPD
2. Cystic fibrosis (CF) (Fig. 66-49) and other congenital forms of bronchiectasis
3. Pulmonary fibrosis: idiopathic, associated with connective tissues disorders, other
4. Primary pulmonary hypertension

There are also several other, rarer indications such as primary bronchoalveloar lung cancer, lymphangioleiomyomatosis, and so on.[228] Depending on the patient's pathophysiology, there are several surgical options: single-lung transplantation, bilateral sequential (double) lung transplantation, heart-lung transplantation, and living-related lobar transplantation. An overall 5-year survival rate of 50% is the benchmark but depends on recipient age and diagnosis. Survival is generally better

BOX 66-12 ***Indications and Contraindications for Lung Transplantation***

INDICATIONS

- Untreatable end-stage pulmonary, parenchymal, or vascular disease
- Absence of other major medical illnesses
- Substantial limitation of daily activities
- Projected life expectancy less than 50% of 2- to 3-year predicted survival
- New York Heart Association Class III or IV functional level
- Rehabilitation potential
- Satisfactory psychosocial profile and emotional support system
- Acceptable nutritional status
- Disease-specific mortality exceeding transplant-specific mortality over 1 to 2 years

RELATIVE CONTRAINDICATIONS

- Age > 65 years
- Critical or unstable clinical conditions (e.g., shock, mechanical ventilation, extracorporeal membrane oxygenation)
- Severely limited functional status with poor rehabilitation potential
- Colonization with highly resistant or virulent bacteria, fungi, or mycobacteria
- Severe obesity defined as a body mass index greater than >30 kg/m^2
- Severe or symptomatic osteoporosis
- Other medical conditions not resulting in end-organ damage (e.g., diabetes mellitus, systemic hypertension, peripheral vascular disease, gastroesophageal reflux, patients with coronary artery disease s/p coronary artery stenting or percutaneous transluminal coronary angioplasty)

ABSOLUTE CONTRAINDICATIONS

- Untreatable advanced dysfunction of another major organ system (e.g., heart, liver, kidney)
- Active malignancy within the previous 2 years
- Noncurable chronic extrapulmonary infection
- Chronic active viral hepatitis B, hepatitis C, and HIV
- Significant chest wall or spinal deformity
- Documented nonadherence or inability to follow through with medical therapy, office follow-up, or both
- Untreatable psychiatric or psychological condition associated with inability to cooperate or comply with medical therapy
- Absence of a consistent or reliable social support system
- Substance addiction (e.g., alcohol, tobacco, narcotics) that is either currently active or was active within the previous 6 months

Based on Orens JB, Estenne M, Arcasoy S, et al: International guidelines for the selection of lung transplant candidates: 2006 update, J Heart Lung Transplant *25: 745, 2006.*

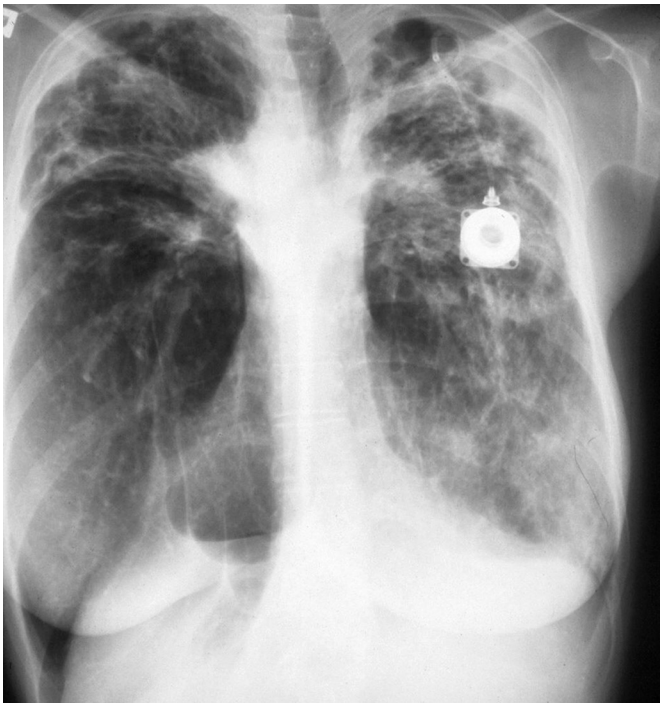


Figure 66-49. Chest radiograph of a patient with cystic fibrosis for bilateral lung transplantation. The chest image shows a typical pattern of bronchiectasis. A subcutaneous intravenous injection reservoir is seen over the upper left chest.

with double-lung than with single-lung transplants, with the exception of older pulmonary fibrosis patients, for whom there is no outcome difference between the two procedures.

Anesthetic airway management is most commonly done with a DLT. The advantage of using a DLT in transplantation is that it allows direct continuous access to both lungs for suctioning, oxygenation, and examination of the bronchial anastomoses. Several advances have allowed the use of DLTs for transplantation. The use of segmental bronchial lavage at induction via an SLT, before placement of the DLT facilitates suctioning via the DLT in patients with copious secretions. Monitoring includes invasive arterial and pulmonary catheters and transesophageal echocardiography in most centers. Anesthetic maintenance is based mainly on IV infusions because of the frequent need for airway access (suctioning, bronchoscopy), which causes problems in maintaining a stable level of inspired anesthetic vapor. Despite advances in lung preservation techniques, it is optimal to limit the donor lung ischemic period to 4 hours.

There are wide variations in the frequency of use of CPB during lung transplantation; some centers always use CPB and some centers almost never use it. CPB temporarily decreases postoperative gas exchange, increases intraoperative blood loss, and increases the duration of postoperative mechanical ventilation. There is no net decrease in short- or long-term mortality attributable to CPB. Extracorporeal membrane oxygenation (ECMO) is used in some centers in place of CPB intraoperatively.[229] ECMO is also used increasingly for postoperative respiratory support.

The intraoperative anesthetic complications depend, in large part, on the underlying lung disease. Emphysema patients are prone to hypotension on induction from positive-pressure ventilation (see COPD in "Preoperative Evaluation," discussed earlier). Problems in patients with CF include the inability to both deal with thick bronchial secretions and adequately ventilate these patients. CF patients, because they have both increased inspiratory and expiratory flow resistances, may benefit from slow inspiratory phase ventilation with a high airway pressure.[230] Because of the severely

decreased lung compliance, this method of ventilation causes little hemodynamic compromise in this subgroup of patients, if air trapping is avoided. Other recipient disease-specific problems include: hemodynamic collapse on induction because of right-heart dysfunction in primary pulmonary hypertensives, the poor tolerance of pulmonary fibrosis patients for OLV, and the risk of pneumothoraces in patients with lymphangiomyomatosis.

SUBSEQUENT ANESTHESIA FOR THE PULMONARY TRANSPLANT RECIPIENT

Many lung transplant recipients subsequently require anesthesia for related or unrelated surgical problems.[231] The frequency with which they present for surgery may be caused by complications of immunosuppression (e.g., infection, tumor, renal failure) or complications of the transplantation (e.g., bronchial stenosis, bronchiolitis obliterans). Most transplant recipients can be managed according to routine anesthetic practice including optimal perioperative respiratory care, antibiotic prophylaxis, and maintenance of immune suppression. Results of recent blood gas analysis, chest radiographs, and CT scans are vital in managing these patients. Most adults with bronchial anastomoses have no problem with endotracheal intubation. If endobronchial intubation or a DLT is used, a bronchoscopy should be performed first to assess the bronchial anastomoses, and the intubation should be done with fiberoptic guidance.

Single-lung transplant recipients with native lung emphysema are a specific concern. They have a marked imbalance in pulmonary compliance, with the native lung highly compliant and the donor lung of normal or reduced (if there is rejection) compliance. However, the major proportion of the pulmonary blood flow is usually to the allograft. With standard methods of positive-pressure ventilation, dynamic hyperinflation of the emphysematous lung with hemodynamic instability and problems with gas exchange may develop in these patients. They may require the use of a DLT and independent lung ventilation techniques, reducing the airway pressure and minute ventilation in the native lung, if positive-pressure ventilation is required.

LUNG VOLUME REDUCTION

Although resection of bullae is a well-established thoracic surgical procedure, the use of multiple wedge resections to reduce lung volume and improve symptoms in severe emphysema (lung volume reduction) is a procedure in evolution. Depending on the patient and center, this procedure may be unilateral or bilateral and performed by thoracotomy, sternotomy, or VATS. The surgery is more effective in patients with heterogeneous lung disease, where the most severely affected areas (often apical) can be resected, than in patients with homogenous types of emphysema (e.g., α1-antitrypsin deficiency). Patients with extremely severe disease (FEV_1 or D_Lco <20% predicted) have poor survival after surgery.[232] This procedure is now most commonly seen as an option for patients with severe emphysema who have contraindications to transplantation.

Immediate postoperative improvements in symptoms and pulmonary function are common, and many patients are able to discontinue or reduce home oxygen therapy. These changes are the result of a decompression of the airways and a reduction of airflow resistance and work of breathing,[233] which results in a dramatic fall in auto-PEEP (intrinsic PEEP) with a corresponding increase in dynamic compliance. Despite the encouraging changes in early postoperative pulmonary function, the improvement in respiratory function as a result of this surgery is transient.[234] However, this must be viewed in the context of the short life expectancy of patients with this degree of emphysema and the potential for improvement in their quality of life from the operation.

Anesthetic management is similar to that for other patients with severe COPD having thoracic surgery (see COPD in Preoperative Evaluation, discussed earlier) with the risk of hypotension on induction caused by auto-PEEP and the need for excellent analgesia to avoid postoperative mechanical ventilation.[235] This procedure is now performed in some centers using one-way valves placed bronchoscopically in the most involved segments to cause collapse of severely emphysematous distal lung regions,[236] thus avoiding surgery.

PULMONARY HEMORRHAGE

Massive hemoptysis is defined as expectoration of more than 200 mL of blood in 24 to 48 hours. The commonest causes are carcinoma, bronchiectasis, and trauma (blunt, penetrating, or secondary to a pulmonary artery catheter). Death can occur quickly as a result of asphyxia. Management requires four sequential steps: lung isolation, resuscitation, diagnosis, and definitive treatment. The anesthesiologist is often called to deal with these cases outside of the operating room. There is no consensus on the best method of lung isolation for these cases. The initial method for lung isolation will depend on the availability of appropriate equipment and an assessment of the patient's airway. All three basic methods of lung isolation have been used: DLTs, SLTs, and bronchial blockers. Fiberoptic bronchoscopy is usually not helpful to position endobronchial tubes or blockers in the presence of torrential pulmonary hemorrhage, and lung isolation must be guided by clinical signs (primarily auscultation). DLTs will achieve rapid and secure lung isolation. Even if a left-sided tube enters the right mainstem bronchus, only the right upper lobe will be obstructed. However, suctioning large amounts of blood or clots is difficult through the narrow lumina of a DLT. An option is initial placement of the SLT for oxygenation and suctioning and then replacement with a DLT either by laryngoscopy or with an appropriate tube exchanger. An uncut single-lumen ETT can be advanced directly into the right mainstem bronchus or rotated 90 degrees counterclockwise for advancement into the left mainstem bronchus.[237] A bronchial blocker will normally pass easily into the right mainstem bronchus and is useful for right-sided hemorrhage (90% of pulmonary artery catheter–induced hemorrhages are right-sided). Except for cases with blunt or penetrating trauma, after lung isolation and resuscitation

have been achieved, diagnosis and definitive therapy of massive hemoptysis are now most commonly performed by coiling of the pulmonary artery false aneurysm in interventional radiology.[238]

PULMONARY ARTERY CATHETER–INDUCED HEMORRHAGE

Hemoptysis in a patient with a pulmonary artery catheter must be assumed to be caused by perforation of a pulmonary vessel by the catheter until proven otherwise. The mortality rate may exceed 50%. This complication seems to be occurring less than previously, possibly related to stricter indications for the use of pulmonary artery catheters and more appropriate management of the catheters with less reliance on wedge measurements. Therapy for pulmonary artery catheter–induced hemorrhage should follow an organized protocol with some variation depending on the severity of the hemorrhage (Box 66-13).

BOX 66-13 *Management of the Patient With a Pulmonary Artery Catheter*

Induced Pulmonary Hemorrhage

- Initially position the patient with the bleeding lung dependent.
- Perform endotracheal intubation, oxygenation, airway toilet.
- Isolate the lung by endobronchial double- or single-lumen tube or bronchial blocker.
- Withdraw the pulmonary artery catheter several centimeters, leaving it in the main pulmonary artery. Do not inflate the balloon (except with fluoroscopic guidance).
- Position the patient with the isolated bleeding lung nondependent. Administer positive end-expiratory pressure to the bleeding lung if possible.
- Transport the patient to medical imaging for diagnosis and embolization if feasible.

During Weaning From Cardiopulmonary Bypass

Weaning from CPB is one of the situations in which pulmonary artery catheter–induced hemorrhage is most likely to occur. Management of the pulmonary artery catheter during CPB by withdrawal from a potential wedge depth and observing the pulmonary artery pressure waveform to avoid wedging during CPB may decrease the risk of this complication. When hemoptysis does occur in this situation, there are several management options available (Fig. 66-50). The anesthesiologist should resist the temptation to rapidly reverse the anticoagulation to quickly discontinue CPB, because this can lead to fatal asphyxiation from hemorrhage. Resumption of full CPB ensures oxygenation while the tracheobronchial tree is suctioned and then visualized with fiberoptic bronchoscopy. The use of a pulmonary artery vent may be required to decrease the pulmonary blood flow sufficiently to define the bleeding site (usually the right lower lobe). The pleural cavity should be opened to assess the lung parenchymal damage. Conservative management with lung isolation, to avoid lung resection, is optimal therapy if possible. In patients with persistent hemorrhage who are not candidates for lung resection, temporary lobar pulmonary artery occlusion with a vascular loop during and after weaning from CPB may be an option.

Posttracheostomy Hemorrhage

Hemorrhage in the immediate postoperative period after a tracheostomy is usually from local vessels in the incision such as the anterior jugular or inferior thyroid veins. Massive hemorrhage 1 to 6 weeks postoperatively is most commonly caused by tracheoinnominate artery fistula.[239] A small sentinel bleed occurs in most patients before a massive bleed. The management protocol for tracheoinnominate artery fistula is outlined in Box 66-14.

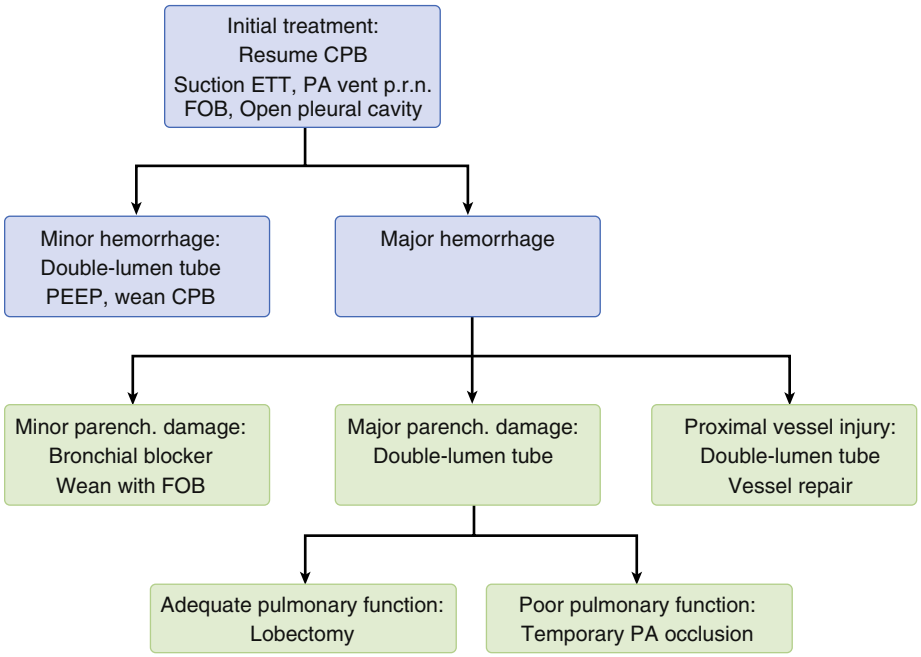


Figure 66-50. Flow diagram of management of massive hemoptysis during weaning from cardiopulmonary bypass. *CPB*, cardiopulmonary bypass; *ETT*, endotracheal tube; *PA*, pulmonary artery; *FOB*, fiberoptic bronchoscopy; *Parenc.*, lung parenchyma.

PULMONARY THROMBOENDARTERECTOMY

Pulmonary thromboendarterectomy is a potentially curative procedure for chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is a progressive disorder that responds poorly to conservative therapy, and pulmonary thromboendarterectomy is its most appropriate treatment, with a perioperative mortality of approximately 4%, which is less than lung transplantation. The majority of patients with CTEPH present for medical evaluation late in the disease because many have not had an obvious episode of deep venous thrombosis or pulmonary embolus, and the progression of the disease is insidious. Patients present with severe dyspnea on exertion and signs of right-sided heart failure. Surgical candidates have hemodynamically significant pulmonary vascular obstruction (pulmonary vascular resistance >300 dynes/sec/cm^{-5}), with potentially accessible proximal areas of thromboemboli.

An inferior vena cava filter is often placed prophylactically before surgery. Surgery is performed via a midline sternotomy with CPB with or without periods of deep hypothermic circulatory arrest (DHCA). Anesthetic management is essentially the same as for a patient with primary pulmonary hypertension for lung transplantation, with the exception that there is no need for lung isolation, so airway management is done with a standard ETT. Monitoring includes femoral and pulmonary artery catheters, TEE, processed electroencephalography, and rectal/bladder thermometers.[240]

These patients are at risk of hemodynamic collapse because of right ventricular failure from hypotension during induction of general anesthesia. Induction may be performed with etomidate or ketamine to avoid hypotension. Support of systemic vascular resistance with noradrenaline or phenylephrine is usually required. If DHCA is used, it is preceded by mannitol and methylprednisolone to try to decrease cerebral cellular edema and to improve free-radical scavenging. The speed of warming and cooling is controlled on CPB to maintain a temperature gradient less than 10° C between the blood and bladder/rectal temperatures. Periods of DHCA are usually limited to 20 minutes. Massive pulmonary hemorrhage occurs rarely during CPB in these cases. Management of pulmonary hemorrhage is done according to the algorithm outlined in Figure 66-50. The instillation of phenlyephrine 10 mg and vasopressin 20 U diluted in 10 mL saline via the ETT may be beneficial. Postoperatively, the patients are kept sedated, intubated, and ventilated for at least 24 hours to decrease the risk of reperfusion pulmonary edema. Noradrenalin or vasopressin infusions may be used to elevate the systemic vascular resistance and decrease cardiac output to decrease pulmonary blood flow.

BOX 66-14 *Management of Tracheoinnominate Artery Fistula Hemorrhage*

- Overinflate the tracheostomy cuff to tamponade the hemorrhage.
- If this fails:
  - Replace the tracheostomy tube with an oral endotracheal tube. Position the cuff with fiberoptic bronchoscopic guidance just above the carina.
  - Apply digital compression of the innominate artery against the posterior sternum using a finger passed through the tracheostomy stoma.
- If this fails:
  - Slowly withdraw the endotracheal tube and overinflate the cuff to tamponade.
  - Proceed with definitive therapy: sternotomy and ligation of the innominate artery.

BRONCHOPULMONARY LAVAGE

Bronchopulmonary lavage (BPL) is a treatment during which up to 10 to 20 L of normal saline is instilled and then drained in 500- to 1000-mL aliquots through one side of a DLT into one lung under general anesthesia until the effluent is clear.[241] It may then be performed on the contralateral lung during the same anesthetic or during a subsequent anesthetic after a period of several days for recovery. It is the most effective treatment modality for symptomatic pulmonary alveolar proteinosis. This lung disease results from accumulation in the alveoli of a lipoprotein material similar to surfactant.[242] This disease seems to have an immune component, and some patients respond to conservative medical therapy with granulocute-macrophage colony-stimulating factor.[243] Other pathologic states that have been treated by bronchopulmonary lavage include cystic fibrosis, asthma, radioactive dust inhalation, lipoid pneumonitis, and silicosis, all without convincing success.

General anesthesia is induced and maintained with intravenous infusions as for lung transplantation. Airway management is done with a left-sided DLT.[244] The patient is kept in the supine position during the procedure.

Because of transmitted hydrostatic pressure from the lavage lung to the pulmonary circulation, oxygenation increases during the filling phase and decreases during the emptying phase in synchrony with changes in the pulmonary blood flow distribution. These changes are usually transient and well tolerated. In severely hypoxemic patients presenting for BPL a variety of maneuvers have been used (such as inflation of a PA catheter balloon in the pulmonary artery (PA) of the lavage lung while adding NO to the ventilated lung[245] or the use of ECMO) to maintain oxygenation.

Usually 10 to 15 L is instilled and more than 90% is recovered, leaving a deficit of less than 10%. At the end of the procedure, the lavaged lung is thoroughly suctioned. A dose of furosemide (10 mg) is administered to increase diuresis of absorbed saline. If the plan is to proceed to a lavage of the contralateral lung, there is a period of at least 1 hour of TLV to allow recovery of the lavaged lung, during which arterial blood gases are monitored. If there is a persistent large alveolar-arterial oxygen gradient, the procedure is terminated at this stage and the patient will undergo lavage of the other lung at a later date. The postprocedure, after reintubation with an SLT, is a fiberoptic bronchoscopic inspection performed for suctioning. Conventional ventilation with PEEP is continued, usually for less than 2 hours. Observation in the intensive care

unit for 24 hours is part of the routine procedure. Some patients require lavage every few months, whereas others remain in remission for years.

MEDIASTINAL MASSES

Patients with mediastinal masses, particularly masses in the anterior or superior mediastinum, or both, present unique problems for the anesthesiologist. Patients may require anesthesia for biopsy of these masses by mediastinoscopy or VATS, or they may require definitive resection via sternotomy or thoracotomy. Tumors of the mediastinum include thymoma, teratoma, lymphoma, cystic hygroma, bronchogenic cyst, and thyroid tumors. Mediastinal masses may cause obstruction of major airways, main pulmonary arteries, atria, and the superior vena cava. During induction of general anesthesia in patients with an anterior or superior mediastinal mass, airway obstruction is the most common and feared complication. It is important to note that the point of tracheobronchial compression usually occurs distal to an endotracheal tube (Fig. 66-51), and it is not possible to forcibly pass an endotracheal tube through the airway once it has collapsed. A history of supine dyspnea or cough should alert the clinician to the possibility of airway obstruction on induction of anesthesia. Life-threatening complications may occur in the absence of symptoms in children. The other major complication is cardiovascular collapse secondary to compression of the heart or major vessels. Symptoms of supine presyncope suggest vascular compression.

Anesthetic deaths have mainly been reported in children. These deaths may be the result of the more compressible cartilaginous structure of the airway in children or because of the difficulty in obtaining a history of positional symptoms in children. The most important diagnostic tool for the patient with a mediastinal mass is the CT scan of the trachea and chest. Children with tracheobronchial compression noted to be greater than 50% on CT scan cannot be safely given general anesthesia.[246] Flow-volume loops, specifically the exacerbation of a variable intrathoracic obstructive pattern (expiratory plateau) when supine, are unreliable[247] for predicting which patients will have intraoperative airway collapse.[248] Transthoracic echocardiography is indicated for patients with vascular compression symptoms.

MANAGEMENT

General anesthesia will exacerbate extrinsic intrathoracic airway compression in three ways. First, reduced lung volume occurs during general anesthesia and tracheobronchial diameters decrease according to lung volume. Second, bronchial smooth muscle relaxes during general anesthesia, allowing greater compressibility of large airways. Finally, third, paralysis eliminates the caudal movement of the diaphragm seen during spontaneous ventilation. This eliminates the normal transpleural pressure gradient that dilates the airways during inspiration and minimizes the effects of extrinsic intrathoracic airway compression.

Management of these patients is guided by their symptoms and the CT scan (Boxes 66-15 and 66-16). Patients with "uncertain" airways should have diagnostic procedures performed under local or regional anesthesia whenever possible. Patients with "uncertain" airways requiring general anesthesia need a step-by-step induction of anesthesia with continuous monitoring of gas exchange and hemodynamics. This "NPIC" (*noli pontes ignii consumere*; i.e., "don't burn your bridges") anesthetic induction can be an inhalation induction with a volatile anesthetic such as sevoflurane or IV titration of propofol with or without ketamine, maintaining spontaneous ventilation until either the airway is definitively secured or the procedure is completed.[249] Awake intubation of the trachea before induction is a possibility in some adult patients if the CT scan shows an area of noncompressed distal trachea to which the endotracheal tube can be advanced before induction. If muscle relaxants are required, ventilation should first be gradually taken over manually to ensure that positive-pressure ventilation is possible, and only then can a short-acting muscle relaxant be administered (Box 66-17).

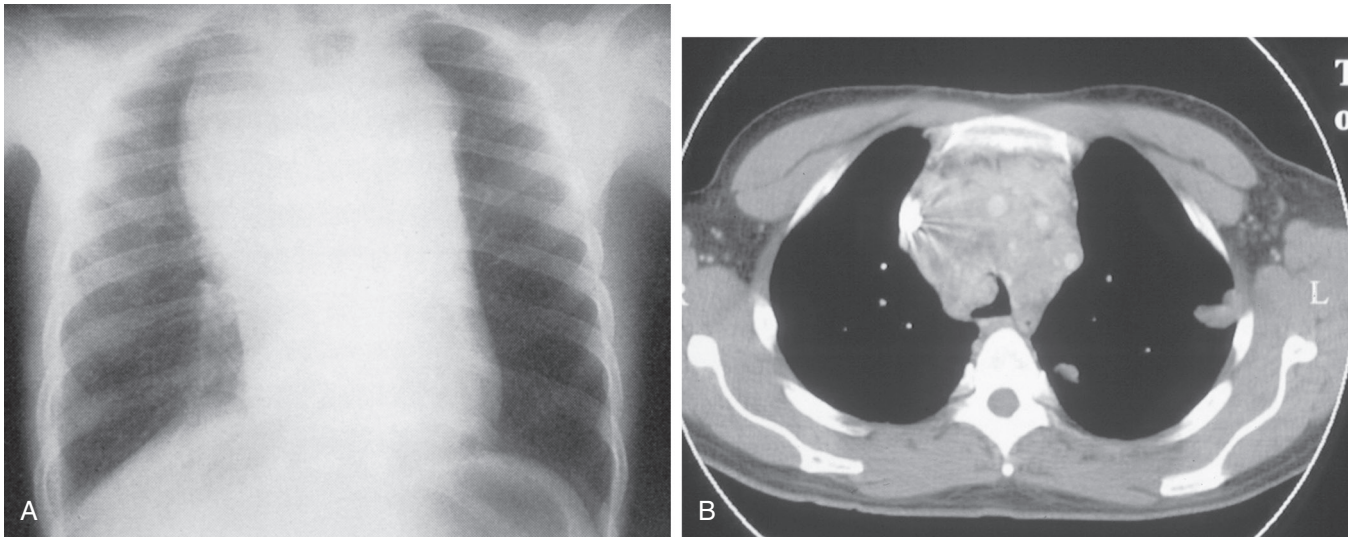


Figure 66-51. A, Chest radiograph of an adult patient with an anterosuperior mediastinal mass. This mass was a lymphoma. **B,** A thoracic CT scan with contrast just above the level of the carina shows partial compression of the carina and right mainstem bronchus. This patient has an "Uncertain" airway.

BOX 66-15 *Grading Scale for Symptoms in Patients with an Anterior or Superior Mediastinal Mass*

- Asymptomatic
- Mild: Can lie supine with some cough/pressure sensation
- Moderate: Can lie supine for short periods but not indefinitely
- Severe: Cannot tolerate supine position

BOX 66-16 *Stratification of Patients with Mediastinal Masses Regarding Safety for General Anesthesia*

- Safe: (I) Asymptomatic adult with CT minimal tracheal/bronchial diameter >50% of normal
- Unsafe: (I) Severely symptomatic adult or child; (II) children with CT tracheal/bronchial diameter <50% of normal, regardless of symptoms
- Uncertain: (I) Mild/moderate symptomatic child with CT tracheal/bronchial diameter >50% of normal; (II) mild/moderate symptomatic adult with CT tracheal/bronchial diameter <50% of normal; (III) adult or child unable to give history

CT, Computed tomography.

BOX 66-17 *Management for All Patients with a Mediastinal Mass and an Uncertain Airway for General Anesthesia*

- Determine optimal positioning of patient preoperatively.
- Secure airway beyond stenosis when patient is awake, if feasible.
- Have rigid bronchoscope and surgeon available at induction of anesthesia.
- Maintain spontaneous ventilation if possible (noli pontes ignii consumere).
- Monitor for airway compromise postoperatively.

Development of airway or vascular compression requires that the patient be awakened as rapidly as possible and then other options for the procedure be explored. Intraoperative life-threatening airway compression usually has responded to one of two therapies: either repositioning of the patient (it must be determined before induction if there is a position that causes less compression and fewer symptoms) or rigid bronchoscopy and ventilation distal to the obstruction (this means that an experienced bronchoscopist and equipment must always be immediately available in the operating room for these cases). The rigid bronchoscope, even if passed into only one mainstem bronchus, can be used for oxygenation during resuscitation (see Rigid Bronchoscopy, discussed earlier).[250] Once adequate oxygenation has been restored, the rigid bronchoscope can be used to position an airway exchange catheter, over which an ETT is passed after the bronchoscope is withdrawn. An alternative technique to secure the airway with rigid bronchoscopy is to first mount an ETT over a small rigid bronchoscope (e.g., 6 mm) and then perform rigid bronchoscopy using the bronchoscope to deliver the ETT distal to the obstruction.[251]

BOX 66-18 *Predictors of Airway Compromise in Children with a Mediastinal Mass*

- Anterior location
- Histologic diagnosis of lymphoma
- Superior vena cava syndrome
- Radiologic evidence of major vessel compression or displacement
- Pericardial or pleural effusion

Based on Lam JCM, Chui CH, Jacobsen AS, et al: When is a mediastinal mass critical in a child? An analysis of 29 patients, Pediatr Surg Int *20:180, 2004.*

Institution of femorofemoral CPB before induction of anesthesia is a possibility for some adult patients who are "unsafe" for NPIC general anesthesia. The concept of CPB "standby" during attempted induction of anesthesia is fraught with danger[252] because there is not enough time after a sudden airway collapse to establish CPB before hypoxic cerebral injury occurs.[253] Other options for "unsafe" patients include local anesthetic biopsy of the mediastinal mass or biopsy of another node (e.g., supraclavicular), preoperative radiotherapy with a nonradiated "window" for subsequent biopsy, preoperative chemotherapy or short-course steroids, and CT-guided biopsy of a mass or drainage of a cyst. The salient points in managing a patient with an anterior or superior mediastinal mass include[254]:

1. In virtually all children and adults with a mediastinal mass, diagnostic procedures and imaging can be performed, if necessary, without subjecting the patient to the risks of general anesthesia.[255]
2. An extrathoracic source of tissue for diagnostic biopsy (pleural effusion or extrathoracic lymph node) should be sought as an initial measure in every patient.
3. Regardless of the proposed diagnostic or therapeutic procedure, the flat, supine position is never mandatory.
4. In the high-risk child (Box 66-18) without extrathoracic lymphadenopathy or a pleural effusion, prebiopsy steroid therapy is justifiable.[256] In this case, coordination with oncology, surgery, and anesthesiology is essential to organize timing of the biopsy. An alternative to preoperative steroids in the cooperative high-risk patient includes irradiating the tumor while leaving a small area covered with lead for subsequent biopsy.

With improved awareness of the risk of acute intraoperative airway obstruction in these patients, life-threatening events are now less likely to occur in the operating room. In children, these events now tend to occur preoperatively if the patient is forced to assume a supine position for imaging. In adults, acute airway obstruction is now more likely to occur postoperatively in the recovery room.[257] Vigilance must be maintained throughout the entire perioperative period.

THYMECTOMY FOR MYASTHENIA GRAVIS

Myasthenia gravis is a disease of the neuromuscular junction; affected patients have weakness caused by a decreased number of acetylcholine receptors at the motor

end plate.[258] Patients may or may not have an associated thymoma. Thymectomy is frequently performed to induce clinical remission, even in the absence of a thymoma. The effects of muscle relaxants are modified by this disease; myasthenic patients are resistant to succinylcholine and are extremely sensitive to nondepolarizing blockers. Thymectomy may be performed via full or partial sternotomy, or with a minimally invasive approach via a transcervical incision or VATS. For thymectomy with a thymoma, a sternotomy is used. In the absence of an identifiable tumor, minimally invasive techniques are commonly used. Ideally, the use of neuromuscular relaxation is avoided. Induction of anesthesia with propofol, remifentanil, and topical anesthesia of the airway facilitates intubation without the use of muscle relaxants. Alternatively, inhalational induction with a halogenated agent such as sevoflurane may be performed.[259] For sternotomy, combined general and thoracic epidural anesthesia is a useful technique.

Most patients take pyridostigmine, an oral anticholinesterase, and many patients take immunosuppressive medication (e.g., corticosteroids). On the day of surgery, pyridostigmine dosing should ensure that the patient's usual regimen is provided during the immediate perioperative period. A few patients require IV dosing with neostigmine until they are able to resume oral intake of pyridostigmine. A scoring system was devised for prediction of the need for prolonged mechanical ventilation after thymectomy via sternotomy.[260] Among the criteria that contributed to the predicted need for support were disease duration longer than 6 years, chronic respiratory illness, pyridostigmine dosage greater than 750 mg/day, and vital capacity less than 2.9 L. The relevance of this score has diminished with better preoperative preparation and minimally invasive surgery.[261] Referral for surgery early in the course of the disease and stabilization of symptoms with medication and plasmapheresis, combined with an increased use of minimally invasive approaches, have made the need for postoperative ventilation infrequent. In optimized patients, mean hospital length of stay can be reduced to 1 day after minimally invasive, and 3 days after transsternal thymectomy.[262] Patients should remain on their full medical regimen postoperatively. The remission from myasthenia gravis after thymectomy occurs slowly over a period of months to years.

POSTOPERATIVE MANAGEMENT

EARLY MAJOR COMPLICATIONS

There are multiple potential major complications that can occur in the immediate postoperative period after thoracic surgery, such as torsion of a remaining lobe after lobectomy, dehiscence of a bronchial stump, or hemorrhage from a major vessel. Fortunately, these are infrequent and when they do occur, the principles of management are as outlined earlier for common and specific procedures. Among these possible complications, two will be discussed in more detail: (1) respiratory failure, because it is the most common cause of major morbidity after thoracic surgery; and (2) cardiac herniation, because, although it is rare, it is usually fatal if it is not quickly diagnosed and appropriately treated.

Respiratory Failure

Respiratory failure is a leading cause of postoperative morbidity and mortality in patients undergoing major lung resection. Acute respiratory failure after lung resection is defined as the acute onset of hypoxemia (PaO_2 <60 mm Hg) or hypercapnia ($Paco_2$ >45 mm Hg), or the use of postoperative mechanical ventilation for more than 24 hours or reintubation for controlled ventilation after extubation. The incidence of respiratory failure after lung resection is between 2% and 18%. Patients with decreased respiratory function preoperatively are at increased risk of postoperative respiratory complications. In addition, age, the presence of coronary artery disease, and the extent of lung resection play major roles in predicting postoperative morbidity and mortality. Crossover contamination, because of the failure of lung isolation intraoperatively during lung resection in patients with contaminated secretions, can result in contralateral pneumonia and postoperative respiratory failure.[263] Mechanical ventilation during the postoperative period after lung resection is associated with the risk of acquired nosocomial pneumonia and bronchopleural fistula.

Decreased pulmonary complications in high-risk patients are associated with the use of thoracic epidural analgesia during the perioperative period.[2] The prevention of atelectasis and secondary infections have been attributed to better preservation of the functional residual volume, efficient mucociliary clearance, and alleviation of the inhibiting reflexes acting on the diaphragm in patients receiving epidural analgesia.[264] Chest physiotherapy, incentive spirometry, and early ambulation are crucial to minimize pulmonary complications after lung resection. For an uncomplicated lung resection, early extubation is desirable to avoid potential complications that can arise as a result of prolonged intubation and mechanical ventilation. Current therapy to treat acute respiratory failure is supportive therapy attempting to provide better oxygenation, treat infection, and provide vital organ support without further damaging the lungs.

Cardiac Herniation

Acute cardiac herniation is an infrequent but well described complication of pneumonectomy, where the pericardium is incompletely closed or the closure breaks down.[265] It usually occurs immediately or within 24 hours after chest surgery and is associated with a more than 50% mortality rate. Cardiac herniation may also occur after a lobar resection with pericardial opening, or in other chest tumor resections involving the pericardium or in trauma.[266] When cardiac herniation occurs after a right pneumonectomy, the clinical presentation is caused by impairment of the venous return to the heart with a concomitant increase in CVP, tachycardia, profound hypotension, and shock. An acute superior vena cava syndrome ensues because of the torsion of the heart.[267] In contrast, when the cardiac herniation occurs after a left-sided pneumonectomy, there is less cardiac rotation, but the edge of the pericardium compresses the myocardium.

This may lead to myocardial ischemia, the development of arrhythmias, and ventricular outflow tract obstruction. Cardiac herniation occurs after chest closure because of the pressure difference between the two hemithoraces. This pressure difference may result in the heart being extruded through a pericardial defect.

Management for a patient with a cardiac herniation should be considered as dire emergent surgery. The differential diagnosis should include massive intrathoracic hemorrhage, pulmonary embolism, or mediastinal shift from improper chest drain management. Early diagnosis and immediate surgical treatment by relocation of the heart to its anatomic position with repair of the pericardial defect or by the use of analogous or prosthetic patch material is key to patient survival. Because these patients have undergone a previous thoracotomy, all precautions should be taken for a "redo" exploration. This includes the use of large-bore intravenous catheters and an arterial line. Maneuvers to minimize the cardiovascular effects include positioning the patient in the full lateral position with the operated side up. Because time is crucial, an SLT is used. Vasopressors or inotropes, or both, are required to support the circulation while exploration takes place. The use of TEE intraoperatively and after resuscitation and relocation of the heart can be considered during pericardial patch repair to prevent excessive compression of the heart by the repair.[268] In general, patients undergoing an emergency thoracic reexploration remain intubated and are transferred to the intensive care unit postoperatively.

POSTOPERATIVE ANALGESIA
(See Chapter 98)

Studies before 1990 consistently report a 15% to 20% rate of major respiratory complications (i.e., atelectasis, pneumonia, respiratory failure) within the first 3 days after thoracic surgery.[1] This time of onset may relate to the unique pattern of recovery of pulmonary function after thoracotomy, which shows a delay in the initial 72-hour postoperative period that is not seen with other major surgical incisions.[269] The incidence of postthoracotomy respiratory complications has shown an overall decline to less than 10%, whereas the cardiac complication rate has not changed.[2] Improvements in postoperative care, specifically pain management, are the major cause of this decline.

There are multiple sensory afferents that transmit nociceptive stimuli after thoracotomy (Fig. 66-52). These include the incision (intercostal nerves T4-T6), chest drains (intercostal nerves T7-T8), mediastinal pleura (vagus nerve, CN X), central diaphragmatic pleura (phrenic nerve, C3-C5),[270] and ipsilateral shoulder (brachial plexus). There is no one analgesic technique that can block all of these various pain afferents, so analgesia should be multimodal. The optimal choice for an individual patient depends on patient factors (i.e., contraindications, preferences), surgical factors (i.e., type of incision), and system factors (i.e., available equipment, monitoring, nursing support). The ideal postthoracotomy analgesic technique will include three classes of drugs: opioids, antiinflammatory agents, and local anesthetics.

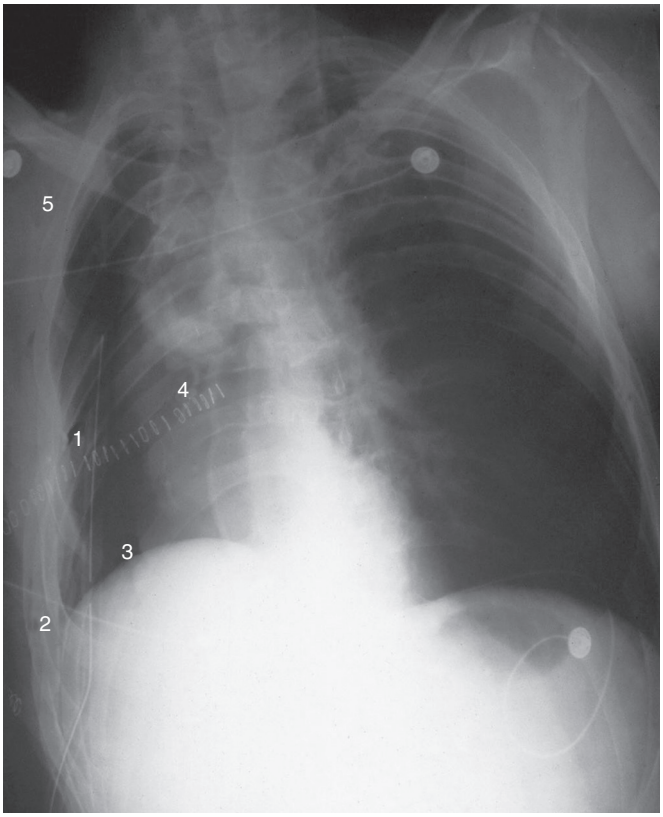


Figure 66-52. Multiple sources of afferent transmission of pain sensations after thoracotomy. *1*, Intercostal nerves at the site of the incision (usually T4-T6); *2*, intercostal nerves at the site of chest drains (usually T7-T8); *3*, phrenic nerve afferents from the dome of the diaphragm; *4*, vagal nerve innervation of the mediastinal pleura; *5*, brachial plexus.

SYSTEMIC ANALGESIA

Opioids

Systemic opioids alone are effective in controlling background pain, but the acute pain component associated with cough or movement requires plasma levels that produce sedation and hypoventilation in most patients. Even when administered by patient-controlled devices, pain control is generally poor[271] and patients have interrupted sleep patterns when serum opioid levels fall below the therapeutic range.

Nonsteroidal Antiinflammatory Drugs

NSAIDs can reduce opioid consumption more than 30% after thoracotomy and are particularly useful in treating the ipsilateral shoulder pain that is often present postoperatively and is poorly controlled with epidural analgesia. NSAIDs act through reversible inhibition of cyclooxygenase (COX), which has antiinflammatory and analgesic effects but can also be associated with decreased platelet function, gastric erosions, increased bronchial reactivity, and decreased renal function. Acetaminophen is an antipyretic/analgesic with weak COX inhibition and can be administered orally or rectally in doses of up to 4 g/day. It is effective against shoulder pain and has a low toxicity compared with more potent COX-inhibiting NSAIDs.[272]

Ketamine

Low-dose intramuscular ketamine (1 mg/kg) is equivalent to the same dose of meperidine and causes less respiratory depression. Ketamine can also be administered as a low-dose intravenous infusion and may be useful in patients who are refractory to other therapies or if there is a contraindication to more common techniques.[273] The possibility of psychomimetic effects with ketamine is always a concern but is rarely seen with analgesic, subanesthetic doses.

Dexmedetomidine

Dexmedetomidine, a selective adrenergic α_2-receptor agonist, has been reported as a useful adjunct for postthoracotomy analgesia and can significantly decrease the requirement for opioids when used in combination with epidural local anesthetics. Maintenance infusion doses for analgesia in children and adults are in the range of 0.3 to 0.4 μg/kg/h.[274] It is associated with some hypotension, but it seems to preserve renal function.

LOCAL ANESTHETICS/NERVE BLOCKS

Intercostal Nerve Blocks

Regional blocks of the intercostal nerves supplying the dermatomes of the surgical incision can be an effective adjunct to methods of postthoracotomy analgesia. These can be done percutaneously or under direct vision when the chest is open. The duration of analgesia is limited to the duration of action of the local anesthetic used, and the blocks will need to be repeated to have any useful effect on postoperative lung function. Indwelling intercostal catheters are an option but they can be difficult to position reliably percutaneously. Nerve blocks are useful supplements for the pain associated with the multiple small-port incisions and chest drains after VATS. It is important to avoid injection into the intercostal vessels, which are adjacent to the nerve in the intercostal groove. It is also important to place the block near the posterior axillary line to be certain to block the lateral cutaneous branch of the intercostal nerve. Total bupivacaine dose for a single session of blocks should not exceed 1 mg/kg (e.g., for a 75-kg patient: 3 mL bupivacaine 0.5% with epinephrine 1:200,000 at each of 5 levels).

Intrapleural Analgesia

Intrapleural local anesthetics produce a multilevel intercostal block. The analgesia is extremely dependent on patient position, infusion volume, chest drains, and the type of surgery. Despite occasional successes, most clinicians have not found the reliability of intrapleural techniques adequate to justify their use on a routine basis.[275]

Epidural Analgesia

The routine use of neuraxial analgesia for postthoracotomy patients is a relatively recent concept. Spinal injection of opioids can have a duration of analgesia that approaches 24 hours after thoracotomy. Because of the concerns of possible infection with subarachnoid catheters and the need to repeat spinal injections, investigation and therapy have focused on epidural techniques.

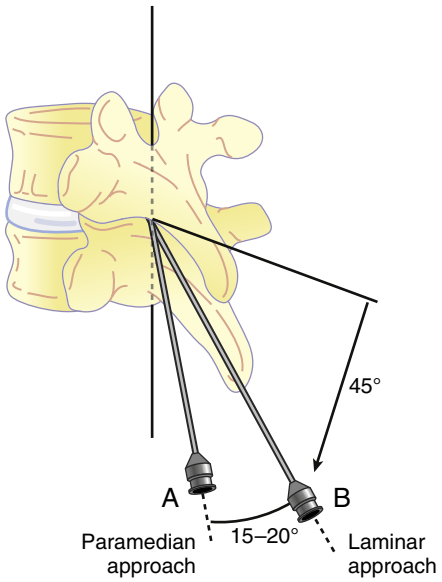


Figure 66-53. A, The paramedian approach to the epidural space is now favored by most anesthesiologists at the midthoracic levels. The needle is inserted 1 cm lateral to the superior tip of the spinous process and the advanced perpendicular to all planes to contact the lamina of the vertebral body immediately below. The needle is then "walked" up the lamina at an angle rostrally (45 degrees) and medially (20 degrees) until the rostral edge of the lamina is felt. The needle is then advanced over the edge of the lamina seeking a loss of resistance on entering the epidural space after traversing the ligamentum flavum. **B,** The laminar approach is favored by some practitioners. The needle is inserted next to the rostral edge of the spinous process and advanced straight without any angle from the midline. *(Reprinted with permission from Ramamurthy S: Thoracic epidural nerve block. In Waldman SD, Winnie AP, editors:* Interventional pain management. *Philadelphia, 1996, Saunders.)*

A meta-analysis of respiratory complications after various types of surgery has shown that epidural techniques reduce the incidence of respiratory complications.[276] Lumbar epidural analgesia has been replaced by thoracic epidural analgesia for thoracic surgery, with infusions of local anesthetic and opioid. These combinations provide better analgesia at lower doses than either drug will alone.[277] The use of epidural infusions has an excellent record for patient safety when used on routine postoperative surgical wards.[278] The use of a paramedian approach to the epidural space in the midthoracic levels (Fig. 66-53) has improved the success rate for many clinicians. Ultrasonographic guidance has not yet proved to be as useful for thoracic epidural catheter placement as it has for other types of regional blockade.[279]

Research has shed light on the pharmacology that underlies the synergy between local anesthetics and opioids to produce segmental epidural analgesia. In a double-blind randomized study, Hansdottir and associates[280] compared epidural infusions of lumbar sufentanil, thoracic sufentanil, and thoracic sufentanil plus bupivacaine for postthoracotomy analgesia. Infusions were titrated for equianalgesia at rest. Thoracic sufentanil plus bupivacaine provided significantly better analgesia with movement and less sedation than the other infusions. Although sufentanil dosages and serum levels were significantly lower

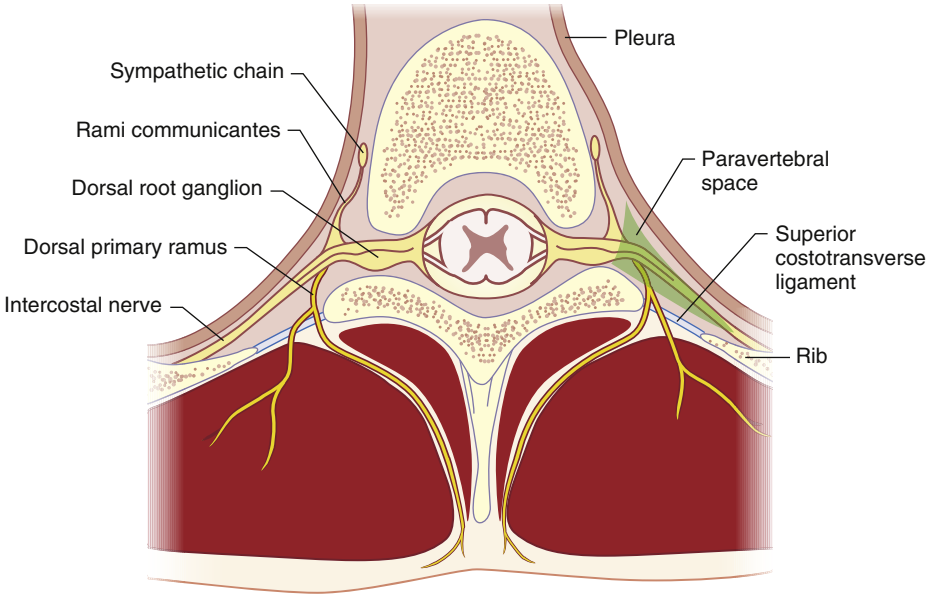


Figure 66-54. Diagram of the paravertebral space. The space is bound medially by the vertebral body, posteriorly by the costotransverse ligaments and the heads of the ribs, and anteriorly by the endothoracic fascia and parietal pleura. *(From Conacher ID, Slinger PD: Post-thoracotomy Analgesia. In Kaplan J, Slinger P, editors:* Thoracic anesthesia, *ed 3, Philadelphia, 2003, Churchill Livingstone.)*

in the combined sufentanil plus bupivacaine group than in the other two groups, lumbar cerebrospinal fluid levels of sufentanil at 24 and 48 hours were higher in the combined group than in the thoracic sufentanil group. This suggests that the local anesthetic facilitates entry of the opioid from the epidural space into the cerebrospinal fluid.

In patients with severe emphysema, thoracic epidural analgesic doses of bupivacaine do not cause any significant reduction in lung mechanics or increase in airway resistance.[281] In volunteers, a thoracic level of epidural blockade increases FRC.[282] This increase is largely caused by an increase in thoracic gas volume caused by a fall in the resting level of the diaphragm without a fall in tidal volume. Differences in lipid solubility that create relatively minor clinical differences in the effects of opioids when used systemically cause major differences in the effects of these same opioids when used neuraxially. The highly lipid-soluble agents (e.g., fentanyl, sufentanil) are associated with narrow dermatomal spread, rapid onset, and low incidence of pruritis/nausea, and can be potentiated by epinephrine. However, these lipid-soluble agents have significant absorption and systemic effects when used as epidural infusions.[283] For incisions that cover many dermatomes (e.g., sternotomy) or for procedures that have combined abdominal and thoracic incisions (e.g., esophagectomy), the hydrophilic opioids (e.g., morphine, hydromorphone) are preferable.

Paravertebral Block

The paravertebral space is a potential space deep to the endothoracic fascia that the intercostal nerve traverses as it passes from the intervertebral foramen en route to the intercostal space (Fig. 66-54). A catheter can be placed in the thoracic paravertebral space either percutaneously or by approaching the space anteriorly and directly when the chest is open intraoperatively.

There is also a combined percutaneous/direct-vision method in which the tip of the Tuohy needle is advanced percutaneously into the paravertebral space under direct vision either during open thoracotomy or VATS. The tip of the needle is seen to enter the paravertebral space and the pleura is not punctured. Saline is injected via the Tuohy needle to hydrodissect the paravertebral space, and an epidural catheter is passed into the pocket that has been created in the paravertebral space and then secured at the skin. The use of ultrasonographic guidance has been a major advance for percutaneous paravertebral injections and catheter placement (Fig. 66-55).[284]

Paravertebral local anesthetics provide a reliable multilevel intercostal blockade that tends to be unilateral, with a low tendency to spread to the epidural space. Clinically the analgesia is comparable with that from epidural local anesthetics.[285] Studies comparing paravertebral versus thoracic epidural analgesia for thoracotomies have suggested the following advantages for paravertebral blockade[286]: comparable analgesia; fewer failed blocks; decreased risk of neuraxial hematoma; and less hypotension, nausea, or urinary retention. Because there is an option to place the paravertebral catheter under direct vision, this may contribute to the lower incidence of failed blocks versus thoracic epidural analgesia.

Paravertebral infusions in combination with NSAIDs and systemic opioids are a reasonable alternative to epidural techniques in children or patients with contraindications to neuraxial blockade.[57] Using common therapeutic doses (e.g., 0.1 mL/kg/h of bupivacaine 0.5%), serum bupivacaine levels can approach toxic levels by 4 days.[287] An alternative regime for paravertebral infusions is lidocaine 1% (1 mL/10 kg/h; maximum 7 mL/h). It has not yet been demonstrated whether paravertebral analgesia can contribute to a decrease in respiratory morbidity in high-risk cases, which has been shown for thoracic epidural analgesia.[288]

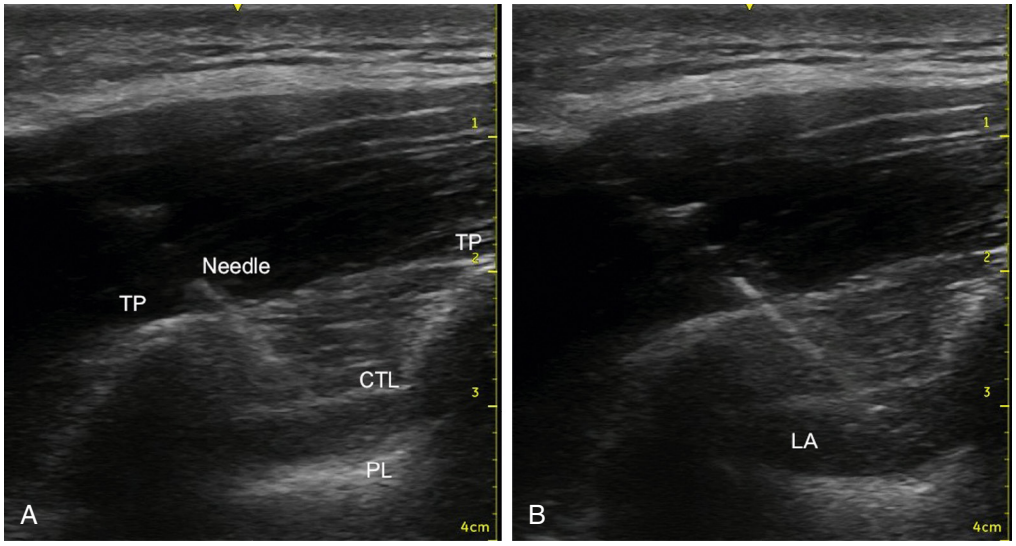


Figure 66-55. Ultrasound-guided paravertebral blockade. **A,** With the ultrasound probe in the parasagittal plane, a needle has been advanced from the cephalad border of the probe directed caudally passing under the transverse process *(TP)* of the thoracic vertebra. The paravertebral space is between the costotransverse ligament *(CTL)* and the parietal pleura *(PL)*. **B,** A bolus of local anesthetic *(LA)* has been injected into the paravertebral space, so a catheter can then be passed into the space. *(Courtesy Dr. M. Fiegel.)*

POSTOPERATIVE PAIN MANAGEMENT PROBLEMS

Shoulder Pain

After thoracotomy, as much as 80% of patients with a functioning epidural describe ipsilateral shoulder pain. Shoulder pain occurs after both thoracotomy and VATS and is thought to be primarily referred pain of diaphragmatic irritation transmitted by phrenic nerve afferents.[274] Other factors, including patient position during operation and major bronchus transection, have been incriminated, although the mechanisms are not clear. Several other causes of shoulder pain should be considered when evaluating a patient with shoulder pain postoperatively:

1. A chest drain placed too far into the apex of the hemithorax will irritate the parietal pleura and cause shoulder pain. The postoperative chest radiograph should be reviewed and the chest drain partially withdrawn if this is suspected as the cause.
2. The posterior end of a large posterolateral thoracotomy incision may not be well blocked by a functioning thoracic epidural, and this may be described as shoulder pain. The extent of the sensory block should be determined on the skin. If inadequate block is a possibility, the thoracic epidural analgesia can be "topped-up."
3. Patients with chronic arthralgia of the shoulder may experience an exacerbation from the intraoperative positioning of the ipsilateral arm. It is important to ask about shoulder problems preoperatively and to position the arms in a manner that does not exacerbate shoulder problems.

Shoulder pain is refractory to thoracic epidural analgesia and requires antiinflammatory agents with or without opioids. Shoulder pain is usually transient and is often resolved completely by the second postoperative day. There are several reports of the use of nerve blocks to treat postthoracotomy shoulder pain. Phrenic nerve infiltration and interscalene brachial plexus block[289] have had some success but carry a risk of causing diaphragm dysfunction.

Postthoracotomy Neuralgia and Chronic Incisional Pain

The transition of acute pain syndromes, associated with thoracic surgery, to chronic ones such as postthoracotomy neuralgia, may be partially preventable with analgesic regimens that prophylactically block nerves and desensitize peripheral nerve endings and dorsal horn cells of nerves that are damaged by surgery.[290]

MANAGEMENT OF OPIOID-TOLERANT PATIENTS

The opioid-tolerant patient requiring thoracic surgery presents a significant challenge. Patients may be using physician-prescribed opioids for pain related to their thoracic pathology or other chronic pain syndromes. Active abusers of narcotics or those in a rehabilitation program who are receiving daily methadone are also included in this group. Whenever possible, patients should take their regular analgesia or methadone preoperatively; otherwise substitute opioids must be provided. The opioid doses required to produce adequate postoperative analgesia are increased.

A multimodal analgesic regimen is optimal. A choice must be made regarding the method of increased opioid delivery, either systemically or through an epidural solution. An increased narcotic dose may be provided in the epidural solution, or standard narcotic concentrations may be used in the epidural with additional systemic narcotic. DeLeon-Casasola and Yarussi[291] report that higher epidural doses of opioids are able to curtail the appearance of narcotic withdrawal in most patients. More frequently, the patient receives a standard or slightly increased concentration of opioid in the epidural infusion and additional systemic opioid to minimize the occurrence of withdrawal. A convenient way to provide drug delivery in patients not immediately able to take oral medication is in the form of a transdermal fentanyl patch. Systemic

opioids can be provided as a continuous IV infusion or in oral form.

Patient-controlled analgesic techniques are often difficult to manage in these patients and they may be best managed with fixed dosage regimens that are modified as needed. Ultimately, after dose titration the patient may be receiving both increased epidural opioid and greater than preoperative doses of systemic opioid, without significant side effects. Patients in whom epidural bupivacaine-morphine analgesia is inadequate may respond to a switch to bupivacaine-sufentanil.[292] Patients in drug rehabilitation programs with methadone may be reluctant to modify their methadone dose perioperatively, having struggled to establish a stable dose in the past. They frequently can take their full methadone dose throughout the perioperative period.

Supplemental therapies to be considered for these patients include adding epinephrine 5 μg/mL to the epidural infusion solution and the addition of low-dose continuous IV ketamine infusions.[293] All opioid-tolerant patients require frequent adjustment of analgesic doses. Despite this, pain scores of 4 to 5 out of 10 with movement are often the lowest that are achievable. The increased analgesic requirements of opioid-tolerant patients are for a longer duration postoperatively than the usual need for analgesia in opioid-naive patients.

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Chapter 67

Anesthesia for Cardiac Surgical Procedures

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Key Points

- Common cardiac surgical procedures in adults include coronary revascularization with either cardiopulmonary bypass (CPB) or off pump, as well as cardiac valve repair or replacement for valvular regurgitation or stenosis, surgical management of heart failure (e.g., ventricular assist devices, extracorporeal membrane oxygenation, cardiac transplantation), initial repair of or reoperation for congenital heart disease, surgical ablation of atrial fibrillation, pericardiocentesis or pericardiectomy, and repair of traumatic injuries to the heart or thoracic aorta.
- Patients undergoing "redo" cardiac surgery (i.e., those who have previously had a median sternotomy) warrant special concern about the possibility of sudden, massive hemorrhage (see also Chapter 61). At least 2 units of blood should be immediately available for all such cases.
- The choice of anesthetic drugs and techniques for inducing anesthesia should include consideration of the patient's cardiac pathophysiology and other comorbid conditions. Hypotension may result from vasodilation secondary to decreased sympathetic tone induced by anesthetics, particularly in patients with poor left ventricular function. Conversely, hypertension may occur from preinduction anxiety or sympathetic stimulation caused by laryngoscopy and endotracheal intubation.
- During the prebypass period, hemodynamic and metabolic stability of the patient should be achieved while making preparations for CPB. The degree of surgical stimulation varies markedly during this period.
- CPB activates the extrinsic and intrinsic coagulation pathways and alters platelet function through the influence of hemodilution, hypothermia, and contact activation by bypass circuit materials (see also Chapter 62).
- Problems that may occur during the postbypass or postoperative time periods include hypotension resulting from surgical or technical failure, left or right ventricular dysfunction, vasoplegic syndrome, or left ventricular outflow tract obstruction. Other potential problems include dysrhythmias, pulmonary complications (e.g., atelectasis, bronchospasm, mucus or blood plugging of the endotracheal tube, pulmonary edema, hemothorax, pneumothorax), the potential for awareness, metabolic disturbances (e.g., hypokalemia, hyperkalemia, hypocalcemia, hypomagnesemia, hyperglycemia), and bleeding and coagulopathy.
- In 2007, with an update in 2011, the Society of Thoracic Surgeons (STS) and the Society of Cardiovascular Anesthesiologists published a joint statement on practice guidelines for transfusion and blood conservation in cardiac surgery. The guidelines include recommendations regarding the following: (1) use of drugs that decrease postoperative bleeding, including antifibrinolytic drugs; (2) techniques for conserving blood, including cell saver sequestration, retrograde priming of the pump, and normovolemic hemodilution; and (3) implementation of transfusion algorithms supported with point-of-care testing (see also Chapters 61 and 63).
- The incidence of overt postoperative stroke after isolated coronary artery bypass grafting surgery has decreased significantly to 1.2% despite the more frequent and current prevalence of diabetes mellitus and hypertension. The major risk factor

KEY POINTS—cont'd

for central nervous system injury or dysfunction is particulate and microgaseous emboli; other factors include cerebral hypoperfusion and the inflammatory response to surgery and CPB.

- Current STS guidelines state that blood glucose levels should be maintained at less than 180 mg/dL throughout the perioperative period, although many centers treat cardiac surgical patients somewhat more aggressively with continuous insulin infusions in an attempt to keep glucose levels lower than 150 mg/dL. Hypoglycemia should be avoided.
- Postoperative pain after median sternotomy or thoracotomy causes enhanced sympathetic tone and may lead to myocardial ischemia secondary to increased heart rate, pulmonary vascular resistance, myocardial work, and myocardial oxygen consumption. Furthermore, pain may cause "splinting" that interferes with the patient's ability to cough and clear secretions and leads to postoperative respiratory insufficiency.
- Common procedures performed in "hybrid" operating rooms or cardiac interventional suites include electrophysiology procedures, percutaneous management of valvular lesions, placement of occlusion or umbrella devices to close atrial or ventricular septal defects, insertion of percutaneous ventricular assist devices, and stenting of thoracic or abdominal aortic aneurysms.

CARDIOVASCULAR DISEASE IN THE TWENTY-FIRST CENTURY

AGE, GENDER, AND RACE

An estimated 82,600,000 U.S. adults (<1 in 3) have one or more types of cardiovascular disease (CVD), of whom approximately half are 60 years old or older.[1] The prevalence of CVD will likely increase because of the "graying" of the United States (i.e., the aging of our population) and the increasing incidences of obesity and hypertension.[2] Although mortality from coronary artery disease (CAD) specifically has decreased since the 1970s, CVD remains the leading cause of death for both men and women in the United States (Fig. 67-1). Furthermore, approximately 7,453,000 inpatient cardiovascular operations and procedures are performed yearly in the United States, with direct and indirect costs totaling approximately $300 billion.[1] As the current health care reforms expand treatment coverage, these costs will probably increase.[2]

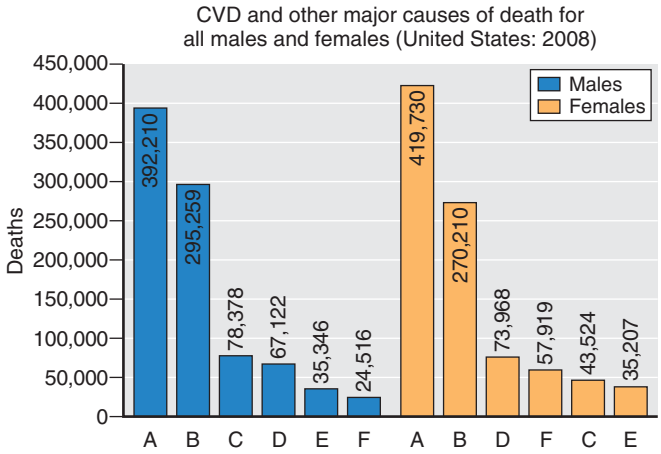


Figure 67-1. Cardiovascular disease (CVD) and other major causes of death for all male and female members of the U.S. population in 2008. *(From Roger VL, Go AS, Lloyd-Jones DM, et al: Heart disease and stroke statistics—2012 update: a report from the American Heart Association,* Circulation *2012;225:e2-e220.)*

Despite the common perception that CVD affects mainly men, this is true only in younger age groups. The sex distribution of CVD changes with age; CVD becomes equally prevalent between the sexes by the age of 60 years, and by the age of 80 years, more women than men are affected.[1] The impact of CVD on the health status of U.S. women has gained recognition and is the focus of public education efforts such as the "Go Red for Women" campaign sponsored by the American Heart Association (AHA) and the "Red Dress" project sponsored by the Department of Health and Human Services, the National Institutes of Health, and the National Heart Lung and Blood Institute.[3] Furthermore, a series of editorials and articles in the *Journal of Thoracic and Cardiovascular Surgery*[4] and gender-specific practice guidelines for coronary artery surgery in the *Annals of Thoracic Surgery*[5] have emphasized sex differences that affect patients who undergo cardiac surgical procedures. For example, using internal mammary artery (IMA) grafts significantly reduces mortality in patients of both sexes, but, until more recently, these grafts were underused in women.[5] Although some studies have shown that women's short-term survival is worse than men's after coronary artery bypass grafting (CABG) surgery,[6] others have found that 5-year post-CABG survival is actually better in women than in men.[7]

Mortality resulting from CVD has been consistently more frequent in black than white patients.[1] In 2008, the overall CVD-related death rate per 100,000 persons was 390.4 for black male patients, 287.2 for white male patients, 277.4 for black female patients, and 200.5 for white female patients. Furthermore, racial disparities have been reported in outcomes after CABG: both unadjusted mortality rates and mortality rates adjusted for patient-related characteristics are higher in black patients than in

white patients.[8] In fact, as an unfortunate consequence of the public release of quality information through CABG "report cards" in certain states, institutions and individual surgeons may use "racial profiling" in selecting patients for CABG.[9] For example, in New York State, physicians' avoidance of racial and ethnic minorities, who may be at a higher risk for poor outcomes, may have temporarily widened the disparity in CABG use among white versus black and Hispanic patients.

GENETIC INFLUENCES

Evolving rapidly beyond racial considerations (which are increasingly losing their medical and scientific meaning in the "melting pot" of the United States), *perioperative genomics* is the study of the unique biologic makeup of surgical patients. This field holds promise for uncovering the biologic reasons that patients with similar risk factors can have dramatically different perioperative clinical outcomes.[10] Patients with complex comorbid conditions are exposed to controlled trauma in the cardiac surgical operating room (Fig. 67-2). The hope is that preoperative risk assessment and outcome prediction will soon include testing for genetic markers related to individual differences in inflammatory, thrombotic, and vascular responses to stress related to cardiopulmonary bypass (CPB) and to the operation itself.

One example is the prevention of perioperative myocardial infarction (MI). Mechanisms in the pathogenesis of myonecrosis include the complex acute inflammatory response to surgery and CPB. Functional genetic variants in cytokine and leukocyte-endothelial interaction pathways are independently associated with the severity of myonecrosis after cardiac surgery.[11] Increased concentrations of the most extensively studied inflammatory marker, C-reactive protein (CRP), are associated with increased mortality in patients who undergo CABG.[12] Both increased baseline plasma CRP levels and acute phase increase in postoperative plasma CRP levels are genetically determined.[13] Another pathophysiologic process in perioperative MI is coagulation variability with a tendency toward thrombosis. Polymorphisms in platelet activation[14] and thrombin formation[15] have been associated with myocardial injury and with mortality after cardiac surgery.

Genetic factors have been associated with other postoperative complications. Common genetic variants of CRP and interleukin-6 (IL-6) are significantly associated with the risk of stroke[16] and cognitive decline after cardiac surgery.[17] Angiotensin-converting enzyme (ACE) gene polymorphisms predict a patient's risk of respiratory complications that necessitate prolonged mechanical ventilation after cardiac surgery.[18]

In summary, researchers are just beginning to discover genetic and molecular determinants that predispose patients to adverse events after cardiac surgery.[10] Rapid metabolic phenotyping approaches to diagnostic testing may soon be available for use in preoperative risk stratification, as well as real-time intraoperative diagnosis that affects decisions regarding monitoring and surgical and critical care.[19,20]

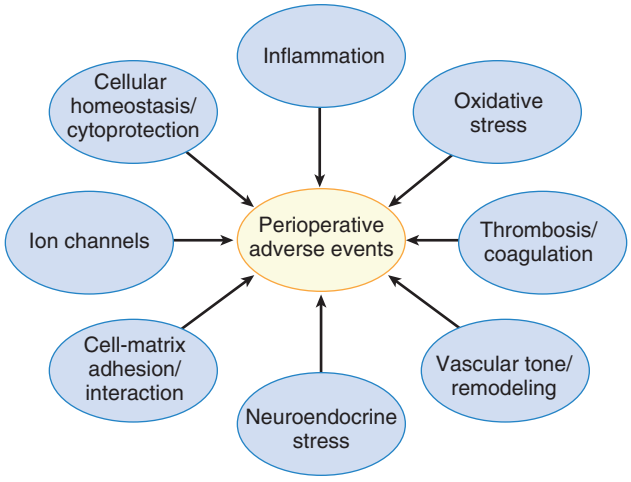


Figure 67-2. Biologic systems and mechanistic pathways genetically associated with perioperative adverse events. *(Redrawn from Podgoreanu MV, Schwinn DA: New paradigms in cardiovascular medicine: emerging technologies and practices: perioperative genomics,* J Am Coll Cardiol *46:1965-1977, 2005.)*

APPROACH TO ANESTHESIA FOR THE ADULT CARDIAC PATIENT

PREOPERATIVE EVALUATION, PREPARATION, AND MONITORING

Heart and Vascular System

Electrocardiography. Standard monitoring of cardiac surgical patients by electrocardiography (ECG) involves using the five-lead electrode system (see Chapter 47). An electrode is placed on each extremity, and one precordial electrode is placed in the V_5 position (on the left anterior axillary line at the fifth intercostal space). Ischemia detection is greatest (75%) with the V_5 lead. This sensitivity increases to 80% when lead II is paired with a V_5 lead.[21] The addition of a second precordial lead, V_4, increases the sensitivity, thus making it possible to detect nearly 100% of ischemic episodes.[22] Currently, most ECG monitors can perform ST-segment analysis automatically with high sensitivity and specificity for detecting ischemia.

Despite appropriate lead selection and the use of automated ST-segment monitoring, perioperative ECG monitoring has important limitations. Visual inspection of the ECG on the monitor has low sensitivity in diagnosing ischemic changes, and automated ST-segment analysis depends on the computer's ability to set the isoelectric and J-point reference points accurately. During cardiac surgical procedures, the set points should be checked before and after bypass, especially persistent changes in heart rate, because the reference points chosen at the beginning of the case may not be accurate under conditions that may arise later.[23]

Arterial and Central Venous Pressure Monitoring. Invasive arterial cannulation and monitoring comprise a standard of care for cardiac surgical patients (see also Chapter 45). Patients' comorbidities often include labile hypertension, atherosclerotic CVD, or both. Furthermore, cardiac surgical technique frequently causes sudden, rapid changes in arterial blood pressure resulting from factors such as direct compression of the heart, impaired venous return caused by retraction and cannulation of the great

vessels, and arrhythmias resulting from mechanical stimulation.[24] In addition, sudden, significant blood loss may induce hypovolemia and hypotension. Finally, during nonpulsatile CPB, noninvasive blood pressure recordings are not accurate. Intraarterial monitoring provides continuous, real-time, beat-to-beat assessment of arterial perfusion pressure and waveform throughout the cardiac surgical procedure. Having an indwelling arterial catheter also enables the frequent drawing of arterial blood for laboratory analyses.[24]

Although the radial artery is the most commonly accessed site, the femoral, brachial, ulnar, dorsalis pedis, posterior tibial, and axillary arteries can also be used. The pressures measured in the peripheral arteries are different from the central aortic pressure because the arterial waveform becomes progressively more distorted as the signal is transmitted down the arterial system.[24] Although the mean arterial pressure (MAP) measured in the peripheral arteries is usually similar to the central aortic pressure, this may change after CPB is initiated.[25] When cannulating a radial artery, one should consider the native state of the collateral circulation in the hand and the possible surgical use of a radial artery free graft as an arterial conduit. If a radial arterial graft is to be harvested, it is usually taken from the nondominant hand or arm; thus, the arterial line should be placed on the dominant side.

Central venous access is also standard of care during cardiac surgery. In addition to monitoring central venous pressure (CVP), central venous access provides a portal for intravascular volume replacement, pharmacologic therapy, and the insertion of other invasive monitors, such as pulmonary artery (PA) catheters. In addition, a CVP catheter can be used to measure the filling pressure of the right ventricle and estimate intravascular volume status.[24] Although the CVP does not directly reflect left-sided heart filling pressure, it may be used as an estimate of left-sided pressures in patients with good left ventricular (LV) function. Following trends is more useful than relying on an individual measurement.[24] In many patients, using a central venous catheter may offer a better risk-to-benefit ratio than using a PA catheter.[26] For the accurate measurement of pressure, the distal end of the catheter must lie within one of the large intrathoracic veins or the right atrium.[24]

An internal jugular vein is most commonly selected for catheterization because it provides ease of approach and optimal distance from the operative field. A femoral or subclavian vein can be considered as well, but groin access can be challenging in obese patients and may be inappropriate if femoral bypass cannula placement or vein graft harvesting is necessary. The subclavian approach is also imperfect because it is associated with an increased risk of catheter obstruction during sternal retraction.

The use of ultrasound is being rapidly adopted throughout the United States for facilitating the placement of central venous catheters and reducing the complications associated with them.[27] Although ultrasound-guided central catheter placement is easily accomplished and appears to improve patients' outcomes, concerns regarding the associated costs of the required hardware and training are reasons for the lack of universal adoption of this technique (Box 67-1).

BOX 67-1 ***Some of the Recognized Benefits of and Concerns About Ultrasound-Guided Central Venous Cannulation***

BENEFITS*

Greater success rate on first attempt
Fewer overall attempts
Better access in patients with difficult neck anatomy (e.g., resulting from obesity or prior surgery)
Fewer complications (e.g., carotid artery puncture, anticoagulant-enhanced bleeding)
Visible vessel patency, anatomic variants
Relatively inexpensive technology

CONCERNS

Need for personnel to be trained to maintain aseptic technique when using sterile probe sheaths
Requirement for additional training
Inability to show surface anatomy
Potential loss of landmark-guided skills when needed for emergency central venous catheterization

Modified from Kaplan JA, Reich DL, Savino JS, editors: Kaplan's cardiac anesthesia: the echo era, *ed 6, St. Louis, 2011, Saunders, p 426.*
*Ultrasonic guidance of internal jugular vein cannulation can be particularly advantageous in patients with difficult neck anatomy (e.g., short neck, obesity) or prior neck surgery, anticoagulated patients, and infants.

BOX 67-2 ***Conditions Resulting in Discrepancies Between Pulmonary Capillary Wedge Pressure and Left Ventricular End-Diastolic Pressure***

PCWP > LVEDP

Positive-pressure ventilation
PEEP
Increased intrathoracic pressure
Non-West lung zone III PAC placement
Chronic obstructive pulmonary disease
Increased pulmonary vascular resistance
Left atrial myxoma
Mitral valve disease (e.g., stenosis, regurgitation)

PCWP < LVEDP

Noncompliant left ventricle (e.g., ischemia, hypertrophy)
Aortic regurgitation (premature closure of the mitral valve)
LVEDP > 25 mm Hg

Modified from Tuman KJ, Carroll CC, Ivankovich AD: Pitfalls in interpretation of pulmonary artery catheter data, Cardiothorac Vasc Anesth Update *2:1, 1991.*
LVEDP, Left ventricular end-diastolic pressure; *PAC,* pulmonary artery catheter; *PCWP,* pulmonary capillary wedge pressure; *PEEP,* positive end-expiratory pressure.

PULMONARY ARTERY CATHETERIZATION. The PA catheter is a flow-directed catheter typically placed through an introducer in the central venous compartment via the internal jugular, subclavian, or femoral vein (see also Chapter 45). This catheter can measure PA pressure (PAP), CVP, and pulmonary capillary wedge pressure (PCWP). However, the PCWP can both overestimate and underestimate LV filling pressure (Box 67-2). Some PA catheters are designed with a thermistor to register blood temperature changes, which are used to calculate right-sided heart cardiac output (CO)

or ejection fraction (EF) by thermodilution. PA catheters may also have oximetric capabilities to measure mixed venous oxygen saturation ($S\bar{v}O_2$). Thus, a PA catheter can be used to assess intravascular volume status, measure CO, measure $S\bar{v}O_2$, and derive hemodynamic parameters.[24]

The CO, the amount of blood delivered to the tissues by the heart, is of particular interest to cardiac anesthesiologists. The product of stroke volume and heart rate, CO is affected by preload, afterload, heart rate, and contractility. PA catheters capable of measuring CO continuously were introduced into clinical practice in the 1990s.[24] The correlation of continuous CO measurements with those measurements obtained by using the intermittent thermodilution method is good in physiologically and thermally stable prebypass and postbypass periods.

Continuous monitoring of $S\bar{v}O_2$ provides a means to estimate the adequacy of oxygen delivery relative to oxygen consumption.[24] Decreases in $S\bar{v}O_2$ may indicate decreased CO, increased oxygen consumption, decreased arterial oxygen saturation, or decreased hemoglobin concentration. If it is assumed that oxygen consumption and arterial oxygen content are constant, changes in $S\bar{v}O_2$ should reflect changes in CO.[24] However, London and colleagues found that continuous $S\bar{v}O_2$ monitoring did not lead to better outcomes than standard PA catheter monitoring.[28]

Pacing PA catheters are also commercially available. Electrode PA catheters include five electrodes for atrial, ventricular, or atrioventricular (AV) sequential pacing. Paceport PA catheters (Edwards Lifesciences, Irvine, CA) have a port for the insertion of a ventricular wire or of both atrial and ventricular wires for temporary pacing.

The risk-to-benefit ratio involved in using PA catheters has been a subject of controversy since the 1990s. Complications of PA catheter placement include those mentioned in the section on CVP placement, as well as transient arrhythmias, complete heart block, pulmonary infarction, endobronchial hemorrhage, thrombus formation, catheter knotting and entrapment, valvular damage, and thrombocytopenia.[24] In addition, a common complication is incorrect interpretation of the data obtained from the PA catheter, with resultant incorrect treatment of the patient.[29] Schwann and colleagues published a large, international, prospective observational study showing that using a PA catheter was associated with a more frequent risk of a composite mortality and morbidity outcome than using a CVP alone in patients undergoing CABG surgery.[26] Smaller observational trials have also associated the PA catheter with increased morbidity and decreased survival in cardiac surgical patients.[30,31]

Currently, the trend in the United States is to be selective in deciding which patients may benefit from a PA catheter, especially with the widespread use of transesophageal echocardiography (TEE). Absolute contraindications to PA catheter placement include tricuspid or pulmonic valvular stenosis, right atrial (RA) or right ventricular (RV) masses, and tetralogy of Fallot.[24] Relative contraindications include severe arrhythmias and newly inserted pacemaker wires (which may be dislodged by the catheter during insertion). Clearly, patients undergoing low-risk cardiac surgical procedures can be managed safely without PA catheter placement.[24] However, many cardiac surgeons and anesthesiologists still use the device in high-risk cardiac operations and in patients with right-sided heart failure (HF) or pulmonary hypertension, particularly to assist in postoperative management (Box 67-3).

BOX 67-3 ***Possible Clinical Indications for Pulmonary Artery Catheter Monitoring***

Major procedures involving large fluid shifts or blood loss in patients with

Right-sided heart failure, pulmonary hypertension
Severe left-sided heart failure not responsive to therapy
Cardiogenic or septic shock or multiple organ failure
Hemodynamic instability requiring inotropes or intraaortic balloon counterpulsation
Surgery of the aorta requiring suprarenal cross-clamping
Hepatic transplantation
Orthotopic heart transplantation

Modified from Kaplan JA, Reich DL, Savino JS, editors: Kaplan's cardiac anesthesia: the echo era, *ed 6, St. Louis, 2011, Saunders, p 435.*

Transesophageal Echocardiography. TEE is used in many, if not most, cardiac surgical procedures in the current era. See Chapter 46 for a thorough discussion of this extraordinarily valuable diagnostic and monitoring modality.

Central Nervous System

Risk for Injury. The incidence of overt postoperative stroke after isolated CABG decreased significantly from 1.6% in the year 2000 to 1.2% in the year 2009, despite the greater prevalence of diabetes mellitus and hypertension in the current era.[32] A more subtle entity, postoperative cognitive decline (POCD), has also been described in numerous studies.[33] However, the measurement of POCD is complicated by variations in the tests used to assess cognitive function, the timing of these tests, and the diagnostic and statistical definitions of decline.[34] Furthermore, studies have shown that compared with nonsurgical and healthy controls, patients who undergo CABG have similar rates of cognitive decline 1 year postoperatively.[35,36]

Risk factors for CNS injury or dysfunction after cardiac surgery are listed in Box 67-4.[37] The most common cause is thought to be particulate or microgaseous emboli.[38,39] Other factors include cerebral hypoperfusion, particularly in patients with cerebrovascular disease, and the inflammatory response to surgery and CPB.[40,41]

Monitoring

Transesophageal and Epiaortic Echocardiography. TEE allows direct visualization of the first segment of the ascending aorta, the middle distal segment of the aortic arch, and a good portion of the descending thoracic aorta. However, the distal segment of the ascending aorta and the proximal midportion of the aortic arch cannot be visualized well because of the interposition of the trachea and bronchi between the TEE probe and these aortic structures. Instead, epiaortic imaging with a handheld, high-frequency probe placed over the ascending aorta or

BOX 67-4 *Mechanisms of and Contributing Factors to Neurologic Lesions*

EMBOLIZATION

HYPOPERFUSION

INFLAMMATION

INFLUENCING FACTORS

Aortic atheromatous plaque
Cerebrovascular disease
Altered cerebral autoregulation
Hypotension
Intracardiac debris
Air
Cerebral venous obstruction on bypass
Cardiopulmonary bypass circuit surface
Reinfusion of unprocessed shed blood
Cerebral hyperthermia
Hypoxia

From Kaplan JA, Reich DL, Savino JS, editors: Kaplan's cardiac anesthesia: the echo era, *ed 6, St. Louis, 2011, Saunders, p 1070.*

TABLE 67-1 **GRADING AORTIC ATHEROSCLEROSIS**

Aortic Atheromatous Disease	Echocardiographic Findings
Grade 1	Normal or mild intimal thickening
Grade 2	Severe intimal thickening No protruding atheromas
Grade 3	Atheroma protruding <5 mm into the lumen
Grade 4	Atheroma protruding ≥5 mm into the lumen
Grade 5	Atheroma of any size with a mobile component

Modified from Béique FA, Joffe D, Tousignant G, Konstadt S: Echocardiography-based assessment and management of atherosclerotic disease of the thoracic aorta, J Cardiothorac Vasc Anesth *12:206-220, 1998.*

aortic arch can be used to visualize aortic segments that are in the TEE probe's "blind spot."

The echocardiographic finding of atheromatous disease of the aorta has been linked to CNS injury in cardiac surgical patients.[42] Atherosclerosis of the ascending aorta is present in 20% to 40% of cardiac surgical patients, and the percentage increases with age. The severity of atheromatous disease of the aorta is a strong predictor of death and stroke after CABG (Table 67-1).[43] Using TEE to guide cannula placement or surgical technique significantly reduced the stroke rate in a series of 500 consecutive patients compared with controls in a statewide database.[44] Avoiding instrumentation of the ascending aorta (the "no touch technique") in patients with severe aortic atherosclerosis has been advocated.[45] The addition of epiaortic scanning of the ascending aorta increases the sensitivity of intraoperative echocardiography in identifying significant atheromatous disease in this segment of the aorta. Certainly, this combination of techniques is superior to surgical palpation in detecting such disease.[46]

CEREBRAL OXIMETRY. Cerebral oximetry uses near-infrared spectroscopy technology similar to that used in pulse oximeters (see also Chapter 49). Light-emitting electrodes are placed on the patient's forehead, lateral to the midline, and over both frontal cortices. Because the skull is translucent to infrared light, and because oxygenated blood and deoxygenated blood have different absorption characteristics when exposed to infrared light of two different wavelengths, regional cerebral oxygen saturation (rSO_2) can be computed from the returning signal. The design of the cerebral oximeter enables it to measure change from the patient's own established baseline and to monitor both frontal lobes simultaneously.

The use of near-infrared spectroscopy has been studied in the perioperative setting; a relative decrease in rSO_2 to less than 80% of the preoperative baseline or to absolute levels less than 50% increased the incidence of adverse postoperative outcomes.[47,48] These outcomes include POCD,[49] stroke,[50] organ dysfunction, mortality,[51,52] and length of hospital stay.[53] A physiologically derived treatment algorithm for management of perioperative cerebral oxygen desaturation has been proposed (Fig. 67-3).[54] As noted by Murkin,[37] an important confounder in evaluating the role of monitoring cerebral oximetry is the efficacy of treatment for cerebral desaturation.

A baseline rSO_2 that is low even though the patient is breathing supplemental oxygen (absolute value ≤50%) is an independent risk factor for 30-day and 1-year mortality.[55] A baseline rSO_2 could act as a refined marker for preoperative risk stratification and help clinicians identify patients who require more intensive monitoring and care in the postoperative period.[55,56]

TRANSCRANIAL DOPPLER. Transcranial Doppler (TCD) involves the ultrasonic interrogation of blood flow velocity through the middle cerebral or common carotid arteries as an indirect measure of cerebral blood flow.[47] The technology has been used extensively as a research tool. For example, in conjunction with cerebral oximetry, TCD has been used to delineate the limits of cerebral autoregulation during CPB.[57] TCD can also detect cerebral emboli. Contrary to previous information, an association between TCD-detected emboli and POCD is questionable.[58,59]

A primary limitation of TCD technology has been its inability to discern gaseous from solid emboli.[47,58] Other general limitations of TCD technology include the following: (1) the quality of information is heavily user dependent; (2) accuracy requires stable and precise probe placement, which can be quite cumbersome; and (3) information is affected by patient-related characteristics, such as skin thickness. These difficulties have limited use of this technology in the perioperative setting.[47]

ELECTROENCEPHALOGRAPHY AND BISPECTRAL INDEX MONITORING. The electroencephalogram (EEG), recorded from multiple adhesive or screw-in scalp electrodes, represents surface cerebral cortical activity (see also Chapters 13 and 14). Awake patients produce a pattern of EEG readings that differs from the pattern produced by patients who are under anesthesia. Establishing a baseline and monitoring the changes from that baseline form the premise of EEG monitoring. Changes in the frequency of EEG signals (slower brain waves) and the reduction of wave amplitude may indicate changes in cortical neuronal function that warrant concern.

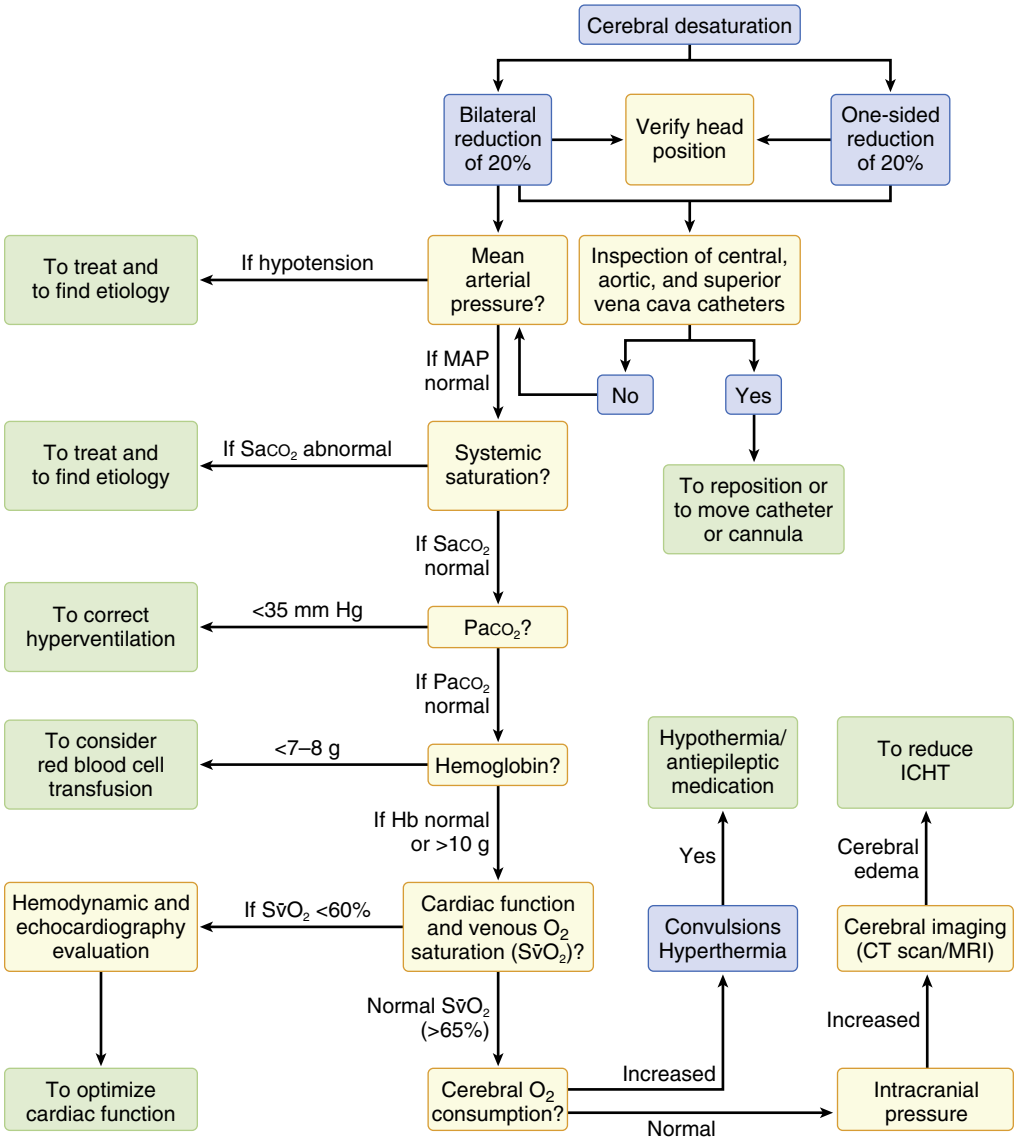


Figure 67-3. Algorithm for the use of brain oximetry. *CT,* Computed tomography; *ICHT,* intracranial hypertension; *MAP,* mean arterial pressure; *MRI,* magnetic resonance imaging; O_2, oxygen; $Paco_2$, partial pressure of arterial carbon dioxide; Sao_2, arterial oxygen saturation; $S\bar{v}O_2$, mixed venous oxygen saturation. *(Redrawn from Denault A, Deschamps A, Murkin JM: A proposed algorithm for the intraoperative use of cerebral near-infrared spectroscopy,* Semin Cardiothorac Vasc Anesth *11:274-281, 2007.)*

Multichannel EEG monitoring is not routinely used in cardiac surgery. However, a resurgence of interest in single- or dual-channel processed EEG monitoring, such as the bispectral index (BIS), has occurred.[47,60,61] The BIS has been studied as a means to monitor for intraoperative awareness, to reduce overall anesthetic consumption, and to provide information on cerebral perfusion. However, controversy surrounds the usefulness of BIS monitoring in reducing intraoperative awareness.[47,62-64] Similarly, the effectiveness of BIS monitoring in either guiding the safe reduction of anesthetic dosing or contributing to the success of fast tracking has not been demonstrated by randomized clinical trials in cardiac surgical patients.[60]

With respect to cerebral ischemia, sudden EEG changes during cardiac surgery and CPB can be attributable to correctable problems such as superior vena cava (SVC) obstruction or severe decrease in CO.[60] The latest iteration of the BIS monitor incorporates bilateral frontal EEG channels, which may increase its ability to detect unilateral frontal ischemia, especially if anesthesia is stable, if the insult is sudden, extended, or located in the frontal area, and if the preoperative EEG was normal.[60,65] However, many variables may confuse EEG interpretation during cardiac surgery. These include hypothermia, the pharmacologic suppression of EEG signals, and interference produced by pump mechanics. In addition, the EEG measures only cortical activity, so ischemic or embolic injury that occurs below the level of the cortex may go undetected. Therefore, the EEG and derived indices are neither sensitive nor specific in detecting cerebral ischemia.[60]

Summary. Currently, evidence-based recommendations cannot be made regarding the efficacy of treatment for abnormal values. Although not yet recognized as a clinical standard of care, neuromonitoring will likely continue to be the subject of significant research effort.

Renal System

Acute kidney injury (AKI) after cardiac surgery remains a significant cause of postoperative morbidity, increased cost of care, later development of chronic kidney disease, and short-term as well as long-term mortality (see also Chapter 101).[66] Although the pathogenesis of AKI is multifactorial,

control of some specific factors may limit its incidence in cardiac surgical patients. Bellomo and associates identified six major injury pathways of cardiac surgery–associated AKI: toxins (both exogenous and endogenous), metabolic factors, ischemia-reperfusion injury, neurohormonal activation, inflammation, and oxidative stress.[67]

Randomized trials of specific potential preventive measures for AKI after cardiac surgery are few. Certainly, all potentially nephrotoxic drugs should be avoided in the perioperative period (Box 67-5).[66,68] Hydration is, of course, a universally accepted component of strategies to prevent contrast nephropathy.[68] Unfortunately, no pharmacologic strategy has definitive efficacy in preventing early AKI.[68] Atherosclerosis of the ascending aorta appears to be an independent risk factor for AKI.[67]

Intraoperative TEE should be used to identify patients at increased risk for thromboembolic phenomena.[67,68] Although observational studies have suggested a possible benefit of off-pump procedures and avoidance of aortic manipulation, definitive evidence is lacking.[67,68] For cardiac surgical cases that require CPB, the duration of aortic cross-clamping should be limited if possible, especially in patients who are at a higher-than-normal risk for renal complications, such as patients with preexisting renal insufficiency.[67] Hemodynamic instability should be addressed quickly, and intravascular volume should be maintained or rapidly restored.[67,68] Finally, perioperative hyperglycemia should be avoided.[67,68]

Clearly, definition of measures that may prevent AKI after cardiac surgery is needed.[67,68] The cost of this complication to the patient and to society is probably higher than previously thought.[66]

BOX 67-5 *Drugs That Contribute to Kidney Injury*

Radiocontrast agents
Aminoglycosides
Amphotericin
Nonsteroidal antiinflammatory drugs
β-Lactam antibiotics (specifically contribute to interstitial nephropathy)
Sulfonamides
Acyclovir
Methotrexate
Cisplatin
Cyclosporine
Tacrolimus
Angiotensin-converting enzyme inhibitors
Angiotensin receptor blockers

Modified from Bellomo R, Kellum JA, Ronco C: Acute kidney injury, Lancet *380:756-766, 2012.*

Endocrine System

Glucose Control. Hyperglycemia in surgical patients is a consequence of the inflammatory or stress response to the trauma of surgery. Components of this response include an endocrine response (i.e., increased production of counterregulatory hormones such as cortisol, growth hormone, glucagon, and catecholamines) (Fig. 67-4), an immune response resulting in increased cytokine production, an autonomic response resulting in increased sympathetic stimulation, and altered insulin signaling. These changes increase glucose production, decrease glucose elimination during CPB, and induce insulin resistance, thereby causing hyperglycemia.[69]

All patients are at risk for developing hyperglycemia during cardiac surgery. Older patients, diabetic patients, and patients with CAD are particularly prone to perioperative hyperglycemia. Although cardiac surgery without CPB initiates a stress response, CPB increases this response manyfold.[69] The degree of hyperglycemia depends on several variables associated with the use of CPB, such as the pump prime fluid selected and the degree of hypothermia induced. Epinephrine and other inotropic drugs may contribute to hyperglycemia after CPB by stimulating hepatic glycogenolysis and gluconeogenesis.

Impaired fasting glucose blood levels before cardiac surgery and persistently increased glucose levels during and immediately after surgical procedures are predictive of longer hospital stay and increased perioperative morbidity and mortality in both diabetic and nondiabetic patients.[70,71] However, in diabetic patients undergoing cardiac operations, hyperglycemia may only partly explain the increased risk for adverse outcomes.[71] Immunologic abnormalities common to diabetic patients, such as decreased chemotaxis, phagocytosis, opsonization, bacterial killing, and antioxidant defense, also promote adverse outcomes by increasing diabetic patients' risk of infection.[72]

Glucose blood levels should be controlled, beginning in the preoperative period and continuing until discharge.[73] However, in a classic study, patients were randomly assigned to intensive intraoperative insulin treatment (to maintain glucose levels at 80 to 100 mg/dL) or to standard insulin treatment (to keep glucose levels <200 mg/dL).[74] Surprisingly, the investigators reported a statistically nonsignificant increase in the incidence of death and stroke in the group receiving intensive insulin treatment. The precise value necessary for achieving glycemic control during surgical procedures is not well defined.[71,75] Current Society of Thoracic Surgeons (STS) guidelines state that blood glucose levels should be kept lower than 180 mg/dL throughout the perioperative period.[76] Some cardiac surgical centers more aggressively administer continuous insulin infusions in an attempt to keep glucose levels lower than 150 mg/dL.

Thyroid Hormone. Abnormal thyroid function ultimately affects cardiac function in many ways (Table 67-2). During cardiac surgery, the effect of CPB on thyroid hormone production is uncertain. Both increased and decreased levels of thyroid hormone can occur during or immediately after CPB. Free triiodothyronine (T_3), the biologically active form of the thyroid hormone, is frequently reduced in cardiac patients because of the reduced activity of the 5′-monodeiodinase responsible for converting thyroxine (T_4) into T_3 in peripheral tissues.[77] This low T_3 syndrome has been described in patients with impaired contractility and enhanced risk for MI and HF, as well as in adults and children after CPB.[78] Preexisting

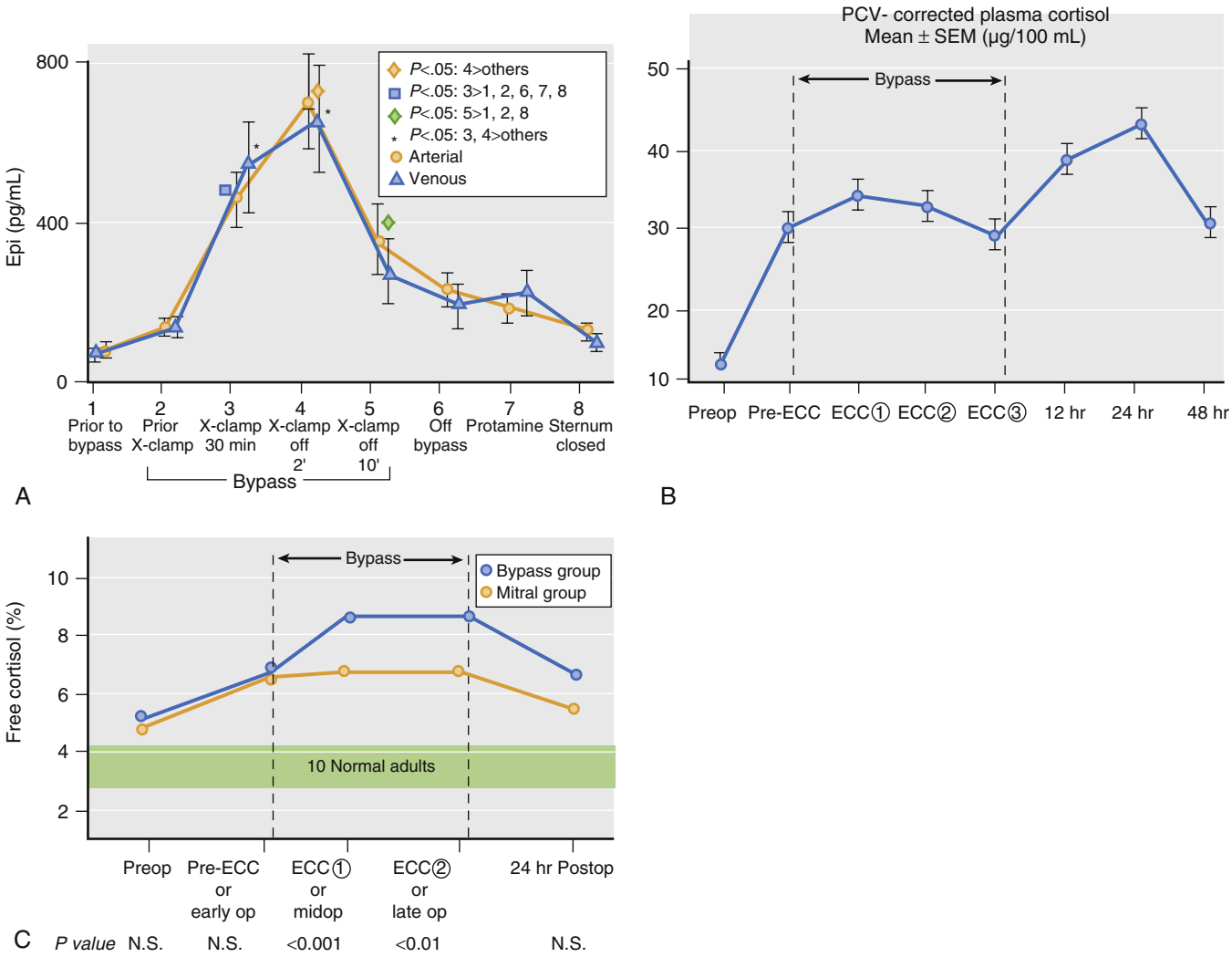


Figure 67-4. A, Plasma levels of epinephrine (Epi) during cardiac surgery. *Bars* indicate standard error of the mean. *X-clamp,* Cross-clamp. **B** and **C,** Levels of cortisol during cardiac surgery. *ECC,* Extracorporeal circulation; *Midop,* intraoperatively; *N.S.,* not significant; *op,* operatively; *PCV,* packed cell volume; *Postop,* postoperatively; *Preop,* preoperatively. (**A**, *Redrawn from Reves JG, Karp RB, Buttner EE, et al: Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man,* Circulation *66:49-55, 1982;* **B** *and* **C**, *from Taylor KM, Jones JV, Walker MS, et al: The cortisol response during heart-lung bypass,* Circulation *54:20-25, 1976.)*

TABLE 67-2 **EFFECTS OF THYROID DYSFUNCTION ON HEMODYNAMICS AND CARDIAC FUNCTION**

Parameter	Normal Values	Hyperthyroidism	Hypothyroidism
Blood volume (% of normal value)	100	105.5	84.5
Heart rate (beats/min)	72-84	88-130	60-80
Cardiac output (L/min)	4.0-6.0	>7.0	<4.5
Systemic vascular resistance (dyne•sec•cm^{-5})	1,500-1,700	700-1,200	2,100-2,700
Left ventricular ejection fraction (%)	>50	>65	≤60
Isovolumic relaxation time (msec)	60-80	25-40	>80

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thyroid dysfunction can occasionally be severely aggravated by CPB because of hypothermia, nonpulsatile blood flow, and reduced conversion of T_4 to T_3.

Notably, hypothyroidism is more common in female than in male patients undergoing CABG.[79] Zindrou and associates noted a 17% higher mortality rate in women who underwent CABG while receiving thyroxine replacement therapy for hypothyroidism.[80] A review of the literature by Edwards and colleagues concluded that ensuring a perioperative euthyroid state in women with hypothyroidism who were undergoing CABG could be helpful in reducing the perioperative mortality of these patients.[5] Although subclinical hypothyroidism and low T_3 syndrome have an effect on CABG outcome in both women and men, further studies are needed before routine preoperative evaluation of thyroid function can be recommended.[81]

Hematologic System

Bleeding is the primary complication of cardiac operations that require CPB (see also Chapter 62). In fact, 10% to 15% of blood product use in the United States is associated with cardiac surgery, and this fraction is increasing, largely because of the increasing complexity of cardiac surgical procedures.[82] Real-world data obtained from a large sample of patients and entered into STS Adult Cardiac Surgery Database suggest that 50% of patients who undergo cardiac surgical procedures receive a blood transfusion. Complex cardiac operations such as "redo" procedures, aortic operations, and the implantation of ventricular assist devices (VADs) require blood transfusion much more often than do simpler operations.[83,84] Donor blood is viewed as a scarce resource that is associated with increased health care costs and significant risk to patients (see also Chapters 61 to 63). Furthermore, perioperative blood transfusion is associated with worse short-term and long-term outcomes.[85,86] Hence, reducing bleeding and blood transfusions has become a major focus of quality improvement efforts in cardiac surgery.[82]

Heparin as an Anticoagulant

Overview of Heparin. Since its discovery by Jay McLean, MD, in 1915, heparin has stood the test of time and remains the primary anticoagulant used in cardiac operations that require CPB. The mechanism underlying heparin's anticoagulant effect centers on the heparin molecule's ability to bind simultaneously to antithrombin III and thrombin. Modern nomenclature refers to antithrombin III as antithrombin (AT). The binding process is mediated by a unique pentasaccharide sequence that binds to AT. The proximity of AT and thrombin, mediated by the heparin molecule, allows AT to inhibit the procoagulant effect of thrombin by binding to the active-site serine residue of the thrombin molecule.[87] The inhibitory effect of AT is increased 1000-fold in the presence of heparin. The heparin-AT complex can affect several coagulation factors, but factor Xa and thrombin are the most sensitive to inhibition by heparin, and thrombin is 10 times more sensitive to the inhibitory effects of unfractionated heparin than is factor Xa.[88]

Only approximately one third of the heparin molecules in a dose of heparin contain the critical pentasaccharide segment that is needed for high-affinity binding to AT.[89] Thus, relatively large doses are required to produce the anticoagulant effect necessary for CPB. In fact, dosing of heparin for CPB is somewhat empiric. After a baseline activated clotting time (ACT) is measured (the normal range is 80 to 120 seconds), a dose of 300 to 400 units/kg of heparin is given as an intravenous bolus. Commercially available assays are used for calculating the patient's dose-responsiveness to heparin in vitro. Some practitioners administer heparin at the dose that is indicated by such an in vitro dose-response assay. Subsequent heparin dosing for extracorporeal circulation (ECC) is targeted at maintaining ACT values longer than 480 seconds. Also available is a heparin concentration monitor that uses protamine titration analysis for ex vivo calculation of the whole blood heparin concentration. This result is often used as an adjunct to the ACT value of 480 seconds in confirming an adequate heparin concentration for CPB. Unfortunately, ACT test results vary substantially with clinical conditions and the particular platform used for measurement. Thus, the evidence supporting the use of a threshold of 480 seconds is almost entirely anecdotal.

The dose of heparin used in patients on CPB is based on early landmark work published by Bull and coauthors in 1975.[90] A small study that sought evidence of thrombin activity during CPB in nonhuman primates and pediatric patients found results supporting a safe lower limit for ACT of 400 seconds.[91] In 1979, Doty and colleagues proposed a simplified dosing regimen guided by ACT values without dose-response curves.[92] The data and recommendations from these few studies constitute the primary basis for current heparin dosing protocols.

Despite heparin's historic and continued role in anticoagulation for patients maintained on CPB, it is not a perfect anticoagulant. Intrinsic and extrinsic pathway coagulation occurs despite heparin administration, and platelets can still be activated by contact with bypass circuitry and by heparin directly.[93,94] Alternative anticoagulants are discussed briefly in the section on heparin-induced thrombocytopenia (HIT).

Monitoring of Anticoagulation. Using ACT to monitor the effectiveness of heparin is not an exact science (see also Chapter 62). Tremendous variability is observed in patients' anticoagulation responses to a given dose of heparin; reasons for this variability include variations in levels of heparin-binding proteins and AT. Hence, ACT values correlate poorly with actual heparin concentrations. Nevertheless, since the publication of Bull and colleagues' early work,[90] ACT has been the mainstay of anticoagulation monitoring in cardiac operations that require CPB.

Many different ACT measurement devices are commercially available, and each uses a different platform for clot detection and endpoint signaling. However, they all involve the addition of whole blood to a tube or channel containing a contact-phase activator. The activator can be celite, kaolin, glass, or any combination thereof. The sample is warmed to 37° C before the measurement technique is performed. Clot formation occurs, and the measurement ends when a change in velocity, pressure, oscillation, electromagnetic forces, or even color is observed, depending on the particular platform of measurement.[95]

Several clinical variables can affect the ACT (Table 67-3). In addition to physiologic variations, the design of ACT measurement devices (which varies across their many manufacturers) also affects ACT normal and therapeutic values. ACTs also correlate poorly with whole blood and plasma heparin levels, and responses to heparin differ somewhat between adult and pediatric

TABLE 67-3 CLINICAL VARIABLES THAT CAN AFFECT THE ACTIVATED CLOTTING TIME

Hemodilution	Prolongs ACT in heparinized patients
Hypothermia	Prolongs ACT
Thrombocytopenia	Prolongs ACT
Platelet inhibitors	Prolongs ACT
Platelet lysis	Shortens ACT
Aprotinin	Prolongs only celite ACT
Surgical stress	Shortens ACT

ACT, Activated clotting time.

patients.[96] Some authors argue that, because of its poor correlation with heparin concentration, ACT alone is not an adequate monitor of heparin efficacy, and that simultaneous or adjunct monitoring of heparin concentration should also be used during CPB. Prolongation of ACT by non–heparin-related clinical factors, such as hypothermia, hemodilution, or quantitative or qualitative platelet abnormalities, is a well-documented phenomenon, and the anesthesiologist must understand these factors to determine whether it is safe to reduce the heparin dose when the ACT is prolonged. The poor correlation between ACT and measured heparin concentration also makes it possible that a dose reduction will render the heparin concentration inadequate, even when the ACT remains within an acceptable range.

Some point-of-care (POC) monitors, such as the Hepcon HMS system (Medtronic Perfusion Systems, Minneapolis, Minn.), use a protamine titration assay to calculate the heparin concentration. Despotis and associates suggest that monitoring and maintaining heparin concentration—and thus giving larger doses of heparin—actually protect the hemostatic system and may decrease transfusion requirements.[97] However, other investigators have not been able to confirm that higher doses of heparin confer better hemostatic protection; markers of ongoing coagulation are essentially the same whether traditional ACT monitoring or heparin concentration monitoring is used.[98]

The high-dose thrombin time (HiTT) is a modification of the thrombin time that is designed to measure the high levels of heparin that are used during CPB.[99] Unlike ACT, the HiTT correlates well with heparin concentration, both before and during CPB, and it is not affected by hemodilution and hypothermia. As a measure of thrombin inhibition, the HiTT is a more specific test of heparin's effect on thrombin than ACT, and it appears to possess less artifactual variability.[94] Aprotinin and preoperative heparin infusions do not affect HiTT values.[99]

Protamine and Reversal of Anticoagulation. Protamine, which has been in clinical use for as long as heparin has, remains the heparin reversal drug of choice in cardiac surgery. The protamine dose required to reverse heparin is somewhat controversial. In the first published study to examine this question, Bull and associates chose a dose of 1.3 mg protamine for every 100 units of heparin to provide a slight excess of protamine from a projected needed amount of 1.2 mg for every 100 units of heparin.[100] In current practice, dosing usually follows one of the following protocols:

1. Protamine is administered according to the total amount of heparin given (i.e., 1 to 1.3 mg protamine per 100 units of heparin). This method may result in luxuriant protamine doses, which reduce any theoretic or real risks of heparin rebound but may put the patient at higher risk for bleeding events because of the anticoagulant effect of protamine.[95,101]
2. Protamine is administered at a dose calculated from the heparin concentration, which is measured by a protamine titration assay. If the heparin concentration is not measured, the protamine dose can be graphically derived by plotting ACT values throughout the case and creating heparin dose-response curves. The amount of protamine used in this method is based on the circulating concentration of heparin in the patient at the time of reversal. Because, theoretically, no excess protamine exists, these patients may be at risk for heparin rebound and therefore may require additional protamine. In a small study conducted in patients undergoing valve surgery, administering protamine in two divided doses by titration resulted in a larger dose but reduced bleeding, presumably by treating heparin rebound.[102]

Unique Hematologic Considerations in Cardiac Surgery.

Hematologic Effects of Cardiopulmonary Bypass. The hematologic effects of CPB are myriad. Exposure of blood to the surfaces of the extracorporeal circuit is a profound stimulus for inflammatory up-regulation, and activation of the hemostatic system is a component of the normal inflammatory response. According to traditional models of hemostasis, ECC activates both the intrinsic and extrinsic coagulation pathways and directly impairs platelet function. Intrinsic pathway activation can occur by contact activation and the conversion of factor XII to factor XIIa on the various surfaces of the CPB circuit.[103] The tissue factor generated from the wound and the circulating tissue thromboplastin combine to cause the extrinsic activation of coagulation by cell-mediated hemostasis, which involves tissue factor–bearing leukocytes and activated endothelial cells. Tissue factor pathway generation of thrombin has a primary role in CPB-associated hemostasis abnormalities (Fig. 67-5).[103,104]

In addition to activating both extrinsic and intrinsic coagulation pathways, CPB directly impairs platelet function through a variety of mechanisms. Platelets express on their surface numerous glycoproteins that serve as receptors for several circulating ligands, such as fibrinogen, thrombin, and collagen (Fig. 67-6).[103] The components of the bypass circuit adsorb circulating proteins that can serve as foci for platelet attraction and adherence. These surface-bound platelets activate and release the contents of their cytoplasmic granules, which can then serve as localized sources of thrombin generation, or they may embolize to initiate microvascular thrombosis.[103]

Fibrinolytic activity is also increased by CPB. Contact activation leads to the activation of factor XII, prekallikrein, and high-molecular-weight kininogen (HMWK), which causes endothelial cells to produce tissue plasmin activator (t-PA), and lysis of fibrin and fibrinogen ensues (Fig. 67-7).[103]

The vascular endothelium is itself an active substrate that is sensitive to circulating mediators, and it expresses and releases anticoagulant and procoagulant factors. When exposed to hypoxia or inflammatory mediators during CPB, the endothelium responds and can induce a relatively prothrombotic state marked by tissue factor up-regulation, accelerated platelet adhesion, and increased expression of leukocyte adhesion molecules (Fig. 67-8).[103,105]

Heparin Resistance, Altered Heparin Responsiveness, and Antithrombin. Heparin resistance is marked by the inability to raise the ACT to therapeutic levels after administration of the recommended doses of unfractionated heparin. Some investigators have defined heparin resistance as an ACT of less than 480 seconds after 500 units/kg of intravenous heparin are administered.[106,107]

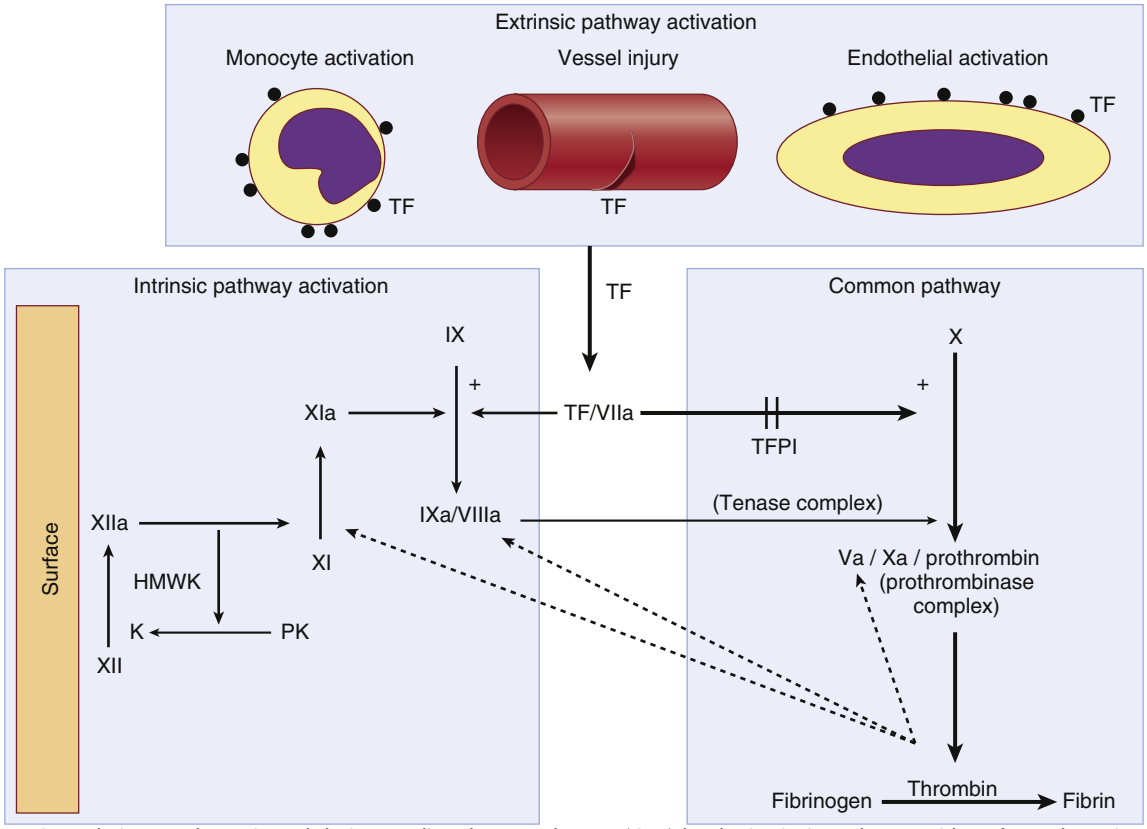


Figure 67-5. Coagulation can be activated during cardiopulmonary bypass (CPB) by the intrinsic pathway, with surface adsorption and activation of factor XII, high-molecular-weight kininogen (HMWK), and prekallikrein (PK). Activation of the extrinsic pathway during CPB occurs with tissue injury, as well as with systemic inflammation, and it leads to monocyte and endothelial expression of tissue factor (TF). TF, in combination with factor VIIa, starts the common pathway with the activation of factor X to factor Xa. Assembly of the prothrombinase complex on phospholipid surfaces leads to the production of thrombin and conversion of fibrinogen to fibrin. Tissue factor pathway inhibitor (TFPI) inhibits TF/VIIa. Thrombin can overcome this TFPI blockade by activating factors XI, VIII, and V and initiating activation of factor X by the tenase complex. *K,* Kallikrein. *(From Kottke-Marchant K, Sapatnekar S: Hemostatic abnormalities in cardiopulmonary bypass: pathophysiologic and transfusion considerations,* Semin Cardiothorac Vasc Anesth *5:187-206, 2001.)*

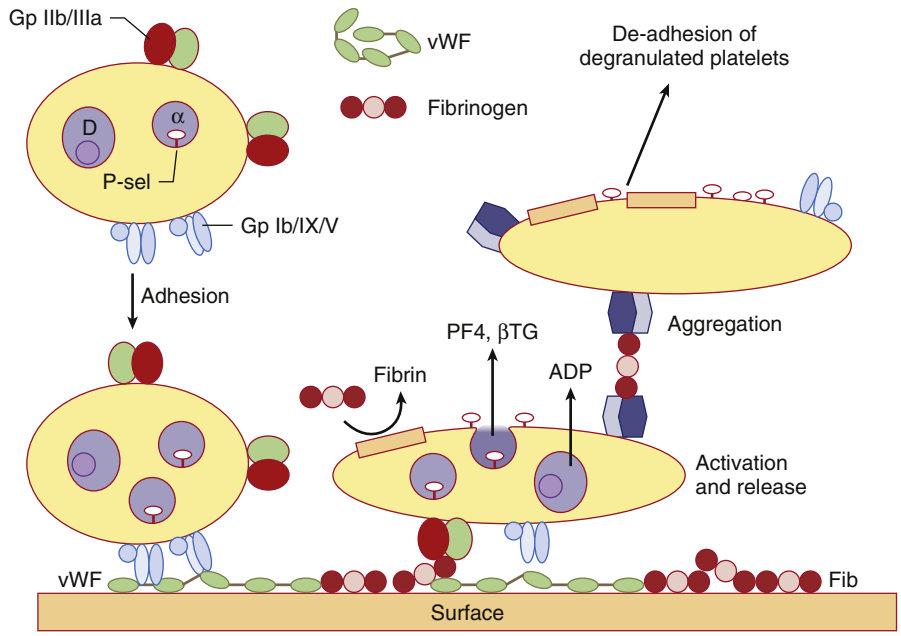


Figure 67-6. Platelet activation by cardiopulmonary bypass materials is facilitated by rapid adhesion and conformational alteration of plasma proteins, including von Willebrand factor (vWF) and fibrinogen (Fib). Platelets adhere to vWF through the glycoprotein (Gp) Ib/IX/V surface glycoprotein and to fibrinogen through the Gp IIb/IIIa receptor. Platelet adhesion stimulates intracellular signaling, which leads to degranulation of α granules (platelet factor 4 [PF4] and β-thromboglobulin [βTG]) and phospholipid reorganization with the formation of coagulation complexes and fibrin formation. Release of adenosine diphosphate (ADP) from dense granules and activation of the Gp IIb/IIIa receptor also occur and lead to the aggregation of platelets to the adherent layer. Because of shear forces, adherent and aggregated platelets can detach from the membrane and circulate in a degranulated state or form small microaggregates that lodge in the distal vasculature. *(From Kottke-Marchant K, Sapatnekar S: Hemostatic abnormalities in cardiopulmonary bypass: pathophysiologic and transfusion considerations,* Semin Cardiothorac Vasc Anesth *5:187-206, 2001.)*

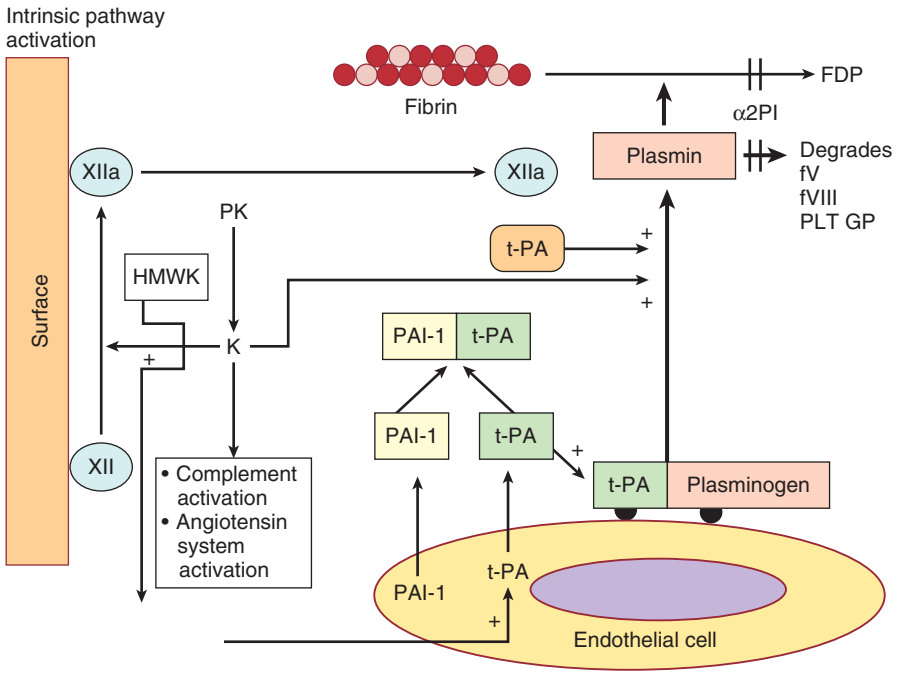


Figure 67-7. The fibrinolytic system results in the degradation of fibrin by plasmin. The intrinsic factors participate in the fibrinolytic system. Adsorption and activation of factor XII, high-molecular-weight kininogen (HMWK), and prekallikrein (PK) occur on the cardiopulmonary bypass material surfaces. Kallikrein (K) and factor XIIa participate in the conversion of plasminogen to plasmin. Plasminogen is also activated by tissue plasminogen activator (t-PA), which is released from endothelial cells, along with its inhibitor, plasminogen activator inhibitor-1 (PAI-1). Plasmin degrades not only fibrin but also coagulation factors V and VIII (fV and fVIII) and platelet surface glycoproteins (PLT GP). Kallikrein plays additional roles in the activation of complement and the angiotensin system, and HMWK accelerates fibrinolysis by stimulating endothelial production of t-PA. *FDP,* Fibrin degradation product; *α2PI*, α2 plasmin inhibitor. *(From Kottke-Marchant K, Sapatnekar S: Hemostatic abnormalities in cardiopulmonary bypass: pathophysiologic and transfusion considerations,* Semin Cardiothorac Vasc Anesth *5:187-206, 2001.)*

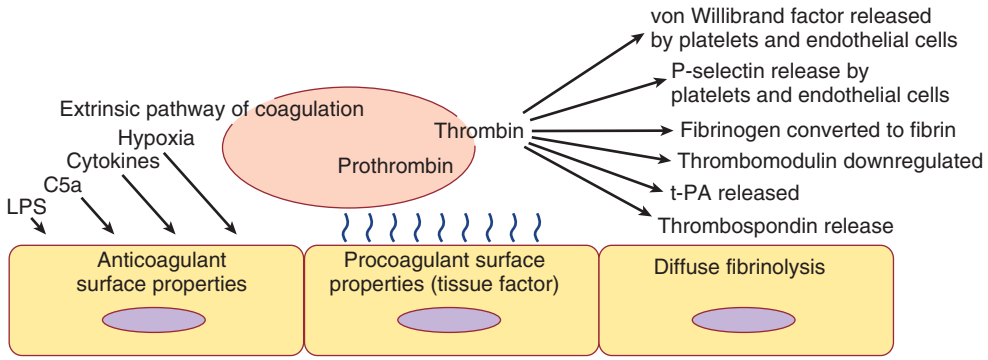


Figure 67-8. Procoagulant endothelial cell activation. When endothelial cells are activated, they express tissue factor, which converts prothrombin to thrombin. Thrombin has multiple biologic actions: (1) stimulation of the release of von Willebrand factor and P-selectin, which cause platelet clumping and platelet, neutrophil, and endothelial cell adhesion; (2) conversion of fibrinogen to fibrin, the solid component of clot; (3) down-regulation of the thrombomodulin/protein C and S systems; (4) release of tissue plasminogen activator (t-PA), which catalyzes the formation of plasmin; and (5) release of thrombospondin, which binds to t-PA, prevents its breakdown by plasminogen activator inhibitor-1 (PAI-1), and accelerates the formation of plasmin. *LPS,* Lipopolysaccharide. *(From Boyle EM Jr, Verrier ED, Spiess BD: Endothelial cell injury in cardiovascular surgery: the procoagulant response,* Ann Thorac Surg *62:1549-1557, 1996.)*

Others have defined heparin resistance as an ACT of less than 400 seconds at any time during the course of CPB and heparin administration.[108] Heparin resistance can result from a congenital deficiency or abnormality of AT, which requires treatment with AT to restore heparin's anticoagulant properties. More often, however, heparin resistance is the result of an acquired condition caused by the patient's disease status and physiologic state. Giving these patients larger doses of heparin may augment the ACT value; therefore, a more accurate term for describing these clinical findings is altered heparin responsiveness.[109] This alteration can result from an acquired AT deficiency, increased levels of heparin-binding proteins, activated platelets, sepsis, or other conditions. In a small study of cardiac surgical patients stratified by their history of preoperative heparin use, altered heparin responsiveness was found in approximately 40% of the patients who had received preoperative heparin therapy.[107]

Reported risk factors for altered heparin responsiveness include AT levels less than 60% of normal, preoperative heparin therapy, and a platelet count greater than 300,000/μL.[108] Ranucci and associates also found that low postoperative AT levels were predictive of a longer length of stay in the intensive care unit (ICU),[110] and others have associated low AT levels with adverse myocardial outcomes.[111] Not all heparin resistance is AT mediated; thus, it is critical to understand the physiologic factors that contribute to the altered heparin responsiveness so that appropriate treatment can be instituted.[112-115]

The most common treatment for altered heparin responsiveness is supplemental heparin. In refractory cases, treatment with AT concentrate, or recombinant AT, in doses that are calculated to produce 80% to 100% AT activity, restores heparin responsiveness. When AT is used for this purpose, careful neutralization with protamine and attention to hemostasis are essential because AT augments the effect of heparin and thereby slightly increases postoperative bleeding.[112]

Heparin Rebound. Heparin rebound is clinical bleeding that occurs within approximately 1 hour of protamine neutralization. It is accompanied by coagulation test results indicating residual heparinization, such as a prolonged partial thromboplastin time (PTT) or thrombin time and increased anti–factor Xa activity. Mechanisms of heparin rebound include slow dissociation of protein-bound heparin after protamine clearance, more rapid clearance of protamine than of heparin, lymphatic return of extracellular sequestered heparin, and the clearance of an unknown heparin antagonist.[109] Heparin rebound is rare, yet it is more likely to occur when the protamine dose is based on the residual heparin concentration at the end of CPB than when protamine is given as a ratio to the total heparin administered, because using this ratio usually results in a slight "overdose." With coagulation monitoring, heparin rebound is easily prevented or treated with supplemental protamine.

Heparin-Induced Thrombocytopenia. HIT is an immune-mediated prothrombotic disorder that occurs in patients exposed to heparin. Antibodies form against the protein platelet factor 4 (PF4) when PF4 has formed a complex with heparin. Although PF4 is found in only trace amounts in human plasma and is stored in platelet α granules, the presence of heparin increases plasma PF4 concentrations 15- to 30-fold by displacing bound PF4 on endothelial cell surfaces. PF4 is also expressed on the surface membrane of activated platelets by membrane fusion with the α-granule membrane; thus, PF4 is exposed and available to bind with heparin.[116] The resulting PF4-heparin complex on the platelet surface is recognized by a specific immunoglobulin G (IgG), which binds to the complex and leads to immunologically mediated platelet activation. Hyperaggregability of these activated platelets is the hallmark of HIT and is responsible for its prothrombotic complications.

A common presentation in patients with HIT is a reduction in the platelet count to less than 100,000/μL or to less than 50% of the baseline count.[117] The incidence of seroconversion after CPB and heparin exposure is quite frequent (20% to 50%).[117,118] However, the reported prevalence of clinical HIT after CPB is only 1% to 3%.[118] Thus, the risk of HIT in cardiac surgical patients with postoperative seroconversion is less than 10%. The strength of the immunologic response, not the mere presence of PF4 or heparin antibodies, may determine which patients are prone to HIT and are at risk for thromboembolic complications.[117,118] The presence of preoperative antibody, in addition to postoperative antibody, has been associated with increased morbidity after cardiac surgery.[119] This morbidity takes the form of gut ischemia, renal dysfunction, limb ischemia, and other prothrombotic events.

Management of the cardiac surgical patient with HIT must include a careful risk-to-benefit analysis. The likelihood that a patient has true disease and is at increased risk for a thrombotic event must be weighed against the risks posed by using an alternative anticoagulant to heparin. The urgency of the surgical procedure is also an important factor that can affect decision making. It is preferable, when possible, to defer the operation until antibody titers have become undetectable or only weakly positive, which may occur after 90 days.[118] If surgical postponement is not practical, then other therapeutic options must be considered (Boxes 67-6 and 67-7). Currently, the direct thrombin inhibitors are used as the anticoagulants of choice. Hirudin and argatroban are approved by the U.S. Food and Drug Administration (FDA) for use in patients with HIT-related thrombosis.[120] The use of these drugs as anticoagulants for CPB is fraught with hemorrhagic complications. Bivalirudin has been approved by the FDA for use in percutaneous interventions and, because of its short half-life, has been favored as an anticoagulant for CPB in patients with HIT.[121-124] However, no drug other than heparin has FDA approval for specific use as an anticoagulant in patients undergoing CPB.[109] Boxes 67-6 and 67-7 summarize therapeutic options and alternative anticoagulant strategies for the patient with HIT whose

BOX 67-6 ***Therapeutic Options for Anticoagulation for Cardiopulmonary Bypass in Patients With Heparin-Induced Thrombocytopenia***

1. Ancrod
2. Low-molecular-weight heparin or heparinoid (test first)
3. Alternative thrombin inhibitor (hirudin, bivalirudin, argatroban)
4. Using a single dose of heparin, promptly neutralizing it with protamine, *and*
   a. Delaying surgery so antibodies can regress *or*
   b. Using plasmapheresis to decrease antibody levels *or*
   c. Inhibiting platelets with iloprost, aspirin and dipyridamole (Persantine), abciximab, or RGD blockers

In all cases:

1. No heparin in flush solutions
2. No heparin-bonded catheters
3. No heparin lock intravenous ports

No agent is currently indicated for anticoagulation in cardiopulmonary bypass.

RGD, Receptor glycoprotein–derived.

Modified from Kaplan JA, Reich DL, Savino JS, editors: Kaplan's cardiac anesthesia: the echo era, *ed 6, St. Louis, 2011, Saunders, p 966.*

BOX 67-7 ***Potential Alternative Anticoagulants for Cardiopulmonary Bypass***

Ancrod
Low-molecular-weight heparins
Factor Xa inhibitors
Bivalirudin or other direct thrombin inhibitors (hirudin, argatroban)
Platelet receptor inhibitors

From Kaplan JA, Reich DL, Savino JS, editors: Kaplan's cardiac anesthesia: the echo era, *ed 6, St. Louis, 2011, Saunders, p 967.*

operation cannot be deferred until seronegativity is documented. Figure 67-9 delineates how each alternative drug inhibits factor Xa, thrombin, or fibrinogen.

Protamine Reactions. Protamine is associated with several hemodynamic effects that can be categorized by their presentation and mechanism. Adverse reactions to protamine range from moderate hypotension to more profound and hemodynamically significant reactions that can increase in-hospital mortality risk.[125,126] The clinical presentation of these reactions serves as a starting point for understanding their mechanistic relationships. Commonly, these reactions are classified as type I, type II, or type III. A type I protamine reaction involves isolated hypotension, with normal to low filling pressures and normal airway pressures. This reaction is usually mild and responds to volume infusion, slowing of protamine infusion, and the gentle titration of vasoactive medications. Type II reactions include moderate to severe hypotension and include features of anaphylactoid reactions, such as bronchoconstriction. Anaphylactoid reactions include protamine sensitivity reactions that are classically immunologic or allergic in that they are immunoglobulin E (IgE) antibody mediated. Nonimmunologic mechanisms may involve IgG antibodies or complement activation. Type III reactions are thought to be caused by large heparin-protamine complexes that lodge in the pulmonary circulation, cause the release of mediators, and result in severe hypotension and elevated PA pressures that may lead to acute RV failure. This is obviously a profound response, resulting in global cardiovascular collapse or necessitating the reinstitution of CPB because of intractable RV failure. Fortunately, catastrophic hypotension and intractable RV failure are relatively rare events on the spectrum of protamine reactions.[126]

Mechanistic explanations for protamine reactions include endothelial nitric oxide release, mast cell degranulation, and histamine release associated with rapid infusion.[109] A study by Kimmel and colleagues found that neutral protamine Hagedorn insulin use, documented fish allergy, and a history of nonprotamine medical allergies were independent risk factors for protamine hypersensitivity reactions.[127] In this study, 39% of patients who presented for cardiac surgery had one or more of these risk factors. Other possible but unconfirmed risk factors include prior exposure to protamine, a history of vasectomy, decreased LV function, and hemodynamic instability.[127] The site of injection does not influence the incidence of protamine reactions.[128] Pretreatment with histamine blockade is not preventive.[109]

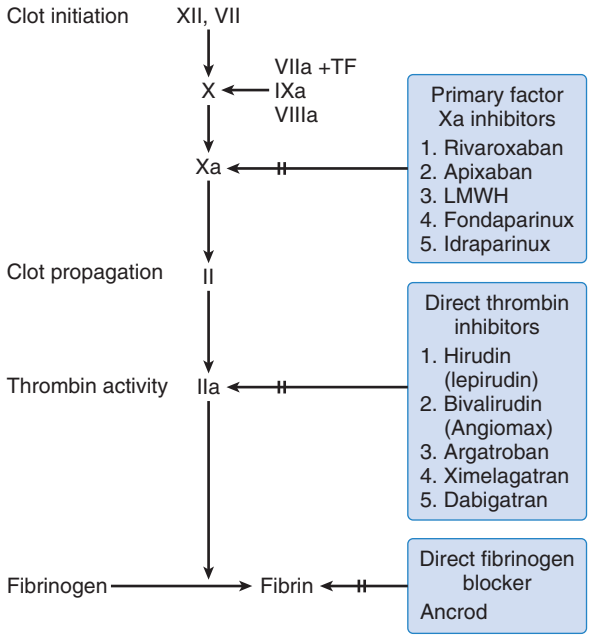


Figure 67-9. Alternatives to heparin. Newer anticoagulants are shown in the boxes on the *right side* of the figure; these drugs inhibit factor Xa, thrombin, or fibrinogen. *LMWH,* Low-molecular-weight heparin. *(From Kaplan JA, Reich DL, Savino JS, editors:* Kaplan's cardiac anesthesia: the echo era, *ed 6, St. Louis, 2011, Saunders, p 968.)*

The following principles summarize the treatment options for all patients and for those at risk for intraoperative protamine reactions:

1. Protamine should be administered slowly (i.e., over ≥5 minutes).
2. In patients with documented adverse events related to protamine, consideration should be given to *not* rechallenging the patient with protamine. Pharmacologic alternatives to protamine can be considered, or a decision can be made not to reverse heparin. Consideration may be given to using non–heparin-based CPB, performing off-pump coronary artery bypass (OPCAB) with an alternative to heparin, or, if heparin is used, administering nonprotamine heparin reversal drugs such as PF4 or heparinase, or simply waiting for heparin's effects to dissipate.
3. Hypotension associated with protamine reversal of heparin often is ameliorated by simply slowing or pausing protamine infusion while volume is infused through intravenous lines or the aortic cannula. Vasoactive medications, such as phenylephrine or ephedrine, or increased inotropic support may be necessary.
4. Severe or intractable hypotension, with or without evidence of pulmonary circulatory involvement, bronchospasm, or overt RV failure, demands immediate aggressive attention, intervention, and planning for a potential return to CPB. Steps to consider include the following:
   a. Reheparinization to prepare the patient for a return to CPB and to reduce heparin-protamine complex size. If hemodynamics permit, a low dose of heparin

(70 units/kg) may be tried first while supportive treatment continues, followed by a full CPB dose of heparin (300 units/kg) if it becomes necessary to return the patient to CPB.

b. Inotropic support, either by infusion or by intermittent bolus administration, is warranted. Epinephrine and norepinephrine are acceptable options, and milrinone may be considered if the patient's hemodynamic status permits.

c. If the patient's hemodynamic status allows, nebulized albuterol is helpful in the management of bronchospasm and elevated airway pressures.

Antifibrinolytic Therapy: Prophylaxis for Bleeding. Prophylactic use of antifibrinolytic drugs before CPB reduces bleeding and transfusion requirements in cardiac surgical patients in randomized trials and in multiple meta-analyses.[129] The most well-known antifibrinolytic drugs include the synthetic lysine analogues ε-aminocaproic acid (EACA) and tranexamic acid (TA) and the serine protease inhibitor aprotinin. Presumably, the blood-sparing effects of the synthetic drugs result from the inhibition of fibrinolysis by their binding to the lysine-binding sites on plasmin. This also has platelet protective properties because plasmin's antiplatelet effects are also inhibited by antagonist binding.

Aprotinin is a direct enzymatic inhibitor of plasmin and has other protease-inhibiting properties that confer its antiinflammatory and antikallikrein effects. However, aprotinin was notably associated with increases in post-CPB creatinine values and other adverse organ system outcomes in large-scale observational trials.[130] When a randomized prospective trial showed an increase in mortality in the aprotinin group, despite a reduction in bleeding, the drug was removed from the global market.[131] Although the causes of death in the aprotinin-treated patients were not found to be related to thrombosis or other drug-related effects, aprotinin was rendered unavailable for commercial use for years after publication of this study. The decision to remove aprotinin from clinical use was revisited on reevaluation of these study data,[131] and aprotinin has been reintroduced in Canada and other countries specifically for use as labeled in CABG surgery.

Hypercoagulable States. The use of antifibrinolytics has become common in cardiac operations that require CPB. The use of antifibrinolytic drugs and prohemostatic drugs and blood products to treat bleeding has brought to light the risk of thrombosis in CPB, during which feedback mechanisms are critical and homeostasis is perturbed. All patients incur this risk of thrombosis as consumptive coagulopathy increases, but the risk is greatly increased in patients with congenital or acquired thrombophilic states.[132] These states may be important in view of current practices that involve pharmacologically inhibiting fibrinolytic pathways in cardiac surgical patients.

The factor V Leiden (FVL) mutation is the most common inherited thrombophilic disorder; its prevalence is 3% to 7% in white populations.[132,133] Mechanistically and clinically, FVL has been implicated in thrombotic complications in cardiac operations, most often those involving a period of circulatory arrest and the use of antifibrinolytics.[134-136] In a review of FVL mutation, Donahue gave the following summation and recommendations[132]:

- Cardiac surgical patients who are heterozygous for the FVL mutation bleed less than do noncarriers.
- The risk of early graft thrombosis may be increased in patients with FVL deficiency.
- The use of antifibrinolytic drugs may increase thrombotic risk in patients with FVL.
- Anecdotal evidence suggests that in patients with FVL mutation who are exposed to deep hypothermic circulatory arrest, antifibrinolytics increase thrombotic risk.

For further information on congenital thrombophilic states, the reader is referred to a review article by Crowther and Kelton.[137]

Cardiac Surgical Patients Taking Anticoagulant or Antithrombotic Drugs. Antithrombotic therapy in cardiac surgical patients has many roles and applications. Patients with ischemic heart disease can be managed short- or long-term with pharmacologic drugs that may include aspirin, AT inhibitors (heparins), direct thrombin inhibitors, or an array of platelet inhibitors (adenosine diphosphate [ADP] receptor inhibitors and glycoprotein IIb/IIIa [Gp IIb/IIIa] receptor inhibitors). Patients with a history of peripheral vascular disease, valvular heart disease, or low ventricular ejection states can similarly be managed with some form of antithrombotic therapy that may also include warfarin. Frequently, patients arrive for surgery while receiving multiple antithrombotic medications. Thus, postoperative bleeding is a common but challenging complication of cardiac surgery, especially when the bleeding risk posed by CPB itself is considered.

The use of percutaneous coronary interventions such as angioplasty and intracoronary stent deployment for ischemic heart disease has led to the use of antithrombotic medications to maintain stent patency and to prevent stent thrombosis. The American College of Cardiology and AHA (ACC/AHA) guidelines for percutaneous coronary intervention recommend (on the basis of class I evidence) the use of both aspirin and clopidogrel for at least 1 year after drug-eluting stent placement.[138] The administration of thienopyridine antiplatelet drugs in addition to aspirin increases the risk of bleeding after cardiac surgery[139]; however, it is unclear whether aspirin alone increases this risk. Abundant evidence (mostly level B evidence from small, retrospective, nonrandomized studies) suggests that the ADP receptor antagonist clopidogrel (Plavix) has been associated with excessive perioperative bleeding in patients who undergo CABG.[140,141] This trend has even been reported in the OPCAB population, although not consistently.[142-144] Some authors have recommended a 5- to 7-day delay after discontinuation of clopidogrel in patients who require CABG. However, two more recent studies suggested that a 3-day delay may be sufficient to lessen bleeding risk and provide safe outcomes.[145] Furthermore, most surgeons do not wait the recommended 5 to 7 days before proceeding with CABG.[146] It is likely that a 5- to 7-day delay is not necessary, but some interval between the discontinuation of clopidogrel and CABG is supported by the available evidence.[139]

Patients with a history of Gp IIb/IIIa receptor blockade as a part of their acute coronary syndrome management are at risk of increased bleeding and blood component use when they are given abciximab, especially within 12 hours of cardiac surgery.[147-149] Shorter-acting Gp IIb/IIIa receptor antagonists do not seem to increase bleeding or adverse outcomes and in fact may improve myocardial outcomes when Gp IIb/IIIa blockers are in use.[150] The interval between the discontinuation of antiplatelet therapy and cardiac or noncardiac surgery is critical to preventing thrombotic events without increasing the risk of bleeding. These decisions regarding the cessation of therapy can be guided by knowledge of drug pharmacology and testing of antiplatelet drug efficacy.

Enoxaparin, a low-molecular-weight heparin, increases transfusion rates and the risk of surgical reexploration when it is used in association with CPB.[151] Low-molecular-weight heparin may also decrease heparin responsiveness.[152,153]

Patients who present for cardiac surgery with residual warfarin effects may benefit by having enhanced anticoagulation during CPB. Postoperatively, if excessive bleeding is noted and is confirmed by hemostasis testing, factor replacement can be performed with blood products or pharmacologic prothrombin complex concentrates.

Patients with atrial fibrillation may be maintained on new antithrombotic therapeutic drugs that include AT drugs (dabigatran) and factor Xa inhibitors (rivaroxaban). These drugs are potent and long-acting, and they have no antidote, so one would expect that treating cardiac surgical patients with these drugs would increase their bleeding risk. These drugs have only relatively recently been prescribed for atrial fibrillation; no recommendations on their use in cardiac surgery currently exist.

In summary, patients who present for cardiac surgery with preexisting, pharmacologically induced inhibition of the hemostatic system may have undesirable post-CPB bleeding. The diagnosis and treatment of this complication should be the same whether the derangement is a function of CPB itself, coexisting pharmacologic inhibition, or both. The management and treatment of persistent postoperative bleeding are discussed in the section on problems in the postoperative period.

INDUCTION OF ANESTHESIA AND THE PREBYPASS PERIOD

Premedication

The anesthesiologist should ensure that appropriate medications are administered with a sip of water on the morning of surgery. With a few exceptions, patients should receive their usual long-term medications, particularly β-adrenergic blocking drugs, on the day of surgery. The clinician should be aware that ACE inhibitors (ACEIs), if administered on the day of surgery, may increase the patient's propensity for hypotension.[154] With respect to aspirin, it is well recognized that aspirin administration in the early postoperative period reduces the risk of ischemic complications after CABG surgery.[155] However, patients who receive aspirin immediately preoperatively may have more mediastinal bleeding and greater transfusion requirements. A consensus statement published by the STS recommends that low-intensity antiplatelet drugs (e.g., aspirin) be discontinued before cardiac surgery to reduce patients' blood transfusion requirements, but this should be done only in purely elective cases in patients without acute coronary syndromes.[82]

However, drugs that inhibit the platelet P2Y12 receptor should be discontinued before operative coronary revascularization (either on-pump or off-pump), if possible.[82] The interval between drug discontinuation and operation is determined from the drug's pharmacodynamics but may be as short as 3 days for irreversible inhibitors of the P2Y12 platelet receptor. POC tests are available to measure platelet ADP responsiveness. These tests are not perfect; they lack sensitivity and specificity.[156-158] Nonetheless, POC tests that show normal platelet ADP responsiveness after administration of an initial dose of clopidogrel indicate P2Y12 resistance with as much as 85% specificity.[156,158] More accurate tests are available but are not POC tests.[156,159] The routine addition of P2Y12 inhibitors to aspirin therapy early after CABG may increase the risk of reexploration and subsequent operation and is not indicated by available evidence except in those patients who satisfy the criteria for ACC/AHA guideline–recommended dual antiplatelet therapy (e.g., patients who present with acute coronary syndromes or who have recently received drug-eluting coronary stents).

The prospect of undergoing cardiac surgery provokes anxiety in most patients. Furthermore, the insertion of intravenous and arterial catheters is painful and must be done before anesthesia is induced. The resultant anxiety and pain can lead to undesirable sympathetic stimulation, with consequent tachycardia and hypertension. The first step in preventing this cycle is thoroughly explaining the anticipated anesthetic techniques and procedures to the patient. Premedication with a narcotic or anxiolytic drug, or both, to mitigate pain and anxiety is usually indicated before the patient is transported to the operating suite. Supplemental intravenous drugs—commonly midazolam and possibly fentanyl—are usually necessary during radial artery cannulation before anesthesia is induced. However, in patients with low CO secondary to congestive HF (CHF), sedation should be performed judiciously to avoid myocardial depression and resultant hypotension. Moreover, in patients with significant pulmonary hypertension, oversedation and respiratory depression leading to hypercapnia or hypoxia must be avoided.

Induction of Anesthesia

In preparing for induction, the clinician should have the following drugs immediately available: vasopressors (e.g., phenylephrine, ephedrine, calcium chloride, readily available vasopressin), one or more inotropes (e.g., ephedrine; epinephrine; readily available norepinephrine, dopamine, or dobutamine), one or more vasodilators (e.g., nitroglycerin, nitroprusside, nicardipine), an anticholinergic drug (atropine), antiarrhythmic drugs (e.g., lidocaine, esmolol, magnesium, amiodarone, adenosine), and heparin.[160] Commonly administered drugs should be drawn up and ready for administration by bolus or infusion, as appropriate; agents that are used less commonly should be readily available in the operating room. Protamine should

be readily available, but many institutions require that protamine be stored in unique packaging or at a separate, nearby location to prevent inadvertent, inappropriate, or premature administration.

Furthermore, the selected antibiotic should be ready to administer according to Surgical Care Improvement Project (SCIP) guidelines. The STS recommends a cephalosporin as the primary prophylactic antibiotic for cardiac surgery; the drug should be administered within 1 hour before incision.[161] In patients who are allergic to penicillin, vancomycin is administered within 2 hours of incision. Finally, antifibrinolytic drugs are commonly used to minimize bleeding and the need for transfusion during cardiac surgery. The only currently available antifibrinolytic drugs are TA and EACA; both reduce total blood loss and decrease the number of patients who require blood transfusion during cardiac procedures.[82]

Anesthetic drugs and techniques for inducing anesthesia should be selected with consideration of the patient's cardiac pathophysiology and other comorbid conditions. No single "recipe" can guarantee hemodynamic stability during anesthetic induction. Hypotension may result from a relatively hypovolemic state and vasodilation secondary to a reduction in sympathetic tone induced by anesthetics. Hypotension is particularly common in patients with poor LV function. Conversely, in patients with good myocardial function, hypertension may occur during induction because of preinduction anxiety or sympathetic stimulation caused by laryngoscopy and endotracheal intubation.

The radial artery or an alternative site should be cannulated before induction of anesthesia to monitor arterial pressure on a beat-to-beat basis. If the radial artery is being harvested as a vascular conduit, the contralateral radial or brachial artery or a femoral artery can be cannulated. Noninvasive blood pressure measurement can be used to check the accuracy of pressure readings if the arterial catheter is "positional" or "dampened." Of course, basic monitors, including the ECG and pulse oximeter, should also be used during the induction of anesthesia. During any cardiac surgical procedure, central venous access is necessary to facilitate volume infusion, possibly including transfusion therapy, and to ensure that vasoactive agents are administered directly into the central circulation. A central venous catheter, a PA catheter, or both can be placed either before or after anesthesia is induced, although an increasing number of anesthesiologists defer central line placement until after anesthetic induction. The urinary bladder catheter, nasogastric tube, TEE probe, and any additional temperature monitors (e.g., a nasopharyngeal probe) are positioned after induction of anesthesia.

When choosing anesthetic drugs and doses during induction and maintenance, one should consider any pharmacodynamic properties that could affect arterial blood pressure, heart rate, or CO, as well as the desirability of "early" extubation of the trachea (i.e., within a few hours after the operation is completed). Anesthesia is most commonly induced with an opioid and a sedative-hypnotic (etomidate, thiopental, propofol, or midazolam). All anesthetics decrease arterial blood pressure by decreasing sympathetic tone, decreasing systemic vascular resistance (SVR), inducing bradycardia, or directly depressing myocardial function. The only exception is ketamine, which has sympathomimetic effects; however, in patients with catecholamine depletion, ketamine's sympathomimetic effects may not counterbalance its direct negative inotropic effects. Because of their pharmacologic complexities, all anesthetic agents should be administered judiciously in patients who are critically ill or who have poor LV function.

Muscle relaxants are usually given early in the sequence of anesthetic induction, particularly if relatively large doses of opioids are administered, to minimize chest wall rigidity (see also Chapter 34). With the routine use of fast track anesthesia techniques, including a trend toward earlier extubation, volatile anesthetics are often chosen as the primary maintenance anesthetic. The predominant effect of isoflurane, desflurane, and sevoflurane is dose-dependent vasodilation with resultant decreases in SVR and arterial blood pressure. These volatile anesthetics may have an advantage in inducing preconditioning, which is particularly important in patients undergoing either CABG with CPB or OPCAB, in which myocardial ischemic insults are likely. The volatile anesthetic agents have several cardioprotective effects, including triggering the preconditioning cascade and mitigating reperfusion injury.[162] However, nitrous oxide probably should be avoided because it can increase gaseous bubble size and adversely affect pulmonary vascular resistance (PVR).

Pre–Cardiopulmonary Bypass Period

After anesthesia is induced, several important details must be remembered, especially positioning (see also Chapter 41). Methods of positioning the arms vary according to institutional practice, but one must avoid causing brachial plexus injury by hyperextending the arms, ulnar nerve injury by improperly padding the olecranon, radial nerve injury by compressing the upper part of the arm against the sternal retractor support posts, or finger injury by entrapping the finger against the metal edge of the surgical table. Proper positioning also ensures that arterial catheters previously placed in the radial, ulnar, or brachial arteries are not "dampened." The head should be padded and occasionally repositioned during the procedure to prevent occipital alopecia, which can occur several days postoperatively. The eyes should be taped, possibly lubricated, and definitely free from pressure. Pressure-related injury to any soft tissue will potentially be exacerbated by hypothermia and decreased perfusion during CPB. All monitors and tubing should be checked after final positioning to ensure that none are kinked, entrapped, tangled, or inaccessible. Additionally, antibiotics must be administered (with documentation) within 1 hour of incision (vancomycin within 2 hours). Arterial blood gases and blood chemistry (electrolytes, glucose, and calcium), as well as baseline ACT, should be measured shortly after anesthesia is induced. If a continuous mixed venous PA catheter has been inserted, mixed venous hemoglobin oxygen saturation should be measured to calibrate the device.

During the prebypass period, the anesthesiologist's main goal is to maintain the hemodynamic and metabolic stability of the patient while making preparations for CPB. The degree of surgical stimulation varies

markedly during this period. Positioning the patient, inserting additional monitors, preparing the skin, and harvesting the saphenous vein or veins cause only minimal sympathetic stimulation. Therefore, hypovolemic patients and those with poor ventricular function may be susceptible to hypotension during these periods. In contrast, chest incision, sternal splitting, and harvesting of the IMA involve more intense surgical stimulation. These events may cause hypertension, tachycardia, and dysrhythmias, even in previously hypotensive patients. However, just before CPB is initiated, during the cannulation of the great vessels, surgical stimulation is again minimal, and manipulation of the heart and great vessels may transiently decrease venous return and cause a precipitous decline in blood pressure. The anesthesiologist must be ready to treat all hemodynamic aberrations with the vasopressor, inotropic, vasodilator, antiarrhythmic, and anticholinergic drugs mentioned earlier.

In preparation for CPB, anticoagulation must be achieved. Heparin is still the standard drug used and is administered through a central venous catheter at an initial dose of 300 to 400 units/kg. The onset of anticoagulation is almost immediate, but generally, the drug is allowed to circulate for 3 to 5 minutes before its effect is measured. The ACT must increase to at least 300 seconds before CPB is initiated, although most institutions use at least 400 seconds as their standard. Additional heparin is administered, if necessary, to increase the ACT to the desired level. Subsequently, it is common to administer an antifibrinolytic drug (EACA or TA) in an attempt to minimize bleeding and the need for transfusion during cardiac surgery.

After heparinization, the next major step in the prebypass phase is vascular cannulation. One or more large veins or the right atrium is cannulated so that all systemic venous blood is diverted to the pump oxygenator. Additionally, a large artery, usually the ascending aorta, is cannulated so that oxygenated blood is delivered back to the arterial circulation. Heparin is always administered before cannulation. Usually, arterial cannulation is established before venous cannulation to allow rapid intravascular volume or blood resuscitation if necessary. Complications of aortic cannulation include arterial dissection, hemorrhage and resultant hypotension, inadvertent cannulation of the aortic arch vessels, and embolic phenomena caused by dislodged atherosclerotic plaque or by air introduced into or entrained around the aortic cannula. Complications of venous cannulation include hypotension from blood loss, dysrhythmias, and surgical mechanical compression of the heart or great vessels. When arterial cannulation is successful and the cannula has been inspected to ensure that no air is present, volume can be administered in 100-mL increments to treat bleeding and hypovolemia. If necessary, dysrhythmias are treated by cardioversion, medications, or rapid initiation of CPB.

Patients undergoing redo cardiac surgery (i.e., those who have previously had a median sternotomy) warrant special concern about the possibility of sudden, massive hemorrhage. At least 2 units of blood should be immediately available for all redo cases. Frequently, the surgeon will elect to use an oscillating saw in these patients, but mediastinal structures adherent to the underside of the sternum may nevertheless be injured. If the right atrium, right ventricle, great vessels, or an existing coronary graft is cut, the surgeon may elect to initiate CPB on an emergency basis. Therefore, the anesthesiologist should have a systemic dose of heparin prepared. As soon as the patient is heparinized, the femoral or aortic arterial cannula is inserted, and the cardiotomy suckers can be used to create venous return (so-called sucker bypass).

Onset of Cardiopulmonary Bypass

With the onset of CPB, to guard against malposition of the aortic or venous cannula, the perfusionist checks the aortic inflow line pressure and for signs of inadequate venous return while the anesthesiologist checks for persistently low arterial pressure, unilateral blanching of the face, or any swelling in the neck veins, face, or conjunctiva. Once full bypass is established and aortic ejection by the heart has ceased, ventilation and inhaled drugs can be discontinued. If a PA catheter is present, it is pulled back 3 to 5 cm to minimize the risk of pulmonary perforation as the pulmonary arteries collapse. Prebypass urine output is recorded and emptied so that urine output during CPB can be monitored separately. The TEE probe may be used to watch for LV distention with the onset of CPB, which may indicate aortic valve regurgitation or other hemodynamic problems. Once CPB is established, the probe is left in the unlocked (neutral) position until the cardiac chambers are de-aired and the patient is weaned from CPB.

To ensure adequate anesthetic depth, supplemental intravenous sedative-hypnotics are administered, or a volatile agent is administered through a vaporizer connected to the oxygenator gas inlet of the CPB circuit. Administration of muscle relaxant is continued to prevent spontaneous ventilation, movement, or shivering during hypothermia and rewarming.

WEANING FROM CARDIOPULMONARY BYPASS

Preparations for Weaning From Cardiopulmonary Bypass: The "CVP" Mnemonic

Fortunately, for most patients, separation from CPB is a relatively uneventful process. A review by Licker and colleagues emphasized that the key to successful weaning from bypass is clear communication among members of the operating room team.[163] In a study conducted at the Mayo Clinic in Rochester, Minnesota,[164] a strong correlation was noted between the frequency of technical errors and poor communication or coordination among the surgeon, anesthesiologist, and perfusionist.

Regarding clinical issues, several criteria should be met in all cardiac surgical cases before weaning from CPB is attempted. Morris, Romanoff, and Royster suggest a mnemonic, "CVP," to help the clinician remember the main tasks necessary for the successful termination of CPB (Table 67-4).[165] Each letter of CVP represents several tasks or important points to remember that begin with that letter.

The first "C" stands for cold and refers to the patient's temperature at the time of weaning from CPB, which should be 36° C to 37° C. Neither the temperature of the

TABLE 67-4 ELEMENTS OF ROMANOFF AND ROYSTER'S "CVP" MNEMONIC FOR WEANING PATIENTS FROM CARDIOPULMONARY BYPASS

C	V	P
Cold	Ventilation	Predictors
Conduction	Visualization	Pressure
Cardiac output	Vaporizer	Pressors
Cells	Volume expanders	Pacer
Calcium		Potassium
Coagulation		Protamine

From Romanoff ME, Royster RL: The postcardiopulmonary bypass period: weaning to ICU transport. In *Hensley FA, Martin DE, Gravlee GP, editors:* A practical approach to cardiac anesthesia, *ed 4, Philadelphia, 2008, Lippincott Williams & Wilkins, pp 230-260.*

venous blood returning to the CPB circuit nor the nasopharyngeal temperature should ever exceed 37° C because hyperthermia may increase the risk of postoperative neurologic complications (see the section on temperature).

The second "C" stands for conduction and refers to cardiac rate and rhythm. A heart rate of 80 to 100 beats/minute is usually desirable. Bradycardia is treated with epicardial pacing wires and/or with β-adrenergic drugs that have chronotropic and dromotropic, as well as inotropic, properties. Tachycardia (i.e., heart rate >120 beats/minute) is also undesirable. Sinus tachycardia may result from anemia, hypovolemia, "light" anesthesia, or the administration of chronotropic drugs; treatment is tailored to the presumed cause. Rhythm is also an important factor in optimizing CO. Third-degree AV block requires pacing, ideally AV pacing. Sinus rhythm is preferable, particularly in patients with poor LV compliance, who are especially dependent on an "atrial kick" to achieve adequate filling. If supraventricular tachycardia is present, direct synchronized cardioversion is often warranted. In addition, pharmacologic therapy with amiodarone, esmolol, verapamil, or adenosine may be used in the initial treatment of or to prevent the recurrence of supraventricular tachycardia.

The third "C" stands for CO or contractility. Contractility may be estimated from TEE or PA catheter data, if available.

The fourth "C" refers to cells (i.e., red blood cells [RBCs]). The patient's hemoglobin concentration should be 7 to 8 g/dL, or slightly higher, before weaning from CPB. If the hemoglobin concentration is less than 6.5 g/dL when rewarming commences, the perfusionist and anesthesiologist can consider hemoconcentration or transfusion of a unit of packed RBCs (PRBCs).

The fifth "C" is for calcium, which should be immediately available for possible administration to treat hypocalcemia and hyperkalemia. Ionized calcium levels should be measured after rewarming to help direct therapy. Although calcium is not administered routinely, if ionized calcium levels are in the low-normal range, SVR can be beneficially increased by calcium administration.

The sixth "C" stands for coagulation. After protamine is administered, ACT is measured. In patients at risk for coagulation abnormalities, prothrombin time, PTT, and platelet count should also be measured a few minutes later. Examples of patients at risk for coagulation abnormalities include the following: those with long CPB times; those with extreme hypothermia, elective circulatory arrest, or both, during CPB; and those with chronic renal failure. Platelet function tests may be useful in patients taking platelet inhibitors (e.g., clopidogrel or aspirin). (For further discussion of patients having emergency surgery who are taking warfarin or who have been exposed to thrombolytic drugs, antiplatelet Gp IIb/IIIa agents, or direct thrombin inhibitors see the sections on the "hematologic system" and on bleeding and coagulopathy.)

The first "V" is for ventilation of the lungs. As CPB is discontinued, the venous outflow line is gradually occluded, and PA blood flow is gradually restored. Pulmonary ventilation and oxygenation must be reestablished, thus allowing the lungs to become the site of gas exchange again. Ideally, the lungs are initially reinflated manually, with a few sustained inflations to a peak pressure of approximately 30 cm H_2O. If an IMA has been grafted to a coronary artery, the anesthesiologist must examine the surgical field during these inflations to ensure that the grafted artery is not overstretched, which could disrupt the distal anastomosis. Additionally, the compliance of the lungs is judged by these initial inflations, and bronchodilators can be administered if necessary. The surgeon should remove any fluid or blood from the pleural spaces and ensure that any pneumothorax is treated with a chest tube.

The second "V" is for visualization of the heart, both directly in the surgical field (where the right-sided chambers are visible) and on the TEE, to estimate global and regional contractility. Furthermore, the degree of chamber filling (hypovolemic, euvolemic, or distended) can be estimated. In addition, one can do a final check for air within the cardiac chambers with TEE examination.

The third "V" is for vaporizer, meaning that if volatile agents were used to ensure lack of awareness or to control blood pressure during CPB, the clinician usually reinstitutes a low dose immediately after weaning. However, because all the volatile agents decrease contractility and blood pressure, these effects can confuse the differential diagnosis of hypotension and myocardial dysfunction during weaning.

The final "V" is for volume expanders. When all products from the pump have been exhausted and if blood transfusion is not indicated, crystalloid and albumin or hetastarch should be readily available to increase preload rapidly if necessary.

As for the letter "P" in the CVP mnemonic, Morris, Romanoff, and Royster explained that the first "P" represents the need to be aware of predictors of adverse cardiovascular outcome.[165] For example, preoperative low EF and prolonged CPB often predict difficulty in weaning the patient from CPB and the need for inotropic support. In addition, emergency surgery in patients with acute coronary syndrome may lead to myocardial stunning. Furthermore, inadequate surgical repair (e.g., incomplete coronary revascularization) may result in ongoing ischemia.

The second "P" is for pressure. Calibration and rezeroing are accomplished shortly before the patient begins being weaned from CPB. Any discrepancy between the distal (usually radial) arterial pressure and the central aortic pressure should be recognized. Occasionally, the surgeon may need to insert a temporary aortic root cannula or a longer-lasting femoral arterial cannula to

monitor systemic blood pressure accurately during and after the termination of CPB.

The third "P" is for pressors, meaning vasopressors and inotropic agents that should be immediately available. A vasodilator, such as nitroglycerin, nicardipine, or nitroprusside, also should be immediately available.

The fourth "P" is for pacer because an external pacemaker should be readily available for all patients. Pacing is often needed to treat bradycardia. In patients with heart block, ideally, an AV sequential pacemaker is used to maintain the atrial kick.

The fifth "P" is for potassium because hypokalemia may contribute to dysrhythmias, and hyperkalemia may result in conduction abnormalities. In addition, the patient's ionized calcium level is usually checked; most clinicians have a low threshold for administering additional calcium chloride. Furthermore, magnesium (2 to 4 g) is usually administered before CPB is terminated. Although magnesium's efficacy in preventing postoperative atrial or ventricular dysrhythmias has not been clearly demonstrated, hypomagnesemia is common after CPB. The risk-to-benefit ratio for administering a 2- to 4-g dose is low.

The final "P" is for protamine. Many institutions require that protamine be uniquely packaged or kept in a nearby but separate area to ensure that the drug is not prematurely administered. (Administration during ongoing CPB is a disastrous error.) Nevertheless, it should take but a few moments to retrieve protamine when the surgeon, anesthesiologist, and perfusionist agree that it is time to reverse anticoagulation.

Termination of Cardiopulmonary Bypass

After all the preparations described previously have been made and the patient's ventilation has been reestablished, the venous return to the pump is reduced by gradually clamping the venous line. The patient's intravascular volume is carefully increased by continued inflow through the aortic or other arterial cannula. Ventricular distention should be avoided because it increases wall tension and myocardial oxygen consumption. The pump flow into the aorta is lowered, in effect moving into a "partial bypass" phase, in which some of the venous blood still goes into the pump and some passes through the right ventricle and lungs to be ejected into the aorta by the left ventricle. Some clinicians reduce the pump flow to half flow rather than gradually reducing venous return to the pump. Once loading conditions are optimal and contractility appears adequate, the aortic inflow line may be clamped to separate the patient from CPB.

If CPB has been successfully terminated but cardiac performance is not optimal, preload can be increased by infusing additional blood from the pump into the aortic cannula, usually in 100-mL increments in adult patients. Monitoring the left intraventricular volume in a qualitative fashion by TEE, observing the right ventricle directly, and monitoring the filling pressures give a good estimate of the adequacy of preload. At this point, the anesthesiologist and surgeon jointly determine whether myocardial filling and performance are adequate. This determination can best be accomplished by using TEE to observe the global and regional function of both ventricles. Supplemental information can be obtained by measuring CO, if possible. Afterload can also be optimized at this point. Usually, 95 to 125 mm Hg is a desirable systolic pressure in adult patients in the immediate postbypass period, whereas increased systolic blood pressure should be avoided to prevent excessive stress on suture lines in the heart and aorta. If the patient is hemodynamically unstable and additional time is needed to administer initial or additional inotropes or vasoconstrictors, CPB can be reinstituted by unclamping the venous outflow line and directing all flow to the oxygenator again (Fig. 67-10).

Once protamine is administered, the reinstitution of CPB becomes a more complicated process because the patient must first be reheparinized. Therefore, final checks of cardiac function, heart rate and rhythm, preload, afterload, and perfusion should be made jointly by the anesthesiologist and the surgeon. The venous cannula or cannulas are usually removed after the initial test dose of protamine is given. Many surgeons remove the aortic cannula only after at least half of the protamine dose has been administered. The rate and mode of protamine administration (incremental small boluses versus continuous infusion) vary according to institutional and individual clinicians' practices, but a large dose of protamine should never be administered as a rapid bolus.

Table 67-5 shows the characteristics and treatment modalities of specific TEE-diagnosed difficulties that may be encountered during weaning and termination from CPB.[163]

POSTBYPASS PERIOD

Common Problems After Cardiopulmonary Bypass

Awareness. The potential for the patient's awareness must be assessed during and after CPB (see also Chapter 50). The incidence of this distressing complication is more frequent in cardiac operations than in other cases.[64,166] Although patients may sweat during the rewarming period, usually because of perfusion of the thermoregulatory site in the hypothalamus with warm blood, sweating may also result from awareness if anesthetic concentrations are low during the period when the brain becomes normothermic. Awareness may be more likely if considerable time has elapsed since any sedative-hypnotic or narcotic has been administered, if small doses of anesthetic drugs were administered during CPB, or if the patient is young. Consideration should be given to continuing to administer a volatile anesthetic agent once pulmonary ventilation is reestablished and to administering additional sedative-hypnotic doses, an opioid, or both. Some clinicians begin infusing an anesthetic agent such as propofol or dexmedetomidine shortly after weaning the patient from CPB and continue it during and after transport to the ICU or cardiac recovery area.

Published studies support the hypothesis that the use of depth-of-anesthesia monitors such as the BIS can decrease the incidence of intraoperative awareness in patients at high risk for this problem[63,64] (see also Chapter 50). However, falsely high BIS values during cardiac surgery have been attributed to interference from pump head rotation, pacemakers, and hypothermia itself.[167]

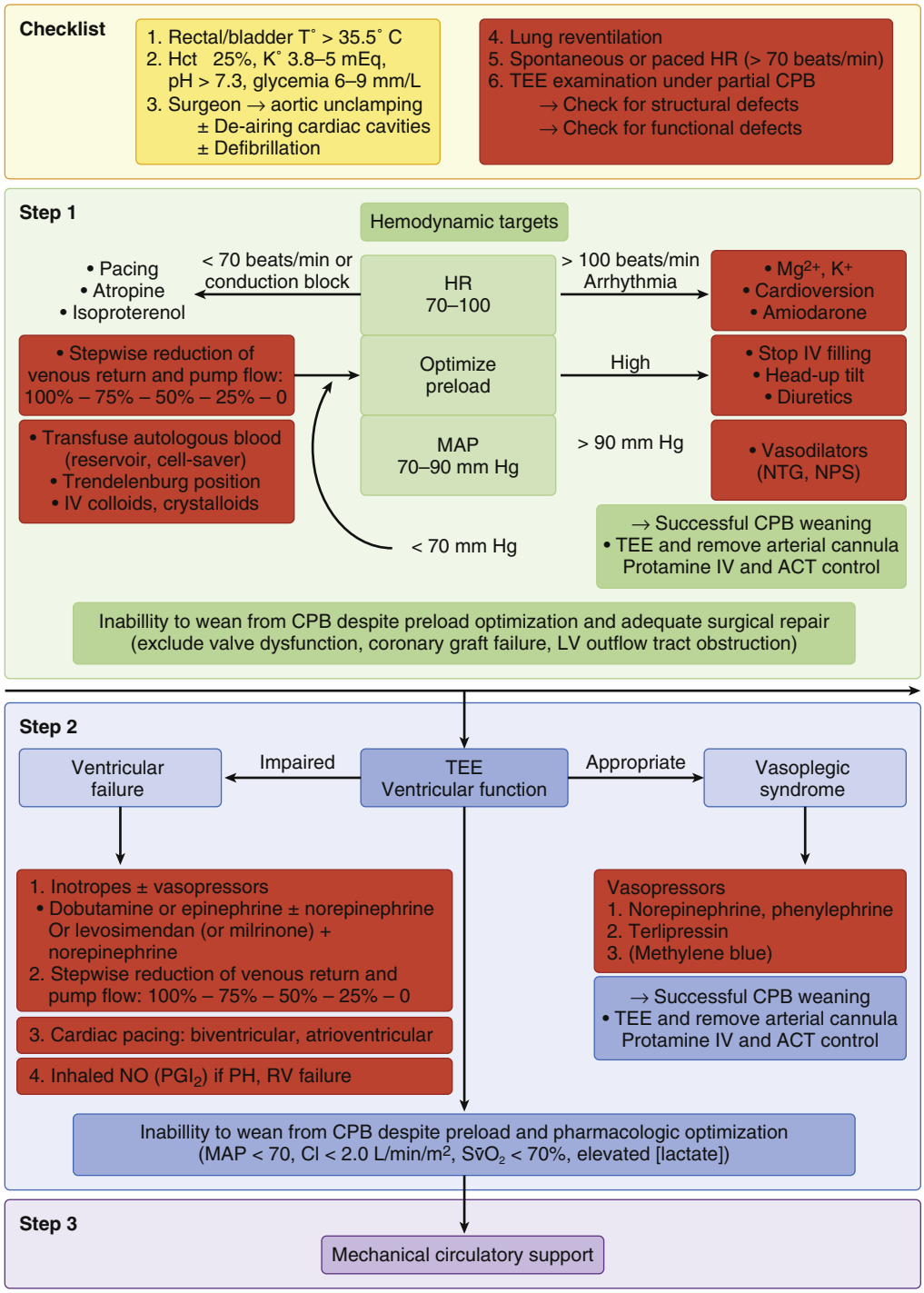


Figure 67-10. Algorithm for weaning from cardiopulmonary bypass (CPB). *ACT,* Activated clotting time; *Hct,* hematocrit; *HR,* heart rate; *IV,* intravenous; K^+, potassium; *LV,* left ventricular; *MAP,* mean arterial pressure; Mg^{2+}, magnesium; *NO,* nitric oxide; *NPS,* sodium nitroprusside; *NTG,* nitroglycerin; PGI_2, prostacyclin; *PH,* pulmonary hypertension; *RV,* right ventricular; $S\bar{v}O_2$, mixed venous oxygen saturation; *TEE,* transesophageal echocardiography. *(From Licker M, Diaper J, Cartier V, Ellenberger C, et al: Clinical review: management of weaning from cardiopulmonary bypass,* Ann Card Anaesth *15:206-223, 2012.)*

Furthermore, because processing of the raw EEG and data smoothing to generate the BIS number occur over 15 to 30 seconds, the BIS number lags slightly behind clinical events.

Another important decision to be made is whether additional neuromuscular blocking drugs are needed during and after weaning from CPB. Use of a peripheral nerve stimulator may facilitate this decision (see also Chapter 53). Although movement of the patient may serve as an indication of the patient's awareness, such movement can be extremely dangerous if it results in dislodgment of the aortic or venous cannulas. Furthermore, shivering can occur because of the "afterdrop" in temperature after a period of hypothermic CPB (see also Chapter 54). Because shivering can increase oxygen demand by 300% to 600%, it should be prevented by administering a neuromuscular blocking drug.

Cardiovascular Decompensation. Failure of the left or right ventricle is one of the common causes of cardiovascular decompensation during or shortly after weaning from CPB. Such failure may result in part from preexisting

TABLE 67-5 **CHARACTERISTICS AND TREATMENT MODALITIES OF WEANING DIFFICULTIES**

	Surgical or Technical Failure	Ventricular Dysfunction	Vasoplegic Syndrome	Left Ventricular Outflow Tract Obstruction
Diagnostic criteria	**TEE** Valvular regurgitation or stenosis Patient-prosthesis mismatch Paraprosthetic leakage Intracardiac shunt Occluded vascular graft	**1. TEE** ↓ Contractility of LV and RV Dilated LV and RV ↓ Relaxation 2. Hemodynamics ↓ CO and ↓ MAP	**1. TEE** Preserved ventricular contractility **2. Hemodynamics** ↑ Or normal CO and ↓ MAP	**TEE** Systolic anterior motion of anterior mitral leaflet LV septal hypertrophy Pressure gradient in LV outflow tract
Incidence	2-6%	15-40%	4-20%	5-10% after mitral valve surgery
Risk factors	Team and operator's experience, qualification Low surgical volume Extended disease, difficult anatomy	Age (>65 yr), female sex CHF, low LVEF LV diastolic dysfunction Previous MI, COPD eGFR <60 mL/min Extensive CAD, left main CAD Reoperation, emergency, combined procedure Prolonged CPB	Preoperative therapy with ACEI or angiotensin II antagonist, β-blockers, heparin High EuroScore Prolonged CPB Low LVEF (<35%)	Myxomatous mitral valve Hyperdynamic LV Short distance between MV coaptation point and LV septum
Specific treatment	**Reoperation** Secondary repair or valve replacement Shunt closure Additional coronary bypass graft	**1. Drugs** Adrenergic agonists (dobutamine, epinephrine, dopamine) Phosphodiesterase inhibitors (milrinone) Calcium sensitizer (levosimendan) Systemic vasodilators (NTG, NPS) Pulmonary vasodilators (NO, PGI_2) **2. Electromechanical Support** Biventricular pacing Intraaortic balloon pump Extracorporeal membrane oxygenation Ventricular assist device	**Vasopressors** Phenylephrine Norepinephrine Terlipressin Methylene blue	**1. Medical** Volume expansion Inotrope discontinuation β-blockers **2. Surgical** Septal bulge resection MV repeat repair or replacement

From Licker M, Diaper J, Cartier V, Ellenberger C, et al: Clinical review: management of weaning from cardiopulmonary bypass, Ann Card Anaesth *15:206-223, 2012.*
ACEI, Angiotensin-converting enzyme inhibitor; *CAD,* coronary artery disease; *CHF,* congestive heart failure; *CO,* cardiac output; *COPD,* chronic obstructive pulmonary disease; *CPB,* cardiopulmonary bypass; *eGFR,* estimated glomerular filtration rate; *LV,* left ventricular, left ventricle; *LVEF,* left ventricular ejection fraction; *MAP,* mean arterial pressure; *MI,* myocardial infarction; *MV,* mitral valve, *NO,* nitric oxide; *NPS,* nitroprusside sodium; *NTG,* nitroglycerin; *PGI_2,* prostacyclin; *RV,* right ventricle; *TEE,* transesophageal echocardiography.

chronic ventricular dysfunction exacerbated by the ischemia-reperfusion injury that occurs during CPB with cardioplegia-induced cardiac arrest. In operations involving revascularization for CAD, myocardial injury resulting in postbypass ischemia or infarction is particularly likely. Causes include thrombosis, particulate or air emboli in a coronary graft or a native coronary artery, kinking of the graft, a distal suture causing constriction, coronary spasm, incomplete myocardial preservation during CPB, and incomplete revascularization secondary to distal disease or inoperable vessels. Another possibility is acute mitral regurgitation (MR) of the native valve resulting from papillary muscle ischemia or rupture. In the case of valvular surgery, a prosthetic valve may be malpositioned with a perivalvular leak, the valve may be malfunctioning, or ventricular dysfunction may be unmasked after mitral valve replacement or repair for MR.

Usually, LV dysfunction is amenable to inotropic therapy or combination therapy with positive inotropic and vasodilator drugs to optimize CO. Sympathomimetic amines (i.e., catecholamines such as epinephrine, norepinephrine, dopamine, and dobutamine) and phosphodiesterase inhibitors (e.g., milrinone) are commonly used as first-line therapy (see Chapters 20 and 28 for specific drug pharmacology and doses). Small boluses of ephedrine (5 to 20 mg) or diluted epinephrine (2 to 10 μg) may be administered initially to treat ventricular dysfunction and hypotension temporarily while infusions are being prepared. Milrinone, an inodilator, improves CO but significantly reduces SVR; concomitant use of an arterial vasoconstrictor is often necessary. Nitroglycerin is usually administered if ischemia is suspected. Occasionally, a mechanical assist device, such as an intraaortic balloon pump (IABP) or VAD, is necessary.

RV dysfunction or failure may also occur after CPB, usually because of inadequate myocardial protection, inadequate revascularization with resultant RV ischemia or infarction, preexisting pulmonary hypertension, intracoronary or pulmonary air embolism, chronic mitral valve disease, or tricuspid regurgitation (TR). Such RV failure may be evidenced by RV distention and hypokinesis on TEE, as well as by elevations in CVP and PA pressure (PAP). Therapy for RV failure includes increasing preload and inotropic support; milrinone, dobutamine, and isoproterenol are the usual first-line drugs. Other pharmacologic drugs occasionally used to induce pulmonary vasodilation include nitroglycerin and nitroprusside. One potential problem with the use of intravenous inodilator and vasodilator agents is that their effects are not limited to the pulmonary circulation. SVR must be adequate to maintain RV perfusion pressure. Inhaled drugs such as nitric oxide (see also Chapter 104), epoprostenol (Flolan), and inhaled iloprost are considered in refractory cases. Adjuncts to decrease PVR include hyperventilation (higher respiratory rate) to induce mild hypocapnia and preventing hypoxemia and acidosis. Rarely, patients may require support with an RVAD.

Inappropriate vasodilation with a low SVR is another common cause of immediate post-CPB cardiovascular decompensation that may result in unacceptable hypotension. Predisposing factors include long-term administration of medications such as ACEIs or angiotensin receptor blockers (ARBs), prolonged duration of CPB, severe anemia with decreased viscosity, acid-base disturbances, and sepsis. Treatment with infusion of a vasoconstrictor drug such as phenylephrine, norepinephrine, vasopressin, or, rarely, methylene blue is usually successful.

Dysrhythmias. Normal sinus rhythm is ideal because it provides an atrial contribution to ventricular filling and a normal synchronized contraction of the ventricles (see also Chapter 47). However, either supraventricular or ventricular arrhythmias can occur in the immediate postbypass period. Ventricular flutter or fibrillation must be treated immediately with defibrillation. Internal paddles are applied directly to the heart to deliver 10 to 20 J of electricity. If ventricular arrhythmias persist or recur, an antiarrhythmic drug, usually lidocaine or amiodarone, is infused. Persistent or recurrent ventricular fibrillation should prompt concern regarding the adequacy of coronary blood flow.

Atrial fibrillation is the most common dysrhythmia after cardiac surgery, although it usually develops 2 to 5 days postoperatively. Atrial fibrillation or atrial flutter that occurs in the immediate postbypass period can often be converted to normal sinus rhythm with synchronized cardioversion, especially if sinus rhythm was present before CPB. Hypokalemia should be corrected. Magnesium is thought to have a low risk-to-benefit ratio and may modify the ventricular response rate and promote conversion to sinus rhythm. The primary drug used to treat atrial fibrillation is amiodarone, administered as a bolus followed by a continuous infusion. Other drugs sometimes used for rate control and initial treatment include esmolol, diltiazem, and digoxin.[168] Initiation of a long-acting β-adrenergic blocker (e.g., atenolol or metoprolol) is common on the first postoperative day. Prophylactic strategies to decrease the incidence of postoperative atrial fibrillation are being investigated because prevention may decrease the number of days spent in the ICU and the total length of stay in the hospital.[169,170]

When bradycardia, complete heart block, or asystole develops after CPB, temporary epicardial pacing wires are used to provide electrical pacing. Sinus bradycardia may respond well to atrial pacing. If asystole or complete heart block is present, AV sequential pacing is preferable because, as with normal sinus rhythm, it provides an atrial kick to promote adequate filling of the LV chamber and synchronized ventricular contraction. However, if no organized atrial rhythm is present (as in patients with atrial fibrillation) and the ventricular response rate is slow, ventricular pacing is the only option. With this mode of pacing, synchronization of ventricular contraction is less efficient, without atrial augmentation to ventricular filling, which is particularly detrimental in patients with poor LV compliance.

Bleeding and Coagulopathy. Although inadequate surgical hemostasis is a common reason for blood loss after CPB, coagulopathy resulting from excessive contact activation, platelet dysfunction, and fibrinolysis can occur and must be excluded. Historically, the most common causes of excessive bleeding in cardiac surgical patients have been related to platelet activation, platelet consumption, and hyperfibrinolysis induced by the extracorporeal circuit, and these conditions are especially pronounced in older patients.[171] Despite the use of high-dose heparin, thrombin generation remains ongoing during CPB. This results in microvascular coagulation and fibrinolysis and has deleterious effects on platelet function.

Patients who are taking antithrombotic medication before cardiac operations constitute yet another subset of patients at risk for post-CPB bleeding, and information obtained preoperatively about the degree of platelet inhibition should be used to assess its contribution to bleeding. Chen and colleagues found that preoperative testing of platelet function can identify patients at highest risk for perioperative bleeding and transfusions and may further reduce perioperative transfusion requirements.[172]

An evidence-based approach to the diagnosis and treatment of residual post-CPB microvascular bleeding entails the timely detection and treatment of specific causes of coagulopathy.[173] (Diagnosis and treatment of this complication are further discussed in the section on postoperative bleeding and coagulopathy.) Patients with postoperative bleeding benefit from POC testing incorporated into a transfusion algorithm that uses pharmacologic and transfusion therapies. Algorithms are designed to minimize unnecessary and indiscriminate blood product transfusion.[172,174]

Metabolic Disturbances. Hypokalemia is relatively common after CPB and may contribute to the development of dysrhythmias. Causes include diuresis secondary to preoperative diuretics, mannitol administration during CPB, and aggressive treatment of hyperglycemia with insulin administration. Hypokalemia contributes to increased automaticity and may lead to atrial or ventricular arrhythmias. Therefore, hypokalemia should be corrected by the carefully monitored administration of potassium through

an infusion pump at a rate of 10 to 20 mEq/hour, with frequent measurement of potassium, as well as glucose and arterial blood gases.

Hyperkalemia also occurs occasionally after CPB and is usually caused by large doses of cardioplegia or by extracellular shifts associated with respiratory or metabolic acidosis. Hyperkalemia is more likely to occur if renal function is impaired. Occasionally, hyperkalemia is severe enough to interfere with conduction. It can be treated with moderate hyperventilation or the administration of calcium, a combination of glucose and insulin, or both.

Hypocalcemia can occur after CPB, particularly in bleeding patients who are receiving multiple blood transfusions with large amounts of citrate. This phenomenon is exacerbated by hypothermia and low-output states. Hypocalcemia should be corrected because it may reduce cardiac contractility. Intermittent boluses of 10% calcium chloride or calcium gluconate (250 to 1000 mg) are administered.

Hypomagnesemia is common in the postbypass period and is associated with postoperative dysrhythmias, myocardial ischemia, and ventricular dysfunction.[175] Causes include hemodilution with magnesium-free fluids during CPB and diuresis. If hypomagnesemia is suspected, magnesium can be administered in amounts of 1 to 2 g intravenously over 15 minutes. Many centers routinely administer 2 to 4 g of magnesium during weaning or after CPB in an attempt to minimize the incidence of ventricular and atrial arrhythmias.

Hyperglycemia is extremely common after CPB (see the earlier section on the endocrine system). Poor perioperative glycemic control in patients undergoing CABG is associated with increased morbidity and mortality.[71,73] In patients with diabetes, maintaining serum glucose less than or equal to 180 mg/dL during CABG reduces morbidity and mortality, lowers the incidence of wound infections, reduces hospital length of stay, and enhances long-term survival.[71,73] In nondiabetic patients undergoing CABG surgery, maintaining serum glucose at less than 180 mg/dL has also improved perioperative outcomes. Current STS guidelines recommend that blood glucose should be kept at less than 180 mg/dL for the duration of ICU care and at less than 150 mg/dL in patients who require more than 3 days of ICU care as a result of ventilator dependency, the need for inotropes, mechanical device support, antiarrhythmic drugs, or renal replacement therapy.[76]

Pulmonary Complications. Respiratory failure is a very common complication of cardiac surgery (see the section on respiratory insufficiency in problems in the postoperative period). Pulmonary complications that arise immediately after CPB vary from mild to severe and include atelectasis, bronchospasm, hemothorax, pneumothorax, endobronchial intubation, mucus plugs or blood clots in the endotracheal tube, pulmonary edema, and pulmonary dysfunction that varies from a mild increase in the alveolar-arterial oxygen gradient to a form of adult respiratory distress syndrome (ARDS) known as postperfusion lung syndrome.

Atelectasis is a common cause of decreased arterial oxygenation in the postbypass period because during CPB either the lungs are not ventilated or very small tidal volumes are used. Ideally, the lungs are fully reinflated manually before machine ventilation is reestablished during weaning from CPB. During controlled ventilation, it is common to apply positive end-expiratory pressure after CPB and in the immediate postoperative period. Chronic obstructive pulmonary disease (COPD) or any preexisting tendency toward bronchospasm may be exacerbated during CPB. Treatment includes inhaled β_2-agonists (e.g., albuterol), inhaled anticholinergic drugs (e.g., ipratropium), epinephrine, and corticosteroids.

Hemothorax is caused by the accumulation in the pleural cavity of blood and clot, which should be surgically removed before chest closure. Pneumothorax may result from entry of the pleural cavity during dissection of the IMA or from excessive positive-pressure ventilation of the lungs. Pneumothorax may not manifest until after chest closure; it is treated by inserting a chest tube.

Endobronchial intubation may occur when the patient's head is partially hidden from the anesthesiologist's view. The expansion of both lungs should be confirmed during initial full ventilation before weaning from CPB, when the chest is open, so that a good view of both lungs may be obtained. If any blood or mucus is present in the endotracheal tube, it should be suctioned during and after weaning from CPB.

Pulmonary edema may be cardiogenic because of preexisting HF exacerbated by the additional fluid load in the pump prime. Ultrafiltration during CPB and diuresis during and after CPB may minimize such pulmonary edema. Noncardiogenic pulmonary edema may occur after prolonged CPB with sequestration of neutrophils in the pulmonary capillaries and elevation of lysosomal enzyme activity, resulting in a localized "inflammatory response" and increased capillary permeability. Other causes of ARDS include multiple pulmonary emboli and transfusion reactions (transfusion-related acute lung injury).

Chest Closure

Hemodynamic deterioration may occur during chest closure because of cardiac tamponade in patients with ongoing bleeding. Other reasons for severe hypotension during chest closure include hypovolemia, ischemia secondary to kinking of an arterial or venous coronary graft, and impairment of RV contractility and venous return in patients with significant myocardial edema. TEE can be particularly useful in determining the cause of hypotension during chest closure because it can quickly reveal tamponade, hypovolemia, RV or LV global dysfunction, and severe new wall motion abnormalities. Reopening the chest may be necessary while treatment is instituted. Occasionally, the patient's sternum cannot be closed because of hemodynamic instability; in such cases, only skin closure is attempted, and plans are made to return to the operating room for sternal wiring after a period of myocardial recovery in the ICU.

Transport to the Intensive Care Unit

After all incisions are closed and dressings are applied, provided the patient is hemodynamically stable, the next step is transport to the ICU. Monitoring should not be

completely interrupted even for a few moments—the ideal transport monitoring system has a "brick" that can be ejected from the operating room monitor and is compatible with the transport monitor. If such equipment is not available, sequential disconnection of monitoring devices is advised so that an online monitor is always visible.

On arrival in the ICU or cardiac recovery area, a transfer of the patient and the patient's information from one team to another, termed handoff or handover, occurs. Handoff failures have been identified as a significant source of medical errors, both between and within teams.[176-178] Implementing a handoff protocol reduces information omission and reduces errors. The process is intended to be strictly sequential: monitoring should be transferred before ventilator transfer, and all phase 1 items should be completed before information transfer.[179,180] Using formal, sequential handoff procedures does not increase the duration of the process.[181] The following sequence is suggested[181] (Wahr J, personal communication, November 17, 2012):

Phase 1: Equipment and Technology Handover

1. Monitoring transferred to ICU equipment
2. Ventilator function initiated
3. Infusions and fluids checked
4. Chest drains secured and on suction
5. Vital signs confirmed to be stable, ventilator functioning well, infusions running appropriately
6. Anesthesiologist, nurse, and surgeon confirm that they are ready for information transfer

Phase 2: Information Handover

1. Anesthesiologist presents
   a. Patient-specific information (age, weight, medical and surgical history, allergy status, baseline vital signs, pertinent laboratory results, diagnosis, current condition and vital signs)
   b. Anesthetic information (intraoperative course and any complications, lines present, blood transfusion or fluid totals, paralytics or opioids, antibiotics, current infusions, vital sign parameters or limits, pain relief plan, laboratory values)
2. Surgeon presents: surgical course (diagnosis, operation performed, surgical findings, complications, blood loss, drains, antibiotic plan, deep vein thrombosis prophylaxis, medication plan, tests to be done, nutrition, key goals for the next 6 to 12 hours)

Phase 3: Questions and Discussion

In all cases, the anesthesiologist should remain with the patient until hemodynamic stability and overall stability are ensured.

CARDIOPULMONARY BYPASS

CPB is a form of extracorporeal (*extra* = "outside of," *corporeal* = "the body") circulation (ECC) in which the patient's blood is rerouted outside the vascular system, and the function of the heart, the lungs, and, to a lesser extent, the kidneys is temporarily assumed by surrogate technology. The circuitry and equipment used to facilitate this substitution are topics of the next section of this chapter.

CIRCUITRY AND EQUIPMENT

The most common and most complicated ECC procedure is CPB. The goal of CPB is to provide a motionless and bloodless field for the surgeon by rerouting the patient's entire CO around both the heart and the lungs. Other ECC techniques include left heart bypass (LHB), cardiopulmonary support (CPS), and extracorporeal membrane oxygenation (ECMO).

The pumps, tubing, artificial organs, and monitoring systems used in CPB are diagrammed in Figure 67-11. Simply stated, venous blood is intercepted as it returns to the right atrium and is diverted through the *venous line* of the CPB circuit to a *venous reservoir*. The *arterial pump* functions as an artificial heart by withdrawing blood from the reservoir and propelling it through a *heat exchanger*, an artificial lung (the *oxygenator*), and an *arterial line filter* before returning it through the *arterial line* to the patient's arterial system. Additional pumps and components are used to assist in the operation to manage shed blood (the *pump sucker*), decompress the heart (*vent*), and deliver the *cardioplegia solution*.

Blood Tubing

The tubing used to connect the various components and conduct blood into and out of the patient's vascular system is medical-grade polyvinyl chloride. For decades, the blood-tubing interface was untreated polyvinyl chloride. However, the newer generation of polyvinyl chloride tubing has surface coatings and other modifications that significantly alter the bioreactivity of the surface. Collectively, these coatings have been shown to reduce plasma levels of markers of subclinical coagulation, attenuate the increase of cytokines and other inflammatory markers, and shorten intubation times.[182-184]

Venous Reservoirs

Blood reservoirs perform an important function in the conduct of CPB by facilitating the displacement of a large volume of blood out of the circulation at strategic times during the operation. Positioned between the venous line and the arterial pump, blood reservoirs may be collapsible plastic bags or clear plastic hard-shelled containers. Hard-shelled reservoirs include an integral filtration mechanism with a screen and depth filters through which blood must pass before leaving the outlet of the vessel. Almost universally, hard-shelled reservoirs have integrated positive- and negative-pressure release valves, which are necessary for the application of vacuum to the reservoir to augment venous drainage. If vacuum-assisted venous drainage is employed, the vacuum pressure in the reservoir should be maintained at the minimum necessary, and entrainment of air from the surgical field into the venous line should not be permitted. Reservoir pressures in excess of 60 mm Hg have been shown to increase microbubble counts measured in the circuit's arterial infusion line dramatically.[185]

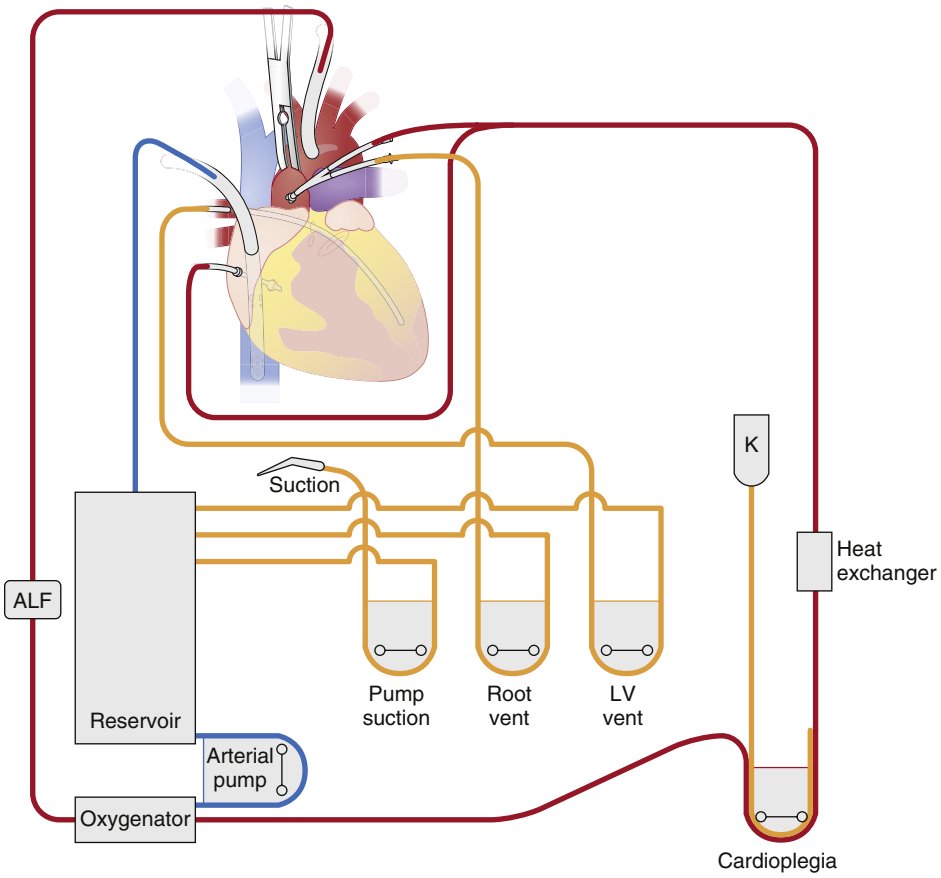


Figure 67-11. A typical cardiopulmonary bypass circuit interfaced with a patient. *ALF,* Arterial line filter; *K,* potassium; *LV,* left ventricular.

Arterial Pumps

The pumping device used to replace the function of the heart generally uses one of two primary technologies: a roller pump or a centrifugal pump. Roller pumps are positive-displacement pumps that function by occluding a point in a piece of tubing and then rolling the occlusive point of contact along a length of the tubing. This process forces the fluid in the tubing to move forward in front of the occlusive point while simultaneously drawing in fluid behind the occlusive point. Centrifugal pumps, in contrast, are nonocclusive kinetic pumps that generate flow by magnetically coupling the high-speed revolution of a reusable motor to the plastic plates, fins, or channels inside a disposable cone. This process produces a constrained vortex that propels fluid through the opening on the side of the cone while drawing fluid into the point of the cone. Both pump technologies are traumatic to the formed elements in blood; however, centrifugal pumps are thought to be less traumatic than roller pumps.[186]

Each type of pump poses unique risks that must be appreciated. Roller pumps, by virtue of their occlusive nature, are capable of generating extremely high positive and negative pressure and are also able to pump massive quantities of air. Consequently, the national standard of care requires that these pumps be servoregulated to reduce their speed automatically when either high pressure or air is detected in the path of the blood. In contrast, centrifugal pumps, being nonocclusive, are unable to generate extremely high or low pressure. Additionally, if a large bolus of air is introduced into the disposable cone, the air will remain in the cone, thus displacing the blood, and the pump will be unable to generate forward flow. This feature prevents centrifugal pumps from pumping large volumes of air. However, the lack of a point of tubing occlusion inside the pump allows retrograde flow from the patient's high-pressure arterial system backward through the arterial line, filter, and oxygenator and ultimately into the low-pressure venous reservoir. This situation may occur whenever the pump's revolutions per minute are reduced below a critical threshold. A large-bore one-way valve or a computer-activated electronic clamp can be positioned in the arterial line to eliminate the possibility of retrograde arterial flow and inadvertent exsanguination of the patient.

Heat Exchanger

Heat exchangers are essential to CPB because they facilitate the management of the patient's blood temperature. Throughout the period of CPB, 20% to 35% of the patient's circulating blood volume is outside the body and is exposed to the ambient temperature of the operating suite, which can cause hypothermia. Therefore, in all CPB procedures, an inherent need exists to warm the blood before CPB is terminated. Additionally, for many surgical procedures, some amount of hypothermia, from mild (35° C) to profound (18° C), is desirable to reduce the patient's metabolic rate. In these cases, the heat exchangers may be used to reduce the temperature of the blood when CPB is initiated and then to warm the blood before CPB is terminated.

Oxygenator

The oxygenator substitutes for the patient's native lungs and performs the essential function of gas exchange. Several similarities exist between the native lung and the oxygenator: Both have a gas space and a blood space, both are driven by passive diffusion gradients, and both use a membrane to separate the blood from the gas. In the oxygenator, the membrane is usually made from microporous polypropylene. This material is extruded into thin straws with an outer diameter of 200 to 400 μm, a wall thickness of 20 to 50 μm, and a total surface area of 2 to 4 m^2. Typically, oxygenators have a static priming volume of 135 to 340 mL and are capable of arterializing up to 7 L/minute of typical venous blood.[187]

The native lung uses the conductive airways for both inspiration and expiration and depends on a certain tidal volume and respiratory rate to refresh the gas in the alveolar space regularly. The oxygenator, however, has separate gas inlet and outlet ports and can refresh the gas inside its gas space (the internal lumen of the straws) with a continuous flow or "sweep" of gas through the oxygenator. The blood space of an oxygenator is the space around the outside of the straws. Venous blood entering the oxygenator is directed across the outside of the fibers while gas is concurrently circulated through the inside of the fibers. Pressure gradients between the blood space and the gas space drive oxygen across the membrane and into the blood, whereas carbon dioxide is driven out of the blood and into the gas phase. Similarly, volatile anesthetic agents can be delivered to the patient through the oxygenator's sweep gas. Unlike the membrane in the native lung, however, the oxygenator's membrane is not a true membrane. The microscopic (0.5- to 1.0-μm) pores on the sides of the fibers are small enough to prevent plasma and the formed elements of blood from leaking through but are still large enough to allow gas to pass through. Therefore, care must be taken to ensure that the pressure in the gas space never exceeds the pressure in the blood space, or gaseous emboli will form in the blood. In appreciation of the risks inherent in using a pressurized gas space, most oxygenators are designed with multiple gas outlet ports. In any case, caution should be exercised to ensure that the outlet of the gas phase cannot become occluded.

Arterial Line Filter

In the United States, arterial line filters are used in more than 95% of CPB procedures in adults. These filters are placed in the arterial line as the last component through which blood passes before it returns to the patient. With pore sizes of 20 to 40 μm, arterial line filters increase the patient's safety by removing particulate and gaseous microemboli. To remove bubbles from the blood path effectively, arterial line filters must be continuously "purged" by allowing a small amount of blood to recirculate from the top of the filter back into the venous reservoir. Many ECCs are designed to capitalize on this continuous arterial shunt with the incorporation of a flow-through blood gas sensor that continually monitors the blood gas concentrations in the postoxygenator blood. These in-line blood gas measurements are generally reliable and can be used for the early identification of trends and precise management of oxygenator performance.

SEQUENCE OF EVENTS

Although the approach to surgical procedures that require CPB varies among institutions, all procedures loosely follow a predictable sequence of events. At any institution, CPB requires circuit selection and priming, anticoagulation, cannulation, initiation and maintenance of CPB, myocardial protection, and finally, weaning and termination from CPB.

Circuit Selection and Priming

When selecting the components for an extracorporeal circuit, the perfusionist first calculates the highest blood flow that may be necessary during the procedure. Typically, the highest blood flow is approximately 2.4 to 3.0 L/minute/m^2 or 60 to 70 mL/kg/minute. The calculated flow is then compared with the rated flow for the components of the ECC circuit. This flow rating represents the highest blood flow rate at which the component can perform its function within the acceptable range of hydraulic forces (pressure and shear stress) without causing an unacceptable amount of blood trauma.

The combination of components included in the ECC determines the prime volume of the circuit, or the volume of balanced electrolyte solution necessary to de-air the circuit completely. This prime volume is the main cause of the hemodilution associated with CPB. Therefore, the perfusionist must calculate the patient's resultant hematocrit (HCTr), which is the patient's predicted hematocrit after the patient's preoperative blood volume is mixed with the asanguineous prime volume of the ECC. The HCTr is computed by dividing the patient's calculated volume of RBCs into the calculated total volume of distribution represented by the addition of the ECC prime volume to the patient's blood volume (Box 67-8). An adult patient's intravascular volume of distribution will increase by 20% to 35% when CPB is initiated. This increased volume of distribution dilutes not only all the proteins and formed elements of the blood but also plasma levels of drugs. If this dilution is not anticipated, the patient's depth of anesthesia and circulating concentrations of many pharmacologic drugs may be reduced when CPB is initiated.

BOX 67-8 *Resultant Hematocrit Formula*

HCTr = Patient's preoperative red blood cell volume / Total volume of distribution at the start of CPB

$$\mathbf{HCTr} = (\mathbf{BVp} \times \mathbf{HCT}) / (\mathbf{BVp} + \mathbf{PVc})$$

$$\mathbf{HCTr} = (\mathbf{kg} \times \mathbf{75} \times \mathbf{HCT}) / (\mathbf{kg} \times \mathbf{75}) + \mathbf{PVc}$$

where

HCTr = resultant hematocrit
BVp = patient's blood volume
kg = patient's weight in kg
PVc = prime volume of the extracorporeal circuit

CPB, Cardiopulmonary bypass.

The solution used to prime the CPB circuit is generally a balanced electrolyte solution containing normal plasma concentrations of many of the standard blood ions. Various drugs may be added to the solution to attenuate the dilutional effect of CPB on those ions (e.g., albumin, heparin, bicarbonate) or to discourage edema formation or encourage diuresis of the prime fluid by the patient (e.g., mannitol).

Anticoagulation

With the circuit primed and the vessels exposed, standard procedure requires that the patient be fully anticoagulated before cannulation. Dosing of heparin and monitoring of the ACT are discussed earlier in this chapter. Many commercial devices are designed to monitor the ACT, and although the ACT is used as if it were a standardized test, the results produced by different instruments are far from standardized. We have shown that these devices, when used on the same pool of heparinized blood, can produce ACT results that vary by as much as 40% (see Fig. 67-6).

The ACT test is not used to monitor heparin levels but to monitor the anticoagulant effects of heparin and other anticoagulants. Thus, elevated ACT measurements taken before, during, or after CPB may be influenced by variables other than heparin (e.g., hypothermia, hemodilution, coagulopathy, and anticoagulants).

Although controversial, some studies suggest that subclinical coagulation may progress despite acceptable ACT times during CPB and that maintaining higher circulating heparin levels may reduce this process.[98,188] POC heparin level tests are commercially available and may be used to monitor circulating heparin levels in CPB-supported patients. Indeed, some centers monitor both the circulating level of heparin and its anticoagulant effects and administer heparin intermittently throughout the procedure to maintain a predetermined therapeutic heparin level, as well as a minimally acceptable ACT.

Heparin dosing may be based on the patient's weight (300 to 400 units/kg) or determined by a dose-response curve. Heparin dose-response curves are determined in vitro by measuring the ACT of the patient's blood at baseline (without heparin) and after a known concentration of heparin (2.5 units/mL) is added. By graphing the ACT in seconds against the blood concentration of heparin, one can extrapolate the blood concentration of heparin needed to achieve a target ACT acceptable for CPB. Most patients need circulating blood heparin concentrations between 1.5 and 3.0 units/mL to achieve an ACT of 480 seconds. A commercial device designed to automate this process is available; from the patient's height, weight, sex, and heparin dose-response test results, the machine calculates the appropriate patient-specific heparin dose to administer during CPB.

Cannulation

Every CPB procedure requires a high-flow cannula in a large vein and another such cannula in a large artery for withdrawing blood from and returning blood to the patient (Table 67-6). Most procedures include additional cannulas for administering cardioplegia solutions to the heart and removing (venting) blood and air from

TABLE 67-6 COMMON APPROACHES TO VENOUS AND ARTERIAL CANNULATION FOR CARDIOPULMONARY BYPASS

Procedure	Venous	Arterial	Cardioplegia	Vent	Comments
CABG	2-stage approach in the RA	Ascending aorta	Root and/or CS	Aortic root	Patients with low EF or failure to wean from CPB may benefit from LV venting
AVR	2-stage approach in the RA	Ascending aorta	Root and/or CS, plus handheld selective once the root is open	LV and aortic root	None
MVR	Bicaval	Ascending aorta	Root and/or CS	LV and aortic root	None
Aortic root replacement, not including the arch	2-stage approach in the RA	Ascending aorta	Root and/or CS	LV and aortic root	The closer the repair is to the head vessels, the more difficult aortic cannulation becomes
Aortic arch	2-stage approach in the RA	Axillary or femoral artery	Root and/or CS	LV and aortic root	CS cardioplegia unlikely if the coronaries are unobstructed
Redo procedures	Femoral vein	Femoral artery	Root and/or CS	Aortic root and/or LV	Only in extreme cases (i.e., when the heart is tightly adhered to the back of the sternum, or any time that the heart is lacerated during sternotomy)
Other intracardiac procedures	Bicaval	Ascending aorta	Root and/or CS	LV and aortic root	Any procedure that requires opening the RA or excessive surgical retraction

AVR, Aortic valve repair or replacement; *CABG,* coronary artery bypass grafting; CPB, cardiopulmonary bypass; *CS,* coronary sinus; *EF,* ejection fraction; *LV,* left ventricle; *MVR,* mitral valve repair or replacement; *RA,* right atrium.

the chambers of the heart (Fig. 67-12). Different surgical procedures require different cannulation techniques, the most common of which are described here.

The target for venous cannulation is generally the right atrium. The right atrium is the central repository for all venous blood, and the RA appendage is conveniently accessible through a sternotomy. Although RA cannulation is optimal for most cardiac surgical cases, the cannula may not perform well when the heart is being retracted. Significant retraction of the heart is necessary to access some posterior coronary arteries for bypass or to access the mitral valve through a left atriotomy. Because of surgical retraction involving the right atrium, the venous cannulation site for mitral valve repair or replacement procedures is generally moved away from the right atrium to the SVC and inferior vena cava (IVC). If a single cannula is placed in each vena cava, venous blood can be intercepted just before it enters the right atrium so that the cannula can provide acceptable drainage throughout the procedure. The right atrium may also be approached through the femoral vein. A femoral venous cannula extends the entire length of the IVC and rests with its openings in the right atrium.

An improperly sized or positioned venous cannula obstructs the flow of blood into the ECC circuit. This may elevate CVP and encourage extravasation of blood volume from the vascular compartment into the extracellular compartment (third spacing). Therefore, it is important to evaluate the performance of the venous cannula or cannulas when CPB is initiated. Properly placed venous cannulas allow complete decompression of the right side of the heart, as indicated by a CVP and PAP of zero and a nonpulsatile arterial blood pressure.

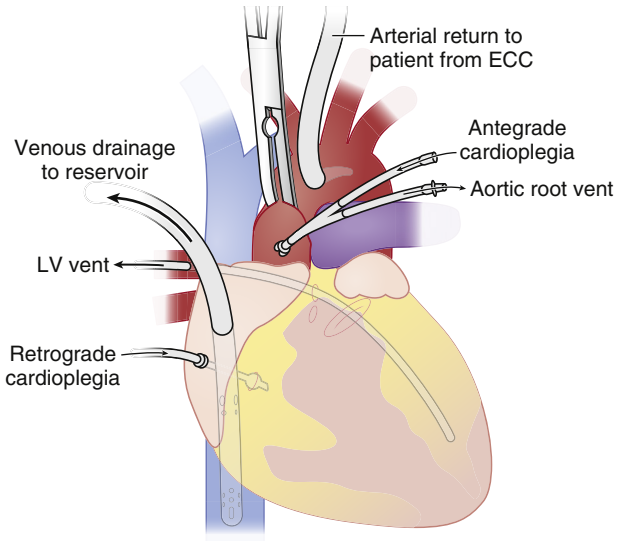


Figure 67-12. A common cannulation approach for cardiopulmonary bypass (CPB) procedures. Two cannulas are necessary to provide CPB. A cannula in the right atrium provides venous drainage to the extracorporeal circuit (ECC), and an arterial cannula placed in the ascending aorta allows arterial return to the patient from the ECC. Additional cannulas are necessary to protect the heart after cross-clamping. Cardioplegia can be administered in antegrade fashion through a special needle placed in the ascending aorta between the aortic valve and the aortic cross-clamp. Retrograde cardioplegia can be delivered directly into the coronary sinus through a special balloon-tipped cannula. Vent cannulas are used to decompress the heart while the aorta is clamped and to remove bubbles before cross-clamp removal. The aortic root vent is integrated into the antegrade cardioplegia needle, and the left ventricular (LV) vent cannula is inserted through the right superior pulmonary vein.

The ECC returns oxygenated blood to the patient through the arterial cannula. For CABG and valve procedures, the standard target for the arterial cannula is the portion of the ascending aorta below the aortic arch but 3 to 4 cm above the aortic valve. The alternative approaches of axillary or femoral artery cannulation are used in procedures that require the manipulation of much of the aortic root, arch, or both. Axillary artery cannulation is generally facilitated by the anastomosis of a tube graft to the side of the axillary artery to provide access for the arterial cannula without interrupting blood flow to the right arm. An added benefit of axillary cannulation for aortic arch procedures is that clamping the innominate artery allows antegrade cerebral perfusion to be performed during a period of circulatory arrest. Femoral arterial cannulation involves inserting the cannula through the femoral artery and into the abdominal aorta. Blood flow to the thorax is directed in retrograde fashion upward into the aorta. Ischemia of the cannulated limb is a risk commonly associated with femoral arterial cannulation, and dissection of the cannulated artery is a risk associated with the cannulation of any arterial site. Iatrogenic aortic dissection at the cannulation site occurs in approximately 200 procedures annually in the United States, with a resultant mortality of 48%.[189] Proper cannula placement and patency should be confirmed before CBP is initiated.

With venous and arterial cannulas in place, the heart and the lungs can be bypassed. However, additional cannulas are needed to facilitate aortic cross-clamping and cardiac arrest. For example, cardioplegia cannulas can be placed in the ascending aorta, and then the aorta can be occluded by placing a large vascular clamp (i.e., a cross-clamp) across it. Occluding the aorta between the arterial cannula and the antegrade cardioplegia cannula interrupts blood flow from the arterial line of the ECC to the coronary arteries, thereby initiating a period of global myocardial ischemia. Intermittent or continuous administration of cardioplegia through the antegrade and retrograde cardioplegia cannulas (see Fig. 67-12) serves to attenuate the ischemic insult (by a mechanism discussed later).

Bronchial pulmonary vascular connections deliver approximately 1% of the CO to the lungs, from where it is subsequently returned to the left side of the heart. In patients with chronic pulmonary disease, this recirculation may increase to more than 10% of CO. During the period when the aorta is cross-clamped, this blood volume will distend the left side of the heart and the pulmonary vasculature if the blood is not actively removed. Additionally, intracardiac procedures inherently introduce air into the left-sided chambers, and this air must be removed before the patient is weaned from CPB.

Vent cannulas facilitate decompression and de-airing of the heart. The heart is most commonly vented at the aortic root or directly from the left ventricle. Aortic

root vents use the same cannula that is used to deliver antegrade cardioplegia (see Fig. 67-12) and draw blood and air from the left ventricle across the aortic valve and into the reservoir of the ECC circuit. Because the antegrade cardioplegia needle has a small gauge and is positioned above the aortic valve, root vents have several significant limitations: they cannot be used when antegrade cardioplegia is being administered, and they are ineffective in decompressing the left ventricle when the cross-clamp has been removed. These limitations are not generally significant during an uncomplicated CABG procedure, but for CABG in patients with severely compromised ventricular function and for all intracardiac procedures, direct LV venting becomes essential. Typically, LV vents are introduced through the right superior pulmonary vein and are advanced through the left atrium, across the mitral valve, and into the left ventricle (see Fig. 67-12). The 10- to 14-Fr cannula used for this purpose offers significantly better venting capacity than does the root vent. Flows in the range of several liters per minute can be drawn through these cannulas when necessary, and because these cannulas are inserted directly inside the left ventricle, they are very effective in removing air bubbles that remain after an intracardiac procedure has been completed. Additionally, because the LV vent is separate from the cardioplegia cannula, it can be used to decompress the heart during antegrade cardioplegia administration, which may be necessary for patients with aortic insufficiency. Unfortunately, numerous case reports exist of injuries to patients that resulted from air being pumped into the heart through malfunctioning vent lines. The proper function of the vent pump should be confirmed at the field before the pump is connected to the patient.

Initiation and Maintenance of Cardiopulmonary Bypass

Once the patient is anticoagulated and cannulated, CPB may be initiated. Before initiating CPB, it is good practice to verify the patency of the arterial cannula. After the proper position of this cannula is confirmed, CPB may be initiated by removing the clamps on the venous line between the venous cannula and the reservoir. The patient's blood then passively drains into the ECC. Simultaneously, the arterial pump on the CPB machine begins to infuse the mixture of prime solution and autologous blood into the patient through the arterial cannula. Evaluating the performance of the venous and arterial cannulas is very important during the initial seconds of CPB. The pressure in the arterial line of the ECC should be maintained at less than 300 mm Hg to prevent excessive trauma to the formed elements of the blood. Venous cannula position is evaluated mainly by examining the patient's hemodynamics. Provided the venous cannula is adequately draining the venous return to the heart, right-sided heart pressure (CVP and PAP) should decrease to 0 mm Hg, and the arterial blood pressure should reach a normal mean pressure (50 to 90 mm Hg) while also becoming nonpulsatile.

The arterial trace usually becomes nonpulsatile as the heart is emptied and the pumping force is changed from the ventricle to the nonpulsatile arterial pump of the heart and lung machine. However, patients with aortic insufficiency continue to have a pulsatile arterial trace despite complete venous drainage (CVP and PAP = 0 mm Hg) because of regurgitation of blood from the arterial cannula across the incompetent aortic valve and back into the left ventricle. If right-sided heart pressure does not reduce to 0 mm Hg, the arterial trace remains pulsatile, and arterial pump flow cannot be increased to full flow; in that case, the position of the venous cannula must be reevaluated. Once full flow has been achieved, the function of the heart and lungs will have been completely transferred to the CPB machine; the anesthesiologist then can turn off the ventilator, and hypothermia of the patient can be initiated.

The initiation of CPB is often associated with a period of hypotension, which can be managed with the administration of an α-agonist (e.g., phenylephrine) into the venous reservoir of the ECC circuit (Fig. 67-13). Although it is common for cerebral oximetry values to reduce transiently at this point, acutely reduced cerebral oximetry values on CPB initiation may provide the first indication of poor SVC drainage or selective perfusion of a single aortic head vessel.[190-192] Markedly changed cerebral oximetry values warrant additional confirmation of cannula position and function. While CPB is maintained, the adequacy of perfusion is continuously evaluated by monitoring hemodynamic variables. Blood flow from the arterial pump can be manipulated across a range of 1.6 to 3.0 L/minute/m^2 to deliver an arterial blood pressure of 50 to 90 mm Hg and $S\bar{v}O_2$ greater than 65%. Any hypotension or hypertension that occurs despite adequate flow and $S\bar{v}O_2$ can be treated by adjusting the patient's SVR with vasoconstrictors or vasodilators.

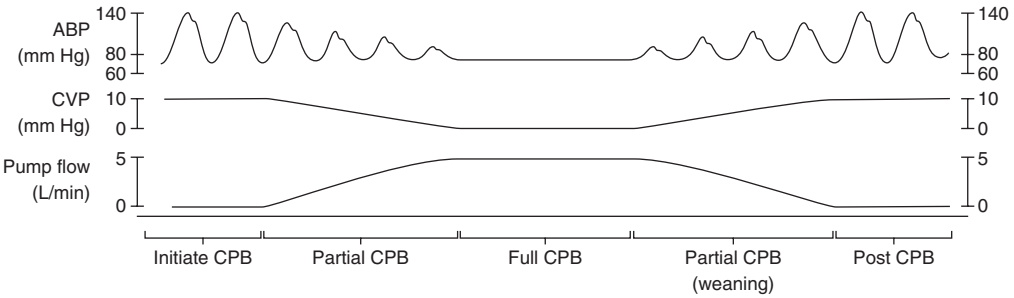


Figure 67-13. Illustration of a patient's hemodynamics before cardiopulmonary bypass (CPB), during the initiation of CPB, during full CPB, while weaning from CPB, and after CPB. *ABP,* Arterial blood pressure; *CVP,* central venous pressure.

Arterial blood gas samples should be taken at least every 30 minutes to assess the performance of the oxygenator and to monitor the patient for the development of acidosis and proper anticoagulation status. Base deficit values of −5 or less can be corrected with sodium bicarbonate, but the underlying cause of the acid production should ultimately be addressed. Increased perfusion flow and pressure may be indicated. ACTs shorter than the institutional parameter acceptable for CPB (usually ≥400 seconds) should be treated with a heparin bolus administered into the ECC.

Urine output is also monitored during CPB as an indicator of perfusion flow and pressure. However, poor urine production during CPB has not been shown to predict postoperative renal insufficiency. Rather, age, preoperative renal function, the duration of CPB, and EF have been correlated with postoperative renal dysfunction.[193]

Myocardial Protection

To provide a motionless field for the surgeon, the heart is arrested in diastole by the administration of a potassium-enriched cardioplegia solution to the heart. Interrupting myocardial electromechanical activity is the single most important step in reducing the heart's metabolism. Potassium-induced arrest alone reduces the heart's myocardial oxygen consumption by 90%. It is common to augment this reduction with hypothermia by administering cold cardioplegia solution. The combined influence of potassium arrest and myocardial temperatures lower than 22° C reduces myocardial oxygen consumption by 97% and enables the tissue to withstand a complete interruption of blood flow for periods of 20 to 40 minutes. Once the surgical procedure is completed, myocardial arrest can be reversed by reperfusing the heart with warm normokalemic blood.

The ingredients of cardioplegia solutions vary considerably from institution to institution, save that potassium is always used as the arrest agent. Whereas some centers may use a very simple solution of potassium-enriched whole blood, others may choose a more complex solution with a variety of chemical additives. The trend in clinical practice has been not to use purely crystalloid cardioplegia solutions; instead, most centers now use some form of blood cardioplegia. The ratio of blood to crystalloid is generally 4:1 or 8:1. The crystalloid solution is often mixed with arterialized whole blood from the ECC circuit in an exact ratio by placing two different-sized tubes (the larger drawing from the arterial line of the ECC and the smaller drawing from the bag of cardioplegia solution) through a single roller pump and splicing the two tubes together downstream from the outlet of the pump. Generically, the chemicals added to the cardioplegia solutions are designed to make the solution slightly hypertonic to reduce edema, and these chemicals include a buffer to counter the heart's production of acidic metabolites and a substrate for energy or catalysts to assist the heart in the production of adenosine triphosphate. Typically, solutions with two different potassium concentrations are used during the procedure. For inducing cardioplegic arrest, a "high-K" solution with a potassium concentration of approximately 20 to 30 mEq is used. After isoelectric arrest is induced, the solution is changed to a "low-K" mixture with a potassium concentration of approximately 10 mEq.

These solutions can be administered in *antegrade* fashion into the coronary arteries via the aortic root, through a needle placed between the aortic cannula and the aortic valve, or in *retrograde* fashion into the coronary veins, via a balloon-tipped cannula placed in the coronary sinus. Antegrade cardioplegic delivery is the most physiologic approach. However, when the patient has pronounced CAD or aortic valve insufficiency, antegrade administration may not uniformly deliver cardioplegia to the myocardium. Retrograde cardioplegia administration also has limitations. For example, the free wall of the right ventricle and the posterior third of the septum (the distribution territory of the right coronary artery [RCA]) are poorly perfused by retrograde delivery.[194] Additionally, the microvascular areas of the heart that are perfused by retrograde cardioplegia are less able to sustain normal myocardial energy metabolism.[195] Thus, the most complete technique for myocardial protection involves both antegrade and retrograde delivery. In fact, it is not uncommon for cardioplegia to be delivered simultaneously in both antegrade and retrograde fashion.

Cardioplegia is commonly administered intermittently in a volume-dosing regimen. After an initial arrest dose of approximately 1000 to 1500 mL of "high-K" solution is administered, perfusion of the heart is suspended for a period of 10 to 40 minutes while the surgeon works on the heart. Then, periodically throughout the procedure, 200- to 500-mL doses of "low-K" solution are administered to deliver nutrients to the cells and maintain the potassium concentration. Intraoperative evaluation of the adequacy of myocardial protection is empirical and based on the quiescence of the ECG, the time since the last dose was administered, and the temperature of the heart. The filling state of the ventricular chambers should also be evaluated. If the vent lines are not keeping the heart empty, it will warm more quickly and the heart muscle will be under tension. This state increases myocardial oxygen consumption and compromises myocardial protection. To reinstitute the electromechanical activity of the heart, warm, normokalemic blood is infused into the coronary arteries. This may be done by administering a "hot shot" through the cardioplegia cannulas or by simply removing the cross-clamp.

Weaning and Termination of Cardiopulmonary Bypass

The process of weaning the patient from the heart and lung machine requires an increased level of communication and awareness among the anesthesiologist, perfusionist, and surgeon. Before weaning and termination, the patient should be rewarmed and the heart de-aired. Regular cardiac electrical activity should be confirmed and supported with a pacemaker if necessary. Ventilation of the lungs must be resumed and laboratory values confirmed and corrected if needed. By slowly reducing venous drainage to the ECC and transfusing volume from the reservoir to the patient, normal filling volume can be returned to the heart. As the CO is returned to normal, flow from the arterial pump of the heart and lung machine is decreased and eventually terminated. Immediately after the termination of CPB,

the patient is often hemodynamically supported by volume replacement with the blood remaining in the ECC, frequently supplemented with vasopressors or inotropic agents (see the earlier section on weaning from CPB).

When the patient is hemodynamically stable, protamine can be administered to reverse the anticoagulatory effect of heparin. The administration of protamine to the patient is a sentinel event that must be communicated clearly by the anesthesiologist to the perfusionist and surgeon. In the event of inadvertent return of blood containing protamine to the ECC through the pump sucker, the blood remaining in the circuit may coagulate and render the circuit unusable for urgently reinstituting CPB. Therefore, all cannulas should be removed before the action of heparin is fully reversed, and the blood remaining in the ECC should be salvaged by centrifugation or hemofiltration for return to the patient by the anesthesiologist.

Protamine inactivates heparin by irreversibly binding with the strongly acidic heparin molecule to form a stable salt with no anticoagulant effects. POC tests are available for several ACT machines to calculate a patient-specific protamine dose.[196] If an automatically generated protamine dose-response curve is not available, many institutions calculate the protamine dose needed from the total dose of heparin delivered to the patient. This calculation usually results in the administration of 1 to 1.3 mg of protamine for every 100 units of heparin given. Protamine should be administered slowly over a period of 5 to 10 minutes to reduce the risk of hypotension. After protamine administration, ACTs should return to baseline. An increased ACT may indicate residual heparin or may be the result of a coagulation deficiency that necessitates additional laboratory tests, such as coagulation panel tests, heparin assays, platelet function analysis, thromboelastography, or any combination of these investigations.

OTHER ISSUES

Temperature

Deliberate hypothermia is a reliable method of neuroprotection and is often used during routine CPB. Deep hypothermia unquestionably confers cerebral protection when the circulation must be arrested during cardiac surgery. Even mild hypothermia (as little as 1° C to 2° C) minimizes the severity of cerebral ischemia in animal models. Various suggested mechanisms for the neuroprotective effects of hypothermia have been tested in animal models (Table 67-7).[197] Hypothermia may attenuate the effects of cerebral ischemia by creating a favorable balance between oxygen supply and demand and by decreasing the cerebral metabolic rate of oxygen. Hypothermia not only reduces the metabolic rate but also delays the release of excitatory amino acids, neurotransmitters that play an important role in the process of neuronal death. Additionally, hypothermia reduces the permeability of brain arterioles and prevents blood-brain barrier dysfunction. Hypothermia may also interfere with the inflammatory response by suppressing the adhesion of polymorphonuclear leukocytes in the damaged region.

However, after performing a meta-analysis, Rees and colleagues concluded that no definitive evidence for a neuroprotective effect of hypothermia during routine CPB exists,[198] although the studies examined in that analysis had some important limitations. For example, the timing of hypothermia may have limited its protective value. Hypothermia is always initiated after aortic cannulation and the onset of bypass, but macroembolization to the brain is unlikely during this period because the heart is excluded from the circulation by the aortic cross-clamp. Instead, the periods of highest risk for microembolization and macroembolization are during and shortly after aortic manipulation, cross-clamping, and unclamping because aortic cannulation and cross-clamping are performed near the start of CPB, when the brain is not yet cold. Similarly, the aortic cross-clamp is removed near the end of CPB, usually after the patient has been rewarmed.

In contrast, hyperthermia is known to be deleterious. Elevation of body temperature by as little as 2° C decreases cerebral tolerance to ischemia. Hyperthermia delays neuronal metabolic recovery and increases excitotoxic neurotransmitter release, oxygen free radical production, intracellular acidosis, and blood-brain barrier permeability, with subsequent multifocal breakdown at sites in the thalamus, hippocampus, and striatum (see Table 67-7). Hyperthermia also affects protein kinase activity and destabilizes the cytoskeleton. Clinically, fever and hyperthermia worsen the prognosis of hospitalized patients with stroke.[199]

In the 1990s, some centers began using normothermic cardioplegia to improve cardiac outcomes while avoiding deliberate hypothermia. This practice of "warm heart surgery" was debated because of concern that the neuroprotective effects of hypothermia would be lost. Subsequent studies produced inconsistent results with respect to the incidence of stroke and postoperative neurocognitive decline. Such differences in neurologic outcome may have resulted from variations in the temperature management strategies used in different "warm heart surgery" studies; these variations ranged from allowing a downward "drift" that resulted in actual mild hypothermia to active rewarming that may have led to inadvertent cerebral hyperthermia.[200]

TABLE 67-7 PROTECTIVE EFFECTS OF HYPOTHERMIA AND DELETERIOUS EFFECTS OF HYPERTHERMIA DURING CEREBRAL ISCHEMIA

Hypothermia	Hyperthermia
Favorable balance between oxygen supply and demand	Imbalance between oxygen supply and demand
↓ Excitotoxic neurotransmitter release	↑ Excitotoxic neurotransmitter release
↓ Blood-brain barrier permeability	↑ Blood-brain barrier permeability
↓ Inflammatory response	↑ Inflammatory response
	↑ Free radical production
	↑ Intracellular acidosis
	Destabilized cytoskeleton

From Hindler K, Nussmeier NA: Central nervous system risk assessment. In *Newman M, Fleisher L, Fink M, editors:* Perioperative medicine: managing for outcome, *Philadelphia, 2008, Saunders, pp 69-88.*

In patients undergoing CPB, cerebral hyperthermia during the rewarming period may aggravate any cerebral injury that has occurred. Aggressive rewarming was once commonly practiced to prevent the "afterdrop" in temperature that usually occurs after CPB is discontinued, but this practice can cause cerebral hyperthermia at the exact moment when cerebral embolization is most likely. Therefore, rewarming should be gradual and should start early enough to achieve stability of the desired temperature before CPB is terminated.[201]

The surgeon should also be aware of the limitations of any temperature-monitoring site used during CPB. Brain parenchymal temperature cannot be measured directly during cardiac surgery; rather, it must be estimated from tympanic, nasopharyngeal, esophageal, rectal, bladder, skin surface, pulmonary arterial, or jugular venous bulb temperature. However, concordance between cerebral temperature and temperatures measured at most of these sites is poor.[202,203] Jugular bulb temperature is generally considered to be the gold standard because the proximity of the jugular bulb to the carotid artery origins and the aortic cannula makes jugular bulb temperature more similar to brain temperature than are temperatures measured at other commonly used sites.[203,204] Temperatures measured at the nasopharyngeal, esophageal, bladder, rectal, or skin surface sites underestimate jugular bulb temperature during rewarming.[202,203] Because monitoring jugular bulb temperature is not usually feasible, monitoring the temperature of the blood in the arterial line that exits the oxygenator [203] or in the PA[202] may be the best way to estimate global brain temperature.

Hyperthermia that develops postoperatively may be just as hazardous as intraoperative hyperthermia. Temperatures exceeding 38.5° C are common during the first 48 hours after cardiac surgery and occur in nearly 40% of patients.[205] This postoperative hyperthermia is known to be correlated with increased cognitive dysfunction 6 weeks after cardiac surgery.[206] Therefore, hyperthermia in the postoperative period should be treated with antipyretics and, if necessary, active body surface cooling.

In summary, patients maintained on CPB should be rewarmed early and slowly. No monitored temperature should be allowed to exceed 36.5° C to 37.0° C. This practice prevents cerebral overheating.

Blood Gas Management

Temperature has a significant effect on the solubility of gases in solution. Specifically, in blood gas analysis, the carbon dioxide concentration (and consequently the pH) is profoundly altered by changes in temperature. As temperature decreases, the partial pressure of arterial carbon dioxide ($Paco_2$) decreases as carbon dioxide becomes more soluble in plasma. Therefore, inducing hypothermia during CPB poses a dilemma in terms of how best to approach acid-base management at lower temperatures (i.e., whether *temperature-corrected* or *temperature-uncorrected* blood gas values should be used to manage the patient's care). This question has been the basis for a decades-old debate: alpha-stat versus pH-stat blood gas management (Table 67-8).

Alpha-Stat Hypothesis. In aqueous systems, neutrality (pN) is said to occur when $[H^+] = [OH^-]$. The dissociation of water depends on temperature; therefore, the pH value at which pN occurs varies with the temperature. Acid-base comparative physiologic studies of animals whose blood temperature varies (i.e., ectotherms and poikilotherms) suggest that blood and intracellular pH values parallel the temperature-related changes seen in the neutrality of water.[207] From these findings emerged the alpha-stat strategy, which endeavors to maintain intracellular electrochemical neutrality across all temperatures.

Maintaining this neutrality requires an appropriate buffering system. It is thought that protein buffering is largely responsible for maintaining this temperature-pH relationship. Specifically, the imidazole group of the amino acid histidine has a dissociation constant (p*Ka*) value similar to that of blood. Therefore, if carbon dioxide stores are held constant during cooling, the ionization state (termed alpha) will remain constant. This may be important because the ionization state affects both the structure and the function of proteins. Keeping the charge state constant (alpha-stat) by allowing blood pH to change with the neutrality of water is thought to be essential for maintaining the most physiologically beneficial

TABLE 67-8 SUMMARY OF BLOOD GAS MANAGEMENT STRATEGIES

Strategy	Goal	Implementation	Total CO_2 Content	Theoretic Benefits
Alpha-stat	Achieve electrochemical neutrality by maintaining a constant OH^-/H^+ ratio	Use normal *temperature-uncorrected* blood gas values	Constant	Preserves enzyme function and cerebral autoregulation
pH-stat	Maintain constant pH	Use normal *temperature-corrected* blood gas values	Increases	Produces more homogeneous brain cooling; decreases brain O_2 consumption
Combination	Maintain constant pH during cooling, then restore electrochemical neutrality before circulatory arrest	During the cooling phase, use *temperature-corrected* values, then switch to *temperature-uncorrected* values before interrupting flow; use *temperature-corrected* values during the rewarming period	Initially increases during cooling, then returns to baseline	Produces homogeneous brain cooling, then restores neutrality; improves $CMRO_2$

$CMRO_2$, Cerebral metabolic rate of oxygen; *CO_2*, carbon dioxide; *O_2*, oxygen; *OH^-/H^+*, ratio of hydroxyl ion to hydrogen ion.

structure and function of enzymes during hypothermia. Research suggests that when the alpha-stat strategy is used, cerebral autoregulation remains largely intact until deep hypothermic temperatures are reached.[208]

To manage acid-base balance during hypothermic CPB by using the alpha-stat approach, one must maintain temperature-*un*corrected blood gas values. The term *un*corrected is often confusing because it refers to the values that the blood gas machine typically reports without being programmed to correct the values to the actual temperature of the patient. For example, blood drawn from a patient undergoing CPB at 18° C is measured in a blood gas machine, which anaerobically warms the sample to 37° C and reports values at normothermia. With alpha-stat management, one would strive for normal temperature-uncorrected results, which would theoretically maintain intracellular electrochemical neutrality.

pH-Stat Hypothesis. An alternative strategy is the pH-stat approach to acid-base management. The pH-stat strategy endeavors to maintain a constant pH despite changes in temperature. Hibernating animals tend to follow this strategy. To counter the tendency of cooling blood to follow the neutrality of the water curve and become more alkalotic as temperature decreases, these animals increase their blood carbon dioxide content and maintain normal pH at hypothermic body temperatures.

Carbon dioxide is a potent cerebral vasodilator; therefore, the increase in carbon dioxide content during pH-stat management uncouples cerebral autoregulation; cerebral blood flow increases independent of cerebral metabolic demand. These effects are thought to be neuroprotective for infants maintained on CPB who may have aortopulmonary collateral vessels and also to promote deep homogeneous cooling of the brain before circulatory arrest.[209] However, during rewarming, the higher cerebral blood flow that results from using pH-stat management may increase the embolic load sent to the brain.

Using the pH-stat strategy with CPB involves managing blood gas parameters with temperature-*corrected* values by programming the blood gas machine to correct the values to the patient's body temperature. During bypass, decreasing blood temperature increases the solubility of carbon dioxide and, consequently, results in decreased $Paco_2$ values. Therefore, the perfusionist must either decrease the "sweep speed" of the air-oxygen mixture or, less commonly, add carbon dioxide to the oxygenator ventilation system to increase the carbon dioxide content and maintain a $Paco_2$ of 40 mm Hg (and normal pH) as the temperature of the blood decreases. The extracorporeal circuitry must be equipped with an in-line blood gas analyzer so that $Paco_2$ levels can be continually monitored during CPB.

Which Strategy Is Best? In adult patients, several independent, prospective randomized trials have shown that using alpha-stat management during moderate hypothermia produces better neurologic outcomes than observed with pH-stat management. These and other data have led to an evidence-based recommendation (ACC/AHA class I, level A) that alpha-stat management be used in adults undergoing moderate hypothermic CPB.[200,210] It is unclear which strategy is superior in adults when deep hypothermia is used with or without circulatory arrest.

In pediatric CPB, however, several human and animal studies suggest that pH-stat management may be more beneficial than alpha-stat management for infants. These studies showed that pH-stat management produced more homogeneous cooling, less oxygen consumption, and better cerebral metabolic recovery than did alpha-stat management. The clear trend in pediatric CPB is to use pH-stat alone or in combination with alpha-stat (i.e., to use pH-stat during cooling and alpha-stat during rewarming) when deep hypothermia is used.[211]

Inflammatory Response to Cardiopulmonary Bypass

Since the 1980s, much has been written about the rapid and profound inflammatory response that CPB elicits. Surgical stress itself causes an inflammatory response, which CPB aggravates by subjecting the patient's blood to contact with foreign surfaces, ischemia and reperfusion, and gaseous and particulate microembolization, which initiate and amplify multiple redundant and interconnected immune cascades. With the onset of CPB, the increased expression of *initiator* substances (including endotoxin, tumor necrosis factor [TNF], and nuclear factor κB, as well as anaphylatoxins and cytokines) stimulates *effector* cells (including polymorphonuclear neutrophils, platelets, and endothelial cells) to up-regulate adhesion molecules and release cytotoxic oxygen radicals and proteases. This response can produce tissue injury of varying degree in a variety of organ systems.

Numerous clinical approaches have been shown to reduce the inflammatory response measurably in cardiac surgical patients (Fig. 67-14). These approaches can be loosely grouped into three primary categories: modification of surgical and perfusion techniques, modification of circuit components, and pharmacologic strategies.

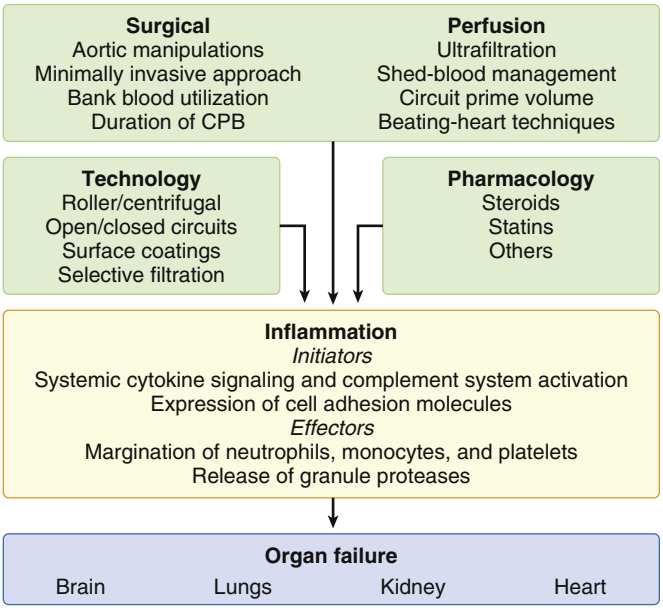


Figure 67-14. Brief review of the current understanding of the many variables that influence the inflammatory response in patients undergoing cardiopulmonary bypass (CPB).

Modification of Surgical Techniques or Perfusion Techniques

Modification of Surgical Technique. The movement toward minimally invasive cardiac surgery is at least partly motivated by the goal of reducing inflammation in the patient. The term *minimally invasive* may refer to procedures that use modified surgical techniques, including miniature incisions with or without robotic assistance, and to procedures that use classic surgical approaches but that minimize or eliminate the use of CPB and thus exposure to the ECC (e.g., OPCAB). Although OPCAB does not eliminate the patient's inflammatory response, it may produce less expression of inflammatory cytokines than does CABG with CPB.[212] However, it may be that the OPCAB-related reduction in inflammation is minimal in the days after the surgical procedure.[213] Moreover, any improvements in outcomes that may be attributable to the use of OPCAB instead of standard CABG are probably not exclusively caused by elimination of the ECC. Rather, minimizing or eliminating aortic manipulation, particularly in patients with severe atherosclerosis, may independently reduce the incidence of stroke.[45]

Modification of Perfusion Techniques. Reasons for the lack of consensus on the exact contribution of CPB to the inflammatory process include the issue that perfusion practice is far from standardized.[210] Various perfusion techniques and technologies have been shown to reduce inflammation, including shed-blood management,[214] ultrafiltration,[215,216] temperature management,[197] circuit miniaturization,[217,218] and on-pump beating-heart techniques.[219]

Perfusion Technology

In addition to the ways in which perfusion technology is used, the type of technology used may moderate the inflammatory response to CPB. No consensus exists regarding which arterial pump technology, roller pumps or centrifugal pumps, is less hemolytic. Some investigators have shown that using modified surface materials in the CPB circuit, such as heparin coatings, may reduce inflammation.[220-222] Additionally, selective filtration of leukocytes with an in-line leukocyte filter has been proposed as a method for reducing the concentration of activated leukocytes and inflammation. Warren and associates,[223] in a review of 63 studies, concluded that leukocyte filtration may have some modest benefits, but definitive evidence of any improvement in inflammatory-mediated complications is insufficient. Additionally, hemoconcentrators may be able to remove inflammatory mediators from circulation through large-volume zero-balance ultrafiltration techniques,[216] but little evidence exists of significant clinical improvements in the adult CPB population.

Pharmacologic Strategies

After decades of laboratory studies and clinical trials, a rigorously vetted pharmacologic approach to reducing inflammation in CPB-supported patients is still lacking. The best-established drug, aprotinin, was removed from the market in 2007 because of concerns about an increased risk of acute kidney failure after administration.[130] Thus, the clinician is left to select from a short list of drugs whose use is supported only by mixed mechanistic results and insipid evidence of improved clinical outcomes.

Corticosteroids have been used in cardiac surgery for decades for their immunosuppressive and antiinflammatory effects. The results of meta-analyses of small randomized clinical trials of methylprednisolone or dexamethasone have yielded conflicting results.[224,225] These drugs may reduce the incidence of atrial fibrillation, but they may also increase gastrointestinal bleeding, and they did not influence postoperative mortality or cardiac or pulmonary complications.[224,225] The first large (4494 patients) randomized controlled clinical trial of the use of routine corticosteroids during cardiac surgery in adults showed that high-dose (1 mg/kg) dexamethasone did not reduce the 30-day incidence of major adverse events (death, MI, stroke, renal failure, or respiratory failure).[226]

One meta-analysis of randomized controlled studies of the use of prophylactic preoperative statins to reduce inflammatory mediators concluded that evidence indicates that statins reduce plasma concentrations of IL-6, IL-8, TNF-α, and CRP when doses of 20 to 80 mg/day are administered for 1 day to 3 weeks preoperatively.[227] In a Cochrane Database review of 11 randomized controlled trials performed in patients undergoing on- or off-pump cardiac surgical procedures, pooled analysis showed that statin pretreatment before surgery reduced the incidence of postoperative atrial fibrillation and was associated with a shorter length of stay in the ICU but failed to influence mortality.[228] Finally, a meta-analysis of 14 studies of ketamine, which may also have antiinflammatory effects, suggests that ketamine administration significantly reduces the IL-6 response to surgery.[229]

DEEP HYPOTHERMIC CIRCULATORY ARREST

DHCA involves reducing the patient's core temperature to profoundly hypothermic levels (15° C to 22° C) before globally interrupting blood flow to the body, draining all the blood out of the patient, and collecting it in the ECC reservoir. In adults, this procedure is primarily used during surgical repair of the aorta, especially in cases of dissection or aneurysm involving the transverse arch.

Deliberate hypothermia with systemic cooling is the only reliable method of neuroprotection during complete global ischemia. Some clinicians also put ice bags on the patient's head to augment or maintain cerebral cooling. Pharmacologic approaches to neuroprotection, such as administering steroids to reduce inflammation or barbiturates or propofol to induce burst suppression, are used in some centers, although evidence to support their efficacy in the setting of complete global ischemia is scant. Furthermore, if the EEG is monitored, it is important to induce EEG isoelectricity with hypothermia before commencing the period of circulatory arrest rather than relying on supplemental barbiturates or propofol to provide neuroprotection.[230]

The equipment and circuitry of the heart and lung machine used for DHCA procedures are not generally different from those used for standard CPB procedures. Blood gas management during cooling and rewarming for DHCA procedures typically follows the alpha-stat

management scheme in adult patients and the pH-stat management scheme in pediatric patients (see the earlier section on blood gas management). Systemic cooling is begun when CPB is initiated and is continued until the temperature of the patient is low enough to provide adequate protection for the anticipated duration of circulatory arrest. When deciding what temperature is "adequate," one must give top priority to protecting the brain. Because no clinically feasible method for measuring brain temperature is available, surrogate temperatures must be used to estimate core temperature (see the earlier section on temperature). A time lag exists between the time that arterial blood reaches a target temperature and the time that the brain's parenchymal tissue equilibrates with the blood temperature. Consequently, when aggressive cooling is used, arterial blood temperature underestimates brain temperature. For an average-sized adult, cold arterial perfusion at full CO flow should be continued for 20 to 30 minutes after the "goal" arterial blood temperature is reached to ensure that the brain has had sufficient time to cool. For an anticipated circulatory arrest period of 30 to 40 minutes, a temperature of 18° C to 20° C is probably adequate; however, slightly warmer temperatures may be acceptable if a shorter period of arrest is used or if cerebral perfusion is maintained.[231] It is also good practice to monitor temperatures at multiple sites on the patient, in addition to blood temperature, to observe the relative change over time during cooling and rewarming. Furthermore, the EEG provides a good pharmacodynamic endpoint for the cerebral effects of cooling; hypothermia-induced EEG isoelectricity should be present before elective circulatory arrest commences.[231]

As the patient cools, the viscosity of blood will increase. At a temperature of 18° C, the viscosity of blood with a hematocrit of 30% to 35% increases to three to four times its normal level. Cardiac surgical textbooks suggest that hemodilution is important in minimizing any microcirculatory disturbances that may occur because of increased blood viscosity. Consequently, some clinicians may target a hematocrit value that is appropriate to the patient's temperature during DHCA, approximately 18% to 20%. However, the results of a study performed in piglets by Duebener and colleagues suggested that a hematocrit of 30% is preferable if DHCA is used.[232]

When the patient has reached an appropriate core temperature as determined by temperatures measured at multiple sites and after adequate time for equilibration, the arterial blood flow from the pump is stopped, and the patient's blood is drained into the ECC reservoir. During the period of circulatory arrest, the blood in the ECC reservoir should be recirculated to prevent stasis and maintain the desired temperature. Gas flow to the oxygenator should be discontinued to prevent profound hypocapnia. Reperfusion should be initiated with cold blood. An initial period (5 to 10 minutes) of cold reperfusion may enhance cerebral protection by removing accumulated metabolic products from the cerebral capillary beds while maintaining a low cerebral metabolic rate of oxygen.

The risk of neurologic injury after cardiac surgery involving DHCA extends into the postoperative period because cerebral vascular resistance is increased and cerebral blood flow is decreased for several hours after the procedure. In addition, hyperthermia, possibly secondary to a systemic inflammatory response, is common in the postoperative period and should be treated aggressively.

In an effort to reduce the period of cerebral ischemia during circulatory arrest, selective cerebral perfusion techniques have been developed. Selective antegrade cerebral perfusion can be accomplished by directly cannulating the left common carotid artery,[233] or perfusion can easily be delivered through the right common carotid artery when the aortic cannulation approach for CPB involves cannulating the axillary or innominate artery.[234] Axillary cannulation facilitates the delivery of arterial blood from the ECC to the entire circulatory system during cooling and rewarming or, with the addition of a clamp to the proximal innominate artery, selectively into the right common carotid and radial arteries. Because of the proximity of the arterial cannula to the right radial artery, arterial blood pressure monitored in the right radial artery may be significantly higher than pressure monitored in the left radial or femoral artery. Consequently, right radial arterial pressure should not be used to control perfusion during cooling and rewarming. During delivery of selective antegrade cerebral perfusion, cold arterial blood from the extracorporeal circuit should be delivered to maintain the cerebral blood pressure between 30 and 60 mm Hg. The perfusion flow rates necessary to achieve this pressure vary depending on the site or sites of arterial cannulation. Direct cannulation of only the left common carotid artery requires the least flow, whereas cannulation of multiple head vessels or of the axillary artery (which perfuses the right common carotid, right internal thoracic artery, and right arm) requires higher flow rates. Subsequently, flow rates of 150 to 1500 mL/minute have been reported. Selective retrograde cerebral perfusion is delivered through a snared cannula introduced into the right atrium and advanced into the SVC; this type of perfusion can be initiated after the patient's systemic perfusion is discontinued. Cold oxygenated blood from the ECC can be administered at a flow rate (≈5 mL/kg/minute) high enough to maintain SVC pressure between 35 and 40 mm Hg.[235] Although some debate remains about whether selective cerebral perfusion of any kind is necessary to achieve optimal neurologic outcome after DHCA procedures,[236] investigators generally agree that antegrade cerebral perfusion, when used properly, is superior to retrograde perfusion.[237,238]

LEFT HEART BYPASS

If a descending aortic aneurysm or aortic dissection is to be surgically replaced with a tube graft, blood flow through the patient's thoracic aorta must be interrupted. The application of vascular clamps to this major vessel acutely increases the afterload of the heart and produces global ischemia in all parts of the body distal to the clamp. Patients with compromised cardiac function or those undergoing a surgical procedure in which the duration of ischemia will be unacceptably long require some method of circulatory support. Temporary interposition of a shunt (e.g., a Gott shunt) around the area of repair is the simplest approach, but it does not offer the level of support that can be achieved with LHB or CPB.

For these procedures, the approach is usually through a left thoracotomy incision, which provides excellent access to the left atrium. The simplest approach to LHB is to withdraw blood from the left atrium with a centrifugal pump and return the blood to the patient's femoral artery. This *simple* LHB circuit gives the clinician excellent control of blood flow distal to the clamps and therefore the ability to manipulate the afterload against which the heart must work. However, the complexity of some surgical procedures requires that full CPB be used.

Surgical complications are not uncommon in these patients and include hypoxia, hypothermia, and exsanguination. A double-lumen endotracheal tube or bronchial blocker is often used to isolate the left lung from the right. After left thoracotomy and exposure of the aneurysm, ventilation of the left lung is discontinued. Patients with preexisting lung dysfunction or traumatic lung injury associated with aortic dissection may have difficulty maintaining oxygenation with a single lung. Because of the large surgical exposure required and the sometimes extended duration of the procedure, it is not unusual for the patient to become hypothermic. Furthermore, these procedures carry an elevated risk of blood loss and the consequent need for rapid replacement of fluids and blood products. It is often advisable to use *complete* LHB to reduce these risks.

Figure 67-15 illustrates the simple-circuit and complete-circuit approaches to LHB. The major difference between a complete LHB circuit and the standard CPB circuit is the position of the reservoir in the circuit and the position of the venous cannula in the patient. In a complete LHB circuit, the reservoir does not receive the blood returning from the patient as in the CPB circuit. With the reservoir out of the pathway of the blood, the effective surface area of the ECC is reduced; this reduction attenuates contact activation of the blood and minimizes the need for high-dose heparinization.

In both circuits, the management goal is the same—to keep arterial blood pressure higher than 60 mm Hg both proximal and distal to the aortic cross-clamp throughout the procedure. However, the complete LHB circuit gives the clinician the ability to manage hypoxia, hypothermia, and blood loss. The addition of an oxygenator to the circuit makes it possible to augment the patient's ventilation and oxygenation. The heat exchanger is used to maintain normothermia. The reservoir facilitates the addition of large volumes of fluid or blood products in the event of hemorrhage, hypovolemia, or both.

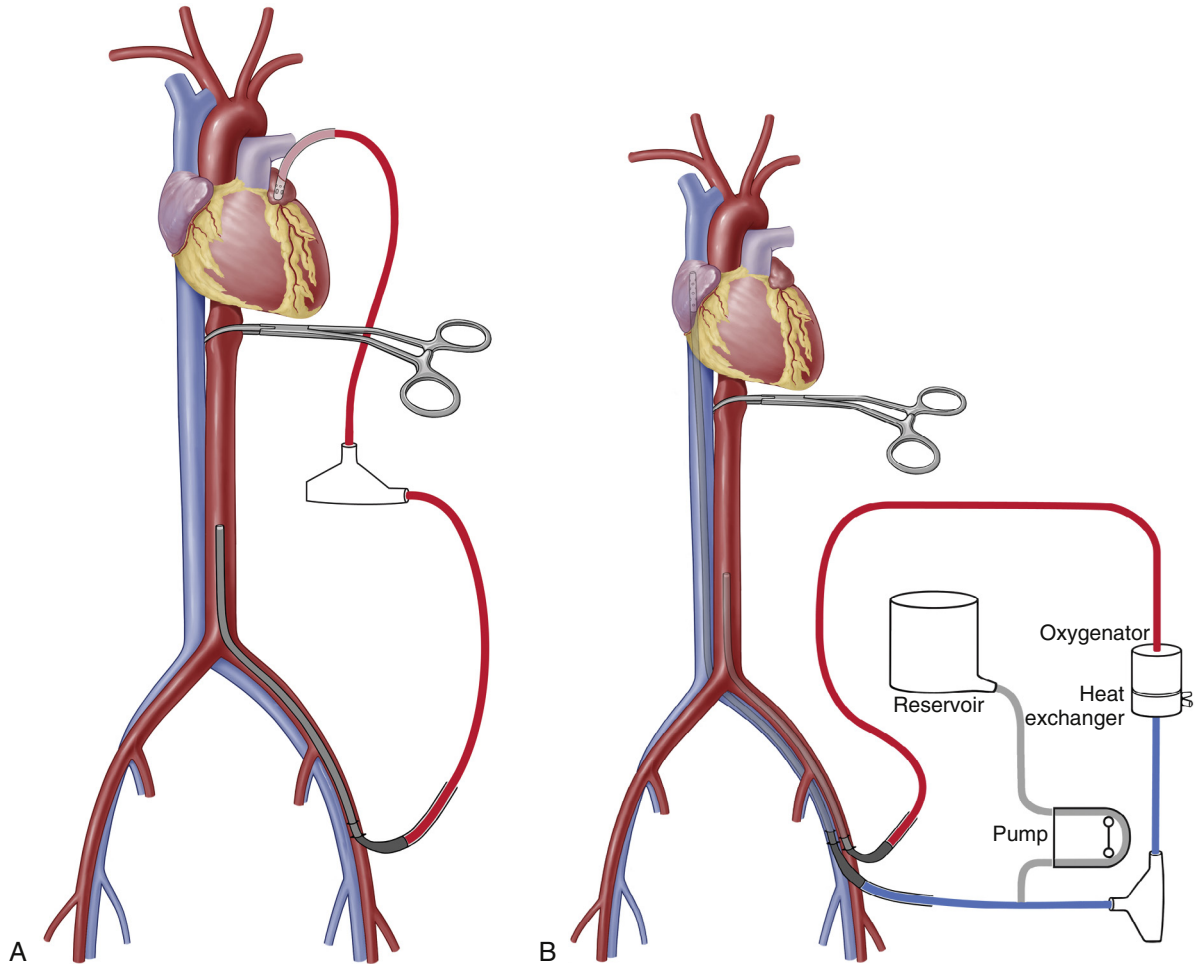


Figure 67-15. Left heart bypass (LHB) diagram. **A**, Simple LHB (left atrium, cone, and femoral artery). **B**, Complex LHB (including an oxygenator, heat exchanger, and reservoir for fluid administration).

CARDIOPULMONARY SUPPORT AND EXTRACORPOREAL MEMBRANE OXYGENATION CIRCUITS

For all practical purposes, no difference exists between a CPS circuit and an ECMO circuit. Both consist of a CPB circuit without a reservoir, an arterial line filter, or any of the ancillary pumps that are used during cardiac surgery (i.e., pump suction, vent, and cardioplegia). Because the reservoir is removed from the circuit, these systems are considered closed. Closed circuits have a static internal volume and cannot unload the patient's vascular system.

The removal of the reservoir and filters from the circuit has advantages and disadvantages. The chief advantage is that the surface area of the circuit is significantly reduced, which facilitates a reduced anticoagulation regimen with an initial heparin dose of 75 to 150 units/kg and a continuous infusion of heparin at 25 to 75 units/kg/hour to maintain ACTs of 180 to 250 seconds. The chief disadvantage is that the closed circuits are less able to trap emboli. Special precautions should be taken when connecting a closed ECC to the patient's cannulas, injecting fluids and medications into the circuit, or sampling from the venous line. Additionally, because of the reduced anticoagulation regimen, blood stasis in the circuit should be avoided, and periods of low flow should be minimized.

In intensive care settings, ECMO or CPS is used to support the heart, lungs, or both for days or weeks. The newer generation of centrifugal pumps and hollow-fiber oxygenators perform acceptably well during these long-term applications and are becoming more commonly used in desperate situations (Fig. 67-16).

SPECIFIC CARDIOVASCULAR DISEASE STATES

CORONARY ARTERY DISEASE

Pathophysiology of Coronary Disease

Coronary Anatomy. Understanding the coronary anatomy is important to understand the pathophysiology of CAD and the anesthetic care of patients undergoing myocardial revascularization. Two main coronary arteries take off from the aorta and supply the myocardium: the left main coronary artery (LMCA) and the RCA. The LMCA subsequently divides into the left anterior descending (LAD) coronary artery and the left circumflex artery (LCx). The LAD courses down the interventricular

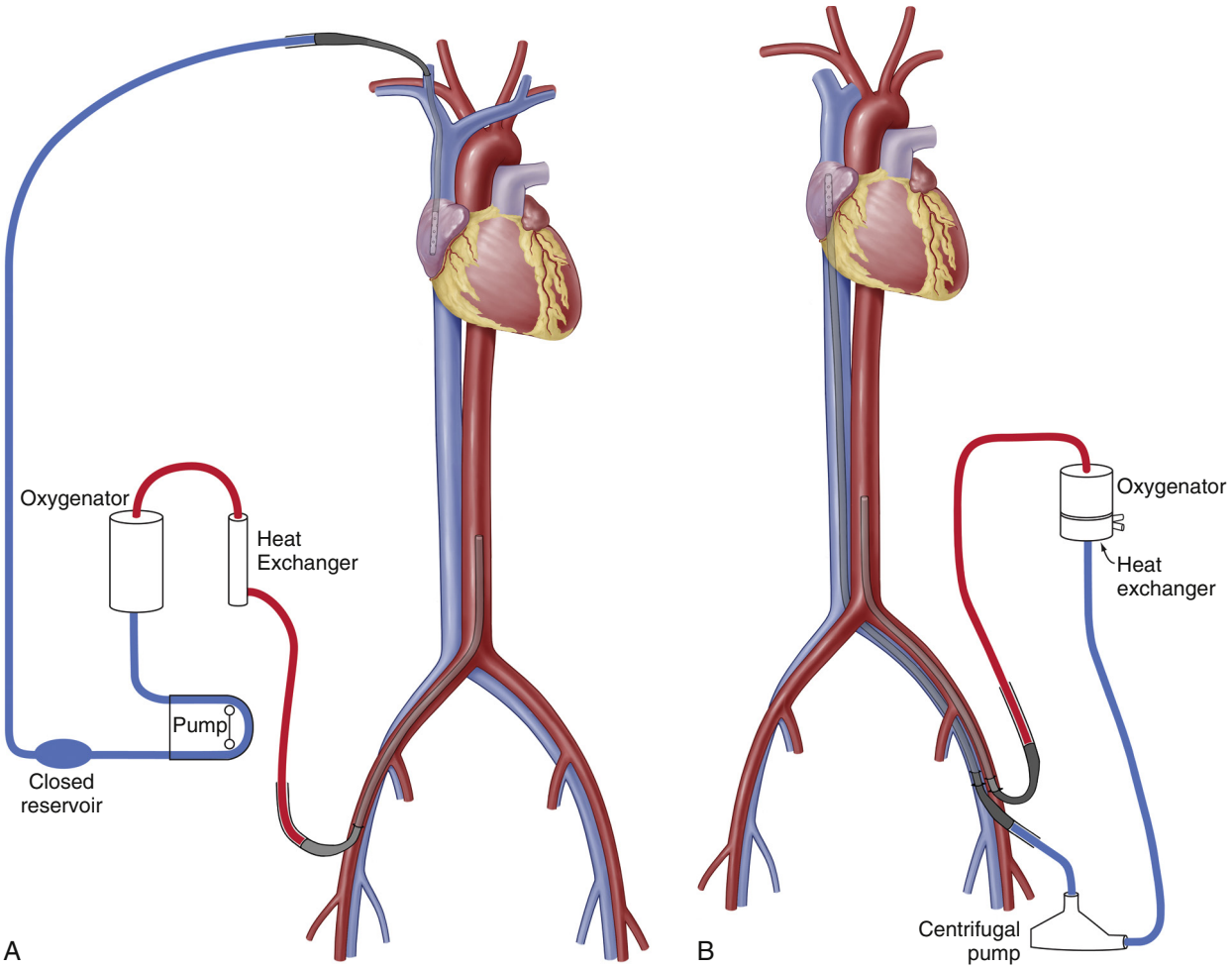


Figure 67-16. A, Patient cannulated through the internal jugular vein and femoral artery, with a traditional extracorporeal membrane oxygenation circuit. **B,** Patient cannulated through the femoral vein and femoral artery, with a simple cardiopulmonary support circuit.

groove and gives rise to the diagonal and septal branches. The diagonal branches of the LAD supply the anterolateral aspect of the heart. The septal branches supply the interventricular septum, as well as the bundle branches and the Purkinje system. The LAD itself terminates at the apex of the left ventricle. The other branch of the LMCA, the LCx, courses along the left AV groove and gives rise to one to three obtuse marginal branches that supply the lateral wall of the left ventricle. In 45% of patients, the sinus node arterial supply arises from the LCx. In 15% of patients, the LCx gives rise to the posterior descending artery, which supplies the posterior inferior aspect of the left ventricle ("left-dominant" system).

The RCA traverses the right AV groove and supplies the right anterior wall of the right ventricle through its acute marginal branches. In 85% of the population, the RCA gives rise to the posterior descending artery supplying the posterior inferior aspect of the left ventricle ("right-dominant" system). The AV node arterial branch arises from the dominant artery to supply the node, the bundle of His, and the proximal part of the bundle branches. In addition, in 55% of the population, the sinus node arterial supply arises from the RCA.

Determinants of Myocardial Oxygen Supply and Demand. The balance of oxygen supply versus demand is somewhat complex (Figs. 67-17 and 67-18). Oxygen supply is determined by the oxygen content of arterial blood and by coronary blood flow. Extraction of oxygen from arterial blood is maximal at rest. As demand increases (with exercise or hemodynamic stress), the oxygen supply to the myocardium must also increase.

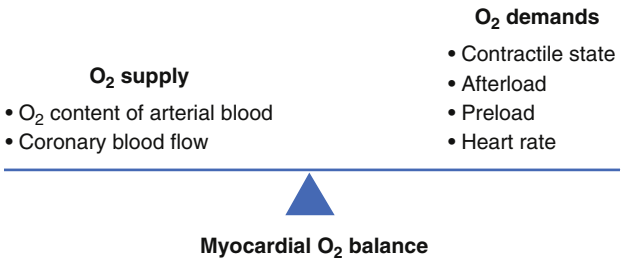


Figure 67-17. Factors determining myocardial oxygen (O_2) supply and demand. *(From Mittnacht AJC, Weiner M, London MJ, Kaplan JA: Anesthesia for myocardial revascularization. In Kaplan JA, Reich DL, Savino JS, editors:* Kaplan's cardiac anesthesia: the echo era, *ed 6, St. Louis, 2011, Saunders, p 524.)*

Determinants of blood flow in normal coronary arteries include the pressure differential across the coronary bed (i.e., the coronary perfusion pressure) and coronary vascular resistance. The coronary perfusion pressure for the left ventricle is the aortic blood pressure during diastole minus the LV end-diastolic pressure (LVEDP); thus, elevations in LVEDP impede subendocardial blood flow. Because coronary stenosis causes vessels to dilate maximally distal to the stenosis, manipulating coronary perfusion pressure is an important means of controlling coronary blood flow (and preventing or treating myocardial ischemia). However, because the determinants of myocardial oxygen balance interact in a complex manner, altering any one of them can have multiple effects. For example, a rise in blood pressure increases coronary blood flow but also increases afterload, thereby elevating wall tension and oxygen demand.

The duration of diastole is another important factor affecting oxygen supply to the myocardium because 70% to 80% of coronary arterial blood flow occurs during the diastolic phase of the cardiac cycle. During the systolic phase, cardiac contraction increases intraventricular cavitary pressure and coronary vascular resistance, thus impeding myocardial perfusion. The total time per minute spent in diastole is a function of the heart rate, but a nonlinear relationship exists between heart rate and the duration of diastole (Fig. 67-19). This is a major reason for the use of β-blockers as antiischemic drugs, both for long-term therapy and for preventing even small increases in heart rate during the perioperative period.

The oxygen content of blood depends on hemoglobin-bound oxygen and, to a lesser extent, dissolved oxygen. Although a high hemoglobin level gives the blood high oxygen-carrying capacity, the minimum level of hemoglobin necessary to avoid ischemia has not been well defined in clinical studies. Factors that affect this limit include the severity of CAD, the heart rate, perfusion pressure, and myocardial wall thickness and tension.

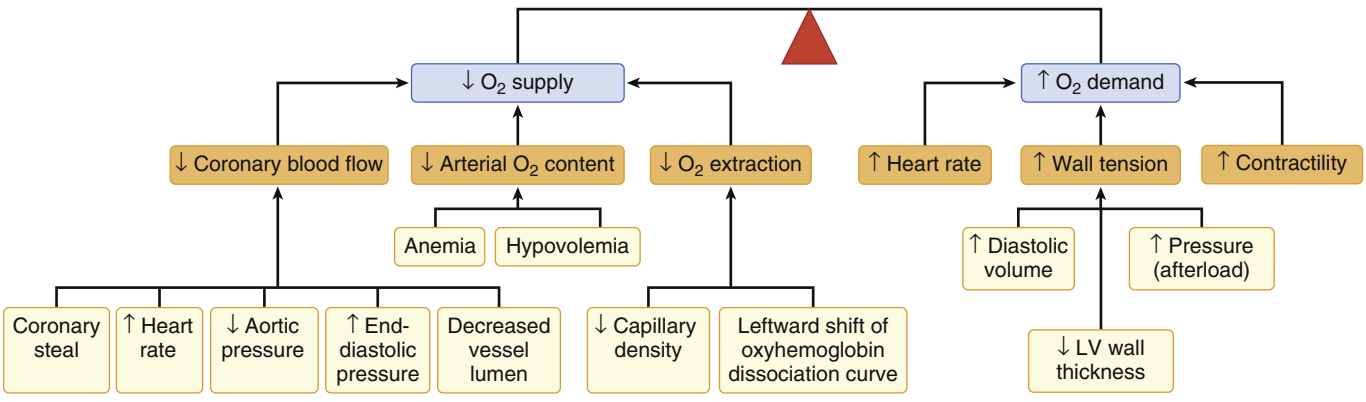


Figure 67-18. Summary of factors that affect myocardial oxygen supply and demand. *LV,* Left ventricular. *(From Green MS, Okum GS, Horrow JC: Anesthetic management of myocardial revascularization. In Hensley FA, Martin DE, Gravlee GP, editors:* A practical approach to cardiac anesthesia, *ed 5, Philadelphia, 2013, Lippincott Williams & Wilkins, pp. 319-358; modified from Crystal GJ: Cardiovascular physiology. In Miller RD, editor:* Atlas of anesthesia, *vol 8,* Cardiothoracic anesthesia, *Philadelphia, 1999, Churchill Livingstone, p 1:1.)*

Furthermore, delivery of oxygen to myocardial tissue also depends on a high partial pressure of oxygen (PO_2), and actual release of oxygen from hemoglobin occurs according to the oxyhemoglobin dissociation curve. A leftward shift of this curve caused by alkalosis, hypothermia, or low levels of 2,3-diphosphoglycerate decreases the release of oxygen.

In patients undergoing myocardial revascularization, reductions in myocardial oxygen supply may occur because of hypotension, tachycardia, anemia, or coronary vasoconstriction, as well as increases in demand secondary to tachycardia or increased afterload. Although myocardial ischemia is certainly possible without any changes in systemic hemodynamics, vigilant monitoring for imbalances in myocardial oxygen supply versus demand, as well as monitoring for the development of ischemia, is necessary throughout the perioperative period. Myocardial ischemia may be detected by ECG monitoring and ST-segment analysis, as well as by TEE monitoring for the development of regional wall motion abnormalities.

On-Pump Coronary Artery Bypass Grafting Surgery

Preoperative Evaluation. Typically, patients undergoing CABG have had extensive preoperative assessment of their cardiac disease (see Chapter 38). Coronary artery anatomy should be noted, particularly a high-grade lesion in the LMCA or proximal LAD coronary artery or triple-vessel disease. Ventricular function, assessed by angiography or echocardiography, is usually recorded as an estimated EF. Other cardiac disease discovered in the preoperative workup should be noted and understood, including valvular abnormalities such as concurrent MR, aortic stenosis (AS), aortic insufficiency, atrial septal defect (ASD) or ventricular septal defect (VSD), or ventricular aneurysm. The anesthesiologist should be aware of any abnormal cardiac rhythm on the ECG or noted in the history, such as atrial fibrillation or other supraventricular tachycardia (which may lead to hemodynamic instability or increase the patient's risk of an embolic neurologic complication), left bundle branch block or a prolonged PR interval (which may progress to a more advanced heart block), or complete heart block, which may be underlying a paced rhythm. Antiarrhythmic therapy, with either pharmacologic drugs or devices such as a pacemaker or automated implantable cardioverter-defibrillator (ICD), should be noted.

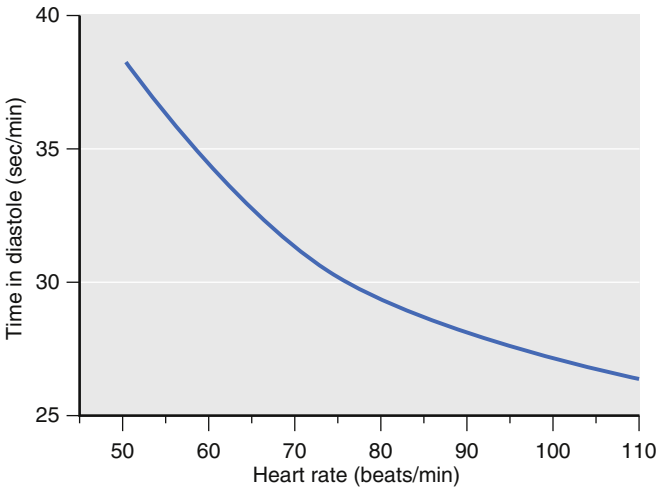


Figure 67-19. Total time spent in diastole each minute plotted as a function of heart rate in beats per minute. The reduction in diastolic interval leads to diminished left ventricular blood flow as heart rate increases. *(From Green MS, Okum GS, Horrow JC: Anesthetic management of myocardial revascularization. In Hensley FA, Martin DE, Gravlee GP, editors:* A practical approach to cardiac anesthesia, *ed 5, Philadelphia, 2013, Lippincott Williams & Wilkins, pp 298.)*

Various models for assessing overall risk have been developed that include certain factors associated with increased risk: poor LV function (history of CHF or LVEF <30%), advanced age, obesity, emergency surgery, combined procedures (e.g., valve repair or replacement combined with CABG), prior cardiac surgery, and history of diabetes or renal failure (Table 67-9).[239,240] The ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery recommends using a published model to assess patients' risk for mortality, morbidity, and length of hospital stay, but only as a level IIa recommendation (level of evidence C).[241]

Premedication. In the current era, cardiac surgical patients often have same-day admissions. Frequently, the only premedication they receive is midazolam on the morning of the surgical procedure, to allay anxiety. However, small additional doses of midazolam, fentanyl, or both may be administered during line placement (please see the section on induction of anesthesia and the prebypass period); this may be particularly important in patients with CAD, to minimize undesirable sympathetic stimulation that could cause tachycardia and hypertension. However, administration of these drugs should be incremental and judicious in patients with low CO or significant pulmonary hypertension.

No single anesthetic agent or combination of anesthetic drugs is suitable for anesthetic induction and maintenance in every patient undergoing CABG surgery. Induction of anesthesia for coronary revascularization is often achieved by administering a benzodiazepine (typically midazolam) in combination with a narcotic, usually fentanyl, and a muscle relaxant.[240] However, either etomidate or propofol in combination with a narcotic has frequently been used. The goal is to avoid wide swings in hemodynamics with induction and with subsequent intubation. Typically, volatile agents are used throughout the prebypass, bypass, and postbypass periods to limit the total fentanyl dose to 10 to 15 μg/kg. In addition, the volatile anesthetics have several cardioprotective effects, including triggering the preconditioning cascade and mitigating reperfusion injury.[162] Additional midazolam may be given to ensure that intraoperative awareness is avoided.

One factor in the choice of specific anesthetic agents and doses is the patient's preexisting LV function. Patients with normal LV function can have a significant sympathetic response to surgical stimulation that results in hypertension and tachycardia. Use of β-blockers, additional propofol, higher doses of a volatile anesthetic agent, or vasodilators may be warranted if this situation develops. Conversely, in patients with poor LV function, hypotension may develop with the administration of

TABLE 67-9 RISK FACTORS USED IN VARIOUS RISK-STRATIFICATION SCHEMAS FOR CORONARY ARTERY BYPASS GRAFT SURGERY

	Montreal	Cleveland	Newark	New York	Northern New England	Society of Thoracic Surgery
Emergency	+	+	+	+	+	+
Poor LV function or congestive heart failure	+	+	+	+	+	+
Redo operation	+	+	+	+	+	+
Gender or small size	–	+	+	+	+	+
Valve disease	–	+	+	+	–	–
Advanced age	+	+	+	+	+	+
Renal disease	–	+	+	+	+	–
Obesity	+	–	+	–	–	–

Modified from Green MS, Okum GS, Horrow JC: Anesthetic management of myocardial revascularization. In Hensley FA, Martin DE, Gravlee GP, editors: A practical approach to cardiac anesthesia, ed 5. Philadelphia, 2013, Lippincott Williams & Wilkins, pp 293-318.
LV, Left ventricular.

anesthetic agents because of a reduction in CO or vasodilation, or both. Such patients may require vasopressor or inotropic pharmacologic support, or both.

Another factor in the choice of anesthetic agent is the possibility of early extubation within 4 to 6 hours of arrival in the ICU (so-called fast tracking). Patients who have good preexisting cardiac function and who will be undergoing CABG as an isolated procedure are usually candidates for fast tracking. This strategy necessitates the use of agents in dosages that would not keep the patient sedated or render the patient unable to ventilate adequately for a prolonged period. Early extubation may not be appropriate in patients with poor cardiac function, severe pulmonary disease, or obesity or in those undergoing emergency procedures, CABG combined with other procedures, or redo operations.

Monitoring. Monitoring for patients scheduled to undergo coronary revascularization surgery has evolved since the 1960s, in an effort to detect intraoperative ischemia. The standard American Society of Anesthesiologists (ASA) monitors and invasive arterial blood pressure monitoring (with noninvasive blood pressure backup) are always used. Typically, both leads II and V_5 are used for continuous monitoring, as well as automated ST-segment analysis to improve the chances of detecting ischemia.[242]

PA catheters are used less commonly now than in the past because several studies have shown that using such catheters does not improve outcome.[243] In fact, the risks inherent in the use of these catheters may actually exceed the benefits.[26] Certainly, the absolute PAP is not diagnostic of ischemia, although waveform changes may be more predictive. For example, the appearance of a new V wave on the PCWP tracing indicates ischemic papillary muscle dysfunction. In addition, specialized PA catheters allow derivation of several indices of cardiac function, including CO, cardiac index, and $S\bar{v}O_2$. Furthermore, some clinicians believe that the PA catheter is useful in the postoperative period when TEE is not available for continuous monitoring of the patient.

Regional wall motion abnormalities detected by TEE are more sensitive to ischemia than ECG changes or PA catheter waveform and pressure changes.[242] TEE can be used to interrogate regions of the heart representative of all three major coronary arteries simultaneously. This technology is commonly used throughout revascularization procedures to assess regional wall motion by qualitative inspection of radial shortening and wall thickening, and it is particularly useful after revascularization. In addition, TEE is used to assess ventricular preload and contractility, diagnose any valvular abnormalities, evaluate calcific and atherosclerotic lesions at the aortic cannulation sites, and detect LV thrombus and uncommon congenital abnormalities (e.g., ASD or VSD, persistent left SVC). See Chapter 46 for details on the perioperative use of TEE.

Surgical Considerations. Conventional (on-pump) CABG is the most commonly performed procedure in cardiac surgery. A full median sternotomy performed with a sternal saw is standard. Ventilation of the lungs is halted briefly during sawing of the sternum to avoid a pleural tear. An oscillating saw may be used in patients with a previous sternotomy (redo). The risks posed by redo sternotomy include perforation of the right ventricle, damage to existing vein grafts, and ventricular fibrillation from the transmission of electrocautery energy through preexisting sternal wires. Therefore, PRBCs (2 units) should be immediately available, and external defibrillation pads should be positioned before preparation and draping. Furthermore, surgical manipulation of previous vein grafts may result in embolization of atheroma and resultant ischemia. If a complication does occur during sternotomy or exposure of the heart and cannulation sites, emergency bypass may be established by cannulating a femoral artery and vein.

If an IMA is to be used, the surgical table is elevated and often rotated somewhat to the left to facilitate surgical comfort in performing the dissection. Tidal volumes are also reduced to facilitate exposure. Heparin administration usually occurs before the IMA pedicle is clamped, and papaverine may be injected into this vessel. The prebypass period for on-pump CABG may be relatively short (<1 hour) or may require several hours for dissection of the left IMA, right IMA, radial arteries, or any combination of these vessels. In addition, for most CABG procedures, adequate venous conduits must be harvested, and endoscopic saphenectomy is now common.

Before aortic cannulation, TEE or epiaortic echocardiography, or both, provides critical information regarding the presence and precise location of calcification or mobile atheromas in the aortic arch. The surgeon may

request TEE guidance for placement of the retrograde catheter into the coronary sinus; furthermore, if a persistent left SVC is diagnosed, this abnormality may render retrograde cardioplegia problematic.[240] After CPB is initiated, TEE may also be used to ensure correct placement of the LV vent, as well as to verify the absence of LV thrombus in patients with a recent anterior wall MI or aneurysm.

Surgical and technical complications of CABG surgery that manifest as ischemia include (1) poor-quality proximal or distal anastomoses of the grafts, (2) inadvertent incision of the coronary back wall leading to coronary dissection, (3) suturing of the coronary artery closed, (4) inadequate vein graft length resulting in stretching of the vein when the heart is filled, (5) excessive vein graft length leading to kinking of the vein, and (6) vein graft thrombosis.[239] CPB may need to be reinstituted to correct surgical causes of ischemia after revascularization. Heparin should be immediately available if emergency reinstitution of CPB becomes necessary.

After bypass, other causes of ischemia include (1) incomplete revascularization resulting from ungraftable vessels or diffuse distal disease, (2) coronary embolization of air or atheromatous debris, (3) coronary spasm, (4) mechanical factors such as vein graft stretching or occlusion of IMA flow secondary to overinflation of the lungs, and (5) thrombus formation.[239] The treatment of ischemia includes administering various drugs: nitroglycerin or vasopressors when SVR is either high or low; nitroglycerin, a calcium channel blocker (diltiazem, nifedipine, or nicardipine), or both to treat coronary spasm; a vasoconstrictor (usually phenylephrine) to "push" intracoronary air through the vasculature when air embolism is suspected; a β-blocker (usually esmolol) to treat tachycardia; and one or more inotropic agents to increase CO if necessary. In addition, AV sequential pacing may be used to improve rate, rhythm, and hemodynamic stability when appropriate. At times, mechanical support with intraaortic balloon counterpulsation or an LV and/or RV assist device (LAVD or RVAD) may become necessary. Residual effects of cardioplegia, a ventricular aneurysm, or pericarditis may cause ST-segment elevation without actual ischemia.

Off-Pump Coronary Artery Bypass Surgery, Minimally Invasive Coronary Artery Bypass Surgery, and Hybrid Coronary Revascularization

Off-Pump Coronary Artery Bypass Surgery. Awareness of the deleterious effects of CPB has driven advocacy for alternative myocardial revascularization techniques, particularly OPCAB surgery. Proponents of OPCAB cite the low morbidity and mortality of patients who undergo this procedure, as well as faster recovery and reduced procedural costs. Data from the STS suggest that approximately 22% of coronary revascularization procedures are being performed off pump.[244]

The midline sternotomy is the traditional approach used for OPCAB procedures. Potential sources of bypass grafts include the right and left mammary arteries, the saphenous veins, and the radial arteries. The pericardium

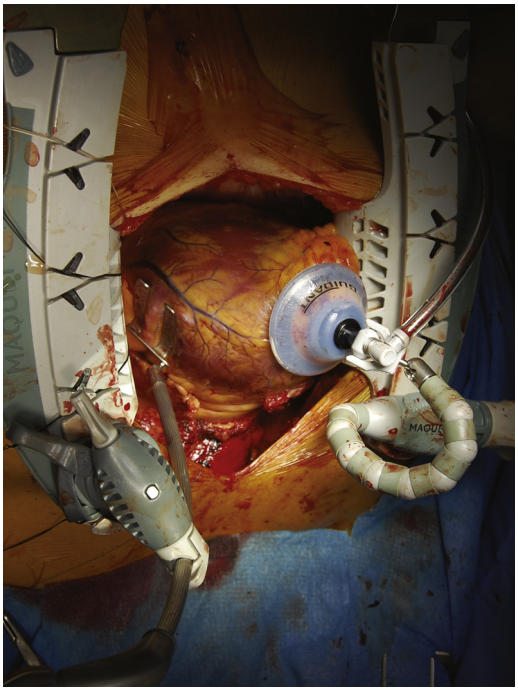


Figure 67-20. Image depicting the first obtuse marginal (OM1) anastomosis during off-pump coronary artery bypass grafting with a saphenous vein graft. The view is from the head of the patient. The previously completed left internal mammary artery–to–left anterior descending coronary artery anastomosis is seen. The Maquet access device (MAQUET, Wayne, NJ) uses suction to position the heart (verticalization) for easy access to the circumflex coronary artery system. *(Courtesy Alexander Mittnacht, MD, Mount Sinai School of Medicine, New York; From Mittnacht AJC, Weiner M, London MJ, Kaplan JA: Anesthesia for myocardial revascularization. In Kaplan JA, Reich DL, Savino JS, editors:* Kaplan's cardiac anesthesia: the echo era, *ed 6, St. Louis, 2011, Saunders, p 524.)*

is incised, reflected, and secured to the edges of the mediastinum. Special sternal retractors allow the placement of adjustable and flexible fixation devices that work by direct surface pressure on the myocardium, by suction, or by both methods. These devices stabilize the target vessel and allow the surgeon to "verticalize" the cardiac apex out of the pericardial well to access the posteriorly and laterally located vessels (Fig. 67-20). Dosing of heparin for OPCAB cases is institution specific; both full-dose and low-dose regimens are currently in use.

When the target vessel and surrounding myocardium are stabilized, an elastic ligature is placed circumferentially around the coronary artery to minimize bleeding as an arteriotomy is performed. Surgical visualization is also optimized by the application of a blower or mister, held by a surgical assistant, that releases sterile irrigation fluid aerosolized in carbon dioxide gas. Under these conditions, one or more distal coronary anastomoses are performed. The proximal connections of saphenous vein grafts or free arterial conduits are anastomosed directly to the aorta with a side-biting clamp. Alternatively, an indirect proximal connection is made by creating a T-graft (end-to-side anastomosis) to a mammary artery that is still connected to a vascular pedicle on the subclavian artery.

Surgical considerations include (1) obtaining adequate exposure of the anastomosis site, (2) restraining cardiac

motion during anastomosis, and (3) preserving myocardium during coronary flow interruption.[245] To achieve the first two goals, the surgeon must use maneuvers that may significantly compromise hemodynamics by several mechanisms, including impairment of biventricular filling, particularly in the thin-walled, easily compressed right ventricle. In addition, altered ventricular filling can result from verticalization of the cardiac ventricular apex (which may kink or partially obstruct venous return) (see Fig. 67-20). Furthermore, myocardial ischemia occurs in native coronary arteries and is exacerbated by temporary elastic suture ligation of a target vessel.[246] Ischemia of distal myocardial segments can occur during anastomosis of bypass grafts, and the degree of functional deterioration depends on the severity of the stenosis and the extent of collateralization.[245]

Therefore, the anesthesiologist must take measures to prevent severe hypotension to minimize the reduction in coronary perfusion caused by these hemodynamic changes and intraoperative myocardial ischemia. Typically, intravascular volume loading (either crystalloid or colloid) and a head-down position of the patient are used, and it is also common to administer a vasoconstrictor drug (either phenylephrine or norepinephrine). When increased mitral insufficiency further exacerbates the hemodynamic changes, repositioning the heart is a simple maneuver that may increase ventricular filling and normalize ventriculoannular geometry.

Monitoring of the patient includes a five-lead ECG and an invasive arterial pressure catheter. PAP and CO measurements or continuous pulse contour CO can be considered.[245] TEE is beneficial, but views are limited during certain portions of the surgical procedure; verticalization of the heart and the application of external compression footplates cause suboptimal imaging. The midesophageal imaging view, rather than the transgastric view, may be best for continuous TEE monitoring while distal coronary anastomoses are performed.

Persistent or worsening ECG change or impending cardiovascular collapse warrants quick action on the part of the anesthesiologist and surgeon. One option is to have a low threshold for the insertion of small, flexible intracoronary stents into the open coronary anastomosis to allow some distal segment flow. Instituting full or partial CPB and placing an IABP are other therapeutic options. Emergency conversion from OPCAB to CABG with CPB, which occurs in approximately 3% of these cases,[247,248] is not an innocuous event. Such unplanned conversions are reportedly associated with an elevated risk of death, stroke, renal failure, wound infections, and respiratory failure.

The short-term outcomes and long-term efficacy of OPCAB surgery continue to be investigated and debated in the literature. Meta-analyses have noted no significant differences in 30-day mortality.[249,250] In the largest multicenter randomized trial to compare on-pump CABG with OPCAB, no difference was seen in 30-day mortality or the composite outcome of death and complications.[251] In contrast, very large observational analyses do suggest a mortality benefit. Hannan and associates found a mortality benefit in 49,830 patients from the New York State registry by using a risk-adjusted analysis (i.e., Cox proportional hazard models and propensity analysis).[252] However, the need for repeat revascularization was greater among OPCAB patients (93.6%) than CABG patients (89.9%).[252] Several large retrospective reviews of traditional CABG versus OPCAB procedures have found a gender-specific survival benefit for women who undergo OPCAB surgery, compared with those who undergo on-pump CABG.[253-255]

Minimally Invasive Coronary Artery Bypass Surgery. The most popular alternative approach to sternotomy is the minimally invasive coronary artery bypass (MIDCAB) through a left anterior thoracotomy, which allows direct-access IMA harvesting and grafting to the LAD artery. Some surgeons harvest the left IMA (LIMA) by using robot-assisted endoscopic technology before making the small incision to complete the LIMA-to-LAD anastomosis through the left anterior thoracotomy incision. In these cases, deflation of the left lung is required for visualization of the anastomosis, accomplished with a double-lumen endotracheal tube or a bronchial blocker. In addition, carbon dioxide is insufflated into the left hemithorax during the period while the lung is deflated.

Usually, the MIDCAB technique involves grafting of only a single vessel, and exposure for this anastomosis may be suboptimal.[245] Challenges for the anesthesiologist in MIDCAB cases include the need for single-lung ventilation while the LIMA is dissected and the anastomosis is performed. Because the graft is only to the LAD in these cases, no extreme positioning of the heart occurs that could significantly compromise hemodynamic status. However, external defibrillator or pacing pads should be attached to the patient before preparing and draping because surgical access to the heart is limited during these procedures.[246]

Hybrid Coronary Revascularization. Hybrid coronary revascularization combines MIDCAB techniques with catheter-based interventions.[256] Ideally, a hybrid operating room is used. The surgical component of the hybrid procedure may be offered in a completely endoscopic fashion, using robotic technology. The goal of such procedures is a very short recovery time.[256] Although the perioperative results and intermediate-term outcomes of hybrid procedures appear to meet the standards of CABG performed with CPB, no data on long-term outcomes are available.

Patients undergoing OPCAB, MIDCAB, or hybrid coronary revascularization do not have a period on CPB. Therefore, rewarming from hypothermia with the pump is not an option. Surface convective warming is somewhat limited because of the need for intrathoracic surgical exposure and access to the patient. Therefore, heating blankets for patients and a warm operating room environment are essential to prevent unacceptable reductions in body temperature.

CARDIAC VALVE LESIONS

Mitral Valve Disease

In the United States and other industrialized nations, mitral valve disease is usually caused by primary

degenerative (i.e., age-associated) or inherited mitral valvular abnormalities or, increasingly, by ischemic heart disease resulting in functional mitral incompetence. In developing countries, conversely, rheumatic heart disease is relatively more prevalent and therefore a more common cause of mitral valve disease.[257] Primary or "organic" mitral valve disease involves abnormalities in the valve itself or in its subvalvular structural components.[258] Mitral valve prolapse, myxomatous degeneration of the mitral valve, rheumatic mitral insufficiency, cleft mitral valve associated with an AV septal defect, and any infiltrative or fibrotic processes caused by systemic diseases are all associated with inherent structural abnormalities of the mitral valve.

Anatomy of the Mitral Valve. The mitral valve leaflets are composed of segments, more easily discernible in the posterior leaflet, that are sometimes referred to as scallops. In the Carpentier classification scheme, the segments of the posterior leaflet are labeled P1, P2, and P3, with P1 laterally oriented and P3 medial (Fig. 67-21). The segments of the anterior leaflet are labeled A1, A2, and A3 and have the same medial and lateral orientation as the segments of the posterior leaflet (see Fig. 67-21). This terminology is used to ensure accurate communication between the surgeon and the echocardiographer, who is often an anesthesiologist, as they attempt to localize valve abnormalities.

Mitral Stenosis.

Pathophysiology. The disease process of rheumatic mitral stenosis (MS) includes thickening, commissural fusion, and increased rigidity of the mitral valve leaflets, as well as thickening, fusion, and contracture of the chordae and papillary heads. Furthermore, with long-standing rheumatic disease, some degree of calcification of the valve apparatus inevitably occurs. Physiologically, these changes result in obstruction at the level of the mitral valve.

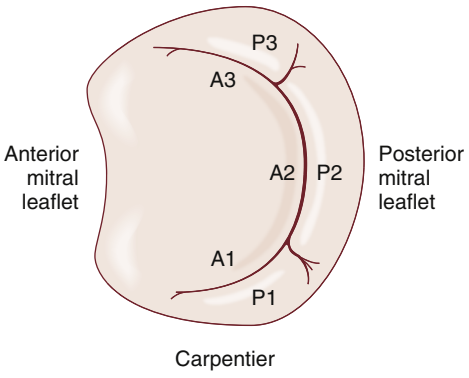


Figure 67-21. Standard terminology as applied to the mitral valve leaflets is illustrated in this image. The anterior and posterior mitral valve leaflets are each divided into three segmental regions. *(From Savage RM, Aronson S, Thomas JD, et al, editors: Comprehensive textbook of intraoperative transesophageal echocardiography, Baltimore, 2005, Lippincott Williams & Wilkins.)*

The normal mitral valve orifice area is approximately 4 to 5 cm^2.[259] Symptoms can occur if the valve area is less than 2.5 cm^2 and can be precipitated by clinical events associated with increased CO and consequent increased flow across the valve; these events include stress, exercise, anemia, pregnancy, and febrile illness (Fig. 67-22). Symptoms do not usually occur at rest unless the mitral valve area (MVA) is less than 1.5 cm^2. Obstructed flow across the mitral valve is associated with a pressure differential or gradient across the valve. The more severe the MS, the greater is the gradient, as long as flow across the valve is held constant.

Transmitral pressure gradients through the mitral valve depend on the volume flow rate. Severe MS may be present with a low measured or calculated gradient across the valve, as in patients with right HF and pulmonary hypertension. An MVA estimate is a more independent measure of the severity of MS. Currently, MS is primarily diagnosed

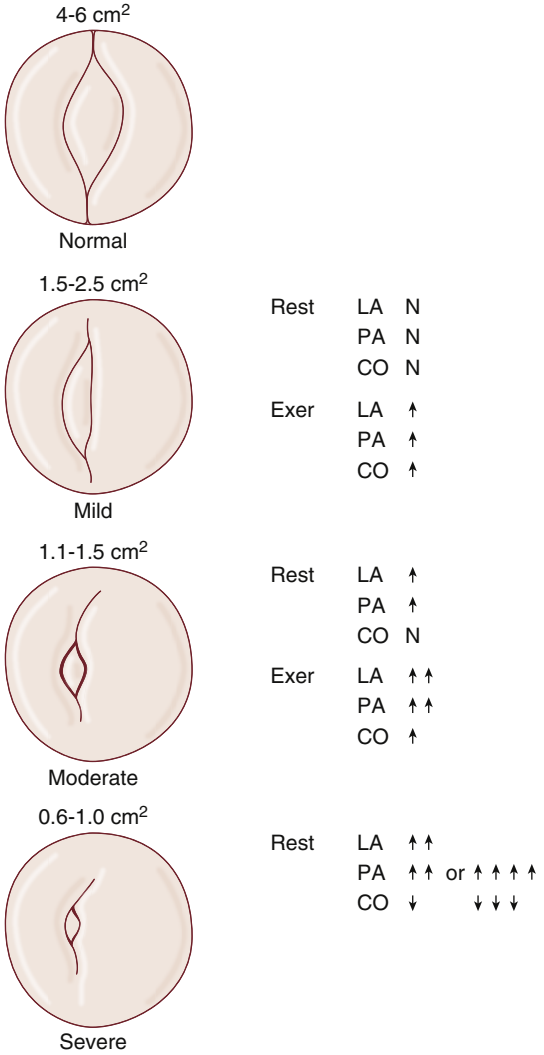


Figure 67-22. Diagrammatic representation of the hemodynamic changes that occur at various stages of severity of mitral stenosis. The valve area is listed above each stage. ↑, increased; ↓, decreased; *CO,* cardiac output; *Exer,* exercise; *LA,* left atrial pressure; *N,* normal; *PA,* pulmonary arterial pressure. *(From Rappaport E: Natural history of aortic and mitral valve disease, Am J Cardiol 35:221-227, 1975.)*

and monitored with echocardiography, although MVA can be calculated during catheterization by using the Gorlin equation.[260] Assessing MS severity by echocardiography involves two-dimensional planimetry of the valve orifice and Doppler-derived measurements of gradient, pressure half-time, and deceleration time. The advent of three-dimensional technology has enabled clinicians to visualize the mitral valve anatomy more accurately (Fig. 67-23).

Management considerations in MS emphasize the pathophysiologic changes that occur in the left atrium, the pulmonary vasculature, the right heart, and the left ventricle. Obstructed mitral inflow with secondary increases in LA pressure (LAP) gradually causes enlargement of the left atrium, which can lead to the onset of atrial fibrillation, thromboembolic complications, or both if low blood flow velocity causes clot formation in the atrium or appendage.

Patients with MS and chronic atrial fibrillation are at increased risk of embolic stroke, at a rate of 7% to 15% per year.[260] Treatment may include anticoagulation with intravenous heparin or oral warfarin, pharmacologic rate control, and pharmacologic or electrical cardioversion for hemodynamically significant or acute-onset atrial fibrillation. In patients scheduled for cardioversion, TEE may need to be performed first to rule out the presence of LA thrombus.[259]

Elevated LAP leads to passive increases in pulmonary venous and arterial pressures. Most patients with MS have a greater PAP than would be expected if PAP were estimated solely from elevations in LAP. These exaggerated pressures are secondary to reactive pulmonary vasoconstriction or histologic changes in the medial and intimal layers of pulmonary arteries and arterioles. PAP sometimes correlates with the severity of MS, but pressures can range widely because of factors such as transmitral pressure gradient, LVEDP, the actual MVA, and a history of chronic pulmonary disease.

The chronic elevation in PAP caused by MS leads to compensatory and decompensatory changes in the right ventricle. Exposure to elevated pressure leads to compensatory RV hypertrophy; however, the response in the right ventricle is less efficient than in the left ventricle because of the shape, wall thickness, and smaller muscle mass of the right ventricle. Because of the right ventricle's relative vulnerability, chronic pulmonary hypertension invariably leads to progressive RV dilation and eventual RV failure.

The effect of MS on the left ventricle is primarily the result of obstruction of diastolic inflow. The narrowed mitral valve orifice leads to prolonged early diastolic mitral inflow and delayed filling of the left ventricle. Late diastolic filling, which occurs during atrial systole, is obviously compromised in patients who have atrial fibrillation secondary to MS. In cases of MS, pressure-volume loops are shifted to the left, so LVEDP and LV end-diastolic volume (LVEDV) are lower. Stroke volume is diminished, especially in clinical situations that result in elevated heart rate and shortened diastolic filling intervals (Fig. 67-24).

LV function or contractility is assumed to be normal in most patients with MS. However, in a review of the literature, Klein and Carroll showed that the assumption of preserved LV contractility in patients with MS is debatable.[261] Instead, the prevalence of LV dysfunction in patients with MS may be as high as 30%. Proposed mechanisms include reduced filling of the left ventricle, muscle atrophy, inflammatory myocardial fibrosis leading to wall-motion abnormalities, scarring of the subvalvular apparatus, abnormal patterns of LV contraction, reduced LV compliance with diastolic dysfunction, increased LV afterload leading to ventricular remodeling, right-to-left septal shift secondary to the effect of pulmonary hypertension on the right ventricle, and coexistent diseases such as systemic hypertension and CAD.[261] The hemodynamic changes associated with MS are summarized in Figure 67-22.



Figure 67-23. Three-dimensional image of a stenotic mitral valve from the left atrial perspective. *(From Lang RM, Tsang W, Weinert L, et al: Valvular heart disease: the value of 3-dimensional echocardiography,* J Am Coll Cardiol *58:1933-1944, 2011).*

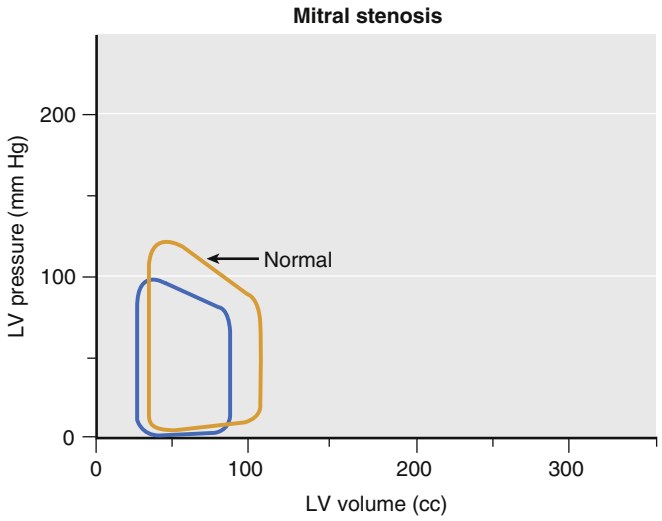


Figure 67-24. Pressure-volume loop in mitral stenosis. *LV,* Left ventricular. *(From Jackson JM, Thomas SJ, Lowenstein E: Anesthetic management of patients with valvular heart disease,* Semin Anesth *1:239, 1982.)*

Anesthetic Management. An understanding and appreciation of the pathophysiologic changes associated with MS form the foundation of anesthetic management in these patients (Table 67-10). Primary concerns in patients with MS include managing ventricular preload, heart rate, and coexisting pulmonary hypertension, as well as potentially diminished RV and LV contractile function. Most patients with valvular heart disease have increased dependency on and sensitivity to ventricular preload. Flow through a stenotic mitral valve requires a higher-than-normal pressure gradient between the left atrium and the left ventricle. Thus, reduction in preload, either from blood loss or from the venodilatory effects of anesthesia, can markedly affect stroke volume, CO, and tissue perfusion. However, in higher grades of MS, LAP may be very high, and the difference between adequate filling pressure and an LAP that leads to congestive failure may be small. Thus, judicious fluid management is required.

In patients with MS, the heart rate should be kept within its normal range. Tachycardia may be poorly tolerated because of the decreased time for diastolic filling. Moreover, pressure gradients are somewhat flow dependent in MS. Elevated flow states, such as pregnancy and increased sympathetic activity from any source, can dramatically increase the pressure gradient across the valve and are reflected in elevated LAP or pulmonary venous pressure. From data obtained by continuous wave Doppler interrogation of the inflow velocities across the mitral valve, the pressure gradient is derived through the use of a modified form of Bernoulli's equation, $\Delta P = 4v^2$, where v is the measured velocity of blood flow through the valve. Thus, any increase in transvalvular flow rate caused by an increase in heart rate has a significant impact on transvalvular flow dynamics and on LAP.

Atrial contributions to stroke volume may be elevated in patients with MS who are in the early stages of the disease and are not in atrial fibrillation. When atrial fibrillation has occurred, the atrial kick is lost. However, the most important factor in the deterioration of the patient's clinical condition is tachycardia itself, rather than loss of the atrial kick.

Contractility and SVR are usually preserved in MS. If anything, the left ventricle is chronically underloaded, but wall motion abnormalities or global systolic dysfunction develop in a small percentage of MS patients. Usually, SVR is not a factor in augmenting forward flow because stroke volume is determined by the mitral valve orifice area and the diastolic filling interval. It may be appropriate to lower SVR for a left ventricle that has marked systolic dysfunction, but care must be exercised because a reduction in afterload is inevitably accompanied by a reduction in preload, which may not be desirable in patients with significant MS.

RV dysfunction probably poses a greater challenge in treating patients with MS than does LV dysfunction. The chronic elevations in LAP can be persistent in patients with long-standing pulmonary hypertension. In the patient with residual pulmonary vascular disease and irreversible pulmonary hypertension, supporting a failing or marginally functional right ventricle becomes the top clinical priority.

Monitoring includes standard noninvasive modalities and invasive monitoring of blood pressure, CVP, and intraoperative echocardiography. Monitoring PAP and using a PA catheter to monitor CO may be very helpful, but care and judgment must be exercised, given the propensity for PA rupture in patients with long-standing pulmonary hypertension. Inotropic support may be needed for patients with secondary RV dysfunction or failure. Epinephrine and milrinone are good therapeutic options. Management of RV dysfunction includes optimizing acid-base balance and using hypocapnia, hyperoxia, and possibly vasodilators to decrease PVR.

Mitral Regurgitation. The complex anatomic structure of the mitral valve is especially pertinent in any consideration of the pathophysiology and management of patients who present for operative intervention for MR. The mitral apparatus consists of six primary components: the LA wall, the annulus of the mitral valve, the mitral valve leaflets, the chordae tendineae, the papillary muscles, and the wall of the left ventricle. Abnormalities or dysfunction in any component can result in mitral valve incompetence.

MR can be classified as either organic (intrinsic valvular disease) or functional (i.e., related to nonvalvular components of the mitral apparatus).[262] It is common for MR to have a functional and an organic component, as in rheumatic valve disease resulting in annular or LV dilation with superimposed abnormalities of leaflet coaptation. In developed countries, the most common causes of MR are as follows: (1) myxomatous degeneration of the mitral valve resulting in annular dilation, chordal elongation and rupture, and redundant, prolapsing, or flail mitral valve leaflets; and (2) mitral insufficiency caused by ischemic heart disease. The most common indication for surgical repair or replacement of the regurgitant mitral valve is myxomatous degeneration, which includes mitral valve prolapse syndromes.[263] Chronic ischemic or functional MR is present in 10% to 20% of patients with CAD and, unlike MR with primary valvular causes, it does not involve abnormalities in the morphology of the mitral valve.[264] Nonetheless, the long-term morbidity and mortality associated with this type of MR are significant.[258]

The severity of MR is assessed in the context of whether the MR is acute or chronic. Symptom presentation,

TABLE 67-10 PATHOPHYSIOLOGIC CHANGES ASSOCIATED WITH MITRAL STENOSIS

	LV Preload	Heart Rate	Contractility	Systemic Vascular Resistance	Pulmonary Vascular Resistance
Mitral stenosis	↑	↓	Maintain	Maintain	↓

From Townsley MM, Martin DE: Anesthetic management for the surgical treatment of valvular heart disease. In Hensley FA, Martin DE, Gravlee GP, editors: A practical approach to cardiac anesthesia, *ed 5, Philadelphia, 2013, Lippincott Williams & Wilkins, p 340.*

LV, Left ventricular.

physical examination, hemodynamics, and echocardiography all provide useful information for ascribing a severity grade (Table 67-11). Echocardiographic assessment is particularly important for guiding intraoperative decisions about the need for intervention and the adequacy of repair or replacement of the mitral valve. As with MS, several echocardiographic parameters, both two-dimensional and Doppler-derived, can be used to grade the severity of MR (Table 67-12). The advent of three-dimensional technology and current calculation software greatly improved clinicians' ability to assess the severity and identify the precise cause of MR (Fig. 67-25).

Pathophysiology. The incompetent mitral valve allows retrograde passage of blood from the left ventricle into the left atrium during systole. The magnitude of the regurgitant volume is a function of the size of the regurgitant orifice, the pressure differential between the left atrium and the left ventricle, and the duration of the regurgitant cycle.[262] Thus, higher systolic driving pressures, as in hypertension, can increase the regurgitant volume. Loading conditions are important as well, especially whenever functional changes in annular and LV geometry are important components of the mechanism of MR. These conditions should be considered during the intraoperative evaluation of MR because anesthetic effects on afterload and preload can drastically alter the severity of MR from its baseline level, as seen in preoperative echocardiographic or catheterization assessments.

LV function and pressure tend to be normal in patients with chronic MR. EF is often normal or supranormal unless the ventricle has decompensated with chronic MR or is acutely ischemic. A normal EF can be misleading, and masked ventricular dysfunction may be revealed after valve repair or replacement. The left atrium serves as a low-pressure pathway during systolic ejection, so that EF overestimates ventricular function.

When MR has an acute onset, LAP is elevated, because LA compensatory changes have had no time to occur. A v wave may be present on the LAP, PAP, or PCWP recordings. In contrast, in chronic MR, the LAP increases are less dramatic because of compliance changes in the left atrium as a function of chamber dilation.

The long-term sequelae of MR are related to chronic pressure and volume effects on the left atrium and the left ventricle. The left ventricle is exposed to a chronic, isolated volume-overload state. Eccentric hypertrophy of the left ventricle develops, causing chamber enlargement without significant increases in wall thickness. Forward CO is preserved because of eccentric hypertrophy and the low impedance of the left atrium—a physiologic equivalent of afterload reduction. The larger stroke volume ejected by the left ventricle is composed of the normal venous return into the left atrium in addition to the regurgitant volume from the previous cardiac cycle. In the early stages of MR, LVEDP is relatively normal because of

TABLE 67-11 ACUTE AND CHRONIC MITRAL REGURGITATION

Characteristic	Chronic Compensated	Chronic Decompensated	Acute
Symptom onset	None	Gradual DOE	Abrupt CHF
Physical Examination			
Blood pressure	Normal	Normal	↓
Pulmonary congestion	None	Variable	↑↑↑↑
Hemodynamics			
LA pressure	Normal	↑	↑↑
v wave	Absent	Variable	↑
Echocardiography			
LV size	↑	↑↑	Normal
LA size	↑	↑	Normal
MR jet v wave	Absent	Variable	↑

From Otto CM: Valvular heart disease: prevalence and clinical outcomes. In Otto CM, editor: Valvular heart disease, *ed 2, Philadelphia, 2004, Saunders, pp 1-17.*

CHF, Congestive heart failure; *DOE,* dyspnea on exertion; *LA,* left atrial; *LV,* left ventricular; *MR,* mitral regurgitation; *arrows* indicate relative increase (*↑*) or decrease (*↓*) in comparison with normal.

TABLE 67-12 CLASSIFICATION OF THE SEVERITY OF MITRAL VALVE REGURGITATION IN ADULTS

	Mitral Valve Regurgitation		
	Mild	**Moderate**	**Severe**
Qualitative			
Angiographic grade	1+	2+	3-4+
Color Doppler jet area	Small central jet (<4 cm^2 or <20% left atrial size)	Signs of MR greater than mild but no severe MR	Vena contracta width >0.7 cm with large central jet (area >40% of left atrium) or with a wall-impinging jet swirling in left atrium
Doppler vena contracta width (cm)	<0.3	0.3-0.69	≥0.7
Quantitative			
Regurgitant volume (mL/beat)	<30	30-59	≥60
Regurgitant fraction (%)	<30	30-49	≥50
Regurgitant orifice area (cm^2)	<0.2	0.2-0.39	≥0.4
Additional Criteria			
Left atrial size			Enlarged
Left ventricular size			Enlarged

From Bonow RO, Carabello BA, Chatterjee K, et al: 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, J Am Coll Cardiol *52:e1-142, 2008.*

MR, Mitral regurgitation.

compliance changes of the left ventricle. With time, however, compensatory eccentric hypertrophy fails to preserve LV systolic function, and gradual systolic failure ensues, as noted on pressure-volume loops (Fig. 67-26). In patients with MR, deciding on the timing of surgical intervention is an important duty of the referring cardiologist because LV systolic performance can deteriorate to a point that full functional recovery after valve surgery may not be possible.

The LA is exposed to increases in volume and pressure. The LA dilates to compensate for the regurgitant volume

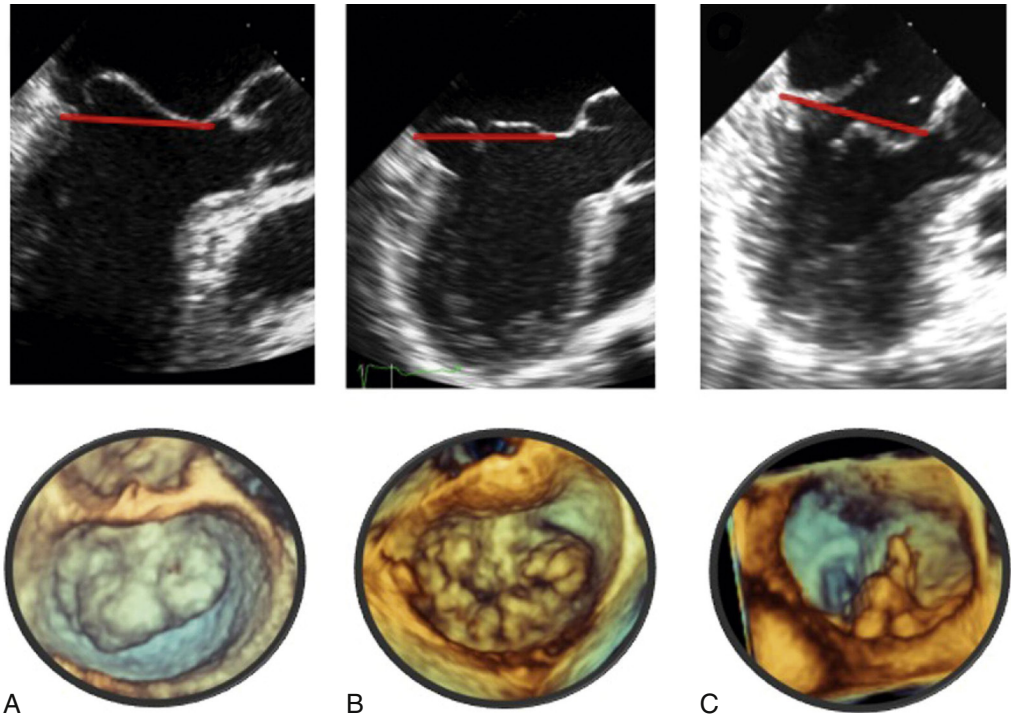


Figure 67-25. Differential diagnosis of mitral leaflet prolapse. Two-dimensional (2D) transesophageal echocardiography (TEE) long-axis view demonstrating anterior leaflet prolapse (**A,** *top*) with a three-dimensional (3D) transesophageal example as seen from the left atrium (**A,** *bottom*). Leaflet prolapse should be diagnosed when the free edge of the leaflet overrides the plane of the mitral annulus during systole. 2D TEE long-axis view demonstrating bileaflet billowing of the mitral valve with prolapse resulting from chordae tendineae elongation (**B,** *top*) with a 3D transesophageal example as seen from the left atrium (**B,** *bottom*). Leaflet billowing is diagnosed when systolic excursion of the leaflet body occurs into the left atrium resulting from excess leaflet tissue, with the leaflet free edge remaining below the plane of the mitral annulus. 2D TEE long-axis view demonstrating flail valve resulting from chordae rupture (**C,** *top*) with a 3D transesophageal example of P2 flail as viewed from the left atrium (**C,** *bottom*). *(From Lang RM, Tsang W, Weinert L, et al: Valvular heart disease: the value of 3-dimensional echocardiography,* J Am Coll Cardiol *58:1933-1944, 2011.)*

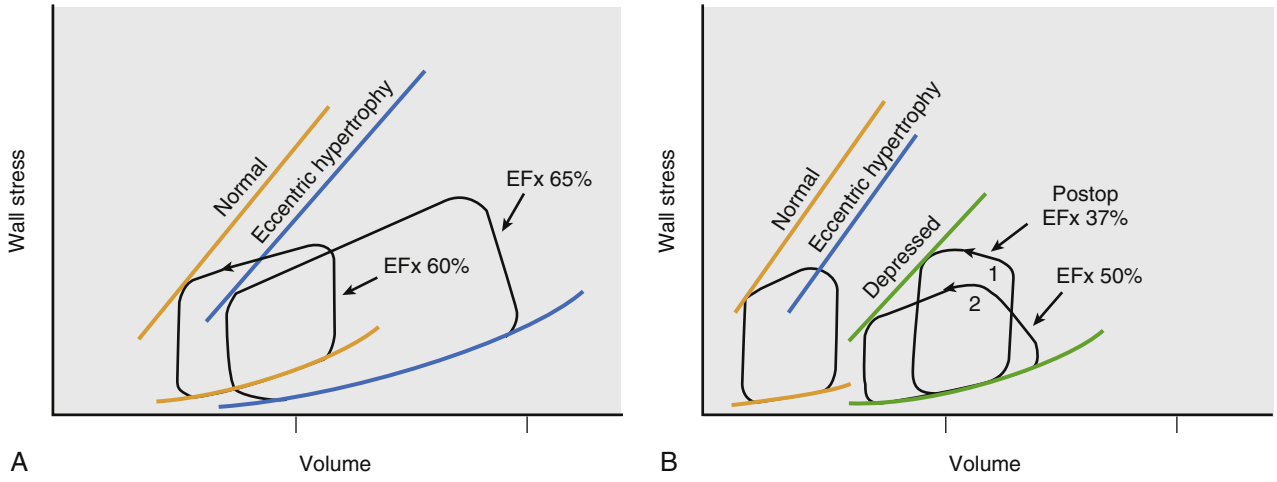


Figure 67-26. Diagram of wall stress–volume loops and end-systolic volume–wall stress relationships in severe mitral regurgitation. **A,** As in aortic regurgitation, the shift to the right of the diastolic and end-systolic relationships allows the volume-overloaded left ventricle to maintain a high stroke volume. Mean wall stress during ejection is somewhat reduced, and in mitral regurgitation the ejection fraction (EFx) is high normal when contractility is normal. **B,** With the development of depressed contractility, the end-systolic wall stress–volume relationship is shifted to the right preoperatively. Despite severely depressed contractility, the ventricle is able to deliver a nearly normal EFx because of the very large ventricular volume and the relatively low mean wall stress during ejection (beat 2, EFx = 50%). Contractility remains depressed after mitral valve replacement (Postop), and with correction of the low-impedance leak, the ventricle must now deliver the total stroke volume into the aorta against higher wall stress; the EFx therefore falls to 37% (beat 1).

during systole, and in the early stages of MR, preservation of near-normal LAP and protection of the pulmonary vasculature is likely. Progressive LA enlargement commonly leads to atrial fibrillation, which occurs in approximately 50% of patients who are about to undergo surgical correction of MR. However, patients with MR appear to be at a lower risk for thromboembolic complications than are patients with MS.

When LAP compliance thresholds are reached, LAP and PAP become elevated. Eventually, if chronically exposed to elevated PAP, the right ventricle progressively enlarges, and RV dysfunction develops.

Anesthetic Management. In the anesthetic management of MR, the primary goal is maintaining forward systemic flow. In chronic, compensated MR, maintaining preload, judiciously reducing afterload, and keeping the heart rate in the high-normal range may be adequate (Table 67-13).

As with most compensated forms of valvular heart disease, patients with hemodynamically significant MR are sensitive to ventricular loading conditions. Augmenting preload may be prudent in the interval before anesthetic induction. However, MR is dynamic; ventricular distention can lead to the expansion of an already dilated mitral annulus and thus worsen MR.

The heart rate should be maintained in the high-normal range (i.e., 80 to 100 beats/minute). Bradycardia has dual detrimental effects on MR: it lengthens the systolic period, thus prolonging regurgitation, and it increases the diastolic filling interval, which can lead to LV distention. A sinus rhythm is preferred, but with less dependency on the atrial kick in chronic, compensated MR than in stenotic valvular heart disease.

LV contractility may be preserved in early compensated MR. However, EF indices are poorly correlated with LV systolic function in patients with moderate to severe MR, and underlying systolic dysfunction may be woefully underestimated. Hypotension in patients with significant MR can be managed to a certain degree by manipulating heart rate and volume, but persistent hemodynamic instability may be best treated with inotropic support. Dobutamine, low-dose epinephrine, and milrinone are all acceptable inotropic choices, depending on the clinician's interpretation of the monitor data.

With respect to SVR, the general rule of thumb for patients with MR is to decrease afterload so that forward CO is maximized. Adequate anesthetic depth, systemic vasodilators, inodilators, and at times, mechanical reduction of afterload with an IABP may be clinical options, depending on the situation. Direct-acting α_1-agonists increase SVR and blood pressure, lower heart rate and may worsen the MR. Temporary use of small doses of ephedrine may be a better choice, after which inotropic support should be considered if a persistent need exists to augment pressure.

Both PAP and PVR may be elevated in patients with either acute or long-standing MR. Secondary changes in RV size and function may be important clinical considerations. Factors that may increase PVR and unfavorably load an already dysfunctional right ventricle (e.g., hypoxia, hypercarbia, and acidosis) should be remedied whenever possible.

Finally, in the patient with acute, severe MR and cardiogenic shock from ischemic rupture of a papillary muscle, pharmacologic support of the left ventricle, often accompanied by mechanical support with IABP counterpulsation, may be necessary.

Hypertrophic Obstructive Cardiomyopathy and the Mitral Valve. Hypertrophic obstructive cardiomyopathy (HOCM) may result in dynamic valvular insufficiency, as well as LV outflow tract (LVOT) obstruction. In addition, surgical attempts to repair an incompetent mitral valve can create iatrogenic LVOT obstruction.

Classically, HOCM is a familial disease transmitted with autosomal dominant inheritance. Inheritance and phenotypic expressions are heterogeneous and vary in their manifestations. Some mutations in genes that code for cardiac sarcomere proteins can cause hypertrophy of segments of the ventricle. Septal involvement is common, but HOCM can involve other areas of the left ventricle as well.[265] This disease is the most common cause of sudden death in young people, but it can also cause death and morbidity in older patients.

When the basal septum of the left ventricle is affected, the LVOT can narrow. Depending on the shape of the ventricle and the mitral valve, dynamic outflow tract obstruction can occur, paired with mitral valve insufficiency. As the outflow tract is narrowed by hypertrophy, the basal septum and the anterior leaflet of the mitral valve come into close proximity. The hypertrophy and the reduced septal–anterior leaflet distance can create a channel that narrows to the point of creating a pressure gradient across the outflow tract. This obstructed flow and its pressure gradient lead to progressive compensatory hypertrophy that, in turn, further narrows the outflow tract and worsens the gradient. As blood is ejected through this narrowed outflow channel during systole, the velocity of blood through the narrowed orifice increases. This increased blood velocity creates a Venturi effect that pulls the anterior leaflet of the mitral valve or the chordal structures into the outflow tract, thus leading to mechanical and dynamic obstruction of the LVOT and also causing MR because of a coaptation defect of the mitral valve.[266] Echocardiographically, this is termed systolic anterior motion (SAM) of the mitral

TABLE 67-13 PATHOPHYSIOLOGIC CHANGES ASSOCIATED WITH MITRAL REGURGITATION

	LV Preload	Heart Rate	Contractility	Systemic Vascular Resistance	Pulmonary Vascular Resistance
Mitral regurgitation	↑ or ↓	↑, maintain	Maintain	↓	↓

From Townsley MM, Martin DE: Anesthetic management for the surgical treatment of valvular heart disease. In Hensley FA, Martin DE, Gravlee GP, editors: A practical approach to cardiac anesthesia, *ed 5, Philadelphia, 2013, Lippincott Williams & Wilkins, p 346.*

LV, Left ventricular.

valve (Fig. 67-27). Such dysfunctional mitral valve motion is seen in cardiac surgical patients who present for surgical management of known HOCM (i.e., for surgical myomectomy, mitral valve repair, or both).

Sometimes, SAM is noted preoperatively or as an incidental finding at the time of surgery in patients who present for surgical revascularization or mitral valve repair. Furthermore, SAM may be created iatrogenically as a result of surgical mitral valve repair. In patients with MR who are to undergo mitral valve repair, echocardiographic assessment and surgical inspection are performed to elucidate the mechanism of the mitral insufficiency. The patient may have ruptured or elongated chordal attachments, redundant or prolapsing leaflet tissue, or annular dilation that reduces effective leaflet coaptation. Frequently, multiple contributing factors are present. Surgical treatment can involve just a simple annuloplasty ring in the case of isolated annular dilation, but it more commonly involves resection of diseased segments of the mitral valve, possibly chordal reassignment or reconstruction, and a ring valvuloplasty.

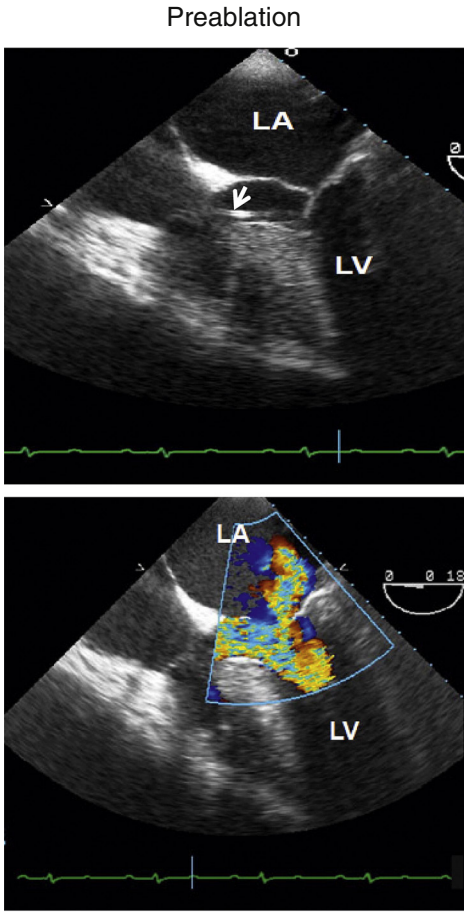


Figure 67-27. Transesophageal echocardiographic images. *Top,* Two-dimensional image shows a narrowed left ventricular outflow tract with systolic anterior motion (*arrow*). *Bottom,* Color Doppler image shows high-velocity signals in mosaic color; eccentric mitral regurgitation is directed posterolaterally. *LA,* Left atrium; *LV,* left ventricle. *(From Naguch SF, Bierig M, Budoff MJ, et al: American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with hypertrophic cardiomyopathy,* J Am Soc Echocardiogr *24: 473-498, 2011.)*

Depending on LV geometry and size and the physical characteristics of the mitral valve, surgical repair may bring the anterior leaflet and the coaptation point of the valve into close approximation with the interventricular septum and the LVOT. That septal coaptation point can narrow enough to create a gradient in the outflow tract, so that the anterior leaflet is pulled into the LVOT by the Venturi effect, leading to obstruction and secondary mitral insufficiency. This anterior displacement of the mitral coaptation point and the amount of the extra anterior leaflet have been proposed to be mechanisms for SAM, thus leading to the development of surgical techniques that can reduce the incidence of SAM in high-risk patients.[267] Anesthetic management of obstructive cardiomyopathy centers on fluid and pharmacologic interventions to decrease the magnitude of the obstruction and, at the same time, lessen the severity of the mitral insufficiency. Most patients with outflow tract abnormalities have normal to supranormal contractility.

Generally, inotropic agents should not be used. The thick, hypertrophied ventricle usually has reduced compliance and is very load sensitive, so that outflow tract obstruction increases in hypovolemic conditions. Thus, optimizing preload and ventricular filling is appropriate both in managing the patient with LVOT and in assessing the need for surgical reconstruction of the LVOT, mitral valve repair, or both. Afterload reduction should be avoided because it worsens the obstruction. Conversely, increasing the afterload decreases the trans–outflow tract gradient and leads to a reduction of SAM and outflow tract obstruction. Hence, vasoconstrictors such as phenylephrine and vasopressin should be considered. In both congenital and iatrogenic LVOT obstruction, the degree of obstruction is dynamic. Obstruction is exacerbated by hypercontractile states and elevations in heart rate; therefore, reducing the heart rate with β-adrenergic blockade should be considered.

Continuous, skilled echocardiographic assessment and interpretation are important for optimal intraoperative management of these patients. Assessing the severity and mechanism of outflow tract obstruction and determining whether to reinstitute CPB to revise the repair or replace the valve are not innocuous decisions, and they must be carefully made jointly by the anesthesiologist and the surgeon, ideally with input from the appropriate cardiologist.

Aortic Valve Disease

Aortic Stenosis

Pathophysiology. AS is the most common cardiac valve lesion diagnosed in the United States. Marked increases in the annual volume of aortic valve replacements have occurred recently, especially in older and high-risk patients.[268]

AS is often caused by congenital defects in the valve because 1% to 2% of people are born with a bicuspid aortic valve.[268] Inheritance has been found to play a role, with an autosomal dominant pattern and a variable penetrance.[269] A bicuspid aortic valve that does not yet show any signs of damage nevertheless tends to open and close with abnormal folding and creasing, leading to scarring and calcification and ultimately culminating in AS with or without aortic regurgitation (AR). Although patients with a bicuspid

aortic valve are asymptomatic until late in the disease process, severe, symptomatic AS or AR may develop in midlife. In addition, the abnormal motion of these bicuspid leaflets causes some turbulent flow into the aorta, which eventually can lead to dilatation and subsequent rupture or dissection.[270,271] A typical "fish-mouth" opening of the aortic valve in a midesophageal, cross-sectional TEE view of the valve is a telltale sign of a bicuspid aortic valve.

Acquired AS is usually the result of senile degeneration with sclerosis and calcification of the valve. The prevalence of AS increases with age; it is now seen in 2% to 4% of adults who are older than 65 years old, and this prevalence is expected to increase.[268,272] A clear association is reported between clinical risk factors for atherosclerotic disease (e.g., the process of chronic inflammation) and the development of AS.[272,273] In developed countries, rheumatic disease is a less common cause of AS, and AS is usually associated with concomitant AR.

A typical pressure-volume loop for AS is shown in Figure 67-28. In patients with AS, the obstruction of LV outflow increases peak systolic wall stress, resulting in chronic pressure overload that directly stimulates parallel replication of sarcomeres in the left ventricle and consequently causes concentric ventricular hypertrophy. The peak pressure generated by the left ventricle during systole is much higher than normal because of the high transvalvular pressure gradient. Concentric LV hypertrophy nearly always develops as a result of the increases in pressure load (Fig. 67-29). This increased load also leads to diastolic dysfunction, an increase in LVEDP, and subendocardial ischemia.

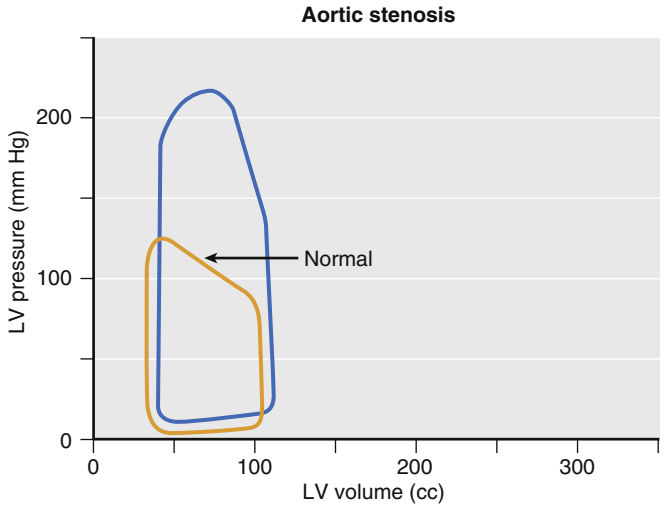


Figure 67-28. Pressure-volume loop in aortic stenosis. *LV,* Left ventricular. *(Modified from Jackson JM, Thomas SJ, Lowenstein E: Anesthetic management of patients with valvular heart disease,* Semin Anesth *1:239, 1982.)*

Echocardiography and intraoperative TEE in particular play important roles in the diagnosis and ultimate management of patients with AS, both in the outpatient setting and during surgical aortic valve replacement. The severity of AS can be assessed from various echocardiographic parameters. One that is commonly used is the aortic valve area (AVA). The normal range of the AVA is 3 to 4 cm^2; AS is graded as severe if the AVA is reduced to 1 cm^2 or less.[274] Another parameter commonly used to determine the severity of AS is the gradient across the aortic valve; AS is considered severe if the mean gradient is greater than 40 mm Hg.[259] Echocardiography can be used to examine multiple aspects of the pathophysiology of AS, including the severity of AS, any structural abnormalities of the valve causing LVOT obstruction, and any accompanying disease that can be found in the other heart valves.

With TEE, the best views for evaluating the aortic valve are the midesophageal aortic valve short-axis view, the midesophageal long-axis view, and the transgastric views. Midesophageal views are helpful in ascertaining the shape of the aortic valve and the cause of AS (Fig. 67-30), whereas transgastric views are helpful in obtaining gradient measurements across the valve and the LVOT (Fig. 67-31). In addition, both the midesophageal and the transgastric views can be used to measure the dimensions of the aortic valve annulus and the LVOT; these measurements are helpful in making surgical decisions related to the size of the valve.

Patients with AS who have not yet developed symptoms should be closely monitored over time for progression of the disease. Patients who develop symptoms (including decreased exercise tolerance and exertional dyspnea, angina, CHF, and syncope) are considered for valve replacement. A delay in surgical intervention in symptomatic patients can worsen their prognosis.[272]

ANESTHETIC MANAGEMENT. Premedication may alleviate a patient's anxiety regarding cardiac surgery, and it helps to prevent perioperative tachycardia in patients with AS.

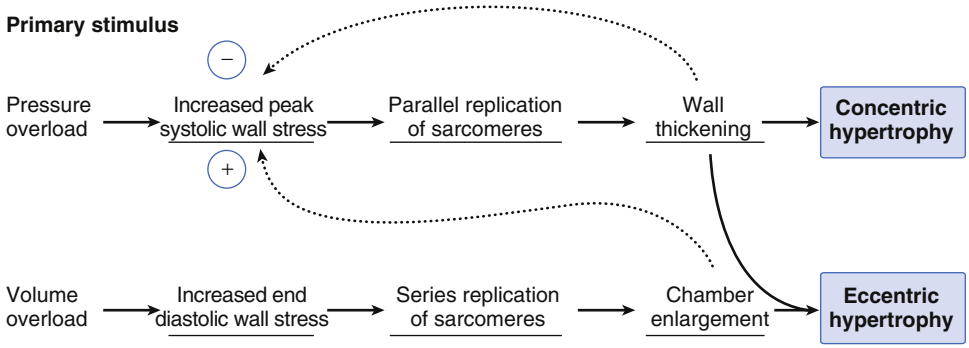


Figure 67-29. The increased peak systolic wall stress resulting from chronic pressure overload directly stimulates concentric ventricular hypertrophy, which tends to counteract or "normalize" the elevated ventricular wall stress. *(From Grossman W, Jones D, Mclaurin LP: Wall stress and pattern of hypertrophy in the human left ventricle,* J Clin Invest *56:56, 1975.)*

Monitoring in these patients includes standard noninvasive modalities and invasive monitoring of blood pressure and CVP. Depending on the severity of the AS, pulse pressure may be as low as 50 mm Hg or less. Insertion of a PA catheter may be considered to monitor PAP and CO during surgical procedures and particularly in the postoperative period. However, patients with AS are at risk for developing dangerous arrhythmias during PA catheter placement. TEE is almost always used if no contraindications to probe placement exist; the measurements obtained yield extremely valuable information (Fig. 67-32; see also Figs. 67-30 and 67-31).[275,276]

The anesthetic management of patients with AS centers on avoiding fluctuations in the patient's hemodynamics while achieving adequate anesthetic depth. Induction of anesthesia should not involve any medication that could have negative inotropic or vasodilatory effects. Any drugs that could cause tachycardia should also be avoided. Furthermore, every effort should be made to ensure that the patient stays in sinus rhythm. In patients with AS, the atrial kick may contribute as much as 40% of the total CO. Therefore, to treat any possible arrhythmia, external cardioversion pads should be considered, preferably before anesthesia is induced.

Finally, the presence of severe AS reduces the usefulness of cardiopulmonary resuscitation (CPR) for maintaining CO sufficient to meet the patient's physiologic needs. Table 67-14 summarizes the goals of anesthetic care of a patient with AS.

Aortic Regurgitation

Pathophysiology. AR is the flow of blood from the aorta backward into the left ventricle during the diastolic phase of the cardiac cycle. Chronic AR is more prevalent than acute AR and carries a much better prognosis. However, the precise prevalence of AR—acute and chronic—remains unknown.[277]

Chronic AR and acute AR have their own etiologies. Causes of chronic AR include congenital lesions, degenerative processes, and rheumatic disease, but idiopathic causes seem to be the most common.[277] These processes cause malcoaptation of the aortic valve leaflets by producing abnormalities in the leaflets themselves or dilation of the aortic valve annulus, the aortic root, or both. Abnormalities of the aortic valve leaflets include congenital conditions (e.g., bicuspid aortic valve), endocarditis, rheumatic disease, inflammatory diseases, certain connective tissue diseases, and chest wall trauma causing injury to an aortic valve leaflet. Dilation of the proximal aortic root may be caused by annuloaortic ectasia resulting from long-term chronic hypertension or simply from

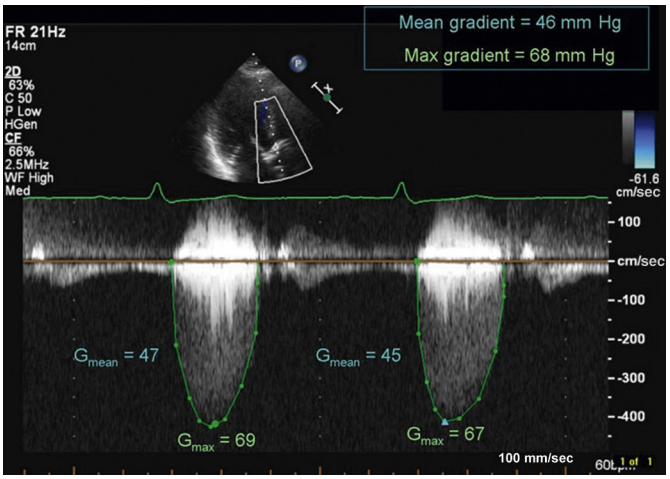


Figure 67-31. Quantification of the degree of aortic stenosis with continuous Doppler. G_{max}, maximum gradient; G_{mean}, mean gradient. *(From <http://web.stanford.edu/group/ccm_echocardio/cgi-bin/mediawiki/index.php/Aortic_stenosis_assessment>. [Accessed 21.08.14])*

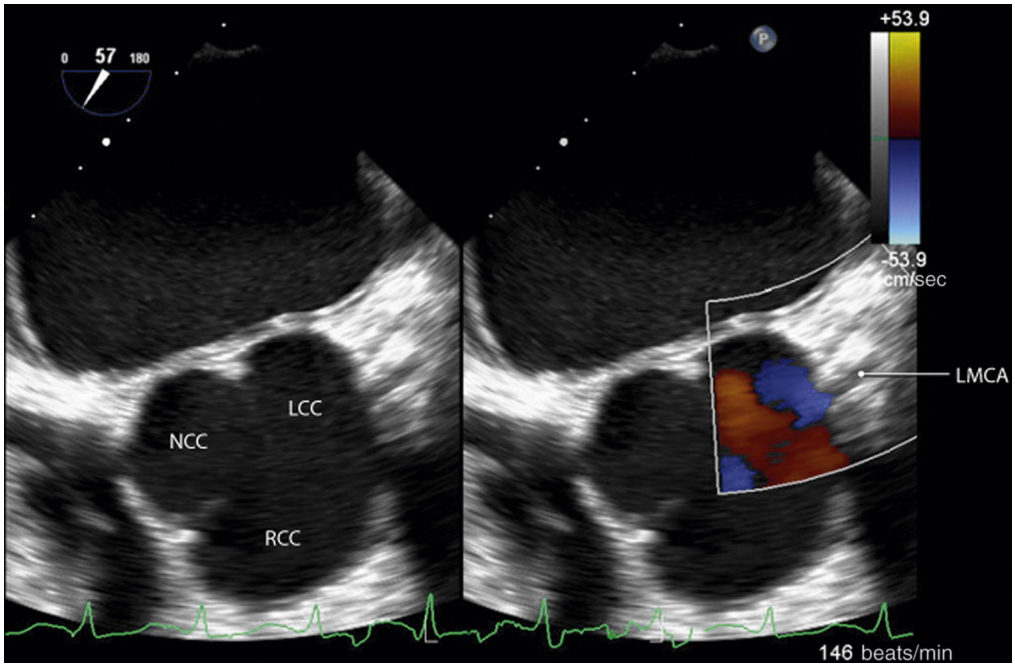


Figure 67-30. Midesophageal aortic short-axis view. *LCC,* Left coronary cusp; *LMCA,* left main coronary artery; *NCC,* noncoronary cusp; *RCC,* right coronary cusp. *(From Virtual TEE: <http://pie.med.utoronto.ca/tee>.)*

the normal aging process.[278] Other aortic valve annular or aortic root causes of AR include Marfan syndrome, syphilis, congenital diseases such as osteogenesis imperfecta and Ehlers-Danlos syndrome, and idiopathic causes.[277,278]

Chronic Aortic Regurgitation. Patients with chronic AR may remain asymptomatic for years or even decades. The left ventricle undergoes a process of remodeling resulting from series replication of sarcomeres and the development of eccentric ventricular hypertrophy and chamber enlargement in the presence of a chronically increasing volume of regurgitation (see Fig. 67-29). Although the pressure-volume loop is shifted far to the right in patients with chronic AR, the LVEDP remains relatively normal because the LVEDV increases slowly (Fig. 67-33). Forward flow is improved by peripheral vasodilation. Typically, a normal EF is maintained by a large stroke volume. However, over time, increases in LV wall stress and afterload result. Eventually, as LV dilation and hypertrophy progress, irreversible LV dysfunction develops, and patients become symptomatic. As a compensatory mechanism for poor CO, sympathetic constriction of the peripheral vasculature occurs to maintain blood pressure, but this adaptation exacerbates regurgitation and further reduces CO.

In addition to a detailed history and physical examination, diagnostic modalities such as magnetic resonance imaging, radionuclide angiography, and exercise stress testing are used to assess AR. However, echocardiography remains the most important diagnostic tool (Fig. 67-34). The severity of AR is assessed qualitatively: regurgitation of less than 20% of the total LV stroke volume is considered mild, 20% to 39% is considered moderate, 40% to 60% is considered moderately severe, and more than 60% is considered severe.

Several semiquantitative echocardiographic modalities are used to assess AR. These include color flow mapping, in which the ratio of the AR jet width to the width of the LVOT is used to ascertain the severity of the condition. Jets that appear to be central in flow may appear to be larger than they actually are because of the entrainment of fluids.[277] This possibility should be considered when one is evaluating a centrally directed jet as compared with an eccentrically directed jet. The vena contracta, the narrowest part of the regurgitant jet, can be measured to determine the severity of AR (see Fig. 67-34). A vena contracta measurement of 6 mm or greater carries a sensitivity of 95% and a specificity of 90% for the presence of severe AR.[279] A vena contracta of less than 0.3 mm indicates mild AR. The pressure half-time of the AR jet can be measured echocardiographically. A pressure half-time of less than 200 msec indicates severe AR. In addition, holodiastolic flow reversal in the descending aorta signifies moderate-to-severe AR.

Although patients with chronic AR can remain asymptomatic for decades, symptoms of left-sided HF eventually occur, such as exercise intolerance, dyspnea, and paroxysmal nocturnal dyspnea or orthopnea. Afterload reduction may become necessary as the disease progresses. In addition, a few patients present with angina despite having normal coronary arteries; this angina results from poor coronary perfusion resulting from low diastolic aortic pressure. A difficult decision for the cardiologist is at what point

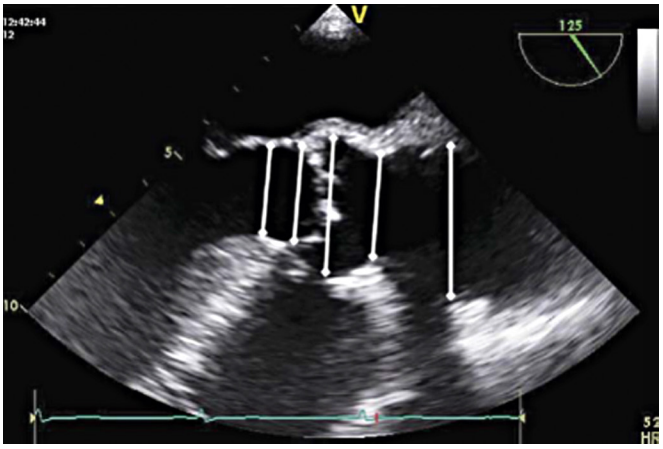


Figure 67-32. Intraoperative transesophageal echocardiographic measurements of the aortic valve annulus, including the diameter of the left ventricular outflow tract (to exclude severe asymmetric septal hypertrophy), aortic valve annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta (*arrows, from left to right*). *(From Pasic M, Buz S, Dreysse S, et al: Transapical aortic valve implantation in 194 patients: problems, complications, and solutions,* Ann Thorac Surg *90:1463-1469; discussion 1469-1470, 2010.)*

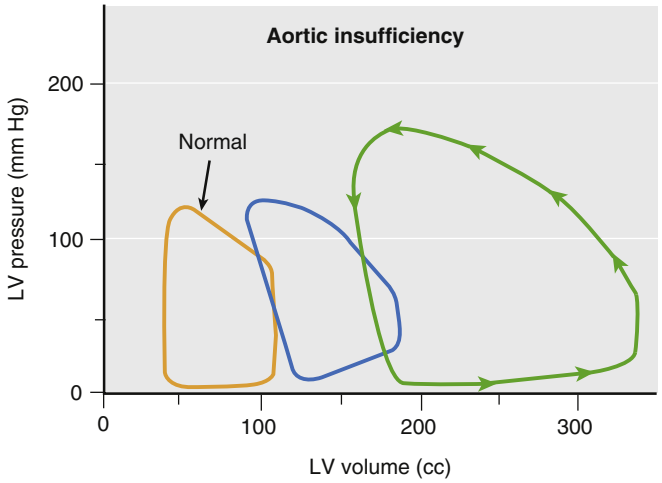


Figure 67-33. Pressure-volume loop in aortic regurgitation (AR). Acute AR, *middle loop;* chronic AR, *right loop. LV,* Left ventricular. *(Modified from Jackson JM, Thomas SJ, Lowenstein E: Anesthetic management of patients with valvular heart disease,* Semin Anesth *1:239, 1982.)*

TABLE 67-14 **PATHOPHYSIOLOGIC CHANGES ASSOCIATED WITH AORTIC STENOSIS**

	LV Preload	Heart Rate	Contractility	Systemic Vascular Resistance	Pulmonary Vascular Resistance
Aortic stenosis	↑	↓ (sinus)	Maintain constant	↑	Maintain constant

LV, Left ventricular.

From Townsley MM, Martin DE: Anesthetic management for the surgical treatment of valvular heart disease. In Hensley FA, Martin DE, Gravlee GP, editors: A practical approach to cardiac anesthesia, *ed 5, Philadelphia, 2013, Lippincott Williams & Wilkins, p 327.*

in the course of the disease surgery should be performed to prevent the development of irreversible LV dysfunction, especially in patients with severe chronic AR.[276,277]

Acute Aortic Regurgitation. Acute AR is less common than chronic AR but carries a more ominous prognosis. Common causes of acute AR include trauma, bacterial endocarditis, and aortic dissection. Rarely, acute AR occurs as an idiopathic complication, such as after aortic valvuloplasty. The focus of the pathophysiology of acute AR is that it causes an acute increase in the volume coming into the left ventricle. Because the left ventricle has not had time to undergo the process of eccentric hypertrophy, as it does in chronic AR, it is unprepared to accommodate this sudden increase in volume. As shown in Figure 67-33, this sudden increase in the LVEDP causes a rightward shift in the pressure-volume loop.[278] A sympathetic response is activated; tachycardia and an increased contractile state are the chief compensatory mechanisms for maintaining adequate CO. Unless acute AR is managed appropriately, these compensatory mechanisms rapidly fail. Furthermore, the sympathetic response causes sympathetic constriction of the peripheral vasculature, thereby increasing SVR and further worsening the AR. LV function can deteriorate rapidly, necessitating emergency surgery. Vasodilator therapy may temporarily stabilize the patient during transport to the operating room.[277]

Anesthetic Management. The anesthetic management of patients with AR should include maintaining a relatively fast heart rate (≈90 beats/minute) and a relatively low SVR while maintaining preload and contractility. Table 67-15 summarizes the goals of anesthetic care for a patient with AR. Light premedication is recommended. Regarding the choice of drugs for general anesthesia in these patients, medications that cause bradycardia or high blood pressure should be avoided because these changes worsen the degree of AR and can precipitate LV failure.

Preoperative placement of an arterial catheter and central venous catheter is standard, and a PA catheter may be considered if PAPs are high. In the prebypass period, TEE allows the anesthesiologist to determine the cause and severity of the AR, evaluate LV size and function, and assess the function of the other cardiac valves. Furthermore, TEE assessment in the immediate postbypass period confirms the proper positioning and function of the new aortic valve.

Weaning from CPB may be complicated by preexisting LV dysfunction. Furthermore, mechanical aortic valve replacement results in a mild transvalvular pressure gradient. Therefore, inotropic agents may be needed to improve LV function. Preload augmentation must be continued to maintain the filling of the dilated left ventricle.

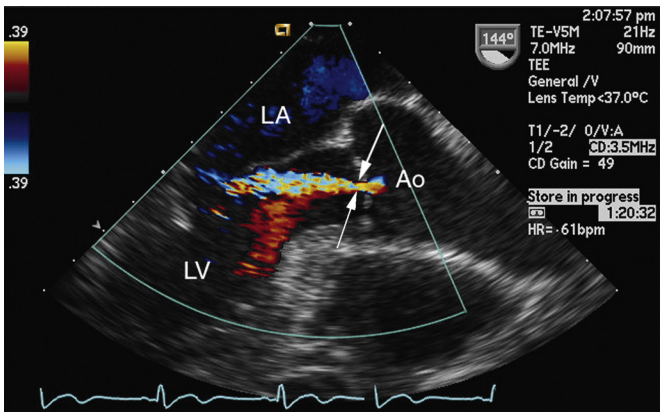


Figure 67-34. Vena contracta. Calipers measure the narrowest portion of the aortic regurgitant jet, which corresponds to an approximation of the regurgitant orifice area. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle. *(From Perino AC, Reeves ST, editors:* A practical approach to transesophageal echocardiography, *ed 2, Philadelphia, 2008, Lippincott Williams & Wilkins, p 232.)*

Other Valvular Disease

Tricuspid Valve Disease

Tricuspid Regurgitation. Right-sided valvular disease in adults is most often a manifestation of pulmonary hypertension secondary to intrinsic lung disease, pulmonary vascular disease, or left-sided cardiac disease. Primary TR can be rheumatic, traumatic, or infectious. Secondary or functional TR can be a manifestation of cor pulmonale, primary pulmonary hypertension, or left-sided cardiac disease that results in elevated pulmonary vascular pressures. Functional TR is frequently present in patients undergoing aortic and particularly mitral valve surgery. Severe TR is now considered a class 1 indication for concomitant tricuspid valve repair or replacement in patients undergoing left-sided heart valve surgical procedures.

Tricuspid valvular disease is predominately regurgitant. Patients with significant TR may have symptoms of dyspnea and evidence of elevated RA pressure (e.g., hepatomegaly, peripheral edema). Compensatory changes with long-standing TR involve RV and RA chamber dilation. Because of RA enlargement, many patients exhibit atrial fibrillation. Long-standing TR and RV enlargement can result in RV systolic dysfunction, which leads to further chamber enlargement, tricuspid annular dilation, and worsening of TR severity. If the tricuspid insufficiency is secondary to RV pressure overload states, as with pulmonary hypertension, RV hypertrophy ensues. This hypertrophy and increased RV pressure can lead to leftward displacement of the interventricular septum and impaired *LV* systolic and diastolic performance.

Anesthetic management concerns include preload preservation and appropriate inotropic support as

TABLE 67-15 **PATHOPHYSIOLOGIC CHANGES ASSOCIATED WITH AORTIC REGURGITATION**

	LV Preload	Heart Rate	Contractility	Systemic Vascular Resistance	Pulmonary Vascular Resistance
Aortic regurgitation	↑	↑	Maintain	↓	Maintain

LV, Left ventricular.

From Townsley MM, Martin DE: Anesthetic management for the surgical treatment of valvular heart disease. In Hensley FA, Martin DE, Gravlee GP, editors: A practical approach to cardiac anesthesia, *ed 5, Philadelphia, 2013, Lippincott Williams & Wilkins, p 335.*

dictated by the clinical situation. If the TR is secondary to elevations in pulmonary vascular pressure or resistance, efforts to reduce PVR will be beneficial. Forward flow can be maximized by high-normal heart rates. Surgical annuloplasty, although usually successful, can leave residual TR or create an elevated pressure gradient across the tricuspid valve.[279]

Tricuspid Stenosis. Tricuspid stenosis (TS) is a relatively rare clinical finding in adults. Patients with TS may have significant RA enlargement and possibly atrial fibrillation. Chronic elevation of RA pressure leads to IVC dilation, jugular venous distention, and hepatic congestion. Clinical symptoms and signs can include hepatomegaly (with or without hepatic dysfunction), ascites, peripheral edema, fatigue, and dyspnea.[279,280]

TS results in reduced RV filling. The normal tricuspid valve area is 7 cm^2, and ventricular filling is compromised once the valve area falls to less than 1.5 cm^2. The severity of TS is usually assessed echocardiographically by measuring the Doppler-derived transvalvular gradient. Mild TS is associated with a gradient of 2 mm Hg or less; moderate TS, 2 to 6 mm Hg; and severe TS, greater than 6 mm Hg.[281]

Anesthetic management centers on maintaining preload and controlling heart rate. Overt tachycardia should be avoided because it significantly shortens the interval for diastolic filling, which must be prolonged in these patients. The target heart rate is not frank bradycardia, because CO may not be optimal, but the heart rate should be in the low-normal range. When atrial fibrillation is not part of the clinical picture, preserving AV synchrony is important for maintaining RV output. Although RV inotropic failure is not usually a major concern in isolated TS, it may be when TS is a part of multivalvular heart disease or ischemic heart disease, thus warranting consideration of inotropic support. SVR should be maintained because the fixed obstruction at the level of the tricuspid valve prevents a compensatory increase in preload if afterload declines.

Pulmonic Valve Disease

Pulmonic Stenosis. Pulmonic valvular disease can be congenital or acquired. Pulmonic stenosis (PS) is caused by congenital valve abnormalities in 95% of cases.[279] Elevated transvalvular pressure gradients lead to RV hypertrophy, dilation, and eventual failure. Treatments include balloon valvuloplasty, surgical valvotomy, and valve replacement. Subvalvular muscular infundibular obstruction can result from long-standing PS. Tachycardia and hypovolemia can precipitate a dynamic clinical condition in which outflow tract obstruction is accentuated. Management strategies include judicious heart rate control, preload maintenance, and inotropic support if RV systolic failure occurs.

Pulmonic Insufficiency. Pulmonic insufficiency (PI) can result when pulmonic valves are rendered incompetent during childhood balloon valvuloplasty for congenital PS or surgical valvotomy for tetralogy of Fallot or its variants. PI may also be associated with rheumatic heart disease, pulmonary embolus, carcinoid syndrome, trauma, Marfan syndrome, idiopathic dilation of the pulmonary trunk, and endocarditis.[279] Most patients are asymptomatic, but long-standing severe PI can lead to symptomatic RV dilation and failure, warranting replacement of the pulmonic valve.

Anesthetic management requires being mindful of the primary cardiac or pulmonary disease that led to the pulmonic valvular insufficiency (e.g., endocarditis, emboli, and multifactorial causes of pulmonary hypertension). In primary PI, anesthetic management goals may include maintaining preload, supporting contractility, and reducing PVR by lowering the $Paco_2$ and increasing the fraction of inspired oxygen (FiO_2).

Minimally Invasive Valve Surgery

Cosgrove, Sabik, and Cohen were among the first surgeons to modify the traditional approach to cardiac surgery and pioneer the concept of minimally invasive cardiac surgery.[282] The rapid development and refinement of minimally invasive techniques have resulted in the realizations that minimally invasive cardiac surgery does not compromise patients' safety or surgical exposure and that results are comparable to those of traditional open procedures. Mihaljevic and colleagues published a series of 1000 minimally invasive valve operations performed between 1996 and 2003 and noted the following benefits: reduced bypass and cross-clamp times, reduced stroke and MI rates, reduced length of hospital stay, and a higher rate of discharges home rather than to another facility.[283]

Minimally Invasive Aortic Valve Surgery. The surgical approach to the aortic valve can be made through several different incisions, including a right parasternal incision, upper hemisternotomy, or lower hemisternotomy.[282] To achieve arterial access, a surgical decision may be made to cannulate the femoral artery.[283] Alternatively, if aortic atheromatous disease precludes retrograde aortic arterial flow, the surgeon may attempt aortic cannulation through an incision directly into the aorta, or through the axillary artery.[282,284] Venous bypass drainage can be accomplished by cannulating the right atrium (if surgical exposure is not compromised) or through the femoral vein. Positioning of the distal drainage portion of the femoral vein cannula in the IVC, right atrium, or distal segment of the SVC is guided and confirmed by TEE (Fig. 67-35).[283] To reduce the incidence and magnitude of retained intracavitary LV air, carbon dioxide can be insufflated into the surgical field.[282] Because surgical exposure is limited, sterile transcutaneous defibrillator pads should be placed before preparing and draping, should the need to defibrillate arise.[284]

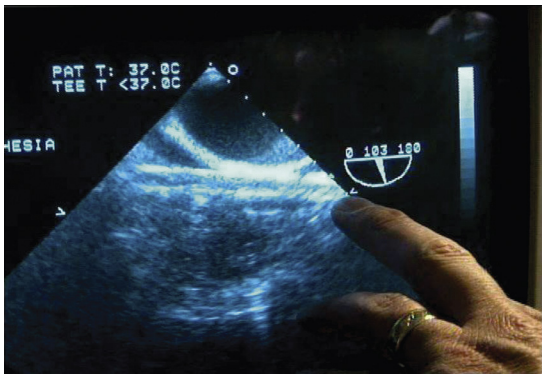


Figure 67-35. Venous cannula placement through the inferior vena cava–right atrium into the superior vena cava.

In general, anesthetic monitoring considerations are similar to those for standard approaches to valvular heart surgery. However, in the absence of direct visualization, TEE is even more valuable in these procedures because of the importance of assessing bypass cannula placement and ensuring adequate ventricular de-airing.[284] If retrograde cardioplegia is required, TEE may be used to guide a transjugular retrograde catheter into the coronary sinus.

One report of a large series of minimally invasive aortic valve procedures included more than 900 patients. Compared with the national average, these patients had decreased blood product use (with 53% of first-time aortic valve surgery patients receiving no blood products) and higher rates of discharge home (including 40% of the octogenarian patients).[285]

Minimally Invasive Mitral Valve Surgery. The mitral valve can be accessed through a lower hemisternotomy, a right parasternal incision excising the cartilaginous portions of the third and fourth ribs, or a right thoracotomy through a 4-cm incision.[286] The mitral valve is then exposed through the left atrium or by a transseptal approach through the right atrium. Visualization of the valve for repair or replacement can be achieved in the following ways: by direct inspection and instrumentation; by "port access" under thoracoscopic guidance and video assistance, which can involve voice-activated, robotic movement of the thoracoscopic instruments; or by a more complete endoscopic technique using the DaVinci robotic system (Intuitive Surgical, Inc., Sunnyvale, Calif) (see also Chapter 86). The DaVinci system uses robotic arms and instrumentation controlled by the surgeon sitting at a remote, computer-enhanced, three-dimensional imaging console to assist in completing the surgery.[287]

Endoscopic or minimally invasive mitral procedures usually involve CPB with aortic and venous cannulas placed through the femoral artery and vein. In addition, the surgeon may choose to use novel aortic occlusion devices that allow a bloodless operative field and the delivery of cardioplegia (Fig. 67-36). However, this catheter is challenging to position in the aortic root and necessitates intraoperative fluoroscopy or echocardiography to confirm the catheter's position definitively. Known concerns and risks include catheter migration into the heart across the aortic valve and distal migration with occlusion of the brachiocephalic trunk.[284] Alternatively, the aorta can be occluded directly with flexible cross-clamps introduced through small chest wall incisions. The Chitwood transthoracic aortic cross-clamp (Scanlan International, Inc., St. Paul, Minn) and the Cosgrove Flex Clamp (Cardinal Health, McGaw Park, IL) are being used for this purpose (Fig. 67-37).[286] Cardioplegia needles may be inserted under direct vision or thoracoscopic guidance.[284] Retrograde cardioplegia, although not necessarily used in all patients, can be accomplished by directly cannulating the coronary sinus with a retrograde catheter at the operative site (RA approach) or by placing a percutaneous coronary sinus catheter in the internal jugular vein and positioning it under echocardiographic guidance. Secondary operative considerations include the unique positioning of the patient for the use of robotic instrumentation. Most minimally invasive approaches require a 30-degree "right side up" position.

Regarding anesthetic management, adequate surgical visualization often necessitates offering selective lung ventilation with the use of a double-lumen tube or bronchial blocker. Monitoring considerations are similar to those for standard approaches to valvular heart surgery, including a five-lead ECG, an invasive arterial catheter, and central venous access. Furthermore, a PA ventilation (PA vent) catheter is placed in a manner similar to placement of a PA catheter.[284] These two catheters differ in two important ways. First, the PA vent is flimsier than a PA catheter; therefore, during its placement, the anesthesiologist will encounter a significant amount of noise in the tracings. Second, the PA vent does not have as many ports as a PA catheter does, which means that the cardiac anesthesiologist cannot monitor the $S\bar{v}O_2$ and CO or cardiac index.

The outcomes of minimally invasive mitral valve surgery have been encouraging**.** Although prospective trials comparing minimally invasive mitral valve surgery and standard approaches are limited, developments in technology and an integrated team approach may facilitate favorable postoperative outcomes.[286] Reports describe mortality and morbidity rates comparable to those of full-sternotomy approaches, with reduced postoperative bleeding and trends toward reduced length of hospital stay and a higher rate of discharge home.[282,283]

Transcatheter Aortic Valve Implantation. Symptomatic patients with severe AS have a poor prognosis; the mortality at 1 year in medically treated patients is

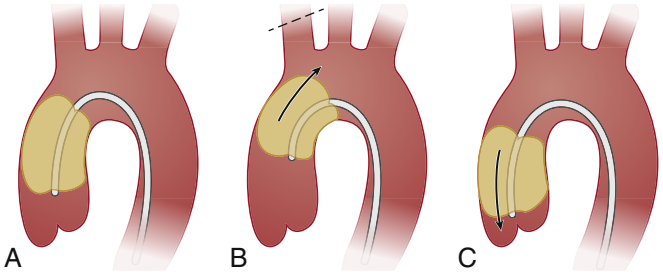


Figure 67-36. A, Drawing of a well-positioned EndoClamp in the ascending aorta. **B,** Distal migration of the EndoClamp and potentially obstructing flow to the innominate artery. **C,** Proximal migration of the EndoClamp that may prevent adequate aortic occlusion or cardioplegia. *(Modified with permission from Kottenberg-Assenmacher E, Kamler M, Peters J: Minimally invasive endoscopic port-access intracardiac surgery with one lung ventilation: impact on gas exchange and anaesthesia resources,* Anaesthesia *62:231-238, 2007; from Vernick WJ, Woo JY: Anesthetic considerations during minimally invasive mitral valve surgery,* Semin Cardiothorac Vasc Anesth *16:11-24, 2012.)*



Figure 67-37. Chitwood transthoracic aortic cross-clamp (Scanlan International, Inc., St. Paul, Minn) seen before use. *(From Vernick WJ, Woo JY: Anesthetic considerations during minimally invasive mitral valve surgery,* Semin Cardiothorac Vasc Anesth *16:11-24, 2012.)*

50%.[288] Transcatheter aortic valve implantation (TAVI) is an alternative treatment option in patients with severe AS for whom cardiac surgery and traditional aortic valve replacement pose substantial risks, particularly patients of advanced age who have extreme comorbidities (e.g., porcelain aorta, prior radiation therapy, frailty, severe hepatic or pulmonary disease).[289-291] The technologic advances made in the development of TAVI procedures are ingenious. However, the procedure is associated with significant 30-day mortality (8% to 10%), as well as short-term and long-term morbidity, including stroke, need for permanent pacemaker insertion, access complications, valve embolization, renal failure, cardiac rupture, aortic rupture, cardiac tamponade, and bleeding.[292,293] Published guidelines regarding the TAVI procedure recommend specialized multidisciplinary heart teams that include cardiologists, cardiac surgeons, anesthesiologists, intensivists, nurses, and others.[294] The hybrid operating room or cardiac catheterization laboratory (CCL) where the procedure is performed must have adequate space, expert echocardiography, emergency supplies, support from colleagues, and immediate access to CPB technicians and a cardiac surgeon if necessary.

The TAVI procedure requires either retrograde (through the femoral artery) or anterograde (through the apex of the left ventricle) access to the aortic valve annulus (Fig. 67-38).[294,295] Typically, general anesthesia is needed for transapical procedures.[292] Large-bore intravenous access, an arterial catheter, and central venous access are essential, as is a PA catheter in patients with preexisting pulmonary hypertension. A TEE probe is introduced after induction. External defibrillation pads are placed and connected to the defibrillator before the procedure begins (ventricular fibrillation can result from manipulation of catheters within the heart or from rapid ventricular pacing).[292] Because a period of rapid ventricular pacing is required during deployment of the valve, a transvenous lead for temporary pacing is inserted, typically through the femoral or subclavian vein (or, in the case of transapical procedures, sewn directly on the epicardial surface).[292]

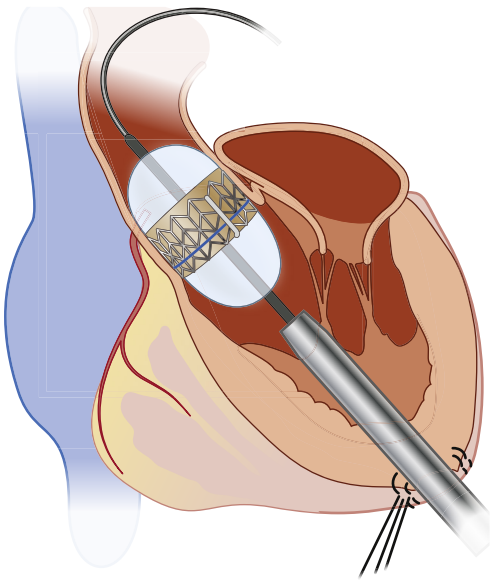


Figure 67-38. Schematic of transapical aortic valve implantation. The prosthesis is implanted within the native annulus by balloon inflation. *(From Walther T, Ralk V, Borger MA, et al: Minimally invasive transapical beating heart aortic valve implantation: proof of concept,* Eur J Cardiothorac Surg *31:9-15, 2007.)*

TEE has a central role in evaluating annulus size, aortic disease, ventricular function, and MR, as well as determining reasons for hemodynamic instability.[295,296] A balloon valvuloplasty of the aortic valve precedes the insertion of a bioprosthetic valve, which is crimped on a valvuloplasty balloon catheter and implanted by inflation. The device is guided into position through the combined use of real-time TEE and fluoroscopy. Immediately after inflation, TEE is employed to measure the degree and source of any AR and to examine the aorta for any aortic dissection.[295,296]

A major challenge during the TAVI procedure is maintaining hemodynamic stability. In patients with severe concentric LV hypertrophy and intravascular volume depletion, hemodynamic status may deteriorate rapidly because of ventricular pacing, intracardiac guidewire or catheter manipulation, or balloon aortic valvuloplasty itself.[292] Avoiding prolonged hypotension and the cycle of hypotension, subendocardial ischemia, and low output is critical to prevent hemodynamic collapse. The frequency and duration of rapid ventricular pacing episodes may need to be limited to allow enough time between episodes for spontaneous circulation to recover. Vasopressors (norepinephrine, epinephrine, or phenylephrine), administered as incremental boluses or as a continuous infusion, may be necessary. Constant communication among team members is essential throughout this multidisciplinary procedure.

Although general anesthesia is used for transapical procedures, some experienced institutions are performing transfemoral implantation with conscious sedation and monitored anesthesia care.[297] The advantages of this approach include the ability to monitor the awake patient's neurologic status continuously, greater hemodynamic stability, and possibly reduced postprocedure length of stay in the ICU compared with an approach using general anesthesia.[297] However, general anesthesia is required if TEE is necessary during a procedure (not all centers use TEE for transfemoral TAVI).

The TAVI procedure requires state-of-the-art imaging capability, as well as the immediate availability of personnel to secure surgical access and institute CPB.[291] The short-term efficacy of TAVI, as shown by echocardiographic measurements, is good.[293] However, evidence on long-term outcomes awaits further data collection in national TAVI registries.[292,294]

Other Uses of the Minimally Invasive Approach. Minimally invasive surgical approaches can also be used to treat tricuspid valve disease,[298] as well as ASDs. Newer developments in the operative treatment of ischemic heart disease have led to the consideration of hybrid procedures in patients with multivessel CAD. This essentially means that patients with multivessel CAD can undergo percutaneous coronary intervention with a LIMA graft to the LAD coronary artery during the same hospital admission.[299] Additionally, some clinicians have attempted to combine minimally invasive valvular surgery with

percutaneous catheter intervention for coexisting ischemic heart disease.

Notably, early trials of Heartport technology with endoaortic occlusion catheters showed an elevated risk for intraluminal aortic injury and aortic dissection.[284] Although clamps such as the Chitwood transthoracic aortic cross-clamp and the Cosgrove Flex Clamp are being increasingly used, endoaortic occlusion technology may offer an alternative when standard aortic cross-clamping is contraindicated.[286]

HEART FAILURE

HF can be defined as a complex clinical syndrome caused by any structural or functional cardiac disorder that impairs the ability of the heart (as a pump) to meet the metabolic demands of the body. Thus, HF can result from an impairment of diastolic filling, systolic ejection, or both. Once HF is present, progressive cycles of deterioration and transient compensation ensue that may continue for years. Essentially, increases in end-diastolic volumes are compensated for by endogenously promoted diuresis, which is compensated for by sympathetic activation. This activation promotes further diuresis, which then requires compensation by further sympathetic activation, and so on. As the syndrome progresses, the hemodynamic changes, the cycles of fluid retention and relative hypovolemia, and bodily hypoperfusion perturb many neuroendocrine, humoral, and inflammatory feedback loops (Box 67-9), with resulting progressive and inexorable cycles of physical and functional deterioration of the heart and major bodily organs. In the United States, more than 6 million people currently have HF, and its prevalence is estimated at 10% in people older than 65 years old. Although survival with HF has improved, the mortality associated with heart failure remains high, and at least 50% of patients with HF are expected to die within 5 years of diagnosis.

BOX 67-9 ***Pathophysiology of Heart Failure: From Injury to Clinical Syndrome***

1. Causes
   a. Myocardial injury
      i. Ischemia
      ii. Toxins
      iii. Volume overload
      iv. Pressure overload
   b. Genetic perturbation
2. Cardiac remodeling
   a. Myocyte growth
      i. Concentric hypertrophy
      ii. Eccentric hypertrophy
   b. Interstitial fibrosis
   c. Apoptosis
   d. Sarcomere slippage
   e. Chamber enlargement
3. Clinical heart failure milieu
   a. Pump performance
   b. Circulatory dynamics
   c. Metabolic abnormalities

The ACC/AHA guidelines for the evaluation and management of chronic HF place patients in four classes based on the stages of the syndrome (Box 67-10).[300] Early in the course of the disease, ventricular contractility is maintained by adrenergic stimulation and activation of the renin-angiotensin-aldosterone and other neurohormonal and cytokine systems.[301,302] Patients in this stage would be considered to be in ACC/AHA class B. However, these compensatory mechanisms become less effective over time, and ventricular dilatation and fibrosis occur, progressively worsening cardiac function. This produces a chronic state of low perfusion and, ultimately, refractory end-stage HF, labeled class D in the ACC/AHA classification scheme. The New York Heart Association (NYHA) functional classification system is also used to assess the severity of functional limitations and correlates fairly well with prognosis (Box 67-11). Some patients may remain asymptomatic for years despite ventricular remodeling, dilatation, and decreased EF.

Medical Management of Heart Failure

Medical strategies for treating developing HF aim to limit disease progression, prolong life, and improve quality of life as the syndrome progresses. Medical therapies, such as ACEIs, β-blockers, diuretics, inotropic agents, and antiarrhythmics, represent the usual standard of care for HF patients. In general, β-blockers, ACEIs, and ARBs (for those who cannot tolerate ACEIs) are class I indications in the current ACC/AHA guidelines for class A and

BOX 67-10 ***American College of Cardiology/ American Heart Association Classification of Chronic Heart Failure Stages***

A: High risk for heart failure
Hypertension, diabetes mellitus, coronary artery disease, family history of cardiomyopathy
B: Asymptomatic heart failure
Previous myocardial infarction, left ventricular dysfunction, valvular heart disease
C: Symptomatic heart failure
Structural heart disease, dyspnea, fatigue, impaired exercise tolerance
D: Refractory end-stage heart failure
Marked symptoms at rest despite maximal medical therapy

From Hunt SA, Abraham WT, Chin MH, et al: 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the International Society for Heart and Lung Transplantation, J Am Coll Cardiol *53:e1-e90, 2009.*

BOX 67-11 ***New York Heart Association Heart Failure Symptom Classification System***

NYHA Class	Level of Impairment
I:	Ordinary physical activity not limited by symptoms
II:	Ordinary physical activity somewhat limited by dyspnea
III:	Exercise limited by dyspnea during a mild workload
IV:	Dyspnea at rest or with very little exertion

NYHA, New York Heart Association.

B patients with HF who have cardiac structural abnormalities and who have not yet developed symptoms of HF.[300] Signs and symptoms of HF (class C) are class I indications for the use of certain β-blockers that have been shown to prolong life (e.g., bisoprolol, carvedilol, and sustained release metoprolol), ACEIs, and ARBs. Diuretics and salt restriction should be added for patients with fluid retention. The implantation of devices for cardiac resynchronization therapy and defibrillatory capability is recommended, and revascularization and valve repair or replacement should be performed as appropriate. In both symptomatic and asymptomatic patients, current ACC/AHA guidelines list several additional potential therapies with class II and III indications.

However, even multidrug regimens may not prevent progression toward class D HF. A patient who has reached this category has a 2-year mortality risk greater than 75%. Thus, surgical intervention at less advanced stages of HF has become common in an attempt to prevent the inexorable progression of the syndrome.

Surgical Management of Heart Failure

In previous years, the only established surgical treatment option for advanced HF was cardiac transplantation,[300] which is associated with excellent survival rates and functional capacity. However, certain surgical interventions can retard or even potentially reverse progression of the disease (in conjunction with pharmacologic and other strategies), and the 2009 ACC/AHA guidelines stated that all stages of HF are class I indications for specific surgical interventions (e.g., coronary revascularization, valve repair or replacement).

CAD is the most common cause of HF,[303] and it is the second most common indication for heart transplantation in the United States; CAD accounted for approximately 24% of all transplants performed between January 1988 and May 2012.[304] (The first most common indication is idiopathic dilated cardiomyopathy, which accounted for approximately 33% of all cases.) Worldwide, ischemic cardiomyopathy is now the second most common indication for heart transplantation, accounting for 38% of all registered cases.[305] Similar to the U.S. experience, nonischemic cardiomyopathy has been the most common indication worldwide, accounting for 53% of all registered cases.

Where viable myocardium and feasible targets exist, revascularization of the failing heart can improve cardiac function and NYHA functional class.[306,307] It can also slow remodeling and decrease the incidence of arrhythmias,[308] and it has been demonstrated to improve survival. For example, Liao and associates found that among patients with CHF, survival was improved in patients who underwent revascularization compared with those who did not.[306] The optimal method of revascularization has not been conclusively determined, however, and studies continue to examine the issue of whether percutaneous coronary stenting is as effective as the gold standard intervention, CABG, in promoting long-term survival. The issue may be further complicated in certain subpopulations of patients (e.g., those with diabetes), by surgical technique (e.g., on-pump versus off-pump CABG), and by the type of stent used (e.g., bare metal versus drug coated).

Carefully selected patients with advanced CHF and MR receive several benefits from mitral valve repair or replacement, including a progressive decrease in LVEDV, a progressive improvement in LVEF, improvements in functional status (decreased NYHA class, improved 6-minute walk-test performance, and improved peak oxygen consumption), reverse remodeling, and lower long-term mortality risk.[309,310] The importance of appropriate patient selection is paramount, however, if optimal benefits are to be realized; the best results occur when mitral valve repair or replacement is undertaken before the geometric and functional derangements of the valve reach certain levels. Several key predictors of lack of reverse remodeling have been identified: LV end-diastolic dimension greater than 6.5 cm, LV end-systolic dimension greater than 5.1 cm, large LA volume, high LV sphericity index, and severely depressed LVEF.[233,311-313] The optimal type of repair remains a subject of ongoing study, as does the issue of whether mitral repair or replacement affords the greater survival benefit to these often older and highly comorbid patients. Clearly, the quality of any repair greatly influences its outcome.

The effectiveness and potential survival benefits of combining revascularization with other surgical procedures (e.g., valve repair or replacement, ventricular reshaping) have been and continue to be the subject of large, multicenter investigations. Surgical ventricular restoration (reshaping) has thus far not been shown to improve survival, decrease symptoms, or increase exercise tolerance in patients with HF when the procedure is performed in conjunction with revascularization.[314]

In addition to common surgical interventions, electrophysiologic interventions play a key role in the modern management of HF. Large, international, multicenter trials have demonstrated improved survival, decreased risk of hospitalization, decreased incidence of sudden cardiac death, improvements in LVEF, decreased LV volumes, and decreased symptoms in both symptomatic and asymptomatic patients with HF treated with cardiac resynchronization therapy (biventricular pacing), ICDs, or both.[315-319]

Today, when pharmacologic, electrophysiologic, and surgical interventions fail to stave off the inevitable progression of HF, mechanical circulatory support (MCS) with VADs is commonly used. Short-term MCS is generally used as a "bridge to immediate survival," a "bridge to recovery," or a "bridge to next decision" after an acute cardiac event. Patients with advanced HF who have little expectation of ventricular recovery (or who have not recovered despite short-term support) now regularly receive intermediate- and long-term VAD support as a potential bridge to transplantation. Since 2002, transplant-ineligible patients may receive approved LVADs as "destination therapy," a final treatment strategy shown to confer a survival advantage compared with medical management alone. Heart transplantation remains, of course, the ultimate surgical intervention for end-stage HF, but the number of patients with HF far exceeds the number of donor organs available each year worldwide, and MCS with a VAD is currently the best option for most patients with advanced and end-stage HF.

The use of VADs as a bridge to cardiac transplantation was previously shown to improve the survival rates and outcomes of patients with decompensated HF and was also found to improve multiorgan function during the time spent on VAD support.[320-325] This has been the rationale for the tremendous increase in the use of bridging technology.

However, the most recent analyses from the International Society for Heart and Lung Transplantation (ISHLT) indicated that among patients who received transplants between July 2004 and June 2009, bridging to transplantation with pulsatile or nonpulsatile VADs did not actually confer a statistically significant survival advantage.[305] Further, in an analysis of survival in patients who received transplants between January 2002 and June 2009, those who were bridged with pulsatile or nonpulsatile VADs actually had poorer 6-month posttransplant survival than (but equivalent 7-year survival to) patients who were not bridged. However, as discussed in the 2011 ISHLT report, the preponderance of deaths in the early years of this technology and the statistical methods used to perform the analyses may have great bearing on our current thinking, and further analyses are currently under way because overall, there *does* seem to be a survival advantage in more recent years with modern devices and our more extensive collective experience with patient management. Thus, the indication for bridging (e.g., elective versus "required" because of severe decompensation) may be a vitally important part of the selection criteria going forward. In this regard, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile plays an important role in appropriate patient selection and the timing of intervention.[326] The INTERMACS profile characterizes patients with HF on the basis of clinical status and symptoms (Table 67-16).[327]

With regard to destination therapy in the United States, the most recent statistics from the INTERMACS registry indicate that overall survival has dramatically increased since the introduction of continuous flow devices: 1-year survival is 74%, and 2-year actuarial survival is 80%.[328] This finding is extremely significant considering the approximate 25% rate of 1-year survival originally shown in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, which led to FDA approval of the HeartMate VE for destination therapy in September 2002.

First-generation, pulsatile VADs were approved as bridges to recovery beginning in the early 1990s (e.g., the ABIOMED BVS 5000 in 1992) and as bridges to transplantation in the middle to late 1990s (e.g., the HeartMate IP in 1995, the Novacor in 1998, and the HeartMate VE in 1998). These devices have now been supplanted worldwide by second- and third-generation, nonpulsatile devices, which generate continuous flow and have the advantages of being small, silent, valveless, and fully implantable. In addition, the current generation of devices is associated with significantly fewer perioperative and long-term complications than were pulsatile support devices.

At the time of this writing, the most commonly used long-term VAD in the United States is the HeartMate II (Thoratec Laboratories, Pleasanton, Calif.). The HeartMate II is a small axial flow pump that continuously draws blood from the LV apex by the action of a rapidly rotating impeller and returns the blood to the ascending aorta in a nonpulsatile fashion. It has been approved in the United States as a bridge to transplantation since 2008 and as destination therapy since 2010. Complication rates with the HeartMate II are dramatically lower than with the previous generation of pulsatile devices, and the durability of the device far exceeds that of the HeartMate I (>5 years, compared with only approximately 18 months). The current rate of successful bridging to transplantation with the HeartMate II is approximately 79%.

Total artificial hearts exist (e.g., the CardioWest temporary Total Artificial Heart [TAH-t], Syncardia Systems, Tucson, Ariz.; and the AbioCor Implantable Replacement Heart [IRH], Abiomed, Inc., Danvers, Mass.). The CardioWest TAH-t is FDA approved (and approved and available in Europe and Canada) as a bridge to transplantation and has had renewed popularity because of its 79% successful rate of bridging patients to transplantation, with a lower incidence of adverse neurologic events than is associated with approved VADs. According to the manufacturer, more than 1100 TAH-t devices have been implanted. The AbioCor IRH is currently approved in the United States only as destination therapy under a Humanitarian Device Exemption for transplant-ineligible patients with end-stage HF. At the time of this writing, very few AbioCor IRHs have been implanted, so relatively little experience exists with this device in humans.

TABLE 67-16 INTERAGENCY REGISTRY FOR MECHANICALLY ASSISTED CIRCULATORY SUPPORT: PROFILES FOR PATIENT SELECTION*

Profile	Description
1	Critical cardiogenic shock
2	Progressive decline on inotropic support
3	Stable but inotrope dependent
4	Resting symptoms home on oral therapy
5	Exertion intolerant
6	Exertion limited
7	Advanced NYHA class III symptoms

From Kirklin JK, McGiffin DC, Pinderski LJ, et al: Selection of patients and techniques of heart transplantation, Surg Clin North Am *84:257-287, xi-xii, 2004.*

NYHA, New York Heart Association.

*The use of mechanical circulatory support (MCS), frequent arrhythmias, and being a "frequent flyer" can modify the profile. In general, patients with Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles 3 and 4 currently are believed to represent the best balance between risk and indication for MCS in attempts to optimize survival.

Cardiac Transplantation

Discovery of the immunosuppressive agent cyclosporine in the early 1980s made cardiac transplantation an accepted surgical option for end-stage HF.[329] Currently, 1-year survival is 85% or more, and 5-year survival is approximately 70%.[305] Patients 30 to 59 years old tend to have the best survival, as do recipients who required transplantation because of nonischemic cardiomyopathy.

Most candidates for cardiac transplantation have class D HF that has been maximally treated medically but is nevertheless likely to result in death in less than 1 year.

Such patients typically are in cardiogenic shock or have a chronic low-output state that necessitates mechanical or inotropic support, but candidates also include patients with advanced symptomatic HF and peak oxygen uptake less than 10 mL/kg/minute (with the achievement of an anaerobic threshold), patients with NYHA class IV HF caused by advanced hypertrophic or restrictive cardiomyopathy, patients with refractory angina pectoris and inoperable CAD, and patients with life-threatening ventricular arrhythmias that are refractory to all appropriate medical and surgical treatment. Usually, the patient's EF is less than 20%. However, patients with NYHA class III HF who are at risk for sudden death related to malignant arrhythmias are sometimes placed on the waiting list.

In the United States, cardiac transplantation is performed in member centers of the United Network for Organ Sharing (UNOS), an umbrella organization responsible for coordinating organ procurement, organ allocation, and statistical information. The UNOS allocates donor hearts according to each patient's priority status, ABO group compatibility, body size match, and distance from the donor center. The highest priority is given to inpatients supported by mechanical circulatory assist devices for acute hemodynamic decompensation, patients maintained on assist devices who have significant device-related complications, patients requiring continuous infusion of single or multiple high-dose intravenous inotropic medications, and patients with a life expectancy of less than 7 days without transplantation.

The most common diagnoses in adult patients with HF who require cardiac transplantation include idiopathic or ischemic cardiomyopathy and complex congenital heart disease (CHD). Less common diagnoses include viral cardiomyopathy, postpartum cardiomyopathy, refractory valvular disease, primary myocardial diseases (e.g., sarcoidosis, amyloidosis), and drug-induced myocardial disease.

The selection criteria have been broadened for both heart recipients and heart donors.[327] For example, patients with HF in two previously excluded categories—those with diabetes and those older than 65 years old—are now considered transplantation candidates in many centers.[330] In addition, although centers generally prefer donors to be younger than 35 years old, the age criterion has been expanded to include suitable donors (e.g., those without cardiac risk factors or evidence of CAD) who are 60 years old or older. Major contraindications to heart transplantation that continue to steer patients toward destination therapy with a VAD instead of transplantation include older age, renal dysfunction, and high body mass index.[327] Modifiable risk factors (e.g., pulmonary hypertension) remain the subject of ongoing clinical investigation. Classically, a PVR greater than 5 dyne•sec•cm^{-5} that is unresponsive to pulmonary vasodilators indicates a "fixed" elevated PVR, which has been associated with an increased risk for early mortality after orthotopic heart transplantation.[331]

The manner in which the donor heart is implanted has also changed, with a shift away from the classic biatrial technique (originally described by Lower and Shumway in 1960) to the bicaval Wythenshawe technique described in the early 1990s (Fig. 67-39). The advantages of a bicaval implantation technique include shorter hospital stays, reduced postoperative dependence on diuretics, and lower incidences of LA dilatation, atrial dysrhythmias, conduction disturbances, mitral and tricuspid valve incompetence, and RV failure. Furthermore, several series that compared the classic Shumway technique with the bicaval technique showed greater 12-month survival in the bicaval group.[332,333]

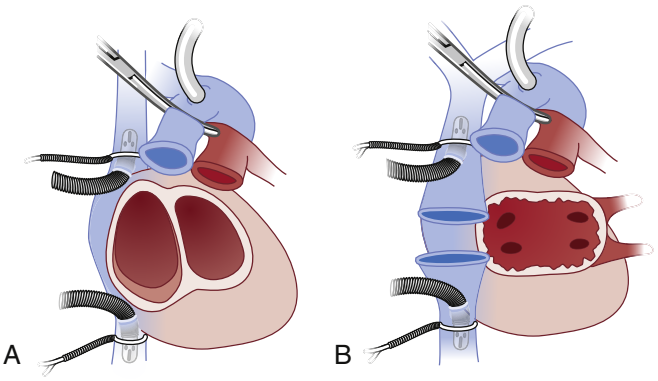


Figure 67-39. Surgical techniques for cardiac transplantation. **A,** Biatrial technique. The donor heart is anastomosed to the main bulk of the recipient's native right and left atria. **B,** Bicaval technique. The donor left atrium is anastomosed to a single left atrial cuff, including the pulmonary veins, in the recipient.

An even more recent implantation technique further reduces the size of the native LA remnant to two islands containing the pulmonary veins on either side. This is called a total technique.

Because the recipient sinoatrial node is no longer routinely retained with either of the modern bicaval techniques, the concept of two P waves on the posttransplant ECG is now only of historical interest. Posttransplantation physiology, however, remains unchanged: the requisite denervation of the donor organ during harvesting results in the absence of both direct afferent and efferent neural innervation via autonomic or somatic neural pathways after implantation in the recipient. In plain English, the transplanted heart functions in isolation from the recipient's nervous system, although the potential for direct activation of myocardial receptors (e.g., myocardial adrenergic receptors) by circulating factors is retained, as are all intrinsic myocardial reflexes and mechanisms (e.g., the Starling mechanism, the Anrep effect, the Bowditch effect, the vasoconstrictive effect on coronary arteries of hypocarbia). The loss of parasympathetic tone in the transplanted heart means that the resting heart rate is faster than normal, and heart rates of approximately 90 to 110 beats/minute are usual (and, in fact, are necessary to maintain CO in many cases).

A clear understanding of what remains intact and what is lost in the transplanted heart dictates and guides posttransplant anesthetic management. Adequate preload is critical. Direct-acting drugs (e.g., epinephrine, dobutamine, norepinephrine, isoproterenol) and pacing are maximally and immediately effective when needed to increase inotropy or chronotropy, respectively, in the transplanted heart. Primarily indirect-acting drugs (e.g., ephedrine, dopamine) rely mostly on the release of epinephrine and norepinephrine from the adrenal glands. Digoxin retains

its direct inotropic effect on the heart through inhibition of sodium-potassium adenosine triphosphatase, with resultant buildup of intramyocardial calcium, but loses its potential to decrease chronotropy (a parasympathetically mediated effect on the AV node). One should not expect a decrease or increase in heart rate after the administration of medications that cause bradycardia (e.g., fentanyl) or tachycardia (e.g., meperidine, pancuronium) as a side effect. Anticholinergic medications (e.g., atropine, glycopyrrolate) are not expected to increase heart rate in the denervated heart but are always administered at the time of reversal of muscle relaxation by acetylcholinesterase inhibitors (e.g., neostigmine) to decrease the potential adverse extracardiac cholinergic effects of the anticholinesterase group.

The denervated heart is subject to accelerated atherosclerotic disease, causing a significant 5-year incidence of CAD in transplant recipients, but these recipients do not experience angina. Significant dysrhythmias or arrhythmias in a transplanted heart should be considered harbingers of ischemia until proven otherwise.

CONGENITAL HEART DISEASE IN ADULTS

Background and Current Perspective

Medical and surgical advances in CHD surgery since the 1960s have significantly reduced the death rates of patients with CHD. Today, 85% to 95% of babies born with CHD can reach adulthood, and the number of adults with CHD now exceeds the number of children.[334] Adult patients who present with CHD can have extremely complex conditions that require careful assessment and operative planning. They may present for cardiac surgery for the first time or for further palliative correction, either definitively or for residua. Most patients with CHD face a lifetime of significant challenges,[335] ranging from the complications of long-term antibiotic prophylaxis to thromboembolic ventricular dysfunction resulting from cardiac arrhythmias and pulmonary hypertension.

Preoperative Anesthetic Considerations

The unique problems of this population include the multisystem effects of single-ventricle physiology, cyanosis, systemic right ventricle, complex intracardiac baffles, and failing subpulmonary right ventricle.[334] The initial assessment, history taking, and physical examination of an adult patient with CHD must be broadly systemic to capture any noncardiac organ involvement. A full review of each organ system is beyond the scope of this chapter, but readers are referred to the excellent review articles by Chassot and Bettex[335] and by Lovell.[336] Appropriate consultation with the patient's cardiologist (pediatric or adult), as well as access to old medical records, is valuable, especially for patients who have complex CHD or have undergone complex surgical procedures. Preoperative echocardiography is extremely helpful in understanding the anatomy and cardiac function, both primary and compensatory, of patients with CHD.

One of the early clinical decisions to be made for an individual patient involves determining the appropriateness of surgical care in a given institution. Obviously, emergency procedures give very little latitude, but elective procedures should warrant careful assessment, especially of the abilities and experience of the anesthesiologist who will be caring for a patient with complex corrected or palliated CHD. In 2001, the Thirty-second Bethesda Conference on CHD advocated the creation of regional centers for the care of adults with CHD (ACHD centers), whose personnel would include a cardiac anesthesiologist and other subspecialists with expertise in the management of patients with CHD.[337] The conference recommended that all adult patients with complex (Box 67-12) and moderate (Box 67-13) CHD be referred to such ACHD centers. Current U.S.[338] and Canadian[334] updates to these guidelines echo these recommendations.

BOX 67-12 *Types of Adult Congenital Heart Disease of Great Complexity*

- Conduits, valved or nonvalved
- Cyanotic congenital heart disease (all forms)
- Double-outlet ventricle
- Eisenmenger syndrome
- Fontan procedure
- Mitral atresia
- Single ventricle (also called double inlet or outlet, common, or primitive)
- Pulmonary atresia (all forms)
- Pulmonary vascular obstructive disease
- Transposition of the great arteries
- Tricuspid atresia
- Truncus arteriosus or hemitruncus
- Other abnormalities of atrioventricular or ventriculoarterial connection not included here (i.e, crisscross heart, isomerism, heterotaxy syndromes, ventricular inversion)

From Warnes CA, Williams RG, Bashore TM, et al: ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Adults with Congenital Heart Disease). Developed in collaboration with the American Society of Echocardiography, Heart Rhythm Society, Angiography and Interventions and Society of Thoracic Surgeons, Circulation *118:2395-2451, 2008.*

Intraoperative Anesthetic Considerations

In-depth discussion of the anesthetic management of particular congenital heart defects in adult patients is not the purpose of this section. However, a few basic principles are essential for all anesthesiologists to know, especially those who do not have specialized training in cardiac anesthesia or CHD but who may be faced with an older patient with CHD who needs urgent noncardiac surgery.

The anesthetic care presents a challenge and requires detailed knowledge of the anatomy and physiology of the lesion.[336] A skilled multidisciplinary team is very helpful for providing optimal management.[339,340] During the preoperative assessment of an adult with CHD, an extensive review should be conducted to elicit signs of CHF, cyanosis, or compromised peripheral vascular disease. Anesthetic considerations are lesion specific and are discussed in several reviews.[336,341,342]

Principle 1: The Presence or Absence of Cyanosis. Cyanosis is usually a marker for complex CHD. Chronic cyanosis can lead to the development of abnormalities of

BOX 67-13 ***Diagnoses in Adult Patients With Congenital Heart Disease of Moderate Complexity***

Aorto–left ventricular fistula
Anomalous pulmonary venous drainage, partial or total
Atrioventricular septal defect (partial or complete)
Coarctation of the aorta
Ebstein anomaly
Infundibular right ventricular outflow obstruction of significance
Ostium primum atrial septal defect
Patent ductus arteriosus (not closed)
Pulmonary valve regurgitation (moderate to severe)
Pulmonary valve stenosis (moderate to severe)
Sinus of Valsalva fistula or aneurysm
Sinus venosus atrial septal defect
Subvalvular or supravalvular aortic stenosis (except HOCM)
Tetralogy of Fallot
Ventricular septal defect with:
- Absent valve or valves
- Aortic regurgitation
- Coarctation of the aorta
- Mitral valve disease
- Right ventricular outflow tract obstruction
- Straddling tricuspid or mitral valve
- Subaortic stenosis

From Warnes CA, Williams RG, Bashore TM, et al: ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Adults with Congenital Heart Disease). Developed in collaboration with the American Society of Echocardiography, Heart Rhythm Society, Angiography and Interventions, and Society of Thoracic Surgeons, Circulation *118:2395-2451, 2008.*
HOCM, Hypertrophic obstructive cardiomyopathy.

RBC production and hemostasis. Elevated levels of erythropoietin in cyanotic patients can lead to a hyperviscosity syndrome and elevated neurologic risk. Risk factors include coexistent systemic hypertension, atrial fibrillation, and a history of phlebotomy and microcytosis.

In any patient with cyanotic CHD, the anesthesiologist should establish intravenous fluid therapy and monitor urine output to minimize the circulatory effects of perioperative fasting, dehydration, and intraoperative hypovolemia. These conditions cause hyperviscosity, which can be associated with hemostatic abnormalities. Long-term administration of antiplatelet medications to ensure conduit patency should be noted. Arterial pressure monitoring should be considered. The decision whether to measure CVPs should be approached with caution and should involve consultation with a cardiologist familiar with CHD and with the patient's diagnosis. This decision also requires a complete understanding of the patient's anatomy and underlying cardiac function, as well as the proposed surgical intervention. A caval-pulmonary connection, such as the bidirectional Glenn shunt or Fontan procedure, elevates the patient's risk of thrombosis from indwelling venous catheters.

Principle 2: The Presence or Absence of Intracardiac or Extracardiac Shunts. Intracardiac shunts are classically located at the level of the atria or ventricles. The magnitude of the shunt is often expressed in terms of the ratio of pulmonary blood flow (Qp) to systemic blood flow (Qs): Qp/Qs. Balanced flow is the hallmark of normal physiology. A Qp/Qs ratio greater than 1 is generally consistent with acyanotic heart disease and luxuriant pulmonary blood flow. A Qp/Qs ratio less than 1 would be consistent with the clinical manifestation of cyanotic heart disease. Chassot and Bettex remind us in their review article of important subcharacteristics of intracardiac shunts[335]:

1. The direction of shunt flow is important. Shunts can be right, left, or bidirectional. Shunt flow can be influenced by changes in driving pressure across a shunt or pressure in the receiving chamber. The high intrathoracic pressure that can occur with mechanical ventilation, coughing, the Valsalva maneuver, bronchospasm, or positive end-expiratory pressure can actually reverse the direction of a left-to-right shunt or at least make it bidirectional. Therefore, paradoxical embolization by clot or air is a real risk in patients with intracardiac shunts and warrants fastidious attention to de-airing intravenous lines and careful administration of drugs by syringes through ports in intravenous lines.
2. The size of the intracardiac defect is important. Shunts are commonly labeled as restrictive or nonrestrictive according to their blood velocity or pressure characteristics measured at catheterization or by echocardiography. Large defects with associated low pressure gradients across them have nonrestrictive flow. In addition, larger defects can be expected to have a greater effect on downstream structures and pressures. Small defects with high pressure or gradients restrict the amount of blood flow. The mainstays of the anesthetic management of shunt lesions are understanding and controlling factors that may influence the direction and magnitude of the shunt. Shunt flow and direction are directly influenced by both PVR and SVR. Elevated SVR and decreased PVR generally increase the magnitude of and propensity for left-to-right shunting. Conversely, decreased SVR decreases the magnitude of left-to right shunting, as do elevations in PVR. Mechanical ventilation, the inspired oxygen concentration, carbon dioxide levels, and the hemodynamic effects of anesthetic drugs are all used to achieve certain therapeutic goals in relation to shunt management. Oxygen is a potent pulmonary vasodilator, as is a lower $Paco_2$. If the clinical problem is luxuriant pulmonary blood flow, a high FiO_2 is not optimal and should be avoided. Similarly, the direction and magnitude of the shunt flow determine whether one should hyperventilate a patient to achieve a low $Paco_2$ or tolerate a high-normal $Paco_2$.
3. In the presence of a shunt, the potential enlargement of receiving chambers and high downstream pressure are important. A shunt above the level of the AV valves, such as a left-to-right shunt at the atrial level, usually causes right-sided chamber enlargement. Defects or shunts below the AV valves, such as a VSD or patent ductus arteriosus (PDA), initially result in

left-sided chamber enlargement. Shunts at both locations increase pulmonary blood flow and, with time, can lead to potentially irreversible elevations in PVR and pulmonary pressure. Furthermore, exposure to elevated pulmonary pressure and afterload leads to RV enlargement, RV failure, bidirectional shunting, and in the most extreme cases, reversal of shunt direction and cyanosis, as in patients with Eisenmenger syndrome.

Extracardiac shunts can be native to CHD (e.g., aberrant pulmonary venous return), surgically created (e.g., Blalock-Taussig shunt placement in some cases of cyanotic heart disease), or compensatory (e.g., aortopulmonary collateral formation with long-standing cyanotic heart disease). Special mention of certain aortopulmonary shunts, used commonly in the past to palliate some forms of cyanotic heart disease, is warranted. The proximal connection may be to the ascending aorta, brachiocephalic trunk, or subclavian artery. Because blood flow through this type of shunt is dependent on systemic blood pressure, systemic hypotension may lead to worsening hypoxemia. Furthermore, long-term exposure to these extracardiac shunts can result in left-sided chamber enlargement and dysfunction secondary to chronic volume overload.

Principle 3: The Presence of Pulmonary Hypertension. Pulmonary arterial hypertension is defined as a mean PAP greater than 25 mm Hg or greater than 30 mm Hg with exercise. Some degree of pulmonary hypertension develops in 5% to 10% of adult patients with CHD. This is associated with exercise intolerance and decreased functional capacity, which appear to have important prognostic implications.[340]

The anesthetic management of patients with pulmonary hypertension can be challenging. Invasive monitoring and careful anesthetic titration may be required. Regional anesthesia may be used for appropriate procedures, but neuraxial blocks should be administered with caution. Patients with significant pulmonary hypertension are very sensitive to preload; therefore, hypovolemia, whether primary (from blood loss) or secondary (from vasodilation), should be treated immediately and aggressively. Pulmonary hypertension can be managed pharmacologically and mechanically. Factors associated with decreasing PVR and, subsequently, reductions in PAP are listed in Box 67-14.[336]

Principle 4: The Presence of Ventricular Dysfunction. As in adult patients with heart disease that is not congenital, the presence of ventricular dysfunction is an important risk factor for morbidity and mortality, both in the perioperative period and in the long term. Regarding RV dysfunction, predictors of a poor outcome may include pulmonary hypertension, pulmonic valve incompetence, and consequent dysfunction of the subpulmonic ventricle.[342] LV dysfunction has been observed in patients with repaired tetralogy of Fallot, which is associated with male gender, LV enlargement, duration of shunt before repair, history of arrhythmia, QRS duration, ICD, and moderate to severe RV dysfunction.[343]

BOX 67-14 ***Factors Associated With Decreasing Pulmonary Vascular Resistance and Reductions in Pulmonary Artery Pressure***

Decrease in Pulmonary Vascular Resistance

- Increasing PaO_2
- Hypocapnia
- Alkalemia
- Minimizing intrathoracic pressure
  - Spontaneous ventilation
  - Normal lung volumes
  - High-frequency and jet ventilation
  - Avoidance of sympathetic stimulation
  - Deep anesthesia
- Pharmacologic methods
  - Isoproterenol
  - Phosphodiesterase III inhibitors
  - Prostaglandin infusion (PGE_1 and PGI_2)
  - Inhaled nitric oxide

Increase in Pulmonary Vascular Resistance

- Sympathetic stimulation
  - Light anesthesia
  - Pain
- Acidemia
- Hypoxia
- Hypercapnia
- Hypothermia
- Increased intrathoracic pressure
  - Controlled ventilation
  - Positive end-expiratory pressure
  - Atelectasis

From Lovell AT: Anaesthetic implications of grown-up congenital heart disease, Br J Anaesth *93:129-139, 2004.*
PaO_2, Partial pressure of arterial oxygen.

OTHER CARDIAC PROCEDURES

Surgical Ablation of Atrial Fibrillation

In the United States, 2.7 to 6.1 million persons are estimated to have atrial fibrillation.[1] Among Medicare patients 65 years old or older, the prevalence of atrial fibrillation increased from 3.2% in 1992 to 6.0% in 2002 and is higher in older patients.[344] Stroke remains the most feared complication of atrial fibrillation; stroke risk is fourfold to fivefold higher in patients with atrial fibrillation than in patients without this arrhythmia. Additionally, atrial fibrillation causes 24% of strokes in patients older than 80 years old.[1]

With regard to persistent atrial fibrillation, both the left atrium and the pulmonary veins have been implicated in the pathogenesis and maintenance of persistent atrial fibrillation. Paroxysmal atrial fibrillation, conversely, may result from the juxtaposition of the pulmonary vein endothelium and the LA endocardium. The transition of the electrical signal from one type of tissue to the other is probably responsible for this arrhythmia.

The classic Maze procedure is currently the most effective curative therapy for atrial fibrillation.[345,346] To simplify the procedure and improve its results, Cox and colleagues modified the operation twice, hence its current name, the Cox-Maze III procedure.[345] This procedure appears to cure atrial fibrillation in 99% of cases.[346] Current indications for the Cox-Maze III operation include

drug intolerance, arrhythmia intolerance, and recurrent embolic events.[347]

Ablative treatments for atrial fibrillation involve making RA and LA incisions and cryolesions to interrupt the multiple reentrant circuits that cause atrial fibrillation. Isolating the pulmonary veins and excising the LA appendage (LAA) are integral parts of the Maze procedure, which requires CPB (for 45 to 60 minutes, if the operation is performed by an experienced surgeon) and cardiac arrest.[348-350] This procedure can be performed through a minimally invasive chest incision, as an alternative to sternotomy, while the patient is undergoing CPB and is in cardiac arrest with cardioplegia.

A study done by Prasad and co-workers found that the Cox-Maze III procedure effectively cured atrial fibrillation when the operation was performed alone or concomitantly with coronary or valve procedures.[347] In patients who underwent such concomitant operations, the Cox-Maze III procedure did not significantly add to the mortality or morbidity associated with the revascularization or valve repair procedure.

The underuse of the Maze procedure in the past probably reflected the procedure's perceived complexity. Currently, newer technologies enable the rapid creation of lines of conduction blockade, which surgeons use to ablate atrial fibrillation in patients undergoing concomitant cardiac surgical procedures. These technologies include alternate energy sources such as radiofrequency (RF) and microwave energy, ultrasound, cryotherapy, and laser (Table 67-17). These technologies are also used in minimally invasive surgical ablation procedures to cure isolated atrial fibrillation.[346] Furthermore, the development of epicardial probes has facilitated off-pump ablation of atrial fibrillation in the beating heart.

Because cardiac structures can be visualized directly during open surgical procedures, ablation lines can be created safely, thus avoiding the complication of pulmonary vein stenosis. An epicardial approach to ablation eliminates the risk of esophageal injury.[345,346] The advantage of a surgical approach is the ease of excising the LAA, which virtually eliminates the risk of stroke. However, isolation of the pulmonary vein and excision of the LAA can now be done through the minimally invasive "keyhole approach" (Fig. 67-40) or a thoracoscopic approach.[351] Both approaches can be used without the need for CPB.[346] As experience with the Cox-Maze procedures increases and the technology continues to advance, the goal is to improve patients' quality of life and free them from the need for antiarrhythmic and anticoagulant medications.

TABLE 67-17 ENERGY SOURCES FOR SURGICAL ABLATION OF ATRIAL FIBRILLATION

Energy Type	Endocardial Application	Epicardial Application	Flexible Probe	Assess Transmural	No Char	Rapid
Radiofrequency*	+	+	+	+	–	+
Microwave	+	+	+	–	+	+
Cryothermy	+	+	–	–	+	–

From Gillinov AM, Blackstone EH, McCarthy PM: Atrial fibrillation: current surgical options and their assessment, Ann Thorac Surg *74:2210-2217, 2002.*
*Radiofrequency energy may be delivered in unipolar or bipolar fashion. A commercially available bipolar instrument allows the operator to assess transmurality.

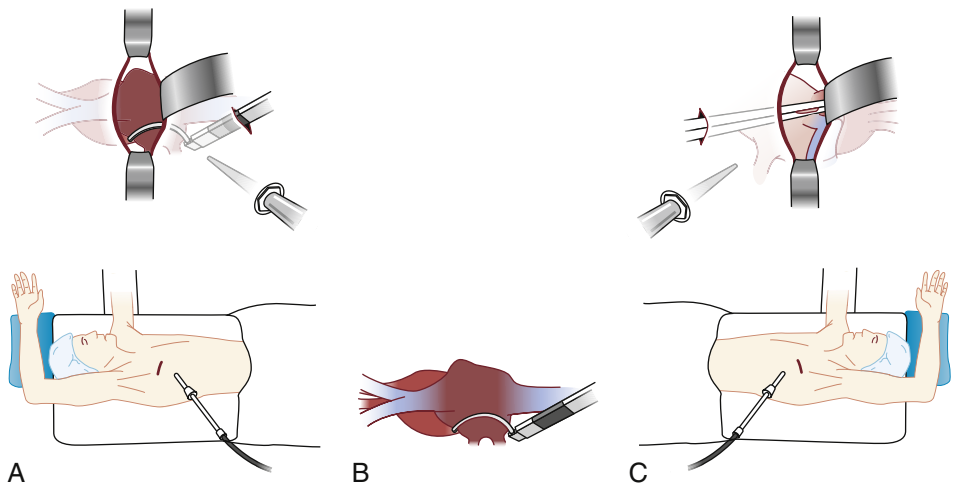


Figure 67-40. "Keyhole" approach for minimally invasive epicardial pulmonary vein isolation with excision of the left atrial appendage. **A,** Access to the right pulmonary veins is gained through a keyhole incision under endoscopic guidance. **B,** A bipolar radiofrequency clamp is used to isolate the left atrial cuff adjacent to the right pulmonary veins. **C,** Stapled excision of the left atrial appendage after the left pulmonary veins are isolated with a technique similar to that shown for the right pulmonary veins. *(From Gillinov AM, Wolf RK: Surgical ablation of atrial fibrillation,* Prog Cardiovasc Dis *48:169-177, 2005.)*

Pericardial Tamponade and Constrictive Pericarditis

Pericardial Tamponade. The pericardial sac has two layers: the outer, parietal pericardium; and the inner, visceral pericardium (epicardium), which is directly adherent to the surface of the heart. The normal amount of fluid between the two layers is 15 to 30 mL, which generates a pressure that is 5 mm Hg less than the CVP and approximates the pleural pressure.

Cardiac tamponade occurs when the volume of fluid trapped in the pericardial sac increases and compresses the heart, thereby compromising CO.[352] In classic tamponade, the circulation adapts by increasing the systemic venous and pulmonary venous pressures to equalize with the pericardial pressure so that total collapse of the cardiac chambers is prevented.[353] The PCWP and the LV, RV, and RA diastolic pressures increase to equalize with the pressure in the pericardium. As a result, the atrial and ventricular diastolic transmural pressures are essentially zero, a hallmark of pericardial tamponade. Although this virtual loss of pressure reduces the stroke volume, high adrenergic tone helps to partially preserve CO by increasing the heart rate.

If enough fluid accumulates, the pericardium reaches a stage at which it can no longer distend; therefore, the total pericardial volume no longer changes throughout the respiratory cycle.[353] This results in a phenomenon referred to as ventricular interdependence, wherein any change in the volume of one side of the heart causes the opposite change in the volume of the other side. During inspiration, increased venous return and filling of the right heart cause the interatrial and interventricular septa to bulge to the left, and opposite changes occur during expiration. Such ventricular interdependence is evident on echocardiography.

Ventricular interdependence manifests clinically as pulsus paradoxus,[354] an exaggeration of the normal diminution of the radial pulse on inspiration (Fig. 67-41). *Pulsus paradoxus* is defined as a drop in systolic blood pressure exceeding 10 mm Hg during inspiration.[355] In particularly severe cases, no brachial or radial pulse may be palpable on inspiration.[356]

Cardiac tamponade is not necessary to cause pulsus paradoxus. Wide swings in intrathoracic pressure and conditions such as pulmonary embolism or hypovolemic shock can also give rise to the phenomenon. Additionally, patients with cardiac tamponade may not have pulsus paradoxus if they have coexisting aortic insufficiency, ASD, or preexisting elevated LVEDP resulting from LV hypertrophy or dilatation.

Figure 67-42 illustrates the pressure-volume relationship in the pericardium, depending on whether the effusion is accumulating slowly or rapidly.[356] This "J"-shaped curve suggests that a sudden increase in pericardial fluid volume of 100 to 200 mL can increase pericardial pressure to 30 mm Hg or more and cause severe cardiac tamponade. The faster the fluid accumulation, the more severe is the hemodynamic compromise. Causes of this type of acute tamponade include rupture of a thoracic aortic aneurysm, traumatic mediastinal injury, and accidental puncture of a cardiac chamber or blood vessel in the CCL.[353]

When accumulation of pericardial fluid is slower, compliance of the parietal pericardium is greater, and changes in volume produce smaller rises in pressure than they would if fluid accumulated more rapidly. As pericardial volume increases, so does intrapericardial pressure, with

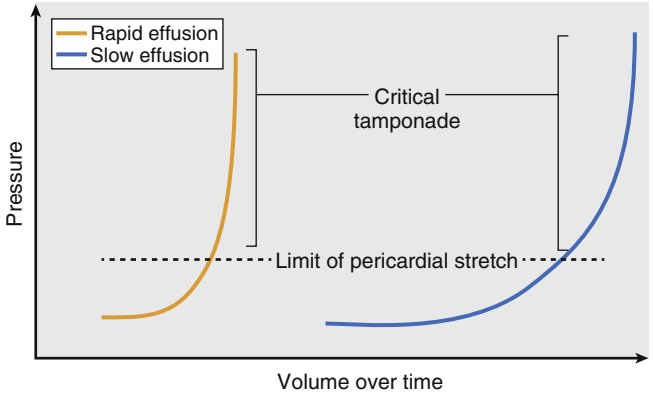


Figure 67-42. Cardiac tamponade. Pericardial pressure-volume (or strain-stress) curves are shown in which the volume increases slowly or rapidly over time. On the *left,* rapidly increasing pericardial fluid first reaches the limit of the pericardial reserve volume (the initial flat segment) and then quickly exceeds the limit of parietal pericardial stretch, thus causing a steep rise in pressure, which becomes even steeper as smaller increments in fluid cause a disproportionate increase in the pericardial pressure. On the *right,* a slower rate of pericardial filling takes longer to exceed the limit of pericardial stretch because more time is available for the pericardium to stretch and for compensatory mechanisms to become activated. *(From Spodick DH: Acute cardiac tamponade,* N Engl J Med *349:684-690, 2003).*

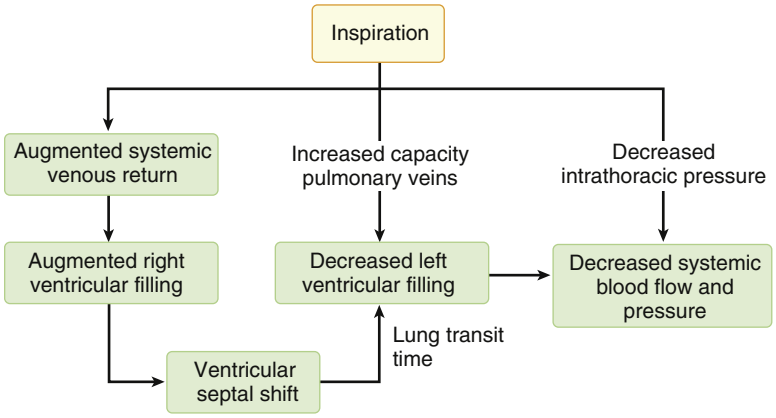


Figure 67-41. Physiology of paradoxical pulses in cardiac tamponade. *(From Fowler NO: Diseases of the pericardium. In Harvey WP, de Leon AC Jr, Leonard JJ, et al, editors:* Curr Probl Cardiol *2:6-38, 1978.)*

a compensatory increase in CVP to maintain a gradient to allow cardiac filling.[352] When pericardial compliance cannot increase further, the intrapericardial pressure gradually equalizes with the pressures in the cardiac chambers. CO gradually declines, accompanied by a compensatory tachycardia, peripheral vasoconstriction, and increased contractility.

Symptoms and Signs of Pericardial Tamponade. Patients with pericardial tamponade may present with pain or feelings of fullness in the chest, dyspnea, lethargy, fever, cough, weakness, fatigue, anorexia, or palpitations.[352] The Beck triad may appear as a combination of three signs of severe tamponade: low blood pressure, increased jugular venous pressure, and distant heart sounds. However, patients whose tamponade develops secondary to a chronic medical condition (e.g., malignant disease, end-stage renal disease, collagen vascular disease) may not present with the classic findings of the Beck triad.

Echocardiographic Features of Pericardial Tamponade. Of the various echocardiographic signs of cardiac tamponade (Box 67-15), one of the best established is diastolic collapse of the right atrium or right ventricle. RV collapse, seen in early diastole, appears as an invagination of the RV free wall (Fig. 67-43). In contrast, RA collapse is seen in late diastole and early systole and appears as an invagination of the RA wall (see Fig. 67-43). The timing of the collapse of the two chambers is related to the lowest intracavitary pressures in those chambers (i.e., early diastole for the right ventricle and late diastole for the right atrium). The presence of both RV and RA collapse indicates hemodynamically significant pericardial effusion. Left-sided heart collapse is rarely seen, both because the thickness and stiffness of the left ventricle enable it to resist collapse and because the left atrium is located posteriorly. However, in patients with very large effusions, fluid does accumulate behind the left atrium and eventually collapses this chamber.[357] The presence of LA collapse is highly specific for tamponade.[356]

Anesthetic Management of Pericardial Tamponade. Indications for pericardiocentesis (surgical drainage of the pericardial effusion) were summarized by Soler-Soler and co-workers (Box 67-16).[358] Surgical intervention for pericardial disease warrants invasive monitoring, which should involve an intraarterial catheter and possibly a central venous catheter.

In patients who are severely hemodynamically compromised, one surgical option is to perform pericardiocentesis or subxiphoid exploration using local anesthesia[359] and inducing general anesthesia after the tamponade has

BOX 67-15 *Doppler Echocardiographic Signs of Cardiac Tamponade*

- Exaggerated inspiratory variation of the two ventricles (inspiratory expansion of the right ventricle and simultaneous compression of the left ventricle; reciprocal changes in the expiratory phase)
- Right atrial collapse
- Right ventricular collapse
- Left atrial collapse
- Left ventricular collapse
- Inferior vena cava plethora
- Abnormal increased respiratory variation in transvalvular blood flow velocities (mitral and aortic flow reduction in the inspiratory phase)

From Pepi M, Muratori M: Echocardiography in the diagnosis and management of pericardial disease, J Cardiovasc Med (Hagerstown) *7:533-544, 2006.*

BOX 67-16 *Indications for Pericardiocentesis and Surgical Drainage*

Pericardiocentesis is indicated in patients with overt clinical tamponade, in patients with suspected purulent pericarditis, and in patients with idiopathic chronic large pericardial effusion.

Indications for surgical drainage are tamponade, either unresolved or relapsing after pericardiocentesis, and persistent active illness 3 weeks after hospital admission.

Pericardial drainage does not seem to be warranted in the initial management of patients with large pericardial effusions without clinical tamponade because of its low diagnostic yield and poor influence on the evolution of pericardial effusion. Even the presence of echocardiographic right chamber collapse (suggesting raised intrapericardial pressure) does not by itself warrant pericardial drainage because most of these patients do not develop overt tamponade.

Modified from Soler-Soler J, Sagrista-Sauleda J, Permanyer-Miralda G: Management of pericardial effusion, Heart *86:235-240, 2001.*

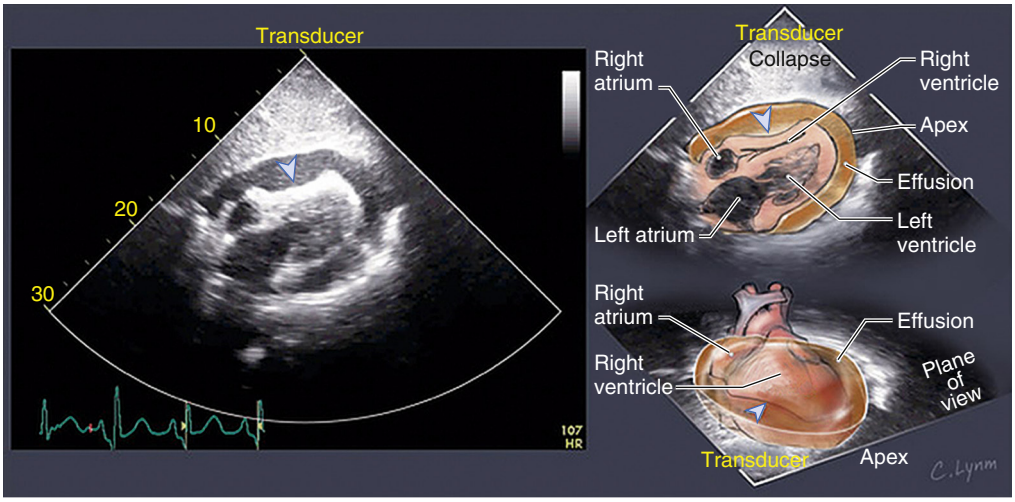


Figure 67-43. Echocardiogram (and drawings) showing pericardial effusion causing cardiac tamponade. A subcostal view in early diastole shows a large circumferential pericardial effusion compressing the heart, with the right ventricle completely collapsed (*arrowheads*). *(From Roy CL, Minor MA, Brookhart MA, et al: Does this patient with a pericardial effusion have cardiac tamponade?* JAMA *297:1810-1818, 2007.)*

been partially relieved. If general anesthesia is planned, the watchwords in the management of cardiac tamponade are *fast*, *full*, and *strong*. Intravenous fluids should be administered before induction of anesthesia to optimize preload. Increasing intravascular volume helps to increase the effective filling pressures of the heart, restore the gradient between the chambers, and increase arterial pressure.

Any manipulation that can decrease venous return to the heart should be avoided. This includes controlled positive-pressure ventilation with large tidal volumes, which may significantly decrease preload and CO.[359] Instead, if general anesthesia is required, one option is to allow the patient to breathe spontaneously until the pericardial sac is opened.[359] Alternatively, a ventilation pattern of high rate and low tidal volumes can be used to minimize mean airway pressure.

Drugs that may cause myocardial depression should be avoided. Additionally, bradycardia should be avoided because tachycardia is the most important compensatory mechanism for preserving CO. The use of ketamine to induce general anesthesia for creation of a pericardial window has been described.[360]

Once cardiac tamponade is relieved, endogenously generated and exogenously administered catecholamines may cause sudden, severe increases in blood pressure and heart rate. This phenomenon should be anticipated and treated.

Constrictive Pericarditis

Pathophysiology. Constrictive pericarditis is said to be present when the diastolic filling of the heart is restricted by a thickened and adherent pericardium. Several causes of constrictive pericarditis have been identified, including infectious processes. In addition, radiation to the chest area and cardiac surgery itself have emerged as additional causes of constrictive pericarditis over the past few decades.[361] If the two pericardial layers—visceral and parietal—become adherent as a result of fibrosis and calcification of the pericardium, the space between the two layers is obliterated.[361]

Signs and Symptoms of Constrictive Pericarditis. Typically, patients with constrictive pericarditis present with signs and symptoms of right-sided HF. A high driving pressure across the valves causes a rapid filling of the ventricles in diastole and results in sudden increase in the ventricular pressures. As the ventricular pressures exceed the atrial pressures, flow abruptly stops, and pressures are elevated and equalized in all four chambers.[361]

Another sign seen in constrictive pericarditis is the Kussmaul sign (an exaggeration of the *x* and *y* descent on the CVP tracing), which is elicited in response to increased blood return to the right side of the heart on inspiration. Because the thickened pericardium no longer allows the heart to expand to accommodate all the blood flowing into it, the pressure generated by this returning volume is transmitted to the central venous system.[362]

As in pericardial tamponade, pulsus paradoxus is also usually seen in constrictive pericarditis. However, in some cases, thickening of the pericardium can shield the myocardium from the effects of the respiratory cycle; therefore, pulsus paradoxus may not be that obvious. Dyspnea and orthopnea are common in patients with constrictive pericarditis because the low CO caused by constrictive pericarditis severely reduces the patient's exercise tolerance and, in extremely advanced cases, causes cardiac cachexia and muscle wasting.[363] Ascites and peripheral edema may also be seen. Echocardiography is particularly helpful in differentiating constrictive pericarditis from other disease processes with similar presenting symptoms, such as restrictive cardiomyopathy.[363,364]

Anesthetic Considerations for Pericardiectomy. The definitive treatment for constrictive pericarditis is pericardiectomy.[365] This procedure is usually performed through a sternotomy, but it can also be performed through a left thoracotomy incision. In patients with severe cases of the disease, pericardiectomy may involve stripping the pericardium off the heart, which may necessitate the use of CPB.

The anesthetic management of a patient undergoing pericardiectomy for constrictive pericarditis is similar to that of a patient having a surgical intervention for pericardial effusion and tamponade. However, because the pericardium may need to be "peeled" from the surface of the heart, pericardiectomy carries an additional risk of arrhythmia and injury to the myocardium itself, including rupture of one of the chambers. Measures should be taken to avoid and treat arrhythmias and massive intraoperative bleeding.

Cardiac and Aortic Trauma

Penetrating Cardiac Injury. With the increase in violent crime over the past few decades, the number of cases of gunshot and stab wounds to the heart has risen. Patients with penetrating cardiac injury may be critically unstable because of hemorrhage or cardiac tamponade, or they may have a benign injury to the heart.[366] Hemodynamic and ECG changes may be deceptively absent in many cases. The absence of these changes does not rule out the presence of life-threatening injury to the heart or its surrounding structures.[367] Echocardiography can identify fluid or blood around the heart and can inform the surgical decision regarding whether to perform a sternotomy or to use an alternative approach.[366,368]

The anesthetic management of patients with penetrating cardiac injury is similar to that of other trauma patients. Unstable patients require emergency surgical intervention. The anesthesiologist must ascertain that blood is available on first knowledge of impending surgery for penetrating cardiac injury. With critically unstable patients, the anesthesiologist must secure the airway, establish intravenous access, and place the monitoring lines while the surgical incision is being made. An assistant can be very helpful in efficiently caring for such a patient. In planning the induction of anesthesia and the securing of the airway, the anesthesiologist should assume that the patient probably has a full stomach and volume depletion. Monitoring lines should include an arterial line and a central venous catheter. Barring any contraindications, on the basis of the scant history that may be available at that time, TEE should be considered as an additional monitor. Anesthesia management involves attempting to maintain stable hemodynamics and prevent recall. As in any trauma case, if the patient is unstable, controlled postoperative ventilation is usually preferred, including transportation to the ICU with full monitoring and ventilatory support.

Traumatic Aortic Injury. Blunt aortic injury, which can result in either traumatic aortic transection (TAT) or acute rupture, is one of the most common causes of death from blunt trauma, second only to head injury. On arrival at the hospital, only 25% of patients with blunt thoracic trauma and resultant aortic injury (TAT or acute rupture) are alive.[369] Furthermore, the prognosis of patients who survive the initial injury and remain untreated is poor: 30% die within the first 6 hours, 50% die in the first 24 hours, and 90% die within the first 4 months.[370]

In blunt trauma to the chest, the mechanism of injury to the thoracic aorta is sudden traction on the relatively immobile portion of the aorta, the isthmus, as a result of sudden deceleration.[369] The isthmus is distal to the left subclavian artery, proximal to the third intercostal artery, and fixed to the left PA by the ligamentum arteriosum. This area of attachment of the ligamentum arteriosum acts as a hinge for movement of the aortic arch; thus, it receives the brunt of the shearing force during violent injury to the chest area. Hence, it is the most common location for rupture of the aorta (50% to 70%), followed by the ascending aorta or the aortic arch in 18% and the distal thoracic aorta in 14% of cases.[369] The spectrum of injuries to the thoracic aorta in blunt thoracic trauma ranges from simple subintimal hemorrhage to complete aortic transection.

The diagnosis of the aortic injury may be made on the basis of a plain chest radiograph, computed tomography, angiography, or TEE. TEE can also detect cardiac tamponade, left pleural effusion, hypovolemia, ventricular dysfunction from myocardial contusion, or vascular injuries from penetrating chest wounds.[371] Diagnosing TAT with TEE requires recognition of a mural flap at the site of intimal disruption and corresponding deformities of the aortic wall caused by a contained rupture. A gap of more than 7 mm between the probe and the aorta at the level of the proximal descending thoracic aorta, in addition to blood between the aortic wall and the pleura, strongly suggests disruption of the aorta. TEE can also be useful in monitoring the progression of a small intimal tear or as a screening tool for patients who have a normal mediastinum after blunt thoracic trauma.

Management of TAT focuses on the high risk of rupture that this injury entails. The unpredictable timing of this event adds to the concerns regarding these patients. Aggressive management of blood pressure in the preoperative period is necessary to minimize the risk of rupture.[372] Systolic blood pressure should not exceed 100 mm Hg, and the heart rate should not exceed 100 beats/minute. The use of β-blockers and nitroglycerin or sodium nitroprusside infusions is recommended.

Intraoperative monitoring should include an arterial catheter and central venous access. The keys to anesthetic management of patients with TAT are avoiding wide swings in systolic blood pressure and continuously monitoring the patient for end-organ ischemia. Because many operations on patients with TAT are performed on an emergency basis, it may be necessary to use a modified rapid-sequence induction. Despite all precautions, marked swings in blood pressure are often seen during induction and laryngoscopy. Agents such as nitroglycerin and esmolol should be immediately available to treat any undesirable hypertension during endotracheal intubation, TEE probe insertion, and surgical incision.

Surgical repair of injuries to the ascending aorta or aortic arch typically requires CPB with DHCA. Injuries to the descending thoracic aorta may require open repair of a short segment. Challenges include preservation of vital organs, particularly the spinal cord. In open procedures, use of partial LHB can facilitate the operation and at the same time preserve visceral organ and spinal cord perfusion. This technique also prevents aggravation of any other injuries that the patient may have sustained because this type of bypass does not require heparin.[370] Although open repair is possible, transcutaneous endovascular aortic repair has emerged as the preferred intervention whenever possible, (STS class I recommendation; level of evidence B)[373,374] (see Chapter 69).

Ischemic and Other Emergencies in the Cardiac Catheterization Laboratory

With rapid advances in interventional cardiology, the number of patients in the United States and Europe who undergo interventional therapy in a CCL is increasing. Such emergencies include coronary artery dissection, free rupture, tamponade, foreign body embolism, and wire entrapment. Patients may be at high risk for complications in the CCL if they have unfavorable coronary anatomy or severe ventricular dysfunction. In some cases, cardiac surgery and cardiac anesthesia services should be consulted and placed on standby for a possible emergency intervention. Rapid surgical intervention, such as revascularization or temporary mechanical support, is crucial to reducing the mortality and morbidity of patients who suffer angiography-related accidents.

When ischemic complications occur during cardiac catheterization with percutaneous transluminal coronary angioplasty and stenting, pharmacologic intervention and, possibly, a device such as an IABP or VAD may be used to stabilize the patient's hemodynamic condition before the patient is transferred to the operating room on an urgent or emergency basis for open coronary revascularization. Patients may be intubated on an emergency basis in the CCL. Patients with coronary dissection or severe ischemia may require CPR during transport to the operating room.[375] Although the anesthesiologist, cardiologist, or both may lead these resuscitative efforts, all members of the catheterization team—physicians, nurses, and technologists—should complete a course in basic CPR; additionally, certification in advanced cardiac life support, with annual recertification, is strongly urged.[376]

If the patient is not already intubated, the choice of induction agents should be tailored to the patient's hemodynamic condition; one should avoid hypotension and tachycardia while keeping in mind the patient's NPO (nothing by mouth) status. Perioperative monitoring of these patients should include an arterial line and central intravenous access, which should be established as soon as possible. TEE can be of immense importance in both diagnosing the cardiac problem and monitoring the patient intraoperatively.

Other procedures performed in the CCL, invasive vascular laboratory, and electrophysiology laboratory—notably aortic aneurysm stenting and ablation procedures—may

also require operating room backup. A dedicated surgical team should be available in the event of a life-threatening complication. Planning for the possibility of conversion to an open procedure, such as in cases of an aneurysm leak or catheter perforation of a major blood vessel or cardiac chamber, is imperative. A hybrid interventional cardiovascular suite is ideal for such events.[291] In institutions without such a hybrid suite, urgent transportation to a general operating room may be necessary.

Optimal care also depends on the ready availability of a stat laboratory. Blood gas analysis, as well as the assessment of electrolytes and hemoglobin or hematocrit, is important in urgent situations. Patients undergoing procedures for coronary revascularization may be receiving platelet inhibitor drugs. Conventional coagulation tests may not be sufficient for diagnosing clinical bleeding in these patients; tests that evaluate platelet function are useful.[377]

Compared with elective cardiac surgical procedures, emergency cardiac surgery carries higher mortality and morbidity risks, especially if the patient is in cardiogenic shock.[378] Identifying high-risk patients going to the CCL for interventional procedures, as well as communication about these high-risk patients among the interventional cardiologists, cardiac surgeons, and cardiac anesthesiologists, is of prime importance in improving the outcome of these emergency procedures.

PROCEDURES IN THE CARDIAC CATHETERIZATION LABORATORY AND THE HYBRID OPERATING ROOM

GENERAL CONSIDERATIONS

Since the 1990s, the scope of activity in the CCL and electrophysiology laboratory has greatly increased and has diverged considerably from the simple diagnosis and evaluation of valvular heart disease, CAD, and CHD.[289,290,376,379] Procedures and interventions in these settings are more complex and often involve acutely ill patients.[290] Cardiac anesthesiologists may find themselves in a relatively isolated environment with bulky equipment, subdued lighting, and limited access to the patient.[375,379] Assistance from surgical colleagues, if required, may not be readily available, nor may the services of anesthesia support personnel, the pharmacy, and the stat laboratory. Finally, for patients with moderate or severe cardiac disease who have undergone heavy sedation or general anesthesia, a suitable recovery area may be in a distant location.

Because fluoroscopy is frequently used during interventional procedures in the CCL and hybrid operating rooms, it can present a significant risk of radiation exposure to both patients and health care workers. The potential hazards of ionizing radiation include skin injuries and cellular mutation, which can lead to leukemia, bone cancer, and birth defects. The radiation safety program at the Centers for Disease Control and Prevention (CDC) has developed the concept that radiation doses should be "as low as reasonably achievable" (ALARA). Exposure to radiation can be minimized by three means: distance, time, and shielding.[376] The distance between the person and the source should be maximized because the dose rate varies with the inverse square of that distance. In addition, the person's exposure time should be minimized because the dose rate and time are directly related. Finally, personal shielding and shielding of the radiation source should be maximized.

The rad is a unit of absorbed dose, which is the energy imparted to matter by ionizing radiation per unit mass of irradiated material at the point of interest.[376] The rem is a unit of effective dose, which is the estimated total body dose. Health care personnel in a radiation environment must wear a dosimeter badge to track cumulative radiation exposure. The dosimeter should be worn on areas at highest risk for frequent exposure, such as the thyroid collar, and outside any shielding garments. Corrective action is recommended if an individual (patient or provider) receives more than 5 rem/year to the whole body (Box 67-17).[376] In the case of pregnant women, the total radiation exposure to the fetus throughout gestation should be no more than 0.05 rad/month or 0.5 rad total.

Identifying patients at risk for a reaction to iodinated contrast material is another consideration unique to procedures performed in the CCL or hybrid suite. A previous anaphylactoid reaction and a history of atopic conditions such as asthma are the most significant risk factors for acute hypersensitivity reactions.[376] Premedication regimens with histamine (H_2) blockers and steroids are recommended for the highest-risk atopic patients, particularly those with a known prior reaction. Current options include giving 50 mg oral prednisone 13 hours, 7 hours, and 1 hour before the procedure or 200 mg intravenous hydrocortisone, with or without H_2 blockers, 2 hours before the cardiac catheterization.[376]

In patients with renal insufficiency, radiocontrast media–induced nephropathy is a concern, and diabetic patients are at particularly high risk for acute renal failure after exposure to contrast agents.[375,376] These effects can be minimized through careful contrast administration and limitation of the total dose. Preprocedural and postprocedural hydration with normal saline solution, sodium bicarbonate, or both is recommended.[376] However, in patients with severe HF or near–end-stage

BOX 67-17 ***Maximum Allowable Radiation Limits for Medical Workers***

Whole body	5 rem/yr (50 mSv/yr)
Skin	50 rad/yr (500 mGy/yr)
Lens of eye	2 rad/yr (20 mGy/yr)
Fetus (for pregnant worker)	0.5 rad (5 mGy) for total pregnancy or 0.05 rad/mo (0.5 mGy/mo) (estimated by abdominal badge under lead apron
Cumulative exposure (lifetime)	1 rem × age (10 mSv × age)

Modified from Bashore TM, Balter S, Barac A, et al: 2012 American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions expert consensus document on cardiac catheterization laboratory standards update: a report of the American College of Cardiology Foundation Task Force on Expert Consensus documents, J Am Coll Cardiol *59:2221-2305, 2012.*

renal disease, one must be careful to avoid volume overload.[375,376] Elevated serum creatinine levels are common after the administration of radiocontrast media, and these levels should be monitored for 72 or more hours in patients at risk. Two definitions (an incremental increase >0.5 mg/dL or a rise >25% in serum creatinine level) are now accepted as indicators of contrast-induced nephropathy. Fortunately, renal dysfunction is usually transient and rarely progresses to acute renal failure.

HYBRID OPERATING ROOM

To address some of the issues regarding the technologic and procedural demands regarding surgical and imaging equipment for selected endovascular and transcatheter procedures, hybrid operating rooms have been built in many institutions. These rooms have complete dual capabilities for procedures that require fluoroscopy, open surgery, or both. Ideally, such rooms are within or adjacent to the regular surgical suite. The physical location of such hybrid rooms may represent an advance in care in that key personnel are more readily available to handle unanticipated complications and emergencies.

The types of procedures that are performed in the CCL or the hybrid operating room vary according to institutional preferences but may include (1) electrophysiology procedures, (2) percutaneous management of valvular lesions, (3) the use of occlusion or umbrella devices to close an ASD or VSD or a PDA, (4) percutaneous VADs, and (5) stenting of abdominal or thoracic aortic aneurysms.[289-291]

Although requirements vary depending on the nature of the procedure, sedation or anesthesia improve the efficacy and safety of many procedures.[379] Providing stable hemodynamics for organ perfusion and preservation during anesthesia is an important goal. Some procedures can be performed with the aid of monitored anesthesia care or regional blocks, provided a certain patient comfort level can be achieved. However, during difficult and lengthy procedures, patients may have trouble staying still. In many cases, a general anesthetic regimen may be the best option. If indicated, general anesthesia with endotracheal intubation provides a controlled situation: the patient's comfort is maximized, and the airway is secured.[375] Use of a laryngeal mask or a standard mask airway is also possible, but the constant diaphragmatic movements that occur during spontaneous ventilation may interfere with fluoroscopic visualization of cardiac and vascular structures. In the absence of significant complications or comorbid conditions, the patient may be allowed to emerge from anesthesia before being transferred to the CCL recovery area and, eventually, to a hospital floor. In more complex cases, the patient may be transferred to an ICU.

Percutaneous mitral valve repairs (e.g., correction of MR and commissurotomy for MS) share the same advantages as TAVI with respect to avoiding sternotomy, implementing CPB, and cross-clamping the aorta.[289] These procedures are similarly performed with the patient under general anesthesia, with fluoroscopic and TEE guidance.[290]

Percutaneous closure procedures are used to close ASDs and, less commonly, VSDs, as well as PDAs and fenestrations.[290,379] Echocardiography is used to help guide device placement and confirm a successful result. If TEE is used, general anesthesia is necessary. If intracardiac echocardiography is used, the procedure can potentially be performed with sedation only.[290] Large-bore peripheral or femoral venous access is needed, and a radial arterial line is often placed.

Percutaneous VADs (TandemHeart, Cardiac Assist, Inc., Pittsburg, Pa., and Impella Recover LP 2.5 and 5.0, Abiomed, Inc., Danvers, Mass.) are placed in patients undergoing high-risk coronary interventions or ablation procedures or who are in cardiogenic shock.[290] These devices can produce CO that completely replaces LV function with nonpulsatile blood flow. Hence, pulse oximetry and noninvasive blood pressure measurement may not work properly. Either sedation or general anesthesia can be used, depending on the patient's hemodynamic status and ability to cooperate. Invasive monitoring is available because arterial cannulation is used during the procedure.[290] Large-bore intravenous access is desirable because a large amount of blood loss is possible. Surgical backup is necessary during these procedures.

Endovascular abdominal aortic aneurysm repair is a minimally invasive but high-risk procedure. Further details of endovascular repair of abdominal aortic aneurysms appear in Chapter 69.

ELECTROPHYSIOLOGIC PROCEDURES

Anesthetic Considerations for Supraventricular Arrhythmia Surgery and Ablation Procedures

Invasive cardiac electrophysiology studies are now common procedures in the CCL. RF catheter ablation has, in many cases, replaced pharmacologic antiarrhythmic therapy for the treatment of recurrent or persistent tachyarrhythmias. Tachyarrhythmias appropriate for this treatment include those with a focal origin and, more commonly, those with a reentrant circuit. Electrophysiologic studies in the CCL usually involve inducing the tachycardia, mapping it, and performing transcatheter RF ablation. Three to five electrode catheters are inserted percutaneously by venous access or by retrograde aortic catheter insertion and a transseptal approach. The catheters are positioned within the heart to allow induction of the arrhythmia and recording at key sites. The arrhythmia may be induced with pacing maneuvers that introduce critically timed ectopic beats to establish reentrant excitation. Heightened adrenergic tone, usually achieved by administering isoproterenol, may be necessary.

Arrhythmia induction is unpleasant and requires some sedation. Although many procedures in the CCL and electrophysiology laboratory are performed by using mild to moderate sedation (with fentanyl and midazolam) administered by trained nonanesthesia personnel and local anesthetic infiltration at the site of catheter placement by the cardiologist, an anesthesiologist is needed for patients and procedures with complications.[290] General anesthesia with endotracheal intubation is generally chosen for longer procedures and those that absolutely require the patient's immobility during critical lesion

placement.[380] Usually, a small dose of opioid, an induction agent, an intermediate-duration muscle relaxant, and a volatile agent are used.[380] However, many agents commonly used as part of the anesthetic technique may affect cardiac rhythm (e.g., lidocaine), and the use of such agents should be discussed with the electrophysiologist. All inhalational agents affect the conduction system of the heart, whereas most intravenous induction agents have little effect on this system.[379] Once the arrhythmia's site of origin has been identified, the electrode catheter is positioned in direct contact with this site, and RF energy is delivered through the catheter. Any patient movement during ablation can result in catheter dislodgment and potential damage to normal conduction tissue.

Monitoring of patients undergoing catheter-based ablation of atrial fibrillation includes direct arterial pressure monitoring. Furthermore, LAA thrombus must be excluded with TEE examination before catheter-based ablation and surgical manipulations. Finally, esophageal temperature monitoring is critical because even a small increase in temperature (0.1° C) is reported to the electrophysiologist, who immediately terminates RF energy and cools the catheter tip with intraprobe saline.[380]

If catheter RF ablation fails, pulmonary vein foci isolation and catheter ablation or a surgical approach may be required. Further details are provided in the section of this chapter on surgical ablation of atrial fibrillation.

Pacemaker or Automated Implantable Cardioverter-Defibrillator Insertion, Generator Change, and Laser Lead Extraction

ICDs are capable of pacing, as well as detecting and correcting, tachyarrhythmias (e.g., with shocks or antitachycardia pacing) (Box 67-18).[380] Considerable progress has been made with respect to reducing device size, lengthening battery life, and improving treatment algorithms. Such devices are often indicated for patients with advanced HF to decrease their risk of sudden death.[315] Thus, many of these patients have multiple comorbidities, including a history of ventricular tachycardia (VT) or ventricular fibrillation, low EF, and CAD.

BOX 67-18 ***Implantable Cardioverter-Defibrillator***

- Implantable cardioverter-defibrillators (ICDs) are capable of pacing, as well as providing tiered therapy for tachyarrhythmias (e.g., shocks, antitachycardia pacing).
- Modern devices are inserted almost exclusively with percutaneous techniques.
- ICDs are indicated for the primary or secondary prevention of sudden cardiac death.
- ICDs have been shown to reduce the incidence of total mortality compared with standard treatment alone.
- ICDs are indicated for individuals who survive sudden cardiac death without a reversible cause, individuals with ischemic cardiomyopathy and an ejection fraction ≤30%, and individuals with ischemic or nonischemic cardiomyopathy, an ejection fraction ≤35%, and New York Heart Association class II or III heart failure symptoms.

From Kaplan JA, Reich DL, Savino JS, editors: Kaplan's cardiac anesthesia: the echo era, *ed 6, St. Louis, 2011, Saunders, p 92.*

The insertion of current devices usually involves percutaneous techniques performed in the CCL.[380] The procedure includes defibrillation testing. External cardioverter-defibrillator pads are placed and connected before the procedure begins.[290,380] These pads are used to induce ventricular fibrillation and to serve as backup if the implanted device fails. Monitored anesthesia care is usually chosen, but brief unconsciousness is needed for defibrillation testing. If the patient has severe comorbidities or anxiety, general anesthesia may be needed. Such patients require close monitoring, often involving an arterial catheter, because of the potential for rapid blood pressure changes during the testing process. It may take some time for hemodynamic variables to return to baseline after tests involving purposeful fibrillation followed by defibrillation.

Laser extraction of an ICD lead that is infected or damaged is another procedure that may be of long duration and require general anesthesia. The lead may be firmly attached to the endocardium, thus necessitating the use of a special coaxial laser device that slides over the lead to help burn it free. Myocardial perforation with ensuing cardiac tamponade is a rare but potentially lethal complication of this procedure.[375]

Biventricular Pacing

In many patients with advanced HF, defects in sinus or AV node function, intraventricular conduction defects (commonly left bundle branch block), or both delay the onset of LV or RV systole.[381] This lack of coordination between the left and right ventricles further reduces CO and may increase mortality risk in these patients.[318] Cardiac resynchronization therapy is a variant of traditional AV pacing that involves placing additional pacing leads on the lateral wall of the left ventricle in a coronary vein (accessed through the coronary sinus). Both ventricles can then be paced in a carefully timed manner to resynchronize RV and LV contraction, thus improving mechanical efficiency and CO.

Anesthesiologists are sometimes asked to provide sedation during these procedures, which may be somewhat lengthy. These patients have extremely low EFs and may have associated comorbidities, including valvular heart disease, pulmonary hypertension, and RV dysfunction.[290] Patients may not be able to breathe comfortably while lying flat, and they may easily become hemodynamically unstable because of vasodilation or hypercapnia as sedation is administered. As noted by Shook and Savage,[290] the anesthesiologist must be ready to convert to general anesthesia at any time during the case.

PROBLEMS IN THE POSTOPERATIVE PERIOD

LOW CARDIAC OUTPUT SYNDROME

Although improvements in myocardial protection have occurred during the past decades, it is well documented that significant declines in LV function after CABG and other cardiac operations occur in the first 8 to 24

postoperative hours.[382] A combination of ischemia and reperfusion injury after cardiac surgery contributes to an energy deficit state in the myocardium that limits uptake of exogenous energy substrates from blood (Box 67-19). Prolonged aortic cross-clamp time, incomplete revascularization, or poor myocardial preservation adds additional risk. In particular, patients with preexisting LV dysfunction experience a delay in myocardial recovery after cardiac surgery and require measures to relieve the workload of the heart. Furthermore, preexisting diastolic dysfunction is associated with an increased risk of difficulty in weaning from CPB and ongoing need for vasoactive support during the postbypass period and in the ICU.[383]

Criteria used to define low CO syndrome (LCOS) include a cardiac index of less than 2.4 L/minute/m^2, elevated lactate levels, and urine output of less than 0.5 mL/hour for more than 1 hour.[384] In addition, $S\bar{v}O_2$ is a good indicator of LCOS in that it reflects the balance between CO and systemic O_2 demand.

Postoperative management of patients at high risk for LCOS requires a physiologic approach. Optimizing preload and reducing afterload help maximize cardiac function. Both tachycardia and bradycardia should be avoided, and postoperative arrhythmias should be treated. In addition, shivering should be prevented because it raises the heart rate by increasing oxygen demand. Postoperative deep sedation and muscle relaxation are often used to reduce myocardial workload by reducing the body's overall metabolic demand by 25% to 30%.

BOX 67-19 ***Risk Factors for Low Cardiac Output Syndrome After Cardiopulmonary Bypass***

- Preoperative left ventricular dysfunction
- Valvular heart disease requiring repair or replacement
- Long aortic cross-clamp time and total cardiopulmonary bypass time
- Inadequate cardiac surgical repair
- Myocardial ischemia and reperfusion
- Residual effects of cardioplegia solution
- Poor myocardial preservation
- Reperfusion injury and inflammatory changes

From Kaplan JA, Reich DL, Savino JS, editors: Kaplan's cardiac anesthesia: the echo era, *ed 6, St. Louis, 2011, Saunders, p 1028.*

Pharmacologic support is often needed to improve contractility as the patient is weaned from CPB and, eventually, recovering in the ICU (Table 67-18).[384,385] Catecholamines (β-adrenergic agonists) and phosphodiesterase inhibitors are the main classes of pharmacologic agents used for this purpose. Catecholamines (e.g., epinephrine, norepinephrine, dopamine, dobutamine, dopexamine, isoproterenol) are often the first line of therapy. They exert positive inotropic action by stimulating the β_1 receptor, which leads to increased intracellular cyclic adenosine monophosphate (cAMP). The predominant hemodynamic effect of a specific catecholamine depends upon the degree to which the α, β_1, β_2, and dopaminergic receptors are stimulated (see Chapters 16 and 20 for specific drug pharmacology and doses.) Phosphodiesterase inhibitors (e.g., milrinone, amrinone), sometimes termed inodilators, may be used either as first-line therapy or added to β-adrenergic therapy. Phosphodiesterase inhibitors augment β-adrenergic stimulation by inhibiting the breakdown of cyclic adenosine monophosphate. When these drugs are added to catecholamine infusions, the result is an additive or possibly synergistic increase in inotropy. Phosphodiesterase inhibitors also induce systemic and pulmonary vasodilation. Hence, they are particularly useful in patients with pulmonary hypertension, RV failure, or aortic or mitral valve regurgitation.

Although not yet available in the United States, a newer class of drugs—calcium sensitizers, such as levosimendan—exhibits potent inodilatory properties.[386,387] Levosimendan works by increasing myocyte sensitivity to calcium by stabilization of the calcium binding to troponin C. This increases calcium sensitivity during systole and enhances myocardial contractility without causing calcium overload during diastole. Therefore, inotropic performance is enhanced, whereas diastolic performance is preserved. Like phosphodiesterase inhibitors, levosimendan may augment inotropy without significantly increasing myocardial oxygen consumption.

RV failure may also be present in patients with LCOS, and it manifests as elevated PA and CVP pressures. Echocardiography can be diagnostic—findings include an enlarged and poorly contracting right ventricle, often with significant TR. The management of RV failure consists of ensuring adequate RV filling and maintaining adequate systemic pressures to prevent RV ischemia. Afterload reduction with agents effective in the pulmonary

TABLE 67-18 **RELATIVE POTENCY OF COMMONLY USED VASOACTIVE DRUGS**

		Cardiac			Peripheral Vasculature	
	Dose	Heart Rate	Contractility	Vasoconstriction	Vasodilation	Dopaminergic
Norepinephrine	2–40 μg/min	+	++	++++	0	0
Dopamine	1–4 μg/kg/min	+	+	0	+	++++
	4–20 μg/kg/min	++	++–+++	++–+++	0	++
Epinephrine	1–20 μg/min	++++	++++	++++	+++	0
Phenylephrine	20–200 μg/min	0	0	+++	0	0
Vasopressin	0.01–0.03 units/min	0	0	++++	0	0
Dobutamine	2–20 μg/kg/min	++	+++–++++	0	++	0
Milrinone	0.375–0.75 μg/kg/min	+	+++	0	++	0
Levosimendan	0.05–0.2 μg/kg/min	+	+++	0	++	0

From Hollenberg SM, Parrillo JE: Acute heart failure and shock. In Crawford MH, DeMarco J, Paulus WJ, editors: Cardiology, *ed 3, Philadelphia, 2010, Saunders, p 964.*

circulation is helpful. Milrinone may reduce PVR and improve CO. Nitric oxide and inhaled prostaglandins are selective for pulmonary vasodilation. Other measures to decrease PVR include hyperventilation (higher respiratory rate) to induce mild hypocapnia and aggressive treatment of hypoxemia and acidosis.

ARRHYTHMIAS

Atrial Arrhythmias

Postoperative arrhythmias (Table 67-19) are seen in a significant number of patients who undergo cardiac surgery; atrial fibrillation is the most common (27% to 40%).[388,389] Patients are at highest risk for new-onset atrial fibrillation 2 to 3 days after cardiac surgery.[389] This arrhythmia can potentially prolong the patient's hospital stay and increase management costs by causing hemodynamic compromise or thromboembolic complications in the postoperative period.[390]

Many potential risk factors have been studied in efforts to predict the occurrence of postoperative atrial fibrillation. With advancing age, dilatation of the atrium interrupts cell-to-cell electrical coupling between atrial muscle fibers. Other preoperative risk factors for postoperative atrial fibrillation include a history of atrial fibrillation, chronic obstructive pulmonary disease, valve surgery, and postoperative withdrawal of a β-blocker or ACEI.[389] Perioperative factors include inadequate atrial protection during surgery, pericardial inflammation, autonomic imbalance during the postoperative period, change in atrial size with fluid shifts, electrolyte (potassium and magnesium) abnormalities, and excessive production of catecholamines.[391] Reduced risk has been associated with the postoperative administration of β-blockers, ACEIs, potassium supplementation, and nonsteroidal antiinflammatory drugs (NSAIDs).[389]

Treatments for atrial fibrillation include both pharmacologic agents and electrical stimulation. Many studies have shown that β blockade significantly reduces the incidence of postoperative atrial fibrillation and that withdrawal of β-blockers increases risk.[392,393] The use of amiodarone for prophylaxis or treatment has also been studied.[394] Most recently, an inexpensive antiinflammatory drug, colchicine, has been studied as a means to prevent postoperative atrial fibrillation.[170] Synchronized cardioversion is reserved for patients who show signs of hemodynamic instability during atrial fibrillation.[395] In the absence of hemodynamic instability, pharmacologic agents are used with the goal of preventing a rapid ventricular response. Drugs usually employed for this purpose include calcium channel blockers, β-blockers, magnesium, and amiodarone. Expert consultation should be obtained before treatment is initiated, especially in a stable patient.[393,395]

Ventricular Arrhythmias

Although ventricular arrhythmias occur after cardiac surgical procedures, sustained ventricular arrhythmias are relatively uncommon. Associated factors may include hemodynamic instability, electrolyte abnormalities, hypoxia, hypovolemia, ischemia or infarction, acute graft closure reperfusion, and the use of inotropic agents.[395]

Ventricular arrhythmias can range from simple premature ventricular complexes (PVCs) to VT. Simple PVCs do not pose a significant risk of life-threatening ventricular arrhythmia. Conversely, complex ventricular arrhythmias, including both frequent PVCs (>30/hour) and nonsustained VT, may make patients prone to sudden death, especially in the long term. Sudden death is even more likely if ventricular function is also compromised. A study of 126 patients with postoperative complex ventricular ectopy found a mortality rate of 75%.[395] Patients with sustained ventricular arrhythmias have a poor prognosis in both the short and the long term.

Patients who are asymptomatic and hemodynamically stable do not usually require immediate treatment for PVCs or even short runs of nonsustained VT, although any reversible causes should be corrected. Conversely, patients with VT accompanied by hemodynamic instability need immediate synchronized cardioversion.[396] Amiodarone is reserved for hemodynamically stable

TABLE 67-19 POSTOPERATIVE RATE AND RHYTHM DISTURBANCES

Disturbance	Usual Causes	Treatments
Sinus bradycardia	Preoperative or intraoperative β blockade	Atrial pacing β-Agonist Anticholinergic
Heart block (first, second, and third degree)	Ischemia Surgical trauma	Atrioventricular sequential pacing Catecholamines
Sinus tachycardia	Agitation or pain Hypovolemia Catecholamines	Sedation or analgesia Volume administration Change or stopping of drug
Atrial tachyarrhythmias	Catecholamines Chamber distention Electrolyte disorder (hypokalemia, hypomagnesemia)	Change or stopping of drug Treatment of underlying cause (e.g., vasodilator, give K^+/Mg^{2+}) Possible need for synchronized cardioversion or pharmacotherapy
Ventricular tachycardia or fibrillation	Ischemia Catecholamines	Cardioversion Treatment of ischemia; possible need for pharmacotherapy Change or stopping of drug

Modified from Kaplan JA, Reich DL, Savino JS, editors: Kaplan's cardiac anesthesia: the echo era, *ed 6, St. Louis, 2011, Saunders, p 1030.*
K^+, Potassium; Mg^{2+}, magnesium.

patients with VT or an uncertain rhythm. Ventricular fibrillation should be treated promptly with electrical defibrillation.[395] For long-term management of ventricular arrhythmias, in addition to antiarrhythmic agents, electrophysiologic studies or placement of an ICD should be considered.

Bradyarrhythmias

Bradyarrhythmias are not uncommon in the immediate postoperative period. In most cases, a temporary epicardial pacemaker is sufficient. In a small percentage of patients, a permanent pacemaker may be necessary, especially in patients with sinus node dysfunction or AV conduction disturbances after either CABG or valve repair.[395] Patients who need a permanent pacemaker may receive either a single-chamber or a dual-chamber pacemaker. Multiple factors dictate which particular device would most benefit an individual patient.[397]

BOX 67-20 ***Vasodilators Available for the Treatment of Perioperative Hypertension***

Adenosine
α_1-Adrenergic antagonists
α_2-Adrenergic agonists
Angiotensin-converting enzyme inhibitors (enalaprilat)
Angiotensin II antagonists
Atrial natriuretic peptide (nesiritide)
β_2-Adrenergic agonists
Dihydropyridine-type calcium channel blockers*
Dopamine agonists
Hydralazine
Nitrovasodilators*
Phosphodiesterase enzyme inhibitors
Prostaglandins

From Levy JH: Management of systemic and pulmonary hypertension, Tex Heart Inst J *32:467-471, 2005.*
**Intravenous vasoactive therapies in widespread use to treat perioperative hypertension.*

HYPERTENSION

Immediately after cardiac surgery, the patient remains prone to hemodynamic instability, including hypertension.[398] Causes of postoperative hypertension are often multifactorial and may include withdrawal from preoperative antihypertensive medications (e.g., β-blockers and centrally acting α_2-agonists), pain, hypoxemia, hypercarbia, and hypothermia. However, arterial vasoconstriction usually plays a central role in acute postoperative hypertension.[399] The hazards of untreated postoperative hypertension include increased myocardial work and oxygen consumption, MI, rhythm disturbances, cerebrovascular accidents, increased bleeding, and even suture line disruption. In the postoperative period, deepening sedation to control a hypertensive episode may not be the best or the only possible approach, particularly if early extubation (fast tracking) is desirable.[398,399]

Several pharmacologic agents are available for use as antihypertensive agents (Box 67-20). The drugs most commonly used in clinical practice are the nitrovasodilators and the dihydropyridine-type calcium channel blockers. Because of its antiischemic effects and familiarity, nitroglycerin is often the first agent used to treat hypertension in patients who have undergone coronary revascularization. However, nitroglycerin is not always effective in such patients because it primarily causes venodilation rather than arterial dilation. In addition, patients tend to develop tolerance to nitroglycerin.[399]

Because arterial vasoconstriction plays an important role in the development of hypertension after cardiac surgery, the therapeutic agent chosen should usually be one that effectively reduces this vasoconstriction. Sodium nitroprusside, a nonspecific venous and arterial vasodilator, is a common choice. However, theoretically, nitroprusside can cause coronary steal.[399] Furthermore, patients with renal failure eliminate sodium nitroprusside more slowly than normal, which makes them vulnerable to the toxic effects of this drug's metabolites (cyanide and thiocyanate).

Fenoldopam is a short-acting dopamine agonist that causes arterial-specific vasodilation by stimulating D_1-receptors. Unlike sodium nitroprusside, fenoldopam increases renal blood flow to produce diuresis and natriuresis.[400] Nevertheless, the results of most clinical trials regarding the renal protective effects of fenoldopam are equivocal. In addition, severe hypertension may require higher doses of fenoldopam, which may be associated with undesirable increases in heart rate.

Dihydropyridine-type calcium channel blockers, such as nicardipine and clevidipine, selectively relax arterial resistance vessels without negative inotropic or dromotropic (conduction) effects and cause generalized vasodilation of the renal, cerebral, intestinal, and coronary vascular beds. Although these drugs cost more than the older agents (nitroglycerin and nitroprusside), nicardipine and clevidipine are recommended by some experts as first-line treatment for cardiac surgical patients with acute hypertension that requires immediate control.[399]

It is important to ensure that the patient's intraarterial pressure is monitored adequately when any vasoactive agent is administered. Vasoconstriction or poor perfusion of the extremities may create a discrepancy between central aortic and peripheral arterial pressures. In addition, a radial arterial catheter may be "positional" if hand positioning is suboptimal, or "dampening" of the tracing may result from poor perfusion of the distal extremities. Occasionally, during the perioperative period, the cardiac anesthesiologist or surgeon must replace a distal peripheral arterial catheter (e.g., with a femoral arterial catheter) to ensure that the effects of vasoactive therapy are monitored accurately.

RENAL INSUFFICIENCY

Perioperative renal failure that necessitates dialysis occurs in approximately 2% of patients.[193] Although the definition of renal insufficiency or failure varies among studies, three useful criteria are (1) a serum creatinine level more than 44 mmol/L (>0.5 mg/dL) higher than its preoperative value, (2) a serum creatinine level more than 50% greater than its preoperative value, and (3) a serum creatinine level more than 177 mmol/L (>2.0 mg/dL).[401] Another definition of acute renal insufficiency involves a classification scheme that uses the acronym RIFLE (Table 67-20).[402]

TABLE 67-20 RIFLE* CLASSIFICATION SCHEME FOR ACUTE RENAL FAILURE

	GFR Criteria	Urine Output Criteria
Risk	Plasma creatinine increased 1.5× or GFR decrease >25%	<0.5 mL/ kg/hr × 6 hr
Injury	Plasma creatinine increased 2× or GFR decrease >50%	<0.5 mL/kg/hr × 12 hr
Failure	Plasma creatinine increased 3×, acute plasma creatinine ≥350 μmol/L, or acute rise ≥44 μmol/L	<0.3 mL/kg/hr × 24 hr or anuria × 12 hr
Loss	Persistent acute renal failure = complete loss of kidney function >4 wk	
ESKD	End-stage kidney disease (>3 mo)	

From Kuitunen A, Vento A, Suojaranta-Ylinen R, Pettilä V: Acute renal failure after cardiac surgery: evaluation of the RIFLE classification, Ann Thorac Surg *81:542-546, 2006.*

ESKD, End-stage kidney disease; *GFR,* glomerular filtration rate.
*Acronym for risk, injury, failure, loss, and end-stage kidney disease.

BOX 67-21 ***Aims of and Treatment Modalities to Reduce or Prevent the Development of Postoperative Renal Dysfunction***

1. Maintain adequate oxygen delivery—by ensuring adequate cardiac output, adequate oxygen-carrying capacity, and proper hemoglobin saturation.
2. Suppress renovascular constriction—by ensuring adequate volume preload and use of infusions of mannitol, calcium entry blockers, and angiotensin-converting enzyme inhibitors.
3. Promote renal vasodilation—by dopaminergic agents, prostaglandins, and atrial natriuretic peptide.
4. Maintain renal tubular flow—by loop diuretics and mannitol (which may act to prevent tubular obstruction, which can cause cellular swelling, ischemia, and death).
5. Decrease oxygen demand—by the use of loop diuretics and mild cooling.
6. Attenuate ischemic reperfusion injury—as a result of the release of oxygen free radicals and calcium ions.

Modified from Sear JW: Kidney dysfunction in the postoperative period, Br J Anaesth *95:20-32, 2005.*

Preoperative risk factors that are commonly associated with postoperative renal dysfunction after cardiac operations include preexisting renal insufficiency, type 1 diabetes mellitus, age older than 65 years, major vascular surgery, arteriopathy, genetic predisposition, and recent exposure to nephrotoxic agents (e.g., radiocontrast dyes, bile pigments, aminoglycoside antibiotics, and NSAIDs).[193,401] Ejaz and colleagues showed that in addition to serum creatinine, serum uric acid is a significant predictor of AKI.[403] In addition, several intraoperative factors may predispose a patient to renal dysfunction, including the need for emergency surgery, repeat cardiac surgery, valve surgery, and a CPB time exceeding 3 hours.[193,401] Other perioperative risk factors for renal dysfunction after cardiac surgery are hypovolemia, hypotension resulting from either hypovolemia or LCOS, and embolic phenomena. Furthermore, damage to nephrons in the medullary region of the kidney results in acute tubular necrosis; hypoxia is a common cause of damage to the nephrons in this region.[401]

Postoperative renal insufficiency in cardiac surgical patients is associated with longer ICU stay, longer overall hospital stay, and increased mortality.[193,401] Thus, this disorder should be prevented whenever possible. On the basis of studies conducted in patients with radiocontrast nephropathies, investigators theorized that hydration before radiocontrast media are administered may protect the kidneys.[401] Because the mechanism of renal injury after CPB appears similar to that triggered by the administration of radiocontrast dyes, it is thought that adequate hydration and maintaining normovolemia can help to prevent postoperative renal dysfunction in cardiac surgical patients.[401]

Several treatment modalities have been suggested to prevent or ameliorate postoperative renal dysfunction (Box 67-21).[401] Basic supportive therapy involves ensuring adequate CO, perfusion pressure, and intravascular volume. Discontinuing any nephrotoxic drug (NSAIDS, certain antibiotics) is usual. Diuretics are not helpful and may be harmful.[404] Although dopamine has no demonstrated efficacy, some studies suggest that fenoldopam, a D_1-receptor agonist, may improve renal function in cardiac surgical patients.[405] Unproven pharmacologic therapies include mannitol, calcium channel blockers, ACEIs, atrial natriuretic peptide, and *N*-acetylcysteine. Finally, if dialysis is needed, continuous dialysis may be better than intermittent dialysis.[406]

CENTRAL NERVOUS SYSTEM DYSFUNCTION

The risk of overt postoperative stroke has decreased to 1% to 2% since the 1980s.[32,407] However, an increased risk of neurologic complications remains in older patients,[408] as well as in patients undergoing combined CABG and valvular heart surgery or other complex cardiac surgical procedures.[409] Risk factors for overt neurologic complications are listed in Box 67-4. Importantly, 40% of strokes do not occur intraoperatively but manifest in the postoperative period.[200,407] The impact of overt stroke is profound in terms of worse adjusted hospital outcomes, longer ICU and postoperative stays, and poorer downstream survival.[407]

A less well-defined entity, POCD, is far more common. Delirium is included in the definition of POCD, as are deficits of memory, concentration, and psychomotor speed. Early cognitive loss, once thought to be transient, may persist for 5 years after cardiac surgery in as many as 40% of patients.[410] Formerly, POCD was assumed to be caused by physiologic disturbances resulting from CPB. However, more recent studies have confirmed that POCD occurs with similar frequencies after on-pump cardiac surgery, off-pump cardiac surgery, coronary stenting, and noncardiac surgery.[33] Hence, current attention focuses on factors related to surgical stress, anesthetic agents, and patient-related predisposing factors, particularly the degree of preoperative cerebrovascular disease.[33,411] In fact, surgical procedures are likely to uncover a patient's

susceptibility to cognitive loss that was already present and would eventually manifest even without surgery, usually as a result of the progression of cerebrovascular disease.[411] Although POCD is less devastating than stroke, its potential impact on quality of life and overall health care resource use is still profound.[47]

Neuroprotection Strategies

Numerous strategies have been tried to decrease the incidence and severity of neurologic injury in cardiac surgical patients. The most common nonpharmacologic approaches emphasize the reduction of macroemboli and microemboli. As described in earlier sections of this chapter, these strategies include avoiding aortic atheroma by using transesophageal or epiaortic echocardiography, optimizing the placement of the aortic cannula in the aorta, avoiding partial occlusion clamping of the aorta for proximal anastomoses by using a single cross-clamp, and, in selected patients, avoiding all cross-clamping of the aorta (the "no touch" technique).[44-46] Other strategies to minimize particulate microemboli include the routine use of arterial filtration in the cardiopulmonary circuit and use of the cell saver before reinfusing blood suctioned into the cardiotomy, to remove particulate and lipid material.[412] Strategies to minimize air microemboli include carefully removing air after any procedure involving opening a cardiac chamber, and flooding the field with carbon dioxide to minimize embolism of air entrained into the heart from the surgical field.[413] Eliminating CPB by performing off-pump CABG surgery has been touted as a means to reduce emboli in selected patients, but this approach has not decreased POCD rates at 1 or 5 postoperative years.[414] Because approximately 40% of strokes occur in the postoperative period,[200,407] embolism prevention remains important after surgical procedures. Many of these late-occurring strokes are probably caused by atrial fibrillation. Early pharmacologic or electrical correction and adequate anticoagulation are mandatory (see the section on arrhythmias in the postoperative period).

Other nonpharmacologic approaches include perioperative temperature control, as well as blood gas management (alpha-stat or pH-stat) during hypothermic CPB. These considerations are discussed in the section on CPB.

Diabetes is recognized as a risk factor for stroke and delirium after cardiac operations.[415] Even in nondiabetic patients, hyperglycemia is extremely common during cardiac surgical procedures because of the stress response to surgery (as well as CPB), the resultant increases in circulating catecholamines and cortisol, and hypothermia-induced reductions in insulin effectiveness.[200] Experimental evidence has revealed a relationship between hyperglycemia and worse outcome after different types of neurologic injury. However, attenuating the hyperglycemic response to cardiac surgery or CPB has proved difficult. Furthermore, concerns exist regarding inducing even a single episode of severe hypoglycemia with aggressive attempts to control glucose levels.[416] Furthermore, in a randomized, prospective study of 400 cardiac surgical patients managed with either tight glucose control (the use of intravenous insulin to maintain intraoperative glucose levels at 80 to 100 mg/dL) or conventional management (glucose level <200 mg/dL), the investigators found a significantly higher incidence of stroke in the tight-control group.[74] More recent STS guidelines recommend that in both diabetic and nondiabetic patients, blood glucose levels should be maintained at 180 mg/dL or lower.[76] Hyperglycemia is usually controlled more easily during the postoperative period than in the intraoperative period during and immediately after CPB.

The influence of intraoperative hemodynamics may influence neurologic and other outcomes. The prospective, randomized trial conducted by Gold and colleagues compared maintaining "normal" MAP (minimum of 50 mm Hg) with keeping the MAP elevated (target of 80 to 100 mm Hg).[417] These investigators found that the overall incidence of combined cardiac and neurologic complications was significantly lower in the high-MAP group. In another study,[418] investigators noted a higher frequency of hypoperfusion-type "watershed" strokes in patients who underwent cardiac surgical procedures with a MAP that was at least 10 mm Hg lower during CPB than before CPB. The current recommendation is to maintain higher targets for MAP (i.e., >50 mm Hg) in patients at high risk for neurologic injury.[200] More recent evidence suggests a wide range of MAP at the lower limit of autoregulation in individual patients, thus making estimation of this target difficult. Real-time monitoring of autoregulation with the cerebral oximetry index may provide a more rational means for individualizing MAP during CPB.[57]

Numerous studies of cardiac surgical patients have tested drugs aimed at ameliorating neurologic injury.[419] Because high-risk patients can be identified and a defined therapeutic window exists, pharmacologic protection would be very desirable. However, no definitively proven drug therapy currently exists for the prevention or treatment of neurologic injury after cardiac surgery.

Postoperative Management of Central Nervous System Injury or Dysfunction

Postoperative stroke may be suggested by the patient's inability to follow commands or move all extremities shortly after the surgical procedure. Neurologic consultation should be obtained, including diagnostic imaging. Diffusion-weighted magnetic resonance imaging is the most sensitive and accurate imaging technique for postoperative cardiac surgical patients.[420] It detects more microembolic lesions than does conventional magnetic resonance imaging and is better able to find multiple watershed lesions.

Management of CNS injury or dysfunction after cardiac operations consists of general supportive measures. Hypotension should be avoided, and consideration should be given to using volume expansion, inotropic augmentation (pharmacologic or mechanical), or vasoactive medications (vasopressin or phenylephrine) to support blood pressure and brain perfusion. The brain oxygen supply-demand balance should be optimized through adequate oxygenation, sedation, and strict temperature control. Hyperthermia (fever) should be aggressively controlled. Both hyperglycemia and hypoglycemia should be avoided. Lytic therapy is of little use in cardiac surgery because it poses a risk of postoperative surgical bleeding.

POCD can manifest subtly, being evident only with psychometric testing, or, at the other extreme, it can manifest as postoperative delirium. *Delirium* is defined as an acute and overt change in cognition and attention, which may include alterations in consciousness and disorganized thinking.[421] In the cardiac surgical literature, the reported incidence of delirium depends greatly on the methods used for delirium assessment, varying from 3% (chart review only) to 8% (interviews with nurses); however, with rigorous daily mental status testing and the application of a validated diagnostic algorithm, the incidence may be as high as 53%.[422]

Risk factors include preexisting cognitive impairment, poor preoperative functional status, prior stroke or transient ischemic attack, depression, alcohol abuse, and abnormal preoperative laboratory values (glucose, sodium, potassium, and albumin).[421] Precipitating factors for delirium in the postoperative period include intraoperative and postoperative medications, particularly sedatives and analgesics. The postoperative environment in the ICU often results in sleep deprivation and overstimulation, contributing to the onset of delirium.[421] Complications of hospitalization and surgical procedures, including those that result in prolonged controlled ventilation and reduced mobility, also contribute to the development and severity of delirium.

Nonpharmacologic postoperative strategies to prevent delirium are listed in Table 67-21. Medications, including those used to control pain and anxiety, are a common cause. Some studies have found that using dexmedetomidine for sedation in the ICU reduces the incidence of delirium compared with using benzodiazepines (midazolam and lorazepam).[423,424] For patients who develop agitation, the mainstay of treatment is a thorough review of medications, as well as removing other precipitating factors, such as low CO or perfusion state, metabolic disorders (e.g., hyperglycemia), fluid and electrolyte disturbances (hypoglycemia or hyperglycemia and uremia), constipation, urinary retention, and environmental noise. For patients in whom these nonpharmacologic interventions are not sufficient, an antipsychotic, usually haloperidol, is considered first-line therapy for agitation associated with delirium.[425]

Delirium may accelerate cognitive decline in patients with Alzheimer disease or cause a type of posttraumatic stress disorder in younger patients.[421] The long-term mental health implications of delirium have not been fully studied but may include impairment of functional recovery.

TABLE 67-21 **PREVENTION OF DELIRIUM AFTER SURGICAL PROCEDURES**

Module	Postoperative Interventions
Cognitive stimulation	Orientation (clock, calendar, orientation board) Avoidance of cognitively active medications
Improvement in sensory input	Glasses Hearing aids and amplifiers
Mobilization	Early mobilization and rehabilitation
Avoidance of psychoactive medication	Elimination of unnecessary medications Pain management protocol
Fluid and nutrition	Fluid management Electrolyte monitoring and repletion Adequate nutrition protocol
Avoidance of hospital complications	Bowel protocol Early removal of urinary catheters Adequate central nervous system oxygen delivery, including supplemental oxygen and transfusion for very low hematocrit Postoperative complication monitoring protocol

Modified from Rudolph JL, Marcantonio ER: Postoperative delirium: acute change with long-term implications, Anesth Analg *112:1202-1211, 2011.*

Other Nerve Injuries

Peripheral nerve injury frequently follows cardiac surgical procedures.[426] In a review article, Sharma and coauthors reported injury rates of 1.5% to 24% for the brachial plexus.[427] Numbness, weakness, pain, decreased reflexes, and diminished coordination in an extremity are suggestive of peripheral nerve injury. Sensory findings in the fourth and fifth fingers, consistent with ulnar neuropathy, are most common. The mechanisms of injury are most often related to the use of a sternal retractor and compression of the brachial plexus, although upper extremity neuropathy can occur as a consequence of arm positioning as well.

Other neurologic complications include injury to the phrenic nerve, which can result from use of slushed ice in the pericardial well to provide surface cooling for the heart.[426,427] Furthermore, injuries to the recurrent laryngeal nerve, sympathetic chain neuropathy (Horner syndrome), and saphenous nerve injury after harvesting of the long saphenous vein have been reported.[426] Symptoms of peripheral nerve injuries are usually self-limited and improve with time and, if needed, with physical therapy.

RESPIRATORY INSUFFICIENCY

Even after uncomplicated cardiac surgery, a midline sternotomy (or thoracotomy) and lung manipulation cause significant reductions in total lung capacity, vital capacity, forced expiratory volume in 1 second (FEV_1), and functional residual capacity, as well as atelectasis and increased intravascular lung water.[428] These changes may result in arterial hypoxemia because of a mismatch between ventilation and perfusion, which diminishes lung compliance and increases the work of breathing.[429] More severe postoperative respiratory insufficiency that causes difficulty in weaning may reflect intrinsic pulmonary problems (e.g., COPD, atelectasis, pneumonia, surgical trauma to the lungs), ARDS related to CPB or transfusion (transfusion-related acute lung injury), pulmonary embolism, or cardiogenic pulmonary edema secondary to low CO.

Preoperative efforts to minimize pulmonary complications after cardiac surgery include optimizing pulmonary function for patients undergoing elective surgical procedures. With regard to the surgical approach, investigators have theorized that off-pump surgery causes fewer changes in pulmonary mechanics than on-pump surgery. In fact, the use of CPB[430,431] and the duration of CPB[432] have been identified as risk factors for prolonged ventilation (>48 hours).

In previous decades, management after cardiac surgery included overnight mechanical ventilation. Certainly, it is clinically important to have a period of controlled ventilation to allow rewarming and emergence from anesthesia, optimize cardiac function, and ensure hemodynamic stability and the absence of unacceptable bleeding. However, many patients are currently extubated within 3 to 6 hours of arriving in the postoperative care unit (fast tracking), if appropriate criteria have been met (Box 67-22). In planning for fast tracking, one should avoid using high-dose narcotic anesthetic techniques; in addition, the postoperative administration of analgesics and sedatives, as well as any muscle relaxants, must be done at appropriate doses and with appropriate timing.[433] Furthermore, strategies to avoid ventilator-associated pneumonia should be employed. These include formal infection control programs, handwashing, maintaining adequate endotracheal tube cuff pressure, avoiding gastric overdistention, semirecumbent positioning of the patient, scheduled drainage of condensate from ventilator circuits, daily sedation "vacation," adequate nutritional support, early removal of endotracheal and nasogastric tubes, and avoiding unnecessary reintubation.[429,430]

Pain management should be included in postoperative efforts to minimize pulmonary complications. Sternotomy pain may limit the patient's ability to cough and perform deep breathing exercises, and incisional leg pain resulting from saphenous vein harvesting may prevent early ambulation, thus increasing the risk of pulmonary complications. The reader is referred to the later section on pain after cardiac surgery for other options for improving postoperative pain control and thereby minimizing splinting and complications such as lobar collapse, pneumonia, and increased duration of hospitalization.

Fortunately, only a few patients require prolonged mechanical ventilation after cardiac surgical procedures. Data from the STS National Adult Cardiac Surgery Database,[434] the Cardiac Surgery Registry of the New York State Department of Health,[432] and the Cardiothoracic Centre-Liverpool[430] show that approximately 5.5% of patients who undergo CABG require mechanical ventilation for more than 48 postoperative hours. Independent preoperative risk factors for prolonged ventilation include advanced age, preoperative ventilation, elevated serum creatinine levels, EF less than 30%, valve surgery, previous cardiac surgery, urgent or emergency surgery, recent MI, peripheral vascular disease, current smoking, FEV_1 less than 70% of the predicted value, and the use of CPB.[430]

Prolonged postoperative ventilation is most commonly caused by cardiac dysfunction.[435] Patients with marginal cardiac function may require diuresis, afterload reduction, or inotropy. Pulmonary-related reasons for the inability to wean from mechanical ventilation include noncardiogenic pulmonary edema, pneumonia, severe COPD, ARDS, and pulmonary embolism. Nonpulmonary complications such as persistent postoperative bleeding, neurologic complications (including stroke and delirium), renal insufficiency or failure, gastrointestinal complications, and sepsis also may result in a need for prolonged mechanical ventilation. In a large study of ventilator dependency (i.e., ventilation for >72 hours) after cardiac surgery, survival was 76% at 30 days, 49% at 1 year, and 33% at 5 years.[435]

BOX 67-22 ***Criteria to Be Met Before Early Postoperative Extubation***

Neurologic: Awake, neuromuscular blockade fully dissipated (head lift ≥5 sec), can follow instructions, able to cough and protect airway
Cardiac: Stable without mechanical support, cardiac index ≥2.2 L/min/m^2, MAP ≥70 mm Hg, no serious arrhythmias
Respiratory: Acceptable chest radiograph and ABGs (pH ≥7.35), minimal secretions, comfortable on CPAP or T-piece with spontaneous respiratory rate ≤20 breaths/min, MIP ≥25 cm H_2O; alternatively, a successful SBT defined as RSBI <100 and a PaO_2/FiO_2 ≥200
Renal: Diuresing well, urine output >0.8 mL/kg/hr, not markedly fluid-overloaded from operative or CPB fluid administration or SIRS
Hematologic: Chest tube drainage minimal
Temperature: Fully rewarmed, not actively shivering

From Kaplan JA, Reich DL, Savino JS, editors: Kaplan's cardiac anesthesia: the echo era, *ed 6, St. Louis, 2011, Saunders, p 1049.*
ABG, Arterial blood gas; *CPAP,* continuous positive airway pressure; *CPB,* cardiopulmonary bypass; *FiO_2,* fraction of inspired oxygen; *MAP,* mean arterial pressure; *MIP,* maximal inspiratory pressure; *PaO_2,* partial pressure of arterial oxygen; *RSBI,* rapid shallow breathing index; *SBT,* spontaneous breathing trial; *SIRS,* systemic immune response syndrome.

BLEEDING AND COAGULOPATHY

Bleeding is common after cardiac surgery and CPB. Of the blood product usage in the United States, 15% to 20% occurs in association with cardiac surgery.[436-438] Yet despite ongoing clinical research and economic concerns, the management of coagulopathy and bleeding continues to vary substantially among institutions and across the globe. Spiess and associates found that the frequency of transfusion varies from 3% to 92% among institutions,[439] a similar variation to that shown in an international cardiac surgery database.[440]

Transfusion to treat coagulopathy or anemia is sometimes indicated, but it carries a cost in terms of health care resources and patients' outcomes. A study of more than 1900 cardiac surgical patients found that patients who received transfusions had a 70% increased risk of death and a doubling of their 5-year mortality rate, after adjustment for comorbidities, compared with patients who received no transfusions.[85] A multinational study showed that differences in transfusion practices among countries may account for differences in outcomes.[441] A study of 10,000 patients who underwent CABG from the Cleveland Clinic database confirmed the association of transfusion with early and late (i.e., 10-year) mortality; this study used a balancing score to account for confounding.[442] In addition, Marik and Corwin performed a meta-analysis of 45 trials that examined complications of transfusion therapy and found that mortality was increased in transfused patients (odds ratio, 1.7, 95% confidence interval, 1.4 to 1.9).[443]

Guidelines and Recommendations

The STS and the Society of Cardiovascular Anesthesiologists (SCA) published a joint statement in 2007 and an update in 2011 regarding practice guidelines for transfusion and blood conservation in cardiac surgery.[82,444] They

noted six factors that appear to be important predictors of blood product transfusion in cardiac surgery:

1. Advanced age
2. Low preoperative RBC volume (i.e., preoperative anemia or low body surface area)
3. Preoperative antiplatelet or antithrombotic medications
4. Complex or redo operation
5. Emergency operation
6. Noncardiac comorbidities

The Task Force gave specific recommendations on blood conservation that included the following five points[444]:

1. Consideration should be given to the use of drugs that either increase preoperative blood volume (e.g., erythropoietin) or decrease postoperative bleeding (e.g., antifibrinolytic drugs).
2. Techniques of conserving blood, including cell saver sequestration and retrograde priming of the pump, should be included in the operative plan.
3. To spare the patient's blood from the insult of CPB, normovolemic hemodilution or platelet-rich plasmapheresis can be considered.
4. Institutions should implement transfusion algorithms supported with POC testing.
5. A multimodal application of all of the previously mentioned guidelines is the best way to conserve blood.

These recommendations are parallel to and completely congruous with the tenets of patient blood management, which is a novel approach to blood transfusion that focuses on patient-centered therapies. The three pillars of patient blood management are as follows:

1. Preoperative optimization of RBC mass
2. Perioperative minimization of RBC loss
3. Perioperative optimal treatment of anemia

Definition of Bleeding and Transfusion Triggers

The decision to transfuse the cardiac surgical patient is one that should be made with great caution and careful consideration because allogeneic transfusion has several associated risks. The excessively bleeding patient who has a surgical source of bleeding should be carefully assessed, and often, allogeneic blood products are required to maintain hemoglobin and the integrity of hemostasis until the source of bleeding is found. Patients who have excessive microvascular bleeding from a coagulopathic cause should have careful testing of the hemostatic system, usually with POC monitoring, to assess which blood products or pharmacologic products are needed. (This subject is discussed in the following section on transfusion algorithms.) The problem in defining a trigger for transfusion is the ambiguity of the definition of bleeding. Many sources state that excessive chest tube drainage can be defined as more than 250 mL of bleeding per hour for at least 2 consecutive hours, or 300 mL of bleeding in a single hour. In addition to defining the severity of bleeding, these criteria also often help clinicians determine whether to return the patient to the operating room for surgical exploration.

Knowing when to transfuse RBCs is equally challenging because the triggers for transfusion often rely on hemoglobin level, which is a poor surrogate for tissue oxygen delivery. It is well known that cardiac surgery and CPB are associated with anemia, which poses certain risks.[445] These risks include renal failure,[446] other end-organ morbidity, and even mortality,[445] all of which have been demonstrated observationally in well-designed multivariate analyses. However, the lowest tolerable hemoglobin level clearly differs among patient populations and remains ill-defined in the literature. Nevertheless, the STS/SCA guidelines for blood conservation provide a framework for transfusion triggers within which most patients are treated appropriately. These triggers include a hemoglobin level of at least 6 g/dL during CPB and 6 to 7 g/dL before and after CPB.[444] However, underlying comorbidities can and do raise the minimum safe hemoglobin or hematocrit level.

Coagulation Monitoring

If only standard laboratory testing is available, monitoring the coagulopathic patient in the operating room is limited to monitoring hemoglobin concentration, prothrombin time or International Normalized Ratio, activated PTT, platelet count, and levels of fibrinogen and fibrin degradation products. These parameters are of limited utility in the post-CPB patient because they do not interrogate platelet function and because their turnaround time is too slow to allow timely initiation of therapy. For these reasons, without POC testing of hemostasis, transfusion therapy is often initiated empirically and indiscriminately.

The platelet count provides quantitative information about platelet concentrations but little, if any, qualitative information about platelet function. Platelet counts lower than 100,000/μL are often viewed as the cutoff for thrombocytopenia, but counts greater than 50,000/μL do not correlate with postoperative bleeding. Laboratory measures of platelet function, including bleeding time, aggregometry, and cytometry, are not rapid (requiring >1 hour to produce results) and therefore are impractical for obtaining timely information intraoperatively. When unacceptable microvascular bleeding occurs, no matter what the platelet count, CPB-induced platelet dysfunction is often assumed to be the culprit; however, platelet function can now be measured at the point of care.

POC monitors may be able to provide more timely information about the coagulation cascade than can laboratory measures and to assess the dynamic nature of platelet function sequentially. Such monitors are designed to test segments of the hemostatic system. The viscoelastic tests are dynamic measures of whole blood clot formation and can measure platelet integrity and the strength of the platelet-fibrinogen bond. These tests include thromboelastography (TEG; Haemonetics, Braintree, MA), Sonoclot (Sienco, Arvada, CO), and rotational thromboelastometry (ROTEM; Tem Innovations GmbH, Munich, Germany). The response of platelets to an agonist stimulus is another means of measuring platelet function. Platelet function can be measured at the point of care in this manner by the Platelet Function Analyzer-100 (PFA-100; Siemens Healthcare, Malvem, PA), PlateletWorks

(Helena Laboratories, Beaumont, TX), VerifyNow (Accriva Diagnostics, San Diego, CA), and the Multiplate analyzer (Roche Diagnostics, Rotkreuz, Switzerland).[447] POC monitors have also shown promise in stratifying bleeding risk for patients who come to the operating room after receiving antithrombotic drugs, such as clopidogrel, prasugrel, or Gp IIb/IIIa receptor inhibitors.[448-452] Finally, POC monitors provide data to support the implementation of institutional policies and practices directed at blood conservation and transfusion in cardiac surgical patients.[444]

Pharmacologic Treatment

Pharmacologic drugs used for hemostasis in CPB are used both prophylactically to prevent hyperfibrinolysis and therapeutically to treat bleeding. Antifibrinolytic drugs are used before CPB to prevent the inevitable activation of fibrinolysis and coagulation that result from contact between blood and the extracorporeal circuit. The STS/SCA guidelines provide the strongest evidence-based support for the use of synthetic antifibrinolytic agents in blood conservation. The evidence for the use of aprotinin for reducing perioperative bleeding in cardiac operations was reappraised in the updated guidelines because of conflicting reports of renal dysfunction and other adverse outcomes.[82]

In structural terms, the synthetic antifibrinolytic agents are lysine analogues. They bind to plasminogen and plasmin, thus inhibiting their ability to bind to lysine residues on fibrin and thereby impeding fibrinolysis. The two synthetic antifibrinolytic agents that are used clinically are EACA (Amicar) and TA. They differ primarily in potency and elimination half-life: TA is 6 to 10 times more potent and has a longer half-life than EACA.[453]

Dose regimens for the synthetic antifibrinolytic agents are anything but standardized. Generally, the dose of EACA is a 50 to 150 mg/kg load followed by an infusion of 15 to 25 mg/kg/hour; the dose of TA may be a 10 to 30 mg/kg load followed by an infusion of 1 to 15 mg/kg/hour. However, many other dosing strategies are described in the literature.[454-459]

Meta-analyses of the literature on antifibrinolytic drugs have come to different conclusions about the relative safety of these drugs[129]:

- Aprotinin, TA, and EACA significantly reduce blood loss compared with placebo.
- Aprotinin, EACA, and TA reduce PRBC transfusion rates by approximately 25% to 50%.
- Aprotinin and EACA reduce rates of surgical reexploration; reductions also were seen with TA but were not statistically significant.
- Another systematic review revealed that when observational trials are added to the meta-analyses of randomized controlled trials, aprotinin appears to have an adverse effect on survival and renal function.[460]

Because both EACA and TA are renally excreted, they should not be given to patients with upper urinary tract bleeding; the concentration of the drug in the renal collection system could cause thrombosis and obstructive nephropathy.[109]

Regarding aprotinin, Royston and associates published the first findings of reduced bleeding in cardiac surgical patients in 1987.[461] Numerous subsequent studies demonstrated that aprotinin reduces the bleeding associated with cardiac surgery and CPB.[444] Aprotinin is a bovine-sourced protein, and episodes of anaphylaxis have been reported.[462-464] The risk of anaphylaxis with reexposure is reported to be approximately 2.8%.[465] However, aprotinin was a routine part of perioperative care in cardiac surgical patients until 2006, when published reports suggested adverse outcomes that had not been found in previous randomized controlled studies.[130,466] After several observational studies confirmed these adverse outcomes and a single randomized controlled trial suggested an increase in mortality associated with aprotinin, the FDA and other global agencies suspended the marketing of aprotinin.[131]

Other pharmacologic drugs that may be used in cardiac surgical bleeding are mentioned in the STS/SCA Task Force guideline update.[82] Using desmopressin was classified as "not unreasonable" in patients with characteristics known to be responsive to desmopressin (von Willebrand factor or factor VIII deficiencies, cirrhosis, aspirin use, and uremic platelet dysfunction).[444] Desmopressin is administered in doses of 0.3 to 0.4 μg/kg, which are usually given slowly over 20 to 30 minutes to reduce the drug's propensity to cause hypotension. The use of recombinant factor VIIa (factor rVIIa) was reevaluated, but the published class IIb recommendation was unchanged in the update.[82] Factor VIIa use was classified as "not unreasonable" for treating intractable life-threatening hemorrhage that is unresponsive to traditional therapies.[444]

Factor rVIIa increases the amount of thrombin to promote hemostasis. It was initially developed as a therapy for patients with hemophilia and has since been used "off-label" to treat cardiac surgical patients with intractable bleeding after operation and CPB. Factor VIIa may serve as an activator of factors IX and X and may also bind directly to platelets, thus leading to localized activation of factor X and subsequent generation of thrombin on the surface of platelets (Fig. 67-44).[467]

A few observational studies have associated factor rVIIa administration with reductions in bleeding in patients

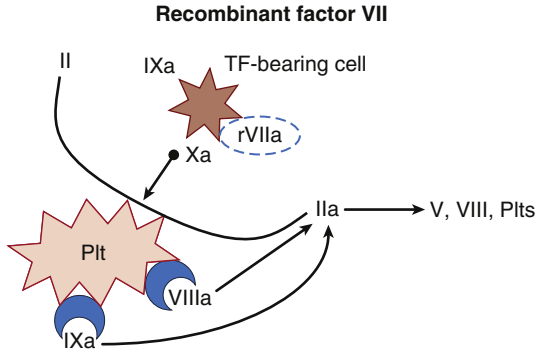


Figure 67-44. The use of factor rVII promotes cell-based hemostasis and active potentiation of coagulation activity. The initiation stage takes place when tissue-factor (TF)–bearing cells present tissue factor to its ligand, factor VII. The subsequent activation of factors IX and X occurs on the TF-bearing cell. Thrombin is activated and feeds back to activate factors VIII and V and platelets (Plts). The activated platelet phospholipid surface then provides the receptors for the activated factors VIIIa and IXa and for coagulation to continue.

with significant perioperative hemorrhage during cardiac surgery, and a systematic review of cardiac surgical studies recommended the use of this substance when standard therapies have failed.[437,468-470] A multicenter randomized trial in cardiac surgery found that patients treated with factor rVIIa had less bleeding than did control patients; however, a nonsignificant trend toward increased adverse events in the treated patients caused the study to be halted and the recommendations to proceed with caution when considering administration of this drug.[471] Meta-analysis of randomized trials in patients without hemophilia (but not solely cardiac surgical patients) suggested that prophylactic factor rVIIa use can reduce bleeding and transfusions, but therapeutic use caused a nonsignificant increase in thrombosis. Prophylactic use of factor rVIIa is not recommended in cardiac surgery.

Point-of-Care Algorithms

The STS/SCA blood conservation guidelines strongly encourage multimodal efforts to reduce transfusion rates and conserve blood products (see also Chapters 61 to 63). Studies that used transfusion algorithms paired with POC data to guide therapy have found these measures to be both efficacious and cost effective.[82,444] Examples of standard POC algorithms, one using the TEG and one using the ROTEM, are shown in Figures 67-45 and 67-46, respectively. Algorithms can be constructed to incorporate any particular dynamic POC monitor or monitors.[173,174,472-476] Studies that have incorporated many different varieties of POC tests have generally shown a reduction in or even the elimination of transfusions when POC is used.[474] As a general recommendation, the POC instrument or instruments used should be able to measure some aspect of platelet function. This can be a standard whole blood platelet test such as the PFA-100 or the VerifyNow, or it can be a viscoelastic test of dynamic clot formation. The viscoelastic test in the TEG measures both platelet function and the platelet response to ADP and arachidonic acid. Many TEG-guided algorithms have been studied and shown to reduce blood product use effectively in cardiac surgery-related hemorrhage. A more recent approach to POC algorithm includes using ROTEM and an algorithm that includes early treatment with fibrinogen and prothrombin complex concentrates (see Fig. 67-46).[477] This sort of approach to bleeding postpones the moment when allogeneic blood products are needed and thus has been successful in reducing their use. Preliminary work suggests that no increase in thrombotic events occurs with this "pharmacologic" approach to bleeding, but large-scale studies have not yet been conducted.

In summary, interdisciplinary approaches to blood conservation are vital to the care of cardiac surgical patients. Perioperative and critical care personnel must use a series of combined approaches to reduce transfusions and the adverse effects of transfusion and anemia. Important to this approach is a sound algorithmic procedure that incorporates POC testing, pharmacology, and rational blood product use to improve outcomes.

PAIN

Pain after cardiac surgery can have many sources, including the sternotomy incision, chest tubes, vascular cannulation sites, and leg incisions (see also Chapter 98).[478] Chest surgical procedures through thoracotomy are especially debilitating because of pain and consequent respiratory dysfunction.[479] Some of the deleterious effects of postoperative pain after cardiac surgery are caused by the stress response and resultant inflammation and enhanced sympathetic tone, which can increase the heart rate, PVR, myocardial work, and myocardial oxygen consumption, all leading to myocardial ischemia.

Pain after cardiac surgical procedures can also cause respiratory complications related to diaphragmatic dysfunction. Moreover, the patient's pain may cause voluntary reduction of muscular movement in the thorax and abdomen, a phenomenon often described as "splinting," which may interfere with the patient's ability to cough and clear secretions. However, at present, evidence to state definitively that any postoperative analgesic technique significantly affects morbidity or mortality after cardiac surgery is insufficient.[480]

Unrelieved pain does have psychological effects. Pain-related anxiety, depression, and sleep deprivation may contribute to delirium in patients in the intensive care setting. A primary benefit of effective pain control is patient satisfaction. So-called fast-track anesthesia, entailing

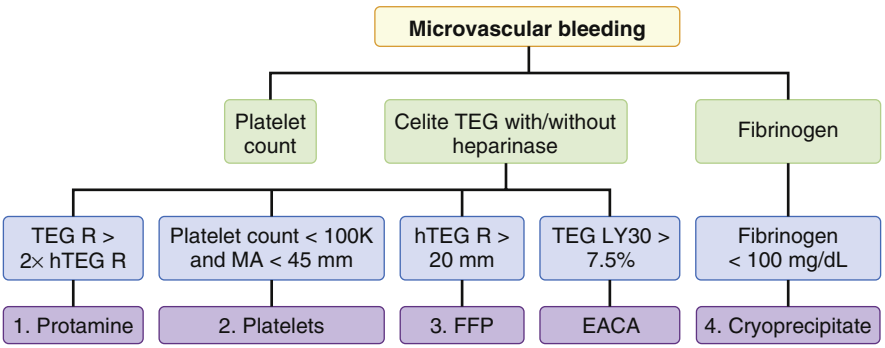


Figure 67-45. Algorithm for transfusion requirements in the thromboelastography (TEG) group in a study. Once bleeding was diagnosed, patients received transfusions based on the results of tests in the algorithm. Based on the assumption that bleeding is often platelet related and on the finding that the platelet count and TEG results return promptly, therapy was given in the numbered order of priority. *EACA,* ε-Aminocaproic acid; *FFP,* fresh-frozen plasma; *hTEG,* heparinase-activated TEG; *LY30,* lysis index at 30 minutes; *MA,* maximum amplitude; *R,* reaction time. *(From Shore-Lesserson L, Manspeizer H, DePerio M, et al: Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery,* Anesth Analg *88:312-319, 1999).*

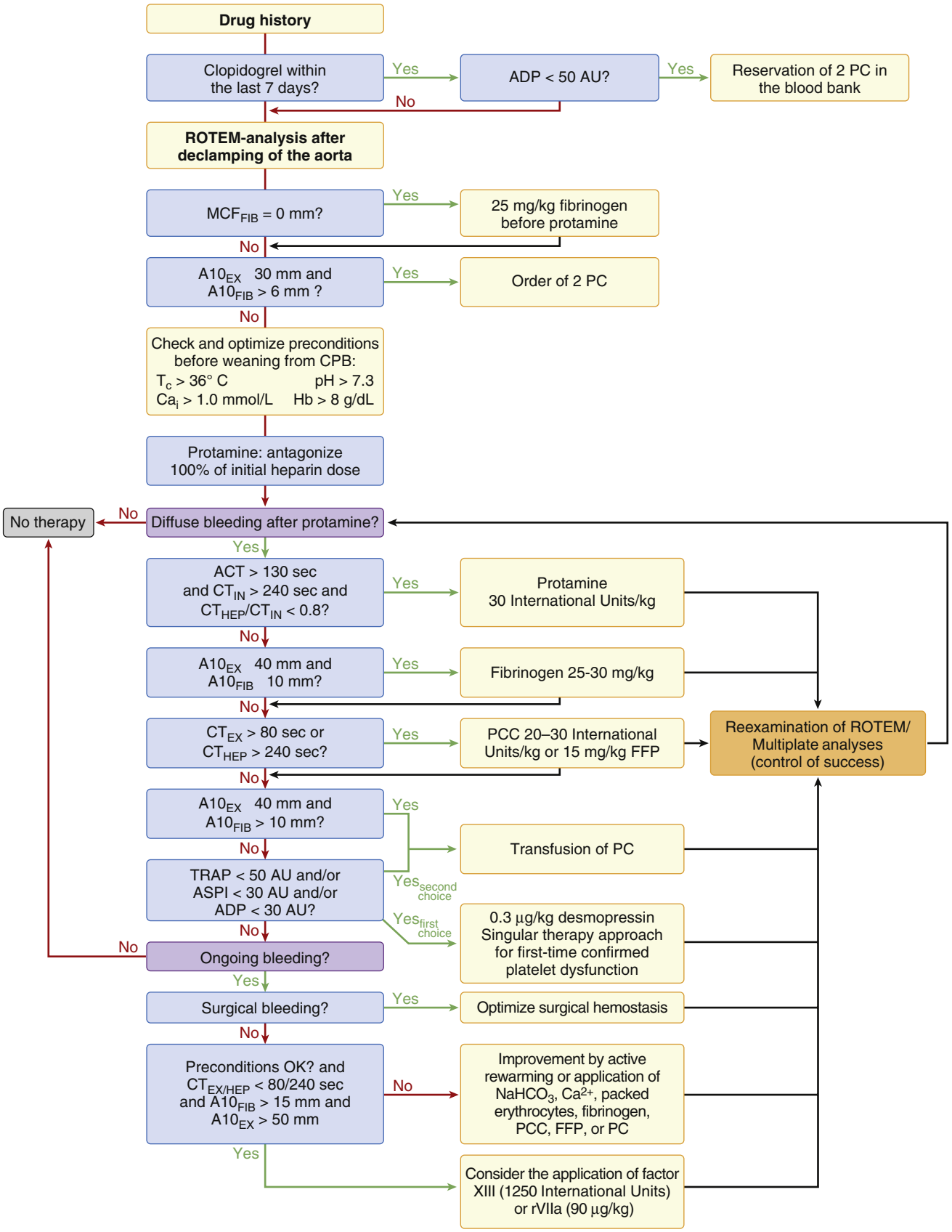


Figure 67-46. Hemostatic therapy algorithm using point-of-care testing. *ACT,* Activated clotting time; *ADP,* ADPtest; *ASPI,* ASPitest; *AU,* aggregation unit; *A10,* amplitude of clot firmness 10 minutes after clotting time; *Ca^{2+},* calcium; *Ca_i,* ionized calcium; *CPB,* cardiopulmonary bypass; *CT,* clotting time; *EX,* EXTEM; *FFP,* fresh frozen plasma; *FIB,* FIBTEM; *Hb,* hemoglobin concentration; *HEP,* HEPTEM; *IN,* INTEM; *MCF,* maximum clot firmness; *$NaHCO_3$,* sodium bicarbonate; *PC,* pooled platelet concentrate; *PCC,* prothrombin complex concentrate; *TRAP,* TRAPtest. The manufacturers of ROTEM (rotational thromboelastometry) and Multiplate were Tem International GmbH and Verum Diagnostica GmbH, respectively, both of Munich, Germany. *(From Weber CF, Gorlinger K, Meininger D, et al: Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients,* Anesthesiology *117:531-547, 2012.)*

earlier extubation, a relatively brief stay in the ICU, faster discharge from the hospital, and lower overall cost, has become a standard of care for the cardiac anesthesiologist. Effective pain control probably helps achieve these goals.

Opioids remain the gold standard for pain control after cardiac surgery, but these drugs have side effects that include nausea, vomiting, urinary retention, decreased gastric motility, pruritus, sedation, and respiratory depression. A meta-analysis showed small incremental benefits for morphine analgesia that was patient controlled compared with nurse controlled in the treatment of postoperative pain after cardiac surgery.[481]

Intrathecal and epidural local anesthetics and narcotics have increasingly been used to improve analgesia in patients undergoing cardiac surgical procedures. However, neither meta-analyses nor randomized trials of central neuraxial analgesia in cardiac surgical patients have shown that these techniques improve outcome.[482-484] Nevertheless, in some studies, thoracic epidural analgesia did significantly reduce pain and the risk for dysrhythmias, pulmonary complications, and time to tracheal extubation, and it reduced analog pain scores at rest and with activity. Intrathecal analgesia modestly decreased systemic morphine use and pain scores but significantly increased the incidence of itching.[482,483] Although a major concern with the use of intrathecal and particularly epidural analgesia in cardiac surgery is the administration of anticoagulation during the operation and consequent fear of spinal cord damage from a possible epidural hematoma,[484] this complication is rare.[483] Other techniques include the use of bilateral single-shot paravertebral blocks[485] or intercostal nerve blocks followed by a subcutaneous continuous infusion of local anesthetic agents.[486]

Because all analgesics have side effects, some authors have suggested that it is better to use combinations of drugs or techniques (i.e., multimodal analgesia; see also Chapter 98). Theoretically, multimodal analgesia may allow the use of smaller doses of all analgesics and thus reduce the severity of the dose-related side effects of any single drug used.[487] However, despite the appeal of the idea of multimodal analgesic techniques, cyclooxygenase-2–selective inhibitors, as well as nonselective NSAIDs, are contraindicated after cardiac surgery because of the potential for thromboembolic adverse effects.[488]

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Chapter 68

Anesthesia for Correction of Cardiac Arrhythmias

SAMUEL A. IREFIN

Key Points

- Cardiac arrhythmias are caused by disorders of impulse formation, disorders of impulse conduction, or both. Cardiac arrhythmias may be life-threatening because of a reduction in cardiac output and/or myocardial blood flow or precipitation of a more serious arrhythmia.
- Radiofrequency ablation is the therapy of choice for many types of cardiac arrhythmias.
- Electrophysiologic studies are used to map out normal and abnormal intracardiac structures. In this process, the mechanism of arrhythmia is delineated and ablation can be performed at the same time.
- Pacing technologies have been developed to treat heart failure resulting in increases in pulse pressure, left ventricular stroke volume, cardiac index, and wedge pressure.
- Implantable pacemakers are placed for treatment of symptomatic bradycardia with the ability to respond to changing hemodynamic demands.
- The development of implantable cardioverter-defibrillators (ICDs) to terminate ventricular tachyarrhythmias by delivering high-voltage shocks to the ventricle has revolutionized therapy for cardiac arrhythmias.
- The main purpose of ICD placement is to prevent sudden cardiac death resulting from hemodynamically unstable ventricular arrhythmias.
- An ICD can be placed for cardiac resynchronization. Cardiac resynchronization therapy improves heart failure symptoms, quality of life, exercise capacity, and electrocardiographic variables.
- Anesthetic management of patients for correction of cardiac arrhythmias depends on associated comorbid illness and the procedure that is planned.

Cardiac arrhythmias are caused by disorders of impulse formation, disorders of impulse conduction, or both. Disorders of impulse formation include enhancement or depression of automaticity, parasystolic activity, and triggered activity. Disorders of conduction include decremental conduction, reentry, entry block, exit block, concealed conduction, and supernormal conduction.[1]

At the present time, radiofrequency catheter ablation has replaced antiarrhythmic drug therapy as the treatment of choice for many types of cardiac arrhythmias. Before the 1980s, cardiac electrophysiology was primarily used to confirm mechanisms of arrhythmias, with management mainly by pharmacologic means. As a result of shortcomings in antiarrhythmic drug therapy (including the results of randomized trials), radiofrequency ablation and implantable cardioverter-defibrillators (ICDs) were developed.[2,3]

HISTORICAL PERSPECTIVES

The treatment of cardiac arrhythmias with device-based therapy may have begun in 1899, when Prevost and Batteli[4] noted almost as an afterthought that direct electric shock could terminate ventricular fibrillation in dogs. Hooker and colleagues[5] showed 3 decades later that the passage of electric current across the heart can initiate and terminate ventricular fibrillation. In 1947, Beck[6] saved the first human life by the successful use of cardiac defibrillation in a 14-year-old boy who developed ventricular fibrillation during a thoracic procedure and went on to achieve full recovery. These early achievements provided the foundation for the landmark work of Mirowski and Mower,[7] which ultimately led to the development of ICDs

in humans in 1980. During the past 3 decades, an increase has occurred in the numbers of patients with pacemakers and ICDs for the correction of cardiac arrhythmias.

SCOPE OF CARDIAC ARRHYTHMIAS

Cardiac arrhythmias are common (see also Chapters 47 and 48). Some cardiac arrhythmias are life-threatening, and others are merely a nuisance. Cardiac arrhythmias are caused by abnormalities in impulse formation or conduction that lead to slow or fast, regular or irregular heart rhythms. At the present time, it is not difficult to treat slow rhythms because available pacemakers are able to adapt slow function to the needs of the body.[8] The situation is different, however, for patients with rapid rhythms. Rapid rhythms may originate anywhere in the heart and result from various mechanisms. These mechanisms may be focal, meaning that the abnormal impulse formation is confined to a small area, or they may be the result of an impulse running in a circuit composed of several interconnected cardiac cells. Such a circuit may be small or large, as in atrial flutter and in arrhythmias in which the normal atrioventricular conduction system and an extra connection between the atrium and the ventricle are incorporated into the circuit of the arrhythmia.[9]

Pharmacologic interventions originally were used to terminate and prevent rapid rhythms. However, antiarrhythmic drugs may have serious side effects and sometimes may even facilitate the occurrence of life-threatening arrhythmias and sudden death.[10] As a result of these effects, techniques were developed for localizing the site of origin or pathway of an arrhythmia and then isolating or destroying the tissue that is responsible. By employing an intracardiac catheter, the site of origin or pathway of an arrhythmia can be identified and the rhythm disturbance corrected by applying radiofrequency, laser, ultrasound, microwave energy, or freezing temperatures to the tissue causing the arrhythmia.

Heart failure is a major problem in elderly patients (see also Chapter 80). Although pharmacologic treatment of heart failure has improved, outcome generally remains poor. New pacing technologies may be used to treat selected patients with heart failure. For many years, permanent pacing has been used to treat symptomatic bradycardia, and pacing may alleviate heart failure when associated with heart block. Several studies have examined the use of conventional dual-chamber atrioventricular–right ventricular pacing for treatment of heart failure in the absence of symptomatic bradycardia or heart block.[3,11] Biventricular pacing aims to restore synchronous cardiac contraction. When ventricular dyssynchrony is reduced, the heart is able to contract more efficiently and increase left ventricular ejection fraction and cardiac output, while working less and consuming less oxygen.[12] In addition, reestablishment of left ventricular synchrony can increase left ventricular filling times, decrease pulmonary capillary wedge pressure, and reduce mitral regurgitation.

NORMAL CARDIAC RHYTHM

In the normal heart, the dominant impulse arises in the sinus node with a rate of 60 to 100 beats/minute (Fig. 68-1). During sleep, the rate may decrease to 30 to 50 beats/minute.[13] Episodes of sinus pauses up to 3 seconds, sinoatrial block, junctional rhythms, and first-degree and second-degree atrioventricular nodal block that occur quite often (especially in trained athletes) are considered to be normal variants.[8]

The impulses generated from the sinoatrial node propagate along three intraatrial conduction pathways: the anterior, middle, and posterior internodal tracts. These tracts are not discrete pathways, but groups of cells that conduct slightly faster than the atrial myocardium.[14] The internodal tracts give rise to interatrial fibers. The electric impulse, whether propagated in the atrial myocardium or along the internodal tracts, converges on the atrioventricular junction. The atrioventricular node located in the atrioventricular junction ultimately receives the impulses generated from the sinoatrial node. The impulses are delayed in the atrioventricular node before they are finally distributed to the ventricular myocardium via the His-Purkinje system.

Normally, the heart rate increases with exercise to at least 85% of the age-predicted maximum of 220 minus age in years; failure to do so is termed chronotropic incompetence. Sinus arrhythmia is defined as sinus rhythm with P-to-P variations of more than 10% (Fig. 68-2). Sinus arrhythmia is due to cyclic variations in vagal tone commonly related to respiration (the rate is faster with inspiration and slower with expiration).[15] Sinus arrhythmia disappears with exercise, breath-holding, and atropine, and is more likely to be seen in individuals who do not have heart disease.[16]



Figure 68-1. Normal sinus rhythm. *(Courtesy M. Kanj, MD, Cleveland Clinic, Cleveland, OH.)*



Figure 68-2. Sinus arrhythmia. *(Courtesy M. Kanj, MD, Cleveland Clinic, Cleveland, OH.)*

CARDIAC ARRHYTHMIAS

Cardiac arrhythmia is caused by a disorder of impulse generation, impulse conduction, or a combination of both. Cardiac arrhythmia may be life-threatening because of a reduction in cardiac output, reduction in myocardial blood flow, or precipitation of a more serious arrhythmia.[17] Arrhythmias may be described based on (1) rate (bradycardia or tachycardia), (2) rhythm (regular or irregular), (3) origin of impulse (supraventricular, ventricular, or artificial pacemaker), (4) impulse conduction (atrioventricular, ventriculoatrial, or block), (5) ventricular rate, or (6) special phenomena (e.g., preexcitation).

Reentry is a common electrophysiologic mechanism that predisposes to most ventricular arrhythmias and to most supraventricular tachyarrhythmias. The most common mechanism of reentry is based on the model originally proposed by Erlanger and Schmitt and later modified by Wit.[1] This model postulates the presence of a ring or loop of cardiac tissue that is functionally separate from neighboring tissue and the presence of transient or permanent unidirectional block in a portion of the loop. Unidirectional block may be anatomic in origin (e.g., bundle branches, fibrosis, dual pathways, atrioventricular node plus accessory pathway) or functional (e.g., ischemia, drug effect).

Atrial flutter is a macro-reentrant arrhythmia identified by flutter waves, often best seen in the inferior leads at 250 to 350 beats/minute (Fig. 68-3). Patients often present with a 2:1 atrioventricular conduction with a ventricular rate of 150 beats/minute, although the atrioventricular conduction ratio can change abruptly. Atrial fibrillation is a narrow-complex tachyarrhythmia and is the most common in the general population (Fig. 68-4). It is associated with significant morbidity. The prevalence of atrial fibrillation in the general population increases exponentially with age, from 0.9% in individuals 40 years of age to 5.9% in individuals older than age 65 years (see also Chapter 80). The most important risk factors for development of atrial fibrillation in the general population are structural heart disease, valvular heart disease, and left ventricular hypertrophy.[18] Atrial fibrillation is a significant contributor to the development of angina and stroke, with an estimated stroke risk in untreated individuals of 3% to 5%.[19]

Ventricular tachyarrhythmia is defined as three or more consecutive ectopic beats at a rate more rapid than 100 beats/minute (Fig. 68-5).[20] Ventricular tachyarrhythmia is traditionally classified as nonsustained or sustained. Sustained ventricular tachyarrhythmia is defined as ventricular tachyarrhythmia lasting more than 30 seconds. Nonsustained ventricular tachyarrhythmia is defined as ventricular tachyarrhythmia that terminates spontaneously within 30 seconds. Sustained ventricular tachyarrhythmia also is traditionally classified as monomorphic (one site of origin) or polymorphic (two or more sites of origin).[20] Monomorphic ventricular tachyarrhythmia usually results from reentry, and the site of reentry depends in part on the type of heart disease. In patients with coronary artery disease, the reentry circuit is usually located in ventricular myocardium, whereas in dilated cardiomyopathy with left bundle branch block, bundle branch reentry is common.[21] Monomorphic ventricular tachyarrhythmia may occur in individuals with an otherwise normal heart, whereas polymorphic ventricular tachyarrhythmia may occur in acquired states that produce a marked prolongation of the Q-T interval. Nonsustained ventricular tachyarrhythmia is frequently asymptomatic, but may produce palpitations, weakness, and presyncope.[21]

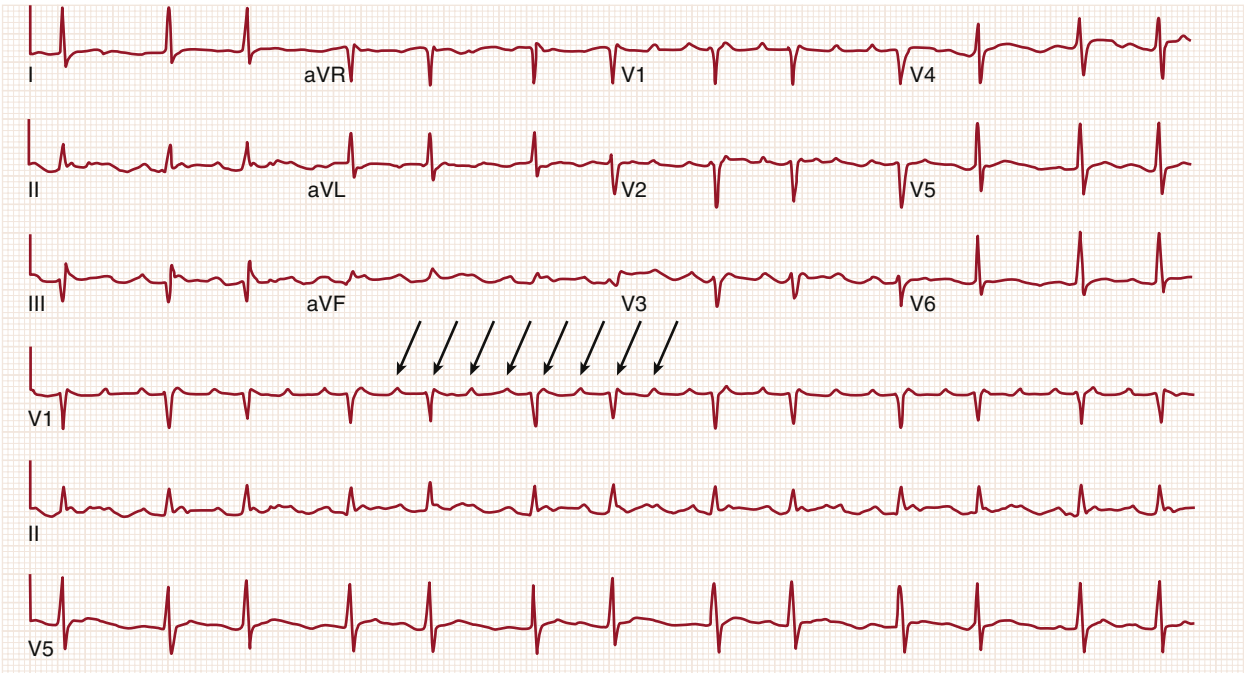


Figure 68-3. Atrial flutter. Note the flutter wave pattern in lead V1 (*arrows*). *(Courtesy M. Kanj, MD, Cleveland Clinic, Cleveland, OH.)*

Torsade de pointes is a French term translated as "twisting of the points." It is a syndrome composed of polymorphic ventricular tachyarrhythmia (Fig. 68-6). It may be due to various medications or electrolyte imbalances. Torsade de pointes is usually paroxysmal, but is frequently symptomatic and often produces loss of consciousness. It occasionally degenerates to ventricular fibrillation. Ventricular fibrillation accounts for 80% to 85% of sudden cardiac deaths.[21]

Ventricular fibrillation is usually preceded by ventricular tachyarrhythmia, but also may occur as a primary arrhythmia (Fig. 68-7). More recent studies suggest that ventricular fibrillation results from multiple wavelengths that disperse randomly, using the leading circle form of reentry.[21] The most common cause of ventricular fibrillation is acute myocardial infarction. It also is observed in patients with chronic ischemic heart disease, hypoxia resulting from any cause, acidosis, hypokalemia, and massive hemorrhage.

INDICATIONS FOR CORRECTION OF CARDIAC ARRHYTHMIAS

Intracardiac electrophysiologic studies can give valuable information about normal and abnormal electrophysiology of intracardiac structures (see also Chapters 47, 48, and 108). These studies are used to confirm the mechanism of an arrhythmia, to delineate its anatomic

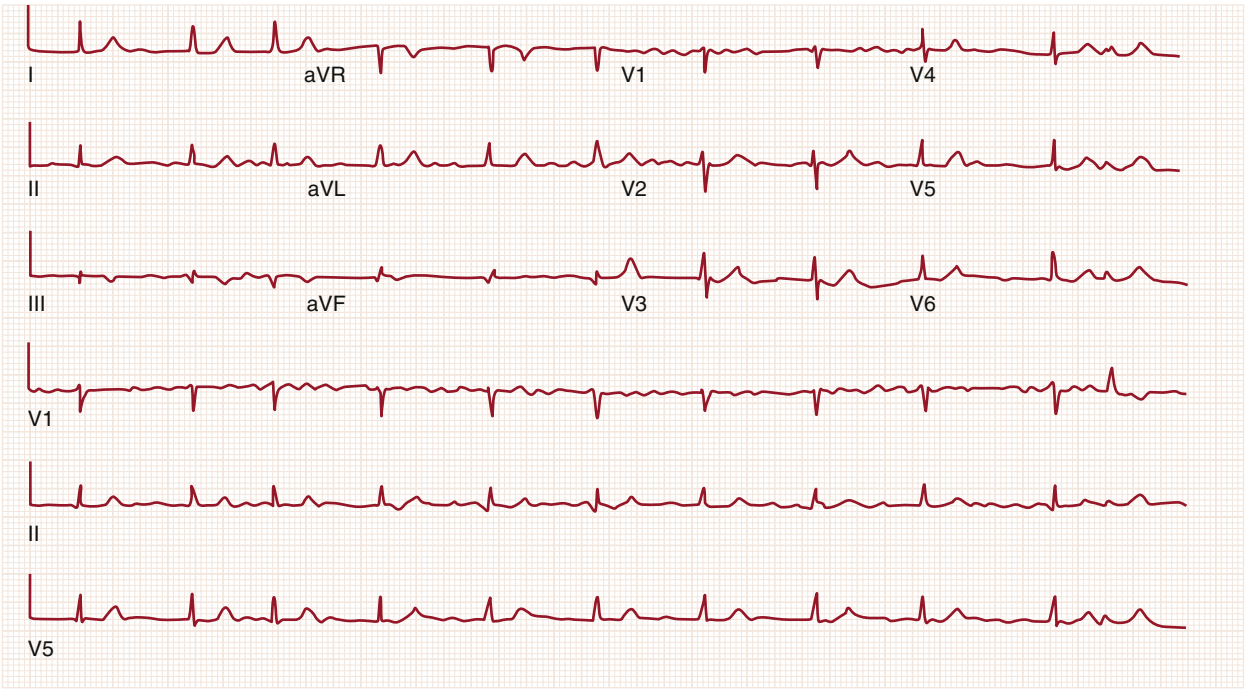


Figure 68-4. Atrial fibrillation. *(Courtesy M. Kanj, MD, Cleveland Clinic, Cleveland, OH.)*

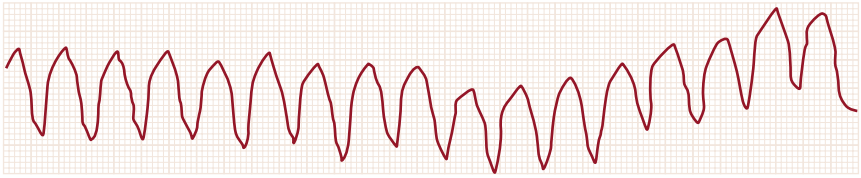


Figure 68-5. Ventricular tachycardia. *(Courtesy M. Kanj, MD, Cleveland Clinic, Cleveland, OH.)*

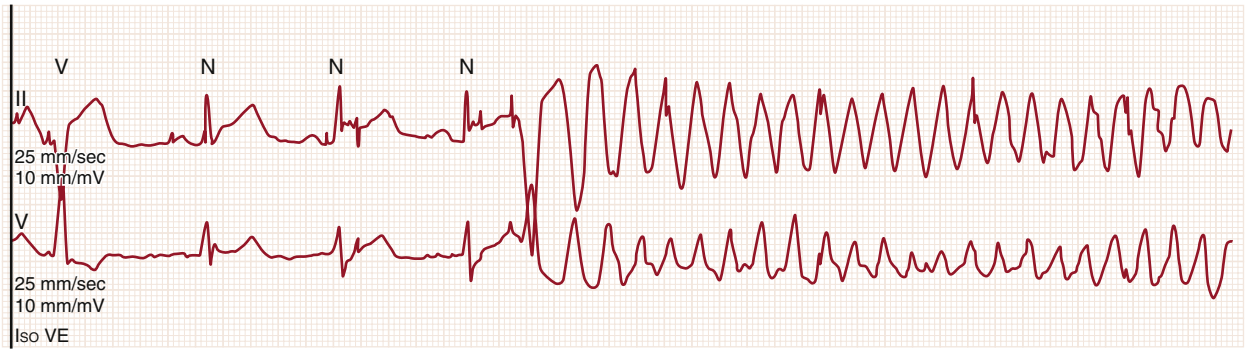


Figure 68-6. Torsade de pointes. *(Courtesy M. Kanj, MD, Cleveland Clinic, Cleveland, OH.)*

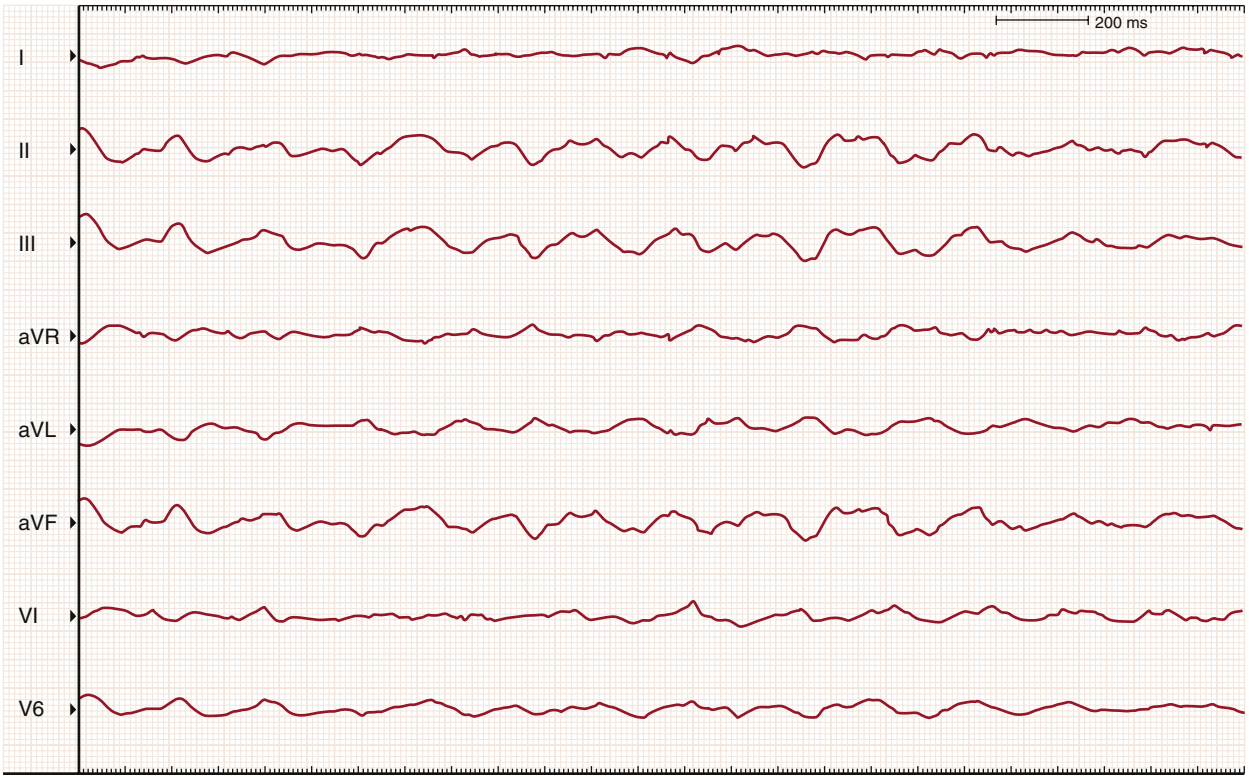


Figure 68-7. Ventricular fibrillation. *(Courtesy M. Kanj, MD, Cleveland Clinic, Cleveland, OH.)*

substrate, and to ablate it. The electric stability of the ventricles also can be assessed, as can the effects of an antiarrhythmic regimen.

In addition, pacing technologies have been developed to treat heart failure with promising results, leading to improvement in morbidity and mortality in patients with heart failure. Hemodynamic responses to biventricular pacing include an increase in the rate of elevation of left ventricular pressure and increases in pulse pressure, left ventricular stroke work, cardiac index, and wedge pressure.[22] Cardiac resynchronization therapy improves ventricular function without increasing myocardial energy consumption, in contrast to the effect of inotropic agents, such as dobutamine.[12] In addition, cardiac resynchronization therapy may reverse left ventricular remodeling over time.[23]

PERMANENT PACING

Indications for pacemaker therapy have increased in recent years and now include the treatment of bradyarrhythmias and heart failure according to the American College of Cardiology and American Heart Association guidelines.[24] These guidelines discuss indications for pacing in patients with sinus node dysfunction, acquired atrioventricular block, chronic bifascicular and trifascicular block, hypersensitive carotid sinus, and neurally mediated syndromes. The guidelines direct the treating physician in selecting patients who would benefit from device therapy.

A Swedish team led by Sennings and Elmqvist implanted the first pacemaker in 1958.[25] A thoracotomy was required, and pacing was done through electrodes sutured to the epicardium. In these early systems, significant problems with changes in pacing threshold, lead infection, and lead breakage were common. Transvenous lead implantation subsequently developed by Furman and colleagues[26] would resolve many of these issues. In 1958, Furman successfully paced an elderly patient with a catheter electrode inserted transvenously. Other investigators took on the challenge of solving various technical problems, such as device miniaturization; longer life batteries; and stable, reliable lead material.[27] As the indication for implantation expanded from atrioventricular conduction disturbances to management of sinus node dysfunction, the need for implantable pacemakers grew in proportion.[27] Technology evolved rapidly with the development of lithium-iodide batteries that had greater longevity. Electronic advances then led to major miniaturization using integrated circuits as opposed to discrete components. Lead materials used in today's pacemaker rely on silicone and polyurethane, which are more biocompatible and reliable than earlier materials. With these technical refinements, present-day pacemakers are small and can pace reliably for 8 to 10 years before generator replacement is needed. The primary functional challenge for contemporary pacemakers is to maintain the heart rate based on circulatory needs, pacing in a manner that mimics the natural physiology of excitation and conduction. In a healthy heart, the sinus node is modulated by the autonomic nervous system, and its rate is determined by a multiplicity of factors, such as physical activity, emotion, and blood pressure. Not only the rate, but also the activation sequence and atrioventricular conduction time vary with demand; these requirements also must be

considered. Rate is controlled by pacemaker discharge, and the excitation and conduction sequence depends on the placement of pacing electrodes. Approximately 120,000 pacemakers are implanted each year in the United States. Indication for implantation for most of these cases is sick sinus syndrome. Other indications include atrioventricular block, carotid sinus hypersensitivity, malignant vasodepressor syndrome, and hypertrophic cardiomyopathy.[28] The primary purpose of implantable pacemakers is to treat symptomatic bradycardia. With the extraordinary developments that have occurred in pacemaker therapy for the traditional indication—bradycardia—new uses are now beginning to be explored. Pacemakers have progressed from large, fixed-rate, single-chamber devices to multiprogrammable, multichamber devices with the ability to respond to changing hemodynamic demands. As technology advances, other possible uses are likely to be conceived.

RESYNCHRONIZATION THERAPY

Cardiac resynchronization is a pacing therapy aimed at improving coordination of atria and both ventricles. This therapy has been demonstrated to be effective for patients with heart failure who have conduction delay and left ventricular systolic dysfunction.[29] In addition, this therapy can reduce hospital readmission rates and improve quality of life in patients with heart failure.[30]

Cardiac resynchronization therapy improves heart failure symptoms, quality of life, exercise capacity, hospitalization, and echocardiographic variables.[31] It is indicated in patients with drug-refractory, symptomatic New York Heart Association functional class III and IV heart failure of either ischemic or nonischemic origin.[30] In addition, these patients are protected from associated risk for sudden cardiac death when combined with an ICD system.[29]

The development of an automatic internal defibrillator, or ICD, began in the 1960s. External cardiac defibrillation was increasingly being used in coronary care units for the treatment of ventricular fibrillation and sudden cardiac death. Although the idea of automatic external defibrillation had been discussed initially by Zycoto, Mirowski and colleagues[32] were the first to champion and begin practical development of an automatic internal device. In 1969, Mirowski and Mower developed the prototype of today's automatic internal defibrillator.[33]

The primary goal of all defibrillators is to terminate ventricular tachyarrhythmias by delivering high-voltage shocks to the ventricle. As with implantable pacemakers, defibrillating devices need to be small and reliable and have adequate longevity. ICDs have evolved not only to perform this function but also to take on additional tasks, such as antitachycardia pacing of the ventricle, dual-chamber pacing, and termination of atrial tachyarrhythmias.

A key difference between pacing and defibrillation of the heart is that for pacing only a very small mass of myocardium needs to be stimulated, whereas for defibrillation, most, if not all, of the myocardium must be stimulated. Because the myocardium is easily excitable throughout diastole, a small wave of depolarization during pacing can readily propagate throughout the whole heart. In contrast, during ventricular fibrillation, multiple reentrant wavefronts usually occur that are continuously changing in location and size and must be quelled. To defibrillate successfully, most of these wavefronts must be interrupted simultaneously; to achieve this, it is necessary to capture most of the tissue that is in a state of relative refractoriness.[34] One unique property of defibrillation success is that it is probabilistic.[35] The same energy that can defibrillate the heart on one occasion may be unsuccessful at another time.

The main purpose of ICD placement is to prevent death from hemodynamically unstable ventricular tachyarrhythmias. Although advances in technology have made these devices much more flexible in terms of arrhythmia detection and electric therapy potions, their main purpose is to reduce sudden cardiac death, which claims approximately 300,000 lives in the United States annually. Secondary prevention of sudden cardiac death in patients who have survived cardiac arrest is another major indication for ICD placement. In such patients and especially in patients of this group for whom no reversible or curable cause can be found, ICD implantation has been repeatedly documented to provide a major mortality benefit.[36] Interest in managing atrial tachyarrhythmias also has grown significantly in recent years. It is now recognized that approximately 30% of patients with ventricular tachyarrhythmia also have atrial tachyarrhythmias.[37] Such atrially initiated tachyarrhythmias can worsen patient symptoms, can result in inappropriate ventricular shocks, and may be responsible for initiating ventricular tachyarrhythmias that can exacerbate other pathologic processes, such as heart failure. New strategies for treatment and prevention of atrial tachyarrhythmias are incorporated into devices that are capable of defibrillation and antitachycardia pacing in the atrium and ventricle, in addition to combined dual-chamber pacing.[38]

The relative ease of ICD implantation and longevity of current defibrillators have made them a valuable tool in primary prevention. Patients no longer must survive cardiac arrest to justify the risk in ICD implantation.

PREOPERATIVE EVALUATION

Most patients who require pacemaker or ICD placement have significant cardiovascular disease. In addition, correction of cardiac arrhythmia may require radiofrequency catheter ablation. Radiofrequency catheter ablation has proved highly effective in the treatment of atrioventricular nodal reentrant and accessory pathway tachycardias. Indications for pacemaker and ICD placement continue to evolve as the utility of these devices continues to increase. Although most pacemaker placement is done with local anesthetic infiltration, ICD placement may require monitored anesthesia care or in some cases general anesthesia. The modern ICD unit is capable of delivering the full spectrum of therapy for ventricular tachyarrhythmias and for bradycardia therapy with dual-chamber pacing or sensing, rate modulation, and mode-switching features.

As mentioned earlier, ICD placement has two common indications. One is continued ventricular tachyarrhythmias despite adequate drug therapy, and the other is

history of sudden cardiac arrest that is not associated with myocardial infarction. Preoperative evaluation processes necessary for placement of an ICD should be complete by the time the decision is made to place the device (see also Chapters 38 and 39). These patients need a thorough preoperative evaluation. This evaluation includes electrophysiologic testing to determine the inducibility of ventricular tachycardia and electrophysiologically guided drug therapy. Preoperative pulmonary function tests may be necessary in patients on amiodarone to evaluate possible toxicity of this drug, which can result in chronic obstructive pulmonary disease or interstitial lung disease. In some instances, the underlying pathophysiology of malignant ventricular arrhythmias is related to ischemic or idiopathic cardiomyopathy.[39] These patients often present with poor left ventricular function and more frequent incidence of congestive heart failure. Patients with a history of congestive heart failure should be in optimal condition before surgery.

Generally, all patients who present for correction of cardiac arrhythmia require preoperative evaluations including electrocardiogram (ECG), chest radiograph, hemoglobin value, and electrolyte levels. Patients should receive nothing by mouth (NPO) for at least 8 hours before the procedure. In addition, patients who require device and lead extractions because of malfunction or infection may require blood product transfusions during the procedure. Consequently, type and crossmatch of blood products is frequently necessary for these procedures (also see Chapter 61).

ANESTHETIC CONSIDERATIONS

Pacemakers

Permanent implantable pacemakers have been the standard modality of treatment for patients with all types of bradyarrhythmias. A significant number of these patients present with sick sinus syndrome and are older. Consequently, devices are placed under general anesthesia in these patients. As a result of more recent advances in pacemaker technology, these devices now can be placed as a therapeutic modality to alter hemodynamic states. Surgeons used to be primarily responsible for device insertion. Now the task falls under the services of cardiologists. Device placement is commonly performed in the cardiac catheterization suite under local anesthesia on an outpatient basis. Patients at high risk who have complicated disease now present for pacemaker insertion, however, in addition to those with indications more recently identified by the American College of Cardiology and American Heart Association for these devices. In light of these increased indications, the expertise of anesthesiologists is needed for monitoring and perioperative care of these patients.

Monitored Anesthesia Care

Currently, most pacemaker insertions are performed by cardiologists. Most of these cases are performed under local anesthesia with sedation. Depending on the level of training, administration of sedatives and analgesics can be provided by nurses.

In instances that require deeper sedation for a patient's comfort or for critically ill patients with hemodynamic instability, monitored anesthesia care by an anesthesiologist may be required (see also Chapter 89). Adequate monitoring and resuscitation equipment are required in such situations. The goal of monitored anesthesia care is to provide analgesia, sedation, and anxiolysis, while ensuring rapid recovery with minimal or no side effects. Any sedative-hypnotic medication may be used during monitored anesthesia care with a wide variety of delivery systems.[40] Subanesthetic concentrations of inhaled agents also have been used to supplement local anesthetics. Newer drugs, such as centrally mediated α_2-agonists, have been shown to produce anxiolysis, sedation, and reduced requirements for supplemental analgesic medications during monitored anesthesia care.

General Anesthesia

Patients requiring pacemaker placement rarely require general anesthesia for placement. If general anesthesia is required, it should be directed toward underlying cardiac pathophysiology, indications, complications, and hemodynamic goals. Immediate access to life-support equipment, such as a cardiac defibrillator and a transcutaneous pacemaker, is necessary if the device is being placed under general anesthesia.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR

Since the 1980s, indications for use and implantation of ICDs have steadily increased. Over the past 2 decades, ICDs have undergone a significant evolution. In the 1970s and 1980s, ICD placement usually required thoracotomy for placement of epicardial patches.

PREOPERATIVE EVALUATION

As mentioned earlier, common indications for ICD implantation include continued ventricular tachyarrhythmias unresponsive to adequate pharmacotherapy and history of sudden cardiac arrest unassociated with myocardial infarction. Newer indications include patients with various forms of the congenital long QT syndrome.[41] Patients with long QT syndrome who have survived an episode of cardiac arrest or documented polymorphic ventricular tachyarrhythmia, especially if on pharmacotherapy at the time, are increasingly being evaluated as ICD candidates. In addition, patients with hypertrophic cardiomyopathies and without a history of sudden death are usually evaluated for ICD placement.[42] In these patients, sustained ventricular arrhythmias, nonexertional syncope, or a strong family history of sudden death with early age of presentation strongly indicates ICD implantation.

In all instances, the evaluation that is necessary for ICD implantation is completed by the time the decision is made to place the device (see also Chapters 38 and 39). Electrophysiologic studies may have been done to determine the forms of arrhythmias present. When the pathophysiology of ventricular arrhythmias is related to

idiopathic or ischemic cardiomyopathy,[43] these patients may present with poor left ventricular function and a high incidence of congestive heart failure. Consequently, they should be optimized as much as possible preoperatively.

ANESTHETIC CONSIDERATIONS

In the 1980s, ICD implantation was done with epicardial leads via thoracotomy under general anesthesia with one-lung ventilation. The technologic development of implantable ICDs with transvenous lead systems has simplified their implantation. Consequently, it was reasoned that ICDs can be placed under deep sedation with little or no intervention by the anesthesiologist analogous to what is needed for pacemaker placement.[44] Placement of an ICD under general anesthesia may be safer and more comfortable for the patient, however. Patients who present for ICD placement are often critically ill with cardiopulmonary comorbidity. These patients often present with ejection fractions of less than 30% and require vasopressors to support hemodynamics during the procedure. In addition, some form of general anesthesia is necessary for intraoperative testing of defibrillating thresholds.

Monitored Anesthesia Care

Small, new-generation devices and transvenous lead systems lend themselves to the use of local anesthesia and intravenous sedation for ICD implantation. Midazolam and fentanyl are usually the drugs of choice when an ICD is placed under monitored anesthesia care (see also Chapter 89). Monitoring includes pulse oximetry, five-lead ECG, and noninvasive blood pressure. Depth of anesthesia is monitored clinically. One of the major aspects of ICD placement is testing the device. Testing the device may require deep sedation or general anesthesia because the shocks associated with this procedure can be very painful. The presence of an anesthesiology team may be necessary for ICD placement under monitored anesthesia care.

General Anesthesia

Most patients who present for ICD placement typically have comorbidities such as ventricular tachycardia, congestive heart failure with ejection fraction less than 30%, coronary artery disease, pulmonary hypertension, chronic renal insufficiency, or valvular heart disease. These patients may be unable to lie flat for the prolonged period necessary for placement of the ICD. In addition, they may require close hemodynamic monitoring during testing of the device. General anesthesia should be considered in these patients. When general anesthesia is chosen, in addition to standard monitoring, an arterial line may be added. External cardioverter-defibrillator pads are required for all ICD placements. These are employed in cases in which an implanted defibrillator fails. General anesthesia also may be requested for anxious and extremely nervous patients. Because pacemakers and ICDs are placed percutaneously, anesthesiologists must be vigilant for possible complications, such as myocardial infarction, stroke, possible cardiac injury (perforation or tamponade), and pneumothorax from subclavian vascular access.

EXTRACTION OF DEVICES

As a result of continued growth and expanding indications for pacemakers and ICD placement, leads may require extraction because of mechanical dysfunction, the need to upgrade to more complex devices, or local or systemic infection. Lead extractions are probably one of the most challenging procedures that a cardiac electrophysiologist faces today.

Indications for lead extractions can be divided into two categories—patient-related and lead-related. Patient-related indications include infection, ineffective therapy (high defibrillation threshold), perforation, migration, embolization, induction of arrhythmias, venous thrombosis, unrelenting pain, device interactions, and device upgrades.[45] Lead-related indications include lead recalls, lead failure, and lead interactions.[46] Lead extraction is performed via powered sheaths through which energy is delivered to the tip in the form of excimer laser light or electrocautery. These systems burn through scar tissue adherent to the wall of the lead throughout its course. The potential for life-threatening complications, such as lead fracture, venous or myocardial rupture, and tamponade, makes general anesthesia with invasive monitors a prudent choice for lead extractions.

POSTOPERATIVE CARE

Postoperative care of patients with pacemaker or ICD implantation depends on various factors surrounding the implantation of the device (see also Chapter 96). As mentioned earlier, most of these patients are quite ill with significant comorbidities. It is not unusual for patients to have congestive heart failure with an ejection fraction less than 30% as a result of poor left ventricular function. Consequently, it is imperative to have these patients monitored in the postanesthesia care unit, especially if the device is placed or extracted under general anesthesia. The spectrum of recovery sites after these procedures may vary from postprocedure units to a coronary intensive care unit. Most of these procedures are done on an outpatient basis, and anesthesia is tailored to ensure rapid recovery after implantation.

CORRECTION OF CARDIAC ARRHYTHMIAS WITH ABLATION THERAPY

Catheter ablation is a safe and curative option for most cardiac arrhythmias, with 85% to 98% cure rates among the arrhythmias treated most frequently.[47] The rate of major complications is less than 3%.[47] Cardiac ablation therapy involves the delivery of energy through a catheter that is usually placed in the endocardial position in the heart, destroying myocardial tissue that is responsible for the tachyarrhythmia (Fig. 68-8). Multiple electrodes are inserted to locate the arrhythmia and ablate it. Usually the diagnostic portions of the ablation study are done during the same procedure.[48] The efficacy of catheter ablation depends on accurate identification of the site of origin of the arrhythmia. When the site is identified, the electrode catheter is positioned in direct contact with

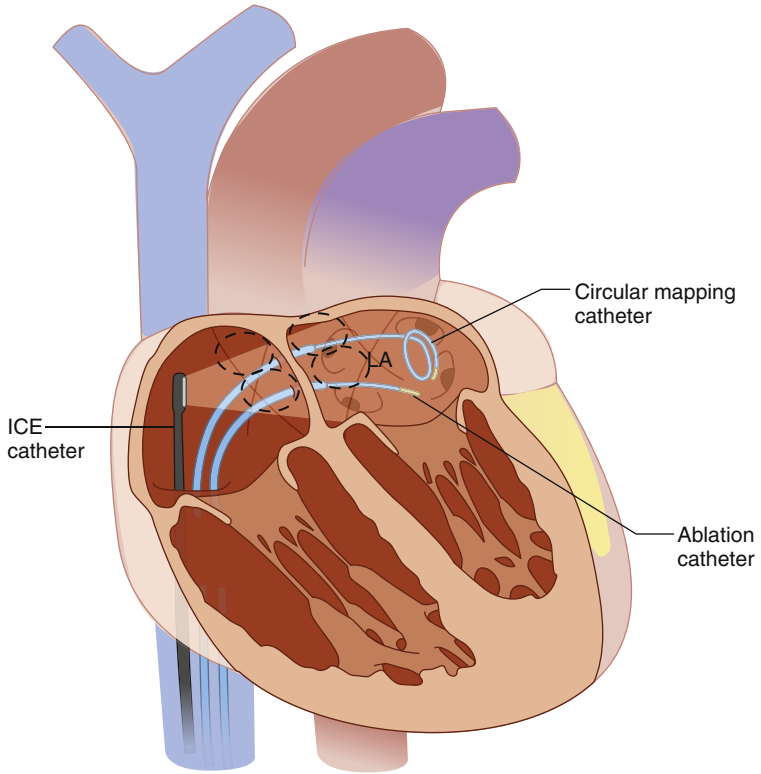


Figure 68-8. Catheter placement during ablation procedures. Mapping and ablation catheters were placed under the guidance of intracardiac echocardiography. *ICE,* Intracardiac echocardiography. *(Courtesy O. Wazni, MD, Cleveland Clinic, Cleveland, OH.)*

the site of the arrhythmia, and radiofrequency energy is delivered through the catheter to destroy it.

The current generated by radiofrequency is alternating current and is delivered at cycle lengths of 300 to 750 kHz when used for catheter ablation.[49] It causes resistive heating of the tissue in contact with the electrode. The degree of tissue heating is inversely proportional to the radius to the fourth power.[50] Consequently, the lesions created by radiofrequency energy are small. Although electric injury may be a contributing factor, the primary mechanism of tissue destruction by radiofrequency current is thermal injury. Acute lesions created by a radiofrequency current consist of a central zone of coagulation necrosis surrounded by a zone of hemorrhage and inflammation.[51] Cardiac arrhythmias that can be treated with radiofrequency ablation include paroxysmal supraventricular tachycardia, Wolff-Parkinson-White syndrome, atrial flutter, atrial fibrillation, and idiopathic ventricular tachycardia. Most cardiac arrhythmias treated with radiofrequency ablation are not life-threatening but have a significant impact on a patient's quality of life.[52] Advantages of radiofrequency ablation of cardiac arrhythmias include relief of symptoms, improvement in functional capacity and quality of life, and elimination of the need for lifelong antiarrhythmic drug therapy. The principal disadvantage is the risk for complications, which varies depending on the type of ablation procedure and skill of the operator.

ANESTHETIC CONSIDERATIONS

Catheter ablation was introduced into clinical practice in 1982. Initially, ablation was performed with direct electric shocks.[53] As a result of several advantages over direct current, radiofrequency ablation has replaced direct current ablation. These advantages include the absence of skeletal and cardiac muscle stimulation, minimal discomfort during delivery of energy, the possibility of performing the procedure in conscious patients, and the discrete nature of resulting lesions.[51]

Most cardiac ablation therapy for correction of arrhythmias can be performed under moderate sedation or monitored anesthesia care. In some of these cases, deep sedation may be required as the case progresses. In a few cases, general anesthesia may be required if the patient is anxious or cannot tolerate lying in the supine position for an extended period. General anesthesia may be implemented for these patients with standard American Society of Anesthesiologists monitors with adequate vascular access. Catheter ablation is the first-choice treatment for most cardiac arrhythmias. It is a safe treatment and is usually effective as a single procedure. Because it is curative in many patients, it is offered to all patients who would otherwise be committed to long-term drug therapy.

FUTURE TRENDS

Correction of cardiac tachyarrhythmias has improved dramatically in the past 2 decades. Emphasis has shifted from pharmacologic therapy to nonpharmacologic therapy of tachyarrhythmias; this has led to a significant increase in the numbers of radiofrequency catheter ablations and defibrillator implantations. These developments were triggered by technologic advances that showed superiority of

these procedures over the use of antiarrhythmic drugs.[54] As a result, treatment of supraventricular tachycardias and tachycardias involving accessory atrioventricular pathways will probably remain the domain of catheter ablation. The cure rate of patients treated with catheter ablation is very high. In addition, treatment of life-threatening ventricular tachyarrhythmia will remain in the domain of ICDs for the foreseeable future. The role of ICD therapy has been clearly defined with respect to prolongation of life and has been expanded to include primary prophylaxis of sudden death in high-risk populations.[55]

The demand for perioperative care in the electrophysiology suite, especially for those undergoing ablation procedures, has resurrected the use of high-frequency jet ventilation (HFJV) in recent years.[56] Although the use of HFJV in the electrophysiology suite is relatively new, studies have demonstrated improved outcomes and decreases in procedure time.[57] HFJV has been demonstrated to provide a more stable environment, especially in the posterior wall of the atrium. As a consequence, in the future HFJV use will increase and provide an attractive alternative to the conventional mode of ventilation during catheter ablation.[19,58] The anesthetic implications of this modality in the electrophysiology suite has recently been reviewed.[59]

As a result of these developments, the presence of an anesthesiology team will continue to increase in cardiology suites. Patients who are being cared for in these areas are sicker with significant comorbidities. The role of conscious sedation will continue to diminish in the performance of these procedures. These patients will require full monitoring and care under the direction of an anesthesiologist.

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Chapter 69

Anesthesia for Vascular Surgery

EDWARD J. NORRIS

Key Points

- Perioperative management of patients undergoing vascular surgery requires an understanding of the underlying pathophysiology of the specific vascular lesion.
- Major vascular surgery is particularly challenging to the anesthesiologist because these are high-risk operations in a patient population with a high prevalence of either overt or occult coronary artery disease, which is the leading cause of perioperative and long-term mortality after vascular surgery.
- Accurate clinical assessment of the pretest probability of significant coronary artery disease is necessary for prudent use and rational interpretation of preoperative cardiac testing.
- Guidelines on perioperative cardiovascular evaluation and care suggest that coronary intervention is rarely necessary to simply decrease the risk for surgery unless such intervention is indicated, irrespective of the preoperative context. Prophylactic coronary revascularization has not been shown to reduce perioperative or long-term morbidity after major vascular surgery. Medical therapy is the cornerstone for the management of coronary artery disease.
- Patients should take their usual cardiovascular medications throughout the perioperative period. Antiplatelet therapy requires special consideration and must be individualized to each patient.
- Prevention and treatment of perioperative myocardial ischemia require careful control of the determinants of myocardial oxygen supply and demand. ST-segment monitoring, particularly with computerized ST-segment analysis, should be used to detect myocardial ischemia during the perioperative period.
- Initiation of perioperative β-adrenergic blocker therapy has potential benefits and risks.
- All patients who require statin therapy on an ongoing basis should also receive statins in the perioperative period.
- The clinical usefulness of any intraoperative monitoring technique ultimately depends on patient selection, accurate interpretation of data, and appropriate therapeutic intervention.
- Maintenance of vital organ perfusion and function by the provision of stable perioperative hemodynamics is more important to overall outcome after aortic surgery than is the choice of anesthetic drug or technique.
- The pathophysiology of aortic cross-clamping and unclamping is complex and depends on many factors, including the level of the cross-clamp, the extent of coronary artery disease and myocardial dysfunction, intravascular blood volume and distribution, activation of the sympathetic nervous system, and the anesthetic drugs and techniques.
- The degree of preoperative renal insufficiency is the strongest predictor of postoperative renal dysfunction.
- Endovascular aortic surgery has become an established less invasive alternative to conventional open aortic repair. Endoleak, or the inability to obtain or maintain complete exclusion of the aneurysm sac from arterial blood flow, is a complication specific to endovascular aortic repair.
- The primary clinical utility of cerebral monitoring during carotid endarterectomy is to identify patients in need of carotid artery shunting; second, such monitoring is used to identify patients who may benefit from an increase in arterial blood pressure or change in surgical technique.
- Postoperative hypothermia is associated with many undesirable physiologic effects and may contribute to adverse cardiac outcome.

The perioperative management of patients undergoing vascular surgery is one of the most challenging and controversial areas in the field of anesthesiology. Given the frequent occurrence of coexisting disease in elderly patients (see also Chapter 80), the hemodynamic and metabolic stress associated with arterial cross-clamping and unclamping, and the ischemic insults to vital organs, including the brain, heart, kidneys, and spinal cord, perioperative morbidity and mortality are more frequent with vascular surgery than with most other surgical procedures. Anesthesia care must focus on preservation of vital organ function, with a strong emphasis on the heart, which is the single most important cause of morbidity after vascular surgery. The clinical controversies associated with vascular surgery are diverse and involve aspects of preoperative, surgical, anesthetic, and postoperative management. The controversy associated with routine preoperative screening for coronary artery disease (CAD), as well as appropriate treatment if detected, has particular importance (see also Chapters 38 and 39). A specific anesthetic technique has not been established because vascular procedures often lend themselves to local, regional, general, or combined techniques.

In the 1970s, vascular surgery was recognized as a risk factor for perioperative cardiac morbidity. In the 1980s, the focus shifted to risk stratification in an effort to identify patients who were at the most frequent risk for morbid outcomes. In the 1990s, intensive clinical investigation involving anesthetic technique, sympatholytic drugs, hemodynamic control, and analgesic technique was undertaken and provided important insight into the prevention, treatment, and mechanisms of cardiac and other morbidity. During this time, a guideline-based approach to health care was initiated, primarily in the United States (see also Chapter 102). Over the last decade, a paradigm shift occurred away from routine preoperative screening for CAD with a focus on risk stratification and invasive treatment of CAD to an intensive strategy of perioperative cardiac risk reduction using medications and risk factor modification (see also Chapters 38 and 39). Additionally, over the last decade the multidisciplinary field of endovascular surgery has provided less invasive approaches or alternatives to conventional vascular reconstruction. These less invasive procedures, initially offered to patients traditionally considered unfit for open surgery, are being widely applied to the larger cohort of patients undergoing vascular surgery.

The goal of this chapter is to review issues related to the perioperative care of patients undergoing vascular surgery and to address the underlying controversies. For simplicity, the five major categories of vascular surgical procedures are discussed separately: abdominal aortic surgery, thoracoabdominal aortic surgery, endovascular aortic surgery, lower extremity vascular surgery, and carotid surgery.

ATHEROSCLEROSIS

Cardiovascular diseases place an enormous burden on health care systems worldwide and are the leading cause of death and disability in the United States. Their underlying pathologic process is atherosclerosis, a slowly progressing chronic disorder of the arterial wall that compromises the blood supply to any or all of the vital organs or the extremities and leads to the clinical manifestations of myocardial infarction (MI), stroke, and gangrene. The lesions of atherosclerosis occur primarily in large and medium-sized arteries and tend to form at sites with disturbed laminar flow, such as branch points. The most common sites are the coronary arteries, carotid bifurcation, abdominal aorta, and iliac and femoral arteries (Fig. 69-1). Although atherosclerotic lesions result from a variety of complex pathogenetic processes, progression of atherosclerosis occurs in several stages. The initial lesion of atherosclerosis, the fatty streak, starts in early childhood and is initiated by intimal accumulation of low-density lipoprotein (LDL) particles. The fatty streak lesion consists largely of T cells and lipid-laden macrophages called foam cells. With the progressive accumulation of apoptotic and degenerated foam cells, cell debris, and cholesterol crystals, the fatty streak progresses to an atheromatous plaque with a necrotic lipid core. A more complex lesion develops with the formation of a fibrous cap of variable thickness composed of collagen and proliferated smooth muscle cells. The advanced lesions of atherosclerosis represent a progression of the fibroatheromatous plaque, with an expanded lipid-rich core, accumulation of calcium, and disruption of endothelial integrity. Physical disruption of the plaque's fibrous cap permits contact between flowing blood elements, including platelets and coagulation proteins, and the highly thrombogenic material located in the lesion's lipid core, such as collagen and tissue factor, which results in thrombus formation (i.e., atherothrombosis) or, in the case of intraplaque hemorrhage, plaque progression. Atherothrombosis may lead to complete vascular occlusion at the site of plaque rupture or detach to become an embolus that can block blood flow distal to its origin.

The American Heart Association Committee on Vascular Lesions has provided a numerical classification of histologically defined atherosclerotic lesion types.[1] Figure 69-2 outlines the most updated classification.[2] Lesion types I, II, and III are always small and clinically silent. With the development of type IV lesions, the pathways to clinical disease vary (see Fig. 69-2). Although lesions IV through VI may progress such that they obstruct the lumen of a medium-size or large artery and produce a clinical event (i.e., MI, ischemic stroke, or extremity ischemia), the clinical manifestations of atherosclerotic disease are most often associated with type VI lesions. The criteria for type VI histology are often interrelated and include one or more of the following: surface defect, hematoma, and thrombosis. Regression of lipid from lesion types IV, V, and VI may result in lesion morphology similar to that of type VII and VIII lesions.

Established risk factors for atherosclerosis-related cardiovascular disease are male gender, age, family history of premature cardiovascular disease, high levels of LDL cholesterol, low levels of high-density lipoprotein (HDL) cholesterol, diabetes, obesity, hypertension, and smoking. Newer and emerging risk factors include homocysteine, fibrinogen, lipoprotein(a), apolipoproteins B and A-I, and high-sensitivity C-reactive protein (hsCRP). Atherosclerosis usually has no early warning signs, making primary prevention difficult and often delaying risk modification until the

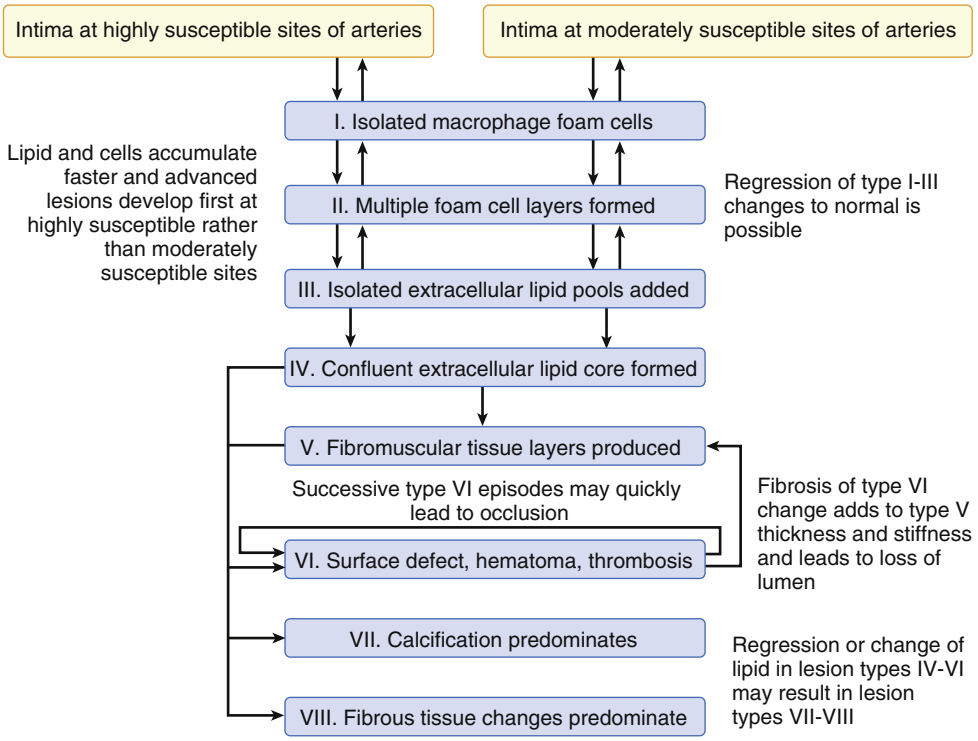


Figure 69-1. Outline of the sequence in the evolution of atherosclerotic lesions from type I to type IV and of the various possible subsequent pathways of progression to lesion types beyond type IV. The diagram lists the main histologic characteristics of each sequential step (lesion type). *Thick or* differentiate between the relative ease with which lesions develop at specific sites, or they indicate the relative frequency and importance of a pathway section. (From Stary HC: Natural history and histological classification of atherosclerotic lesions: an update, *Arterioscler Thromb Vasc Biol* 20:1177-1178, 2000.)

disease has progressed to an advanced stage. Established pharmacologic strategies against atherosclerosis are largely limited to treating hypertension and hyperlipidemia and controlling hemostasis to prevent thrombotic complications. Inhibitors of hydroxymethylglutaryl coenzyme A (i.e., statins) are the lipid-modifying drugs of choice and their efficacy in lowering LDL cholesterol and the risk for cardiovascular events is well established in large outcome-based clinical trials.[3] Antiplatelet drugs, including aspirin and thienopyridines such as clopidogrel, are widely used to prevent vascular events in patients with cardiovascular disease.

Inflammation in the arterial wall plays a fundamental role in both atherogenesis and atheroprogression.[4] Serum markers of inflammation, such as hsCPR, are being used in cardiovascular risk stratification. hsCPR levels are correlated with risk for death and MI and with the development of peripheral vascular disease. As a result of this new understanding, inflammation has become a therapeutic target in the prevention and treatment of atherosclerosis and its complications. Statins have important antiinflammatory modes of action that are independent of LDL cholesterol lowering. For example, treatment with statins decreases hsCRP in patients with atherosclerosis by 13% to 50% in contrast to placebo, and decreased levels of hsCRP while receiving statins is associated with improved clinical outcome.

PREOPERATIVE EVALUATION

COEXISTING DISEASE

Patients undergoing vascular surgery have a frequent incidence of coexisting disease, including diabetes mellitus, hypertension, renal impairment, and pulmonary disease, all of which should be assessed and, if possible, optimized before surgery (see also Chapters 38 and 39). Because of the systemic nature of atherosclerotic disease, patients with vascular disease frequently have arterial disease affecting multiple vascular territories. CAD is the leading cause of perioperative mortality at the time of vascular surgery, and long-term survival after vascular procedures is significantly limited by the frequent occurrence of morbid cardiac events.[5] Less than 10% of patients who undergo vascular surgery have normal coronary arteries, and more than 50% have advanced or severe CAD. Unrecognized MI (determined by wall motion abnormalities at rest in the absence of a history of MI) and silent myocardial ischemia (determined by stress-induced wall motion abnormalities in the absence of angina) often occur in vascular surgery patients (23% and 28%, respectively) and are associated with increased long-term mortality and adverse cardiac events.[6] Left ventricular systolic dysfunction is five times more common in patients with vascular disease than in matched controls.[7] It is not clear whether any specific category of vascular disease is associated with a greater likelihood of coexisting CAD. Some investigators have shown a similar incidence and severity of CAD in patients with aortic, lower extremity, and carotid disease. Others have shown that patients with lower extremity vascular disease are more likely to have significant CAD and to experience perioperative morbidity. Medical therapy is the cornerstone of the management of CAD.

PERIOPERATIVE AND LONG-TERM CARDIAC OUTCOMES

Preoperatively, the potential for MI and death in patients undergoing vascular surgery must be considered (Table 69-1). Nonfatal and fatal MIs are the most important and specific outcomes that determine perioperative cardiac morbidity. When multiple recent studies are pooled, the

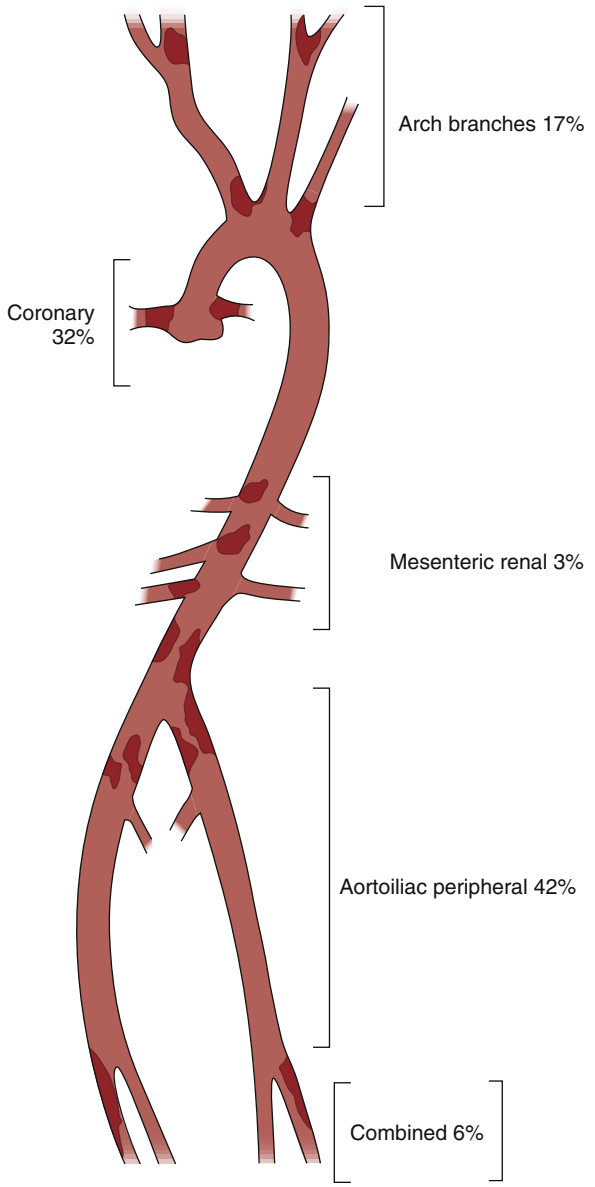


Figure 69-2. Distribution of atherosclerotic lesions. Plaques occur at the origins of large vessels and at bifurcations. Distribution and relative severity differ based on risk factors. (From Zwolak RM, Cronenwett JL: Pathophysiology of vascular disease. In Yeager MP, Glass DD, editors: *Anesthesiology and vascular surgery,* East Norwalk, Conn, 1990, Appleton & Lange, pp 3-29.)

TABLE 69-1 RATES OF MYOCARDIAL INFARCTION AND DEATH IN PATIENTS UNDERGOING VASCULAR SURGERY

Study	MI (%)	Death (%)	Comments
Short-Term Follow-Up (in Hospital or 30-Day)*			
Ouyang et al[184]	8	0	Small study
Raby et al[185]	2.3	0.06	Aortic, lower extremity, carotid
Mangano et al[186]	4.1	2.3	Vascular patient only reported
Bode et al[117]	4.5	3.1	All lower extremity
Christopherson et al[39]	4.0	2.0	All lower extremity
Mangano et al[187]	5.0	0	Vascular patient only reported
Fleisher et al[188]	6.0	3.0	Vascular patient only reported
Pasternack et al[189]	4.5	1.0	Aortic, lower extremity, carotid
Krupski et al[190]	2.1	2.9	Aortic, lower extremity
Baron et al[74]	5.9	4.0	All aortic
Norris et al[40]	3.3	5.4	All aortic
Fleron et al[80]	5.5	4.1	All aortic
McFalls et al[8]	8.4	3.2	Aortic, lower extremity
Average	4.9	2.4	
Long-Term Follow-Up (in Hospital and After Discharge)*			
Raby et al[185]	7.4	5.1	20-mo follow-up
Mangano et al[186]	4.7	3.5	15-mo follow-up
Mangano et al[191]	19.4	13.5	24-mo follow-up
Hertzer et al[25]	12		60-mo follow-up
Krupski et al[192]	3.9	11.2	24-mo follow-up
McFalls et al[8]	22		30-mo follow-up
Average	8.9	11.2	

MI, *Myocardial infarction.*

*For short-term follow-up, outcomes are reported for the duration of the hospital stay or 30 days, and death from MI was classified as both MI and death. For long-term follow-up, MI was not included as a subset of death because the cause of death was often unknown. The incidence of MI is underestimated in the long-term part of the table.

overall prevalence of perioperative MI and death is 4.9% and 2.4%, respectively. When outcomes are assessed over the long term (2 to 5 years), the prevalence of MI and death is 8.9% and 11.2%, respectively. This perioperative and long-term morbidity and mortality persist despite aggressive medical and surgical therapy.[8]

GUIDELINE-BASED APPROACH

A guideline-based approach to health care is relatively new and originated primarily in the United States. The American College of Cardiology (ACC) Foundation and the American Heart Association (AHA) jointly produced guidelines in the area of cardiovascular disease for more than 2 decades. The ACC/AHA Task Force on Practice Guidelines published "Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery" in 1996. This evidence-based approach to perioperative evaluation and management was updated in 2002 and 2007,[9,10] and in 2009.[11] New guidelines will be published in 2014. A stepwise approach (simplified from the 2007 guidelines) to perioperative cardiac evaluation and care for noncardiac surgery is provided in Chapter 38. The authors emphasize that the purpose of the preoperative evaluation is not to give medical clearance but rather to perform an evaluation of the patient's current medical status; make recommendations concerning the evaluation, management, and risk for cardiac problems; and provide a clinical risk profile that the patient and caregivers can use in making treatment decisions that may influence perioperative and longer term cardiac outcomes. The overriding theme of the perioperative guidelines is that intervention is rarely

necessary to simply lower the risk associated with surgery unless such intervention is indicated irrespective of the preoperative context. Thus, preoperative testing should not be performed unless it is likely to influence patient care. The particular challenge that the vascular surgery patient presents is emphasized throughout the document. Aspects of the updated guidelines and their evidence-based approach will be discussed throughout this chapter.

CARDIAC RISK ASSESSMENT

The preoperative cardiac assessment presents an opportunity to initiate and optimize pharmacologic management, perform appropriate diagnostic and therapeutic interventions, and adjust overall care to decrease not only perioperative risk but also long-term risks from cardiovascular events. The challenge for clinicians is to accurately assess risk for cardiac morbidity while maintaining a cost-effective, clinically relevant, and evidence-based strategy. The ACC/AHA stepwise approach considers vascular surgery distinct from other noncardiac surgical procedures and is reviewed in detail in Chapter 38. Only issues specific to vascular surgery are reviewed in this chapter.

After assessment of cardiac risk, the additional challenge exists of modifying perioperative management to reduce risk by adjusting or adding cardiac medications (e.g., β-adrenergic blocker), direct coronary intervention (e.g., percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]), modifying or intensifying perioperative management (e.g., invasive hemodynamic monitoring), or changing preoperative plans (e.g., performing endovascular aortic repair rather than open aortic repair). Coordination is essential among surgeons, anesthesiologists, and cardiologists, each of whom may have different criteria for risk assessment and different objectives for risk modification.

Clinical Risk Indices

Assessing cardiac risk in patients before vascular surgery is a controversial and difficult task (see also Chapters 37 and 38). Although risk indices are a cost-effective screening method for determining which patients may require further cardiac evaluation (i.e., additional risk stratification with noninvasive technologies), the high pretest probability of CAD in vascular surgery patients makes the risk index somewhat less useful. Vascular surgery–specific indices have been recently developed to optimize the prediction of perioperative mortality[12] and cardiac morbidity[13] in patients undergoing elective and urgent vascular surgery. Risk indices do not provide specific risk prediction for individuals, but rather place patients in general risk categories, most commonly designated as low (cardiac risk generally < 1%), intermediate (cardiac risk of 1% to 5%), or high (cardiac risk often > 5%). Clinical risk variables identified by logistic regression in vascular surgery cohorts can be used along with noninvasive cardiac testing to optimize preoperative assessment of cardiac risk before vascular surgery. From the registry of the Coronary Artery Revascularization Prophylaxis (CARP) trial, the absence of multiple preoperative cardiac risk variables identifies patients with the best long-term survival after elective vascular surgery.[14]

Previous Myocardial Infarction

In patients undergoing cardiac evaluation before vascular surgery, unrecognized MI (determined by rest wall motion abnormalities and no history of MI) is highly prevalent (23%) and associated with increased long-term cardiac risk.[6] Diabetes and heart failure are important predictors of unrecognized MI. Current guidelines recommend waiting 4 to 6 weeks after an uncomplicated MI before proceeding with elective surgery[11] and risk stratification with stress testing and assessment of ventricular function during this period.[15] Vascular surgery is often not elective, and urgent or emergent surgery may be required for patients with symptomatic aortic aneurysm, crescendo transient ischemic attacks from carotid disease, or limb-threatening ischemia from iliac or femoral occlusive disease. In these instances, the patient must proceed to surgery with careful perioperative medical management and surveillance.

Previous Coronary Artery Bypass Surgery

Patients who have undergone prior (<5 years) CABG and are without current symptoms of angina or heart failure appear to have a relatively infrequent incidence of cardiac morbidity after noncardiac surgery. However, previous coronary revascularization may not provide the same level of protection against MI and death after major vascular surgery. Results from the randomized, prospective CARP trial demonstrated that an aggressive strategy of prophylactic coronary artery revascularization before vascular surgery in patients with stable cardiac symptoms does not improve short-term outcome or long-term survival.[8] At 2.7 years after randomization, mortality was 22% and 23% in patients with and without revascularization, respectively. Postoperative MI, defined by increased troponin levels, occurred in 12% and 14% of patients with and without revascularization, respectively. Among those randomized to revascularization, patients undergoing CABG had fewer perioperative (6.6% versus 16.8%) and late postoperative (9.9% versus 23.7%) MIs than did patients undergoing PCI despite more diseased vessels in the CABG group (3.0 versus 2.2).[16] Completeness of the revascularization procedure (CABG > PCI) was the predominant variable accounting for this difference. The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE)-V Pilot Study investigated in a randomized fashion the role of prophylactic coronary revascularization in high-risk (three or more clinical risk variables and extensive stress-induced ischemia on noninvasive cardiac testing) patients undergoing major vascular surgery, although concern has been raised about the integrity of investigations from the Poldermans group at Erasmus University.[17-19] Preoperative coronary revascularization was not associated with improved short-term or long-term outcome compared with best medical treatment.[17] No significant difference was found in the composite end point of all-cause death or nonfatal MI at 30 days (43% versus 33%) or during 1-year follow-up (49% versus 44%) between patients randomized to revascularization or no revascularization. Unlike the CARP trial, no difference was observed in the incidence of perioperative cardiac events between patients treated with CABG or PCI. The results of these

two randomized trials are congruent with the current ACC/AHA guidelines on perioperative management[11] and CABG.[20] Specifically, preoperative revascularization should be reserved for patients with unstable cardiac conditions or advanced coronary disease, for whom a survival benefit with CABG has been established. Periprocedural complications after CABG are substantially more frequent in patients with peripheral arterial disease than in those without such disease.[21] These complications may preclude or alter the timing of subsequent vascular surgery.

Previous Percutaneous Coronary Intervention

The role of prophylactic percutaneous coronary revascularization in the preoperative management of vascular surgery patients is controversial.[8,17] PCI probably should be limited to patients with unstable active CAD.[11] Patients with peripheral vascular disease are often not ideal candidates for PCI. These interventions require placement of a large-diameter introducer sheath in the femoral artery, which predisposes to pseudoaneurysm and compromised blood flow to the lower extremities.[22] PCI can be performed through the brachial artery, but it is technically difficult. PCI in patients with peripheral arterial disease, as opposed to those without peripheral arterial disease, is associated with less frequent procedural success, more frequent in-hospital cardiovascular complications, and mortality.[23] Current guidelines indicate that PCI before noncardiac surgery, including vascular surgery, is of no value in preventing perioperative cardiac events, except in patients in whom PCI is independently indicated for unstable active cardiac conditions.[11]

The optimal interval between PCI and subsequent vascular surgery is unknown (see also Chapters 37 and 38). Current perioperative guidelines provide a comprehensive review of this topic and offer recommendations based on clinical data and expert opinion.[11] The type of coronary intervention, the need for dual antiplatelet therapy, the risk for bleeding from surgery, the risk in terminating antiplatelet therapy, and the urgency of the surgery all must be carefully considered.

Noninvasive Diagnostic Cardiac Testing

Accurate clinical assessment of the pretest probability of significant CAD is extremely important. In general, noninvasive cardiac testing before vascular surgery is best directed at patients considered to be at intermediate clinical risk. Such testing should not be undertaken if it is unlikely to alter patient management and should not be considered as a preliminary step leading to coronary revascularization. A revascularization procedure is rarely needed solely for the purpose of getting a patient through the perioperative period. Extensive cardiac evaluation before vascular operations can result in morbidity, delays, and patient refusal to undergo vascular surgery. A complete review of this subject is found in Chapter 38.

Cardiac Catheterization and Prophylactic Revascularization

The largest series on outcome in vascular surgery patients is that of Hertzer and colleagues[24] from the Cleveland Clinic. These investigators performed cardiac catheterization in 1000 consecutive patients scheduled to undergo peripheral vascular surgery (aortic aneurysm resection, carotid endarterectomy, and lower extremity revascularization). The incidence and severity of CAD were assessed according to the following classification: normal coronary arteries; mild-to-moderate CAD with no lesion exceeding 70% stenosis; advanced, compensated CAD with one or more lesions exceeding 70% stenosis but with adequate collateral circulation; severe, correctable CAD with more than 70% stenosis in one or more coronary arteries; and severe inoperable CAD with greater than 70% stenosis in one or more coronary arteries and severe distal disease or poor ventricular function. The most remarkable findings were that only 8.5% of patients had normal coronary arteries and 60% had advanced or severe coronary lesions (>70% stenosis). Even when CAD was not suspected by the clinical history, more than a third of patients had advanced or severe coronary lesions (Table 69-2).

In the Hertzer series, patients with severe correctable CAD were offered CABG before their vascular surgery, patients with normal or mild-to-moderate CAD went directly to vascular surgery, and those with severe inoperable CAD were treated on an individual basis. Combined mortality rates over the immediate- and long-term (4.6-year follow-up) postoperative period are shown in Table 69-3.[25] Of the 216 patients who underwent coronary revascularization (CABG), 12 (5.5%) died after this surgery. This mortality rate is more frequent than that reported for patients undergoing CABG surgery without peripheral vascular disease (1% to 2%). Perhaps the risks associated with CABG should be seriously considered as part of the preoperative evaluation of these patients. When overall early and late mortality (>5 years) is considered, death occurred in 12% versus 26% of patients who did or did not undergo CABG. Although these data

TABLE 69-2 RESULTS OF CORONARY ANGIOGRAPHY IN 1000 PATIENTS WITH PERIPHERAL VASCULAR DISEASE

	Clinical CAD					
	None		Suspected		Total	
Angiographic Classification	*No.*	*%*	*No.*	*%*	*No.*	*%*
Normal coronary arteries	64	14	21	4	85	8.5
Mild-to-moderate CAD	218	49	99	18	317	32
Advanced, compensated CAD	97	22	192	34	289	29
Severe, correctable CAD	63	14	188	34	251	25
Severe, inoperable CAD	4	1	54	10	58	5.8

CAD, *Coronary artery disease.*

Data from Hertzer NR, Beven EG, Young JR, et al: Coronary artery disease in peripheral vascular patients: a classification of 1000 coronary angiograms and results of surgical management, *Ann Surg* 199:223-233, 1984.

appear to support the beneficial effect of CABG on outcome, the mortality from CABG itself (5.5%) reduces its apparent benefits.

Two randomized clinical trials have been performed to determine the impact of prophylactic coronary artery revascularization on outcome after open aortic and lower extremity arterial vascular surgery.[8,17] Of the 5859 patients screened in the CARP trial,[8] 1190 underwent coronary angiography based on a combination of clinical risk factors and noninvasive stress imaging data.[26] The incidence and severity of CAD on these angiograms were 43% of patients had one or more major coronary arteries with at least a 70% stenosis suitable for revascularization (and were randomized to either revascularization or no revascularization before vascular surgery); 31% had nonobstructed coronary arteries; 18% had coronary stenosis considered unsuitable for revascularization; and 5% had left main coronary artery stenosis of 50% or more. The CARP trial showed that prophylactic revascularization (by CABG or PCI) was generally safe but did not improve long-term outcome after vascular surgery. Long-term mortality (2.7 years) was 22% in the revascularization group and 23% in the group considered inappropriate for revascularization (Fig. 69-3). Although the trial was not designed to test the short-term benefit of prophylactic revascularization, perioperative outcomes were not decreased, including death (3.1% versus 3.4%) and MI (12% versus 14%). The CARP trial results can be applied to most of the vascular surgery patients; however, they cannot be extrapolated to patients with unstable cardiac symptoms, left main coronary artery disease, aortic stenosis, or severe left ventricular dysfunction because these conditions excluded patients from study participation. The DECREASE-V trial[17] screened 1880 vascular surgery patients, 430 of whom with three or more clinical risk factors underwent noninvasive stress testing using stress-echo or perfusion imaging. Patients with extensive stress-induced ischemia (26%) were randomly assigned to

TABLE 69-3 **PERIOPERATIVE AND LATE CARDIAC DEATHS AFTER PERIPHERAL VASCULAR RECONSTRUCTION IN PATIENTS MONITORED OVER A 5-YEAR PERIOD ACCORDING TO CORONARY ANGIOGRAPHIC CLASSIFICATION**

Clinical Features	Total No. Patients	*Normal or Mild-to-Moderate CAD*		*Advanced, Compensated CAD*		*Severe, Correctable CAD*				*Severe, Inoperable CAD*		*Total Cardiac Deaths*	
						With CABG		*No CABG*					
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Men	685	10/242	4.1	33/204	16	13/174	7.5	6/24	25	14/41	34	76	11
Women	315	5/160	3.1	12/85	14	12/42	29	3/11	27	8/17	47	40	13
Age <70 yr	722	10/328	3.0	29/198	15	19/148	13	3/20	15	13/28	46	74	10
Age >70 yr	278	5/74	6.8	16/91	18	6/68	8.8	6/15	40	9/30	30	42	15
Normotensive	403	7/185	3.8	15/102	15	8/82	9.8	2/15	13	8/19	42	40	9.9
Hypertensive	597	8/217	3.4	30/187	16	17/134	13	7/20	35	14/39	36	76	13
Nondiabetic	830	12/348	3.4	28/232	12	17/183	9.3	8/30	27	13/37	35	78	9.4
Diabetic	170	3/54	5.5	17/57	30	8/33	24	1/5	20	9/21	43	38	22
Total	1000	15/402	3.7	45/289	16	25/216	12	9/35	26	22/58	38	116	12

CAD, *Coronary artery disease.*

Data from Hertzer NR, Young JR, Beven EG, et al: Late results of coronary bypass in patients with peripheral vascular disease. II. Five-year survival according to sex, hypertension, and diabetes, *Cleve Clin J Med* 54:15-23, 1987.

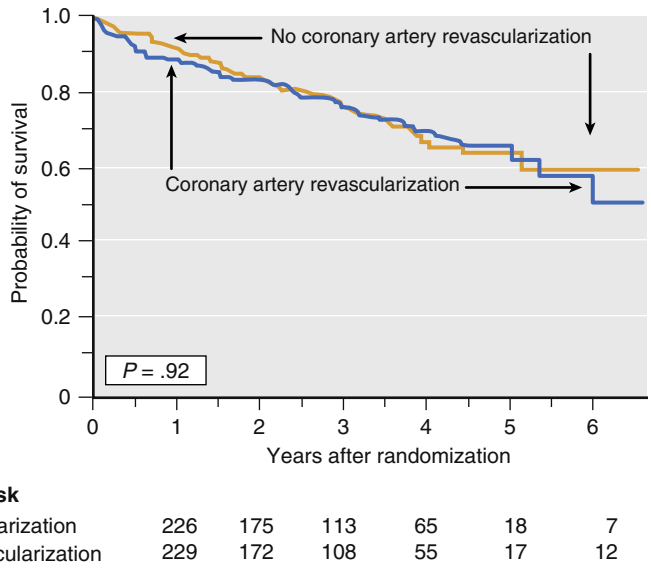


Figure 69-3. Long-term survival in patients randomized to undergo coronary artery revascularization or no coronary artery revascularization before elective major vascular surgery (Coronary Artery Revascularization Prophylaxix trial). Kaplan-Meier estimates were used to generate survival curves from the time of randomization for all patients. (From McFalls EO, Ward HB, Moritz TE, et al: Coronary-artery revascularization before elective major vascular surgery, *N Engl J Med* 351:2796-2804, 2004.)

revascularization or no revascularization. Coronary angiography showed two-vessel disease in 24%, three-vessel disease in 67%, and left main coronary artery disease in 8%. Prophylactic coronary revascularization (CABG or PCI) did not improve perioperative or long-term outcome (Table 69-4). The incidence of all-cause death or nonfatal MI at 30 days in patients who underwent revascularization or who did not was 43% versus 33%, respectively. The incidence of the composite end point at 1 year was similar, 49% versus 44%, respectively. As noted previously, this trial has come under scrutiny based on concerns of unfortunate scientific misconduct by the principal investigator.

The lack of benefit of prophylactic coronary revascularization in the CARP and DECREASE-V trials is difficult to reconcile with the more favorable data from Hertzer and co-workers[24] and other studies (Coronary Artery Surgery Study [CASS][27] and Bypass Angioplasty Revascularization Investigation [BARI][28]), but is consistent with current guideline recommendations.[11] Clearly, issues are involved that go beyond critical coronary lesions; perhaps the current understanding of the pathophysiology of perioperative MI is incomplete. For example, perioperative MI may be caused by culprit lesions (i.e., vulnerable plaques with high likelihood of thrombotic complications) often located in coronary vessels *without* critical stenosis.[29] For this type of MI (atherothrombotic), perioperative strategies aimed at reducing potential triggers of coronary plaque destabilization and rupture may be more appropriate than those leading to coronary revascularization. Demand ischemia is likely the predominant cause of perioperative MI, which has been confirmed by a recent angiographic study.[30]

ASSESSMENT OF PULMONARY FUNCTION

Postoperative pulmonary complications are potentially serious in patients undergoing vascular surgery, with the most significant morbidity seen in patients undergoing open aortic procedures (see also Chapters 67 and 103). The most important pulmonary complications are atelectasis, pneumonia, respiratory failure, and exacerbation of underlying chronic disease. Given the prevalence of cigarette smoking in this population, chronic obstructive pulmonary disease (COPD) and chronic bronchitis are common and, when present, place the patient at increased risk for postoperative pulmonary complications. When clinical assessment suggests severe pulmonary compromise, pulmonary function tests may be useful in evaluating and optimizing respiratory function (see also Chapters 39 and 51). Preoperative analysis of arterial blood gases should be used to establish a baseline for postoperative comparison. Baseline hypercapnia (partial pressure of arterial carbon dioxide > 45 mm Hg) indicates a more frequent risk for postoperative morbidity. Bronchodilator therapy may be indicated on the basis of results of pulmonary function tests, although the risk for β-adrenergic agonist–induced arrhythmia or myocardial ischemia also must be considered. Preoperative treatment with a short course of glucocorticoids (prednisone 40 mg/day for 2 days) may be helpful for patients with significant COPD or asthma. Evidence of pulmonary infection should be treated with appropriate antibiotics. Although improved pulmonary outcome with regional anesthesia is not clear, patients with significant pulmonary disease may benefit from epidural techniques. Use of these techniques in the postoperative period helps avoid respiratory depression from systemic opiates (see also Chapter 98). Pulmonary complications in the postoperative period are difficult to avoid. Incentive spirometry and continuous positive airway pressure do provide benefit.[31] Given proper pulmonary care, even patients with severe pulmonary insufficiency, however, may undergo aortic surgery with acceptable morbidity and mortality outcomes.[32]

Assessment of Renal Function

Chronic renal disease is common in vascular surgery patients and is associated with an increased risk for death and cardiovascular disease (see also Chapters 37 and 52).[33] Chronic renal disease strongly predicts long-term

TABLE 69-4 PERIOPERATIVE AND LONG-TERM PATIENT OUTCOMES FROM THE DUTCH ECHOCARDIOGRAPHIC CARDIAC RISK EVALUATION APPLYING STRESS ECHOCARDIOGRAPHY (DECREASE)-V -V TRIAL

	Revascularization No. (%)	No Revascularization No. (%)	HR (95% CI)	*P* Value
No. Patients	**49**	**52**		
Events before surgery				
All-cause mortality	2 (4.1)	0		0.23
Myocardial infarction	1 (2.1)	0		
Composite	3 (6.1)	0		0.11
Events up to 30 days after surgery				
All-cause mortality	11 (22.5)	6 (11.5)	2.2 (0.74-6.6)	0.14
Myocardial infarction	17 (34.7)	16 (30.8)		
Composite	21 (42.9)	17 (32.7)	1.4 (0.73-2.8)	0.30
Events up to 365 days after surgery				
All-cause mortality	13 (26.5)	12 (23.1)	1.3 (0.55-2.9)	0.58
Myocardial infarction	18 (36.7)	19 (36.5)		
Composite	24 (49.0)	23 (44.2)	1.2 (0.68-2.3)	0.48

CI, *Confidence interval*; HR, *hazard ratio*.

From Poldermans D, Schouten O, Vidakovic R, et al: A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery. The DECREASE-V Pilot Study, *J Am Coll Cardiol* 49:1763-1769, 2007.

TABLE 69-5 **INCIDENCE OF MYOCARDIAL ISCHEMIA* DURING THE PREOPERATIVE, INTRAOPERATIVE, AND POSTOPERATIVE PERIODS IN VASCULAR SURGERY PATIENTS**

Study	Preoperative	Intraoperative	Postoperative	Overall
Pasternack et al[189]				
Aortic/lower extremity	40	38	48	61
Carotid	38	41	54	68
Ouyang et al[184]	13	21	63	
McCann and Clements[193]	14	38		
Mangano et al[186]	20	25	41	
Raby et al[194]		18	30	
Christopherson et al[39]	8	11	40	40
Boylan et al[83]				35
Norris et al[40]	3†	4†	15†	16
Average	19	25	42	44

*Percentage of patients with myocardial ischemia as detected by continuous Holter monitor and ST-segment analysis.
†Unpublished data.

mortality in patients with symptomatic lower extremity arterial occlusive disease irrespective of disease severity, cardiovascular risk, and concomitant treatment.[34] Cardiovascular disease is independently associated with a decline in renal function and the development of kidney disease.[35] Serum creatinine and creatinine clearance are used to assess renal function perioperatively. A preoperative serum creatinine level more than 2 mg/dL is an independent risk factor for cardiac complications after major noncardiac surgery.[36] Preoperative creatinine clearance less than 60 mL/minute is an independent predictor of both short-term and long-term mortality after elective vascular surgery.[37] Perioperative β-adrenergic blocker[38] and statin[37] administration decrease risk for death in vascular surgery patients with renal impairment. Atherosclerotic disease in the abdominal aorta or renal arteries may compromise renal blood flow and renal function. Conversely, renal artery stenosis causes hypertension through renin-induced and angiotensin-induced vasoconstriction. Hypertension itself may cause renal insufficiency or failure. Diabetic nephropathy is also common (see also Chapter 39). Superimposed on baseline abnormalities in renal function are the preoperatively and intraoperatively administered angiographic dyes, which are directly nephrotoxic. Renal ischemia occurs with interruption of renal blood flow from aortic cross-clamping. Even with infrarenal aortic cross-clamps, renal blood flow may decrease despite normal systemic arterial blood pressure and cardiac output. Embolic plaque can be showered into the renal arteries, especially when suprarenal aortic cross-clamps are applied and released. Fluctuations in intravascular volume and cardiac output can compromise renal perfusion during the intraoperative and postoperative periods. In one series of more than 500 patients, the prevalence of acute renal failure was 7% after abdominal aortic reconstruction.

PERIOPERATIVE MYOCARDIAL ISCHEMIA

ETIOLOGY AND PREVENTION

Ischemic cardiac morbidity is the most common cause of perioperative death in the United States[5] (see also Chapter 39). Myocardial ischemia in the perioperative period is a strong predictor of adverse cardiac events after vascular surgery. Myocardial ischemia results from an imbalance between myocardial oxygen supply and demand, for which many causes exist during the perioperative period. Virtually every determinant of myocardial O_2 supply and demand can be altered by factors common with vascular surgery, including intravascular fluid shifts, blood loss, pain, increased release of catecholamines, hypothermia, altered coagulability, and ventilatory insufficiency. Tachycardia, intravascular hypervolemia, and anemia are particularly detrimental because they simultaneously decrease O_2 supply and increase O_2 demand. The prevention and treatment of perioperative myocardial ischemia require careful control of these and other determinants of myocardial O_2 supply and demand, as well as other physiologic changes that can precipitate ischemia.

Table 69-5 summarizes eight studies showing the relative incidence of preoperative, intraoperative, and postoperative myocardial ischemia. The two studies with the most infrequent rates of intraoperative myocardial ischemia followed a protocol that included rigorously controlled intraoperative heart rate and arterial blood pressure.[39,40] Norris and associates[40] continued this "tight" hemodynamic control into the postoperative period and reported a lower rate (15%) of postoperative myocardial ischemia. Excellent control of perioperative hemodynamics, especially heart rate (<85 beats/minute), likely decreases the incidence of myocardial ischemia. An even slower heart rate control (<70 beats/minute) may reduce myocardial ischemia after vascular surgery[41]; some added risk exists with this approach.[42] The heart rate should clearly be controlled, but also the underlying cause should be determined. The common recommendation is to maintain arterial blood pressure within 20% of baseline. However, a more rational approach that appropriately addresses patients with hypertension or hypotension is described in Figure 69-4. Perioperative statin therapy also reduces the incidence of myocardial ischemia after vascular surgery.[43]

The optimal hematocrit value for vascular surgery patients is not clear. An increased incidence of myocardial ischemia and cardiac morbidity occurs in vascular surgery patients if hemoglobin concentrations are less than 9.0 g/dL in the early postoperative period. Therefore, hemoglobin concentrations should be maintained at

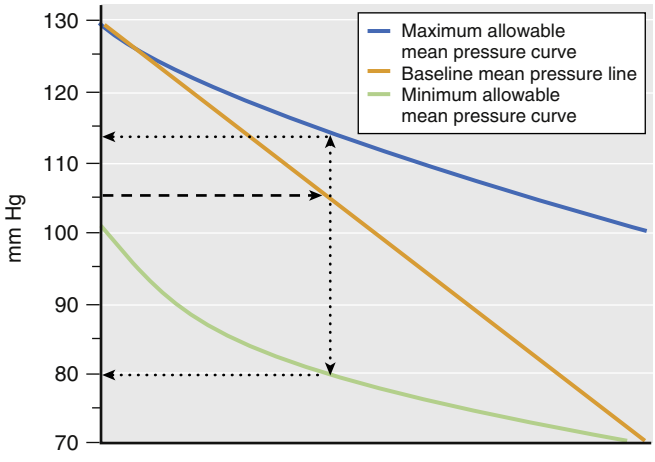


Figure 69-4. Nomogram used to determine minimum and maximum mean blood pressure limits. The nomogram is used by reading the baseline mean arterial pressure (MAP) from the left-hand axis horizontally onto the diagonal baseline mean pressure line. The point of intersection on this line is then extended vertically to intersect with the minimum and maximum allowable mean pressure curves. A patient with a baseline MAP of 105 mm Hg, shown in the figure, would have an allowable MAP range of 80 to 114 mm Hg. (From Norris EJ, Beattie C, Perler BA, et al: Double-masked randomized trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia in abdominal aortic surgery, *Anesthesiology* 95:1054-1067, 2001.)

greater than 9.0 g/dL in vascular patients, especially those at significant risk for ischemic cardiac morbidity. Accordingly, a "liberal" transfusion trigger should be considered (see also Chapter 61).

MONITORING FOR MYOCARDIAL ISCHEMIA

Three methods are used to detect myocardial ischemia during the perioperative period: surface electrocardiogram (ECG), transesophageal echocardiography (TEE), and pulmonary artery catheterization (see also Chapters 45 to 47). The sensitivity and specificity for detection of ischemia, the level of training required, and the cost of these methods differ and are important considerations. Monitoring for ischemia is important during and after vascular surgery. Ischemia may lead to infarction, especially when the ischemia is sustained over time (>2 hours).[44] Accordingly, the clinical determinants of myocardial O_2 supply and demand should be optimal in an attempt to resolve the ischemic condition.

Serial measurement of cardiac-specific biomarkers in the postoperative period is used to monitor for myocardial injury after vascular surgery. Measurement of cardiac troponin T or I facilitates the detection of myocardial damage over less specific biomarkers and allows the detection of very small injury. Data from the CARP and Ventavis Inhalation With Sildenafil to Improve and Optimize Pulmonary Arterial Hypertension (VISION) trials support the use of perioperative cardiac troponin as a means of stratifying high-risk patients after vascular surgery.[45,46] Although not supported by current guidelines, routine surveillance of cardiac troponin after vascular surgery probably should be used for the detection of cardiac events and postoperative risk stratification.[47]

PERIOPERATIVE β-ADRENERGIC BLOCKER THERAPY

Perioperative β-adrenergic blocker therapy is an important and controversial topic, particularly in patients undergoing vascular surgery, and is reviewed more fully in Chapters 38 and 39. Patients receiving chronic β-adrenergic blocker therapy should continue taking β-adrenergic blockers throughout the perioperative period. However, β-adrenergic blockers should not be used as the initial or primary treatment of tachycardia caused by perioperative events, such as hypovolemia, anemia, pain, or infection, because these conditions require prompt treatment of the underlying cause. Treatment of tachycardia caused by the sympathetic stimulation associated with surgical stress should be considered in high-risk patients, particularly those with known ischemic potential (i.e., ischemia on preoperative testing). Hypotension and bradycardia should be avoided. Acute initiation of large-dose β-adrenergic blockade in the perioperative period should be avoided. If a decision is made to initiate β-blocker treatment in the perioperative period in an effort to reduce cardiac risk, the safest approach may be to initiate therapy with a small dose and titrate to effect over a 7- to 10-day period before the planned surgery. Perioperative β-adrenergic blocker therapy can decrease the number of patients referred for preoperative cardiac testing. However, such testing should not be eliminated, and its risk-to-benefit ratio should be carefully assessed.

PERIOPERATIVE STATIN THERAPY

In addition to their lipid-lowering properties, statins have beneficial antiinflammatory, plaque-stabilizing, and antioxidant effects (see also Chapter 39). Over the last decade, statin use has emerged as a promising strategy for the prevention of perioperative cardiovascular complications in patients undergoing vascular surgery.[48] This approach is supported by the double-blind, placebo-controlled DECREASE-III trial. Unfortunately, controversy exists regarding this trial because of scientific misconduct identified by a recent investigation by Erasmus University.[19] Statin use can help preserve renal function after aortic surgery and improve graft patency after lower extremity bypass surgery.

Although current guidelines recommend the use of statins in all patients with peripheral arterial disease, the optimal timing and dosing of statins for perioperative use has not been established. Because no intravenous (IV) preparations are available, statins should be given that have a prolonged half-life or a slow-release formula.[49] Interruption of statin therapy after aortic surgery can increase cardiac risk.[49,50] Data from the DECREASE III trial suggest that this risk may be avoided if the interruption is brief (2 days) and an extended-release statin is used.[42] Current ACC/AHA guidelines should guide overall use. Because side effects can occur and are difficult to assess clinically in the perioperative period, serial measurements of creatine kinase and liver function are advisable until safety has been established.

HEMODYNAMIC MONITORING

The appropriate level of invasive hemodynamic monitoring (see also Chapter 45) in patients undergoing vascular surgery is a controversial issue. Multiple considerations determine the need for monitoring and are often not the same for all vascular patients. Given the frequency of coexisting disease, the potential for fluid shifts and blood loss, and the physiologic changes associated with cross-clamping and unclamping, virtually all patients undergoing major vascular surgery should be monitored with an intraarterial catheter. This allows beat-to-beat blood pressure monitoring, accurate determination of diastolic pressure, and sampling of arterial blood for diagnostic purposes. The radial artery is most commonly selected for cannulation because of its superficial location and the presence of collateral circulation. The need to verify collateral blood flow is questionable. The Allen test can be used to assess collateral flow in the palmar arch, but evidence suggests that ischemic injury can occur in patients with a normal Allen test result and that no injury occurs in patients with an abnormal Allen test result when the radial artery is cannulated. When the radial artery is difficult to cannulate, the ulnar or axillary arteries are alternative sites. The axillary artery can be cannulated by the Seldinger technique, but extreme care should be taken to avoid injecting air when flushing an axillary catheter because the tip may lie close to or inside the aortic arch and thus allow air to enter the cerebral circulation. Whenever possible, the femoral arteries should be avoided in patients with peripheral vascular disease.

Vascular surgery patients often have a large discrepancy in arterial blood pressure between the right and left arms as a result of atherosclerotic lesions in the subclavian or axillary arteries; such discrepancy results in a falsely low arterial blood pressure in the ipsilateral arm.[51] Patients scheduled for carotid surgery have a frequent incidence of right and left arm arterial blood pressure differences. To avoid pseudohypotension, arterial blood pressure should be verified in both arms, and the arm with the higher pressure should be used for monitoring during surgery. Both arms may have falsely low arterial blood pressure as a result of bilateral disease. In this case, the femoral artery may be the best option for monitoring.

The utility of central venous and pulmonary artery catheters for hemodynamic monitoring of patients during vascular surgery is controversial. The surgical procedure often determines the degree of fluid shifting and blood loss and thus the usefulness of invasive monitoring. The patient's underlying cardiac, pulmonary, and renal status also need to be considered. Although cardiovascular function is highly dependent on adequate ventricular filling (i.e., the heart cannot pump out more blood than it receives), values of central venous pressure and pulmonary artery occlusion pressure do not correlate with values of measured circulating blood volume.[52] Additional information, such as stroke volume and cardiac output, are often important when extreme stress is placed on an already impaired heart. The indications for central venous pressure and pulmonary artery catheter monitoring are discussed in further detail in the subsequent sections.

The role of TEE (see also Chapter 46) in the perioperative period has expanded rapidly over the last decade. TEE is useful in identifying anatomic and functional cardiac abnormalities and is a sensitive monitor for detection of myocardial ischemia. During complex aortic reconstruction, TEE provides important real-time information on cardiac filling and function and is particularly useful when unexplained hemodynamic instability is encountered.

ABDOMINAL AORTIC RECONSTRUCTION

Anesthesia for conventional abdominal aortic reconstruction requires an understanding of the pathophysiology, extensive knowledge of the surgical procedure, the ability to interpret sophisticated hemodynamic data, and skillful pharmacologic control and manipulation of hemodynamics. Preoperative and intraoperative communication with the surgical team is essential. All open operative procedures on the abdominal aorta and its major branches require large incisions and extensive dissection, clamping and unclamping of the aorta or its major branches, varying duration of organ ischemia-reperfusion, significant fluid shifts and temperature fluctuations, and activation of neurohumoral and inflammatory responses. The major objectives of surgical treatment of the aorta are to relieve symptoms, reduce the frequency of associated complications, and in the case of aortic aneurysm, prevent rupture. Over the last two decades, the growth and development of catheter-based technology for the treatment of peripheral arterial disease have generated tremendous interest for less invasive methods to treat aortic disease. Endovascular aortic aneurysm repair (discussed later) has become an established less invasive alternative to conventional open repair, and its use has expanded to more than 75% of elective repairs and 30% of rupture repairs.[53] The endovascular field continues to evolve rapidly with new devices, innovations, and indications for aortic disease.

NATURAL HISTORY AND SURGICAL MORTALITY

Abdominal Aortic Aneurysm

Abdominal aortic aneurysms (AAAs) occur frequently in elderly men, with an incidence approaching 8% (see also Chapter 80). Increasing age, smoking, family history of AAA, and atherosclerotic disease are established risk factors. Although the prevalence is less frequent in women, the risk factors for AAA are similar to those in men. More than 30,000 deaths result from rupture of AAAs each year in the United States.[54] The number of hospital discharges each year with the first diagnosis of aortic aneurysm is nearly 70,000. Approximately 40,000 patients undergo repair of AAA each year in the United States, at a cost likely to exceed a billion dollars. The incidence of AAA appears to be increasing and is age and gender dependent.

AAA is a multifactorial disease associated with aortic aging and atherosclerosis. Although no unified concept of pathogenesis exists, genetic, biochemical, metabolic, infectious, mechanical, and hemodynamic factors may

contribute to the development of AAA disease. Adventitial elastin degradation (elastolysis), a hallmark of AAA formation, may be the primary event. Chronic inflammation plays a fundamental role in the destruction of connective tissue in the aortic wall. Concomitant aortoiliac occlusive disease is present in approximately 20% to 25% of patients with AAA. Approximately 5% of patients undergoing abdominal aortic resection have inflammatory aneurysms. Rare causes of AAA disease include trauma, mycotic infection, syphilis, and Marfan syndrome.

Most AAAs are detected incidentally when imaging is performed for other reasons or through screening programs. The natural history of AAA disease is progressive enlargement and ultimate rupture and death. The diameter and rate of expansion of asymptomatic AAAs are the best predictors of the risk for rupture. Current guidelines emphasize that it is not possible to recommend a single threshold diameter for operative intervention that can be generalized to all patients. Yet, elective repair should be undertaken in all patients with AAA 6 cm or larger in diameter. Although some controversy exists regarding elective AAA repair when its diameter is in the 5.5- to 5.9-cm range, the risk for rupture of a 5.5-cm aneurysm (per year) is equal to or greater than the risk for perioperative mortality, and thus surgical repair is indicated. The 1-year incidence of probable rupture in patients refusing or unfit for elective repair is 9.4%, 10.2%, and 32.5% for aneurysms 5.5 to 5.9 cm, 6.0 to 6.9 cm, and 7.0 cm or greater, respectively.[55]

Over 90% of AAAs are less than the current threshold (5.5 cm) for surgical repair at the time of detection. Randomized controlled trials in patients with AAAs 4.0 to 5.5 cm in diameter have provided important insight into the natural history of small asymptomatic aortic aneurysms.[56] Four trials have demonstrated that surveillance of small aneurysms (4.0 to 5.5 cm) is a safe management option and that early repair (open or endovascular surgery) did not result in any long-term survival benefit. Surgical repair is often considered if small aneurysms become symptomatic or expand more than 0.5 cm in a 6-month period. Although significant interest exists in medical treatment (e.g., antibiotics, β-adrenergic blockers, statins) to delay or reverse expansion of small aneurysms, evidence for a protective effect is limited.[57] Aneurysms less than 4.0 cm in diameter are thought to be relatively benign in terms of rupture and expansion.

Perioperative mortality from elective resection of infrarenal AAAs has progressively declined from 18% to 20% during the 1950s, 6% to 8% in the mid-1960s, 5% to 6% in the early 1970s, and 2% to 4% in the 1980s, at which time it plateaued. A publication of data from 1000 consecutive elective open infrarenal abdominal aneurysm repairs over a 15-year period reported a perioperative mortality rate of 2.4%.[58] Hertzer and co-workers[59] reported a mortality rate of 1.2% for 1135 consecutive elective open infrarenal abdominal aortic repairs at the Cleveland Clinic. This single-center mortality rate is considerably less than the mortality rates of 5.6% to 8.4% reported from large national data sets. These more frequent mortality rates on the national level suggest that all of the technologic and treatment advances over the last 2 decades have not had an impact on outcomes of patients requiring open AAA repair. Regionalization of patient care and endovascular treatments currently hold the most promise for improvement in operative mortality.

For ruptured AAAs, perioperative mortality has not changed significantly over the last 4 decades and remains nearly 50%, with few exceptions. Including patients with rupture who die before reaching a hospital, the overall mortality rate after rupture may very well exceed 90%.

The long-term durability of open infrarenal AAA repair is excellent and well established. The incidence of late graft complications is infrequent (0.4% to 2.3%). Postoperative survival rates after repair of nonruptured AAA are 92% at 1 year and 67% at 5 years.

Aortoiliac Occlusive Disease

The infrarenal aorta and the iliac arteries are two of the most common sites of chronic atherosclerosis. Because of the diffuse and progressive nature of aortoiliac atherosclerosis, plaque enlargement may reduce blood flow to the lower extremities below a critical level and result in symptoms of ischemia. Unlike patients with aortic aneurysmal disease, patients undergo surgery for aortoiliac occlusive disease only if they are symptomatic. Surgical intervention is indicated for disabling intermittent claudication and limb-threatening ischemia. Intervention is directed toward restoring peripheral pulsatile circulation to relieve claudication and toward preventing amputation. Patients with localized aortoiliac occlusive disease typically have claudication because collateral circulation adequate to prevent critical lower extremity ischemia usually exists. Perioperative mortality is lower in patients undergoing aortoiliac reconstruction than in those undergoing abdominal aortic surgery.

Therapeutic options for managing aortoiliac occlusive disease include anatomic or direct reconstruction (i.e., aortobifemoral bypass), extraanatomic or indirect bypass grafts (i.e., axillofemoral bypass), and catheter-based endoluminal techniques (i.e., percutaneous transluminal angioplasty with or without stent insertion). Aortobifemoral bypass is viewed as the gold standard in treating aortoiliac occlusive disease. Extraanatomic bypass grafts are generally reserved for specific indications, usually patients with infection, failure of previous reconstruction, or prohibitive risk. Reduced long-term patency and inferior functional results are frequently the trade-off for lower perioperative morbidity and mortality. Catheter-based endoluminal techniques, such as percutaneous transluminal angioplasty, are used for relatively localized disease and may be reasonable alternatives to aortobifemoral bypass in 10% to 15% of patients with aortoiliac occlusive disease.

Renal and Visceral Arterial Insufficiency

Atherosclerosis is the most common cause of renal artery stenosis. Occlusive lesions are located almost exclusively in the proximal segment and orifice of the renal artery and are usually an extension of aortic atherosclerosis. Fibromuscular dysplasia is an important, but less common, cause of renal artery stenosis and most frequently involves the distal two thirds of the renal arteries. Hemodynamically significant renal artery stenosis may cause hypertension by activation of the renin-angiotensin-aldosterone system, and bilateral involvement may result in renal failure. Patients with renovascular hypertension

frequently have poorly controlled hypertension despite maximal medical therapy. These patients often have severe bilateral renal artery stenosis and may have recurrent congestive heart failure or flash pulmonary edema. Indications for intervention include control of hypertension and salvage of renal function. Operative interventions include aortorenal bypass, extraanatomic bypass (hepatorenal or splenorenal bypass), or transaortic endarterectomy. Suprarenal or supraceliac aortic cross-clamping is frequently required for open operative interventions. Percutaneous transluminal angioplasty with stenting of the renal artery is used as the first-line treatment in selected patients.

Stenosis at the origin of the celiac and mesenteric arteries occurs as a result of extension of aortic atherosclerosis. The inferior mesenteric artery is by far the most commonly involved, followed by the superior mesenteric artery and the celiac artery. Occlusion of a single vessel rarely causes ischemic symptoms because of the extensive nature of visceral collateralization. However, occlusion or significant stenosis of any two vessels may compromise collateral flow sufficiently to give rise to chronic visceral ischemia. Operative repair of visceral artery stenosis is reserved for symptomatic patients. Operative interventions include transaortic endarterectomy and bypass grafts, which frequently require supraceliac aortic cross-clamping. Mortality rates for such procedures range from 7% to 18%. To avoid the high mortality associated with open repair, percutaneous transluminal angioplasty with stenting has increasingly been applied in patients with chronic visceral ischemia. Acute visceral artery occlusion can be caused by an embolus or, less commonly, by thrombosis. To avoid the extremely high mortality associated with acute visceral ischemia, diagnosis and surgical intervention must occur before gangrene of the bowel develops.

AORTIC CROSS-CLAMPING

The pathophysiology of aortic cross-clamping is complex and depends on many factors, including level of the cross-clamp, status of the left ventricle, degree of periaortic collateralization, intravascular blood volume and distribution, activation of the sympathetic nervous system, and anesthetic drugs and techniques. Most abdominal aortic reconstructions require clamping at the infrarenal level. However, clamping at the suprarenal and supraceliac levels is required for suprarenal aneurysms and renal or visceral reconstructions and is frequently necessary for juxtarenal aneurysms, inflammatory aneurysms, and aortoiliac occlusive disease with proximal extension. These higher levels of aortic occlusion have a significant impact on the cardiovascular system, as well as on other vital organs rendered ischemic or hypoperfused. Ischemic complications may result in renal failure, hepatic ischemia and coagulopathy, bowel infarction, and paraplegia. With endovascular aortic repair now common, an increasing proportion of patients undergoing open repair have anatomically complex aneurysms, many of which require suprarenal cross-clamping.[60]

Hemodynamic and Metabolic Changes

The hemodynamic and metabolic changes associated with aortic cross-clamping are summarized in Box 69-1.

BOX 69-1 ***Physiologic Changes With Aortic Cross-Clamping* and Therapeutic Interventions***

HEMODYNAMIC CHANGES

↑ Arterial blood pressure above the clamp
↓ Arterial blood pressure below the clamp
↑ Segmental wall motion abnormalities
↑ Left ventricular wall tension
↓ Ejection fraction
↓ Cardiac output†
↓ Renal blood flow
↑ Pulmonary occlusion pressure
↑ Central venous pressure
↑ Coronary blood flow

METABOLIC CHANGES

↓ Total body oxygen consumption
↓ Total body carbon dioxide production
↑ Mixed venous oxygen saturation
↓ Total body oxygen extraction
↑ Epinephrine and norepinephrine
- Respiratory alkalosis‡
- Metabolic acidosis

THERAPEUTIC INTERVENTIONS

Afterload reduction
  Sodium nitroprusside
  Inhalational anesthetics
  Amrinone
  Shunts and aorta-to-femoral bypass
Preload reduction
  Nitroglycerine
  Controlled phlebotomy
  Atrial-to-femoral bypass
Renal protection
  Fluid administration
  Distal aortic perfusion techniques
  Selective renal artery perfusion
  Mannitol
  Drugs to augment renal perfusion
Other
  Hypothermia
  ↓ Minute ventilation
  Sodium bicarbonate

*These changes are of greater significance with longer duration of cross-clamping and with more proximal cross-clamping.
†Cardiac output may increase with thoracic cross-clamping.
‡When ventilatory settings are unchanged from preclamp levels.

The magnitude and direction of these changes are complex, dynamic, and vary among experimental and clinical studies. However, several important factors must be considered (Box 69-2). The systemic cardiovascular consequences of aortic cross-clamping can be dramatic, depending primarily on the level at which the cross-clamp is applied. Arterial hypertension above the clamp and arterial hypotension below the clamp are the most consistent components of the hemodynamic response to aortic cross-clamping at any level. The increase in arterial blood pressure above the clamp is primarily due to the sudden increase in impedance to aortic blood flow and the resultant increase in systolic ventricular wall tension or afterload. However, factors such as myocardial contractility, preload, blood volume, and activation of the

BOX 69-2 ***Factors That May Influence the Magnitude and Direction of Physiologic Changes Occurring With Aortic Cross-Clamping***

Level of aortic cross-clamp
Species differences
Anesthetic agents and techniques
Use of vasodilator therapy
Use of diverting circulatory support
Degree of periaortic collateralization
Left ventricular function
Status of the coronary circulation
Volume status
Neuroendocrine activation
Duration of aortic cross-clamp
Body temperature

sympathetic nervous system also may be important.[61] Cross-clamping of the aorta at or above the diaphragm results in the most profound increases in arterial blood pressure unless diverting circulatory support or IV vasodilators are used.

Changes in cardiac output and filling pressure with aortic cross-clamping are not consistent and require an integrated approach in understanding the direction and magnitude of such changes (Fig. 69-5). Cross-clamping of the proximal descending thoracic aorta increases mean arterial, central venous, mean pulmonary arterial, and pulmonary capillary wedge pressure by 35%, 56%, 43%, and 90%, respectively, and decreases the cardiac index by 29%.[62] Heart rate and left ventricular stroke work are not significantly changed. Supraceliac aortic cross-clamping increases mean arterial pressure by 54% and pulmonary capillary wedge pressure by 38%.[63] Ejection fraction, as determined by two-dimensional echocardiography, decreases by 38%. Despite normalization of systemic and pulmonary capillary wedge pressure with anesthetic agents and vasodilator therapy, supraceliac aortic cross-clamping causes significant increases in left ventricular end-systolic and end-diastolic area (69% and 28%, respectively), as well as wall motion abnormalities indicative of ischemia in 11 of 12 patients (Table 69-6). Aortic cross-clamping at the suprarenal level causes similar but smaller cardiovascular changes, and clamping at the infrarenal level is associated with only minimal changes and no wall motion abnormalities.

The marked increases in ventricular filling pressure (preload) reported with high aortic cross-clamping have been attributed to increased afterload and redistribution of blood volume, which is of prime importance during thoracic aortic cross-clamping. The splanchnic circulation, an important source of functional blood volume reserve, is central to this hypothesis. The splanchnic organs contain nearly 25% of the total blood volume, nearly two thirds (>800 mL) of which can be autotransfused from the highly compliant venous vasculature into the systemic circulation within seconds.[64] Primarily because of smaller splanchnic venous capacitance, blood volume is redistributed from vascular beds distal to the clamp to the relatively noncompliant vascular beds proximal to the clamp (see Fig. 69-5). Both passive and active mechanisms lower splanchnic venous capacitance with thoracic aortic cross-clamping. Cross-clamping the aorta above the splanchnic system dramatically reduces splanchnic arterial flow, which produces a significant reduction in pressure within the splanchnic capacitance

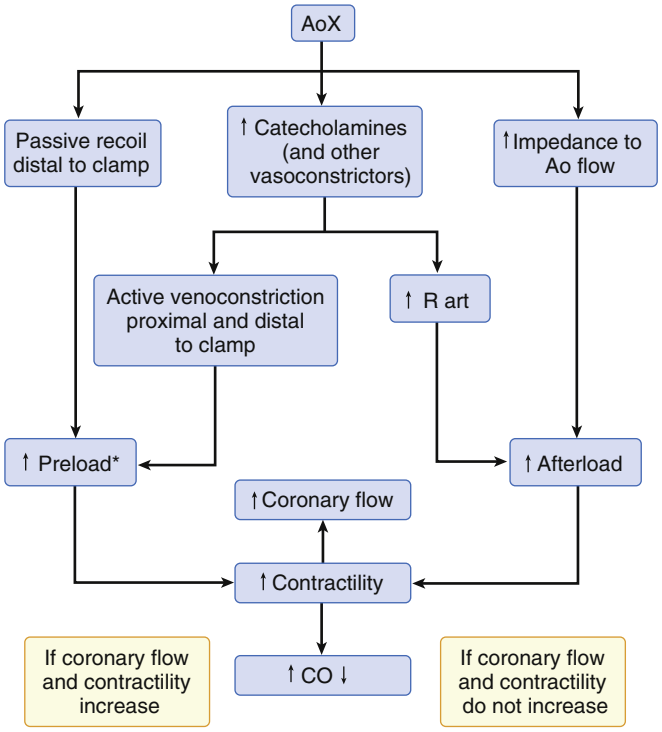


Figure 69-5. Systemic hemodynamic response to aortic cross-clamping. Preload (*asterisk*) does not necessarily increase with infrarenal clamping. Depending on splanchnic vascular tone, blood volume can be shifted into the splanchnic circulation and preload will not increase. *Ao,* Aortic; *AoX,* aortic cross-clamping; *CO,* cardiac output; R art, arterial resistance. (Modified from Gelman S: The pathophysiology of aortic cross-clamping, *Anesthesiology* 82:1026-1060, 1995.)

TABLE 69-6 PERCENT CHANGE IN CARDIOVASCULAR VARIABLES ON INITIATION OF AORTIC OCCLUSION

	Percent Change After Occlusion		
Cardiovascular Variable	***Supraceliac***	***Suprarenal-Infraceliac***	***Infrarenal***
Mean arterial blood pressure	54	5*	2*
Pulmonary capillary wedge pressure	38	10*	0*
End-diastolic area	28	2*	9*
End-systolic area	69	10*	11*
Ejection fraction	−38	−10*	−3*
Patients with wall motion abnormalities	92	33	0

*Statistically different ($P < .05$) from group undergoing supraceliac aortic occlusion.

From Roizen MF, Beaupre PN, Alpert RA, et al: Monitoring with two-dimensional transesophageal echocardiography: comparison of myocardial function in patients undergoing supraceliac, suprarenal-infraceliac, or infrarenal aortic occlusion, *J Vasc Surg* 1:300-305, 1984.

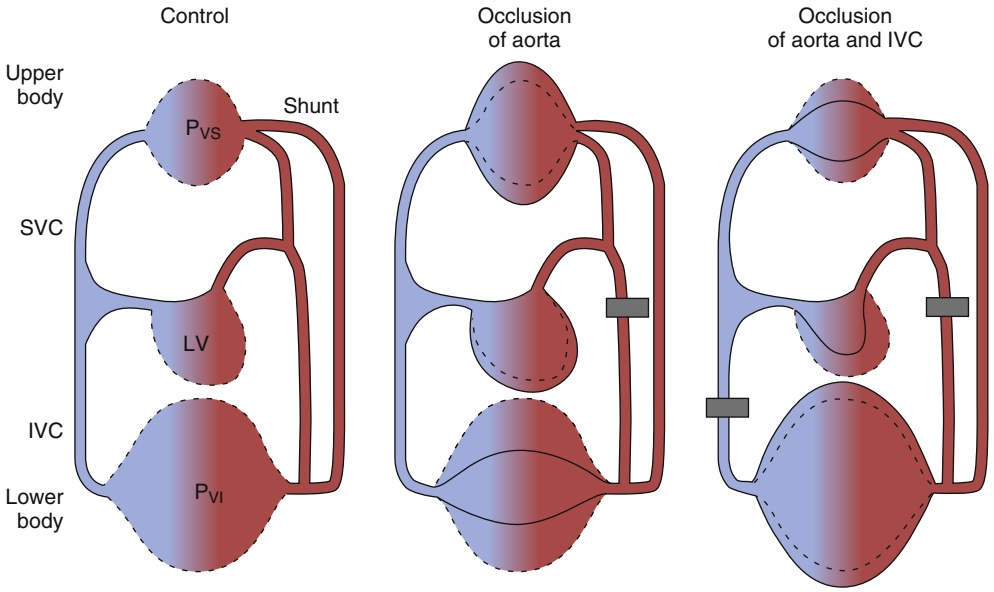


Figure 69-6. Schematic drawing of the circulation. Compliant regions (*dashed lines*) of the upper and lower part of the body and end-diastolic volumes of the left ventricle in control state (*left panel*) are shown after occlusion of the aorta alone (*middle panel*) and combined occlusion of the aorta and inferior vena cava (*right panel*). *IVC,* Inferior vena cava; *LV,* left ventricle; P_{VS} and P_{VI}, pressure in compliant regions of the upper and lower body, respectively; *Shunt,* physiologic shunt; *SVC,* superior vena cava. (From Stokland O, Miller MM, Ilebekk A, et al: Mechanism of hemodynamic responses to occlusion of the descending thoracic aorta, *Am J Physiol* 238:H423-H429, 1980.)

vessels.[52] This decreased pressure allows the splanchnic veins to passively recoil and increase venous return to the heart and blood volume proximal to the clamp. Thoracic aortic cross-clamping also results in significant increases in plasma epinephrine and norepinephrine, which may enhance venomotor tone both above and below the clamp. The splanchnic veins are highly sensitive to adrenergic stimulation. The major effect of catecholamines on the splanchnic capacitance vessels is venoconstriction, which actively forces out splanchnic blood, reduces splanchnic venous capacitance, and increases venous return to the heart.[52]

Several animal studies support the blood volume redistribution hypothesis. Cross-clamping the thoracic aorta in dogs results in marked increases in mean arterial pressure and end-diastolic left ventricular pressure (84% and 188%, respectively) and no significant change in stroke volume.[65] In this same experimental model, simultaneous cross-clamping of the thoracic aorta and the inferior vena cava resulted in no significant change in mean arterial pressure or preload (Fig. 69-6). Stroke volume was reduced by 74%. By transfusing blood (above the clamps) during this period of simultaneous clamping, the authors reproduced the hemodynamic effect of thoracic aortic cross-clamping alone. This study also demonstrated that thoracic aortic cross-clamping is associated with a significant and dramatic increase (155%) in blood flow above the level of the clamp whereas no change in blood flow occurred with simultaneous aortic and inferior vena cava clamping. In other animal models, the proximal aortic hypertension and increased central venous pressure occurring after thoracic aortic cross-clamping were completely reversed by phlebotomy.[66] Aortic cross-clamping at the thoracic and suprarenal levels in dogs both resulted in proximal aortic hypertension, but only occlusion at the thoracic level increased central venous pressure.[67] In this study, thoracic aortic occlusion increased blood volume in organs and tissues proximal to the clamp whereas no such increase occurred with suprarenal aortic cross-clamping. These experimental data strongly support the hypothesis of blood volume redistribution during aortic cross-clamping and help explain the marked differences in hemodynamic responses observed after aortic cross-clamping at different levels.[63]

Afterload-dependent increases in preload also occur with aortic cross-clamping, usually in the setting of impaired myocardial contractility and reduced coronary reserve. The impaired left ventricle may respond to increased afterload with an increase in end-systolic volume and a concomitant reduction in stroke volume (afterload mismatch). The reduction in stroke volume may be due to limited preload reserve, myocardial ischemia, or inability of the heart to generate a pressure-induced increase in contractility (the Anrep effect). If right ventricular function remains normal, the preclamp right ventricular stroke volume added to the increased left ventricular end-systolic volume results in left ventricular dilation and elevated end-diastolic volume. If corrective measures are not undertaken, overt left ventricular overload may result, with severe peripheral organ dysfunction and pulmonary edema.

Most clinical studies indicate that cardiac output decreases with thoracic aortic cross-clamping (without vasodilator therapy or diverting circulatory support), whereas most animal studies show no significant change or an increase in cardiac output. However, the status of the left ventricle clearly plays a major role. Whereas a normal intact heart can withstand large increases in volume without significant ventricular distention or dysfunction, an impaired heart with reduced myocardial

contractility and coronary reserve may respond to such increase in volume conditions with marked ventricular distention as a result of acute left ventricular dysfunction and myocardial ischemia. Although impaired myocardial contractility and reduced coronary reserve are rare in animal experiments, such disorders are frequent in the elderly population undergoing aortic reconstruction. The increase in ventricular loading conditions seen with thoracic and supraceliac cross-clamping[62,63] in the clinical setting may increase left ventricular wall stress (afterload), with resultant acute deterioration of left ventricular function and myocardial ischemia. Impaired subendocardial perfusion caused by high intramyocardial pressure may be the cause of wall motion abnormalities and changes in ejection fraction. Reflex mechanisms causing immediate feedback inhibition may also explain the reduction in cardiac output with aortic cross-clamping. For example, baroreceptor activation resulting from increased aortic pressure should depress the heart rate, contractility, and vascular tone. Thoracic aortic cross-clamping with the use of vasodilator therapy to normalize ventricular loading conditions maintains or increases cardiac output.[68]

The metabolic effects of aortic cross-clamping are summarized in Box 69-1. Cross-clamping of the thoracic aorta decreases total-body O_2 consumption by approximately 50%. For reasons that are unclear, O_2 consumption decreases in tissues above the clamp. In clinical studies, increased mixed venous O_2 saturation occurs with aortic cross-clamping above the celiac axis. This increase in mixed venous O_2 saturation may be explained by a reduction in O_2 consumption that exceeds the reduction in cardiac output, thus decreasing total body O_2 extraction. Central hypervolemia and increased arteriovenous shunting in tissues proximal to the aortic clamp may play a role in reducing total body O_2 extraction.

Arterial blood pressure, blood flow, and O_2 consumption distal to a thoracic aortic cross-clamp decrease by 78% to 88%, 79% to 88%, and 62%, respectively, from baseline values before clamping. Blood flow through tissues and organs below the level of aortic occlusion is dependent on perfusion pressure and is independent of cardiac output. Administration of sodium nitroprusside to maintain proximal aortic pressure above the cross-clamp at preclamp levels has been shown to further reduce arterial pressure distal to the clamp by 53%. As discussed later, these data have significant implications regarding vital organ protection during aortic cross-clamping.

The cardiovascular response to infrarenal aortic cross-clamping is less significant than with high aortic cross-clamping (see Table 69-6). Although several clinical reports have noted no significant hemodynamic response to infrarenal cross-clamping, the hemodynamic response generally consists of increases in arterial pressure (7% to 10%) and systemic vascular resistance (20% to 32%), with no significant change in heart rate. Cardiac output is most consistently decreased by 9% to 33%. Reported changes in ventricular filling pressure have been inconsistent. Blood volume redistribution may affect preload with infrarenal aortic cross-clamping (see Fig. 69-5). In this situation, blood volume below the clamp shifts to the compliant venous segments of the splanchnic circulation above the clamp, thereby dampening the expected increase in preload. The preload changes with infrarenal aortic cross-clamping also may depend on the status of the coronary circulation. Patients with severe ischemic heart disease responded to infrarenal aortic cross-clamping with significantly increased central venous (35%) and pulmonary capillary (50%) pressure, whereas patients without CAD had decreased filling pressure. Echocardiographically detected segmental wall motion abnormalities occur in up to 30% of patients during infrarenal aortic reconstruction, with over 60% occurring at the time of aortic cross-clamping. Patients with aortoiliac occlusive disease may have less hemodynamic response to infrarenal aortic cross-clamping than do patients with AAA disease, perhaps as a result of more extensive periaortic collateral vascularization.

Renal Function and Protection

Preservation of renal function is of significant importance during aortic reconstructive surgery. Acute renal failure occurs in approximately 3% of patients undergoing elective infrarenal aortic reconstruction, and mortality resulting from postoperative acute renal failure is more frequent than 40%. Despite significant improvements in the perioperative care of these patients, the frequent incidence of morbidity and mortality resulting from acute renal failure has remained largely unchanged over the last several decades. Most of the morbidity associated with significant postoperative renal dysfunction is nonrenal.

The adequacy of renal perfusion "cannot" be assumed by urine output. Although urine output is closely monitored and often augmented during aortic surgery, intraoperative urine output does not predict postoperative renal function. Procedures requiring aortic cross-clamping above the renal arteries dramatically reduce renal blood flow. Experimental studies report an 83% to 90% reduction in renal blood flow during thoracic aortic cross-clamping. Infrarenal aortic cross-clamping in humans is associated with a 75% increase in renal vascular resistance, a 38% decrease in renal blood flow, and a redistribution of intrarenal blood flow toward the renal cortex. These rather profound alterations in renal hemodynamics occurred despite no significant change in systemic hemodynamics, and they persisted after unclamping. The sustained deterioration in renal perfusion and function during and after infrarenal aortic cross-clamping has been attributed to renal vasoconstriction, but the specific pathophysiologic process remains unknown. Renal sympathetic blockade with epidural anesthesia to a T6 level does not prevent or modify the severe impairment in renal perfusion and function that occurs during and after infrarenal aortic cross-clamping. Although plasma renin activity is increased during aortic cross-clamping, pretreatment with converting enzyme inhibitors before infrarenal aortic cross-clamping does not attenuate the decreased renal blood flow and glomerular filtration rate. Other mediators, such as plasma endothelin, myoglobin, and prostaglandins, may contribute to the decreased renal perfusion and function after aortic cross-clamping.

Acute tubular necrosis accounts for nearly all the renal dysfunction and failure after aortic reconstruction. The degree of preoperative renal insufficiency remains the strongest predictor of postoperative renal dysfunction. In

addition to aortic cross-clamping–induced reductions in renal blood flow, ischemic reperfusion injury, intravascular volume depletion, embolization of atherosclerotic debris to the kidneys, and surgical trauma to the renal arteries all contribute to renal dysfunction.

Mannitol, loop diuretics, and dopamine are used clinically in an attempt to preserve renal function during aortic surgery. Significant controversy exists regarding the use of these drugs, as well as the mechanisms by which they may offer a protective effect. Although not proved, pharmacologic "protection" before aortic cross-clamping is believed to be beneficial, and is therefore given. The use of mannitol 12.5 g/70 kg to induce osmotic diuresis before aortic cross-clamping is ubiquitous in clinical practice. Mannitol improves renal cortical blood flow during infrarenal aortic cross-clamping and reduces ischemia-induced renal vascular endothelial cell edema and vascular congestion. Other mechanisms by which mannitol may be beneficial include acting as a scavenger of free radicals, decreasing renin secretion, and increasing renal prostaglandin synthesis.

Loop diuretics and low-dose dopamine (1 to 3 μg/kg/minute) are used to protect the kidneys from aortic cross-clamp–induced injury by increasing renal blood flow and urine output intraoperatively. Routine use of these drugs is common for patients with preoperative renal insufficiency and for procedures requiring suprarenal aortic cross-clamping. Intraoperative use of these drugs requires increased surveillance of intravascular volume and electrolytes during the postoperative period. Therapy with these drugs could actually be harmful because of hypovolemia and resultant renal hypoperfusion. In addition, dopamine's positive inotropic and chronotropic activity may cause tachycardia and increase myocardial O_2 consumption in patients with limited coronary reserve. Although I have virtually abandoned the prophylactic use of dopamine, diuretics are often given to patients with low urine output after aortic unclamping, particularly those maintained on chronic diuretic therapy.

Fenoldopam mesylate, a selective dopamine type 1 agonist that preferentially dilates the renal and splanchnic vascular beds, has shown some promise as a renoprotective drug. However, its role in the prevention of renal dysfunction after aortic surgery is not known. Statin use is associated with preserved renal function after aortic surgery requiring suprarenal aortic cross-clamping.[69] Remote ischemic preconditioning reduces the incidence of renal impairment after open aortic surgery.[70]

Optimal systemic hemodynamics, including maintenance of intravascular volume, is generally considered the most effective means of renal protection during and after aortic cross-clamping. The goal is to achieve a preload adequate to allow the left ventricle to cope with cross-clamping–induced changes in contractility and afterload while maintaining cardiac output. However, in providing such therapy, excessive intravascular volume should be avoided, because it may lead to inappropriate increases in preload or pulmonary edema in patients with decreased myocardial reserve.

Therapeutic Strategies

Patients with preexisting impaired ventricular function and reduced coronary reserve are most vulnerable to the stress imposed on the cardiovascular system by aortic cross-clamping. Rational therapeutic strategies to prevent the deleterious effect of aortic cross-clamping primarily include measures to reduce afterload and maintain a normal preload and cardiac output. Vasodilators, positive and negative inotropic drugs, and controlled intravascular volume depletion (i.e., phlebotomy) may be used selectively.

Patients with impaired ventricular function requiring supraceliac aortic cross-clamping are the most challenging. Myocardial ischemia, reflecting an unfavorable balance between myocardial O_2 supply and demand, may result from the hemodynamic consequences of aortic cross-clamping. Controlled (i.e., slow clamp application) supraceliac aortic cross-clamping is important to avoid abrupt and extreme stress on the heart. Both afterload and preload reduction are often required. Afterload reduction, most commonly accomplished with the use of sodium nitroprusside (predominantly an arteriolar dilator), is necessary to unload the heart and reduce ventricular wall tension. In a large series of patients requiring cross-clamping of the descending thoracic aorta, stable left ventricular function was maintained with sodium nitroprusside during cross-clamping. Sodium nitroprusside most likely allowed adequate intravascular volume before unclamping, which resulted in stable unclamping hemodynamics. Although isoflurane can provide hemodynamics comparable to those provided by sodium nitroprusside during thoracic aortic cross-clamping, I do not advocate its use to control proximal hypertension in patients with significantly impaired ventricular function. Though not widely used, amrinone provides hemodynamic control equivalent to that of sodium nitroprusside during abdominal aortic surgery. A normal preload is equally important and involves careful IV fluid titration and vasodilator administration. Nitroglycerin is commonly used because it increases venous capacity more than does sodium nitroprusside.

In patients without evidence of left ventricular decompensation or myocardial ischemia during supraceliac aortic cross-clamping, a proximal aortic mean arterial pressure of up to 120 mm Hg is acceptable. The surgeon may request lower proximal arterial pressure if friable aortic tissue is encountered. Blood flow below the aortic clamp depends on pressure and decreases further during therapy with vasodilators. In this setting, vital organs and tissues distal to the clamp are exposed to reduced perfusion pressure and blood flow. Though infrequent, maintenance of adequate cardiac output may require active intervention with inotropic drugs.

AORTIC UNCLAMPING

The hemodynamic and metabolic effects of aortic unclamping are listed in Box 69-3. The hemodynamic response to unclamping depends on many factors, including the level of aortic occlusion, total occlusion time, use of diverting support, and intravascular volume. Hypotension, the most consistent hemodynamic response to aortic unclamping, can be profound, particularly after removal of a supraceliac cross-clamp (Fig. 69-7). Reactive hyperemia in tissues and organs distal to the clamp and the resultant relative central hypovolemia are the

BOX 69-3 *Physiologic Changes With Aortic Unclamping* and Therapeutic Intervention*

Hemodynamic Changes

↓ Myocardial contractility
↓ Arterial blood pressure
↑ Pulmonary artery pressure
↓ Central venous pressure
↓ Venous return
↓ Cardiac output

Metabolic Changes

↑ Total body oxygen consumption
↑ Lactate
↓ Mixed venous oxygen saturation
↑ Prostaglandins
↑ Activated complement
↑ Myocardial-depressant factor(s)
↓ Temperature
Metabolic acidosis

Therapeutic Interventions

↓ Inhaled anesthetics
↓ Vasodilators
↑ Fluid administration
↑ Vasoconstrictor drugs
- Reapply cross-clamp for severe hypotension
- Consider mannitol
- Consider sodium bicarbonate

*These changes are of greater significance with longer duration of cross-clamping and with more proximal cross-clamping.

dominant mechanisms of the hypotension. Washout of vasoactive and cardiodepressant mediators from ischemic tissues, as well as humoral factors, may also contribute to the hemodynamic responses after unclamping the aorta. These humoral factors and mediators, which may also play a role in organ dysfunction after aortic occlusion, include lactic acid, renin-angiotensin, O_2 free radicals, prostaglandins, neutrophils, activated complement, cytokines, and myocardial-depressant factors.[61]

Avoidance of significant hypotension with unclamping requires close communication with the surgical team, awareness of the technical aspect of the surgical procedure, and appropriate administration of fluids and vasoactive drugs. It is essential that correction of preoperative fluid deficits, maintenance of intraoperative fluid requirements, and replacement of blood loss be accomplished before unclamping. Vasodilators, if used, should be gradually reduced and discontinued before unclamping. The inspired concentrations of volatile anesthetics should be decreased. Moderate augmenting of intravascular volume by administration of fluids (~500 mL) during the immediate prerelease period is indicated for infrarenal unclamping. More aggressive intravascular fluid administration is required in the period immediately preceding supraceliac unclamping. Maintaining increased central venous or pulmonary capillary wedge pressure during the cross-clamp period is not indicated and may result in significant overtransfusion of fluids and blood products. If significant hypotension results, gradual release of the aortic clamp and reapplication or digital compression are important measures in maintaining hemodynamic stability during unclamping. Although vasopressor requirements are minimal after release of the infrarenal clamp, significant support is often needed after the removal of supraceliac clamps. Caution must be observed when vasopressor support is used in this setting because profound proximal hypertension may occur if reapplication of the cross-clamp is required above the celiac axis. In addition, hypertension should be avoided to prevent damage to or bleeding from the vascular anastomoses.

ANESTHETIC MANAGEMENT

Intraoperative Monitoring

The potential for significant and rapid blood loss cannot be underestimated. The author most commonly uses one 8.5-Fr internal jugular catheter and one or two large-bore peripheral catheters. A hemostatic valve with a side port is placed on the 8.5-Fr catheter to accept either a central venous or a pulmonary artery catheter. Placement of an arterial catheter should be routine in all patients undergoing aortic reconstruction. As with other vascular procedures, the radial artery is most commonly selected for cannulation because of its superficial location, easy accessibility, and low complication rate. A noninvasive blood pressure cuff should be placed on the arm contralateral to the arterial catheter in the event of catheter malfunction.

A central venous catheter should be used for all open aortic procedures. It allows monitoring of CVP and administration of drugs directly into the central circulation. The routine, nonselective use of pulmonary artery catheter monitoring is not recommended for patients undergoing infrarenal abdominal aortic reconstruction. For these procedures, pulmonary artery catheters should be considered for patients with significant left ventricular dysfunction (ejection fraction < 30%), a history of congestive heart failure, significant renal impairment (preoperative creatinine > 2.0 mg/dL), or cor pulmonale. In patients with good left ventricular and pulmonary function, CVP correlates well with left ventricular filling pressure. I routinely insert a pulmonary artery catheter for all patients requiring supraceliac aortic cross-clamping. The invasive monitoring catheters can be placed before or after induction of general anesthesia. The advantage of preinduction catheter placement is assessment of the patient's awake (i.e., baseline) cardiovascular status, which allows correction of significant abnormalities in cardiac filling and function before induction.

With selective use, accurate interpretation of data, and rational treatment strategies, pulmonary artery catheter monitoring may be beneficial in high-risk patients undergoing complex aortic reconstruction. Yet, the clinical value of pulmonary artery catheter monitoring in high-risk patients has not been established.[71] Clinical studies over the last 2 decades have yielded quite conflicting and variable results, including both increases and decreases in mortality. The National Heart, Lung and Blood Institute and the Food and Drug Administration (FDA)[72] sponsored a large prospective, randomized trial that compared goal-directed therapy guided by a pulmonary artery catheter with standard care without the use of a pulmonary artery catheter in high-risk surgical patients. The result found no benefit in treatment guided by a pulmonary

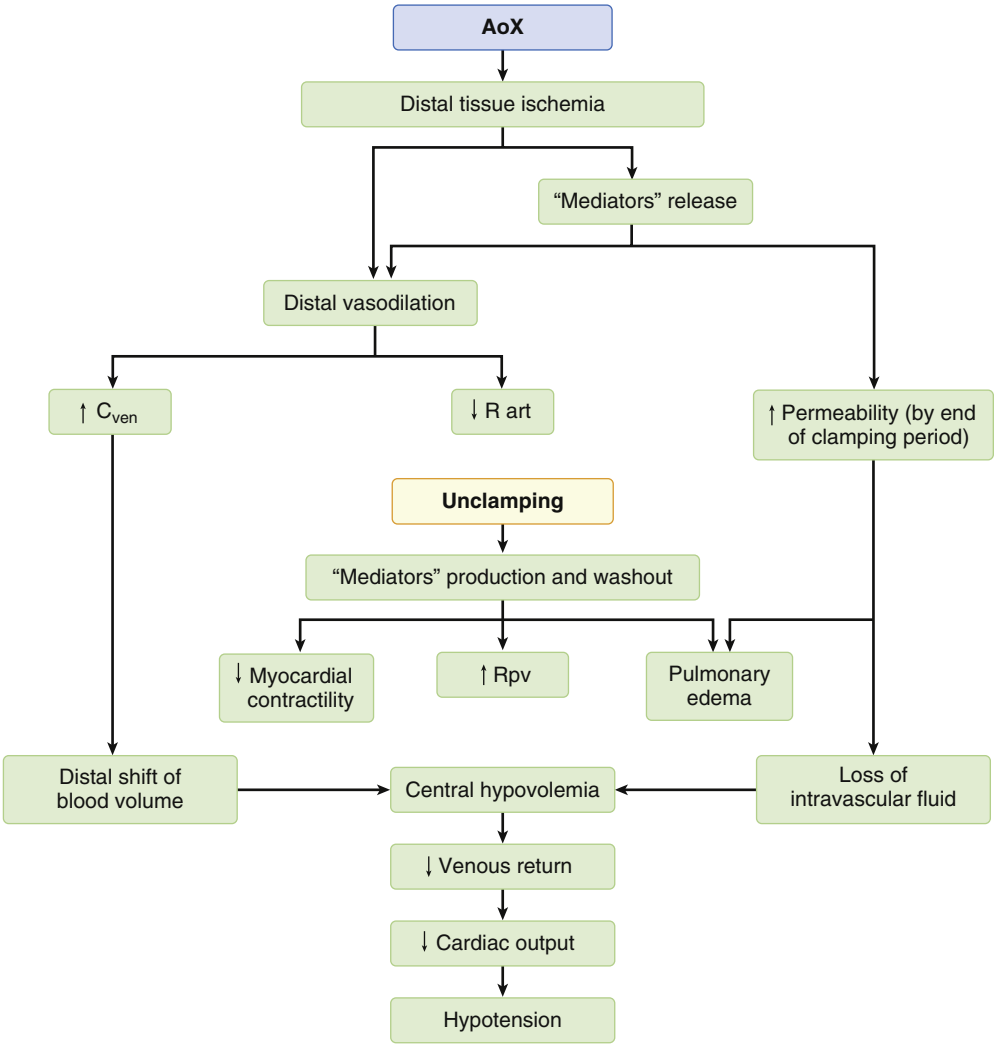


Figure 69-7. Systemic hemodynamic response to aortic unclamping. *AoX,* Aortic cross-clamping; C_{ven}, venous capacitance; *R art,* arterial resistance; *Rpv,* pulmonary vascular resistance. (From Gelman S: The pathophysiology of aortic cross-clamping and unclamping, *Anesthesiology* 82:1026-1060, 1995.)

artery catheter.[73] Yet this study did not find an increase in mortality with insertion and use of a pulmonary artery catheter.

Two-dimensional TEE has been used intraoperatively to assess global ventricular function, guide intravascular fluid therapy, and monitor for myocardial ischemia. Continuous monitoring of ventricular function is commonly obtained with a single short-axis view at the level of the midpapillary muscle. Using this same view, visualization of the left ventricle at end-diastole allows rapid assessment of ventricular filling (preload). Ejection fraction area can be calculated by use of the left ventricular end-diastolic and end-systolic area. In patients undergoing abdominal aortic reconstruction, echocardiographic short-axis left ventricular end-diastolic area, end-systolic area, and ejection fraction area correlate closely with changes in corresponding left ventricular volume and ejection fraction obtained by radionuclide angiography. Patients requiring supraceliac aortic cross-clamping have significant increases in end-diastolic area and significant decreases in ejection fraction on echocardiography that are not completely normalized with vasodilators and frequently are not detected by pulmonary artery catheter monitoring.[63]

TEE can also reveal abnormalities in left ventricular wall motion and wall thickening. The relationship between these abnormalities and coronary perfusion has been established experimentally and clinically, and such abnormalities may precede ECG evidence of ischemia. The short-axis view at the level of the midpapillary muscles allows assessment of all three major coronary distributions. TEE-detected segmental wall motion abnormalities may occur in up to 37% of patients during infrarenal aortic reconstruction and in more than 90% of patients requiring supraceliac aortic cross-clamping. The natural history of echocardiographic segmental wall motion abnormalities was studied in 156 patients undergoing noncardiac surgery who were at risk for cardiac morbidity. The 24 patients undergoing aortic surgery had the highest incidence of new segmental wall motion abnormalities (38%). Surprisingly, the incidence of new segmental wall motion abnormalities did not differ in patients with known CAD and those with cardiac risk factors only. Ischemic episodes detected by TEE correlated poorly with postoperative cardiac complications. The authors also reported a discordant relationship between new segmental wall motion abnormalities and ischemic changes on the ECG. In a subsequent report, a subset of

285 patients who were at high risk for cardiac complications and were undergoing noncardiac surgery were studied with continuous intraoperative use of a two-lead ECG, 12-lead ECG, and TEE for the detection of ischemia. A lack of concordance was found among the three different ischemia monitors. When compared with preoperative clinical data and intraoperative monitoring in which a two-lead ECG was used, routine monitoring for myocardial ischemia with TEE or a 12-lead ECG during noncardiac surgery had little incremental clinical value in identifying patients at high risk for perioperative ischemic outcomes. Thus, available data are insufficient to define the sensitivity and specificity of segmental wall motion abnormalities as a marker for myocardial ischemia or as a predictor of perioperative ischemic outcomes.

The optimal intraoperative monitoring techniques for patients undergoing abdominal aortic reconstruction have not been established. Existing clinical studies offer insufficient data to conclusively answer the question of whether pulmonary artery catheter or TEE monitoring improves outcome. The clinical usefulness of any monitoring technique ultimately depends on patient selection, accurate interpretation of data, and appropriate therapeutic intervention.

Autologous Blood Procurement

Elective abdominal aortic reconstruction may result in substantial blood loss and warrants the routine crossmatching of 4 to 6 units of packed red blood cells (RBCs). Suprarenal aneurysms and other more complex aortic reconstructions often demand even greater allogeneic blood availability. Over the last 2 decades, concerns regarding the safety, availability, and acceptability of allogeneic blood have led to greater use of autologous blood procurement (see also Chapters 61 and 63). Preoperative autologous donation, intraoperative cell salvage, and acute normovolemic hemodilution have all been used during aortic surgery to reduce or eliminate exposure to allogeneic blood and the associated risks for transfusion-related complications.

Intraoperative cell salvage is the most widely used technique and in some centers is considered routine. The equipment is expensive and requires significant training and expertise. An early, nonrandomized study reported a 75% reduction in the number of allogeneic RBC units transfused during elective aortic surgery with the use of cell salvage. Later randomized studies have reported conflicting results. The routine use of cell salvage during aortic surgery may not be cost-effective ($250 to $350 per case), and thus it may best be reserved for a select group of patients with an expected large blood loss. The equivalent of at least 2 units of washed blood must be recovered for this technique to be cost-effective. A cost-effective option is to use the cell salvage reservoir for blood collection and activate the full salvage process only if large blood loss occurs.

Acute normovolemic hemodilution is often used in conjunction with intraoperative cell salvage during aortic surgery. Two randomized studies reported that the combined use of hemodilution and cell salvage reduced the allogeneic blood requirement in patients undergoing aortic surgery. As with cell salvage alone, this benefit is probably greater with procedures involving higher blood loss. Another randomized study found that the combined use of the two techniques during aortic surgery was cost neutral in comparison to standard allogeneic transfusion. Hemodilution does not worsen myocardial ischemia and may improve hemodynamic tolerance to aortic cross-clamping in patients with CAD.

Anesthetic Drugs and Techniques

A variety of anesthetic techniques, including general anesthesia, regional (epidural) anesthesia, and combined techniques, have been used successfully for abdominal aortic reconstruction. Combined techniques most commonly use a lumbar or low thoracic epidural catheter in addition to a "light" general anesthetic. Local anesthetics, opioids, or, more commonly, a combination of the two may be administered by bolus or continuous epidural infusion. Maintenance of vital organ perfusion and function by the provision of stable perioperative hemodynamics is more important to overall outcome than is the choice of anesthetic drug or technique.[40] Therefore, the specific anesthetic technique for patients undergoing abdominal aortic reconstruction is important insofar as it allows rapid and precise control of hemodynamic parameters. Given the frequent incidence of cardiac morbidity and mortality in patients undergoing aortic reconstruction, factors that influence ventricular work and myocardial perfusion are of prime importance.

Induction of general anesthesia should ensure that stable hemodynamics are maintained during loss of consciousness, laryngoscopy and endotracheal intubation, and the immediate postinduction period. A variety of IV anesthetics (propofol, etomidate, thiopental) are suitable. The addition of a short-acting, potent opioid such as fentanyl 3 to 5 μg/kg) usually provides stable hemodynamics during and after induction of anesthesia. Volatile anesthetics may be administered in low concentrations before endotracheal intubation during assisted ventilation as an adjunct to blunt the hyperdynamic response to laryngoscopy and endotracheal intubation. Esmolol 10 to 25 mg, sodium nitroprusside 5 to 25 μg, nitroglycerin 50 to 100 μg, and phenylephrine 50 to 100 μg should be available for bolus administration during induction if needed to maintain appropriate hemodynamics.

Maintenance of anesthesia may be accomplished with a combination of a potent opioid (fentanyl or sufentanil) and an inhaled anesthetic (sevoflurane, desflurane, or isoflurane) (i.e., balanced anesthesia). Patients with severe left ventricular dysfunction may benefit from a pure opioid technique, but a balanced anesthetic technique allows the clinician to take advantage of the most desirable characteristics of potent opioids and inhaled volatile anesthetics while minimizing their undesirable side effects. Nitrous oxide can be used to supplement either an opioid or an inhaled anesthetic. I typically use low-dose isoflurane in 50% N_2O and fentanyl 12 to 18 μg/kg. Approximately 50% of the opioid dose is administered during induction of anesthesia and before skin incision. When epidural local anesthetics are used, this author uses the same technique and reduces the fentanyl dose to 6 to 8 μg/kg.

Various regional anesthetic and analgesic techniques have been used effectively during and after aortic reconstruction. For over 2 decades, interest has focused on

the use of regional anesthetic and analgesic techniques to reduce the incidence of perioperative morbidity in patients undergoing aortic reconstruction. The benefits of combined general and epidural anesthesia intraoperatively, with or without epidural analgesia continued into the postoperative period, remain controversial.[40,74-78] Moreover, studies that have reported improved outcome do not determine whether the benefit results from the intraoperative anesthetic technique or the postoperative analgesic regimen (or a combination of the two). In a randomized trial using epidural morphine in patients undergoing aortic surgery, Breslow and associates[79] found attenuation of the adrenergic response and a less frequent incidence of hypertension in the postoperative period. A large randomized trial reported no reduction in nonsurgical complications with the use of intrathecal opioid.[80] The effects of the anesthetic or analgesic technique on the incidence of perioperative myocardial ischemia have received considerable attention. Four randomized trials, with nearly 450 combined patients undergoing aortic reconstruction, failed to demonstrate a reduction in the incidence of perioperative,[40,81] intraoperative,[82] or postoperative[77] myocardial ischemia when epidural techniques were used. Additionally, randomized trials have not demonstrated a reduction in the incidence of cardiovascular, pulmonary, or renal complications after aortic surgery with the use of epidural techniques.[40,74,76,77,83]

The duration and intensity of postoperative care after aortic surgery are critically dependent on the physiologic derangements incurred during the perioperative period (i.e., depression of consciousness, hypothermia, excessive intravascular fluids, incisional pain, ileus, and respiratory depression), as well as on the development of certain less common, but more severe postoperative complications (i.e., MI, pneumonia, sepsis, renal failure, and decreased tissue perfusion). Length of hospital stay may therefore be considered the outcome variable most directly proportional to an integrated final negative effect of all significant perioperative morbidity (excluding in-hospital death) and the variable most likely to be altered by the anesthetic or analgesic technique. Randomized trials have not demonstrated any reduction in length of hospital stay after aortic surgery with the use of regional techniques.* Norris and colleagues[40] reported the results of a randomized clinical trial comparing alternative combinations of intraoperative anesthesia (i.e., general or combined epidural and general) and postoperative analgesia (i.e., IV patient-controlled analgesia or epidural patient-controlled analgesia) with respect to length of stay after abdominal aortic surgery. Two unique features of the trial included a factorial design (Fig. 69-8), which allowed the inclusion of all four combinations of intraoperative anesthesia and postoperative analgesia and the ability to separate the influence of time period and technique, and a double-blind design, which helped eliminate investigator and treating physician bias. The study rigorously protocolized perioperative management, standardized postoperative surgical care, and optimized postoperative pain management. Although the overall length of stay was much shorter (median, 7.0 days) than

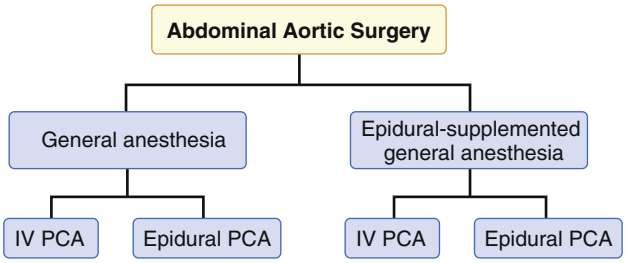


Figure 69-8. Outline of factorial study design. This design allows the inclusion of all four possible combinations on intraoperative anesthesia and postoperative analgesia and the ability to separate the influences of time period and technique. Data analysis by treatment group, intraoperative treatment, postoperative treatment, and any epidural activation, as well as simultaneous consideration of both intraoperative and postoperative treatments in the same model (factorial analysis), is possible and allows improvement in outcome to be attributed to the intraoperative anesthesia, postoperative analgesia, the combination of the two, or to unrelated factors. *IV,* Intravenous; *PCA,* Patient-controlled analgesia. (From Norris EJ, Beattie C, Perler B, et al: Double-masked randomized trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia in abdominal aortic surgery, *Anesthesiology* 95:1054-1067, 2001.)

that reported in other studies,[74,75,77,83] we were not able to demonstrate a reduction in length of stay or direct medical costs based on anesthetic or analgesic technique (Table 69-7). The overall incidence of postoperative complications in the trial was low and not different based on anesthetic or analgesic technique. Postoperative pain was well controlled overall, with similar pain scores in both analgesic treatment groups. Thus, if perioperative care and pain relief are optimized, epidural anesthetic and analgesic techniques for aortic surgery offer no major advantage or disadvantage over general anesthesia and IV patient-controlled analgesia.

The use of epidural local anesthetics in combination with general anesthesia during aortic reconstruction poses several problems, including hypotension at the time of aortic unclamping and the need for increased intravascular fluid and vasopressor requirements. Supraceliac aortic cross-clamping may significantly exaggerate these disadvantages, and, as a result, some clinicians avoid epidural local anesthetics for such procedures. Epidural opioids without local anesthetics can be used for procedures requiring supraceliac aortic cross-clamping. Epidural local anesthetic can be given later, after aortic unclamping, when hemodynamics and intravascular volume have stabilized. For low thoracic or high lumbar epidural catheters, the initial bolus should be limited to 6 to 8 mL of local anesthetic. Additional local anesthetic is administered by continuous infusion at 4 to 6 mL/hr with adjustments based on hemodynamics and inhaled anesthetic requirements during surgery. Although elective aortic reconstruction via the retroperitoneal approach using straight epidural anesthesia (no general anesthetic) has been reported, this technique is not recommended for routine use.

Emergence from anesthesia should be conducted after restoration of circulation and establishment of adequate organ perfusion. Hemodynamic, metabolic, and temperature homeostasis must be achieved before skin

*References 39, 73, 75, 76, 79, 82.

TABLE 69-7 **DURATION OF HOSPITAL STAY AND DIRECT MEDICAL COSTS BY RANDOMIZED TREATMENT ASSIGNMENT FOR PATIENTS SURVIVING TO DISCHARGE AFTER ABDOMINAL AORTIC SURGERY**

	GA-IVPCA	RSGA-IVPCA	GA-EPCA	RSGA-EPCA	Total	*P* Value
No. of Patients	35	36	36	44	151	
Duration of hospital stay (days)*	7.0 (2.2)	8.0 (2.8)	7.0 (2.0)	7.0 (2.8)	7.0 (2.2)	.833†
Range	4-43	5-28	5-20	5-18	4-43	
95% CI	7.0-13.3	7.4-10.2	6.9-8.8	7.6-9.6	7.9-9.7	
Direct medical costs ($U.S. 1997)*						
Inpatient	12,413 (2867)	13,786 (4413)	12,492 (3111)	13,767 (3900)	12,793 (3777)	.242
Physician	10,394 (5993)	10,288 (4538)	9,609 (3866)	9,790 (3567)	9,934 (4072)	.459
Total	22,674 (8783)	23,001 (6079)	22,182 (3914)	22,727 (3961)	22,674 (4903)	.851

CI, Confidence interval; *GA-EPCA,* general anesthesia and epidural patient-controlled analgesia; *GA-IVPCA,* general anesthesia and intravenous patient-controlled analgesia; *RSGA-EPCA,* regional supplemented general anesthesia and epidural patient-controlled analgesia; *RSGA-IVPCA,* regional supplemented general anesthesia and intravenous patient-controlled analgesia.

*Values are median ($SD_{resistant}$).

†No significant difference in length of stay was observed between intraoperative treatment groups (GA versus RSGA; $P = .416$), postoperative treatment groups (IVPCA versus EPCA; $P = .673$), epidural activation (GA-IVPCA versus RSGA-IVPCA, RSGA-EPCA, and GA-EPCA; $P = 854$), or factorial analysis ($P = .648$).

From Norris EJ, Beattie C, Perler B, et al: Double-masked randomized trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia in abdominal aortic surgery, *Anesthesiology* 95:1054-1067, 2001.

closure; otherwise, patients should be transported to the intensive care unit (ICU) with their trachea intubated and their ventilation controlled. Early extubation of the trachea is not generally attempted in patients with supraceliac aortic cross-clamp times longer than 30 minutes, patients with poor baseline pulmonary function, or patients requiring large volumes of blood or crystalloid during surgery. At the start of skin closure, inhaled anesthetics are discontinued, N_2O is increased to 70%, and any residual neuromuscular blockade is reversed. I routinely insert a large nasal airway after induction of anesthesia, but before systemic heparinization in all patients for whom extubation is planned in the operating room. Hypertension and tachycardia are aggressively controlled during emergence by the use of short-acting drugs such as esmolol, nitroglycerin, and sodium nitroprusside. Patients are placed in a recumbent, head-up position, and N_2O is discontinued. If spontaneous ventilation is adequate, the trachea is extubated. Some centers advocate extubation of all patients in the ICU after a period of stability has been established. In these cases, mild sedation with a benzodiazepine such as midazolam is appropriate.

Temperature Control

Postoperative hypothermia is associated with many undesirable physiologic effects and may contribute to adverse outcomes (see also Chapter 54). Normothermia should be maintained before skin incision by increasing ambient temperature in the operating room, applying warm cotton blankets, and warming IV fluids. If significant hypothermia occurs early in the procedure, normothermia is extremely difficult to achieve, and emergence and tracheal extubation may be delayed. During surgery, all fluids and blood products should be warmed before administration. A forced-air warming blanket should be applied over the upper part of the body. The lower part of the body should not be warmed because doing so can increase injury to ischemic tissue distal to the cross-clamp by increasing metabolic demands.

THORACOABDOMINAL AORTIC SURGERY

Open repair of the thoracoabdominal aorta is widely regarded as the most challenging surgical procedure in terms of overall anesthetic and perioperative management. Surgical repair is required for a spectrum of disease, including degenerative aneurysm, acute and chronic dissection, intramural hematoma, mycotic aneurysm, pseudoaneurysm, penetrating aortic ulcer, coarctation, and traumatic aortic tear. Since the first thoracoabdominal aortic aneurysm (TAA) repair in 1955, tremendous advances have been made in the field. These advances have led to significant reductions in operative mortality and perioperative complications. However, even in centers where numerous procedures are performed, morbidity and mortality are frequent, especially in patients with dissecting or ruptured aneurysms. To successfully care for these patients, the anesthesiologist must be knowledgeable in the areas of one-lung ventilation; extracorporeal circulatory support, including circulatory arrest; renal and spinal cord protection; induced hypothermia; invasive hemodynamic monitoring, including TEE; massive transfusion; and management of coagulopathy. Intraoperative management requires a team effort with intimate cooperation among surgeons, anesthesiologists, perfusionists, nurses, and electrophysiologic monitoring staff. Endovascular stent-graft repair of lesions that affect the descending thoracic and thoracoabdominal aorta is evolving rapidly. As discussed later, accumulating experience with stent-graft repair of thoracic aortic aneurysm, dissection, and traumatic tear has demonstrated this modality to be an effective alternative to open repair for select patients.

ETIOLOGY AND CLASSIFICATION

Aneurysms of the thoracoabdominal aorta occur primarily because of atherosclerotic degenerative disease (80%) and chronic aortic dissection (17%).[84] The remainder

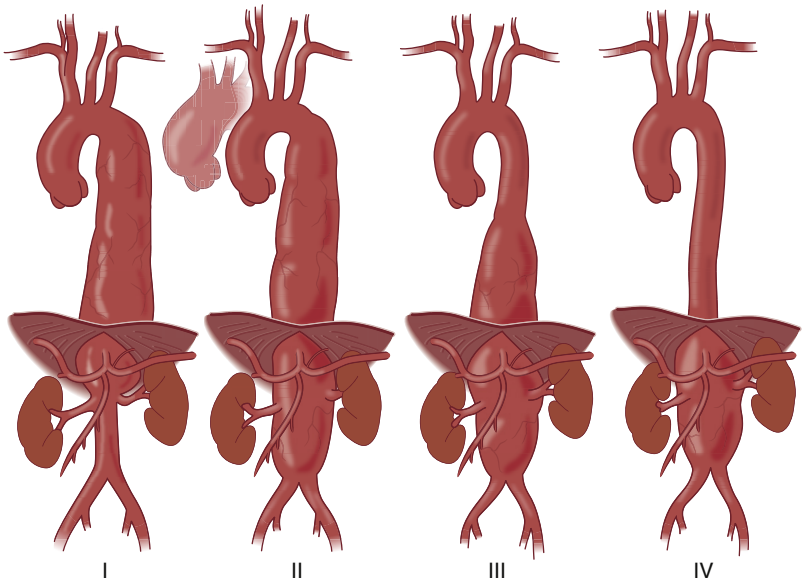


Figure 69-9. The Crawford classification of thoracoabdominal aortic aneurysms is defined by anatomic location and the extent of involvement. Type I aneurysms involve all or most of the descending thoracic aorta and the upper abdominal aorta; type II aneurysms involve all or most of the descending thoracic aorta and all or most of the abdominal aorta; type III aneurysms involve the lower portion of the descending thoracic aorta and most of the abdominal aorta; and type IV aneurysms involve all or most of the abdominal aorta, including the visceral segment. (Modified from Crawford ES: Thoracoabdominal and supra-renal abdominal aortic aneurysm. In Ernst CB, Stanley JC, editors: *Current therapy in vascular surgery*, Philadelphia, Decker, 1987, pp 96-98.)

are caused by either trauma or connective tissue diseases involving the aortic wall from conditions such as Marfan syndrome, cystic medial degeneration, Takayasu arteritis, or syphilitic aortitis.[85] The true incidence of TAA is unknown, but population studies suggest a prevalence much less than that of infrarenal AAA. Degenerative and dissecting TAAs differ in their associated risk factors, extent of aortic involvement, and natural history. Thus, complete characterization of each TAA is required to formulate a comprehensive treatment plan. Development of both degenerative and dissecting TAAs is ultimately related to weakening of the aortic wall. Although the natural history of TAA without surgery is uncertain, enlargement tends to be progressive and nonoperative management is generally associated with a poor prognosis. With progressive enlargement, nutritional blood flow to the aorta is compromised. The increasing diameter is associated with increased wall tension, even when arterial pressure is constant (law of Laplace). The frequent incidence of associated systemic hypertension enhances aneurysm enlargement.

Degenerative and dissecting TAAs are symptomatic at initial evaluation in 57% and 85% of patients, respectively. The most common initial complaint is back pain. Additional symptoms can be caused by compression of organs or structures adjacent to the aneurysm. Aortic rupture, as a manifestation of TAA, occurs with equal frequency (9%) in both degenerative and dissecting aneurysms. Rupture of the thoracic and abdominal segments occurs with equal frequency and primarily in patients with aneurysms larger than 5 cm. Surgical repair is usually recommended when aneurysm diameter exceeds 6 cm, but earlier repair may be offered to patients with Marfan syndrome and those with a strong family history of an aortic aneurysm.

In addition to cause, aneurysms of the thoracoabdominal aorta may be classified according to their anatomic location. In 1986, Crawford and colleagues,[84] recognizing the correlation between aneurysm extent and clinical outcome, proposed a classification based on the extent of aortic involvement (Fig. 69-9). The Crawford classification defines aneurysms as types I, II, III, and IV and is appropriately applied to aneurysms of all causes (degenerative and dissecting). Type I aneurysms involve all or most of the descending thoracic aorta and the upper abdominal aorta. Type II aneurysms involve all or most of the descending thoracic aorta and all or most of the abdominal aorta. Type III aneurysms involve the lower portion of the descending thoracic aorta and most of the abdominal aorta. Type IV aneurysms involve all or most of the abdominal aorta, including the visceral segment. Types II and III are the most difficult to repair because they involve both the thoracic and the abdominal segments of the aorta. Patients with Crawford type II aneurysms are at greatest risk for paraplegia and renal failure from spinal cord and kidney ischemia during cross-clamping. Even with extracorporeal circulatory support, an obligatory period occurs when blood flow to these organs is interrupted because the origin of the blood flow is between the cross-clamps. For this reason, protective measures to prevent ischemic injury are important in reducing morbidity.

Aortic dissection, with or without aneurysm formation, has likewise been classified according to the extent of aortic involvement. The most widely used classification, proposed by DeBakey and colleagues, defines aortic dissection as types I, II, and III (Fig. 69-10). Type I aneurysms begin in the ascending aorta and extend throughout the entire aorta. These lesions are usually repaired via a two-stage approach, with the first procedure on the ascending aorta and aortic arch and the second procedure on the descending thoracic aorta. Type II aneurysms are confined to the ascending aorta. Both types I and II often involve the aortic valve and cause aortic regurgitation, and sometimes they involve the ostia of the coronary arteries. Type III aneurysms begin just distal to the left subclavian artery and extend either to the diaphragm (type IIIA) or to the aortoiliac bifurcation (type IIIb). Another commonly used classification of aortic dissection is the Stanford classification. This more simplified

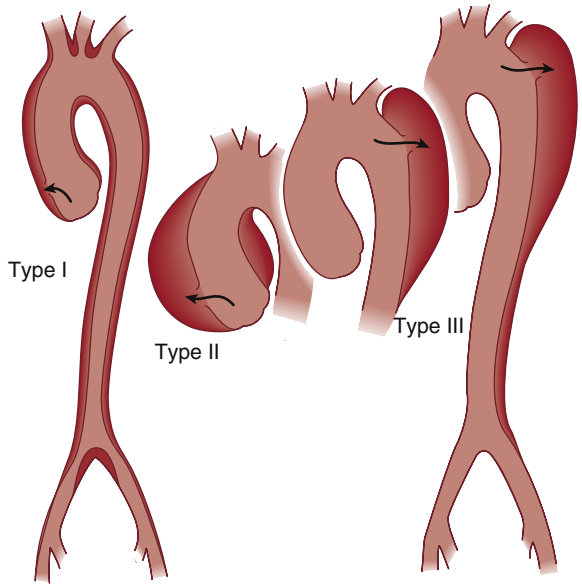


Figure 69-10. The DeBakey classification of dissecting aneurysms of the aorta. Type I has an intimal tear in the ascending aorta with dissection extending down the entire aorta. Type II has an intimal tear in the ascending aorta with dissection limited to the ascending aorta. Type III has an intimal tear in the proximal descending thoracic aorta with dissection either limited to the thoracic aorta (type IIIA) or extending distally to the abdominal aorta or aortoiliac bifurcation (type IIIB). (Adapted from DeBakey ME, Beall AC Jr, Cooley DA, et al: Dissecting aneurysms of the aorta, *Surg Clin North Am* 46:1045-1055, 1966.)

classification divides aortic dissection into those that involve the ascending aorta (Stanford type A) and those that do not involve the ascending aorta (Stanford type B). Aortic dissection is also classified by duration, with those less than 2 weeks classified as acute and those greater than 2 weeks classified as chronic. This classification has very significant mortality implications, with much higher mortality in the acute phase.

Acute aortic dissection involving the ascending aorta (DeBakey types I and II, Stanford type A) is a surgical emergency that requires immediate cardiac surgical repair (see also Chapter 67). Acute dissections involving the descending aorta (DeBakey type III, Stanford type B) are most often treated conservatively (i.e., arterial blood pressure, heart rate, and pain control) because surgical repair has no proved benefit over medical or interventional treatment in stable patients. Early surgical intervention may be required for a variety of reasons, including aneurysmal formation, impending rupture, organ or leg ischemia, and inadequate response to medical therapy. In approximately 20% to 40% of patients with chronic aortic dissection, significant aneurysmal dilatation of the descending thoracic or thoracoabdominal aorta will develop.

MORBIDITY AND MORTALITY

Despite tremendous development in surgical and anesthetic technique, mortality, and complication rates remain frequent for open surgical repair of TAA. Patients who undergo replacement of the entire thoracoabdominal aorta (Crawford extent type II) have the most frequent perioperative risk. Contemporary mortality rates reported from large institutions range from 5% to 14%. Statewide and nationwide mortality rates may be considerably more frequent (~20%). The perioperative mortality rate may significantly underestimate the risk associated with TAA repair. In a large statewide series, the mortality with elective TAA repair was 19% at 30 days and 31% at 365 days.[86]

The incidence of paraplegia or paraparesis in patients undergoing surgical repair of TAA is reported to be 3.8% to 40%, depending on complex factors such as anatomic location, the duration of cross-clamping, the use of protective measures, the degree of dissection, and whether the aneurysm has ruptured. Extensive dissecting TAA repair carries the highest risk for neurologic deficit. A contemporary report of 210 consecutive open TAA repairs reported three patients with paraplegia and two with temporary paraparesis for an overall rate of neurologic deficit of 2.4% (1.4% permanent).[87] Renal failure occurs in 3% to 30% of patients, depending on similar factors noted earlier. Overall, approximately 6% of patients need postoperative dialysis after TAA repair, which is associated with high mortality (30% to 60%). Gastrointestinal complications occur in approximately 7% of patients and are associated with a mortality approaching 40%. Not surprisingly, pulmonary complications are the most common problem associated with TAA repair. The incidence of postoperative pulmonary insufficiency approaches 50%, with 8% to 14% of patients requiring tracheostomy. As with all other vascular surgical procedures, cardiac complications are common and a leading cause of perioperative mortality. In general, perioperative mortality and major complication rates after open isolated descending thoracic aortic replacement are lower than those described for TAA repair.

PREOPERATIVE PREPARATION AND MONITORING

Open surgical TAA repair requires extensive preoperative evaluation and planning. The evaluation and management of coexisting cardiac and pulmonary disease are discussed earlier in this chapter. Before the day of surgery, the anesthesiologist and vascular surgeon should discuss, at a minimum, extent of the aneurysm and technique of surgical repair, plans for distal aortic perfusion, monitoring for spinal cord ischemia, renal and spinal cord protection, hemodynamic monitoring, and ventilation strategy.

Blood loss during TAA repair can be profound, and the need for massive transfusion must not be underestimated. This author routinely has 15 units of packed RBCs and 15 units of thawed fresh frozen plasma immediately available in the operating room, and additional units must be readily obtainable. I use a large cooler to store blood products on ice in the operating room so that they can be returned to the blood bank if not used. Platelets should be readily available as well. A dedicated critical care technician is helpful in assisting with laboratory testing and retrieving products from the blood bank (also see Chapter 61).

Large-bore IV access is obviously important, especially if partial bypass (in contrast to full bypass) is planned,

because it is difficult or impossible for the perfusionist to administer fluid or blood products into the closed partial bypass circuit. This author routinely inserts three 8.5-Fr catheters into the internal jugular and antecubital veins. One of these accepts a pulmonary artery catheter, and the other two are connected to a rapid infuser system that allows the delivery of up to 1500 mL/minute of blood products at a temperature of 37° to 38° C. A right radial arterial catheter is used for aneurysms involving the proximal descending thoracic aorta because occasionally the cross-clamp is placed proximal to the left subclavian artery, thus occluding flow to the left upper extremity. When distal aortic perfusion techniques are used, I monitor arterial blood pressure distal to the cross-clamps. This can be accomplished with the placement of a right femoral arterial catheter, or the surgical team can place a catheter directly into the femoral artery or distal aorta. This catheter monitors perfusion pressure to the kidneys, spinal cord, and mesenteric circulation during the time when the cross-clamps are high on the descending aorta and the lower body region is perfused by a shunt or bypass circuit. Radial and femoral arterial pressure should be simultaneously displayed on the anesthesiologist's monitor and a monitor visible to the surgeons and the perfusionists. TEE is used routinely during TAA repair (see also Chapter 46). When TEE is used by a properly trained individual, assessment of left ventricular end-diastolic volume, myocardial ischemia, and valvular function is possible. It is also possible to determine the size and the extent of the aneurysm.

A double-lumen endobronchial tube should be inserted for the purpose of one-lung ventilation (see also Chapter 66). One-lung ventilation provides optimal visualization of the surgical field and reduces retraction-related trauma to the left lung. A left-sided endobronchial tube is optimal because it is more easily positioned and less likely to become malpositioned. Additionally, risk exists for occluding the right upper lobe bronchus with a right-sided tube. I position all double-lumen tubes under direct vision using a fiberoptic bronchoscope because it facilitates quick and definitive placement and allows direct visualization of the distal trachea and mainstem bronchi. Occasionally, when the left mainstem bronchus is compressed by a large aneurysm, the lumen does not accommodate an endobronchial tube. In this situation, a right-sided endobronchial tube might be necessary. Rarely, the right mainstem bronchus may be compressed by a large aneurysm. The double-lumen tube is usually changed, if possible, to a single-lumen tube at the completion of surgery. This facilitates ICU management of pulmonary hygiene and reduces resistance to breathing during weaning in the postoperative period. The airway is often edematous after surgery, and it may be difficult or impossible to change the double-lumen tube without tube-changing catheters.

Many centers use electrophysiologic monitoring with somatosensory evoked potentials (SSEPs) or motor evoked potentials (MEPs) to monitor for spinal cord ischemia (see also Chapter 49). These monitoring techniques may be helpful in both identifying the important intercostal arteries that perfuse the spinal cord and confirming successful reimplantation into the aortic graft. If spinal cord ischemia is identified, cross-clamps can often be repositioned, upper or lower body blood pressure can be increased to augment perfusion through collateral channels, or other measures may be taken to protect the spinal cord (i.e., cerebrospinal fluid [CSF] drainage, induced hypothermia, or intrathecal pharmacologic agents). These techniques are discussed later. Three general problems exist with SSEP monitoring when used during TAA repair. First, sensory monitoring is more likely to detect lateral and posterior sensory column ischemia and is a poor monitor for the anterior motor column. As a result, paraplegia can occur despite normal SSEP signals. Second, inhaled anesthetics and hypothermia can significantly interfere with SSEP signals. Third, ischemia affects peripheral nerves, and ischemia in the lower extremities delays conduction from the usual stimulation sites (e.g., posterior tibial nerve). To eliminate the peripheral nerves as a confounding factor, spinal stimulation via a lumbar epidural electrode can be used, which may be more specific for ischemic injury than peripheral monitoring alone. Lower extremity and peripheral nerve ischemia can be avoided with the use of distal aortic perfusion techniques. To avoid lower extremity ischemia from occlusion of the left femoral artery at the insertion site of the retrograde perfusion cannula, some surgeons suture a small-caliber graft onto the femoral artery (end to side) for insertion of the cannula, which allows both antegrade and retrograde perfusion. These limitations of SSEP monitoring probably accounted for the lack of improvement in neurologic outcome in a large prospective series of TAA repairs. In this same series, the incidence of false-negative responses was 13% and that of false-positive responses was 67%, thus making identification of critical spinal arteries impossible.

The transcranial MEP technique has been used successfully to monitor the anterior columns of the spinal cord. The technique is relatively simple and can be viewed as a "train-of-four" for the brain and spinal cord. Electrical stimulation over the motor cortex activates α-motor neurons, and evoked electromyographic responses are obtained in lower extremity muscle. Only electromyogenic responses are specific for the status of the motor neurons in the anterior horn gray matter. Bilateral recording needles should be placed in the popliteal fossae (i.e., popliteal nerve) and bilateral surface electrodes over the gastrocnemius and tibialis anterior muscles. Bilateral stimulating needles are routinely placed in the popliteal fossae to monitor direct muscle responses and the level of neuromuscular blockade. During aortic cross-clamping, MEPs are monitored every minute. A reduction in MEP amplitude to less than 25% of baseline is considered an indication of spinal cord ischemia and requires corrective measures. Because signal averaging is not required and the anterior horn cells react with an almost immediate functional loss after the onset of ischemia, the technique can be used to rapidly identify intercostal arteries supplying the spinal cord. Additionally, the technique can be used to evaluate the adequacy of distal aortic perfusion and the patency of reimplanted critical intercostal arteries. Careful titration of a short-acting neuromuscular blocker is required to maintain a stable level of neuromuscular blockade. Complete neuromuscular blockade makes MEP monitoring impossible. I use a continuous infusion

technique to maintain electrical muscle amplitude at approximately 50% of baseline. Isoflurane, desflurane, sevoflurane, and N_2O depress synaptic conduction and significantly decrease the amplitude of myogenic MEPs. Although modifications of the stimulating technique have improved monitoring with inhaled anesthetics somewhat, a total IV anesthetic technique may be optimal. Fentanyl and ketamine have little effect on myogeneic MEPs and have been used successfully as a combined anesthetic in a large series of patients undergoing TAA repair with MEP monitoring.[87] This series of 210 consecutive patients had the lowest rate of neurologic deficit (2.4%) and permanent paraplegia (1.4%) reported.[87]

Body temperature should be monitored at two sites (core and peripheral) to assess cooling and warming when bypass techniques are used. However, an important difference exists between full and partial bypass with regard to temperature monitoring. With full bypass, perfusion is usually into the ascending aorta, and typically the upper body core temperature (i.e., nasopharynx or esophagus) cools and warms fastest, whereas the lower body temperature changes more slowly. With partial bypass, the opposite is true. The blood from bypass is returned into the femoral artery, and the lower part of the body (i.e., rectum or bladder) changes before the upper part changes. This difference is important to recognize to achieve complete cooling and warming because the lagging temperature should be the end point for cooling and warming.

ANESTHETIC MANAGEMENT

Simple Aortic Cross-Clamping

Descending thoracic and thoracoabdominal aortic surgery can be performed without extracorporeal support (i.e., left heart bypass or cardiopulmonary bypass). The "clamp-and-sew" technique has had relatively favorable outcomes, but these cases are from institutions with extensive clinical experience and the shortest cross-clamp times. Advocates of this technique favor its surgical simplicity. However, the benefits of avoiding the complexity and complications of bypass must be weighed against the risk for vital organ ischemia and complications such as renal failure and paraplegia.

Other than the location and extent of the aneurysm, the duration of cross-clamping on the aorta is the single most important determinant of paraplegia and renal failure with the clamp-and-sew technique. Clamp times of less than 20 to 30 minutes are associated with almost no paraplegia. When clamp times are between 30 and 60 minutes (the vulnerable interval), the incidence of paraplegia increases from approximately 10% to 90% as time progresses. Because clamp times are typically in this range or longer, specific adjuncts directed against end-organ ischemic complications are often used. Such adjuncts include epidural cooling for spinal cord protection, regional hypothermia for renal protection, and inline mesenteric shunting to reduce visceral ischemia.

When the simple clamp-and-sew technique is used, application of the aortic cross-clamp results in significant proximal hypertension, which requires active pharmacologic intervention. Management strategies have been discussed previously in the section on abdominal aortic reconstruction. Briefly, both sodium nitroprusside and isoflurane have been used successfully to control the proximal hypertension associated with high aortic cross-clamping. Isoflurane is best reserved for patients with good myocardial function. Vasodilators, such as sodium nitroprusside, must be used with caution because they can result in significant overperfusion of the body proximal to the clamp and very low pressures distally. Nitroglycerin can be used to normalize preload and cardiac filling and thus reduce ventricular wall tension. Although nitroglycerin does not control proximal hypertension well as a single agent, it is very helpful when used in combination with sodium nitroprusside. Management of aortic unclamping has been discussed earlier.

Left Heart Bypass

Maintaining lower body perfusion with the use of retrograde distal aortic perfusion reduces ischemic injury and improves outcome, provided the pressure is high enough to perfuse the organs. The simplest method of providing distal aortic perfusion is a passive conduit or shunt. The heparin-bonded Gott shunt was developed to avoid the need for systemic heparinization and is used to divert flow passively from the left ventricle or proximal descending thoracic aorta to the distal aorta. Some centers place a temporary axillary-to-femoral artery graft to function as a shunt during aortic cross-clamping.

Partial bypass, also referred to as left heart bypass or left atrial-to-femoral bypass, is the most commonly used distal aortic perfusion technique (Fig. 69-11). This technique allows adjustment of blood flow and usually draws blood

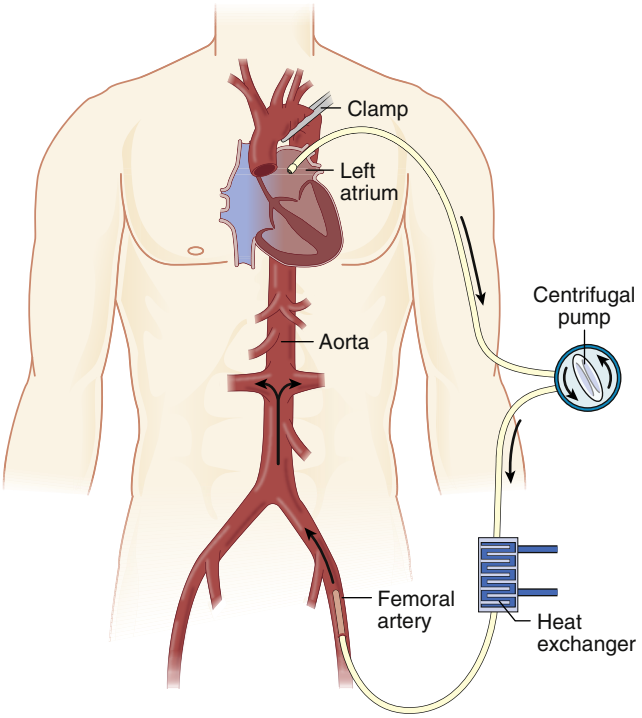


Figure 69-11. Diagram of left atrial-femoral bypass. The left atrium and the left femoral artery are cannulated, and a centrifugal pump is used with heparin-coated tubing. A heat exchanger may be added into the circuit for cooling and rewarming.

from the left atrium and returns blood to the left femoral artery. A centrifugal pump is used (Biomedicus, Eden Prairie, Minn), and full-dose systemic heparin is not needed because the circuit is coated with heparin. The typical heparin dose for partial bypass is 100 units/kg. With this technique, an oxygenator is unnecessary because only the left side of the heart is bypassed. Insertion of a heat exchanger into the circuit allows cooling and warming, which is beneficial but not absolutely essential. Variations of left heart bypass include cannulating the aortic arch or proximal descending thoracic aorta instead of the left atrium. With this circuit, the left ventricle is relieved of the increased afterload during aortic cross-clamping. With left atrial cannulation, the left ventricle is relieved of preload and cardiac output is reduced. Either way, proximal hypertension is controlled, the work of the ventricle is decreased, and perfusion is provided to the distal aorta. My colleagues and I have had even greater success with cannulation of a pulmonary vein instead of the left atrium. This method accomplishes the same effect as with atrial cannulation but is associated with less atrial irritability. When hypothermia (30° C) is combined with atrial cannulation, approximately 15% of patients experience new atrial fibrillation. Although most patients revert to sinus rhythm on rewarming, direct cardioversion may be required.

During left heart bypass, it is essential that arterial blood pressure be monitored above and below the aortic cross-clamps. I simultaneously display radial and femoral artery pressure and aim for a mean arterial pressure of 80 to 100 mm Hg above the cross-clamp and at least 60 mm Hg below the cross-clamp. Careful control of intravascular volume, bypass pump flow, and vasoactive drugs is required to achieve the target blood pressures. Management of left heart bypass requires continuous communication and cooperation between the surgeon, anesthesiologist, and perfusionist. We typically set the initial pump flow to approximately 50% of the patient's cardiac output with application of the proximal aortic clamp. Flow is then adjusted to maintain target proximal and distal pressures. Administration of vasodilators is very infrequently required at this stage. With no vital organ ischemia, the surgeon can complete the proximal anastomoses in an unhurried fashion. With sequential aortic clamping, intercostal arteries can be reimplanted with minimal adjustments of pump flow. Pump flow is eventually reduced significantly during reimplantation of the visceral and renal arteries. At this time, distal perfusion is only to the lower extremities. We routinely use moderate hypothermia (32° C) during bypass to protect the vital organs during obligate periods of ischemia. After completion of the distal anastomoses, pump flow is increased, and the patient is actively warmed to 37° C.

Deep Hypothermic Circulatory Arrest

Complex aneurysms involving the aortic arch often require elective cardiopulmonary bypass with an interval of deep hypothermic (15° C) circulatory arrest (DHCA) because cerebral blood flow is transiently interrupted during surgery (see also Chapter 67). Bypass can be accomplished by cannulation of the femoral artery and the femoral vein (i.e., femoral-femoral bypass). During the interval of DHCA, some centers also use anterograde (i.e., innominate artery) or retrograde (i.e., internal jugular vein) selective cerebral perfusion with cold oxygenated blood to extend the safe maximum duration of circulatory arrest. Without this technique, 45 to 60 minutes is thought to be the safe limit of DHCA, but 90 minutes has been reported with selective cerebral perfusion.

DHCA also may be necessary whenever the location, extent, or severity of aortic disease precludes placement of a proximal aortic clamp during thoracic or thoracoabdominal aortic repair. This is often the case in patients with previous aortic arch repair, in which adhesions and scarring make application of the proximal aortic cross-clamp difficult or impossible during TAA repair. DHCA eliminates the need for proximal aortic clamping and allows a bloodless field for the proximal aortic anastomosis. Some centers advocate the routine use of DHCA during complex aortic reconstruction because deep hypothermia may provide better end-organ and spinal cord function. This potential benefit must be carefully weighed against the risks associated with prolonged cardiopulmonary bypass and circulatory arrest. After completion of the proximal anastomosis and intercostal artery–to-graft anastomoses under DHCA, the aortic graft is cannulated and bypass flow is reestablished to the upper part of the body. During a period of hypothermic low bypass flow, the distal anastomoses are completed and then rewarming is initiated.

Anesthetic Technique

No single anesthetic technique is best for TAA repair. Usually, balanced anesthesia is provided with a combination of an opioid, a low-dose potent volatile anesthetic, a benzodiazepine, and a muscle relaxant. A total IV technique may be optimal if transcranial MEP monitoring is used. Induction of general anesthesia should be slow and controlled. Hypertension should be avoided because acute stress on the aneurysm can cause rupture. The heart rate should be maintained at or below baseline because myocardial ischemia is often related to the heart rate. Extubation should always take place in the ICU and only after a significant period of hemodynamic and metabolic stability. The postoperative analgesic regimen should focus on pain control and stable hemodynamics.

Spinal Cord Ischemia and Protection

Paraplegia is a devastating complication of aortic surgery. The incidence of paraplegia is reported to be 0.5% to 1.5% for coarctation repair, 0% to 10% for thoracic aneurysm repair, 10% to 20% for thoracoabdominal repair, and as high as 40% for extensive dissecting TAA repair.

The spinal cord receives its blood supply from two posterior arteries (≈25%) and one anterior spinal artery (≈75%) (Fig. 69-12). The posterior spinal arteries, which supply the sensory tracts in the spinal cord, receive flow from the posterior and inferior cerebellar arteries, the vertebral arteries, and the posterior radicular arteries. The anterior spinal artery, which supplies the motor tracts in the spinal cord, is formed by two branches of the intracranial portion of the vertebral arteries. The upper cervical segment of the spinal cord receives most of its blood flow from the vertebrals. The thoracic portion of the anterior

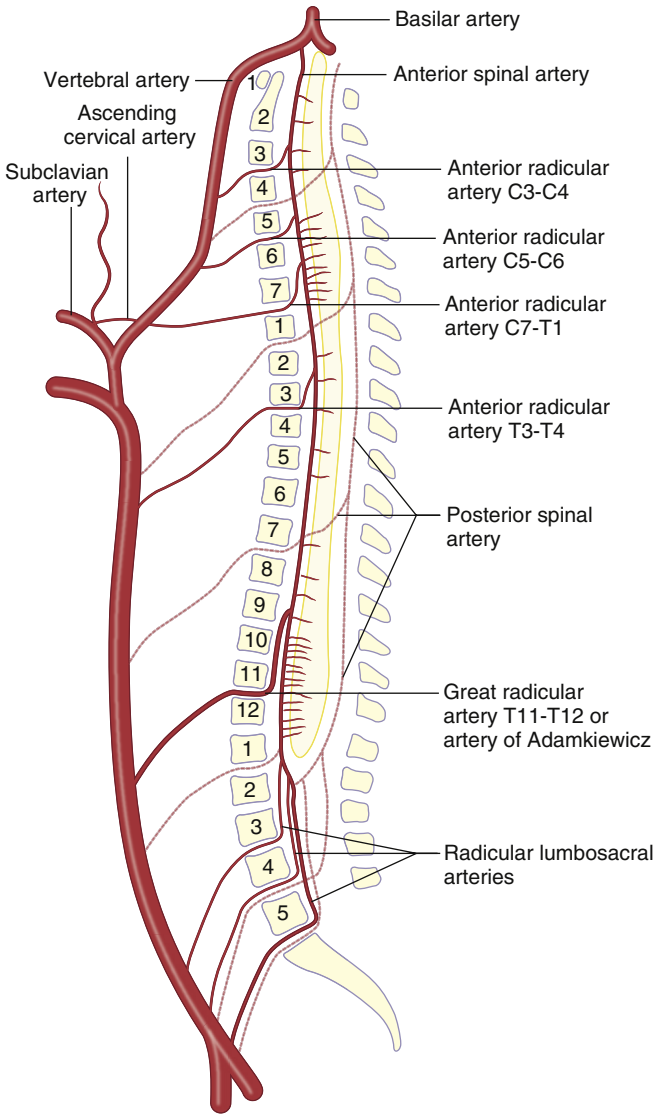


Figure 69-12. Diagram of the blood supply to the spinal cord showing the anterior and posterior radiculomedullary branches seen in a lateral view. The primary blood supply to the thoracolumbar portion of the spinal cord is derived from the artery of Adamkiewicz; its origin varies but usually branches off the aorta in the T9 to T12 region. (From Djindjian R: Arteriography of the spinal cord, *Am J Roentgenol Radium Ther Nucl Med* 107:461-478, 1969.)

spinal artery is supplied by the anterior radicular arteries (one or two cervical, two or three thoracic, and one or two lumbar). The largest of the radicular arteries is called the great radicular artery (GRA) or the artery of Adamkiewicz. The GRA is the major blood supply to the lower two thirds of the spinal cord. The segmental supplier of the GRA is variable (T5-L5) but is located between T9 and T12 in approximately 75% of cases. The variation in origin of the GRA explains why even infrarenal aortic aneurysm repair is associated with a 0.25% incidence of paraplegia. The specific impact of extensive segmental artery sacrifice on spinal cord perfusion during TAA repair is poorly understood.

Various methods can facilitate preventing ischemic injury to the spinal cord. Distal aortic perfusion with extracorporeal support reduces the incidence of paraplegia. Any of the various methods of distal bypass are likely to be beneficial when the anticipated cross-clamp time is longer than 30 minutes, but they are probably not beneficial when cross-clamp time is less than 20 minutes. CSF drainage is frequently used to improve spinal cord perfusion during TAA repair and is often used in combination with distal aortic perfusion. Spinal cord perfusion pressure is defined as distal mean aortic pressure minus CSF pressure or central venous pressure, whichever is greatest. Autoregulation of spinal cord blood flow is similar to cerebral autoregulation, and blood flow is relatively constant over the range of 50 to 125 mm Hg. During hypoxia or hypercapnia, autoregulation is lost, and flow becomes linearly related to perfusion pressure. Thus, significant flow may remain even at very low perfusion pressure. Drainage of CSF is important because CSF pressure often increases (by 10 to 15 mm Hg) with cross-clamping of the descending thoracic aorta. The increase in CSF pressure reduces spinal cord perfusion pressure and increases the likelihood of ischemic spinal cord injury.

Despite evidence from animal studies that CSF drainage protects the spinal cord, clinical use of this technique is controversial. One randomized trial reported a reduced incidence of paraplegia, but another reported no benefit. Most of the evidence in support of CSF drainage comes from nonrandomized historical cohort studies in which the technique is used in combination with other adjuncts, such as intrathecal papaverine and hypothermic partial bypass. Coselli and colleagues[88] offered the strongest evidence supporting the efficacy of CSF drainage. They conducted a prospective, randomized clinical trial to evaluate the impact of CSF drainage on the incidence of spinal cord injury after Crawford type I and II TAA repair. CSF drainage resulted in an 80% reduction in the relative risk for a postoperative deficit. Nine patients in the control group (13%) had paraplegia or paraparesis versus only two patients in the CSF drainage group (2.6%). Left heart bypass, moderate heparinization, permissive mild hypothermia, and reimplantation of patent intercostal and lumbar arteries were performed in both treatment groups. The target CSF pressure was 10 mm Hg. CSF drainage also reverses delayed-onset neurologic deficit after open and endovascular TAA repair.[89]

Although CSF drainage is widely used during TAA repair, it has risks. Potential complications include headache, meningitis, chronic CSF leakage, spinal or epidural hematoma, and subdural hematoma. The possibility of intraspinal pathologic processes should be considered in any patient with a postoperative lower extremity neurologic deficit. A retrospective review of 230 patients who underwent TAA repair with CSF drainage at my institution reported eight subdural hematomas (3.5%).[90] High-volume CSF drainage was identified as a risk factor for its occurrence. Six patients had subdural hematomas detected during hospitalization, with an associated mortality of 67%. Two patients were seen in a delayed fashion, and both required an epidural blood patch to control chronic CSF leakage.

Hypothermia is probably the most reliable method of neuroprotection from ischemic injury. By reducing O_2 requirements by approximately 5% for each degree centigrade, a twofold prolongation of tolerated cross-clamp time is achieved by cooling even to mild hypothermia (34° C). Because the reduction in metabolic rate is linearly related to temperature, moderate or profound hypothermia provides even greater protection. Both systemic and regional spinal cord cooling is beneficial. Systemic hypothermia can been achieved with either full cardiopulmonary bypass (with or without DHCA) or partial bypass. Cooling to 30° to 32° C with left atrial-to-femoral bypass in conjunction with CSF drainage was associated with no permanent neurologic sequelae in a series of 20 patients despite a relatively long average cross-clamp time (≈70 minutes).[91] My colleagues and I have since used this technique in more than 600 patients cooled to 32° C, with a 5% incidence of paraplegia. Although some risk is incurred when a beating heart is subjected to moderate hypothermia, the benefits appear to outweigh the risks. Supraventricular and ventricular dysrhythmias respond well to cardioversion or mild warming to 33° to 34° C. Regional cooling of the spinal cord by cold perfusion of the GRA with blood or crystalloid provides significant protection during spinal ischemia in animal models. Regional cooling is beneficial in humans who received epidural infusions of 4° C saline. Even if active cooling is not used, it is advantageous to allow patients to passively cool to 33° to 34° C during TAA repair. With passive cooling, the challenge is rewarming after the surgical repair. This is most easily accomplished with the use of a forced-air blanket over the upper part of the body. The lower body region should not be actively warmed because warming ischemic tissue increases metabolic requirements, acidosis, and ischemic injury.

Many drugs have been studied in an attempt to reduce the incidence of ischemic spinal cord injury. Barbiturates provide significant protection. Corticosteroids provide protection in dogs but were beneficial in humans only when they were combined with CSF drainage. Calcium channel blockers were not consistently shown to be protective against spinal cord ischemia. *N*-methyl-D-aspartate (NMDA) receptor antagonists have been investigated because ischemic injury appears to be related to increased levels of excitatory amino acids (particularly glutamate), which allow increased permeability to Ca^{2+} ions and high intracellular Ca^{2+} concentrations. Dextrorphan (a noncompetitive NMDA receptor antagonist) shows promise during spinal cord ischemia. Magnesium, another NMDA receptor antagonist, improves recovery from spinal cord ischemia in rat and dog models when administered intrathecally. Naloxone is protective in patients with traumatic spinal cord injuries and in a rabbit model of spinal ischemia. Naloxone also shows promise when combined with CSF drainage in patients undergoing TAA repair. Intrathecal papaverine appears to be protective, especially when combined with CSF drainage. Other agents under investigation include levosimendan, allopurinol, adenosine, ziconotide, activated protein C, and desferrioxamine. Other than the use of corticosteroids and naloxone at a few centers, most of these agents are considered investigational.

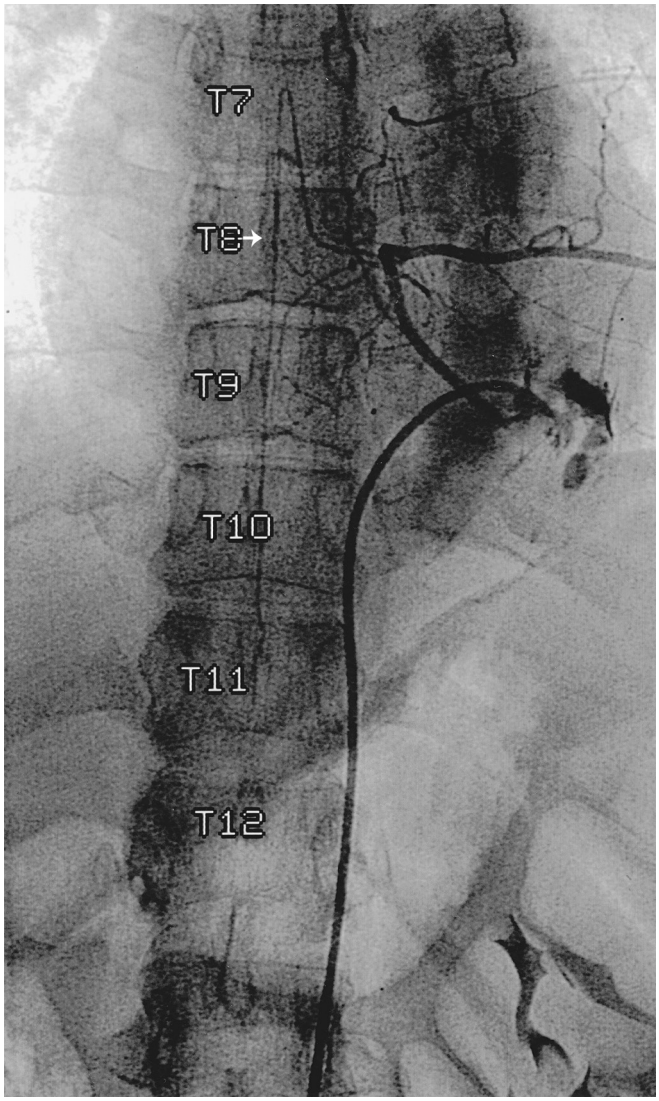


Figure 69-13. Spinal cord angiogram of an extensive degenerative thoracoabdominal aortic aneurysm. Selective injection of the intercostal artery at T8 (*arrow*) demonstrates the great radicular artery and the extensive paravertebral collateralization.

Preoperative spinal cord angiography has been used in patients with TAA. The rationale for this highly invasive angiographic procedure is that precise identification of intercostal arteries giving rise to the GRA will allow focused reimplantation of these vessels during surgical repair and help prevent spinal cord injury. Selective intercostal angiography identifies the GRA when an intercostal branch is found making a cephalad hairpin turn to enter the spinal canal and supply a midline longitudinal artery (i.e., the anterior spinal artery) (Fig. 69-13). The GRA can be identified in 43% to 86% of patients studied with traditional angiography. Higher detection rates for GRA localization have been reported with computed tomographic angiography (CTA) and magnetic resonance angiography (MRA), with the latter achieving rates of nearly 100%.[92]

The importance of reimplanting the intercostal arteries identified as supplying the GRA is not universally accepted. Even in patients with an identified and reimplanted GRA, spinal cord injury is not always prevented. Some investigators have concluded that preoperative localization of the GRA has little impact on neurologic outcome after TAA repair. A report from my institution[93] found no improvement in overall neurologic outcome with preoperative spinal cord angiography, but it offered important insight regarding the type of aneurysm, identification of the GRA, and neurologic outcome. In patients undergoing TAA repair for extensive degenerative aneurysms, spinal cord injury occurred in 0 of 45 patients versus 10 (12%) of 81 patients with and without an identified GRA, respectively. In contrast, identification of the GRA was not helpful in the case of chronic expanding aortic dissection, with 3 (15%) of 20 patients versus 3 (6%) of 49 patients suffering spinal cord injury with and without an identified GRA, respectively. The investigators hypothesized that mural thrombus in degenerative aneurysms results in the occlusion of many intercostal arteries and favors the development of extensive paravertebral collateral channels (see Fig, 69-13). Identification of a GRA allows focused reimplantation with uniform success. In patients with chronic dissection, most intercostal arteries are patent, collateralization is minimal, and reimplantation of one or two intercostal arteries may be insufficient to supply blood flow to the spinal cord. This collateral blood supply concept is further supported by clinical studies demonstrating that clamping the segmental supplier to the GRA during TAA repair does not produce critical spinal cord ischemia in the majority of patients.[94] Sufficient collateral blood supply, independent of the GRA, must therefore exist to maintain spinal cord integrity.

Delayed-onset neurologic deficits are common after TAA repair.[95] In a large series of 2368 TAA repairs, 93 (3.9%) patients had postoperative paraplegia or paraparesis, 34 (37%) of whom initially had intact spinal cord function but a deficit developed later.[96] Preoperative renal dysfunction, acute dissection, and extent type II TAA are significant predictors of delayed neurologic deficit. Postoperative hypotension and CSF drain malfunction may play an important role in the development of these deficits. Neurologic function can frequently be recovered by maintaining an optimal arterial blood pressure and CSF drainage.

Renal Ischemia and Protection

Renal failure after TAA repair results from preexisting renal dysfunction, ischemia during cross-clamping, thrombotic or embolic interruption of renal blood flow, and hypovolemia and hypotension. Approximately 6% of patients require postoperative dialysis, even in centers with the most clinical experience. The associated mortality can be high. The primary predictor of postoperative renal failure is preoperative renal dysfunction. The duration of cross-clamp time is very important with the clamp-and-sew technique.

Retrograde distal aortic perfusion techniques are widely used to preserve renal function during the cross-clamp period. Adequate bypass flow and arterial blood pressure are essential for maintaining renal function. Systemic and regional hypothermia, by reducing O_2 requirements, protects the kidneys during ischemia. Some centers advocate the use of DHCA in the treatment of distal TAAs (i.e., extent type III and IV) to preserve renal function.

The role of pharmacologic protection is somewhat controversial. Mannitol 12.5 to 25 g/70 kg is often given before cross-clamping. Mannitol improves renal cortical blood flow and the glomerular filtration rate in animal models of ischemia. Endothelial cell swelling is decreased, and an osmotic diuresis occurs. Evidence demonstrates free radical scavenging with mannitol and subsequent protection from ischemia in animals. Loop diuretics are sometimes given, but these drugs have been less effective than mannitol in experimental models. In clinical studies, the prophylactic use of loop diuretics has not been shown to improve outcome or reduce the need for dialysis for patients with acute renal failure. Dopamine given in low doses (1 to 3 μg/kg/minute) dilates renal blood vessels and increases renal blood flow and urine output. Despite these beneficial effects, whether dopamine provides renal protection during ischemia is not clear. Fenoldopam mesylate, a selective dopamine type 1 agonist that preferentially dilates the renal and splanchnic vascular beds, has shown some promise as a renoprotective drug.

At the present time, optimal renal protection during TAA surgery should rely on hypothermia, mannitol, and prevention of hypotension and hypoperfusion of the kidneys.

Coagulation and Metabolic Management

Coagulopathy is a frequent complication during TAA repair. A dilutional coagulopathy in which platelets become deficient after approximately one blood volume of replacement develops during massive transfusion (see also Chapters 61 and 62). At between one and two blood volumes of replacement, coagulation factors are diluted to levels low enough to increase bleeding. Other contributing factors are residual heparin; ischemia of the liver, in which most coagulations factors are produced; and persistent hypothermia after weaning from bypass. With the early use of fresh frozen plasma and platelets, severe coagulopathy often can be avoided. The prothrombin time, partial thromboplastin time, fibrinogen level, and platelet count should be measured frequently. Cryoprecipitate may be necessary to correct coagulopathy, especially when the prothrombin time and partial thromboplastin time are prolonged and hypervolemia prevents the administration of significant volumes of fresh frozen plasma. When coagulopathy persists despite these efforts, ε-aminocaproic acid is beneficial as antifibrinolytic therapy, and desmopressin can be given to increase circulating levels of von Willebrand factor and factor VIII. Normothermia should be achieved by complete rewarming before separation from bypass, by increasing ambient temperature after separation from bypass, and by forced-air warming over the upper body skin surface.

Analysis of arterial blood gases and electrolyte levels should be performed frequently. Sodium bicarbonate should be given to treat the metabolic acidosis that occurs during and after cross-clamping. Hyperkalemia should be treated aggressively, especially in oliguric or anuric

patients. Calcium chloride and sodium bicarbonate are the primary acute treatments of hyperkalemia.

ENDOVASCULAR AORTIC REPAIR SURGERY

Endovascular surgery is one of the most exciting developments in the treatment of vascular disease and is revolutionizing current treatment modalities for aortic disease. The endovascular approach was initially developed as a less invasive alternative to elective open AAA repair and to provide a treatment option for patients considered to be poor surgical candidates. Over the last 2 decades, an explosive increase has occurred in the use of endoluminal devices to treat AAA. These devices accounted for nearly 50% of elective repairs of AAA in Medicare beneficiaries during the period 2001 to 2004.[97] Interest in endoluminal aortic grafting has rapidly expanded beyond the abdominal aorta to include disease of the thoracic and thoracoabdominal aorta and, most recently, the ascending aorta and aortic arch. Endovascular grafting has also emerged as a viable alternative to open repair of aortic dissection, rupture, and traumatic injury. As experience with endoluminal techniques increases, along with continued refinement of stent-graft devices, the endovascular approach will be applied to more patients with increasingly complex aortic disease.

EVOLUTION OF STENT-GRAFT DEVICES

The transluminal placement of an endovascular stent-graft to treat arterial disease began experimentally in the late 1960s. The feasibility of this technique for the treatment of AAA was established experimentally some 2 decades later. In 1991, Parodi and colleagues[98] reported the first clinical use of the technique in five patients with infrarenal AAAs. They described the placement of an endoluminal, stent-anchored, Dacron tube graft via retrograde cannulation of the common femoral artery under local or regional anesthesia. Balloon expansion of the stents fixed the ends of the graft to the aortic wall and excluded the aneurysm from the systemic circulation. The technique was satisfactory in three of the five patients.

After nearly a decade of refinements, in 1999 the FDA approved the use of two endovascular stent-graft devices for repair of infrarenal AAAs in the United States. FDA approval of these devices was granted without the usual requirement for a randomized controlled trial. Instead, the FDA allowed a concurrent "matched" group of patients treated by open repair to serve as a control group. Additional stent-graft devices have received regulatory approval in the United States, and several are approved for use by other governments around the world. Since regulatory device approval, a rapid increase in endovascular AAA repair has occurred nationwide. The stent-grafts used for infrarenal AAA repair are usually modular bifurcated devices made of synthetic fabric reinforced by a stainless steel or nitinol (nickel-titanium alloy) framework that can be compressed within a catheter-based delivery and deployment system. The larger main trunk is designed for the infrarenal aorta and the two smaller branches are for the iliac arteries. Proximal external barbs or hooks aid device fixation to the aortic wall. A device with a suprarenal bare stent component is available for transrenal fixation without compromising renal blood flow.

The emergence of endovascular repair of the descending thoracic aorta quickly followed the success achieved with the infrarenal aorta. The initial report of stent-grafts for the treatment of descending thoracic aortic aneurysms was by Dake and co-workers in 1994.[99] Using custom-designed self-expanding stent-grafts, they reported a 100% technical success rate in 13 patients. In 2005, the FDA approved the use of a thoracic stent-graft device for the treatment of descending thoracic aortic aneurysms. Additional devices have received FDA approval, and several are commercially available around the world. Devices are tubular, with one or two components and a variable bare stent configuration. Current generation devices have been used extensively for a spectrum of aortic disease, including aneurysms, dissections, penetrating ulcers, ruptures, and traumatic transections.

Fenestrated stent-grafts have been developed to facilitate the endovascular repair of juxtarenal and pararenal aortic aneurysms. These highly customized devices have openings in the graft fabric that align with arteries branching off the aorta, thereby maintaining end-organ perfusion while excluding the aneurysm. A modular fenestrated device received FDA approval in 2012. Alignment stents can be used to secure the position of the fenestration with the orifice of the aortic branch vessel.

Branched stent-grafts are also used in the endovascular repair of complex aneurysms that span aortic branch vessels. Directional branches off the graft body are custom-designed based on patient-specific anatomy derived from three-dimensional aortic imaging and reconstruction. Endovascular procedures on the thoracoabdominal aorta and aortic arch often require these novel stent-grafts. These devices are currently in use in Europe and await FDA approval in the United States.

ENDOVASCULAR TECHNIQUE

The endovascular approach can be undertaken without the large incisions, extensive dissections, prolonged aortic cross-clamp times, and significant blood loss and fluid shifts associated with open repair. The arterial access site for endovascular stent-graft placement is selected on the basis of vessel size and degree of obstructing atherosclerotic disease. The technique most commonly requires bilateral transverse groin incisions to expose the common femoral arteries. In patients with severely diseased femoral or iliac arteries, balloon angioplasty or local endarterectomy can be performed to allow passage of the delivery system. Adjunctive retroperitoneal procedures may be necessary in up to 20% of patients during endovascular AAA. Indications include small external iliac arteries that limit femoral access and a concomitant iliac artery aneurysm that precludes distal fixation of the stent-graft in the common iliac artery. In these cases, a transverse lower abdominal incision with retroperitoneal dissection exposes the iliac artery, and a synthetic conduit is sutured (end to side or end to end) onto the common iliac

artery. The delivery system is endoluminally placed into the aorta through this iliac conduit. At the termination of the procedure, the conduit can be ligated, attached to the external iliac artery (interposition graft), or attached to the common femoral artery (iliofemoral bypass graft). Although adjunctive retroperitoneal procedures may allow a larger number of patients to undergo endovascular aortic repair, such procedures are associated with an increased risk for complications, greater blood loss, longer procedure time, and longer hospital length of stay than endovascular repair with standard femoral access. Obviously, the advantage of endovascular techniques being less invasive than open repair is reduced when adjunctive procedures are required. Adjunctive procedures may also be needed with endovascular repair of the thoracic aorta. One series involving patients with a spectrum of aortic disease reported that 25% of patients needed open surgical access to the aorta and 21% needed left subclavian–carotid transposition to provide an adequate proximal fixation site.

Although adjunctive surgical procedures may be needed, the technical skill required for endovascular aortic surgery is primarily catheter based. Thus, appropriately trained cardiologists, radiologists, and vascular surgeons can deliver endovascular treatment of aortic disease. A multispecialty approach is commonly used and offers patients the expertise of both surgical and catheter-based specialists. Even though no standard has been set, the requirements for endovascular aortic surgery are the same wherever it is performed. The standard operating room environment is ideal from the surgical and anesthesia standpoint, particularly when conversion to an open repair is required. The operating room must be equipped with endovascular supplies, portable radiologic imaging tools, and an angiographic table. Angiographic suites often have superior radiographic imaging tools and angiographic tables and are better equipped to deal with ionizing radiation. The superior imaging may reduce radiation exposure and decrease contrast dye loads. In an effort to provide an optimized environment for multispecialty endovascular intervention, many centers are constructing sophisticated operative angiographic suites in or adjacent to the operating room.

Endovascular stent-grafting of the aorta requires preprocedural diagnostic imaging to precisely evaluate and delineate the aortic anatomy. CTA and MRA have been established as the gold standard for preprocedural evaluation. For AAAs, length and diameter of the proximal neck, location of important aortic and iliac side branches (accessory renal arteries, inferior mesenteric artery, and hypogastric arteries), and distal fixation site characteristics must be determined. Significant aneurysm neck angulation, short neck length, large neck diameter, and severe aortic calcification currently exclude many patients from endovascular repair.

Endovascular stent-grafts are often custom-made for each patient based on aortic anatomy. Each endovascular stent-graft delivery device has a unique method of deployment, and many individual variations in technique are possible. First-generation endografts were not fully stented and required balloon expansion of the proximal portion at the time of deployment. Metal hooks in the proximal portion were embedded into the aortic wall with balloon inflation, which resulted in complete aortic occlusion, not unlike aortic cross-clamping. These unsupported endografts were prone to complications such as migration and kinking. Distal migration during proximal endograft deployment was particularly troublesome with intrathoracic endograft placement. Induced hypotension, adenosine-induced asystole, and induced ventricular fibrillation have all been used successfully to reduce endograft migration during deployment. Current-generation endografts are fully stented (i.e., stent-grafts) and self-expanding. Balloon expansion is not required at the time of deployment. Stent-graft migration at the time of deployment is largely prevented, and associated complications are reduced. A unique trilobed aortic balloon can be used to expand the stent-graft for aortic apposition after deployment without complete aortic occlusion. Though no longer a requirement, mild induced hypotension (with nitroglycerin or sodium nitroprusside) can be used selectively during stent-graft deployment.

Hybrid procedures (a combination of open surgical and endovascular stenting) have expanded the endovascular approach to include aortic aneurysms involving major branches that originate from the aorta. Type IV TAA repair can be accomplished with open visceral and renal bypass followed by stent-graft implantation over the "debranched" visceral segment. Similar approaches are being used to treat complex aneurysms that involve the aortic arch. Hybrid procedures rarely require aortic cross-clamping. In patients with aneurysmal disease of the entire aortic arch, the traditional "elephant trunk" procedure has been combined with a second-stage stent-graft procedure of the descending thoracic aorta. The distal end of the elephant trunk serves as the proximal attachment site for the stent graft.

ANESTHETIC MANAGEMENT

Local, regional, and general anesthesia techniques have all been described for endovascular aortic repair shortly after its introduction. Several regional techniques have been used, including paravertebral, spinal, continuous spinal, epidural, and combined spinal and epidural. General anesthesia was commonly used with early-generation devices because the surgical procedure times were often long. As centers have gained experience with newer-generation devices, procedure times have been reduced and local and regional techniques are used more often, most commonly with IV sedation. A sedation technique using dexmedetomidine with local anesthesia has been reported.[100] Despite procedural advances and the established feasibility of local and regional anesthesia, these techniques have not become accepted on a large scale. An analysis of anesthesia type based on data from the EUROSTAR registry (5557 endovascular repairs of infrarenal aortic aneurysm) reported the use of local, regional, and general anesthesia in 6%, 25%, and 69% of patients, respectively.[101] The influence of anesthesia type on outcome based on the EUROSTAR data indicates that the use of local or regional anesthesia may reduce ICU admission, hospital length of stay, and early complications.[101] Further analysis of high-risk patients from this registry

suggests that a mortality benefit may exist when local or regional anesthesia is used.[102] A retrospective analysis of 229 endovascular AAA repairs using local anesthesia with IV sedation or general anesthesia reported similar rates of cardiac and pulmonary morbidity.[103] Reduced intraoperative fluid requirements[103,104] and less vasopressor support[104] have been reported with the use of local anesthesia. Given the retrospective nature of these reports and the significant selection bias regarding assignment of anesthetic technique, specific recommendations regarding the use of local, regional, and general anesthesia are premature. As with open aortic repair, maintenance of vital organ perfusion and function by the provision of stable perioperative hemodynamics is probably more important to overall outcome than is the choice of anesthetic technique.

I commonly use a general anesthetic technique for endovascular aortic repair in patients requiring extensive groin dissection or any retroperitoneal dissection and those requiring complex repairs, where conversion to open repair may be more likely. A balanced technique using relatively short-acting agents maximizes management flexibility. Opioid requirements are usually minimal (fentanyl 2 to 4 μg/kg), and postoperative pain is easily managed. Esmolol, sodium nitroprusside, nitroglycerin, and phenylephrine should be available and used to maintain appropriate hemodynamics. Epidural and spinal anesthesia are used selectively based primarily on patient and surgeon preference.

Placement of a radial artery catheter should be routine for all endovascular aortic repairs. It should be placed on the right side because a catheter may be placed percutaneously in the left brachial artery for aortic angiography. Central venous and pulmonary artery catheter monitoring are rarely used. Two large-bore peripheral IV catheters are recommended. Although blood loss and fluid requirements are not usually excessive, the potential for rapid blood loss is real. The possibility of acute aortic rupture necessitates the availability of fluids, blood, and a rapid infusion device. Catheterization of the bladder is required for most procedures. Monitoring of urine output can help guide fluid management, particularly when large volumes of heparinized flush solution and radiographic contrast material are used and when diuretics (i.e., mannitol or furosemide) are administered. Fluid management is directed primarily at maintaining normovolemia. Isotonic HCO_3^- infusion is often used in patients with renal dysfunction to reduce the incidence of contrast-induced nephropathy.[105] Active patient warming is frequently necessary to prevent hypothermia, particularly with longer procedures.

Endovascular repairs involving the descending thoracic aorta require additional preparation and monitoring. These procedures are often performed in the operating room under general anesthesia. Although current-generation devices are much less prone to graft migration during deployment, pharmacologically (i.e., sodium nitroprusside or nitroglycerin) induced hypotension (i.e., systolic blood pressure < 100 mm Hg) is commonly used during deployment. TEE monitoring is frequently used and can be extremely helpful in identifying proximal and distal stent-graft landing zones, entry and exit points of dissections, true and false lumens, and aneurysm exclusion. Paraplegia is a recognized complication after endovascular repair of the descending thoracic aorta and is reported to be as high as 8%.[88] Concomitant or previous abdominal aortic repair and long-segment thoracic aortic exclusion appear to be important risk factors. Postoperative hypotension may play a role as well. CSF drainage reverses delayed-onset neurologic deficit after endovascular TAA repair,[89] prompting some centers to use perioperative CSF drainage in all high-risk patients. Intraoperative spinal evoked potential monitoring plus temporary (15 minutes) balloon occlusion of the thoracic aorta before stent-graft deployment is a means to evaluate the patient's risk for spinal cord ischemia.[106]

COMPLICATIONS

Endoleak

The inability to obtain or maintain complete exclusion of the aneurysm sac from arterial blood flow, termed endoleak, is a complication specific to endovascular aortic repair. The concern is that any pressurization of the aneurysm sac (i.e., endotension) can lead to aneurysm enlargement and rupture. Endoleaks can be detected by arteriography, computed tomographic scanning, magnetic resonance imaging, and duplex ultrasound scanning. A classification system developed for endoleak describes four distinct types.[107] Type I endoleak occurs when the seal between the stent-graft and the aortic wall at the proximal or distal attachment sites is inadequate. Type II endoleak occurs when there is retrograde filling of the aneurysm sac from patent intercostal, lumbar, inferior mesenteric, or testicular arteries. Type III endoleak is due to structural failure of the stent-graft that allows blood to flow directly into the aneurysm sac. The structural failure may be due to tears in the graft fabric or separation of individual components of a modular endograft. Type IV endoleak relates directly to the porosity of the graft material. Type V endoleak refers to persistent pressurization of the aneurysm sac after endovascular repair without an identified leak on imaging studies. Endoleaks are also classified as primary (after deployment) or secondary (after initial seal).

The rate of occurrence of endoleak depends on many factors, including the endograft device, the method of deployment, vascular anatomy, and progression of disease. Management of endoleak after endograft placement is controversial and ranges from observation with periodic imaging surveillance to immediate endovascular or surgical correction. Types I and III endoleaks are associated with an increased risk for rupture and are almost uniformly treated aggressively. Although type II endoleaks do not often require urgent treatment and many spontaneously thrombose, they are associated with aneurysm enlargement. Type IV endoleaks are usually self-limited and rarely require specific treatment. Type V endoleaks require intervention if aneurysm growth is detected. Endovascular extension grafts, coil embolization, and conversion to open repair have been used successfully to repair endoleaks.

Early Complications

In addition to primary endoleaks, early complications include access vessel trauma, inadvertent stent deployment over vital branch vessel, aneurysm rupture, pelvic and lower extremity ischemia, acute renal failure, MI, stroke, paraplegia, and postimplantation syndrome (PIS). PIS is a weakly defined yet relatively common condition associated with features of a systemic inflammatory response such as leukocytosis, fever, and elevation of inflammatory mediators. Although transient and usually well tolerated, PIS is associated with an increased length of hospital stay.

Late Complications

Late complications are most often related to endoleak but also include degeneration of the proximal neck, limb occlusion, device migration or fatigue (kinking or collapse), endograft infection, aneurysm enlargement, open conversion, and rupture. Lifelong surveillance imaging is mandatory for the early detection and management of these complications. Approximately 20% of patients will require catheter-based or limited surgical reintervention after endovascular infrarenal aortic aneurysm repair.

Outcomes

Endovascular repair of AAAs was originally developed to provide a treatment option for patients considered to be poor surgical candidates. Early studies reported better hemodynamic stability, reduced stress response, decreased rate of systemic complications and shorter postoperative length of stay, and improved respiratory function and analgesic control than with open aortic repair. Based on these early reports and without the benefit of long-term outcome data or randomized clinical trials, endovascular aneurysm repair has been applied to a large proportion of patients with AAAs. Large retrospective cohort studies and prospective registries subsequently established the safety and efficacy of endovascular repair. Several prospective randomized controlled trials in Europe and the United States followed to answer several critical questions related to the broad application of endovascular technology in patients fit and unfit for open repair.

A meta-analysis of 163 studies involving 28,862 patients assessed safety and efficacy outcomes after endovascular repair of asymptomatic AAA.[108] The operative mortality was 3.3%. Technical success (complete aneurysm exclusion) rate was 82.7%. The rate for primary conversion to open repair was 3.8%, and for secondary conversion to open repair 3.4% (overall 5.4%). The postoperative rupture rate was 1.3% and was associated with a 44.4% mortality rate. A type I endoleak developed in 10.5% of patients, with an annual rate of 8.4%. A type II, III, or IV endoleak developed in 13.7% of patients, with an annual rate of 10.2%. A definite improvement in outcome was reported over the study period (1992 to 2002). Another meta-analysis involving 19,804 patients undergoing endovascular repair of infrarenal aortic aneurysm between 2000 and 2004 reported a 30-day mortality rate of 1.6% and 2.0% in randomized and nonrandomized trials, respectively.[109] Device deployment was successful in 97.6% of patients. Technical success was achieved in 81.9% at discharge and 88.8% at 30 days. Secondary intervention to treat endoleak or to maintain graft patency was required in 16.2% of patients.

In a study of 45,660 Medicare beneficiaries who underwent either endovascular or open repair of an AAA between 2001 and 2004, perioperative mortality was lower after endovascular repair (1.2% versus 4.8%), and the reduction in mortality increased with age (8.5% difference for those 85 years or older).[97] Conversion from endovascular repair to open repair occurred in 1.6% of patients. Endovascular repair was associated with fewer major complications, shorter length of hospital stay (3.4 days versus 9.3 days), and a greater likelihood of being discharged home (94.5% versus 81.6%). Late survival was similar between cohorts, although the survival curves did not converge until after 3 years. By the fourth year, rupture was more likely to occur after endovascular repair (1.8% versus 0.5%), as was aneurysm-related intervention (9.0% versus 1.7%).

Prospective randomized controlled trials comparing endovascular and open repair of asymptomatic infrarenal AAA (in patients fit for open repair) have been undertaken to determine comparative morbidity and mortality, and the need for reintervention. A recent meta-analysis of all prospective, randomized trials (2899 patients) reported short-term (30-day), intermediate-term (up to 2 years), and long-term (3 years or longer) outcomes.[110] The primary conversion rate for endovascular repair was 0.6%. Length of hospital stay and ICU stay were shorter with endovascular repair. There were no differences in perioperative complications, including stroke, MI, and renal failure. The 30-day all-cause mortality was less with endovascular repair (relative risk [RR]: 0.35, 95% confidence interval [CI]: 0.19 to 0.64). At intermediate follow-up, the all-cause mortality had a nonsignificant difference (RR: 0.78, 95% CI: 0.57 to 1.08), the aneurysm-related mortality was lower (RR: 0.46, 95% CI: 0.28 to 0.74), and the reintervention rate higher (RR: 1.48, 95% CI: 1.06 to 2.08) for endovascular repair compared to open repair. At long-term follow-up, no difference was found in all-cause mortality (RR: 0.99, 95% CI: 0.85 to 1.15) or aneurysm-related mortality (RR: 1.58, 95% CI: 0.20 to 12.74) whereas the difference in reintervention persisted (RR: 2.54, 95% CI: 1.58 to 4.08).

The Endovascular Aneurysm Repair (EVAR)-2 trial was designed to compare endovascular repair versus no intervention in patients deemed unfit for open AAA repair.[111] A total of 338 patients with AAAs greater than 5.5 cm, older than 60 years of age, and deemed unfit for open repair because of comorbid conditions were randomized to undergo endovascular repair or no intervention. All patients received best medical treatment for their comorbid conditions. Operative mortality (30 day) for the endovascular group was 9%. The overall mortality rate at 4 years was 64%, and no difference was found between the endovascular group and the no-intervention group in aneurysm-related mortality or all-cause mortality. Although more deaths from aneurysm rupture occurred in the no-intervention group, the initial high mortality in the endovascular group resulted in no late differences in mortality. The authors concluded that endovascular repair did not improve survival over no intervention, had little effect on health-related quality of life, and was associated with a need for continued monitoring and reintervention,

at substantially increased cost. In-hospital mortality for the highest risk patients undergoing endovascular aortic aneurysm repair in the United States may be lower than that reported in EVAR-2, suggesting that these high-risk patients should not be denied endovascular repair.[112]

LOWER EXTREMITY REVASCULARIZATION

Lower extremity arterial insufficiency, or peripheral arterial disease, is a common condition that affects as many as 10 million people in the United States, and its incidence is increasing annually. Because individuals with lower extremity peripheral arterial disease are most often asymptomatic or have symptoms other than classic intermittent claudication, the true prevalence of the disease is unknown. In a population-based study of individuals 55 years of age and older, the prevalence of peripheral arterial disease was 19.1% (16.9% in men and 20.5% in women). The prevalence of peripheral arterial disease in primary care practices in the United States is frequent (29%), and the condition is often unrecognized (44%). Arterial disease of the upper extremity does occur but is much less common than lower extremity involvement.

Atherosclerosis is the most common cause of peripheral arterial disease. Risk factors for atherosclerosis of the lower extremity are the same as for other vascular areas and include advanced age, male sex, hypertension, smoking, hyperlipidemia, and diabetes. Infrainguinal atherosclerosis may involve the femoral artery, popliteal artery, and any of the infrapopliteal arteries. The superficial femoral artery is the most common site of major atherosclerotic involvement below the inguinal ligament. Nonatherosclerotic causes of peripheral arterial disease include embolism, thromboangiitis obliterans (Buerger disease), immune arteritis, radiation arteritis, giant cell arteritis, adventitial cystic disease, fibromuscular dysplasia, and homocysteinemia.

As previously noted, peripheral arterial disease is a very strong indicator of generalized atherosclerosis and is a risk marker for other vascular conditions, including CAD, cerebrovascular disease, and aneurysmal disease. For example, patients with concomitant CAD and peripheral arterial disease have a higher prevalence of triple-vessel coronary disease than do patients with CAD alone. Additionally, over 20% of patients with peripheral arterial disease have a 70% or greater carotid artery stenosis. It is well documented that patients with peripheral arterial disease are at higher risk for cardiovascular morbidity and mortality than individuals without peripheral arterial disease. The increased cardiovascular risk may not be entirely due to atherosclerosis because these patients may have an enhanced prothrombotic state secondary to platelet activation[113] and a high prevalence of diverse hypercoagulable states.[114] The natural history of atherosclerotic lower extremity peripheral arterial disease is illustrated in Figure 69-14.

ACUTE ARTERIAL OCCLUSION

Acute peripheral arterial occlusion occurs primarily as a result of embolism and thrombosis. Pseudoaneurysm after invasive procedures in which the femoral artery is cannulated is a much less common cause of acute ischemia. The vast majority of emboli to the lower extremity originate in the heart, with intermittent atrial fibrillation and myocardial infarction being the most common causes of emboli. Although rheumatic heart disease is now a rare cause of embolic occlusion, prosthetic heart valves may be a source of emboli. Other causes of embolization include bacterial endocarditis, atrial myxoma, paradoxical venous emboli, and atheromatous debris from proximal aneurysms. Arterial emboli often lodge at vessel bifurcations. Common sites in the lower extremity include the femoral artery bifurcation, iliac artery bifurcation, and popliteal artery.

Thrombotic occlusions probably outnumber embolic occlusions by a ratio as high as 6:1. Acute arterial thrombosis of native vessels almost always occurs in the setting of severe and long-standing atherosclerosis. It can be viewed as the terminal event in the progression of atherosclerosis. Thrombosis of vascular bypass grafts is common and may result in acute ischemia. The high prevalence of diverse hypercoagulable states in patients with peripheral arterial disease may predispose such patients to thrombosis.[114]

The clinical computed tomography manifestation of acute arterial occlusion varies depending on the location of the obstruction and the extent of collateral circulation. In patients with a sudden onset of acute extremity ischemia, the occlusion often occurs abruptly and without the preexisting development of collateral pathways. Although ischemic symptoms are often more severe in patients with embolic occlusion than in patients with thrombotic occlusion, differentiation between embolic and thrombotic occlusion may be difficult. Acute occlusion of a previously patent extremity artery is a dramatic event characterized by pulselessness, pain, pallor, paresthesia, and paralysis (the five Ps). Absence of pulses and pallor are early manifestations. The sudden onset of pain is very common, and it may be intense. Motor weakness and paresthesia are usually late manifestations of severe ischemia.

Acute ischemia needs to be evaluated rapidly because irreversible tissue injury can occur within 4 to 6 hours. Initial management usually involves immediate anticoagulation to prevent propagation of thrombus, stabilization and control of coexisting medical conditions, and arteriography. Immediate surgical revascularization is generally indicated in the profoundly ischemic extremity. Patients with embolization to a nonatherosclerotic extremity are frequently managed with femoral thromboembolectomy under local anesthesia. Management of patients with peripheral arterial disease who are suspected of having thrombotic occlusion requires arteriography to determine the severity and anatomic location of the occlusion. Angioplasty or thrombolytic therapy may be performed in conjunction with arteriography. Intraarterial thrombolysis is often used as an initial intervention in an effort to unmask the culprit lesion responsible for the occlusive event. Patients are frequently scheduled for lower extremity bypass surgery the following day, pending evaluation of lower extremity blood flow. The frequent use of heparin anticoagulation and thrombolytics has significant implications for the anesthesiologist because regional anesthesia is not an option in an anticoagulated patient.

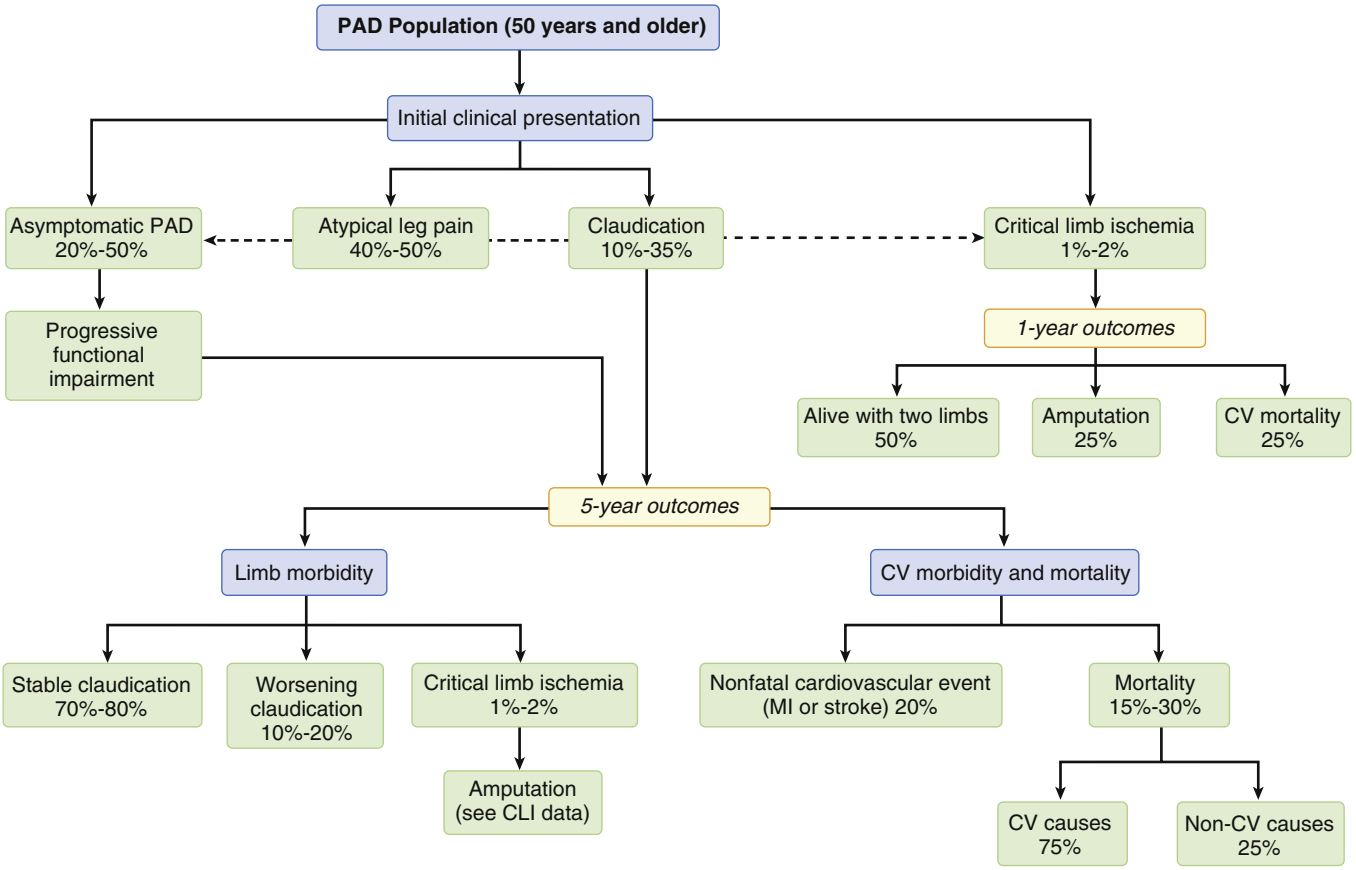


Figure 69-14. The natural history of atherosclerotic lower extremity peripheral arterial disease (*PAD*). Individuals with atherosclerotic lower extremity PAD may be asymptomatic (without identified ischemic leg symptoms, albeit with a functional impairment) or have leg symptoms (classic claudication or typical leg symptoms) or present with critical limb ischemia (*CLI*). All individuals with PAD face a risk for progressive limb ischemic symptoms, as well as a high short-term cardiovascular ischemic event rate and increased mortality. These events rates are most clearly defined for individuals with claudication or CLI and less well-defined for individuals with asymptomatic PAD. *CV,* Cardiovascular; *MI,* myocardial infarction. (From Hirsch AT, Haskal ZJ, Hertzer NR, et al: ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation, *J Am Coll Cardiol* 47:1239-1312, 2006.)

Morbidity and mortality rates in this patient population are frequent, particularly in patients requiring significant operative intervention.

CHRONIC ARTERIAL OCCLUSION

Chronic arterial insufficiency is most often secondary to long-standing atherosclerosis in which the arterial lumen of the lower extremity becomes progressively stenosed by atherosclerotic plaque. When the stenosis approaches total occlusion, the marked reduction in blood flow leads to thrombotic occlusion. Hemodynamically significant stenosis and total-vessel occlusion commonly exist in the lower extremity with no or very minimal symptoms. The development of collateral vessels around a stenosed or occluded arterial segment often prevents clinical symptoms until multiple occlusions exist in major vessels. Thus, most patients with peripheral arterial disease are asymptomatic. Patients with symptoms most commonly have mild intermittent claudication—pain or fatigue in the muscles of the lower extremity caused by exertion and relieved with rest. The pain usually occurs in the muscle group distal to the site of arterial insufficiency. With disease progression, severe disabling intermittent claudication or rest pain—critical limb ischemia—can develop.

Noninvasive testing with the ankle-brachial index (ABI) is the clinical standard for documenting the presence and severity of peripheral arterial disease. The ABI is determined by dividing ankle systolic pressure by brachial systolic pressure. Normally, the ABI is between 1.0 and 1.1; a value less than 0.9 indicates arterial disease proximal to the point of measurement. The ABI approximates the degree of arterial insufficiency; claudication occurs with indexes ranging from 0.3 to 0.9, disabling claudication or rest pain with indexes less than 0.5, and gangrenous extremities with indexes less than 0.2.

One of the most important aspects of peripheral arterial disease is that it is a very strong marker for early mortality. In patients with peripheral arterial disease the risk for amputation is much less than the risk for death.

A low ABI is a strong predictor for disease progression, but it is also one of the strongest risk factors for all-cause mortality. Claudication is associated with a high rate of mortality but is relatively benign in terms of lower extremity outcome.

SURGICAL MANAGEMENT

Accepted treatments of lower extremity arterial disease include both nonoperative and operative modalities. Nonoperative options include lifestyle and risk factor modification, exercise programs, and pharmacologic therapy. Operative options include percutaneous endovascular modalities and surgical reconstruction. Endovascular techniques include more established therapies such as intraarterial thrombolytic therapy, balloon catheter embolectomy, transluminal balloon angioplasty, and angioplasty and stent placement, as well as new technologies such as novel angioplasty balloons, atherectomy and laser angioplasty systems, cryotherapy, and placement of nitinol and drug-eluting stents. Surgical procedures include endarterectomy, bypass grafting (primary or revision), and amputation.

Lower extremity arterial reconstruction is performed both for severe disabling claudication and critical limb ischemia (limb salvage). The choice of operative approach depends primarily on the location and distribution of arterial occlusions. Several surgical approaches are used in patients with lower extremity arterial insufficiency. For occlusion distal to the inguinal ligament, a femoral-popliteal bypass with an autologous great saphenous vein (reversed) graft is most often the procedure of choice. Graft patency rates with this approach are reported to be 59% at 5 years and 38% at 10 years. The saphenous vein may be used in situ (not reversed), but this technique is more demanding and requires excision of the valves to allow adequate flow. Human umbilical vein and polytetrafluoroethylene grafts can be used when an autologous saphenous vein is unavailable, which is often the case when patients have previously undergone coronary artery bypass or lower extremity bypass. The cephalic and basilic veins from the upper extremities are sometimes used as a graft. Harvesting vein from the upper extremities has obvious implications with regard to IV catheter placement and the use of regional anesthesia.

In patients with aortoiliac disease who are not candidates for aortobifemoral bypass because of coexisting medical diseases, an extraanatomic procedure (axillofemoral or femorofemoral bypass) is an alternative approach that is thought to be a less stressful procedure. Distal arterial reconstruction with a bypass to the tibial, peroneal, or pedal vessels is almost exclusively performed for limb salvage. Prosthetic grafts have very high failure rates, and every attempt is made to harvest adequate autologous vein.

PREOPERATIVE PREPARATION AND MONITORING

Preoperative assessment and optimization of cardiac risk were discussed previously (see also Chapters 38 and 39). It is extremely important that long-term cardiac and respiratory medications be given the morning of surgery. Continuing chronic β-adrenergic blocker therapy is particularly important because acute withdrawal can be associated with significant morbidity. Current, recent, and anticipated use of hemostasis-altering drugs should be established and discussed with the surgical team. In most instances, antiplatelet therapy with aspirin should be continued. Preoperative termination of other antiplatelet therapy, such as thienopyridine derivatives, should be made on an individual basis.

Monitoring for lower extremity arterial revascularization should include an intraarterial catheter that permits continuous blood pressure monitoring to optimize coronary artery and lower extremity graft perfusion, as well as blood sampling for diagnostic laboratory testing. A urinary bladder catheter is usually indicated because the duration of the procedure may be long and urine output may be useful for assessing intravascular volume and cardiac output. Although central venous catheters are not necessarily helpful in routine cases, central venous pressure monitoring should be considered for patients with significant renal dysfunction, in whom intravascular volume should be carefully monitored, and for patients with significantly impaired ventricular dysfunction or congestive heart failure. In these patients, pulmonary artery catheter monitoring may be helpful, but given the relatively low potential for blood loss and third-space fluid loss with lower extremity vascular procedures, the pulmonary artery catheter is usually reserved for patients with active congestive heart failure or unstable angina. Our criteria for using invasive hemodynamic monitoring have been described previously.[39] As discussed earlier, computerized ST-segment monitoring is helpful in monitoring for myocardial ischemia.

REGIONAL VERSUS GENERAL ANESTHESIA

The most appropriate regimen of intraoperative anesthesia and postoperative analgesia for high-risk patients undergoing vascular surgery remains controversial. Competing concerns regarding both the quality and escalating costs of perioperative care have challenged clinicians to establish practice standards that are both safe and efficient. Postoperative complications after vascular surgery are common and have an adverse impact on both clinical outcome and resource use. Improvement in clinical outcome and reduced use of medical resources in patients undergoing vascular surgery may result from the use of one particular regimen of anesthesia and analgesia over another. If such improvement can be achieved, selection of the most appropriate anesthetic and analgesic regimen would then be of great benefit to patients, providers, payers, and society.

The question of whether regional or general anesthesia is preferable for vascular surgery has been debated for years. Early nonrandomized trials were inadequately designed to answer the questions. They were prone to significant bias because many clinicians had the unsupported belief that regional anesthesia was safer for patients with advanced cardiac or pulmonary disease. Even the prospective studies must be interpreted cautiously because many suffer from deficiencies in design and methodology, including nonuniform patient populations,[78,115,116] lack of

standardization or control of perioperative treatments,[†] use of nonequivalent modalities for postoperative pain relief,[74,78,81,115-117] and possible investigator bias.[‡] Many clinical trials have attempted to optimize the delivery and management of anesthetic techniques, which may mask the true risks associated with the anesthetic. An example is the strict hemodynamic control, transfusion thresholds, and postoperative analgesia regimens that have been used in clinical trials.[39,40] The physician must also appreciate that the overall complication rates reported in clinical trials may seem high, but this may be explained by the aggressive surveillance commonly used in clinical trials. In general, it is often best to choose the anesthetic and analgesic techniques that are most familiar to a particular institution—for example, because unfamiliarity and mismanagement of epidural catheters can cause serious complications. I think that overall optimization of perioperative care, rather than anesthetic or analgesic selection, is the most important factor in improving outcome after vascular surgery.

In some situations, one anesthetic technique (regional or general) is preferable to the other. The patient may have a preference for one technique over another based on multiple factors. Regional techniques should be avoided in patients who are uncooperative, demented, or unable to lie flat. Needle or catheter placement can be difficult in patients with severe spine deformity or previous spinal instrumentation. Local infection, neurologic disease affecting the lower part of the body, and hemostasis-altering drugs are all considered, to varying degrees, a contraindication to regional anesthesia. Anticoagulant and antiplatelet therapy is common in the vascular surgery population and often precludes the use of spinal or epidural techniques. Symptomatic bleeding within the neuraxis (spinal or epidural hematoma) is a potentially devastating complication of neuraxial anesthesia that can lead to permanent neurologic injury. I view preoperative anticoagulation with heparin or warfarin and any active thrombolytic therapy as contraindications to the use of spinal and epidural anesthesia. In patients in whom such agents have recently been discontinued, very careful consideration should be given on an individual basis before performing neuraxial techniques. The anesthesiologist must take into consideration the specific drug used, the duration of discontinuance, current coagulation status, and concomitant administration of medications affecting hemostasis. The use of regional techniques during intraoperative systemic heparinization does not appear to represent a significant risk. Although it has been recommended that surgery be canceled when blood is obtained through the neuraxial needle, support for this recommendation is lacking. Much more importantly, it has also been recommended that epidural catheters not be removed until anticoagulants have been discontinued in the postoperative period.[118] The use of and indications for low-molecular-weight heparin (LMWH) continue to increase, and evidence suggests a significant risk for spinal or epidural hematoma when regional techniques are used in conjunction with these drugs. Current recommendations suggest that regional techniques be delayed at least 12 to 24 hours after the last dose of LMWH.[118] The use of antiplatelet agents is a complex topic, and it is important to note the pharmacologic differences among the drugs when regional techniques are desired.[118] Although some centers routinely check a bleeding time in patients who have taken aspirin in the 7 days before a planned regional anesthetic technique, no evidence indicates that bleeding time is useful in this setting. In general, when a regional technique is desired for a patient with any question of a coagulation abnormality, spinal anesthesia with the smallest diameter needle is preferable to epidural anesthesia. A comprehensive consensus report on neuraxial anesthesia and anticoagulation is available and should be read by all clinicians.[118]

Given the relative risks associated with neuraxial anesthesia in patients receiving anticoagulant or antithrombolytic therapy, some clinicians advocate the broader use of peripheral nerve blocks, such as sciatic, femoral, popliteal, and ankle (see also Chapter 57). Continuous catheter techniques can be used to provide both anesthesia and postoperative analgesia. High-resolution ultrasound imaging of neural structures, percutaneous electrode guidance, and the use of stimulating catheters have been introduced into clinical practice. Peripheral nerve blocks are probably associated with fewer systemic and neuraxial side effects, but little clinical information is available in the vascular surgical population. Because of the large volume of local anesthetics frequently used for peripheral nerve blocks, the issue of systemic toxicity must be considered. Caution should be considered with the use of peripheral nerve block in an anticoagulated patient, particularly when the neural structures are deep or located in close proximity to vascular structures.

Because regional anesthesia does not require airway instrumentation, neuromuscular blocking agents, or volatile agents, it has traditionally been a prevailing belief that regional anesthesia is preferable in patients with significant pulmonary disease. Although it is true that instrumentation of the airway may precipitate bronchospasm or increase the risk for nosocomial infection, general anesthesia with endotracheal intubation does allow complete airway and ventilation control, the ability to effectively administer inhaled bronchodilators, and the ability to easily suction airway secretions. A reduction in time to extubation after aortic surgery is a fairly consistent theme with regional anesthesia and analgesia, but this does not appear to have any impact on clinically relevant pulmonary outcomes.[40,74,78,83]

Epidural analgesia has been championed over parenteral opioid analgesia as a means of optimizing postoperative pulmonary function by improving pain control and respiratory muscle function. Although epidural analgesia can provide excellent postoperative pain control and may improve postoperative lung function (i.e., increased tidal volume and vital capacity), clinical studies do not support a consistent finding of improved pulmonary outcomes. Overall, little evidence from well-designed clinical studies exists to demonstrate improved pulmonary outcome with regional anesthesia and analgesia.[119] Because postoperative maneuvers to increase mean lung volumes are of proved benefit in preventing postoperative pulmonary complications, it has been recommended that maneuvers to encourage deep breathing, such as deep-breathing

[†] References 74, 76, 78, 81, 83, 115-117.

[‡] References 39, 74, 76-78, 81, 83, 115-117.

TABLE 69-8 **CARDIAC AND VASCULAR OUTCOMES IN STUDIES OF REGIONAL VERSUS GENERAL ANESTHESIA IN VASCULAR SURGERY PATIENTS**

		Death		MI		Myocardial Ischemia		CHF		Graft Occlusion		
Study	No. of Patients	*RA* (%)	*GA* (%)	*RA* (%)	*GA* (%)	*RA* (%)	*GA* (%)	*RA* (%)	*GA* (%)	*RA* (%)	*GA* (%)	Comments
Cook et al[120]	101	2	6	4	2							Spinal anesthesia, lower extremity surgery
Tuman et al[116]	80	0	0	0	8			5	10	3	20	Aortic and lower extremity surgery
Baron et al[74]	167	4	5	6	6	20	19	6	8			Aortic surgery
Christopherson et al[39]	100	2	2	4	4	35	45			4	22	Lower extremity surgery
Davies et al[76]	50	8	4	8	4			12	8			Aortic surgery
Garnett et al[81]	99	0	4	6	10	58	51	6	10			Aortic surgery
Bode et al[117,121]	423	3	3	5	4			10	9	6	4	Spinal and epidural anesthesia, lower extremity surgery
Bois et al[77]	114	2	2	4	8	18	19	5	0			Aortic surgery
Boylan et al[83]	40	0	0	5	5	32	38	11	5			Aortic surgery
Norris et al[40*]	168	5	5	4	0	16	17	1	0			Aortic surgery, double-blinded study

CHF, Congestive heart failure; *GA,* general anesthesia; *MI,* myocardial infarction; *RA,* regional anesthesia.
*Any epidural use included in regional anesthesia group.

exercises, incentive spirometry, and chest physiotherapy, should be the focus of preventive efforts.[119]

Cardiac morbidity is the most common cause of death in patients undergoing surgery, and the incidence of perioperative cardiac morbidity is 10 times more frequent in vascular surgery patients than in nonvascular surgery patients.[5] Eleven prospective randomized trials evaluating the effects of regional versus nonregional anesthesia or analgesia in vascular surgical patients have reported on cardiac outcomes and death. Three studies (Bode and associates,[117] Christopherson and co-workers,[39] and Cook and colleagues,[120]) compared pure regional (spinal or epidural) versus general anesthetic techniques in lower extremity vascular patients. Tuman and colleagues[116] compared combined epidural and general versus general anesthetics in aortic and lower extremity surgical patients. Six studies (Baron and co-workers,[74] Bois and co-workers,[80] Boylan and associates,[83] Davies and associates,[76] Garnett and colleagues,[80] and Norris and colleagues[40]) compared epidural and nonepidural anesthetic or analgesic techniques (or both) in aortic surgical patients. Fleron and co-workers[80] compared intrathecal opioid versus IV analgesia in aortic surgical patients. Of note, only the report by Norris and associates[40] had a double-blinded design. The results of these studies, involving more than 1300 patients, are shown in Table 69-8.

In summary, no study demonstrated any difference in outcome with regard to mortality, MI, myocardial ischemia, or congestive heart failure. Only the study by Tuman and colleagues[116] reported a difference in cardiac outcome. Outcome was significantly improved by epidural anesthesia and analgesia, but only when more subtle outcomes (i.e., dysrhythmias) were included. Christopherson and co-workers[39] (i.e., the Perioperative Ischemia Randomized Anesthesia Trial [PIRAT]) and Norris and associates[40] (i.e., PIRAT II) found no difference in cardiac events or myocardial ischemia as detected by continuous Holter monitoring over a 3-day postoperative period. In these studies from my institution, strict intraoperative and postoperative protocols were used to guide and optimize perioperative management and postoperative analgesia. Bode and colleagues[117] described the largest randomized trial, which included a spinal anesthesia group in addition to general and epidural groups. There were no differences in cardiac events in any of the three groups. Of note, a failed spinal or epidural technique in this trial was associated with 9% mortality, as opposed to 2% for all successful general and regional anesthetics.[116]

One of the most interesting and clinically significant findings in these randomized trials is the beneficial effect of regional anesthesia on lower extremity graft patency in the postoperative period. Two of the studies (Tuman and colleagues[116] and Christopherson and co-workers[39]) reported a fivefold greater incidence of graft occlusion after general (relative to regional) anesthesia. Most graft occlusions occurred in the first 1 to 3 days after surgery, after which the established difference in the incidence of graft occlusion between anesthetic techniques was maintained over time (6 weeks and beyond) (Fig. 69-15). This time course suggests that anesthetic technique may have played a role in graft occlusion. Bode's group[121] reported an overall very low incidence of graft occlusion, but differences in hemodynamic management, surgical technique, and the patient population may explain these findings. For example, intraoperative intravascular angioscopy was used to inspect the grafts to confirm patency before completion of surgery, and all patients were cared for in an intensive care setting for 48 hours after surgery. Thus, optimization of care with respect to graft patency may negate any beneficial effect of regional techniques. It is also important to keep in mind that none of these studies were specifically designed to evaluate surgical outcome (i.e., graft patency)

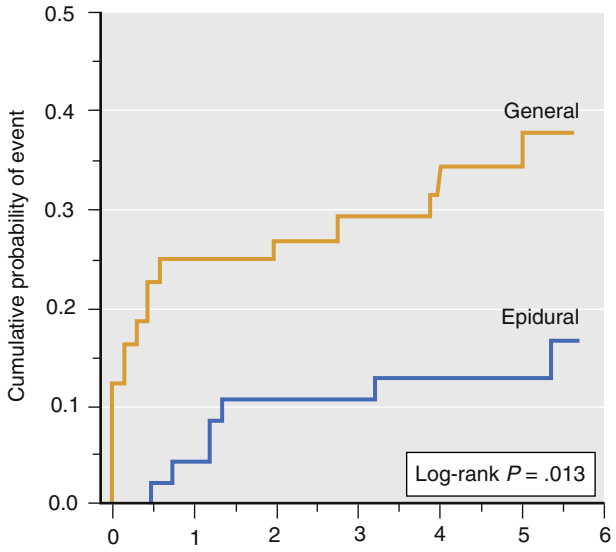


Figure 69-15. Cumulative probability of reoperation for regrafting, thrombectomy, or amputation over a 6-week follow-up period. Reoperation was significantly more frequent after general than after epidural anesthesia. (From Christopherson R, Beattie C, Norris EJ, et al: Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Perioperative Ischemia Randomized Anesthesia Trial Study Group, *Anesthesiology* 79:422-434, 1993.)

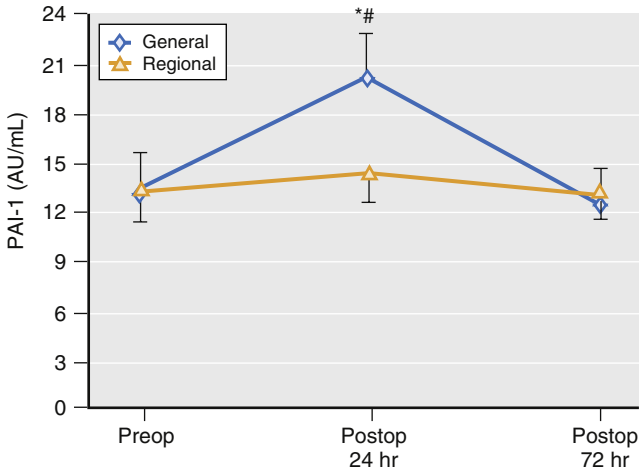


Figure 69-16. Plasminogen activator inhibitor-1 (PAI-1) levels in activity units (AU) per milliliter measured preoperatively and at 24 and 72 hours postoperatively after lower extremity revascularization. PAI-1 levels in the general anesthesia group increased from 13.6 ± 2.1 AU/mL to 20.2 ± 2.6 AU/mL at 24 hours and returned to baseline at 72 hours. In contrast, PAI-1 levels in the RA group remained unchanged over time. (Modified from Rosenfeld BA, Beattie C, Christopherson R, et al: The effects of different anesthetics regimens on fibrinolysis and the development of postoperative arterial thrombosis. Perioperative Ischemia Randomized Anesthesia Trial Study Group, *Anesthesiology* 79:435-443, 1993.)

in a prospective manner. A retrospective review of more than 300 primary femoropopliteal-tibial bypass procedures reported no differences in graft thrombosis rates for epidural (14%) or general anesthesia (9.4%).[122]

The proposed mechanism for the benefit of regional anesthesia is the effect of the anesthetic technique on coagulation. General anesthesia is associated with a hypercoagulable state in the early postoperative period, whereas regional anesthesia attenuates this effect. Tuman and colleagues[116] demonstrated this by thromboelastography and Rosenfeld and co-workers[123] by increased plasminogen activator inhibitor (Fig. 69-16) and fibrinogen levels. Fibrinolysis is decreased after general anesthesia and is normal after regional anesthesia. These findings may be related to attenuation of the surgical stress response with regional anesthesia because a link appears to exist among stress, catecholamines, and acute-phase reactants, such as plasminogen activator inhibitor and fibrinogen.[123-125] Platelet reactivity is also enhanced in the presence of a stress response.[125] Another important mechanism for the increased lower extremity graft patency with regional anesthesia may be the increased lower extremity blood flow associated with sympathectomy.

In the postoperative period, Breslow and associates[126] demonstrated differences in the adrenergic response with general versus regional anesthesia (Fig. 69-17). Epinephrine and norepinephrine are increased after general anesthesia relative to regional anesthesia. The cortisol response after general anesthesia is also greater than after regional anesthesia.[126] This stress response is associated with increased blood pressure and hemodynamic liability during the intraoperative and early postoperative periods after general anesthesia compared with regional anesthesia.[40,127] When the hemodynamic parameters are controlled pharmacologically, however, no difference is found related to anesthetic technique in myocardial ischemia or cardiac morbidity.[39,40,117]

Postoperative pain is recognized as one of the many factors contributing to the surgical stress response. In studies comparing epidural analgesia with parenteral opioid analgesia for control of postoperative pain after major surgery, improved pain control with epidural techniques is often reported. A recent meta-analysis review supports the view that epidural analgesia provides better postoperative analgesia than parenteral opioids.[128] However, the historical studies that form the basis of the meta-analysis review have often neglected to control, specify, and, most importantly, optimize treatment in the nonepidural arms of their studies. Unfortunately, this issue remains a significant limitation in more recent trials.[78,129] Epidural analgesic techniques will probably continue to outperform "suboptimal" nonepidural analgesic techniques. I believe that IV patient-controlled analgesia is the optimal mode of delivery for opioid analgesia and should be used as the nonepidural arm for all postoperative pain studies. Postoperative epidural analgesia does not consistently outperform IV patient-controlled opioid analgesia. Of particular note, patient-controlled epidural analgesia outperforms both intermittent-bolus and continuous-infusion epidural analgesia. Thus, the mode of delivery is an important factor with both epidural and parenteral opioid analgesia. The clinician also needs to keep in mind that the superior pain control reported with epidural techniques is relative, with adequate pain control consistently reported for parenteral analgesia. In the only double-blinded trial in vascular surgery patients, Norris and colleagues[40] reported no difference in postoperative pain scores in patients randomized to either patient-controlled epidural analgesia or

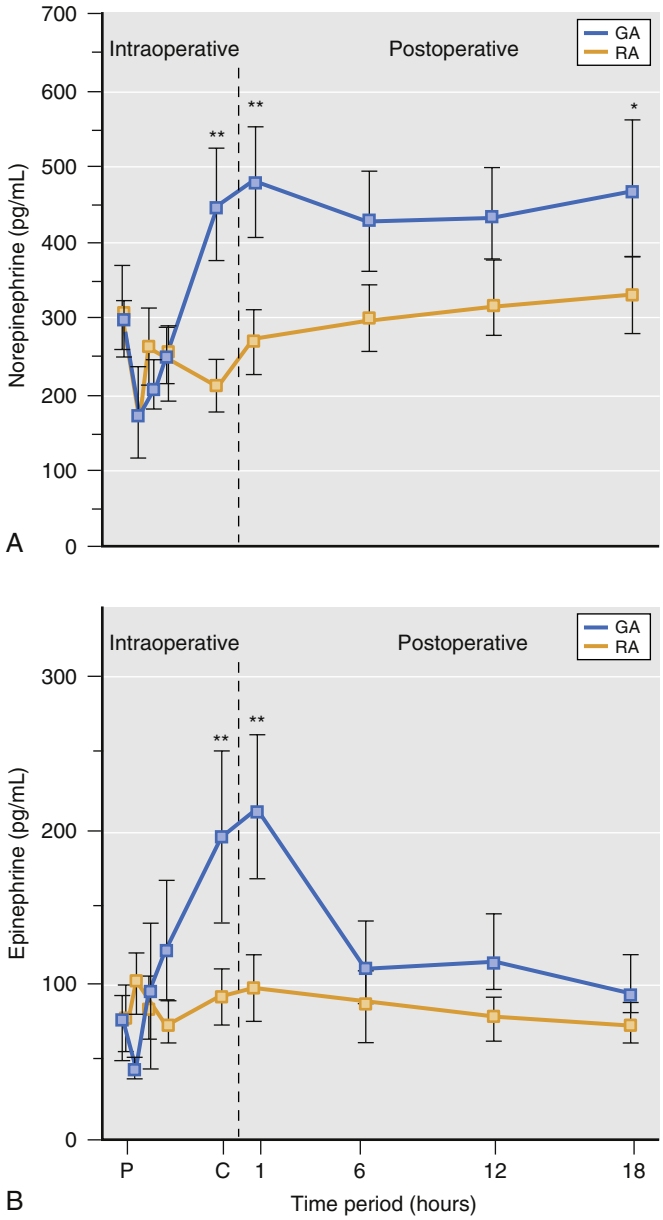


Figure 69-17. Plasma norepinephrine (**A**) and epinephrine (**B**) concentrations before induction of anesthesia (*P*), at skin closure (*C*), and at *1, 6, 12,* and *18* hours after lower extremity revascularization. *GA,* General anesthesia with postoperative parenteral morphine by patient-controlled analgesia; *RA,* regional (epidural) anesthesia with postoperative epidural analgesia by patient-controlled analgesia. (Modified from Breslow MJ, Parker SD, Frank SM, et al: Determinants of catecholamine and cortisol responses to lower extremity revascularization. The PIRAT Study Group, *Anesthesiology* 79:1202-1209, 1993.)

patient-controlled IV analgesia after aortic surgery. In this trial, postoperative pain management (i.e., epidural and IV) was optimized, continued for 72 hours, and managed by an acute pain service. Postoperative epidural catheter failure may occur in up to 6% of patients.

ANESTHETIC MANAGEMENT

A variety of anesthesia techniques, including general anesthesia, regional (i.e., epidural or spinal) anesthesia, and combined techniques, are widely used for lower extremity reconstruction. General anesthesia is usually delivered with use of a balanced technique consisting of opioids, volatile inhaled anesthetics, N_2O, and neuromuscular blockade. Induction of anesthesia should proceed in a controlled fashion such that a stable hemodynamic profile is maintained. Maintenance of anesthesia may be accomplished with a low-dose inhaled anesthetic (i.e., isoflurane, desflurane, or sevoflurane) in 50% N_2O and opioid (fentanyl 3 to 5 μg/kg). Because virtually all patients are extubated in the operating room, high doses of opioid are generally avoided. The goal is to maintain stable hemodynamics and prevent myocardial ischemia during the intraoperative and postoperative periods. Judicious use of β-blockers and vasoactive drugs is often necessary.

Regional anesthesia can be accomplished with spinal or epidural techniques. Disadvantages of spinal anesthesia include the limited duration of action in the setting of a surgical procedure that is somewhat unpredictable in length and complexity. The level of sympathetic block is somewhat less controllable than with the epidural technique. Hypotension can occur with either technique and should be treated promptly with judicious use of fluids and vasopressors. An advantage of an epidural technique is the ability to continue drug delivery into the postoperative period for analgesia and attenuation of the stress response. A lumbar epidural catheter is ideal for lower extremity vascular procedures. The dermatomes that need to be anesthetized are innervated at the same level where the catheter is inserted, because the incision is usually in the L1 to L4 region. Small volumes of local anesthetic are recommended because a T10 block is generally sufficient. Usually, 9 to 12 mL (including the test dose) is sufficient for the initial dose, and more drug is given as needed. Because vascular surgery patients are generally advanced in age and thus prone to higher block levels, larger doses may result in high sympathetic blockade with significant hypotension.[130] A high sympathetic block is problematic because of decreased coronary perfusion and excessive fluid and vasopressor requirements. Congestive heart failure may result in the postoperative period when the sympathectomy resolves and the intravascular space contracts. When administering an epidural test dose, careful attention should be directed to both heart rate and blood pressure. Blood pressure may be a more reliable indicator of an intravascular injection because vascular surgery patients may have little or no increase in heart rate as a result of β-blocker therapy and decreased β-adrenergic responsiveness secondary to aging. When hypotension results from sympathectomy, a low-dose phenylephrine infusion is helpful in reducing IV fluid requirements. I think this approach is more physiologic than administration of large fluid volumes.

POSTOPERATIVE CONSIDERATIONS

Pain and anxiety require especially careful attention in the postoperative period because the stress response and myocardial ischemia are of greatest concern at this time. Intravascular volume should be optimized, significant anemia avoided (hemoglobin maintained at > 9.0 g/dL), and heart rate and arterial blood pressure carefully

controlled. Computerized ST-segment analysis is helpful in identifying ischemic changes. Peripheral pulses should be checked frequently to verify lower extremity graft patency. Increasing arterial blood pressure augmentation and anticoagulants may be necessary when peripheral perfusion is limited. Urgent surgery may be required to reopen clotted or stenotic grafts.

Postoperative analgesia can be provided by IV or epidural opioids delivered by patient-controlled analgesia or epidural opioids with local anesthetics delivered by continuous infusion or patient-controlled analgesia. For epidural patient-controlled analgesia, a dilute concentration of local anesthetic should be used to allow neurologic evaluation of the lower extremities to rule out spinal or epidural hematoma. Bupivacaine 0.0625% is ideal in this regard. Fentanyl 5 μg/mL can be added and the solution infused at 2 mL/hr, with an on-demand (patient-controlled analgesia) bolus of 2 to 4 mL and a lockout interval of 10 minutes.

CAROTID ENDARTERECTOMY

The strong association between stroke and carotid artery disease is well known. The principal cause of carotid artery disease is atherosclerosis, which most commonly involves the bifurcation of the common carotid artery with frequent extension into both the internal and external carotid arteries. The clinical manifestations of carotid artery disease represent a spectrum of conditions, with fatal or debilitating stroke secondary to cerebral infarction at one end of the spectrum and ranging successively through nondebilitating stroke, transient ischemic attack, and amaurosis fugax (transient attack of monocular blindness) to an asymptomatic bruit. Cerebrovascular sequelae of carotid atherosclerosis may result either from embolization of thrombus or atheromatous debris or from a reduction in flow (hypoperfusion) secondary to stenosis. The latter probably accounts for less than 10% of the cerebrovascular sequelae of carotid atherosclerosis. Although much is known about the genesis and evolution of atherosclerosis, significantly less is known about the circumstances that lead to plaque instability and rupture. Regardless of the mechanism, the degree of cerebral injury depends on such factors as plaque morphology, characteristics of the embolus, duration of hypoperfusion, cerebrovascular vasoreactivity, integrity of the circle of Willis, and cerebral collateral circulation. A multisociety guideline is available for the management of carotid artery disease.[131]

Stroke is a major public health burden worldwide. It is the fourth leading cause of death and the leading cause of serious, long-term disability in the United States. Stroke is also a major contributor to health care costs. The direct and indirect costs of stroke in the United States in 2008 are estimated at $65.5 billion.[132] Approximately 780,000 people experience a new (≈600,000) or recurrent (≈180,000) stroke each year in the United States.[132] Annually, more than 950,000 hospitalizations and 165,000 deaths occur from stroke. Well-defined risk factors exist in patients with stroke, the most important of which is hypertension. Approximately 83% of strokes are ischemic (i.e., cerebral thrombosis or embolism), and 7.6% of ischemic strokes result in death within 30 days of initial evaluation.[133] Extracranial atherosclerotic disease accounts for up to 20% of all ischemic strokes. Less than 20% of strokes are preceded by a transient ischemic attack. Despite a well-documented decline in stroke mortality, the annual incidence rate of stroke may be increasing. This increase is probably due to growth in high-risk populations. The incidence of perioperative stroke in unselected patients, patients with asymptomatic carotid bruit, and patients with at least 50% carotid stenosis undergoing general anesthesia and surgery is approximately 0.1%, 1.0%, and 3.6%, respectively.

Although treatment options to reverse the effect of acute ischemic stroke are limited, outcomes may be improved with appropriate therapy. The only approved therapy is IV recombinant tissue plasminogen activator. Given the narrow 3- to 4.5-hour treatment window from the onset of symptoms, prompt evaluation and diagnosis of ischemic stroke are critical. With the exception of acute stroke after carotid endarterectomy, surgical treatment of patients with acute ischemic stroke is controversial and not generally recommended because of limited data and perceived high risk. Endovascular treatment of patients with acute ischemic stroke is undergoing intense investigation. Emergency angioplasty and stenting, mechanical disruption of arterial clot, and mechanical extraction of thrombi are interventions currently being evaluated.[134] The AHA and American Stroke Association have guidelines for the early management of patients with ischemic stroke.[135]

INDICATIONS

Endarterectomy of the carotid bifurcation has been used to reduce symptoms and prevent stroke for more than 50 years. Although the efficacy of carotid endarterectomy for prevention of ipsilateral stroke in patients with and without symptoms has been demonstrated in large-scale randomized clinical trials,[136,137] multiple factors including perioperative risk, comorbidities, and life expectancy must be considered in the overall assessment. In centers of excellence, it is a low-risk procedure with excellent long-term durability. Carotid endarterectomy is the most common peripheral vascular surgical procedure performed in the United States, with an estimated 130,000 procedures performed annually. The rate and number of carotid endarterectomies have fluctuated significantly since the early 1970s. With marked growth in the specialty of vascular surgery and an expanding list of surgical indications, the number of carotid endarterectomies performed in nonfederal hospitals increased from 15,000 in 1971 to 107,000 in 1985 and then declined substantially over the next 5 to 6 years. The decline was probably due to publications questioning the indications for the procedures and isolated reports citing excessively frequent rates of operative morbidity and mortality.

In 1992, a marked increase in the number of carotid endarterectomies occurred after the results of two large-scale, prospective randomized trials were published. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial both reported definitive results for symptomatic patients with high-grade carotid stenosis (70% to 99%).[136,138] In NASCET, follow-up at 2 years showed a stroke rate for surgical patients of 9% versus 26% for medical patients. This

benefit of carotid endarterectomy has persisted at 8 years of follow-up.[139] In the European Carotid Surgery Trial, the long-term stroke rate was 2.8% for surgical patients, excluding a perioperative stroke and death rate of 7.5%, and 16.8% for medically managed patients.

The efficacy of carotid endarterectomy in asymptomatic patients with carotid stenosis has been evaluated in five randomized trials.[137,140-143] The Carotid Artery Surgery Asymptomatic Narrowing Operation Versus Aspirin trial, the first to publish its results, concluded that carotid endarterectomy was not indicated for asymptomatic patients with 50% to 90% carotid stenosis.[140] Unfortunately, this study was seriously flawed and the results questioned. The Mayo Asymptomatic Carotid Endarterectomy Study was terminated early because of a significantly increased number of MIs and transient cerebral ischemic events in the surgical group.[141] Most of these events were not related to the surgery itself but rather to the absence of aspirin in the surgical group. The Department of Veterans Affairs trial was designed to compare the effects of carotid endarterectomy plus aspirin versus medical treatment (i.e., aspirin) in asymptomatic male patients with 50% or greater carotid stenosis.[142] This trial demonstrated a significant reduction in ipsilateral neurologic events in the surgical group (8%) versus the medical group (20.6%). However, the combined incidence of stroke and death was not different between study groups. The Asymptomatic Carotid Atherosclerosis Study (ACAS) demonstrated that patients with asymptomatic carotid stenosis (≥60%) who were treated with carotid endarterectomy and aspirin have a reduced 5-year risk for ipsilateral stroke compared with patients treated with aspirin alone (5.1% versus 11.0%).[137] These results reflect only a 5.9% absolute risk reduction in 5 years, which is just above 1% per year. Of note, improvement in outcome for patients randomized to undergo endarterectomy in this trial did not reach significance until 3 years after surgery. The European Asymptomatic Carotid Surgery Trial, the largest trial to date, largely replicated the results of ACAS, but in a somewhat more pragmatic setting.[143] This trial demonstrated that patients with asymptomatic carotid stenosis (≈70%) on ultrasound who were treated by immediate carotid endarterectomy plus medical treatment have a reduced 5-year risk for stroke compared with patients treated with medical therapy alone (6.4% versus 11.8%). Of note, half of this 5-year benefit involved disabling or fatal strokes.

Although landmark randomized clinical trials have defined individuals who are likely to benefit from carotid endarterectomy (and set the standard for developing evidence-based practice guidelines throughout the world), it has been suggested that the significant increase in the number of carotid endarterectomies performed over the last decade may be due in part to the extrapolation of trial results to patients and settings not directly supported by the trials. For example, both NASCET and ACAS restricted enrollment to patients younger than 80 years of age, and both trials carefully selected institutions and surgeons to optimize the results of surgery. Additionally, subgroup analysis of ACAS could not demonstrate a significant benefit for women.[137]

With the advent of a second interventional treatment modality, percutaneous carotid angioplasty and stenting (discussed later), and the evolution of intensive medical therapy, this issue has become more complex.

PERIOPERATIVE MORBIDITY AND MORTALITY

Although the randomized trials just noted have demonstrated a protective effect of carotid endarterectomy on ipsilateral stroke, the critical determinants of benefit for any given patient must include the overall perioperative event rate and expected long-term survival. Thus, the perioperative stroke and death rate for carotid endarterectomy needs to be very low to maintain the beneficial effects of surgery over medical therapy alone. Further, to compensate for the perioperative risk associated with surgery, the patient must have a reasonable life expectancy (12 to 18 months). The 30-day stroke and death rate of 2.3% for asymptomatic patients in ACAS (1987 to 1993) and 5.0% for symptomatic patients in NASCET (1988 to 1991) are often cited as benchmarks. More recent reports suggest a considerably less frequent event rate. For example, a prospective database study of 13,316 carotid endarterectomies performed in 2007 and 2008 reported a 30-day stroke and death rate of 1.3% in asymptomatic patients and 2.9% in symptomatic patients.[144] The 30-day mortality was significantly more frequent in patients who developed a stroke than in those who did not (12.9% versus 0.6%). Patients with high-risk anatomy, such as restenosis and contralateral carotid arterial occlusion, have the highest risk for perioperative stroke and death. Neurologic deficits occur more commonly in patients with poorly controlled preoperative hypertension and in those with hypertension or hypotension postoperatively. The incidence of perioperative MI in patients undergoing carotid endarterectomy ranges from 0% to 5%. Recent reports suggest the incidence of MI is relatively low. The General Anesthesia versus Local Anesthesia for Carotid Surgery (GALA) trial (discussed later) results reported only 13 patients of 3526 (0.37%) had a perioperative MI.[145] The four fatal perioperative MIs accounted for only 8.9% of the total 30-day mortality. Although the role of carotid endarterectomy in patients older than 80 years of age remains a concern, recent reports suggest that carotid endarterectomy can be performed safely in the very elderly and those deemed high risk, with combined stroke or death rates being comparable to those found in randomized trials (NASCET and ACAS).

PREOPERATIVE ASSESSMENT

The optimal preoperative assessment for patients undergoing carotid endarterectomy continues to be debated (see also Chapter 38). Patients with recently symptomatic carotid disease present a particular challenge because strong evidence exists to support surgical intervention within 2 weeks after manifestation of symptoms, thus limiting the time available for evaluation and optimization of relevant comorbidities as well as the initiation of new medications.[146] The medical management of patients with asymptomatic carotid disease should be optimized and includes β-blockers, statins, and antiplatelet agents. Poorly controlled hypertension should be addressed with

the patient's internist. The gradual decreasing of the arterial blood pressure over several weeks before surgery will restore intravascular volume, reset cerebral autoregulation to a more normal range, and improve perioperative management. Poorly controlled diabetes also warrants preoperative optimization, which may improve perioperative outcome.[147]

CAD is common in patients undergoing carotid endarterectomy and is a leading cause of both early and late mortality. Hertzer and co-workers[148] performed coronary angiograms in 506 patients scheduled for carotid endarterectomy and found significant (>70%) stenosis in one or more coronary artery, CAD in 83% of patients suspected of having CAD, and CAD in 40% thought to have no CAD. Despite the known frequent incidence of CAD in patients undergoing carotid endarterectomy, preoperative studies for the evaluation of myocardial function or ischemic potential are rarely undertaken. Exceptions to this practice are patients with unstable angina, recent MI with evidence of ongoing ischemia, decompensated congestive heart failure, and significant valvular disease. In general, specialized cardiac testing would be unlikely to result in cancellation of the procedure or alter perioperative management. Further, the relatively infrequent overall rates of perioperative nonfatal and fatal MI after carotid endarterectomy make aggressive strategies leading to prophylactic coronary revascularization less appealing.[145] A recent clinical trial reported on the safety and efficacy of coronary angiography and revascularization in preventing postoperative cardiac ischemic events after carotid endarterectomy. In a randomized fashion, 426 patients with no history of CAD were randomized to either coronary angiography before carotid endarterectomy (216 patients) or carotid endarterectomy without coronary angiography (210 patients). In the angiography group, 68 patients had a significant stenosis of the coronary arteries and underwent revascularization with PCI (66 patients) or CABG (2 patients). PCI was performed 1 to 8 days before surgery and always consisted of angioplasty and stenting. No patients in the angiography group had a postoperative cardiac ischemic event or complication related to PCI, whereas 9 patients in the group without angiography had an ischemic event (one fatal MI and eight ischemic events treated medically). Although all PCI patients received dual-antiplatelet therapy, no major bleeding or neck hematomas were observed. Long-term follow-up was not reported.

Patients with combined carotid stenosis and CAD requiring coronary revascularization represent somewhat of a management dilemma because it is often unclear which disease should be treated first.[149] The severity of carotid and coronary disease must be evaluated in terms of clinical symptoms and anatomic lesions, and a decision must be made to perform a combined, staged (carotid endarterectomy first), or reverse-staged (CABG first) procedure. Carotid revascularization is recommended before CABG (staged procedure) in patients with symptomatic carotid disease and bilateral severe asymptomatic carotid stenosis. The optimal management of severe unilateral asymptomatic carotid stenosis in patients undergoing CABG is unclear. The only randomized clinical trial to date randomized 185 patients with severe unilateral asymptomatic carotid stenosis undergoing CABG to a staged or combined procedure (94 patients) or a reverse-staged procedure (90 patients).[150] Although the perioperative mortality rates were equivalent (~1.0%), the 90-day stroke and death rates were significantly lower in the staged and combined group (1.0% versus 8.8%). Given the overall paucity of high-quality evidence, management of an individual patient should be guided by careful assessment of the relative severity of the coronary and carotid disease with particular emphasis on both surgeon-specific and institution-specific results in these patient populations. Carotid artery angioplasty and stenting is widely being applied as an alternative revascularization modality before staged CABG. More recently, a combined procedure (carotid angioplasty/stenting and CABG) has been introduced. In a small feasibility and safety study (90 patients), carotid artery angioplasty and stenting under local anesthesia followed immediately by CABG reported a 30-day stroke and death rate of 2.2%.[151]

ANESTHETIC MANAGEMENT

Anesthetic management goals for carotid endarterectomy include protection of the heart and brain from ischemic injury, control of the heart rate and arterial blood pressure, and ablation of the surgical pain and stress responses. These goals must be achieved with another important goal in mind—to have an awake patient at the end of surgery for the purpose of neurologic examination.

The preoperative visit is particularly important in patients undergoing carotid surgery. During this visit, a series of arterial blood pressure and heart rate measurements are obtained from which acceptable ranges for perioperative management can be determined. Patients are instructed to continue all long-term cardiac medications up to and including the morning of surgery. Aspirin therapy should be continued throughout the perioperative period. As noted earlier, discontinuation of aspirin therapy may be related to an increased rate of MI and transient ischemic events in patients undergoing carotid endarterectomy. When patients arrive at the hospital on the day of surgery, they are queried regarding any new cardiovascular or cerebrovascular symptoms. Long-term cardiovascular medications not taken at home should be administered in the preoperative holding area whenever possible. Patient reassurance is particularly important at this time because anxiety is associated with increases in heart rate, systemic vascular resistance, and myocardial O_2 consumption, which in this patient population could precipitate myocardial ischemia.

ECG monitoring should include continuous leads II and V_5 for detection of rhythm disturbances and ST-segment changes. Online ST-segment analysis can be particularly helpful. An intraarterial catheter for beat-to-beat blood pressure monitoring should be considered routine. Noninvasive arterial blood pressure measurement in the contralateral arm is recommended. Central venous and pulmonary artery catheters are rarely indicated for carotid surgery. The rare patient with uncompensated heart failure or recent MI with ongoing ischemia requiring emergent surgery is a possible exception. If such monitors are used, the subclavian or femoral insertion sites are most

practical because inadvertent carotid puncture could compromise blood flow as a result of hematoma. In my experience, the most common reason for central access is difficult or inadequate peripheral access. IV access for fluid and drug administration can be accomplished with a single, secure, medium-bore (16-gauge) catheter. Because both arms will be tucked to the patient's sides, the IV catheter must run well after patient positioning.

General Anesthesia

Any of the drugs commonly used to induce anesthesia, maintenance anesthetics, and nondepolarizing muscle relaxants can be used safely during carotid endarterectomy, given that stable hemodynamics are maintained and the patient is awake at the end of the procedure. A conventional technique is as follows. Sedative premedication (e.g., midazolam) has the potential to compromise early neurologic assessment and is universally avoided. After placement of routine monitors and administration of O_2 by facemask, small doses of opioid (e.g., fentanyl 0.5 to 1 μg/kg) are administered during arterial line placement. Induction of anesthesia is accomplished with incremental dosages of propofol supplemented with additional opioid (total fentanyl dose 2 to 4 μg/kg). Etomidate also may be used and is preferred in patients with limited cardiac reserve. Neuromuscular relaxation with a short-acting to intermediate-acting nondepolarizing muscle relaxant such as vecuronium facilitates tracheal intubation. Esmolol is particularly effective in blunting the increases in heart rate and blood pressure during laryngoscopy and endotracheal intubation and is used liberally during the induction period. Arterial blood pressure responses during and after endotracheal intubation are unpredictable in this patient population, and the clinician must be prepared for immediate treatment of extremes in blood pressure. My preference is to use short-acting drugs, such as phenylephrine 50 to 100 μg for hypotension and sodium nitroprusside 5 to 25 μg for hypertension. Patients with poorly controlled hypertension (diastolic blood pressure >100 mm Hg) require special care. These patients are often intravascularly volume depleted and may have significant hypotension with induction of anesthesia. Administration of fluids intravenously (5 mL/kg), careful titration of anesthetics, and immediate treatment of hypotension are especially important.

Anesthesia is maintained with 50% N_2O in O_2 and low-dose (i.e., less than half the minimum alveolar concentration [MAC]) inhaled volatile anesthetics. Isoflurane is often preferred because fewer ischemic electroencephalographic (EEG) changes occur during carotid occlusion than with halothane or enflurane. Studies using EEG and regional cerebral blood flow (rCBF) measurements suggest that the critical rCBF (the rCBF below which EEG changes of cerebral ischemia occur) is lower for isoflurane than for halothane or enflurane. Sevoflurane is a good alternative because its critical rCBF in patients undergoing endarterectomy is similar to that determined with isoflurane[152] and it may facilitate more rapid emergence.[153] Additional opioid is rarely administered after skin incision. I do not use a cervical plexus block or request local anesthetic infiltration for skin incisions because the surgical stimulation is minimal and arterial blood pressure needs to be frequently supported. A combined remifentanil and propofol anesthetic technique has been reported but offered little advantage over inhaled anesthetics.[154]

Despite only modest surgical stimulation, hemodynamic fluctuations are common during carotid endarterectomy. Arterial blood pressure and heart rate are controlled within predetermined and individualized ranges during the surgical procedure with short-acting drugs whenever possible (esmolol, phenylephrine, nitroglycerin, and sodium nitroprusside). Arterial blood pressure should be maintained in the high-normal range throughout the procedure and particularly during the period of carotid clamping in an attempt to increase collateral flow and prevent cerebral ischemia. In patients with contralateral internal carotid artery occlusion or severe stenosis, induced hypertension to approximately 10% to 20% above baseline is advocated during the period of carotid clamping when neurophysiologic monitoring is not used. Arterial blood pressure preservation or augmentation can be accomplished by maintaining light levels of general anesthesia or by administering sympathomimetic drugs such as phenylephrine and ephedrine. Some caution must be exercised when using vasopressors to augment blood pressure during carotid endarterectomy because the increases in blood pressure and heart rate may increase myocardial O_2 requirements, as well as the risk for myocardial ischemia[155] or infarction. The restrictive use of vasopressors for specific instances of cerebral ischemia has been advocated.[156] In one report, induced hypertension during the period of carotid occlusion was not associated with myocardial ischemia.[157]

Surgical manipulation of the carotid sinus with activation of the baroreceptor reflexes can cause abrupt bradycardia and hypotension. Cessation of surgical manipulation promptly restores the hemodynamics, and infiltration of the carotid bifurcation with 1% lidocaine usually prevents further episodes. Infiltration may, however, increase the incidence of both intraoperative and postoperative hypertension. I do not advocate routine infiltration of the carotid bifurcation.[158]

With closure of the deep fascial layers in the neck, isoflurane is discontinued, N_2O is increased to 70%, and ventilation is controlled manually. On application of the surgical dressings, drugs used to reverse neuromuscular blockade (i.e., neostigmine) are administered, and O_2 is increased to 100%. At this time external stimuli to the patient are decreased by quieting the room, turning off the overhead surgical lights, and placing the patient in a head-up recumbent position. Ventilation is gently assisted until the patient exhibits spontaneous eye opening or movement. With rare exceptions, all tracheas are extubated after neurologic integrity is established. Neurologic deficits on emergence require immediate discussion with the surgeon about the need for angiography, reoperation, or both. The period of emergence and extubation may be associated with marked hypertension and tachycardia, which may require aggressive pharmacologic intervention. Tight hemodynamic control during this period is likely to be more demanding than during induction. Greater hemodynamic stability and decreased pharmacologic intervention during emergence have been reported in patients undergoing carotid endarterectomy

with propofol versus isoflurane. In addition, a significantly less frequent incidence of myocardial ischemia on emergence was found in the propofol group than in the isoflurane group (1 of 14 versus 6 of 13). Of particular note, all patients with myocardial ischemia on emergence had systolic blood pressure higher than 200 mm Hg.

Regional and Local Anesthesia

Regional and local anesthetic techniques for carotid endarterectomy have been in use for more than 50 years, and many centers consider them to be the techniques of choice. Regional anesthesia is accomplished by blocking the C2 to C4 dermatomes by use of a superficial, intermediate, deep, or combined cervical plexus block (see also Chapter 57). Adequate anesthesia can be obtained with an isolated superficial or intermediate cervical plexus block, likely as a result of spread of local anesthetic to the cervical nerve roots.[159] Local infiltration of the incisional site and surgical field can also provide the necessary sensory blockade. A recent systematic review including over 10,000 cervical plexus blocks for carotid endarterectomy found that the deep (or combined) block was associated with a higher serious complication rate rated to the injecting needle compared with a superficial (or intermediate) block (0.25% versus 0%).[160] The conversion rate to general anesthesia was also higher with the deep block (2.1% versus 0.4%). No difference was found in the incidence of serious systemic complications between the blocks. Although the incidence of serious complications from a cervical plexus block is infrequent, near-toxic levels of local anesthetic occurs in almost half of patients after superficial and deep cervical plexus block.[161] Although no major complications related to local anesthetic toxicity occurred, some caution should be exercised when requesting the surgeon to supplement with additional local anesthetic.

Regional and local anesthesia allows continuous neurologic assessment of the awake patient, which is widely considered to be the most sensitive method for detecting inadequate cerebral perfusion and function. Awake monitoring reduces the need for shunting and avoids the expense associated with indirect monitors of cerebral perfusion. Other advantages that have been reported include greater stability of blood pressure and decreased vasopressor requirements, reduced operative site bleeding, and reduced hospital costs. Potential disadvantages of local or regional anesthesia include an inability to use pharmacologic cerebral protection with anesthetics, patient panic or loss of cooperation, seizure or loss of consciousness with carotid clamping, and inadequate access to the airway should conversion to general anesthesia be necessary. The reported incidence of intraoperative neurologic changes during carotid endarterectomy under local or regional anesthesia varies widely (2.4% to 24%). Rates of conversion from regional anesthesia to general anesthesia of approximately 2% to 6% have been reported. Phrenic nerve paresis is common after cervical plexus block and is of little clinical consequence except in patients with severe COPD or contralateral diaphragmatic dysfunction.

Regional and local anesthesia requires significant patient cooperation throughout the procedure and is best maintained with constant communication and gentle handling of tissues. Supplemental infiltration of local anesthetic by the surgeon, especially at the lower border and ramus of the mandible, is frequently helpful. Sedation, if used at all, must be kept to a minimum to allow continuous neurologic assessment. The surgical drapes are "tented" over the head and face area to minimize claustrophobic anxiety. Levels of consciousness, speech, and contralateral handgrip are assessed throughout the procedure. If both arms are tucked to the patient's side, handgrip can be assessed with the use of a squeaky toy. Blood pressure is augmented with phenylephrine when patients exhibit neurologic changes during carotid artery test clamping or after shunt placement. A 2- to 3-minute test clamp in awake patients allows prompt identification of those who would benefit from shunt placement. Patient acceptance of regional anesthesia is frequent and common, as evidenced by a 92% preference for repeat cervical plexus block for future carotid endarterectomy. Perhaps, no absolute contradiction to regional anesthesia for carotid endarterectomy exists. I avoid regional anesthesia under the following circumstances: strong preference for general anesthesia expressed by the patient (i.e., claustrophobia), language barriers that make communication difficult, and difficult vascular anatomy. Difficult anatomy is usually manifested by a patient with a short neck and a high (more cephalad) bifurcation and may require vigorous submandibular surgical retraction.

Regional Versus General Anesthesia

For decades, the impact of anesthetic technique on outcome for carotid endarterectomy has been debated and studied. Until recently, nonrandomized studies dominated and largely supported that regional anesthesia was associated with significant reductions in the risk for perioperative death, stroke, MI, and pulmonary complications.[162] The lack of randomized data was addressed with the landmark GALA trial.[145] This multicenter, randomized controlled trial included 3526 patients with symptomatic or asymptomatic internal carotid stenosis from 95 medical centers in 24 countries. Patients were randomly assigned to carotid endarterectomy under general anesthesia (1753 patients) or local anesthesia (1773 patients) between 1999 and 2007. The primary outcome was a composite of perioperative death, MI, and stroke (including retinal infarction). The main finding was that anesthetic technique was not associated with a significant difference in the composite end point (4.8% for general versus 4.5% for local). Anesthetic technique was not associated with a significant difference in secondary outcomes, including duration of surgery, duration of ICU stay, length of hospital stay, or quality of life at 1 month after surgery. Other outcomes, including cranial nerve injury (10.5% versus 12.0%), wound hematoma (8.3% versus 8.5%), wound hematoma requiring reoperation (2.6% versus 2.3%), and chest infection, (2.0% versus 1.9%) were similar between patients receiving general anesthesia and local anesthesia, respectively. Of note, 4.4% of patients under local anesthesia (93% received a cervical plexus block) had complications that lead to cancellation of surgery or conversion to general anesthesia. Important limitations of the GALA trial include lack of standardization, absence of blinding, and possible investigator bias. Using patient-level data from the GALA trial, a recent report found that local anesthesia had a cost-effectiveness benefit over general anesthesia.[163]

Although randomized clinical trials, such as GALA, are considered to be the gold standard in clinical research, the conclusions are not always generalizable and therefore may not reflect actual practice in treating unselected patients. A recent report from a large international vascular registry, including 20,141 carotid endarterectomies performed in 10 countries between 2003 and 2007, found that anesthetic technique had no effect on perioperative mortality (0.5% overall) or stroke rate (1.5% overall).[164] These real-world results complement the data from the GALA trial. Thus, using major perioperative complications as a guide, there is no reason to routinely prefer one anesthetic technique over the other for carotid endarterectomy. The ultimate decision to use general anesthesia or regional anesthesia should be based on surgeon and the anesthesiologist experience and patient preference.

CARBON DIOXIDE AND GLUCOSE MANAGEMENT

Cerebrovascular CO_2 reactivity is part of the complex autoregulatory system to control cerebral blood flow. Normal cerebral autoregulation responds to acute changes in $Paco_2$ by decreasing cerebral blood flow (i.e., vasoconstriction) with hypocapnia and increasing cerebral blood flow (i.e., vasodilatation) with hypercapnia. In patients with carotid artery stenosis or occlusion, ipsilateral cerebral blood flow may be impaired because of poor intracerebral collateral blood flow. In the setting of poor collateralization and resultant cerebral hypoperfusion, cerebral resistance vessels in the hypoperfused territories will dilate in an effort to maintain cerebral blood flow. These chronically dilated resistance vessels may demonstrate a diminished or absent (i.e., vasomotor paralysis) cerebral blood flow response to CO_2. Impaired cerebrovascular reactivity to hypercapnia may play a role in the development of stroke ipsilateral to carotid stenosis or occlusion. Although one might expect that impaired CO_2 reactivity would increase the risk for cerebral ischemia after carotid artery clamping, the results of intraoperative cerebral monitoring suggest that no such relationship exists. Impaired cerebrovascular reactivity to CO_2 will significantly improve after carotid endarterectomy.

Control of ventilation and CO_2e during general anesthesia is a matter of some controversy. Hypercapnia may cause a "steal" phenomenon (i.e., shunting of blood away from hypoperfused territories with dilated vasculature) and is generally avoided. Hypocapnia, with its associated cerebral vasoconstriction, has been advocated to promote a reversal of this steal phenomenon. However, little clinical evidence exists for this "reverse" steal effect. Additionally, experimental data do not support the use of hypocapnia as a therapeutic maneuver to produce a favorable redistribution of blood flow during focal cerebral ischemia. Indeed, in this animal model of focal cerebral ischemia, hypocapnia ($Paco_2$ of 23 mm Hg) actually increased the size of the region at risk for ischemia. It is therefore common practice to maintain normocapnia or mild hypocapnia during carotid endarterectomy.

Evidence demonstrates increased ischemic injury to neural tissue when ischemia occurs in the presence of hyperglycemia. Data from The Johns Hopkins Hospital found that operative-day glucose greater than 200 mg/dL at the time of carotid endarterectomy was associated with an increased risk for perioperative stroke or transient ischemic attack, MI, and death.[147] Thus, until additional data become available, it may be beneficial to maintain a blood glucose level below 200 mg/dL in patients undergoing carotid endarterectomy. If hyperglycemia is treated with insulin preoperatively or intraoperatively, the blood glucose level should be carefully monitored, especially during general anesthesia, to avoid the dangers of hypoglycemia.

NEUROLOGIC MONITORING AND CEREBRAL PERFUSION

Intraoperative monitoring for cerebral ischemia or hypoperfusion and, more recently, for cerebral emboli during carotid endarterectomy is controversial (see also Chapter 49). Monitoring techniques include internal carotid artery stump pressure determinations, rCBF measurements, EEG monitoring, SSEP monitoring, transcranial Doppler ultrasonography (TCD), and cerebral oximetry monitoring. The rationale for the use of such monitoring is based on the need to prevent intraoperative strokes. The primary clinical utility of cerebral monitoring is to identify patients who may benefit from shunting during the period of arterial clamping. Secondarily, cerebral monitoring is used to identify patients who may benefit from blood pressure augmentation or change in surgical technique. Despite a tremendous amount of investigative effort, only limited data support the assumption that cerebral monitoring actually improves patient outcome after carotid endarterectomy. To further complicate the issue, several large series have reported excellent results from carotid endarterectomy with routine shunting, routine no shunting, and selective shunting using one or more of the methods discussed later. In a review, the mean reported stroke rate with routine shunting was 1.4% and for routine no shunting was 2%.[165] The mean perioperative stroke rates for selective shunting were 1.6% using stump pressure, 1.6% using EEG, 1.8% using SSEP, and 4.8% using TCD.[165]

Carotid Artery Stump Pressure

The internal carotid artery stump pressure represents the back-pressure resulting from collateral flow through the circle of Willis via the contralateral carotid artery and the vertebrobasilar system. The advantages of monitoring carotid stump pressure are that it is inexpensive, relatively easy to obtain, and continuously available during carotid clamping (dynamic stump pressure). Despite these advantages, few centers use stump pressure monitoring. A recent single center report of 1135 consecutive carotid endarterectomies under general anesthesia used a stump pressure of below 45 mm Hg as a guide for selective shunting.[166] The 30-day stroke rate was 3% for patients selectively shunted (21%), 0.5% for patients not shunted (79%), and 1% overall. The overall 30-day mortality was 0.5%. Of note, no patient had a stroke caused by global intraoperative cerebral hypoperfusion. A recent prospective randomized trial comparing routine shunting versus selective shunting based on stump pressure below 40 mm Hg in 200 patients undergoing carotid endarterectomy under

general anesthesia found both methods were associated with an infrequent perioperative stroke rate (0% versus 2%).[167] The two strokes in the selective shunting cohort were related to carotid artery thrombosis. No patients died perioperatively. Although an old method, stump pressure monitoring appears to have survived the test of time.

Regional Cerebral Blood Flow

rCBF measurements during carotid endarterectomy are obtained by IV or ipsilateral carotid artery injection of radioactive xenon and analysis of decay curves obtained from detectors placed over the area of the ipsilateral cortex supplied by the middle cerebral artery. Measurements are typically obtained before, during, and immediately after carotid clamping. This technology, combined with the EEG monitoring, has provided important insight into the relationship between rCBF and EEG evidence of cerebral ischemia and the critical rCBF associated with various anesthetics.[168,169] The critical rCBF varies depending on the volatile anesthetic used. In patients receiving N_2O plus a volatile anesthetic, rCBF is approximately 20, 15, 10, and 10 mL/100 g of brain tissue per minute for halothane, enflurane, isoflurane, and sevoflurane, respectively.[152,168,169] The expense and the expertise required to make and interpret these blood flow measurements have limited the use of this technology to only a few centers.

Electroencephalography

Many centers advocate intraoperative use of EEG monitoring for the detection of cerebral ischemia and subsequent selective shunting (see also Chapter 49). The full 16-channel strip-chart EEG and the processed (compressed spectral array) EEG monitor are used for this purpose. Although the processed EEG monitor is more easily interpreted, it is less sensitive than the raw EEG monitor. Significant ischemic EEG changes occur in 7.5% to 20% of monitored patients during carotid clamping under general anesthesia. Significant EEG changes occur more frequently in patients with contralateral carotid disease than in those without (14.3% versus 5.1%). The presence of a contralateral carotid occlusion may increase the rate of significant ischemic EEG changes to nearly 50% during carotid clamping. Because contralateral occlusion is highly predictive of ischemic EEG changes with carotid clamping, it has been recommended that EEG monitoring be eliminated in this circumstance. Ischemic EEG changes may also be seen with shunt malfunction, hypotension, or cerebral emboli.

When the electroencephalogram is used for cerebral ischemia monitoring during carotid endarterectomy, a stable physiologic and anesthetic milieu is mandatory. Isoflurane, desflurane, and sevoflurane produce similar ECG changes at equipotent levels and, when used at 0.5 MAC, allow for reliable ECG cerebral ischemia monitoring.

The clinical usefulness of intraoperative EEG monitoring for ischemia during carotid endarterectomy is limited by several factors. First, it may not detect subcortical or small cortical infarcts. Second, false-negative results (i.e., neurologic deficit with no ischemic EEG changes intraoperatively) are not uncommon. Patients with preexisting stroke or reversible neurologic deficits may have a particularly high incidence of such results. Third, EEG monitoring is not specific for ischemia and may be affected by changes in temperature, blood pressure, and anesthesia depth. Fourth, false-positive results (i.e., no perioperative neurologic deficit with significant ischemic EEG changes intraoperatively) occur because not all cerebral ischemia uniformly proceeds to infarction. Finally, intraoperative EEG monitoring is inherently limited because most intraoperative strokes are thought to be thromboembolic and most perioperative strokes occur postoperatively. At present, no consistent data demonstrate that EEG monitoring is clearly superior to other methods of intraoperative cerebral monitoring or that the use of EEG monitoring improves outcome.

Somatosensory Evoked Potentials

SSEP monitoring is based on the response of the sensory cortex to electrical impulses from peripheral sensory nerve stimulation. The sensory cortex, being primarily supplied by the middle cerebral artery, is at risk during carotid artery clamping. SSEP monitoring, unlike EEG monitoring, is able to detect subcortical sensory pathway ischemia. Characteristic SSEP tracings (i.e., decrease in amplitude, increase in latency, or both) occur with decreased rCBF and are abolished in primates when flow decreases to less than 12 mL/100 g of brain tissue per minute. No specific reduction in amplitude or increase in latency has been established as a physiologic marker of impaired rCBF under operative conditions in humans. Anesthetics, hypothermia, and blood pressure may affect SSEPs significantly, and false-negative results have been reported. The validity of SSEPs as an intraoperative monitor of cerebral ischemia during carotid endarterectomy has not been definitively established.

Transcranial Doppler Ultrasonography

TCD allows continuous measurement of mean blood flow velocity and detection of microembolic events in the middle cerebral artery (see also Chapter 49). These parameters have important clinical implications because most perioperative neurologic deficits are thought to be thromboembolic in origin. With TCD, intraoperative embolization has been detected in more than 90% of patients undergoing carotid endarterectomy. Most intraoperative emboli are characteristic of air and are not associated with adverse neurologic outcomes. TCD may provide useful information regarding shunt function, malfunction, and the incidence of emboli during shunt insertion. Embolization during carotid artery dissection may indicate plaque instability and the need for early carotid artery clamping. Embolization during dissection and wound closure is associated with operative stroke. One center has reported that combined TCD monitoring and completion angiography resulted in a reduction in the intraoperative stroke rate from 4% to 0%. Early postoperative embolization has been detected in more than 70% of patients after carotid endarterectomy and is exclusively particulate in nature. Most TCD-detected emboli occur in the first 2 to 3 hours after surgery. Persistent particulate embolization in the early postoperative period has been shown to predict thrombosis and the development of a major neurologic deficit. Frequent early postoperative TCD embolic signals have been demonstrated to be highly predictive of early postoperative ipsilateral focal

cerebral ischemia. Intervention with dextran has been shown to reduce and ultimately stop sustained embolization after carotid endarterectomy. Perioperative microembolization is more common in women and patients with symptomatic carotid disease. TCD monitoring has been reported to detect early asymptomatic carotid artery occlusion and hyperperfusion syndrome after carotid endarterectomy. Although TCD monitoring holds some promise, conclusive evidence demonstrating improved outcome has not been reported. Additionally, the high rate of technical failures significantly limits the clinical utility of this monitoring modality.[170]

Cerebral Oxygenation

Direct monitoring of cerebral oxygenation can be obtained with jugular bulb venous monitoring. Such monitoring allows determination of the arterial–jugular venous O_2 content difference and jugular venous O_2 saturation and therefore provides information on global cerebral O_2 metabolism. Jugular venous samples are obtained from a catheter inserted into the jugular bulb ipsilateral to the surgical site. Continuous fiberoptic jugular venous oximetry catheters are available as well. Significant technical and methodologic shortcomings have limited the clinical application of this monitoring during carotid endarterectomy.

Near-infrared spectrophotometry is a noninvasive technique that allows continuous monitoring of regional cerebral O_2 saturation through the scalp and skull. Similar to pulse oximetry, cerebral oximetry is based on the different absorption characteristics of the near-infrared spectrum of oxygenated and deoxygenated hemoglobin. However, unlike pulse oximeters, cerebral oximeters measure the O_2 saturation of hemoglobin in the entire tissue bed (i.e., brain tissue and arterial and venous blood), which is predominately venous blood, and therefore approximates venous blood O_2 saturation. A commercially available cerebral oximetry sensor is applied to the forehead skin ipsilateral to the surgical site, and regional cerebral O_2 saturation from a small sample of the frontal cortex below the sensor is provided. To date, wide patient-to-patient variability in baseline cerebral O_2 saturation and the lack of a clinical threshold of a decrease in cerebral O_2 saturation predictive of the need for shunt placement have impeded the widespread use of this novel monitoring modality.

POSTOPERATIVE CONSIDERATIONS

Most neurologic complications (transient and permanent) after carotid endarterectomy are explained by intraoperative embolization, hypoperfusion during carotid clamping, and postoperative embolization or thrombosis from the endarterectomy site. It is generally accepted that most neurologic complications are related to surgical technique. Thromboembolic (rather than hemodynamic) factors appear to be the major mechanism of perioperative neurologic complications and most occur in the postoperative period. Neurologic complications attributable to carotid artery thrombosis may occur with an incidence as frequent as 3.3% and are associated with a high rate of major stroke or death despite immediate operative intervention. Other important, but less common neurologic complications include intracerebral hemorrhage and cerebral hyperperfusion. The reported incidence of intracerebral hemorrhage after carotid endarterectomy ranges from 0.4% to 2.0%. Most intracerebral hemorrhages occur 1 to 5 days after the operation and are associated with significant morbidity and mortality.

Hypertension is common in the postoperative period after carotid endarterectomy. Not surprisingly, patients with poorly controlled preoperative hypertension often have severe hypertension postoperatively. The causes are not well understood, but surgical denervation of the carotid sinus baroreceptors is probably contributory. Regional anesthesia is associated with less hypertension. Other causes of postoperative hypertension, such as hypoxemia, hypercapnia, bladder distention, and pain, should be excluded or treated. Because neurologic and cardiac complications may be associated with postoperative hypertension, blood pressure should be aggressively controlled to near preoperative values after surgery. Short-acting drugs are the safest and most effective. Patients with persistent hypertension can be converted to longer-acting IV or oral agents before discharge from the ICU.

Postoperative cerebral hyperperfusion syndrome is an abrupt increase in blood flow with loss of autoregulation in the surgically reperfused brain and is manifested as headache, seizure, focal neurologic signs, brain edema, and possibly intracerebral hemorrhage. Unfortunately, little is actually known about the cause and management of this syndrome. Typically, this syndrome does not occur until several days after carotid endarterectomy. Patients with severe postoperative hypertension and severe preoperative internal carotid artery stenosis are believed to be at increased risk for this syndrome. However, more recent data do not corroborate this common belief and suggest that recent contralateral carotid endarterectomy may be predictive of cerebral hyperperfusion.[171]

Postoperative hypotension occurs almost as frequently as hypertension after carotid endarterectomy. Carotid sinus baroreceptor hypersensitivity or reactivation probably plays an important role. Postoperative hypotension may be more common after regional anesthesia. To avoid cerebral and myocardial ischemia, hypotension should be corrected promptly. Cardiac output is frequently normal or elevated and systemic vascular resistance reduced in hypotensive patients after carotid endarterectomy. Intensive surveillance for evidence of myocardial and cerebral ischemia and judicious use of fluids and vasopressors are recommended for postoperative hypotension. In most cases the hypotension resolves over a period of 12 to 24 hours.

Cranial and cervical nerve dysfunction after carotid endarterectomy is well documented in the literature. Although most injuries are transient, permanent injuries can lead to significant disability. Patients should be examined for injury to the recurrent laryngeal, superior laryngeal, hypoglossal, and marginal mandibular nerves shortly after extubation. Unilateral recurrent laryngeal nerve injury may result in ipsilateral true vocal cord paralysis in the paramedian position. Although most patients have hoarseness and an impaired cough mechanism, the injury is usually well tolerated. However, bilateral recurrent laryngeal nerve injury and resultant bilateral vocal cord paralysis can result in life-threatening upper airway obstruction. This situation must be anticipated in

patients who have previously undergone contralateral carotid endarterectomy or neck surgery.

Carotid body denervation may occur after carotid endarterectomy as a result of surgical manipulation. Unilateral loss of carotid body function may result in an impaired ventilatory response to mild hypoxemia and is rarely of clinical significance. Bilateral carotid endarterectomy is associated with loss of the normal ventilatory and arterial pressure responses to acute hypoxia and an increased resting partial pressure of arterial CO_2. In this situation, the central chemoreceptors are the primary sensors for maintaining ventilation, and serious respiratory depression may result from opioid administration. Fortunately, most patients require little more than acetaminophen or ketorolac for postoperative pain.

Wound hematoma probably occurs more frequently than reported in the literature. In the North American Symptomatic Carotid Endarterectomy Trial,[136] 5.5% of patients had wound hematomas. Most cases are the result of venous oozing and require little more than external compression for 5 to 10 minutes. Expanding hematomas require prompt evaluation at the bedside and immediate evacuation if airway compromise is evident. Aggressive postoperative blood pressure control may help reduce the incidence of hematoma.

Although some clinicians believe that intensive care monitoring is not routinely required after carotid surgery, a significant number of patients do require intensive monitoring and active intervention. I think all patients should be monitored in an intensive care setting for at least 8 hours after carotid endarterectomy, because most events requiring intervention occur within this timeframe.[172,173]

ENDOVASCULAR TREATMENT OF CAROTID DISEASE: CAROTID ARTERY STENTING

Endovascular treatment of carotid disease is an innovation in evolution for stroke prevention and currently involves percutaneous transluminal angioplasty and stenting. Significant procedural advancements include the use of dual antiplatelet therapy, self-expanding stents, and emboli protection devices. Over the last decade, major randomized clinical trials comparing carotid endarterectomy with carotid artery stenting have been published. A recent systematic review of randomized trials (16 trials involving 7572 patients) found that endovascular treatment (including balloon angioplasty or stenting) was associated with an increased risk for periprocedural stroke or death compared with endarterectomy.[174] Of note, the increase in risk appeared to be limited to patients 70 years of age and older. Endovascular treatment was associated with lower risks for MI, cranial nerve palsy, and access site hematomas. The rate of ipsilateral stroke after the periprocedural period was not different between treatment groups. Among patients unfit for surgery, the rate of death or stroke did not differ between endovascular treatment and medical care. Updated guidelines provide specific recommendations for revascularization of symptomatic and asymptomatic patients.[131]

The carotid artery stenting procedure consists of the following steps: femoral access, aortic arch angiogram, selective cannulation of the common carotid artery origin and angiogram, guidewire advancement into the external carotid artery, carotid sheath placement and advancement into the common carotid artery, placement of embolic protection device, balloon angioplasty of lesion, advancement of stent delivery catheter across dilated lesion, deployment of self-expanding stent, balloon dilatation of stent, completion angiogram, and access site management. The femoral artery approach is considered standard, but brachial artery and high radial artery access have been reported with high procedural success. Embolic protection devices are considered mandatory and include distal protection in the form of a filter or occlusion balloon and proximal protection in the form of flow interruption or flow reversal. Cardiologists and radiologists currently perform a large percentage of these procedures in specialized endovascular suites.

Most carotid artery stenting procedures are performed under local anesthesia with light or no sedation to facilitate patient cooperation and continuous neurologic assessment. In addition to routine monitors, an arterial line is placed for continuous blood pressure monitoring. Some degree of hemodynamic instability is common in patients during and after carotid artery stenting. Bradycardia and hypotension occur much more frequently after carotid artery stenting with balloon angioplasty than without angioplasty.[175] A recent, large retrospective study reported asystole in 4.9% of patients after carotid stenting.[176] Asystole was more likely to occur in patients undergoing a right-sided procedure, in those with significant contralateral stenosis, and in those with a reduced left ventricular ejection fraction. The administration of prophylactic atropine before balloon inflation decreases the incidence of intraoperative bradycardia and cardiac morbidity in primary carotid stenting patients.[177]

POSTOPERATIVE MANAGEMENT OF VASCULAR SURGERY PATIENTS

Vascular surgery patients require special attention during the postoperative period because most complications occur postoperatively and other problems may arise that require immediate attention. Conventional practice is to monitor all vascular surgery patients in an ICU setting after surgery. Some centers have set up specialized vascular step-down units in which lower risk patients can be evaluated frequently by specialized nursing staff. There are, however, no clinical trials to support this practice.

Myocardial ischemia and cardiac morbidity occur most frequently in the postoperative period. Patients should be carefully monitored for signs and symptoms of myocardial ischemia, realizing that up to 90% of ischemic episodes are asymptomatic. Troponin surveillance may be beneficial in high-risk patients. The determinants of myocardial O_2 supply and demand should be optimized for all patients (Fig. 69-18) to prevent ischemia before it develops. β-Blocker and statin therapy should be continued throughout the postoperative period. Dysrhythmias are common and may be secondary to ischemia or to sympathectomy associated with regional anesthesia.

Besides myocardial ischemia and cardiac morbidity, other problems include coagulopathy, from either residual

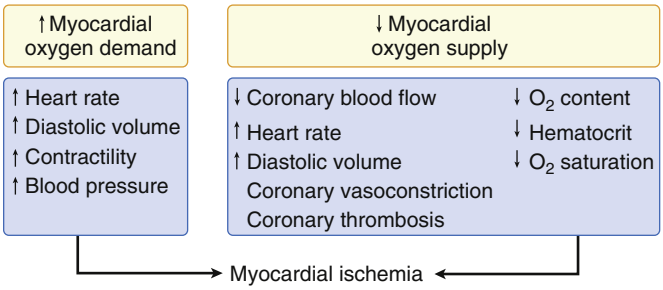


Figure 69-18. Determinants of myocardial oxygen supply and demand that lead to myocardial ischemia. During the perioperative period, virtually every determinant is altered by factors such as fluid shifts, blood loss, pain, catecholamines, altered coagulability, and ventilatory insufficiency. (Modified from Beattie C, Fleisher LA: Perioperative myocardial ischemia and infarction, *Int Anesthesiol Clin* 30:1-17, 1992.)

heparin or dilutional coagulopathy after massive transfusion. Even in the absence of coagulopathy, bleeding through fresh vascular anastomoses may occur when significant postoperative hypertension is untreated. Hypovolemia occurs after aortic surgery as a result of significant third-space fluid loss and bleeding. Hypovolemia may lead to hypotension and hypoperfusion of vital organs or lower extremity vascular grafts. Graft occlusion in the lower extremities occurs in 3% to 10% of patients after lower extremity or aortic surgery and should be recognized immediately and surgically corrected. Lower extremity pulses should be checked at hourly intervals. Some patients require the administration of heparin or dextran to prevent thrombosis when the surgical repair is questionable or when patients have diffuse atherosclerotic disease.

Residual hypothermia in the early postoperative period is associated with an increased incidence of myocardial ischemia and cardiac morbidity; therefore, body temperature should be carefully monitored and controlled in all vascular surgery patients. In the early postoperative period, vascular surgery patients have a twofold to threefold greater incidence of myocardial ischemia when core temperature is less than 35° C.[178] Even mild hypothermia of approximately 35° C is associated with a 200% to 700% increase in norepinephrine levels,[179,180] generalized vasoconstriction,[181] and increased blood pressure in postoperative patients.[179] Shivering occurs and increases total-body O_2 consumption by approximately 40% in the typical elderly vascular patient.[182] In a prospective randomized trial, the relative risk for early postoperative cardiac morbidity was reduced by 55% when normothermia was maintained by use of a forced-air warming system.[183]

The stress response needs to be controlled in the postoperative period. This includes preventing the potential triggers for myocardial ischemia such as pain, anemia, hypothermia, hemodynamic extremes, and ventilatory insufficiency. In mechanically ventilated patients, the weaning period is especially stressful, and myocardial ischemia occurs frequently during this time. Careful sedation and expeditious weaning are desirable. When possible, extubation in the operating room is less stressful and is preferable for carotid and lower extremity vascular surgery patients. For more invasive surgical procedures (TAA and AAA), postoperative mechanical ventilation is usually necessary.

Vascular surgery continues to challenge the anesthesiologist, given the significant physiologic stress superimposed on a relatively elderly patient population with a high incidence of coexisting disease. Clinical studies and society guidelines provide insight into the preoperative assessment and optimization of cardiac risk, the implications of anesthetic technique, and the diagnosis, prevention, and treatment of myocardial ischemia in vascular surgery patients. These studies and guidelines have improved our ability to care for vascular surgery patients with reduced morbidity and better overall outcome.

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Chapter 70

Anesthesia for Neurologic Surgery

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Key Points

- For the purposes of planning a strategy for controlling intracranial pressure (ICP), the clinician should consider the four subcompartments of the intracranial space: cells, interstitial and intracellular fluid, cerebrospinal fluid (CSF), and blood.
- The clinician should make a preoperative assessment of the probable intracranial compliance reserve as the basis for selection of appropriate anesthetic drugs and techniques.
- The venous side of the cerebral circulation is a largely passive compartment that is often the cause of increased ICP, or "tightness," of the surgical field but is commonly overlooked by clinicians.
- Cerebral perfusion pressure (CPP) should be supported at or near waking normal levels in patients with recent cerebral injuries (e.g., traumatic brain injury [TBI], subarachnoid hemorrhage [SAH]), and spinal cord injury because of low resting cerebral blood flow and impaired autoregulation.
- When neurosurgical procedures are performed in the sitting position, blood pressure should be corrected to the level of the external auditory meatus, and mean arterial pressure (MAP) should be maintained at 60 mm Hg in normotensive adults.
- The minimal standard of care for monitoring to detect venous air embolism (VAE) in at-risk situations includes the precordial Doppler and end-tidal carbon dioxide analysis.
- Despite encouraging preclinical data, therapeutic mild hypothermia cannot currently be advocated in the care of head-injured patients in the intensive care unit (ICU) or during the operative management of patients with intracranial aneurysms because of negative human trial results for those patient groups.
- The most important consideration in the anesthetic management of patients undergoing clipping or coiling after acute SAH is the prevention of paroxysmal hypertension with its attendant risk of aneurysm rerupture. Nonetheless, adequate perfusion pressure is needed if temporary clips are used during management of cerebral vasospasm.
- Although induced hypotension is rarely used electively in aneurysm surgery, the clinician must be ready to reduce blood pressure immediately and accurately in the event of aneurysm rupture.
- Tracheal intubation of a head-injured patient with an undefined cervical spine injury can be accomplished using rapid-sequence induction with manual in-line stabilization (the occiput held rigidly to the backboard), with only a very small risk of injury to the spinal cord.
- CPP (CPP = MAP – ICP) should be supported at 60 mm Hg in the first 48 to 72 hours after TBI in adults.
- Hypocapnia has the potential to cause cerebral ischemia, particularly in a recently injured brain and in a brain beneath retractors; it should be used only when absolutely necessary for the control of critically increased or uncertain ICP.

This chapter provides guidelines for the management of common situations in neurosurgical anesthesia. Issues that arise in connection with a wide variety of neurosurgical procedures—those constituting a checklist that the practitioner should review before undertaking anesthesia for any neurosurgical procedure—are reviewed first, followed by procedure-specific discussions. This chapter assumes familiarity with the cerebral physiology and effects of anesthetics as described in Chapter 17, and with neurologic monitoring as described in Chapter 49. Carotid endarterectomy and carotid angioplasty and stenting are discussed in Chapter 69.

RECURRENT ISSUES IN NEUROANESTHESIA

Several basic elements of neurosurgical and neuroanesthetic management are recurrent and, in the absence of an established understanding between surgeon and anesthesiologist, should be discussed and agreed upon at the outset of every neurosurgical procedure (Box 70-1). The list varies by procedure and may include the intended surgical position and requisite positioning aids; intentions with respect to the use of steroids, osmotic agents/diuretics, anticonvulsants, and antibiotics; the surgeon's perception of the "tightness" of the intracranial space and the remaining intracranial compliance reserve; appropriate objectives for the management of blood pressure, carbon dioxide tension, and body temperature; anticipated blood loss; the intended use of neurophysiologic monitoring (which may impose constraints on the use of anesthetics or muscle relaxants, or both); and, sometimes, the perceived risk of air embolization. The considerations driving the decisions made about these issues are presented in this section. One additional recurrent issue, brain protection, is discussed briefly in the section on aneurysms and arteriovenous malformations (AVMs) and in detail in Chapter 17.

CONTROL OF INTRACRANIAL PRESSURE AND BRAIN RELAXATION

The necessity of preventing increases in intracranial pressure (ICP) or reducing ICP that is already increased is recurrent in neuroanesthesia. When the cranium is closed, the physician's objectives are to maintain adequate cerebral perfusion pressure (CPP) (CPP = mean arterial pressure [MAP] – ICP) and prevent the herniation of brain tissue between intracranial compartments or through the foramen magnum (Fig. 70-1).[1] When the cranium is open, the issue may be to provide relaxation of the intracranial contents to facilitate surgical access or, in extreme circumstances, reverse ongoing brain herniation through craniotomy. The principles that apply are similar whether the cranium is open or closed.

The various clinical indicators of increased ICP include headache (particularly headache that awakens the patient at night), nausea and vomiting, blurred vision, somnolence, and papilledema. Computed tomography (CT) findings suggestive of either increased ICP or reduced intracranial compliance reserve include midline shift, obliteration of the basal cisterns, loss of sulci, ventricular effacement (or enlarged ventricles in the event of hydrocephalus or ventricular trapping), and edema. Edema appears on a CT scan as a region of hypodensity. The basal cisterns appear on CT as a black (fluid) halo around the upper end of the brainstem (Fig. 70-2). They include the interpeduncular cistern, which lies between the two cerebral peduncles, the quadrigeminal cistern, which overlies

BOX 70-1 *Recurrent Issues in Neuroanesthesia*

- Control of intracranial pressure/brain relaxation
- Management of $Paco_2$
- Management of arterial blood pressure
- Use of steroids
- Use of osmotherapy
- Use of diuretics
- Use of anticonvulsants
- Patient positioning
- Pneumocephalus
- Venous air embolism
- Monitoring
- Intravenous fluid management
- Hypothermia
- Glucose management
- Emergence from anesthesia

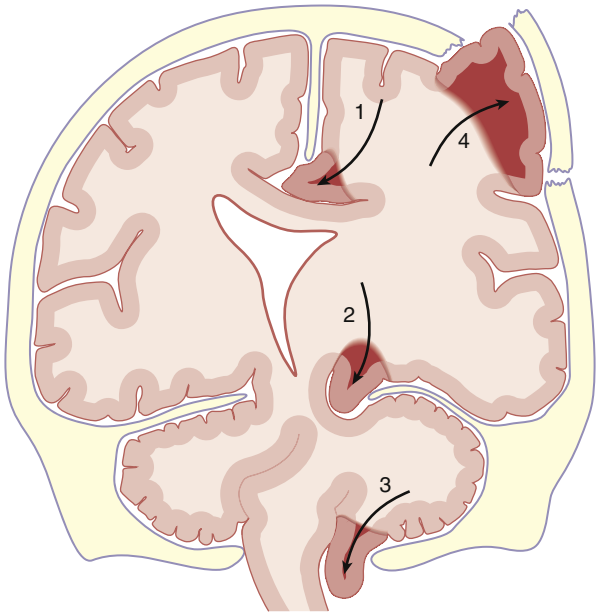


Figure 70-1. Schematic representation of various herniation pathways: *(1)* sub-falcine, *(2)* uncal (transtentorial), *(3)* cerebellar, and *(4)* transcalvarial. *(From Fishman RA: Brain edema,* N Engl J Med *293:706-711, 1975.)*

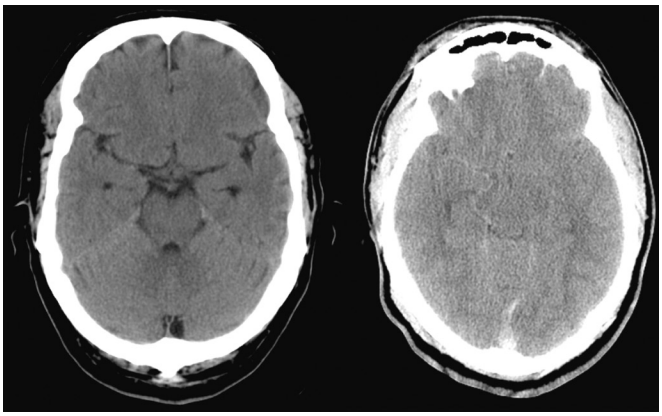


Figure 70-2. Computed tomography (CT) scan depicting normal *(left)* and compressed *(right)* basal cisterns. The basal, or perimesencephalic, cerebrospinal fluid (CSF) space consists of the interpeduncular cistern (anterior), the ambient cisterns (lateral), and the quadrigeminal cisterns (posterior). In the right panel, the cisterns have been obliterated in a patient with diffuse cerebral swelling (caused by sagittal sinus thrombosis). *(Courtesy Ivan Petrovitch.)*

the four colliculi, and the ambient cisterns, which lie lateral to the cerebral peduncles.

Figure 70-3 presents the pressure-volume relationship of the intracranial space. The plateau phase occurring at low volumes reveals that the intracranial space is not a completely closed one, and that there is some compensatory latitude. Compensation is accomplished principally by the translocation of cerebrospinal fluid (CSF) and venous blood to the spinal CSF space and the extracranial veins, respectively. Ultimately, when the compensatory potential is exhausted, even tiny increments in volume of the intracranial contents can result in substantial increases in ICP. These increases have the potential to result in either herniation of brain tissue from one compartment to another (or into the surgical field) (see Fig. 70-1), with resultant mechanical injury to brain tissue, or in reduction of perfusion pressure, leading to ischemic injury.

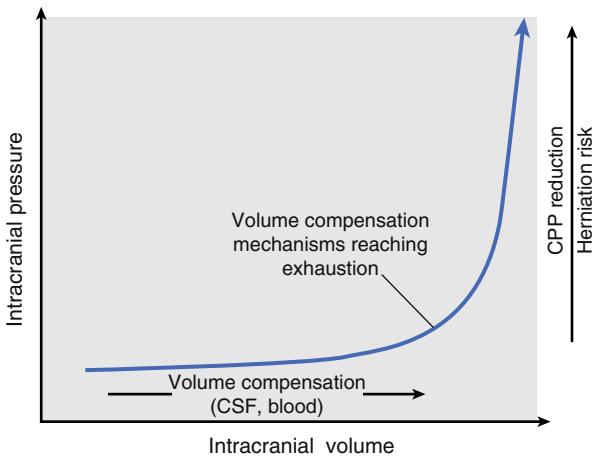


Figure 70-3. The intracranial pressure–volume relationship. The horizontal portion of the curve indicates that there is initially some latitude for compensation in the face of an expanding intracranial lesion. That compensation is accomplished largely by displacement of cerebrospinal fluid (CSF) and venous blood from intracranial to extracranial spaces. Once the compensatory latitudes are exhausted, small-volume increments result in large increases in intracranial pressure with the associated hazards of herniation or of decreased cerebral perfusion pressure (CPP), resulting in ischemia.

Several variables can interact to cause or aggravate intracranial hypertension (Fig. 70-4). For clinicians faced with the problem of managing increased ICP, the objective is, broadly speaking, to reduce the volume of the intracranial contents. For mnemonic purposes, the clinician can divide the intracranial space into four subcompartments (Table 70-1): cells (including neurons, glia, tumors, and extravasated collections of blood), fluid (intracellular and extracellular), CSF, and blood.

1. *The cellular compartment.* This compartment is largely the province of the surgeon. However, it may be the anesthesiologist's responsibility to pose a well-placed diagnostic question. When the brain is bulging into the surgical field at the conclusion of evacuation of an extradural hematoma, the clinician should ask whether a subdural or extradural hematoma is present on the contralateral side that warrants either immediate burr holes or immediate postprocedure radiologic evaluation.
2. *The CSF compartment.* There is no pharmacologic manipulation of the CSF space with a time course and magnitude that is relevant to the neurosurgical operating room. The only practical means of manipulating the size of this compartment is by drainage. A tight surgical field can sometimes be improved by passage of a brain needle by the surgeon into a lateral ventricle to drain CSF. Lumbar CSF drainage can be used to improve surgical exposure in situations with no substantial hazard of uncal or transforamen magnum herniation.

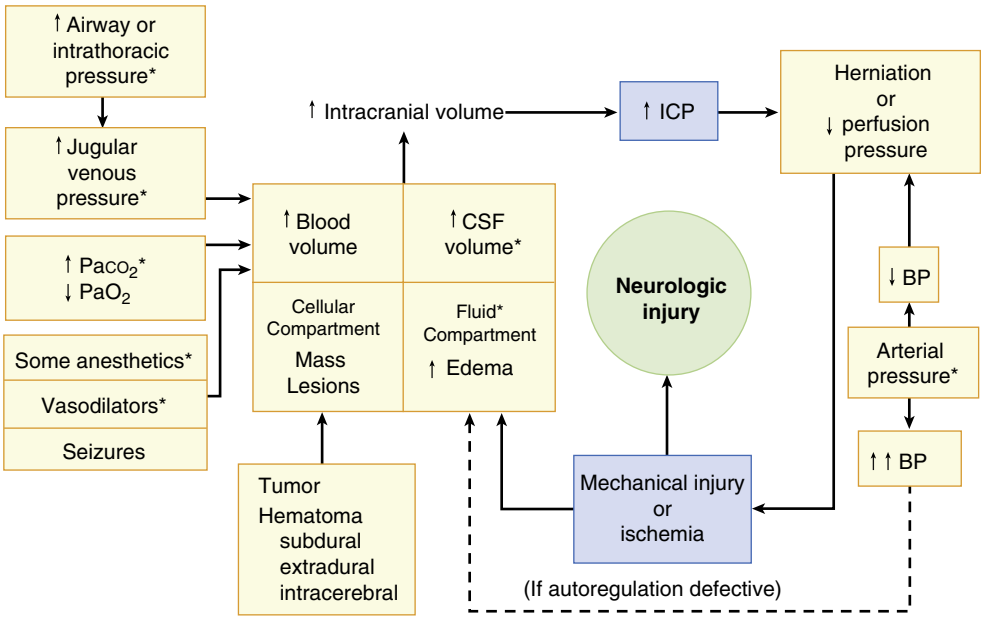


Figure 70-4. The pathophysiology of intracranial hypertension. The figure depicts the manner in which increases in the volumes of any or all of the four intracranial compartments, blood, cerebrospinal fluid (CSF), fluid (interstitial or intracellular), and cells, result in intracranial pressure (ICP) increases and eventual neurologic damage. The elements that are most readily under the control of the anesthesiologist are indicated with asterisks (*). (Control of CSF volume requires the presence of a ventriculostomy catheter.) *BP,* Blood pressure.

3. *The fluid compartment.* This compartment can be addressed with steroids and osmotic/diuretic agents. The use of these agents is discussed later.
4. *The blood compartment.* This compartment receives the anesthesiologist's greatest attention because it is the most amenable to rapid alteration. The blood compartment should be viewed as having two separate components: venous and arterial.

With respect to the blood compartment, the venous side of the circulation should initially be considered. It is largely a passive compartment and often overlooked. Despite this passivity, engorgement of this compartment is a common cause of increased ICP or poor conditions in the surgical field (Fig. 70-5). A head-up posture to ensure good venous drainage is the standard in neurosurgical anesthesia and critical care. Obstruction of cerebral venous drainage by extremes of head position or circumferential pressure (cervical collars, endotracheal tube ties) should be avoided. Anything that causes increased intrathoracic pressure can also result in obstruction of cerebral venous drainage. Relevant phenomena include kinking or partial obstruction of endotracheal tubes, tension pneumothorax, coughing or straining against the endotracheal tube, or gas trapping as a result of bronchospasm. Neuromuscular blockade (see Chapter 34) is usually induced during craniotomies unless a contraindication is present. Such a blockade would prevent a sudden cough that can cause a dramatic herniation of cerebral structures through the craniotomy.

Thereafter, the arterial side of the circulation should be considered. Attention to the effect of anesthetic drugs and techniques on cerebral blood flow (CBF) (see Chapter 17) is an established part of neuroanesthesia because, in general, increases in CBF are associated with increases in cerebral blood volume (CBV).[2-4] The notable exception to this rule occurs in the context of cerebral ischemia caused by hypotension or vessel occlusion, at which times CBV may increase as the cerebral vasculature dilates in response to a sudden reduction in CBF. However, the relationship generally applies, and attention to the control of CBF is relevant in situations in which intracranial volume compensation mechanisms are exhausted or ICP is already increased. The general approach is to select anesthetics and to control physiologic variables in a manner that avoids unnecessary increases in CBF. The variables that influence CBF are listed in Box 70-2 and are discussed in Chapter 17.

TABLE 70-1 INTRACRANIAL COMPARTMENTS AND TECHNIQUES FOR MANIPULATION OF THEIR VOLUME

Compartment	Volume Control Methods
1. Cells (including neurons, glia, tumors, and extravasated blood)	Surgical removal
2. Fluid (intracellular and extracellular)	Diuretics Steroids (principally tumors)
3. CSF	Drainage
4. Blood	
Arterial side	Decrease cerebral blood flow
Venous side	Improve cerebral venous drainage

SELECTION OF ANESTHETICS

The question of which anesthetics are appropriate, especially in the context of unstable ICP, arises frequently. Chapter 17 provides relevant information in detail, and only broad generalizations are described.

In general, intravenous anesthetic, analgesic, and sedative drugs are associated with parallel reductions in CBF and cerebral metabolic rate (CMR) and consequently will not have adverse effects on ICP. Ketamine, given in large doses to patients with a generally normal level of consciousness before anesthesia, is the exception. Autoregulation and carbon dioxide (CO_2) responsiveness is generally preserved during the administration of intravenous anesthetics (see Chapter 17).

By contrast, all of the volatile anesthetics can be, depending on physiologic and pharmacologic circumstances, dose-dependent cerebral vasodilators. The order of vasodilating potency is approximately halothane → enflurane → desflurane → isoflurane → sevoflurane. As noted in Chapter 17, the CBF differences among desflurane, isoflurane,

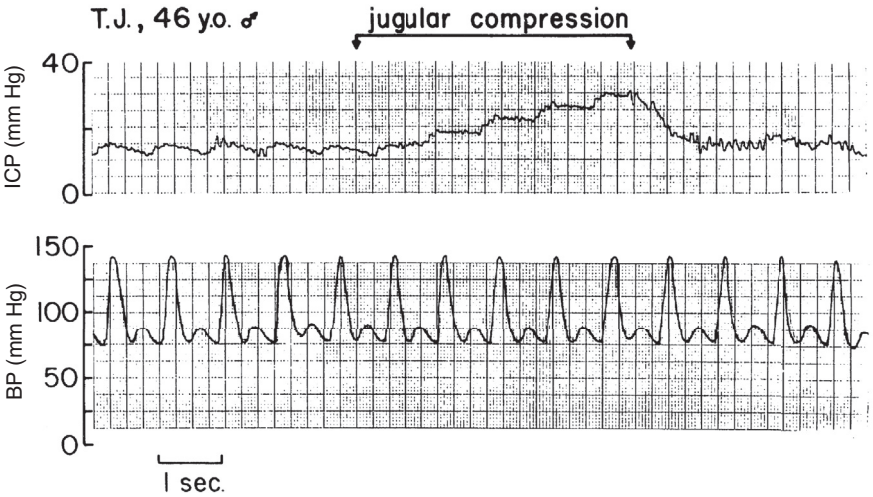


Figure 70-5. The effect of cerebral venous outflow obstruction on intracranial pressure (ICP) in a patient with an intracerebral hematoma. Bilateral jugular compression was applied briefly to verify the function of a newly placed ventriculostomy. The ICP response illustrates the importance of maintaining unobstructed cerebral venous drainage.

and sevoflurane are most likely not clinically significant. The net CBF effect of a volatile anesthetic depends on the interaction of several factors: the concentration of the anesthetic, the extent of previous CMR depression, simultaneous blood pressure changes acting in conjunction with previous or anesthetic-induced autoregulation abnormalities, and simultaneous changes in partial pressure of carbon dioxide in the arterial blood ($Paco_2$) acting in conjunction with any disease-related impairment in CO_2 responsiveness.

Nitrous oxide (N_2O) can also be a cerebral vasodilator. The CBF effect of N_2O is greatest when it is administered as a sole anesthetic; least when it is administered against a background of narcotics, propofol, or benzodiazepines; and intermediate when it is administered in conjunction with volatile anesthetics (see Chapter 17).

Despite the vasodilatory potential of both N_2O and volatile anesthetics, experience dictates that the latter, usually in concentrations less than the minimum alveolar concentration (MAC), when administered as components of a balanced anesthetic technique in combination with opioids, can be used in most elective and many emergency neurosurgical procedures. However, there are infrequent exceptions. Because both N_2O and volatile anesthetics can be vasodilators in some circumstances, when the compensatory latitude of the intracranial space has been exhausted and physiology is abnormal, omitting them on a just-in-case basis may be prudent. In a somnolent, vomiting patient with papilledema, a large tumor mass, and compressed basal cisterns; or in a traumatic brain injury (TBI) victim with an expanding mass lesion or obliterated cisterns and sulci on CT, a predominantly intravenous technique should be used until the cranium and dura are open and the effect of the anesthetic technique can be assessed by direct observation of the surgical field. Although inhaled anesthetics are entirely acceptable components of most anesthetics for neurosurgery, in circumstances in which ICP is persistently increased or the surgical field is persistently "tight," N_2O and volatile anesthetics[5,6] should be replaced by intravenous anesthetics.

BOX 70-2 ***Factors That Influence Cerebral Blood Flow***

- Pao_2
- $Paco_2$
- Cerebral metabolic rate
  - Arousal/pain
  - Seizures
  - Temperature
  - Anesthetics
- Blood pressure/status of autoregulation
- Vasoactive agents
  - Anesthetics
  - Pressors
  - Inotropes
  - Vasodilators
- Blood viscosity
- Neurogenic pathways (intra- and extra-axial)

See Regulation of Cerebral Blood Flow and Effects of Anesthetics on Cerebral Blood Flow and Cerebral Metabolic Rate in Chapter 17 for detailed discussion.

Older neuromuscular blockers (D-tubocurarine, metocurine, mivacurium, atracurium) can release histamine and should be given in small, divided doses. Although succinylcholine can increase ICP, the increases are small and transient. Moreover, the increases can be blocked by a preceding dose of metocurine 0.03 mg/kg (and probably other nondepolarizer neuromuscular blocking drugs) and, in at least some instances, are not evident in patients with common emergency neurosurgical conditions (TBI, subarachnoid hemorrhage [SAH]).[7,8] Succinylcholine in conjunction with proper management of the airway and MAP can be used when rapid endotracheal intubation is needed.

From the material just presented and from the discussion of cerebral physiology in Chapter 17, a systematic clinical approach should easily follow. A schema for approaching the problem of an acute increase in ICP or acute deterioration in conditions in the surgical field is presented in Box 70-3.

If the problem has not resolved satisfactorily after following the approach in Box 70-3, Box 70-4 presents options for resolution. CSF drainage was discussed

BOX 70-3 ***High Intracranial Pressure ("Tight Brain") Checklist***

1. Are the relevant pressures controlled?
   a. Jugular venous pressure
      i. Extreme head rotation or neck flexion?
      ii. Direct jugular compression?
      iii. Head-up posture?
   b. Airway pressure
      i. Airway obstruction?
      ii. Bronchospasm?
      iii. Straining, coughing; adequately relaxed?
      iv. Pneumothorax?
      v. Excessive PEEP or APR ventilation?
   c. Partial pressure of CO_2 and O_2 ($Paco_2$, PaO_2)
   d. Arterial pressure
2. Is the metabolic rate controlled?
   a. Pain/arousal?
   b. Seizures?
   c. Febrile?
3. Are any potential vasodilators in use?
   a. N_2O, volatile agents, nitroprusside, calcium channel blockers?
4. Are there any unrecognized mass lesions?
   a. Hematoma
   b. Air ± N_2O
   c. CSF (clamped ventricular drain)

APR, Airway pressure release; *CSF,* cerebrospinal fluid; *PEEP,* positive end-expiratory pressure.

BOX 70-4 ***Methods for Rapid Reduction of Intracranial Pressure and Brain Volume (After Review of the Checklist in Box 70-3)***

- Further reduction of $Paco_2$ (to not <23-25 mm Hg)
- CSF drainage (ventriculostomy, brain needle)
- Diuresis (usually mannitol)
- CMR suppression (barbiturates, propofol)
- MAP reduction (if dysautoregulation)
- Surgical control (i.e., lobectomy or removal of bone flap)

earlier. Hyperosmolar solutions are frequently used (see the subsequent section "Osmotherapy and Diuretics"). Barbiturates have long been the most widely used drugs for inducing reduction in CMR, with the objective of causing a coupled reduction in CBF and CBV. Propofol has gained popularity for this application. However, although the use of barbiturates is supported by intensive care unit (ICU) experience, demonstrating efficacy in ICP control[9] (if not outcome), no such experience has been accumulated for propofol. Furthermore, a frequently fatal syndrome of metabolic acidosis and rhabdomyolysis has been recognized in patients who have received prolonged propofol infusions in the ICU setting.[10,11]

MANAGEMENT OF $Paco_2$

The anesthesiologist and the surgeon should agree on the objectives with respect to $Paco_2$. Induction of hypocapnia was once a routine part of the management of intracranial neurosurgical procedures. The rationale is principally that the concomitant reduction in CBF (see Chapter 17, Fig. 17-7) and CBV will result in a reduction in ICP, or "brain relaxation." The rationale is valid.[12] However, two considerations should influence the clinician's use of hyperventilation. First, the vasoconstrictive effect of hypocapnia can cause ischemia in certain situations. Second, the CBF-lowering and ICP-lowering effect is not sustained.[13]

Hypocapnia-Induced Cerebral Ischemia

A normal brain is unlikely to be damaged by the typical clinical use of hyperventilation. However, this may not be the case in certain pathologic conditions.

Normal Brain. Current data[14-18] indicate that in normal subjects, ischemia will not occur at a $Paco_2$ greater than 20 mm Hg. However, in one investigation,[17] electroencephalogram (EEG) abnormalities and paresthesia occurred in volunteers hyperventilating to $Paco_2$ values less than 20 mm Hg, and these effects were reversed by hyperbaric oxygenation, suggesting that they may truly have been caused by ischemia. Accordingly, given that a $Paco_2$ of less than 20 to 25 mm Hg offers very little additional benefit in terms of improvement in intracranial compliance, acute reduction of $Paco_2$ should be no more than 22 to 25 mm Hg in previously normocapnic persons.

Injured Brain. Preventing herniation, maintaining ICP less than 20 mm Hg, minimizing retractor pressure, and facilitating surgical access remain priorities that may justify hypocapnia. Yet hyperventilation is potentially deleterious and should not be overused. Hyperventilation can result in ischemia,[19-29] especially when baseline CBF is low,[30] as is commonly the case in the first 24 hours after injury.[31-37] An increased frequency of brain regions with very low CBF has been demonstrated in head-injured patients who were acutely hyperventilated.[19,28,29] In addition, low levels of jugular venous oxygen saturation ($SjvO_2$) can be increased and lactate levels in the jugular venous effluent can be decreased by reducing the degree of hyperventilation.[21,30,38]

The deleterious effect of hyperventilation is difficult to prove. Muizelaar and colleagues[22] performed a study that included a near normocapnic group in which $Paco_2$ was maintained at approximately 35 mm Hg, and a hypocapnic group in which $Paco_2$ was maintained in the vicinity of 25 mm Hg. Outcomes at 3 and 6 months after injury were not different. However, in a subset of patients with the best initial motor scores, outcome was better in the normocapnic group. These patients with good motor scores probably represented a subgroup in which the severity of injury was such that, although they needed tracheal intubation, their clinical condition may have been such that hyperventilation was not necessarily required for control of ICP and who therefore had little to gain from hyperventilation. Thus "prophylactic" hyperventilation seemed inadvisable. That conclusion has been extrapolated far beyond the circumstances of relatively mild TBI.

Hyperventilation should not be an automatic component of every "neuroanesthetic." There should be an indication for its institution (usually increased or uncertain ICP or the need to improve conditions in the surgical field, or both). Hyperventilation has the potential to cause an adverse effect and should be withdrawn as the indication for it subsides. The concern regarding the hazards of hypocapnia, which evolved in the context of TBI, has influenced all of neurosurgery. In particular, it is now widely avoided in the management of SAH because of the low CBF state that is known to occur.[39] In addition, brain tissue beneath retractors can have a similarly reduced CBF.[24,40] However, hyperventilation, used as briefly as possible, is still very much a component of "rescue therapy," when herniation is imminent or in progress, or when conditions in the surgical field are too difficult to allow surgery to proceed.

Duration of Hypocapnia-Induced Reduction in Cerebral Blood Flow

The effect of hypocapnia on CBF is not sustained. Figure 70-6 is a nonquantitative representation of changes in CBF and CSF pH occurring in association with a sustained period of hyperventilation. With the onset of hyperventilation, the pH of both CSF and the brain's extracellular fluid space increases, and CBF decreases abruptly. However, the cerebral alkalosis is not sustained. By alterations in function of the enzyme carbonic anhydrase, the concentration of bicarbonate in CSF and the brain's extracellular fluid space is reduced, and in a time course of 8 to 12 hours, the pH of these compartments returns to normal.[41] Simultaneously, CBF returns toward normal levels.[41,42] The implications are twofold. First, patients should be hyperventilated for only as long as a reduction in brain volume is required. Prolonged but unnecessary hyperventilation can lead to a circumstance wherein subsequent clinical events call for additional maneuvers to reduce the volume of the intracranial contents and incremental hyperventilation is not feasible. If, after adaptation, $Paco_2$ is already in the 23 to 25 mm Hg range, additional hyperventilation may risk pulmonary barotrauma. Second, in a patient who has been hyperventilated for a sustained period (e.g., 2 days in an ICU setting), restoration of $Paco_2$ from values in the vicinity of 25 mm Hg to typical normal

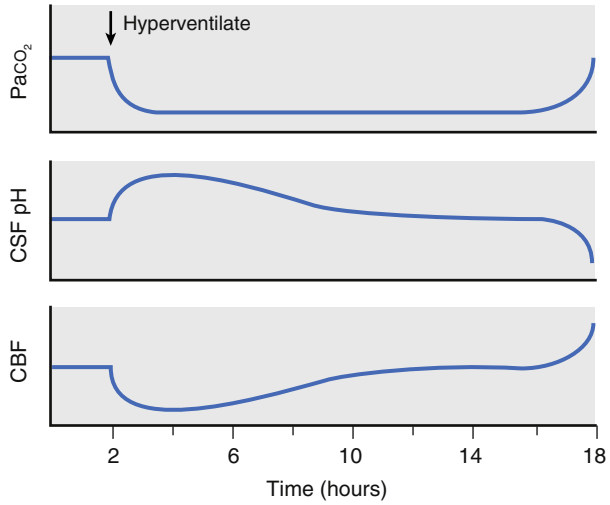


Figure 70-6. Partial pressure of carbon dioxide in the arterial blood ($Paco_2$), cerebral blood flow (CBF), and cerebrospinal fluid (CSF) pH changes with prolonged hyperventilation. Although the decreased arterial $Paco_2$ (and the systemic alkalosis) persists for the duration of the period of hyperventilation, the pH of the brain and CBF return toward normal over 8 to 12 hours.

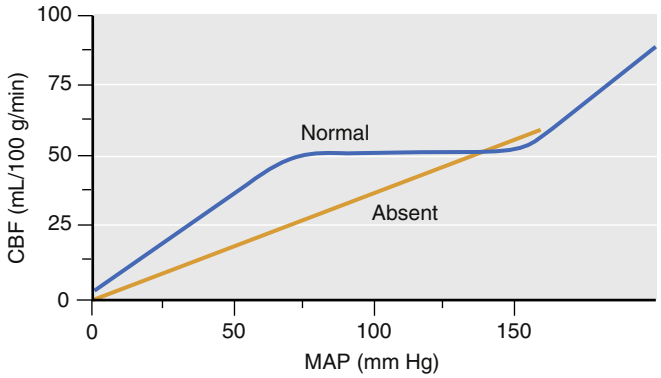


Figure 70-7. Normal and absent autoregulation curves. The "absent" curve indicates a pressure-passive condition in which cerebral blood flow (CBF) varies in proportion to cerebral perfusion pressure (CPP). This curve is drawn to indicate subnormal CBF values during normotension, as have been shown to occur immediately after head injury[21] and subarachnoid hemorrhage.[39] The potential for modest hypotension to cause ischemia is apparent. *MAP,* Mean arterial pressure.

values (e.g., 40 mm Hg) should ideally be accomplished slowly. A sudden increase in $Paco_2$ from 25 to 40 mm Hg in a patient who has been chronically hyperventilated will have the same physiologic effect that a rapid change from 40 to 55 mm Hg would have in a previously normocapnic patient.

If hypocapnia has been required as an adjunct to brain relaxation during craniotomy, $Paco_2$ should also be allowed to increase once the retractors are removed (if dural closure requirements permit) to minimize the residual intracranial pneumatocele (see the section on Pneumocephalus).

MANAGEMENT OF ARTERIAL BLOOD PRESSURE

Acceptable arterial blood pressure limits should similarly be agreed on at the beginning of a neurosurgical procedure. One of the prominent themes of contemporary neurosurgery is that CPP should be maintained at normal or even high-normal levels after acute central nervous system insults and during most intracranial neurosurgical procedures. This concept has evolved from the growing appreciation that CBF is frequently very low in some brain regions after acute neurologic insults, in particular TBI and SAH. Two additional factors should be considered. The first is that the autoregulatory response to decreasing blood pressure may not be intact throughout the brain. Figure 70-7 depicts the ischemic hazard that attends the circumstance of a low resting CBF and absent autoregulation even at blood pressure levels considered safe when autoregulation is intact. In addition, maintenance of arterial pressure is also relevant to brain compressed under retractors[24] because the effective perfusion pressure is lowered by increased local tissue pressure.

Although the only supportive data are anecdotal, we nonetheless believe that an aggressive attitude toward arterial blood pressure support should also be given to patients who have sustained a recent spinal cord injury, to a spinal cord that is under compression or at risk for compression or vascular compromise because of a disease process (most commonly cervical spinal stenosis with or without ossification of the posterior longitudinal ligament) or an intended surgical procedure, and to those patients undergoing surgery involving retraction of the spinal cord. We believe that arterial blood pressure during anesthesia in these patients should be maintained as closely as possible to, and certainly within, 10% of average awake values.

STEROIDS

The administration of steroids for the purpose of reducing or limiting the formation of edema has a well-established place in neurosurgery. The efficacy of steroids in reducing the edema and increased blood-brain barrier (BBB) permeability associated with tumors (and only tumors) is well confirmed.[43-46] Although the time course of this effect is relatively rapid, it is too slow for the management of acute intraoperative events. However, administration beginning 48 hours before an elective surgical procedure has the potential to reduce edema formation and improve the clinical condition by the time of craniotomy.[43,47,48] Although clinical improvement occurs within 24 hours,[47] a reduction in ICP may not occur for 48 to 72 hours after the initiation of therapy.[47] Steroids somehow improve the viscoelastic properties of the intracranial space before a reduction in edema occurs, although the mechanism remains undefined.[48] The practice of administering steroids to patients with TBI has been abandoned as a result of controlled trials that demonstrated either no benefit or deleterious effects.[49]

OSMOTHERAPY AND DIURETICS

Hyperosmolar agents and diuretics are used widely in neurosurgery and neurocritical care to reduce the volume of the brain's intracellular and extracellular fluid

compartments. Both osmotic and loop diuretics have been used. Although loop diuretics can be effective,[50] hyperosmolar agents are more widely used.

Mannitol

Mannitol is used most commonly intraoperatively because of its long history of rapid and effective reduction of brain volume. The doses vary from 0.25 g/kg to 100 g "for all comers"; 1.0 g/kg is the most common dose. However, a systematic study in TBI demonstrated that an equivalent initial ICP-reducing effect can be achieved with 0.25 g/kg, although that effect cannot be as sustained as when larger doses are used.[51] Others use doses greater than 1.0 g/kg.[52] Mannitol should be administered by infusion (e.g., over 10 to 15 minutes). Sudden exposure of the cerebral circulation to extreme hyperosmolarity can have a vasodilatory effect, which can produce brain engorgement and increased ICP, both of which do not occur with slower administration.

Mannitol enters the brain and, over a reasonably short time course, appears in the CSF space.[53] The possibility that the mannitol that gains access to the parenchyma aggravates swelling has resulted in varying degrees of reluctance among clinicians to administer mannitol.[54] Most clinicians nonetheless find it to be a mainstay of ICP management. Is it only effective when some degree of BBB integrity is preserved in a significant portion of the brain? Clinicians respond to this concern by making empirical use of this agent; that is, if it is effective in reducing ICP or improving conditions in the surgical field, repeated doses are administered. The use of hyperosmolar agents is theoretically limited by an upper acceptable osmolarity limit of approximately 320 mOsm/L (although the data supporting the validity of that limit is "soft"[55]). However, in life-threatening situations, the use is frequently empirical, and incremental doses (e.g., 12.5 g of mannitol) are administered until a clinical response is no longer observed.

Hypertonic Saline

In the critical care environment (see Chapter 105), the use of hypertonic saline (HTS) in place of mannitol is increasing.[56] Although the initial ICP effects of equiosmolar doses of mannitol and HTS are very similar,[57-60] HTS may have some advantages in the ICU, where repeated administration makes the adverse effects (e.g., diuresis, renal injury) more likely to have clinical significance. In addition, there are anecdotal reports of HTS being effective in patients who were refractory to mannitol.[61,62] Although there is enthusiasm for HTS,[61,63,64] supporting data are limited.[65] Furthermore, because of the variations in HTS concentrations (3%, 7.5%, 15%, 23.4%) and osmolar loads in the various studies, it is difficult to make specific recommendations.

Diuretic Combinations

The combination of a loop diuretic (usually furosemide) and an osmotic diuretic is sometimes used. The superficial rationale is that mannitol establishes an osmotic gradient that draws fluid out of brain parenchyma and that the furosemide, by hastening excretion of water from the intravascular space, facilitates the maintenance of that gradient. A second mechanism may add additional justification for the practice of combining the two diuretics. Neurons and glia have homeostatic mechanisms to ensure regulation of cell volume. Neurons and glia that shrink in response to an increased osmolarity in the external environment recover their volume rapidly as a consequence of the accumulation of so-called *idiogenic osmoles*, which serve to minimize the gradient between the internal and external environments. One of those idiogenic osmoles is chloride. Loop diuretics inhibit the chloride channel through which this ion must pass and thereby retard the normal volume-restoring mechanism.[66,67] These diuretic combinations may cause hypovolemia and electrolyte disturbances.

The normal volume regulatory mechanisms of neurons and glia may also be relevant to the phenomenon of rebound swelling. Rebound is commonly attributed to the prior use of mannitol and assumed to be a function of the accumulation of mannitol in cerebral tissue. Although possible, the rebound may in fact be hypertonic rebound rather than mannitol rebound. After a sustained period of hyperosmolarity of any etiology, rebound swelling of neurons and glia (which have accumulated idiogenic osmoles) may occur in the event that systemic osmolarity decreases rapidly toward normal levels. Rebound cerebral swelling can certainly occur after an episode of extreme increase in blood glucose concentration. The use of HTS rather than mannitol will not obviate this phenomenon.

ANTICONVULSANTS

The general principle is that any acute irritation of the cortical surface has the potential to result in seizures. This includes acute neurologic events such as TBI and SAH.[68,69] Cortical incisions and brain surface irritation by retractors may similarly be potential foci. Given the relatively benign nature of contemporary anticonvulsants (e.g., levetiracetam), routine administration to patients undergoing most supratentorial craniotomies, as well as to patients who have sustained a significant recent TBI[68] or a SAH, seems appropriate in the absence of a contraindication. There is no necessity for rapid administration because the intention is to prevent seizures during the postoperative period.

POSITIONING

The intended surgical position and the necessary positioning aids should be agreed upon at the outset. The commonly used positions and positioning aids and supports are listed in Box 70-5 (see Chapter 41).

General Considerations

The prolonged duration of many neurosurgical procedures should be taken into account in all positions. Pressure points should be identified and padded carefully. Pressure and traction on nerves must be avoided. Given the high risk of thromboembolic complications in neurosurgical patients, precautions including support hose and sequential compression devices are warranted. For cranial procedures, some component of head-up posturing (e.g., 15 to 20 degrees) is used to ensure optimal venous drainage.

BOX 70-5 ***Common Neurosurgical Positions and Positioning Aids***

Positions

- Supine
- Lateral (park bench)
- Semi-lateral (Jannetta)
- Prone
- Sitting

Positioning Aids/Supports

- Pin ("Mayfield") head holder
- Radiolucent pin head holder
- Horseshoe head rest
- Foam head support (e.g., Voss, O.S.I., Prone-View)
- Vacuum mattress ("bean bag")
- Wilson-type frame
- Andrews ("hinder binder")-type frame
- Relton-Hall (four-poster) frame

The conspicuous exception occurs with evacuation of a chronic subdural hemorrhage, after which patients are usually nursed flat to discourage reaccumulation of fluid. Patients are occasionally also maintained flat after CSF shunting to avoid overly rapid collapse of the ventricles.

Supine

The supine position is used with the head neutral or rotated for frontal, temporal, or parietal access. Extremes of head rotation can obstruct the jugular venous drainage, and a shoulder roll can attenuate this problem. The head is usually in a neutral position for bifrontal craniotomies and transsphenoidal approaches to the pituitary. The head-up posture is best accomplished by adjusting the operating table to a chaise longue (lawn chair) position (flexion, pillows under the knees, slight reverse Trendelenburg). This orientation, in addition to promoting cerebral venous drainage, decreases back strain.

Semilateral

The semilateral position, also known as the Jannetta position, named after the neurosurgeon who popularized its use for microvascular decompression of the fifth cranial nerve, is used for retromastoid access. It is achieved by lateral tilting of the table 10 to 20 degrees combined with a generous shoulder roll. Again, extreme head rotation, sufficient to cause compression of the contralateral jugular vein by the chin, should be avoided.

Lateral

The lateral position can be used for access to the posterior parietal and occipital lobes and the lateral posterior fossa including tumors at the cerebellopontine angle and aneurysms of the vertebral and basilar arteries. An axillary roll is important for preventing brachial plexus injury.

Prone

The prone position is used for spinal cord, occipital lobe, craniosynostosis, and posterior fossa procedures. The prone position has also been aptly referred to as the *Concorde position*, because for cervical spine and posterior fossa procedures, the final position commonly entails neck flexion, reverse Trendelenburg, and elevation of the legs. This orientation serves to bring the surgical field to a horizontal position. There should be a plan for detaching and reattaching monitors in an orderly manner to prevent an excessive monitoring "window." Awake tracheal intubation and prone positioning may be warranted in patients with an unstable cervical spine in whom an unchanged neurologic status should be confirmed before induction of anesthesia in the final surgical position. This approach is also sometimes performed in obese patients.

The head can be secured in a pin head holder (applied before the turn) or positioned on a disposable foam head rest or, less frequently, a horseshoe head rest. A complication of the prone position, which requires constant attention, is retinal ischemia and blindness caused by orbital compression causing central retinal vessel occlusion. It must be intermittently confirmed (i.e., every 15 minutes) and after any surgery-related head or neck movement that pressure has not come to bear on the eye. However, not all postoperative vision loss (POVL) is a result of direct orbital compression (see Chapter 100). Ischemic optic neuropathy actually appears to be a more frequent cause of POVL than pressure-causing occlusion of central retinal vessels. The cause-and-effect relationships associated with ischemic optic neuropathy are uncertain, but low arterial pressure, low hematocrit level, lengthy surgical procedures, and large intravascular volume fluid administration are statistically associated with the phenomenon.[70] POVL is discussed extensively in Chapter 100.

Direct pressure can also result in various degrees of pressure necrosis of the forehead, maxillae, and chin, especially with prolonged spinal procedures. Pressure should be distributed as evenly as possible over facial structures. Other pressure points to check include the axillae, breasts, iliac crests, femoral canals, genitalia, knees, and heels. When the arms are placed in the "stick 'em up" position, traction on the brachial plexus must be avoided. That can usually be accomplished by not exceeding a "90-90" position (arms abducted not >90 degrees; elbows extended not >90 degrees) with care taken to ensure that the elbow is anterior to the shoulder to prevent wrapping of the brachial plexus around the head of the humerus. An antisialagogue (e.g., glycopyrrolate) and an adhesive (e.g., benzoin) may help reduce loosening of the tape used to secure the endotracheal tube.

An objective during prone positioning, especially for lumbar spine surgery, is the avoidance of compression of the inferior vena cava. Impairment of vena cava return diverts blood to the epidural plexus and increases the potential for bleeding during spinal surgery. Minimizing vena cava pressure is an objective of all spinal surgery frames and is accomplished effectively by the Wilson, Andrews, and Jackson variants. However, this does introduce a risk of air embolism,[71,72] although severe clinical occurrences have been very infrequent.[73]

There should be attention to preventing injury to the tongue in the prone position. With both cervical and posterior fossa procedures, it is frequently necessary to flex the neck substantially to facilitate surgical access. This reduces the anterior-posterior dimension of the oropharynx, and compression ischemia of the base of the tongue (as well as the soft palate and posterior wall of

the pharynx) can occur in the presence of foreign bodies (endotracheal tube, esophageal stethoscope, oral airway). The consequence can be macroglossia, caused by accumulation of edema after reperfusion of the ischemic tissue causing airway obstruction of rapid onset after extubation (discussed later). Accordingly, placing unnecessary paraphernalia in the oral cavity and pharynx should be avoided. Omitting the oral airway entirely is unwise because the tongue may then protrude between and be trapped by the teeth as progressive swelling of facial structures occurs during a prolonged prone procedure. A rolled gauze bite block prevents this problem without adding bulk to the oropharynx.

Sitting

There have been several reviews of large experiences with the sitting position.[74-78] All concluded that the sitting position can be used with acceptable rates of morbidity and mortality. However, these reports were prepared by groups that perform 50 to 100 or more of these procedures per year, and the hazards of the sitting position may be more frequent for teams who have fewer occasions to use it. The sitting position can be avoided by using one of its alternatives (prone, semilateral, lateral). However, this position will continue to be used because even surgeons who are inclined to use alternative positions may opt for it when access to midline structures (e.g., the quadrigeminal plate, the floor of the fourth ventricle, the pontomedullary junction, and the vermis) is required. Nonetheless, alternative positions for posterior fossa surgery are available and should be considered when contraindications to the sitting position exist.

Achieving the Sitting Position. The properly positioned patient is more commonly in a modified recumbent position as shown in Figure 70-8 rather than truly sitting. The legs should be kept as high as possible (usually with pillows under the knees) to promote venous return. Ideally, the head holder should be attached to the back portion of the table (see Fig. 70-8, *A*) rather than to the portions under thighs or legs[79] (see Fig. 70-8, *B*). This permits lowering of the head and closed chest massage if necessary, without the necessity of first taking the patient out of the head holder.

When procedures are performed in the sitting position, the clinician should think in terms of measuring and maintaining perfusion pressure at the level of the surgical field. This is best accomplished by referencing transducers to the level of the external auditory canal. If a manual blood pressure cuff on the arm is used, a correction* to allow for the hydrostatic difference between the arm and the operative field should be applied.

A series of hazards are associated with the sitting position. Circulatory instability, macroglossia, and quadriplegia are discussed in this section. Pneumocephalus is discussed in its own section. Venous air embolism (VAE) and paradoxical air embolism (PAE) are discussed in Venous Air Embolism. Several of these hazards are also relevant when cervical spine and posterior fossa procedures are performed in nonsitting positions but occur with greater frequency in the sitting position.

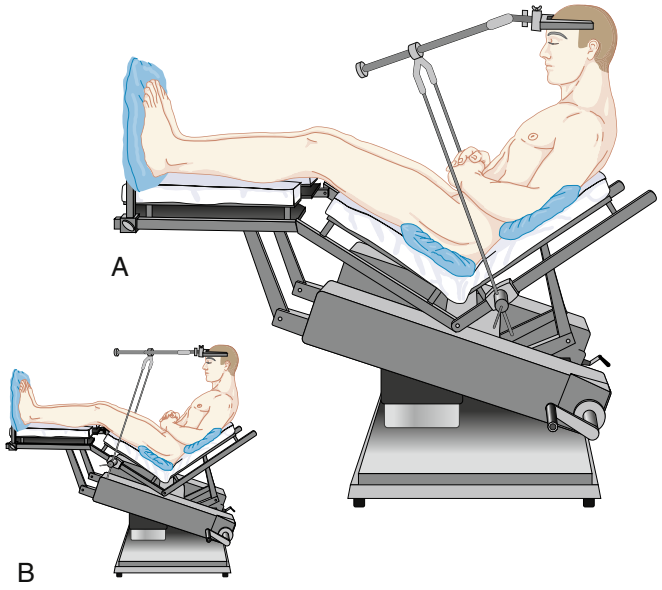


Figure 70-8. The sitting position. The patient is typically semirecumbent rather than sitting. **A,** The head-holder support is correctly positioned so that the head can be lowered without the necessity to first detach the head holder. **B,** This configuration, with the support attached to the thigh portion of the table, should be avoided. *(From Martin JT:* Positioning in anesthesia and surgery, *Philadelphia, 1988, Saunders, with permission.)*

Cardiovascular Effects of the Sitting Position. Hypotension should be avoided. Prepositioning hydration; compressive stockings; and slow, incremental adjustment of table position are appropriate. Intravenous vasopressor administration may be required in some patients. However, in most healthy subjects the hemodynamic changes are of a nonthreatening magnitude. In a study of healthy anesthetized adult subjects ages 22 to 64 years old, Marshall[80] observed relatively modest changes. Mean arterial blood pressure was relatively unaffected, whereas wedge pressure, stroke volume, and cardiac index decreased—the latter by approximately 15%—although there was some variation with the anesthetics used. The combination of an unchanged MAP (which in general requires the use of a light, high sympathetic tone anesthetic) and a reduced cardiac index implies that systemic vascular resistance (SVR) increased. Their calculations and the observations of other investigators[81] reveal significant increases in SVR. For patients in whom an abrupt increase in SVR may be poorly tolerated, the sitting position may represent a physiologic threat and alternative positions should be considered. A pulmonary artery catheter may be warranted only when there is clinical or historical evidence of antecedent coronary artery or valvular heart disease.

During procedures performed in the sitting position, MAP should be transduced at or corrected to head level to provide a meaningful index of CPP. Specifically, CPP (MAP – Estimated ICP) should be maintained at a minimum value of 60 mm Hg in healthy patients in whom it is reasonable to assume a normal cerebral vasculature.

*A column of blood 32 cm high exerts a pressure of 25 mm Hg.

The safe lower limit should be raised for elderly patients, for those with hypertension or known cerebral vascular disease, or for those with degenerative disease of the cervical spine or cervical spinal stenosis who may be at risk for decreased spinal cord perfusion, and in the event that substantial or sustained retractor pressure must be applied to brain or spinal cord tissue.

Macroglossia. There have been sporadic reports of upper airway obstruction after posterior fossa procedures in which swelling of pharyngeal structures, including the soft palate, posterior pharyngeal wall, and base of the tongue, has been observed.[46,82] These episodes have been attributed to edema formation at the time of reperfusion after trauma or prolonged ischemia, occurring as the result of foreign bodies (usually oral airways) causing pressure on these structures in the circumstances of lengthy procedures with sustained neck flexion (which is usually required to improve access to posterior structures). It is customary to maintain at least two fingerbreadths between the chin/mandible and the sternum/clavicle to prevent excessive reduction of the anterior-posterior diameter of the oropharynx. In addition, it is our practice to position patients with the oral airway in place and then, once the final head position is achieved, withdraw it and replace it with a gauze roll between the teeth. Consideration of the macroglossia phenomenon may also be relevant as clinicians contemplate the use of transesophageal echocardiography (TEE) in the neurosurgery suite. The centers that routinely use TEE in neurosurgery mostly use pediatric diameter probes to avoid trauma to pharyngeal and perilaryngeal structures.

Quadriplegia. The sitting position has been implicated as a cause of rare instances of unexplained postoperative quadriplegia. It has been hypothesized[83] that the neck flexion that is a common concomitant of the seated position may result in stretching or compression of the cervical spinal cord. This possibility may represent a relative contraindication to the use of this position in patients with significant degenerative disease of the cervical spine, especially when there is evidence of associated cerebral vascular disease. The arterial blood pressure management implications are mentioned in the preceding section on cardiovascular effects. It may also represent a justification for somatosensory evoked response monitoring during the positioning phase of a sitting procedure for patients perceived to be at high risk. (Also see Chapter 49.)

PNEUMOCEPHALUS

The issue of pneumocephalus arises most often in connection with posterior fossa craniotomies performed with a head-up posture.[84,85] During these procedures, air may enter the supratentorial space, much as air enters an inverted pop bottle. Depending on the relationship of the brainstem and temporal lobes to the incisura, the pressure in the air collection may or may not be able to equilibrate with atmospheric pressure. This phenomenon has relevance to the use of N_2O because any N_2O that enters a trapped gas space augments the volume of that space. In those (probably uncommon) intraoperative circumstances where there is, in fact, a completely closed intracranial gas space, the use of N_2O may result in an effect comparable with that of an expanding mass lesion. We do not view N_2O as absolutely contraindicated because, before dural closure, intracranial gas is probably only rarely trapped. Nonetheless, attention to this possibility is important when one is presented with the problem of an increasingly "tight" brain during a posterior fossa craniotomy.[86,87]



Figure 70-9. Postoperative computed tomographic scan demonstrating a large pneumocephalus after a subfrontal approach to a suprasellar glioma. Immediately postoperatively, the patient was confused and agitated, and he complained of a severe headache.

During a posterior fossa procedure done in a head-up posture, when surgical closure has reached a stage such that the intracranial space has been completely sealed from the atmosphere, N_2O should be omitted because of the possibility of contributing to a tension pneumocephalus. Note that the use of N_2O up to the point of dural closure may actually represent a clinical advantage[88] because the gas pocket can be expected to shrink more rapidly because of the presence of N_2O (because N_2O diffuses much more quickly than nitrogen). Tension pneumocephalus is often naively viewed as exclusively a function of the use of N_2O. However, tension pneumocephalus can most certainly occur as a complication of intracranial neurosurgery entirely *unrelated* to the use of N_2O.[89] It is one of the causes of delayed awakening or nonawakening after both posterior fossa and supratentorial procedures (Fig. 70-9).[89,90] It occurs because air enters the cranium when the patient is in a head-up position at a time when the volume of the intracranial contents has been reduced because of some combination of hypocapnia, good venous drainage, osmotic diuresis, and CSF loss from the operative field. When the cranium is closed and the patient is returned to the near supine position, CSF,

venous blood volume, and extracellular fluid return or reaccumulate and the air pocket becomes an unyielding mass lesion (because of the very slow diffusion of nitrogen). It may cause delayed recovery of consciousness or severe headache. Among supratentorial craniotomies, the largest residual air spaces occur after frontal skull base procedures in which energetic brain relaxation measures are used to facilitate subfrontal access (see Fig. 70-9). At the end of these procedures, typically done in a supine/brow-up position, the intracranial dead space cannot be filled with normal saline as is commonly done with smaller craniotomy defects, and there may be a large residual pneumatocele. We doubt that the possible occurrence of this phenomenon represents a contraindication to N_2O. However, withdrawal of N_2O may be appropriate at the time of scalp closure. The diagnosis of pneumocephalus is established by a brow-up lateral radiography or, more commonly, a CT scan. The treatment is a twist-drill hole followed by needle puncture of the dura.

Residual intracranial air should be considered at the time of repeat anesthesia, both neurosurgical and nonneurosurgical. Air frequently remains evident on CT scan for more than 7 days after a craniotomy.[91] Pneumocephalus can also develop de novo in the postoperative period in patients who have a residual dural defect and a communication between the nasal sinuses and the intracranial space.[92]

VENOUS AIR EMBOLISM

The rate of occurrence of VAE varies according to the procedure, the intraoperative position, and the detection method used. During posterior fossa procedures performed in the sitting position, VAE is detectable by precordial Doppler in approximately 40% of patients and by TEE in as much as 76%.[93-96] The incidence of VAE during posterior fossa procedures performed in nonsitting positions is much less (12% using precordial Doppler in the report of Black and colleagues[76]), and it is probable but unproven that the average volume of air entrained per event is also smaller. The rate of VAE is apparently lower with cervical laminectomy (25% using TEE in the sitting position versus 76% for posterior fossa procedures[95]). Although VAE is principally a hazard of posterior fossa and upper cervical spine procedures, especially when they are performed in the sitting position, it can occur with supratentorial procedures. The most common situations involve tumors, most often parasagittal or falcine meningiomas, that encroach on the posterior half of the sagittal sinus (Fig. 70-10) and craniosynostosis procedures, typically performed in children.[97,98] Pin sites can also serve as VAE access sites. Accordingly, pin head holders should be removed after the patient has been taken out of significant degrees of the head-up positioning. Spontaneous ventilation (with the attendant intermittent negative intrathoracic pressure) will increase the risk of air entrainment. A 6% incidence of Doppler-detectable VAE was reported in a recent series of deep-brain stimulator placement procedures performed in spontaneously breathing patients.[99]

The common sources of critical VAE are the major cerebral venous sinuses, in particular the transverse, the sigmoid, and the posterior half of the sagittal sinus, all of which may be noncollapsible because of their dural attachments. Air entry may also occur via emissary veins, particularly from suboccipital musculature, via the diploic space of the skull (which can be violated by both the craniotomy and pin fixation) and the cervical epidural veins. It is believed (but not confirmed by systematic study) that the VAE risk associated with cervical laminectomy is more likely when the exposure requires dissection of suboccipital muscle with the potential to open emissary veins to the atmosphere at their point of entry into occipital bone. There is also anecdotal evidence[100] that air under pressure in the ventricles or subdural space can occasionally enter the venous system, perhaps along the normal egress route of the CSF.

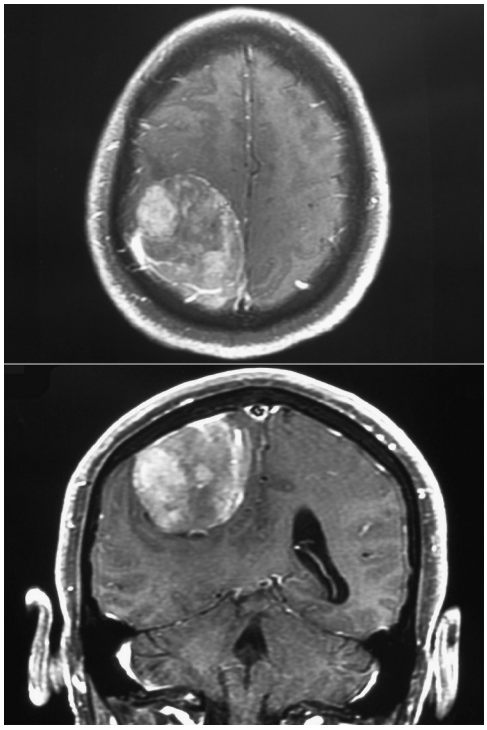


Figure 70-10. Axial *(top)* and coronal *(bottom)* magnetic resonance images of a parasagittal meningioma. Resection of meningiomas arising from the dural reflection overlying the sagittal sinus or from the dura of the adjacent convexity or falx often entails a risk of venous air embolism because of the proximity of the sagittal sinus (the triangular structure at the superior end of the interhemispheric fissure in the bottom panel).

Detection of Venous Air Embolism

The monitors used for the detection of VAE should provide (1) a high level of sensitivity, (2) a high level of specificity, (3) a rapid response, (4) a quantitative measure of the VAE event, and (5) an indication of the course of recovery from the VAE event. The combination of a precordial Doppler and expired CO_2 monitoring meets these criteria and is the current standard of care. Doppler placement in a left or right parasternal location between the second and third or third and fourth ribs has a very high detection rate for gas embolization,[101] and when good heart tones are heard, maneuvers to confirm adequate placement appear to be unnecessary. The TEE is

more sensitive than the precordial Doppler (Fig. 70-11) to VAE[102] and offers the advantage of also identifying right-to-left shunting of air. However, its safety during prolonged use (especially with pronounced neck flexion) is not well established. Expired nitrogen analysis is theoretically attractive. However, the expired nitrogen concentrations involved in anything less than catastrophic VAE are very small and push the available instrumentation to the limits of its sensitivity.[103]

Figure 70-12 presents the physiologic and monitor response to an air embolic event, and Box 70-6 offers an appropriate management response to such an event.

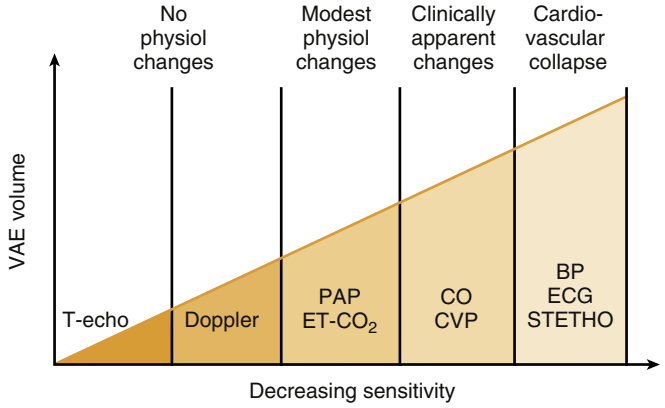


Figure 70-11. The relative sensitivity of various monitoring techniques to the occurrence of venous air embolism. *BP*, Blood pressure; *CO*, cardiac output; *CVP*, central venous pressure; *ECG*, electrocardiogram; *ET-CO_2*, end-tidal carbon dioxide; *PAP*, pulmonary artery pressure; *Stetho*, esophageal stethoscope; *T-echo*, transesophageal echo.

Which Patients Should Have a Right Heart Catheter?

Essentially, all patients who undergo sitting posterior fossa procedures should have a right heart catheter placed. Although life-threatening, VAE is relatively uncommon, a catheter that permits immediate evacuation of an air-filled heart is occasionally the sine qua non for resuscitation. The latitudes are much wider with the nonsitting positions, and it is frequently appropriate, after a documented discussion with the surgeon, to omit the right heart catheter. The perceived risks of VAE associated with the intended procedure, and the patient's physiologic reserve are the variables that contribute to the decision. Microvascular decompression of the fifth cranial nerve for tic douloureux or the seventh cranial nerve for hemifacial spasm are examples of procedures

BOX 70-6 ***Management of an Acute Air Embolic Event***

1. Prevent further air entry
   - Notify surgeon (flood or pack surgical field)
   - Jugular compression
   - Lower the head
2. Treat the intravascular air
   - Aspirate right heart catheter
   - Discontinue N_2O
   - Fio_2: 1.0
   - Pressors, inotropes
   - Chest compression

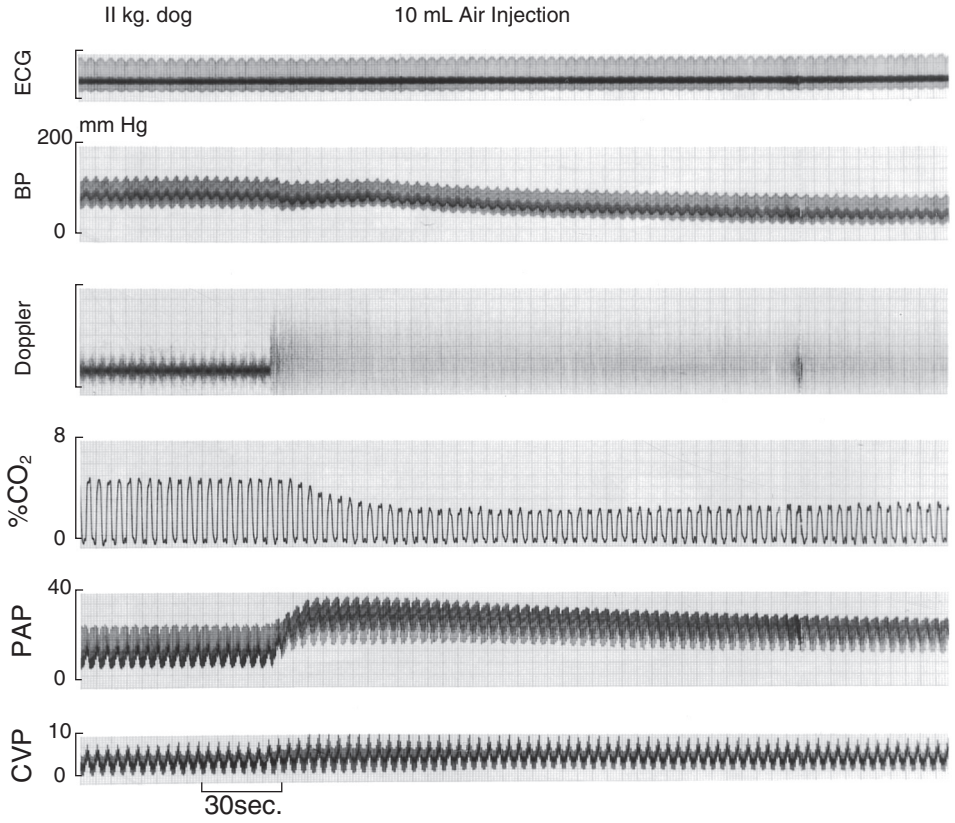


Figure 70-12. The responses of the electrocardiogram (ECG), arterial pressure, pulmonary artery pressure (PAP), pan-tidal CO_2 concentration, a precordial Doppler and central venous pressure (CVP) to the intravenous administration of 10 mL of air over 30 seconds to an 11-kg dog.

for which the right heart catheter is usually omitted. The essentially horizontal semilateral position and the very limited retromastoid craniectomy that is required have resulted (at our institution) in a very low incidence of Doppler-detectable VAE. One should know the local surgical practices, particularly with respect to the degree of head-up posture, before becoming casual about omitting the right atrial catheter. With regard to the Jannetta procedure, the necessary retromastoid craniectomy is performed in the angle between the transverse and sigmoid sinuses, and venous sinusoids and emissary veins in the suboccipital bone are common. If this procedure is performed with any degree of head-up posturing, the risk of VAE may still be substantial.

Which Vein Should Be Used for Right Heart Access?

Although some surgeons may ask that neck veins not be used, a skillfully placed jugular catheter is usually acceptable. In a very limited number of patients, high ICP may make the head-down posture undesirable. In others, unfavorable anatomy with an increased likelihood of a difficult cannulation and hematoma formation may also encourage the use of alternate access sites.

Positioning the Right Heart Catheter

The investigation of Bunegin and colleagues suggested that a multi-orificed catheter should be located with the tip 2 cm below the superior vena caval–atrial junction and a single orificed catheter with the tip 3 cm above the superior vena caval–atrial junction.[104] Although these small distinctions in location may be relevant for optimal recovery of small volumes of air when cardiac output is well maintained, for the recovery of massive volumes of air in the face of cardiovascular collapse, anywhere in the right atrium should suffice. Confirmation of right heart placement can be accomplished by (1) radiography or (2) intravascular electrocardiography (ECG).[105] Although there is no literature to support the practice, with catheter access via the right internal jugular vein, a measured placement to the level of the second or third right intercostal space should suffice when the catheter passes readily. The intravascular electrocardiography technique makes use of the fact that an ECG "electrode" placed in the middle of the right atrium will initially "see" an increasing positivity as the developing P-wave vector approaches it (Fig. 70-13), and then an increasing negativity as the wave of atrial depolarization passes and moves away from it. The resultant biphasic P wave is characteristic of an intraatrial electrode position. The technique requires that the CVP catheter become an exploring ECG electrode. This is accomplished by filling the catheter with an electrolyte solution (bicarbonate is best) and attaching an ECG lead (the leg lead if lead II is selected) to the hub of the CVP catheter. Commercial CVP kits with an ECG adapter are available. The ECG configurations that will be observed at various intravascular locations are shown in Figure 70-13. To minimize the microshock hazard, a battery-operated ECG unit is preferable, and any unnecessary electrical apparatus should be detached from the patient during catheter placement.

Paradoxical Air Embolism

The possibility of the passage of air across the interatrial septum via a patent foramen ovale (PFO), which is known to be present in approximately 25% of adults, is a concern.[106] The risk is major cerebral and coronary morbidity. However, the precise definition of the morbidity that can actually be attributed to PAE is not clear. Although the minimal pressure required to open a probe patent foramen ovale is not known with certainty, the necessary gradient may be as much as 5 mm Hg. In a clinical investigation, Mammoto and colleagues observed that PAE occurred only in the context of major air embolic events, suggesting that significant increases in right heart pressures are an important predisposing factor of the occurrence of PAE.[107] Several clinical investigations have examined factors that influence the right atrial pressure (RAP) to left atrial pressure (LAP) gradient. The use of PEEP increases the incidence of a positive RAP to pulmonary wedge pressure gradient[108] and generous fluid administration (e.g., 2800 mL/patient versus 1220 mL/control patient[109]) reduces it. As a result, the use of positive end-expiratory pressure

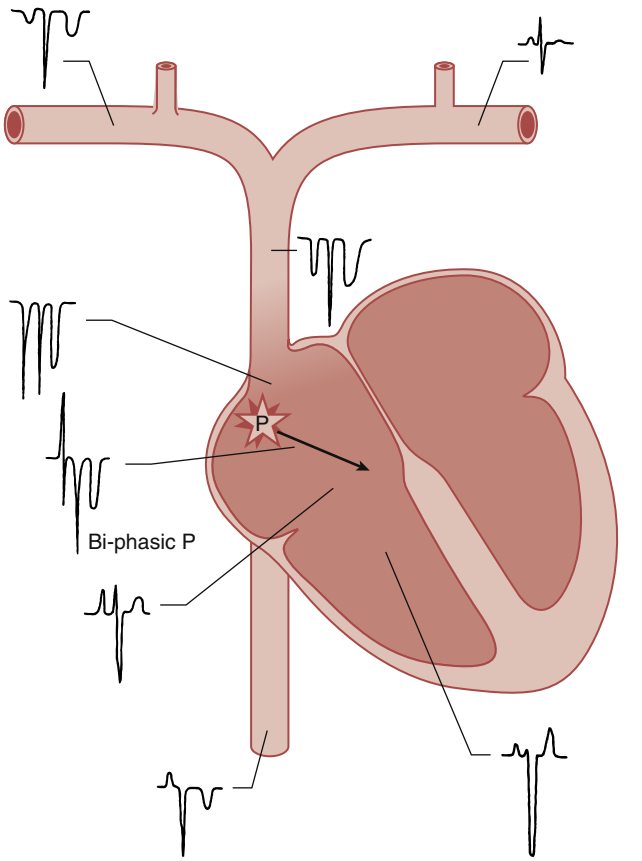


Figure 70-13. Electrocardiogram (ECG) configurations observed at various locations when a central venous catheter is used as an intravascular ECG electrode. The configurations in the figure will be observed when Lead II is monitored and the positive electrode (the leg electrode) is connected to the catheter. *P* indicates the sinoatrial node. The *black arrow* indicates the P-wave vector. Note the equi-biphasic P wave when the catheter tip is in the mid–right atrial position.[105]

(PEEP), which was once advocated as a means of preventing air entrainment, was abandoned. Subsequently, the practice of more generous fluid administration for patients undergoing posterior fossa procedures evolved. However, even when mean LAP exceeds mean RAP, PAE can still occur because transient reversal of the interatrial pressure gradient can occur during each cardiac cycle.[110]

Some centers have advocated performing bubble studies preoperatively with either precordial ECG[96] or transcranial Doppler (TCD)[111] or prepositioning using TEE[112] to identify patients with a PFO with a view to using alternatives to the sitting position in this subpopulation.[95,113] Some centers thereafter advocate the use TEE to identify paradoxical embolization intraoperatively[95,114] (see Chapter 46). However, none of these practices has become a community-wide standard of care.[78] Furthermore, because the morbid events attributable to PAE have been relatively infrequent, surgeons who are convinced that the sitting position is optimal for a given procedure[78] are loath to be dissuaded from using it on the basis of what may seem like the very minor possibility of an injury to the patient occurring by this mechanism.

Transpulmonary Passage of Air

Air can sometimes traverse the pulmonary vascular bed to reach the systemic circulation.[115-117] Transpulmonary passage is more likely to occur when large volumes of air are presented to the pulmonary vascular filter.[118,119] In addition, pulmonary vasodilators, including volatile anesthetics, may decrease the threshold for transpulmonary passage.[118-120] The magnitude of differences among anesthetics does not appear to mandate any related "tailoring" of anesthetic techniques. However, N_2O should be discontinued promptly after even apparently minor VAE events because of the possibility that air may reach the left-sided circulation either via a PFO or the pulmonary vascular bed.

Box 70-6 presents an approach for responding to an acute VAE event. It includes raising venous pressure by direct compression of the jugular veins. PEEP and the Valsalva maneuver were once advocated. However, both PEEP[108] and the release of a Valsalva maneuver increase the risk of PAE, and the relative superiority of jugular venous compression in raising cerebral venous pressures has been confirmed.[121,122] Furthermore, the impairment of systemic venous return caused by the sudden application of substantial PEEP may be undesirable in the face of the cardiovascular dysfunction already caused by the VAE event.

It has been recommended that a patient who has sustained a hemodynamically significant VAE should be placed in a lateral position with the right side up. The rationale is that air will remain in the right atrium, where it will not contribute to an air lock in the right ventricle and where it will remain amenable to recovery via a right atrial catheter. The first difficulty is that this repositioning is all but impossible with a patient in a pin head holder. In addition, the only systematic attempt to examine the efficacy of this maneuver, albeit performed in dogs, failed to identify any hemodynamic benefit.[123]

BOX 70-7 ***Relative Indications for Intraarterial Pressure Monitoring***

- Elevated intracranial pressure
- Ischemia or incipient ischemia of neural tissue
  - Recent subarachnoid hemorrhage
  - Recent head injury
  - Recent spinal cord injury
  - Intended or possible temporary vessel occlusion
- Circulatory instability
  - Trauma
  - Spinal cord injury (spinal shock)
  - Sitting position
  - Possible barbiturate coma
- Possibility of induced hypotension
- Possibility of induced hypertension
- Anticipated or potential major blood loss
  - Aneurysm clipping
  - Arteriovenous malformations
  - Vascular tumors
  - Tumors involving or adjacent to major venous sinuses
  - Craniofacial reconstruction
  - Extensive craniosynostosis procedures
- Anticipated light anesthesia without paralysis
- Brainstem manipulation, compression, dissection
- Anticipated cranial nerve (CN) manipulation (especially CN V)
- Advantageous for postoperative intensive care
  - Hypervolemic therapy
  - Head injury
  - Diabetes insipidus
- Incidental cardiac disease

Nitrous Oxide

Nitrous oxide diffuses into air bubbles trapped in the vascular tree and, accordingly, N_2O should be eliminated after a clinical VAE event to avoid aggravating the cardiovascular impact. As noted earlier, the PAE phenomenon adds an additional reason for eliminating N_2O *after* the occurrence of VAE. When major VAE occurs, no matter how the RAP-LAP gradient was manipulated before the event, RAP increases abruptly with respect to LAP,[124] and major VAE results in an acutely increased risk of PAE in patients with a PFO.[107] Should N_2O be used in patients at risk for VAE? Some clinicians may decide that it is the "path of least resistance" to simply avoid it and to avoid having to worry about the considerations it creates. However, N_2O can be used with the knowledge that it neither increases the incidence of VAE[125] nor aggravates the hemodynamic response to VAE provided that it is eliminated when VAE occurs.[126]

MONITORING

Neurologic monitoring techniques are discussed in Chapter 49. Invasive monitoring is frequently appropriate in neurosurgery. Some of the numerous indications for an arterial catheter are listed in Box 70-7.

Patients with increased ICP may be intolerant of the vascular engorgement associated with sudden hypertension occurring as a consequence of light anesthesia. Surgical relief of increased ICP may be associated with sudden hypotension as brainstem compression is relieved.

Beat-by-beat arterial pressure monitoring also serves as an important depth of anesthesia monitoring and as a neurologic injury early warning system. Much of the brain is insensate. As a consequence, the intracranial portion of many neurosurgical procedures is not very stimulating and, to achieve circulatory stability, relatively light anesthesia is often necessary. There should be constant attention to the possibility of sudden arousal (most often associated with cranial nerve traction or irritation). This is especially important when paralysis is precluded by the use of electromyographic recording from facial muscles to monitor cranial nerve integrity. Blood pressure responses may reveal imminent arousal; they may also serve to warn a surgeon of excessive or unrecognized irritation, traction, or compression of neurologic tissue. These occur most often with posterior fossa procedures involving brainstem or cranial nerves, and abrupt changes should be reported to the surgeon immediately.

The use of right heart catheters for air retrieval is discussed in the section Venous Air Embolism. In the absence of VAE risk and in the presence of good peripheral venous access, we rarely place right heart catheters for neurosurgical procedures. Antecedent cardiac disease may justify a pulmonary arterial catheter. The use of the precordial Doppler is also described in the section Venous Air Embolism.

INTRAVENOUS FLUID MANAGEMENT

The general principles of fluid management for neurosurgical anesthesia are (1) maintain normovolemia and (2) avoid reduction of serum osmolarity. The first principle is a derivative of the concept presented in the section "Management of Arterial Blood Pressure," which is that it is generally ideal to maintain a normal MAP in patients undergoing most neurosurgical procedures and neurosurgical critical care. Maintaining normovolemia is simply one element of maintaining a normal MAP. The second principle is a derivative of the observation that lowering serum osmolarity results in edema of both normal and abnormal brain.[127,128] Administering fluids that provide free water (i.e., fluids that do not have sufficient nonglucose solutes to render them iso-osmolar with respect to blood) lowers serum osmolarity if the amount of free water administered is in excess of that required to maintain ongoing free water loss. Normal saline and lactated Ringer solution are the fluids most often used intraoperatively. At 308 mOsm/L, normal saline is slightly hyperosmolar with respect to plasma (295 mOsm/L). It has the disadvantage that large volumes can cause hyperchloremic metabolic acidosis.[129] The physiologic significance of this acidosis, which involves the extracellular but not the intracellular fluid space, is unclear. At a minimum, it has the potential to confuse the diagnostic picture when acidosis is present. As a result, many clinicians use predominately lactated Ringer solution. Although lactated Ringer solution (273 mOsm/L) is in theory not ideal for replacement of blood and third space loss or insensible losses, it serves as an entirely reasonable compromise for meeting both needs simultaneously and is very suitable in most instances. It is a hypo-osmolar fluid, and in a healthy experimental animal, it is possible to reduce serum osmolarity and produce cerebral edema with a large volume of lactated Ringer solution.[128] In the setting of large-volume fluid administration (e.g., significant blood loss, multiple trauma), it is the authors' practice to alternate, liter by liter, lactated Ringer solution, and normal saline.

The crystalloid versus colloid discussion is a recurrent one. It arises most commonly in the context of the patient with TBI. Although there are numerous fervent beliefs regarding this issue, there has in fact been only a single demonstration that the reduction of colloid oncotic pressure (COP) in the absence of a change of osmolarity can actually contribute to an augmentation of cerebral edema in the setting of experimental head injury.[130] The transcapillary membrane pressure gradients that can be produced by reduction of COP are in fact very small by comparison of those created by changes in serum osmolarity. Nonetheless, it appears that those small gradients, probably in the setting of an experimental BBB injury of intermediate severity, have the potential to augment edema. A fluid administration pattern should be selected that, in addition to maintaining normal serum osmolarity, prevents substantial reductions in COP. For the majority of elective craniotomies, which entail only modest fluid administration, this does not require the administration of colloid solutions. However, in situations requiring substantial volume administration (e.g., multiple trauma, aneurysm rupture, cerebral venous sinus laceration, filling pressure support during barbiturate coma), a combination of isotonic crystalloid and colloid may be appropriate.

Which Colloid Solutions Should Be Used?

Colloid administration has created increasing concern about not only its efficacy but its safety (as discussed in Chapter 61). Based on empirical local experience, we view albumin to be a reasonable choice. However, there are conflicting opinions and cross-currents in the literature (especially noted in Chapter 61). An analysis of the subset of patients in the SAFE (Saline versus Albumin Fluid Evaluation) trial with severe TBI (Glasgow Coma Scale [GCS] score, 3 to 8) revealed increased mortality among those who received albumin.[131] However, there are several reasons to be suspicious of that conclusion. First, SAFE trial patients were not originally randomized on the basis of TBI characteristics and, by chance, there were imbalances in TBI-related characteristics that appear to have placed the albumin group at greater risk.[132] Second, the 4% albumin solution used was hypo-osmolar (274 mOsm/L) and might have been expected to aggravate edema.[133] Furthermore, there is no compelling physiologic explanation for an albumin-specific hazard. The formation of cerebral edema that is more difficult to clear is an inevitable suspicion.[134] However, if valid, that should be a class effect relevant to all colloids (including fresh frozen plasma and starches) rather than being albumin specific. Furthermore, albumin has been used in TBI by others with no evidence of adverse effects.[135,136] In addition, in contrast to alleged adverse effects in the context of TBI are suspected beneficial effects in two other cerebral injury conditions, SAH and stroke, both of which are the subject of ongoing phase III clinical trials.[137,138] At best, the existing literature may justify consideration of limiting albumin volumes in patients

with severe head injury. The indications and concerns for colloids, and especially albumin administration, have been recently expressed (see Chapter 61).

The various starch-containing solutions should be used cautiously in neurosurgery because, in addition to a dilutional reduction of coagulation factors, they interfere directly with both platelets and the factor VIII complex.[139] The coagulation effects are proportional to the average molecular weight and the hydroxyethyl group substitution ratio of the starch preparation (also see Chapters 61 and 62). There have been several reported instances of bleeding in neurosurgical patients that were attributed to hetastarch administration. However, all of those have involved circumstances in which the manufacturer's recommended dosage limit was exceeded[140] or in which the starch was administered up to the recommended limit on successive days, probably resulting in an accumulation effect.[141] The latitudes are wider with the more recently available small molecule/lower substitution ratio preparations. These preparations have a record of safety when used in the operating room in general[142] and have been administered uneventfully to patients with severe TBI.[143] The decision about whether to use these products is frequently a matter of local bias. Although hetastarch solutions can be used in neuroanesthesia, the clinician should respect the manufacturers' recommended dose restrictions and should use additional restraint in situations where there are other reasons for impairment of the coagulation mechanism. Recent concern about adverse effects on renal function in patients who have received starches in critical care situations have made some reluctant to use these compounds in any setting. The dextran-containing solutions are generally avoided because of their effects on platelet function.

There is longstanding interest in the use of hypertonic fluids for the resuscitation of polytrauma victims in general, and of patients with TBI in particular. However, there has yet to be a scientifically convincing demonstration of improvement in outcome in either group in association with hypertonic solutions.[144]

GLUCOSE MANAGEMENT

There is a widespread notion that increased plasma glucose aggravates a cerebral ischemic insult. This may be true for an acute ischemic event in a previously normal brain, but that should not be extrapolated to the idea that all "neuro patients" should be submitted to very tight glycemic control. The potential benefits of a lower plasma glucose concentration in the event of an acute ischemic episode (which have not been well confirmed in humans) should be outweighed by the very clear demonstrations that the injured brain (e.g., TBI, SAH) becomes "hypoglycemic" and suffers metabolic distress at plasma glucose levels that are satisfactory for normal brain.[145-148] This may be because injury can produce a state of hyperglycolysis.[146,149] Although severe hyperglycemia should be treated to reduce infection rates, patients with acute injuries (e.g., TBI, SAH) should not be submitted to very tight control. As one reviewer said, "extra sweetness [is] required"[150] by the injured brain. The authors' intraoperative intervention threshold is 250 mg/dL, the objective being to reduce plasma glucose to less than 200/dL. A recently published guideline recommends an ICU objective of less than 180 mg/dL in patients with cerebral injuries but cautions that plasma glucose not be allowed to decrease to less than 100 mg/dL.[151] The NICE-Sugar study's control group range of 140 to 180 mg/dL[152] is probably also a reasonable target. However, control should only be undertaken when processes to prevent hypoglycemia are firmly in place, and the lower the targets, the more comprehensive the hypoglycemia prevention processes must be (see Chapter 39).

HYPOTHERMIA

The effects of hypothermia on cerebral physiology and its potential cerebral protective mechanisms are presented in Chapter 17. There have been numerous laboratory demonstrations on the efficacy of mild hypothermia (32° C to 34° C) in reducing the neurologic injury occurring after standardized cerebral and spinal cord ischemic insults. On that basis, the use of induced hypothermia in the management of cerebral vascular procedures, in particular aneurysms and sometimes AVMs, became widespread. However, an international multicenter trial of mild hypothermia in 1001 relatively good-grade patients undergoing aneurysm surgery revealed no improvement in neurologic outcome.[153] The routine use of intraoperative hypothermia will probably diminish.

Because ischemia is recognized to make a postinsult contribution to neuronal injury after TBI,[21,154] hypothermia was also studied in laboratory models of TBI.[155] It was effective and resulted in a prospective multicenter trial in which hypothermia (33°C) was induced within 8 hours of injury and was maintained for 48 hours. No outcome benefit was evident.[156] Post hoc subgroup analysis indicated that patients younger than 45 years old who arrived at the tertiary care facility with a temperature less than 35°C who were randomly assigned to the cooling limb of the trial did have an improved outcome. A second trial in which more rapid induction of hypothermia was accomplished (35°C by 2.6 hours, 33°C by 4.4 hours) was undertaken. However, the results were similarly negative.[157]

Based on a lack of demonstrated efficacy in humans, routine use of hypothermia in neurosurgery cannot be advocated in a standard text such as "Anesthesia." The decision to use it, usually in the context of aneurysm surgery, is local. The authors continue to use mild hypothermia selectively, most commonly in patients perceived to be at an especially high risk of intraoperative ischemia. If hypothermia is used, cardiac dysrhythmia and coagulation dysfunction can occur if body temperatures become too low. Patients should be rewarmed adequately before emergence to avoid shivering and hypertension.

By contrast with clinical neurosurgery, the use of hypothermia after cardiac arrest is now practiced widely. Two multicenter trials demonstrated improved neurologic outcome among survivors of witnessed cardiac arrest cooled to 32° C to 34° C within 4 hours and maintained at that temperature for 12 to 24 hours.[158,159] Widespread clinical application has been advocated by an international task force.[160]

Although mild hypothermia is perceived to convey the hazard of coagulation dysfunction and dysrhythmia, neither has been evident in elective neurosurgery in the temperature ranges typically used (32° C to 34° C).

The issue of where body temperature should be recorded to best reflect brain temperature has been addressed.[161] It appears that esophageal, tympanic membrane, pulmonary arterial, and jugular bulb temperature are all very similar and provide a reasonable reflection of deep brain temperature, whereas bladder temperature does not. During craniotomies, superficial layers of cortex may be substantially cooler than deep brain and central temperatures.

EMERGENCE FROM ANESTHESIA

Most practitioners of neuroanesthesia feel that there is a premium on a "smooth" emergence: one free of coughing, straining, and arterial hypertension. The avoidance of arterial hypertension is desired because arterial hypertension can contribute to intracranial bleeding and increased edema formation.[162-167] In the face of a poorly autoregulating cerebral vasculature, hypertension also has the potential, through vascular engorgement, to contribute to an increase in ICP. Much of the concern with coughing and straining has a similar basis. The sudden increases in intrathoracic pressure are transmitted to both arteries and veins, producing transient increases in both cerebral arterial and venous pressure, with the same potential consequences: edema formation, bleeding, and elevation of ICP. Coughing is a specific concern with certain individual procedures. In the circumstances of transsphenoidal pituitary surgery in which a surgeon has opened, and subsequently taken pains to close, the arachnoid membrane to prevent CSF leakage, there is a belief that coughing has the potential to disrupt this closure because of the sudden and substantial increases in CSF pressure. Opening a pathway from the intracranial space to the nasal cavity conveys a substantial risk of postoperative meningitis. In other procedures, notably those that have violated the floor of the anterior fossa, air can be driven into the cranium and, in the event of a flap-valve mechanism, cause a tension pneumocephalus. This latter event can only happen when coughing occurs after the endotracheal tube has been removed.

There is a paucity of systematically obtained clinical data to give a perspective to the actual magnitude of the risks associated with emergences that are not considered smooth. Two retrospective studies have revealed that increased postoperative arterial blood pressure was associated with intracerebral bleeding after craniotomy.[166,167] However, whether hypertension occurring at emergence causes postoperative intracerebral bleeding is not clear. Also, the relationship between hypertensive transients at emergence and edema formation is unconfirmed. In anesthetized animals, sudden and very substantial increases in arterial pressure can result in a breach of the BBB with extravasation of tracers.[163] However, there are no data to confirm that the pressure transients associated with the typical coughing episode or typical emergence hypertensive transient are in fact associated with increased edema formation. Nonetheless, it seems reasonable to take measures, to the extent that these measures do not themselves add potential patient morbidity, to prevent these occurrences.

A common method for the management of systemic hypertension during the last stages of a craniotomy is the expectant and/or reactive administration of lidocaine and vasoactive agents, most commonly labetalol and esmolol.[168] Other drugs, including hydralazine, enalapril, and diltiazem, have been used to good effect. Administration of dexmedetomidine during the procedure also reduces the hypertensive response to emergence[169] and hypertension in the postanesthesia care unit.[170]

There are also many approaches to the prevention of coughing and straining. The authors have several biases. We encourage trainees to include in their anesthetic technique "as much narcotic as is consistent with spontaneous ventilation at the conclusion of the procedure." That practice is based on the same physiologic effect that justifies the administration of codeine and related compounds as antitussive medication (i.e., the depression of airway reflexes by narcotics). We also have the bias that patients emerge more rapidly and smoothly when the last inhaled anesthetic to be withdrawn is nitrous oxide and that clinicians should seek to avoid the "neither here nor there" phase of anesthesia that occurs in patients who are stimulated in the face of residual exhaled concentrations of volatile anesthetic on the order of 0.2 to 0.3 MAC. A common practice among neuroanesthetists near the conclusion of a craniotomy is the relatively early discontinuation of the volatile anesthetic with supplementation, if necessary, of residual nitrous oxide with propofol by either bolus increments or infusion at rates in the range of 12.5 to 25 μg/kg/hr.

An additional principle relevant to the emergence from neurosurgical procedures is that emergence should be timed to coincide not with the final suture but rather with the conclusion of the application of the head dressing. Many a good anesthetic for neurosurgery has been spoiled by severe coughing and straining that occurs in association with endotracheal tube motion during the application of the head dressing. Another nuance of our practice has been to withhold administration of neuromuscular antagonists, such as neostigmine, as long as possible as a "hedge" against misjudgment while lightening a patient in the later stages of the procedure. The administration of lidocaine is another apparently effective technique for reducing airway responsiveness and the likelihood of coughing/straining as the depth of anesthesia is reduced in anticipation of emergence. We commonly administer 1.5 mg/kg of intravenous lidocaine just before the head movement associated with applying the dressing.

Because of the premium placed on minimizing coughing and straining and hypertension, there may be a temptation to extubate from the trachea before complete recovery of consciousness. This may be acceptable in some circumstances. However, it should be undertaken with caution when the circumstances of the surgical procedure make it possible that neurologic events have occurred that will delay recovery of consciousness, or when there may be less cranial nerve dysfunction. In these circumstances, it would, in general, be best to wait until the likelihood of the patient's recovery of consciousness is confirmed or until patient cooperation and airway reflexes are likely to have recovered.

SPECIFIC PROCEDURES

Many of the considerations relevant to individual neurosurgical procedures are generic ones that have already been presented in the preceding section on Recurrent Issues. The descriptions that follow will highlight only procedure-specific issues (Box 70-8).

SUPRATENTORIAL TUMORS

Craniotomies for excision or biopsy, or both, of supratentorial tumors are among the most common neurosurgical procedures. Gliomas and meningiomas are among the most frequent tumors. The relevant preoperative considerations include the patient's ICP status and the location and size of the tumor. Location and size of the tumor give the anesthesiologist an indication of the surgical position, the potential for blood loss, and will sometimes reveal a risk of air embolism. The VAE risk is infrequent for the majority of supratentorial tumors. However, lesions (usually convexity meningiomas) that encroach upon the sagittal sinus may convey a substantial risk of VAE. Full VAE precautions, including a right atrial catheter, are usually reserved for only the supratentorial tumors that lie near the posterior half of the superior sagittal sinus.

Excision of craniopharyngiomas and pituitary tumors with suprasellar extension may entail dissection in and around the hypothalamus (see Fig. 70-17). Irritation of the hypothalamus can elicit sympathetic responses including hypertension. Damage to the hypothalamus can result in a spectrum of physiologic disturbances, notably water balance. Diabetes insipidus is the most likely, although the cerebral salt-wasting syndrome can potentially occur. The latter has been very infrequent. The various disturbances of water balance typically have a delayed onset, beginning 12 to 24 hours postoperatively, rather than in the operating room. Postoperative temperature homeostasis may also be disturbed.

Patients who undergo a craniotomy involving a subfrontal approach sometimes manifest a disturbance of consciousness in the immediate postoperative period. Retraction and irritation of the inferior surfaces of the frontal lobes can result in a patient who is lethargic and does not awaken "cleanly" and may exhibit either delayed emergence or some degree of disinhibition, or both. Patients exhibiting this phenomenon are sometimes referred to as "frontal lobey." The phenomenon is more likely to be evident when there has been bilateral subfrontal retraction than when it occurs only unilaterally. The anesthetic implication is that the clinician should be more inclined to confirm return of consciousness before extubating the patient rather than to extubate expectantly. A further implication taken by these authors (though not confirmed by any systematic study) is that a less liberal use of fixed anesthetics (narcotics, propofol infusions) may be appropriate when there is to be bilateral subfrontal retraction. This is based on the rationale that low residual concentrations of these anesthetics that are compatible with reasonable recovery of consciousness in the majority of patients may be less well tolerated in this population. Subfrontal approaches are most commonly used in patients with olfactory groove meningiomas and patients with suprasellar tumors including craniopharyngiomas and pituitary tumors with suprasellar extension.

BOX 70-8 *Specific Procedures*

- Supratentorial tumors
- Aneurysms and arteriovenous malformations
- Traumatic brain injury
- Posterior fossa procedures
- Transsphenoidal surgery
- Awake craniotomy/seizure surgery
- Stereotactic procedures
- Neuroendoscopic procedures
- Neuroradiologic procedures
- Cerebrospinal fluid shunting procedures
- Pediatric neurosurgery
- Spinal surgery

Preoperative Preparation

Patients with a significant tumor-related mass effect, especially if there is tumor-related edema, should receive preoperative steroids. If the patient is not receiving steroids, it is the anesthesiologist's responsibility to find out why. A 48-hour course is ideal (see the previous discussion of steroids), although 24 hours is sufficient for a clinical effect to be evident. Dexamethasone is the most commonly used agent. A regimen such as 10 mg intravenously or orally followed by 10 mg every 6 hours is typical. Because of the concern about producing CO_2 retention in a patient whose intracranial compliance is already abnormal, patients with any substantial mass effect are usually not premedicated outside of the operating room with anything beyond full-dose reassurance (see Chapter 38).

Monitoring

Institutional practices vary; however, we almost invariably place arterial catheters for craniotomies under general anesthesia. Preinduction placement may be appropriate in patients with severe mass effect and little residual compensatory latitude. At a minimum, we achieve intraarterial monitoring before pin placement. It is the period of induction and pinning during which hypertension, with its attendant risks in a patient with impaired compliance and autoregulation, is most likely to occur. Arterial lines also facilitate careful management of blood pressure during emergence. Procedures with a substantial blood loss potential (e.g., tumors encroaching on the sagittal sinus, large vascular tumors) may also justify central venous catheters when peripheral venous access is limited. If not already present for other indications, is ICP monitoring ever warranted for intraoperative management? In our opinion, the answer is no. We have sufficient understanding of the potential impact of anesthetics and techniques that we should be able to manage induction of anesthesia blindly. Once the cranium is open, observation of conditions in the surgical field provides equivalent information (see also Chapter 49.)

Management of Anesthesia

The principles governing the choice of anesthetic drugs are presented in the previous section Control of Intracranial Pressure and Brain Relaxation.

ANEURYSMS AND ARTERIOVENOUS MALFORMATIONS

Contemporary management of intracranial aneurysms calls for early intervention after SAH, ideally within 24 hours and certainly within 48 hours.[171] That intervention may entail either operative clipping or an endovascular approach.[171] The latter is discussed in the subsequent section Interventional Neuroradiology (see Chapter 90).

Early intervention was originally undertaken only in patients in the better neurologic grades—that is, grades I-III and perhaps IV of the World Federation of Neurosurgeons classification (Table 70-2) or grades I-III of the Hunt-Hess classification (Table 70-3)—but is now recommended for the majority of patients.[171] If early intervention is not feasible and a surgical approach is intended, surgery is usually delayed for 10 to 14 days to be safely beyond the period of maximal vasospasm risk (i.e., days 4 to 10 post-SAH).

The rationale for early intervention is several-fold. The sooner the aneurysm is clipped or obliterated, the less the likelihood of rebleeding (and rebleeding is the principal cause of death for patients hospitalized after SAH[172]). Second, the management of the ischemia caused by vasospasm involves volume loading and induced hypertension. Early occlusion of the aneurysm eliminates the risk of rebleeding associated with this therapy. Prior surgical practices entailed maintaining the patient on bed rest until approximately day 14 when the period of spasm risk had passed. Early aneurysm clipping reduces the period of hospitalization and reduces the incidence of the medical complications (i.e., deep vein thrombosis, atelectasis, pneumonia) associated with a lengthy period of enforced bed rest.

Early intervention makes the surgeon's task more difficult. The brain in the early post-SAH period is likely to be more edematous than after a 2-week delay. Furthermore, some degree of hydrocephalus is very common after blood contaminates the subarachnoid space. In fact, 10% or more of SAH victims eventually require permanent CSF diversion.[171] Early intervention may also somewhat enhance the risk of intraoperative aneurysmal rupture because of the lesser period of time for a clot to organize over the site of the initial bleed. All of this places a substantial premium on techniques designed to reduce the volume of the intracranial contents (see Control of Intracranial Pressure and Brain Relaxation earlier in this chapter) to facilitate exposure and minimize retraction pressures.

TABLE 70-2 WORLD FEDERATION OF NEUROSURGEONS SUBARACHNOID HEMORRHAGE SCALE

WFNS Grade	GCS Score	Motor Deficit
I	15	Absent
II	14-13	Absent
III	14-13	Present
IV	12-7	Present or absent
V	6-3	Present or absent

WFNS, World Federation of Neurosurgeons; *GCS*, Glasgow Coma Scale.

TABLE 70-3 HUNT-HESS CLASSIFICATION OF NEUROLOGIC STATUS AFTER SUBARACHNOID HEMORRHAGE

Category	Criteria*
Grade I	Asymptomatic, or minimal headache and slight nuchal rigidity
Grade II	Moderate to severe headache, nuchal rigidity, no deficit other than cranial nerve palsy
Grade III	Drowsiness, confusion, or mild focal deficit
Grade IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances
Grade V	Deep coma, decerebrate rigidity, moribund appearance

* Serious systemic disease, such as hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease, and severe vasospasm seen on arteriography, results in placement of the patient in the next less favorable category.

Preoperative Evaluation

Many patients scheduled for intracranial aneurysm clipping will come directly from the ICU, and elements of their management while there may influence their immediate preoperative status.

Intravenous Fluid Management. Some patients develop the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) after SAH and are appropriately managed with fluid restriction. However, hyponatremia after SAH is likely to be the result of the cerebral salt-wasting syndrome that probably occurs as a result of the release of a natriuretic peptide by the brain.[173,174] Cerebral salt-wasting syndrome is characterized by the triad of hyponatremia, volume contraction, and high urine sodium concentrations (>50 mmol/L), and its occurrence is correlated with the occurrence of symptomatic vasospasm.[175] The distinction between cerebral salt-wasting syndrome and SIADH is important. SIADH, which is characterized by normovolemia or mild hypervolemia, is treated by volume restriction. Cerebral salt-wasting syndrome is associated with a contracted intravascular volume. Fluid restriction and further volume contraction may be especially deleterious in the post-SAH patient and should be avoided.[176-178] Although the clinical distinction between these two causes of hyponatremia (SIADH and cerebral salt-wasting syndrome) may be difficult, management of both is relatively simple: administration of isotonic fluids using intravascular normovolemia as the end point (see also Chapter 59).

Vasospasm. The anesthesiologist should determine whether vasospasm has occurred and what, if any, therapies for it have been undertaken. Vasospasm is thought to be caused by the breakdown products of the hemoglobin that has accumulated around the vessels of the circle of Willis after SAH. A specific mechanism/mediator has

not been identified. Calcium channels are thought to be involved, and there is also suspicion that the nitric oxide and endothelin systems may be contributory.[178,179]

When there is a clinical suspicion of vasospasm (typically because of a change in sensorium or new neurologic deficit), surgery is usually deferred and TCD, angiography, or other imaging is performed. Confirmed vasospasm is commonly treated with the "Triple H" therapy described subsequently and sometimes by balloon angioplasty or intraarterial vasodilators.[180]

For patients proceeding to surgery, hypotension should be avoided[171] and CPP should usually be maintained intraoperatively at values near the waking normal range. The association of hypotension with poor outcome,[181] and the potential for hypotension to cause or aggravate cerebral ischemia in the patient with some degree of vasospasm is now recognized.[182-184] This concern should extend even to patients classified as World Federation of Neurosurgeons grade I who may have regions of cerebral ischemia[39] that are subclinical when the patient is normotensive.

In the ICU (see also Chapter 105), the regimens used to treat vasospasm usually involve some combination of hypervolemia, hemodilution, and hypertension. The science behind hypervolemic-hypertensive therapy is soft and the efficacy of neither Triple H therapy nor volume expansion in isolation has been proved by prospective study.[185-187] The relative importance of the rheologic and blood pressure effects is undefined, although there is evidence for the relevance of blood pressure elevation in isolation.[187-190] Phenylephrine and dopamine are the most commonly used pressors; exact pressor choice should be primarily governed by systemic cardiovascular considerations. The end point for pressor administration varies. Most commonly, the objective is an increase in MAP of approximately 20 to 30 mm Hg above baseline systolic pressure. However, it has been reported that augmentation of cardiac output with dobutamine, without simultaneous MAP increase, augments CBF in vasospastic territories.[187] It is also believed that the hematocrit should be reduced to the low 30s, but this should not be a primary clinical objective. Commonly, hematocrit reduction occurs secondarily as a result of attempts to produce hypervolemia as a part of the effort to increase blood pressure.

Calcium-Channel Blockers. Calcium-channel blockers are an established part of the management of SAH. Administration of nimodipine decreases the incidence of morbidity caused by cerebral ischemia after SAH,[191] although it was not associated with any reduction in the incidence of vasospasm as detected by angiography.[192] Patients presenting to the operating room after SAH should already be receiving nimodipine. Because nimodipine must be administered orally in North America, nicardipine has been evaluated as an intravenous alternative. The multicenter nicardipine trial[193,194] revealed a reduced incidence of symptomatic vasospasm but no improvement in outcome. As a consequence, nimodipine remains the standard. Calcium-channel blockers (i.e., verapamil, nicardipine, nimodipine[195-198]) are also used intraarterially as a primary treatment for medically-refractory vasospasm. Milrinone and papaverine are similarly administered. [197,199]

Other Pharmacologic Therapies. Several other agents/drug classes have been considered for the prevention of vasospasm and delayed ischemic deficits. None of them is approaching the status of standard therapy. A recent study of the endothelin antagonist clazosentan revealed improved mortality without improvement in the outcome of survivors. After several small trials suggested a beneficial effect of magnesium, a recent larger randomized, placebo-controlled trial reported no improvement in outcome among patients in whom magnesium was initiated within 4 days of SAH.[200] Several small trials have examined the post-SAH administration of statins. Meta-analysis revealed only nonsignificant trends toward reduced incidence of delayed cerebral ischemia and death.[201] Although some centers have already implemented statin therapy as part of the local routine, widespread adoption will probably have to await the completion of larger trials. Recently (January 2013), the phosphodiesterase inhibitor cilostazol, administered orally post clipping, was reported to reduce vasospasm and delayed cerebral infarctions substantially.[202] That trial was nonblinded, and cilostazol is a platelet inhibitor as well as a vasodilator. Although the results were promising, verification of both safety and efficacy will probably be required before wide application.

Antifibrinolytics. Antifibrinolytics have been administered in an attempt to reduce the incidence of rebleeding. Although they accomplish this end, long courses do so at the cost of an increased incidence of ischemic symptoms and hydrocephalus, with an overall adverse effect on outcome. However, early, brief courses of antifibrinolytics continued until the aneurysm is secured may have a net favorable effect on outcome.[171]

Subarachnoid Hemorrhage–Associated Myocardial Dysfunction. SAH can result in a largely reversible, "stunning"-like myocardial injury. The severity of the dysfunction correlates best with the severity of the neurologic injury[203] and is sometimes sufficient to require pressor support.[204] The mechanism is uncertain but is thought to be catecholamine mediated.[205] Troponin elevation occurs commonly, though typically reaching levels less than the diagnostic threshold for myocardial infarction.[206] Peak troponin levels correlate with the severity of both neurologic injury and echocardiographic myocardial dysfunction.[204,207]

ECG abnormalities are common after SAH[200] (see also Chapter 47). In addition to the classic canyon T waves (Fig. 70-14), nonspecific T-wave changes, Q-T prolongation, ST-segment depression, and U waves have been described. There is typically no relationship between the ECG changes and echocardiographic myocardial dysfunction.[206] ECG abnormalities do not herald evolving or impending cardiac disease.[208] Accordingly, when ventricular function is adequate and ECG patterns other than those that are typical of myocardial ischemia are observed, no specific interventions or modifications of patient management are warranted, other than attention to the possibility of dysrhythmias. In particular, an increased Q-T interval (>550 msec) occurs frequently after SAH, especially in patients with more severe SAH,[207]

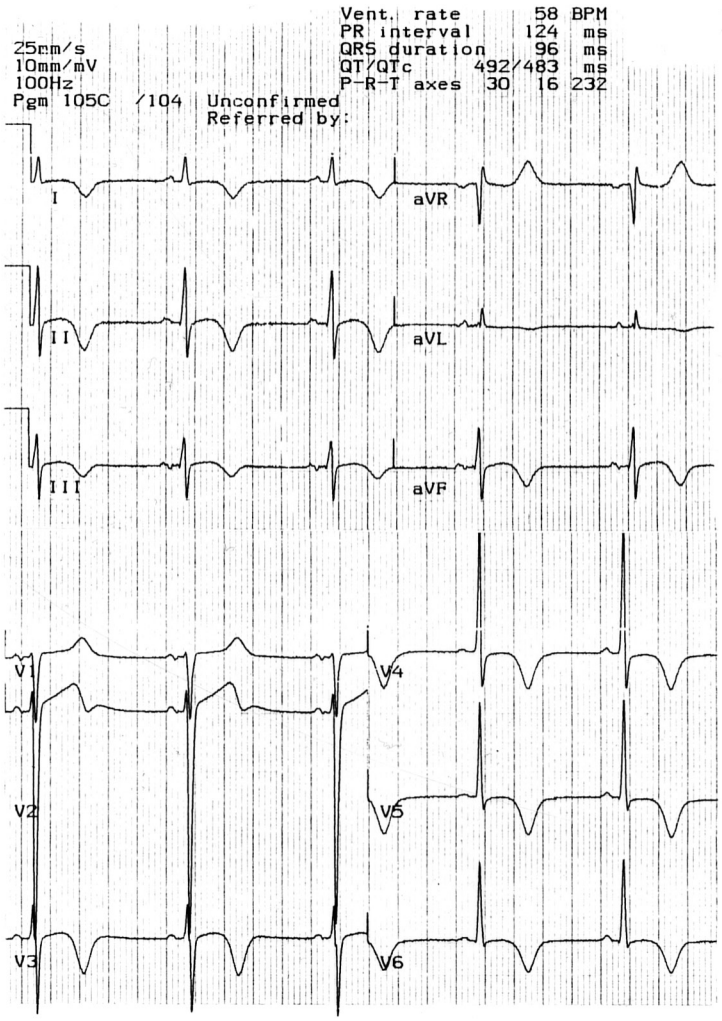


Figure 70-14. Electrocardiogram abnormalities associated with subarachnoid hemorrhage. The canyon T waves that may be seen after subarachnoid hemorrhage are evident.

and has been associated with an increased incidence of malignant ventricular rhythms including torsades de pointes.[209]

Anesthetic Technique

Important considerations include the following:

1. Absolute avoidance of acute hypertension with its attendant risk of rerupture.
2. Achievement of intraoperative brain relaxation to facilitate surgical access to the aneurysm.
3. Maintenance of a high-normal MAP to prevent critical reduction of CBF in recently insulted and now marginally perfused areas of brain, or in regions critically dependent on collateral pathways.
4. Preparedness to perform precise manipulations of MAP as the surgeon attempts to clip the aneurysm or to control bleeding from a ruptured aneurysm or during periods of temporary vascular occlusion.

Monitoring

An arterial line is invariably appropriate. A central venous catheter may be appropriate if peripheral access is inadequate (see also Chapter 49).

Anesthetic Selection. Any technique that permits proper control of MAP is acceptable. However, in the face of increased ICP or a tight surgical field, an inhaled anesthetic technique may be less suitable. The prevention of paroxysmal hypertension is the only absolute requirement in patients undergoing aneurysm clipping. Rebleeding kills[172] and the poorly organized clot over the aneurysms of patients undergoing early post-SAH clipping makes them particularly prone to rebleeding. A rebleed at induction is frequently fatal. The escaping arterial blood is more likely to penetrate brain substance because it cannot dissect through the CSF space (filled with clot), and the ICP increase is extreme because of the poor compliance of the intracranial space (swollen brain, hydrocephalus).

Induced Hypotension. The routine use of induced hypotension has essentially vanished (see previous section Management of Arterial Blood Pressure). Nonetheless, the anesthesiologist should be prepared to reduce blood pressure immediately and precisely if called upon to do so. Preparation must occur before the episode of bleeding. We prepare a sodium nitroprusside infusion before induction. It is placed in line at a Y-injection port at the hub of an intravenous catheter. A carrier drip flows steadily such

that any change in nitroprusside infusion rate is reflected as rapidly as possible in the central compartment. There are theoretical pros and cons for various hypotensive agents. However, the choice should ultimately be made on the basis of which regimen, in the hands of the individual practitioner, results in the most precise control of MAP. There are rare occasions when the anesthesiologist is asked to control MAP in the range of 40 to 50 mm Hg, in the face of active arterial bleeding. This can be extremely difficult in a patient who is hypovolemic at the beginning of the bleeding episode. It is our practice to maintain normovolemia.

Induced Hypertension. Relative hypertension may be requested during periods of temporary arterial occlusion (see the later section Temporary Clipping) to augment collateral CBF. In addition, after clipping of the aneurysm, some surgeons will puncture the dome of the aneurysm to confirm adequate clip placement and may request transient elevation of the systolic pressure to 150 mm Hg. Phenylephrine is suitable in either instance.

Hypocapnia. Hypocapnia has traditionally been used as an adjunct to brain relaxation. However, the practice has been questioned on the basis of the concern that it will aggravate ischemia (see the earlier section Management of $Paco_2$). It is now generally avoided unless ICP/brain relaxation circumstances demand it.

Lumbar Cerebrospinal Fluid Drainage. Cerebrospinal fluid drainage has been used to facilitate exposure. However, its use appears to be diminishing because surgeons have appreciated that the same brain relaxing effect can be achieved by release of CSF from the basal cisterns. If a lumbar CSF drain is placed, it is appropriate to avoid excessive loss of CSF. A sudden reduction in the transmural pressure gradient across the dome of the aneurysm (by sudden reduction of ICP consequent upon substantial CSF drainage) should be avoided because of the theoretical concern that this decompression might encourage rebleeding. Having verified the patency of the drainage system, it is usual to leave it closed until the surgeon is opening the dura. The drain is then opened and allowed to drain freely to floor level. Drainage should be discontinued promptly after final withdrawal of the retractors to allow CSF to reaccumulate and to thereby reduce the size of the potential pneumocephalus. The drain is usually removed immediately postoperatively.

Mannitol. Some surgeons use mannitol relatively aggressively (e.g., 2 g/kg). In part, it is used to facilitate exposure and reduce retractor pressures, but there is evidence that it may have additional benefits. Specifically, there are data derived in both animals and man that indicate that mannitol may have a CBF-enhancing effect in regions of moderate CBF reduction.[210-213] The mechanism is not defined. Reduction of interstitial tissue pressure around capillaries and/or an alteration of blood rheology have been proposed as contributors. Typically, mannitol is administered in a dose of 1 g/kg just before dural opening. Surgeons who believe in its CBF-enhancing effect may request a second 1 g/kg approximately 15 minutes before an anticipated temporary occlusion.

Temporary Clipping. Many surgeons limit inflow to an aneurysm during application of the permanent clip by placing a temporary clip proximally on the feeding vessel. It is occasionally necessary to trap the aneurysm (i.e., to temporarily occlude the vessel on both sides of the aneurysm) to complete the dissection of the neck and apply the clip. This is more common with larger aneurysms. With giant aneurysms in the vicinity of the carotid siphon, the inferior occlusion may be performed at the level of the internal carotid artery via a separate incision in the neck. A clinical survey by Samson and colleagues of the neurologic outcome after temporary occlusion in normothermic, normotensive adults revealed that occlusions of fewer than 14 minutes were invariably tolerated. The likelihood of an ischemic injury increased with longer occlusions and reached 100% with occlusions in excess of 31 minutes.[214] In another institution, the threshold for ischemic injury was 20 minutes of occlusion.[215] An informal 7-minute rule is sometimes applied to individual periods of temporary occlusion. Typically, MAP should be sustained at high-normal levels during periods of occlusion to facilitate collateral CBF.

Brain Protection. We do not select anesthetic drugs on the basis of putative brain-protective effects. Maintenance of MAP to ensure collateral flow and perfusion under retractors, efficient brain relaxation to facilitate surgical access and reduce retractor pressures, limitation of the duration of episodes of temporary occlusion, and perhaps mild hypothermia are the important brain protection techniques. Specific anesthetic drugs have been promoted as brain protectants (see the discussion in Chapter 17). Propofol and etomidate are au courant. However, there have been no convincing laboratory demonstrations that propofol provides any greater tolerance to a standardized ischemic insult than does anesthesia with a volatile anesthetic. Attempts to demonstrate protection by etomidate in an animal model of focal ischemia actually demonstrated an adverse effect of etomidate.[216] Furthermore, a clinical investigation during aneurysm clipping revealed decreases in brain tissue PO_2 in association with administration of etomidate, which contrasted with the brain PO_2 increases that occurred with the introduction of desflurane. During subsequent temporary vessel occlusion, tissue pH decreased alarmingly in patients receiving etomidate and was unchanged with desflurane.[217] Etomidate probably should not be used because of a lack of sufficient data regarding its efficacy. With respect to the volatile anesthetics, attempts in the laboratory to confirm the once proclaimed protective efficacy of isoflurane have demonstrated that there are no differences among the various volatile anesthetics in terms of their influence on outcome after focal or global ischemia in the laboratory.[216,218-220] Nor has there been any demonstration of greater protective efficacy with concentrations of volatile anesthetics sufficient to cause EEG suppression as opposed to more modest (e.g., 1.0 MAC) levels.[220,221] Nonetheless, these animal investigations suggest that a standardized experimental ischemic insult is better

tolerated, relative to the awake state, by animals receiving a volatile anesthetic.[219,220,222] In addition, data derived in animals also suggest that there may also be a relative protective advantage to an anesthetic that includes a volatile anesthetic compared with a strict N_2O-narcotic technique.[220,222] The magnitude of the differences among anesthetics and the absence of proof of relevance in patients precludes advocacy of a particular anesthetic regimen in a standard text. The important anesthetic objectives are precise hemodynamic control and timely wake-up, and those two constraints should dictate the choice of the anesthetic regimen for the majority of aneurysm procedures. Among anesthetics, it is only the barbiturates for which additional protective efficacy has been demonstrated convincingly (see Chapter 17). Because of their potentially adverse effects on hemodynamics and wake-up, they are not ideal for routine use. They should probably be reserved for situations in which a prolonged vessel occlusion is unavoidable, and in that circumstance, it would be ideal that the ischemic hazard be first confirmed by observation of the EEG response to a temporary occlusion.[223]

The patient with or at substantial risk for vasospasm probably benefits from a minimum hemoglobin greater than that which is commonly accepted in stable ICU patients (i.e., >7 g/dL). The best available information suggests a minimal hemoglobin value of 9 g/dL.[190,224]

Hypothermia. As noted in the section Hypothermia, a prospective trial of mild hypothermia in patients undergoing aneurysm surgery revealed no improvement in neurologic outcome.[153] Nonetheless, some neurosurgical teams that were already using mild hypothermia (32° C to 34° C) are continuing its use for procedures in which temporary vessel occlusion may occur. The institutions that use the lower temperatures are those in which the team is willing to accept a delay in emergence from anesthesia to achieve sufficient rewarming to avoid the extreme hypertension that can occur when a patient is awakened at low body temperatures.

Neurophysiologic Monitoring. Evoked responses and EEG have been used for monitoring,[223,225] although neither technique has been used widely. EEG monitoring can be used as a guide to management during the period of flow interruption or to guide the administration of CMR-reducing anesthetic agents given before occlusion.[223] At some institutions, the surgeon places an electrode strip over the region of cortex at risk during the intended occlusion. However, the more commonly used skin surface frontal-mastoid derivation is probably sufficient to reveal a major ischemic event. In most circumstances, if occlusion is deemed necessary, a temporary occlusion is performed and the EEG is observed. If the EEG shows significant slowing, the common practice is to release the clip, raise the MAP, and proceed with as brief as possible a period of occlusion or intermittent episodes of temporary occlusion. If the necessity for a sustained period of occlusion seems likely, it may be appropriate to administer barbiturates (discussed earlier) to produce burst suppression. These events are very infrequent (see also Chapter 49).

Intraoperative Angiography. Intraoperative angiography is an increasingly common component of the management of intracranial aneurysms. It does not have substantial implications for the anesthesiologist. However, any apparatus around the patient's head must be organized to allow C-arm access without snagging airway and monitoring equipment.

Special Considerations for Specific Aneurysms

The most common procedures are performed for aneurysms arising in or close to the circle of Willis. The vessels of origin may be the anterior communicating artery; the middle cerebral artery; the anterior cerebral artery; the ophthalmic artery; the tip of the basilar artery; the posterior communicating artery; and, less frequently, the posterior cerebral artery. These procedures are relatively similar for the anesthesiologist and typically require a supine position with the head turned slightly away from the operative side.

Ophthalmic Artery Aneurysms. Access to the origin of the ophthalmic artery, which is the first intradural branch of the carotid artery, is made difficult by the anterior clinoid process and the optic nerve. As a result, these aneurysms frequently require temporary vascular occlusion**.** The surgeon commonly first exposes the carotid artery in the neck. When the surgeon reaches the stage of seeking definitive access to the neck of the aneurysm, he or she will occlude first the carotid artery in the neck and then the intracranial portion of the carotid artery immediately proximal to the origin of the posterior communicating artery. A catheter is placed in the excluded segment and put to suction. Blood loss, which is usually minimal, should be monitored.

Vertebrobasilar Aneurysms. These procedures are typically performed in the lateral position. The exposure may involve a combined middle and posterior fossa approach, with some attendant, although minor, risk of venous air embolism. Cortical or skin surface EEG monitoring is of less relevance with vertebral-basilar aneurysms. Auditory and or somatosensory evoked responses have been used.[226] As with any other procedure involving the potential for mechanical or vascular injury to the brainstem, cardiovascular responses should be monitored and sudden changes in response to surgical manipulation should prompt immediate notification to the surgeon. Spontaneous ventilation may be appropriate for procedures involving surgical manipulation of the vertebral arteries, the vertebrobasilar junction, and the middle portion of the basilar artery. Apnea, gasping, or other sudden changes in ventilatory pattern during manipulation of the vasculature provide important, though somewhat nonspecific, warning of compromise of the vascular supply of the brainstem.[227] Now largely supplanted by endovascular approaches, management of these aneurysms sometimes requires cardiopulmonary bypass and deep hypothermic circulatory arrest.[228]

Vein of Galen Aneurysms. These "aneurysms" are congenital dural arteriovenous fistulas, usually treated in the neonate using endovascular methods, and share considerations relevant to AVMs. These include anticipation of

the possibility of the cerebral dysautoregulation phenomenon and are considered subsequently.

Arteriovenous Malformations

For the majority of intracranial AVMs, the general considerations are similar to those appropriate to aneurysm surgery: avoidance of acute hypertension and the capability to accurately manipulate arterial blood pressure in the event of bleeding. A problem specific to AVMs is the phenomenon of perfusion pressure breakthrough, or cerebral dysautoregulation.[229,230] It is characterized by an often sudden engorgement and swelling of the brain, sometimes with a relentless cauliflowerlike protrusion from the cranium. It tends to occur in the advanced stages of lengthy procedures on large AVMs, or it may be the cause of otherwise unexplained postoperative swelling and hemorrhage. The phenomenon is not entirely understood. An AVM provides a high-volume, low-resistance pathway that chronically diverts blood from adjacent and therefore marginally perfused vascular territories. Perhaps these tissues have long been maximally vasodilated and are incapable of vasoconstricting when exposed to a higher-pressure head after acute obliteration of the AVM. Although this explanation superficially fits the clinical occurrence, experimental data are not entirely consistent with this mechanism.[229-232] At least some component of the hyperemia is not passive, and neurogenic or paracrine mechanisms may be involved.

Anesthetic Technique. The management constraints are essentially the same as those relevant to aneurysm surgery, although the risk of intraoperative rupture is much less. Institutional practices will vary. We do not use induced hypotension unless it is necessitated by bleeding. We reason that the effects on the surrounding brain of devascularizing the AVM would be best appreciated if the devascularization occurs at normal pressures. If refractory brain swelling occurs, tight blood pressure control is essential, and reducing MAP may be of use to control swelling. The latter is based on the notion that CBF through the involved area is pressure-passive and will decrease as MAP is reduced. With severe episodes of swelling, we have used (in addition to hypotension, which we use cautiously because of the associated ischemia risk) hypocapnia, hypothermia, and barbiturates. The latter three techniques probably serve to reduce the bulk of only normal brain tissue, hypocapnia via a direct effect on CBF and barbiturates and hypothermia via the coupled effects of reduction of CMR on CBF. Induced hypothermia is also an adjunct to minimizing the barbiturate doses. In all of neurosurgery, we seek to prevent postoperative hypertension; however, in AVM surgery this should be accomplished with the greatest care because of the concern that the dysautoregulating brain adjacent to the resected AVM will develop edema or hemorrhage if hypertension occurs.

HEAD INJURY

Intubating the Trachea of a Head-Injured Patient

The anesthesiologist's first interface with the patient who has sustained a TBI may come as a result of a request for assistance with airway management. Patients with GCS scores of 7 to 8 (Table 70-4) or less require intubation and controlled ventilation for ICP or airway control, or both. Patients with less severe TBI may also require intubation because of trauma-related cardiopulmonary dysfunction or, when uncooperative, to facilitate diagnostic procedures. The anesthesiologist, in choosing the intubation technique, may encounter a number of conflicting constraints (Box 70-9). These include: (1) elevated ICP; (2) a full stomach; (3) uncertain cervical spine status; (4) uncertain airway status (e.g., presence of blood, possible laryngeal-tracheal injury, possible skull base fracture); (5) an uncertain volume status; (6) an uncooperative or combative patient; and (7) hypoxemia. There is no correct technique, and the best approach is determined by the relative weight of these various factors along with the degree of urgency. The anesthesiologist must not be distracted by placing an excessive initial emphasis on ICP. The anesthesiologist needs to keep sight of the ABCs of resuscitation: securing the airway, guaranteeing gas exchange, and stabilizing the circulation are higher initial priorities than ICP. Do not risk losing the airway or causing severe hypotension for the sake of preventing coughing on the tube or brief hypertension with intubation.

TABLE 70-4 THE GLASGOW COMA SCALE

Eyes opening	
Never	1
To speech	2
To pain	3
Spontaneously	4
Best verbal responses	
None	1
Garbled or incomprehensible sounds	2
Inappropriate words	3
Confused but conversant	4
Oriented	5
Best motor responses	
None	1
Extension (decerebrate rigidity)	2
Abnormal flexion (decorticate rigidity)	3
Withdrawal	4
Localizes pain	5
Obeys commands	6
Score	3-15

BOX 70-9 ***Factors That May Be Relevant During Intubation of the Head-Injured Patient***

- Full stomach
- Uncertain cervical spine stability
- Uncertain airway
  - Blood
  - Airway injury (larynx, crico-arytenoid cartilage)
  - Skull-base fracture
- Uncertain volume status
- Uncooperative/combative
- Hypoxemia
- Increased intracranial pressure

The Cervical Spine

The possibility of causing or aggravating an injury to the cervical spine is a relevant concern. Approximately 2% of blunt trauma victims who reach a hospital and 8% to 10% of TBI victims with GCS scores less than 8 have a fracture of the cervical spine.[233,234] Those incidences suggest that a hypnotic-relaxant-direct laryngoscopy approach for all patients with a closed head injury might convey a measurable risk of injuring the cervical cord. Nonetheless, although the literature contains contradictions, several published series have concluded that rapid-sequence induction does not convey significant risk of neurologic injury.[235-238] However, it is possible that the incidence of intubation-related neurologic injury is underreported. An informal survey reported by Criswell and associates[239] indicated that there have been more such events than one can infer from the published literature.[240,241] Nonetheless, the literature argues that we will "get away with it" most of the time, and the majority of patients with TBI requiring airway control are intubated using a hypnotic-relaxant-direct laryngoscopy sequence. It is the (probably minority) opinion of these authors that the possibility of devastating spinal cord injury exists, probably most so with injuries in the atlanto-occipital region, which are also difficult to identify radiologically, and that the anesthesiologist should identify circumstances in which time latitudes allow more detailed examination or radiologic evaluation. When there is any uncertainty regarding the airway or the cervical spine, direct laryngoscopy (with vigorous atlanto-occipital extension) should probably be avoided when the exigencies of the situation do not require an immediate rapid-sequence induction. The nasal route can be considered if the clinical context warrants, bearing in mind that risk of infection may be increased with skull base fracture and CSF leak. The anesthesiologist should use discretion (e.g., in the presence of an obvious facial smash, the nasal route should be avoided) and be sensitive to unusual resistance in passing the endotracheal tube.

When a hypnotic-relaxant sequence is used (and the exigencies of airway control will frequently demand it), the standard approach includes the use of cricoid pressure and in-line axial stabilization. In-line traction was once favored but has been supplanted by stabilization because of the perceived risk of over distraction and cord injury in the event of gross instability. The largest of the clinical series that concluded that oral intubation with anesthesia and relaxation is reasonable[235] used in-line stabilization with the patient's occiput held firmly on the backboard, limiting the amount of "sniff" that was feasible (Fig. 70-15). There is no question that in-line stabilization, properly performed, makes laryngoscopy somewhat more difficult; however, it serves to decrease the amount of atlanto-occipital extension necessary to achieve visualization of the glottis.[242] This is probably because performing the laryngoscopy against the assistant's counterpressure results in greater compression of the soft tissue structures of the tongue and floor of the mouth. Some recommend leaving the back half of the cervical collar in place during laryngoscopy (see Fig. 70-15) because it functions as a strut between the shoulder and the occiput and serves to further limit atlanto-occipital extension.



Figure 70-15. Intubating the acute trauma patient with an uncertain cervical spine. A hypnotic and a relaxant have been administered. One assistant maintains in-line axial stabilization with the occiput held firmly to the backboard; a second applies cricoid pressure. The posterior portion of the cervical collar remains in place to limit atlanto-axial extension. *(Reproduced with permission from Stene JD: Anesthesia for the critically ill trauma patient. In Siegel JH, editor:* Trauma: emergency surgery and critical care, *Melbourne, 1987, Churchill Livingstone, pp 843-862.)*

In a resuscitation situation, before initiating a hypnotic-relaxant sequence, the anesthesiologist should confirm the availability of cricothyrotomy equipment and of someone to make immediate, skilled use of it if necessary. The recently injured brain is very intolerant of hypoxia and hypotension.[243] It is inevitable that there is sometimes failed tracheal intubation. In the extensive experience of the Cowley Shock-Trauma Center in Baltimore, the cricothyrotomy/tracheostomy rate is 0.3%.[244] As is the case in many other situations, the laryngeal mask may be a very useful device for temporizing in the face of a failed intubation and may also provide access for intubation as an alternative to cricothyrotomy.

As noted in Chapter 17, although succinylcholine can cause ICP increases, these increments are small and probably do not occur in patients with serious cerebral injuries.[8] Accordingly, succinylcholine should not be viewed as contraindicated in the TBI victim. If there is an urgent need to secure the airway (to guarantee oxygenation and control CO_2 tension), and if succinylcholine is in other respects the appropriate drug to achieve that end, it should be used.

What should the anesthesiologist do with the patient whose cervical spine has not been cleared? That situation should arise with decreasing frequency. The once standard "three views" (with their inherent difficulties and substantial false-negative rates) have been supplanted by CT scanners that allow rapid, thin-slice evaluation, with sagittal reconstruction. A large meta-analysis concluded that "modern multislice helical CT alone is sufficient to rule out traumatic, unstable cervical spine injuries."[245] However, some remain concerned that CT may fail to identify ligamentous injuries that would be evident on magnetic resonance imaging (MRI).[246] With respect to a conscious patient who has not yet undergone complete radiologic evaluation, several clinical surveys have

confirmed that patients who are alert, nonintoxicated, and free of significant distracting injuries invariably have pain, midline tenderness, limitation of voluntary movement, or neurologic signs[247-249] if they have a cervical spine fracture. Despite the frequency with which an anesthesiologist may encounter patients still wearing their cervical collars because their necks have not yet been cleared, no special precautions appear warranted in the asymptomatic, alert patient.

Anesthetic Technique

Choice of Anesthetic Drugs. Craniotomies are most commonly performed for the evacuation of subdural, epidural, or intracerebral hematomas. The anesthetic approach is similar for all three techniques. The guiding principles have been discussed in the section Control of Intracranial Pressure and Brain Relaxation. In general, anesthetics that are known to be cerebral vasoconstrictors are preferable to those that have the potential to dilate the cerebral circulation. All of the intravenous anesthetics, except perhaps ketamine, cause some cerebral vasoconstriction and are reasonable choices, provided they are consistent with hemodynamic stability. All of the inhaled anesthetics (N_2O and all of the volatile anesthetics) have some cerebral vasodilatory effect. Although their administration frequently is consistent with acceptable ICP levels and appropriate conditions in the surgical field, when the ICP is out of control (or unknown), or the surgical field is tight, eliminating the inhaled anesthetics in favor of fixed agents is appropriate. For patients who are likely to remain tracheally intubated postoperatively, an anesthetic based primarily on a narcotic, such as fentanyl, and a muscle relaxant usually serves well. Any muscle relaxant is acceptable with the proviso that those that can release histamine (now rarely used) should be titrated in small increments. When immediate tracheal extubation is a possibility (e.g., the patient with an acute epidural hematoma who had a lucid interval before witnessed deterioration), the technique should be modified after the opening of the cranium. Introduction of inhaled anesthetics or the use of shorter-acting intravenous agents can be undertaken as guided by observation of the surgical field. If N_2O is contemplated at any time, the anesthesiologist must remember the possibility, in the setting of missile injury or compound skull fracture, of intracranial air.

Monitoring. The anesthesiologist should appreciate that the priority is to open the cranium as rapidly as possible.[250] After achieving intravenous access, the risks and benefits of delaying craniotomy for line placement should be considered carefully. An arterial line, often placed after induction in urgent situations, is appropriate for essentially all acute trauma craniotomies. Peripheral venous access is sufficient in the majority of situations. Sudden hypotension after dural opening with high ICP can occur as brainstem compression is relieved.[251] Appropriate intravascular volume resuscitation should mitigate this occurrence. Infrequently, the management of a depressed skull fracture over the sagittal sinus justifies a precordial Doppler and, subject to the surgeon's assessment of VAE risk, a right heart catheter.

Arterial Blood Pressure Management. The concept that the injured brain is extremely vulnerable to what would otherwise be a minor insult (e.g., modest hypotension, moderate hypoxia), has been well confirmed in the laboratory.[252,253] Although clinically the cause-effect relationships are not absolutely confirmed, several surveys demonstrate the association of otherwise minor degrees of hypotension and hypoxia with poor outcome in both adult[243,254-259] and pediatric patients with TBI.[260] This vulnerability to hypotension probably arises because many patients have brain regions with precariously low CBF in the first 2 to 3 days after TBI[21,31,36,261,262] and autoregulation is frequently defective.[35,263,264] The characteristic behavior of CBF after TBI is an initially low CBF followed by a gradual increase over 48 to 72 hours to normal, or sometimes even slightly hyperemic, levels.* There is considerable evidence that low postinsult CBF values correlate with a poor eventual outcome,† and a large percentage of patients who die after TBI have pathologic changes consistent with ischemia.[154] These observations have resulted in a general emphasis among neurosurgeons, neurointensivists, and anesthesiologists on aggressive support of arterial blood pressure in the patient with TBI.

What constitutes an appropriate arterial blood pressure? Systematic studies, in particular those conducted at the University of Edinburgh, revealed that indices of the adequacy of cerebral perfusion derived from $SjvO_2$ and TCD data begin to deteriorate below a mean CPP (CPP = MAP – ICP) of 70 mm Hg,[255,269,270] and many centers adopted 70 mm Hg as the CPP target. A clinical investigation by Robertson and colleagues comparing the ICU management of patients with TBI at CPPs of 70 and 50 mm Hg demonstrated that, although indices of cerebral well-being were improved by the former, there was no outcome advantage, apparently because of the cardiopulmonary morbidity associated with achieving a sustained CPP of 70 mm Hg.[271] As a result, many groups and authorities have adopted 60 mm Hg as the minimal CPP management objective.[265,272-275] The Brain Trauma Foundation's most recent recommendations, however, give clinicians wide latitude in offering a recommendation of CPP targets "within the range of 50 to 70 mm Hg" in adults.[68] Age-related CPP targets of 40 to 50 mm Hg have been recommended for children.[276,277]

"Maintain CPP at 60 mm Hg in the first 2 to 3 days after TBI" is probably reasonable general advice. However, clinicians may encounter other views, including the argument that a "one-size-fits-all" approach inevitably denies the heterogeneity of pathophysiology among patients with TBI. It is certainly true that not all patients with TBI have low CBF and not all have absent autoregulation. Although an initially low post-injury CBF is probably the most common clinical occurrence, hyperemia does occur.[33,37,266,278,279] It tends to occur in patients with mass lesions rather than contusions, although even those patients have an immediate post-injury period of low CBF, with delayed hyperemia peaking at 24 hours or later.[32,33,266,267,279] Hyperemia may also be more common in children.[280] (Also see Chapter 93.) There is evidence

*References 21, 31, 35, 36, 261, 265, 266.
†References 21, 34, 255, 262, 267, 268.

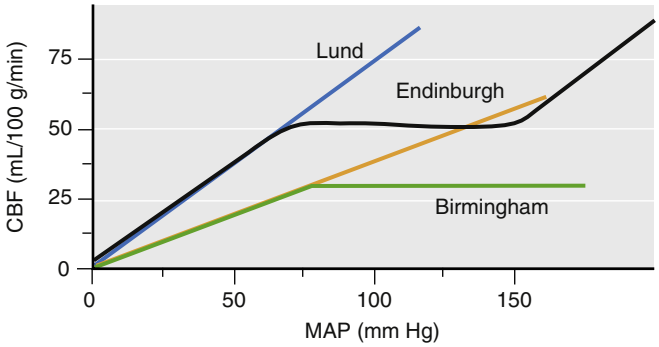


Figure 70-16. The relationship of cerebral blood flow (CBF) to blood pressure after head injury. There are three cerebral perfusion pressure (CPP) management strategies (see text) driven by differing beliefs about common pathophysiologic derangements. The most commonly held strategy is Edinburgh (so named for the institution of the original proponents); it emphasizes low postinjury CBF, impaired autoregulation, and the necessity to support CPP (mean arterial pressure [MAP] – intracranial pressure [ICP]) to 60 to 70 mm Hg. The Lund concept emphasizes the contribution of hyperemia to the occurrence of elevated ICP. That approach uses antihypertensive agents to reduce blood pressure while maintaining CPP greater than 50 mm Hg.[292] That CPP target has increased, in the most recent iteration, to 60 to 70 mm Hg, with allowance for occasional reduction to 50 mm Hg.[294] An approach emanating from the University of Alabama, identified as *Birmingham*, entails pharmacologically induced hypertension. That approach is based on the belief that autoregulation is largely intact and that hypertension will result in cerebral vasoconstriction with concomitantly reduced cerebral blood volume and ICP.[299,300]

that not all patients with TBI benefit from increases in CPP. Patients with TBI and impaired autoregulation, low baseline flows, increased ICP, and low initial GCS score are most likely to benefit.[281-284] Accordingly, "targeted" therapy has been advocated.[285-291] However, techniques to discriminate the various flow states (serial CBF measurement, TCD, $SjvO_2$) are not universally available. Some institutions, which have the necessary data analysis capacity, take another approach to targeted therapy. They identify a nominal "optimal CPP" by examining the changes in ICP that occur in response to variations in MAP. The range of MAPs in which the smallest $\Delta ICP/\Delta MAP$ occurs is taken to be the range within which autoregulation functions most efficiently and is the target range for that individual patient.[286,287] This approach is not feasible in most ICUs. As a result, and despite the theoretic attractiveness of targeted therapy, the CPP of 60 as an objective is more common.

There are at least two alternative approaches to blood pressure management in patients with TBI (Fig. 70-16). The Lund concept is based on the premises that arterial blood pressure causes hydrostatically driven edema accumulation, and that edema formation can be further aggravated by subnormal COP and crystalloid administration.[292-294] As originally described, the Lund approach in part entailed relative dehydration (furosemide, crystalloid restriction), albumin administration to maintain a normal COP, and the administration of metoprolol and clonidine to lower blood pressure to a CPP target of 50 to 55 mm Hg. At its inception, the approach was controversial because it ran counter to the perceptions of many clinicians of the importance of maintaining a CPP of 70 mm Hg and because of the later demonstration that a negative fluid balance in patients with TBI is deleterious.[257] Over time (and in parallel with a relaxation the higher CPP targets by others[68,265,272,273]), the Lund proponents have modified their approach. Normovolemia is now the clinical objective, and CPP is 60 to 70 mm Hg in most patients. The latter has made the approach somewhat less controversial. However, CPP may be reduced to 50 to 60 mm Hg when ICP is not well controlled,[135] and that element remains controversial.[295] Although the proponents of the Lund approach assert improvements in outcome, those reports invariably entail either no control group or comparisons with nonconcurrent controls.[136,296-298] The approach has not been adopted in North America.

The second approach, promoted by neurosurgeons at the University of Alabama at Birmingham (sometimes called the "Rosner concept" after its chief proponent), is that induced hypertension can be used as an adjunct to ICP control.[21,299,300] The underlying concept is that autoregulation is at least partially preserved after TBI and that an increased MAP results in autoregulation-mediated vasoconstriction with a concomitant reduction in CBV and, therefore, ICP. These investigators reported a very satisfactory local experience,[300] but others have reported that induced hypertension was either ineffective or deleterious as a means of reducing increased ICP.[12,301] The Rosner approach now appears to have few advocates.

What should the anesthesiologist managing the patient with TBI do in the face of these various approaches? Perfusion pressure support of varying degrees is a theme that is common to of all of them, and the careful support of CPP at or just above the 60-mm Hg range is probably the most reasonable general approach. When establishing normovolemia alone does not accomplish that objective, phenylephrine, norepinephrine, and dopamine have all been used. With that CPP recommendation offered, it must be acknowledged that convictions vary and anesthesiologists should come to an understanding with the local traumatologists and neurosurgeons as to CPP targets.

Hyperventilation. The use of hypocapnia has been reviewed in detail in the section Management of $Paco_2$. The effectiveness of acute hypocapnia in reducing ICP is well confirmed.[12] But there is substantial evidence that hyperventilation is potentially deleterious[21,22,27-29,302] and should not be overused. That evidence suggests that hyperventilation and the concomitant vasoconstriction can result in ischemia,[19,27-30] especially when baseline CBF is low,[30] as is likely to be the case in the first 48 to 72 hours after head injury.[21,31,36,37] The expert panel convened by the Brain Trauma Foundation specified that prophylactic hyperventilation is "not recommended," and that "hyperventilation should be avoided during the first 24 hours after injury when CBF is often critically reduced."[68] The available information argues that hyperventilation should be used selectively rather than routinely in the management of patients with TBI. Maintaining ICP less than 20 mm Hg, preventing or reversing herniation, minimizing retractor pressure, and facilitating surgical access are still important objectives in the

management of the patient with TBI, and to the extent that these objectives cannot be accomplished by other means, hyperventilation may still be appropriate. Once again, the anesthesiologist should agree on management variables with the surgical team at the outset of all procedures.

Intravenous Fluid Management. Intravenous fluid management of the patient with TBI was addressed earlier in the section Intravenous Fluid Management. The important principles are that fluids should be chosen invariably to prevent reduction of serum osmolarity and should probably be chosen to prevent profound reduction of colloid oncotic pressure—that is, in the circumstances of a large-volume resuscitation (arbitrarily, greater than half a circulating volume), using a mix of colloids and crystalloids is probably appropriate. The clinical objective should be the maintenance of intravascular normovolemia, in part as an adjunct to MAP and CPP support. A chronic negative fluid balance, as can occur with the combination of modest fluid restriction and liberal use of osmotic diuretics, has been shown to be deleterious and should be avoided.[257] The severely injured brain can liberate sufficient thromboplastin into the circulation to result in a consumptive coagulopathy.[303-305] Appropriate laboratory tests and replacement should be performed. The clinician may also find a serum osmolarity determination early in the course of anesthetic management useful in appreciating the cumulative effects of prior administration of mannitol or HTS. The use of hypertonic solutions and the relevant attributes of colloid solutions were discussed in the section Intravenous Fluid Management. Because of the ischemia that can be a component of TBI, the minimal acceptable hemoglobin level should probably be more than that accepted in stable critical care patients (i.e., 7 g/dL). There is relatively little information to provide guidance (also see Chapters 61 and 105). However, one investigation, which presented observations of $PbtO_2$, suggested 9 g/dL as a hazard threshold in patients with TBI.[224]

Monitoring

Jugular Venous Oxygen Saturation. $SjvO_2$ monitoring has been used to guide the management of patients with TBI.* The underlying concept is that a marginal or inadequate CBF results in an increasing oxygen extraction, a widening arteriovenous content difference, and reduction of $SjvO_2$. Normal subjects have $SjvO_2$ values between 60% and 75%. An $SjvO_2$ less than 50% for 5 minutes is commonly accepted as constituting jugular desaturation. There have been numerous reports of low $SjvO_2$ values improving with interventions including reducing hyperventilation, increasing MAP, or inducing hypervolemia. $SjvO_2$ measurement makes an assessment of global oxygen extraction. It might be expected to have limited sensitivity to focal events, and instances in which focal inadequacy of perfusion was not reflected by low $SjvO_2$ have been reported.[27-29,37] An additional limitation inherent to the unilateral placement of the catheter is the observation by Stocchetti and colleagues,[308] who observed that there was an average side-to-side difference between simultaneous jugular bulb saturations of 5.3 ± 5% and that side-to-side differences in hemoglobin saturation of up to 15% were common.[308]

Despite the reported successes with $SjvO_2$ monitoring,[38,309,310] we do not believe that the method is sufficiently well defined to justify advocating widespread intraoperative application. In the ICU, it appears to be potentially useful as a trend monitor that may serve to identify the level of CPP or hyperventilation below which cerebral perfusion begins to be compromised, with the proviso that there is a significant potential for false-negative results.[27-29,37] The technique also has a potential use beyond warning of inadequate perfusion. High $SjvO_2$ values may serve to identify the patient with elevated ICP in whom hyperemia is an important contributing factor and in whom aggressive attempts to decrease CBF (i.e., hyperventilation, barbiturates) may be beneficial.

Brain Tissue PO_2. Brain tissue PO_2 ($PbtO_2$) has been used to guide the management of both TBI and SAH, and there have been limited reports of improvement in outcomes thereby.[301-315] A $PbtO_2$ equal to or more than 20 to 25 mm Hg is viewed as normal, and values equal to or less than 10 to 15 mm Hg are assumed to convey a substantial risk of hypoxic injury. One investigation reported that 29% of patients with TBI with GCS scores equal to or less than 8 have brain regions with $PbtO_2$ equal to or less than10 mm Hg despite meeting CPP and ICP targets of equal to or more than 60 mm Hg or less than 25 mm Hg, respectively.[274] This would seem to encourage the use of these monitors. However, $PbtO_2$ monitors suffer from the inverse of the problem that prevails with $SjvO_2$ monitoring: they provide very focal information about the oxygenation status of only small regions of brain surrounding the tip. If they are placed remotely from focal injuries to provide a global measure of oxygenation, they may not see adverse events in at-risk but salvageable perilesional tissue.[316] They may similarly fail to be a useful therapeutic guide if they are within irredeemably injured brain. The use of $PbtO_2$ monitoring is neither standardized nor widespread.

Intracranial Pressure Monitoring for Nonneurologic Surgery in the Brain-Injured Patient. In the ideal situation, neurosurgical consultation is readily available and, appropriately, the anesthesiologist rarely has to make the decision for surgery. It may, however, be necessary for the anesthesiologist to participate in this decision. The relevant variables include:

1. *The level of consciousness.* If there has been a loss of consciousness at any time (or amnesia for the event in the absence of witnesses) or if the GCS score is less than 15, a CT scan should be obtained. If the CT scan reveals compressed basal cisterns (indicative of an exhaustion of supratentorial compensatory latitudes), midline shift, or effaced ventricles, and probably any intracranial lesion (e.g., contusion, small subdural), an ICP monitor should be considered for surgery, with general anesthesia performed within at least 48 hours after TBI. Excessive comfort should not be taken

*References 27-30, 38, 255, 270, 271, 306, 307.

from a good GCS score. Patients with good scores can talk and deteriorate or talk and die after a TBI associated with loss of consciousness. Delayed deterioration has been observed as much as 4 days after the initial injury.[317,318] Patients with lesions, usually contusions, in the frontal and frontotemporal region, and especially those with medial temporal lesions, are most at risk for this phenomenon. Modest expansion of lesions in this location (i.e., close to the uncus and the incisura where herniation occurs) can result in herniation even at relatively low ICPs (e.g., ≈20 mm Hg). At our institution, neurosurgeons would recommend avoiding an anesthetic in these patients and would certainly advise ICP monitoring if lengthy general anesthesia were unavoidable.

2. *Time since injury*. The longer the patient has had to declare his or her clinical course, the less pressing is the need for ICP monitoring. Delayed deterioration has been observed for as much as 48 hours,[317] and 4.5 days in separate investigations,[318] and a patient with a demonstrable CT lesion and a GCS score less than 15 is a candidate for a monitor during this time frame.
3. *Nature and duration of the intended procedure*. The risks of an untoward ICP event are inevitably greater in a 6-hour spine instrumentation in the prone position than in a 20-minute debridement and suturing of an arm laceration.

Hypothermia

There is clearly an ischemic component to the pathophysiology of TBI, and mild induced hypothermia has been shown to be highly protective in experimental cerebral ischemia. On that basis, the study of hypothermia after experimental TBI was undertaken, and improvements in outcome were demonstrated.[155] Several local, prospective trials of hypothermia after TBI were performed.[319-322] Because those trials appeared to indicate good patient tolerance of sustained mild hypothermia (32° C to 34° C) and improvement in ICP and outcome, a multicenter trial was performed. That trial, which required induction of hypothermia within 8 hours of injury, revealed no overall benefit.[156] Because of concern that 8 hours was not sufficiently rapid, a second trial, which achieved the target temperature in 2.5 hours, was performed. It too was negative for benefits.[157] As a result, there is no established role for hypothermia in TBI management as of this writing. However, interest and investigation appears likely to continue. Post hoc analysis of the two trials just cited revealed improved outcome in patients with intracerebral hematoma who were randomized to hypothermia.[323] A multicenter trial of hypothermia to treat increased ICP after TBI is underway in Europe.[324] (Also see the section Hypothermia.)

POSTERIOR FOSSA PROCEDURES

Most of the topics relevant to posterior fossa procedures (Table 70-5) have been discussed in the section Recurrent Issues. These include the sitting position and its cardiovascular effects and complications (quadriplegia, macroglossia), pneumocephalus, and VAE and PAE. The use of the sitting position to facilitate surgery in the posterior fossa increases the likelihood of all of these phenomena, though they are relevant to nonsitting positions as well. This section reviews the cardiovascular events associated with direct stimulation of the brainstem and their possible implications for postoperative management.

TABLE 70-5 CONSIDERATIONS RELEVANT TO POSTERIOR FOSSA PROCEDURES AND THE LOCATION OF THE RELATED DISCUSSION IN THIS CHAPTER

Consideration	Chapter Section, Subsection
Hemodynamic effects of the sitting position	Positioning, Sitting
Venous air embolism	Venous Air Embolism
Paradoxical air embolism	Venous Air Embolism
Hemodynamic effects of brainstem and cranial nerve manipulation	Posterior Fossa Procedures
Macroglossia	Positioning, Sitting
Pneumocephalus	Pneumocephalus
Quadriplegia	Positioning, Sitting

Brainstem Stimulation

Irritation of the lower portion of the pons and the upper medulla and of the extra-axial portion of the fifth cranial nerve can result in a number of cardiovascular responses. The former two areas are most often stimulated during procedures on the floor of the fourth ventricle and the last during surgery at or near the cerebellopontine angle (e.g., acoustic neuromas, microvascular decompression of fifth [tic douloureux], seventh [hemifacial spasm], or ninth [glossopharyngeal neuralgia] cranial nerves). The responses may include bradycardia and hypotension, tachycardia and hypertension, or bradycardia and hypertension, and ventricular dysrhythmias.[325] Meticulous attention to the ECG and a directly transduced arterial pressure during manipulation in this region are necessary to provide the surgeon with immediate warning of the risk of damage to the adjacent cranial nerve nuclei and respiratory centers. Pharmacologic treatment of the dysrhythmias that occur may serve to attenuate the very warning signs that should be sought.

Irritation and injury of posterior fossa structures that may have occurred during surgery should be taken into account in planning extubation and postoperative care. In particular, procedures involving dissection on the floor of the fourth ventricle entail the possibility of injury to cranial nerve nuclei or postoperative swelling in that region, or both. Cranial nerve dysfunction, particularly of nerves IX, X, and XII, can result in loss of control and patency of the upper airway, and swelling of the brainstem can result in impairment of both cranial nerve function and respiratory drive. The posterior fossa is a relatively small space, and its compensatory latitudes are even more limited than those of the supratentorial space. Relatively little swelling can result in disorders of consciousness, respiratory drive, and cardiomotor function. There should be an interaction between the anesthesiologist and the surgeon in making decisions about whether

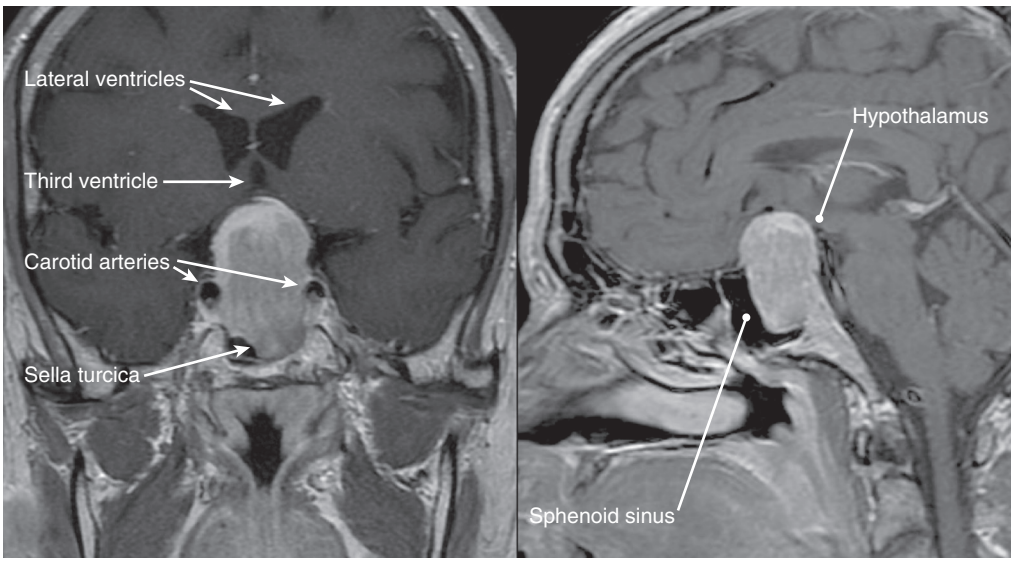


Figure 70-17. Pituitary tumor with suprasellar extension. The *left panel* shows the proximity of the tumor to the carotid arteries (which lie within the cavernous sinuses) and the potential for distortion of the ventricular system. The optic chiasm (not seen) lies above the sella in the path of the upwardly expanding tumor. The *right panel* shows that tumors that lie above the sella (including craniopharyngiomas, which arise in this location) abut and can invade the hypothalamus. The more radio-dense (whiter) cap over the superior and anatomic right lateral aspects of the tumor mass is a normal pituitary gland.

extubation is appropriate and where postoperative observation should occur (i.e., ICU or non-ICU).

Spontaneous ventilation was once advocated for procedures that entailed a risk of damage to the respiratory centers. Spontaneous ventilation is now rarely used because the proximity of the cardiomotor areas to the respiratory centers should permit cardiovascular signs to serve as an indicator of impending injury to the latter. It is our opinion that respiratory pattern is more likely to be a relevant monitor when the threat to the brainstem is the result of vessel occlusion (as might occur with accidental interruption of perforating vessels during vertebrobasilar aneurysm surgery[326]) than when it is because of direct mechanical damage caused by retraction of or dissection in the brainstem.

Various electrophysiologic monitoring techniques may be used during posterior fossa surgery. These include somatosensory evoked responses, brainstem auditory evoked responses, and electromyographic monitoring of the facial nerve. The last requires that the patient not be paralyzed or have a constant state of incomplete paralysis. Somatosensory evoked response monitoring imposes some constraints with respect to the selection of anesthetics. These are discussed in Chapter 49.

Balloon Compression of the Trigeminal Ganglion

This is another situation in which a dysrhythmia may occur. The procedure attempts to produce a neuropraxia of the fifth cranial nerve by the rapid inflation of a Fogarty-type balloon within Meckel's cave.[327,328] The balloon is introduced percutaneously through the cheek and beneath the maxilla. The procedure is best accomplished with a general anesthetic because both the entry of the needle into Meckel's cave and the balloon compression (lasting several minutes) are intensely stimulating. A relatively profound, although transient, bradycardia occurs and is sought as confirmation of adequate compression. External pacemaker pads have been advocated but in our experience are unnecessary.

TRANSSPHENOIDAL SURGERY

The transsphenoidal approach to the sella turcica is used for the excision of tumors that lie within the sella or its environs (Fig. 70-17). The majority of these lesions are tumors arising from the pituitary gland, and the most common of these are prolactin-secreting microadenomas and nonsecreting macroadenomas. Patients with the former are usually women who present with secondary amenorrhea or galactorrhea, or both. The nonsecreting adenomas tend to manifest with mass effects (headache, visual disturbance, hypopituitarism) and are typically larger at the time of diagnosis. Patients may also present with hypopituitary states as a result of dysfunction of the normal gland caused by compression by the tumor mass. There are three other less common pituitary tumors: growth hormone–secreting lesions, which result in acromegaly; adrenocorticotropic hormone (ACTH)-secreting tumors, which cause Cushing disease; and a very rare thyroid-stimulating hormone–secreting lesion, which results in hyperthyroidism. A detailed review of the perioperative management of this group of patients is available.[329]

Preoperative Evaluation

The important preoperative considerations relate to the patient's endocrine and visual status. In general, as a pituitary lesion expands and compresses the pituitary tissue, normal glandular function is compromised. Hormonal function is lost in the following sequence: first, gonadotrophins; second, growth hormone; third, ACTH; and fourth and last, thyroid-stimulating hormone. A decrease in

ACTH secretion results in a hypoadrenal state. Attention to this is critical because an Addisonian crisis can ensue, especially under the stress of surgery. Profound hypocortisolism, with associated hyponatremia, should be corrected preoperatively. Deficiency in thyroid function is uncommon. However, if significant hypothyroidism is present, it should be corrected preoperatively because hypothyroid patients have a diminished tolerance to the cardiovascular depressant effects of anesthetics. Attention to other manifestations of pituitary hypersecretion is also important. Hypertension, diabetes, and central obesity are common concomitants of ACTH-secreting adenomas (Cushing disease). Patients with advanced acromegaly can develop an enlarged tongue and a narrowed glottis, and the airway should be evaluated accordingly. The dermis is thickened and vascular cannulation can be more difficult. Hypertension and a cardiomyopathy may also occur. (See also Chapter 38.)

Monitoring

Many practitioners place an arterial catheter, and this facilitates monitoring of blood pressure as the nasal mucosa is injected with epinephrine containing local anesthetic solutions. Access for blood sampling is also a useful adjunct to postoperative care if diabetes insipidus develops. Blood loss is usually modest. However, the cavernous sinuses, through which the carotid arteries pass (see Fig. 70-17), form the lateral boundary of the sella and may be entered during the resection of large tumors. Entry into these structures can lead to catastrophic blood loss. In addition, in some patients there is an extensive venous sinus connecting the two cavernous sinuses that may cover the entire dural lining of the sella, rendering a transsphenoidal approach hazardous. It has, on occasion, actually precluded this approach to the pituitary gland.

Anesthetic Technique

The latitudes are broad with respect to choice of agent, although tumors with suprasellar extension (see Fig. 70-17) can occasionally cause hydrocephalus and add increased ICP constraints to the anesthetic technique. The procedure is performed in the supine position, usually with some degree of head-up posture to avoid venous engorgement. A pharyngeal pack prevents the accumulation of blood in the stomach (which causes vomiting) or in the glottis (which contributes to coughing at extubation). A RAE-type tube secured to the lower jaw at the corner of the mouth opposite the surgeon's dominant hand (e.g., the left corner of mouth for a right-handed surgeon) is suitable. A small esophageal stethoscope and temperature probe can lie with the endotracheal tube. Covering the entire bundle with a towel drape (a plastic sheet with an adhesive edge) placed just below the lower lip, so that it hangs from the lower jaw like a veil, protects it from contact with the preparation solutions.

The procedure is commonly performed with a C-arm image intensifier (lateral views), and the head and arms are relatively inaccessible once the patient is draped. It is appropriate to establish the nerve stimulator at a lower extremity site. The surgical approach is via the nasal cavity, usually through an incision made under the upper lip or via the nares. During the approach, the mucosal surfaces within the nose are infiltrated with a local anesthetic and epinephrine solution, and the patient should be observed for the occurrence of dysrhythmias.

Surgical preferences for CO_2 management vary. In some instances, hypocapnia is requested to reduce brain volume and minimize the degree to which the arachnoid bulges into the sella. One of the important surgical considerations is the avoidance, when possible, of opening the arachnoid membrane leading to leakage of CSF. Postoperative CSF leaks can be persistent and are associated with a considerable risk of meningitis. By contrast, when there is suprasellar extension of a tumor, a normal CO_2 level helps deliver the lesion into the sella for excision.[330] As an alternative method to accomplish this, some surgeons have resorted to "pumping" of saline into the lumbar CSF space.[331]

A smooth emergence (see the section Emergence from Anesthesia) from anesthesia is desirable, especially if the CSF space has been opened (and resealed with fibrin glue or by packing the sphenoid sinus with fat or muscle). Repeated intense Valsalva maneuvers, as with coughing or vomiting, may contribute to the reopening of a CSF leak and worsen the risk of subsequent meningitis. The airway should be cleared of debris including formed clots. In situations in which there is concern that a persistent CSF leak may occur, the surgeon may place a lumbar CSF drain to maintain CSF decompression in the early postoperative period.

Diabetes Insipidus

The antidiuretic hormone is synthesized in the supraoptic nuclei of the hypothalamus and is transported down the supraoptic-hypophyseal tract to the posterior lobe of the pituitary gland. This portion of the pituitary gland is frequently spared during transsphenoidal tumor excisions. Even when it is excised, water homeostasis commonly normalizes, presumably because the ADH is released from the cut end of the tract. When the pituitary stalk is transected, and sometimes even when the posterior lobe of the pituitary gland is left intact, transient diabetes insipidus may occur. Diabetes insipidus very rarely arises intraoperatively; it usually occurs 4 to 12 hours postoperatively. The clinical picture is one of polyuria in association with a rising serum osmolality. The diagnosis is made by comparison of the osmolalities of urine and serum. Hypo-osmolar urine in the face of an elevated and rising serum osmolality strongly supports the diagnosis. In the presence of bona fide diabetes insipidus, urine-specific gravity is low (i.e., ≤1.002), though this analysis is now rarely performed.

When the diagnosis of diabetes insipidus is established, the following fluid management regimen is appropriate: hourly maintenance of fluids plus two thirds of the previous hour's urine output. (An acceptable alternative is the previous hour's urine output – 50 mL + maintenance.) The choice of fluid is dictated by the patient's electrolyte levels. In general, the patient is losing fluid that is hypo-osmolar and relatively low in sodium. Half-normal saline and 5% dextrose in water are commonly used as replacement fluids. Beware of hyperglycemia when large volumes of 5% dextrose in water are used. An unacceptable fluid regimen that has been used calls for maintenance

fluids plus the previous hour's urine output. This has the potential to put the anesthesiologist and the patient in a "chase your tail" situation. Should the patient become iatrogenically fluid–overloaded, this regimen precludes his or her returning to isovolemia, and where the maintenance fluid allowance is generous, it guarantees that the patient will become increasingly hypervolemic. If the hourly requirement exceeds 350 to 400 mL, desmopressin acetate is often administered.

AWAKE CRANIOTOMY AND SEIZURE SURGERY

Awake craniotomies are performed when tumors or epileptic foci lie close to cortical areas required for either speech or motor function, or to mesial-temporal structures critical to short-term memory. Many patients have so-called temporal lobe epilepsy. There is commonly a structural lesion visible on MRI. Sometimes there is a history of remote trauma.

Presurgical Evaluation

Before the resection, most patients have undergone a Wada test or video-telemetry, or both.[332] More recently, functional testing using MRI or positron emission tomography, or both, has also been introduced to the presurgical evaluation. The Wada test involves selectively anesthetizing the cerebral hemispheres, usually by injection of amobarbital (Amytal) sodium into the carotid artery to localize the hemisphere that controls speech or to confirm that there is bilateral representation for short-term memory, or both. Speech is an issue when the posterolateral portions of the temporal lobe are involved, and memory is the concern when the involvement is mesial.

Anesthesia for Electroencephalogram Electrode Placement

Video-telemetry is performed to permit localization of the seizure focus that is responsible for the clinically problematic events. This usually requires prior placement of either subdural strip electrodes (via burr holes) or a subdural electrode grid (requiring a craniotomy). Electrodes are sometimes placed deep into the parenchyma, usually within the temporal lobe (placed stereotactically via burr holes), or they are positioned to look at the inferior surfaces of the temporal lobe. The latter is commonly accomplished with so-called foramen ovale electrodes. These electrodes are placed using a needle similar to an epidural needle. The point of entry is approximately 2 cm lateral to the angle of the mouth. The needle is passed through soft tissue, under the temporal process of the zygomatic bone and medial to the ramus of the mandible, up to the base of the skull in the vicinity of the foramen ovale. Typically, this procedure is performed as a MAC, although small doses of anesthetics, most often propofol, are usually required at the time of stimulation by the needle of the periosteum at the base of the skull. After placement of the relevant electrodes, the patient's seizure medication is discontinued and the patient remains in an observation unit with EEG and behavior recorded continuously. In this manner, the EEG events associated with the clinically significant seizure events and their anatomic origin can be identified.

Preanesthetic Evaluation and Preparation

At the preoperative interview, the patient should be educated about the nature and duration of the procedure and the limitations on patient movement. A description of both the aura and the seizures to facilitate recognition of impending events should be obtained, and it should be ascertained whether the patient is subject to having grand mal convulsions. If intraoperative electrocorticography to identify seizure foci is intended, it is common to discontinue or reduce by half the anticonvulsants according to the perceived risk of uncontrolled seizures. Premedicants with an anticonvulsant effect (e.g., benzodiazepines) should not be used because they may interfere with intraoperative EEG localization (see also Chapter 38).

Anesthetic Technique

The objectives of the anesthetic technique are as follows:

1. To minimize patient discomfort associated with the potentially painful portions of the procedure and with the prolonged restriction of movement.
2. To ensure patient responsiveness and compliance during the phases of the procedure that require assessment of speech, memory, or motor/sensory responses to cortical stimulation.
3. To select anesthetic techniques that produce minimal inhibition of spontaneous seizure activity.

There are probably many ways of providing sedation that are consistent with the objectives just cited. The techniques used range from minimal sedation approaches, through deep sedation during which intermittent unresponsiveness is achieved with spontaneous ventilation and an unprotected airway, to asleep-awake-asleep techniques with intermittent airway management with a laryngeal mask airway (LMA) or endotracheal tube, sometimes with positive-pressure ventilation. From the outset, the anesthesiologist should appreciate that the essential element of an anesthetic for an awake craniotomy is the local anesthetic technique. Sedation cannot compensate for inadequate anesthesia of the scalp, as is accomplished by nerve blocks (Fig. 70-18), and pin site infiltration. Although the anesthesiologist can contribute enormously to the patient's comfort and tolerance of the painful components of the procedure and the prolonged immobilization, the anesthesiologist must not get trapped into thinking that it is his or her responsibility to provide a general anesthetic equivalent in a spontaneously breathing patient with an unprotected and all but inaccessible airway.

For sedation, there are many options. Many clinicians (including the authors) use principally propofol,[333,334] sometimes supplemented with infusion of remifentanil (e.g., 0.02 to 0.05 μg/kg/min) or dexmedetomidine (e.g., 0.2 μg/kg/hr). Other combinations, including propofol with either fentanyl or remifentanil and dexmedetomidine with or without remifentanil, are reasonable.[335-337] Great care should be taken in administering additional sedative drugs, especially narcotics whose respiratory depressant effects will be synergistic with propofol. This is especially relevant in the presence of pin fixation, which severely restricts the anesthesiologist's capacity to intervene quickly in the event of excessive respiratory depression or loss of patency of the airway. Propofol

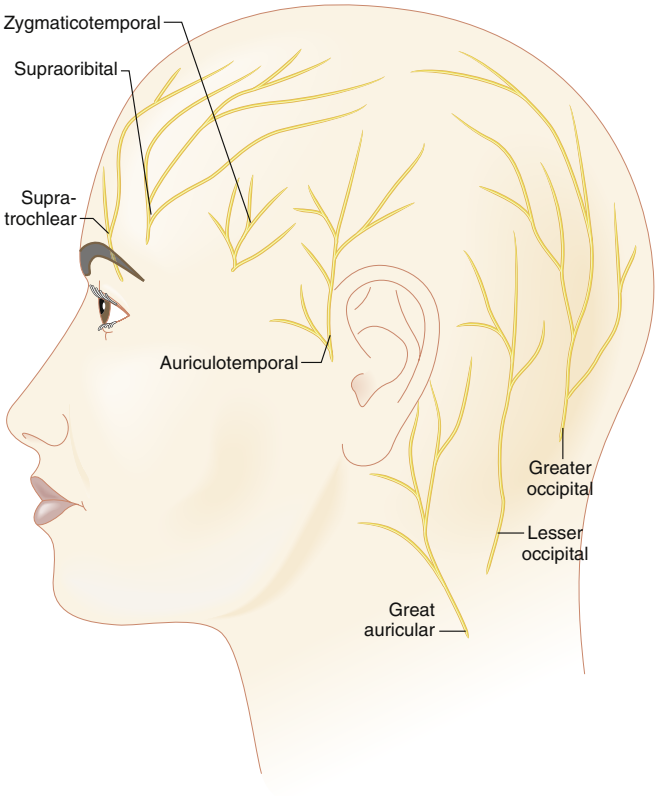


Figure 70-18. The cutaneous nerves of the scalp.

should be discontinued at least 15 minutes before EEG recording. Despite prompt awakening, propofol leaves a residual EEG footprint characterized by high-frequency, high-amplitude beta activity that can obscure the abnormal activity that is being sought in the cortical surface EEG.[333] The use of dexmedetomidine, which in addition to sedation and anxiolysis provides some analgesia with minimal respiratory depression, is increasing.[337-341] Satisfactory conditions for functional testing, including brain stimulation for speech mapping and electrocorticography, have been reported with dexmedetomidine infusions ongoing at rates between 0.1 and 0.5 μg/kg/hr during the testing.[337,339,342,343] The occurrence of delays in achieving satisfactory patient responsiveness has also been reported,[340,344] and using only relatively modest infusion rates (i.e., 0.1-0.2 μg/kg/hr) during neurocognitive testing appears advisable.[342] Administration of antiemetics (ondansetron or dexamethasone, or both) should probably be routine, especially if narcotics are administered.

Various groups have reported the use of the LMA with either spontaneous or controlled ventilation during the craniotomy, with cessation of sedative administration and LMA removal once the brain surface is exposed.[338-340,342,345,346] It is obvious that many approaches can be effective, but it should be noted, for the most part, that the LMA techniques have been used in patients who were *not* in pin fixation of the head. An awake-asleep-awake technique using insertion, removal, and replacement of an endotracheal tube has been reported, but a customized tube that allows installation of local anesthetic in the glottis and trachea was used.[347]

Routine, noninvasive monitors are almost always sufficient. Reliable capnography, to provide breath-by-breath confirmation of airway patency and respiratory drive, is essential if deep sedation is intended for any portion of the procedure. These procedures are often lengthy. Attention to the details of patient comfort (warming blankets, a sheepskin, room temperature) improve patient tolerance.

The uncomfortable phases of the procedure are pin head holder placement (not all groups use a pin head holder) and the craniotomy. Many patients also find manipulation of the dura, in particular traction on subtemporal dura, painful. The actual manipulation of supratentorial brain parenchyma is painless. The volume of local anesthetic used to infiltrate pin sites and perform the scalp nerve blocks can be substantial. It is appropriate for the anesthesiologist to keep track of, and provide advice about, the doses of local anesthetics used.

The anesthesiologist should participate actively at the time of head positioning. The more sniff that can be achieved before the final lockdown of the head holder, the wider the latitudes will be for sedating the patient, while maintaining spontaneous ventilation and a patent airway. During positioning of the patient, there should also be attention to the need to maintain visual access to the face. A clear line of sight to the face is necessary to present the patient with images to name as part of speech testing and to identify the occurrence of facial motor responses during mapping of the motor strip.

In general, after the dural opening is complete, for seizure-related resections, cortical surface EEG recording is performed to locate the seizure focus. If no seizure activity is observed, provocative maneuvers may be requested.[348] Methohexital in a dose of approximately 0.3 mg/kg is generally safe and effective. Etomidate, approximately 0.05 to 0.1 mg/kg, has also been used. Localization of seizure focus can also be accomplished during light general anesthesia (e.g., N_2O /fentanyl/low-dose isoflurane). During general anesthesia, alfentanil, in a bolus dose of 30 to 50 μg/kg[349,350]; etomidate in doses of 0.2 to 0.3 mg/kg[351,352]; and remifentanil, as a bolus of 2.5 μg/kg[353] have been reported to be effective in activating seizure foci. Hyperventilation may also help activate seizure foci.[354]

After localization by EEG (or initially in nonseizure-related resections), functional testing is performed by electrical stimulation of the cortical surface with observation for motor, sensory, or speech interruption effects. During cortical stimulation, the anesthesiologist should be prepared to treat grand mal convulsions. Seizures usually stop with cessation of stimulus or with irrigation of the cortex with cold saline. When they are not self-limited, pharmacologic intervention (e.g., with propofol in increments of 0.5 to 1.0 mg/kg), may be warranted. However, propofol should be withheld briefly until it is clear that the seizure is not going to terminate spontaneously because it may interfere with subsequent EEG localization for some time.[333]

STEREOTACTIC PROCEDURES

Stereotactically-guided procedures are performed for numerous indications including biopsy of small, deep-seated lesions and placement of deep brain stimulation electrodes. The latter are placed most commonly for the

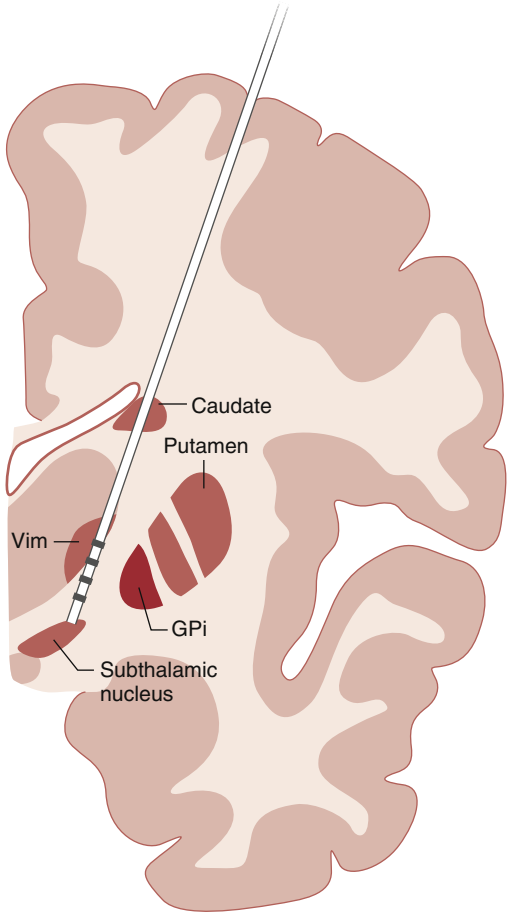


Figure 70-19. Deep-brain stimulation electrode target sites. The most commonly targeted nuclei for the treatment of movement disorders are the subthalamic nucleus, the ventral intermediate nucleus of thalamus (Vim), and the internal segment of globus pallidus (GPi).

treatment of movement disorders (Parkinson disease, essential tremor, and dystonias)[355] and sometimes for a variety of other conditions (Tourette disorder, obsessive-compulsive disorder, and depression). Procedures related to movement disorders most often target the subthalamic nucleus, the internal segment of the globus pallidus, or the ventral intermediate nucleus of the thalamus (Fig. 70-19).[355] The mechanism of the beneficial effect of deep brain stimulation is not well understood. A prominent theory is that the abnormal motor patterns are caused by synchronized oscillations in neural circuits involving several basal ganglia nuclei, as well as the cortex, and that high-frequency stimulation of any of several points along the pathway can interfere with the oscillation.[356]

Preoperative evaluation should include ensuring that the coagulation process is intact and that the patient is not taking platelet-inhibiting agents (including herbal medications). There should be careful explanation of the procedure, its likely duration, and the necessary restraints on patient movement.

Several constraints will confront the anesthesiologist including:

1. *Airway access*. Commonly, the stereotactic frame, of which there are many variations, is placed using local anesthetic and the patient undergoes an imaging study before being brought to the operating room. In some instances, the frame will prevent mask application and ventilation, laryngoscopy, and neck extension. If a general anesthetic is to be used, an awake intubation occasionally may be required. The frame is often anchored to the operating room table. If sedation is to be used, the anesthesiologist should have certain knowledge of how to remove the device rapidly in an urgent situation (including knowledge of the whereabouts of the requisite key or spanner device).
2. *The effect of anesthetics on microelectrode recordings and symptoms*. Localization of deep brain stimulation electrodes typically involves the combination of stereotaxis with fine tuning by identification of the electrophysiologic footprint specific to the targeted nucleus (e.g., the subthalamic nucleus, globus pallidus interna). The sedative agents used must not interfere with that signature. The nature and duration of the effects of anesthetics (which probably vary from nucleus to nucleus) have not been systematically defined. Some surgeons and electrophysiologists may request, on a just-in-case basis, that no sedative agent whatsoever be given. That is likely to be unnecessarily restrictive. Comprehensive reviews are available.[357-359] In short, benzodiazepines probably have the greatest potential to interfere and, for the time being, are best avoided. Propofol has been reported to cause severe dyskinesias in patients with movement disorders,[360] but has nonetheless been used quite frequently. At a minimum, a substantial interval between propofol administration and recording should be planned. Dexmedetomidine in low doses has been used quite widely without reports of interference with signals.[361] Remifentanil, in part because of its rapid clearance, is probably also a reasonable choice, although it too has been reported to suppress Parkinsonian tremor.[362]
   The cessation of the patient's symptoms upon stimulation, without the occurrence of unacceptable side effects, is also an important end point for determining the adequacy of deep brain stimulation position and stimulus parameters. The symptoms must not be suppressed by the sedative agents. This can occur with propofol.[363] Satisfactory electrophysiologic recordings and preservation of the tremor have been reported in Parkinsonian patients who received dexmedetomidine in a dose sufficient to maintain a lethargic response to normal speech.[337,361,364]
   An additional issue that arises in some patients with movement disorders is the problem of obtaining high-quality radiologic images in the presence of a persistent tremor. Sedation immediately preceding the stereotactic placement may be inevitable. Propofol has been used, but the window between propofol administration and subsequent recording should be as long as possible.
3. *Intracerebral hematoma and prevention of hypertension*. Intracerebral hematoma is a serious, potential intraoperative complication of stereotactic procedures. Prevention and prompt treatment of hypertension are among the anesthesiologist's important objectives.

The concern is that, in the face of multiple needle passes through the brain, hypertension will precipitate development of an intracerebral hematoma. In the event of a substantial hematoma, an urgent craniotomy may be required, and the anesthesiologist should be prepared from the outset for this eventuality.

As noted in the section Venous Air Embolism, because of spontaneous ventilation, there is some hazard of VAE during deep brain stimulation placement.[99]

NEUROENDOSCOPIC PROCEDURES

Excision of some intraventricular lesions (e.g., colloid cysts, fenestration of the lamina terminalis or the floor of the third ventricle for treatment of hydrocephalus) can be accomplished endoscopically. Access is usually achieved through burr holes placed over the frontal or occipital horns of the lateral ventricle. The important anesthetic consideration relates to the irrigation fluid (which should be warmed) used to maintain clear visualization, just as is done in orthopedic arthroscopy procedures. Obstruction to the effluent limb produces rapid increases in ICP that are commonly associated with sudden changes in vital signs**.** An increase in blood pressure and decrease in heart rate (a Cushing-type response) is classic, but the heart rate component is less reliable. Cardiovascular changes may also, but less predictably, represent mechanical irritation of intracranial (e.g., hypothalamic) structures. The surgeon should be notified immediately of any sudden hemodynamic changes. The decision of whether intra-arterial monitoring is warranted should be made with the surgeon.

NEURORADIOLOGIC PROCEDURES

A wide variety of interventional procedures are performed for the evaluation and treatment of intracranial and extracranial disease. These include attempts to obliterate aneurysms, devascularize tumors and AVMs, and occlude arteriovenous fistulas. An extensive review is available[365] (see also Chapter 90).

Tumors and Arteriovenous Malformations

Hyperventilation may be appropriate in an attempt to divert flow away from normal brain and toward a lesion that is intended to receive the occlusive device or material. When the interventionalist is attempting to place glue in high-flow lesions (e.g., AVMs, fistulas), the anesthesiologist may be asked to reduce systemic blood pressure to prevent glue passage into the draining veins or systemic venous system. The choice of hypotensive agent depends on the anesthetist's experience and systemic cardiovascular considerations. Adenosine, which produces temporary flow cessation, is almost certainly the most effective means of accomplishing this objective.[366]

Intracranial Aneurysms

The International Subarachnoid Aneurysm Trial and subsequent meta-analysis have confirmed the broad applicability of endovascular treatment of aneurysms,[367,368] and the majority of aneurysms are currently managed by those approaches. Nonetheless, a substantial number of patients continue to undergo operative clipping,[369] primarily those with wide-necked aneurysms, diseased or occluded proximal vessels, and otherwise complex anatomy.

Many aneurysm-related procedures, in particular those involving the treatment of vasospasm by selective intraarterial installation of vasodilators (papaverine, calcium-channel blockers) or more commonly by balloon dilatation, can be accomplished without the involvement of an anesthesiologist. The duration of a procedure, individual patient factors, and sometimes the necessity for precise physiologic control may result in requests for monitored anesthesia care or general anesthesia. A chin-tucked position (to remove the bones of the face from the line of the anteroposterior radiograph source) and absolute immobility are commonly needed by the radiologist and, as a result, when the anesthesiologist's assistance is requested, it is often because a general anesthetic is perceived to be necessary. In addition, anesthesiologists may become involved during the resuscitation stage in the event of vascular rupture or of the migration of an intravascular device to an incorrect location. In the event of rupture, the interventionist may request blood pressure reduction while the coil packing of the aneurysm is completed hastily. In addition, immediate reversal of heparinization is required. When detachable devices, such as coils and balloons (the latter now used infrequently), are misplaced and ischemia ensues, fluid loading and pressor administration may be requested to improve collateral CBF while the device is retrieved. A dedicated arterial line is usually warranted. This may or may not be available via a port in the interventionist's vascular access sheath.

CEREBROSPINAL FLUID SHUNTING PROCEDURES

Cerebrospinal fluid shunts are inserted for the relief of a variety of hydrocephalic states and pseudotumor cerebri. Hydrocephalus can be communicating or noncommunicating. In a noncommunicating hydrocephalus, CSF egress from the ventricular system is obstructed. This can occur as a result of blood or infection in the ventricular system or tumors in or adjacent to the ventricular system. In communicating hydrocephalus, the CSF escapes from the ventricular system but is not absorbed by the arachnoid villi. This occurs most commonly secondary to infection or blood in the CSF space. Some degree of communicating hydrocephalus is particularly common after SAH.

Placement of a ventriculoperitoneal shunt is the most common procedure. Usually a catheter is inserted via a burr hole into the frontal horn of the lateral ventricle on the nondominant (usually the right) side. A reservoir is placed subcutaneously adjacent to the burr hole and the drainage limb passes via a subcutaneous tunnel to a point near the epigastrium, where it is inserted into the peritoneal space via a very small laparotomy. A moderate degree of muscle relaxation may be helpful. A distended stomach can result in an inadvertent gastrostomy. Sometimes, most commonly in pediatric patients, there may be an obstruction at more than one level in the

ventricular system and a so-called double-barreled shunt becomes appropriate. In this instance, there are two proximal ends, usually one in a lateral ventricle and one in the fourth ventricle. This latter procedure is usually performed in the prone position, whereas the majority of ventriculoperitoneal shunts are done supine.

Occasionally, when there is a communicating hydrocephalus, a lumboperitoneal shunt is inserted. The patient is placed in a lateral position and a catheter is put in the lumbar CSF space via a Tuohy-type needle. The catheter is tunneled subcutaneously around to the anterior abdominal wall and inserted into the peritoneal space via a small laparotomy.

Anesthetic Management

Invasive monitoring is generally not required. The anesthetic technique should be chosen to avoid further increases in ICP. Moderate hyperventilation ($Paco_2$ 25 to 30 mm Hg) is customary. Because these procedures are not performed in the context of acute injury states, there is less concern about adverse effects of hypocapnia. The target $Paco_2$ should be agreed upon at the outset with the surgeon. The procedure is usually performed in the supine position, with the table turned 90 degrees. Blood pressure may decrease abruptly when the ventricle is first cannulated (as brainstem pressure is relieved). Infrequently, brief pressor support is required. Burrowing the subcutaneous tunnel can produce a sudden painful stimulus. There is only minor postoperative discomfort. Unlike the majority of neurosurgical patients, shunt patients are often nursed flat after their procedures in an attempt to prevent an excessively rapid collapse of the ventricular system. Empirically, there is a small incidence of subdural hematoma after shunting, and the tearing of bridging veins at the time of rapid brain shrinkage is a suspected cause.

Pediatric Ventriculoperitoneal Shunts

Shunts are probably more commonly performed in children than in adults. Common indications are hydrocephalus occurring in association with meningomyelocele, neonatal intraventricular hemorrhage, and posterior fossa tumors. Although one can never be casual about the management of these patients, open fontanelles seem to provide some margin for error in younger patients and, in addition, palpation of the fontanelles provides on-line trend monitoring of ICP. Despite its theoretic considerations, inhaled inductions using volatile anesthetics are empirically well tolerated, even in children with closed fontanelles. We would avoid the inhaled induction technique in a child who was already stuporous. When an intravenous line is available, a propofol-relaxant induction sequence is preferable. For children in whom cannulation of a peripheral vein cannot be accomplished readily, an inhaled induction with sevoflurane is a common approach, with initiation of controlled ventilation, by bag and mask, as rapidly as possible. After establishing controlled ventilation, an ideal course at this point is to establish an intravenous line and administer a muscle relaxant and perhaps an induction agent, and then intubate the trachea in these optimal circumstances. Anesthesia is most commonly maintained thereafter with 60% to 70% N_2O, mechanical hyperventilation, and volatile agent as required. For children older than 6 months of age who are not stuporous at the outset, we commonly administer 2 to 3 μg/kg of fentanyl in the belief that this procedure is not entirely pain-free postoperatively, and that a smoother emergence can be accomplished with a narcotic background (see also Chapter 93).

PEDIATRIC NEUROSURGERY

Table 70-6 identifies common pediatric procedures and their anesthetic considerations. The most frequent procedures are probably the placement and revision of CSF shunts (discussed in the preceding section). The majority of pediatric tumors occur in the posterior fossa. Most are near the midline and many are associated with hydrocephalus. For pediatric posterior fossa procedures, VAE risk, monitoring, and treatment are similar for adults and children and have been previously discussed. A Doppler is invariably indicated and right heart catheters are generally placed when procedures are done in the sitting position. Craniosynostosis procedures have the potential for substantial blood loss that is roughly proportional to the number of sutures involved. There is a significant VAE risk that justifies the use of a precordial Doppler.[97] Children with neuraxial tumors can present for emergent palliative radiotherapy and may have acutely increased ICP or impending herniation. Intractable pain combined with analgesic tolerance, steroid use causing centripetal obesity, and the side effects of other chemotherapeutic agents may be complicating factors (see also Chapter 93).

SPINAL SURGERY

Table 70-7 summarizes the many issues that may arise in the context of spinal cord or spinal column procedures undertaken by neurosurgeons.

Surgery on the spinal column is reviewed in detail in Chapter 79. The relevant electrophysiologic monitoring techniques are described in Chapter 49. Prone positioning has previously been discussed and postoperative visual loss is discussed in Chapter 100.

The physiology of the spinal cord is, in general, similar to that of the brain: CO_2 responsiveness, BBB, autoregulation, high metabolic rate and blood flow (though somewhat less than the brain), and substantial ischemic vulnerability of gray matter. However, measures to reduce spinal cord swelling, analogous to ICP reduction maneuvers, are rarely used. The anesthesiologist should be attentive to situations in which there is significant compression of the spinal cord. This arises most often in the setting of cervical spinal stenosis and should be assumed to be present with fracture dislocation of the spinal column. For these patients, we place arterial catheters and support blood pressure carefully. We believe that in these settings, and in patients with recent spinal cord injury, blood pressure should be maintained near to waking normal levels. Blood pressure support is less important when the issue is nerve root rather than spinal cord compression. The presence of spinal stenosis and chronic cord compression is frequently, but not invariably, associated with lower extremity hyperreflexia and ankle clonus. Awake

TABLE 70-6 PEDIATRIC NEUROSURGICAL DISORDERS AND THEIR ANESTHETIC CONSIDERATIONS

Age Group	Lesion	Pathogenesis	Anesthetic Considerations
Neonates	Intraventricular hemorrhage	Subependymal vascular rupture	Associated problems of prematurity
	Depressed skull fracture	Forceps injury	Associated cerebral edema
	Meningocele	Out-pouching of meninges through skull defect	Large size creates airway management difficulty Prone or lateral position Repair may increase ICP Variable blood loss
	Encephalocele	Out-pouching of meninges and brain through skull	As above
	Meningomyelocele	Protrusion of meninges and nerve roots through spina bifida	Prone or lateral position Respiratory restriction after covering large defects
Infants	Hydrocephalus	Varied	Increased ICP
	Arnold-Chiari malformation	Posterior fossa contents compressed in foramen magnum	Brainstem compression with neck flexion ± Hydrocephalus/Increased ICP; ± Meningomyelocele; Postoperative respiratory depression
	Craniosynostosis	Premature fusion of cranial sutures	Open or endoscopic procedure Substantial blood loss Air embolism Supine or prone
	Craniofacial dysostosis	Developmental abnormality	Lengthy procedures Substantial blood loss Brain retraction Air embolism Endotracheal tube damage
	Vascular malformations	Varied	Congestive heart failure Large blood loss Induced hypotension
	Subdural hematoma	Trauma	Associated injuries
Older pediatrics	Posterior fossa tumors	Ependymoma Astrocytoma Medulloblastoma Teratoma Brainstem glioma	Hydrocephalus Increased ICP Prone or sitting position Air embolism Brainstem compression Postoperative cranial nerve dysfunction or brainstem swelling or compression

ICP, Intracranial pressure.

TABLE 70-7 ANESTHETIC CONSIDERATIONS AND POSITION REQUIREMENTS ASSOCIATED WITH VARIOUS SPINAL SURGICAL PROCEDURES

Spinal Segment and Surgical Condition	Problems and Considerations	Positions Used and Comments
Cervical region: Spinal stenosis, trauma, rheumatoid arthritis, degenerative disk disease	Maintain neutral neck position to avoid cord compression	Supine/anterior approach for most discectomies Posterior approach (prone or sitting) for laminectomy and pedicle screws
	Maintain perfusion pressure near waking normal levels	If existing cord compression, recent cord injury, or if cord retraction is required
	Hypotension (spinal shock)	Occurs with complete cervical cord injury
	Postoperative respiratory insufficiency	Occurs with cervical cord injury
	Air embolism	With sitting laminectomies
Anterior cervical discectomy	Retractor compression of airway	Supine
	Postoperative swelling/airway compression	Traction may be required for graft insertion
	Postoperative cranial nerve dysfunction	ETT cuff deflation/reinflation after retractor placement
Cervical instability	Awake intubation	Prone or supine
	Awake positioning	
	Manual in-line stabilization for intubation (if awake intubation is not feasible)	

TABLE 70-7 ANESTHETIC CONSIDERATIONS AND POSITION REQUIREMENTS ASSOCIATED WITH VARIOUS SPINAL SURGICAL PROCEDURES—cont'd

Spinal Segment and Surgical Condition	Problems and Considerations	Positions Used and Comments
Thoracolumbar region: degenerative disease, spinal stenosis, trauma	Major position change	Prone, lateral, or knee-chest
	Awake intubation and position	If unstable, post trauma and/or major position change required
	Blood loss	Especially with redos, instrumentations, and spinal stenosis; risk of occult aorto- iliac or major venous injury
	Air embolism	Infrequent
	POVL	Etiology unclear; associated with long prone procedures, low hematocrit, large EBL, and hypotension; patient variables may contribute (see Chapter 100)
Vertebral metastasis	Large blood loss	Prone or anterolateral/retroperitoneal Lung separation for lesions above L1
Spinal cord tumors	Maintain perfusion pressure during retraction	Prone
Procedures with major neurologic risk	Wake-up test (now rare)	Rehearse with patient
	Somatosensory evoked responses	Anesthetic agent restrictions
	Motor evoked responses	Anesthetic/relaxant restrictions
	Pedicle screw EMG	Relaxant restriction

EMG, Electromyogram; *ETT,* endotracheal tube; *POVL,* postoperative vision loss.

intubation may be warranted when there is instability of the cervical spinal column and in some instances of severe cervical spinal stenosis in which it is perceived that minor degrees of flexion or extension, or both, might critically aggravate spinal cord compression. Preintubation discussion and agreement with the surgeon is appropriate.

Acknowledgment

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Chapter 71

Anesthesia for Bariatric Surgery

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Key Points

- In the United States, more than 200 million people are overweight or obese. Worldwide, more people are obese than are malnourished. Obesity is becoming the largest single preventable cause of death and represents a cause of major morbidity and mortality.
- Metabolic syndrome includes abdominal obesity, decreased high-density lipoprotein, increased insulin, glucose in tolerance, and hypertension and is present in approximately 50 million people in the United States alone.
- The greatest risk factor for sleep apnea is obesity, including increased oral and pharyngeal tissue. This condition makes ventilation through a mask, tracheal intubation, and even extubation more challenging.
- Choices for medical management of obesity are limited and not usually successful alone. Changes in behaviors are important for success.
- Surgery for obesity is recommended at a body mass index (BMI) of 40 kg/m^2 or BMI greater than 30 kg/m^2 when comorbidities such as hypertension, diabetes, and hypercholesterolemia are expected to improve with weight loss secondary to surgical therapy. In clinical trials, long-term survival is better in surgically treated groups as compared with medically managed patients.
- Preoperative evaluation should focus on cardiopulmonary issues and securing an airway, along with other concerns such as diabetes, hypertension, and obstructive sleep apnea (see also Chapter 38).
- Selection of anesthetic drugs should be based on lipid solubility and increased incidence of lingering respiratory depression effects.
- Preparation and positioning (see Chapter 41) are keys to successful airway management. Preoperative pressure support ventilation should be used adjunctively if possible.
- Intraoperative ventilation is assisted by complete paralysis, moderate positive end-expiratory pressure, tidal volumes based on ideal body weight, and recruitment maneuvers as needed.
- Common serious postoperative complications are deep vein thrombosis and surgical staple line issues.
- Obese patients presenting for non–weight loss surgery benefit from anesthetic approaches similar to those used for bariatric surgery.

OBESITY AS A DISEASE

Obesity is one of the great epidemics of the twenty-first century.[1] Worldwide, obesity was considered a rarity until the middle of the previous century,[2] but now 1.6 billion overweight individuals and more than 400 million obese people live on the planet, including a significant proportion of the adult population in the United States.[3-5] Current estimates are that more than 78 million Americans, or 35.7% of the U.S. adult population,[6] are overweight or obese. Obesity and its associated health concerns are now major causes of morbidity and mortality resulting in an enormous impact on health care spending. More than 300,000 deaths per year in the United States and approximately $147 billion[7,8] in annual health care spending are attributable to obesity, thus placing this condition second only to smoking as a preventable cause of death.[7]

Obesity can be defined as a disease because it is a physiologic dysfunction of the human organism with environmental, genetic, and endocrinologic etiologies.[7] Obesity most frequently develops when food caloric intake exceeds energy expenditure over a long period of

time. Factors influencing obesity involve either energy intake or energy expenditure, and they are influenced by genetic, behavioral, cultural, and socioeconomic factors.[9] For example, some syndromes are associated with obesity, including leptin deficiency, Prader-Willi syndrome, and Lawrence-Moon-Biedl syndrome.[4] Metabolic factors can influence energy regulation, including hormones, peptides, nutrients, uncoupling proteins, and neural regulatory substances emanating from gut, liver, brain, and fat cells, but most of these factors are not well understood.

The body mass index (BMI) is the most widely applied classification tool used to assess individual weight status.[10] The BMI is specifically defined as the patient's weight, measured in kilograms, divided by the square of the patient's height, measured in meters, to yield a measurement bearing units of kilograms per square meter (kg/m^2). Figure 71-1 shows a family of iso-BMI curves for BMI ranging from 13 to 50 and mapped on axes for height (in both inches and centimeters) and weight (in both pounds and kilograms). By using this system, patients are classified according to BMI, and the associated risk of developing health problems is shown in Table 71-1. Patients are considered overweight if they have a BMI between 25 and 29.9 kg/m^2, and they are classified as obese with a BMI between 30 and 49.9 kg/m^2. The obese classification is further subdivided into class 1 (BMI range, 30 to 34.9 kg/m^2), class 2 (35 to 39.9 kg/m^2), and class 3 (40 to 49.9 kg/m^2). Patients with a BMI of 50 kg/m^2 or greater are classified as superobese. As BMI increases beyond normal weight, the risk of developing serious health problems rises greatly and can be correlated with the individual's waist circumference (Table 71-2). Malnourishment and malnutrition are commonly offered as explanations for the finding that underweight patients are also at increased risk for developing illnesses.

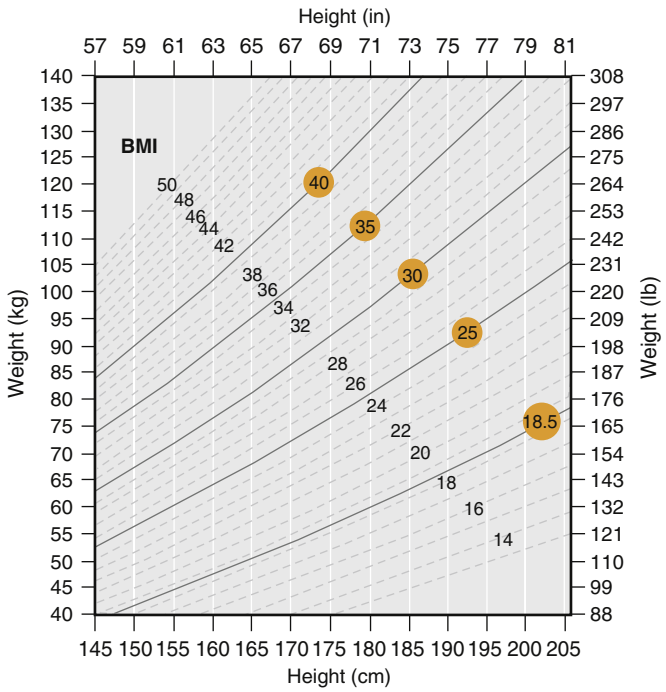


Figure 71-1. A family of iso–body mass index (iso-BMI) curves for BMI ranging from 13 to 50 and mapped on axes for height (in both centimeters and inches) and weight (in both kilograms and pounds).

Certain specific diseases are commonly associated with obesity, and obesity is often accompanied by multiple, and not single, comorbid states.[9] These disorders frequently include insulin resistance, type 2 diabetes mellitus, obstructive sleep apnea (OSA), asthma, chronic obstructive pulmonary disease, hypoventilation, cardiovascular disease, hypertension, certain malignant diseases, and osteoarthritis.[1,11-21] Virtually every organ system can be included in the extended list of health risks associated with having an abnormally elevated BMI. A listing of the most common specific disease states along with their obesity-associated risk is detailed in Table 71-3. As a result, obesity is also associated with early death.[10,22] Of the health risks included in Table 71-3, metabolic syndrome and OSA merit additional attention because they pose special concerns for the anesthetic care of obese patients.

METABOLIC SYNDROME

The clustering of a group of defined metabolic and physical abnormalities is now referred to as *metabolic syndrome*.[23] Patients with metabolic syndrome commonly have abdominal obesity, reduced levels of high-density lipoprotein (HDL), hyperinsulinemia, glucose intolerance, hypertension, and other characteristic features,[17] as listed in Box 71-1. Specific criteria for diagnosing metabolic syndrome are included in Table 71-4. The diagnosis requires that at least three of the following be present: abdominal obesity, elevated fasting glucose, hypertension, low HDL, and hypertriglyceridemia.[24] Weight gain with visceral obesity is a major predictor of metabolic syndrome. The clinical approach uses waist circumference, rather than BMI, to define the adipose mass

TABLE 71-1 LEVELS OF RISK ASSOCIATED WITH INCREASING BODY MASS INDEX

Classification	BMI (kg/m^2)	Risk of Developing Health Problems
Underweight	<18.5	Increased
Normal weight	18.5-24.9	Least
Overweight	25.0-29.9	Increased
Obese		
Class 1	30.0-34.9	High
Class 2	35.0-39.9	Very high
Class 3	40.0-49.9	Extremely high
Superobese	≥50	Exceedingly high

BMI, Body mass index.

TABLE 71-2 WAIST CIRCUMFERENCE AND RISK

	BMI (kg/m^2)		
Waist Circumference	Normal Weight	Overweight	Obese Class 1
<102 cm (♂) <88 cm (♀)	Least risk	Increased risk	High risk
≥102 cm (♂) ≥88 cm (♀)	Increased risk	High risk	Very high risk

♂, Male; ♀, female; *BMI,* body mass index.

component contributing to metabolic syndrome because BMI has been shown to be a relatively insensitive indicator of the risk for obesity-associated metabolic and cardiovascular diseases. Waist circumference, but not BMI, reflects abdominal subcutaneous adipose tissue as well as abdominal visceral adipose tissue and is therefore a better index of central, or truncal, fat mass.

In the United States, approximately 50 million people have metabolic syndrome, thus giving it an age-adjusted prevalence of almost 24%. Of these patients, more than 83% meet the criterion of abdominal obesity. The incidence of metabolic syndrome increases with age, with more than 40% of the U.S. population affected with obesity by the age of 60 years.[23] Men are affected more commonly than women, and Hispanics and South Asians appear to be particularly susceptible. Its frequency is lower in African American men than in whites. Metabolic syndrome may result from use of some commonly prescribed drugs, including corticosteroid, antidepressant, and antipsychotic agents. Protease inhibitors used to treat human immunodeficiency virus (HIV) infection can induce metabolic syndrome secondary to insulin resistance.

Patients with metabolic syndrome have an increased risk for cardiovascular disease events and are at increased risk for all causes of mortality. Metabolic syndrome increases the risk of type 2 diabetes, which itself is an important risk factor for atherosclerotic disease and may be considered a coronary heart disease equivalent.[16,23] Metabolic syndrome is also associated with many other conditions, such as polycystic ovary syndrome, nonalcoholic fatty liver disease, gallstones, sleep disturbances, sexual impotence, and some forms of cancer. This syndrome has considerable overlap with obesity for comorbid states, as detailed in Table 71-3. In multiple trials involving nearly 1900 patients, morbidly obese individuals had much greater weight loss following bariatric surgery than after nonsurgical therapy, with amelioration of most of the diseases associated with morbid obesity in a year's time.[25] Metabolic syndrome is resolved by bariatric surgery in more than 95% of patients who achieve the expected weight loss.[26] This finding makes it clear that bariatric surgery is a metabolic intervention and not simply a weight management procedure.[27]

TABLE 71-3 HEALTH RISKS ASSOCIATED WITH INCREASING BODY MASS INDEX

Metabolic syndrome	30% of middle-aged people in developed countries have features of metabolic syndrome
Type 2 diabetes	90% of type 2 diabetic patients have a BMI of >23 kg/m^2
HTN	5× risk in obesity 66% of HTN is linked to excess weight 85% of HTN is associated with a BMI >25 kg/m^2
CAD and stroke	3.6× risk of CAD for each unit change in BMI Dyslipidemia progressively develops as BMI increases from 21 kg/m^2 with rise in small-particle low-density lipoprotein 70% of obese women with HTN have left ventricular hypertrophy Obesity is a contributing factor to cardiac failure in >10% of patients Overweight or obesity plus HTN is associated with increased risk of ischemic stroke
Respiratory effects (e.g., OSA)	Neck circumference of >43 cm in men and >40.5 cm in women is associated with OSA, daytime somnolence, and development of pulmonary HTN
Cancers	10% of all cancer deaths among nonsmokers are related to obesity (30% of endometrial cancers)
Reproductive function	6% of primary infertility in women is attributable to obesity Impotence and infertility are frequently associated with obesity in men
OA	Frequent association in older adults with increasing body weight; risk of disability attributable to OA is equal to heart disease and greater than any other medical disorder of older patients
Liver and gallbladder disease	Overweight and obesity are associated with nonalcoholic fatty liver disease and NASH; 40% of patients with NASH are obese; 20% have dyslipidemia 3× risk of gallbladder disease in women with a BMI of >32 kg/m^2; 7× risk if BMI >45 kg/m^2

BMI, Body mass index; *CAD,* coronary artery disease; *HTN,* hypertension; *NASH,* nonalcoholic steatohepatitis; *OA,* osteoarthritis; *OSA,* obstructive sleep apnea.

BOX 71-1 ***Features Associated With Metabolic Syndrome***

Abdominal obesity
Atherogenic dyslipidemia (↑ TGs, ↓ HDL cholesterol, ↑ ApoB, ↑ small LDL particles)
Elevated blood pressure
Insulin resistance ± glucose intolerance
Proinflammatory state (↑ hs-CRP)
Prothombotic state (↑ PAI-1, ↓ FIB)
Other (endothelial dysfunction, microalbuminuria, polycystic ovary syndrome, hypoandrogenism, nonalcoholic fatty liver disease, hyperuricemia)

ApoB, Apolipoprotein-B; *FIB,* fibrinogen; *HDL,* high-density lipoprotein; *hs-CRP,* high-sensitivity C-reactive protein; *LDL,* low-density lipoprotein; *PAI-1,* plasminogen activator inhibitor; *TGs,* triglycerides.

TABLE 71-4 CLINICAL CRITERIA FOR DIAGNOSING METABOLIC SYNDROME*

Criteria	Defining Value
Abdominal obesity	Waist circumference >102 (>88) cm in men (women)
Triglycerides	≥150 mg/dL
HDL cholesterol	<40 (<50) mg/dL in men (women)
Blood pressure	≥130/85 mm Hg
Fasting glucose	≥110 mg/dL

HDL, High-density lipoprotein.
*Three of five criteria must be met.

Inflammatory processes appear to play an important role in metabolic syndrome.[19] Adipose tissue has two major functions: (1) storage and release of energy-rich fatty acids and (2) secretion of proteins required for endocrine and autocrine regulation of energy metabolism. Adipocytes exert their metabolic effects by release of free fatty acids, a process enhanced by the presence of catecholamines, release of glucocorticoids, increased β-receptor agonist activity, and reduction of lipid storage mediated by insulin. Visceral adipose tissue has been identified as an important source of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), as well as antiinflammatory cytokines such as adiponectin. Increased levels of proinflammatory cytokines likely contribute to the etiology of insulin resistance primarily by obstructing insulin signaling and contributing to down-regulation of peroxisomal proliferator-activated receptor-γ, processes that are fundamentally important regulators of adipocyte differentiation and control. Additionally, insulin resistance may promote inflammation through diminution of insulin's antiinflammatory effects. Finally, oxidative stress is increased in obesity, primarily as a result of excessive intake of macronutrients and a concomitant increase in metabolic rate. These factors may also contribute to the inflammatory response noted in obesity.[19]

Native immune responses act aberrantly in obese individuals. Natural killer (NK) cell cytotoxic activity is depressed in obesity, as are plasma levels of cytokines such as IL-12, IL-18 and interferon-γ known to regulate NK cell function.[28] Other cytokines (primarily IL-6 and TNF-α) and adipokines (leptin, adiponectin, and adipose-derived resistin) are two additional major groups of inflammatory proteins produced and released by adipose and adipose-associated tissue.[19] Both serum and adipose tissue obtained from obese subjects consistently have elevated levels of IL-6 and TNF-α, and circulating levels of IL-6 are consistently increased in individuals having either type 2 diabetes or impaired glucose tolerance. Proteins such as leptin and adiponectin, which are produced primarily by adipocytes, are classified as adipokines. Although leptin is primarily involved in appetite control, its immunologic effects include protection of T lymphocytes from apoptosis and regulation of T-cell activation and proliferation. Reduced leptin levels may increase appetite and slow metabolism, but they may also increase susceptibility to the toxicity of proinflammatory stimuli, such as endotoxin and TNF-α. Elevated leptin levels are proinflammatory, and this feature likely plays an important role in the progression of heart disease and diabetes, especially in obese patients. Serum levels of adiponectin correlate with insulin sensitivity and do not rise in obesity. Significantly reduced adiponectin levels are found in patients with type 2 diabetes. Adiponectin reduces both TNF-α production and activity. It also inhibits IL-6 production. Resistin, an adipokine that induces insulin resistance, is induced by endotoxin and cytokines. Resistin acts at the cellular level to up-regulate production of proinflammatory cytokines, most likely through the nuclear factor κB (NFκB) pathway. Resistin appears to present a molecular link among metabolic signaling, inflammatory processes, and the development of cardiovascular disease. Resistin levels have been associated with inflammatory markers apparently independently of BMI in humans.[19]

An understanding of the role of NFκB in insulin resistance is required to appreciate fully the links between obesity and inflammation. Both free fatty acids and TNF-α act through intracellular inflammatory cascade pathways to arrest insulin signaling. This process is mediated by activation of transcription factors present within the cell cytoplasm, which, following their translocation to the nucleus, eventually bind to transcription factors regulating the inflammatory process. The cytoplasm also contains NFκB, another transcription factor whose activation is implicated in a number of diseases, including diabetes. NFκB is also induced by hypoxia, and it increases production of proinflammatory cytokines TNF-α and IL-6, both of which are frequently increased in patients with OSA syndrome.[19] Therefore, inflammation provides the common linkage underlying the association of obesity, metabolic syndrome, and OSA.[29]

OBSTRUCTIVE SLEEP APNEA AND HYPOPNEA SYNDROME

OSA and obstructive sleep hypopnea are related conditions characterized by recurrent episodes of upper airway obstruction occurring during sleep (see Chapters 14 and 38).[30] OSA is defined as episodic complete cessation of airflow during breathing lasting 10 seconds or longer despite maintenance of neuromuscular ventilatory effort, occurring five or more times per hour of sleep, and accompanied by a decrease of at least 4% in arterial oxygen saturation (Sa_{O_2}). Obstructive sleep hypopnea is defined as episodic partial reduction of airflow of more than 50% lasting at least 10 seconds, occurring 15 or more times per hour of sleep, and accompanied by a decrease of at least 4% in the Sa_{O_2}. The diagnosis can be made only in patients who undergo polysomnography, or a sleep study, during which the patient's electroencephalogram, electrocardiogram, electrooculogram, capnogram, nasal or oral airflow, esophageal pressure, arterial blood pressure, pharyngeal and extremity electromyograms, pulse oximetry, and room noise are typically monitored and recorded.[30] Results of polysomnography are reported as the apnea/hypopnea index (AHI), which is derived from the total number of apneas and hypopneas divided by the total sleep time. A normal lower limit for AHI has not yet been defined in an epidemiologic study of healthy subjects. Most sleep centers commonly use an AHI between 5 and 10 events per hour as a normal limit. The severity of OSA/hypopnea syndrome (OSAHS) is arbitrarily defined, but recommendations for disease classification are as follows[30]:

Mild disease: AHI of 5 to 15 events per hour
Moderate disease: AHI of 15 to 30 events per hour
Severe disease: AHI of greater than 30 events per hour

Because of the risks of developing systemic and pulmonary hypertension, left ventricular hypertrophy, cardiac arrhythmias, cognitive impairment, persistent daytime somnolence, and other factors, treatment is recommended for patients with either moderate or severe disease. Treatment partly depends on the severity of the

sleep-disordered breathing, but the consensus view is that patients with moderate or severe disease should be treated with continuous positive airway pressure (CPAP) during sleep. Other conservative treatment measures may include weight loss, avoidance of alcohol before bedtime, and sleeping on one's side.

Obesity is the greatest risk factor for OSAHS. Approximately 70% of patients (≤80% of men and ≤50% of women) with OSAHS are obese. Severe sleep apnea disease is more common in men, and a strong negative correlation between the AHI and minimum Sa_{O_2} has been observed. The diagnosis of OSAHS may be missed until the patient presents for surgery. In a study of 170 patients presenting for surgery, only 15% had already been diagnosed with sleep apnea, but on preoperative testing, 76% of the patients in the study were found to have OSAHS.[31] I believe it is important for obese patients presenting for bariatric surgery to undergo preoperative polysomnography testing for OSAHS. Preoperative diagnosis and appropriate interventional management can have the following benefits: less postoperative sleep deprivation, improved response to analgesic and anesthetic drugs, and normalization of cardiovascular disturbances.[32]

Anatomically, obese patients with OSAHS typically have increased amounts of adipose tissue deposited into oral and pharyngeal tissues including the uvula, tonsils, tonsillar pillars, tongue, aryepiglottic folds, and lateral pharyngeal walls. An inverse relationship exists between the degree of obesity and pharyngeal area. Deposition of fat in the lateral walls decreases the size of the airway and changes the shape of the oropharynx into an ellipse with a short transverse and long anteroposterior axis.[33-35] This configuration can contribute to both the development and severity of airway obstruction and can also increase the expectation that it will be more difficult to maintain airway patency during mask ventilation and to perform direct laryngoscopy for endotracheal intubation with general anesthesia.[36,37] Additionally, airway obstruction following tracheal extubation is likely to be complicated by the use of opiate and sedative drugs needed for postoperative pain management because these drugs tend to decrease pharyngeal dilator tone and increase the likelihood of upper airway collapse.[36]

OSA also plays an important role in inflammation and metabolic syndrome.[19,29] The hypopneic and apneic events that occur in OSAHS are part of the cycle of events that involves both arousal from rapid eye movement (REM) sleep and oxyhemoglobin desaturation. Sympathetic nervous system activation results as patients with untreated OSA undergo cyclic episodes of hypoxia and reoxygenation. This process leads to elevation of proinflammatory cytokines and may also induce oxidative stress of vascular endothelium, thus inducing an even more heightened state of systemic inflammation in obese patients with OSA.[29] Levels of many different inflammatory mediators, including IL-6, high-sensitivity C-reactive protein (hs-CRP), leptin, TNF-α, IL-1, reactive oxygen species, and adhesion molecules, such as intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), are increased in patients with OSAHS.[19] Thus, obesity, metabolic syndrome, and OSAHS are interrelated diseases that significantly alter a patient's inflammatory disease profile and increase multiple health risks, particularly those of cardiovascular and airway origin. Surgical intervention causes weight loss and improves obesity-related respiratory disease,[13] but significant and sustained increases in plasma adiponectin levels can occur. In addition, both IL-6 and hs-CRP levels[38] decrease as well as improve NK cell function, and they increase IL-12, IL-18, and interferon-γ plasma levels.[28]

NONSURGICAL MANAGEMENT OF OBESITY

The primary goals of nonsurgical management of obesity involve weight loss, treatment of abnormalities associated with metabolic syndrome, and prevention of type 2 diabetes and cardiovascular disease–related events. Treatment of metabolic syndrome needs to follow an aggressive, multifaceted approach to address multiple underlying metabolic abnormalities and coexistent risk factors simultaneously.[23] Appropriate initial treatment of obesity and metabolic syndrome is therapeutic lifestyle change. This change includes dietary modification, weight loss, physical activity, and discontinuation of smoking. The treatment aim is improvement in health, and it is the primary reason for advocating weight loss. Modification of energy homeostasis is not easily achieved because a strong brain-gastrointestinal axis drives both food intake and satiety. This axis has hormonal components involving endogenous production of ghrelin, an orexigenic peptide that is produced by the foregut of the stomach and that stimulates appetite.[39] Therefore, the effects of treatment on risk factors and comorbidities at the systems, organ, cell, and molecular levels should be monitored. Treatment success should be reflected in the decreasing need to treat other coexisting diseases.

The goal for weight loss in therapeutic lifestyle change is not achievement of normal or ideal body weight. Even a modest weight loss, in the range of 5% to 10% from the patient's presentation weight, can result in significant initial improvement in the comorbidities of diabetes, dyslipidemia, and hypertension by lowering total cholesterol and triglyceride levels, raising HDL cholesterol, lowering arterial blood pressure, and lowering blood glucose values while reducing insulin resistance.[23,40] Obesity guidelines stress the need for weight reduction using behavioral change to reduce caloric intake and increase physical activity. Reduced-energy diets are more effective and healthier for achieving long-term weight loss. Long-term maintenance of any weight loss achieved is best accomplished with the inclusion of regular exercise as a staple of the weight-reduction regimen. Regular physical exercise improves several risk factors associated with obesity and metabolic syndrome.[41] The standard exercise recommendation is a daily minimum of 30 minutes of moderate-intensity physical activity that is practical to perform. Larger weight loss goals are more appropriate for more profoundly obese individuals who are contemplating surgical interventions. Even with surgery, ideal weight is hardly ever achieved, and after a number of years at a plateau, weight gain often recurs. In some patients, especially those with severe comorbidities, simple prevention of additional weight gain may be the most reasonable goal.

Beyond the beneficial effects of therapeutic lifestyle change, specific intervention may be required to treat the dyslipidemia and hypertension associated with obesity and metabolic syndrome.[42] Most commonly, patients with metabolic syndrome have elevated triglyceride levels and low HDL cholesterol levels. Many patients receive statin therapy as the treatment of choice when low-density lipoprotein (LDL) cholesterol levels are excessive. Statins reduce cardiovascular disease risk in patients with type 2 diabetes and metabolic syndrome. Ezetimibe, which selectively inhibits intestinal cholesterol absorption, can be combined with statin therapy to further reduce LDL cholesterol by 15% to 20%. Fibrates effectively decrease triglyceride levels while increasing HDL cholesterol. Fibrates lower LDL cholesterol levels mildly, but when combined with statin therapy, fibrates may increase the risk of myopathy. Omega-3 fatty acids decrease triglyceride levels and improve insulin resistance in patients with metabolic syndrome. These fatty acids are often used in combination therapy with other classes of hypolipidemic drugs. Nicotinic acid is highly effective in raising HDL cholesterol levels in patients with metabolic syndrome. Nicotinic acid decreases the concentration of small, dense LDL particles and also lowers serum levels of lipoprotein (a).[42]

Dietary salt restriction and therapeutic lifestyle change are the primary means to address hypertension in obesity and metabolic syndrome. Patients whose blood pressure is higher than 140/90 mm Hg require antihypertensive drug therapy. No specific antihypertensive agent is recommended as a first-line treatment in these patients, and generally the goal of antihypertensive therapy requires that polypharmacy be employed. A considerable element of the risk reduction resulting from antihypertensive therapy is decreasing arterial blood pressure.

The treatment of insulin resistance and hyperglycemia in metabolic syndrome, type 2 diabetes, and obesity is usually achieved with oral hypoglycemic drugs.[42] Several different drug groups (and drugs within each group) that work through various mechanisms of action are available to treat hyperglycemia. These include α-glucosidase inhibitors, sulfonylureas, meglitinides, D-phenylalanine derivatives, diguanides, and thiazolidinediones.[42] Anesthetic implications include the need to assess and treat abnormal blood glucose levels in the perioperative period while being especially careful in the use of insulin in patients who are both insulin resistant and temporarily unable to continue oral medication. The anesthetic management of patients who are taking metformin is not clear. Postoperative lactic acidosis can develop in patients using this drug. This possibility has led some physicians routinely to cancel or delay surgical procedures if metformin has been ingested within 48 hours of the scheduled surgery. Other physicians, however, have their patients continue taking metformin, both before and after surgery, without interruption if possible. Overall, patients taking metformin have a reduced risk for complications. It appears that metformin may be safely used in the perioperative period.[43]

Patients with metabolic syndrome and obesity may also be prescribed antiplatelet therapy. The American Heart Association currently recommends that low-dose aspirin be used as a form of primary prevention in patients with metabolic syndrome whose 10-year risk for cardiovascular disease is 10% or greater as determined by Framingham risk scoring.

BEHAVIORAL INTERVENTIONS AND MODIFICATION

Behavioral interventions and behavioral modification are essential for obese patients to change their learned habits related to eating and physical activity to produce weight loss and long-term weight reduction.[42] This applies to both nonsurgical and surgical approaches to weight loss. The key features of typical behavioral programs include self-monitoring, goal setting, nutrition and exercise education, stimulus control, problem solving, cognitive restructuring, and relapse prevention. Patients often benefit from referral to multidisciplinary weight loss programs that incorporate diet, physical activity, and behavioral interventions to achieve their weight loss goals because these combined interventions provide the best weight loss and weight maintenance results without pharmacologic or surgical intervention. However, it is essential to identify and treat patients with eating disorders or major psychiatric disorders who require specialized psychiatric and psychological treatment to achieve meaningful weight loss.

PHARMACOTHERAPY FOR WEIGHT LOSS

Recommendations for pharmacotherapy as a treatment of obesity first and foremost stress lifestyle and behavioral modifications as the initial approaches to weight loss.[29] Patients who do not reach their established reasonable weight loss goals by a combination of diet and exercise may be directed to pharmacotherapy to increase weight loss. Some weight loss drugs have been approved by the U.S. Food and Drug Administration (FDA) and are currently prescribed for long-term use. These drugs are typically used adjunctively with diet and exercise for patients having a BMI of 30 or greater (≥27 for patients with obesity-related risk factors or comorbid diseases). In current practice, only two categories of weight loss drugs (appetite suppressants and lipase inhibitors) have been approved, and only two drugs are currently available for the specific indication of weight loss—phentermine and orlistat.[42] Phentermine, an adrenergic reuptake inhibitor, augments adrenergic signaling within the central nervous system and peripheral tissues. Phentermine decreases appetite and food intake and increases resting metabolic rate to promote weight loss. Its side effects include tachycardia and hypertension. Orlistat, a lipase inhibitor, reversibly binds to lipase and prevents both absorption and digestion and absorption of certain dietary fats. Because orlistat also interferes with the absorption of fat-soluble vitamins, patients using this drug need to supplement fat-soluble vitamins A, D, E, and K. Orlistat has significant gastrointestinal side effects including diarrhea, steatorrhea, flatulence, fecal incontinence, and oily rectal discharge. A third drug, sibutramine, which is a centrally acting serotonin-orepinephrine reuptake inhibitor that suppresses appetite and increases thermogenesis, was

removed from the United States market in 2010 because of an increased risk of stroke and acute coronary syndrome.

DIETARY AND HERBAL MEDICATIONS

Allison and colleagues reviewed the literature on dietary and herbal medications for weight loss.[44] These drugs are marketed as food supplements, thereby escaping the purview of the FDA. Even though these supplements cannot legally claim to treat a disease, they can claim to reduce the risk of a disease. According to the review, claims for weight loss have been made for multiple products such as chitosan, chromium picolinate, conjugated linoleic acid, ephedra alkaloids (*ma huang*),[45] and *Garcinia cambogia*.[44] Most of the reports involving these compounds are from poor-quality studies without any randomization, control groups, or blinding, thereby placing in question both the efficacy and safety of these compounds. The only studies involving herbals that have consistently demonstrated weight loss involve combinations of ephedrine and caffeine.[46,47] Pharmacologically, this effect is expected because ephedrine, an adrenergic agonist, is known to be an appetite suppressant and a thermogenic agent. For this reason, *ma huang*, a natural source of the ephedra alkaloid, is added to most, if not all, dietary supplements marketed for weight loss. The success of ephedrine as a weight loss drug, in combination with caffeine and or aspirin, is well established. Unfortunately, multiple cases of cardiac and neurologic issues, including hypertension, stroke, seizure, and even death have been reported,[48] possibly related to the inconsistent doses in the preparations and the lack of medical supervision in people consuming these products for weight loss. Consequently, the National Institutes of Health has banned these products from any recommended weight loss regimen.

IMPLANTED ELECTRICAL STIMULATORS

Implantable gastric stimulators are subcutaneously placed devices that resemble cardiac pacemakers and stimulate along the lesser curvature of the stomach. These gastric stimulators have been tried since the early 2000s and have been found to cause modest weight loss with few side effects.[49,50] These studies have been performed in Europe, and trials are ongoing in the United States. One study documented a 25% excess weight loss, improved response to oral glucose tolerance test, decreases in blood pressure, and an improvement in symptoms of gastroesophageal reflux disease, along with an increased parasympathetic drive. No serious side effects were noted in the first 65 patients reported on in this study[49] or in the 20 patients followed in another study.[50] Ghrelin levels may play a role in the success of these devices.

SURGICAL MANAGEMENT OF OBESITY

Adult obesity is rooted in childhood obesity. One of the principal predictors of adult obesity is childhood obesity. Large children grow up and become large adults. Unfortunately, pediatric obesity is the most common childhood nutritional disorder in the United States. This is one of the tragedies of the current obesity epidemic: the significant and increasing prevalence of obesity in the young. The concern has increased such that public policy has been developed to regulate placement of vending machines in schools and availability of sweetened snacks and soft drinks in public places as a means to help control the epidemic of pediatric obesity. The diagnosis of pediatric obesity, however, is commonly attained by a definition rendered by the Centers for Disease Control and Prevention (CDC) that uses BMI-, age-, and sex-specific clinical growth charts.[51] These percentile curves apply to the ages of 2 to 20 years, and because BMI exhibits nonlinear variation during growth, percentile ranges are used. The CDC defines children with BMIs in the 5th to 85th percentiles as having "healthy weight." Children whose BMIs are in the 85th to 95th percentile are "at risk for overweight," whereas those having BMIs higher than the 95th percentile are classified as "overweight." These children were previously regarded as "overweight" and "obese," respectively. This switch in terminology continues to be a source of confusion. Exceeding the 99th percentile is referred to as extreme pediatric obesity.

The National Health and Nutrition Examination Survey (NHANES) 2007 to 2008 data show that the prevalence rates of overweight children for age 2 to 5 years, 6 to 11 years, and 12 to 19 years are 10.4%, 19.6%, and 18.1%, respectively. Gender does not appear to influence the prevalence of overweight children after the age of 6 years. However, in the cohort of children 2 to 5 years old, girls have exhibited a doubling in prevalence of obesity since the 1990s, whereas boys have undergone an increase of only 25%. Some developing countries have childhood obesity prevalence rates higher than those of the United States.[52] This finding indicates that adolescent obesity is becoming pervasive.

Treatment of pediatric obesity is based on the balance of caloric intake and expenditure. These lifestyle changes are most successful with family intervention and support. The three pillars of success in this treatment are better eating habits, increased physical activity, and decreased sedentary activity.[53] Success involves more than education of the child and family; it incorporates goal setting, self-monitoring, incentives, and stimulus control. Drugs approved for the treatment of pediatric obesity include orlistat, which is discussed earlier in this chapter.

Although in 2000, less than 1% of all bariatric surgery patients in the United States were younger than 20 years of age,[54] the total number continues to increase. More adolescents are presenting for weight loss surgery, usually gastric banding, after failing to reduce weight and/or comorbidities in medically supervised and pharmacologically assisted weight loss programs. Even though many adult bariatric surgery programs are well qualified to provide safe and effective perioperative care for these patients, they may not be as well equipped to handle the unique metabolic and psychological needs of teenagers. Because of the shorter duration of obesity and fewer age-related comorbidities, adolescent patients have shorter length of stay and lower immediate postoperative mortality when compared with adults.[54]

Consent is an important issue in this population. Is parental consent to a semielective, relatively high-risk

procedure appropriate? Does the child really understand the concept of high risk of death in the month after surgery? These and other such questions of ethics in medicine need to be addressed, but they are beyond the scope of this chapter.

The rapid increase in the prevalence of both morbid obesity and superobesity, together with the increased risk of early demise within the obese population, has significantly increased the number of bariatric surgical procedures performed annually. The term *bariatric surgery* refers to surgical alteration of the small intestine or stomach with a view toward producing weight loss. It is estimated that more than 225,000 bariatric surgical procedures are performed annually in the United States. Care of obese patients is not limited to obesity surgery, however, because these patients present for all types of operations. Nonetheless, the benefits of surgical treatment of obesity now appear to have clear endocrinologic and cardiovascular value for reversing pathophysiologic effects of metabolic syndrome, type 2 diabetes, and other comorbidities of obesity, in addition to providing a mechanical means of enhancing weight loss.[55-61] Several alternative procedures are performed in bariatric surgery, which has evolved from early procedures based on creating malabsorptive gut pathways to newer procedures aimed at altering hormonal regulation of caloric intake drive and satiety.[62] The available operations all fall into one of two groups at present: (1) gastric restrictive procedures and (2) procedures that combine gastric restriction with induction of nutrient malabsorption.[63-72]

RESTRICTIVE PROCEDURES

The surgical goals of restrictive operative procedures are to reduce and limit the patient's food intake capacity.[69] These goals are most commonly achieved by creating a small pouch from the proximal stomach just distal to the gastroesophageal junction. Construction of the newly created pouch allows it to drain through only a narrow opening. This configuration increases the mechanical resistance to gastric emptying for ingested solids, whereas emptying of liquids proceeds normally. The vertical band gastroplasty (VBG) was a widely practiced restrictive procedure in the 1990s and early 2000s, but it has been largely replaced by the minimally invasive laparoscopic gastric band procedure (LGB), which is illustrated in Figure 71-2. A specific advantage of the LGB is avoidance of permanent alteration of gastric anatomy through tissue stapling. Laparoscopic gastric banding has an exceptional safety record with an exceedingly low operative mortality, although reoperation rates for minor problems are nontrivial.[72]

MALABSORPTIVE PROCEDURES

The surgical goal of malabsorptive procedures is to cause weight loss both by gastric restriction and nutrient malabsorption. Historically, early surgical procedures involved creation of a long jejunoileal bypass. Patients achieved significant weight reduction, but this was commonly accompanied by an unacceptable incidence of serious vitamin and protein malabsorption, osteoporosis, and hepatic failure.

At present, gastric bypass (GBP), which is illustrated in Figure 71-3, and biliary pancreatic diversion (BPD) are the two commonly performed malabsorptive operations, and both have achieved success in safety and efficacy.[69] Newer modifications, such as robotic bariatric surgery[73] and the single-incision transumbilical laparoscopic[74] approach to bariatric surgery, are used to achieve the same surgical manipulation of the gastrointestinal tract, and they alter only the cost of the procedure and decrease the wound size and resultant cosmesis of the operation performed. GBP is more commonly performed than BPD, and it is considered the safer of the two malabsorption procedures. GBP involves the creation of a small gastric pouch by stapling or banding the stomach. This results in an element of gastric restriction. GBP also involves the creation of a Roux-en-Y anastomosis, in which the small gastric pouch is directly connected to the middle portion of the jejunum.[75] The path for food through the gastrointestinal tract subsequently bypasses the gastric remnant and the upper portion of the duodenum. This procedure can be performed with a laparotomy incision or by using laparoscopic techniques.[74,76] Although this operation is considered safe, the associated perioperative mortality is higher than that of LGB.[66] Additionally, some important long-term complications such as vitamin B_{12} deficiency, anemia, incisional hernia, cholelithiasis, and staple line failure occur with significant frequency. Often, cholecystectomy is performed concurrently to prevent future cholelithiasis.[77]

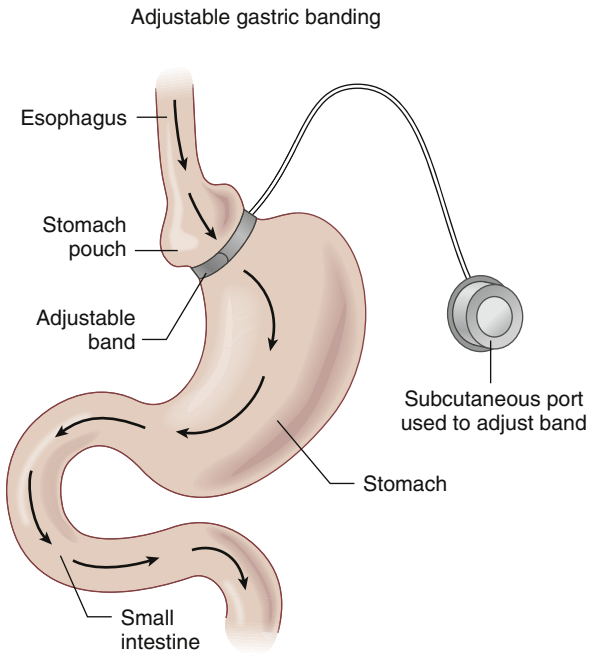


Figure 71-2. Gastric banding: An adjustable band is placed on the stomach. Connected to the band is a piece of tubing with a port at the other end. The port is placed just under the skin. To adjust the tightness of the band, a special needle is inserted in the port. Fluid can be added to the band to make the passageway smaller or remove fluid from the band to make the passageway larger.

BPD is also a form of Roux-en-Y GBP reconstructive alimentary anatomy in which the bypassed intestinal segment includes the portion of duodenum at the point of entry of biliary and pancreatic secretions. This allows the bypassed intestine to be exposed to bile and pancreatic juice. The antrum is removed to avoid peptic ulceration, and food intake is only affected to a limited degree. The essential element of this operation is division of the small intestine about midlength, with the distal end of the alimentary limb anastomosed to a generous gastric remnant. The more proximal biliopancreatic limb is anastomosed to the alimentary limb approximately 50 cm from the ileocecal valve. Following either the GBP or BPD form of bariatric operation, patients require lifelong follow-up and may need micronutrient replacement long term.

HEALTH BENEFITS OF BARIATRIC SURGERY

The two most significant outcome measures of bariatric surgical success are weight loss and resolution of comorbidities. Major effects of bariatric operations have been nicely summarized in three extensive meta-analyses,[57,78,79] as well as in a major literature review.[78] Absolute weight loss averaged 46.4 kg for BPD, 43.5 kg for GBP, 39.8 kg for VBG, and 28.6 kg for gastric banding. This magnitude of weight loss is far greater than what is commonly achievable by nonsurgical methods, and it is considerably closer to patients' desired and expected weight loss. Long-term maintenance of weight loss of this magnitude can also be maintained for more than a decade.

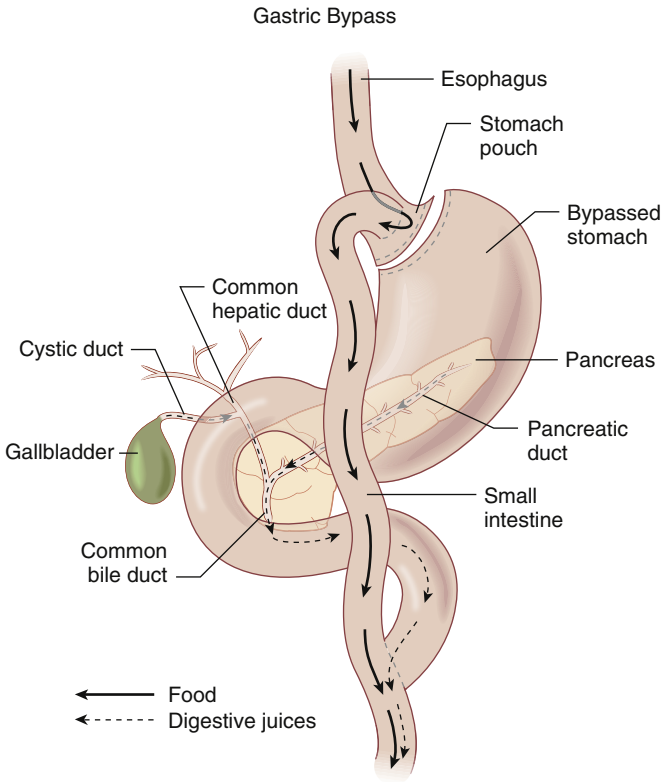


Figure 71-3. Roux-en-Y gastric bypass: Part of the stomach is detached from the rest, to create a small pouch. The pouch is connected to a lower part of the small intestine by a piece of small intestine, resembling a Y. As a result, parts of the stomach and small intestine are bypassed. However, digestive juices (bile acids and pancreatic enzymes) can still mix with the food, thus enabling the body to absorb vitamins and minerals and reducing the risk of nutritional deficiencies.

Improvements in obesity-related and metabolic syndrome–related comorbidities have also been evaluated.[57,79-81] Diabetes improved in more than 85% of patients and resolved in more than 75% overall (98.9% for BPD, 87.3% for GBP, 71.6% for VBG, and 47.9% for gastric banding). Resolution of diabetes following surgery is inversely related to the preoperative duration of the disease and occurs more in those patients whose diabetes is controlled using oral hypoglycemic agents. This finding clearly distinguishes surgical treatment of obesity as an important endocrinologic intervention, especially because the modest improvement in diabetes management that is produced by nonsurgical weight loss is accompanied by relapsing disease in nearly 100% of patients within 5 years. Surgical effects on hyperlipidemia are similarly impressive. Approximately 70% of the entire population experienced improvement, with greatest, intermediate, and least change occurring after BPD, GBP, and gastric banding, respectively. Hypertension resolved in more than 60% of patients, and it improved in more than 18% more patients. Postsurgical effects on hypertension were greatest after BPD (83%), intermediate after GBP (67.5%) and VBG (69%), and least after gastric banding (43%). Resolution of OSAHS seems to be independent of the specific bariatric surgical procedure employed; resolution occurred overall in 85.7% of patients. Postsurgical improvements in other comorbidities have also been demonstrated; improvement in fatty infiltration of the liver, enhanced respiratory function and reduced asthmatic symptoms, reversal of the cardiomyopathy of obesity, and improvements in joint pain and mobility have all been reported.[61,82-86] The reduction in obesity-related comorbidities endures, as determined by 5-year follow-up assesments.[87] Although bariatric surgery has been shown to provide greater weight loss when compared with nonsurgical lifestyle interventions, comorbidities do resolve and risk factors do improve similarly with successful conservative treatments.[81]

ANESTHETIC MANAGEMENT OF THE BARIATRIC SURGICAL PATIENT

Patients undergoing bariatric surgery are receiving what is now the best long-term treatment for morbid obesity. However, their presurgical state is an agglomeration of abnormal physiologic conditions involving multiple organ systems. For that reason, considerable risks of mortality and morbidity are associated with all types of bariatric surgery. Preoperative risk stratification can be used to identify patients at highest risk for significant morbid or fatal events related to bariatric surgery.[88] However, detailed planning of anesthesia care for the perioperative, intraoperative, and postoperative phases must be pursued for the purposes of patients' safety.

PREOPERATIVE EVALUATION

The preoperative assessment for anesthesia should include consideration of hypertension, diabetes, heart failure, and obesity hypoventilation syndrome (see also Chapters 14 and 38). Results of the patient's sleep study are important. An AHI score greater than 30, implying severe sleep apnea, is a warning sign and a predictor for rapid and severe desaturation during induction of anesthesia. CPAP levels more than 10 cm H_2O imply a patient with the potential for difficult ventilation by mask.

Another useful piece of information in the preoperative evaluation is gleaned by examining the history of prior surgical procedures, their anesthetic challenges (i.e., ease or difficulty in securing the airway, intravenous access), need for admission to an intensive care unit, surgical outcomes, and the weight of the patient at that time. This information may either help ease some concerns or allow us to better prepare for the upcoming anesthetic care. Recommended preoperative laboratory evaluations include fasting blood glucose, lipid profile, and serum chemistries (evaluating renal and hepatic function), complete blood count, ferritin, vitamin B_{12}, thyrotropin, and 25-hydroxyvitamin D.

If appropriately evaluated, ideally prepared, and optimally managed perioperatively, even patients with well-known coronary artery disease (CAD) have morbidity and mortality comparable to those in patients without CAD.[89] The effect of OSA on perioperative risk remains controversial,[90] but most patients are screened for OSA with overnight oximetry or polysomnography, or both, if appropriate. If identified with OSA and recommended for CPAP, then patients are encouraged to initiate therapy at home, and this therapy should be continued throughout the perioperative period.

Liver function abnormalities are common in this patient population, especially nonalcoholic fatty liver disease, with the extent of disease a determining factor for perioperative risk and postoperative outcomes. Cirrhotic liver disease with portal hypertension may be considered a contraindication to bariatric surgery.[90] Gastrointestinal symptoms of dyspepsia may indicate the presence of *Helicobacter pylori* infection, which requires treatment by standard medical regimen.

Factors that may be considered contraindications for bariatric surgery include unstable CAD, uncontrolled severe OSA, uncontrolled psychiatric disorder, mental retardation (IQ < 60), inability to understand the surgery, perceived inability to adhere to postoperative restrictions, continued drug abuse, and malignant disease with a poor 5-year survival prognosis. In most situations, preoperative management of the medical morbidities can help optimize risk and convert high-risk patients to patients with acceptable risk.

The anesthetic care of patients with OSA is complicated by the side effects of anesthetic drugs on an already compromised respiratory system. The common comorbidities in this patient population only accentuate the problem.[91] The change in perioperative risk based on the anesthetic agent used is deduced only from anecdotal reports of different cases. Few trials have been conducted to answer that question definitively. Several questions commonly arise and cannot yet be answered on the basis of scientific evidence: Is it safe to perform procedures in patients with sleep apnea and treat them as outpatients or day surgery patients? What procedures pose sufficient risk to the patient to recommend an overnight hospital stay? Does narcotic use affect this decision? Would the increased role of nonsteroidal antiinflammatory drugs change these recommendations? Factors such as neck size and open versus laparoscopic surgery are being studied with regard to their impact on outcomes. Further research on these and other patient safety–related questions is continuing.

INTRAOPERATIVE CARE

Obese patients present special challenges for the anesthesia provider in airway management, positioning, monitoring, choice of anesthetic technique and anesthetic drugs, pain control, and fluid management. Many of these issues are equally important in the postoperative care of these patients. The most significant and best studied are airway management, including endotracheal intubation, pulmonary physiology, and techniques of maintaining adequate blood oxygenation and lung volume. Specific interventions, techniques, and approaches employed by the anesthesia care team providing anesthesia for obese patients are important determinants of outcomes.

Patient Positioning

Even though no evidence-based studies are available to demonstrate that obese patients have more frequent complications from positioning, it seems fairly intuitive that morbidly obese patients do require extra care in positioning (see also Chapter 41). Even in the supine position, rhabdomyolysis from pressure on gluteal muscles, thus leading to renal failure[92] and death,[93] has been reported. For obese patients placed in the prone position, cushioning gel pads or other weight-bearing rolls may have excessive weight placed on them. Pressure points must be checked carefully, and even though pressure sites may be carefully padded, skin breakdown can still occur. This may cause tissue necrosis and infections, especially in lengthy surgical procedures.[94] It is difficult to protect the dependent hip from pressure effects with patients placed in the lateral decubitus position. Obese patients have excess axillary tissue that may make it impossible or unnecessary to place a traditional axillary roll in this position. In the lithotomy position, the challenge may be in supporting the weight of the patient's legs by using regular, and not oversized, stirrups. To minimize the risk of tissue compression injury or development of compartment syndrome, the duration during which legs are held in stirrups should be as short as possible.[95]

Airway Management

No positioning issue is more important than positioning of the obese individual for laryngoscopy and endotracheal intubation (see also Chapters 41 and 55). These procedures are often considered to be much more difficult to perform in obese patients than in patients having a normal BMI. Difficulty with laryngoscopy and intubation usually results from an obese patient's short, thick neck, large tongue, and significant redundant pharyngeal soft tissue. However, the

correlation between morbid obesity and difficult laryngoscopy and tracheal intubation is not universally observed in clinical practice. It is possible that no difference exists between laryngoscopy and intubation in thin and obese patients. Success is likely to result from a simple but important approach to clinical care, with careful attention paid to patient positioning before induction of general anesthesia. Appropriate positioning plays an important role in providing optimal conditions for successful placement of the endotracheal tube under direct vision.

Studies have been conducted to determine the incidence of difficult laryngoscopy or intubation in the obese population, with mixed findings. One study found an association between oropharyngeal Mallampati classification and BMI as predictors of difficult laryngoscopy.[96] During laryngoscopy, the patients' heads were placed in optimum sniffing position, regardless of BMI. In a study conducted exclusively in obese patients, BMI was not found to be associated with intubation difficulties.[37] A high Mallampati score was identified as a predictor of "potential intubation problems," but intubation by direct laryngoscopy was successful in 99 of 100 patients studied. All patients were positioned with pillows or towels under their shoulders, with the head elevated and neck extended. Another group studied both lean and obese patients and found a Mallampati score of III or IV to be the only independent risk factor for difficult intubation in the obese patients in the study.[97] The authors demonstrated that the Mallampati score had low specificity and low positive predictive values (62% and 29%, respectively) for difficult intubation. They concluded that intubation was more difficult in the obese patients. During intubation, patients were placed in a semirecumbent position (30-degree elevation) with the head in the sniffing position.

In another study, ultrasound was used to quantify the amount of soft tissue between the skin and the anterior aspect of the trachea at the level of the vocal cords.[98] These authors also assessed the airway by measurement of thyromental distance, mouth opening, degree of neck mobility, Mallampati score, neck circumference, and presence of OSA. Only an abundance of pretracheal soft tissue measured ultrasonically and neck circumferences were found to be positive predictors of difficult intubation with laryngoscopy performed with patients in the sniffing position. A meta-analysis of 35 studies was conducted to determine the diagnostic accuracy of preinduction tests for predicting difficult intubation in patients having no airway disease.[99] The incidence of difficult intubation in obese patients was three times higher compared with the nonobese population. This finding may have resulted from suboptimal patient positioning, which was not clearly described in any of the preceding studies. Patient positioning, including ramped positioning or elevating the upper body and head of morbidly obese patients to align the ear with the sternum horizontally, improves laryngoscopic view.[100] In this study, morbidly obese patients were assigned to be in either sniffing position or ramped position for airway management. The study demonstrated a statistically significant difference in laryngeal view, with ramped position providing the superior view.

Based on the evidence from randomized controlled trials and other literature on airway management of obese patients, the trachea should be readily intubated by direct laryngoscopy if the patient is placed carefully in ramped position. This positioning can be achieved using commercially available positioning devices[101] or by building a ramp from blankets or sheets to achieve the desired placement of the patient's head relative to the thorax.[102] Obese patients must be examined for the common objective signs of potential difficult intubation, which include small mouth opening, large and protuberant teeth, limited neck mobility, and retrognathia. Alternative airway management techniques include the use of videolaryngoscope equipment for intubating obese patients,[103] because this equipment is rapidly becoming more readily available. Performance of a topicalized direct laryngoscopy with modest sedation in an awake patient can also be used to assess laryngoscopic view in deciding whether to proceed with induction of general anesthesia or fiberoptic intubation in an awake and sedated patient. Of course, the equipment for emergency airway management, including laryngeal masks and a fiberoptic bronchoscope, should be immediately available.

Another area that requires specific attention during the perioperative period is the obese patient's pulmonary physiology. It is especially important to appreciate techniques to maintain oxygenation and lung volume in caring for the obese patient. First, obese patients have multiple pulmonary abnormalities, including decreased vital capacity, inspiratory capacity, expiratory reserve volume, and functional residual capacity. Second, closing capacity in obese individuals is close to or may fall within tidal breathing, particularly in the supine or recumbent position. Moreover, both lung compliance and respiratory system compliance are low in obesity because patients breathe at lung volumes that are abnormally low.[104] As a result of the underlying physiology, the obese patient is likely to undergo rapid oxygen desaturation, particularly during periods of apnea such as occurs during induction of general anesthesia. The presence of OSA by itself does not independently increase the risk of the patient desaturating during induction of general anesthesia as long as appropriate precautions are instituted.[105] However, after induction of anesthesia and tracheal intubation, patients may continue to derecruit gas exchange units throughout the anesthetic course.[106] Various maneuvers have been studied to preserve oxygenation and maintain lung volume specifically in the obese population.

In one study of the rate of development of hypoxemia in patients during apnea, patients received 100% oxygen by facemask to achieve denitrogenation before induction of general anesthesia.[106] The apneic period was continued after induction of anesthesia until peripheral oxygen saturation (SpO_2) decreased to 90%. Obese patients reached the end point in less than 3 minutes, whereas it took 6 minutes in patients having a normal BMI. Efforts to prevent atelectasis formation and desaturation during induction of general anesthesia in obese individuals include application of continuous positive airway pressure (CPAP) during preoxygenation,[107-109] as well as mask application of positive end-expiratory pressure (PEEP), and mechanical ventilation following induction of anesthesia.[109] Use of

10 cm H_2O CPAP during preoxygenation with the patient in the supine position resulted in a higher arterial partial pressure of oxygen (PaO_2) after intubation and decreased the amount of atelectasis that developed.[83] The combination of CPAP during preoxygenation and PEEP or mechanical ventilation after induction significantly increased the nonhypoxemic apnea duration from 2 minutes, found in controls not receiving CPAP or PEEP, to 3 minutes. Use of 7.5 cm H_2O CPAP during 3 minutes of preoxygenation while supine, however, did not change the time required for obese patients to desaturate to an SpO_2 of 90%.[108] Preoxygenation using 25-degree head-up (back inclined), as opposed to supine, positioning without positive airway pressure did increase the elapsed time needed for anesthetized, apneic, obese individuals to desaturate to an SpO_2 of 92%.[110] The patients in head-up position had a significantly higher PaO_2 after preoxygenation, just before induction. The obesity-associated gas exchange defect depended on the waist-to-hip ratio, an index of the distribution of adipose tissue surrounding the thorax.[111] This study further demonstrated that morbidly obese men are more likely to have poorer pulmonary gas exchange than are morbidly obese women.

In a study conducted to assess the relationship between patient positioning and the development of hypoxemia in obese patients during apnea after anesthetic induction and intubation, patients were ventilated with a 50% oxygen/50% air mixture for 5 minutes before the ventilator circuit was disconnected.[112] Apnea was continued until the SpO_2 decreased to 92%, at which time ventilation was resumed. Patients in the supine position reached the end point in 2 minutes, but it took 30 seconds longer if the supine position with the back elevated 30 degrees was used and 1 minute longer if a 30-degree reverse Trendelenburg position was used. Use of a 30-degree reverse Trendelenburg position in obese patients undergoing bariatric surgery was also shown to reduce the alveolar-to-arterial oxygen difference, as well as increase total ventilatory compliance and reduce peak and plateau airway pressures when compared with the supine position.[113] Vital capacity decreases to a greater extent under general anesthesia in obese patients compared with patients of normal weight.[114]

Various intraoperative maneuvers to maintain lung volume and oxygenation have also been studied. Increasing tidal volume incrementally from 13 to 22 mL/kg in obese patients ventilated under general anesthesia did not improve the gas exchange defect but did increase airway pressures.[115] Use of 10 cm H_2O PEEP has a greater effect in obese patients compared with normal subjects on improving ventilatory mechanics, increasing PaO_2, and decreasing alveolar-to-arterial oxygen difference during general anesthesia with neuromuscular blockade.[116] In addition to PEEP alone, use of a recruitment maneuver such as sustained lung inflation to 55 cm H_2O for 10 seconds, followed by application of PEEP, has been demonstrated to prevent atelectasis from developing and to improve oxygenation, whereas neither PEEP nor a recruitment maneuver alone achieved the same degree of maintenance of pulmonary function.[117]

Pneumoperitoneum during laparoscopic procedures increases pulmonary resistance and decreases dynamic lung compliance.[118] During pneumoperitoneum, alterations in body position, tidal volume, and respiratory rate had no effect on the alveolar-to-arterial oxygen difference in obese patients.[119] During pneumoperitoneum for laparoscopic bariatric surgery, alveolar recruitment by repeated sustained lung inflation to 50 cm H_2O followed by mechanical ventilation with 12 cm H_2O PEEP increased PaO_2 intraoperatively, at the expense of causing hypotension that required vasopressor use.[120] In an attempt to optimize PEEP in obese patients undergoing LGB surgery, a normal functional residual capacity was maintained with 15 ± 1 cm H_2O PEEP. Infusion of intravascular volume expanders was required to prevent PEEP-induced hemodynamic compromise.[121]

In summary, the most favorable patient position or optimal amount of PEEP during preoxygenation, induction of anesthesia, or intraoperatively has not been clearly established for the obese patient. Furthermore, the application of noninvasive modes of ventilation including pressure support and bilevel ventilation delivered by mask for preoxygenation, induction, and maintenance of anesthesia to maintain oxygenation and ventilatory mechanics in obese patients has not been sufficiently studied. Ideal patient positioning, use of PEEP, and special modes of ventilation just before emergence and extubation to maintain pulmonary function and gas exchange after extubation have not been identified. Currently, no published guidelines are available to address the issues of maintenance of oxygenation and ventilatory mechanics in obese patients undergoing general anesthesia. Considering both the airway management issues detailed previously and the oxygenation, lung volume, and ventilatory mechanics issues described here for obese individuals, anesthesia care providers should position patients to achieve the combined goals of providing a superior laryngoscopic view for ease of endotracheal intubation while establishing optimal conditions for oxygenation and preservation of pulmonary mechanical function.

It is the practice at our institution that obese patients are initially placed in a ramped position and are then moved into a reverse Trendelenburg position, if needed, to achieve a 25- to 30-degree incline of the thorax before preoxygenation. Patients are then given 100% oxygen under positive pressure. For those patients receiving CPAP at home for OSA, my colleagues and I use CPAP or pressure support ventilation by facemask at a pressure level identical to the patient's home CPAP setting. Otherwise, CPAP of 8 to 10 cm H_2O is appropriate. Following induction of anesthesia, 10 to 12 cm H_2O PEEP can be maintained intraoperatively, but care must be taken to treat any hypotension that may occur. Finally, if the patient's position must be changed intraoperatively, the patient must be returned to the head-up position before emergence and tracheal extubation.

In preparation for emergence from anesthesia, neuromuscular blockade must be fully reversed before the trachea is extubated. Given the advent of a pressure support ventilation mode on many newer models of anesthesia machines, the bariatric patient can be maintained by pressure support during emergence once spontaneous ventilation has resumed. When adequate muscle strength has returned, as demonstrated by sustained tetanus using

the nerve stimulator and performance of a 5-second head lift, the awake patient who is following commands can be tracheally extubated. Pressure support or CPAP can be delivered immediately by mask applied to the face, as is done during preoxygenation prior to induction of anesthesia. Various devices are available to provide CPAP during patient transport from the operating room. We use CPAP during recovery, especially in those patients already prescribed CPAP for their OSA. The basic premise that must be respected with regard to airway management and its integral relationship with pulmonary function is that morbid obesity incurs significant derangements of lung function and pulmonary mechanics. These factors must be managed carefully to minimize intraoperative and postoperative pulmonary complications.[122,123]

Anesthetic Drugs and Dosing

Anesthetic drugs such as opioids, propofol, and benzodiazepines are all well known to have exaggerated responses in patients with OSA. They may decrease pharyngeal musculature tone, which is essential in maintaining airway patency.[36,124] Volatile anesthetics diminish ventilatory response to carbon dioxide, at least in children with tonsillar hypertrophy, in the setting of OSA. Spontaneously breathing tracheally intubated children, with a history of OSA, have depressed ventilation and many have apnea with 0.5 μg/kg of intravenous fentanyl (see also Chapter 92). Although these data are from the pediatric literature, it would be prudent to apply the same principles in obese adult patients until proven otherwise. It therefore becomes attractive to use short-acting drugs and nondepressors of ventilation such as the α_2-agonist dexmedetomidine. This approach should, at least in theory, speed up the return to baseline respiratory function.[94]

Doses of commonly used anesthetic drugs can be determined using total body weight (TBW) or ideal body weight (IBW), based on lipid solubility. In the past, IBW was interpreted to mean fat-free weight, thus implying that it could be used as a substitute for lean body weight or, more correctly, lean body mass (LBM), usually approximated as 120% of IBW. LBM is a good weight approximation to use for doses of hydrophilic medications. As expected, volume of distribution is changed in obese patients with regard to lipophilic drugs. This is especially true of benzodiazepines and barbiturates, among the commonly used anesthetic drugs. Two exceptions to this rule are procainamide[125] and remifentanil,[126] which even though highly lipophilic, have no relationship between properties of the drug and their volume of distribution.[127] Consequently, commonly used anesthetic drug dosing is based on IBW for propofol, vecuronium, rocuronium and remifentanil. In contrast, doses of midazolam, succinylcholine, cisatracurium, fentanyl, and sufentanil should be determined on the basis of TBW. Another caveat to this recommendation is that maintenance doses of propofol should be based on TBW and, conversely, on IBW for sufentanil.[127] This implies that one can use, based on the patient's weight, larger amounts of benzodiazepines, fentanyl, or sufentanil, although these are best titrated to desired clinical effect. Conversely, based on real body weight, smaller amounts of propofol are needed to anesthetize the patient.

With vecuronium or rocuronium, the initial dose should be based on IBW, with additional doses based on monitoring with a peripheral nerve stimulator (see Chapter 53). Complete blockade in the morbidly obese patient is necessary not just for the surgeon's convenience but also to facilitate mechanical ventilation. The drug chosen is not as important as the depth of the state of paralysis.

Volatile anesthetics are chosen based on physical characteristics of tissue solubility, which are expressed as blood-gas partition coefficients and fat-blood partition coefficients. Desflurane may be the anesthetic of choice based on consistent and rapid recovery profile, as opposed to sevoflurane and propofol.[128,129] Some anesthesiologists state that the differences in immediate recovery between sevoflurane and desflurane are not clinically significant.[130]

Even though nitrous oxide provides some analgesic effect and is rapidly eliminated, we prefer to avoid it based on the high oxygen demands in obese patients. The entry of nitrous oxide into air spaces in short intraabdominal surgical procedures may not be a significant factor, but in bariatric surgery, especially when done laparoscopically, any increase in bowel gas volume could make a challenging surgical procedure even more difficult for the surgeon.

Induction of Anesthesia

Obesity, the risk of aspiration of gastric contents, and the need to provide aspiration prophylaxis have been the subjects of considerable debate.[131] Abdominal bloating or fullness and female sex are associated with delayed gastric emptying of solids and liquids in diabetic patients.[132] Although many obese patients have type 2 diabetes, separate studies of gastroesophageal reflux during anesthesia have not demonstrated body habitus to be a predictor of reflux rates.[133] Gastric fluid volume and pH have been shown to be the same in obese patients who are fasting or who have oral intake of up to 300 mL of clear liquid 2 hours before being anesthetized.[134] Obesity itself does not increase the risk of aspiration of gastric contents. However, acid aspiration prophylaxis, including histamine (H_2)–receptor agonists or proton pump inhibitors, must be considered in patients having identifiable risks of aspiration. Awake fiberoptic intubation may also be considered in such patients.[36]

Based on experience from obstetric practice (see also Chapter 77), regional anesthesia, especially epidural and spinal, is safe and feasible in patients with large body habitus.[94] However, regional anesthesia is technically more difficult because of the physical challenge of placing the catheters and the tendency of these catheters to migrate out of the epidural space. Special equipment, in terms of longer needles or special ultrasound probes, may be needed for the correct placement of catheters in these patients. Care should be exercised with drug doses in these catheters because of the increased cephalad spread of the drug and the block as a result of the smaller epidural space compared with normal-weight patients.[135,136] The degree of respiratory compromise suffered by obese patients is also greater than in normal-weight patients with a high regional block.

Little evidence suggests that epidural pain management improves overall outcomes. Because the trend of

laparoscopic surgery is increasing compared with open laparotomies, this becomes less of an issue. In the morbidly obese patient who is having an open laparotomy, use of a thoracic epidural catheter to control pain has the most important benefit of reducing the attenuation of vital capacity postoperatively.[137]

Obesity itself does not require invasive monitoring, so GBP surgery can be performed safely with routine monitoring. The indications for invasive monitoring stem from the comorbidities present in these patients. Because these disorders tend to run together in patients needing surgery, the incidence of invasive monitoring in these patients thereby increases.[138] Morbidly obese patients having serious comorbidities such as obesity-hypoventilation syndrome, who present with pulmonary hypertension and cor pulmonale, may require a pulmonary artery catheter or intraoperative evaluation by transesophageal echocardiography. The rationale for central venous access may stem from difficulties in peripheral access, rather than any other indication. Many patients receive an inferior vena cava filter prophylactically because of the high risk of deep vein thrombosis and pulmonary embolism associated with obesity and bariatric surgery.[139] This procedure is often performed through the right internal jugular vein on the day before bariatric surgery, thus making it possible to have a central venous catheter left in place for the operation at the time the filter is inserted. It is recommended that a central line inserted at the time of surgery should be placed under ultrasound guidance to decrease complications as well as to increase ease of placement. Similarly, difficulty in noninvasive blood pressure measurements, secondary to body habitus–related difficulty in appropriate cuff placement, may be an indication for arterial catheter placement. Analysis of arterial blood gases may help to guide intraoperative ventilation and extubation of the trachea.

Postoperative pain management (see also Chapter 98) in patients undergoing weight loss surgery can involve intravenous analgesia, patient-controlled analgesia (PCA), or thoracic epidural analgesia (TEA). No data are available to prove the superiority of one technique over the other. In our practice, my colleagues and I tend to reserve epidural anesthesia for patients undergoing open GBP. Even with these drawbacks, we have approximately an 80% success rate with supermorbidly obese patients. Opioid-based PCA with local anesthetic wound infiltration and adjunct nonnarcotics is a reasonable alternative approach for most patients. Injection of local anesthetic in the incision site before making the incision may result in preemptive analgesia. Adjunct analgesia with nonnarcotic medications, unless contraindicated, decreases opioid requirements and thereby opioid-induced side effects as well.

Intraoperatively, using the appropriate table for the patient's weight is critical because the consequences of having a table not rated to the patient's weight can be serious for both the patient and the operating room personnel. It may be useful to keep the patient strapped throughout the period of sedation and sleep. Along with a safety strap, it may also be useful to apply a bean bag under the patient to keep the patient from sliding off the operating room table. Thermal management in the operating room is best accomplished by forced-air warmers (see also Chapter 54). Arm boards may need extra padding to keep the patient from having the arm and shoulder out of an anatomic position. If the arms are to be tucked by the side of the patient, then wide, well-padded sleds may be useful.

Intravenous fluid requirements are greater than predicted, and even a relatively short, 2- to 3-hour case may need 4 to 5 L of crystalloid fluid to prevent acute tubular necrosis (ATN) in the kidneys. Hypovolemia, which can cause a protracted prerenal state and contribute to the development of ATN, can be prevented by appropriate hydration. Retrospective data from the University of Pittsburgh Medical Center suggest that primary acute renal failure after weight loss surgery occurs in approximately 2% of patients. Other predisposing factors are BMI greater than 50 kg/m^2, prolonged surgical time, prior history of renal disease, and intraoperative hypotension.[140]

POSTOPERATIVE MANAGEMENT

In our practice, we prefer to have postbariatric surgery patients stay at the same location consistently. This allows skilled nursing and ancillary care to be provided to patients on a consistent basis. These patients are kept on their CPAP or biphasic positive airway pressure (BiPAP) machines as much as possible with monitoring of SpO_2 by pulse oximetry recommended. At the Hospital of the University of Pennsylvania in Philadelphia, patients identified as having difficult airways are distinguished with armbands, and with visible signs on their beds, their hospital charts, and on the electronic medical records for the remainder of their hospital stay. Additionally, a note by the attending anesthesiologist explaining the difficulty in intubation, as well as the means used to secure the airway in the operating room, is available in the room. In case of an unexpected emergency intubation, for whatever reason, we believe that this extra information is extremely useful to the resuscitation team.

MANAGEMENT OF COMPLICATIONS

Bariatric surgery is considered very safe, but not without potential complications, which are increasingly predictable.[141] In-hospital mortality rates for LGB and open GBP surgery are 0.27% and 0.81%, respectively, a statistically significant difference.[140] Mortality is associated with a need for reoperation during the same hospitalization,[142] with intestinal leakage a serious complication accounting for a large number of patient deaths.[143] Risk factors also include comorbid conditions of congestive heart failure or renal failure.

Morbidity occurring during the immediate postoperative in-hospital period typically falls into one of four categories of complications: wound, gastrointestinal, pulmonary, and cardiovascular. The complication rates are significantly lower in each category for patients undergoing laparoscopic rather than open procedures, and they range from 1.35% (wound complications) to 4.52% (gastrointestinal complications) following LGB and from 1.98% (wound complications) to 5.33% (gastrointestinal complications) following open GBP.[140] Table 71-5 provides a categoric listing of both specific and nonspecific complications of bariatric surgery.

TABLE 71-5 SPECIFIC AND NONSPECIFIC COMPLICATIONS OF BARIATRIC SURGERY

	All Surgical Procedures	Gastric Banding	Roux-en-Y
Early	Bleeding Infection Dehydration Peritonitis Bowel obstruction Perforation Pneumonia DVT or PE Death	Band slippage Band malfunction Infection at band site	Leak from anastomotic site
Late	Cholelithiasis Cholecystitis Pouch dilation GERD or dysphagia Herniation at surgical site Nutritional issues Vitamin deficiencies, especially fat-soluble vitamins and vitamin B_{12}	Anorexia Band slippage Band malfunction Infection at band site	Small bowel obstruction Marginal ulcers Pancreatitis Stricture

DVT, Deep vein thrombosis; *GERD,* gastroesophageal reflux disease; *PE,* pulmonary embolism.

The most common complications requiring reoperation include postoperative intraabdominal bleeding, anastomotic leakage, suture line dehiscence, small bowel obstruction, and deep wound infection,[143-148] all of which may require general anesthesia for laparotomy. Despite deep vein thrombosis prophylaxis therapy in the perioperative period, patients can also present postoperatively with deep vein thrombosis or pulmonary embolism and require anesthesia for placement of an inferior vena cava filter device. As mentioned earlier, filters are often placed before bariatric surgery.[139]

In all cases requiring reoperation shortly after the original bariatric procedure, it is prudent to review the anesthesia record. Specific attention should be paid to the documentation of patient position and technique employed for airway management in the prior anesthetic regimen. Patients may be hypovolemic from blood loss, inadequate hydration, vasodilatation, and insensitive fluid losses associated with fever and infection. It is especially important to consider additional or new risks of aspiration of gastric contents. These risks may result from the presence of postoperative ileus, small bowel obstruction, and surgical creation of a Roux-en-Y gastric bypass limb that excludes the pylorus as an element of protection from reflux of intestinal contents. Decompression of the gastric pouch in patients undergoing surgery to relieve small bowel obstruction can be achieved with careful introduction of a nasogastric or orogastric tube just before induction of general anesthesia. Although this may increase the risk of violating a fresh, competent anastomotic suture line, communication between anesthesiologist and surgeon can be pursued to determine the risks and benefits of performing this maneuver. During the ensuing laparotomy, any perforation of a fresh suture line resulting from the attempt to decompress the gastrointestinal tract can be repaired immediately, and the nasogastric or orogastric tube can subsequently be left in place for continued postoperative drainage.

Depending on the extent of reoperation, requirement for volume resuscitation, blood transfusion, degree of peritonitis with anastomotic leak, presence of sepsis, or other significant continued risks to health, patients undergoing reoperation may require prolonged postoperative ventilation. Requirements for postoperative pain management may also be considerably different from those associated with the initial bariatric procedure. In patients who are sufficiently hemodynamically stable immediately before reoperation, an epidural catheter can be placed before induction for pain management as part of the postoperative care. This is especially valuable in obese patients undergoing laparotomy, as described earlier in this chapter.

Certain potential major complications require surgical intervention weeks, months, or even years after a bariatric surgical operation has been performed. Patients may develop anastomotic strictures or ulcers, ventral hernias, gastrogastric fistulas, and severe reflux disorders requiring additional surgery.[77] Small bowel obstruction may appear weeks after the surgical procedure.[147] Patients may desire cosmetic operations to remove excess skin or liposuction procedures to sculpt dysmorphic body areas following significant weight loss. Patients may also require adjustment of a gastric band or pursue band removal. The anesthetic considerations for such patients should include a review of the prior anesthetic record to glean information regarding airway and pain management. The degree of weight loss achieved and the resolution of comorbidities, including diabetes, hypertension, and OSA, may significantly alter the approach used in the bariatric operation.

Some patients develop significant neurologic complications following GBP surgery.[149-151] These complications are known to include polyneuropathy, polyradiculoneuropathy, myelopathy, encephalopathy, and optic neuropathy. Myelopathy occurs most frequently but does not manifest until approximately 10 years postoperatively.[149] These patients have demonstrable nutritional deficiencies, but except for the vitamin B_{12} and copper deficiencies found in patients with myelopathy, no specific nutritional profile has been reported to correlate with neurologic complications. Although neurologic symptoms accompanying weight loss surgery are not likely to result in additional surgery, they represent new or additional comorbidities that should be fully considered by the anesthesiologist caring for patients having previously undergone bariatric surgery.

The nutritional and metabolic complications of bariatric surgery also include protein and protein-calorie malnutrition. Patients may have excessive weight loss occurring either too rapidly or beyond the predetermined goals, steatorrhea or severe diarrhea, hypoalbuminemia, marasmus, edema, and hyperphagia.[77,152-154] In cases of severe malnutrition, patients may require enteral or parenteral nutrition therapy. Surgical revision may be required to correct excessive weight loss and hypoalbuminemia. Under such circumstances, an anesthetic regimen accounting for decreased drug binding effects of a low serum albumin level must be considered.

CONSIDERATIONS FOR MANAGEMENT OF THE OBESE PATIENT PRESENTING FOR NONBARIATRIC SURGERY

Few studies have evaluated the importance of morbidity in obese patients during common surgical procedures. A study by Dindo and co-workers of 6336 patients did not find any difference in the incidence or severity of complications after elective general surgery, except surgical site infections.[155] Other studies assessed the effect of obesity on wound infections and showed that these infections are increased.[156,157] Multiple studies demonstrated that obese patients are at higher risk after gynecologic, orthopedic, cardiovascular, urologic, and transplantation surgery, whereas other studies did not show obesity-related risk differences.[158,159]

From the data of Dindo and associates regarding complications and the type of surgical procedure,[155] operative severity and open laparoscopic surgery were independent risk factors for postoperative complications. These investigators found no differences in the type of postoperative complications in obese and nonobese groups. This study provided data to decrease the prejudice that patients with obesity are implied to have a higher incidence of postoperative complications. This preconception may pertain more to the perception of the medical team as a result of technical difficulties on the anesthetic and surgical end. Surgical procedures may have lasted longer, approximately 25% more time for laparoscopic than for open cholecystectomy in morbidly obese patients. Significantly, the wound infection rate was much better after laparoscopic than after open surgery, a finding that supports the practice of performing laparoscopic surgery, rather than the alternative, in obese patients.

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Chapter 72

Anesthesia and the Renal and Genitourinary Systems

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Key Points

- Innervation of the intraabdominal components of the genitourinary system—the kidney and the ureter—is primarily thoracolumbar (T8-L2). The nerve supply of the pelvic organs—the bladder, the prostate, the seminal vesicles, and the urethra—is primarily lumbosacral with some lower thoracic input.
- The spinal level of pain conduction for the external genitourinary organs is S2-4, except for the testes (T10-L1).
- The kidneys receive 15% to 25% of the total cardiac output, with most of this blood directed to the renal cortex. Renal medullary papillae are more vulnerable to ischemic insults. Kidneys successfully autoregulate their blood flow between 60 and 160 mm Hg mean arterial pressures.
- The glomerular filtration rate (GFR) is the best measure of glomerular function. Creatinine clearance is a good measure of the GFR; urine output is not.
- Hypervolemia, acidemia, hyperkalemia, cardiorespiratory dysfunction, anemia, and bleeding disturbances are manifestations of chronic renal failure.
- Although renal transplantation reverses most of the abnormalities in end-stage renal disease, dialysis improves only some, and introduces additional complications of its own.
- Newer techniques, such as laser prostatectomy, are making transurethral resection of the prostate (TURP) syndrome a rare event. TURP syndrome is a constellation of symptoms caused by the absorption of hypotonic bladder irrigants. Cardiovascular and neurologic changes are due to hypoosmolality, hyponatremia, hyperglycinemia, hyperammonemia, and hypervolemia.
- Regional anesthesia offers several advantages over general anesthesia for standard, but not laser, TURP. Yet, 30-day mortality rates remain unchanged at 0.2% to 0.8%.
- Laparoscopic surgery in urology frequently requires insufflation of carbon dioxide into the retroperitoneal space. In lengthy procedures, pneumomediastinum and subcutaneous emphysema of the head and neck may occur.
- Extracorporeal shock wave lithotripsy (ESWL) causes significant physiologic changes related to immersion if a water bath is used. Shock waves can cause arrhythmias and injury to the lungs. Pregnancy and untreated bleeding disorders are contraindications to ESWL.
- Regarding renal tumors, 5% to 10% extend into the renal vein, inferior vena cava, and right atrium. Complications ranging from circulatory failure to embolization of tumor during surgery may occur. Cardiopulmonary bypass may be necessary for surgery.
- Radical prostatectomy causes significant blood loss sometimes including intraoperative venous air emboli. Regional anesthesia with spontaneous ventilation is associated with less blood loss than general anesthesia and intermittent positive-pressure ventilation. Other advantages of epidural anesthesia include a decreased incidence of deep vein thrombosis and preemptive analgesia. Whether outcomes are dependent on the choice of anesthesia is not clear.
- Robotic radical prostatectomy is associated with reduced blood loss and postoperative pain compared with open radical prostatectomy. Anesthetic concerns are related to steep head-down tilt (also see Chapter 41) and pneumoperitoneum and include hypercarbia, hypoxemia, increased intraocular and intracranial pressures, decreased perfusion pressure to lower extremities, and positional injuries.

TABLE 72-1 PAIN CONDUCTION PATHWAYS AND SPINAL SEGMENT PROJECTION OF PAIN OF THE GENITOURINARY SYSTEM

Organ	Sympathetics, Spinal Segments	Parasympathetics	Spinal Levels of Pain Conduction
Kidney	T8-L1	CN X (vagus)	T10-L1
Ureter	T10-L2	S2-4	T10-L2
Bladder	T11-L2	S2-4	T11-L2 (dome), S2-4 (neck)
Prostate	T11-L2	S2-4	T11-L2, S2-4
Penis	L1 and L2	S2-4	S2-4
Scrotum	NS	NS	S2-4
Testes	T10-L2	NS	T10-L1

NS, Not significant for nociceptive function.

Patients requiring anesthesia for renal and genitourinary surgery are frequently at the extremes of age. In addition to the physiologic changes of aging in older patients (see also Chapter 80), concomitant cardiovascular and respiratory comorbidity is common. A medical history, physical examination, and appropriate laboratory tests are necessary to evaluate concomitant disease. In pediatric urologic patients, a careful history should exclude other nonurologic congenital lesions (see Chapter 93).

Urologic procedures are performed mostly on the kidneys, adrenals, ureters, urinary bladder, prostate, urethra, penis, scrotum, testis, and spermatic cord. Because their sensory nerve supply is primarily thoracolumbar and sacral outflow (Table 72-1), these structures are well adapted for regional anesthesia.

INNERVATION OF THE GENITOURINARY SYSTEM

The parts of the genitourinary system that are in the abdomen receive their nerve supply from the autonomic nervous system by means of sympathetic and parasympathetic pathways. The pelvic urinary organs and genitalia are supplied by somatic and autonomic nerves. Table 72-1 summarizes the pain conduction pathways and spinal levels of the genitourinary system.

KIDNEY AND ABDOMINAL URETER

Sympathetic nerves to the kidney originate as preganglionic fibers from the eighth thoracic through the first lumbar segments and converge at the celiac plexus and aorticorenal ganglia (Fig. 72-1). Postganglionic fibers to the kidney arise mainly from the celiac and aorticorenal ganglia. Some sympathetic fibers may reach the kidney via the splanchnic nerves. Parasympathetic input is from the vagus nerve.[1] Sympathetic fibers to the ureter originate from the tenth thoracic through the second lumbar segments and synapse with postganglionic fibers in the aorticorenal and superior and inferior hypogastric plexuses. Parasympathetic input is from the second through fourth sacral spinal segments.[1] Nociceptive fibers travel along the sympathetics to the same spinal segments.

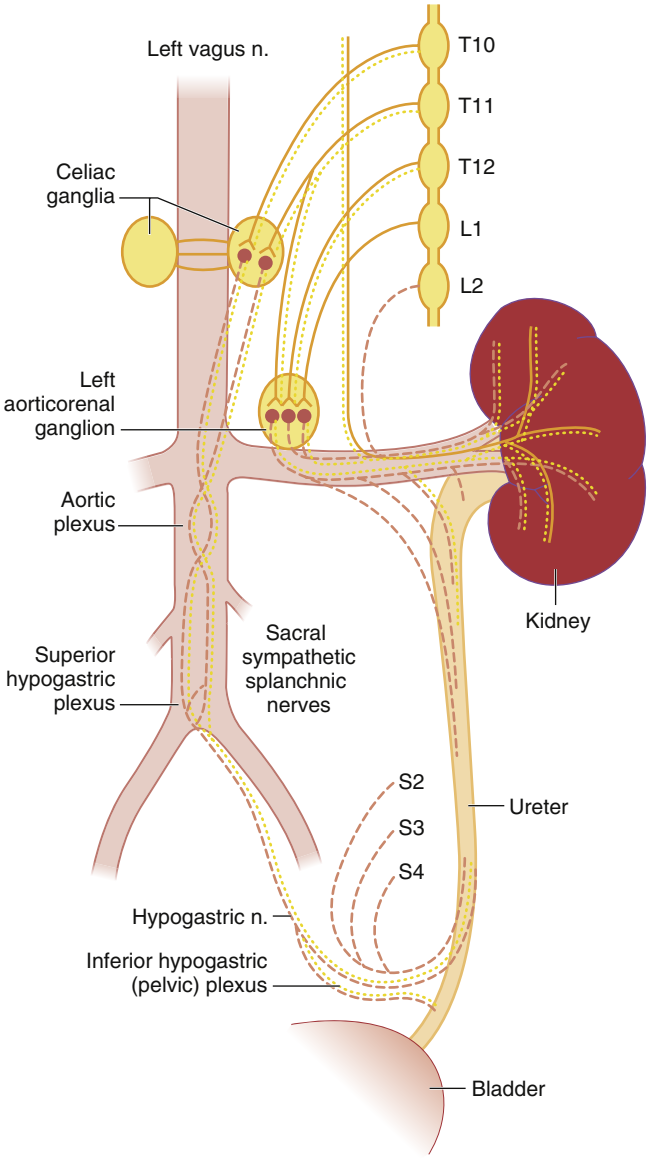


Figure 72-1. Autonomic and sensory innervation of the kidney and ureters. *Solid line* indicates preganglionic fibers; *dashed line* indicates postganglionic fibers; and *dotted line* indicates sensory fibers. *(From Gee WF, Ansell JF: Pelvic and perineal pain of urologic origin. In Bonica JJ, editor:* The management of pain, *ed 2, Philadelphia, 1990, Lea & Febiger, pp 1368-1378.)*

Pain from the kidney and ureter is referred mainly to the somatic distribution of the tenth thoracic through the second lumbar segments—the lower part of the back, flank, ilioinguinal region, and scrotum or labia. Effective neural block of these segments is necessary to provide adequate analgesia or anesthesia.

BLADDER AND URETHRA

Sympathetic nerves to the bladder and urethra originate from the eleventh thoracic to the second lumbar segments, travel through the superior hypogastric plexus, and supply the bladder through the right and the left hypogastric nerves.[2] Parasympathetic nerves arise from the second through the fourth sacral segments

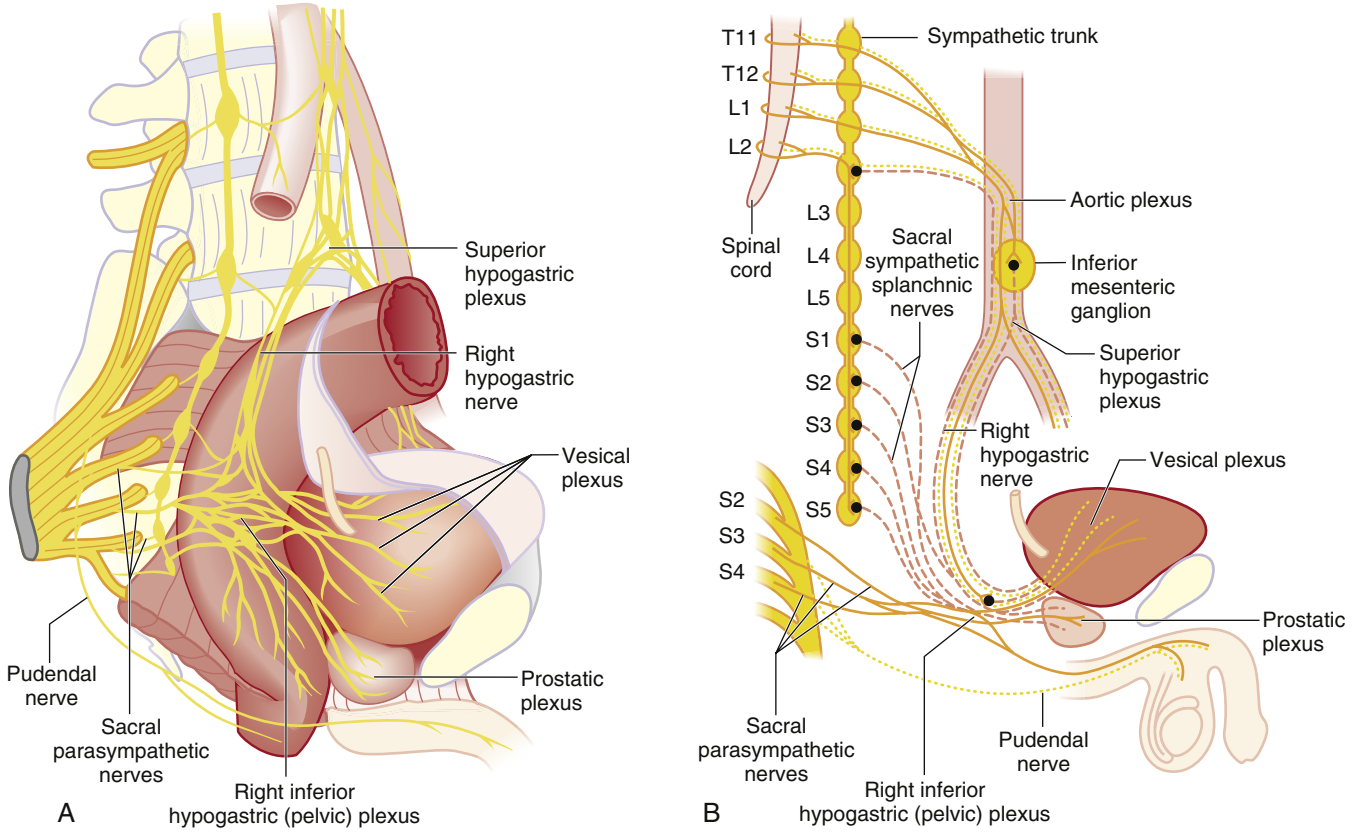


Figure 72-2. A, Nerve supply of the urinary bladder and prostate showing the relationship of the various nerve structures to the large intestine and their distribution in the bladder and prostate. **B,** Schematic illustration showing the segmental nerve supply to the bladder, penis, and scrotum. *Solid lines* indicate preganglionic fibers; *dashed lines* indicate postganglionic fibers; and *dotted lines* indicate sensory fibers. *(From Gee WF, Ansell JF: Pelvic and perineal pain of urologic origin. In Bonica JJ, editor:* The management of pain, *ed 2, Philadelphia, 1990, Lea & Febiger, pp 1368-1378.)*

and form the pelvic parasympathetic plexus, which is joined by the hypogastric plexus. Vesical branches proceed toward the bladder base, where they provide the nerve supply to the bladder and proximal part of the urethra (Fig. 72-2). Parasympathetic fibers are the main motor supply to the bladder (with the exception of the trigone) and far outnumber sympathetic fibers in the bladder.[2]

The afferents carrying sensations of stretch and fullness of the bladder are parasympathetic, whereas pain, touch, and temperature sensations are carried by sympathetic nerves. Sympathetic fibers are predominantly α adrenergic in the bladder base and urethra, and β adrenergic in the bladder dome and lateral wall. Knowledge of these aspects of neuroanatomy is important to appreciate the pharmacologic effects on the urologic system of neural ablation or regional block and drugs with adrenergic or cholinergic effects.[2]

PROSTATE AND PROSTATIC URETHRA

The prostate and the prostatic urethra receive sympathetic and parasympathetic supply from the prostatic plexus arising from the pelvic parasympathetic plexus, which is joined by the hypogastric plexus. The spinal origin of the nerve supply is primarily lumbosacral (see Fig. 72-2).[2]

PENIS AND SCROTUM

The autonomic supply to the penile urethra and the cavernous tissue comes from the prostatic plexus. Somatic fibers from the pudendal nerve (S2-4) supply the external sphincter. The dorsal nerve of the penis, the first branch of the pudendal nerve, is its main sensory supply. The scrotum is innervated anteriorly by the ilioinguinal and genitofemoral nerves (L1 and L2) and posteriorly by perineal branches of the pudendal nerve (S2 and S4).[2]

TESTES

The testes descend from their intraabdominal location to the scrotum during fetal development. Because they share their embryologic origin with the kidney, their nerve supply is similar to that of the kidney and upper part of the ureter and extends up to the T10 spinal segment.[2]

RENAL BLOOD FLOW

The kidneys receive approximately 15% to 25% of total cardiac output, or 1 to 1.25 L/min of blood through the renal arteries, depending on the state of the body. Most of the blood is received by the renal cortex, with only 5% of cardiac output flowing through the renal medulla, which

makes the renal papillae vulnerable to ischemic insults. Renal blood flow is regulated by various mechanisms that control the activity of vascular smooth muscle and alter vascular resistance. Sympathetic tone of renal vessels increases during exercise to shunt renal blood flow to exercising skeletal muscle; similarly, renal blood vessels relax during the resting condition of the body. Sympathetic stimulation resulting from surgery can increase vascular resistance and reduce renal blood flow, whereas anesthetics may reduce renal blood flow by decreasing cardiac output.

Glomerular capillaries separate afferent arterioles from efferent arterioles. Glomerular capillaries are high-pressure systems, whereas peritubular capillaries are low-pressure systems. Consequently, the glomerular capillaries are a fluid-filtering system, whereas the peritubular capillaries are a fluid-absorbing system. The vasa recta, a specialized portion of peritubular capillaries formed from efferent arterioles, are important in the formation of concentrated urine by a countercurrent mechanism. An intrinsic mechanism that causes vasodilation and vasoconstriction of renal afferent arterioles regulates the autoregulation of renal blood flow. A decrease in mean arterial pressure also decreases renal blood flow and eventually affects the glomerular filtration rate (GFR) when the pressure decreases to less than 60 mm Hg. A persistently low mean arterial pressure greater than 60 mm Hg affects renal blood flow, but does not affect the GFR because of the intrinsic mechanism of autoregulation (Fig. 72-3). Autoregulation maintains mean arterial pressure between 60 mm Hg and 160 mm Hg in intact and denervated kidneys.[3]

Although knowledge of neuroanatomy and renal blood flow is essential to provide adequate anesthesia, a thorough understanding of renal physiology and pharmacology is equally important. Genitourinary surgical patients frequently have mechanical or functional renal disease. Anesthetics and surgery can significantly alter renal function. Conversely, renal dysfunction significantly affects the pharmacokinetics and pharmacodynamics of anesthetics and adjuvant drugs. Evaluation of a patient with renal disease is discussed later.

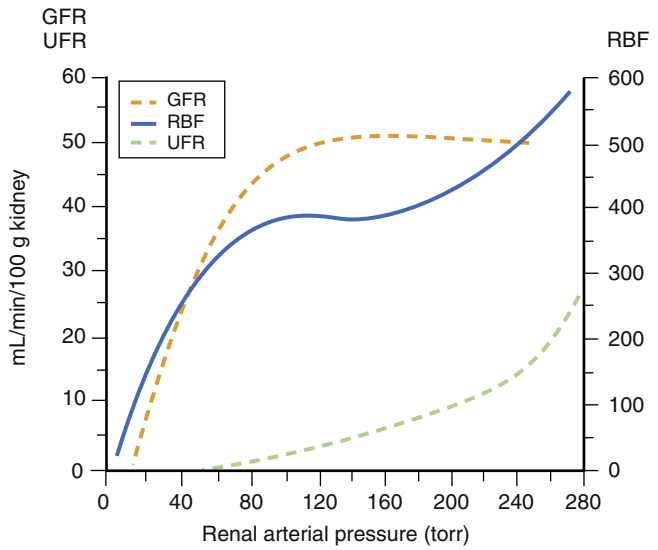


Figure 72-3. Autoregulation of renal blood flow (RBF) and the glomerular filtration rate (GFR). The relationships between RBF, GFR, and urine flow rate (UFR) and mean renal arterial pressure in dogs are shown as renal arterial pressure is varied from 20 to 280 mm Hg. Autoregulation of RBF and GFR is observed between about 80 mm Hg and 180 mm Hg. *(Redrawn from Hemmings HC: Anesthetics, adjuvants and drugs and the kidney. In Malhotra V, editor:* Anesthesia for renal and genitourinary surgery, *New York, 1996, McGraw-Hill, p 18.)*

ANESTHESIA FOR PATIENTS WITH RENAL DISEASE

EVALUATION OF RENAL FUNCTION

Renal disease can be discovered incidentally during a routine medical evaluation, or patients may exhibit evidence of renal dysfunction, such as hypertension, edema, nausea, and hematuria (see Chapter 23). The initial approach in both situations should be to assess the cause and severity of renal abnormalities. In all cases, this evaluation includes (1) an estimation of disease duration, (2) a careful urinalysis, and (3) an assessment of the GFR. The history and physical examination, although equally important, are variable among renal syndromes; specific symptoms and signs are discussed in sections on each disease entity. Further diagnostic categorization is based on anatomic distribution: prerenal disease, postrenal disease, and intrinsic renal disease. Intrinsic renal disease can be divided further into glomerular, tubular, interstitial, and vascular abnormalities. Laboratory tests useful in evaluating renal function are described next (Table 72-2).

TABLE 72-2 **COMMONLY ORDERED RENAL FUNCTION TESTS**

Test Name	Reference Range	Units
Urea nitrogen	5-25	mg/dL
Creatinine	0.5-1.5	mg/dL
Sodium	133-147	mmol/L
Potassium	3.2-5.2	mmol/L
Chloride	94-110	mmol/L
CO_2	22-32	mmol/L
Uric acid	2.5-7.5	mg/dL
Calcium	8.5-10.5	mg/dL
Phosphorus	2.2-4.2	mg/dL
Urinalysis, routine		
Color	Straw-amber	
Appearance	Clear-hazy	
Protein	0	mg/dL
Blood	Negative	
Glucose	0	mg/dL
Ketones	0	mg/dL
pH	4.5-8.0	
Specific gravity	1.002-1.030	
Bilirubin	Negative	
Urinalysis, microscopic		
Red blood cells	0-3	per high-power field
White blood cells	0-5	per high-power field
Casts	0-2	per low-power field

From Miller ED Jr: Understanding renal function and its preoperative evaluation. In Malhotra V, editor: Anesthesia for renal and genitourinary surgery, *New York, 1996, McGraw-Hill, p 9.*

GLOMERULAR FUNCTION

Glomerular Filtration Rate

The GFR is the best measure of glomerular function. Normal GFR is approximately 125 mL/min. Manifestations of reduced GFR are not seen, however, until the GFR has decreased to 50% of normal. When GFR decreases to 30% of normal, a stage of moderate renal insufficiency sets in. Patients remain asymptomatic with only biochemical evidence of a decline in GFR (i.e., an increase in serum concentrations of urea and creatinine). Further workup usually reveals other abnormalities, such as nocturia, anemia, loss of energy, decreasing appetite, and abnormalities in calcium and phosphorus metabolism.

As the GFR decreases further, a stage of severe renal insufficiency begins. This stage is characterized by profound clinical manifestations of uremia and biochemical abnormalities, such as acidemia; volume overload; and neurologic, cardiac, and respiratory manifestations. At the stages of mild and moderate renal insufficiency, intercurrent clinical stress may compromise renal function further and induce signs and symptoms of overt uremia. When the GFR is 5% to 10% of normal, it is called end-stage renal disease (ESRD), and continued survival without renal replacement therapy becomes impossible. Although most clinical abnormalities of corticotropin-releasing factor are reversed by renal transplantation, the response to dialysis is highly variable (Table 72-3).

Blood Urea Nitrogen

The blood urea nitrogen (BUN) concentration is not a direct correlate of reduced GFR. BUN is influenced by nonrenal variables, such as exercise, bleeding, steroids, and massive tissue breakdown. The more important factor is that BUN is not elevated in kidney disease until the GFR is reduced to almost 75% of normal.[4]

Creatinine and Creatinine Clearance

Measurements of creatinine provide valuable information regarding general kidney function. Creatinine in serum results from turnover of muscle tissue and depends on daily dietary intake of protein. Normal values are 0.5 to 1.5 mg/100 mL; values of 0.5 to 1 mg/100 mL are present during pregnancy. Creatinine is freely filtered at the glomerulus, and apart from an almost negligible increase in content because of secretion in the distal nephron, it is neither reabsorbed nor secreted. Serum creatinine measurements reflect glomerular function (Fig. 72-4),[4] and creatinine clearance is a specific measure of GFR. Creatinine clearance can be calculated by the following formula derived by Cockcroft-Gault that accounts for age-related decreases in GFR, body weight, and sex:

$$\text{Creatinine clearance (mL/min)} = [(140 - \text{Age}) \times \text{Lean body weight (kg)}]/[\text{Plasma creatinine (mg/dL)} \times 72]$$

This value should be multiplied by 0.85 for women because a lower fraction of body weight is composed of muscle.

TABLE 72-3 **CLINICAL ABNORMALITIES IN CHRONIC RENAL FAILURE AND THEIR RESPONSE TO DIALYSIS AND ERYTHROPOIETIN TREATMENT**

Improved by Dialysis	Improved by Adding Erythropoietin	Variable Response	Not Improved	Develop after Dialysis Therapy
Volume expansion and contraction	Fatigue	Secondary hyperparathyroidism	Increased lipoprotein level	Adynamic osteomalacia
Hypernatremia and hyponatremia	Impaired mentation	Hyperuricemia	Decreased high-density lipoprotein level	β_2-Microglobulinemia
Hyperkalemia and hypokalemia	Lethargy	Hypertriglyceridemia	Impaired growth and development	Muscle cramps
Metabolic acidosis	Pallor	Protein-calorie malnutrition	Infertility and sexual dysfunction	Dialysis dysequilibrium syndrome
Hyperphosphatemia	Anemia	Headache	Amenorrhea	Hypotension and arrhythmias
Hypocalcemia	Bleeding diathesis	Peripheral neuropathy	Sleep disorders	Hepatitis
Vitamin D–deficient osteomalacia		Restless legs syndrome	Pruritus	Idiopathic ascites
Carbohydrate intolerance		Paralysis	Lymphocytopenia	Peritonitis
Hypothermia		Seizures	Splenomegaly and hypersplenism	Leukopenia
Asterixis		Myopathy		Hypocomplementemia
Muscular irritability		Arterial hypertension		
Myoclonus		Cardiomyopathy		
Coma		Accelerated atherosclerosis		
Congestive heart failure or pulmonary edema		Vascular calcification		
Pericarditis		Hyperpigmentation		
Uremic lung		Peptic ulcer		
Ecchymoses		Gastrointestinal bleeding		
Uremic frost		Increased susceptibility to infection		
Anorexia				
Nausea and vomiting				
Uremic fetor				
Gastroenteritis				

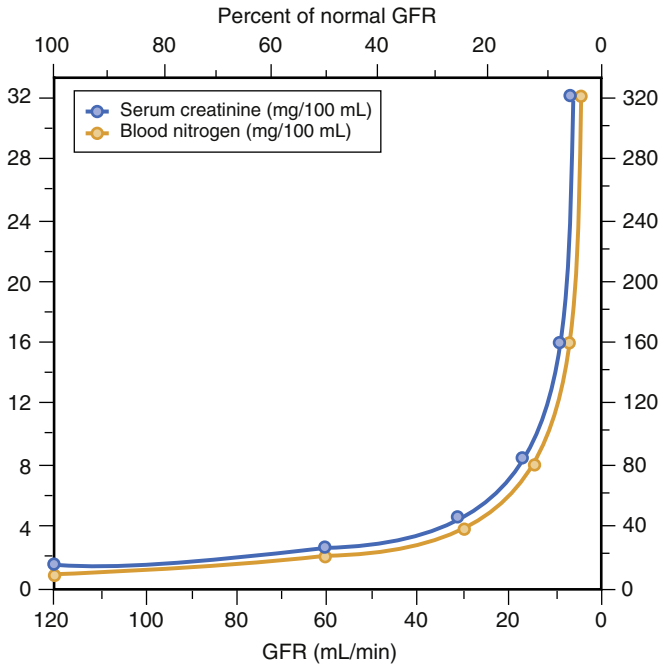


Figure 72-4. Theoretic relationship between blood urea nitrogen and creatinine versus glomerular filtration rate (GFR). *(Redrawn from Kassirer JP: Clinical evaluation of kidney function-glomerular function,* N Engl J Med *285:385, 1971.)*

Because there is such a wide range in normal values, a 50% increase in serum creatinine concentration, indicative of a 50% reduction in GFR, may go undetected unless baseline values are known. Also, excretion of drugs dependent on glomerular filtration may be significantly decreased despite what might seem to be only slightly elevated serum creatinine values (1.5 to 2.5 mg/100 mL). The serum creatinine concentration and clearance are better indicators of general kidney function and GFR than are similar measurements of urea nitrogen (Box 72-1). There are disease states, however, in which even the serum creatinine can be affected independent of the GFR (Table 72-4).

TUBULAR FUNCTION

Concentration

Urinary specific gravity is an index of the kidney's concentrating ability, specifically, renal tubular function. Determination of urinary osmolality (i.e., measurement of the number of moles of solute [osmoles] per kilogram of solvent) is a similar, more specific test. Excretion of concentrated urine (specific gravity, 1.030; 1050 mOsm/kg) is indicative of excellent tubular function, whereas a urinary osmolality fixed at that of plasma (specific gravity 1.010; 290 mOsm/kg) indicates renal disease. The urinary dilution mechanism persists after concentrating defects are present, so a urinary osmolality of 50 to 100 mOsm/kg still may be consistent with advanced renal disease.

Protein

Patients without renal disease can excrete 150 mg of protein per day; greater amounts may be present after strenuous exercise or after standing for several hours. Massive proteinuria (i.e., >750 mg/day) is always abnormal and usually indicates severe glomerular damage.

BOX 72-1 ***Conditions Affecting BUN Independently of Glomerular Filtration Rate***

INCREASED BUN

- Reduced effective circulating blood volume (prerenal azotemia)
- Catabolic states (gastrointestinal bleeding, corticosteroid use)
- High-protein diets
- Tetracycline

DECREASED BUN

- Liver disease
- Malnutrition
- Sickle cell anemia
- SIADH

BUN, Blood urea nitrogen; *SIADH,* syndrome of inappropriate secretion of antidiuretic hormone.

TABLE 72-4 **CONDITIONS AFFECTING SERUM CREATININE INDEPENDENTLY OF GLOMERULAR FILTRATION RATE**

Condition	Mechanism
Conditions Causing Elevation	
Ketoacidosis	Noncreatinine chromogen
Cephalothin, cefoxitin	Noncreatinine chromogen
Flucytosine	Noncreatinine chromogen
Other drugs—aspirin, cimetidine, probenecid, trimethoprim	Inhibition of tubular creatinine secretion
Conditions Causing Decrease	
Advanced age	Physiologic decrease in muscle mass
Cachexia	Pathologic decrease in muscle mass
Liver disease	Decreased hepatic creatine synthesis and cachexia

Glucose

Glucose is freely filtered at the glomerulus and is subsequently reabsorbed in the proximal tubule. Glycosuria signifies that the ability of the renal tubules to reabsorb glucose has been exceeded by an abnormally heavy glucose load and is usually indicative of diabetes mellitus. Glycosuria also may be present in hospitalized patients without diabetes who are receiving intravenous glucose infusions.

ADDITIONAL DIAGNOSTIC TESTS

Urinalysis and Appearance

Gross and microscopic observation of urine and its sediment, along with determination of urinary pH, specific gravity, protein content, and glucose content, is one of the most readily available, inexpensive, and informative laboratory tests. The gross appearance of urine may indicate the presence of bleeding or infection in the genitourinary tract. Microscopic examination of urinary

sediment may reveal casts, bacteria, and various cell forms, supplying diagnostic information in patients with renal disease.

Serum and Urine Electrolytes

pH and Blood Gases. Sodium, potassium, chloride, and bicarbonate concentrations should be determined if impairment in renal function is suspected. The results of these tests usually remain normal until frank renal failure is present, however, and hyperkalemia does not occur until patients are uremic.[5] Measuring urinary sodium or chloride excretion is especially useful when attempting to differentiate between causes of hyponatremia, as seen in volume contraction (whether a decrease in total circulatory volume or a decrease in effective arterial blood volume), versus conditions associated with increased salt loss, such as the syndrome of inappropriate secretion of antidiuretic hormone, salt-losing nephropathy, or adrenal insufficiency.[6] If significant renal disease is present, patients consuming a diet high in animal protein may have metabolic acidosis.

Electrocardiogram. The electrocardiogram (see Chapter 47) reflects the toxic effects of potassium excess more closely than determination of the serum potassium concentration.

Imaging Studies

Computed Tomography Scan of Kidneys. A stone protocol computed tomography (CT) scan of the kidneys, ureter, and bladder has become the study of choice for the detection of kidney stones because of its ability to detect stones of all kinds, including uric acid stones and nonobstructing stones in the ureter. Masses in the kidney can be evaluated using either contrast-enhanced CT or renal ultrasound.[6]

Computed Tomography Angiography. Computed tomography angiography is used for the evaluation of renal artery stenosis and is emerging rapidly as a useful study. Although it is comparable to magnetic resonance angiography as a noninvasive tool, it requires the use of iodinated contrast material, which may cause renal dysfunction in patients with chronic kidney disease.[7]

Magnetic Resonance Imaging with Magnetic Resonance Angiography. The use of magnetic resonance imaging (MRI) with magnetic resonance angiography has revolutionized the evaluation of renovascular disease. The test is highly sensitive, but tends to overestimate the degree of stenosis. Its accuracy in detecting fibromuscular dysplasia causing renal artery stenosis has not been well validated. MRI also can be used to evaluate renal masses. The main advantages of MRI are that it is a noninvasive test and does not require iodinated contrast material.

IMPORTANT PATHOPHYSIOLOGIC MANIFESTATIONS OF CHRONIC RENAL FAILURE (See also Chapter 23)

Hypervolemia

Total-body contents of Na^+ and H_2O are increased in chronic renal failure (CRF),[4] although this increase might not be clinically apparent until the GFR is reduced to very low levels. Weight gain is usually associated with volume expansion and is offset by the concomitant loss of lean body mass. The combination of loop diuretics with metolazone, which acts by inhibiting the Na-Cl cotransporter of the distal convoluted tubule, can overcome diuretic resistance.

TABLE 72-5 METABOLIC ACIDOSIS IN CHRONIC RENAL FAILURE

	$Paco_2$ (mm Hg)	pH	HCO_3^- (mEq/L)	K^+ (mEq/L)
Preoperative	32	7.32	17	5
Intraoperative	40	7.25	18	5.3
Postoperative	44	7.21	19	5.6
	48	7.18	19	5.9

The patient is a 36-year-old man with severe diabetic nephropathy and end-stage renal failure undergoing cadaver renal transplantation. Preoperatively, the patient has a chronic metabolic acidosis (HCO_3^-, 17 mEq/L) with partial respiratory compensation ($Paco_2$, 32 mm Hg; pH 7.32). Potassium is high normal at 5 mEq/L. Intraoperatively, he is given "standard" mechanical minute ventilation, and with "normal" $Paco_2$ (40 mm Hg), the metabolic acidosis is unmasked (pH 7.25), and potassium increases to 5.3 mEq/L. His trachea is extubated at the end of the procedure, but graft function is sluggish, and the metabolic acidosis remains unchanged. With residual opioid-induced narcosis, moderate CO_2 retention occurs ($Paco_2$, 44 mm Hg and 48 mm Hg), pH decreases further to 7.18, and a dangerous degree of hyperkalemia develops (K^+, 5.9 mEq/L).

Acidemia

Although urine can be acidified normally in most patients with CRF, these patients have a reduced ability to produce ammonia. In the early stages, the accompanying organic anions are excreted in urine, and the metabolic acidosis is of the non–anion gap variety. With advanced renal failure, a fairly large "anion gap" can develop (to approximately 20 mmol/L), however, with a reciprocal decrease in plasma HCO_3^- concentration. This acidemia is usually corrected by hemodialysis. Although acidemia is well compensated in moderate CRF, patients can become acidemic and hyperkalemic[8] in the postoperative period (Table 72-5).

Hyperkalemia

The approximate daily filtered load of K^+ is 700 mmol. Most of this filtered load is reabsorbed in tubule segments, and most of the K^+ excreted in the final urine reflects events governing K^+ handling at the level of the cortical collecting tubule and beyond. K^+ excretion in the gastrointestinal tract is augmented in patients with CRF. Hyperkalemia may be precipitated, however, in numerous clinical situations, including protein catabolism, hemolysis, hemorrhage, transfusion of stored red blood cells (see Chapter 61), metabolic acidosis, and exposure to various medications that inhibit K^+ entry into cells or K^+ secretion in the distal nephron.

Cardiac and Pulmonary Manifestations

Hypertension is a common complication of CRF and ESRD (see Chapter 39). Because hypervolemia is the major cause of hypertension in uremia, normotension

is usually restored by the use of diuretics in predialysis patients or by dialysis in ESRD patients. Despite therapy, patients continue to be hypertensive because of the vasodilators required for the management of overwhelming hyperreninemia. Patients generally have left ventricular hypertrophy and accelerated atherosclerosis (disordered glucose and fat metabolism). Pericarditis can be observed in patients with inadequate dialysis versus patients with CRF who undergo regular dialysis.

A unique form of pulmonary congestion and edema can occur even in the absence of excessive intravascular volume and is associated with normal or mildly increased intracardiac and pulmonary capillary wedge pressure. This entity, characterized radiologically by peripheral vascular congestion giving rise to a "butterfly wing" distribution, is due to increased permeability of alveolar capillary membranes. This "low-pressure" pulmonary edema and the cardiopulmonary abnormalities associated with excessive intravascular volume usually respond promptly to vigorous dialysis.[9]

Hematologic Manifestations

Chronic renal failure usually causes a normochromic, normocytic anemia. Anemia is generally observed when the GFR decreases to less than 30 mL/min and is due to insufficient production of erythropoietin by the diseased kidneys. Other factors are iron deficiency, either related to or independent of blood loss from repeated laboratory testing, blood retention in the dialyzer, or gastrointestinal bleeding.[10] Treatment of anemia with iron, darbepoetin alfa, and human recombinant erythropoietin (Table 72-6) restores a normal hematocrit and avoids repetitive red blood cell transfusions, reduces the requirement for hospitalization, and decreases cardiovascular mortality by about 30%.[11]

Prolongation of the bleeding time because of decreased activity of platelet factor 3, abnormal platelet aggregation and adhesiveness, and impaired prothrombin consumption contributes to the clotting defects. The abnormality in platelet factor 3 correlates can be corrected with dialysis, although prolongation of the bleeding time can be observed in well-dialyzed patients. Abnormal bleeding times and coagulopathy in patients with renal failure may be managed with desmopressin, cryoprecipitate, conjugated estrogens, blood transfusions, and erythropoietin use.[10]

TABLE 72-6 MANAGEMENT GUIDELINES FOR CORRECTION OF ANEMIA OF CHRONIC RENAL DISEASE

Erythropoietin	
Starting dosage	50-150 U/kg/wk IV or SC (once, twice, or three times per week)
Target hemoglobin	11-12 g/dL
Optimal rate of correction	Increase hemoglobin by 1-2 g/dL over 4 wk
Darbepoetin alfa	
Starting dosage	0.45 mg/kg administered as single IV or SC injection once weekly 0.75 mg/kg administered as a single IV or SC injection once every 2 wk
Target hemoglobin	12 g/dL
Optimal rate of correction	Increase hemoglobin by 1-2 g/dL over 4-wk period
Iron	
Monitor iron stores by TSat and serum ferritin	
If patient is iron-deficient (TSat <20%; serum ferritin <100 g/L), administer iron, 50-100 mg IV twice per week for 5 wk; if iron indices are still low, repeat the same course	
If iron indices are normal but hemoglobin is still inadequate, administer IV iron as outlined above; monitor hemoglobin, TSat, and ferritin.	
Withhold iron therapy when TSat >50% or ferritin >800 ng/mL (>800 g/L)	

IV, Intravenous; *SC,* subcutaneous; *TSat,* percent transferrin saturation.

EFFECTS OF DRUGS IN PATIENTS WITH REDUCED RENAL FUNCTION

Most anesthetic drugs are weak electrolytes and are lipid soluble in the un-ionized state; they are extensively reabsorbed by renal tubular cells (see Chapters 26 and 30). Termination of their action does not depend on renal excretion; redistribution and metabolism produce this effect. After biotransformation, these drugs are excreted in urine as water-soluble, polar forms of the parent compound. They are usually pharmacologically inactive, and their retention is harmless.[10] Most drugs with prominent central and peripheral nervous system activity in this category include most narcotics, barbiturates, phenothiazines, butyrophenone derivatives, benzodiazepines, ketamine, and local anesthetics.[12] Several drugs are lipid insoluble or are highly ionized in the physiologic pH range, however, and are eliminated unchanged in urine. Their duration of action may be extended in patients with impaired renal function. Drugs in this category include muscle relaxants, cholinesterase inhibitors, thiazide diuretics, digoxin, and many antibiotics (Table 72-7).[13]

Opioids

Renal failure has implications of major clinical importance with respect to morphine and meperidine (see Chapter 31). For the fentanyl congeners, the clinical importance of renal failure is less marked.[14]

Morphine is an opioid with active metabolites that depend on renal clearance mechanisms for elimination. Morphine is principally metabolized by conjugation in the liver, and the water-soluble glucuronides (morphine-3-glucuronide and morphine-6-glucuronide) are excreted via the kidney. The kidney also plays a role in the conjugation of morphine, accounting for nearly 40% of its metabolism.[15] Patients with renal failure can develop high levels of morphine-6-glucuronide and life-threatening respiratory depression.[14] In view of these changes induced by renal failure, morphine might not be a good choice in patients with severely altered renal clearance mechanisms.

The clinical pharmacology of meperidine also is significantly altered by renal failure. Normeperidine, the chief metabolite, has analgesic and central nervous system (CNS) excitatory effects.[16] Because the active metabolites

TABLE 72-7 DRUGS USED OR ENCOUNTERED IN ANESTHESIA PRACTICE THAT SIGNIFICANTLY DEPEND ON RENAL ELIMINATION

Completely Dependent	Partially Dependent
Digoxin, inotropes (used frequently; monitoring of blood levels indicated in chronic renal failure)	Intravenous anesthetics—barbiturates
Others—aminoglycosides, vancomycin, cephalosporins, and penicillins	Muscle relaxants—pancuronium
	Anticholinergics—atropine, glycopyrrolate
	Cholinesterase inhibitors—neostigmine, edrophonium
	Others—milrinone, hydralazine, cycloserine, sulfonamides, and chlorpropamide

are subject to renal excretion, this potential CNS toxicity secondary to normeperidine accumulation is especially a concern in patients in renal failure.

The clinical pharmacology of the fentanyl congeners is not grossly altered by renal failure, although a decrease in plasma protein binding potentially can alter the free fraction of the fentanyl class of opioids.[14] Fentanyl clearance is not altered by renal failure. As with fentanyl, sufentanil pharmacokinetics are not altered in any consistent fashion by renal disease, although greater variability exists in the clearance and elimination half-life of sufentanil when patients have impaired renal function.[17] An increased clinical effect is likely with alfentanil in renal failure because of a decreased initial volume of distribution and an increased free fraction of alfentanil.[18] No delay in recovery after alfentanil administration should be expected, however. Neither the pharmacokinetics nor the pharmacodynamics of remifentanil are altered by impaired renal function.[18]

Hydromorphone,[19] as the parent drug, does not substantially accumulate in hemodialysis patients. Conversely, an active metabolite, hydromorphone-3-glucuronide, quickly accumulates between dialysis treatments, but seems to be effectively removed during hemodialysis. With careful monitoring, hydromorphone can be used safely in patients who require dialysis. It should be used with caution, however, in patients with a GFR less than 30 mL/min and who have yet to start dialysis or who have withdrawn from dialysis.

Inhaled Anesthetics

All inhaled anesthetics (see Chapters 25, and 26) are biotransformed to some extent, with the nonvolatile products of metabolism eliminated almost entirely by the kidney.[20] Reversal of the CNS effects of inhaled anesthetics depends on pulmonary excretion; therefore, impaired kidney function would not alter the response to these anesthetics. From the viewpoint of selecting an anesthetic that would not be harmful to patients with mild or moderate impairment of renal function, all the modern potent anesthetics are suitable. Enflurane is biotransformed to inorganic fluoride, but levels after 2 to 4 hours of anesthesia average only 19 μM in patients with mild to moderate kidney disease, significantly lower than the nephrotoxic threshold of 50 μM, which is frequently reported after the administration of methoxyflurane.[21,22] This level of fluoride should not cause further renal impairment. Fluoride levels after isoflurane increase by only 3 to 5 μM,[23] and by only 1 to 2 μM after halothane[22]; therefore, these anesthetics have no nephrotoxic potential.

Desflurane and sevoflurane, two newer inhaled anesthetics, are remarkably different in their molecular stability and biotransformation. Desflurane is highly stable and resists degradation by soda lime[24] and the liver. The mean inorganic fluoride concentration after 1 minimum alveolar concentration (MAC)-hour exposure to desflurane was less than 1 μM.[25] The safety of desflurane in renal failure patients has been confirmed.[26] In addition, more sensitive indices of renal function—urine retinol-binding protein and β-*N*-acetylglucosaminidase—showed no evidence of renal damage. Prolonged exposure to desflurane (7 MAC-hours) has been associated with normal renal function.[26]

Sevoflurane is not very stable. Soda lime causes it to decompose,[27] and it is biotransformed by the liver. Plasma inorganic fluoride concentrations approaching nephrotoxic levels (50 μmol/L)[28] have been reported after prolonged inhalation of sevoflurane. No evidence of gross changes in renal function was found in humans, however.[29] In one study, sevoflurane was used at low flow (1 L/min), and there was no relationship to compound A and renal function.

Inhaled anesthetics cause a transient reversible depression in renal function. GFR, renal blood flow, urine output, and urinary excretion of sodium are decreased (Table 72-8). Probable mechanisms include reduced renal blood flow, loss of renal autoregulation, neurohumoral factors (e.g., antidiuretic hormone, vasopressin, renin), and neuroendocrine responses. Although most inhaled anesthetics have been shown to reduce GFR and urinary excretion of sodium, their effects on renal blood flow have yielded conflicting results, which can be explained by differences in experimental methodology. Data suggest that renal blood flow is maintained with halothane, isoflurane, and desflurane,[30,31] but it is decreased with enflurane and sevoflurane.[32,33]

Intravenous Anesthetics

Reversal of CNS effects after the administration of ultrashort-acting barbiturates such as thiopental and methohexital occurs as a result of redistribution, and hepatic metabolism is the sole route of elimination of these drugs (see Chapter 30). Thiopental is 75% to 85% bound to albumin,[34] the concentration of which may be markedly reduced in uremia. Because it is a highly bound drug, reduced binding permits a greater proportion of an administered dose of thiopental to reach receptor sites. In addition, thiopental is a weak acid, with its pK_a in the

TABLE 72-8 EFFECTS OF VARIOUS ANESTHETICS ON RENAL FUNCTION

	RBF	GFR	Urine Output	Urine Solutes
General anesthesia	↓	↓	↓	↓
Intravenous anesthetics				
Thiopental	↔	↓	↓	↓
Midazolam	↔	↔	↓	↔
Fentanyl/droperidol	↔	↔	↓	↓
Fentanyl (high dose)	↔	↔	↔	↔
Inhaled anesthetics				
Halothane	↔	↓	↓	↓
Enflurane	↓	↓	↓	↓
Isoflurane	↔	↓	↓	↓
PEEP	↓	↓	↓	o
Regional anesthesia				
Epidural (with epinephrine)	↓	↓	↓	o
Epidural (without epinephrine)	↔	↔	↔	o
Spinal	↔	↔	↔	o

From Hemmings HC Jr: Anesthetics, adjuvant drugs and the kidney. In Malhotra V, editor: Anesthesia for renal and genitourinary surgery, *New York, 1996, McGraw-Hill, p 20.*

GFR, Glomerular filtration rate; *PEEP,* positive end-expiratory pressure; *RBF,* renal blood flow; ↔, no significant change; o, significant data; ↓, decrease.

Although conflicting reports of anesthetic effects on RBF have been reported because of different investigative methods, the current literature seems to support these data.

physiologic range; acidosis results in more un-ionized, nonbound, active thiopental. In combination, these changes produce an increase in the free fraction of thiopental from 15% in normal patients to 28% in patients with CRF.[35] With thiopental metabolism essentially unchanged in renal disease, the dose to produce and maintain anesthesia should be reduced.[35] The same considerations are true for methohexital, although metabolism plays a slightly greater part in the termination of its therapeutic effect.[36]

Propofol does not adversely affect renal function as reflected by measurements of creatinine concentration. Prolonged infusions of propofol may result in the excretion of green urine because of the presence of phenols in the urine. This discoloration does not affect renal function. Urate excretion is increased after the administration of propofol and is usually manifested as cloudy urine when urate crystallizes under conditions of low pH and temperature.[37]

There are no reports of the disposition of narcotics and tranquilizers when used in large dosage for anesthesia in uremic patients. These drugs are extensively metabolized before excretion; therefore, when combined with 30% to 50% nitrous oxide, they should not have a particularly prolonged effect. The benzodiazepines, especially diazepam,[13] have a long half-life and tend to accumulate. Because of the greater ease of reversibility of the potent inhaled anesthetics versus intravenous drugs, inhaled anesthetics may offer some advantages for the induction of general anesthesia in uremic patients.

Muscle Relaxants and Their Antagonists (See Chapters 34 and 35)

Succinylcholine has been used without difficulty in patients with decreased or absent renal function. Its metabolism is catalyzed by pseudocholinesterase to yield the nontoxic end products succinic acid and choline. The metabolic precursor of these two compounds, succinylmonocholine, is excreted by the kidneys. Large doses of succinylcholine, which might result from prolonged infusion, should be avoided in patients with renal failure. Although pseudocholinesterase levels are reduced in uremia,[38] these reductions are insufficient and cause a prolonged block. Hemodialysis has been reported to have no effect on cholinesterase levels.[39]

Administration of succinylcholine causes a rapid, transient increase of 0.5 mEq/L in the serum potassium concentration. In traumatized, burned, or neurologically injured patients, the increase may be 5 to 7 mEq/L, probably as a consequence of denervation supersensitivity of the muscle membrane to succinylcholine and to acetylcholine,[40] which can result in cardiovascular collapse. An exaggerated increase in serum potassium could be particularly dangerous in uremic patients with hyperkalemia; therefore, the use of succinylcholine is inadvisable, unless the patient has undergone dialysis within 24 hours before surgery. If the patient has recently undergone dialysis or has normal serum potassium, the use of succinylcholine is reportedly safe.

The disposition of nondepolarizing muscle relaxants has been well studied. Renal failure influences the pharmacology of nondepolarizing muscle relaxants by producing either decreased elimination of the drug or its metabolites by the kidney or decreased activity of enzymes that metabolize the drug, such as in the case of mivacurium (Table 72-9). Consequently, the duration of action of muscle relaxants may be prolonged in patients with renal failure.

Approximately 40% to 50% of pancuronium is excreted in urine. A portion of this excretion occurs after biotransformation to the less active metabolite 3-hydroxypancuronium.[41] Pancuronium has a prolonged terminal elimination half-life in patients with reduced renal function (see Table 72-9)[42]; therefore, it should be administered cautiously, particularly when several doses are required.

Two nondepolarizing muscle relaxants, atracurium and vecuronium, were introduced into clinical practice during the early 1980s. Atracurium is degraded by enzymatic ester hydrolysis and nonenzymatic alkaline degradation (Hofmann elimination) to inactive products that are not dependent on renal excretion for termination of action.[43] Predictably, their terminal elimination half-life and indices of neuromuscular blockade (onset, duration, and recovery) are the same in patients with normal and absent renal function.[44]

Approximately 30% of a dose of vecuronium is eliminated by the kidneys. Lynam and colleagues[45] found that the duration of neuromuscular blockade after the administration of vecuronium was longer in patients with renal failure than in patients with normal renal function (99 versus 54 minutes) because of a longer elimination half-life (83 versus 52 minutes) and lower plasma clearance

TABLE 72-9 PHARMACOKINETICS DATA FOR NONDEPOLARIZING MUSCLE RELAXANTS IN NORMAL AND ANEPHRIC PATIENTS

Drug	Patients Studied	Elimination Half-life (hr)	Clearance (mL/kg/min)	Volume of Distribution (L/kg)
Vecuronium	Normal	0.9	5.3	0.20
	Anephric	1.4	3.1	0.24
Atracurium	Normal	0.3	6.1	0.18
	Anephric	0.4	6.7	0.22
Pancuronium	Normal	1.7	1	0.14
	Anephric	8.2	0.3	0.14
Rocuronium	Normal	0.71	2.9	0.207
	Anephric	0.97	2.9	0.264
Cisatracurium	Normal	—	5.2	0.031
	Anephric	—	—	—
Mivacurium	Normal	0.03	106	0.278
	Anephric	0.06	80	0.478

TABLE 72-10 PHARMACOKINETICS DATA FOR CHOLINESTERASE INHIBITORS IN NORMAL, ANEPHRIC, AND RENAL TRANSPLANT PATIENTS

Drug	Patients Studied	Elimination Half-life (hr)	Clearance (mL/kg/min)	Volume of Distribution (L/kg)
Neostigmine	Normal	1.3	8.4	0.7
	Anephric	3*	3.9*	0.8
	Renal transplant	1.7	9.4	1.1
Pyridostigmine	Normal	1.9	8.6	1.1
	Anephric	6.3*	2.1*	1
	Renal transplant	1.4	10.8	1
Edrophonium	Normal	1.9	8.2	0.9
	Anephric	3.6*	2.7*	0.7
	Renal transplant	1.4	9.9	0.9

*$P < .05$ versus normal.

(3.1 mL/kg/min versus 5.3 mL/kg/min). In a related area, an interaction between the solvent of cyclosporine (Kolliphor EL) with atracurium and vecuronium has been reported, with the action of these muscle relaxants potentiated in cats,[46] but it is unknown whether such potentiation also occurs in human renal transplant recipients.

Cisatracurium is the single *cis* isomer of atracurium. Organ-independent mechanisms (Hofmann elimination) account for 77% of the total clearance of cisatracurium. Because renal excretion accounts for only 16% of the elimination of cisatracurium, renal failure should have little effect on its duration of action.[44]

The short-acting drug mivacurium is metabolized by plasma pseudocholinesterase. Its effect has been shown to be lengthened by 10 to 15 minutes in patients with ESRD, most likely because of a decrease in plasma cholinesterase activity in these patients associated with uremia or hemodialysis[47,48] and a decrease in the mivacurium requirement by infusion in anephric patients.[48]

The elimination half-life of rocuronium is increased in renal failure because of an increase in the volume of distribution with no change in clearance. This explanation might account for a longer duration of action in anephric patients, although its clinical significance is uncertain.[49]

Pharmacokinetics data for the cholinesterase inhibitors neostigmine, pyridostigmine, and edrophonium for normal, anephric, and renal transplant patients are presented in Table 72-10; there are no major differences among the three drugs.[50-52] Renal excretion is of major importance for the elimination of all three reversal drugs, with approximately 50% of neostigmine and 70% of pyridostigmine and edrophonium excreted in urine. Excretion of all the cholinesterase inhibitors is delayed in patients with impaired renal function to the same or perhaps to a slightly greater extent than is elimination of muscle relaxants. Reappearance of neuromuscular blockade after pharmacologic reversal of neuromuscular blockade in a patient with renal failure is, in most cases, due to some other cause. Table 72-10 contains data indicating that the pharmacokinetics of all the cholinesterase inhibitors is similar in healthy patients and in patients with well-functioning newly transplanted kidneys.

Vasopressors and Antihypertensive Drugs (See Chapter 16)

Patients with severe renal disease are frequently given antihypertensive and other cardiovascular medications. More than 90% of the thiazides[53] and 70% of furosemide[54] are excreted by the kidneys and they have prolonged durations of action in patients with abnormal or absent renal function. Propranolol is almost completely metabolized in the liver, and esmolol is biodegraded by esterases in the cytosol of red blood cells; therefore, their effects are not prolonged in patients with abnormal or absent renal function.[55] The calcium channel–blocking agents nifedipine, verapamil, and diltiazem are extensively metabolized in the liver to pharmacologically inert products; they can be administered in usual doses to patients

with renal insufficiency.[56] Nitroglycerin is useful because it is metabolized rapidly, with less than 1% excreted unchanged in urine.[57]

Sodium nitroprusside has had a resurgence in use since its initial introduction as a hypotensive drug in the 1920s. Cyanide is an intermediate in the metabolism of sodium nitroprusside, with thiocyanate being the final metabolic product. Although cyanide toxicity as a complication of sodium nitroprusside therapy is well described,[58] it is less well appreciated that thiocyanate is also potentially toxic. The half-life of thiocyanate is normally more than 4 days, and it is prolonged in patients with renal failure.[58] Hypoxia, nausea, tinnitus, muscle spasm, disorientation, and psychosis have been reported when thiocyanate levels are more than 10 mg/100 mL. Sodium nitroprusside is less desirable for prolonged administration than either trimethaphan or nitroglycerin.

Hydralazine is slower acting than the other three drugs discussed previously. Its action is terminated by hydroxylation and subsequent glucuronidation in the liver, with approximately 15% excreted unchanged in urine.[59] The elimination half-life of hydralazine is prolonged in patients with uremia; therefore, caution is required when it is administered.[60] After a single intravenous dose of 0.5 mg/kg of labetalol, the volume of distribution, clearance, and elimination half-life were similar in patients with ESRD and in healthy volunteers.[61] Esmolol is independent of renal function because it is metabolized by red blood cell cytosol esterases.[62]

If administration of a vasopressor is necessary, a direct β-adrenergic–stimulating drug such as phenylephrine would be effective. This type of vasopressor causes the greatest interference with renal circulation. Although β-adrenergic–stimulating drugs such as isoproterenol maintain heart and brain perfusion without renal vasoconstriction, they also increase myocardial irritability. When possible, it is best to substitute simple measures such as blood volume expansion for drug therapy. If these measures are inadequate, β-adrenergic–stimulating drugs or dopamine should be used.

ACUTE KIDNEY INJURY AND HEMODIALYSIS

Until recently the definition of acute kidney injury (AKI) was not standardized.[63] Authors have used terms such as renal insufficiency, renal dysfunction, acute renal failure (ARF), and renal failure requiring dialysis somewhat interchangeably. Parameters used to define these terms include (Fig. 72-5) absolute and percentage changes in creatinine values, absolute and percentage changes in estimated GFRs, and reduction in output.[64] The incidence of AKI depends on the type of surgery and preexisting kidney function (Box 72-2 and Table 72-11).

In cardiac surgery, incidence is between 7.7% and 11.4%[65] when defined broadly, whereas frequency of AKI requiring dialysis is generally lower, ranging between less than 1% and 5%. In gastric bypass surgery, the incidence is 8.5%[66] and after aortic aneurysm surgery, it is around 15% to 16%.[67] Similarly, liver transplant is also associated with a high frequency of AKI. It is reported that 48% to 94%[68] of patients suffer from acute worsening renal function after liver transplantation.

In noncardiac surgery, several independent risk factors for AKI have been identified by Kheterpal and co-workers[69]: age, emergent surgery, liver disease, body mass index, high-risk surgery, peripheral vascular disease, and chronic obstructive pulmonary disease (requiring chronic bronchodilator therapy). Based on incremental score, the frequency of renal failure increased, ranging between 0.3% and 4.5%, respectively.

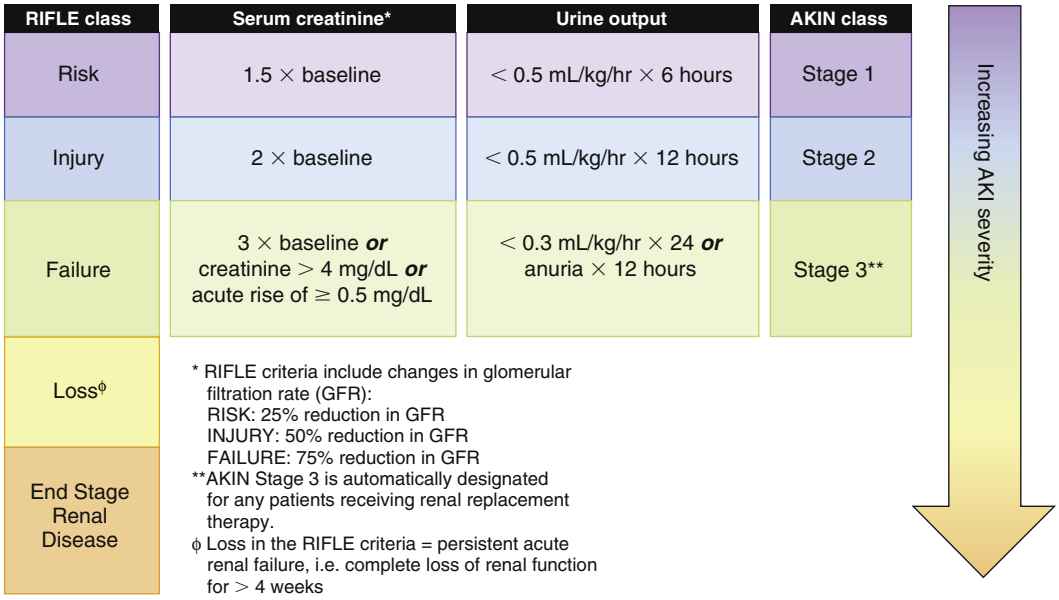


Figure 72-5. Parameters used to define acute kidney injury. *(From Mehta RL, Kellum JA , Shah SV, et al: Acute Kidney Injury Network: Report of an initiative to improve outcomes in kidney injury,* Crit Care *11:R31, 2007.)*

PERIOPERATIVE MANAGEMENT OF PATIENTS WITH ACUTE KIDNEY INJURY

Although many factors have been shown to contribute to AKI in surgical patients, there are few interventions demonstrated to prevent AKI. Of these interventions, there is no obvious cure for perioperative renal injury. Although a complete review of such interventions is beyond the scope of this chapter, some deserve mention.[64]

Dialysis

Dialysis may not decrease perioperative AKI; however, it can treat the associated acidosis, hyperkalemia, and hypervolemia. For certain surgeries, such as aortic, dialysis actually reduces 30-day mortality rates in patients who develop loss of renal function.[70] As many as 75% of these survivors regain kidney function and become independent of dialysis.

BOX 72-2 ***Risk Factors for Development of Postoperative Acute Kidney Injury***

Preoperative Factors

- Preoperative renal dysfunction
- Increasing age
- Heart disease (ischemic or congestive)
- Smoking
- Diabetes mellitus
- ASA PS 4 or 5

Intraoperative Factors

- Emergency surgery or intraperitoneal, intrathoracic, suprainguinal vascular surgeries
- Erythrocyte transfusion
- Inotrope use
- Aortic cross-clamp time
- CPB: furosemide use, urine output, need for a new pump run

Postoperative Factors

- Erythrocyte transfusion
- Vasoconstrictor use
- Diuretic use
- Antiarrhythmic drug use

Data from Abelha FJ, Botelho M, Fernandes V, et al: Determinants of postoperative acute kidney injury, Crit Care *13:R19, 2009; and Parolari A, Pesce LL, Pacini D, et al: Risk factors for perioperative acute kidney injury after adult cardiac surgery: role of perioperative management,* Ann Thorac Surg *93:584-591, 2012.*

ASA PS, American Society of Anesthesiologists Physical Status classification; *CPB,* cardiopulmonary bypass.

Nondialytic Management

Optimal therapy for renal dysfunction is not clear as to whether such as ACE-I therapy or diuretic therapy prevents decline in kidney function around the time of surgery.[65]

Normal hemodynamic variables probably should be preserved during the operative period in an attempt to prevent AKI. Scavengers of oxygen free radicals such as mannitol and *N*-acetylcysteine have been given to prevent ischemia-reperfusion injury. Recent studies, however, have failed to show benefit in reduction of AKI in cardiac surgery patients. For years, mannitol was administered before aortic clamping, especially suprarenal clamping, during abdominal aortic aneurysm surgery. It is not clear whether this approach reduces the incidence of renal failure in this population of patients.[71]

Both dopamine[72] and atrial natriuretic peptide initially showed promise in the prevention of AKI because of their vasoactive effects leading to increased renal blood flow. Studies have shown neither dopamine nor atrial natriuretic peptide to be associated with improved mortality. Likewise, fenoldopam, a selective renal dopamine receptor agonist, initially showed potential renoprotective benefit. In large studies, fenoldopam was not beneficial in prevention of AKI.[73]

RENAL AND GENITOURINARY PROCEDURES

TRANSURETHRAL RESECTION OF THE PROSTATE

Pathophysiology of Prostate Hypertrophy

The prostatic gland consists of four closely integrated zones—the anterior, peripheral, central, and preprostatic zones. Each zone consists of secretory, smooth muscle, and fibrotic tissue. All four zones are enclosed in one capsule. The gland is rich in blood supply. Arteries and veins penetrate the prostatic capsule and branch inside the gland. The venous sinuses adjacent to the capsule are particularly large. Nodules begin to develop by the fourth decade of life in the preprostatic zone and form middle, lateral, and posterior lobes. The middle and posterior lobes are most often associated with symptoms of urinary tract obstruction.[74]

TABLE 72-11 COMMON CAUSES OF POSTOPERATIVE DECREASED URINE OUTPUT AND ACUTE KIDNEY INJURY

	Site of Defect		
	Prerenal	**Renal**	**Postrenal**
Differential Diagnoses	Hypotension Absolute Relative Hypovolemia Absolute Relative (e.g., IAH)	Acute tubular necrosis Ischemia-reperfusion Radiocontrast Acute interstitial nephritis	Urinary catheter obstruction Catheter kinking Debris Prostatic hypertrophy Bladder spasm Urinary retention

From Chenitz KB, Lane-Fall MB: Postoperative oliguria, Anesth Clin *2012;513-526.*

Surgical Procedures

Transurethral resection of the prostate (TURP) is performed by inserting a resectoscope through the urethra and resecting prostatic tissue with an electrically powered cutting-coagulating metal loop or using laser-vaporization energy. This can be accomplished with either a monopolar TURP (M-TURP) or bipolar TURP (B-TURP) technique. Laser energy for TURP has also been used for many years. With each technique, as much prostatic tissue as possible is resected, but the prostatic capsule is usually preserved. If the capsule is violated, large amounts of irrigation solution can be absorbed into the circulation via the periprostatic, retroperitoneal, or peritoneal space.

Bleeding during TURP is common, but usually controllable; however, when large venous sinuses are opened, hemostasis becomes difficult. If bleeding becomes uncontrollable, the procedure should be terminated as quickly as possible, and a Foley catheter should be passed into the bladder and traction applied to it. The catheter's inflated balloon exerts lateral pressure on the prostatic bed and reduces bleeding. Bleeding requiring transfusion occurs in approximately 2.5% of TURP procedures.[75]

Irrigation Solutions

Ideally, an irrigation solution for TURP should be isotonic, electrically inert, nontoxic, transparent, easy to sterilize, and inexpensive. Such a solution does not exist. Distilled water is electrically inert and inexpensive and has excellent optical properties, but it is extremely hypotonic. When absorbed into the circulation in large amounts, plain water causes hemolysis, shock, and renal failure.

Numerous nearly isotonic irrigation solutions are available. Commonly used solutions are glycine 1.2% and 1.5%, mannitol 3% to 5%, glucose 2.5% to 4%, sorbitol 3.5%, Cytal (a mixture of sorbitol 2.7%, and mannitol 0.54%), and urea 1% (Table 72-12). These solutions are purposely moderately hypotonic to preserve their transparency.

Although these irrigation solutions cause no significant hemolysis, excessive absorption of them can lead to other complications, such as pulmonary edema and hyponatremia. In addition, the solutes can have adverse effects. Glycine can cause cardiac and retinal toxic effects, mannitol rapidly expands the blood volume and can cause pulmonary edema in cardiac patients, and glucose can cause severe hyperglycemia in diabetic patients. These complications are discussed in detail later.

TABLE 72-12 OSMOLALITY OF IRRIGATION SOLUTIONS USED FOR TRANSURETHRAL RESECTION OF THE PROSTATE

Solution	Osmolality (mOsm/kg)
Glycine, 1.2%	175
Glycine, 1.5%	220
Sorbitol, 3.5%	165
Mannitol, 5%	275
Cytal (see text)	178
Glucose, 2.5%	139
Urea, 1%	167

Replacement of distilled water with nearly isosmotic solutions has eliminated hemolysis and its sequelae as a complication of M-TURP. The incidence of severe CNS problems associated with extreme hyponatremia, such as convulsions and coma, has been reduced. The other major problem associated with the absorption of large volumes of irrigating solution, overhydration, still remains, however. With B-TURP and laser-TURP (L-TURP) techniques normal saline as the bladder irrigating solution can be used which significantly helps to minimize or eliminate TURP syndrome.

Anesthetic Techniques

Previously, spinal anesthesia was the most frequently used anesthetic for TURP in the United States, and it is believed to be the technique of choice when traditional M-TURP is performed. Spinal anesthesia provides adequate anesthesia for the patient with good relaxation of the pelvic floor and the perineum for the surgeon. The signs and symptoms of water intoxication and fluid overload can be recognized early because the patient is awake. Accidental bladder perforation also is recognized easily if the spinal level is limited to T10 because the patient would experience abdominal or shoulder pain. Satisfactory regional anesthesia for TURP involves achieving an anesthetic block level that interrupts sensory transmission from the prostate and bladder neck. In addition, the uncomfortable sensation of bladder distention must be considered.[76,77]

As explained earlier, the visceral pain sensation from the prostate and bladder neck is transmitted by afferent parasympathetic nerve fibers derived mostly from the second and third sacral roots traveling with the pelvic splanchnic nerves. Bladder sensation is supplied by sympathetic nerves of the hypogastric plexus, derived from nerve roots extending inferiorly from T11 to L2. Regional anesthesia resulting in a sensory level to T10 is required to eliminate the discomfort caused by bladder distention and other aspects of this procedure; however, slightly lower sensory levels often suffice for smaller lesions. In one study in which bladder pressure was monitored and kept low, anesthetic levels to T12 or L1 were adequate, but midlumbar blocks to L3 were not.[78] Sensory levels above T9 should not be sought because the capsular sign (i.e., pain on perforation of the prostatic capsule) would not be present should perforation occur.

Subarachnoid anesthesia is generally preferred over continuous epidural anesthesia for the following reasons. It is technically easier to perform in elderly patients, and the duration of surgery is generally not long. The incomplete block of sacral nerve roots that occasionally occurs with the extradural technique is usually avoided with subarachnoid anesthesia.

Caudal and sacral blockade also has been used effectively for prostate surgery, and bladder distention is avoided with the use of continuous irrigation. Caudal anesthesia has been used effectively in high-risk patients undergoing laser prostatectomy.[79] Hemodynamic stability is the main advantage with this technique. Local infiltration of the perineum and the prostatic fossa also has been advocated by some anesthesiologists for limited TURP procedures, although the operative analgesia afforded

by local infiltration is not comparable in quality to spinal anesthesia. General anesthesia may be necessary in patients who require ventilatory or hemodynamic support, have a contraindication to regional anesthesia, or refuse regional anesthesia.

Advantages of Regional Anesthesia over General Anesthesia

Regional anesthesia offers several advantages over general anesthesia for TURP (see Chapter 56). The incidence of deep vein thrombosis is decreased, and the amount of operative blood loss is reduced with regional anesthesia compared with general anesthesia. The reduction in operative blood loss when regional rather than general anesthesia is used has been shown to be the case in other pelvic procedures in addition to TURP, such as cystectomy and major vaginal surgery.[80] The decrease in systemic blood pressure secondary to the sympathetic blockade produced by the regional technique was determined not to be the only factor in reducing blood loss. Good evidence indicates that peripheral venous pressure and central venous pressure decrease during regional anesthesia and spontaneous ventilation. It is postulated that this decrease in peripheral venous pressure might result in reduced blood loss during prostatic and other surgery.

Additional factors influencing blood loss during TURP are the vascularity and size of the gland and the duration of surgery. An increase in fibrinolysis during prostate resection as a result of the release of urokinase from prostate tissue also factors into the blood loss that occurs. Other factors that affect blood loss during TURP include the size of the gland, the duration of the procedure, the number of sinuses opened during resection, the presence of infection, and prostate inflammation from repeated or recent catheterizations. These factors make it difficult to compare studies evaluating blood loss during TURP or to arrive at conclusive findings based on meta-analysis.[75,77]

Patients undergoing prostatectomy are prone to deep vein thrombosis for many reasons, including advanced age and the presence of malignancy, cardiac disease, varicose veins, and obesity. In this case, the increased blood flow resulting from the sympathetic blockade of regional anesthesia may play a role in reducing deep vein thrombosis formation.[81] Regional anesthesia decreases the hypercoagulable tendency in the postoperative period and helps maintain normal coagulation and platelet function; these benefits are believed to be due to modulation of the neuroendocrine response to tissue injury. Homeostasis of the neuroendocrine system and the immune response are better preserved after regional anesthesia than after general anesthesia.[81]

TURP is associated with a particular set of complications with anesthetic implications. These problems must be considered, along with the usual considerations, such as the general health of the patient, the length of the procedure, and patient and surgeon preferences, when choosing an anesthetic technique.

The use of regional anesthesia for TURP allows monitoring the patient's mental status intraoperatively. Excessive vascular absorption of a hypoosmolar bladder irrigating fluid during the procedure produces numerous problems with cardiovascular and neurologic implications. A change in the patient's mental status provides an early indication that excessive absorption of irrigating fluid has occurred. These changes are described more fully in the next section.

Visual disturbances, such as blurred vision and transient blindness, have been reported in association with TURP (see Chapter 100). The biotransformation of absorbed glycine to ammonia has been implicated in these and other CNS abnormalities. Another potential complication during TURP is bladder perforation secondary to overdistention with irrigation fluid or contact of the bladder wall with the surgeon's resectoscope. Conscious patients might experience symptoms related to perforation well before it becomes apparent to the surgeon, alerting the operating team early on. Signs and symptoms of bladder perforation include bradycardia, hypotension, restlessness, diaphoresis, nausea, abdominal pain, dyspnea, shoulder pain, and hiccups. Extraperitoneal perforation may be manifested as pain in the periumbilical, inguinal, or suprapubic area. Intraperitoneal bladder perforation, a less frequent event, may cause symptoms related to diaphragmatic irritation (i.e., pain referred to the upper part of the abdomen, precordial area, shoulder region, or neck).[81]

Regional anesthesia for TURP offers some advantages over general anesthesia. Although laboratory monitoring of electrolytes is useful intraoperatively, a change in mental status in a conscious patient provides an early indication of electrolyte disturbances. Bladder perforation is recognized earlier in a conscious or lightly sedated patient, as noted previously.

Sensory levels above T9 are undesirable because pain caused by perforation of the prostatic capsule (capsular sign) would not be apparent to the patient if this complication occurs. Another benefit of regional anesthesia for TURP is a decreased requirement for analgesics in the immediate postoperative period compared with general anesthesia.[82]

Morbidity and Mortality after Transurethral Resection of the Prostate

Although spinal anesthesia offers certain distinct advantages over general anesthesia for TURP surgery, mortality and many markers of patient outcome have been similar for both groups. What constitutes the safest anesthetic for prostatectomies was debated in 1924, with proponents of regional anesthesia gaining ground quickly thereafter.[83] The 30-day mortality rate associated with M-TURP is reported to be 0.2% to 0.8%.[77] Mortality rates are similar in patients receiving regional anesthesia or general anesthesia.[84] With mortality rates as low as 0.2%, however, many more patients need to be studied than previously examined in any of the studies to draw a meaningful and statistically significant conclusion.[76] The postoperative morbidity rate in one study was 18%.[77] Increased morbidity was found in patients with resections exceeding 90 minutes, gland size larger than 45 g, acute urinary retention, and age older than 80 years.[77] Ashton and coworkers[85] studied 250 men undergoing TURP and observed one postoperative myocardial infarction (0.4%) resulting in one death. The incidence of postoperative complications, including myocardial infarction, pulmonary embolism,

cerebrovascular accidents, transient ischemic attacks, renal failure, hepatic insufficiency, and the need for prolonged ventilation, is similar when comparing patients receiving regional anesthesia with patients receiving general anesthesia.[75,77]

Many investigators have studied postoperative cognitive function after TURP performed under general versus regional anesthesia. Most studies have failed to show any significant difference in cognitive function in patients receiving regional anesthesia and patients receiving general anesthesia.[86] Postoperative behavioral changes in TURP patients are believed to be related to fluid absorption and increased cerebral fluid; cerebral oximetry studies have confirmed this relationship.[87] Preoperative mental impairment in elderly patients also influences postoperative mental function, which makes another case against the use of heavy sedation in these patients.

COMPLICATIONS OF TRANSURETHRAL RESECTION OF THE PROSTATE

Absorption of Irrigating Solution

Because the prostate gland contains large venous sinuses, it is inevitable that irrigating solution would be absorbed. Simple principles govern the amount of absorption: (1) The height of the container of irrigating solution above the surgical table determines the hydrostatic pressure driving fluid into prostatic veins and sinuses, and (2) the time of resection is proportional to the quantity of fluid that is absorbed. On average, 10 to 30 mL of fluid is absorbed per minute of resection time, with 6 to 8 L absorbed in some procedures lasting up to 2 hours. Whether patients experience complications as a consequence of the absorption of irrigating fluid depends on the amount and type of fluid absorbed.[88,89]

Excessive Circulatory Volume, Hyponatremia, and Hypoosmolality

Solutions such as normal saline and lactated Ringer's solution would be well tolerated when absorbed intravascularly, but these electrolyte solutions are highly ionized and facilitate the dispersion of high-frequency current from a monopolar resectoscope. Solutions of nonelectrolytes, such as glucose, urea, glycine, mannitol, sorbitol, and Cytal, have replaced distilled water. Of all the irrigating solutions available today (see Table 72-12), glycine and Cytal are the two most commonly used.[88]

Replacement of distilled water with nearly isosmotic solutions has eliminated hemolysis and its sequelae as a complication of TURP. The incidence of severe CNS problems associated with extreme hyponatremia, such as convulsions and coma, has been reduced[89]; however, the other major problem associated with the absorption of large volumes of irrigating solution, overhydration, remains. Under usual conditions, only 20% to 30% of a load of crystalloid solution remains in the intravascular space; the remainder enters the interstitial space. When intravascular pressure is increased, movement of fluid into the interstitial space and the development of pulmonary edema are favored. Whether symptoms of circulatory overload develop in a given patient depends on the patient's cardiovascular status, the amount and rapidity of absorption of irrigating fluid, and the extent of surgical blood loss.[89]

The situation is dynamic, and patients must be monitored carefully. In this regard, spinal or epidural anesthesia, supplemented with only light intravenous sedation, has the advantage of allowing the patient's subjective judgment to contribute to assessment of his condition during surgery. In addition, the cardiovascular depression associated with the administration of potent inhaled anesthetics is avoided. Another advantage of regional anesthesia is that the sympathetic block that it produces increases venous capacitance and tends to mitigate intraoperative fluid overload. When the block dissipates, venous capacity acutely decreases, and circulatory overload can occur.

Concomitant with the excessive intravascular volume caused by significant absorption of irrigating fluid are usually hyponatremia and hypoosmolality. TURP syndrome has been typically described as being caused by hyponatremia and subsequent water intoxication. It is now recognized that the classic CNS signs of TURP are not caused by hyponatremia per se, but are due to the accompanying acute serum hypoosmolality that allows movement of water into cells and causes cerebral edema.[88,89]

The use of nonelectrolyte isosmotic irrigating solutions has reduced the incidence of severe CNS complications because extreme extracellular fluid hypoosmolality does not occur, and the subsequent development of cerebral edema is avoided.[88,89] That CNS symptoms occur at all is probably due to the fact that the incidence and extent of hyponatremia are unchanged. The concentration of extracellular sodium must be in the physiologic range for depolarization of excitable cells and production of the action potential. CNS symptoms, which include irritability, apprehension, confusion, and headache, provide early warning signs of rapidly developing hyponatremia. Further progression of hyponatremia (sodium ≤ 102 mEq/L) and decreased serum osmolality lead to the development of seizures and coma. The CNS effects become apparent at sodium levels less than 120 mEq/L. The cardiovascular effects of severe hyponatremia include negative inotropy, hypotension, and dysrhythmias. At sodium levels less than 115 mEq/L, electrocardiogram changes are made manifest by QRS widening and ST-segment elevation.[81]

When extracellular sodium levels are less than 100 mEq/L, consciousness is lost, and convulsions may ensue.[89] Signs and symptoms of cardiovascular dysfunction secondary to hyponatremia also may occur, including arrhythmias, hypotension, and pulmonary edema.[90] It is often impossible, however, to separate the latter events from events attributable to fluid overload.

Glycine Toxicity

Since the early 1980s, attention has turned to the absorption of glycine (HO_2—CCH_2—NH_2), a nonessential amino acid, as a possible cause of some CNS symptoms associated with TURP. In one publication, five cases of transient blindness were attributed to glycine toxicity.[91] Glycine has a distribution similar to that of aminobutyric acid, the latter being an inhibitory transmitter in the brain; it has been suggested that glycine is a major inhibitory

transmitter acting in the spinal cord and brainstem.[91] Normal plasma glycine levels are 13 to 17 mg/L, whereas levels of 1029 mg/L were measured during one episode of blindness. Twelve hours later, the glycine level in this case had declined to 143 mg/L, by which time vision had returned; however, an overall correlation between plasma glycine levels and CNS toxicity has not been established. This relationship, although interesting, still must be considered speculative. Glycine also has been implicated in the myocardial depression and hemodynamic changes associated with TURP syndrome.[92]

Ammonia Toxicity

Absorption of glycine can result in CNS toxicity because of oxidative biotransformation of glycine to ammonia.[93,94] In a report of delayed awakening after TURP in three patients,[93] an association with elevated blood ammonia concentrations was noted. Blood ammonia levels of 500 M were noted in this and another case report.[94] Deterioration of CNS function is said to occur when ammonia levels are greater than 150 M. In a prospective study examining glycine metabolism, blood ammonia levels were increased postoperatively in 12 of 26 patients in whom 1.5% glycine was used as the irrigating solution for TURP.[93] Blood glycine levels also were measured. Glycine and ammonia levels did not correlate; the opposite relationship was prevalent. High ammonia levels were not associated with CNS symptoms of toxicity. Although the investigators postulated that delayed awakening and other CNS symptoms were due to ammonia toxicity, it is unclear whether this hypothesis is correct.

Perforation

Another common complication of TURP is perforation of the bladder.[95] Perforations usually occur during difficult resections and are most often made by the cutting loop or knife electrode. Some are made by the tip of the resectoscope, whereas others result from overdistention of the bladder with irrigation fluid. Most perforations are extraperitoneal, and in a conscious patient they result in pain in the periumbilical, inguinal, or suprapubic regions. The urologist may also note the irregular return of irrigating fluid. Less often, the perforation is through the wall of the bladder and is intraperitoneal, or a large extraperitoneal perforation may extend into the peritoneum. In such cases, pain may be generalized in the upper part of the abdomen or be referred from the diaphragm to the precordial region or the shoulder. Other signs and symptoms, such as pallor, sweating, abdominal rigidity, nausea, vomiting, and hypotension, have been reported; the number and severity depend on the location and size of the perforation and the type of irrigating fluid. In an early series of 2015 cases in which the incidence of complications of TURP was examined, perforation occurred in 25 patients (1.2%).[96] Four deaths and five additional major complications occurred in 12 patients in whom suprapubic cystostomy was delayed more than 2 hours after perforation. Distilled water was the bladder irrigant in most of these cases; therefore, it is unclear whether these morbidity and mortality data are still relevant.

Transient Bacteremia and Septicemia

The prostate harbors many bacteria, which can be a source of intraoperative and postoperative bacteremia through the prostatic venous sinuses. This risk is increased further by the presence of an indwelling urinary catheter. Bacteremia is usually asymptomatic and easily treated with commonly used antibiotic combinations that are effective against gram-positive and gram-negative bacteria; however, septicemia may occur in 6% to 7% of patients.[77] Common manifestations include chills, fever, and tachycardia. In severe cases, bradycardia, hypotension, and cardiovascular collapse can occur, with mortality rates of 25% to 75%. Aggressive treatment with antibiotics and cardiovascular support is warranted.

Hypothermia

Irrigating fluids stored at room temperature are frequently used during TURP. Heat loss as a result of irrigation and significant absorption of this fluid can lead to a decrease in the patient's body temperature and cause shivering. The use of warmed irrigating solutions has been shown to be efficacious in reducing heat loss and the resultant shivering.[97] Although one may believe that warming of fluids might cause increased bleeding because of vasodilation, such is not the case, as shown by study of Heathcote and Dyer.[98] The use of systemic and intrathecal opioids decreases postoperative shivering from cold.[99]

Bleeding and Coagulopathy

A hypertrophied prostate is highly vascular, and operative bleeding can be significant. The blood is washed into the draining bucket and mixed with ample quantities of irrigant fluid. Estimation of blood loss is inaccurate and extremely difficult. Efforts have been made to quantify blood loss based on resection time (2 to 5 mL/min of resection time) and size of the prostate in grams (20 to 50 mL/g); however, these guidelines are rough estimates at best, and the patient's vital signs and serial hematocrit values should be monitored to assess the blood loss and need for transfusion. Because adrenergic receptors are abundant in prostate tissue, the use of adrenergic agonists would cause vasoconstriction of prostatic blood vessels and a decrease in blood loss.

Abnormal bleeding after TURP occurs in less than 1% of cases; it is believed by some clinicians to be due to systemic fibrinolysis secondary to plasmin. The prostate releases plasminogen activator, which converts plasminogen to plasmin. Other clinicians believe that the fibrinolysis is secondary to disseminated intravascular coagulation triggered by the systemic absorption of resected prostate tissue, which is rich in thromboplastin.[75] If primary fibrinolysis is suspected, aminocaproic acid can be effective when given intravenously in a dose of 4 to 5 g during the first hour, followed by 1 g/hr.[75]

Treatment of Transurethral Resection of the Prostate Syndrome

Treatment of TURP syndrome (Table 72-13) consists of fluid restriction and a loop diuretic such as furosemide. Hypertonic saline (3% sodium chloride) is rarely, if ever, necessary and should be considered only in patients with severe hyponatremia. CNS complications of hypertonic

TABLE 72-13 **SIGNS AND SYMPTOMS OF TRANSURETHRAL RESECTION OF THE PROSTATE SYNDROME**

Cardiovascular and Respiratory	Central Nervous System	Metabolic	Other
Hypertension	Agitation/confusion	Hyponatremia	Hypoosmolality
Bradyarrhythmias, tachyarrhythmias	Seizures	Hyperglycinemia	Hemolysis
Congestive heart failure	Coma	Hyperammonemia	
Pulmonary edema and hypoxemia	Visual disturbances (blindness)		
Myocardial infarction			
Hypertension			

saline include cerebral edema and pontine myelinolysis.[76,89] Cardiovascular support should be provided as necessary.

Anesthetic considerations for TURP should include positioning (see Chapter 41). TURP is usually performed in the lithotomy position with a slight Trendelenburg tilt. This positioning results in changes in pulmonary blood volume; a decrease in pulmonary compliance; a cephalad shift of the diaphragm; and a decrease in lung volume parameters such as residual volume, functional residual volume, tidal volume, and vital capacity. Cardiac preload may increase. Nerve injuries to the common peroneal, sciatic, and femoral nerves can occur.[76]

B-TURP, L-TURP, AND MICROWAVE ABLATION OF PROSTATE

Traditional M-TURP electrode prostate surgery has been challenged with new urethral prostate resection techniques. B-TURP offers the advantage of a bipolar electrode resection, which allows normal saline to be used as the bladder irrigating fluid. The electrical current is self-contained in the bipolar design, which prevents it from dispersing through the bladder irrigating fluid or patient. Using normal saline avoids the morbidity associated with hypoosmolar bladder irrigants, such as glycine if absorbed, but does not prevent the possibility of volume overload.

Issa[100] reviewed 16 studies conducted over a 10-year period comparing the safety properties of M-TURP and B-TURP. They found a statistically significant decrease in overall complication rate, transfusion rate, and TURP syndrome with B-TURP. A randomized outcome study by Chen and colleagues,[101] in which M-TURP and B-TURP were compared, found that B-TURP was associated with significantly less fluid absorption, less change in serum sodium and in hemoglobin, and comparable urologic efficacy in prostate symptom scores. Two meta-analytic studies comparing M-TURP and B-TURP also reported favorable outcomes in the B-TURP groups.[102,103] A prospective, randomized trial comparing complications and clinical outcomes 18 months after TURP, concluded that fewer postoperative readmissions, faster postoperative recovery, and equivalent long-lasting results were found in B-TURP than in M-TURP.[104]

L-TURP is replacing conventional TURP. Laser therapy delivers vaporization energy creating a thin resecting coagulation treatment zone during prostate resection. The neodymium:yttrium-aluminum-garnet (Nd-YAG) laser has been replaced by holmium and potassium-titanyl-phosphate lasers. The laser incorporates a 532-nm wavelength energy that is selectively absorbed by hemoglobin. When directed to the prostate, the laser vaporizes a layer of tissue in millimeter resection zones. An evolution of these lasers has occurred from 80 to 120 watts, to the currently available 180-watt laser. The increased wattage provides more efficient tissue ablation resulting in a decreased TURP resection time. These lasers produce varying degrees of coagulation and vaporization of prostate tissue. The main advantages over M-TURP include minimal blood loss (50 to 70 mL) and minimal fluid absorption, which should nearly eliminate these two major complications of TURP; however, other potential complications are introduced, including coagulation through the prostatic fossa and sloughing of prostatic debris in the postoperative period, with subsequent urinary obstruction and urinary retention.[105-109] Protective eyewear and a means to evacuate the smoke plume are needed.[110] In critically ill patients, caudal anesthesia has been used successfully for L-TURP because the use of continuous irrigation combined with minimal bleeding obviates the need for copious irrigation and minimizes bladder distention.[79]

Hanson and associates[111] reviewed the anesthetic implications of the newer prostate laser resection therapies. The described advantages included minimal bladder irrigating fluid absorption, a minimized risk of TURP syndrome, potential to perform the procedure on anticoagulated patients, delivery in an outpatient setting, and less emphasis on describing regional as the preferred anesthetic technique. General anesthesia is acceptable because of the decreased risk of TURP syndrome.

In a systematic review of randomized, controlled trials evaluating the efficacy and safety of L-TURP techniques versus conventional TURP for symptomatic benign prostatic obstruction, the authors observed that L-TURP provided slightly greater improvement in urinary symptoms and flow. Laser procedures resulted in fewer transfusions and strictures and shorter hospitalizations. Reoperation was required more often after laser procedures.[112] As suggested, L-TURP is feasible when anticoagulation therapy withdrawal is considered a significant patient risk perioperatively.[113]

When M-TURP, B-TURP, and bipolar plasma vaporization TURP were compared in a prospective, randomized long-term comparison study, capsular perforation and intraoperative bleeding were less in bipolar plasma vaporization TURP. Postoperative hematuria, blood transfusion, and clot retention rates were higher in M-TURP.[114]

Transurethral microwave thermotherapy (TUMT) ablation of the prostate is considered a minimally invasive office-based technique that can be performed under local or sacral block. High-energy TUMT has received

reconsideration for use instead of current TURP techniques in certain patient populations. It can be performed as an outpatient procedure and lacks significant side effects. Although it is still reported to be less effective than TURP in relieving urinary outflow obstruction long term, it is an option especially in elderly or high-risk patients.[115]

LASER LITHOTRIPSY

Laser lithotripsy is used for ureteral stones that are low in the ureter and not amenable to extracorporeal shock wave lithotripsy (ESWL). A pulsed dye laser is generated with a laser beam of 504-nm wavelength passing through an organic green dye.[116] This laser beam is easily absorbed by the stones, and pulsatile energy is released that causes disintegration of the stones. The beam is carried over a bare wire passed through a rigid ureteroscope, which is longer and more pointed than a cystoscope, so the risk of ureteral perforation exists. Ideally, general anesthesia with paralysis should be maintained to avoid patient movement. If regional anesthesia is chosen, a spinal level of T8 to T10 is required. The bare laser wire is sharp and can cause mucosal injury to the ureter. These lasers are not well absorbed by red blood cells or other tissues, however, which provides safety against tissue coagulation or thermal injury. Because the laser beam is reflective, the user, other personnel, and the patient should wear protective eyeglasses. Some hematuria always occurs; good intravenous hydration is recommended.[116]

LAPAROSCOPIC SURGERY IN UROLOGY

Urologic laparoscopic surgery continues to pioneer new surgical approaches for treatment of diseases previously performed by an open surgery. Advances in this area now routinely include laparoscopic varicocelectomy, hernia repair, adrenalectomy, partial adrenalectomy, renal pelvis or ureter percutaneous stone retrieval, nephrectomy, radical prostatectomy, extra-adrenal pheochromocytoma, nephropexy, pyeloplasty, nephrectomy, partial nephrectomy, and cystectomy. Many of these surgeries are robot assisted for tumor resection and reconstruction. During robotic laparoscopic surgery, the surgeon is stationed in the operating room away from the operating room table while working at a computer console with a three-dimensional view of the operating field and manual controls at the console for robotic instruments placed in the abdomen via laparoscopy trocars.

For radical prostatectomy, the objectives of laparoscopic surgery are to reduce perioperative morbidity compared with conventional surgery and allow a more precise operative procedure. The quality of surgery can be improved by better visualization of the operative site as a result of optical magnification and the maneuverability of the laparoscope, which provides a hitherto unobtainable anatomic view. The laparoscopic approach not only improves the postoperative course, but also allows better preservation of periprostatic vascular, muscular, and neurovascular structures.[117]

A unique challenge in nephron-sparing laparoscopic surgery is achieving successful renal hypothermia for renal preservation during renal artery occlusion. Techniques described for renal hypothermia include laparoscopic deployed ice slush kidney surface cooling (preferred option), endoscopic retrograde cold saline infusion, and transarterial renal hypothermia via femoral artery catheter approach.

Although all the conventional complications and concerns associated with laparoscopy are applicable to urologic procedures, two unique problems also are identified. First, because the urogenital system is mainly retroperitoneal, the large retroperitoneal space and its communications with the thorax and subcutaneous tissue are exposed to the insufflated carbon dioxide. Significant subcutaneous emphysema can occur in these patients and may extend all the way up to the head and neck.[118] The upper airway is at risk for compromise in the most severe cases because of pharyngeal swelling secondary to submucous carbon dioxide. This complication should be kept in mind before extubation of the trachea in these patients. Second, the procedures can be lengthy, allowing for sufficient absorption of carbon dioxide to result in acidemia and marked acidosis.[118] Because of significant increases in intra-abdominal and intrathoracic pressure as a result of insufflated carbon dioxide, a steep Trendelenburg position, and lengthy procedures, general anesthesia with controlled ventilation is the method of choice. Despite adequate intravascular hydration, intraoperative oliguria may occur and be followed by diuresis in the immediate postoperative period. Although the exact mechanism is unclear, increased perirenal pressure exerted by the insufflated gas in the retroperitoneal space is a likely explanation.

EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

Extracorporeal shock wave lithotripsy has become the treatment of choice for disintegration of urinary stones in the kidney and upper part of the ureter. The first clinical model of the lithotripter introduced into common practice (Dornier HM-3) used a water bath in a steel tub and a metal gantry chair to support the patient suspended in a sitting position. This first-generation lithotripter is still used in some institutions and presents complex challenges of immersion physiology and monitoring difficulties. Second-generation and third-generation lithotripters (e.g., Siemens, Lithostar, Wolf Piezolith, Dornier HM-4, MFL 5000, MPL 9000) have evolved mainly in the direction of eliminating the water bath and minimizing patient discomfort. All lithotripters share similar technologic principles in having three main components: (1) an energy source, most commonly a spark plug (alternatively, an electromagnetic membrane or piezoelectric elements); (2) a system to focus the shock wave, such as ellipsoid or reflecting mirrors; and (3) fluoroscopy or ultrasound to visualize and localize the stone in focus.[119]

Technical Aspects

An electrode (or spark plug) located in an ellipse creates a spark causing explosive vaporization of water. The sudden expansion of air bubbles created sets up a pressure wave (shock wave) which is focused by the ellipse to a

focal point called the F2 focus (the tip of the electrode is the F1 focus). The shock wave travels through water and body tissues without significant localized dissipation of energy because the acoustic impedance of the two media is similar. When the shock wave arrives at the entry surface of the stone, however, it encounters a sudden change in impedance that causes it to release compressive energy. Similarly, when the wave exits on the opposite surface of the stone, an interface is encountered again, and shock wave energy is released. Repeat applications cause the stone to disintegrate. Shock wave energy is most concentrated in the F2 focal zone and rapidly decreases beyond it.[120]

Biomechanical Effects of Shock Wave Therapy

For shock waves to be most effective, the stone should remain in the F2 focus during treatment.[79] Pressure energy measurements show an exponential decrease beyond this small focal zone. The kidneys and the kidney stone follow the up-and-down movements of the diaphragm during respiration. The stone is likely to move in and out of focus during respiration. In the past, ventilatory techniques such as decreased tidal volumes with increased respiratory rates and high-frequency jet ventilation have been used to increase the efficacy of the treatment.[121] However with contemporary lithotripsy machines, sedation and therefore spontaneous ventilation is the only option.

For effective stone disintegration, shock waves should reach the stone unimpeded. The flank area should be kept free of any medium that would provide an interface for the dissipation of shock wave energy. Nephrostomy dressings should be removed, and the nephrostomy catheter should be taped clear of the blast path. Although shock waves pass through most tissues relatively unimpeded, they do cause tissue injury, the extent of which depends on the tissue exposed and the shock wave energy at the tissue level. Skin bruising and flank ecchymoses can occur at the entry site. Painful hematoma in the flank muscles may occur. Hematuria is almost always present at the end of the procedure and results from shock wave–induced endothelial injury to the kidney and ureter. Adequate hydration is necessary to prevent clot retention. Lung tissue is especially susceptible to injury by shock waves. Air trapped in alveoli presents a classic water (tissue)-air interface to the shock wave and causes dissipation of energy. Massive hemoptysis and death from pulmonary damage have been reported in laboratory animals after a single exposure of the thorax to a shock wave.[122] Shock wave–induced hemoptysis in a child and a pulmonary contusion with life-threatening hypoxemia in an adult have been reported.[123,124] Children are more likely to sustain pulmonary damage from shock waves because of the shorter distance of the lung bases from the kidneys than in adults. It is recommended that a Styrofoam sheet or Styrofoam board be placed under the back in children to shield the lung bases from shock waves during ESWL.[123,124]

Shock wave–induced cardiac arrhythmias previously reported in 10% to 14% of patients undergoing lithotripsy are extremely rare nowadays.[125,126] These arrhythmias are believed to be due to mechanical stress on the conduction system exerted by the shock waves. The intricate grounding system of the lithotripter ensures that any current-induced arrhythmias are unlikely. Artifacts on electrocardiogram also are common. Artifacts and arrhythmias usually disappear when the lithotripsy is stopped.

Physiologic Changes during Immersion Lithotripsy

Water immersion with the Dornier HM-3 lithotripter produces significant changes in the cardiovascular and respiratory systems (Box 72-3).

Anesthetic Choices for Lithotripsy

Anesthetic regimens used successfully for lithotripsy include general anesthesia, epidural anesthesia, spinal anesthesia, flank infiltration with or without intercostal blocks, and analgesia-sedation, including patient-controlled analgesia.[127-135] General anesthesia offers the advantages of rapid onset and control of patient movement. Ventilatory variables can be controlled to decrease stone movement with respiration. With epidural anesthesia using loss of resistance to air to identify the epidural space, only the smallest amount of air necessary should be injected. Air in the epidural space provides an interface and can cause dissipation of shock wave energy and local tissue injury. Korbon and associates[136] found a decrease in epidural compliance and pain on injection with repeat epidurals for subsequent lithotripsies in their patients. In animal experiments, they were able to show epidural tissue damage after injection of air and exposure to shock waves.[137] It is reassuring, however, that in most lithotripsies performed under epidural anesthesia worldwide, neurologic injury has not been a problem.[138]

The main disadvantage of epidural anesthesia is its slow onset. Spinal anesthesia offers a reasonable alternative with its rapid onset. The incidence of hypotension (the patient is in a sitting position for treatment) is higher, however. In one series, the incidence of hypotension with general, epidural, and spinal anesthesia was 13%, 18%, and 27%, respectively.[139] Local anesthetic infiltration of the flank with or without intercostal blocks provides adequate anesthesia when combined with intravenous sedation and avoids hypotension.[127] Intravenous analgesia-sedation in various combinations has been used successfully.[129,130]

BOX 72-3 *Changes on Immersion during Lithotripsy*

Cardiovascular	Increased	Central blood volume
	Increased	Central venous pressure
	Increased	Pulmonary artery pressure
Respiratory	Increased	Pulmonary blood flow
	Decreased	Vital capacity
	Decreased	Functional residual capacity
	Decreased	Tidal volume
	Increased	Respiratory rate

Newer Lithotripters

Newer lithotripters have no water bath, and they tend to use multifunctional tables that allow other procedures, such as cystoscopy and stent placement, to be accomplished without moving the patient off the table. The shock waves are tightly focused; therefore, they cause less pain at the entry site, and intravenous analgesia-sedation is the mainstay of anesthesia with these newer lithotripters. Other incidental interventions, such as cystoscopy, stone manipulation, or stent placement, alter anesthetic requirements. Many of these newer lithotripters have a much smaller focal zone for the shock waves. It is even more imperative that adequate analgesia and sedation be provided, so that stone excursion with respiration is limited to the focal zone. Most analgesia-sedation combinations are adequate. Even patient-controlled analgesia with alfentanil and a combination of propofol and alfentanil has been used.[140,141] Many centers routinely use general anesthesia with short-acting inhaled or intravenous anesthetics and use laryngeal mask airway for ventilation.

Contraindications

Pregnancy and untreated bleeding disorders are the only contraindications to lithotripsy. Women of childbearing age must have a pregnancy test that is documented to be negative before lithotripsy. Standard tests of coagulation, such as the platelet count, prothrombin time, and partial thromboplastin time, should be obtained as indicated by medical history. Pacemakers, automatic implanted cardioverter-defibrillators (AICDs), abdominal aortic aneurysm, orthopedic prostheses, and obesity are no longer considered contraindications.

Patients with pacemakers can be treated safely if the pacemaker is pectorally placed and the following precautions are observed (see Chapter 48).[142-144] Pacemaker programmability should be established before the treatment, and the pacemaker should be switched to a nondemand mode in case the shock waves interfere with pacemaker function. Alternative means of pacing should be available. Although most pacemakers located pectorally are at a safe distance from the blast path, some may be damaged. Weber and co-workers[142] examined 43 different pacemakers and found that 3 were affected. Dual-chamber pacemakers tend to be more sensitive to interference. Treatment should be started at a low energy level and gradually increased while observing pacemaker function.

Manufacturers of AICDs and lithotripters have considered an AICD a contraindication for lithotripsy; however, patients with AICDs have been treated successfully with lithotripsy.[143] AICD devices should be shut off immediately before lithotripsy and then reactivated immediately after treatment.[145]

Patients with small aortic aneurysms have been treated safely, provided that the stone is not close to the aneurysm. Orthopedic prostheses, such as hip prostheses and even Harrington rods, are not a problem if they are not in the blast path, which is usually the case. Positioning of obese patients may be problematic at times. Not only do extremely obese patients present anesthetic challenges related to obesity, but also focusing of the stone may be extremely difficult in the very obese. It is prudent for focusing of the stone to be attempted before administering any anesthetic in this high-risk population.

RADICAL SURGERY IN UROLOGY

Radical surgery includes radical nephrectomy, radical cystectomy, and radical retropubic prostatectomy. Common features include lengthy procedures, associated sudden and significant blood loss, and attention to renal function preservation. With radical nephrectomy, significant cardiorespiratory changes attendant to the flank position are a concern. Respiratory changes include decreases in thoracic compliance, tidal volume, vital capacity, and functional residual capacity. Dependent atelectasis is common and can lead to hypoxemia. Pneumothorax may occur and can have significant respiratory and hemodynamic consequences intraoperatively. It is common to see a decrease in blood pressure when the kidney rest is raised. This decrease is usually due to compression of the inferior vena cava. In addition, hepatic encroachment on the vena cava and mediastinal shift may reduce venous return and stroke volume further. Cervical plexus, brachial plexus, and common peroneal neuropathies can occur because of stretch or compression of nerves in the lateral position.

Radical Nephrectomy for Renal Cell Carcinoma

The most common malignancy of the kidney is renal cell carcinoma; 85% to 90% of all solid renal masses are renal cell carcinoma.[146] Because renal cell carcinoma is refractory to chemotherapy and radiation therapy, surgical resection or ablation can offer curative treatment of localized disease (Box 72-4). Recently, resection of the ipsilateral adrenal gland has been reserved for patients with large upper pole lesions or when the adrenal gland is enlarged or appears abnormal.[147] Partial nephrectomy (nephron-sparing surgery) is considered for patients with small lesions or bilateral tumors or for patients at risk because of other diseases, such as diabetes or hypertension.[146-149]

In 5% to 10% of patients, the tumor extends into the renal vein and the inferior vena cava and right atrium.

BOX 72-4 ***Anesthetic Implications of Radical Nephrectomy for Tumors***

- 85%-90% are for renal cell cancer
- 5%-10% extension to the IVC and right atrium
- Large-bore IV access, A-line, IJV line (preferably on left side if IVC is involved)
- Paraneoplastic syndrome
- Hypercalcemia, eosinophilia; increased prolactin, erythropoietin, and glucocorticoids
- Occurs more frequently in men than women
- Chronic smoking history usually associated
- CAD, COPD
- Renal failure

CAD, Coronary artery disease; *COPD,* chronic obstructive pulmonary disease; *IJV,* internal jugular vein; *IVC,* inferior vena cava.

Tumor extension into the inferior vena cava and atrium occurs more frequently with right-sided renal cell carcinoma. Several problems can occur in these patients, ranging from circulatory failure as a result of complete occlusion of the vena cava by tumor to acute pulmonary embolization of tumor fragments during surgery. To operate on these patients safely, the extent of the lesion must be defined preoperatively. Cardiopulmonary bypass can be required. Central venous pressure in such cases might not reflect intravascular volume accurately, because venous return through the inferior vena cava is impaired by the thrombus and intraoperative transesophageal echocardiography may be of value.[150] A decrease in venous return also predisposes the patient to hypotension during induction of anesthesia. Venous obstruction can lead to dilation of the epidural veins and the development of abdominal wall and retroperitoneal collaterals. The emphasis is on appropriate preoperative preparation, which is possible only when the full extent of the lesion has been defined.[149]

Radical Prostatectomy

Localized prostate cancer is treated by either radiation therapy or radical prostatectomy (Box 72-5). Radical prostatectomy has become more commonly performed because of routine prostate-specific antigen testing in men older than 50 years and popularization of the nerve-sparing surgery to reduce the risk of impotence. Although originally described in 1905 via the transperineal approach, the retropubic approach is mostly used now. The prostate, the ejaculatory ducts, the seminal vesicles, and part of the bladder neck are removed along with the pelvic lymph nodes.

Traditionally, the procedure was performed by open laparotomy, but laparoscopic and robotic surgery are being used more frequently. A potential intraoperative problem with open radical prostatectomy is hemorrhage and massive blood loss requiring blood transfusion. Autologous predonation, preoperative recombinant erythropoietin therapy, intraoperative isovolemic hemodilution, and cell salvage are commonly practiced to reduce the patient's exposure to allogeneic blood. Early postoperative complications, including deep vein thrombosis, pulmonary embolism, hematoma, seroma, and wound infection, occur in 0.5% to 2% of cases.[151] Late complications include incontinence, impotence, and bladder neck contracture.[152] Patients undergoing radical prostatectomy are placed supine in steep Trendelenburg position with the back extended, which places the pubis above the head. Air embolism from the prostatic fossa caused by a gravitational gradient between the prostatic veins and the heart has been reported.[153]

BOX 72-5 ***Anesthetic Implications of Radical Prostatectomy***

- Disease of the elderly
- CAD, COPD, and renal dysfunction
- Significant blood loss
- Wide-bore IV access and invasive monitoring
- Acute normovolemic hemodilution versus autologous blood donation
- Hyperextended position
- Nerve injuries, soft tissue injury, joint dislocations
- Venous air embolism
- Anesthesia
- Benefits of regional anesthesia versus general anesthesia debated
- Not known to influence mortality
- Epidural anesthesia with spontaneous ventilation decreases blood loss
- General or combined anesthesia with IPPV increases blood loss

CAD, Coronary artery disease; *COPD,* chronic obstructive pulmonary disease; *IPPV,* intermittent positive-pressure ventilation; *IV,* intravenous.

Comparison of Anesthetic Techniques for Radical Prostatectomy

Epidural anesthesia, spinal anesthesia, general anesthesia, and combined epidural and general anesthesia have been used for this surgery. For the epidural component of combined techniques, a thoracic or a lumbar approach to anesthesia or analgesia has been used, and spontaneous ventilation or intermittent positive-pressure ventilation (IPPV) has been used for the general anesthesia component. Many investigators have reported their findings in comparing the three anesthetic techniques for radical retropubic prostatectomy,[154-157] and certain trends emerge.

Intraoperative blood loss is significantly less if epidural anesthesia or a combined epidural and general anesthetic with spontaneous ventilation is used. In one study, blood loss in the general anesthesia and the combined anesthesia group with IPPV was significantly more than in the epidural anesthesia group despite little difference in arterial pressure among the three groups.[154] It was postulated that the increased venous pressure as a result of IPPV was the most likely cause of increased bleeding in the general and the combined anesthesia groups during radical prostatectomy. Previous studies have shown that central and peripheral venous pressure is lower in patients during spontaneous ventilation under epidural anesthesia or combined epidural-general anesthesia than in patients receiving IPPV during general anesthesia.[158] Epidural anesthesia alone or when added to a general anesthetic decreases the risk of thromboembolism,[159] decreases postoperative pain and analgesic requirements,[160] and speeds recovery of bowel function. The length of stay and the cost of hospitalization can be decreased with the judicial use of epidural anesthesia and established clinical pathways.[161,162] In one study, 80% of patients were satisfactorily discharged after 1 day, and the mean length of stay was 1.34 days.[163]

Possible differences in patient outcome with general versus epidural anesthesia are not clear. Local practices are therefore based on the preferences of the urologist, the anesthesiologist, and the patient.

Robotic Assisted Radical Prostatectomy

Many surgical advantages of robotic assisted radical prostatectomy (RARP) are described, including better visualization, more controlled finer movements of robotic arms allowing better dissection, decreased blood loss, less scarring and pain, shorter recovery time, faster return to daily activity, and possibly improved continence and potency

rates (although these last outcomes have been suggested only given the short-term follow-up at this time). Anesthetic concerns are primarily related to steep head-down tilt and pneumoperitoneum required for surgery.

Ventilatory and respiratory changes resulting from pneumoperitoneum include decreased compliance, increased airway pressures, and increased ventilation-perfusion mismatch. Application of positive end-expiratory pressure improves oxygenation in these patients.[164] Hypercapnia develops within 15 to 30 minutes of carbon dioxide insufflation with resultant hypercarbia, acidosis, tachycardia, arrhythmias, and other deleterious hemodynamic and CNS effects.[165] Increase in mechanical ventilation can obviate these changes in most patients, and most healthy patients tolerate the changes even though they are clinically significant. Extraperitoneal insufflation of carbon dioxide is associated with larger increases in arterial P_{CO_2} than in intraperitoneal insufflation.[166] Hemodynamic changes include decreased venous return with decreased cardiac output despite an increase in filling pressures indicative of increased intrathoracic pressures.

Physiologic changes resulting from steep Trendelenburg position include hemodynamic effects such as decreased perfusion pressure of lower extremities, increased mean arterial pressure at the circle of Willis, increased central blood volume, decreased cardiac output, and a decreased perfusion of vital organs in a normovolemic patient. Increased myocardial oxygen consumption, ischemia, arrhythmias, and decreased oxygen delivery are potential risks in patients with cardiac disease. Despite an observed twofold to threefold increase of right- and left-sided filling pressures in ASA I and II patients during RARP, Lestar and colleagues[167] observed no significant changes in cardiac performance. Respiratory effects of steep head down tilt—decreased compliance, reduced vital capacity and functional residual capacity, 20% decrease in lung volumes, and ventilation-perfusion mismatch—compound the effects of pneumoperitoneum. Pulmonary congestion and edema have been reported in susceptible patients. A transient increase in serum creatinine secondary to pneumoperitoneum during robotic prostatectomy has been reported.[168] Regurgitation in this position in patients with history of reflux increases their risk of aspiration of gastric contents. Maintaining normothermia may be a problem in some cases because of prolonged pneumoperitoneum with dry cold gases.

Other significant effects of steep head down tilt include increased intracranial pressure, increased intraocular pressure, venous air embolism, brachial plexopathy, arthralgias, compartment syndrome, and finger injuries. It has been recommended to perioperatively assess the function of a patient with a ventriculoperitoneal shunt scheduled for any laparoscopic procedure.[169] Issues of increased intracranial pressure or consequences of a malfunctioning shunt with pneumoperitoneum in steep Trendelenburg position need to be realized. Kalmar and associates concluded patients overall clinically tolerated the influence of prolonged steep Trendelenburg position with CO_2 pneumoperitoneum on cardiovascular, cerebrovascular (including cerebral perfusion pressure and oxygenation), and respiratory homeostasis during robotic prostatectomy.[170] Significant increases in intraocular pressure have been reported in robotic prostatectomy, but the clinical significance is unknown.[171] Of concern is the reporting of at least six cases of postoperative visual loss following radical prostatectomy, three open and three robot-assisted laparoscopic prostatectomy cases.[172] Chemosis (conjunctival edema) is common in RARP, but is usually self-limiting once the patient is taken out of the steep Trendelenburg position.

Compared with retropubic radical prostatectomy, RARP is usually associated with much less blood loss, except for one study.[173] Mild to moderate pain is expected postoperatively, and low pain scores of 0 to 4 have been reported after retropubic radical prostatectomy and robotic assisted radical prostatectomy using preemptive analgesia with ketorolac given intraoperatively combined with rescue opiate or nonopiate analgesia.[174] Most patients are discharged home the day after surgery. The use of robots in urologic surgery has been extended to include radical cystectomy, pyeloplasty, and renal and adrenal surgery in adults and children, and newer indications are developing. Other considerations in robotic surgery focus on the rigidly placed intraabdominal trocars attached to the robotic arms. Patient movement during the surgery could result in visceral or vascular injury. A constant need to assess degree of muscle relaxation intraoperatively is suggested. A plan among the perioperative team to dismantle the robotic arms in the unlikely event of cardiac arrest and need for advanced cardiac life support measures needs to be rehearsed.

UROGENITAL PAIN SYNDROMES

Pain syndromes of the urogenital system can result from infection, anatomic anomaly, obstructive uropathy, nerve entrapment, or malignancy. The site, referral pattern, and quality of pain aid the clinician in identifying the source of pain—visceral, somatic, or neuropathic—and appropriate treatment (see Chapter 98).

BENIGN RENAL TUMORS

Flank pain is a common symptom in adults with angiomyolipomas, which consist of abnormal growth of blood vessels, smooth muscle, and fat. This benign neoplasm can create a mass effect that affects renal function and acute worsening of pain should raise suspicion for rupture and hematoma formation. Angiomyolipomas can be associated with tuberous sclerosis, but are more commonly found in otherwise healthy individuals. Treatment is symptomatic with acetaminophen and neuromodulatory agents. Care should be taken with nonsteroidal anti-inflammatory drug (NSAID) use because renal function can be compromised.

PEDIATRIC TUMORS

Wilms' tumor (nephroblastoma) generally occurs unilaterally and is painless on initial presentation (see Chapter 93). It may be associated with congenital malformations such as Beckwith-Wiedemann syndrome. Treatment consists of surgical resection most often

supplemented by chemotherapy, because the tumor is highly responsive to this modality. Perioperative pain can be addressed with epidural anesthesia, acetaminophen, and opioids. Chemotherapy-induced neuropathy can best be treated with antineuropathic agents.

RENAL CELL CARCINOMA

Renal cell carcinoma is described as having a classic triad of hematuria, flank pain, and renal mass; however, pain can be a late presentation and may indicate metastatic disease. In cases of metastasis, prognosis is often poor and pain is widespread. Early consideration of an intrathecal catheter for continuous delivery of opioids, local anesthetic, or ziconotide can improve patient quality of life. Flank pain may be due to stretching of the Gerota fascia, and metastasis is primarily local along the renal vein and inferior vena cava or into the intercostal nerves, which produces segmental neuralgia. In these cases, intercostal nerve blocks and neurolysis or radiofrequency can be of use and accomplished under fluoroscopic or ultrasound guidance.

INFECTIOUS RENAL DISEASES

Infectious renal diseases producing flank pain include pyelonephritis and perinephric abscess. Fever is an important associated finding that suggests the presence of infection. Because the kidneys are retroperitoneal organs, peritoneal signs are absent. Differential diagnosis must include inflammatory or infectious disease of surrounding organs, including lower lobe pneumonia, pancreatitis, appendicitis, and cholecystitis. Oral or parenteral narcotics are effective for pain control in the acute setting. Systemic antibiotics are curative in most cases, although surgical intervention may be warranted, and a focal nidus for infection (stone, urethral reflux, recurrent urinary tract infections) should be pursued.

NEURALGIAS

Pseudorenal pain syndromes are caused by entrapment of nerves colocalized with the urinary system in the lower abdomen and groin. Neuralgia of the genitofemoral nerve is common after hernia surgery, given its close proximity and variable relation to the spermatic cord. Pain radiates to the inguinal ligament via the femoral branch and to the testicle via the genital branch. Injury to the iliohypogastric or ilioinguinal nerves can occur with lower abdominal incisions or trocar placement for laparoscopy, resulting in neuralgia radiating to the lower abdomen and groin. Pain sensation is generally neuropathic in these conditions and dermatomal testing will reveal sensory deficits. Nerve blocks can be performed under ultrasound guidance[175] to help establish the diagnosis, differentiate from urogenital pain, and for therapeutic benefit. Antineuropathic drugs are also of help should nerve injury be confirmed (see Chapter 64).

POLYCYSTIC KIDNEY DISEASE

Polycystic kidney disease is most often inherited in an autosomal dominant manner and can lead to massive enlargement of the kidneys with compromised renal function. Renal pain is caused by distention of the cysts and stretching of the Gerota fascia. Hemorrhage into the cysts, rupture of the cysts, or infection can exacerbate pain. Percutaneous drainage of renal cysts can relieve the symptoms. Opioids are appropriate in the acute phase.

OBSTRUCTIVE UROPATHY

Obstruction of the urinary tract causes severe, spasmodic pain in the flank. Pain from the upper third of the ureter may be referred to the lower abdomen and back, pain from the middle third to the iliac fossa, and pain from the lower third to the suprapubic and groin area. Minimal fluid intake and a high concentration of stone-forming salts predispose to nephrolithiasis. Renal colic, hematuria, and radiopaque stones on radiography (70% to 75% of calculi) or noncontrast CT confirms the diagnosis.[176] Opioids and NSAIDs are best for severe symptoms. Ketorolac through the intramuscular or intravenous route may be of use if oral medications are not tolerated. Of note, intravenous hydration has not demonstrated benefit despite widespread use.

URINARY RETENTION

Bladder pain is most commonly described as a poorly localized ache in the suprapubic region, typical of visceral pain. Acute bladder distention is manifested as severe suprapubic pain with associated urinary frequency. This can occur postoperatively after surgery without Foley catheter placement or after neuraxial local anesthetic and opioid administration resulting in urinary retention. Initial presentation can include emergence delirium. Drainage of the bladder, either by voiding or by catheterization, is recommended when volume exceeds 600 mL to avoid overdistention of the bladder with associated sequelae. Obstruction from urethral stone or prostatic hypertrophy should be addressed if present.

INTERSTITIAL CYSTITIS

Interstitial cystitis (painful bladder syndrome) is a chronic pain condition marked by suprapubic pain related to bladder filling and symptoms of increased frequency and urgency in the absence of infection or malignancy.[177] Pathologic features of interstitial cystitis that may be evident, but are not necessary to make the diagnosis, include Hunner ulcers (discrete, bleeding areas on the bladder wall) and glomerulations (petechial bleeding after distention). The proposed pathophysiology is thought to be a deficient glycosaminoglycan layer that allows increased permeability of the bladder wall, resulting in inflammation and pain. Options for pain control include pentosan polysulfate (intended to repair the glycosaminoglycan layer), amitriptyline, antihistamines, dimethyl sulfoxide instillation, sacral nerve stimulators, and cystectomy.

UROTHELIAL TUMORS

The most common urothelial tumor is transitional cell carcinoma of the bladder. Painless hematuria is the most

common manifestation, although patients may complain of bladder irritability if there is involvement of the muscular layers. Surgical treatment includes fulguration, transurethral resection, or cystectomy. Pain control is best accomplished with NSAIDs, acetaminophen, opioids, and neuromodulatory agents.

TESTICULAR PAIN

Testicular pain can be the result of trauma, torsion, infection, or neoplasm. Trauma or torsion necessitate immediate restoration of blood flow, and emergency surgical exploration is the treatment of choice. Orchitis or epididymitis should be suspected based on a thorough history and if signs of localized or systemic infection accompany pain. Tumors of the testis are most often malignant; however, extratesticular tumors within the scrotum are usually benign. The earliest sign of tumor is usually a painless testicular mass. Pain is a late sign and is usually described as a dull ache or heaviness owing to mass effect, and it is most effectively addressed through debulking via surgery or radiotherapy.

PROSTATITIS

Acute prostatitis is usually caused by a bacterial infection and responds to antibiotic therapy. Chronic prostatitis has been more recently referred to as *chronic pelvic pain syndrome* to reflect that there is little certainty that inflammation of the prostate is responsible for symptoms.[178] Symptoms include genital/pelvic pain and sexual dysfunction, often accompanied by lower urinary tract symptoms. Moderate improvement has been noted with antibiotics, α-blockers, antiandrogens, NSAIDS, and pelvic floor physiotherapy.

PROSTATE CANCER

Adenocarcinoma of the prostate is the most common male cancer and is usually painless and discovered incidentally through routine physical examination. Epidural anesthesia can be of use for acute pain control if brachytherapy with seeding is part of treatment. Lumbar or sacral pain with prostatic cancer may be a sign of metastatic disease to bone. High-dose opioids and bisphosphonates are indicated, and placement of an intrathecal catheter should be considered early.

PRIAPISM

Priapism is a prolonged erection over 4 hours in duration and can be ischemic (veno-occlusive) or nonischemic (arterial). The former represents an acute emergency, and prompt therapy should be instituted to control pain and prevent subsequent impotence from fibrosis of the corpora cavernosa. Treatment consists of a penile dorsal nerve block (performed at the pubic symphysis with needle entry into the subpubic space), which must be performed with local anesthetic without epinephrine, after which aspiration of blood or intercavernosal phenylephrine can be performed.[179] Nonischemic priapism is most commonly posttraumatic and results from creation of an arteriolar-sinusoidal fistula. This type of priapism is typically not as painful and responds to conservative management. Sickle cell priapism is treated with hydration, alkalinization, and blood transfusion to increase hemoglobin to more than 10 mg/dL.

PEYRONIE DISEASE

Peyronie disease is a condition that causes severe penile pain during sexual intercourse because of excess curvature. The treatment of choice is surgery and NSAIDs as necessary for pain.

FEMALE GENITAL PAIN

Vulvodynia is a chronic pain condition associated with sexual inactivity or dysfunction because of vulvar pain. *Vestibulitis* refers to vulvodynia confined to the vestibule. Some success with tricyclic antidepressants, Sitz baths, local estrogen creams, and pudendal nerve blocks has been reported. Vaginismus is associated with increased tone of the muscles of the pelvic floor (pubococcygeus and levator ani) producing spasms and painful sexual dysfunction. Dyspareunia is defined as recurrent and persistent genital pain before or after intercourse not solely explained by infection, trauma, lubrication, or vaginismus. Psychological factors often play a major role. Treatment involves pelvic floor physiotherapy and desensitization techniques. Opioids are not indicated.

CHRONIC PELVIC PAIN

Chronic dysmenorrhea can be addressed with ovulation suppression or use of NSAIDs, which decrease uterine lining thickness and cramping via an antiprostaglandin effect.[180] Chronic pelvic pain may also be due to endometriosis, pelvic congestion, adhesions, or pelvic inflammatory disease—each of which is most responsive to correction of the underlying disorder for relief of pain. Cancer of the cervix or uterus can cause severe lower abdominal pain and requires aggressive opioids and referral for superior hypogastric plexus neurolysis or intrathecal medications.

ROLE OF SYMPATHETIC BLOCKS

The pelvic viscera in men and women—the urogenital organs, the distal colon, and the rectum—are supplied by afferent fibers from the distal lumbar sympathetic chain. Interruption of these pathways can be achieved with a superior hypogastric plexus block. The superior hypogastric plexus is a retroperitoneal structure situated along the anterior surface of the L5 and S1 vertebrae. It can be blocked using fluoroscopic guidance and instillation of phenol or ethanol.[181,182] The ganglion impar is another promising target for neurolysis, supplying mixed somatic, autonomic, and visceral fibers to the distal urethra, vulva, perineum, and distal third of the vagina. It can be blocked along the anterior surface of the sacrococcygeal junction.

GENERAL CONSIDERATIONS

Specific to renal compromise, meperidine and morphine should be avoided because of the accumulation of renally

excreted metabolites, including normeperidine and morphine-3-glucuronide, which lower the seizure threshold, and morphine-6-glucuronide, which maintains activity at the μ-opioid receptor. The antiprostaglandin effect of NSAIDs can also decrease renal blood flow in susceptible patients. These agents must be used with caution.

General considerations for genitourinary pain management follow the same principles of pain management elsewhere in the body. For nonmalignant acute pain, nonnarcotic medications such as acetaminophen, aspirin, and NSAIDs are indicated as first line drugs. Tricyclic antidepressants and anticonvulsant agents are useful adjuncts, particularly for neuropathic pain. Opioids may be indicated in the short term. For malignancy, opioids are often necessary and in high doses. When oral administration is not feasible, parenteral administration of narcotics should be used.

Interventional techniques are an integral part of pain control in chronic urogenital pain syndromes and particularly for malignancy. Appropriate blocks can obviate or greatly reduce the need for systemic analgesics. If intractable pain persists despite optimized oral or intravenous therapy, a tunneled catheter trial can be performed and an implantable drug delivery system should be considered. Continuous intrathecal infusions minimize fluctuation of drug levels in cerebrospinal fluid and allow for significant analgesia and use of spinal adjuncts (local anesthetic, ziconotide) and opioids with significantly lessened dose-limiting side effects.

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Chapter 73

Anesthesia and the Hepatobiliary System

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Key Points

- All volatile anesthetics decrease hepatic blood flow, but desflurane and sevoflurane have the least significant effect on total hepatic blood flow and hepatic oxygen delivery, whereas halothane induces the most profound reductions in hepatic blood flow.
- Advanced liver disease may impair the elimination, prolong the half-life, and potentiate the clinical effects of several drugs, including morphine, meperidine, alfentanil, vecuronium, rocuronium, mivacurium, benzodiazepines, and dexmedetomidine. These drugs should be used cautiously in patients with cirrhosis or end-stage liver disease from any cause, and their dosage and administration should be adjusted accordingly.
- Abnormal liver enzyme test results may be seen in up to 4% of normal individuals and up to 36% of psychiatric patients, although the prevalence of clinically significant hepatic dysfunction in these individuals is less than 1%, thus suggesting that further costly preoperative testing is unnecessary in asymptomatic patients.
- Patients with asymptomatic elevations in serum transaminase levels (less than two times normal values) may undergo surgery with minimal impact on perioperative outcome.
- Retrospective data suggest that patients with acute hepatitis from any cause are at increased risk for hepatic failure and death after elective surgery. Thus, elective surgery should be delayed in these individuals until resolution of acute hepatocellular dysfunction can be confirmed.
- Asymptomatic patients with any form of chronic hepatitis should be carefully assessed before elective surgery, and meticulous care should be taken to maintain hepatic perfusion in the perioperative period and to avoid any hepatotoxic drugs or significant hypotension that could precipitate liver failure or hepatic encephalopathy.
- Based on large retrospective studies, patients with cirrhosis who are undergoing abdominal surgery, especially those in Child-Turcotte-Pugh (CTP) class C, appear to have an increased risk of perioperative death. Elective surgery in these individuals should be avoided, if possible, in favor of less invasive procedures.
- Postoperative jaundice may occur as a result of intraoperative hepatobiliary injury, anesthetic-induced hepatotoxicity, severe hepatic hypoperfusion (e.g., cardiogenic or hypovolemic shock), and a variety of medications.
- Patients with the most advanced forms of liver disease (e.g., CTP class B or C cirrhosis) should receive management designed to maximize hepatic perfusion and hepatic oxygen delivery and to prevent and treat the complications of hepatic encephalopathy, cerebral edema, coagulopathy, hemorrhage, and portal hypertension.

The liver is the largest organ in the body, and it plays a critical role in the homeostasis of many physiologic systems, including nutrient and drug metabolism, synthesis of plasma proteins and critical hemostatic factors, and detoxification and elimination of many endogenous and exogenous substances.[1] Acute or chronic liver dysfunction can impair the response to anesthesia and surgery in several critical ways, whereas certain anesthetics and hemodynamic disturbances can induce unique and serious alterations in postoperative hepatic function.

This chapter reviews the anesthetic implications of acute and chronic liver disease, the impact of anesthetics

on hepatic function, evaluation of perioperative changes in liver function test results and hepatobiliary function, and periprocedural considerations for some selected surgical procedures involving the liver and gallbladder.

EFFECT OF ANESTHETICS ON HEPATIC FUNCTION

This section focuses on the impact of volatile and intravenous anesthetics on liver blood flow and hepatic function. Halothane hepatitis and related volatile anesthetic–induced hepatotoxicity are discussed in Chapter 26.

VOLATILE ANESTHETICS

Volatile anesthetics variably influence blood flow to the liver, whereas intravenous anesthetics and opioids probably have a less significant impact. However, many potential confounding variables can influence hepatic blood flow and liver function, including the animal species studied, the subject's age, intravascular volume status, the type of mechanical ventilation used, body position at the time of physiologic measurements, simultaneous surgical procedures, changes in arterial blood pressure, concomitant use of vasopressors and local anesthetics, and alterations in hemoglobin and arterial oxygen concentrations. Yet reasonably firm conclusions can be reached regarding the impact and probable clinical significance of anesthetic drugs on hepatic function in normal and cirrhotic patients.

The impact of volatile anesthetics on hepatic blood flow (including hepatic arterial and portal venous blood flow), oxygen delivery, and hepatic oxygen supply-to-demand ratios has been determined for all the major volatile anesthetics, primarily in rat and pig experimental models. Human studies also support the findings of these early experimental investigations.[2,3] Many measurement techniques have been used to assess hepatic and portal venous blood flow, although plasma clearance of indocyanine green is most commonly used to assess hepatic blood flow. Transesophageal echocardiography can also evaluate hepatic vein flow, but it is only an indirect measurement of hepatic perfusion and oxygenation (see also Chapter 46). A novel technique involving pulsed Doppler probes implanted in animals and in humans undergoing cholecystectomy has allowed accurate measurement of hepatic arterial and portal vein blood flow.[4] Most anesthetics decrease portal blood flow (PBF) because of decreased cardiac output; however, hepatic arterial blood flow (HABF) may increase, although often not sufficiently to restore total hepatic blood flow (THBF) to normal values.[5] THBF is equal to the sum of PBF and HABF. Mean arterial blood pressure (MAP) and cardiac output decrease with all volatile anesthetics, but a more pronounced reduction in PBF, HABF, and THBF occurs with halothane and enflurane than with isoflurane and sevoflurane (Fig. 73-1).[2-4,6-10] These changes generally apply across a range of minimum alveolar concentrations (MACs). Volatile anesthetics also alter portal venous and hepatic arterial vascular resistance to variable degrees; these changes, in conjunction with decreases in cardiac output, MAP, and mesenteric sympathetic tone, modify the hepatic vascular supply.[11]

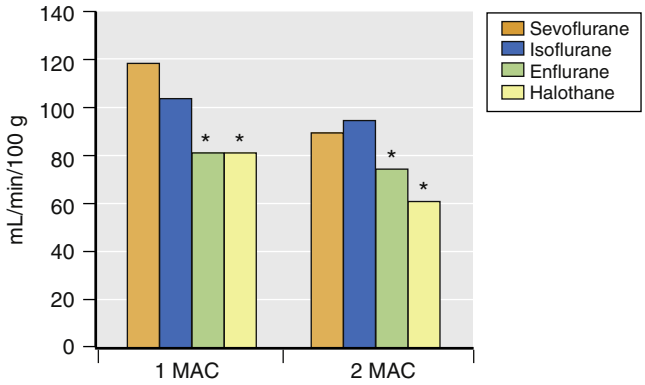


Figure 73-1. Impact of halothane, enflurane, isoflurane, and sevoflurane at 1.0 and 2.0 minimum alveolar concentration (MAC) on total hepatic blood flow (THBF) in dogs. THBF decreased with increasing anesthetic concentrations of each volatile agent. Sevoflurane and isoflurane were similar in their modest effect on THBF, whereas halothane caused a dramatic decrease in THBF, especially at 2-MAC exposure. *Differs from sevoflurane and isoflurane at comparable MAC values ($P < .05$). *(Data from Frink EJ, Morgan SE, Coetzee A, et al: The effects of sevoflurane, halothane, enflurane, and isoflurane on hepatic blood flow and oxygenation in chronically instrumented greyhound dogs,* Anesthesiology *76:85-90, 1992.)*

Although all volatile anesthetics decrease MAP and PBF, halothane has a more consistently dramatic impact on HABF. Halothane causes vasoconstriction in the hepatic arterial vascular bed, as reflected by an increase in hepatic arterial resistance.[4,12] In vivo videomicroscopy after halothane exposure in rats demonstrated reduced sinusoidal blood flow as a result of decreased sinusoidal diameter, thus providing direct evidence of vasoconstriction at the microvascular level.[12] In contrast, isoflurane increased flow velocity in hepatic sinusoids and in this way preserved microvascular blood flow more than halothane or enflurane.[12] Benumof and colleagues demonstrated markedly reduced HABF after halothane administration in two patients during hepatic arteriography; hepatic blood flow returned to normal 20 minutes after discontinuation of halothane anesthesia.[13]

Halothane also reduces hepatic oxygen delivery and hepatic venous oxygen saturation (Fig. 73-2).[14] These changes are related to decreased MAP and more dramatic reductions in cardiac output with halothane than with any other volatile anesthetics.[5] Gelman and associates demonstrated that during surgical stress in pigs, fentanyl or isoflurane anesthesia, which decreases MAP by less than 30%, provided adequate oxygen supply, whereas halothane anesthesia, which decreases arterial blood pressure more than 30%, provided inadequate hepatic oxygen supply.[9] This finding also applied to episodes of hepatic ischemia, in which fentanyl or isoflurane provided better protection than halothane or enflurane. In addition to vascular changes, hepatic function, as measured by serum transaminase levels, also suggests an unfavorable impact of halothane versus isoflurane.[3]

Volatile anesthetic–induced alterations in hepatic blood flow are, in part, mediated by an autoregulatory

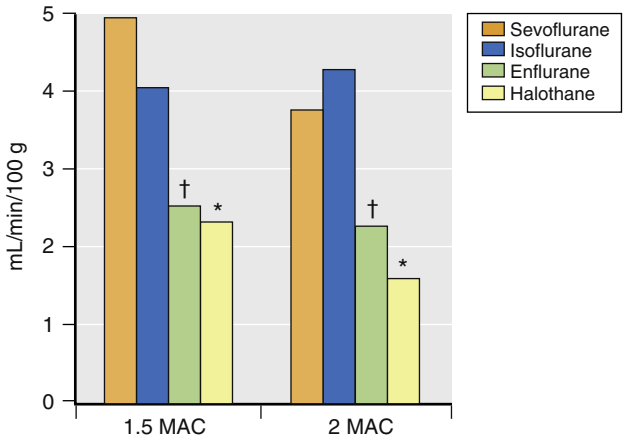


Figure 73-2. Impact of halothane, enflurane, isoflurane, and sevoflurane at 1.5 and 2.0 minimum alveolar concentration (MAC) on hepatic arterial oxygen delivery in chronically instrumented dogs. Halothane produced the greatest reduction in hepatic arterial oxygen delivery, whereas sevoflurane and isoflurane had insignificant effects on oxygen delivery at any MAC level. *Differs from isoflurane and sevoflurane at comparable MAC values ($P < .05$). †Differs from sevoflurane at comparable MAC values ($P < .05$). *(Data from Frink EJ, Morgan SE, Coetzee A, et al: The effects of sevoflurane, halothane, enflurane, and isoflurane on hepatic blood flow and oxygenation in chronically instrumented greyhound dogs,* Anesthesiology *76:85-90, 1992.)*

mechanism that maintains constant THBF. This physiologic adaptation is termed the *hepatic arterial buffer response* (HABR), which matches reductions in PBF with increases in HABF to maintain total blood flow to the liver constant in the presence of profound hypovolemia, indirect effects of major abdominal surgery, or severe hemorrhage.[15] Halothane disrupts this compensatory response, whereas sevoflurane and isoflurane maintain HABR.[15,16] Sevoflurane further suppresses hepatic arterial vasoconstriction and thus maintains HABF more effectively than does halothane.[17] Sevoflurane is also consistently equivalent or superior to isoflurane in maintaining HABF, hepatic oxygen delivery, and oxygen delivery-to-consumption ratios.[10,18,19] In addition, laboratory studies demonstrated insignificant changes in conventional liver function test results after exposure to isoflurane or desflurane, with the most favorable profiles with desflurane and sevoflurane as compared with other volatile anesthetics.[3,20-23]

The encouraging results obtained with sevoflurane versus older volatile anesthetics are further supported by the observation that compound A produced by prolonged, low-flow sevoflurane anesthesia does not adversely affect hepatic function in adult surgical patients as determined by liver function testing or measurement of arterial ketone body ratios, a putative measure of hepatocyte function.[24-28] In a large clinical study of sevoflurane, Bito and co-workers noted mild postoperative increases in bilirubin and transaminase values in 100 surgical patients receiving low- and high-flow sevoflurane or isoflurane anesthesia, but no evidence of clinical hepatotoxicity.[28] Routine liver function test results are often mildly increased after surgery and anesthesia with volatile anesthetics, although the specific contribution of the anesthetic itself is debatable.[3,24,25,29]

Administration of either sevoflurane[26,27,30] or desflurane[31,32] to human volunteers not undergoing surgery produced no significant abnormalities in liver function test results, thus suggesting that other perioperative surgical factors may induce mild, transient alterations in plasma transaminase levels. In fact, early human investigations found steep decreases in estimated hepatic blood flow immediately after the induction of anesthesia correlated with the decreases in arterial blood pressure.[33] Hepatic blood flow rapidly returned to normal soon after the start of surgery, a finding suggesting global reductions in cardiac output and blood pressure as mechanisms responsible for the reduced hepatic blood flow, rather than a sustained adverse influence of specific volatile or intravenous anesthetics on hepatic blood flow. In experimental and human ischemia-reperfusion injury studies,[34,35] sevoflurane had favorable effects on hepatic function through an ischemic-preconditioning effect. These data are consistent with the favorable cardiac ischemic-preconditioning effect of sevoflurane.

Desflurane had effects similar to those of isoflurane on hepatic blood flow and function when assessed in animal and human investigations. In chronically instrumented dogs, Merin and associates demonstrated slight but significant decreases in THBF at 1.75 MAC as a result of decreased PBF, but no significant differences between desflurane and isoflurane in any measure of hepatic blood flow over a range of MAC values.[36] Armbruster and coworkers observed decreased THBF at 1 MAC desflurane in pigs, but only at levels of hypotension unlikely to be encountered clinically and without alterations in liver function test results.[21] Other canine data suggested better preservation of THBF with desflurane than with halothane or isoflurane (Fig. 73-3).[37] Subsequent studies in human volunteers examining hepatic function rather than hepatic blood flow failed to demonstrate any hepatotoxic effects of desflurane.[30-32]

In contrast to healthy volunteers and surgical patients, substantially less information is available describing the impact of anesthetics on hepatic function in patients with advanced liver disease. Desflurane and isoflurane may not change perioperative liver function test results in adult surgical patients with chronic liver disease.[38] Experimental models of hepatic injury showed lesser increases in hepatic enzymes and no evidence of microscopic hepatocyte injury with sevoflurane compared with halothane-treated rats.[39] Isoflurane was more efficient at preserving hepatic blood flow in cirrhotic animals than is ketamine or halothane,[40] although other studies showed no difference in hepatic function in cirrhotic rats exposed to fentanyl, halothane, enflurane, or isoflurane.[41] However, halothane decreases both hepatic blood flow and hepatic function and should not be given to patients with advanced liver disease. Given the current availability of other volatile anesthetics and the overall marked decreased use of halothane, this issue is primarily of historical interest. Moreover, as a consequence of the hepatotoxic potential of halothane, halothane should not be used in healthy adults or in any patient with significant hepatic dysfunction.

In this regard, other anesthetics devoid of hepatotoxicity are available. Xenon, an inert gas first described as

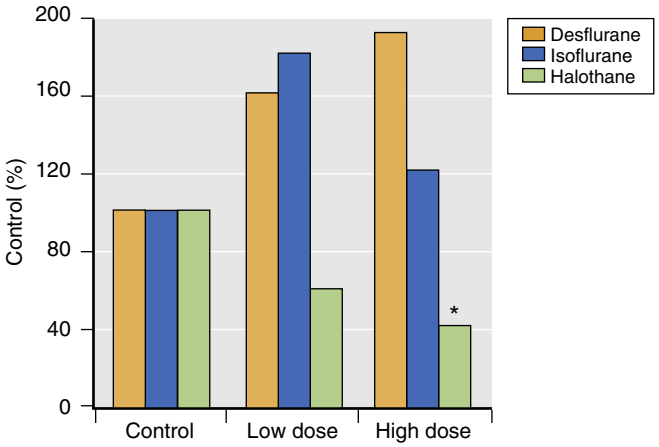


Figure 73-3. Influence of low- and high-dose desflurane, halothane, and isoflurane on total hepatic blood flow (THBF) as measured with radioactive microspheres in chronically instrumented dogs. In contrast to desflurane and isoflurane, which increased THBF, halothane caused a significant decrease in THBF at high doses. *Significantly different from conscious control ($P < 0.05$). *(Data from Hartman JC, Pagel PS, Proctor LT, et al: Influence of desflurane, isoflurane and halothane on regional tissue perfusion in dogs,* Can J Anaesth *39:877-887, 1992.)*

having anesthetic properties in 1951,[42] has been considered to be an ideal inhaled anesthetic because it is nonexplosive and nonflammable, exhibits low toxicity, has no known teratogenic effects, and has rapid induction and recovery profiles resulting from its extremely low blood-gas coefficient of 0.115, the lowest of all known anesthetics.[43,44] Xenon has no significant effect on left ventricular function, systemic vascular resistance, or systemic blood pressure. [44-46] Its hemodynamic profile is similar to that of propofol anesthesia in humans,[45] and it caused less hypotension and had no effect on left ventricular function when compared with isoflurane in human studies.[46,47] Although animal investigations suggested a substantial increase in cerebral perfusion with xenon when compared with intravenous anesthetics, xenon has no effect on other regional organ perfusion, including liver perfusion. It does not alter HABF, and given the absent effect on cardiac output, it should, in theory, have no impact on THBF (unlike all other volatile anesthetics). It also does not alter liver function tests. In an experimental model, Reinelt and colleagues noted higher hepatic venous oxygen content levels in pigs exposed to 73% to 78% xenon versus intravenous anesthesia with pentobarbital and buprenorphine.[48] These observations were believed to be secondary to a possible reduction of plasma catecholamine levels and subsequent reduced hepatic metabolism and increased hepatic venous oxygen content. Xenon may therefore prove to be an ideal anesthetic with regard to hepatic perfusion. Larger clinical trials in patients with both normal and abnormal hepatic function are necessary before definitive conclusions can be reached relative to its safety in patients with acute and chronic liver disease.

In summary, the influence of volatile anesthetics on hepatic blood flow and function is complex and is related not only to features unique to the anesthetic itself but also to other patient-related variables such as the severity of underlying liver dysfunction, the presence of advanced age, and the impact of surgical stress and intraabdominal surgical manipulation. However, sevoflurane, desflurane, and isoflurane have been consistently shown to preserve hepatic blood flow and function better than halothane or enflurane.

INTRAVENOUS ANESTHETICS

When compared with volatile anesthetics, less information is available regarding the impact of intravenous anesthetics on hepatic function (see also Chapters 31 to 33). Early investigations suggested that etomidate and thiopental decreased hepatic blood flow, either from increased hepatic arterial vascular resistance or from reduced cardiac output and blood pressure,[49] whereas ketamine has little impact on hepatic blood flow, even in large doses.[50] With the use of sensitive radiolabeled microsphere determinations of organ blood flow in animals, propofol was found to increase THBF in both the hepatic arterial and portal venous circulations, thus suggesting a significant splanchnic vasodilator effect of this drug.[51,52] THBF was maintained in some animal models even with significant reductions in MAP,[53] whereas other animal models showed decreased mean hepatic blood flow despite increased MAP, a finding attributed to species-specific effects of propofol.[54] Limited human data suggest a more favorable splanchnic and hepatic oxygen delivery balance with propofol than with halothane.[55] Meierhenrich and colleagues demonstrated increased hepatic blood flow with propofol in humans by using transesophageal echocardiographic, Doppler-derived measurements of hepatic blood flow, a technique considered more accurate than hepatic clearance of indicator dyes.[56] Studies using indicator dyes in humans and animals suggested decreased hepatic blood flow with propofol,[57,58] whereas other animal investigations using techniques not involving dye showed improved hepatic blood flow under propofol anesthesia.[52,59] Overall, an antioxidant effect may occur with propofol in patients undergoing liver surgery and orthotopic liver transplantation (see also Chapter 74),[60,61] although the ultimate effect of this drug on ischemia-reperfusion injury may be modest, at best, in these patient populations. In summary, based on limited clinical and experimental data, it appears that intravenous anesthetics have only a modest impact on hepatic blood flow and no meaningful adverse influence on postoperative liver function when blood pressure and cardiac output are adequately maintained.

CENTRAL NEURAXIAL ANESTHESIA

The effect of spinal or epidural anesthesia on liver blood flow and hepatic function is not clearly an anesthetic drug–induced alteration in hepatic function (see Chapter 56). Kennedy and colleagues showed that hepatic blood flow decreased during high spinal and epidural anesthesia and appeared to mirror simultaneous reductions in MAP.[62,63] Other animal data suggested reduced PBF and unchanged HABF with high epidural blockade, thus causing a decrease in THBF.[64] This finding was confirmed in humans undergoing thoracic epidural anesthesia in which echocardiography confirmed reductions in hepatic venous blood flow.[65] These adverse changes

may be reversed and hepatic blood flow maintained with the administration of vasopressors (e.g., dopamine or ephedrine) to restore PBF[66–68] or fluid administration to maintain normal arterial blood pressure,[69] although vasopressors may actually further reduce hepatic blood flow.[65] Presumably, hypotension-induced reductions in hepatic blood flow are secondary to decreased splanchnic blood flow and thus reduced PBF. The impact of absorbed local anesthetic, with or without epinephrine, on cardiac output or splanchnic vascular resistance is unknown.

EFFECT OF HEPATIC DYSFUNCTION AND HEPATOBILIARY DISEASE ON ANESTHETIC DRUG PHARMACOKINETICS

Liver disease may have a significant impact on drug metabolism and pharmacokinetics as a result of alterations in protein binding, reduced levels of serum albumin and other drug-binding proteins, altered volume of distribution because of ascites and increased total-body water compartments, and reduced metabolism secondary to abnormal hepatocyte function (see Chapters 24 and 74). In addition, sedatives and opioids may have exaggerated effects in patients with advanced liver disease and may either induce or worsen hepatic encephalopathy.[70] The impact of long-term alcohol ingestion on hepatic enzyme induction may also influence the ultimate effect of drugs in patients with cirrhosis.

The impact of liver disease on drug disposition depends not only on the elimination pathways for a given drug but also on the severity of the underlying hepatic dysfunction. The efficiency of drug removal by the liver is determined by several factors, including hepatic blood flow, hepatic enzyme activity and efficiency, the extent of plasma protein binding, cholestasis-induced alterations in the enterohepatic circulation and metabolism of enteral drugs, and the presence of portosystemic shunts that exclude certain drugs from elimination by the diseased liver.[71] In addition, the influence of liver disease on drug elimination differs for enteral and parenteral drugs.[70] In general, severe liver disease predictably alters the metabolism of drugs with large extraction ratios, such as lidocaine and meperidine, in which clearance primarily depends on hepatic blood flow or portosystemic shunting. Conversely, the metabolism of low-extraction drugs, such as the benzodiazepines, is influenced mainly by protein binding, in which unbound drug is available for elimination, and by intrinsic hepatic clearance and metabolism, which are reduced in accordance with the severity of hepatocellular dysfunction.[70,71] However, an increased free fraction of a drug because of reduced levels of plasma proteins may counter the impact of reduced hepatic metabolism and lead to modest changes in the ultimate effect of the drug.[71] Finally, greater free fractions of available drug as a result of reduced protein binding may lead to greater drug deposition in tissues (and a potentially increased volume of distribution), which in conjunction with reduced hepatic metabolism may increase drug half-life.[71] It is thus evident that drug pharmacokinetics in the presence of advanced liver disease is complex. The impact on different classes of drugs is discussed separately.

OPIOIDS

The significantly reduced metabolism of morphine in patients with advanced cirrhosis leads to a prolonged elimination half-life, markedly increased bioavailability of orally administered morphine, decreased plasma protein binding, and potentially exaggerated sedative and respiratory-depressant effects (see also Chapter 31).[71] Although extrahepatic metabolism may contribute to morphine clearance in patients with cirrhosis, the administration interval should be increased 1.5- to 2-fold in these patients and the oral dose of the drug reduced because of increased bioavailability.[71] Similar changes occur with meperidine, in which a 50% reduction in clearance and a doubling of the half-life have been observed. In addition, clearance of normeperidine is reduced, and patients with severe liver disease may experience neurotoxicity from accumulation of normeperidine.[71]

In contrast to these drugs, fentanyl is a highly lipid-soluble synthetic opioid that has a short duration of action after a single intravenous bolus dose because of rapid redistribution into storage sites. With repeated administration or continuous infusions, accumulation may occur and lead to prolonged effects.[71] Because fentanyl is almost completely metabolized in the liver, its elimination should be predictably prolonged in patients with advanced liver disease. However, fentanyl elimination is not appreciably altered in patients with cirrhosis.[71,72] Whether the limited extent of liver disease in the study patients affected the pharmacokinetic data or whether continuous infusions or repeated doses in cirrhotic patients produce more exaggerated and pronounced effects is unknown.

Sufentanil, a more potent but similar synthetic lipophilic opioid, is also extensively metabolized by the liver and is highly protein bound. Single-dose pharmacokinetics is not significantly altered in patients with cirrhosis, although the impact of continuous infusions and reduced protein binding is as ill-defined for sufentanil as for fentanyl.[73] Alfentanil, a short-acting opioid less potent than fentanyl, is also exclusively metabolized by the liver and is highly protein bound.[71] However, unlike with fentanyl or sufentanil, the half-life of alfentanil is almost doubled in patients with cirrhosis, and higher free fractions of the drug are observed; these higher free fractions can potentially lead to a prolonged duration of action and enhanced effects.[74,75] Remifentanil is a synthetic opioid with an ester linkage that allows for rapid hydrolysis by blood and tissue esterases; such hydrolysis leads to high clearance, rapid elimination, and recovery that is almost independent of the dose or duration of infusions.[76] Predictably, the clearance and elimination of remifentanil are indeed unaltered in patients with severe liver disease or in those undergoing liver transplantation.[71,77-79]

SEDATIVE-HYPNOTIC DRUGS

Thiopental has a small hepatic extraction ratio, and therefore its metabolism and clearance should be adversely affected in patients with liver disease (see also Chapter 32). However, the elimination half-life of thiopental is unchanged in cirrhotic patients, possibly

because of a large volume of distribution.[80,81] A prolonged effect from standard doses of thiopental thus seems unlikely in this patient population. In contrast, other intravenous anesthetics, including methohexital, ketamine, etomidate, and propofol, are highly lipid soluble, are metabolized by the liver, have a large hepatic extraction ratio, and should have diminished clearance in the presence of advanced liver disease.[76] Despite this pharmacokinetic profile, etomidate clearance is unchanged in cirrhotic patients, although increased volumes of distribution may prolong the elimination half-life and result in unpredictable recovery times.[82] Other investigators have shown altered pharmacokinetics of etomidate infusions in cirrhotic patients, presumably because of the drug's impaired hepatic clearance.[83] In contrast to the situation in cirrhotic patients, etomidate requirements in individuals with obstructive jaundice, as measured by predefined bispectral index values, were significantly less than in control patients. [84] Methohexital and propofol also have an elimination kinetic profile in cirrhotic individuals that is similar to that observed in normal patients,[76] both after single-bolus administration of propofol[85] and after propofol infusion,[86] an effect that may result from extrahepatic metabolism of propofol.[87] However, mean clinical recovery times may be longer after discontinuation of propofol infusions in cirrhotic patients.[86] The reduced clearance of midazolam in patients with end-stage liver disease produces prolonged elimination half-lives.[88,89] In conjunction with reduced protein binding and increased free fractions of midazolam, a prolonged duration of action and an enhanced sedative effect should be anticipated in patients with severe liver disease, especially after multiple doses or prolonged infusions. Similar changes have also been observed with diazepam.[89]

Dexmedetomidine, an α_2-adrenergic agonist with sedative and analgesic properties, is primarily metabolized in the liver with minimal renal clearance. Data from patients with hepatic failure of varying severity demonstrated significantly decreased clearance, prolonged half-lives, and lower bispectral index values than in normal control patients.[90] Dosage adjustments are therefore indicated when dexmedetomidine is used in patients with significant hepatic dysfunction. This evidence mirrors, in part, findings from dexmedetomidine use in individuals with renal dysfunction, in whom prolonged sedation despite unchanged pharmacokinetics has been attributed to altered protein binding, a factor that also applies to patients with hepatic dysfunction.[91,92]

In summary, despite substantial hepatic metabolism of most intravenous anesthetic induction agents, limited evidence from single-dose pharmacokinetic studies suggests that cirrhosis has minimal impact on the pharmacokinetic profile of sedative-hypnotic drugs. Given that the clinical effect and duration of action of benzodiazepines are more pronounced in the presence of severe liver disease, it would therefore be prudent to administer these drugs cautiously when using repeated dosing or prolonged infusions, either in the operating room or in the intensive care unit, where drug accumulation, prolongation of effects, and increased risk of hepatic encephalopathy can be anticipated.

NEUROMUSCULAR BLOCKING DRUGS

In contrast to opioids and intravenous anesthetics, more comprehensive information is available regarding the impact of cirrhosis on the pharmacokinetics and pharmacodynamics of neuromuscular blocking drugs (see also Chapter 34). Vecuronium is a steroidal muscle relaxant that undergoes hepatic elimination.[93,94] This drug has decreased clearance, a prolonged elimination half-life, and prolonged neuromuscular blockade in patients with cirrhosis (Fig. 73-4).[95,96] The impact of alcoholic liver disease is less definite, with clearance and elimination half-lives typically unchanged.[97] Rocuronium also undergoes hepatic metabolism and elimination.[98] Hepatic dysfunction can increase the volume of distribution of rocuronium, thus prolonging its elimination half-life,[98] as well as producing a longer clinical recovery profile and return of normal twitch tension.[98,99] Gao and associates observed a 24% decrease in rocuronium infusion requirement in 17 patients during the anhepatic phase of liver transplantation.[100] Although the initial clinical recovery of neuromuscular function is not affected by liver disease, larger initial doses or repeated administration will typically prolong the effect of rocuronium in the presence of significant hepatic dysfunction.[98]

The increased volume of distribution for some drugs observed in cirrhotic patients can also prolong the elimination half-life of pancuronium.[101] Muscle relaxants that undergo organ-independent elimination, such as atracurium (nonspecific ester hydrolysis) and cisatracurium (Hofmann elimination), have elimination half-lives and clinical durations of action similar to those observed in normal patients and in patients with end-stage liver disease.[102-104] The unique elimination of mivacurium by plasma cholinesterase is, however, altered by cirrhosis.

Mivacurium is associated with significantly longer recovery of twitch tension and has a longer elimination half-life (18 versus 34 minutes in normal versus cirrhotic patients, respectively) and a longer residence time in patients with hepatic failure than in normal patients, a finding closely correlated to reduced plasma cholinesterase activity in cirrhotic patients.[105-107] This reduced activity is related to reduced clearance by plasma cholinesterase of the two active isomers of mivacurium, *cis-trans* and *trans-trans*.[107] Infusion rates of mivacurium should be adjusted accordingly in patients with advanced liver disease. The impact of liver disease on mivacurium's pharmacokinetics is likely of historical interest, as the drug is no longer available in the United States. The changes observed with mivacurium are predictably expected with succinylcholine if decreased plasma cholinesterase levels are present because of advanced liver disease. Lowered cholinesterase levels have been observed in these individuals,[108] and they may prolong the effect of succinylcholine.

Sugammadex "reverses" neuromuscular blockade from steroidal neuromuscular blocking drugs (vecuronium and rocuronium) by a mechanism completely different from that of neostigmine. Sugammadex encapsulates rocuronium, so it cannot cause neuromuscular blockade. The sugammadex-rocuronium complex is then transported through perfusion mainly to the kidney for excretion. Sugammadex is excreted unchanged in the urine.[109]

In summary, cirrhosis and other forms of advanced liver disease predictably reduce the elimination of vecuronium, rocuronium, and mivacurium and prolong the duration

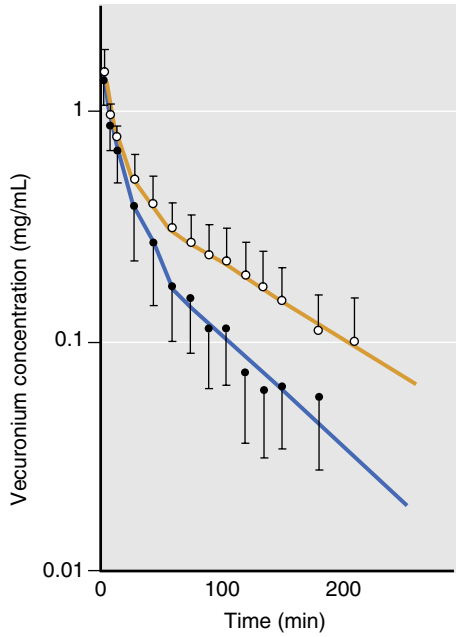


Figure 73-4. Disappearance of vecuronium from plasma after a single bolus dose of 0.2 mg/kg. A semilogarithmic plot of plasma concentration versus time shows that the vecuronium concentration remained at a much higher level during the elimination phase in patients with cirrhosis (*open circles*) than in normal control patients (*black circles*). This difference reflects the markedly decreased plasma clearance of vecuronium, increased elimination half-life, and increased duration of neuromuscular blockade in patients with cirrhosis versus normal individuals. *(From Lebrault C, Berger JL, D'Hollander AA, et al: Pharmacokinetics and pharmacodynamics of vecuronium (ORG NC 45) in patients with cirrhosis,* Anesthesiology *62:601-605, 1985.)*

of neuromuscular blockade, especially after repeated doses or the use of prolonged infusions. Atracurium and cisatracurium are not dependent on hepatic elimination and can be used without modification of dosing in patients with end-stage liver disease. Careful monitoring of neuromuscular function is recommended whenever muscle relaxants are used in this patient population.

RISK FACTORS FOR POSTOPERATIVE HEPATOBILIARY COMPLICATIONS

The anesthesia literature is replete with detailed descriptions of preoperative assessment of cardiac and renal risk for noncardiac surgery.[110,111] Because preoperative risk factors for the development of postoperative hepatic dysfunction or failure after nonhepatic surgery have not been clearly elucidated, anesthesiologists have based decisions regarding the care of patients with preoperative hepatic dysfunction on data derived in the 1960s and 1970s. Unfortunately, prospective studies addressing these issues in the current era of newer anesthetic and surgical techniques are lacking. Assessment of risk factors for postoperative hepatic insufficiency requires consideration of the following: (1) asymptomatic elevations in preoperative liver enzyme test results; (2) acute hepatitis (viral, drug, toxin), steatosis, chronic hepatitis, and cirrhosis; and (3) the types of surgical procedures that potentially predispose to postoperative liver dysfunction.

ASYMPTOMATIC PREOPERATIVE LIVER ENZYME TEST ABNORMALITIES

Unnecessary laboratory test screening may reveal abnormally elevated liver enzyme test results in otherwise healthy patients. Abnormalities in standard liver enzyme tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase, occur in 0.1% to 4% of the general population,[112,113] as well as in as many as 36% of psychiatric patients, in whom alcohol and illicit drug abuse is prominent.[114] However, the overall prevalence of clinically significant hepatic dysfunction in asymptomatic patients is less than 1%. A retrospective analysis of 91 noncirrhotic patients with serum liver enzyme levels greater than 1.5 times normal who were undergoing surgery reported no development of hepatic failure or postoperative complications related to hepatic dysfunction.[115] Of these patients, 34 had hepatology consultations resulting in additional laboratory and ultrasonographic testing that failed to influence either the management or outcome of their cases. Thus, pursuing more extensive evaluation with costly tests such as ultrasonography, radionuclide imaging, or liver biopsy is rarely indicated.

In general, the most appropriate initial approach to a surgical patient with abnormal liver enzyme test results consists of a detailed history and physical examination. Symptoms of fatigue, anorexia, nausea, vomiting, biliary colic, pruritus, fever, or dark-colored urine warrant further evaluation because these findings may suggest clinically active hepatobiliary disease and thus potentially preclude elective surgery. If, however, the patient is asymptomatic, the significance of abnormal enzyme test results can be questioned. The patient should be further asked about a history of associated diseases such as chronic hepatitis, a family history of Wilson disease, hemochromatosis, α_1-antitrypsin deficiency, diabetes mellitus, hyperthyroidism or hypothyroidism, and previous transfusion history. All medications, including vitamins and herbal or other homeopathic remedies, should be reviewed for potential hepatotoxic side effects. The patient should be further questioned regarding alcohol or other illicit drug use, the presence of tattoos, sexual promiscuity, and consumption of raw seafood because they are potential risk factors for infectious hepatitis.

Physical examination may reveal findings consistent with active liver disease, such as icterus, palmar erythema, spider angiomas, gynecomastia, hepatosplenomegaly, ascites, or peripheral edema. Although these findings invariably suggest a diagnosis of cirrhosis, it is reasonable to repeat the test if a complete history and physical examination fail to suggest a cause of the biochemical abnormality. Minor increases in liver enzyme test results are defined as less than twice the normal value,[116] and, given a negative history and physical examination, they do not warrant additional testing before anesthesia and surgery.[115] Assessment of larger increases in liver enzyme test results requires an analysis of the specific abnormality.

AST and ALT are sensitive indicators of hepatocyte integrity. AST is present in hepatocyte cytoplasm and mitochondria, but it is also ubiquitous in cardiac and skeletal muscle; in kidney, brain, pancreas, and lung tissue; and in red and white blood cells. AST is therefore a less specific index of cellular injury than is ALT, which is

primarily found in the cytoplasm of hepatocytes. Both enzymes are released when the hepatic cell membrane is injured, although a correlation appears to exist between the degree of injury and serum aminotransferase levels. The AST/ALT ratio may also be helpful in distinguishing between alcohol-induced hepatitis and viral hepatitis. Alcohol tends to damage hepatocyte mitochondria preferentially, thereby causing an elevation in AST usually greater than twice the ALT.[117] In addition, ALT activity is diminished in patients with alcohol-induced liver disease because these individuals tend to have deficiencies of pyridoxal 5-phosphate, a vitamin necessary for ALT function. In contrast, a decrease in the AST/ALT ratio is more consistent with a diagnosis of viral hepatitis. Aminotransferases also increase in choledocholithiasis, cholangitis, and ischemic hepatitis. Ischemic hepatitis may not uncommonly produce levels greater than 10,000 International Units/L.

Similar to AST, alkaline phosphatase is present in many tissues, including bone, intestine, kidney, and placenta, as well as in leukocytes. The enzyme catalyzes the hydrolysis of orthophosphate from ester substrates at an alkaline pH. In hepatocytes, alkaline phosphatase is synthesized by biliary epithelial cells and is released in relation to the degree of bile duct obstruction. Measuring serum γ-glutamyltransferase (GGT), an enzyme found predominantly in hepatocytes and biliary epithelial cells, may aid in distinguishing between hepatic and bone causes of increased alkaline phosphatase. Although GGT is a very sensitive indicator of the presence or absence of hepatobiliary disease, by itself it lacks specificity because it is also increased in patients with myocardial infarction, renal disease, diabetes mellitus, and chronic obstructive pulmonary disease. If both alkaline phosphatase and GGT levels are elevated, the abnormality probably reflects hepatobiliary disease. Increased levels of alkaline phosphatase and GGT usually occur in extrahepatic bile duct obstruction and intrahepatic cholestasis from infiltrative diseases such as sarcoidosis, from mass lesions such as primary or metastatic carcinoma, or from drug-induced cholestasis.

Although liver enzyme elevation is an indication of active disease, synthetic hepatic function is best measured by serum bilirubin, albumin, and the prothrombin time. The bilirubin concentration in plasma varies in accordance with its production and inversely with hepatic clearance. Hepatic microsomal enzymes convert unconjugated bilirubin to the more water-soluble form, thereby permitting excretion in bile and preventing central nervous system toxicity. Total bilirubin levels represent both conjugated (direct bilirubin) and unconjugated (indirect bilirubin) forms. Unconjugated hyperbilirubinemia suggests hemolysis or an inherited disorder of bilirubin metabolism such as Gilbert syndrome. If more than 50% of the total serum bilirubin is conjugated, cholestasis or hepatocellular dysfunction is implied. Albumin is synthesized solely in the liver and, in healthy adults, has a half-life of approximately 21 days. The normal level of 3.5 g/dL usually decreases in long-standing and severe liver disease but is also influenced by overall nutritional status.

Finally, hepatobiliary dysfunction can cause an abnormal prothrombin time by impairing synthesis of the essential clotting factors II (prothrombin), VII, IX, and X. Hepatic synthesis of these factors depends on vitamin K, a fat-soluble vitamin found in certain foods and produced by intestinal bacteria, so abnormalities in prothrombin activity (as expressed by the international normalized ratio [INR]) may also occur in patients with malnutrition or malabsorption syndromes. The plasma half-time of these vitamin K–dependent factors is very short (<24 hours), and hence the INR responds rapidly to changes in synthetic function. This rapid response makes this test a more sensitive index of hepatic function than serum albumin.

Although no prospective, randomized, controlled studies have been designed to assess the perioperative risk of anesthesia or surgery in asymptomatic patients with elevated liver enzyme test results, a suggested approach to these patients is outlined in Figure 73-5.

ACUTE HEPATITIS

The diverse roles of the liver in drug metabolism, hemostasis, and coagulation function, in association with surgery and anesthesia-related alterations in hepatic perfusion, make it an organ extremely susceptible to clinically important hepatocellular injury induced by viruses or by alcohol or other drugs. Consensus opinion, based largely on data derived from older, predominantly retrospective studies, is that acute hepatitis, whether viral, alcohol induced, or drug induced, is a risk for the development of hepatic failure or death after elective surgery. In 1982, Powell-Jackson and co-workers described 36 patients who underwent exploratory laparotomy for either suspected extrahepatic biliary tract obstruction or intraabdominal malignancy, all of whom were ultimately found to have viral or alcoholic hepatitis, cirrhosis, or Budd-Chiari syndrome.[118] Of these patients, 61% suffered significant morbidity, including postoperative liver failure, and 31% died within 1 month of surgery. One hundred percent of patients with histologically proven hepatitis died. Greenwood and associates also reported high mortality rates in patients with alcoholic hepatitis who were undergoing open liver biopsy.[119] Bell and colleagues, however, noted that survival rates were not influenced by the presence of biopsy-proven hepatitis in 164 patients with alcoholic cirrhosis who required emergency portocaval shunts for esophageal variceal bleeding.[120]

In the current era of advanced diagnostic testing and imaging in which nonoperative management of extrahepatic biliary tract obstruction can be performed with endoscopic retrograde cholangiopancreatography (ERCP), invasive procedures such as open liver biopsy or exploratory laparotomy can be avoided. The preponderance of earlier information on perioperative morbidity and mortality indicates that elective surgery should be delayed in patients with acute hepatitis of any origin until resolution of hepatocellular dysfunction can be confirmed.[70] The influence of the type of surgery on patients with hepatitis is described later.

STEATOSIS AND STEATOHEPATITIS

Patients with chronic, asymptomatic increases in serum aminotransferase levels are often found by liver biopsy to

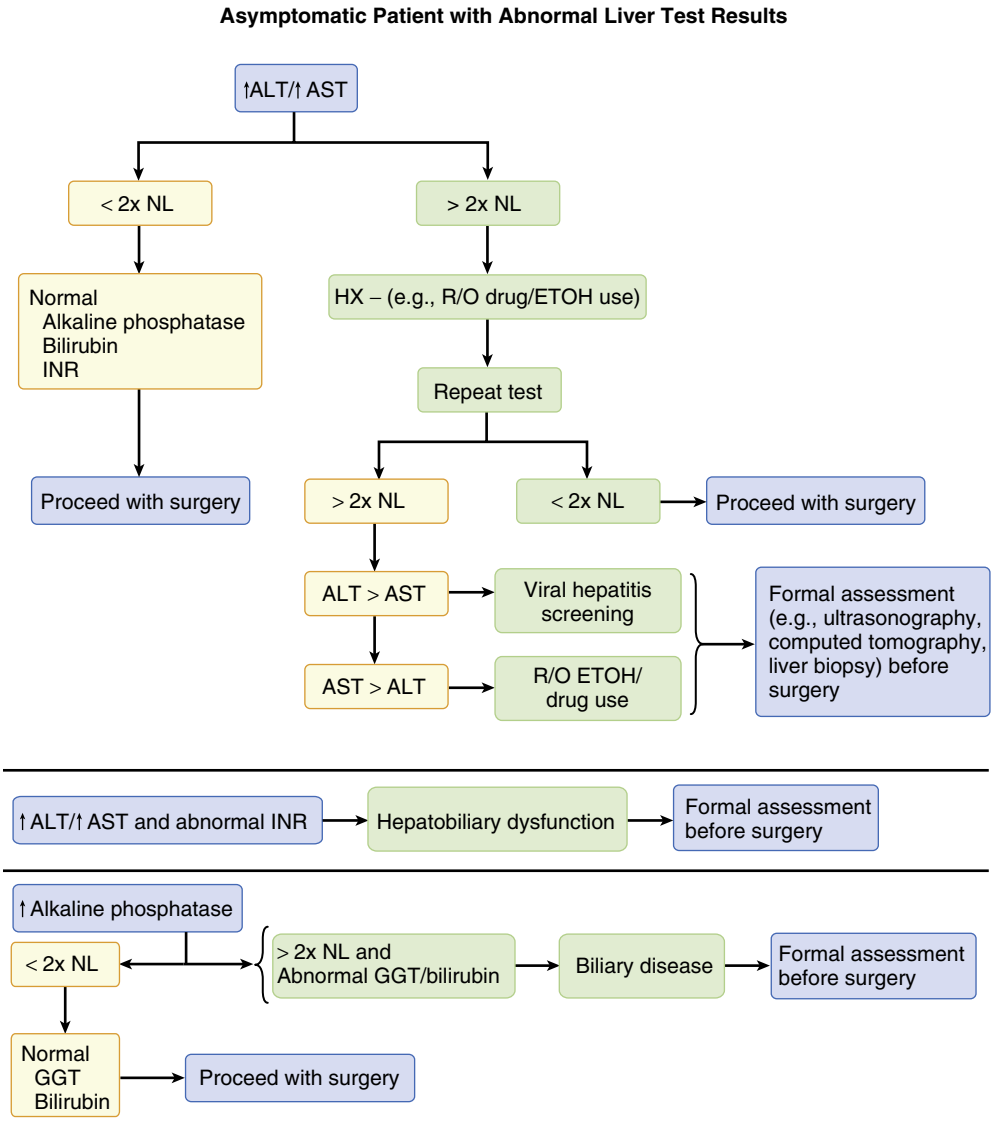


Figure 73-5. Approach to asymptomatic patients with abnormal liver test results who are presenting for surgery. *ALT,* Alanine aminotransferase; *AST,* aspartate aminotransferase; *ETOH,* ethanol; *GGT,* γ-glutamyltransferase; *HX,* history; *INR,* international normalized ratio; *NL,* normal; *R/O,* rule out.

have steatosis (fatty liver) or steatohepatitis.[121] Hultcrantz and co-workers studied 149 asymptomatic patients with at least a 6-month history of elevated aminotransferase levels that were found incidentally during routine laboratory screening.[122] Liver biopsy confirmed the diagnosis of steatosis in 64% of these patients, most of whom were obese or diabetic or had a history of excessive alcohol use. In a subsequent study, Hay and colleagues demonstrated a 21% incidence of steatohepatitis in a similar patient population.[121] Both studies concluded that chronic hepatitis or cirrhosis cannot be differentiated from steatosis or steatohepatitis based solely on clinical laboratory or noninvasive radiologic or ultrasonographic criteria. In a retrospective analysis of 135 patients who underwent hepatic resection, Behrns noted an increased incidence of postoperative liver failure and mortality when histopathologic examination revealed hepatocytes with greater than 30% fatty infiltration.[123] Brolin and associates noted a 6% incidence of biopsy-proven nonalcoholic steatohepatitis and subclinical cirrhosis in patients undergoing gastric bypass surgery; postoperative mortality was higher in affected patients than in those with normal hepatic histologic features.[124] Despite recommendations to the contrary,[125] steatosis and steatohepatitis should probably be considered significant risk factors for postoperative complications, especially after abdominal procedures. For this reason, patients with asymptomatic, chronic (>6 months) elevations in hepatic enzyme levels should be thoroughly evaluated before elective surgery.

CHRONIC HEPATITIS

The extent of anesthetic or surgical risk imposed by chronic forms of hepatitis primarily relates to the severity of associated hepatic synthetic dysfunction. Runyon retrospectively studied 20 asymptomatic patients who had chronic hepatitis B or C and were undergoing general or spinal anesthesia for a total of 34 surgical procedures, most of which were at operative sites distant from the liver.[126] Liver enzyme test results did not worsen postoperatively, nor did any patient experience postoperative liver failure or death. Higashi and colleagues assessed the postoperative outcomes of 119 patients with chronic hepatitis who were undergoing liver resection for primary hepatocellular

carcinoma (HCC).[127] Patients with the most impaired liver enzyme test results had a higher incidence of hepatic failure, recurrent HCC, and death.[128] Abnormal liver enzyme test results in an otherwise healthy patient reflect either a subclinical acute process such as viral or toxin-mediated hepatitis or a chronic disorder such as chronic hepatitis.

Asymptomatic patients with any form of chronic hepatitis should be screened before elective surgery for evidence of hepatic dysfunction, with the INR being the most sensitive indicator of the severity of hepatocellular dysfunction. When surgery cannot be avoided, hepatic perfusion should be maintained, and factors that could precipitate liver failure, hepatic encephalopathy, or both, should be avoided (see later).

CIRRHOSIS AS A PERIOPERATIVE RISK FACTOR

Cirrhosis is a syndrome of end-stage liver disease pathologically characterized by severe fibrosis and nodular regeneration of the liver parenchyma (see also Chapter 74). Alcohol abuse remains the most common cause of cirrhosis. Other causes include chronic hepatitis, primary biliary cirrhosis, hemochromatosis, Wilson disease, and idiopathic cirrhosis. The Child-Turcotte-Pugh (CTP) and the Model for End-Stage Liver Disease (MELD) scoring systems are the most frequently used tools to predict perioperative risk in cirrhotic patients undergoing abdominal surgery, exclusive of portosystemic shunt procedures (Table 73-1).[129,130] The CTP scoring system assigns points based on levels of serum albumin and bilirubin, the INR, the degree of ascites, and the presence and grade of encephalopathy and stratifies risk in order of severity as class A, B, or C. Several studies have used this system to predict perioperative outcome in cirrhotic patients undergoing a variety of surgical procedures. Originally used to predict mortality following transjugular intrahepatic portosystemic shunt (TIPS) procedures, the MELD (see later) scoring system uses serum bilirubin, creatinine, and INR in a calculation that predicts survival in patients with end-stage liver disease: MELD = 3.78 (serum bilirubin) (mg/dL) + 11.2 (INR) + 9.57 (serum creatinine) + 6.43. A score of 40 or more is equated with a predicted mortality rate higher than 70%, whereas a score lower than 9 predicts less than a 2% mortality rate.

Garrison and co-workers retrospectively evaluated outcomes in 100 patients with histologically proven cirrhosis who were undergoing surgery predominantly for biliary tract procedures (cholecystectomy, choledochotomy), as well as for gastroduodenal repair, colon and small bowel resection, and open liver biopsy.[131] An overall operative mortality rate of 30% and an additional perioperative morbidity rate of 30% were noted, with sepsis-mediated multiorgan system failure the major cause of death (87%). When stratified to CTP classes A, B, or C, mortality was 10%, 31%, and 76%, respectively. Excluding the CTP classification, the authors also performed a multivariate analysis of other perioperative variables and concluded that preoperative prolongation of the prothrombin time, decreased serum albumin, and a total leukocyte count greater than 10,000/cm^3 predicted increased mortality. Finally, operative mortality was considerably higher in patients requiring urgent versus elective surgery (57% versus 10%). More than a decade later, Mansour and associates retrospectively analyzed 92 cirrhotic patients who were undergoing abdominal procedures and described nearly identical results, with mortality rates of 10%, 30%, and 82% in patients with CTP classes A, B, and C, respectively.[132] Other retrospective studies have also shown increased perioperative risk during major abdominal surgery, especially under emergency circumstances and in CTP class C cirrhotic patients.[133-136]

Rice and colleagues, however, described the lack of predictability of the CTP classification in patients with chronic liver failure who were undergoing not only abdominal surgery but also coronary bypass grafting, orthopedic procedures, and other peripheral surgical procedures.[137] In this retrospective analysis of 40 patients, perioperative prolongation of the INR and clinical evidence of encephalopathy were the only variables most closely associated with increased mortality (10 and 35 times that of normal individuals, respectively).

Ziser and co-workers, in the largest of all these retrospective studies, established an 11.6% 30-day mortality rate in 773 patients with cirrhosis who were undergoing a variety of surgical procedures involving local, regional, or general anesthesia.[138] Multivariate analysis identified male gender, CTP class C, ascites, azotemia, perioperative infection, higher American Society of Anesthesiologists (ASA) physical classification, a diagnosis of cryptogenic cirrhosis, and surgery of the respiratory system as risk factors independently associated with mortality. Further analysis identified additional risk factors for perioperative complications (Fig. 73-6). Teh and associates retrospectively reported the utility of the MELD score in predicting mortality of cirrhotic patients undergoing nonhepatic surgery.[139] Comparing 777 cirrhotic patients undergoing major surgery with 303 cirrhotic patients undergoing minor procedures, the authors showed that MELD score, age, and ASA classification could quantify risk of mortality in cirrhotic patients, independent of the procedure

TABLE 73-1 MODIFIED CHILD-TURCOTTE-PUGH SCORING SYSTEM

	Modified CTP Score*		
Parameters	**A**	**B**	**C**
Albumin (g/dL)	>3.5	1.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3
Bilirubin (mg/dL)†	<2	2-3	>3
Ascites	Absent	Slight-moderate	Tense
Encephalopathy	None	Grade I-II	Grade III-IV

From Pugh RNH, Murray-Lyon IM, Dawson JL, et al: Transection of oesophagus for bleeding of oesophageal varices, Br J Surg *60:646-649, 1973.*

CTP, Child-Turcotte-Pugh.

*Class A = 5 to 6 points, B = 7 to 9 points, and C = 10 to 15 points.

†For cholestatic diseases (e.g., primarily biliary cirrhosis), the bilirubin level is disproportionate to the impairment in hepatic function, and an allowance should be made. For these conditions, assign 1 point for a bilirubin level less than 4 mg/dL, 2 points for a bilirubin level of 4 to 10 mg/dL, and 3 points for a bilirubin level greater than 10 mg/dL.

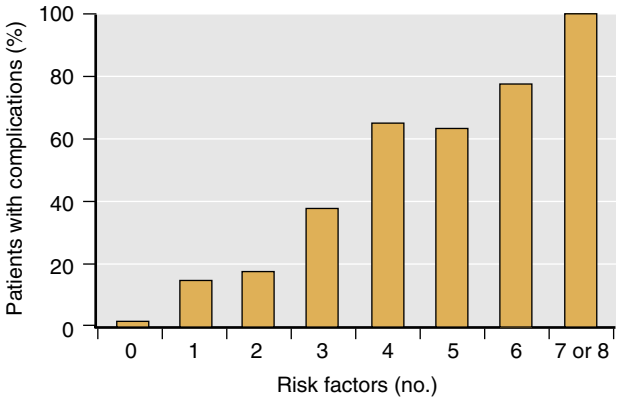


Figure 73-6. Effect of the number of risk factors on the perioperative complication rate in cirrhotic patients undergoing surgery. Risk factors included the Child-Turcotte-Pugh score, the presence of ascites, a diagnosis of cirrhosis other than primary biliary cirrhosis, serum creatinine concentration, a diagnosis of chronic obstructive pulmonary disease, preoperative infection, preoperative upper gastrointestinal bleeding, higher American Society of Anesthesiologists physical status score, intraoperative hypotension, and higher surgical severity score. *(From Ziser A, Plevak DJ, Wiesner RH, et al: Morbidity and mortality in cirrhotic patients undergoing anesthesia and surgery,* Anesthesiology *90:42-53, 1999.)*

performed.[139] The MELD scoring system appears to be accurate in predicting perioperative mortality in cirrhotic patients undergoing nontransplant surgery.[140-142]

Despite the lack of prospective studies, cirrhosis is likely a major risk factor for patients undergoing nonhepatic surgery; elective surgery is considered contraindicated in CTP class C patients.[143] In addition, elective surgery probably should be avoided in cirrhotic patients with a prolonged INR, hypoalbuminemia, and evidence of preoperative infection or encephalopathy. Alternatives to extensive abdominal procedures, such as cholecystostomy or laparoscopic cholecystectomy versus open cholecystectomy, should be considered for the treatment of cholelithiasis.[144,145] Preoperative decompression of portal hypertension by TIPS may also improve postoperative outcomes in certain patients.[146] Finally, elective abdominal surgery should probably be avoided if a diagnosis of cirrhosis is made fortuitously at the time of surgery.[124]

SURGICAL PROCEDURES THAT INCREASE THE RISK OF POSTOPERATIVE LIVER FAILURE

In addition to the severity of preoperative hepatic dysfunction, the actual surgical procedure performed may be the most important risk factor for postoperative liver failure.[147] Under normal circumstances, the liver is able to adapt to changes in perfusion pressure by altering either HABF or PBF. In a diseased state, pathologic changes may diminish the capacity of this dual blood supply and predispose the liver to the deleterious effects of surgery. Abdominal surgery per se appears to reduce THBF significantly. Surgical manipulation of the splanchnic bed may reduce both PBF and HABF, in part because of resultant systemic arterial hypotension mediated by prostacyclin-induced dilation of the venous capacitance vessels.[148] The effect of pneumoperitoneum on hepatic blood flow remains controversial. However, Meierhenrich and colleagues, using transesophageal echocardiography, noted an increase in hepatic perfusion with carbon dioxide insufflation in healthy patients undergoing laparoscopic hernia repair.[149]

In addition to surgery of the biliary tract, stomach, and colon, hepatic resection for HCC is a known risk factor for the development of liver failure in patients with preoperative hepatic dysfunction. Most patients with HCC have liver dysfunction associated with either chronic hepatitis or cirrhosis.[128,150] The diminished functional hepatic reserve of these patients may decrease the amount of tissue that can be resected without compromising viable parenchyma and causing liver failure, the most common cause of death after this surgical procedure. Wu and coworkers retrospectively analyzed cirrhotic patients undergoing hepatic resection for HCC based on their degree of hepatic dysfunction.[151] By limiting the amount of tissue resection in patients with significant hepatic dysfunction (i.e., poorer CTP class), the authors noted 5-year survival rates comparable to those in patients with less severe forms of cirrhosis who underwent more extensive resections. Perioperative hemorrhage is a common occurrence in cirrhotic patients undergoing resection for HCC because of contributing factors such as portal hypertension, coagulation abnormalities, and highly vascular adhesions in patients with previous abdominal surgery. Preoperative evaluation of patients with HCC by indocyanine green 15-minute retention,[151,152] or by direct measurement of the hepatic venous pressure gradient,[153] can be beneficial in predicting postoperative outcomes in cirrhotic patients undergoing hepatic resection for HCC.

Cardiothoracic surgery is associated with a high mortality rate in patients with preexisting liver disease.[138,154,155] Hepatic dysfunction is often exacerbated by cardiopulmonary bypass (CPB), although the precise mechanism of this dysfunction has not been clearly elucidated. In a canine model of hypothermic nonpulsatile CPB, Koizumi and colleagues noted a decrease in PBF and HABF without a concomitant change in hepatic oxygen metabolism.[158] Normothermic CPB was associated with a similar decline in PBF, but HABF was maintained. Increasing the dose of fentanyl from 10 to 50 μg/kg/hr significantly suppressed HABF and impaired hepatic oxygen metabolism in both normothermic and hypothermic CPB, thus suggesting the possibility of fentanyl-mediated peripheral venous pooling and subsequent lowering of cardiac output. Okano and co-workers assessed hepatosplanchnic oxygenation in 25 patients with no history of hepatic dysfunction who were undergoing elective coronary artery bypass grafting with either normothermic (>35° C) or hypothermic (<32° C) CPB.[156] Hepatic venous desaturation and functional impairment of hepatic sinusoidal endothelial cells occurred in both groups, but hepatocellular dysfunction was not observed.

In addition to the possible effects of hepatic artery and portal venous perfusion, other potential determinants of hepatic dysfunction after CPB include hypotension, low cardiac output syndrome, hypoxemia, microembolism or macroembolism, cytokine and oxygen free radical formation, and the influence of vasoactive and anesthetic drugs.

Small retrospective studies showed 11% to 30% mortality rates in CTP class A and B patients undergoing nonemergency cardiac surgery.[154,155,157] Although more deaths occurred in the CTP class B group, significant morbidity, particularly in the form of postoperative hemorrhage and infection, was seen in the CTP class A patients. Noncardiac, thoracic surgery has also been suggested as a risk factor for postoperative mortality in patients with cirrhosis, although the basis for this association remains speculative.[138]

Finally, patients with cirrhosis have an increased risk of developing both inguinal and umbilical hernias possibly related to an increase in intraabdominal pressure related to ascites. Successful surgical repair of an umbilical hernia under general anesthesia and of an inguinal hernia under local anesthesia have been described for all CTP classifications.[159,160]

POSTOPERATIVE JAUNDICE

Postoperative jaundice occurs as a result of overproduction and underexcretion of bilirubin, direct hepatocellular injury, or extrahepatic obstruction.[161] Most causes of postoperative jaundice manifest within 3 weeks of surgery and can be classified as either mild (<4 mg/dL) or severe (>4 mg/dL). Box 73-1 lists the most common causes of postoperative jaundice based on the nature of the pathophysiology.[161] If jaundice is secondary to hemolysis, the liver's capacity to conjugate bilirubin (normal rate of production, ≈250 to 300 mg/day) has been exceeded. Hemolysis-induced anemia is therefore associated with unconjugated (indirect) hyperbilirubinemia and, in the perioperative period, can usually be attributed to either drug-induced or mechanically induced erythrocyte destruction. The primary mechanisms by which certain drugs cause hemolysis and subsequent jaundice are as follows: (1) the drug adsorption type, whereby an antibody (immunoglobulin G [IgG]) reacts with a drug bound to the red blood cell membrane; (2) the neoantigen type (so-called innocent bystander), whereby the drug combines with the erythrocyte membrane and an antibody reacts with the newly formed antigenic site to activate the complement cascade; and (3) the autoimmune type, caused by an autoantibody (IgG) to erythrocytes. Medications commonly used perioperatively and associated with one or more forms of hemolytic anemia are listed in Box 73-2.[162]

The degree of associated jaundice is related to the rate of hemolysis and excess production of bilirubin, with the neoantigen mechanism most likely to cause acute anemia, hemoglobinuria, and renal failure. The diagnosis is made by the laboratory constellation of anemia, indirect hyperbilirubinemia, positive direct antiglobulin test, low serum haptoglobin, and a peripheral blood smear noteworthy for fragmented erythrocytes and reticulocytosis. Mechanical destruction of erythrocytes can also occur from surgically implanted prosthetic heart valves or from intrinsically diseased valves.[163]

Multiple blood transfusions can increase levels of unconjugated bilirubin because approximately 10% of stored whole blood undergoes hemolysis within 24 hours of transfusion (see also Chapter 61). Each 0.5-L unit of blood stored in citrate-phosphate-dextrose-adenine (CPDA-1) yields 7.5 g of hemoglobin, which is then converted to approximately 250 mg of bilirubin.[164] Multiple units of blood may therefore overwhelm the liver's ability to conjugate and excrete bilirubin. Finally, reabsorption of extravasated blood, as occurs with retroperitoneal or intraabdominal hematomas, may increase the bilirubin load and cause postoperative jaundice. This cause is not uncommon after major trauma or repair of ruptured aortic aneurysms.

Hepatocellular injury can cause postoperative jaundice (as previously discussed) by drug-induced, ischemic, or virally mediated mechanisms. In addition to potential anesthetic-induced hepatotoxicity, some commonly prescribed drugs can cause hepatocellular injury that mimics either hepatitis or cholestasis based on liver test abnormalities (Tables 73-2 and 73-3). With the exception of acetaminophen, which can directly cause hepatocyte necrosis, drug-induced hepatotoxicity is primarily the result of either idiosyncratic reactions or alterations in bile flow resulting in cholestasis.

Postoperative jaundice may also result from hepatic hypoperfusion. Cardiogenic and noncardiogenic shock can decrease HABF and PBF and cause hepatocellular

BOX 73-1 ***Etiology of Postoperative Jaundice by Time Course***

Immediate postoperative jaundice (<3 wk)
- Hemolysis
- Anesthesia
- Hypotension or hypovolemia
- Drugs
- Infection or sepsis
- Bleeding or resorption of hematoma
- Bile duct ligation, stricture, or surgical injury
- Hepatic artery ligation
- Retained common duct stone
- Postoperative pancreatitis or cholecystitis
- Acute viral hepatitis
- Gilbert syndrome or Dubin-Johnson syndrome
- Inflammatory bowel syndrome
- Heart failure
- Pulmonary postoperative jaundice
- Blood transfusion

Delayed postoperative jaundice (>3 wk)
- Drugs
- Blood transfusion
- Status after intestinal bypass
- Total parenteral nutrition

BOX 73-2 ***Medications Associated With Hemolysis***

- Acetaminophen
- Cephalosporins
- Hydralazine
- Ibuprofen and other nonsteroidal antiinflammatory drugs (e.g., diclofenac, tolmetin)
- Insulin
- Intravenous contrast media
- Penicillin and all derivatives (e.g., ampicillin, methicillin)
- Procainamide
- Ranitidine
- Sodium thiopental

necrosis. Marked elevations in aminotransferase levels are common, with hyperbilirubinemia usually a late finding. In addition to hemodynamic alterations in hepatic blood flow, sepsis or the systemic inflammatory response syndrome is associated with cholestasis and jaundice, presumably because of the effects of circulating endotoxins or other inflammatory mediators on bile formation and flow.[165] Finally, viral hepatitis should be eliminated as the cause of postoperative jaundice because viral exposure may have occurred before surgery.

TABLE 73-2 **DRUG-INDUCED HEPATOTOXICITY**

Agent	Hepatocellular Cytotoxicity	Cholestasis	Steatosis
Acetaminophen[204]	✓		
Alcohol[205]		✓	
Allopurinol[206]	✓		
Amiodarone[207]		✓	
Amoxicillin/clavulanic acid[208]			✓
Aspirin[209]	✓	✓	
Azathioprine[208]	✓		✓
Bleomycin[210]		✓	
Bosentan[211]	✓		
Calcium channel blockers[208]	✓		
Captopril[212]			✓
Carbamazepine[208]	✓		✓
Chlorpromazine[213]			✓
Cisplatin[214]		✓	
Cyclosporine[208]			
Danazol[215]	✓		
Dantrolene[216]	✓		
Dapsone[217]	✓		✓
Disulfiram[218]	✓		
Enalapril[208]	✓		
Erythromycin[219]			✓
$FeSO_4$[220]	✓		
Floxuridine[191]	✓		
Gold[205]	✓		
Isoniazid[221]	✓		
Ketoconazole[212]	✓		✓
Methimazole[222]			✓
Methotrexate[223]	✓	✓	
Methyldopa[224]	✓		
Nafcillin[205]			✓
Nevirapine[212]	✓		
Niacin[225]	✓		
Nitrofurantoin[211]	✓		
NSAIDs[226-228] (diclofenac, naproxen, indomethacin, piroxicam, etodolac, oxaprozin)	✓		✓ (sulindac)
Pemoline[229]	✓		
Penicillins (oxacillin)[219]			✓
Phenytoin[216]	✓		
Propafenone[212]			
Propylthiouracil[228]	✓		✓
Quinidine[227]			
Rifampin[230]	✓		✓
Riluzole[231]	✓		✓
Steroids, anabolic[232]	✓		
Steroids, oral contraceptives[193]			✓
Sulfonamides[228]	✓		
Tacrine[233]	✓		
Tamoxifen[212]	✓	✓	✓
Tetracycline IV[234]	✓	✓	
Ticlopidine[227]			✓
Tolcapone[235]	✓		
Total parenteral nutrition[236]			✓
Trazodone[216]	✓		✓
Valproic acid[237]		✓	
Vitamin A[238]	✓	✓	
Zafirlukast[239]	✓		

$FeSO_4$, Ferrous sulfate; *IV,* intravenous; *NSAIDs,* nonsteroidal antiinflammatory drugs.

TABLE 73-3 **HERBAL PRODUCTS AND HEPATOTOXICITY**

Herbal	Hepatocellular	Cholestasis
Black cohosh[240]	✓	
Celandine[241]		✓
Chaparral[242]	✓	
Comfrey[243]	✓	
Echinacea[244]		
Germander[245]	✓	
Jin bu huan (levotetrahydropalmatine)[246]	✓	
Kava[247]	✓	
Margosa oil[208]	✓	
Mu huang[248]	✓	
Sassafras[208]		✓
Skullcap[249]	✓	
Yerba[208]	✓	

Obstruction of the common bile duct by a gallstone, stricture, or tumor can result in failure to excrete conjugated bilirubin (obstructive jaundice) with significant perioperative morbidity and mortality. Factors associated with a poor outcome after surgery in patients with obstructive jaundice include extrahepatic obstruction as a result of malignancy, malnutrition, hypoalbuminemia, low hematocrit (<30%), azotemia, and the level and duration of hyperbilirubinemia.[166,167] Dixon and colleagues cited an overall mortality rate of 9.1% in a retrospective analysis of 373 patients requiring surgery for obstructive jaundice, but a 60% mortality rate for patients with anemia, malignancy, and marked hyperbilirubinemia (>11 mg/dL).[168] Of paramount significance is the association of acute renal failure with obstructive jaundice.[169,170] The incidence of postoperative acute renal failure is approximately 8% to 10% and correlates directly with the degree of hyperbilirubinemia, with mortality rates as high as 70% to 80% reported. Neither bilirubin nor bile acids themselves are directly nephrotoxic, but experimental evidence suggests a negative chronotropic, vasodilatory, and diuretic effect of bile salts that results in systemic and thus renal hypoperfusion. The changes appear to be related to enhanced absorption of endotoxin from the gastrointestinal tract because of low intestinal levels and high serum levels of bile acids. This process stimulates release of inflammatory mediators, in particular endothelin, a potent renal vasoconstrictor that leads to a further decline in renal perfusion.[171,172] Other experimental data have implicated endotoxemia-induced nitric oxide release as a further mediator of renal hypoperfusion.[173] Clinicians rely on the limitations of urine output as a method of monitoring renal perfusion. It is more reliable to monitor effective blood volume and cardiac function with either a central venous or pulmonary artery catheter or to perform transesophageal echocardiography, with the goal of maintaining renal perfusion by augmenting cardiac output.[114] No data have documented the clinical benefit of mannitol, furosemide, or dopamine in perioperative renal protection,[111,174] and the potential benefit of endothelin receptor blockers has yet to be thoroughly assessed in clinical studies.[171]

PERIOPERATIVE MANAGEMENT OF PATIENTS WITH ASYMPTOMATIC OR CHRONIC LIVER DYSFUNCTION

The goal of perioperative management of patients with asymptomatic elevations in aminotransaminase, alkaline phosphatase, or bilirubin levels or in patients with preexisting chronic liver disease is prevention of acute liver failure or further hepatic deterioration. Acute liver failure, defined by encephalopathy in the setting of acute liver injury (e.g., viral hepatitis, toxin ingestion, idiosyncratic drug reaction, sepsis, or shock), is further categorized into hyperacute, acute, or subacute forms based on the time interval between the onset of jaundice and encephalopathy (0 to 7 days, 8 to 28 days, or >28 days, respectively).[175] Patients with the hyperacute form of acute liver failure tend to have a more favorable survival rate (35%), whereas those with the acute and subacute forms have poorer prognoses, with mortality rates of 93% and 86%, respectively.[175] Perioperative risks should be identified, and therapy should be directed to minimize hepatotoxicity and maximize hepatic oxygen delivery. For example, drugs such as acetaminophen or combined drugs such as acetaminophen with hydrocodone probably should not be administered to patients with asymptomatic increases of liver enzyme test results or chronic liver dysfunction. In patients with cholelithiasis and biliary tract obstruction, the use of opiates should be limited preoperatively because these drugs can cause spasm of the choledochoduodenal sphincter (sphincter of Oddi) and a subsequent increase in intrabiliary tract pressure.[176,177] These effects appear to be more pronounced for fentanyl, morphine, and meperidine and less severe for opiate agonist-antagonists.[176,177] Intraoperatively, opiates may be used with the recognition that the possible development of sphincter of Oddi spasm can be treated directly with naloxone or by relaxing smooth muscle tone with either glucagon or nitroglycerin[177,178] (which induces release of nitric oxide[179,180]).

Remifentanil has an effect similar to that of other opiates on the sphincter of Oddi. Fragen and colleagues studied remifentanil given to six healthy adult volunteers who underwent radionuclide imaging of the gallbladder before and after remifentanil infusion.[181] The recovery time for dye to appear in the duodenum after discontinuation of the infusion was significantly greater than in the control phase of the study. The authors noted, however, that this delay in recovery of gallbladder function was shorter than in studies using morphine or meperidine. Finally, no data support the benefit or detriment of regional versus general anesthesia, nor do data suggest particular anesthetic agents that should be administered or avoided in patients with preexisting hepatic dysfunction, with the exception of halothane, as previously discussed.

Patients with more advanced liver disease (e.g., CTP class B or C cirrhosis) require an anesthetic plan designed to maximize hepatic oxygen delivery and prevent and treat the complications of encephalopathy, cerebral edema, coagulopathy, hemorrhage, and portal hypertension. Hepatic encephalopathy commonly occurs in patients with chronic liver disease because of the following: accumulation of circulating neurotoxins such as

unmetabolized ammonia, gut-derived false neurotransmitters, γ-aminobutyric acid (GABA), and endogenous GABA receptor agonists; altered neurotransmission by the excitatory neurotransmitter glutamate; or altered cerebral energy homeostasis.[182] Clinically, hepatic encephalopathy is manifested by neuropsychiatric abnormalities ranging from subtle personality changes and cognitive dysfunction to more advanced depression of consciousness, delirium, and coma. Clinical signs include abnormalities in psychometric testing and apraxia, as well as the more severe findings of asterixis, hyperreflexia, and decerebration. When hepatic encephalopathy occurs with acute liver failure, it often has a rapid onset and is invariably complicated by cerebral edema. Cerebral edema develops as a result of the osmotic effect of accumulated glutamine that produces astrocyte cell swelling or as a result of cerebral vasodilation caused by loss of autoregulation, or because of both mechanisms.[183] These patients invariably require urgent liver transplantation.

Many factors may precipitate hepatic encephalopathy in patients with chronic liver disease. Potassium levels should be monitored, and hypokalemia should be treated to decrease the effect of decreased potassium levels on renal production of ammonia. Arterial pH should be maintained near normal because systemic alkalemia is also noted to increase the diffusion of ammonia across the blood-brain barrier, a process that can potentially worsen the degree of encephalopathy.[182] Effective circulating blood volume should be maintained, and anemia should be corrected to maintain hepatic oxygenation and promote the metabolism of circulating toxins. Benzodiazepines should be used judiciously because they may activate the central GABA-benzodiazepine receptor ligand and worsen hepatic encephalopathy. All psychoactive drugs have potentially deleterious effects on hepatic encephalopathy by further suppressing a vulnerable central nervous system. Moreover, propofol can be used as an anesthetic for cirrhotic patients undergoing endoscopic procedures. Compared with benzodiazepines and opioids, propofol appears to have a greater safety profile; it allows for a more rapid and predictable awakening, it does not precipitate hepatic encephalopathy, and it is associated with few side effects, as well as having no effects on liver function tests.[184-189] Hepatic encephalopathy is also a recognized complication of the TIPS procedure.[190]

When patients remain obtunded or comatose after anesthesia and surgery, therapy is often directed toward decreasing ammonia production. Lactulose is administered either by nasogastric tube or by enema to create an osmotic, cathartic effect and to lower intestinal pH, thereby decreasing the survival of ammonia-producing bacteria.[191] Flumazenil, a specific antagonist of central benzodiazepine receptors, can improve the level of consciousness in selected cirrhotic patients with severe hepatic encephalopathy.[192]

Perioperative hemorrhage in patients with significant liver dysfunction may occur because of bleeding diatheses or the complications of portal hypertension, or both. Synthetic hepatic function, as measured by the INR, is useful to assess the severity of the coagulopathy and to gauge therapy, including the subcutaneous administration of vitamin K, transfusion of fresh frozen plasma, use of recombinant factor VII or other factors, and plasmapheresis.[193] In patients with acute liver failure, plasmapheresis may have potential benefit because it promotes rapid correction of coagulopathy while minimizing the chances of excessive intravascular volume, but this approach has not been validated.[194]

Hemorrhage may also occur as a result of gastrointestinal bleeding from rupture of esophageal or gastric varices as a complication of portal hypertension. Intraoperatively, it is advisable to avoid the placement of a transesophageal echocardiography probe, to avoid initiation of bleeding in patients with esophageal varices. Pharmacologic therapy for acute esophageal variceal bleeding includes use of the combination of vasopressin and nitroglycerin, somatostatin, or octreotide, a synthetic analogue of somatostatin.[195,196]

Portal hypertension may also lead to the development of ascites. Ascites occurs in patients with advanced liver disease secondary to renal retention of sodium and water and localization of this excess fluid in the peritoneal cavity because of portal hypertension. In addition to the general measures of sodium and water restriction and diuretic therapy, therapeutic paracentesis may be indicated if a patient presents for surgery with tense ascites.[197] Relief of tense ascites may improve pulmonary gas exchange and reduce the risk of gastric aspiration. Care should be taken, however, to prevent circulatory collapse by the concomitant administration of intravenous colloid solutions because intravascular volume reequilibration occurs 6 to 8 hours after the removal of a larger volume of ascitic fluid.[195] Finally, patients with end-stage liver disease are at risk for the development of either hepatorenal or hepatopulmonary syndrome. *Hepatorenal syndrome* is a state of functional renal failure characterized by azotemia, hyperosmolar urine, and urinary sodium excretion less than 10 mEq/L.[198] Although the pathogenesis of this syndrome has not been clearly elucidated, there appears to be a decrease in renal perfusion pressure related to systemic vasodilation in combination with a loss of renal autoregulation because of increased sympathetic activity.[197] The diagnosis of hepatorenal syndrome in patients with end-stage liver disease usually signals the need for orthotopic liver transplantation. In the event that transplantation is not possible, management is supportive and consists of the use of intravenous volume challenges and large-volume paracentesis to relieve tense ascites.

Hepatopulmonary syndrome, which is defined by the triad of end-stage liver disease, increased alveolar-arterial gradient, and intrapulmonary vascular dilation, is characterized by the clinical features of digital clubbing, cyanosis, dyspnea, platypnea, and orthodeoxia, in addition to the other clinical characteristics of portal hypertension. *Orthodeoxia,* defined as arterial oxygen desaturation that is more pronounced in the upright position and relieved by recumbency, is a common phenomenon of hepatopulmonary syndrome.[199] The pathogenesis of hepatopulmonary syndrome is considered to be primarily related to intrapulmonary vascular dilation, which is diagnosed by contrast-enhanced echocardiography, perfusion lung scanning, or pulmonary arteriography. Current pharmacologic therapy for this disorder is limited; however, orthotopic liver transplantation may lead to a reversal of these pulmonary changes.

ANESTHETIC CONSIDERATIONS FOR PROCEDURES INVOLVING THE LIVER AND BILIARY SYSTEM

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT PROCEDURE

TIPS is a percutaneously created intrahepatic connection of the portal and systemic circulations. This procedure is typically used in patients with end-stage liver disease to decrease portal pressure and attenuate the complications related to portal hypertension, such as variceal bleeding or refractory ascites. Diversion of PBF into the hepatic vein is achieved by placement of an expandable intraparenchymal tract (Fig. 73-7).

Although most patients can undergo TIPS placement with sedation, some clinicians prefer to use general anesthesia in selected patients because of the prolonged nature of the procedure, the potential respiratory-depressant effects of sedatives in cirrhotic patients with underlying pulmonary dysfunction as a result of ascites and/or hypoxemia from the hepatopulmonary syndrome, and concern regarding possible gastric aspiration. Regardless of the anesthesia technique chosen, appropriate intravascular volume resuscitation is often necessary before the procedure, especially in patients who have had variceal bleeding. In addition, patients with cirrhosis who are undergoing a TIPS procedure frequently have severe coagulopathy that requires preprocedural procoagulant therapy.

Several complications can occur during placement of TIPS that may require intervention by the anesthesiologist. Pneumothorax or neck vessel injury can occur during vessel puncture. These complications may be reduced by ultrasonographic guidance during jugular vein puncture. Additionally, cardiac dysrhythmias can be mechanically induced during intracardiac catheter passage. Finally, acute, life-threatening hemorrhage caused by hepatic artery puncture in conjunction with a hepatic capsular tear or by extrahepatic portal venous puncture can occur. Hemodynamic status can deteriorate, with the development of pulmonary edema and congestive heart failure, in patients with borderline cardiac reserve.[200]

HEPATIC RESECTION

Preoperative considerations (as previously described) before hepatic resection involve risk assessment primarily using CTP and MELD scores (see also Chapter 74). Surgical procedures should be limited to patients with CTP class A and significantly compensated CPT B status. MELD scores higher than 10 pose significant risk of postoperative liver failure in cirrhotic patients with HCC. Severe thrombocytopenia or large varices represent major perioperative risk factors and should preclude surgery.[201] Significant anemia and coagulopathy, if present, should be corrected preoperatively. Decisions regarding the choice and doses of anesthetics should account for any baseline hepatic parenchymal dysfunction, as well as the potential postoperative dysfunction resulting from resection of a major portion of the liver parenchyma. No data show hepatoxicity with either sevoflurane or desflurane, and thus both drugs are safe to administer, provided hepatic hypoperfusion is avoided. Indeed, hepatic preconditioning with sevoflurane has been shown to decrease postoperative complications in patients undergoing hepatic resection.[35]

Although the risk of significant intraoperative blood loss is well known and the need for appropriate monitoring and sufficient vascular access to permit rapid transfusion is widely accepted, overall fluid management during major hepatic resection is controversial. At some centers, fluid and blood administration is used liberally, beginning early in the course of resection, with the goal of increasing intravascular volume as a buffer against sudden blood loss. Other centers favor maintenance of low central venous pressure during resection to minimize blood loss from hepatic venous radicals, major hepatic veins, or the vena cava. These sites typically contribute to most bleeding during hepatic resection. Notably, reduction of intrahepatic venous pressure can also be achieved by using a modest degree of the Trendelenburg position, an approach that potentially maintains or even increases cardiac preload and cardiac output, as well as reducing the risk of air embolism from disrupted hepatic veins. In patients without preexisting renal dysfunction, the latter approach does not appear to have a significant impact on postoperative renal function.[202]

Although basic postoperative management concerns are similar to those of other major abdominal procedures, several aspects of care are notable. Intravenous fluids should be supplemented with either sodium or potassium phosphate, which is often needed to prevent severe hypophosphatemia and to facilitate liver regeneration. Decreased clearance of hepatically metabolized drugs is important in selecting and titrating methods of postoperative analgesia.

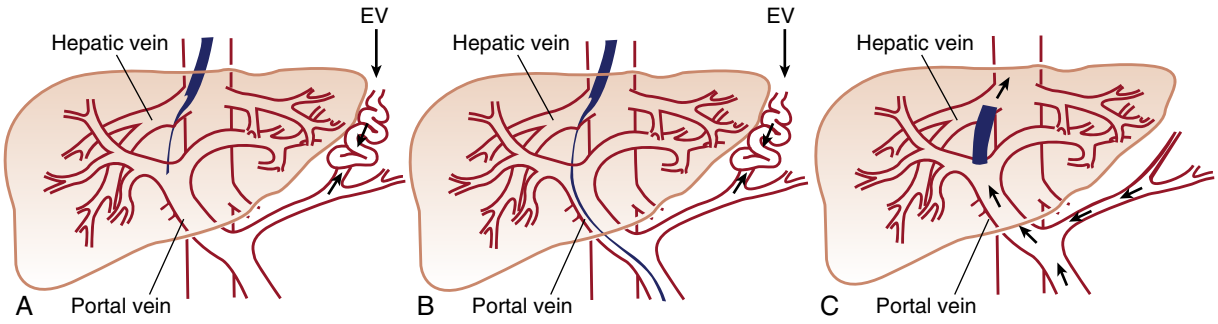


Figure 73-7. Transjugular intrahepatic portosystemic shunt (TIPS) procedure. A stent (or stents) is passed through the internal jugular vein over a wire into the hepatic vein (**A**); dilated esophageal varices (EV) are apparent. The wire and stent or stents are then advanced into the portal vein (**B**), after which blood can pass through the portal vein into the hepatic vein and bypass and decompress dilated esophageal veins (**C**). *(Reproduced with permission from University of Michigan Health System: <www.med.umich.edu/1libr/topics/liver09.htm/>*

HEPATIC CRYOTHERAPY

Hepatic cryotherapy involves the application of material at subzero temperature by multilumen probes positioned intraoperatively under sonographic guidance. This procedure is used to treat nonresectable malignant hepatic tumors. Preanesthetic considerations for hepatic cryotherapy are similar to those for hepatic resection. Heat conservation measures should be instituted during the procedure, with continual monitoring of core temperature. Intraoperative bleeding is rarely significant enough to cause hemodynamic instability. Postoperative pulmonary, renal, and coagulation problems may manifest as sequelae of the "cryoshock syndrome," even after a procedure with unequivocal intraoperative stability.[203]

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Complete references available online at expertconsult.com

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Chapter 74

Anesthesia for Abdominal Organ Transplantation

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Key Points

- Survival after abdominal organ transplantation continues to improve.
- The imbalance between organ supply and demand is increasing.
- To increase the supply of organs, living donors and extended criteria deceased donors are being used more frequently.
- Knowledge of the pathophysiologic changes associated with end-stage disease is required to provide optimal care for patients undergoing transplant surgery.
- The kidney is the most frequently transplanted organ.
- Kidney transplant recipients are older and are more likely to have chronic illnesses than in the past.
- The perioperative and long-term risk of cardiovascular disease is increased in patients with end-stage renal disease.
- Maintenance of renal perfusion pressure in the perioperative period is critical for graft function.
- Liver transplant recipients are older in age and have more comorbidities than in the past.
- The Model for End-stage Liver Disease (MELD) score prioritizes candidates for organ allocation.
- The pathophysiologic changes associated with liver disease affect nearly every organ system.
- Intraoperative care requires preparation for massive transfusion, management of coagulation abnormalities, and hemodynamic instability.
- Pancreatic transplantation is definitive treatment for diabetes mellitus.
- Pancreatic transplants are performed simultaneously with kidney transplantation (SPK), after kidney transplantation (PAK), or alone (PTA).
- Patients who are younger than 50 years with diabetes and end-stage renal disease benefit from simultaneous kidney and pancreas transplantation.
- Frequent monitoring of blood glucose concentrations is required during the perioperative period.
- Diabetic patients are at significant risk for cardiovascular disease.

ABDOMINAL ORGAN TRANSPLANTATION

The success of transplantation over the past decade corresponds to improved survival for recipients. Three-year posttransplant recipient survival is 80% for livers and 90% for patients receiving kidneys (Fig. 74-1). Three-year survival for liver transplantation matches that of heart transplantation. Increasingly, indications for transplantation have broadened. Patients with conditions previously considered contraindications, such as advanced age and some types of cardiopulmonary disease, are no longer precluded from transplantation.

Among the various organs, the kidney is the most transplanted organ. In 2011, more than 17,000 kidney transplants were performed. In the same year, liver was the second most commonly transplanted organ, with more than 6300 transplants performed. The heart is third, with more than 2000 transplants.

As of mid-year 2011, there are over 275,000 patients living with functioning transplants in the United States.

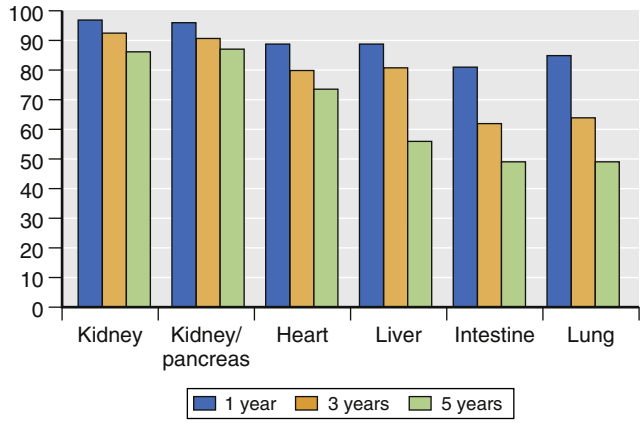


Figure 74-1. Patient survival 1, 3, and 5 years after transplant, by organ. Data are for U.S. transplants performed during 1997 to 2004. *(From http://optn.transplant.hrsa.gov/latestData/rptStrat.asp. Accessed December 2012)*

This number has nearly doubled in the past 8 years. The majority of these patients are kidney recipients (180,000), followed by liver (62,000), heart (25,000) and lung (10,000) recipients. Thoracic organ transplantation is reviewed elsewhere (see Chapters 66 and 67). Approximately 1000 intestinal recipients are living with functioning grafts.

Despite these successes, the number of patients who could benefit from transplantation far exceeds those who receive an organ. The imbalance between supply and demand is highlighted by the size of the waitlists for each organ, which is approximately threefold the number of annual transplants for kidney (more than 54,000) and double the number of annual transplants (more than 12,000) for liver. In 2011, for every two patients who undergo liver transplantation, one patient dies on the liver waitlist. For every three patients who undergo kidney transplantation, one patient dies while waiting for a kidney.[1]

Solutions to organ shortage include living donor transplantation, which is used more commonly for kidney transplants (one third of kidney transplants in 2011) than liver transplantation (less than 5% of liver transplants in 2011). Other strategies include the use of extended criteria donors, which is discussed in detail elsewhere (see Chapter 75).

The evaluation of patients for transplantation varies among transplant centers, but the goals are similar. These include ascertaining that: (1) transplantation is indicated for the management of the prospective recipient, (2) comorbidities do not preclude transplantation, and (3) emotional and social resources permit a major surgery and its associated rehabilitation, including compliance with long-term immunosuppression therapy. The center's transplant selection committee typically consists of physicians (nephrologist and hepatologist for kidney and liver transplantation, respectively), transplant surgeon, psychiatrist, dietitian, social worker, and additional consultants as indicated. Anesthesiologists consult for patients with high operative risk, such as pulmonary hypertension, coronary artery disease (CAD), or patients with prior anesthetic complications.

Reasons to deny transplantation vary among transplant centers. Critically ill patients receiving life support, vasopressors, or dialysis have decreased posttransplant survival.[2] Additional comorbidities can exacerbate the risk to a level that may be unacceptable to some centers. Medical reasons include comorbidities such as significant CAD, moderate or severe pulmonary hypertension, metastatic disease, uncontrolled intracranial hypertension, and untreated sepsis. Psychosocial contraindications include alcohol or recreational drug use, and the lack of social support, which might preclude compliance with immunosuppression regimens, follow-up care, or both. Age alone is generally not a contraindication.

The success of organ transplantation relies heavily on a highly specialized team approach that includes the organ procurement organization, transplant coordinators, nurses, physicians, and allied health care providers. With the exception of kidney transplantation, most abdominal organ transplants are performed at tertiary medical centers with extensive resources available to support the program. Many of these centers have specialized anesthesia teams, particularly for liver transplantation.

This chapter reviews the anesthetic considerations for kidney, liver, pancreas, and intestinal transplantation in adults. The overall care of pediatric patients is described in Chapter 93. The management of heart and lung, but not renal, is described in Chapter 94. In Chapter 95, the intensive care clinical care is described in pediatric patients who are receiving a kidney transplant.

KIDNEY TRANSPLANTATION

The first kidney transplantations were performed in the 1950s; however, renal transplantation did not become widespread until the development of effective immunosuppression in the 1960s. Since then, kidney transplantation has become the most common organ transplant surgery performed. Kidney transplants have steadily increased over the past 40 years worldwide, with the growth of kidney transplant programs throughout Europe, North America, and Asia, as well as in many developing countries. There are differences in the distribution of living versus cadaveric donor organs between regions; many countries in Africa and Asia rely exclusively on living donation, whereas many countries in Europe perform mainly cadaveric renal transplants.[3] During the past decade in the United States, there has been a steady increase in the number of patients on the kidney transplant waitlist (Fig. 74-2). The demographics of patients on the waitlist have changed; patients are older (more than half are older than age 50) and are more likely to have developed end-stage renal disease (ESRD) secondary to chronic hypertension and advanced diabetes. The incidence of chronic kidney disease (CKD) among individuals older than 65 years continues to increase in the United States (Fig. 74-3). Although it is not known how many patients with CKD progress to ESRD, the prevalence of ESRD in the United States has steadily increased over the past 30 years. At the end of 2009, nearly 900,000 people in the United States were being treated for ESRD.[4] The waiting time for kidney transplantation has increased in the United States as well, reflecting that the need for organs outstrips

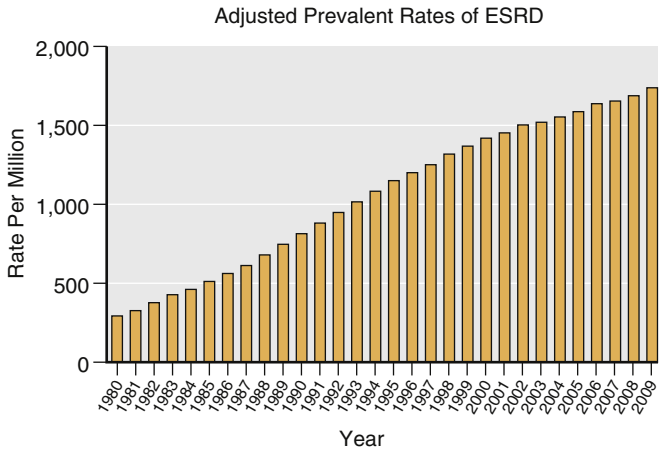


Figure 74-2. Prevalent rates of end-stage renal disease (ESRD). Although the prevalence is increasing, the number of new cases per year has been stable since 2001. *(From* Kidney Disease Statistics for the United States, *National Kidney and Urologic Diseases Information Clearinghouse, NIH Publication No. 12-3895, June 2012.)*

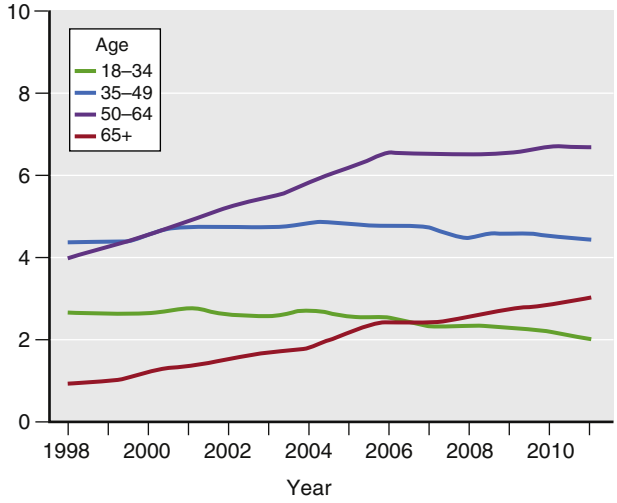


Figure 74-3. Adult kidney transplants in thousands, by year. The lines illustrate trends in recipient age. The number of recipients aged 50 to 64 years and older than 65 years is increasing over the past decade. *(OPTN & SRTR Annual Data Report 2011. U.S. Department of Health and Human Services Health Resouces and Services Administration, p 28, figure KI 4.2)*

the organ supply. Recent data showed that there were more than 80,000 patients on the waitlist in the United States (active and inactive), and approximately 16,000 kidney transplants were performed in 1 year. More than 5000 patients were removed from the waitlist in the same year because of death, whereas almost 2000 were removed after becoming too ill for transplantation.[5] These national trends reflect a kidney transplant population that is older and more likely to suffer from chronic diseases, which has significant implications regarding perioperative risk during kidney transplant. Nevertheless, current 3-year posttransplant survival for adults is 96% for living donor kidney transplants and 90% for deceased-donor transplants.[1]

Paired kidney donations have increased from fewer than 100 per year in 2006 to more than 400 per year in 2011. Paired donation consists of two incompatible donor-recipient pairs exchanging kidneys to create two compatible pairs. With the development of donor chain transplants and establishment of a national system for paired donation, these techniques are expected to become more common.

INDICATIONS FOR KIDNEY TRANSPLANTATION

Kidney transplantation is indicated in patients with ESRD caused by any one of a variety of underlying conditions. Glomerular disease, congenital diseases, and polycystic kidney disease are common indications in younger patients. Nephropathies associated with hypertension and diabetes are now the most common indications for kidney transplantation in the United States.[6] Renal graft failure is an increasingly common indication for transplantation in the United States as well.[7]

PATHOPHYSIOLOGY OF END-STAGE RENAL DISEASE

End-stage renal disease refers to the final progression of CKD, when renal function is irreversibly impaired and the development of uremia is imminent. Essential functions of the kidney include regulation of the ionic composition of the plasma, maintenance of fluid volumes, elimination of nitrogenous wastes and drugs, synthesis of erythropoietin, and adjustment of plasma pH. Significant declines in glomerular filtration rate (GFR) and urine production occur when these critical functions are significantly damaged, resulting in the clinical manifestations of uremia. After the development of ESRD, renal replacement therapy is required. ESRD has an effect on nearly every organ system, and it has a major impact on patient mortality despite chronic therapy including hemodialysis.

ESRD results in abnormalities of fluid balance and electrolytes. With the onset of uremia and oliguria, expansion of the extracellular fluid volume ensues, presenting with edema, hypertension, and signs and symptoms of volume overload. Disorders of sodium, calcium, magnesium, and phosphate can result in chronic changes in bone metabolism, hyperparathyroidism, and vascular calcifications. The development of hyperkalemia, with its effects on the myocardium, is the most critical electrolyte abnormality. Failure of the renal elimination of organic acids results in the development of an anion-gap metabolic acidosis.

ESRD has a significant effect on the cardiovascular system. Cardiovascular disease is the most common cause of morbidity and mortality in patients with ESRD, accounting for 35% to 40% of all deaths in patients receiving hemodialysis.[8] As GFR decreases, the risk of cardiac mortality increases.[9] Following successful kidney transplantation, cardiovascular disease remains the most common cause of death.[10] Kidney transplant recipients are at increased risk for the development of myocardial infarction (MI), congestive heart failure, and atrial fibrillation.[11-13] ESRD increases the development of atherosclerosis and is a major risk factor for the development of ischemic vascular disease, which can affect the coronary, cerebrovascular, and peripheral vascular systems. The likelihood of CAD, which

can present as angina, MI, arrhythmia, or sudden cardiac death, is even greater in patients with ESRD, hypertension, and diabetes. Hypertension may be the etiology of ESRD in nearly 30% of patients, or conversely, hypertension may result from hyperreninemia, hypervolemia, and renal vasculature changes associated with ESRD. Concentric left ventricular hypertrophy and diastolic dysfunction occur in the early stages of CKD, and are the two most common echocardiographic abnormalities in patients with ESRD.[14] Patients with ESRD are at particular risk for diastolic congestive heart failure, especially in the setting of excessive intravascular volume. Heart failure owing to dilated cardiomyopathy with decreased systolic function can occur in patients with ESRD as well. The cardiorenal syndrome is defined by an interconnection between the renal and cardiac systems, where the decline of one organ influences the decline of the other. There is evidence that correction of renal function by renal transplantation can improve systolic dysfunction and reverse left ventricular dilation and hypertrophy.[15] A variety of arrhythmias can occur in ESRD because of progression of cardiac disease, myocardial ischemia, or electrolyte disturbances. Atrial fibrillation occurs in 13% to 27% of patients on hemodialysis, and it is associated with a significant risk of stroke.[16] Pericardial disease is common in patients with uremia, manifesting as pericarditis or pericardial effusion.

Characteristic hematologic and hemostatic abnormalities occur with ESRD. Normochromic, normocytic anemia secondary to lack of erythropoietin is common and may be exacerbated by iron deficiency, chronic inflammation, and bone marrow fibrosis. Anemia decreases quality of life in ESRD and is associated with adverse cardiac outcomes. Erythropoiesis-stimulating drugs and iron are commonly prescribed for the treatment of uremic anemia, and hemoglobin levels of 11 to 12 gm/dL are typically achieved[17] (see Chapters 61 and 63). ESRD is associated with abnormal hemostasis because of a broad spectrum of platelet function abnormalities, including decreased platelet activity, aggregation, and adhesiveness. Production of von Willebrand factor and factor VIII is decreased. Historically, renal failure increases the likelihood of bleeding; however, ESRD is also associated with a hypercoagulable state owing to complex abnormalities involving increased coagulation and endothelial activation.[18] These hematologic changes of hypercoagulability resolve in patients with ESRD after successful kidney transplantation.[19]

Gastrointestinal signs and symptoms including nausea, vomiting, abdominal pain, and abnormal gastric motility occur in ESRD patients. Using electrogastrography, impairments in gastric myoelectrical activity exist in patients with symptomatic ESRD as compared to patients with normal renal function.[20] Patients with ESRD have delayed gastric emptying, regardless of the timing of their last oral intake. The presence of diabetes, obesity, or both can further impair gastric emptying.

Central nervous system and neuromuscular abnormalities can occur in ESRD secondary to uncleared nitrogenous molecules. These abnormalities can range from mild changes in memory or attention to signs and symptoms of neuromuscular irritability. Severe neurologic manifestations of uremia with asterixis, seizures, and decreased mental status are rare with regular dialysis. Autonomic and peripheral neuropathies can occur in patients with ESRD and are possibly reversible with kidney transplantation.

ANESTHESIA FOR KIDNEY TRANSPLANTATION: PREOPERATIVE EVALUATION

Before kidney transplantation, patients typically undergo a prolonged and intense pretransplant evaluation by a multidisciplinary transplant committee to determine their candidacy for transplantation. In general, the preoperative evaluation of patients for kidney transplant should focus on the multiorgan manifestations of ESRD, with the goals of risk stratification and optimization of the medical status of the patient before transplant (see Chapter 39). Cadaveric kidney transplantation is an urgent procedure, because harvested organs tolerate a finite duration of cold ischemia, usually less than 24 hours. Living donor kidney transplants are scheduled well in advance, allowing for a more thorough preoperative assessment before surgery.

Before surgery, patients receiving hemodialysis should be maintained on their regular dialysis schedules, whether hemodialysis or peritoneal dialysis. Ideally, dialysis should be performed before surgery, especially in patients with excessive intravascular volume or with documented hyperkalemia or acidosis. A comprehensive laboratory panel that includes electrolytes, complete blood count, and platelet count is appropriate before surgery. A type and screen or type and cross for packed red blood cells should be obtained (see Chapter 61). Although major blood loss during routine kidney transplantation is not common, the surgery involves major vascular structures with the potential for rapid bleeding. Documentation of an increased potassium level immediately before surgery, especially with electrocardiogram (ECG) changes consistent with hyperkalemia, should prompt consideration of immediate dialysis to correct potassium levels before surgery. Preoperative vital signs should be closely assessed, especially heart rate and arterial blood pressure trends in hospitalized patients. Preoperative intravascular volume status should be assessed. Comparing the patient's current weight to their known euvolemic weight, or "dry weight," may be helpful. Patients undergoing surgery immediately after dialysis may be significantly hypovolemic and prone to intraoperative hypotension. Orthostatic assessments and the presence of resting hypotension and increased heart rate may identify significant hypovolemia. Preoperative volume resuscitation with non–potassium-containing saline solutions or colloids can prevent hypotension on induction of anesthesia. Conversely, patients who have preoperative body weights heavier than their euvolemic weight may have an excessive intravascular volume, and they may be prone to congestive heart failure during kidney transplantation. A thorough cardiopulmonary examination is indicated in all patients, and findings of significant excessive intravascular volume may be an indication for immediate preoperative dialysis before surgery.

As discussed previously, the current demographic of kidney transplant patients has a frequent association with cardiac disease, which has a major effect on

posttransplant outcome. As a result, preoperative cardiac evaluation is of critical importance in this patient group (see Chapter 39). Compared with the routine preoperative evaluation of noncardiac surgery patients, which focuses on the perioperative period, the renal transplant patient should be assessed to consider both short- and long-term cardiac outcomes. The goal of the preoperative cardiac evaluation is ultimately to decrease the morbidity and mortality associated with cardiovascular disease in kidney transplant candidates. Although decisions regarding candidacy in high-risk patients are usually made well before surgery, the anesthesiologist should be involved in the routine cardiac risk assessment of the kidney transplant patient before surgery. The main focus of the preoperative cardiovascular assessment in kidney transplant patients is to identify occult ischemic heart disease in an asymptomatic patient.

The 2007 American College of Cardiology Foundation/American Heart Association (ACC/AHA) Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery suggests a preoperative algorithm designed to assist in the risk stratification of surgical patients. The algorithm identifies active cardiac conditions that are associated with major risk (unstable coronary syndromes, decompensated heart failure, significant arrhythmia, and severe valvular disease) and then stratifies patients based on functional capacity. No further testing is recommended when functional status is adequate (more than four metabolic equivalent tasks [METS]). If functional status is less than four METS, further ischemia testing is then determined by the type of surgery (low, intermediate, or high risk) and by the presence of further risk factors (history of ischemic heart disease, heart failure, diabetes, renal insufficiency, and cerebrovascular disease).[21] Kidney transplantation is considered an intermediate-risk procedure in the ACC/AHA Guidelines. The utility of the 2007 ACC/AHA Guidelines to detect patients with ischemic heart disease has been called into question in the kidney transplant population.[22] Silent myocardial ischemia can occur more frequently in patients with ESRD than in the general population, making the detection of unstable coronary syndromes more difficult. One study reported that chest pain presenting at the time of acute MI was less common in patients with ESRD requiring dialysis compared with patients not using dialysis (44% versus 68%).[23] Decreased functional status might not be a specific or sensitive indicator of cardiovascular risk in kidney transplant candidates. One study of 204 kidney transplant candidates examined the effectiveness of various guidelines to detect asymptomatic CAD. Of the 204 patients, 178 underwent noninvasive ischemia testing; 17 patients with ischemia were identified. The authors determined that if the ACC/AHA guidelines had been strictly applied to this group of patients, only 39 of the 178 candidates would have undergone noninvasive testing, and only 4 of the 17 patients with ischemia would have been detected.[24] Finally, renal insufficiency is itself a risk factor. The unique characteristics of ESRD patients, along with discrepancies among guidelines, has called into question the applicability of available recommendations regarding cardiac testing in the kidney transplant population.[22]

Noninvasive testing methods for CAD have been well studied in the kidney transplant population. In studies that compared either dobutamine stress echocardiography (DSE) or myocardial perfusion studies with angiography in patients with renal failure, both methods had decreased accuracy compared to their accuracy in nonrenal failure patients. DSE had sensitivities of 0.44 to 0.89 and specificities of 0.71 to 0.94. Myocardial perfusion studies had sensitivities of 0.29 to 0.92 and specificities of 0.67 to 0.89.[22] Although noninvasive testing has variable sensitivity and specificity for CAD in transplant cohorts, abnormal noninvasive test results correlate with adverse cardiac events and mortality in patients with ESRD. A meta-analysis of studies using either DSE or myocardial perfusion studies in patients with ESRD demonstrated that patients with inducible ischemia or fixed defects had a significantly increased risk of cardiac death compared to patients with normal studies.[25]

Before 2010, several guidelines and consensus-based recommendations regarding preoperative cardiac risk assessment in kidney transplant candidates had been published. The risk assessment of asymptomatic kidney transplant candidates is of prime importance.[26,27] Likewise, surveys of practice patterns in the United States demonstrate a spectrum of approaches for the screening of asymptomatic kidney transplant candidates.[28,29] Although preoperative cardiac evaluation recommendations have not been standardized for kidney transplant candidates, a stepwise process including a comprehensive cardiovascular history and assessment of signs and symptoms of advanced cardiac disease, assessment of functional status, and identification of risk factors should be assessed.

A baseline ECG is an appropriate initial screening test in most kidney transplant patients, especially in patients older than 40 years. ECG abnormalities associated with cardiac disease are common in patients with ESRD. A preoperative ECG should be obtained in patients with known CAD, peripheral vascular disease, and cardiac symptoms.[22] Noninvasive testing may be considered in asymptomatic patients with multiple risk factors for CAD. Using a revised list of risk factors, one study demonstrated an improvement in the sensitivity and specificity for the detection of occult CAD in transplant candidates compared to using the established ACC/AHA risk factors.[24] Based on this study's results, risk factors associated with an increased risk of CAD in renal transplant candidates include diabetes, history of cardiovascular disease, more than 1 year of dialysis, left ventricular hypertrophy, age older than 60 years old, smoking, hypertension, and dyslipidemia.[22] Preoperative assessment of left and right ventricular function by echocardiography is an appropriate test in most kidney transplant candidates.[22] The likelihood of structural cardiac abnormalities and the potential for left ventricular dysfunction in ESRD is significant, and transthoracic echocardiography provides detailed information regarding resting cardiac function and structure with few testing risks.

An increased prevalence of occult pulmonary hypertension occurs in patients with ESRD receiving dialysis. A 40% incidence of pulmonary hypertension existed in a series of 58 ESRD patients receiving chronic

hemodialysis. The mechanism involves both uremia-induced pulmonary vasoconstriction and increased cardiac output secondary to an arteriovenous fistula. Pulmonary hypertension may be reversible after kidney transplantation. The identification of pulmonary hypertension is important because its presence in patients with ESRD is associated with decreased survival.[30] A screening ECG can identify patients with pulmonary hypertension (see Chapter 47). In addition, right heart catheterization is likely indicated in patients with evidence of significant pulmonary hypertension by echocardiography.

Patients with cardiac conditions may remain on transplant lists for a long duration (i.e., many months or even years) before undergoing transplantation. During this time, cardiac disease can progress. Although routine periodic noninvasive screening in asymptomatic patients awaiting transplant is not warranted, patients with known cardiac disease should undergo regular repeat cardiac assessments; however, the ideal frequency of assessments is not known.[22]

A detailed list of the patient's cardiovascular medications should be obtained, and the patient should be clearly advised which medications should be taken before surgery. In general, most patients with ESRD receive multiple medications for the chronic treatment of hypertension; however, the ideal combination of drugs is not clear. Strategies for the perioperative administration of antihypertensive blood pressure medications are important; however, the urgency of donor kidney transplantation often allows only the immediate preoperative administration of antihypertensive medications. Perioperative β-adrenergic blocker therapy apparently decreases the incidence of perioperative MI and mortality in high-risk and intermediate-risk surgical patients,[31,32] but perioperative β-adrenergic blockade has not been effective in other studies with low–cardiac risk patients and with patients with diabetes.[33,34] One study demonstrated that perioperative β-adrenergic blockade decreased short- and long-term mortality in renal failure patients undergoing vascular surgery.[35] To clarify this issue, there are unfortunately no randomized, prospective trials that have investigated perioperative β-adrenergic blockade in kidney transplant patients. The ACC/AHA 2007 Guidelines recommend that patients previously receiving β-adrenergic blockers should continue to receive them.[21] Based on recommendations for nontransplant surgical patients, perioperative β-adrenergic blockade may be initiated in renal transplant candidates with known CAD, with CAD risk factors (diabetes, heart failure, and atherosclerosis), and with myocardial ischemia that occurs during preoperative noninvasive stress testing.[22] In asymptomatic kidney transplant patients not previously receiving β-adrenergic blockers without two or more CAD risk factors, perioperative β-adrenergic blockade should not be initiated because of the risk of perioperative bradycardia and hypotension observed in nontransplant cohorts.[22]

Patients with ESRD are at risk for atherosclerosis and may be receiving lipid-lowering medications at the time of surgery. Although there are no studies that definitively show that hyperlipidemia therapy improves outcomes in ESRD, lipid-lowering medications probably should be continued during the perioperative period in patients previously receiving them.[22]

As mentioned previously, there is an increasing prevalence of diabetes in the kidney transplant population. There have been many studies assessing the risks and benefits of glycemic control with intravenous insulin therapy in surgical patients. A recent meta-analysis found that the use of perioperative insulin infusions is associated with episodes of hypoglycemia, although overall mortality may be reduced.[36] A multinational randomized trial in intensive care unit (ICU) patients comparing "tight" glucose control with intensive insulin therapy (target glucose levels ranging 81 to 108 mg/dL) to conventional insulin therapy (target glucose levels < 180 mg/dL) demonstrated a more frequent 90-day mortality with tight glucose control.[37] Perioperative glycemic therapy should be started in patients with diabetes who are undergoing kidney transplant, yet a benefit from strict blood glucose control in the kidney transplant population has not been demonstrated in the literature. On the morning of surgery, blood glucose levels should be measured, and insulin therapy may be initiated in patients before surgery for significant hyperglycemia, with appropriate serial blood glucose measurements during the perioperative period. As in all types of surgery, orally administered antihyperglycemic medications should be withheld on the morning of surgery in patients with non–insulin-dependent diabetes (see Chapter 39).

ANESTHESIA FOR KIDNEY TRANSPLANT: INTRAOPERATIVE MANAGEMENT

General anesthesia with endotracheal intubation is the preferred anesthetic method for kidney transplantation in most kidney transplant centers. The goals of anesthesia are to facilitate an adequate depth of anesthesia while maintaining hemodynamic stability and to provide appropriate muscle relaxation to facilitate surgical conditions. As mentioned previously, patients with ESRD are considered a risk for aspiration of gastric contents secondary to the presence of uremic gastropathy and other conditions, such as obesity (see Chapter 71) and diabetes. An oral nonparticulate antacid and intravenous administration of an H-2 blocker, such as ranitidine, probably should be given before induction of anesthesia. A rapid-sequence induction of anesthesia with continuous cricoid pressure is the preferred method of induction for general anesthesia. Succinylcholine can be used safely in standard doses in patients with ESRD when potassium levels are within normal limits (usually <5.5 mEq/L). Potassium transiently increases 0.5 to 1.0 mEq/L for 10 to 15 minutes before returning to baseline levels in patients with ESRD and those with normal renal function.[38] A modified rapid sequence induction using rocuronium 0.8 to 1.2 mg/kg intravenously is an appropriate substitute for succinylcholine when hyperkalemia or other contraindications to succinylcholine exist. A meta-analysis of 26 studies that compared the intubating conditions produced by succinylcholine and rocuronium found that intubation conditions were clinically similar when propofol was used as the induction anesthetic.[39] The hemodynamic response to laryngoscopy may be accelerated in patients with ESRD with underlying chronic hypertension. Tachycardia and hypertension can be attenuated with supplemental

opioids, esmolol, lidocaine, or nitroglycerin titrated to effect. Following the stress of tracheal intubation kidney transplant patients may develop hypotension before surgical incision, especially in patients who have been rendered hypovolemic from recent dialysis or in patients receiving renin-angiotensin blocking drugs.

Intraoperative monitoring may be limited to standard noninvasive monitors in younger, healthier transplant recipients and in select living donor recipients. Intraarterial blood pressure monitoring can be beneficial, especially in patients with uncontrolled hypertension, CAD, or heart failure. Pulmonary artery catheter or transesophageal echocardiographic monitoring may be considered in patients with advanced CAD, left or right ventricular dysfunction, and pulmonary hypertension. Central venous pressure monitoring is a standard monitoring technique in some centers; however, central venous pressure is not a reliable monitor of fluid status or responsiveness.[40] The insertion of a central line provides reliable venous access for intravascular fluid resuscitation and transfusion, and access for administration of immunosuppression drugs and vasoactive infusions. Large-bore venous access is necessary for appropriate intravascular volume administration in the perioperative period. Intravenous access can be challenging in some kidney transplant patients, because intravenous sites may be limited by the presence of an upper extremity arteriovenous fistula. Conversely, central venous access may be difficult to accomplish in patients with ESRD who have undergone multiple previous central venous dialysis catheter placements, especially if central venous thrombosis has been documented.

Maintenance of anesthesia is typically performed using a combination of intravenous and inhaled anesthetics. Volatile inhaled anesthetics are titrated to the level of surgical stimulation, which varies during the phases of the procedure. Desflurane and isoflurane are not associated with nephrotoxicity. Although sevoflurane has potential nephrotoxic effects from the metabolites compound A and fluoride ion, detrimental effects on renal function have not been demonstrated in patients with renal insufficiency[41,42] (see Chapter 26). A study of 200 renal transplant recipients retrospectively compared outcomes in recipients that received anesthetics using sevoflurane versus isoflurane. There was no difference between patient groups in postoperative creatinine levels, the need for dialysis, or graft rejection up to 6 months after transplantation.[43] Although large prospective studies are lacking in kidney transplant patients, the use of sevoflurane during kidney transplantation appears to be a reasonable anesthetic choice.

Analgesia during the intraoperative period can be provided with the synthetic opioids fentanyl, sufentanil, alfentanil, and remifentanil, because their pharmacokinetics and pharmacodynamics are not affected by renal insufficiency. Morphine, oxycodone, and meperidine should be used sparingly in patients with renal failure, because these drugs have active metabolites that accumulate in these patients (see Chapter 30).

Appropriate neuromuscular blockade during kidney transplantation is important for optimizing surgical conditions (see Chapters 34 and 35); however, recovery from neuromuscular blockade may be variable in patients with ESRD, regardless of the drug used.[6] Both vecuronium and rocuronium have prolonged durations of action in renal failure patients, because their clearances rely both on renal and hepatic metabolism. Cisatracurium is likely the muscle relaxant of choice in patients with ESRD, because it undergoes organ-independent clearance. Pancuronium is primarily eliminated by the kidneys, and probably should be avoided in patients with renal failure. For patients with ESRD who are undergoing kidney transplantation, judicious use of neuromuscular blocking drugs is a necessity. Titration to surgical conditions and close monitoring of the level of neuromuscular blockade are crucial (see Chapter 53).

The surgical procedure involves placement of the renal allograft in the left or right extraperitoneal fossa, although the right side is usually preferred (Fig. 74-4). A vertical curvilinear incision 20 to 25 cm long is typically made, extending from the pubis symphysis to above the anterior superior iliac spine. The abdominal musculature is divided, and the peritoneum is entered and retracted. During the initial incision and dissection, surgical stimulation is increased and hemodynamic responses may be exaggerated in some patients. Adequate analgesia, depth of anesthesia, and muscle relaxation should be appropriately titrated to effect. The external iliac vein and artery are identified and mobilized. Occasionally, different vascular structures are chosen for the renal anastomoses. Heparin may be administered before clamping of the vessels. The external iliac vein is clamped first, and the renal vein anastomosis is performed. Next, the external iliac artery is clamped and the renal artery anastomosis is performed. During the anastomoses of the renal vessels, expansion of intravascular volume with normal saline should be initiated. Furosemide and mannitol are administered before reperfusion to stimulate diuresis. Mannitol, along with adequate intravascular volume resuscitation, decreases the likelihood of acute tubular necrosis in renal transplantation.[44] Adequate intravascular volume expansion with crystalloid or colloids increases renal blood flow, which improves immediate graft function.[6] At the time of removal of the vascular clamps, additional intravascular volume expansion may be required to stabilize hemodynamics. On rare occasions, removal of vascular clamps may be associated with acute bleeding requiring further resuscitation and transfusion. Hypotension following reperfusion will result in hypoperfusion of the graft. Hypotension may precipitate renal injury owing to ischemia and can contribute to vascular thrombosis of the graft. Appropriate decreases in the depth of volatile anesthetic and volume expansion will maintain adequate renal perfusion pressures in most patients. In the event of hypotension, adrenergic vasopressors are typically avoided because of renal vasoconstrictive effects. Hypotension unresponsive to volume expansion may require interventions to increase cardiac output, especially in high-risk patients. Invasive hemodynamic monitoring is invaluable in this situation. Dopamine is typically the first vasoactive infusion used in kidney transplant patients; however, this is controversial. In an

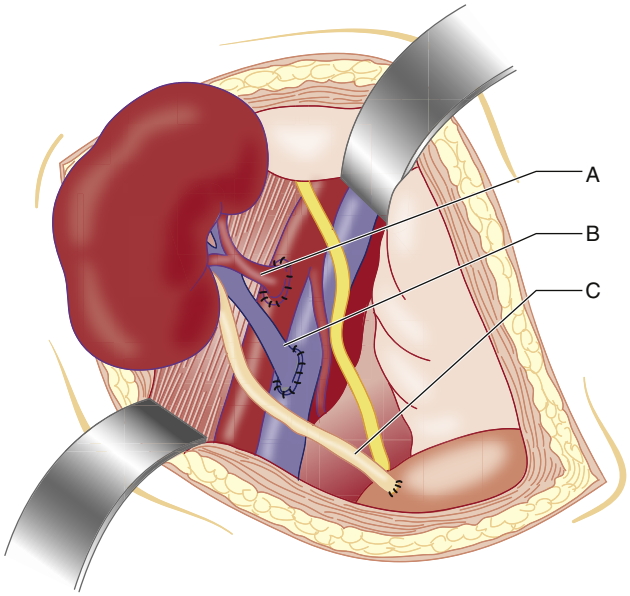


Figure 74-4. Renal transplantation. **A,** Renal artery anastomosis performed end-to-side to the external iliac artery. **B,** Renal vein anastomosis performed end-to-side to the external iliac vein. **C,** Ureteral anastomosis to the bladder mucosa. *(From Hardy JD:* Hardy's Textbook of Surgery*, ed 2. Philadelphia, 1988, JB Lippincott.)*

observational study of 105 kidney transplants, there was no difference in renal function parameters in recipients who received dopamine versus those who did not.[45] Furthermore, dopamine can increase heart rate and myocardial oxygen requirements potentially inducing myocardial ischemia in patients with CAD. The routine perioperative use of dopamine in kidney transplants has not been recommended because it has not been proven to prevent graft complications.[22] After completion of the vascular anastomoses, the donor graft ureter is implanted into the recipient bladder. The bladder is filled with antibiotic saline irrigation solution by way of a three-way Foley catheter, allowing for implantation of the donor ureter. A temporary ureteral stent may be placed as well. After completion of the bladder anastomosis, the wound is closed in layers. Neuromuscular blockade should be maintained until the fascial layer has been closed to prevent straining or coughing that could potentially disrupt the graft position or vascular connections. During emergence, exaggerated hemodynamic responses are common, especially in patients with poorly controlled hypertension. Appropriate titration of short-acting drugs to attenuate these responses upon emergence is helpful, especially in patients at risk for CAD. Careful neuromuscular blockade monitoring and appropriate administration of reversal agents are central to avoiding postoperative pulmonary complications (see Chapters 34 and 35). Likewise, ESRD patients may demonstrate delayed emergence from anesthesia and have exaggerated responses to opioids and sedative-hypnotics. Extubation of the trachea should occur after the patient demonstrates the ability to protect the airway, because kidney transplant patients are still considered a risk for aspiration of gastric contents at the completion of surgery.

ANESTHESIA FOR KIDNEY TRANSPLANT: POSTOPERATIVE MANAGEMENT

After extubation of the trachea, the kidney transplant recipient requires careful monitoring in the postanesthesia care unit. Close monitoring of urine output in the initial postoperative period is important. Acute decreases in urine output should initiate a rapid evaluation of the etiology and appropriate treatment. A prerenal etiology should be treated with aggressive intravascular volume resuscitation. In some patients, additional invasive hemodynamic monitoring may be required. Postrenal etiologies owing to technical problems with the ureteral anastomosis may require early surgical re-exploration. Postoperative complications include vascular thromboses (1% to 2%), wound hematomas (1% to 2%), and infection. High-risk patients with advanced cardiac and pulmonary disease may require further postoperative monitoring in the intensive care setting. Variable rates of admission to ICUs have been reported by different centers, but in general, postoperative intensive care admissions for kidney transplant recipients are much less common than for liver and kidney-pancreas transplant recipients. One single-center study of 1015 consecutive kidney transplants over a 10-year period found an ICU admission rate of 6%. The mortality rate in patients that required intensive care admission may be more frequent (40%) than in other nontransplant ICU patients (20%). Most patients were admitted for sepsis and required ventilator support.[46]

Postoperative pain control is usually provided with synthetic opioid analgesics without active metabolites (see Chapter 98). Pain after kidney transplant is highly variable; in some patients, pain may be severe and challenging to treat effectively. Patient-controlled opioid analgesia is commonly initiated in the postanesthesia care unit. Regional anesthesia for kidney transplantation is controversial. One report demonstrated effective postoperative analgesia in kidney transplant recipients with epidural analgesia.[47] However, the concern for uremic coagulopathy and the potential for hypotension with epidural analgesia has limited its use in kidney transplant recipients. One pilot study in kidney transplant recipients demonstrated that a supplemental transversus abdominis plane block before incision improved postoperative pain scores and decreased opioid requirements compared with control patients who received standard opioid therapy and acetaminophen.[48]

ORGAN MATCHING AND ALLOCATION

Organ matching for kidney transplantation involves several steps to determine compatibility between donor and recipient. Initially, matching of the major ABO blood group is determined for all donors and recipients. Before the transplant surgery, a crossmatch is performed by mixing recipient blood with donor blood cells. This crossmatch is performed to identify any recipient antibodies that are reactive against donor antigens. Histocompatibility matching is an important part of the matching process, in which the human lymphocyte antigen (HLA) profile of the recipient is determined and compared with the HLA

profile of the donor. Organ rejection by the recipient's immune system is mediated by the recognition of mismatched (non-self) HLAs located on the surface of donor cells. Many standard HLAs are compared between potential donors and recipients before transplantation. In general, survival rates are worse with HLA-mismatched grafts. Although better immunosuppression has improved the overall survival rates for kidney transplants during the past 3 decades, the graft loss rate for HLA-mismatched kidneys has remained twice as frequent as HLA-matched grafts.[49] For all potential recipients awaiting a deceased donor, their HLA profile is compared to the donor profile, and an appropriate donor-recipient pairing is made based on the best match. For living donors, HLA matching is performed well in advance of the surgery.

Currently, deceased-donor kidneys in the United States, unlike other organs, are allocated primarily based upon the recipient's accrued time on the waitlist. With improvements in immunosuppression, HLA matching is not as prominently weighted in the kidney allocation process as previously. Despite the increase in living donor transplants within the past 20 years, efforts have been made to revise the current deceased-donor kidney allocation system in the United States to allocate organs to the highest acuity patients, similar to liver graft allocation. Ideally, a new allocation system would decrease the number of recipient deaths before transplant while matching donor and recipient characteristics to maximize posttransplant recipient survival.

ANESTHESIA FOR PATIENTS AFTER KIDNEY TRANSPLANTATION

After successful kidney transplantation, most patients are classified as having National Kidney Foundation stage 2 or 3 CKD with usual GFRs more than 30 mL/min. GFR typically deteriorates by 1.4 to 2.4 mL/min/yr in renal transplant recipients.[50] Posttransplant mortality increases as renal graft function deteriorates. Renal function is followed closely within the first few years after transplant to assess for rejection, which is identified by worsening organ function. In post–kidney transplant patients undergoing nontransplant surgery, renal function should be assessed before surgery. Most patients will be under the care of a nephrologist within the first years of a kidney transplant; assessment of the patient's medical records or renal function tests should be obtained preoperatively. Rejection should be ruled out before nontransplant surgery, as surgery during an episode of rejection can increase morbidity.[51]

Cardiovascular disease is the most common cause of death in kidney transplant patients. As described previously, cardiovascular disease is involved in the pathogenesis of renal failure and is a consequence of kidney disease. Ischemic heart disease, cerebrovascular disease, and peripheral vascular disease significantly affect the survival of kidney transplant patients. Progression of preexisting CAD can occur in the posttransplant patient, as immunosuppression contributes to the development of de novo hyperlipidemia, hypertension, and diabetes. The incidences of hypertension (80%), hyperlipidemia (60% to 80%), and new-onset diabetes (25%) are increased in kidney transplant recipients.[50] Obesity and the development of metabolic syndrome are common after kidney transplant (see Chapter 71). More than 60% of renal transplant patients received a diagnosis of metabolic syndrome within 6 years following kidney transplant in one study.[52] Because long-term studies on cardiac outcomes following nontransplant surgery in kidney transplant recipients are lacking, specific recommendations for regular cardiovascular testing are lacking as well. For previous kidney transplant patients undergoing nontransplant surgery, the ACC/AHA guidelines for the preoperative evaluation for noncardiac surgery should be used to guide preoperative cardiovascular testing[21] (see Chapter 38).

Other disease processes related to kidney disease and immunosuppression should be sought. Kidney transplant patients are at increased risk for posttransplant malignancies, anemia, and osteodystrophy. Infection is a constant concern in kidney transplant recipients, because they are at risk for both opportunistic and community-acquired infections. Cytomegalovirus (CMV) infection is the most common infection in kidney transplant patients, and it is rarely acquired by transfusion (see Chapter 61). CMV-negative blood should be used when transfusions are required in patients who are CMV negative.

Anesthesia for nontransplant surgery can be accomplished safely with general, regional, and local sedation techniques. Most anesthetic drugs are safe in posttransplant patients, assuming the presence of adequate hepatic and renal function.[51] Although preoperative creatinine may be near normal in kidney transplant recipients, GFR in these patients is usually reduced, resulting in prolongation of the activity of drugs cleared by the kidneys. Obviously, drugs that cause nephrotoxicity should be avoided.

PANCREAS TRANSPLANTATION

Surgical treatment for diabetes includes pancreas transplant alone (PTA) and, in patients with diabetes and ESRD, pancreas after kidney transplant (PAK) and simultaneous pancreas-kidney transplant (SPK). Usually, whole pancreas is transplanted from deceased donors. Less commonly, the distal pancreas is transplanted from a living donor. In 2008, there were 432 pancreas transplants performed in the United States (223 PTAs and 209 PAKs), and 826 SPKs. The total number of pancreas transplants performed in the United States for all three groups has decreased annually over the past several years (Fig. 74-5). The reasons for this decline are not well understood.[53] The 5-year patient survival for pancreas transplant is 90% for PTA, 86% for PAK, and 88% for SPK. The 5-year graft survival for pancreas transplant is 73% for SPK, 52% for PTA, and 55% for PAK.[5]

INDICATIONS FOR PANCREAS AND KIDNEY-PANCREAS TRANSPLANTATION

Pancreas transplantation provides patients with insulin-dependent diabetes mellitus a permanent source of endogenous insulin, thus restoring normoglycemia. SPK and PAK transplants are indicated in patients with diabetes

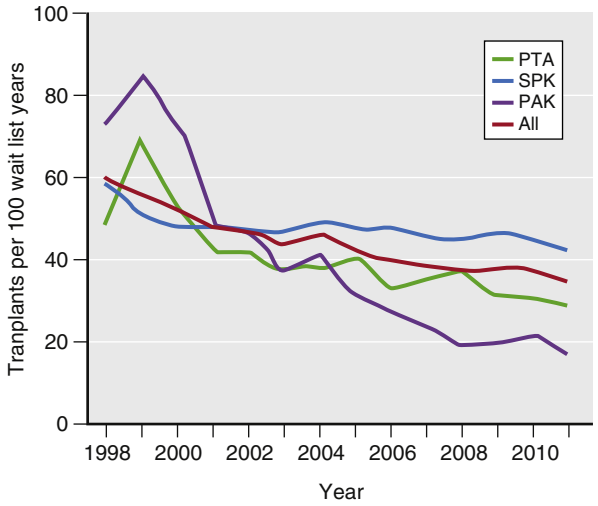


Figure 74-5. Pancreas transplant rates per 100 waitlist years. The pancreas transplantation rate is decreasing. *PTA,* Pancreas transplant alone; *SPK,* simultaneous pancreas-kidney transplant; *PAK,* pancreas transplant after kidney transplant. *(OPTN & SRTR Annual Data Report 2011. U.S. Department of Health and Human Services Health Resouces and Services Administration, p 7, Figure PA 1.4)*

and ESRD who are deemed appropriate candidates for kidney transplantation or who have already undergone kidney transplantation. PTA is indicated in patients with diabetes without indications for kidney transplantation and who have a history of severe frequent metabolic complications, or who have a history of problems maintaining insulin therapy that result in intractable diabetic complications.[54] Most patients who undergo pancreas transplant have type 1 diabetes mellitus. Rare indications for pancreas transplant include select cases of type 2 diabetes mellitus, chronic pancreatitis that has developed endocrine deficiency, cystic fibrosis with endocrine deficiency, and prior total pancreatectomy.

For patients with diabetes and ESRD, those younger than 50 years have better survival than older patients when undergoing pancreas transplantation at the time of kidney transplantation.[55] The survival benefit in SPK may be due to long-term decreases in CAD complications.[56] For patients with normal renal function who undergo PTA, long-term survival appears be the same as in patients receiving chronic insulin therapy[57]; however, pancreas transplant has a favorable effect on the progression of retinopathy. The progression of retinopathy is decreased or reversed in a significant percentage of PTA patients compared to diabetic patients treated with conventional insulin therapy.[58]

PATHOPHYSIOLOGY OF PANCREATIC INSUFFICIENCY

Type 1 diabetes mellitus occurs secondary to destruction of pancreatic islet cells resulting in a permanent functional loss of the endogenous production of insulin, necessitating life-long exogenous insulin therapy. The underlying cause of type 1 diabetes mellitus remains unknown. Type 2 diabetes mellitus results from peripheral resistance to the effects of insulin. Both diseases produce chronic increases of blood glucose concentrations resulting in the multiorgan manifestations of diabetes.

The chronic complications of diabetes that have the greatest effect on patient morbidity and survival are those that affect the cardiovascular system. CAD, cerebrovascular disease, and peripheral vascular disease occur in patients with diabetes owing to acceleration of atherosclerosis. Both macrovascular and microvascular disease occurs. Patients with diabetes develop CAD earlier, are more likely to have atypical symptoms, and have a higher mortality rate from MI than nondiabetics.[59] Peripheral and autonomic neuropathies develop in diabetes, resulting in gastroparesis, lower extremity paresthesia, ulcerations, orthostatic hypotension, and labile heart rate and arterial blood pressure. Patients with diabetes have a high cumulative prevalence of blindness (16%), renal failure (22%), lower extremity amputation (12%), MI (21%), and stroke (10%)[60] (see Chapter 39).

Acute complications of type 1 diabetes mellitus typically involve conditions associated with severe hyperglycemia, such as diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic coma. Hypoglycemia is a direct result of exogenous insulin administration. Patients with type 1 diabetes are prone to large fluctuations in blood glucose levels. Hypoglycemic episodes contribute to acute morbidity and mortality in diabetic patients.

ANESTHESIA FOR PANCREAS TRANSPLANTATION: PREOPERATIVE EVALUATION

The preoperative evaluation for the patient undergoing pancreas transplantation involves an assessment of all of the potential acute and chronic complications of type 1 diabetes. Pancreas transplant centers pursue a comprehensive, multidisciplinary evaluation and selection process before listing candidates. This evaluation should address the organ systems most affected by long-standing diabetes, including the cardiovascular, renal, and neurologic systems. Assessment for the presence and severity of CAD should be undertaken in all candidates, including noninvasive ischemia testing, evaluation of ventricular function, and coronary angiography in select patients. Previously, patients considered for pancreas transplantation were younger than 40 years and had a lower risk for the cardiac and vascular sequelae of diabetes. Older patients are now considered for pancreas transplantation, but have a significantly higher risk for CAD and vascular disease.[61] Strategies to reduce cardiac complications, such as maintenance of β-adrenergic blockade and continuation of drugs that decrease blood lipid concentrations during the perioperative period, should be applied when appropriate.[21]

In most cases, pancreas transplantation involves a deceased-donor organ with a 24-hour maximum cold ischemia time; therefore, pancreas transplantation is considered an urgent procedure. Preoperative evaluation by the anesthesiologist should focus on any acute changes in the patient's medical status, especially those involving acute diabetic complications such as ketoacidosis and hypoglycemia. Blood glucose measurements should be assessed closely before surgery, and recent insulin administration should be noted. Evaluation of renal function in

all candidates is important before surgery. Most patients with diabetes listed for pancreas transplant have ESRD as well and will undergo SPK. A full evaluation of electrolytes, including creatinine and potassium, should be obtained before surgery. Serial trends in heart rates and arterial blood pressures in hospitalized patients should be assessed, as most patients will have a history of hypertension requiring multiple medications, especially patients with renal failure. Preoperative assessment of intravascular volume status is especially important in patients with ESRD on hemodialysis (see Chapter 38). Finally, a directed physical examination focusing on the airway and cardiopulmonary system should be performed. The incidence of difficult tracheal intubations in patients with long-standing diabetes was thought to be more frequent because of anatomic changes of the upper airway; however, two recent reports did not concur.[62,63] Nevertheless, attention to anatomic signs of a potentially difficult airway is important in patients with diabetes, especially those with cervical arthritis and significant obesity.

ANESTHESIA FOR PANCREAS TRANSPLANTATION: INTRAOPERATIVE MANAGEMENT

General anesthesia with endotracheal intubation is required for all types of pancreas transplantation. The surgical procedure is typically prolonged, and an adequate depth of anesthesia and muscle relaxation is required for optimal surgical conditions. Diabetic patients and those with ESRD have a high likelihood of gastropathy and may have an increased risk for aspiration of gastric contents. Administration of an oral nonparticulate antacid preoperatively should be considered. A rapid-sequence induction of anesthesia with continuous cricoid pressure is the safest approach to securing the airway. Patients with diabetes, ESRD, cardiovascular disease, and autonomic neuropathy may be prone to wide fluctuations in heart rate and arterial blood pressure. Vital signs should be closely monitored, and maintenance of hemodynamic stability should be a primary anesthetic goal, especially during and immediately following anesthetic induction. Invasive monitoring is standard for pancreas transplantation. Arterial monitoring allows for beat-to-beat arterial blood pressure measurements, as well as access for analysis of arterial blood gases and blood glucose monitoring. Central venous access may be indicated for central administration of vasoactive infusions and immunosuppression drugs. Central venous pressure monitoring is used in some centers; however, the usefulness of this practice has been questioned, as central venous pressure might not be a reliable indicator of intravascular fluid responsiveness.[40] Arterial line placement before induction of anesthesia may be considered, especially in patients with severe hypertension or CAD. Anesthesia is typically maintained with a balanced technique using volatile anesthetics, opioids, and muscle relaxants. In patients with renal failure, medications should be chosen that are not dependent on the kidneys for elimination. All the caveats for the anesthetic management of patients undergoing kidney transplantation should be applied for patients undergoing SPK.

A midline surgical incision is made for both pancreas and kidney-pancreas transplant surgeries. Extensive retraction necessitates adequate muscle relaxation. Prolonged exposure of the abdominal viscera results in significant third-space losses; adequate volume expansion with crystalloid or colloids is often required. The pancreas graft is usually placed in the iliac fossa. The arterial vascular supply to the pancreas graft is usually provided by an anastomosis to the iliac artery. Venous drainage from the pancreas graft can be delivered to either the iliac vein or the native portal vein. Usually the venous outflow from the pancreas is delivered to the iliac vein, which is associated with a lower rate of venous thrombosis. Alternatively, venous outflow may be directed to the native portal vein, which is the physiologically normal pattern of pancreatic venous efflux. There appears to be no significant advantage to portal venous drainage over systemic venous drainage for pancreas transplantation.[56]

Pancreatic exocrine drainage can be delivered to either the bladder or the intestine (Fig. 74-6). Although enteric pancreatic drainage is physiologically normal, this method is associated with surgical complications that can result in graft dysfunction, thrombosis, and early rejection. Exocrine drainage to the bladder allows for measurement of urinary amylase levels, which can be used to diagnose early rejection episodes before blood glucose levels are affected. Exocrine bladder drainage is associated with urologic complications and metabolic acidosis. Currently, most pancreas transplants utilize enteric drainage as there is no difference in graft or patient survival compared to bladder drainage.[64,65]

Prior to completion of the vascular anastomoses during pancreas transplantation, blood glucose levels should be assessed at least hourly as levels frequently fluctuate in brittle diabetic patients. Blood glucose should be maintained at less than 200 mg/dL, using intravenous insulin and dextrose infusions if necessary. Sliding scale insulin infusion protocols may be applied. Dextrose prevents the development of ketoacidosis during the early stages of the procedure. Before unclamping of the vascular anastomoses, adequate volume resuscitation should be initiated. Adequate cardiac preload and normal arterial blood pressures should be the hemodynamic goals before unclamping.

After unclamping of the vascular connections, adequate perfusion pressure to the graft is critical. Hypotension should be corrected rapidly, and intravascular volume status should be optimized. If hypotension occurs because of myocardial dysfunction, intracardiac pressure monitoring or transesophageal echocardiography can assist in the diagnosis and may help to guide therapy. Blood transfusions, colloids, and vasoactive medications may be required for the treatment of hypotension after reperfusion of the pancreatic graft. Therapy should also be guided by frequent arterial blood gas analyses with assessment of electrolytes and hemoglobin.

One of the most important intraoperative care points for pancreas transplantation is the management of blood glucose following pancreas reperfusion. After unclamping, the pancreas may release insulin into the circulation within several minutes. Blood glucose should be measured approximately every 30 minutes for the remainder

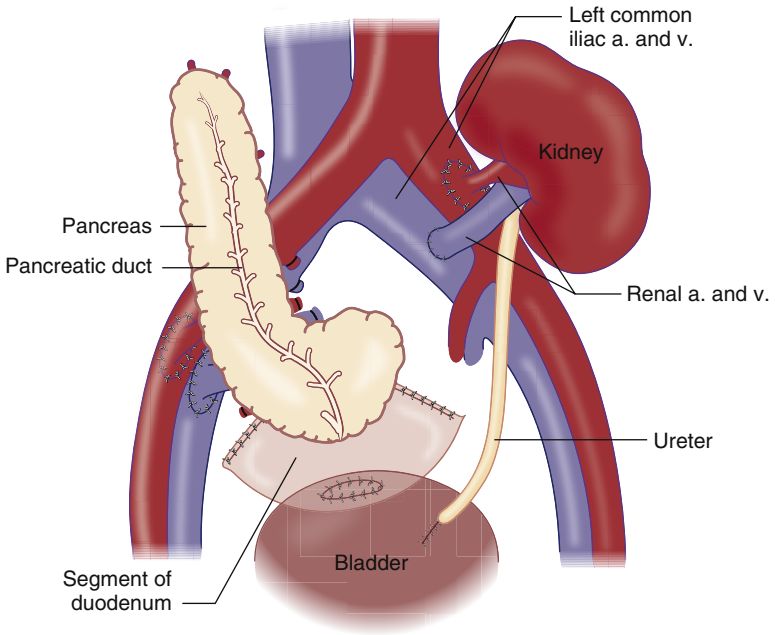


Figure 74-6. Pancreas transplantation. Bladder drainage is through a pancreatic duodenocystostomy. A renal transplant is shown with the common iliac vessels used for vascular anastomoses. *(Modified from Moody FG, editor:* Surgical Treatment of Digestive Diseases*, ed 2. St Louis, 1990, Mosby–Yearbook.)*

of the procedure. After successful transplantation, insulin requirements rapidly decline, and patients may be at risk for hypoglycemia. Delayed graft function can be identified by the presence of hyperglycemia. In this event, insulin infusion should be titrated to maintain blood glucose levels less than 200 mg/dL.[60]

ANESTHETIC MANAGEMENT OF PANCREAS TRANSPLANTATION: POSTOPERATIVE MANAGEMENT

After the completion of surgery, complete reversal of neuromuscular blockade, hemodynamic stability, normothermia, and the ability of the patient to protect the airway will facilitate tracheal extubation. Pancreas transplant patients should be monitored closely in the postanesthesia care unit and ICU. Regular blood glucose measurements should be continued in the postoperative period to avoid hypoglycemia. Electrolytes, complete blood count, and analysis of arterial blood gas should be obtained immediately postoperatively, because acid-base disturbances, anemia, and electrolyte imbalances are common. Euvolemia should be maintained. Depending on the patient's age and underlying risk for CAD, serial troponins and ECG may be assessed for the presence of myocardial ischemia or infarction, because cardiac symptoms may be lacking in this population. Postoperative pain can be severe, given the extensive surgical wound and duration of surgery. Postoperative pain usually is managed with opioids in the perioperative period with transition to patient controlled analgesia in the early postoperative period (see Chapter 98). Epidural analgesia may be appropriate for pancreas transplant recipients, although the possibility of hypotension in the early postoperative period can be problematic. For SPK, the usual postoperative strategies for kidney transplant patients including close monitoring of urine output should be applied.

Surgical complications occur in 7% to 9% of all pancreas transplants and usually require reoperation. Technical complications are associated with the potential for graft loss and patient morbidity.[66] Graft thrombosis is the most important early complication and requires emergent surgical exploration. Intra-abdominal bleeding can occur secondary to coagulopathy induced by anticoagulation for the treatment of graft thrombosis. Late complications include bladder or enteric leaks, intra-abdominal sepsis, and rejection.

ORGAN MATCHING AND ALLOCATION

The organ matching process for pancreas transplantation is similar to that for kidney transplant organ matching. Blood group and HLA matching are initially performed to match the donor and recipient, followed by a crossmatch at the time of surgery. There has been a trend over the past decade toward less stringent HLA matching for all forms of pancreas transplantation. Despite this trend, pancreas transplant graft survival rates continue to improve, likely because of enhancements in surgical techniques and immunosuppression.[66,67]

Most organs allocated for pancreas transplantation are for diabetic recipients younger than 40 years. However, over the past decade, the average transplant recipient's age has become older because of the allocation of more organs for patients with type 2 diabetes.[61] In the United States, pancreas allocation is regulated initially for local distribution, followed by regional and national distribution. Unlike kidney transplantation, technical complications are the most common cause of pancreas transplant

graft failure. Donor risk factors that affect pancreas graft survival include donor age older than 45 years, donor body mass index (BMI) greater than 30 kg/m^2, and cerebrovascular or nontraumatic cause of death.[68] These factors have a significant effect on donor organ selection.

ANESTHESIA FOR PATIENTS AFTER PANCREAS TRANSPLANTATION

After successful pancreas transplantation, long-term normoglycemia is expected. For patients with a history of previous pancreas transplant presenting for surgery, a comprehensive posttransplant history of any episodes of surgical complications and episodes of rejection should be obtained. Blood glucose concentrations should be measured on the day of surgery. A detailed history and review of medical records focusing on CAD, renal disease, and vascular disease is critical, because pancreas transplant patients have a high prevalence of these conditions. Furthermore, disease progression can occur despite successful pancreas transplantation. There are no studies of cardiac outcomes in pancreas recipients undergoing nontransplant surgery; therefore, a stepwise approach to the preoperative cardiac evaluation, guided by the 2007 ACC/AHA Guidelines, is a reasonable approach for pancreas recipients undergoing subsequent nontransplant surgery.[21]

LIVER TRANSPLANTATION

In 1963, shortly after the effectiveness of azathioprine and prednisone was established for renal transplantation, Dr. Thomas Starzl performed the first human liver transplant.[69] The recipient, a 3 year-old child with biliary atresia, died in the operating room from massive hemorrhage caused by venous collaterals and uncontrollable coagulopathy. Four years later, Starzl performed the first successful transplant in an 18-month-old infant with hepatocellular carcinoma. The advent of cyclosporine in 1979, followed by the 1983 pronouncement of the National Institutes of Health Consensus Conference that liver transplantation was no longer experimental, ushered in the era of liver transplantation. Over the ensuing decades, liver transplantation centers were established around the world, and the field matured following continued improvements in surgical technique, immunosuppression, and the management of coagulopathy and infections.

The number of disciplines that have contributed to the advances in liver transplantation illustrates the team approach involved in the care of the liver transplant recipient. Hepatologists, surgeons, nephrologists, specialists in critical care medicine and infectious disease, anesthesiologists, pediatricians, radiologists, and pathologists have important roles. Key team members extend beyond physicians and include transplant coordinators, nurses, blood bank personnel, and procurement organizations.

Liver transplantation is unique among abdominal organ transplants in that a dedicated team is typically involved because of the unique challenges encountered during liver transplant surgery. The United Network of Organ Sharing (UNOS), which manages the U.S. organ transplant system under contract with the U.S. Department of Health and Human Services, recognizes the important role of anesthesiologists in the perioperative care of liver transplant candidates. In 2011, UNOS instituted a requirement that U.S. liver transplant programs designate a Director of Liver Transplant Anesthesia who meets qualifications based on experience and training. These qualifications parallel similar requirements for the transplant surgeon and physician (hepatologist). In addition, UNOS delineated the clinical responsibilities of the Director of Liver Transplant Anesthesia, which include preoperative assessment of transplant candidates, participation in candidate selection, intraoperative management, postoperative visits, and participation in mortality and morbidity conferences.[70] Lastly, the director is expected to maintain current knowledge in the field of transplant anesthesia by participating in continuing medical education activities related to transplantation.

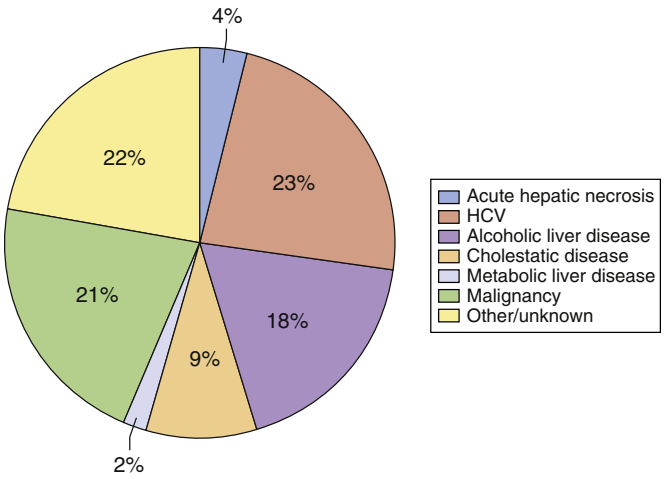


Figure 74-7. Indications for Adult Liver Transplants in the United States, 2011. *HCV: hepatitis C virus. (Adapted from OPTN & SRTR Annual Data Report 2011. U.S. Department of Health and Human Services Health Resouces and Services Administration, p 88, Figure Li 4.9)*

INDICATIONS FOR LIVER TRANSPLANTATION

Liver transplantation is the only definitive treatment for decompensated cirrhosis, unresectable primary hepatic malignancies, acute liver failure, and metabolic disease. Of these indications, decompensated cirrhosis accounted for 75% of adult liver transplants performed in the United States in 2011, followed by malignancy in 21%, acute liver failure in 4%, and metabolic disease in 2%.[1]

Cirrhosis is further categorized into hepatitis C viral disease (23% of the total transplants performed in 2011 in the United States), alcoholic liver disease (18%), cholestatic disease (9%), and a miscellaneous category (22%) that includes nonalcoholic steatohepatitis (NASH), autoimmune disease, and others (Fig. 74-7).

Advances in the treatment of chronic liver disease, particularly antiviral therapy and transjugular intrahepatic portosystemic shunt (TIPS) placement, have led to improvements in survival over the past decade.[71] In selected patients with advanced cirrhosis and active

TABLE 74-1 PROGNOSIS: COMPLICATIONS OF CIRRHOSIS

Event	Survival
Variceal bleeding	65%-70% at 1 year*
Ascites	48%-60% at 1 year†
Hepatorenal syndrome	50% at 3 months‡
Encephalopathy (grade 2/3)	40%-50% at 1 year§

Survival after complications is poor compared with 90% patient survival at 1 year after liver transplantation.
*Thomopoulos K, Theocharis G, Mimidis K, et al: *Dig Liver Dis* 38:899, 2006.
†Fernandez J, Navasa M, Planas R, et al: *Gastroenterology* 133:818, 2007.
‡Alessandria C, Ozdogan O, Guevara M, et al: *Hepatology* 41:1282, 2005.
§Stewart C, Malinchoc M, Kim W, Kamath P: *Liver Transplant* 13:1366, 2007.

variceal bleeding, early placement of TIPS improved 1-year survival to 86% compared with 61% in a group randomized to similar therapy without early TIPS.[72] However, when life-threatening complications of liver failure such as encephalopathy, ascites, gastrointestinal bleeding or uremia develop, survival is improved by liver transplantation (90% 1-year survival) compared with medical therapy (Table 74-1). Referral for liver transplantation is appropriate in the presence of an index complication of cirrhosis.

Chronic liver disease and cirrhosis is the fifth leading cause of death in the United States for individuals aged 45 to 64 years; it is surpassed only by cancer, heart disease, accidents (unintentional injury), and chronic respiratory diseases. Among all age groups, liver disease accounted for more than 33,000 deaths in 2011, making it the twelfth leading cause of death.[73]

TRENDS IN LIVER TRANSPLANTATION

Over the past decade, the proportion of transplants performed for malignancy and cirrhosis owing to NASH is increasing. Malignancy accounted for just 4% of liver transplants in 2001, whereas it accounted for 21% in 2011. Currently NASH is the third most common indication for transplantation, and by 2025 it is expected to overtake cirrhosis owing to hepatitis C as the single most frequent indication for liver transplantation.[74] The number of transplants performed for hepatitis C has decreased from 31% to 23% of liver transplants over the past decade (2001 to 2011).[1]

The total number of liver transplants performed in the United States increased from 3900 in 1998 to 6000 in 2006. The number has since stabilized at approximately 6000 per year.[1] European transplant centers perform a similar number of transplants per year (approximately 6000) for similar indications.[75] During the past decade, the number of patients (adult and pediatric) living with a functioning liver transplant more than doubled, from 30,000 in 2001 to 62,000 in 2011.[1]

The median time to transplant in the United States for the period ending in 2011 was 12.6 months (interquartile range, 1.6-72 months).[76] Waiting times in the United States decreased drastically with the implementation of the current allocation system in 2002, which deemphasized wait times for organ allocation. Median wait times have steadily increased since 2005; however, this is overshadowed by geographic variation in waiting times across various regions, termed *donation service areas*, within the United States.[77]

Over the past decade, the proportion of recipients aged 50 years or older increased from 58% to 77%. The proportion of recipients aged 65 years or older has increased by 50%.[1] Although fewer females undergo liver transplant compared to males, the gender gap is narrowing. Finally, the trend toward combined organ transplantation, particularly liver-kidney transplant, has continued and in 2011 represented approximately 7% of transplants.

The primary limitation to liver transplantation is the continuing organ shortage, which has resulted in the death of approximately 12% of waitlisted transplant candidates each year for the past decade.[1] This number has plateaued, but the number of patients removed from the waitlist because they are too sick to undergo transplant has doubled over the past 3 years. Responses to these concerns have resulted in the use of expanded-criteria donors, including grafts donated after cardiac death, which increased from less than 2% of liver transplants in 2001 to 6% in 2011.[1] Living donation has decreased over the past 10 years, particularly for adult recipients. In 2001, more than 400 living donor grafts were transplanted into adult recipients. In 2011, fewer than 200 adults received living donor grafts.[1] This change highlights the concern over postoperative complications in living donors, particularly those providing a larger liver mass, as is the case with right lobe donation. Two living donor deaths were reported in 2010, further illustrating the risk to living donors.

The recurrence of hepatitis C after successful liver transplantation has been increasingly recognized as a challenge. Because hepatitis C is the most common indication for transplantation, recurrent infection and graft failure represents a formidable issue. The deleterious effects of immunosuppression on viral replication have led many centers to attempt to withdraw steroids in selected patients with viral infections.

The number of pediatric liver transplants in the United States has been stable at 500 to 600 per year over the past decade (2002 to 2011; see Chapter 93). During the same period, approximately 10% to 15% of pediatric recipients in the United States received grafts from living donors, down from 20% to 25% in the prior decade.[1] The most common indication for transplant in pediatric recipients is cholestatic disease (47%), followed by malignancy (14%), metabolic disease (13%), and acute hepatic necrosis (11%).[1] The European Liver Transplant Registry (ELTR) reports similar numbers of pediatric recipients, approximately 10% of the total number of liver recipients.[78]

PATHOPHYSIOLOGY OF END-STAGE LIVER DISEASE

Cirrhosis is the end product of chronic parenchymal inflammation and necrosis, which results in fibrosis and disruption of hepatic architecture. Resistance to blood flow leads to portal hypertension and the formation of vascular shunts between portal and systemic veins.[79]

When the pressure gradient between the portal and hepatic veins exceeds 10 to 12 mm Hg, portal hypertension is severe, and complications such as ascites, esophageal variceal bleeding, encephalopathy, and hepatorenal syndrome occur. Decompensated cirrhosis affects nearly every other organ system.[80] The preoperative assessment of liver transplant candidates requires a knowledge of the pathophysiologic changes associated with decompensated cirrhosis.

Cardiovascular Complications

Hyperdynamic circulation—characterized by a high cardiac output, low arterial blood pressure, and low systemic vascular resistance—is the hallmark of end-stage liver disease. Patients appear well perfused despite systolic arterial pressures less than 100 mm Hg. Pulmonary arterial pressures may be mildly elevated because of increased flow; however, the pulmonary vascular resistance (PVR) is usually within the normal range. These patients have an elevated intravascular volume that is sequestered into a dilated splanchnic vascular bed. The effective circulating volume is typically reduced.

Hyperdynamic circulation is the result of portal hypertension-induced production of vasodilators such as natriuretic peptides, vasoactive intestinal peptide, endotoxin, glucagon, and particularly nitric oxide.[81] Elevated production of nitric oxide has been observed to precede the formation of the hyperdynamic circulation in cirrhosis. The overproduction of vasodilators is responsible for reduced circulatory responsiveness to sympathetic stimulation.[82] Clinically, this frequently results in a need for increased doses of vasopressors.

In addition, patients with cirrhosis can have other cardiac functional abnormalities that are not immediately apparent in the baseline state. These abnormalities define a condition termed *cirrhotic cardiomyopathy* and include systolic and diastolic dysfunction, cardiac resistance to β-adrenergic stimulation, and electrophysiologic abnormalities. Systolic incompetence is revealed by physiologic or pharmacologic stress and is manifested by an inability to increase cardiac output in response to exercise, and an inability to increase ejection fraction despite an increase in end-diastolic volume. The severity of cardiac dysfunction seems to be correlated directly with the severity of liver disease.[83] Diastolic dysfunction has been described in patients with cirrhosis as well, on the basis of diagnostic echocardiographic findings of abnormalities in transmitral flow during diastole. These abnormalities consist of a decrement or reversal of the E/A wave ratio and prolongation of E wave deceleration time, reflecting ventricular resistance to diastolic filling. Diastolic dysfunction manifests as sensitivity to changes in cardiac filling and results in vulnerability to heart failure.

Autonomic dysfunction is present in a significant proportion of cirrhotic patients. It presents as chronotropic and hemodynamic incompetence in response to hemodynamic challenges. Prolonged QTc interval is also observed in patients with cirrhosis, and care should be taken when treating these patients with drugs known to prolong the QT interval.[84]

Risk factors for CAD in patients with cirrhosis are similar to those of other patient populations: hypertension, dyslipidemia, age, gender, and obesity. However, NASH has been recognized as an increasingly important cause for transplantation and carries with it the risks of obesity, diabetes, and chronic inflammatory state. The optimal test for identifying cirrhotic patients with significant CAD is unclear. Because many of these patients cannot exercise, pharmacologic stress testing is most commonly used. Unfortunately, studies investigating the predictive value of noninvasive functional testing, particularly dobutamine stress echocardiography, have generally shown poor sensitivity and varying negative predictive value (75% to 89%).[85] Thus, among liver transplantation candidates, consideration should be given to proceeding with coronary angiography if the patient is judged to have a high likelihood of CAD.[86] For less complex surgeries, however, this may not be warranted. There is evidence that patients with treated CAD have posttransplant survival similar to patients without angiographic evidence of CAD.[87]

Pulmonary Complications

As many as 50% to 70% of patients with chronic liver disease complain of shortness of breath.[88] The differential diagnosis includes ventilation-perfusion abnormalities associated with underlying obstructive airways disease, fluid retention, pleural effusion, and decreased lung capacities secondary to large volume ascites. Alpha-1 antitrypsin deficiency has both lung and liver manifestations, as does cystic fibrosis. In addition, there are two types of vascular abnormalities unique to the setting of portal hypertension, and they have significant morbidity and mortality. These abnormalities, hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN), are unique entities that have discrete implications on liver transplant candidacy.

HPS is present in up to 20% of patients who present for liver transplantation.[89] The diagnostic criteria for HPS include portal hypertension, PaO_2 less than 80 mm Hg on room air (or alveolar-arterial oxygen gradient greater than 15 mm Hg), and evidence of intrapulmonary vascular dilation (IPVD).[90] Demonstration of IPVD can be made by contrast-enhanced echocardiography or by perfusion lung scanning using technetium-labeled macroaggregated albumin. In the absence of HPS, microbubbles and albumin macroaggregates injected into the venous circulation are trapped by the pulmonary capillary bed. The delayed (more than three cardiac cycles) appearance of microbubbles in the left atrium (on echocardiography) or increased (>5%) extrapulmonary uptake of technetium-labeled macroaggregated albumin suggests the presence of IPVD, which results in a massive increase in pulmonary capillary diameter, from between 8 to 15 μm to 50 to 500 μm. This increase, together with the usually hyperdynamic circulation of the cirrhotic patient, allows insufficient time for oxygen diffusion through the entire stream of capillary blood. As a result, the central stream of poorly oxygenated blood is functionally shunted. This lesion is typically correctable with the administration of oxygen. Because IPVDs predominate in the bases of the lungs, standing worsens hypoxemia compared with the supine position (orthodeoxia).

TABLE 74-2 **RIGHT HEART CATHETERIZATION DATA FROM FOUR REPRESENTATIVE PATIENTS WITH CIRRHOSIS AND SIMILAR ELEVATIONS IN MEAN PULMONARY ARTERY PRESSURE***

Patient	Mean PA Pressure (mm Hg)	Pulmonary Capillary Wedge Pressure (mm Hg)	Cardiac Output (L/m)	Pulmonary Vascular Resistance (dynes·sec·cm^{-5})	Diagnosis
1	35	10	5	400	Primary pulmonary hypertension
2	35	10	10	200	Hyperdynamic circulation
3	35	25	5	160	Fluid overload
4	35	25	10	80	Fluid overload in a patient w/ hyperdynamic circulation

PA, Pulmonary artery.
*Note that only the first patient has primary pulmonary hypertension, as evidenced by elevated pulmonary vascular resistance.

The natural history of HPS is usually one of progressive hypoxemia. Liver transplantation can be expected to correct hypoxemia in greater than 85% of patients, although it may take up to 1 year to do so.[91] In patients with HPS, survival with transplantation is considerably more frequent than without transplantation. Previously, $PaO_2 \leq 50$ mm Hg was considered a predictor of increased mortality with or without transplantation. However, in the largest single-center series of liver transplantation for HPS, the overall 5-year survival was 76%, comparable to transplantation in patients without HPS.[92] These findings suggest that timely transplantation in patients with HPS results in good outcomes. Accordingly, allocation exception points have been assigned to patients with HPS and room air $PaO_2 < 60$ mm Hg.[93]

PPHTN is defined as pulmonary hypertension in the presence of portal hypertension in a patient without other predisposing factors. The European Respiratory Society Task Force on Hepatopulmonary Disease diagnostic criteria are: (1) clinical evidence of portal hypertension with or without hepatic disease; (2) mean pulmonary artery pressure of 25 mm Hg at rest or 30 mm Hg during exercise; (3) mean pulmonary artery occlusion pressure less than 15 mm Hg or transpulmonary gradient (mean PA pressure minus wedge pressure) greater than 12 mm Hg; and (4) PVR greater than 240 dyn·s·cm^{-5} or 3 Wood Units.[94]

The requirement for calculation of the PVR is a reflection of the fact that many patients with cirrhosis have mildly elevated mean pulmonary artery pressure based simply on an elevated cardiac output (Table 74-2). Mild, moderate, and severe PPHTN are defined by mean PA pressure less than 35 mm Hg, 35 to 50 mm Hg, and greater than 50 mm Hg, respectively.

The prevalence of PPHTN is 2% in a population of patients with known portal hypertension,[95] as compared with 0.13% in an unselected population.[96] The prevalence is 4% to 6% among liver transplant candidates.[97] The occurrence of PPHTN is unrelated to the severity of the underlying liver disease. Similar to HPS, the symptoms of PPHTN are nonspecific, commonly consisting of dyspnea, generalized weakness, and decreased exercise tolerance.

The single best screening study for PPHTN is two-dimensional transthoracic echocardiography, which estimates right ventricular systolic pressure using the velocity of the tricuspid regurgitant jet. In the absence of pulmonary valvular stenosis, right ventricular systolic pressure is a good estimate of pulmonary arterial systolic pressure. Transthoracic echocardiography screening has a sensitivity of 97% and a specificity of 77% in diagnosing moderate to severe PPHTN in patients undergoing pretransplantation workup.[98] Right-sided cardiac catheterization is necessary, however, to confirm elevated pressures and to measure PVR.

Moderate and severe PPHTN are associated with increased mortality during liver transplantation. In a multicenter study of 36 patients with PPHTN who underwent liver transplantation, more than one third of the patients died during the hospitalization (within 3 weeks of surgery). Nonsurvivors (12 of 13 patients) had mean PA pressures greater than 35 mm Hg.[99] In addition to elevated mortality, the effect of successful liver transplantation on the natural course of PPHTN is unpredictable. Some patients experience a resolution with transplant, some continue to require medical therapy, and in some cases PPHTN worsens. This suggests that patients with moderate or severe PPHTN should undergo treatment for PPHTN before liver transplantation.

Vasodilator therapy consists of prostanoids (epoprostenol), phosphodiesterase inhibitors (sildenafil), and endothelin antagonists (bosentan). Calcium channel blockers, often used in noncirrhotic patients with pulmonary hypertension, are contraindicated in patients with cirrhosis because the associated mesenteric vasodilation worsens portal hypertension. Patients who respond to treatment sufficiently to reduce their mean PA pressure below 35 mm Hg and PVR below 400 dyn·s·cm^{-5} should be considered suitable transplant candidates.[99,100]

Renal Dysfunction

Renal dysfunction in patients with cirrhosis is the result of renal hypoperfusion and avid retention of sodium. Hepatorenal syndrome (HRS) is a prerenal abnormality caused by circulatory derangements of advanced cirrhosis. It is considered a functional disorder, based on successful transplantation of kidneys from patients with HRS.[101] Renal function is an important risk factor for mortality, a fact that is emphasized by its presence as one of only three variables used in calculating the Model for End-Stage Liver Disease (MELD) score.

In addition to HRS, patients with cirrhosis are also at risk for other causes of renal dysfunction, such as parenchymal renal disease, sepsis, nephrotoxicity, and hypovolemia. HRS is a diagnosis of exclusion, and other treatable causes must

be ruled out. HRS accounts for only about one fourth of the cases of acute kidney injury in hospitalized cirrhotic patients.[102] In patients with cirrhosis and ascites, the incidence of HRS is nearly 40% at 5 years.[103]

HRS is caused by the local production of vasodilators, particularly nitric oxide, in patients with portal hypertension. Splanchnic vasodilation leads to a decrease in the effective circulating blood volume and a decrease in arterial blood pressure, which activates the sympathetic, renin-angiotensin-aldosterone, and vasopressin systems. The net result is a severe reduction in renal perfusion and glomerular filtration.

Type I HRS is characterized by rapidly progressive renal failure and a doubling of serum creatinine over 2 weeks after a precipitating cause such as spontaneous bacterial peritonitis, sepsis, gastrointestinal bleeding, or surgical stress. Patients with type I HRS have a median survival of 2 to 4 weeks without therapy.[104,105] Patients with type II HRS have a median survival of about 6 months.[106]

Although renal vasoconstriction is the proximate cause of HRS, therapy aimed at directly increasing renal perfusion by the use of prostaglandins, dopamine agonists, or endothelin antagonists has not proven to be successful. Vasoconstrictor therapy targeting the underlying splanchnic vasodilation is more effective.[107]

These therapies include arginine vasopressin, somatostatin, and α-agonists such as norepinephrine and midodrine, combined with volume expansion. Terlipressin, the most studied vasopressor for HRS, is not available in the United States.[108,109]

Placement of a TIPS lowers portal pressures and can decompress the splanchnic circulation. Pilot studies have shown that a TIPS is capable of reversing both types of HRS, but because of extensive exclusionary criteria in trials and the risk of worsening hepatic encephalopathy, a TIPS might not be suitable for all patients with HRS.[110]

Liver transplantation is the definitive therapy for HRS. For patients with HRS who are transplant candidates, renal replacement therapy is the typical bridge to transplantation. Although renal recovery is anticipated, 35% of patients with pretransplant HRS will continue to require support in the immediate postoperative period, compared with 5% of patients without pretransplant HRS.[111] During the First International Liver Transplantation Society Expert Panel Consensus on Renal Insufficiency in Liver Transplantation, it was recommended that patients who received dialysis at least twice weekly for more than 6 weeks before liver transplantation be considered for combined liver-kidney transplantation.[112]

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a serious, albeit reversible neuropsychiatric complication that is a feature of both chronic and acute liver disease. Manifestations range from subtle, subclinical abnormalities to overt neurologic and behavioral derangements that are readily apparent at the bedside.

HE has been attributed to hyperammonemia, but the severity of HE does not necessarily correlate with ammonia levels. A number of other factors and mechanisms also contribute to HE, including other gut-derived neurotoxins, γ-aminobutyric acid (GABA) and other endogenous GABA-receptor agonists, oxidative stress, inflammatory mediators, hyponatremia, and abnormal serotonin and histamine neurotransmission.[113,114]

The initial step in evaluating the patient with liver disease who presents with encephalopathy is to rule out causes other than HE. The differential diagnosis includes other metabolic causes such as uremia, sepsis, glucose and electrolyte abnormalities, and endocrinopathies. Structural and vascular central nervous system lesions or infections should also be considered. Because cirrhotic patients are exquisitely sensitive to sedative medications and have impaired hepatic (and often renal) metabolism, a careful search for possible drug-related encephalopathy should be undertaken. Once other potential causes have been eliminated, the next step should be a systematic search for an underlying cause or precipitating factor, such as infections (e.g., spontaneous bacterial peritonitis, sepsis) or gastrointestinal bleeding.

Therapy to reduce ammonia levels consists of the nonabsorbable disaccharide lactulose and nonabsorbable antibiotics such as neomycin, metronidazole, and rifaximin. Nonabsorbable antibiotics appear to be equally effective to nonabsorbable disaccharides, but concerns about toxicity associated with long-term administration limit their use.

Ascites

Ascites is the most common complication of cirrhosis leading to hospitalization.[115] Patients have ascites should be referred for liver transplantation evaluation in the absence of contraindications. Nonhepatic causes account for 15% of ascites and include malignancy, cardiac failure, renal disease, pancreatitis, and tuberculosis. Paracentesis is an important aid in diagnosis.[115] A serum-ascites albumin gradient greater than 1.1 mg/dL indicates portal hypertension with 97% accuracy.[116] Rapid correction of hyponatremia is undesirable because patients with cirrhosis are at risk for central pontine myelinolysis, a potentially devastating neurologic complication. Observations in liver transplant recipients suggest limiting correction to less than 16 mEq/L during the intraoperative period.[117]

Once ascites becomes refractory to maximum standard medical therapy, therapeutic options are limited and include serial paracentesis, liver transplantation, TIPS placement, and peritoneovenous shunt.

Risk factors for development of spontaneous bacterial peritonitis include a prior episode of this acute infection, gastrointestinal bleeding, and an ascites albumin level of less than 1.5 g/dL. Long-term antibiotic prophylaxis with norfloxacin or trimethoprim/sulfamethoxizole is recommended for patients who have survived an episode of spontaneous bacterial peritonitis.[115]

Varices

Cirrhosis increases portal pressure as a result of chronic inflammation. Fibrosis and regenerative nodules cause resistance to splanchnic flow and lead to formation of portosystemic collaterals. Progression of portal hypertension leads to increased local production of nitric oxide and exacerbates splanchnic vasodilation. Rupture of the

high-pressure collaterals that are formed is a highly lethal and feared complication of portal hypertension.

Portal hypertension is diagnosed by measurement of the wedged hepatic venous pressure (WHVP). Although this is not a direct measure of portal pressure, WHVP has been demonstrated to correlate well with it.[118] This measurement is taken by advancing a catheter into a hepatic vein to the wedge position. To correct for the contribution of increased intra-abdominal pressure from ascites, a free hepatic venous pressure or an inferior vena cava (IVC) pressure should be subtracted from the measured WHVP to give the hepatic venous pressure gradient (HVPG). A normal HVPG is 3 to 5 mm Hg. Patients with varices have HVPGs of 10 to 12 mm Hg or greater.

Esophagogastroduodenoscopy is the gold-standard procedure for diagnosing varices. Risk for variceal bleeding correlates with size of varices, presence of red wale marks, and variceal pressure (i.e., HVPG). Therapeutic decisions are based on these observations and measurements. Nonselective β-adrenergic blockers reduce portal pressure by two mechanisms: a decrease in cardiac output (β_1) and splanchnic vasoconstriction (β_2). For patients who cannot tolerate β-adrenergic blockers or in whom they are contraindicated, another option for primary prophylaxis of variceal bleeding is endoscopic ligation. The TIPS procedure had been considered a backup procedure for variceal bleeding, but recently has been advocated for early treatment in select patients.[72] However, TIPS is associated with a higher incidence of encephalopathy; despite this, TIPS may decrease mortality in select patients.[72]

Acute variceal bleeding should be managed with a combination of intravascular volume resuscitation, correction of severe coagulopathy, pharmacologic manipulation of portal pressure, and endoscopic variceal ligation. Aggressive intravascular volume replacement can lead to resistant or recurrent bleeding because bleeding is a pressure-related phenomenon.[119,120] Elective intubation of the trachea for airway protection is often warranted. Medications to reduce portal pressure include vasopressin and somatostatin. Although β-adrenergic blockers can reduce portal pressures, their effect on systemic pressures makes them undesirable in this setting. Early endoscopic variceal ligation in combination with pharmacotherapy is the preferred treatment for acute variceal bleeding. Balloon tamponade can be effective for resistant variceal bleeding, but is associated with significant complications, including esophageal rupture and aspiration. It is recommended as a bridge to more definitive therapy such as surgical shunt, TIPS, or liver transplantation.

Hemostasis

Hemostasis is a dynamic process that is the product of interaction between coagulation, platelets, and fibrinolysis, resulting in the formation and revision of clot (see Chapter 62). Liver disease affects all of these components, both quantitatively and qualitatively. The liver is the site of synthesis for all procoagulant and anticoagulant factors, with the exception of tissue thromboplastin (III), calcium (IV), and von Willebrand factor (VIII). It is also the site for clearance of activated factors.

Patients with cirrhosis are customarily considered to have a bleeding diathesis based on abnormal results in conventional tests of coagulation, such as prothrombin time (PT) and partial thromboplastin time (PTT). However, such tests reflect the activity of only a portion of the procoagulant factors, and do not consider the concomitant decrease in anticoagulant factors, which are not assessed. It is the balance of procoagulant and anticoagulant forces, not the isolated measurement of either portion of the coagulation system, that indicates the effective generation of thrombin. Not surprisingly, PT and PTT abnormalities correlate poorly with bleeding complications following invasive procedures, such as liver biopsy.[121] There is evidence that decreased levels of protein C in cirrhotic patients balance the decreased levels of procoagulants, which can leave thrombin generation in vivo unaltered.[122]

If procoagulants predominate because of disproportionate reductions of anticoagulants (protein S and C, antithrombin III), accompanied by an increase in procoagulants (FVIII), a hypercoagulable state results.[123,124] This possibility is supported by studies reporting venous thromboembolism associated with cirrhotic and noncirrhotic liver disease.[125,126]

Thrombocytopenia is a well-known feature of cirrhosis. The primary cause is splenic sequestration in the setting of portal hypertension. Elevated levels of von Willebrand factor compensate for decreased platelets counts, augmenting the platelet–endothelial cell interaction on vessel walls.

The fibrinolytic system in cirrhotic patients has many abnormalities, which may account for accelerated fibrinolysis. The liver is the site of tissue plasminogen activator clearance, and elevated tissue plasminogen activator levels have been noted in patients with cirrhosis.[127] The liver is also the site of synthesis for plasmin inhibitors, such as plasmin activator inhibitor-1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI). A balance of factors that promote and inhibit fibrinolysis is desired. Commonly used studies for assessing the presence and severity of accelerated fibrinolysis include euglobulin clot lysis time and thromboelastography.

Disseminated intravascular coagulation (DIC) is primarily a thrombotic diathesis, followed by widespread secondary fibrinolysis. As factors are consumed, DIC becomes a bleeding diathesis of factor and platelet deficiency. Whether or not DIC is a feature of stable chronic liver disease is controversial. Standard laboratory tests cannot distinguish between consumption and decreased synthesis, and so have little utility. Instead, assays to assess for excessive thrombin production are used. These assays include the cleaved by-products of coagulation factor activation such as prothrombin fragment F1+2, fibrinopeptide A, and thrombin-antithrombin complexes. These assays suggest that overt DIC is not a feature of stable chronic liver disease[128]; however, accelerated intravascular coagulation and fibrinolysis has been described, which is a low-grade consumptive process.[129] Patients who exhibit accelerated intravascular coagulation and fibrinolysis are at increased risk of DIC in the presence of a known stimulus, such as sepsis or spontaneous bacterial peritonitis.

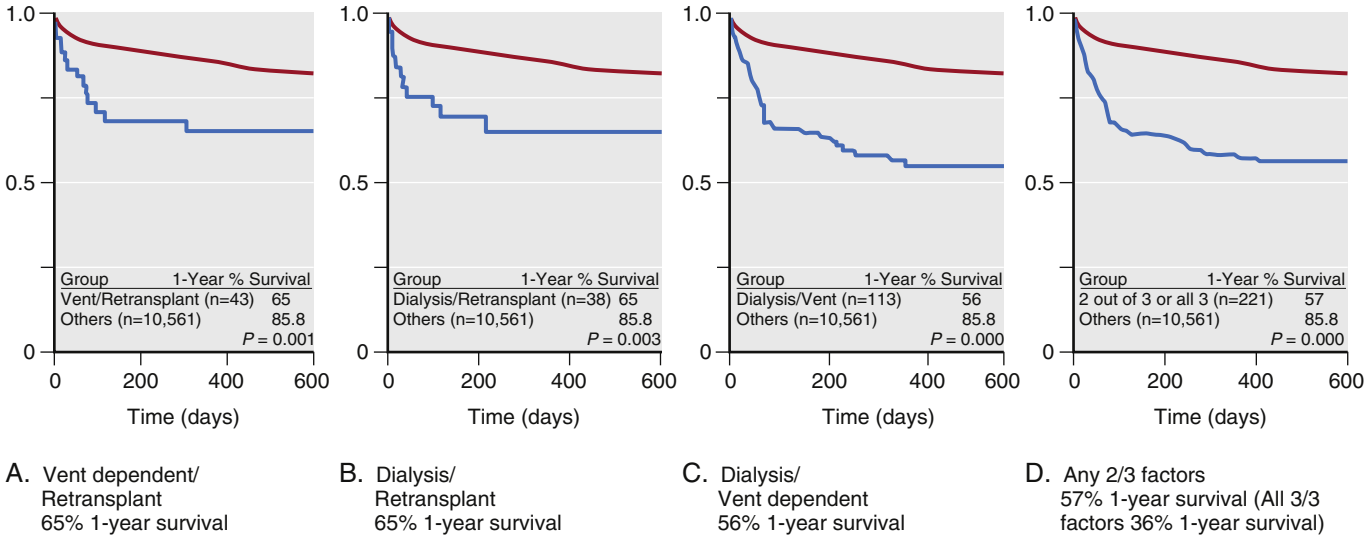


Figure 74-8. Risk factors for posttransplant survival. The four panels compare posttransplant survival between a reference group of 10,000 posttransplant patients (the uppermost Kaplan-Meier curve in all panels, 1-year post transplant survival 86%) and (**A**) patients undergoing retransplantation who are ventilator dependent (1-year posttransplant survival, 65%), (**B**) patients undergoing retransplantation who are undergoing dialysis (1-year posttransplant survival, 65%), (**C**) patients who are ventilator dependent and undergoing dialysis (1-year posttransplant survival, 56%), and (**D**) patients with any two or all three risk factors (1-year posttransplant survival, 57% with any two factors; 1-year posttransplant survival, 36% with three factors). *(From Desai NM, Mange KC, Crawford MD, et al: Predicting outcome after liver transplantation: utility of the model for end-stage liver disease and a newly derived discrimination function,* Transplantation *77:99-106, 2004.)*

SURGICAL PROCEDURE

Preoperative Considerations

In 2011, the median time to transplant in the United States was 12.6 months (interquartile range, 1.6 to 72 months).[76] As a result, a transplant candidate can be months removed from their initial evaluation when a suitable donor graft is identified. Therefore, the prospective recipient's evaluation should be reviewed while arrangements are made for donation. Candidates undergo an extensive preoperative assessment by multiple teams that typically include the surgical team, hepatologists, cardiologists, pulmonologists, psychiatrists, and social workers. In the event of unique comorbidities, additional consultants are involved as needed. Of particular interest to the anesthesiologist are interim changes in health status, hospitalizations (the possibility of infection should be considered with new-onset encephalopathy, variceal bleed, ascites, or hemodynamic deterioration), details of the initial and any subsequent cardiopulmonary evaluation (assess for the presence of coronary disease, heart failure, pulmonary hypertension, or arrhythmia), and renal status (acute kidney injury).

Patients predicted to have decreased survival 1-year after transplant represent a high-risk group and include patients undergoing retransplantation or those supported by mechanical ventilation, infusions of vasopressors, and renal replacement therapy (Fig. 74-8).[2] Patients with oliguria, acidemia, or dependent on renal replacement therapy may benefit from intraoperative renal replacement therapy.[130,131]

A protocol should be in place to notify the blood bank of the pending transplant, which results in the setup of red blood cells and plasma in a volume according to institutional protocol. If any delay is anticipated in the availability of blood products, for instance in the event of antibodies, the blood bank personnel should notify the transplant coordinator and anesthesiologist. In the presence of red cell antibodies, our institutional policy is to set up compatible red cells for the start and completion of the transplant, and to use compatibility-unknown red cells in the event of large transfusion requirements (see Chapter 61).

The surgical procedure is divided into three distinct stages. During the preanhepatic or dissection stage, the liver is mobilized and vascular structures (suprahepatic and infrahepatic vena cava, portal vein, and hepatic artery) are identified. The anhepatic phase begins with clamping of these vessels and hepatectomy of the native liver and continues during the implantation of graft. Reperfusion, usually via the portal vein, starts the neohepatic phase, which continues through completion of the remaining vascular anastomosis (usually the hepatic artery), anastomosis of the bile duct, hemostasis, and abdominal closure.

Intraoperative Management

Intraoperative personnel and monitoring vary among liver transplant services based on institutional practice, caseload, and resources. Most centers allocate two anesthesia providers to liver transplants; however, the qualifications of these providers vary. A typical arrangement in an academic setting consists of an attending anesthesiologist experienced in liver transplantation and a senior resident. In private practice settings, the second provider may be a second anesthesiologist, a certified nurse anesthetist, a licensed health care provider such as a perfusionist, or some combination of these.

Anesthesia typically begins with a rapid sequence induction because of the emergent nature of the surgery, preoperative administration of oral immunosuppressants/bowel decontamination antibiotics, and the presence of ascites. An arterial catheter is placed either before induction of anesthesia or, more commonly, immediately thereafter. Large-bore intravenous access is obtained. Either a triple-lumen 9-French introducer is placed centrally, or in the event of significant concern over blood loss (as is the case for retransplantation or in patients with extensive prior abdominal surgery) two double-lumen 9-French introducers are placed in a central vein. Sites designated for venovenous bypass are avoided, if possible. A pulmonary artery catheter is commonly used in adult patients; however, if the recipient has had a recent negative evaluation for pulmonary arterial hypertension, a pulmonary artery catheter may be avoided. Transesophageal echocardiography is increasingly used during the procedure. In a survey of high-volume liver transplant centers, more than 85% of respondent anesthesiologists (n = 217) reported using transesophageal echocardiography to some degree.[132] Most performed a limited-scope examination, and only 12% were board certified in echocardiography. Transesophageal echocardiography appears to be associated with a low likelihood of hemorrhagic complications, even in the presence of esophageal varices.[133] Some liver transplant centers avoid pulmonary artery catheter insertion in the event that transesophageal echocardiography is used, although a pulmonary artery catheter may be necessary when continuous intraoperative monitoring of pulmonary artery pressures is desired or for postoperative hemodynamic and fluid management in the ICU. New technologies, including arterial pressure waveform analysis and three-dimensional echocardiography, do not correlate with thermodilution-derived parameters and are not currently advocated for routine use intraoperatively.[134,135]

A rapid infusion system capable of high transfusion flow rates (>500 mL/min) is typically used. Such systems incorporate a reservoir, pump, filters, heat exchanger, and safety features designed to avoid and monitor for the presence of blood or air embolism, hypothermia, and line occlusion. Rapid infusion systems facilitate volume replacement and transfusion management.

The effects of the anesthetic technique on patient outcome are unknown. At the authors' center, a balanced anesthetic is used; this typically consists of a volatile anesthetic in low to moderate concentrations (0.5 to 1.0 minimum alveolar concentration, [MAC]) to ensure unconsciousness, whereas an opioid, usually fentanyl, is chosen to blunt the sympathetic response to stimulation and to provide a smooth transition for postoperative analgesia. In recipients with fulminant hepatic failure and cerebral edema, volatile anesthetics are avoided or used cautiously in low concentrations, in many cases with intracranial pressure monitoring (see later). In either case, periods of hypotension during the surgery may require temporary discontinuation of the volatile anesthetic. Midazolam, with minimal hemodynamic effects, can be used for its amnestic effects during these hypotensive periods. Historically, the volatile anesthetic of choice has been isoflurane, which preserves splanchnic blood flow better than previously used volatile drugs.[136] Studies in healthy humans have confirmed the vasodilator effects of isoflurane on the hepatic circulation, compared with the vasoconstrictor effects of halothane.[137] This beneficial effect on hepatic oxygen supply can be advantageous to the newly reperfused graft. The effects of desflurane on hepatic blood flow have been evaluated with conflicting results. In animals, desflurane decreased total hepatic blood flow in a dose-dependent fashion at concentrations up to 1.0 MAC; however, in a human study that excluded patients with liver disease, liver blood flow was slightly more rapid with desflurane than with isoflurane, although this effect was not statistically significant.[138] Another study compared the effects of sevoflurane and desflurane on hepatic blood flow and hepatocellular integrity in older patients[139] (see Chapter 80). Both anesthetics resulted in decreases in gastric mucosal pH and increases in cytosolic liver enzymes. The authors conclude that hepatocyte function is well preserved (lidocaine metabolism to monoethylglycinexylidide was unaffected by either agent), but disturbances of hepatocellular integrity and gastric tonometry suggest that splanchnic perfusion and oxygen delivery to the liver are decreased. Whether the increased metabolism of sevoflurane (100-fold that of desflurane) is detrimental to the liver is unknown, but it seems unlikely that the metabolites of sevoflurane cause liver damage.[140] Compound A, a breakdown product of sevoflurane found to be nephrotoxic in animals, has not been shown to cause renal toxicities in humans, even during low-flow sevoflurane administration[141] (see Chapter 26).

Cisatracurium is an attractive choice for neuromuscular blockade in patients undergoing liver transplantation because of its organ-independent elimination and diminished histamine release[142] (see Chapter 34). In patients with end-stage liver disease, the volume of distribution of cisatracurium is larger than that in healthy control patients. Hepatic clearance is also increased in patients with liver disease; this results in similar elimination half times and similar duration of action (time to 25% recovery). Other reports have suggested the use of rocuronium during liver transplantation, because the duration of the neuromuscular block appears to be a useful predictor of primary allograft function. All patients whose recovery time was longer than 150 minutes experienced primary graft dysfunction.[143]

Preanhepatic Stage

The preanhepatic stage begins with surgical incision and ends with vascular exclusion and hepatectomy of the native liver. Using conventional caval interposition technique, vascular exclusion of the liver is accomplished by cross-clamping the portal vein, the suprahepatic IVC, the infrahepatic IVC, and the hepatic artery (Fig. 74-9). If a piggyback technique is used, the native retrohepatic vena cava is preserved (Fig. 74-10).

The preanhepatic phase involves dissection and mobilization of the liver and identification of the porta hepatis. With abdominal incision and drainage of ascites, hypovolemia can occur. This should be treated in an anticipatory fashion with colloid-containing fluid to minimize changes in preload. In the presence of preexisting

coagulopathy, fresh frozen plasma is indicated soon after incision, although some authors have challenged the need for fresh frozen plasma during orthotopic liver transplantation (OLT).[144,145] In Europe, prothrombin complex concentrates (PCCs), which contain vitamin K–dependent factors (II, VII, IX, and X), are increasingly used as an alternative to plasma transfusion to avoid the risk of transfusion-related acute lung injury and transfusion-associated circulatory overload[146,147] (see Chapter 61). The so-called four-factor PCCs available in Europe contain therapeutic levels of factor VII in addition to Protein C and S, and differ from the three-factor PCCs available in the United States.[148] The primary concern related to PCC administration is thromboembolic complications, which vary according to the patient's underlying disease, dosing, and the constituents in each of the commercially available PCC products.[149] Another product, recombinant activated factor VII, was evaluated during liver transplantation and was found to improve coagulation study results, but did not result in a decrease in transfusion requirements.[150,151] Recombinant factor VIIa has been linked to an increased risk of arterial, but not venous, thromboembolic events.[152] Thromboelastography or standard laboratory tests (prothrombin time, fibrinogen, and platelet count) are used to guide the correction of coagulopathy.[153,154] Some authors disagree with the premise that coagulation monitoring is associated with blood product transfusion requirements during OLT.[155] However, in coagulopathic cardiac surgery patients, therapy guided by point-of-care testing using thromboelastometry resulted in fewer transfusions of red blood cells and plasma and improved 6-month survival.[156] Considerable institutional variation exists in transfusion practices for OLT, as do variations in patient acuity as evidenced by MELD scores. However, these differences in transfusion requirements might not be accounted for by variations in blood loss during the procedure.[157] Fibrinolysis is unusual during the preanhepatic phase of the surgery; therefore, cryoprecipitate administration is typically unnecessary. Hyponatremia should not be corrected rapidly. A perioperative increase of 21 to 32 mEq/L in the serum sodium level was associated with central pontine myelinolysis in one report, whereas an increase of less than 16 mEq/L was not.[117,158] Citrate intoxication (ionized hypocalcemia resulting from the infusion of citrate-rich blood products in the absence

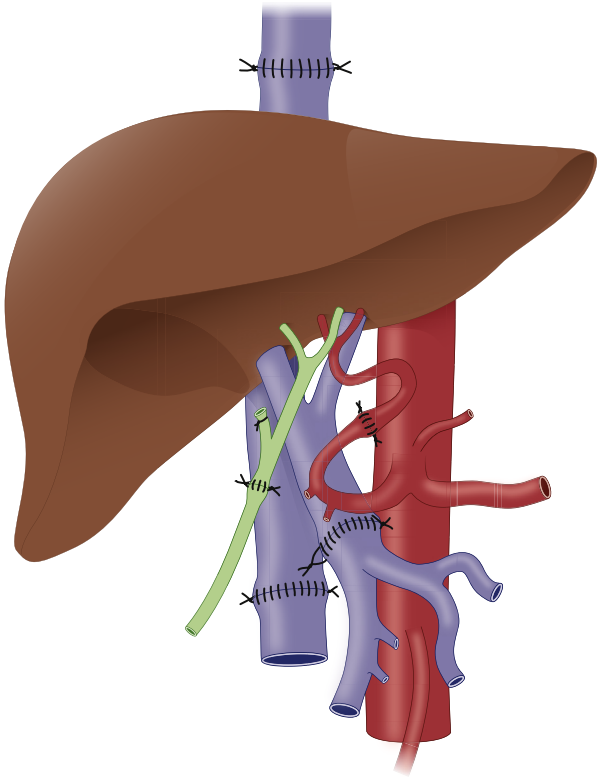


Figure 74-9. Liver transplantation. Classic caval interposition technique illustrating anastomoses of the suprahepatic and infrahepatic inferior vena cava, the portal vein, the hepatic artery, and the bile duct. *(From Molmenti E, Klintmalm G:* Atlas of Liver Transplantation. *Philadelphia, 2002, Saunders.)*

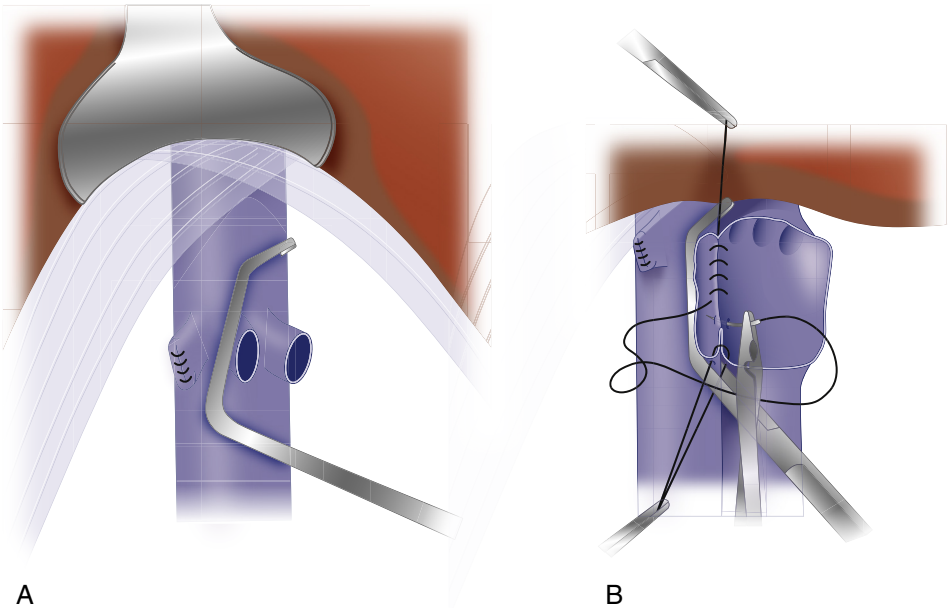


Figure 74-10. Liver transplantation. **A,** Piggyback technique illustrating partial vena caval clamping and an oversewn native right hepatic vein. **B,** Preservation of the native retrohepatic vena cava and hepatic venous cuff anastomosis. *(From Molmenti E, Klintmalm G:* Atlas of Liver Transplantation. *Philadelphia, 2002, Saunders.)*

of hepatic function) is avoided by the administration of calcium chloride (see Chapter 61). Ionized hypomagnesemia also results from citrate infusion, but values of ionized magnesium gradually return to normal after graft reperfusion.[159] The clinical significance of this remains speculative, but cardiovascular function may be affected. Aggressive treatment of hypokalemia is best avoided, particularly in preparation for reperfusion and the associated increase in serum potassium. Hyperkalemia should be avoided by the administration of diuretics and insulin accompanied by glucose or, in the event these are ineffective, by intraoperative dialysis. In the absence of insulin administration, supplemental glucose is usually not required except in pediatric patients or those with severe disease, such as fulminant hepatic failure. Hyperglycemia should be avoided, because glucose levels greater than 180 mg/dL are associated with an increase in surgical site infections in liver transplant recipients.[160] Blood gases, electrolytes, glucose, ionized calcium, and hemoglobin levels should be assessed regularly, and as frequently as hourly in the event of massive blood loss or preexisting abnormalities. Point-of-care testing facilitates rapid turnaround times for laboratory values. Coagulation studies are typically assessed at the beginning of the surgery, after correction of specific deficiencies, after reperfusion, and in the presence of microvascular bleeding.

The maintenance of urine output is desirable; however, the use of low-dose dopamine for this reason is unproven.[161,162] Hypothermia should be avoided. Core temperature control can be aided with heated venovenous bypass during the anhepatic phase. Regardless of whether bypass is used, forced-air warming blankets should be positioned beneath the patient and over the lower and upper body (see Chapter 54). Bleeding during this phase of surgery is related to the degree of preexisting coagulopathy, the presence and severity of portal hypertension, and the duration and complexity of the surgical procedure, which is adversely affected by prior abdominal surgery and adhesions.[163,164]

Anhepatic Stage

The anhepatic stage begins with the occlusion of vascular inflow to the liver, and it ends with graft reperfusion. Cross-clamping of the suprahepatic and infrahepatic IVC decreases venous return by as much as 50%. Venovenous bypass (VVB) diverts IVC and portal venous flow to the superior vena cava via the axillary vein, attenuates the decrease in preload, improves renal perfusion pressure, lessens splanchnic congestion, and can delay the development of metabolic acidosis.[165] However, the use of VVB is not without risk. Air embolism, thromboembolism, and inadvertent decannulation can be fatal or result in significant morbidity.[166] VVB is not uniformly used at all centers. A recent meta-analysis of three trials failed to reveal any difference in the incidence of renal failure or blood transfusion requirements between patients randomized to VVB compared with patients in whom the technique was not used.[167] The use of the "piggyback" technique, with IVC preservation, decreases the need for VVB.[168]

Hepatectomy is followed by hemostasis and vascular anastomoses of the suprahepatic and infrahepatic IVC and the portal vein. Despite the absence of hepatic clotting factor production during the anhepatic stage, blood loss is usually limited by vascular clamping of the inflow vessels to the liver. However, fibrinolysis may begin during this stage because of an absence of liver-produced plasminogen activator inhibitor, which results in the unopposed action of tissue plasminogen activator. The use of antifibrinolytics varies among centers (discussed later).

Neohepatic Stage

Reperfusion of the graft through the portal vein begins the neohepatic stage. Reperfusion is associated with abrupt increases in potassium and hydrogen ion concentrations, an increase in preload, and a decrease in systemic vascular resistance and blood pressure. Hypothermia, monitored through a centrally placed catheter, is a marker for the presence of graft outflow into the central circulation. Life-threatening hyperkalemia, clinically detectable by changes in the EKG, requires prompt treatment. Calcium chloride and sodium bicarbonate are the drugs of choice for the acute treatment of hyperkalemia. If time permits, albuterol and insulin are also effective. Intraoperative dialysis should be considered early in the procedure for patients with oliguria with elevated potassium levels.

The hallmark of the postreperfusion syndrome (PRS) is systemic hypotension and pulmonary hypertension occurring within the first 5 minutes after reperfusion of the graft. Approximately one in three patients undergoing OLT have profound hypotension after reperfusion. The cause is uncertain, but a number of factors have been implicated, such as hyperkalemia, acidosis, hypothermia, emboli (air or thrombotic), and vasoactive substances. Risk factors for hyperkalemia in the early postreperfusion period are elevated preanhepatic potassium levels and the use of donated-after-cardiac-death donor organs.[169] A retrospective study of 321 patients identified suboptimal grafts (higher degree of steatosis) and graft cold ischemia time as risk factors for PRS.[170] In this study all cases of PRS, defined as mean blood pressure less than 60 mm Hg, occurred in suboptimal donors with graft cold ischemia times longer than 6 hours. The authors defined suboptimal grafts as those from donors older than 50 years, those with a history of cardiac arrest, hypotension, need for high-dose inotropic drugs, ICU stay longer than 5 days, or elevated liver fat content. The PRS group had higher postreperfusion K^+ levels (at 1 and 5 minutes), and lower postreperfusion temperature (at 1 minute) than in the group without PRS.

In addition, other critical events such as severe, acute bleeding resulting in hemodynamic compromise and necessitating massive transfusion can occur at any point during the surgery. Arrhythmias and intracardiac thromboembolism can also occur at any time intraoperatively, but are more likely after reperfusion.[171,172]

Hepatic arterial anastomosis and biliary reconstruction are generally performed after venous reperfusion, although in pediatric patients the arterial anastomosis may be completed before reperfusion. Signs of graft function that might be observed in the operating room and early postoperative period include decreased calcium requirements, improvement in acidosis, increased urine

output, a rise in core temperature, and bile output from the graft.[71,173]

Antifibrinolytics

Fibrinolysis is most severe after reperfusion and is caused by abrupt increases in tissue plasminogen activator from graft endothelial cell release. Antifibrinolytic drugs and cryoprecipitate may be required. In studies before 1997, the benefits of antifibrinolytic drugs for OLT, typically defined as a decrease in blood loss or transfusion requirements, were not present in prospective, randomized, blinded studies. Nearly all these studies evaluated aprotinin. In contrast, tranexamic acid and ε-aminocaproic acid have not been studied extensively. In 2001, a randomized, blinded study from the Mayo Clinic showed a decrease in erythrocyte requirements (median of 5 units versus 7 units) with aprotinin compared with placebo.[174] The European Multicenter Study of Aprotinin in Liver Transplant (EMSALT) also showed a decrease in red blood cell usage with both large dose (2×10^6 kallikrein inhibiting units [KIU] loading dose followed by 1×10^6 KIU/h) and regular dose (2×10^6 KIU loading dose followed by 0.5×10^6 KIU/h) aprotinin compared with placebo (red blood cell requirements of 1500, 1750, and 2450 mL, respectively).[175] The authors report no difference in the prevalence of thromboembolic events in the aprotinin groups compared with control group. It was noted that the three patients who developed hepatic artery thromboses were in the control group. These three events may have been related to surgical technical issues, whereas the thrombotic events in the aprotinin group (pulmonary emboli, right coronary occlusion) were less likely attributable to the surgery. It is unclear whether antifibrinolytic drugs increase the risk of thrombotic events.[176] Fibrinolysis is an unpredictable event, and the risks of thrombosis are unknown. Aprotinin intensifies the likelihood of increases in creatinine levels in the first week after liver transplantation, but not with an increased need for renal replacement therapy.[177] Aprotinin was withdrawn from world markets in 2008 because of higher mortality in patients who received aminocaproic acid during cardiac surgery.[178]

Postoperative Care

The goals of the immediate postoperative period are to ensure a smooth transition from anesthesia and surgery (maintain hemodynamic stability, metabolic homeostasis, adequate analgesia), monitor graft function (transaminase levels, prothrombin time, bilirubin levels, bile and urine output, acid-base status), and maintain surveillance for known complications (bleeding, bile leaks, vascular thrombosis, primary nonfunction). The use of steroids leads to hyperglycemia, which can require insulin infusion. (See Chapters 95 and 102.)

The lack of bile output, accompanied by hemodynamic instability, suggests primary nonfunction of the graft, which may require urgent retransplantation. Conversely, a functioning liver graft facilitates early neurologic recovery, cardiovascular stability, and improved renal function, signs that can occur within hours of the completion of surgery.

Hepatic artery thrombosis can lead to graft necrosis, necessitating retransplantation. Within the first 2 to 3 postoperative days, markedly abnormal transaminase levels are common because of graft ischemia or injury during procurement, preservation, and reperfusion. After this period, hepatic enzyme and bilirubin levels that do not trend downward suggest the possibility of hepatic artery thrombosis, which should lead to prompt evaluation via Doppler ultrasonography.

Postoperative pain control is generally achieved with opioids, including patient-controlled analgesia (see Chapter 98). Analgesic requirements may be decreased compared with other major abdominal surgery.[179,180] Epidural analgesia is contraindicated because of coagulopathy, which usually preexists, or develops during the perioperative period.

The timing of tracheal extubation and termination of postoperative mechanical ventilation is not clear.[181,182] Early extubation of the trachea, including endotracheal tube removal in the operating room, is feasible in select patients. However, the benefits of immediate extubation appear limited to the potential of decreased resource utilization, which might not be fully realized in centers that direct posttransplant patients to ICUs regardless of their need for ventilatory support. As a result, many centers prefer to see clear signs of graft function before extubation.

ACUTE LIVER FAILURE

Acute liver failure (ALF; previously termed *fulminant hepatic failure*) is defined as the appearance of encephalopathy together with coagulopathy (international normalized ratio ≥ 1.5) in a patient without previous liver disease who has an illness of less than 26 weeks in duration. ALF is a rare entity with an incidence of approximately 2000 cases per year in the United States. Drug-related toxicity, primarily acetaminophen, accounts for more than half of the cases of ALF in the United States. Other causes include idiopathic, acute viral hepatitis, autoimmune, and ischemic. In the United States, approximately 45% of patients recover spontaneously, 25% undergo liver transplantation, and 30% die.[183] Etiology has a significant bearing on outcome; patients with acetaminophen toxicity, ischemic injury, or hepatitis A have the most favorable prognosis, whereas those with non-acetaminophen drug-induced liver injury, acute hepatitis B, Wilson's disease, or autoimmune hepatitis have poor prognoses in the absence of transplantation.[184]

Evidence of portal hypertension and cirrhosis is absent because of the rapid progression of disease. Acute decompensation of chronic liver disease, termed *acute on chronic liver disease,* is a separate condition with different etiologies, therapy, and prognostic indicators.

Although various etiologies of ALF exist, there are manifestations that are common to all patients with massive hepatic necrosis. The most serious, and lethal, is acute cerebral edema and intracranial hypertension. Effects on other organ systems include coagulopathy, circulatory dysfunction and hypotension, acute kidney injury, and metabolic derangements.

General measures to reduce cerebral edema include maintaining the patient in a 30-degree, head-up position, and making sure the head is in neutral position so as not to impede venous return. Once a patient is intubated, muscle relaxants should be considered to minimize rises in intracranial pressure from coughing, bucking, and shivering. Mannitol can be used to induce an osmotic diuresis, but may have limited utility in the patient with compromised renal function. Another option may be hypertonic saline, ideally targeting a serum sodium of 145 to 155 mEq/L. Current recommendations are to maintain normocarbia and to reserve hyperventilation for response to acute rises in intracranial pressure. Barbiturates can be used to decrease cerebral metabolism; however, their use may be limited by hypotension.

Monitoring techniques for cerebral edema and intracranial hypertension are controversial (also see Chapter 70). Serial head computed tomography (CT) images are not sensitive indicators of intracranial hypertension. CT can, however, provide information on structural abnormalities such as intracranial hemorrhage. Although many centers place an intracranial pressure (ICP) monitor to guide therapy in patients with stage III-IV coma, there are no randomized controlled studies to support this practice. Furthermore, ICP monitor placement is not a benign procedure, frequently entailing aggressive correction of coagulopathy and transport to and from the operating room for a critically ill, fragile patient. Nonetheless, ICP monitors are invaluable for guiding acute therapy, and for helping to determine who might no longer be a viable candidate for transplantation. In addition to measuring ICP, these monitors allow calculation of cerebral perfusion pressure ([CPP] = mean arterial pressure [MAP] – intracranial pressure [ICP]), which should be kept between 50 and 80 mm Hg. In one case series, a sustained CPP less than 40 mm Hg for greater than 2 hours was associated with a poor neurologic outcome. An effective protocol for managing intracranial hypertension in patients with stage III or IV encephalopathy has been described and resulted in a 95% response to treatment in episodes of ICP greater than 20 mm Hg. Furthermore, in this prospective series, ICP was monitored in all patients, and no patients died of isolated cerebral edema. The authors used a protocol that included activated recombinant factor VII (rFVIIa) to correct coagulopathy before ICP placement. Significant bleeding complications from ICP monitoring were not encountered.[185]

The decision regarding which patients should receive a transplant, based on who might recover spontaneously or who is unlikely to benefit from transplantation, is one of the most difficult decisions encountered during the management of patients with liver disease. The two most widely used prognostic models are the Clichy or Paul Brousse Hospital criteria and the King's College Hospital criteria. The Clichy criteria recommend transplantation for patients in stage III or IV coma, based on age and factor V levels.[186] There is no distinction made for etiology of ALF, which is considered a weakness of these criteria. The King's College Hospital criteria are superior for predicting outcomes in patients with ALF based on acetaminophen toxicity. However, the negative predictive value is less than 50% in patients who have not used acetaminophen.[187] Thus, patients who fail to fulfill these criteria include a number of patients who will die without proper consideration for transplantation.

In patients with ALF who are undergoing an invasive procedure, correction of thrombocytopenia to 50,000 platelets/mm^3 or greater and international normalized ratio (INR) to 1.5 or less is suggested.[184,188] Treatment thresholds are less clear for patients who are not bleeding, but prophylactic therapy is advised for severe abnormalities (e.g., platelet count ≤ 10,000/mm^3, INR > 7, and fibrinogen < 100 mg/dL.[184] Use of rFVIIa is reserved for rapid correction in patients who cannot tolerate a large volume of plasma. This agent may carry a thrombotic risk and is contraindicated in hypercoagulable conditions, which include pregnancy and Budd-Chiari syndrome.

Hypotensive patients with ALF should undergo intravascular volume status and cardiac function assessment before consideration of inotropes or vasopressors. Vasopressors can be used to treat either systemic hypotension or to maintain an adequate CPP. Based on recommendations for septic patients, norepinephrine should be used. The use of vasopressin is controversial because there is evidence that its use is associated with increases in ICP.[189] However, another study in which terlipressin was used did not reveal similar increases in ICP.[190]

LIVING DONOR LIVER TRANSPLANTATION

See Chapter 75.

PEDIATRIC LIVER TRANSPLANTATION

See Chapters 94 and 95.

ORGAN MATCHING AND ALLOCATION

The primary criteria used to match donor liver grafts with recipients are ABO blood type and graft size. ABO-incompatible transplantation (ILT) is generally limited to emergent situations, and as many as half of the adult recipients in early reports required retransplantation. Subsequent reports have identified patient populations with more favorable outcomes after ILT. Recipients with blood type O and pediatric patients tolerate ILT better than others.[191] Nonetheless, ILT remains a technique reserved for emergent situations.

In the United States, a national registry maintained by UNOS allocates organs to transplant candidates. In Europe, organs are allocated to transplant centers that subsequently identify the most suitable candidate from their waitlist. UNOS considers only disease severity, and no longer uses waiting time, when allocating deceased-donor liver grafts. Older systems used the Child-Turcotte-Pugh (CTP) score to determine disease severity (Table 74-3). Beginning in 2002, the MELD score replaced the CTP score. The MELD score is a mathematic formula that incorporates the serum bilirubin, creatinine level, and INR. It is considered more objective because there is no reliance on subjective physical examination to determine the presence and severity of findings, such as ascites or encephalopathy. The MELD score is a continuous scale,

TABLE 74-3 PUGH'S MODIFICATION OF THE CHILD-TURCOTTE CLASSIFICATION*

	Points		
Variable	**1**	**2**	**3**
Encephalopathy	None	1-2	3-4
Ascites	Absent	Slight	Moderate
Prothrombin time (sec prolonged)	<4	4-6	>6
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Bilirubin (mg/dL)	<2	2-3	>3

*Child-Pugh class A, 5-6; class B, 7-9; class C, 10-15.
Adapted from Weisner RH, McDiarmid SV, Kamath PS, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl *7:567-580, 2001 (p 568).*

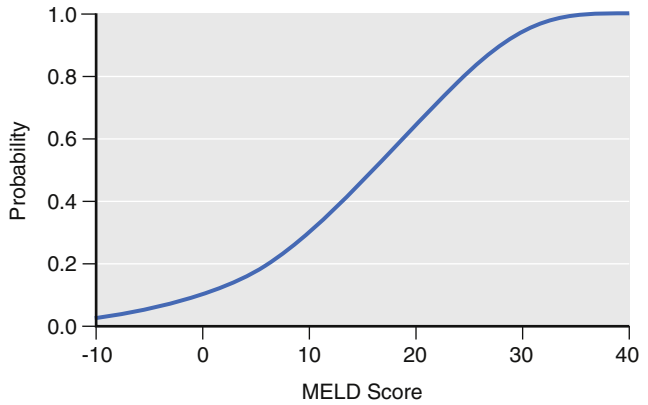


Figure 74-11. Relationship between Model for End-Stage Liver Disease (MELD) score and 3-month mortality in hospitalized (pretransplant) patients with cirrhosis. *(From Wiesner RH, McDiarmid SV, Kamath PS, et al: MELD and PELD: application of survival models to liver allocation,* Liver Transplant *7:567-580, 2001.)*

rather than categorical (found in the CTP score), which provides more discriminatory ability since disparate risks are not grouped within a single category. In addition, the inclusion of the creatinine level (not found in the CTP score) reflects the prognostic importance of renal dysfunction on advanced liver disease. The MELD score is an excellent predictor of 90-day pretransplant (waitlist) mortality (Fig. 74-11). The MELD score is regarded as a major advance in liver organ allocation, although it will undoubtedly continue to undergo refinement.

Hepatocellular carcinoma (HCC) can progress to inoperable status before manifesting changes in the MELD score, which disadvantages patients with HCC. As a result, UNOS policy grants exception points to patients with HCC to allocate organs equitably to patients with this condition.[192] Although there have been several adjustments to the MELD exception points awarded, patients with HCC appear to be advantaged compared with those without HCC; therefore, additional adjustments may be needed.[193] Waitlisted patients with HPS also receive exception points. UNOS policy does not specify the number of points allocated, but instead indicates that the exception should provide a chance of transplantation within 3 months. Evidence suggests that as a group, patients with HPS may have accrued a survival advantage compared with nonexception status candidates as a result of this policy; however, more analysis is needed before modifications are made.[194]

Most liver transplant candidates have MELD scores less than 25; only 2% of the waitlist has a MELD score greater than 25.[1] Candidates with MELD scores less than 15 have better survival without transplantation.[195] However, when the qualities of the donor graft are taken into account using the donor risk index, candidates with MELD scores of 12 to 14 benefit from liver transplant in the event that a favorable (low donor risk index) graft is transplanted.[196]

ANESTHESIA FOR PATIENTS AFTER LIVER TRANSPLANTATION

Liver transplant recipients with functioning grafts typically metabolize drugs in a normal fashion, but graft function must be assessed rather than assumed. The prothrombin time (or INR) is an excellent marker of synthetic function. In patients with grafts with impaired synthetic function, clotting abnormalities can be corrected with vitamin K or fresh frozen plasma; ascites managed with diuretics, albumin administration, or paracentesis; and the risk of encephalopathy minimized with lactulose administration and careful use of sedatives.

Careful adherence to sterile technique is required to prevent infectious complications in this immunosuppressed population. A stress dose of corticosteroids is required for patients receiving chronic supplementation. Renal function should be assessed and managed carefully to avoid an exacerbation of immunosuppressant-associated renal impairment. Hypertension is a common finding in patients whose condition is managed with calcineurin inhibitors such as cyclosporine. Drugs known to decrease hepatic blood flow, such as propranolol, should be avoided. Regional anesthesia is an option in patients with acceptable clotting status.

INTESTINAL TRANSPLANTATION

Intestinal transplantation is indicated in patients with irreversible intestinal failure and an inability to continue total parenteral nutrition.[197] Impending liver failure, lack of central vein access, frequent line infections or recurrent episodes of dehydration despite intravenous fluid supplementation can lead to intolerance to total parenteral nutrition. Intestinal failure is the inability to maintain adequate nutrition via the alimentary tract, commonly because of surgical removal or congenital absence of more than 70% of the small bowel (short-gut syndrome).

Approximately 130 intestinal transplants were performed in the United States in 2011.[1] The number of small bowel transplant candidates has declined since 2006, most likely because of improved medical management. In 2011, nearly 60% of waitlisted candidates were younger than 18 years (>40% were younger than 5 years). Almost half of intestinal grafts were transplanted with another organ in 2011; the remainder were transplanted as isolated intestinal transplants (Fig. 74-12). In the past, the most common accompanying organ was the liver; in 2011, it was the pancreas. The median time to transplant

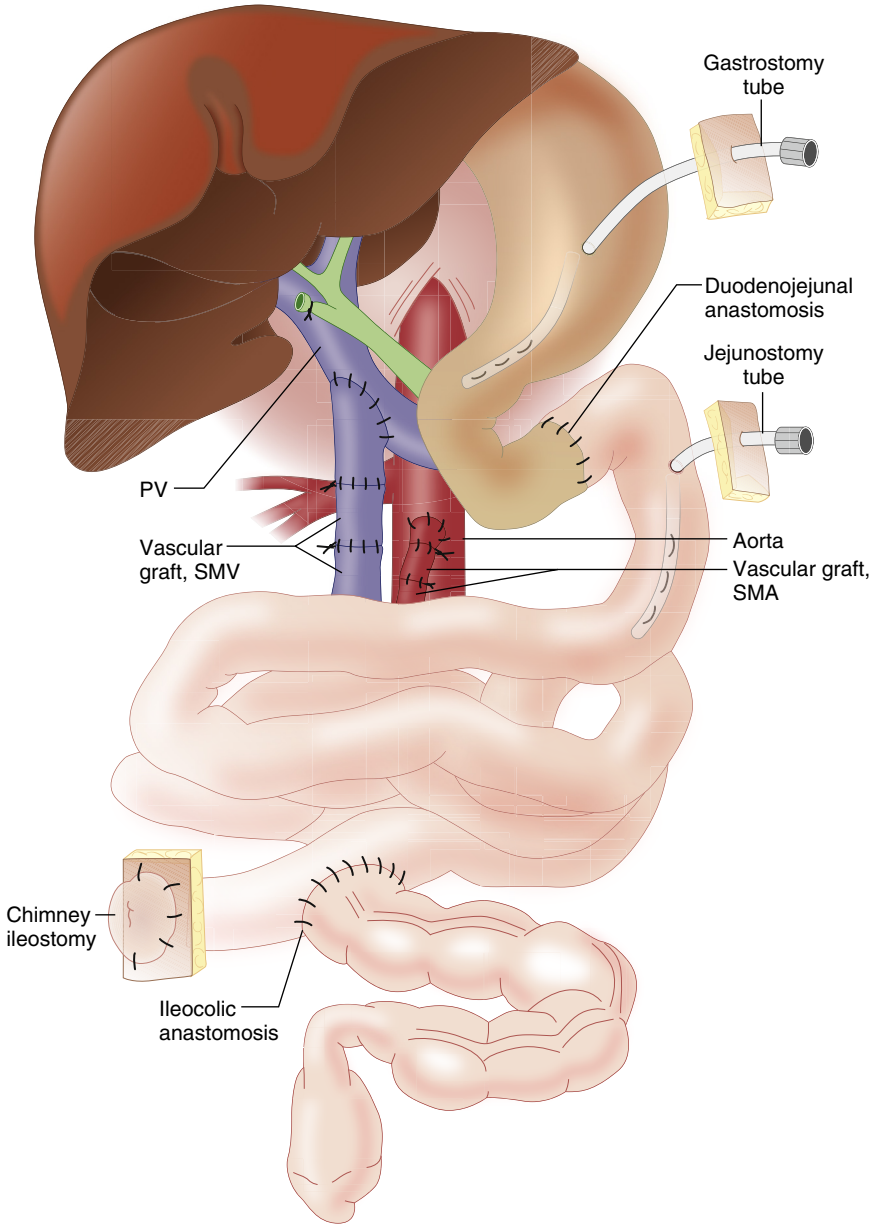


Figure 74-12. Intestinal transplantation. The implanted donor intestine is illustrated. *SMA,* Superior mesenteric artery; *SMV,* superior mesenteric vein. *(Modified from Abu-Elmagd K, Fung J, Bueno J, et al: Logistics and technique for procurement of intestinal, pancreatic and hepatic graft from the same donor,* Ann Surg *232:680-687, 2002.)*

in 2011 was 15 months for patients younger than 18 years of age, and 3 months for those aged 18 years or older. Patient survival after intestinal transplantation is improving. One-year survival is approximately 80%, and 5-year survival approaches 50%.

Intestinal transplant candidates should undergo an age-appropriate cardiovascular evaluation, with particular attention to vascular access. Because of the need for chronic indwelling vascular access, thrombosis and obstruction of central veins is common (vanishing vein syndrome) in patients presenting for intestinal transplantation. Doppler ultrasonography, contrast venography or magnetic resonance angiography, or all three, are indicated before surgery.[198]

Intraoperative blood loss varies based on whether other organs are transplanted simultaneously and on the extent of abdominal adhesions present from prior surgeries. Rapid infusion devices should be available. Patients are frequently hypercoagulable; care should be taken to avoid therapies that can increase the risk of thromboembolism.

Repeat hospitalization is common after transplantation, occurring in 85% by 6 months after transplant and in nearly all recipients by 4 years. Infection is responsible for 50% of mortality.[199] Other complications include acute rejection (fever, bloody stools), chronic rejection, graft-versus-host disease in 6%, and lymphoproliferative disease in 7% to 8%.[200]

MULTIVISCERAL TRANSPLANTATION

Multivisceral transplant includes the small intestine, stomach, liver, spleen, and the duodenopancreatic complex. Modified multivisceral transplant includes the visceral organs without the liver.[200] The indications for multivisceral transplant have been widened because of

the technically advantageous nature of the procedure, which involves a decreased number of anastomoses compared to combined liver-intestinal transplant. This is particularly favorable for infants. When the liver is included, the risk of stenosis or thrombosis of the portal anastomosis is avoided.[201]

POSTABDOMINAL TRANSPLANTATION COMPLICATIONS

Surgical Complications

Early postoperative surgical complications include postoperative bleeding, drainage leaks (bile, urine, pancreatic secretions), and vascular thrombosis. The risk of bleeding and thrombosis is lessened when a balance is maintained between procoagulants and anticoagulants (protein S and C, antithrombin). Because standard laboratory tests monitor only coagulation, this balance may be difficult to assess in the absence of viscoelastic tests, which evaluate whole blood clotting.

Complications vary based on donor graft qualities and recipient characteristics. For instance, hepatic artery thrombosis is more common in pediatric recipients because of the small caliber of the vessel, and bile leaks are more common after liver transplantation using grafts from cardiac death donors (see Chapter 75).[202]

Infection

After the immediate postoperative period, infection is the primary cause of death. Immunosuppressive medications, used to prevent rejection, are largely responsible for this risk. Bacterial infections predominate during the early postoperative period. Surgical site infections, intra-abdominal abscesses, and infected hematomas are common. In this immunosuppressed population, multidrug-resistant organisms are common. In liver transplant recipients, bacterial translocation or bile leaks can result in peritonitis, cholangitis, and perihepatic abscesses. In a recent study of liver transplant recipients, 47% of ICU patients had bloodstream infections, 35% had intra-abdominal abscesses, and 17% had ventilator-associated pneumonia.[203] Prompt diagnosis and treatment with minimally invasive drainage techniques should be considered over early laparotomy. When this approach fails, laparotomy is indicated.

Prolonged endotracheal intubation and indwelling central venous and urinary catheters are a common source of infection. These devices should be removed as early as possible in the postoperative period. In the meantime, strict aseptic technique is required when accessing indwelling catheters and tubes.

Comorbidities, such as diabetes and renal dysfunction, can increase the risk of infection. Viral and fungal infections are more likely after the first postoperative week. Risk factors for fungal infection in liver transplant patients include preexisting viral hepatitis, diabetes mellitus, multiple organ system failure, prolonged parenteral nutrition, long-term mechanical ventilation, and increased antibiotic use.[204] Common sites of fungal infection include oral, esophageal, pulmonary, and intracerebral. Invasive fungal infections, despite prolonged treatment with amphotericin or itraconazole, are associated with a poor prognosis.

Immunosuppression

Acute rejection is an important cause of graft dysfunction at 1 week and beyond, occurring in as many as one quarter of liver recipients.[205] The goals of immunosuppression are to prevent graft loss and to avoid the adverse consequences of antirejection regimens.[205] Immunosuppression for solid organ transplant is divided into initial (induction) and maintenance phases. Calcineurin inhibitors cyclosporine and tacrolimus (formerly FK506) are the foundation for the majority of induction and maintenance regimens. Both agents inhibit transcription of interleukin (IL)-2 and other cytokines, primarily in helper T lymphocytes. Both manifest renal toxicity, which is caused by afferent arteriolar vasoconstriction and a reduction in GFR. The resulting azotemia is reversible with a reduction of dosage. Hypertension is due to vasoconstriction and sodium retention, and typically appears within the first weeks of treatment. Neurologic toxicity includes tremors, headaches, seizures, and even focal neurologic abnormalities. Mycophenolate mofetil therapy is a beneficial adjunct by allowing a reduction in the doses of calcineurin inhibitors.

In addition to tacrolimus, the most widely used drug, there are many other drugs available.[206] Sirolimus, an inhibitor of the protein mTOR, is used for calcineurin-sparing effects and in patients transplanted for hepatocellular carcinoma to reduce recurrence.[207] Basiliximub, a monoclonal antibody to CD25, has been used as an alternative to steroids for the induction of immunosuppression in liver transplantation.[208]

New immunosuppressive drugs are typically introduced for use in renal transplantation before they are applied in liver transplantation. Of note, recipients of liver grafts require less immunosuppression than do recipients of other organs, and liver grafts confer protection on other organs transplanted from the same donor. This effect is an example of the privileged immune status of the liver.[205]

The diagnosis of rejection requires a biopsy. The threshold for performing a biopsy should be low, albeit with an awareness that other conditions can mimic the histologic changes seen with rejection. For instance, diffuse lymphocytic infiltration of the kidney can be seen with rejection or lymphoproliferative disorder, and recurrent hepatitis C in the liver can resemble rejection.

Malignancy

Immunosuppressant drugs increase the susceptibility of transplant recipients to malignancy.[209] This effect is primarily related to the level of immunosuppression, but production of transforming growth factor-β may also be responsible.

The spectrum of malignancy is wide ranging and includes cancers seen with HIV-infection, a condition also associated with immunosuppression. Lymphoma regression occurs if the immunosuppressive agent is discontinued early.

In a retrospective study of more than 250,000 solid organ transplant recipients, Hodgkin lymphoma risk factors included male sex, young age, and Epstein-Barr

virus (EBV) seronegativity at the time of transplant.[210] In a study of 175,000 solid organ recipients (primarily kidney and liver recipients), malignancy was identified in more than 10,000 patients, a standardized incidence ratio (SIR) of greater than 2 compared with the general population.[211] The cancer sites with the highest relative risk included Kaposi sarcoma (SIR = 61), lip (SIR = 17), skin, nonmelanoma (SIR = 14), liver (SIR = 12), vulva (SIR = 8), and non-Hodgkin lymphoma (SIR = 8).

Posttransplant lymphoproliferative disorder (PTLD) is associated with a proliferation of B cells after transplantation in response to infection with EBV. Clinical presentation varies from a mononucleosis-like syndrome to malignant lymphoma. Pediatric patients are at increased risk due to a lower likelihood of prior exposure to EBV. Diagnosis is made by biopsy of the affected area, which can include the graft. Treatment consists of a reduction of immunosuppression levels and antiviral therapy against EBV, primarily ganciclovir. Individuals at high risk, such as patients who are seronegative for EBV or who receive a graft from a seropositive donor, should be maintained on antiviral prophylaxis.

The mean latency period for all cancers is 3 to 5 years after transplant, although specific malignancies exhibited unique time intervals. Cancer sites vary depending on the organ transplanted; for example, renal transplant recipients have a 100-fold greater than expected risk of developing carcinoma in the native kidney.[212] The reasons are unclear, but prolonged dialysis before transplantation may be a risk factor.[213] The use of specific immunosuppressive drugs also affects the relative risk of various cancers. For example, OKT3, which contains antibodies directed against T lymphocytes, is associated with an increased incidence of PTLD. Antibodies directed against B lymphocytes (rituximab) can reduce the incidence of PTLD. Sirolimus is not associated with cancer risk, and in fact may have antitumor effects.

Long-Term Survival

Long-term survival is affected by common diseases, such as hypertension, hyperlipidemia, and diabetes mellitus.[214] Three years after liver transplantation, cardiovascular disease and de novo malignancy are the major causes of mortality.[215] Recurrent rejection and hepatitis C account for most of the hepatic causes of mortality.

CONCLUSIONS

Abdominal organ transplantation has matured over the past 30 years. From its beginning as an experimental procedure, it has become the best hope for survival in the case of liver transplantation, and the best option for an independent life without morbidity in the case of renal and pancreatic transplantation. Challenges for the future include a solution to the organ shortage, methods to minimize the likelihood of disease recurrence, and pharmacologic advances aimed at limiting the side effects of immunosuppression.

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Chapter 75

Anesthesia for Organ Procurement

VICTOR W. XIA • RANDOLPH H. STEADMAN

Key Points

- The shortage of organs available for transplantation is a worldwide problem.
- The discrepancy between the number of patients waiting for organ transplantation and the available organs has widened.
- Most organs in the United States are donated after brain death, but organs from cardiac death and living organ donors are increasing.
- Brain-dead donors have physiologic alterations that must be actively managed to ensure that the organs are suitable for transplantation (also see Chapter 76).
- Determining brain death and cardiac death should follow national guidelines and local institutional protocols (also see Chapter 76).
- The anesthesiologist must have an awareness of the ethical and legal issues related to the declaration of death and organ donation.
- Expansion of the donor pool through the inclusion of extended criteria, such as high-risk donors, addresses the organ shortage and decreases waiting-list mortality.
- The use of extended criteria high-risk organs significantly impacts recipient outcomes and presents challenges to perioperative management.
- Ischemia-reperfusion injury in organ transplantation is unavoidable; however, management strategies can lessen the likelihood of postoperative graft failure.
- Goal-directed donor management can improve the number of organs transplanted per donor.
- Preclinical studies on the prevention or reduction of ischemia-reperfusion injury are promising, but they have not been widely implemented into clinical practice.
- Living organ donor kidney transplantation has increased, whereas the use of living donors for liver transplantation varies by country.

INTRODUCTION

Organ transplantation requires the donation and successful procurement of a human organ. The success of organ transplantation relies on a functioning donor graft. The majority of organs used for transplantation in the United States are from donors after the declaration of brain death (donation after brain death, [DBD]). Organs from donation after cardiac death (DCD) and living organ donation are in the minority but have increasingly been used in recent years[1] (also see Chapter 76). Organs procured from these sources have different characteristics and present varying challenges in management. For instance, DBD donors often have significant physiologic alterations and hemodynamic instability that is associated with brain death. These alterations and instability, if not treated, will lead to organ deterioration and may prevent the organ from being suitable for transplantation. In contrast, DCD donors have an obligatory period of hypotension of varying duration before cardiac arrest. The resulting compromise in perfusion can exacerbate reperfusion injury and can lead to an increased incidence of posttransplant biliary dysfunction.

The shortage of organs is a worldwide problem and is the most important obstacle in organ transplantation. The gap between the number of patients waiting for transplant and the available organs has widened (Fig. 75-1). In September 2012, more than 114,000 transplant candidates were wait-listed in the United States through the United Network for Organ Sharing (UNOS). Of these, 74,000 were active candidates; however, less than 30,000 candidates were expected to undergo transplant surgery in 2012.[2] The majority of candidates were awaiting kidney grafts, with a smaller number awaiting liver, heart, and lung grafts. Many strategies were implemented to decrease the gap between the demand and supply, including public awareness campaigns and updates to the organ allocation system. Organ donation rates and the number of organs transplanted per donor vary substantially across geographic regions. Per 100 eligible deaths in the United States in 2009, the organ

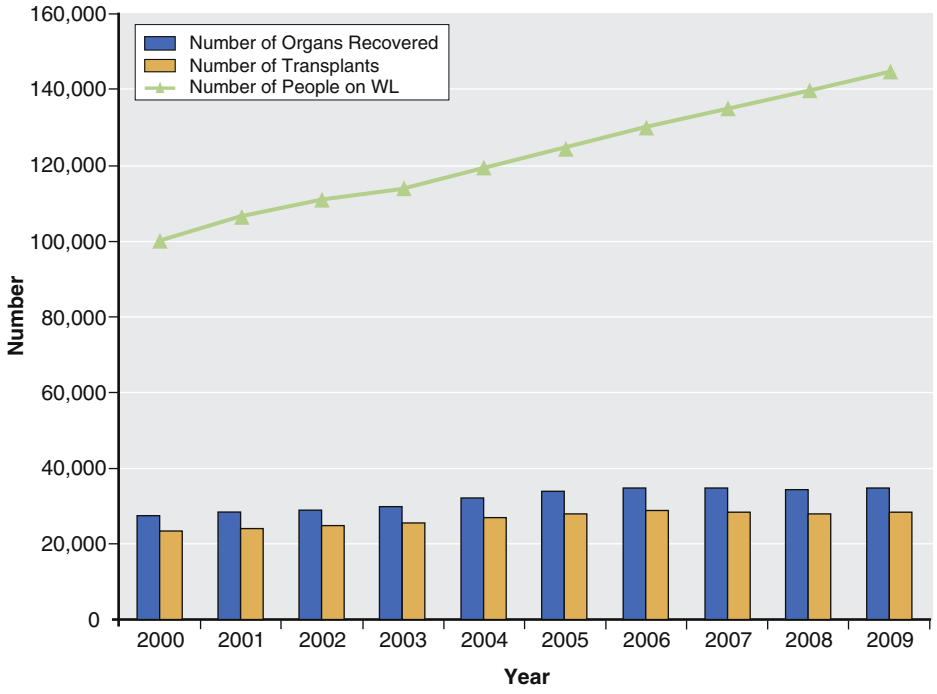


Figure 75-1. The gap between the number of patients on the waiting list (WL) for transplantation and the number of transplants performed each year in the United States is increasing every year. A significant number of procured organs are not used for transplantation. *(Data available at http://optn.transplant.hrsa.gov. Accessed June 30, 2012.)*

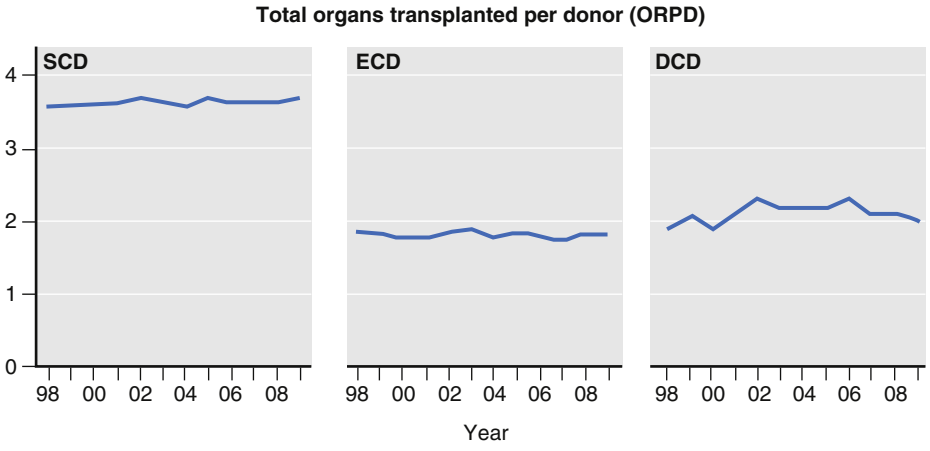


Figure 75-2. Total organs transplanted per donor based on donor type. *DCD,* Donation after cardiac death; *ECD,* extended criteria donor; *SCD,* standard criteria donor.

donation rate varied from a low of 51 to a high of 91.[3] To increase the number of organs for transplant, many programs have expanded the donor pool by using extended criteria donors (ECDs). Not surprisingly, the number of organs transplanted per donor varies according to donor category: ECD, DCD, or standard criteria donor (SCD). The number of organs transplanted from DCD donors is similar to ECDs, primarily attributable to the ability of the kidney to tolerate the longer periods of ischemia associated with organ procurement after DCD (Fig. 75-2). The use of living-related and living-unrelated donors is widespread in countries with moral or legal objections to brain death and is an important worldwide donor source. Many policies have been proposed to promote the best practices in organ donation.[1,4]

Organ transplantation is a complex process that requires close coordination among many specialized teams. The procurement organizations, transplant coordinators, social workers, nurses, surgeons, internists, intensivists, and anesthesiologists are involved in the process. To maximize the number of organs transplanted (Fig. 75-3) and to preserve the best possible function of donated organs, anesthesiologists need to understand the pathophysiologic derangements associated with donation and ischemia-reperfusion injury. In addition, anesthesiologists must be aware of the ethical and legal issues related to the declaration of death and organ donation.

MANAGEMENT OF ORGAN DONORS AFTER DECLARATION OF BRAIN (NEUROLOGIC) DEATH

DBD provides approximately 80% of donated organs in the United States. Organ procurement from DBD donors can only occur after the declaration of death. The concept of brain death emerged in the 1950s when clinicians encountered patients whose brain function had ceased, but the function of other organs was maintained by preserved cardiac perfusion in the presence of mechanical ventilation. In

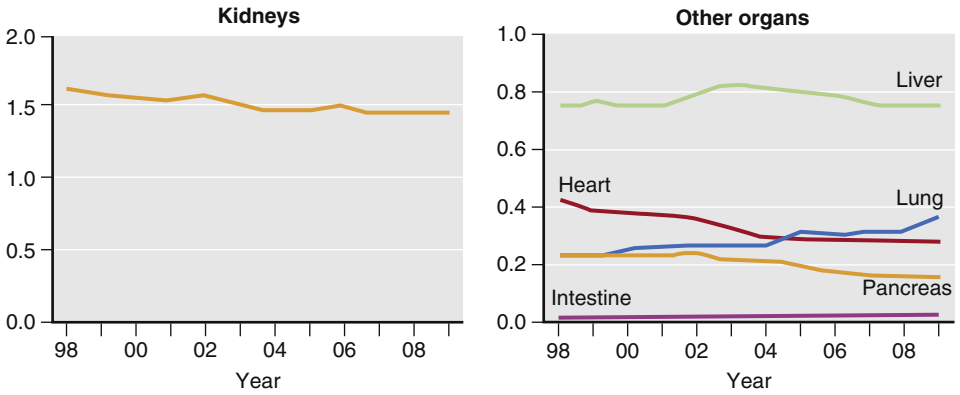


Figure 75-3. Organs transplanted per deceased organ donor. *(Data from the Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR):* OPTN/SRTR 2010 annual data report, *Rockville, Md, 2011, Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, p. 127.)*

1968, a Harvard Ad Hoc Committee on Irreversible Coma established a set of criteria that has been widely used today for the determination of brain death[5] (also see Chapter 76). In the United States, the Uniform Determination of Death Act was approved in 1981 by the National Conference of Commissioners on Uniform State Laws, in cooperation with the American Medical Association, the American Bar Association, and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Although the criteria for the declaration of brain death were based on ethical principles established several decades ago, the criteria remain valid today.[6]

Although the concept of brain death has been widely accepted in Western cultures, minor variations in definition and implementation exist in different countries. Despite these differences, the clinical criteria are similar.[7] A larger difference exists among different cultures in accepting and implementing the brain death criteria. In fact, brain death has not reached a legal status in some countries, such as China.

DIAGNOSIS AND DETERMINATION OF BRAIN DEATH

In 1995 and updated in 2010, the American Academy of Neurology published practice parameters for the determination of brain death (also see Chapter 76).[6] To determine brain death, physicians must confirm the presence of the following three findings: irreversible coma, absence of brainstem reflexes, and absence of respiratory drive after a carbon dioxide (CO_2) challenge. Reversible cerebral dysfunction caused by hypothermia, hypotension, or residual drug effects must be excluded. A lack of brainstem activities is confirmed by the lack of a pupillary response to light, corneal reflex, gag and cough reflexes, ocular movements, and facial motor response. The absence of respiratory drive is assessed with an apnea test (CO_2 challenge) in patients without a history of CO_2 retention. During the apnea test, the patient is mechanically ventilated with 100% oxygen for at least 10 minutes to attain partial arterial pressure of oxygen (PaO_2) greater than 200 mm Hg in the presence of a normal partial arterial pressure of carbon dioxide ($Paco_2$) (35 to 45 mm Hg). The patient is then disconnected from the ventilator while oxygenation is preserved via an insufflation catheter or a T-piece connected to the endotracheal tube. The apnea test is positive if no respiratory movements are observed for 8 to 10 minutes and the $Paco_2$ is at or greater than 60 mm Hg. A positive apnea test confirms the lack of brainstem control of ventilation. If the test is inconclusive but the patient is hemodynamically stable and adequately oxygenated, then the test may be continued for a longer period (10 to 15 minutes). In clinical practice, ancillary tests can be used when the neurologic examination is indeterminate or the apnea test cannot be performed. The tests that have been used for this purpose include electroencephalography, cerebral angiogram, computed tomographic angiography, magnetic resonance angiography, somatosensory-evoked potentials, and transcranial Doppler imaging[6] (also see Chapter 49).

PATHOPHYSIOLOGIC CHANGES WITH BRAIN DEATH

A variety of pathophysiologic changes are associated with brain death. The pathophysiologic mechanisms of brain death have profound effects at the molecular, cellular, and tissue levels. The clinical presentations associated with brain death may be complex and vary from patient to patient. They can be further complicated by prior pathologic abnormalities, disease, and therapy. The typical pathophysiologic changes associated with brain death are further described in Table 75-1.

CARDIOVASCULAR RESPONSES TO BRAIN DEATH

The cardiovascular system is closely regulated by the central neural system. Cardiovascular responses to brain death usually consist of two phases. The first phase is characterized by sympathetic discharge (catecholamine storm), which causes intense vasoconstriction or elevated systemic vascular resistance (hypertensive crisis), tachycardia, and a redistribution of blood volume with visceral ischemia. Acute myocardial injury can occur in brain-dead donors without a history of coronary artery disease.[8] Echocardiographic evidence of myocardial dysfunction is observed in 40% of brain-dead donors under consideration for heart donation.[9] At times, parasympathetic activation can result in bradycardia. After the sympathetic discharge of the first phase, the loss of sympathetic tone, decreased cardiac output, blunted hemostatic responses, and severe peripheral vasodilatation (vasoplegia) characterize the second phase. In addition to neurohormonal disturbances, other contributing factors include

TABLE 75-1 **PATHOPHYSIOLOGIC CHANGES ASSOCIATED WITH BRAIN DEATH**

Signs and Symptoms	Pathophysiologic Changes	Incidence
Hypertension	Catecholamine storm	80%-90%
Hypotension	Vasoplegia, hypovolemia, reduced coronary blood flow, myocardial dysfunction	80%-90%
Bradycardia and other arrhythmias	Catecholamine storm, myocardial damage, reduced coronary blood flow	25%-30%
Pulmonary edema	Acute blood volume diversion, capillary damage	10%-20%
Diabetes insipidus	Posterior pituitary damage	45%-80%
Disseminated intravascular coagulation	Tissue factor release, coagulopathy	30%-55%
Hypothermia	Hypothalamic damage, reduced metabolic rate, vasodilation and heat loss	Varied
Hyperglycemia	Decreased insulin concentration, increased insulin resistance	Common

blood loss, intravascular depletion attributable to capillary leakage, osmotic therapy for rising intracranial pressure (ICP), and diabetes insipidus.

The first phase is correlated with ischemia in various parts of the brain and is attributable to an increase of ICP, and the second phase is caused by cerebral herniation and spinal cord ischemia. Although the first hypertensive phase generally represents a transient period in the progression to brain death, the second hypotensive phase is profound and sustained. Failure to correct these cardiovascular derangements results in poor organ perfusion and inadequate tissue oxygenation, which will threaten the viability of the donated organs.

RESPIRATORY RESPONSES TO BRAIN DEATH

An increase in systemic vascular resistance after brain death results in blood shifting from the systemic circulation to the more compliant pulmonary circulation. The resulting increase in hydrostatic pressure in the pulmonary circulation causes pulmonary capillary leakage and pulmonary edema. Sympathetic activity triggers a sterile systemic inflammatory response, initiating infiltration of neutrophils and increasing pulmonary endothelial permeability, which further contributes to lung injury. Proinflammatory cytokines are released at the alveoli and are associated with early graft failure and mortality after lung transplantation. The inflammatory response in brain-dead donors is associated with the deterioration in cardiac function and a shift to anaerobic metabolism. Hormonal instability can reduce alveolar fluid clearance, resulting in significant accumulation of extravascular lung water. If ventilation is not supported, then respiratory arrhythmia progresses to apnea and cardiac arrest.[10,11]

ENDOCRINE, METABOLIC, AND STRESS RESPONSES TO BRAIN DEATH

Brain death is frequently associated with pituitary failure and disturbances of cortisol, thyroid hormones, antidiuretic hormone, and insulin. Posterior pituitary function in brain-dead donors is frequently lost. The development of central diabetes insipidus results in severe fluid and electrolyte derangements and can be observed in up to 90% of brain-dead donors.[10] Anterior pituitary function in brain death can also be affected, resulting in a deficiency in triiodothyronine (T_3) and thyroxine (T_4), adrenocorticotropic hormone, thyroid-stimulating hormone, and human growth hormone. Thyroid hormonal deficiency may be similar to the euthyroid sick syndrome commonly observed in the non–brain injured patient with multisystem organ failure. Hyperglycemia is commonly encountered in brain-dead donors because of decreased insulin concentrations and increased insulin resistance. Hypothalamic function and control of body temperature are lost. Although hyperpyrexia may initially occur, hypothermia follows, which is caused by a reduction in metabolic rate and muscle activity, in combination with peripheral vasodilation. Disseminated intravascular coagulation is present in up to one-third of isolated patients with head injuries and is believed to be caused by the release of tissue thromboplastin from brain tissue.[11]

DONATION AFTER CARDIAC (CIRCULATORY) DEATH

Before the acceptance of brain death, all organs procured were from donors who suffered a cardiac demise (DCD, previously known as donation from a non–heart-beating donor). After the establishment of the Harvard criteria for brain death, DBD quickly became the principal source of organ donation. However, an interest in the use of DCD organs has been renewed in recent years, driven by the persistent shortage of DBD donors and the lack of acceptance of brain death in some countries. Policies and protocols developed by health care organizations now encourage DCD organs, and their use is increasing in the United States and other countries. In the United States over the 5-year period from 2004 to 2009, the number of DCD donors more than doubled and accounted for over 10% of donors in 2009[12] (Fig. 75-4). During the same period, the number of living donors dropped slightly from 7000 to 6600.[3] Kidney grafts accounted for over 95% of the organs transplanted from living donors during this period. The American Society of Anesthesiologists established a Sample Policy for Organ Donation after Cardiac Death, with the recommendation that its members actively participate in the development of institutional DCD protocols.

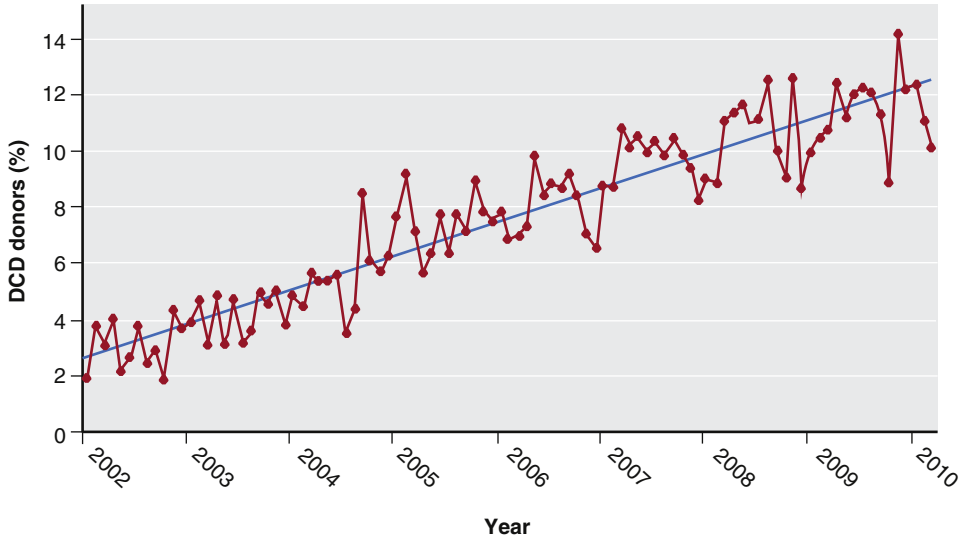


Figure 75-4. Percent of donations after cardiac death (DCDs) by year. *(Redrawn from Wynn JJ, Alexander CE: Increasing organ donation and transplantation: the U.S. experience over the past decade,* Transpl Int *24:324, 2011.)*

DCD donors are divided into five categories: I, patients dead on arrival at the hospital arrival; II, unsuccessfully resuscitated patients; III, patients in whom cardiac arrest is imminent; IV, cardiac arrest in brain-dead donors; V, unexpected arrest in the intensive care unit (ICU). Categories III and IV are considered as controlled DCDs, whereas the remaining categories are considered uncontrolled DCDs. Controlled DCD implies that life-support withdrawal can be planned and the transplant team is awaiting the cardiac arrest and is ready for rapid organ recovery. In contrast, uncontrolled DCD implies the patient has experienced an unanticipated cardiac arrest, and organ donation is considered only after an unsuccessful resuscitation. Warm ischemia time is significantly longer in uncontrolled DCDs. Currently, most DCD donors for organ transplantation are controlled DCD donors. Successful use of the uncontrolled DCD grafts has been reported in several studies.[13]

DCD donors usually suffer from irreversible brain or spinal injury but do not meet the brain death criteria. The prognosis for a meaningful quality of life is poor. Withdrawal of therapy must be based on a clinical decision of futility and conform to the wishes of the patient and family. The consideration of the withdrawal of life-sustaining therapies must be independent from any discussion related to transplantation. The transplantation team cannot be involved in this decision. Drugs can be used to relieve pain and anxiety and to provide comfort for the patient during withdrawal. Therapies designed to improve graft quality, but without benefit to the patient, are controversial; however, therapies with minimal impact on the patient that improve organ survival are allowed in some protocols.

Declaration of cardiac death should follow procedures proposed by national organizations and policies adopted by the local institution.[14,15] After a decision has been made to withdraw support, the trachea is extubated and life support is stopped. A physician who is not involved with organ transplantation declares cessation of cardiac function. Declaration of cardiac death is not different from clinical practice, which requires a clinical examination to confirm pulselessness or the absence of an arterial waveform. The duration between cessation of cardiovascular activities and the declaration of cardiac death is usually 2 to 5 minutes to ensure irreversibility. Organ procurement starts after death is declared.

Although organs procured from DCD donors are not exposed to the physiologic derangements of brain death, they are at greater risk for ischemia-reperfusion injury than organs from DBD donors. This potential results from hypoxemia and ischemia in a warm environment, which is unique during DCD procurement. The time elapsed from extubation to cardiac death is an important factor for determining the suitability of organ donation. If spontaneous breathing and/or heart function continues for a prolonged period after life support withdrawal, then the organs may not be suitable for transplantation, particularly in donors with comorbidities. To assist physicians in predicting how long a patient will sustain life after the withdrawal of life support, a 6-variable score was developed by the University of Wisconsin (Table 75-2). A low score (8 to 12) means that breathing and/or cardiac function will continue for some time. A high score (19 to 24) means that apnea and cardiac arrest are imminent.[16]

The two separate definitions and procedures used for DBD and DCD have led to a new debate about the definition and determination of death. A uniform concept of death, which combines all previous criteria for death, is emerging. A growing consensus is that all criteria used to diagnose human death rely on the demonstration of the irreversible loss of the capacity to breath, combined with the irreversible loss of the capacity for consciousness. The irreversible loss of these two functions equates to human death.[17]

Category III (impending cardiac arrest) DCD is the ideal source for organ transplant. Kidneys from DCD donors are frequently used. Several studies have showed that, despite a higher incidence of delayed graft function (DGF), kidneys from DCD donors have comparable short- and long-term graft survival.[13] Livers from DCD donors have a higher likelihood of postoperative biliary complications such as diffuse ischemic cholangiopathy with intrahepatic biliary stricture and may also have a higher incidence of primary

TABLE 75-2 UNIVERSITY OF WISCONSIN CRITERIA FOR DONATION AFTER CARDIAC DEATH EVALUATION TOOL

Variables	Points
Spontaneous respiration after 10 minutes	
Respiratory rate >12 breaths/min	1
Respiratory rate <12 breaths/min	3
Tidal volume >200 mL	1
Tidal volume <200 mL	3
Negative inspiratory force >20 cm H_2O	1
Negative inspiratory force <20 cm H_2O	3
No spontaneous respiration	9
Body mass index (kg/m²)	
<25	1
25-29	2
≥30	3
Vasopressors	
None	1
1 pressor	2
≥2 pressors	3
Patient age (yr)	
0-30	1
31-50	2
>50	3
Intubation	
Endotracheal tube	3
Tracheostomy	1
Oxygenation after 10 minutes	
O_2 saturation >90%	1
O_2 saturation 80%-90%	2
O_2 saturation <80%	3

University of Wisconsin score: 8-12, high probability; 13-18, moderate probability; and 19-24, low probability for continuing to breathe after extubation.

Lewis J, Peltier J, Nelson H, et al: Development of the University of Wisconsin Donation After Cardiac Death Evaluation Tool, Prog Transplant *13:265-273, 2003.*

graft nonfunction (PNF) and DGF compared to grafts from DBD donors.[18] Ischemic cholangiopathy occurs more frequently if the donor is older, is overweight, and has a prolonged ischemic period. Heart and lungs are susceptible to ischemia and only a few cases of the successful use of such grafts from DCD donors have been reported.[16]

ISCHEMIA-REPERFUSION INJURY AND ORGAN PRESERVATION

Ischemia-reperfusion injury of transplanted grafts is unavoidable. It is easy to understand that an interruption of the blood supply during the ischemic period results in metabolic and pathophysiologic changes. Surprisingly, restoration of blood flow and reoxygenation can also cause tissue injury, as well as profound immune and inflammatory responses.[19,20]

Ischemia-reperfusion injury results from a wide range of pathologic processes. During ischemia, a lack of oxygen supply leads to a depletion of adenosine triphosphate (ATP) and glycogen. Without ATP, sodium-potassium (Na-K) pumps cannot maintain ion gradients across the cellular membrane. As a result, extracellular sodium ions move into cells, causing swelling. Vascular permeability is increased since intracellular cyclic adenosine monophosphate (cAMP) levels and adenylate cyclase activity is decreased.[19] The restoration of the blood supply causes a series of pathophysiologic changes that lead to tissue injury. Reperfusion-related injuries include necrosis, apoptosis (programmed death), and autophagy-associated cell death. Reperfusion also activates autoimmune responses including natural antibody recognition of neoantigens, activation of the complement system, activation of innate and adaptive immune responses, and cell migration to the affected area.

After procurement, organs are routinely stored in a cold (4° C) preservation solution to slow the metabolic rate. Various cold-storage solutions are used worldwide with the University of Wisconsin (UW) solution one of the most widely used. The UW solution contains high potassium and adenosine to supply ATP during cold storage. Recently, histidine-tryptophan-ketoglutarate (HTK) solution, originally developed for cardioplegia and subsequently applied to organ preservation in Europe, has gained popularity in the United States.[21] The potential for hyperkalemia during organ reperfusion (particularly with the liver) increases when the UW solution is used, compared with the HTK solution. However, the graft is typically flushed with colloid before reperfusion, regardless of the solution used, which decreases the likelihood of severe hyperkalemia. Recent data suggest that the HTK solution may be associated with poor graft function in abdominal organ transplantation.[22,23] Organ-specific solutions, such as Perfadex solution (manufactured by Vitrolife in Göteborg, Sweden) for the lung and Celsior solution (manufactured by Genzyme in Cambridge, MA) for the heart, are available. Although cold ischemia time should be minimized, the various storage times vary by organ. Generally accepted cold ischemia times are 24 hours for the kidney, 12 hours for the liver, 6 hours for the heart, and 4 hours for the lung. Even within these time windows, however, shorter storage times are preferred. In one study, reperfusion syndrome was avoided during liver transplantation when the cold ischemia time was less than 6 hours.[24] However, longer storage times allow transportation of the graft to the highest acuity patient.

In addition to the preservation solution, various techniques have been used to minimize the effects of storage, including continuous perfusion (as opposed to flushing) with a hypothermic or normothermic solution.[25] The potential advantage for perfusion techniques is a reduction in proinflammatory cytokine expression, as well as less activation of adhesion molecules and migration of leukocytes.[25] Recent reviews of data from the Scientific Registry of Transplant Recipient (SRTR) suggest an association between machine perfusion and a reduction in DGF, particularly in high-risk donors.[26] In addition, the function of procured organs can be assessed during normothermic perfusion preservation, which is particularly useful for heart grafts. However, normothermic continuous perfusion uses red blood cells and costly equipment, making it less practical.[27] Nonetheless, oxygen can be added into the perfusion

solution, which may restore cellular levels of ATP.[28] Several pharmacologic and biologic agents have been tested in animal models and preclinical trials; some, including recombinant agents that block leukocyte adhesion, have shown promise.[29,30] Preconditioning with volatile anesthetics has been shown to protect tissue from ischemia-reperfusion injury in animal models.[31] In human trials, volatile anesthetics have some beneficial effects in the setting of myocardial infarction, minimizing ischemia-reperfusion injury, although the data remain inconclusive.[32]

EXTENDED CRITERIA DONOR

Traditionally, DBD organ donors are young and otherwise healthy until stricken by an isolated cerebral event or head injury (SCDs). As the numbers of patients waiting for transplant increase, many centers have extended donor criteria to minimize waiting-list mortality. Many terms, including suboptimal donor, marginal donor, inferior donor, nonstandard donor, and high-risk donor, have been used.[33] The criteria that make up the ECD group are more elusive and evolving. Donor characteristics of ECDs vary from organ to organ but generally include advanced age, prolonged cold ischemia time, inferior organ function, and other comorbidities.[33,34] In kidney transplantation, SRTR defines ECD kidneys as those whose relative risk of graft failure is greater than 1.7 when compared with normotensive donors aged 10 to 39 years who exhibit normal renal function and who did not die as a result of a cerebrovascular accident. These include grafts from donors 60 years of age or older, as well as donors aged 50 to 59 years who have two of the following characteristics: history of hypertension, death caused by cerebrovascular accident, or preterminal serum creatinine level greater than 1.5 mg/dL[12] (Box 75-1). In liver transplantation, important ECD variables include advanced age, prolonged hospital stay, prolonged ischemia time, and macrosteatosis[35] (Box 75-2). In lung transplant, low PaO_2 values (<300 mm Hg) at the time of harvest, purulent secretions confirmed by bronchoscopy, and smoking more than 20 pack-years are significant factors for early- and long-term adverse outcomes.[36]

Recently, a donor risk index (DRI) has been defined for liver grafts. DRI is a quantitative assessment of the risk of graft failure associated with the donor. Liver DRI is calculated from several donor characteristics including increasing age, decreasing height, DCD graft (yes or no), split or partial grafts (yes or no), African-American race (yes or no), cause of death other than anoxia or cerebrovascular accident, national (versus regional) sharing, and cold ischemia time longer than 8 hours.[37] Despite an increased risk of graft failure, moderate-to-high acuity transplant candidates who receive a high DRI graft have a survival benefit compared with those remaining on the wait-list.[38] Calculation of the DRI can help physicians make a decision to accept or reject a donor offer; however, the calculation requires a projected cold ischemia time. Machine perfusion and dual kidney transplantation have been shown to reduce DGF in ECD kidney transplantation.[26]

The use of ECD or high-risk DRI grafts has implications on intraoperative management. In a study of liver transplantation, several donor characteristics are associated with a high incidence of intraoperative hyperkalemia in adults: DCD grafts, prolonged ischemia time, and prolonged donor hospital stay before procurements.[39] ECD liver grafts are also associated with postreperfusion syndrome, intraoperative bleeding, and postoperative reoperation.[40]

BOX 75-1 ***Extended Donor Criteria for Kidney Donors***

Donors >60 years of age
Donors 50 to 59 years of age with two of the following three characteristics:
- History of hypertension
- Death caused by cerebrovascular accident
- Preterminal serum creatinine level >1.5 mg/dL

From Port FK, Bragg-Gresham JL, Metzger RA, et al: Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors, Transplantation *74:1281, 2002.*

BOX 75-2 ***Extended Donor Criteria for Liver Donors***

Model 1: Extended Criteria Donor (ECD) Score*

Donor age: >55 years
Donor hospital stay: >5 days
Cold ischemia: >10 hr
Warm ischemia: >40 min

Model 2: Donor Risk Index (DRI)†

Age (four categories): >40, >50, >60, >70 years
Cause of death (two categories): cerebrovascular accident (lower risk) versus other
Race: African American (higher risk) versus other
Donation after cardiac death (DCD): yes or no
Partial or split graft: yes or no
Height: increasing risk as height decreases below 170 cm
Regional or national share: yes or no
Cold ischemia time

Model 3: (D-MELD)‡

Donor age
Laboratory MELD score

* From Cameron AM, Ghobrial RM, Yersiz H, et al: Optimal utilization of donor grafts with extended criteria: a single-center experience in over 1000 liver transplants, Ann Surg 243:748, 2006.
† From Feng S, Goodrich NP, Bragg-Gresham JL, et al: Characteristics associated with liver graft failure: the concept of a donor risk index, Am J Transplant 6:783, 2006.
‡ From Halldorson JB, Bakthavatsalam R, Fix O, et al: D-MELD, a simple predictor of post liver transplant mortality for optimization of donor/recipient matching, Am J Transplant 9:318, 2009.

MANAGEMENT OF ORGAN DONORS BEFORE PROCUREMENT

As previously discussed, various physiologic derangements are common in DBD donors. If not treated, these derangements can lead to graft deterioration, resulting in organs unsuitable for transplantation. A discussion of treatment strategies follows.

CARDIOVASCULAR MANAGEMENT

Although both hypertension and hypotension are associated with brain death and can result in poor perfusion to the organs, hypotension is more profound and difficult to treat. Maintaining adequate intravascular volume is probably the most effective therapy for vasoplegia. No evidence demonstrates that a specific crystalloid solution is superior to another. Adequate resuscitation, as evidenced by a mean arterial pressure of 60 to 100 mm Hg, may decrease cytokine levels and increase the number of organs available for transplantation.[41] Large doses of starch-based colloids should be avoided because they may be associated with DGF[42] (also see Chapter 61).

When hemodynamic stabilization is not achieved with fluid resuscitation, vasoactive drugs should be considered. Dopamine is most commonly used in this setting. If a large dose of dopamine is required, then a second vasoactive agent can be added. Dopamine and other catecholamines have beneficial antiinflammatory and immunomodulatory effects. Vasopressin is recommended as the initial therapy of choice for potential heart donors by the American College of Cardiology.[43] Vasopressin reduces catecholamine requirements and is an effective treatment for diabetes insipidus.

For a potential heart donor, cardiac function should be assessed, with early interventions to improve the donor procurement rate. Echocardiography is useful since it can identify both functional and structural abnormalities (also see Chapter 46). Functional abnormalities identified in the early stage can be managed before heart transplantation, whereas structural abnormalities may preclude transplantation. Coronary angiography is useful in older donors with suspected or known coronary artery disease. Myocardial damage caused by catecholamine storm may be prevented or attenuated by controlling cardiovascular responses, which may increase the number of heart transplants.[11] However, large doses of norepinephrine are associated with increased cardiac graft dysfunction and increased recipient mortality.[44]

Excessive intravascular fluid therapy may have detrimental effects and should be avoided in lung donors. Fluid restriction increases the number of lung grafts available for transplantation.[10] Because this practice creates a conflict of interest on the basis of which organs will be procured, particularly between the lungs and kidneys, fluid management should be balanced to optimize overall donation potential.[10] The goal is to maintain a euvolemic state and to maintain arterial blood pressure and cardiac output with the least amount of vasoactive support possible. Invasive hemodynamic monitoring may be used to guide intravascular fluid therapy (also see Chapter 59).

PULMONARY MANAGEMENT

The lungs are vulnerable to injury and, consequently, are one of the most difficult organs to preserve. Only 15% to 25% of donated lungs are used in transplantation. Current pulmonary management for potential lung donors favors small tidal volume ventilation. The focus of pulmonary management is to recruit and retain lung units while limiting tidal volume and inspiratory pressure. This strategy is extrapolated from studies in acute respiratory distress syndrome. Specific approaches to ventilator management for the donor are variable, but a common approach is a low tidal volume (6 to 8 mL/kg), low fraction of inspired oxygen concentration (FiO_2), and relatively high positive end-expiratory pressure (PEEP).[45] Pulmonary recruitment maneuvers, using pressure-controlled ventilation and high PEEP (15 cm water [H_2O]), followed by a return to conventional volume-controlled ventilation with a lower PEEP, are recommended by others. The administration of aerosolized terbutaline increases alveolar fluid clearance via β-adrenergic stimulation.[46] As previously discussed, a large amount of intravascular fluid and/or large-dose vasopressors are associated with impaired graft function in potential lung donors.[10]

Adequate gas exchange and good oxygenation are the most important indicators of the functional quality of the lung. However, an initial PaO_2/FiO_2 ratio less than 300 mm Hg should not be used as grounds for exclusion. Reversible processes such as secretions, pulmonary edema, and atelectasis can affect the PaO_2/FiO_2 ratio. Bronchoscopy is generally performed to remove mucous plugs that are present.

TEMPERATURE

Donor management should include active warming to maintain a body temperature above 35° C before and during organ procurement (also see Chapter 54).

HORMONES, STEROIDS, AND ELECTROLYTES

Hormonal deficiency is common in brain-dead donors and hormonal replacement is beneficial.[8,10] Exogenous replacement of antidiuretic hormone in brain-dead donors improves graft function in kidney, liver, and cardiac recipients.[10] Thyroid hormone replacement improves the number of organs transplanted per donor.[41] However, most studies showing advantages to hormone supplement are retrospective; adequately powered randomized trials are lacking.

The systemic inflammatory response associated with brain death leads to pulmonary infiltration of neutrophils and the elevation of interleukins. The systemic inflammatory response of the donor is associated with graft failure and recipient mortality. Methylprednisolone administration can moderate the inflammatory response and may improve oxygenation, reduce lung water, and increase lung yield. Methylprednisolone administration can also decrease inflammation in the liver, heart, and kidney.

Intravascular volume replacement is essential in the management of diabetes insipidus. After administering initial fluid to correct hypovolemia, hypernatremia should be treated by giving a hypotonic solution.[10] Studies have demonstrated that donor hypernatremia (>155 mmol/L) is associated with poor post–liver transplant outcomes.[47] Analysis of heart donors in Europe showed increased recipient mortality when donor sodium was less than 130 or greater than 170 mmol/L.[48] Correction of severe hypernatremia before organ procurement appears to attenuate post–transplant liver dysfunction.[10] Hyperglycemia in the donor is common and exacerbated

by steroid therapy. Poor glucose control adversely affects donor renal function.[49] Insulin management should target a glucose level between 120 and 180 mg/dL.

DONOR MANAGEMENT GOALS

Recent recommendations stress the use of standardized donor management with specific preprocurement goals designed to increase the number of organs transplanted per donor. The objective of donor management goals (DMGs) is to maintain cardiovascular, pulmonary, renal, and endocrine homeostasis. However, goals typically vary from center to center and in published reports (Table 75-3). In 2009, a study examined six preset clinical DMGs and found that compliance with all six goals significantly improved the number of organs transplanted. However, the benefit was more obvious in SCDs than in ECDs for unclear reasons.[50]

TABLE 75-3 DONOR MANAGEMENT GOALS (DMGS), AS REPORTED BY VARIOUS AUTHORS

Preset Clinical End Points	Six DMGs*	Eight DMGs†	Ten DMGs‡
Mean arterial pressure (mm Hg)	≥60	60-120	60-100
Central venous pressure (mm Hg)	≤10 (or serum osmolality 285-295 mmol/L)	4-12	4-10
Final sodium (mmol/L)	≤155	≤155	135-160
Pressors	≤1 (1 plus vasopressin to treat DI is acceptable)	≤1 or low dose	≤1 and low dose
PaO_2 (mm Hg) or PaO_2/FiO_2 ratio	PaO_2 ≥300 while on 100% oxygen (or $Paco_2/FiO_2$ ratio >3)	Final PaO_2 >100	PaO_2/FiO_2 ratio: >300 on PEEP = 5 cm H_2O
Arterial blood gas: pH	7.25-7.50	7.30-7.50	7.30-7.45
Glucose (mg/dL)		≤150	<150
Urine output (mL/kg/h) in 4 hours before procurement		0.5-3.0	1-3
Ejection fraction of left ventricle			>50%
Hemoglobin (mg/dL)			>10

DI, Diabetes insipidus; *FiO_2,* fraction of inspired oxygen concentration; *$Paco_2$,* partial arterial pressure of carbon dioxide; *PaO_2,* partial arterial pressure of oxygen; *PEEP,* positive end-expiratory pressure.

**Hagan ME, McClean D, Falcone CA, et al: Attaining specific donor management goals increases number of organs transplanted per donor: a quality improvement project,* Prog Transplant *19(3):227-231, 2009.*

†Franklin GA, Santos AP, Smith JW, et al: Optimization of donor management goals yields increased organ use, Am Surg *76(6):587-594, 2010.*

‡Malinoski DJ, Daly MC, Patel MS, et al: Achieving donor management goals before deceased donor procurement is associated with more organs transplanted per donor, J Trauma *71(4):990-995,* 2011, discussion, p 996.

A prospective study examined eight common DMGs and confirmed that meeting or exceeding seven out of eight DMGs increased organ recovery and transplantation rates. Some goals are more important than others. An analysis of individual goals showed terminal PaO_2 (>100 mm Hg or >80 mm Hg on FiO_2 ≤40%), low pressor use (≤1 pressor dose and low dose), and glucose concentration of or less than 150 mg/dL were independent predictors of the high-organ yield. Lungs were 10 times more likely to be transplanted when the PaO_2 was maintained above 100 mm Hg. Tight glucose control was a significant predictor for pancreas and lung transplantation. Thoracic organs were the most affected organs by the achievement of DMGs.[51]

Another study used 10 predefined DMGs, and compliance with 8 or more out of 10 goals increased the likelihood of providing more than 4 organs per donor. Among the 10 preset goals, 4 individual goals were highly significant for organ yield: (1) central venous pressure (CVP) between 4 to 10 mm Hg, (2) ejection fraction greater than 50%, (3) PaO_2/FiO_2 ratio greater than 300 mm Hg, and (4) serum sodium less than 150 mmol/L. Other variables (e.g., age, serum creatinine concentration, thyroid hormone therapy) were also important predictors of the number of organs recovered.[41] Early achievement of DMGs is important. Donors with four or more organs transplanted per donor have significantly more individual DMGs met at the time of consent. Efforts should focus on early management in patients with catastrophic brain injury until the intent to donate is known[52] (also see Chapter 76). One study showed that only 15% of donors met DMGs at the time of consent, although the rate was higher immediately before organ procurement.

MANAGEMENT OF DONORS AFTER CARDIAC DEATH

The majority of DCD donors are patients awaiting cardiac arrest in the ICU (category III). To minimize warm ischemia time, life support is usually withdrawn in the surgical unit. However, the family's desire to be present has led some institutions to withdraw life support in other nearby locations. The procurement team should not take part in patient management before a determination of irreversible death, which includes the period during which withdrawal of support and declaration of death occur. The administration of pharmacologic drugs for the purpose of maximizing donation potential, particularly therapies capable of hastening death, is controversial. However, narcotics and benzodiazepines are commonly continued and can be titrated to blunt sympathetic responses. Premortem administration of heparin can facilitate organ procurement but, because of the bleeding risk, is omitted in some institutional policies. Most protocols require specific consent for premortem donor therapy.

Invasive premortem techniques for reducing warm ischemia time have been described. These include cannulation of the femoral artery and vein before the withdrawal of life support, which allows rapid infusion of cold preservation solution after the declaration of death. These cannulas can also be used for extracorporeal membrane oxygenation (ECMO) after death. However, the

postmortem use of ECMO to restore the blood flow to vital organs generates vigorous debate, which highlights the ongoing ethical questions in donor management—the need to protect the best interest of the dying patient, while facilitating his or her wish to donate.[10]

MANAGEMENT OF ORGAN DONOR DURING PROCUREMENT SURGERY

Anesthesia care for organ procurement is required only in the case of brain-dead donors. The majority of organ procurement occurs at community hospitals, not tertiary medical centers. As a result, the logistics of organ procurement, the social circumstances, and the unusual sequence of intraoperative events may seem intimidating to the anesthesiologist.

Surgical techniques may vary, depending on whether single or multiple organs are procured. Generally, wide exposure of the surgical field is established via a midline laparotomy extended by sternotomy. A cannula is placed in the aorta to flush the organs with the cold preservation solution. Ice is applied to the surgical field to further protect the organs. The organs are removed with their vascular structures after isolation in an order according to their susceptibility to ischemia, with the heart first and the kidney last.

Most donors arrive in the surgical unit already tracheally intubated and supported by the intravenous administration of vasoactive drugs. During procurement surgery, patients can have movements resulting from spinal reflexes; therefore, neuromuscular blockers are desirable. Spontaneous spinal reflex or surgical stimulation can cause catecholamine release and hypertension. Hypertension can be managed by a number of drugs including vasodilators, opiates, and anesthetics; however, volatile anesthetics are commonly preferred. As previously mentioned, volatile anesthetics may provide additional benefits that include ischemic preconditioning and the reduction of ischemia-reperfusion injury.[53]

The intravascular administration of fluids and vasoactive drugs can treat blood loss and cardiovascular instability caused by surgical manipulation. Maintaining hemodynamic stability allows surgeons to procure the organs without further damage to the organs. Vasodilators such as phentolamine or alprostadil (for lung recovery) may be administered during cross-clamping with the goal of decreasing systemic vascular resistance and allowing an even distribution of the preservation solution. Clinically significant bradycardia in brain-dead donors does not respond to atropine; therefore, a direct-acting chronotrope such as isoproterenol should be readily available (also see Chapter 76). Heparin is usually administered before cross-clamping the aorta. If recovery of the heart or lung is anticipated, then pulmonary artery catheters and/or CVP catheters need to be withdrawn before cross-clamping. If lung recovery is anticipated, then the lungs are ventilated well beyond cross-clamping. Communication between the surgical team and the anesthesiologist is crucial to ensure optimal organ quality. As soon as the organs are perfused with the cold solution, mechanical ventilation and anesthesia care can be stopped.

MANAGEMENT OF LIVING ORGAN DONORS

Living donor organ transplantation has been successfully used as an alternative to deceased donor transplantation. In the United States the number of living donor organ transplants is increasing, primarily attributable to living donor kidney transplantation. In some Asian countries such as Japan and Korea, living donor transplantation is a standard procedure since donation after brain death is unusual because of cultural beliefs in these countries. Living donor organ transplantation has some advantages. The procedure can be scheduled as elective surgery at the same facility, which allows donor and recipient surgeries to be coordinated and the cold ischemia time to be minimized. Additionally, the graft is not exposed to the physiologic alterations associated with DBD or DCD donors. Living donors direct their donation to a specific recipient; therefore, the timing of the transplant can be optimized for the recipient, and prolonged waiting times associated with deceased donor transplantation are typically avoided. As a result, the recipient is generally in better overall condition. Although living organ transplantation has its advantages, it exposes healthy donors to medical risks. Additional concerns are potential decreased quality of life and an adverse financial impact after donation. The ethical aspect of living organ donation, particularly liver donation, continues to be vigorously scrutinized.[54,55]

Living donation should be preceded by a thorough medical, psychologic, and social evaluation that confirms the absence of contraindications and the lack of coercion. The informed consent includes full disclosure of possible complications and is facilitated by a patient advocate in many institutions with no relationship to the recipient. In the past, donors were typically related to the prospective recipient. Although the total number of living related donors is not increasing, the numbers of living unrelated (mostly kidney) donors has significantly increased in the last 10 years. Living unrelated donors now account for 28% of all living kidney donors in the United States.[56,57] Recently, paired or chain donation for kidney transplantation has been widely publicized. Paired donation allows two recipients with incompatible living donors to exchange donors, improving the graft match for both recipients. In chain donation, more than two donor-recipient pairs are involved. Similar to the expansion of deceased donor criteria, living donor criteria have been extended to include donors of advanced age and those with obesity.[58]

LIVING KIDNEY DONOR

Because the kidney is a paired organ, the kidney is a natural choice for living donation. The first successful kidney transplant was a living organ transplant performed between identical twins in 1954. Now, living donors account for approximately 40% of kidney transplants in the United States.[59] Living donor kidney transplantation provides the optimized timing for transplant and can avoid pretransplant dialysis, which is associated with improved survival.[56] In addition, living donor grafts provide better function and last longer than grafts from deceased donors.[60] A wide range of medical

and nonmedical factors need to be considered to ensure donor safety. To ensure a sufficient reserve after donation, many transplant centers use a glomerular filtration rate (GFR) greater than 80 mL/min/1.73 m^2 as a cutoff for donation. GFR is typically estimated by the measurement of urine creatinine clearance. If the estimated GFR is marginal, then radioactive and nonradioactive tracers can provide additional information.[61] Some centers allow a lower GFR.[62]

Traditionally, living kidney donor surgery was performed via open nephrectomy via a subcostal lateral incision. Now, it is commonly performed via laparoscopy. With this approach, donors experience less postoperative pain, a faster recovery, and a shorter hospital stay.[62] Either the left or the right kidney can be used for transplant; however, the left kidney is usually preferred because of the easier surgical exposure and longer vascular supply. The right kidney has a short vein, and its artery courses posterior to the inferior vena cava.

The patient is placed in a lateral position with the table flexed and the kidney rest elevated (also see Chapter 41). The surgical procedure begins with mobilization of the kidney with subsequent identification and dissection of the ureter, renal vein, and artery, and separation of the adrenal vein. When the right donor nephrectomy is performed, additional steps include duodenal mobilization and separation of the kidney from the liver. After mobilization of the kidney and clamping of the vascular structures, the kidney is retrieved through a small incision by either a hand-assisted or non–hand-assisted technique. Donor nephrectomy can be performed via a transabdominal route but is increasingly accomplished via a retroperitoneal approach using minimally invasive techniques. The advantage of a retroperitoneal approach is less manipulation of intraabdominal viscera. Single-incision donor nephrectomy has been described using uniquely designed devices. Recently, robotic-assisted laparoscopic living donor nephrectomy has been reported.[62,63] This technique may further decrease the trauma and discomfort to the donor (also see Chapter 87).

Anesthetic management of elective laparoscopic donor surgery on a healthy patient is similar to that used for elective laparoscopic nephrectomy. Standard noninvasive monitors are usually sufficient. One or two large-bore peripheral intravenous lines are usually placed. Transfusion of red blood cells is rare; however, type and screen, or type and cross for 1 to 2 units of blood, is routine practice in some centers in case of injury to major vessels. General anesthesia is required for laparoscopic nephrectomy and general anesthesia combined with epidural anesthesia is often used if open nephrectomy is planned.

Although laparoscopic nephrectomy on a healthy patient may be routine, some concerns in addition to potential blood loss exist. High intraabdominal pressure reduces venous return and has been associated with postoperative renal dysfunction. Lower insufflation pressure may prevent compression of the renal veins and parenchyma.[64] Adequate intravascular fluid administration appears to be the best strategy to preserve kidney function. Some advocate liberal fluid administration (10 to 20 mL/kg/hr), although laparoscopic nephrectomy is typically associated with minimal blood loss. Others use urinary output as an indicator for fluid management. To ensure that the urinary output is greater than 2 mL/kg/hr, fluid is usually given in excess of the physiologic need throughout the procedure. The surgeon may request the administration of furosemide and/or mannitol during the surgery for the purpose of increasing urine output. The preferred type of fluid for intravascular volume expansion during donor nephrectomy is not known. In the absence of evidence, most centers use an isotonic crystalloid solution. Nitrous oxide is best avoided because of a concern over bowel distention and poor surgical exposure. Intravenous heparin (3000 to 5000 international units [IU]) is often administered immediately before the renal vessels are clamped. Protocols may vary among institutions, and close communication with the transplant surgeon is essential. If hypotension occurs after adequate fluid replacement, then dopamine and ephedrine are preferable to direct-acting vasopressors to minimize vasoconstriction in the graft. After the kidney is retrieved, anesthesiologists should be prepared for a quick closure and ensure that neuromuscular blockade is reversed (also see Chapter 35).

Mild or moderate pain after laparoscopic nephrectomy originates from the port insertion, the abdominal incision, pelvic organ manipulation, diaphragmatic irritation, and/or ureteral colic. Postoperative pain can be easily managed in most patients with supplemental intravenous opioids in the early postoperative period and later with oral opioids and acetaminophen. Nonsteroidal antiinflammatory drugs should be used with caution because of their potential prostaglandin-mediated adverse renal effects. Pain after open nephrectomy with subcostal lateral incision is severe and can last several days, which can limit the patient's efforts to breathe, cough, and move, leading to atelectasis and postoperative infection. Postoperative epidural analgesia should be considered for pain relief in these patients (also see Chapter 98).

Postdonation complications reported to the Organ Procurement and Transplantation Network (OPTN) within 6 weeks of surgery include the need for blood transfusion (0.4%), readmission (2.1%), interventional procedures (0.9%), and reoperation (0.5%).[59] A study of more than 80,000 living kidney donors showed a 90-day mortality of 3.1 per 10,000 donors (0.03%) and remains unchanged in the last 15 years.[65] Pulmonary embolism occurred in 0.1% of donors and is the main cause of mortality.[59] Kidney donors are at moderate risk for developing venous thromboembolism; therefore, intermittent pneumatic compression devices and prophylactic heparinization are recommended until ambulation. A decrease of approximately 30% in GFR can be expected after donation, and most donors will maintain a GFR greater than 60 mL/minute at 3 months.[62] Donor nephrectomy does not appear to increase long-term mortality or end-stage renal disease. Within the donor population, the likelihood of postdonation chronic kidney disease, hypertension, and diabetes is relatively higher among certain subgroups, such as African-American and obese donors, but the impact of unilateral nephrectomy on the lifetime risks of adverse events in these subgroups is unknown because the risks without nephrectomy have not been defined.[59]

LIVING LIVER DONOR

Living donor liver transplantation (LDLT) was first introduced in 1988 for pediatric recipients[66] and later expanded to adult recipients. Although LDLT is commonly performed in some Asian countries, it only consists of a small portion (<5%) of overall liver transplants performed in the United States.[1] The primary concern, that of harm to a healthy, altruistic donor, is greater in LDLT, compared with kidney donation.

The liver's remarkable reserve, coupled with its unique capacity to regenerate, forms the basis for LDLT. After resection of as much as two thirds of the liver, the donor's liver regains its original size in 2 to 3 weeks.[67] A portion of the adult liver (typically the left lobe or left lateral segment) transplanted to a pediatric recipient will grow with the recipient. Most LDLTs are electively performed in patients with chronic liver disease. Emergent LDLT is uncommon but is occasionally performed for acute liver failure. LDLT performed in patients with very advanced disease generates considerable debate.

The determination of donor liver volume and anticipated graft size is unique to LDLT. Formulas using demographics, including body weight, height, age, and sex, have been developed. Methods using radiologic or ultrasonic measurements also have been proposed.[68] Accurate estimation of donor liver volume and intended liver graft volume is critical to avoid small-for-size syndrome in the recipient and to preserve adequate remnant liver volume in the donor.[69] For pediatric LDLTs, the left lateral segment (segments II and III) or a total left hepatic lobectomy (segments II, III, and IV) is generally enough to provide sufficient liver mass (Fig. 75-5) (also see Chapter 93). From a surgical point of view, a left hepatectomy is less complex, and the duration of surgery is shorter. Since the first report in 2002, more living donor left lobectomies are performed using laparoscopy.[70] For adult-to-adult LDLT, right hepatic lobectomy is usually required. The surgical technique for right hepatectomy involves separation of the right hepatic lobes (segments V, VI, VII, and VIII) from the left (see Fig. 75-5). Compared with left hepatectomy, right hepatectomy is technically more challenging and associated with more perioperative risk. Right hepatectomy results in a graft weighing 500 to 1000 grams, which leaves the donor with approximately one third of the original liver mass. If one donor cannot provide sufficient liver mass, then a technique using two donors to one recipient has been reported.[71] For a small recipient, the left lobe of a large donor organ may suffice.

Anesthetic management starts with a preoperative discussion with the donor patient and family that addresses the risks and concerns associated with the procedure. Most transplant programs provide extensive educational materials, discussion, and support, beginning well before the day of surgery. General anesthesia with neuromuscular blockade is required for living liver donation surgery (also see Chapter 34). The patient is placed in a supine

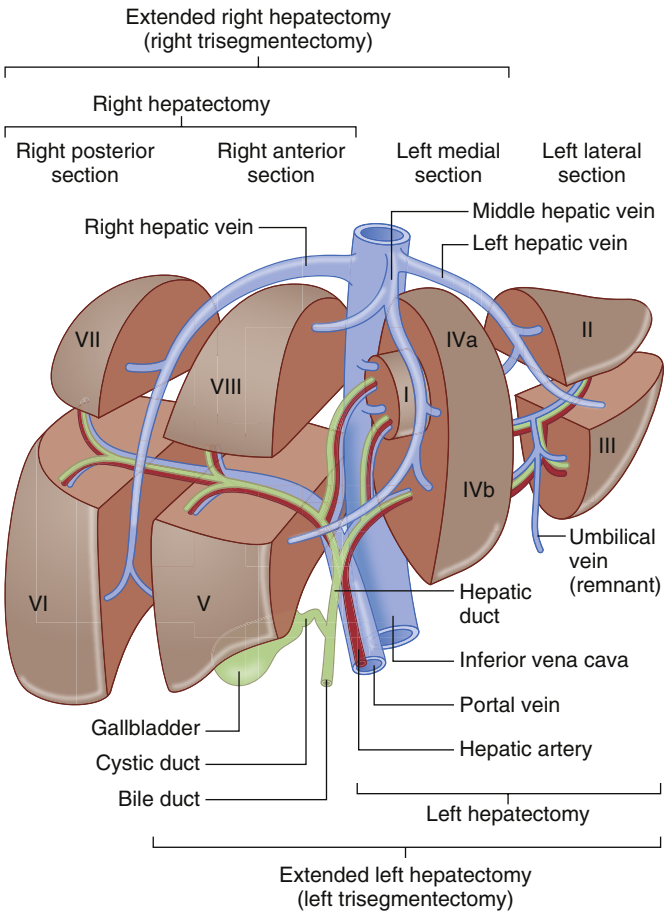


Figure 75-5. Segmental liver anatomy illustrates the segments resected during various partial hepatectomies. *(Redrawn from Steadman RH, Braunfeld M, Park H: Liver and gastrointestinal physiology. In Hemmings HC, Egan T, editors:* Pharmacology and physiology in anesthesia: foundations and clinical applications. *Philadelphia, 2013, Saunders, p 475-486.)*

position and intraoperatively uses the reverse Trendelenburg position to facilitate the exposure of the liver (also see Chapter 41). Two large-bore intravenous catheters are placed. Standard noninvasive monitors and arterial blood pressure monitoring are typically used. A nasogastric tube is placed for decompression of the stomach and surgical exposure.

An L-shaped or standard bilateral subcostal incision with a midline extension is frequently used in living donor surgery. During mobilization of the liver and its vasculature, manipulation of the liver occasionally results in decreased venous return to the heart with episodes of hypotension. The return of the liver to its orthotopic position will relieve the venous obstruction; alternatively, administering short-acting vasoactive agents and/or a fluid bolus will generally treat the problem. Most blood loss occurs during transection of the liver parenchyma. With surgical devices specifically designed for hepatectomy, blood loss during living donor hepatectomy is significantly reduced. After the vasculature of the donor lobe is clamped and divided, the graft is removed, and the vasculature and bile duct are oversewn. The abdomen is closed after hemostasis is achieved.

Blood loss during hepatectomy is a major concern and is associated with adverse outcomes. Placement of the CVP catheter and the use of low CVP (<5 cm H_2O) technique are advocated in some centers to reduce blood loss and transfusion requirements.[72] Low CVP reduces blood loss by increasing venous drainage from the hepatic sinusoids and decreasing blood backflow.[72] In addition, low CVP may reduce graft edema and improve postoperative graft function.[64] Low CVP is most often achieved by intravascular fluid restriction and sometimes by drugs, including diuretics and vasodilators.[72] Others consider the placement of a CVP catheter and low CVP technique unnecessary during hepatic resection surgery because of the inability to demonstrate a relationship between CVP and blood loss.[73] Other factors, including steatosis, body weight, and sex, may be more important than CVP in influencing blood loss during living donor hepatectomy.[74] Potential drawbacks of the low CVP technique are the risk of CVP catheter placement and difficulty reversing hemodynamic disturbances in the event of massive bleeding. Others point out that the use of low CVP originates from early experience with hepatectomy several decades ago, when blood loss was significant. With improved surgical techniques and equipment, blood loss during hepatectomy has been dramatically reduced, making CVP placement and monitoring unnecessary.[73,74] At the authors' institution, CVP placement is rarely used. Peripheral venous pressure measurements in the arm may be measured as an alternative to conventional CVP measurements.[75]

Several other blood-saving strategies have been used in living donor hepatectomy. These include cell salvage techniques and preoperative donation of 1 to 2 units of autologous blood, which reduces the chance of allogeneic blood transfusion (also see Chapter 63). Intraoperative isovolemic hemodilution with retrieval of 1 to 2 units of blood in the surgical unit can minimize the likelihood of blood transfusion.[76] The application of one or more of the blood-saving strategies previously listed is usually sufficient in the vast majority of patients.[73] After the graft is removed, excessive intravascular volume should be avoided because it may impede venous return and result in congestion of the remnant liver.[64]

Most living liver donors can be extubated at the end of the procedure in the surgical unit and transferred to the postoperative care unit. Discontinuation of mechanical ventilation reduces intrathoracic pressure, which reduces congestion in the remnant liver. Admission to the ICU is generally unnecessary but preferred in some institutions. Caution is required with the use of intravenous analgesics and opioids in the immediate postoperative period. The remnant liver is assumed to have some degree of insufficiency, although this assumption has not been thoroughly investigated.[64] Optimal perfusion of the remnant liver is achieved by the maintenance of adequate cardiac output and an avoidance of hypovolemia, anemia, and hypothermia-induced coagulopathy.[64]

The use of epidural anesthesia for postoperative pain control in living donor surgery remains controversial (also see Chapter 98). Similar to other upper abdominal surgery, postoperative epidural analgesia provides excellent pain control with less sedation, compared with intravenous patient-controlled analgesia.[77] By facilitating pulmonary toilet, epidural analgesia reduces the risk of respiratory infections. Despite these advantages, preoperative placement of a thoracic epidural catheter is routinely performed in some transplant centers and is entirely avoided in others. The difference of practice originates from the development of postoperative coagulopathy in patients after donor hepatectomy. Postoperatively, thrombocytopenia occurs while the prothrombin and activated partial thrombin times are prolonged. These changes peak on postoperative day 2 to 3, followed by a steady trend toward normalization in the following days.[78] Thus concern over the potential development of an epidural hematoma is the basis for avoiding epidural catheter placement. Several studies examining the use of the epidural catheter in this population report no adverse effects. In a study of 755 donors who received an epidural catheter for postoperative pain management, no complications associated with the epidural catheter were reported.[79] Another study including 242 living liver donors also showed that epidural analgesia seems to be a safe option when carefully used.[78] Another piece of evidence supporting epidural placement is that hypercoagulability, not hypocoagulability measured by thromboelastography (TEG), can develop in the majority of patients after hepatectomy.[80] Despite the low overall incidence of epidural hematoma, these studies are criticized for a lack of power to assess the risk of this rare event. If the epidural catheter is placed, then the catheter should not be removed until satisfactory coagulation parameters have been retained, which usually takes 3 to 5 days.[64] If the epidural catheter is not placed, then patient-controlled analgesia is used. The choice of pain-control strategy is influenced by the patient's expectations, surgical preferences, institutional consensus, postoperative monitoring capabilities, and nursing staff familiarity with the various techniques.

Worldwide, a number of LDLT-related donor complications, including mortality, have been reported.[81,82]

A recent multicenter observational study of 760 adult-to-adult LDLTs with up to 12 years of follow-up revealed that 40% of donors had complications (Table 75-4).[83] A total of 19% of donors had more than one complication. Although most of the complications were not associated with residual disability, some were severe. Infection is the most common complication and biliary complications such as bile leaks or stricture can be difficult to treat and can lead to prolonged hospital stays with the possibility of further surgery. Higher preoperative creatinine levels, intraoperative hypotension, and intraoperative transfusion are associated with donor complications. Increased institutional experience is not associated with decreased complications.[81] One report of 1263 living donor hepatectomies found that donors who had a right hepatectomy had higher complication rates than donors who underwent left hepatectomy surgery.[64,82]

LIVING LUNG DONOR

Living lung transplantation is an alternative to deceased lung transplantation. Typically, two donors are used for one recipient in living lung transplantation, although the use of a single living donor has been reported.[84] If two donors are involved, then careful coordination and timing of the anesthetic induction of the two donors and recipient are required. The right lower lobe of one donor and the left lower lobe of the second donor are implanted in the recipient in place of the whole right and left lungs. Donor lobectomy requires sufficient bronchial, arterial, and vein cuffs to permit successful anastomoses. A bronchial air leak can result in a prolonged need for chest tube drainage, which lengthens hospital stay.

After the induction of general anesthesia, a single-lumen endotracheal tube is usually placed initially to facilitate fiberoptic bronchoscopic examination before incision. Once a decision is made to proceed, a left-sided double-lumen endotracheal tube later replaces the single-lumen endotracheal tube. Standard noninvasive monitors, intraarterial blood pressure monitoring, and capnography may be sufficient. After placing the donor in the lateral decubitus position and rechecking the double-lumen tube position by fiberoptic bronchoscope, a thoracotomy is performed. Intraoperative cardiorespiratory and metabolic homeostasis minimizes the risk of postoperative complications. Prostaglandin E_1 is usually intravenously administered to dilate the pulmonary vessels with titration according to systemic blood pressure (hypotension needs to be avoided). After mobilization is complete, the lung is reinflated for 5 to 10 minutes, followed by the administration of heparin and a steroid. Transection of the lung is performed after the lung is recollapsed.

Thoracic epidural analgesia is a useful adjunct for perioperative care. The epidural catheter may be placed hours before surgery.[64] Although this approach may be questionable in patients undergoing heparinization, the superiority of postoperative analgesia and the avoidance of atelectasis and infection appear to justify the risk of donor epidural catheterization.[85]

TABLE 75-4 **TYPE AND FREQUENCY OF COMPLICATIONS OF LIVING LIVER DONORS**

Complications	Frequency (%)
Infections	13.2
Pleural effusion	11.0
Bile leak or biloma	8.1
Incisional hernia	6.6
Psychologic difficulty	5.6
Neuropraxia	3.4
Ascites	2.8
Unplanned reexploration	2.7
Pulmonary edema	2.1
Bowel obstruction	1.6
Intraabdominal abscesses	1.2
Pulmonary embolism	1.0
Pneumothorax	0.8
Deep vein thrombosis	0.8
Biliary stricture	0.7
Portal vein thrombosis	0.5
Inferior vena cava thrombosis	0.4
Total	**40**

Modified from Abecassis MM, Fisher RA, Olthoff KM, et al: Complications of living donor hepatic lobectomy—a comprehensive report, Am J Transpl *12:1208-1217, 2012*

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Chapter 76

Brain Death

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Key Points

- The first description of cessation of brain functions using a concept similar to the modern definition of brain death appeared in 1959, although the subject became more controversial after the development of organ transplantation. Criteria for brain death were first published in 1968, a year after the first heart transplantation. Although cultural and religious diversity may lead to great differences in attitudes toward brain death and no global consensus in diagnostic criteria exists, the concept of brain death as defining the death of the individual is widely accepted and many countries have published recommendations or legal requirements for the diagnosis of brain death, particularly as a necessary prerequisite for organ donation.
- The traditional concept of death has used the cessation of cardiac and respiratory functions as its basis because of the acceptance of simple and nonmedical concepts: that life begins with the first inspiration after birth, that death comes with the last expiration, and that cardiac activity ceases within a few minutes of the last expiration. In contrast, the modern concept of brain death adopts the conclusions of modern biologic science (central integrator theory of the brain): that the central nervous system (CNS), including the brainstem, is the control center for the living organism; that cessation of CNS functions represents cessation of the harmony of life; and that without CNS control, the living organism is nothing more than an aggregation of living cells. However, this notion has become controversial, because not all brain-dead patients inevitably deteriorate to cardiovascular collapse in a short time and they can assimilate nutrients, fight infections, heal wounds, and carry out a pregnancy.
- Trauma to the brain or cerebrovascular injury produces brain edema. Because the brain is covered by a rigid bony skull, edema is accompanied by an increase in intracranial pressure, which, if sufficiently high, exceeds arterial blood pressure. When cerebral circulation ceases, aseptic necrosis of the brain ensues. Within 3 to 5 days, the brain becomes a liquefied mass. Such increased intracranial pressure compresses the entire brain, including the brainstem, and total brain infarction follows.
- Clinical studies indicate that hypothalamic and anterior pituitary functions are preserved to some degree for a certain period after the onset of brain death. The response of the immune system to stimulation is modified considerably after total and irreversible loss of CNS functions. Hormonal changes and inflammatory responses after brain death are the theoretical and scientific basis of hormonal therapy for hemodynamic stabilization of brain-dead organ donors.
- During the process of brain death after head injury or intracranial bleeding, intracranial pressure increases and compression of the brainstem leads to marked hypertension and bradycardia (i.e., Cushing phenomenon). At the onset of brain death by tonsillar herniation, sudden decrease of arterial blood pressure occurs, but the arterial pressure gradually returns to normal with the spinal cord gaining automaticity.
- Determination of brain death confirms the irreversible cessation of all functions of the entire brain, including the brainstem. Irreversibility means that no treatment may be reasonably expected to change the condition. Although testing all functions of the brain is conceptually impossible, the cessation of all functions of the brain is practically determined by loss of consciousness, loss of brainstem responses, apnea, and confirmatory tests.

KEY POINTS—cont'd

- Cerebral death, the so-called persistent vegetative state, refers to cessation of the functions of the cerebral cortices. It is not the equivalent of death.
- It is true that cultural and religious diversities may affect the notion of death, but there is a significant variability in policies and practices for determining brain death internationally and even among states and hospitals.
- Tests to confirm brain death include an electroencephalogram, evoked responses, and measurement of blood flow.
- The concept of brain death has been developed with the development of organ transplantation. The "dead-donor rule," which requires that patients must be declared dead before the removal of any life-sustaining organs and the retrieval of organs for transplantation should not cause the death of a donor, is the ethical and legal axiom.
- Because of a critical shortage of organs for transplantation, not only donation after brain death but also donation after circulatory death has been increasing.
- Because of their intact spinal cord and the presence of somatic and visceral reflexes, brain-dead patients require special anesthetic management, including use of muscle relaxants, vasodilators, and perhaps sedation and analgesia. Anesthesiologists should understand the medical and legal definitions of death and the ethical concepts behind them.

INTRODUCTION

Because advancements in medicine have changed the definition and concept of death, legislation also must change accordingly. This issue results from progress in organ transplantation and the increasing number of patients who have a living body but nonfunctioning brain, which is a consequence of discoveries in resuscitative and life support techniques. Such refinements in critical care medicine mean that neurologists, neurosurgeons, and anesthesiologists must be able to make an appropriate diagnosis of death. Although cultural and religious diversity may lead to great differences in attitudes toward brain death and no global consensus exists on diagnostic criteria, the concept of brain death as defining the death of the individual is widely accepted[1,2] and many countries have published recommendations or legal requirements for the diagnosis of brain death as a necessary prerequisite for organ donation.[3,4]

HISTORY

In 1902, Cushing[5] first reported cessation of cerebral circulation when intracranial pressure exceeded arterial blood pressure in monkeys. He also described the use of artificial ventilation to prolong cardiac function for 23 hours after cessation of spontaneous respiration in a patient with a brain tumor. In 1959, Bertrand and colleagues[6] reported the maintenance of respiration by mechanical means for 3 days after death of a patient with otitis media who had circulatory collapse. Repeated seizures had preceded a deep coma. Autopsy revealed extensive brain necrosis of the cerebral and cerebellar cortices, basal ganglia, and brainstem nuclei, which was attributed to cessation of cerebral circulation during artificial ventilation. Wertheimer and colleagues[7] proposed criteria for new clinical states, "death of the nervous system." Also in 1959 appeared the first description of cessation of brain functions using a concept similar to the modern definition of brain death (i.e., *le coma dépassé* or irretrievable coma) by Mollaret and co-workers.[8] Mollaret and Goulon[8] differentiated coma depasse from other coma states, such as vegetative state.

These historical reports support the argument that the concept of brain death is independent of and was established before the start of organ transplantation from brain-dead patients. The heated discussion on brain death started after the first heart implantation by Barnard in 1967, in which the heart was procured after circulatory-determined death in a patient who satisfied criteria for coma depasse. One year later, the ad hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death published its criteria for brain death and defined "irreversible coma as a new criterion for death."[9] The committee deliberations focused on a whole-brain formulation to define brain death. The criteria of "irreversible coma" include (1) unreceptivity and unresponsitivity, (2) no movements or breathing, (3) no reflex, (4) flat electroencephalogram (EEG), and (a) all of these tests shall be repeated at least 24 hours with no change, and (b) exclusion of hypothermia (below 90° F [32.2° C]) or central nervous system (CNS) depressants. In 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research[10] defined the brain as the "primary organ" and justified the application of a whole-brain definition for brain death in the United States. The whole-brain formulation of brain death was acknowledged by statute in the *Uniform Determination of Death Act* (UDDA)[11] by stating that "an individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions or (2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made in accordance with accepted medical standards." This formulation is the one most commonly applied worldwide and forms the foundation for legal codification in many

Western nations. Numerous criteria on brain death have been offered by institutions, state agencies, expert groups, and governments.[1,2,4,12,13] The American Academy of Neurology (ANN) published guidelines for determining brain death in adults in 1995.[12] Guidelines for pediatric patients were published in 1987 by a multisociety task force.[14]

After the publication of UDDA by the President's Commission, there remains considerable controversy whether "brain death" can be defined as the death of a human being, because procurement of organs for transplantation is permitted from the brain-dead patients and medical interventions for brain-dead patients should (can) be withdrawn for medical futility and considering the dignity of the patients' end of life. In 2008, the President's Council on Bioethics published a white paper ("Controversies in the Determination of Death")[15] addressing the issues regarding brain death. The white paper proposed a new term, *total brain failure,* instead of *whole brain death.* Critics have argued that the whole brain is not dead in patients who satisfied the criteria of brain death. One example is the possible presence of integrated neuroendocrine function; such as the persistent release of pituitary hormones like prolactin, growth hormone, luteinizing hormone, and thyroid-stimulating hormone. Second is existence of cases showing remaining electroencephalographic activity, uptake of radioactive material on cerebral blood flow studies, or blood flow in the cerebral angiograms. The white paper also abandoned the concept of "the somatic integration" and the assumption that the brain is the "integrator" of somatic function. The brain has been considered as an integrator of the body, and the brain is necessary for the functioning of the organism as a whole. Therefore, "a patient on a ventilator with a totally destroyed brain is merely a group of artificially maintained subsystems since the organism as a whole has ceased to function." However, this rationale was criticized by Shewmon[16-18] with presentation of cases of persistent homeostasis of liver, kidneys, cardiovascular and endocrine systems, maintenance of body temperature, wound healing, defense functions against infections and foreign bodies (immune system), development of a febrile response to infection, cardiovascular and hormonal stress responses to unanesthetized incision for organ retrieval, successful gestation of a fetus in a brain-dead pregnant woman, sexual maturation of a brain-dead child, and proportional growth of a brain-dead child. The white paper developed a new account of wholeness of a living organism as fundamental work. "Determining whether an organism remains a whole depends on recognizing the persistence or cessation of the fundamental vital work of a living organism—the work of self-preservation, achieved through the organism's need-driven commerce with the surrounding world."[15]

The guidelines for determining brain death in adults and in pediatrics were updated in 2010[19] (Box 76-1) and 2011[20] (Boxes 76-2 and 76-3), respectively.

BOX 76-1 ***Checklist for Determination of Brain Death***

Prerequisites (All Must be Checked)

1. Coma, irreversible and cause known
2. Neuroimaging explains coma
3. Central nervous system depressant drug effect absent (if indicated, toxicology screen; if barbiturates given, serum level <10 μg/mL)
4. No evidence of residual paralytics (electrical stimulation if paralytics used)
5. Absence of severe acid-base, electrolyte, endocrine abnormality
6. Normothermia or mild hypothermia (core temperature >36° C)
7. Systolic blood pressure >100 mm Hg
8. No spontaneous respirations

Examination (All Must be Checked)

1. Pupils nonreactive to bright light
2. Cornea reflex absent
3. Oculocephalic reflex absent (tested only if C-spine integrity ensured)
4. Oculovestibular reflex absent
5. No facial movement to noxious stimuli at supraorbital nerve or temporomandibular joint
6. Gag reflex absent
7. Cough reflex absent to tracheal suctioning
8. Absence of motor response to noxious stimuli in all four limbs (spinally mediated reflexes are permissible)

Apnea Testing (All Must be Checked)

1. Patient is hemodynamically stable
2. Ventilator adjusted to provide normocarbia ($Paco_2$ 34 to 45 mm Hg)
3. Patient preoxygenated with 100% FiO_2 for >10 minutes to PaO_2 >200 mm Hg
4. Patient well-oxygenated with a PEEP of 5 cm H_2O
5. Provide oxygen via a suction catheter to the level of the carina at 6 L/min or attach T-piece with CPAP at 10 cm H_2O
6. Disconnect ventilator
7. Spontaneous respirations absent
8. Arterial blood gas drawn at 8 to 10 minutes, patient reconnected to ventilator
9. Pco_2 >60 mm Hg or 20–mm Hg rise from normal baseline value

OR

10. Apnea test aborted

Ancillary Testing (Only One To Be Performed; To Be Ordered Only If Clinical Examination Cannot Be Fully Performed Because of Patient Factors or If Apnea Testing Inconclusive or Aborted)

1. Cerebral angiogram
2. HMPAO SPECT
3. EEG
4. TCD

Time of death (DD/MM/YY): _____
Name of physician and signature: _____
_____

Wijdicks EFM, Valelas PN, Gronseth GS, Greer DM: Evidence-based guideline update: determining brain death in adults—report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology *74:1911, 2010.*

EEG, Electroencephalogram; *HMPAO,* hexamethylpropyleneamine-oxime; *SPECT,* single photon emission computed tomography; *TCD,* transcranial Doppler ultrasonography.

BOX 76-2 ***Summary Recommendations for the Diagnosis of Brain Death in Neonates, Infants, and Children***

1. Determination of brain death in neonates, infants, and children relies on a clinical diagnosis based on absence of neurologic function with a known irreversible cause of coma. Coma and apnea must coexist to diagnose brain death. This diagnosis should be made by physicians who have evaluated the history and completed the neurologic examinations.
2. Prerequisites for initiating a brain death evaluation are as follows:
   a. Hypotension, hypothermia, and metabolic disturbances that could affect the neurologic examination must be corrected before examination for brain death.
   b. Sedatives, analgesics, neuromuscular blockers, and anticonvulsant agents should be discontinued for a reasonable period based on elimination half-life of the pharmacologic agent to ensure they do not affect the neurologic examination. Knowledge of the total amount of each agent (milligram per kilogram) administered, because hospital admission may provide useful information concerning the risk for continued medication effects. Blood or plasma levels to confirm high or supratherapeutic levels of anticonvulsants with sedative effects that are not present should be obtained (if available) and repeated as needed or until the levels are in the low to midtherapeutic range.
   c. The diagnosis of brain death based on neurologic examination alone should not be made if supratherapeutic or high therapeutic levels of sedative agents are present. When levels are in the low or in the midtherapeutic range, medication effects sufficient to affect the results of the neurologic examination are unlikely. If uncertainty remains, an ancillary study should be performed.
   d. Assessment of neurologic function may be unreliable immediately after cardiopulmonary resuscitation or other severe acute brain injuries, and evaluation for brain death should be deferred for 24 to 48 hours or longer if concerns exist or inconsistencies are found in the examination.
3. Number of examinations, examiners, and observation periods:
   a. Two examinations, including apnea testing with each examination separated by an observation period, are required.
   b. The examinations should be performed by different attending physicians involved in the care of the child. The apnea test may be performed by the same physician, preferably the attending physician who is managing ventilator care of the child.
   c. Recommended observation periods are as follows:
      (1) 24 Hours for neonates (37 weeks of gestation to term infants 30 days of age)
      (2) Twelve hours for infants and children (>30 days to 18 years)
   d. The first examination determines the child has met neurologic examination criteria for brain death. The second examination, performed by a different attending physician, confirms that the child has fulfilled criteria for brain death.
   e. Assessment of neurologic function may be unreliable immediately after cardiopulmonary resuscitation or other severe acute brain injuries and evaluation for brain death should be deferred for 24 to 48 hours if concerns exist or inconsistencies are found in the examination.
4. Apnea testing:
   a. Apnea testing must be performed safely and requires documentation of an arterial $Paco_2$ 20 mm Hg above the baseline $Paco_2$ and 60 mm Hg or greater with no respiratory effort during the testing period to support the diagnosis of brain death. Some infants and children with chronic respiratory disease or insufficiency may be responsive only to supranormal $Paco_2$ levels. In this instance, the $Paco_2$ level should increase to 20 mm Hg or greater above the baseline $Paco_2$ level.
   b. If the apnea test cannot be performed because of a medical contraindication or cannot be completed because of hemodynamic instability, desaturation to less than 85%, or an inability to reach a $Paco_2$ of 60 mm Hg or greater, an ancillary study should be performed.
5. Ancillary studies:
   a. Ancillary studies (electroencephalography and radionuclide cerebral blood flow) are not required to establish brain death unless the clinical examination or apnea test cannot be completed.
   b. Ancillary studies are not a substitute for the neurologic examination.
   c. For all age groups, ancillary studies can be used to assist the clinician in making the diagnosis of brain death, to reduce the observation period, or when (1) components of the examination or apnea testing cannot be completed safely as a result of the underlying medical condition of the patient; (2) uncertainty exists about the results of the neurologic examination; or (3) if a medication effect may interfere with evaluation of the patient. If the ancillary study supports the diagnosis, the second examination and apnea testing can then be performed. When an ancillary study is used to reduce the observation period, all aspects of the examination and apnea testing should be completed and documented.
   d. When an ancillary study is used because there are inherent examination limitations (i.e., points 1 to 3 in 5c), components of the examination done initially should be completed and documented.
   e. If the ancillary study is equivocal or concern exists about the validity of the ancillary study, the patient cannot be pronounced dead. The patient should continue to be observed until brain death can be declared on clinical examination criteria and apnea testing or a follow-up ancillary study can be performed to assist with determination of brain death. A waiting period of 24 hours is recommended before further clinical reevaluation or repeat ancillary study is performed. Supportive patient care should continue during this period.
6. Declaration of death:
   a. Death is declared after confirmation and completion of the second clinical examination and apnea test.
   b. When ancillary studies are used, documentation of components from the second clinical examination that can be completed must remain consistent with brain death. All aspects of the clinical examination, including the apnea test, or ancillary studies must be appropriately documented.
   c. The clinical examination should be carried out by experienced clinicians who are familiar with infants and children and have specific training in neurocritical care.

From Nakagawa TA, Ashwqal S, Mathur M, et al; Society of Critical Care Medicine; Section on Critical Care and Section on Neurology of the American Academy of Pediatrics; Child Neurology Society: Guidelines for the determination of brain death in infants and children: an update of the 1987 Task Force recommendations. Crit Care Med *39:2139–2155, 2011.*

BOX 76-3 ***Neurologic Examination Components to Assess for Brain Death in Neonates, Infants, and Children, Including Apnea Testing***

Reversible conditions or conditions that can interfere with the neurologic examination must be excluded before brain death testing.

1. Coma. The patient must exhibit complete loss of consciousness, vocalization, and volitional activity.
   a. Patients must lack all evidence of responsiveness. Eye opening or eye movement to noxious stimuli is absent.
   b. Noxious stimuli should not produce a motor response other than spinally mediated reflexes. The clinical differentiation of spinal responses from retained motor responses associated with brain activity requires expertise.
2. Loss of all brainstem reflexes, including:
   a. Midposition or fully dilated pupils that do not respond to light. Absence of pupillary response to a bright light is documented in both eyes. Usually the pupils are fixed in a midsize or dilated position (4 to 9 mm). When uncertainty exists, a magnifying glass should be used.
   b. Absence of movement of bulbar musculature, including facial and oropharyngeal muscles. Deep pressure on the condyles at the level of the temporomandibular joints and deep pressure at the supraorbital ridge should produce no grimacing or facial muscle movement.
   c. Absent gag, cough, sucking, and rooting reflex. The pharyngeal or gag reflex is tested after stimulation of the posterior pharynx with a tongue blade or suction device. The tracheal reflex is most reliably tested by examining the cough response to tracheal suctioning. The catheter should be inserted into the trachea and advanced to the level of the carina, followed by one or two suctioning passes.
   d. Absent corneal reflexes. Absent corneal reflex is demonstrated by touching the cornea with a piece of tissue paper, a cotton swab, or squirts of water. No eyelid movement should be seen. Care should be taken not to damage the cornea during testing.
   e. Absent oculovestibular reflexes. The oculovestibular reflex is tested by irrigating each ear with ice water (caloric testing) after the patency of the external auditory canal is confirmed. The head is elevated to 30 degrees. Each external auditory canal is irrigated (one ear at a time) with approximately 10 to 50 mL of ice water. Movement of the eyes should be absent during 1 minute of observation. Both sides are tested with an interval of several minutes.
3. Apnea. The patient must have the complete absence of documented respiratory effort (if feasible) by formal apnea testing demonstrating a $Paco_2$ 60 mm Hg or greater and 20 mm Hg or greater increase above baseline.
   a. Normalization of the pH and $Paco_2$ measured by arterial blood gas analysis, maintenance of core temperature above 35° C, normalization of blood pressure appropriate for the age of the child, and correcting for factors that could affect respiratory effort are a prerequisite to testing.
   b. The patient should be preoxygenated using 100% oxygen for 5 to 10 minutes before initiating this test.
   c. Intermittent mandatory mechanical ventilation should be discontinued once the patient is well oxygenated and a normal $Paco_2$ has been achieved.
   d. The patient's heart rate, blood pressure, and O_2 saturation should be continuously monitored while observing for spontaneous respiration effort throughout the entire procedure.
   e. Follow-up blood gases should be obtained to monitor the rise in $Paco_2$ while the patient remains disconnected from mechanical ventilation.
   f. If no respiratory effort is observed from the initiation of the apnea test to the time the of measured $Paco_2$ 60 mm Hg or greater and 20 mm Hg or greater above the baseline level, the apnea test is consistent with brain death.
   g. The patient should be placed back on mechanical ventilator support, and medical management should continue until the second neurologic examination and apnea test confirming brain death is completed.
   h. If oxygen saturations fall below 85%, hemodynamic instability limits completion of apnea testing, or a $Paco_2$ level of 60 mm Hg or greater cannot be achieved, the infant or child should be placed back on ventilator support with appropriate treatment to restore normal O_2 saturations, normocarbia, and hemodynamic parameters. Another attempt to test for apnea may be performed at a later time, or an ancillary study may be pursued to assist with determination of brain death.
   i. Evidence of any respiratory effort is inconsistent with brain death, and the apnea test should be terminated.
4. Flaccid tone and absence of spontaneous or induced movements, excluding spinal cord events such as reflex withdrawal or spinal myoclonus.
   a. The patient's extremities should be examined to evaluate tone by passive range of motion, assuming that no limitations exist to performing such an examination (e.g., previous trauma) and the patient is observed for any spontaneous or induced movements.
   b. If abnormal movements are present, clinical assessment to determine whether these are spinal cord reflexes should be done.

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In contrast, brainstem definition for brain death was first pronounced in 1976 by the Conference of Medical Royal Colleges and their Faculties in the United Kingdom.[21] The document in 1995 entitled "Criteria for the Diagnosis of Brain Stem Death"[22] encouraged the use of the more correct term *brainstem death* rather than *brain death* and gave a definition of death, stating that "death is defined as the irreversible loss of the capacity for consciousness, combined with the irreversible loss of the capacity to breathe."

In Japan, brain death can be determined only for organ transplantation donor candidates in law, and death of individuals can be diagnosed with the traditional criteria in other situations.

TRADITIONAL CONCEPT OF DEATH OF AN ORGANISM

In Greek antiquity, two concepts existed regarding the body cavity, where "the principle of life," now known as "function of the brain," was housed. One is that of Plato, and another is Aristotle's. Plato first postulated the tripartite soul in the *Republic* and *Timaeus*. The first part is the

reason, the second is emotion, and the third is appetite or desire. Reason, which we might today call consciousness, is the reappearance of the God's soul (the divine), housed in the ideally shaped vessel, in which all distances from the center are the same (i.e., the head). The second soul, emotion, is located in the heart. It affects circulation, and its manifestations—such as pulse rate—are functions that correlate with what we think of as the autonomic nervous system. The neck is constructed as a kind of isthmus or boundary between the head and the chest to ensure that reason is not affected by emotion. The third part of the soul—that is, the appetite for food and drink or sexual desire—is the least noble part. It is housed in the stomach, separated from the heart by the diaphragm and thought to be punished by the bitterness of bile. However, we cannot interpret this too literally, because it was meant to be a sort of analogy for consumption by the ordinary citizen. Plato considered death to be the separation of reason from the mortal body, whereas Socrates, in his *Apology,* confessed that he did not know the fate of reason after death. The vegetative state in today's neurophysiology, is, according to Plato, the equivalent of death.

Unlike Plato, Aristotle, who is known as the founding father of genetics, stressed experience, or empirical knowledge, rather than abstract thinking. Aristotle postulated that all functions of the brain were housed in the heart, which he considered the most important organ of the body—the seat of the intelligence and the origin of motion and sensation. Other organs surrounding it, such as the brain and lungs, existed simply to cool the heart. Aristotle dissected dogs, horses, grasshoppers, crickets, and other living creatures to understand the reasons why, for instance, dogs cannot give birth to horses. He thought that animals "cook" foods in their digestive tracts and that blood transports nutrients to each organ from the heart. This transport corresponds to the electrical signals in the nerves in today's neurophysiology. According to Aristotle, the lungs cool the heart and the cranium serves as a cooling apparatus for liquefying a transmitter, a kind of "pneuma."

In Aristotle's system, the vehicle that conveys commands from the control center to the peripheral organs and tissues, roughly equivalent to the electrical signals of the nervous system in today's neurophysiology, was assumed to be something like vapor or gas. This concept is the basis from which the idea of "pneuma" (breath or spirit) originates. God created man (Adam) out of the dust of the earth and inspired the breath of life into his nostrils, and a man became a living soul. Later, Eve was created from Adam's rib and, with God's breath, became a living soul as well. This story might call to mind the first cry of the neonate, which is the first activity of life caused by the God's "inspiration." This creative breathing, or inspiration, is the subject of Botticelli's painting *The Birth of Venus,* in which Zephyr, the west wind, puffs vigorously as his wife Chloris gently blows her warm breath on Venus, who stands on a shell. Aristotle's idea postulating the heart as the principal seat of the spirit had a profound influence on Western scientific thought for a long period. William Harvey's discovery, described in his *Circulation of Blood* (1628) is considered as the final scientific development of Aristotle's ideas, and Aristotle is the thinker most cited in Harvey's book.

All living organisms take in oxygen by respiration, distribute the O_2 to peripheral tissues through circulation, and then excrete metabolites by means of the circulation and through respiration. Respiration and circulation are vital to the living organism. Respiration is the functional expression of the brainstem, and cessation of brainstem functions leads to the cessation of respiration. Because the brainstem maintains its function through its supply of O_2 and nutrients, cessation of circulation ultimately leads to cessation of respiration. The functions of the brain, heart, and lungs are mutually dependent and share the basic role of maintaining life. An organism dies when one of these life-sustaining organ systems ceases to function. The traditional concept of death of an organism emphasized the cessation of respiration or circulation, without consideration of the role of the brain. This occurred because assessment of brain function was not easy to accomplish. When mechanical ventilation was not widely used, cessation of brain functions related directly to cessation of respiration and assessment of brainstem functions was unnecessary.

THE CONCEPT OF BRAIN DEATH

Brain death represents death of the organism and not merely death or necrosis of the brain in a living body. The organism is an aggregation of living cells, although an aggregation of living cells does not necessarily constitute an organism. An organism exists only when the cell aggregation is under the control of modulating systems such as the CNS, the endocrine system, and the immune system. After any one of these systems ceases to function, death is inevitable unless artificial measures can be taken. The physiologic significance of brain death and cardiac death is essentially equal, and both represent an irreversible loss of communication between the control center and peripheral cells and tissues, as well as loss of modulation of an aggregation of cells. Without these systems, harmonious functioning of individual cells as constituents of the whole organism ceases. Because total and irreversible elimination of immune or endocrine function is not of practical significance, the concept of endocrine or immune death has not developed.

Brain-oriented death can have three forms, defined by the structures (1) whole-brain death, (2) brainstem death, and (3) neocortical death.[23] Whole-brain death and brainstem death are different in their anatomic interpretation, but both are defined as the irreversible cessation of the organism as a whole. Critical roles of brainstem to maintain "life" are well known.[24] Brainstem is (1) the through-station for almost all hemispheric input and output, (2) the center that generates arousal (which is essential for consciousness), and (3) the center of respiration. Further, brain lesion (caused by massive traumatic injury, intracranial hemorrhage, or anoxia) mostly progresses from thalami to the brainstem with increased intracranial pressure. The brainstem is often the last structure to be injured in brain damage. Therefore, brainstem death, which is diagnosed with irreversible (1) loss of consciousness, (2) loss of brainstem reflexes, and (3) apnea, can be defined as death of a human being. Possibly, most of

the brain functions vital to life could be replaced with computers and drugs and the circulatory functions maintained for months or years. The only function advanced technology cannot provide is that constituting humanity or personality, both of which are possibly products of the telencephalon. Therefore, "loss of personality" can be defined with irreversible coma and loss of the capacities for thought, reason, and feeling (irreversible loss of critical cerebral function, or neocortical death). However, it is impossible to ascertain scientifically the inward state of an individual. A case was reported in which functional magnetic resonance imaging (fMRI) revealed retaining the ability to understand spoken commands and to respond to them through brain activity in a patient fulfilling the clinical criteria for a diagnosis of vegetative state.[25] Neocortical death should and can be clearly differentiated from brain death, and it should not be regarded as death of a human being.

MECHANISM OF BRAIN DEATH

Brain injury has a number of sources, such as traumatic or cerebrovascular injury and generalized hypoxia, all of which produce brain edema. Based on the pathologic mechanisms involved, brain edema is classified as vasogenic or cytotoxic.[26] Because it is rare that only one mechanism operates exclusively, the label of vasogenic or cytotoxic is only relative. Vasogenic edema is induced by an increase in cerebrovascular permeability after leaking of serum proteins into the brain parenchyma (i.e., after destruction of the blood-brain barrier). Chemical mediators such as histamine, serotonin, angiotensin, bradykinin, and prostaglandins can disrupt blood-brain barrier function.[27] Cytotoxic brain edema occurs in hypoxic and ischemic conditions and results from disturbance of cellular osmoregulation, a process that depends primarily on energy-dependent functioning of ionic pumps. The disturbance of osmoregulation increases entry of water into brain parenchyma. Although in a pure form of cytotoxic edema the blood-brain barrier would remain basically intact, cytotoxic edema would nevertheless disturb blood flow and induce hypoxia and vasogenic edema. Recent studies have revealed that water channels, aquaporins (AQPs), play important roles in the brain edema formation and resolution after brain injury. AQP4, the most abundant AQP in the CNS, may have dual effects on the brain edema formation and resolution. In the early stage it may facilitate edema formation, but at later points it may be important for the clearance of water from the brain into blood vessels.[28]

Brain edema may be focal at first, but it then spreads throughout the whole brain in a predictable sequence. Because the brain is covered by a rigid bony skull, its edema is accompanied by an increase in intracranial pressure. The critical cerebral perfusion pressures (CPPs) are in the range of 10 to 20 mm Hg (CPP = mean arterial pressure [MAP] – intracranial pressure). Cerebral blood perfusion is lost with less than these critical CPPs (see also Chapters 17 and 70). When cerebral circulation ceases, aseptic necrosis of the brain ensues. Within 3 to 5 days, the brain becomes a liquefied mass, a condition known as respirator brain.[29] Such increased intracranial pressure compresses the entire brain, including the brainstem, and uncal and tonsillar herniation and total brain infarction follow.[30] Brain damage mostly progresses from the thalami to the lower medulla, although not necessarily in a gradual fashion. The medulla oblongata has the longest survival time, and that important finding places emphasis on damage to the lower centers to determine brain death.[31] On the other hand, aside from the usual first pattern of brain death, in which CPP fell to the critical level, Palmer and Bader[32] found the second pattern, in which the intracranial pressure did not exceed the MAP with maintenance of CPP, using brain tissue oxygenation ($Pbto_2$). They suggested that the mechanism for fall in $Pbto_2$ to 0—that is, brain death—might have been primary metabolic failure of the brain.

Brainstem lesion that spares the thalami and cerebral cortex can exist with a hemorrhagic origin. In that case, brainstem death in the absence of clinical brainstem functions despite intact intracranial circulation can be declared by the U.K. criteria. However, such cases with absence of all brainstem functions with apnea but some residual functions of arousal (ascending reticular activating system [RAS]), which is clinically undetected, have never been reported.[23]

NEUROPHYSIOLOGIC BASIS OF BRAIN DEATH

AREAS OF THE BRAIN INVOLVED IN BRAIN DEATH

By definition, brain death is a total irreversible cessation of functioning of the brain. However, "the whole brain" does not require the irreversible cessation of functioning of every brain neuron. Rather, it requires only the irreversible cessation of all clinical functions of the brain, namely, those measurable at the bedside by clinical examination.[2] The brain includes all the CNS structures except the spinal cord. It is generally agreed that brain death does not include lower portions of the spinal cord (caudal from C2), because their location outside the skull spares them from compression during brain edema. Histologic studies of human spinal cord in cases of brain death revealed divergent pathologic findings ranging from histologically intact tissues to complete destruction.[29]

The United Kingdom[21,22,33] and some other countries[3,4] supported a rather exceptional criterion for brain death, one that excludes involvement of the bilateral cerebral cortices. This state, known as brainstem death, does not require recording of an EEG for its diagnosis. In the United Kingdom, no confirmatory test (including an EEG) is required.[34] Grigg and colleagues[35] reported that 11 of 56 clinically brainstem-dead patients (19.6%) had electroencephalographic activity and 2 patients (3.6%) even demonstrated sleeplike cortical electroencephalographic activity for as long as 168 hours, although none of the patients recovered.[35] The rationale for excluding the cerebral cortices is based on the facts that the brainstem, not the cerebral cortices, plays the major role in controlling whole-body vital activities such as respiration,

circulation, and other homeostatic functions and that the reticular formation forms the basis of consciousness. However, some investigators strongly recommend confirmatory tests (EEG, transcranial Doppler, or brainstem auditory evoked potential) in supporting the diagnosis of brainstem death, especially when it is not possible to carry out all of the brainstem tests (e.g., in the presence of high spinal cord injury[36] or if the residual effect of sedative agents cannot be excluded[37]).

AROUSAL AND CONSCIOUSNESS

Moruzzi and Magoun[38] demonstrated the essential role of the brainstem reticular core in activating the cortical EEG. Segundo and associates[39] showed that destruction of the brainstem reticular core leads to a loss of consciousness in laboratory animals. These observations gave birth to the concept of the ascending reticular activating system (ARAS). Although the central insight of this concept—that structures in the brainstem regulate the state of consciousness—still holds true, the ARAS is no longer regarded as a monolithic unit, nor is it restricted to the classically defined reticular nuclei of the brainstem. Maintenance of wakefulness or control of the sleep-wake cycle does not depend exclusively and unalterably on any single region of the brain.[40] With the advance of anatomic and physiologic techniques, neurochemically specific wake-promoting cell groups within the ARAS were identified.[41] These wake-promoting cell groups are (1) noradrenergic cells in the locus coeruleus, (2) serotoninergic cells in the raphe nuclei, (3) acetylcholinergic cells in the pedunculopontine tegmentum and laterodorsal tegmentum, (4) glutamatergic cells in the midbrain, and (5) dopaminergic cells in the substantia nigra compacta and ventral tegmental area. Projections from these pontine and midbrain wake-promoting cells travel dorsally to activate the thalamocortical systems and ventrally to activate the hypothalamocortical and basalocortical systems. Cell groups in the forebrain also promote wakefulness in addition to these ARAS wake-promoting cell groups, such as histaminergic cells in the tuberomammillary nuclei of the posterior hypothalamus, hypocretin (orexin)-containing cells in the lateral hypothalamus, cholinergic cells in the basal forebrain, neuropeptide Y–containing cells in the suprachiasmatic nucleus, and glutamatergic cells in the ventromedial prefrontal cortex. Functions of the neocortex, which play major roles in consciousness, depend on these arousal systems.

In brain death, the patient is believed to have no consciousness, no intellectual activity, and therefore no true humanity. This state is defined as deep coma and is the basis for the concept of brainstem death.

RESPIRATION

The primary respiratory center, consisting of the inspiratory and expiratory neurons, is located in the reticular core of the medulla oblongata. Various abnormal patterns of respiration (e.g., gasping, apneusis, irregular and shallow respirations) are observed in laboratory animals and humans with brainstem lesions. In brain death, spontaneous respiration does not occur in patients even when $Paco_2$ reaches 55 to 60 mm Hg. Confirming apnea is one of the keys for determining brain death. Mechanical stimulation of the carina to induce the cough reflex may be helpful in detecting residual functioning of the medullary respiratory neurons.

Development of neurogenic pulmonary edema caused by brain insult is well known. Catecholamine surge with enhanced sympathetic discharges and release of neuropeptide Y cause pulmonary vasoconstriction and increase in pulmonary capillary hydrostatic pressure. The lungs are also damaged by loss of vasomotor tone, hypotension, and development of systemic inflammatory responses.[42]

CARDIOVASCULAR FUNCTIONS

The central neurons that control the circulatory system distribute diffusely in the pontine and medullary reticular core. Of these neurons, the vasomotor and cardioaccelerating neurons undergo negative-feedback control through the carotid and aortic sinus nerves, which relay at the nucleus tractus solitarius. Activation of these cells induces sympathetic nervous outflow, thereby increasing the heart rate and arterial blood pressure. Hypertension then suppresses these cells through the feedback mechanism, and circulation returns to preactivation levels.

During the process of brain death after head injury or intracranial bleeding, intracranial pressure increases, and compression of the brainstem leads to marked hypertension and bradycardia (i.e., the Cushing phenomenon). In an animal model of brain death, a precise mechanism of cardiovascular responses by the progression of CNS ischemia as a result of an expanding supratentorial mass was studied. When the entire cerebrum was ischemic, vagal activation with resultant decrease in heart rate, mean arterial pressure, and cardiac output was observed. As ischemia progressed rostrally to approach the pons, sympathetic stimulation was added to vagal stimulation, leading to bradycardia and hypertension (the Cushing phenomenon). When the entire brainstem became ischemic, the vagal cardiomotor nucleus became ischemic, with unopposed sympathetic stimulation, leading to tachycardia, hypertension, and high blood levels of catecholamine (i.e., autonomic storm or catecholamine surge).[43,44] Some authorities think that myocardial damage may occur at this stage of autonomic storm, which may contribute to the early failure of some transplants and obscure or complicate the histologic manifestations of rejection in others.[42] However, in humans, this stage of tachycardia and hypertension may be brief, and attempts to reduce blood pressure may not be necessary or even recommended.[44]

When intracranial pressure is elevated, arterial blood pressure suddenly decreases (Fig. 76-1). This sudden decrease is the sign of tonsillar herniation (i.e., herniation of the cerebellar tonsils) through the foramen magnum on the cervical spinal cord, in which outflow of the cardioaccelerating and vasomotor neurons to the spinal cord suddenly ceases. This is one typical onset for brain death. Such dramatic changes in arterial blood pressure are not observed in other types of brain death, such as that induced by hypoxia or those involving other

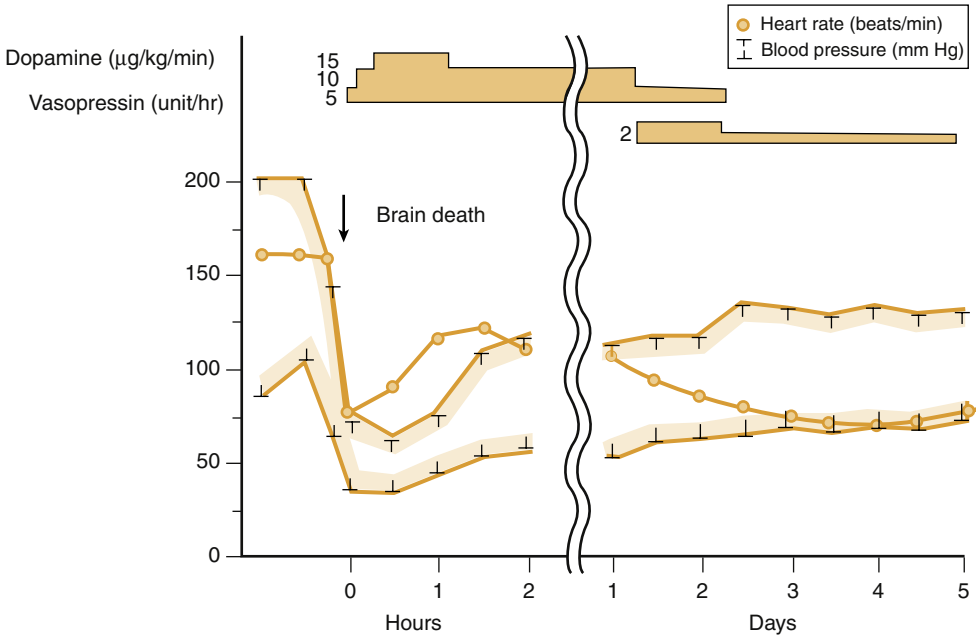


Figure 76-1. The representative time course of arterial blood pressure and heart rate before and after brain death. The 18-year-old male patient was involved in a traffic accident. Sustained hypertension was followed by a sudden and marked decrease in blood pressure. Dopamine was administered to increase blood pressure, which gradually became stable. Doses of dopamine were tapered and finally became unnecessary.

intricate factors. Adequate volume replacement with balanced salt solution or colloid solution and, in some cases, blood transfusion is required. Inotropic agents, such as dopamine, epinephrine, and norepinephrine, are sometimes required to maintain an adequate blood pressure. The vasomotor and cardioaccelerating neurons of the spinal cord (located in the lateral horn) obtain automaticity within several days of disconnection from the supraspinal structures, and arterial blood pressure returns to normal without supplementation with vasopressors.[45] This situation is familiar to anesthesiologists because background arterial blood pressure is usually normal in tetraplegic patients.

After the establishment of brain death, different types of autonomic spinal cord reflexes develop, such as elevation of arterial blood pressure because of bladder distention. Surgical stimulation–induced hypertension and tachycardia are well known by anesthesiologists in tetraplegic patients. A similar phenomenon has been observed in brain-dead patients.[46] Vasodilators or general anesthesia, or both, should be used during the donation operation.[47] Although the cardioaccelerating and vasomotor neurons are located in the brainstem, changes in arterial blood pressure are not used as an index of brainstem function.

REGULATION OF BODY TEMPERATURE

Rodbard[48] suggested that the neural mechanisms governing homeostatic temperature control developed in the hypothalamus from circulatory control neurons in the course of evolution from reptile to mammal. Body temperature is regulated when changes in blood temperature stimulate heat-sensitive receptors in the hypothalamus. Nerve impulses from cold receptors in the skin also can activate heat-producing neurons. The most important heat producers are the skeletal muscles, brain, liver, and heart. The greatest heat radiator is the skin, especially that on the hands. Local electrical stimulation of the heat-producing center induces shivering and constriction of blood vessels in the skin, activating vasomotor nerves and decreasing blood flow. Warming of the heat-loss center suppresses vasomotor nerve activity and in this way increases blood flow through the skin.

In brain death, the neural connection between the temperature-regulating center and peripheral body tissues is lost and the patient becomes poikilothermic. When criteria from the National Institute of Neurological Diseases and Stroke were applied to establish brain death, such patients showed only a "tendency for the temperatures to be subnormal."[29] In contrast, when brain death was established using the criterion of cessation of all brainstem functions, "poikilothermia was found in all patients later than 24 hours after brain death."[49] Even if infection occurs, fever should not develop in cases of brain death, because the temperature-regulating centers no longer function. After brain death, body temperature tends to be hypothermic, even with vigorous application of external heat.

HYPOTHALAMIC-PITUITARY ENDOCRINE FUNCTIONS

No criteria used to establish brain death attempt to determine whether functions of the hypothalamus are preserved. Clinical studies have indicated that hypothalamic and anterior pituitary functions are preserved to a certain degree for a certain period after the onset of brain death. Schrader and co-workers[50] reported normal levels of anterior pituitary hormones, the half-lives of which are less than 1 hour, such as thyroid-stimulating hormone, prolactin, growth hormone, and luteinizing hormone, as well as positive test results for the hypothalamic hormone, luteinizing hormone–releasing hormone, and thyrotropin-releasing hormone, for 2 to 24 hours after determination of brain death. Sugimoto and associates[51]

confirmed that concentrations of these hormones were normal for more than 1 week.

In contrast, the level of vasopressin, a hormone produced in the hypothalamus and stored in the posterior pituitary, decreased sharply after brain death.[51] However, the occurrence of diabetes insipidus is variable. In one study, many patients did not have diabetes insipidus after brain death.[52] Another study found that 24 (77%) of 31 patients with brain death had clinical diabetes insipidus.[53] When arginine vasopressin is added to the infusion in cases of brain death with diabetes insipidus, the heart beat can be maintained for several months.[54] It was reported that plasma levels of the thyroid hormones triiodothyronine (T_3) and thyroxin (T_4) were decreased markedly after brain death.[55] However, the decline in T_3 plasma levels is not uniform in brain-dead patients. Frequently the decline in T_3 is accompanied by a parallel increase in reverse T_3. This condition is similar to euthyroid sick syndrome.

The diaphragma sellae protects the pituitary gland from compression caused by swelling of the brain. Blood supply to the pituitary gland comes mostly from the superior, middle, and inferior nine arteries and the capsular arteries. The portal venous system is another source of blood supply to the anterior lobe. In brain death, blood supply through the superior hypophyseal artery and the portal vein can easily be blocked. However, blood supply through the cavernous portion of the internal carotid artery and its branches, such as the inferior hypophyseal artery and the capsular artery, may be spared.[56] Morphologic studies of brain death indicate that damage to the anterior lobe is incomplete but severe, whereas the posterior lobe is relatively preserved.[51] However, because vasopressin is synthesized in the hypothalamus and transferred to the posterior lobe of the pituitary through axoplasmic flow along the long axon, depletion of this hormone may be greater than would be expected from the slight morphologic damage seen in the posterior lobe.

In studies on brain death, the hypothalamic hormones, such as growth hormone–releasing hormone, corticotropin-releasing hormone, thyroxine-releasing hormone, and luteinizing hormone–releasing hormone were found in trace to subnormal levels.[51,57] Schrader and co-workers[50] reported a normal growth hormone response to hypoglycemic stimulation. Arita and associates[58] also demonstrated that insulin and arginine increased growth hormone levels in brain-dead patients. Hypoglycemia affects glucoreceptors in the ventromedial nucleus to stimulate growth hormone–releasing hormone and corticotropin-releasing hormone release and stimulates growth hormone or adrenocorticotropic hormone release, indicating that some hypothalamic function may be preserved. However, the origin of the hypothalamic hormones released in brain death cannot be identified. Results from morphologic studies on the hypothalamus are controversial. Walker and colleagues[29] reported that the neurons with lytic changes were intermingled with relatively normal cells, a result that may account for the sustained secretion of hypothalamic hormones. In contrast, Sugimoto and co-workers[51] observed extensive necrosis of the hypothalamus after the sixth day of brain death and postulated a nonbrain supply of these hormones, such as the pancreas, intestine, or adrenal gland. The hypothalamus receives its blood supply through the branches of the superior hypophyseal and posterior communicating arteries; therefore, blood flow to the hypothalamus, at least its basal part, may be preserved in relatively mild instances of intracranial hypertension.

Hormonal therapy for hemodynamic stabilization of brain-dead organ donors has been developed and recommended. The Cardiac Work Group of the Crystal City Conference led by United Network for Organ Sharing (UNOS) recommended a heart donor management algorithm that included four-drug hormonal resuscitation (T_3, vasopressin, methylprednisolone, and insulin) for donors with a left ventricular ejection fraction less than 45% or with unstable hemodynamics,[59] and Organ Procurement and Transplantation Network (OPTN)/UNOS multivariate studies on hormonal treatment of brain-dead donors (T_3/T_4, methylprednisolone, and arginine vasopressin) revealed significant increases in the number of organs transplanted and in 1-year survival of kidneys and hearts.[60] However, some investigators failed to observe any hemodynamic or metabolic benefit of the use of T_3 in adult cadaveric organ donors,[61] and it was also reported that not T_4 administration but rather steroid administration and desmopressin and diuretic usage were associated with organ yield.[62] It is suggested that thyroid hormones have some beneficial role only in unusual cases of prolonged donor management—that is, longer than 24 to 48 hours.[63]

THE IMMUNE SYSTEM AND INFLAMMATION

The CNS exerts significant influence over the immune system. Even if the immune system is intact, its response to stimulation is modified considerably after total and irreversible loss of CNS functions. Increased levels of inflammatory mediators, such as cytokines (interleukin-1β[IL-1β], IL-6, tumor necrosis factor–α [TNF-α])[64,65] and adhesion molecules (E-selectin, intercellular adhesion molecule–1 [ICAM-1], vascular cell adhesion molecule [VCAM-1])[66,67] in blood and organs are observed in brain-dead patients, and it is thought that these cytokines are responsible for some of the endocrine and acute-phase reactant abnormalities found in these patients and for the low success rates after organ transplantation. Brain death also may induce a systemic inflammation. The possible mechanisms are (1) inflammatory mediators are released from the ischemic brain; (2) the catecholamine surge causes anerobic metabolism, which induces nuclear factor–κB (NF-κB) activation or flow-induced shear stress of the endothelial cells or induces ischemia in the gut; (3) metabolic changes after brain death modulate the inflammatory response; and (4) neuropeptides are released from the nervous system and play a role in inflammation.[68]

BRAINSTEM REFLEXES

Various brainstem reflexes are used to diagnose brain death, such as pupillary, oculocephalic, oculovestibular, and cough reflexes. Preservation of the cough reflex indicates preservation of the brainstem respiratory center. All the brainstem reflexes (except those of the respiratory

centers) need not be present for the organism to be said to be alive, but they are tested to confirm preservation of brainstem functions.

CRITERIA AND TESTS FOR DETERMINING BRAIN DEATH

Determination of brain death confirms the irreversible cessation of all functions of the entire brain, including the brainstem.[12] Irreversibility means that no treatment may be reasonably expected to change the condition. The responsible disorder may be thought of as structural, and it does not result from functional and potentially reversible causes such as drug intoxication, hypothermia, or metabolic or endocrine disturbance. The passage of time is also an essential component in determining that a lesion is irremediable. Although testing all functions of the brain is conceptually impossible, the cessation of all functions of the brain is practically determined by loss of consciousness, loss of brainstem responses, apnea, and confirmatory tests, including the lack of electroencephalographic activity.

LOSS OF CONSCIOUSNESS AND UNRESPONSIVENESS

The patient should be in coma and scored as 3 on the Glasgow Coma Scale. Motor responses of the limbs or facial muscles to painful supraorbital pressure should be absent. Motor responses (i.e., the Lazarus sign) may occur spontaneously during apnea testing[69] and are considered to have a spinal origin. This sign is often observed during hypoxic or hypotensive episodes. Other spontaneous movements from spinal origin are observed.

PUPILS

The shape of the pupils can be round, oval, or irregular. The size of the pupils may vary from 4 to 9 mm, but in most cases is 4 to 6 mm.[12,70] Sympathetic cervical pathways can be intact in the state of brain death, connect with the radially arranged fibers of the dilator muscle, and dilate the pupils.

BRAINSTEM RESPONSES

The tests for brainstem responses vary in different countries. The criteria of the American Academy of Neurology[19] include light reflex, oculocephalic reflex, caloric (vestibular) test, corneal reflex, facial muscle movement to a noxious stimulus, pharyngeal (gag) reflex, and tracheal (cough) reflex.

APNEA TEST

Apnea testing is mandatory for the determination of brain death and considered the most important testing, but controversies have existed about it. Its safety is a major issue. During the apnea test, marked hypotension or severe cardiac arrhythmias,[70] or both, and pneumothorax may occur[71] and the intracranial pressure can increase markedly. The apnea test should be performed as the last test after the other tests fulfill the criteria of brain death. Goudreau and associates[72] reported that during the apnea test complications such as a marked blood pressure decrease or the development of ventricular arrhythmia developed in 27 (39%) of 70 patients with pretest unfavorable factors but developed in only 11 (15%) of 74 patients without them. They pointed out that inadequate preoxygenation and acid-base or electrolyte abnormalities were the major unfavorable pretest factors. Preparation before the apnea test is required. Prerequisites are (1) normotension (systolic blood pressure ≥100 mm Hg), (2) normothermia (core temperature >36° C), (3) euvolemia, (4) eucapnia ($Paco_2$ 35 to 45 mm Hg), and (6) no prior evidence of carbon dioxide retention. Preoxygenation with 100% O_2 for at least 10 minutes is required before apnea testing to PaO_2 greater than 200 mm Hg. Ventilator requirements should be evaluated, and the patient should be well-oxygenated with low positive end-expiratory pressure (5 cm H_2O). During apnea testing, 100% O_2 is delivered at 6 L/min through a catheter placed at the level of the carina or attached T-piece with continuous positive airway pressure at 10 cm H_2O.[12,19,70] Apnea testing should be aborted if systolic blood pressure decreases to less than 90 mm Hg or O_2 saturation (SpO_2) decreases to less than 85% for longer than 30 seconds. A bolus of intravenous phenylephrine 100 μg is recommended in the case of hypotension.

Another issue is the appropriate level of $Paco_2$ to be achieved. After equipment for analyzing blood gases became widespread, the importance of the value of $Paco_2$ rather than the time for observation of apnea was confirmed. An increase in $Paco_2$ decreases pH in the cerebrospinal fluid, which stimulates the medullary respiratory chemical center. The normal ventilatory response to the increase in $Paco_2$ rises linearly to 80 mm Hg, and then the slope becomes less steep and peaks at approximately 150 mm Hg in dogs.[73] Damage in the medullary respiratory center may affect the level of $Paco_2$ for development of spontaneous respiration. The level of $Paco_2$ at which spontaneous respiration resumes is also modified by PaO_2. Wijdicks[4] reported that although most of all brain death guidelines in the world required apnea tests (71 of 80 nations), only 41 of 71 guidelines defined a definite $Paco_2$ target value, and he concluded that if the premise of documenting apnea using hypercarbia to maximally stimulate the respiratory centers was accepted, it could be concluded that in half of the countries the apnea test was not performed adequately. The exact level of $Paco_2$ to be achieved is still unknown, but the American Academy of Neurology criteria define various prerequisites and the procedure of apnea testing and adopt the level of $Paco_2$ 60 mm Hg or greater[12,19,70] and the U.K. criteria requires a $Paco_2$ target of 6.65 kPa (50 mm Hg).[34]

PREREQUISITES FOR DIAGNOSING BRAIN DEATH

Several disorders mimic brain death and can lead to an erroneous diagnosis. The absence of these conditions must be confirmed and the following factors considered before the criteria for brain death are applied.

DEEP COMA

The patient must be in a deep coma, and the cause of the coma must be identified. Organic brain damage must be confirmed as a prerequisite for diagnosing brain death. Drug intoxication, severe electrolyte, acid-base or endocrine disturbance, hypothermia, and other common treatable disorders should be ruled out.

BODY TEMPERATURE

After cessation of brainstem and hypothalamic functions and after complete disconnection of the spinal cord from supraspinal brain structures, the patient becomes poikilothermic and body temperature tends to be hypothermic, even with vigorous warming. Because hypothermia suppresses CNS function and can lead to misdiagnosis of brain death, body temperature must be within normal range (i.e., hypothermia must be corrected) before the criteria for brain death are applied.

ABSENCE OF CARDIOVASCULAR COLLAPSE

When intracranial pressure increases, systemic hypertension occurs as a result of the Cushing phenomenon. This is followed by a sudden decrease in blood pressure because of sudden interruption of vasomotor output from the brainstem and hypothalamus to the spinal cord. Hypotension usually resolves spontaneously within several days because of restoration of spontaneous activity of the spinal cord's vasomotor neurons. Hypotension may result in compromised cerebral perfusion leading to loss of electroencephalographic activity, thus causing a spurious diagnosis. Therefore, administration of a vasopressor to achieve relative normotension should be considered; vasopressor therapy will occasionally restore electroencephalographic activity in the determination of brain death.

CLINICAL DIAGNOSIS OF BRAIN DEATH

The guidelines and clinical diagnosis for determining brain death differ in various countries[3,4] and among institutions in the United States and Canada. However, the principle seems similar,[1,3,4,12] and clinical diagnosis of brain death should be performed in the following three steps:

1. Establishing the cause of disease
2. Excluding certain potentially reversible syndromes that may produce signs similar to brain death
3. Demonstrating clinical signs of brain death: coma, brainstem areflexia, and apnea

Confirmatory tests in the determination of brain death are not always mandatory, but they are desirable, especially when the clinical picture is confusing. In general, two examinations separated by at least 6 hours are required to establish the diagnosis of brain death. Most codes mandate that the clinical diagnosis be confirmed by two or three physicians who are independent of the transplantation team, and at least one of the physicians is required to be a specialist in neurology, neurosurgery, or anesthesiology.

SPECIAL CONSIDERATIONS

SPINAL CORD REFLEXES AND SURGERY

The CNS structures essential to the definition of brain death do not include the spinal cord. Histologic studies have shown that the spinal cord is the best preserved part of the CNS in cases of brain death, and results have ranged from grossly normal histology to edema, neuronal loss, neurolysis, and, rarely, infarction.[29]

Spontaneous and reflex movements are found in brain-dead patients. Spontaneous body movements may be observed during the apnea test, while the body is being prepared for transport, at the time of a skin incision for the retrieval of organs, or in synchrony with the respirations produced by mechanical ventilation.[1] In 5 of 60 cases of brain death after terminally turning off the ventilator or during apnea tests, Ropper[69] reported bizarre, seemingly purposeful movements of the upper extremities, termed the Lazarus sign, in which the arms flexed quickly to the chest from the patient's side, the shoulders adducted, and in some patients, the hands crossed or opposed just below the chin. Saposnik and associates[74] reported that 15 (39%) of 38 patients who fulfilled criteria for brain death showed spontaneous or reflex movements; the most common movement was finger jerks, and the undulating toe flexion sign, triple flexion response, Lazarus sign, pronation-extension reflex, and facial myokymia also were seen. Health care staff should remember that a patient may move in response to noxious stimulation and that full curarization is required for surgical procedures involving brain death.

CONSIDERATIONS REGARDING CHILDREN

The child's brain is a developing organ, and it is believed that the anatomic neurodevelopment continues by 2 years of age or beyond the first decade of life (see also Chapters 93 and 95). During this time, changing patterns of vulnerability to injury and different responses to the injury itself occur.[75] Furthermore, the presence of open fontanelles and open sutures in young children makes the skull an expandable chamber. Intracranial pressure may not exceed mean arterial blood pressure, and cerebral blood flow continues. It is generally assumed that the child's brain is more resistant to insults leading to death, although this issue is controversial and lacks convincing clinical documentation.[14]

The need for facilitation of end-of-life decision and organ procurement in infants and children has increased. In 1987, the Task Force for the Determination of Brain Death in Children endorsed the *Determination of Death Act* and offered the Guidelines for the Determination of Brain Death in Children.[14] The multisociety task force revised the 1987 guidelines after reviewing literature published from 1987 with clarifying the grade of recommendations (see Boxes 76-2 and 76-3).[20] Although 1987 guidelines excluded neonates younger than 7 days of age, in the revised guidelines the exclusion of recommendations was restricted to preterm infants younger than 37 weeks of gestational age, because insufficient data were available, some of the brainstem reflexes may not

be completely developed, and assessment of the level of consciousness in critically ill, sedated, and intubated neonates is difficult. Although an ancillary study (EEG) was mandatory in infants younger than 1 year of age in the 1987 guidelines, in the revised guidelines, ancillary studies (EEG and cerebral blood flow) were changed to be optional. Further, unspecified values of several subjects in the 1987 guidelines were specified in the revised guidelines. In the United Kingdom, where brainstem death criteria are adopted, the brain death criteria for children are as follows: after 2 months of age, criteria should be the same as in adults; between 37 weeks of gestation and 2 months of age, it is rarely possible to diagnose brain death confidently; and before 37 weeks of gestation, the criteria for brain death cannot be applied.[76,77] In Japan, organ donation from a brain-dead child younger than 15 years has been legal from 2009 with family consent, and the most rigid criteria in the world are applied to declare brain death in children younger than 6 years (Table 76-1). Computed tomography (CT) or MRI examination is mandatory in children as a prerequisite to clarify the causes of brain insults. Further, a possibility of child abuse should be excluded if the child is younger than 18 years of age.

VARIABILITY IN POLICIES AND PRACTICES FOR DETERMINING BRAIN DEATH

Although the concept of brain death as defining the death of the individual is widely accepted, significant variability exists in policies and practices for determining brain death among nations and even within a nation—that is, among states and hospitals. Wijdicks[4] reported that of 80 countries examined, legal standards on organ transplantation were present in 55 countries (69%) and practice guidelines for brain death for adults were present in 70 countries (88%). All guidelines specified exclusion of confounders, irreversible coma, absent motor response, and absent brainstem reflexes. Although apnea testing is one of the most important tests for determining brain death, a few guidelines do not require apnea

TABLE 76-1 **COMPARISON OF PEDIATRIC BRAIN DEATH GUIDELINES BETWEEN THE UNITED STATES AND JAPAN**

	United States (Updated Guidelines)	Japan
1. Age-related exclusion	Preterm infants <37 wk gestational age	Preterm infants <12 wk in corrected age
2. Core body temperature	>35° C (95° F)	<6 yr: ≥35° C (95° F), ≥6 yr: 32° C (89.6 ° F)
3. Arterial blood pressure	Age-dependent Above normal value for the age – 2 SD	Age-dependent <1 yr ≥65 mm Hg 1 year ≤13 yr: ≥65 + (age × 2) mm Hg ≥13 years: ≥90 mm Hg
4. Number of examinations	Two examinations	Two examinations
5. Number of examiners	Two (different attending physicians must perform the first and second examinations)	Two (neurosurgeon, neurologist, anesthesiologist, intensive care physician, emergency medicine physician, or pediatrician: board-certified)
6. Observation interval between neurologic examinations	Age-dependent Term newborn (37 wk gestation) to 30 days of age: 24 hr 31 days to 18 yr: 12 hr	Age-dependent <6 yr: 24 hr ≥6 yr: 6 hr
7. Reduction of observation period between examinations	Permitted for both age groups if EEG or CBF consistent with brain death	Not permitted
8. Apnea testing	Two apnea tests required unless clinically contraindicated	Two apnea tests required
9. Final P_{CO_2} threshold for apnea testing	≥60 mm Hg and ≥20 mm Hg above the baseline Pa_{CO_2}	≥60 mm Hg
10. Ancillary study	Not required except in cases in which the clinical examination and apnea test cannot be completed Term newborn (37 wk gestation) to 30 days of age: EEG or CBF are less sensitive in this age group; CBF may be preferred >30 days to 18 yr: EEG and CBF have equal sensitivity	EEG is mandatory
11. Time of death	Time of the second examination and apnea test (or completion of ancillary study and the components of the second examination that can be safely completed)	Time of second examination and apnea test
12. Others		CT or MRI is mandatory to identify the cause of brain insults A child having a possibility of abuse is excluded

From Nakagawa TA, Ashwqal S, Mathur M, et al; Society of Critical Care Medicine; Section on Critical Care and Section on Neurology of the American Academy of Pediatrics; Child Neurology Society: Guidelines for the determination of brain death in infants and children: an update of the 1987 Task Force recommendations. Crit Care Med *39:2139-2155, 2011.*

CBF, Cerebral blood flow; *CT,* computed tomography; *EEG,* electroencephalogram; *MRI,* magnetic resonance imaging; *SD,* standard deviation.

testing. Further, significant differences exist in the area of the brain (whole brain versus brainstem), in requirement of confirmatory tests (EEG, brainstem evoked potentials, cerebral angiogram), number of examinations (and time interval between examinations), method of apnea testing (baseline $Paco_2$, target value of $Paco_2$, time of disconnection from the ventilator, oxygenation method during the test), time of observation from the insults, number and required expertise of examining physicians, critical thresholds of temperature and arterial blood pressure, and legal time of death. Furthermore, because brain death practices are largely determined by individual hospitals in the United States and Canada, significant variabilities among hospital policies and guidelines for brain death were found. Wijdicks[4] and other investigators stressed the need to standardize the practice of neurologic determination of death.[78,79] Wide variation in practices was also reported in the pediatric population[80,81] and in the brainstem death criteria in the United Kingdom,[37] despite the existence of clear guidelines for performing the test.[82-84]

Jeffe and colleagues[85] surveyed understanding of the concept and diagnostic tests of brain death in American board-certified neurologists in 2010. They sent a questionnaire to 500 neurologists and analyzed 192 returned forms. The most common (48%) justification for understanding brain death as an individual death was "a high brain concept (irreversible loss of consciousness)," followed by "loss of integrative unity (27%)" and "the irreversible lack of vital work of an organism (12%)." Although criteria for determining brain death in the United States do not require lack of some remaining functions of the brain, many neurologists responded that certain brain functions remaining are not compatible with diagnosis of brain death, including EEG activity (70%), evoked potential activity (56%), hypothalamic neuroendocrine function (9%), brain blood flow (52%), and normal brainstem pathology (19%). This survey indicates that American neurologists have neither a consistent rationale for accepting brain death as death nor diagnostic tests for brain death.

ANCILLARY TESTS FOR BRAIN DEATH

Tests that confirm the loss of bioelectrical activity of the brain or the cerebral circulatory arrest are not always mandatory for adults (Box 76-4). In several European, Central American, South American, and Asian countries, ancillary testing is required by law.[1,2,4] In the United States, the choice of tests is left to the discretion of the physician. Ancillary tests can reduce the time of observation and are strongly recommended when uncertainties exist about the reliability of certain aspects of the clinical examinations and in situations in which the apnea testing cannot be completed. Young and associates[86] proposed criteria for ideal confirmatory ancillary tests:

1. No instances of false positive findings should occur—that is, when the test confirms "brain death," none should have recovered or have the potential to recover.
2. The test should be independently sufficient to establish that brain death is or is not present.
3. The test should not be susceptible to confounders, such as drug effects or metabolic disturbances.
4. The test should be standardized in technology, technique, and classification of results.
5. The test should be available, safe, and readily applied. Testing should not be restricted to only a few research centers; ideally it could be applied within any intensive care unit (ICU) and the technique should be reliable and mastered without difficulty.

BOX 76-4 ***Methods of Ancillary Testing for the Determination of Brain Death***

1. Cerebral angiography
   a. The contrast medium should be injected in the aortic arch under high pressure and reach both anterior and posterior circulations.
   b. No intracerebral filling should be detected at the level of entry of the carotid or vertebral artery to the skull.
   c. The external carotid circulation should be patent.
   d. The filling of the superior longitudinal sinus may be delayed.
2. Electroencephalography
   a. A minimum of eight scalp electrodes should be used.
   b. Interelectrode impedance should be between 100 and 10,000 Ω.
   c. The integrity of the entire recording system should be tested.
   d. The distance between electrodes should be at least 10 cm.
   e. The sensitivity should be increased to at least 2 μV for 30 minutes with inclusion of appropriate calibrations.
   f. The high-frequency setting should not be set below 30 Hz, and the low-frequency setting should not be above 1 Hz.
   g. Electroencephalography should demonstrate a lack of reactivity to intense somatosensory or audiovisual stimuli.
3. Transcranial Doppler (TCD) ultrasonography
   a. TCD is useful only if a reliable signal is found. The abnormalities should include either reverberating flow or small systolic peaks in early systole. A finding of a complete absence of flow may not be reliable owing to inadequate transtemporal windows for insonation. There should be bilateral insonation and anterior and posterior insonation. The probe should be placed at the temporal bone, above the zygomatic arch and the vertebrobasilar arteries, through the suboccipital transcranial window.
   b. Insonation through the orbital window can be considered to obtain a reliable signal. TCD may be less reliable in patients with a prior craniotomy.
4. Cerebral scintigraphy (technetium-99m exametazime [HMPAO])
   a. The isotope should be injected within 30 minutes after its reconstitution.
   b. Anterior and both lateral planar image counts (500,000) of the head should be obtained at several time points: immediately, between 30 and 60 minutes later, and at 2 hours.
   c. A correct intravenous injection may be confirmed with additional images of the liver demonstrating uptake (optional).
   d. No radionuclide localization in the middle cerebral artery, anterior cerebral artery, or basilar artery territories of the cerebral hemispheres (hollow skull phenomenon).
   e. No tracer in superior sagittal sinus (minimal tracer can come from the scalp).

Wijdicks EFM, Valelas PN, Gronseth GS, Greer DM: Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology *74:1911, 2010.*

In all cases, ancillary tests should be used in conjunction with appropriate clinical judgment.

ELECTROENCEPHALOGRAPHIC RECORDING

The EEG is the most widely available neurophysiologic test and is used in many countries and institutions as a confirmatory test for brain death (whole-brain death) (see also Chapters 49 and 50).[1,4] Loss of bioelectrical brain activity as shown on the EEG (i.e., isoelectric EEG) is a reliable confirmatory test for brain death. However, several problems must be considered. An isoelectric EEG can be found after drug intoxication (false positive), such as occurs with barbiturates,[87] and, conversely, residual electrical activity may persist after brainstem death or even in some patients who met clinical criteria for brain death (false negative).[35,88]

Electrocerebral inactivity (ECI) or electrocerebral silence (ECS) is defined as no electroencephalographic activity above 2 μV/mm when recording from scalp electrode pairs placed 10 cm or more apart and with interelectrode impedances less than 10,000 Ω but more than 100 Ω. Ten guidelines for electroencephalographic recordings are as follows[89]:

1. A minimum of eight scalp electrodes should be used.
2. Interelectrode impedances should be less than 10,000 but more than 100 Ω.
3. The integrity of the entire recording system should be tested.
4. Interelectrode distances should be at least 10 cm.
5. Sensitivity must be increased from 7 μV/mm to at least 2 μV/mm for at least 30 minutes of the recording, with inclusion of appropriate calibrations.
6. Filter settings should be appropriate for the assessment of ECS.
7. Additional monitoring techniques should be employed when necessary.
8. No electroencephalographic reactivity should occur to intense somatosensory, auditory, or visual stimuli.
9. Recordings should be made only by a qualified technologist.
10. A repeat EEG should be performed if doubt about ECS exists.

EVOKED RESPONSES

Brainstem auditory evoked potentials (BAEPs) and median nerve somatosensory evoked potentials (SSEPs) are used for the diagnosis of brain death. Unlike EEG signals, the early components of BAEPs and SSEPs are minimally affected by sedative drugs and anesthetics. However, drugs and metabolic derangements affect middle and late BAEPs and SSEPs.[86] BAEPs are signals generated in the auditory nerves and brainstem after an acoustic stimulus. BAEPs consist of five identifiable waves generated from specific brainstem structures along the auditory pathways. Wave I represents the eighth nerve compound action potential; wave II, the eighth nerve and cochlear nerves; wave III, the lower pons, including the superior olive; and waves IV and V, the upper pons and the midbrain, as high as the inferior colliculus.[90] Brainstem abnormalities can be detected with BAEPs. The loss of waves III to V or II to V or no reproducible BAEP on both sides is usually regarded as brain death,[88] although wave I sometimes remains. Preexisting deafness or severe peripheral auditory system damage may lead to a false-positive diagnosis.

After electrical stimulation of a peripheral nerve, waves of SSEPs are generated from the neural structures along the afferent somatosensory pathways: the brachial plexus, the upper cervical cord, the dorsal column nuclei, the ventroposterior thalamus, and the sensory cortex.[90] "Practice Parameters for Determining Brain Death in Adults," published in *Neurology,* recommended bilateral absence of N20-P22 responses with median nerve stimulation as a confirmatory laboratory test.[12] Facco and coworkers[91] reported that the absence of components later than N13, which represents postsynaptic activity in the central gray matter of the cervical cord, or N13 and P13 dissociation, was reliable to confirm brain death. These investigators also recommended the combined use of BAEPs and SSEPs for determining brain death. Sonoo[92] considered a loss of N18 potential, which is supposedly generated at the cuneate nucleus in the medulla oblongata, as reliable for the diagnosis of brain death.[92]

CEREBRAL PERFUSION AND METABOLISM

Possible mechanisms for brain death include an obstruction of circulation by cerebral swelling, and thus the demonstration of absent intracranial circulation indicates irreversible cerebral damage (see also Chapter 17). However, because in some situations, cerebral perfusion may be maintained despite documented brain death,[32] Heran and associates[93] state that it is important to understand the situation in which these false negative results may arise, to assess the results in context and consider other options for confirmation of brain death. Table 76-2 shows the advantages and disadvantages of ancillary tests for determination of cerebral blood flow in the setting of brain death.[93]

ANGIOGRAPHY

Contrast Catheter Angiography

Four-vessel cerebral angiography is a traditional gold standard modality among ancillary tests for brain death. This method is primarily an anatomic and not a physiologic demonstration of perfusion, although nonquantitative inferences about perfusion rates may be made. The greatest advantage of catheter angiography for the determination of brain death is that it is not influenced by CNS depressant drugs or hypothermia. This method has been widely recommended to confirm brain death.[88,94,95] "Practice Parameters for Determining Brain Death in Adults" recommended conventional angiography as a confirmatory test, and the following criteria were identified[12]: no intracerebral filling should be seen at the level of the carotid bifurcation or circle of Willis; the external carotid circulation is patent; and filling of the superior longitudinal sinus may be delayed. Drawbacks of this method are that the patients need to be transported to the radiology suite and it is an invasive examination that needs an experienced neuroradiologist and may

TABLE 76-2 COMPARISON OF ANCILLARY TESTS FOR DETERMINATION OF CEREBRAL BLOOD FLOW IN THE SETTING OF BRAIN DEATH

Test	Definition	Minimum Flow Limit (mL/100 g/min)	Advantages	Disadvantages	Consensus
DSA	Digital subtraction angiography	0	Direct visualization of CBF	Invasive Exposure to iodinated contrast Not readily available Not portable Expensive	Reference standard for NDD assessment Not preferred test because of invasiveness
SPECT	Single-photon emission computed tomography	5	Widely available Portable Low cost Whole brain coverage	Not quantitative Poor spatial resolution	Reference standard for NDD assessment
PET	Positron emission tomography	0	Quantitative Can assess multiple factors, including oxygen consumption, by using different radioligands Repeated measurements possible Whole brain coverage	Impractical for daily use Not portable Expensive	Reference standard for CBF assessment Not useful in NDD
Xe-CT	Xenon computed tomography	0	Quantitative Allows simultaneous CT-based imaging techniques Can be repeated within 10 min	Available in only a few academic centers because not FDA approved Not portable Limited brain coverage (6 cm) Delivery of Xe gas may present challenges	Reference standard for CBF assessment Not useful in NDD because of limited availability
MRA	Magnetic resonance angiography	Depends on technique of acquisition, but considered very low (<10)	No contrast necessary Can be combined with other MR-based techniques	Not readily available Scanning time lengthy Not portable Expensive	Limited data but promising
MRP	Magnetic resonance perfusion	8	Whole brain coverage Can be combined with other MR-based techniques Repeatable	Not quantitative for CBF Not readily available Not portable	Likely not useful because not quantitative
CTA	Computed tomography angiography	Unknown but likely very low (<10)	Readily available Rapid acquisition	Exposure to iodinated contrast Not portable	Limited data but most promising as ubiquitous technology
CTP	Computed tomography perfusion	0	Readily available Rapid acquisition Quantitative*	Exposure to iodinated contrast and ionizing radiation Limited anatomic coverage (2-4 cm) Requires postprocessing of data Relies on intact blood-brain barrier Not portable	Limited data but holds promise, especially if anatomic coverage extended
TCD	Transcranial Doppler ultrasound	Unknown	Rapid Noninvasive Portable	Does not quantify CBF Difficult to perform One measurement for each hemisphere	Not deemed useful in NDD

Modified from Heran MK, Heran NS, Shemie SD: A review of ancillary tests in evaluating brain death. Can J Neurol Sci *35:409, 2008.*
CBF, Cerebral blood flow; *FDA,* U.S. Food and Drug Administration; *NDD,* neurologic determination of death.
*Controversy exists regarding its true quantitative abilities.

yield severe complications, such as vasospasm, subintimal injection, arterial dissection, and thromboembolism, leading to a false image of absent flow and cerebral ischemia. Intraarterial (aortic arch) or intravenous (vena cava) digital subtraction angiography has been shown to be as effective as conventional four-vessel angiography, is less invasive, and is easier to perform.[96]

Radionuclide Angiography

Confirmation of brain death using conventional dynamic radionuclide angiography with blood pool agents has been used for a long time.[97] Such investigations are less invasive than others and may be carried out at the bedside using a mobile scintillation camera, but they cannot image the posterior fossa well. Radioligands such as technetium-99m hexamethylpropyleneamine-oxime (HMPAO), which cross the blood-brain barrier and are picked up and held by viable cells for several hours, are recommended to confirm brain death.[98] The lack of uptake of isotope in brain parenchyma (i.e., the hollow skull phenomenon) is characteristic for brain death.[12] ^{99m}Tc-HMPAO single-photon emission computed tomography (SPECT) provides much more precise regional information and has been proved effective in the diagnosis of brain death both in children and adults.[99,100] The lack of signal from the intracranial compartment and the normal uptake in other parts of the head produces the "empty light bulb" and "hot nose" signs.[99,100] Munari and coworkers confirmed the reliability of SPECT in the diagnosis of brain death and recommended that it should be a good candidate for the standard diagnostic modality.[101]

Computed Tomography

CT angiography has been useful as a noninvasive test to confirm brain death.[102] After intravenous injection of contrast media, time-density analysis of a specific area can be performed with a CT scanner equipped with a software program that can evaluate blood flow. CT angiography has several advantages[102]: (1) it is easily accessible around the clock and present in almost all hospitals with an ICU, (2) it is fairly inexpensive, (3) imaging requires only minutes, (4) it delivers conventional CT images at the same imaging session and can also be combined with CT perfusion imaging, (5) it is noninvasive except for intravenous injection of the contrast agent, and (6) the images are easy to interpret. However, significant divergence with catheter angiography was observed; CT angiography demonstrated some opacified proximal anterior cerebral artery segments, although absence of intracranial flow was noted with catheter angiography,[103] which may relate to contrast stasis with CT angiography.

The xenon-CT cerebral blood flow method has been applied to the confirmation of brain death.[92] This technique is quantitative and allows coregistration of flow data with CT anatomy. Pistoria and associates[104] suggested that an average global flow of less than 5 mL/100 g/min confirms brain death.

MAGNETIC RESONANCE

Magnetic resonance (MR) imaging (MRI) and MR angiography have been used for the confirmation of brain death with the advent of MRI-compatible ventilators.[105,106] MRI allows an assessment of intracranial contents and is particularly helpful in defining abnormalities in the posterior fossa, which may be obscured by bone artifact inherent in CT. Although currently experimental and limited in spatial resolution, phosphorus and proton MR spectroscopy (MRS) has been proposed for the determination of brain death.[107,108] MRS can demonstrate the total absence of high-energy phosphorus compound (including adenosine triphosphate, leaving only one single peak of inorganic phosphate in ^{31}P MRS and massive lactate concentration in ^{1}H MRS. Diffusion-weighted MRI, which detects the molecular diffusion of water, has been proposed as an adjunct in the diagnosis of brain death, because it can identify widespread cerebral ischemia.[109]

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

Transcranial Doppler ultrasonography (TCD) is a safe, noninvasive, and inexpensive method that can be performed at the bedside. However, the test requires skill and knowledge in its application to insonate the major intracranial arteries. The Neurosonology Research Group of the World Federation of Neurology created a task force group to evaluate the role of TCD as a confirmatory test for determining brain death and offered the criteria for the diagnosis of cerebral circulatory arrest.[110] According to the criteria, cerebral circulatory arrest can be confirmed if the following extracranial and intracranial Doppler sonographic findings have been recorded and documented both intracranially and extracranially and bilaterally on two examinations at an interval of at least 30 minutes:

1. Systolic spikes or oscillating flow in any cerebral artery can be recorded by bilateral transcranial insonation of the internal carotid artery (ICA) and middle cerebral artery (MCA), respectively, or any branch or other artery that can be recorded (anterior and posterior circulation).
2. The diagnosis established by the intracranial examination must be confirmed by the extracranial bilateral recording of the common carotid artery, ICA, and vertebral arteries.
3. The lack of a signal during transcranial insonation of the basal cerebral arteries is not a reliable finding because this can be due to transmission problems.
4. Ventricular drains or large openings of the skull as in decompressive craniotomy possibly interfering with the development of the intracranial pressure are not present.

According to the report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, the sensitivity of TCD for diagnosis of brain death ranges from 91% to 100%.[111] In a meta-analysis of 10 studies concerning TCD examination, two high-quality studies showed a sensitivity of 95% and a specificity of 99% to detect brain death, and all 10 studies showed a sensitivity of 89% and a specificity of 99%.[112] Poularas and co-workers[113] reported that when they examined 40 clinically brain-dead patients by TCD and angiography the agreement between the TCD and angiography

to confirm brain death was 100%. Young and associates,[86] however, strongly recommend that because of numerous caveats and lack of precise guidelines, TCD should not be, at this time, recommended as the sole test of brain perfusion in the case of suspected brain death.

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) imaging involves intravenous injection of radiotracers labeled with positron-emitting nuclides (e.g., O-15, carbon-11, nitrogen-13). These radionuclides are incorporated into organic compounds chemically similar to those present in the body, and several physiologic parameters can be measured. A few of the reports about the use of PET in the setting of brain death indicated the utility of PET in the confirmation of brain death. No detectable glucose metabolism was reported using fluorine-18 fluorodeoxyglucose (^{18}F-FDG) in brain-dead patients.[114] On the other hand, Medlock and colleagues[115] reported a clinically brain-dead 2-month-old infant with no cerebral electrical activity who demonstrated the persistence of glucose metabolism by PET. These investigators speculated that the preservation of glucose metabolism was partly caused by glial cells, which are more resilient than neurons. The use of PET in the investigation of comatose or brain-dead patients is still in an early stage of development and limited by its high cost and need for special facilities. Laureys and associates[116] suggested that functional neuroimaging is providing new insights into cerebral activity in patients with severe brain damage and that measurements of cerebral metabolism and brain activations in response to sensory stimuli with PET, functional MRI, and electrophysiologic methods can provide information on the presence, degree, and location of any residual brain function.

ORGAN DONATION

The concept of brain death has been developed with the development of organ transplantation, and the main purpose of diagnosis of brain death is that it permits multiple vital organ procurement for transplantation (see also Chapter 75). In 2010, the World Health Assembly led by World Health Organization (WHO) endorsed revised Guiding Principles on Human Cell, Tissue and Organ Transplantation, referring to both living and deceased donations, to provide an orderly, ethical and acceptable framework for the acquisition and transplantation of human cells, tissues, and organs for therapeutic purposes. In guiding principles, it is stated that tissues and organs may be removed from the bodies of deceased persons for the purpose of transplantation if (1) any consent required by law is obtained and (2) there is no reason to believe that the deceased person objected to such removal.[117] The dead-donor rule[118] is the ethical and legal axiom. Because of a critical shortage of organs for transplantation, various measures have been proposed to improve the rate of organ donation from brain-dead patients, such as "required request" and "presumed consent."[117,118] Furthermore, "non–heart beating organ donor,"—that is, "donation after circulatory death (DCD)" protocols, in which life-sustaining therapy is withheld for an imminently dying patient with the removal of the transplantable organs after the patient's cardiac arrest, have been introduced. Such protocols have gained popularity, especially after a qualified endorsement by the Institute of Medicine.[121,122] However, the protocols are not new and special, because before the acceptance of donation after brain death (DBD), cadaveric donations were from patients who had been declared dead by cardiorespiratory criteria and many of the renal transplantations performed have used organs retrieved after determination of cardiac arrest. Although warm ischemic injuries limit the potential for DCD, not only kidney but also liver, pancreas, and lungs, which are rather vulnerable to ischemia, are now being retrieved by DCD and successfully transplanted.[123] The warm ischemia time (WIT) in DCD begins at the withdrawal of life-sustaining cardiorespiratory support and ends at the end of cardiopulmonary function when cold perfusion is established, and a number of attempts to reduce the length and degree of WIT have been performed to improve the outcomes of transplants from DCD to reduce ischemic injury. Although DBD, unlike DCD, has an opportunity to maintain or even improve the condition of organs before retrieval by optimal donor management and minimizing WIT, various risk factors exist to aggravate injury to donor's organs and consequently increase propensity to rejection, such as cardiovascular instability and generalized inflammatory and hormonal changes.[122] Therefore, many therapeutic goals and treatment guidelines have been proposed to maximize use of organs procured from cadaver donors.[59,60,124,125]

DCD is classified into five categories by the modified Maastricht classification: category I (dead on arrival), II (unsuccessful resuscitation), and V (unexpected arrest in patients in the ICU) belong to uncontrolled DCD, whereas category III (anticipated cardiac arrest) and IV (cardiac arrest in a brain-dead donor) belong to controlled DCD, in which organ retrieval is performed after death resulting from the planned withdrawal of life-sustaining cardiorespiratory support.[126] The DCD may be used when the donor does not fulfill brain death criteria. Although the controlled DCD is the most common form of DCD, logistical and ethical difficulties remain: the robust diagnosis and reason for medical futility to justify treatment withdrawal is mandatory.[127] It is also necessary that the decision to withdraw or withhold life-sustaining cardiorespiratory support should be independent and made before any consideration of organ donation.[123] In addition, diagnosis of death requires the determination of *irreversibility,* but some cases of autoresuscitation (spontaneous return of the circulation after circulatory arrest) after cardiac arrest have been reported. Most criteria allow death to be confirmed (and therefore organ retrieval to begin) after 5 minutes of continuous cardiorespiratory arrest, which is empirically believed to be sufficient interval to ensure that both consciousness and respiration have ceased and autoresuscitation should not occur. However, the Institute of Medicine acknowledges the uncertainty and lack of scientific evidence for irreversibility for the 5-minute interval.[122,127-129] As in adults, DCD has been applied for children in the past decade as a result of the chronic

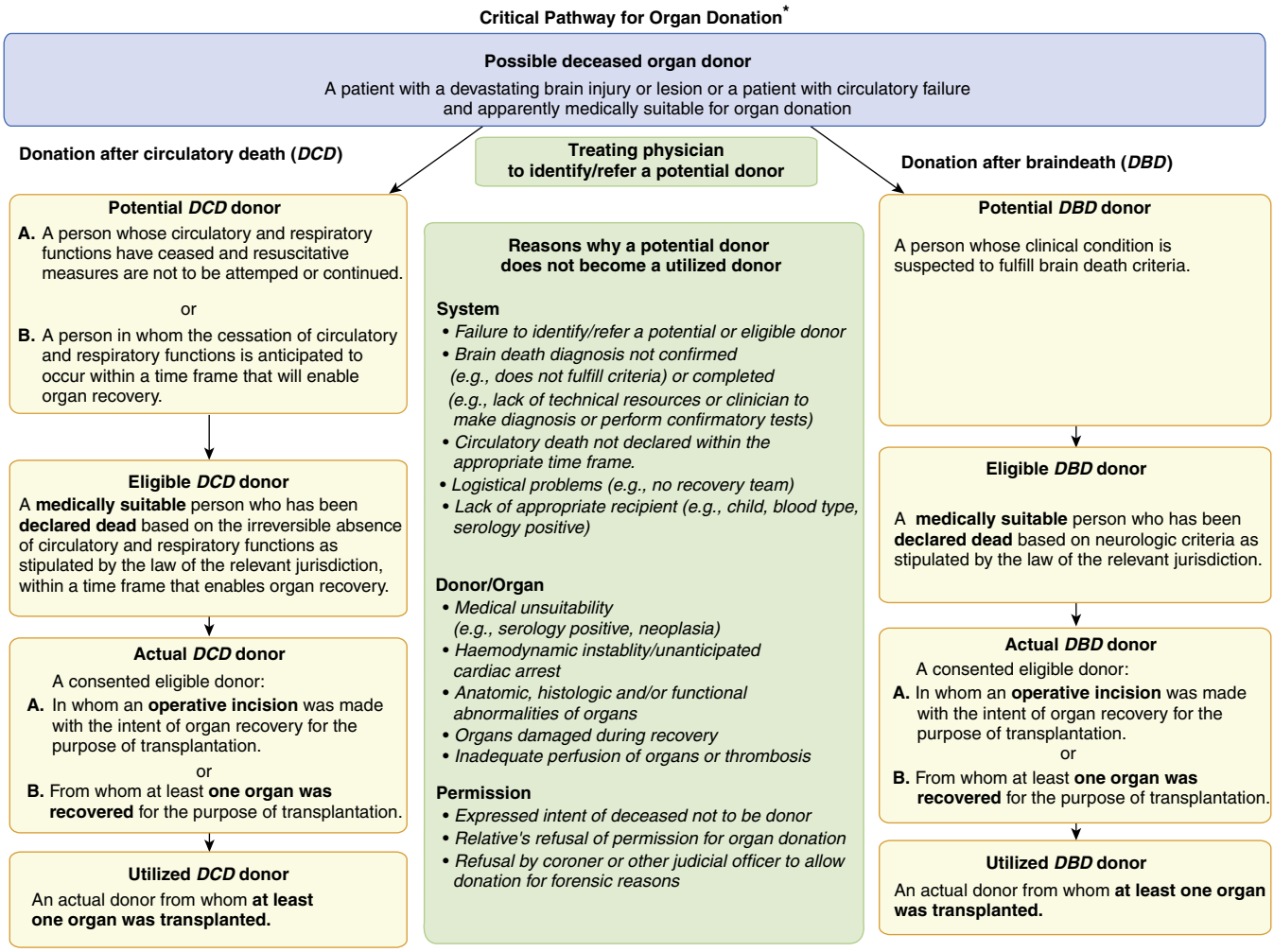


Figure 76-2. The critical pathways for donation after brain death and donation after circulatory death, as published by the World Health Organization. *(From Dominguez-Gil B, Delmonico FL, Shaheen FAM, et al: The critical pathway for deceased donation: reportable uniformity in the approach to deceased donation.* Transplant Int *24:373, 2011.)*

shortage of organs for transplantation and death is confirmed after 5 minutes of continuous circulatory arrest.[77]

Organ donation and transplant rates vary widely across the globe. A number of countries, such as Spain, Portugal, France, Italy, and the United States, have deceased donation rates over 20 per million of population, whereas the rates were less than 20 per million of population in the United Kingdom, the Netherlands, and Australia in 2009.[130] The contribution of DCD to overall donor numbers varies internationally, too. Whereas DCD accounts for a substantial proportion of overall deceased organ donors in the Netherlands and the United Kingdom, DCD is virtually nonexistent in Germany and Portugal.[123] The WHO recently issued the critical pathway for both DCD and DBD, a tool that can be applicable to every country and every area of specific hospitals, regardless of the level of development of the related health care system or its baseline experience on deceased organ donation (1) to provide a common systematic approach to the deceased organ donation process, considering both DBD and DCD; (2) to provide a useful and common tool for assessing the potential of deceased donation, evaluation performance in the deceased donation process and identifying areas for improvement; and (3) to create a common scenario or trigger in which the prospective identification and referral of a possible deceased organ donor can be undertaken (Fig. 76-2).[131]

Anesthesiologists should have ample knowledge about brain death and organ donation, because they would be involved not only in anesthetic management of a brain-dead patient for organ procurement but also in brain death diagnosis. In brain-dead patients, brainstem function with or without cortical functions is absent, and theoretically the patients are unconscious. However, because the spinal cord is intact and somatic and visceral reflexes remain,[1,69] special care is required for anesthesia management. Muscle relaxants are necessary to suppress motor activity mediated by spinal reflexes. Vasodilators usually are employed to suppress hypertension and tachycardia by noxious stimuli. However, some have the opinion that sedation and analgesia should be given with muscle relaxation for organ donation, especially in cases of brainstem brain death,[47] although analgesic and anesthetic agents are theoretically unnecessary. Van Norman[119] stressed

that anesthesiologists must have specific knowledge about the medical and legal definitions of death, as well as the ethical concepts behind them, and when anesthesiologists face anesthetic management for organ donation, they should consider the conditions of brain-dead patients and furthermore determine whether they really are brain dead.

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Chapter 77

Anesthesia for Obstetrics

PAMELA FLOOD • MARK D. ROLLINS

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Key Points

- The normal physiologic changes of pregnancy begin in the first trimester, affect all organ systems, and alter pharmacokinetic and pharmacodynamic responses to many drugs commonly used in anesthesia.
- All women in labor are considered to have a full stomach and an increased risk for pulmonary aspiration of gastric contents during induction of anesthesia. Drugs and clinical approaches for aspiration prophylaxis should be considered before all surgical procedures during pregnancy.
- Uterine blood flow increases progressively during pregnancy from approximately 100 mL/minute in the nonpregnant state to 700 mL/minute (~10% of cardiac output) at term gestation. Consequently, hemorrhage during pregnancy carries significant morbidity and is a leading cause of maternal death in the United States and worldwide. Early recognition with timely intervention, optimal team performance, and appropriate blood transfusions are all essential to improving patient outcome.
- Uterine and placental blood flow depend on maternal cardiac output and are directly related to uterine perfusion pressure and inversely related to uterine vascular resistance. Decreased perfusion pressure can result from maternal hypotension secondary to hypovolemia, aortocaval compression, sympathetic blockade, and decreased systemic resistance from either general or neuraxial anesthesia. Phenylephrine in boluses or as an infusion is not only effective in reducing hypotension but also has less transfer to the fetus and results in less fetal acidosis than ephedrine.
- The fetal oxyhemoglobin dissociation curve is left-shifted and the maternal oxyhemoglobin dissociation curve is right-shifted, facilitating oxygen transfer to the fetus. Fetal O_2 saturation does not exceed 60% even with 100% O_2 delivery to the mother. Maternal $Paco_2$ decreases from 40 mm Hg to approximately 30 mm Hg during the first trimester. This reduction facilitates carbon dioxide transfer across the placenta, which is primarily limited by blood flow and not diffusion.
- Maternal-fetal exchange of most drugs and other substances occurs primarily by diffusion. The rate of diffusion and peak levels in the fetus depend on maternal-to-fetal concentration gradients, maternal protein binding, molecular weight of the substance, lipid solubility, and the degree of ionization of that substance.
- Labor is a continuous process separated into first, second, and third stages. The first stage of labor includes the change of the uterine cervix from a thick closed tube to an opening of approximately 10 cm through which the fetus can be expelled. This stage is further divided into latent and active phases.
- Neuraxial anesthesia does not affect the duration of the first stage of labor or increase the risk for cesarean delivery. Also, epidural analgesia inserted early in labor does not increase the risk for cesarean delivery.
- Neuraxial analgesia is the most reliable and effective method of reducing pain during labor. Adequate analgesia is achieved with blockade of T10 to L1 during the first stage of labor and requires extension to include T10 to S4 during the second stage of labor.
- Hypertensive disorders of pregnancy complicate 5% to 10% of worldwide pregnancies and lead to more frequent rates of maternal and fetal mortality. Patients with preeclampsia have an increased risk for cerebral hemorrhage, pulmonary edema, and coagulopathy. Systolic and diastolic blood pressure higher than 160/110 mm Hg should be treated to prevent intracerebral hemorrhage.

PHYSIOLOGIC CHANGES DURING PREGNANCY AND DELIVERY

During pregnancy and the peripartum period, substantial changes in maternal anatomy and physiology occur secondary to (1) changes in hormone activity, (2) increased maternal metabolic demands and biochemical alterations induced by the fetoplacental unit, and (3) mechanical effects of an enlarging uterus.[1,2] These physiologic changes have a significant impact on anesthetic physiology, pharmacology, and management techniques required during pregnancy and present even greater implications for patients with comorbidities.

CARDIOVASCULAR CHANGES

Changes in the cardiovascular system occur throughout gestation and include (1) an increase in intravascular volumes and changes in hematology, (2) an increase in cardiac output, (3) a decrease in vascular resistance, and (4) the presence of supine hypotension. Table 77-1 and the following sections provide additional details of these changes.

Intravascular Volumes and Hematology

Maternal intravascular fluid volume begins to increase in the first trimester secondary to changes in the renin-angiotensin-aldosterone system promoting sodium absorption and water retention. These changes are likely induced by rising progesterone from the gestational sac. Plasma protein concentrations accordingly decrease with a 25% decrease in albumin and 10% decrease in total protein at term compared with nonpregnant levels.[3] Consequently, colloid osmotic pressure decreases from 27 to 22 mm Hg over the time of gestation.[4] At term, the plasma volume has increased approximately 50% above prepregnancy values and the red cell volume has increased only approximately 25%. The greater increase in plasma volume creates a physiologic anemia of pregnancy. The hemoglobin (Hb) normally remains at 11 g/dL or greater even at term, and smaller values at any time during pregnancy are concerning for anemia.[1] Overall oxygen delivery is not reduced by this anemia because of the subsequent increase in cardiac output. The additional intravascular fluid volume of approximately 1000 to 1500 mL at term helps compensate for the estimated blood loss of 300 to 500 mL typically associated with vaginal delivery and the estimated blood loss of 800 to 1000 mL that accompanies a standard cesarean section. After delivery, uterine contraction creates an autotransfusion of blood often in excess of 500 mL that offsets the blood loss from delivery. Leukocytosis is common in pregnancy unrelated to infection. Leukocytosis is defined as a white blood cell (WBC) count greater than 10,000 WBCs/mm^3 of blood. In pregnancy, the normal range can extend to 13,000 WBCs/mm^3. Neutrophilia increases at term and is exacerbated in labor, often to 34,000 WBCs/mm^3. These changes revert to normal over 4 to 5 days after delivery.[5]

Pregnancy is a hypercoagulable state with a marked increase in factor I (fibrinogen) and factor VII and lesser increases in other coagulation factors (see Table 77-1). Factors XI and XIII and antithrombin III are decreased, and factors II and V typically remain unchanged. These changes result in an approximately 20% decrease in prothrombin time (PT) and partial thromboplastin time (PTT) in normal pregnancy. Platelet count may remain normal or slightly decreased (10%) at term as a result of dilution. However, 8% of otherwise healthy women have a platelet count less than 150,000/mm^3.[6] In the absence of other hematologic abnormalities, the cause is usually gestational thrombocytopenia, during which time the platelet count does not

TABLE 77-1 CHANGES IN THE CARDIOVASCULAR SYSTEM DURING PREGNANCY

Cardiovascular Parameter	Value at Term Compared With Nonpregnant Value
Intravascular fluid volume	Increased 35%-45%
Plasma volume	Increased 45%-55%
Erythrocyte volume	Increased 20%-30%
Cardiac output	Increased 40%-50%
Stroke volume	Increased 25%-30%
Heart rate	Increased 15%-25%
Systemic vascular resistance	Decreased 20%
Pulmonary vascular resistance	Decreased 35%
Central venous pressure	No change
Pulmonary capillary wedge pressure	No change
Femoral venous pressure	Increased 15%
Coagulation System	
Increased factors	I, VII, VIII, IX, X, XII, and von Willebrand factor
Decreased factors	XI, XIII, antithrombin III, and tPA
Platelets	Decreased 0%-10%
Clinical Studies	
Electrocardiography	Heart rate dependent decrease in PR and QT intervals Small QRS axis shift to right (first TM) or left (third TM) ST depression (1 mm) in left precordial and limb leads Isoelectric T-waves in left precordial and limb leads Small Q-wave and inverted T-wave in lead III
Echocardiography	Heart is displaced anteriorly and leftward Right-sided chambers increase in size by 20% Left-sided chambers increase in size by 10%-12% Left ventricular eccentric hypertrophy Ejection fraction increases Mitral, tricuspid and pulmonic valve annuli increase Aortic annulus not dilated Tricuspid and pulmonic valve regurgitation common Occasional mitral regurgitation (27%) Small insignificant pericardial effusions may be present

TM, Trimester.
Data from references 1, 2, 283.

usually decrease to less than 70,000/mm^3. However, this syndrome is not associated with abnormal bleeding. Gestational thrombocytopenia is due to a combination of hemodilution and more rapid platelet turnover and is a diagnosis of exclusion. Other more consequential diagnoses such as idiopathic thrombocytopenic purpura and HELLP syndrome (hemolysis, elevated liver enzyme levels, and low platelet count) must be excluded (see section on maternal comorbidities and coagulopathies).

Thromboelastography (TEG) is a test of blood coagulation that examines the end result of coagulation and can provide information about clotting variables, including platelet function and the role of other coagulation factors (see also Chapter 61). At term gestation, TEG analysis reflects the hypercoagulable state with decreased time to start of clot formation (R), decreased time to specified clot strength (K), increased rate of clot formation (α), and increased clot strength (MA).[7] Although the timing and degree of change in TEG analysis varies with each parameter, many of the changes begin to occur within the first trimester.[8]

Cardiac Output

By the end of the first trimester, maternal cardiac output typically increases approximately 35% above prepregnancy values and continues to increase 40% to 50% above nonpregnant values by the end of the second trimester, where it remains throughout the third trimester. This increased cardiac output is secondary to increases in both stroke volume (25% to 30%) and heart rate (15% to 25%). Labor further increases cardiac output, which fluctuates with each uterine contraction. Increases above prelabor values of 10% to 25% occur during the first stage and 40% in the second stage. The largest increase in cardiac output occurs immediately after delivery, when cardiac output can increase by 80% to 100% more than prelabor values. This abrupt increase is secondary to the autotransfusion from the final uterine contraction, reduced vascular capacitance from loss of the intervillous space, and decreased lower extremity venous pressure from release of the aortocaval compression. This large fluctuation in cardiac output presents a unique postpartum risk for patients with cardiac disease, especially those with fixed valvular stenosis and pulmonary hypertension. Cardiac output returns toward prelabor values approximately 24 hours postpartum and decreases substantially toward prepregnant values by 2 weeks postpartum, with complete return to nonpregnant levels between 12 and 24 weeks after delivery.

Systemic Vascular Resistance

Although cardiac output and plasma volume increase, systemic blood pressure decreases in an uncomplicated pregnancy secondary to a reduction in systemic vascular resistance. Although affected by positioning and parity, systolic, diastolic, and mean blood pressure may all decrease 5% to 20% by 20 weeks gestational age and then gradually increase toward nonpregnant values as the pregnancy progresses.[9] Diastolic arterial blood pressure decreases more than systolic arterial blood pressure. Central venous and pulmonary capillary wedge pressures do not change during pregnancy, despite the increased plasma volume, because venous capacitance increases.

Aortocaval Compression

Aortocaval compression by the gravid uterus as a result of supine positioning is associated with a decrease in systemic blood pressure. Supine hypotension is experienced by nearly 15% of women at term (defined as a decrease in mean arterial pressure > 15 mm Hg with an increase in HR > 20 beats/minute)[10] and is often associated with diaphoresis, nausea, vomiting, and changes in mentation. This group of symptoms is known as supine hypotension syndrome. At term, the inferior vena cava is almost completely occluded in the supine position with the return of blood from the lower extremities through the epidural, azygos, and vertebral veins that become engorged (Fig. 77-1, *A*). Also, significant aortoiliac artery compression occurs in 15% to 20% of pregnant women. Vena caval compression in the supine position causes a decrease in both stroke volume and cardiac output of 10% to 20% (see Fig. 77-1, *B*), and may exacerbate venous stasis in the legs and thereby result in ankle edema, varices, and increased risk for venous thrombosis.

Most pregnant women have compensatory adaptations that reduce the supine hypotension despite aortocaval compression. One compensatory response is a reflexive increase in peripheral sympathetic nervous system activity. This increase in sympathetic activity results in increased systemic vascular resistance and permits arterial blood pressure to be maintained despite the reduced cardiac output. Consequently, the reduced sympathetic tone from neuraxial or general anesthetic techniques impairs the compensatory increase in vascular resistance and exacerbates the impact of hypotension from supine positioning. Compression of the lower abdominal aorta by the gravid uterus reduces arterial pressure in the lower extremities; however, decreases in systemic blood pressure as measured in the maternal arms are not reflective of this change.[11] Consequently, even without maternal symptoms, uterine and placental blood flow may be substantially decreased from supine aortocaval compression. Even with a healthy term pregnancy, prolonged maternal hypotension can significantly decrease uterine blood flow and lead to progressive fetal acidosis.[12]

Therefore, supine positioning is avoided during use of neuraxial techniques for labor analgesia and cesarean deliveries. Reducing the compression of the inferior vena cava and abdominal aorta with left tilt mitigates the degree of hypotension and helps maintain uterine and fetal blood flow. This is accomplished by positioning the patient laterally or by elevating the right hip 10 to 15 cm with a blanket, wedge, or table tilt.

Increased venous pressure below the level of compression of the inferior vena cava diverts venous blood return from the lower half of the body via the paravertebral venous plexuses to the azygos vein. Flow from the azygos vein enters the superior vena cava to bypass the obstruction and maintain venous return to the heart. Dilation of the epidural veins in pregnancy may make unintentional placement of the epidural catheter more likely. An unintended intravascular bolus of local anesthetic solution could result. An unintended intravenous bolus of local anesthetic can have significant

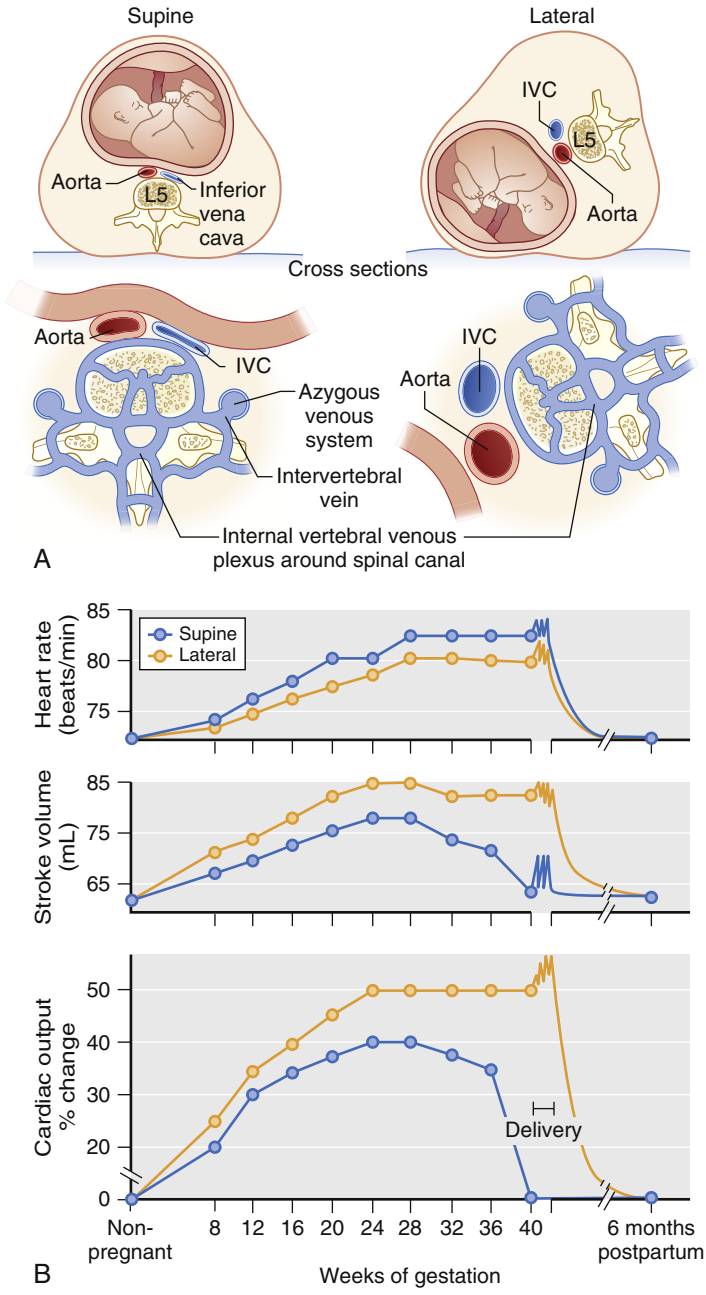


Figure 77-1. Cross-sectional views of aortocaval compression from the gravid uterus in the supine position with loss of compression in the lateral position (**A**). Alterations in heart rate, stroke volume, and cardiac output for both supine and lateral positioning with increasing gestation of pregnancy (**B**). *IVC,* Inferior vena cava. (Reprinted with permission from Bonica JJ, editor: *Obstetric analgesia and anesthesia,* Amsterdam, 1980, World Federation of Societies of Anaesthesiologists.)

consequences on the cardiovascular and central nervous systems with the possibility of complete hemodynamic collapse, seizures, and death. A small, nontoxic test dose is thus employed to decrease the likelihood of unrealized intravascular placement with initiation of neuraxial blockade. This technique is described in the section on epidural analgesia.

The cardiovascular changes of a normal pregnancy are significant. In cardiac auscultation an accentuated first heart sound (S_1) can be heard, with an increased splitting noted from dissociated closure of the tricuspid and mitral valves. A third heart sound (S_3) is often heard in the final trimester, and a fourth heart sound (S_4) can also be heard in a few pregnant patients as a result of increased volume and turbulent flow. Neither the S_3 nor S_4 has clinical significance. In addition, a benign grade 2/6 systolic ejection murmur is typically heard over the left sternal border and is secondary to mild regurgitation at the tricuspid valve from the annular dilation associated with the increased cardiac volume. Table 77-1 details the effects of pregnancy on the electrocardiogram and echocardiography. Women who present with chest pain, syncope, high-grade flow murmurs, and clinically significant shortness of breath or severe arrhythmias should undergo appropriate diagnostic investigation and referral.

RESPIRATORY SYSTEM CHANGES

Pregnancy results in significant alterations in (1) the upper airway, (2) lung volumes and minute ventilation, and (3) O_2 consumption and metabolic rate (Table 77-2).

TABLE 77-2 **CHANGES IN THE RESPIRATORY SYSTEM AT TERM**

Pulmonary Parameter	Value Near Term Compared With Nonpregnant Value (%)
Minute ventilation	Increased 45-50
Tidal volume	Increased 40-45
Respiratory rate	Increased 0 to 15
Lung Capacities and Associated Volumes	
Total lung capacity	Decreased 0-5
Vital capacity	No change
Inspiratory capacity	Increased 5-15
Inspiratory reserve volume	Increased 0-5
Tidal volume	Increased 40-45
Functional residual capacity	Decreased 20
Expiratory reserve volume	Decreased 20-25
Residual volume	Decreased 15-20
Oxygen Consumption	
Term	Increased 20
Labor (first stage)	Increased 40 above prelabor value
Labor (second stage)	Increased 75 above prelabor value
Respiratory Measures	
FEV_1	No change
FEV_1/FVC	No change
Closing capacity	No change

Data from Cheek TG, Gutsche BB: Maternal physiologic alterations. Hughes SC, Levinson G, Rosen MA, editors: *Shnider and Levinson's anesthesia for obstetrics,* ed 4. Philadelphia, 2002, Lippincott Williams & Wilkins; and Gaiser R: Physiologic changes of pregnancy. In Chestnut DH, Polley LS, Tsen LC, et al, editors: *Chestnut's obstetric anesthesia: principles and practice.* Philadelphia, 2009, Elsevier.

The Upper Airway

During pregnancy, capillary engorgement occurs with increased tissue friability and edema of the mucosal lining of the oropharynx, larynx, and trachea. As a result, an increased risk for bleeding exists during manipulation of the upper airway, in addition to an increased risk of difficult ventilation and intubation of the trachea. Suctioning of the airway and placement of devices (nasal instrumentation should be avoided) should be performed gently to prevent bleeding. Furthermore, there is increased risk for airway obstruction during ventilation and both laryngoscopy and tracheal intubation are more difficult. Also, after extubation, the airway may be compromised as a result of edema, with subsequent risk for airway obstruction in the immediate recovery period.

Consequently, attempts at laryngoscopy should be minimized and a smaller size cuffed endotracheal tube (6.0 to 6.5 mm internal diameter) used to minimize the chances of difficult placement secondary to airway edema. Airway edema can be more severe in patients with coexisting preeclampsia, in upper respiratory tract infections, and after active pushing as a result of associated increased venous pressure.[13] In addition, pregnancy-associated weight gain, particularly in women of short stature or with coexisting obesity, can create a difficult laryngoscopy because of a shorter neck and increased breast tissue. In all cases, a patient's position should be optimized and all airway instrumentation should be available before attempts are made at intubation of the trachea.

Minute Ventilation and Oxygenation

The increased O_2 demand and carbon dioxide production of the growing placenta and fetus cause minute ventilation to be increased 45% to 50% more than nonpregnant values in the first trimester and for the remainder of the pregnancy. This larger minute ventilation is attained primarily as a result of a larger tidal volume and a slight increase in respiratory frequency. Maternal $Paco_2$ decreases from 40 mm Hg to approximately 30 mm Hg during the first trimester as a reflection of the increased minute ventilation. Arterial pH, however, remains only mildly alkalotic (typically 7.42 to 7.44) because of metabolic compensation with increased renal excretion of bicarbonate ions (HCO_3^- is typically 20 or 21 mEq/L at term). Early in gestation, maternal room air PaO_2 is more than 100 mm Hg because of the presence of hyperventilation and the associated decrease in alveolar CO_2. Later, PaO_2 becomes normal or even slightly decreased, most likely reflecting small airway closure with normal tidal volume ventilation and intrapulmonary shunt. Arterial oxygenation can be significantly improved by moving the patient from the supine to the lateral position. Maternal Hb is right shifted, with the P50 (partial pressure of O_2 at which Hb is 50% saturated with oxygen) increasing from 27 to approximately 30 mm Hg. The higher P50 in the mother and lower P50 in the fetus mean that the fetal blood has higher affinity for O_2 and offloading of O_2 across the placenta is facilitated.

At term, O_2 consumption is increased by 20%. During the first stage of labor, O_2 consumption increases above prelabor values by 40% and during the second stage it is increased by 75%. The pain of labor can result in severe hyperventilation causing $Paco_2$ to occasionally decrease below 20 mm Hg.

Lung Volumes

During pregnancy, the expanding uterus forces the diaphragm cephalad and creates a 20% decrease in functional residual capacity (FRC) by term (see Table 77-2). This reduction is made up of nearly equal reductions in both the expiratory reserve volume (ERV) and residual lung volume (RV). However, closing capacity (CC) remains unchanged and creates a reduced FRC/CC ratio. This creates more rapid small airway closure with reduced lung volumes, and in the supine position FRC can be less than CC for many small airways, giving rise to atelectasis. Vital capacity does not change with pregnancy. The combination of increased minute ventilation and decreased FRC results in a more rapid rate at which changes in the alveolar concentration of inhaled anesthetics can be achieved.

During induction of general anesthesia, desaturation, and subsequent hypoxemia occur more rapidly than in a nonpregnant patient because of decreased O_2 reserve (secondary to decreased FRC) combined with increased O_2 uptake (resulting from increased metabolic rate). Preoxygenation before general anesthesia is critical for patient safety to mitigate these physiologic changes. Inhalation of either 100% O_2 for 3 minutes before induction of anesthesia, or four vital capacity breaths of 100% O_2 over the 30 seconds immediately before emergent induction is required to prevent hypoxia while intubating the trachea. The increased airway edema makes both ventilation and tracheal

intubation more difficult and further increases the potential for complications and morbidity of general anesthesia in pregnancy.

GASTROINTESTINAL CHANGES

After midgestation, the induction of general anesthesia places pregnant women at increased risk for regurgitation, aspirating gastric contents, and developing acid pneumonitis. The stomach and pylorus are moved cephalad by the gravid uterus. This repositions the intraabdominal portion of the esophagus intrathoracic and decreases the competence of the lower esophageal sphincter muscle. Higher progesterone and estrogen levels of pregnancy further reduce lower esophageal sphincter tone. Gastrin, secreted by the placenta, increases gastric hydrogen ion secretion and lowers the gastric pH in pregnant women. These changes in combination with the increased gastric pressure from the enlarged uterus increase the risk for acid reflux in pregnancy. Maternal gastric reflux with subsequent esophagitis (heartburn) increases with the pregnancy duration and is common in pregnant women.[14] In addition, gastric emptying is decreased with the onset of labor, pain, anxiety, or administration of opioids, and increased gastric contents can further increase the risk for aspiration. However, gastric emptying is not prolonged in pregnancy before labor.[15] Epidural analgesia using local anesthetics alone does not further delay gastric emptying. In contrast, epidural boluses of fentanyl do delay gastric emptying.[16]

All women in labor are considered to have a full stomach and an increased risk for pulmonary aspiration of gastric contents during induction of anesthesia. To reduce this risk, a nonparticulate antacid, a rapid sequence induction of anesthesia technique including cricoid pressure, and endotracheal intubation are considered routine parts of general anesthesia in a pregnant woman past midgestation. Reducing the production and severity of acid pneumonitis is the basis for the administration of antacids to pregnant women before induction of anesthesia. In addition to a nonparticulate antacid such as sodium citrate (30 mL) before induction of general anesthesia, metoclopramide can be useful for decreasing the gastric fluid volume of pregnant women in active labor who require general anesthesia. It can significantly decrease gastric volume in 15 minutes, although prior opioid administration reduces the effectiveness of metoclopramide.[17] Histamine-2 (H_2)-receptor antagonists increase gastric fluid pH in pregnant women approximately 1 hour after administration. A recent Cochrane review notes that a combination of antacids plus H_2 antagonists is more effective than no pharmacologic intervention and better than antacids alone in decreasing gastric acidity.[18] Current American Society of Anesthesiologists (ASA) guidelines for obstetric anesthesia state, "Before surgical procedures (i.e., cesarean delivery, postpartum tubal ligation), practitioners should consider the timely administration of non-particulate antacids, H2 receptor antagonists and/or metoclopramide for aspiration prophylaxis."[19]

HEPATIC AND BILIARY CHANGES

Blood flow to the liver does not change significantly with pregnancy. The markers of liver function, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin, increase to the upper limits of normal with pregnancy. Plasma protein concentrations are reduced during pregnancy, and the decreased serum albumin levels can result in elevated free blood levels of highly protein-bound drugs. Plasma cholinesterase (pseudocholinesterase) activity is decreased approximately 25% to 30% from the 10th week of gestation up to 6 weeks postpartum.[20-22] Although neuromuscular transmission should be analyzed before extubation, the clinical consequence of the reduced cholinesterase activity is unlikely to be associated with more marked prolongation of the neuromuscular block resulting from succinylcholine or mivacurium. Alkaline phosphatase levels more than double secondary to placental production. The risk for gallbladder disease is increased during pregnancy with incomplete gallbladder emptying and changes in bile composition. Cholecystectomy during pregnancy is required in between 1 in 1600 to 1 in 5000 pregnancies.[23]

Renal Changes

Renal blood flow and the glomerular filtration rate are increased 50% to 60% by the third month of pregnancy and remain elevated until 3 months postpartum. Therefore, the clearance of creatinine, urea, and uric acid are increased in pregnancy, and the upper laboratory limits for blood urea nitrogen and serum creatinine concentrations are decreased approximately 50% in pregnant women. Levels of urine protein and glucose are commonly increased as a result of decreased renal tubular resorption capacity. The upper limits of normal in pregnancy in a 24-hour urine collection are 300 mg protein and 10 g glucose.

Neurologic Changes

Pregnant patients are considered more sensitive to both inhaled and local anesthetics. They have a reduced minimum alveolar concentration (MAC) for inhaled anesthetics.[1,2] The MAC of a volatile anesthetic is reduced by 40% in animals[24,25] and 28% in humans during the first trimester of pregnancy.[26] However, MAC or immobility in response to volatile anesthetics occurs at the level of the spinal cord. An electroencephalographic based study suggests that anesthetic effects of sevoflurane on the brain are similar in the pregnant and nonpregnant state.[27] The underlying mechanism of reduced MAC in pregnancy remains unclear; it is likely multifactorial, and many postulate progesterone may have a role.

Pregnant women are more sensitive to local anesthetics. The same level of either spinal or epidural neuraxial blockade is achieved with a smaller dose of local anesthetic compared with that in nonpregnant individuals. At term the epidural veins are engorged, which decreases the size of the epidural space and volume of cerebrospinal fluid (CSF) in the subarachnoid space. However, CSF pressure does not increase with pregnancy until labor, when it increases in a pulsatile manner with both uterine contractions and pushing.[28] Although the decreased volume of these spaces facilitates the spread of local anesthetics, the local anesthetic dose requirement is decreased for neuraxial block as early as the first trimester, before

significant aortocaval compression or other mechanical- or pressure-related changes occur.[29] Consequently, the increased nerve sensitivity and decrease in local anesthetic dose requirements are likely biochemical in origin.

UTEROPLACENTAL PHYSIOLOGY

The placenta is composed of both maternal and fetal tissues and is the interface of maternal and fetal circulation systems. It provides a substrate for physiologic exchange between the two systems. The placenta is made up of a basal and a chorionic plate that are separated by the intervillous space. Maternal blood is delivered to the placenta by the uterine arteries and enters the intervillous space via the spiral arteries. The fetal blood arrives at the placenta via two umbilical arteries that form umbilical capillaries that cross the chorionic villi. After placental exchange, nutrient-rich and waste-free blood is returned from the placenta to the fetus through a single umbilical vein.

UTERINE BLOOD FLOW

An understanding of uteroplacental blood flow is critical for appropriate clinical care. Uterine blood flow increases progressively during pregnancy from about 100 mL/minute in the nonpregnant state to 700 mL/minute (~10% of cardiac output) at term gestation. Approximately 80% of the uterine blood flow perfuses the intervillous space (placenta) and the remainder perfuses the myometrium. Uterine blood flow has minimal autoregulation, and the vasculature remains essentially fully dilated during pregnancy. Uterine and placental blood flow depend on maternal cardiac output and are directly related to uterine perfusion pressure and inversely related to uterine vascular resistance. Decreased perfusion pressure can result from maternal hypotension secondary to hypovolemia, aortocaval compression, or sympathetic blockade and decreased systemic resistance from either general or neuraxial anesthesia. Increased uterine venous pressure also can decrease uterine perfusion. This can occur from supine positioning with vena caval compression, frequent or prolonged uterine contractions, or significant prolonged abdominal musculature contraction (Valsalva) during pushing. Additionally, extreme hypocapnia ($Paco_2$ < 20 mm Hg) occasionally associated with hyperventilation secondary to labor pain can reduce uterine blood flow with resultant fetal hypoxemia and acidosis.

Neuraxial blockade does not alter uterine blood flow as long as maternal hypotension is avoided, but decreases in maternal blood pressure during neuraxial or general anesthesia should be immediately corrected.

Endogenous maternal catecholamines and exogenous vasopressors may cause increasing uterine arterial resistance and decreasing uterine blood flow depending on the class and amount given. In a pregnant ewe model, use of α-adrenergic vasopressors—methoxamine and metaraminol—increases uterine vascular resistance and decreases uterine blood flow, whereas administration of ephedrine did not reduce uterine blood flow despite drug-induced increases in maternal arterial blood pressure.[30] As a result, ephedrine was previously considered the vasopressor of choice for the treatment of hypotension caused by the administration of neuraxial anesthesia to pregnant women. In complete contrast, more recent human trials demonstrate the use of phenylephrine (α-adrenergic agonist) for treatment of neuraxial-induced hypotension or use of phenylephrine as a prophylactic infusion at the time of spinal placement is not only effective in preventing hypotension, but also is associated with less fetal acidosis and base deficit than use of ephedrine.[31-34] Other methods to reduce maternal hypotension with induction of regional or general anesthesia are discussed in the section on anesthesia for cesarean delivery.

PLACENTAL EXCHANGE

Oxygen Transfer

The delivery of O_2 from the mother to the fetus depends on a variety of factors, including the ratio of maternal to fetal placental blood flow, the O_2 partial pressure gradient between the two circulations, the diffusion capacity of the placenta, the respective maternal and fetal Hb concentrations and O_2 affinities, and the acid-base status of the fetal and maternal blood (Bohr effect). O_2 delivery to the fetus is facilitated primarily because the fetal oxyhemoglobin dissociation curve is left-shifted (greater O_2 affinity) while the maternal oxyhemoglobin dissociation curve is right-shifted (decreased O_2 affinity). Fetal PaO_2 is normally 40 mm Hg and never more than 60 mm Hg, even if the mother is breathing 100% O_2.[35] This is because significant O_2 has been extracted before arrival at the fetoplacental unit. Animal studies note that in the face of decreased O_2 delivery, fetal O_2 consumption can be maintained with increased O_2 extraction until the maternal O_2 delivery is approximately 50% of its normal state.[36,37] CO_2 easily crosses the placenta and is limited by blood flow and not diffusion.

Drug Transfer

Maternal-fetal exchange of most drugs and other substances less than 1000 Daltons occurs primarily by diffusion. The rate of diffusion and peak levels in the fetus depend on maternal-to-fetal concentration gradients, maternal protein binding, molecular weight of the substance, lipid solubility, and the degree of ionization of that substance. The maternal blood concentration of a drug is typically the primary determinant of how much drug will ultimately reach the fetus. The high molecular weight and poor lipid solubility of nondepolarizing neuromuscular blocking drugs result in limited ability of these drugs to cross the placenta (see also Chapter 34). Succinylcholine has a low molecular weight but is highly ionized and therefore does not readily cross the placenta unless given in large nonclinical doses. Thus, during administration of a general anesthetic for cesarean delivery, the fetus or neonate is not paralyzed. Both heparin and glycopyrrolate have minimal placental transfer because they are highly charged. In contrast, placental transfer of volatile anesthetics, benzodiazepines, local anesthetics, and opioids is facilitated by the relatively low molecular weights of these drugs. As a general consideration, drugs that readily cross the blood-brain barrier also readily cross the placenta.

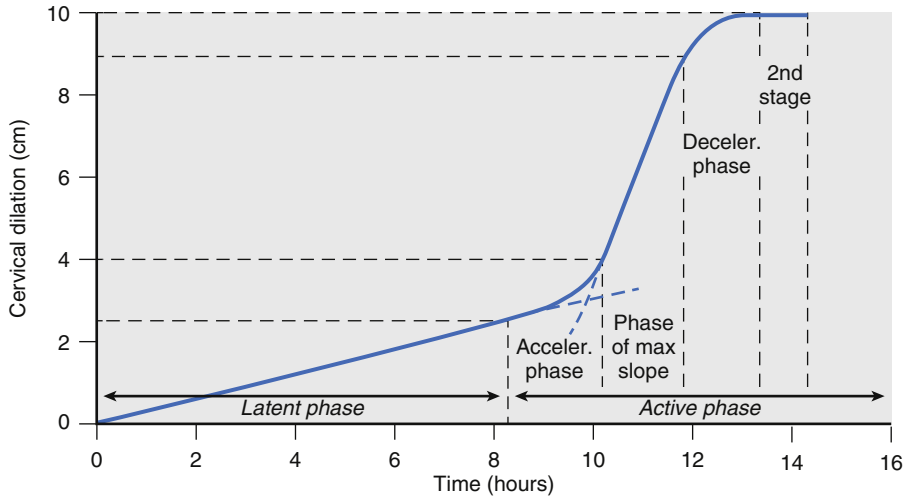


Figure 77-2. Friedman's original sigmoid model of the progress of cervical dilation over time based on an analysis of 500 nulliparas at term. Since the model's development, the existence of a deceleration (*Deceler.*) phase has been discounted and the actual time frame has expanded, likely as a result of physiognomic and treatment-related changes. *Acceler,* Acceleration. (Reproduced with permission from Friedman E: Primigravid labor: a graphicostatistical analysis, *Obstet Gynecol* 6:567-589, 1955.)

Fetal blood is more acidic than maternal blood, and the lower pH creates an environment in which weakly basic drugs, such as local anesthetics and opioids, cross the placenta as nonionized molecules and become ionized in the fetal circulation. Because this newly ionized molecule has more resistance to diffusion back across the placenta, the drug may accumulate in the fetal circulation and reach levels higher than the maternal blood. This process is referred to as ion trapping. During fetal distress (lower pH in the fetal circulation), higher concentrations of these weakly basic drugs can be trapped.[38] High amounts of local anesthetics in the fetal circulation decrease neonatal neuromuscular tone. Extremely high levels, such as those associated with unintended maternal intravascular local anesthetic injection, result in a variety of fetal effects, including bradycardia, ventricular arrhythmias, acidosis, and severe cardiac depression. Placental transfer and fetal uptake of specific analgesic and anesthetic drugs are detailed later in the sections on methods of labor analgesia and anesthesia for cesarean delivery.

FETAL CIRCULATION AND PHYSIOLOGY

The fetal blood volume increases throughout gestation. Approximately two thirds of the fetal-placental blood volume is contained within the placenta.[39] During the second and third trimester, the fetal blood volume has been estimated to be approximately 120 to 160 mL/kg of fetal body weight.[40] Thus, the total blood volume of a term normal fetus is approximately 0.5 L. Although fetal liver function is not yet mature, coagulation factors are synthesized independent of the maternal circulation. The serum concentrations of these factors increase with gestational age and do not cross the placenta. However, fetal clot formation in response to tissue injury is decreased in comparison to that in adults. The anatomy of the fetal circulation helps decrease fetal exposure to potentially high concentrations of drugs in umbilical venous blood. Approximately 75% of umbilical venous blood initially passes through the fetal liver, which may result in significant drug metabolism before the drug reaches the fetal heart and brain (first-pass metabolism). Fetal and neonatal enzyme system activities are lower than those of adults, but most drugs can be metabolized. In addition, drugs entering the fetal inferior vena cava via the ductus venosus are initially diluted by drug-free blood returning from the fetal lower extremities and pelvic viscera. These anatomic characteristics of the fetal circulation markedly decrease fetal plasma drug concentrations compared to maternal concentrations.

LABOR PROGRESS

Labor begins with the onset of repetitive uterine contractions that result in the dilation of the cervix. In reality, however, preparation for labor may begin several hours or days before active labor with an inflammatory process mediated by cellular infiltration and release of local cytokines that result in softening of the cervix. The signals that orchestrate the onset of spontaneous labor are not precisely known. Organized, regular uterine contractions result in progressive cervical dilation and effacement. When spontaneous labor does not occur at an appropriate time, labor may be induced for fetal or maternal indications with various pharmacologic and physical methods.[41]

Labor is a continuous process separated into first, second, and third stages. The first stage of labor includes the change of the uterine cervix from a thick, closed tube to an opening of approximately 10 cm through which the fetus can be expelled. This stage is further divided into a latent phase and an active phase. The second stage of labor begins when the cervix is fully dilated and ends with the expulsion or birth of the fetus. The third stage of labor is the delivery of the placenta. The time course of the first stage of labor was first studied by Emanuel Friedman who described a sigmoidal relationship between cervical dilation and time (Fig. 77-2). The sigmoidal nature of the relationship has since been challenged in that little evidence

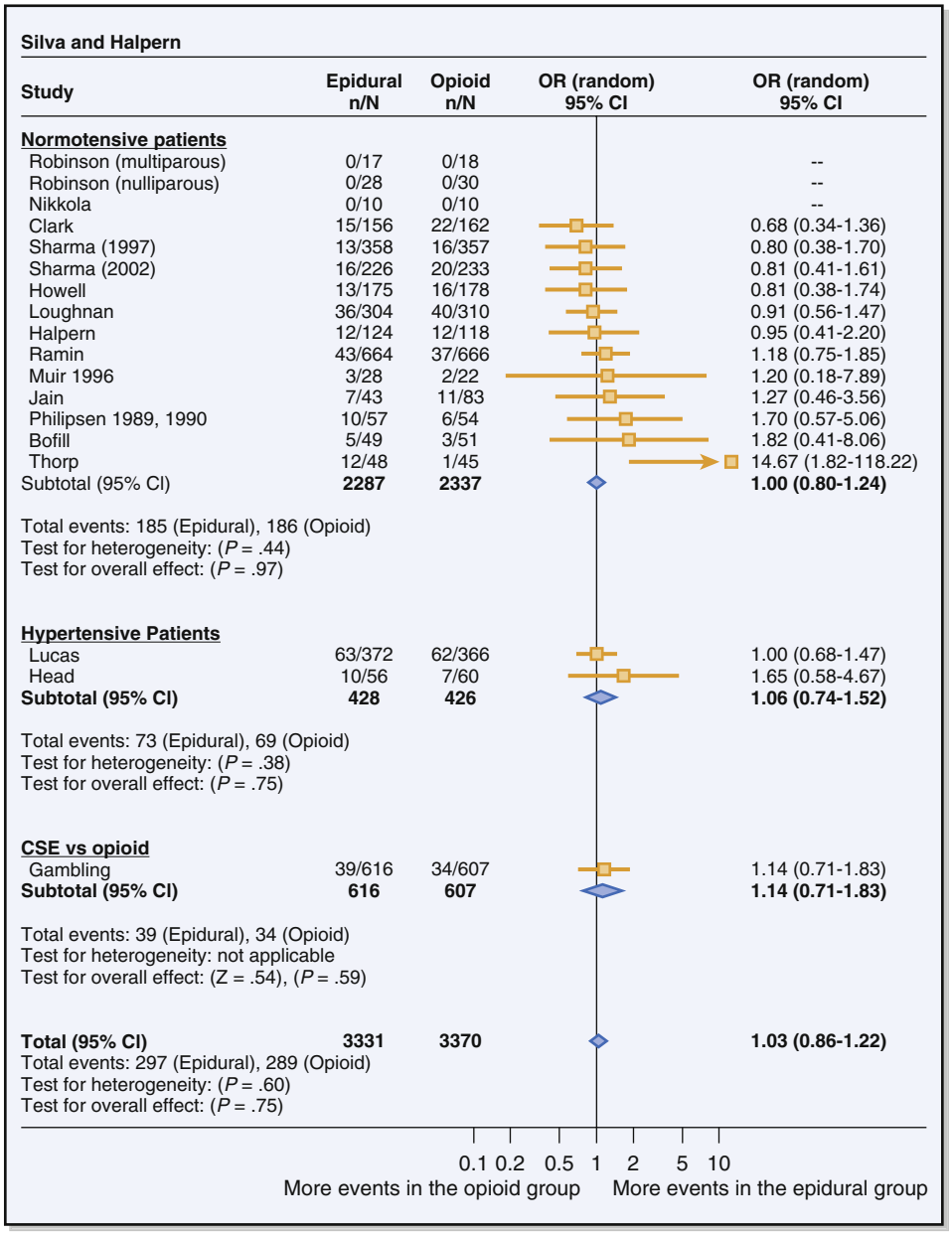


Figure 77-3. The number of patients who had a cesarean section, the odds ratio (*OR*), and 95% confidence interval (*CI*) are shown for each study. The size of the box is proportional to the weight of the study in the meta-analysis. The scale is logarithmic. *N*, Total number of patients in the analysis; *n*, number of events (Reproduced with permission from Leighton, BL, Halperhn SH: Epidural analgesia and the progress of labor. In Halpern SH, Douglas MJ, editors: *Evidence-based obstetric anesthesia,* Oxford, 2005, Blackwell.)

exists for a deceleration phase as the cervix approaches complete dilation (10 cm). However, the separation of the first stage of labor into an early slow phase termed *latent labor* and a more rapid phase of active labor has stood the test of time and advances in modeling techniques.[42,43]

Labor may be referred to as abnormal on the basis of having abnormally slow latent labor, arrest in the active phase, or arrest of descent (failure of stage 2). Dystocia is defined as abnormal labor and may be a result of inadequate uterine contractions, mismatch of fetal and pelvic size, or abnormal fetal position. The Montevideo unit is traditionally used by obstetricians to assess the adequacy of uterine contractions. The Montevideo unit is defined as the intensity of contractions (in millimeters of mercury, as measured with an intrauterine pressure catheter) multiplied by the number of contractions that occur in 10 minutes. The diagnosis of dystocia is based on deviation from normal values derived from populations; however, significant variability exists among individual laboring women. Multiparity has been consistently associated with faster labor. Various demographic and genetic factors contribute to the variability in labor progress.[42-47] Greater maternal weight, older age, and larger fetal size have been associated with slower labor.[42,45,48] Evidence also indicates a hereditary role in labor progress from epidemiologic studies.[49] Specifically, β_2-adrenergic and oxytocin receptor polymorphisms have been implicated in mediating variability in labor progress.[44-46] Abnormally poor response to intrinsic or extrinsic oxytocin may result in abnormal contractility, as would abnormally strong response to β_2-adrenergic agonists and native catecholamines, which inhibit contractility.

Many observational studies have suggested that epidural analgesia is associated with slower labor progress.[45,50] This association has been repeatedly noted in observational trials but has not been replicated in prospective randomized trials (Fig. 77-3). It is not clear that

epidural analgesia *causes* slower labor progress. Rather, various confounding variables could result in this association. Clearly, patients with more exposure to severe pain would be more likely to request analgesia and more likely to request it earlier. Large prospective studies in which patients were randomly assigned to early or late neuraxial anesthesia have invariably concluded that neuraxial anesthesia does not affect the length of the first stage of labor or increase the risk for cesarean delivery and that epidural analgesia placed early in labor does not increase the risk for cesarean delivery.[51-55] Some have hypothesized that the difference between the findings of earlier observational trials and more recent randomized controlled trials might be due to a change to lower concentrations of local anesthetics in regional anesthesia regimens. This is not the case, because a comparison with an older regimen that used 0.25% bupivacaine and a lower dose regimen using 0.1% bupivacaine found no difference in the rate of cesarean delivery.[56] The lack of association makes physiologic sense because uterine smooth muscle is not innervated by motor nerves and thus not affected by local anesthetics. No physiologic mechanism is known by which blockade of sensory transduction or local anesthetic activity would impede uterine contractility. In contrast, several prospective trials suggest that neuraxial anesthesia may cause a modest prolongation of the second stage of labor of approximately 15 minutes.[57,58] This may occur because maternal delivery of the fetus normally requires the participation of abdominal and pelvic skeletal muscle, and diminution of motor nerve transmission and lack of sensory feedback could impede coordinated pushing. Local anesthetic dose can be reduced in the second stage if the blockade is too dense to allow for coordinated expulsion efforts. When the labor is comfortable for the pregnant patient, tolerance for a longer second stage may allow uterine contractions to lower the fetal station before active efforts for vaginal delivery begin.[59]

LABOR AND FETAL MONITORING

Intrapartum fetal monitoring was created in an effort to evaluate fetal well-being and detect fetal distress earlier in labor to allow intervention before any permanent fetal injury. Electronic fetal monitoring (EFM) combines interpretation of fetal heart rate (FHR) monitoring and uterine contraction monitoring. FHR monitoring was developed in the 1960s and has been used increasingly, with 85% of laboring women monitored in 2002.[60] Practitioner variability is frequent in interpretation of the FHR tracings.[61,62] A meta-analysis comparing EFM to intermittent FHR auscultation noted the use of EFM reduced the risk for neonatal seizures (relative risk: .50), but not the risks for perinatal mortality or cerebral palsy.[63] The use of this monitoring increased rates of both operative and cesarean deliveries.[63,64]

FHR monitoring is most commonly accomplished with a surface Doppler ultrasound transducer (external monitoring), but it may be necessary to apply a fetal scalp electrode to obtain accurate continuous FHR monitoring (internal monitoring). For internal monitoring, a peak or threshold voltage of the fetal R wave from the scalp electrode is used to measure FHR. Of note, a fetal scalp electrode can be placed only if the cervix is minimally dilated and the membranes are ruptured. The fetal brain and heart rate respond to fetal asphyxia from activation of peripheral and central chemoreceptors and baroreceptors, as well as a result of various fetal CNS metabolic changes.[65] The changes in FHR produce specific patterns and characteristics that provide an evaluation of the fetal state. The nomenclature, interpretation, and management principles for FHR monitoring were updated in 2009 by the American Congress of Obstetricians and Gynecologists (ACOG).[64] These current guidelines are detailed later, and related terminology is presented in Boxes 77-1 and 77-2. An understanding of the specific uterine contraction and FHR monitoring terminology

BOX 77-1 *Fetal Heart Rate Monitoring Pattern Definitions*

Baseline

The mean FHR rounded to increments of 5 bpm during a 10-minute segment, excluding:
- Periodic or episodic changes
- Periods of marked FHR variability
- Segments of baseline that differ by more than 25 bpm

The baseline must be for a minimum of 2 minutes in any 10-minute segment, or the baseline for that period is indeterminate. In this case, one may refer to the prior 10-minute window for determination of baseline.
- Normal FHR baseline: Rate is 110 to 160 bpm.
- Tachycardia: FHR baseline is greater than 160 bpm.
- Bradycardia: FHR baseline is less than 110 bpm.

Baseline Variability

Fluctuations occur in the baseline FHR that are irregular in amplitude and frequency.

Variability is visually quantitated as the amplitude of peak-to-trough in beats per minute.
- Absent: Amplitude range is undetectable.
- Minimal: Amplitude range is detectable but 5 bpm or fewer.
- Moderate (normal): Amplitude range is 6 to 25 bpm.
- Marked: Amplitude range is greater than 25 bpm.

Acceleration

A visually apparent abrupt increase (onset to peak in < 30 seconds) occurs in the FHR.

At 32 weeks gestation and beyond, an acceleration has a peak of 15 or more bpm above baseline, with a duration of 15 seconds or more but less than 2 minutes from onset to return.

Before 32 weeks gestation, an acceleration has a peak of 10 or more bpm above baseline, with a duration of 10 seconds or more but less than 2 minutes from onset to return.

Prolonged acceleration lasts 2 minutes or more but less than 10 minutes.

If an acceleration lasts 10 minutes or longer, it is a baseline change.

Sinusoidal Pattern

Visually apparent, smooth, sine wave–like, undulating pattern occurring in FHR baseline, with a cycle frequency of 3 to 5 cycles per minute that persists for 20 minutes or longer.

Data from Macones GA, Hankins GD, Spong CY, et al: The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines, *J Obstet Gynecol Neonatal Nurs* 37:510-515, 2008.
bpm, Beats per minute; *FHR,* fetal heart rate.

BOX 77-2 ***Fetal Heart Rate Monitoring Deceleration Definitions***

Characteristics of Early Deceleration

Visually apparent, usually symmetric gradual decrease and return of the FHR occurs, associated with a uterine contraction.
A gradual FHR decrease is defined as from the onset to the FHR nadir of 30 seconds or more.
The decrease in FHR is calculated from the onset to the nadir of the deceleration.
The nadir of the deceleration occurs at the same time as the peak of the contraction.
In most cases, the onset, nadir, and recovery of the deceleration are coincident with the beginning, peak, and ending of the contraction, respectively.

Characteristics of Late Deceleration

Visually apparent, usually symmetric gradual decrease and return of the FHR occurs, associated with a uterine contraction.
A gradual FHR decrease is defined as from the onset to the FHR nadir of 30 seconds or greater.
The decrease in FHR is calculated from the onset to the nadir of the deceleration.
The deceleration is delayed in timing, with the nadir of the deceleration occurring after the peak of the contraction.
In most cases, the onset, nadir, and recovery of the deceleration occur after the beginning, peak, and ending of the contraction, respectively.

Characteristics of Variable Deceleration

Visually apparent abrupt decrease in FHR occurs.
Abrupt FHR decrease is defined as from the onset of the deceleration to the beginning of the FHR nadir of less than 30 seconds.
The decrease in FHR of 15 bpm or greater occurs, lasting 15 seconds or longer and less than 2 minutes in duration.
When the variable decelerations are associated with uterine contractions, their onset, depth, and duration commonly vary with successive uterine contractions.

Characteristics of Prolonged Deceleration

Visually apparent decrease occurs in the FHR below the baseline.
Decrease in FHR from the baseline that is 15 bpm or more lasting 2 minutes or more but less than 10 minutes.
If a deceleration lasts 10 minutes or longer, it is a baseline change.

Data from Macones GA, Hankins GD, Spong CY, et al: The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines, *J Obstet Gynecol Neonatal Nurs* 37:510-515, 2008.
FHR, Fetal heart rate.

and clinical implications is critical for optimal communication during emergent situations among anesthesiologists, obstetricians, midwives, and labor nurses.

CONTRACTION MONITORING

Uterine contractions can be monitored externally or with an intrauterine pressure transducer. External monitors allow determination only of contraction frequency, whereas internal monitors also allow quantitative measurement of intrauterine pressure. Uterine contractions are quantified over a 10-minute window that is averaged over a 30-minute window with recent guidelines provided by the ACOG.[64] Normal contractions are defined as five or fewer contractions in 10 minutes, averaged over a 30-minute window. Tachysystole is defined as uterine activity greater than five contractions in 10 minutes, averaged over a 30-minute window. Tachysystole applies to both spontaneous and augmented labor and should always be qualified as to the presence or absence of associated FHR decelerations. The terms *hyperstimulation* and *hypercontractility* are no longer defined and should be abandoned. Treatment of tachysystole during labor may differ depending on the clinical situation, but may include sublingual or intravenous (IV) nitroglycerin[66] to briefly relax the uterus, as well as the use of β_2-adrenergic drugs such as terbutaline.

FETAL HEART RATE TRACING

The FHR tracing is used as a nonspecific reflection of fetal acidosis. It should be interpreted over a time course in relation to the clinical context and other known maternal and fetal comorbidities, because multiple factors other than fetal acidosis can influence the FHR tracing. Box 77-1 defines FHR baseline, variability, and accelerations. Box 77-2 details FHR tracing deceleration characteristics. Late decelerations are a result of uteroplacental insufficiency causing relative fetal brain hypoxia during a contraction. The resulting sympathetic outflow elevates the fetal blood pressure and activates the fetal baroreceptors and an associated slowing in the FHR. A second type of late deceleration is from myocardial depression in the presence of increasing hypoxia.[67] Early decelerations tend to mirror the uterine contraction and are believed to be in response to a vagal stimulus, which may or may not be the result of fetal head compression. However, other sources note these may be a benign variant of the "reflex" late deceleration that rather mirrors the uterine contraction and might evolve into a more typical late deceleration.[68] Variable decelerations are associated with umbilical cord compression. A sinusoidal FHR pattern is associated with placental abruption and is ominous.[69] In general, minimal-to-undetectable FHR variability in the presence of decelerations is associated with fetal acidosis.[70] Severe decelerations (<70 beats/minute for >60 seconds) are associated with fetal acidemia and are extremely ominous, particularly with the absence of variability.[71] These patterns and characteristics are used to define the FHR categories in the following section.

FETAL HEART RATE CATEGORIES

A three-tiered FHR category classification system is currently recommended for fetal assessment.[64] This system evaluates the fetus for a given moment of the assessment, and it must be recognized the fetal condition may move back and forth from one category to another over time. Specific terminology used for categorization is defined in Boxes 77-1 and 77-2.

Category I FHR tracings are considered normal and are predictive of a normal fetal acid-base state at the time of observation, and no specific management is required. All of the following criteria must be present: (1) baseline FHR of 110 to 160 beats/minute, (2) moderate baseline FHR variability, (3) no late or variable decelerations, (4) early decelerations may be present or absent, and (5) accelerations may be present or absent.

Category II FHR tracings are considered indeterminate and include all tracings not in categories I or III. Examples include but are not limited to fetal tachycardia, absence of induced accelerations after fetal stimulation, prolonged decelerations more than 2 minutes but less than 10 minutes, and recurrent late decelerations with moderate baseline variability. Category II tracings are not predictive of abnormal fetal acid-base status and require continued monitoring and reevaluation in light of the entire clinical picture. In some cases, additional tests may be obtained or intrauterine resuscitative measures taken to improve the fetal condition.

Category III FHR tracings are considered abnormal and are associated with an abnormal fetal acid-base state at the time of observation. Category III tracings include either a sinusoidal FHR pattern or absent FHR variability with recurrent late decelerations, recurrent variable decelerations, or bradycardia. These tracings require prompt patient evaluation and efforts to improve the fetal condition. These interventions may include intrauterine resuscitation with change in maternal position, discontinuation of labor augmentation, treatment of maternal hypotension, use of supplemental O_2, and treatment of tachysystole if present. If the FHR tracing does not improve, expeditious delivery should proceed.

LABOR ANALGESIA

Childbirth is a pinnacle event in a family's life that is surrounded by many beliefs and traditions, some of which are founded in science and others more historical. In this context, several nonpharmacologic techniques have been used to relieve the pain of childbirth throughout history, including acupuncture,[72] massage,[73,74] and hypnosis.[75] Drugs were not used in Western medicine to relieve pain in childbirth until the mid-1800s, most famously when the English Queen Victoria chose to inhale chloroform for analgesia during the birth of Prince Leopold.

For most women, labor is intensely painful. However, the time course of pain intensity is highly variable, dynamic, and unpredictable. Some women will experience severe pain only just before the second stage of labor, whereas others will report severe pain from their first contraction. Rarely do women not experience any pain in labor and give birth unexpectedly under inopportune conditions.[76] The source of these differences in labor pain is not completely known but may be in part genetic. In one study, Asian women reported more pain in labor than women of other ethnic backgrounds.[42,45] This association was also found with a single nucleotide polymorphism in the β_2-adrenergic gene.[45] Other factors may include pelvic size and shape, fetal presentation, and whether the contractions are augmented.

NONPHARMACOLOGIC LABOR PAIN MANAGEMENT

Many patients prefer to use nonpharmacologic methods of pain management during all or part of labor. Acupuncture can be effective in treating postoperative pain after cesarean section,[77] but it is not as effective for analgesia during labor. In a recent meta-analysis, labor pain was compared between patients who received acupuncture and those who reviewed sham acupuncture (superficial needling lateral to an actual acupuncture point). The patients reported a small but statistically significant effect of acupuncture (4% to 6%) that lasted for only 30 minutes.[78] Unfortunately, most of the trials were not properly blinded, increasing the likelihood of bias.

Several trials have found a reduction in pain and anxiety during the first stage of labor with the use of massage. A Cochrane review on massage in labor identified seven randomized trials of massage, six of which were judged to have low or unclear risk for bias.[74] During the first stage of labor, pain was reduced in the massage group by –0.98/10 (confidence interval [CI], 1.17 to 0.47). No difference was found in the use of pharmacologic pain relief between groups or in pain report during the second and third stages of labor. One study of 60 women found that massage decreased anxiety.[79]

Hypnosis has been used both as a relaxation technique and for management of pain during labor. When hypnosis was compared with standard care, no evidence was found that pain was less after hypnosis, nor was evidence found for a difference in satisfaction with pain relief.[74]

Other nonpharmacologic techniques include the breathing techniques described by Lamaze, the LeBoyer technique, transcutaneous nerve stimulation, hydrotherapy, presence of a support person, intradermal water injections, and biofeedback. A retrospective national survey of women's childbearing experiences found that although neuraxial methods of pain relief were considered the most helpful and effective, nonpharmacologic methods of tub immersion and massage were rated more or equally helpful in relieving pain compared with the use of opioids.[80] Although many nonpharmacologic techniques seem to reduce the perception of labor pain, most published studies lack the rigorous scientific methodology for useful comparison of these techniques to pharmacologic methods.

CONSIDERATIONS FOR PHARMACOLOGIC TREATMENT OF PAIN IN LABOR

Preprocedural assessment is required for any patient who is a potential candidate for neuraxial analgesia and should be considered as a preparation for potential obstetric emergency. Assessment of all laboring women for risk factors for neuraxial analgesia and general anesthesia is recommended, because in the event an emergency decision is made to proceed with either procedure, sufficient time may not be available for adequate, safe evaluation and discussion with the patient. In otherwise healthy women, routine laboratory testing is not required.[19] Although any laboring woman has the potential to require cesarean section, labor takes many hours and requires adequate nutrition and hydration. While balancing these two considerations, the ASA has recommended that moderate amounts of clear liquids be allowed during the administration of neuraxial analgesia and throughout labor and, furthermore, a period of abstention from solids before the placement of neuraxial analgesia is not required.[19]

SYSTEMIC MEDICATIONS

The first systemic medications used for labor analgesia were herbal and plant preparations. Plant extracts used for labor analgesia include motherwort and rice bran syrup,[81] but these treatments have not been prospectively studied, and it is unknown whether these treatments provide analgesic benefit. Extracts of the poppy plant that contain opium have analgesic properties that are clearly a result of their activation of the μ-opioid receptor. Many other natural and synthetic drugs that also act via activation of the μ-opioid receptor provide statistically and clinically significant labor analgesia. Opioids are used commonly for labor analgesia because they are mostly inexpensive and widely available. They can be administered intramuscularly without the need for IV access. In current practice, long-acting opioids used for labor analgesia include morphine, hydromorphone, and meperidine. Worldwide, meperidine is the most commonly used long-acting opioid in obstetric practice[82] but, unfortunately, the most likely to result in side effects. It is typically administered intravenously in doses of up to 25 mg or intramuscularly in doses up to 50 mg. Maternal half-life is 2 to 3 hours, and fetal and newborn half-life is significantly longer (13 to 23 hours) with an active, potentially neurotoxic metabolite (normeperidine) that can accumulate with repeated doses. With increased dosing and shorter intervals between doses and delivery, risk to the newborn is increased, including lower Apgar scores and prolonged time to sustained neonatal respiration.[83]

Morphine is rarely used for labor pain. Like meperidine it has an active metabolite (morphine-6-glucuronide) with a half-life that is longer in neonates than in adults, and it produces significant maternal sedation. Obstetricians may use intramuscular morphine combined with phenergan for analgesia, sedation, and rest termed "morphine sleep." This combination produces analgesia and sedation for approximately 2.5 to 4 hours, with an onset of 10 to 20 minutes and is used most commonly in latent labor.

More recently, the shorter acting fentanyl and ultra–short-acting remifentanil have entered clinical practice. Fentanyl has a short duration and no active metabolites. When given in small IV doses of 50 to 100 μg/hr, no significant differences are seen in neonatal Apgar scores and respiratory effort compared with those in newborns of mothers not receiving fentanyl.[84]

Remifentanil has entered clinical practice as an alternative to neuraxial analgesia for patients with contraindications and in some settings as an alternative for patients who simply do not desire neuraxial anesthesia. Overall, short-acting and long-acting opioids do not show a significant difference in pain relief. One exception is that remifentanil may offer some advantage over other opioids in efficacy.[73] In addition, remifentanil offers an important safety advantage when used in active labor in that it is an ultra short acting opioid highly metabolized by placental esterase and thus the fetal-to-maternal ratio is small. The metabolism of remifentanil depends completely on tissue tissue and plasma esterases, which are fully mature in the fetus. Thus, remifentanil does not depend on the maturity of any organ for its degradation and is more rapidly metabolized in the fetoplacental unit than in the maternal plasma. In the pregnant ewe model, the maternal-to-fetal ratio of remifentanil is approximately tenfold,[85] and the ratio was similar in human studies.[86] Because of these characteristics, more remifentanil can be administered to the mother at times close to delivery than would be considered safe for longer acting opioids that rely on slower metabolism by the liver. Remifentanil is more effective than long-acting opioids[73]; however, the improvement in pain relief may be because larger doses of remifentanil were given compared with doses of meperidine.[87] Another study comparing remifentanil to meperidine and fentanyl noted improved analgesia with remifentanil in the first hour, with return to no difference between opioids after 3 hours.[88] A randomized controlled trial comparing epidural analgesia to use of a remifentanil patient-controlled analgesia noted lower pain scores in the epidural group.[89] Although there was higher maternal sedation in the remifentanil group, there were no differences in fetal outcome measures. The major risk of remifentanil in labor is maternal respiratory depression. Careful surveillance is required to ensure adequate oxygenation throughout treatment.

INHALED ANALGESIA

Inhaled anesthetics were the first treatments for labor analgesia used in modern times. The first woman anesthetized for childbirth in the United States was Fanny Longfellow, the wife of the poet, Henry Wadsworth Longfellow. Longfellow acted as anesthesiologist to his wife who was highly criticized for her decision to accept anesthesia. In the United Kingdom, Emma Darwin, wife of Charles Darwin, was anesthetized with chloroform for the last two of her eight births, also with her famous husband acting as anesthesiologist. Six years later, British Queen Victoria was administered chloroform for analgesia by Dr. John Snow during the birth of Prince Leopold.[90] Despite disapproval from religious authorities, pregnant women in the United States and Britain voted with their swollen feet and began requesting anesthesia for childbirth. However, as volatile anesthetics became more commonly used in childbirth, side effects were more commonly encountered. Neonatal depression and maternal gastric aspiration were reported as volatile techniques became more commonly used for operative delivery.[91-93] Delivery was complicated by aspiration of gastric contents in 66 women from 44,016 deliveries (0.15%) between 1932 and 1945. The preventive fasting measures recommended by Mendelsohn became cornerstones of obstetric anesthesia practice. Reduction of stomach contents by restricting intake, provision of nonparticulate antacids, and improvement of anesthetic-induction technique have improved the safety of volatile anesthetics in pregnancy, which are in modern times almost exclusively used as general anesthetics for cesarean section rather than for pain relief during vaginal delivery. Volatile anesthetics are no longer used for labor analgesia. Nitrous oxide, however, is still commonly used worldwide and is welcomed by many parturients as a less invasive approach to pain relief in labor.

In 1881, Stanislav Klikovitch described the use of N_2O for labor in Russia.[94] Klikovitch recommended mixing N_2O with O_2 and intermittent use of the gas with contractions. N_2O is currently used commonly in this manner

for labor analgesia in Europe, Scandinavia, and Australia, but only uncommonly in the United States. Typically it is blended with O_2 in a 50:50 ratio or slightly greater for patient-inhaled self-administration. N_2O provides significant pain relief with a median reduction of pain score of 14/100 (95% CI −4 to −24) in a meta-analysis that included data from three studies.[95] Compared with placebo or no treatment, N_2O is associated with a median reduction in pain score of 3.5 in 10 (95% CI 3.3 to 3.8) in one study of 509 parturients.[95] Some studies have demonstrated moderate analgesia in response to inhaled N_2O (8 in 10 to 6 in 10),[96] whereas others have shown no difference in visual analogue pain scores.[97] Paradoxically, many of the women who were enrolled in the previously mentioned negative study by Carstoniu and colleagues[97] wished to continue its use after the study period. Women in other studies have reported significant "benefit" to its use, and the majority who used it during labor stated that they would choose it as a form of pain relief for subsequent labors.[98,99] The analgesic effect of N_2O may be confounded by sedative or relaxing effects that offer benefit to the parturient apart from or in addition to analgesia. Without the coadministration of opioids, use of 50% N_2O in O_2 is safe and does not result in hypoxia, unconsciousness, or loss of protective airway reflexes.[100] In addition, no decrease in uterine contractility or neonatal depression occurs regardless of duration of use.

NEURAXIAL ANALGESIA

Neuraxial analgesia is the most reliable and effective method of reducing pain during labor.[80] However, it is encumbered by small but real and predictable risks.

Timing of Placement

The optimal timing for the placement of a neuraxial anesthetic has been extensively studied. In a 2011 updated Cochrane review of 38 trials including 9658 parturients, epidural analgesia offered better pain relief compared with placebo (median reduction 3.4 in 10 (95% CI 1.3 to 5.4) and reduced the need for additional pain medication.[101] However in these trials, the use of neuraxial analgesia was associated with an increased risk of requirement for assisted vaginal birth (relative risk [RR] 1.4, 95% CI 1.3 to 1.6), motor blockade (RR 32, 95% CI 4 to 232), urinary retention (RR 17, 95% CI 5 to 60), longer second stage of labor (mean diiference [MD] 13.7 minutes, 95% CI 6.7 to 20.7 minutes), and risk for cesarean section for fetal distress (RR 1.4, 95% CI 1.03 to 1.97). However, the rate of cesarean section and neonatal Apgar scores were not different. Therefore, epidural analgesia can provide superior analgesia, but at the cost of an increased likelihood of instrument delivery and a prolonged second stage of labor (see earlier discussion of labor progress). Does the stage of labor at which the neuraxial analgesic was placed influence the ensuing time course of labor? As discussed previously, older studies in which larger doses of local anesthetic were used that did not use random allocation of treatment found that early initiation of epidural analgesia is associated with a longer first stage of labor. Blinding of patient and investigator in studies of a complex intervention, such as neuraxial analgesia, is difficult, but inadequate blinding and random allocation leaves the results of the trial subject to concerns for bias. In 2011, a meta-analysis including prospective, well-randomized trials was conducted to test the hypothesis that neuraxial analgesia placement during the early first stage of labor is associated with prolonged first stage of labor.[102] Six studies of 15,399 parturients compared placement of neuraxial analgesia at 3-cm cervical dilation or less to placement only in active labor. No increase was found in the incidence of cesarean section, and the first stage of labor was not prolonged. Thus, if a parturient chooses neuraxial analgesia despite the increased risk for a prolonged second stage and maternal fever, no evidence indicates that any point in the first stage of labor is "too early" to initiate analgesia. Current ASA guidelines note that maternal request for labor pain relief is sufficient justification for intervention and the decision should not depend on an arbitrary cervical dilation.[19]

Epidural Analgesia

Epidural analgesia is most commonly initiated after placement of a catheter into the epidural space between L2-3 and L4-5. Initial dosing of local anesthetic through the needle within the epidural space is not recommended because of potential unintended intravascular placement and rapid onset of local anesthetic toxicity, including seizures, arrhythmias, and cardiovascular collapse. Analgesia should be initiated with a test dose consisting of a dose of local anesthetic that would not be harmful if injected intravascularly but that would induce an altered sensorium, most commonly described as dizziness or a sensation of buzzing in the ears or numbness in the lips. This dose should be sufficient to cause numbness and motor block in the lower extremities if inadvertently injected into the spinal fluid but would not cause significant sensory effects if injected into the epidural space. Thus, the "test dose" tests for inadvertent intravascular or intrathecal placement of the catheter.[103] Some clinicians favor inclusion of a small dose of epinephrine in the test dose so that if the placement were intravascular, a slight tachycardia would ensue. However, the utility of the inclusion of epinephrine has been debated in the setting of pregnancy because the sensitivity and specificity of small changes in heart rate in the setting of uterine contractions may not be adequate. A prospective blinded randomized study of 59 laboring women administered an IV injection of 0, 1, 2, or 3 mL of 1.5% lidocaine with 1:200,00 epinephrine to mimic an epidural test dose, measured the sensitivity and specificity for this intervention with a blinded observer.[104] In all cases, the total volume injected was diluted with normal saline for a final volume of 3 mL. For women receiving either the 2- or 3-mL test dose (lidocaine with epinephrine), the sensitivity was 100% (100% negative predictive value), but examination of the women who received only saline noted the specificity was only 79% with 11 of 15 true negative results. Although the 100% sensitivity will indeed prevent unrecognized intravascular catheter placement, a 21% false-positive rate is problematic because these catheters would be inappropriately removed. The risk for adverse effects from intravascular injection of local anesthetic is mitigated by the use of slow and low concentrations of local

anesthetic infusions rather than repeated bolus doses of concentrated local anesthesia.

Intrathecal and Combined Spinal Epidural Analgesia

Intrathecal analgesia for labor can be used independently of epidural analgesia, or more commonly combined with the placement of an epidural catheter so that when the analgesic effect of the intrathecal dose dissipates, analgesia can be maintained with an epidural infusion. However, intrathecal analgesia alone is useful when the duration of labor can be reasonably estimated. For example, what should be done if a multiparous parturient in the second stage of labor requests analgesia? Opioid combined with a small dose of local anesthetic is quick to perform, provides rapid analgesia, and dissipates when no longer needed. When an epidural catheter is placed in addition to the intrathecal dose, no loading dose is required because the parturient will have analgesia from the spinal dose that will normally last until an epidural infusion can reach a steady state. In this setting, identification of an intrathecal catheter may be less reliable because the patient already has analgesia. However, typical doses of local anesthetic in combined spinal epidural placements provide analgesia without motor block, and the detection of an intravascular catheter as discussed previously may have value.[104]

Neuraxial Analgesic Medications

Any preservative-free local anesthetic can be used in an epidural catheter. Most commonly, bupivacaine and ropivacaine are used because the ratio of sensory to motor blockade is greater than that for lidocaine or 2-chloroprocaine. Epidural lidocaine and 2-chloroprocaine are usually reserved for surgical anesthesia, rather than labor analgesia, in which preserved motor function during the procedure is not desirable.

During the 1990s, intrathecal lidocaine and 2-chloroprocaine were associated with multiple case reports of transient neurologic symptoms and longer lasting cauda equine syndrome.[105,106] Notably, most but not all cases were associated with high concentration—that is, hyperbaric preparations. In vitro, high concentrations of all local anesthetics cause neuronal necrosis or apoptosis; this is likely to be the cause of cauda equina syndrome, but the cause of transient neurologic symptoms is at present not clear.[107] Transient neurologic symptoms and cauda equina syndrome also have been reported with intrathecal bupivacaine[108]; however, the risk for transient neurologic symptoms is greater with lidocaine than bupivacaine (RR 5.1; 95% CI 2.5 to 10.2).[109]

Epidural analgesia for labor began in 1909 when Stoeckel reported 141 cases of caudal epidural anesthesia.[110] Since that time, lumbar epidural analgesia has replaced caudal anesthesia for labor. A search is ongoing for the perfect analgesic recipe that would provide excellent analgesia with no motor blockade or other maternal or fetal effects. This combination has yet to be described. In more recent years, lower concentrations of local anesthetic have been used alone or combined with opioids and multiple other analgesic adjuvants to reduce motor blockade and improve sensory blockade. All local anesthetics cause dose-dependent sympathetic blockade. At higher concentrations, maternal hypotension can result in fetal asphyxia. Epidural bupivacaine (0.625% to 0.125%) or ropivacaine (0.625% to 0.2%) are most commonly used for obstetric analgesia because of the reduced motor block. Ropivacaine and levobupivacaine were synthesized to reduce cardiotoxicity that occurs with inadvertent intravascular bolus doses of bupivacaine. However, with the small doses of local anesthetic currently used for labor analgesia, cardiotoxicity is uncommon.

The addition of lipid-soluble opioids, fentanyl 1 to 3 μg/mL or sufentanil 0.1 to 0.5 μg/mL allowed the reduction of local anesthetic dose with associated decreased motor blockade, preserved analgesia, and enhanced maternal satisfaction.[111] Unfortunately, no epidural opioid only regimen provides adequate analgesia without unacceptable side effects. The most troublesome complication that limits the dose of epidural fentanyl is itching. Patient-controlled epidural analgesia allows the patient to dose the epidural catheter with the use of a pump that has a maximum amount of drug per hour to prevent toxicity. In one study, patients who self-administered local anesthetic as needed in labor used less drug and had similar pain relief.[112]

The search for the perfect labor epidural drug combination has led to the use of other adjuvant drugs that can reduce the dose of local anesthetic that is required. Most of these drugs act through activation of adrenergic receptors. Epinephrine is a nonselective adrenergic agonist activating α_1-, α_2-, β_1-, and β_2-adrenergic receptors. Activation of α_1-receptors in the epidural vasculature causes vasoconstriction that delays the vascular uptake of local anesthetic and opioid.[113] Additional analgesia is likely provided by epinephrine through activation of α_2-adrenergic receptors.[114] The dose of epidural epinephrine is typically dilute (1:400,000 to 1:800,000) secondary to concern for uterine artery vasoconstriction by systemic effects of higher doses. Neostigmine reduces the degradation of synaptic epinephrine and has effects similar to those of low-dose epinephrine.[115-117] Intrathecal neostigmine causes an unacceptable incidence of nausea and vomiting,[115] and epidural neostigmine does not seem to offer any advantage over epinephrine (see also Chapter 97). Clonidine is a relatively selective α_2-adrenergic antagonist that when added to dilute local anesthetic solution provides adjuvant analgesia.[118,119] Although clearly effective for labor analgesia, within the United States epidural clonidine carries a U.S. Food and Drug Administration (FDA) warning that states it is "not recommended for obstetrical, postpartum or perioperative pain management as the risk of hemodynamic instability (e.g., hypotension, bradycardia) may be unacceptable in this population." Monitoring recommendations related to this statement declare that in "a rare obstetrical, postpartum, or perioperative patient, potential benefits may outweigh possible risks." Dexmedetomidine is a significantly more selective α_2-adrenergic receptor agonist that is not approved for epidural use in the United States.[120] However, one randomized controlled trial found that it was efficacious combined with epidural bupivacaine.[121]

Neuraxial Complications

In addition to the neuraxial drug–related complications noted previously, administration of epidural analgesia can

result in rare but severe toxicity. The earliest experiments with spinal cocaine resulted in severe post–dural puncture headache. Leakage of spinal fluid is thought to result in vascular hyperemia, migraine physiology and traction on pain-sensitive fibers may contribute. The incidence, severity, and duration of post–dural puncture headaches are related to the size of the needle and the shape of the tip. Spinal needles used for combined spinal epidural technique range from 25 to 29 gauge and result in an incidence of post–dural puncture headache of less than 1%.[122,123] Epidural catheters are most commonly placed through a 17- or 18-gauge blunt-tipped needle, and thus the incidence of post–dural puncture headache is reported at 30% to 80%.[122] Given the similarity of symptoms to those of migraine headache and the related physiology, post–dural puncture headaches have been treated with drugs that are useful in migraine with variable success. Caffeine is effective to treat the pain of a post–dural puncture headache in the short term likely because of its vasoconstrictive effects,[124] but the duration of the headache is likely related to healing of the rent in the dura. In the setting of dural puncture with an epidural needle, the needle may be replaced at a different interspace or an intrathecal catheter may be placed. If an intrathecal catheter is placed, unintentional injection of an epidural anesthetic dose must be carefully avoided. After an unintended dural puncture, placement of a spinal catheter can provide excellent analgesia and alleviates the need for multiple repeat epidural attempts with the potential of a second accidental dural puncture.[125] The incidence of post–dural puncture headache after a wet tap may or may not be reduced with this technique in comparison to epidural replacement, but labor analgesia is more quickly established with a spinal catheter.[125] When strict aseptic technique is used, infection is uncommon with spinal and epidural anesthesia.[126,127]

The epidural space is highly vascular, and vessels are likely punctured, often in epidural needle placement. However, with normal platelets and coagulation factors, epidural hematoma is extremely uncommon, with an estimated upper limit of 4.6×10^{-5} in the obstetric population.[128] Although rare, back pain and persistent motor blockade are potential signs of epidural hematoma and should be thoroughly evaluated. All parturients should be monitored postpartum until complete resolution of epidural blockade. Direct nerve damage from an epidural or spinal needle placed for labor is exceedingly rare because they are placed below the level of the conus medularis. Damage attributed to direct neurologic injury has been estimated at 0.6 in 100,000 with epidural and 3 in 100,00 with spinal analgesia.[129-131] Postpartum back pain is common regardless of whether neuraxial analgesia has been used after childbirth. However, no evidence indicates that it is more common when neuraxial analgesia is used for labor. Several trials have identified an association between increased maternal temperature and epidural use as a secondary outcome.[132] Attribution of causality is difficult in this setting because temperature increases with advancing labor likely as a result thermogenic cytokines.[132,133] Epidurals are also more likely to be placed later in labor and thus may be associated with higher temperature that results from the intense metabolic activity of labor (also see Chapters 56 and 98 for related information regarding epidural anesthesia and analgesia).

OTHER REGIONAL NERVE BLOCKS

Local anesthetic nerve blocks have been used for many years to relieve labor pain, mostly by obstetricians.[134] For a paracervical block, local anesthetic is injected lateral to the cervix at 4 o'clock and 10 o'clock, taking care to avoid vascular structures. The paracervical block is effective to relieve pain of cervical dilation but does not affect cramping pain from contraction of the uterine corpus. However, paracervical block does reduce pain in the second stage of labor. Paracervical block is more effective for relief of labor pain in contrast to placebo or intramuscular meperidine.[135] No difference was found in pain relief comparing paracervical block to patient controlled analgesia with IV fentanyl.[136] Paracervical block can be complicated by injection of local anesthetic into the presenting fetal head, which can have devastating consequences. Intense fetal monitoring is warranted for a time after the procedure. More commonly, side effects of transient fetal bradycardia and maternal local anesthetic toxicity have been reported.[137-139] The technique of paracervical block has become safer with more superficial injection ensured by a needle guide and more dilute solutions of local anesthetic.

The pudendal nerve is derived from sacral nerve roots and can be blocked with local anesthetic using a transvaginal or transperineal approach to treat pain during the second stage of labor and for episiotomy repair. A pudendal nerve block can be helpful but is not as effective as a subarachnoid block with fentanyl and bupivacaine.[140] Pudendal block can impede the urge to push during the second stage of labor.[141] Other complications include a high rate of block failure; systemic local anesthetic toxicity; ischiorectal or vaginal hematoma; and, rarely, fetal injection of local anesthetic (see also Chapters 56 to 58 regarding regional anesthesia).

ANESTHESIA CONSIDERATIONS FOR OPERATIVE DELIVERY

Low-dose epidural analgesia can be inadequate for assisted vaginal delivery with forceps or vacuum. In this setting, higher concentration local anesthetic can be administered through an indwelling epidural catheter or a "second-stage spinal" can provide excellent perineal analgesia. Supplementation of an indwelling epidural catheter with 5 to 10 mL of 1% to 2% lidocaine or 2% to 3% 2-chloroprocaine is usually adequate, depending on whether vacuum or forceps are being used. Pudendal nerve block also can be considered for operative delivery.

ANESTHESIA FOR CESAREAN DELIVERY

MATERNAL RISKS AND CONSIDERATIONS

Cesarean delivery rates in the United States increased by 50% between 1998 and 2008, rising from 22% to 33% of all births.[142] Although maternal mortality has substantially

decreased during the first half of the twentieth century, the rate of maternal mortality is 10 times higher with cesarean delivery than vaginal delivery, based on a retrospective study of 1.5 million deliveries between 2000 and 2006.[143] Perhaps some of the women who died were in an emergent situation and required general anesthesia rather than a neuroaxial technique. Pregnant women who undergo general anesthesia for cesarean delivery are at increased risk for mortality from pulmonary aspiration of gastric contents and failed intubation of the trachea, inadequate ventilation, or both compared with those under neuraxial blockade, particularly in emergent situations. However, the RR has decreased over time. Data in the United States from 1979 to 1990 noted a 16.7 increased mortality risk with use of general anesthesia for cesarean delivery compared with neuraxial blockade[144]; between 1997 to 2002, the risk ratio was only 1.7 with general anesthesia.[145] In addition to improved maternal safety, use of epidural or spinal anesthesia for cesarean delivery minimizes neonatal anesthetic exposure and allows the mother to see the child almost immediately after birth. Although a variety of anesthetic considerations for cesarean delivery exist, the following discussion is a general summary and other sources can provide additional information.[146,147]

All pregnant women should undergo a preoperative evaluation, regardless of planned delivery mode or type of anesthetic technique, with appropriate risk and benefit counseling. The current status of the fetus and obstetric management plan also should be determined in conjunction with the anesthetic plan. In addition, appropriate equipment and medications should always remain readily available to safely provide general anesthesia for an emergent or unanticipated situation. Although the rates of significant maternal aspiration of gastric contents with induction of general anesthesia are difficult to determine, the mortality from such an event is estimated at 5% to 15% based on retrospective data.[148,149] As mentioned previously, ASA guidelines recommend, "timely administration of nonparticulate antacids, H_2 receptor antagonists, and/or metoclopramide for aspiration prophylaxis" before obstetric surgical procedures.[19] The decision to use general anesthesia or neuraxial block for cesarean delivery is determined by a variety of factors that include the fetal condition and urgency of delivery, maternal comorbidities, presence of a previously placed epidural for labor analgesia, surgical considerations, and maternal wishes. At present, most cesarean deliveries in developed countries are performed with neuraxial techniques.

SPINAL ANESTHESIA

If an epidural catheter is not already placed, spinal anesthesia is typically used for nonemergent cesarean deliveries. Compared with an epidural, this type of neuraxial block is quicker and easier to place, allows adequate operating conditions in a shorter time, provides a denser block, is more cost effective, and is less likely to fail (failure rate < 1%).[150,151] The chance of significant maternal hypotension is greater with spinal anesthesia than with epidural anesthesia. Left uterine displacement with appropriate administration of fluids and use of vasopressors can minimize the associated hypotension. Although IV administration of crystalloid or colloid can reduce the degree of hypotension after spinal anesthesia for cesarean delivery,[152] a randomized controlled trial comparing colloid versus crystalloid noted that use of colloid was superior to crystalloid preload.[153] Another study noted that giving colloid with spinal placement is equally beneficial in reducing hypotension compared with use of prior administration of a colloid.[154] However, concern exists regarding the safety of synthetic colloids as part of intraoperative and critical care resuscitation (see also Chapter 61).

Previously ephedrine was considered the vasopressor of choice to manage hypotension caused by neuraxial anesthesia in pregnancy; however, phenylephrine in boluses or as an infusion is not only effective in reducing hypotension but also has less transfer to the fetus and results in less fetal acidosis than ephedrine.[31,34,155] Lastly, despite the concerns of hypotension, spinal anesthesia is safe to administer in preeclamptic patients.[156,157]

Although various local anesthetics could be used for spinal blockade, hyperbaric bupivacaine 10 to 15 mg is frequently used to achieve an adequate (T4) block level. Neither patient height nor weight affect block extension,[158] although dosing may require adjustment at extremes of the height spectrum. Adjuncts, such as fentanyl, sufentanil, and epinephrine, may be added to improve the quality of the block. Preservative-free morphine 0.10 to 0.25 mg is frequently administered with spinal to reduce postoperative pain for 18 to 24 hours after the anesthetic has dissipated.

EPIDURAL ANESTHESIA

If an epidural catheter has already been inserted for labor analgesia, it provides an excellent method to provide surgical anesthesia for cesarean delivery. A catheter-based technique allows for the ability to titrate the local anesthetic to the proper block height and provide additional local anesthetic administration during the case. For patients who do not already have a catheter in place, this technique may be chosen if the cesarean procedure is anticipated to take additional time, or if maternal comorbidities would favor a more gradual, controlled onset of epidural anesthesia. Achieving surgical block conditions takes longer with an epidural than spinal technique, but can be rapid enough for use in many urgent situations if already in place and used for maternal analgesia. Although use of a rapid-onset local anesthetic such as 3% 2-chloroprocaine to attain a T4 level in a newly placed catheter may take 10 minutes,[159] extension of a T10 level with a density for labor analgesia to a T4 level for surgical anesthesia can be obtained in approximately 5 minutes using 3% 2-chloroprocaine or alkalinized 2% lidocaine.[160] Several local anesthetics may be used if rapid onset is not needed, and typical local anesthetic volumes required range between 10 and 20 mL, depending on whether the epidural is already in use. The administration of epidural local anesthetic should occur in divided doses to ensure that the catheter has not migrated into the intravascular or intrathecal space. Block quality can be improved with addition of epinephrine 1:200,000, fentanyl 50 to 100 μg, or

sufentanil 10 to 20 μg. Epidural clonidine 50 to 100 μg can be useful in patients with preexisting chronic pain or severe hypertension if the benefit is judged to outweigh the risk for hypotension and bradycardia. Epidural morphine 3 to 5 mg is frequently administered to improve postoperative pain.

COMBINED SPINAL EPIDURAL ANESTHESIA

Use of a combined spinal epidural for cesarean delivery may be optimal in some situations because it combines the benefits of the spinal and epidural techniques. This technique allows the rapid onset of a dense reliable block while allowing the block time or height to be extended with use of the epidural catheter. Possible disadvantages include the presence of an untested catheter and the possibility of a misplaced or nonfunctioning epidural. More details of this type of neuraxial block are discussed in the previous section on labor analgesia.

GENERAL ANESTHESIA

In certain emergent situations (e.g., fetal bradycardia, maternal hemorrhage or coagulopathy, uterine rupture, maternal trauma) general anesthesia may be needed for cesarean delivery because of its rapid and reliable characteristics. In addition, it allows for a controlled airway, controlled ventilation, and improved hemodynamic stability in comparison to neuraxial anesthesia.

Appropriate equipment preparation, knowledge of patient comorbidities, airway examination, and familiarity with the difficult airway algorithm are necessary preparation for delivering a safe anesthetic whether general or neuraxial. The ASA difficult airway algorithm[161] has been modified slightly by some authors for use in the setting of cesarean delivery, and a previously published example is provided in Figure 77-4. In addition, a suggested approach for cesarean delivery with general anesthesia is detailed in Box 77-3. Clear concise communication among all members of the perioperative team is especially critical in urgent or emergent situations to maximize patient safety and minimize procedural complications. Open lines of communication are essential around the time of induction of anesthesia, airway management, and surgical incision. If endotracheal intubation fails, surgical incision should commence only when the patient can be reliably ventilated with a facemask or laryngeal mask airway (LMA).[19] The LMA has a high success rate for placement in obstetric patients; it does not protect against aspiration of gastric contents and should be used primarily for rescue of a failed intubation. The LMA has been used without observed aspiration or presence of hypoxia in a prospective study of over 1000 patients having elective cesarean section.[162,163] Anesthesia-related mortality from airway difficulties may occur during emergence and in the recovery period, as well as during induction. Improper monitoring, provider inexperience, emergent situations, and patient obesity all increase patient risk.[164] Emergent cesarean delivery is an uncommon but predictable emergency that can be practiced by teams using simulation.

Induction of Anesthesia: Intravenously Administered Drugs

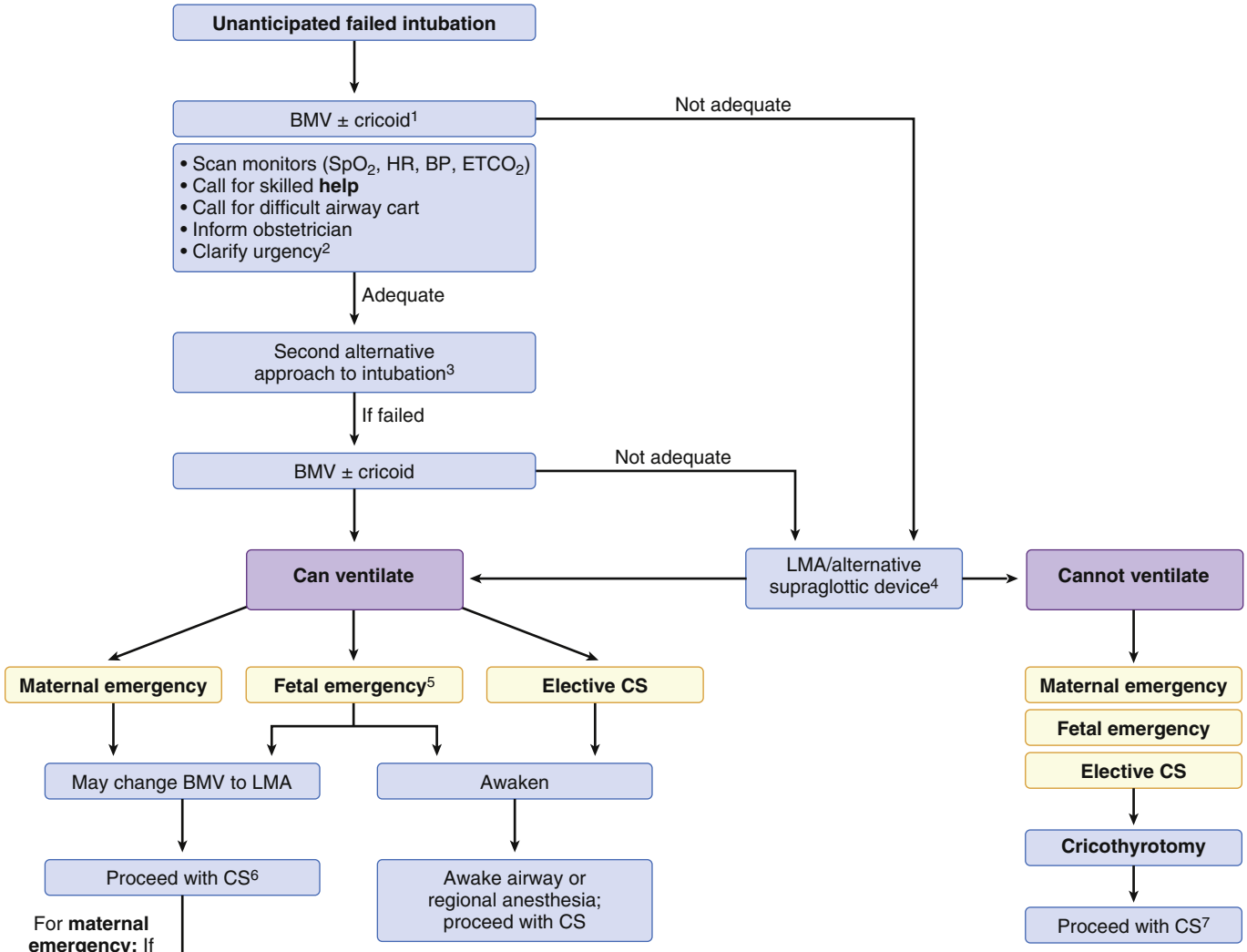
Sodium thiopental 4 to 6 mg/kg intravenously is still used in many countries for induction of anesthesia and was previously the most commonly used drug for induction of anesthesia within the United States (see also Chapter 30). At present, propofol is the most commonly used for induction of general anesthesia for cesarean delivery and is able to induce unconsciousness in approximately 45 seconds. Like sodium thiopental, it can result in significant hypotension and has an umbilical artery (UA) to umbilical vein (UV) ratio of 0.7.[165] Propofol administration does not affect neonatal Apgar scores with typical intravenous induction doses (2.5 mg/kg), but repeated or larger cumulative doses (9 mg/kg) are associated with significant newborn depression.[166] The exact reason for the lack of effects on the newborn is unclear, but is likely the result of a combination of rapid redistribution into the maternal tissues, first-pass metabolism in the neonatal liver, further dilution with blood from the lower extremities with an anesthetic that traverses the ductus venosus into the lower vena cava, and higher fetal brain water content that reduces its central effect.

Etomidate is quick acting and its rapid hydrolysis results in a relatively short duration of action. Unlike thiopental and propofol, etomidate has minimal effects on maternal hemodynamics, but has higher rates of nausea and vomiting and can increase risk for seizures in patients with decreased seizure threshold. At typical induction doses (0.3 mg/kg), decreased neonatal cortisol production for less than 6 hours was noted with unclear clinical significance.[167]

Ketamine inhibits the *N*-methyl-D-aspartate receptor and has analgesic, amnestic, and hypnotic properties while having only minimal respiratory depression effects. At typical induction doses (1 to 1.5 mg/kg), ketamine causes central stimulation of the sympathetic nervous system and inhibits the reuptake of norepinephrine. This helps maintain arterial pressure, heart rate, and cardiac output. It is an ideal choice for a pregnant woman in hemodynamic compromise resulting from bleeding. No neonatal depression is observed with standard induction dosing.[168] Larger doses can increase uterine tone, reduce uterine arterial perfusion, and lower maternal seizure threshold. In certain situations, ketamine may be used in smaller intravenous doses (<0.25 mg/kg) as a profound analgesic, but often causes unwanted hallucinations, which can be reduced with coadministration of benzodiazepines. Care should be taken if it is used for analgesia and conscious sedation that repeated dosing does not result in loss of consciousness with an unprotected airway that would increase the risk for pulmonary aspiration.

Muscle Relaxants

Uterine muscle tone is not affected by skeletal muscle relaxants, and in standard doses all classes of muscle relaxants are poorly transferred to the fetus (see also Chapter 34). Succinylcholine 1 to 1.5 mg/kg intravenously has rapid onset (30 to 45 seconds) and short duration of action. After administration, it is hydrolyzed in the plasma by pseudocholinesterase and only small amounts cross to the fetus because it is highly ionized and poorly lipid



1 ***Cricoid pressure*** should be released if thought to be impairing visualization of the larynx or impeding ventilation by bag and mask (BMV) or with LMA.
2 All cases, including ***semiurgent***, must be classified as urgent or elective type cases for the purposes of subsequent management decisions.
3 Canadian Airway Focus Group (1998) ***recommends only 2 attempts*** at intubation in the pregnant patient (***vs. 3 or 4 attempts*** in other recommended algorithms). However, if the airway has not been traumatized, good oxygenation is being well maintained, and there is a high likelihood of success at a third attempt, then a third attempt may be reasonable. It should be noted, ***any successive attempts*** should be done after optimizing head position ***and*** that ***different*** techniques/equipment (bougie, intubating LMA, glidescope, fiberoptic intubation, etc.) are tried for ***each*** of the successive attempts.
4 ***If initial BMV is inadequate but ventilation by LMA (classic or proseal) or alternative supraglottic device is adequate,*** might consider proceeding with CS directly if absolute emergency ***or*** only make second or third attempt at intubation ***if*** mother is at higher risk for aspiration and/or slow difficult CS is anticipated.
5 In the event of a ***fetal emergency only*** and a situation in which mother can be ventilated, there are ***two options:*** one may proceed with unprotected airway for sake of fetus or if mother is at higher risk than usual for aspiration, desaturation, or subsequent failure to ventilate or loss of airway (recent large meal, morbidly obese, airway significantly traumatized in failed intubation attempts, etc.), one may choose to awaken the mother and proceed to regional anesthesia or awake airway. This latter course of action may clearly put the fetus at great risk but follows the principle of "Mother comes first."
6 ***Anesthesia management details*** should be at the ***discretion*** of the anesthesiologist, bearing in mind his or her own practice and preference and any patient or obstetric issues unique to each case: (1) additional doses of succinylcholine or return to spontaneous ventilation, (2) choice of maintenance anesthetic agents, and (3) elective change to LMA or other supraglottic devices even if BMV remains easy and effective.
7 ***In the three cannot-ventilate situations,*** maternal and fetal ***emergencies*** should proceed to CS immediately after ***transtracheal airway***. Arguably in ***elective*** CS, the fetus will be stressed by now and hence CS should also be seriously considered at this point.

Figure 77-4. Algorithm for management of unanticipated difficult airway in obstetric patients. *BMV,* Bag-mask ventilation; *BP,* blood pressure; *CS,* cesarean section; *$ETCO_2$,* end-tidal carbon dioxide; *HR,* heart rate; *LMA,* laryngeal mask airway; *SpO_2,* oxygen saturation. (Redrawn from Balki M, Cooke M, Dunington S, et al: Unanticipated difficult airway in obstetric patients: development of a new algorithm for formative assessment in high-fidelity simulation, *Anesthesiology* 117:883-897, 2012, with permission.)

soluble. It is undetectable in umbilical cord samples unless larger maternal doses are administered (2 to 3 mg/kg), and exceedingly high maternal doses (10 mg/kg) are needed to inadvertently create neonatal neuromuscular blockade.[169] After succinylcholine administration, maternal muscle strength should always be monitored because prolonged weakness can occur if the hydrolytic enzyme has a reduced plasma concentration or has an atypical form or if muscle weakness is exacerbated by prior administration of magnesium sulfate.

BOX 77-3 ***Suggested Sequence for General Anesthesia for Cesarean Section***

1. Administer a nonparticulate oral antacid (sodium citrate) before induction of anesthesia with consideration for metoclopramide or a histamine-2 blocker
2. Place standard monitors, maintain left uterine displacement, and ensure suction, airway equipment, and appropriate drugs are readily available.
3. Ensure the patient has a working intravenous catheter and start an infusion of crystalloid solution.
4. If time permits (nonemergent), administer prophylactic antibiotics and participate in time-out checklist.
5. Preoxygenate/denitrogenate patient for more than 3 minutes or 4 maximal (vital capacity) breaths over 30 seconds with 100% oxygen.
6. When the surgeon is ready and patient prepared, an assistant should apply cricoid pressure (and maintain until the position of the endotracheal tube is verified).*
7. Notify and confirm with the surgeon that the patient is ready for induction of anesthesia.
8. Administer induction agent and muscle relaxant in rapid sequence, wait 30 to 60 seconds, and then initiate direct laryngoscopy for tracheal intubation. Consider using etomidate or ketamine if concern for hypotension exists.
9. After confirming endotracheal tube placement, communicate to surgeon to proceed with incision.
10. Administer 50% nitrous oxide in oxygen with 0.5 to 0.75 minimum alveolar concentration of a halogenated anesthetic.
11. Adjust minute ventilation to maintain normocarbia (end-tidal carbon dioxide 30 to 32 mm Hg).
12. After delivery, anesthesia may be augmented by administering opioids, barbiturates, or propofol while continuing the volatile anesthetic. Additional muscle relaxant may be considered if necessary.
13. Administer oxytocin and assess uterine tone.
14. Extubate the trachea when the patient is awake and following commands and neuromuscular blockade is fully reversed.

*Not all agree that cricoid pressure is efficacious or required in every patient.

Modified from Lucero JM, Rollins MD: Obstetrics. In Miller RD, Pardo MC, editors: *Basics of anesthesia,* ed 6. Philadelphia, 2011, Elsevier, p 531.

Rocuronium may be considered as an alternative to succinylcholine for muscle relaxation. It allows adequate relaxation for endotracheal intubation in less than 60 seconds at intravenous doses of 0.9 to 1.2 mg/kg.[170,171] This is an attractive alternative to succinylcholine in clinical settings outside the United States in which sugammadex is available for reversal, because even after an intravenous intubating dose of 0.9 to 1.2 mg/kg body weight, the neuromuscular blocking effect can rapidly be reversed by a large intravenous dose of sugammadex (12 to 16 mg/kg body weight), which makes the total duration of action shorter than after an equipotent dose of succinylcholine (also see Chapter 35). Like succinylcholine, nondepolarizing muscle relaxants do not cross to the fetal circulation in amounts that would cause neonatal weakness.[172] However, if large doses of nondepolarizing neuromuscular blockers are given over long periods, significant neonatal neuromuscular weakness can occur. Although cholinesterase inhibitors may be administered to the neonate, treatment is primarily respiratory support until the drug is eliminated. Neonatal elimination of muscle relaxants may be significantly longer than adult elimination.

In the case of administration of magnesium sulfate, a distinct potentiation occurs of the effect of any nondepolarizing agents, with subsequently prolonged recovery time. The choice and dosing of neuromuscular blocking agents should therefore take into account the interaction with magnesium sulfate and the potential risk for muscle weakness resulting from residual neuromuscular block in the recovery room or postanesthesia care unit. As a consequence, neuromuscular monitoring based on an objective monitoring technique (see also Chapter 53) should be used to assess neuromuscular function in these patients.

Maintenance of General Anesthesia

After induction, general anesthesia is most frequently maintained with a volatile anesthetic agent with or without N_2O. Volatile anesthetics help reduce the incidence of maternal recall. Although the MAC to prevent movement in response to a painful stimulus is reduced in pregnancy, electroencephalographic evidence suggests that anesthetic effects of halogenated agent on the brain are similar in the pregnant and nonpregnant state.[27] Volatile anesthetics are highly lipid soluble, have a low molecular weight, and are readily transferred to the fetus. Fetal concentrations depend on both the maternal plasma concentrations and duration of the anesthetic before delivery. After delivery, opioids, propofol, benzodiazepines, or a combination are administered and a halogenated anesthetic typically provided at 0.5 MAC. These additional drugs are administered only after the cord is clamped to prevent any transfer to the neonate and associated respiratory depression. Use of only volatile anesthetics at higher concentrations is associated with increased blood loss secondary to uterine atony because all volatile anesthetics are uterine muscle relaxants.[173]

General anesthesia for cesarean delivery is frequently used in cases of fetal distress because it is so rapid and reliable. Clearly, a fetus depressed before delivery often becomes a depressed neonate. A Cochrane review of studies of uncomplicated cesarean deliveries that compared regional blockade and general anesthesia concluded that "No significant difference was seen in terms of neonatal Apgar scores of six or less and of four or less at one and five minutes and need for neonatal resuscitation."[174] The study noted neither method of anesthesia was superior for neonatal outcome.

If large concentrations of volatile anesthetics are administered for a prolonged time, neonatal flaccidity, cardiorespiratory depression, and decreased tone may be anticipated. If neonatal depression is due to volatile anesthetics, the infant should respond to assisted ventilation to facilitate exhalation of the anesthetics. Consequently, physicians able to assist neonatal ventilation should be present at all cesarean deliveries performed with the patient under general anesthesia. In addition, communication to all perioperative physicians is critical if extended anesthetic time is anticipated before delivery.

MATERNAL COMORBIDITIES

HYPERTENSIVE DISORDERS

Hypertensive disorders of pregnancy are among the most common causes of maternal morbidity and are associated with more frequent rates of maternal and fetal mortality.[175] Hypertensive disorders of pregnancy complicate 5% to 10% of pregnancies worldwide and preeclampsia is diagnosed in 3% of pregnancies.[175] The World Health Organization (WHO) has identified hypertension as the leading cause of maternal death, accounting for 16% of mortality associated with pregnancy.[176] Chronic hypertension may precede pregnancy and may or may not be complicated by superimposed preeclampsia.

Although some variations exist in hypertensive definitions worldwide, the following are used in the United States by the ACOG based on a working group in 2013.[177]

Gestational hypertension is defined as the onset of hypertension (systolic blood pressure [SBP] > 140 mm Hg or diastolic blood pressure [DBP] > 90 mm Hg) after 20 weeks gestation in a previously normotensive parturient without proteinuria.

Preeclampsia is defined as hypertension (SBP > 140 mm Hg or DBP > 90 mm Hg) after 20 weeks gestation associated with proteinuria. Preeclampsia is diagnosed when urine protein is greater than 300 mg/day or, alternatively, there is a protein/creatinine ratio of at least 0.3. In 2013, massive proteinuria (> 5g in 24 hours) and fetal growth restriction were eliminated as considerations of severe preeclampsia. In addition, the term *mild preeclampsia* is no longer used. Now only *preeclampsia* or *preeclampsia with severe features* are defined. Severe features of preeclampsia include an SBP of 160 mm Hg or greater or DBP of 110 mm Hg or greater on two separate occasions at least 4 hours apart while on bed rest; thrombocytopenia; impaired liver function with twice normal concentrations of liver enzymes; right upper quadrant pain; progressive renal insufficiency with serum creatinine greater than 1.1 mg/dL or a doubling of serum creatinine without other known renal disease; pulmonary edema; and new onset cerebral or visual abnormalities. In the absence of proteinuria, preeclampsia can be diagnosed with new onset hypertension as previously defined and presence of a severe feature.[177]

Hemolysis, increased liver enzymes, and low platelet count syndrome (HELLP) is defined as preeclampsia associated with hemolysis, elevated liver enzymes, and low platelet count. Eclampsia is preeclampsia complicated by seizure activity. The incidence of preeclampsia has increased likely as a result of increases in maternal age and obesity, whereas the risk for eclampsia has decreased because of more widespread prenatal care and the use of prophylactic magnesium.[175,178] The cause of preeclampsia is not known, but hypotheses include maladaptation of the placental circulation, immunologic rejection of paternal antigens, and maternal genetic and environmental factors. Constitutional, genetic, and hemodynamic factors have been proposed for the causes of early preeclampsia.[179,180] Pregnant women who develop preeclampsia before 34 weeks gestation have lower cardiac output and higher vascular resistance than those who develop later, less severe disease when measured at 20 weeks gestation before the onset of signs.[181]

Patients with preeclampsia have an elevated risk for cerebral hemorrhage, pulmonary edema, and coagulopathy. Current guidelines recommend treating SBP more than 160 mmHg for prevention of intracerebral hemorrhage.[177] Initial treatment typically includes labetalol and hydralazine. Other considerations are increased airway edema with associated difficulty of intubation and increased rates of postpartum atony related to the use of magnesium sulfate. Methylergonovine (methergine) should be used cautiously in patients with preeclampsia because it may lead to hypertensive crisis.

Women with a diagnosis of preeclampsia should have their platelet count checked before initiation of regional anesthesia or removal of an epidural catheter. Patients with severe preeclampsia should have additional coagulation studies, including prothrombin time (PT) with international normalized ratio (INR) and activated partial thromboplastin time, before neuraxial anesthesia. Coagulopathy is a contraindication to regional anesthesia. Although the risk for spinal hematoma is lower in pregnant women than in the elderly,[130] in one study 68% of patients who had spinal hematomas after neuraxial blockade had preexisting coagulopathy.[182]

COAGULOPATHIES

Thrombocytopenia complicates 10% of pregnancies as a result of several etiologic factors.[183,184] Thrombocytopenia may be preexisting or can develop as a result of the pregnancy. As discussed earlier, thrombocytopenia that develops after 20 weeks gestation may be a sign of preeclampsia. However, most thrombocytopenia in pregnancy is benign, gestational thrombocytopenia. Platelet count is expected to decrease by approximately 10% in normal pregnancy.[185] Autoimmune thrombocytopenia, antiphospholipid syndrome, and liver disease are less common.[184] Glucocorticoids and IV immunoglobulin can be used to elevate platelet counts in certain types of severe disease but require several days to be effective.[186] No platelet count is universally accepted as safe for epidural placement. Most anesthesiologists agree that placement of an epidural in the setting of a platelet count greater than 100,000/mm^3 is safe and epidural placement with platelets less than 50,000/mm^3 is unsafe. Disagreement exists about the safety of epidural placement at platelet counts between 50 and 100,000/mm^3.[187] Ironically, disagreement regarding threshold for platelet transfusion often occurs around similar values during surgical procedures (see also Chapters 61 and 62).

Women with von Willebrand disease are at increased risk for bleeding intrapartum and postpartum.[188] Prophylactic treatment is recommended for women with von Willebrand factor (VWF) less than 50 international units/dL. Because of the multiple types and subtypes of von Willebrand disease that have different responses to therapy, it is imperative that hematologic studies be part of the management to help guide the most appropriate therapy. In type I von Willebrand disease, a partial reduction in the quantity of VWF is seen. Women with type I von Willebrand disease usually do not need prophylactic treatment because their VWF typically rises in the third trimester of pregnancy to greater than 50 international units/dL. Desmopressin can

be used in women with type 1 von Willebrand disease to release VWF. Type 2 Willebrand disease is characterized by a defect in the function of VWF, and facilitation of release is not helpful. Parturients with type 3 von Willebrand disease almost always require replacement of VWF before delivery, because they have almost no intrinsic VWF. Although concern should be elevated for epidural hematoma, women with normal factor levels can have regional anesthesia in the setting of a normal platelet count.[189]

Factor V Leiden is an abnormal variant of factor V that acts as a cofactor that allows activation of thrombin by factor Xa. The factor V Leiden variant cannot be easily degraded by activated protein C and thus leads to hypercoagulability. Patients with factor V Leiden abnormality do not intrinsically have an increased risk for epidural hematoma, but they may be maintained on anticoagulants for prophylaxis or treatment of deep venous thrombosis (DVT).[190]

OBESITY

Increasing rates of maternal obesity (prepregnancy body mass index ≥ 30 kg/m^2) and metabolic syndrome in pregnancy are thought to be causes for the increased rate of preeclampsia (see also Chapter 71).[175] The immunologic abnormalities associated with metabolic syndrome may have commonality with those implicated in preeclampsia.[175] Obese parturients are at increased risk for larger babies, prolonged labor, and caesarean section.[48,191] Cesarean section for these women is also at greater risk with increased rates of failed tracheal intubation, increased wound infections, thromboembolism, and increased mortality.[192,193] Sleep apnea is more common in obesity and is a risk factor for hypoventilation after treatment with systemic opioids and difficult tracheal intubation when general anesthesia is required. Epidural anesthesia is more difficult in obese parturients and the risk for inadvertent epidural venous catheter insertion and dural puncture is higher.[194] An early anesthesia consultation is advised for morbidly obese women regardless of planned delivery mode.

CARDIAC DISEASE

Women with cardiac anomalies were often advised not to attempt pregnancy (see also Chapter 39). Before advances in cardiopulmonary bypass, only the mildest congenital cardiac anomalies were compatible with normal survival to adulthood. Children who benefited from palliative and curative surgeries often ignored this advice and provided evidence that most women with congenital heart disease can have successful pregnancies with the proper surveillance. However, the normal physiologic changes of pregnancy including an increase in cardiac output, decrease in peripheral vascular resistance, and increase in pulmonary blood flow can be challenging in the setting of some congenital lesions. Regurgitant valvular lesions and left-to-right shunts are tolerated better than stenotic lesions because the increased volume and decreased systemic vascular resistance favor forward flow.[195] In mitral stenosis, the combination of increased heart rate and increased volume lead to increased left atrial pressure and risk for atrial fibrillation and left heart failure.[195] The most common cyanotic congenital cardiac lesion is tetralogy of Fallot. This lesion consists of a large ventricular septal defect, overriding aorta, pulmonic stenosis, and right ventricular hypertrophy. Tetralogy of Fallot is normally repaired in infancy with a patch to close the ventricular septal defect and widening of the pulmonic outflow tract. Most patients do well with a successful repair; however, the increased intravascular volume in pregnancy can bring out insufficient widening of the pulmonic outflow tract. Consultation of a cardiologist specializing in obstetrics and an echocardiographic evaluation are recommended during pregnancy. These patients are also at risk for heart block because of abnormalities in ventricular conduction as a result of the condition or of surgery.[196] Epidural analgesia is recommended for women with congenital heart disease to obviate the portion of the increased cardiac output tachycardia attributable to labor pain. In women with aortic stenosis, the decrease in afterload that occurs with epidural analgesia may need to be countered with a carefully titrated α-adrenergic agonist to prevent tachycardia and ischemia.

Anticoagulation is required for women with artificial heart valves, some congenital heart disease, pulmonary hypertension, and cardiomyopathy. It is necessary to carefully time stopping anticoagulation to allow for epidural placement and birth while restarting before a clot can form. For this reason, women are usually maintained on heparin at the end of pregnancy, pending delivery, because of its quick offset. If IV heparin was used, it should be stopped 2 to 4 hours before the procedure and normal coagulation status (PTT or activated clotting time [ACT]) documented before neuraxial instrumentation or removal of an epidural catheter.[197] If conversion to intravenous heparin cannot take place before labor, warfarin should be stopped and neuraxial analgesia deferred until the PT is within normal limits and the INR is documented at less than 1.5. Low-molecular-weight heparin (LMWH) has been used frequently for prophylaxis of DVT in pregnancy. Unlike unfractionated heparin, the anticoagulant effects of LMWH cannot be reliably measured, and it is not reversible with protamine. Epidural analgesia should not be placed within 24 hours of therapeutic dose and 12 hours of prophylactic dose LMWH. The epidural catheter should be removed 2 hours before the next dose, but at least 24 hours should pass before the next dose if blood is found in the needle or catheter.[197] Prophylactic dosing of unfractionated heparin or LMWH is often increased in later trimesters, and care should be taken that the patient is being given dosing that is within guidelines.[197] Nonsteroidal antiinflammatory drugs do not in themselves increase risk for spinal hematoma, but can increase risk in combination with other anticoagulants.[197] If labor begins before neuraxial analgesia can safely be given, IV remifentanil and N_2O are alternatives in some settings.[198,199]

PULMONARY DISEASE

As previously detailed in the section on pulmonary changes, adaptations in the respiratory system are required to meet the metabolic demands of the mother and fetus with increases in minute ventilation, decreased O_2 reserve, and increased airway edema most notable (see also Chapter 39).

Community-acquired pneumonia is the most common nonobstetric infectious complication that results in maternal death.[200] Aspiration of gastric contents is also

more common during endotracheal intubation in pregnant than in nonpregnant patients because of laxity of the gastroesophageal junction combined with anatomic changes from the expanding uterus.[201] Strict fasting recommendations, rapid-sequence tracheal intubation, and antacids are used before general anesthesia in pregnancy.

DVT and pulmonary embolism are more common in pregnancy as a result of hormonal changes. Significant risk factors are factor V Leiden, prothrombin G20210A, protein S, protein C and antithrombin deficiency, and antiphospholipid antibodies.[202] Patients diagnosed with DVT or pulmonary embolism in pregnancy will need prolonged anticoagulation and will require delivery planning with a brief hiatus for regional anesthesia and delivery.

Cystic fibrosis is a common autosomal dominant disorder in women of northern European origin. With improved medical care, women with cystic fibrosis are living to reproductive years and beyond. Pregnancy is uncommon in women with cystic fibrosis (216 pregnancies in 24,000 women), but when it occurs, careful multidisciplinary care is required.[203] The disease is caused by a mutation in the cystic fibrous membrane conductance regulator in epithelial cells, which causes abnormalities in the lungs, pancreas, intestines, and hepatobiliary systems. The major issues in pregnancy are restrictive lung disease and diabetes.

NEUROLOGIC DISORDERS

Multiple sclerosis is a neuroinflammatory disorder that disproportionately affects young women (also see Chapter 39). Pregnancy is associated with a decrease in the incidence of relapse, although a postpartum increase does occur. Multiple sclerosis is a disease of demyelination, and thus theoretic concern exists that local anesthetic toxicity may be enhanced. Cases of worsening symptoms after regional anesthesia have been reported; however, it is hard to impute causality in a relapsing and remitting disease. Nevertheless, the lowest effective concentration possible should be given and vasoconstrictive agents should not be given.

Neurofibromatosis is an autosomal dominant disorder that occurs in 1 in 3000 individuals, with variable manifestations. It is characterized by café-au-lait lesions on the skin, cutaneous neurofibromas, Lisch nodules of the iris, bone abnormalities, and tumors of the spinal cord and cranial nerves.[203] Neurofibromas often grow in pregnancy. Disagreement exists as to whether neuraxial anesthesia is contraindicated in women with neurofibromatosis because of the incidence of vascular spinal tumors. Epidural hematoma has been reported in a woman with neurofibromatosis in the setting of a spinal tumor.[204] The hormonal changes of pregnancy may cause tumor growth, and a knowledge of lesion location and current clinical symptoms is needed to avoid instrumentation of tumors and safely deliver neuraxial anesthesia.[205]

ANESTHESIA FOR ABNORMAL PRESENTATIONS

Higher order multiple births are frequently delivered by cesarean section because of the likelihood of cord entanglement and possibility of head entrapment. Twin pregnancy can be delivered vaginally but may present difficulties at delivery. If the second twin is not in the vertex position, epidural anesthesia can provide abdominal muscle relaxation and analgesia to allow for version or manual extraction.[206-208] In addition, it provides analgesia and perineal relaxation for instrumented delivery if needed, and the ability for conversion to cesarean delivery if the second twin becomes distressed or is unable to be delivered vaginally. The same considerations apply for external cephalic version of a singleton breech presentation. Anesthetic rather than analgesic concentrations are required for appropriate conditions. External cephalic version has an overall success rate (all gestational ages) of approximately 60%, with risks for abruption, fetal bradycardia, rupture of membranes, and need for emergent delivery. For these reasons, anesthesiologists should be immediately available in case need for emergent delivery occurs.

Shoulder dystocia occurs when after the delivery of the head, the shoulders cannot be delivered secondary to impaction on the maternal pelvis. This is an obstetric emergency. It is associated with prolonged gestation, labor induction, obesity, high fetal weight, prolonged dilation from 8 to 10 cm, and epidural analgesia.[209,210] Prolonged gestation and slow difficult delivery make epidural analgesia more desirable, so the association between epidural analgesia and shoulder dystocia is not likely to be causal. However, epidural analgesia provides good conditions for rescue of the infant in the case of shoulder dystocia. Recommended procedures for the management of shoulder dystocia include the McRoberts maneuver, in which the mother's legs are flexed and pushed tightly to her abdomen with application of suprapubic pressure.[211] The muscle relaxation and pain relief offered by epidural analgesia facilitate this process. However, the Gaskin maneuver requires placing the mother on her hands and knees, which may not be possible to sustain with the use of higher dose epidural local anesthetic because of inadequate motor strength. If these maneuvers are unsuccessful, pushing the fetus back into the pelvis and emergent cesarean delivery may be required. Deliveries with shoulder dystocia have an increased risk for postpartum hemorrhage and fourth-degree lacerations.[212]

OBSTETRIC EMERGENCIES

A variety of emergent conditions may manifest during the care of obstetric patients. These urgent situations frequently involve maternal hemorrhage, fetal distress, or both. To optimize the clinical outcome, prior preparation and excellent communication among all members of the peripartum care team are essential.

OBSTETRIC HEMORRHAGE

Hemorrhage during pregnancy carries significant morbidity and is a leading cause of maternal death worldwide.[213,214] In addition, the need for blood transfusion is the most common indicator of severe maternal morbidity based on 2008 to 2009 U.S. peripartum hospitalization data.[215] Most of these hemorrhage-related deaths are preventable, and appropriate training, simulation, team

communication, and education are all essential elements needed to improve patient outcome.[216,217] Common difficulties with hemorrhage management include inaccurate determination of blood loss, unrecognized hemorrhage risk factors, delayed intervention, and improper or inadequate transfusion of blood products. Various causes of peripartum hemorrhage and management of obstetric hemorrhage are discussed in greater detail in the following section.

Placenta Previa and Accreta

Placenta previa is diagnosed when the placenta is located low in the uterus and in front of the presenting fetus, either covering or encroaching on the cervical os. The incidence is approximately 0.5% of all pregnancies. Associated risk factors include advanced maternal age, assisted pregnancy, multiparity, prior placenta previa, and uterine scarring from infection or prior surgery. Placenta previa normally manifests as painless vaginal bleeding, with the first occurrence being self-limited. The diagnosis is confirmed or determined by ultrasonography. Cesarean delivery is required with placenta previa unless the placenta significantly changes position during gestation to 2 cm or more away from the cervical os before the time of delivery.

The term *placenta accreta* is often used to include the three subtypes of accreta vera, increta, and percreta. Placenta accreta vera is an abnormal adherence to the myometrium with an absent decidual line of separation. Placenta increta is abnormal implantation and growth of the placenta into the myometrium, and placenta percreta is growth of the placenta through the uterine wall with placental implantation onto surrounding tissue that might include bladder, bowel, ovaries, or other organs surrounding the uterus. Presence of accreta occurs in approximately 0.04% of pregnancies in developed countries; however, the rate is increasing and a recent study in Utah noted a rate of 0.12% based on 2002 to 2006 data.[218] In a multiinstitutional cohort study, the sensitivity for detecting placenta accreta using ultrasound or magnetic resonance imaging was 93% and 80% with specificities of 71% and 65%, respectively.[219] Rates of accreta are significantly affected by the presence of placenta previa and the number of prior hysterotomies. In patients with a known placenta previa, the rates of accreta are 3%, 11%, 40%, and more than 60% with zero, one, two, and three or more prior uterine incisions, respectively.[220] Unfortunately, the diagnosis of accreta is not certain until the time of hysterotomy, and in patients with significant risk factors, massive hemorrhage could occur, regardless of imaging study result.[19,217] If the diagnosis of placenta accreta or percreta is likely before delivery, preoperative interventions such as bilateral common iliac artery balloon catheter insertion or selective embolization of uterine vessels near the time of delivery could be considered, but efficacy remains unclear.[221-223]

Vasa Previa

Vasa previa is a rare condition in which velamentous insertion of umbilical vessels occurs so that these fetal vessels traverse the fetal membranes and are positioned over the cervical os.[224,225] The incidence is between 0.04% and 0.02% of pregnancies and carries significant fetal morbidity and mortality if not diagnosed antenatally. In a study of 155 women, neonatal survival was 97% with antenatal diagnosis and only 44% without diagnosis before delivery.[226] If undiagnosed, vaginal bleeding may be noted at the time of membrane rupture and represents fetal blood loss rather than maternal. Previously undiagnosed vasa previa represents an obstetric emergency requiring immediate cesarean delivery, typically done under general anesthesia because of its rapidity. In cases in which the diagnosis is known antenatally, cesarean delivery is performed before labor. The optimal gestational age for delivery is not definitively established, but delivery by cesarean at approximately 36 weeks of gestation is suggested with consideration for administration of steroids for fetal lung maturity and consideration of maternal hospitalization between 28 and 32 weeks gestation in the case of the need for urgent preterm delivery.[224,225]

Placental Abruption

Placental abruption is defined as partial or complete separation of the placenta from the uterine wall after 20 weeks gestation but before delivery. The incidence is approximately 1% of pregnancies, and risk factors include advanced maternal age, chorioamnionitis, cocaine use, excessive alcohol use, hypertension, premature rupture of membranes, history of abruption, smoking, and trauma. Abruption often manifests with vaginal bleeding and uterine tenderness with examination. However, a significant volume of blood can be trapped behind the placenta and remain in the uterus. As for any situation with massive bleeding in pregnancy, coagulopathy resulting from massive blood loss can frequently occur. Therefore, appropriate laboratory panels should be obtained and preparation for massive transfusion and administration of additional coagulation factors initiated, taking into account the need for close collaboration with transfusion medicine or blood bank expertise (see later discussion of management of massive obstetric hemorrhage).

Uterine Rupture

Uterine rupture can be a life-threatening emergency for both mother and fetus. The occurrence rate for women undergoing a trial of labor after cesarean delivery ranges between 0.4% and 1% and includes a range of pathologic processes from cases of scar dehiscence to complete uterine wall rupture.[227] Other risk factors for uterine rupture include fetal malposition, instrumented delivery, macrosomia, excessive oxytocin administration, rapid delivery, trauma, and tumor. Typical clinical presentation includes fetal bradycardia, cessation of uterine contractions, abdominal pain, vaginal bleeding, and loss of station. A nonreassuring FHR tracing is the most reliable and sensitive clinical sign, and breakthrough pain may be present in only a minority of patients and unrelated to epidural use.[228-230] If trial of labor after cesarean delivery is the planned method of delivery, the American College of Gynecology recommends that an obstetrician, anesthesiologist, and nursing staff be immediately available to the laboring patient so that an emergent cesarean delivery and possible hemorrhage management can be started immediately if a rupture occurs.[231]

Uterine Atony

Postpartum uterine atony and associated hemorrhage is the leading cause of maternal death worldwide and is increasing in incidence.[232,233] Risk factors include chorioamnionitis; excessive use of oxytocin during labor, high parity, long labor, macrosomia, multiple births, prolonged labor, retained products of conception, and use of volatile anesthetics, magnesium sulfate, or terbutaline. After bimanual massage, oxytocin should be administered as the initial treatment and prophylactic drug for uterine atony. Specific dosing of oxytocin varies across institutions and countries.[234] Although the WHO recommends 20 international units of oxytocin administered in 1 L of crystalloid after uncomplicated cesarean delivery, it may be that somewhat less is needed in most situations.[235] Although a dilute oxytocin solution administered over a long time has minimal hemodynamic effects and is typically well tolerated, larger doses and bolus infusion can result in significant hypotension, tachycardia, nausea, and headache. If oxytocin is not sufficient in controlling postpartum hemorrhage, methylergonovine 0.2 mg intramuscularly, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) 0.25 mg intramuscularly, or prostaglandin E_1 (PGE_1) 600 μg orally, sublingually, vaginally, or rectally should be considered. These drugs can have a variety of side effects.[236] Side effects of methylergonovine, an ergot derivative, include nausea, hypertension (systemic and pulmonary), and coronary artery spasm, and it is relatively contraindicated in patients with preeclampsia and those with cardiac disease. $PGF_{2\alpha}$ is associated with pulmonary hypertension, bronchospasm, desaturation, nausea, and tachycardia and is contraindicated in patients with asthma. PGE_1 does not have significant cardiovascular effects but may result in mild hyperthermia. If postpartum hemorrhage is not controlled with drugs, invasive and surgical techniques described in the following section should be considered.

Management of Massive Obstetric Hemorrhage

Successful management of a massive obstetric hemorrhage requires excellent communication and coordination of all perioperative disciplines, including anesthesiologists, obstetricians, labor and operating room nurses, neonatologists, interventional radiologists, gynecologic surgeons, and blood bank staff. A list of general considerations for management of a massive obstetric hemorrhage and resuscitation is provided in Box 77-4. Early diagnosis of hemorrhage and timely intervention are key to minimizing patient morbidity and mortality. Although few studies regarding hemorrhage in obstetrics exist, many studies have been published from the military and trauma hospitals regarding transfusion ratios and transfusion triggers (see also Chapters 61 and 81). Specific ratios of fresh frozen plasma (FFP) and platelets with or without packed red blood cells (PRBCs) for management of massive obstetric hemorrhage have been recommended.[217,237,238] These ratios approach 1 unit of PRBCs to 1 unit of FFP, with 1 platelet plasmapheresis unit transfused for each 4 to 6 units of PRBCs. These higher ratios are recommended to decrease the incidence of coagulopathy and acidosis. Although frequent laboratory studies with use of point-of-care testing if available is optimal, transfusion of blood products should initially be guided by the clinical situation and patient assessment rather than waiting for laboratory values to return. In addition, cryoprecipitate should be considered if decreased fibrinogen is present or likely and only on rare occasions should recombinant activated factor VII be used. Although doses of 70 to 90 μg/kg reduce obstetric hemorrhage, multiple adverse events have been reported to the FDA with the off-label use of treating massive hemorrhage with factor VIIa.[239-241] Cell salvage has been used successfully in numerous published cases of obstetric

BOX 77-4 ***Considerations in the Management of Massive Obstetric Hemorrhage***

- If massive hemorrhage is anticipated, have a multidisciplinary meeting for planning and consider arranging for use of blood salvage, placement of iliac balloon catheters, arterial embolization, or a combination of these in advance.
- Call for additional personnel (anesthesiologists, obstetricians, nurses, gynecologic surgeons, and interventional radiologists).
- Obtain a brief medical history and perform a clinical assessment of the patient.
- Perform short time-out procedure (as defined by the World Health Organization) with all present personnel.
- Place large-bore intravenous catheters (16 to 14 gauge).
- Place invasive monitoring lines (arterial and central venous lines).
- Repeat laboratory tests frequently and use point-of-care testing if available (complete blood count, arterial blood gases, electrolytes, ionized calcium, and coagulation studies).
- Use fluid warmers and forced air warmer.
- Place bladder catheter to measure urine output.
- Place lower extremity compression devices to minimize chance of thromboembolism.
- Prime rapid infusion blood delivery system.
- Bring equipment in case of cardiac arrest (e.g., ACLS cart) into operating room.
- Designate a person for recording and tallying blood products and blood loss.
- Obtain direct communication with blood bank and central laboratory and request prioritization of workflow to your location.
- Request blood products as needed in "packs" of correct ratio (PRBCs/FFP/platelets).
- During significant hemorrhage, transfuse products based on clinical situation rather than waiting for laboratory results.
- Prepare for general anesthesia.
- Ensure vasopressors and uterotonics are immediately available.
- Administer calcium appropriately during rapid transfusion of blood products to prevent low ionized calcium levels.
- Reserve intensive care unit bed for postoperative care.
- Consider use of blood salvage.
- Consider cryoprecipitate (fibrinogen < 100 mg/dL).
- Consider factor VIIa (off-label hemostatic use) only after approximately 10 units PRBCs and factor replacement using FFP and cryoprecipitate.
- Consider use of interventional radiology for arterial embolization if patient is stable for transport.
- Consider other surgical options, including uterine balloon tamponade, compression sutures, and hysterectomy
- Make time to debrief after event with all disciplines

Based on management suggestions from the California Maternal Quality Care Collaborative (CMQCC) Hemorrhage Task Force <*http://www.cmqcc.org*>; and Gallos G, Redai I, Smiley RM: The role of the anesthesiologist in management of obstetric hemorrhage, *Semin Perinatol* 33:116-123, 2009.

FFP, Fresh frozen plasma; *PRBC,* packed red blood cells.

hemorrhage despite the theoretic concern of amniotic fluid embolism.[242,243] The use of a salvage device with a leukocyte reduction filter has been demonstrated to remove tissue factor, α-fetoprotein, fetal squamous cells, bacteria, and other undesirable contaminants.[243,244] Although two reports of hypotension related to the use of cell salvage exist,[245] the technique is appropriate for use in massive obstetric hemorrhage. In parturients who are Rh negative, anti-D immunoglobulin should be used as soon as possible in coordination with Kleihauer-Betke testing to prevent alloimmunization because variable amounts of fetal RBCs will be transfused to the mother with use of cell salvage. When standard resuscitation methods are not adequate to control the obstetric hemorrhage, the peripartum obstetric team should consider use of invasive options, including compression sutures, uterine balloon tamponade, ligation of uterine vessels, and use of interventional radiology for arterial embolization if stable for transport. Based on a 2007 systematic review of the literature, no single invasive option is significantly better than another, and all have success rates of approximately 85% to 90%.[246] If these options fail or are not feasible, a hysterectomy should be performed.

AMNIOTIC FLUID EMBOLISM

The rate of amniotic fluid embolism (AFE) is between 1:20,000 and 1:83,000 live births, with a 1999 database rate of 1:20,646 singleton pregnancies.[247,248] Signs and symptoms of AFE include hypotension, respiratory distress, hypoxia, disseminated intravascular coagulation (DIC), altered mental status, and hemodynamic collapse. This constellation of clinical features must be differentiated from other more common conditions that mimic AFE (i.e., venous air embolism, pulmonary embolism, cardiac dysfunction, massive hemorrhage, and pulmonary aspiration). The mechanism of AFE remains unclear, but it is no longer believed to be embolic, but rather an anaphylactoid reaction.[247,249] Previously, it was clinical practice to diagnose AFE based on the presence of fetal squamous cells in the maternal pulmonary circulation at autopsy, but the presence of these cells is frequently noted in the pulmonary circulation of otherwise unremarkable pregnant women around the time of labor and delivery. Consequently, determining the occurrence of an AFE is a clinical diagnosis of exclusion and no diagnostic laboratory test for AFE currently exists, even postmortem. AFE is managed with supportive care, frequently focused on intubation, ventilation, cardiopulmonary resuscitation, inotropic support, management of DIC, and correction of arterial hypoxemia.

OTHER OBSTETRIC EMERGENCIES

Certain urgent situations may occur around the time of labor and delivery that require tailored anesthetic care to optimize both the maternal and fetal outcome. Cord prolapse through the cervical os can result in abrupt fetal bradycardia. Rates of umbilical cord prolapse range between 0.1% and 0.6%.[250] The risk is significantly increased with the presence of transverse lie, breech presentation, multiple gestations, and an abnormally long umbilical cord. In addition, cord prolapse may occur around the time the membranes are ruptured if an abnormal fetal presentation is present or the mother has polyhydramnios. Diagnosis is confirmed with visualization or palpation of the cord in the vaginal canal below the presenting fetal part. Intervention typically consists of elevating the compressing fetal part back into the pelvis off of the cord until an urgent cesarean delivery can be performed. Use of an in situ epidural catheter or spinal technique can be considered as long as the FHR tracing is reassuring, but general anesthesia is frequently used in the event of fetal compromise.

Uterine inversion occurs in approximately 0.04% of deliveries[251] and is usually associated with hypotension, pain, and significant blood loss. Risk factors include excessive cord traction before placental separation, location of the placenta at the fundus, and presence of placenta accreta. Treatment goals include relaxation of the uterus to aid replacement, maternal fluid resuscitation, and increased uterine tone after replacement to reduce postpartum hemorrhage. Uterine relaxation can be quickly and reliably achieved using either intravenous nitroglycerine or volatile anesthetics.[252-254] The mother's hemodynamic condition may guide the choice of therapy. If the initial uterine intervention and replacement is not successful with nitroglycerine because of lack of relaxation, maternal pain, hemodynamic instability, or other logistics, transfer to the operating room should occur. A rapid sequence intubation with standard precautions for recent pregnancy followed by use of volatile anesthetic administration will allow needed uterine relaxation, pain control, and procedural conditions for uterine replacement. Only on rare occasion are vaginal maneuvers unsuccessful and laparotomy required. After uterine replacement, the uterine cavity should be explored for perforation, laceration, or retained products. Afterward, appropriate examination uterotonic drugs can be started.

Lacerations of the vagina, cervix, and perineum are the most common injuries associated with vaginal birth. Significant bleeding can be concealed in hematomas, and maternal hypotension and tachycardia may be the first signs of the injury. Retroperitoneal hematomas are rare but can represent substantial life-threatening blood loss that requires exploratory surgery. Anesthetic management to allow surgical repair or exploration depends on the hemodynamic state of the mother and can include use of local anesthetic at the site, neuraxial blockade, or—in severe hemodynamic compromise—use of general endotracheal anesthesia. Equally important is the hemodynamic assessment and initiation of resuscitation efforts for the mother. Even small unrecognized lacerations can result in significant blood loss.

NONOBSTETRIC SURGERY DURING PREGNANCY

PERIOPERATIVE CONSIDERATIONS

Although elective surgery is not performed during pregnancy, the requirement of surgery during pregnancy is

not uncommon; between 0.75% and 2% of pregnant women will require surgery. The most common indications are acute appendicitis and cholecystitis, maternal trauma, and cancer.[255]

ANESTHETIC TOXICITY

All general anesthetic drugs cross the placenta. Although no clear evidence exists for toxicity of specific anesthetic drugs in humans, data in rodents and primates suggest that exposure to general anesthetic drugs, including volatile anesthetics, propofol, and ketamine, induce inappropriate neuronal apoptosis that is associated with long-lasting behavioral abnormalities.[256-258] These preclinical results are concerning, but whether these drugs cause toxicity in humans is not known. The critical period of rapid synaptic development is extended in humans from the prenatal period through 2 years of postnatal life.[259] Analyses of existing human data have found conflicting evidence. In a population-based cohort evaluating the effect of general anesthesia before birth, evidence suggested that multiple exposures increase the risk for learning disability in language, mathematics, or reading.[259] The results of these types of studies are difficult to interpret because the reason for the anesthesia cannot be separated from the impact of the anesthesia. Also, current studies have not included data on the timing, type, or duration of anesthesia. No studies found an excess of birth defects in women who underwent general anesthesia during pregnancy, but most found a small increase in the risk for preterm delivery or miscarriage.[260-262] In general, the second trimester is preferred for surgical intervention because this is a period after much organogenesis has taken place and yet it minimizes the risk for preterm labor associated with the third trimester. Monitoring for contractions is recommended, and in some situations suppression with magnesium sulfate or indomethacin is recommended after surgery. Because the long-term impact of general anesthesia on the fetus is unknown, regional anesthesia is favored when possible for the surgical procedure, but should not be undertaken unless both the anesthesiologist and surgeon are experienced in using the technique for a given procedure.

PERIOPERATIVE FETAL HEART RATE MONITORING

After 18 weeks, FHR monitoring is practical; after 25 weeks, FHR variability is a reliable sign of fetal well-being. The ACOG states, "although there are no data to support specific recommendations regarding non-obstetric surgery and anesthesia in pregnancy, it is important for non-obstetric physicians to obtain obstetric consultation before performing non-obstetric surgery. The decision to use fetal monitoring should be individualized and each case warrants a team approach for optimal safety of the woman and her baby."[263] Under general anesthesia the loss of FHR variability may not be indicative of fetal academia but may be a result of anesthetic alteration of autonomic tone. Fetal bradycardia is more concerning and can be affected by hypothermia, maternal acidosis, or the maternal administration of drugs such as β-blockers that cross the placenta and reduce FHR.

ANESTHETIC MANAGEMENT

As mentioned earlier, for theoretic fetal considerations, regional anesthesia is preferred when possible to general anesthesia for nonobstetric surgery in pregnancy. Very practical maternal considerations also favor regional anesthesia. The increase in peripheral blood flow induced by pregnancy results in airway edema and friability. These changes can be present from the second trimester. Mallampati classification is more predictive of difficult intubation in pregnancy. Increased difficulty of intubation in pregnancy should be considered, and equipment for advanced airway should be readily available before intubation is attempted. Equally important to anesthetic technique is avoidance of decreased uterine blood flow and oxygen delivery to the fetus. Considerations similar to those discussed in the section on anesthesia for cesarean delivery should be undertaken for any nonobstetric surgery during pregnancy. The anesthetic plan should optimize the maternal and fetal condition. Perioperative team planning should include consultation with an obstetrician and perinatologist regarding plans for unexpected events, including need for emergent cesarean section or possible maternal arrest.

POSTOPERATIVE PAIN CONTROL

Maternal pain control after nonobstetric surgery is of paramount importance to maternal well-being (see also Chapter 98). When surgery is conducted under regional anesthesia, the epidural can be continued for postoperative analgesia. Postoperative systemic opioids including those used in patient-controlled analgesia, cross the placenta and may reduce FHR variability. However, no evidence has shown that this is detrimental to the fetus. If the fetus is born prematurely shortly after exposure to maternal systemic opioids, respiratory support may be necessary. Nonsteroidal antiinflammatory drugs, though useful adjuvant analgesics outside of pregnancy, should be used with caution in pregnancy. They are associated with an increased risk for miscarriage and fetal malformation when used in early pregnancy and premature closure of the ductus arteriosus and oligohydramnios when used after 30 weeks gestation.[264] Acetaminophen is generally accepted as safe in pregnancy.

After surgery, both the FHR and uterine activity should be monitored. Preterm labor can be managed with appropriate tocolytic drugs. Postoperative pain relief medications may make it difficult for the patient to note early contractions and patient perception should not be considered a substitute for standard monitoring. In addition, thrombosis prophylaxis should be instituted unless surgically contraindicated.

ADVANCED CARDIAC LIFE SUPPORT IN PREGNANCY

The protocol for advanced cardiac life support (ACLS) in pregnancy is similar to that recommended for other

BOX 77-5 *Factors Important in Maternal Laparoscopy*

Use an open technique to enter the abdomen.
Monitor maternal end-tidal P_{CO_2} (4- to 4.6-kPa range) with or without arterial blood gas to avoid fetal hypercarbia and acidosis.
Maintain low pneumoperitoneal pressure (1.1 to 1.6 kPa) or use a gasless technique.
Limit the extent of Trendelenburg or reverse Trendelenburg position and initiate any position slowly.
Monitor fetal heart rate and uterine tone when feasible.

Modified from Reitman E, Flood P: Anesthetic considerations for non-obstetric surgery in pregnancy, *Br J Anaesth* 107(suppl 1):i72-i78, 2011.

adult cardiac arrest situations, except that compression of the maternal great vessels by the pregnant uterus greatly impedes the success of external cardiac massage (see also Chapter 108). Cesarean delivery should be performed not later than 4 minutes after maternal cardiac arrest.[265] Although potentially beneficial for the fetus if viable, its primary goal is to improve ACLS effectiveness and improve maternal survival by increasing venous return to the heart with ACLS maneuvers and improving thoracic compliance and maternal ventilation.[266] In addition, if the maternal cardiac arrest may have been caused by local anesthetic toxicity, lipid rescue should be initiated.[267]

SPECIFIC SURGICAL TECHNIQUES

Laparoscopy

Surgery for appendicitis and cholecystitis are common in pregnancy. These surgeries are most commonly performed with a laparoscopic technique outside of pregnancy and are being done more commonly with laparoscopy because of reduced morbidity for the mother and potentially a decreased incidence of preterm labor as a result of reduced manipulation of the uterus.[268] Open appendectomy may have a slightly less frequent rate of fetal mortality compared with laparoscopic appendectomy, although maternal morbidity is more frequent.[269] However, a comparison of laparoscopy and laparotomy has considered over 2 million pregnancies in Sweden and no difference in fetal outcome was identified between the two techniques.[270] Left uterine displacement must be maintained after the second trimester to facilitate uterine perfusion and ventilation maximized to prevent maternal CO_2 retention and acidosis. With increased abdominal pressure from insufflation, maternal cardiac output and uteroplacental perfusion may decrease. Thus, the smallest possible intraabdominal pressure should be used. According to the guidelines issued by the Society of American Gastrointestinal Endoscopic Surgeons regarding laparoscopic surgery during pregnancy,[271] whenever possible, surgery should be deferred to the second trimester and indications for the use of laparoscopic techniques are the same as in nonpregnant patients. Specific considerations for these types of procedures are listed in Box 77-5. Fetal and uterine status should be monitored, and careful attention should be paid to maternal end-tidal P_{CO_2}. During laparoscopic surgery, gradients between end-tidal CO_2 and arterial CO_2 are typically less than 3 mm Hg, and arterial blood gas monitoring is not needed unless otherwise indicated.[272] An open technique is preferred to enter the abdomen. Aortocaval compression should be avoided. Finally, low pneumoperitoneal pressure (<1.6 kPa) should be used. A systematic review of laparoscopic surgery for appendicitis during pregnancy noted that trimester timing did not influence the complication rate, the need for conversion to open was less than 1%, and a lower rate of preterm delivery was found with laparoscopic approach in contrast to open.[269]

Trauma

The most common cause of maternal death in the United States is trauma. Initial primary and secondary survey should be directed toward maternal well-being, with consideration of the physiologic changes induced by pregnancy (see also Chapter 81). Gestational age is an important variable in trauma evaluation. During the first trimester, the fetus is protected by the bony pelvis and damage is unlikely in the absence of severe hypoperfusion. However, as pregnancy progresses, the uterus is not only exposed but also causes pressure on the maternal inferior vena cava and aorta, potentially compromising perfusion and resuscitation. After 20 weeks gestation, left uterine displacement should be implemented as the initial step. Blunt trauma carries a risk for intrauterine fetal demise, fetal injury, placental abruption, and uterine rupture. These dangers should be evaluated with fetal heart monitoring ultrasonography, computed tomography, or exploratory laparotomy when indicated.[273] The consequences for ACLS are discussed earlier in the chapter.

Cardiac Surgery

The physiologic changes induced by pregnancy can put inordinate strain on patients with preexisting heart disease (see also Chapter 67). In particular, patients with severe mitral or aortic valvular obstruction are at risk from the increased intravascular volume and cardiac output required to support an ongoing pregnancy. New techniques in percutaneous balloon valvuloplasty can obviate open cardiac intervention in pregnancy and have been associated with reduced fetal and neonatal mortality.[274,275] Cardiopulmonary bypass increases risk to the fetus as a result of nonpulsatile perfusion, low perfusion pressures, emboli to the uteroplacental unit, and maternal release of catecholamines.[276] Higher pump flows (>2.5 $L/min/m^2$) and perfusion pressures (>70 mm Hg) are recommended to support uteroplacental blood flow.[277,278] Normothermic bypass and pulsatile flow may better preserve uteroplacental perfusion and improve fetal survival. Particularly during hypothermic bypass, acid-base disturbances can be observed. Hypocapnia should be avoided because it causes uteroplacental vasoconstriction, and hypercapnia causes acidosis and fetal acidosis with reduced cardiac function.

Neurosurgery

Neurosurgical emergencies from hemorrhage secondary to aneurysm rupture or arteriovenous malformation are not uncommon during pregnancy (see also Chapter

70). It is unclear whether pregnancy increases the risk for rupture. However, the risk for intracranial hemorrhage is increased by hypertensive diseases of pregnancy. In patients who are not pregnant, usual anesthetic treatment might include controlled hypotension, hypothermia, hyperventilation, and osmotic diuresis. These techniques need to be conducted with particular care in pregnancy. Reduction of mean arterial pressure below 70 mm Hg may significantly reduce uteroplacental perfusion, and use of fetal monitoring should be considered as a guide to fetal well-being. If hypothermia is used, the FHR will be reduced but will increase with rewarming. In fetal lambs, hypothermia to less than 18° C caused irreversible fetal acidosis and hypoxia, likely as a result of uterine vascular constriction,[279] and in case reports, fetal bradycardia with a strong maternal temperature, dependence was noted below 33° C.[280] Extreme hyperventilation also can cause uterine artery vasoconstriction and reduce uterine perfusion. Osmotic diuresis, used to reduce brain edema, may cause negative fluid shifts in the fetus. Mannitol in particular may accumulate in the fetus, leading to hyperosmolarity, reduced renal blood flow, and increased plasma sodium concentration.[281] Loop diuretics are an alternative but should be used with care and monitoring of amniotic fluid volume.

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Chapter 78

Anesthesia for Fetal Surgery and Other Fetal Therapies

MARK D. ROLLINS

Key Points

- Most fetal anomalies are not appropriate for in utero treatment. A condition or situation appropriate for fetal treatment must cause ongoing irreversible harm to the fetus that would be mitigated with early treatment and occur before a gestational age at which the fetus could tolerate ex utero neonatal intervention.
- A multidisciplinary approach with thorough open communication is essential to the success of each fetal intervention.
- Maternal safety and the principle of "do no harm" should be the prime principle in determining the most appropriate therapeutic option and perioperative plan. A thorough maternal and fetal evaluation and frank discussion of risks and benefits by all team members with the mother is required to determine an appropriate care plan.
- Although open fetal surgery typically requires general anesthesia, most minimally invasive techniques can be effectively performed using local or neuraxial anesthesia.
- Randomized controlled clinical trials show improved outcomes with use of both fetoscopic laser photocoagulation of placental vessels to treat twin-to-twin transfusion syndrome and intrauterine open fetal surgery to treat myelomeningocele.
- In addition to anesthetic considerations associated with nonobstetric surgery during pregnancy, fetal surgery requires planning for fetal anesthesia and analgesia, fetal monitoring, uterine relaxation, and postoperative fetal monitoring and tocolysis.
- Membrane separation, preterm premature rupture of membranes, and preterm labor remain the most common complications and significant cause of morbidity and suboptimal outcome with fetal surgery.
- Further research into optimal anesthetic techniques for various fetal interventions is essential to improve patient outcomes and advance the field of fetal surgery.

Only recently have medical professionals focused on the human fetus as a patient, able to undergo surgery or medical intervention. This development has been primarily driven by systematic improvements in prenatal diagnosis, imaging technology, and surgical equipment. Although many fetal surgical procedures are available only at highly specialized institutions, some prenatal interventions are considered conventional therapy and have become more widespread. This chapter reviews the unique pathophysiological processes of various fetal and placental conditions amenable to intervention, current outcome data, specific procedural considerations, and perioperative anesthesia considerations.

Most fetal abnormalities are not appropriate for antenatal intervention and are more amenable to treatment after delivery. However, some anatomic malformations may result in irreversible end-organ damage and would benefit from intervention before birth. This has led to the theory that surgical or procedural correction in utero could allow normal fetal development and might mitigate much of the detrimental pathologic process observed.[1] Other defects, such as congenital airway obstruction, can be managed intrapartum by keeping the uteroplacental unit intact while the defect is repaired or airway secured, without the urgency that would be associated with attempting similar procedures immediately after birth.

Prerequisite guidelines for performing fetal surgery were initially developed more than 30 years ago at a multidisciplinary meeting with participants from 13 medical centers representing five countries.[2] Over time these guidelines have evolved and include (1) the fetal lesion is accurately diagnosed; (2) the progression and severity of the anomaly is predictable and well understood; (3) other severe associated anomalies that would contraindicate fetal intervention are excluded; (4) if left untreated before birth, the fetal abnormality would lead to fetal demise, irreversible organ damage, or severe postnatal morbidity, and, therefore, intervening before birth would benefit the neonatal outcome; and (5) the maternal risk is acceptably infrequent.[1,3]

All interventions should be preceded by a thorough multidisciplinary team deliberation of the clinical case. Discussions should focus on a comprehensive risk benefit analysis and providing the family appropriate counseling that includes options for elective termination of pregnancy or continuation of pregnancy without fetal therapy. Potential risks to the mother should be part of the informed consent, with a thorough and detailed maternal preoperative evaluation as part of the process to ensure maternal risks are minimal.[4,5]

The advancement of fetal surgery has benefited from a multidisciplinary approach and establishment of the International Fetal Medicine and Surgery Society to disseminate techniques and outcome data through an international registry. Medical centers offering fetal treatment rely on surgeons and anesthesiologists devoted to the care and counseling of these complex maternal and fetal patients, as well as the expertise of radiologists, perinatologists, geneticists, neonatologists, social workers, and numerous other support staff. A bioethics committee derived from both the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics has provided guidelines for fetal treatment centers that recommend a comprehensive informed consent and counseling process, maternal-fetal research oversight, use of a multidisciplinary approach, and participation in a collaborative data-sharing fetal therapy network.[6]

Fetal surgery is broadly categorized into three types of intervention: minimally invasive procedures, open procedures, and intrapartum procedures. A summary of conditions considered for fetal intervention with corresponding rationale and treatment is displayed in Table 78-1.

Minimally invasive fetal procedures include (1) percutaneous interventions guided by ultrasound, also known as fetal image–guided surgery for intervention or therapy (FIGS-IT), and (2) fetal endoscopic surgery using small endoscopic instruments dually guided by direct fetoscopic camera view and simultaneous real-time

TABLE 78-1 FETAL CONDITIONS CURRENTLY CONSIDERED FOR INTERVENTION

Fetal Condition	Therapy Rational	Type	Intervention
Fetal anemia or thrombocytopenia	Prevention of heart failure and fetal hydrops	FIGS-IT	Intrauterine transfusion
Aortic stenosis, intact atrial septum, or pulmonary atresia	Prevention of fetal hydrops, myocardial dysfunction, and hypoplastc left (and right) heart	FIGS-IT	Percutaneous fetal valvuloplasty or septoplasty
Lower urinary tract obstruction	Bladder decompression with reduction in renal dysfunction, pulmonary hypoplasia, oligohydramnios, and limb malformation	FIGS-IT or fetoscopy	Percutaneous vesicoamniotic shunting or fetoscopic posterior valve laser ablation
Twin reverse arterial perfusion	Prevention of high-output cardiac failure in the normal twin by stopping flow to acardiac twin	FIGS-IT or fetoscopy	Umbilical radiofrequency ablation or fetoscopic coagulation
Twin-twin transfusion syndrome	Reduction of twin-twin blood flow and prevention of cardiac failure	Fetoscopy	Fetoscopic laser photocoagulation of placental vessels
Amniotic band syndrome	Prevention of limb loss	Fetoscopy	Fetoscopic band ablation
Congenital diaphragmatic hernia	Prevention of pulmonary hypoplasia	Fetoscopy	Fetoscopic tracheal occlusion
Myelomeningocele	Reduction in hydrocephalus and hindbrain herniation with improved neurologic function	Open	Closure of fetal defect through hysterotomy
Sacrococcygeal teratoma	Prevention of high-output cardiac failure, hydrops, and polyhydramnios	FIGS-IT or open	Ablation of tumor vasculature or open fetal tumor debulking
Congenital cystic adenomatoid malformation	Reversal of pulmonary hypoplasia and cardiac failure	FIGS-IT or open	Thoracoamniotic shunting or open surgical resection
Fetal airway compression	Secured open airway and/or circulatory support to prevent respiratory compromise at birth	Open intrapartum	Ex-utero intrapartum therapy that allows stabilization while on uteroplacental circulation

Modified from Partridge EA, Flake AW: Maternal-fetal surgery for structural malformations, Best Pract Res Clin Obstet Gynaecol *26:669-682, 2012.*
FIGS-IT, Fetal image-guided surgery for intervention or therapy.

ultrasound imaging. Fetal endoscopic surgery is typically accomplished percutaneously, but sometimes requires a small maternal minilaparotomy. With these minimally invasive approaches, the risks for preterm labor and delivery are reduced compared with those in open procedures that include a hysterotomy. Unlike in open fetal procedures, the mother can safely undergo a vaginal delivery for this and future pregnancies. However, the risk for preterm premature rupture of membrane (PPROM) remains significant.

Open fetal procedures involve a maternal laparotomy, a hysterotomy, and the need for intraoperative uterine relaxation. These procedures incur significantly more risk to both the fetus and mother than minimally invasive procedures. These increased risks include PPROM, oligohydramnios, preterm labor and delivery, uterine rupture, and fetal mortality.[7,8] Additional maternal and fetal risks include not only the anesthetic risks noted for nonobstetric surgery during pregnancy (see also Chapter 77), but also pulmonary edema, hemorrhage, membrane separation, and chorioamnionitis.[4] Cesarean delivery is required after an open fetal procedure and for all future pregnancies owing to the increased risk for uterine dehiscence or rupture at the site of the hysterotomy.

For fetuses with known airway compromise or obstruction, an ex utero intrapartum therapy (EXIT) procedure[9] allows continued fetal support by the intact uteroplacental unit (placental bypass) while the fetal airway is secured or other procedures completed without the concern for postnatal respiratory compromise, hypoxia, and asphyxia. Examples of congenital lesions treated with EXIT procedures include cystic hygroma, lymphangioma, cervical teratomas, and other congenital syndromes with potential for airway compromise. Extracorporeal membrane oxygenation (ECMO) can be initiated during an EXIT procedure for a fetus with significant cardiopulmonary disease. Fetal surgical procedures in excess of 2.5 hours have been successfully performed using placental bypass with normal umbilical cord carbon dioxide and pH values at delivery.[10] The EXIT procedure has become a widely practiced fetal intervention for a growing list of indications.

Much of the success of fetal therapy in the past 3 decades can be attributed to extraordinary advances in both ultrasonography and magnetic resonance imaging (MRI), which have substantially improved the accuracy of prenatal diagnosis and expanded our understanding of the pathophysiologic factors of various untreated fetal abnormalities.

Significant advancements in ultrasonographic transducer hardware and digital signal processing have resulted in better image resolution with more accurate differentiation of abnormal fetal anatomy, wider fields of view, and improvement in the dynamic range for both near-field and far-field signal-to-noise ratio. Use of this improved ultrasonographic imaging as a real-time guide has enabled practitioners to develop and perform various diagnostic tests and fetal therapies more precisely and safely. Examples of fetal ultrasound-guided diagnostic procedures include first-trimester chorionic villus sampling, embryofetoscopy, amniocentesis, fetal blood sampling, and fetal biopsies.[11] These diagnostic advances allow more accurate prenatal consultation, the ability to intervene at an earlier gestational age, and usually enough time to change the location of antepartum care and the delivery plan if needed. Live ultrasound is typically used to guide all minimally invasive fetal procedures and is also critical to initial portions of open fetal procedures and fetal monitoring.

MRI has undergone technologic improvements that reduced image acquisition time, decreased motion artifacts, and enhanced image resolution to a point at which fetal MRI is frequently used in conjunction with ultrasound to better detect and evaluate anatomic pathologic processes.[12]

In addition to advances in imaging technology, decades of procedural innovations and research have provided the basis for the in utero fetal interventions used clinically today. Initial pioneers in the field of fetal therapy include Sir (Albert) William Liley. In the early 1960s, Liley[13] was the first to successfully treat erythroblastosis fetalis with an intraperitoneal blood transfusion that allowed the transfused red cells to be absorbed into the fetal circulation through the subdiaphragmatic lymphatics and thoracic duct.[14] Unfortunately, initial attempts to perform fetal blood transfusion through direct cannulation of the umbilical vessels were unsuccessful until 1981, when a reliable technique that employed fetoscopy was described.[15,16] With improved imaging resolution, the standard technique quickly became direct needle access of the umbilical vessels using ultrasound guidance. In the early 1970s, Liggins administered corticosteroids to the fetus via the maternal circulation to increase surfactant production in preterm fetuses at risk for respiratory distress syndrome.[15] Fetal surgery began in the early 1980s after rigorous research efforts and technical advancements in sheep[17-19] and monkey[20] models. Harrison and colleagues[21] performed the first successful human fetal surgery by creating a vesicostomy in a fetus with a congenital lower urinary tract obstruction resulting in bilateral hydronephrosis. Working with Harrison in the early 1980s, Rosen[22,23] refined fetal anesthetic techniques in monkeys[20] to improve intraoperative uterine relaxation and clinical outcome before employing them for the first human fetal surgeries and then detailing these techniques in the literature. Since the early 1980s, great advances have been made in the development of minimally invasive percutaneous surgical techniques, fetoscopy, and procedural aspects of open fetal surgery with hysterotomy. Fetal therapy also has advanced in its outcome evaluation from published case reports and series to prospective randomized controlled trials.[24]

Fetal surgery is a reasonable therapeutic intervention for certain correctable fetal anomalies with predictable, life-threatening, or serious developmental consequences. With all types of fetal intervention, meticulous planning and a multidisciplinary team approach are critical to a successful outcome. The following sections provide a review and summary of the congenital lesion, outcome data, procedural considerations, and perioperative anesthesia considerations for the various conditions currently amenable to fetal intervention.

INDICATIONS, PROCEDURES, AND OUTCOMES

ANEMIA AND INTRAUTERINE TRANSFUSION

The incidence of fetal anemia secondary to rhesus D (RhD) sensitization has decreased since the introduction of RhD immunoglobulin prophylaxis in the late 1960s, to rates of approximately 1 in 1000 pregnancies.[25] However, other red blood cell (RBC) antigens, parvovirus B19 infection, maternal-fetal hemorrhage, and homozygous thalassemia also cause fetal anemia and combine to reach a rate of approximately 6 cases in 1000 live births.[25,26] Although spectral analysis examining bilirubin levels in serial amniotic fluid samples was originally used to detect fetal anemia and determine the timing of therapy, most treatment centers currently rely on noninvasive Doppler studies of the middle cerebral artery (MCA).[26] An increased peak MCA blood flow velocity more than 1.5 multiples of the median is a threshold that has proved accurate in detecting moderate-to-severe fetal anemia requiring intervention.[27,28] The value of this peak velocity threshold may be increased with each serial transfusion treatment to decrease the false positive rate. Fetal blood sampling from the umbilical vein just before starting the intrauterine transfusion (IUT) is the gold standard for determining the degree of fetal anemia. IUT is not used before 18 to 20 weeks gestational age because reliable umbilical vein access is not possible. For cases requiring earlier intervention, intraperitoneal transfusion may initially be the intervention of choice.[29]

IUTs are typically performed using local anesthesia, with minimal maternal sedation and analgesia required. However, the anesthesiologist should be prepared for an emergent cesarean delivery at any time during the procedure if the fetus is at a viable gestational age. Using ultrasound image guidance, a 20- or 22-gauge needle is used to access the umbilical vein. The access point is typically near the placental cord insertion to provide stability (Fig. 78-1). Puncture of the umbilical artery rather than the vein is associated with prolonged bleeding and fetal bradycardia secondary to spasm.[25] Occasionally a free loop of the umbilical cord or intrahepatic portion of the umbilical vein may be used. The umbilical cord probably has no pain receptors, but needle access of the intrahepatic portion of the umbilical vein would stimulate pain receptors with passage of the needle into the fetus. Fentanyl attenuates the fetal stress response from intrahepatic fetal needle placement.[30] Yet, in one recent study, fetal stress hormone changes with IUT were unrelated to site of needle placement.[31] However, these results are difficult to interpret because hormone levels may primarily be determined by changes secondary to the underlying fetal anemia and associated hemodynamic alterations that are then changed with intravascular volume expansion. Given this uncertainty, fentanyl is administered to the fetus before use of an intrahepatic approach.

A muscle relaxant can be administered to the fetus to decrease the likelihood of fetal movement that could dislodge the needle or sheer the umbilical vein.[32] The volume of type O, rhesus (Rh)-negative, irradiated, viral

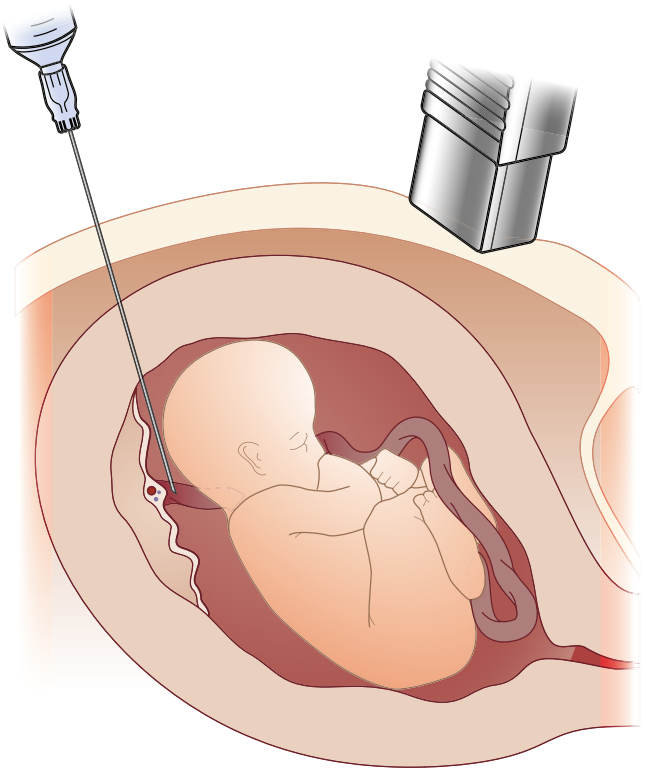


Figure 78-1. Diagram of cordocentesis procedure used in intrauterine transfusion. *(Redrawn from Ralston SJ, Craigo SD: Ultrasound-guided procedures for prenatal diagnosis and therapy,* Obstet Gynecol Clin North Am *31:101-123, 2004.)*

screened, packed RBCs transfused is estimated from the gestational age, estimated fetal weight, donor unit hemoglobin (Hb), and pretransfusion Hb.[33] The rate of transfusion is typically 5 to 10 mL/min with a target of 45% to 55% hematocrit. Steady intravascular location of the needle tip can be assessed with Doppler imaging throughout the transfusion injection. Periodic sampling is used to guide the final transfusion volume. After IUT therapy, fetal Hb levels decrease approximately 0.3 g/dL/day[34] and multiple repeat IUTs are typically required at 1- to 3-week intervals, depending on the rate of Hb decline.

Perinatal fetal loss rate is approximately 2% per IUT, and transient fetal bradycardia (8%) is a common complication.[35] In a series of 740 IUTs performed to treat 254 fetuses, the overall survival rate was 89%, with a 1.6% rate of fetal loss directly attributed to a procedural complication per IUT.[36] Rates of other complications per IUT included emergency cesarean delivery (2%), intrauterine infection (0.3%), and rupture of membranes (0.1%).[36] The survival rates are somewhat less for hydropic fetuses. In a retrospective study of 210 fetuses undergoing 593 IUTs, a 92% survival rate occurred in nonhydropic fetuses and a 78% survival rate in hydropic fetuses.[37] A few fetal treatment centers have published survival rates that exceed 95%.[38,39] A long-term outcome study of 291 children (median age of 8.2 years with a range of 2 to 17 years of age) who underwent IUT during gestation for hemolytic disease found a 4.8% rate of neurodevelopmental impairment, including cerebral palsy (2.1%), severe developmental delay (3.1%), and bilateral deafness (1.0%).[38]

Severe fetal hydrops was independently associated with neurodevelopmental impairment.

CONGENITAL HEART DEFECTS

Congenital heart anomalies occur with a frequency of 8 to 10 per 1000 live births (see also Chapter 94).[40] Of these, 3.5 to 4.0 per 1000 require intervention in infancy.[41-43] Ultrasound imaging allows diagnosis of cardiac defects as early as 12 to 14 weeks gestation.[44] The majority of fetal cardiac interventions include (1) aortic balloon valvuloplasty for treatment of critical aortic stenosis and evolving hypoplastic left heart syndrome (HLHS), (2) atrial septostomy for highly restrictive or intact atrial septum seen in HLHS, and (3) pulmonic valvuloplasty for pulmonary atresia or intact ventricular septum and hypoplastic right ventricles.[45] In utero treatment attempts to halt or reverse the morbid effects of the cardiac lesion before irreversible consequences occur. Early childhood mortality from severe cardiac defects, such as HLHS, remains in the range of 25% to 35%.[46,47] Survivors have significant associated abnormalities in neurologic development.[48,49] These fetal cardiac procedures focus on opening a stenotic valve or enlarging a restricted opening.

The most commonly performed procedure is an aortic valvuloplasty for aortic stenosis with evolving HLHS. Current selection guidelines for fetal aortic valvuloplasty focus on the presence of significant aortic stenosis, evolving HLHS, and the potential for a technically successful procedure and biventricular postnatal outcome.[46,50] Significant aortic stenosis maintains fetal circulation primarily through the low-resistance foramen ovale and diminishes left ventricular development. For this procedure,[51] the fetus is ideally positioned with the left chest anterior, and ultrasound is used to guide the percutaneous passage of an 18- or 19-gauge needle through the uterus, through the fetal chest, and into the apex of the left ventricle (Fig. 78-2, *A*). Maternal local anesthesia infiltration or neuraxial block is typically used for these procedures, and fetal resuscitation drugs must be readily available. In some cases, general anesthesia may be preferred for uterine relaxation to facilitate an external version to change fetal positioning and improve cannula trajectory. Before cannula insertion, intramuscular fentanyl and a paralytic agent are administered to the fetus with ultrasound guidance, as detailed in the discussion of fetal anesthesia and analgesia. The cannula tip is ideally positioned in the left ventricle, directly in front of the opening of the stenotic aortic valve and aligned with the left ventricular outflow tract. A balloon catheter with guidewire is passed through the cannula into the stenotic valve and positioned in the aortic annulus, where it is inflated and deflated multiple times (Fig. 78-2, *B*). Similar techniques are used for pulmonary valvuloplasty and atrial septoplasty.[52] In certain cases, a small laparotomy is used to facilitate improved cannula alignment with the cardiac lesion. Technical success for fetal aortic valvuloplasty is 70% to 75% using an angioplasty balloon over a guidewire.[50,53,54] Fetal complication rates from centers in Linz, Austria (n = 24) and Boston (n = 70) for fetal aortic valvuloplasty include, respectively, fetal bradycardia (17% and 38%), pericardial effusion (13% and 14%), ventricular thrombosis

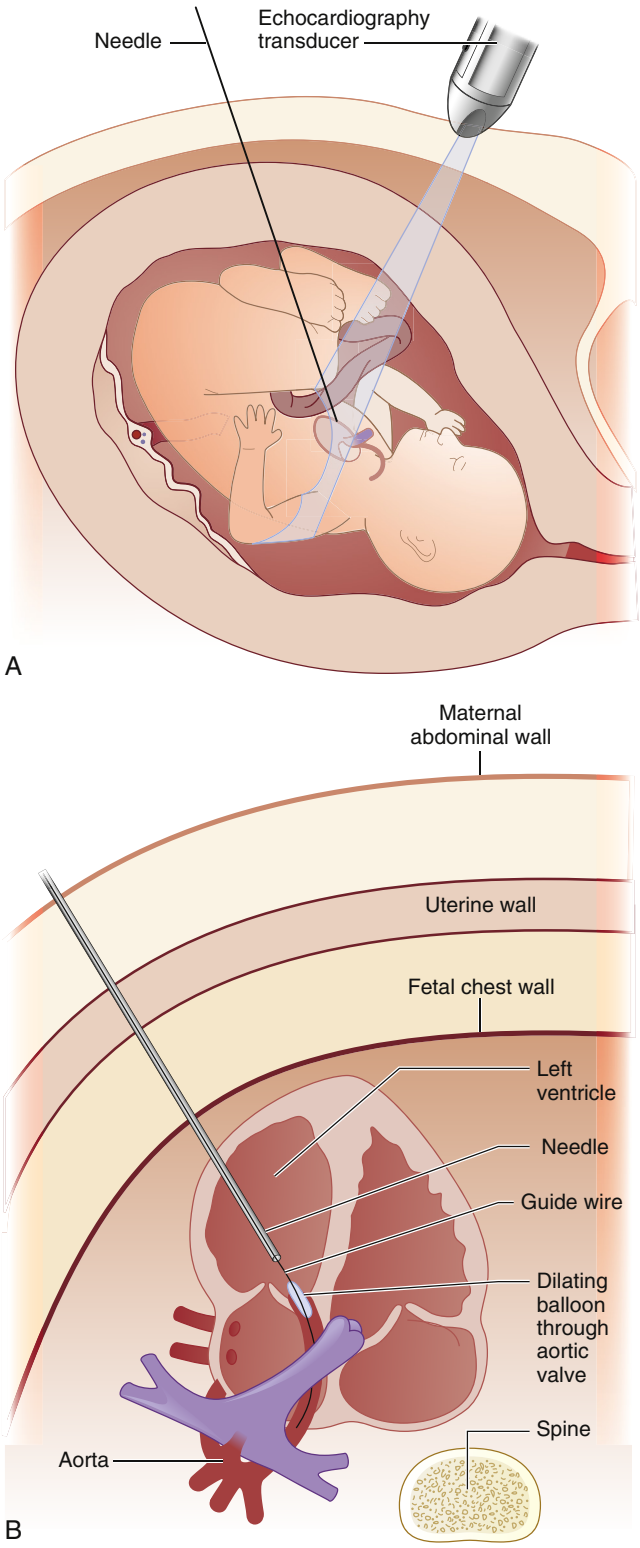


Figure 78-2. A, Depiction of ideal fetal position and insertion needle orientation. The fetal left chest is anterior, and the pathway from maternal abdomen entry point to the apex of the left ventricle is unobstructed. **B,** This linear cannula course continues from left ventrical apex to the aortic valve. *(Redrawn from Tworetzky W, Wilkins-Haug L, Jennings RW, et al: Balloon dilation of severe aortic stenosis in the fetus: potential for prevention of hypoplastic left heart syndrome—candidate selection, technique, and results of successful intervention,* Circulation *110:2125-2131, 2004; with permission from Lippincott Williams & Wilkins.)*

(21% and 15%), and fetal death (13% and 8%).[50,51,53] Approximately 40% of technically successful cases result in aortic regurgitation and minimal subsequent left ventricular growth. However, the left ventricular ejection fraction increases and aortic and mitral valvular growth improves.[45] Biventricular circulation is present at birth in approximately 30% of the successful cases.

In addition to treatment of aortic stenosis, other cardiac anomalies have been treated in utero. Outcomes from a small series of fetal atrial septostomies are promising; however, the defect created by the balloon dilation tends to close over time unless a stent is placed (which can be difficult to accurately deploy).[55,56] Pulmonary valvuloplasty for pulmonary atresia and prevention of hypoplastic right ventricle was technically successful in 7 of 11 procedures, but long-term outcome data are unavailable.[45,57] In utero placement of cardiac pacing can treat fetal cardiac arrhythmias unresponsive to conventional management with transplacentally administered antiarrhythmic drugs.[58] Unfortunately, these initial attempts have been largely unsuccessful.

OBSTRUCTIVE UROPATHY

Congenital obstructive uropathy occurs in approximately 1 in 1000 pregnancies.[59] These obstructions can be bilateral or unilateral and occur at the ureteropelvic junction, at the ureterovesical junction, or at the level of the urethra. If the obstruction is urethral or bilateral, significant developmental consequences occur (Box 78-1). Rates of perinatal mortality in these cases are as frequent as 90%, and survivors have more than 50% renal impairment.[60]

Posterior urethral valves are the most common cause of congenital bilateral hydronephrosis in male fetuses. Urethral obstruction is the most common cause in females, with other possible causes including ectopic ureter, ureterocele, megacystis megaureter, multicystic kidney, or other complex pathologic processes.[61] Ultrasound investigations of oligohydramnios resulting from the decreased fetal urine output easily detect these uropathies with high sensitivity and specificity. Fetal MRI should be considered in cases of severe oligohydramnios as an additional imaging technique to determine the presence of associated fetal anomalies.[60,62] A grading system based on ultrasound imaging of renal diameter can determine the severity of hydronephrosis.[63] The associated morbidity predicted for each type of uropathy depends on obstruction location, duration, gender, and gestational age at onset.[64] Preterm delivery allows neonatal urinary tract decompression, but morbidity from pulmonary immaturity prevents early intervention and limits the efficacy of this approach. Placement of an in utero fetal vesicoamniotic shunt for treatment of lower urinary tract obstruction (LUTO) allows decompression of the fetal bladder and urinary tract into the amniotic cavity. In animal studies, in utero intervention for LUTO improves dysplastic renal histologic conditions, increases amniotic fluid volume, and improves lung development. The translation of these results to fetal treatment of human LUTO remains controversial.[65]

An algorithm with specific criteria for karyotype, presence of additional abnormalities assessed by ultrasound, and fetal urinalysis are used to characterize the obstruction severity and improve both selection for in utero treatment and outcomes.[66] Poor prognosis is associated with earlier presentation during gestation, a more intense severity of oligohydramnios, associated structural abnormalities, and increased concentrations of fetal urine electrolytes, osmolality, protein, and β_2-microglobulin.[64,67] Each case should be thoroughly investigated to determine whether other anomalies are present and if the fetus is a suitable candidate for intervention.

Vesicoamniotic catheter shunt placement started in the 1980s. The shunt allows fetal bladder decompression in an effort to improve renal development and reduce the pulmonary hypoplasia associated with oligohydramnios. These valveless, double-coiled shunts are inserted percutaneously with ultrasonographic guidance and local anesthesia. One coil remains in the urinary bladder and the other in the amniotic cavity. Prior infusion of fluid into the amniotic cavity can aid in proper placement. Common problems associated with these catheters include difficult placement, subsequent occlusion, and position migration (malfunction occurs in up to 60% of cases).[68] Fetal complications include trauma, iatrogenic abdominal wall injury, gastroschisis, and amnioperitoneal leaking.[64] Vesicoamniotic shunting prevents the physiologic cycle of urine accumulation and emptying that is required for normal bladder development and is associated with bladder wall fibrosis in animal models.[69-71] Maternal complications include PPROM, preterm labor and delivery, and infection.[64] Neonatal survival rates after fetal vesicoamniotic shunting vary in the literature from 40% to 90%, with approximately 50% of survivors having normal renal function.[65,72-74] Currently, a multicenter, randomized controlled trial is underway (the Percutaneous Shunting in Lower Urinary Tract Obstruction [PLUTO] trial) comparing the perinatal mortality and renal function of fetuses with LUTO treated by either vesicoamniotic shunting or conservative noninterventional care with planned follow-up until 5 years of age.[75,76] Outcome data may be available in the next few years.

Fetal cystoscopy is a recent technique that allows prenatal diagnosis with visualization of the fetal urethra and prenatal treatment with ablation of the urethral obstruction. Cystoscopy facilitates diagnosis by allowing differentiation

BOX 78-1 ***Developmental Consequences of Fetal Urethral Obstruction***

- Oligohydramnios
  - Potter's facies (prominent infraorbital folds)
  - Hypoplastic lungs
  - Flexion contracture
- Hydronephrosis
  - Type 4 cystic dysplasia
  - Renal failure
- Hydroureter and megacystis
  - Abdominal muscle deficiency
  - Prune belly

Data from Harrison MR, Filly RA, Parer JT, et al: Management of the fetus with a urinary tract malformation, JAMA *246:635-639, 1981.*

between LUTO resulting from urethral atresia and posterior urethral valves. Two small case series show that use of fetal cystoscopy changed the diagnosis between these two pathologic processes in 25% to 36% of cases previously diagnosed by ultrasound imaging.[76-78] Fetal cystoscopy to ablate posterior urethral valves with laser fulguration may increase survival compared with expectant management, but improved perinatal survival over that with vesicoamniotic shunting has not been shown.[76]

Selective fetal intervention with shunting or cystoscopy for LUTO restores amniotic fluid volume, prevents pulmonary hypoplasia, and improves perinatal mortality. However, the effects on medium-term and long-term renal function, bladder function, and other morbidities remain unclear and additional research is needed.[79]

TWIN REVERSED ARTERIAL PERFUSION SEQUENCE

Twin reversed arterial perfusion (TRAP) sequence is an abnormality of monozygotic twins that affects approximately 1 in 35,000 pregnancies, 1 in 100 monozygotic twin gestations, and 1 in 30 triplet gestations.[80] In this condition, one of the monozygotic twins has an absent or nonfunctioning heart and no share in the placenta. The nonviable twin is perfused with retrograde blood flow from the other twin that flows through arterioarterial anastomoses; blood returns to the normal twin by venovenous anastomoses that bypass the placenta. The inadequate perfusion of the recipient twin (primarily occurring retrograde through the umbilical artery) results in a lethal set of anomalies that include acardia and acephalus. Because the normal or "pump" twin generates blood flow for both itself and the nonviable twin, it is at risk for high-output congestive heart failure and preterm birth secondary to the increased uterine volume from polyhydramnios and increased size of the hydropic nonviable twin.[81] If untreated, TRAP sequence is associated with a 35% to 55% risk for intrauterine death of the normal pump twin, with survivors having an average gestational age of 29 weeks.[82,83] Diagnosis is confirmed with ultrasound findings of reverse flow to the nonviable twin by the umbilical artery. The goal of therapy is to interrupt the vascular communication between the two twins in an effort to prevent cardiac failure in the pump twin. Successful treatment of TRAP sequence results in cessation of flow in the recipient twin's umbilical artery and the death of this anomalous nonviable fetus.

Several approaches can accomplish these goals, including selective delivery of the nonviable fetus by hysterotomy, ligation, or transection of the cord using laser or bipolar diathermy; cord coagulation using coils or other thrombogenic material; and ablative therapy directed at the acardiac fetus near the base of the cord using laser, alcohol, or radiofrequency techniques.[84-87] In a single institution, retrospective review of 118 TRAP sequence cases treated with fetoscopic bipolar cord coagulation, the rate of miscarriage was significantly more frequent if the procedure was performed before 19 weeks gestation (45% versus 3%) and the overall survival rate was 71%.[88] Treatment with endoscopic laser photocoagulation of the vascular anastomoses or radiofrequency ablation at the base of the umbilical cord within the abdomen of the acardiac twin (Fig. 78-3) are also viable therapeutic options.[84,89] A multicenter retrospective review of 60 TRAP sequence cases treated with endoscopic laser coagulation noted survival rates near 80% and a median gestational age at delivery of 37.4 weeks.[90] Use of radiofrequency ablation in 26 TRAP sequence cases at a single center demonstrated a 92% survival rate of the viable fetus with a mean gestational age of 35.6 weeks at delivery.[89] A retrospective case series combined with a meta-analysis of six prior studies reported 88 pregnancies with TRAP sequence treated with radiofrequency ablation resulting in an 85% survival rate of the viable fetus.[86] In case-matched studies comparing radiofrequency ablation and fetoscopic bipolar cord coagulation, survival rates were similar,[91] despite a more frequent rate of PPROM with use of fetoscopic procedures in contrast to needle-based procedures.[86,92]

Minimally invasive procedures to treat TRAP are typically performed with maternal infiltration of local anesthesia at the fetoscope insertion site, although neuraxial anesthesia is also used. Ultrasound guidance and assessment is used as part of all these therapies, and procedure success is confirmed by absence of flow to the nonviable acardiac twin at the end of the procedure and again approximately 12 to 24 hours later. We still cannot determine the optimal gestational age or other criteria for intervention.

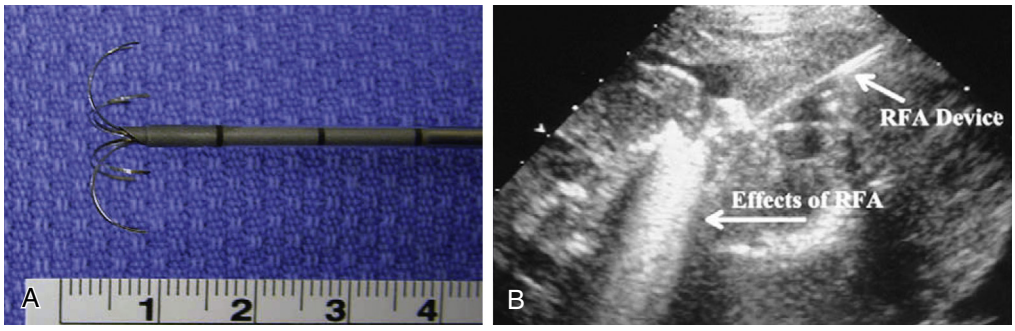


Figure 78-3. A, Photograph of a radiofrequency ablation (*RFA*) device with tines deployed. Scale below device in centimeters. **B,** Intraoperative ultrasound image shows adequate position of the RFA device (tines deployed), with evidence of effects on the fetal tissues (regional increased echogenicity) as energy is applied. *(Figures reproduced with permission from Hopkins LM, Feldstein VA: The use of ultrasound in fetal surgery,* Clin Perinatol *36:255-272, 2009.)*

TWIN-TO-TWIN TRANSFUSION SYNDROME

Monochorionic twins share the same placenta and typically have intertwin vascular connections that create shared blood flow between the two fetuses. A significant number of these chorionic vascular anastomoses can result in unequal placental blood flow between the two monochorionic twins, creating a significant degree of intertwin discordance that can lead to twin-to-twin transfusion syndrome (TTTS). The occurrence of TTTS is approximately 1 to 3 per 10,000 births.[93,94] Monochorionic twinning occurs in approximately 20% to 25% of twin pregnancies, with TTTS complicating 10% to 15% of these monochorionic gestations.[93,95,96] TTTS usually manifests after the first trimester and is typically recognized at midgestation.[95,97]

Normally, the umbilical artery carries deoxygenated blood to the surface of the placenta, where gases and nutrients are exchanged with the maternal circulation. The returning venous blood flow is "paired" with the arterial flow, and the two components lie next to each other (Fig. 78-4). This fetal-placental vascular configuration (cotyledon) represents normal anatomy. A variety of abnormal unidirectional and imbalanced vascular connections are present in TTTS (Fig. 78-5). In TTTS, a branch of the umbilical artery descends into the placenta and cotyledon, but instead of connecting with a paired vein, it connects with a vein that brings blood to the other twin, and this results in an arteriovenous anastomosis between the two fetuses.[98] Although some intertwin arteriovenous vascular architecture is found in 90% to 95% of monochorionic twins, the shared blood flow is balanced by the presence of arterioarterial and venovenous bidirectional connections, which are found in 85% to 90% and 15% to 20% of monochorionic twin placentas, respectively.[93,99,100] The presence of arterioarterial connections is viewed as protective by allowing the overall resistances and blood flow to equalize between the twins and is associated with a significant reduction in TTTS.[96,101]

The complex pathophysiology of TTTS is dynamic and secondary to a variety of humoral, biochemical, hemodynamic, and functional changes in the two fetuses.[97,102] The increased blood flow to the recipient twin leads to polycythemia, polyuria, and polyhydramnios and can cause hypertrophic cardiomyopathy, hydrops fetalis, and fetal death. The donor twin (often described as the "stuck" or "pump" twin) is typically hypovolemic, growth-restricted, and confined against the endometrium in an oligohydramniotic sac. This twin is primarily at risk for renal failure, cardiac failure, and hydrops fetalis secondary to the high cardiac output state.

The diagnosis of TTTS requires (1) a monochorionic diamniotic pregnancy and (2) a significant discrepancy in amniotic fluid volumes with ultrasound measurements of the maximal vertical pocket (MVP) of less than 2 cm in the oligohydramniotic twin and the MVP greater than 8 cm in the polyhydramniotic twin.[93,96] Twin size discordance and the presence of intrauterine growth restriction are often present in TTTS, but are not considered necessary to confirm the diagnosis. Although a variety of staging systems exist for determining the severity of TTTS, the most commonly used is the Quintero staging

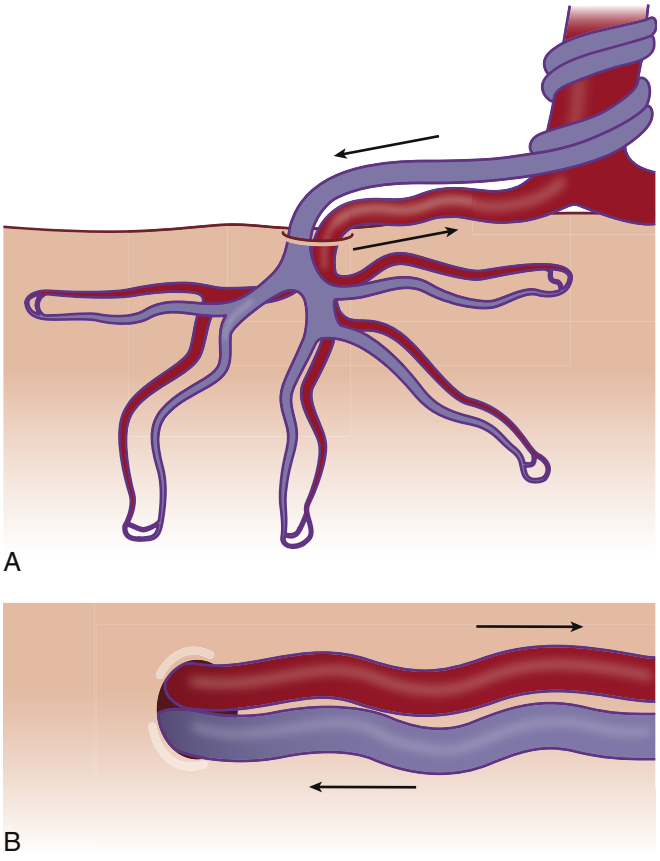


Figure 78-4. A, Normal placenta angioarchitecture (cotyledon). **B,** Superficial view of bidirectional flow into and out of a cotyledon. *(Redrawn from Rand L, Lee H: Complicated monochorionic twin pregnancies: updates in fetal diagnosis and treatment,* Clin Perinatol *36:417-430, 2009.)*

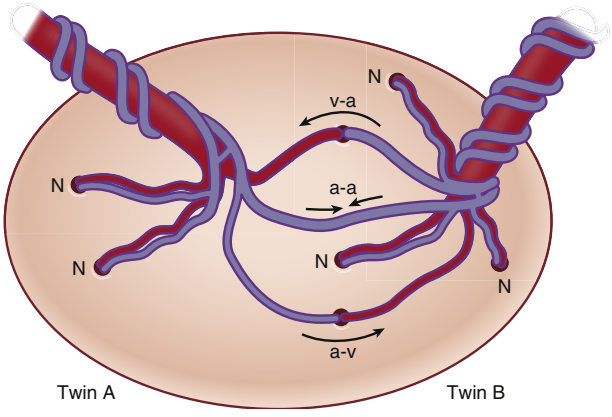


Figure 78-5. Depiction of various types of vascular anastomoses present in monochorionic placentas. *a-a,* Arterioarterial anastomosis; *a-v,* arteriovenous anastomosis; *N,* normal angioarchitecture (cotyledon); *v-a,* venoarterial anastomosis. *(Modified with permission from Simpson LL: Twin-twin transfusion syndrome,* Am J Obstet Gynecol *208:3-18, 2013.)*

system (Table 78-2), which is based on ultrasound findings.[103,104] The progression of hypertrophic cardiomyopathy in the fetal recipient is detailed in a scoring system presented by Rychlik and colleagues[105] that provides a more detailed assessment of TTTS severity when combined with the Quintero staging system.[96]

Fetuses with TTTS are at risk for PPROM, preterm delivery, and neurologic injury with white-matter lesions and long-term disability.[106] Neurodevelopmental impairment is associated with a low gestational age at birth.[106-108] Multiple sources note TTTS results in more than 80% fetal mortality with 15% to 50% risk for significant morbidity in surviving neonates.[96,102,109] However, other sources disagree with this statistic and note an 86% overall survival rate with conservative management of stage I TTTS.[93,110] Although outcome data stratified for the advanced stages of TTTS are limited, a more frequent mortality rate is likely associated with more advanced progression of the disease.[93,110]

Several therapeutic management techniques have been developed to treat TTTS. Amnioreduction can help control polyhydramnios and thereby reduce the risk for both preterm labor and maternal respiratory distress. Also, placental blood flow may improve by decreasing amniotic hydrostatic pressure on the placental vasculature. Serial amnioreductions can improve placental perfusion and decrease the rate of preterm deliveries.[111] A retrospective review of 223 twin sets with TTTS found that use of amnioreduction resulted in an overall birth survival rate of 78%, with survival rates of 65% for recipient twins and 55% for donor twins at 1 month of age.[112] Another review of 112 TTTS cases reported a 60.9% perinatal survival rate with use of amnioreduction.[113] Use of an ultrasound-guided needle to create a surgical septostomy was hypothesized to improve TTTS outcome by equalizing the amniotic pressure between the two fetal sacs. In a prospective randomized trial comparing serial amnioreduction to septostomy, no survival difference was found between the techniques.[114] Septostomy is rarely used for TTTS treatment because it offers no outcome advantage, and the creation of a single amniotic sac can increase the risk for umbilical cord entanglement. Selective feticide with the goal of improving the chance for survival of the other twin is accomplished using techniques described in the section on twin reverse arterial perfusion. It is typically used only for the most severe cases of TTTS.

Selective fetoscopic laser photocoagulation (SFLP) of the vascular anastomoses between the two twins is the best therapeutic approach for treating TTTS (stages II to IV) between 18 and 26 weeks gestation.[93,96] By detailed fetal ultrasound examination, the location of the placenta, cord insertions, and fetal orientation and anatomy are confirmed before the start of the procedure. Either maternal neuraxial blockade or local anesthesia infiltration from maternal skin to myometrium can be used. Using ultrasound guidance, a 3-mm trocar or cannula is inserted percutaneously over a wire into the recipient twin's amniotic sac and directed perpendicular to the longitudinal axis of the donor twin.[97,109] The fetoscope is inserted into the trocar sheath and the laser fiber bundle inserted into the fetoscope guide. Vessels that cross the membrane dividing the amniotic sacs are visualized, and the abnormal connecting vessels are selectively laser coagulated, with an effort to spare the normal cotyledons.[95,98] Ideally this creates two separate placental regions with each supplying an individual fetus. Nonselective laser ablation of all crossing vessels is typically avoided because it is associated with more frequent rates of intrauterine fetal demise and is likely to unnecessarily ablate some normal placental vessels.[95,115] Ablation of all abnormal connecting vasculature is not necessary for the procedure to be successful.[116] After laser ablation, amnioreduction is also performed in an effort to decrease the risk for preterm labor.

A 2004 randomized multicenter trial compared laser therapy to amnioreduction for treatment of severe TTTS diagnosed between 15 and 26 weeks gestation.[117] Rates of at least one twin survival were more frequent in the laser treatment group at both 28 days (76% versus 56%, $P < .01$) and 6 months of life (76% versus 51%, $P < .01$). In addition, neurologic outcomes were better in the laser treatment group. A large subgroup of survivors from this trial was followed prospectively for 6 years. No additional change in either survival rate or long-term neurologic outcome was found in comparison to the original 6-month data.[118] A meta-analysis of studies published between 1997 and 2007 also determined that TTTS treated with laser ablation resulted in a higher overall fetal survival rate than that of amnioreduction.[119] This conclusion was echoed in a Cochrane review of treatment for TTTS.[120] Long-term neurologic outcome in TTTS survivors who underwent SFLP remains unclear, with rates of major neurologic abnormalities in survivors ranging from 6% to 25%.[96,107] A recent longitudinal study examining neurodevelopmental outcome at 6 years of age in 190 children who underwent SFLP for TTTS reported mild neurologic impairment in 11.6% and severe neurologic impairment in 8.9% of these children.[121]

Some practitioners advocate use of a specific sequence when coagulating the various types of abnormal anastomoses in an effort to create a net flux of blood from the recipient to the donor and thereby reduce the chance for hemodynamic compromise and hypotension during the

TABLE 78-2 STAGES OF TWIN-TWIN TRANSFUSION SYNDROME

Stage	Ultrasound Findings
I	Oligohydramnios in donor twin sac with MVP <2 cm and polyhydramnios in recipient twin sac with MVP >8 cm
II	Stage I criteria AND no visualization of donor twin bladder with over 1 hr of ultrasound observation
III	Stage II criteria AND (1) absent or reversed umbilical artery end-diastolic flow, (2) reversed ductus venosus a-wave flow, OR (3) pulsatile flow in the umbilical vein
IV	Either stage I or stage II criteria AND fetal hydrops in either twin
V	Fetal demise in either or both twins as assessed by absent fetal cardiac activity

Staging data based on criteria from Quintero RA, Morales WJ, Allen MH, et al: Staging of twin-twin transfusion syndrome, J Perinatol *19:550-555, 1999.*
MVP, Maximal vertical pocket.

procedure in the donor twin.[122] Initially, superficial arteriovenous anastomoses that contain a donor artery are ablated, then arteriovenous anastomoses with a recipient artery, then the arterioarterial anastomoses, and finally ablation is performed at the venovenous anastomoses. In a single institution review of 99 consecutive SFLP procedures for treatment of TTTS, twins treated with this sequence had better survival rates than twins whose SFLP procedure was performed without a specific sequence.[122] A prospective multicenter trial comparing use of sequential SFLP to nonsequenced SFLP found that use of sequential SFLP significantly improved the 30-day survival of both twins, as well as the donor twin survival rate.[123] However, use of this sequential technique is associated with longer operative times and increased case difficulty, particularly with a placenta located on the anterior uterine wall.

The most common complication of SFLP is PPROM with subsequent preterm labor and delivery. PPROM rates vary widely across studies, but PPROM has been reported to occur in 12% to 30% of SFLP cases for TTTS with a rate of preterm labor and delivery before 32 weeks in gestation in approximately 30% of cases.[95,96] Other possible complications include placental abruption, need for a second SFLP procedure, placement of the trocar through the placenta, hemorrhage, and possible membrane perforation resulting in limb entrapment and ischemia.[95,96]

In conclusion, treatment of TTTS with SFLP results in superior outcomes in contrast to amnioreduction. Additional research is needed to determine optimal timing, further technique refinement, and long-term neurologic outcome for the treatment of TTTS with SFLP.

AMNIOTIC BAND SYNDROME

Amniotic band syndrome (ABS) includes a wide variety of fetal anomalies associated with fibrous bands that entangle or constrict various parts of the fetus or umbilical cord in utero. The resulting malformations include limb and digit amputations, craniofacial abnormalities, visceral defects, and body wall defects. The incidence is approximately 1 in 3000 to 1 in 15,000 live births.[124,125] The primary cause and pathogenesis of ABS remains unknown, but these defects appear secondary to either a vascular insult or other cause of abnormal perfusion to the affected area.[126] Theories behind the cause of ABS include a primary defect in embryonic development, an early amniotic membrane rupture resulting in the creation of amniochorionic bands, and a vascular disruption early in pregnancy.[124,127,128] Perhaps this category of abnormalities is composed of subcategories from different causes.

Diagnosis is determined by findings on ultrasound imaging consistent with characteristic fetal anomalies of the involved anatomy. Visualization of the bands themselves is not a necessary component of the diagnosis.[129] Fetal MRI can aid in diagnosis as a complimentary technique to ultrasound, but the efficacy of its use is currently limited to case reports and a small case series.[130] In cases of limb entrapment, increasing band constriction decreases both venous and arterial flow. This decreased perfusion can eventually result in amputation distal to the constriction. In an otherwise normal fetus, use of fetoscopic-guided sectioning of the band with a laser can restore distal blood flow and may improve functional outcome in some cases.[131] Efficacy of the technique is based on review of cases in the literature, which note some favorable outcomes and a frequent rate of PPROM.[124,131] In addition to outcome studies, validation of proposed classification schemes is needed, as well as prognostic factors affecting intervention outcomes.[124]

CONGENITAL DIAPHRAGMATIC HERNIA

Approximately 1 in 2500 newborn infants has a congenital diaphragmatic hernia (CDH).[132] During early gestation, abdominal contents herniate into the thoracic cavity and compress the fetal lungs. This results in significant neonatal morbidity and mortality from pulmonary hypoplasia, respiratory insufficiency, and pulmonary hypertension. Survival rates have improved to between 60% and 92% over the past 20 years at tertiary care centers.[133-137] These highly specialized centers offer care that includes surfactant administration, specialized ventilation techniques to minimize lung trauma, surgical closure of the defect, and availability of ECMO therapy. Mortality rates vary greatly with the severity of pulmonary hypertension and respiratory dysfunction.[133] Fetal intervention for CDH aims to improve fetal lung development and prevent the morbidity of pulmonary hypoplasia.

In utero repair of diaphragmatic hernia in lamb models reversed both the parenchymal hypoplasia and pulmonary vascular changes associated with CDH.[17] Initial human in utero intervention focused on open repair of the fetal diaphragm with limited success.[138,139] However, these initial interventions advanced fetal surgery techniques and paved the way for a minimally invasive approach to CDH intervention.

Initial open intervention experience found that a fetal abdominal patch was necessary to accommodate the added abdominal viscera. The patch allowed closure without increasing intraabdominal pressure and compromise of ductus venosus blood flow. These open interventions also determined that reduction of the herniated liver compromised umbilical circulation and significantly increased fetal mortality. Performing both subcostal and thoracotomy incisions on the fetus improved surgical exposure, allowed the reduction of viscera by pushing and pulling techniques, and facilitated the reconstruction of a diaphragm with a prosthetic patch.[140] Other lessons learned include (1) the advantage of opening the uterus with a stapling device to ensure effective hemostasis; (2) improved techniques of uterine closure; and (3) use of fibrin glue to help prevent amniotic fluid leaks. However, adequate control of postoperative uterine tone remained a substantial problem. In a prospective clinical trial sponsored by the National Institutes of Health, in utero CDH treatment using an open technique for fetuses without herniation of the liver into the thorax did not improve neonatal survival compared with standard postnatal treatment.[141]

After these efforts, a minimally invasive approach was pursued, focused on tracheal occlusion. Fetal lungs secrete over 100 mL/kg/day of fluid that exits the trachea and mouth into the amniotic cavity. In fetal lamb models, tracheal occlusion restricts the normal outflow of the

TABLE 78-3 POSTNATAL SURVIVAL IN FETUSES WITH LEFT-SIDED CONGENTIAL DIAPHRAGMATIC HERNIA AND INTRATHORACIC LIVER HERNIATION BASED ON FETAL LUNG TO HEAD RATIO

	Postnatal Management		Fetoscopic Tracheal Occlusion	
LHR (mm)*	Fetuses n (%)	Survival n (%)	Fetuses n (%)	Survival n (%)
0.4-0.5	2	0	6	1 (16.7)
0.6-0.7	6	0	13	8 (61.5)
0.8-0.9	19	3 (15.8)	9	7 (77.8)
1.0-1.1	23	14 (60.8)		
1.2-1.3	19	13 (68.4)		
1.4-1.5	11	8 (72.7)		
≥1.6	6	5 (83.3)		
Total	86	43 (50)	28	16 (57.1)

Modified from Jani JC, Nicolaides KH, Gratacos E, et al: Fetal lung-to-head ratio in the prediction of survival in severe left-sided diaphragmatic hernia treated by fetal endoscopic tracheal occlusion (FETO), Am J Obstet Gynecol*;195:1646-1650, 2006.*
CDH, Congenital diaphragmatic hernia; LHR, lung area–to-head circumference ratio.
*The LHR measurements were obtained at 23 to 29 weeks gestation.

fetal lung fluid and provides an increase in pulmonary hydrostatic pressure. This increased pressure pushes the viscera out of the thorax, promotes expansion of the hypoplastic lung, and thereby improves lung growth and development.[142,143] Fetal reversible tracheal occlusion[144,145] replaced primary repair in utero for the treatment of CDH. Initially, a tracheal foam plug was inserted in the fetal airway during open surgery, but it failed to provide adequate occlusion.[146] Later, metallic hemoclips were placed around the trachea after meticulous neck dissection.[146] Unfortunately, survival with this initial open tracheal occlusion procedure was poor (15%) and lower than survival in CDH fetuses receiving postnatal standard treatment (38%).[147]

Subsequently, minimally invasive fetal endoscopic surgical techniques replaced the open technique for placement of the clips. These procedures are performed with local or neuraxial maternal anesthesia with administration of fetal anesthesia by intramuscular injection. A variety of occlusive devices, including cuffs, plugs, valves, and balloons, were attempted at various medical centers.[148] Currently, percutaneous endoscopic endotracheal intubation is used to place a small detachable occlusive balloon in the fetal trachea.[149,150] With initial procedures it was left in place until delivery (see discussion on EXIT procedures), but more recently, it is deflated and removed before term with a second fetal endoscopic surgical techniques procedure. The balloon removal may improve type II pneumocyte function, increase surfactant production, and allow a vaginal delivery when appropriate.[148] These techniques decrease morbidity from CDH, with definitive surgical repair planned postnatally.[142,151]

Use of ultrasound imaging to determine the ratio of fetal lung area to head circumference (LHR) and the presence of thoracic liver herniation ("liver up" versus "liver down") are the most reliable prognostic indicators of fetal CDH outcome.[148,152,153] Evaluation of survival in fetuses with left-sided CDH and intrathoracic liver herniation managed postnatally noted no survival with an LHR of 0.7 or less and a survival rate 72.7% or greater with an LHR 1.4 or greater (Table 78-3).[154] Unfortunately, the LHR increases exponentially with gestational age and is less useful after 28 weeks gestation.[155] The Antenatal CDH Registry Group normalized the LHR to

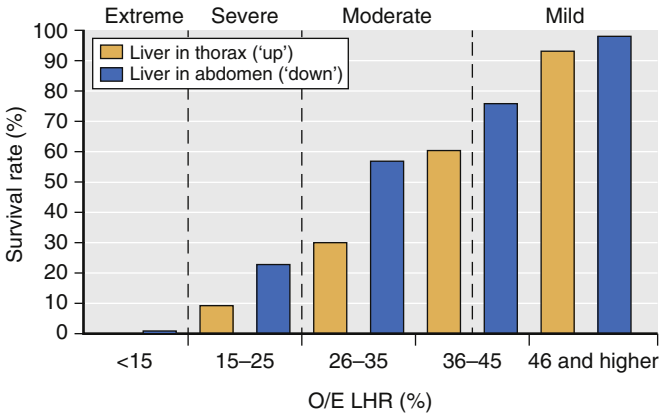


Figure 78-6. Survival rates of fetuses with isolated left-sided congenital diaphragmatic hernia (CDH), depending on measurement of the observed to expected lung area to head circumference ratio (o/e LHR) and position of the liver. *(Redrawn from Deprest JA, Nicolaides K, Gratacos E: Fetal surgery for congenital diaphragmatic hernia is back from never gone,* Fetal Diagn Ther *29:6-17, 2011.)*

gestational age by creating an observed-to-expected LHR (o/e LHR)[156] that correlates well with survival rate (Fig. 78-6).[157-159] More recently, fetal MRI measurement of lung volume (as an assessment of pulmonary hypoplasia) correlates well with neonatal survival in fetuses with isolated CDH.[134,160]

A prospective randomized trial (1999 to 2001) evaluated endoscopic fetal tracheal occlusion for prenatal treatment of CDH using both clip and balloon occlusion techniques.[161] Inclusion criteria included a 22- to 28-week gestational age, left-sided thoracic liver herniation, and a LHR of less than 1.4. The trial was closed early, and no benefit in survival or reduction in 90-day morbidity was found with prenatal treatment (n = 11) compared with control (n = 13) (survival rates of 73% versus 77%). Additionally, rates of PPROM and preterm delivery were more frequent in the fetal intervention group, with 100% of the fetoscopic intervention group having PPROM.[161] The inclusion of fetuses with an LHR of up to 1.4 may have decreased the ability to determine a significant difference, because many of these fetuses were likely to survive with standard postnatal tertiary medical care (see Table 78-3).

Three European medical centers, the Fetal Endoscopic Tracheal Occlusion (FETO) task force, began collaboration for treatment of severe cases of CDH with a high risk for mortality (LHR <1.0 and liver herniation into the hemithorax).[156,162] Because of concern for tracheal damage by very early tracheal balloon placement,[163] the tracheal balloon was placed at 26 to 28 weeks gestation and removed before birth. Data from 210 FETO task force cases through 2008 (mean gestational age of 27 weeks, LHR <1.0, and primarily left-sided CDH) were compared with historic postnatal treatment controls (1995 to 2004). Use of prenatal reversible tracheal occlusion significantly improved the survival rate (47% versus 20% in historic controls), and delivery occurred at a median gestational age of 35.3 weeks.[162] In addition, mean operating time was minimal (<10 minutes) and more than 95% of procedures were successful on the first attempt. Some of the survival benefit with in utero treatment may represent selection bias and improvement in both technique and neonatal care over time.

A more recent (2008 to 2010) randomized, controlled, single-institution trial compared cases of severe CDH (LHR <1.0 with liver herniation) randomized to either FETO (n = 21) at 26 to 30 weeks gestation or standard postnatal care (n = 20).[164] All treatment group fetuses were delivered by planned EXIT procedure at 38 weeks gestational age to allow controlled tracheal balloon removal. The overall survival rate was significantly greater in the FETO intervention group than in the postnatal management group (52.6% versus 5.3%). In 2009, a multicenter randomized Tracheal Occlusion to Accelerate Lung growth trial (TOTAL) began enrollment (http://www.totaltrial.eu).[165] It compares postnatal management to both late (30 to 32 weeks gestation) FETO intervention for moderate lung hypoplasia and earlier FETO intervention (27 to 30 weeks gestation) for severe lung hypoplasia. This trial uses o/e LHR criteria, and balloon occlusion removal is planned for 34 weeks gestation, with postnatal management standardized by a consensus protocol. Long-term outcome data on pulmonary and neurologic development are needed to better determine if and when FETO should be offered for individual cases of severe CDH.

MYELOMENINGOCELE

Spina bifida includes all defects with incomplete neural tube closure. Myelomeningocele (MMC) is the most common type of spina bifida and results in protrusion of the meninges and spinal cord through a developmental defect in the vertebrae, overlying muscles, and skin. MMC occurs during the third and fourth weeks of gestation with incomplete embryonic neural plate development. Folate supplementation in the maternal diet has decreased the rate of MMC nearly 50%, but the benefit reached a plateau without eliminating the disorder and MMC remains at a rate of approximately 1 in 3000 live births.[166,167] Improved prenatal screening with α-fetoprotein measurement and ultrasonography allows the possibility of pregnancy termination, and it is estimated that 25% to 40% of MMC pregnancies are terminated. MMC can result in lifelong morbidity and disability, including loss of motor and sensory function based on lesion level, bowel and bladder dysfunction, sexual dysfunction, hydrocephalus, Arnold-Chiari type II malformation, tethered cord, and impaired cognition.[168,169] If uncorrected in utero, surgical closure of the spinal defect must be performed within a few days after birth. Nearly 80% of children with MMC also require ventriculoperitoneal shunting for hydrocephalus.[170] Even with successful shunting, complications of central hypoventilation, vocal cord dysfunction, and swallowing difficulties can persist because of an associated Arnold-Chiari malformation.[169] The mean intelligence quotient in patients with MMC who underwent ventriculoperitoneal shunting is 80 (low normal).[171] Neonates with spina bifida have a 14% mortality rate by 5 years of age and a 35% mortality rate in those with known brainstem dysfunction and Arnold Chiari type II malformation.[166,171]

The cause of MMC remains unknown. The abnormalities and deficits of MMC are hypothesized to be the result of two separate mechanisms. The primary cause is anatomic malformation with abnormal development of the spinal cord and associated tissues. Secondary damage is likely created by exposure of these open neural elements to the amniotic fluid and direct trauma. Consequently, the ability to close the defect in utero and isolate the neural tissue from contact with the intrauterine environment has the potential to improve outcome in contrast to delaying closure until after birth.

This hypothesis has been supported by animal models that found improved neonatal neurologic function with fetal closure of the defect in utero.[172-174] Ultrasound assessment demonstrates that central and peripheral neurologic injury is progressive during gestation.[175,176] Improved motor function has been observed at 2 years of age in children with MMC who underwent cesarean delivery before labor onset compared to those delivered vaginally or by cesarean delivery after onset of labor.[166,177] Therefore, women with fetuses with MMC typically undergo cesarean delivery before onset of labor or rupture of membranes in an effort to minimize any additional injury to the open neural elements.

The rationale for fetal intervention for MMC is to improve functionality and quality of life.[178] Prenatal repair for MMC is performed with an open fetal surgical technique that requires both maternal laparotomy and hysterotomy. Considerations for anesthesiologists involved in open MMC repair include participation in comprehensive, multidisciplinary, preoperative maternal evaluation and counseling; preparation for potential intraoperative hemorrhage; planning an anesthetic that provides profound uterine relaxation; administration of analgesia and muscle relaxant directly to the fetus; intraoperative fetal assessment with preparation for potential fetal resuscitation or urgent delivery; and postoperative maternal analgesia and postoperative uterine and fetal monitoring.[179] Perioperative considerations for open fetal surgery are detailed later in the discussion of anesthetic management and considerations and management of open procedures.

MMC in utero surgery typically occurs mid–second trimester, before 26 weeks gestation. Initial human studies found that in utero repair reversed the hindbrain

TABLE 78-4 **OBSTETRIC AND FETAL AND NEONATAL COMPLICATIONS FOR MANAGEMENT OF MYELOMENINGOCELE STUDY PATIENTS***

	Prenatal (N = 78) (%)	Postnatal (N = 80) (%)	*P* Value
Maternal Outcomes			
Chorioamniotic membrane separation	20 (26)	0	<.001
Oligohydramnios	5 (6)	0	.03
Pulmonary edema	16 (21)	3 (4)	.001
Placental abruption	5 (6)	0	.03
Spontaneous membrane rupture	36 (46)	6 (8)	<.001
Spontaneous labor	30 (38)	11 (14)	<.001
Blood transfusion at delivery	7 (9)	1 (1)	.03
Hysterotomy site thin, partial, or completely dehisced at delivery	27 (36)	N/A	—
Fetal Outcomes			
Fetal bradycardia during repair	8 (10)	0	.003
Mean gestational age at birth (weeks)	34.1 ± 3.1	37.3 ± 1.1	<.001
Mean birth weight (g)	2383 ± 688	3039 ± 469	<.001
Respiratory distress syndrome	16 (21)	5 (6)	.008

Modified from Ferschl M, Ball R, Lee H, et al: Anesthesia for in utero repair of myelomeningocele, Anesthesiology *118:1211-1223, 2013.*

*The rates of maternal and fetal and fetal and neonatal complications observed in the prenatal and postnatal repair groups in the Management of Myelomeningocele Study[182] are listed with corresponding statistical significance. Although other complication outcomes were evaluated, only those determined to be different between the two groups are included in the table. Percentage of complications within each experimental group is noted in parentheses.

herniation of the Arnold-Chiari II malformation and decreased the requirement for ventriculoperitoneal shunt placement before 1 year of age.[180] In addition, a 1999 series of 10 fetuses undergoing in utero MMC closure at 22 to 25 weeks gestation found improved lower extremity function among 6 of 9 fetuses compared with expected function based on the level of lesion, with one fetal death at 25 weeks gestation from preterm delivery and associated respiratory insufficiency.[7] A recent randomized, prospective clinical trial completed between 2003 and 2010 at three U.S. medical centers examined the risks, benefits, and outcome of open in utero repair for MMC compared with standard postnatal repair among 183 patients.[181] Open fetal repair reduced the need for ventriculoperitoneal shunting and improved lower extremity motor function at 30 months of age. However, prenatal repair significantly increased the risk for various fetal and maternal complications, including spontaneous membrane rupture, oligohydramnios, partial or complete uterine dehiscence, and preterm birth with increased risk for respiratory distress syndrome (Table 78-4). Two perinatal deaths occurred in each group. Trial participants will undergo future assessment at 6 to 9 years of age to determine potential long-term benefit from the prenatal repair.

Throughout the duration of the trial a moratorium was in effect in the United States on in utero repair for MMC outside the clinical trial. With the favorable outcomes of this trial, additional medical centers are offering in utero repair for MMC. Results of this trial should not be generalized to patients outside the inclusion criteria of the study and should be considered only at medical centers that can develop a practice with significant volume and depth of resources.[182] It was recently recommended that this procedure be offered only at medical facilities with the expertise, multidisciplinary teams, services, and facilities to provide the intensive care required for these patients, with rigorous patient selection maintained.[183]

Until further advancement occurs in the surgical technique, equipment, and information from experimentation in animal models demonstrating significant benefit of endoscopic repair, prenatal repair of MMC will require an open surgical approach. A recent European trial of minimally invasive endoscopic intrauterine MMC repair resulted in a surprisingly high rate of maternal and fetal complications.[184] In a series of 19 patients who underwent endoscopic prenatal repair for MMC, 3 fetuses died intraoperatively and another three procedures were stopped because of severe hemorrhage from the procedure. Among the patients completing the procedure, fetal intervention was associated with improved neurologic function compared with matched control neonates who underwent postnatal intervention. However, the endoscopic fetal repair resulted in significantly more complications, and the authors concluded that this technique is unsuitable for current clinical practice, pending further advances.[184]

SACROCOCCYGEAL TERATOMA

The incidence of sacrococcygeal teratoma (SCT) is approximately 1 in 27,000 to 40,000 live births.[185,186] These teratomas are typically diagnosed by ultrasound in the second trimester of pregnancy and may grow rapidly (>150 cm^3/week), with some reaching sizes of 1000 cm^3 or more.[187] The larger tumors function as a substantial arteriovenous shunt that creates a low resistance state and leads to the development of high-output cardiac failure. Perinatal mortality varies greatly in different published series, ranging from 16% to 63%.[186] Fetuses with a large SCT are associated with the development of placentomegaly, polyhydramnios, and hydrops fetalis and have a high rate of in utero mortality. In addition, fetuses with SCT are at risk for intrapartum dystocia, tumor rupture with hemorrhage, and urinary obstruction. Cesarean delivery is frequently required.

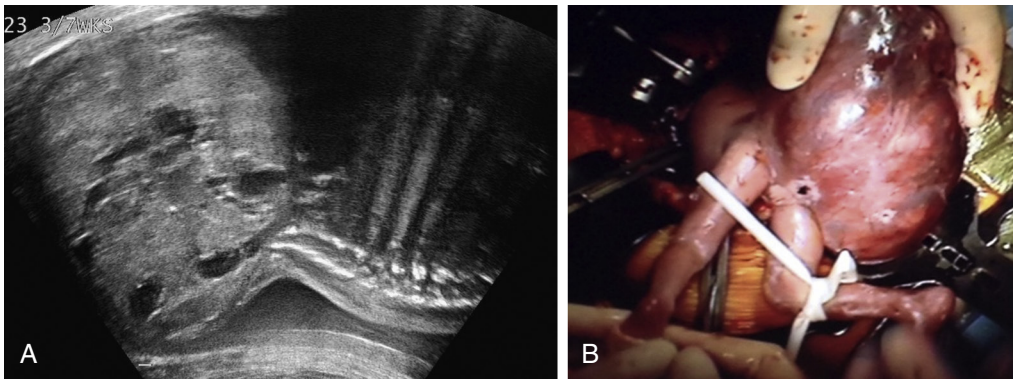


Figure 78-7. A, Ultrasound image of fetus with sacrococcygeal teratoma (SCT). Note sacral origin of mass. **B,** Fetus with SCT undergoing in utero mass resection. Note tourniquet on left leg placed momentarily before intravenous catheter placement in saphenous vein. *(Courtesy Dr. Anita Moon-Grady, Department of Pediatrics, University of California, San Francisco, Calif.)*

Tumor staging is based on the Altman criteria and determined by the volume of the tumor external or internal to the pelvis.[188] Stage I tumors are entirely external to the pelvis, with no presacral portion, and therefore suitable for fetal intervention. In contrast, stage IV tumors are located entirely in the pelvis and abdomen and are not considered amenable for fetal resection.[187] Fetal MRI can assist in tumor staging and determining the location of the tumor.[189] Fetuses diagnosed with SCT before 30 weeks gestation or with rapidly growing tumors have a poor prognosis, but may benefit from in utero intervention. Radiofrequency ablation, thermocoagulation, and cyst drainage have been employed to treat SCT in utero, but the benefit remains unclear.[10,185,186] SCTs have been resected in utero (Fig. 78-7) with successful outcomes, but the timing and criteria for fetal intervention remain unclear.[10,187,190] Fetal teratoma resection has a high risk for fetal hemorrhage; consequently, intraoperative placement of a venous catheter in a fetal hand, leg, or umbilical cord vein is important for the ability to transfuse compatible blood and crystalloid fluids or rapidly administer resuscitation drugs.

In certain cases, fetal SCT may lead to maternal mirror syndrome, in which maternal physiology mimics the abnormal circulatory physiology of the hydropic fetus.[191] The mother develops hypertension with increased peripheral and pulmonary edema that result from a hyperdynamic state. Maternal mirror syndrome does not resolve immediately with correction of the fetal pathophysiology, and can result in life-threatening maternal complications.[191]

CONGENITAL PULMONARY LESIONS

Congenital pulmonary airway malformations (CPAM), also known as congenital cystic adenomatoid malformations, are benign nonfunctioning pulmonary tumors composed of cystic and solid components that are usually contained within a single lung lobe.[192,193] These fetal lesions complicate approximately 1 in 25,000 pregnancies.[194] Other possible fetal lung abnormalities that require differentiation include bronchopulmonary sequestration, congenital lobar emphysema, and peripheral bronchial atresia.[195] CPAM includes five subtypes that are based on cyst size, characteristics of the epithelial lining, cyst wall thickness, and the presence of mucous cells, cartilage, and skeletal muscle.[196,197] Prenatal ultrasonography categorizes lesions as macrocystic (cysts >5 mm in diameter) or microcystic (cysts <5 mm in diameter), with microcystic lesions having a more solid or echogenic image. Prognosis depends primarily on size and growth characteristics of the CPAM rather than lesion type.[198] To normalize tumor volume to fetal size, a ratio of ultrasound measures of CPAM volume to fetal head circumference (CVR) was evaluated as a predictor of hydrops fetalis and other postnatal outcomes.[199,200] CVR is calculated from the volume of an ellipse (cubic centimeters) using the formula length × height × width × .52)/fetal head circumference (centimeters). Based on retrospective data from 71 fetuses, a CVR less than 0.56 predicts no adverse postnatal outcome (100% negative predictive value), whereas a CVR greater than 0.56 had a positive predictive value for adverse postnatal outcome of 33%.[199] In addition, a CVR greater than 1.6 is associated with greater risk for hydrops fetalis.[193,199,200] A recent retrospective analysis of a series of 24 fetuses with a CVR greater than 1.6 found that an abnormal echocardiogram with hydrops was a significant predictor of mortality and need for fetal intervention.[201]

Some lesions regress with minimal impact, whereas others grow in size. Typically, small lesions regress in the third pregnancy trimester and can be surgically resected after birth or managed conservatively without surgical intervention.[202] Large lesions can compress the great vessels, create pulmonary hypoplasia, and cause cardiac compression and mediastinal shift that often results in hydrops fetalis (secondary to heart failure). Patients with CPAM tumors associated with hydrops fetalis have a survival rate of less than 5% without intervention.[203] Large cystic lesions can be decompressed in utero by placement of shunt catheters between the cysts and the amniotic cavity (Fig. 78-8). Use of fetal analgesics and muscle relaxants delivered intramuscularly with ultrasound guidance may decrease the fetal stress response and prevent fetal movement during critical portions of the procedure. Shunt placement can prevent or reverse hydrops formation, with definitive resection deferred until after birth.[204] In a retrospective analysis of 24 nonhydropic fetuses with severe mediastinal shift, treated with thoracoamniotic shunting at 27 weeks gestation, postnatal survival was 87.5%, whereas 50 fetuses undergoing thoracentesis or thoracoamniotic shunting had a survival of only 66%.[205,206] In some CPAM

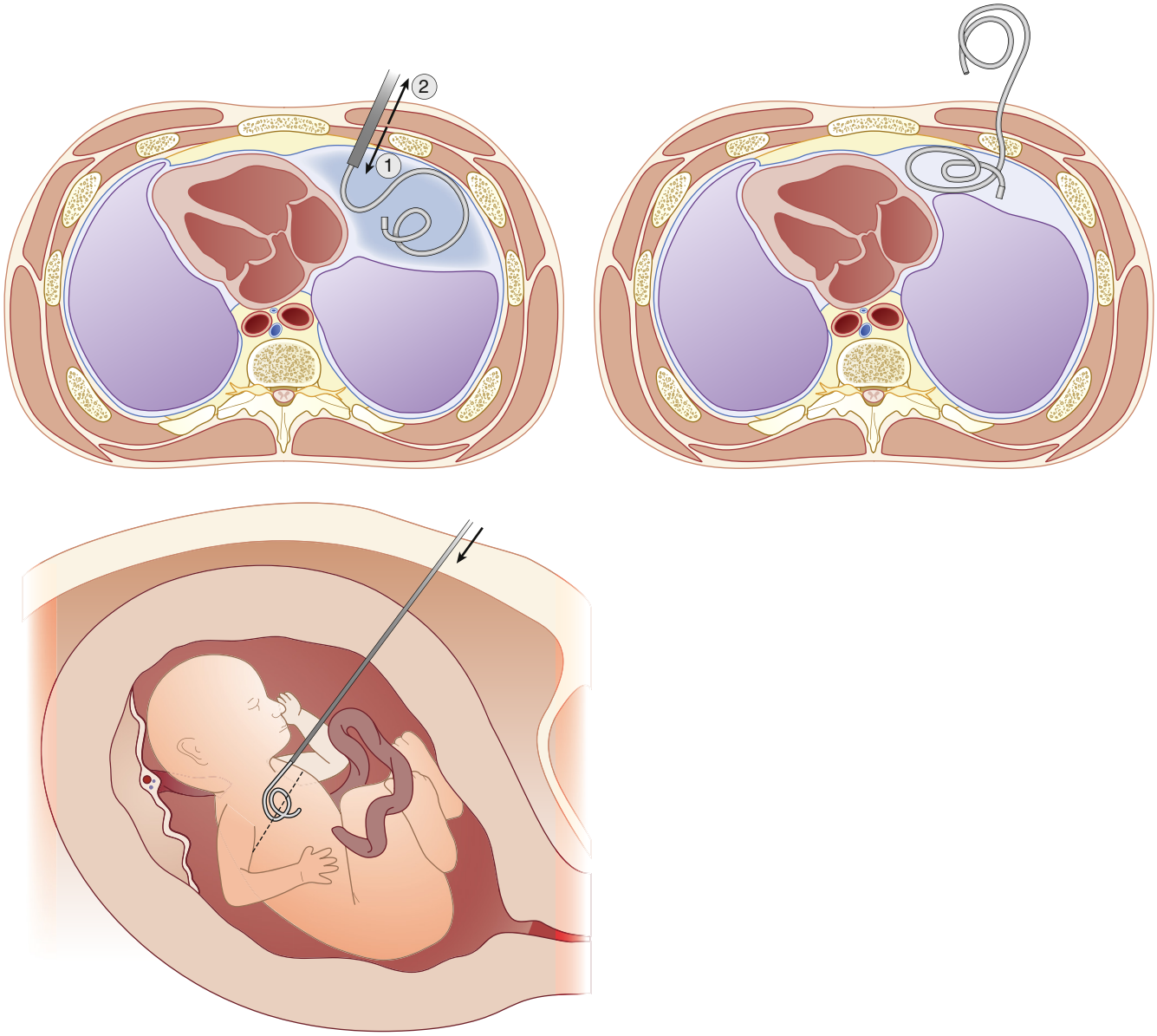


Figure 78-8. Thoracic shunt insertion (*top left* and *right*) and deployment (*bottom left*). *(Redrawn from van Mieghem T, Baud D, Devlieger R, et al: Begin equation minimally invasive fetal therapy,* Best Pract Res Clin Obstet Gynaecol *26:711-725, 2012.)*

lesions, shunts are ineffective because cysts are not in communication with each other, shunts malfunction, or they become displaced. In addition, shunt placement can cause fetal hemorrhage or chorioamnionitis.[207] Thoracoamniotic shunt placement has also successfully decompressed large congenital pleural effusions caused by fetal chylothorax that otherwise would result in hydrops fetalis, pulmonary compression, and fetal or neonatal death.[208]

Some CPAMs inappropriate for shunting can be resected with open fetal lobectomy (Fig. 78-9). Similar to open SCT resection, potential exists for significant fetal hemorrhage and need for in utero fetal resuscitation. Open resection of CPAM lesions associated with hydrops fetalis has resulted in a 30-day postnatal survival rate of 50%, with tumor resection allowing for compensatory lung growth and resolution of hydrops fetalis.[209] Maternal treatment with betamethasone also can improve hydrops fetalis and improve outcome in some fetuses with CPAM.[210] A retrospective analysis of 24 fetuses with predominantly microcystic CPAM and hydrops fetalis determined that steroid treatment improved survival in contrast to resection under open fetal surgery.[192]

In some instances, use of an EXIT procedure with fetal thoracotomy, mass resection, and a secured airway before delivery has been a successful approach for tumors with persistent mediastinal compression.[211] In a series of nine fetuses with large lung masses (CVR 1.9 to 3.6 at term) who underwent an EXIT-to-resection procedure, all procedures were successful, with no significant operative complications.[211]

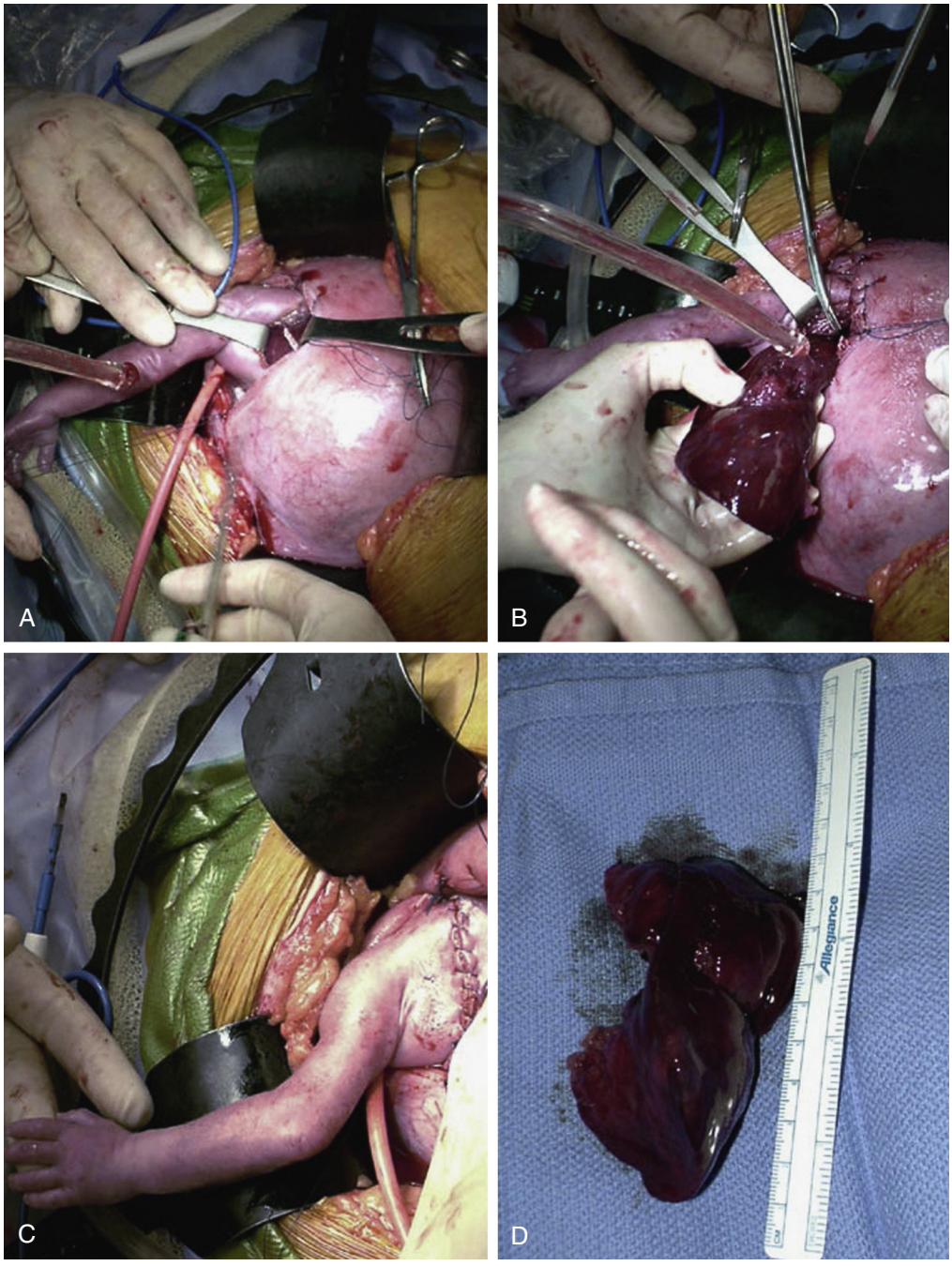


Figure 78-9. A, Open resection of fetal congenital pulmonary airway malformation (CPAM) with fetal thoracotomy shown. **B,** Resected CPAM mass. **C,** Primary closure of fetal thoracotomy. **D,** Pathologic specimen of resected CPAM mass. *(Courtesy Dr. Anita Moon-Grady, University of California, San Francisco Fetal Treatment Center, San Francisco, Calif.)*

PREOPERATIVE ASSESSMENT AND COUNSELING

Many considerations for perioperative management of women undergoing maternal-fetal surgery are analogous to those for nonobstetric surgery during pregnancy (see also Chapter 77). Maternal safety is the primary focus when determining a plan that will optimize fetal outcome. All members of the multidisciplinary team should be actively involved in maternal counseling, patient assessment, and perioperative planning. Optimum functioning of a fetal treatment program requires effective communication among the members of a multidisciplinary team, including surgeons, ultrasonographers, maternal fetal medicine physicians, anesthesiologists, nurses, genetic counselors, and social workers. Regularly scheduled multidisciplinary care meetings help ensure coordination of a complete and appropriate perioperative plan, ensure availability of the necessary equipment and personnel at the time of the procedure, and maximize the chance for optimal outcomes for both mother and fetus. Participation of the anesthesiologist is critical to preoperative maternal assessment to determine whether maternal risk is acceptably infrequent for potential fetal benefit. An understanding of the physiologic changes of pregnancy (for details, see Chapter 77) and their effects on anesthetic management is necessary for appropriate perioperative planning and risk assessment. In addition to details of the pregnancy

course on maternal health, information from imaging studies should also be obtained to guide surgical planning and aide in fetal drug dosing.

Maternal counseling regarding risks and benefits of the procedure should be thorough and unbiased and convey the most recent outcome and complication data about the planned intervention. For nonurgent procedures, counseling is typically a multiple-day process. The team must convey the specific condition's natural history and diagnostic limitations and whether associated anomalies are detected.[212] Discussions should focus on specific implications to the mother, the pregnancy, the fetus, postnatal care, future pregnancies, any data regarding intermediate and long-term outcomes for the proposed intervention, and all alternatives.[6] Similar discussions also should include alternative options such as nonintervention and the possibility of pregnancy termination if applicable. To provide uniform counseling, all providers should counsel the patient regarding information specific to their discipline, but be aware of the general risks and benefits of the fetal process and the proposed procedure. Distinctions should be made between interventions that are evidence based, and those that are innovative or experimental. Mothers should be informed about the planned timing and method of delivery, future reproductive implications, and—if a hysterotomy is planned—the risk for uterine rupture and need for cesarean delivery with this and all future pregnancies. Fertility does not appear to be affected by open fetal surgery, but the risk for uterine rupture or dehiscence before delivery is significant and comparable or even greater than that associated with a prior cesarean delivery performed with a classic incision.[213]

In some situations, consultation with a palliative care provider, clergy, or ethicist may be desired or required. In addition, the sequence of events should be outlined in detail, so that all questions can be answered. In most circumstances it is important that the partner or other supporting individuals be included in the counseling process, to ensure they have a better understanding of the rationale behind the treatment decisions. However, the wishes of the mother assume ultimate priority during pregnancy. Thorough counseling regarding fetuses with pediatric surgical disorders reduces parental anxiety.[11,214] Most mothers prefer specific realistic information provided in an empathetic manner, no matter how dire, and want to be allowed to hope for the best possible outcome.[215] If the fetus is of viable gestational age, additional counseling is required about the mother's wishes for possible emergent delivery and neonatal resuscitation in the event of unplanned fetal distress unresponsive to in utero treatment. Finally, the fetal intervention should not proceed until the patient has had adequate time to carefully consider all the information and offered her informed consent.

INTRAOPERATIVE MANAGEMENT AND CONSIDERATIONS

Unlike most surgical procedures performed during pregnancy in which the fetus is merely a bystander (e.g., maternal appendectomy), fetal surgery involves two surgical patients. Consequently, in addition to maternal considerations for anesthetic administration during pregnancy, it is essential to understand the impact of surgery and anesthetic administration on fetal physiology, methods for fetal analgesia and anesthesia, techniques for fetal monitoring, intraoperative anesthetic management, and postoperative care for both mother and fetus.

FETAL PHYSIOLOGY AND MONITORING

During fetal surgery, procedural and pharmacologic interventions can adversely affect fetal physiology directly or affect it indirectly by alterations in uteroplacental or fetoplacental circulation and gas exchange. Appropriate fetal monitoring facilitates early intervention. Changes in anesthetic technique, adjustment of maternal hemodynamics, and early initiation of in utero resuscitation of the fetus can decrease the risk for intraoperative fetal hypoxia, hemodynamic compromise, or demise. In addition to the physiologic effects of medications administered to the mother or fetus, a detailed knowledge of the fetal cardiovascular, neurologic, and placental physiology provides the basis for optimal fetal care. Uteroplacental and fetoplacental physiology, including uterine perfusion, placental gas exchange, and drug transfer are detailed in Chapter 77, which also discusses the effects of maternal positioning, maternal neuraxial anesthesia, and administration of general anesthesia on the uteroplacental unit.

Fetal cardiac output depends primarily on heart rate.[216] Fetal myocardium is less compliant than adult myocardium, with changes in preload having minimal effect on cardiac output.[217] Constraining forces of the fluid-filled lungs also limit ventricular filling and restrict increases in cardiac output in response to additional preload.[218] The normal fetal cardiac output (sum of right and left ventricular output) is in the range of 425 to 550 mL/min/kg throughout gestation.[216]

Fetal blood volume increases during gestation, and approximately two thirds of the fetal-placental blood volume resides within the placenta.[219] During the second trimester, fetal blood volume is estimated to be approximately 120 to 160 mL/kg of fetal body weight.[220] After midgestation, fetal blood volume can be estimated based on gestational age (GA) using the equation, estimated fetal blood volume (mL) = 11.2 × GA − 209.4.[221] In normal pregnancy, the mean fetal Hb increases linearly from 11 g/dL at 17 weeks gestation to 15 g/dL at 40 weeks gestation with a standard deviation of ±1 g/dL.[222]

Fetal lung epithelium produces more than 100 mL/kg/day of fluid that fills the lungs and facilitates appropriate pulmonary growth and development. Excess lung fluid exits the trachea and is either swallowed or flows into the amniotic fluid. Although fetal liver function is immature, coagulation factors are synthesized independent of the maternal circulation and do not cross the placenta. The serum concentrations of these factors increase with gestational age (Table 78-5),[223] but fetal clot formation in response to tissue injury is decreased in contrast to that in adults throughout gestation.

Manipulation of the fetus or umbilical cord during open fetal procedures can affect fetal cardiac output,

TABLE 78-5 **COAGULATION SCREENING TESTS IN FETUSES AND FULL-TERM NEWBORNS**

	Weeks Gestation			
Test*	**19-23**	**24-29**	**30-38**	**Newborns**
PT (s)	32.5 (19-45)	32.2 (19-44)	22.6 (16-30)	16.7 (12-24)
PT (INR)	6.4 (1.7-11.1)	6.2 (2.1-10.6)	3.0 (1.5-5.0)	1.7 (0.9-2.7)
aPTT (s)	169 (83-250)	154.0 (87-210)	104.8 (76-128)	44.3 (35-52)
TCT (s)	34.2 (24-44)	26.2 (24-28)	21.4 (17-23)	20.4 (15-25)

Modified from Reverdiau-Moalic P, Delahousse B, Body G, et al: Evolution of blood coagulation activators and inhibitors in the healthy human fetus, Blood *88:900-906, 1996.*

aPTT, Activated partial prothrombin time; *INR,* international normalized ratio; *PT* = prothrombin time; *s,* seconds; *TCT,* thrombin clotting time.

*Normal values for coagulation tests determined from umbilical cord sampling. Values are the mean, followed in parentheses by the lower and upper boundaries, including 95% of the population studied.

regional distribution of fetal circulation, or blood flow in the umbilical cord. During open procedures, the fetal circulation can be severely impaired by direct compression of the umbilical cord, inferior vena cava, or mediastinum. Fetal heart rate (FHR) monitoring during minimally invasive procedures is also important. During IUT, the transfusion needle can lacerate umbilical vessels with unanticipated fetal movement, and use of laser therapy for TTTS can disrupt surface placental vessels critical to fetal blood flow. During labor, FHR monitoring with external Doppler or a fetal scalp electrode is commonly employed to assess fetal well-being. However, during fetal procedures, echocardiography, pulse oximetry, and ultrasound imaging of umbilical artery flow are the primary methods for fetal assessment. After exposure of the fetal head during an EXIT procedure, insertion of a fetal scalp electrode has been used successfully for FHR monitoring.[224] It remains unclear whether fetal oximetry or heart rate monitoring is more sensitive to decreased umbilical-fetal blood flow. In a fetal lamb model examining the effects of umbilical cord compression, Hb desaturation was detected by fetal pulse oximetry before the onset of bradycardia.[225] However, FHR deceleration has been shown to precede fetal Hb desaturation with use of fetal pulse oximetry monitoring during labor.[226]

Intraoperative ultrasonography allows imaging of FHR, cardiac contractility, and cardiac filling, as well as Doppler assessment of umbilical cord flow. Both absent and reversed umbilical artery diastolic flow are associated with increased perinatal morbidity and mortality.[227] In many cases, ultrasonography assessment of fetal well-being can be only intermittent. This is because ultrasonography can be periodically required to guide the intervention or, during portions of the case, the probe placement can interfere with the surgical procedure.

When prolonged fetal bradycardia, Hb desaturation, or significant changes in umbilical artery flow dynamics occur during a fetal procedure, steps should be undertaken promptly to improve uterine perfusion, ensure the uteroplacental interface is intact, and relieve any compression of the umbilical cord or placenta. In some cases, ex utero fetal resuscitation may be necessary if the fetus was previously determined to be of a viable gestational age.

In utero, the fetus is unable to thermoregulate and depends on maternal body temperature. Induction of general anesthesia, surgical exposure, and hysterotomy can reduce fetal temperature dramatically. Fetal sheep studies demonstrate the fetus is unable to generate heat through thermogenesis [228] and decreases in fetal temperature can lead to tachycardia and hypertension in utero. In contrast, human reports associate hypothermia with fetal bradycardia.[229] Consequently, monitoring of temperature and maintenance of maternal euthermia with use of forced air warming likely improves fetal well-being during minimally invasive procedures. During open fetal surgery, use of warmed fluid for intrauterine irrigation and monitoring of both maternal core and amniotic fluid temperatures are also important.

FETAL ANESTHESIA AND ANALGESIA

The capability of the fetus to perceive pain remains controversial. The fetus exhibits pituitary-adrenal, sympathoadrenal, and circulatory stress responses to noxious stimuli as early as 18 weeks gestation.[230,231] Although invasive fetal procedures elicit a stress response,[30,232] this response is mediated at the level of the spinal cord, brainstem, and/or basal ganglia and does not necessarily correlate with conscious perception of pain that requires the cortex.[233] Administration of opioid in preterm neonates blunts major hormonal responses to surgery (including changes in plasma adrenaline, noradrenaline, glucagon, aldosterone, corticosterone, glucose, and lactate).[234] Providing adequate anesthesia and analgesia is associated with both attenuation of the deleterious effects and improved outcomes.[232] Stress responses secondary to invasive fetal procedures are blunted with opioid administration,[30] but reduction of plasma stress hormone levels is not necessarily evidence of adequate analgesia.[233]

Pressure, temperature, and vibration sensory nerve terminals develop in human skin between 6 and 10 weeks gestation.[235] Skin nerve terminals required for peripheral sensory nociception likely develop between 10 and 17 weeks gestation. Noxious stimuli follow a reflex arc of afferent fibers that synapse on spinal cord interneurons, which then synapse with motor neurons. A fetus can reflexively withdraw from a noxious stimulus by 19 weeks gestational age, without input from the cerebral cortex.[236]

The perception of pain requires not only intact neural pathways from the periphery to the primary sensory cortex, but also higher cortical structures.[236] Using histologic studies of other thalamocortical circuits, thalamic pain fibers likely reach the somatosensory cortex at 24 to 26 weeks gestation.[236] Thalamic projections reach the visual

subplate at 20 to 22 weeks,[237] the visual cortex at 23 to 27 weeks,[238] and the auditory cortical plate at about 26 to 28 weeks to gestation.[239] However, fetuses are unlikely to experience pain before 24 weeks gestation because the cortex requires additional growth and development to establish the extensive neural network of pathways to other central nervous system (CNS) structures.

This timeline is supported by electroencephalographic (EEG) studies that demonstrate a substantial increase in cortical activity. Cortical EEG activity is present only 2% of the time in fetuses at 24 weeks gestation[240] and increases to being present 80% of the time by 34 weeks gestation, with EEG patterns becoming more distinct.[241]

Both the long-term impact of untreated fetal stress and the timing of fetal pain perception remain unknown. Given this uncertainty and the more than 30-year history of safe anesthetic administration in neonates and fetuses undergoing invasive procedures,[242-244] analgesia should be given during fetal surgery.[245] Anesthetic goals include prevention of fetal movement, inhibition of circulatory stress response, adequate pain relief, and potentially even fetal amnesia.

Opioid analgesics can be transferred to the fetus by maternal administration or direct intramuscular or intravenous umbilical cord administration using ultrasound guidance. For most invasive procedures that can cause noxious fetal stimulation, fetal intramuscular administration of fentanyl 10 to 20 μg/kg (or other opioid in equivalent dosing) is used to provide analgesia immediately before the intervention.[30,179,244] This can be achieved percutaneously using ultrasound guidance or under direct vision when a hysterotomy is performed. Some physicians administer prophylactic intramuscular atropine 20 μg/kg with opioids to minimize the risk for fetal bradycardia.[246,247] Fetal movement can be prevented by intramuscular or umbilical vessel administration of muscle relaxant using ultrasound guidance.[179,243,244,246] Drugs that have been used include pancuronium or vecuronium with doses of 0.3 mg/kg intramuscularly or 0.1 to 0.25 mg/kg intravenously. The onset of fetal paralysis varies with the specific drug and dose, but typically occurs in 2 to 5 minutes, with an approximate duration of 1 to 2 hours.[248] In many instances, opioid, anticholinergic, and muscle relaxant are combined in a single injection. Maternal administration and placental transfer of intravenous remifentanil provides adequate fetal immobility during fetoscopic interventions that involve only the umbilical cord or placenta.[244,249]

For open fetal procedures, placental transfer of maternally administered general anesthesia with volatile anesthetics provides fetal anesthesia. These anesthetics readily transfer across the placenta, with fetal concentration and the fetal-to-maternal (F/M) ratio depending on both the maternal inspired anesthetic concentration and the duration of maternal anesthetic administration. In human studies of anesthetic levels at the time of cesarean delivery (~10-minute duration of general anesthesia), isoflurane and halothane both have an F/M ratio of approximately 0.7.[250] Although placental transfer of desflurane and sevoflurane may be similar, published human F/M data are not currently available in the literature. Nitrous oxide has an F/M ratio of 0.83 after only 3 minutes of administration.[251]

High levels of volatile anesthetic can depress fetal myocardium and lead to increasing fetal acidosis.[252] In animal models, volatile anesthetic concentrations often employed for uterine relaxation (>2 minimum alveolar concentration [MAC]), demonstrate significant reductions in maternal cardiac output with associated decrease in uterine perfusion up to 30%.[253] Animal models of maternal halothane administration have shown increases in both placental and fetal vascular resistance resulting in increased fetal cardiac afterload.[254] A retrospective analysis of echocardiographic data from clinical cases of open fetal surgery and EXIT procedures reveals a moderate-to-severe left ventricular systolic fetal cardiac dysfunction with use of high concentrations of desflurane.[255] In addition, case reports have described epileptiform EEG activity and generalized tonic-clonic seizures in both adults and children exposed to high levels of sevoflurane.[256] Therefore, high concentrations of volatile anesthetic administration, useful for maternal uterine relaxation, might not be the optimal anesthetic for the fetus despite years of successful use. Remifentanil has significant placental transfer and prevents fetal movement during TTTS laser photocoagulation therapy.[249,257] Some prefer to administer maternal remifentanil and nitroglycerin as part of the anesthetic for open fetal or EXIT procedures to decrease the amount of volatile anesthetic.[246,249] Currently, no evidence indicates that any one anesthetic method provides an improved fetal or maternal outcome compared with other anesthetic methods.

Anesthetics affect neonatal brain development and create histologic changes, as well as learning and memory deficits.[258-261] Yet, specific long-term effects of anesthetics on human brain function in neonates or fetuses are currently inconclusive. In 2007, a U.S. Food and Drug Administration advisory committee concluded that based on available data, no change in clinical anesthetic practice was warranted.[260,262] It is currently unknown whether propofol has more widespread effects on neurodevelopment than do volatile anesthetics.[261] The use of a volatile anesthetic for maternal anesthesia, as the primary agent for fetal anesthesia during open fetal surgery or EXIT procedures, will likely continue in the absence of additional neurocognitive outcome data. In addition, whether in utero exposure to anesthetic drugs compared with postnatal exposure has any effect on neurocognitive outcome is not known.

MANAGEMENT OF MINIMALLY INVASIVE PROCEDURES

The same considerations that apply to nonobstetric surgery during pregnancy (see Chapter 77) should be followed for fetal procedures. For most FIGS-IT procedures (see Table 78-1), use of monitored anesthetic care with infiltration of local anesthetic into the abdominal wall provides an adequate level of maternal comfort. Administration of additional opioid, benzodiazepine, or other anesthetic can be used for maternal analgesia and anxiolysis, titrated to avoid deep sedation and the associated increased risk for pulmonary aspiration of gastric

contents or respiratory compromise during pregnancy. In addition, use of supplemental anesthetic drugs possibly decreases the likelihood of fetal movement via placental transfer.[249,263] Local anesthetic infiltration can be used for fetoscopic procedures, which typically employ endoscope trocars that are only 1 to 5 mm in diameter.[264] In certain instances, neuraxial anesthesia may be a preferable approach for fetoscopic procedures, and communication with other team members is essential to determine the best technique for the individual procedure and patient. Neuraxial techniques can be beneficial when multiple insertion sites are required, maternal immobility must be ensured, a mini-laparotomy must be performed, or concern exists about adequate patient comfort or appropriate patient cooperation during the procedure.[95,119] General anesthesia is rarely necessary for percutaneous procedures unless placental location and fetal orientation present potential technical difficulty or uterine exteriorization is needed.

Although maternal intravenous fluid administration should be guided by standard intraoperative requirements, use of significant amounts of pressurized uterine crystalloid irrigation into the amniotic cavity during fetoscopic surgery should be avoided because it has resulted in maternal pulmonary edema.[265]

In cases of IUT, cord blood sampling, or thoracic shunt placement, fetal movement may displace the needle or catheter and result in trauma, bleeding, or compromise of the umbilical circulation. In one study of fetoscopic surgery, maternal administration of a remifentanil infusion (0.1 μg/kg/min) reduced fetal movement and improved operating conditions compared with maternal administration of diazepam.[249] Although maternally administered opioids and benzodiazepines can reduce fetal motion,[117] they do not guarantee immobility for procedures directly involving the fetus. Fetal immobility can be safely achieved with direct fetal intramuscular or umbilical venous administration of muscle relaxant, as described in the previous section on fetal anesthesia and analgesia. For invasive fetal procedures that involve potentially noxious stimulation to the fetus, such as shunt catheter placement or cardiac septoplasty, an opioid should be administered either intramuscularly or intravenously.[30,243] When general anesthesia is employed, placental transfer of a volatile anesthetic provides fetal anesthesia and prevents fetal movement, but supplemental opioids can also be administered for fetal analgesia.

Weight-based unit doses of atropine 20 μg/kg and epinephrine 10 μg/kg should be immediately available in individually labeled syringes for direct administration to the fetus by the surgeon in emergent situations of fetal compromise. These medications require sterile transfer to the surgical field, meticulous labeling, and accurate dosing before commencement of the procedure. When emergently required, the surgeon can administer the indicated medication by a variety of routes, including intramuscular, intravenous, or intracardiac, depending on the procedure and urgency of the situation. If gestational development is compatible with extrauterine life, the anesthesiologist should be prepared to emergently provide general maternal anesthesia, and the obstetric team should be prepared to perform an emergency cesarean delivery if fetal bradycardia persists despite efforts to resuscitate in utero.

MANAGEMENT OF OPEN PROCEDURES

Although most women undergo cesarean delivery with neuraxial anesthesia, general anesthesia is primarily employed for fetal surgery requiring a hysterotomy. Unlike minimally invasive fetal procedures, open fetal surgery requires profound uterine relaxation, often entails additional fetal monitoring beyond intermittent ultrasonography; involves more fetal surgical stimulation, fetal hemodynamic perturbation, and risk for fetal compromise; and requires direct administration of some drugs to the fetus. The anesthesiologist and other team members should be prepared for significant maternal and fetal blood loss, and the need for maternal and fetal resuscitation, including emergent delivery. A volatile anesthetic is commonly administered to provide maternal and fetal anesthesia, as well as uterine relaxation, which may require a concentration of more than 2 MAC.[266] The perioperative considerations for open fetal surgery are detailed in Box 78-2.

Single, weight-based, unit doses of medications for fetal analgesia and muscle relaxation as previously detailed in the discussion on fetal anesthesia and analgesia should be available for administration by the surgical team. In addition, resuscitation medications (atropine 20 μg/kg, epinephrine 10 μg/kg, and crystalloid 10 mL/kg) should be prepared preoperatively for immediate availability in the emergent treatment of intraoperative fetal hemodynamic compromise. Cross-matched blood should be available for maternal transfusion. For procedures with a high risk for fetal hemorrhage, appropriate blood for fetal transfusion (i.e., O-negative, cytomegalovirus-negative, irradiated, leukocyte-depleted, maternally cross-matched) should be readily available.

Drugs and approaches should be used to minimize aspiration of gastric contents. Uterine tocolytics (i.e., indomethacin) should be given to the mother preoperatively. An epidural catheter is placed preoperatively for administration of postoperative analgesia. FHR is assessed and baseline cardiac echocardiography and ultrasound imaging of umbilical cord flow characteristics are performed before anesthetic induction and are intermittently reevaluated throughout the initial period of anesthetic administration to assess the effect on the fetus of the maternal positioning, anesthetic administration, and any maternal hemodynamic changes. The gravid uterus is displaced leftward and general anesthesia is induced with a rapid sequence technique identical to patients undergoing nonobstetric surgery during pregnancy (see also Chapter 77).

After anesthetic induction and before maternal skin incision, conventional concentrations of anesthetics are administered to the mother (~1 MAC); ventilation is controlled to maintain eucapnia (end-tidal CO_2 [$ETCO_2$] levels of 30 to 32 mm Hg); and fetal attitude, presentation, and placental location are reassessed by ultrasound. An invasive maternal intraarterial pressure catheter is placed when administration of a nitroglycerin infusion is planned for uterine tocolysis. If an intraarterial catheter is not placed, a maternal arm is positioned to remain

BOX 78-2 *Perioperative Considerations for Open Fetal Surgery**

Preoperative

- Complete maternal history and physical examination
- Complete fetal workup to exclude other anomalies
- Imaging studies to determine fetal lesion and placental location
- Maternal counseling by multidisciplinary team and presurgical team meeting
- Lumbar epidural placement with test dose before use
- Prophylactic premedications: Nonparticulate antacid (aspiration), rectal indomethacin (tocolysis)
- Blood products typed and crossmatched for potential maternal and fetal transfusion; fetal blood should be type O-negative, leukocyte depleted, irradiated, cytomegalovirus negative, and crossmatched against the mother
- Obtain estimate of fetal weight to aid in weight-based fetal dosing
- Sequential compression devices on lower extremities for thrombosis prophylaxis

Intraoperative

- Left uterine displacement and standard monitors
- Preoxygenation for 3 minutes before induction
- Rapid sequence induction and intubation
- Maintain maternal FiO_2 greater than 50% and end-tidal carbon dioxide 28 to 30 mm Hg
- Ultrasound to determine fetal and placental positioning
- Urinary catheter placed; additional large-bore intravenous access device placed, with or without arterial line
- Activation of upper, lower, or both forced air warmers to maintain maternal normothermia
- Prophylactic antibiotics administered
- Fetal resuscitation drugs and fluid transferred to scrub nurse in sterile fashion
- After skin incision, high concentrations of volatile anesthetic (2 to 3 minimum alveolar concentration) started or other technique for uterine relaxation (i.e., IV nitroglycerin)
- Blood pressure maintained with IV phenylephrine, ephedrine, and/or glycopyrrolate; typical goal is to maintain mean arterial pressure within 10% of preinduction baseline with appropriate heart rate
- Consider increasing vapor or adding IV nitroglycerin if uterine tone remains increased
- Placement of fetal monitors if needed (e.g., fetal pulse oximeter, intrauterine temperature probe)
- IM fetal administration of opioid and neuromuscular blocking agent after hysterotomy; an anticholinergic also may be given with the opioid
- Placement of fetal IV access device if significant fetal blood loss anticipated
- External irrigation of fetus with warmed saline as needed
- Crystalloid restriction to less than 2 L to reduce risk for maternal pulmonary edema; consider colloid administration
- IV loading dose of magnesium sulfate once uterine closure begins
- Discontinue volatile agents and/or nitroglycerin once magnesium sulfate load is complete
- Administer propofol, opioids, nitrous oxide as needed
- Activate epidural for postoperative analgesia
- Monitor neuromuscular blockade carefully because of magnesium sulfate
- Extubate trachea when patient is fully awake

Early Postoperative Considerations

- Continue tocolytic therapy
- Patient-controlled epidural analgesia
- Monitor uterine activity and fetal heart rate
- Ongoing fetal evaluation

Modified from Ferschl M, Ball R, Lee H, et al: Anesthesia for in utero repair of myelomeningocele, Anesthesiology *118:1211-1223, 2013.*
FiO_2, Fraction of inspired oxygen; *IM,* intramuscular; *IV,* intravenous; *MAC,* minimum alveolar concentration.
*This summary may need to be modified depending on the type of open fetal surgery and patient comorbidities.

accessible in case unexpected invasive pressure monitoring is required intraoperatively (e.g., maternal hemodynamic instability). A large-bore venous catheter is placed for treatment of unexpected excessive hemorrhage. However, intravenous fluids administered to the mother are minimized (<2 L) to decrease the risk for perioperative pulmonary edema associated with the use of tocolytics, such as magnesium sulfate or administration of large doses of nitroglycerine during fetal surgery.[267] Some fetal surgery teams are more restrictive with intraoperative fluid administration (<500 mL), but no clinical trials have demonstrated benefit of severe intravenous fluid restriction in this setting.[267]

Typical maternal hemodynamic goals include maintaining systolic arterial blood pressure within 10% of baseline values and mean arterial pressure greater than 65 mm Hg. Phenylephrine administration can be used to treat maternal hypotension with minimal changes in the fetal acid-base status.[268] Bolus administration of ephedrine or glycopyrrolate can assist in maintaining maternal heart rate and cardiac output.[269] Administration of a maternal nondepolarizing muscle relaxant is usually unnecessary with administration of appropriate concentrations of volatile anesthetics, but may be used to improve operative conditions. If it is used, appropriate neuromuscular monitoring should be employed to carefully assess neuromuscular function with appropriate pharmacologic reversal of blockade before tracheal extubation, particularly with concurrent use of magnesium sulfate, which significantly potentiates neuromuscular blockade (see also Chapter 53).

Before skin incision, the inspired concentration of volatile anesthetic is increased, and before uterine incision, the volatile anesthetic end-tidal concentration is further increased (≥2 MAC) to provide profound uterine relaxation. If uterine relaxation is assessed to be inadequate by appearance of contractions or palpation, administration of additional volatile agent (up to 3 MAC) or intravenous nitroglycerin as an infusion or in small boluses (50 to 200 μg) is useful to decrease uterine tone.[270] Administration of intravenous propofol and remifentanil with desflurane at 1.5 MAC has provided adequate uterine relaxation in one retrospective study.[255] For rare patients with contraindications to either volatile anesthetics or induction of general anesthesia, a neuraxial technique in conjunction with intravenous administration of nitroglycerin in doses up to 20 μg/kg/min has been used successfully.[270] This technique may have increased risk for maternal pulmonary edema

secondary to the large doses of nitroglycerin and should be reserved for cases with a specific benefit from the technique. Although uterine relaxation is required for successful open fetal surgery, use of nitroglycerin may affect fetal vascular tone, resulting in alterations in cerebral blood flow and increased likelihood of fetal cerebral ischemia, as well as intraventricular and periventricular hemorrhage.[271] Currently, no specific anesthetic technique demonstrates significant improvement in fetal outcome.

Periodic ultrasonography is used to assess FHR and fetal cardiac function. In some open fetal procedures, pulse oximetry or additional direct fetal monitoring can be employed after the hysterotomy is performed, as discussed in the section on fetal physiology and monitoring. Rarely, when uncertainty exists regarding fetal condition, umbilical cord blood gas measurements can be obtained. As described in the prior section on fetal anesthesia and analgesia, an opioid and a muscle relaxant can be administered to the fetus intramuscularly either before uterine incision with ultrasound guidance of the injection needle or under direct vision after uterine incision. Intramuscular atropine also can be administered concurrently to reduce opioid-induced fetal bradycardia.

After uterine exposure and ultrasound placental mapping, a small hysterotomy is created away from the placenta. A stapling device with absorbable lactomer staples is used to extend the incision. The staples prevent hemorrhage from the relaxed uterus and seal the amniotic membranes to the uterine endometrium. Uterine blood loss can be rapid and difficult to estimate. Vigilant observation of the surgical field and careful maternal monitoring are essential to avoid missing occult hemorrhage. Lost amniotic fluid is replaced with warmed crystalloid to bathe the exposed fetus. Intrauterine temperature is closely monitored to prevent hypothermia and associated fetal circulatory compromise.[229]

For fetal mass resections or other open procedures with high risk for significant fetal blood loss, an intravenous catheter should be placed in a fetal limb for blood and fluid transfusions. Sterile microbore tubing can be passed over the surgical drape, primed, and connected to the catheter, allowing fetal intravenous administration by the anesthesiologist. All blood or fluids transfused to the fetus should be warmed. In urgent situations, fluids can be transfused directly into the umbilical vein through catheter access obtained in the operative field if a fetal peripheral intravenous line is not available.

In the rare event of maternal hemodynamic collapse, if maternal resuscitation has been unsuccessful in restoring adequate maternal hemodynamics after 4 minutes, the fetus should be delivered emergently to relieve aortocaval compression, improve maternal resuscitation efforts, and increase the chance for maternal survival.[272] A neonatologist and neonatal resuscitation team should be readily available in case of emergency delivery, and newborn resuscitation should proceed according to the current recommended guidelines.[273]

After completion of the fetal procedure, an initial dose of magnesium sulfate 4 to 6 g intravenously over 20 minutes is typically administered during uterine closure to reduce myometrial contractility[274] (see also Chapter 77). After the bolus, an intravenous infusion of magnesium sulfate 1 to 2 g/hr) is initiated to maintain uterine quiescence into the postoperative period. The inspired concentration of volatile anesthetic or intravenous nitroglycerin infusion is significantly decreased or discontinued after the magnesium sulfate bolus is complete. After an epidural test dose, epidural anesthesia is initiated. Maternal anesthesia is maintained with epidural anesthesia, supplemented by administration of intravenous opioid, inhaled N_2O, and/or intravenous propofol; this allows adequate time for elimination of the volatile agents during surgical closure of the abdominal incision. The mother's trachea is extubated after she awakens and after confirming adequate neuromuscular recovery and hemodynamic stability.

POSTOPERATIVE MANAGEMENT AND CONSIDERATIONS

In addition to postoperative concerns associated with a cesarean delivery (i.e., pain management, prevention of venous thromboembolism, monitoring for hemorrhage, avoiding wound infection), postoperative care of patients undergoing fetal surgery also focuses on tocolysis and fetal monitoring. For minimally invasive procedures such as cordocentesis or IUT, tocolysis is typically not required. For more invasive percutaneous procedures (e.g., shunt catheter placement, endoscopic techniques), some fetal surgery teams administer preoperative prophylactic tocolytic agents such as indomethacin, and rarely additional drugs are required in the postoperative period.

After open fetal surgery, patients frequently experience early uterine contractions and require continuous uterine monitoring for 2 or 3 days. Management of postoperative preterm labor after fetal surgery is a challenge and has led to significant fetal morbidity.[120] Magnesium sulfate infusions initiated intraoperatively are continued for approximately 24 hours or more postoperatively. Additional tocolytic agents (e.g., indomethacin, terbutaline, nifedipine) are often necessary. Administration of indomethacin requires periodic monitoring by fetal echocardiography because premature closure of the ductus arteriosus is a known complication of therapy.

The fetus is evaluated postoperatively by ultrasonography. Continuous FHR monitoring is used in the postoperative period, with a predetermined plan established for management of fetal distress. The duration of monitoring is based on gestational age, fetal condition, and plan for fetal distress. Potential fetal morbidity includes infection, fetal heart failure, fetal intracranial hemorrhage, and fetal demise. If maternal pulmonary edema is suspected, a chest radiograph should be obtained. With significant compromise, critical care admission may be required along with tracheal intubation, mechanical ventilation, hemodynamic monitoring, supplemental oxygen administration, upright positioning, and diuretic therapies.

For minimally invasive procedures, satisfactory postoperative analgesia is typically achieved by administration of oral opioid-based pain medications. For open procedures, postoperative epidural analgesia can be provided for several days using a dilute solution of local

anesthetic and opioid. Intravenous opioids administered with a patient-controlled device can be used in place of an epidural or after the epidural is discontinued. Use of opioids can decrease FHR variability [275] and create some difficulty in interpretation of the FHR tracing. Inadequate postoperative pain control can increase plasma oxytocin levels and increase the risk for preterm labor.[272]

After open fetal procedures, patients are at high risk for PPROM, preterm labor, infection, and uterine rupture. In addition to these risks, periodic assessment of fetal well-being, growth, and integrity of the pregnancy necessitate the mother remain near the fetal treatment institution for the first few weeks after the procedure. The possibility of preterm delivery may necessitate a course of steroids to improve fetal lung maturity. After open procedures, cesarean delivery is often planned for 37 weeks gestation but may be required earlier with the onset of preterm labor. The recent hysterotomy increases the chance for uterine rupture and associated need for emergent cesarean delivery.

MANAGEMENT OF EX UTERO INTRAPARTUM TREATMENT PROCEDURE

Although the initial purpose of the EXIT procedure was to provide a controlled and stable means to remove the obstructive device previously placed in the fetal airway for in utero treatment of CDH, the EXIT procedure has expanded into a technique used for a variety of other fetal disorders (Box 78-3).[246,276-280] These include conditions that compromise the fetal airway, such as large neck masses, congenital high airway obstruction, or severe micrognathia. The EXIT procedure allows the fetus to remain supported by the placental unit with adequate oxygenation and perfusion while surgical repair and resuscitation interventions are performed in a controlled manner. The procedure has been used successfully to treat fetuses requiring intrathoracic mass resection, in separation of conjoined twins, and as a bridge to extracorporeal support.

The primary goals of the EXIT procedure are to maintain a prolonged state of uterine relaxation, to delay placental separation, and to sustain placental-fetal perfusion. Similar to open fetal surgery, EXIT procedures are frequently performed under general anesthesia, employing high concentrations (≥2 MAC) of volatile anesthetic to ensure uterine relaxation. Neuraxial anesthesia in combination with remifentanil, nitroglycerin, or both also has been used successfully.[270,280,281-282] Multiple reviews of the anesthesia, surgical, and obstetric considerations for the EXIT procedure have been published.[246,276-280] The overall preoperative and intraoperative approach for anesthetic management is similar to that previously described for open fetal surgery (see Box 78-2). The primary difference occurs after delivery of the fetus, when uterine relaxation is no longer required. Thus, after delivery of the neonate, anesthetic management becomes similar to management of a cesarean delivery with general anesthesia.

A detailed multidisciplinary meeting is extremely valuable before the start of the EXIT procedure. It is essential to ensure that all required supplies for fetal monitoring; airway management; maternal, fetal, and newborn resuscitation; and postdelivery care are obtained before entering the operating room. In addition to fetal ultrasonography, a pulse oximeter and $ETCO_2$ indicator are used to monitor the fetus and assist with confirmation of a secured airway. Similar to open fetal surgery, weight-based doses of atropine, epinephrine, and calcium are prepared for possible emergency fetal resuscitation. A sterile fetal ventilation circuit with an air/O_2 source and manometer is prepared in addition to multiple sizes of endotracheal tubes, laryngoscopes, and neonatal-sized laryngoscope blades for fetal tracheal intubation. Sterile tourniquets, intravenous catheters, crystalloid and blood (i.e., O-negative, CMV-negative, leukocyte depleted, maternally cross-matched) should be available for fetal venous access and volume replacement if needed.

Anesthetic considerations for the mother are similar to those for open fetal surgery (see Box 78-2). They include possible placement of an epidural catheter for postoperative analgesia, large-bore intravenous access, invasive monitoring readily available or placement of an intraarterial catheter, possible need for uterotonic drugs after delivery of the placenta, and cross-matched maternal blood in the operating room. Maternal anesthetic induction and tracheal intubation are similar to general anesthetic

BOX 78-3 ***Fetal Indications for the Ex Utero Intrapartum Therapy Procedure***

- Cervical mass
  - Cystic hygroma
  - Goiter
  - Hemangioma
  - Lymphangioma
  - Neuroblastoma
  - Teratoma
- Craniofacial anomaly
  - Severe micrognathia
  - Severe retrognathia
- Lung mass
  - Bronchopulmonary sequestration
  - Congenital cystic adenomatoid malformation
- Mediastinal mass
  - Lymphangioma
  - Teratoma
- Congenital high airway obstruction syndrome
  - Laryngeal atresia/stenosis
  - Tracheal atresia/stenosis
- Ex utero intrapartum therapy to extracorporeal membrane oxygenation
- Aortic stenosis with intact/restrictive atrial septum
  - CDH with severe pulmonary compromise
  - Hypoplastic left heart syndrome with intact/restrictive atrial septum
- Reversal of tracheal occlusive device placed during fetal surgery to treat CDH
- Conjoined twins

Data from Garcia PJ, Olutoye OO, Ivey RT, et al: Case scenario: anesthesia for maternal-fetal surgery: the Ex Utero Intrapartum Therapy (EXIT) procedure, Anesthesiology *114:1446-1452, 2011; and Ngamprasertwong P, Vinks AA, Boat A: Update in fetal anesthesia for the ex utero intrapartum treatment (EXIT) procedure.* Int Anesthesiol Clin *50:26-40, 2012.*

CDH, Congenital diaphragmatic hernia.

techniques employed for cesarean delivery, and maintenance of appropriate maternal hemodynamics is critical to ensuring adequate fetal perfusion (see also Chapter 77). Similar to techniques used for open fetal surgery, high concentrations of a volatile anesthetic (≥2 MAC) with or without intravenous administration of nitroglycerin (bolus doses of 50 to 200 μg or as an infusion) may be required for adequate prolonged uterine relaxation. Fetal anesthesia from transplacental transfer of maternal volatile anesthetic can be supplemented by fetal intramuscular administration of an opioid (e.g., fentanyl 5 to 15 μg/kg or morphine 0.1 mg/kg, depending on the indication) and a paralytic agent (rocuronium 1 to 3 mg/kg or pancuronium 0.1 to 0.3 mg/kg). Sometimes intramuscular atropine 20 μg/kg) is given to prevent fetal bradycardia.[246,276] The intramuscular fetal anesthetic drugs can be administered either before uterine incision using ultrasound guidance of the injection needle or under direct vision after performing the hysterotomy. There is significant variation in fetal serum fentanyl concentrations based on umbilical cord blood sampling during EXIT procedures.[283] Although possible causes for this observed variability are multiple, it is likely that significant variability also may exist with fetal serum concentrations of muscle relaxants and other agents administered to the fetus, making their pharmacologic actions less predictable.

Intravenous remifentanil administered to the mother rapidly crosses the placenta; some practitioners provide maternal anesthesia for EXIT procedures with neuraxial block supplemented with remifentanil infusions (0.1 to 0.2 μg/kg/min) and report adequate fetal immobilization without use of the intramuscular fetal anesthetic drugs previously described.[257,280,281] An alternative anesthetic approach uses maternal neuraxial anesthesia combined with intravenous administration of nitroglycerin in an effort to avoid many of the risks associated with administration of general anesthesia as previously described.[270,280-282,284] Significant doses of intravenous nitroglycerin 1 to 10 μg/kg/min are often required to achieve adequate prolonged uterine relaxation. Although nitroglycerin crosses the placenta, a significant amount is metabolized at the placental interface, and there are minimal fetal effects.[270,282] Invasive monitoring with a maternal intraarterial catheter is recommended when prolonged use of nitroglycerin is planned, and the patient should be monitored for onset of pulmonary edema. No prospective clinical trials have been conducted to determine the best anesthetic technique for the EXIT procedure.

After assessment of appropriate uterine relaxation, the placental border is determined by ultrasonography. A small initial hysterotomy is extended outside the placental border with a stapling device to prevent excessive blood loss. If the EXIT procedure is performed to facilitate fetal intubation or neck mass resection, only the fetal head and shoulders are initially delivered (Fig. 78-10). For more extensive procedures requiring access to the thorax or other anatomic locations, the entire body may be delivered.

Before hysterotomy, the fetus is monitored with echocardiography and ultrasonographic evaluation of umbilical cord flow. After hysterotomy, a pulse oximeter probe is placed on the fetal hand and shielded from ambient light. Warmed crystalloid fluids are irrigated continuously in the uterine cavity to maintain fetal temperature and prevent placental separation or spasm of umbilical vessels. Care should also be taken to avoid inadvertent compression or unnecessary manipulation of the umbilical cord, which could lead to vascular reactivity and decreased flow.



Figure 78-10. During an ex utero intrapartum therapy procedure, the head and upper torso of a fetus with a neck mass are delivered and the airway secured using direct laryngoscopy. *(Courtesy Dr. Anita Moon-Grady, University of California, San Francisco Fetal Treatment Center, San Francisco, Calif.)*

Depending on the indication, the duration of an EXIT procedure ranges from a few minutes (e.g., intubation) to several hours (intrathoracic mass resection, neck mass resection with tracheostomy, or ECMO cannulation). Anesthetic techniques have successfully provided safe maternal and fetal anesthesia with uterine relaxation and uteroplacental stability over several hours.[285] Before ventilation of the fetal lungs, fetal oxyhemoglobin saturation is typically 40% to 70%.[286] After initiating ventilation of the fetal lungs, oxyhemoglobin saturation should increase significantly to above 90%. When fetal lung ventilation fails to result in an appropriate increase in oxyhemoglobin saturation, this represents an indication for ECMO initiation before clamping the umbilical cord and fetal delivery.[287] An $ETCO_2$ indicator is also beneficial in confirming correct placement of the endotracheal tube. If needed, pulmonary surfactant may be administered once the endotracheal tube is placed. Transporting the neonate to the intensive care area for further care requires significant vigilance to ensure the critical, tentative airway remains secured.

Once the fetus is delivered, the inspired concentration of the volatile agent is significantly decreased, the nitroglycerin infusion stopped, or both to allow the uterus to contract and diminish the risk for maternal hemorrhage.[276,288] N_2O, propofol, and/or an opioid can be administered to maintain adequate anesthesia. Oxytocin is routinely administered and additional uterotonic drugs are given when necessary, as detailed in Chapter 77. Once the patient is hemodynamically stable with appropriate uterine tone, epidural analgesia may be initiated.

CONCLUSIONS AND FUTURE CONSIDERATIONS

Establishment of organized, multidisciplinary, and comprehensive fetal intervention programs at a variety of academic centers is critical to improving patient outcomes with innovative surgical techniques, improved diagnostic and treatment strategies, and clinical trials powered to address long-term neonatal outcome, as well as associated maternal and neonatal morbidity. Advancement of surgical technology and prenatal diagnostic and management strategies is likely to decrease both maternal and fetal risk and allow safe intervention for additional congenital anomalies and treatment of less severe abnormalities. Examples of future improvements might include dynamic tracheal occlusive devices to treat CDH, in utero placement of fetal pacemakers, and endoscopic repair of MMC. In addition, stem cell and gene therapy research may lead to novel fetal treatment that allows normal development despite presence of a congenital anomaly.[289] Improvements in managing preterm labor and delivery would greatly improve outcome in fetal therapy. Preterm birth is associated with morbidities such as respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage that all have long-term impact on the child and carry substantial cost.[290]

Fetal surgery is a relatively new and rapidly evolving area of clinical medicine. In utero treatment raises complex and difficult ethical, social, and legal issues that go far beyond that of most adult or pediatric surgical interventions and include questions regarding maternal rights, access to care, and the option for pregnancy termination.[291]

Evaluation of each new therapy or change in treatment strategy should be conducted in multicenter clinical trials only after appropriate translational research and animal studies are completed and demonstrate a potential benefit. This transition from innovative breakthrough, to randomized clinical trial, to standard care must be managed in a responsible and ethical framework. In addition, in utero treatment outcomes from new institutions with minimal experience and intervention for patients outside the strict inclusion criteria of clinical trials are likely to result in less favorable results with increased morbidity compared with the outcomes demonstrated at more established fetal treatment centers participating in the clinical trials.[292] To address these concerns, a bioethics committee from the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics provided recommendations for centers offering fetal therapy.[6] A summary of these recommendations includes a thorough informed consent process, appropriate institutional research safeguards, involvement of a multidisciplinary team, and the need for open collaborative research networks. Although this approach has high financial costs, thorough basic science, and translational and clinical research in fetal therapy is essential to appropriately manage the unique risks and benefits of future innovations. Appropriate patient selection (both maternal and fetal) and timing of the intervention also need to be better established.

The principal of *primum non nocere* argues that until a therapy is appropriately tested in animal models, it is unethical to pursue in human trials.[293,294] Advances in fetal surgery not only require determination of fetal benefit but also must be powered to appropriately evaluate additional fetal and maternal morbidity. A recent study comparing intrauterine endoscopic MMC repair to matched controls found frequent complication rates to mothers and fetuses and a frequent rate of fetal mortality.[184] Although the endoscopic repair demonstrated a benefit of segmental spine neuroprotection, it was concluded by the authors that, "before considering clinical implementation of fetal endoscopic MMC closure as standard care, the frequency of complications should be appropriately reduced and results assessed in larger groups over a longer period of time."[184]

Only the results of animal research and descriptive summaries of clinical series currently guide clinical anesthetic care for fetal surgery. Further rigorous research is needed to determine optimal anesthetic techniques to ensure maternal and fetal cardiovascular stability, to evaluate the best gestational age of anesthetic exposure, to assess the impact of anesthetic management strategies on myometrial tone and uteroplacental perfusion, and to improve our ability to determine the adequacy of fetal anesthesia to cause immobility and blockade of the fetal stress response.[295,296]

Areas of clinical growth of the field include the potential need for anesthesia and other subspecialty training programs in fetal treatment and the development of standard guidelines for fetal anesthesia and perioperative care of these unique procedures. Fetal treatment is a relatively new, rapidly evolving field of clinical medicine that holds great promise for treating morbid conditions and improving quality of life over the entire lifetime of the patient. Equally significant are the research efforts, technologic advancements, and ethical standards that must be supported to achieve these goals.

Complete references available online at expertconsult.com

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Chapter 79

Anesthesia for Orthopedic Surgery

MICHAEL K. URBAN

Key Points

- Older age is a significant risk factor for poor outcome after orthopedic surgery. Older patients presenting for orthopedic surgery often have multiple comorbid conditions that must be considered in the perioperative anesthetic plan.
- Patients with arthritis (osteoarthritis, rheumatoid arthritis, ankylosing spondylitis) have special problems that must be addressed in an anesthetic plan.
- For many orthopedic procedures, regional anesthesia may reduce perioperative complications compared with general anesthesia and provide superior postoperative analgesia.
- Fat embolism syndrome is a well-recognized complication of orthopedic trauma and major joint replacement. Early intervention and stabilization of these patients may avoid significant morbidity.
- Corrective surgery for spinal deformities (scoliosis, kyphosis, kyphoscoliosis) presents a significant challenge to the anesthesiologist. These patients are at risk for large blood loss, pulmonary complications, neurologic deficits, and postoperative loss of vision. Changes in anesthetic management may reduce the incidence of some of these complications.

Patients undergoing orthopedic procedures can be particularly challenging for anesthesiologists. These patients represent a broad scope of problems, ranging from an elderly patient with multiple comorbid conditions to a young, deceptively healthy trauma patient who may have associated injuries that can have a significant impact on the type of anesthetic administered. It is imperative that the anesthesiologist examine the entire patient and not just focus on the area of surgery. In this regard, a complete medical history is important because it may reveal chronic connective tissue diseases that may alter the anesthetic plan.

The field of orthopedics also is changing in many ways that affect the anesthesia care of these patients. Demand for joint replacements in the active aging population is increasing, with the expectation of regional anesthesia, a postoperative pain management plan, and early hospital discharge. More orthopedic procedures are now performed as ambulatory surgery, and the anesthesiologist becomes responsible for which patients can be discharged and how their pain is to be managed. Adult spinal surgery also is dramatically increasing. These procedures can be the most challenging to the anesthesiologist because of difficult airways, hours patients spend in the prone position, large blood loss, and significant postoperative pain.

This chapter discusses the perioperative factors that potentially alter outcome after orthopedic surgery. Complications associated with specific procedures are emphasized with regard to recognition of such complications, avoidance when possible, and management. Choice of the best anesthetic based on current evidence for a given orthopedic procedure also is discussed. In many cases, the pros and cons of regional versus general anesthesia are presented, but this chapter does not concentrate on the technical aspects of regional anesthesia. This chapter provides guidance for anesthesia for patients undergoing common orthopedic procedures.

PREOPERATIVE EVALUATION

All patients presenting for orthopedic surgery warrant a thorough preoperative medical evaluation (also see Chapter 38). Any orthopedic patient could represent an anesthetic challenge. Specific types of patients, however, are more likely to have orthopedic surgery and are more likely to have perioperative complications.

GERIATRIC ORTHOPEDIC PATIENTS

In 2011, 13% of the U.S. population (41 million) was older than 65 years of age and at least 20 million of these individuals had "advanced" osteoarthritis (see also Chapter 80). In the same year over 600,000 knee replacements were performed. By 2030, the number of U.S. citizens older than 65 years of age is expected to almost double to 72 million.[1] This means that older patients with multiple comorbid conditions will be having increasingly more orthopedic procedures, including total joint replacements.

Postmenopausal and age-associated osteoporosis affects older individuals, increasing their risk for fractures. Age-associated osteoporosis may be the result of increased circulating parathyroid hormone and decreased vitamin D, growth hormone, and insulin-like growth factors.[2] With osteoporosis, a disproportionate loss of trabecular (structural) bone occurs, placing the patient at risk for stress fractures. Although all bones are theoretically at risk, the thoracic and lumbar spine, proximal femur, proximal humerus, and wrist are at the highest risk.[3] Compression fractures of the thoracic and lumbar spine also are common and may require surgical intervention. Osteoporosis compromises the incidence and quality of postoperative fusions. The National Osteoporosis Foundation recommends measuring bone mineral density at the hip or spine in patients at risk and postmenopausal women. Osteoporosis can be partially treated with increased dietary calcium intake and vitamin D and doing weight-bearing and muscle-strengthening exercises,[4] but this population is at risk for fractures with minimal-impact trauma and the pain-relieving joint replacements.

The mortality after hip and knee arthroplasty surgery ranges from 0.4% to 4.6%, depending on primary versus revision replacement surgery.[5-9] Recent studies suggest that the in-hospital mortality and morbidity after total joint arthroplasty may be decreasing (0.13% to 0.18%), although increased major complications may occur.[9,10] The in-hospital mortality after repair of hip fractures is 4.8%, and mortality increases to 30% after the first year after hospitalization. The major risk factor for perioperative mortality in all of these studies was advanced age, and the most frequent perioperative complications were cardiopulmonary issues.[11,12] In their review of 1636 consecutive hip and knee replacements, Parviz and colleagues[7] reported a 6.4% incidence of serious postoperative complications, with the most frequent complication associated with cardiac comorbidities. The reported incidence of a perioperative myocardial infarction at an orthopedic hospital was 0.6% of all nonambulatory procedures (~8000), and 6.5% of those patients were at risk for myocardial ischemia.[13] A nationwide cohort study from the Netherlands reported a significant increase in perioperative myocardial ischemia in the first 2 weeks after total hip replacement (25-fold) and after total knee replacement (31-fold) surgical procedures compared with matched control nonsurgical patients.[14]

Postoperative Complications

Cardiac Complications. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend preoperative cardiac testing in patients at increased cardiac risk on the basis of clinical risk profile, functional capacity, and type of surgery.[15] The ACC/AHA classify orthopedic surgery as intermediate-risk surgery, which in most cases involves intermediate-risk patients. Older patients have an increased risk for perioperative myocardial morbidity and mortality after orthopedic surgery (see also Chapter 80). The possible reasons for this increased risk are as follows: (1) Many elderly patients have multiple medical comorbid conditions,[16,17] (2) elderly patients have limited functional capacity, (3) some orthopedic procedures initiate a systemic inflammatory response syndrome, (4) some orthopedic procedures are associated with significant blood loss and fluid shifts, and (5) postoperative pain is a major management problem after orthopedic surgery[18] (see also Chapters 61 and 98). All these factors can trigger a stress response leading to tachycardia, hypertension, increased oxygen demand, and myocardial ischemia.

Because a significant incidence of postoperative cardiac complications occurs after orthopedic surgery, and it is difficult to assess the functional status of these patients owing to the limitations imposed by their orthopedic disease, many of these patients are subjected to preoperative cardiac testing. Data for orthopedic surgery showing that preoperative risk stratification or coronary revascularization, or both, has an effect on outcome are limited, however (see also Chapters 37 and 38). A report by Salerno and associates[9] suggested that preoperative abnormal noninvasive cardiac testing rarely changed medical management before orthopedic surgery. The Decrease-II study questioned the value of preoperative cardiac testing in patients of intermediate risk before noncardiac surgery.[19] In the Coronary Artery Surgery Study (CASS) Registry, Eagle and colleagues[20] reported that coronary artery bypass graft surgery offered no advantage before orthopedic surgery in reducing cardiac mortality. Similar results have been obtained using percutaneous coronary intervention. Postoperative myocardial infarction and death have not been reduced for noncardiac surgery in patients at cardiac risk when preceded by percutaneous coronary intervention.[21,22] In patients in whom percutaneous coronary intervention involved the placement of stents, restenosis and thrombosis are added risks if antiplatelet therapy has to be discontinued before surgery and increased perioperative bleeding if these medications are not discontinued.[23]

If preoperative cardiac testing and revascularization does not decrease postoperative cardiac morbidity, hemodynamic stress reduction might be the answer. Numerous studies have indicated that the use of perioperative adrenergic β-blockers can reduce myocardial ischemia and postoperative myocardial infarctions.[19,24,25] Several more recent reports have questioned the efficacy of β-blockers in preventing postoperative cardiac complications, particularly in patients at intermediate risk.[26,27] In older patients undergoing orthopedic procedures, β-blockers should be continued perioperatively in patients taking long-term β-blockers and initiated in patients at the highest risk, with a target heart rate less than 80 beats/minute.[24,28]

Patients undergoing orthopedic procedures who are at risk for perioperative cardiac complications should be assessed postoperatively for myocardial ischemia. The diagnosis of a postoperative myocardial infarction is important because these events can be associated with significant cardiac morbidity and mortality if not treated appropriately. In addition, the decision to initiate postoperative physical therapy and rehabilitation, activities that are imperative for optimal mobility in orthopedic patients, depends on whether there has been a diagnosis of a postoperative myocardial infarction. The introduction of plasma cardiac troponin I analysis has markedly increased the ability to detect myocardial damage.

Increases in the plasma concentrations of cardiac troponin I are highly specific for cardiac injury and are a more specific marker for a myocardial infarction after orthopedic surgery than the creatine kinase MB isoenzyme.[29,30]

Respiratory Complications. The changes in the respiratory system secondary to age may predispose older patients to increased postoperative pulmonary complications. These changes include a progressive decrease in arterial O_2 tension, an increase in closing volumes, and a decrease of approximately 10% in the forced expiratory volume in 1 second (FEV_1) with each decade of life. Many of these changes are the result of alterations in chest wall mechanics, which are exacerbated in older patients with arthritis. Older patients who have sustained hip fracture have significantly lower PaO_2 values than other surgical patients of comparable ages.[31] The hypoxia in these patients may reflect the previously noted respiratory changes caused by age, as well as the embolization of bone marrow debris to the lungs after arthroplasty surgery. In addition, with high rates of obesity and obstructive sleep apnea (OSA) prevalent among patients undergoing arthroplasty and spine surgery, respiratory concerns and complications should remain in the forefront of our attention. Patients with OSA are at increased risk for perioperative complications. In a retrospective analysis of patients undergoing hip and knee arthroplasty, OSA was associated with an increased incidence of postoperative transfer to an intensive care unit (ICU).[32] Insufficient evidence exists to propose the best perioperative management of patients with OSA; however, preoperative screening using tools such as the STOP-Bang questionnaire and prudent postoperative management would appear to be the best approach.[33]

Neurologic Complications. After cardiac and pulmonary complications, confusion or delirium is the third most common complication seen in older patients after orthopedic surgery. In 2004, $69 billion from Medicare was spent on the treatment of hospital-acquired delirium. Delirium is associated with an increased length of hospital stay, poor functional recovery, progression to dementia, and increased mortality.[34,35] Postoperative delirium manifests as attention and awareness deficits, including acute confusion, reduced ability to focus, change in cognition, irritability, anxiety, paranoia, and hallucinations. Delirium develops acutely, but generally has a fluctuating course over several days (see also Chapter 80).[36] Some patients manifest a hypoactive form of delirium, confused but quiet and nondisruptive, which can be difficult to diagnose. The major risk factors for postoperative delirium are advanced age, alcohol use, preoperative dementia or cognitive impairment, psychotropic medications, and multiple medical comorbid conditions. Perioperative events that may trigger delirium include hypoxemia, hypotension, hypervolemia, abnormal electrolytes, infection, sleep deprivation, pain, and administration of benzodiazepines and anticholinergic medications.

Aging alters the pharmacokinetics and pharmacodynamics of most medications, including anesthetics and analgesics. The "usual" adult doses of these medications may have longer and more profound central nervous system (CNS) effects on older patients. Strategies used to reduce the incidence of postoperative delirium include identifying risk factors and vulnerable and affected patients early, preserving orientation, early mobilization, adequate pain control, maintenance of normal sleep cycles, and avoidance of psychotropic medications. Because in most cases patients present with a change in mental status, delirium represents a diagnosis of exclusion. The diagnosis is obtained by conducting a neurologic examination to rule out focal deficits; blood laboratory analysis to eliminate electrolyte abnormalities, hypercarbia, and hypoxemia; a review of all medications to eliminate unnecessary central-acting medications; and adequate pain management. The treatment options range from simple observation with the assignment of a caregiver to pharmacologic management to provide sedation and anxiolytics to prevent the combative patient from harming self or others. Atypical antipsychotics, which are devoid of extrapyramidal side effects, are effective for the acute treatment of delirium.

BOX 79-1 ***Gurd's Diagnosis of Fat Embolism Syndrome***

Major Features (At Least One)

Respiratory insufficiency
Cerebral involvement
Petechial rash

Minor Features (At Least Four)

Pyrexia
Tachycardia
Retinal changes
Jaundice
Renal changes

Laboratory Features

Fat microglobulinemia (required)
Anemia
Thrombocytopenia
High erythrocyte sedimentation rate

From Gurd AR, Wilson RI: The fat embolism syndrome, J Bone Joint Surg Br *56:408-416, 1974.*

FAT EMBOLISM SYNDROME

Fat embolization is a well-known complication of skeletal trauma and surgery involving instrumentation of the femoral medullary canal.[37] Fat embolism syndrome (FES) is a physiologic response to fat within the systemic circulation. Fat embolization and FES are not synonymous. The embolization of fat can be detected in almost all patients who sustain a pelvic or femoral fracture, but the incidence of FES is less than 1%.

The clinical manifestations of FES include respiratory, neurologic, hematologic, and cutaneous signs and symptoms. The manifestation of FES can be gradual, developing over 12 to 72 hours, or fulminant, leading to acute respiratory distress and cardiac arrest. Gurd and Wilson[38] in 1974 suggested major and minor criteria to be used for the diagnosis of FES (Box 79-1). The presence of any one major finding plus four minor criteria and evidence of fat microglobulinemia was required for the diagnosis of FES. The requirement for fat droplets in the circulation has been

BOX 79-2 ***Schonfeld Fat Embolism Syndrome Index****

Sign	Score
Petechial rash	5
Diffuse alveolar infiltrates	4
Hypoxemia: PaO_2 less than 70 mm Hg, FiO_2 100%	3
Confusion	1
Fever greater than 38° C (>100.4° F)	1
Heart rate greater than 120 beats/minute	1
Respiratory rate greater than 30 breaths/minute	1

From Schonfeld SA, Ploysongsang Y, DiLisio R, et al: Fat embolism prophylaxis with corticosteroids: a prospective study in high risk patients. Ann Int Med *99:438-443, 1983.*

* Score greater than 5 required for diagnosis of fat embolism syndrome.

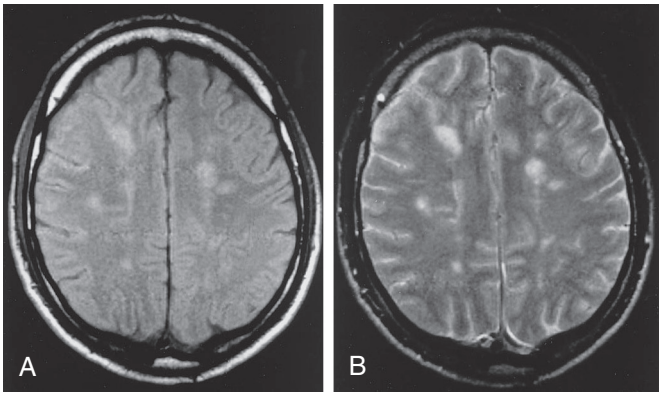


Figure 79-1. Cerebral fat embolism. Multiple hyperintense lesions on proton density–weighted (**A**) and T2-weighted (**B**) magnetic resonance images in the centrum semiovale. *(From Stoeger A, Daniaux M, Felber S, et al: MRI findings in cerebral fat embolism,* Eur Radiol *8:1590-1593, 1998. © Springer-Verlag.)*

criticized, however, because fat droplets can be detected in the blood of healthy volunteers, and their presence in trauma patients is not always associated with FES.

In addition, Gurd and Wilson[38] recommended the daily assessment of fat droplets in blood, hypothesizing that a change in the quantity of fat would correlate with symptoms. More recent investigations have indicated that the quantity of fat in the circulation does *not* correlate with the severity of FES symptoms or the development of acute respiratory distress syndrome (ARDS).[39]

A petechial rash is pathognomonic of FES, with the rash usually present on the conjunctiva, oral mucosa, and skin folds of the neck and axillae. This is reflected in the Schonfeld FES index, which ranks signs and symptoms of FES in relation to their incidence of presentation (Box 79-2).[40] Respiratory signs also are common in FES; approximately 75% of patients present with mild hypoxemia and radiologic evidence of bilateral alveolar infiltrates, but less than 10% progress to ARDS. Neurologic manifestations of FES range from drowsiness and confusion to obtundation and coma. CNS symptoms have developed in the absence of significant pulmonary complications and may represent the passage of fat droplets across an atrial septal defect or other atrioventricular shunt.[41] Magnetic resonance imaging of the brain of these patients has revealed lesions characteristic of fat embolization (Fig. 79-1).

The pathophysiology of FES is unclear, but it probably involves two processes: the embolization of fat and bone marrow debris, which can mechanically obstruct the capillaries of end organs and the triggering of a systemic inflammatory response.[37] Using transesophageal echocardiography (TEE) during total hip arthroplasty (THA), embolization of bone marrow debris has been detected in the right heart at the time of insertion of the cemented femoral prosthesis (Fig. 79-2).[42,43] In some patients, this embolization resulted in segmental wall motion abnormalities, elevated pulmonary arterial pressures, decreased right ventricular function, and, in one case, cardiac arrest and death.[43,44]

In most cases, the embolic events during THA are clinically benign, but some patients still progress to FES. The fat emboli lodged in the microvasculature of the lung and other end organs are metabolized to free fatty acids, which trigger a systemic inflammatory response. This inflammatory response involves the invasion of inflammatory cells, the release of cytokines, and, in the lung, pulmonary endothelial damage and ARDS.[45]

The treatment of FES is supportive with early resuscitation and stabilization to minimize the stress response to hypoxemia, hypotension, and diminished end-organ perfusion. Patients at risk for developing FES should be monitored with pulse oximetry, and tracheal intubation and mechanical ventilation should be instituted before respiratory failure. Although 10% of patients with FES may require mechanical ventilation, in most of these patients the symptoms resolve within 3 to 7 days. Corticosteroids have been studied extensively in the management of FES, with many investigators reporting beneficial effects, but other reports contradict these results.[46,47] Well-controlled studies with defined outcomes are required before corticosteroids can be recommended in the treatment of FES.

SPECIAL CONSIDERATIONS IN CONDITIONS LEADING TO ORTHOPEDIC SURGERY

Osteoarthritis

Approximately 22% of the U.S. population (46 million) has been diagnosed as having arthritis, and 8% (17 million) have limitations in physical activity because of arthritis.[48] Osteoarthritis is the most common type of arthritis and involves the loss of articular cartilage and associated inflammation. In most cases, osteoarthritis is a disease of aging, with 90% of women and 85% of men demonstrating the radiologic loss of articular cartilage after age 65 years.[49] Clinical manifestations include pain, crepitance, reduced mobility, and deformity of involved joints. Physical examination of the hands may reveal spurring and swelling of the distal interphalangeal joints (Heberden nodes) and proximal interphalangeal joints (Bouchard nodes).

Although osteoarthritis has no systemic manifestations, the anesthesiologist should be cognizant of previous orthopedic surgeries (including joint replacements) and which joints are painful and have limited mobility.

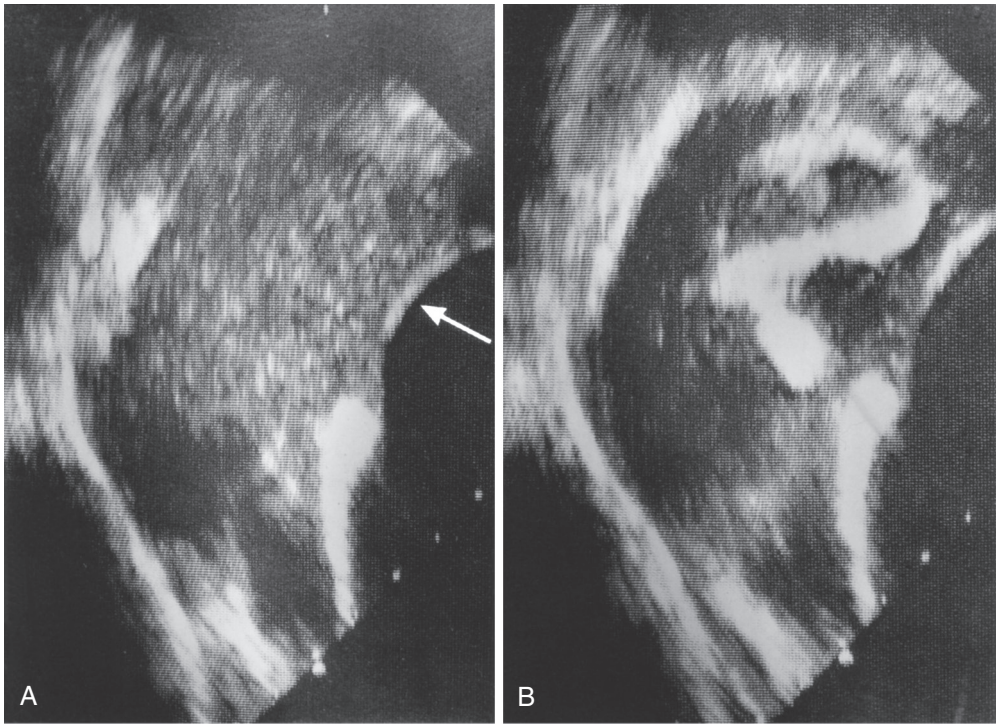


Figure 79-2. Right atrium during echocardiography. **A,** Multiple, small emboli (*arrow*) in the right atrium. **B,** Large embolus (7 cm long), which is probably a cast of the femoral vein. *(Modified from Christie J, Burnett R, Potts HR, et al: Echocardiography of transatrial embolism during cemented and uncemented hemiarthroplasty of the hip,* J Bone Joint Surg Br *76:409-412, 1994.)*

This information is important for surgical positioning and the choice of an appropriate anesthetic. An axillary block of the brachial plexus for forearm surgery is inappropriate in a patient with significant ipsilateral shoulder arthritis. Although the operative site would be completely anesthetized, the patient may complain of painful shoulder movement during the procedure. The appropriate regional anesthetic would include the arthritic shoulder; an appropriate anesthetic might be an interscalene block.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory form of arthritis that affects approximately 1% of adults, with a prevalence two to three times higher in women than in men. RA is characterized by persistent joint synovial tissue inflammation leading to bone erosion, destruction of cartilage, and loss of joint integrity. RA is also a systemic disease, affecting multiple organ systems.[50] It often progresses through multiple exacerbations and remissions, but 20% to 30% of affected individuals become permanently disabled within 3 years of diagnosis.

The diagnosis of RA is primarily clinical. Patients commonly present with pain and stiffness in multiple joints. RA is characterized by morning stiffness often lasting more than 1 hour after initiating activity. Usually the wrists and metacarpophalangeal joints are involved; this distinguishes RA from osteoarthritis, which often affects distal interphalangeal joints. The symptoms may emerge over weeks and months, progressing from one joint to multiple joints, and may be accompanied by symptoms of anorexia, fatigue, and weakness. The rheumatoid joints are usually boggy, tender to the touch, and warm. Patients may have prominent epitrochlear, axillary, and cervical lymph node enlargement. Subcutaneous nodules (rheumatoid nodules) may surround joints, extensor surfaces, and bony prominences.

No single diagnostic laboratory test confirms the diagnosis of RA, but rheumatoid factor, an antiimmunoglobulin antibody, is elevated in 90% of patients with RA. In addition, C-reactive protein and erythrocyte sedimentation rate are elevated in patients with RA and are often used to monitor the course of the disease. RA also must be differentiated from other diseases that manifest as polyarthropathies, including seronegative spondyloarthropathies, connective tissue diseases (scleroderma, lupus), fibromyalgia, hemochromatosis, polyarticular gout, polymyalgia rheumatica, and sarcoidosis.

Because joint destruction begins early with RA, disease-modifying antirheumatic drugs should be initiated immediately with the therapeutic goal of preservation of function and quality of life. The most commonly used disease-modifying antirheumatic drugs include methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, infliximab (Remicade), and etanercept (Enbrel). These medications are associated with an increased risk for infection, which is a significant concern in patients with joint replacements. Pharmacotherapy also usually involves a nonsteroidal antiinflammatory drug (NSAID) and oral or intraarticular glucocorticoids. Patients with RA who are taking NSAIDs should be assessed for gastrointestinal side effects and renal complications. Glucocorticoids, although highly effective at relieving symptoms, should be used at low doses and sparingly because of their side effects, which include osteoporosis, cataracts, cushingoid symptoms, and hyperglycemia. Patients taking significant quantities of glucocorticoids need stress-dose steroids for their operations.

Because of the myriad systemic problems associated with RA and the side effects of the medications administered

TABLE 79-1 ANESTHETIC CONSIDERATIONS FOR PATIENTS WITH RHEUMATOID ARTHRITIS

Airway	Limited TMJ movement
	Narrow glottic opening
Cervical spine	Atlantoaxial instability
Cardiac	Pericarditis
	Cardiac tamponade
Eyes	Sjögren's syndrome
Gastrointestinal	Gastric ulcers secondary to ASA, steroids
Pulmonary	Diffuse interstitial fibrosis
Renal	Renal insufficiency secondary to NSAIDs

ASA, Acetylsalicylic acid; *NSAIDs,* nonsteroidal antiinflammatory drugs; *TMJ,* temporomandibular joint.

to manage RA, the anesthetic considerations can be complex (Table 79-1). The skin is often susceptible to tearing from adhesive tape and bruising from automated blood pressure devices and pressure from positioning. Airway management can be particularly challenging in patients with RA and requires preplanning even in patients receiving regional anesthesia because of the complexity of their airways (see later discussion). Synovitis of the temporomandibular joint may significantly limit mandibular motion and mouth opening in these patients. Arthritic damage to the cricoarytenoid joints may result in diminished movement of the vocal cords, resulting in a narrowed glottic opening; this is manifested preoperatively as hoarseness and stridor. During laryngoscopy, the vocal cords may appear erythematous and edematous, and the reduced glottic opening may interfere with passage of the endotracheal tube.[51] Risk also increases for cricoarytenoid dislocation with traumatic endotracheal intubations.

Arthritis of the cervical spine is common in patients with RA. Anterior subluxation of C1 on C2 (atlantoaxial subluxation) may occur in 40% of patients with RA, with symptoms of progressive neck pain, headaches, and myelopathy (Fig. 79-3). Posterior and vertical migration of the odontoid process is less common. Flexion of the head in the presence of atlantoaxial instability could result in the displacement of the odontoid process into the cervical spine and medulla and compression of the vertebral arteries (Fig. 79-4). This may precipitate quadriparesis, spinal shock, and death. Preoperative cervical flexion-extension radiographs should be evaluated in patients with RA who have limited neck movement and neurologic symptoms. If the distance from the anterior arch of the atlas to the odontoid process exceeds 3 mm, the patient should undergo an awake fiberoptic tracheal intubation and the cervical spine should be protected with a cervical collar during the procedure. These patients require postoperative monitoring with pulse oximetry and judicious administration of opioid analgesics because emergent airway management, including tracheotomy, is extremely difficult.

The anesthesiologist also should be aware of several extraarticular manifestations of RA, which could potentially result in significant perioperative morbidity. Patients with RA frequently are affected with acute pericarditis. Restrictive pericarditis is characterized by



Figure 79-3. Magnetic resonance image of a patient with advanced rheumatoid arthritis shows invagination of the odontoid process of C2 (*arrow*) through the foramen magnum, compressing the brainstem. Notice the degeneration of C4 and C5, a common problem in rheumatoid arthritis.

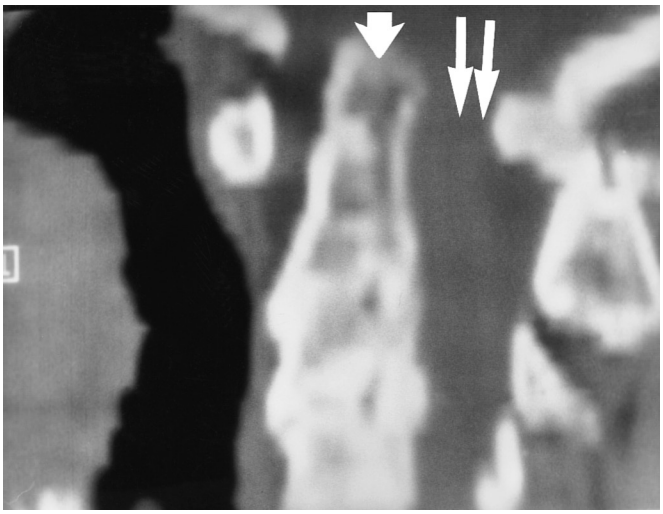


Figure 79-4. Computed tomography scan of the neck shows moderate subluxation of C1 and C2. The odontoid *(single arrow)* tends to compress the spinal cord (*double arrow*) against the posterior arch of C1, especially during neck flexion.

dyspnea, right heart failure, fever, chest pain, pericardial friction rub, and pulsus paradoxus. Patients with RA who have these symptoms should be evaluated by echocardiography. Pleural disease and intrapulmonary nodules can occur in RA, but are usually asymptomatic. Some patients with RA also may have diffuse interstitial fibrosis

with pneumonitis, producing symptoms of progressive dyspnea and a chronic cough. Pulmonary function tests show a restrictive ventilatory pattern. This pattern can progress to respiratory insufficiency, pulmonary hypertension, and right heart failure. These patients would be at higher risk with any orthopedic procedure.

Overlapping connective tissue syndromes also occur. Patients with RA can develop Sjögren's syndrome, which is associated with drying of the eyes and corneal and conjunctival lesions. It is usually treated with artificial tears and ophthalmic ointments, which should be continued perioperatively. Patients with RA and chronic constitutional systems may develop Felty syndrome, which includes splenomegaly, lymphadenopathy, anemia, thrombocytopenia, and leukopenia involving the neutrophils.

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory arthritic disease that results in fusion of the axial skeleton. Ankylosing spondylitis involves ossification of the axial ligaments progressing from the sacral lumbar region cranially, resulting in a significant loss of spinal mobility (Fig. 79-5). These patients are a significant challenge to the anesthesiologist with regard to airway management because of the reduced movement of their cervical spines and their temporomandibular joints. In most cases, awake fiberoptic endotracheal intubation is required for general anesthesia. The increased rigidity of the thoracic spine in most cases also necessitates intraoperative controlled mechanical ventilation. Although sometimes neuraxial anesthesia can be an attractive alternative to general anesthesia, in these patients the ossification of the spinal ligaments closes the intervertebral spaces, which may block access to the epidural space and prevent successful spinal anesthesia. In some cases, caudal epidural anesthesia may be a feasible alternative approach.

Extraskeletal manifestations of ankylosing spondylitis include aortic insufficiency, cardiac conduction abnormalities, iritis, upper lobe fibrobullous disease, and pleural effusions. Strict attention to intraoperative positioning is needed to avoid fracture of the fused spine with concomitant spinal cord trauma.

Achondroplasia

Achondroplasia is the most common cause of dwarfism, with short stature, short trunk, and disproportionate development. The estimated incidence is 1 in 26,000. Achondroplasia is transmitted by an autosomal dominant gene. Affected individuals are of normal intelligence and can lead a full and productive life. Their associated medical problems often require orthopedic surgical intervention, however, with the risk for perioperative complications.[52-54] The most serious complication of achondroplasia is premature fusion of the base of the skull resulting in a narrowed cervical canal, foramen magnum stenosis, or both. Kyphoscoliosis with potential neurologic symptoms is another common complication associated with this genetic condition. These affected individuals undergo numerous orthopedic (spinal) procedures, including suboccipital craniotomy for foramen magnum stenosis, correction or stabilization of kyphoscoliosis, and laminectomies for spinal nerve root compressions.

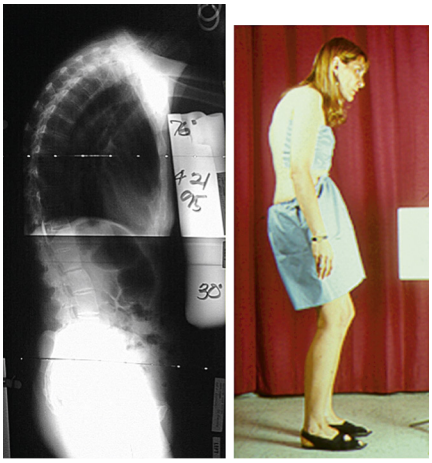


Figure 79-5. Patient with ankylosing spondylitis, exhibiting significant kyphosis of the spine. Note significant kyphosis in the lateral radiograph.

Conventional laryngoscopy and tracheal intubation can be difficult and dangerous in achondroplastic dwarfs. Laryngeal exposure via direct visualization may be difficult in dwarfs with cervical kyphosis, and neck flexion should be avoided in dwarfs with atlantoaxial instability or foramen magnum stenosis. Awake fiberoptic tracheal intubation is the safest approach to securing the airway in these patients. Intravenous sedation should be administered judiciously during the preparation of the airway because many of these patients experience central sleep apnea owing to brainstem compression. Severe episodes of sleep apnea also can occur in these patients without any other clinical evidence of cord compression.

When the airway is secured, dwarfs can still represent an anesthetic challenge because of restrictive lung disease and pulmonary hypertension. Pulmonary hypertension develops from chronic hypoxemia and hypercarbia secondary to airway obstruction, sleep apnea, and thoracic kyphoscoliosis. Preoperative spirometry can be difficult to interpret in a dwarf, with successive changes in measurements more useful than absolute values.[55] An echocardiogram should be obtained before major surgery to assess the degree of pulmonary hypertension and intracardiac shunts. Pulmonary hypertension leading to cor pulmonale is the most common and devastating cardiovascular complication that develops in dwarfs. In these patients, the anesthetic must avoid aggravating pulmonary hypertension (hypoxemia and acidosis) and ensure adequate cardiac output and end-organ perfusion. In many cases, it is safer to allow the patient to remain intubated and monitored in the ICU until fully awake and spontaneously ventilating.

ORTHOPEDIC PROCEDURES IN CHILDREN WITH SPECIAL CONDITIONS

The anesthetic management of pediatric patients undergoing orthopedic surgery is beyond the scope of this chapter (see also Chapters 92 and 93). In most cases, care of pediatric patients would be similar to that for other surgical procedures, except that in many cases regional

TABLE 79-2 **ANESTHETIC CONSIDERATIONS FOR PATIENTS WITH OSTEOGENESIS IMPERFECTA**

Airway	Risk for fractures of the mandible, maxillary surface, and cervical spine
Bleeding	Platelet abnormalities
Cardiac	Congenital and valvular heart disease, cystic degeneration of proximal aorta
Eyes	Exophthalmos—prone positioning
Hyperthermia	Malignant hyperthermia, hydration, possible cooling
Positioning	Risk for repeated fractures
Pulmonary	Kyphoscoliosis—restrictive lung disease
Regional anesthesia	Fractures, intraosseous injections

anesthesia might be a preferred alternative to general anesthesia. However, a few pediatric diseases predispose children to multiple orthopedic procedures.

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is inflammation of the synovium of the joints that occurs before 16 years of age. JIA is classified into five types, as follows:

1. Oligoarthritis accounts for 50% of JIA and involves fewer than five joints; often these patients also have uveitis.
2. Polyarthritis involves arthritis in five or more joints.
3. Systemic arthritis accounts for 10% to 20% of JIA and is characterized by associated high fevers, rash, and nonarticular organ involvement.
4. Enthesitis-related arthritis affects the spine, hips, and attachment points of tendons to bones.
5. Psoriatic arthritis includes psoriasis and arthritis.

As in adult RA, the disease is chronic with quiescent periods interspersed with acute exacerbations. Also as in adult RA, airway issues can make tracheal intubation difficult and potentially dangerous. In most cases, fiberoptic intubation should be performed, and this can be done after the child has been anesthetized and is breathing spontaneously. Muscle relaxants should be reserved until the airway is secured. In contrast to adult RA, pulmonary disease is uncommon, but patients with JIA can have associated pleuritis, pleural effusions, and pneumonitis. Pericarditis is common in patients with JIA, and it responds to steroid therapy. Some patients with JIA also have myocarditis and conducting system abnormalities. In addition, vascular access in patients with JIA can be extremely difficult because of fragile veins and a tendency to bruise and bleed easily. As with adult RA, patients with JIA are managed with similar groups of medications with similar potential complications.

Osteogenesis Imperfecta

Osteogenesis imperfecta is a rare autosomal dominant inherited disease that results in extremely brittle bones because of a defect or deficiency in type I collagen production.[56,57] Repeated and multiple bone fractures are the most significant clinical manifestation of this disease (Table 79-2). In the most extreme form, multiple fractures occur during delivery and are often fatal. In the milder variations, the individual is affected by multiple fractures produced with seemingly inconsequential force or trauma. Fractures are more common in the lower extremity, with the femur being the most commonly broken bone. Fracture deformities of the pelvis can lead to acetabular protrusions into the abdomen. Kyphoscoliosis is common secondary to decreased ligamentous stability. Affected children usually have a blue sclera because of defective collagen production. Impaired platelet function with increased perioperative bleeding also occurs.

Although osteogenesis imperfecta has been associated with malignant hyperthermia, this has not been verified by muscle biopsy (see also Chapter 43).[58] Hyperthermia and metabolic acidosis can, however, be common intraoperative clinical manifestations of osteogenesis imperfecta. Associated cardiac abnormalities include patent ductus arteriosus, septal defects, and acquired aortic regurgitation and cystic degeneration of the proximal aorta (see also Chapters 93 and 94).

The fragility of connective tissue and bones in osteogenesis imperfecta demands extreme care in positioning and padding during anesthesia. The area under the blood pressure cuff must be padded, and for longer procedures insertion of an arterial catheter avoids the repeated inflation of the cuff and the risk for a humeral fracture. Because patients with osteogenesis imperfecta often have reduced mobility of the cervical spine, tracheal intubation must be achieved with minimal neck manipulation. Fiberoptic intubation techniques in many cases would be the prudent approach. The administration of succinylcholine should be avoided for the induction of anesthesia not only because of the theoretic risk for hyperkalemia and hyperthermia but also because muscle fasciculations may produce bony fractures. Patients with osteogenesis imperfecta should have a preoperative echocardiogram, and any abnormal findings should be managed accordingly.

The bleeding status of patients with osteogenesis imperfecta should be evaluated preoperatively to prepare for the perioperative transfusion of platelets. In some cases, desmopressin (DDAVP) may reverse the platelet abnormality. Because of the risk for intraoperative hyperthermia and metabolic acidosis, patients with osteogenesis imperfecta should be aggressively hydrated, and, if necessary, active cooling should be instituted. Regional anesthesia is an attractive alternative to general anesthesia, but must be approached with caution to avoid bone punctures and intraosseous injections (see also Chapters 57 and 58).

Cerebral Palsy

Cerebral palsy is a nonprogressive motor impairment arising from lesions in the brain that occurred during the early stages of development—in utero (75%), at birth (10%), and soon after birth (15%) (see also Chapter 93). The cause of cerebral palsy remains unclear; however, intrapartum asphyxia, which was originally thought to be the major cause of the disease, may be responsible for only 10% of the cases. Perioperative infections and low birth weight may play a much more important role. Cerebral palsy is divided into four major classifications to describe the different movement impairments: spastic, athetoid/dyskinetic, ataxic, and mixed. Spastic cerebral palsy, which is the most common type, results from

damage to the corticospinal tract, motor cortex, or pyramidal tract. Many of these affected children also have epilepsy and cognitive disorders.[59]

Although the neurologic deficit in cerebral palsy is nonprogressive, the secondary orthopedic consequences of the disease lead these patients to multiple surgical procedures. Normal skeletal development requires stress from the musculature to attain proper shape and size. Without these stresses or with abnormal stresses, as in cerebral palsy, various angular joint deformities and gracile (thin) shafts and abnormal articular joints develop. Orthopedic surgeries often involve loosening of tight muscles (hip adductor and iliopsoas release), releasing fixed joints, straightening abnormal twists (derotational osteotomy of the femur), rhizotomies to reduce spasm, and spinal surgery to correct kyphoscoliosis.

Patients with cerebral palsy have significant gastroesophageal reflux and poor laryngeal reflexes, placing them at risk for pulmonary aspiration. In most cases, surgical procedures in patients with cerebral palsy require general anesthesia with tracheal intubation, even if also accompanied by regional anesthesia to reduce the need for systemic anesthetics and to provide postoperative analgesia. Postoperative epidural analgesia with local anesthetic alone eliminates the potential complications of opioids and permits continued dosing with diazepam to relieve spasms. Regional anesthesia also may shorten emergence from general anesthesia, which can be prolonged because of inherent cerebral damage and the effects of antiseizure medications. Postoperative pulmonary complications are common owing to multiple causes, including aspiration, poor respiratory effort, and reduced thoracic compliance. After major surgical procedures, cerebral palsy patients should be observed in a monitored setting for several hours.

REGIONAL VERSUS GENERAL ANESTHESIA

Many orthopedic procedures are well suited for regional anesthetic techniques (see also Chapters 57 and 92). The controversy as to whether regional anesthesia has an advantage over general anesthesia has been debated for decades without clear evidence documenting the superiority of one method. Regional anesthesia may reduce the incidence of major perioperative complications with certain surgical procedures, however, including deep vein thrombosis (DVT), pulmonary embolism (PE), blood loss, respiratory complications, and death.[60-62] In addition, regional anesthetic techniques provide superior pain relief after orthopedic surgery.[63] Peripheral nerve blocks employing long-acting anesthetics or catheters provide both excellent intraoperative anesthesia and superior postoperative analgesia.[64,65] Regional anesthesia may provide preemptive analgesia, and some evidence exists that regional analgesia may block the progression of severe acute postoperative pain into a chronic pain syndrome.[66] In addition to improved pain control, functional outcome in the form of physical therapy milestones may benefit from both regional anesthesia and analgesia.[67]

As stated earlier, orthopedic patients often pose difficult airway management problems. Regional anesthesia avoids manipulation of the airway, and conscious patients can aid in the safest and most comfortable positioning for surgery. It is prudent, however, to recognize the warnings of Benumof[68]: "Use of regional anesthesia in the patient with a recognized difficult airway does not solve the problem of the difficult airway; it is still there." A well-defined plan for the management of the airway must be devised for these patients in the event of a regional anesthetic failure or the need to secure the airway during an emergency.

A further advantage to the use of regional anesthetic techniques for orthopedic surgery has been the suggestion of decreased intraoperative blood loss. Since 1966, 17 randomized trials of patients undergoing THA have shown diminished blood loss with regional anesthesia compared with the same procedure performed under general anesthesia.[69] Modig[70] compared blood loss in patients undergoing THA randomly assigned to epidural anesthesia, general anesthesia with spontaneous ventilation, and general anesthesia with positive-pressure ventilation. The epidural group showed the smallest blood loss, but no significant relationship between arterial blood pressure and blood loss was identified. The authors suggested that epidural anesthesia reduces venous blood pressure (measured in the operative wound), which is the significant factor in determining surgical bleeding.

PERIOPERATIVE MANAGEMENT OF ORTHOPEDIC PATIENTS

THROMBOPROPHYLAXIS IN ORTHOPEDIC SURGERY

Thromboembolic complications remain one of the leading causes of morbidity and mortality after orthopedic surgery.[71,72] THA, total knee arthroplasty (TKA), and hip and pelvic fracture surgery have the highest incidence of venous thromboembolism, including DVT and PE. Patients with DVT and PE are at risk for short-term and long-term morbidity and mortality. Patients with a symptomatic PE have an 18-fold higher risk for death than patients with a DVT alone. The short-term complications of survivors of acute DVT and PE include prolonged hospitalization, bleeding complications related to DVT and PE treatments, local extension of the DVT, and further embolization. Long-term complications include postthrombotic syndrome (hypoxemia and pulmonary hypertension) and recurrent DVTs.

Because venous thrombi consist of fibrin polymers, anticoagulants should be administered for the prevention and treatment of DVT. Thrombolytics should be administered only in the event of a severe, possibly fatal PE. Perioperative treatment should follow the guidelines of the Ninth American College of Chest Physicians Conference on postoperative DVT and PE.[73-74] Low-molecular-weight heparin (LMWH) is recommended over unfractionated heparin (intravenous or subcutaneous) for initial therapy of DVT and PE. LMWHs do not require monitoring for the degree of anticoagulation. Although DVT prophylaxis may be more efficient when started preoperatively, the risk for surgical bleeding also increases. LMWH for thromboprophylaxis should be started either 12 hours or more preoperatively, or 12 hours or more postoperatively,

rather than within 4 hours or less preoperatively or 4 hours or less postoperatively (grade 1B).[74,75] Extended prophylaxis to 35 days after surgery in the outpatient period would be supported in most patients undergoing major orthopedic surgery (grade 2B).[74] Risk factors for the development of PE after surgery are advanced age, obesity, previous PE and DVT, cancer, prolonged bed rest, and thrombophilia. Thombophilia is a prothrombotic condition that increases the risk for perioperative DVT. Many are hereditary conditions that increase the activity of coagulation factors. Factor V Leiden is the most common hereditary thrombophilia associated with DVT. Warfarin (Coumadin) is often employed in the long-term treatment of DVT, with a target international normalized ratio (INR) of 2.5 maintained for the duration of therapy. Warfarin exerts its anticoagulant effect by blocking vitamin K–dependent coagulation factors (predominantly factor VII); thus a lag occurs in biologic effectiveness while endogenous factor activity decays and new inactive factors are synthesized. Therefore, because the anticoagulation effects of warfarin may take days and its biologic activity can be unpredictable, many have advocated the use of LMWH. In the United States, LMWH (enoxaparin) is administered at 30 mg every 12 hours, and considerably higher doses of LMWH are administered for DVT treatment. In all cases, spinal hematoma is a risk after neuraxial anesthesia.

Recently alternatives to warfarin and LMWH have been developed. Fondaparinux, a synthetic pentasaccharide, is a selective inhibitor of factor Xa and has a plasma half-life of approximately 18 hours. When administered once daily, fondaparinux produces a predictable anticoagulant response.[76] Dabigatran is a thrombin inhibitor with a plasma half-life of approximately 8 hours, which is prolonged in individuals with renal insufficiency. Dabigatran will prolong the activated partial thromboplastin time, but this effect is not linear and should not be used as an indication of the degree of anticoagulation. At present, the only reversal agent available for dabigatran is recombinant factor VIIa.

The American College of Chest Physicians guidelines do not recommend the sole use of aspirin for DVT prophylaxis after THA, TKA, and hip fracture surgery. Some recent reports, however, have supported the use of aspirin, pneumatic compression, and early mobilization as the sole effective prophylaxis for DVT after THA and TKA.[77]

The use of perioperative anticoagulants has a significant impact on the use of regional anesthesia, in particular neuraxial anesthesia, with the potential risk for an epidural hematoma. The American Society of Regional Anesthesia (ASRA) published and updated consensus conference recommendations with regard to the use of anticoagulants and regional anesthesia.[78] Full anticoagulation is a contraindication to regional techniques. The risk for an epidural hematoma is significantly increased with the use of LMWH, so the ASRA issued the recommendations listed in Box 79-3.

Aspirin and NSAIDs do not appear to increase the risk for an epidural hematoma after neuraxial anesthesia.[79] The latest ASRA recommendations for patients receiving warfarin and other anticoagulants are listed in Box 79-4.

BOX 79-3 ***Anesthetic Management of the Patient Receiving Low-Molecular-Weight Heparin***

1. The anti-Xa level is not predictive of the risk for bleeding. We recommend against the routine use of monitoring of the anti-Xa level (grade 1A).
2. Antiplatelet or oral anticoagulant medications administered in combination with LMWH increase the risk for spinal hematoma. Education of the entire patient care team is necessary to avoid potentiation of the anticoagulant effects. We recommend against concomitant administration of medications affecting hemostasis, such as antiplatelet drugs, standard heparin, or dextran, regardless of LMWH dosing regimen (grade 1A).
3. The presence of blood during needle and catheter placement does not necessitate postponement of surgery. We suggest that initiation of LMWH therapy in this setting should be delayed for 24 hours postoperatively and that this consideration be discussed with the surgeon (grade 2C).
4. Preoperative LMWH.
   - Patients on preoperative LMWH thromboprophylaxis can be assumed to have altered coagulation. In these patients, we recommend that needle placement should occur at least 10 to 12 hours after the LMWH dose (grade 1C).
   - In patients receiving higher (treatment) doses of LMWH, such as enoxaparin 1 mg/kg every 12 hours, enoxaparin 1.5 mg/kg daily, dalteparin 120 units/kg every 12 hours, dalteparin 200 units/kg daily, or tinzaparin 175 units/kg daily, we recommend delay of at least 24 hours to ensure normal hemostasis at the time of needle insertion (grade 1C).
   - In patients administered a dose of LMWH 2 hours preoperatively (general surgery patients), we recommend against neuraxial techniques because needle placement would occur during peak anticoagulant activity (grade 1A).
5. Postoperative LMWH. Patients with postoperative LMWH thromboprophylaxis may safely undergo single-injection and continuous catheter techniques. Management is based on total daily dose, timing of the first postoperative dose and dosing schedule (grade 1C).
   - *Twice-daily dosing.* This dosage regimen is associated with an increased risk for spinal hematoma. The first dose of LMWH should be administered no earlier than 24 hours postoperatively, regardless of anesthetic technique, and only in the presence of adequate (surgical) hemostasis. Indwelling catheters should be removed before initiation of LMWH thromboprophylaxis. If a continuous technique is selected, the epidural catheter may be left indwelling overnight, but must be removed before the first dose of LMWH. Administration of LMWH should be delayed for 2 hours after catheter removal.
   - *Single-daily dosing.* The first postoperative LMWH dose should be administered 6 to 8 hours postoperatively. The second postoperative dose should occur no sooner than 24 hours after the first dose. Indwelling neuraxial catheters may be safely maintained. However, the catheter should be removed a minimum of 10 to 12 hours after the last dose of LMWH. Subsequent LMWH dosing should occur a minimum of 2 hours after catheter removal. No additional hemostasis-altering medications should be administered because of the additive effects.

From Horlocker TT, Wedel DJ, Rowlingson JC, et al: Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (third edition), Reg Anesth Pain Med *35:64-101, 2010.*

LMWH, Low-molecular-weight heparin.

BOX 79-4 *Regional Anesthetic Management of the Patient on Oral Anticoagulants*

1. Caution should be used when performing neuraxial techniques in patients recently discontinued from long-term warfarin therapy. In the first 1 to 3 days after discontinuation of warfarin therapy, the coagulation status (reflected primarily by factor II and X levels) may not be adequate for hemostasis despite a decrease in the INR (indicating a return of factor VII activity). Adequate levels of II, VII, IX, and X may not be present until the INR is within reference limits. We recommend that the anticoagulant therapy must be stopped (ideally 4 to 5 days before the planned procedure) and the INR must be normalized before initiation of neuraxial block (grade 1B).
2. We recommend against the concurrent use of medications that affect other components of the clotting mechanisms and may increase the risk for bleeding complications for patients receiving oral anticoagulants and do so without influencing the INR. These medications include aspirin and other NSAIDs, ticlopidine and clopidogrel, UFH, and LMWH (grade 1A).
3. In patients who are likely to have an enhanced response to the drug, we recommend that a reduced dose be administered. Algorithms have been developed to guide physicians in the appropriate dosing of warfarin based on desired indication, patient factors, and surgical factors. These algorithms may be extremely useful in patients at risk for an enhanced response to warfarin (grade 1B).
4. In patients receiving an initial dose of warfarin before surgery, we suggest that the INR should be checked before neuraxial block if the first dose was given more than 24 hours earlier or if a second dose of oral anticoagulant has been administered (grade 2C).
5. In patients receiving low-dose warfarin therapy during epidural analgesia, we suggest that their INR be monitored on a daily basis (grade 2C).
6. Neurologic testing of sensory and motor function should be performed routinely during epidural analgesia for patients on warfarin therapy. To facilitate neurologic evaluation, we recommend that the type of analgesic solution be tailored to minimize the degree of sensory and motor blockade (grade 1C).
7. As thromboprophylaxis with warfarin is initiated, we suggest that neuraxial catheters should be removed when the INR is less than 1.5. This value was derived from studies correlating hemostasis with clotting factor activity levels greater than 40%. We suggest that neurologic assessment be continued for at least 24 hours after catheter removal for these patients (grade 2C).
8. In patients with INR greater than 1.5 but less than 3, we recommend that removal of indwelling catheters should be done with caution and the medication record reviewed for other medications that may influence hemostasis that may not affect the INR (e.g., NSAIDs, ASA, clopidogrel, ticlopidine, UFH, LMWH) (grade 2C). We also recommend that neurologic status be assessed before catheter removal and continued until the INR has stabilized at the desired prophylaxis level (grade 1C).
9. In patients with an INR greater than 3, we recommend that the warfarin dose be held or reduced in patients with indwelling neuraxial catheters (grade 1A). We can make no definitive recommendation regarding the management to facilitate removal of neuraxial catheters in patients with therapeutic levels of anticoagulation during neuraxial catheter infusion (grade 2C).

From Horlocker TT, Wedel DJ, Rowlingson JC, et al: Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (third edition), Reg Anesth Pain Med *35:64-101, 2010.*

ASA, Acetylsalicylic acid; *INR,* international normalized ratio; *LMWH,* low-molecular-weight heparin; *UFH,* unfractionated heparin.

LOWER EXTREMITY SURGERY

Arthroscopy

Arthroscopic procedures for the knee, hip, and ankle are increasingly performed as ambulatory procedures (see also Chapter 89). These cases can be particularly challenging for the anesthesiologist who must decide on the appropriateness of the patient and procedure for outpatient surgery and an anesthetic that is adequate for the procedure, but also provides the patient's expectation of an uncomplicated postoperative recovery with minimal pain.

Limited data are available to determine which patients are inappropriate adult ambulatory patients. In most centers, morbidly obese patients and patients with sleep apnea require monitored observation overnight after procedures in which systemic anesthetics and analgesics have been administered.[33] The presence of stable preexisting disease does not increase the incidence of postoperative complications in ambulatory patients, but the American Society of Anesthesiologists (ASA) grade 3 and 4 patients should have a medical clearance that documents the stability of their medical conditions. It follows then that medically unstable patients are not outpatient surgical candidates.

In a prospective study of 1088 patients for ambulatory surgery, Pavlin and co-workers[80] reported that the most important factors in determining discharge time were pain, nausea and vomiting, unresolved neuraxial blocks, and urinary retention. This study emphasizes the role of anesthesia in prolonging ambulatory surgical stay. General anesthesia is a safe and effective anesthetic for arthroscopic surgery, but it has been associated with increased postoperative nausea and vomiting and pain. A properly designed regional anesthetic may reduce the importance of some of these factors.

Arthroscopic knee surgery can be performed with a combination of extraarticular and intraarticular injections of local anesthetics. Short-duration local anesthetics are often combined with longer acting local anesthetics (bupivacaine) and morphine to provide postoperative analgesia. Intraarticular morphine does not provide significant additional analgesia after arthroscopic knee surgery. For more involved arthroscopic procedures, such as an anterior cruciate ligament repair, surgical relaxation is also required. Spinal anesthesia with pencil-point atraumatic needles to prevent postdural puncture headaches provides excellent operating conditions for these procedures.

Problems related to neuraxial anesthesia for ambulatory surgery include unpredictable onset and regression of the spinal blockade, urinary retention, and transient neurologic symptoms (TNS). A dose of 45 mg of isobaric spinal mepivacaine results in a mean motor block of 142 ± 37 minutes. Using 30 to 40 mg of spinal chloroprocaine, Yoos and Kopacz[81] reported 155 ± 34 minutes to ambulation in outpatient surgical patients. TNS are

symptoms of pain in the gluteal region that can radiate down both legs and appear within a few hours to 24 hours after an uneventful spinal anesthetic.[82,83] The incidence of TNS is more frequent after outpatient surgery performed in the lithotomy position and in patients undergoing knee arthroscopy. The pain can vary from mild to severe, last 2 to 5 days, and is best treated with NSAIDs. TNS is more common after a spinal anesthetic with lidocaine (~14%) than with mepivacaine (6.5%) and bupivacaine (<1%). For ambulatory patients, the benefit of short-acting spinal anesthetic must be weighed against the risk for developing TNS. For postoperative analgesia after anterior cruciate ligament repairs, a femoral nerve block with a long-acting local anesthetic is superior to intraarticular injections. Because the quadriceps muscle is blocked, it is important for the patient to be fitted with a knee brace before ambulation. Blocking the saphenous nerve in the adductor canal may provide postoperative analgesia without also interfering with early ambulation.[84]

Hip arthroscopy has become a common outpatient procedure for the diagnosis and treatment of pathologic processes in the hip. The patient can be placed in either the supine or the lateral position (operative side up) with 50 to 75 lb of traction applied to the operative limb to gain access to the joint with the arthroscope. In positioning the patient, the anesthesiologist must ensure that the perineal post is padded and not compressing the pudendal nerve and that excessive traction for prolonged periods is not applied (see also Chapter 41). Because complete muscle relaxation is required for the procedure, the patient must have either a general anesthetic or a neuraxial block. A lumbar plexus block can be performed for postoperative analgesia.

Hip Fractures

Hip fractures in older individuals are common (1 in 50 individuals older than 60 years of age), and as previously stated are associated with significant morbidity and mortality (1-year mortality of 30%).[5] The high perioperative complication rate is related to many factors, including cardiac conditions, pulmonary conditions, DVT, and delirium. Postoperative confusion and delirium are common, reported in 50% of older patients after the repair of hip fractures and associated with increased mortality.[34-36] In many cases, dehydration and electrolyte abnormalities contributed to this delirium. In one study, the incidence of hyponatremia was 4% and was associated with a sevenfold increase in hospital mortality.[85]

These patients often arrive in the hospital in pain and under considerable stress, which may elicit signs and symptoms of myocardial ischemia. Although preoperative preparation is essential, delaying surgery may exacerbate these problems and increase the incidence of complications. Early surgery (<12 hours) has resulted in lower pain scores, decreased length of hospital stay, and reduced perioperative complications.[86] However, early surgery has not been associated with increased overall survival in contrast to delaying surgery. Using geriatric services has been shown to improve outcomes, especially better lower limb function.[87]

Patients with hip fracture are often dehydrated and anemic because the fracture site can accommodate considerable extravasated blood. Blood hematocrit values are often normal because of the contracted blood volume in a dehydrated patient. A normal intravascular blood volume should be restored before anesthesia and surgery; this is best achieved with central venous catheter monitoring. Central venous catheter monitoring also may prevent overhydration, which can precipitate congestive heart failure. Placement of an arterial catheter permits accurate blood pressure monitoring during surgery and the ability to follow serial arterial blood gases. Hypoxemia, possibly owing to fat embolization, has been a major determinant of mortality in these patients.

Several studies have reported improved outcome with regional anesthesia compared with general anesthesia in these patients.[61] Patients undergoing hip fracture surgery have the greatest risk for death from a PE.[71] In a meta-analysis of patients undergoing the repair of femoral neck fractures, the incidence of DVT was almost four times greater in the patients who received general versus regional anesthesia.[88] A spinal anesthetic with isobaric 0.5% bupivacaine provides a stable regional anesthetic of sufficient duration to complete the surgical repair. Epidural anesthesia with postoperative analgesia is usually not indicated, because in most cases aggressive postoperative anticoagulation is instituted.[73] Intravenous sedation during the procedure must be coupled with the ability of the patient to remain adequately oxygenated. Long-acting benzodiazepines should be avoided because of their association with postoperative confusion. In many cases, these patients require postoperative monitoring in an ICU-like setting.

PELVIC FRACTURES

Pelvic fractures are often the result of significant trauma to the lower trunk and hence are accompanied by additional injuries, including chest (21%), head (16%), and liver and spleen (8%).[89] The 3-month mortality for pelvic fractures approaches 14%. Acute mortality directly related to the pelvic fracture may result from retroperitoneal bleeding. An indication for emergency exploratory surgery after a pelvic fracture would include persistent hypotension and increasing abdominal girth. Injuries to the bladder and urethra are also often associated with pelvic fractures; thus urology clearance is usually indicated before inserting a Foley catheter. Because there is a significant risk of DVT and PE, many of these patients require a temporary inferior vena cava filter before surgery.

Recent reports suggest that the optimal time for stabilization of a pelvic fracture is within the first week of trauma; however, associated injuries often delay the operation. An optimal anesthetic may be the combination of a general anesthetic with the placement of an epidural catheter for postoperative analgesia. Because iatrogenic sciatic nerve injury is the most frequent surgical complication (~18%), the use of intraoperative neuromuscular monitoring precludes dosing of the epidural catheter during the procedure and dictates waiting to dose the catheter until after the preservation of lower extremity movement and sensation has been confirmed. In most cases, these patients require monitoring with arterial and central venous catheters, as well as the placement of large-gauge venous catheters in the event of sudden surgical hemorrhage.

HIP AND KNEE ARTHROPLASTIES

As the population ages and remains physically active through their sixth decade, major orthopedic joint replacement procedures are increasingly more common. Between 1991 and 2010, the number of annual TKA procedures in Medicare patients increased 162% from 93,230 to 243,802.[90] The rate of major adverse events after hip and knee arthroplasties is 6.4%, and as stated earlier the most important risk factor is advanced age (see also Chapter 80).[4-10] The most common complications after THA and TKA are cardiac events, PE, pneumonia and respiratory failure, and infection.[5,10,91,92] Older patients with major comorbidities, including cardiac disease, pulmonary disease, and diabetes, should have a complete preoperative medical evaluation. In addition, obesity, particularly in a patient who has undergone TKA, can be a problem anesthetically, as well as postoperatively, with regard to OSA and infections.[33,92] Many of these patients require prolonged postoperative monitoring in the postanesthesia care unit or ICU (see also Chapter 96).

THA may be performed via an anterior or lateral approach. The anterior approach offers the advantage of exposure without violation of the muscles, but restricts full access to the femur, with the risk for lateral femoral cutaneous nerve injury. The lateral posterior approach provides excellent exposure to the femur and the acetabulum with minimal muscle damage, but increases the risk for posterior dislocation. Most surgeons prefer the lateral posterior approach, which places the patient in the lateral decubitus position, surgical side up, for the operation. The anesthesiologist must be aware that this position may compromise oxygenation, particularly in obese and severely arthritic patients, as a result of ventilation-perfusion mismatch. In addition, to prevent excessive pressure on the axillary artery and brachial plexus by the dependent shoulder, an anterior roll or pad must be placed beneath the upper thorax.

The nerve supply to the hip joint includes the obturator, inferior gluteal, and superior gluteal nerves. Regional anesthesia for THA is best achieved with a spinal or epidural anesthetic. Although most studies suggest decreased postoperative respiratory complications, including a reduction in the incidence of DVT and PE with regional anesthesia compared with rates in general anesthesia, some controversy still remains.[61] A lumbar paravertebral block may be used for postoperative analgesia when postoperative anticoagulation requires removal of the epidural catheter.[93]

Blood loss during THA can be significant, and with revision procedures the patient can lose 1 to 2 L of blood. Several studies have shown that controlled hypotensive epidural anesthesia with mean arterial blood pressures of 50 to 60 mm Hg can reduce intraoperative blood loss to as low as 200 mL for primary THAs.[94] Older patients (mean age 72 years) were able to tolerate this degree of blood pressure reduction without cognitive, cardiac, or renal complications.[95] In addition to reduced overall blood loss during THA, hypotensive anesthesia may improve the prosthesis-to-bone fixation by limiting bleeding in the femoral canal.[96] An intravenous bolus injection of tranexamic acid or intraoperative fibrin spray also have been shown to reduce blood loss after joint arthroplasty.[97]

The femoral prosthesis can be fixed to the femoral canal through methyl methacrylate cement or bony ingrowth. Cemented fixation of the femoral prosthesis has been complicated by the bone-cement implantation syndrome, which may result in intraoperative hypotension, hypoxia, and cardiac arrest and FES postoperatively (Fig. 79-6; see Fig. 79-2).[42-44] Several mechanisms have been suggested for these events, including embolization to the circulation of bone marrow debris during pressurization of the femoral canal, toxic effects of circulating methyl methacrylate monomer, and release of cytokines during reaming of the femoral canal that promote the formation of microthrombi with subsequent pulmonary vasoconstriction. The intravenous

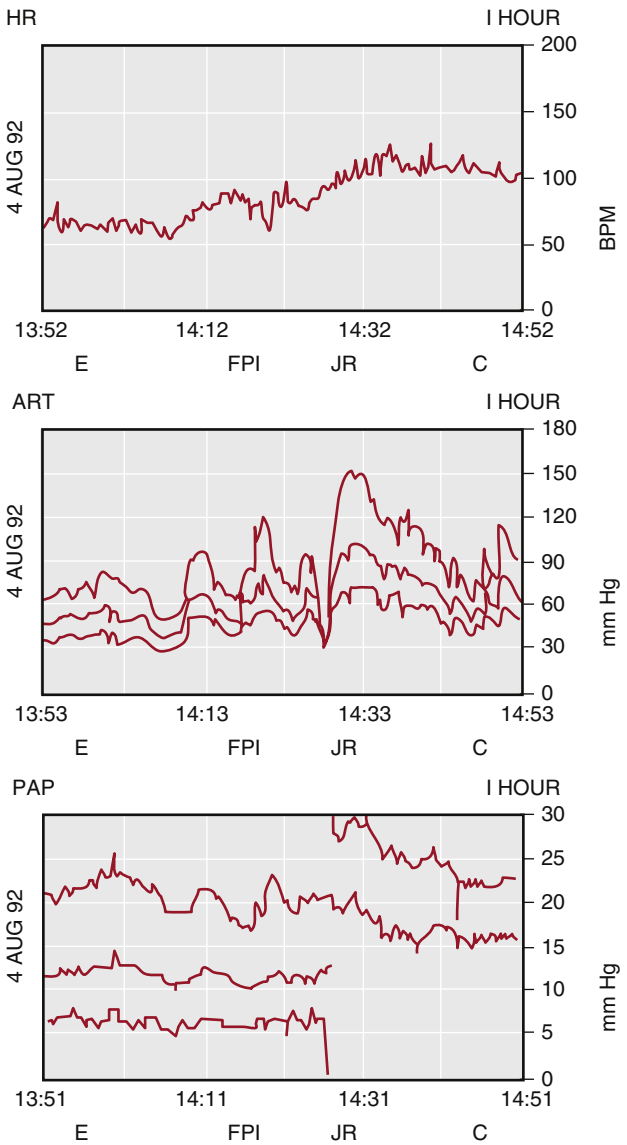


Figure 79-6. Intraoperative heart rate (*HR*), systemic arterial blood pressure (*ART*), and pulmonary arterial pressure (*PAP*) tracings of a patient undergoing revision total hip arthroplasty. *E,* Induction of epidural anesthesia; *FPI,* insertion of a cemented femoral prosthesis; *JR,* reduction of prosthetic hip joint, producing hypotension with rebound from epinephrine injection; *C,* wound closure. *(From Urban MK, Sheppard R, Gordon MA, et al: Right ventricular function during revision total hip arthroplasty,* Anesth Analg *82:1225-1229, 1996.)*

injection of the cement monomer in dogs induces systemic hypotension, but not most of the other systemic events, including myocardial depression, which are manifested during the FES.[98] The embolization of intramedullary debris is the most likely explanation for the FES, because this debris can be visualized in the right heart using TEE (see Fig. 79-2).

The hypotensive events that follow bone marrow embolization should be treated with epinephrine. In addition, the hemodynamic consequences of bone marrow embolization can be ameliorated through high-pressure pulsatile lavage of the femoral canal and drilling a vent hole in the femur before prosthesis insertion. Risk factors for this complication include revision surgery, a long-stem femoral prosthesis, THA for a pathologic fracture, preexisting pulmonary hypertension, and the quantity of cement used. These patients should be monitored with arterial and central venous catheters.

During THA, embolization of a blood thrombus is possible. The hip is dislocated and the femoral vein is probably obstructed during reaming and insertion of the femoral prosthesis, resulting in blood stasis and blood clot formation. With relocation of the hip and unkinking of the femoral vein, the embolic material generated is released into the circulation. At some institutions an intravenous bolus of heparin is administered before dislocation of the hip. TKA also is becoming a major orthopedic procedure in the aging population, and these patients require the same preoperative medical evaluation as outlined for patients undergoing THA. The innervation of the knee includes the tibial nerve, the common peroneal nerve, the posterior branch of the obturator nerve, and the femoral nerve. Although general anesthesia can be safely provided for TKA, a prospective case-controlled study found general anesthesia with endotracheal intubation to be a major risk for nonsurgical complications after TKA.[60] Regional anesthesia in the form of a neuraxial block (spinal or epidural) or a combination of a femoral and sciatic block can be provided for the surgery. However, in TKAs for valgus deformities, sciatic nerve blocks may prevent the early detection of sciatic and peroneal nerve palsies.

Patients who have undergone TKA have severe postoperative pain, and several studies have reported a reduction in postoperative complications and improved outcomes when this pain is managed with regional anesthesia.[99-101] Single-injection femoral nerve blocks in combination with intravenous and epidural patient-controlled analgesia have been employed to manage postoperative pain and improve functional recovery. When LMWH is used for DVT prophylaxis, the infusion of local anesthetics through continuous femoral nerve catheters may be used in place of patient-controlled epidural anesthesia.

A pneumatic tourniquet is routinely inflated over the thigh during TKA to reduce intraoperative blood loss and provide a bloodless field for cement fixation of the femoral and tibial components. When the tourniquet is deflated, however, blood loss begins and usually continues for the next 24 hours. Tourniquets are usually inflated to a pressure 100 mm Hg above the patient's systolic blood pressure for 1 to 3 hours. Nerve injury after extended tourniquet inflation (>120 minutes) has been attributed to the combined effects of ischemia and mechanical trauma. A peroneal nerve palsy, which is a recognized complication of TKA (incidence of 0.3% to 10%), may be caused by the combination of tourniquet ischemia and surgical traction.[102] Horlocker and colleagues[102] reported an incidence of combined tibial and peroneal nerve dysfunction in 7% of patients who had undergone TKA that was associated with younger age, the presence of preoperative flexion deformities, and longer total tourniquet times. When prolonged tourniquet inflations are required, deflating the tourniquet for 30 minutes of reperfusion may reduce neural ischemia.

Pain related only to tourniquet inflation also may occur after 60 minutes, despite the presence of a regional anesthetic that is adequate for the surgery. It has been postulated that tourniquet pain is caused by the unblocking of unmyelinated C fibers during recession of a neuraxial block. The addition of opioids to spinal or epidural anesthesia may ameliorate tourniquet pain. After tourniquet release, mean arterial blood pressure decreases significantly, partly owing to the release of metabolites from the ischemic limb into the circulation and the decrease in peripheral vascular resistance. In patients with known preexisting sciatic neurapraxias, neuropathic pain, and vascular disease in the operative leg, the operation can be performed without a tourniquet.

Many patients have symptomatic arthritis of both knees and require bilateral TKA to achieve functional improvement in pain and lifestyle. However, controversy still exists as to whether both knees should be replaced sequentially in a single operation (simultaneous bilateral total knee arthroplasty [SBTKA]) or as a two-staged procedure, usually separated by several months. The advantages of SBTKA include exposure to the risks of one anesthetic, one postoperative course of pain, reduced rehabilitation and hospitalization, and an earlier return to baseline function. However, SBTKA has been associated with a higher incidence of serious perioperative complications, including myocardial infarction, fat embolization, and thromboembolic events. Serious postoperative complications are more prevalent in older patients with cardiovascular disease.[102-106] Patients undergoing SBTKA also require increased numbers of blood transfusions, are more likely to be transferred to a rehabilitation center, and have a higher incidence of postoperative ICU admissions.

Two more recent reports suggest that SBTKA can be performed without major complications.[107,108] Urban and associates[107] reported that with regional anesthesia and aggressive clinical management, which included 24-hour postoperative monitoring in an ICU, patients undergoing SBTKA had a major complication rate similar to that in matched control patients undergoing unilateral TKA, with a significantly higher incidence of FES and cardiac arrhythmias than patients undergoing unilateral TKA, possibly because of an enhanced inflammatory response.[109] Using published reports of patients who underwent SBTKA and who were at risk for postoperative complications, Urban and associates[107] published guidelines for the exclusion of patients from SBTKA (Box 79-5).

BOX 79-5 ***Patients Excluded for Single Operation for Bilateral Total Knee Arthroplasty***

Age ≥75 years
ASA class III
Active ischemic heart disease (positive stress test)
Poor ventricular function (LVEF <40%)
Oxygen-dependent pulmonary disease
Patients considered at increased risk for morbidity and mortality
- IDDM
- Renal insufficiency
- Pulmonary hypertension
- Steroid-dependent asthma
- Morbid obesity (BMI >40)
- Chronic liver disease
- Cerebrovascular disease

ASA, American Society of Anesthesiologists; *BMI,* body mass index; *IDDM,* insulin-dependent diabetes mellitus; *LVEF,* left ventricular ejection fraction.

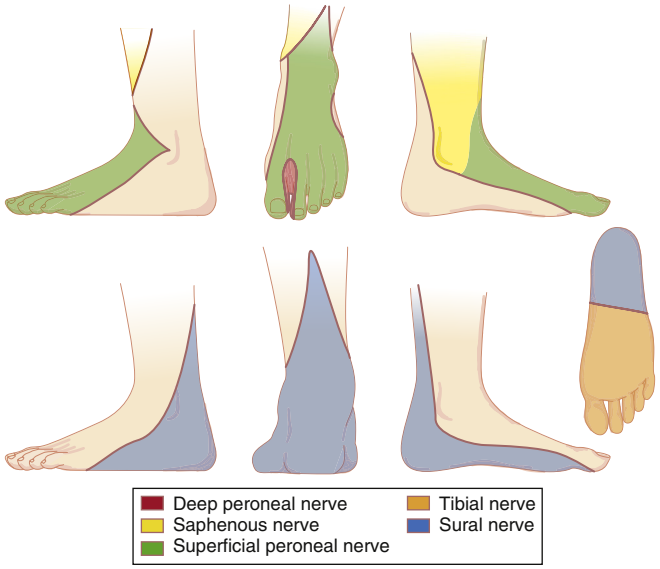


Figure 79-7. Cutaneous distribution of anesthesia produced by an ankle block. *(From Carron H, Korborn GA, Rowlingson JC:* Regional anesthesia: techniques and clinical applications, *New York, 1984, Grune & Stratton.)*

FOOT AND ANKLE SURGERY

Regional anesthesia that combines sciatic and femoral nerve blocks is sufficient for all surgical procedures below the knee that do not require a thigh tourniquet. The femoral nerve innervates the medial leg to the medial malleolus, and the remainder of the leg below the knee, including the foot, is innervated by the common peroneal nerve and tibial nerve, both branches of the sciatic nerve. The sciatic nerve is usually blocked high in the popliteal fossa to ensure anesthesia to the tibial and peroneal nerves. The nerves are identified through the use of a nerve-stimulating needle with foot inversion as the motor response or with ultrasound guidance. For procedures that also involve the medial aspect of the leg, the femoral nerve (saphenous nerve) can be blocked on the medial aspect of the leg, just below the knee. The popliteal sciatic nerve block has been shown to reduce postoperative pain and opioid requirements after foot and ankle surgery, when performed as a single preoperative injection or as a continuous catheter infusion.[109-112]

Acute compartment syndrome exists when edema and blood accumulate within a confined osseofascial space, compromising the circulation and tissues within that space.[113,114] If not treated promptly, the pressure in the compartment leads to muscle and nerve ischemia and necrosis, with potential loss of limb. Compartment syndrome can occur after fractures of the tibia, followed less commonly by fractures of the femur and ankle. Delay in diagnosis and treatment (surgical decompression) is the most common cause of serious complications. Pain out of proportion to the clinical situation is the usual early symptom. Thus, after the surgical repair of tibial and ankle fractures, a discussion with the surgeon with regard to the risk for compartment syndrome should occur before administering long-acting sciatic nerve blocks.

The ankle block is used for surgical procedures on the foot that do not require the use of a thigh tourniquet, although an ankle-level Esmarch tourniquet may be used. Because the block is primarily an infiltrative block, it usually is not performed by eliciting a paresthesia.

Five terminal nerves are usually blocked to provide complete anesthesia to the foot: (1) posterior tibial nerve, which provides sensation to the plantar surface; (2) saphenous nerve, which innervates the medial malleolus; (3) deep peroneal nerve, which supplies the interspace between the great and second toes; (4) superficial saphenous nerve, which supplies the dorsum of the foot and the second through the fifth toes; and (5) sural nerve, which supplies the lateral foot and lateral fifth toe (Fig. 79-7). Mineo and Sharrock[115] reported that the ankle block performed at the midtarsal level with 30 mL of 0.75% bupivacaine provided a mean duration of 17 hours of analgesia with safe blood levels of local anesthetic.

UPPER EXTREMITY SURGERIES

Surgery for the upper extremity, from the shoulder to the hand, can be performed successfully by blocking the brachial plexus at several points until it branches into peripheral nerves (Table 79-3). Several methods are used to document the optimal location for neural blockade of the brachial plexus, including eliciting a paresthesia, motor nerve stimulation, ultrasound guidance, and perivascular infiltration. Regional anesthesia for the upper extremity also can provide postoperative analgesia using long-acting local anesthetics or continuous catheter techniques.

Regional anesthesia for shoulder surgery (see also Chapters 57 and 58) has not gained wide acceptance because of the thought by anesthesiologists and surgeons that it is often inadequate for surgical anesthesia and the concern for postoperative neurologic symptoms (PONS). Several studies have reported 97% or greater successful surgical anesthesia using the interscalene block (ISB) approach to the brachial plexus with documentation of a paresthesia or the use of a nerve stimulator or ultrasound guidance to locate the optimal site of injection.[116-119]

TABLE 79-3 BRACHIAL PLEXUS ANESTHESIA

Site of Block	Stimulated Brachial Plexus	Response
Interscalene	Roots, trunks	Shoulder to hand
Supraclavicular	Trunks (middle, inferior)	Upper arm to hand
Infraclavicular	Lateral cord	Forearm flexion
		Hand pronation
	Posterior cord	Wrist extension
	Medial cord	Fingers and thumb
Axillary	Median nerve	Forearm pronation
		Wrist flexion
	Ulnar nerve	Finger flexion
		Thumb opposition
	Radial nerve	Wrist extension

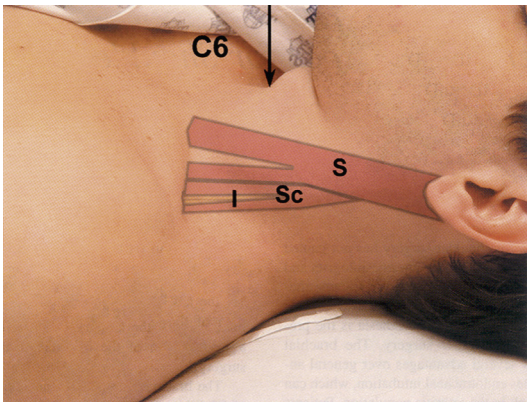


Figure 79-8. Interscalene approach to brachial plexus. At the level of the cricoid cartilage (*C6*), the anesthesiologist's finger is rolled laterally from the posterior border of the sternocleidomastoid muscle (*S*) into the interscalene groove (*I*) between the anterior and middle scalene muscles (*Sc*). The needle is inserted at point *I* and directed 45 degrees caudad and perpendicular to all planes. *(From Urban MK: The interscalene block for shoulder surgery,* Tech Shoulder Elbow Surg *5:61-65, 2004.)*

The brachial plexus is formed from the ventral rami of C5-T1 nerve roots. After these roots pass between the anterior and middle scalene muscles, they fuse into three trunks (superior C5-6, middle C7, inferior C8-T1). During performance of the ISB, local anesthetic is injected between the scalene muscles at the level of the cricothyroid notch (C6) (Fig. 79-8).

The major acute complications and side effects associated with ISB are respiratory depression, intravascular injection with seizures and cardiac arrest, pneumothorax, epidural and spinal anesthesia, Horner syndrome, hoarseness, and dysphagia. The ipsilateral phrenic nerve is blocked in all patients undergoing ISB, resulting in hemidiaphragmatic paresis.[120] Because hemidiaphragmatic paresis may result in a 25% reduction in pulmonary function, patients with severe respiratory disease may not tolerate an ISB without the addition of mechanical ventilation. An ISB would be contraindicated in patients after pneumonectomy on the contralateral side and for bilateral operative procedures. The supraclavicular approach to the brachial plexus with ultrasound guidance may provide effective shoulder anesthesia without complete ipsilateral paresis of the phrenic nerve.[121]

TABLE 79-4 INTERSCALENE BLOCK COMPLICATIONS: POSTOPERATIVE NEUROLOGIC SYMPTOMS

Reference	Acute Symptoms (%)	Chronic Symptoms (%)
Conn et al[122]	—	2
Urban and Urquhart[116]	9	0.4
Borgeat et al[123]	14	0.2
Faryniarz et al[118]	1.4	0
Liguori et al[117]	10	0

Because of the proximity to major vascular structures (vertebral artery, carotid artery, jugular vein), CNS toxicity is usually cited as a major risk of ISB. The reported incidence of CNS effects has been very low, however. Conn and associates[122] reported that ISB resulted in 3 of 100 patients experiencing CNS symptoms and only one seizure. Urban and Urquhart[116] reported that 2 of 266 patients had CNS symptoms and none had seizures.

PONS related directly to brachial plexus anesthesia is often cited as the reason to avoid regional anesthesia for shoulder and hand surgery. The few large studies that have attempted to ascertain the extent of nerve injury associated with ISB have concluded that although some patients may have neurologic issues after surgery, many of the problems cannot be attributed to the anesthetic and most of them resolve (Table 79-4). In the retrospective study by Conn and associates,[122] 2 of 100 patients had PONS that persisted for 7 months and 18 months, respectively. In the prospective analysis of 266 patients by Urban and Urquhart,[116] 9% reported paresthesias on the day after surgery, two thirds of which resolved after 2 weeks and one that persisted beyond 6 weeks. Liguori and colleagues[117] reported the incidence of PONS after ISB performed with either the documentation of a paresthesia (10 of 108) or the use of a nerve stimulator (11 of 109), with a median duration of 2 months and resolution of all cases of PONS within 1 year.

Arthroscopic shoulder surgery is often performed in the sitting (beach chair) position. Hypotensive and bradycardic events, some progressing to asystolic arrest, have been associated with shoulder surgery in the sitting position under regional anesthesia.[124] There is some evidence that these events are the result of a cardiac inhibitory reflex, the Bezold-Jarisch reflex, which occurs in response to diminished ventricular volume (venous pooling in the sitting position) and a hypercontractile ventricle. Prophylactic administration of β-blockers, anxiolytics, and intravenous fluids reduces the incidence of these events.[125]

For surgery from the elbow to the hand, the brachial plexus can be blocked via either the infraclavicular block approach or the axillary approach. Blockade of the nerves to the arm at the axilla can be achieved by a transarterial technique or the stimulation of a single nerve or multiple nerves. Advocates of the multiple paresthesia technique cite the report by Thompson and Rorie,[126] which states that within the axillary sheath the nerves are separated by discrete septa. Using a transarterial approach, Urban and Urquhart[116] reported a success rate of 93%. Advocates of the paresthesia or nerve stimulator technique for

the axillary block argue that the transarterial approach may produce a hematoma with the potential for ischemic damage to the brachial plexus. When the transarterial axillary block was used in 242 patients for forearm and hand surgery, 23% of the patients complained of tenderness and bruising at the axilla, and 19% had acute PONS.[116]

The infraclavicular block to the brachial plexus may be the best approach for elbow surgery, and it may result in less patient discomfort and PONS when used for forearm and hand surgery compared with the axillary approach, although objective evidence is still lacking.[127,128] Using the nerve stimulator technique, two large series of infraclavicular blocks reported 90% to 94% success with only posterior cord stimulation, whereas other reports still recommend a double stimulation technique. Performing the infraclavicular block with ultrasound guidance may avoid the need for multiple needle passes and the complications of vascular puncture and pneumothorax.[129]

Forearm and hand surgery also can be performed under intravenous regional anesthesia. Intravenous regional anesthesia is a simple technique that involves exsanguinating the arm by wrapping it with a tight band, inflating an upper arm tourniquet to approximately 250 mm Hg, and injecting in a hand vein approximately 50 mL of a short-acting local anesthetic (0.5% lidocaine). A second tourniquet, proximal to the first, is often inflated 15 minutes later with subsequent deflation of the first, to minimize tourniquet pain. This technique is limited to short surgical procedures (~1 hour). Complications occur when the tourniquet fails during initial anesthetic injection or the tourniquet is deflated early (<30 minutes), risking systemic local anesthetic toxicity.

SPINAL SURGERY

In the United States with an active, aging population, 4.6 million individuals will require spinal surgery at some time during their life. Spinal surgery includes a wide variety of procedures ranging from a microdiskectomy for a herniated disk to complex reconstructive surgery for spinal deformities. These procedures can be simple or involve fusions at multiple levels, anterior or posterior approaches, and considerable blood loss. A few procedures, such as a diskectomy, can be performed under regional anesthesia.[130]

Most spinal surgeries require general anesthesia. In this patient population with preexisting arthritic conditions, tracheal intubation often poses a challenge (Box 79-6). Awake, sedated fiberoptic intubation of many of these patients is the safest approach to general anesthesia. This is the standard of care in a patient with cervical spinal instability who requires posterior stabilization. These patients should be intubated first with a flexible fiberoptic bronchoscope, then positioned prone for surgery sedated but awake (if possible) and assessed for movements of upper and lower extremities before the induction of general anesthesia. Some patients with reduced but stable cervical mobility, may be intubated using glide scope technology after the induction of general anesthesia.

The careful positioning of patients for spinal surgery is an important shared responsibility of the anesthesiologist and surgeon (see also Chapter 41). As stated previously, patients at risk for spinal cord compression should be positioned under light sedation, then observed for upper and lower extremity movement before inducing general anesthesia. Because some posterior cervical spine decompressions are done in the sitting position, preparations must be made for the possibility of a venous air embolism. Complex spinal deformity procedures often require anterior and posterior approaches to the spine. For a low lumbosacral anterior approach, the patient is supine with the legs spread wide. Pelvic retraction during this procedure may compromise blood flow to the legs, and a pulse oximeter placed on a toe may be used as a monitor for compromised lower extremity blood flow. Patients undergoing anterior thoracolumbar procedures are usually positioned in the lateral decubitus position, in which attention must be focused on the dependent arm and leg and the position of the neck. Table 79-5 outlines possible complications from prone positioning for these spinal procedures.

Postoperative airway management in patients after single-stage multilevel anterior, posterior, or both cervical spinal decompressions and fusions should be a major concern of the anesthesiologist. Postoperative complications include dysphagia (12%), dysphonia (4%), and

BOX 79-6 ***Predictors of a Difficult Endotracheal Intubation***

Facial dissymmetry (trauma)
Tracheal deviation
Cervical fractures
Small mouth opening (interincisor gap)
Inability to visualize the faucial pillars and uvula (Mallampati)
Limited neck range of motion
Prominent incisors
Distance between thyroid cartilage and mandible less than 6 cm
Narrow maxillary arch

TABLE 79-5 COMPLICATIONS OF THE PRONE POSITION*

Airway	ETT kinking, dislodgment Upper airway edema
Neck	Hyperextension or hyperflexion Cervical rotation—compromised blood flow to brain
Eyes	Orbital pressure—central retinal artery occlusion, supraorbital nerve Corneal abrasion
Abdomen	Pressure transmitted to epidural veins, increased bleeding
Upper extremity	Brachial plexus stretch—arms out Ulnar nerve compression—arms at the side
Lower extremity	Flexion of hips—occlusion of femoral vein, DVT, kinking of vascular grafts Pressure lateral to fibula—peroneal nerve palsy Pressure on iliac crest—lateral femoral cutaneous nerve

*See Chapter 41.
DVT, Deep vein thrombosis; *ETT,* endotracheal tube.

airway compromise (up to 14%).[131] Tissue trauma from the procedure often causes airway edema, which can progress to complete airway obstruction. Reported risk factors for postoperative respiratory complications are length of surgery, volume of infused crystalloid, obesity, revision surgery, four or more levels fused, and fusion of C2. A protocol for the management of these patients should be established such that patients at risk for postoperative airway complications are monitored with emergency airway equipment and specialists available and/or the patients kept intubated overnight and extubated when upper airway edema has subsided.

Posterior lumbar fusions for degenerative disk disease are often accompanied by anterior fusions to stabilize the surgical area and increase the success of the fusions. The anterior open procedures have recently been replaced in many cases by minimally invasive techniques, including transperitoneal anterior lumbar interbody fusion and extreme lateral interbody fusion.[131] To reduce the risk for nerve root injury during disk excision, intraoperative electromyographic monitoring is used, which precludes the use of neuromuscular blocking drugs. Large-bore venous access out of proportion to the usual blood loss should be secured in these patients, because the techniques are performed in close proximity to major vascular structures that are at risk for iatrogenic injury.

Complex corrective surgery of the spine includes patients with scoliosis, kyphosis, kyphoscoliosis, and revision surgery on patients with previous thoracolumbar fusions. Kyphosis is an exaggerated anterior flexion of the spine, as seen in ankylosing spondylitis. Scoliosis is defined as a lateral rotation of the spine greater than 10 degrees accompanied by vertebral rotation. Scoliosis is classified as idiopathic, congenital, or neuromuscular. Congenital scoliosis is the result of early embryonic errors in vertebral column formation, and half of the cases are associated with other organ system anomalies. Adolescent idiopathic scoliosis is common, present in 2% to 4% of children 10 to 16 years of age. Only 10% of these adolescents have curves that require some type of medical intervention. Surgical intervention occurs when the curve magnitude estimated by the Cobb method is more than 40 degrees (Fig. 79-9) and the likelihood of curve progression is strong. Most idiopathic scoliosis curves are right-sided; a left thoracic curve is more likely to be associated with other thoracic anomalies.

Thoracic scoliosis results in a narrowed chest cavity producing a decrease in chest wall compliance and restrictive lung disease. Cobb angles of greater than 65 degrees usually cause significant decreases in lung volumes. Although exercise tolerance is an important determinant of the effects of the severity of the curve on respiratory function, formal pulmonary function studies should be obtained before surgery. This information guides decisions regarding the extent of surgery permitted at one time and the requirement for postoperative ventilatory support. A vital capacity of less than 40% of the normal range is predictive of the requirement for postoperative ventilation. The major abnormality in arterial blood gases is hypoxemia, secondary to ventilation-perfusion inequalities caused by alveolar hypoventilation.



Figure 79-9. Radiograph of a patient with scoliosis. The Cobb angle is an angle formed by a line drawn perpendicular to the top of the superior vertebra of the scoliotic curve and a similar perpendicular line drawn along the bottom of the inferior vertebra. The Cobb angle in this patient is 62 degrees. *(From Reamy BV, Slakey JB: Adolescent idiopathic scoliosis: review and current concepts,* Am Fam Med *64:1-10, 2001.)*

Chronic hypoxemia produces elevated pulmonary vascular resistance, which ultimately leads to cor pulmonale. An echocardiogram should be assessed for pulmonary hypertension and right ventricular hypertrophy. In patients with pulmonary hypertension, the electrocardiogram may reveal evidence of right ventricular hypertrophy and right atrial enlargement.

Surgical spinal corrections involving high anterior thoracic levels or video-assisted thoracoscopic surgery require the isolation of one lung. One-lung ventilation traditionally has been achieved with a double-lumen endotracheal tube. In single-staged anterior then posterior spinal fusions and for postoperative ventilation, the double-lumen endotracheal tube must be replaced with a single-lumen endotracheal tube. A single-lumen endotracheal tube with an enclosed bronchial blocker also can provide one-lung ventilation, but has the advantage of being left in place as a single-lumen endotracheal tube with the blocker deflated at the end of the anterior procedure.[132] In patients with restrictive lung disease, adequate oxygenation may be difficult during one-lung ventilation and may require continuous positive airway pressure to the nonventilated lung and positive end-expiratory pressure to the ventilated lung.

Surgery for the correction of spinal deformities is usually associated with large blood losses. Multiple factors have been suggested to influence the magnitude of this blood loss, including surgical technique, operative time, number of vertebral levels fused, anesthetics, mean arterial blood pressure, platelet abnormalities, dilutional coagulopathy, and primary fibrinolysis.[133] Several techniques have been employed to reduce this blood loss and limit the need for homologous blood transfusions, including proper positioning of the patient to reduce intraabdominal pressure, surgical hemostasis, deliberate

controlled hypotensive anesthesia, reinfusion of salvaged blood, intraoperative normovolemic hemodilution, use of pharmacologic agents that promote clot formation, and preoperative donation of autologous blood.

Controlled hypotensive anesthesia has been used commonly in limiting blood loss during idiopathic scoliosis corrections in adolescents, but must be used with caution in older patients.[134] In a young healthy patient, a mean arterial pressure of 50 to 60 mm Hg is well tolerated, but higher pressures may be required in adult patients with cardiovascular disease. In addition, perfusion of the spinal cord during deformity-correcting surgery may be exquisitely sensitive to low perfusion pressures. The adequacy of end-organ perfusion can be estimated with invasive monitoring, a urine output of 0.5 to 1 mL/kg/hr, and periodic blood gas analysis looking for evidence of metabolic acidosis.[135] In addition, central venous oxygen saturation with an arterial blood gas provides an indication of end-organ oxygen supply and demand. Although an increase in heart rate during hypotensive anesthesia may indicate anemia, hypovolemia or "light" anesthesia, the use of a β-blocker to reduce the risk for myocardial ischemia and ameliorate renin release with concomitant pressure rebound when the surgery has ended eliminates this physiologic marker. Synthetic lysine analogues, such as aminocaproic acid and aprotinin, a polypeptide with serine protease inhibitor activity, also have been used to limit blood loss during these procedures by reducing fibrinolysis, but there may be concern because of more recent findings in postoperative cardiac cases.[136]

A postoperative neurologic deficit is one of the most feared complications of complex spinal reconstructive surgery. In a large survey of 97,586 spinal surgeries, neurologic deficits occurred in 0.55% of the cases.[137] To reduce this complication, Vauzelle and colleagues[138] introduced the concept of waking the patient up during surgery to determine the functional integrity of the spinal cord. This test is limited to gross motor movements of the lower extremities and can be influenced by anesthetics and the cognitive integrity of the patient. In addition, complications related to the test include inadvertent extubation of the patient during movement in the prone position, air embolism during a deep inspiration, and dislodgment of the instrumentation during violent movements.

Multimodal intraoperative monitoring has become the standard of care for complex reconstructive spinal surgery.[139] This monitoring includes somatosensory evoked potential (SSEP), motor evoked potential (MEP), and electromyogram (EMG) monitoring. EMGs are used to monitor nerve root injury during pedicle screw placement and nerve decompressions (see also Chapter 49). The posterior (sensory) portion of the spinal cord is evaluated using SSEP monitoring. MEPs assess the integrity of the anterior (motor) spinal cord. Potential adverse effects of MEP monitoring include cognitive deficits, seizures, bite injuries, intraoperative awareness, scalp burns, and cardiac arrhythmias. It is advisable to employ a soft bite block during MEP monitoring to prevent tongue biting and dental damage. MEP monitoring should be avoided in patients with active seizures, vascular clips in the brain, and cochlear implants. In SSEPs, an impulse is sent from a peripheral nerve and measured centrally. In MEPs, an impulse is triggered in the brain and monitored as movement of a specific muscle group. SSEPs and MEPs are evaluated with regard to amplitude—strength—of the signal and latency—time it takes the signal to travel through the spinal cord—compared with the patient's nonsurgical control values.

Numerous physiologic factors attenuate SSEP and MEP monitoring, including hypotension, hypothermia, hypocarbia, hypoxemia, anemia, and anesthetics. The potent inhaled agents reduce the amplitude of the signal and increase latency in a dose-dependent manner. If a volatile anesthetic is used for the anesthesia, the concentration should be kept at approximately half minimum alveolar concentration and not varied throughout the procedure. Nitrous oxide produces a decrease in the amplitude of the signal and may have to be eliminated during MEP monitoring. Total intravenous anesthesia has been used successfully for MEP and SSEP monitoring.

MEPs are the least affected by opioids, midazolam, and ketamine, but are depressed by propofol. The depressant effect of propofol is diminished, however, with ketamine, such that the best total intravenous anesthetic may be an infusion of an opioid, ketamine (at low doses), and propofol.[140,141] Muscle relaxants cannot be administered during MEP monitoring.

Postoperative visual loss (POVL) is another devastating complication of spinal surgery (see also Chapter 100). POVL is rare after spinal surgery (≤0.1%) and may be caused by ischemic optic neuropathy (ION), retinal artery or vein occlusion, and cortical brain ischemia. In an attempt to delineate the cause of POVL, the ASA Committee on Professional Liability established a POVL registry to collect detailed information on these cases.[142] Most patients with central retinal artery occlusion had evidence of unilateral ocular trauma, suggesting a role for improper head positioning. ION was the most common cause of POVL after spinal surgery. ION can be divided into anterior ION and posterior ION depending on the visual field cut and whether edema to the optic disk is present early (anterior ION) or later (posterior ION). Both types are the result of reduced blood flow or oxygen delivery from end-arteriole branches of the ophthalmic artery.

The ASA registry of 93 POVL cases after spinal surgery reported that most patients were relatively healthy and that blood loss greater than 1000 mL and duration in the prone position for longer than 6 hours were present in 96% of the cases. ION occurs in the absence of direct pressure on the eye. In a multicenter case-control study that compared the 80 adult patients with ION in the ASA registry to 315 adult patients who had undergone central spinal fusion without ION, the risk factors for ION identified were obesity, Wilson frame use, length of surgery, blood loss, and decreased colloid use with fluid replacement.[143] Because ION occurred in the absence of vascular injury to other critical organs and in cases in which neither hypotension nor anemia was reported, optic nerve blood supply may be uniquely vulnerable to hemodynamic perturbations in the prone position.

Patients experience considerable pain after multilevel spinal fusions with instrumentation (see also Chapter 98). Most of these patients are initially treated with intravenous opioids, but because of the multiple side effects of

these drugs, a multimodality approach with other agents has been recommended. For lumbar fusions, an epidural catheter placed at a level above the incision can be used for patient-controlled epidural anesthesia infusions of local anesthetics and opioids. For procedures involving more extensive spinal levels, intrathecal morphine administered during surgery has been shown to provide reliable postoperative pain control.[144] NSAIDs may have a negative influence on the success of spinal fusions, however. For opioid-tolerant patients, subanesthetic doses (0.2 mg bolus, then 2 mcg/kg/hr) of ketamine reduced postoperative pain after posterior spine fusions.[145]

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Chapter 80

Geriatric Anesthesia

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Key Points

- An important principle of aging is a progressive loss of functional reserve in all organ systems, with considerable variation from person to person.
- Older patients are more sensitive to anesthetic drugs. Less medication is usually required to achieve a desired clinical effect, and drug effects are often prolonged. Hemodynamic responses to intravenous anesthetics may be exaggerated because of interactions with the aging heart and vasculature.
- The incidence of postoperative delirium is substantially more frequent in patients with preoperative dementia.
- The ability to predict patients at high risk for postoperative delirium has enabled proactive interventions to prevent or attenuate the severity or duration of postoperative delirium. The cornerstone of management of delirium is the recognition and treatment of any predisposing or precipitating factors for delirium.
- Postoperative cognitive dysfunction (POCD) in older patients occurs in the first days to weeks after surgery. POCD is well documented, and early POCD is reversible.
- Perioperative management of depression is a lower priority than management of the patient's more acute medical illnesses.
- Although advance directives can be helpful in perioperative decision making, accurate documentation of advance care planning is often lacking for many older patients.
- In older patients perioperative complications lead to poor outcome. The most important risk factors for perioperative complications in older patients are age, the patient's physiologic status and coexisting disease (American Society of Anesthesiologists class), whether the surgery is elective or urgent, and the type of procedure.
- The success of surgical intervention in geriatric patients depends partly on whether patients can return to their previous level of activity and independence.
- Recognizing acute illness and exacerbation of chronic disease in older adults can be challenging. Not infrequently, acute illness may have an atypical presentation.

Defining and implementing optimal perioperative care for older adults is of increasing importance to all stakeholders in health care, including consumers, insurers, and government agencies. Health care reform legislation has focused an increasing emphasis on cost containment, value, and rigorous assessment of meaningful outcomes for older patients. The demographic considerations are sobering. The U.S. Census 2010 data revealed the number of persons older than 65 years of age in the United States had increased to 40.4 million, with 21.7 million 65 to 74 years old, and 13.1 million 75 to 84 years of age, with 5.5 million over the age of 85 years. The average life expectancy was 78.2 years. It is estimated that by 2030, 20% of U.S. citizens will be older than 65 years. By 2034, baby boomers in the United States will all be over 70 years of age. By 2050 those over 85 years of age will represent 14% of the population over 65 years.[1] Worldwide, nearly 2 billion people will be over 60 years of age.[2]

Older individuals frequently access health care. In 2003, older patients represented roughly 12% of the U.S. population, accounted for one third of all hospitalizations and 43.6% of inpatient hospital charges.[3] Patients 65 years of age and older have surgery at a rate 2 to 3 times that of younger patients and tend to have longer hospital stays.[4]

CORE CONCEPTS IN THE ANESTHETIC MANAGEMENT OF THE OLDER PATIENT

Two important principles must be kept in mind when discussing the physiology of aging. First, aging is associated with a progressive loss of functional reserve in all organ systems. Second, the extent and onset of these changes vary from person to person. In most older patients, physiologic compensation for age-related changes is adequate and underlying limitation in physiologic reserve may become evident only during times of physiologic stress, including exercise, illness, and surgery. Anticipating the interaction of underlying disease, limited end-organ reserve, and the stress of the perioperative period should aid the perioperative physician in providing the best care possible.

MECHANISMS OF AGING

Aging is a universal and progressive physiologic process characterized by declining end-organ reserve, decreased functional capacity, increasing imbalance of homeostatic mechanisms, and an increasing incidence of pathologic processes.[5] Aging is now viewed as an extremely complex multifactorial process with interaction of various pathways to differing degrees and effect.[6] Theories of aging may be grouped into broad categories including evolutionary and physiologic mechanisms. These may also be defined according to the "programmed" or biologic clock theory, in which genetic mechanisms program declining function, and "error" theories, in which environmental damage to processes lead to impaired function and progressive decline. These processes of aging overlap and may be further defined by the organizational level of an organism in which a given process occurs. Changes at one level influence processes at another level. Molecular effects will influence cellular function, which in turn causes alterations in major organ systems and may ultimately exert evolutionary pressure by influencing survival and reproduction. Theories of aging have been reviewed.[5,7] These are summarized in Table 80-1.

CENTRAL NERVOUS SYSTEM

With aging, several important processes occur that are of interest to the anesthesiologist.[8] These changes may be further modified by other underlying pathologic or age-related processes.[9] Memory decline occurs in more than 40% of persons over 60 years of age but is not a universal finding.[10] Importantly, age-related memory decline can dramatically affect performance of the activities of daily living (ADL).

Structurally, a decrease occurs in the volume of both gray matter and white matter in the central nervous system (CNS).[11] Regions of the brain are affected in a selective and differential manner. The decrease in gray matter volume is likely secondary to neuronal shrinkage as opposed to neuronal loss. A small overall loss occurs of neurons from the neocortex.[8] This decrease in neuron number is not as massive as older studies had indicated. Some neocortical areas do not lose any neurons with aging. There may be 15% loss, however, of white matter with aging.[8] These structural changes result in gyral atrophy and increased ventricular size. Shrinkage in the subcortical white matter and hippocampus may be accelerated by hypertension and vascular disease.

Whether the aging process alters the number of synapses present in the cortex is controversial. Data from nonhuman primates suggest significant regional reductions with aging in the neurotransmitters dopamine, acetylcholine, norepinephrine, and serotonin.[12] Levels of glutamate, the primary neurotransmitter in the cortex,

TABLE 80-1 **CLASSIFICATION AND BRIEF DESCRIPTION OF THEORIES OF AGING**

Biologic Level and Theory	Description
Evolutionary	
Mutation accumulation	Mutations that affect health at older ages are not selected against
Disposable soma	Somatic cells are maintained only to ensure continued reproductive success; after reproduction, soma becomes disposable
Antagonistic pleiotropy	Genes beneficial at younger age become deleterious at older age
Molecular	
Gene regulation	Aging is caused by changes in the expression of genes regulating both development and aging
Codon restriction	Fidelity and accuracy of mRNA is impaired as a result of inability to decode codons in mRNA
Error catastrophe	Decline in fidelity of gene expression with aging results in increased fraction of abnormal proteins
Somatic mutation	Molecular damage accumulates primarily to DNA and genetic material
Dysdifferentiation	Gradual accumulation of random molecular damage impairs regulation of gene expression
Cellular	
Senescence-telomere theory	Phenotypes of aging are caused by an increase in frequency of senescent cells as a result of telomere loss or cell stress
Free radical	Damage caused by free radical production from oxidative metabolism
Wear-and-tear	Accumulation of normal injury
Apoptosis	Programmed cell death
System	
Neuroendocrine	Alterations in neuroendocrine control of homeostasis leads to physiologic change
Immunologic	Decline in immune function leads to altered incidence of infection and autoimmunity
Rate-of-living	Assumes a fixed amount of metabolic potential for every living organism (live fast, die young)

Modified from Weinert BT, Timiras PS: Invited review: theories of aging. J Appl Physiol *95:1707, 2003. With permission.*

are not affected. Coupling of cerebral electrical activity, cerebral metabolic rate, and cerebral blood flow remains intact in older individuals.

Although biochemical and anatomic changes have been described in the aging brain, the exact mechanisms causing changes in functional reserve are unclear. Decreases in brain reserve manifest by decreases in functional ADL, increased sensitivity to anesthetic medications, increased risk for perioperative delirium, and increased risk for postoperative cognitive dysfunction (POCD).

Neuraxial changes include a reduction of the area of the epidural space, increased permeability of the dura, and decreased volume of cerebrospinal fluid. The diameter and number of myelinated fibers in the dorsal and ventral nerve roots are decreased in older individuals. In peripheral nerves, inter–Schwann cell distance is decreased, as is conduction velocity. These changes tend to make older individuals more sensitive to neuraxial and peripheral nerve blocks.[13]

CARDIOVASCULAR CHANGES

Primary changes in the vasculature, or arterial aging, cause important secondary changes in the heart and other end organs including the brain and kidney. The process of vascular aging is accelerated by the presence of primary cardiovascular disease, including hypertension and atherosclerosis, as well as other risk factors such as diabetes, tobacco abuse, and obesity. Primary changes in cardiac function also occur with advancing age. Morphologic changes include decreased myocyte number, thickening of the left ventricular wall, and decreases in both conduction fiber density and the number of sinus node cells.[14] Functionally, these changes translate to decreased contractility, increased myocardial stiffness and ventricular filling pressures, and decreased β-adrenergic sensitivity.[14] Breakdown of elastin in the proximal thoracic aorta and proximal branches of the great vessels leads to progressive central aortic dilatation, increased thickness of the arterial wall, and increased vascular stiffness with advancing age.[15] Alterations in nitric oxide–induced vasodilatation also contribute.[16] Functionally, these changes are readily observed in terms of an elevated mean arterial pressure and increased pulse pressure.[17,18]

Increased vascular stiffness leads to important secondary responses in the heart. Functionally, the vascular system acts as both a cushion and a conduit to ensure the mechanically efficient and smooth delivery of blood to the periphery. In youth, the cardiac pump and the blood vessels are optimally coupled to maximize efficiency.[19] With increased resistance in the blood vessels, the velocity of conduction of pulse waves down the vascular tree increases. Increased pulse wave velocity results in earlier reflection of pulse waves from the periphery. In younger humans, wave reflection occurs later as a result of slower propagation such that reflected waves reach the heart after aortic valve closure. This timing preserves pressure in the compliant central aorta, promoting coronary blood flow during diastole. In the setting of increased pulse wave velocity with wave reflection occurring earlier, reflected pulse waves reach the heart during the latter phases of ejection, resulting in an increased cardiac load.[18] Alterations in left ventricular afterload lead to left ventricular wall thickening, hypertrophy, and impaired diastolic filling.[20] Decreased ventricular compliance and increased afterload combine to cause compensatory prolongation of myocardial contraction. This occurs at the expense of decreased early diastolic filling time. Under these conditions the contribution of atrial contraction to late ventricular filling becomes more important and explains why cardiac rhythm other than sinus is often poorly tolerated in older adults and why older patients are often preload sensitive.

Peripheral blood pressure measurements probably do not accurately represent central aortic pressures. In youth, pulse pressure amplification occurs as pulse waves travel down the vascular tree. This is observed as an increase in systolic pressure of 10 to 15 mm Hg between the central aorta and the periphery, with a slight decrease in diastolic and mean pressures. With aging, this is lost, which results in an augmentation of central aortic pressure (Fig. 80-1). Several methods have been described to estimate changes in aortic stiffness. These include noninvasive technologies to measure aortic pulse pressure, pulse wave velocity, and aortic augmentation index.[21] Increased vascular stiffness as assessed by these methods is associated with adverse cardiovascular events.[22,23] Differential responses to drugs with regard to central aortic pressure and peripheral arterial pressure may have important implications for treatment of cardiovascular disease.[21]

Changes in the autonomic system with aging include a decrease in response to β-receptor stimulation and an increase in sympathetic nervous system activity.[24] Decreased β-receptor responsiveness is secondary to both decreased receptor affinity and alterations in signal transduction.[25] Decreased β-receptor responsiveness assumes functional importance when increased flow demands are placed on the heart. Normally β-receptor–mediated mechanisms act to increase heart rate, venous return, and systolic arterial pressure while preserving preload reserve. In contrast, the attenuated β-receptor response in older individuals during exercise and stress is associated with decreased maximal heart rate and decreased peak ejection fraction. This causes the increased peripheral flow demand to be met primarily by preload reserve, making the heart more susceptible to cardiac failure.[14] Sympathetic nervous system activity increases with aging. Although changes in β-receptor responsiveness are well defined, it is controversial whether the aging process alters the α-receptor response. Increased resting sympathetic nervous system activity may contribute to increases in systemic vascular resistance and mechanical stiffening of the peripheral vasculature.[14] This explains in part the exquisite sensitivity of many older patients to interventions that decrease sympathetic tone. Clinically, these autonomic changes lead to a greater likelihood of adverse intraoperative hemodynamic events and decreased ability to meet the metabolic demands of surgery.

Although the age-related changes in cardiovascular physiology are generally well tolerated, several pathophysiologic states deserve mention. Impairment of diastolic relaxation leads to diastolic dysfunction in the aging heart. In its severest form, diastolic dysfunction may manifest as diastolic heart failure, now referred to

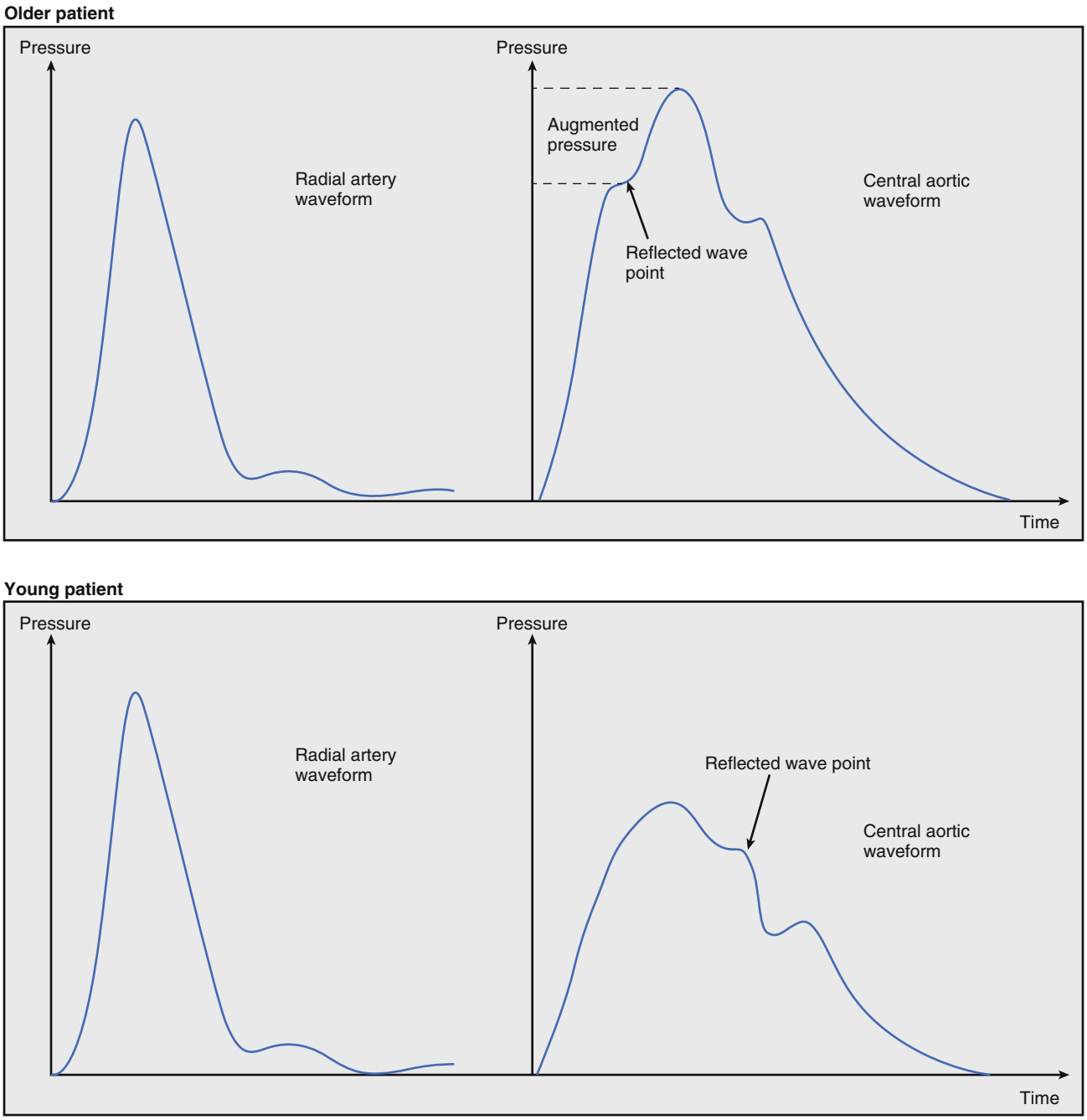


Figure 80-1. Illustration of the influence of increased vascular stiffness on peripheral (radial) and central (aortic) derived pressures. Note the similarity of peripheral radial pressures in individuals with normal (*lower left panel*) and increased (*upper left panel*) vascular stiffness. In young individuals with normal vascular stiffness, central aortic pressures are lower than radial pressures (*lower panels*). In contrast, in older individuals with increased vascular stiffness, central aortic pressures are increased and can approach or equal peripheral pressures as a result of wave reflection and central wave augmentation during systole (*top panels*). *(Redrawn from Barodka VM, Joshi BL, Berkowitz DE, et al: Implications of vascular aging [Review article],* Anesth Analg *112:1048-1060, 2011. With permission)*

as heart failure with preserved ejection fraction (HFpEF). Predisposing disease states for HFpEF include hypertension with left ventricular hypertrophy, ischemic heart disease, hypertrophic cardiomyopathies, and valvular heart disease. HFpEF is twice as prevalent in females.[26] Population-based studies suggest that diastolic dysfunction is common and associated with an increase in all-cause mortality.[27] Furthermore, in patients with clinically evident heart failure, ejection fraction is preserved in over half, with 40% manifesting overt HFpEF. Mortality in the cohort with preserved ejection fraction is similar to that in patients with reduced ejection fraction (HFrEF).[28] The pathophysiologic process includes decreased left ventricular compliance during diastole, resulting in greatly increased left ventricular diastolic pressure with retrograde conduction to the pulmonary circulation, which causes pulmonary venous congestion and pulmonary edema. HFpEF is often related to systemic blood pressure

and does not necessarily imply volume overload. Diagnosis can be difficult because the clinical picture appears identical to that of left ventricular systolic failure. Making the correct diagnosis is important because interventions commonly employed in systolic failure—such as diuretics and inotropes—may exacerbate diastolic dysfunction.[29] Echocardiography is the diagnostic modality of choice. Classically, echocardiography will demonstrate preserved or hyperdynamic left ventricular systolic function and characteristic changes of flow velocity at the mitral valve. Left ventricular systolic dysfunction and diastolic dysfunction often coexist. Pulmonary arterial pressures increase in aging, and HFpEF may be a contributing factor.[30]

Aortic valve sclerosis and mitral annular calcification are common echocardiographic findings in older adults. These represent non–flow-limiting calcifications around the aortic and mitral valves, respectively. Aortic valve sclerosis is common in older individuals and is associated with an increase in the risk for adverse cardiovascular and coronary events.[31]

RESPIRATORY CHANGES

Alterations in control of respiration, lung structure, mechanics, and pulmonary blood flow place older adults at increased risk for perioperative pulmonary complications. Ventilatory responses to hypoxia, hypercapnia, and mechanical stress are impaired secondary to reduced CNS activity.[32] In addition, the respiratory depressant effects of benzodiazepines, opioids, and volatile anesthetics are exaggerated.[32,33] These changes compromise the usual protective responses against hypoxemia after anesthesia and surgery in older patients.

Structural changes in the lung with aging include the loss of elastic recoil after reorganization of collagen and elastin in lung parenchyma. This combined with altered surfactant production leads to an increase in lung compliance. Increased compliance leads to limited maximal expiratory flow and a decreased ventilatory response to exercise.[34] Loss of elastic elements within the lung is associated with enlargement of the respiratory bronchioles and alveolar ducts and a tendency for early collapse of the small airways on exhalation, leading to an increased risk for air trapping and hyperinflation. Progressive loss of alveolar surface area occurs secondary to increases in size of the interalveolar pores of Kohn. The functional results of these pulmonary changes are increased anatomic dead space, decreased diffusing capacity, and increased closing capacity, all leading to impaired gas exchange.

Changes in chest wall compliance result in greater elastic load during inspiration, with an increased work of breathing. Loss of height and calcification of the vertebral column and rib cage leads to a typical barrel chest appearance with diaphragmatic flattening. The flattened diaphragm is mechanically less efficient, and function is further impaired by a significant loss of muscle mass associated with aging.

Although alterations in lung volumes occur with aging, total lung capacity is relatively unchanged. Residual volume increases by 5% to 10% per decade. Therefore, vital capacity decreases. Closing capacity—the volume at which small dependent airways start to close—increases with age. Although functional residual capacity is unchanged or slightly increased, closing capacity is unaffected by body position. Change in the relationship between functional residual capacity and closing capacity causes an increased ventilation-perfusion mismatch and represents the most important mechanism for the increase in the alveolar-arterial gradient for oxygen observed in aging.[35]

TABLE 80-2 NORMAL VALUES FOR ARTERIAL PARTIAL PRESSURE OF OXYGEN

Age (yr)	Mean and Range (mm Hg)
20-29	94 (84-104)
30-39	91 (81-101)
40-49	88 (78-98)
50-59	84 (74-94)
60-69	81 (71-91)

From Nunn J: Nunn's applied respiratory physiology, *ed 4, Oxford, Butterworth-Heinemann, 1995, p 269.*

In younger individuals, closing capacity is less than functional residual capacity. At 44 years of age, closing capacity equals functional residual capacity in the supine position, and at 66 years of age, in the upright position.[35] When closing capacity encroaches on tidal breathing, ventilation-perfusion mismatch occurs. When functional residual capacity is below closing capacity, shunt will increase and arterial oxygenation will fall. This effect is observed in the decreased resting arterial oxygen (O_2) tension with aging and impairs the effectiveness of breathing O_2 before induction of general anesthesia (Table 80-2). Another effect of increasing closing capacity in concert with depletion of muscle mass is a progressive decrease in forced expiratory volume in 1 second (FEV_1) by 6% to 8% per decade. Increases in pulmonary vascular resistance and pulmonary artery pressure occur with age and may be secondary to decreases in the cross-sectional area of the pulmonary capillary bed.[36] Hypoxic pulmonary vasoconstriction is blunted in older adults and may cause difficulty with one-lung ventilation.

Older patients may have an increased sensitivity for bronchoconstriction and a diminished response to treatment with inhaled β-agonists.[37] Alterations in immune responses in older adults may lead to an increased susceptibility to environmental exposure and lung injury.[38]

RENAL AND VOLUME REGULATION

Structural and functional changes occur in the kidney as part of normal aging. Nephrosclerosis is observed with increasing age but may not correlate with decreases in glomerular filtration rate (GFR).[39] Renal blood flow decreases approximately 10% per decade after 40 years of age, with a decline in GFR of 8 mL/min/1.73 m^2 from a baseline of 140 mL/min/1.73 m^2.[40]

With normal aging, serum creatinine remains relatively unchanged in the face of a progressive decrease in creatinine clearance. This occurs because muscle mass also decreases with aging. Therefore, serum creatinine is a poor predictor of renal function in older individuals.[40,41]

This concept is important in proper dosage adjustment for medications excreted by the kidneys.

Functional changes in the kidneys with aging include alterations in response to abnormal electrolyte concentrations and the ability to concentrate and dilute urine.[42] Renal capacity to conserve sodium is decreased. Overall, the older patient has a tendency to lose sodium in the setting of inadequate salt intake. This paired with a decreased thirst response may place the older patient at risk for dehydration and sodium depletion. The older patient also has a diminished ability to respond properly to an increased salt load, as evidenced by increased sodium retention and expansion of the extracellular volume during the perioperative period. This change assumes importance under conditions of limited fluid intake.

HEPATIC CHANGES

Liver volume decreases approximately 20% to 40% with aging. Hepatic blood flow decreases approximately 10% per decade.[43] A variable decrease occurs in the liver's intrinsic capacity to metabolize drugs. Effects on phase I reactions predominate. Decreases in hepatic blood flow may decrease maintenance dose requirements in drugs that are rapidly metabolized. The pharmacokinetics of drugs that are slowly metabolized are more affected by innate liver capacity than blood flow.[44]

COGNITIVE ISSUES IN OLDER ADULTS

DEMENTIA

Dementia is common in the geriatric population. In the population 65 years of age and older, 5% to 8% of people experience dementia. For those 75 years of age and older, 18% to 20% suffer dementia. For individuals over 85 years of age, more than one third may have dementia.[45] Dementia has many causes, with Alzheimer disease accounting for the majority of cases. The main perioperative management issues concerning the demented patient include detection, informed consent, possible anesthetic interactions causing delayed emergence, postoperative delirium, pain management, and increased mortality.

Many instruments of varying length are available to test for cognitive impairment.[46] However, accurate diagnosis of dementia is not always easy. For dementia screening, the AD8, an 8-item questionnaire that distinguishes between people who have dementia and people who do not, is a quick and reliable instrument.[47] For preoperative evaluation of baseline cognitive status, rather than detection of dementia, the Short Blessed Test allows for quick screening.[48] In addition, insight may be gained by speaking with the patient's family concerning baseline function and ADL. Some of the instruments for testing cognition may be used to help guide the physician in determining the patient's capacity to consent.[49]

The patient with dementia may display one of a number of psychiatric symptoms, including agitation, depression, and sleep disturbances.[50] Many of the drugs used to manage dementia and its symptoms interact with general anesthetics,[51] causing delayed emergence. It is unclear whether use of the bispectral index (BIS) monitor (see also Chapter 50) or other processed electroencephalography methods for guidance of drug administration is helpful because dementia does alter baseline BIS values.[52] When determining an anesthetic plan, no anesthetic technique or drug has been shown to be superior in older patients. However, patient cooperation may be an issue with regional anesthesia (see also Chapters 56 and 57).

Dementia is critical in risk stratification for postoperative delirium. The incidence of postoperative delirium is substantially more frequent in individuals with preoperative dementia than in those without.[53]

Pain management in the patient with dementia is challenging for several reasons (see also Chapter 98). Pain assessment can be difficult.[54] Despite use of the best available pain assessment instruments, decreased pain scores and opioid administration occur postoperatively in patients with dementia.[55] Pain management can be more nursing intensive because patient-controlled analgesia often is not an option in these patients. Furthermore, the clinician must maintain a delicate balance between opioid CNS effects and the role of poorly treated pain in precipitating delirium.[56,57]

Dementia has many associated comorbidities, including vascular disease, diabetes, alcoholism, and neurodegenerative disease (e.g., Parkinson, Huntington). Dementia is associated with a 2.18 (1.10 to 4.32) relative risk for developing a patient-related adverse event during an unplanned acute hospital admission.[53,58] Long-term postoperative mortality is related to the presence of dementia,[59] with the severity of cognitive impairment being associated with higher mortality.[60]

Whether general anesthesia accelerates the progression of senile dementia is controversial.[61,62] Certainly, much evidence exists both in vitro and in animal models suggesting that inhaled anesthetics enhance amyloid β oligomerization,[63] increase plaque density in transgenic mice (human *APP* gene),[64] induce caspase-3 activation (one of the final steps of apoptosis), and increase amyloid β protein (Aβ) levels in cell culture.[65] However, in humans, recent retrospective data suggest that long-term cognitive decline is neither independently attributable to surgery (and anesthesia) or illness, nor have surgery (and anesthesia) or illness been associated with accelerated progression of dementia.[66,67] Unfortunately, no prospective human data convincingly answer this question. Thus, the relationship between anesthetic exposure and accelerated progression of dementia remains unclear; "Available human studies on anesthesia and Alzheimer disease are inconclusive because they are under-powered or confounded by coincident illness, independent risk factors for dementia and, of course, surgery."[68]

DELIRIUM

The overall prevalence of delirium in older patients after surgery has been estimated to be 10%.[69] The incidence of postoperative delirium in older patients varies widely depending on the type of surgery, underlying comorbidities, and intensive care unit (ICU) stay. For

instance, cardiac surgery and hip fracture repair may have an increased incidence over that of other procedures.[69] Delirium occurs in 60% to 80% of patients in the ICU.[70]

Postoperative delirium has profound financial implications. Delirium is associated with prolonged hospital stay, increased incidence of nursing home placement, and an increased incidence of postoperative complications.[71] Overall 2 to 3 million older patients per year sustain delirium during their hospital stay, involving more than 17.5 million inpatient days.[70] The total direct 1-year health costs attributable to delirium range from $143 billion to $152 billion nationally.[72] Adding to these costs, the occurrence of postoperative delirium is associated with an accelerated trajectory of cognitive decline in patients with underlying dementia.[73]

Delirium and POCD are not the same. Postoperative delirium is an acute confusional state with alterations in attention and consciousness. On the other hand, POCD is a decline in a variety of neuropsychological domains (e.g., memory, executive function, speed of processing). Delirium is a syndrome characterized by acute onset of variable and fluctuating changes in level of consciousness accompanied by a range of other mental symptoms. By convention, the presence or absence of delirium is based on application of diagnostic criteria articulated in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV): "The essential feature of a delirium is a disturbance in consciousness that is accompanied by a change in cognition that cannot be better accounted for by a preexisting or evolving dementia"[74] (Box 80-1). Postoperative delirium may have several presentations with the hyperactive ("wild man"), hypoactive ("out of it"), and mixed (hypoactive alternating with hyperactive) presentations accounting for 1%, 68%, and 31% of cases, respectively.[75]

Several instruments are available to diagnose delirium. The Confusion Assessment Method (CAM)[76] is the most widely used instrument in North America. The CAM is a bedside rating scale developed to assist clinicians not trained in psychiatry in the rapid and accurate diagnosis of delirium in clinical settings. The CAM is designed to be administered by any clinician, including physicians or nurses, and may be administered by trained lay interviewers. Geriatricians, nurses, and trained lay interviewers perform as well as psychiatrists in rating the CAM.[77] The sensitivity of the CAM against the gold standard of psychiatric diagnosis is 94% to 100%, with specificity 90% to 95%.[76] The CAM-ICU has been adapted for measuring delirium in ventilated patients in the ICU.[78]

Many possible pathophysiologic mechanisms can account for delirium. Delirium may be associated with inflammatory mediators or alterations in one of several neurotransmitter systems.[79] Although we do not yet fully understand the basic mechanisms of delirium, in the geriatrics paradigm, delirium epitomizes an atypical presentation of disease[80] in which acute illness is manifested in the most vulnerable organ system, or "the weakest link"—in this case, the brain. This theory holds that the normal aging process can be characterized as homeostenosis, the progressive constriction of each organ system's ability to respond to stress.[81] In addition, the aging brain is more likely to be affected by diseases and drugs that cloud the sensorium. The sum of these effects leads some older adults to be teetering on the brink of neurodysfunction. Add any stressor, and these individuals develop acute worsening of their mental status. Based on the concept that "lack of brain reserve" predisposes older patients to delirium when exposed to stress, investigators have examined which preexisting vulnerability factors predispose older patients to delirium.

In medical patients, Inouye and Charpentier[82] developed a risk model for delirium that showed that the greater the number of preexisting vulnerability factors, the less acute are the stressors required to invoke delirium. The important preexisting vulnerability factors defined in the medical model of delirium are advanced age, visual impairment (visual acuity <20/70), severe illness (apache score >16), cognitive impairment (Mini–Mental State Examination score <24), and dehydration (blood urea nitrogen-to-creatinine [BUN/Cr] ratio ≤18). Kalisvaart and associates[83] attempted to validate the medical risk factor model of delirium in older patients who have had hip surgery. Their study showed the usefulness of the medical risk factor model in predicting postoperative delirium in surgery patients and supports the concept that when more preexisting vulnerability factors are present, a more frequent risk is seen for postoperative delirium.

The ability to predict patients at high risk for postoperative delirium has enabled the clinician to enact proactive interventions to prevent or attenuate the severity or duration of postoperative delirium. Thus, a cornerstone of management of delirium is the recognition and treatment of any predisposing or precipitating factors for delirium (Box 80-2). Interventions consisting of standardized protocols for the management of known risk factors for delirium (e.g., cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration) result in significant reductions in the number and duration of episodes of delirium in hospitalized older patients.[84] Another simple, nonpharmacologic intervention helpful in delirium prevention is early proactive geriatric consultation in the medical

BOX 80-1 ***Diagnostic and Statistical Manual of Mental Disorders IV Diagnostic Criteria for 293.0 Delirium***

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention
B. A change in cognition (e.g., memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia
C. The disturbance develops over a short time (usually hours to days) and tends to fluctuate during the course of the day
D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiologic consequences of a general medical condition

From American Psychiatric Association: Diagnostic and statistical manual of mental disorders, *4th ed, Text Revision (DSM-IV-TR), Washington, DC, 2000, American Psychiatric Publishing.*

BOX 80-2 ***Predisposing and Precipitating Factors for Postoperative Delirium***

Demographic characteristics: Age older than 65 years, male
Cognitive impairment or depression
Functional impairment
Sensory impairment, especially visual and hearing
Decreased oral intake
Drugs: Polypharmacy, alcoholism, psychoactive, sedatives, opioids, anticholinergic
Comorbidity: Severe illness and neurologic disease
Some types of surgery: High-risk surgery (American Heart Association guidelines) and orthopedic surgery
Intensive care unit admission
Pain
Sleep deprivation
Immobility or poor physical condition

Modified from Inouye SK: Delirium in older persons. N Engl J Med *354:1157-1165, 2006.*

management of patients.[85] More recent studies have examined prophylactic administration of antipsychotics in high-risk patients. Both haloperidol and the atypical antipsychotics may have some efficacy when used in this capacity.[86,87] Anesthetic-specific interventions include correction of metabolic and electrolyte disorders and perioperative continuation of pharmacologic therapy for neuropsychiatric disorders. Other interventions may be aimed at decreasing exposure to any known pharmacologic drugs triggering delirium (e.g., opioids, benzodiazepines, dihydropyridines, antihistamines).[88] Type of anesthesia (regional versus general) and intraoperative hemodynamic complications have not been associated with delirium.[89,90] However, the incidence of postoperative delirium may be decreased by using lighter levels of sedation during regional anesthetic techniques.[91]

An increased incidence of delirium occurs with larger intraoperative blood loss, more postoperative blood transfusions, and postoperative hematocrit less than 30%.[89] However, recent randomized controlled trials have found no impact of blood transfusion strategy on severity or incidence of delirium.[92]

Systematic reviews of postoperative pain management with opioids demonstrate that meperidine is the only opioid consistently associated with delirium.[93] No difference in cognitive outcome is seen when comparing fentanyl, morphine, and hydromorphone. In addition, no difference in cognitive outcome is noted when comparing epidural and intravenous opioid administration.[93] Two important pain management techniques associated with decreased incidence of postoperative delirium include the use of peripheral nerve blockade[94] and the use of multimodal pain therapy featuring gabapentin.[95] One might also consider opioid rotation, a well-described approach to decreasing opioid-induced delirium in the management of cancer pain.[96] (See also Chapters 98 and 99.)

Should delirium occur despite preventive measures, it is important to first provide supportive care and focus on prevention of complications. Next, the clinician should diligently search for and treat any underlying precipitating medical causes. If pharmacologic intervention is needed, algorithms for pharmacologic treatment of delirium have been outlined in several more recent reviews.[97] Typical and atypical antipsychotics are similar in efficacy for the treatment of delirium, with the atypical agents having fewer extrapyramidal side effects.[98]

POSTOPERATIVE COGNITIVE DYSFUNCTION

Short-term changes in cognitive test performance during the first days to weeks after surgery are well documented and typically involve multiple cognitive domains, such as attention, memory, and psychomotor speed (see also Chapter 99). POCD is important because it affects quality of life and has significant social and financial implications.[99]

Unfortunately, POCD is not a formally recognized condition with DSM criteria. Rather, the criteria for POCD are based on changes between preoperative and postoperative scores on a set of neuropsychological tests that evaluate a broad range of cognitive domains.[100] The time point at which POCD is said to exist has not been clearly defined. In addition, patient subjective complaints of POCD have not always been borne out by objective testing. The most important risk factor for POCD is increasing age.[101] In comparing all age groups, POCD is clearly more frequent in older individuals.[102]

Initial uncontrolled observational studies in patients undergoing coronary artery bypass graft (CABG) procedures reported a 36% incidence of cognitive decline at 6 weeks and a 42% incidence of cognitive decline at 5 years postoperatively (see also Chapter 67).[103,104]

However, later investigations addressing the issue of neurocognition and CABG procedures, including comparison with nonsurgical control groups, concluded that long-term POCD may result from factors other than anesthesia and surgery. First, patients with underlying coronary artery disease, regardless of whether they undergo surgery, have lower baseline cognitive test scores than controls without coronary artery disease.[105] Second, long-term cognitive outcome of on-pump and off-pump CABG is similar.[106] Third, long-term neurocognitive performance in CABG and nonsurgical controls with comparable coronary artery disease is similar.[107] These data suggest that the cause of long-term cognitive changes after anesthesia and surgery may be related to underlying cerebrovascular disease risk factors. However, in contrast to the studies mentioned previously, other investigators report that cardiovascular risk factors are not predictive of POCD.[108] The reported incidence of cognitive dysfunction after major noncardiac surgery in patients older than 65 years of age is 26% at 1 week and 10% at 3 months.[100]

Postoperative cognitive decline after major noncardiac surgery is reversible in most cases, but may persist in approximately 1% of patients.[109] Chronic POCD is important to identify because of its association with more frequent 1-year mortality.[102] The identified risk factors for long-term POCD after noncardiac surgery include age (odds ratio [OR] 2.58 [1.42 to 4.70]), infectious complication in the first 3 months postoperatively (OR 2.61 [1.02 to 6.68]), and POCD at 1 week postoperatively (OR 2.84 [1.34 to 5.96]).[109]

POCD has been attributed to multiple causes. The most likely causative elements include medications, surgery, or issues with the patient. Whether anesthesia contributes to long-term POCD is controversial and an area of intense clinical and laboratory investigation.[110] Studies comparing coronary angiography (sedation) versus total hip replacement versus CABG report similar incidence of POCD at 3 months in all three groups, suggesting that POCD may be independent of both surgery and anesthesia.[108] The cause of long-term POCD may be more related to underlying patient comorbidities than other factors. Minimal cognitive impairment could be a risk factor for postoperative cognitive deficits.[111] Similarly, in orthopedic surgery, dementia is a risk factor for POCD.[112] Future studies examining underlying minimal cognitive impairment may help better define patients at risk for long-term POCD.

In conclusion, current evidence suggesting POCD occurs in the first days to weeks after surgery is well documented, especially in older patients. For the most part, this early POCD is reversible. However, in a small percentage of patients, POCD may persist. Unfortunately, no well-defined anesthesia best practice to prevent POCD has been determined. The regional versus general anesthesia approach shows no difference in POCD incidence, and no anesthetic drug is associated with less POCD. At present no specific treatment for POCD is available.

DEPRESSION

Depression is estimated to occur in 8% to 16% of the community-dwelling population over the age of 65 years.[113] Preoperative depression is an independent predictor of postoperative delirium.[114] Depression predicts greater risk for major adverse cardiac events.[115] After CABG, preoperative and persistent postoperative depression carry an increased risk for death over that of patients without depression.[116]

Antidepressants should be continued during the perioperative period because their cessation may increase symptoms of depression and confusion.[117] Perioperative management of depression is a lower priority than management of the patient's more acute medical illnesses. However, preoperative assessment of mood and cognition is important for baseline data to provide the practitioner with a yardstick to measure against when evaluating postoperative delirium, dementia, or depression.

CONSENT, SURROGATE DECISION MAKERS, AND ADVANCE DIRECTIVES

Issues of consent and end-of-life decisions for older adults are complex and familiar to the practicing anesthesiologist. The most important principle in health care decision making for older patients is autonomy.[118] However, autonomy implies mental competence. The legal standards for competence include the abilities to communicate a choice, understand relevant information, appreciate the current situation and its consequences, and manipulate information rationally.[119] Cognitive and sensory difficulties frequently jeopardize informed consent in frail older patients. Dementia, depression, hearing difficulties, and stroke all may interfere with the ability to make independent decisions. If one's ability to make decisions becomes severely impaired, a surrogate must give consent. However, caution must be exercised in this situation. A low rate of agreement has been demonstrated when comparing the health care decisions made by surrogates and the desires of the older patients involved.[120]

Advance directives, when available, can be extremely helpful, but even with them, difficult problems remain. Accurate documentation of advance care planning is often lacking.[121] Patients presenting to the operating room with "do not resuscitate" orders are an increasingly common problem reviewed recently.[122] The presence of "do not resuscitate" status does not appear to influence short-term surgical outcome.[123,124]

RISK ASSESSMENT AND PREOPERATIVE EVALUATION

THE ROLE OF COMPLICATIONS

Increased life expectancy, safer anesthesia, and less invasive surgical techniques have made it possible for a greater number of geriatric patients to be considered for surgical intervention (see also Chapter 38). Although it is possible to safely manage older surgical patients during the perioperative period, surgical mortality and morbidity are increased in this patient population.[125] Many factors contribute to surgical morbidity and mortality,[126] but in older patients, perioperative complications are directly related to poor outcome.[127] Major perioperative complications increase with age[128] and are associated with more frequent mortality.[129] The most important risk factors for perioperative complications in older adults are age, physiologic status, and coexisting disease (American Society of Anesthesiologists [ASA] class), whether the surgery is elective or urgent, and the type of procedure.

How does aging alter surgical risk? The association between age and surgical risk is related to the aging process and its ongoing decrease in functional organ reserve and associated increased incidence of chronic systemic disease processes. It is difficult to disentangle the effects of aging alone from those caused by concurrent disease. Acute and chronic pathologic insults occur in the setting of a decreased physiologic reserve that can have profound effects on the usual compensatory mechanisms. These factors become especially confusing in considering perioperative risk in older patients. Extremes of age do incur additional risk. For instance, when compared with younger patients, patients 90 years of age or older are more likely to die during hospitalization after hip fracture repair.[130] However, chronologic age is a less important risk factor for complications than the sum of underlying comorbidities.[131] Thus, age alone should not necessarily be a deterrent from surgery.

Emergency surgery is an independent predictor of adverse postoperative outcomes in older surgical patients undergoing noncardiac surgery.[131,132] Poorer preoperative physiology and preparation has a large influence on these results. Emergent care presents special problems,

such as atypical presentations, alterations in the pulmonary and circulatory system, and fluid and electrolyte balance changes secondary to modifications in metabolic needs and body composition with aging that complicate resuscitation.

Surgical mortality in older patients varies widely according to procedure.[133] The fact that risk varies widely depending on the type of surgery is well recognized. The current guidelines for cardiovascular evaluation of patients undergoing noncardiac surgery provide a useful means of categorizing procedures into those of low, intermediate, and high risk.[134]

PREOPERATIVE EVALUATION

Age and Age-Related Disease

Several principles should be kept in mind when performing preoperative evaluation of the geriatric patient (see also Chapter 38). First, a high index of suspicion is necessary for disease processes commonly associated with aging. Common diseases of older adults may have a major impact on anesthetic management and require special care and diagnosis. Second, of the many types of postoperative complications that may occur in older individuals, neurologic, pulmonary, and cardiac morbidities are the most common,[135] and the anesthesiologist should pay attention to these specific organ systems (anesthetic physiology of cardiovascular disease, neurologic, and pulmonary disorders is discussed in Parts VI and V of this edition). Third, the degree of functional reserve of specific, pertinent organ systems—as well as the patient as a whole—should be assessed before surgery. Laboratory and diagnostic studies, history, physical examination, and determination of functional capacity should attempt to evaluate the patient's physiologic reserve. This will help better predict how the patient will manage the stress of surgery and anesthesia.

Functional Status and Assessment of Functional Reserve

The greatest concern of older patients and the most important outcome in determining the success of surgical intervention in geriatric patients is whether patients can return to their previous level of activity and independence. Evidence suggests that the current level of function is helpful in predicting long-term outcomes in medical patients.[136] A variety of instruments are available to evaluate functional activity[137] and health-related quality of life.[138] Commonly used screening tools for determining patient independence and functional level for the preoperative assessment are the ADL and instrumental activities of daily living (IADL) checklists. ADL represents activities involved in physical day-to-day self-care, and the IADL represents more complex tasks. These instruments are useful for indicating specifically how a person is performing at the present time. When they are used longitudinally over time, they serve as documentation of a person's functional improvement or deterioration. IADL and ADL assessments are important for their predictive ability. For instance, any ADL impairment is associated with a relative risk of 1.9 (1.2 to 2.9, 95% confidence interval [CI]) for 90-day mortality in medical patients. Any IADL impairment is associated with a relative risk of 2.4 (1.4 to 4.2, 95% CI) for 90-day mortality in medical patients.[136] Furthermore, any impairment of one to two ADL is associated with a 1.47 (1.08 to 2.01, 95% CI) hazard ratio of recovering independent function from a disability.[139]

Frailty

Frailty refers to a multisystem loss of physiologic reserve that makes a person more vulnerable to disability during and after stress. It is a clinical syndrome characterized by weight loss, fatigue, and weakness. Chronic inflammation and endocrine dysregulation appear to be key drivers in the underlying pathophysiology of this process.[140-143] The components of the frailty syndrome include mobility, muscle weakness, poor exercise tolerance, unstable balance, and factors related to body composition such as weight loss, malnutrition, and muscle wasting[143,144] (Box 80-3). The incidence of frailty in the community-dwelling population older than 65 years of age is approximately 6.9%.[145]

Frailty is a prognostic factor for poor outcomes.[145,146] When followed over a period of 3 years, frailty is predictive of disability, hospitalization, and death. Studies in various

BOX 80-3 *Criteria Used to Define Frailty**

Weight Loss Criterion

The patient is asked the question, "In the last year, have you lost more than 10 lb unintentionally (i.e., not as a result of dieting or exercise)?"

Patients answering "Yes" are categorized as frail by the weight loss criterion.

Exhaustion Criterion

The patient is read the following two statements: (1) I felt that everything I did was an effort; (2) I could not get going. The question is asked, "How often in the last week did you feel this way?" The patient's response is rated as follows: 0 = rarely or none of the time (<1 day); 1 = some or little of the time (1 to 2 days); 2 = a moderate amount of the time (3 to 4 days); or 3 = most of the time.

Patients answering "2" or "3" are categorized as frail by the exhaustion criterion.

Physical Activity Criterion

The patient is asked about weekly physical activity.

Patients with low physical activity are categorized as frail by the physical activity criterion.

Walk Time Criterion

The patient is asked to walk a short distance and timed.

Patients who are slow walkers are categorized as frail by the walk time criterion.

Grip Strength Criterion

The patient's grip strength is measured.

Patients with decreased grip strength are categorized as frail by the grip strength criterion.

Modified from Fried LP, Tangen CM, Walston J, et al: Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci *56:M146-M156, 2001.*

*Frailty is defined as a clinical syndrome in which three or more of the frailty criteria are met.

surgical populations have identified frailty as an independent risk factor for major morbidity, mortality, protracted length of stay, and institutional discharge.[147-151]

SPECIAL PERIOPERATIVE CONSIDERATIONS FOR THE OLDER PATIENT

ATYPICAL PRESENTATION OF DISEASE

Recognizing acute illness and exacerbation of chronic disease in older adults can be challenging. Not infrequently, acute illness may have an atypical presentation.[152] For instance, the appearance of pneumonia in the older patient may be heralded by such uncharacteristic features as confusion, lethargy, and general deterioration of condition.[153,154] Significant differences may be seen in the presentation of disease in patients who have dementia and those who do not. The nonspecific presentation of disease in older people is primarily linked to the presence of dementia rather than a characteristic feature of the aging process.[155]

POLYPHARMACY

Polypharmacy occurs in 61% of acutely hospitalized older patients.[156] The number of medications used is directly proportional to the likelihood of having an adverse drug reaction. The anesthesia provider must be familiar not only with potential interactions between the medications a particular patient is taking but also clearly must understand the interaction with medications introduced in the perioperative period.

MALNUTRITION, IMMOBILITY, AND DEHYDRATION

In the community-dwelling aged population, malnutrition has been reported to occur in 16.9% of females and 11.4% of males.[84] Among the acutely hospitalized older patients, the prevalence of malnutrition is 52%.[156] Surgical patients who are malnourished have increased morbidity, mortality,[157] and length of stay.[158] No uniformly accepted definition of malnutrition in older adults has been determined.[159] The diagnosis of malnutrition should be made on the basis of both preoperative history and physical and laboratory tests.

Bed rest induces loss of skeletal muscle, which may influence functional capacity.[160] Bed rest also leads to ventricular atrophy, hypovolemia, and orthostatic intolerance.[161] In 2008, dehydration accounted for greater than 99,000 Medicare admissions.[162] Dehydration is often associated with hypernatremia and accompanied by infection.

TRAUMA

The leading cause of traumatic injury and death in the population over 65 years of age is unintentional falls (see also Chapter 81).[163] Substance abuse, particularly alcohol, is often an underappreciated factor in these events.[164,165] Alcohol disorders may be present in 5% to 14% of older patients in the emergency department.[166]

Falls are a common problem both in and out of the hospital. As with any traumatic injury, prevention is the primary goal. Simple interventions, including identifying patients at risk, physical therapy, modification of the environment, and avoiding medications associated with orthostatic hypotension, may mitigate risk.[167] Age is associated with increased mortality with many types of traumatic injuries. This may result from a variety of factors, including decreased reserve, comorbidity, and multiple medications, particularly anticoagulants. For instance, mortality and functional outcome after head injury is considerably worse in older patients with preinjury anticoagulation or antiplatelet therapy.[168,169]

The American College of Surgeons has recognized that older patients should have a lower threshold for transport to a trauma center.[170] However, evidence exists that older patients are often undertriaged. This may occur as a result of inaccuracy of standard criteria in this population or to an age bias in referral patterns.

CHRONIC PAIN

Chronic pain occurs in 25% to 50% of community-dwelling older persons (see also Chapter 64).[171] Surveys of nursing home residents show arthritis is the most prevalent indication for analgesics (41.7% of residents), followed by bone fracture (12.4%) and other musculoskeletal conditions (9.7%). More residents (76.8%) have chronic pain than acute pain (19.9%), and 3.0% have both chronic and acute pain.[172]

Chronic pain is frequently undetected, and the current use of pain medication should be reviewed.[173] The consequences of persistent pain in older patients are numerous and include depression, sleep disturbance, and impaired ambulation.[171]

ANESTHETIC MANAGEMENT

CLINICAL PHARMACOLOGY

Factors that affect the pharmacologic responses of older patients are well described and include changes in plasma protein binding, body content, drug metabolism, and pharmacodynamics.

The main plasma binding protein for acidic drugs is albumin and for basic drugs is α_1-acid glycoprotein. The circulating level of albumin decreases with age, whereas α_1-acid glycoprotein levels increase. The effect of alterations in plasma binding protein on drug effect depends on which protein the drug is bound to and the resulting change in fraction of unbound drug. The relationship is complex, and, in general, changes in plasma binding protein levels are not a predominant factor in determining how pharmacokinetics are modified with aging.

Changes in body composition with aging reflect a decrease in lean body mass, an increase in body fat, and a decrease in total body water. We might infer that a decrease in total body water could lead to a smaller central compartment and increased serum concentrations after

bolus administration of hydrophilic drugs. The increase in body fat might result in a greater volume of distribution, with the potential to prolong the clinical effect of lipophilic medications.[174,175]

As discussed previously, alterations in both hepatic and renal clearance occur with aging. Depending on the degradation pathway, decreases in liver and kidney reserve can affect a drug's pharmacokinetic profile.

The clinical response to anesthetic medications in older adults may be the result of alterations in sensitivity of the target organs (pharmacodynamics). A given anesthetic's physical properties and alterations in receptor numbers or sensitivity will determine the relative influence of pharmacodynamic alterations on anesthetic effect in older patients. Generally, older individuals are more sensitive to anesthetic drugs. Less medication is usually required to achieve a desired clinical effect, and drug effect is often prolonged. Undesired hemodynamic perturbations also tend to occur more frequently and in greater magnitude. Hemodynamic responses to intravenous anesthetics may be exaggerated as a result of interactions with the aging heart and vasculature. Expected compensatory or reflex responses are often blunted or absent because of physiologic changes associated with normal aging and age-related disease. Regardless of the cause of altered pharmacologic effect, the aged patient usually requires a downward adjustment in medication dose.

CLINICAL PHARMACOLOGY OF SPECIFIC AGENTS

Table 80-3 summarizes the clinical pharmacology of anesthetic drugs in older patients.

TABLE 80-3 CLINICAL PHARMACOLOGY OF ANESTHETIC AGENTS IN OLDER PATIENTS

Drug	Brain Sensitivity	Pharmacokinetics	Dose
Inhaled agents	↑	—	↓
Thiopental	—	↓Initial distribution volume	↓
Etomidate	—	↓ Initial distribution volume ↓ Clearance	↓
Propofol	↑	↓ Clearance	↓
Midazolam	↑	↓ Clearance	↓
Morphine	↑	↓ Clearance	↓
Sufentanil	↑	—	↓
Alfentanil	↑		↓
Fentanyl	↑	—	↓
Remifentanil	↑	↓ Clearance ↓ Central compartment volume	↓ ↓
Pancuronium	NA	↓ Clearance*	↓*
Atracurium	NA	—	—
Cisatracurium	NA	—	—
Vecuronium	NA	↓ Clearance	↓

NA, Not applicable.
*See text.

Inhaled Anesthetics

The minimum alveolar concentration (MAC) decreases approximately 6% per decade for most inhalation anesthetics. A similar pattern is observed for MAC-awake.[176] The mechanism of action of inhalation anesthetics is related to altered activity of neuronal ion channels associated with nicotinic, acetylcholine, γ-aminobutyric acid ($GABA_A$), and glutamate receptors. Perhaps with aging, alterations in ion channels, synaptic activity, or receptor sensitivity may occur to account for these changes in pharmacodynamics.

Intravenous Anesthetics and Benzodiazepines

Although thiopental is not often used in modern anesthesia, certain pharmacologic principles are important (see also Chapter 30). No change in brain sensitivity to thiopental occurs with age,[177] yet the dose of thiopental required to achieve anesthesia decreases with age. The age-related decrease in thiopental dose is related to an age-related decrease in the initial distribution volume of the drug. The decrease in initial distribution volume results in higher serum drug levels after a given dose of thiopental in older patients.[177] Likewise, in the case of etomidate, age-dependent changes in pharmacokinetics (decreased clearance and initial volume of distribution) rather than altered brain responsiveness account for the decrease in etomidate dose requirement in the older patient.[178] The brain becomes more sensitive to the effects of propofol with age.[179] In addition, clearance of propofol is reduced. These additive effects are associated with a 30% to 50% increased sensitivity to propofol in older adults.[174]

The dose requirement of midazolam to produce sedation during upper gastrointestinal tract endoscopy is decreased approximately 75% in older patients.[180] These changes are related to both increased brain sensitivity and decreased drug clearance.[181]

Opiates

Age is an important predictor of postoperative morphine requirements, with older patients needing less drug for pain relief (see also Chapter 31).[182] Morphine and its metabolite morphine-6-glucuronide have analgesic properties. Morphine clearance is decreased in older adults.[183]

Morphine-6-glucuronide depends on renal excretion.[184] Patients with renal insufficiency may have impaired elimination of morphine glucuronides, and this may account for some of the enhanced analgesia from a given dose of morphine in the older patient.[185]

Shafer[174] provided a comprehensive review of the pharmacology of sufentanil, alfentanil, and fentanyl in older patients. Sufentanil, alfentanil, and fentanyl are approximately twice as potent in older patients. These findings are primarily related to an increase in brain sensitivity to opioids with age, rather than alterations in pharmacokinetics.

Aging is associated with changes in both the pharmacokinetics and pharmacodynamics of remifentanil. An increase in brain sensitivity to remifentanil occurs with age. Remifentanil is approximately twice as potent in

the older adults, and half the bolus dose is required.[186] The volume of the central compartment, V1, and clearance decrease with age, and approximately one-third the infusion rate is required in the older adult.[186]

Neuromuscular Blocking Drugs

Generally, age does not significantly affect the pharmacodynamics of muscle relaxants (see also Chapter 34). Duration of action may be prolonged, however, if the drug depends on liver or renal metabolism. One would expect that pancuronium clearance would decrease in older patients because of its dependence on renal excretion. Yet, changes in pancuronium clearance with aging are controversial.[187,188] Atracurium depends to a small extent on hepatic metabolism and excretion, and elimination half-life is prolonged in older individuals. Clearance is unchanged with age, suggesting that alternative pathways of elimination (ester hydrolysis and Hofmann elimination) assume importance in older patients.[189] Cisatracurium undergoes Hofmann degradation and is unaffected by age. Plasma clearance of vecuronium is slower in older patients.[188] The age-related prolonged duration of action of vecuronium may reflect decreases in renal or hepatic reserve.[190] Rocuronium is associated with a prolonged duration in older patients, and recovery after administration of sugammadex may be delayed.[191,192]

Neuraxial Anesthesia and Peripheral Nerve Blocks

Age has no effect on duration of motor blockade with bupivacaine spinal anesthesia (see also Chapter 56).[193] The time of onset is decreased, however, and spread is more extensive with hyperbaric bupivacaine solution.[193,194] Effects of age on duration of epidural anesthesia have not been determined with 0.5% bupivacaine.[195] When using 0.75% ropivacaine for peripheral nerve block, age is a major factor in determining duration of motor and sensory blockade.[196]

ANESTHETIC TECHNIQUE

Advantages of Specific Drugs in Older Adults

Perioperative care should be tailored to comorbid disease and requirements of the surgical procedure. Several comments concerning pharmacologic and physiologic management are in order, however. A role may exist for shorter acting anesthetics in caring for older patients. A more predictable method of opioid titration may be to use a shorter acting opioid, such as remifentanil. By adjusting the bolus and infusion doses, the variability in remifentanil pharmacokinetics is considerably less than for other intravenous opioids.[197] Similarly, shorter acting muscle relaxants probably should be used. An increased incidence of residual neuromuscular block and pulmonary complications occur in patients receiving pancuronium in contrast to atracurium or vecuronium[198] (see also Chapters 34 and 35). When comparing inhaled anesthetics, there does not appear to be a significant difference in recovery profile of cognitive function. Desflurane is associated with the most rapid emergence.[199,200]

Generally, it is unclear what constitutes the optimal physiologic management to produce the best surgical outcomes. Yet, hemodynamic responses to anesthesia and surgery may be associated with adverse outcome. These findings are in opposition to earlier work suggesting hypotension can be well tolerated in older patients.[90] A recent study reports a strong association between 30-day mortality and hypotension in the presence of low BIS and low minimum alveolar gas concentrations during noncardiac surgery.[201] An association between severity and duration of intraoperative hypotension and 1-year mortality in older patients also has been reported.[202] It is unclear if these studies are identifying a susceptible population with decreased end-organ reserve based on sensitivity to anesthetics or suggesting a potential therapeutic target for intraoperative management. However, earlier studies have demonstrated that older patients can safely receive controlled hypotensive anesthesia (mean arterial blood pressure range of 45 to 55 mm Hg) during orthopedic procedures without increased risk.[90] Further controversy surrounds the question of whether better outcomes are obtained with goal-directed therapy when hemodynamic monitoring is used to optimize hemodynamics and fluid administration. No benefit is thought to exist for therapy directed by pulmonary artery catheter over standard care in older, high-risk surgical patients requiring intensive care.[203]

Regional Versus General Anesthesia

The difference in outcome between regional and general anesthesia in older patients is not clear.[204] Many types of surgery, including major vascular and orthopedic procedures, have been studied.[205,206] Furthermore, the incidence of POCD is similar with regional versus general anesthesia.[207] Yet, other specific effects of regional anesthesia may provide some benefit. First, regional anesthesia affects the coagulation system by preventing postoperative inhibition of fibrinolysis.[208] Deep vein thrombosis or pulmonary embolism may occur in 2.5% of patients after certain high-risk procedures.[209] Regional anesthesia may decrease the incidence of deep vein thrombosis after total hip arthroplasty.[210] These findings are controversial, however, because similar results have not been reported with total knee arthroplasty.[211] In lower extremity revascularization, regional anesthesia is associated with a decreased incidence of postoperative graft thrombosis in contrast to that with general anesthesia.[212] Second, the hemodynamic effects of regional anesthesia may be associated with decreased blood loss in pelvic and lower extremity surgery.[213,214] Third, regional anesthesia does not necessitate instrumentation of the airway and may allow patients to maintain their own airway and level of pulmonary function. Older patients are likely more susceptible to hypoxemic episodes in the recovery room. Patients who undergo regional anesthesia may have a lower risk for hypoxemia.[215] However, it is unclear whether fewer pulmonary complications occur with regional versus general anesthesia. Finally, well-conducted regional anesthesia has opiate-sparing effects that may benefit older patients after total joint arthroplasty.[216]

POSTOPERATIVE CONSIDERATIONS

Postanesthesia Care Unit

No guidelines for postanesthesia care unit (PACU) management relate specifically to older patients because many issues of anesthetic recovery are shared by all age groups (see also Chapter 96). Postoperative management of pulmonary problems is of particular importance because the most important patient-related factors for postoperative pulmonary complications are age and ASA status.[217] In the PACU, older patients have a greater reported incidence of postoperative desaturation.[218] In addition, the aged may be at higher risk for aspiration secondary to the progressive decrease in laryngopharyngeal sensory discrimination and associated dysfunctional swallowing.[219] Urinary retention is more common in older adults[220]; nausea and vomiting are not.[221]

Treatment of Acute Postoperative Pain

Experimental and clinical studies provide support for the notion of an age-related decrease in pain perception.[222,223] However, whether the observed changes are caused by the aging process or reflect other age-associated effects such as an increased presence of comorbid disease is not known.[224] A greater problem occurs in cognitively impaired patients. Alzheimer disease is associated with a decrease in reported pain.[225] In contrast to older persons without dementia, patients with Alzheimer disease appear to perceive pain less intensely and with a corresponding decrement in its affective component.[226]

Although the sensory-discriminative component of pain is maintained in patients with Alzheimer disease, pain tolerance increases with the severity of dementia.[227] The basic principles of evaluation of pain in older patients are similar to those in other age groups. In addition, aging alters functional organ reserve and pharmacokinetics. Thus, the combination of pain assessment and drug dose adjustment provides challenges in the management of postoperative pain in older patients. Many of the principles of postoperative pain management in older patients are discussed in Chapters 64 and 98. Several general principles should be kept in mind when managing frail, older patients. For one, multiple modalities of analgesia should be considered, such as intravenous patient-controlled analgesia and regional nerve blocks, which will enhance analgesia and reduce opioid toxicity. This principle is especially important in frail elders, who often tolerate systemic opioids poorly. Second, the use of site-specific analgesia is a helpful adjunct. Certain operative sites, such as the upper extremity, are especially amenable to local nerve blocks. Third, whenever possible, nonsteroidal antiinflammatory drug preparations should be used to spare opioids, enhance analgesia, and decrease inflammatory mediators. Unless the patient has a contraindication or strong concern exists about hemostasis or peptic ulceration, nonsteroidal antiinflammatory drugs should generally be administered.[228] Opioid-based postoperative pain management may be used in older patients. However, it is imperative to keep in mind the alterations in dose requirements that occur with age.

Iatrogenic Complications

Numerous hazards of hospitalization exist for the older surgical patient. Iatrogenic complications are common and of increased severity in older adults.[229]

Those of importance to the anesthesiologist include adverse drug events, dehydration, delirium, and functional decline. Adverse drug events have a reported prevalence of 14.6% in hospitalized patients 70 years of age and older and are associated with both the number of new inpatient medications and admission cognitive status. Patients experiencing an adverse drug event often incur a longer length of stay and functional decline.[230-232]

OUTCOMES

The goal of a surgical intervention should be to preserve or improve activity and independence while avoiding disability.[233] Although many procedures can be performed with relatively low mortality rates, functional recovery may be challenging and require significant time for many high-risk older patients.[129] After major abdominal surgery, functional recovery may take up to 6 months or longer for patients older than 60 years.[234] Many patients undergoing vascular surgery experience a decline in capacity for independent function.[235] Postoperative complications are common in hospitalized older patients, with the incidence ranging from 20% to 50% and associated with both short-term and long-term mortality.[236]

For older patients requiring admission to an ICU, survival to discharge is most closely related to severity of illness at the time of admission, and age and prehospital functional status correlate most closely with long-term survival.[237] Recovery is often a long process, with many elders requiring assistance with IADL up to 1-year after discharge.[238]

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Chapter 81

Anesthesia for Trauma

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Key Points

- Successful perioperative anesthesia care for patients who have undergone acute trauma depends on an understanding of trauma system design and surgical priorities.
- Successful emergency airway management is based on having a clear plan, such as the American Society of Anesthesiologists algorithm for difficult airways adapted for trauma. In general, rapid-sequence induction of anesthesia and in-line cervical stabilization, followed by direct laryngoscopy or video laryngoscopy, is the safest and most effective approach. The use of cricoid pressure is controversial and is no longer a class I recommendation.
- Recognition of hemorrhagic shock is at the center of advanced trauma life support. Hemorrhagic shock indicates the need for rapid operative treatment, with the possibility of a damage control approach. Although establishing an adequate airway remains the initial priority, obvious hemorrhage should be concurrently addressed through immediate application of tourniquets or direct pressure.
- Resuscitation during acute hemorrhagic shock has undergone a significant change in emphasis. Current recommendations are to maintain deliberate hypotension during active bleeding by limitation of crystalloid infusion. Recognizing the impact of early coagulopathy in trauma, a "hemostatic" resuscitation should be employed, with an emphasis on maintenance of blood composition by early transfusion of red blood cells, plasma, and platelets and viscoelastic monitoring (see also Chapter 61) when available.
- Management of patients with severe traumatic brain injury (see also Chapter 70) requires monitoring and maintenance of cerebral perfusion and oxygenation for successful operative and intensive care management.
- Trauma anesthesiology includes a substantial component of critical care practice (see also Chapter 101). Use of intraoperative advanced ventilator strategies, including permissive hypercapnia and facilitated spontaneous ventilation (bilevel or airway pressure release ventilation), may improve outcomes.
- Prehospital, interhospital, and intrahospital transport of critically injured patients is the province of the trauma anesthesiology team and requires planning and attention to detail.

Unintentional injury is the leading cause of death between the ages of 1 and 45 years in the United States and the fifth leading cause of death overall.[1] Because it affects primarily the young, trauma is *the* leading cause of years of life lost before the age of 75 years. The World Health Organization (WHO) estimates that injury is the leading cause of death worldwide for both men and women from the age of 15 to 44 years; and by 2020, injuries will be the third leading cause of death and disability in all age groups.[2] Unlike in developed nations, where road traffic deaths are predicted to decrease by 2020, annual road traffic mortality is expected to increase by 80% in low- and middle-income countries.[3]

Globally, approximately 16,000 people die of injuries every day and approximately 5.8 million people every year, which corresponds to an annual mortality rate of 97.9 per 100,000 population. Mortality from injury underrepresents the true burden of disease inasmuch as hundreds of people require hospital treatment for every death. According to the 2002 *World Report on Violence and Health,* injury accounts for 12.2% of the total burden of disease.[4] In contrast to other disease and health conditions, morbidity and disability as a result of injury account for a disproportionate number of deaths in children and young adults. This leads to a major burden on health sector and social welfare services, and the

economic consequences include both the cost of care and a substantial amount of lost productivity.

Globally, more than nine people die every minute from injuries or violence. The three leading causes of injury and violence-related deaths are road traffic incidents, suicides, and homicides.[5] Many patients in the world have little or no access to trauma care. In the United States, research shows that receiving care at a Level I trauma center can decrease the risk for death among seriously injured patients by 25%.[6] The Centers for Disease Control and Prevention (CDC) National Center for Injury Prevention and Control and the WHO Violence and Injury Prevention program have several global projects under way that are aimed at building trauma-response capacity to decrease this burden of injury.

Management of trauma patients presents unique challenges to the health care system because they require resource-intensive care, they have multiple injuries to multiple body systems, and their acute injuries overlie and interact with a variety of chronic medical conditions. Anesthesia providers in practice at designated trauma centers are involved in the care of trauma patients, beginning with airway and resuscitation management in the emergency department (ED) and proceeding through the operating room (OR) to the intensive care unit (ICU). Trauma patients represent a significant proportion of all OR cases managed during night and weekend shifts. Critical care and pain management specialists often see trauma patients as a significant fraction of their practice, depending on the overall purpose of their respective medical centers. Yet even practitioners at outpatient surgery centers encounter trauma patients in need of reconstructive, orthopedic, or plastic surgery.

At the same time, very few anesthesiologists in the United States consider trauma their primary specialty. This is distinct from European practice, in which an anesthesiologist also works in the prehospital environment, as an ED director, or as leader of a hospital's trauma team. The U.S. model, in which many anesthesiologists treat trauma patients but few do so exclusively, has led to a relative dearth of research, publication, and education in this field, except for publications resulting from trauma in a military situation (i.e., wars), which is discussed later in this chapter. This situation is unfortunate because nonmilitary domestic trauma is a rapidly evolving field of study that presents unique challenges to the clinician and one in which improvements in care can have a dramatic impact on society as a whole.

Anesthesia for trauma patients is different from routine OR practice. Most urgent cases occur during off-hours, when the most experienced OR and anesthesia personnel may not be available. In small hospitals and military and humanitarian practice, austere conditions may influence the resources available. Patient information may be limited, and allergies, genetic abnormalities, and previous surgeries may create sudden crises. Hopefully, with the increasing dependence of medicine on information technology (computers), such patient information will become more readily available. Patients are frequently intoxicated, with full stomachs and the potential for cervical spine instability. Simple operations may become complicated, and specialty surgical and anesthesia equipment may be required on short notice. Patients often have multiple injuries requiring complex positioning, multiple procedures, and the need to consider priorities in management. Occult injuries, such as tension pneumothorax, can be manifested at unexpected times. Fortunately, there does not appear to be a higher risk for medical liability associated with the provision of anesthesia for trauma versus nontrauma surgical anesthesia cases.[7] Successful perioperative care of these patients requires a good understanding of the basics, supplemented by preparation, flexibility, and the ability to react quickly to changing circumstances.

As with other endemic diseases, successful treatment of trauma extends well beyond the boundaries of an individual hospital. Community-based prevention has included efforts to incorporate airbags in motor vehicles, mandate helmet use on motorcycles, encourage citizens to wear seat belts, punish intoxicated drivers, and promote responsible handgun ownership.[8] These measures have had an impact on the demographics of injury in much the same fashion that smoking cessation, dietary modification, and routine mammography have affected the incidence of heart disease and cancer. When prevention fails, outcomes after injury are heavily influenced by the community's commitment to an organized system of trauma care.[9]

A systems approach to the delivery of trauma care improves outcome. Trauma care systems represent a continuum of integrated care that is a coordinated effort between out-of-hospital and hospital providers with close cooperation of medical specialists in each phase of care. In 1998, the first Academic Symposium to Evaluate Evidence Regarding the Efficacy of Trauma Systems (the Skamania Conference) systematically reviewed the published literature in an effort to quantify the understanding of trauma system effectiveness at that time and to chart a course to outline future research endeavors.[10,11] The Skamania Symposium concluded that treatment at a trauma center versus a nontrauma center is associated with fewer inappropriate deaths and less disability. This conclusion was substantiated in 2006 by a *New England Journal of Medicine* study showing that mortality is reduced when care is provided at a trauma center versus a nontrauma center.[12] Studies in the United States have shown that a reduction in unnecessary deaths from more than 30% to less than 5% occurred in trauma centers compared with general hospitals and that a regionalized system with triage criteria and dedicated trauma centers also reduces the potentially preventable mortality rate to as infrequent as 1% to 3%. However, based on a U.S. study evaluating rates of mortality after implementation of a statewide trauma system program, a mean of *9 years* elapsed after passage of enabling legislation before a significant benefit in survival was achieved.[13]

The degree to which the trauma system is organized and regulated varies widely from state to state across the United States. States such as Maryland, Pennsylvania, Connecticut, and Illinois have established protocols for the care of trauma patients that begin at the moment of first contact with the emergency medical system. In other states the system may be more fragmentary, and care may vary widely across jurisdictions. Mature trauma systems

include protocols for patient triage and transport, standards for hospitals providing trauma care, and data collection systems that facilitate benchmarking. Although some states have written their own standards for certifying trauma hospitals, the most influential national document is *Resources for Optimal Care of the Injured Patient,* published by the American College of Surgeons Committee on Trauma in 2006.[14] This reference offers standards for accreditation of trauma hospitals based on the availability of key resources, the volume of trauma patients treated, and the institutional commitment to prevention and education. The presence of an experienced anesthesiologist and the immediate availability of an open OR are both core resource standards for accreditation of a level 1 trauma center. Patient outcomes are improved when a hospital pursues and attains designation as a trauma center.[15,16]

The numerous innovations in trauma care that have occurred in just the past decade dictate the need for ongoing education, including targeted hemostatic resuscitations; "damage control" surgical techniques; diagnostic modalities such as high-speed computed tomography (CT), angiography, and focused abdominal ultrasound; and perfusion-focused strategies for managing traumatic brain injury (TBI). The coming decades will see new pharmacologic therapies for shock and reperfusion, new strategies for achieving hemostasis, and better patient monitoring. Improving patient outcomes requires a commitment to continuing education on the part of the anesthesiologists and every member of the trauma team.

This chapter provides an overview of important areas of trauma care for the anesthesiologist. We begin with a description of the initial approach to an injured patient, followed by discussions of emergency airway management, resuscitation, and care of patients with central nervous system (CNS) injuries. We briefly cover the needs of orthopedic and reconstructive surgery patients and then conclude with a discussion of postoperative and critical care issues for the trauma anesthesiologist.

PRIORITIZING TRAUMA CARE

The Advanced Trauma Life Support (ATLS) course of the American College of Surgeons is the most widely recognized training program for trauma physicians of all disciplines.[17] Although not comprehensive in subspecialty areas, the ATLS curriculum nonetheless provides a framework and a common language for the care of injured patients. ATLS is based on a primary survey that includes simultaneous efforts to identify and treat life-threatening and limb-threatening injuries, beginning with the most immediate. This focus on urgent problems first is captured by the "golden hour" catchphrase and is the most important lesson of ATLS. Put simply, better outcomes are achieved with faster diagnosis and treatment. Resolution of urgent needs is followed by a meticulous secondary survey and further diagnostic studies designed to reduce the incidence of missed injuries. Knowing the basics of ATLS is essential for *any* physician who interacts with trauma patients. Figure 81-1 is a simplified representation of the ATLS protocol.

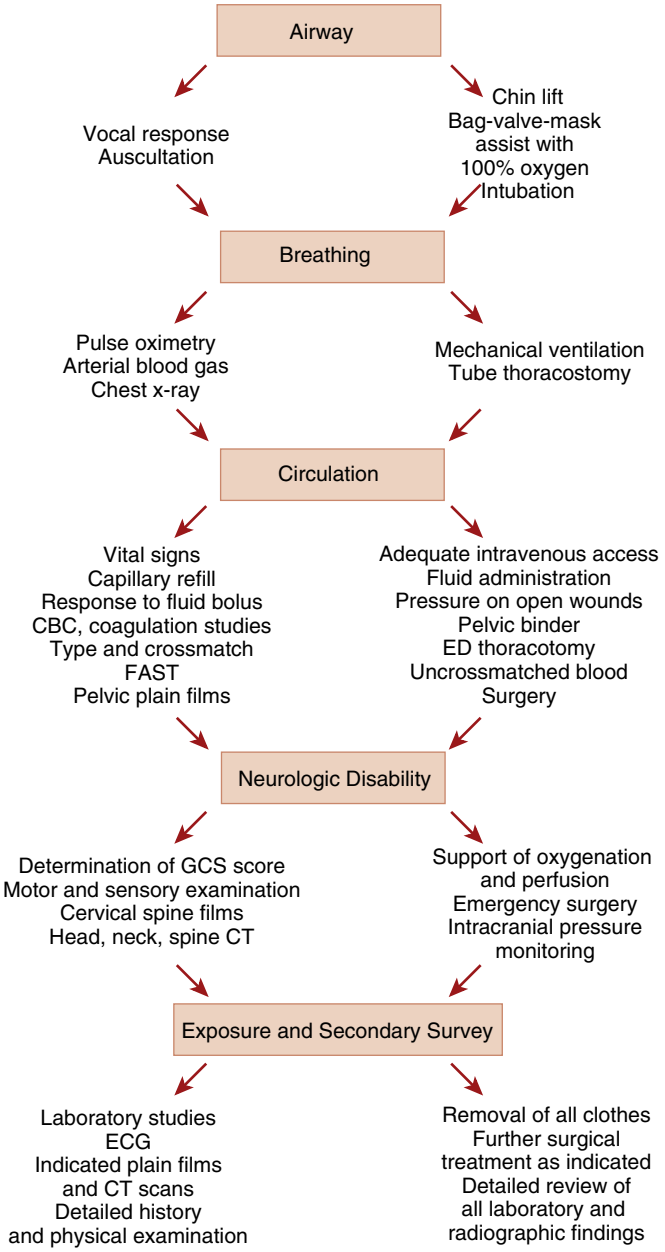


Figure 81-1. Simplified assessment and management of the trauma patient. *CBC,* Complete blood count; *CT,* computed tomography; *ECG,* electrocardiogram; *ED,* emergency department; *FAST,* focused assessment by sonography for trauma; *GCS,* Glasgow Coma Scale. *(Modified from the Advanced Trauma Life Support curriculum of the American College of Surgeons.)*

ATLS emphasizes the ABCDE mnemonic—airway, breathing, circulation, disability, and exposure (see also Chapter 108). Verification of a patent airway and acceptable respiratory mechanics is of primary importance because hypoxia is the most immediate threat to life. Inability to oxygenate the patient will lead to permanent brain injury and death within 5 to 10 minutes. Trauma patients are at risk for airway obstruction and inadequate respiration for the reasons listed in Box 81-1. Endotracheal intubation, whether performed in the prehospital environment or in the ED, must be confirmed immediately by capnometry. Esophageal intubation or endotracheal tube dislodgement

BOX 81-1 *Causes of Obstructed Airway or Inadequate Ventilation in a Trauma Patient*

Airway Obstruction

Direct injury to the face, mandible, or neck
Hemorrhage in the nasopharynx, sinuses, mouth, or upper airway
Diminished consciousness secondary to traumatic brain injury, intoxication, or analgesic medications
Aspiration of gastric contents, blood, or a foreign body (i.e., dentures, broken teeth, soft tissue)
Misapplication of oral airway or endotracheal tube (esophageal intubation)

Inadequate Ventilation

Diminished respiratory drive secondary to traumatic brain or high cervical spine injury, shock, intoxication, hypothermia, or oversedation
Direct injury to the trachea or bronchi
Pneumothorax or hemothorax
Chest wall injury
Aspiration
Pulmonary contusion
Cervical spine injury
Bronchospasm secondary to smoke or toxic gas inhalation

are common and devastating if not promptly corrected. When cardiac arrest exists, end-tidal carbon dioxide values may be very low; direct laryngoscopy should be performed if there is any question about the location of the endotracheal tube (see also Chapter 55).

If establishment of a secure airway and adequate ventilation requires a surgical procedure such as a tracheostomy, tube thoracostomy, or open thoracotomy, this procedure must precede all others. Indeed, these procedures are commonly performed in the ED, often before the arrival of an anesthesiologist. Subsequent surgery to convert a cricothyroidotomy to a tracheostomy or close an emergency thoracotomy may then follow in the OR.

Hemorrhage is the next most pressing concern inasmuch as ongoing blood loss is inevitably fatal. The symptoms of shock are presented in Box 81-2. Shock is presumed to result from hemorrhage until proved otherwise. Assessment of the circulation consists of an early phase, during active hemorrhage, and a late phase, which begins when hemostasis is achieved and continues until normal physiology is restored. In the early phase, diagnostic efforts focus on the five sites of bleeding detailed in Table 81-1, the only areas in which exsanguinating hemorrhage can occur. Immediate actions to control hemorrhage can include application of pelvic binders for bleeding associated with pelvic fractures or tourniquet application for extremity injuries. Any surgical procedure to diagnose or control active hemorrhage should be immediately transported to the OR. This includes exploration of the neck or pericardium to rule out hemorrhage in sensitive compartments. In the OR, the trauma surgeon focuses on anatomic control of hemorrhage, whereas the anesthesiologist is responsible for restoring the patient's physiology. Goals for early and late resuscitation are discussed in more detail later.

After management of the circulation is assessment of the patient's neurologic status by calculation of the Glasgow Coma Scale (GCS) score (Box 81-3)[18]; examination of the pupils for size, reactivity, and symmetry; and determination of sensation and motor function in each of the extremities. Significant abnormalities on the neurologic examination are an indication for immediate cranial CT. Most trauma patients with a diminished GCS score will have nonoperative

BOX 81-2 *Signs and Symptoms of Shock*

Pallor
Diaphoresis
Agitation or obtundation
Hypotension
Tachycardia
Prolonged capillary refill
Diminished urine output
Narrowed pulse pressure

TABLE 81-1 **DIAGNOSTIC AND THERAPEUTIC OPTIONS FOR MANAGEMENT OF TRAUMATIC HEMORRHAGE**

Site of Bleeding	Diagnostic Modalities	Treatment Options
Chest	Chest x-ray Thoracostomy tube output Chest CT	Observation Surgery
Abdomen	Physical examination Ultrasound (FAST) Abdominal CT Peritoneal lavage	Surgical ligation Angiography Observation
Retroperitoneum	CT Angiography	Angiography
Long bones	Physical examination Plain x-rays	Fracture fixation Surgical ligation
Outside the body	Physical examination	Direct pressure Surgical ligation

CT, Computed tomography; *FAST,* focused assessment by sonography for trauma.

BOX 81-3 *Glasgow Coma Score**

Eye-Opening Response

4 = Spontaneous
3 = To speech
2 = To pain
1 = None

Verbal Response

5 = Oriented to name
4 = Confused
3 = Inappropriate speech
2 = Incomprehensible sounds
1 = None

Motor Response

6 = Follows commands
5 = Localizes to painful stimuli
4 = Withdraws from painful stimuli
3 = Abnormal flexion (decorticate posturing)
2 = Abnormal extension (decerebrate posturing)
1 = None

*The Glasgow Coma Score is the sum of the best scores in each of three categories.

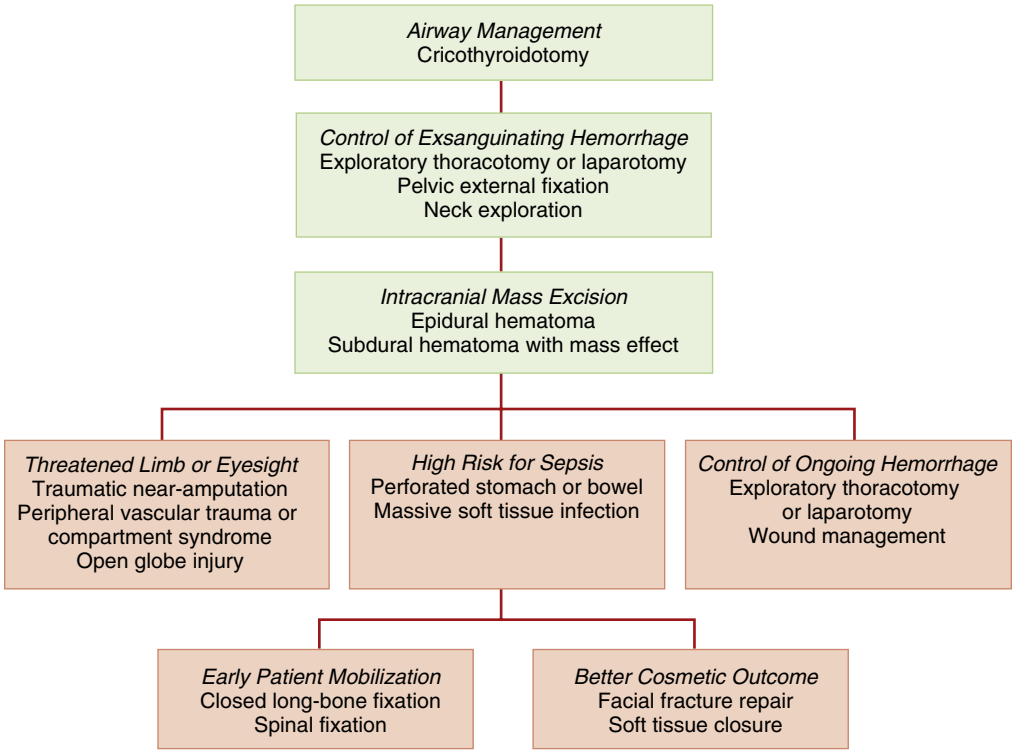


Figure 81-2. Surgical priorities in a trauma patient. *(Reprinted with permission from Dutton RP, Scalea TM, Aarabi B: Prioritizing surgical needs in the patient with multiple injuries,* Probl Anesth *13:311, 2001.)*

conditions, but for the few who require operative evacuation of an epidural or subdural hematoma, timeliness of treatment has a strong influence on outcome. Patients with unstable spinal canal injuries and incomplete neurologic deficits will also benefit from early surgical stabilization.

The final step in the primary survey is complete exposure of the patient and a head-to-toe search for visible injuries or deformities, including deformities of bones or joints, soft tissue bruising, and any breaks in the skin. The anesthesiologist can assist in this procedure by support of the head and neck, maintenance of the airway, and care in manipulating the spine.

After the primary survey a more deliberate secondary examination should be undertaken that includes a thorough history and physical examination, diagnostic studies, and subspecialty consultation. Any remaining injuries are diagnosed at this time and treatment plans established. Indications for urgent or emergency surgery also may arise during the secondary survey. The presence of a limb-threatening injury as a result of vascular compromise, compartment syndrome, or a severely comminuted fracture is one such indication. Although the awakening, breathing, coordination, delirium monitoring and management, and early mobility (ABCDE) issues must be addressed first, a pulseless extremity, compartment syndrome, near-amputation, or massively fractured extremity must go to the OR as soon as the patient is otherwise stable.

Another category of urgency arises in patients with a time-dependent potential for systemic infection. Because sepsis is a leading cause of complications and death in trauma patients, open injuries should be thoroughly debrided—and closed if appropriate—at the earliest opportunity (see also Chapters 101 and 102). Other urgent indications for surgery include perforation of the bowel, open fracture, and extensive soft tissue wounds. The frequency of infectious complications of open fractures increases in a linear fashion with time from the moment of injury until operative debridement[19] although a recent meta-analysis has challenged the traditional 6-hour rule for initial debridement.[20] Nonetheless, the need for early surgery must be balanced against the need for diagnostic studies, adequate preoperative resuscitation, and the priority of other cases.

Figure 81-2, an algorithm for prioritizing surgical management in trauma patients, is presented with the understanding that individual situations will vary according to available resources and patient response to therapy. A trauma patient often will arrive at the OR with the need for more than one surgical procedure by more than one surgical service. A trauma patient may have injuries requiring emergency surgery coexisting with injuries that can be repaired at any time. The anesthesiologist plays an important role in determining which procedures to perform, in which order, and which procedures should be postponed until the patient is more stable.

ANESTHESIA IN WAR AND AUSTERE CONDITIONS

"While it is evident that the general principles of anesthesia are not affected by the circumstances of war, it is equally evident that it is our duty to assiduously seek those means in anesthesia which are especially suited to the exigencies of battle."[21]

Although written in 1942, these words are still true today, and many of the principles developed from earlier

wars still apply on the modern battlefield or in a large-scale disaster (see also Chapter 83). Recent conflicts and events have allowed anesthesiologists, nurse anesthetists, and other providers to help improve management of traumatically injured patients in the areas of anesthesia, resuscitation, and damage control surgery. Management of battlefield casualties typically follows the same flow as outlined earlier, but with special consideration in the areas of prehospital interventions, resuscitation, technologic and logistic support, patient movement, mass casualty management, and surgical interventions.[22] Pain management considerations also may be affected by the nature of the injuries and transport considerations.[23]

Modern advancements in battle armor, prehospital interventions, provision of forward surgical support, and resuscitative strategies have had an impact on survival from combat injuries. During the most recent conflicts in Iraq and Afghanistan, the killed-in-action rate decreased to 13.9% from 20.2% in Vietnam and World War II.[24] This is mirrored by a similar reduction in the case fatality rate. Paradoxically, the ability to get many of the severely wounded patients to a hospital (e.g., rapidly by helicopter) has led to an increase in the "died-of-wounds" rate. Most likely this rate would be even higher if not for improvements in surgical management such as damage control techniques, improved ICU care, earlier recognition of abdominal compartment syndrome, liberal use of fresh whole blood (see also Chapter 61), and institution of a theater-wide trauma system approach.

One of the major advances in battlefield medical support has been the rapid movement of patients out of the theater of operations to more comprehensive medical facilities. Even in the late l960s, wounded soldiers were evacuated out of Vietnam within 3 days of injury. In the most recent conflict, the time from injury in the Middle East until return to the United States is frequently less than 81 hours for even the most seriously injured patients.[25] This may include initial in-theater damage control surgery followed by one or two aeromedical evacuation missions lasting up to 12 hours with a critical care air transport team (CCATT). In preparation for such rapid movement, the anesthesiologist must ensure that perioperative interventions such as airway management, pain control, and adequacy of resuscitation are addressed before transfer. In addition, anesthesiologists are frequently assigned to a CCATT as the physician team member based on their overall skill set and ability to provide support en route to critically ill or injured patients. Beyond the support provided during wartime, the CCATT also has proved useful for the movement of critical patients during large-scale disasters such as occurred after Hurricane Katrina in 2005.[26]

Mass casualty situations are not uncommon in wartime conditions, although the role of the anesthesiologist will vary depending on the number of patients and requirements for urgent surgical interventions. Given the limited number of anesthesia providers in most combat-related scenarios, often they are not involved in the triage process. If available, however, anesthesia support can enhance emergency airway management, establishment of venous access, and supervision of resuscitative efforts. Only 10% to 20% of arriving casualties require immediate lifesaving interventions, although a much larger percentage will ultimately require surgical procedures.[27] A well-developed trauma system is persistently evolving, and management of mass casualty scenarios will become routine.[28]

Overall, anesthetic management of battlefield casualties is similar to that for patients in a civilian trauma setting; however, many factors must be considered in the perioperative plan for a combat casualty.[29] Environmental considerations such as extremes of temperature, availability of water, contamination with sand, lack of consistent electricity, and other aspects may have to be taken into consideration. Logistic support chains may be long and unable to provide sufficient supplies in the early phases of a conflict. Deployable equipment, such as drawover vaporizer systems or portable ventilators, may be different from those used during

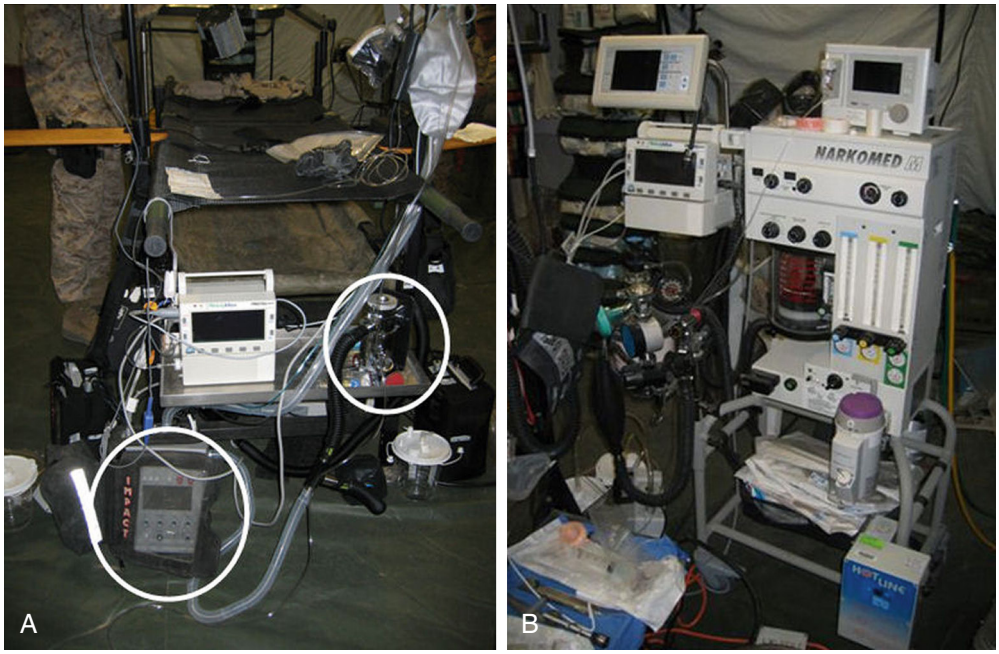


Figure 81-3. Deployable military anesthesia equipment. **A,** Drawover vaporizer and portable ventilator *(circled)* in field hospital. **B,** Portable anesthesia machine. *(Used with permission from CPT Bruce Baker, MD, USN.)*

peacetime, so predeployment training is vital (Fig. 81-3).[30] In addition, techniques such as total intravenous (IV) anesthesia and regional anesthesia or analgesia will frequently be used and thus require familiarity with their management and associated equipment (see also Chapter 57).[29]

Optimal care of wartime casualties or victims of large disasters requires not only familiarity with a broad range of anesthetic principles and techniques but also the ability to be flexible in the face of a rapidly changing environment. With special training in airway management, provision of anesthesia and sedation, resuscitation, and pain management, anesthesiologists may find themselves involved in triage, emergency management, and perioperative and critical care.

EMERGENCY AIRWAY MANAGEMENT

The American Society of Anesthesiologists (ASA) algorithm for management of difficult airways modified for trauma (see also Fig. 55-2) is a useful starting point for the trauma anesthesiologist, whether in the ED or the OR (see also Chapter 55).[31,32] The concept of the algorithm is an important one. The anesthesiologist should have a plan for the initial approach to the airway and for coping with any difficulties that might develop. Figure 81-4 is a typical algorithm for emergency intubation of an unstable trauma patient. Note that it differs from the ASA algorithm in that reawakening the patient is seldom an option because the need for emergency airway control will presumably remain. Once the decision to obtain a definitive airway is made, efforts will continue until a cuffed tube is in position in the trachea, whether by conventional intubation or via a surgical approach. Failure to commit to a surgical airway soon enough results in bad outcomes more commonly than do complications of a procedure that might have been unnecessary.

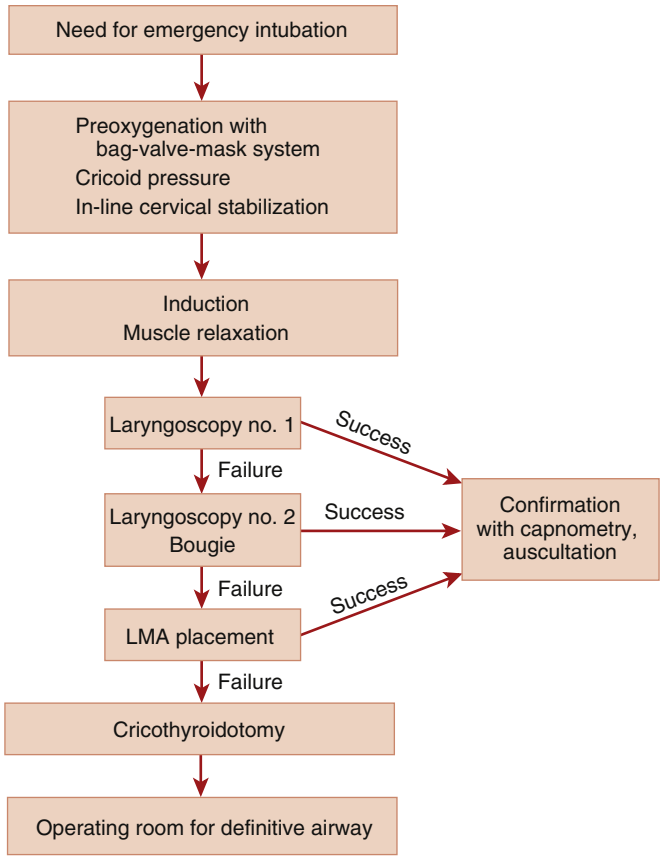


Figure 81-4. Emergency airway management algorithm used at the R. Adams Cowley Shock Trauma Center, presented as an example. Individual practitioners and trauma hospitals should determine their own algorithm, based on available skills and resources. *LMA,* Laryngeal mask airway.

INDICATIONS

The goal of emergency airway management is to ensure adequate oxygenation and ventilation while protecting the patient from the risks for aspiration. Endotracheal intubation is commonly required and is specifically indicated in the following conditions:

- Cardiac or respiratory arrest
- Respiratory insufficiency (see Box 81-1)
- Airway protection
- Need for deep sedation or analgesia, up to and including general anesthesia
- Transient hyperventilation of patients with space-occupying intracranial lesions and evidence of increased intracranial pressure (ICP)
- Delivery of a 100% fraction of inspired oxygen (FiO_2) to patients with carbon monoxide poisoning
- Facilitation of the diagnostic workup in uncooperative or intoxicated patients

APPROACH TO ENDOTRACHEAL INTUBATION

In general, monitoring standards for airway management should be the same in the ED and OR, including an electrocardiogram (ECG), blood pressure, oximetry, and capnometry. Appropriate equipment, including an O_2 source, bag-valve-mask ventilating system, mechanical ventilator, suction, and a selection of laryngoscope blades, endotracheal tubes, and devices for managing difficult tracheal intubations, should be available in any location where emergency intubation is likely, including the ED.

Endotracheal intubation is best accomplished in almost all cases with a modified rapid-sequence approach by an experienced clinician. Although concern may exist that the use of neuromuscular blocking drugs and potent anesthetics outside the OR will be associated with a more frequent complication rate, in fact the opposite is more likely correct. Anesthesia and neuromuscular blockade allow the best tracheal intubating conditions on the first approach to the airway, which is advantageous in an uncooperative, hypoxic, or aspirating patient. Attempts to secure the airway in an awake or lightly sedated patient increase the risk for airway trauma, pain, aspiration, hypertension, laryngospasm, and combative behavior. Experienced providers, supported by appropriate monitoring and equipment, have achieved results of medication-assisted intubation outside the OR that are equivalent to those for emergency tracheal intubation within the OR (Table 81-2).[33-35]

TABLE 81-2 DRUG-ASSISTED INTUBATIONS OUTSIDE THE OPERATING ROOM

Author	No. Patients	Problems
Talucci et al[35]	260	No hemodynamic or neurologic complications
Stene et al[34]	>3,000	No difference from OR
Rotondo et al[33]	204	No difference from OR
Karlin*	647	None noted

Modified from Karlin A: Airway management of trauma victims, Probl Anesth *13:283, 2001.*
OR, Operating room.
*Unpublished data.

PROPHYLAXIS AGAINST PULMONARY ASPIRATION OF GASTRIC CONTENTS

A trauma patient should always be treated as having a full stomach and at risk for aspiration of gastric contents during induction of anesthesia (see also Chapter 55). Reasons include ingestion of food or liquids before the injury, swallowed blood from oral or nasal injuries, delayed gastric emptying associated with the stress of trauma, and administration of liquid contrast medium for abdominal CT scanning. As with obstetric anesthesia (see also Chapter 77), nonparticulate antacids should be given to a trauma patient before induction of anesthesia if time and patient cooperation exist.

Cricoid pressure—the Sellick maneuver—has been recommended to be applied continuously during emergency airway management from the time the patient loses protective airway reflexes until endotracheal tube placement and cuff inflation are confirmed. The Sellick maneuver consists of elevating the patient's chin (without displacing the cervical spine) and then pushing the cricoid cartilage posteriorly to close the esophagus. However, cricoid pressure may worsen the laryngoscopic grade of view in up to 30% of patients[36] without providing effective prevention of aspiration of gastric contents.[37] In a recent prehospital study evaluating the impact of cricoid pressure on subsequent intubation success, discontinuing cricoid pressure usually facilitated intubation of the trachea without worsening the grade of laryngoscopic view.[38] Thus, cricoid pressure should be released in the trauma patient if a difficult intubation can be facilitated. The lack of evidence supporting the use of cricoid pressure and its potential to make intubation more difficult led the American Heart Association to recommend discontinuation of its use during cardiac arrest situations.[39] Additionally, the Eastern Association for the Surgery of Trauma Practice Management Guidelines for emergency tracheal intubation have removed it as a class 1 recommendation.[40]

In the traditionally defined rapid-sequence induction of anesthesia, any attempt at ventilation between administration of medication and intubation is avoided, presumably because positive-pressure ventilation may force gas into the patient's stomach, leading to regurgitation and aspiration. Sellick's original paper described ventilation during cricoid pressure in patients with full stomachs with the belief that cricoid pressure during mask ventilation would prevent gastric inflation.[41] Although this may be true, cricoid pressure reduces tidal volumes, increases peak inspiratory pressure, or prevents ventilation.[37] On the other hand, the increase in O_2 consumption in trauma patients necessitates preoxygenation whenever possible. If preoxygenation is not possible as a result of facial trauma, decreased respiratory effort, or agitation, *rapid desaturation is a possibility. Positive-pressure ventilation during all phases of induction provides the largest possible O_2 reserve during emergency airway management and will help mitigate hypoxia if intubation proves difficult. In this situation, large tidal volumes and high peak inspiratory pressures should be avoided. Application of cricoid pressure during attempts at positive-pressure ventilation should be considered to reduce gastric inflation, but it may prevent effective ventilation in some patients necessitating discontinuation.

PROTECTION OF THE CERVICAL SPINE

Standard practice dictates that all victims of blunt trauma be assumed to have an unstable cervical spine until this condition is ruled out. The airway management of these patients receives much attention from anesthesiologists because direct laryngoscopy causes cervical motion, with the potential to exacerbate spinal cord injury (SCI). Stabilization of the cervical spine will generally occur in the prehospital environment, with the patient already having a rigid cervical collar in place. This collar may be kept in place for several days before the complete gamut of tests to rule out cervical spine instability have been completed (see later discussion). The presence of an "uncleared" cervical spine mandates the use of in-line manual stabilization (not traction) throughout any attempt at intubation.[17] This approach allows removal of the front of the cervical collar to facilitate wider mouth opening and jaw displacement; however, this may slightly lengthen the time to intubation and worsen laryngeal visualization during laryngoscopy.[42] In-line stabilization has been tested through considerable clinical experience and is the standard of care in the ATLS curriculum. Emergency awake fiberoptic intubation, though requiring less manipulation of the neck, is generally very difficult because of airway secretions and hemorrhage, rapid desaturation, and lack of patient cooperation and is best reserved for cooperative patients with known cervical instability under controlled conditions. Indirect video laryngoscopy with systems such as the Bullard laryngoscope[43] or GlideScope[44,45] offer the potential to enjoy the best of both worlds: an anesthetized patient and decreased cervical motion.[46,47] In comparative studies of direct laryngoscopy, video laryngoscopy, fiberoptic intubation, blind nasal intubation, or cricothyrotomy—in patients with known cervical cord or spine injuries, or both—there is no difference in neurologic deterioration with technique used, and no clear evidence that direct laryngoscopy worsens outcome.[48]

PERSONNEL

Emergency endotracheal intubation requires more assistance than an intubation performed under controlled conditions (see also Chapter 7). Three providers are required to ventilate the patient and manage the airway,



Figure 81-5. Emergency intubation of a trauma patient, immobilized on a long spine board. The front of the cervical collar is removed once in-line manual stabilization of the spine is established, allowing for cricoid pressure and greater excursion of the mandible. *(Reprinted with permission from Dutton RP: Spinal cord injury,* Int Anesthesiol Clin *40:111, 2002.)*

administer medications, and provide in-line cervical stabilization; a fourth provider may be needed to provide cricoid pressure if deemed appropriate. Figure 81-5 is an illustration of this approach. Additional assistance may be required to restrain a patient who is combative as a result of intoxication or TBI.

The immediate presence of a surgeon or other physician who can expeditiously perform a cricothyroidotomy is desirable. Even if a surgical airway is not required, additional experienced hands may prove useful during difficult intubations. The surgeon may also wish to inspect the upper airway during laryngoscopy if trauma to the face or neck has occurred. Urgent tube thoracostomy may prove necessary in some trauma patients to treat the tension pneumothorax that develops with the onset of positive-pressure ventilation.

ANESTHETICS AND INDUCTION OF ANESTHESIA

Any IV anesthetic administered to a trauma patient in hemorrhagic shock may cause profound hypotension and even cardiac arrest as a result of inhibition of circulating catecholamines. Although propofol is the mainstay of IV induction in the OR, its use in trauma patients is especially problematic because of its vasodilatory and negative inotropic effects. Moreover, the effects of hemorrhagic shock on the brain potentiate anesthetics, with propofol doses as small as one tenth of normal producing deep anesthesia in animals in shock.[49] Etomidate is a frequently espoused alternative because of its cardiovascular stability in contrast to other IV hypnotic drugs in the trauma population,[50-52] although its inhibition of catecholamine release may still produce hypotension.

Ketamine continues to be popular for induction of anesthesia in trauma patients because it is a CNS stimulant.[53] However, it is also a direct myocardial depressant.[54,55] In normal patients the effect of catecholamine release masks cardiac depression and results in hypertension and tachycardia. In hemodynamically stressed patients the cardiac depression may be unmasked and lead to cardiovascular collapse.[56]

Hypotension will develop in patients with hypovolemia with the administration of any anesthetic because of interruption of compensatory sympathetic outflow and the sudden change to positive-pressure ventilation. Previously healthy young patients can lose up to 40% of their blood volume before hypotension occurs, thereby leading to potentially catastrophic circulatory collapse with induction of anesthesia, regardless of the anesthetic chosen. The dose of anesthetic must be decreased in the presence of hemorrhage, including no anesthetic at all in patients with life-threatening hypovolemia. Rapid-sequence induction of anesthesia and endotracheal intubation may proceed with muscle relaxants alone, although onset time may be prolonged in a patient with circulatory impairment. Subsequent patient recall of intubation and emergency procedures is highly variable and affected by the presence of coexisting TBI, intoxication, and the depth of hemorrhagic shock (see also Chapters 13 and 14). Decreased cerebral perfusion inhibits memory formation but cannot be reliably associated with any particular blood pressure or chemical marker. Administration of 0.2 mg of scopolamine (a tertiary ammonium vagolytic) may inhibit memory formation in the absence of anesthetic drugs in this situation, but it may interfere with subsequent neurologic examination because of its long half-life. Small doses of midazolam will reduce the incidence of patient awareness but also can contribute to hypotension. Although recall of ED and OR events is not unusual in this circumstance, anesthesia provider liability appears to be limited; an analysis of intraoperative awareness lawsuits in the ASA Closed Claims Database revealed no claims related to surgery in trauma patients.[57]

NEUROMUSCULAR BLOCKING DRUGS

Succinylcholine remains the neuromuscular blocker with fastest onset—less than 1 minute—and shortest duration of action—5 to 10 minutes (see also Chapters 34 and 35). These properties make it popular for rapid-sequence induction of anesthesia. Although the use of succinylcholine may allow return of spontaneous respiration before the development of significant hypoxia in the "cannot intubate, cannot ventilate" situation, this is unlikely to be of benefit in an emergency intubation in a trauma patient. The anesthesiologist should not rely on return of spontaneous breathing in time to salvage a difficult airway management problem but should instead proceed with efforts to obtain a definitive airway, including cricothyroidotomy if other possibilities have been exhausted.

Administration of succinylcholine is associated with several adverse consequences. Increases in serum potassium of 0.5 to 1.0 mEq/L are expected, but in certain patients K^+ may increase by more than 5 mEq/L.[58] A hyperkalemic response is typically seen in burn victims and those with muscle pathology secondary to direct trauma, denervation (as with SCI), or immobilization. Hyperkalemia is not seen in the first 24 hours after these injuries, and succinylcholine may be used safely for acute

airway management. Patients at risk are those with underlying pathologic processes before their traumatic event or those undergoing subsequent surgery in the weeks to months after injury.

Succinylcholine causes an increase in intraocular pressure and should be used cautiously in patients with ocular trauma.[59] Succinylcholine may also increase intracranial pressure (ICP),[60] so its use in patients with brain trauma is controversial. In both these cases, however, hypoxia and hypercapnia may be as damaging as the transient increase in pressure caused by the drug. If the use of succinylcholine will lead to faster intubation, its benefits may outweigh its risks. The provider must weigh the use of succinylcholine in each individual situation based on the acuity of CNS injury, the anticipated speed with which intubation can be accomplished, and the likelihood that hypoxia will develop.

Alternatives to succinylcholine include rocuronium 0.9 to 1.2 mg/kg and vecuronium 0.1 to 0.2 mg/kg. Rocuronium is preferred because it has a more rapid onset of action than that of vecuronium. Also, large doses of rocuronium can be immediately reversed with a relatively new antagonist, sugammadex. Basically, the combination of rocuronium and sugammadex provides all the advantages of succinylcholine, but none of the complications. Because these drugs have no significant cardiovascular toxicity, large doses can be administered to achieve rapid (1- to 2-minute) paralysis.

Specific situations will always exist in which maintaining spontaneous ventilation during intubation is the preferred manner in which to proceed. If patients are able to maintain their airway temporarily but have clear indications for an artificial airway (e.g., penetrating trauma to the trachea), slow induction with ketamine or inhaled sevoflurane through cricoid pressure will enable placement of an endotracheal tube without compromising patient safety.

ADJUNCTS TO ENDOTRACHEAL INTUBATION

Equipment to facilitate difficult intubation should be readily available wherever emergency airway management is performed (see also Chapter 55). The particular equipment available depends on the preferences of the anesthesiologist; the usefulness of most special equipment depends more on previous experience than on any intrinsic properties of the device. Certain items deserve mention, however, because they are frequently cited as aids to management of a difficult airway.

The gum elastic bougie, or intubating stylet, is an inexpensive and easily mastered adjunct for management of a difficult airway. The stylet is placed through the vocal cords via direct laryngoscopy, and the endotracheal tube is then advanced over the stylet into the trachea. Placement of the bougie is easier than direct placement of an endotracheal tube because of both its smaller diameter and the ability of an experienced operator to feel it enter the trachea even when the glottic opening cannot be visualized. The bougie is passed under the epiglottis and gently advanced; if resistance is met, the bougie is withdrawn, rotated slightly, and advanced again. In this fashion the anesthesiologist can blindly palpate the larynx until the bougie advances into the trachea. The bougie also can be used with indirect video laryngoscopy systems such as the GlideScope (Verathon, Bothell, Wash) and is especially useful in the ED when the sniffing position cannot be used because of uncertainty about the cervical spine. The GlideScope may provide improved visualization (based on the Cormack score) and facilitate safe intubation in patients wearing a cervical collar.[61]

The laryngeal mask airway (LMA) (LMA North America, San Diego, Calif) is recommended in the ASA algorithm for management of a patient with a difficult airway. The LMA can be used as a guide for intubation when an unsuspected difficult intubation is encountered in a trauma patient; an endotracheal tube may be placed blindly through the lumen of the LMA and into the trachea, or a fiberoptic bronchoscope may be used to guide the tube through the LMA. The LMA is an appropriate rescue device for a difficult airway situation in trauma, provided no major anatomic injury or hemorrhage is present in the mouth and larynx. In our practice the LMA has most commonly been used as a bridge to emergency tracheostomy because it allows more controlled conditions than a cricothyroidotomy.

ORAL VERSUS NASOTRACHEAL INTUBATION

The most recent ATLS guidelines suggest that practitioners providing emergency airway management should proceed with the method of intubation with which they are most proficient.[17] In general, oral intubation is preferable to nasal intubation in the emergency setting because of the risk for injury to the brain from nasal instrumentation in the presence of a basilar skull or cribriform plate fracture. Furthermore, nasal intubation poses a risk for sinusitis in a patient who will be mechanically ventilated for longer than 24 hours, and use of a smaller diameter tube will also increase the difficulty of subsequent airway suctioning and fiberoptic bronchoscopy. If nasal intubation is most likely to be successful in a given situation, however, this is the route that should be used. Change to an oral tube with a larger internal diameter can occur once the patient's condition has stabilized.

FACIAL AND PHARYNGEAL TRAUMA

Trauma to the face and upper airway poses particular difficulties for the anesthesiologist. Serious skeletal derangements may be masked by apparently minor soft tissue damage. Failure to identify an injury to the face or neck can lead to acute airway obstruction secondary to swelling and hematoma. Laryngeal edema is also a risk in patients who have suffered chemical or thermal injury to the pharyngeal mucosa. Intraoral hemorrhage, pharyngeal erythema, and change in voice are all indications for early intubation.

In general, both maxillary and mandibular fractures will make ventilation by mask more difficult, whereas mandibular fractures will make endotracheal intubation easier. Palpation of the facial bones before manipulation of the airway will alert the anesthetist to these possibilities. Patients with injuries to the jaw and zygomatic arch often have trismus. Although the trismus will resolve with the administration of neuromuscular blocking agents,

preinduction assessment of airway anatomy may be difficult. Bilateral mandibular fractures and pharyngeal hemorrhage may lead to upper airway obstruction, particularly in a supine patient, although intubation may be easier because of loss of skeletal resistance to direct laryngoscopy. A patient arriving at the ED in the sitting or prone position because of airway compromise is best left in that position until the moment of anesthetic induction and intubation.

RESUSCITATION FROM HEMORRHAGIC SHOCK

Resuscitation refers to restoration of normal physiology after injury. Resuscitation from hemorrhagic shock refers specifically to restoration of normal circulating blood volume, normal vascular tone, and normal tissue perfusion. Resuscitation begins immediately after injury, via the patient's own compensatory mechanisms, and continues through the prehospital, ED, OR, and ICU phases of care.

PATHOPHYSIOLOGY OF HEMORRHAGIC SHOCK

During massive hemorrhage an imbalance occurs between systemic O_2 delivery and O_2 consumption. Blood loss leads to hemodynamic instability, coagulopathy, decreased O_2 delivery, decreased tissue perfusion, and cellular hypoxia. The initial response to hemorrhage takes place on the macrocirculatory level and is mediated by the neuroendocrine system. Decreased arterial blood pressure leads to vasoconstriction and release of catecholamines to preserve blood flow to the heart, kidney, and brain, whereas other regional beds are constricted. Pain, hemorrhage, and cortical perception of traumatic injuries lead to the release of hormones and other inflammatory mediators, including renin, angiotensin, vasopressin, antidiuretic hormone, growth hormone, glucagon, cortisol, epinephrine, and norepinephrine.[62] This response sets the stage for the microcirculatory response that follows.

Individual ischemic cells respond to hemorrhage by taking up interstitial fluid, thus further depleting intravascular fluid.[63] Cellular edema may choke off adjacent capillaries and result in the no-reflow phenomenon, which prevents reversal of ischemia even in the presence of adequate macroperfusion.[64] Ischemic cells produce lactate and free radicals, which accumulate in the circulation if perfusion is diminished. These compounds cause direct damage to the cell and form the bulk of the toxic load that washes back to the central circulation when flow is reestablished. Ischemic cells also produce and release inflammatory factors—prostacyclin, thromboxane, prostaglandins, leukotrienes, endothelin, complement, interleukins, tumor necrosis factor, and others.[65] Figure 81-6 shows the inflammatory response to shock, with an emphasis on immune system amplification. This inflammatory response, once begun, becomes a disease process independent of its origin. Such alterations lay the foundations for subsequent

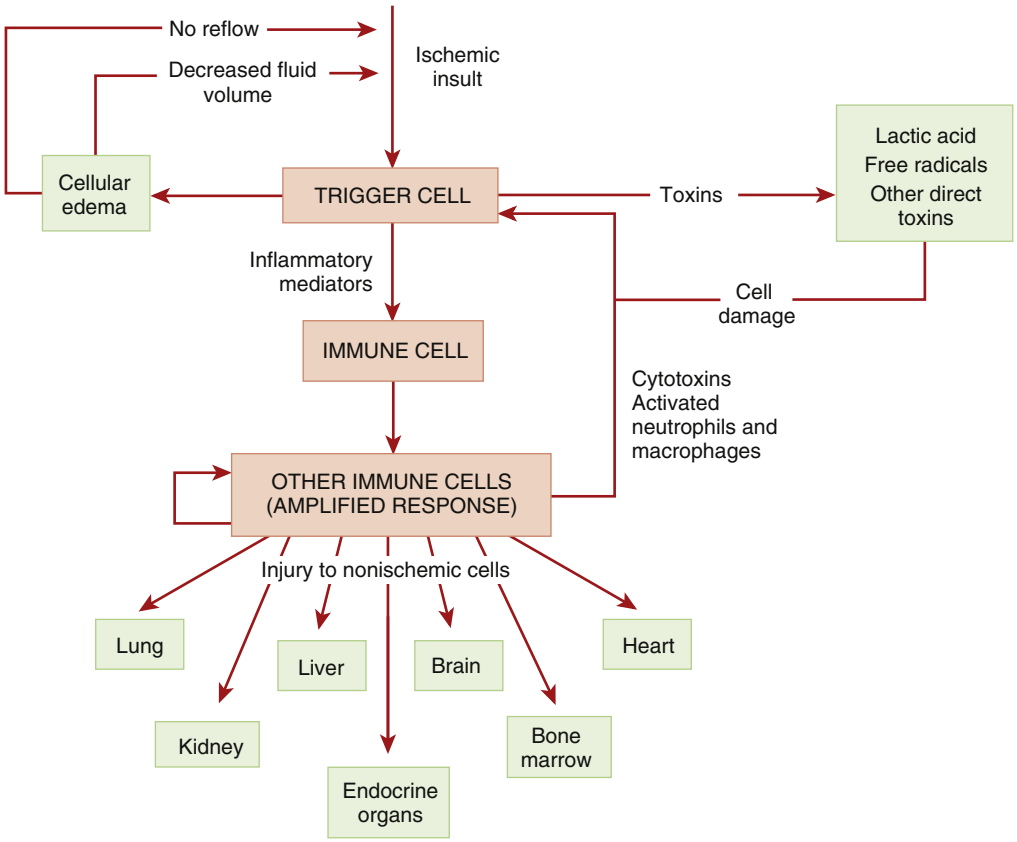


Figure 81-6. The "shock cascade." Ischemia of any given region of the body will trigger an inflammatory response that will impact nonischemic organs even after adequate systemic perfusion has been restored. *(Reprinted with permission from Dutton RP: Shock and trauma anesthesia. In Grande CM, Smith CE, editors:* Anesthesiology clinics of North America: trauma. *Philadelphia, 1999, WB Saunders, pp 83-95.)*

development of multiple organ failure, a systemic inflammatory process that leads to dysfunction of different vital organs and accounts for high mortality rates.[66]

Specific organ systems respond to traumatic shock in specific ways. The CNS is the prime trigger of the neuroendocrine response to shock, which maintains perfusion to the heart, kidney, and brain at the expense of other tissues.[67] Regional glucose uptake in the brain changes during shock.[68] Reflexes and cortical electrical activity are both depressed during hypotension; these changes are reversible with mild hypoperfusion but become permanent with prolonged ischemia. Failure to recover preinjury neurologic function is a marker for a poor prognosis, even when normal vital signs are restored.[69]

The kidney and adrenal glands are prime responders to the neuroendocrine changes associated with shock and produce renin, angiotensin, aldosterone, cortisol, erythropoietin, and catecholamines.[70] The kidney maintains glomerular filtration in the face of hypotension by selective vasoconstriction and concentration of blood flow in the medulla and deep cortical area. Prolonged hypotension leads to decreased cellular energy and an inability to concentrate urine (renal cell hibernation), followed by patchy cell death, tubular epithelial necrosis, and renal failure.[71]

The heart is preserved from ischemia during shock because of maintenance of or even an increase in nutrient blood flow, and cardiac function is well preserved until the late stages. Lactate, free radicals, and other humoral factors released by ischemic cells all act as negative inotropes and, in a bleeding patient, may produce cardiac dysfunction as the terminal event in the shock spiral.[72] A patient with cardiac disease or direct cardiac trauma is at great risk for decompensation because a fixed stroke volume inhibits the body's ability to increase blood flow in response to hypovolemia and anemia. Tachycardia is the patient's only option, with potentially disastrous consequences on the O_2 supply-demand balance in the heart. Therefore, shock in older patients may be rapidly progressive and not respond predictably to fluid administration.[73]

The lung is the filter for the inflammatory by-products of the ischemic body. Immune complex and cellular factors accumulate in pulmonary capillaries and lead to neutrophil and platelet aggregation, increased capillary permeability, destruction of lung architecture, and acute respiratory distress syndrome (ARDS)[74,75] (see also Chapter 101). The lung is the sentinel organ for the development of multiple organ system failure (MOSF) in a patient with traumatic shock.[76,77] Pure hemorrhage, in the absence of hypoperfusion, does not produce pulmonary dysfunction.[78] Traumatic shock is obviously more than just a hemodynamic disorder.

The gut is one of the earliest organs affected by hypoperfusion and may be the prime trigger of MOSF. Intense vasoconstriction occurs early and frequently leads to a no-reflow phenomenon, even when the macrocirculation is restored.[79] Intestinal cell death causes a breakdown in the barrier function of the gut that results in increased translocation of bacteria to the liver and lung, thereby potentiating ARDS.[80]

The liver has a complex microcirculation and may experience reperfusion injury during recovery from shock.[81] Hepatic cells are also metabolically active and contribute to the ischemic inflammatory response and to irregularities in blood glucose.[82] Failure of synthetic function of the liver after shock is almost always lethal.

Skeletal muscle is not metabolically active during shock and tolerates ischemia better than do the other organs. The large mass of skeletal muscle, though, makes it important in the generation of lactic acid and free radicals from ischemic cells. Sustained ischemia of muscle cells leads to an increase in intracellular sodium and free water, with an aggravated depletion of fluid in the vascular and interstitial compartments.[83]

ACUTE TRAUMATIC COAGULOPATHY

During resuscitation from hemorrhagic shock, attention must also be directed to avoidance or correction of coagulopathy (see also Chapter 61). In patients with identical injury severity scores (ISS), the presence of coagulopathy is associated with at least a twofold to fourfold increase in mortality[84,85]; thus, current resuscitation strategies focus on coagulopathy and shock during the initial and subsequent resuscitation. The presence of trauma-induced coagulopathy (TIC)—defined as a "multifactorial, global failure of the coagulation system to sustain adequate hemostasis after major trauma"—has an endogenous component linked to hypoperfusion and tissue injury referred to as acute traumatic coagulopathy (ATC).[86] A proposed mechanism for the development of ATC is endothelial activation of protein C secondary to the traumatic inflammatory response described earlier.[87] Activated protein C (APC) is generated by thrombomodulin-thrombin complex production as a result of tissue hypoperfusion. APC inactivates factors Va and VIIIa, and in combination with the reduction in thrombin availability for fibrin formation, supports the development of ATC.[88] Additionally, degradation of the endothelial glycocalyx as a result of hypoperfusion may play a supporting role in ATC.[89]

By clinical definition, ATC starts by the early presence of reduced clot strength as demonstrated by viscoelastic monitoring and changes in laboratory-based coagulation testing associated with an increase in mortality and likelihood of receiving a massive transfusion.[90] Davenport and colleagues[90] proposed a clot amplitude threshold of less than 35 mm at 5 minutes using ROTEM (Tem Innovations, Munich, Germany) analysis, which predicted the subsequent need for a massive transfusion with a detection rate of 77% and false-positive rate of 13% (see also Chapter 61). Similar results have been obtained using RapidTEG (Haemonetics, Niles, Ill) viscoelastic testing.[91] Laboratory-based coagulation testing is of limited utility in early detection of ATC because of time considerations. However, Frith and associates[92] found patients with a prothrombin ratio of greater than 1.2 on admission to have larger transfusion requirements and increased mortality.[92] Regardless of the means used to detect coagulopathy in the severely traumatized patient undergoing resuscitation for hemorrhagic shock, the resuscitation itself should include consideration for early treatment of ATC.

In addition to the described cascade, hyperfibrinolysis occurs in some of the more severely injured patients and contributes to ATC.[93,94] The mechanism behind this early fibrinolysis is not clearly understood but may be related

to hypoperfusion-induced APC formation resulting in the consumption of plasminogen activator inhibitor. The latter normally serves to down-regulate tissue plasminogen activator (tPA), which promotes fibrin clot degradation. The reported incidence of hyperfibrinolysis varies significantly based on the methods and cutoffs used to diagnose fibrinolysis, but its presence is clearly associated with the increased mortality and transfusion requirements seen with ATC.

INITIAL RESUSCITATION

Fluid administration is the cornerstone of resuscitation (see also Chapters 59 and 108). Intravascular volume is lost to hemorrhage, uptake by ischemic cells, and extravasation into the interstitial space. Administration of IV fluids will predictably increase cardiac output and arterial blood pressure in a hypovolemic trauma patient. The ATLS curriculum advocates rapid infusion of up to 2 L of warmed isotonic crystalloid solution in any hypotensive patient, with the goal of restoring normal arterial blood pressure.[17]

Conversely, fluid administration during active hemorrhage may be counterproductive. Dilution of red cell mass reduces O_2 delivery and contributes to hypothermia and coagulopathy. Increased arterial blood pressure leads to increased bleeding as a result of disruption of clots and reversal of compensatory vasoconstriction.[95] The result of aggressive fluid administration is often a transient increase in arterial blood pressure, followed by increased bleeding, another episode of hypotension, and the need for more volume administration. This vicious circle has been recognized since the First World War and remains a complication of resuscitation therapy today. The ATLS manual characterizes such patients as "transient responders" with active, ongoing hemorrhage.[17] Resuscitation of these patients should be considered in the following two phases:

- Early: While active bleeding is still ongoing
- Late: Once all hemorrhage has been controlled

Managing late resuscitation is driven by end-point targets and consists of giving enough fluid to maximize O_2 delivery. Early resuscitation is much more complex because the risks associated with aggressive intravascular volume replacement (Box 81-4), including the potential for exacerbating hemorrhage and thus prolonging the crisis, must be weighed against the risk for hypoperfusion and ischemia.

Deliberate hypotensive management is an accepted standard of anesthetic care for elective surgical procedures such as total joint replacement, spinal fusion, radical neck dissection, reconstructive facial surgery, and major pelvic or abdominal procedures.[96] Application of this technique to the initial management of hemorrhage is controversial and has been the focus of numerous laboratory and clinical research efforts. In 1965, Shaftan and colleagues[97] published the results of a study of coagulation in dogs that demonstrated that the formation of a soft extraluminal clot limits bleeding after arterial trauma. This study compared the quantity of blood lost from a standardized arterial injury under a variety of conditions. The least blood loss occurred in hypotensive animals (whether hypotensive from hemorrhage or from administration of a vasodilator), followed by the control group and then vasoconstricted animals. The largest amount of blood was lost in animals that underwent vigorous reinfusion during the period of hemorrhage.

BOX 81-4 ***Risks of Aggressive Volume Replacement during Early Resuscitation****

Increased blood pressure
Decreased blood viscosity
Decreased hematocrit
Decreased clotting factor concentration
Greater transfusion requirement
Disruption of electrolyte balance
Direct immune suppression
Premature reperfusion
Increased risk for hypothermia

*Most complications of volume resuscitation arise from increased hemorrhage volume or excessive hemodilution.

Laboratory data have shown the benefits of limiting intravascular fluid volumes and blood pressure in actively hemorrhaging animals.[98-101] In the most sophisticated models, direct assessment of cardiac output and regional perfusion showed no difference between moderate-volume or large-volume resuscitation in terms of cardiac output, arterial blood pressure, or regional perfusion of the heart, kidneys, and intestines. Moderate resuscitation to a lower than normal blood pressure improved perfusion of the liver.[102] Burris and co-workers[103] studied both conventional resuscitation fluids and various combinations of hypertonic saline and dextran and found that rebleeding was correlated with higher mean arterial pressure (MAP) and that survival was best in groups resuscitated to lower than normal MAP. The optimum target blood pressure for resuscitation varied with the composition of the fluid used.[103] A 1994 consensus panel on resuscitation from hemorrhagic shock noted that mammalian species are capable of sustaining MAP as low as 40 mm Hg for periods as long as 2 hours without deleterious effects. The panel concluded that spontaneous hemostasis and long-term survival were maximized by reduced administration of resuscitation fluids during the period of active bleeding in an attempt to keep perfusion only just above the threshold for ischemia.[104]

The literature contains two prospective studies of deliberate hypotensive resuscitation in trauma patients and preliminary data from a third study. The first was that of Bickell and colleagues[105] and Martin and associates[106] in 1994. The investigators randomized victims of penetrating torso trauma to one of two treatment groups: standard of care (up to 2 L of crystalloid infused in the prehospital setting) or delayed resuscitation (no fluid until the patient reached the OR). This well-managed 37-month study eventually included 598 patients. Average times of transport and care were 30 minutes from injury to the ED and then 50 minutes before reaching the OR; the fluid-restricted group received an average of about 800 mL of fluid during this time. The immediate-resuscitation group received an average of 2500 mL of crystalloid and 130 mL of blood over this same period. Although substantially different during the period of study, blood pressure on arrival at the OR was similar in both groups, which the authors took as evidence that the unresuscitated group had achieved spontaneous hemostasis. Survival to hospital discharge in the delayed-resuscitation group was significantly

TABLE 81-3 RESULTS OF A RANDOMIZED TRIAL OF DELIBERATE HYPOTENSIVE RESUSCITATION*

	Conventional	Hypotensive	Total
Patients enrolled	55	55	110
Male	46	41	87
Blunt trauma	22	31	53
Penetrating trauma	33	24	57
Injury severity score	19.65	23.62 ($P = .11$)	
Predicted survival	0.94	0.90 ($P = .19$)	
SBP during study period	114	100 ($P < .001$)	
Survived to discharge	51	51	
Died	4	4	

SBP, Systolic blood pressure.
*Probability of survival was calculated based on published historical data.

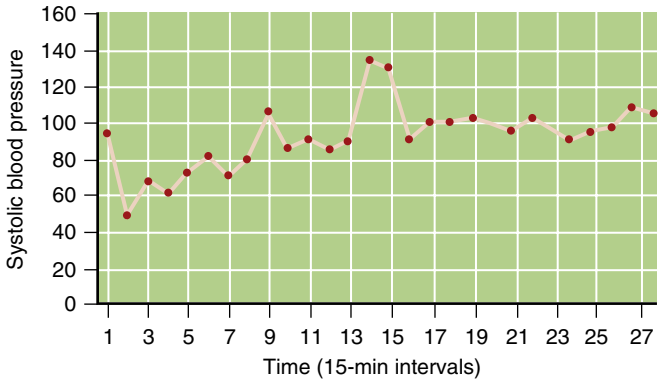


Figure 81-7. Typical systolic blood pressure measurements of a patient undergoing damage control surgery for a grade V liver injury during deliberate hypotensive management. Oscillations of blood pressure are common during early resuscitation as a result of ongoing hemorrhage and bolus fluid administration. Once hemorrhage is controlled, blood pressure will stabilize.

improved over the immediate-resuscitation group (70% versus 62% [$P < .04$]). No data were presented on the conduct of anesthesia after arrival at the OR but before control of hemorrhage or on the incidence of rebleeding after volume loading and induction of anesthesia in patients who had achieved hemostasis preoperatively.

A retrospective review of trauma admissions to the Los Angeles Medical Center published in 1996 supported these findings. Patients brought to the hospital by private conveyance fared substantially better than those delivered by paramedics, even with high levels of injury severity.[107] Further corroboration was provided by retrospective examination of outcomes in a population of hemorrhaging trauma patients who received fluids via a commercial rapid infusion system (RIS, Haemonetics, Niles, Ill) during initial resuscitation.[108] The survival rate of this group was compared with that predicted by the institution's trauma registry. Patients who received fluid by the rapid infusion system, when compared with case-matched controls, had a survival rate of only 56.8% versus 71.2% for patients of similar age with similar injuries ($P < .001$).

This retrospective review was followed in 2002 by the second prospective trial of delayed resuscitation in trauma patients.[109] Patients with systolic blood pressure lower than 90 mm Hg and clinical evidence of blood loss were randomized to fluid resuscitation titrated to a systolic blood pressure of 100 mm Hg (normal group) or 70 mm Hg (study group) until the end of surgical interventions to control hemorrhage. The results of this study are summarized in Table 81-3. As in the Bickell study, hypotension allowed spontaneous resolution of hemorrhage and autoresuscitation; blood pressure would increase without exogenous fluid administration once hemostasis was achieved. The typical patient began with a low initial pressure, followed by recovery to the vicinity of the target, overshoots and undershoots as bleeding and fluid administration continued, and an eventual rise above the target when the hemorrhage resolved, even in the absence of further fluid administration (Fig. 81-7). The 93% overall survival rate in this study was more frequent than predicted from historical data and substantially more frequent than seen in Bickell's group. This reflects the exclusion of patients who died in the prehospital phase or arrived at the trauma resuscitation unit in a moribund condition. It may also reflect improvements in overall care, an observation effect (i.e., patients in both groups received better care than did patients not in the study), or a bias in subject recruitment. Over the first 24 hours, lactate and base deficit cleared to normal in both groups and required similar amounts of fluid and blood products, thus suggesting that both groups were reaching an equivalent resuscitation end point. The authors concluded that administration of fluids to an actively hemorrhaging patient should be titrated to specific physiologic end points, with the anesthesiologist navigating a course between the Scylla of increased hemorrhage and the Charybdis of hypoperfusion.

In the most recent study, Morrison and colleagues compared a hypotensive resuscitative strategy targeting a MAP of 50 mm Hg to one targeting a MAP of 65 mm Hg with conventional resuscitation for patients requiring emergent surgery. In a preliminary report, they found that patients in the hypotensive resuscitation group had a lower, early postoperative mortality, a reduced incidence of coagulopathy, and lower mortality related to coagulopathy. Taken in combination, the current consensus at major trauma centers is to allow for hypotensive resuscitation. While the optimal arterial blood pressure remains controversial, a reasonable approach is to target a systolic pressure of less than 100 mm Hg with MAP between 50 to 60 mm Hg.[110]

Finally, the effect of anesthetic drugs on the body's response to hemorrhage is an important difference between deliberate hypotension occurring in the elective operative setting and hemorrhagic shock occurring in the ED. Trauma patients who are hypertensive receive a minimum of anesthetics, even for induction of anesthesia, because of the obvious effect of these drugs on arterial blood pressure. A hypotensive trauma patient is thus in a state of profound vasoconstriction, as opposed to a patient undergoing elective intraoperative hypotension who is vasodilated by general anesthesia before any blood loss. Table 81-4 summarizes the physiologic contrasts between these two states. It should be noted that blood loss without shock does not produce systemic complications such as ARDS in experimental models.[78] Based on this physiology, the recommended goals for early resuscitation are expressed in Box 81-5, and an algorithm for management is presented in Figure 81-8. The emphasis in

TABLE 81-4 DIFFERENCES IN PRESENTATION BETWEEN SURGICAL PATIENTS UNDERGOING ELECTIVE DELIBERATE HYPOTENSION AND EMERGENCY TRAUMA CASES*

Aspect	Elective	Trauma
Intravascular volume	Euvolemic	Hypovolemic
Temperature	Normal	Likely hypothermic
Capillary beds	Dilated	Constricted
Level of general anesthesia	Deep	Usually light
Preexisting mental status	Normal	May be impaired
Coexisting injuries	None	May be significant
Comorbid conditions	Known and managed	Unknown

*Each of these factors produces a real or perceived contraindication to the use of deliberate hypotensive technique in the trauma patient.

BOX 81-5 *Goals for Early Resuscitation**

Maintain systolic blood pressure of 80 to 100 mm Hg
Maintain hematocrit of 25% to 30%
Maintain prothrombin time and partial thromboplastin time in normal ranges
Maintain platelet count at greater than 50,000 per high-power field
Maintain normal serum ionized calcium
Maintain core temperature higher than 35° C
Maintain function of pulse oximeter
Prevent increase in serum lactate
Prevent acidosis from worsening
Achieve adequate anesthesia and analgesia

*Fluid administration to limit hypoperfusion is balanced against an undesirable increase in blood pressure and thus bleeding.

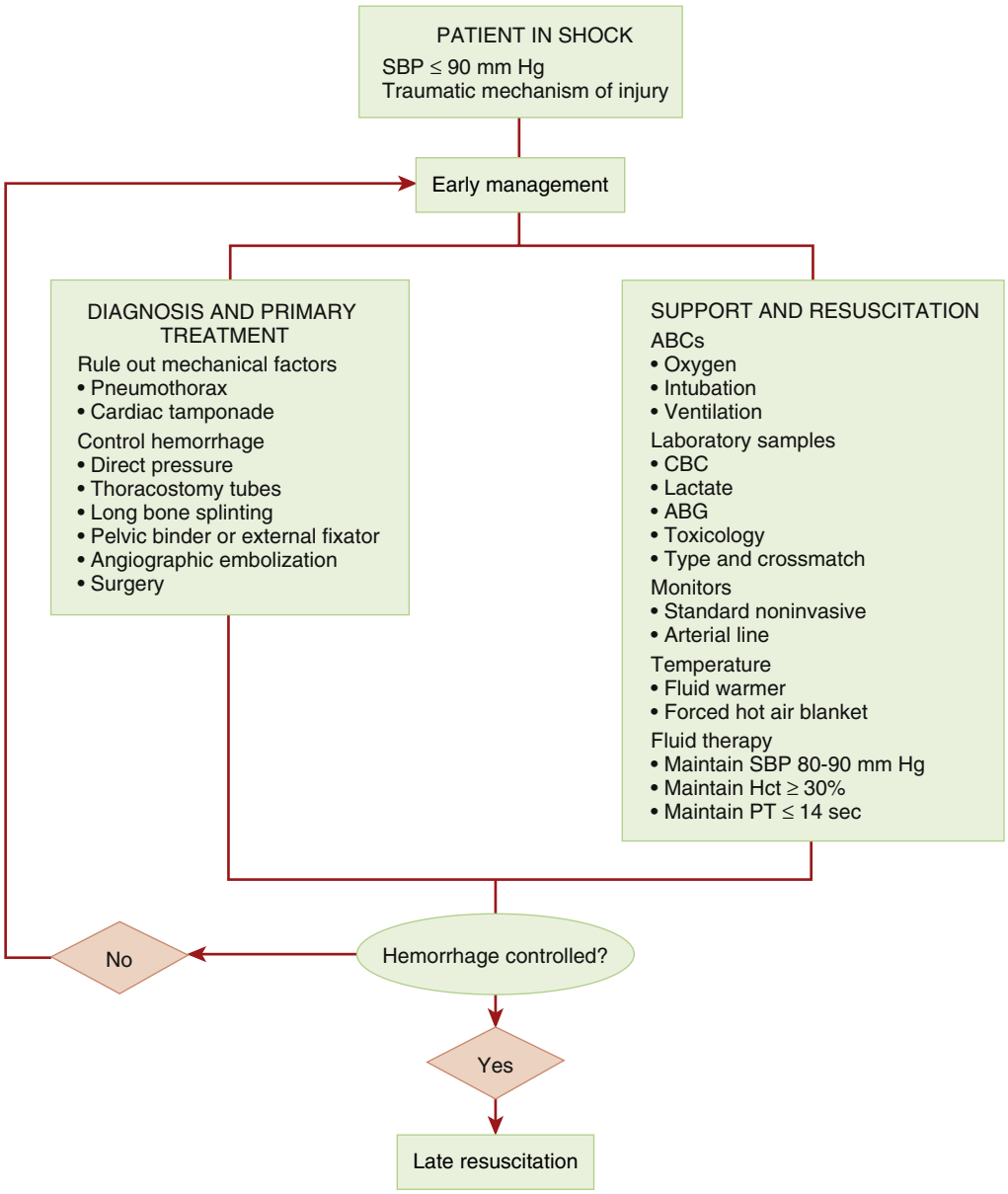


Figure 81-8. Algorithm for management of early hemorrhagic shock. *ABCs,* Airway, breathing, circulation; *ABG,* arterial blood gas; *CBC,* complete blood count; *Hct,* hematocrit; *PT,* prothrombin time; *SBP,* systolic blood pressure.

this situation must be on rapid diagnosis and control of ongoing hemorrhage; vascular volume should be restored and anesthesia provided together by shifting the patient from a vasoconstricted to a vasodilated state while facilitating hemostasis by maintenance of a decreased arterial blood pressure.

HEMOSTATIC RESUSCITATION

As discussed earlier, management of the early coagulopathy associated with trauma must be incorporated into the overall resuscitation strategy—often referred to as a hemostatic resuscitation. Little utility is found in targeting end points of resuscitation in the face of ongoing hemorrhage. Life-threatening coagulopathy is one of the most serious complications of patients in profound shock from massive hemorrhage and is generally predictable at an early stage.[111]

The majority of trauma patients initially present with normal or prothrombotic coagulation profiles. As discussed earlier, the most seriously injured are likely to present with evidence of hypocoagulability, accelerated fibrinolysis, or both, with evidence of ATC.[112,113] The patient's coagulation status must be assessed to initiate appropriate therapy as part of the early resuscitation. Standard laboratory tests such as prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), fibrinogen level, and platelet count are still the most common coagulation assays in clinical use, despite considerable evidence that they provide an extremely incomplete picture of in vivo hemostasis,[114,115] that they are poor predictors of clinical bleeding,[116] and that they do not provide an adequate basis for rational targeted hemostatic resuscitation.[117] Although significantly increased admission PT and PTT levels are predictive of increased mortality from injury,[85] they do not provide a realistic target for resuscitation. In addition, the delay between admission and obtaining the values may be significant when earlier treatment would be beneficial. Moderately increased values may have little clinical significance, and correction to "normal" values may require large amounts of resuscitation fluids, especially fresh frozen plasma (FFP). In the absence of active clinical bleeding, attempts to normalize laboratory values have the potential to introduce transfusion-related and intravascular volume–related complications

These deficiencies underscore the need for reliable point-of-care hemostatic monitoring with clinical relevance in situations of generalized coagulopathy resulting from massive hemorrhage. Increasing evidence indicates that viscoelastic monitoring technologies such as thromboelastography and ROTEM are superior for detecting clinically relevant hemostatic abnormalities in trauma and surgical patients with massive bleeding and diffuse coagulopathy[118,119] (see also Chapter 61). Schöchl and colleagues[120] published a detailed review on the use of viscoelastic monitoring on targeted resuscitations. Both viscoelastic and standard coagulation tests are generally performed after warming specimens to 37° C and do not reflect the potentially considerable effects of hypothermia on in vivo hemostasis.[121]

Because of evidence that severely injured trauma patients are likely to develop an early and aggressive endogenous coagulopathy separate from later loss and dilution of clotting factors compounded from hypothermia and acidosis,[85,88,122] the practice of hemostatic resuscitation has become commonplace in the most severely injured patients with shock and ongoing hemorrhage. This entails the early and aggressive use of hemostatic products combined with red blood cells (RBCs) as the primary resuscitation fluids to avoid rapid deterioration into the "bloody vicious cycle" and the classic lethal triad of hypothermia, acidosis, and coagulopathy.[123] Two very distinct paradigms of hemostatic resuscitation have emerged: (1) the damage control resuscitation model, which uses preemptive administration of empiric ratios of blood and hemostatic products to approximate whole blood, often according to an established institutional massive transfusion protocol[124-127] (Fig. 81-9); and (2) goal-directed hemostatic resuscitation approaches (also often protocol based), which generally use point-of-care viscoelastic monitoring combined with the prompt administration of hemostatic concentrates[114,115,120,128] (see also Chapter 61).

The application of damage control resuscitation relies on hypotensive resuscitation and limited crystalloid usage, as discussed previously in conjunction with the administration of empiric ratios of blood and hemostatic products. In a retrospective review of combat casualties, Borgman and colleagues[129] found a mortality rate of 65% in patients receiving less than 1 unit plasma for every 4 units RBCs, but only 20% in those with a ratio of 1:2 or above. Evidence exists of a survivor bias because patients bleeding more rapidly were likely to die after receiving RBCs but before plasma could reach the bedside. Although the issue of a survivor bias does exist, this approach has been substantiated in published reviews.[129,130] Currently a ratio of 1:1:1 is most commonly adopted, although some experts believe that the amount of FFP can be reduced in most cases.

In addition to the hypocoagulability associated with ATC, fibrinolysis is especially deleterious in severely injured trauma patients and carries an associated mortality well upward of 50%.[112,131] Many patients with primary fibrinolysis from severe hemorrhagic shock may never survive to reach the ICU. The recently concluded Clinical Randomisation of an Antifibrolytic in Significant Haemorrhage 2 (CRASH-2) trial is the only class I evidence showing a 30-day survival benefit for a resuscitative therapy including tranexamic acid (TXA).[132] Subgroup analysis showed that the benefit was greatest when therapy was instituted within 1 hour of admission. A subsequent analysis, however, showed that mortality actually increased when therapy was instituted after 3 hours, suggesting that the risks of therapy outweighed the benefits in patients who survived beyond that timeframe.[133] Many resuscitative protocols for massive hemorrhage now include the early administration of TXA based on this and subsequent studies.[134]

Other potential drugs that may play a role in hemostatic resuscitation include recombinant activated human coagulation factor VII (rFVIIa), prothrombin complex concentrates (PCC), and fibrinogen concentrates. rFVIIa

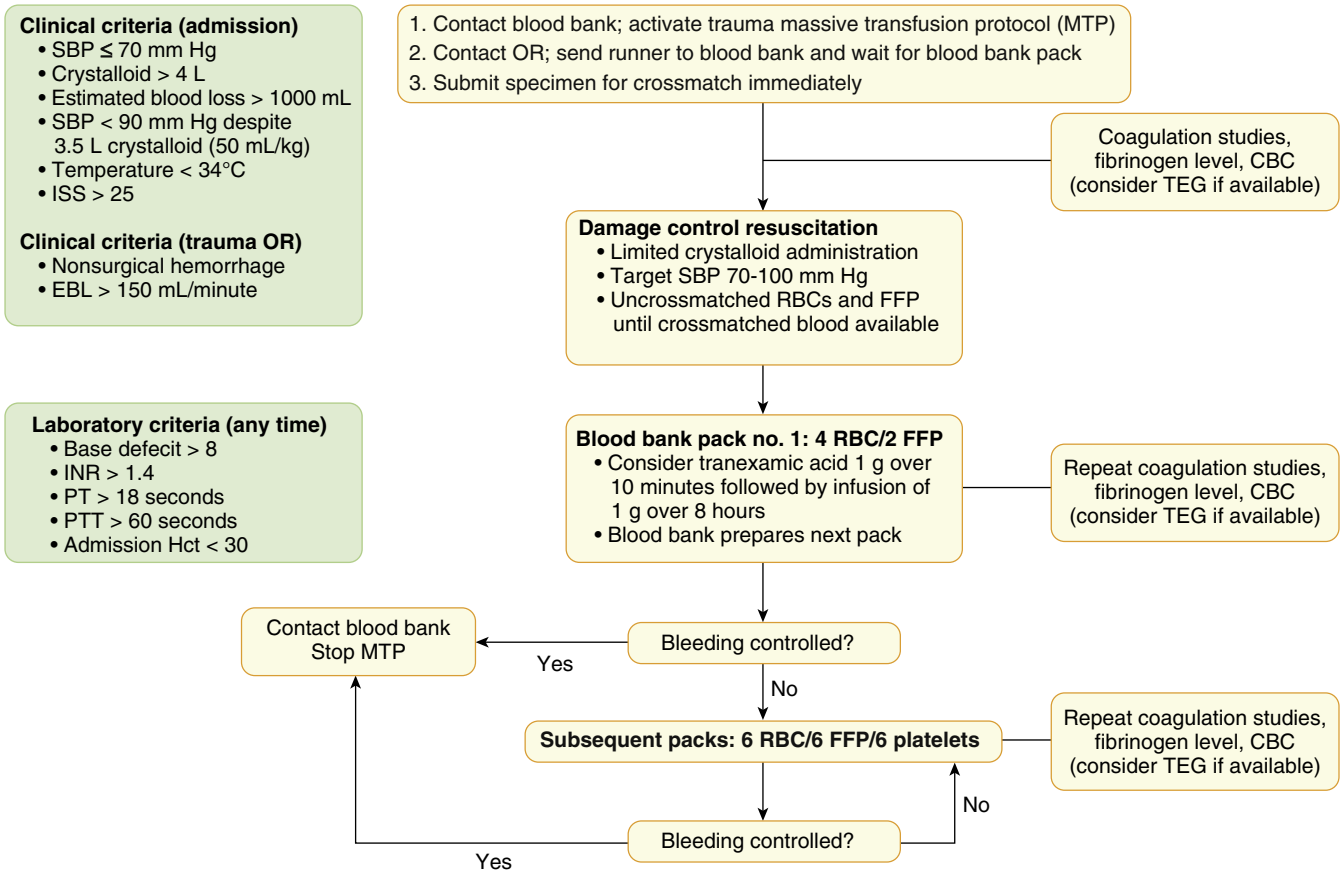


Figure 81-9. Example of a massive transfusion protocol using specified ratios of blood products. *CBC,* Complete blood count; *EBL,* estimated blood loss; *FFP,* fresh frozen plasma; *INR,* international normalized ratio; *ISS,* injury severity score; *OR,* operating room; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *RBC,* red blood cell; *SBP,* systolic blood pressure; *TEG,* thromboelastogram.

is licensed for the treatment of patients with hemophilia with active or anticipated hemorrhage and known antibodies to factor VIII (see also Chapters 59 and 61). The observation of rapid hemostasis in this population led to the anecdotal use of rFVIIa in other congenital and acquired coagulopathies, including the dilutional coagulopathy of traumatic hemorrhage. Factor VIIa in pharmacologic doses works by triggering a burst of thrombin on the surface of platelets activated by exposed tissue factor, which produces rapid clot formation. Because tissue factor is required, coagulation is limited to the site of vascular injury, and inappropriate clotting of uninjured organs or vessels, though an acknowledged risk, occurs at only low frequency.[135] Prospective trials of rFVIIa have demonstrated decreased blood loss in patients undergoing elective open prostate surgery[136] and rapid reversal of coagulopathy in patients taking warfarin.[137] Retrospective reports have suggested a role for rFVIIa in the management of acute traumatic hemorrhage,[138] gastrointestinal hemorrhage secondary to cirrhosis,[139] hemorrhage after cardiovascular surgery[140] and liver transplantation,[141] and intracranial hemorrhage in both neonates[142] and older patients.[143] One small placebo-controlled trial of rFVIIa in hemorrhaging trauma patients has demonstrated decreased blood loss, decreased transfusion requirements, and improved outcome,[144] although a large, randomized trial failed to show a mortality benefit.[145]

Experience with PCCs in clinical practice is limited. PCC has been used for many years for the treatment of congenital coagulation disorders and is recommended for reversing oral anticoagulation. PCCs contain coagulation factors II, VII, IX, and X. Differences exist among products in the concentrations of these factors and other constituents, including heparin, protein C, and protein S, so results obtained with one product may not be obtained with a different formulation. Fibrinogen concentrates also may have a role in a hemostatic resuscitation for the patient with a coagulopathy with low levels of fibrinogen.[146]

VULNERABLE PATIENT POPULATIONS

Clinical trials of deliberate hypotensive resuscitation have avoided the application of this technique to populations perceived to be at greater risk for ischemic complications,[105,109] including patients with known ischemic coronary disease, older patients, and those with injuries to the brain or spinal cord (see also Chapters 39, 70, and 80). The prohibition against hypotension in patients with TBI is especially well established because of the observed disparity in outcome between TBI patients who experience hypotension and those who do not.[147,148] Older trauma patients suffer worse outcomes from similar injuries than younger patients, presumably because of their reduced

physiologic reserve.[149] Clinical care of these patients is focused on avoidance of ischemic stress and rapid correction of hypovolemia. It may well develop, however, that deliberate hypotensive management to enable rapid control of hemorrhage is equally beneficial in vulnerable populations. No clinical trials to date have been conducted on this subject, but a laboratory study did find a benefit of deliberate hypotension in animals with both TBI and hemorrhagic shock.[150] Absent convincing evidence in humans, deliberate hypotension in older patients or patients with brain injury should generally be avoided.

RESUSCITATION FLUIDS

Isotonic crystalloids (normal saline, lactated Ringer solution, Plasma-Lyte A) are the initial resuscitative fluids administered to any trauma patient (see also Chapter 59). They have the advantage of being inexpensive, readily available, nonallergenic, noninfectious, and efficacious in restoring total body fluid. They are easy to store and administer, they mix well with infused medications, and they can be rapidly warmed to body temperature. Disadvantages of crystalloids include their lack of O_2-carrying capacity, their lack of coagulation capability, and their limited intravascular half-life. More recent laboratory data have implicated specific crystalloid solutions as immunosuppressants and triggers of cellular apoptosis.[151] Unlike necrosis, apoptosis is highly regulated and involves gene modulation and complex pathways of signal transduction. It seems clear that apoptosis is an important element of reperfusion injury. In a rat model of controlled hemorrhage, animals receiving lactated Ringer solution showed an immediate increase in apoptosis in the liver and small intestine after resuscitation.[152] Neither whole blood nor hypertonic saline increased the amount of apoptosis.

Hypertonic saline solutions, with or without the addition of polymerized dextran (HS or HSD), have been extensively studied in resuscitation from hemorrhagic shock.[153] In theory, HS will draw fluid into the vascular space from the interstitium and thereby reverse some of the nonhemorrhagic fluid loss caused by shock and ischemia. A given amount of HS will thus have an enhanced ability to restore intravascular volume in contrast to an equivalent volume of an isotonic solution. This has made HS a popular choice for fluid resuscitation under austere conditions. HSD is licensed for prehospital use in some European countries and is used for resuscitation by units of the U.S. military. Multiple studies of otherwise lethal hemorrhage in animals have demonstrated improved survival after resuscitation with HSD versus either normal saline solution or the components of HSD alone. Studies of the efficacy of HSD in trauma patients have been inconclusive[154]; the most obvious benefit occurred in a subset of polytraumatized patients with both hemorrhage and TBI, in whom improved neurologic status was demonstrated in those who received HSD as a resuscitation fluid. Indeed, HS is commonly used as an osmotic agent in the management of TBI with increased ICP.[155]

Colloids, including starch solutions and albumin, have been advocated for rapid plasma intravascular volume expansion (see also Chapter 61). Like crystalloids, colloids are readily available, easily stored and administered, and relatively inexpensive. As with hypertonic solutions, colloids will increase intravascular volume by drawing free water back into the vascular space. When IV access is limited, colloid resuscitation will restore intravascular volume more rapidly than crystalloid infusion will and at a lower volume of administered fluid. Colloids do not transport O_2 or facilitate clotting; their dilutional effect will be similar to that of crystalloids. Systematic reviews continue to show no benefit of colloids over crystalloids in the setting of trauma resuscitation,[156] although this topic continues to generate significant controversy and would benefit from several well-conducted, randomized trials.[157] Recent concerns, however, have been expressed about specific colloids such as 6% hetastarch and an adverse effect on renal function (see also Chapter 61).[158]

Many of the risks of aggressive intravascular fluid administration just summarized are related to dilution of the circulating blood volume. Recognition of this fact and continued improvement in the safety of donated blood led to increased use of blood products in the management of early hemorrhagic shock (see also Chapter 61). The risk for systemic ischemia is decreased by the maintenance of an adequate hematocrit, and the potential for dilutional coagulopathy can be decreased by the early administration of plasma. The composition of resuscitation fluids may be as important as the rate and timing of administration. A 4-year retrospective review of a cohort of critically injured patients who underwent emergency surgery examined the outcomes of short-term care based on the number of units of blood transfused.[159] One hundred forty-one patients received massive blood transfusions (≥20 units of RBCs) during preoperative and intraoperative resuscitation. The number of blood units did not differ between survivors (30%) and nonsurvivors (70%). Eleven variables were significantly different: aortic clamping for control of arterial blood pressure, use of inotropic drugs, time with a systolic blood pressure higher than 90 mm Hg, time in the OR, temperature less than 34° C, urine output, pH lower than 7.0, PaO_2/FiO_2 ratio less than 150, $Paco_2$ more than 50 mm Hg, K^+ more than 6 mM/L, and calcium less than 2 mM/L. Of these, the presence of the first three variables in the face of transfusion of more than 30 units of packed RBCs was invariably fatal. Total blood loss and the amount of transfused blood were less critical than the depth and duration of shock. These concerns led to the concept of damage control surgery, which emphasizes rapid control of active hemorrhage.[160]

RBCs are the mainstay of treatment of hemorrhagic shock. With an average hematocrit of 50% to 60%, a unit of RBCs will predictably restore O_2-carrying capacity and expand intravascular volume as well as any colloid solution. RBCs of blood type A, B, or AB carry major incompatibility antigens that may precipitate a lethal transfusion reaction if given to a patient with the opposite blood type. Because RBCs also carry dozens of minor antigens that can cause reactions in susceptible patients, crossmatching is desirable when time allows (typically approximately 1 hour from the time a sample reaches the blood bank until the RBCs reach the patient). Type-specific blood requires less time for delivery from the blood bank

(usually ~30 minutes) and may be an appropriate alternative in some situations. Type O blood—the universal donor type—can be given to patients of any blood type with little risk for a major reaction.[161] This is the preferred approach for patients who arrive at the ED in hemorrhagic shock. If O-positive blood is given to a Rhesus-negative woman who survives, prophylactic administration of anti-Rh_0 antibody is indicated.

Risks of RBC administration include transfusion reaction, transmission of infectious agents, and hypothermia (see also Chapter 61 for details). For example, RBCs are stored at 4° C and will decrease the patient's temperature rapidly if not infused through a warming device or mixed with warmed isotonic crystalloid at the time of administration.

Plasma requires blood typing but not crossmatching; delay in availability of plasma is caused by the need to thaw frozen units before they can be administered. Busy trauma hospitals will often maintain a supply of prethawed plasma (thawed fresh plasma as opposed to FFP) that can be issued quickly in response to an emergency need; in smaller hospitals it is important to request plasma early in resuscitation if it is likely to be needed. Very busy centers are experimenting with keeping 2 to 4 units of prethawed type AB (universal donor) plasma available in the trauma resuscitation unit. Units are kept ready in this way for 2 days at a time; if not used on an emergency basis, the units are returned to the blood bank and released to the next patient needing plasma. Whether this approach improves outcomes has not yet been studied.

Platelet transfusion should normally be reserved for patients with clinical coagulopathy with a documented low serum level (>50,000 per high-power field). When the patient is in shock, however, and blood loss is likely to be substantial, platelets should be empirically administered in proportion to RBCs and plasma (1:1:1), as discussed earlier for DCR. Transfused platelets have a very short serum half-life and should be administered only to patients with active coagulopathic bleeding. Platelets should not be administered through filters, warmers, or rapid infusion systems because they will bond to the inner surfaces of these devices, thereby reducing the quantity of platelets actually reaching the circulation (see also Chapter 61).

Rapid transfusion of banked blood carries the risk for inducing citrate intoxication in the recipient. Harvested blood units are treated with citrate to bind free Ca^{2+} and thus inhibit the clotting cascade. Consecutive administration of multiple units of banked blood leads to a correspondingly large dose of citrate, which may overwhelm the body's ability to mobilize free Ca^{2+} and have a profound negative inotropic effect on the heart. Unrecognized hypocalcemia is a cause of hypotension in patients after massive transfusion and persists despite an adequate volume of resuscitation. Ionized Ca^{2+} levels should be measured at regular intervals in a hemorrhaging patient, and Ca^{2+} should be administered as needed (in a separate IV line from transfusion products) to maintain serum levels greater than 1.0 mmol/L.

RESUSCITATION EQUIPMENT

Intravascular fluid resuscitation of any kind is impossible in the absence of IV access. Immediate placement of at least two large-bore catheters (16 gauge or larger) is recommended during the primary assessment of any trauma patient.[17] Practitioners should have a low threshold for placement of a large-caliber central line in any patient in whom antecubital or other peripheral placement attempts have been unsuccessful. Potential sites for central line placement include the internal jugular, subclavian, and femoral veins, each of which has its own benefits and potential risks. The internal jugular approach, though familiar to most anesthesiologists, will require removal of the cervical collar and manipulation of the patient's neck and is not recommended in the acute setting unless other options have been exhausted. The femoral vein is easily and rapidly accessed and is an appropriate choice in patients without apparent pelvic or thigh trauma who require urgent drug or fluid administration. Caution should be used in patients with penetrating trauma to the abdomen because fluids infused via the femoral vein may contribute to hemorrhage from an injury to the inferior vena cava or iliac vein; these patients should have IV access placed above the diaphragm if possible. Femoral vein catheterization carries a high risk for the formation of deep venous thrombosis (DVT),[162] thus limiting use of this approach to the acute setting. Femoral lines should be removed as soon as possible after the patient's condition stabilizes. The subclavian vein is the most common site for early and ongoing central access in a trauma patient because the subclavian region is easily visible and seldom directly traumatized. This approach carries the highest risk for the development of pneumothorax, although many patients will already have indications for tube thoracostomy in one or both chest cavities; when possible, this is the preferred side for placement of a subclavian line. Placement of an arterial line facilitates frequent laboratory analysis and allows close monitoring of blood pressure; this should be undertaken as soon as possible but should not impede other diagnostic or therapeutic maneuvers.

The anesthesiologist should work to maintain thermal equilibrium (see also Chapter 54) in any trauma patient. Although deliberate hypothermia has been suggested as a management strategy for both hemorrhagic shock[163] and TBI,[164] insufficient evidence exists to support this approach. Hypothermia will potentiate dilutional coagulopathy and systemic acidosis, and shivering and vasoconstriction in response to cold will demand an additional metabolic effort that may predispose the patient to myocardial ischemia. Hypothermia also greatly increases the subsequent risk for sepsis. Because many trauma patients arrive at the ED cold from exposure to the elements, early active warming measures are required. All IV fluids should be prewarmed or infused through a warming device. The patient should be kept covered with warmed blankets whenever possible, and the environment should be kept warm enough to make the patient comfortable. If hypothermia has already developed, the use of forced hot air warming is strongly indicated to restore normothermia. Even though all these measures are routine and obvious in the OR, the anesthesiologist can perform a valuable service by ensuring that they are available and applied in the ED, CT scanner, and angiography suite as well.

Commercial rapid-infusion devices are of great benefit in trauma care, particularly in the presence of hemorrhagic

BOX 81-6 ***Benefits of a Fluid Infusion System in Resuscitation from Hemorrhagic Shock***

- An active mechanical pump enables fluid administration rates up to 1500 mL/minute
- Compatible with crystalloid, colloid, packed red blood cells, washed salvaged blood, and plasma (*not* platelets)
- Reservoir allows for mixing of products in preparation for rapid blood loss
- Fluids infused at a controlled temperature (38° to 40° C)
- Able to pump simultaneously through multiple intravenous lines
- Fail-safe detection systems to prevent infusion of air
- Accurate recording of fluid volume administered
- Portable enough to travel with patient between units

BOX 81-7 ***Goals for Late Resuscitation****

- Maintain systolic blood pressure higher than 100 mm Hg
- Maintain hematocrit above individual transfusion threshold
- Normalize coagulation status
- Normalize electrolyte balance
- Normalize body temperature
- Restore normal urine output
- Maximize cardiac output by invasive or noninvasive measurement
- Reverse systemic acidosis
- Document decrease in lactate to normal range

*Fluid administration should be continued until adequate systemic perfusion is restored.

shock. These machines offer benefits when large quantities of fluid resuscitation are likely (Box 81-6). Early experience with these devices demonstrated higher patient temperature and reduced acidosis at the conclusion of the initial surgery,[165] although rapid infusers may contribute to overinfusion of fluids, inappropriately increased arterial blood pressure, and contribute to rebleeding.[108] Application of the principles described earlier can prevent this complication; basal fluid administration should be kept low (200 to 500 mL/hr), with small fluid boluses given in response to measured systolic blood pressure less than 80 to 90 mm Hg. In practice, fluid boluses are given alternately with anesthetics, with the goal of reaching a normal depth of anesthesia without increasing systolic arterial blood pressure.

LATE RESUSCITATION

Box 81-7 summarizes end points for late resuscitation, and Figure 81-10 presents an algorithm for management. IV fluid administration is an integral, mandatory component. The adequacy of resuscitation should not be judged by the presence of normal vital signs, but by restoration of organ and tissue perfusion. The role of the anesthesiologist-intensivist is to recognize the presence of ongoing shock after traumatic hemorrhage and to resuscitate the patient with the appropriate type and amount of fluids intravenously at the appropriate time.

Late resuscitation begins once bleeding is definitively controlled by surgery, angiography, or the passage of time. The goal at this time is to restore normal perfusion to all organ systems while continuing to support vital functions. Hypoperfusion caused by hemorrhagic shock triggers a predictable cascade of biochemical events that will cause physiologic derangements persisting long after adequate blood flow is restored. The extent of hypoperfusion—the depth and duration of shock—dictates the magnitude of subsequent organ system failure. Unfortunately, traditional vital sign markers such as arterial blood pressure, heart rate, and urine output are insensitive to the adequacy of resuscitation. Occult hypoperfusion syndrome is common in postoperative trauma patients, particularly young ones.[166] This syndrome is characterized by a normal blood pressure maintained by systemic vasoconstriction; decreased intravascular volume and cardiac output; and organ system ischemia. The patient will be at frequent risk for MOSF if the hypoperfusion is not promptly corrected.

The search for the optimal end point of resuscitation has led to several different hemodynamic, acid-base, and regional perfusion targets. Table 81-5 summarizes modalities that are available to gauge the adequacy of resuscitation, along with the shortcomings of each technique. Although the flow of blood to tissue beds is a determinant of tissue perfusion, pressure should also be an important consideration. The left ventricular stroke work index is a variable that accounts for both flow and pressure. Furthermore, left ventricular power output has been used to quantify left ventricular performance. These indices were compared with purely flow-derived hemodynamic and O_2 transport variables as markers of perfusion and outcome in critically injured patients during resuscitation.[167] A consecutive series of 111 patients were monitored with a volumetric pulmonary artery catheter during the first 48 hours of resuscitation. The ability to clear lactate in less than 24 hours and survival were studied. Survivors exhibited significantly higher stroke work and left ventricular power output than did nonsurvivors. In addition to heart rate, these were the only variables that were significantly related to lactate clearance and survival. The higher stroke work and left ventricular power output in survivors were related to better ventricular-arterial coupling and therefore more efficient cardiac function.

Monitoring resuscitation with invasive monitors is gradually changing to noninvasive approaches that assess the return of adequate metabolism, respiration, and O_2 transport in peripheral tissue beds. One such technique is tissue O_2 monitoring (skin, subcutaneous tissue, or skeletal muscle). Skeletal muscle blood flow decreases early in the course of shock and is restored later during resuscitation, thus making the skeletal partial pressure of O_2 a sensitive indicator of decreased flow.[168,169] Early goal-directed treatment of septic shock,[170] with an emphasis on measurement of mixed-venous O_2 saturation, has influenced the care of trauma patients, and many ICUs are now using continuously measured venous oxygenation to guide resuscitation. Stroke volume variation, the change in arterial pressure driven by the respiratory cycle, is emerging as another less invasive measure of fluid volume status; increased variation in arterial pressure during positive-pressure ventilation is a reliable predictor of decreased intravascular volume.[171]

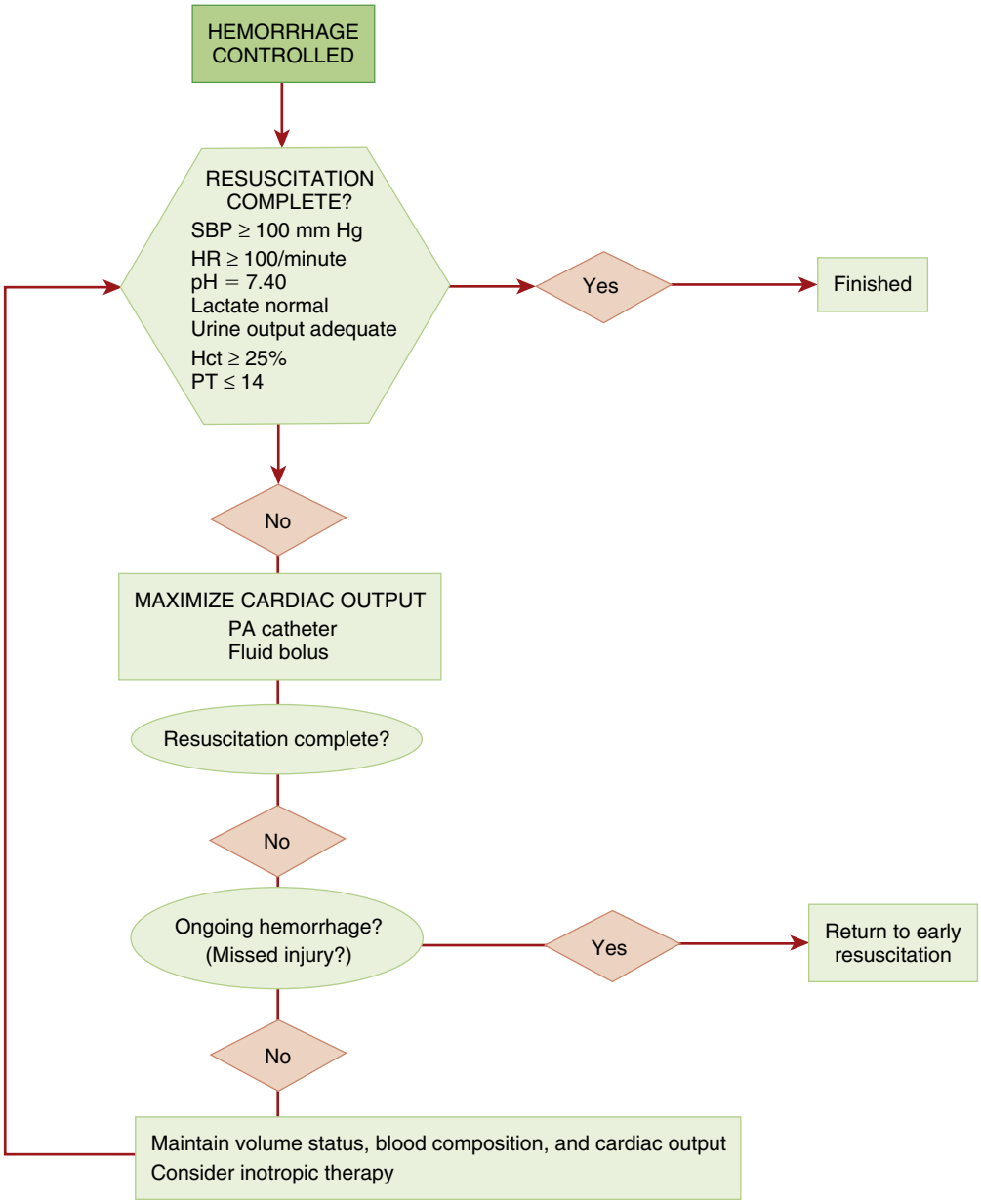


Figure 81-10. Algorithm for management of late hemorrhagic shock. *Hct,* Hematocrit; *HR,* heart rate; *PA,* pulmonary artery; *PT,* prothrombin time; *SBP,* systolic blood pressure.

Tissue hypercapnia may be a universal indicator of critically reduced perfusion. Measurement of gastric Pco_2 by gastric tonometry may be a reliable monitor in trauma patients as an indicator of restoration of splanchnic blood flow, and distal gut pH is also a reliable indicator.[172] The most proximal area of the gastrointestinal tract, the sublingual mucosa, is a useful site for measurement of Pco_2 ($Pslco_2$).[173] When $Pslco_2$ exceeded a threshold of 70 mm Hg (normal, 45.2 ± 0.7 mm Hg), its positive predictive value for circulatory shock was 100%.[174] Inadequate tissue perfusion, as indicated by these specific monitors or by the traditional systemic markers of serum lactate, base deficit, and decreased pH, must be treated promptly once ongoing hemorrhage is controlled. The rate at which lactate returns to normal after shock is strongly correlated with outcome; failure to normalize within 24 hours is associated with a greater risk for MOSF and eventual death.[166,175]

TRAUMA TO THE CENTRAL NERVOUS SYSTEM

CNS trauma accounts for almost half of all trauma death postmortem examinations in population-based analyses[176] or after trauma center admission (see also Chapter 70).[177] In addition, more than 90,000 Americans are disabled by TBI[178] and 8000 to 10,000 by SCI[179] each year. As with hemorrhagic shock, CNS trauma consists of both the primary injury, in which tissue is disrupted by mechanical force, and a secondary response, in which the body's reaction to the injury plays an important role. Mitigation

TABLE 81-5 **MODALITIES FOR ASSESSMENT OF SYSTEMIC PERFUSION**

Technique	Shortcomings
Vital signs	Will not indicate occult hypoperfusion
Urine output	May be confounded by intoxication, diuretic therapy, circadian variation, or renal injury
Systemic acid-base status	Confounded by respiratory status
Lactate clearance	Requires time to obtain laboratory result
Cardiac output	Requires placement of a pulmonary artery catheter, or use of noninvasive technology
Mixed-venous oxygenation	Difficult to obtain, but a very accurate marker
Gastric tonometry	Requires time to equilibrate, subject to artifact
Tissue oxygenation	Emerging technology, appears beneficial
Stroke volume variation	Emerging technology, requires an arterial line
Acoustic blood flow	Investigational technology, unproved

of secondary CNS injury depends on prompt diagnosis and early, goal-directed therapy. Although primary CNS injuries cannot be minimized other than with preventive strategies, secondary injury accounts for much of the death and disability that follows trauma.[180] The initial management of these patients can significantly affect outcome. Attention to the ABCDE approach is paramount to successful resuscitation, and the trauma anesthesiologist should be intimately involved in this process. Critical care management of TBI patients is covered elsewhere in this volume (see also Chapter 105). What follows is a brief discussion of the early management of these patients.

Trauma produces shear forces that result in primary damage to neuronal cell bodies and axons and to the vasculature. The pathophysiologic processes of secondary injury includes metabolic failure, oxidative stress, and a cascade of biochemical and molecular events leading to both delayed necrotic and apoptotic cell death.[181] Secondary injury is often exacerbated by tissue hypoxia or ischemia and by inflammatory responses, and outcomes from TBI are influenced by a large number of interacting factors. Individual drugs such as free radical scavengers, antiinflammatory agents, and ion channel blockers have been effective in animals but have had little impact or yielded disappointing results in human trials.[182] Long-term outcome cannot be predicted from TBI; thus, full resuscitative efforts should be initiated and continued, even in the most severely injured. In a recent review of the Trauma Registry of the German Society for Trauma Patients looking at over 50,000 patients, outcome prediction was most accurate using the GCS motor score and pupil reactivity. In patients with bilateral fixed and dilated pupils, a good outcome was still seen in 8% of patients.[183]

Patients with mild TBI (GCS score of 13 to 15) who maintain a stable GCS score for 24 hours after injury are very unlikely to deteriorate further, although they are at risk for several postconcussive effects, including headache, memory loss, emotional lability (including aggressive behavior and violence), and sleep disturbance.[184] Currently, recognition of long-term effects of mild TBI—and a better understanding of the pathophysiologic processes—have led to prevention strategies and interventional programs for these patients. Specifically, soldiers returning from battle and athletes who experience repetitive mild brain injuries—and even those with a single episode—are at risk. The most frequently proposed cellular mechanism is diffuse axonal injury, associated with alterations in many physiologic processes. As early as 2 hours after severe TBI, increased levels of soluble amyloid β–peptide and deposition of amyloid plaques are evident in brains of 30% of survivors, regardless of their age. An acute, single-incident TBI occurs in 20% to 30% of patients with Alzheimer disease or parkinsonism but in only 8% to 10% of control subjects. TBI researchers and the U.S. National Football league have now identified chronic traumatic encephalopathy (CTE), a condition typically seen in retired or aging athletes, in younger patients. CTE may be caused by large accumulations of τ proteins in the brain that kill cells in the regions responsible for mood, emotion, and executive functioning.[185,186]

Moderate TBI (GCS score of 9 to 12) may be accompanied by intracranial lesions that require surgical evacuation, and early CT is strongly indicated. Early tracheal intubation, mechanical ventilation, and close observation may be required in the management of patients with moderate TBI because of combative or agitated behavior and the potentially catastrophic consequences of respiratory depression or pulmonary aspiration occurring during diagnostic evaluation. Extubation of the trachea can be undertaken if the patient is hemodynamically stable and appropriately responsive after the diagnostic workup. Treatment of secondary brain injury is accomplished by early correction and subsequent avoidance of hypoxia, prompt intravascular fluid resuscitation, and management of associated injuries. The timing of indicated noncranial surgery in these patients is highly controversial because early surgery can increase the episodes of hypoxia and hypotension.[187] Whereas neurologic outcomes can decrease after early surgery,[188,189] delayed surgery can increase the incidence of pulmonary and septic complications in orthopedic and soft tissue surgeries.[190,191] An increased risk has not been described with early surgery, although a definitive prospective trial has not yet been reported.

Neurologic monitoring of patients with moderate TBI consists of serial assessment of consciousness and motor and sensory function (see also Chapter 49). Deterioration of the GCS score is an indication for urgent CT to establish the need for craniotomy or invasive monitoring of ICP. If frequent neurologic monitoring is not possible because of general anesthesia continuing longer than 2 hours, aggressive analgesia, or prophylaxis against delirium tremens, invasive ICP monitoring is indicated.[148] Although mortality from moderate TBI is infrequent, almost all patients will have significant long-term morbidity.

Severe TBI is classified as a GCS score of 8 or less at the time of admission and carries a significant risk for mortality. Patients with severe TBI have mortality three times that of patients with other types of traumatic injury.[192] Early,

rapid management focused on restoration of systemic homeostasis and perfusion-directed care of the injured brain will produce the best possible outcomes in this difficult population. Guidelines for all aspects of the management of patients with severe TBI have been published by the American Association of Neurological Surgeons and Brain Trauma Foundation, now in the third edition.[148] The clinical pathway in place at the R. Adams Cowley Shock Trauma Center in Baltimore appears in Figure 81-11.

A single episode of hypoxemia (PaO_2 < 60 mm Hg) occurring in a patient with severe TBI can double the incidence of mortality.[193] Prehospital tracheal intubation is controversial. Previously, intubation of the trachea before arriving at the hospital was advocated because providing

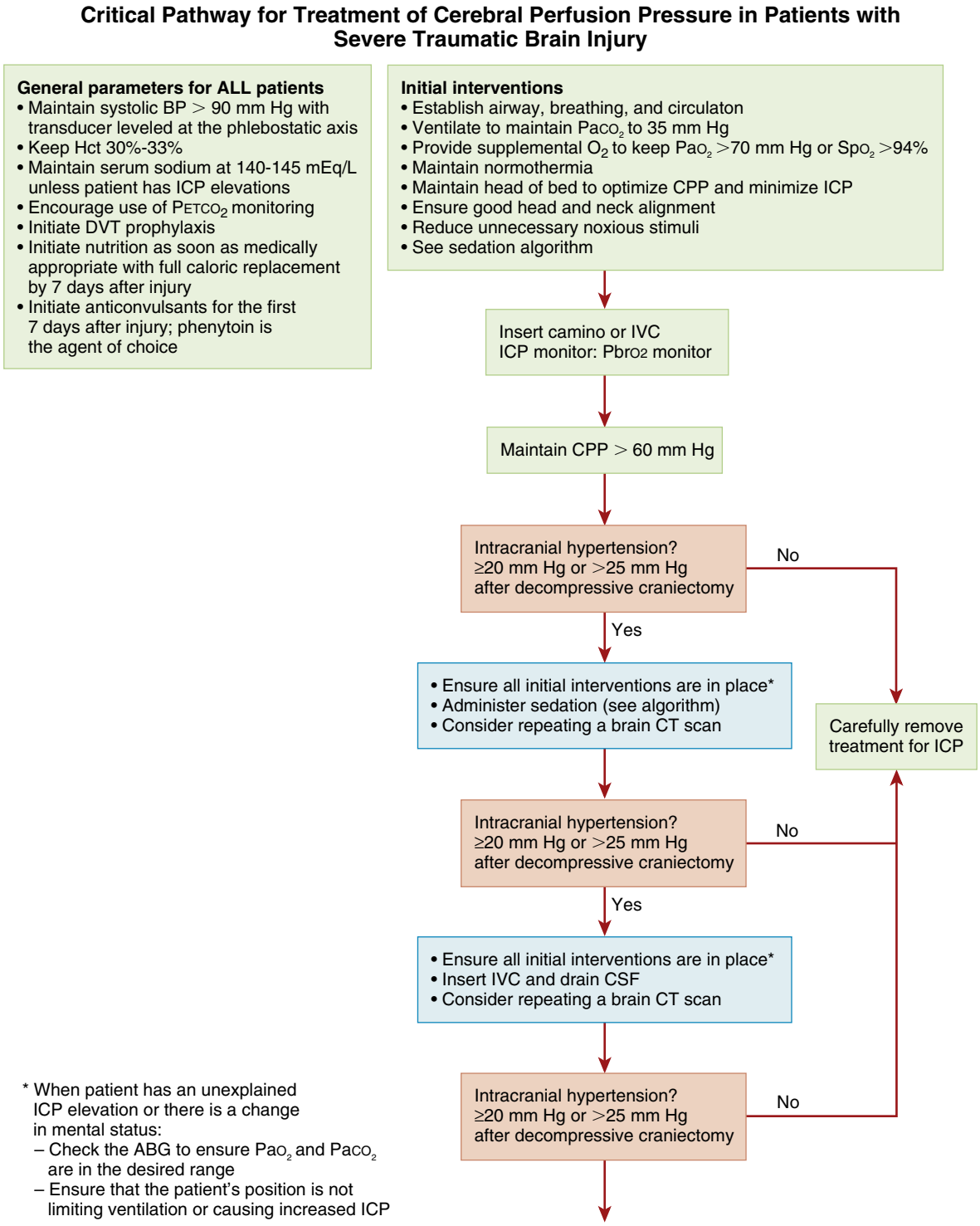


Figure 81-11. Clinical pathway for management of severe traumatic brain injury. The goal of therapy is to maintain cerebral perfusion pressure above 60 mm Hg by support of the circulation and control of intracranial pressure. Progressively more intensive therapies are added until this goal is achieved. *ABG,* Arterial blood gas; *BP,* blood pressure; *CBF,* cerebral blood flow; *CPP,* cerebral perfusion pressure; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *DVT,* deep venous thrombosis; *Hct,* hematocrit; *ICP,* intracranial pressure; *IVC,* intraventricular catheter.

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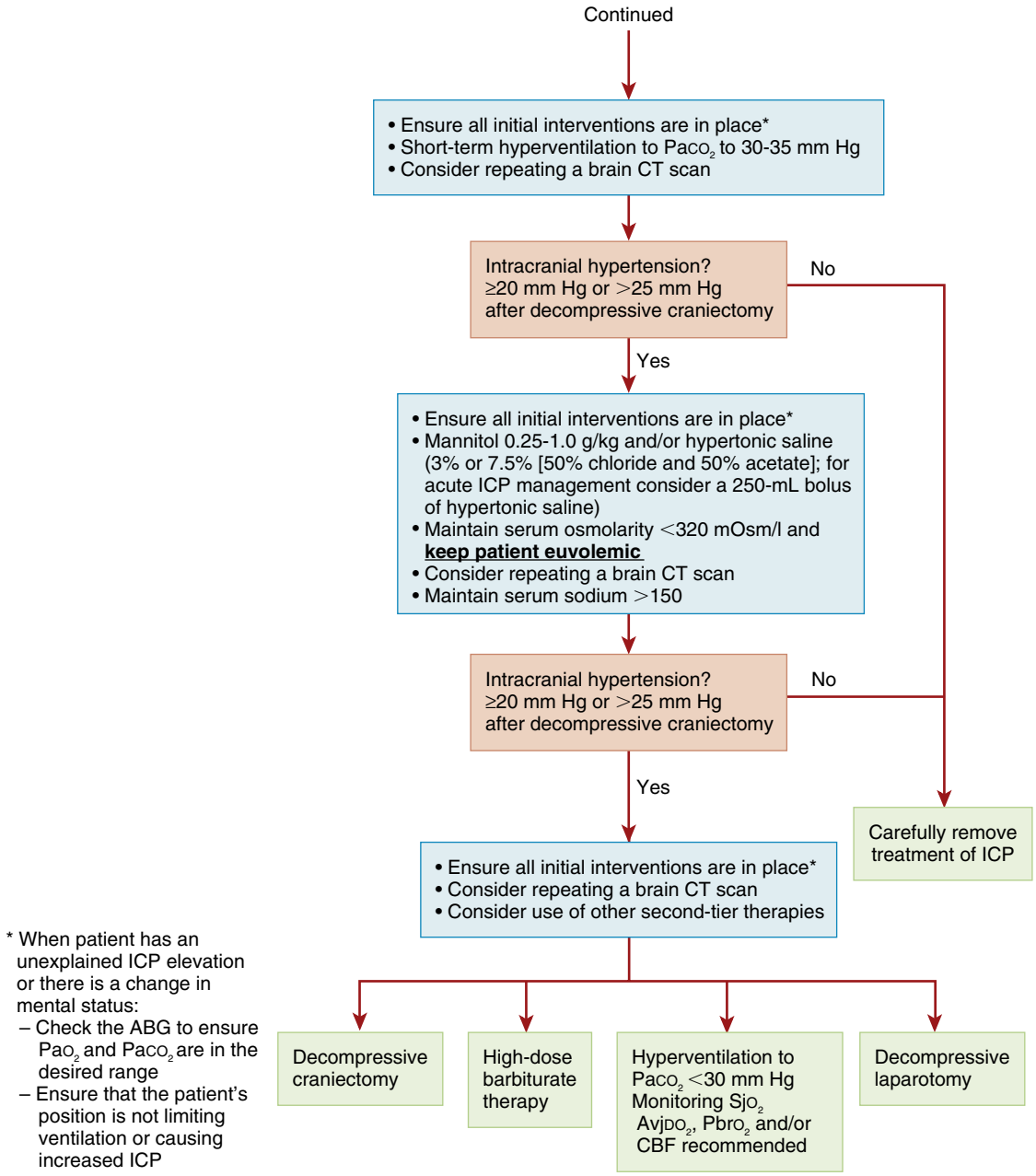


Figure 81-11, cont'd

a definitive airway allowed adequate O_2 to be delivered to the brain, benefiting the patients. Yet worsened neurologic outcomes have been described with attempts at prehospital tracheal intubation in adult trauma patients.[194,195] The first prospective trial of prehospital intubation, conducted in urban Australia, randomized patients with severe TBI—defined as evidence of head trauma and GCS of less than 9—to intubation by paramedics in the field or by physicians on the arrival to hospital.[196] Of 312 patients, the proportion with favorable outcome was 51% in the paramedic group, compared to 39% in the hospital tracheal intubation group (P = .046). Because no international standard or consensus exists, the patient should be transported as rapidly as possible to a facility capable of managing severe TBI or to the nearest facility capable of tracheal intubation of the patient and initiation of systemic resuscitation. The sine qua non is adequacy of systemic oxygenation, by whatever means this can best be accomplished.

The patient with TBI will frequently require perioperative monitoring to include ICP, brain temperature, arterial pressure, and cerebral oxygenation (see also Chapter 49). ICP may be monitored through the use of an intraparenchymal probe or intraventricular catheter and should be maintained at less than 20 mm Hg. A variety of monitoring devices have been used to assess adequacy of cerebral oxygenation, including jugular venous O_2 saturation, positron emission tomography, near-infrared spectroscopy, and direct brain tissue oxygenation ($Pbto_2$) monitoring.[197] Brain tissue hypoxia, may be corrected by increasing FiO_2, blood transfusion, inotropic support, or sedation, if increased ICP results in decreased cerebral blood flow.[198-201] Small studies suggest an improvement in

Glasgow Outcome Score (GOS) and mortality with brain O_2–targeted strategies, but no overall consensus exists.

Finally, patients with severe TBI are also at risk for non-CNS organ failure. A retrospective review of patients with isolated TBI found a frequent incidence of subsequent organ failure: 89% developed dysfunction of at least one nonneurologic organ system. Takotsubo cardiomyopathy may develop in the setting of severe TBI and lead to severe myocardial dysfunction in the patient with brain injury.[202] The reasons for development include interplay between the neuroendocrine system and the injured brain. A catecholamine surge that occurs after TBI may manifest as subendocardial ischemia, leading to biventricular heart failure, even in young, previously healthy patients. This cycle may be exacerbated during OR procedures when vasoactive drugs might be administered. β-Adrenergic blockade may be protective in human studies in patients with brain injuries. Retrospective database reviews have indicated improved neurologic outcome and reduced morbidity and mortality in patients receiving periinjury β-adrenergic blockade.[203-206]

TRAUMATIC BRAIN INJURY AND CONCOMITANT TRAUMA

Patients with isolated head injuries can be managed with traditional ventilatory strategies, but those with chest trauma, aspiration, or massive resuscitation after shock are at high risk for the development of acute lung injury (ALI) (see also Chapters 70 and 101). The classic teaching of no or low-level positive end-expiratory pressure (PEEP) to prevent increased ICP is inappropriate because hypoxemia may not be corrected. With adequate intravascular volume resuscitation, PEEP does not increase ICP or decrease cerebral perfusion pressure (CPP)[207] and may actually decrease ICP as a result of improved cerebral oxygenation.[208] Patients who develop ALI after TBI are at risk for cerebral hypoxia.[209] A double-hit model has been proposed as the cause of ALI secondary to CNS trauma—severe TBI leads to a systemic inflammatory response, which then primes the lungs to be more susceptible to injurious ventilator strategies or other mediators of lung injury. ALI and cardiac insufficiency after TBI may lead to compromised systemic oxygenation and therefore a decrease in cerebral O_2 delivery.[210] Hyperventilation therapy (e.g., at a $Paco_2$ of 25 mm Hg), long a mainstay in the management of patients with TBI, is no longer recommended as a prophylactic treatment. A range of $Paco_2$ between 30 and 35 mm Hg should be induced with hyperventilation to 30 mm Hg only for episodes of increased ICP that cannot be controlled with sedatives, drainage of cerebrospinal fluid, neuromuscular blockade, osmotic drugs, or barbiturate coma.[147] Hyperventilation during the first 24 hours is of particular concern because of the critical reductions in perfusion during this timeframe. However, these recommendations should be taken in context and modified in the face of unstable clinical circumstances such as an expanding mass lesion or signs of imminent herniation.[211]

The most challenging of all trauma patients are those with severe TBI and coexisting hemorrhagic shock. A single episode of hypotension, defined as systolic blood pressure lower than 90 mm Hg, is associated with an increase in morbidity and doubled mortality after severe TBI.[193] Hypotension together with hypoxia increases mortality 30-fold. Current recommendations are to maintain a patient with severe TBI in a euvolemic state. Therefore, *fluid resuscitation is the mainstay of therapy,* followed by vasoactive infusions as needed. The ideal fluid has not been defined, but perhaps hypertonic saline solutions are optimal. Correction of anemia from acute blood loss is the first priority; however, an optimal target hematocrit has not been defined. Animal models and healthy human subjects support maintaining a hemoglobin lower than 7 g/dL because impaired brain function may occur with lower values, yet a hemoglobin lower than 10 g/dL may be detrimental to recovery from TBI.[212] At this time it is not clear what optimal transfusion trigger should be used (see also Chapter 61). After the initial ABCDE management of a patient with severe TBI, a stepwise approach to maintenance of CPP is initiated, with a currently recommended goal range of 50 to 70 mm Hg, as discussed in Chapter 70.

Decompressive craniectomy is a surgical procedure used to control severely increased ICP and prevent herniation after stroke, and it is now used for the same indications after severe TBI.[213] Decompressive craniectomy is indicated for selected anatomic patterns of TBI, such as when CPP cannot be maintained despite vigorous application of the previously described therapies, including barbiturate coma. Relieving ICP by removal of a piece of cranium and use of a dural patch may improve mortality and morbidity in patients who might not otherwise survive.[214] Decompressive laparotomy may be indicated in patients with severe TBI if coexisting injuries or vigorous intravascular volume infusion have increased intraabdominal compartment pressure to greater than 20 mm Hg. Increased abdominal pressure worsens pulmonary mechanics, thus necessitating higher MAP to maintain arterial O_2 saturation. This increase in ventilating pressure will increase intrathoracic pressure and impair venous drainage from the head and consequently decrease CPP. The use of decompressive celiotomy as a therapy to reduce ICP was recently described.[215] The concept of multiple compartment syndrome in patients with severe TBI has been proposed.[216] Fluid therapy, ALI, or both may increase intraabdominal pressure and intrathoracic pressure, thereby increasing ICP. Further fluid administration to support cerebral perfusion or increasing ventilatory support to treat ALI further exacerbates this problem. This can create a cycle that ultimately produces multiple compartment syndrome and necessitates opening of the abdomen, even in the absence of primary abdominal trauma. Isolated TBI can thus become a multisystem disease.

Like hyperventilation therapy, the use of hypothermia to treat severe TBI has changed. Early studies demonstrated that moderate, systemic hypothermia reduces both the rate of cerebral edema and mortality after cortical injury in laboratory animals.[217,218] Small clinical series in humans also suggested improved outcome in patients with TBI when hypothermia was maintained for 24 or 48 hours.[219,220] However, a multicenter, randomized trial of hypothermia (33° C) versus normothermia

demonstrated no improvement in outcome in a population of patients with severe TBI.[221] Patients who were hypothermic on admission and then were randomized to the normothermia group had a worse outcome than those who were left hypothermic, thus leading to the recommendation that patients with severe TBI who are hypothermic on admission not undergo active rewarming. Current Brain Trauma Foundation guidelines present only level III evidence suggesting decreased mortality if target temperatures are maintained for more than 48 hours and that prophylactic hypothermia is associated with better long-term neurologic outcomes.[148]

MANAGEMENT OF INTRACRANIAL PRESSURE IN THE OPERATING ROOM

Although most interventions for management of a patient with severe TBI will occur in the ICU, urgent cranial or noncranial surgery can be indicated (see also Chapter 49).

The previously described therapies should be continued throughout the perioperative period, including positional therapy (when possible), aggressive hemodynamic monitoring and resuscitation, administration of osmotic agents (with attention to maintaining euvolemia), and deep levels of analgesia and sedation. Appropriate anesthetic choices include opioids and low concentrations of volatile anesthetics. Pharmacologic management of TBI is the mainstay of the anesthesiologist's role in the operating room. Intraoperative management of elevated ICP may be accomplished with osmotic diuretics or hypertonic saline. No difference was noted in long-term outcomes between mannitol and hypertonic saline on outcomes at 6 months, although hypertonic saline may potentiate small short-term improvements is cerebral blood flow and CPP.[222,223] A meta-analysis of common drugs used in intraoperative management of patients with TBI, including propofol, barbiturates, opioids, benzodiazepines, and corticosteroids showed corticosteroids to be the only drug associated with an increase in mortality. The other drugs had acute benefit in reductions in ICP and sedation, but no appreciable long-term benefit.[182,224]

SPINAL CORD INJURY

SCI after trauma affects some 10,000 Americans each year.[179] Blunt trauma accounts for the majority of SCI: 40% from motor vehicle collisions, 30% from falls, and 15% as a result of penetrating trauma.[225] Cervical spine injuries occur in 1.5% to 3% of all major trauma. Half of all SCIs involve the cervical spine, usually between the C4 and C7 levels. Complete quadriplegia occurs in half of SCI cases. It is important to realize that more than 40% of trauma patients who have SCI may also have other significant injuries, including TBI.

Most spinal injuries are in the lower cervical spine, just above the thorax, or in the upper lumbar region, just below the thorax. Blunt SCI is most common in the regions of the cord that are most flexible, especially at the junctions between flexible and inflexible segments. The vertebral column is divided longitudinally into three columns: anterior, middle, and posterior; injuries to any two of these three columns suggest biomechanical instability. These are the patients who will often require urgent surgical stabilization. Patients with unstable cervical spine injuries who meet criteria for emergency intubation, should undergo rapid-sequence induction (see section on protection of the cervical spine). SCI at midthoracic levels is less common because of the rotational stabilization provided by the rib cage and intercostal musculature.

SCI is commonly accompanied by radiographically visible injury to the bony spine and concomitant disruption of the muscles, ligaments, and soft tissues that support it. However, clinically significant injury to the cervical spinal cord can occur in the absence of visible skeletal injury. This entity, known as spinal cord injury without radiographic abnormality (SCIWORA) is more common in children and is presumably the result of temporary hyperdistraction or torsion of the neck insufficient to disrupt the bony skeleton.[226]

Primary injury to the spinal cord sustained at the moment of trauma may be exacerbated by secondary factors (Fig. 81-12). The combination of biochemical changes, vascular disruption and electrolyte abnormalities can lead to cellular changes and worsening of SCI lesions up to 3 days after injury.[227] SCI includes sensory deficits, motor deficits, and both. Incomplete deficits may be worse on one side than the other and may improve rapidly in the first minutes after injury. Complete deficits—representing total disruption of the spinal cord at one level—are much more ominous, with generally little improvement seen over time. Spine injuries above the level of T4-6 are accompanied by significant hypotension because of inappropriate vasodilatation, loss of cardiac inotropy, and bradycardia resulting from denervation of the cardiac accelerator fibers (neurogenic shock). (Note the distinction between *neurogenic shock* and the incorrect term *spinal shock,* which refers to a loss of reflexes.) Functioning of the lower cord will gradually return, along with restoration of normal vascular tone. Diagnosing cervical spine instability can be difficult. The Eastern Association for the Surgery of Trauma has published guidelines regarding which patients require cervical spine radiographs, which views and studies should be obtained, and how to determine the absence of significant ligamentous injury in an unconscious patient.[228] The need for magnetic resonance imaging versus the adequacy of CT to diagnose SCI is not clear. The most commonly missed cervical fractures are at the C1-2 and C7-T1 levels, usually because of the result of inadequate imaging.

Early intubation of the trachea is almost universally required for patients with cervical spine fracture and quadriplegia. Ventilatory support is almost always required for patients with a deficit above C4, because they will lack sufficient diaphragmatic function. Patients with levels from C6 to C7 may need support because of impairment in respiratory muscle function resulting from (1) loss of chest wall innervation, (2) paradoxical respiratory motion, (3) inability to clear secretions, and (4) decreased lung and chest wall compliance. Early tracheal intubation is recommended and, if elective, often can be accomplished by awake fiberoptic bronchoscopy or video laryngoscopy before hypoxia renders the patient anxious and uncooperative.[229,230] Also, two retrospective studies have evaluated the need for tracheal intubation

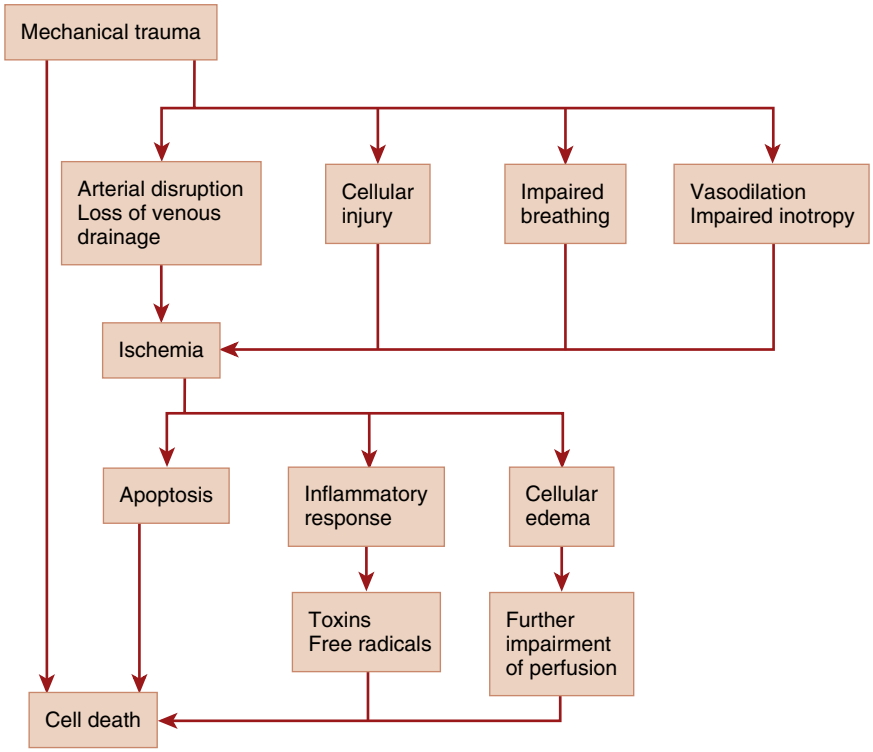


Figure 81-12. Mechanisms of spinal cord injury. Mechanical trauma to the spinal cord is exacerbated by systemic hypoperfusion or hypoxia. *(Reprinted with permission from Dutton RP: Spinal cord injury,* Int Anesthesiol Clin *40:109, 2002.)*

in patients with cervical SCI. Como and colleagues[231] identified 119 patients, 45 of whom had complete SCI. All patients with injuries at C5 and above required intubation, and 71% of these progressed to tracheostomy. A second study of 178 patients with complete cervical SCI showed 70% of patients required tracheostomy, particularly those with an injury between C4 and C7.[231] Spontaneous ventilation and extubation of the trachea are possible after surgical stabilization and resolution of neurogenic shock, although pneumonia is a common and recurrent complication that frequently necessitates tracheostomy to facilitate pulmonary toilet.[230]

Although administration of a glucocorticoid steroid bolus in patients with blunt SCI and deficit was recommended, current guidelines suggest caution. Large-dose glucocorticoid therapy has resulted in a small, but statistically significant, improvement in neurologic level after SCI in two large multicenter trials: the National Acute Spinal Cord Injury Study (NASCIS) II and III.[232,233] However, the NASCIS results have been challenged for several reasons.[234-236] The positive benefits seen with high-dose steroid administration were driven by results in a few subpopulations and were not present in a majority of patients. The improvement in spinal level seen after steroid administration has not been shown to lead to increased survival or improved quality of life, and the results have not been reproducible in other studies of acute SCI. Current recommendations by the American Association of Neurological Surgeons and the American College of Surgeons state that steroid administration is an *option* and should be undertaken with the knowledge that harmful side effects are more consistent than any proved benefit.[237]

INTRAOPERATIVE MANAGEMENT OF SPINAL CORD INJURY

A patient about to undergo surgical reduction and fixation of a spinal column fracture presents challenges for the anesthesiologist. First and foremost is the need for intubation of the trachea in a patient with a known injury to the cervical spine (see also Chapter 55). Direct laryngoscopy with in-line stabilization is appropriate in the emergency setting and in unconscious, combative, or hypoxemic patients when the status of the spine is not known.[238] Tracheal intubation can occur in the OR, in an awake, alert, and cooperative patient by several methods known to produce less displacement of the cervical spine, presumably with less risk for worsening an unstable SCI. A common technique in current clinical practice is awake fiberoptic intubation. Although the nasal route is associated with an easier path to intubation in most patients, it can lead to an increased risk for sinusitis in the ICU if the trachea is not extubated at the end of the procedure. Oral intubation may be more challenging technically but will be of greater value if the patient remains mechanically ventilated. Blind nasal intubation, transillumination with a lighted stylet, and use of an intubating LMA, GlideScope, or Bullard laryngoscope, or any of a variety of other instrument systems for indirect laryngoscopy are acceptable. Again, in comparative studies of direct laryngoscopy, video laryngoscopy, fiberoptic examination, blind nasal intubation, or cricothyrotomy in patients with known cervical cord or spine injuries, no difference is seen in neurologic deterioration with technique used and no clear evidence exists that direct laryngoscopy worsens outcome. Clinicians are

advised to use the equipment and techniques with which they are most familiar. The important concept is to successfully achieve tracheal intubation while minimizing motion of the cervical spine and preserving the ability to assess neurologic function after positioning.[48]

A patient with a partial deficit and visible spinal canal impingement on imaging studies is considered an emergency because of the potential for regaining neurologic function after decompression. Patients with either no deficit or complete deficit may require surgical stabilization to facilitate mobilization, but are less urgent cases. Hemodynamic instability may complicate urgent and emergent spinal surgery. Hypotension from neurogenic shock is characterized by an inappropriate bradycardia resulting from loss of cardiac accelerator function and unopposed parasympathetic tone. However, this situation can be difficult to distinguish from hypotension resulting from acute hemorrhage, and a trial of fluid administration is still indicated, subject to the end points of resuscitation listed earlier. Once hemorrhage has been controlled or ruled out, patients who have maintenance of an increased MAP more than 85 mm Hg for 7 days after SCI may have improved functional recovery. This approach is highly controversial and remains an option in treatment according to the American Association of Neurological Surgeons.[237]

ORTHOPEDIC AND SOFT TISSUE TRAUMA

Musculoskeletal injuries are the most frequent indication for operative management in most trauma centers (see also Chapter 79). Orthopedic trauma, like TBIs and SCIs, can be associated with long-term pain and disability. In addition to physical handicaps that these patients may endure, orthopedic injuries incurred in both civilian and military settings lead to long-term psychological trauma.[239-241] The length of many procedures, particularly in patients with multiple extremity injuries, necessitates attention to body positioning, maintenance of normothermia, fluid balance, and preservation of peripheral blood flow.

For the last 15 years, the emphasis in trauma management of a multiply injured patient has included early stabilization of long-bone, spine, pelvic, and acetabular fractures. Failure to do so results in increased morbidity, pulmonary complications, and length of hospital stay.[242] In one study, only 2% of patients with femoral shaft fractures stabilized within the first 24 hours of injury had pulmonary complications, in contrast to 38% of patients in whom fracture stabilization was delayed for more than 48 hours.[243]

SPECIFIC CONDITIONS

Hip fracture is a common, morbid, and costly event among older adults (see also Chapter 80). Frequently, patients with isolated hip fracture present to the OR for urgent repair. Regional anesthesia is associated with decreased odds of inpatient mortality and pulmonary complications among patients with hip fracture in contrast to general anesthesia.[244] A retrospective cohort of 18,158 patients undergoing surgery for hip fracture in 126 hospitals showed that 5254 (29%) received regional anesthesia. Although unadjusted rates of mortality and cardiovascular complications did not differ by anesthesia type, regional anesthesia was associated with a decreased adjusted odds of mortality (odds ratio: .710, 95% confidence interval [CI] .541, .932, $P = .014$) and pulmonary complications (odds ratio: .752, 95% CI .637, 0.887, $P < .0001$) relative to general anesthesia.[245]

Dislocation of the hip is common after high-energy trauma and is frequently accompanied by fracture of the acetabulum. Whereas the fracture itself can be safely managed on a delayed basis or nonoperatively, the dislocation is a medical emergency that must be promptly addressed if the patient is to have a good functional outcome. Failure to promptly diagnose and reduce a dislocated hip joint is a significant risk factor for avascular necrosis of the femoral head. Reduction typically requires a very deep level of sedation, which may be facilitated by nondepolarizing neuromuscular blockade (see also Chapters 34 and 35). For this reason the anesthesiologist is commonly involved.[246] Although a dislocated hip can be reduced in a spontaneously breathing sedated patient, an acutely injured patient is at high risk for aspiration of gastric contents. Any patient who will be undergoing surgery in the near future (such as for an open long-bone fracture or exploratory laparotomy) should be tracheally intubated at the time of reduction and maintained with appropriate sedation and analgesia until reaching the OR. Other patients who may require intubation even for uncomplicated reductions include those who are inebriated or uncooperative, hemodynamically unstable, or suffering from pulmonary dysfunction. Additionally, successful postoperative fracture reduction is more difficult to achieve in morbidly obese patients (see also Chapter 71) than in those with normal body mass index.[247]

Unlike acetabular fractures, fracture of the pelvic ring requires immediate recognition and management by the trauma team. Hemorrhage, even exsanguination, is common after a major pelvic ring fracture and is a leading contributor to early death after motor vehicle collisions. Bleeding occurs from multiply disrupted venous beds in the posterior pelvic bowl; if the pelvis as a whole is unstable, no anatomic barrier exists to continued expansion of this retroperitoneal bleeding. Surgical exploration by way of the peritoneum is usually unrewarding because the bleeding vessels are not easily accessed.[248] In the past, therapy consisted of supportive volume resuscitation, external fixation of the unstable pelvis, and angiography. Despite this multidisciplinary approach, mortality remained frequent in these patients, partially because of the inability of angioembolization to control venous bleeding from the rich venous plexuses associated with the most severe fractures. The technique of preperitoneal packing has been adopted by many U.S. trauma centers. Preperitoneal packing via laparotomy is a rapid method for controlling pelvic fracture–related hemorrhage that can supplant the need for emergent angiography and reduces transfusion requirements and mortality.[249] Endotracheal intubation is usually undertaken on an emergency basis in a hypotensive patient, and the anesthesiologist may remain with the patient throughout the initial hours of stabilization to manage sedation, analgesia, transport, and ongoing

resuscitation needs. In the absence of an orthopedic specialist, temporary stabilization and tamponade of some pelvic fractures can be accomplished with use of a specially made pelvic binder, the pelvic portion of military antishock trousers, or a bed sheet knotted tightly around the bony pelvis.[250] Mechanically unstable pelvic ring fractures are associated with increased fluid and blood resuscitation volumes, significantly more frequent presence of concomitant injuries, and increased ventilation and ICU stay, rate of MODS, sepsis, and rate of mortality.[251]

Open fractures should be pulse-lavaged and debrided as soon as possible after injury to minimize the risk for infectious complications. If ongoing resuscitation or unstable TBI precludes the patient from early management in the OR, this procedure can be performed at the bedside. Despite the frequency of open fractures, their management remains one of the greatest and most debated orthopedic challenges. Timing of surgical fixation in open fractures is often surgeon-specific or center-specific, because little consensus exists among orthopaedic surgeons as to optimal treatment.[252]

The advantages and disadvantages of regional and general anesthesia are summarized in Boxes 81-8 and 81-9. Regional anesthesia seems to decrease postoperative morbidity and mortality[245,253,254] (including cognitive measures of function), but clinically measurable benefits may not be seen in patients receiving combined general and regional techniques.[255-257]

One prevalent concern in the management of an orthopedic trauma patient is the concomitant use of regional anesthesia, analgesia, or both and prophylaxis for venous thromboembolism, as discussed in Chapter 79.

Intraoperative transesophageal echocardiography (TEE) has shown that most patients undergoing long-bone fracture manipulation experience microembolism of fat and marrow.[258] Most patients suffer no discernible clinical impact from this phenomenon, but some will experience a significant acute inflammatory response. After long-bone fractures, some lung dysfunction occurs in almost all patients, ranging from minor laboratory abnormalities to full-blown fat embolism syndrome (FES). A lack of universally accepted diagnostic criteria combined with concomitant pulmonary and cardiovascular dysfunction accounts for the varying incidence reported in the literature. Clinically significant FES occurs in 3% to 10% of patients but is likely underdiagnosed in patients with multiple injuries or a high ISS.[259] Patients with coexisting lung injury are at additional risk for FES. Signs include hypoxia, tachycardia, mental status changes, and, classically, a petechial rash on the axillae, upper arms and shoulders, chest, neck, and conjunctivae. FES should be considered whenever the alveolar-arterial O_2 gradient deteriorates in conjunction with decreased pulmonary compliance and CNS deterioration. Under general anesthesia, the CNS changes will not be apparent but may be manifested as failure to awaken after surgery. If central hemodynamic monitoring is available, pulmonary artery pressure is elevated, often accompanied by decreases in the cardiac index. Diagnosis in the OR is largely based on the clinical findings after ruling out other causes of hypoxemia. Fat globules in urine are nondiagnostic, but lung infiltrates seen on chest radiography confirm the presence of lung injury and the need for appropriate ventilatory management with O_2, higher PEEP, and possible longer-term mechanical ventilatory support.[260,261] Treatment includes early recognition, administration of O_2, and judicious fluid management.[262] A change in the orthopedic procedure may be indicated, such as converting intramedullary nailing of the femur to external fixation.

Acute compartment syndrome of the extremities is defined as a "condition in which increased pressure within a limited space compromises the circulation and function of the tissues within that space."[263] The most common cause of compartment syndrome is edema secondary to muscle injury and associated hematoma formation. Although most commonly associated with traumatic injuries, compartment syndrome also can occur as a result of causes associated with trauma, including reperfusion injury, burns, drug overdose, and prolonged limb compression (Box 81-10). The most common fractures associated with the development of compartment syndrome are those of the tibial shaft (40%) and forearm (18%).[264,265] Forearm compartment syndrome requiring fasciotomy predominantly affects males and can occur after either a fracture or soft-tissue injury. A further 23% of cases are caused by soft tissue injuries without fracture.[266] Although no randomized, prospective trials

BOX 81-8 *Advantages and Disadvantages of Regional Anesthesia for Trauma*

Advantages

Allows continued assessment of mental status
Increased vascular flow
Avoidance of airway instrumentation
Improved postoperative mental status
Decreased blood loss
Decreased incidence of deep venous thrombosis
Improved postoperative analgesia
Better pulmonary toilet
Earlier mobilization
Lower incidence of long-term pain syndromes

Disadvantages

Peripheral nerve function difficult to assess
Patient refusal common
Requirement for sedation
Hemodynamic instability with placement
Longer time to achieve anesthesia
Not suitable for multiple body regions
May wear off before procedure(s) conclude

BOX 81-9 *Advantages and Disadvantages of General Anesthesia for Trauma Patients*

Advantages

Speed of onset
Duration: Can be maintained as long as needed
Allows multiple procedures for multiple injuries
Greater patient acceptance
Allows positive-pressure ventilation

Disadvantages

Impairment of global neurologic examination
Requirement for airway instrumentation
Hemodynamic management more complex

BOX 81-10 *Risk Factors for the Development of Compartment Syndrome*

Orthopedic
Fractures and operative repair

Vascular
Reperfusion injury
Hemorrhage with hematoma formation
Ischemia from arterial and venous injuries

Soft Tissue
Crush injury
Burns
Prolonged compression in immobile state

Iatrogenic
Casts and circular dressing
Use of pneumatic antishock garment
Intraosseous fluid replacement in infant or child
Pulsatile lavage with extravasation
Extravasation from venous or arterial puncture site

Miscellaneous
Snakebite
Acute exertion

have been conducted, regional anesthesia does not blunt detection of compartment syndromes as long as there is not an associated dense motor block.[267]

Fasciotomy is usually indicated when compartment pressure approaches 20 to 30 mm Hg below diastolic pressure in any patient with a worsening clinical condition, a documented rising tissue pressure, major soft tissue injury, or a history of 4 to 6 hours of total ischemia of an extremity. Prophylactic fasciotomy may be indicated in patients with warm ischemic time in excess of 2 hours, ligation of the major veins in the popliteal region or distal part of the thigh, and crush injuries. Early or prophylactic fasciotomy decreases subsequent muscle loss.[268]

Crush syndrome is the general manifestation of crush injury caused by continuous prolonged pressure on one or more extremities[269] and is commonly found in patients who have been trapped in one position for an extended period. Muscle injury secondary to ischemia causes myoglobinuria, which can lead to acute renal failure and subsequent profound electrolyte disturbances. The most critical treatment consists of crystalloid fluid resuscitation; a total body fluid deficit of 15 L may occur in severe rhabdomyolysis.[270] Osmotic diuresis with mannitol and alkalinization of urine with sodium bicarbonate to prevent precipitation of myoglobin in the renal tubules are controversial.[271,272] The preferred therapy for renal failure secondary to rhabdomyolysis at the shock trauma center is continuous renal replacement therapy and hemofiltration.[273] Most of these patients eventually have full recovery of native renal function.[274]

SOFT TISSUE TRAUMA

Assessment of soft tissue injury is critical in the management of a trauma patient. Muscular coverage is necessary for the viability of any orthopedic repair, but it may be jeopardized by avulsion at the time of injury, ischemia from elevated compartment pressure, and ongoing bacterial infection in open wounds. Acute surgical management of soft tissue injury is straightforward: all dead or devitalized tissue must be debrided and the wound thoroughly irrigated to reduce the load of bacterial contaminants. When muscle or fascia involvement is significant, serial debridement at frequent intervals is necessary to establish a margin of completely viable tissue. Vacuum dressings for large soft tissue wounds are gaining in popularity because continuous negative pressure over the wound surface removes contaminants and encourages blood flow.[275] When serial debridement establishes viable tissue at all margins of the wound, arrangements for definitive closure can be made. Closure may be as simple as a split-thickness skin graft or as complex as free tissue transfer of muscle and fascia from an uninjured portion of the body, with attendant arterial and venous anastomoses.

A degloving injury results in significant soft tissue loss, usually in the extremities. Multiple plastic surgery and reconstructive procedures may be necessary. General anesthesia is usually required, although combining it with epidural or regional block analgesia may confer the benefits of both techniques. Close consultation with the surgical teams is suggested.

Superficial vacuum dressings can be changed at the bedside under light sedation, but patients with deep wound dressings may require general anesthesia. The need for repeated surgeries is an important consideration for the anesthetic technique. Anesthesia for free tissue transfer surgery requires meticulous attention to detail because these operations can be quite protracted. Every effort should be made to facilitate perfusion of the grafted vessels, including keeping the patient warm, euvolemic, and comfortable and maintaining the hematocrit in the rheologically favorable range of 25% to 30%. The use of epidural anesthesia and analgesia is controversial, with some surgeons favoring it for its vasodilatory effects and others being concerned that it will induce a steal phenomenon that will actually limit flow in the denervated free tissue.[276] The use of vasopressors in microsurgery is generally avoided. Yet in one study, the vasopressor used did not cause more complications.[277]

OTHER TRAUMATIC INJURIES

HEAD AND NECK SURGERY

With the exception of emergency exploration of penetrating trauma to zone II of the neck (from the clavicles up to the angle of the mandible), most surgical repair of head and neck trauma will occur in the subacute phase, after complete resuscitation and secondary diagnostic studies (see also Chapter 85). Anesthetic management of these patients is not substantially different from that for similar elective procedures, although coexisting injuries may influence patient positioning, airway management, and ventilator settings.[278,279] Surgery on the mandible and maxilla will be facilitated by nasotracheal intubation, but a secure airway should be not jeopardized by attempting to switch from an oral to a nasal tube in a

patient in whom visualization of the larynx might be difficult because of traumatic swelling or body habitus. It is safer in these cases for the surgeon to either work around an oral tube secured behind the second molar (to allow dental occlusion) or place a tracheostomy if the need for intubation and mechanical ventilation is likely to be protracted. Surgery on the zygoma and the nasal, orbital, and ethmoid bones will be possible with an oral endotracheal tube. Securing the endotracheal tube to the molar with a fine-gauge wire will help stabilize it through the operation. All of these surgeries will lead to significant soft tissue swelling in the immediate postoperative period, often necessitating several days of continued intubation and sedation until sufficient venous drainage has occurred to allow safe extubation of the trachea. Though not by itself definitive, the presence of an air leak when the endotracheal tube cuff is deflated is suggestive that the airway will remain patent once the tube is removed.

CHEST INJURIES: PULMONARY

Injuries to the lung parenchyma that produce pneumothorax can be managed by tube thoracostomy to relieve tension, drain accumulated blood, and apply suction to the pleural space until the air leak spontaneously resolves (see also Chapter 66). Bleeding from the low-pressure pulmonary circulation is usually self-limited. Thoracostomy is uncommon but becomes necessary when evidence exists of mediastinal injury, chest tube output exceeds 1500 mL in the first hours after injury, tracheal or bronchial injury and massive air leak are apparent, or the patient is hemodynamically unstable with evident thoracic pathology.[17] Blood collected from the pleural space is generally free of clotting factors and can be directly reinfused with any of several commercial systems.[280] Hemorrhage necessitating surgery may be from injured intracostal or internal mammary arteries or from the lung parenchyma. Staple resection of injured lung or even anatomic lobectomy is not uncommon, particularly after penetrating trauma.

Although double-lumen endotracheal intubation is desirable during urgent thoracotomy, this should not be the initial approach. Rapid-sequence induction with a large-caliber (at least 8.0 mm in internal diameter) conventional endotracheal tube will allow diagnostic bronchoscopy and protect the patient from aspiration until passage of a gastric tube can reduce the stomach contents. The change to a double-lumen tube can then be made under controlled conditions in the presence of adequate oxygenation, anesthesia, and muscle relaxation. Tolerance of single-lung ventilation is variable in the trauma population and depends in large part on the absence of significant pathologic findings in the ventilated lung. Many patients with blunt thoracic injury have bilateral pulmonary contusions and will require increased FiO_2 and high levels of PEEP to maintain adequate oxygenation, even when both lungs are ventilated.

Although chest trauma requiring pneumonectomy has historically resulted in mortality approaching 100%, a recent multicenter retrospective review reported on a series of survivors of this surgery.[281] Intraoperative deaths are the result of uncontrollable hemorrhage, acute right ventricular failure, and air embolism. Patients who survive the initial procedure are at risk for early postoperative morbidity and mortality. Fluid management may be complicated by the need to weigh ongoing resuscitation against the treatment of right ventricular failure. Blunt thoracic trauma requiring pneumonectomy is often associated with abdominal and pelvic trauma. Volume replacement must be judicious, and the use of a pulmonary artery catheter (placed with care in a postpneumonectomy patient) or TEE may be beneficial. Echocardiography will also play an important role in assessing right ventricular function and pulmonary hypertension (see also Chapter 46). Treatment of right ventricular failure after traumatic pneumonectomy is difficult.[282] During hypovolemic shock a disproportionate increase occurs in pulmonary vascular resistance with respect to systemic vascular resistance,[283] as well as frequent mortality with combined hemorrhagic shock and pneumonectomy.[284] With severe right heart dysfunction it is desirable to maintain a higher preload than normal. Several therapeutic approaches have been used to treat right ventricular failure, including close monitoring of pulmonary artery pressure, the use of diuretics for volume overload, and administration of pulmonary vasodilators. Because this injury is rare and the number of patients reported in the literature is small, the best therapy is difficult to identify. A recent case report describes the use of nitric oxide to successfully treat pulmonary hypertension after posttraumatic pneumonectomy[285] (see also Chapter 104). Extracorporeal support also has been used to sustain patients through the perioperative period, although the technical challenges are substantial and successful weaning may require days to weeks on bypass. Early initiation has been beneficial in our experience, with a recent survival rate of approximately 60%.

Tracheobronchial injury can result from either blunt force or penetrating trauma. Penetrating injuries are usually more promptly diagnosed and treated. Blunt trauma most commonly results in an injury to the tracheobronchial tree within 2.5 cm of the carina and may initially be unrecognized. The presence of subcutaneous emphysema, pneumomediastinum, pneumopericardium, or pneumoperitoneum, without apparent cause, should alert the practitioner to possible tracheobronchial injury.[286] Despite bronchoscopy and helical CT scanning, a small injury may never be delineated. If the resultant injury is an incomplete tear, it may heal with stenosis, subsequent atelectasis, pneumonia, pulmonary destruction, and sepsis. When surgery is required for a delayed, incomplete tracheobronchial injury, pulmonary resection may be required if significant tissue destruction has occurred, whereas complete transection may be amenable to reconstruction with preservation of pulmonary tissue. The level of injury dictates the surgical approach. Cervical injuries are approached through a transverse neck incision, left bronchial injuries via a left thoracotomy, and tracheal or right main bronchial injuries via a right thoracotomy. In the cervical region it is sometimes possible to access a longitudinal tear of the posterior membranous trachea by opening the anterior trachea and operating around the endotracheal tube.

CHEST INJURIES: TRAUMATIC AORTIC INJURY

Traumatic aortic injury (TAI) must be ruled out in any patient with a high-energy injury, such as occurs with a motor vehicle accident or a fall from a height. The incidence of TAI has decreased in recent years because of the increased presence of airbags in motor vehicles; a majority of cases in the past decade have been caused by side-impact collisions.[287] Aortic injury occurs most commonly just distal to the left subclavian artery and is the result of sheer forces between the mobile heart and aortic arch and the immobile descending thoracic aorta. TAI is manifested as a continuum of injury from a small intimal flap to free transection contained by the surrounding mediastinum and pleura. The diagnosis is made by screening chest radiography, followed by definitive angiography, CT, or TEE. Surgical or endovascular repair is indicated for most patients with TAI because of the high risk for rupture in the hours and days after injury.[288] Various techniques have been described for this highly morbid surgery, with the best results attributed to partial bypass techniques using inflow from the left atrium, a centrifugal pump, and outflow to the descending aorta.[289] Selective nonoperative management of high-risk patients with TAI has been described.[290,291] Treatment is similar to that in patients with uncomplicated type B aortic dissection and consists of β-adrenergic blockade to minimize the cardiac rate–pressure product. Endovascular repair is the evolving standard for TAI with a decreased mortality and morbidity rate.[292-294]

CHEST INJURIES: RIB FRACTURES

Rib fractures are the most common injury resulting from blunt chest trauma. The fracture itself generally requires no specific treatment and will heal spontaneously over a period of several weeks. Therapy is directed at minimizing pulmonary complications secondary to these fractures, such as pain, splinting, atelectasis, hypoxemia, and pneumonia. Of particular concern are rib fractures in older adults (older than 55 years of age). Older patients with rib fractures have twice the mortality and thoracic morbidity of younger patients with similar injuries. Epidural anesthesia should be used liberally in patients with severe pain, older adults, and patients with preexisting compromised pulmonary function. Data support a 6% decrease in morbidity and mortality in older patients when epidural anesthesia is used[295]; however, a recent meta-analysis failed to identify a reduction in mortality.[296] Epidural analgesia may minimize or avoid complications of splinting and pain such as hypoxemia, hypoventilation, the need for tracheal intubation, and the possibility of pneumonia. Endotracheal intubation is reserved for patients who are unable to oxygenate or ventilate or who require protection of the airway.

Fracture of multiple neighboring ribs will result in the flail chest syndrome, characterized by paradoxical chest wall motion during spontaneous ventilation. Not all patients with a flail chest require positive-pressure ventilation, and endotracheal intubation should be reserved for those who meet the usual criteria. Patients who are not initially intubated should be observed closely in the ICU for signs of worsening respiratory function. Increasing cases have been reported of the use of noninvasive positive-pressure ventilation (NIPPV) for lung injury secondary to trauma.[297] For these patients who subsequently require intubation for a surgical procedure, the anesthesiologist will need to determine the safety of extubation postoperatively. NIPPV is associated with fewer cases of pneumonia, which may lead to fewer tracheostomies and decreased ICU length of stay. A successful technique has been early extubation to a mask delivering continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP).[298] Concomitant pulmonary injury, especially lung contusion, is commonly associated with flail chest. Pulmonary contusion will cause shunting, which will lead to hypoxemia. This syndrome may progress rapidly in the hours and days after injury. An initially clear chest radiograph does not exclude the possibility of a pulmonary contusion, and, again, close observation is warranted if signs of significant chest wall trauma are present. As with all patients after traumatic injury, a high degree of suspicion along with a continuous search for missed injuries is warranted. No specific therapy exists for a pulmonary contusion, and therapy is directed at the associated injuries or resultant hypoxemia. Early and aggressive implementation of a lung-protective strategy is crucial in the treatment of patients with significant pulmonary contusion to minimize progression to ARDS or concomitant ventilator-associated lung injury.

CHEST INJURIES: CARDIAC INJURY

Blunt cardiac injury is a rare and poorly understood phenomenon that must be considered in any patient who has sustained a frontal impact to the chest. Bruising or edema of the myocardium is functionally indistinguishable from myocardial ischemia and may be causally related in that the pathophysiology of cardiac contusion may involve forcible dislodgement of unstable atherosclerotic plaque. If the patient is hemodynamically stable and the ECG does not demonstrate conduction disturbances or tachyarrhythmias, blunt cardiac injury can be safely excluded.[299] If either a new tachyarrhythmia or conduction disturbance subsequently develops or the patient has unexplained hypotension, other causes (hypovolemia, renal failure) should be ruled out first. If the workup is negative, transthoracic echocardiography (TTE) should be performed. Right ventricular dysfunction resulting in hypotension may be overlooked while more common causes of hypotension in the trauma patient are being evaluated. TEE is superior to TTE in obese patients or those with injuries to the chest wall that make it difficult to obtain adequate acoustic windows, but it will generally require intubation and deep sedation to perform (see also Chapter 71). Once diagnosed, blunt cardiac injury should be managed as ischemic cardiac injury, with completion of resuscitation and then careful control of fluid volumes, administration of coronary vasodilators, and monitoring and symptomatic treatment of rhythm disturbances. Anticoagulation with aspirin or heparin should be approached on a case-by-case basis as determined by the patient's other injuries. Cardiology consultation is appropriate if the patient may benefit from coronary angiography followed by angioplasty or stenting of stenotic vessels.

Patients with penetrating cardiac trauma and blunt trauma causing rupture of one or more chambers (usually the atria) are often not seen by the trauma center because of a frequent rate of prehospital mortality.[300] Those who do not die immediately of free exsanguination into the thoracic cavity will have pericardial tamponade and can be extremely unstable in the first minutes after admission. This condition is diagnosed by clinical suspicion, focused assessment with sonography for trauma (FAST), and direct inspection during ED thoracotomy. Relief of the tamponade and clamp or suture control of the cardiac injury may allow restoration of spontaneous circulation and necessitate urgent transition to the OR for definitive hemostasis and chest closure. Cardiopulmonary bypass may be required for support during repair of cardiac injuries.

ABDOMINAL INJURY

The need for exploratory laparotomy, once the mainstay of the trauma surgeon, has declined because FAST and high-resolution CT have reduced the incidence of negative abdominal explorations, whereas angiographic embolization of hemorrhaging vessels in the liver and spleen has reduced the need for open procedures. Urgent celiotomy, when it does occur, will typically follow the principles of damage control, as described earlier.[160] The abdomen is opened and packed tightly in all four quadrants. Systematic exploration is undertaken in each quadrant in turn, with time taken only for control of hemorrhage and rapid staple closure of open gastrointestinal injuries. The abdomen is packed open at the conclusion of the procedure, a sterile drape is used to cover exposed viscera, and the patient is moved to the ICU to complete resuscitation. Definitive treatment of nonlethal injuries and restoration of bowel continuity are deferred until a second operation 24 to 48 hours later.

Anesthetic management of emergency celiotomy should follow the principles of early resuscitation outlined earlier. Adequate IV access is required, as well as continuous arterial pressure monitoring. Use of cell salvage devices can reduce the patient's exposure to banked blood, although reinfusion is generally deferred if there has been significant contamination by bowel contents. A rapid infusion system is advantageous for preservation of intravascular volume and normothermia during periods of heavy bleeding. Subsequent abdominal surgeries will be needed in hemodynamically stable patients and should not present unusual anesthetic challenges. Subsequent reconstructive procedures can become technically difficult as scarring and adhesions develop; the anesthesiologist should be prepared for a long anesthetic procedure with the potential for significant hemodynamic compromise.

SELECTED PATIENT POPULATIONS

TRAUMA AND PREGNANCY

Trauma to pregnant patients is associated with a frequent risk for spontaneous abortion, preterm labor, or premature delivery, depending on the location and magnitude of the mother's injury (see also Chapter 77). Early consultation with an obstetrician is desirable for any pregnant trauma patient, for both immediate management and long-term follow-up. The best treatment of the developing fetus consists of rapid and complete resuscitation of the mother. Trauma patients in the first trimester of gestation may not realize that they are pregnant; for this reason human chorionic gonadotropin testing is part of the initial laboratory studies for any injured woman of childbearing age. Serious trauma occurring during the period of fetal organogenesis may induce birth defects or miscarriage because of the effects of medications, pelvic irradiation, or hemorrhage leading to placental ischemia. Indicated radiologic tests should not be deferred, but shielding of the pelvis should be provided whenever possible.[301] Patients who do not spontaneously miscarry should be advised of the potential risks for birth defects and be referred for counseling if desired.[302] Dilatation plus curettage of the uterus is advisable after miscarriage to avoid toxicity arising from retained products of conception.[303]

Trauma occurring in the second or third trimester of pregnancy necessitates early ultrasonographic examination to determine fetal age, size, and viability. Monitoring of the fetal heart rate is indicated if the pregnancy is sufficiently advanced that the fetus would be viable if delivered. Preterm labor is very common in this population and should be treated with β-adrenergic agonist drugs or magnesium at the direction of the obstetrician. Delivery should be delayed as long as the fetus is not an unacceptable metabolic stress on the mother. Delivery by cesarean section is indicated if the mother is in extremis, if the uterus itself is hemorrhaging, or if the gravid uterus is impairing surgical control of abdominal or pelvic hemorrhage.[304] Placental abruption can occur in response to substance abuse or abdominal trauma and can precipitate life-threatening uterine hemorrhage. Emergency cesarean section is indicated in these cases. The Kleihauer-Betke blood test can be used to determine if fetal blood has leaked into the maternal circulation[304]; if positive, administration of anti-Rh_0 immune globulin is recommended for any Rh-negative mother carrying an Rh-positive fetus. By the third trimester the uterus is sufficiently enlarged to compress the inferior vena cava when the patient is positioned supine, thereby impairing venous return to the heart and contributing to hypotension. Left lateral uterine displacement is indicated to treat this problem. If the patient is immobilized on a long spine board because of concern for a thoracic or lumbar spinal fracture, the whole board can be tipped to the left. Because the gravid uterus displays abdominal contents upward, elevating the head of the bed may also be required to improve ventilation.

OLDER TRAUMA PATIENTS

Equivalent traumatic injuries will have a markedly more serious outcome in older adults than in younger victims (see also Chapter 80).[305] Decreased cardiopulmonary reserves lead to a higher incidence of postoperative mechanical ventilation in older trauma patients and a much greater risk for MOSF after hemorrhagic shock. Greater care must be taken with intraoperative positioning to avoid pressure injuries. A higher hematocrit achieved by tighter control of administered fluid is generally recommended

to maintain maximized tissue O_2 delivery. Posttraumatic myocardial dysfunction is a significant risk, particularly if the heart rate is elevated secondary to blood loss, pain, or anxiety. Complex operations or large blood loss should encourage the use of TEE, invasive arterial monitoring, and noninvasive monitors of cardiac output and volume status to guide fluid and inotropic therapy.[149] Although prophylactic β-antagonist therapy has been recommended for older patients undergoing major elective surgery,[306] its role in the early management of older trauma patients is unknown. Older patients will have diminished requirements for postoperative analgesia and may respond to sedative medications with inappropriate agitation. Prophylaxis against DVT is important in patients who cannot be immediately mobilized in the postoperative period, as is aggressive pulmonary physiotherapy.

JEHOVAH'S WITNESS PATIENTS

A trauma patient who refuses blood products requires special management. Early identification and control of hemorrhage are obviously important (see also Chapter 61). Deliberate hypotension to limit bleeding may be helpful. Preoperative and intraoperative phlebotomy should be minimized. The use of salvaged red cells (from intraoperative collection or from a chest drainage system) should be discussed with the patient because some Jehovah's Witness patients will allow the use of salvaged blood provided that the entire system remains in continuity with the vasculature.[307] The use of albumin and other substances derived from circulating proteins should be addressed. Early hemodynamic monitoring is indicated to help determine the role of colloid therapy, pressors, and inotropes in maintaining tissue O_2 delivery at the highest possible level. Case reports have described the successful use of rFVIIa and hemoglobin-based O_2 carriers in Jehovah's Witness patients to rapidly correct bleeding and support O_2 delivery, but these agents are not approved for these uses and large case series are not available.[308] In the postacute phase, the use of erythropoietin to promote red cell growth will shorten the period of relative anemia.[309]

POSTOPERATIVE CARE

EMERGENCE AND TRACHEAL EXTUBATION

Initial surgery in a trauma patient is followed by a period of monitoring and ongoing treatment in which the anesthesiologist is closely involved, either in the postanesthesia care unit (PACU) or in the ICU (see also Chapter 96). The adequacy of posttraumatic resuscitation must be confirmed, as outlined earlier, and diagnostic studies of the secondary survey completed. Rapid termination of general anesthesia is highly desirable, particularly in patients with an altered level of consciousness or other evidence of TBI before surgery. Change in mental status from the preoperative baseline is an indication for repeat cranial CT and a search for possible metabolic or toxic derangements.

Although neurologic function should be assessed postoperatively, early extubation of a trauma patient should not be taken for granted. Many patients will require continued ventilator support because of CNS trauma, direct pulmonary or chest wall trauma, massive transfusion, upper airway edema, or ongoing intoxication. Box 81-11 lists the criteria for extubation after urgent or emergency trauma surgery. If any doubt exists about the patient's ability to meet these criteria, the patient should be transported to the PACU or ICU with the endotracheal tube in place. Appropriate analgesic medication should be administered, with sedation if necessary. Twelve to 24 hours of support allows confirmation of successful resuscitation and surgical repair, hemodynamic equilibration, titration of appropriate analgesia, and resolution of intoxication. Many patients can be tracheally extubated easily and safely at this time; those who cannot are at high risk for the development of MOSF—heralded by the development of posttraumatic ARDS—and will usually require days to weeks of subsequent intensive care (see also Chapter 101).

ACUTE PAIN MANAGEMENT

Trauma patients present significant pain management challenges to the clinician because of multiple sites of injury, protracted episodes of care, complicating psychological and emotional issues, and prior or ongoing substance abuse (see also Chapter 98). As with pain management practice in other diseases, trauma patients are frequently undertreated, thus creating a significant source of dissatisfaction. Because trauma patients run the gamut of physiology from healthy young athletes to debilitated older adults, anesthesiologists providing pain management for trauma patients must be prepared for a wide range of needs.

Individual trauma patients will have widely varying requirements for pain medication, so induction of analgesia must be titrated carefully, ideally in a closely monitored environment such as the PACU. Administration of rapidly acting IV agents in small doses at frequent intervals until pain relief is achieved is recommended. This allows the practitioner to determine the patient's basal requirements before starting long-acting medications or

BOX 81-11 *Criteria for Operating Room or Postanesthesia Care Unit Extubation of the Trachea in a Trauma Patient*

Mental Status

Resolution of intoxication
Able to follow commands
Noncombative
Pain adequately controlled

Airway Anatomy and Reflexes

Appropriate cough and gag
Ability to protect airway from aspiration
No excessive airway edema or instability

Respiratory Mechanics

Adequate tidal volume and respiratory rate
Normal motor strength
Required FiO_2 less than 0.50

Systemic Stability

Adequately resuscitated (see earlier)
Small likelihood of urgent return to the operating room
Normothermic, without signs of sepsis

patient-controlled analgesia. Hypotension in response to analgesics is most commonly indicative of hypovolemia and should prompt a search for occult hemorrhage while further resuscitation occurs.

The need for analgesic medication and the duration of requirement for analgesics will be minimized if a comprehensive emotional support system is available to the patient. Trauma, because of its unexpected nature, carries with it a strongly negative psychological overlay that can have a profound effect on how anatomically based pain is perceived by the brain[310] and on how the patient reacts. After an injury the patient may have legal, financial, and family-based concerns, without the ability to immediately address them. The availability of counselors—religious, financial, or legal—who can help the patient and family with these issues is of enormous benefit. The anesthesiologist can help by communicating to the patient a clear description of the injuries, the probable time required for recovery, and the plan for managing pain throughout the course. The anesthesiologist should refer the patient to counseling services as needed and should be alert to the potential for posttraumatic stress disorder (PTSD) in any traumatized patient.[311] Referral to an experienced psychiatrist or psychologist is appropriate if PTSD is hindering the patient's recovery.

The need for analgesic medication is also influenced by the schedule of physical therapy prescribed for the patient. In general, the more active a patient can be after traumatic injury, the lower the risk for pulmonary complications, venous thrombosis, and decubitus ulcers. Though painful in the short term, the sooner the patient is mobilized, the lower are the analgesic requirements in the long term. Early mobilization demonstrates to the patient the path to recovery and contributes to an improved emotional state. One of the goals of analgesia, therefore, is provision of adequate medication to facilitate physical therapy without so sedating the patient that participation is impossible.

Neuropathic pain arises when direct injury occurs to a major sensory nerve and is common after spinal cord trauma, traumatic amputations, and major crush injuries. Neuropathic pain is characterized by burning, intermittent electrical shocks, and dysesthesia in the affected dermatomal distribution. Neuropathic pain must be identified because it responds poorly to the analgesics used for somatic pain. This diagnosis should be considered whenever pain control is poor or the patient has a rising requirement for medications unexplained by anatomic injuries. First-line therapy for neuropathic pain has been revolutionized by the widespread use of gabapentin, an antiepileptic drug with very strong specificity for this problem.[312] Gabapentin therapy is typically initiated at a dose of 200 mg three times daily, with daily titration upward to a maximum of 2 to 3 g/day. If neuropathic pain persists, selective regional anesthesia or analgesia may be indicated in an effort to break the cycle of spinal cord receptor recruitment.[313]

Regional analgesia (see also Chapters 56 and 57) provided through an epidural or brachial catheter should be considered for any trauma patient with a potential to benefit from this approach because it will spare the use of systemic opioids and facilitate early mobilization. Epidural analgesia produces high levels of patient satisfaction and improved pulmonary function after major thoracoabdominal and orthopedic surgery in elective populations[314]; this is very likely true for the trauma population as well. Regional techniques are less useful when the patient has multiple sites of injury or when fractures or open wounds make placement difficult. Although epidural placement in anesthetized patients is relatively contraindicated because of the potential for occult SCI, the risk-to-benefit ratio in many trauma patients favors placement during surgery, when general anesthesia facilitates appropriate positioning and patient cooperation.

SUMMARY

Trauma touches all ages and classes of patients, from young and vigorous to older and frail. Because of its great prevalence, practicing anesthesiologists will encounter trauma patients throughout their careers. Increased public recognition of the consequences of injury has sparked interest in trauma research and education, with the result that diagnostic and therapeutic techniques have evolved rapidly in recent years. The anesthesiologist, as a perioperative physician, is in the ideal position to understand and apply these new techniques.

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Chapter 82

Anesthesia and Prehospital Emergency and Trauma Care

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Key Points

- After World War II, the subspecialty of prehospital emergency medicine evolved with anesthesiology's leadership. In many countries, prehospital emergency medicine is considered the fourth pillar along with anesthesiology, critical care, and pain therapy.
- Emergency medical service (EMS) systems differ between and within countries. When these differences are put together, two primary models have evolved. In the United States, paramedics provide prehospital care for all patients (single-tiered system). In many European countries, EMS-physicians lead the prehospital care for patients requiring advanced life support (two-tiered system).
- The core approach of managing prehospital emergencies involves basic life support (BLS) and advanced life support (ALS).
- Prehospital endotracheal intubation and rapid sequence induction of anesthesia are critical skills in prehospital care. Yet prehospital advanced airway management may be too challenging for inexperienced providers and is associated with increased mortality and poor neurologic outcomes, especially after traumatic brain injury.
- In major trauma, prehospital care must limit the time spent on the scene, controlling hemorrhage, and expediting transport to a trauma center, often ideally via a rescue helicopter. Although this approach has been used both in the military (e.g., Vietnam) and in civilian locations, it is not always possible. Prehospital intravenous fluid resuscitation for major trauma varies in approach. Patients with penetrating torso injuries and hemorrhagic shock may benefit from limited intravenous fluid resuscitation and permissive hypotension, in particular in urban settings. Prevention of the lethal triad of hypothermia, acidosis, and coagulopathy is of paramount importance.
- In acute coronary syndrome (ACS) and stroke, achieving rapid reperfusion of the ischemic tissue is the priority. Because only specialized centers provide 24-hour cardiac catheter service or stroke teams, rapid transport to acute myocardial infarction (MI) or stroke centers is critical. In response to an MI, morphine, oxygen, nitrates, and aspirin (MONA) are the main components of prehospital therapy. Fibrinolysis for MI has been used with significant success in the prehospital setting but requires very close supervision by EMS physicians.

The goal of this chapter is to provide a concise overview of prehospital emergency trauma care and to define the important roles anesthesiologists often play in prehospital medicine.

INTRODUCTION AND HISTORICAL BACKGROUND

In many regions of the world, anesthesiologists serve as the backbone of physician-staffed prehospital emergency medical service (EMS) systems,[1-3] and emergency medicine is considered the fourth pillar, along with anesthesiology, critical care, and pain therapy. The specialty of anesthesiology was also instrumental in the creation of modern prehospital emergency medicine.[4,5]

After World War II, the inadequacy of the civilian ambulance service became all too apparent for wartime-experienced physicians, as vehicle traffic–related injuries and deaths sharply increased and ambulances provided only transport to the hospital. In Germany, this inadequacy led to a call to "bring the doctor to the patient," rather than the more traditional converse arrangement.[1,5] As a consequence, the first surgeon-staffed ambulance,

the *klinomobil*, was implemented 1957 in Heidelberg and functioned as a mobile operating room,[5] a concept that was soon abandoned in favor of physician-staffed ambulances, sometimes referred to as *mobile intensive care units* (ICUs).[6] Similar developments occurred throughout Europe, including Prague, Mainz, Munich, Moscow, and in several Scandinavian countries where physicians began to staff ambulances to respond to vehicle crashes and other accidents.[3,4] In Belfast, Ireland, Frank Partridge was the first to implement a mobile coronary care unit (CCU) that brought a defibrillator to prehospital patients in cardiac arrest attributable to ventricular fibrillation.[7] Over the next decades, several European countries, such as France, Germany, Austria, and Norway, implemented nationwide physician-staffed ambulance services often complemented with the physician-staffed helicopter emergency medical service (HEMS) system.[1-3,8,9] Anesthesiology is currently the dominant medical specialty providing EMS physicians in Europe, and many anesthesiology departments are in charge of staffing ambulances and helicopters with physicians.[3,10]

In the United States, a different development took place. For various reasons, physician-staffed ambulances were not considered an option, so specifically trained emergency medical technicians (EMTs) and paramedics, became the mainstay of the EMS system in North America. A landmark event for the creation of modern EMS systems was the publication of the report *Accidental Death and Disability: The Neglected Disease of Modern Society*, commonly referred to as *The White Paper*, published by the National Academy of Sciences in 1966.[11] Among several remarkable physicians, two anesthesiologists, Peter Safar in Pittsburgh, the father of modern cardiopulmonary resuscitation (CPR), and Eugene Nagel in Miami, were most influential in creating the first paramedic-based EMS system in the United States in the 1960s. Before emergency medicine became its own medical specialty, anesthesiologists were often involved in prehospital emergency care based on their unique expertise in resuscitation, airway management, and critical care. This involvement has dwindled over the last two decades, although it appears that anesthesiology could still play an important role in prehospital emergency care in the United States based on what the recent, widely cited Institute of Medicine report *Emergency Medical Services: At the Crossroads* identified as the major problems in prehospital care, such as prehospital airway management, intravenous fluid resuscitation, rapid sequence induction of anesthesia, and pain therapy[12] (also see Chapters 59, 61, 81, 83, 98, and 101).

ORGANIZATIONAL MODELS OF PREHOSPITAL EMERGENCY CARE

LEVELS OF CARE

Originally, the terms *basic life support* (BLS) and *advanced life support* (ALS) were used only to describe the two different levels of care for CPR (see Chapter 108) but were then expanded to all emergency situations including trauma and pediatric emergencies. Currently, these terms denote the level of care in an organized EMS system and are, which is divided into the BLS and ALS levels. First responders, such as police officers and firefighters, are not part of an EMS system and only provide first aid, operating at a level less than the formal BLS level.

BASIC LIFE SUPPORT

Prehospital care at the BLS level is usually provided by EMTs and does not include advanced and invasive techniques and skills.[13] BLS is focused on the classic ABCs (Airway, Breathing, Circulation) and includes simple airway maneuvers, such as chin lift or jaw thrust, oral and nasal airways, bag-valve-mask ventilation, hemorrhage control, and the administration of oxygen (Box 82-1). During CPR, the use of an automated external defibrillator is considered a BLS skill. BLS-only ambulances are often found in rural areas where the incidence of emergencies is low and volunteer EMTs frequently staff the ambulances.

ADVANCED LIFE SUPPORT

ALS is usually provided by paramedics and flight nurses with a rigorous educational background and includes the use of advanced and invasive techniques (see Box 82-1). In many countries, ALS-level providers are allowed to work somewhat independently, often with only indirect physician control through the use of standing orders and protocols issued by the EMS medical director. The use of drugs is tightly regulated, and physician permission from the emergency department must be sought in cases where drugs outside the approved list are to be administered. Most urban EMS systems use ALS units to provide prehospital care. In EMS systems without EMS physicians responding directly to the scene, the scope of practice of ALS-level providers is usually greater and they are allowed to work more independently. Combat medics in the military frequently operate at the ALS level. EMS physicians, flight nurses, and critical care EMTs provide a level of care above and beyond ALS.

MODELS

A high degree of variability exists on how prehospital care is organized and staffed among different countries. Providing a description of all the nuances of the different EMS systems worldwide is beyond the scope of this chapter. Consequently, this chapter outlines the differences between the two models that primarily differ by their level of direct physician involvement in prehospital emergency care: EMT-based models versus physician-based models. These two models are also known as the U.S. paramedic model and the Franco-German EMS-physician model.[14] Although controversy exists on which model provides superior patient care and outcomes, the design of the EMS system is dictated by tradition and fiscal constraints.

EMT- AND PARAMEDIC-BASED EMS SYSTEMS

In North America, EMTs provide organized prehospital care[15]; only rarely will physicians be directly involved in out-of-hospital patient care on the scene.[16] By U.S.

BOX 82-1 ***Skill Set for Basic Life Support and Advanced Life Support Providers and Prehospital Emergency Physicians***

BASIC LIFE SUPPORT (BLS)

- Basic patient evaluation
- Vital signs and basic monitoring (noninvasive blood pressure, pulsoximetry, heart rate)
- Hemorrhage control via direct pressure or pressure dressing
- Cardiopulmonary resuscitation (CPR) (BLS level) with the use of an automatic external defibrillator
- Bag-valve-mask ventilation
- Oral and nasal airway
- Oral suctioning
- Administration of oxygen
- Basic patient rescue, positioning, and transport skills
- Cervical spine stabilization
- Fracture splinting
- Assisting a patient taking prescribed medication (e.g., albuterol inhaler)

ADVANCED LIFE SUPPORT (ALS)

- Venous access and fluid therapy
- Administration of selected drugs*
- Advanced monitoring (ECG, capnography)
- CPR (ACLS level)
- Manual defibrillation
- Basic 12-lead ECG interpretation
- External pacing
- Endotracheal intubation* (without drugs; some EMS systems allow rapid sequence induction)
- Cricothyroidotomy
- Sedation*
- Needle decompression of tension pneumothorax
- Knowledge of mass casualty incident management and triage
- Knowledge of biologic, chemical, and nuclear agents

PREHOSPITAL EMERGENCY PHYSICIAN

- Unlimited administration of emergency drugs
- Use of narcotics and controlled substances (e.g., fentanyl)
- Prehospital rapid sequence induction and anesthesia
- Advanced airway management
- Chest tube placement
- Advanced 12-lead ECG interpretation
- Advanced techniques (ultrasound, noninvasive ventilation)
- Emergency surgery
- Can assume role of medical incident commander in mass casualty event

ACLS, Advanced cardiac life support; *ECG,* electrocardiogram; *EMS,* emergency medical service.
*Not available in all ALS-level EMS systems.

law, physicians are required in most states to oversee the medical operations of EMS systems, either *online* through direct communication or *offline* as EMS medical directors responsible for developing and implementing standardized treatment protocols. Besides developing standard operating procedures, EMS medical directors are responsible for quality control and improvement and are an integral part of EMT education.[17] In the United States, EMS medical directors are often emergency physicians working in the emergency department of the local hospital.

In the United States, three levels of EMTs can be distinguished by their educational background: EMT-basic (EMT-B), EMT-intermediate (EMT-I), and EMT-paramedic (EMT-P). EMT-B providers usually have between 80 and 120 hours of training and are only allowed to perform BLS skills. The EMT-B level is the minimum level required to work in an organized ambulance service. Often, EMT-B providers staff nonemergent ambulance transport but may also respond to nonemergent calls. EMT-I providers are regulated differently among the individual states, and their skills range between BLS and ALS. Although most states do not allow EMT-I providers to perform endotracheal intubation or administer drugs (except for drugs deemed extremely safe, such as albuterol for asthma), they do allow them to insert an intravenous line. EMT-P providers, on the other hand, are the most advanced level of EMTs who undergo intensive 1- to 2-year training in all the different aspects of advanced prehospital emergency care. Their scope of practice is ALS, and they can perform advanced techniques such as endotracheal intubation, administration of selected drugs, and manual defibrillation. Most developed countries have training requirements for their EMT workforce similar to the United States model.

PHYSICIAN-BASED EMS SYSTEMS

Germany and France represent two well-known examples of countries where physicians are an integral part of prehospital emergency care.[14] These integrated EMS systems combine BLS-level ambulances with physician-staffed ALS ambulances and helicopters in a noncompetitive but complementary fashion. Physician-based EMS systems are always part of a *multi-tiered system* and often use what is referred to as a *rendezvous system* to dispatch two units simultaneously to the scene, one unit staffed with EMTs (BLS or ALS level) and one ambulance carrying the physician. Often, the physician-staffed vehicle is a nontransport vehicle that provides quick response to emergencies without having to move a large and slow truck through traffic. EMS physicians are licensed physicians from various medical specialties who undergo a specialized training in prehospital emergency care. The level of mandatory education varies from country to country. With direct physician involvement in prehospital care, anesthesiologists comprise the largest fraction of physicians and often assume the role of chief emergency physician and medical director.[18,19]

HELICOPTER EMERGENCY MEDICAL SERVICE SYSTEM

In most countries, the HEMS system has become an integral component of the EMS system. With its ability to reach remote locations and cover a wide area rapidly, the HEMS system is a perfect supplement to the ground-based EMS system. Although most are privately organized and funded in the United States, several European countries have implemented a nationwide HEMS network that is strategically distributed to respond to emergency calls from every location in the country. Particularly in rural areas, helicopter rescue is now considered a vital ALS-level responder for all emergencies, including trauma and medical emergencies.[20] EMS helicopters are usually staffed with experienced personnel, typically a paramedic plus a flight nurse or an EMS physician.[9,21] In mass-casualty

incidents, all helicopters from a large area can be concentrated at the scene of the accident within a short period and provide several highly trained ALS teams to support local rescue operations and quickly transport the victims to trauma centers (Figure 82-1). Another area where the HEMS system has become the most important means of evacuation is in mountain rescue operations. Pioneered in the Alps, helicopter evacuation by ALS teams specially trained in mountain rescue techniques is now considered the standard of care in countries such as Switzerland, Austria, Germany, and France (Figure 82-2). In major trauma, transport by helicopter is associated with a significantly increased rate of survival, compared with ground-based EMS system.[22,23] For over 50 years, helicopter evacuation has been dominant in the military, including the Vietnam conflict.



Figure 82-1. Train accident in Wampersdorf, Austria. Mass-casualty incident with 6 fatalities and 17 injured individuals. In addition to more than 50 EMS personnel and EMS physicians on the ground, 5 EMS-physician–staffed helicopters provided invaluable EMS-physician level–backup and transport capacity.



Figure 82-2. In a mountain rescue, HEMS systems have become the standard of care for evacuating individuals from alpine accidents and emergencies. In this rescue, a rescue helicopter supported a complex mock rescue operation from a ski lift in alpine Austria.

COMMUNICATION

Starting with the emergency call, communications is a vital aspect of prehospital emergency care. The implementation of a universal emergency telephone number (9-1-1 in the United States and Canada, 1-1-2 in several European countries, 0-0-0 in Australia, and 9-9-9 in the United Kingdom)[17] was a milestone in prehospital care. Currently, the location of the caller can be automatically identified by the system, often via Global Positioning System (GPS). Mobile phones, including applications for specific conditions, will undoubtedly play an ever-increasing role in the prehospital care of the future.[24-28]

Emergency medical dispatchers determine the type and priority of the response, based on standardized questionnaires, and provide invaluable prearrival instructions to the caller to start potentially lifesaving interventions before the ambulance arrives. For example, dispatcher-assisted CPR improves survival after cardiac arrest.[29,30]

BASIC TECHNIQUES AND SKILLS

PATIENT EXAMINATION AND INITIAL ASSESSMENT ON THE SCENE

Patients in an emergency situation may show a wide range of symptoms, challenging the prehospital care team to obtain a quick tentative diagnosis and start a specific treatment. In contrast to the emergency department, fewer diagnostic tools are available in the prehospital setting. The classic approach, "look, listen, and feel," is still the most important aspect of the patient examination. Most commonly, patients are triaged according to their chief complaint, such as chest pain, rather than by a definitive diagnosis obtained on the scene. The most common chief complaints encountered in the prehospital setting are dyspnea or respiratory distress, cardiac or circulatory problems, altered level of consciousness, and trauma. A rapid assessment of potential hazards on the scene is critical before approaching the patient.

Vital Signs

The initial survey uses the well-known ABCDE mnemonic from advanced cardiac life support (ACLS)[31,32] (also see Chapter 108). The first step is to use acoustic and tactile stimuli to rule out unconsciousness in the patient. The next step is to identify airway (A) obstruction and, if necessary, to secure the airway. While maintaining an open airway, breathing (B) is assessed by observing the respiratory effort and chest rise.[33,34] Respiratory rate, efficacy, work, and pattern of breathing are also assessed. If indicated, supplemental oxygen or assisted ventilation should be administered to support oxygenation and ventilation. Circulation (C) is initially assessed by centrally feeling the pulse at the carotid artery and can be extended to feel pulses proximally and distally on the extremities. The pulse should be assessed for rate, quality, and regularity. To complete C, the capillary refill time should be measured, particularly in children.[35,36] The level of responsiveness and consciousness, disability (D), should

be determined according to the Glasgow Coma Scale (GCS), and a quick pupil check should be performed to determine size and reaction to light. The GCS is a reliable prognostic tool for head trauma[37,38] and other forms of nontraumatic altered levels of consciousness.[39] For children under the age of 3 years, the verbal component of the GCS score has to be adjusted. In case of trauma, exposure and environment (E) are assessed to complete the primary survey. At this point, the patient should be checked from head to toe, including the back after performing a log-roll maneuver.[40]

MONITORING AND EQUIPMENT

Similar to standard monitoring in the surgical department and ICU, monitoring in the prehospital setting has now become considerably standardized and consists of pulse oximetry, noninvasive arterial blood pressure monitoring, electrocardiography (ECG), temperature monitoring, and capnography (also see Chapters 44, 47, and 101).

Pulse Oximetry

After the first prehospital uses in the 1980s,[41] pulse oximeters have become the universal, easy-to-attach and easy-to-use monitor for the patient in the prehospital setting. The improvement of the devices have led not only to smaller machines but also to pulse oximeters with better quality even while in motion and when in the cold.[42,43] Additionally, new features, such as the detection of methemoglobin and carboxyhemoglobin,[44,45] can help diagnose conditions such as carbon monoxide poisoning.

Arterial Blood Pressure

Noninvasive arterial blood pressure measurement is the most common form of blood pressure monitoring in the prehospital setting. Automatic or manual cuffs are mostly applied and use an oscillometric technique with its known limitations.[46] The precision and accuracy of noninvasive oscillometric blood pressure monitoring is reduced by movement during transport. During interhospital transfer of a patient who is critically ill, ICU monitoring with invasive arterial blood pressure monitoring is frequently used.

Electrocardiogram

ECG monitoring has two major goals in the prehospital setting. A 3- or 4-lead ECG or an ECG rhythm obtained from defibrillator paddles is sufficient for a rapid and crude ECG rhythm check (i.e., to distinguish a shockable rhythm from a nonshockable rhythm during CPR).[31] On the other hand, to identify myocardial ischemia or myocardial infarction (MI), a 12-lead ECG is required. When prehospital 12-lead ECGs support the diagnosis of acute MI, patients can then be rapidly directed toward a hospital capable of providing percutaneous coronary interventions (PCIs) with a substantial improvement in door-to-reperfusion time[47-49] (also see Chapter 47).

Temperature Monitoring

Oral, esophageal, and some tympanic thermometers[50-52] are generally reliable tools in the field, considering the more extreme weather conditions in which they have to operate. The most important aspect of measuring body temperature on the scene is to identify hypothermia. Special temperature probes are required to assess severe hypothermia (<28° C) because most commercially available instruments become unreliable at these low temperatures. Patients who have experienced trauma, who are disabled (stroke, coma), or intoxicated, as well as patients in the pediatric or older adult populations, are especially vulnerable to hypothermia, especially during the winter months. Even relatively mild outside temperatures can result in hypothermia with long exposure times[53] (also see Chapter 54).

Capnography

Colorimetric, mainstream, or sidestream capnographs are primarily used in the prehospital setting to identify the correct positioning of the endotracheal tube.[54-56] Continuous monitoring of end-tidal carbon dioxide ($ETCO_2$) allows the monitoring of cardiac output and the efficacy of resuscitation,[57] but capnography is not yet universally used in the EMS system. In cardiac arrest, low carbon dioxide (CO_2) levels are a predictor of a fatal outcome.[58] Hyperventilation may also contribute to a poor outcome[59] and may be prevented by controlling ventilation with the aid of $ETCO_2$ monitoring[60,61] (also see Chapter 51).

Prehospital Point-of-Care Testing

Currently, only point-of-care blood glucose testing is routinely performed by EMS providers. Cardiac troponin, lactate, and blood gas analysis are examples of tests that may have potential utility.[62,63]

Ultrasonography

Small and portable ultrasound machines are applicable in the prehospital setting.[64,65] Diagnostic ultrasound requires a physician on the scene (or online through medical oversight if adequate transmission of the image can be achieved) but offers very interesting possibilities. Focused abdominal sonography for trauma (FAST) is a rapid and reliable technique even in inexperienced hands in the emergency department and could be used in the field.[66] FAST has the potential to improve the triage and management of patients with trauma.[67] During resuscitation from cardiac arrest, cardiac activity is a predictor for return of spontaneous circulation (ROSC)[68] (also see Chapter 58).

PREHOSPITAL AIRWAY MANAGEMENT AND VENTILATION

Swift and safe airway management and ventilation are life-saving interventions that are central to prehospital emergency and trauma care (also see Chapter 55). For anesthesiologists who perform advanced airway management on a daily basis, the reasons why airway management is such a contentious issue in prehospital emergency medicine, particularly in the United States, is difficult to comprehend.[69-75] The reasons are many. The major difference from the operating room environment is, as an EMS saying goes, *"There is no easy airway in the field."* Challenges include a nonstandard environment; difficult access to the patient's head; bad weather and lighting conditions; and blood, vomitus, secretions,

and foreign bodies obstructing the airway. In a patient who is critically ill and who has limited oxygen reserves with increased baseline oxygen consumption, all of these factors contribute to a significantly more difficult prehospital airway management, compared with the operating room, even for the experienced anesthesiologist.[76-81]

Airway Management at the Basic Life Support Level

At the BLS level, in addition to simple airway opening maneuvers, the administration of supplemental oxygen and ventilation via a mask are the most important components in prehospital airway management (also see Chapter 108). Emergency medical technicians are trained and qualified to administer supplemental oxygen, often via a nonrebreather facemask, which creates a significantly higher fraction of inspired oxygen concentration (FiO_2). Furthermore, EMTs are allowed to use nasopharyngeal or oropharyngeal airways to maintain a patent airway and to ventilate the lungs with bag-mask-valve ventilation. The ability to use the Combitube (EasyTube), which is a double-lumen tube with a proximal and distal balloon that was initially developed for ventilation during CPR, is considered a BLS skill.[82,83] The use of other alternative supraglottic airways, such as the King LT (laryngeal tube) or laryngeal masks, is increasingly recommended at the BLS level if adequate training and experience are provided.[84] These alternative airways are safe and easy to apply and have excellent success rates when used by EMTs and paramedics.[85-88] The limitations of these alternative airways are the inability to ventilate if misplaced in the larynx and the lack of airway protection, compared with a cuffed endotracheal tube. Ironically, many anesthesiologists who do not work in EMS medicine are currently unfamiliar with many new alternative airway devices used in prehospital care, such as the King-LT, which has become the standard airway in the field for EMTs, replacing older oropharyngeal devices.[84] Nevertheless, the gold standard for prehospital airway management is still endotracheal intubation, which is associated with improved outcomes, compared with supraglottic devices during CPR.[89]

Ventilation in the prehospital setting is most commonly achieved by bag-mask-valve ventilation. Although fairly common in Europe, only a few EMS services in the United States currently use portable field ventilators to ventilate intubated patients. The major disadvantage of relying on bag-mask-valve ventilation is that minute ventilation and tidal volumes are uncontrolled, often leading to significant hyperventilation that is detrimental in cardiac arrest[59,90,91] and in patients with head trauma.[92-96]

Airway Management at the Advanced Life Support Level

Endotracheal intubation is considered the standard of care in prehospital airway management and a standard intervention for paramedics and EMS physicians; it provides a definitive airway and protection from aspiration of gastric contents (also see Chapter 108). Compared with standard endotracheal intubation in the surgical unit, several differences exist. First, most prehospital tracheal intubations (50% to 70%) are performed in patients with cardiac arrest, obviating the need for induction of anesthesia or paralysis.[97] Most other tracheal intubations in spontaneously breathing patients require sedation or induction of a general anesthesia, which is most commonly performed as rapid sequence induction (RSI). Particular emphasis should be placed on adequate *preoxygenation* since these patients who are critically ill have little to no oxygen reserves.[81,98] The recommended approach is direct, oral laryngoscopy and endotracheal intubation. Recently, the application of cricoid pressure during RSI has become controversial because its use may increase the difficulty of visualizing the glottis.[99] Endotracheal intubation in the field requires confirmation by auscultation and $ETCO_2$ monitoring.

Airway management in the field has a significantly more frequent rate of difficult airway management[78,100,101] and of unrecognized esophageal or endobronchial intubation.[79] Every prehospital provider performing advanced airway management should also be trained in the management of a difficult airway, including the use of alternative airways and the creation of an emergent surgical airway (cricothyroidotomy).[102] Having experienced anesthesiologists as EMS-physicians can significantly reduce the complication rates after prehospital endotracheal intubation.[103-106]

SEDATION, ANESTHESIA, AND PAIN CONTROL IN THE PREHOSPITAL SETTING

The general focus of this section is on the accepted strategies for providing prehospital sedation, induction, and maintenance of anesthesia, and pain control. Drugs commonly used in the field are discussed with an emphasis on the differences with in-hospital use (also see Chapters 30, 31, and 98).

Drugs Commonly Used for Prehospital Sedation, Anesthesia, and Pain Control

In general, not all drugs routinely used in the surgery department for general anesthesia are safe in the prehospital setting.[107] Nonanesthesia personnel, such as paramedics and nurses, are significantly less experienced than anesthesiologists in the use of these drugs; patients who are critically ill often require a special titration of drugs. Therefore drugs used for analgesia, sedation, and anesthesia in the field should have the following desirable properties:

- Wide safety margin, even for inexperienced providers
- Hemodynamic stability
- Minimal respiratory depression
- Ease of administration via different routes (e.g., intravenous [IV], intramuscular [IM], intraosseous [IO], rectal)
- Rapid onset and minimal side effects[108]

Benzodiazepines, such as midazolam (0.05 to 0.2 mg/kg IV) and diazepam (3 to 10 mg IV), are well suited for sedation in adult and pediatric patients, have a wide safety margin, and can be administered via several different routes. However, the lack of analgesic properties usually requires the concurrent administration of a potent analgesic in patients with pain. *Ketamine*, on the other hand, is closer to an ideal agent for prehospital sedation

and analgesia (0.5 to 1 mg/kg IV) and in larger doses for induction of anesthesia (1 to 2 mg/kg IV; 4 to 8 mg/kg IM); it is also ideally suited to provide analgesia and sedation for entrapped patients with trauma during extrication.[109] Ketamine provides potent analgesia and sedation, maintains hemodynamic stability in patients with hypovolemic shock, is a potent bronchodilator, and causes minimal respiratory depression. Because of its hallucinogenic properties, benzodiazepines should be co-administered. Traditionally, the use of ketamine in the patient with a traumatic brain injury has been controversial but, in fact, may be a good choice as an induction of anesthesia in patients with head injuries.[110-112] The new isoform, S(+) ketamine, is twice as potent but otherwise has a similar profile as a racemic drug. *Etomidate* is rarely used for sedation but is often administered as an anesthetic induction agent for RSI in the field (0.2 to 0.3 mg/kg IV). It maintains hemodynamic stability but frequently produces myoclonus, rendering intubating conditions less favorable. Furthermore, etomidate causes adrenocortical suppression and should not be used in patients with sepsis,[113] but the effects of a single dose have not been sufficiently studied in nonseptic patients in the EMS setting.[114,115] Although *propofol* is routinely used in the operating room, it has several disadvantages when used in the prehospital setting. Propofol causes significant hemodynamic instability and respiratory depression, both highly undesirable properties in patients who are critically ill. Barbiturates, such as *thiopental*, have pharmacologic properties and side effects similar to those of propofol and should only be used by experienced providers and only in selected patients, for example, in patients with status epilepticus. The prehospital muscle relaxant of choice for RSI is still *succinylcholine* (1 to 1.5 mg/kg IV),[116] although rocuronium has been successfully used by anesthesiologist in the EMS system.[117] For control of acute pain in the prehospital setting, *opioids* are the drug of choice because of their rapid onset and ability to control severe pain.[118] *Morphine* is considered the gold standard in acute coronary syndrome (ACS) (0.1 to 0.2 mg/kg IV), but in trauma, other opioids such as *fentanyl* (1 to 3 μg/kg IV), *piritramide* (0.1 to 0.2 mg/kg IV), which is currently not available in the United States but is widely used in Europe, and sometimes *tramadol* (50 to 100 mg bolus IV) are more frequently used. Nonopioid analgesics are infrequently used in the prehospital setting, although parenteral formulations of acetaminophen, ibuprofen, and ketorolac have recently become available.

Induction of Anesthesia—Rapid Sequence Induction

The prehospital induction of anesthesia is typically performed as RSI, also known as drug-assisted intubation (DAI) in EMS literature (also see Chapter 55). The goal of prehospital induction of anesthesia is twofold: (1) the safe and swift provision of a definitive airway and ventilation control and (2) the ability to provide potent analgesia and sedation. The actual principles of RSI do not differ from RSI in the emergency department, operating room, or ICU; only the environment in which it is applied is different, as discussed earlier.[71] A standard RSI sequence consists of the steps presented in Box 82-2. As discussed earlier, the usefulness of applying cricoid pressure has been repeatedly questioned. Even more important than in the operating room, a backup plan needs to exist in the event that endotracheal intubation fails. Bag-mask-valve ventilation, the placement of an alternative airway such as a laryngeal mask airway (LMA) or intubating LMA, and a laryngeal tube are all acceptable options. EMS providers must understand that prehospital RSI is not trivial and is associated with significant morbidity and mortality if improperly performed.[119] Life-threatening hypoxemia will ensue if endotracheal intubation is prolonged and ventilation difficult (Figure 82-3).

BOX 82-2 ***Prehospital Rapid Sequence Induction***

1. Preparation of necessary equipment—suction equipment, oxygen, laryngoscopes, endotracheal tube (ETT), Ambu-Bag plus masks, and stylet)
2. Preoxygenation with 100% oxygen (at least 3 minutes)
3. Pretreatment (optional) with small dose of a nondepolarizing neuromuscular-blocking agent such as vecuronium (0.01-0.015 mg/kg IV)
4. Pretreatment (optional) with sedative (midazolam) and/or opioid analgesic (fentanyl)
5. Induction agent (ketamine 2-3 mg/kg IV or etomidate 0.3 mg/kg IV) plus succinylcholine (1-1.5 mg/kg IV)
6. Manual in-line stabilization for patients with trauma (optional) and with suspected cervical spine injury
7. Direct laryngoscopy with oral intubation (use of stylet is recommended)
8. Confirmation of correct ETT placement: bilateral auscultation plus end-tidal carbon dioxide ($ETCO_2$) confirmation

Note: the administration of cricoid pressure (Sellick maneuver) is controversial and is no longer recommended by many authorities.

PREHOSPITAL TRAUMA CARE

The management of a patient who is severely injured is one of the most difficult challenges in prehospital care. The potential for saving lives is probably nowhere more prevalent in the EMS system than in major trauma, which was historically also the driving force behind the creation of the modern EMS systems (see also Chapter 81). Ironically, the details of prehospital trauma care are derived from wars. An analysis of the history of prehospital care closely correlates the military conflict of the time ranging from World War II, Korea, Vietnam, and the Middle East. Accordingly, current experience from combat casualty care during the wars in Iraq and Afghanistan has substantially changed the core strategies in prehospital trauma care in areas such as intravenous fluid resuscitation and the prevention of trauma-induced coagulopathy. These newly gained insights have resulted in major changes in the trauma guidelines over the last years. The most commonly used guideline for prehospital trauma care is Prehospital Trauma Life Support (PHTLS) developed by the National Association of Emergency Medical Technicians (NAEMT) in cooperation with the American College of Surgeons Committee on Trauma (ACS COT).[40] PHTLS is based on the Advanced Trauma Life Support (ATLS) concept that is used as the standard for inhospital trauma

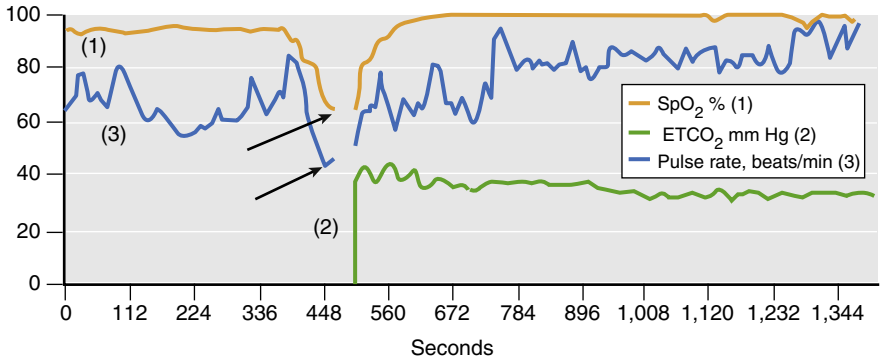


Figure 82-3. Potentially life-threatening desaturation and bradycardia after out-of-hospital rapid sequence induction (RSI) and endotracheal intubation. *$ETCO_2$*, End-tidal carbon dioxide; *SpO_2*, saturation of peripheral oxygen. *(Modified from Dunford JV, Davis DP, Ochs M, et al: Incidence of transient hypoxia and pulse rate reactivity during paramedic rapid sequence intubation,* Ann Emerg Med *42(6):721-728, 2003.)*

care.[120] What are the major changes in ATLS and PHTLS? Trauma life support now places more emphasis on the team approach, advocates for a balanced fluid resuscitation with limited crystalloids (1 L instead of 2 L for initial volume), and recommends the early use of blood products and massive transfusion protocols in patients with hemorrhagic shock (also see Chapters 59 through 62).

The challenges for EMS providers responding to major trauma begin with scene assessment—safety, number of injured individuals, mechanism of injury, injury severity, environmental hazards—and coordination with other first-responder services, such as the police and fire department. Significant pressure exists to minimize on-scene and transport times, based on the "golden hour" and the "platinum 10 minutes" concepts in trauma.[121]

PATIENT EVALUATION ON THE SCENE AND INITIAL MANAGEMENT

Before turning their attention to the individual with trauma, EMS providers must ensure that the accident scene is safe. Crew protection is paramount, particularly in hazardous accidents involving fire, chemicals, electricity, or on busy highways. Motor vehicle accidents often involve more than one person; therefore the EMS team must perform a quick but thorough scan of the entire accident scene and triage all victims. The overarching goal of the initial patient assessment on the scene is to identify life-threatening injuries, which usually follows the well-known ABCDE (**A**irway, **B**reathing, **C**irculation, **D**isability, and **E**xposure or environment) mnemonic. Treatment is immediately initiated if a life-threatening condition is identified—*Treat what kills first,*—which often involves emergent airway management for airway protection, hemorrhage control for major bleeding, or needle thoracostomy for tension pneumothorax. Supplemental oxygen via nonrebreathing facemask should be started on the scene, as well as standard monitoring (ECG, pulse oximetry, arterial blood pressure, capnography) applied. The goal is to maintain oxygen saturation (SpO_2) above 90%. If the respiratory status deteriorates or if the patient is unable to protect his or her airway (e.g., unconsciousness, intoxication, hypoperfusion, direct trauma), then establishing a definitive airway is indicated. Endotracheal intubation after RSI is the recommended approach.

Hemorrhage control is probably the most critical aspect of prehospital trauma care, particularly in combat casualty care. A large fraction of early deaths in trauma can be attributed to exsanguination.[122] The recommended first step in controlling bleeding is the application of direct pressure to the wound, including an appropriate pressure dressing. Compressing the major artery proximal to the wound at pressure points is the next step. In military trauma, the use of tourniquets has been accredited with saving many lives[123,124] and has become the standard of care in major extremity bleeding. Not recommended for decades in civilian trauma, tourniquets have undergone a reappraisal and several organizations now advocate for their use.[125-127] In patients with hemorrhagic shock, two large-bore intravenous lines should be started through which a fluid bolus of 1 liter of a warm crystalloid solution should be administered.[40] This practice, however, has been repeatedly questioned, particularly for penetrating trauma in an urban setting.[128,129] Newer concepts, such as permissive hypotension in the setting of uncontrolled hemorrhage, are advocated and currently under investigation.[130] Despite the initial enthusiasm, small-volume resuscitation with either hypertonic saline or hypertonic-hyperoncotic hydroxyethyl starch solution does not improve clinical outcomes.[131,132] Actually, these starch solutions may cause harm (also see Chapters 59 and 61). The controversy regarding optimal fluid therapy in the field goes hand in hand with the ongoing discussion of whether a "scoop-and-run" (evacuate the site) or a "stay-and-play" (resuscitate on site) or the BLS versus the ALS approach is superior in major trauma.[133] Strong evidence supports minimalistic on-the-scene management (BLS only) for penetrating trauma to the torso; the injury can only be treated by emergent surgery, and aggressive fluid management could actually increase the risk of coagulopathy and blood loss. Irrespective of the current controversy regarding fluid resuscitation in major trauma, the goal is to minimize on-scene time and transport time in major trauma. Helicopter transport has been advocated for patients with major trauma; its expediency reduces mortality[23] and facilitates treatment in a trauma center (Box 82-3).[134] In major head trauma (also see Chapter 70), a modified approach is required in the field:

- Provide adequate oxygenation and avoid hypoxemia (SpO_2 >90%)
- Maintain an adequate cerebral perfusion pressure of >70 mm Hg with a systolic blood pressure (SBP) of at least 90 mm Hg with isotonic or hypertonic fluids

BOX 82-3 *On-scene Triage Criteria for Major Trauma Necessitating Transport to a Trauma Center*

Mechanism of Injury

- Extrication time >20 minutes
- High-speed crash with:
  - Intrusion into passenger compartment >20 cm
  - Speed >40 mph
- Ejection
- Death of another passenger in the same motor vehicle
- Rollover
- Pedestrian or bicyclist hit by motor vehicle
- Motorcycle crash >20 mph or with separation of rider from motorcycle
- Falls >3 m (9.8 feet)

Physiologic Criteria

- Systolic blood pressure <90 mm Hg
- Respiratory rate <10 or >29 breaths per minute
- Glasgow Coma Scale score <14
- Pregnancy

Anatomic Criteria

- Flail chest
- Two or more proximal long bone fractures
- Pelvic fracture
- Penetrating injury to the head, neck, torso, or extremities proximal to the elbow or knee
- Open or depressed skull fracture
- Amputation proximal to the wrist or ankle
- Paralysis

Discretion of Emergency Medical Technician

At the discretion of the emergency medical technician, a person can be declared as having a major trauma. In addition, preexisting conditions of the individual can lead to an upgraded status, such as coronary artery disease, congestive heart failure, severe chronic obstructive pulmonary disease, morbid obesity, or bleeding disorders.

From O'Connor RE: Trauma triage: concepts in prehospital trauma care, Prehosp Emerg Care *10(3):307-310, 2006.*

- Institute endotracheal intubation for patients with a GCS score lower than 9
- Maintain normoventilation ($ETCO_2$ 35 to 40 mm Hg)
- Avoid hyperventilation or hypoventilation

These steps are considered the mainstays of prehospital therapy in traumatic brain injury.[135] However, if cerebral herniation is suspected, then moderate hyperventilation ($ETCO_2$ 30 to 35 mm Hg) and hyperosmolar therapy with mannitol or hypertonic saline should be instituted.

ADULT MEDICAL EMERGENCIES

Most textbooks on prehospital emergency medicine discuss adult medical emergencies under the patient's final diagnosis, such as congestive heart failure, MI, or chronic obstructive pulmonary disease (COPD). This is not, however, how individuals present themselves to the EMS team on the scene. Rather, they usually first express a chief complaint (or lead symptom), such as dyspnea or chest pain. Therefore adult medical emergencies are presented in this text according to the chief complaints. Most adult medical emergencies fall into one of only three separate chief complaints: (1) dyspnea or respiratory distress, (2) cardiac or circulatory problem, and altered level of consciousness.

BOX 82-4 *Common Nontraumatic Causes of Acute Shortness of Breath in Adults*

- Exacerbated chronic obstructive pulmonary disease
- Asthma
- Cardiogenic pulmonary edema (from congestive heart failure)
- Noncardiogenic pulmonary edema (inhalational, related to sepsis)
- Pneumonia
- Pulmonary embolism
- Foreign body obstruction
- Aspiration

Modified from Fowlkes TD: Shortness of breath. In National Association of EMS Physicians, Kuehl AE, editors: Prehospital systems and medical oversight*, Dubuque, Ia, 2002, Kendall and Hunt, pp 665-671).*

DYSPNEA OR RESPIRATORY DISTRESS

Dyspnea is one of the most common presenting symptoms in prehospital care and is associated with a significant mortality rate of 12% to 18%.[136] Each year in the United States alone, 2 million patients with respiratory distress are transported by EMS. As reported in the large Canadian outcome study, Ontario Prehospital Advanced Life Support (OPALS), prehospital ALS decreases mortality in these patients.[136] In adults, acute shortness of breath is most commonly caused by either bronchospasm or pulmonary edema, secondary to congestive heart failure (CHF), but other differential diagnoses such as pulmonary embolism, pneumonia, foreign body obstruction must also be considered[137] (Box 82-4). Identifying the correct diagnosis on the scene is not easy[138-140]; the cause of dyspnea can be multifactorial, for example, the individual with severe COPD and CHF who develops pneumonia.

Patient Evaluation

The most important aspect of the initial evaluation in a patient with acute dyspnea is to identify whether the condition is life threatening with imminent respiratory failure that requires immediate treatment. Physical signs and symptoms indicating a life-threatening condition are cyanosis, tachypnea (respiratory rate >30 per minute), stridor, tachycardia, inability to speak in full sentences (<5 to 6 words), and the use of accessory respiratory muscles.[141] The use of pulse oximetry has quickly become the standard of care in diagnosing hypoxemia and adds an objective measurement of the severity of the respiratory distress. Irrespective of the underlying cause, all patients with respiratory distress should receive high-flow oxygen, ideally through a nonrebreathing facemask. Two of the most common causes of respiratory distress in adults, (1) bronchospasm attributable to asthma and COPD and (2) pulmonary edema attributable to congestive heart failure, are discussed in this text.

Prehospital Management

Bronchospasm: Chronic Obstructive Pulmonary Disease and Asthma. Bronchospasm as a cause for dyspnea is often suggested by the patient's medical history and current medications. Patients with asthma and COPD often use inhaled β-adrenergic agonists and corticosteroids and, in severe cases, also systemic agents. These patients tend to have frequent encounters with the EMS system and emergency departments. In addition to the clinical signs of dyspnea, wheezing and coughing are classic symptoms of bronchospasm. In extreme forms of bronchospasm, no breath sounds can be auscultated, resulting in a "silent chest." A long-standing myth in EMS system states that patients with severe COPD should not receive high-flow oxygen to prevent respiratory arrest.[137] However, these patients often die as a result of hypoxemia and thus should be given the same oxygen therapy as any other patient in respiratory distress.

On-the-scene management of patients with asthma attacks or acute COPD exacerbations is similar and follows the recommended guidelines.[142-144] Besides providing oxygen to prevent hypoxemia, the first line of treatment is inhaled β-agonists plus an anticholinergic agent such as albuterol or salbutamol plus ipratropium, either via nebulized aerosol or a metered-dose inhaler. Often, these patients have already used their inhalers before calling the EMS system; therefore in moderate-to-severe exacerbations, the use of systemic corticosteroids (methylprednisolone, 60 to 125 mg IV bolus dose) is indicated. In life-threatening asthma and COPD exacerbations, intravenous β-agonists (epinephrine, 100 to 200 μg IV bolus dose) are particularly helpful. In the case of impending or actual respiratory arrest, endotracheal intubation is warranted, often after RSI with ketamine as the preferred drug because of its favorable bronchodilating properties. The EMS crew must be vigilant for additional conditions that add to the severity of hypoxemia, such as pneumonia, pneumothorax, anaphylaxis, and pulmonary embolism.

Pulmonary Edema Precipitated by Congestive Heart Failure

Often, acute heart failure is precipitated by additional events such as ACS. Therefore a 12-lead ECG should be obtained to guide prehospital therapy for patients with acute pulmonary edema and rule out acute MI. The treatment consists of three components: oxygen (noninvasive positive-pressure ventilation [NIPPV]), diuretics, and vasodilators.[145] NIPPV, such as continuous positive airway pressure (CPAP), has become a standard therapy in the treatment of acute pulmonary edema in the prehospital setting.[146] NIPPV should be used for most patients with acute pulmonary edema.[147] The subsequent therapy should be guided by the patient's SBP:

- **SBP higher than 140 mm Hg:** NIPPV plus nitrates; nitroglycerin spray or continuous IV infusion is recommended with a starting dose of 10 to 20 μg per minute.
- **SBP 140 to 100 mm Hg:** NIPPV plus nitrates and a diuretic agent (furosemide) are recommended if signs of systemic fluid retention are present.
- **SBP lower than 100 mm Hg:** If hypoperfusion is predominant and signs of cardiogenic shock are present, then these patients require inotropic agents such as dopamine and dobutamine and a carefully titrated volume challenge.
- **Pulmonary edema with signs of ACS:** These patients require ACS-specific management in addition to NIPPV plus nitrates.[147]

The treatment goals are to stabilize the patient, improve oxygenation and perfusion, and reduce dyspnea.

CARDIAC AND CIRCULATORY EMERGENCIES

Acute chest pain and circulatory conditions (e.g., syncope, hypertension) are frequently encountered in the prehospital setting. Significant emphasis has been put on the role of the EMS providers in the management of ST-elevation myocardial infarction (STEMI), but other conditions such as pulmonary embolism, hypertensive emergencies, or dysrhythmias require significant diagnostic and therapeutic skills by the providers in the field (also see Chapter 67). In this overview, the focus is on the most common emergencies resulting in chest pain: ACS, pulmonary embolism, and hypertensive emergencies. ACS is defined as an umbrella term for all ACSs and includes STEMI, non–ST-elevation myocardial infarction (NSTEMI), and unstable angina. Cardiac arrest and CPR are discussed in a separate chapter (new CPR guidelines were published in 2010[31,32,148,149]).

Patient Evaluation

The most important goal in evaluating a patient with acute chest pain or an urgent circulatory condition is to rule out a life-threatening condition such as ACS or pulmonary embolism. Because chest pain is a common complaint, identifying patients who are at high risk among all of the patients with benign conditions such as back spasm, gastroesophageal reflux, or other gastrointestinal disorders, is difficult. History and a physical examination, as well as a 12-lead ECG, often guide the diagnosis. A prehospital 12-lead ECG can be quickly performed by the EMS crew and transmitted to a physician oversight if required; it offers a high sensitivity and specificity for detecting myocardial ischemia and MI. ECG interpretation for ACS may prove difficult in patients with left bundle branch block, ventricular paced rhythm, isolated posterior MI, or an ST-elevation in the ECG lead aVR (augmented ECG lead from the right arm). Assessing the type and quality of the chest pain—stabbing versus burning, radiation, severity, and provocation—is critical in determining the differential diagnosis (Box 82-5). However, up to 30% of patients with ACS have atypical pain symptoms (epigastric discomfort, jaw pain) or no pain at all in the case of silent myocardial ischemia in patients with diabetes.

Prehospital Management Acute Coronary Syndrome

The primary goal for a patient with suspected ACS is to minimize the time to diagnosis and potential reperfusion therapy while maintaining hemodynamic stability on scene and during transport. If STEMI is suspected, then

access to rapid reperfusion therapy is paramount. According to the most recent guidelines, primary PCI is the preferred reperfusion strategy compared with thrombolysis, but a combination of the two may provide additional benefits.[150,151]

Patients with suspected ACS should be immediately monitored by a continuous ECG in addition to arterial blood pressure and oxygen saturation. Rapid access to a defibrillator is mandatory, especially for patients with STEMI, because patients with an acute MI have a high risk of ventricular fibrillation. The most recent guidelines recommend starting supportive therapy on the scene consisting of morphine (pain control), high-flow oxygen, nitrates (if the patient is not hypotensive), and oral aspirin, easily memorized by the well-known MONA acronym—**m**orphine, **o**xygen, **n**itrates, and **a**spirin.[152-153] β-Adrenergic blockers can be considered if the patient exhibits tachycardia and/or is hypertensive. The goal is to reduce myocardial oxygen demand while improving oxygen supply. The 12-lead ECG is a vital component of prehospital care for ACS because it is the only tool that can reliably identify patients who may benefit from prehospital reperfusion therapy (Figure 82-4). The overarching goal is to minimize myocardial ischemia time. If prehospital fibrinolysis is considered, then the "contact to needle" time should be less than 30 minutes. If primary PCI is considered, then the "door to balloon" time should be less than 90 minutes. Out-of-hospital fibrinolysis reduces mortality in patients with STEMI or new onset left bundle branch block[154] but is no longer recommended if the patient can undergo primary PCI within 1 hour. If the 1-hour time limit for primary PCI cannot be met, then prehospital fibrinolysis may improve outcomes.[151] Several fibrinolytic drugs are available, and the choice is often based on the institution. Yet fibrinolytic therapy has several contraindications (Box 82-6) and also has the risk of intracranial hemorrhage resulting in major disability or death in 1% to 2% of the patients.

BOX 82-5 ***Differential Diagnosis of Acute Chest Pain in Adults***

- Acute coronary syndrome (unstable angina, myocardial infarction)
- Pulmonary embolism
- Gastroesophageal reflux
- Peptic ulcer disease
- Gastritis or esophagitis
- Aortic dissection
- Pericarditis
- Pneumonia
- Pneumothorax
- Pleurisy
- Boerhaave syndrome (esophageal rupture)
- Pancreatitis
- Musculoskeletal pain

Pulmonary Embolism. A definitive diagnosis of pulmonary embolism is difficult to establish on the scene because signs and symptoms are nonspecific and no rapid objective test comparable with the 12-lead ECG in ACS is available for on-site diagnosis. Often, the patient's medical history is revealing (e.g., immobilized leg and signs of a preexisting deep venous thrombosis; unilateral and tender swelling in one extremity). The severity of pulmonary embolism directly relates to the size of the clots and ranges from mild symptoms of dyspnea to acutely life-threatening states of cardiogenic shock attributable to acute right-sided heart failure. Classic symptoms of pulmonary embolism include distended neck veins, hypoxemia, tachycardia, tachypnea, and chest pain. More objective, but nevertheless

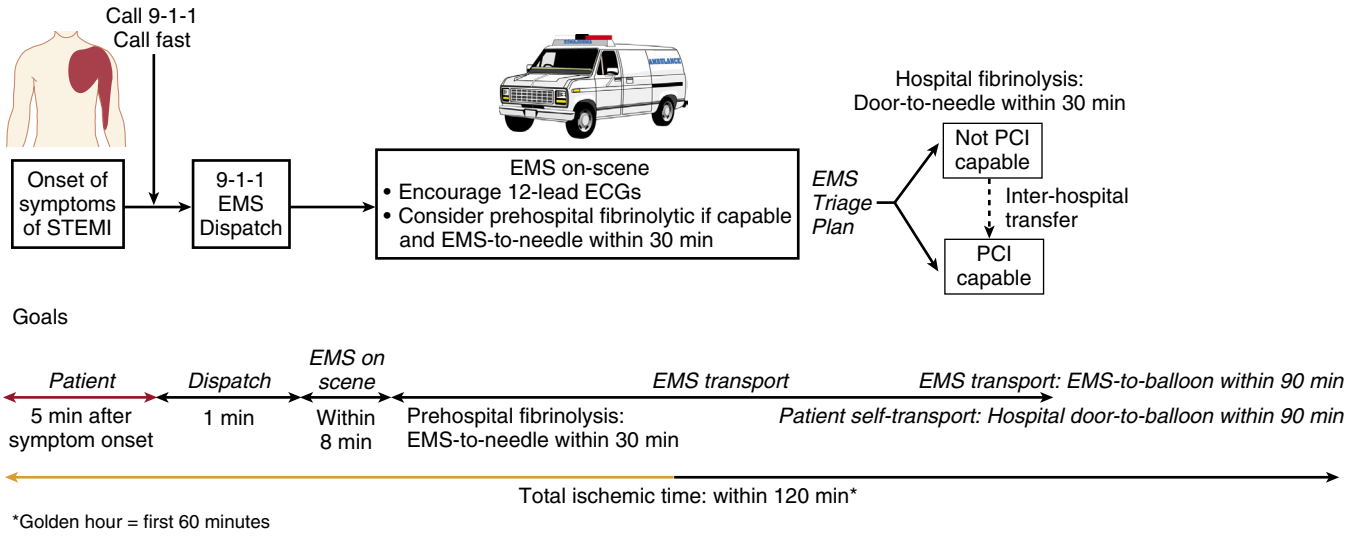


Figure 82-4. Prehospital management priorities in patients with ST-elevation myocardial infarction (STEMI). *ECG,* Electrocardiogram; *EMS,* emergency medical service; *PCI,* percutaneous coronary intervention. *(Data from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction],* J Am Coll Cardiol *44:E1-E211, 2004; and Armstrong PW, Collen D, Antman E: Fibrinolysis for acute myocardial infarction: the future is here and now,* Circulation *107:2533-2537, 2003.)*

BOX 82-6 ***Contraindications of Fibrinolytic Therapy in ST-Elevated Myocardial Infarction (EMI)***

Absolute Contraindications

- Any prior intracranial hemorrhage
- Known structural cerebral vascular lesion (AVM)
- Known malignant intracranial neoplasm (primary or metastatic)
- Ischemic stroke within 3 months EXCEPT acute ischemic stroke within 3 hours
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed head trauma or facial trauma within 3 months

Relative Contraindications

- History of chronic, severe, poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg)*
- History of prior ischemic stroke <3 months, dementia, or known intracranial pathologic condition not covered in the contraindications
- Traumatic or prolonged (>10 minutes) CPR or major surgery (<3 weeks)
- Recent (within 2 to 4 weeks) internal bleeding
- Noncompressible vascular punctures
- For streptokinase or anistreplase: prior exposure (<5 days ago) or prior allergic reaction to these agents
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulants (the higher the INR, the higher the risk of bleeding)

Adapted from American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, Part 8: Stabilization of the patient with acute coronary syndromes, Circulation *112(24 Suppl): IV-89–IV-110, 2005; and O'Connor RE, Brady W, Brooks SC, et al: Part 10: acute coronary syndromes: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,* Circulation *122(18 Suppl 3):S787-S817, 2010.*

AVM, Arteriovenous malformation; *CPR,* cardiopulmonary resuscitation; *DBP,* diastolic blood pressure; *INR,* international normalized ratio, *SBP,* systolic blood pressure.

*Could be an absolute contraindication in low-risk patients with myocardial infarction.

unspecific findings, are new right bundle branch block, symmetric T-wave inversion in the anterior leads (V1-V4), and S_IQ_{III} pattern in the 12-lead ECG.[155] Often the 12-lead ECG is more useful to rule out other conditions such as MI than ruling in pulmonary embolism.

In the absence of an objective means to diagnose pulmonary embolism reliably in the prehospital setting, the management is largely supportive.[156] Applying standard monitoring, administering high-flow oxygen, establishing an intravenous line, and controlling pain with opioid analgesics are considered standard therapy. In severe pulmonary embolism that is usually accompanied with systemic hypotension (SBP <90 mm Hg), circulatory support with inotropic drugs is often required. The prehospital use of heparin in pulmonary embolism is not universally recommended and must be determined on a case-by-case basis, taking into account the likelihood of pulmonary embolism and the severity of symptoms. Prehospital fibrinolysis in pulmonary embolism is not recommended, although it has been successfully used *in extremis*.[157]

BOX 82-7 ***Classification of Acute Hypertensive Episodes***

1. Hypertensive emergency: Also termed *hypertensive crisis.* Hypertension with acute end-organ dysfunction
2. Hypertensive urgency: Hypertensive episode with high risk of imminent end-organ damage that has not yet occurred
3. Acute hypertensive episode: Systolic blood pressure (SBP) >180 mm Hg or diastolic (DBP) >110 mm Hg without signs of evolving or imminent end-organ dysfunction
4. Transient hypertension: Related to anxiety or primary complaint

Modified from Chobanian AV, Bakris GL, Black HR, et al: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, Hypertension *42(6):1206-1252, 2003.*

Hypertensive Emergencies. The EMS often responds to patients with acute hypertensive episodes, but these are rarely true hypertensive emergencies. The classification of hypertensive episodes is very helpful in determining the urgency of a prehospital intervention (Box 82-7). The combination of acute hypertension plus end-organ damage (hypertensive emergency), such as hypertensive encephalopathy, stroke, pulmonary edema, MI, aortic dissection, acute renal failure, and preeclampsia, must be immediately treated, and the progression must be stopped. The goal is to decrease the arterial blood pressure by 20% to 25% within 30 to 60 minutes.[158] However, in the setting of cerebral infarction, arterial blood pressure should be slowly decreased since the ischemic territory may be critically dependent on collateral perfusion pressure. Evidence for benefits of acute antihypertensive treatment is scant; perhaps only very high SBP or diastolic blood pressure (DBP) should be treated.[159] On the other hand, patients with an aortic dissection require swift and aggressive treatment with a target arterial blood pressure of SBP less than 120 mm Hg and a DBP less than 80 mm Hg.[160] The choice of antihypertensive should take into account the underlying pathophysiologic condition. For example, patients with acute hypertension plus ACS and tachycardia might benefit from β-adrenergic blocker and nitroglycerin, whereas in intracranial hemorrhage, labetalol is probably the preferred drug. Depending on availability and approval, urapidil, an α-adrenoceptor antagonist is extremely helpful.

ALTERED LEVEL OF CONSCIOUSNESS

Altered level of consciousness is often encountered in prehospital care. The differential diagnoses are vast, treatment options are limited, and therefore most patients receive only supportive care in the field. The overarching goal is to stabilize vital signs, quickly identify and treat potentially life-threatening conditions, and determine a likely cause.[161] For example, severe hypoglycemia in an unconscious patient can be rapidly detected by point-of-care testing and reversed by the administration of an intravenous glucose bolus. Although this section focuses on general principles, it briefly mentions a few specific conditions, such as stroke or seizure.

Patients with an altered level of consciousness should immediately receive high-flow oxygen and intravenous access, be undressed, and undergo standard monitoring.

BOX 82-8 ***Causes of Altered Level of Consciousness in Adults: Mnemonic AEIOU-TIPS***

Alcohol and airway (hypoxia)
Epilepsy, electrolytes, encephalopathy
Insulin—hypoglycemia
Opioids or overdose
Urea (metabolic)
Trauma or tumor
Infection
Psychiatric
Shock, subarachnoid hemorrhage, or snake bite

Adapted from Wolfe RE, Brown DFM: Coma and depressed level of consciousness. In Marx JA, Hockberger RS, Walls, RM, editors: Rosen's emergency medicine: concepts and clinical practice*, ed 6, Philadelphia, 2006, Mosby–Elsevier.*

The addition of continuous capnography (when available) is helpful to assess adequate ventilation. The level of unconsciousness and a determination of the GCS score should be performed. In the prehospital setting, distinguishing whether the patient is alert (i.e., responsive to verbal commands), is only responsive to painful stimuli, or is completely unresponsive (i.e., unconscious) is often sufficient.[162]

Because patients with impaired consciousness are at risk for pulmonary aspiration of gastric contents, the need for airway protection needs to be assessed. Recommended diagnostic steps on the scene include determining the pupil size and reaction to light, measuring core body temperature and point-of-care blood glucose levels. During the initial neurologic examination, EMS providers must determine whether the main neurologic symptoms are global or whether a focal neurologic deficit is present. Nasal or oral airways may be inserted to keep the airway patent and to test for a gag reflex. Once these basic steps have been accomplished, the EMS team should try to obtain as much information as possible about the patient and the circumstances to narrow the probable causes for the patient's unconsciousness (Box 82-8). Often, this can only be accomplished by involving bystanders and family members. Important aspects are onset and progression of unconsciousness (immediate or delayed), fever, the patient's status before the onset of symptoms, headache, medications and medical history (e.g., hypertension, diabetes, depression), signs of intoxication (e.g., open drug containers, needles, drug paraphernalia), and signs of trauma.

For patients with *hypoglycemia*, the recommended treatment is to administer dextrose ($D_{50}W$, 50 mL = 1 amp) immediately. If an intravenous line cannot be established, then intramuscular glucagon (1 to 2 mg) is a viable alternative. On average, blood glucose levels increase between 100 and 150 mg/dL after this treatment, and patients are fully awake within a few minutes. In patients in whom opioid overdose is suspected (meiosis, respiratory rate <10 per minute), the opioid antagonist naloxone should be administered. The recommended starting intravenous dose is between 0.1 to 0.4 mg, but it should be titrated to clinical effect; that is, to the restoration of spontaneous ventilation and not to complete awakening. A wide range of required dosages may be needed, sometimes requiring as little as 0.2 mg and sometimes up to 10 mg.[162] If too much naloxone is administered, then severe opioid withdrawal symptoms may result. Similarly, if patients with benzodiazepine overdose are aggressively treated with the antagonist, flumazenil, then generalized seizures can result that may be unresponsive to further benzodiazepine treatment.

Only recently have patients with acute stroke received similar attention in prehospital care as patients with acute MI. It is now clear that a comparable "golden hour" exists in acute stroke treatment.[163] Stroke is a leading cause of death in the United States and the number-one cause for disability in adults. Both the rapid identification and the treatment of stroke limit brain damage and improve survival.[164] Classic symptoms of stroke are hemiparesis, aphasia, and altered level of consciousness. Formal prehospital screening tools such as the Cincinnati Prehospital Stroke Scale are useful and should be used.[165]

The goal in prehospital emergency care is the quick identification of stroke and the expeditious transport of the patient to a stroke center with 24-hour computed tomography (CT) scanner availability.[164,166] An emergent CT scan is mandatory to distinguish between hemorrhagic and ischemic stroke. Because of the inability to clinically distinguish between ischemic stroke (85% of cases) and hemorrhagic stroke (15%), prehospital thrombolysis cannot be performed and is contraindicated until hemorrhagic stroke is ruled out. Thus supportive care to stabilize the patient's vital signs and to avoid risk factors that negatively influence outcome, such as hypoxia, hypotension, and hyperglycemia, are the primary treatment goals in stroke in the prehospital setting.[167] Patients with a stroke require supplemental oxygen, intravenous access, continuous ECG, and arterial blood pressure monitoring. Hypoglycemia, as well as hyperglycemia, frequently occurs in patients with a stroke; therefore prehospital blood glucose measurement is mandatory. Arterial blood pressure management in patients with stroke is controversial; aggressive decreasing of SBP can worsen the outcome; some hypertension in a patient with an acute stroke might actually be beneficial. If, on the other hand, end-organ dysfunction is apparent, such as myocardial ischemia or a SBP higher than 220 mm Hg, then cautious antihypertensive treatment should probably be started on the scene.

Seizure is a common disorder observed in the EMS practice. Often, the seizure has abated when the EMS team arrives, and the patient is found in a postictal state that seldom requires intervention. If ongoing, however, the seizure requires aggressive treatment, which typically includes the intravenous administration of benzodiazepines and the prevention of secondary complications such as hypoxemia.[168] Intravenous access is difficult to establish during a generalized seizure, and an intraosseous or intramuscular approach may be required. High-flow oxygen should be administered via a nonrebreathing facemask. Status epilepticus is a state of ongoing, refractory general seizure activity and is a true life-threatening emergency that often requires the induction of general anesthesia.[169]

PEDIATRIC EMERGENCIES

Pediatric emergencies are a major challenge in prehospital care. Between 5% and 8% of EMS calls are pediatric

emergencies.[170,171] During the first years of life, common pediatric emergencies are respiratory problems and febrile seizures. The incidence of trauma increases in older age groups.[170] In this section, the main differences in causes, diagnostic procedures, and treatments between pediatric and adult emergencies are reviewed (also see Chapter 93).

DYSPNEA AND RESPIRATORY DISTRESS

Respiratory distress is one of the most common pediatric emergencies, particularly among young children under the age of 6 years, and is the leading cause for cardiac arrest in children. Airway anatomy, a smaller respiratory reserve attributable to a smaller residual capacity, as well as a higher baseline oxygen consumption, make children more vulnerable to hypoxic events. Infections or foreign body airway obstruction are most prevalent in younger age groups; in older children respiratory disorders such as asthma predominate.

Patient Evaluation

The initial assessment of a child in respiratory distress can be more difficult since children are often agitated and frightened. Important physical signs and symptoms indicative of respiratory distress are tachypnea and intercostal, sternal, and subcostal retractions. Children use accessory muscles to support breathing, which may be demonstrated as head bobbing and nasal flaring. An early sign of respiratory distress is the use of chest wall muscles. Paradoxical breathing movements of the chest and abdomen (see-saw respiration) indicate decompensated respiration.

Prehospital Management

Pediatric respiratory support includes the administration of supplemental oxygen, assisted bag-mask-valve ventilation, or controlled ventilation with a secured airway. Prehospital airway management in children is difficult and significantly more challenging than in the controlled environment of an operating room. As a consequence, the risk of encountering a difficult airway in a child in the field is likely.

Infection. Laryngotracheobronchitis (croup) is a typical emergency of the young child, 6 months to 3 years of age at presentation. Because of its dramatic onset, usually during the night, and combined with sudden loud inspiratory stridor, laryngotracheobronchitis frightens both the child and the parents. Except for a recent minor infection of the upper respiratory tract, the medical history is usually noncontributory.

On-the-scene management of mild croup (without retractions) consists of psychologic support by the EMS team, humidified oxygen via facemask, and transport to a pediatric emergency department. More severe cases with retractions and/or neurologic signs such as apathy or agitation require the administration of oral dexamethasone (0.6 mg/kg once [16 mg max]) and, as a next step, nebulized epinephrine (0.5 mL of 2.25% racemic epinephrine or 5.0 mL of epinephrine 1:1000, irrespective of the weight of the child).[172] The need for prehospital endotracheal intubation is rare.

Epiglottitis, another upper airway infection observed in children, is very dangerous but fortunately very rare. Epiglottitis usually occurs in children aged 2 to 7 years and is characterized by inspiratory stridor, hypersalivation, a high fever, and an inability to swallow. The child's voice sounds muffled. Any anxiety-provoking maneuvers such as excessive examination or establishing an intravenous access should be avoided. Complete airway obstruction can rapidly occur and emergent airway management may become necessary including cricothyroidotomy.[173]

Asthma. Acute asthma exacerbation is a common emergency in children. The prevalence of asthma among children ranges from 5% to 10% and acute exacerbation, an *asthma attack*, is a frequent complication. Asthma is the third most frequent cause of hospitalization among children younger than 15 years of age. Although a severe asthma exacerbation often presents itself with loud wheezing, tachycardia, and a SpO_2 between 92% to 95%, children in a life-threatening asthma attack lose the ability to speak, become quiet, and develop a paradoxical breathing pattern with SpO_2 <92%, pseudonormalization of the heart rate that may progress to bradycardia, and ultimately cardiac arrest. Recent guidelines recommend supportive therapy in mild cases and inhaled β-adrenergic agonists as first-line treatment (albuterol or salbuterol, 2 puffs every 2 minutes; up to 10 puffs) and corticosteroids (oral prednisolone, 1 mg/kg once daily).[174] In life-threatening asthma, intravenous epinephrine may be administered, and patients may require general anesthesia and endotracheal intubation; ketamine is the anesthetic drug of choice because to its favorable broncholytic properties.

Foreign Body Airway Obstruction. Foreign body airway obstruction is a common accident among children younger than 3 years of age, particularly boys. It is characterized by the sudden onset of respiratory distress associated with coughing, gagging, or stridor in a child with no other signs of illness. Foreign body airway obstruction has a prominent place in the current pediatric BLS guidelines.[175] With mild foreign body airway obstruction, when the child can still effectively cough, no immediate action to remove the foreign body by EMS team is necessary. The child should be encouraged to expel the foreign body by coughing. If the obstruction is severe and coughing is ineffective, urgent intervention is required. For children older than 1 year of age, abdominal thrusts (Heimlich maneuver) are recommended (up to five times until the foreign body is expelled) whereas in infants, a series of five back blows in turn with chest thrusts is recommended. If the child becomes unconscious, standard BLS must be initiated.[175] ALS units may inspect the airway with direct laryngoscopy to remove the foreign body under visualization.

CARDIAC EMERGENCIES AND SHOCK

Life-threatening pediatric cardiac emergencies in prehospital emergency care are rare. Yet hypovolemic shock attributable to acute blood loss or diarrheal diseases does occur and requires urgent treatment.

Patient Evaluation

In addition to standard assessment, including mental status assessment, heart rate, pulse quality, and particularly capillary refill time, are good indicators of the volume status of the child.

Prehospital Management

Arrhythmia. Most arrhythmias encountered in the prehospital setting in pediatric patients are secondary; that is, most are the result of an underlying disease and not a primary disease. Bradycardia in children is an ominous sign and often the result of hypoxia or poisoning. If the heart rate is lower than 60 beats per minute and the child shows signs of inadequate end-organ perfusion (e.g., unconsciousness), BLS measures must be initiated and the underlying cause for bradycardia identified and treated. Most tachyarrhythmias, on the other hand, are supraventricular and compensatory and seldom require treatment in the field. If treatment is required, then supraventricular tachycardia can nearly always be controlled by vagal maneuvers, such as carotid sinus massage, or intravenous adenosine. Ventricular tachyarrhythmias are rare in children but clearly more dangerous and typically occur as a consequence of one of two conditions—inherited long-QT syndrome and commotio cordis. In inherited long-QT syndrome, torsade de pointes, which is a special case of ventricular tachycardia, is triggered and may result in cardiac arrest. However, most cases of torsade de pointes are self-limiting and do not require ALS measures, defibrillation, or drug therapy (magnesium is the drug of choice). Commotio cordis describes a scenario during which the chest of a child is struck by an object, such as a baseball or puck, during the critical phase of cardiac repolarization; as a result, ventricular fibrillation is triggered. The fatality rate tends to be high (up to 70%), and defibrillation appears to be the only effective therapy (also see Chapters 45 and 47).

Shock. Hypovolemic shock attributable to acute blood loss or acute diarrheal disease is the most common type, followed by septic, cardiogenic, and distributive shock.[176,177] The top priority in children who developed shock is obtaining rapid vascular access and initiating aggressive fluid resuscitation. Venous access is the first choice; however, if it cannot be rapidly established, then intraosseous access is the next alternative. Intraosseous access provides quick and reliable access, through which intravenous medications and fluids can be administered. An initial fluid bolus of 20 mL/kg of balanced crystalloid, such as lactated Ringer solution, is recommended.[178]

ALTERED LEVEL OF CONSCIOUSNESS

Chief neurologic complaints, such as meningitis, encephalitis, febrile seizure, and coma, are not infrequently encountered in prehospital medicine. Neurologic examination of children is difficult and treatment on the scene is often only symptomatic.

Patient Evaluation

After an evaluation of breathing and circulation, a quick neurologic assessment should be made. A pediatric GCS has been developed that provides age-appropriate responses for neurologic assessment (see Chapter 97).[179] The motor score of the GCS has a good predictive value for outcome after traumatic brain injury.[180] Blood glucose measurement is mandatory on the scene to rule out severe hypoglycemia.

Prehospital Management

Infection. Bacterial meningitis accounts for approximately 30% of the children with meningeal irritation, whereas viral or aseptic meningitis is the cause in approximately 13% of cases managed by EMS providers.[181] Identification of this potentially life-threatening disease is an important challenge for the prehospital provider. Independent predictors of bacterial meningitis obtained from the patient's history and physical examination are the duration of the primary complaint, history of vomiting, and meningeal irritation, cyanosis, petechial bleeding, and altered consciousness.[182] Airway management and fluid resuscitation may be necessary before transferring the child to a pediatric emergency department. If the diagnosis of bacterial meningitis is confirmed, then antibiotic prophylaxis of all individuals who had direct contact with the patient is mandatory.

Seizures. Febrile seizures are the most common seizure disorder in childhood, occurring in 2% to 5% of children, typically between the ages of 6 months and 5 years.[183] Usually the seizure has already terminated when the EMS team arrives and the patient is in a postictal state. An antipyretic therapy may prevent a recurrence of the seizure.

To rule out other underlying conditions for a seizure such as hypoxia, intoxication, infectious reasons, metabolic disorders, trauma, or heatstroke, the child should be hospitalized after the vital signs are stabilized. If seizures recur or are still ongoing (status epilepticus), then the initial assessment should follow the airway, breathing, circulation (ABC) principle. High-flow oxygen should be given and blood glucose tested. For those children in whom intravenous access can be immediately established, a benzodiazepine such as lorazepam 0.05-0.1 mg/kg should be given intravenously. If intravenous access cannot be rapidly established, then the rectal diazepam (0.5 mg/kg) (or intraosseous access) is a good alternative. A second dose of lorazepam (0.1 mg/kg) may be given if the seizure is recurring.[184]

TRAUMA

Among children, trauma is the leading cause of death between ages 1 and 18 years. Boys are more at risk than girls. More than 90% of injuries are blunt and 10% penetrating. The prehospital approach in pediatric trauma, including patient evaluation and management, is very similar to adult trauma; therefore the focus of this text is limited to the pertinent differences between pediatric and adult traumas.

Because of the anatomic differences, children experience different injury patterns, compared with adults. Children have proportionately larger heads and are thus at a higher risk for head injury.[185] Bone fractures involving the growing ends of bones are predominantly observed in children. Softer, more flexible ribs decrease the risk for rib fractures, yet increase the risk for pulmonary contusion. The large body surface area predisposes children to hypothermia with all the associated negative consequences in trauma such as traumatic coagulopathy. Prehospital management of a severely injured child

TABLE 82-1 **DEFINITIONS IN DISASTER MEDICINE**

	Definition	Level of Prehospital Medical Care Possible	Examples
Emergency	Incident that demands urgent action Impact: minutes to hours	Individual medicine	Patient with bicycle accident Stroke Angina
Mass casualty	Large number of casualties in a short period that initially exceeds local logistic support capabilities Impact: hours to days	Triage Increasing level of medical treatment dependent on resources	Airplane crash Train collision Mass poisoning
Disaster	Large number of casualties and destroyed infrastructure; exceeds local response capabilities Supraregional (national) forces are needed to solve the problem Impact: damage and interruption may last long-term (weeks to years)	Triage First aid Significant delay until professional medical help is available, which is usually only after temporary infrastructure is set up	Hurricane Earthquake Tsunami Nuclear disaster (e.g., Chernobyl)

is generally more challenging than that of a severely injured adult. Obtaining rapid intravascular access is difficult in a volume-depleted child, and prehospital providers often resort to intraosseous access in these instances. Airway management in a pediatric patient with trauma is also significantly more difficult compared with adults and carries a higher risk of complications such as esophageal intubation and severe hypoxemia.

THE ABUSED CHILD

Child abuse is common and poses a major challenge for prehospital providers.[186] Typical injuries consistent with child abuse include injuries of different ages, atypical burns, abrasions and hematomas reflecting the form of the beating hand or instrument, shaken baby syndrome, and injuries at unusual locations (e.g., femur fracture in a toddler). A delayed or inconclusive patient history should arouse suspicion. The management goal is to guarantee the well-being of the child. In suspected cases of child abuse, the appropriate authorities must be informed and the child transferred to a hospital or another safe facility (also see Chapter 93).

PREHOSPITAL MASS CASUALTY INCIDENT MANAGEMENT AND DISASTER MEDICINE

Prehospital providers are often faced with incidents during which the number of patients exceeds the capabilities of the rescue squad or local rescue forces; examples are multiple vehicle accidents, fires, and train collisions. These incidents are called *mass casualty incidents* and are defined as having an inadequate ratio of rescuers to victims. Mass casualty incidents are different from disasters; the former can be managed by local and regional resources, whereas *disasters* can only be managed on a national level. Examples of mass casualty incidents are train collisions, and examples of disasters are hurricanes or large earthquakes or tsunamis (Table 82-1). Paramount for both is that in these mass casualty situations, the concept of *triage* must be used; that is, trying to save as many people as possible without being able to provide individual one-on-one care. This approach is necessary to identify those critically injured individuals who can benefit from immediate, life-saving interventions and to conserve resources[187] (also see Chapter 83).

The most important duty of the first team to arrive at the scene is to conduct a quick assessment of the scene including hazards, number of victims, and other pertinent aspects and to communicate this assessment rapidly to the EMS dispatch. During mass casualty events, the EMS dispatch is a crucial resource because it provides accurate and good communication that is required to mobilize adequate additional back-up resources. The initial phase of mass casualty incidents is often chaotic, and overreacting or underreacting is common. Frequent assessment errors include having multiple communicators on site (38%), misidentifying the number of victims (56%), and having unclear information for the resource physician (43%).[188] Prehospital triage information has been deemed appropriate in only one third of mass casualty events.

Concurrent with the individual EMS provider and team's rescue, triage, and treatment efforts, the EMS system will deploy logistics, coordination, and communication teams to the scene of the mass casualty incident to provide on-site local command and control abilities. Typically, this on-site control involves triage areas, where EMS physicians often play an important role in coordinating triage and medical treatment of the victims. In disasters such as hurricanes, national resources such as disaster medical assistance teams (DMAT) or National Guard troops are deployed.

In field triage, different strategies (Simple Triage and Rapid Treatment [START], CareFlight Triage, modified START) show comparable results in correctly identifying the severely injured patients (Table 82-2). In most circumstances, triage cards are used to register and classify triaged patients (Figure 82-5). Triage implies constant reevaluation of victims as conditions of the victims and of available resources continually change.[189] Patients whose injuries are so grave (i.e., traumatic cardiac arrests) that their prognosis is dismal are often classified as *expectant*, and no further medical resources are diverted to their

TABLE 82-2 **TRIAGE GROUPS IN MASS CASUALTY INCIDENTS**

With the aid of triage tags or colored flags, the patients are sorted into four groups.

Triage Tag	Assessment of Treatments Needed	Types of Injuries
Green (minor)	Minor injuries with no immediate need of treatment Psychologic support is needed Patients can walk	Wounds Minor fractures
Yellow (delayed)	Urgent treatment is needed No vital threat is present	Fractures, joint injuries Amputation, major blood loss Burns
Red (immediate)	Vital threat is immediate	Respiratory insufficiency, shock Brain trauma Burns with immediate vital threat Abdominal trauma
Black (expectant)	Patients are dead or moribund	Respiratory arrest, cardiac arrest Head injuries with dismal prognosis



Figure 82-5. Triage tag, front and back, used in field triage. Patients are assigned to one of four categories, according to the severity of their injuries and the need for immediate intervention or rapid transport to a trauma center.

care. Otherwise, these patients would likely consume large quantities of much-needed resources in a futile resuscitative effort.[190] Adequately triaged patients are then either immediately treated on the scene or transported to a hospital. The goal is to not overwhelm the closest local hospital with all victims from the scene but to intelligently, appropriately, and efficiently transfer the victims to multiple surrounding health care facilities.

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Chapter 83

*The Role of the Anesthesia Provider in Natural and Human-Induced Disasters**

DAVID J. BAKER

83A *The Role of the Anesthesia Provider in Natural Disasters*

Key Points

- Disasters may be natural or human-made. Both types produce a surge of casualties that involve both anesthesia providers and intensivists.
- Of the range of natural disasters, earthquakes produce the most casualties requiring an emergency and anesthesiologic response.
- Natural disasters may affect anesthetic practice either directly, as a result of effects on hospital operation and resilience, or indirectly because of the workload from excessive casualties.

For more than 30 years, *Miller's Anesthesia* has been recognized as the most complete single resource regarding modern anesthesia. During these years, the expanding role and responsibility of anesthesia care have required a scholarly analysis of many aspects of medical care overall. In the seventh edition, the potential role of anesthesia in rare major threats to society resulted in David J. Baker's chapter, "Chemical and Biological Warfare Agents: The Role of the Anesthesiologist." This editor's memory is imprinted with radio accounts of the New York City and Washington, DC, September 11, 2001 terrorist attacks and wondering if San Francisco would be the next target. That morning, I was in charge of the operating rooms, and I and others deliberated on how to proceed and whether to leave some operating rooms open—just in case. Fortunately, San Francisco was not hit, and our decision to carry on as usual with our operating room schedules proved to be the right one. This personal experience convinced me that this chapter was and continues to be necessary. My overriding premise, shared by the associate editors, was that although most anesthesia providers will never be exposed to a terrorist attack, they should be familiar with the basic principles of anesthetic care for those "just in case" scenarios.

When planning for this eighth edition, the editors concluded that the chapter in the seventh edition was excellent, but one major component needed to be added—the role of anesthesia in natural disasters such as earthquakes and tsunamis. Some areas are known to be susceptible to natural disasters (e.g., Chile with earthquakes, the Philippines with typhoons, or the Gulf Coast of the United States with hurricanes) and, as we have experienced more recently, other locations are subject to unexpected severe weather, floods, or fires. Because of the unpredictability and magnitude of these events, anesthesia providers can be caught off guard, and for many, it may be the first time they have been called on to provide anesthesia under the strenuous conditions in a natural disaster.

The editors have concluded that this revised and updated chapter by the same author, David J. Baker, provides a global baseline of information for anesthesia providers who may be required to provide clinical emergency care in the face of these unexpected disasters and in locations with limited resources.

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*The views expressed in this chapter are solely those of the author and do not necessarily represent those of Service d'Aide Médicale Urgente (SAMU) de Paris.

INTRODUCTION

The exact definition of disaster medicine is difficult and depends not only on the event but the nature and number of casualties. The working definition used by the World Health Organization (WHO) is "a sudden ecological phenomenon of sufficient magnitude to require external assistance." Such events can exceed a given response system.[1] A better medical approach more suited to the impact of disaster on anesthesia is a potential mass injury or event that causes illness.[1] This definition is gradually gaining acceptance. Eric K. Noji, MD, Consulting Medical Epidemiologist, Centers for Disease Control and Prevention at Johns Hopkins University, has suggested an alternative definition of disaster as "any community emergency that seriously affects people's lives and exceeds the capacity of the community to respond effectively to the emergency."[2]

Dr. Patrick Guérisse of the Emergency Department at CHU Brugmann-Brien, Brussels, has discussed several definitions of a medical disaster[3] and suggests that the term should best be reserved for situations in which the social and medical infrastructure is so damaged by the event that it places extraordinary burdens on fundamental societal functions such as law and order, communication, transportation, and water and food supply.

CLASSIFICATION

Disasters can be classified as natural or human-induced. Both affect anesthesiology and intensive care in terms of the volume of casualties with both injuries and infection. Natural disasters occur regularly and involve mechanisms related to climate and seismic activity. Human-induced disasters, however, involve the accidental or deliberate release of toxic substances and pathogens, explosions, and fire. The anesthesiologic management of conventional trauma and burns is considered in other sections of this book (see also Chapter 81). This chapter deals with the implications for anesthesia in natural disasters and of chemical and biologic agent release as human-induced disasters.

Natural disasters are events produced by meteorologic and geologic causes. These events can sometimes happen with a certain degree of warning (e.g., hurricanes) or with little or no warning (e.g., earthquakes). Natural disasters occur in both developing and developed countries but the impact on poorer nations where the medical infrastructure is already fragile magnifies the effect.

Natural disasters include the following:

- Flooding
- Heat wave
- Fires
- Storms
- Tsunamis
- Earthquakes

Of these, earthquakes are the events that produce most casualties with mass physical trauma that requires an emergency surgical response.

RESPONDING TO NATURAL DISASTER

Natural disasters affect anesthetic practice either directly, because of effects on the local hospital service, or indirectly, as a result of the excess flow of casualties to the degraded hospital facility. The consequences of natural disaster may affect services and infrastructure in developed and developing nations alike, but the effects in developing nations are usually greater and provide the biggest challenge for mounting an emergency medical response.

For anesthesia providers involved with foreign medical teams (FMTs) in nations with limited resources, special understanding and preparation are necessary for an effective intervention. Lind and associates[4] defined a framework necessary for FMTs to be regulated and organized. In the context of earthquakes, the authors define four phases of development.

- Phase 1 (approximately 72 hours): FMTs are not present; therefore, any aid has to be sourced locally during this acute phase.
- Phase 2 (4 to 21 days): FMTs arrive, establish services, and carry out operations for trauma. During the first weeks after an earthquake, trauma workload increases and nontrauma workload decreases.
- Phase 3 (4 to 12 weeks): A slow return to the usual burden of disease. FMTs are established by this phase, but the pressure of local health needs begins to predominate.
- Phase 4 (3 to 6 months): A gradual return occurs to normal functioning of the health services to predisaster levels. The length of time for return to normalcy depends on the magnitude and severity of the earthquake.

Within these phases of disaster, three levels of care are recognized:

- Basic (primary) and immediate emergency care
- Secondary (intermediate level of health care), which includes diagnosis and treatment in hospital
- Tertiary, which involves specialized highly technical care up to state-of-the art standards

Note that individual countries have very different levels of care at the predisaster level. Within this framework a cycle of disaster onset, response, and recovery has been described.[5]

THE IMPACT OF NATURAL DISASTER ON THE WORK OF THE ANESTHESIA PROVIDER

Within the phases of disaster, anesthesia providers are involved as part of the emergency surgical response teams. The overall stages in the deployment of such teams are as follows:

1. Planning and training: Establishing techniques for the use of unfamiliar equipment that is not used in everyday practice in developed nations
2. Response: The provision of anesthesia and high-dependency care at a field level
3. Recovery: Dealing with the chronic effects of trauma and reestablishing the normal local anesthetic practice

In practical terms, natural disasters have considerable implications for the anesthesia provider, including the following:

- The impact on the normal social infrastructure: Natural disasters disrupt communications and essential services, such as water and power supplies. This disruption creates a challenging background through which emergency medical services, including anesthesia, must be mobilized before any organized medical response can be mounted. The 1995 Kobe, Japan earthquake effectively cut off access to the city's main hospital by staff and casualties, because the hospital was located on a separate island from the city.[6]
- Effects on the prehospital response: After natural disasters, anesthesia providers may be involved in prehospital care as part of a standing emergency medical system (EMS), as in France, where the EMS is medicalized,[7] or as part of an onsite surgical intervention to free entrapped patients.[8] In addition, anesthesia providers may be required to provide high-quality anesthesia for the severely injured in a field hospital, where facilities may be basic and often very different from those available in the normal place of work.
- Effects within the hospital: At the hospital, mass casualties will occur requiring initial emergency care and often early surgical intervention. Time for resuscitation, investigation, and preparation of such casualties for surgery is often limited, and resources may be stretched.
- Further management of casualties in critical care: The problems caused by natural disasters are further complicated by the need for the provision of postoperative critical and high-dependency care in normal hospital surroundings, which have themselves been affected by the disaster. The complex equipment in such units depends on power and gas supplies, all of which may be disrupted by the effects of the disaster. Nevertheless, critical care must still be provided for victims of both physical and toxic trauma alike.[9]

It is essential that emergency medical response by national teams be part of a coordinated international response, preferably at the request of the nation affected by the disaster. A piecemeal, "disaster tourism" approach with a short stay and no postoperative patient follow-up presents problems that have been highlighted by van Horning and colleagues.[10]

RESPONDING TO A NATURAL DISASTER: PRACTICAL CONSIDERATIONS

PREPARATION AND PLANNING

Anesthesia providers, including nurse anesthetists, will be involved in phase 2 of disasters as members of the field surgical teams. Planning and preparation of necessary equipment is essential, preferably as part of an existing special response plan that was established before a disaster occurs. The Haiti earthquake of 2010 provided lessons for emergency responders, including that a coordinated effective field response can be created quickly from a major academic center with no special planning for a disaster response in another country.[11] In addition to the preparation logistics, the anesthesia provider must be familiar with the manifesting pathophysiology of victims of natural disasters, which include crush injury, penetrating and blunt trauma, acute lung injury, burns management, drowning, and near drowning. These are characteristics of the specialty of disaster medicine.[12]

TRAINING

Apart from the need for disaster management planning, EMS teams require special training and experience on the available equipment used in disaster situations and the techniques involved in anesthetic care, which are very different from those used in everyday practice in developed countries. For those with military and humanitarian aid experience or who have worked in developing nations where facilities are often basic, the transition to emergency circumstances will be familiar. However, many anesthesia providers have never worked outside the setting of a sophisticated modern hospital with facilities and abilities to support complex high-technology equipment. This group will require training that familiarizes them with the relatively basic equipment and facilities of field anesthesia.

The practical aspects of field anesthesia are discussed later in this chapter.

PREHOSPITAL ON-SITE EMERGENCY CARE

Anesthesia providers may be involved in the onsite management of casualties. This may be as a result of entrapment (such as after earthquakes and collapsed buildings) in which anesthesia may be required for extraction (emergency amputation). Usually, specialist teams are deployed for this purpose. In France, special teams that are part of the prehospital emergency response system, the Service d'Aide Médicale Urgente, are deployed for disaster management as part of their national policy of bringing the hospital to the patient.[13] The equivalent in a paramedical system is the United Kingdom's Hazardous Area Response Team and Urban Search and Rescue Teams (USARs),[14] which can be supplemented by medical teams as required. Also, military medical teams are usually qualified. Such teams are able to provide immediate triage; assessment; and medical care, including surgery.

EARTHQUAKES: A SPECIAL DISASTER SITUATION

Earthquakes are a major cause of death and injury. Over 1 million deaths as a result of seismic activity have been recorded over the past 40 years.[15] Earthquakes affect both developed and developing nations, and in both cases social and medical infrastructure are affected. The effects on developing nations with an often fragile infrastructure are potentially greater. Earthquakes are sudden-impact disasters that strike quickly and without warning. These

are caused by shifts in the plates that form the crust of the earth, known as tectonic plate shift. Where plates meet, fault lines occur that determine the sites of potential earthquakes.[16]

The factors affecting the outcome of an earthquake are as follows[16]:

- Strength of the earthquake
- Degree of planning and preparation
- Local geologic conditions
- Building design
- Demographics: Many densely populated areas exist along fault lines

The strength of an earthquake is measured using the Richter scale. This scale is logarithmic between 1 and 10. A change of one unit on the Richter scale is equivalent to a 10-fold change in ground motion and a 32-fold change in radiated energy. Earthquakes are measured using instrumentation, observation of human effects, or both. Earthquakes above 5 on the Richter scale cause damage. Those above 7 are regarded as major earthquakes. The 2011 northern Japan earthquake registered 8.9 on the Richter scale and triggered a massive tsunami with 30-foot waves that swept inland for 3 miles resulting in the loss of 15,000 people and creating a nuclear meltdown at Fukushima.

THE PREHOSPITAL RESPONSE AFTER AN EARTHQUAKE

Earthquakes can cause injury from the direct effects of the release of energy leading to structural damage and secondary effects from sequelae such as fires, landslides, floods, tsunamis, and the release of toxic substances. Also, health care facilities may be damaged. They must be inspected immediately, before care is given.

The key problems in prehospital casualty management are as follows:

- Hospital autoreferral: Earthquake casualties who are not trapped often take themselves to the nearest hospital, which can rapidly overwhelm the available medical facilities. At times, inappropriate referral (e.g., many patients without significant injury may autorefer to major trauma centers), leads to the inappropriate use of resources.[17]
- Communications: Early breakdown or overload of standard communications systems such as mobile telephones and the internet may occur. Often an overreliance on these systems is seen, and they have not proved resilient under disaster conditions. A further identified problem is the lack of standardization of radiofrequencies among emergency responders.
- Transportation and social infrastructure: Earthquakes may cause direct effects on links to major regional hospitals as was the case in the 1995 Kobe earthquake.[7] In addition, in poorer countries, airport and air traffic capacities may rapidly be overrun as in the 2010 Haiti earthquake.[18] This had a major impact on teams trying to enter the country to provide emergency medical help.
- Entrapment: Most of the fatalities from earthquakes are a result of injury from collapsing buildings or entrapment in the ruins. Death rates rise 67-fold and injury rates rise 11-fold for trapped victims in contrast to those not trapped but injured. Ninety percent of deaths in earthquakes occur as a result of structural collapse.[19] Survival rate decreases with entrapments longer than 24 to 48 hours after the earthquake. A study of more than 3000 earthquake survivors after the 1980 earthquake in Irpinia, Italy showed that 93% of those who were trapped and survived were extricated within the first 24 hours. In contrast, 95% of those who died did so before they could be extricated.[20] The provision of advanced life support in airway, ventilation, and circulatory management is an essential part of the primary rescue response for casualties. In entrapment cases, the anesthesia provider not only administers anesthetics but also general anesthesia and sedation to aid extrication.
- Triage: Triage of earthquake casualties is essential, particularly in settings where medical care is limited. Several systems of triage have been developed, and the anesthesia provider should be familiar with these. Of these, the Simple Triage and Rapid Treatment (START) system is probably the most familiar and has been evaluated.[21] This system emphasizes essential lifesaving measures, but rescuers are instructed not to provide any definitive care procedures at the scene.
- Delays in the delivery of emergency care: Many victims from earthquakes die because of delays in the delivery of lifesaving emergency medical care. Special urban search and rescue teams (USARs) have now been set up around the world and are ready for immediate response in their home country and for rapid deployment elsewhere. The problem still remains in the delays associated with dispatching the teams. Studies have shown that USAR teams require 24 hours for deployment within the United States and longer for international missions. As an example, the first U.S. team to deploy in Turkey after the 1999 earthquake required 48 hours to begin operations.[16]

HOSPITAL RESPONSES

Earthquakes have a direct impact on hospital services,. aggravating an initial imbalance of demand for medical care and surge capacity,[7] particularly evident in a developed country, Japan, with the 2009 Kobe earthquake.[7] All operating services are disrupted, including anesthesia, with loss of power, water, piped gas supplies, and internet technology systems. Most major hospitals around the world now have a general disaster plan. For hospitals within earthquake zones, this plan should be specially modified. It is important that hospital sustainability be a part of any disaster plan.

Other major obstacles delaying the immediate response in hospital include being able to contact off-site staff and arranging their transportation to the facility.

PATIENT MANAGEMENT

In both the developed and developing nation settings, a patient identification and tracking system should be started as soon as possible. In the early stages, identification numbers may have to be assigned until true identities

can be established. Anesthesia providers and surgeons should be aware of the patient flow pattern to hospital, to plan the best use of operating facilities. The following pattern of patient flow to hospital is described by Schutz and Deynes.[16]

- Thirty to 60 minutes after the tremor: Walking wounded with minor injuries and lacerations. These patients should be quickly evacuated to an observation area. Treatment should be postponed until a more detailed appraisal is available.
- More than 60 minutes after the tremor: Victims with more serious injuries such as crush. These patients will be accompanied by paramedical staff or other emergency medical responders and may have received some treatment in the prehospital zone. This wave of casualties may rapidly overwhelm the available hospital resources, and further triage is essential at this stage. The START system mentioned previously will not discriminate between those injured who will consume large quantities of limited supplies and those whose prognosis will remain poor, despite aggressive treatment. To overcome this problem a modified system of triage, Secondary Assessment of Victim Endpoint (SAVE), has been introduced. The objectives of this system are to reduce victim mortality and ensure that resources will be allocated only to those who will benefit from them.[22]

SPECIFIC INJURIES AND ANESTHETIC IMPLICATIONS

Earthquakes will produce a wide range of traumatic injury. Major injuries include skull fractures and intracranial hemorrhage, spinal injuries, and intraabdominal and pelvic trauma. Studies of previous earthquakes have revealed the following major medical complications of trauma:

- Hypothermia
- Wound infection
- Gangrene
- Sepsis
- Acute respiratory distress syndrome (ARDS)
- Exacerbations of chronic pulmonary disease, such as asthma
- Myocardial infarction
- Multiple organ failure
- Crush syndrome

Crush injuries are a major cause of fatality after earthquakes. The mortality from crush syndrome among those requiring renal dialysis may reach 40% or more.[23]

The following life-threatening conditions may arise as a result of crush injury:

- Hypovolemic shock
- Lactic acidosis
- Rhabdomyolysis
- Acute renal failure
- Hypocalcemia
- Hyperkalemia
- ARDS
- Disseminated intravascular coagulation
- Fatal cardiac arrhythmias

The possibility of hyperkalemia is of particular importance given the need in some cases for rapid sequence intubations using suxamethonium (succinylcholine).

FIELD ANESTHESIA

Natural disasters can challenge anesthesia providers because of the need to manage large numbers of casualties over a short period. In essence, standard anesthetic practice has to be followed but in an abbreviated and simplified format in terms of assessment of the patient and the anesthetic techniques used.

RESUSCITATION AND TRIAGE

Disaster anesthesia providers must be familiar with systematic standardized trauma management systems (e.g., Advanced Trauma Life Support [ATLS]),[24] which are used to provide a unified system of care to the victims. Box 83A-1 presents the conventional guidelines for resuscitation and triage of mass casualties (also see Chapters 81 and 108).

PREOPERATIVE ASSESSMENT

History

In the management of mass casualties in the field, a basic and consistent system of preoperative anesthetic management is required. If the patient is conscious, a rapid history can be taken following the AMPLE mnemonic, as follows[11]:

- **A**llergies/Airway problems
- **M**edications (either taken or given on site)
- **P**ast medical history
- **L**ast meal
- **E**nvironment/event

Every patient to undergo emergency anesthesia in the field must be considered to have a full stomach. Injury causes delayed gastric emptying, and normal gastric clearance times may not be appropriate.

BOX 83A-1 ***Primary Responses for Casualties of a Natural Disaster***

RESUSCITATION

Airway maintenance with cervical spine protection
Breathing and ventilation (including the management of chest injury)
Circulation with control of hemorrhage
Disability or neurologic status (AVPU scale)
Exposure (undress the patient for full examination of primary and secondary injuries)
Environment (avoidance of hypothermia and security of the working area)

TRIAGE

P1 Requiring immediate lifesaving surgery
P2 Surgery can be delayed up to 2 hours
P3 Ambulant injured: Treatment can be delayed by several hours
P4 Expectant

AVPU, Acronym for alert, voice, pain, unresponsive.

Physical Examination

Little time may be available for a complete physical examination of the patient before anaesthesia. Instead, an abbreviated essential examination should be used as a basic response. This examination involves the following:

- Measurement of vital signs
- Airway evaluation
- Examination of the heart and lungs
- Evaluation of hemorrhage and hypovolemia
- Assessment of chest, abdominal, and other injuries

FIELD ANESTHETIC EQUIPMENT AND TECHNIQUES

Sophisticated anesthetic workstations typical in developed nations are unlikely to be available or usable at or near the disaster site because of damage to the infrastructure. Therefore, the need exists to be familiar with basic anesthetic equipment designed to work in extreme conditions and equally basic and safe anesthetic techniques. Resources such as bottled gases and power may be in very short supply or nonexistent, so equipment must be used that takes this into account. Anesthetic equipment to be used in natural disasters must meet the following standards:

- Simple to operate
- Rugged and reliable
- Easily transportable

Anesthesia providers in the nineteenth century used simple inhaled anesthetic techniques that could be used in the hospital or outside. Field anesthetic equipment has developed along the lines of simplicity and preservation of the approaches of the early anesthesia providers. Development has been driven by the military, which has a requirement to provide safe general anesthesia in battlefield surroundings.[25] However, providing care in remote areas away from mainstream hospitals presents problems because many anesthetic providers do not have the experience with the equipment or techniques of field anesthesia; also, the equipment used is absent from standard hospital practice and thus, providers are not likely to have acquired necessary skills.

USING FIELD ANESTHETIC EQUIPMENT

Field anesthetic equipment sets should be assembled and used for training before disasters occur. This practice may raise complications with current hospital procedures and regulations where the daily practice is to use sophisticated modern equipment. However, it is necessary that anesthesia providers be completely familiar with the equipment and adept at field techniques before deploying to the site of a disaster.

Field anesthetic equipment sets should contain at minimum the following items:

- Torches and emergency lighting
- Airway management
  - Handheld wide-bore suction device
  - Laryngoscopes: Conventional and visualization devices (see also Chapter 55)
  - Endotracheal tube and laryngeal mask airway
  - Cricothyroidotomy sets
- Essential monitoring
  - SpO_2, electrocardiogram, end-tidal carbon dioxide, and noninvasive blood pressure monitoring devices. These devices are available in a portable form suitable for use in field anesthesia.

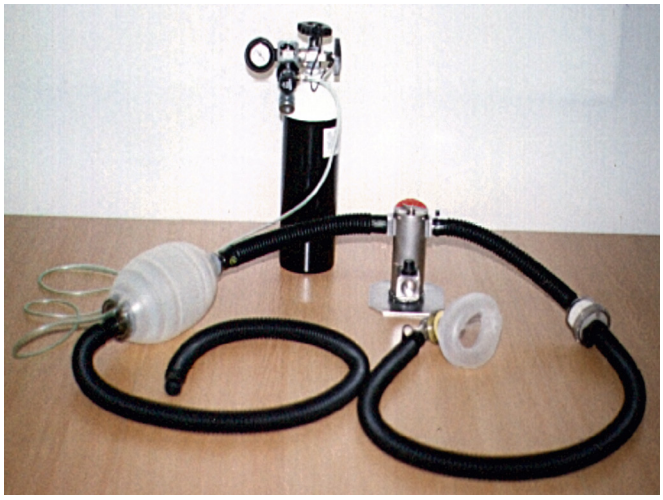


Figure 83A-1. The British Triservice anaesthetic apparatus (TSA). The TSA achieved great success, notably during the Falklands War.

FIELD ANESTHESIA SYSTEMS

A number of field anesthetic systems have been developed (see also Chapter 29). Only two will be mentioned here as representative of the origins and development of field anesthesia. The British Triservice anaesthetic apparatus (TSA) was developed over 35 years ago (Fig. 83A-1). In its simplest form, the circuit relies on draw-over of air as a carrier gas. Originally two vaporizers containing trichloroethylene and halothane were placed in series. Oxygen from a compressed source was supplemented via a regulator and a T-piece. Later the circuit was modified to be used in a ventilatory mode with a self-inflating bag placed distal to the vaporizers. The discovery in 1992 that the vaporizers performed equally well in the draw-over and plenum modes allowed the circuit to be modified with a portable ventilator driving air across a single vaporizer containing isoflurane.

The TSA anaesthetic apparatus achieved great success, notably during the Falklands War[26] and is still widely used around the world. However, it suffers from the disadvantage that the Oxford Miniature Vaporiser 50 (OMV 50, Penlon, Abingdon, United Kingdom) cannot be used with modern anesthetics such as sevoflurane because of the physical characteristics.

A more recent field anesthetic system that uses standard plenum vaporizers is the Magellan machine (Oceanic Medical Products, Atchison, Kan.) (Fig. 83A-2). The Magellan can supplement the level of O_2 in the anesthetic gas using a bottled source or an O_2 concentrator. In this way, precious gas resources are conserved. The main driving gas used in the system is again air, but there is a field anesthetic ventilator (ComPac,

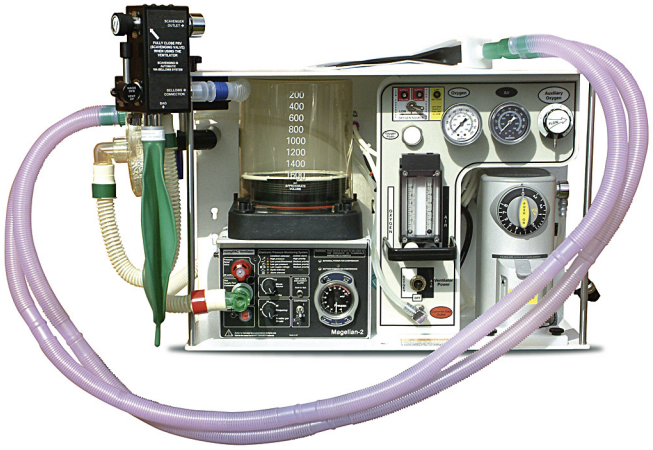


Figure 83A-2. The Magellan anesthesia machine. *(Courtesy Pneupac Ventilation, Smiths Medical International, Luton, United Kingdom.)*

Pneupac, Smiths Medical International, Luton, United Kingdom) built-in that can run from a variety of power sources, including a 28-V vehicle supply (Fig. 83A-3). This turns the Magellan into a plenum system using standard vaporizers without the need for a compressed gas supply

ANESTHETIC TECHNIQUES FOR USE IN NATURAL DISASTERS

No set rules exist for which technique of general anesthesia should be used in disasters. The following factors are used in making the choice:

- Familiarity of anesthesia providers with basic equipment and the ability to train on it in their standard daily practice
- Circumstances and infrastructure
- Availability of anesthetics and equipment that are found in both the developed world and developing nations and, therefore, are familiar to anesthesia providers who may find themselves responding to disasters in developing countries
- Considering the potential workload and the requirement in mass casualty management to provide the greatest good for the greatest number

In general, in extreme disaster conditions only a limited role exists for local analgesic procedures and for epidural and spinal anaesthesia given the collapsed preoperative condition of many of the patients and the nonsterile conditions that often apply. However, in some situations, regional anesthesia techniques have been used successfully before general anesthetic capability is established.[27]

All patients receiving field general anesthesia should be regarded as having a full stomach; therefore, a full rapid sequence induction of anesthetics is required followed by tracheal intubation. Thereafter, a balanced technique should be employed with muscle relaxant, opioid, and ventilation. The actual choice of anesthetics to be used will depend on circumstances and national availability. Drugs requiring refrigerated storage (e.g., suxamethonium chloride/succinylcholine) may not be usable, and



Figure 83A-3. The CompPac portable gas-powered emergency and transport ventilator for use in contaminated environments. *(Courtesy Pneupac Ventilation, Smiths Medical International, Ltd, Luton, United Kingdom.)*

alternatives that are stable at room temperature should be sourced.

The anesthesia technique should be designed to minimize the time spent in postoperative recovery and should aim for awake extubation of the trachea at the end of the surgery. Sufficient analgesia should be given until this can be continued by nursing care.

Anesthesia providers working in developing nations may find that modern anesthetics with suitable rapid induction and emergency profiles may not be available, even in normal practice. Here basic inhaled anesthetics such as ether or halothane, often long since discarded in developed nation practice, may be in daily use. A revision of the properties of such anesthetics should therefore be part of disaster training for anesthesia providers.

INDUCTION OF GENERAL ANESTHESIA IN FIELD ANESTHESIA

The use of intravenous anesthetics depends on availability and experience. Propofol, which has achieved dominance over intravenous barbiturates such as thiopental in recent years, may not be the ideal drug of choice in disaster settings. It is dispensed in solutions that can easily become contaminated in the potentially nonsterile conditions that may prevail in disaster management. However, where circumstances of sterility and storage permit, propofol may be appropriate for rapid procedures such as wound dressing change and burn debridement. Because

BOX 83A-2 *Properties and Administration of Ketamine*

Advantages

Can be given intramuscularly or intravenously as a bolus or infusion
Stable and does not require refrigeration
Basic airway management often can be used with the need for assisted ventilation
Bronchodilator
Analgesic
Rapid recovery

Disadvantages

May be associated with laryngospasm
Increased secretions
Risk for emergence hallucinations (author's note: These are rare in extreme disaster conditions and with children, and they can be controlled using benzodiazepines)

Duration of Anesthesia

Clinical effect up to 30 minutes from bolus depending on dose
Elimination half-life: 2 to 3 hours

Dosage (Adult)

Intravenous induction dose: 1 to 2 mg/kg
Maintenance doses: 0.1 to 0.5 mg/min or half the initial induction dose
Continuous infusion: 10 to 30 mcg/kg/min

of cost, propofol may not be readily available in certain developing nations.

Ketamine, a short-acting but potentially hallucinogenic anesthetic that has been in service for several decades, still remains one of the most useful and safe anesthetics for field anesthesia. Its properties and use are shown in Box 83A-2.

VENTILATION IN THE FIELD AND WHERE HOSPITAL FACILITIES ARE DISRUPTED

Ventilation in the austere conditions that surround disaster requires planning before entering the situation. Ventilation is required as part of emergency balanced anesthesia and for postoperative care in some cases. Consideration must be given to the use of ventilators that are suitable for disaster conditions where main power and compressed gas supplies may be absent. Most hospital ventilators, including those in anesthetic workstations, are not suitable for this setting.

Anesthesia providers should therefore be familiar with portable gas or battery-powered ventilators suitable for use in disaster conditions. A wide range are available, and the following factors are important to consider: (1) Familiarity. Is the device used or known in standard practice? (2) Simplicity of operation. Does the ventilator have the absolute essentials for field use? In disaster anesthesia, most ventilation is part of balanced anesthesia to ensure a rapid recovery and throughput of cases. Thus, complex ventilation modes used in hospital practice are not required. Pneumatic portable ventilators that offer flow generation, time cycling, and preset volume delivery have been tried and tested in field conditions and have been widely used by the military in recent battlefield operations. The Pneupac ComPac ventilator (Pneupac Ventilation, Smiths Medical International, Luton, UK) shown in Figure 83A-3 is a good example of a device that will function without the requirement for compressed O_2 and with a variety of field available power sources.[28]

83B *The Role of the Anesthesia Provider in Chemical and Biologic Warfare Injuries*

Key Points

- The management of chemical and biologic warfare (CBW) injury is a continuing process from the site of release to the hospital. The anesthesia provider may be involved at all stages from the provision of essential early life support through intensive care unit care.
- CBW management requires advanced life support and other specialized skills that are part of the anesthesia provider's sphere of operation.
- CBW injury should not be approached in isolation from the many clinical lessons that already exist from accidental hazardous materials (HAZMAT) releases and natural epidemic infections. CBW release poses a risk to the medical responder, and he or she should be trained and equipped to operate safely in a contaminated or infected zone.
- Chemical and biologic hazards form part of a continuous hazard spectrum. Agents from different parts of the spectrum may have common effects on susceptible somatic systems. Because detection of a released agent may not be immediate, response should be passed on presenting signs and symptoms and may require the provision of life support.

KEY POINTS—cont'd

- Each hazard in the spectrum has four key properties: toxicity, latency, persistency, and transmissibility. The first two determine the management of the patient, and the second two determine the management of the incident.
- A wide range of suggested potential hazards (often loosely described as threats) have been suggested in a climate of apprehension because of the possibility of terrorist attack. On the basis of preexisting military and intelligence information, these potential hazards can be refined down to provide a framework of genuine hazards and management protocols that can be applied across the hazard spectrum.
- CBW agents should not be regarded medically as weapons of mass destruction; instead, they are agents that may cause mass injury. Early life support and specific therapy can break the link between mass injury and mass loss of life.
- Most of the toxic hazards likely in civil life are part of the U.N. HAZMAT classification. Planning for accidental industrial releases is relevant to the management of deliberated CBW release.
- Toxic agents have been used in both military and civil releases over the past 35 years and currently should be regarded as a potential terrorist threat.
- Management of exposed patients depends on the protection of medical responders, early provision of life support, and specific antidote and antimicrobial therapy. Decontamination of patients may cause delays in starting treatment and is not always necessary. Essential advanced life support for acute toxic injury (TOXALS) should be given during decontamination if required. Mass ventilation capability in the hospital is important in the management of respiratory failure from accidental and deliberate chemical and biologic causes.
- Military chemical warfare agents, such as nerve agents, vesicants, pulmonary edemagens, cyanides, and certain toxins, pose the greatest hazard in civil releases. Many industrial chemicals are equally hazardous.
- Classic biologic warfare agents, such as anthrax and plague, manifest as a deliberately induced epidemic with far longer latencies than chemical warfare attack. Anesthetic involvement is usually at the intensive care stage.
- Lessons learned from the current fears of deliberate toxic release will have value for the management of the increasing number of accidental individual and mass toxic exposures that form the greater risk for human life in the twenty-first century.

INTRODUCTION

Until recently, the effects of exposure to chemical and biologic warfare (CBW) agents was a remote area of clinical practice that concerned military specialists, microbiologists, and toxicologists. Since the World Trade Center attack in New York City in September 2001, the level of concern has increased about the possible impact of CBW agents released by terrorists on a civilian population. The attacks in London in July 2005 involved the use of high-explosive devices in a confined space. Toxic effects occurred, and the use of a chemical device by the terrorists was considered by the emergency responders. Anesthesia providers from the helicopter emergency service were among the first to treat the injured onsite.[29] With the continuing real threat of the use of CBW agents by terrorists, anesthesia providers have become more involved in the prehospital and hospital management of CBW injuries. As a result, CBW casualty management, previously dominated by considerations of toxicity and pathogenicity, now includes considerations of modification of outcome by provision of early and continuing life support.

This section discusses the anesthesia aspects of management of casualties who may have been injured or infected after a deliberate exposure to CBW agents. Important lessons for management of CBW incidents can be taken from plans for accidental toxic releases. In some countries, anesthesia providers are part of the initial emergency medical response and are trained in the essentials of personal protection and decontamination.[30] They also may be involved in the initial reception of contaminated casualties at the hospital itself, particularly when autoreferral occurs.[31] Casualties with toxic injuries also may have conventional injuries requiring surgery, and this brings a whole new dimension to the management of operative anesthesia, modified by the effects of a toxic agent. Finally, many of the victims from a CBW attack require immediate and long-term ventilation and other intensive care, which is an area in which anesthesia providers and intensivists are actively involved.

In this chapter, the nature and management of chemical and biologic hazards will be approached first by considering their definition and classification and second by discussion of the properties of key representative agents in terms of pathophysiologic effects. A wide range of potential CBW hazards exist that have been the subject of exhaustive literature, and it is not the intention here to repeat specialized information. Instead, key features of representatives of various classes of hazard are discussed from the standpoint of anesthetic and intensive care practice. Finally, the practical aspects of the involvement of the anesthesia provider and intensivist in management of CBW agent release will be considered. This discussion covers the management of the patients and safe operation during the incident, including detection of release, protection of responding personnel, and decontamination.

APPROACHES TO THE LITERATURE

Many different specialties—both scientific and clinical—have been involved in the study of CBW for over a century. The literature is very extensive and covers a wide clinical range. Of the specialties involved, toxicology, microbiology, and occupational health have been the most dominant and have left their particular influences. Much of the literature relevant to CBW agents predates the Medline era and is not readily accessible from this source. Fortunately many reviews and books exist, particularly in the exhaustively studied area of cholinergic transmission, which makes the careful and relevant work of early researchers still easily accessible to modern anesthetists.[32-38] The reader is advised to consult these resources to gain a working background of the nature of CBW agents.

EVIDENCE-BASED STUDIES

The study of CBW agents in humans has been less extensive than human studies in other areas of clinical medicine. This is understandable because prospective studies that involve exposure of human subjects either willingly or otherwise have been strictly controlled or proscribed by international convention. Despite this, a large amount of information exists in the literature from early clinical volunteer studies and from accidental exposures to chemical warfare agents and many unpublished or previously inaccessible reports are now openly available.[36] In the biologic warfare field, recent reviews are available,[39-41] along with valuable continuing clinical study in the parallel field of accidental (rather than deliberate) infection together with literature on the development of antimicrobial and antiviral agents, which is of immediate relevance to biologic warfare release.

SECRECY

Although considerable information about the pathophysiology and management of CBW cases exists in the open literature, it is highly likely that far more information is still classified by governments involved in the subject and is not easily accessible.[36] Nevertheless, much historical information is available from time-declassified government sources[42] and from searching the sources provided by the *Freedom of Information Act* in the United States. Other nongovernmental organizations, such as the Stockholm International Peace Research Institute, have published extensive information, although this information may have a political bias.[43] By far the most research on CBW agents was carried out by the Soviet Union (Union of Soviet Socialist Republics [USSR]) during the Cold War, and large amounts of this remain unpublished. However, Soviet scientists involved in programs such as Mikrobioprom[44] and the application of genetic engineering to CBW openly published many articles on techniques; these can be accessed through the databases because the major part of the Soviet program started after the signing of the 1972 biologic warfare Treaty,[45] which led to the discontinuation of biologic warfare research by the West.

DEFINITIONS

CLASSIC DEFINITIONS OF CHEMICAL AND BIOLOGIC AGENTS

The accepted classic definition of a chemical warfare agent is a chemical substance that is intended for use in military operations to kill, seriously injure, or otherwise incapacitate people through pathophysiologic effects.[46] Traditionally, riot control agents and herbicides were excluded from this definition, although they have frequently been used in a way that would be compatible with the definition of a chemical warfare agent. Biologic agents were defined by the 1972 biologic warfare treaty as living organisms, whatever their nature, or infective material derived from them, intended to cause disease or death in humans, animals, or plants.[45] Toxins, which are essential part of the pathophysiologic process in bacterial infection, were excluded from the biologic warfare treaty and are regarded essentially as chemical agents.

THE CHEMICAL-BIOLOGIC HAZARD SPECTRUM

Although chemical and biologic agents have traditionally been separated, it is appropriate medically to regard them as part of a continuous spectrum of hazards; this is shown diagrammatically in Figure 83B-1.[47] Agents in Figure 83B-4 are arranged in ascending order of molecular weight through chemical toxic agents through to self-replicating agents such as bacteria and viruses, on the right. The spectral approach to hazards is useful in emphasizing that agents from different parts of the line act in a similar way on the body. The failure of the neuromuscular junction caused by nerve agent anticholinesterases and botulinum toxin is a good example. Bacteria exert their toxic effects through toxins that may affect various somatic systems. The spectral approach serves as a reminder that medical management of CBW injury should respond primarily to system dysfunction rather than to specific etiologic factors.

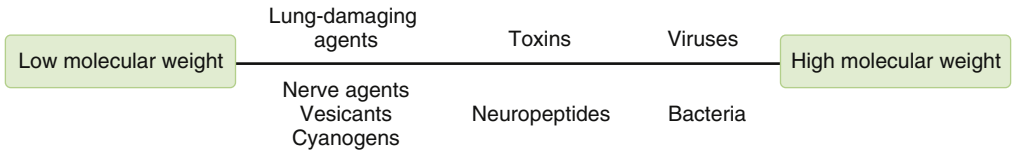


Figure 83B-1. The chemical-biologic hazard spectrum. Agents originally classified as chemical or biologic are arranged in order of ascending molecular weight. Toxins, originally classed as biologic agents, occupy the middle of the spectrum, together with neuropeptides, which normally act as transmitters in the central nervous system. These agents, sometimes called agents of biologic origin, can be synthesized using genetic engineering techniques. *(Modified from Baker DJ: Anesthesia in extreme environmental conditions. Part 2. Chemical and biological warfare. In Grande CG, editor:* Textbook of trauma anesthesia and critical care, *St. Louis, 1993, Mosby–Year Book, p 1331.)*

ESSENTIAL PROPERTIES OF CHEMICAL AND BIOLOGIC WARFARE AGENTS

The four essential properties of hazards within the CBW spectrum are toxicity, latency, persistency, and transmissibility.[38] These four characteristics are common to both chemical and biologic agents and determine the degree of risk and the appropriate response. Toxic effects of CBW agents appear to have a specific latent period. In general, chemical agents and toxins have short periods of latency before the appearance of specific signs and symptoms. In contrast, classic biologic warfare agents have extended latency periods (usually familiar as incubation periods) before the effects of the induced disease begin to appear. Persistency relates to the ability of a toxic agent to remain in the environment into which it was released and is a function of the physicochemical properties of the agent. For chemical agents, the persistency may vary, but for most biologic warfare agents, with the exception of spore-forming agents such as anthrax, persistency is usually very short. Finally, transmission of a hazard may take place as a result of the physical contamination of the victim from a persistent chemical agent or as a result of infection in the case of an airborne agent. Chemical transmission can be contained by decontamination, but biologic warfare agent transmissibility is more difficult to control because of continuing activity.

In summary, toxicity and latency determine the management of the casualty, and persistency and transmissibility determine the management of an incident involving the release of a CBW agent.

TOXICITY AND ITS MODIFICATIONS

Toxicity is usually expressed in terms of median lethal dose (LD_{50}) or LCt_{50}, where C is the concentration of agent inhaled for time (t) required to produce lethality in 50% of the exposed population. LD_{50} usually relates to toxicity via injected routes. In the case of most chemical agents, the inhaled route is usual, so expressions of concentration and time are used.

Haber defined a *lethality coefficient* as follows:

$$W = C \times t$$

where C is the inhaled concentration of toxic agent and t is the time of exposure. In practice, the absorbed amount of agent depends on the respiratory minute volume of the exposed person. This is just one factor modifying the expression of toxicity. Others include life support responses in the case of respiratory failure and the effects of antidotes. The reader is referred to specialized texts for a more detailed discussion.[36]

THE NUCLEAR, BIOLOGIC, AND CHEMICAL WEAPONS CLASSIFICATION

Since the end of World War II, nuclear, biologic, and chemical weapons have by convention been classified together as "NBC" agents, giving rise to a new subsection of warfare, which was developed by both sides during the Cold War. Although all three components are "toxic," the classification ignored the very intense level of physical damage caused by nuclear explosions. Over the years, the term *weapons of mass destruction* (WMDs) has been applied to NBC agents, although the term was originally used by the United Kingdom at the end of World War II.[42] Recently, the term NBC has been altered to reflect the threat perception from the use of explosive devices that can spread radioisotopes (rather than create them as in a fission process) into chemical, biologic, radiologic, and nuclear (CBRN) hazards. CBW agents are defined by their effects after mass release on large populations. The term is not usually applied to the use of such agents for individual or small group poisonings.

MYTH AND REALITY OF CHEMICAL AND BIOLOGIC WARFARE AGENTS AS WEAPONS OF MASS DESTRUCTION

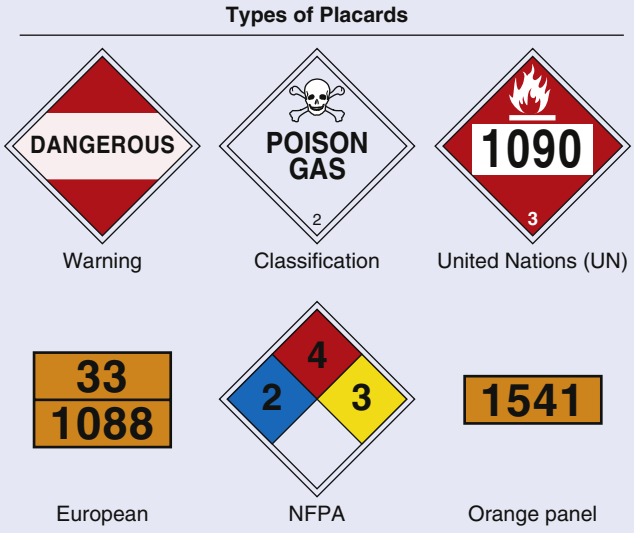
At the end of World War II, the Tizard report[42] appeared, which looked at the future potential of nuclear and biologic weapons, both of which had been used during that conflict. The term *weapons of mass destruction* appears to have been used for the first time in this report because it was thought that both agents would cause mass loss of life. Chemical weapons were added to this group during the 1950s, when the equilibrium of international power depended on analysis of the possession of the three WMD agents. In retrospect, however, the WMD classification is (at least medically) inappropriate. Consideration of the events of World War II showed that nuclear weapons should be classified with conventional weapons systems that cause mass loss of life and destruction to material and the environment, such as the conventional high explosive and firebombing of Germany in the latter part of the war.

CIVIL TOXIC HAZARDS (HAZMAT)

Parallel to the definitions of CBW agents is a classification of hazardous materials used in everyday industrial life. These are usually released by accident. Many of these are as toxic as chemical warfare agents. Such toxic substances are classified as hazardous materials (HAZMAT) and are covered by the U.N. convention controlling the use and transportation of such materials (Box 83B-1).[48,49] A HAZMAT material is defined as that which causes mass injury and death if released from a confined state. The civil equivalent of biologic warfare agent release is natural infection expressed as an epidemic. Another term for HAZMAT is toxic industrial chemicals (TICs). TICs are substances that could be used as improvised chemical agents in a terrorist attack.

BOX 83B-1 *HAZMAT System of Classification*

The U.N. hazardous materials classification for toxic substances (HAZMAT) defines nine classes of hazard. These are identified during production and transportation by a class number and a hazard identification number. Vehicles carrying compounds controlled by HAZMAT must display a plate (the Kemler plate) that carries this essential information for the use of emergency responders. The form of the Kemler plate varies internationally.



Class	Subclass	Hazard Type
1		Explosives
	1.1-1.5	Mass explosion hazard Very sensitive substances
2	2.1	Flammable gases
	2.2	Nonflammable nontoxic gases
	2.3	Toxic gases
3		Flammable liquids
4	4.1	Flammable solids
	4.2	Spontaneous combustion
	4.3	Dangerous substances when wet
5	5.1	Oxidizing substances other than organic peroxides
	5.2	Organic peroxide
6	6.1	Poisons
	6.2	Infectious substances
7		Radioactive substances
8		Corrosive substances
9		Other dangerous substances

NFPA, National Fire Protection Association.

AGENTS OF CHEMICAL AND BIOLOGIC WARFARE: BACKGROUND AND DEVELOPMENT

WORLD WAR I

Chemical agents were used from 1915 to 1918 in World War I. Their use was catalyzed by the battlefield stalemate of trench warfare. They do not fit well with the tactics of a mobile war, which was the case in World War II. Large-scale releases of chlorine and phosgene in 1915 had considerable effects against unprotected troops and caused large numbers of casualties and deaths. It was these early attacks that probably gave rise to the notion of CBW agents being weapons of mass destruction. In fact, chemical weapon injury produced the lowest ratio of dead to wounded of all the arms used during the war at less than 4%,[42] whereas explosive shells had the highest ratio at over 15%. Artillery caused 59% of the overall mortality on all sides. Many different chemical agents were tried during the war, delivered usually by shell fills, but the difficulty was in building sufficiently high concentrations of agent to be lethal and the continuing countermeasures meant that better trained troops with masks were less affected. Although phosgene easily could be regarded as the most lethal of the agents used, causing untreatable toxic pulmonary edema, mustard gas, a vesicant disabling agent, caused the most injuries and removed many from the field of battle (usually temporarily). One overlooked feature of the casualties from World War I is the possibility of mixed toxic and physical trauma. The exact figures are not available, but of 546 American soldiers who died after exposure to chemical warfare agents during the period March to November 1918, 6% also had ballistic injuries.[50] The figures for dead and wounded do not reveal the true extent of the disability caused by exposure to toxic agents, and it is likely that the long-term pathology was high, particularly given the limited postwar medical facilities at that time.

DEVELOPMENT AND USE OF CHEMICAL AND BIOLOGIC WARFARE AGENTS DURING WORLD WAR II

Organophosphate pesticide research by Gerhard Schrader in 1936 led to the development of anticholinesterase "nerve agents" by Germany under conditions of the strictest secrecy during World War II. Although never used in action during that time, nerve agents became the major toxic hazard faced by armies during the Cold War and beyond.[42] A major nerve agent plant was captured by the Russians and rebuilt in the Soviet Union in 1945, giving the USSR a "mass destructive" capability long before it possessed nuclear weapons. A lesson for both military and civil anesthesia providers is that mixed casualties can be expected after the

use of toxic agents, because Soviet commanders saw the use of chemical weapons as part of a normal armamentarium, rather than being exceptional weapons.[51]

Some evidence exists of the use of biologic warfare agents in China by the Japanese, who had a secret unit devoted to the subject since the early 1930s.[42] Plague and clostridia were used in tests on prisoners and against civilian populations. The considerable knowledge gathered was passed on to the United States by the head of the section after his capture and formed the basis of an offensive biologic warfare development program that was terminated in 1972 with the signing of the biologic warfare treaty.

COLD WAR DEVELOPMENT

It is now known that a major Soviet biologic warfare program began in the early 1970s that used genetic engineering and other techniques to develop a whole new range of possible agents, including toxins and "agents of biologic origin," which are probably deployed at the present time.[44] Development of nerve and other agents also continued during the Cold War, along with extensive research into an antidote-based approach to the management of the wounded.

With the end of the Cold War, much of the expertise in USSR laboratories may have moved to other countries, increasing the risk that developed CBW agents and delivery technology may be more easily available to terrorist groups.

THE IRAN-IRAQ WAR

The Iran-Iraq War during the 1980s saw the sustained use of chemical agents and the first application of modern medical techniques to chemical warfare injuries (Box 83B-2). Extensive U.N. investigations established that sulfur mustard and lewisite, both vesicant agents, had been used together with the nerve agent tabun and a toxin agent, mycotoxin.[52,53] Casualties were almost exclusively on the Iranian side and numbered approximately 27,000, with a mortality rate less than 1%. This continued the trend noted during World War I of the low mortality rate for chemical warfare compared with other weapons, and almost certainly reflects the impact of organized medical care for the casualties and techniques of protection. In comparison, the Iraqi attack in 1989 against civilians in the unprotected Kurdish village of Halabja, which had few or no medical facilities, produced 5000 dead.

TERRORIST CHEMICAL AND BIOLOGIC WARFARE RELEASES DURING THE LAST PART OF THE TWENTIETH CENTURY

In 1995, the first recorded terrorist use of a chemical warfare agent against a civilian population occurred with the use of the nerve agent sarin in attacks in Matsumoto and Tokyo, Japan, and for the first time, hospital medical teams were brought into direct contact with a chemical

BOX 83B-2 *Iran-Iraq War Experience With Chemical Warfare Agents*

During the Iran-Iraq War, modern medicine was applied to the treatment of injuries caused by sulfur mustard, tabun, lewisite, and the biologic agent mycotoxin.*,† Although data are limited, there are lessons that should be noted. The most unexpected was the surprisingly low mortality: fewer than 1% of the estimated 27,000 Iranian chemical casualties.‡

Troops with organophosphate exposure fell into four categories. Those with the greatest exposure died in the field. The number appears to have been very small, even though most of the Iraqi attacks were made against unprotected Iranian troops. Those most severely injured who reached medical aid were unconscious, unresponsive, and often in respiratory arrest. The seriously intoxicated had symptoms of dizziness, disorientation, anxiety, salivation, and respiratory difficulty. Those with relatively mild symptoms were often physically difficult to manage because of their disorientation. By far the largest number of casualties required no treatment other than decontamination.

Treatment of mustard exposure during the Iran-Iraq War reflects the experience gained in the management of burn wounds during the 80 years since World War I. Treatment begins with early and thorough decontamination. Early in the course of injury, blistering may not be present. Still, removal of contaminated clothing is important to limit contact time with the agent. Shaving of the affected areas followed by washing mechanically removes and dilutes the agent. Aspiration of blisters, removal of necrotic tissue, and treatment of the skin lesions with silver sulfadiazine cream forms the basis for treatment of skin injury. Respiratory exposure to mustard creates its own set of problems. Depending on the degree of injury, the treatment must be adjusted to the degree of injury. Humidified air or oxygen helps prevent airway obstruction. Bronchodilators, mucolytics, and expectorants are useful. In cases of serious injury, mechanical ventilation with positive end-expiratory pressure and acid-base balance control are used to support the patient until the injuries resolve.

Injury to the eyes was treated with irrigation and antibiotic cream. Pain is treated with systemic medications. Because of weight loss, often in excess of 10 kg (22 lb), nutritional support is instituted to help reduce the significant mortality associated with negative nitrogen balance. Once the patient reaches a setting for definitive care, therapy is divided into two parts: a general supportive treatment for sepsis and dehydration and treatment to eliminate toxins from the body.*

Significant observations from the Iran–Iraq War include the following:

- Decontamination, using soap and water and shaving body hair, was done early. This protected medical personnel and simplified further treatment.
- Comatose casualties of nerve agents who did not have cardiovascular problems were treated with large doses of atropine 50 to 200 mg administered intravenously. Most casualties received 2 mg every 8 hours. Comatose casualties with significant cardiovascular deterioration (such as bradycardia after 2 mg of intravenous atropine) were most often found not to survive.
- Mustard, although it dates from World War I, continues to be an important chemical agent. It is a vesicant but also has effects on multiple organ systems.

*Colardyn F, de Keyser H, Ringoir S, et al: Clinical observation and therapy of injuries with vesicants, *J Toxicol Clin Exp* 6:237-246, 1986.
†*Kadivar H, Adams SC: Treatment of chemical and biological warfare injuries: insights derived from the 1984 Iraqi attack on Majnoon Island,* Mil Med *156: 171-177, 1991.*
‡*Hammick M: All stick and no carrot,* Int Defense Rev Dec *1991, pp. 1323-1327.*

warfare incident during the initial and continuing management of the casualties.[31,54] Unfortunately, because of lack of experience, casualties occurred among the attending emergency staff, but the number of fatalities was low. The incident brought home lessons for medical responders, including anesthesia providers. The first was that the use of a hitherto military chemical warfare agent was possible by a terrorist group. Second, the incident management underlined all the lessons taught by the HAZMAT system, in that secondary casualties occurred among the attending staff as a result of lack of control, protection, and decontamination. Third, fatalities that occurred at the release site were essentially caused by lack of onsite resuscitation. Fourth, the well-documented clinical management of the many thousands of cases that were admitted to hospital provided for the first time a significant clinical database for a population exposed to a nerve agent.[55]

HAZARDS AND THREATS

Confusion between the concept of a hazard and a threat is common. CBW agents are, by definition, hazardous. The term *threat* is usually used in the military context if a hazard has been weaponized and the assailant has the capability and the intention to use the weapon. The relationship may be expressed by the simple equation:

$$\text{Threat} = \text{Hazard} + \text{Capability} + \text{Intention}$$

For a balanced medical response to CBW attack, the reality is that many of the CBW hazards causing public concern are very difficult to weaponize and deliver. This understanding is important for the medical responder because it reduces the likelihood of encountering casualties from CBW attack to a restricted number of agents, the properties and pathophysiology of which can be considered before casualties present.

MODES OF RELEASE OF CHEMICAL AND BIOLOGICAL WARFARE AGENTS

CHEMICAL AGENT RELEASE

Military Release

In warfare, the release of CBW agents is a deliberate action achieved through the use of shells or missiles or through spraying. Aerosol release is the essential technique that allows attack through the respiratory route, but for more persistent agents designed to deny terrain, the use of spray devices is more common. By the end of World War I, delivery of chemical warfare agents was almost exclusively through explosive shells, and at that time nearly 40% of the fills were chemical, indicating the effectiveness of chemical warfare agents on the battlefield.[42] The rise of aerial bombardment before World War II brought great fears that cities would be wiped out by gas attacks, but these fears were never substantiated and it is now realized that dissemination of chemical warfare agents over a wide area (rather than a limited tactical area) by explosion is not easy. During the Cold War, the Russians developed considerable expertise in the use of BM21/24 multiple rocket launchers (Stalin organs) that could rapidly deliver a high concentration of nonpersistent agents, such as hydrogen cyanide, and then allow their dispersal and the entry of nonprotected troops. Missiles such as the Scud were also developed for chemical warfare release at this time, and it was feared that they had been developed for chemical warfare use by Iraq before the Gulf War of 1991.

In the military context, release of toxic agents may be revealed or concealed. Attack, by whatever means, is usually predicted and detectable with the considerable resources that the military can bring to bear in this area, for both chemical and biologic agents. Tuned detection systems are employed wherever there is perceived to be a threat, and the threat itself is usually supported by intelligence information about the hazards concerned, which means that the systems can be tuned. Broad detection systems such as mass spectrography are also employed by CBW reconnaissance units in the field (Box 83B-3).

Release on a Civilian Population

In civil life, toxic agent release is usually accidental and is usually revealed by the circumstances. Road and other transportation accidents, particularly when vehicles carrying HAZMAT identification plates are involved, give an immediate warning about the nature of the problem.[48] Accidental releases, particularly in nations with poor emergency response resources, can be catastrophic, as in the case of the mass release of methyl isocyanate in the Indian city of Bhopal in 1984, which caused over 5000 deaths and 50,000 casualties.[56] Civil populations, unlike their military counterparts, are usually untrained and unprotected against toxic agent release. In addition, the panic induced by the fear of the actions of CBW agents compounds the flexibility of the emergency medical response.

BIOLOGIC WARFARE AGENT RELEASE

The deliberate release of classic biologic warfare agents, such as bacteria or viruses, may not be as easy as the

BOX 83B-3 *Detection Techniques*

Detection: Detecting the presence of a chemical or biologic weapon agent in a contaminated environment. Specific detection techniques include the following:

Agent-specific chemistry
Generic chemical detection techniques
Mass spectrography
Ion current devices
Bioluminescence
Microbial techniques
Chemical and pathologic studies on an affected patient after the attack
Internal versus external detection

Monitoring: Detecting contamination on an exposed patient. Monitoring is important to determine the risk for transmission and the effectiveness of decontamination.

media have led the public to believe. Effective mass release implies aerosol release, and very few of the biologic warfare agents are capable of withstanding the environmental stresses involved. Some, such as anthrax spores, have long been recognized as being sufficiently robust and have therefore attracted the most research attention. The only other bacteria that have probably been used as biologic warfare agents are *Francisella tularensis,* which is spread through infected fodder and causes tularemia, and *Yersinia pestis,* which causes plague and was said to have been used by the Japanese during the World War II campaign against China, and where the vector used was the traditional one of the ratborne flea.[42]

Considerable research work was carried out by the USSR during the Cold War to try to find new ways of delivering biologic agents and for their modification using genetic engineering.[44] This work also developed agents of biologic origin that lie in the middle of the CBW spectrum and produce subtle pathophysiologic effects and are difficult to detect postmortem in the body. In military terms, biologic warfare has always been seen as a debilitating weapon, self-propagating, and of long latency, that could be used to degrade the capability of static enemy formations or key formations operating behind front lines, such as airfields. In the civil context, biologic warfare agents have yet to be used in a terrorist attack, evidence of continued interest exists.[57]

AGENTS

Numerous reviews[34-39,41,45] are available giving details of agents that are regarded as CBW hazards. This section concentrates on selected hazards that can be regarded as being potential threats and that are likely to be encountered by the responding anesthesia provider.

AGENT-SPECIFIC CLINICAL APPROACH: WHAT IS IMPORTANT TO THE ANESTHESIA PROVIDER

In the management of CBW casualties, the anesthesia provider acts as part of a clinical team. To provide a safe and effective response, the following are required:

- Physical, pharmacologic, and immunologic methods of individual protection
- Immediate measures for life support
- Specific antidote therapy
- Consideration of latent effects

In the following section, specific agents have been selected that are representative of classes of hazards and in some cases have been used as weapons of warfare. They are hazards that either can be synthesized relatively easily or are potentially available from stockpiles or reference laboratories.

NERVE AGENTS

Nerve agents are members of a very large group of chemical compounds called organophosphates (OPs), known since the nineteenth century but first examined in detail in the 1930s.[35,36,58] More than 50,000 OP compounds have been synthesized, and several are in regular use as insecticides around the world, including parathion, malathion, and fenthion.[59] Although OPs were originally developed as insecticides, certain highly toxic members of the class—known as nerve agents—have been developed since before World War II specifically for military use. As a result of development by Germany, and later by Russia, the United States, and Great Britain, at least five nerve agents have been produced. The formulae of the more common nerve agents are shown in Figure 83B-2. Tabun (military designation GA) was the first nerve agent to be produced, followed during World War II by sarin (GB) and soman (GD). 2-(Diisopropylamino)ethyl-O-ethyl methylphosphonothioate (VX), N,N-diethyl-2-(methyl-(2-methylpropoxy) phosphoryl) sulfanylethanamine (VR), and cyclosarin (GF) were developed during the Cold War. Cyclosarin (in which the isopropyl group in sarin is replaced by a cyclopropyl group) was found stockpiled in Iraq during the First Gulf War in 1992. Currently the most important nerve agent hazard likely to face the anesthesia provider is sarin (isopropyl methyl phosphonofluoridate), which has been widely produced, stockpiled, and also synthesized and used by terrorists.[31,55]

In terms of physical properties, tabun, VX, and VR are persistent and sarin, soman, and cyclosarin are not. However, soman may be made in a thickened form that is persistent. The relevance of the physicochemical data to the clinical situation is that the nonpersistent agents generally pose a respiratory risk and the persistent agents

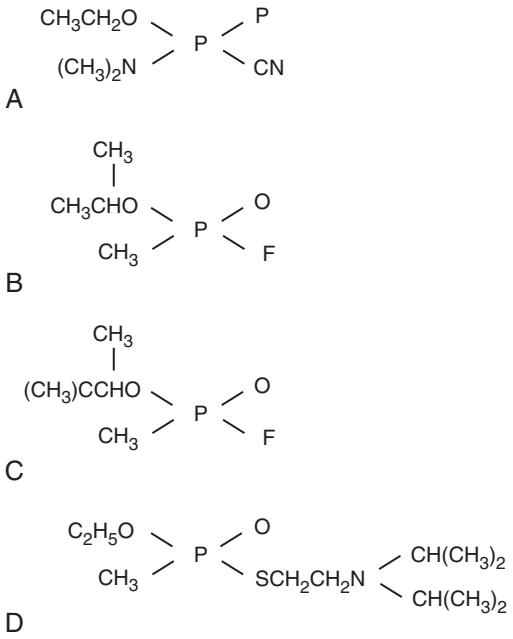


Figure 83B-2. Chemical formulas of organophosphate nerve agents: tabun (GA) (**A**), sarin (GB) (**B**), soman (GD) (**C**), and VX (**D**). (From Baker DJ: Anesthesia in extreme environmental conditions. Part 2. Chemical and biologic warfare. In Grande CG, editor: *Textbook of trauma anesthesia and critical care,* St. Louis, 1993, Mosby–Year Book, p 1331.)

TABLE 83B-1 PHYSICOCHEMICAL PROPERTIES OF NERVE AGENTS

Properties		Tabun (GA)		Sarin (GB)		Soman (GD)		VX	
Molecular weight (Daltons)		162.3		140.1		182.18		267.36	
Specific gravity at 25° C		1.073		1.0887		1.022		1.0083	
Boiling point (° C)		246		147		167		300	
Melting point (° C)		–49		–56		–80		–20	
Vapour pressure (VP) and volatility (Vol)†,‡	° C	VP (mm Hg)	Vol (mg m^{-3})	VP (mm Hg)	Vol (mg m^{-3})	VP (mm Hg)	Vol (mg m^{-3})	VP (mm Hg)	Vol (mg m^{-3})
	0	0.004	38	0.52	4 279	0.044	470.9	—	—
	10	0.013	119.5	1.07	8 494	0.11	1 135.5	—	—
	20	0.036	319.8	2.10	16 101	0.27	2 692.1	0.00044	5.85§
	25	0.07	611.3	2.9	21 862	0.40	3 921.4	0.0007	10.07
	30	0.094	807.4	3.93	29 138	0.61	5 881.4	—	—
	40	0.23	1912.4	7.1	60 959	—	—	—	—
	50	0.56	4512.0	12.3	8 3548	2.60	23 516.0	—	—

From Baker DJ: Anesthesia in extreme environmental conditions. Part 2. Chemical and biologic warfare. In Grande CG, editor: Textbook of trauma anesthesia and critical care, *St. Louis, 1993, Mosby–Year Book, pp 1320-1354.*

are a danger because of absorption through the skin. This means that different agents pose specific risks both to victims and medical attendants.

Nerve agents were originally termed nerve gases, but are in fact liquids with volatilities varying between those of petrol and heavy lubricating oil. None freezes until –40° C (–40° F). They are pale yellow to colorless, odorless, and soluble in water, in which they undergo slow hydrolysis. However, in the presence of strong alkalis and hypochlorite solution, the hydrolysis is rapid and this is the basis of the decontamination of the G agents. Decontamination of V agents with hypochlorite can produce toxic products and is not recommended. Nerve agents can penetrate clothing, skin, and leather. Rubber and synthetic materials, such as polyethylene and butyl rubber, are more resistant. The physical properties of the nerve agents are shown in Table 83B-1.

Actions of Nerve Agents

The main effect of nerve agents is inhibition of acetylcholinesterase (AChE) and butaryl cholinesterase in the cholinergic nervous system (see also Chapter 18). These enzyme systems include the carbamate anticholinesterase and neostigmine, to reverse the action of nondepolarizing neuromuscular blocking drugs. OPs also inhibit other enzymes, notably neurotoxic esterase (NTE). This inhibition causes long-term neurologic effects unrelated to cholinergic changes (organophosphate-induced delayed neuropathy [OPIDN]). The interaction of OPs with AChE is complex and is analogous to the interaction of the enzyme with the natural substrate acetylcholine (Fig. 83B-3).[32] Inhibition of AChE causes a buildup of acetylcholine at muscarinic and nicotinic synapses of the cholinergic nervous system. Thus, central and peripheral signs and symptoms occur that can be directly explained from the classic pharmacologic knowledge of how the cholinergic system operates.

Although the classic effects of OPs are essentially cholinergic, important effects on other receptor systems

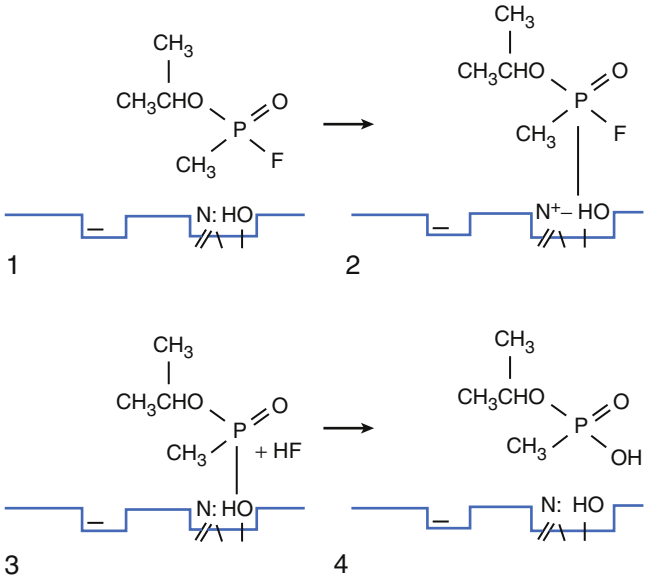


Figure 83B-3. Reaction of acetylcholine and sarin with acetylcholinesterase. *(From Baker DJ: Anesthesia in extreme environmental conditions. Part 2. Chemical and biologic warfare. In Grande CG, editor:* Textbook of trauma anesthesia and critical care, *St. Louis, 1993, Mosby–Year Book, p 1341.)*

occur, notably γ-aminobutyric acid (GABA) and *N*-methyl-D-aspartate, which gives rise to central excitation, causing the initial seizures seen in acute OP poisoning.

The interaction of OPs with AChE is nonreversible after a certain time depending on the nerve agent. The formation of an irreversible complex is known as aging. Each nerve agent has an aging half-life. For sarin, this is about 5 hours, whereas for soman it is only 2 minutes. Tabun and VX both have aging half-lives of 40 hours. After five half-lives, more than 95% of the enzyme AChE has aged and cannot be reactivated. This has important consequences on the window of clinical opportunity[59] for treatment to try to reverse the AChE inhibition (see later section on Oximes).

TABLE 83B-2 SYMPTOMS AND SIGNS OF NERVE AGENT POISONING BY TYPE OF CHOLINERGIC RECEPTOR AND TARGET ORGAN

Receptor	Target Organ	Symptoms and Signs
Muscarinic	Iris muscle ciliary muscle	Miosis; spasm leading to failure of accomodation and pain in the eyes; nausea and vomiting; headache
	Conjunctival vessels	Vasodilation and hyperemia
	Nasal glands	Rhinorrhea and hyperemia
	Bronchial glands	Increased secretion
	Bronchial muscle	Bronchoconstriction; tightness in the chest; expiratory wheezing; dyspnea
	Gastrointestinal tract	Anorexia; nausea; vomiting; abdominal cramps; diarrhea; tenesmus; involuntary defecation
	Sweat glands	Increased activity
	Salivary glands	Increased activity
	Lacrimal glands	Lacrimation (not usually marked)
	Heart	Bradycardia; occasionally tachycardia
	Bladder	Frequency; involuntary micturition
Nicotinic	Skeletal muscle	Weakness; fatigue; fasciculations; cramps; flaccid paralysis (early effects on respiratory muscles may produce dyspnea)
	Autonomic ganglia	Pallor; occasional elevation of blood pressure
Muscarinic and nicotinic	Central nervous system	Anxiety; giddiness; restlessness; headache; withdrawal and depression; memory failure; impaired concentration; slurred speech; depression of respiratory and cardiovascular centers; Cheyne-Stokes respiration

From Baker DJ: Anesthesia in extreme environmental conditions. Part 2. Chemical and biologic warfare. In Grande CG, editor: Textbook of trauma anesthesia and critical care, *St. Louis, 1993, Mosby–Year Book, pp 1320-1354.*

Signs and Symptoms of Nerve Agent Poisoning

The classic signs and symptoms of nerve agent poisoning are shown in Table 83B-2. Poisoning is caused by the accumulation of acetylcholine and not by the OP itself. As a result of stimulation of muscarinic synapses, miosis; ciliary body spasm causing pain[60]; glandular hypersecretion, including salivary, bronchial, and lachrymal; sweating; cardiac effects, including bradycardia (or tachycardia due to the effects on the anomalous sympathetic system), atrioventricular block, and Q-T prolongation; bronchoconstriction; vomiting; severe diarrhea; and fecal incontinence also occur. The nicotinic effects are manifested by fasciculation and paralysis at the skeletal neuromuscular junction. Central effects[61] give rise to apprehension, dizziness, amnesia, seizures, coma, and respiratory depression. Lower chronic doses of OPs lead to irritability, fatigue, loss of concentration, and memory loss.

Clinical Experience With Organophosphate Intoxication

Much of the information about actions of OPs in humans has been gathered from animal studies and management of pesticide poisoning. It should be noted that animal studies do not necessarily represent human reactions, and pesticide studies may not accurately represent the development of the cholinergic syndrome after nerve agent exposure. Although some evidence exists from accidental exposure to sarin and from some human volunteer studies conducted early in the Cold War, the clinical evidence base is smaller than that for pesticide poisoning. During the early stages of the Cold War a number of experimental studies were done on human volunteers exposed to nerve agent, and these have been reviewed by Sidell.[36] The attacks in Japan in 1994 and 1995 also have provided important information concerning the signs and symptoms after sarin release.[31,55]

Clinical Evidence From Recent Military Experience

The Iran-Iraq War produced first-hand clinical information about the effects and management of nerve agent poisoning.[52] Iranian casualties from nerve agents apparently fell into four broad categories. Individuals who suffered the greatest exposure died in the field; filtration mask protection by Iranian troops was severely compromised by their beards, which they had for religious reasons. Despite the fact that Iraqi attacks were made against troops having compromised or poor protection, the number of deaths appears to have been low. The most severely injured who reached medical care were unconscious and unresponsive and often in respiratory arrest. The next group who were seriously poisoned had symptoms of dizziness, disorientation, anxiety, salivation, and respiratory difficulty. Disorientation was a problem, and often cases with only mild symptoms were difficult to manage because of this (this parallels experience gained with the management of OP pesticides). Finally, most of those exposed required only decontamination. Treatment of nerve agent poisoning relied on giving large doses of atropine, usually 50 to 200 mg intravenously. These cases were usually comatose, and the degree of advanced life support given was limited. Most patients received only atropine 2 mg every 8 hours. Comatose patients with significant cardiovascular deterioration usually did not survive.

Clinical Evidence From Pesticide Poisoning

Considerable clinical evidence exists about the effects of OP pesticides from the many thousands of cases that occur in agricultural areas of the world each year.[62] Although these give an overall picture that corresponds to the signs and symptoms described previously, considerable differences exist with nerve agents. It is also likely



Figure 83B-4. Military automatic intramuscular injection device containing nerve agent antidotes. *(ComboPen, Meridian Medical Technologies, Colombia, Md.)*

that the various nerve agents have relatively different effects on the central and nervous systems.

Cardiovascular Effects of Nerve Agents

Critical care management of OP pesticide poisoning has indicated short-term and medium-term cardiac changes.[63,64] After an initial tachycardia (mediated through the anomalous sympathetic nervous system) and a vagally induced bradycardia, ventricular dysrhythmias, including torsade des pointes and prolongation of the Q-T interval may occur. Dysrhythmias have been reported as a poor prognostic sign.

The Treatment of Nerve Agent Poisoning: Antidotes and Life Support

Atropine. Atropine has long been a mainstay in the management of OP poisoning.[58,62] Its antagonistic action against acetylcholine at the muscarinic synapses allows control of the muscarinic effects, the most severe of which is bradycardia. Atropine also has been used for many years in the management of OP pesticide poisoning. However, the relevance of the experience with pesticides to poisoning with nerve agents is not clear.[36] The traditional military response to confirmed or suspected attack with nerve agents is to use a self-administered autoinjector containing atropine 2 mg, a benzodiazepine, and an oxime. An example is shown in Figure 83B-4. During the Cold War, NATO troops were provided with three such devices to be used sequentially. Useful treatment indications have been gained from the Iran-Iraq War[65] and the Japanese terrorist experience.[55] Atropine 2 mg is given intravenously (pediatric dose 0.02 to 0.05 mg/kg) with repeat doses every 5 to 10 minutes until pupillary dilatation occurs and the heart rate increases above 80 beats/minute.[36,66] Atropine infusions may be used for persistent bradycardia in pesticide poisoning.[67]

Oximes. Oximes are compounds capable of reactivating, in some cases, the complex formed by the OP and AChE. Clinically this means that oximes can reverse the actions of OP at the nicotinic receptor and reduce the degree of paralysis.[68,69] Oximes are widely used in the clinical management of both OP pesticide and nerve agent poisonings. Chemically they are monopyridinium or bispyridinium compounds that can bind to the complex and cause the nerve agent molecule to separate from the enzyme. Oximes are a mainstay of the standard military response to nerve agent attacks and are widely used in the management of pesticide poisoning. However, their effectiveness depends on (1) the exact nature of the nerve agent involved and (2) the length of time after the attack before they are given. This is because aging chemical changes take place in the nerve agent–enzyme complex. Aging occurs very rapidly in humans after soman exposure, but less so after exposure to other nerve agents. One of the major problems related to oxime research is the selection of a suitable animal model. Originally monkeys and guinea pigs were both thought to be good models for human OP intoxication, and human treatment protocols were developed from such studies. However, major differences are known to exist between enzyme complex aging rates for primates and those for rodents.[70] The rate of formation of aged enzyme in different species increases in the following order: mouse < rat < guinea pig < rabbit < dog < cow < monkey = human. From erythrocyte studies in humans, the rate of aging is known to be very rapid (half-life 1.3 minutes), indicating that the guinea pig would not be a good model for the use of oximes in humans.

Several oximes are available, and recent years have seen the development of new compounds.[68,69] The most commonly used is pralidoxime (as either the chloride or methane sulphonate [mesylate]). Obidoxime is used in some countries for OP pesticide poisoning and may be effective against tabun. Recent research has concentrated on the rational use of a range of oximes both in terms of the type of oxime used and dose and timing.[68,69,71] HI-6, a Hagadorn oxime, reactivates the soman-enzyme complex, the most difficult clinical situation to treat. However, HI-6 may be useful because of other pharmacologic properties and may be advantageous in the treatment of cyclosarin poisoning and other cases in which obidoxime was previously used.

For most anesthesia providers treating a patient with the symptoms of nerve agent poisoning, a civilian setting is the most likely. Exposure to sarin is the most probable situation, and treatment schedules logically should be based on this premise. Military anesthesia providers may face other hazards, but they would be provided with specialized detection equipment and treatment modalities based on a threat assessment. All nerve agent casualties should receive pralidoxime mesylate initially, in addition to atropine and ventilatory life support.

Practical Treatment Regimen. Oxime therapy should be given simultaneously with atropine.[66,68] A slow intravenous injection of pralidoxime is recommended to prevent laryngospasm, muscle rigidity, and hypertension. Pralidoxime 15 to 30 mg/kg intravenously or intramuscularly is given over 20 minutes for adults and children. This dose may be repeated after 4 hours (or 1 hour if paralysis is worsening). The target therapeutic blood concentration should be 4 μg/mL. However, studies by Worek and colleagues[71] show that the full therapeutic effects of pralidoxime may be achieved at higher concentrations. The same group demonstrated that reinhibition of AChE is a possibility after pralidoxime treatment in human erythrocytes, but the relevance to the whole body is unclear. Sarin is broken down rapidly in the blood by hydrolysis. Oxime treatment in the hospital should continue for as long as atropine is required.

Benzodiazepines. The central actions of OPs give rise to spike discharges and seizures. Benzodiazepines have long

been used to counter this action. Given the known action of OPs at the GABA receptor and the antagonistic action of benzodiazepines at this site, the action may be noncholinergic.[72,73]

Seizures may be an early sign of severe nerve agent poisoning and must be controlled quickly to avoid long-term cerebral damage.

Pyridostigmine Pretreatment. The problem of aging of the OP AChE complex, particularly with soman and the ineffectiveness of oxime therapy, gave rise to a novel military approach to prophylaxis against nerve agent poisoning.[37] Pyridostigmine is a dimethyl carbamate compound with a quaternary nitrogen atom. As a result, it does not penetrate the blood-brain barrier to any extent. In common with other carbamates such as neostigmine and physostigmine, pyridostigmine is an anticholinesterase and has essentially the same action as OPs. In the case of carbamates, the complex formed with the enzyme is readily reversible. The normal treatment dose of pyridostigmine is 30 mg every 8 hours. No plasma protein binding occurs and no drug interactions involving competition for binding sites. Of the absorbed dose, 79% to 90% is excreted unchanged in the urine. The reversibility of the complex formed with AChE is such that the enzyme returns to 90% of normal within 12 hours after the last dose. In addition, at steady state, only 40% of the available AChE is complexed. Given the considerable safety margin that exists in the level of enzyme at cholinergic synapses, treatment with pyridostigmine does not produce any more than mild parasympathetic signs.[74]

The protective action of pyridostigmine against OPs is based on the fact that the carbamylate-complexed AChE is resistant to attack after subsequent exposure to OPs. If a person taking pyridostigmine is exposed to a subsequent potentially lethal dose of OP, a reserve of enzyme is effectively autotransfused into the patient during the subsequent period. This process does not require the presence of an oxime. OP is rapidly hydrolyzed in the bloodstream after exposure and has no further action on the released AChE. The amount of enzyme released from the carbamylate complex is sufficient to restore neuromuscular transmission because of the safety margin that exists at the synapse. However, in severe cases of OP poisoning, life support measures are necessary to bridge the gap between OP attack on the synapse and restoration of the ACHE level through the autotransfusion.

Anesthetic Implications of Pyridostigmine Pretreatment. The anticholinergic actions of pyridostigmine have considerable relevance to normal anesthetic practice. Butaryl cholinesterase, a determinant of the metabolism of succinylcholine, is also inhibited, and prolonged action of this drug may be expected in patients taking pyridostigmine.[75] The carbamate neostigmine is usually given at the end of an operation to reverse the action of nondepolarizing neuromuscular blocking drugs. Pretreatment with a carbamate in a patient who is not subsequently exposed to OP may be expected to produce some resistance to the action of the neuromuscular blocker. Experimental studies indicate that pyridostigmine does not alter the overall characteristics of neuromuscular block in an isolated human forearm, and the neuromuscular effects may be minimal, particularly because more central muscles of respiration such as the diaphragm have a higher safety margin of neuromuscular transmission and are less affected by the pyridostigmine pretreatment.[76] Estimations of the degree of neuromuscular block using fade relationships such as the train-of-four[77] theoretically may be affected by pyridostigmine pretreatment because the determinant of fade is feedback to the prejunctional cholinergic receptor[78] (see also Chapter 18). The hysteresis loops for the onset and offset of fade and paralysis relationships in the isolated forearm are not affected by pyridostigmine pretreatment.[76] The civilian anesthesia provider is referred to more specialized military texts[36,41] for a more complete discussion of pyridostigmine and its clinical actions.

VESICANT AGENTS

Vesicant agents were first used as chemical weapons during World War 1.[42] The most well known is sulfur mustard (1917, commonly known as mustard gas). It was used as a disabling agent and has a long latency of 2 to 4 hours. Its successor, lewisite (1919), an arsenic-based compound (2-chlorovinyl dichloroarsine), is more volatile, has a short latency, and causes immediate eye pain in addition to its vesicant properties.[46] Sulfur mustard is the most commonly encountered vesicant. Although an early chemical warfare agent, it is still widely distributed around the world and its easy synthesis makes it a possible agent for use by terrorists. It has a number of pathologic properties that make it of concern to anesthesia providers. The overall management of mustard gas injury is the domain equally of the surgeon and specialized pulmonary physician.[36,79,80] Intensive care unit (ICU) management presents longer term problems that are mainly respiratory. Eye and skin injuries fall within the aegis of other specialities.

Properties

Sulfur mustard (*bis*-2-chloroethyl sulfide) is a colorless or pale yellow, oily liquid that smells faintly of mustard. Its odor threshold is 1.3 mg/m^3, which is below the concentrations usually reached in a battlefield, and several minutes of detection are possible before incapacitating doses are reached. The LCt_{50} is approximately 1500 mg/min/m.[3] Although the latency of action in cooler climates is approximately 4 hours, information from the Iran-Iraq War, the scene of its most recent use,[81,82] indicates that at higher ambient temperatures, the agent has a far shorter latency and causes significant respiratory damage apart from its classic action as a skin vesicant.

Signs and Symptoms

After exposure to mustard gas, a latent period of 4 to 12 hours occurs, after which ocular symptoms comprising eye pain, blurred vision, and lachrymation are experienced, accompanied by a diffuse erythema of exposed skin with edema and first-degree burns. The groin and genital areas are particularly susceptible. Exposure to high doses produces severe cutaneous injury with necrosis. The burns bear some resemblance to thermal burns, but are very slow to heal and prone to secondary infection.



Figure 83B-5. Cutaneous vesication caused by mustard gas exposure. *(Courtesy Her Majesty's Stationery Office, London, United Kingdom.)*



Figure 83B-6. Eye injury caused by mustard gas exposure. *(Courtesy Her Majesty's Stationery Office, London, United Kingdom.)*

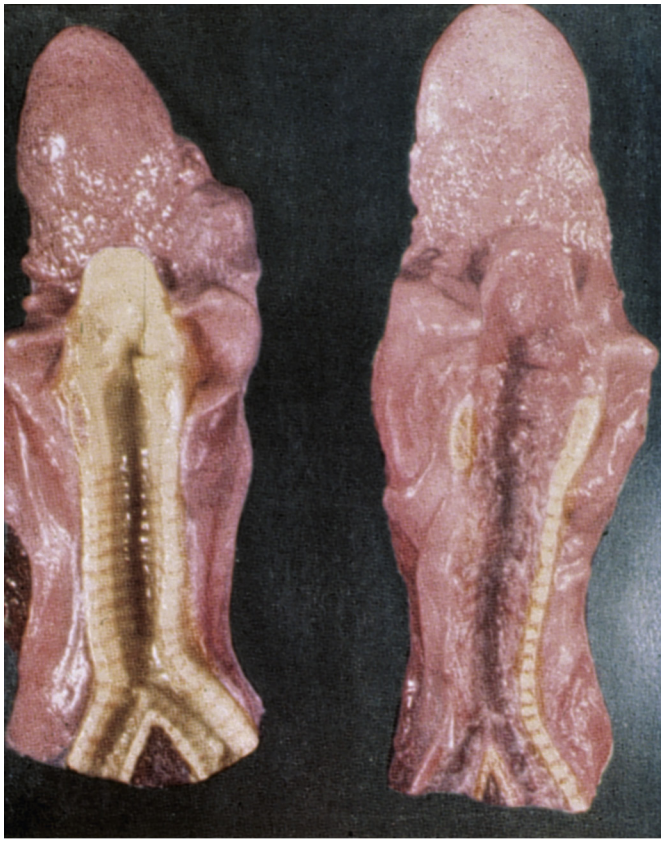


Figure 83B-7. Tracheal injury caused by mustard gas. *(Courtesy Her Majesty's Stationery Office, London, United Kingdom.)*

The bullae characteristic of exposure to mustard agent are filled with a fluid that is not corrosive (Fig. 83B-5). A feature of exposure is that fluid-filled bullae appear for several days afterward in an apparently random way (i.e., not cropped). The eyes are particularly vulnerable to mustard gas, causing a usually temporary blindness (Fig. 83B-6). The fluid in the bullae has itself no vesicant effect.

Respiratory Effects

The respiratory effects of mustard gas exposure are potentially serious, particularly when the ambient temperature is high.[82-84] After exposure, an early tracheobronchitis with dry cough and hoarseness occurs. Heavy exposure will produce severe damage to the tracheal and main bronchial architecture with necrosis, sloughing, and blockage (Fig. 83B-7). A chemical bronchiolitis occurs at lower doses in high ambient temperatures and causes severe bronchospasm, requiring ventilation and intensive care.[82] Lung damage after mustard gas exposure can be severe and permanent, with chronic obstructive pulmonary disease, bronchiectasis, and reactive airways dysfunction syndrome.

Cellular Action of Mustard Agent

Sulfur mustard agent acts at a cellular level forming highly reactive sulfonium ions, which attack DNA by alkylation of sulfhydryl and amino groups.[36] This causes the epithelial manifestations of exposure and also long-term carcinogenesis, particularly of the skin, pharynx, and respiratory tract.

Treatment

Mustard gas exposure has no specific treatment, but experimental studies in animals have shown a combination of sodium thiosulfate, vitamin E, and dexamethasone

can improve survival and reduce organ damage.[36] The key points of treatment are (1) the need for decontamination, (2) the latent period of action, and (3) respiratory support for exposure affecting the respiratory tract. Willems[80] reviewed information concerning the clinical management of mustard gas casualties and found that a proactive approach to airway management and ventilation was evident with endotracheal intubation done early to allow adequate ventilation and assess for debridement of the large airways. Willems reported that the onset of severe respiratory symptoms is a serious development, with a loss of 87% of patients who required ventilation. Another point of concern for longer term management is the leukopenia that follows exposure to mustard gas. This becomes evident 3 to 5 days after exposure and usually reaches its lowest point 7 to 9 days after exposure. Cellular replacement, either peripherally or as marrow, could be considered here because mustard is bound very quickly in the body after exposure and will not cause destruction of new cells.

Recent Clinical Evidence

The Iran-Iraq war during the 1980s saw the extensive use of sulfur mustard and produced a significant amount of clinical information about casualties[81] with both cutaneous and respiratory injuries. The treatment given reflects the experience gained in the treatment of burn injuries since its first use. Decontamination was achieved early to limit the contact time with the agent. Because of the long latency of mustard gas, vesicle formation was often not present at this time. Shaving of the affected areas was done and dilution of the agent by irrigation. The management of the vesicles followed the pattern of aspiration, removal of necrotic tissue, and the use of silver sulfadiazine cream. From the anesthetic standpoint, the respiratory effects found in the casualties were important and unprecedented from the use of mustard in the lower temperature conditions of World War I. Chemical bronchiolitis giving rise to increased airway resistance was reported, together with soiling of the larger airways due to sloughing. Intermittent positive-pressure ventilation with positive end-expiratory pressure was required with ICU support for the more seriously injured cases. Many of these were managed in hospitals around Europe, introducing chemical warfare injury to many anesthesia providers and intensivists for the first time. For the casualties who reached definitive hospital care, the recovery period was often a long one, and patients had cachexia with significant negative nitrogen balance.

LUNG-DAMAGING AGENTS

Lung-damaging agents were formally known as choking agents, a term that does not adequately describe the many levels of the lung at which they act. Lung-damaging agents act at both the upper and lower respiratory tract levels, but their main lethal action is to cause toxic pulmonary edema. Lung-damaging agents were the first to be used as chemical weapons during World War I, with the use initially of chlorine, followed by phosgene. These agents are a universal hazard in military and civilian populations because they are also used widely as industrial feed stocks in many chemical engineering processes. The isocyanates are widely used in this respect, and the accidental release of methyl isocyanate at Bhopal, India in 1984 caused the largest number of casualties ever recorded after toxic release in either war or peace, with over 5000 deaths from toxic pulmonary edema.[85,86] Chemical warfare and HAZMAT sources list many lung-damaging agents.[36,48]

BOX 83B-4 *Properties and Toxic Exposure Levels of Phosgene*

Properties

Chemical name: Carbonyl chloride ($COCl_2$), chloroformyl chloride
Boiling point: 8.2° C (46.76° F)
Vapor pressure: 1215 mm Hg at 20° C (68° F)
Vapor density: 3.5 × air
Breakdown: slow aqueous hydrolysis to HCl and CO_2

Toxic Exposure Levels

1 ppm chronically: Chronic lung disease
>25 ppm/minute: Acute lung effects
50 to 100 ppm/minute: Initial inflammatory response that may be followed by pulmonary edema
>150 ppm/minute: Clinically significant and life-threatening pulmonary edema
Lethal exposure in humans: 800 ppm for 2 minutes

Phosgene

Phosgene[87] has been used as a chemical warfare agent, is an established worldwide industrial hazard, and may be regarded as a potential terrorist threat. It is a model for consideration of other hazards in its class. Phosgene is carbonyl chloride, familiar to earlier anesthesia providers as the product of the reaction of trichloroethylene with soda lime used in circle absorbers. First synthesized in the nineteenth century, phosgene has been in industrial use for over a century but achieved notoriety during World War I, when it was used extensively by both sides from 1915 onward. It caused more than 85% of all deaths from chemical warfare agents.[42] Phosgene is a gas at normal temperatures and is nonpersistent (Box 83B-4). It is less water-soluble than chlorine, its immediate chemical warfare predecessor in 1915, a feature that results in the gas being taken further down the respiratory tree and into the alveoli. Phosgene has been known since World War I to have a dual latency of action, which underlies its essentially dangerous character. The stages after exposure are as follows:

- Stage 1: Immediately after exposure, intense upper respiratory irritation occurs, with coughing, retching, choking, and chest tightness. These symptoms are accompanied by eye irritation and lacrimation. In some cases, death followed exposure to high concentrations of phosgene without development of toxic pulmonary edema. The reason for this is obscure, but it may be related to hypoxia as a result of intense laryngeal or bronchospasm.
- Stage 2: The immediate choking symptoms are followed by a latent period of 2 to 24 hours before the onset of more serious symptoms and signs, including dyspnea,

painful cough, and cyanosis, with increasing signs of pulmonary edema leading to circulatory collapse and cardiac arrest.

Pathophysiology of Toxic Pulmonary Edema. The lung is a delicately balanced system in which the entire cardiac output passes through the pulmonary circulation arranged as a fine capillary mesh in the interstitial space (a loose organization of collagen, elastin, and various cell types). Because of its fragile organizational nature, the lung commonly reacts to toxic challenge by producing pulmonary edema, in which fluid flows from the capillaries to the interstitial space and then to the interalveolar space. Phosgene reacts through covalent attack on many substrate groups, including, NH_2 and SH.[88] Potential cell targets are type I and II pneumocytes and alveolar macrophages. Covalent binding can be seen as the primary attack leading to free radical release. This stage is followed by a secondary attack involving released inflammatory mediators, including prostaglandins (causing vasoconstriction, vasodilatation, and platelet disaggregation), bradykinin (causing increased capillary permeability), 5-hydroxytryptamine (causing constriction of postcapillary vessels), thromboxane A_2 (causing vasoconstriction), and the release of complement activating enzymes (leading to attraction of leukocytes and leukotriene release).

Management of Phosgene Exposure. Patients who have been exposed to phosgene should be removed from the site of exposure as quickly as possible by protected emergency responders. There is usually no requirement for decontamination unless liquid contamination has occurred. Phosgene has no specific antidote, and treatment is based around use of supportive measures and pharmacologic modification of the effects of the inflammatory mediator cascade.[87] One of the firm rules for the management of phosgene exposure dating from World War I was complete bed rest after exposure and observation for 24 hours, and this still applies. No patient who has had a risk for significant exposure should be discharged from the hospital in less than 24 hours unless accompanied by a responsible observer. Provision of specialized respiratory care both at the prehospital and hospital level is necessary. Some cases may require early intubation and ventilation, and more will require O_2 and supported ventilation in the early stages. The method of provision of emergency ventilation is a matter of interest. Recent work in physical trauma has indicated that the "open lung" strategy[89,90] is of value in the prevention of inflammatory cascades by opening the alveoli and keeping them open by use of the correct level of positive end-expiratory pressure. This technique follows the hypothesis that repeated opening and closing of alveoli causes kinin release through the action of shear forces in the alveolar walls. This may be an important lesson for the early management of lungs damaged by phosgene exposure, and the manner of emergency ventilation may be critical. Bag-valve ventilation, which can lead to very high inflation pressures and high flow rates, may be harmful. The use of emergency ventilation strategies that provide controlled flow rates with the early use of positive end-expiratory pressure is more appropriate. These can be provided by the use of small automatic gas-powered ventilators (see Fig. 83A-3). Modern experience of the management of mass casualties with toxic pulmonary edema is limited, but it must be assumed that a considerable proportion who would survive the acute toxic pulmonary edema will go on to develop ARDS unless the appropriate measures are taken. A study by Parkhouse and colleagues[91] demonstrated improved oxygenation, decreased shunt fraction, and decreased mortality in phosgene-exposed pigs who received a protective in contrast to a conventional ventilation strategy.

The Use of Steroids. The use of inhaled and systemic steroids in the treatment of toxic phosgene exposure has been controversial.[92] Recently, however, chlorine has produced some encouraging results in both pig and rat studies. Gunnarsson and associates[93] found that in a study of 18 pigs subjected to 140 ppm chlorine for 10 minutes of inhaled beclomethasone dipropionate produced higher PaO_2 and ventilation-perfusion ratios, with less histologic damage, than the control group. In another study, Wang and colleagues[94] exposed 24 pigs to a higher concentration of 400 ppm for 10 minutes and found that the inhaled steroid budesonide 0.1 mg/kg given within 30 minutes of exposure was associated with more favorable cardiorespiratory symptoms and lower wet lung weights at autopsy. Demnati and co-workers[95] studied the effects of dexamethasone in rats exposed to a high concentration of chlorine (1500 ppm for 5 minutes). They found that the dexamethasone group had significantly reduced pulmonary airway resistance and methacholine-induced bronchoconstriction than the controls. However, species differences in challenges to chemical warfare agents dictate caution when applied to humans. In a clinical area in which few therapeutic options are available, the results provide encouragement for further research and for clinical intervention if the need arises. Borak and Diller[96] reviewed the available evidence for treatment regimens in human phosgene exposure.

Role of Cyclic Adenosine Monophosphate Diesterase Inhibitors. Kennedy and colleagues[97] suggested that aminophylline may protect against phosgene-induced phosgene exposure as a result of its ability to increase cyclic adenosine monophosphate levels. Other compounds, including β-adrenergic agonists, also have this effect and may indicate a new therapeutic direction.

Phosgene and Glutathione Modification. Another promising therapeutic approach is provided by compounds that can increase intracellular reduced glutathione levels as a means of preventing lipid peroxidation–induced phosgene exposure. The rationale behind this approach is that phosgene reacts with cellular SH groups, reduces reduced glutathione redox state, and increases arachidonic acid mediator production and lipid peroxidation. Sciuto and co-workers[98] studied the effects of *N*-acetylcysteine on anesthetized rabbits exposed to 1500 ppm phosgene. The *N*-acetylcysteine–treated group had smaller increases in pulmonary wet weight, lower leukotriene levels, and higher glutathione levels. This work suggests that *N*-acetylcysteine may protect against phosgene exposure by maintaining reduced glutathione levels and inhibiting production of inflammatory leukotrienes.

CELLULAR TOXIC AGENTS (BLOOD AGENTS): HYDROGEN CYANIDE

Hydrogen cyanide (HCN) is one of several agents known originally as *blood agents,* although the term is a misnomer because the agent acts at the cellular mitochondrial level.[99] HCN is a highly volatile liquid used widely in industry and potentially available to terrorists. It has been used since World War I as a chemical warfare agent. Its very short persistence means that decontamination is usually not required after release. It is not absorbed by the activated charcoal of level C respirators (see the section on Involvement of the Anesthesia Provider in the Management of Casualties From Exposure to Chemical and Biologic Warfare Agents), but is removed by impregnating the charcoal with silver salts, with which HCN reacts. HCN in high concentrations is rapidly fatal. The LCt_{50} has been estimated at 200 mg/m^{-3} for 10 minutes. HCN acts by binding to the iron atom in cytochrome oxidase enzymes inhibiting the catalytic function that allows O_2 to act as an electron receptor and produce adenosine triphosphate. Because of this mitochondrial uncoupling, the resulting lactic acidosis theoretically cannot be reversed by restoring oxygenation of the blood by resuscitation measures to improve tissue oxygenation.

Signs and Symptoms

After exposure in humans, the first sign is hyperventilation, which has the effect of increasing the absorbed dose. This is followed by dizziness, rapid loss of consciousness, and seizures, followed by respiratory arrest. At levels that are not fatal, patients report a smell of almonds, a feeling of apprehension, and a metallic taste in the mouth; dyspnea also may occur. Because of the rapid action of HCN, patients with acute intoxication are unlikely to be encountered in hospital. Long-term management of the consequences of HCN poisoning is unlikely, although survivors of near fatal doses can suffer long-term effects, such as intellectual deterioration, mental confusion, and parkinsonism.

Treatment

In the body, HCN is broken down by rhodanese, which detoxifies cyanide to thiocyanate.[100,101] This process can be accelerated by provision of sodium thiosulfate, which provides a store of sulfane sulfur for the enzyme.[102] The usual dose of sodium thiosufate is 50 mL of 25% solution (pediatric dose 1.65 mL/kg of 50% solution). It is usually administered in conjunction with sodium nitrite (300 mg given intravenously over 10 minutes [pediatric dose 0.15 to 0.33 mL/kg of a 3% solution]), which causes the formation of methemoglobin. This acts as a scavenger for HCN and reduces its plasma levels. Sympathomimetic support may be required for hypotension produced by sodium nitrite. HCN also reacts with heavy metals, and this is the basis of the use of dicobalt edetate and hydroxycobalamin as cobalt providers for this reaction. Cobalt ions themselves are toxic, but the toxicity can be countered by giving glucose, which is part of standard therapy. Dicobalt edetate is thought to be more effective in the binding of cyanide ions than methemoglobin despite its secondary effects of hypertension and nausea. It has long been thought that O_2 therapy and ventilation have no role in the treatment of cyanide intoxication because the blood is fully oxygenated in this condition. However, this view has recently been challenged because some studies have shown that O_2 enhances the antidotal effects of the classical cyanide antidotes.[103] Table 83B-3 details current antidote treatment approaches.

TOXINS

Toxins are high molecular weight compounds that are in the middle of the CBW spectrum.[47] They do not reproduce and have characteristics of chemical warfare agents, although they have been considered with biologic agents by international convention. They are produced naturally by bacteria and by organisms ranging from protozoans up to reptiles such as snakes and scorpions.[104] Toxins are hazardous to humans from natural and deliberate exposure, and this has fueled much research into their actions and treatment.[105] Scientifically, they are of considerable interest and are used as research tools to probe natural processes such as nerve conduction and neuromuscular transmission. In the context of toxic warfare, toxins have often been cited as *doomsday weapons,* and considerable public fear exists about their actions. More than 500 toxins have been described, but only a few are suitable for battlefield and terrorist attack because of difficulties in production and their lack of stability in a released aerosol. The characteristics of some common toxins are shown in Table 83B-4.

In the chemical warfare context, the anesthesia provider may encounter toxins as either short latency (neurotoxins, such as botulinum toxin), requiring immediate life support and treatment, or long latency (the DNA toxins, such as ricin), which cause major organ dysfunction and present intensive care problems.

Botulinum Toxin

Botulinum toxin is produced by the anerobe *Clostridium botulinum* and has the reputation of being the most toxic substance by weight, being at least 5000 times more toxic than sarin.[106] Botulism, the natural occurrence of the toxin in food poisoning, is a disease of both humans and animals. Seven different functionally related neurotoxins (A through G) are produced by the parent organism. Botulism is essentially an intoxication, brought on by ingestion of the toxin produced by clostridrial infection of food, usually incorrectly canned meats. Primary botulism, a direct infection, is rare and affects only infants in the human species. The interest of botulinum toxin as a toxic agent is that it can be relatively easily produced by fermentation processes (which have been developed to produce antitoxins) and that it is stable as an aerosol, making mass delivery a theoretic possibility. Calculations that 1 kg of the toxin would be sufficient to destroy every human on the planet have rested on this fact. However, botulinum intoxication can be treated, and this modifies the toxicity considerably. It is estimated that less than 10% of natural cases receiving ventilatory and antitoxin support are fatal. A consensus document examines the risks to civilian populations exposed to botulinum toxin.[107]

Botulinum toxin acts at the nerve terminal of cholinergic synapses and blocks the release of acetylcholine by being taken up into the vesicles and translocated to the

TABLE 83B-3 **ANTIDOTES USED IN THE TREATMENT OF CYANIDE POISONING**

Antidote	Action	Route	Dose	Concurrent Drugs	Duration of Administration	Possible Side Effects
Oxygen	Increases arterial O_2 content, potentiates activity of other antidotes	Inhalation via mask or ETT	High flow via mask or 100% via ETT	O_2 used as primary antidote in all cases	≤24 hr	Unlikely—possible in patients with COPD
Amyl nitrite	Methemoglobin formation	Inhalation	Adult: 0.2 mL Pediatric: 0.2 mL; may need repeating	O_2 (not simultaneously)	30 sec/min	Difficult to achieve effective antidotal levels without cardiovascular collapse
Sodium nitrite	Methemoglobin formation	Intravenous injection	Adult: 300 mg (10 mL of 30 mg/mL 3%) Pediatric: 0.13-0.33 mL/kg of 30 mg/mL (3%) solution (i.e., 4-10 mg/kg body weight)	Adult: Sodium thiosulfate 25 mL of 500 mg/mL, (50%) solution and O_2 Pediatric: Sodium thiosulfate 1.65 mL/kg body weight of 250 mg/mL (25%) solution (~400 mg/kg body weight) and O_2	≥5 min, ≤20 min	Methemoglobinemia, vasodilation, and cardiovascular collapse
Dicobalt edetate	Binding of cyanide ions by dicobalt edetate and by free cyanide ions	Intravenous injection	Adult: 300 mg (20 mL of 15 mg/mL) (15%) Pediatric: 4-7.5 mg/kg (0.3-0.5 mL/kg of 15 mg/mL (15%)	50 mL dextrose (500 g/L) intravenously immediately after each dose and O_2	1 min	Urticaria, edema of face and neck, chest pains, dyspnea, hypotension, seizures
4-DMAP	Methemoglobin formation	Intravenous injection	Adult: 3.25 mg/kg Pediatric: 3.25 mg/kg	O_2 and sodium thiosulfate	1 min	Methemoglobinemia, vasodilation, and cardiovascular collapse; hemolysis; elevated bilirubin and iron (this is unlikely to be relevant to single-dose exposure)
Hydroxycobalamin	Binds cyanide ions	Intravenous injection	Adult: 5-10 g Pediatric: 70 mg/kg	5 g reconstituted in 100 mL 0.9% saline; O_2	20 min	Reddish discoloration to skin and mucous membranes
Sodium thiosulfate	Sulfur donor for endogenous enzymatic conversion of cyanide to thiocyanate	Intravenous injection	Adult: Sodium thiosulfate 25 mL of 500 mg/mL (50%) solution and O_2 Pediatric: Sodium thiosulfate 1.65 mL/kg body weight of 250 mg/mL (25%) solution (~400 mg/kg body weight) and O_2	O_2 and sodium nitrite *or* O_2 and DMAP	10 min	Excess administration may cause hypernatremia

COPD, Chronic obstructive pulmonary disease; *ETT,* endotracheal tube.

TABLE 83B-4 **CHARACTERISTICS OF COMMON TOXINS**

Source	Toxin	Action
Bacteria		
Bacillus anthracis	Anthrax toxin	DNA toxin
Staphylococcus aureus	Staphylococcal enterotoxin B	Enterotoxin
Vibrio cholerae	Cholera toxin	Enterotoxin
Clostridium botulinum	Botulinum toxins	Prejunctional decrease in acetylcholine release
Clostridium perfringens	Perfringens toxin	Necrosis through phospholipase C
Clostridium tetani	Tetanus toxin	Neurotoxin increase in excitability of motor neurons
Protozoa		
Gonyaulax catenella	Saxitoxin	Depolarization block
Fungi		
Fusarium spp.	Tricothecenes	DNA toxin; hemorrhagic syndrome
Plants		
Ricinus communis (castor bean)	Ricin	DNA toxin; hepatorenal Na^+ channel blockade failure
Amphibia		
Colombian frog	Batrachotoxin	Irreversible; Na^+ channel blockade
Reptilia		
Asian cobra *(Naja naja oxiana)*	Cobra toxin	Postsynaptic neurotoxin via phospholipase A_2
Taiwan banded krait *(Bungarus multicinctus)*	α-Bungarotoxin	Acetylcholine receptor blocker
Fish		
Deadly pufferfish	Tetrodotoxin	Na^+ channel blockade

Modified from Baker DJ: Anesthesia in extreme environmental conditions. Part 2. Chemical and biologic warfare. In Grande CG, editor: Textbook of trauma anesthesia and critical care, *St Louis, Mosby–Year Book, 1993, pp 1320-1354.)*

cytoplasm, where it catalyzes the proteolysis of components involved in the calcium-mediated exocytosis of acetylcholine. The inhibition is permanent, and recovery occurs only after the creation of new terminal boutons. The toxin thus blocks neurotransmission, parasympathetic synapses, and peripheral ganglia. The signs and symptoms of botulism can be explained on this basis.

Conventionally, after ingestion of the toxin (the usual route), a latent period of several hours occurs, after which the parasympathetic action produces a dry mouth, followed by signs of a progressive bulbar palsy (dysarthria, dysphasia, and dysphagia) and ocular signs (diplopia and ptosis). These signs are followed by a progressive symmetric descending muscular weakness, leading to respiratory failure requiring prolonged ventilatory support. Neuromuscular testing shows a classic presynaptic decremental pattern to repeated stimuli with posttetanic facilitation. Single-fiber electromyography detects the neuromuscular changes before conventional nerve stimulation; increased jitter and blocking occur, which are reduced by increasing the nerve firing rate.[108] The pattern of signs and symptoms after a deliberate mass inhalation release is not known, but botulinum toxin must be considered along with the nerve agents in any cases manifesting with sudden disturbances of cholinergic transmission.

Conventional level C protection (see section on Personal Protection) and decontamination procedures are effective against the toxin, and several antisera agents are available. A heptavalent antitoxin exists for all the serotypes, but the human efficacy is not known with certainty.[107] Established cases require supportive treatment with antitoxin and positive-pressure ventilation. The latter may be required for some time.

Saxitoxin

Saxitoxin has been suggested as a possible terrorist toxic agent, but no record exists of its production or use in a military context. In nature, it is produced by dinoflagellate sea organisms (causing the "red tide") including *Alexandrium tamarense, Gymnodinium catenatum,* and *Pyridinium bahamense*. The toxin is concentrated in shellfish and is the cause of paralytic shellfish poisoning.[104] The toxin is approximately 20 times more toxic than sarin, having an LD_{50} in mice of 8 μ/kg. Saxitoxin is active by the inhalation route and causes bulbar palsy, respiratory failure, and cardiovascular failure. The toxin acts by blocking voltage-gated sodium channels.[109] Treatment is based on ventilatory and organ support. An antitoxin has been developed in guinea pigs.[110]

Ricin

Ricin is considered a serious terrorist threat because it can be extracted relatively easily from the seeds of the castor bean plant, *Ricinis communus*. Waste from the production of castor oil contains approximately 5% ricin, making it a potential source for terrorists. Ricin has been used in assassinations,[42] and high inhaled concentrations are thought to be fatal. A substantial latent period occurs before generalized signs and symptoms of the inhibition of protein synthesis, which include fever, abdominal pain, diarrhea, weakness, drowsiness, confusion, seizures, coma, cardiovascular collapse, and respiratory failure, all progressing to multiple organ failure and death within 36 to 72 hours. Ricin poses a considerable ICU problem. Treatment is supportive, but an antitoxin has been developed for use in animals.[111,112]

PHARMACOLOGIC AGENTS AND AGENTS OF BIOLOGIC ORIGIN

The events in the Moscow theater siege in 2002[113] highlighted the possible use of substances that were originally developed as anesthetic agents or adjuncts used as "knock down" weapons. In the siege, a substance was released into the air-conditioning system by special forces entering the theater, which led to the deaths from respiratory failure of 127 of 800 of the hostages. The event emphasized the need for immediate life support after toxic attack with short-latency agents. The Russian government, after challenge, declared that the agent used was "fentanyl." Many fentanyl agents have been synthesized

apart from those familiar in clinical practice and some are too toxic for general use. Another possibility is the use of a short-chain neuropeptide. Considerable research effect went into investigating such compounds during the last days of the USSR.[44] Agents such as 3-quinuclidinyl benzylate (BZ or agent-15) (also initially considered as a possible cause of the theater casualties) have been used for many years and are centrally acting anticholinergic agents. Phencyclidine compounds (related to ketamine) and other hallucinogens were tested during the early days of chemical warfare research during the Cold War and should be considered as part of the differential diagnosis of patients presenting with central nervous system symptoms after a possible toxic attack.

CLASSIC BIOLOGIC WARFARE AGENTS

General Considerations

Although many organisms have been suggested as being capable of use as biologic warfare agents, only a few have been studied to the point of being a threat rather than a hazard.[42] Management of deliberate epidemics is the role of specialist physicians, and anesthesia providers are likely to encounter only agents that have serious pulmonary effects and are likely to require ICU care. Many analogies from normal epidemic outbreaks are relevant to deliberate biologic warfare attacks, particularly by terrorists. The severe acute respiratory syndrome (SARS) epidemic in 2004 was a valuable lesson about the spread of a new infectious pathogen in a world linked by fast air travel connections. Although previous slower forms of travel allowed the incubation of symptoms before arrival at the destination, air travel does not, and patients may be asymptomatic at the time of their arrival. All hospital practitioners must now be aware of the possibility of transmission of infection from distant locations. Recent travel history should be an essential part of the initial patient interrogation process.

Anthrax

Bacillus anthracis, an aerobic gram-positive, spore-forming, rod-shaped organism, is one of the few listed "standard" biologic warfare agents that has been proved to be a hazard and a weaponized threat. The natural reservoir of the disease is spores in the soil, and it is these highly resilient spores than form the basis for its use as a biologic agent. During tests in World War II, a whole Scottish island was experimentally contaminated and remained in this condition for over 40 years.[42] Evidence for weaponization of the bacillus by several other countries has been presented. An accidental release from a military installation in the USSR in 1979 claimed more than 100 lives.[43] The Iraq War in 2003 was fought under the shadow of a possible anthrax attack, although no such weapons were found. Although the standard biologic warfare release is by aerosolization of the spores, the agent was distributed in the United States by mail as a powder in 2001 and claimed several lives, demonstrating its terrorist use.

Anthrax exists in cutaneous, gastrointestinal, and pulmonary forms, but the pulmonary form is the major concern of the anesthesia provider and intensivist. In its natural state, pulmonary anthrax is rare, but deliberate release of spores in an aerosol would make the presentation more common.

Physical Findings. The physical findings in pulmonary anthrax are nonspecific, but chest radiography may show signs of effusion or pulmonary edema and mediastinal widening. An immunoassay is available that can detect circulating toxin. The infective dose of anthrax when inhaled is 8000 to 15,000 spores. Spores between 2 and 5 μm reach the alveoli; spores greater than this size are trapped in the upper airways. After trapping, the spores are removed to the mediastinal and hilar lymph nodes by pulmonary macrophagocytes. After a germination period of 1 to 3 days, large amounts of anthrax toxin are released into the circulation, causing the clinical manifestations of the pulmonary form of the disease. An initial insidious phase lasting 1 to 4 days consists of general malaise, fatigue, myalgia, nonproductive cough, and fever. During the next phase of the pulmonary disease, a necrotizing hemorrhagic mediastinitis occurs causing chest discomfort, dyspnea, and stridor. In untreated cases, multiple organ failure follows, which is very refractory to treatment and causes death within 24 to 36 hours. In 50% of cases, hemorrhagic meningitis with coma occurs.

Pathogenesis. Considerable work has been done on the mechanism of the pathogenesis of anthrax infection and the effects of the toxin. This consists of three proteins with a central protective component binding the other two, known as the edema and lethal factors. After transfer to the cytoplasm edema factor, a calmodulin-dependent adenyl cyclase converts adenosine triphosphate to cyclic adenosine monophosphate,[114] which in turn causes tissue edema and suppression of the oxidative burst associated with polymorphonuclear phagocytosis.[115] Lethal factor is thought to be associated with macrophage expression of tumor necrosis factor and interleukin-1, cytokines that are a fundamental part of the systemic inflammatory response.

Treatment. Treatment of anthrax infection has classically been founded on the use of benzylpenicillin, but evidence of resistance has been reported. The current antibiotic recommendation is to use ciprofloxacin 400 mg every 8 hours, and this was widely used as prophylaxis during the 2001 anthrax attacks in the United States. Other approaches may be more appropriate, including doxycycline 200 mg intravenously followed by 100 mg intravenously every 8 hours, gentamycin, erythromycin, or chloramphenicol (Table 83B-5).

The recommended antibiotic prophylaxis is ciprofloxacin 500 mg every 12 hours or doxycycline 100 mg every 12 hours orally. This should be started as soon as possible after exposure.[116] Vaccines have been studied, and the standard Michigan vaccine should be given at 0, 2, and 4 weeks and then at 6, 12, and 18 months, followed by annual boosters. If vaccines are unavailable, antibiotic prophylaxis should be continued for 60 days. For anesthesia providers, intensivists, and other staff working on the longer term care of patients with anthrax, prophylaxis is important, together with careful filter protection of ventilation and disinfection. Wherever possible, disposable circuits should be used.

TABLE 83B-5 TREATMENT FOR PATIENTS EXPOSED TO BIOLOGIC WARFARE AGENTS

Agent	Infective Dose	Incubation Period	Effects (After Inhalation)	Staff Protection	Specific Treatment	Chemoprophylaxis	Vaccine	Mortality if Untreated
Bacillus anthracis	8000-15,000 spores	1-5 days	Mediastinitis, meningitis, MOF	Isolation, vaccination, universal precautions	Ciprofloxacin 400 mg IV tid; doxycycline 200 mg IV once, then 100 mg IV tid; penicillin 2 million units IV 2 hourly plus streptomycin 30 mg/kg IM daily	Ciprofloxacin 500 mg PO bid × 4 wk + vaccinate; doxycycline 100 mg PO bid × 4 wk + vaccinate	Michigan at 0, 2, 4 wk, 6, 12, 18 mo, then annually	Pneumonic, 100%
Yersinia pestis	100-500 organisms	2-3 days	Pneumonia, septicemia, MOF	Isolation, universal precautions	Streptomycin 30 mg/kg IM daily × 10 days; doxycycline 200 mg IV, then 100 mg IV tid × 14 days (chloramphenicol)	Doxycycline 100 mg PO bid × 7 days; tetracycline 500 mg PO daily × 7 days	Greer at 1-3 mo plus 3-6 mo	Pneumonic, 100%
Viral hemorrhagic fevers	1-10 organisms	4-21 days	Coagulopathy, edema, MOF	Isolation, HEPA masks, universal precautions	Ribavirin 30 mg/kg IV once, then 15 mg/kg IV daily × 4 days, then 7.5 mg/kg IV tid × 6 days (immunoglobulin)	NA	None	90% (Ebola-Zaire)
Viral encephalitides	10-100 organisms	2-6 days (VEE) 7-14 days (EEE/WEE)	Encephalitis, seizures, coma, CNS damage	Universal precautions	Supportive, anticonvulsants	NA	Available for VEE, EEE, and WEE	75% (EEE)
Francisella tularensis	10-50 organisms	2-10 days	Pneumonia, pleural effusions	Universal precautions	Streptomycin 30 mg/kg IV daily × 10-14 days; gentamicin 3-5 mg/kg IV od	Doxycycline 100 mg PO bid × 14 days	Live attenuated	35%
Variola organisms	10-100	7-10 days	Rash, secondary pneumonia	Isolation, universal precautions	Cidofovir 5 mg/kg IV once every 2 wk	Vaccinia immunoglobulin	Wyeth	Unvaccinated 30%, vaccinated 3%
Burkholderia mallei	1-10 organisms	10-14 days	Septicemia, pneumonia, lymphadenopathy	Universal precautions	Co-amoxiclav 20 mg/kg IV tid	Tetracycline 500 mg PO daily × 14 days	None	Uncertain: >30% if septicemic
Coxiella burnetii	1-10 organisms	10-14 days	Myalgia, malaise, fever	Barrier nursing	Doxycycline 100 mg PO bid × 5-7 days after exposure × 5 days	Doxycycline 100 mg PO bid for 8-12 days	Q vax	<1%
Brucella spp.	10-100 organisms	5-60 days	Malaise + cough, sacroiliitis, pancytopenia	Barrier nursing	Doxycycline 100 mg PO bid plus rifampicin 900 mg tid PO for 6 wk	Doxycycline and rifampicin for 3 wk	None	<5%
Escherichia	10-100 organisms	1-5 days	Vomiting and diarrhea, renal failure	Barrier nursing	Antibiotics not required	NA	None	<5% *E. coli* O157:H2

Modified from White SM: Chemical and biological weapons: Implications for anaesthetic and intensive care, Br J Anaesth *89:306-324, 2002.*

CNS, Central nervous system; *EEE,* eastern equine encephalitis; *HEPA,* high-efficiency particulate air filter; *IM,* intramuscularly; *IV,* intravenously; *MOF,* multiple organ failure; *NA,* not applicable; *PO,* orally; *VEE,* Venezuelan equine encephalitis; *WEE,* western equine encephalitis.

Plague

Plague was the scourge of the medieval world, and natural outbreaks continued well into the twentieth century. Plague has long been considered a potential biologic warfare agent and was researched extensively by the USSR.[44] The pulmonary form is very serious and requires ICU support. The causative organism, *Y. pestis,* is an anaerobic, gram-negative coccobacillus transmitted to humans by fleas carried by rodents or by animal-human or human-human droplet infection.[117,118] Bubonic, pneumonic, and septicemic forms of plague exist; the latter two are fatal without treatment. Only approximately 100 to 5000 organisms constitute an infective dose. The incubation period is 2 to 3 days, after which a pneumonia develops with malaise, high fever, myalgia, hemoptysis, and finally septicemia. There is dyspnea, stridor, and cyanosis. With the worsening condition, intermittent positive-pressure ventilation is required with aggressive antibiotic treatment. Confirmation of the diagnosis comes from the causative organism in blood, lymph nodes, or sputum cultures. An enzyme-linked immunosorbent assay is available. Pneumonic plague has long been recognized as being fatal, but antibiotic treatment reduces the mortality to at least 60%. The first line of treatment is streptomycin 30 mg/kg every 12 hours for 10 days. Alternatives are gentamycin or chloramphenicol. An inactivated vaccine (Greer vaccine) is available, but its effectiveness is not thought to be high.

Cholera

Cholera is a widespread natural infection originating from the Far East, which caused several epidemics in Europe throughout the nineteenth century. Although cholera is in the domain of the specialized physician, the profound fluid imbalances caused by the disease make admission of patients to the ICU likely in severe cases. Cholera has been suspected of being weaponized, but it can be spread effectively only by causing mass poisoning through the water supply. Outbreaks occurring in China during World War II were thought to be caused in this way.[42]

Pathogenesis. The infection is localized to the small bowel and causes a major outpouring of fluid and electrolytes. Paradoxically, fluid can still be absorbed, and this is the basis of the use of oral rehydration solutions in mass outbreaks in developing countries.

Treatment. The management of cholera is essentially fluid and electrolyte replacement. Traditionally, the intravenous route was used, but modern practice is to use oral rehydration solutions containing electrolytes and glucose,[119] Early rehydration in this way avoids the need for admission to the ICU. In the case of a deliberate cholera epidemic, early rehydration would be a high priority for treatment of mass casualties. Tetracyclines have traditionally been the antibiotic treatment of choice but resistance has been reported.[119]

Glanders

Glanders is an equine disease caused by the gram-negative bacillus *Burkholderia mallei*. It has long been considered a potential biologic warfare agent in a modified form because the organism is known to be highly infectious in the aerosolized form. Acute and chronic forms occur in humans.[120] The septicemic form appears 10 to 14 days after exposure, making the agent one of long latency. It is characterized by a sudden onset of high fever, rigors, and myalgia, with cervical lymphadenopathy, splenomegaly, leukopenia, or leukocytosis. In this form, septic shock and multiple organ failure occur, and the fatality rate without treatment is high. After inhalation of the organism, the acute pulmonary form is seen, with septicemia, bilateral pneumonia, and pulmonary nodular necrosis. The chest radiograph shows miliary shadowing. The severe acute forms of the disease are most likely to concern intensivists, but an oropharyngeal form also occurs with ulceration of the septum and turbinate and a blood-stained mucopurulent discharge and macropapular or pustular rash similar to smallpox. In the chronic form, glanders can produce chronic lymphadenopathy, multiple musculocutaneous abscess formation, and oropharyngeal nodules. The first-line treatment of glanders is an antibiotic combination (co-amoxiclav and sulfadiazine 30 mg/kg^{-1} every 8 hours for 3 weeks). Doxycycline, rifampicin, and ciprofloxacin are second-line drugs. No vaccine against glanders exists.

Viral Diseases Regarded as Potential Biologic Warfare Hazards

A number of viral illnesses are considered to be potential biologic warfare agents. They are the province of the specialized infectious disease physician, and the anesthesia provider is referred to the specialized texts for a broader discussion.

Smallpox. Of the potential biologic warfare viral disease agents, smallpox is placed high on the potential terrorist hazard list because of the continuing presence of laboratory stocks of virus, which is normally promulgated only through human hosts. The success of the worldwide vaccination campaign led the WHO to declare smallpox an extinct disease, and mass vaccination programs were stopped. However, laboratory studies continued, and there is a fear at present that strains could be stolen and used to create a deliberate widespread epidemic in a largely unprotected population. Intensive care may be required for cases contracting overwhelming secondary infection. Although treatment is based on isolation and supportive therapy, there is current interest in the use of the antivirals cidofovir and ribavirin.[121]

INVOLVEMENT OF THE ANESTHESIA PROVIDER IN THE MANAGEMENT OF CASUALTIES FROM EXPOSURE TO CHEMICAL AND BIOLOGIC WARFARE AGENTS

APPROACHES TO MANAGEMENT OF CHEMICAL AND BIOLOGIC WARFARE INCIDENTS

Anesthesia providers may be confronted with the management of victims from the deliberate or accidental release of CBW hazards inside and outside the hospital.

A system of management of such cases is essential that provides for the safety of the medical responders and the correct treatment for the patient. Management should be considered in terms of (1) management of the incident and (2) management of the patient's condition. In terms of the four properties of agents in the CBW spectrum (see the section on Agents of Chemical and Biologic Warfare: Background and Development), management of the incident is determined by persistency and transmissibility, and management of the patient's condition by toxicity and latency.

Many chemical hazards have very limited persistency, and decontamination is not required. Limited persistency means reduced risk for contact transmission to other persons. However, certain chemical agents have long persistency and thus high transmissibility. Many such agents do not pose a significant threat by inhalation, but may be absorbed through the epithelia (e.g., nerve agent VX). For such agents, careful decontamination is essential.

Most classic biologic warfare agents have low persistency, being rapidly degraded by the environment, and depend on host transmission via an incubation period. In such cases, transmissibility is high. Anthrax is a notable exception; its spores have very long persistency, but no infective transmissibility. At the other extreme, the viral hemorrhagic fevers have very short persistency but high infective transmissibility.

MANAGEMENT OF THE INCIDENT

Disaster planning is a process familiar to many anesthesia providers and provides a good model of how to approach toxic releases. A toxic release is a special case of disaster and may be either accidental or deliberate. Plans put in place for a terrorist release of a CBW agent are equally valuable for the more likely case of accidental release. Moles[122] summarized the essential points of disaster planning as follows:

1. The importance of risk assessment: Not all listed hazards are identifiable risks
2. The essential stage of preplanning: Should bring together all the different emergency agencies, such as fire, civil defense, and police, who would be involved in CBW incident management
3. A phased response: Importance of, based on exercises and assessment

PERSONAL PROTECTION

Protection is a key feature of incident management, and anesthesia providers should be familiar with personal protection levels (Box 83B-5), protective suits and masks, and techniques of decontamination. As Box 83-7 shows, several levels of protection are used in the management of toxic releases, but the appropriate level for medical intervention is level C, which allows reasonable tactile dexterity and contact with the patient to provide essential life support and antidote therapy onsite.[49] Level C protection (Fig. 83B-8) is equivalent to that used by the military to provide protection against the most toxic chemical warfare agents and virulent biologic warfare organisms.

DETECTION AND IDENTIFICATION OF THE HAZARD

Unlike military CBW releases, civil incidents may not provide early information about the nature of the hazard (Box 83B-6). Patterns of signs and symptoms manifesting in victims may be the first indication of the nature of the causative agent. Detection and

BOX 83B-5 *Levels of Personal Protection in HAZMAT Incidents*

LEVEL A
Positive-pressure SCBA
Fully encapsulating chemical-resistant suit
Double layer of chemical-resistant gloves
Chemical-resistant boots
Airtight seal between suit and gloves and boots

LEVEL B
Positive-pressure SCBA
Chemical-resistant, long-sleeved suit
Double layer of chemical-resistant gloves
Chemical-resistant boots

LEVEL C
Full-face air-purification device (respirator)
Chemical-resistant suit
Chemical-resistant outer gloves
Chemical-resistant boots

LEVEL D
Equipment does not provide specific respiratory or skin protection and usually consists of regular work clothes

SCBA, Self-contained breathing apparatus.



Figure 83B-8. Civil (**A**) and military (**B**) level C protective respirators and suits. *(Courtesy Service d'Aide Médicale Urgente [SAMU] de Paris, France.)*

BOX 83B-6 ***Management of Chemical and Biologic Warfare Releases: Military and Civil Approaches***

Military: Toxic release is an anticipated event following intelligence. Military have analysis of hazards and threats.

- Tuned detection systems for specified hazards
- Use of generic detection systems
- Ordered responses
- Appreciation of the nature of the event by combat trained personnel

Civilian: Toxic agent release is (usually) an accidental event

- Natural epidemics
- Casualties may be the first indication of the nature of the incident
- No fixed detection systems
- Ability to respond without battlefield constraints
- Widespread HAZMAT system of hazard control
- Uncontrolled and usually ill-disciplined population



Figure 83B-9. Special triage, decontamination, and resuscitation center set up at a Parisian teaching hospital. *(Courtesy Service d'Aide Médicale Urgente [SAMU] de Paris, France.)*

monitoring devices for established military chemical warfare hazards exist but are not widely available in the civil context. Intelligence information may be available for terrorist attacks. In the case of accidental toxic agent release, information would be available from the HAZMAT system and the appropriate classification codes (see Box 83-3).

EARLY PATIENT MANAGEMENT AFTER CHEMICAL AND BIOLOGIC WARFARE RELEASE

If the released hazard is persistent and transmissible, decontamination is essential in the decontamination zone. In some countries, level C–protected medical staff or paramedics can now operate in this area and work alongside fire personnel in providing (1) triage, in terms of whether the patient requires decontamination and the patient's medical status; (2) immediate life support measures (TOXALS); and (3) immediate antidote and other pharmacologic support.

Figure 83B-9 shows a medically operated chemical warfare casualty reception facility in a Parisian hospital. Early life support measures in the decontamination zone are very important[123] (see also Chapter 107). The concept of TOXALS, introduced in 1996,[124] expands the familiar ABCs of life support to relate to toxic releases as follows:

- **A**irway (see also Chapter 55) of the casualty patient must be obviously maintained at all times. In the unconscious casualty, this may involve simple basic airway maneuvers plus suction of the copious secretions associated with chemical poisoning. Occasionally, advanced airway management, such as tracheal intubation, may be required to protect the airway from the excessive secretions and to prevent aspiration of regurgitated stomach contents.
- **B**reathing must be carefully observed until full decontamination and recovery have occurred. Supplemental O_2 will speed the recovery from volatile chemical poisoning. If breathing becomes compromised, artificial ventilation with supplemental O_2 must be administered using a self-inflating resuscitation bag-valve-mask or automatic ventilator. Entrained air must be filtered when ventilating casualties in a contaminated environment.
- **C**irculation must be carefully observed and monitored. Noninvasive blood pressure, pulse oximetry, and electrocardiogram monitoring are all useful indicators of circulatory function. The early establishment of intravenous access aids the administration of fluids and drugs.
- **D**isability (conscious level) should be assessed using the simple *AVPU* scale (**A**lert, responds to **V**oice, responds to **P**ain, **U**nresponsive). This assessment should be repeated at frequent intervals to assess the progress of the casualty.
- **D**rugs, especially the specific antidotes, should be administered when a specific agent has been identified.
- **E**xposure of the casualty is essential not only to assess physical damage, but also to remove all clothes that have been contaminated by the chemical. Approximately 80% of surface contamination is removed by undressing.
- **E**nvironment. The primary management as described may be severely limited by the need for the rescuer to wear protective clothing. Only those skilled in these techniques and trained in protective clothing should enter and treat casualties in a contaminated area. All others should await the casualties' arrival in the cold or clean zone after decontamination.

Identification of the chemical and its specific antidote might take some time. However, this must not delay the basic medical management of the casualty.

Somatic Systems Affected by Toxic Hazards

Early patient management is based on (1) identification information and (2) the manifesting signs and

symptoms. Usually information will be available to help with identification of the agent used. On the basis of manifesting signs and symptoms, it is useful to consider attacks on the various clinical systems as guide to the agent used (Table 83B-6). A wide range of chemical agents affect the respiratory system. These are summarized in Table 83B-7.

TABLE 83B-6 EFFECTS OF CHEMICAL AND BIOLOGIC WARFARE AGENTS ON SOMATIC SYSTEMS

System Affected	Agents
Epithelial	Vesicants (e.g., sulfur mustard), smallpox, ricin
Respiratory	
Upper, lower airway	Vesicants, phosgene
Respiratory control system	Nerve agents, ABO
Gaseous exchange	Pulmonary edemagens
Mechanics of breathing	Nerve agents, neurotoxins
Central nervous system	Nerve agents, cyanide, neuropeptides, agents of anesthetic origin (phencyclidines, BZ)
Peripheral nervous system	Nerve agents, neurotoxins (e.g., botulinum, saxitoxin)
Immune system	Vesicants, ABO (provocation of immune responses, inflammatory responses, organ failure)
Cardiovascular	Nerve agents, ABO
Alimentary, renal	Nerve agents, toxins, infectious agents

ABO, Agents of biologic origin; *BZ,* quinuclidinyl benzilate.

Problems in the Medical Management of Chemical and Biologic Warfare Incidents

Potential problems in managing CBW incidents include:

- Failure to recognize CBW release
- Failure to implement appropriate HAZMAT procedures to limit the number of secondary casualties
- Release of the agent overwhelming available emergency and medical resources
- Insufficient planning and training
- Lack of appropriate protective equipment
- Lack of resuscitation skills for early life support
- Lack of specific knowledge for the management of toxic or infectious hazards
- Panic and hysterical reactions from a frightened general public fueled by irresponsible reporting

These problems may be minimized by careful planning, equipping, and training, with the objective of making a CBW release manageable in the same sense as for other mass disasters.

EFFECTS OF CHEMICAL AND BIOLOGIC WARFARE AGENTS ON ANESTHETIC PRACTICE

MANAGEMENT OF MIXED TOXIC AND PHYSICAL INJURY

Chemical warfare and HAZMAT release may be accompanied by explosion and fire causing associated injuries requiring surgical intervention. The effects of the release

TABLE 83B-7 EFFECTS OF TOXIC AGENTS ON RESPIRATION

Respiratory Component	Effect	Toxic Agent
Central nervous system	Depression of respiratory drive and seizures leading to apnea	Nerve agents, cyanide, neuropeptides
Peripheral nervous system	Neuromuscular paralysis of respiratory muscles	Nerve agents, neurotoxins
Nasopharynx	May become blocked by excess secretions Prodromal rhinitis and rhinorrhea Sneezing	Lung-damaging agents, nerve agents Vesicants Early symptom of mustard agent
Larynx	Irritation, laryngeal spasm	Upper respiratory irritant, lung-damaging agents Riot-control agents, particularly CS and CR (tear gas)
Large airways	Blocked by secretions Blocked by inhaled vomitus Sloughing of walls of trachea and main bronchi, produces "pseudodiphtheritic" membrane, serious cause of large airway obstruction, leading to bronchopneumonia and death	Nerve agents (theoretic) Various agents Vesicant agents
Small airways	Blocked by secretions Cholinergic innervation affected; bronchospasm (relieved by atropine) Chemical bronchiolitis, followed by serious bronchospasm	 Nerve agents Vesicant agents
Alveoli	Toxic pulmonary edema	Various agents, especially lung-damaging agents (latency 6-24 hr) Vesicant agents, particularly if inhaled at high ambient temperature*

From Baker DJ, Rustick JM: Anesthesia for casualties of chemical warfare agents. In Zaitchuk R, Grande C, editors: U.S. Army textbook of military medicine. *Part IV, Vol I. U.S. Department of the Army, Office of the Surgeon General Borden Institute, Washington, DC, 1995, pp 833-856.*

CR, Dibenzoxazepine; *CS,* 2-chlorobenzalmalononitrile (tear gas).

*Data from Willems JL: Clinical management of mustard gas casualties, Ann Med Mil Belg 3(Suppl):1-61:47, 51, 1989.

BOX 83B-7 *Military and Civil Pulmonary Edemagens*

MILITARY

Chlorine
Phosgene
Perfluroisobutylene

CIVIL (INDUSTRIAL INTERMEDIATES CLASSIFIED BY HAZMAT)

Phosgene
Isocyanates
Phenols
Glycols and many others

agent on the subsequent conduct of general anesthesia are important. Many of the agents described earlier affect the condition of the patient and the action of anesthetic agents.

EFFECTS ON THE CONDITION OF THE PATIENT

Shock and toxic airway injury can produce ventilation-perfusion inequality, which affects preoxygenation for emergency induction of anesthesia (see also Chapter 55). The respiratory uptake of anesthetic vapors and alveolar ventilation itself are affected by degrees of shunt and pulmonary edema. Above all, the action of toxic agents may be expected to alter the balance and flow of general anesthesia and may cause delays in recovery, which would be labor-intensive in management. In terms of postoperative intensive care, patients who have been exposed to pulmonary edemagens and to OPs may pose the greatest problem (Box 83B-7).

Intensive Care Implications

Chemical warfare agent exposure may cause several syndromes that require medium-term or even long-term ICU treatment. These include pulmonary edema and ARDS. In the case of OP exposure, it is possible intermediate syndrome may develop,[125,126] with a reparalysis of the patient requiring several days of ventilation. Experience with OP anticholinesterases in this area is lacking, although considerable evidence has been reported from pesticide poisoning.

Many of the infectious agents considered biologic warfare agents can cause infections and even an overwhelming inflammatory response and organ dysfunction. Intensive care is required for cases of systemic inflammatory response syndrome and multiple organ dysfunction syndrome cases (see also Chapter 100). The continued possibility of an avian flu pandemic highlights the need to provide simple mass ventilation systems in high-dependency units. Many patients infected with biologic warfare agents can receive ventilation using simpler machines than those found in the ICU and that can be operated by non-ICU personnel. Mass procurement of devices and training is necessary. The ability of hospitals to provide intermittent positive-pressure ventilation for large numbers of casualties is a necessary step in managing not only epidemics of respiratory disease but also the consequences of a number of the CBW agents in which respiratory failure is the end stage of the pathologic condition.

Complete references available online at expertconsult.com

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Chapter 84

Anesthesia for Eye Surgery

MARC ALLAN FELDMAN

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Key Points

- Understanding ocular anatomy and physiology and the systemic effects of ophthalmic medications is essential to preparing an appropriate anesthesia plan.
- Pressure on the globe or any orbital contents can result in a trigeminovagal or oculocardiac reflex with bradycardia, atrioventricular block, or even asystole.
- The blood supply to the retina is governed by the ocular perfusion pressure, which is determined by the arterial blood pressure and the intraocular pressure (IOP).
- Sufficient concentrations of inhaled anesthetics decrease IOP, whereas ketamine and succinylcholine can increase IOP.
- Sudden increases in IOP in the setting of open globe injury can lead to vitreous loss and blindness.
- Complications of retrobulbar block include retrobulbar hemorrhage, increased IOP, intraarterial injection with convulsions, and subarachnoid injection via the optic nerve sheath with respiratory arrest.
- Nitrous oxide should be avoided for 15 minutes before the insertion of intraocular gas. Nitrous oxide must be avoided for 7 to 45 days after use, or until the gas bubble is resorbed.
- True ophthalmic emergencies, such as chemical burns and central retinal artery occlusions, must be treated within minutes to avoid permanent vision loss. Open globe injuries and other urgent procedures can be scheduled after appropriate NPO status.
- Eye compression from a facemask or positioning can lead to central retinal artery occlusion.

OCULAR ANATOMY

The eye is a sphere measuring approximately 24 mm in diameter. It sits in the pyramidal bony orbit. The wall of the globe has three layers: the sclera, the uveal tract, and the retina.

The sclera is the outermost layer. It is the tough, fibrous white of the eye. The transparent cornea is the anteriormost part of the sclera. Most of the focus power of the eye is from the curvature of the cornea.

The middle layer, the uveal tract, has three structures: the choroid, the iris, and the ciliary body. The choroid is a layer of blood vessels located posteriorly. Bleeding in this layer is one cause of intraoperative expulsive hemorrhage. The pigmented iris controls light entry with muscle fibers that change the size of the pupil. Sympathetic stimulation dilates the pupil by causing iris dilator muscles to contract, whereas parasympathetic stimulation causes miosis, or pupillary constriction, by causing the iris sphincter muscles to contract. The ciliary body lies just behind the iris; it produces aqueous humor. Ciliary muscle fibers adjust the focus by releasing tension on the suspensory fibers, or zonules, of the lens. Opacification of the lens causes a cataract. Uveitis is an inflammatory condition of these structures (iris, choroid, and ciliary body).

The innermost eye layer is the retina. Light stimulates retinal photoreceptors to produce neural signals that the optic nerve carries to the brain. There are no capillaries in the retina; the choroid layer provides the retina with oxygen. Retinal detachment from the choroid layer compromises the retinal blood supply and is a major cause of vision loss. The retinal layer ends approximately 4 mm behind the iris. The area between the limbus of the cornea and the retina is called the *pars plana*. Because there is no retinal layer there, it is a safe entrance site for vitrectomy procedures.

The center of the eye is filled with vitreous gel. This thick fluid has attachments to blood vessels and the optic nerve. Traction of the vitreous on the retina is a cause of

retinal detachment. Scarring, bleeding, or opacification of the vitreous is treated by vitrectomy.

The extraocular muscles move the globe within the orbit. They arise from a fibrous ring near the apex of the orbit and insert on the sclera. The six extraocular muscles lie within a cone behind the eye surrounding the optic nerve, ophthalmic artery and vein, and ciliary ganglion.

The eyelids have an outer layer of skin, a muscle layer, a tarsal plate of cartilage, and a layer of conjunctiva. The conjunctiva is a mucous membrane that lines the inner eyelids and covers the globe up to the corneal-scleral junction.

The lacrimal gland sits in the superior temporal orbit. It releases tears across the surface of the globe. Tears drain via the puncta near the medial canthus of the eyelids. Tears flow through the canaliculi to the lacrimal sac and duct, to drain into the nasopharynx.

The ophthalmic artery provides most of the blood supply to the orbital structures. It is a branch of the internal carotid artery, close to the circle of Willis. The superior and inferior ophthalmic veins drain directly into the cavernous sinus.

Cranial nerves (CN) innervate the ocular structures. The optic nerve (CN II) carries the neural signals from the retina. The oculomotor (CN III), trochlear (CN IV), and abducens (CN VI) control the extraocular muscles. Touch and pain sensation is carried via the trigeminal nerve (CN V). Sensation to the lower lid is via the maxillary nerve. Sensation to the upper lid is via the frontal branch of the ophthalmic nerve. The nasociliary branch of the ophthalmic nerve sends sensory fibers to the medial canthus, lacrimal sac, and ciliary ganglion.

The ciliary ganglion provides sensory innervation to the cornea, iris, and ciliary body. Parasympathetic fibers originate from the oculomotor nerve (CN III) and synapse in the ciliary ganglion before supplying the iris sphincter muscle. Sympathetic fibers originate from the carotid plexus and travel through the ciliary ganglion to innervate the dilator muscle of the iris. Local anesthetic blockade of the ciliary ganglion produces a fixed, mid-dilated pupil.

The facial nerve (CN VII) exits the base of the skull from the stylomastoid foramen. It supplies motor innervation to the orbicularis muscle via the zygomatic branch. Local anesthetic block of the facial nerve can prevent lid squeezing.

OCULOCARDIAC REFLEX

The oculocardiac reflex was first described by Aschner and Dagnini in 1908.[1,2] Traction on the extraocular muscles or pressure on the globe causes bradycardia, atrioventricular block, ventricular ectopy, or asystole. In particular, it is seen with traction on the medial rectus muscle, but it can occur with stimulation of any of the orbital contents, including the periosteum.

The reflex is trigeminovagal. The afferent limb is from orbital contents to ciliary ganglion to ophthalmic division of the trigeminal nerve to the sensory nucleus of the trigeminal near the fourth ventricle. The efferent limb is via the vagus nerve to the heart.[3]

The reflex may be seen more often with procedures under topical anesthesia. Retrobulbar block is not uniformly effective, however, at preventing the reflex. Orbital injections can trigger the response. The response is exacerbated by hypercapnia or hypoxemia.

In the event of arrhythmia, the anesthesiologist first should ask the surgeon to stop manipulations. The ventilatory status is assessed. If significant bradycardia persists or recurs, intravenous atropine is administered in 7-μg/kg increments. Rarely, severe bradycardia or asystole occurs. Although chest compressions might be required to allow the atropine to circulate, usually the heart rhythm returns to normal with cessation of manipulation alone. The response fatigues with repeated stimulation.

Pretreatment with intravenous atropine or glycopyrrolate can be effective. Pretreatment may be indicated in patients with a history of conduction block, vasovagal responses, or β-blocker therapy.

INTRAOCULAR PRESSURE

The blood supply to the retina and optic nerve depends on the intraocular perfusion pressure.[4] This perfusion pressure is defined as the difference between the mean arterial pressure and the intraocular pressure (IOP). High IOP impairs the blood supply, leading to a loss of optic nerve function. After an incision in the globe is made, factors that would increase IOP can cause prolapse and loss of intraocular contents; this can cause permanent vision loss.

The globe is a relatively noncompliant compartment. The volume of the internal structures is fixed except for aqueous fluid and choroidal blood volume. The quantity of these two factors regulates IOP.

Two thirds of the aqueous fluid is actively secreted by the ciliary body by a sodium-pump mechanism. One third comes from passive filtration through vessels on the iris. Aqueous fluid is produced at a rate of 2 μL/min. Aqueous fluid flows over the lens and through the pupil to bathe the inner corneal endothelium. It then enters the angle of the anterior chamber to flow through the trabecular meshwork to the canal of Schlemm. The canal of Schlemm is continuous with channels to the episcleral veins. IOP is primarily regulated by the resistance at the trabecular meshwork. Normal pressure is 10 to 20 mm Hg.

Impairment of aqueous drainage at any point can elevate the IOP. Sclerosis of the trabecular meshwork is believed to cause the chronic pressure elevation in open-angle glaucoma. Closed-angle glaucoma occurs when there is an obstruction to aqueous drainage from closure of the anterior chamber angle. This happens from peripheral iris swelling or anterior displacement. Patients with a preexisting narrow angle may be predisposed to this condition. The acute increase in pressure causes severe pain and is an ophthalmologic emergency.

Changes in choroidal blood volume can increase IOP rapidly. Hypercapnia causes choroidal congestion.[5] Coughing, straining, or vomiting can increase IOP to 30 to 40 mm Hg. Endotracheal intubation can cause similar increases. These increases are transient and are relatively innocuous in a closed eye. In an open eye, such

as after traumatic injury or during cataract surgery, these increases can lead to loss of intraocular contents, hemorrhage, and permanent vision loss.[6]

Extrinsic compression of the eye also increases the IOP. A normal blink increases the IOP by 10 mm Hg. A forceful lid squeeze can increase IOP to more than 50 mm Hg.[7] A poorly placed anesthesia mask can put enough pressure on the eye to reduce blood flow to zero.

Deep inhaled or intravenous (e.g., propofol) anesthesia causes a dose-related reduction in IOP by 30% to 40%.[8] Opioids have little effect. Usual doses of atropine do not cause a significant increase in IOP, even in patients with open-angle glaucoma. Ketamine can cause a modest increase in IOP.

Intravenous succinylcholine causes IOP to increase by 6 to 12 mm Hg[9]; this lasts for 5 to 10 minutes. The use of succinylcholine for induction of anesthesia in cases of open-globe injury with full stomach has been controversial. Loss of vitreous in patients from succinylcholine has not actually been reported.

OPHTHALMOLOGIC DRUGS

Ophthalmologic drugs are systemic medications. Eye drops can have systemic effects and important drug interactions with anesthetics. Acetazolamide is a carbonic anhydrase inhibitor and is used for the treatment of glaucoma to decrease chronically increased IOP. It also induces an alkaline diuresis that can result in potassium depletion. Patients taking acetazolamide should have electrolytes checked preoperatively. Atropine eye drops can cause tachycardia, dry skin, fever, and agitation.[10] Overdose can be treated with incremental doses of physostigmine.

Echothiophate is a topical anticholinesterase drug used to maintain miosis in the treatment of glaucoma. Systemic absorption leads to total body inhibition of plasma cholinesterase. Subsequent administration of succinylcholine can cause prolonged muscle paralysis (see Chapter 34).[11] Inhibition of the metabolism of ester-type local anesthetics may predispose a patient to local anesthetic toxicity. Echothiophate is a long-acting. A return toward normal enzyme activity can take 4 to 6 weeks after discontinuation of the drug.

Mannitol is an osmotic diuretic that causes a decrease in IOP lasting 5 to 6 hours. Patients who receive mannitol during surgery may need a urinary catheter to avoid overdistention of the bladder. Mannitol causes an increase in the circulating blood volume, which can lead to congestive heart failure in patients with poor ventricular function.

Phenylephrine is an α-adrenergic agonist applied topically to dilate the pupil. Systemic absorption of the 10% solution is associated with severe hypertensive reactions.[12] The 2.5% concentration is safer, but can exacerbate hypertension in some patients.

Pilocarpine and acetylcholine are cholinergic drugs used to constrict the pupil and can cause bradycardia and acute bronchospasm.

Timolol maleate is a topical β-blocker used for the treatment of glaucoma. Systemic absorption causes β-blockade, with possible bradycardia, bronchospasm, or exacerbation of congestive heart failure.[13] These concerns are especially important in patients with severe chronic obstructive pulmonary disease.

Tamsulosin hydrochloride (Flomax) has selective α-adrenoreceptor antagonistic properties and binds for a long period to nerves to the iris dilator muscle, affecting iris dilation and leading to complications in cataract surgery. The iris remains floppy even after a 7- to 28-day interruption of the tamsulosin regimen.[14]

PREOPERATIVE EVALUATION (see Chapter 38)

Eye surgery is the most common surgery in the elderly (see Chapter 80). In 2005, the Medicare program paid for nearly 3 million claims for cataract surgery. These outpatient procedures are quick and do not involve blood loss or significant postoperative pain. They are not minor procedures, however; ophthalmic surgery can be a major life event. Establishing a professional relationship reduces anxiety and helps the patient prepare for surgery. Giving information to the patient is just as important as getting information from the patient. An informed patient is more calm, comfortable, and cooperative. The patient needs to know what to expect.

Patients undergoing eye surgery can be a high-risk group. Adults tend to be older. Most patients have other risk factors, such as diabetes, hypertension, and atherosclerosis.[15] Cataracts are a marker for increased mortality in the Nurses' Health Study.[16] Yet, ophthalmic surgery is still low risk. Mortality after eye procedures is more infrequent than for the general surgical population. Backer and colleagues[17] found that eye surgery did not pose the risk of myocardial reinfarction seen with general surgical procedures. Patients' chronic diseases have less effect on outcome with these procedures. In a study of unanticipated hospital admissions after outpatient ophthalmic surgery, age and American Society of Anesthesiologists (ASA) physical status were not significant factors.[18]

There is controversy regarding the best preoperative management. Some clinicians say that because cataract extraction is a low-stress procedure with no blood loss, no preoperative evaluation is needed. Publication of a large, multicenter trial showed no effect of preoperative blood tests and electrocardiogram on postoperative outcome.[19] Another opinion is that every patient must receive a full evaluation to include every possible test, to detect every possible finding, to institute every possible therapy, and to delay as long as possible, so that the patient can be in the best possible condition and have the lowest possible risk. The appropriate approach is likely in between these two approaches. Appropriate preoperative medical consultation is important. A study of malpractice litigation in cataract surgery found that medical consultation accounted for 16% of the liability; this compared with 17% attributed to either local or general anesthesia.[20]

Risk cannot be ignored. Neither should we reduce every risk to the lowest conceivable minimum. The anesthesiologist's goal is to prepare the patient to present an acceptable risk at surgery. Acceptable risk is determined by the medical care team with the informed consent of

the patient. If a patient's condition would indicate inpatient admission for medical treatment, or if a reversible condition would likely lead to a perioperative complication, the risk is unacceptable.

The goal is to develop guidelines that would encourage consistency of care and minimize disruption to patients and the operating room. The following guidelines are presented after review of literature and published guidelines (see Chapters 38 and 80).

PATIENT HISTORY

Previous hospitalizations and surgical procedures are reviewed. Allergies and drug sensitivities are noted. Latex allergy should be addressed specifically. A current list of medications is obtained. Patient factors that could influence anesthetic management include dementia, deafness, language difficulty, restless legs syndrome, obstructive sleep apnea, tremors, dizziness, and claustrophobia. A preoperative patient questionnaire can be very helpful. A thorough review of the patient history helps with perioperative planning and establishing a physician-patient relationship.

PHYSICAL EXAMINATION

Check for signs of major cardiac or pulmonary conditions and problems. Particular attention should be paid to positioning issues, such as severe scoliosis or orthopnea (see Chapter 41).

LABORATORY STUDIES

No routine screening tests have been shown to improve outcome. Yet, laboratory studies should be determined based on the results of the history and physical examination. Generally, the tests that a patient needs before ophthalmic procedures are the same tests a patient would require at a routine examination if surgery were not planned. Tests are chosen when the results are likely to change management. Urgent medical management is obtained for results reaching critical limits. Indications for laboratory studies and critical results are as follows:

- *Electrocardiogram:* New chest pain, decreased exercise tolerance, palpitations, near-syncope, fatigue, or dyspnea; tachycardia, bradycardia, or irregular pulse on examination
  - *Critical results*: Signs of acute ischemia or injury, malignant arrhythmia, complete heart block, atrial fibrillation that is new, or heart rate more rapid than 100 beats/minute
- *Serum electrolytes*: History of severe vomiting or diarrhea, poor oral intake, changes in diuretic management, or arrhythmia
  - *Critical results*: Sodium less than 120 mEq/L or greater than 158 mEq/L; potassium less than 2.8 mEq/L or greater than 6.2 mEq/L
- *Urea nitrogen*: Signs or symptoms of renal decompensation
  - *Critical result*: Greater than 104 mg/dL
- *Serum glucose*: Polydipsia, polyuria, or weight loss
  - *Critical results*: Less than 46 mg/dL or greater than 480 mg/dL
- *Hematocrit/hemoglobin*: History of bleeding, poor oral intake, fatigue, decreased exercise tolerance, or tachycardia
  - *Critical results*: Hematocrit less than 18% or greater than 61%; hemoglobin less than 6.6 mg/dL or greater than 19.9 mg/dL

OPHTHALMIC EVALUATION

Visual acuity of both eyes should be noted. Patients with poor vision in the nonoperative eye face much greater potential functional loss. These patients have a higher anxiety level. If the patient is to be patched overnight, the physician should anticipate the increased need for postoperative assistance for a temporarily blind patient.

The axial length of the globe should be assessed. When ultrasound measurements are available, the axial length should be noted. If no ultrasound is available, a myopic patient likely has an increased axial length. If a posterior staphyloma is present, the risks of injection anesthesia may be dramatically increased. Preoperative glaucoma history, increased IOP, and increased axial length are important risk factors for suprachoroidal hemorrhage. The risk can be reduced with intense control of intraoperative heart rate and arterial blood pressure. Preoperative softening of the globe with a compression device also may decrease risk.

CARDIOVASCULAR EVALUATION

The American Heart Association and American College of Cardiology published guidelines for perioperative cardiovascular evaluation for noncardiac surgery.[21] Ophthalmic procedures, such as cataract extraction, are specifically identified as low-risk procedures. For these procedures, evaluation is focused on patients with major clinical predictors of risk. These major predictors and the evaluation of the patient are reviewed in Chapters 38 and 39.

HYPERTENSION

Hypertension is a common problem in ophthalmic patients. Severe hypertension can lead to perioperative complications (see Chapter 39). Degrees of hypertension have been defined. Stage 3 of severe hypertension is defined as a systolic blood pressure of 180 mm Hg or more or a diastolic blood pressure of 110 mm Hg or more. Elective procedures in patients with sustained stage 3 hypertension should be delayed until after 2 weeks of antihypertensive therapy.

PULMONARY CONSIDERATIONS

Ophthalmic procedures generally require that the patient lie flat comfortably and quietly. If the patient cannot lie flat, or if there is intractable cough, a perioperative complication is more likely. Preoperative risk reduction strategies include cessation of cigarette smoking, treatment of airflow obstruction with bronchodilators or steroids, and administration of antibiotics for respiratory infections.

Patients should be assessed for sleep apnea. Intravenous sedation is often contraindicated in these patients. For some patients, treatment with a mild stimulant such as caffeine can be helpful in keeping them awake and cooperative during a procedure.

ENDOCRINE CONSIDERATIONS (Also see Chapter 39)

Diabetes mellitus is common in patients undergoing ophthalmic surgery. An early morning start for surgery is desirable to lessen the disturbance to the patient's usual daily routine. Severe hyperglycemia and hypoglycemia should be avoided. A fasting blood glucose measurement should be checked preoperatively. Insulin therapy should be used, if needed, to maintain blood glucose at 150 to 250 mg/dL. The potential for autonomic neuropathy needs to be considered, especially when elevating the patient from the supine position.

Patients undergoing long-term steroid therapy generally do not require "stress-dose" steroid treatment for ophthalmic surgery. The patient should be given his or her normal steroid dose on the day of surgery. The physician should be alert to the occasional patient who might require additional glucocorticoid perioperatively. Unexpected hypotension, fatigue, and nausea may be signs of a patient who needs additional steroid.

ANTICOAGULATION

Many patients undergoing ophthalmic surgery take anticoagulants. Perioperative management of anticoagulants involves weighing the relative risks of thrombotic against possible hemorrhagic complications. Either of these results can be devastating to the patient. In a study of more than 19,000 cataract procedures, the incidence of hemorrhagic and thrombotic complications was infrequent.[22]

The risk of thrombotic complications depends on the following:

1. The indication for anticoagulation. Serious complications from arterial thromboembolic disease, such as atrial fibrillation or valvular heart disease, are much more common than complications from venous disease, such as deep vein thrombosis.
2. The risk factors for thromboembolism, especially if and when the patient had a previous episode of thromboembolism.

The risk of hemorrhagic complications depends on the following:

1. The degree of anticoagulation.
2. The hemorrhagic potential of the surgical procedure. Serious hemorrhagic complications are most probable in orbital and oculoplastic surgery; of intermediate probability in vitreoretinal, glaucoma, and corneal transplant surgery; and least likely in cataract surgery.

A consensus is developing that cataract surgery can be performed safely while maintaining patients receiving warfarin. For intermediate-risk procedures, such as some glaucoma surgeries, stopping warfarin intake for 4 days preoperatively is indicated. For high-risk cases for hemorrhage or thrombosis, conversion from warfarin to heparin may be required.

ANESTHETIC TECHNIQUES

REGIONAL TECHNIQUES

Eye surgery usually requires immobility (or akinesia) of the eye and profound anesthesia of the surgical site. Any discomfort during the procedure can be magnified by the patient's anxiety and fear of possible vision loss.[23] Various regional anesthetic techniques have been developed that satisfy the requirements of ophthalmologic surgery and are generally reliable and safe. Discomfort and anxiety are associated with many of these blocks, and so are rare but severe complications. Supplementation with intravenous sedation and continuous patient monitoring are frequently preferred.[24,25] Intravenous sedation also may be associated with an increased incidence of medical events.[26]

Regional anesthesia has several advantages over general anesthesia (see Chapters 57 and 89). The local block gives significant postoperative analgesia. Nausea and vomiting are infrequent. The patient can return to ambulation faster. Most patients meet recovery discharge criteria at the end of surgery, and can bypass a stay in the postanesthesia care unit.

An intravenous infusion is started. Arterial blood pressure, electrocardiogram, and oxygen saturation monitors are placed. Supplemental oxygen is administered with nasal prongs. A foam wedge is placed to keep the knees flexed to prevent lower back pain. An air blower is often placed with the outlet on the chest to eliminate carbon dioxide and oxygen buildup under the drapes and to prevent claustrophobia.

An intravenous administration of midazolam (0.5 to 1 mg), fentanyl (12.5 to 50 μg), and propofol (30 to 50 mg) provides excellent amnesia and sedation for the placement of the blocks. This author omits midazolam and fentanyl in patients with limited cognitive reserve resulting from stroke or mild dementia. For local anesthesia, we use a 1:1 ratio of bupivacaine 0.75% and lidocaine 2% without epinephrine.[27] Hyaluronidase is added to speed tissue penetration. Hyaluronidase can also be important in preventing anesthetic-related damage to the extraocular muscles.[28] A human recombinant brand (Hylenex) is commercially available.

FACIAL NERVE BLOCKS

A facial nerve block is performed when complete akinesis of the eyelids is desired.[29] Three methods for the eyelid block are as follows:

1. *Modified van Lint block:* The needle is placed 1 cm lateral to the orbital rim, and 2 to 4 mL of anesthetic is injected deep on the periosteum just lateral to the superolateral and inferolateral orbital rim. The disadvantages of this block include discomfort, proximity to the eye, and common postoperative ecchymoses.
2. *O'Brien block:* The mandibular condyle is palpated inferior to the posterior zygomatic process and anterior to

the tragus of the ear as the patient opens and closes the jaw. The needle is inserted perpendicular to the skin approximately 1 cm to the periosteum. As the needle is withdrawn, 3 mL of anesthetic is injected.

3. *Nadbath-Rehman block*: A 12-mm, 25-gauge needle is inserted perpendicular to the skin between the mastoid process and the posterior border of the mandible. The needle is advanced its full length, and after careful aspiration, 3 mL of anesthetic is injected as the needle is withdrawn. This blocks the entire trunk of the facial nerve. The patient should be told to expect a lower facial droop for several hours postoperatively. The major disadvantage to this block is the proximity of the injection to important structures, such as the carotid artery and the glossopharyngeal nerve.

RETROBULBAR BLOCK

The retrobulbar block provides excellent akinesia and anesthesia of the eye.[30] A 3-cm, 23- to 25-gauge blunt Atkinson needle is recommended to protect against ocular perforation. The needle is placed at the junction of the inferior and lateral walls of the orbit just above the inferior orbital rim.[31] The needle is advanced approximately 15 mm along the wall of the orbit until it is past the equator of the eye. The needle is turned superiorly to aim toward the superior orbit. The needle is advanced until it enters between the extraocular muscles; 2 to 3 mL of anesthetic solution is injected. Some intorsion on downgaze is expected because the superior oblique muscle is outside the muscle cone and may not be blocked.

Retrobulbar hemorrhage is the most common complication of this block; proptosis and subconjunctival ecchymosis also are seen. Monitoring of the IOP is mandatory. If the pressure becomes elevated, a lateral canthotomy is performed to decompress the orbit. Bleeding outside the muscle cone is seen as subconjunctival ecchymosis without proptosis. After some monitoring, if IOP does not increase, then the surgical procedure can be performed safely.

Intravascular injection can occur despite a negative aspiration test. The total dose of local anesthetic used is small, and even if the total dose is given intravenously, no systemic effects would be likely. Accidental intraarterial injection can give high brain levels via retrograde flow in the internal carotid artery. Central nervous system excitation and seizures can be seen, but are usually highly transient, as the local anesthetic redistributes out of the brain. Obtundation and respiratory arrest have been reported. These prolonged effects are thought to be due to injection into the optic nerve sheath, which is continuous with the subarachnoid space.

Optic nerve damage and ocular perforation with retinal detachment and vitreous hemorrhage also have been reported. Special care must be taken when injecting patients with high myopia. If the axial length of the globe is longer than 25 mm, the eye is larger, and the sclera is thinner, increasing the risk of ocular penetration. A different anesthesia technique may be advisable in such cases.

POSTERIOR PERIBULBAR BLOCK

To prevent retrobulbar hemorrhage, posterior peribulbar anesthesia has become more popular.[32] A blunt, 23-gauge, 7/8-inch Atkinson needle is placed at the junction of the middle and lateral thirds of the lower lid just above the inferior orbital rim; 1 mL of local anesthetic is put just below the orbital septum, 3 mL at the equator, and 2 mL posterior outside the muscle cone. If no bulging is noted at the superior nasal lid area, a second injection of 2 to 3 mL is administered inferonasally. Disadvantages of the technique include a longer onset time (9 to 12 minutes) and lower incidence of complete akinesia. Globe perforation from peribulbar injection has been reported.[33]

SUB-TENON BLOCK

To avoid the complications of sharp needles, a technique was developed using a blunt cannula under the fascia of Tenon.[34] Various lengths of cannulas have been used. Using topical anesthesia with sedation, a speculum is placed to retract the lids. A 2- to 3-mm spot of cautery can be made 5 mm from the limbus in the inferonasal or inferolateral quadrant. A 2-mm snip is made in the conjunctiva with blunt dissection through the fascia of Tenon. A blunt cannula is directed under fascia of Tenon posteriorly, but not beyond the equator of the globe, with injection of 1 to 3 mL of local anesthetic. A small degree of conjunctival edema is often seen. Analgesia is usually excellent.[35]

TOPICAL ANESTHESIA

Cataract surgery can be performed using topical anesthesia alone.[36] This technique arose with the increase in popularity of small incision surgery and phacoemulsification. Topical anesthesia avoids the potential complications associated with retrobulbar and peribulbar injections. In addition, patients have the most rapid visual rehabilitation, with improved vision almost immediately after the procedure. Disadvantages of the technique include the potential for eye movement during surgery, increased patient anxiety, and discomfort from the microscope light.[37] Tetracaine 0.5% and lidocaine 4% have been used successfully. Two drops of tetracaine are given initially. Approximately three more doses of tetracaine or lidocaine are applied every 5 minutes just before surgery.

Appropriate patient selection is crucial. A confident, calm, and cooperative patient usually does well. A nervous, hypersensitive patient may be a better candidate for another technique. Photophobic patients, those with small pupils, or the requirement of a large incision are other problems that may occur.

GENERAL ANESTHESIA

The choice of general versus regional anesthesia is made based on the duration of surgery, the relative risks and benefits of each technique for the patient, and patient preference. Neither technique has been shown to be safer.

In the past, regional anesthesia had an advantage of greatly reduced postoperative nausea and vomiting. With

the advent of shorter-acting general anesthetics and nonopioid analgesia, the incidence of nausea and vomiting has decreased dramatically. Droperidol has been used frequently as an antiemetic, although late postoperative anxiety can occur in some individuals. Ondansetron may be as effective with fewer side effects. A comparison of memory function in patients after general anesthesia or local anesthesia with sedation showed no advantage to either technique.[38]

The goals of general anesthesia include a smooth endotracheal intubation, stable IOP, avoidance of severe oculocardiac reflexes, a motionless field, and smooth emergence. These goals can be accomplished with inhaled volatile anesthesia, balanced opioid anesthesia, or intravenously administered anesthetics, with or without muscle relaxants. The laryngeal mask airway (LMA) can be used for ophthalmologic surgery and may be associated with less coughing on emergence. Because of the inaccessibility of the airway during the surgery, and the risk of laryngospasm or aspiration of gastric contents, LMA should be used only by anesthesia providers who are highly skilled with the technique. In some cases, the LMA may be more appropriate for extraocular surgery.

Nitrous oxide presents a special problem in some vitreoretinal procedures.[39] In the technique called *fluid-gas exchange,* the surgeon injects an intravitreal air bubble to tamponade the retina against the wall of the globe. Sulfur hexafluoride is a poorly soluble gas used to prolong the resorption of intravitreal air bubbles. Nitrous oxide diffuses and causes bubble expansion, with the potential for dangerous increases in IOP. Nitrous oxide should be shut off for 15 minutes before placing the sulfur hexafluoride bubble and should be avoided for 7 to 10 days thereafter.

This problem is potentially worse with a relatively newer drug, perfluoropropane (C3F8), because this drug can persist for weeks. In this case, nitrous oxide should be avoided for at least 1 month, or until the bubble is resorbed. If a patient presenting for nonophthalmic surgery has a history of a recent retinal procedure, it is critical to establish whether the patient has an intravitreal gas bubble before using nitrous oxide. Otherwise, blindness can result.

ANESTHESIA FOR PEDIATRIC OPHTHALMOLOGIC PROCEDURES

Anesthesia for pediatric eye surgery can be considered a subspecialty of its own (see also Chapter 93).[40] Small children may require examination under anesthesia. Intramuscular ketamine sometimes can be a good choice; it can be used when intravenous access may be problematic. Some ophthalmologists prefer ketamine because it does not reduce IOP as barbiturates, and deep levels of inhaled anesthetics do.

The most common eye surgery in children is for strabismus, or misalignment of the eyes. There is generally no severe postoperative pain, but nausea and vomiting are significant 50% to 80% of the time without treatment. Droperidol 5 to 75 μg/kg seems to decrease nausea and vomiting significantly without undue delay of discharge. Ondansetron has similar effects without sedation. If forced ductal testing is used to assess the muscle tightness, the surgeon should be notified if succinylcholine is used. Succinylcholine causes a tonic increase in eye muscle tone, which resolves in approximately 20 minutes.

Strabismus is a common condition, and most children are otherwise healthy. There is a more frequent incidence of strabismus in trisomy 21 or Down syndrome, cerebral palsy, and hydrocephalus. Malignant hyperthermia and myotonic dystrophy are associated with strabismus. Myotonic dystrophy also occurs in patients with ptosis and cataracts.

Cataracts can be seen in children with Pierre-Robin syndrome and phenylketonuria. Patients with Marfan syndrome have a frequent incidence of subluxation or dislocation of the lens. Aniridia, the congenital absence of the iris, is associated with Wilms tumor and hypertension. Congenital glaucoma also occurs with Sturge-Weber syndrome and with seizures and angiomas of the mouth and larynx. Pediatric ophthalmic conditions associated with congenital syndromes are summarized in Table 84-1.

OPHTHALMOLOGIC PROCEDURES

GENERAL PROCEDURES

Most general ophthalmologic procedures are performed with topical or local anesthetic injection techniques. Enucleation can be performed during regional anesthesia, but is usually performed during general anesthesia.

INCISION AND DRAINAGE OF CHALAZION

A chalazion is an eyelid mass that results from chronic inflammation of the meibomian gland. Surgical treatment is indicated when there is inadequate response to conservative methods.

TARSORRHAPHY

The partial or total suturing together of the eyelids is performed to protect the eye and to allow healing of ulcers or exposure problems.

TEMPORAL ARTERY BIOPSY

A biopsy of the temporal artery is performed to diagnose temporal arteritis.

ANTERIOR CHAMBER PARACENTESIS

A tap of the anterior chamber fluid is done for diagnostic testing or to reduce IOP quickly.

ENUCLEATION

Enucleation refers to the removal of the entire eyeball after the muscles and optic nerve have been cut. Indications for surgery are a blind painful eye and intraocular tumors.

CATARACT EXTRACTION

Cataracts are opacities of the crystalline lens of the eye. Cataract extraction is performed under topical or regional block. General anesthesia is rarely used.

TABLE 84-1 **OCULAR MANIFESTATIONS AND PEDIATRIC SYNDROMES**

Ocular Manifestation	Pediatric Syndrome	Ocular Manifestation	Pediatric Syndrome
Strabismus	Trisomy 21		Aniridia
	Cerebral palsy		Sturge-Weber syndrome
	Meningomyelocele		Neurofibromatosis
	Prematurity		Ehlers-Danlos syndrome
	Retinoblastoma		Homocystinuria
	Craniopharyngioma	Retinal hemorrhage	Acquired immunodeficiency syndrome (AIDS)
	Malignant hyperthermia		
	Myotonic dystrophy		Multiple myeloma
	Ehlers-Danlos syndrome	Vitreal hemorrhage	Sickle cell syndromes
Ptosis	Malignant hyperthermia	Orbital tumor	Multiple myeloma
	Myotonic dystrophy	Glioma of the optic nerve	Neurofibromatosis
Cataract	Trisomy 21		
	Myotonic dystrophy	Retinopathy	Diabetes mellitus
	Pierre-Robin syndrome		Hypertension
	Phenylketonuria	Ophthalmopathy	Juvenile diabetes
	Homocystinuria		Graves disease
	Lowe syndrome	Ocular muscle weakness	Myasthenia gravis
	Rubella	Ocular erosions	Stevens-Johnson syndrome (erythema multiforme)
	Sarcoidosis		
	Galactosemia	Conjunctivitis or iritis	Reiter syndrome
	Hypoparathyroidism		Infectious mononucleosis
	Diabetes mellitus		Rheumatoid arthritis
	Glucose-6-phosphate dehydrogenase deficiency	Keratoconjunctivitis sicca	Sjögren syndrome
			Sarcoidosis
Lens subluxation	Marfan syndrome		Systemic lupus erythematosus
	Homocystinuria	Uveitis	Ankylosing spondylitis
	Ehlers-Danlos syndrome		Juvenile arthritis
Glaucoma	Homocystinuria		Sarcoidosis
	Lowe syndrome	Optic neuritis	Multiple sclerosis
	Rubella		

Intracapsular Cataract Extraction

Intracapsular cataract extraction is the total removal of the opaque lens with the lens capsule. It can be done with a cryoprobe. Intracapsular cataract extraction is performed in selected cases of lens subluxation, dislocation, or a lens containing a foreign body.

Extracapsular Cataract Extraction

Extracapsular cataract extraction refers to the removal of the lens, while leaving the posterior lens capsule and zonules intact. A rim of the anterior capsule also is preserved; this provides an excellent location for an intraocular lens implant.

PHACOEMULSIFICATION

Phacoemulsification refers to the use of ultrasonic vibration of fragments of the lens with simultaneous irrigation and aspiration. This technique allows for very small incisions. New techniques are bringing the use of the femtosecond laser for the initial steps of creating corneal incisions, capsulotomy, and fragmenting the lens.[41] Because use of the laser requires patient cooperation and because supplemental oxygen is contraindicated, these parts of the procedure are generally done under local anesthesia.

GLAUCOMA PROCEDURES

Glaucoma is a general term for diseases of the eye characterized by an increase in IOP.

FILTRATION PROCEDURES

Trabeculectomy is a surgical excision of the trabecula to increase the drainage of aqueous humor. Baerveldt and Ahmed devices are glaucoma drainage implants that shunt aqueous fluid out of the eye to drain under the conjunctiva of the orbit.

PROCEDURES FOR THE CORNEA

Penetrating Keratoplasty

A corneal transplant is done to replace an optically poor, infected, or traumatized cornea. Control of IOP and avoidance of patient movement are especially important in these open-globe procedures.

Lamellar Keratoplasty

Instead of a full thickness corneal graft, a layer of the corneal donor is used.[42] A gas bubble can be used to hold the graft in place to adhere to the patient's cornea. In Figure 84-1, intraoperative ocular coherence tomography[43]

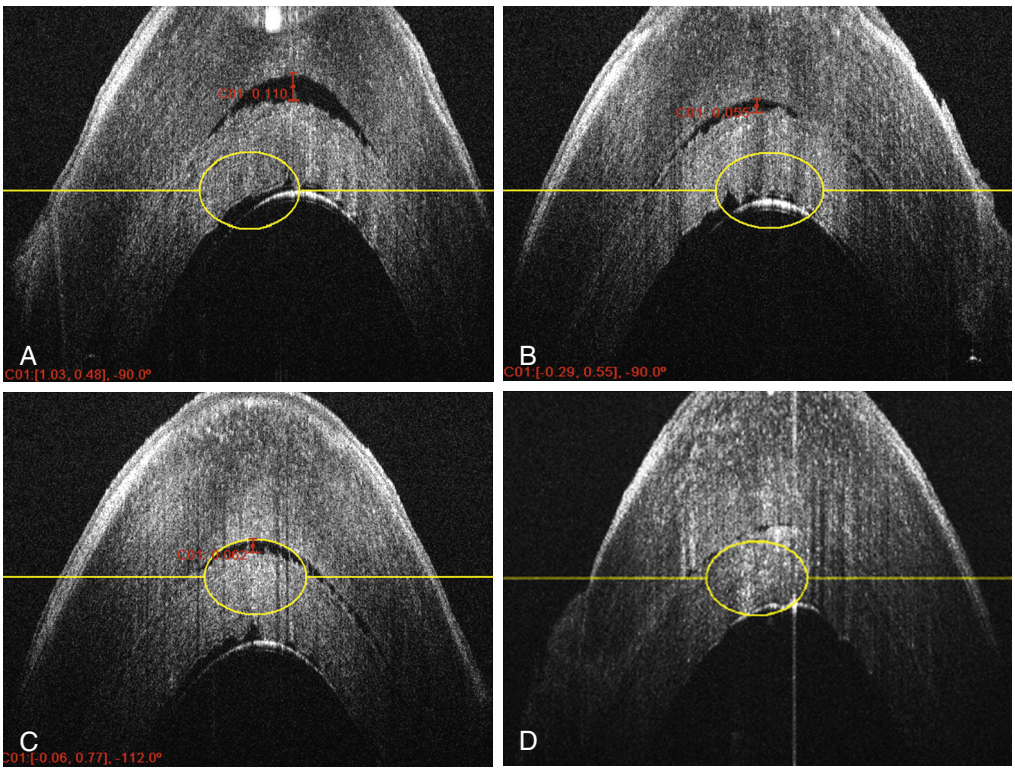


Figure 84-1. Intraoperative optical coherence tomography cross sections in a patient undergoing Descement stripping automated endothelial keratoplasty (DSAEK) immediately after delivery and unfolding of the donor graft (**A**). After elevation of the intraocular pressure, the size of the gap is decreased (**B, C**). After sweeping maneuver, there is no interface gap (**D**). *(Courtesy William J. Dupps.)*

shows how after placement of the corneal graft, the eye is pressurized to cause the graft to adhere.

Radial Keratotomy

A series of incisions is made in the cornea in a spikelike manner to change the shape of the cornea to correct myopia.

Pterygium Excision

A pterygium is an abnormal fold of membrane in the interpalpebral fissure. An excision is generally performed when the abnormal tissue impinges on the cornea, affecting vision, or for cosmetic improvement.

VITREORETINAL SURGERY

Retinal Cryotherapy

A cryoprobe is used for prophylaxis of certain retinal breaks and tears. This technique is used in some patients with retinal tumors and vascular malformations.

Repair of Retinal Detachment

Retinal reattachment involves localizing all tears and holes, creating chorioretinal adhesions, and scleral buckling with silicone belts around the globe to pull the sclera in to support the retina.

Vitrectomy

Vitrectomy is the surgical extraction of the contents of the vitreous chamber and their replacement with a physiologic solution. A posterior vitrectomy is indicated for the removal of foreign bodies, to repair retinal detachments, to remove membranes and media opacities, and to alleviate vitreous traction on the retina. These procedures may be prolonged. Many patients have diabetes or severe chronic hypertension, which can influence the conduct of anesthesia (see Chapter 39).

OCULOPLASTIC SURGERY

Most oculoplastic surgery is performed with local infiltration anesthesia. Some longer, more invasive procedures require general anesthesia.

Ectropion Repair

Ectropion usually results from the effects of aging on the eyelid. Other causes include mechanical or congenital lid pathology. The eyelid is turned outward.

Entropion Repair

Involutional entropion usually results from aging. The eyelid is inverted or turned inward.

Ptosis Repair

Ptosis, or drooping of the upper eyelid, can be congenital (dystrophy of the levator muscle) or acquired from aging or trauma.

Blepharoplasty

Blepharoplasty is plastic surgery of the eyelids to remove redundant tissue that is obstructing vision, or for improved appearance.

DACRYOCYSTORHINOSTOMY

Dacryocystorhinostomy refers to the formation of a communication channel between the lacrimal sac and the nasal cavity. This is performed for congenital or acquired nasolacrimal duct obstruction. It usually requires general anesthesia.

ORBITAL SURGERY

Most orbital surgery is performed using general anesthesia. If the surgery is anterior, local anesthesia can be used. Examples of orbital surgery include the following:

- Repair of blowout fracture
- Drainage of orbital abscess
- Decompression of the optic nerve
- Exenteration of the orbit for malignancy

OPHTHALMOLOGIC EMERGENCIES

Most urgent ophthalmologic procedures do not need to be performed on an emergency basis. This is important because the anesthetic plan must consider the NPO (nil per os, nothing by mouth) status and general medical condition of the patient. This does not apply to true eye emergencies. In these rare conditions, therapy should be started within minutes. Other urgent ophthalmologic conditions can start within 1 to several hours, without a change in outcome.

True Emergencies

Therapy should be started within minutes for chemical burns of the cornea and central retinal artery occlusion.

Urgent Situations

Therapy should be started in 1 to several hours. Urgent situations include open-globe injuries, endophthalmitis, acute narrow-angle glaucoma, acute retinal detachment, corneal foreign body, and lid laceration.

Semiurgent Situations

Therapy should be started within days, but sometimes can be rescheduled for several weeks. Semiurgent situations include ocular tumors, blowout fractures of the orbit, congenital cataract, and chronic retinal detachment.

Open Globe and Full Stomach

A patient with eye trauma presents a challenge to the anesthesia provider. The dilemma is to protect the patient from pulmonary aspiration of stomach contents and to protect the eye from acute changes in IOP, which could cause vitreous loss, retinal detachment, and blindness. A rapid-sequence induction of anesthesia provides rapid control of the airway, but succinylcholine causes a modest increase in IOP. Of course, intubating the trachea during light anesthesia or inadequate neuromuscular blockade can cause large increases in IOP, which needs to be avoided. Attentiveness to neuromuscular monitoring can confirm the adequacy of neuromuscular blockade (see Chapters 34 and 53). Regional anesthetic techniques can also be performed.[44] Factors to consider include the following:

- *Size of the perforation:* Small punctures have higher resistance to vitreous loss with changes in IOP.
- *Pulmonary status:* Patients with decreased functional residual capacity become rapidly hypoxic making a more rapid technique preferable.
- *NPO status:* What is the magnitude of the pulmonary aspiration of gastric contents risk?
- *Length of procedure:* If the surgery is short, and a large dose of nondepolarizing neuromuscular blocker is used, can the block be reversed (see Chapter 35) or will postoperative mechanical ventilation occur?

ANESTHESIA-RELATED EYE INJURIES

Anesthesia providers must be aware of possible ocular damage during anesthesia and surgery (see Chapter 41). If a patient emerges from a general anesthetic complaining of vision impairment, an emergency may exist because of the possibility of central retinal artery occlusion. When using a facemask, care must be taken to avoid applying undue pressure to the eye. Systemic hypotension and anemia also can be contributing factors in vision loss.

A second potential complication is corneal abrasion. General anesthesia decreases basal tear production. Proper eye care with taping of lids with or without an ocular lubricant provides protection. If a patient emerges from general anesthesia with eye pain or a foreign body sensation, the patient must be observed continually to ensure improvement. If left untreated, corneal abrasions can progress to form corneal ulcers.

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Chapter 85

Anesthesia for Ear, Nose, and Throat Surgery

D. JOHN DOYLE

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Key Points

- Difficult airways are more frequently encountered in patients undergoing ear, nose, and throat (ENT) surgery, especially for cancer. Reviewing the results of a preoperative computed tomography (CT) scan or an endoscopic airway examination may help identify pathologic features likely to produce airflow obstruction or complicate tracheal intubation.
- Although the tracheas of ENT patients are often intubated using ordinary polyvinyl chloride endotracheal tubes (ETTs), microlaryngeal, laser-safe and wire-reinforced tubes are frequently employed (see also Chapter 55).
- Endotracheal intubation in an awake patient with a flexible bronchoscope is commonly used when intubation following the induction of general anesthesia would be imprudent. (Also recall that the induction of anesthesia sometimes results in a deteriorated laryngoscopic view) (see also Chapter 55).
- Fiberoptic endotracheal intubation is usually well tolerated, is gentle on the airway, and does not require force to obtain glottic exposure.
- When the airway disorder is so extensive that awake endotracheal intubation is impractical, tracheostomy performed using local anesthesia (with or without judicious intravenous sedation) is usually the best option. In extreme loss-of-airway emergencies, a cricothyrotomy may be preferable to a tracheostomy because cricothyrotomy takes much less time to complete.
- In some head and neck cases, such as in patients undergoing parotid surgery, the need for electrical testing of the facial nerve precludes the extended use of neuromuscular blocking drugs.
- In many patients with head and neck disorders, gentle emergence from anesthesia, free of coughing and straining, is vitally important to prevent emergence rebleeding as a result of venous engorgement.
- Bleeding following tonsillectomy usually occurs within the first 6 postoperative hours, but it can also occur several days later.
- Facial trauma can produce unremitting bleeding and the aspiration of teeth, blood, bone, and tissue fragments, as well as cervical spine injury. Airway trauma can result from blunt or penetrating injuries, burns, inhalational injury, and iatrogenic causes. In both situations, initial management is dictated by the degree of respiratory distress or potential airway compromise, the available equipment, and clinical preferences.
- Intubating the trachea of a patient with laryngeal trauma may result in further injury to the airway or even complete airway loss. If intubation is attempted, it is advised to use a fiberoptic bronchoscope with a small ETT. Positive-pressure ventilation may worsen any subcutaneous emphysema. In some cases, a tracheostomy may be the most prudent course.
- Causes of stridor include inhaled foreign bodies, bilateral vocal cord palsy, airway edema, angioedema, epiglottitis, traumatic injury, subglottic stenosis, and other pathologic entities. Regardless, the first issue in the setting of stridor is whether or not endotracheal intubation or a surgical approach to the airway is immediately

Continued

KEY POINTS—cont'd

necessary to rescue the patient from death or injury. Heliox administered with a nonrebreathing facemask can be helpful as a temporizing measure.

- The chosen anesthetic technique for endoscopic procedures varies with patient and lesion particulars, clinical preferences, and the selected surgical tools (laser, rigid bronchoscope). Total intravenous anesthesia is a popular choice for many of these cases.
- Lasers can be used to vaporize otolaryngologic lesions; however, special precautions are needed to prevent accidental thermal injury or an airway fire (see also Chapter 88), a potentially deadly complication that may also occur during tracheotomy surgery. Oxygen must be kept to a minimum when a significant potential for an airway fire exists. Moreover, nitrous oxide should not be used during airway surgery because it supports combustion just as does oxygen (see also Chapter 88).

On October 16, 1846, Dr. William Morton famously used ether delivered by inhalation to provide general anesthesia to Gilbert Abbott and allow surgeon Dr. John Warren to remove a tumor from Abbott's neck.[1,2] From this first public demonstration of ether anesthesia onward, the relationship between anesthesiology and ear, nose, and throat (ENT) surgery has been vital. Indeed, no other branch of surgery has as great a need for a mutual understanding between the surgeon and the anesthesiologist, with joint procedural planning and close cooperation being crucial. For example, many ENT surgical procedures require that the anesthesia provider share the airway with the surgeon; consequently, a good anesthesia provider must be unusually knowledgeable about ENT procedures and possible effects on the patient.

Anesthesia for ENT surgery encompasses a vast range of procedures varying enormously in complexity, duration, and potential for complications.[3] On any given day, ENT anesthesiologists may be assigned to simple high-volume cases, such as myringotomies and tonsillectomies, to all-day procedures in patients with cancer. They may also encounter patients with severely distorted airway anatomy, sometimes even causing airway obstruction, as well as procedures involving tracheal, glottic, or subglottic surgery that require sharing of the airway in conjunction with the use of special equipment such as surgical lasers. Nasal procedures usually require airway protection from blood and secretions, as well as gentle emergence from anesthesia. Intraoral ENT procedures, such as tonsillectomies, may employ instruments intended to keep the mouth open but that may also unintentionally obstruct the airway. Extreme lateral rotation of the head may be required for some ear procedures. These are just some of the special perils of providing anesthesia for ENT procedures.

SYNOPSIS OF EAR, NOSE, AND THROAT ANATOMY

Figures 85-1 to 85-4 illustrate various aspects of ENT anatomy. The oropharynx extends from the uvula to the hyoid bone. The hypopharynx extends from the hyoid to the cricoid cartilage. The glottis includes both vocal cords, the anterior commissure, and the posterior intra-arytenoid area. The subglottis extends 5 mm (anteriorly) to 10 mm (posteriorly) below the apex of the vocal cords (also known as vocal folds). The larynx, essential to respiration and speech, has a clinically important glottic closure reflex mediated through bilateral superior laryngeal nerves. This reflex serves to protect the airway against aspiration. For example, swallowing activates this protective reflex. On occasion this protective reflex can be

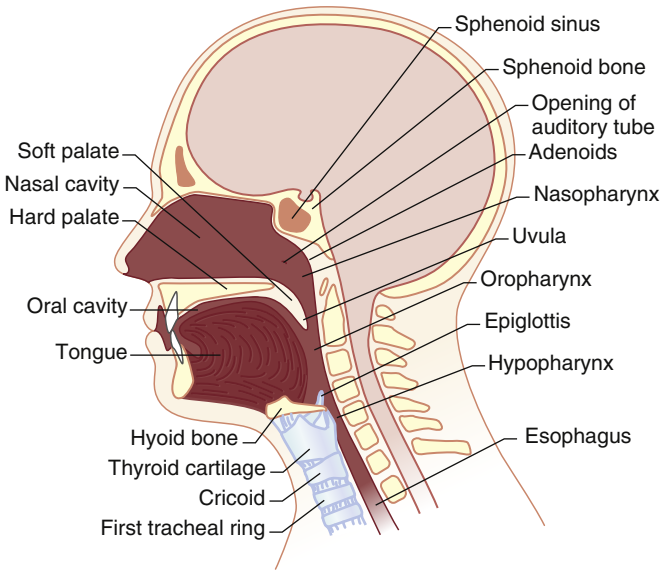


Figure 85-1. Highlights of otolaryngologic anatomy. Note (1) the anterior position of the trachea relative to the esophagus; (2) the oropharynx, extending from the uvula to the hyoid bone; (3) the hypopharynx extending from the hyoid bone to the cricoid cartilage; (4) the cricoid ring, a structure that is pushed posteriorly during the Sellick maneuver component of rapid-sequence induction, done with the intention of occluding the esophagus to help prevent regurgitation of gastric contents; and (5) the location of the first tracheal ring, important as a surgical landmark because most tracheostomies are performed between the second and third tracheal rings. *(From Feldman MA, Patel A: Anesthesia for eye, ear, nose, and throat surgery. In Miller RD, editor:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 2357-2388.)*

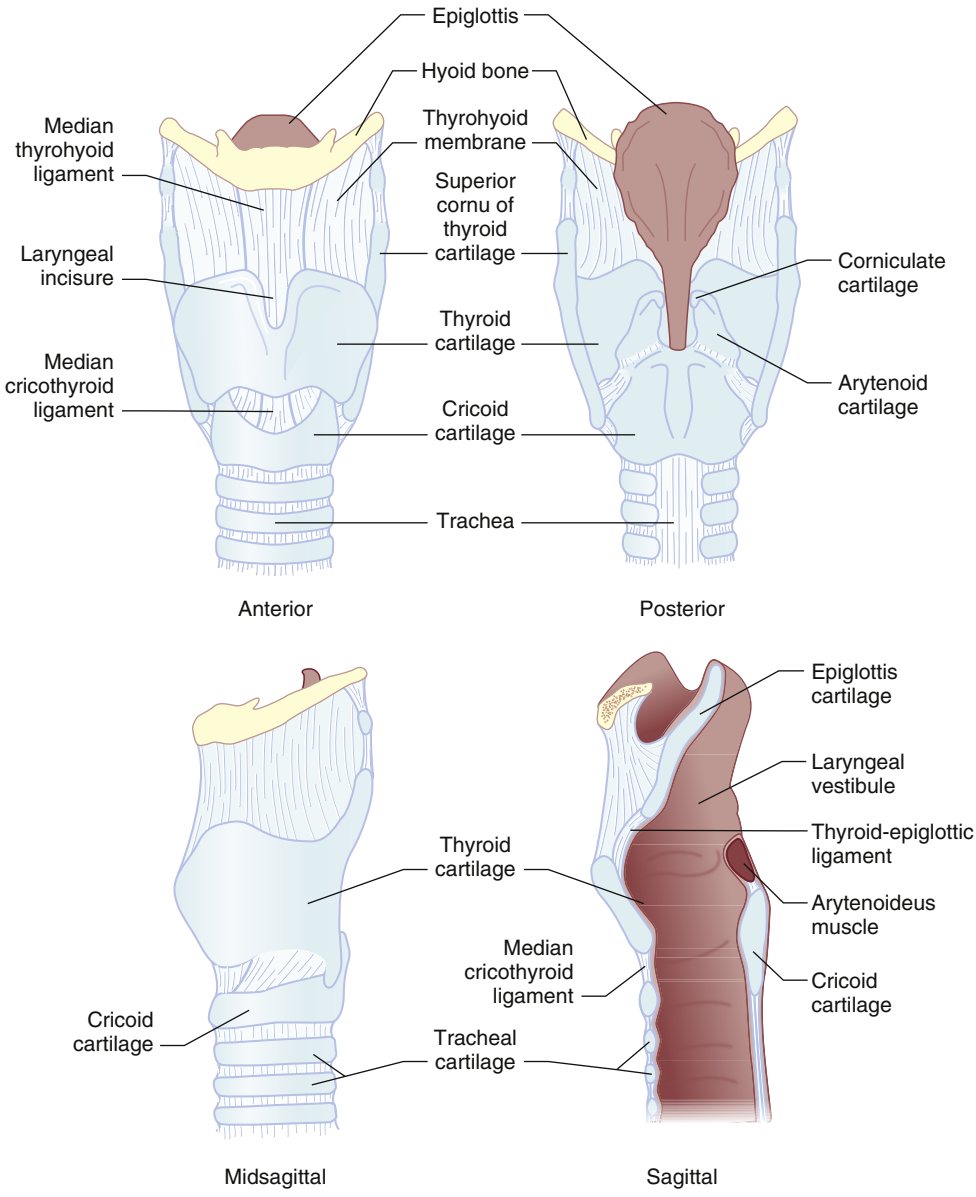


Figure 85-2. Anterior, posterior, midsagittal, and sagittal views of laryngeal anatomy. Note (1) how the cartilaginous tracheal rings are incomplete posteriorly to allow the trachea to collapse slightly to facilitate the passage of food down the esophagus (and to provide orientation during bronchoscopic procedures!); (2) the superior cornu of the thyroid cartilage, an important landmark in the superior laryngeal nerve block because this is close to where the internal branch of the superior laryngeal nerve penetrates the thyrohyoid membrane; and (3) the median cricothyroid ligament and (not labeled) the twin lateral cricothyroid ligaments, known collectively as the cricothyroid ligament and entered in both emergency cricothyrotomy procedures and with emergency transtracheal jet ventilation. *(From Feldman MA, Patel A: Anesthesia for eye, ear, nose, and throat surgery. In Miller RD, editor:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 2357-2388.)*

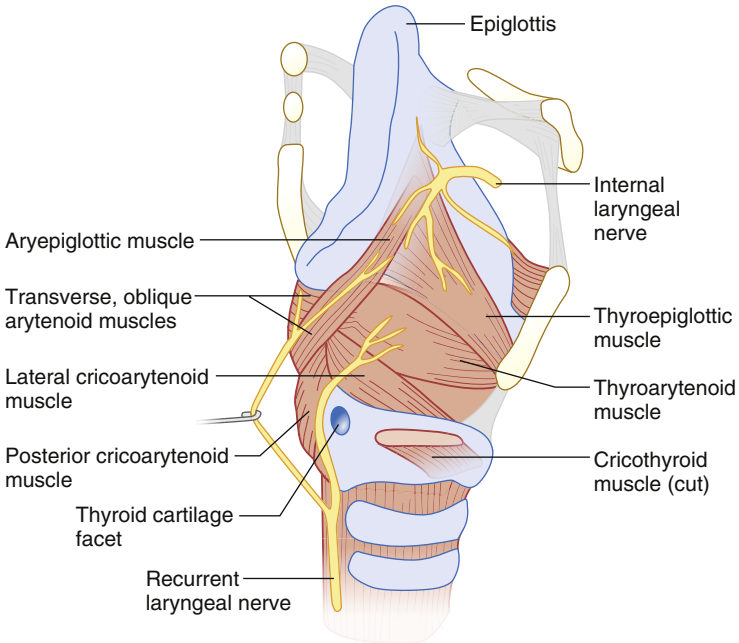


Figure 85-3. Laryngeal anatomy focusing primarily on the internal laryngeal nerve and the recurrent laryngeal nerve. The two recurrent laryngeal nerves provide motor innervation to all the intrinsic muscles of the larynx, except the cricothyroid and inferior pharyngeal constrictor muscles, which are innervated by the external branches of the two superior laryngeal nerves (external laryngeal nerve). Sensory innervation of the larynx down to the vocal cords is supplied by the internal laryngeal nerve branches of the superior laryngeal nerves (internal laryngeal nerve), these in turn being branches of the vagus. Sensory innervation below the vocal cords and to the upper trachea is supplied by the recurrent laryngeal nerves. *(From Schuller DE, Schleuning AJ:* Otolaryngology: head and neck surgery, *ed 8. St. Louis, 1994, Mosby, p 252.)*

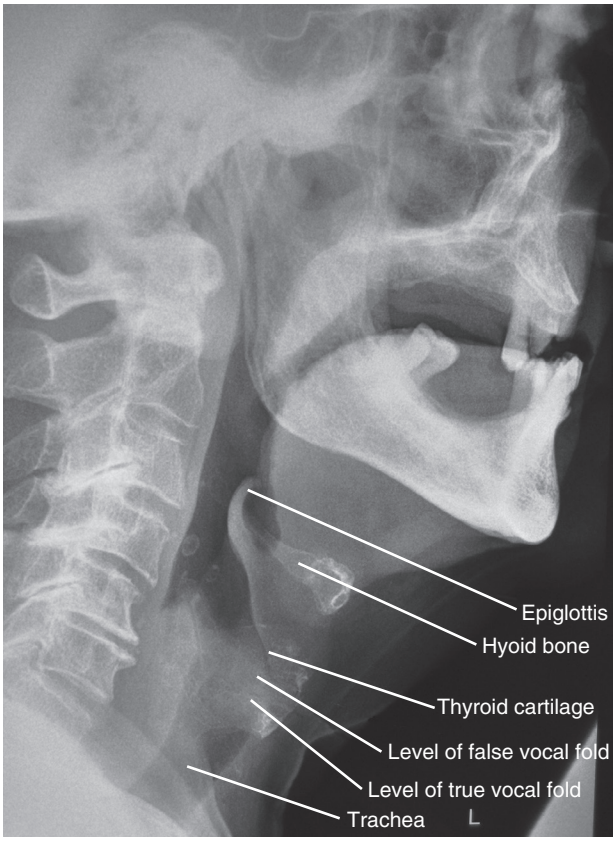


Figure 85-4. Lateral radiograph demonstrating laryngeal anatomy. Notice (1) the normally wafer-thin epiglottis, which serves as a protective cover to the laryngeal inlet during swallowing and may become much larger and "thumb shaped" when edematous (e.g., as a result of pediatric epiglottitis); (2) the limited amount of prevertebral soft tissue in the oropharyngeal and hypopharyngeal regions; when edematous (e.g., as a result of a retropharyngeal abscess), this tissue may expand anteriorly to obstruct the airway; and (3) the hyoid bone, which aids in tongue movement and swallowing and which, if found fractured on autopsy, is suggestive of foul play by throttling or strangulation. (Did you notice the missing teeth?) *(From Feldman MA, Patel A: Anesthesia for eye, ear, nose, and throat surgery. In Miller RD, editor:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 2357-2388.)*

problematic because when sustained spasm of the glottic muscles (a condition known as laryngospasm) occurs,[4-6] gas exchange cannot take place. Laryngospasm is associated with light anesthesia and is frequently triggered by blood or secretions irritating the vocal cords, as often occurs after septoplasty and rhinoplasty surgery. Because it can make ventilation impossible, laryngospasm may constitute a true anesthetic emergency (see later).

Branches of the right and left vagus nerves innervate the larynx. The right vagus nerve gives rise to the right recurrent laryngeal nerve, whereas the left vagus nerve gives rise to the left recurrent laryngeal nerve. The two recurrent laryngeal nerves provide motor innervation to all the intrinsic muscles of the larynx, except the cricothyroid and inferior pharyngeal constrictor muscles, which are innervated by the branches of the superior laryngeal nerves. The internal laryngeal nerve is the internal branch of the superior laryngeal nerve (see Fig. 85-3). It descends to the thyrohyoid membrane, pierces it along with the superior laryngeal artery, and provides sensory innervation to the larynx down to the vocal cords. Sensory innervation below the vocal cords and to the upper trachea is supplied by the recurrent laryngeal nerves (see Fig. 85-3).

Injury to the recurrent laryngeal nerves, which supply most of the laryngeal intrinsic muscles, is a feared but often preventable complication in thyroid surgery and a host of other procedures, including tracheal intubation.[7-12] If the damage is unilateral, the patient may present with hoarseness from unilateral loss of vocal cord abduction occurring in conjunction with intact cricothyroid mediated adduction. This situation causes the affected vocal cord to assume a paramedian position. Bilateral nerve damage can result in dyspnea, stridor, and even full airway obstruction from bilateral vocal cord paramedian positioning. Such patients may require a tracheostomy. Intraoperative neuromonitoring (see also Chapter 49) is often used to reduce the chance of injury to the recurrent laryngeal nerves, especially in thyroid surgery.[13-15]

PREOPERATIVE EVALUATION FOR EAR, NOSE, AND THROAT SURGERY

Although the preoperative evaluation of the surgical patient is discussed in detail in Chapter 38, a few issues are especially pertinent to ENT cases. Many ENT patients, especially those with malignant head and neck diseases, have histories of prolonged tobacco and alcohol use, whereas many others suffer from obesity or obstructive sleep apnea (OSA). Patients with chronic airway obstruction may develop pulmonary hypertension, sometimes leading to right-sided heart failure (cor pulmonale). A history of hoarseness may signal recurrent laryngeal nerve injury or worse, whereas the presence of stridor is *always* a cause for immediate concern. In cases involving the airway, the anesthesiologist and surgeon frequently review available radiographic and video studies to establish an airway plan collaboratively. A history of head and neck radiation for malignancy treatment frequently makes intubation difficult because the structures may become tough and fibrotic ("like wood"), yet they are predisposed to bleeding with instrumentation. A history of snoring may signal that the patient has undiagnosed sleep apnea and is prone to airway obstruction.

ENT cases frequently involve geriatric patients, many of whom are at a high risk for postoperative delirium and cognitive dysfunction (see also Chapter 80).[16-18] Although many ENT procedures involve infrequent risk, some of the large head and neck operations are considered to have "intermediate" surgical risk. A preoperative resting 12-lead electrocardiogram (ECG) is recommended for patients with known coronary heart disease, peripheral arterial disease, or cerebrovascular disease who are undergoing such procedures (see also Chapter 38). Additionally, patients with a history of heart failure, diabetes mellitus, or renal failure who are undergoing intermediate-risk operative procedures benefit from an ECG (see also Chapter 39). Preoperative ECG testing is not indicated in asymptomatic persons undergoing infrequent-risk procedures.

A *preoperative endoscopic airway examination can be performed* in selected patients. This technique uses an

ordinary flexible fiberscope usually used for awake endotracheal intubation to conduct a quick transnasal laryngoscopic examination using topical anesthesia. This examination allows the clinician to determine whether a problematic laryngeal disorder exists, such as supraglottic lesions that would not be apparent by ordinary means. The procedure requires minimal time and patient preparation, and it is well tolerated by patients. A review by Rosenblatt provides ample details.[19]

AIRWAY MANAGEMENT IN OTOLARYNGOLOGY

Both easy and difficult airways are frequently encountered in ENT anesthesia. The American Society of Anesthesiologists (ASA) Difficult Airway Algorithm (or similar algorithm),[20-28] should ordinarily be a starting point for nearly all aspects of ENT airway management. To a large extent, the specific airway management techniques chosen depend on clinical circumstances, the airway management skills and preferences of the anesthesiologist and surgeon, and the available equipment.

The following general management options exist: (1) general endotracheal anesthesia; (2) general anesthesia using a supraglottic airway (SGA) device (e.g., laryngeal mask airway [LMA]); (3) general anesthesia using an ENT laryngoscope (to expose the airway) in conjunction with jet ventilation; (4) use of intermittent apnea; (5) general anesthesia using the patient's natural airway, with or without adjuncts such as jaw positioning devices or nasopharyngeal airways; and (6) local anesthesia in conjunction with intravenous sedation, with the patient breathing spontaneously. The first option is doubtless the most popular. However, the technique chosen and implemented depends on factors such as the perceived difficulty of intubating the trachea with ordinary methods. Evaluation of the airway in this particular respect is also discussed in Chapter 55.

The airway can become obstructed for many reasons. Examples include the following: aspirated foreign bodies; infections such as epiglottitis, diphtheria, or Ludwig angina; laryngospasm; tumors and hematomas impinging on the airway; trauma to the airway; OSA; tonsillar hypertrophy; and airway edema (e.g., from anaphylaxis, prolonged laryngoscopy, or smoke inhalation or burn injury). In most cases, airway management is determined after a discussion between the anesthesia and surgical teams.

Most patients undergoing ENT surgery have their airway managed by tracheal intubation. Although under ordinary circumstances tracheal intubation is straightforward, patients whose tracheas are expected to be difficult to intubate can be identified and usually managed with techniques such as videolaryngoscopy or fiberoptic intubation. A key decision in such cases is whether the tracheal intubation should be performed with the patient awake or following the induction of general anesthesia. Another important decision is what tools or interventions to employ in the event that difficulty with ventilation or intubation is encountered. In exceptional cases, a tracheostomy using local anesthesia must be performed.

Patients for ENT surgery are often managed using an ordinary polyvinyl chloride (PVC) endotracheal tube (ETT), but microlaryngeal tubes (MLTs), laser tubes, and wire-reinforced tubes are also frequently used. Reinforced tubes have the advantages that they are unlikely to kink and they fit especially well into tracheostomy stomas because of their excellent flexibility. Laser tubes are discussed in Chapter 88.

Practical considerations in this setting start with the fact that the tube must be adequately secured using tape or other means; some maxillofacial surgeons suture the tube to the side of the mouth or even tie the tube to the teeth with wire. In addition, the ETT cuff pressures ordinarily must be kept less than 25 mm Hg to avoid ischemic damage to the tracheal mucosa. When nitrous oxide is used, cuff pressures gradually increase as nitrous oxide enters the cuff by diffusion. This is of particular concern in surgical procedures of long duration, such as free-flap surgery.

Before attempting tracheal intubation, its difficulty using direct laryngoscopy can often be predicted. The 11-point airway assessment tool included with the 2003 ASA Difficult Airway Algorithm is an excellent source of information and advice.[20] In addition, following the completion of tracheal intubation, the difficulty (if any) encountered should be summarized. The Intubation Difficulty Scale (IDS) introduced by Adnet and associates can be useful.[29-33] IDS is a numeric score indicating overall intubation difficulty based on seven descriptors associated with intubation difficulty: number of supplementary intubation attempts, number of supplementary operators, alternative techniques used, laryngoscopic grade, subjective lifting force, the use of external laryngeal manipulation, and the characteristics of the vocal cords.

Most endotracheal intubations are achieved using traditional Macintosh and Miller laryngoscopes, although several alternative laryngoscopes have been advocated. When the view at laryngoscopy is suboptimal, the use of introducers such as the Eschmann stylet (gum elastic bougie) can sometimes be very helpful.[34-39] It is used as follows: When a poor laryngoscopic view of the glottic structures is obtained, the introducer should be inserted into the patient's mouth and gently advanced through the glottic opening (in the case of a grade II view) or anteriorly under the epiglottis (in the case of a grade III view). Subtle clicks resulting from the introducer passing over the tracheal rings help confirm proper placement of the introducer. With the introducer held steady, one then "railroads" a tracheal tube over the introducer into the glottis.

Video laryngoscopes such as the GlideScope (Verathon, Bothell, WA), the McGrath (Covidien, Mansfield, MA) video laryngoscope, the Storz video laryngoscope (Karl Storz, Tuttlingen, Germany), and the Pentax AWS (Hoya Corporation, Tokyo) have become particularly valuable, especially in patients with an "anterior" larynx or in patients with cervical spine immobilization.[40-50]

As discussed in Chapter 55, awake endotracheal intubation involves ETT insertion in a conscious or lightly sedated patient. It is usually performed because endotracheal intubation during general anesthesia is judged to be too risky. Some concerns may reflect possible difficulties

with ventilation or endotracheal intubation or possible aspiration of gastric contents. Although fiberoptic intubation using topical anesthesia is the most common approach to awake endotracheal intubation, other methods include awake blind nasal intubation using an Endotrol (or similar) ETT or the use of a Macintosh, Miller, GlideScope, or other laryngoscope with topical anesthesia. Certain airway blocks can be used in addition to topical anesthesia. These are discussed in Chapter 55.

The use of fiberoptic intubation for the airway management of patients undergoing otolaryngologic surgery is popular because this technique works well in the presence of many kinds of airway disease. Although fiberoptic intubation can often be safely performed during complete general anesthesia,[51] many clinicians opt to perform this technique using topical anesthesia with the patient only lightly sedated (awake fiberoptic intubation), depending on the skill level of the anesthesiologist, the cooperation of the patient, and the severity of the pathologic process. A central consideration behind the choice of "awake" versus "asleep" fiberoptic intubation is the safety margin an awake technique allows: If intubation is not successfully accomplished, the patient's ability to maintain his or her own airway remains intact. In addition, during awake intubation, airway reflexes are generally maintained sufficiently to guard against pulmonary aspiration, an important point in patients with a high risk of aspiration of gastric contents. Patients who have recently eaten and have undergone trauma are at especially high risk.

Awake endotracheal intubation is not synonymous with fiberoptic intubation. Awake intubation can be accomplished safely using many other airway devices. Other possible options for awake intubation include, but are not limited to, direct laryngoscopy with Macintosh and Miller laryngoscopes, blind nasal intubation, use of a GlideScope or other video laryngoscope, use of a lighted stylet, and so on.

Typically, in intubation of the trachea in an awake patient, the airway is initially anesthetized with gargled and atomized 4% lidocaine. Superior laryngeal and transtracheal blocks are occasionally also employed. In addition, judicious sedation is usually administered. Midazolam, fentanyl, remifentanil, ketamine, propofol, and clonidine have all been used in this setting. More recently, the use of dexmedetomidine, a selective α_2-agonist with sedative, analgesic, amnestic, and antisialagogue properties, has been reported. A key advantage of dexmedetomidine is that it maintains spontaneous respiration with minimal respiratory depression.[52-55] Patients being sedated with dexmedetomidine are generally easy to arouse. However, this advantage, along with that of maintaining spontaneous respiration, may not occur when very large doses are given.

Doyle described the successful use of the GlideScope in four cases of awake endotracheal intubation.[56] The following potential advantages are as follows: First, the view is generally excellent. Second, the method is less affected by the presence of secretions or blood as compared with the use of fiberoptic intubation. Third, no special restrictions exist on the type of ETT that can be placed when using the GlideScope, but this is not the case for fiberoptic methods. Fourth, the GlideScope is much more rugged than a fiberoptic bronchoscope and is far less likely to be damaged with use. Advancing the ETT into the trachea over the fiberoptic bronchoscope often fails as a result of ETT impingement on the arytenoid cartilages; this is generally not a problem with the GlideScope.

In the end, however, the use of awake fiberoptic intubation in the setting of the patient with airway disease remains steadfastly popular because it is gentle to the airway, is generally well tolerated, and does not require the application of force to obtain glottic exposure.

Special mention needs to be made of the necessity of being fully prepared for dire ENT airway emergencies because these patients may require immediate surgical intervention. In addition to a conventional difficult airway cart, practitioners may wish to maintain a special ENT airway cart with equipment such as that listed in Box 85-1.[57] In addition to these items and unlisted items favored by individual practitioners, ENT surgeons want ready access to an emergency tracheotomy tray, as well as to some form of suspension laryngoscope or rigid bronchoscope. Special attention to the maintenance and cleaning of fiberoptic bronchoscopes is also important, given that they must always be easily accessible and reliable when needed. In the case of electronic fiberscopes incorporating a video display, it is particularly important to establish that illumination settings and white balancing have been correctly set before use.

AIRWAY DISORDERS IN OTOLARYNGOLOGY

Otolaryngologic airway disorders can sometimes present the clinician with tremendous anesthetic and airway challenges. In many such cases, awake endotracheal intubation (e.g., by fiberoptic methods) is the method of choice. When awake intubation is impractical (e.g., overwhelming tumor invasion of the airway, inadequate equipment, limited experience), tracheostomy using local anesthesia

BOX 85-1 *Possible Items for an Ear, Nose, and Throat Airway Emergencies Cart*

- Bag-valve-mask resuscitator (Ambu bag)
- Oropharyngeal and nasopharyngeal airways
- Supraglottic airway collection
- Endotracheal tubes, including microlaryngeal tubes and laser tubes
- Malleable stylets
- Topical anesthesia, with syringes, and atomizers
- Laryngoscope collection with extra bulbs and batteries
- McGill forceps (useful for nasal intubation)
- Boedeker forceps (for use with video laryngoscopes)*
- Airway introducer (gum elastic bougie)
- Tube exchange catheters
- Carbon dioxide detection system
- Video laryngoscope (e.g., GlideScope, McGrath, Pentax-AWS)
- Surgical airway kit (e.g., Melker cricothyrotomy kit)
- Emergency tracheotomy tray
- Fiberoptic bronchoscope

*The Boedeker (curved) intubation forceps is useful for removal of foreign bodies when a video laryngoscope is used.[57]

(with minimal sedation, or no sedation in extreme cases) is sometimes preferred. In such cases, complete airway obstruction is the outcome most feared; this can occur when anesthetic drugs or neuromuscular blocking drugs decrease the tone of the airway musculature, thereby unfavorably changing the airway architecture.

Many ENT pathologic conditions can make airway management difficult. *Airway infections* can include upper airway abscesses, retropharyngeal abscesses, quinsy, Ludwig angina, and epiglottitis (supraglottitis). *Airway tumors* may be present as oral or tongue malignancies, as glottic, supraglottic, and infraglottic tumors, or as anterior mediastinal masses. *Other pathologic conditions* may also complicate airway management, such as congenital malformations (Pierre-Robin sequence, Goldenhar syndrome), periglottic edema (e.g., following rigid bronchoscopy), recurrent laryngeal nerve injury (e.g., following thyroid surgery), maxillofacial trauma, or OSA. Some of the more important of these conditions are discussed in the following paragraphs.

ANGIOEDEMA

Angioedema (former term: angioneurotic edema) is a rapid form of tissue swelling mediated by anomalous activation of the complement system with release of histamine and other inflammatory mediators.[58] It is usually the result of an allergic reaction. Hereditary angioedema is a variant family that arises from an autosomal dominant genetic mutation. Complete loss of the airway can occur in severe cases of either form. Just as with anaphylaxis, epinephrine may be lifesaving when the cause of angioedema is allergic, but treatment with epinephrine is not helpful in cases of hereditary angioedema.[59] Intubation of the trachea is often required in affected patients usually during topical anesthesia with the patient awake or lightly sedated.

ACUTE EPIGLOTTITIS

Epiglottitis, an inflammatory disease of the epiglottis, arytenoids, and aryepiglottic folds, is among the most dreaded of airway-related infections, especially in the pediatric population (see also Chapter 93).[60-64] In the past, victims were usually children 2 to 6 years of age, who were often infected with *Haemophilus influenzae*. Today, a vaccine against *H. influenzae* has reduced the frequency of this tragic affliction. The clinical presentation often includes a sore throat, dysphagia, muffled voice, and fever. Difficulty with swallowing leading to drooling from the mouth may occur. Victims may appear to be systemically ill ("toxic") and assume an open-mouth "tripod" position to ease breathing. Stridor, respiratory distress, and complete airway obstruction may occur. The chief differential diagnosis in children is laryngotracheobronchitis (croup).[65,66]

Examining the child's airway at the bedside may exacerbate the condition, and anything that could bring the child to cry (e.g., needles) should be avoided when possible. A common management approach involves careful inhaled induction of anesthesia using sevoflurane with the child sitting in the anesthesiologist's lap. Then oral intubation of the trachea can be performed using a smaller than usual tracheal tube. The child should receive "deep" anesthesia but should still be breathing spontaneously. Intravenous access and full monitoring should be established as anesthesia is deepened. If at laryngoscopy the airway cannot be identified, one trick is to have someone compress the child's chest, thus generating a small air bubble in the glottis that the person performing the anesthetic can aim for in the trachea. Failure to secure the airway in this manner may necessitate rescue through rigid bronchoscopy, by establishing a surgical airway, or by other means. In the past these children were often then managed by tracheostomy; however, contemporary management usually includes intensive care unit (ICU) admission, throat and blood cultures, conversion to nasotracheal intubation, and intravenous antibiotic therapy.

Epiglottitis can also occur in adults.[67] The first president of the United States, George Washington, is said to have died of it, although being repeatedly phlebotomized (as was the custom of the day) undoubtedly contributed to his demise. Here the situation is less ominous because the adult airway is larger. In cooperative adults, cautious oropharyngeal examination and fiberoptic nasopharyngoscopy help assess the degree of disease. The current consensus is that many adults can be adequately treated in an ICU with inhaled mist, antibiotics, and corticosteroids and that tracheal intubation is necessary only if symptoms of respiratory distress develop (see Chapter 101). Should intubation be needed, awake fiberoptic laryngoscopy is probably the best way to secure the airway in cooperative adults, whereas the use of inhaled induction of anesthesia in adults with a compromised airway is now considered to be more perilous than was once thought.

RETROPHARYNGEAL ABSCESS

Retropharyngeal abscess formation may occur from bacterial infection of the retropharyngeal space following dental or tonsillar infections.[68-74] If the condition is untreated, the posterior pharyngeal wall may advance anteriorly into the oropharynx, with resulting dyspnea and airway obstruction. Other clinical findings may include difficulty in swallowing, trismus, and a fluctuant posterior pharyngeal mass. An abscess cavity may be evident on lateral neck radiographs, and anterior displacement of the esophagus and upper pharynx may be present. Airway management may be complicated by trismus or partial airway obstruction. Because abscess rupture can lead to tracheal soiling, contact with the posterior pharyngeal wall during laryngoscopy and intubation should be minimized. Incision and drainage are the mainstays of treatment. Tracheostomy is often, but not always, required.

LUDWIG ANGINA

Ludwig angina is a multispace infection of the floor of the mouth.[75-79] The infection usually starts with infected mandibular molars and spreads to submandibular, sublingual, submental, and buccal spaces. The tongue becomes elevated and displaced posteriorly, which may lead to loss of the airway, especially when the patient is in the supine

position. As with retropharyngeal abscess, an additional concern is the potential for abscess rupture into the hypopharynx (with possible lung soiling) either spontaneously or with attempts at laryngoscopy and intubation. Airway management options depend on clinical severity, imaging findings (e.g., computed tomography [CT] or magnetic resonance imaging [MRI] findings), and surgical preferences, but elective tracheostomy before incision and drainage remains a classic, if dated, treatment modality.[79] Most experts advocate fiberoptic intubation when possible. In addition, because Ludwig angina is often associated with trismus, nasal fiberoptic intubation is frequently needed.

AIRWAY TUMORS, POLYPS, AND GRANULOMAS

Airway tumors can be benign or malignant (Figs. 85-5 to 85-7), but regardless of their pathologic characteristics, airway obstruction is always a potential concern.[80-83] Discussion with the surgical team concerning the size and location of the tumor, along with a review of any video-recorded nasopharyngeal video examinations, will help determine whether awake endotracheal intubation is needed. Polyps may also be found throughout the airway and can lead to partial or complete airway obstruction. Vocal cord polyps, cysts, and granulomas may result from traumatic intubation, vocal cord irritation from ETT movement, or other causes, especially in women.[84-90] Vocal cord cancer can also occur.[91] The potential also exists for exacerbation of asthma in patients with nasal polyps who receive aspirin, ketorolac (Toradol), and other nonsteroidal antiinflammatory drugs (NSAIDs) (the Samter triad).[92,93]

LARYNGEAL PAPILLOMATOSIS

Patients with laryngeal papillomatosis caused by human papillomavirus (HPV) infection may require frequent application of laser treatment for attempted papilloma eradication.[94-99] In some cases the airway may be close to obstruction because of an overgrowth of lesions. During laser treatment, inspired oxygen concentration should be kept to a minimum, with the avoidance of nitrous oxide, to reduce the chance of an airway fire (see Chapter 88). After treatment, the airway is raw and edematous. Laryngotracheomalacia may occasionally be present, sometimes leading to complete upper airway collapse following extubation of the trachea.

ANESTHESIA FOR PANENDOSCOPY

Panendoscopy, sometimes known as triple endoscopy, involves three diagnostic components: laryngoscopy, bronchoscopy, and esophagoscopy. Such procedures and others involving the larynx, pharynx, or trachea often require specialized ENT laryngoscopes, frequently in conjunction with a small-diameter ETT or a tube specifically designed for laser surgery. Panendoscopy is used in patients with head and neck cancer to search for vocal cord lesions, obtain tissue biopsies, monitor for tumor recurrence, and so on. In such cases, one should consider the following specific issues in discussion with the surgical team: What is the anticipated pathologic process, and how is it expected to affect intubation or ventilation? (In some cases the patient's disease may not allow the use of an ETT, so that jet ventilation or a rigid bronchoscope is needed.) What is the plan for airway management, and how does it affect the delivery of anesthesia? How does the presence of coexisting disease (e.g., coronary artery disease, chronic obstructive pulmonary disease, gastroesophageal reflux disease) affect management? What specialized equipment may be needed? (For example, when airway obstruction is present, the surgeon may employ dilatational balloons, lasers, or a microdébrider to open up the airway).

Five airway options for panendoscopy exist: (1) use of an ETT, typically a narrow-bore MLT that provides the surgeon with a superior glottic view; (2) jet ventilation in conjunction with a rigid ENT laryngoscope, without the use of an ETT; (3) hybrid methods, such as the intermittent use of an SGA or an MLT tube in conjunction with a rigid laryngoscope, jet ventilation, or intermittent apnea; (4) tracheostomy using local anesthesia before inducing general anesthesia; (5) and elective placement of a specially designed transtracheal jet ventilation cannula (e.g., Ravussin jet ventilation catheter before induction[100]). The last two options are only occasionally used for patients with a suspected difficult airway; awake tracheal intubation is the most common approach in patients with a difficult airway. Moreover, when jet ventilation is used, total intravenous anesthesia (TIVA), for example with infusions of propofol and remifentanil, is needed. Finally, when panendoscopy is combined with laser surgery, a laser-safe ETT is often used.[101,102]

Panendoscopy is generally done while the patient is under general anesthesia with the patient's neck flexed and the head extended, usually employing a shoulder roll and a head ring (Jackson position). Typically, an anterior commissure laryngoscope is used and fixed into position by suspension (Fig. 85-8). This technique allows the surgeon's hands to be free and the operating microscope to be used. Other specialized ENT surgical laryngoscopes that are commonly used, often in conjunction with a microscope for laryngeal microsurgery, include the Dedo laryngoscope (Elmed, Addison, IL) and the Universal Modular Glottiscope (Endocraft, Providence, RI). Here, once the laryngoscope is correctly configured ("suspended"), the surgeon brings the operating microscope into the field and uses a variety of microlaryngeal instruments to treat the patient.

A variety of anesthetic techniques can be used for panendoscopy procedures. The most common approach is to perform the procedure while the patient is under general anesthesia with muscle relaxation in conjunction with an MLT-type tracheal tube (Fig. 85-9). This technique is familiar to anesthesiologists, provides both airway protection and control of ventilation, allows for reliable capnographic carbon dioxide (CO_2) measurements, and allows for the use of volatile anesthetics without operating room pollution. Disadvantages of the technique include higher than usual ventilation pressures as a consequence of the tube's narrow diameter, somewhat hindered surgical access, and concerns for tube ignition when a laser is in use.

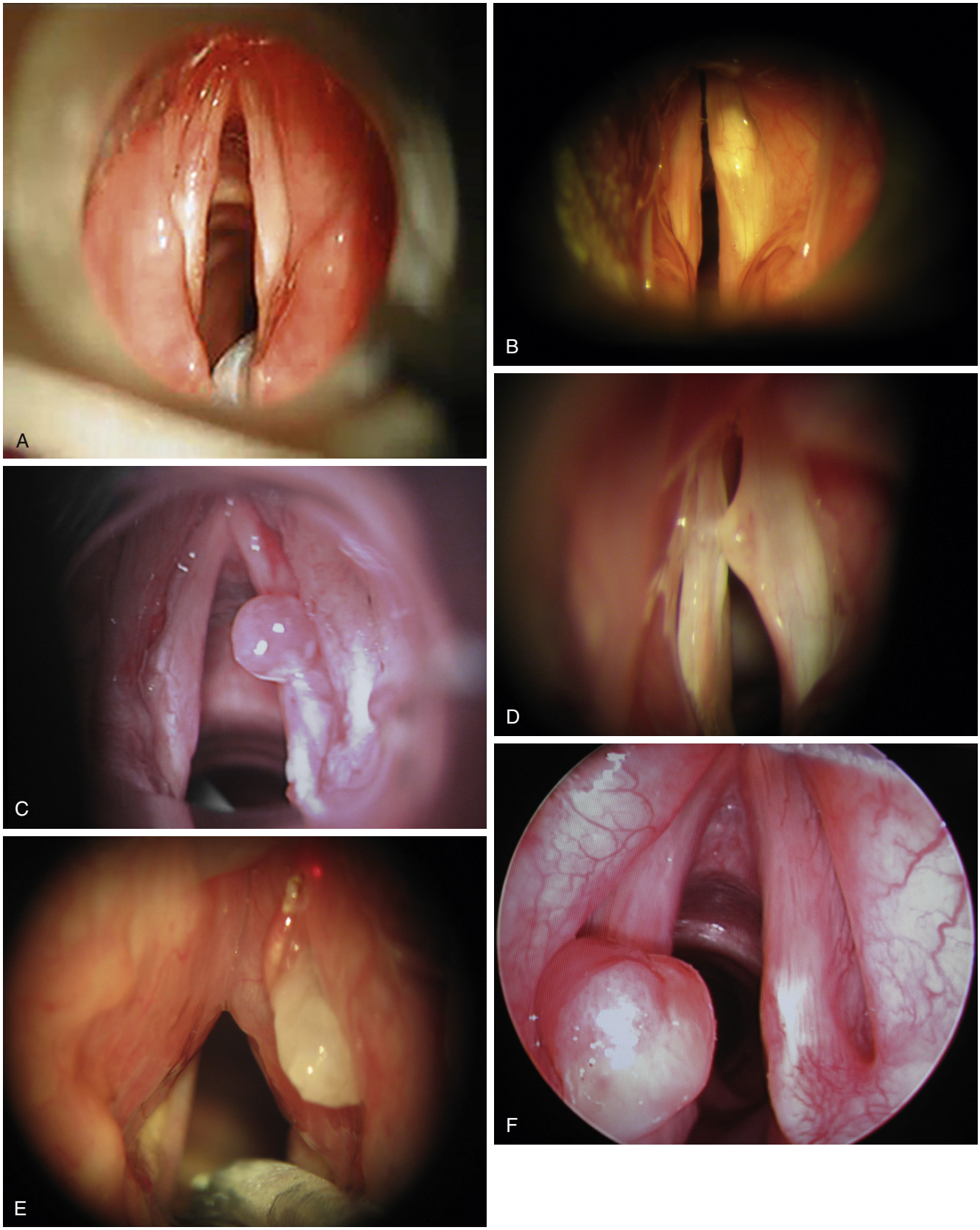


Figure 85-5. Vocal cord lesions with little or no airway compromise. **A,** Normal vocal cord. **B,** Minor right vocal cord lesion. **C,** Granuloma on the middle right vocal cord. **D,** Kissing nodule on the right vocal cord. **E,** Anterior webbing of the vocal cord. **F,** Intubation granuloma. *(From Feldman MA, Patel A: Anesthesia for eye, ear, nose, and throat surgery. In Miller RD, editor:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 2357-2388.)*

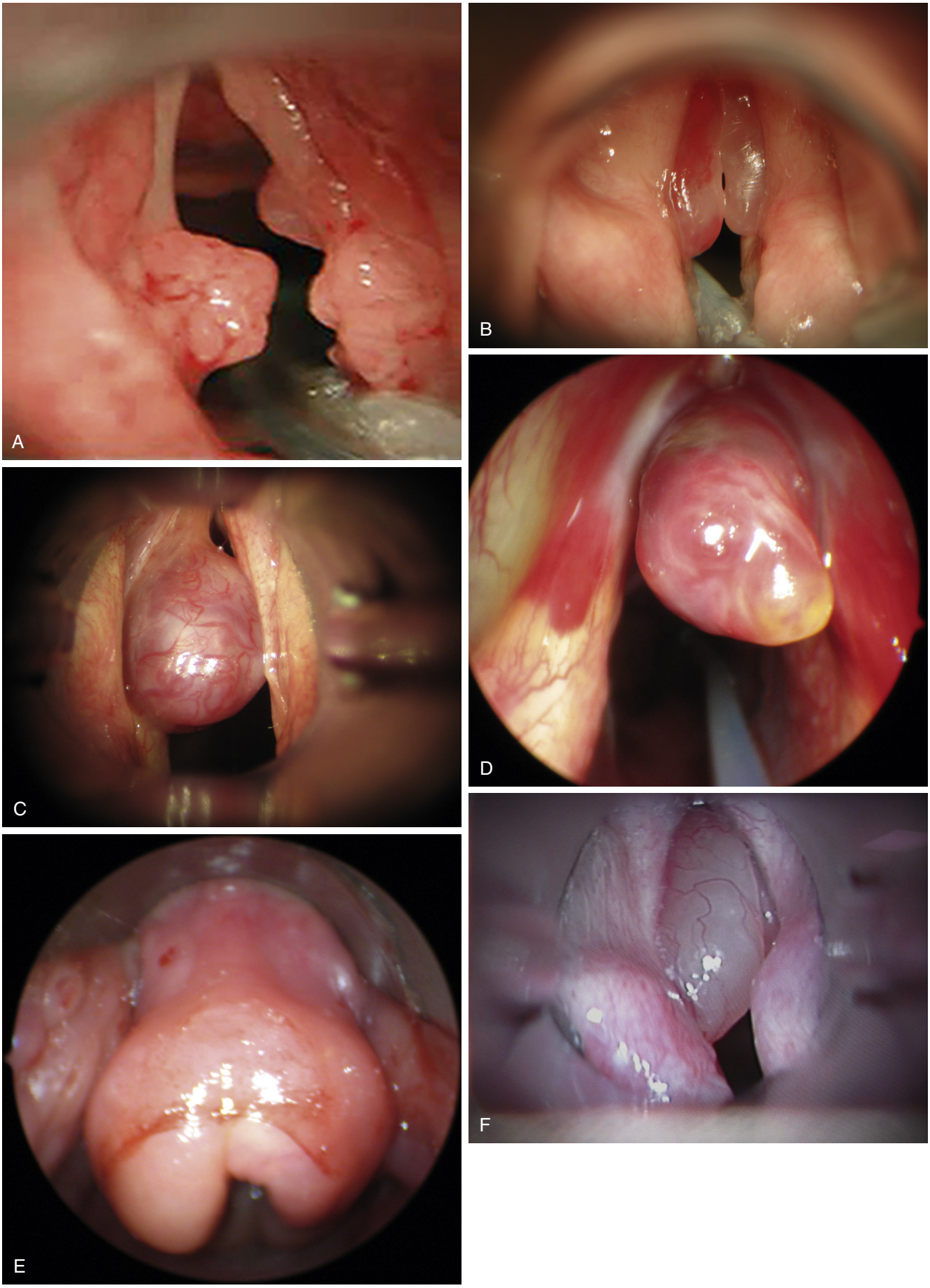


Figure 85-6. Vocal cord lesions with significant airway compromise. **A,** Papilloma of both vocal cords. **B,** Bilateral Reinke edema. **C,** Left vocal cord polyp. **D,** Anterior glottic granuloma. **E,** Epiglottic edema. **F,** Vocal cord cyst. *(From Feldman MA, Patel A: Anesthesia for eye, ear, nose, and throat surgery. In Miller RD, editor:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 2357-2388.)*

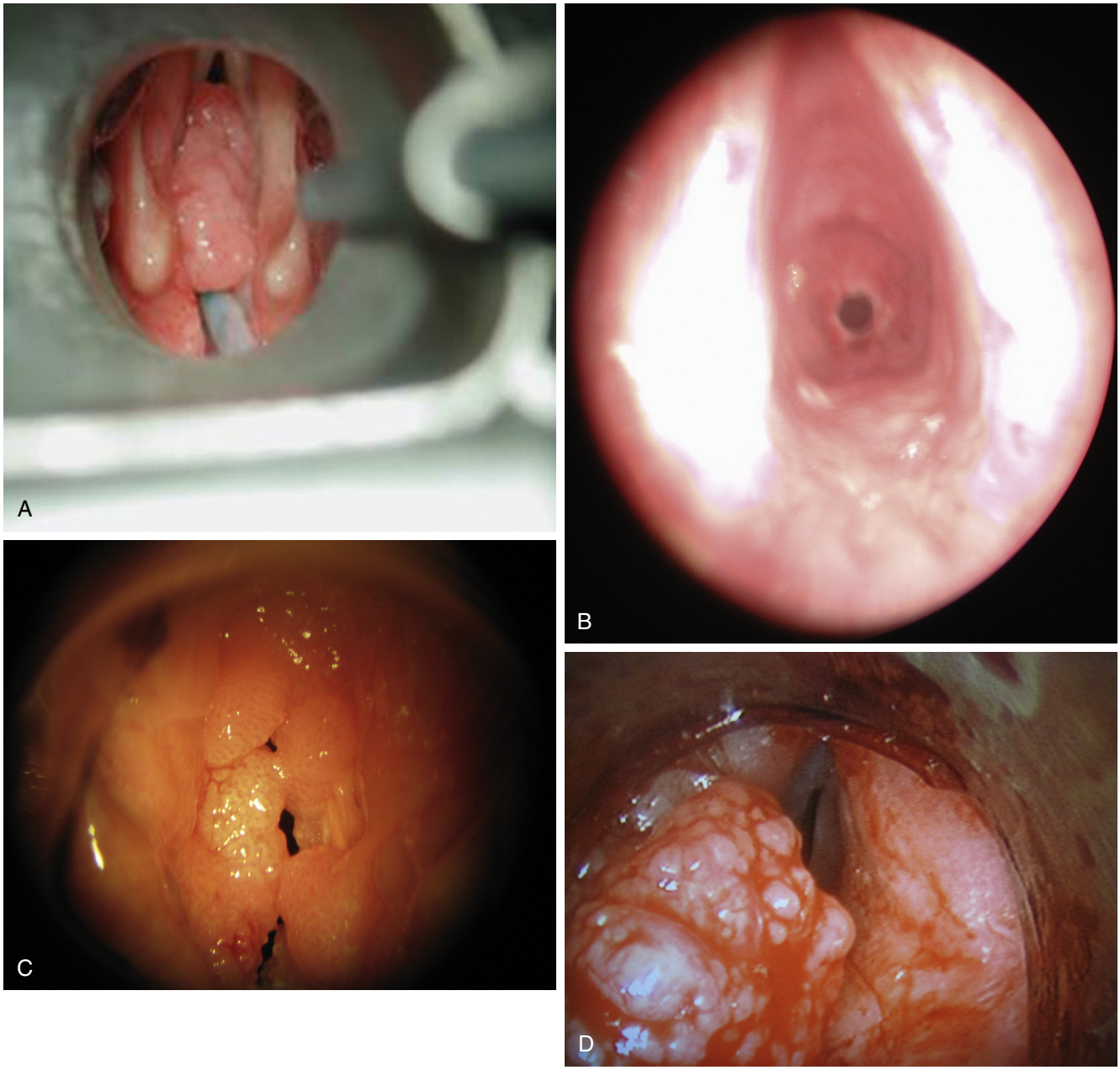


Figure 85-7. Vocal cord lesions with severe airway compromise. **A,** Papilloma of vocal cord. **B,** Severe subglottic stenosis (2-mm airway). **C,** Bilateral papilloma. **D,**Extensive supraglottic carcinoma.

Because a tracheal tube may impair access to some glottic structures, however, some cases are performed using intermittent apnea during general anesthesia and administration of neuromuscular blocking drugs. Disadvantages of this technique include the need for a TIVA technique, the need for repeated intubation-extubation cycles (potentially producing glottic trauma), fragmentation of the surgical work into brief apneic segments, and the repeated interruption of ventilation and oxygenation.

Next, panendoscopy is often performed using supraglottic jet ventilation.[103,104] This technique requires TIVA and entails some special issues because it involves the delivery of high-pressure oxygen pulses (typically 20 to 50 psi in adults, frequently delivered 1 second on/3 seconds off), usually through an adapter that attaches to the surgical laryngoscope. Additionally, subglottic methods (e.g., using a Hunsaker catheter[105,106]) and transtracheal methods of jet ventilation[107-110] have been described. Each pulse of oxygen entrains room air, thus increasing the gas volume delivered and diluting the oxygen concentration (Venturi effect). Disadvantages of jet ventilation include the need for TIVA, the potential for barotrauma (remember that a pressure of 50 psi is equivalent to 3515 cm H_2O), an inability to measure either end-tidal CO_2 ($ETCO_2$) or tidal volume easily, and the fact that the technique is often suboptimal in obese individuals. Finally, a variant of jet ventilation known as high-frequency jet ventilation is sometimes used in these cases,[111,112] often in conjunction with a special ventilator, an intratracheal catheter, and transcutaneous CO_2 monitoring.

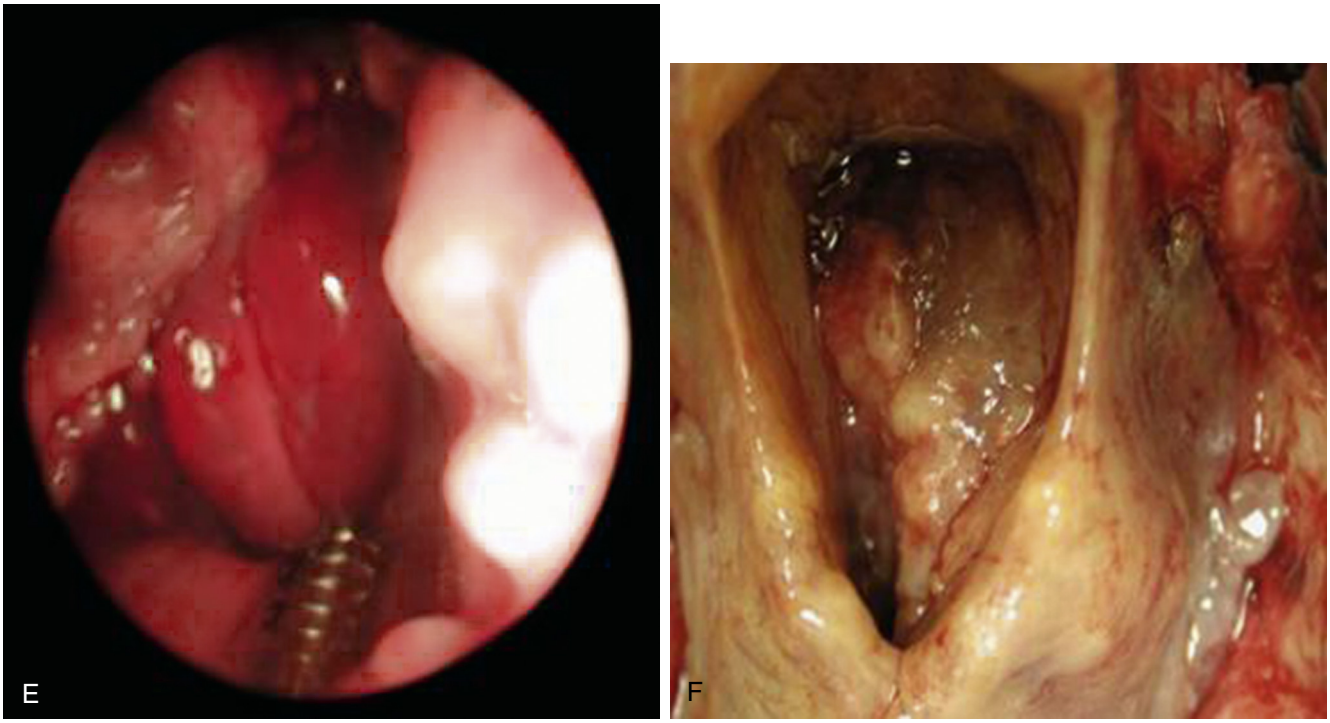


Figure 85-7, cont'd E, Acute epiglottitis. **F,** Laryngeal carcinoma. *(From Feldman MA, Patel A: Anesthesia for eye, ear, nose, and throat surgery. In Miller RD, editor:* Miller's anesthesia, *ed 7. Philadelphia, 2010, Churchill Livingstone, pp 2357-2388.)*

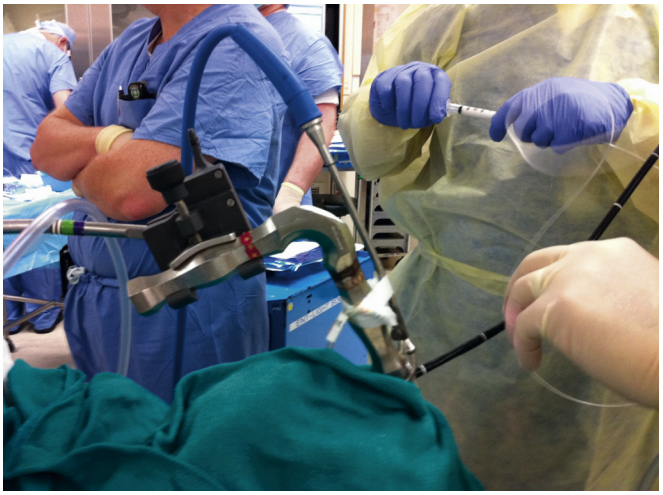


Figure 85-8. Patient undergoing an ear, nose, and throat procedure using a suspended anterior commissure laryngoscope. A jet ventilation attachment is taped to the handle. A fiberoptic bronchoscope with a laser fiber is in use to deliver laser pulses to areas of pathologic tissue. *(Image courtesy Dr. Basem Abdelmalak, Cleveland Clinic.)*

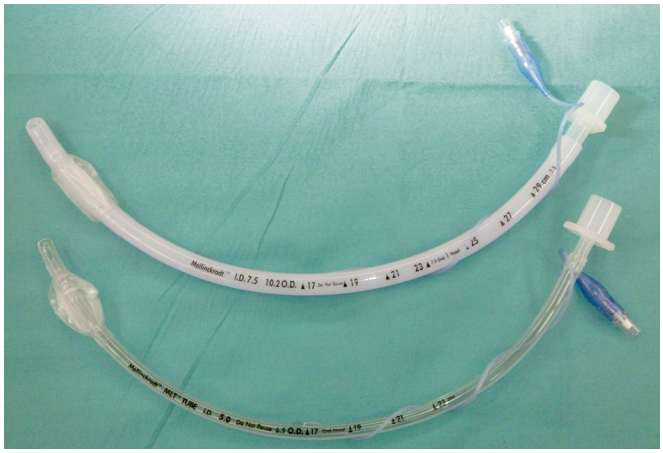


Figure 85-9. Regular 7.5-mm inner diameter (ID) tracheal tube *(top)* in comparison with a 5.0-mm ID microlaryngeal (MLT)–type tracheal tube *(bottom)*. The MLT tube has a narrow lumen that provides the surgeon with improved glottic exposure at the cost of higher ventilation pressures.

OTOLARYNGOLOGIC TRAUMA

Although the topic of anesthesia care for the trauma patient is the subject of Chapter 81,[113] a few special points pertaining to patients who have undergone head and neck trauma should be emphasized. First, patients with head and neck trauma may have a concurrent brain injury or injury to the cervical spine. Until cleared of a possible cervical spine injury, patients should be placed in a rigid cervical collar. In addition, although placing the patient's head in the customary "sniffing" position can facilitate laryngoscopy, this technique is contraindicated in patients with a suspected cervical spine injury for fear of exacerbating any injury. Additionally, jaw thrust and chin lift maneuvers can be more difficult when a cervical collar is used or when comminuted mandibular fractures are present.

Second, facial injuries can produce extensive bleeding, as well as the aspiration of blood, bone, cartilage, teeth, and tissue fragments. Third, the airway may be compromised, especially when bilateral mandibular fractures are present. Airway trauma from blunt or penetrating

injuries, burns, inhalational injury, or even iatrogenic causes may be present. Immediate airway management options include orotracheal intubation (awake versus rapid-sequence induction), a surgical airway carried out using local anesthesia, or even intubation through an open airway in cases of tracheal transection. Oropharyngeal airways may not be tolerated in patients with an intact gag reflex, and inserting a nasopharyngeal airway may exacerbate bleeding.

Although fiberoptic intubation would seem to offer many advantages in trauma cases, clinical experience suggests otherwise, at least in some cases, because navigating through a distorted airway filled with blood and foamy secretions challenges even the most experienced bronchoscopists. Special concerns exist when the trachea is intubated in a patient with laryngeal trauma because this may result in further injury or even complete airway loss (e.g., in the event of inadvertent ETT placement through a laryngeal fracture into the mediastinum). Clinical findings suggestive of laryngeal trauma include abrasions, discoloration, indentation, bleeding, or pain in the region of the larynx, as well as dyspnea, dysphagia, dysphonia, stridor, hemoptysis, subcutaneous emphysema, and hoarseness. Signs of pneumothorax may also be present, whereas fiberoptic endoscopic examination may reveal edema, the presence of bleeding or hematoma, or abnormal vocal cord function. If endotracheal intubation is attempted in this setting, a fiberoptic bronchoscope with a small-diameter ETT can be used carefully, bearing in mind the foregoing concerns about fiberoptic intubation in the trauma setting. Additionally, positive-pressure ventilation by mask or SGA in this setting may worsen any subcutaneous emphysema. A tracheostomy may be the most prudent course in some cases. Finally, the application of cricoid pressure in blunt laryngeal trauma may result in cricotracheal separation and so is contraindicated. In any event, in both facial trauma and airway trauma, initial management is dictated by the degree of respiratory distress or potential airway compromise, the available equipment, and clinical preferences.

Midfacial fractures deserve special mention. These fractures are defined by the Le Fort classification. A Le Fort I fracture is a horizontal fracture that involves the inferior nasal aperture, separating the maxillary alveolus from the rest of the midfacial skeleton. Le Fort II fractures are pyramidal nasomaxillary fractures that break from the upper craniofacial skeleton. Le Fort III fractures, less commonly encountered than the others, involve the separation of the facial skeleton from the skull base. These fractures are illustrated in Figure 85-10.

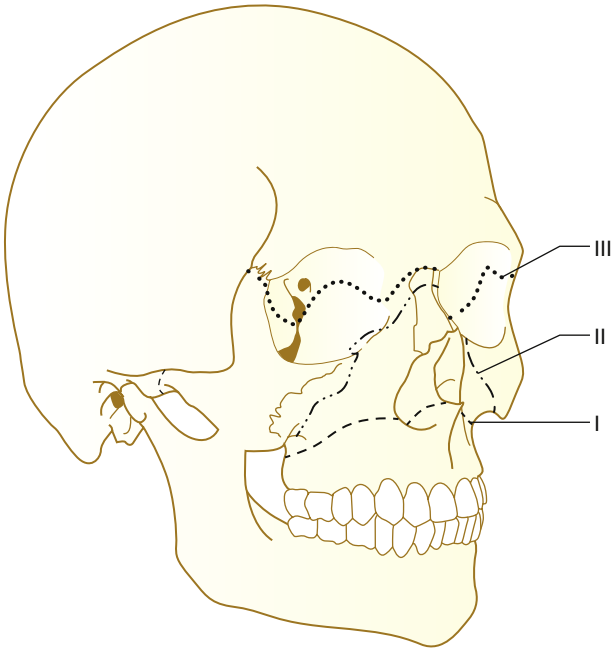


Figure 85-10. Classification of midfacial fractures. Le Fort I: alveolar fracture. Le Fort II: zygomatic-maxillary complex fracture. Le Fort III: cranial facial dysostosis with separation of the midface from the skull. *(From Schuller DE, Schleuning AJ:* Otolaryngology: head and neck surgery, *ed 8. St. Louis, 1994, Mosby, p 157.)*

NASAL SURGERY

Nasal surgery can involve external procedures, procedures within the nasal cavity, surgery involving the nasal bones, and nasal sinus surgery. Besides the usual concerns, preoperative assessment should focus on the suitability of topical nasal vasoconstrictor use, the possibility of undiagnosed OSA, and the potential presence of the Samter triad (nasal polyps, asthma, and a sensitivity to aspirin and NSAIDs that may produce deadly bronchospasm). Because postoperative bleeding is a common complication after nasal surgery, patients should not be taking NSAIDs and aspirin for 1 to 2 weeks preoperatively.

Preoperative planning begins by deciding whether the procedure is best performed with local (usually accompanied by intravenous sedation) or general anesthesia. Although local anesthesia may be suitable for simple procedures such as cauterization or straightforward polypectomy or turbinectomy surgery in adults, often general anesthesia is required. When general anesthesia is chosen, a choice must then be made among a simple facemask (as may be appropriate for pediatric myringotomy surgery), an SGA device (e.g., flexible LMA), and a tracheal tube (e.g., an unkinkable wire-reinforced design). This decision should be made jointly with the surgeon. Although the use of an SGA during ENT surgery has its enthusiasts, negative experiences, such as airway obstruction related to device malpositioning, have led many clinicians to prefer a tracheal tube in such cases.

Patients undergoing rhinoplasty are typically young, healthy individuals requiring reconstruction of the external nose for deformity treatment.[114,115] Septoplasty (correction of a deviated septum)[116-118] and surgery to remove nasal polyps[119-120] are often performed to improve nasal airflow and ventilation of the sinuses. Some malignant lesions require excision of the entire nose with follow-up staged reconstruction using a forehead flap. Open nasal fracture reduction procedures are usually performed after the initial swelling has resolved; if the injury is corrected too late, the bones can be difficult to align and can lead to significant surgical bleeding. General endotracheal anesthesia is usually carried out in such cases, often using a midline reinforced ETT taped to the chin. In closed nasal fracture reduction, the surgeon applies forceful pressure

to realign the nasal bones, a procedure that usually takes only a few seconds but nevertheless is so intensely painful that the procedure is usually preceded by a single induction dose of propofol, followed by airway support as needed as a nasal cast is applied. However, when the reduction is expected to be bloody or otherwise complicated, the airway is usually protected with an ETT or an SGA device. In many of these procedures, nasal packs, stents, and/or casts are placed; nasal stents offer an advantage over packs in that one can breathe through them.

In many ENT cases, a "throat pack" made of a long piece of saline-soaked gauze is stuffed around the ETT to prevent blood and surgical debris from entering the pharynx and larynx. Typically, a few inches of gauze are kept outside the mouth as a reminder of its presence, because an inadvertently retained pack can lead to catastrophic airway obstruction after extubation.[121] In addition to suctioning, many clinicians follow throat pack removal with pre-extubation laryngoscopy and a neck flexion-extension maneuver to encourage any residual clot (the so-called "coroner's clot") to fall past the soft palate into a position where it can be removed under direct vision.

Gentle awakening in nasal surgery is important because coughing and bucking on emergence frequently produce undesirable bleeding. Techniques that are often helpful include the use of a remifentanil infusion and the application of lidocaine down the ETT with the cuff temporarily deflated while the patient is still under deep anesthesia. Oral and gastric suction before emergence will decrease the incidence of postoperative nausea and vomiting (PONV) (see Chapter 97). When nasal packing is used, patients should be advised before induction of anesthesia that, on emergence, they should breathe through the mouth. On awakening, applying pressure on the nose with a facemask should not be done for fear of ruining the surgeon's handiwork. In addition, all postoperative patients with nasal packs will have obstructed nasal passages unless nasopharyngeal airways are incorporated into the nasal pack, and patients with OSA are in particular need of careful postoperative respiratory monitoring. Finally, postoperative pain in these procedures usually does not require opiates, and the use of oral acetaminophen and an NSAID usually suffices (see also Chapter 98).

In many of these procedures, a topical vasoconstrictor such as phenylephrine, oxymetazoline, or cocaine is used. Although these topical agents are important drugs that reduce bleeding and improve visualization during nasal and endoscopic procedures, they sometimes produce cardiovascular toxicity.[122] The cardiovascular effects of cocaine, usually administered as a 4% (40 mg/mL) topical solution, result from the drug's blocking the reuptake of norepinephrine at sympathetic nerve terminals. Consequently, cocaine would not be a first-choice vasoconstrictor in patients with coronary artery disease or hypertension or in patients taking monoamine oxidase inhibitors.[123] When cocaine use is appropriate, the dose should not ordinarily exceed 1.5 mg/kg.

Phenylephrine is an α-adrenergic agonist topical vasoconstrictor either used alone or in combination with lidocaine. The initial dose should not exceed 500 μg (<20 μg/kg in children ≤25 kg). Because severe hypertension sometimes results following phenylephrine use, blood pressure monitoring is particularly important. Instances of unacceptable hypertension should be treated with direct vasodilators or α-receptor antagonists; the use of β-adrenergic and calcium channel blockers should be avoided because they may worsen cardiac output and produce pulmonary edema.[124]

Oxymetazoline, a selective α_1-agonist and partial α_2-agonist imidazoline-derivative, is perhaps the most popular topical vasoconstrictor in ENT surgery, primarily because of its excellent safety profile and availability as an over-the-counter product.[125-127] Three sprays of 0.05% solution are administered in each nostril. This drug should be avoided in patients taking monoamine oxidase inhibitors. However, despite its relative safety, complications have been reported.[128,129]

TONSILLECTOMY AND ADENOIDECTOMY

The adenoids are a mass of lymphoid tissue located posterior to the nasal cavity, in the roof of the nasopharynx. If this tissue become hyperplasic, nasopharyngeal obstruction and a number of related problems can occur such that the adenoids merit surgical removal (adenoidectomy). When removed, the tonsils are usually taken as well. Other indications for tonsillectomy include tonsillar hyperplasia, recurrent tonsillitis, and malignant disease.[130] An especially important consideration here is that chronic oropharyngeal airway obstruction as a consequence of tonsillar hypertrophy can lead to OSA and its attendant complications (daytime sombulence, cor pulmonale, pulmonary hypertension, right ventricular hypertrophy, cardiomegaly). In addition to the usual, preoperative assessment focuses on findings suggestive of OSA, possible cardiac comorbidities, and a history of recurrent upper respiratory tract infections. The presence of a fever or a productive cough may be grounds for postponement of the surgery or for postoperative care in setting of increased vigilance (e.g., ICU or step-down facility), especially in infants (see also Chapter 93).

Induction of anesthesia in adults usually entails administering intravenous drugs, whereas inhaled inductions are popular with children, followed by placement of an intravenous catheter and administration of glycopyrrolate. Oral RAE (named after the inventors Ring, Adair, and Elwyn) tracheal tubes or wire-reinforced tubes, taped in the midline to the mandible, are often preferred by surgeons and are less likely to kink following retractor placement. When a tonsillar or parapharyngeal abscess is present, the patient may have a compromised airway complicated by trismus and pharyngeal edema. Although awake abscess decompression by needle aspiration before the induction of anesthesia is sometimes done, awake fiberoptic intubation is the usual approach in this setting.

At the end of the surgical procedure, the throat pack, if previously placed, should be removed, the oropharynx should then be suctioned, and an orogastric tube should be used to empty the stomach. Extubation is sometimes performed using deep anesthesia but more commonly is carried out when the patient has intact airway reflexes. Coughing on the tracheal tube on emergence may be attenuated by the administration of lidocaine, either

given intravenously or placed down the tracheal tube with the cuff temporarily deflated. Emergence on a light remifentanil infusion can also be beneficial.

Posttonsillectomy hemorrhage is a dreaded surgical emergency, especially in children[131-133] (see also Chapter 93). It usually occurs within the first 6 postoperative hours, but it can also occur several days later. When possible, the patient should receive appropriate intravenous fluids preoperatively (including blood products when necessary). The presence of hypovolemia may dictate a reduction in induction drug dosage or the use of etomidate. Because the stomach may contain a considerable amount of blood, a *rapid-sequence induction* with cricoid pressure is usually performed with a view to protect the airway from aspiration of gastric contents. Vigorous suctioning is also needed to remove the copious oropharyngeal blood likely to be found during laryngoscopy.

ENDOSCOPIC SINUS SURGERY

Endoscopic sinus surgery has become a common ENT procedure. Indications are varied and include conditions such as nasal polyposis, recurrent or chronic sinusitis, epistaxis control, tumor excision, orbital decompression (e.g., for Graves ophthalmopathy), foreign body removal, treatment of sinus mucoceles, and more.[134-136]

Proper anesthetic management helps ensure a good outcome. Considerations in such cases include local versus general anesthesia, SGA device versus ETT, and inhaled anesthesia versus TIVA, and they take into account patient comorbidities, as well as preferences of the surgeon and anesthesiologist. The most important goals are a blood-free surgical field, patient immobility, stable cardiorespiratory conditions, and gentle emergence from anesthesia. Controlled hypotension is sometimes used to improve surgical conditions; when this approach is used, intraoperative β-adrenergic blockade is associated with better operating conditions than when vasodilation drugs are administered.

Despite minimal arterial blood pressure differences, propofol-remifentanil intravenous anesthesia may provide better surgical conditions as compared with a traditional balanced technique (e.g., using an isoflurane-opiate technique), possibly because of lower heart rates and cardiac output.[137] Use of an SGA device is preferred to an ETT because of better surgical conditions and smoother emergence. However, SGA devices are prone to malpositioning and provide less protection from gastric regurgitation as compared with an ETT.[138]

The procedure typically begins with decongestion of the nose and infiltration of 1% lidocaine with 1:100,000 epinephrine, often followed by the bilateral nasal placement of pledgets soaked in 4% cocaine. In most cases, an image-guided surgical system is used; this allows the surgeon to know exactly where he or she is operating by using a preoperative CT scan. This technology allows the surgeon to visualize four different views simultaneously: the coronal, sagittal, and axial CT scan images at the same time as the real time endoscopic view. This system requires a special headset that may preclude the use of electroencephalographic (bispectral index) monitoring (see also Chapter 44).

Given the close proximity of major blood vessels and nerves, the orbit, and the brain, complications are possible, especially when the surgical landmarks are obscured by blood. Some major complications include orbital hematoma formation, blindness from orbital trauma or damage to the optic nerve, formation of cerebrospinal fluid leak, carotid or ethmoid artery invasion, entry into the cranial cavity, severe hemorrhage, and death.

Finally, not all sinus surgery is endoscopic. For example, although now largely replaced by endoscopic methods, the once common Caldwell-Luc procedure involves fenestration of the anterior wall of the maxillary sinus with surgical drainage of this sinus into the nose through an antrostomy.

THYROID AND PARATHYROID SURGERY

The usual indications for thyroid surgery include thyroid cancer, symptomatic thyroid goiter, and failed medical management of hyperthyroidism; the surgical procedure is almost always elective.[139] The most common indication for parathyroid surgery is hypercalcemia from hyperparathyroidism secondary to a benign parathyroid adenoma. When the hypercalcemia is severe, preoperative treatment (e.g., fluids, furosemide, bisphosphonates) may be needed.

Hyperthyroid patients should be treated preoperatively to reduce the risk of thyroid storm (thyrotoxicosis). Thyrotoxic patients may experience sinus tachycardia, atrial fibrillation, myocardial ischemia, congestive heart failure, nervousness, tremulousness, insomnia, heat intolerance, weight loss, and other findings.[140,141]

Large goiters may result in deviation of the larynx, tracheal compression leading to considerable airway narrowing, Horner syndrome, or superior vena cava obstruction, especially with retrosternal extension.[142,143] Preoperative airway evaluation by endoscopic examination and by CT is often useful to determine the extent of the disease and the possibility that sternotomy will be needed.

General anesthesia with tracheal intubation and muscle relaxation is usually employed, although many surgeons routinely use a nerve integrity monitor (NIM) ETT for neuromonitoring,[144-146] in which case neuromuscular blocking drugs must be avoided in the postintubation period. Gentle emergence from anesthesia is necessary to avoid coughing on the ETT and the possibility of hematoma formation from venous engorgement. The use of a small-dose remifentanil infusion (0.01 to 0.05 μg/kg/minute) in the extubation period is a popular means to diminish coughing on the ETT. Although deep extubation also reduces the incidence of bucking and straining, many clinicians avoid this technique wherever possible because of airway obstruction.

Possible complications of thyroid and parathyroid surgery include hematoma formation (possibly resulting in airway impairment), vocal cord dysfunction from recurrent laryngeal nerve injury, pneumothorax, and other conditions. In patients with compressive goiters, postthyroidectomy tracheomalacia may occur following goiter excision. In postoperative patients who have undergone parathyroid and total thyroidectomy, serial calcium levels are taken to detect inadvertent hypocalcemia.

AIRWAY FIRES

An airway fire is a potentially deadly complication that may occur during tracheotomy surgery, during laser surgery to the airway, and elsewhere (see also Chapters 55, 88, and 109). For a fire to occur, the triad of fuel (e.g., ETT, drapes, sponges), oxygen, and an ignition source (e.g., laser or electrocautery) is needed. The ASA published an Operating Room Fires Algorithm (Fig. 85-11),[147] to which the reader is referred. An additional helpful resource is a checklist developed by Dr. B. Abdelmalak (Box 85-2). Prevailing conventional wisdom, at least until recently, holds that cases of airway fire call for immediate removal of the ETT. Although this is a reasonable rule of thumb, it should also be noted that in some patients, removal of the ETT would result in irreversible loss of the airway. Clinicians in such a setting face a particularly difficult choice: leave the ETT in place and risk fire-related injury to the patient, or remove the ETT and risk deadly loss of the airway.

EAR SURGERY

Ear operations range from simple, brief procedures such as myringotomy and tube placement to much more involved procedures such as skull-based surgery. These procedures are best divided into external ear procedures (e.g., removal of exostoses or foreign bodies), middle ear procedures (e.g., myringotomy, tympanoplasty, stapedectomy), mastoid operations (e.g., mastoidectomy), and inner ear procedures (e.g., cochlear implant placement). In such procedures, and especially with inner ear procedures, patients are particularly prone to PONV (see also Chapter 97).

Although many simple procedures can be performed in well-selected individuals by using local anesthesia and intravenous sedation, more complex procedures, especially those requiring an operating microscope (for which immobility is essential), are usually best accomplished using general anesthesia with the presence of a secure airway. Regardless, in all such cases the anesthesiologist must consider issues such as the appropriate form of airway management, whether nitrous oxide is contraindicated, the possibility that postintubation muscle relaxants should be avoided to permit facial nerve monitoring, and the possible need for antiemetic prophylaxis. Most patients require a tracheal tube; the unkinkable, wire-reinforced variety is commonly used to avoid airway trouble following head rotation. Alternatively, preformed tracheal tubes (e.g., RAE tubes) are commonly used.

Nitrous oxide is avoided in middle ear procedures because it diffuses from blood to the middle ear, thereby increasing middle ear pressure and potentially distending any carefully placed tympanic membrane grafts. However, many ENT surgeons now use "underlay" grafts, in which increased middle ear pressures can actually help hold the graft in place, as opposed to older "overlay" grafts, in which a high middle ear pressure would dislocate the graft.

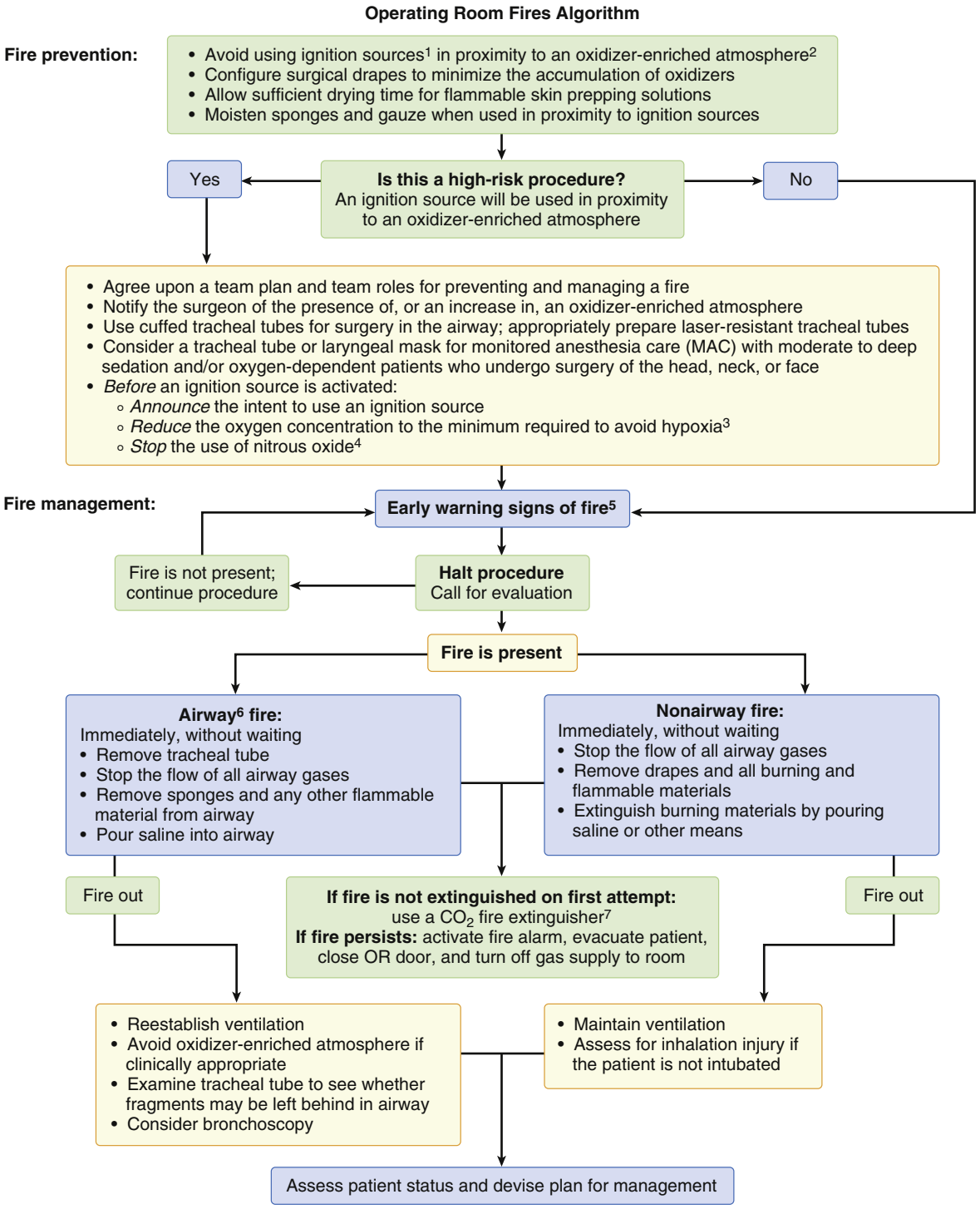
Many middle ear operations are performed to ameliorate hearing loss from infection or inflammation. The most frequent of these procedures, myringotomy with tube placement, is most commonly performed in children by using simple sevoflurane mask anesthesia, in conjunction with acetaminophen or (less commonly) fentanyl to treat postoperative pain. The procedure can usually be safely accomplished without establishing intravenous access.[148]

Stapedectomy, typically performed to treat otosclerosis, is usually performed using general anesthesia and may involve the use of surgical lasers (hence a potential need for laser precautions), as well as facial nerve monitoring (hence a potential need for periods with minimal neuromuscular blockade). The use of a volatile anesthetic in combination with a remifentanil infusion helps provide mild hypotension (which reduces blood loss), as well as surgical immobility. Nitrous oxide can theoretically be used early in the procedure, but it must be avoided later on to avoid damaging possible "overlay" grafts to the tympanic membrane. However, most clinicians simply avoid nitrous oxide entirely, to reduce the incidence of PONV (see also Chapter 97). Gentle emergence, often involving a remifentanil infusion, helps avoid coughing or "bucking" with the tracheal tube present, with possible displacement of the bone prosthesis. Not surprisingly, extubation of the trachea during deep anesthesia is sometimes performed. Ossiculoplasty procedures involve similar considerations.

Common inner ear procedures include surgery to the cochlea, endolymphatic sac, and labyrinth. Patients with pathologic processes in the labyrinth and endolymphatic sac, such as patients with Meniere's disease, often suffer from vertigo and hearing loss and are especially prone to PONV. In cochlear implant surgery, mastoidectomy is performed to implant the signal coupler while the electrode array is implanted into the cochlea, a procedure often taking over 4 hours. Considerations similar to those for stapedectomy apply, including the potential need for nerve monitoring, the avoidance of PONV, and gentle emergence from anesthesia. Some surgeons also request a degree of hypotension as a means to reduce blood loss.

Untreated chronic otitis media often leads to mastoiditis, tympanic membrane perforation, and damage the ossicular chain. Additionally, the formation of a cholesteatoma (an invasive growth of keratinizing squamous epithelium) may spread into the mastoid cavity, inner ear, and even to brain to cause additional damage. When antibiotic treatment fails, mastoidectomy (removing infected material, draining subperiosteal abscesses, and reestablishing middle ear ventilation) may be indicated. Because blood loss can be substantial, controlled hypotension is sometimes requested. The nerve identification and gentle emergence issues discussed earlier often apply as well. Nitrous oxide is often avoided, at least in the later stages, because of the tympanoplasty component of the procedure.

Surgical procedures of the outer ear may be used to correct congenital and acquired malformations. Although these patients often present no special challenges, beware of patients whose malformation is part of Goldenhar syndrome or Treacher Collins syndrome because these patients frequently offer airway challenges. General anesthesia is typically employed, and postoperative pain can be substantial when a rib graft is used.



[1] Ignition sources include but are not limited to electrosurgery or electrocautery units and lasers.
[2] An oxidizer-enriched atmosphere occurs when there is any increase in oxygen concentration above room air level and/or the presence of any concentration of nitrous oxide.
[3] After minimizing delivered oxygen, wait a period of time (e.g., 1 to 3 minutes) before using an ignition source. For oxygen-dependent patients, reduce supplemental oxygen delivery to the minimum required to avoid hypoxia. Monitor oxygenation with pulse oximetry and, if feasible, inspired, exhaled, and/or delivered oxygen concentration.
[4] After stopping the delivery of nitrous oxide, wait a period of time (e.g., 1 to 3 minutes) before using an ignition source.
[5] Unexpected flash, flame, smoke or heat, unusual sounds (e.g., a "pop," snap or "foomp") or odors, unexpected movement of drapes, discoloration of drapes or breathing circuit, unexpected patient movement or complaint.
[6] In this algorithm, airway fire refers to a fire in the airway or breathing cicuit.
[7] A CO_2 fire extinguisher may be used on the patient if necessary.

Figure 85-11. American Society of Anesthesiologists' Operating Room Fires Algorithm. *CO_2*, carbon dioxide; *OR*, operating room. *(From Caplan RA, Barker SJ, Connis RT, et al: Practice advisory for the prevention and management of operating room fires,* Anesthesiology *108:786-801, 2008. <www.asahq.org/~/media/Lifeline/Anesthesia%20Topics/Practice%20Advisory%20for%20the%20Prevention%20and%20Management%20of%20Operating%20Room%20Fires%202013.pdf>.)*

PAROTID AND OTHER SALIVARY GLAND SURGERY

The salivary glands comprise a pair of parotid glands, two submandibular glands, two principal sublingual glands, and a number of minor salivary glands. As exocrine glands, their function is variously to produce saliva, digestive enzymes (amylase), and lubrication, as well as to provide a bacteriostatic function. Indications for submandibular gland surgery include tumors, chronic sialadenitis refractory to medical treatment, and removal of impacted stones. The most frequent parotid disease warranting surgery is a benign neoplasm, frequently a pleomorphic adenoma. Superficial parotidectomy (complete or limited) with facial nerve dissection is the most commonly performed procedure for these lesions, although a simpler enucleation procedure is sometimes also performed.[149-151] Identification of the facial nerve and its branches, often employing nerve stimulation methods, is central to the procedure. For this reason the surgical team usually requests that muscle relaxants be avoided after endotracheal intubation has been achieved.

Besides the usual considerations applying to all surgical patients, preoperative evaluation (see also Chapter 38) of patients for salivary gland surgery should consider any previous head and neck surgery and any history of radiation therapy (which can make mask ventilation difficult). The physical examination should look for tumor displacement of the airway, as well as impaired temporomandibular joint (TMJ) mobility and other predictors of airway difficulties. Available head and neck CT scans or MRI studies should be reviewed with the surgical team, with a focus on airway issues.

During these procedures, complete immobility of the patient is important. Consequently, general anesthesia with endotracheal intubation is usually required, although cases of parotid surgery performed using local anesthesia have been reported.[152] Management of the airway with an LMA for parotid surgery has been described; however, the typical 2- to 4-hour duration of the operation and the need for an operative side-up head position lead most anesthesiologists to use a tracheal tube. Sufficient anesthetic depth and patient immobility are usually achieved using relatively large doses of opioid and inhaled anesthetics, with muscle relaxants avoided to allow facial nerve monitoring for both parotid and (less commonly) submandibular surgery. I frequently employ a single, small dose of rocuronium to facilitate endotracheal intubation, followed by sevoflurane anesthesia in conjunction with a remifentanil infusion (e.g., 0.1 μg/kg/minute) to provide immobility. Finally, preservation of the facial nerve is of prime importance in these operations; consequently, the surgeon often must identify the facial nerve by using a nerve stimulator. This crucial step is not possible if neuromuscular blockade is present.

BOX 85-2 *Management of Airway Fires*

Prevention and Preparedness

1. Keep the O_2 concentration at approximately 30%, or less if possible. Use an O_2/air mixture. Avoid N_2O.
2. Use a "laser-safe" endotracheal tube.
3. Inflate the endotracheal tube cuff with dyed normal saline to provide an early indicator of cuff rupture.
4. Use a pre-prepared 50-mL syringe of saline to extinguish any fire, and flood the surgical field if a fire occurs.
5. Have an extra endotracheal tube available for reintubation in case a fire occurs.
6. Inform the surgical team working on the airway of any situation in which high concentrations of O_2 are being used.

In the Case of an Airway Fire

1. Stop lasering. Stop ventilation. Turn O_2 off (as well as N_2O if it was mistakenly in use).
2. Inform the surgical team, and assign someone to call the control desk for help.
3. Remove the burning endotracheal tube* and drop it in the bucket of water, if available.
4. Put out the fire with your improvised fire extinguisher.
5. The area should be flushed with saline.

When the Fire Is Extinguished

1. Ventilate the patient with 100% O_2 by facemask (or supraglottic airway if appropriate).
2. When the patient is stable, assess the extent of airway damage. Consider using a ventilating rigid bronchoscope; debris and foreign bodies should be removed.
3. Reintubate the patient if significant airway damage is found.
4. When appropriate, arrange for admission to an ICU.
5. Provide supportive therapy, including ventilation and antibiotics, and extubate when appropriate.
6. Tracheotomy may be needed.

Courtesy Dr. B. Abdelmalak, Cleveland Clinic, Cleveland, Ohio.
ICU, Intensive care unit; *N_2O,* nitrous oxide; *O_2,* oxygen.
*Removing the endotracheal tube may be inappropriate in some cases (see text).

SLEEP APNEA SURGERY

OSA involves repetitive partial or complete upper airway obstruction from collapse of the pharyngeal airway during sleep.[153-158] This condition typically occurs despite continued movement of the diaphragm and can lead to apneas (with complete obstruction), hypopneas (with partial obstruction), and respiratory effort–related arousals. The last of these can occur without desaturation, whereas hypoxia itself leads to arousal from sleep, with reopening of the airway and the intake of a breath. Severity is related to the number of these respiratory events per hour as determined by polysomnography. Patients in whom conservative treatment (e.g., weight loss, continuous positive airway pressure, bilevel positive airway pressure, oral appliances) fails may benefit from either surgical modification of the upper airway or, rarely, tracheostomy. Commonly performed procedures include uvulopalatopharyngoplasty, uvulopalatal flap surgery, tonsillectomy and adenoidectomy, genioglossus advancement, maxillomandibular advancement, and other procedures. Sometimes these procedures are performed in combination. Possible comorbidities such as obesity (see also Chapter 71), metabolic syndrome, type 2 diabetes, coronary artery disease, or cor pulmonale should be identified. Patients with OSA can be difficult to intubate tracheally or ventilate by mask, and they are especially prone to postoperative hypoxia. In addition, they frequently have

conditions such as macroglossia, redundant pharyngeal tissue, lingual tonsil hypertrophy, or an anterior larynx, all of which can make direct laryngoscopy difficult.

Clinical features that increase the likelihood that OSA is present include a body mass index greater than 30 kg/m^2, large neck circumference (>17 inches in men; >16 inches in women), a high Mallampati score (3 or 4), and the presence of features such as a large uvula, macroglossia, retrognathia, tonsillar hypertrophy, or a high arched palate. The airway features predisposing to OSA may also lead to a difficult airway. For example, difficult intubation is encountered five to eight times more often in patients with OSA compared with other patients. Additionally, snoring and OSA are independent risk factors for difficult ventilation by mask.

General endotracheal anesthesia is preferable for OSA surgery because of the risk of aspiration of blood from the surgical site and the risk of laryngospasm should blood or secretions make contact with the vocal cords.

Postoperative vigilance is paramount. One reason is that patients with OSA have an increase in postoperative obstructive episodes, peaking on postoperative day 3 and returning to preoperative levels after a week. Consequently, patients with OSA who are undergoing airway surgery are not outpatient candidates. Postoperative airway edema is another concern and constitutes another reason that it is wise to minimize respiratory depressants such as opioids and sedatives postoperatively. Dexamethasone is often given to reduce airway edema.

ZENKER DIVERTICULUM

Zenker diverticulum, first described in 1874, is a herniation or outpouching of pharyngeal mucosa through the posterior wall of the hypopharynx (often between the oblique and horizontal components of cricopharyngeus).[159,160] Typically seen in the sixth to ninth decades of life and occurring in approximately 1 in 800 upper gastrointestinal barium studies, patients may describe regurgitation of undigested food when supine and food caught in the throat (i.e., in the mucosal pouch), as well as coughing, dysphagia, and halitosis. Confirmation of the clinical diagnosis is usually by barium swallow and/or endoscopy.

Surgery can be either open or endoscopic. In the open (transcervical) approach, the diverticulum is exposed through a lateral neck incision and is then resected (diverticulectomy) or tacked superiorly to the prevertebral fascia (diverticulopexy). Cricopharyngeal myotomy may be added to help prevent recurrence. In the endoscopic approach, no skin incision is required; here the surgical procedure usually involves ablating the common wall between the pouch and the cervical esophagus by using an endoscopic stapler, surgical laser, or other means.

Several anesthetic considerations apply. First, patients are frequently older, with applicable comorbidities, such as coronary artery disease. Second, the possibility that food caught in the pouch could end up in the airway is a concern. Additionally, oral medications such as antihypertensives administered the day of surgery may lodge in the pouch and be aspirated. Perhaps preoperative evacuation of the pouch can be performed by applying external pressure before anesthesia, but this is not commonly done because of concerns of causing iatrogenic pulmonary aspiration. More commonly, the patient is positioned with a 30-degree head-up tilt before the induction of anesthesia.

Although awake endotracheal intubation should provide excellent protection against the risk of aspiration of pouch contents, a theoretic concern exists that any coughing during the procedure, either from the use of transtracheal local anesthesia or from the instrumentation, could lead to regurgitation of pouch contents with possible aspiration. A more common technique is the use of rapid-sequence induction of anesthesia, usually with the modification that cricoid pressure is not used, for fear of discharging the pouch contents with the applied pressure. (Application of cricoid pressure is recommended only if the neck of the pouch is below the cricoid cartilage; see Fig. 85-12). Some experts have expressed the concern that using succinylcholine, especially if it is not preceded by a nondepolarizing muscle relaxant, could produce muscle fasciculations that could cause pouch compression (see also Chapter 34). Even after endotracheal intubation, seepage of material around the ETT cuff can occur with surgical manipulation; some clinicians place a moist gauze throat pack to prevent aspiration of this material. Finally, the procedure is occasionally performed using regional anesthesia with deep and superficial cervical plexus blocks (see also Chapter 57).

Care should be taken to avoid perforation of the diverticulum, such as with blind placement of a nasogastric tube or during difficult tracheal intubation. During the surgical procedure, retraction of the carotid sheath may stimulate baroreceptors and initiate arrhythmias, especially bradycardia, whereas significant blood loss and air embolism may occur if major vessels are accidently cut. A smooth awakening from anesthesia that is free from coughing and straining is important to avoid the risks of neck hematoma and the attendant possibility of a compromised airway.

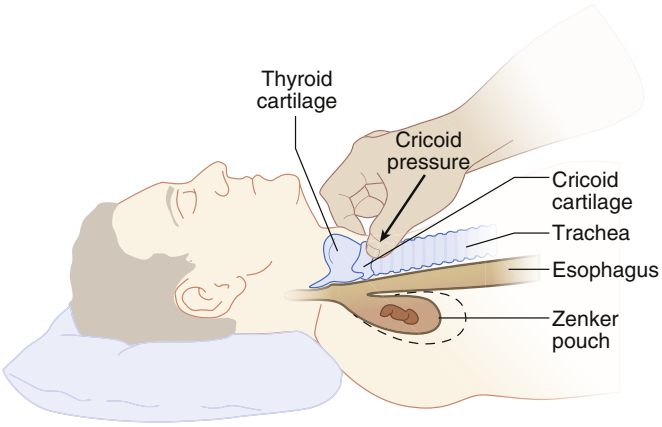


Figure 85-12. Anatomic relationship of the diverticulum to the cricoid cartilage during application of cricoid pressure. *(From Thiagarajah S, Lear E, Keh M: Anesthetic implications of Zenker diverticulum,* Anesth Analg *70:109-111, 1990.)*

ANESTHESIA FOR SURGICAL AIRWAYS: CRICOTHYROTOMY AND TRACHEOSTOMY

Two general approaches exist to create a surgical airway. In dire emergencies one may perform a cricothyrotomy,[161,162] by entering the airway through the cricothyroid membrane. This is done either by inserting a narrow-bore transtracheal ventilation catheter percutaneously through the cricothyroid membrane and employing emergency high-pressure jet ventilation or by inserting a wider-bore tube of sufficient diameter to allow low-pressure ventilation through a conventional resuscitator bag (e.g., "Ambu" bag). This second approach through the cricothyroid membrane can be achieved by using a vertical scalpel incision, identifying the cricothyroid membrane, cutting through the membrane with a horizontal stab incision, and placing (for example) a 6-mm inner-diameter tracheal tube. Alternately, one can use a commercial kit employing (for example) the Seldinger technique (e.g., Melker cricothyrotomy kit, Cook Medical, Bloomington, Ind.). An educational cricothyrotomy video is available at http://www.cookmedical.com/cc/educationMedia.do?mediaId=1522

The second approach to achieving a surgical airway is a tracheostomy.[163,164] (Although the terms "tracheotomy" and "tracheostomy" are used interchangeably by clinicians, based on their Greek roots, the former term refers to cutting into the trachea, whereas the latter refers to the opening that has been created.) This approach is best suited for situations that are not high-level emergencies, takes rather longer to complete, and usually involves entering the airway between the second and third tracheal rings following a careful dissection of the neck tissues. Although it is very often performed using general anesthesia in an intubated ICU patient in whom ventilator weaning has failed, it is sometimes performed using local anesthesia, either employing no sedation (this is the usual case in stridulous patients, especially those requiring Heliox) or using a drug such as dexmedetomidine because of its lack of respiratory depression. In any event, the decision to perform a tracheostomy using local anesthesia is made jointly with the surgeon and depends on the extent of airway disease, the experience of the surgical team, and the degree to which the patient is able to tolerate lying supine with his or her head in extension. In some cases the procedure must be performed with the patient in a semiupright sitting position (see also Chapter 41).

In the case of patients whose tracheas are intubated, at one point in the procedure the anesthesia provider will be asked to withdraw the tracheal tube slowly to permit the airway to be entered without obstruction. Additionally, at this time the airway should be entered using a scalpel and not using cautery, to prevent an airway fire in an oxygen-rich environment.

A number of problems may arise in the postoperative period following a tracheotomy.[165-167] Bleeding, pneumothorax, subcutaneous or mediastinal emphysema, and hypoventilation or airway obstruction may occur immediately after the procedure, whereas possible late complications include tracheal stenosis, tracheoesophageal fistula formation, tracheomalacia, and even tracheal necrosis. Although posttracheotomy bleeding is usually inconsequential, bleeding into the airway may cause the patient to cough and buck forcefully. In addition, major bleeding from a large artery or vein (often the communicating branch of the superior thyroid artery) may necessitate immediate exploration of the surgical field, whereas bleeding from the innominate artery may occur from erosion by the distal end of the cannula. (One hint that the tracheostomy could be applying pressure to the innominate artery is the finding of pulsations in the tracheotomy cannula after initial insertion. Treatment includes inflating the tube cuff and pulling the tube assembly anteriorly to tamponade the bleeding. An oral tracheal tube should then be inserted for management in the operating room.)

Not infrequently, tracheotomy tubes must be changed, for instance because of a cuff leak or because of obstruction from the buildup of secretions. A central concern in this instance is that the replaced tube could enter a false passage rather than the trachea. (This in itself is unfavorable, but should the false passage be inadvertently ventilated, the resulting subcutaneous emphysema could eliminate the possibility of easily reestablishing the airway.) This potential problem eventually disappears as the tracheal stoma matures to form a well-defined and self-supporting orifice. However, this rigidity and tissue support are lacking in a fresh tracheostomy, so that following removal of the tracheostomy tube, the tissue may "collapse in" on itself to block the passage. Consequently, certain precautions when dealing with a fresh tracheostomy tube must be borne in mind. First, for the first week or so, tube changes should be performed in the operating room with a full set of tracheotomy instruments (e.g., cricoid hooks) and a means to intubate "from above" as a last resort if the airway is lost. Second, once the tracheotomy site has begun to mature, it is no longer necessary to carry out tube changes in the operating room, but a full set of instruments (especially cricoid hooks) should still be available. Additionally, changing the tube over a tube changer may also be useful, but some clinicians find that it may unnecessarily complicate matters. Third, before any tube change, the patient should breathe 100% oxygen. Finally, a fiberoptic bronchoscope may be potentially useful in confirming tracheal placement of a tracheostomy tube before attempting any positive-pressure ventilation that could lead to subcutaneous emphysema should the tube, in fact, be malpositioned.

NECK DISSECTION AND LARYNGECTOMY

Neck dissection is commonly performed in isolation or during laryngectomy to prevent or treat any local spread of head and neck malignancy.[168,169] The extent of a neck dissection operation is based on the extent to which the neck's six lymph node levels are involved, as well as on the extent to which additional structures (spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle) are removed. Depending on the degree to which the tumor can be removed and recurrence or spread can be prevented, as well as the extent that phonation and swallowing can be preserved, various surgical options are exercised. Limited disease is sometimes managed by

radiation, by laser and microsurgery, or by partial laryngectomy, thus preserving organ function. In total laryngectomy, the larynx is removed in its entirety, with the airway ending in a stoma formed by bringing the cut end of the trachea to the neck surface (with the result that the trachea now becomes independent of the esophagus.) Often a perforation between the trachea and the esophagus (tracheoesophageal puncture) is made to allow eventual placement of a voice prosthesis.[170] In some cases the procedure is supplemented with microvascular free tissue transfer (free flap).

Anesthesia can be induced through a standard intravenous line, followed by large-bore intravenous and arterial lines placed after induction. A central line can usually be avoided, with systolic pressure variation of the arterial line tracing and other clinical findings to guide fluid replacement. Although nerve function monitoring is usually required during the neck dissection phase, neuromuscular blockade is acceptable at the beginning. When neuromuscular blockade is no longer desirable, opioid infusions (e.g., remifentanil) are often used to maintain adequate analgesia in conjunction with an inhaled anesthetic agent. Many clinicians prefer using a balanced technique in preference to deep inhalational anesthesia or TIVA (propofol with or without remifentanil) to avoid the troublesome hypotension. Excessive intravenous crystalloid administration should be avoided to prevent operative site edema.

In total laryngectomy cases, a tracheostomy is customarily performed near the beginning of the procedure, by using a wire-reinforced ETT placed into the stoma. (Warning: Accidental endobronchial intubation commonly occurs in this setting.) In some cases the patient is turned 180 degrees from the anesthesia machine; care must be taken to ensure that nothing is disconnected in the process. Extubation in such cases is extraordinarily simple; the ETT should be removed from the stoma when extubation criteria are met. Should reintubation ever become necessary, one merely reintroduces the tracheal tube into the stoma. The patient is then simply brought to the postanesthesia care unit with an oxygen mask placed over the stoma, although when a free flap has been performed, the patient is often brought to the ICU intubated, ventilated, and sedated (depending on the surgeon's preferences and local protocols.)

MAXILLARY, MANDIBULAR, AND TEMPOROMANDIBULAR JOINT SURGERY

Maxillectomy surgery may be limited (e.g., removal of one antral wall, such as in a medial maxillectomy), subtotal (e.g., removal of two walls of the antrum), or total (removal of the total maxilla).[171-173] Orbital exenteration sometimes accompanies the procedure should the intraorbital contents be violated by tumor. Indications for maxillectomy include the following: tumors of the maxillary sinus, palate, and other structures; some intractable fungal infections; and other conditions. The procedure is performed using general anesthesia with tracheal intubation and invasive monitoring appropriate to the patient's condition and the extent of the surgery. Although massive blood loss is unusual, precautions should be taken because hemorrhage may occur (e.g., with transection of the internal maxillary artery). Hypotensive anesthesia, when appropriate, can help reduce blood loss. Medial maxillectomy procedures conducted endoscopically do not require anything different from ordinary sinus surgery for anesthesia. When electromyography-based cranial nerve monitoring is employed, long-acting paralytic agents should be avoided.

Surgery of the mandible and TMJ may be carried out by maxillofacial surgeons, as well as by otolaryngologists and plastic surgeons.[174-176] Mandibular surgery can range from simple biopsies to all-day radical procedures involving microvascular osteocutaneous flaps. Awake nasal intubation may be required in some cases. Hypotensive anesthesia is often used for orthognathic procedures to minimize blood loss. In some cases the jaw is wired shut, and reintubation, should it be required postoperatively, can be a challenge.

TMJ dysfunction often manifests with pain and decreased mouth opening. Conditions such as osteoarthritis, synovitis, or fibrosis may be responsible. Most TMJ procedures are performed using general nasotracheal anesthesia. As with mandibular surgery, the presence of very limited mouth opening may dictate that the procedure be done with awake nasal intubation.

EAR, NOSE, AND THROAT LASER SURGERY

Lasers are commonly used in ENT surgery[177-180] (Box 85-3 and Table 85-1). The most widely used laser in ENT surgery is the CO_2 laser, which allows precise cutting with a particularly fine zone of coagulation that reduces bleeding. Tissue vaporization is particularly efficient with this laser because of the excellent absorption of the produced far-infrared photons (10,600-nm wavelength) by water present in tissue. This laser is used in the removal of laryngeal tumors and lingual tonsillar tissue, in the ablation of hemangiomas, and for the resection of some oropharyngeal malignant tumors.

Another popular laser in ENT surgery is the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, which emits photons with a wavelength of 1064 nm. These photons are poorly absorbed by water and thus tend to penetrate tissue more deeply than do those from a CO_2 laser. In addition, light from an Nd:YAG laser can be transmitted through flexible quartz fibers that can be used in conjunction with a flexible fiberoptic bronchoscope for use in treating tracheobronchial lesions.

Because surgical lasers involve high amounts of energy, they have the potential for unintended tissue damage, as well as for causing fires. Stray laser beams can ignite surgical drapes. To mitigate these risks, one should place warning signs outside the operating room, provide opaque coverings on any operating room windows, and issue protective goggles. The presence of high oxygen concentrations near the patient's face can facilitate ignition in this region, so delivering supplementary oxygen by facemask or nasal cannula requires special care. American National Standards Institute standard Z136.3 (Safe Use of Lasers in

Health Care Facilities) provides additional information on this and related matters.

One special concern is that regular ETTs can ignite from a laser beam. In the past, metallic tapes applied in a spiral manner were sometimes used. Today, however, several special-purpose ETTs are available for this purpose (Table 85-2).

The choice of anesthetic technique depends on the clinical circumstances. TIVA techniques for laser ENT surgery are particularly popular and are essential when patients are unintubated and jet ventilation is used. When patients are intubated, a potent inhalational agent such as sevoflurane is often used, although not infrequently an infusion of remifentanil is used as an anesthetic adjunct in such cases (typical rate: 0.05 to 0.1 μg/kg/minute). (Remifentanil, with its vagomimetic effect, is especially useful to limit the heart rate in the face of intense sympathetic stimulation from the effects of the suspension laryngoscope.) Finally, to reduce the chance of a fire, while lasers are in use nitrous oxide should not be used, and the oxygen concentration should be limited to the lowest concentration necessary to maintain acceptable arterial oxygen saturation levels. For additional details, see Chapter 88.

Airway management is often a challenge in laser surgery cases, and the surgeon and anesthesiologist must work together to devise a plan. One issue is whether general anesthesia should be preceded by awake intubation because the presence of airway disease may complicate both ventilation and intubation. Another issue is whether the procedure should be performed using general anesthesia with the patient breathing spontaneously, albeit with assistance, as is sometimes desirable when an anterior mediastinal mass is present. Muscle relaxation is often employed to help ensure an immobile surgical field. In the United States, where sugammadex is still not available (at the time of writing), succinylcholine is often used as an initial relaxant in patients with a potentially difficult airway because its short duration of action adds a measure of safety should the patient become impossible to intubate or ventilate following administration of the drug. Many Europeans would instead be more comfortable using rocuronium as a relaxant, followed by a "sugammadex rescue" should the airway become unmanageable following relaxant administration. Many clinicians, however, simply intubate the patient awake whenever issues of this kind arise.

In some cases the entire surgical procedure is done without intubation. The advantages of this approach are a decreased risk of fire (no ETT to ignite) and improved access to airway structures. Disadvantages include the risk of aspiration with an unprotected airway and potential difficulties in ventilating the patient. Typically in such cases, an anterior commissure laryngoscope or similar device is used in conjunction with TIVA and jet ventilation. In other cases, the laryngoscope is used in conjunction with a small-diameter ETT (e.g., MLT size 5.0), and the procedure is performed while the patient has brief periods of apnea in conjunction with intermittent removal of the ETT to allow unimpaired access to the glottic structures.

Laser vaporization of tissue, especially from CO_2 lasers, often results in a plume of smoke that can be hazardous.

BOX 85-3 ***Some Otolaryngologic Clinical Situations in Which Laser Techniques Can Be Useful***

NOSE
Turbinate reduction
Septoplasty
Removal of nasal obstructions, polyps, synechiae
Treatment of rhinophyma
Treatment of keloids and hypertrophic scars

OROPHARYNX AND PHARYNX
Vaporization of papillomas, leukoplakias, and hemangiomas
Tumor surgery (e.g., partial glossectomy)
Laser-assisted uvulopalatoplasty
Tonsillectomy

LARYNX
Removal of vocal cord polyps and granulomas
Epiglottectomy
Cordectomy
Arytenoidectomy

TRACHEOBRONCHIAL TREE
Treatment of tracheal stenosis
Removal of nodules, polyps, tumors, and fibromas

EAR
Surgery of the stapes
Laser-assisted myringotomy
Cholesteatoma

From Abdelmalak B, Doyle DJ, editors: Anesthesia for otolaryngologic surgery. *Cambridge, UK, 2012, Cambridge University Press.*

TABLE 85-1 **A SAMPLING OF VARIOUS KINDS OF LASERS AVAILABLE FOR CLINICAL USE**

Type	Gas or Solid	Wavelength* (nm)	Color	Fiberoptic Transmissible?
Helium/neon	Gas	633	Red	Yes
Argon†	Gas	500	Blue-green	Yes
CO_2	Gas	10,600	Invisible (far infrared)	No
Ruby	Solid	695	Red	Yes
Nd:YAG	Solid	1,064	Invisible (near infrared)	Yes
KTP	Solid	532	Green	Yes

From Abdelmalak B, Doyle DJ, editors: Anesthesia for otolaryngologic surgery. *Cambridge, UK, 2012, Cambridge University Press.*
KTP, potassium titanyl phosphate; *Nd:YAG,* neodymium:yttrium-aluminum-garnet.
*Wavelengths are given in nanometers (nm). There are 10^9 nm to a meter.
†The argon laser produces blue-green coherent light at a number of wavelengths but most of the energy is at wavelengths 488 nm and 514 nm.

The use of a smoke evacuator at the surgical site along with protective masks that filter out particulate material is often advised, especially when virus particles are present in the vaporized tissue.

Extubation of the trachea in these cases can be challenging. Some patients benefit from the administration of intravenous dexamethasone to reduce edema. Stridor is sometimes encountered after extubation; although this condition may require reintubation, one can sometimes avoid this by the use of inhaled racemic epinephrine or the use of Heliox, a mixture of helium (typically 70%) and oxygen. Extubation over a tube exchanger can be helpful when the need for reintubation is a concern and is expected to be challenging.

Even when the tracheas of patients are extubated conservatively following laser surgery, however, airway problems can arise later. In cases of immediate respiratory distress following laser procedures, consider the following possibilities: tissue edema (e.g., after Nd:YAG laser use), residual muscle relaxant or anesthetic effects, airway secretions, pneumothorax, bleeding, and pneumomediastinum.

TABLE 85-2 SOME TYPES OF LASER ENDOTRACHEAL TUBES IN CLINICAL USE

Name	Description	Intended Use
Laser-Flex	Airtight stainless steel corrugated spiral with a PVC Murphy eye tip and double cuffs. More information is available at http://www.cardinal.com/us/en/distributedproducts/ASP/43168-145.asp	CO_2 or KTP lasers
Laser-Shield II	Silicone rubber tube wrapped with aluminum and wrapped over with Teflon. More information at http://assets.medtronic.com/ent/flipbook-us/files/assets/basic-html/index.html#190	CO_2 or KTP lasers
Lasertubus	Soft white rubber, reinforced with corrugated copper foil and an absorbent sponge; double cuffed. More information at http://www.myrusch.com/images/rusch/docs/A20C.pdf	CO_2 or KTP lasers
Sheridan Laser-Trach	Red rubber design with embossed copper foil and outer covering designed to reduce damage to mucosal surfaces and vocal cords. More information at http://www.teleflex.com/en/usa/productAreas/anesthesia/documents/Sheridan-ET-Tube-Guide.pdf	CO_2 or KTP lasers

From Abdelmalak B, Doyle DJ, editors: Anesthesia for otolaryngologic surgery. *Cambridge, UK, 2012, Cambridge University Press.*

CO_2, Carbon dioxide; *KTP,* potassium titanyl phosphate; *PVC,* polyvinyl chloride.

PHONOSURGERY

Phonosurgery is surgery conducted to improve a patient's voice.[181-185] In many cases the patient's voice has been damaged as a result of unilateral vocal cord paralysis. One common operation used in this setting is medialization of the paralyzed vocal cord (laryngoplasty) so that the normal vocal cord can make contact with the paralyzed side. This procedure is done using local anesthesia with minimal sedation (e.g., 20 mg propofol administered just before the injection of the local anesthetic) because the patient needs to phonate on request. Continuous intraoperative imaging of the vocal cords, especially during phonation, is carried out to achieve the repair. An infusion of dexmedetomidine is sometimes used.

HEAD AND NECK FLAP RECONSTRUCTIVE SURGERY

Tissue transfer in the form of pedicle flap or a microvascular free flap is commonly employed to reconstruct defects created following tumor surgery.[186-188] Potential advantages of such flaps include the avoidance of staged procedures, improved wound healing, superior cosmetic results, and improved tolerance for postoperative radiation therapy. For optimal anesthetic care, anesthesiologists must have a clear understanding of these procedures and their implications for anesthetic management.

A *pedicle flap* is one in which the flap vessels are transferred intact with the rotated flap. If the flap is moved from a distant "donor" site and the flap vessels are reanastomosed to the recipient site vessels, then the tissue is termed a *microvascular free flap*. Examples of myocutaneous pedicled flaps are the pectoralis major flap and the latissimus flap used (for instance) to cover the carotid artery after the point where it is sacrificed and reconstructed using a vein graft. In contrast to pedicle flaps, free flaps provide the surgeon with more options for donor sites. Frequently, separate surgical teams for the donor and recipient sites are employed. Surgery in relation to free flaps can be elective, or it may be performed on an emergency basis to rescue an ischemic flap. Elective procedures tend to be long-duration operations conducted using general anesthesia. An arterial cannula is generally used, although special care must be taken to ensure that the arterial cannula and any additional intravenous catheters are not inadvertently placed at a site where tissue harvesting is planned (e.g., radial forearm flap). Central lines are not usually placed, in part because information about volume status can usually be better achieved using less invasive means such as systolic blood pressure variability. Many of these procedures begin with a tracheostomy and end with the patient being cared for in an ICU while intubated and ventilated. Intraoperative and postoperative flap monitoring is achieved clinically (examination for color, turgor, edema, and capillary refill), as well as by using technical means of blood flow assessment, such as Doppler ultrasound.

Intravenous crystalloids and colloids are administered liberally but cautiously to prevent hypovolemia and hypotension that could lead to ischemic flap failure.

Conversely, excessive fluid leads to detrimental edema formation within the flap. The use of vasopressors such as phenylephrine or norepinephrine is generally discouraged during free flap procedures because these drugs may contribute to graft ischemia as a result of vasoconstriction.

STRIDOR AND HELIOX

Stridor is noisy inspiration resulting from turbulent gas flow in the upper airway. Stridor should always command clinical attention because it is almost always the result of airway obstruction.[189-194] The first issue of clinical concern in the setting of stridor is whether intubation is immediately necessary. If intubation can be delayed for a period of time, a number of potential options can be considered, depending on the severity of the situation and other clinical details. These options include the following: expectant management with full monitoring, 100% oxygen by facemask, and positioning the head of the bed for optimum conditions (e.g., 45 to 90 degrees); use of nebulized racemic epinephrine (e.g., 0.5 to 0.75 mL 2.25% solution in 2.5 mL normal saline) and dexamethasone ([Decadron] 4 to 8 mg intravenously every 8 to 12 hours) when airway edema may be the cause of the stridor; and use of Heliox (70% helium, 30% oxygen). Dexamethasone can take several hours to take full effect, and nebulized cocaine in a dose not exceeding 3 mg/kg can be used instead of racemic epinephrine. Finally, whenever possible, immediate attempts should be made to establish the cause of the stridor (e.g., foreign body, vocal cord edema, arytenoid cartilage dislocation, tracheal compression by tumor).

Not infrequently, stridor occurring after extubation is the result of laryngeal edema, and it may be more problematic in children because of their small airway size. Be aware that as laryngeal edema progresses, diminished stridor may reflect impending total airway obstruction. The specific cause of laryngeal edema can often be established with fiberoptic nasopharyngeal examination, and causes are often classified as supraglottic, or subglottic. Supraglottic edema most commonly follows surgical instrumentation, impaired venous drainage, eclampsia or preeclampsia, hematoma formation, or excessive fluid administration. Finally, subglottic edema may result from traumatic intubation attempts, bucking on the ETT, prolonged intubation, tight-fitting tubes, or excessive cuff pressures.

The manner in which Heliox helps relieve airway obstruction is worthy of note. Some airway-obstructing conditions may be thought of as breathing through an orifice, involving flow through a tube whose length is smaller than its radius. Gas flow through an orifice is always somewhat turbulent. Under such conditions, the approximate flow across the orifice varies inversely with the square root of the gas *density*. This is in contrast to laminar flow conditions, in which gas flow varies inversely with gas *viscosity*. Although the viscosity values for helium and oxygen are similar, their densities are very different. For example, the density for air and oxygen at 20° C is 1.293 and 1.429 g/L, respectively. However, the density of helium at that temperature is only 0.178 g/L.



Figure 85-13. An E-size tank of Heliox, with an attached nonrebreathing facemask in a plastic bag. In this case, the mixture is 70% helium and 30% oxygen, although other mixtures are available. This gas mixture is usually given using a nonrebreathing facemask with a gas flow of 10 L/minute as a temporizing measure in stridulous individuals.

Clinically, Heliox is usually administered from an E-size cylinder through a nonrebreathing facemask starting at a flow of 10 L/minute (Fig. 85-13). When the usual 30% oxygen concentration is too low, one trick is to titrate in additional oxygen by nasal cannula. In summary, a setup to administer Heliox should be readily available in every ENT operating room suite to assist in the treatment of stridor.

ANESTHESIA FOR FACE TRANSPLANTATION

Face transplantation remains a very rare procedure (Fig. 85-14).[195,196] The procedure can be total or partial. The recipient must be able to undergo a very prolonged anesthetic and be free of serious comorbidities. Each procedure is unique with respect to indications, as well as with respect to the nature and the extent of the graft. In the case of the donor, although anesthetic principles similar to conventional organ procurement apply, because of the surgical complexity and time involved, harvesting of the facial graft should ordinarily be performed before harvesting other organs. Although the donor usually has an ETT in place at the time of tissue procurement, a tracheostomy



Figure 85-14. Ms. Connie Culp before (**A**) and after (**B**) the two stages of her face transplant at Cleveland Clinic. Stage 1 was carried out in December 2008 (lead surgeon: Dr. Maria Siemionow). *(Images courtesy the Cleveland Clinic, Cleveland, Ohio.)*

may be performed first to avoid interference with the surgical field. Recipient patients who do not have a tracheostomy may first require awake fiberoptic oral intubation, followed by a tracheostomy. A wire-reinforced ETT is often used. Large-bore catheters are placed to facilitate fluid resuscitation, whereas a central line may be useful to monitor central venous pressure. If a central line is used, however, it must not impinge on the surgical field. Blood and fluid management is no different from that during other long surgical procedures involving microvascular free flaps. As with microvascular surgery, pressors such as phenylephrine or norepinephrine, commonly used to treat hypotension, are discouraged because of the risk of compromising graft perfusion. Finally, there may be periods when muscle relaxation must be avoided to allow nerve identification using electrical stimulation.

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Chapter 86

Administration of Anesthesia by Robots

THOMAS M. HEMMERLING

Key Points

- Robots are able to measure many variables, make decisions, and take actions. Robots in anesthesia can be divided into pharmacologic robots, which deliver drugs to establish or maintain components of anesthesia, and manual robots, which are able to assist or replace human gestures in anesthesia. Decision support systems can be defined in this context as predecessors of robots in anesthesia, because they measure parameters and make decisions, but leave action taking to the human user.
- Decision support systems in the operating room will continue to evolve. Currently, they are often integrated into anesthesia information management systems and limited to reminders of timely and appropriate antibiotic administration and prophylaxis of postoperative nausea and vomiting. Recent research focuses more on the establishment of decision support systems to assist anesthesiologists in complex working environments characterized by multitasking and considerable lack of vigilance or fatigue.
- Decision-support systems can improve outcome; the adherence to them is linked to a constant reminder function in real time.
- Closed-loop systems in anesthesia are pharmacologic robots; they allow the autonomous control of anesthesia; most systems have been developed as research tools for the administration of propofol. All studies confirm an equal or mostly superior performance and maintenance of a given target, in comparison to manual control.
- The control mechanisms range from simple on/off control to model-driven control by proportional-integral-derivative control, with additional possibility of self-adaptation. Sometimes, fuzzy-logic control principles are applied, as well as neural networks. No control mechanism has been shown to be superior.
- Similar to surgical robots, manual robots have been developed that assist anesthesiologists to perform manual gestures, such as endotracheal intubation or regional nerve blocks.
- Tele-anesthesia is the application of telemedicine in anesthesia, mostly reduced to real-time monitoring and audio-video consultation or remote preoperative assessment. Recently, remote-controlled anesthesia delivery has been pioneered.

A robotic surgical system (or any other such system) is an extension of the surgeon's own arms and hands. The surgical robot never makes any movement without the surgeon "moving it," and there is no haptic feedback. Anesthesia's conceptual systems emphasize closed-loop, self-adaptive, control systems: these systems seem closer to the definition of a robot than any current commercially available surgical robot.

WHAT IS A ROBOT?

No clear definition of a robot exists. The word *robota* has been termed by the Czech playwright Karel Capek in his 1920s play, *Rossum's Universal Robots* (RUR). His description is colorful: slaves do human labor joyfully, so that humans can enjoy life without concerns.

Most modern definitions agree that a robot is a device that is self-controlled, consisting of anything from mechanical, electrical, to electronic units. Another common feature is the fact that these devices replace certain human gestures, either intellectual or mechanical. Important features of modern robots are exemplary in industrial robots: the reproducibility of the quality of the work without fatigue; a very high precision, especially in mechanical robots; independence from work conditions; and the absence of any emotional influence.

Robots can consist of the following elements: "effectors," which can be the equivalent of human arms or legs; "sensors," acting as infusion pumps, which perceive the environment and transfer it into information that can be fed to computers; a central processing unit, which works as the brain; and several other electronic, electric, or mechanical pieces of equipment, such as a screen with an interface, that mimic fundamental human functions. What makes robots different from other devices is their ability to function autonomously and their ability to react to their environment, adjust different environments, and analyze their own actions, including correcting previous actions.

The Director of the Centre for Intelligent Machines at McGill University in Montreal, Canada, Gregory Dudek, gives the following definition (http://www.cbc.ca/news/background/tech/robotics/definition.html):

They have to have a way of making measurements of the world, they have to have a way of making decisions — in other words, something like a computer, you could call that thinking informally — and they have to have a way [of] taking actions. And so if a thing has all three parts, we might call it a robot.

In this chapter, we consider decision support systems (DSSs) as predecessors of robotic anesthesia and closed-loop systems as pharmacologic robots in anesthesia, separate from manual robots, which are also described.

DECISION SUPPORT SYSTEMS FOR INTRAOPERATIVE USE IN ANESTHESIA

DSSs are the first bridge between manual, subjective, human anesthesia monitoring and delivery of perioperative care and fully automated systems. Currently, DSSs are mostly used in critical care and intensive care medicine but slowly are being developed in the field of anesthesia. Anesthesiologists face increasingly complex environments with older patients and patients who suffer from complicated diseases that require increasingly more intricate surgeries (see also Chapter 80). Continuing economic pressures require anesthesiologists to multitask to cover remote anesthesia sites, other anesthesia tasks, management tasks, teaching, or simply to cover more than one operating room. Add to this challenging environment a shortage of specialized personnel, and the need for the development of DSSs for anesthesia providers is acutely evident (Table 86-1). DSSs are developed based on six principles[1]:

1. Developing a protocol based on a consensus of users
2. Initial pilot study testing
3. Integration of these protocols into computerized protocols with additional testing
4. Validation using historical data
5. Clinical validation and correction of faults before implementation into daily practice
6. Preparation and use of routine clinical protocols with DSSs

DSSs use algorithms of predefined scenarios to create specific advice: diagnostic suggestions, treatment options, or triage evaluations. These algorithms are based on many inputs, such as patient demographic data, vital signs, blood loss, intravenous (IV) fluid administration, and many other types of advanced information.

The earliest DSSs were mostly a follow-up of the more widespread investigation and use of anesthesia information management systems (AIMS) (see also Chapters 4 to 6). AIMS have been used to design and integrate DSSs, mostly to help anesthesia personnel adhere to clinical protocols.

The most popular DSS used in anesthesia practice is a pop-up menu reminding anesthesiologists to administer antibiotics after induction of anesthesia. An example is a system called smart anesthesia manager (SAM), which is integrated into an AIMS.[2] AIMS are generally used to document and investigate the quality of care in retrospect—that is, after a certain period. Despite the fact that these investigations can lead to quality improvement by changing existing policies, AIMS do not control adherence to given protocols in real time, and avoid important tasks, such as administration of antibiotics. As a result, SAM was developed over a period of 3 months by a collaborative effort of a biomedical engineer, two anesthesiologists, and a database programmer who subsequently tested and refined it over a period of 2 years at the University of Washington in Seattle.

The AIMS has SAM communicate with both the AIMS server and workstation. The SAM server module interacts with the AIMS database to identify issues and create, if necessary, messages that are then displayed using a client module.

The DSS can deliver these messages using pop-up menus on the AIMS screens in the operating room and deliver them directly to a specific anesthesiologist by text (e.g., via a pager or smartphone). The dual-split design

TABLE 86-1 DECISION SUPPORT SYSTEM (DSS): OUTCOMES

	With DSS (N = 75)	Without DSS (N = 75)	P
Events not detected (%)	0.8 ± 3.4	26.5 ± 19.7	<.0001*
Detection delay (sec)	9.1 ± 3.6	27.5 ±18.9	<0.0001*
Critical events/hr	8.4 ± 6.8	9.1 ± 6.7	NS
Low SpO_2/hr	0.7 ± 1.0	1.4 ± 2.2	0.036*
Low RR/hr	3.0 ± 3.0	3.0 ± 3.6	NS
Low MAP/hr	4.7 ± 6.4	3.5 ± 3.6	NS
Low HR/hr	0.3 ± 0.7	0.4 ± 0.4	NS

Data are presented as mean ± SD.
*P <.05 (two-tailed), t-test for continuous data.
DDS, Decision support system; *HR,* heart rate; *MAP,* mean arterial pressure; *RR,* respiratory rate; *SpO_2,* peripheral oxygen saturation.

(i.e., display and text delivery) of the messaging ensures better compliance because the anesthesia provider might not be in the operating room at the site of the AIMS screen at the time of the message delivery, but can receive the text messages provided that the pager or smartphone is active. The SAM message on the AIMS screen is a standard pop-up menu that asks the provider to administer the antibiotic and has to be closed once the action is confirmed.[3]

The implementation of SAM increased compliance to deliver the initial antibiotic dose by 11%,[4] from 88.5% ± 1.4% to 99.3 ± 0.7%. When the compliance to readminister the antibiotic during the course of surgery was examined,[3] the integration of SAM improved compliance by 21%, from 62.5% ± 1.6% to 83.9 ± 3.4%. In an earlier study, a similar system was integrated into an AIMS by O'Reilly and associates[5] that documented adherence to a timely (within 60 minutes of incision) administration of antibiotics over a period of 1 year after implementation of such a DSS. Gradually, the adherence increased from 69.9% to 92.3%.

Another main area in which DSSs have been developed is adherence to guidelines for prophylaxis of postoperative nausea and vomiting (PONV) (see also Chapter 97). Adherence to PONV guidelines is usually quite poor, with one study of over 5000 patients determining that only 38% of patients at frequent risk for PONV were actually prescribed adequate prophylaxis, even with a paper version of the guideline present.[6] A study by Kooij and associates[6] investigated a large number of patients in an anesthesia preadmission clinic in which anesthesiologists evaluated patients before surgery using an AIMS (see also Chapter 38). They then implemented a very simple DSS that calculated the risk factors for PONV. When general anesthesia was selected as the mode of anesthesia, this prompted the message: "This patient has at least three positive risk factors for PONV and is eligible for PONV prophylaxis, but is not prescribed prophylaxis yet. Do you want to prescribe PONV prophylaxis?" To which the anesthesia provider would respond either affirmatively or negatively. Three study periods were created: an initial 8-week control period to examine the initial status of guideline adherence using only a paper version guideline, followed by a 16-week decision support enhanced period and finally, an 8-week postdecision support period in which only a paper version guideline for PONV prophylaxis was available. A significant improvement from 38% to 73% adherence to current guidelines of PONV prophylaxis prescriptions occurred (Fig. 86-1).

However, once the decision support system was no longer in place, the "old" routine of nonadherence to the guidelines resumed and the percentage of guideline adherence declined to the prestudy level. The study results are similar to those of many other studies in which adherence to guidelines of PONV prophylaxis were integrated into an AIMS: that is, when design and implementation of such a DSS is simple, its implementation significantly increases adherence to guidelines.[7] Integrating such a DSS is important because the study clearly showed a lack of learning from example in the respective anesthesiologists. Once the DSS was removed, the old habit of nonadherence returned. DSSs can therefore help decrease human error only when they are constantly present; as learning tools they are no more effective than any other learning tool, and providers will adhere to specific guidelines more frequently when they are constantly reminded. In a subsequent study, Kooij and associates[8] showed that automated reminders in the operating room during surgery do improve adherence to guidelines of PONV prophylaxis and thus improve patient outcome by reducing PONV, especially in high-risk patients. With automated reminders, the percentage of overall PONV

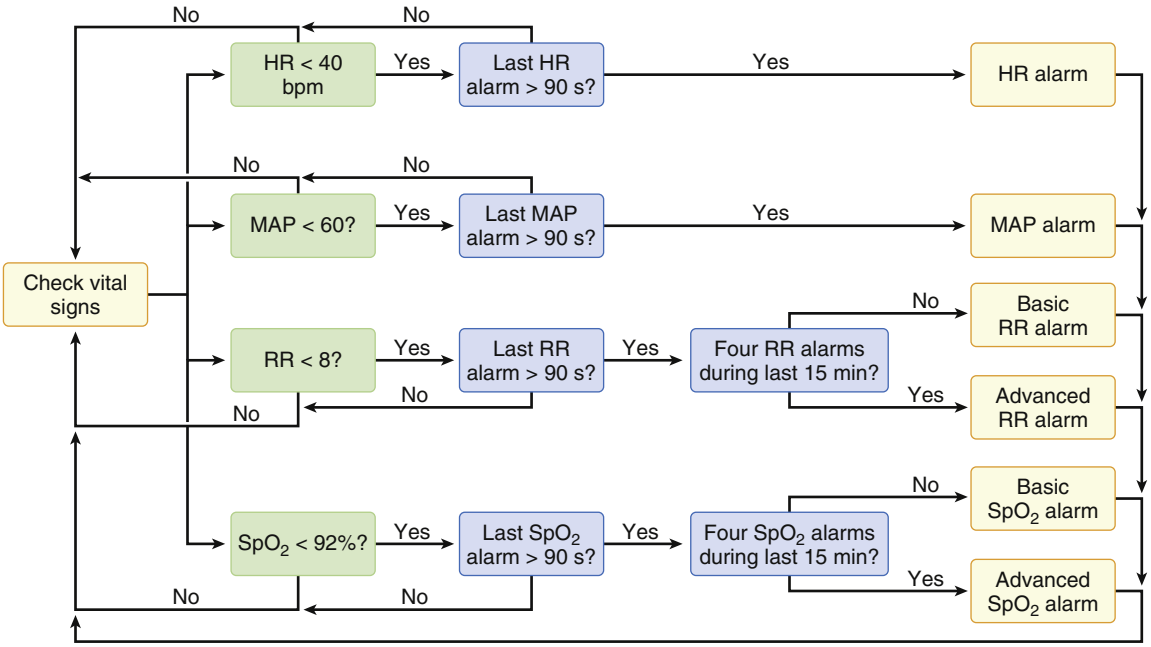


Figure 86-1. Algorithms for decision support system for detecting respiratory and hemodynamic critical events during sedation. *HR,* Heart rate; *MAP,* mean arterial pressure; *RR,* respiratory rate; *SpO_2,* peripheral oxygen saturation.

in high-risk patients was only 31% versus 47% without reminders ($P < .001$).

Most of the DSSs integrated in AIMS have been limited to simple reminders of drug dosing or redosing, reminders for specific monitoring settings, such as turning on standard alarms after separating from cardiopulmonary bypass,[9] and correcting billing reminders.[7,10]

Very few studies have tried to implement DSSs in the anesthesia operating room environment for more complex situations, such as inadequate anesthesia or critical events.

One of the initial descriptions of a DSS, called RESAC for real-time system for advice and control, as a guidance for controlling general anesthesia was published in 1993[11] and used an Atari ST computer for programming. RESAC used 39 parameters, which were retrieved either automatically in real time or by asking the anesthesiologist. The anesthesiologist was also asked to input certain surgery-related data, such as time of surgical stimulation or application of dressings, as well as subjectively chosen limits for patient data, such as heart rate or systemic arterial pressure.

At 1-minute intervals, RESAC then produced text messages concerning the adequacy of anesthesia, with the anesthetist choosing either to follow the decision support information or ignore it. The system had a high error rate; two of the seven patients tested had technical errors and thus the system could not be used. This study's importance lies in the fact that just over 20 years ago, the theoretical structure of an appropriate DSS as an aid to delivery of general anesthesia was presented with many features necessary for the design of such a system: the capability of entering a large set of data, including patient-relevant data in real time and definite time points of surgery, and the ability of the user to set certain personal, subjective target values for parameters such as heart rate or arterial blood pressure. These values could even be altered throughout the course of surgery. Certain design structures can be revisited 20 years later in the design principles of the McSleepy pharmacologic anesthesia delivery robot. A more recent publication evaluated rule-based computer algorithms to detect light (possibly inadequate) anesthesia or unstable arterial blood pressure values using hemodynamic real-time patient data during surgery.[12] Using an AIMS, Krol and Reich[12] constructed a consensus of data that indicated light anesthesia or unstable anesthesia based on data of 162 patients from experienced anesthesiologists. Eighty-one events of light (possibly inadequate) anesthesia were observed. The data of 239 patients undergoing cardiac surgery with cardiopulmonary bypass were investigated for periods of unstable arterial blood pressure values. The authors then developed computer algorithms based on hemodynamic parameters, heart rate, and mean and systolic arterial pressure. To avoid the influence of artifacts, the mean of eight block measurements were taken at 2-minute intervals. However, as of December 2012, the DSS based on these algorithms had not been tested. DSSs are being developed to aid clinicians to detect inadequate anesthesia: groups are working on algorithms based on displaying age-adjusted minimum alveolar concentrations (MAC) alerts[13]; a fuzzy-logic based DSS analyzing systolic arterial blood pressure and heart rate variables as a guidance for anesthetic depth was also proposed[14] but not tested in patients as a real-time guidance device for anesthesia care providers.

The only DSS designed and clinically tested for anesthesia delivery during surgery is part of the hybrid sedation system (HSS).[15] It was specifically developed to recognize critical hemodynamic and respiratory events during sedation with propofol in patients who had received a spinal analgesia. HSS uses the following variables: heart and respiratory rate, mean arterial blood pressure, and peripheral oxygen saturation. Based on individual thresholds, the system creates acoustic alarms that trigger audiovisual pop-up menus offering the various reasons for the alarm, and the treatment options displayed on a touch screen with touch buttons; the anesthesiologist then needs to confirm the actions to be taken, which are recorded for medicolegal reasons. A flow chart describes the algorithms used (see Fig. 86-1).

The acoustic alarms and pop-up menus can be transmitted either via wifi on any smartphone or as text message. The pop-up menus also take into account the possible absence of the anesthesiologist from the operating room and have a specific button that, when pressed, can alert the anesthesiologist to immediately return to the operating room in case of life-threatening emergency (Fig. 86-2).

HSS was tested in patients undergoing surgery with spinal analgesia and propofol sedation; the percentage of critical predefined events detected in a group of 75 patients in whom the DSS was installed was compared to those in another group of 75 patients in whom the critical events were predefined—their definition displayed in the operating room in the visual field of the anesthesiologist, who was advised to react accordingly—but no DSS was made available. Results showed that 25% of critical events go undetected without the DSS and that the response time is usually approximately 30 seconds in comparison to an almost immediate response when pop-up menus of a DSS are used (see Table 86-1).

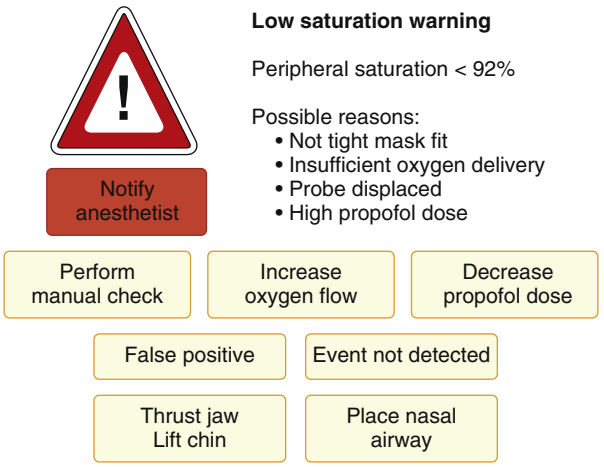


Figure 86-2. The pop-up menu appears with an audible alarm, in this case when the peripheral oxygen saturation drops to levels below 92%. It indicates possible predefined reasons; the user has to click the touch button on the screen to confirm what he or she has done.

As of December 2012, development of DSSs for anesthesia can be described as follows. So far, DSSs have been designed mostly as very simple alert reminders to execute drug dosing at given time intervals, such as for antibiotic administration or prescription, administration of drugs for PONV prophylaxis, or for billing purposes. Some systems have been designed to detect states of inadequate anesthesia, based on analysis of data retrieved from AIMS. First attempts are underway to develop DSSs to help anesthesiologists perform anesthesia, but have not been tested in significant numbers of patients. The only DSS currently tested in a significant number of patients is a system that allows detection of respiratory and critical events, automatically alerts visually and acoustically the anesthesiologist in real time, and offers diagnostic and treatment advice whose execution needs to be confirmed to the system for the pop-up menus to go away. It is clear that the development of DSSs for intraoperative use in anesthesia that assist anesthesiologists in the difficult decision-making process is still in its very infancy.

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CLOSED-LOOP SYSTEMS

WHAT IS A CLOSED-LOOP SYSTEM?

An anesthetic closed-loop control system uses feedback from the patient to automatically adjust the dose of a given drug. The response of the patient, such as the degree of sleep at a given time point, is compared with a targeted, desired response at predefined time intervals with the objective of having a difference = 0 between the measured and desired drug effect. The difference is processed by a controller, which is a central processing unit (CPU) with integrated algorithms.

The most commonly designed and tested closed-loop feedback control systems in anesthesia are the closed-loop control of propofol systems using feedback from BIS monitoring. Figure 86-6 explains different control mechanisms.

The controller uses different algorithms and algorithm constructs to act on the difference between target effect and measured effect.

The most commonly used control mechanisms are as follows.

On/Off Control

On/off control means that at given intervals, the difference between target effect and measured effect is

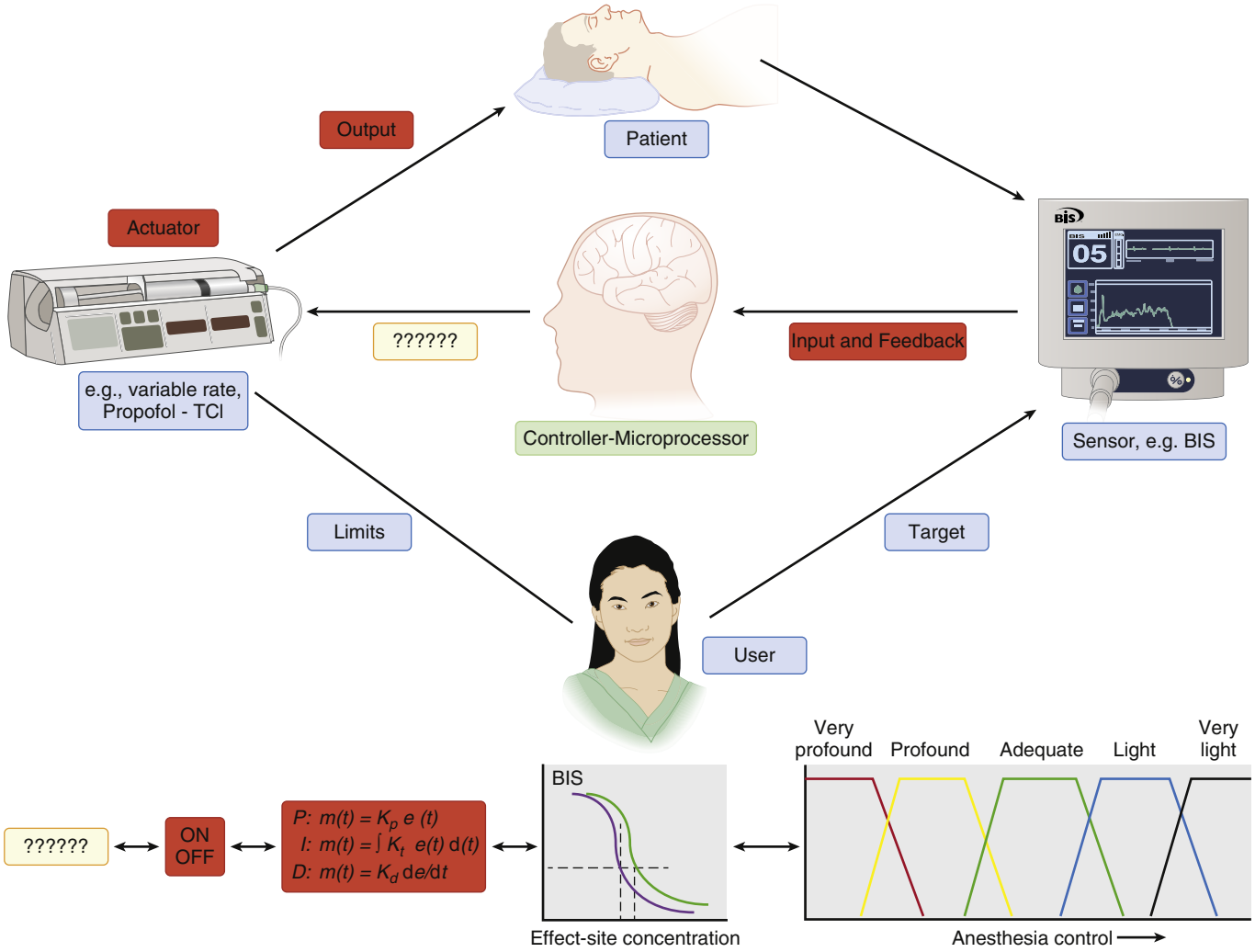


Figure 86-6. Illustration of several control mechanisms; *bottom from left to right:* On/off; proportional integral derivative; model-based; fuzzy logic. *TCI,* Target-controlled infusion.

calculated for the times when this difference is not zero; a fixed dose of a drug, such as a fixed infusion rate, or a bolus is administered. These systems have been used especially for the administration of neuromuscular blocking drugs. They are obviously very simple but can result in astonishing controller performance.

For example, with a neuromuscular blocking drug the infusion pump of a closed-loop control system with an on/off controller delivers 1 mg/kg/hr atracurium in the controller "on" position; when "off," the infusion is interrupted.

Proportional-Integral-Derivative Controller

A PID controller stands for proportional-integral-derivative control mechanisms. The PID controller calculation (algorithm) involves three separate constant parameters: *P* depends on the present error, difference between measured and target effect at present time interval; *I* depends on the accumulation of past errors, past differences between measured and target effect, such as the trend toward overshoot of effect; and *D* is a prediction of future errors, future differences between measured and target effect. These are very popular for closed-loop systems of propofol administration.

Model-Based Control

Model-based control mechanisms were developed hand in hand with the development of pharmacokinetic models for target-controlled infusion of anesthetic drugs. The algorithms are based on the interaction between pharmacodynamic results, such as the effect of a certain drug on the body, and pharmacokinetic phenomena, what the body does to the drug, the compartment of drug distribution, and the elimination process. Some research groups have used these control mechanisms for closed-loop administration of anesthetics. At times these models are individually created by using data from a patient's reaction to a fixed dose at induction. Sometimes, these models are altered in the course of the closed-loop administration and these are called adaptive or self-adaptive.

Rule-Based Control

Rule-based control uses a set of rules that are applied to alter the drug dose to achieve the target effect.

Rule-based mechanisms are used when uncertainty exists about actions, often combined with fuzzy-logic control. The idea behind rule-based system control is the simulation of human behavior, where rules are used to guide treatment strategies. Often, they oversimplify human thinking.

Fuzzy Logic

First termed by Zadeh in 1965, fuzzy logic deals with approximate reasoning rather than precise or exact reasoning. Some of these control systems have been used when neuromuscular blocking drugs have been given via closed-loop controls. Whereas most system controls use either 0 or 1 to act, fuzzy-logic systems use a continuous 0-to-1 thinking strategy, with overlapping categories.

Neural Network

Neural networks try to simulate the human brain. A neural network tries to learn from wrong and right decisions; information streams connect different levels of layers, connected with different neural knots, based on mathematical calculations and algorithms. The knots function like the human brain and decide, "all" or "nothing," to transfer the information from one layer to the next.

Adaptive, or self-adaptive models are those with or without some form of system "learning," in which previous actions of the controller are taken into account and subsequent changes are executed automatically.

VARVEL PARAMETERS IN CONTROLLER PERFORMANCE EVALUATION

The Varvel parameters are performance error (PE), bias or median performance error (MDPE), inaccuracy or median absolute performance error (MDAPE), divergence, and wobble.[25]

The median performance error (MDPE) or bias describes whether the measured values are above or below the target; it describes the direction of the measured values, general overprediction or underprediction, but not the size of the performance error. It is a signed value indicating the "direction" of the performance error.

The median absolute performance error (MDAPE) describes the amplitude of an error—the difference between measured value and target value; such as a MDAPE value of 10% means that 50% of the measured value is within 10% of the target.

Divergence is a time-related parameter that indicates how the inaccuracy of the infusion device changes as time increases. A nonzero value indicates a widening gap between actual serum and target concentrations, whereas a zero value means that performance accuracy does not change over time. A positive value means that the gap between target and measured values widens over time; a negative value means that the measured values converge over time to the target value.

Wobble is a time-related index of changes in performance accuracy and measures the intrasubject variability in performance errors. An increased value of wobble indicates an oscillating behavior of the controller.

No accepted limits exist that represent good controller performance; however, these parameters allow comparison of controller performances of different models and different studies.

CLINICAL PERFORMANCE ASSESSMENT

Clinical performance is defined by the percent of time with a certain offset from the target value. This is more relevant for the clinician; excellent, good, poor, or inadequate control for BIS could mean the measured value within 10%, 11% to 20%, 21% to 25%, and more than 25% off target values, respectively. These classifications are usually chosen by the research groups and can alter from one group to the next and from one target parameter to the next.

The clinical performance values can be valuable for the reader. As an example, when the BIS target is chosen to be at 50 for the controller 80% of the time, the controller manages to keep the BIS values within 10% of the target, which means that during 20% of the time the BIS values are either above 55 or below 45. Let us assume further that during 10% of the time the BIS is at values higher than 55, which are usually values at which strong surgical stimuli might cause a wakeup reaction in some patients. Therefore, during 10% of the time, the BIS controller is in an area at which this risk is elevated. The same applies for the amount of time the controller keeps BIS values at 60 or higher. Therefore, for most clinicians, the clinical performance results are more important than the Varvel controller performance values.

EARLY WORK: THE WORK BY SCHWILDEN AND HIS RESEARCH GROUP

One of the first works on closed-loop feedback control was done in the late 1980s by Schwilden and associates,[26,27] before the introduction of commercially available depth of consciousness monitors.

In 1987, Schwilden and associates used the median electroencephalography (EEG) frequency of the power spectrum and a model-based, adaptive controller to administer methohexital in 13 volunteers. The controller set point was 2 to 3 Hz, and the closed-loop system maintained EEG within this target area 75% of the time. In 1989, they used the same setup for closed-loop application of propofol to a target of 2 to 3 Hz of median EEG frequency of the power spectrum. The average measured EEG frequency was 2.5 ± 0.3.

EARLY CLOSED-LOOP ANESTHESIA WORK: THE RESEARCH GROUPS OF KENNY; CLOSED-LOOP CONTROL OF ANESTHESIA: THE WORK OF KENNY'S GROUP IN GLASGOW, SCOTLAND

In 1999, Kenny and Mantzaridis[28] presented a closed-loop control system of propofol using auditory evoked potentials (AEPs) as measurement for depth of anesthesia; it was similar to the description of the closed-loop system already published as an abstract in 1992.[29]

A 3-second running average of AEP index was used in a personal computer (PC)–based proportional integral control algorithm; the actuator was a target-controlled infusion pump of propofol. Analgesia in 100 patients (mean age 50 years, American Society of Anesthesiologists [ASA] physical status I and II only, undergoing body surface surgery) was provided using target-controlled infusion of alfentanil at a plasma concentration target of 15 ng/mL. Induction of anesthesia was performed without feedback, but instead using preset increments of target concentrations of propofol. The target depth of consciousness, in this case the AEP target, was manually chosen by the user and was in the range of 30 to 40, with a mean of 38. Usually, no neuromuscular blocking drug was given, which probably renders the depth of consciousness monitoring value more susceptible for artifacts. The aim of ventilation was mostly spontaneous breathing during surgery, which was successfully achieved in the majority of the patients, a result that seems independent from closed-loop control but related to this type of anesthesia. The closed-loop control period (duration of anesthesia after induction to end of surgery) was short at 38 minutes, because of the specifics of the surgery. However, the controller performance was generally very good, although the wide range of quality of control indicated that some patients had a rather significant offset from target with results, as shown in Box 86-1. Varvel parameter results were not presented.

A follow-up closed-loop study was conducted with 10 patients (ASA physical status I and II) undergoing major orthopedic surgery for a longer duration (72 minutes) than in the previous study.[29] The researchers used the same type of general anesthesia–that is, a spontaneously breathing patient with a laryngeal mask airway inserted for airway protection and BIS as the monitoring control parameter.[30] Analgesia this time was achieved using epidural analgesia.

This study presents the Varvel performance parameter results and clinical performance values, offset from the target BIS. Whereas the Varvel performance values at an overall MDPE of 2.2%, MDAPE of 8%, and wobble of 7.3% are satisfactory, when compared to their previous study, the clinical performance was not as good.[28] With feedback from AEP, the measured values were within 5% and 15% of the target in 65% and 99% of the time, with BIS feedback, it was only in 34% and 75% of the time, respectively.

The authors explain this with a slightly different patient population, different analgesic technique, different induction of anesthesia method, and different monitoring method of depth of consciousness. In addition, the smaller sample size of 10 patients in the latter study might have contributed to the worse clinical performance. Insufficient control of anesthesia and maintenance of the measured BIS value around a given target in closed-loop systems is usually marked by a phenomenon termed oscillation. Of the 10 patients, 3 showed marked oscillations, the worst in one patient (Fig. 86-7).

In this patient, the initial BIS target was 57, which probably was too high, too close to an arousal barrier, at which point the patient was possibly at risk for waking up as a result of surgical stimuli, insufficiently masked by analgesia. After decreasing the target to 45 at 45 minutes of surgery, the oscillations were reduced. However, the example of oscillations demonstrates a common problem in designing closed-loop systems. In their initial system, Absalom and Kenny did not include adaptive control mechanisms that allow adaptation of control algorithms for an individualized patient over time, something that more recent study groups have done.[31] The higher the BIS value, the closer to the threshold of 60, the more the patient is susceptible to have arousal reactions as a result of surgical stimuli. This also means that good analgesic control

BOX 86-1 ***Control of AEP Index as Percent of Total Closed-Loop Anesthesia Time (Mean [SD], [Range])***

Within target value ± 5%	65.2 (14.1) [10.3 – 89.0]
Within target value ± 10%	89.6 (9.5) [46.7 – 100.0]
Within target value ± 15%	98.7 (4.6) [74.9 – 100.0]

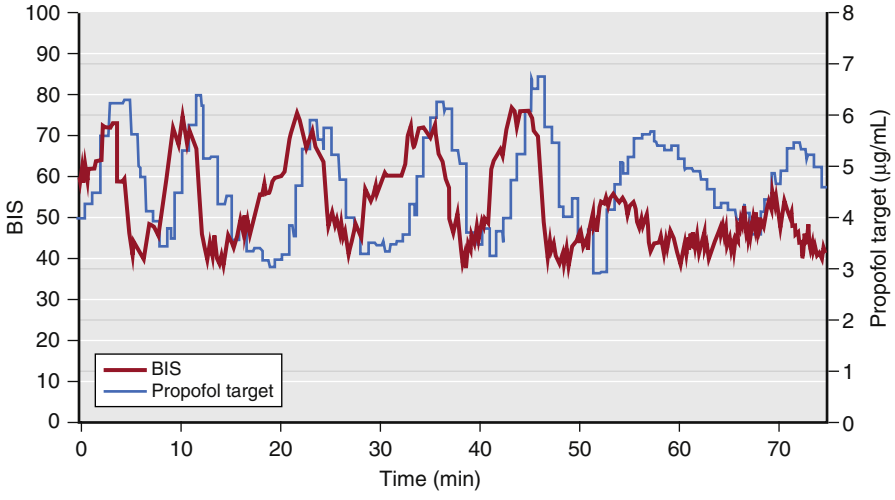


Figure 86-7. Illustration of marked oscillations, worst case in one patient. Oscillations usually indicate poor control performance, a problem all control systems encounter in specific patients. The frequency and magnitude of oscillations with a specific controller is an indication of its performance, the less oscillations occur, the better the controller. *BIS,* Bispectral index. *(From Absalom AR, Sutcliffe N, Kenny GN: Closed-loop control of anesthesia using Bispectral index: performance assessment in patients undergoing major orthopedic surgery under combined general and regional anesthesia,* Anesthesiology *96:67-73, 2002.)*

is important for any closed-loop system of propofol to function properly; waking up reactions during surgery while having insufficient analgesia can occur with total IV anesthesia, independent of whether the anesthesia is automated (see also Chapters 33 and 50).

Kenny's research group tried to improve their control algorithms and presented their results in a follow-up study with 20 patients (mean age 43 years, ASA physical status I and II) undergoing body surface surgery of 27 minutes on average. This study used a very different population and type of surgery compared to their earlier study with unsatisfactory closed-loop control[30] in which patients were older (mean age 67 years) and undergoing major surgery of approximately 70 minutes with epidural analgesia. In comparison to their previous study,[30] the changes in the control algorithms were the use of a newer BIS software, adjustments in the gain constants used in the control algorithms in the second part of the patients (11 to 20), and alteration of the control algorithm to allow effect-site steering, rather than blood site steering in the attempt to avoid oscillations by faster increase in effect-site concentrations with too light anesthesia. Although the Varvel performance parameter values slightly improved from the earlier study, the clinical performance did not change.

The Kenny group also used the closed-loop system for research into the interaction of drugs, such as remifentanil and propofol.[32] This is an important aspect of the development and use of closed-loop systems, which allow the automated administration of propofol without human intervention. Furthermore, anesthesia can be given around a specific target, allowing research into the interactions of propofol and other drugs.

Kenny's group designed a closed-loop system for propofol sedation for colonoscopies using the BIS value as a control parameter, which they tested in 16 patients.[33] Patients were sedated to a clinical sedation target of OAA/S rating of 3, and the achieved BIS target at that clinical value was used as a set point, with the possibility of modifying it in case of clinically insufficient sedation. Interestingly, the performance of their sedation system is better than that of their general anesthesia control, with BIS values within 10% of set point during 81% of the time versus 57% [30] and 71%.[34] Yet, the BIS target was 80 in the sedation study, and even a fully awake patient cannot have a BIS value higher than 99; therefore, a maximum positive offset of 19 cannot be passed in the sedation study.

Important messages from that small-scale study are the propofol doses required to achieve the same clinical sedation end point vary widely, with one patient necessitating a maximum propofol target of 5.6 μg/mL or 160 mg of propofol for induction of an OAA/S state of 3—another argument for automated systems, because empirical drug dosing has significant limitations. A feedback control approach avoids some of these limitations including the feasibility of using BIS monitoring to titrate sedation for nonsurgical procedures. This monitor can also be used as a control parameter for closed-loop sedation (also see Chapter 50).

Summary of Kenny's Work

The efforts of the Kenny research group can be summed up as follows:

1. Kenny and Absalom's group designed one of the first closed-loop propofol sedation systems using BIS feedback and successfully tested it in humans.
2. They used their PID controller–based propofol closed-loop system with feedback from AEPs and BIS; the controller performance was significantly better with AEP feedback than with BIS feedback.
3. The closed-loop system used target-controlled infusion as actuator; the closed-loop feedback control was used for maintenance of anesthesia, but not for induction of anesthesia.
4. They clearly described the problem of oscillations of controlling parameter values and proposed improvements in control design, specifically the use of effect-site concentrations rather than blood or plasma site concentrations. Whether these changes significantly improved controller performance cannot be answered because of the small sample size of their study.
5. They identified the potential of using closed-loop systems as a research tool to investigate drug interactions, as they did between remifentanil and propofol.
6. Although they incorporated control algorithms for application in ASA physical status III and IV patients, they actually never tested them in this patient population; they also only used it in anesthesia without controlled ventilation and neuromuscular blockade.
7. Closed-loop control was mostly for short-term procedures.

CLOSED-LOOP SYSTEMS FROM STRUYS AND DE SMET'S GROUP: FROM CLOSED-LOOP TO ADAPTIVE MODEL-BASED COMPUTER CONTROL

After the earlier work by Schwilden and associates[27] Struys and De Smet's research group chose to design a closed-loop propofol system around model-based controllers, which also are adaptive, meaning the dosing is not only corrected according to the offset between measured and set point target of BIS but also adjusted to individual patient reactions to propofol over time. The exact algorithm is not described in the first study. They first presented their system in 10 patients (ASA physical status I and II) undergoing orthopedic surgery with spinal analgesia of short duration (approximately 30 minutes).[35] Similar to Kenny's group, the actuator was a target-controlled propofol infusion pump, induction was automatic by a stepwise approach, but without feedback from BIS control. Similar to later work by Kenny's group,[33] the sedation target was set clinically, but was more intense at an OAA/S value less than 1 and the BIS target at that point set as the closed-loop target. Because the OAA/S target was lower, the resulting BIS target was also lower than in Leslie's study[33] at an average of 64. The publication is scarce in presenting actual performance parameters, either clinical or others. The graph depicting the difference between the target and measured BIS values over time shows a wide range of offsets.

In a subsequent study,[36] detail is given about the "adaptive" feature of their model-driven closed-loop control system of propofol. A control factor is integrated into the algorithms that analyze the difference between two consecutive measured BIS values, multiplied by a differential factor: Adaptive control corrective factor = (BIS_{T1} – BIS_{T0}) × Differential factor (based on simulation studies, the differential factor was established as 0.05).

The system uses an open-loop, plasma target-controlled infusion, with RUGLOOP (tracking of concentration infusion and data management program) calculating the effect-site plasma target concentrations. Once the target BIS level of 50 was reached during induction, the model was calculated based on paired measurements of BIS levels and calculated plasma target concentrations, thus calculating an individual model for each patient, based on results from an open-loop induction, similar to the Bayes principle.

The study design has some characteristics: first, the sample size is small at 10 patients each group (closed-loop versus open-loop); second, whereas BIS monitoring at a target of 50 was used in the closed-loop group, clinical signs of "adequate anesthesia" were used in the control group. Although this might be reflecting some standard practice, it limits the possibility of comparing the performance of anesthesia control. Therefore, a more rapid extubation of the trachea in the closed-loop group might not only be related to closed-loop control, but also to the fact that BIS was not used in the control group to titrate anesthesia. The comparison of controller performance values, based on Varvel parameters, is also less valid, because BIS was not used as a controlling variable in the control group.

Therefore, the Varvel parameters in Struys' study should be compared with the work from Kenny's group, which used different and simpler control mechanisms without adaptive modeling (Table 86-3).

Whether the integration of model adaption (Struys' group) has improved controller performance in comparison to the simple PID (Absalom and Kenny) is not clear and supports a theory of many control system engineers. Control algorithms seem less important than the time interval of feedback control.

The idea that control algorithms are somewhat less important seems in contrast to a simulation study (simulated 10 patients) by Struys and associates[37] in which the control performance of the aforementioned two closed-loop control systems was compared, favoring the patient-individualized, model-based adaptive closed-loop system with effect-site control over the standard PID controller (Table 86-4). However, the clinical performance (i.e., maintenance of BIS value within 10% of target value), slightly favors the model-based adaptive controller. The PID controller performs better when higher BIS targets (BIS = 70) are maintained, thus avoiding BIS values that are too low; the reverse is true for BIS values that are too high.

The Varvel performance values are better for the model-based adaptive control system than the PID system, except for the MDPE values. These values are less important, because they indicate the direction of the bias of measured value from target value but not its size.

Obviously, this study has its limitation, which is related to the patient simulator; the "historic" data fed into the simulator might have favored the model-driven control system because both the simulator and the model-driven control system used the same type of model. Clinically, both controllers would have probably satisfied adequate anesthesia conditions.

Simulation studies can be used to fine-tune controlling algorithms, as De Smet and colleagues[38] have extensively demonstrated by creating highly complex control models. Whether this relates to improved controller performance in the clinical setting needs to be shown.

Struys and De Smet's work can be summed up as follows:

1. They were one of the first groups introducing the Bayes theorem into closed-loop design, using the information about the individual pharmacokinetic behavior of an individual patient to create an individualized pharmacokinetic model, which they used for their closed-loop feedback system.

TABLE 86-3 COMPARISON OF CONTROLLER PERFORMANCE VALUES BASED ON VARVEL PARAMETERS

	Struys, De Smet et al (2001)	Absalom and Kenny (2003)
PE (%)	–6.23 ± 10.44	
MDPE (%)	–6.6. ± 2.63	–.42 (–.141-0.57)
MDAPE (%)	7.7 ± 2.49	5.63 (4.5-6.75)
Divergence (%/min)	0.024 ± 0.029	
Wobble (%)	5.9 ± 2.33 Mean ± SD	–.024 (–.83-0.35) Mean (95% CI)

CI, Confidence interval; median absolute performance error; *MDPE,* median performance error; *PE,* performance error.

TABLE 86-4 PERCENTAGE OF MAINTENANCE TIME DURING ACCURATE AND INACCURATE CONTROL OF BISPECTRAL INDEX

Performance	BIS Target Level	PID Controller (%)	Model-Based Controller (%)
Percentage time of accurate BIS control (between ± 10 around target)	30	58 ± 4*	67 ± 4*
	50	47 ± 10*	65 ± 12*
	70	44 ± 9	17 ± 7
Percentage time of too-low BIS values (>10 below target)	30	17 ± 6	17 ± 7
	50	27 ± 7	31 ± 13
	70	30 ± 5*	48 ± 20*
Percentage time of too-high BIS values (>10 above target)	30	24 ± 4*	16 ± 8*
	50	26 ± 3*	6 ± 3*
	70	26 ± 5*	4 ± 3*

From Struys MM, et al: Performance evaluation of two published closed-loop control systems using bispectral index monitoring: a simulation study, Anesthesiology *100:640-647, 2004.*

**P < 0.05* between both controllers.

BIS, Bispectral index; *PID,* proportional interactive derivative.

2. They realized the usefulness of adaptive modeling, meaning that the control algorithms could be corrected throughout surgery, depending on how the model performed.
3. Clinically, however, their control system did not perform better than other control systems described in this chapter.
4. They used their closed-loop propofol system mostly for small-scale studies in which they focused on the theoretical development of their models.
5. As with Kenny and Absalom, the Struys and De Smet's group used their closed-loop controlling system in patients with ASA physical status I and II.
6. Closed-loop control was used mostly for short-term procedures of 30 to 45 minutes.

THE CLOSED-LOOP ANESTHESIA DELIVERY SYSTEM: PURI'S RESEARCH GROUP

Puri's research group presented a novel closed-loop anesthesia delivery system in 2007[39] and called it closed-loop anesthesia delivery system (CLADS). The system can be used for both induction and maintenance of anesthesia. As in most other systems, the BIS was used as the control parameter within a standard feedback system, consisting of a commercially available syringe infusion pump, propofol, a microprocessor running a self-made program based on algorithms and communicating with each other using RS 232 ports. An interface allows the user to operate the system manually from a PC. The system allows the user to choose a target BIS value; the maximum infusion rate is related to the ASA physical status classification, with ASA I through III considered low risk and any ASA classification above this as high risk. Whereas BIS values are recorded into the system every 5 seconds, the propofol infusion rate can be changed only every 30 seconds or more. The system uses a proportional integral differential, based on the current infusion rate and the change in BIS values. Before accepting the BIS numbers, the signal quality index also must be checked. Effect delay is based on the time delay for the propofol to produce effect on BIS.[37]

In the first study, they compared 20 patients in whom hypnosis was delivered using CLADS versus 20 patients in whom propofol hypnosis was performed manually to maintain a BIS of 50.[39] Analgesia was maintained using fentanyl 1 μg/kg/hr and muscle relaxation using a bolus administration of vecuronium in both groups. The controller CLADS outperformed the manual group in terms of maintaining the BIS close to the target (target ± 10), on average 87% of the time versus 77% of the time in the manual group.

Even more importantly, CLADS provided a more precise induction of anesthesia, using a significantly smaller dose of propofol, thus creating less overshoot of the BIS target.

In this first study, patients were young, approximately 40 years of age, with normal body weights undergoing elective noncardiac surgery. Puri and associates[40,41] then applied their system to a sicker patient population undergoing cardiac surgery and compared it with manually controlled anesthesia. In the follow-up study using the same design, they included 37 patients, randomized in two groups of 19 and 18 patients (CLADS versus manual propofol control, respectively) undergoing elective cardiac surgery.[41] In this sicker and older population undergoing major surgery, they confirmed their earlier results: the CLADS achieved an induction of anesthesia with less BIS overshoot, this time even resulting in better hemodynamic control. All performance indexes were significantly better in the CLADS group than in the manual group.

They also used CLADS to control postoperative sedation.[41] After cardiac surgery, CLADS was used to maintain a BIS target of 70 for postoperative sedation in the intensive care unit (see also Chapter 101). The performance of CLADS was better than manual performance to maintain the BIS at approximately 70; the mean duration (in percent) of time at which the BIS was between 60 and 80 in the CLADS group was 69% versus 45% in the manual group. Although not specifically described in the results section, an average performance error of −3 in the manual group suggests a trend toward lower BIS values during the average duration of postoperative mechanical ventilation of 6 to 9 hours on average. Whether the longer time from cessation of sedation to tracheal extubation in the manual group is related to a generally deeper sedation or a longer ventilation time is not clear.

Their system performs as well in patients undergoing abdominal or orthopedic procedures in general anesthesia at an altitude of 3505 m.[43] The most interesting result of the study was the confirmation of a previous finding that patients need a larger dose of propofol for induction of anesthesia at higher altitudes than lower altitudes, thereby avoiding subjective influences by using the closed-loop system.[44] Perhaps these patients needed larger doses of propofol to achieve a target BIS. Is this due to a specific patient population or the altitude?

To confirm the robustness of their system even with sicker patients undergoing complex surgery, the same group presented a case series of 13 patients undergoing adrenalectomy for pheochromocytoma.[45] The results were similar to the findings in other patients, with 87% of the time the BIS being within 10% of the target value of 50, similar performance indexes, and good hemodynamic stability. The BIS values in this study population trended toward light anesthesia, with average BIS values of approximately 60; perhaps this indicated an increased risk for awareness, which could be countered by decreasing the target value of BIS.

The same group recently adapted their system for use with volatile anesthetics, calling it "improved anesthetic agent delivery system" (IAADS).[46] They used their system in 40 patients undergoing cardiac surgery, in which 20 patients were assigned to the closed-loop group and 20 patients to the control group. Isoflurane was injected into a low-flow breathing system with a 20 mL syringe and syringe pump.

They used algorithms similar to those in their previous propofol closed-loop system, CLADS; however, the minimal lockout period for any isoflurane changes was not

clear: their CLADS system does not change any infusion rate of propofol in intervals shorter than 30 seconds. The pharmacokinetics of isoflurane are very different with a much longer elimination period, thus changes of isoflurane concentrations should be smaller during a given time.

The uniqueness of the study lies in the fact that two different anesthetics were delivered using a closed-loop system at different times. (1) Induction of anesthesia was performed using CLADS with propofol, or manually administered propofol; (2) the initial anesthesia maintenance before cardiopulmonary bypass (CPB) surgery was performed using IAADS with isoflurane, or manual isoflurane during CPB; and (3) anesthesia was maintained using either closed-loop or manually administered propofol and isoflurane after CPB.

The study might be regarded as more of an exercise of feasibility than of widespread clinical importance; the necessity of using propofol as a continuous infusion during CPB is limited because isoflurane can be injected into the circuit. The overlapping of propofol and isoflurane effect was addressed in the algorithms; the algorithms appeared to work independently. This means that once the propofol infusion was stopped, the isoflurane controller took over, and vice versa. The possible additional effect of either drug on the other was not considered. However, such pharmacokinetic interactive modeling (propofol effect on isoflurane and vice versa) might not be necessary because a constant feedback system is in place—that is, if BIS is still low because propofol is not eliminated, the isoflurane controller delivers less isoflurane and then increasingly more until the propofol effect has disappeared. It is not clear how often the infusion rate of propofol or the isoflurane-dial setting was changed (actually, none of the articles of this research group reveals the number of propofol modifications per hour for the CLADS, only for the manual control). In fact, the isoflurane-dial setting in the manual group was only changed two times before CPB and two times after CPB; no information is given on how often the isoflurane infusion was changed in the IAADS group. More changes might have probably resulted in a better maintenance of the BIS target in the manual group.

Summary of Puri's Work

The efforts of the research group around Puri can be summarized as follows:

1. The CLADS is a PID-controlled closed-loop system of propofol delivery for hypnosis and sedation. Its performance is similar to that of other research groups. The studies were conducted on small numbers of patients (usually 20 patients per group). However, closed-loop applications in major or higher risk surgery, such as cardiac surgery or adrenalectomies for pheochromocytoma, are valuable and interesting.
2. The studies confirm that closed-loop systems are not just reserved for healthy young patients undergoing minor surgery but can equally be used in major surgery and in older and less healthy patients.
3. Puri's group presents one of the few studies of a closed-loop system using volatile anesthetics as the controlled drug; technologically, they use isoflurane as a liquid injected into a breathing circuit via a conventional syringe pump. This kind of closed-loop administration of inhaled anesthetics is fundamentally different from commercially available systems such as the ZEUS (Draeger, Lübeck, Germany) system, which is a target-controlled system, meaning that the end-tidal concentration of any given inhaled anesthetic is maintained regardless of fresh-gas flow, but is not controlled to maintain a given target of unconsciousness.
4. Their system can be used for closed-loop control of propofol sedation. In the multitask environment of an intensive care unit, closed-loop control of propofol sedation might be very helpful (see also Chapter 101).
5. In addition to the need for studies in larger patient populations, more information needs to be provided within each study, especially about the controller function (e.g., the number of propofol infusion rate modifications per hour or changes of isoflurane concentrations with either CLADS or IAADS).

LIU'S RESEARCH GROUP: FROM SINGLE-LOOP CONTROL OF PROPOFOL TO DUAL-LOOP CONTROL OF PROPOFOL AND REMIFENTANIL

In 2006, Liu and colleagues published their novel closed-loop system for propofol-based induction[47] and maintenance of anesthesia.[48] They used a closed-loop system in which feedback control was obtained using BIS monitoring but output was not by a propofol infusion rate, but target-controlled infusion rate of propofol (Fig. 86-8).

Another novelty was the feed-forward loop, which allowed fast correction of a measured BIS value of higher than 60 to avoid awakening of the patient. The target BIS was 50, with minimal and maximal propofol target concentrations set at 1 and 5 μg/mL; however, these could be modified by the user. It also integrated a safety measure when BIS values were recorded as corrupted by artifacts; the last target of propofol was not altered in that situation. Whereas Puri's group had used continuous infusions of fentanyl to provide intraoperative analgesia, Liu's group used a target-controlled infusion of remifentanil, manually controlled, and preemptive standard analgesia. They used their closed-loop system in a preliminary study only for induction of anesthesia, defined as the time between the beginning of anesthesia and achieving a target BIS of 50, therefore, before laryngoscopy or intubation. The randomized trial had 40 patients in two equal groups of 20 for closed-loop induction or manual induction of anesthesia using target-controlled propofol.[47]

In this study, they showed smaller propofol consumption and shorter induction times to reach the target value with closed-loop induction of anesthesia (381 seconds versus 490 seconds in the manual group). No hemodynamic differences were found between the groups with significant but clinically insignificant overshooting of the target in the manual group.

Interestingly, in their larger scale follow-up study of 164 patients, randomized in two groups of 81 (manual target-controlled propofol administration) and 83 (closed-loop group),[48] the duration of the induction of anesthesia was significantly faster in the manual group

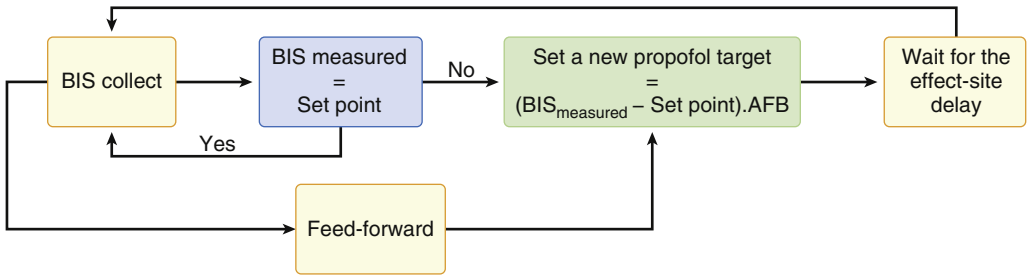


Figure 86-8. The main control algorithm. Effect-site delay was calculated using the pharmacokinetic model of Schneider. The feed-forward term amplified the correction of the propofol target when a measured bispectral index (*BIS*) value greater than 60 was detected. *AFB,* Amplification of the feedback. *(From Liu N, Chazot T, Genty A, et al, Titration of propofol for anesthetic induction and maintenance guided by the bispectral index: closed-loop versus manual control: a prospective, randomized, multicenter study,* Anesthesiology *104:686-952, 2006.)*

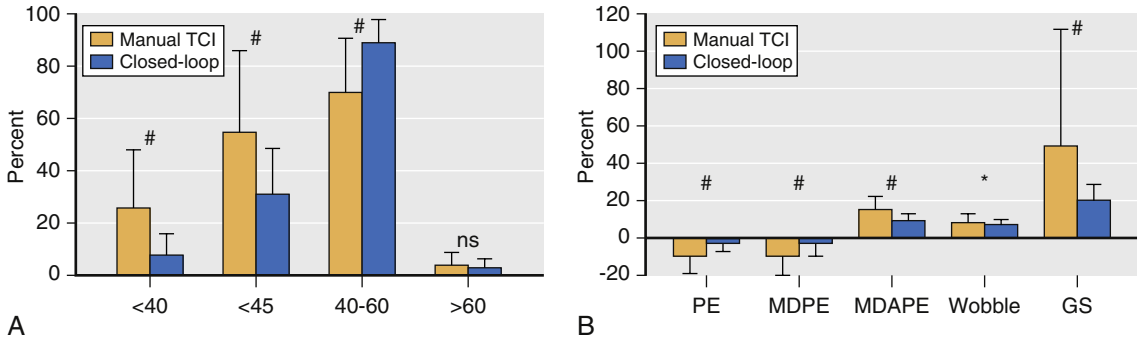


Figure 86-9. A, Efficiency of the system during maintenance of anesthesia. *P < .0001. Bispectral index* (BIS) < 40 = percentage of time when the bispectral index (*BIS*) value was under 40; BIS < 45 = percentage of time when the BIS value was under 45; 40 < BIS < 60 = percentage of time when the BIS value was between 40 and 60; BIS > 60 = percentage of time when the BIS value was greater than 60; closed-loop = closed-loop group. *manual TCI,* Manual target-controlled infusion group guided by the BIS; *ns,* not significant. **B,** Control performance during maintenance of anesthesia. *$P < .05$; †$P < .0001$. *Closed-loop,* Closed-loop group; *manual TCI,* manual target-controlled infusion group guided by the BIS; *GS,* global score; *MDAPE,* median absolute performance error; *MDPE,* median performance error; *PE,* performance error. *(From Liu N, Chazot T, Genty A, et al, Titration of propofol for anesthetic induction and maintenance guided by the bispectral index: closed-loop versus manual control: a prospective, randomized, multicenter study,* Anesthesiology *104:686-952, 2006.)*

than in the closed-loop group (271 seconds versus 320 seconds), using a significantly larger propofol dose. This showed how some "significant" results in small-scale studies can sometimes become insignificant or even the obvious in larger scale studies. Nevertheless in patients approximately 60 years of age, half of whom underwent major surgery, the results of the closed-loop control are impressive: all clinical performance variables as well as the Varvel parameters of systems control efficiency are significantly better with closed-loop control (Fig. 86-9).

The Varvel parameters also depend on the level of BIS value; thus, Liu and co-workers[49] used a composite parameter, called global score (GS) to better describe and distinguish performance differences between control systems and global score, which is calculated as follows: GS = (MDAPE + Wobble)/% of time BIS value between 40 and 60.

Liu's group[51] also showed that closed-loop propofol anesthesia in even the most difficult surgeries in sick patient populations is an appropriate approach. Their study had 20 patients who were undergoing single-lung or double-lung transplantation with clinical control values similar to those in less sick patient populations. The results showed that anesthesia was within acceptable BIS values of 40 to 60 for 84% of the time, with very limited overshoot (<40) in 13% and even less undershoot (>60) in 3%.

Liu and his research group followed their earlier work to create a dual-loop system administering both propofol and remifentanil in closed-loop control using one controlling parameter, the BIS. Their assumptions were that small errors in BIS (the difference between the set point and the measured BIS value) are indications of changes in nociception; therefore, only target concentrations of remifentanil are changed; larger errors are indications of changes in hypnosis (and nociception), and both drug concentrations are changed. They also present an interaction rule, which means that if the controller increases the remifentanil concentration more than three successive times, the propofol concentration is increased as well, regardless of the BIS error. In addition, propofol and remifentanil concentrations cannot be changed in a contrary sense–that is, the controller cannot increase propofol and decrease remifentanil, and vice versa (Fig. 86-10).

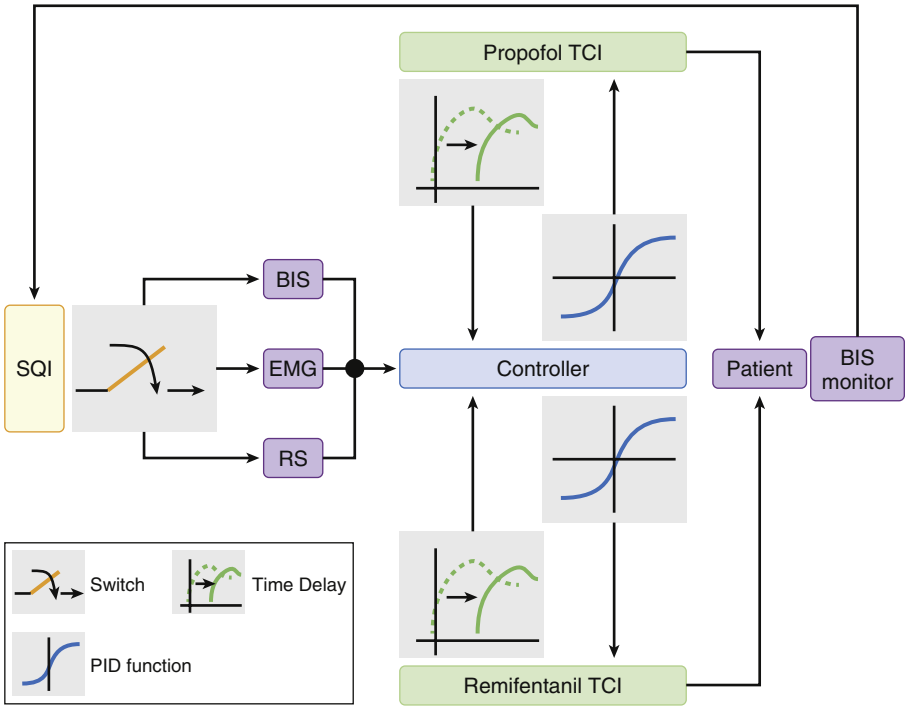


Figure 86-10. Control algorithms for Liu's dual-loop system. *BIS,* Bispectral index; *EMG* electromyogram; *PID,* proportional-integral-derivative; *SR,* suppression ratio; *SQI,* signal quality index. *TCI,* target-controlled infusion.

This dual controller of two PID controllers has the following main elements:

1. Calculation of the BIS error (difference between BIS target and measured value)
2. Feedback amplification (continuous target concentration modification to achieve BIS error = 0)
3. Variable time delay between each drug concentration modification based on pharmacokinetic principles for both drugs and age of the patient
4. Feed-forward rapid response when BIS increases over 60
5. Interaction rule: Remifentanil increases of more than three times trigger propofol concentration increase
6. Maintenance of last target concentration when BIS dysfunction or poor signal quality occur

The assumption that small changes of BIS indicate changes in nociception and larger changes indicate changes in nociception and/or depth of consciousness is a somewhat arbitrary assumption by Liu's research group. Clinically, however, the technique seems to work well.

In 2011, Liu and colleagues published a study of 196 patients undergoing surgery (30% major, 15% ASA physical status III) using either the dual-loop propofol remifentanil control system (N = 83) or manual control (N = 84). As in other closed-loop studies, the dual-loop system achieved better maintenance of BIS values to the target of 50, probably influenced by the generally larger number of concentration changes in comparison to manual control. For propofol there were 26 versus 9 changes per hour manually and for remifentanil 32 changes versus 8 changes per hour manually and by the smaller increments of concentration changes. Obviously, a direct way of judging the performance of remifentanil control separately exists, because they defined nociception through changes in BIS. More conventionally, it is accepted that nociception during general anesthesia is reflected by hemodynamic changes; the study did not find any changes in heart rate or arterial blood pressure control between manual and dual-loop control. There was a 1 minute more rapid extubation time in the dual-loop group, which is of no clinical significance. As in their earlier work, clinical performance (maintenance of BIS within 40 to 60) and avoidance of overshooting (BIS < 40) and undershooting (BIS > 60), as well as systems control, were better in the dual-loop group, with a global score of 26 versus 43 in the manual group.

Liu and colleagues[50] followed their philosophy of extracting two components (one for pain or nociception, one for nociception and or hypnosis) from a depth of consciousness monitoring parameter by using the spectral M-entropy monitor as guidance for their dual-loop control system. The concept is similar to that in their previous work, when they used the BIS.[51] Interestingly, because of the smaller group size (31 patients in the manual group, 30 patients in the dual-loop group) or the use of the entropy monitor, no differences were found between the two groups during either the induction or duration of anesthesia regarding the propofol or remifentanil dose or that the relation between state entropy and response entropy might be a surrogate measure of antinociception,[52] they found no differences in terms of antinociception between the two groups, no significant differences of any response entropy–related performance index, but a significantly better control of hypnosis with state entropy values between 40 and 60 in 80% of the anesthesia time in the dual-loop group versus only 60% in the manual group.

The same research group recently tested their dual-loop system for deep sedation in critically ill patients.[53]

In contrast to Puri's group,[42] which can adjust their controller to different degrees of sedation (for postoperative sedation, they used a target BIS of 70), Liu's controller does not adjust the target BIS value according to the varying demands of sedation. They used the same BIS target of 50 for sedation purposes, which is probably unnecessarily deep for intensive care sedation in most patients (see also Chapter 101). In this small study, 14 patients received manual sedation (manual analogue-sedation because both propofol and remifentanil were used) and 15 patients received automated analogue-sedation using the dual-loop control system for 8 to 24 hours. The BIS was maintained more often within 40 to 60 in the dual-loop control group versus manual control group. This is not surprising when the mean target modifications of propofol and remifentanil per hour were 1 to 2 in the manual group versus 30 to 40 in the dual-loop group. In situations in which deep sedation in critically ill patients is necessary, an automated closed-loop sedation system has the advantage of maintaining a steady sedation state for a longer period. This is especially important in an intensive care unit, where the increased magnitude of care and multitasking responsibilities limit the frequent adjustments of propofol or remifentanil dosing, as indicated with the limited number of dose modifications of 1 to 2 per hour in comparison to most comparative intraoperative studies, in which anesthesia providers manually perform many more frequent infusion rates.

Summary of Liu's Work

The efforts of the research group around Liu can be summed up as follows:

1. Liu and his group have established a wide-ranging multicenter platform, which allows evaluation of the dual-loop system in a large scale of patients, from healthy to very sick patients, undergoing minor to difficult surgeries such as lung transplantation. They studied the system in over 3000 patients (personal communication with Dr. Liu, 2012) without any system-inherent failure or adverse effect. This makes the dual-loop system the closed-loop system with the biggest patient population.
2. The advantage of closed-loop systems over manually administered anesthesia is the larger number of modifications of concentrations of propofol and/or remifentanil that can be given over time. The responsibilities of anesthesiologists and critical care specialists are extensive, and such automatic systems are needed.
3. Undoubtedly, using the theorem that small changes in BIS values are a surrogate for (anti-) nociception is sometimes questioned; no study is available that supports this way of thinking. However, in clinical practice, remifentanil is mostly given because of hemodynamic variable changes, which is also just an indirect, albeit widely accepted, surrogate for nociception. Giving remifentanil by a closed-loop system makes sense. It would be interesting to see how the system would work with other opioids, such as fentanyl or sufentanil.
4. The fact that dual-loop systems maintain anesthesia around a target of 50 might limit its use for sedative purposes; here, Puri's system has the advantage that any BIS value can be chosen by the user.
5. The dual-loop system can be used for induction and maintenance of anesthesia; for induction it has the advantage over manual induction in avoidance of target overshooting. In hemodynamically frail patients, this might lead to better hemodynamic stability during induction of anesthesia.
6. The advantages of slightly shorter extubation times are probably not clinically relevant.
7. Similar to Puri's system, the dual-loop system, or the single-loop propofol control system for that matter, continues with the last concentration of propofol and/or remifentanil in situations of poor signal quality of the depth of consciousness monitor. In high noise areas such as the intensive care unit, where the signal could be absent for a longer period, this could lead to problems. A better adjustment of the concentrations, such as last average over a longer period, might be more suitable. It is not clear how the user overrides the system in these situations—that is, changes from manual to automated control again.

THE ROSTOCK EXPERIENCE: CLOSED-LOOP CONTROL OF TWO GENERAL ANESTHESIA COMPONENTS

In 2009,[54] a research group from Rostock, Germany, presented a multiple-input-multiple-output controller (MIMO) for closed-loop control of target controlled infusion of propofol using BIS feedback and infusion of mivacurium using electromyography (EMG) feedback, based on an abstract presented in 2006.[55]

The two control systems work independently and are based on different control strategies.

The Rostock group used a conventional adaptive generalized predictive controller (aGPC) for control of neuromuscular blockade. An initial bolus is given and the individual reaction to it is used to drive an upstream on-off controller (see also Chapter 53).

For hypnotic closed-loop control, they used an unusual fuzzy proportional, differential plus integral controller. Proportional means the actual difference between the measured BIS value and the target value; differential means the speed of the change between measured BIS and target BIS; and integral is related to the duration of the difference between measured and target BIS. PID controlling is the basis of most closed-loop systems. The Rostock group linked the PID controller with an attempt to categorize the degree of the difference between measured and target BIS, from high negative to high positive—meaning a big negative difference from measured to target BIS (too profound hypnosis, e.g., −40) to a big positive difference (too light anesthesia, e.g., +40) with fuzzy gradual changes possible. The detailed description of the fuzzy PID controller was published in 2003.[56]

In an initial clinical feasibility study in 20 patients (ASA physical status I and II) undergoing orthopedic or general surgeries, hypnosis was induced manually, after

which propofol was administered in closed-loop fashion via BIS (target = 40) feedback for an average of 95 minutes. Analgesia was manually provided using 0.2 to 0.4 μg/kg/minute of remifentanil, a rather significant dose. The clinical controller performance is not published, but the Varvel parameter values are within the range of other closed-loop studies. The study unfortunately lacks a control group and is of small size.

In 2011, the same group published a feasibility study in 20 patients (17 ASA physical status I and II, 3 physical ASA III) undergoing a variety of minor to major surgeries of a mean 2 hours. After a manual induction of anesthesia, a closed-loop control of propofol (feedback: BIS = 40) and mivacurium (feedback: EMG, T1/T0 = 10%, first dorsal interosseus muscle) was initiated. The controller performance of the propofol system was similar to others observed by other research groups, with BIS within 10% of target during 65% of the time; the controller performance of the mivacurium closed-loop system was equally good with 87% of the time within 10% of the target value. Unfortunately, the complete profile of clinical performance is not presented, especially the percentage of time of BIS greater than 60 or BIS less than 35 is not described. In addition, there is no control group. Whether a complete neuromuscular blockade is advantageous for surgery, especially surgery of the extremity, is doubtful. It would be interesting to see the controller performance of the neuromuscular blockade control in areas of what was formerly referred to as a "surgical relaxation," in which possibly a simple upstream on/off controller will control limits. Historically, intense or deep neuromuscular blockade has been discouraged because of fear of prolonged or residual neuromuscular block. In the last 3 years, extending deep neuromuscular blockade to the end of surgery may have had surgical benefits. Furthermore, such a block can be reversed with sugammadex (see also Chapters 34 and 35). Inherent risks exist for postoperative residual paralysis as well as masking of intraoperative awareness, a somehow limited risk with continuous BIS monitoring (see also Chapter 50).

Summary of the Rostock Experience

The efforts of the research group in Rostock are summarized here:

1. This system seems to be stable, promising control system for propofol and mivacurium, BIS, and EMG feedback control system with both arms acting independently but with as good a performance as other closed-loop systems in the literature.
2. So far, they have published only small series of patients (two studies of 20 patients each), the vast majority ASA physical status I and II patients. The system needs to be tested in sicker patients and larger patient populations.
3. So far, their development is in the feasibility stage, with no study published yet with control groups of manual control.
4. Judging from the early results, adding fuzzy logic to a more conventional PID controller does not seem to improve the controller performance significantly.
5. Their system for induction of anesthesia has not been described.

THE WORK OF THE ITAG RESEARCH GROUP

The Intelligent Techniques in Anesthesia (ITAG) research group's focus is on the importance of robot communication with the user.

The first study was published in 2009 and compared four different interfaces, from simple numerical and graphical, to mixed numerical-graphical, and a two-dimensional interface, using the variables of reaction times, response accuracy, and workload in anesthesia care providers.[57] The choice of interface can reduce the workload significantly; in that study setup, the mixed numerical-graphical interface showed the least workload (Fig. 86-11).

The same research group used the results of that study in subsequent designs of closed-loop studies. They incorporated user interfaces that allowed better communications between potential users, either for purely monitoring purposes or manual intervention, and the closed-loop system.[31]

The presented closed-loop propofol system was a self-adaptive system that showed similar performance values (both clinical and as controller performance), as work presented by other research groups. In a randomized controlled trial, 40 patients undergoing surgery of an average 2 hours were randomly located to either closed-loop propofol administration or manual propofol administration to maintain a BIS of 45.

As mentioned before, the system uses a unique user interface to display the closed-loop control, trying to give as much information as possible to the user, including a color-coded BIS display, with yellow to red indicating areas of particular concern of awareness or risk for arousal.

The system has a variety of user interaction opportunities that allow the user to define a distinctive individual profile of propofol control. These include the setting of minimal and maximal propofol infusion rates, the time intervals to calculate the new infusion rate (e.g., 30 seconds), the time interval to calculate an offset trend to be used for self-adaption, and the speed of application and dose of a rescue bolus, which is the equivalent of the fast-forward mechanism Liu and his research group used to counterattack areas in which the BIS value reached 60 when there is a risk for arousal.

The system measures clinical performance (i.e., maintenance of BIS within 10% of target and avoidance of larger offset from the BIS target), median performance error, median absolute performance error, wobble and the global performance index, a composite parameter, similar to Liu's global score in that the higher it is, the better is the performance. In contrast to Liu's global score, it looks specifically at the percentage of excellent and poor control. A high value of global performance index (GPI) is characterized by a high percentage of BIS within ± 10% of the target and low MDAPE, wobble, and percentage of inadequate control. In this study, the GPI for closed-loop control versus manual control was 155 versus 40, respectively.

The same research group designed a closed-loop system for remifentanil administration and then used

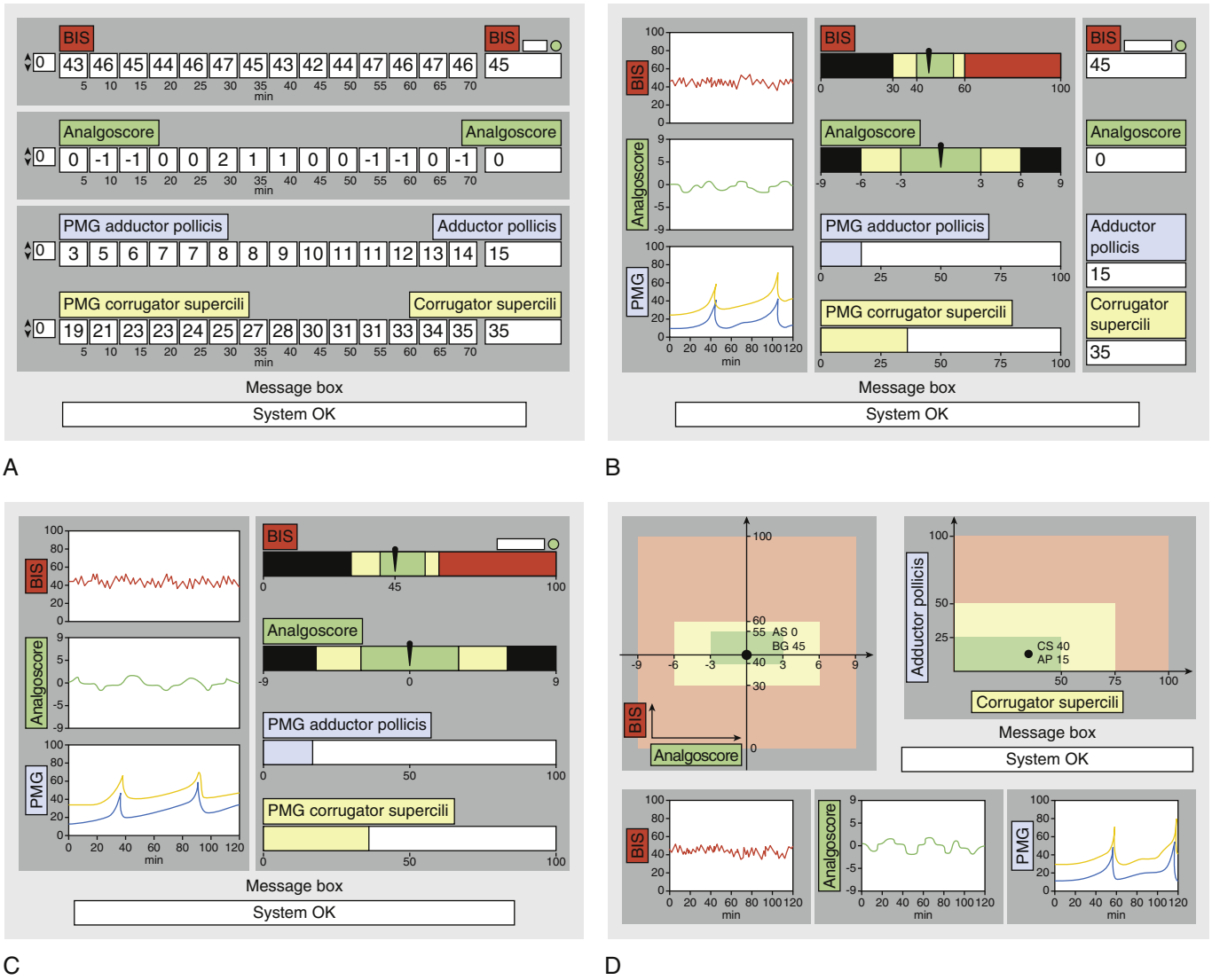


Figure 86-11. A, The numerical display shows trends value every 5 minutes and real-time value for the bispectral index *(BIS),* Analgoscore and phonomyographic *(PMG)* scores at the muscles of the thumb and the eyebrow. **B,** The mixed numerical-graphical display presents graphical trends on the *left,* separated graphical elements at the center, and numerical values on the right. **C,** The graphical display gives rudimentary numerical indications on the graphical elements. **D,** The advanced-graphical display shows two bidimensional scales; one for the BIS (y-axis) and Analgoscore (x-axis), the other for both phonomyographic muscle sites. The *black dot* indicates the real-time value.

the design and control elements to design a pharmacologic robot nicknamed McSleepy. McSleepy has several unique features: it delivers induction and maintenance of anesthesia, hypnosis, analgesia, and muscle relaxation; autonomously it has the capability of live video feeding and telemedical capabilities; it communicates via voice commands with the user, telling him or her to perform certain manual gestures, and it guides during the emergence process; it also has a variety of manual user input possibilities and an intuitive touch screen interface.

It transforms a standard closed-loop system into more of a complete pharmacologic robot.

The features of McSleepy can be summarized as follows:

- Fully automatic or semiautomatic mode (e.g., closed-loop hypnosis control, combined with manual analgesia control)
- Three closed loop controllers for induction and maintenance
  - Self-adaptive PID for hypnosis using BIS or any other depth of consciousness monitoring parameter as feedback
  - Self-adaptive PID for analgesia using the Analgoscore as feedback parameter
  - On/off controller for neuromuscular block using any available neuromuscular blocking device
- Large touch screen interface as communication platform with user
- Four different screens: Setup screen, induction screen, maintenance screen, and emergence screens with automatic change in-between
- Communication with user: Output by voice commands; input at different stages of surgery
- Telemedical capability: Connection via Bluetooth or internet with any wireless device

- Live video feeds
- Recording and monitoring of data
- The concept of McSleepy is based on the experience that anesthesia providers do not like to lose control of what is happening to their patient. Therefore, the anesthesia provider puts in patient data, such as weight, height, ASA physical status classification, and information as to which surgery will be performed, which drugs will be used or whether additional analgesic control is performed. In addition, the user chooses between fully automatic mode, in which all three components of general anesthesia are provided autonomously by the device, or semiautomatic mode, in which only one or more components are controlled autonomously. Therefore, the user or anesthesia provider via the touch screen can use McSleepy to administer anesthesia completely manually, semiautonomously, or fully automatic.

In fully automatic mode, the device allows focus on the patient, including manual ventilation. McSleepy directs and guides the user or anesthesia provider with voice commands. It uses BIS values to advise the user when to commence ventilation via a facemask and uses parameters from the induction screen that provides information on the depth of consciousness, remifentanil dose, and neuromuscular blockade to advise on the right time to intubate the trachea, thus decreasing the workload of the anesthesiologist during induction of anesthesia and allowing focus on other clinical tasks. The targets of BIS, Analgoscore and neuromuscular blockade are automatically chosen in fully automatic mode, but can be manually modified at any time. The user needs to indicate to the device definite steps of surgery, such as intubation, positioning, disinfection, incision, and 20 minutes to the end, which are also used as variables to modify control of drug dosing.

McSleepy uses a moving average infusion rate of a definite time interval before the arrival of the artifact and not just the last infusion rate. The device will not administer a neuromuscular blocking drug if the BIS value is more than 60—that is, to avoid patient awareness while being partially or fully paralyzed. Another built-in safety measure is an automatic delay of 60 seconds between reaching the BIS target for induction and beginning administration of the neuromuscular blocking drug: this gives the anesthesiologist time to push the "cannot ventilate" button on the induction screen to stop the administration of the neuromuscular blocking drug. Once the button "20 minutes to the end" is pushed during surgery, no neuromuscular blocking drug is administered. Manual override is questioned by the device with a reminder that it is 20 minutes to the end of surgery and whether the user wants to proceed. Once the surgery is finished, communicated to the device by the user with a push button, the emergence screen appears and guides the user through the emergence process. This process displays cumulative data of all drugs administered, trends of all parameters, and the present BIS values in reverse color coding, indicating BIS values greater than 60 in a green area. When a definite BIS value of approximately 65 is reached, a voice command indicates to the user that it is time to wake up the patient. The basis for this design is to allow the user to focus visually on the patient or on hemodynamic, respiratory values while voice commands keep the user informed about aspects of anesthesia.[58]

McSleepy was tested in a randomized control trial of 186 patients undergoing elective surgery, mostly major surgery, of an average duration of 3 hours.[59] As other research groups have shown, clinical performance was significantly better in the closed-loop group for control of hypnosis, including avoidance of undershooting and overshooting, whereas the control of remifentanil was equally accurate in the manual and closed-loop groups, as demonstrated by the comparison of the Analgoscore in the two equally sized groups.

A 5-minute significantly quicker emergence occurred in the McSleepy group; however, the clinical relevance after 3 hours of surgery might be limited. The fact that the closed-loop administration avoids significant periods of BIS undershoot (BIS > 60), with the inherent risk for awareness, is clinically more important.

Figure 86-12 is an illustration of the control mechanisms in McSleepy.

The same group also developed a closed-loop system, which integrates a decision support system into a closed-loop propofol sedation system called a hybrid sedation system. The decision support side of the system has been previously described (see section on decision support systems).

The closed-loop system for propofol sedation integrates BIS monitoring, peripheral O_2 saturation, and respiratory rate as sensors into a closed-loop system, using PID controllers. The controller uses an individualized dosing scheme, which is established after an initial bolus is given to the patient and the reaction of the patient is analyzed, thus creating an individualized PID controller (Fig. 86-13).

Summary of the ITAG RESEARCH GROUP WORK

The efforts of the ITAG research group are summarized as follows:

1. The focus of the ITAG group is on the development of an integral pharmacologic robot that can interact with the user. The control mechanisms are of interest, not because they use very different basic controllers—in fact, they use PID and on-off controllers—but because they use surgical time points as control mechanisms, such as positioning, incision, or type of surgery, which can be integrated in the control mechanism.
2. McSleepy offers both fully autonomous and semiautomatic control, thus allowing use in fully manual mode, semiautomatic mode (some anesthesia components are controlled automatically), or fully automatic mode.
3. McSleepy communicates with the user with voice commands, allowing the anesthesiologist to focus on the patient.
4. It incorporates closed-loop safety features such as artifact control, and, in addition, safety features resembling

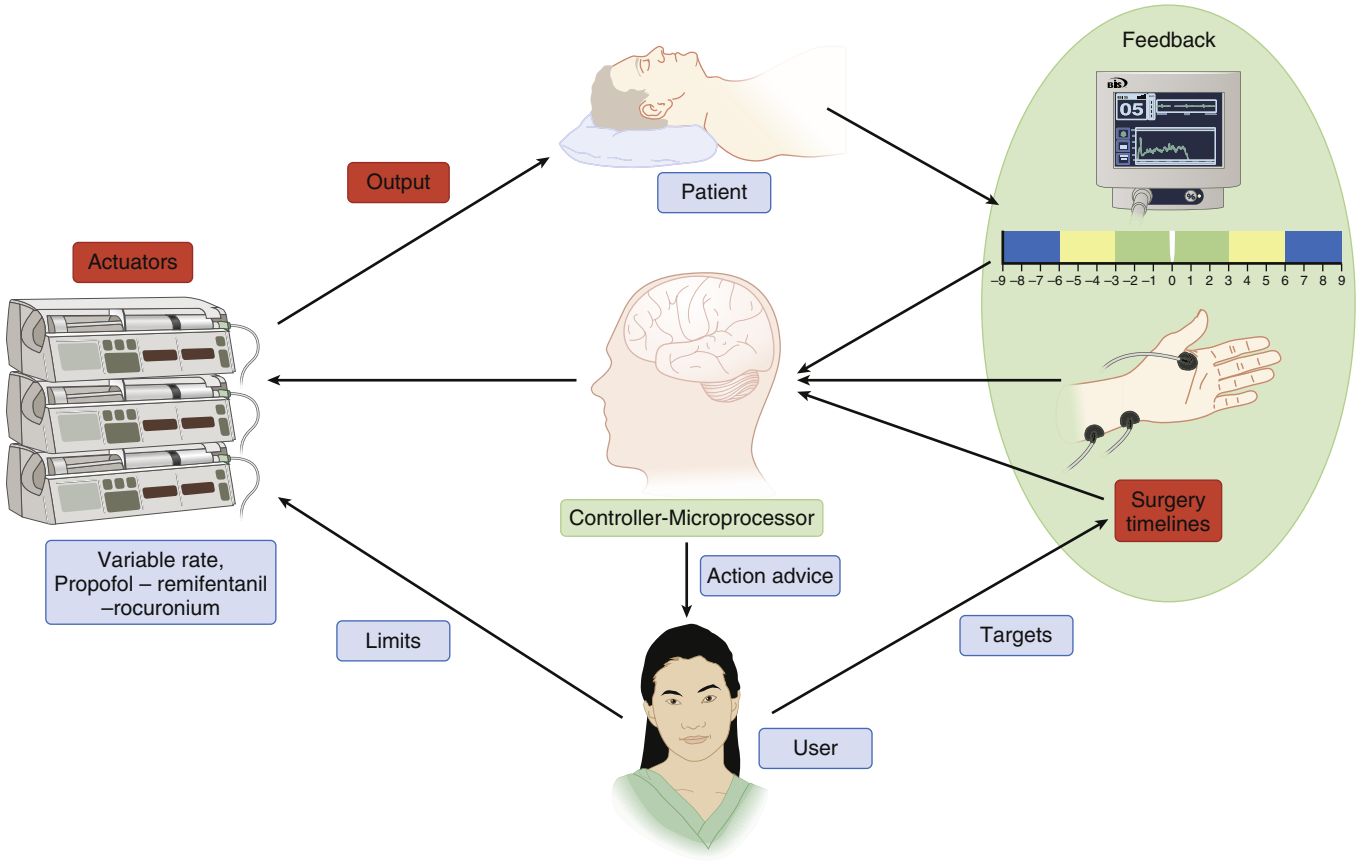


Figure 86-12. Control mechanisms of McSleepy.

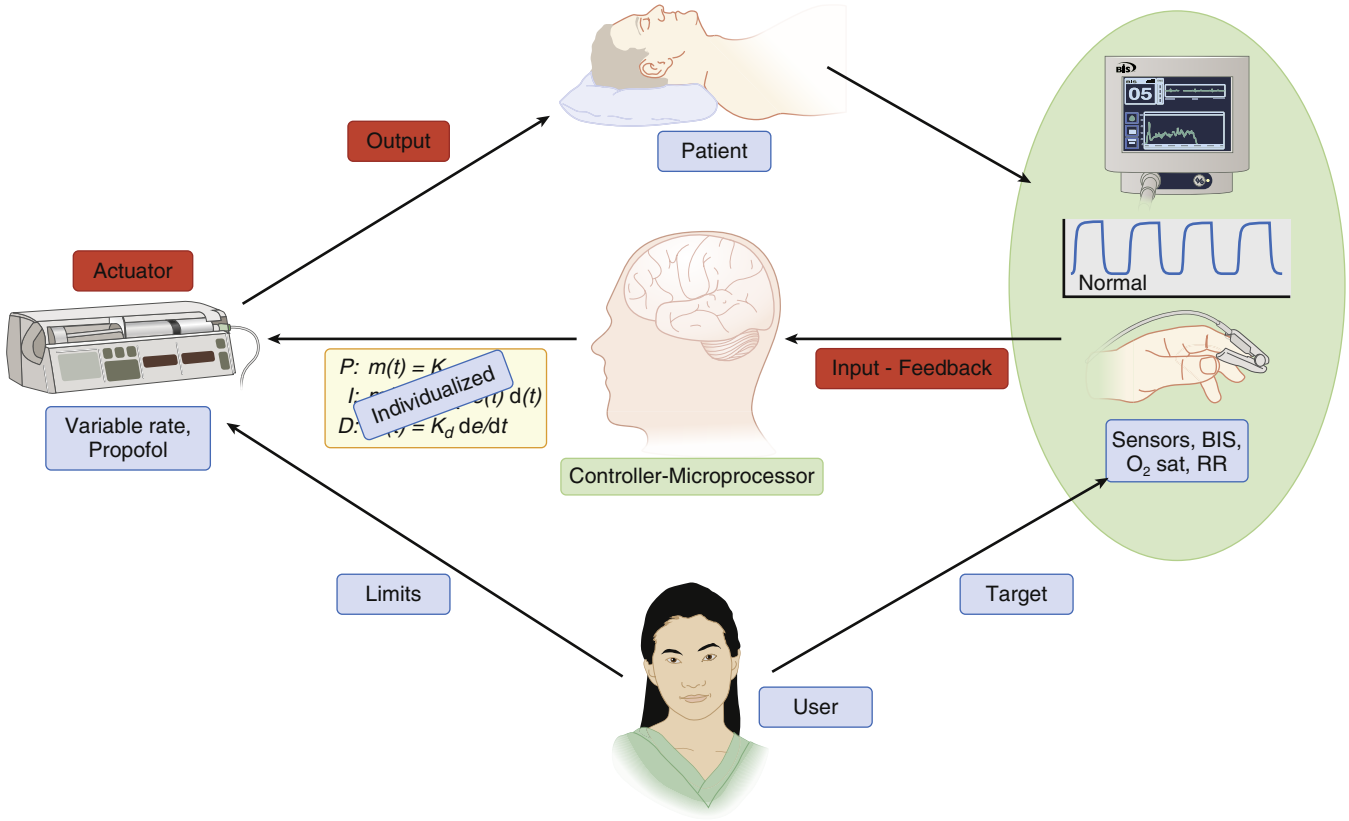


Figure 86-13. Control mechanism of hybrid sedation system. *BIS,* Bispectral index; *O_2 sat,* oxygen saturation; RR, respiratory rate.

common everyday practices, such as the confirmation that facemask ventilation is possible *before* administration of a neuromuscular blocking drug.

5. McSleepy also incorporates telemedical capabilities and video feeds.

CLOSED-LOOP CONTROL SYSTEMS FOR NEUROMUSCULAR BLOCKADE

Closed-loop control systems were designed in the 1980s and primarily used neuromuscular blockade results from electromyography as the feedback method because the device was easy to connect to any closed-loop circuit via an RS232 interface (see also Chapter 53). Interest in these early systems was not so much based on their clinical application, but as a research tool to evaluate the interaction between drugs, specifically the potentiation of neuromuscular blocking drugs by volatile anesthetics. The controllers[97-107] ranged from simple on/off controllers, over classical PID controllers to adaptive model-based controllers; one study group even used a highly complex neural network controller, called a dynamic matrix controller[60] and one a fuzzy-logic controller.[61]

All closed-loop systems started with a manually administered large single bolus of neuromuscular blocking drug to achieve or surpass the desired and mostly profound level of neuromuscular blockade, after which the neuromuscular blockade response was allowed to recover spontaneously, while the closed-loop system started the maintenance of a continuous infusion of a given neuromuscular blocking drug, mostly using the individually calculated reaction of a patient to the bolus dose, thus creating an individualized control mechanism, irrespective of the controller used.

Despite a summary table showing no specific superiority for any type of controlling theorem, the adaptive model-based controller[62] and the dynamic matrix controller are reviewed in this chapter.

The adaptive model-based controller first assumes that a certain model reflects accurately the pharmacokinetic-dynamic relationship of a given drug; Olkkola and associates[62] used a two-compartment model (biophase-effect compartment and central-blood compartment). After a bolus application of the neuromuscular blocking drug, a certain concentration in the biophase is achieved that can be described using a mathematic formula:

$$C_e(t) = \int_0^t dt' \, G(t - t')I(t')$$

This formula describes the relationship between drug input function I (t) and drug concentration in effect compartment $c_e(t)$

And

A second formula describes the relation between concentration $c_e(t)$ and effect E(t):

$$E(t) = \frac{E_{max}[C_e(t)]^{\gamma}}{C_0^{\gamma} + [C_e(t)]^{\gamma}}$$

Certain parameters of these formulas are updated throughout the process of continuous neuromuscular blocking drug administration, thus creating a model-based, adaptive controller. Obviously, the specific parameters of these formulas need to be adjusted for each neuromuscular blocking drug or any other drug, because their uptake and elimination from central compartment to effect-site compartment differs.

Geldner and associates[60] chose a different path; they first performed many cases of general anesthesia with manually guided neuromuscular blockade to establish a neural framework, which was subsequently tested in a validation period. A neural network tries to "act" like a human brain, thereby adapting its action to previous experiences, learning from wrong-right decision making. Using a "dynamic controller," the system is assumed to be able to learn from its right or wrong decisions.[63]

As a basis, the system takes into account, at any given time, the last 20 twitch tension values, calculates a predicted twitch tension response, based on four different infusion rates, and adjusts the actual infusion rate according to the closest match between predicted twitch tension response and target twitch tension response (Fig. 86-14).

The theoretical basis for both model-driven, adaptive as well as neural network–based controllers, is interesting, but no apparent advantage has been found in terms of controller performance of any controller theorem, from very simple on/off controllers to highly complex neural networks, as Table 86-5 shows.

The most important clinical relevance of closed-loop systems for neuromuscular blockade is not so much in their clinical application—that is, the necessity for continuous, steady, or profound neuromuscular blockade is controversial at best, but in their utility for (objective) evaluation of drug interactions, especially the interaction with volatile anesthetics.[64-69]

CLOSED-LOOP CONTROL OF VOLATILE ANESTHETICS

Target-Controlled Infusion of Volatile Anesthetics: The ZEUS Device

It is important to understand that what is called "closed-loop control of volatile anesthetics" is mostly related to the maintenance of a steady end-tidal concentration of volatile anesthetics or oxygen, as is commercially available in the ZEUS Draeger anesthesia machine. Although there is a closed-loop system that continuously measures the end-tidal concentration and regulates the end-tidal concentration to a steady level, irrespective of flow rate, it lacks integrated patient feedback monitoring. Therefore, it is not an automated patient anesthesia delivery system in the sense that the patient's biofeedback is used to guide hypnosis.

The functioning of the system is described as such: "The inspired and expired concentrations are measured by sidestream infrared technology and paramagnetic O_2 sensors. The sample gas flow is fed back to the system, so that the system is completely "closed." In addition, the fresh gas mixture is servocontrolled to keep the inspired O_2 concentration at the targeted level and to maintain a constant ambient pressure at the end of expiration in the

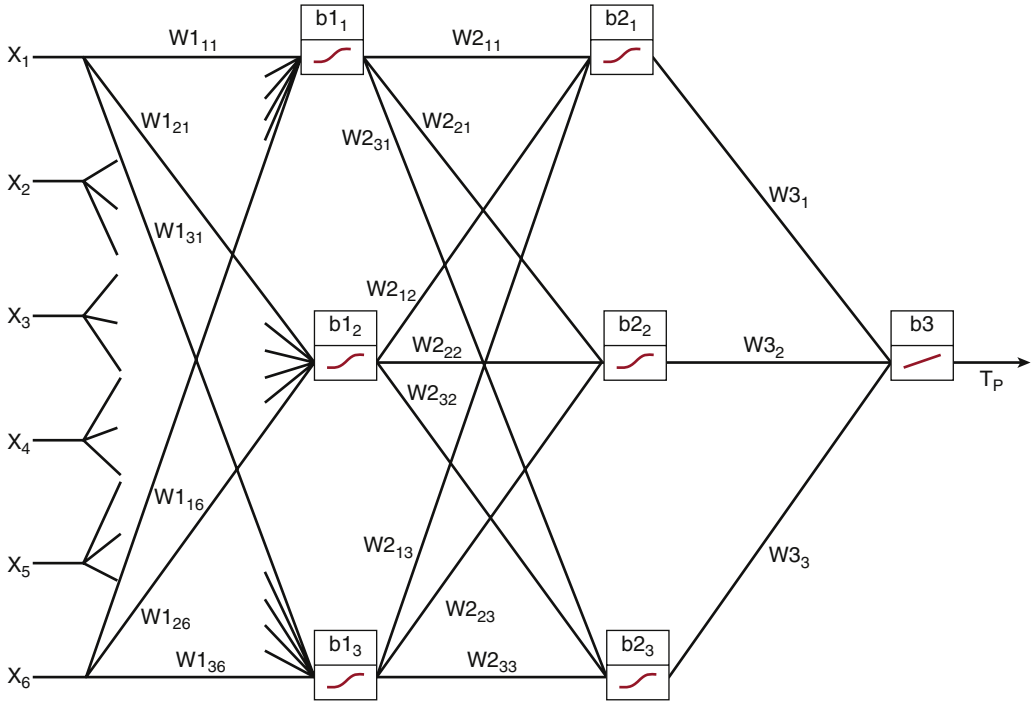


Figure 86-14. Four-level perceptron with activation/regulation knots ("neurones" *b1-b3*), regulation paths (paths *W1-W3*), and last 20 twitch values (x_1-x_{20}), as well as the predicted twitch response T1-Wert (T_p).

TABLE 86-5 **CONTROLLER PERFORMANCE**

First Author	Reference	Year	Agent	Control	Feedback	Target (%)	N	Offset (%)
Asbury	97	1986	PANC	PID	EMG	T1/T0 = 20	40	7
De Vries	98	1986	VEC	On-off	EMG	T1/T0 = 15	28	2
Webster	99	1987	ATR	PID	EMG	T1/T0 = 10	20	1.1
Wait	100	1987	ATR	On-off	EMG	T1/T0 = 5	11	3
Uys	101	1988	ATR	Adaptive model-based	MMG	T1/T0 = 15	11	4
MacLeod	102	1989	ATR	PID	EMG	T1/T0 = 20	36	1.3
Ebeling	103	1991	VEC	Adaptive model-based	EMG	T1/T0 = 10	11	0.65
Olkkola	62	1991	ATR	Adaptive model-based	EMG	T1/T0 = 10	5	1.1
						T1/T0 = 30	5	0.2
						T1/T0 = 50	5	0.1
Kansanaho	104	1997	ATR	Adaptive model-based	EMG	T1/T0 = 10	10	2.9
			VEC				10	4
Edwards	61	1998	ATR	Adaptive fuzzy logic	AMG	TOF = 10	10	0.45
Geldner	60	1999	MIV	Adaptive dynamic matrix	KMG	T1/T0 = 5	20	0.55
Hemmerling	65	2001	CIS	Adaptive model-based	EMG	T1/T0 = 10	56	2-3
Pohl	105	2004	CIS	On-off	EMG	T1/T0 = 10	20	–1.6%
Eleveld	106	2005	ROC	PI	AMG	TOF count 1-2	15	4
Schumacher	107	2006	MIV	Adaptive model-based	EMG	T1/T0 = 10	11	1.8

AMG, Acceleromyography; *ATR,* atracurium; *CIS,* cisatracurium; *EMG,* electromyography; *KMG,* kinemyography; *MIV,* mivacurium; *MMG,* mechanomyography; *PANC,* pancuronium; *PI,* proportional-integral; PID, proportional-integral-derivative; *ROC,* rocuronium; dynamic matrix = neuronal network based; T1/T0, first twitch ratio from twitch height before administration of neuromuscular blocking agent; *TOF,* train of four; *VEC,* =vecuronium.

manual breathing bag. If this pressure declines, fresh gas flow is automatically increased in response; conversely if the pressure rises, fresh gas flow is reduced."[70]

Undeniably, these systems can have some clinical advantages, such less overshoot and undershoot when end-tidal concentrations need to be changed,[71] lower costs,[72] and a reduction in the workload for the anesthesiologist.[70]

However, they do not adjust the concentration of the end-tidal concentrations of volatile anesthetics according to the measured depth of consciousness or any other patient parameter.

CLOSED-LOOP SYSTEMS FOR VOLATILE ANESTHETICS

Few published studies describe the design and clinical testing of truly closed-loop volatile anesthesia delivery systems that use depth of consciousness monitoring as a

feedback parameter. One such system by the Puri research group[46] has already been described.

Another system was presented by the Bern research group of Zbinden and A. Gentilini.[71-73] The system is similar to Puri's and uses isoflurane, now a rarely used volatile anesthetic. The controlling system integrates an outer cascade, feeding back the end-tidal concentration to the system via a simple proportional-integral controller, and an inner controller that incorporates feedback from the BIS into model-based algorithms to maintain a given level of hypnosis.

The safety switch is an electrical push button to switch the gas supply back to the standard dosing system.[74]

The controller samples the BIS every 5 seconds and adjusts the doses accordingly. The Bern group used a model-derived external controller similar to the control models used for intravenous anesthetic drugs.

The system has safety algorithms built in that are plausibility measures. For example, the inner controller recognizes only "true" isoflurane concentration values between 0 and 5 vol%, and all other measured values are disregarded as artifacts, as well as artifact safety measures when the BIS values are prone to electric or other disturbances. In this event, the system switches to a purely model-based administration of isoflurane, set by the anesthesiologist before the procedure. It also incorporates some adaptive-control mechanisms with the hemodynamic and BIS reaction to the skin incision used to adjust the control algorithms individually. In a randomized control trial (patients undergoing major surgery, ASA physical class I through III, N = 10 each group), closed-loop, BIS feedback administration of isoflurane was compared with manual, BIS-guided isoflurane administration with a target BIS of 50 for a mean duration of approximately 2 hours. Analgesia was maintained manually in all patients to sustain blood pressure and heart rate within 20% of the preoperative values. Unfortunately, the clinical performance of the two groups, meaning the percent of time in which the measured BIS value was within 10% of the target value, is not presented; however, the Varvel values favor closed-loop control. An assessment of how clinically important this difference is cannot be made without the presentation of the clinical performance. In addition, the amount of isoflurane concentration changes over time is not presented, which limits the evaluation of the performance of the manual group. If almost no changes in concentration levels were performed in the manual group, this could affect the reproducibility of the results. Significantly fewer episodes were found of BIS values greater than 65 for more than 3 minutes in the closed-loop group than in the manual group, which could mean better outcome by lowering the risk for awareness during surgery.

One issue is the significantly higher alfentanil concentration in the manual group; however, it is possible that this might not have affected the performance results of the study.

CLOSED-LOOP CONTROL OF ANALGESIA

Although adequate monitoring parameters for hypnosis and neuromuscular blockade are available, no such monitoring parameter is available for assessing pain during unconsciousness. However, there is clinical consensus that hemodynamic changes can be used as an indirect parameter to assess pain or nociception. Most anesthesiologists use vital signs as parameters, such as arterial blood pressure and heart rate, in a variable.

The first attempt to use hemodynamic variables clinically was published in 2000.[75] Arterial blood pressure was rated as having a 5/6 importance for pain control, with heart rate as 1/6. A fuzzy-logic controller was used to direct a continuous infusion of alfentanil. Using this controller in eight patients, the mean arterial pressure stayed within 15% of the target in almost 90% of the time; no results for heart rate stability were given. A research group around Gentilini[76-79] in Bern tested a model-based predictive controller for target-controlled alfentanil in 13 healthy patients undergoing minor surgery. The controller only used mean arterial blood pressure.

The model predictive controller with mean arterial pressure as the primary and predicted plasma alfentanil concentration (Pred Cp) as a secondary input variable is depicted (PK = pharmacokinetic).

This feasibility study did not have a control group. The mean absolute deviations from the target mean arterial blood pressure of 70 to 90 mm Hg (individually chosen by the attending anesthesiologist) was 11 mm Hg during surgery, which is equal to a mean offset of approximately 15%. The study does not present how often the alfentanil concentration was changed during surgery.

None of these closed-loop studies compared the controller performance with a control group, which limits the assessment of performance.

One study presented some novelties: the presentation of a new composite pain score, a closed-loop control algorithm, the closed-loop control of remifentanil, and a focus on the user interface; probably one of the first closed-loop studies that took into account the importance of the user interface.[80]

Because all previous closed-loop studies had used hemodynamic parameters as surrogate targets for intraoperative pain perception and nociception, the latter study composed a novel score, called Analgoscore. Analgoscore uses mean arterial blood pressure and heart rate as the basis for a score that ranges from −9 (too profound analgesia) to +9 (insufficient analgesia), with a target of 0 as a perfect balance between analgesic treatment and pain. The score also takes into account other physiologic changes that can influence the antinociception validity of these hemodynamic parameters, such as hypovolemia and vagal reactions. The control mechanism is an adaptive PID controller, which analyzes past offset in integral time intervals and adjusts the infusion rate accordingly.

In a comparative trial, the Analgoscore was used to titrate remifentanil infusion in 27 patients undergoing surgery of almost 2 hours duration. In one group of 16 patients, remifentanil was administered using the closed-loop system. In the control group of 11 patients, anesthesiologists were advised to use the Analgoscore as guidance for remifentanil infusion rate settings with the goal to maintain a value of 0 as much as possible.

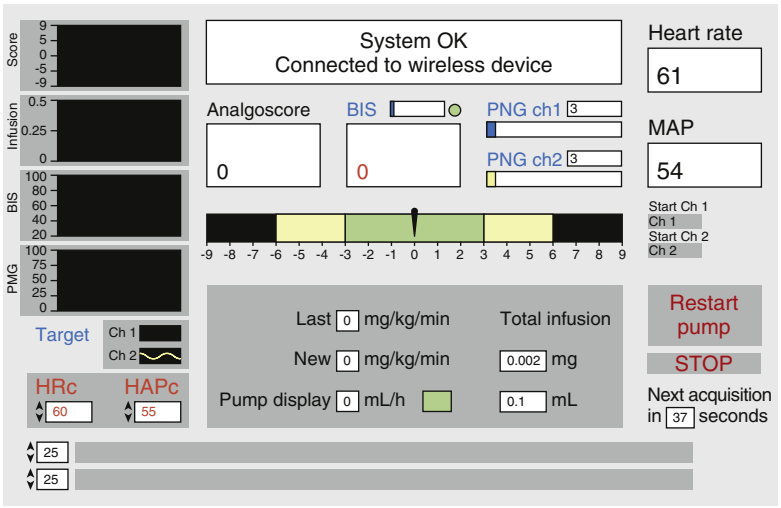


Figure 86-15. User interface. Different areas define different zones of pain control. The range of the Analgoscore is defined from –9 (too profound analgesia) to 9 (insufficient analgesia) in increments of 1. Three control areas were defined, with –3 to +3 representing excellent pain control, –3 to –6 and 3 to 6 good pain control, and –6 to –9 and 6 to 9 inadequate pain control. These areas are color-coded. In addition, a numeric display shows the exact Analgoscore value. Other parameters are displayed: last, new infusion rate of remifentanil in μg/kg/minute and in mL/hr (pump display). The target values for mean arterial pressure (*MAPc*) and heart rate (*HRc*) are displayed, as are the actual heart rate and mean arterial blood pressure every minute. On the *left* side of the interface, trends for Analgoscore, infusion rate, bispectral index (*BIS*), and phonomyography (*PMG*) as an example of parameters reflecting either depth of anesthesia or neuromuscular blockade.

There was a tendency toward more excellent analgesia control (Analgoscore between +3 and –3) in the closed-loop group at 84% of the time versus 70% in the control group. Because the control group used the Analgoscore for pain guidance, specific attention was paid to design a user interface that made this task as easy as possible. The user interface is color-coded, with green indicating the target Analgoscore area, and shows the target and measured values for heart rate and mean arterial pressure, trends, and the last and new infusion rates (Fig. 86-15).

REGULATORY ISSUES: WHY ARE CLOSED-LOOP SYSTEMS NOT YET COMMERCIALLY AVAILABLE?

Based on the presented research, the following assessments of closed-loop systems in comparison to manual anesthesia can be made:

- Better maintenance of a given target
- Less overshooting and undershooting of target
- Quicker reaction to potentially adverse effects, such as BIS values above 60
- Better hemodynamic control
- Tendency toward faster recovery and lower consumption of drugs

In 2008, Manberg and associates[81] described the key product development issues that needed to be addressed with closed-loop systems. It was recently modified according to the recently published literature and to take into account uses of the system for other than for hypnosis.

Selection of all major subcomponents is as follows:

- Drug used (propofol, volatile anesthetic, opioid, neuromuscular blocking drug)
- Infusion pump (peristaltic, piston, syringe, variable rate, target-controlled–based)
- Physiologic control variable (composite score for pain during unconsciousness, electrocardiogram-derivative parameter, neuromuscular blockade monitoring method)
- Monitoring device (stand-alone or integrated)
- Target levels (specific target, range of target, variable, or fixed)
- Controller algorithms (classic on/off PID; model-based; or fuzzy-logic, neural networks; self-adaptive, Bayes principle)
- Single, dual, or triple systems (related to components of general anesthesia, closed-loop controlled)

Assessment and mitigation of all hazards associated with each component, separately and after integration into the system, is a follows:

- Are all risks and performance characteristics known?
  - Were all software and hardware components developed using an effective design control process?
  - Were appropriate software performance models used for testing the potential impact of extreme conditions?
  - Have all international regulatory standards been followed?
  - Have the patient populations and intentions been identified?
    - General anesthesia or sedation?
    - Operating room, intensive care unit, or procedural setting?
    - Elective surgery, ambulatory surgery, intensive care unit analgosedation, procedure suites?

Design and execution of successful clinical trials with meaningful outcome benefit is as follows:

- Selection of primary end point
- A priori identification of clinically relevant degree of improvement of outcome
- Comparison to:
  - Open-loop?
  - Defined treatment algorithm?
  - Standard clinical practice?

It is also evident that decision support systems, which are understudied in anesthesia research, can be a bridge between purely manual anesthesia delivery and robotic anesthesia. The transition from textbook knowledge to decision support systems resembles the step from a typewriter to a computer. Extensive research should be focused in this area in the near future.

TELE-ANESTHESIA

Since late 2000, telemedicine has been a major initiative of the European Union and the World Health Organization (WHO). It is defined as the remote application of medicine and is intended to improve access to high-quality health care in areas where there is a scarcity of such health care facilities. Despite these important initiatives, telemedical applications in anesthesia, called "tele-anesthesia," has been very limited. In theory, tele-anesthesia can be applied to preoperative remote assessment as well as remotely controlled anesthesia delivery.

REMOTE PREOPERATIVE ASSESSMENT

In a pilot study, Wong and associates[82] provided remote clinical consultations in rural areas of central and Northern Ontario, Canada. An anesthesiologist (consultant site) and a nurse (remote site) worked together via an Internet-based portable videocommunication device. With these technologic tools, the anesthesiologist could retrieve the patient's history; do a physical examination, albeit limited to the use of an electronic, digitalized auscultation and visual examination; and assess the airway with a specific airway camera. Unfortunately, this pilot study focused only on the feasibility and degree of satisfaction with the procedure from the patients' and anesthesiologists' perspective, but not on a scientific comparison between remote and local patient preoperative assessment. The validity of the airway assessments obtained using the analogue airway camera is not clear. Several such portable videocommunication units, called remote presence devices, are commercially available and extensively used in surgical rounds across the United States. Remote presence devices can be helpful for consultations in anesthesia, but the validity of these remote consultations in difficult patients needs to be scientifically examined before their widespread use in anesthesia. The early results of use in other fields of medicine is encouraging. The remote presence device is used with a nonexpert local user to perform expert actions, such as remote point-of-care neuromodulation in neurosurgery[83] or assist surgical rounds in surgical intensive care units.[84]

The use of such devices also could be envisioned for preoperative or postoperative rounds in anesthesia patients.

A personal computer–based system with standard audio-video connections via Skype was used to assess patient history and perform an airway assessment autonomously by using the built-in cameras of a modern computer.[85] This system enabled communicating with a patient at home before surgery, establishing the history and airway assessment, without the necessity for the patient to go to a hospital or without necessity of any additional manpower, such as a nurse. Because history taking and airway assessment are the most important features of a preoperative anesthesia assessment, such a system could avoid unnecessary traveling for a majority of patients.

REMOTE LIVE AUDIO-VIDEO MONITORING AND CONSULTATION IN ANESTHESIA

The Internet has made it possible to have Internet-based audio-video communication for live monitoring and consultation. Several case reports have been published in which remote audio-video monitoring, including live patient vital-sign monitoring, were provided over a distance of continents. Remote live audio-video communications has been used to communicate and monitor difficult anesthetic management cases, such as pediatric liver transplantation[86]; more routine cases, such as the live recording of endotracheal intubation[87]; and for the management of difficult intubation.[88]

REMOTE-CONTROLLED ANESTHESIA DELIVERY

A pilot study used a dedicated fiberoptic Internet connection to investigate the feasibility of doing target-controlled propofol infusion via a closed-loop system with EEG feedback. The 11 patients in the study were undergoing general anesthesia in Munich from Erlangen in Germany, a distance of 200 kilometers.[89] The study was successful; however, at one point the Internet connection broke down and one patient was continued with a local propofol infusion. Closed-loop control was performed during 65% of the time and induction was performed manually, with only propofol controlled remotely and by closed-loop. However, the performance of the closed-loop system was unaffected by remote control; the performance was based on the control algorithms and biofeedback system used.

In 2010, the first transcontinental robotic anesthesia was performed between Montreal (remote site) and Pisa (local) site, with all three components of general anesthesia, hypnosis, analgesia, and muscle relaxation controlled remotely via three closed-loop systems, as well as anesthesia from induction to emergence. The endotracheal intubation was monitored live from the remote center and guidance given if necessary; preoperative assessment of the patients was equally performed remotely and locally and

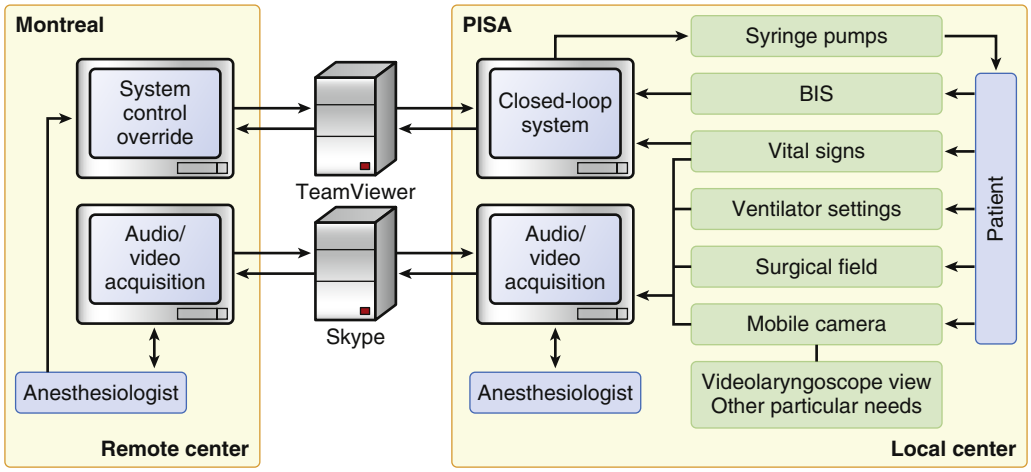


Figure 86-16. Illustration of transcontinental anesthesia setup. *BIS,* Bispectral index.

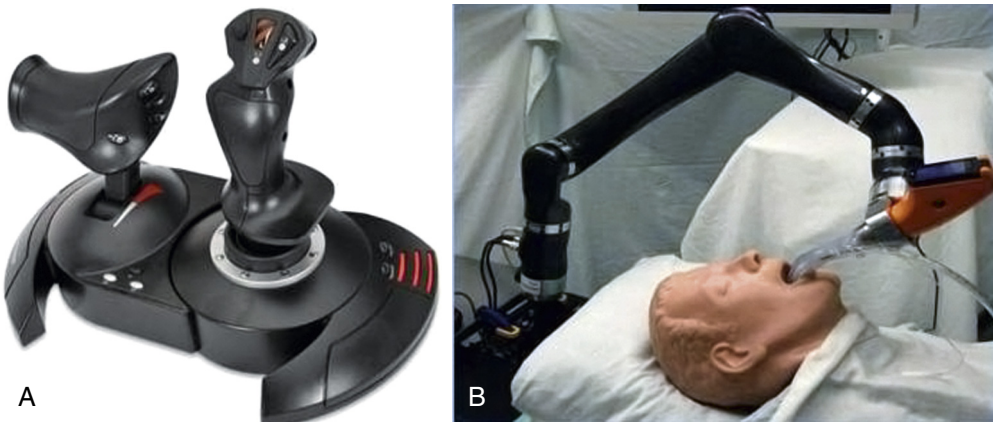


Figure 86-17. The Kepler Intubation system. **A,** Standard game joystick with two handles. **B,** Kepler system consisting of robotic arm, videolaryngoscope in use in airway mannequin.

compared; and four additional cameras allowed remote monitoring: one camera was installed on the head of the local anesthesiologist, a second camera gave a live feed from the ventilator setting and monitoring variables, a third camera gave a live feed from the vital signs monitor, and the fourth camera gave a live feed from the surgical site.[90] Twenty patients were enrolled in this pilot study. Robotic remotely controlled anesthesia was successful in all patients, with no manual or local override necessary. The preoperative assessment of the patient history showed very good agreement between local and remote sites; only the assessment of the Mallampati classification was limited by the quality of the video camera angle (Fig. 86-16).

The latter study shows what is feasible in operating rooms worldwide using current technology, and the high quality of standard, nondedicated Internet connections that allow remote assistance with such anesthetic procedures as:

- Remotely guided videolaryngoscopic intubation
- Remote control of induction, maintenance, and emergence from anesthesia by pharmacologic robots
- Live feeds from key interest areas during surgery: vital sign monitor, ventilator, surgical site, and general overview
- Remote preoperative assessment

MANUAL ROBOTS

ROBOT-ASSISTED INTUBATION OF THE TRACHEA

The work of the anesthesiologist consists of administration of anesthetic drugs, as well as manual gestures from insertion of intravenous cannulas to endotracheal intubation. In the anesthetic sense, a manual robot is the equivalent of a surgical robot, which is an extension of a surgeon's arms and hands but with improved precision and less tremor. Tighe and associates[91] used a DaVinci surgical robot to assist endotracheal intubation in an airway mannequin. One of the DaVinci's robotic arms was equipped with a camera and placed over the head of the mannequin; another arm used a small grasper; and a third arm had a large grasper that allowed hand and arm movements. The fourth arm manipulated the fiberoptic bronchoscope that was inserted nasally and orally. The DaVinci robotic system was not made for this kind of gesture, so the two simulated intubations proved rather difficult; using a $1.5 million robotic system to assist with intubations might be limited to scientific curiosity. The ITAG group from Montreal developed a novel robotic system specifically for endotracheal intubations, called Kepler Intubation system (Fig. 86-17).[92]

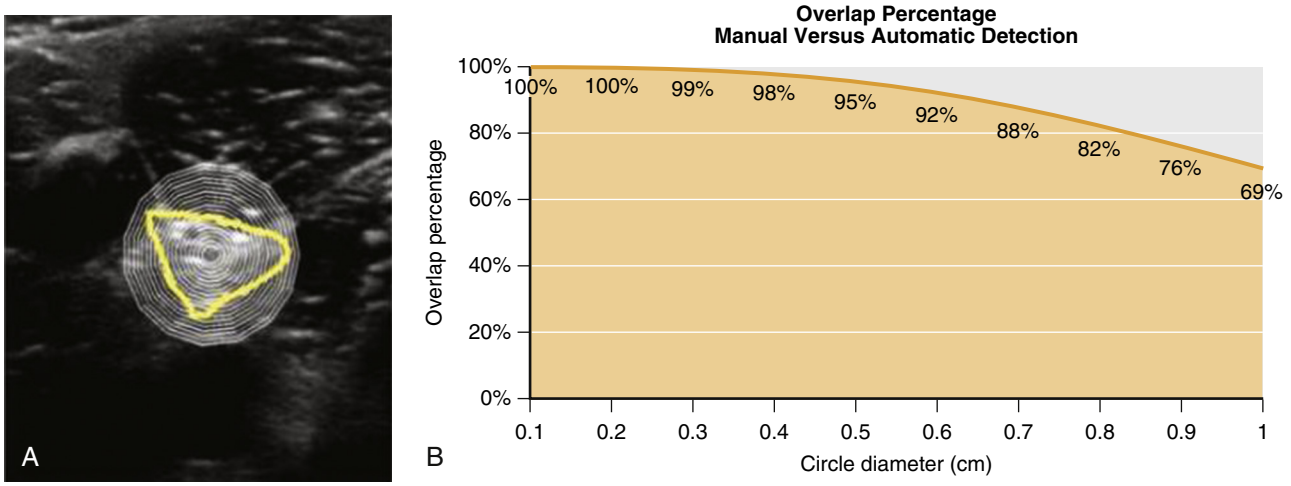


Figure 86-18. A, Automatic nerve detection area (*circle*), manual nerve detection of sciatic nerve in *yellow;* circle is drawn from manually (= automatically) detected nerve center. **B,** Percentage of overlap between automatic and manual detections (manual = *yellow*).

In the first simulation study, endotracheal intubations were successfully performed with direct and indirect views in 30 successful attempts, each showing a considerable learning curve. The system is manipulated using a standard two-part joystick, which is connected with a carbonfiber robotic arm that allows for 6 degrees of freedom and has a standard videolaryngoscope attached. Several live video feeds from inside and outside the throat aided in the alignment of the Kepler for intubation. The advantage of using the Kepler is that its operation is not affected by the user's physical attributes—tall or small, strong or weak users will be able to handle the system equally well. Furthermore, in a third series of 30 intubations, the scope was simply aligned at the top of the mouth and intubation performed automatically using prerecorded movements. The high reproducibility of the intubations was impressive, and these were always performed in exactly 40 seconds, proving the key characteristics of a robot—no fatigue and better reproducibility of the results than humans. The same group followed the simulation study with a trial in 12 patients that had a success rate of 91%; one intubation was not possible because of fogging of the videolaryngoscope and all intubations were performed within 2 to 3 minutes.[93]

It is too early to say where technology in terms of robotic intubations might lead. The question is whether the goal is to simply assist anesthesiologists in this task or replace them and have the whole procedure performed by the robot, autonomously.

MANUAL ROBOTS FOR REGIONAL ANESTHESIA

Regional anesthesia can be a complex procedure; modern regional anesthesia is based on the combined use of an ultrasound device with probe manipulation, synchronous visualization of the nerve on the screen, and a nerve block needle and catheter. In combination with attentiveness to sterile techniques, the medical provider's bimanual coordination might suffer during these manual gestures, as many residents or regional ultrasound novices have experienced. Often, while manipulating the ultrasound probe, the coordination of the needle movements can be difficult and cumbersome. In addition, the mere nerve recognition on the ultrasound screen necessitates thorough training, sometimes a fellowship. Commercially, help is limited but available as either echogenic needles or systems that try to improve the visualization of the needle on the ultrasound screen, such as the advanced needle visualization system (Sonosite, Bothell, WA), which enhances the visibility of the needle by using specific algorithms, and the more cumbersome SonixGPS technology, which shows the relative positions between the needle and the ultrasound image so the needle can be easily positioned in the region of interest. However, these systems simply help to visualize the needle within the ultrasound image. The ITAG group recently published a study in which a specific image recognition software actually identified the nerve autonomously. This software can be used by the anesthesiologist to recognize the nerve and guide a needle to it and can be used as a target area for a completely robotic nerve block.[94] Using proprietary image recognition software on 100 ultrasound images of the sciatic nerve in the popliteal fossa, they were able to detect the nerve center within the automatically defined nerve areal in 99% of the images and showed an overlap between manually defined nerve area and automatically detected nerve area between 100% (1 mm diameter around the nerve center) to 69% (1 cm diameter around the nerve center) (Fig. 86-18).

Developing software that detects nerves can be an important step leading to complete automatic nerve blocks.

Using robotic devices to assist manual gestures involved in regional anesthesia is another means of advancing robotic anesthesia. Tighe and associates[95] performed an ultrasound-guided nerve block and nerve catheter insertion in a regional nerve block mannequin; although the ultrasound probe was placed manually, the block was performed using the DaVinci system similar to their work in robotic intubation. Again, a considerable degree of difficulty was encountered (Fig. 86-19).

The ITAG group designed and developed the Magellan robotic nerve block system and tested it in 13 patients.[96]



Figure 86-19. Manipulation of nerve block needle using the DaVinci system on a regional block mannequin.



Figure 86-20. The Magellan regional block robot in action (*top*) and view from "cockpit" (*bottom*).

Sixteen sciatic nerve blocks were performed, with 100% success rate. The system uses a joystick and a robotic arm with 6 degrees of freedom, which has a standard syringe and needle attached to the end of it. The whole system is managed through a so-called cockpit, which integrates the ultrasound image and live feeds from external video cameras and allows the control of different arm speeds (low to high speed, which can be modified according to the user's preferences) (Fig. 86-20).

At the present stage, the whole system resembles the concept of surgical robots that allow fine-tuned precise handling of the instruments as extension of the user's arms and hands. Future development is envisioned to further automatize the whole process.

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Chapter 87

Anesthesia for Robotically Conducted Surgery

SUMEET GOSWAMI • PRIYA A. KUMAR • BEREND METS

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Key Points

- Robotic surgery has witnessed explosive growth in recent years. In 2011, 360,000 procedures were performed with the Da Vinci system.
- Robotic surgery is accomplished with an autonomous, reprogrammable manipulator designed to move and articulate specialized instruments through programmed motions that achieve a specific task. A robot can be given three-dimensional coordinates from any imaging device (e.g., computed tomography) that allows it to recognize surfaces on which it will perform a specific, programmed task.
- Robotically assisted surgery involves mechanical devices that move by a motorized system under partially programmed control and that can be instantly controlled or modified by a surgeon's intervention.
- Computer-assisted surgery involves systems that are manually controlled by the surgeon and that include a tracking system, sensors, and end-effector instruments. This system provides direct and continuous control of movements.
- *Telesurgery* refers to the ability to perform surgery using computer-assisted instruments from a remote location.
- *Telemanipulation* refers to the ability to produce electronically precise instrument movements from a remote location.
- *Telepresence* refers to the virtual projection of images from remote sites. Virtual projection allows the surgeon to visualize intended robotic movements at distant locations. It also enables telementoring, which is supervision and instruction from a remote location.
- Robotically assisted surgical thoracic procedures have increased the duration of required general anesthesia. Concomitantly, the duration of one-lung ventilation has been taken to new time extremes, which has given us insight into the respiratory physiology of prolonged one-lung ventilation. As surgeons gain expertise with robotically assisted surgery, operative times are expected to shorten dramatically to approach those for traditional open surgery.
- Because of the proximity of the side cart to the patient, the patient must be guarded against inadvertent contact from the motions of the robotic arms. Even more important, after the instruments are engaged to the arms of the robot and are inside the patient, the patient's body position cannot be modified unless the instruments are disengaged entirely and removed from the body cavity.

Robotic surgery is the resulting transformation of the minimally invasive surgical evolution. Robotic devices are being introduced to surgery because they allow unprecedented control and precision of surgical instruments in minimally invasive procedures. The anticipated benefits of robotic or robot-assisted surgery to the patient include less pain and trauma, shorter hospital stays, quicker recovery, and a better cosmetic result. With these technologic innovations, new anesthetic implications for patient care are being discovered. As surgery evolves into the robotic era, anesthesiologists should keep abreast of these changes and their effect on patient care and safety.

Surgical robots are being used in numerous operating rooms around the world. These are not true autonomous robots that perform surgical tasks; rather, they are mechanical "helping hands" that offer assistance in various fields of surgery. These machines still require human intervention to operate or to provide input instructions. Robotic devices are used to help surgeons, not to replace them.

HISTORY

The word *robot* was first used by Capek in his play *Rossum's Universal Robots* in 1921. It is derived from the Czech word *robota,* meaning "forced labor."[1] Robots were first developed by the National Aeronautics and Space Administration (NASA) for use in space exploration.[2] These devices, or telemanipulators, were capable of performing manual tasks aboard a spacecraft or out in space. The slave devices were controlled electronically from a remote master control on Earth or aboard a spacecraft. Telemanipulators were used extensively aboard NASA's space shuttle missions between 1983 and 1997. Research in trajectory and missile guidance systems eventually led to highly precise targeting mechanisms. Precision pointing at targets, such as the Earth and stars, was crucial for Spacelab telescope experiments. Telemanipulators such as the Instrument Pointing System were specifically designed for extreme accuracy (±1.2 arcsec). Scientists at NASA Ames Research Center were responsible for developing virtual reality. The idea took root with contributions from a visual programming language and Dataglove, an interactive device that facilitates tactile sensing and fine-motion control. Their integration made it possible to interact with three-dimensional virtual scenes. It took the integration of robotic engineering and virtual reality, however, to develop a dexterous telemanipulator for the anastomoses of nerves and vessels in hand surgery.

From these applications, it became apparent to the U.S. Department of Defense (DOD) that virtual reality and telepresence might serve a useful function in treating wartime casualties on the battlefield. Through virtual reality, the surgeon could be brought to the patient's side, an idea described by the term *telepresence*. Data from wounded casualties of the Vietnam War estimated that, of all wounded soldiers, one third died of head and massive injuries, and an additional one third died of exsanguinating hemorrhage, but had the potential to survive if they were treated in time.[2] The DOD sought to improve medical presence on the battlefield given that one third of casualties could be saved. Telepresence allowed a surgeon located aboard an aircraft carrier to perform surgery (with the aid of telemanipulation) on wounded soldiers located in a remote location on the battlefield. With this idea in mind, the DOD funded much of the research in telemanipulation for remote mobile surgical units that would allow for telepresence.

Another impetus for the development of robotic surgery came from the inherent limitations of laparoscopic surgery. Mouret performed the first video laparoscopic cholecystectomy in Lyons, France, in 1987.[3] In 1988, Perissat and coworkers[4] presented this innovation to the Society of American Gastrointestinal Endoscopic Surgeons, and an exponential spread of laparoscopic surgical procedures began. Although laparoscopic surgery provided great benefit for patients, it brought tremendous surgical limitations, such as loss of three-dimensional vision, impaired touch sensation, and poor dexterity provided by the long instruments and the fulcrum effect. The fulcrum effect is a nonintuitive motion of the instrument tips in the opposite direction around a fixed point, usually at the skin entrance site. New skills had to be learned. Initial attempts to surmount the burdens of endoscopic surgery provided the impetus for robotic support systems that can enhance surgical skills and control of instruments.

The first surgical robotic devices appeared in the 1980s for use in stereotactic brain surgery. In 1992, ROBODOC (Integrated Surgical Systems, Sacramento, CA) was introduced for grinding bone to make space for prostheses in hip replacement surgery. Positioning robots were introduced by the mid 1990s. The Automated Endoscopic System for Optimal Positioning (AESOP; Computer Motion, Goleta, Calif.) was introduced for voice-controlled optimal camera positioning, and Laparoscopic Assisted Robotic Systems (LARS; John Hopkins University, Baltimore, Md.), an automated robot, was introduced for organ retraction.[5] The first master-slave manipulator for medical use was developed at Stanford Research Institute in 1991. The goal was to have computer algorithms that translate a surgeon's master manual movements to end-effector slave instruments at a remote site. Early designs had only four degrees of freedom, but by 1992, a German prototype was developed with six degrees of freedom (Fig. 87-1).[6] In 1994, Intuitive Surgical (Sunnyvale, Calif.) obtained technologic rights from the Stanford Research Institute, and a prototype DaVinci system was released in 1997.

Engineers realized that the distance between patient and surgeon had an upper limit, beyond which accuracy and dexterity of instrument control would become degraded. Latency is the time it takes to send an electric signal from a hand motion to actual visualization of the hand motion on a remote screen. The lag time to send an electric signal to a geosynchronous satellite at 22,300 miles above the Earth and return is 1.2 seconds. This transmission delay would prohibit practical surgery. Humans can compensate for delays of less than 200 msec. Longer delays compromise surgical accuracy. Tissue moves when force is applied to it, and with a visual delay greater than 200 msec, the movement would not be noticed fast enough to avoid cutting in an unintended place.

The most optimistic attempt to provide telesurgical presence over long distances was undertaken using high-bandwidth fiberoptic ground cable. The latency time of 155 msec allowed Marescaux and colleagues[7,8] to perform a robot-assisted laparoscopic cholecystectomy between New York City and Strausbourg, France, in 2001. In 2003, a telerobotic surgical service was established between a teaching hospital in Canada and a community hospital 250 miles away. This service was designed to provide telerobotic assistance by an expert surgeon to a community-based surgeon. Some of the procedures performed included laparoscopic Nissen fundoplication, laparoscopic right hemicolectomy, laparoscopic sigmoid–anterior resection, and laparoscopic hernia repair.[9]

Recent years have witnessed an explosive growth in robotic surgery. In 2000, 1500 robotic procedures were performed. In 2004, more than 20,000 robotic procedures were performed. In 2011, 360,000 surgical procedures were performed worldwide with the da Vinci Surgical System. Of the estimated 360,000 surgical procedures, approximately 146,000 were hysterectomies and approximately 113,000 were prostatectomies. [10]

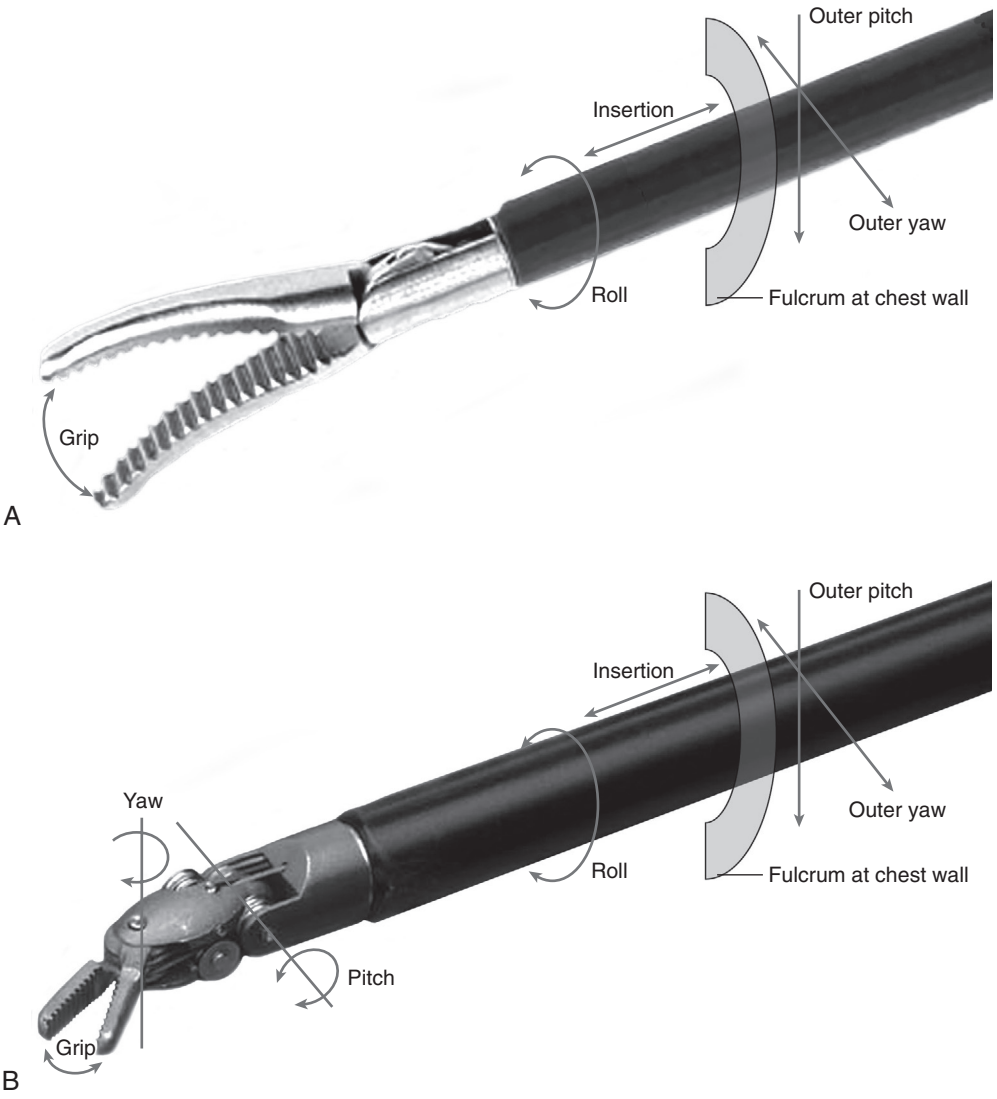


Figure 87-1. Degrees of freedom (DOF) in motion. **A,** Conventional laparoscopic instruments have only four DOF and grip. Insertion (i.e., movement in the *z*-axis), roll, and movement along the *x*- and *y*-axes outside the body relative to a fulcrum point constitute the four DOF. **B,** Depiction of the EndoWrist instrument with two added intracorporeal joints, producing seven DOF. (Copyright © 1999 Intuitive Surgical, Sunnyvale, Calif.)

ROBOTIC SYSTEMS

The word *robot* is a ubiquitous term that describes an autonomous device capable of various tasks (see the previous section on history). Industrial robots used in assembly lines perform highly precise, repetitive tasks. The robots are preprogrammed offline, and tasks are invoked on command. Robots used in orthopedic surgery and neurosurgery are examples.[11] Precise tasks, such as drilling and probe insertion, are based on registration. Registration is a mathematical process that allows location and anatomic orientation in three dimensions based on data derived from preoperative computed tomography (CT) or magnetic resonance imaging (MRI).

A second type of robot is defined as an assist device, such as AESOP. These robots are used to control instrument location and guidance. Assist-device robots are not autonomous; they need input cues from an operator.

A third type of robot is a telemanipulator. These robots are under constant control of an operator. These devices mimic the operator's hand motions in an exact or scaled motion. Several telemanipulator robotic devices are available throughout the world. The da Vinci Robotic Surgical System (Fig. 87-2) and the ZEUS Surgical System (Fig. 87-3) were developed in parallel; these two systems are similar with only minor differences. The ZEUS system was subsequently shelved after its competitor, Intuitive Surgical, acquired the company. The da Vinci Robotic Surgical System is described in this chapter as a representation of most modern surgical robots. It has been approved by the U.S. Food and Drug Administration (FDA) for use in urologic procedures, general laparoscopic surgical procedures, gynecologic procedures, transoral otolaryngology procedures, general thoracoscopic procedures, and thoracoscopically assisted cardiotomy procedures.[12]

The components of the da Vinci system include: a Surgeon Console, a patient-side cart, EndoWrist instruments, and an optical vision tower (see Fig. 87-2). The surgeon sits comfortably at the console (Fig. 87-4) and is able to view a high definition, three-dimensional image inside the patient body. The viewing space provided is similar to a double-eyepiece microscope (Fig. 87-5). At the console, the surgeon is actually looking at two separate monitors; each monitor displays one channel of the stereo endoscope to an eye, creating a virtual three-dimensional stereoscopic image of the surgical field (Fig. 87-6, *A*). The



Figure 87-2. The da Vinci Robotic Surgical Si System: two surgical consoles, patient-side cart with four mounted surgical arms, and an optical tower. (Courtesy Intuitive Surgical, Sunnyvale, Calif.)

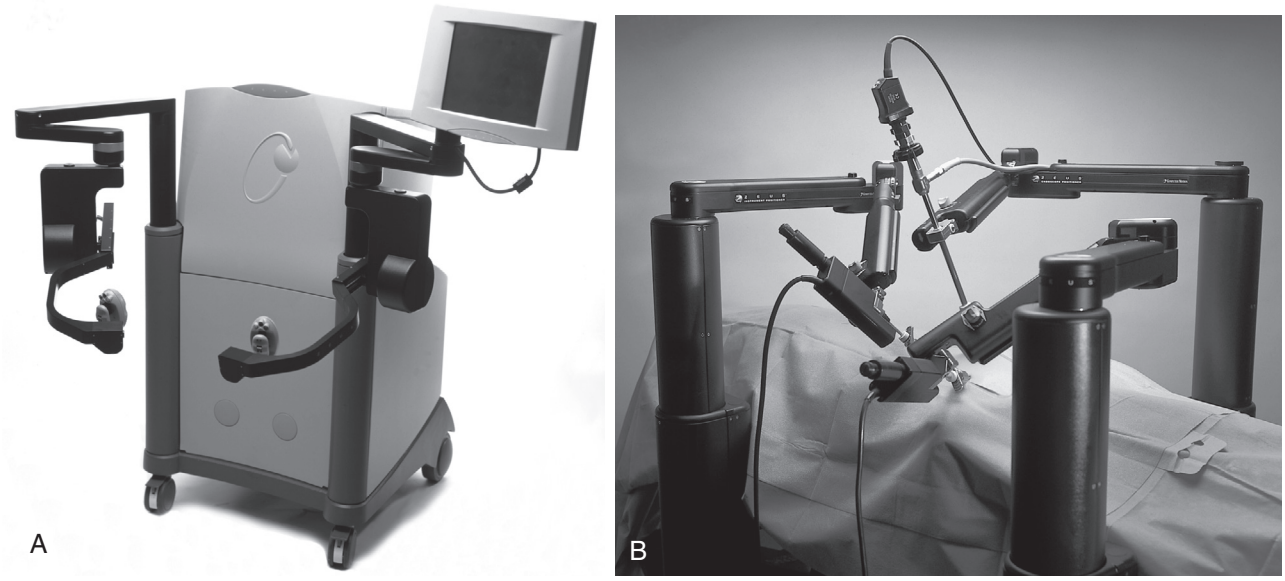


Figure 87-3. A, The console of the ZEUS robotic telemanipulation system consists of a video monitor and two instrument handles that translate the surgeon's hand motions into an electric signal that moves the robotic instruments. **B,** Two table-mounted AESOP arms hold instruments, and a third arm controls the camera. (Courtesy Computer Motion, Sunnyvale, Calif.)

surgeon's fingers grasp the master controls underneath the display (see Fig. 87-6, *B*). The master controls are made of levers that attach to index fingers and thumbs of each hand. Wrist movements replicate the movements of the instruments at the end of the robotic arms. The console has a foot pedal that disengages the robotic motions (i.e., clutching), another that allows adjustment of the endoscopic camera, and a third pedal for controlling the energy of electric cauterization. The surgeon sits at the console and controls the telescope arm and three robotic manipulator arms. The da Vinci Si system, introduced in 2009, has dual console capability to support training and collaboration during robotic surgery.

The patient-side cart (Fig. 87-7) has four arms that can be manipulated by the surgeon through real-time computer-assisted control. The first two arms represent the surgeon's right and left arms, to hold the instruments, and the third arm positions the endoscope. The endoscope consists of dual, independent optical channels capable of transmitting digital images to the console's visual monitor. The optional fourth arm enables the surgeon to hold another instrument or perform additional tasks, such as holding counter traction and following running sutures. The system allows the surgeon to be physically remote from the patient (Fig. 87-8). The cart is bulky and heavy, and it has to be wheeled to the vicinity of the patient's surgical area and locked into place. Because of the proximity of the side cart to the patient, the patient must be guarded against inadvertent contact from the motions of the robotic



Figure 87-4. The da Vinci Robotic Surgical System: the surgeon console. (Courtesy Intuitive Surgical, Sunnyvale, Calif.)



Figure 87-5. The da Vinci Robotic Surgical System: stereo viewer that creates a virtual three-dimensional stereoscopic image. (Courtesy Intuitive Surgical, Sunnyvale, Calif.)

arms. Even more important, after the instruments are engaged to the arms of the robot and inside the patient, the patient's body position cannot be modified unless the instruments are disengaged entirely and removed from the body cavity. Any patient movement can be disastrous. The clutching buttons allow the robotic arms to be grossly positioned without moving the instruments within the trocars or access ports. A clutching function allows surgical assistants to exchange various instruments.

The EndoWrist instruments (Fig. 87-9) are designed to have seven degrees of motion—a range of motion even greater than the human wrist. Seven degrees of motion include three arm movements (in-out, up-down, side-to-side), and three wrist movements—yaw (side-to-side, left and right), pitch (up and down), and roll or rotational. The seventh degree of freedom is grasping or cutting. The system design incorporates a frequency filter that eliminates hand tremor greater than 6 Hz. Motion scaling also can be invoked up to a ratio of 5:1 (i.e., the surgeon moves 5 cm, and the robot moves 1 cm). Scaling allows for work on a miniature scale. The instruments in the body cavity must remain sterile, but interface with nonsterile robotic arms. Detachable disposable instruments facilitate this interface. Each type of instrument requires different forces and motion scaling intrinsic to the task, and each type requires specific computer software processing. Additional operating room staff members are required for detaching and exchanging task-specific instruments throughout the case. Monitors are positioned on top of the tower so that all individuals in the operating room have a view of the surgical field.

The optical tower contains the computer equipment needed to integrate the left and right optical channels to provide stereoscopic vision and to run the software needed to control the kinematics of the robotic arms. The computer interfaces the translated motion of the surgeon's hands to a digital code that moves mechanical levers, motors, and cables that allow the robot to articulate the exact motions of the surgeon's hand.

The ZEUS Surgical System (see Fig. 87-3) is another example of a master-slave telemanipulator. It uses the assistance of the AESOP Robotic System for visualization. The system is basically one mechanical arm used by the physician to position the endoscope, which is a surgical camera inserted into the patient. Foot pedals or voice-activated software allow the physician to position the camera, leaving his or her hands free to continue operating on the patient. The manipulators of the ZEUS system are freely mounted on the operating table, similar to the AESOP. It provides tremor filtering and motion scaling from 2:1 to 10:1.

An obstacle that still needs research is tactile sensing. The feedback that the robot offers for the surgeon's applied force is inferior. The robot offers some sensation, but the applied force does not correlate well with the force applied to the tissues. This correlation varies with the type of instrument and depends on the torque applied; the operator must rely on visual cues from tissue distortion to gauge how much pressure is being generated.

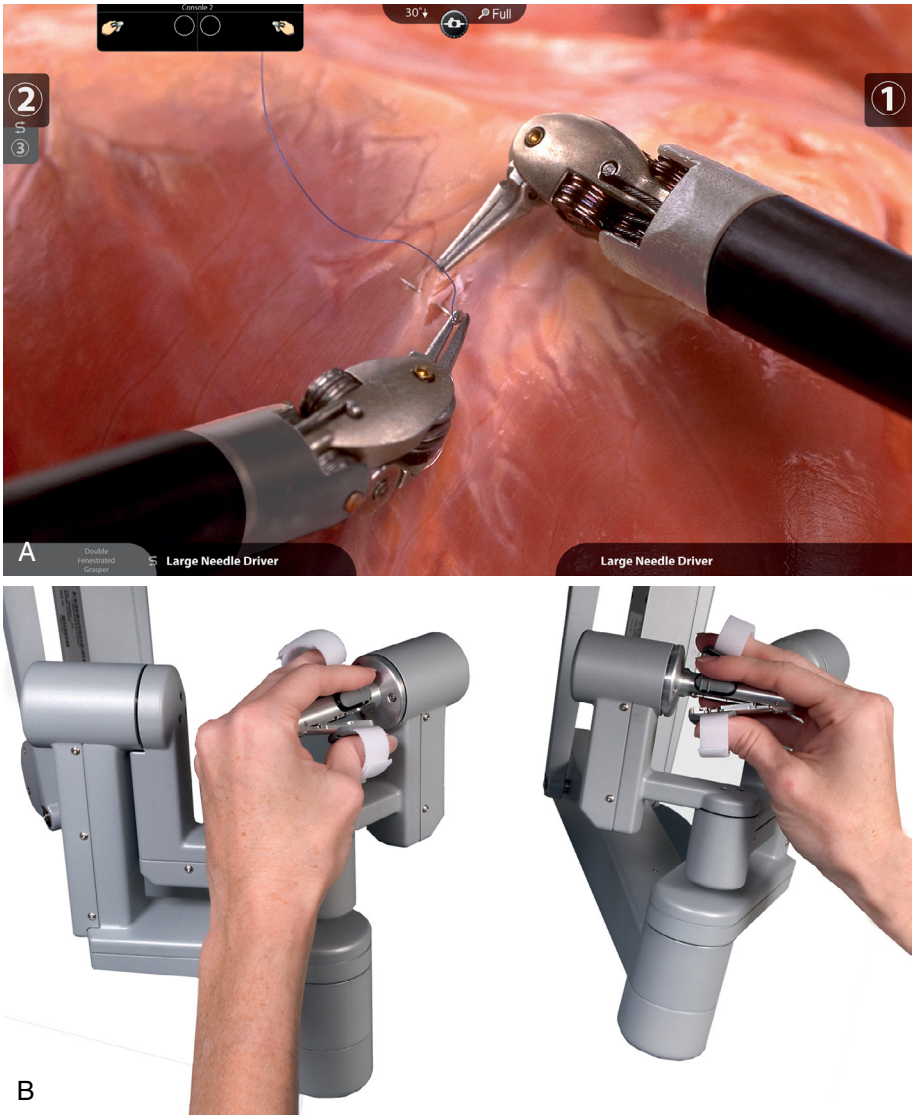


Figure 87-6. The da Vinci Robotic Surgical System. **A,** Virtual three-dimensional stereoscopic image of the surgical field. **B,** Master controls that translate the surgeon's hand, wrist, and finger movement into real-time movements of surgical instruments inside the patient. (Courtesy Intuitive Surgical, Sunnyvale, Calif.)



Figure 87-7. The da Vinci Robotic Surgical System: patient-side cart. (Courtesy Intuitive Surgical, Sunnyvale, Calif.)

CARDIAC SURGERY (ALSO SEE CHAPTER 67)

Application of conventional endoscopic instruments has paved the way for several cardiac procedures to be performed with robotic assistance. Internal mammary artery harvesting was successfully performed thoracoscopically in 1997 by Nataf.[13] In 1998, Loulmet and colleagues[14] reported the first totally endoscopic coronary artery bypass surgery. Cardiothoracic applications of robotically assisted surgery have expanded and include atrial septal defect closures,[15-17] mitral valve repairs,[18] patent ductus arteriosus ligations,[19] totally endoscopic coronary artery bypass grafting,[20,21] minimally invasive atrial fibrillation surgery,[22,23] and left ventricular pacemaker lead placement.[24] Although technical advances in minimally invasive surgery have introduced techniques that are performed through very small ports and may eventually make surgical sternotomy obsolete, surgeons still must be trained and prepared to convert to an open sternotomy if the need arises.

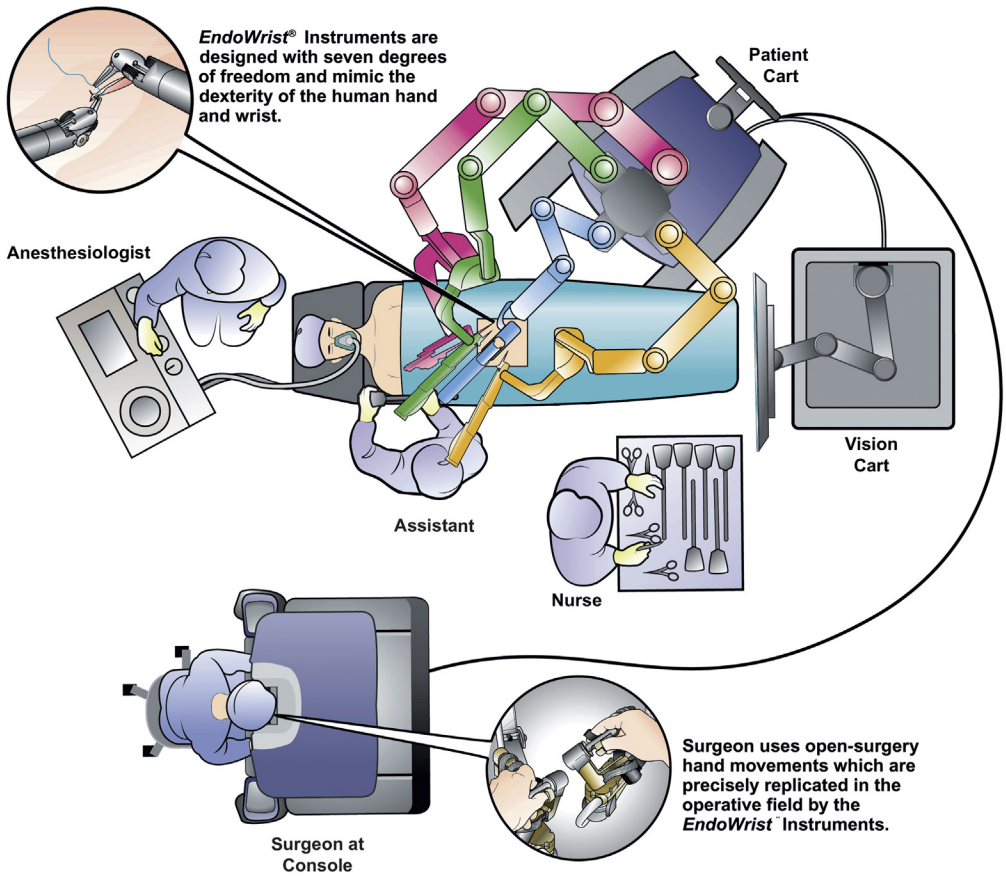


Figure 87-8. Operating room schematic of the use of a robotic surgical system in general surgery. (Courtesy Intuitive Surgical, Sunnyvale, Calif.)



Figure 87-9. The EndoWrist instrument of the da Vinci Robotic Surgical System mimics the natural kinematics of the surgeon's hand and wrist. This design allows degrees of freedom. (Courtesy Intuitive Surgical, Sunnyvale, Calif.)

BOX 87-1 *One-Lung Ventilation Strategy*

1. Use $FiO_2 = 1.0$.
2. Begin one-lung ventilation with pressure control ventilation, maintaining a plateau pressure of <30 cm H_2O.
3. Adjust respiratory rate so that $Paco_2$ approaches 40 mm Hg.
4. Perform analysis of arterial blood gases periodically.
5. Apply continuous positive airway pressure to nonventilated lung.
6. Apply positive end-expiratory pressure to ventilated lung.

Anesthesiologists need to acquire familiarity with and expertise in cardiac and thoracic anesthesia, as both organ systems need to be managed safely. The ability to perform and maintain one-lung ventilation is mandatory, as is the management of associated physiologic changes (Box 87-1). Preoperative assessment of lung function is indicated if a patient has significant lung disease. Poor pulmonary function test results or pulmonary hypertension may be contraindications to robotically assisted cardiac surgery because one-lung ventilation may be poorly tolerated. Robotic surgery may require unprecedented, prolonged, one-lung ventilation, which may challenge the extent of our understanding of respiratory physiology. Continuous monitoring of cardiac function with transesophageal echocardiography (TEE) is the standard of care and is used for several procedures required for safer robotically assisted surgery.

ADMINISTRATION OF CARDIOPULMONARY BYPASS

Robotic cardiac surgery may require placement of several additional cannulae before administration of cardiopulmonary bypass (CPB) (also see Chapter 67). Typically, the femoral vessels are accessed as cannulation sites for CPB. Because of the potential for iatrogenic dissection or related injury during cannulation of these vessels, some centers advocate prior radiologic imaging to rule out severe atherosclerotic disease. Venous cannulation is usually accomplished with the percutaneous insertion of a 21-to 28-French (Fr) multiorifice cannula via the femoral vein under real-time TEE guidance. This cannula can be either one or two stage. The tip of the single-stage cannula is placed at the right atrial (RA)–inferior vena cava (IVC) junction. The tip of the two-stage cannula is placed in the superior vena cava (SVC). The choice of venous cannula can vary according to surgeon preference. Some surgeons place a two-stage venous cannula, whereas others prefer a single-stage IVC cannula and an additional percutaneous cannula in the SVC via the right internal jugular vein to empty the heart completely. Cannulation of SVC is accomplished with a percutaneous 15-to 18-Fr Biomedicus cannula (Medtronics, Minneapolis, Minn.) using the Seldinger technique. The tip of the SVC cannula is placed just before the RA-SVC junction. Some surgeons prefer an armored SVC neck cannula because of its resistance to occlusion or kinking by the long transthoracic aortic cross-clamp. At the time of insertion, the cannula is typically flushed with 5000 units of heparin to ensure its patency, or a dilute heparin solution can be infused into the cannula through a microdrip set. A midesophageal, bicaval view on the TEE may be helpful for guidance in positioning of both SVC and IVC cannulae (Fig. 87-10). An alternative to the SVC cannula may be to float a 9-Fr balloon-tipped catheter into the main pulmonary artery via a right internal jugular introducer. This pulmonary artery venting cannula has a much smaller diameter compared with the SVC cannula and allows passive venting of the pulmonary artery at approximately 50 mL/min.[25] Venous drainage is facilitated with either vacuum or kinetic assistance.[25,26] Typically a 17-to 21-Fr catheter is placed in the femoral artery for arterial cannulation. To prevent retrograde aortic dissection, the guide wire should be visualized on TEE imaging in the descending aorta before placement of the arterial cannula.

For myocardial protection, cardioplegia can be administered by antegrade and retrograde delivery routes. After ensuring a competent aortic valve on TEE, a Heartport Straight-shot (Heartport, Redwood City, Calif.) antegrade cardioplegia catheter can be placed into the proximal ascending aorta directly through a right chest wall stab incision. A long-shafted aortic cross-clamp can then be placed distal to the cardioplegia catheter via another stab incision. Alternatively, a 100-cm, 10.5-Fr catheter (EndoClamp; Edwards Lifesciences, Irvine, Calif.) with a distal balloon can be advanced into the ascending aorta via a femoral introducer sheath. The balloon, when inflated, functions as an endovascular cross-clamp, whereas the lumen opening at the tip is used to deliver antegrade cardioplegia. It is of utmost importance to maintain accurate positioning of the balloon of this catheter in the ascending aorta to avoid inadvertent migration and occlusion of coronary circulation or innominate artery obstruction. This can be ensured by simultaneously monitoring arterial pressures in bilateral radial artery catheters, and by visualizing the position of the endoballoon in real time on TEE. [25] In patients with significant aortic insufficiency or severe coronary artery disease, a retrograde cardioplegia catheter may be placed. A percutaneously placed retrograde cardioplegia catheter can be positioned in the coronary sinus via the right internal jugular vein under TEE guidance. It is positioned by rotating (torquing) the catheter under TEE guidance. The proximal coronary sinus can be imaged in midesophageal four-chamber view by advancing and retroflexing the TEE probe. The catheter and the coronary sinus can also be visualized in midesophageal two-chamber view. On correct placement of the catheter, inflation of the coronary sinus balloon changes the RA trace to right ventricular trace. Because these catheters are not heparin coated, 5000 units of heparin should be given intravenously to the patient before placement of this catheter.

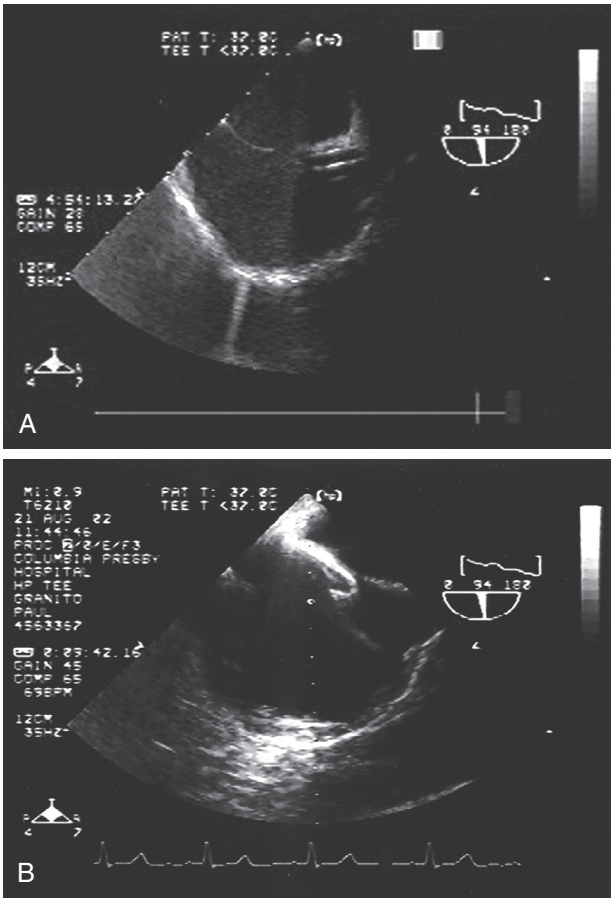


Figure 87-10. A, Ultrasound image of the superior vena cava cannula. **B,** Ultrasound image, bicaval view, depicting the inferior vena cava containing a J guide wire. Both views are helpful in correctly placing cardiopulmonary bypass venous cannulas.

MITRAL VALVE SURGERY

In 1997, two independent groups reported the first robotically assisted mitral valve repair.[27,28] In November 2002, the FDA approved the use of robot-assisted surgery for performing mitral valve repair. Minimally invasive mitral valve repair, initially done through minithoracotomy incisions, could now be performed with a closed chest; however, mitral valve replacements required a small thoracotomy to introduce the new prosthetic valve.

The monitoring requirements and the plan for induction of anesthesia for robotic mitral valve surgery are similar to the open procedure. In addition, bilateral radial artery catheters can be placed to monitor inadvertent innominate artery obstruction by the endoclamp catheter. The plan for induction of anesthesia is similar to that of the open procedure.[29] After the induction of anesthesia, one-lung ventilation is achieved with the use of a double-lumen endotracheal tube, or a single-lumen endotracheal tube with a bronchial blocker. Proper tube position is confirmed with fiberoptic bronchoscopy. A TEE probe is inserted to assess heart and valve function and to guide the placement of a pulmonary artery catheter and other cannulae for CPB. Transcutaneous defibrillation and pacing pads are also applied. Specialized cannulae are placed for the conduction of CPB and cardioplegia as described in the previous section.

The patients are positioned in a modified left lateral position with the right shoulder tilted approximately 30 degrees to the left, with the arm being positioned along the right side. The pelvis is kept relatively flat to facilitate femoral cannulation. Attention should be directed to ensuring that undue tension is not placed on the brachial plexus. The right femoral vessels are exposed, and left-sided single-lung ventilation is established. The surgeon then determines the proper location for port access, which can vary according to a patient's body habitus. After docking the surgical cart, it is imperative to prevent the patient from moving, to prevent any organ injury from the rigid trocars and the instruments. Robot-assisted mitral valve repair is usually accomplished with a 2- to 3-cm right inframammary incision in either the fourth or fifth intercostal space, which provides an excellent view of the leaflets and the annulus.[30] Trocars are inserted around this incision for the placement of robotic arms. After administering heparin according to an activated clotting time-guided protocol, the femoral vein and artery are cannulated as described in the previous section. After initiating cardiopulmonary bypass, the ascending aorta is cross-clamped with either the endoclamp or a transthoracic aortic cross-clamp that is passed percutaneously through the right axilla. The robotic arms are engaged through their respective trocars lateral to the minithoracotomy incision, while the camera arm passes directly through the thoracotomy incision.

Before terminating cardiopulmonary bypass, TEE is used to evaluate the function of the mitral valve, to assess residual valvular regurgitation, and to confirm the disappearance of intracardiac air (see Chapter 46). The anterior leaflet of the mitral valve is inspected further for systolic anterior motion. At the end of the procedure, the double-lumen endotracheal tube is changed to a single-lumen endotracheal tube over a tube changer. Patient selection is important for optimal results (see Chapter 66). Box 87-2 lists the risk factors that make patients unsuitable candidates for robotic mitral valve surgery.[31]

BOX 87-2 *Exclusion Criteria for Robotically Assisted Mitral Valve Repairs*

- Severely calcified mitral annulus
- Severe pulmonary hypertension
- Ischemic heart disease
- Surgery requiring multiple valve repairs
- Previous surgery to right hemithorax
- Severe aortic and peripheral atherosclerosis

No data are present on the difference in outcomes in patients with higher body mass index (BMI) undergoing this procedure. The increases in equipment and intraoperative costs are offset by postoperative quality of life and early return to work. [32]

ATRIAL SEPTAL DEFECT REPAIR

Operations for atrial septal defects are similar to those for mitral valve repairs except that a minithoracotomy is not required.[15] A closed-chest procedure is possible. Similar to all robotic procedures that demand entrance into the thoracic cavity, single-lung ventilation must be instituted during surgery. Atrial septal defect repairs also require opening the heart and preventing any blood from entering the heart; this is facilitated by jugular and femoral vein cannulation and snaring the inferior vena cava and SVC (see also Chapter 67). Cardiopulmonary bypass with cardioplegia administration into the aortic root is used to arrest the heart. Methods of cardiopulmonary bypass using endovascular clamping are described in the previous section.

No data are present on the difference in outcomes in patients with higher BMI who are undergoing this procedure. Cost effectiveness data on patients undergoing atrial septal defect repair are also not available.

INTERNAL MAMMARY ARTERY HARVEST

After induction of anesthesia, single-lung ventilation with a double-lumen tube, a Univent tube, or a bronchial blocker is instituted. The position of the tube is confirmed by bronchoscopy. The patient is positioned in a 30-degree right lateral position. External defibrillation and pacing pads are applied to the left posterior chest and anterolateral right chest. Raising the left arm provides more exposure and stretches the skin overlying the left anterolateral chest. The opposite can be done to the right chest when harvesting only the right internal mammary artery.

CO_2 insufflation, between 5 and 10 mm Hg, is needed to provide exposure by pushing the mediastinal fat pad medially and enlarging the space between the sternum and heart to provide a better view. For harvesting both internal mammary arteries, insufflation of the left hemithorax is sufficient to expose the right internal mammary artery because of the leftward position of the heart[33] and to improve the angle of sight. Insufflation is begun in increments of 2 to 4 mm Hg. The insufflation flow rate is

adjusted automatically to achieve a preset intrathoracic pressure limit. Caution should be exercised when insufflating the thorax in patients who have poor left ventricular function or are hypovolemic (central venous pressure < 5 mm Hg).

Patients should have their intravascular volume status increased before proceeding to full insufflation. CO_2 insufflation and one-lung ventilation increase central venous pressure and pulmonary artery pressure by a small amount.[34] Bilateral pneumothoraces are deliberately produced when doing bilateral internal mammary artery harvest. Most patients studied tolerate small bilateral pneumothoraces for short duration.[35]

CORONARY ARTERY BYPASS GRAFTING (also see Chapter 67)

Robotically-assisted total endoscopic coronary artery bypass graft surgery (also see Chapter 67) has been found to be safe and effective with angiographic patency data comparable to the open procedure.[21] The major exclusion criteria for robotic coronary artery bypass grafting are listed in Box 87-3.[21]

Patients are prepared and monitored for anesthesia in a manner similar to that for mitral valve surgery (discussed under Mitral Valve Surgery). TEE is used routinely as the standard of care for determining cardiac function and for confirming catheter placement. Pulmonary artery catheters are used judiciously in the appropriate patient population. The patient is positioned the same as for internal mammary artery takedown, and trocar positions are placed as depicted in Figure 87-11.

When cardiopulmonary bypass is anticipated, the left femoral artery is cannulated with a 17- or 21-Fr remote access perfusion catheter (Fig. 87-12) with an aortic occlusion balloon. Box 87-4 lists exclusion criteria for endovascular cardiopulmonary bypass. The remote access perfusion catheter allows anterograde flow of 4 or 5 L/min. The cannula has a separate lumen for delivering cardioplegia to the aortic root beyond the occlusion of the balloon. The aortic cannula is positioned in the ascending aorta, 2 cm above the aortic valve, with TEE guidance (Fig. 87-13). The endovascular balloon is inflated with a volume equal to the diameter (in milliliters) of the sinotubular junction of the aorta. A balloon pressure greater than 300 mm Hg usually provides complete occlusion of the aorta.[36] Residual flow around the balloon can be seen and monitored with color flow on TEE. The use of bilateral radial arterial lines is useful in detecting the migration of the occlusion balloon toward the innominate artery. Proximal migration of the balloon can be seen most easily with TEE, preventing balloon herniation through the aortic valve.

After full cannulation and being poised for cardiopulmonary bypass, the right lung is allowed to collapse, and left lung ventilation is begun. The ventilator is adjusted to provide an end-tidal CO_2 partial pressure of 35 to 40 mm Hg. Ports can be placed safely after the right-sided pneumothorax has formed. CO_2 is insufflated into the right hemithorax and continued at a pressure of 5 to 10 mm Hg; this allows the affected lung to collapse further and provides a larger visual field. It also may prevent mediastinal shifts during one-lung ventilation when large tidal volumes are used, such as in a patient with emphysematous lungs. Insufflation to produce a deliberate pneumothorax is ineffective when the sternum is elevated above the anterior surface of the heart. For this reason, some surgeons provide sternal lift retractors to increase the retrosternal space and provide better exposure.[37] Articulating stabilizers passed through a subxiphoid port can stabilize the anterior surface of the heart to facilitate grafting.[38] Ventricular function is evaluated with TEE before termination of cardiopulmonary bypass. At the end of the procedure, the double-lumen endotracheal tube is changed to a single-lumen endotracheal tube over a tube exchanger. Robot-assisted, beating-heart coronary artery bypass grafting can be safely accomplished with appropriate patient selection. Obese patients (see Chapter 71) might benefit from total endoscopic coronary artery bypass graft surgery, as the robotic procedure does not increase the rate of intraoperative or postoperative complications when compared with the traditional procedure.[39] Cost effectiveness data comparing robotically assisted total endoscopic coronary artery bypass graft surgery with the traditional approach are not available.

BOX 87-3 ***Exclusion Criteria for Robotically Assisted Endoscopic Coronary Artery Bypass Grafting***

- Contraindication to one-lung ventilation
- Ejection fraction < 30% or decompensated heart failure (NYHA class III or IV)
- Moderate to severe aortic and mitral valve disease
- MI in preceding 30 days or MI requiring emergent CABG or postinfarction angina
- Calcified or intramyocardial LAD artery or diffuse LAD artery disease
- Large heart within left chest
- Morbid obesity (BMI > 35 kg/m^2)
- Severe peripheral vascular disease
- Severe noncardiac health issues
- Previous thoracic surgery, pleural adhesions, or radiation therapy of mediastinum or thorax

BMI, Body mass index; *CABG,* coronary artery bypass graft; *LAD,* left anterior descending; *MI,* myocardial infarction; *NYHA,* New York Heart Association.

ATRIAL FIBRILLATION SURGERY

Atrial fibrillation is a common rhythm disturbance encountered in clinical practice (see also Chapter 68). The Cox maze procedure is often the first choice to treat medically resistant atrial fibrillation. Excellent long-term results occur with this procedure.[40] In this procedure, right and left atriotomies are combined with cryoablation to interrupt reentrant rhythms and to restore sinus rhythm. Traditionally, this procedure has involved median sternotomy and cardiopulmonary bypass. With the evolution of technology such as cryotherapy, microwave, and radiofrequency, new handheld devices have become available for use in minimally invasive surgery.

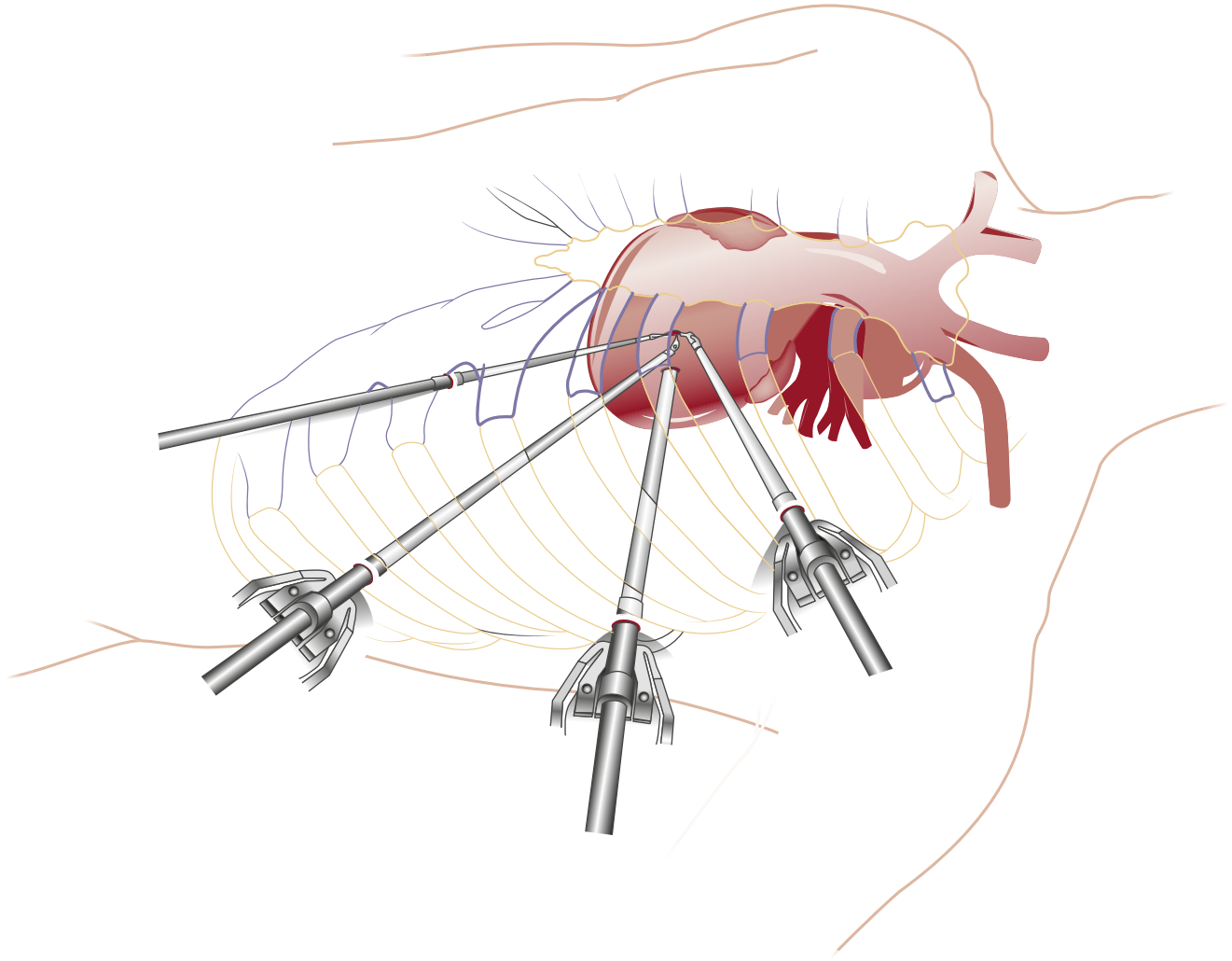


Figure 87-11. Incision ports for coronary artery bypass grafting. Trocars are placed in the third, sixth, and eighth intercostal spaces. Similar port positions are used for bilateral internal mammary artery dissection.

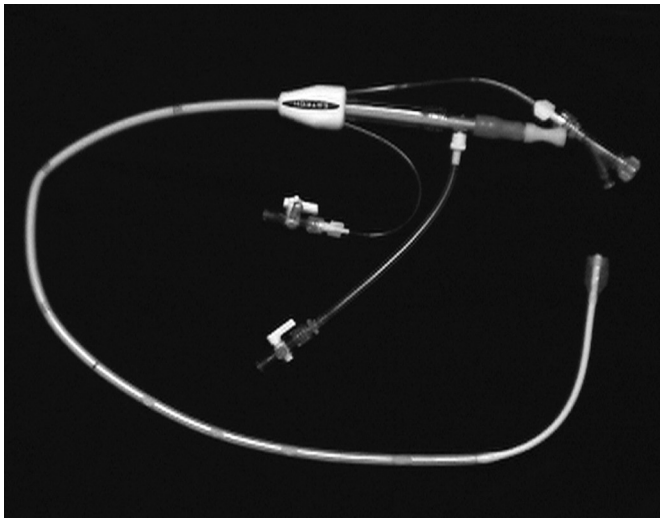


Figure 87-12. Remote Access Perfusion (Estech Systems, Plano, Tex.) catheter. The endovascular catheter has a cylindrical balloon for endovascular aortic clamping. The catheter provides anterograde perfusion of the aortic arch at a rate of 5 L/min and cardioplegia administration to the aortic root.

BOX 87-4 ***Contraindications to Use of Endovascular Cardiopulmonary Bypass System***

- Major vascular disease of iliac, femoral, and abdominal aorta found by Doppler ultrasound imaging
- Severe atherosclerosis
- Aortic diameter >4 cm
- Moderate to severe aortic valve incompetence

Many approaches have been used for minimally invasive atrial fibrillation ablation surgery. The approach using the da Vinci system via right minithoracotomy with peripheral cannulation and cardiopulmonary bypass is the most commonly used approach.[22] A total endoscopic approach on a beating heart also has been described.[41] Recently, a remote robotic navigation system (Sensei X; Hansen Medical, Mountain View, Calif.) has been developed for intracardiac catheter manipulation. In a small study, this system is equally effective while significantly reducing the overall fluoroscopy time when compared with manual catheter ablation.[42]

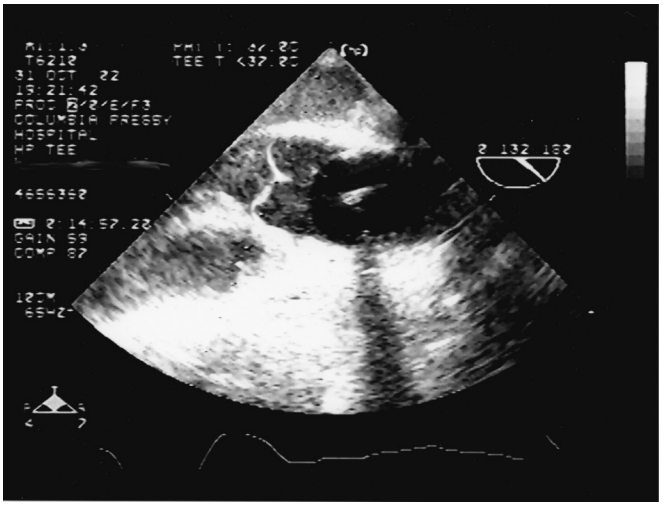


Figure 87-13. Ultrasound image of Remote Access Perfusion (Estech Systems, Plano, Tex.) catheter balloon in situ. Transesophageal echocardiography allows the anesthesiologist to keep track of the migration of the catheter balloon. The balloon should be positioned in the ascending aorta 2 to 4 cm distal to the aortic valve. Right radial pressure catheter signal damping can detect balloon malposition when occlusion of the innominate artery occurs.

In patients undergoing total endoscopic approach, the procedure is performed without cardiopulmonary bypass on a beating heart with the patient in the supine position. In addition to the standard monitors, invasive arterial and central venous pressures are monitored. A pulmonary artery catheter can be used in appropriate patients. After induction of anesthesia, the trachea is intubated with a double-lumen endotracheal tube, and its position is confirmed by a fiberoptic bronchoscope. A TEE probe is inserted to facilitate intraoperative cardiac monitoring and to rule out a clot in the left atrial appendage. External defibrillator pads are applied to the chest. After one-lung (left) ventilation is instituted, the right lung is collapsed, and the right hemithorax is insufflated with CO_2. Three, 1-cm port access incisions are made at the level of the third, fourth, and fifth intercostal spaces on the anterior axillary line for the robotic arms and the endoscope. The heart is then exposed after dissecting the pericardium and, using a microwave probe (Flex10; Boston Scientific, Natick, Mass.), a continuous circular lesion is produced encircling the pulmonary veins. Arrhythmias in the early postoperative period are treated with amiodarone and β-adrenergic blocker therapy.[41,43]

Outcome data in patients with a higher BMI are not available for this procedure. Cost effectiveness data on patients undergoing robotic atrial fibrillation surgery are also not available.

LEFT VENTRICULAR LEAD PLACEMENT

Some surgical groups have developed a total endoscopic robotic approach that involves the placement of right atrial and ventricular leads via standard transvenous approach, and the placement of left ventricular lead via small incisions in the left hemithorax.[44-46] The robotic approach was developed because of the high rate of immediate failure and late failure associated with the standard approach to left ventricular lead placement.[24] In patients undergoing the total endoscopic robotic approach, general anesthesia is induced after application of standard monitors and insertion of an arterial line. After induction of general anesthesia, the trachea is intubated with double-lumen endotracheal tube. The position of the endotracheal tube is verified with a fiberoptic bronchoscope. Subsequently, a TEE probe and a pulmonary artery catheter are inserted. The patient is placed in a posterolateral thoracotomy position. One-lung (right) ventilation is instituted. The left lung is excluded, and the left hemithorax is insufflated with CO_2 at a pressure of 8 to 10 mm Hg.

Robotic arms are inserted by incisions in the fifth and ninth intercostal spaces in the posterior axillary line, and the camera is inserted in the seventh intercostal space. The pacing lead is introduced through a working port and attached between the first and second obtuse marginal between the base and the apex. A second pacing lead is attached near the second obtuse marginal, and the pericardium is closed over the leads. Both leads are tunneled to an incision in the axilla and retested for threshold pacing requirements. The lead with the best threshold is connected to the pacemaker, whereas the other lead is capped and secured to the fascia for future use. If a right-sided pacing lead is needed, it is inserted transvenously at this time and connected to the biventricular pacemaker. This approach allows for reliable entry into the chest for left ventricular lead insertion, while allowing complete cardiac access for mapping.

No data are present on the difference in outcomes in patients with higher BMI undergoing this procedure. Cost effectiveness data on patients undergoing left ventricular lead placement surgery are also not available.

ROBOTIC-ASSISTED THORACOSCOPIC SURGERY

Although video-assisted thoracoscopic surgery (VATS) is well established, its use is limited to simple procedures. Few centers perform complex procedures such as pulmonary lobectomies and thymectomies using VATS.[47] Perhaps robotic surgery will be able to overcome some of the limitations of conventional VATS (see also Chapter 66).

Compared with minimally invasive surgery performed in other regions of the body, robotic-assisted thoracoscopic surgery (RATS) presents different challenges. The surgical challenges include rigidity of the chest wall and movement of heart, lungs, and mediastinum. The anesthesia-related challenges include prolonged one-lung ventilation and hemodynamic instability associated with CO_2 insufflation of the hemithorax.

Patient positioning plays a major role in exposing otherwise inaccessible areas, because mediastinal structures are heavy and mobile and change position in response to gravity (see also Chapter 41). Supine or slight lateral decubitus (raising one side 15 to 30 degrees) position is ideal for anterior mediastinum pathology. A 90-degree lateral position may be optimal for hilar masses and lobectomies. A nearly prone position can create better

exposure for posterior mediastinal masses.[48] CO_2 insufflation also has a big role in achieving adequate exposure by pushing the mediastinum to the opposite site, while compressing the lung away from the operative site. It also reduces fogging and removes cautery smoke. The disadvantage of CO_2 insufflation is hemodynamic instability.

As the use of robotics in surgery has increased, its role in thoracic surgery has evolved over the last few years. The procedures being performed include multiple esophageal procedures, including Heller myotomy, resection of esophageal masses,[49] and esophagectomy.[50] Other procedures being performed include lobectomies,[51] resection of mediastinal masses, and thymectomy.[47]

Whether outcomes are improved in patients with higher BMI undergoing this procedure is not known. RATS costs significantly more than VATS with similar complication rates; cost-effectiveness data are not available.[52]

UROLOGIC SURGERY

The first use of robotics in urology began in the late 1980s, when a robotic frame was developed for transurethral resection of the prostate (see Chapter 72). The frame was constructed to support the six-axes Unimate Puma robot (initially designed by Unimation, Danbury, Conn.). The safety of this device was derived from the steel circular frame that restricted and confined the robot to a precise arc of resection. Procedures could be performed more rapidly with a robotic instrument, and because hemostasis was required only once at the end of the procedure, there was less time for absorption of irrigation fluid. The Puma robot has been used to resect prostate tissue safely.[53]

The percutaneous access robot (PAKY-RCM; URobotics, Baltimore, Md.) was developed in 1996, and was later replaced by Tracker in 2003. This robot is used with fluoroscopy or CT guidance to improve the accuracy of needle placement in percutaneous nephrolithotomy and tissue biopsy. The AESOP system (discussed earlier) also has been used successfully in laparoscopic urologic surgery. The most advanced systems currently being used in urology are master–slave systems, such as the da Vinci Robotic Surgical System. The procedures that have been performed using da Vinci systems include radical prostatectomy,[54] radical cystectomy,[55] radical and simple nephrectomy, live donor nephrectomy, pyeloplasty, and adrenalectomy.[56]

ROBOTICALLY ASSISTED RADICAL PROSTATECTOMY

Guillonneau and Vallancien[57] were the first to show the feasibility and efficacy of laparoscopic radical prostatectomy. Since then, robotically assisted radical prostatectomy (RAPR) has become one of the most common procedures to be performed with robotic assistance. In 2011, more than 113,000 procedures were performed worldwide.[10] The learning curve seems to be much shorter with RAPR compared with the laparoscopic approach.

The most common technique used for RAPR seems to be the transperitoneal and antegrade approach, developed by Ficarra and colleagues[54] at the Vatikutti Institute of Urology (Detroit, Mich.). Outcome data, such as the transfusion rate, urinary continence recovery, erectile function, and oncologic outcomes with RAPR, compare favorably with those for laparoscopic or traditional retropubic approaches.[58-61] The operating times also can be similar to the traditional retropubic technique after the operator has learned the technique.

The plan for anesthetic induction for RAPR is similar to that of the open procedure. After inducing anesthesia, an arterial line can be inserted for blood pressure monitoring and frequent phlebotomy. Two large-bore intravenous lines should be considered when the potential for large blood loss is foreseen. Anesthesia can be maintained with a volatile anesthetic. Neuromuscular blockade is paramount in avoiding any movements by the patient while the surgical instruments are within the abdominal cavity. After placing the patient in the lithotomy position, pneumoperitoneum is created through an umbilical puncture needle, and the maximum pressure is set to 15 mm Hg. The trocar is inserted according to the standardized Heilbronn approach using a semilunar five-trocar arrangement, with a sixth in the suprapubic area.[62] A procedure with some modification of the Montsouris technique is used.[63] The patient is placed in steep Trendelenburg position to improve visualization in the surgical field. Because of the potential for long operative times, careful attention should be paid to patient positioning to prevent neuropathies (also see Chapter 41). Silicone gel pads should be placed at every pressure point. Some surgeons advocate tucking the patient's arms while the patient is awake to maintain optimal comfort and avoidance of neurapraxia.[63] Injury to the common peroneal nerve is one of the most common complications of lithotomy position. Other nerves at risk during lithotomy include the femoral, obturator, and sciatic nerves. Patients placed in an exaggerated Trendelenburg position are also at risk of developing brachial plexus neuropathies.[64] The effect of pneumoperitoneum can be attributed to increased intraabdominal pressure and hypercarbia. Some anesthesiologists use pressure-controlled ventilation to improve respiratory mechanics. In a small study of patients undergoing RAPR, pressure-controlled ventilation demonstrated no advantage over volume-controlled ventilation regarding respiratory mechanics or hemodynamic variables, except greater dynamic compliance and lower peak airway pressure. [65] Venous air embolism can occur in this procedure when the insufflation pressure exceeds venous pressure during the setting of a vascular injury. The incidence of venous air pressure is lower in RAPR when compared with an open procedure.[66] Steep Trendelenburg position and pneumoperitoneum can result in increased intracranial pressure. Despite increased intracranial pressure, cerebral perfusion pressure is usually maintained because of simultaneous increase of mean arterial pressure and central venous pressure.[67] Prolonged steep Trendelenburg position may be relatively contraindicated in patients with a history of stroke or cerebral aneurysm. Ophthalmologic injuries such as permanent vision loss, vision defects, and retinal tear have been reported after

RAPR.[64] The exact mechanism of ophthalmologic injuries is unknown. Some physicians, however, advocate for the use of an orogastric tube and lubrication of the eyes and closure of eyelids with tape or goggles to minimize the potential for gastric content causing eye contamination in the steep Trendelenburg position.

Urine output cannot be used as a measure of intravascular volume status because the bladder is opened during the procedure and the urine drains into the operative field. This can lead to overestimation of blood loss by mixing of urine and blood. Some institutions limit intraoperative intravenous fluids to reduce edema of the head and neck from positioning and to improve visualization in the operative field by reducing urine output. An endotracheal tube cuff-leak test is recommended before tracheal extubation in patients that have been subjected to prolonged, steep Trendelenburg position, because this position can result in airway edema and postoperative airway distress in some patients.[68] RAPR is associated with higher positive margin rate when compared with laparoscopic prostatectomy in patients with higher BMI.[69,70] Compared with laparoscopic prostatectomy, the higher cost of RAPR can be offset by the small gain in decreased risk of early harm and positive margin in high-volume medical centers.[71]

ROBOT-ASSISTED RADICAL CYSTECTOMY

Robot-assisted radical cystectomy (RARC) is an emerging alternative for treatment of invasive bladder cancer (see also Chapter 72). Using the six-port approach and the da Vinci system, pelvic lymphadenectomy and cystoprostatectomy are performed. The specimen is removed in a bag through a 5- to 6-cm suprapubic incision. Through this incision, the bowel is exteriorized, and a neobladder is created extracorporeally. Subsequently, urethroneovesical anastomosis is performed with robotic assistance.[72] RARC may have a less frequent rate of complications than in patients undergoing an open procedure.[73,74] Long-term oncologic results of RARC are still not available.[73] When the effect of complications is considered, RARC is more cost effective than open radical cystectomy; this effect is more pronounced in patients undergoing ileal conduit. [75]

The difference in outcomes in patients with higher BMI undergoing this procedure is not known. Cost effectiveness data for patients undergoing RARC are also not available.

GENERAL SURGERY

Robotic technology has defined itself in the field of gastrointestinal laparoscopic surgery.[1] The first surgical operation using robotic telemanipulation was a laparoscopic cholecystectomy performed in 1997 in Brussels, Belgium.[76] Robot-assisted surgical techniques permit the surgeon to provide the smallest possible incision and smallest surgical stress. This technology allows surgeons to work on a very small scale in cramped spaces. Virtually all gastrointestinal procedures have been performed safely by surgeons using this technology. Procedures most commonly performed include cholecystectomy, fundoplication, Heller myotomy, bariatric surgery, and colectomy.[77]

Robotic surgery overcomes some of the disadvantages of conventional laparoscopic procedures with three-dimensional imaging, elimination of motion reversal, motion scaling, and filtering of resting tremors, while offering an ergonomically comfortable position. Other reported advantages of robotic surgery over laparoscopic surgery are less intraoperative blood loss,[78] a short learning curve, superior imaging, and greater freedom of movement.[79] Robotic laparoscopic surgery also is associated with high patient satisfaction.[80] As long-term outcome data on laparoscopic robotic surgery are lacking,[78] the higher cost[81,82] and longer operating time[78] may prove to be a deterrent to some surgical programs.

ANESTHETIC CONSIDERATIONS

In the operating room, the usual monitors are used for the patient. Some clinicians advocate the placement of a second noninvasive cuff as an alternative should the first fail, when arms are "tucked" and not available for access during surgery. Bilateral peripheral intravenous access is valuable because the left upper extremity is not immediately available during the surgery. Anesthesia can be maintained with a volatile anesthetic. Neuromuscular blockade (see Chapter 34) is paramount in avoiding any movements by the patient while the surgical instruments are within the abdominal cavity. An orogastric tube and a urinary bladder catheter are placed. Eye lubricant and eye lid closure need to be assured. Convective-air body warmers are applied whenever possible.

In the supine position, the patient is prepared and draped, and the abdominal cavity is insufflated with CO_2 to a pressure not to exceed 20 mm Hg. The trocar for the camera is placed manually. Incision ports for Nissen fundoplication and cholecystectomy are shown in Figures 87-14 and 87-15. The side cart robot is brought very close to the patient's head to engage the other trocars with visual guidance from the robotic camera. Because of the proximity of the side cart to the patient's head, there is limited access to the patient's airway and neck, and the head must be guarded against inadvertent collision with the robotic arms when moving.[83,84] After the robot is engaged, the patient's body position cannot be changed. The surgical team should be capable of rapidly disengaging the robotic device if an airway or anesthesia emergency arises. As with any laparoscopic procedure that requires a pneumoperitoneum with CO_2, ventilator adjustments may be required to normalize the exhaled CO_2. Some surgeons argue that the benefit of invasive arterial monitoring does not outweigh the risks.[84] This issue should be considered for each patient based on a risk–benefit analysis.

GYNECOLOGIC SURGERY

Robotic surgery in gynecology was first described in 1999 for fallopian tubal anastomoses[74,75] after sterilization or tubal ligation. Robotic techniques are being used to perform gynecologic procedures, such as sacral

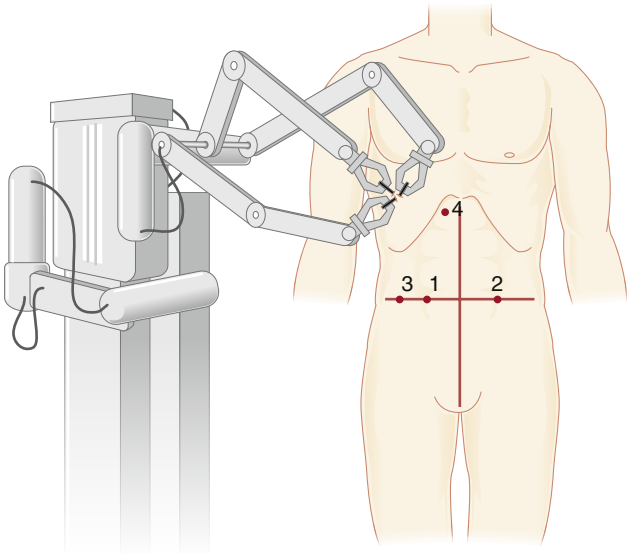


Figure 87-14. Numbered incision ports for Nissen fundoplication and location of the robotic arms.

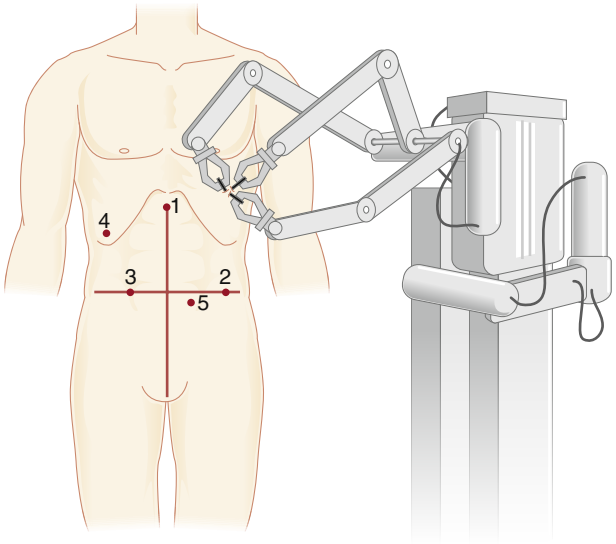


Figure 87-15. Numbered incision ports for cholecystectomy and location of the robotic arms.

colpopexy, myomectomy, treatment of endometriosis, simple and radical hysterectomy, salpingo-oophorectomy, ovarian cystectomy, and repair of vesicovaginal fistula.[76,77] In 2011, 146,000 hysterectomies were performed worldwide.[10] Despite the increasing popularity of robotic-assisted gynecologic surgery, there is little evidence to demonstrate lower incidence of complication when compared with open procedures.[85-87] Robotic gynecologic surgery is associated with similar morbidity, longer operative time, and higher cost when compared with open procedures.[82,86,87] The differences in outcomes in patients with higher BMI undergoing robotic gynecologic surgery are not known. Anesthesiologists should consider the physiologic effects of steep Trendelenburg position and pneumoperitoneum when providing anesthesia for these procedures. [88]

NEUROSURGERY

From the late 1980s to 1993, neurosurgeons investigated the use of robots to position resection probes and devices precisely within neural parenchyma to provide minimally invasive surgery and to protect normal tissue (see also Chapter 70). The da Vinci robot has been adapted to perform transnasal endoscopic skull base procedures, even though it was not designed for use in neurosurgery.[89] Robots such as NeuroMate (Renishaw plc, Gloucestershire, U.K.) have been developed to procure CT or MRI information to enable surgeons in performing accurate stereotactic procedures such as epilepsy surgery, performing biopsies, placement of ventricular reservoirs for chemotherapy, and placement of deep brain stimulator leads. [90-93] CyberKnife (Accuray, Sunnyvale, Calif.) is an image-guided, frameless, stereotactic radiosurgery system for treatment of spinal tumors. A major potential benefit of radiosurgical treatment of spinal lesions is that this can be performed in an outpatient setting, with rapid recovery.[94] The integration of various disciplines, such as robotics, machine intelligence, nanotechnology, and sophisticated computational networking, could revolutionize the practice of neurosurgery in the twenty-first century.

No data are present regarding the difference in outcomes in patients with higher BMI who are undergoing robotic neurosurgical procedures. Cost effectiveness data for robotic neurosurgery are not available.

ORTHOPEDIC SURGERY

The first medical application of robotics was in orthopedic surgery. There are two main types of robotic systems being used in orthopedic surgery: autonomous and haptic (see also Chapter 79). In 1992, Paul,[95] a veterinarian who worked in collaboration with International Business Machines (Armonk, N.Y.), developed a robotic system that could be used for hip replacement in dogs. The research collaboration resulted in the first surgical robot—ROBODOC (Integrated Surgical Systems, Davis, Calif.)—an autonomous robotic system. The earliest trials with ROBODOC were performed on patients undergoing total hip replacement. The femoral implant was placed into an axial canal of the proximal shaft of the femur. This femoral canal was formed with higher precision by a robot compared to the manual method.[95] The robot obtained its visual or coordinate cues from image-based information, such as from an MRI image or CT scan, and titanium pins placed in the femoral condyles and the greater trochanter. The robot recognized the three titanium registration pins and compared their location relative to the data obtained from CT. In this manner, the robot had a perfect sense of the position of the femur in three-dimensional space and could perform precise milling of the femoral canal. The remainder of the surgery proceeded manually. Autonomous robotic systems have fallen out of favor as they are associated with increased operating times and blood loss.[96,97] These systems are also associated with an increased risk of litigation.[98]

The Robotic Arm Interactive Orthopedic System (RIO; MAKO Surgical Corporation, Fort Lauderdale, Fla.) and Acrobot System (The Acrobot Company, London, U.K.) are examples of commercially available haptic robotic systems. These systems require active participation of the surgeon and use preoperative CT scans to create a three-dimensional model of the knee. The surgeon uses this model preoperatively to plan the sizing and placement of components and intraoperatively to "merge" the preoperative model with the actual anatomy of the knee. During the procedure the surgeon views the three-dimensional model of the knee on the monitor while manipulating the burr. The robotic arm provides auditory and haptic feedback, limiting the rotating burr to resect the bone within the preplanned cutting zone. Such haptic systems have a short learning curve and allow the surgeon to have greater precision.[99,100]

No data are present on the difference in outcomes in patients with higher BMI who are undergoing robotic orthopedic procedures. Robotic arthroplasty surgery has similar outcomes with significantly higher costs. [101]

SUMMARY

The use of robots in surgery is likely to increase in the future because of enhanced precision, multiple degrees of freedom, tremor filtering, and the ability to fuse preoperative (CT and MRI) and intraoperative images to guide the surgeon.

Although robotic systems have improved a great deal in dexterity, technically, much needs to be done to realize the full potential of this surgery. Current areas of research include the development of sensory input, and the ability to relay touch sensation from the robotic instruments to the surgeon. Some laboratories are also working to develop instruments for surgical anastomosis that requires no sutures. The possibility of automating some of these tasks in the operating room is another exciting and controversial idea. In the future, robots will be regarded less as mechanical devices and more as information systems. Robotic systems may also make long-distance consultation and guidance possible by experienced surgeons. The latest innovation in robotics is that of image-guided surgery, in which a surgeon is able to see in real time the scanner images superimposed on the surgical field. The human anatomy will be rendered translucent, and the exact location of any vital structure will be clearly visible. Preoperative diagnostic imaging in combination with virtual reality simulators will allow the surgeon to rehearse complex procedures in advance and to program the robot to avoid any vital structures during surgery.

Visualization systems are being developed that will improve surgery on mobile structures, such as the beating heart. Advances in motion gating technology will allow the heart to appear as if it were standing still. This will be done by properly timing a strobe light that is synchronized with the heart rate to achieve the proper virtual image of the heart standing still.[2]

Anesthesiologists need to be aware of this fast-changing field and the effects on anesthetic techniques and delivery. Initially, robotically assisted procedures increased the duration of general anesthesia. As surgeons gain expertise with robotically assisted surgery, operative times decrease dramatically. As the size and cost of robotic systems decrease and potentially improved outcome data become available, robotic systems are likely to become less of a marketing tool and more a technological innovation to improve patient care. As with all innovations, we make progress with optimistic caution.

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Chapter 88

Anesthesia for Laser Surgery

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Key Points

- Lasers are characterized by wavelength, power, and duration of pulse.
- High-energy lasers (classification risk, Class 3 or 4) should be supervised by a laser safety officer.
- Laser energy can be transmitted at full strength at a distance from the source.
- Eyes are the most vulnerable organ.
- Laser goggles must be matched to the frequency of the wavelength and energy level.
- Airway fires are a significant risk when using lasers in or near the airway.
- High fraction of inspired oxygen concentration (FiO_2) significantly increases the risk of airway fires.
- Nitrous oxide (N_2O) is not a safe diluting gas for airway fire risk.

Laser is an acronym for *light amplification by stimulated emission of radiation*—a highly collimated beam of photons at a single frequency. Lasers are ubiquitous in the modern world and are increasingly used in the operating room (OR). Understanding the technology is important to safe anesthetic practice. Some of the same properties that make laser energy useful also make it a safety threat to both the patient and the staff.

Although any intense light source can cause biologic effects, lasers are unique in their precision. The critical features of laser light are the following:

1. Collimation—precisely aligned beam that can be seen on the moon
2. Coherence—light in phase
3. High-power density
4. Narrow spectrum of frequency
5. Can be pulsed for less than 10^{-11} seconds (femtosecond range)

Lasers were first developed in the 1950s with a history of conflicting primacy claims and protracted patent battles somewhat akin to the discovery of anesthesia. Its use in surgery followed shortly thereafter, but the extent of the applications continues to progress rapidly.

PHYSICS OF LASER

The original observation that electromagnetic radiation occurred only in discrete amounts, called *quanta*, was made by Max Planck,[1] for which the Nobel Prize was awarded in 1918. The energy of these quanta is proportional to the frequency of radiation:

$$E = h\nu$$

where h is Planck's constant (6.6×10^{-34} joule-seconds) and ν is the frequency.

Einstein's work on the photoelectric effect[2] (Nobel Prize, 1921) found that light was quantized (photons) and that transitions in electron energy states orbiting in an atom emit photons of characteristic frequencies. Certainly, the reverse is true—photons can raise electrons to higher energy states and can cause a current to flow. Because photon frequency (ν) and wavelength (λ) are related by the speed of light, $c = \nu\lambda$, Planck's postulation can also be expressed as:

$$E = ch/\lambda$$

Thus photons at a higher frequency (or shorter wavelength) have more energy.

Typical light sources such as the sun or an incandescent light bulb produce a range of wavelengths. This spectrum can be separated by a prism or rainbow. The atoms in a heated gas, for instance, have a spectrum of energies based on Boltzmann statistics. The photon radiation pattern changes with the temperature or the radiation source (hence the difference between the color spectrum of an incandescent bulb and daylight), but the pattern contains a range of frequencies (Fig. 88-1).

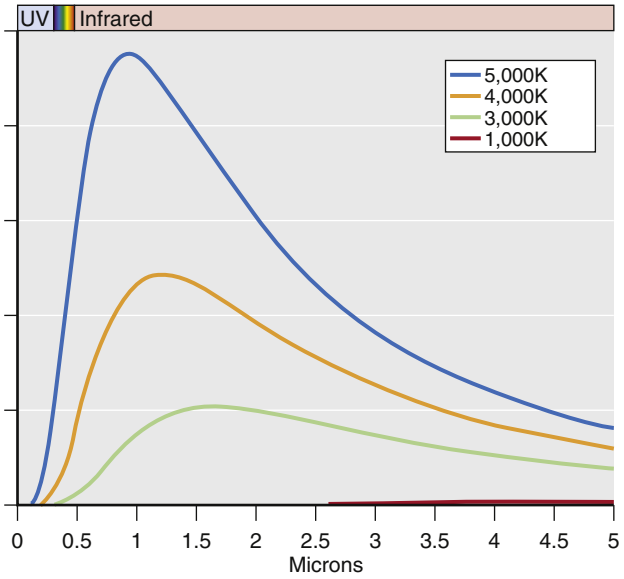


Figure 88-1. Higher temperature objects radiate at a higher intensity and shorter wavelengths.

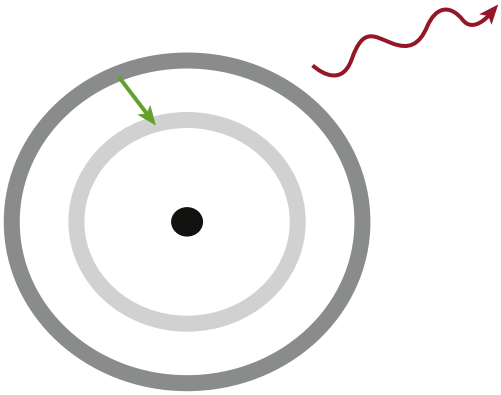


Figure 88-2. Spontaneous emission.

The laser phenomenon requires a detailed look at electron-photon interaction. Electrons orbit in atoms in discrete energy levels called *quantum states*. They can be pushed to higher energy states by collision with photons but will eventually return to the lower state emitting a photon. Because only specific energy levels are permissible, the emitted photon has only certain allowed energy levels and thus frequency. The phase and direction of photon emission is random in spontaneous energy transitions (Fig. 88-2). In the physical process of fluorescence, photons from higher energy light (or x-rays) cause excitation of the fluorescent atoms to glow at their characteristic frequency.

Lasers radiate not only in a narrow frequency but also with uniform phase and direction. Einstein proposed the phenomenon of stimulated emission based on theoretic arguments. Stimulated emission (as opposed to spontaneous emission) is a process during which an emitted photon triggers another excited state atom to emit at exactly the same phase and direction and energy level (Fig. 88-3).

Lasers are designed to amplify stimulated photon discharge, causing more stimulation and photon release. Typically, the laser cavity is mirrored at each end to reflect the emitted photons to increase the population of stimulated photons and thus the signal (an optical resonator); hence, the full explanation of the *laser* acronym: *l*ight *a*mplification by *s*timulated *e*mission of *r*adiation.

Some subtlety exists in ensuring that the stimulation will be amplified. Stimulated photons have three possible fates: (1) escape as part of the working beam, (2) absorption by a nonexcited atom, or (3) stimulating an excited atom to emit as well. For a laser to amplify the photon discharge, the population of excited atoms must be larger than those in the ground state—*population inversion*. An external photon source (another laser or a flash lamp) or possibly a chemical means can induce the excitation. In practice, more energy states are involved (three- or four-level lasers), depleting the absorbing ground state. Other means of removing nonexcited atoms are possible, such as chemical dissociation (excimer laser) or gas separation.

TYPES OF LASERS

One method of categorizing the types of lasers is based on the physical process used. Even these broad categories have many nuances and are undergoing active development (Fig. 88-4).

- **Solid-state laser.** The lasing material is solid crystalline, similar to the first ruby laser, or a synthetic gem crystal known as *yttrium-aluminum-garnet* (YAG)—not to be confused with solid-state electronics, which includes diode lasers.
- **Gas laser.** Carbon dioxide (CO_2) and helium are common types. CO_2 is a particularly efficient type and is used for industrial metal cutting, as well as for medical uses.
- **Excimer laser.** A pair of disparate gas molecules forms a dimer in the excited state. The gas pair is usually a noble gas, such as xenon or argon, and a reactive halide, such as bromine or fluorine. The gases are complexed only in the excited state (under pressure with electron discharge) and rapidly dissociate after emission, preserving population inversion (i.e., the condition of having enough high-energy states distributed in a material that a chain-reaction of stimulated emission can occur). Their spectrum is in the ultraviolet range. In medical use, they function more by ablating tissue than causing a burn.
- **Dye laser.** An organic dye is used as the laser medium. These lasers have a large variety of wavelengths and high power. The wide spectrum available allows matching specific pigments (for tattoo removal), hemoglobin absorption, and a variety of skin lesions. The dyes and suspension media are often carcinogens, so care must be used in handling them.

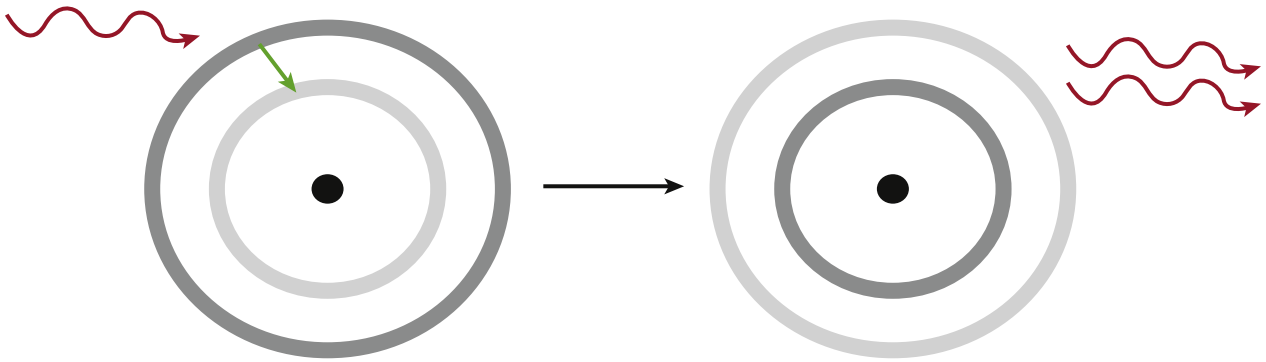


Figure 88-3. Stimulated emission. The emitted photon has the same direction and frequency as the triggering photon.

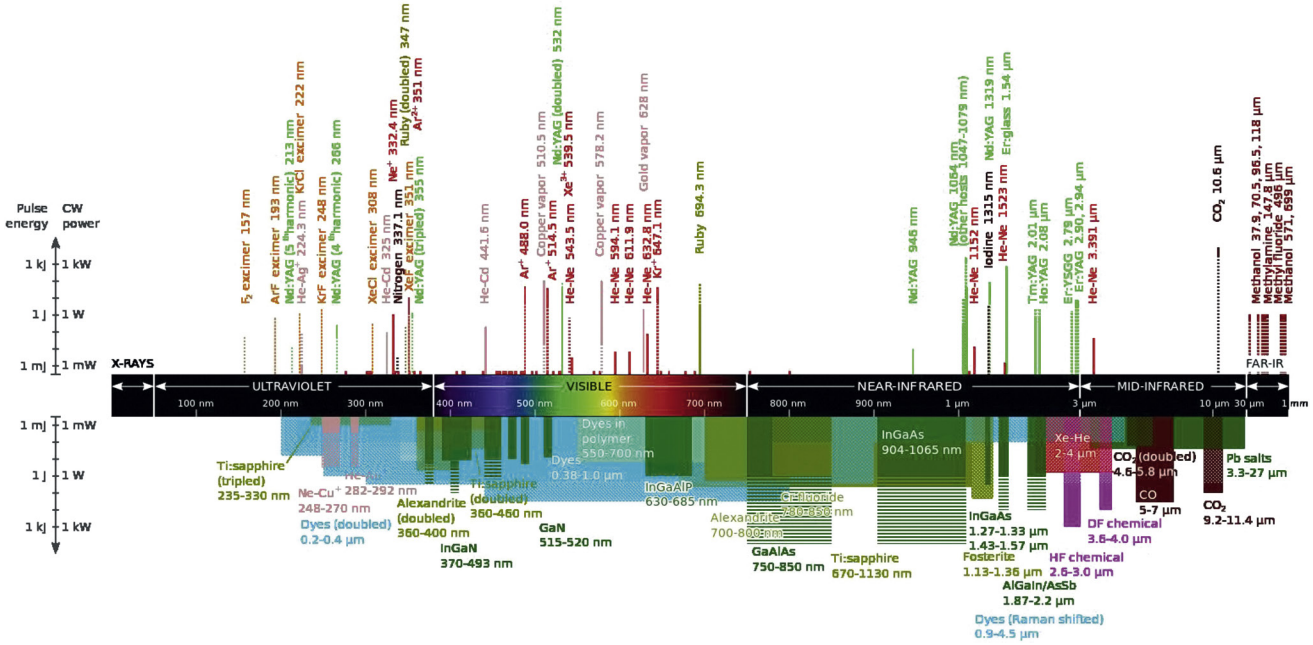


Figure 88-4. Commercially available lasers by power and wavelength. Power is shown in the vertical axis. Distinct frequency lasers are shown above, and wavelength ranges are below. *Blue,* Dye lasers; *green,* solid-state and semiconductor lasers; *red,* gas and excimer lasers. *(From Danh. Wikipedia Commons. <*http://en.wikipedia.org/wiki/File:Commercial_laser_lines.svg*> Accessed 11/22/2013.)*

- **Diode or semiconductor laser.** A specially constructed semiconductor layer on a silicon substrate can lase when electron and *holes* combine. The excitation can be from an optical or electrical source. These are now the most common lasers made and are used in consumer electronics (e.g., laser pointers, CDs, and DVD players), as well as sensors, pointers, and communication devices.

LASER MODES AND SETTINGS

There are a few *knobs* that can be adjusted for laser treatment.

1. Timing mode—continuous wave (CW) or pulsed. The length of pulse varies with the physics of the generating system but can be shortened by physical or electrical means (i.e., mode-locked). Interest in ultrashort length pulses—femtoseconds—is increasing.
2. Energy level. Specified in watts for continuous, and joules for pulsed. Lasers are typically used in two modes: continuous and pulsed.

CW lasers are produced from photons continuously escaping the amplification chamber. Several methods can produce pulsed lasers: (1) by either mechanically or electrically changing the reflection properties of the amplification chamber walls; (2) by using an intermittent pumping source to excite the lasing sequence, such as another pulsed laser or flash lamp; and (3) by mode locking, in which variations in phase are summed, causing interference patterns and allowing extremely short pulses.

BIOLOGIC EFFECT

Light has a biologic effect solely from absorption in tissue (Grotthus-Draper law), specifically by raising electrons to higher energy states that, in turn, can raise kinetic

energy (heat) or cause chemical reactions. Lasers have been applied to medicine since 1962.[3] The current uses are widespread and evolving. Boulnois categorized the biologic effects into four types.[4]

- **Electromechanical effects.** A pulsed laser causes a shock wave and thus an actual mechanical impulse. One common application is in stone lithotripsy for ureteral calculi. Laser lithotripsy using holmium:YAG (Ho:YAG) is at least as effective as extracorporeal shock,[5] and low-frequency high-power shocks are more effective in experimental models.
- **Thermal effects.** Similar to other surgical techniques (electrocautery from radiofrequency currents, harmonic scalpel), localized heat can cauterize and separate tissue, allowing bloodless incisions. Laser thermal effects differ little from other surgical sources[6] except that they can be more finely focused with high-energy density and delivered via fiberoptic strands. Bolliger found that airway lesions were well managed by laser, electrocautery, or argon plasma coagulation.[7] In some cases, laser coagulation may offer an advantage when laser frequencies that are absorbed by specific tissues such as the retina or hemangiomas are chosen. One treatment for port-wine stains involves pulse-dye tuned to hemoglobin, with surface dermal cooling to protect the surrounding tissue.[8]
- **Photoablative effects.** These effects come from the molecular disruption and ablation of tissue, with the resultant gases removing heat and protecting the surrounding tissue from thermal injury. Photoablative effects can be either at the microscopic level (femtosecond lasers for corneal surgery) or at a macroscopic level (photoselective vaporization of the prostate).[9]
- **Photochemical effects.** Photochemical effects are the newest area of interest and the least well proven mechanistically. Low-level laser therapy (LLLT) has been used in a wide variety of surgical and nonsurgical conditions. Various theories suggest that specific wavelengths can modify enzyme systems,[10] change electron transport and tissue oxidation states,[11] or be mediated via nitric oxide.[12] Although ongoing research is required, it is suggested that neurologic injuries may be effectively treated with certain wavelengths.[13]

COMMON LASER OPERATIONS

Defining the full scope of applications for lasers in surgery is difficult. In general, lasers are used for surface procedures and for endoscopic procedures during which the energy can be routed by fiberoptic bundles. Some of the more common laser surgical procedures are performed in dermatology, dentistry, laryngology, and ophthalmology.

DERMATOLOGY

The use of lasers in dermatology, from removal of lesions to wound care, has been long established and quite extensive.[14] Most procedures are office based, use topical analgesics, and do not involve anesthesiologists,[15] except possibly with children.[16]

DENTISTRY

The use of lasers in dentistry involves treatments for the discoloration of teeth, periodontal disease, and oral lesions.[17]

LARYNGOLOGY

The use of lasers in laryngology involves endoscopic resection of laryngeal cancers, either office based for smaller lesions[18] or with rigid suspension microlaryngoscopy.[19,20] Precise coagulation of vascular lesions without damage of the phonatory surface is another common application. Additionally, lasers are used in resecting papillomatosis (also see Chapter 85).[21]

OPHTHALMOLOGY

Lasers are extensively used, including with glaucoma surgery, during procedures in which very short pulses can target small cell clusters, for corneal shaping for vision correction,[22] and in retinal surgery with wavelengths that are transparent to the cornea but absorbed by pigmented retinal cells. Corneal surgery can be performed either by surface ablation of stromal tissue (typically with short-wavelength excimer lasers) or by creating subsurface flaps with femtosecond pulses at 1053 nm and allowing the microbubbles of plasma to separate tissue.[23] Most ocular surgeries are performed with topical or retrobulbar nerve–regional block and intravenously administered sedation. Low-level laser therapy can replace higher energy interventions in retinal disease (also see Chapter 84).[24]

RISKS OF LASER USE: STANDARDS AND REGULATIONS

SAFETY FRAMEWORK

Laser safety in the clinical setting is a multidisciplinary responsibility occurring at several organizational levels. Medical facilities are responsible for implementing safety programs and policies that adequately control the hazards associated with laser use.

In the National Academy Sciences Institute of Medicine report, "To Err is Human: Building a Safer Health System," *safety* is defined as "freedom from accidental injury."[25] Further, the National Patient Safety Foundation (NPSF) emphasizes that safety is a function of a coordinated effort that depends on interactions at many points and is not a result of an individual or a device.[26] The provision of safe laser use in the OR requires a team approach with the establishment of safe practices enforced by cooperative input and vigilance from all providers present (also see Chapter 109).

REGULATORY AGENCIES

A number of agencies oversee laser regulations, especially regarding its use in health care. The International

Electrotechnical Commission (IEC) is the body of the main standards, especially for Europe, but U.S. standards closely follow them. The guidelines come from an international technical committee (TC-76) with expert guidance from many organizations.[27] The specific IEC technical report is IEC 60825-8, "Safety of Laser Products—Part 8: Guidelines for the Safe Use of Laser Beams on Humans."[28]

Japanese guidelines are published by the Japanese Standards Association under JIS C 6802:2011, "Safety of Laser Products."

In the United States, laser safety guidelines are created by the American National Standards Institute (ANSI). The current laser safety guidelines are ANSI Z136.1–2007,[29] and the health care specific guidelines are ANSI Z136.3–2011.[30] Medical lasers are regulated by the U.S. Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (FFDCA), Chapter V, Subchapter C—Electronic Product Radiation Control. The FDA publishes its standards (online) under Title 21, Chapter 1.J.1024.10.[31] The FDA regulations use the older class Roman numerals I through IV categories and include requirements for labeling and the need for various safety mechanisms.

Other than the FDA, no other mandatory federal agency standards or regulations specifically govern the safe clinical use of medical lasers, but accepted standards exists that facilities may voluntarily adopt and to which they may adhere. Several organizations focus on laser safety in general, including the FDA's Center for Devices and Radiological Health (CDRH), ANSI, the Occupational Safety and Health Administration (OSHA), and the nonprofit, Conference of Radiation Control Program Directors (CRCPD). Many states have regulations and guidelines as well. The FDA suggested a set of regulations in 1983 that have been adopted and modified by several states.[32] The CRCPD is attempting to establish a "Model State" standard.[33]

OSHA is the main U.S. agency that enforces safety and health legislation in the workplace. At present, OSHA does not have a comprehensive laser safety standard, but this organization publishes a technical manual on laser hazards,[34] endorses ANSI Z136.1–2007, and can issue citations attributable to the lack of compliance with other safety standards. The Joint Commission (TJC) (formerly the Joint Commission on Accreditation of Healthcare Organizations [JCAHO]) uses ANSI Z136.1–2007 and ANSI Z136.3–2011 as its guidelines. Under these guidelines, medical facilities appoint a laser safety officer (LSO) who is formally trained to administer the overall institutional safety program, which includes monitoring and enforcing the control of laser hazards. Currently, data regarding the incidence of laser-related injuries to patients and workers are incomplete. However, some safeguards to encourage reporting of potential safety breaches are in place, including (1) requiring laser manufacturers to report unusual incidents or injuries, and (2) the Safe Medical Devices Act of 1990, which mandates that clinicians report all serious injuries incurred from the use of a medical device.

Professional society taskforces have consensus statements that recommend how to prevent and manage OR hazards (also see Chapter 6). In 2008 and 2013, the American Society of Anesthesiologists (ASA) Task Force on Operating Room Fires issued practice advisories for the prevention and management of OR fires, with specific comments regarding lasers[35] (also see Chapter 109).

Considering the inherent risk in the medical application of lasers, state and federal safety guidelines and societal standards should be followed to ensure regulatory safety compliance, to provide a framework for identifying and controlling the risks of laser use, and to develop effective safety educational and training programs to better protect patients, employees, and property. Establishing a safe and compliant medical laser program requires access to standards and training. The Laser Institute of America (LIA) is an independent professional body, allied with OSHA,[36] that functions as secretariat of the ANSI standards. The LIA offers conferences and training materials and courses, including the certification for Certified Medical Laser Safety Officers.[37]

LASER RISK CLASSIFICATION

Lasers pose a safety risk to OR personnel. Because the beam is highly collimated, it can travel with minimal attenuation outside the intended surgical field either directly or by reflection. The likely biologic risk is for retinal damage because the structure of the eye concentrates the beam and has pigments tuned to visible wavelengths. Thermal effects (i.e., skin burns) come from heating with long exposures and high intensity and depend on local tissue susceptibility.

The current classification for laser devices from the IEC 60825-1 standard is based on safety risk. Four classifications, some with modifiers, cover safety and warning features (Fig. 88-5), the required level of training, and controls.

- **Class 1 lasers.** Are safe under all normal uses, even with optical magnification, although a strong lens might sufficiently concentrate the energy to cause damage. Class 1M is a subcategory for diffuse beams that could be harmful when viewed under magnification but not under expected conditions.
- **Class 2 lasers.** Are safe because of the blink reflex, which limits exposure to under one fourth of a second. A typical example is a laser pointer. Class 2M is safe for the same reason, as long as magnifying optics are not used. Class 2 lasers are confined to the visible range (400 nm to 700 nm) with any nonvisible emissions only at Class 1 levels. Class 2 lasers could be hazardous to patients in whom the blink reflex is suppressed.
- **Class 3 lasers.** Are split into two groups on the basis of intensity. Class 3R lasers are within five times the acceptable emission limit of Class 2 in the visible range and five times Class 1 outside that range. Class 3B is above that level and is able to cause direct ocular injury. Viewing reflections off matte surfaces are safe for Class 3 lasers.
- **Class 4 lasers.** Include high-powered lasers that can cause fire and injury even when viewing diffuse reflections.

Calculating actual exposure limits is complex. It depends on wavelength, intensity, duration, and type of injury (ocular versus thermal). Lasers used in medical



Figure 88-5. The International Electrotechnical Commission (IEC) laser warning label for Class 2 and higher.

facilities should have been classified by their manufacturer, unmodified, and properly maintained. As previously discussed, in the United States, medical lasers are regulated by the FDA under the FFDCA. Occupational exposure limits are set by OSHA, using guidelines from ANSI Z136.1–2007 for maximum permissible exposure (MPE) to the retina, based on wavelength and exposure time.

Many devices still in operation use the older classification scheme (ANSI Z136.1 or IEC 825), as do U.S. safety regulations. These are Roman numerals I through IV and roughly correspond to the current classes as listed:

- **Class I lasers.** Are safe under all conditions. Have very low power, or the laser is completely contained (e.g., CD players).
- **Class II lasers.** Are safe because of the blink reflex. Visible range with blink keeps exposure levels under one fourth of a second. Up to 1 mW.
- **Class IIa lasers.** Are safe for up to 1000 seconds of continual viewing.
- **Class IIIa lasers.** Are dangerous if viewed for longer than 2 minutes. May not be safe under magnification. Up to 5 mW power.
- **Class IIIb lasers.** Even momentary exposure can cause retinal damage, although indirect reflections should be safe. Laser goggles should be worn. Up to 500 mW.
- **Class IV lasers.** Are greater than 500 mW. Can easily cause ocular injury or burns. Even reflections off a matte surface can cause injury.

The revised ANSI Z-136.1–2007 guidelines now use the IEC Class 1 through 4 categories. In the ANSI Z-136.1–2007 guidelines, Class 3B and Class 4 handling should include key control, remote interlock connector, activation warning system (audio warning), window protection, protective goggles, training, and supervision by a laser safety officer (Table 88-1).

SPECIFIC LASER HAZARDS

The same properties that give lasers their clinical value also pose threats to patient and provider safety. These risks fall into three categories: (1) atmospheric contamination, (2) gas embolism, and (3) inappropriate energy transfer.

To place the relative safety risks in context, a review of laser safety databases for urologic procedures revealed that 46% of the reported incidents were machine problems (i.e., fiber breakage), followed by eye injuries, including permanent blindness. Seven deaths occurred, three from ureteral perforation and four from gas embolism.[38] As expected in this surgical population, airway fires were not represented.

ATMOSPHERIC CONTAMINATION: LASER PLUME

Tissue destruction during surgical laser procedures produces a complex particulate aerosol and smoke plume. Research confirms that this plume can contain compounds and toxic gases such as polyaromatic hydrocarbons, hydrogen cyanide, formaldehyde, benzene, and cellular material (dead and alive).[39,40] Fine particulates (mean size 0.31 μm; range 0.1 to 0.8 μm) and combustion by-products are easily dispersed throughout the respiratory tract. Animal studies link inhalation of the laser plume with pulmonary damage, which can lead to reduced mucociliary function, airway inflammation, interstitial pneumonia, bronchiolitis, and emphysema.[41-43]

The laser plume has in vitro mutagenic and teratogenic potentials. The mutagenic potential of the plume from a CO_2 laser on 1 g of tissue is equivalent to inhaling the smoke from three unfiltered cigarettes. This toxic potential is one half of that produced by electrosurgical units but is considerably more than that produced by Nd:YAG contact probes.[44]

Although controversial, the laser plume has the potential to transmit viable microorganisms into the atmosphere.[45-47] However, reviews have not found strong evidence of danger.[48] Viral DNA has been detected in plume from human papilloma virus (HPV)[49] in condylomas and skin warts,[50] but evidence for transmission to humans is weak. On its web site, OSHA notes that "no documented transmission of infectious disease through surgical smoke" has been published (see OSHA web site statement regarding Laser/Electrosurgery Plume: https://www.osha.gov/SLTC/laserelectrosurgeryplume/). A recent review of the literature assessing the infectivity of HPV in the plume is contradictory and scanty.[51] Inoculation of bovine papillomavirus (BPV) DNA from a surgical plume produced bovine fibropapillomas in three calves.[52] Other studies showed plume particle viability but no infectivity in susceptible cell lines.[53] Investigation into a laser surgeon's development of laryngeal papillomatosis, after laser treatment of a patient, revealed that the lesions in both the patient and the surgeon shared the same, albeit common, HPV serotypes.[54] A recent case report detailed two cases of HPV-induced airway cancers in surgeons using extensive lasering.[55] The incidence of HPV infection in laser surgeons specializing in the treatment of papillomas and condylomas is comparable to the incidence in the general public.[56] Human immunodeficiency virus (HIV) was not detected in electrosurgical smoke plume[57] in one study, and only noninfectious DNA fragments were found in a CO_2 laser plume from HIV-infected tissue pellets.[58]

Smoke evacuators are 99% effective at eliminating the plume when situated within 1 centimeter of the target site.[59] Accordingly, their use in the OR is strongly advised and supported by OSHA. The Centers for Disease Control and Prevention (CDC) states that surgical suction systems are not interchangeable with the preferred smoke evacuator suction unit.[60] In addition, using high-filtration masks that filter plume particulates down to 0.3 to 0.1 μm when dry is essential. Of note, viral particles are too small to be filtered reliably, and standard surgical masks filter particles as small as 3 μm.

EMBOLISM

The Nd:YAG laser system has been associated with venous gas embolism. Specifically, the gas coolant for the laser tip has been the responsible system element. During hysteroscopic surgery, while using an Nd:YAG laser, an accidental inflation of the uterine cavity by coolant resulted in deaths.[61] A sheathed quartz fiber (with coaxial coolant gas running) produced a massive and fatal gas embolism in another case.[62] Liquid (saline) coolant is a safer option during hysteroscopy, but fluid overload is possible.[63] If a coolant gas must be used, then CO_2 may be less harmful after embolization than nitrogen or air. Venous gas embolization has occurred at other sites, including tracheal tumor with an Nd:YAG laser,[64,65] during laparoscopic procedures,[66] and during nasal surgery using a CO_2 laser.[67] Continuous airway CO_2 monitoring may help with the detection of embolization. During laparoscopic surgery with CO_2 insufflation, mechanical hyperventilation should be adjusted to compensate for intraabdominal CO_2 absorption and cephalic displacement of the diaphragm, and a watchful eye must be maintained for the potential development of subcutaneous emphysema.

ENERGY TRANSFER TO AN INAPPROPRIATE LOCATION

Currently, medical lasers can all transmit an unattenuated and potentially destructive beam through air. If the

TABLE 88-1 SAFETY RECOMMENDATIONS FOR OPERATING VARIOUS CLASSES OF LASERS

	Classification						
Requirements Subclause	Class 1	Class 1M	Class 2	Class 2M	Class 3R	3B	Class 4
Laser safety officer 10.1	Not required, but recommended for applications that involve direct viewing of the laser beam				Not required for visible emission, but required for nonvisible emission	Required	
Remote interlock 10.2	Not required					Connect to room or door circuits	
Key control 10.3	Not required					Remove key when not in use	
Beam attenuator 10.4	Not required					When in use, prevents inadvertent exposure	
Emission indicator device	Not required				Indicates laser is energized for nonvisible wavelengths	Indicates laser is energized	
Warning signs 10.5	Not required					Follow precautions on warning signs	
Beam path 10.6	Not required	Class 1Ma as for Class 3B	Not required	Class 2Mb as for Class 3B	Terminate beam at end of useful length		
Specular reflection 10.7	No requirements	Class 1Ma as for Class 3B	No requirements	Class 2Mb as for Class 3B	Prevent unintentional reflections		
Eye protection 10.8	No requirements				Required if engineering and administrative procedures not practicable and MPE exceeded		
Protective clothing 10.9	No requirements				Sometimes required	Specific requirements	
Training 10.10	No requirements	Class 1Ma as for Class 3R	No requirements	Class 2Mb as for Class 3R	Required for all operator and maintenance personnel		

NOTE: This table is intended to provide a convenient summary of precautions. See text of this standard for complete precautions. From IEC 60825-1:1993+A1:1997+A2:2001 Safety of laser products, p. 108.

intended target is not accurately being sighted, then laser activation can result in injury to patients and OR personnel or damage to property. Laser ignition of any combustible fuel (e.g., surgical drapes, plastic endotracheal tubes [ETTs], ointment on the skin) may also occur either by unintentional direct beam strike or by reflectance and scatter of the beam off of specular surfaces.

TISSUE AND VESSEL PERFORATION

Off-target laser energy may perforate a viscus[68,69] or a blood vessel (if the vessel is too large to be cauterized: diameter >5 mm). Pneumothorax has been reported after a laser laryngeal procedure.[70] Of note, with an Nd:YAG system, the depth of tissue injury may not be immediately apparent. Complications such as viscus, tissue plane, or vascular perforation (with resultant complications) may not occur until edema and necrosis have become maximal several days postoperatively.

EYE INJURY AND EYE PROTECTION

Laser light, because of its special qualities of beam collimation, coherence, and high-energy density, poses optical safety hazards not associated with light from conventional sources. The extent of damage is determined by the laser irradiance, exposure duration, and beam size. The site of laser-induced ocular damage depends on the output wavelength. Visible and near-infrared light (400 to 1400 nm) can damage the retina. Argon, potassium titanyl phosphate (KTP):Nd:YAG, or ruby lasers are likely to focus on that structure with resultant rapid permanent damage to the retina.[71] Ultraviolet and far-infrared light is absorbed by the anterior structures. Infrared energy from a CO_2 laser causes corneal and lens injury.[72] With sufficiently powered lasers, permanent ocular damage can occur within a fraction of a second.

The blink reflex is too slow to guard against laser injury. Proper protective eyewear with side shields and appropriate filtering capabilities and optical density (specific for the type of laser to be used) are safety essentials for all present in the OR. The nonoperated eyes of patients should be taped closed and covered with saline-soaked opaque material or a metal shield.[73] CO_2 lasers emit far-infrared frequencies that are unable to pass through any clear glass or plastic lenses. Regular eyeglasses, fitted with side shields, may be sufficient protection, but contact lenses are not. All other lasers emit energy that requires specific colored lenses. Nd:YAG lasers require green-tinted goggles (which can make skin color assessment and monitor reading difficult), or clear lenses (Nd:YAG Protection Glass; Surgical Laser Technologies, Malvern, PA), which have a special coating opaque to near infrared. Argon or krypton lasers require amber-orange lenses, and KTP:Nd:YAG lasers require a red filter. The wrong eyewear will not protect. All protective eyewear must be donned before entering the OR. Glass windows in the unit must be covered during the use of lasers, and cautionary warning signs should be posted as described in ANSI Z136.3–2011 (also see Chapter 84).

LASER GOGGLES

Laser goggles need to be matched to the frequency of the Class 3 or Class 4 wavelength and still allow sufficient vision for safe medical care. In particular, it may be necessary to still see the weaker aiming beam at a different wavelength. IEC 60285-8 suggests that remote video observation may be an alternative to protective eyewear, as long as no risk of fiber breakage or the inadvertent direct exposure occurs.

Laser goggles are typically labeled with the wavelength and attenuation in decibels (dB) or optical density (OD). An OD of 6 at 1064 nm for Nd:YAG will attenuate the transmitted energy by $10^{-6.}$ The required OD should be calculated that reduces the maximum accessible emission (MAE) or power to below the MPE. Unfortunately, the goggles themselves may not physically withstand the laser strike.[74]

EN-207 is a more stringent IEC standard[75] that includes not only the degree of filtering but the resistance of the goggles to the laser itself, including reradiated energy. EN-207 markings include an *L number* that indicates the maximum power permitted (a logarithmic scale ranging from L1 through L10), and a DIRM modifier:

Marking	*Mode*
D	Continuous wave (cw)
I	Long pulse > 1 μs
R	Short pulse 1 ns to 1 μs
M	Femtosecond < 1 ns

The power limits are presented in EN-207 and differ for mode of operation (DIRM shown in the table above) and the wavelength range (180 to 315 nm, 315 to 1400 nm and > 1400 nm).

OPERATING ROOM FIRE

The ignition and propagation of fire requires a triad of components: ignition source, fuel, and oxidizer. All parts of the *fire triad* (Fig. 88-6) are ubiquitous in ORs and may

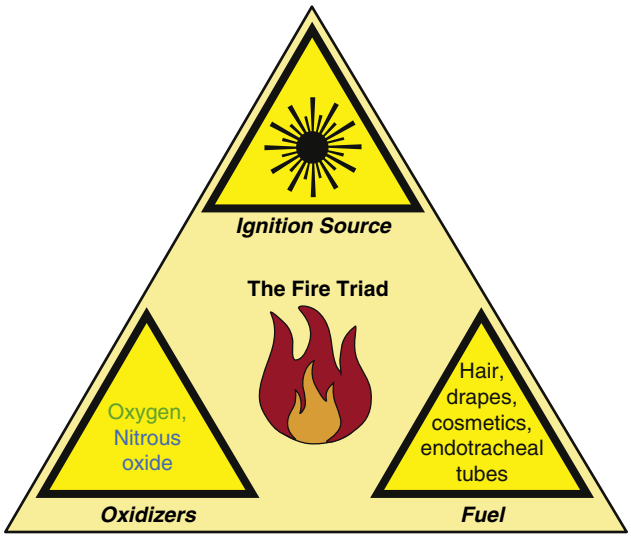


Figure 88-6. The fire triad.

be in close proximity of each other during laser surgeries. Lasers are highly effective and rapid sources of ignition.[76,77] Laser operators need to be well versed and compliant with the standards and codes in place for the safest practice during laser use. Given the right fuel, ignition may occur with oxygen as the primary oxidizer at 21% (room air) or at lower percentages in certain conditions.[78] Ignition potential is amplified in the presence of an enriched oxidizer concentration. This is true for either of the two prevalent OR oxidizers: oxygen or nitrous oxide (N_2O). Anesthesiologists and laser operators must work together to ensure the lowest possible fraction of inspired oxygen concentration (FiO_2) at critical points in all laser procedures. Common sources of fuel in the OR include the ETT and other plastic items, drapes and towels, and alcohol-based preparation solutions. Less common fuels include hair and skin ointments, which highlight the need for reminding patients to be ready for surgery with the face free of makeup and no products in the hair.

Although a feared complication, the actual incidence of surgical fires per year in the United States varies widely, depending on the report, and is not clearly defined. The Emergency Care Research Institute (ECRI), an independent nonprofit health service research agency, estimates between 550 and 650 surgical fires occur every year; an extremely small percentage of approximately 65 million annual surgical cases. Further, the ECRI reports that a high percentage of these surgical fires occur in the airway (34%) and head or face (28%)[79,80] A report from TJC gives the incidence of OR fires at 20 to 30 per year.[81] A report from 1984 that examined the complications associated with several thousand CO_2 laser surgeries reports the incidence of airway fires at 0.14%.[82] Even higher (and older) estimates on the incidence of ETT fires during laser procedures of the airway are 0.5% to 1.5%.[83,84] Surgical fire represents the most common major complication of endoscopic airway laser surgery and may result from direct or indirect laser beam contact with the ETT.[85] Smoldering particles of tissue from the surgical site can ignite an ETT.[86] In an otolaryngologic survey published in 2011, during endoscopic airway and tracheal surgery, a laser was the ignition source in 26 of 27 fires, 15 of which involved the ignition of an ETT and 7 of which had the FiO_2 at 0.21.[76] A survey of otolaryngologists reported on 100 fires, with electrosurgery causing 59%, lasers causing 32%, and light cords causing the remaining 7%. Supplemental oxygen was involved in 81%; in 31% of these cases, the ETT caught fire.[87]

INSPIRED OXIDIZERS AND OPERATING ROOM FIRES

When laser use is planned, the concentration of inspired oxidizers must be considered. Ignition is facilitated and combustion is more intense in oxidizer-enriched environments, which occurs with the use of either oxygen or N_2O. The risk associated with N_2O might not be readily apparent. In its resting state, N_2O has no free oxygen. An oxygen analyzer will reflect the dilution of oxygen by N_2O (with a lowered FiO_2) when the two gases are used together. However, N_2O easily exothermically dissociates, releasing heat and free oxygen. The fire risk of an oxygen and N_2O mixture should be considered equivalent to administering 100% oxygen. In an updated 2013 ASA Practice Advisory for the Prevention and Management of Operating Room Fires, the majority of the ASA taskforce members "…strongly agree that the use of nitrous oxide (N_2O) should be avoided in settings that are considered high risk for fire."[35]

Materials that resist ignition at a low FiO_2 may vigorously combust with an added oxidizer. As the temperature of the environment increases, the required FiO_2 needed to support combustion decreases. Flaming combustion can occur at warm conditions in oxygen concentrations as low as 14% to 16% (National Fire Protection Agency 921 Guide for Fire and Explosion Investigations 1998). The 2013 ASA practice advisory does not give a maximum allowable FiO_2 for procedures at high risk for fire but states that it should be "kept as low as clinically feasible…" to "…avoid hypoxia." Few clinicians would agree to allow laser use in the presence of an FiO_2 level greater than 0.4, or 0.5, which is considered dangerous in in vitro studies.[88] Most want the FiO_2 under 0.3 in high-risk fire settings. A 2013 analysis of the ASA Closed Claims database, which dates back to 1985, found that laser fires during general anesthesia occurred with inspired oxygen concentrations greater than 30%.[89] Analyses such as this one are used to establish *best practice* approaches to patient care.[90] As a consequence, many institutions have enacted policies mandating the use of safer ETTs and an FiO_2 below 30% for all intraoral surgeries with a provision to use an ignition source.[91] When available, diluting 100% oxygen with helium offers a small advantage over an air-nitrogen mixture attributable to its higher thermal conductivity that can delay the ignition of an ETT for a few seconds.[92,93] The index of flammability is reduced by only 1% to 2%.[94] Additionally, helium's lower density reduces the Reynolds number,* transition to turbulent flow, and thus increased resistance to flow, allowing the use of a smaller ETT.[95,96] Finally, reducing inspired FiO_2 does not protect from an increased airway oxygen concentration until expired concentration also decreases, which can take several minutes when low fresh gas flows are used.[97]

MONITORED ANESTHESIA CARE AND OPERATING ROOM FIRES

Surgical fire is the second most common injury that results in liability during monitored anesthesia care.[98] Oxygen-enriched environments are usually present in OR fires during anesthesia for upper body surgeries, which creates an exceedingly high-risk setting for fire because all three essential elements—ignition source, fuel, and oxidizers—are in close proximity.[99] Accordingly, in 2009, the ECRI and the Anesthesia Patient Safety Foundation (APSF) came out in support of guidelines for the use of oxygen administration during upper body surgeries.[80] Suggested for these procedures is the use of only nonoxygen-enriched air for any open delivery of gas via facemask or nasal cannula to the face when an ignition source will be present. If the spontaneously breathing patient,

*The Reynolds number is a dimensionless ratio of inertial and viscous forces, predicting the steadiness of fluid flow.

sedated or not, needs supplemental oxygen to maintain an acceptable oxygen blood saturation, then the airway should be secured with an ETT or laryngeal mask airway (LMA).[100] A theoretical concern is that supplemental oxygen, which is heavier than air, will be trapped in the drapes and pool around the patient's face and upper body.[101]

If a general anesthetic must be avoided, then the goal for using supplemental oxygen should be to use the minimum concentration of oxygen judiciously to maintain acceptable blood oxygen saturation. Simply lowering the flow of 100% oxygen to an open delivery site will not allow for control of the delivered FiO_2. However, predelivery blending of oxygen with air will do so.[102] A venturi apparatus is an option.[103] The ECRI recommends options such as the use of an oxygen blender or the use of a three-gas anesthesia machine that has a common gas outlet.[80] To attach the facemask or the nasal cannula tubing to the breathing circuit, a 5-mm ETT connector is attached to the Y-piece of the circuit.[100] The implementation of an *open face* draping scheme should be considered to dissipate the collection of added oxygen lingering around the surgical site.[104]

GENERAL ANESTHESIA AND AIRWAY FIRES

When the surgical site is within or near the airway, coordination between the anesthesia and surgical teams is essential to consider the need for an ETT, which tube type to use, the oxygen enrichment plan, and mode of ventilation. If intubation is planned, then varied intubation options exist and include an assortment of available ETTs and jet ventilation catheters. A few oxygenation-ventilation strategies include ventilating through a cuffed or tightly fitting ETT, either continuously or intermittently using a ventilator with apnea during episodic removal of the ETT to allow unobstructed access to the surgical field. Either supraglottic or infraglottic catheter positioning may be selected for jet ventilation. In addition, the choice of anesthetic must be considered. There are series using sevoflurane and spontaneous ventilation[105]; however, volatile anesthetics are not reliably delivered to the patient if jet ventilation is required, and the vapors can pollute the OR. Finally, although the volatile anesthetics currently used in clinical practice are nonflammable and nonexplosive in clinically relevant concentrations,[106] when exposed to flame, they may pyrolyse to potentially toxic compounds.[107] As such, the ANSI Z136.3–2011 standard conservatively recommends not using volatile anesthetics during airway laser surgery.

ETT fires have their own set of elevated risks for the patient and require swift corrective measures. With the right conditions and if properly managed, an ignited ETT may cause little if any harm. However, catastrophic injury may occur.[108,109] If ignited and combustion breaches the ETT with its centrally flowing reservoir of oxidizer, a *blowtorch* scenario in the airway can occur (Fig. 88-7). The potential for far-reaching thermal injury to the pulmonary tract exists. In addition, products of complete and partial combustion including smoldering debris, particulate matter, toxic gases, and compounds may cause further insult.

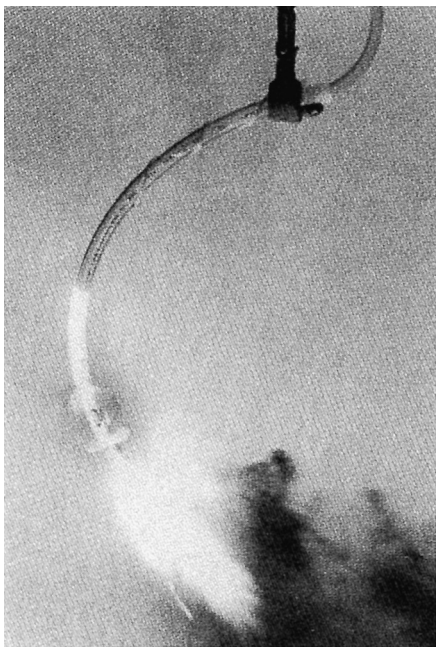


Figure 88-7. Blowtorch ignition of an endotracheal tube. *(No authors listed: Airway fires: reducing the risk during laser surgery,* Health Devices *19:109, 1990.)*

When using a laser near the airway, the updated 2013 ASA Practice Advisory strongly agrees that "laser resistant tracheal tubes [and catheters] should be used, and that the tube choice should be appropriate for the procedure and the laser…" If a cuffed tube is used, then the cuff should be filled with saline rather than air whenever feasible.[35] Methylene blue–dyed saline may help speed identification of cuff breaches.[110] Added protection from ignition may be achieved by using water-soaked sponges around the tube at the site of work and at the glottis. These sponges may seal leaks of oxygen around an ill-fitting ETT cuff, segregating the higher FiO_2 being delivered to the patient from the ambient air above the glottis and may protect the tube from laser strikes by adding a layer of water-saturated protection.

ENDOTRACHEAL TUBE COMPOSITION AND COMBUSTION-RELATED PROPERTIES

Standard polyvinyl chloride (PVC), red rubber, and silicone ETTs are candidates for use during laser procedures near the airway, but all are ignitable and require protective measures. Their dissimilar properties, reactions to various laser types, and by-products of combustion have been studied. Studies show that PVC easily absorbs far-infrared light and is vulnerable to CO_2 laser. Smith and colleagues[76] found a rapid (less than a 2-second) ignition of PVC ETTs exposed to 5 W CO_2 laser at 100% oxygen. Using a canine model, Ossoff and colleagues[111] studied CO_2 laser–ignited fires of PVC, red rubber, and silicone ETTs and found that all ignited into blowtorch scenarios in the setting of 1% halothane, 30% oxygen, and 70% N_2O. The effects of intraluminal fire on the larynx and trachea were assessed. Of the ETTs studied, the PVC type was not only the type that most readily ignited, but it

also deposited carbonaceous debris and caused the most severe burns and cellular damage. The PVC ETT also produces more toxic by-products of combustion, such as hydrochloric acid. The red rubber ETT was more ignition-resistant and produced less debris and tissue inflammation. Silicone ETTs took the longest exposure to ignite, but the finding of silica ash raised concern for possible remote development of silicosis. Other studies[82,112] have similar findings, except Ossoff[92] found red rubber ETTs were slower to ignite than silicone ETTs.

On the other hand, energy from Nd:YAG and visible laser light is not easily absorbed by clear PVC ETTs; however, if anything (e.g., blood, tissue, lettering on the ETT) disrupts the transparency, then energy will be absorbed at that point and will place the ETT at high risk for ignition. In a 1991 study, 1 minute of continuous exposure to an Nd:YAG laser at 70 W and 100% oxygen flowing produced no damage to the PVC ETT when aimed at the unmarked clear portion of a PVC ETT. However, when aimed at the ETT markings, ignition occurred at 2.6 seconds, and when aimed at blood or mucus, ignition occurred in less than 6 seconds.[113] This same research group and another demonstrated that none of the three commonly used ETT materials—PVC, red rubber, and silicone—are safe when exposed to Nd:YAG laser energies.[114,115]

LASER-RESISTANT ENDOTRACHEAL TUBE

Various strategies for the protection of ETTs from laser-strike damage have been evolving since the 1970s. Standard ETTs may be rendered more resistant to ignition by wrapping them with protective material, or the alternative is to use laser-resistant tracheal tubes (LRTTs), which are ETTs prefabricated with protective layering. In every case involving the use of lasers, the risk of airway fire must be considered and appropriate precautions taken if any appreciable chance of ignition is present.

The first ETT laser protection option was a do-it-yourself wrapping with laser-resistant materials. Flammable-resistant, smooth, and flexible tapes including aluminum and copper foil and metallic-coated plastic are typically used. These tapes are available through trade and craft stores and have proven to slow laser ignition.[116,117]

Although the practice of using metallic tapes to create LRTTs is well supported in the older medical literature, practitioners should realize that none of these products have FDA approval for this use. Practitioners opting to use the metal tapes to hand-wrap ETTs incur significant liability and patient safety risk. Even the one FDA-approved wrap, Merocel Laser-Guard Protective Wrap, is no longer marketed as a result of poor demand.

FDA-approved LRTTs are commercially available. These LRTTs vary in design and intended use. Some of these products are no longer on the market, including the Norton, Xomed Laser-Shield, and Bivona Fome-Cuff ETTs. The Xomed Laser-Shield was withdrawn from use after its involvement in three airway fires, one of which resulted in a death.[118] The Medtronic Laser-Shield II ETT (Medtronic ENT, Jacksonville, Fla) is a redesigned version of the Xomed tube. Some of the other currently available LRTTs include the Sheridan Laser-Trach (Hudson RCI/Teleflex/Medical, Research Triangle Park, NC), Rusch Lasertubus (Teleflex/Medical, Research Triangle Park, NC), and the Mallinckrodt Laser-Flex, now branded as the Covidien Laser Oral/Nasal Tracheal Tube Dual Cuffed Murphy Eye (Covidien, Mansfield, Mass).

The available LRTTs are made of metal or have a nonmetal tube core with a metallic overlay. The nonmetal core LRTTs are the following: (1) The Medtronic Laser-Shield II, which is intended for use with CO_2 and KTP lasers, is a silicone tube core wrapped with a flexible aluminum overlay topped by a fluoroplastic layer. It is a single-cuffed LRTT with dry methylene blue indicator in the unprotected silicone elastomer cuff. The covering is specified to withstand (in vitro) 35,000 W/cm^2 of CO_2 laser energy or 11,000 W/cm^2 of KTP energy for 3 minutes. In a laboratory test, a continuous laser beam at 20 W vaporized the fluoroplastic film, but the tube above the cuff did not perforate or ignite.[119] Blood on the surface of the tube did not result in ignition or burn-through, even when tested at increased beam power of 38 W.[120] (2) The Sheridan Laser-Trach, which is also intended for use with CO_2 and KTP lasers, is a red rubber tube core with a copper foil overlay. It has an unprotected single cuff. The tube above the cuff took 60 seconds to perforate when subjected to 40 W of continuous CO_2 laser, but it was readily ignited by a high-power Nd:YAG laser.[121] (3) The Rusch Lasertubus is intended for use with all medical laser types. It is has a central tube of flexible white rubber, "reinforced with corrugated copper foil and absorbent sponge" per product information provided by the manufacturer, Teleflex Medical, and has a dual cuff-inside-a-cuff system. Bench testing of this product by Teleflex Medical showed no damage to the tube integrity when exposed to a CO_2 laser at 20 W for 40 seconds. In independent testing, the area above the cuff withstood 90 seconds of a Nd:YAG laser set at 25 W and a CO_2 laser at 75 W.[122]

A metal LRTT is the Covidien Laser Oral/Nasal Tracheal Tube Dual Cuffed (Laser-Flex), and is intended for use with CO_2 and KTP lasers. It has an airtight flexible armored stainless steel shaft and two independent cuffs, positioned in series. It was shown that the shaft above the cuffs withstood 1 minute of a 69 W CO_2 laser. The shaft did not hold up to Nd:YAG laser at high power.[123] With the CO_2 laser set at 38 W, this tube ignited one out of four times when dry and had almost immediate combustion if blood was on the surface.

All LRTTs are merely *resistant* to laser damage. None, either metal wrapped or all metal, have protected shafts that are completely safe under all conditions, and all cuffed LRTTs have vulnerable cuffs and tips. LRTTs are no replacement for vigilant and thoughtful care by all present in the OR.

PROTECTION OF THE ENDOTRACHEAL CUFF

The thin pliable plastic or elastomeric envelope of the standard high-volume, low-pressure cuff found on ETTs and LRTTs is at risk for puncture from misdirected laser energy. If unrecognized, cuff punctures allow delivered gas, which is likely oxygen-enriched, to travel above the incompetent cuff and flood the surgical field, creating a high risk for an airway fire if using a laser. Other than the

Bivona Fome-Cuff, which is no longer available, no other cuffs remain inflated after puncture. If laser use near the airway is planned, then implementing cuff-protective strategies such as the following is essential: (1) Use saline to fill the cuff. A cuff puncture may extinguish a small fire. The updated 2013 ASA Practice Advisory notes that the majority of members and consultants strongly agree that "the tracheal cuff of the laser tube should be filled with saline rather than air, when feasible."[35] (2) Tint the saline in the cuff with methylene blue to act as an early marker of cuff puncture.[35] (3) Place the cuff as far away as possible (distal in the trachea) from the site of laser use. (4) Use moistened cotton pledgets or sponges to cover any exposed cuff. The usefulness of these practices in preventing or delaying cuff ignition from CO_2 laser exposure has been confirmed.[124,125]

JET VENTILATION

Optimal surgical conditions for procedures necessitating an unobstructed airway can be obtained with jet ventilation, which can occur from a supraglottic position (requiring no instrumentation of the airway) or through a flexible and small diameter jet ventilation catheter. In this mode of ventilation, Bernoulli's principle can explain the establishment of acceptable oxygenation and ventilation, despite the delivery of a relatively low volume of gas from the ventilator. Jet ventilation uses a high-pressure gas source to deliver a narrow high-velocity gas stream. This, in turn, creates a low-pressure microenvironment around the stream that causes the entrainment of surrounding gas. The entrained gas advances along with the primary gas stream, resulting in an additive effect and the delivery of a larger volume of gas to the patient. Concern about the potential absorption of carbon monoxide from the entrained laser plume by the patient during airway procedures prompted Goldhill and colleagues[126] to examine this possibility. They found no significant increase in carboxyhemoglobin during Nd:YAG bronchoscopy.

Jet ventilation, when used correctly and in accordance with safety precautions, has a low complication rate that includes the risk of barotrauma, pneumothorax, and crepitus. Concern existed over the potential for jet ventilation to cause distal bronchial seeding with active virus during laser resection of laryngeal papillomas. Shikowitz and associates[127] found no evidence of this in 96 patients who had multiple laser procedures. However, Cozine and colleagues in a multiinstitutional survey that examined 15,701 CO_2 laser airway surgeries found a higher rate of ventilatory complications with jet ventilation than with a standard ETT (Fig. 88-8), but the only fatality was caused by an ETT fire. The investigators concluded that no single mode of ventilation proved superior during laser surgery.[128]

During supraglottic jet ventilation, an intermittent gas stream is directed at the glottis through a small metal tube, such as a ventilating bronchoscope or even a 12-gauge blunt needle.[129,130] A retrospective review of 942 cases of microdirect laryngoscopy using endolaryngeal jet ventilation found only four complications.[127] Supraglottic jet ventilation has the advantage of using no flammable material in the airway during ventilation. However, oxygen-enriched air is free to flow back and enrich the air at the tissue targeted by the laser. Fires have been reported with this technique.[131]

A few catheter options exist for infraglottic ventilation. Rigid metal catheters that are nonflammable are available but cumbersome for the surgeon to work around. Nonmetal catheters used during laser procedures need to be appropriate. The Laser Jet catheter, made of polytetrafluoroethylene (Acutronic Medical Systems, Hirzel, Switzerland) and the Hunsaker Mon-Jet tube (product 7080100, Medtronic ENT, Jacksonville, Fla) are not flammable but can be deformed or punctured by CO_2 laser impact.[132]

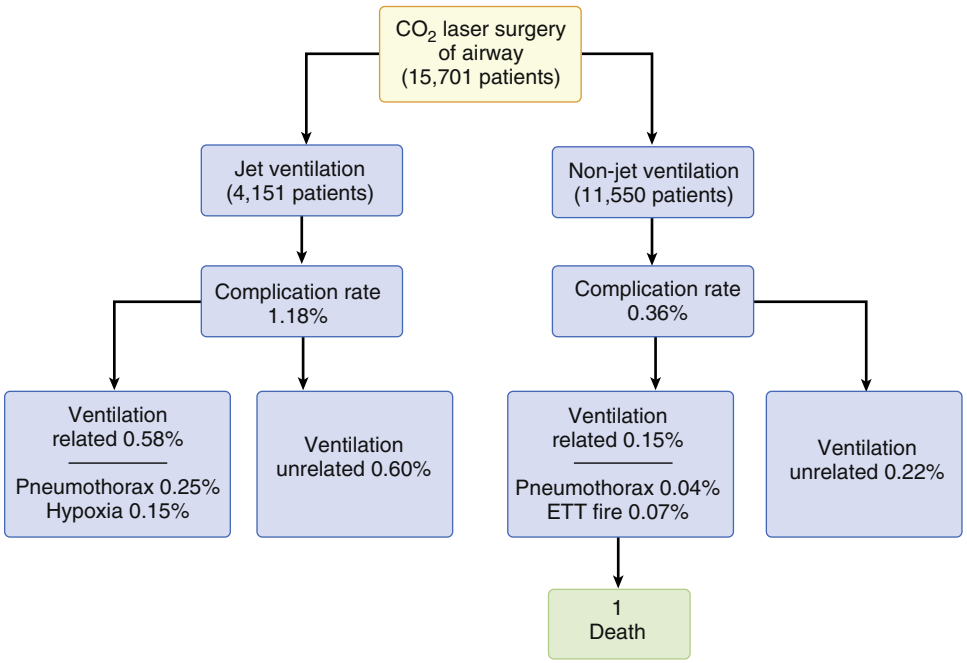


Figure 88-8. Complications of laser airway surgery. Pneumothorax was common with jet ventilation, but potentially lethal airway fires occurred with endotracheal intubation. *ETT,* Endotracheal tube. *(Data from Cozine K, Stone JG, Shulman S, et al: Ventilatory complications of carbon dioxide laser laryngeal surgery,* J Clin Anesth *3:20-25, 1991.)*

To further reduce obstruction of the surgical field by ventilatory appliances, perhaps all instrumentation could be removed by using spontaneous ventilation or intermittent apnea, with general anesthesia provided by nasal insufflation or bronchoscopic delivery of a volatile inhaled anesthetic[105,133] or an intravenous anesthetic.[100,134] Another common technique is modest hyperventilation, followed by intermittent tracheal extubation by the surgeon for periods of 90 to 120 seconds, during which time the laser is used.[135,136] Pulse oximetry adds a measure of safety by confirming adequate oxygenation from a denitrogenated pulmonary residual capacity during apnea.

OTHER CONSIDERATIONS

Although not specifically related to laser procedures in the airway, vagal hyperactivity often occurs during instrumentation of the trachea and during suspension laryngoscopy, in particular. Immediate recognition and treatment, which potentially includes the release from suspension and the intravenous administration of a vagolytic drug, are essential. Intense (deep) neuromuscular blockade is often a surgical need during laser on minute targeted areas in the airway. The paraneoplastic syndrome, occasionally observed with small cell and other types of endobronchial tumors, may lead to prolonged weakness after the administration of neuromuscular blocking drugs[137] (also see Chapters 52 and 53).

AIRWAY AND OTHER FIRES ON THE SURFACE OF THE PATIENT

In the event of a potential or actual OR fire, a timely and prompt response is imperative. Early warning signs of combustion need immediate communication to others in the OR and a full investigation. These signs may include suspicious odors, sounds, or visuals such as unexplained drape movements, flash, or discoloration of materials. If the patient is awake, then unanticipated complaints of discomfort or restlessness and moving on the table may be important signs. If a fire is detected, then the current ASA OR Fire Management Practice Advisory states that the event should be immediately announced, the procedure halted, and fire management tasks initiated.

The ASA OR Fire Management Practice Advisory and the ECRI have nearly identical algorithms for the essential steps of handling airway or other fires on the surgical patient[35,80] (see the ASA document for the complete Operating Room Fires Algorithm).[35] The essentials are provided:

Fire in the airway:

1. Remove the tracheal tube or breathing circuit fire. Hand it off to be extinguished and inspected.
2. Stop airway gas flow (consider disconnecting the circuit).
3. Remove all flammable and burning materials from the airway.
4. Pour saline or water into the patient's airway (to extinguish the fire and cool the tissues).

Nonairway fire:

1. Stop airway gas flow.
2. Remove drapes, flammable, or burning material from the patient.
3. Extinguish any burning items.

After the airway fire is extinguished:

1. Reestablish ventilation by mask. Avoid supplemental oxygen or N_2O, if possible.
2. Examine the ETT to evaluate whether fragments have been left in the airway. Consider bronchoscopy to assess injury and to remove foreign bodies.
3. Assess the patient's status, and devise a plan for ongoing care.[†]

After the nonairway fire is extiguished:

1. Assess the patient's status, and devise a plan for ongoing care.[†]
2. If not intubated, assess for smoke inhalation.

If the fire is not extinguished on the first attempt, then:

1. Use a CO_2 fire extinguisher.
2. If the fire persists, then:
   a. Activate the alarm system.
   b. Evacuate the patient, if feasible, and follow institutional protocol.
   c. Close the door to the OR.
   d. Shut off the medical gas supply to the OR.

[†] Assessment might include the involvement of other specialties. Perhaps a surgeon could perform a rigid bronchoscopy or bronchial lavage. Perhaps the trachea should be reintubated or a tracheotomy performed. A chest radiograph should be obtained. Pulmonary damage attributable to heat or smoke inhalation, or both, may necessitate prolonged tracheal intubation and mechanical-controlled ventilation. Humidification, bronchoscopy, and management of carbon monoxide or cyanide toxicity may be needed.[138] An expert consultation in burn management should be obtained to help evaluate and devise a plan for burns on the surface of the patient.

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Chapter 89

Ambulatory (Outpatient) Anesthesia

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Key Points

- The use of ambulatory surgery continues to increase, mostly as a result of less invasive surgery, improved patient selection and preparation, and an expansion in office-based practice.
- Few absolute contraindications exist to ambulatory surgery. Patients should not be excluded on the basis of arbitrary limits, such as age, body mass index, or American Society of Anesthesiologists physical status classification system.
- Effective preoperative assessment is required to evaluate and prepare patients and is essential for the delivery of safe, high-quality, and efficient ambulatory surgery.
- Many anesthetics and techniques can be used for ambulatory surgery. Of prime importance, experience and careful attention to detail are required to deliver high-quality rapid recovery with minimal side effects.
- Spinal anesthesia may extend the range of patients and procedures suitable for ambulatory surgery, but it requires the use of small doses of bupivacaine combined with opioids or short-acting local anesthetics to avoid prolonged recovery.
- Sedative techniques can facilitate a wide variety of procedures performed in the hospital, office, or remote settings. However, sedation is no safer than general anesthesia and requires the same standards of personnel, monitoring, and perioperative care as for patients undergoing general or regional anesthesia.
- Multimodal analgesia, using combinations of local or regional anesthesia, acetaminophen, and nonsteroidal antiinflammatory drugs, provide effective relief of pain. The reduced need for opioids decreases the incidence and intensity of adverse effects.
- Antiemetic prophylaxis should be based on individual patient risk. Multimodal regimens are required for patients and procedures known to be associated with increased risk for complications.
- Patients should be discharged with written information concerning aftercare, return to normal activities, follow-up evaluation, and a contact telephone number. This advice must include early warning signs and the appropriate action to take.
- Ambulatory surgery remains very popular with patients with infrequent rates of adverse events and complications. One important component of success in ambulatory surgery and anesthesia is minimal postoperative nausea and vomiting.

Ambulatory surgery has its origins in Glasgow, Scotland, where, between 1898 and 1908, James Henderson Nicoll performed almost 9000 ambulatory surgery procedures on children, nearly half of whom younger than 3 years of age.[1] Contrary to the prevailing philosophy, which advocated prolonged bed rest after surgery, Nicoll encouraged early mobilization and home follow-up by a visiting nurse to reduce high cross-infection rates and overcome bed shortages and financial constraints. A few years later, Ralph Milton Waters opened his Downtown Anesthesia Clinic in Sioux City, Iowa, allowing adult patients to return home within a few hours of difficult dental extractions, abscess drainage, or reduction of minor fractures.[2] Further progress was slow until the dangers of prolonged bed rest and the economic advantages of shorter stays began to be recognized toward the middle of the twentieth century. The first hospital-based ambulatory surgical units were opened in Grand Rapids, Michigan, in 1951 and in Los Angeles, California, in 1952, and somewhat later at London's Hammersmith Hospital in the United Kingdom in 1969.[3] At the same time, the first free-standing ambulatory surgery center opened in Phoenix, Arizona,[4] rapidly followed by many others across North America in the 1970s and 1980s.

The development of ambulatory anesthesia as a recognized subspecialty was enhanced by the formation of

the Society for Ambulatory Anesthesia (SAMBA) in 1984[5] and the British Association of Day Surgery in 1989. These and nine other national societies came together in 1995 to form the International Association for Ambulatory Surgery (IAAS), an umbrella organization dedicated to the worldwide promotion of ambulatory surgery.

Ambulatory surgery has expanded far beyond performing simple procedures on healthy patients. Currently, a broad range of major procedures are performed in patients who frequently have complex preexisting medical conditions. The availability of improved anesthetic and analgesic drugs minimizes the anesthetic side effects and facilitates the recovery process, as do the increasing availability of minimally invasive surgical techniques. Equally important has been a philosophical change that challenged outdated and conservative practices, demanding inpatient procedures. Ambulatory surgery now accounts for approximately 80% of the elective surgeries in the United States.[6] Ambulatory surgery also constitutes a large proportion of elective surgical activity in the United Kingdom and in many other countries, although rates for individual procedures still vary across countries in Europe.[7]

DEFINITIONS

Although ambulatory surgery is widely practiced, the precise definition can vary across countries and health care systems. For consistency, we have used the definition proposed by the cofounder of the IAAS: "A surgical day case is a patient who is admitted for investigation or operation on a planned non-resident basis and who none the less requires facilities for recovery. The whole procedure should not require an overnight stay in a hospital bed."[8] This definition requires the patient to be managed with the intention of same-day discharge from the outset, in addition to admission, operation, and discharge all occurring on the same calendar day. Including management intention in the definition ensures no incentive is provided to discharge a planned inpatient at short notice, who would be without all of the preparation and support that make ambulatory surgery such a high-quality form of care.

Short-stay surgery embraces all of the principles of ambulatory surgery and includes a postoperative overnight hospital stay. This may be because of significant comorbidities, lack of social support, or a procedure that is either too extensive or performed too late in the day to be compatible with same-day discharge. We have included short-stay surgery in this chapter because the objectives of minimizing physiologic disturbance to improve the quality of recovery and reduce the length of stay are the same as those of ambulatory surgery and much of the perioperative management is similar.

BENEFITS OF AMBULATORY SURGERY

The major incentive to perform more ambulatory surgery is the high quality of patient care it can achieve as a result of reduced tissue trauma, enhanced recovery with minimal adverse events, and the provision of effective postoperative analgesia, appropriate information, and postoperative support. Patients appreciate the more efficient scheduling of surgery, not requiring the availability of a hospital bed, and the comfort and convenience of recovering in the familiar home environment. Financial advantages exist to ambulatory surgery in eliminating the costs associated with overnight admission. In both the United States and the United Kingdom, procedures that are compatible with ambulatory surgery receive the same payment (from insurance companies and regional budget holders, respectively), irrespective of the length of stay. Therefore, if a patient does stay overnight, the extra costs are borne by the facility. In the United Kingdom, a few procedures currently attract a slightly higher level of funding when performed on an ambulatory basis,[9] to incentivize best practice and finance any necessary pathway redesign.

FACILITIES FOR AMBULATORY SURGERY

In the United States, the American Society of Anesthesiologists (ASA) provides guidelines on ambulatory surgical facilities,[10] including adherence to local regulations, staffing requirements, and minimum equipment standards. Quality standards are set and enforced by government regulation, licensing, or accreditation. In the United States and Canada, hospital-based ambulatory surgical facilities receive accreditation through The Joint Commission (TJC), Det Norske Veritas (DNV), and the Healthcare Facilities Accreditation Program (HFAP). Ambulatory surgery centers and office-based surgery locations can receive accreditation through the Accreditation Association for Ambulatory Health Care (AAAHC), American Association for Accreditation of Ambulatory Surgery Facilities (AAAASF), or TJC. In the United States, the Centers for Medicare & Medicaid Services (CMS) has its own inspection program in addition to accepting accreditation decisions from the listed organizations.

A multitude of designs exist for ambulatory surgical facilities. Some have been purpose designed, and others have evolved by adapting existing facilities. The facilities delivering ambulatory care services also vary by country, but they can be broadly categorized into four models of care, each with its own advantages and disadvantages.[11]

HOSPITAL INTEGRATED

The simplest model of ambulatory surgery is one with shared inpatient surgical facilities, but with separate areas for preoperative preparation and recovery of ambulatory patients. This model of care was previously regarded as inefficient and brings the risk for ambulatory procedures being delayed or even canceled in favor of more major inpatient procedures or emergency pressures. However, by dedicating certain operating sessions to ambulatory surgery and using strict protocols, efficiency can be almost equal to that of a self-contained unit.[12] The design is very flexible, allowing the proportions of ambulatory and inpatient surgery to vary from day to day,

and, as new procedures are transferred to ambulatory surgery, it does not require all the equipment and skills of the operating room to be duplicated in a separate facility. It is also relatively inexpensive to expand the size of the preoperative and postoperative areas as ambulatory surgery grows.

HOSPITAL SELF-CONTAINED

These self-contained units are functionally and structurally separate from inpatient facilities with their own reception, admission areas, operating rooms, recovery areas, and administrative facilities. This design ensures functional separation from urgent and emergency work, yet all the backup facilities of the main hospital are readily available nearby. In many ways it is an ideal model of care; however, the capacity for ambulatory surgery is finite, and an inevitable need exists for duplication of operating room equipment and skills for procedures that are still commonly performed on both an ambulatory and inpatient basis.

FREESTANDING

Freestanding ambulatory surgery centers ensure complete separation from inpatient and emergency work. This improves efficiency and allows complete focus on ambulatory care. There is a risk of not being able to manage perioperative complications safely, although the typically good patient selection and preparation minimize this potential problem. However, unless the unit has some capacity for overnight stays, any unanticipated admission will need transfer to a nearby hospital, which somewhat limits the complexity of the patients and procedures undertaken. Ambulatory surgery centers vary from highly specialized, single-surgery facilities to multispecialty generalists, with a wide range of sizes.

OFFICE-BASED

Performing ambulatory surgery, diagnostic procedures, or both in a facility associated with a physician's office is a rapidly expanding area of care within the United States.[6] The main advantages are increased convenience for the patient and surgeon and smaller total procedure costs. Office-based services are much less regulated than ambulatory surgery centers, and especially unless accredited, they may have more significant equipment, personnel, and environmental limitations with lower ability to manage perioperative complications.

PATIENT SELECTION CRITERIA

SURGICAL FACTORS

The development of minimally invasive surgery, improvements in surgical technique and pain control, and the availability of shorter-acting anesthetics have dramatically increased the range of surgical procedures compatible with same-day discharge. The duration of surgery is now relatively unimportant, with the extent of surgical trauma being the more significant determinant. There should be no expectation of continuing blood loss, large perioperative fluid shifts, or the need for complex or specialized postoperative care. Surgical complications remain the single greatest cause of unanticipated hospital admission,[13,14] but provided these are infrequent and can be detected before discharge, ambulatory surgery should still be the plan. When discharge on the day of surgery is not possible, many patients require a single night in the hospital, making even more procedures suitable for short-stay surgery. In the United States and the United Kingdom, an overnight stay for an ambulatory surgery procedure receives no additional payment, so the extra costs are borne by the facility. The British Association of Day Surgery publishes a directory of over 150 different surgical procedures and suggests aspirational targets for the proportions of each that are suitable for either ambulatory or short-stay surgery.[15] A selection of these are shown in Table 89-1.

TABLE 89-1 SELECTION OF SURGICAL PROCEDURES THAT CAN BE PERFORMED ON AN AMBULATORY BASIS

Specialty	Examples of Surgical Procedures
Breast surgery	Excision or biopsy, including wide local excision, sentinel node biopsy, simple mastectomy, microdochotomy, and other operations on nipple
General surgery	Perianal fistulae, pilonidal sinus, hemorrhoidectomy, open or laparoscopic hernia repair, laparoscopic cholecystectomy, adrenalectomy, splenectomy, fundoplication, and gastric banding
Gynecology	Cervical surgery, laparoscopic tubal ligation, oophorectomy, hysterectomy, female incontinence surgery, and anterior and posterior repair
Head and neck	Dental procedures, excision of salivary glands, thyroidectomy, and parathyroidectomy
Ophthalmology	Cataract surgery, strabismus surgery, vitrectomy, nasolacrimal and all eyelid surgery
Orthopedics	Diagnostic and therapeutic arthroscopic surgery, anterior cruciate ligament repair, carpal tunnel release, bunion surgery, fracture reductions and removal of metalwork, lumbar microdiscectomy, minimally invasive hip surgery, and unicompartmental knee surgery
Otolaryngology	Myringotomy and tympanoplasty, rhinoplasty, procedures on nasal septum and turbinates, polypectomy, adenotonsillectomy, laryngoscopy, and endoscopic sinus surgery
Urology	Endoscopic bladder and ureteric surgery, transurethral laser prostatectomy, circumcision, orchidectomy, laparoscopic nephrectomy, pyeloplasty, and prostatectomy
Vascular surgery	Varicose vein surgery, dialysis fistula creation, and transluminal arterial surgery

Laparoscopic cholecystectomy is now a routine ambulatory surgical procedure in many countries, and increasingly same day discharge is seen as safe and beneficial with the use of many more advanced laparoscopic procedures, including fundoplication,[16] hysterectomy,[17] nephrectomy,[18] pyeloplasty,[19] and gastric banding.[20] Even complex procedures traditionally associated with a prolonged period of hospitalization have been performed on a short-stay basis, with some patients discharged the same day, including those undergoing awake craniotomy for tumor resection[21,22] and minimally invasive hip arthroplasty.[23] One series of 2000 patients undergoing laparoscopic Roux-en-Y gastric bypass for morbid obesity reported 84% being discharged within 23 hours, with a readmission rate of less than 2%[24] (see also Chapter 71). Patients undergoing less invasive procedures, such as diagnostic or therapeutic hysteroscopy, are leaving ambulatory surgery into the procedure room, outpatient clinic, or office. [25]

Postoperative pain and the ability to control it in the home environment is a major challenge for outpatient surgery. Discussed later in this chapter, high-volume local infiltration analgesia (LIA)[26] and the use of home delivery of local anesthetics through wound catheters[27] are helping to extend the boundaries.

Perhaps the greatest barrier to the development of ambulatory surgery is conservatism, based on an incorrect concern about serious complications that might occur after discharge. For example, despite convincing data that most primary hemorrhages are evident within 6 to 8 hours of tonsillectomy,[28,29] an overnight stay is still routine in some countries whereas others discharge 80% of patients or more on the day of surgery.[7] Similarly, ambulatory thyroid surgery was first shown to be safe and effective in 1986,[30] yet its widespread adoption has been slow,[31] predominantly because of concerns about bleeding and airway compromise. Such complications are rare, especially when surgery is undertaken by specialists who perform a high volume of cases, allowing short times to discharge to be achieved.[32] Performing thyroidectomy under local anesthesia also appears to increase ambulatory surgery rates,[33] perhaps because of the careful surgical technique required. In the case of breast surgery, concerns about postoperative psychological support has delayed transfer of mastectomy and other cancer operations into ambulatory care, although it is now recognized that early discharge improves the psychological well-being of these patients by minimizing the time away from home.[34] Challenging conventional wisdom also may be beneficial; for example, discontinuing the routine use of drains after mastectomy or axillary node clearance results in no significant increase in morbidity, including from wound seroma, while facilitating same-day discharge.[35]

MEDICAL FACTORS

In the past, ambulatory surgery has relied on relatively rigid patient selection criteria in the attempt to limit the occurrence of postoperative complications. In practice, however, most of these criteria predict the occurrence of treatable perioperative adverse events, but not the need for unanticipated admission or readmission.[36] Although an index combining age, length of surgery, and preexisting conditions, such as peripheral or cerebrovascular disease, can identify a group at higher risk for hospital admission, the specificity is poor and same-day discharge is still the most likely outcome.[37] Ambulatory surgery is very safe, with a perioperative mortality of less than 1 in 11,000,[38] better than that in the general population. The safety of ambulatory surgery continues to be excellent despite increasing surgical and patient complexity.[39-41]

Relatively few absolute contraindications now exist to ambulatory surgery. Patient suitability should be assessed on the basis of overall health, taking into account both the risks and benefits of early discharge, and certainly not determined by arbitrary limits, such as age, body mass index (BMI), or ASA physical status.[42] Chronic conditions should be relatively stable and must be optimally treated before any elective procedure, irrespective of the planned postoperative management. Many stable chronic diseases, such as diabetes, asthma, or epilepsy, are often better managed by patients, and ambulatory surgery facilitates this by easing the disruption to their daily routine.[42] A distinction should be made between preexisting conditions that will make a patient more difficult to manage on the day of surgery and those that increase the occurrence of late postoperative problems, thereby acting as a relative contraindication to ambulatory surgery.[43]

A good example is obesity, which is associated with numerous perioperative problems for the surgeon, anesthesiologist, and operating room personnel (see also Chapter 71). These may require the availability of experienced staff and specialized equipment, such as longer instruments and wider operating trolleys for safe care, but any risks are resolved soon after immediate recovery and are not prevented by overnight hospitalization. Obese patients benefit from ambulatory management with early mobilization, the use of short-acting drugs, and avoidance of opioid analgesia.[43] Obesity does not increase the rate of unanticipated admission, postoperative complications, readmission, or other unplanned contact with health professionals after discharge.[44] Even morbid obesity (BMI > 40 kg/m^2) is no longer considered an absolute contraindication to same-day discharge.[42] Obesity increases the likelihood of further comorbidities, but these should be evaluated in their own right.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) occurs in the general population but is much more common in obesity. Nonetheless, most cases can be managed safely and effectively on an ambulatory basis.[45] Perioperative problems, such as difficult endotracheal intubation and airway obstruction, should be anticipated.[46] However, patients undergoing more invasive surgery, especially involving the chest or airway, or those requiring large doses of perioperative opioids may be less suitable.[45] Difficulty may arise when OSA is suspected but has not yet been definitively diagnosed and treated. A simple questionnaire, supplemented with some basic measurements (e.g., STOP-Bang), can identify most patients at high risk for OSA,[47] who should then have the diagnosis confirmed and treatment instituted before surgery. In children, OSA is now one of the main indications for tonsillectomy and this has been seen as

a relative contraindication to ambulatory surgery. However, one recent study has shown that same-day discharge is still safe in the absence of other comorbidities.[48]

Age

Medical and social problems increase with age and should be evaluated and managed individually rather than applying an arbitrary upper age limit for ambulatory surgery (see also Chapters 80 and 93). The risk for death or readmission within 7 days of surgery in patients over 65 years of age are 41 per 100,000 and 2.53%, respectively.[49] Although somewhat more frequent than values from younger patients, the major risk factors appear to be very advanced age (older than 85 years of age), more invasive surgery, and recent inpatient hospital care.[49] The frequency of perioperative adverse cardiovascular events also increases with age. Overall, older patients had a twofold increase in the risk for intraoperative adverse cardiovascular events; however, this was seen not as a contraindication to ambulatory surgery but rather as indicating the need for more careful intraoperative management.[50] In contrast, the incidence of postoperative complications seems to be reduced in older patients.[50,51] In particular, older patients appear to experience far less postoperative pain, dizziness, nausea, and vomiting than younger patients[50, 52] and do not require a higher rate of unplanned admission or readmission. One study suggests a reduced incidence of postoperative cognitive dysfunction in older patients after ambulatory surgery compared to similar procedures performed on an inpatient basis,[53] presumably because of the use of short-acting anesthetic techniques and reduced separation from their familiar home environment.

At the other age extreme, the lower limit for ambulatory surgery may vary depending on the expertise and specialization of the individual institution. Premature babies have a higher risk for postoperative apnea, and hence ambulatory surgery may be inadvisable until they have reached an appropriate postconceptual age (PCA). Evaluation of several historic and retrospective studies suggests the risk for postoperative apnea is less than 5% once PCA exceeds 48 weeks, provided gestational age was at least 35 weeks, the infant was not anemic, and no apnea occurred in the recovery room.[54] However, because considerable variability exists in the incidence of apnea and the relatively small sample size of these studies, the postconceptual age at which risk becomes acceptably low is controversial,[55] with a value of 60 weeks most commonly taken as the cutoff for ambulatory management.[56,57] Caffeine administration appears to markedly reduce the incidence of postoperative apnea in babies who were premature,[58] but this is not seen as a substitute for careful patient selection.[56] Spinal anesthesia may offer advantages to infants who were premature undergoing abdominal surgery in the first week of life, but it is distressing to the infant and has a high (28%) failure rate.[59] Compared with older studies involving more soluble anesthetics, sevoflurane and desflurane were associated with lower rates of postoperative apnea after hernia surgery in infants born at less than 37 weeks gestation and under 47 weeks PCA.[60] Although no airway interventions were required to manage apnea, episodes still occurred throughout the 12-hour postoperative observation period and were equally common with either anesthetic.[60]

Cardiovascular Disease

Hypertension is the most common cardiovascular disease and has been a frequent cause for delay and cancellation of ambulatory surgery. Although hypertension is an important risk factor for long-term health, a meta-analysis of nearly 13,000 patients showed that it increased the risk for perioperative complications by only 1.35 times,[61] an amount that may be clinically insignificant. In ambulatory surgery patients, hypertension resulted in an approximate 2.5-fold increase in the risk for perioperative cardiovascular events,[51] but these were relatively minor. Hypertension is not an independent risk factor for perioperative cardiovascular complications if the diastolic pressure is less than 110 mm Hg.[62] Higher arterial blood pressures may predispose to perioperative ischemia, arrhythmias, and cardiovascular lability, but no clear evidence indicates that deferring surgery reduces perioperative risk. In the United Kingdom, surgery should not be canceled solely on the basis of increased arterial blood pressure.[61] In practice, poorly controlled hypertension is usually identified at the preoperative evaluation and can be treated before surgery is scheduled. Delaying surgery until hypertension is controlled is unlikely to be beneficial.[63]

Patients with known hypertension should continue to take their chronic medication, especially if these include β-adrenergic blockers. Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists are sometimes withheld on the morning of surgery to prevent hypotension after induction of anesthesia.[64] Yet a transient and moderate decrease in arterial blood pressure will respond well to intravenously administered fluids and vasopressors. As β-adrenergic blockers should not be abruptly stopped,[65] patients may become less confused if they are advised to take all of their cardiac medications up to and including the day of surgery.[66]

Patients are generally unsuitable for ambulatory surgery if they have severe unstable angina that causes marked limitation of activity or pain at rest. In the absence of complications, such as arrhythmias or ventricular dysfunction, cardiac risk is not decreased beyond 3 months after myocardial infarction or revascularization procedures.[67] Exercise tolerance is a major determinant of perioperative risk[67] and the inability to climb a flight of stairs (~4 metabolic equivalent tasks [METs] of activity) is highly predictive (89%) of a postoperative cardiopulmonary complication.[68]

Patients taking anticoagulants and antiplatelet drugs require careful evaluation to balance the risk for perioperative bleeding against the risk in withholding therapy. For minimally invasive procedures, the international normalized ratio can be briefly decreased to the low or subtherapeutic range, with the usual dose of oral anticoagulation resumed immediately after the procedure.[65] If the risk for bleeding or thromboembolism is high, low-molecular-weight heparin can be used as bridging therapy.[69] Antiplatelet therapy should be continued for the recommended intervals in patients with bare metal and drug-eluting coronary artery stents, because premature

discontinuation is associated with a 25% to 30% risk for stent occlusion, which in turn has a more than 60% risk for myocardial infarction and 20% to 45% risk for death.[70]

SOCIAL FACTORS

In general, if a patient's living arrangements were adequate before surgery, they should also be suitable after surgery. Some adaptations may be necessary if the patient's mobility is severely compromised by their procedure—for example, by the use of casts. Access to a telephone to summon assistance is a minimum requirement, but is rarely problematic with the ubiquitous availability of mobile telephones. Patients usually live within a reasonable traveling distance of the surgical unit, but this may be impractical in rural or sparsely populated areas. Journeys of hundreds or thousands of miles are not unheard of in parts of Scandinavia after ambulatory surgery.[43] For patients who live far away, consideration should be given to the provision of emergency care close to home and for the comfort of the patient during the journey. Patients who choose to travel long distances after ambulatory surgery usually are very satisfied with their care.[71] Hospital hotels, which provide nearby accommodation but little or no nursing care, are a higher-cost alternative for the patient and have largely been abandoned as an impractical option.

A universal safety feature is to require all patients having surgery under general anesthesia or sedation to be discharged with a responsible adult escort and to have someone stay with them for the next 24 hours. If the 24-hour companion is mandated, patients often disregard postoperative instructions and send their escorts away if they feel well at home.[72] In the United States, it is standard practice to require that patients who have received other than unsupplemented local anesthesia be discharged with a responsible adult[10]; if not, surgery is postponed. A Canadian single-institution study reported discharging patients alone when their escort fails to arrive,[73] yet this practice did not appear to increase emergency room visits or readmission rates within 30 days. The Association of Anaesthetists of Great Britain and Ireland has suggested that an escort may be required in most (but not all) cases,[42] with exceptions when the surgery is relatively minor and anesthesia brief so the patient is not compromised by the sedative effects of anesthesia or analgesia by the time of discharge.[43] If patients are discharged alone, they should not drive themselves home[74]; several serious accidents have occurred, especially after the use of sedative doses of benzodiazepines.

PREOPERATIVE ASSESSMENT

THE ROLE OF PREOPERATIVE ASSESSMENT

An effective preoperative assessment process is essential for the delivery of safe, high-quality, and efficient ambulatory surgery.[63] Rather than trying to select specific, low-risk groups of patients, ambulatory surgery is increasingly seen as the default option for a wide range of surgical procedures, with inpatient care chosen only for those with insurmountable barriers to early discharge. Other than identifying this small group of patients, preoperative assessment is primarily required to evaluate and optimize patients and to provide appropriate information (Table 89-2). These assessment and optimization functions can be further distilled into two key questions: "Is there any benefit to this patient of being in hospital overnight after surgery?" and "Is there anything that needs to be done to enable this patient to be a day case?"[63]

MECHANISMS AND TIMING OF PREOPERATIVE ASSESSMENT

The timing of preoperative assessment is crucial, because it must be done early enough in the pathway to allow for any necessary investigations and optimization without delaying the planned procedure. This becomes increasingly difficult as the interval between the decision to operate and the date of surgery becomes shorter. Ideally, preoperative assessment should immediately follow the decision to operate, by providing a "one-stop shop." This type of service, in which preoperative assessment immediately follows the surgical consultation, is highly valued by patients,[75] although it can be difficult to manage because of variations in the demand for the service. An alternative is to use a basic screening tool to identify those patients who can proceed directly to surgery and those who require further investigation or management (Fig. 89-1).

A case can be made for all patients to be seen in a preoperative assessment clinic; however, in practice this places

TABLE 89-2 **THE FOUR KEY FUNCTIONS OF A PREOPERATIVE ASSESSMENT AND PREPARATION SERVICE FOR AMBULATORY SURGERY**

Function	Examples
1. Identify absolute contraindications to ambulatory surgery	Inability to identify a responsible caregiver other than for minor surgery with full and rapid recovery anticipated; severe uncorrectable cardiovascular disease
2. Identify need for optimization	Patient requires further investigation, therapeutic modification, or intervention to improve functional status; identify a friend, relative or neighbor to act as caregiver
3. Highlight issues for anesthesiologist or other staff (which may alter management but do not preclude ambulatory surgery)	Potentially difficult intubation necessitating advanced airway management skills; malignant hyperpyrexia–susceptible patient requiring trigger-free anesthetic; latex allergy; obese patient requiring operating table/trolley with high weight limit and extra width
4. Provide patient information	Written information on preoperative preparation, medication management, preoperative fasting, etc.

a major demand on resources and is also inconvenient for patients who may need to take additional time off work. Screening allows many patients to undergo assessment by telephone or questionnaire, with clinic attendance required only if unexpected problems are uncovered or if requested by the patient. When telephone assessment was chosen for all young healthy patients scheduled for minor breast surgery, only 2% of patients had problems identified that required further assessment in the ambulatory surgery center.[76] By using a computerized information gathering and triage tool, combined with some basic information about the planned procedure, approximately one third of ambulatory patients did not need to see an anesthesiologist before the day of surgery.[77] This approach eliminates the need for a face-to-face assessment before the day of surgery but does not eliminate an evaluation of the patient's medical information in advance of surgery. In contrast, advance face-to-face preoperative assessment is more advisable for older patients, in whom multiple comorbidities, polypharmacy, and social problems are all more likely.[78] Early discharge planning is also important for older patients, to address environmental issues that can be improved to support recovery.[79]

In the United Kingdom, preoperative assessment is usually performed by nurses working closely to protocols and supported by anesthesiologists who provide advice and personally assess the more complex patients.[80] In the United States, anesthesiologist-led, protocol-driven preoperative assessment is often used for healthy patients having minor procedures. However, these preoperative evaluation clinics are frequently used in U.S. hospitals, not just for ambulatory patients with more complex medical or surgical issues but also for the majority of the inpatient surgery that is admitted on the morning of surgery. More complex patients have their anesthesia preassessment performed by an anesthesiologist. A comprehensive preoperative history and physical evaluation by a nurse practitioner is often also provided in the preoperative assessment clinic for the surgeon. Using a nurse practitioner to assist in preoperative evaluation maintains patient safety and satisfaction, frees valuable resources, and increases staff satisfaction.[81] Appropriately trained nurses were just as effective as trainee medical staff in detecting information likely to influence subsequent patient management, but they ordered significantly fewer unnecessary tests.[82]

Patients generally rate their preoperative assessment clinic experience very favorably, with their greatest concerns relating to waiting times.[83] Scheduling appointments of approximately twice as long for patients of ASA physical status grades III and IV than for those of grades I and II reduced backlogs and reduced maximum waiting times for preoperative assessment to an acceptable level of about 10 minutes.[84]

PREOPERATIVE INVESTIGATION

The history and physical examination remain key elements of preoperative risk assessment, despite the availability of more sophisticated technologies.[67] In fact, most

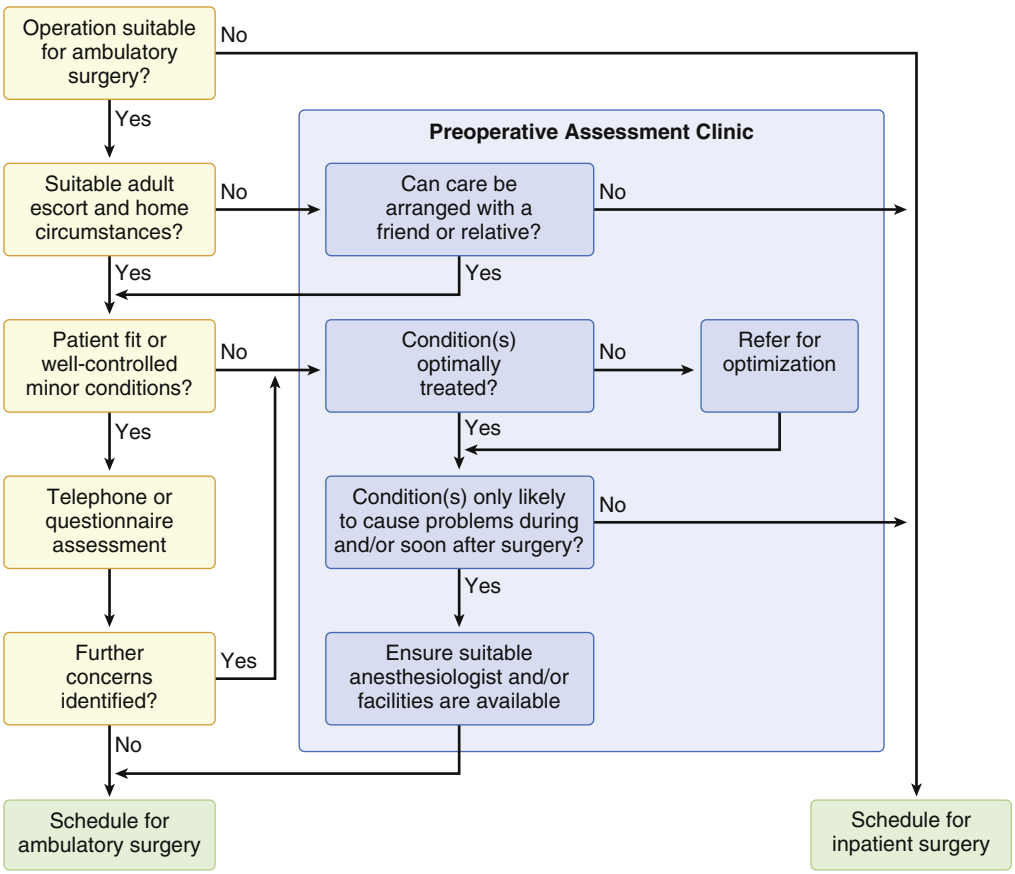


Figure 89-1. Flowchart illustrating the basic process for selecting patients for ambulatory surgery. The pathway incorporates a screening process for patients who may not require a full face-to-face assessment in the clinic. (Modified from Smith I, Hammond C: Day case surgery. In Radford M, Williamson A, Evans C, editors: *Preoperative assessment and perioperative management,* Cumbria, Calif, 2011, M&K Books, with permission.)

useful information can be obtained from the history, supplemented by simple observation of the patient.[85] Basic physical examination, such as routine chest auscultation, is often considered unhelpful in adult ambulatory surgery patients,[63,86] because findings that are unaccompanied by symptoms or functional limitation do not alter management. Although aortic stenosis may remain asymptomatic until it is quite severe, chest auscultation may be unreliable in its detection. In one high-risk population, 31% of patients without a detectable murmur nevertheless had some degree of aortic stenosis that was moderate or severe in 10% of cases,[87] whereas 31% of patients with a suggestive murmur did not have aortic stenosis on echocardiography. Ten patients with severe aortic stenosis (valve area 1 cm^2 or less, gradient 35 to 58 mm Hg) tolerated an unmodified anesthesia regimen for electroconvulsive therapy on 144 occasions without problems,[88] suggesting that ambulatory surgical patients with undiagnosed aortic stenosis may not inevitably be at excessive risk, when combined with appropriate procedure selection.

It is recognized that routine laboratory investigations are unhelpful because they mainly generate false-positive results or do not alter subsequent management.[89] In addition, such tests increase costs, are unpleasant and time-consuming for patients, and may lead to repeat testing with even further expense and delays. Consequently, many authorities recommend more selective testing, based on indications from the patient's clinical evaluation and demographics.[90,91]

Because comorbidities become more prevalent with age, more preoperative testing may be advocated for older patients.[91] However, even this may be excessively conservative. In patients 70 years of age or older, routine preoperative blood test results were not predictive of postoperative complications.[92] Although preoperative eletrocardiograms (ECGs) of patients over 50 years of age detected abnormalities, such as bundle branch blocks, predictive of postoperative myocardial infarction, the recordings did not provide additional predictive value to that obtained from the patient history.[93] One large pilot study demonstrated that the elimination of all preoperative testing resulted in no increase in adverse events in the perioperative period and did not alter the rate of unanticipated admission or readmission within 30 days compared to indicated testing.[94]

PATIENT PREPARATION

Preoperative assessment plays a fundamental role in preparing patients for their ambulatory surgery experience. This may include ensuring appropriate social support is in place, checking that preexisting conditions are optimally treated, and providing information.

PROVISION OF INFORMATION

Patients need to be informed about what will happen on the day of surgery, because a well-prepared patient is likely to be more relaxed and more satisfied with the service provided.[63] A well-informed patient is also more likely to comply with important instructions and protocols, such as fasting intervals and management of regular medications. Many patients are disproportionately worried about highly unlikely outcomes, such as death and awareness,[95] yet somewhat less concerned about more common consequences such as nausea, vomiting, and postoperative discomfort. The preoperative discussion should be able to allay the anxiety associated with unlikely risks. It was found that a specially designed website with text, animation, and video significantly increased patients' knowledge about anesthesia when compared with a combination of verbal and written information.[96]

Patients should be given specific information, preferably supplemented in writing, about how to manage their usual medications in the preoperative period. Some drugs (e.g., warfarin) should be stopped several days before surgery[69] and some hypoglycemic agents omitted before surgery.[97] However, other important medications should not be omitted.[66,70]

Information about medications should include over-the-counter and herbal products, which are commonly used but often regarded by patients as harmless and safe.[98] Despite some serious consequences and interactions associated with herbal medications,[99] not all practices specifically ask and advise patients about these products on a routine basis[100] (see also Chapter 40).

PREOPERATIVE FASTING

Almost universal agreement now exists that the safe fasting interval for clear liquids is no more than 2 hours, in contrast to 6 hours for light meals (see also Chapter 38).[101,102] These fasting intervals result in safe gastric volumes even in obese adults,[103] children,[104] and patients with diabetes and gastrointestinal (GI) reflux.[102] Indeed, a 2-hour interval is probably conservative, given that the stomach empties clear fluids exponentially, with a half-time of approximately 10 minutes.[105]

Despite guidelines based on decades of research, implementation remains poor, with many patients fasting for excessive periods and experiencing significant discomfort.[106,107] Rather than focusing on a minimum fasting time, patients should be encouraged to keep drinking until the latest time necessary for safety to reduce preoperative dehydration and its associated consequences.[102] In practice, this may mean asking patients to have a drink just before they leave home or even providing a drink on arrival if surgery is still more than 2 hours away. Advising patients to drink on the morning of surgery also makes it easier for them to take their medications. Practices such as chewing gum before surgery also may not be as harmful as previously suspected. No evidence exists of a clinically important increase in gastric volume associated with gum chewing in adults,[102] although in children it may promote gastric emptying and could also serve as a useful route for premedication[108] (see also Chapters 92 to 95 in the section on pediatric anesthesia).

Besides feelings of thirst and hunger, excessive fasting also results in hypoglycemia in significant numbers of patients, with 14% of fasted healthy female ambulatory surgical patients having an admission blood glucose value of 45 mg/dL (2.5 mmol/L) or less.[109] Preoperative oral carbohydrates have been shown to improve subjective

well-being, reduce thirst and hunger, and reduce postoperative insulin resistance, although convincing evidence of reduced length of stay is lacking.[102]

PREMEDICATION

Premedication traditionally refers to the administration of medications to relieve anxiety before surgery. However, the term encompasses any medication given in the preoperative period and therefore includes prophylactic analgesia and antiemesis agents, as well as drugs used to promote gastric emptying or counteract acid secretions.

Management of Anxiety

The use of anxiolytic premedication is now uncommon in ambulatory anesthesia,[110,111] probably because of concerns that these medications will delay recovery. In fact, a recently updated meta-analysis found no evidence that anxiolytic premedication delayed the discharge of ambulatory patients, although impaired performance in some tests of psychomotor function was found and the authors questioned the relevance of some of the older studies to modern ambulatory practice now that short-acting anesthetics are the norm.[112]

Anxiety is nevertheless common in ambulatory surgery patients,[110] with up to two thirds showing symptoms. A preoperative visit by an anesthesia provider reduces preoperative anxiety, but only if conducted immediately before surgery, rather than in the ambulatory surgery unit or in a preoperative clinic.[113] This finding must be treated with caution, however, because anxiety was high in all groups from this atypical population, with high stress levels and little of the usual perioperative family support.[113] Other studies have shown that a preoperative consultation more than 2 weeks before surgery can reduce patient anxiety and improve satisfaction, especially if the anesthesiologist was perceived as empathic.[114] Patient satisfaction was further improved when their intraoperative care was provided by the same anesthesiologist who performed the preoperative consultation.[114]

Anxiolytic Premedication

Given the high levels of reported anxiety, doubtless some patients will benefit from anxiolytic premedication, but what is the optimal regimen? Oral midazolam provided more anxiolysis than temazepam but also produced more sedation and amnesia, resulted in more oversedated patients, and delayed recovery.[115] Oral alprazolam produced comparable anxiety reduction to midazolam without causing amnesia,[116] but it also caused greater impairment of psychomotor function in the early postoperative period. Neither premedication delayed clinical recovery, but this may be a relatively crude assessment tool, because recovery primarily depends on other factors. Intravenous (IV) midazolam given shortly before induction of anesthesia reduced both anxiety and postoperative nausea.[117] Yet such relatively late administration will not reduce anxiety while the patient waits preoperatively and is more akin to a coinduction technique, which will be considered later. Intravenously administered midazolam may be useful in a patient who needs to have an uncomfortable procedure before surgery, such as mammographic needle localization, in which satisfaction with both the procedure and subsequent breast biopsy was improved.[118]

Anxiolytic premedication may have other possible advantages. Oral midazolam reduced preinduction of anesthesia heart rate and arterial blood pressure and also reduced the propofol dose required for induction of anesthesia[119]; however, the perception of anxiety was not reduced. Intramuscular midazolam improved self-reported postoperative psychological and pain recovery,[120] whereas oral diazepam reduced urinary catecholamine and cortisol levels in ambulatory surgical patients.[121] The clinical significance of these findings is unclear.

Premedication is more commonly used in children (see also Chapter 93). Premedication with oral midazolam 0.2 mg/kg reduced emergence agitation associated with sevoflurane anesthesia without significant delay in recovery,[122] and even a dose of 0.5 mg/kg does not delay recovery.[123] However, other patients have experienced delayed recovery at this dose[124,125] while not always having a reduction in anxiety.[125] Premedication with oral midazolam may itself provoke anxiety in children, but giving the child a small toy to play with first was effective in reducing this anxiety.[126] Unfortunately, the effect of the toy as an alternative to midazolam was not evaluated. Play therapy and distraction can be powerful tools in preventing anxiety in children, although achieving an adequate effect may require quite an elaborate approach. When two professional performing artists dressed as clowns entertained children during the preinduction period, using a variety of techniques including magic tricks, gags, music, games, puppets, word games, and soap bubbles, preoperative anxiety was reduced far more than could be achieved by midazolam premedication or the presence of a parent.[127] A preoperative educational program portrayed as a "Saturday morning club" also reduced anxiety,[128] although the authors questioned whether the benefits achieved were worth the time and resources required. A simpler and highly effective approach is to allow children to watch age-appropriate video clips or movies during anesthetic induction with IV (South Korea) or inhaled (Canada) techniques.[129,130]

Because of variable efficacy and the potential for delayed recovery, alternatives to benzodiazepine premedication have been sought. In children, oral transmucosal fentanyl reduced preoperative anxiety and postoperative agitation, but a high incidence of predictable side effects, such as postoperative nausea and vomiting (PONV) and delayed discharge, limited its usefulness.[131] Selective α_2-adrenergic agonists have potentially useful sedative and analgesic effects, yet despite years of study they still have no clearly defined role in ambulatory surgery in which their advantages outweigh the risks for adverse events.[132] Clonidine is commonly used in pediatric practice, particularly to reduce agitation during emergence,[133] but the promising results of clinical trials do not always translate well into routine clinical practice and its effects on induction anxiety are less persuasive.[134]

Analgesic Premedication

Ambulatory patients are commonly premedicated with prophylactic oral analgesia in the expectation of achieving analgesic levels in the early postoperative period. Because

the duration of action of acetaminophen (paracetamol) is relatively short (4 to 6 hours), it is unlikely to provide worthwhile postoperative analgesia, other than for an extremely short procedure. When patients received oral acetaminophen 1 g an hour before arthroscopic knee surgery, barely a third had plasma levels in the therapeutic analgesic range 30 minutes after arriving in recovery, whereas therapeutic levels were consistently achieved with intraoperative IV administration.[135]

The nonsteroidal antiinflammatory drugs (NSAIDs) are consistently more effective as analgesic premedicants. Some evidence indicates that NSAIDs have a small preemptive analgesic effect (i.e., they achieve a superior effect if given before rather than after surgery),[136,137] although one of the studies most strongly supporting this conclusion has recently been called into question.[138] Preoperative parecoxib followed by postoperative valdecoxib significantly reduced the opioid analgesic requirements and the incidence of opioid-related adverse effects after laparoscopic cholecystectomy.[139] As well as providing effective postoperative analgesia, etoricoxib premedication had an anesthetic-sparing effect during ambulatory ankle surgery.[140] Using a common dental model of postoperative pain, preoperative ibuprofen, diclofenac, and acetaminophen with codeine effectively controlled early postoperative pain.[141] Similarly, rofecoxib and ketorolac were equally effective in controlling postoperative pain after ambulatory surgery,[142] as were ibuprofen and ketorolac.[143] Sustained-release preparations of NSAIDs improve convenience by allowing earlier preoperative administration and a prolonged postoperative effect. Modified-release ibuprofen 1.6 g delayed the time until rescue analgesia was required after ambulatory third molar surgery in contrast to standard ibuprofen.[144]

Selective cyclooxygenase-2 (COX-2) inhibitors are no more effective and offer few advantages over traditional NSAIDs in ambulatory surgery, although they may be preferred by surgeons. Despite any inhibition of platelet function, the amount of blood loss seen during high-risk surgery, such as tonsillectomy, was not reduced in comparison to nonselective NSAIDs.[145,146] Attempts to limit GI adverse effects, which are rare in acute use, has introduced other side effects and led to some drugs being withdrawn.[147] Selective COX-2 inhibitors may be better tolerated in patients with aspirin-sensitive asthma.[148]

Several other drugs have been evaluated for premedication. Controlled-release oxycodone did not improve pain scores or reduce opioid requirements within 24 hours of ambulatory gynecologic laparoscopic surgery.[149] In combination with ibuprofen, pregabalin 150 mg reduced median pain scores at rest and in motion after gynecologic laparoscopic surgery, but did not reduce postoperative analgesic requirements.[150] Perioperative administration of pregabalin 75 mg provided short-lived pain reduction after laparoscopic cholecystectomy, and a meta-analysis confirmed limited analgesic benefit, no reduction in opioid side effects, and increased sedation from its use.[151] Even less effective was pretreatment with magnesium sulfate 4 g, which had no impact on postoperative pain or analgesic consumption in patients undergoing ambulatory ilioinguinal hernia repair or varicose vein surgery.[152]

Prophylactic Antiemetics

Patients at moderate-to-frequent risk for PONV should receive prophylactic antiemetics, which may be given after induction of anesthesia or as premedication, depending on the specific drug (see also Chapter 97). Preoperative steroids can provide both analgesic and antiemetic prophylaxis. Premedication with dexamethasone improved the quality of recovery with reduced nausea, pain, and postoperative opioid consumption and better return to normal activities after ambulatory gynecologic laparoscopic surgery,[153] but to achieve all these benefits required a dose of 0.1 mg/kg rather than the much less effective 0.05 mg/kg. For adults, this is approximately 8 mg of dexamethasone, which improved quality of recovery through reduced nausea, pain, and fatigue after ambulatory laparoscopic cholecystectomy.[154] The long-term side effect profile of this dose of dexamethasone has not yet been evaluated.

Antacid and Gastrokinetic Premedication

The incidence of aspiration of gastric contents is infrequent in fasted elective surgical patients. Despite improvements in several surrogate measures, insufficient evidence exists of clinical benefit (i.e., a reduction in morbidity or mortality from aspiration) to recommend the routine use of antacids, metoclopramide, H_2-receptor antagonists, or proton pump inhibitors before elective ambulatory surgery.[101,102] Patients who are receiving these medications chronically should take them before surgery. Patients who regularly suffer from significant acid reflux in the fasted state will also benefit from the head-up tilt position during induction of anesthesia. This approach also may be useful in the super-morbidly obese patient undergoing bariatric surgery, in whom the use of prophylactic proton pump inhibitors and sodium citrate may be considered.[46]

ANESTHETIC TECHNIQUES

CHOICE OF TECHNIQUE

Ambulatory surgery requires the same basic standards as inpatient surgery in terms of facilities, staffing, and provision of equipment for delivery of anesthetic drugs, monitoring, and resuscitation. Quality, safety, efficiency, and the cost of drugs and equipment are all important considerations in choosing an anesthetic technique for ambulatory surgery. The choice of specific anesthetic drugs or techniques should enable appropriate and controllable intraoperative conditions followed by rapid recovery with minimal side effects and a prompt return to normal psychomotor activity. Achieving these aims also requires careful attention to the details of analgesia, antiemesis, and fluid management and requires experienced staff to deliver a high-quality, efficient, and cost-effective service.

No single ideal anesthetic drug or technique for ambulatory surgery exists, and the choice depends on both surgical and patient factors. General anesthesia commonly remains the most popular technique with both patients and surgeons, in some cases despite clear benefits of local or regional anesthetic techniques.[155] Spinal anesthesia can be useful for lower extremity and perineal procedures,

but must be modified for use in the ambulatory setting by the use of low-dose techniques[156,157] or short-acting drugs[158] to prevent delays in discharge because of residual motor or sympathetic block. Infiltration of local anesthesia, peripheral nerve blocks, or both facilitate the recovery process by reducing postoperative pain and minimizing the need for opioid analgesics after general anesthesia and should be used whenever possible. Many ambulatory procedures also can be performed using local anesthetic techniques, supplemented, if necessary, with sedatives, or analgesic drugs, or both.

GENERAL ANESTHESIA

General anesthesia remains a popular choice with patients, surgeons, and anesthesia providers. Induction of general anesthesia is typically achieved with a rapid and short-acting IV anesthetic, although inhaled induction is often used in children and needle-phobic adults. IV drugs are also popular for maintenance of anesthesia, especially where the availability of target controlled infusion (TCI) systems simplifies delivery,[159] but the use of short-acting inhaled anesthetics, with or without nitrous oxide, is more common. No single anesthetic technique is clearly superior for ambulatory surgery. Other factors, such as the experience of the anesthesiologist, the use of adjuvant drugs, and the art of anesthesia, are still important to deliver the best quality care.[160]

INTRAVENOUS ANESTHESIA

Methohexital is occasionally used to induce anesthesia for ambulatory surgery in the United States, especially when propofol is in short supply, but is possibly no longer available in the United Kingdom. Thiopental results in prolonged postoperative sedation, especially after repeat administration for maintenance of anesthesia, and has little or no role in ambulatory anesthesia. The same applies to benzodiazepines and ketamine when used at the doses needed to induce general anesthesia. Etomidate is associated with myoclonus, pain on injection, and a high incidence of PONV. Although reformulation in a lipid solvent can reduce some of these disadvantages,[161] persisting concerns about suppression of adrenal steroidogenesis[162] have curtailed its use. The search for new and improved IV anesthetic drugs continues, with several promising compounds under evaluation.[163,164] However, for now, propofol remains the most practical IV anesthetic for ambulatory anesthesia.

Propofol

Propofol has many of the properties of an ideal anesthetic induction drug and is popular because it rapidly and smoothly induces anesthesia without airway irritation and results in a rapid recovery with an infrequent incidence of PONV[165] and a clear head. Propofol does have some disadvantages, however, including pain on injection, involuntary movements, transient apnea, and hypotension after induction of anesthesia. Numerous strategies have been proposed to reduce pain on injection, of which the most effective are the use of a large antecubital vein or pretreatment with lidocaine in conjunction with venous occlusion.[166] Alternative preparations of propofol, such as those containing bisulfite[167] or comprising medium- and long-chain triglycerides,[168,169] have had a modest or negligible effect in reducing injection pain, whereas some formulations significantly increase pain.[170] The addition of lidocaine remains more effective at reducing pain than the choice of propofol formulation.[171]

Some of the adverse effects of propofol can be minimized by reducing the propofol dose by coinduction with adjuvant drugs, the most common being midazolam. Pretreatment with midazolam 0.1 mg/kg allowed anesthesia to be induced with a decreased propofol dose and also attenuated the resultant hemodynamic changes.[172] A substantial decrease in the propofol dose can be achieved even when midazolam is administered up to 10 minutes before induction of anesthesia, a technique that also can make the induction experience for the patient more pleasant.[173] However, this approach may delay recovery. Midazolam 0.03 mg/kg, halved the required propofol dose but significantly impaired psychomotor recovery, even though awakening times were not delayed.[174] Coinduction with short-acting opioids, such as alfentanil, can improve the quality of induction and ease of laryngeal mask airway (LMA) insertion, but at the expense of an increased incidence of hypotension and prolonged apnea.[175] Similarly, fentanyl reduced propofol dose and improved conditions for LMA insertion, but also prolonged respiratory depression.[176] Furthermore, the use of 1 μg/kg[177] or fixed doses of 75[178] to 100 μg[179] of perioperative fentanyl increase the incidence of PONV. Giving an initial bolus of 30 mg of propofol reduced the total propofol induction dose to a degree similar to that achieved by 2 mg of midazolam.[180] This technique, which has been termed propofol autocoinduction,[181] can reduce propofol dose and hypotension to a degree comparable to that with midazolam pretreatment but without delaying recovery.

The pharmacokinetics of propofol allow it to be used as a variable rate infusion to maintain anesthesia, either in association with N_2O or combined with alfentanil or remifentanil as total intravenous anesthesia (TIVA). Recovery after anesthesia maintained with propofol is typically no faster compared to volatile anesthetics after an induction dose of propofol,[165] and initial awakening may be delayed compared to that with the shorter-acting inhaled anethetics.[189] These differences in emergence times are no more than 2 to 3 minutes[182] and so not of clinical significance. Recovery to home readiness may occur up to 15 minutes sooner after propofol than isoflurane but is no faster than sevoflurane or desflurane.[182] One consistent feature of propofol anesthesia is a less frequent incidence of PONV in contrast to the use of inhaled anesthetics.[165,182,183] However, even this benefit has been described as of doubtful clinical relevance, except when the baseline incidence of PONV is very frequent.[183] The reduction in PONV achieved by TIVA, specifically the use of propofol and the omission of N_2O, was similar to that produced by the use of single-drug antiemetic prophylaxis.[184]

Delivery of propofol is increasingly performed by TCI, which is commercially available in most countries except the United States.[159] In contrast to manual infusions, TCI makes the delivery of propofol easier, with

fewer interventions required by the anesthesiologist.[185] However, it does not improve the quality of anesthesia, shorten recovery time, or reduce adverse events[185,186]; although the quality of trials performed to date is poor, TCI systems calculate the predicted plasma propofol concentration and considerable variation exists between this and the actual measured value.[186] Further sources of error are introduced when the effect site, rather than the plasma concentration, is targeted.[187] Currently two different pharmacokinetic models are in commercial use, both derived from healthy subjects. The choice of model may make relatively little difference in the young, fit patient, but performance differs considerably in older patients[187] and neither model is reliable in the morbidly obese.[187,188]

INHALED ANESTHETICS

Volatile anesthetics remain the most popular choice for the maintenance of ambulatory anesthesia because of their ease of administration, controllability, and rapid emergence. Halothane and enflurane are now of historical interest only, and use of isoflurane has declined considerably as less-soluble, shorter-acting drugs have become available.

Sevoflurane

The low solubility and minimal airway irritation of sevoflurane make it a readily controllable, short-acting anesthetic for ambulatory surgery.[189] In contrast to isoflurane, sevoflurane resulted in significantly earlier awakening and orientation, caused less postoperative drowsiness, and facilitated earlier discharge by an average of 25 minutes.[182] Compared to propofol, orientation occurred earlier but the time to home readiness was similar.[182] The lack of airway irritation with sevoflurane means that rapid increases in inspired concentration are well tolerated,[190] facilitating control of anesthetic depth. This is in contrast to the cough reflex[191] and transient increases in heart rate and blood pressure, which sudden changes in isoflurane or desflurane concentration may provoke.[192]

Lack of airway irritation makes sevoflurane almost ideal for inhaled induction, which may be especially desirable in children and needle-phobic adults.[189] An 8% bolus induction of sevoflurane in adult patients can be faster than with propofol, with a similar rate of different side effects.[193] Sevoflurane induction also caused significantly less depression of mean arterial pressure than propofol in older patients and was equally as well accepted as an induction choice.[194] Using sevoflurane for volatile induction and maintenance of anesthesia (VIMA) has several benefits for ambulatory patients, but is associated with a greater incidence of PONV than when propofol is used for induction, maintenance, or both of anesthesia.[189] This appears to be in part due to coadministered opioids, which are rarely needed with VIMA, because omitting the opioids minimizes the problem.[177,193,195] In children, the rapid emergence from sevoflurane (and desflurane) anesthesia is associated with a high incidence of emergence delirium, especially if inadequate measures are in place to control postoperative pain.[196] Numerous strategies have been evaluated to reduce emergence delirium. Midazolam premedication is ineffective, but supplemental use of fentanyl 1 μg/kg, propofol, ketamine, and α_2-adrenergic agonists all reduce agitation to some degree.[133] Although emergence delirium is undesirable, it is not associated with any long-term consequences and does not delay recovery room discharge.[197]

Desflurane

With its low blood solubility, desflurane should be an ideal anesthetic for ambulatory anesthesia. However, meta-analysis of 25 randomized studies showed that patients receiving desflurane followed commands, had their trachea extubated, and were oriented only 1.0 to 1.2 minutes earlier than those receiving sevoflurane for up to 3.1 hours.[198] No differences were found in recovery room stay[199] or incidence of PONV.[198] Concerns about the more frequent incidence of airway irritation with desflurane may limit the rapidity with which anesthetic depth can be altered,[192] although relatively few problems were encountered in patients spontaneously breathing desflurane through an LMA when coadministered with fentanyl.[200,201] Although desflurane has lower fat solubility than sevoflurane, the rate of diffusion into the fat compartment is extremely slow with either inhaled anesthetic; therefore, lower fat solubility does not make the case for use of desflurane as the ideal agent for morbidly obese patients unless procedure length is very long. In practice, some studies of ambulatory surgery in the morbidly obese have found more rapid recovery after desflurane than sevoflurane,[202] whereas others found emergence and recovery to be similar with either drug.[203]

ANESTHETIC ADJUVANTS

Some adjuvant drugs are frequently administered to supplement the effects of general anesthesia and in an effort to reduce adverse effects.

Nitrous Oxide

Although N_2O is by far the oldest anesthetic drug still in use, its role is regularly questioned. N_2O is weakly emetogenic, yet its omission only significantly decreases vomiting when the baseline incidence is high and has no effect on nausea or the complete control of PONV.[204] This may be because the alternatives, specifically a higher inhaled anesthetic concentration or the use of supplemental opioids, also induce PONV. In addition, the risk for awareness resulting from the omission of N_2O is of a magnitude similar to any reduction in PONV,[204] somewhat reducing the usefulness of this strategy. N_2O retains a place in modern ambulatory anesthesia because its use improves the quality and safety of induction of anesthesia, facilitates faster recovery, and reduces overall costs.[205]

Opioid Analgesics

The indiscriminate use of opioid analgesics should be discouraged in ambulatory surgery to avoid PONV and unplanned admission.[206,207] Although long-lasting drugs such as morphine are especially detrimental, even the ultra–short-acting opioid remifentanil resulted in a 35% incidence of PONV when used with desflurane and multimodal prophylaxis, compared with only 4% when all opioids were avoided.[208] For minor to intermediate

ambulatory surgery procedures, the routine administration of as little as 1 μg/kg of fentanyl serves only to increase the incidence of PONV,[209] and its omission does not worsen postoperative pain, provided prophylactic analgesia is ensured with local anesthetic infiltration and preoperative NSAIDs.[177] However, small doses of fentanyl may be useful to provide additional analgesia toward the end of more painful procedures.

Opioids are an essential component of TIVA, but the antiemetic effect of propofol minimizes the incidence of PONV in contrast to the use of the same opioid with inhaled anesthetics.[210] Compared to alfentanil, remifentanil provides more effective suppression of intraoperative responses without prolonging awakening.[211]

Nonopioid Analgesia

For longer or more invasive procedures, IV acetaminophen given toward the end of surgery also can have a beneficial effect,[135,212] comparable to that of the opioid tramadol.[213] In a laboratory pain model using volunteers, the analgesic effect of acetaminophen was inhibited by commonly used 5-HT_3 antiemetic drugs, such as ondansetron and tropisetron.[214] However, a more recent study confirmed that no discernible interactions occurred under typical clinical conditions of use.[215] For shorter procedures, acetaminophen can be given orally before the anesthetic, at much lower cost.

Cardiovascular Drugs

Although intraoperative hemodynamic disturbances are usually managed by increasing the primary anesthetic concentration, administering an opioid analgesic, or both, it may be more appropriate to treat these responses with cardiovascular drugs. Using an infusion of esmolol as an alternative to alfentanil to control heart rate reduced emergence times after arthroscopy,[216] and substituting esmolol for remifentanil reduced nausea after gynecologic laparoscopy.[208] Using a combination of esmolol and nicardipine to blunt increases in heart rate and arterial blood pressure, respectively, prevented the need for increases in inspired anesthetic concentration and consequently shortened emergence and recovery times.[217] Ambulatory patients who received esmolol intraoperatively for hemodynamic control also had significantly smaller requirements for postoperative opioid analgesia.[217,218] Administration of a continuous infusion of esmolol during laparoscopic gynecologic surgery reduced sevoflurane consumption by 18%, shortened recovery room stay, reduced postoperative pain scores, and reduced fentanyl requirements.[219] In a similar study, an esmolol infusion decreased intraoperative remifentanil requirements and again resulted in lower postoperative pain scores and halved the dose of rescue fentanyl.[220] Labetalol may be a cost-effective alternative to esmolol for longer cases, especially in older patients, in whom it is less likely to cause inadvertent hypotension.[221]

Neuromuscular Blocking Drugs

Neuromuscular blocking drugs (NMBDs) may be used in ambulatory anesthesia to facilitate endotracheal intubation or to provide profound surgical relaxation (see also Chapter 34). Although several of the available compounds are suitable, muscle pain after administration of succinylcholine and concerns about residual neuromuscular block from intermediate-duration NMBDs after brief procedures have fueled the search for alternatives. The search for a nondepolarizing equivalent to succinylcholine has been unsuccessful. The most promising candidate to date, rapacuronium, was withdrawn from clinical use because of a frequent incidence of severe bronchospasm, although other factors such as inconvenient administration, declining use of endotracheal intubation, and large costs also contributed to its lack of commercial success.[222] The search for a rapid-onset, short-acting nondepolarizing NMBD continues with investigation of several fumarate compounds, which can be antagonized by L-cysteine.[223]

An alternative to short-acting NMBDs is terminating the neuromuscular blockade with sugammadex, which can rapidly and completely reverse rocuronium (or vecuronium) independent of the degree of residual neuromuscular block[224] (see also Chapter 35). Sugammadex is used in multiple countries outside the United States, but it is very expensive compared to neostigmine. Currently no reliable evaluations have been done on the cost-effectiveness of sugammadex in routine clinical practice. Although improved recovery times resulting from the elimination of residual neuromuscular block by sugammadex may potentially be cost-effective, this depends on the productivity of staff during the time saved and would probably require major changes to the workflow for actual benefits to be realized.[224]

Endotracheal intubation also can be achieved without the use of NMBDs, thereby avoiding all of their adverse effects. This practice is most common in children, for procedures in which airway protection is required but not prolonged muscle relaxation (see also Chapter 93). The optimum technique depends on personal experience and preference, but most commonly involves deep sevoflurane anesthesia[225] or propofol supplemented by remifentanil or alfentanil.[226] For adults, a dose of remifentanil 3 μg/kg with propofol 2 mg/kg is recommended,[227] but satisfactory conditions can be obtained with remifentanil 2 μg/kg, thereby reducing the side effects of bradycardia and hypotension.

AIRWAY MANAGEMENT

Many ambulatory surgical patients can be managed with an LMA, which results in a significantly less frequent incidence of sore throat, hoarseness, coughing, and laryngospasm compared to inserting a tracheal tube.[228] The LMA can occasionally cause pressure trauma to a variety of cranial nerves, in particular the recurrent laryngeal nerve, whereas hoarseness and vocal cord injuries are common after the use of endotracheal intubation during short-term anesthesia.[229] The LMA is relatively easy to insert with patients in the prone position,[230] making it a simple way of managing procedures such as pilonidal sinus repair or surgery to the short saphenous vein. Patients undergoing minor-to-intermediate surgery using a TIVA technique may sometimes receive oxygen through a simple Hudson-type mask (Fig. 89-2),[207] but most patients require a more secure form of airway such as an LMA.

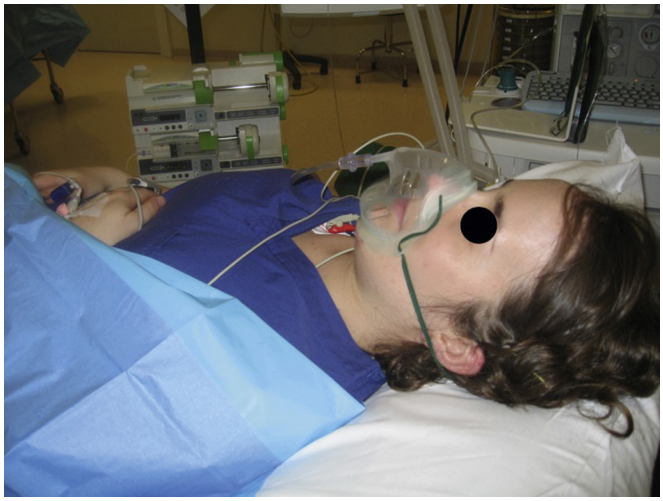


Figure 89-2. Patient receiving total intravenous anesthesia spontaneously breathing oxygen through a Hudson mask. (From Stocker ME, Philip BK: Adult general anaesthesia. In Smith I, McWhinnie D, Jackson I, editors: *Oxford specialist handbook of day surgery,* London, 2011, Oxford University Press, p. 63, with permission.)

Traditionally, endotracheal intubation has been advocated for laparoscopic procedures and surgery in obese patients, but further development of the LMA and more confidence in its use may be changing this. The ProSeal LMA (LMA, San Diego, Calif) has been modified to provide increased seal pressure, reduce gastric inflation, provide for gastric drainage, and, therefore, allow potentially better protection against aspiration of gastric contents while maintaining similar insertion characteristics.[231] At least one large consecutive series by an experienced user appears to support these benefits in routine clinical practice, without the constraints of a clinical trial.[232] During laparoscopic cholecystectomy, the ProSeal LMA provided adequate pulmonary ventilation without gastric distention in nonobese patients, although it was somewhat less effective than endotracheal intubation in the obese.[233] A useful clinical benefit is considerably smoother emergence with significantly less coughing. Use of the LMA for laparoscopic cholecystectomy remains controversial,[234] however, until the true incidence of regurgitation and the ability of the ProSeal LMA to protect against aspiration is better established.

Provided safety can be ensured, avoiding endotracheal intubation by using the ProSeal LMA for laparoscopic surgery appears to offer considerable advantages. In laparoscopic gynecologic procedures, the ProSeal LMA was associated with lower pain scores at 2 and 6 hours, with reduced analgesic requirements and less nausea at the same assessment points.[235] Similarly, in females undergoing gynecologic laparoscopic or breast surgery, it reduced the absolute risk for PONV by 40% and also reduced sore throats, analgesic requirements, and recovery room stay.[236] During laparoscopic gastric banding, the ProSeal LMA reduced the intraoperative stress response and also shortened recovery room stay and hospital discharge.[237]

Since the LMA patents expired, many manufacturers have introduced similar designs, but often using different materials to produce a low-cost disposable product. Often little or no data are available on the effectiveness or safety of these generic products.[238] Furthermore, the success of the LMA led to the development of many new supraglottic airways of myriad designs. Some of these may offer advantages in ambulatory surgery,[239] although little or no comparative data exist with the LMA. The manufacturers of new airways are currently able to market these without comparative trial data being available, because most of the regulatory requirements relate to manufacturing process and quality control, rather than efficacy and safety in clinical use.[240] Where comparative trials or case series do exist, they often lack power to provide a reliable estimate of the device's failure rate.[241] Comparative studies in children are even less common.[242] Anesthesiologists should therefore be wary of the claims made for new airway devices until they have been adequately evaluated.[243]

REGIONAL ANESTHESIA

Spinal Anesthesia

The use of spinal anesthesia makes ambulatory surgery accessible to some patients for whom the risks of general anesthesia are excessive (see also Chapters 56 and 57). It also increases patient choice, allows participation in intraoperative decision making (e.g., in sports injuries), and provides beneficial postoperative analgesia. Various ambulatory surgical procedures, such as prostatectomy, female incontinence surgery, and ankle and foot surgery, are well suited to spinal anesthesia.

The profuse availability of fine-gauge, pencil-point spinal needles has reduced the incidence of significant postdural puncture headache to 0.5% to 1%.[244,245] The main challenge now is to prevent prolonged motor block or impairment of joint position sense from delaying discharge. Although lidocaine has an appropriate duration for ambulatory surgery, its use in spinal anesthesia has virtually ceased as a result of a high incidence of transient neurologic syndrome (TNS).[246] Until recently, bupivacaine was the most obvious alternative, being devoid of TNS, but causing unacceptable delays in home discharge if used in standard doses.

For its acceptance in ambulatory surgery, bupivacaine spinal anesthesia needs to be "modified."[247] Reducing the dose of bupivacaine shortens recovery, whereas the use of patient positioning or the addition of adjuvants, such as fentanyl, ensures adequate analgesia for surgery. These techniques can be summarized as selective spinal anesthesia (SSA), defined as "the practice of employing minimal doses of intrathecal agents so that only the nerve roots supplying a specific area and only the modalities that require to be anaesthetised are affected."[248] SSA provides analgesia suitable for surgery, and light touch, temperature, proprioception, motor, and sympathetic function are all preserved.[248] This results in remarkable cardiovascular stability but can make the block difficult to test, and patient cooperation is important to the success of this technique.

A variety of SAA regimens have been described,[157] which typically permit discharge within a little over 3 hours after surgery.[249] The addition of fentanyl marginally delays

recovery and is associated with pruritus[249] (although most cases do not require treatment), but also reduces postoperative pain and analgesic requirements.[250] For unilateral knee arthroscopy, 4 to 5 mg of hyperbaric bupivacaine appears to be sufficient without adjuvants, provided the patient is kept in the lateral position.[250] Clonidine has also been used to supplement low-dose spinal anesthesia, but it may prolong motor block, exacerbate hypotension, and delay voiding.[132]

Spinal anesthesia may contribute to postoperative urinary retention. This is uncommon in low-risk patients, but may be more likely in older patients, with certain procedures and when more than 7 mg of bupivacaine is used.[247] The risk for urinary retention is particularly high after inguinal hernia surgery,[251] but simple infiltration anesthesia is often sufficient for this procedure and may be a more appropriate choice.[155,252]

New Drugs for Ambulatory Spinal Anesthesia

With the increasing popularity of ambulatory spinal anesthesia, some older local anesthetics have been reevaluated and, in some countries, marketed for spinal use. Of these, prilocaine, procaine, articaine, and 2-chloroprocaine appear the most promising, with mepivacaine largely discounted because of a high incidence of TNS.[158] Hyperbaric prilocaine has a faster onset and shorter duration than the plain preparation, with patients receiving 40 mg of 2% hyperbaric prilocaine being home ready in 208 ± 68 minutes.[253] This is comparable to discharge times reported with low-dose bupivacaine plus fentanyl,[249] although 13% of the patients receiving hyperbaric prilocaine required supplementation for inadequate analgesia toward the end of surgery, which was scheduled to last for less than an hour.[253] The duration of 2-chloroprocaine is even shorter, with recovery being significantly faster than that of low-dose bupivacaine[254] or articaine[158] and comparable to that of lidocaine.[255] Indeed, some have questioned whether the duration may be too short, especially where teaching and other logistical factors prevent surgery being undertaken in a predictably rapid time.[256]

Ambulatory spinal anesthesia that relies on short-acting local anesthetics should be compared with the cardiovascular stability of SSA. Prilocaine 20 mg combined with 20 μg fentanyl was associated with a lower incidence of clinically significant hypotension compared with bupivacaine 7.5 mg with fentanyl 20 μg.[257] The dose of bupivacaine and the dose of fentanyl used in both groups was somewhat higher than usual, however, and this is also the lowest dose of prilocaine to be successfully used in spinal anesthesia to date.[158]

Epidural Anesthesia

Epidural analgesia is seldom used in adult ambulatory anesthesia (see also Chapter 56). Although it allows the block duration to be extended by using a catheter technique, this is offset by the time required in establishing the block and less certainty of success, as well as the risk for inadvertent intravascular injection or dural puncture. In knee arthroscopy, recovery after 15 to 20 mL of epidural 3% 2-chloroprocaine was more rapid than spinal procaine with 20 μg fentanyl[258] and also had a decreased incidence of pruritus. Recovery after epidural 3% 2-chloroprocaine required fewer top-up injections and permitted discharge an hour sooner after ambulatory knee arthroscopy than with 1.5% epidural lidocaine.[259] However, the use of epidural 2-chloroprocaine has a more frequent incidence of back pain.[260]

In children, caudal epidural analgesia—for example, using levobupivacaine 0.5 to 1 mL/kg of 0.25 %—is popular for postoperative pain relief.[57] The technique is most useful for bilateral surgery or other situations in which the maximum safe dose would not permit an adequate volume for wound infiltration. After circumcision, caudal analgesia was no better than parenteral or systemic analgesia or dorsal nerve block in reducing analgesic requirements, nausea, or vomiting.[261] However, motor block and leg weakness were significantly more common in boys receiving a caudal block. The addition of clonidine[262] or dexmedetomidine[263] augments caudal analgesia, but concerns remain about the frequency of sedative and hemodynamic side effects and the risk for neurotoxicity.[132,262]

Intravenous Regional Anesthesia

Intravenous regional anesthesia (IVRA) (Bier's block) is a simple, reliable method of analgesia most commonly used in the upper limb, but sometimes also used effectively in the lower extremity.[264] In the United Kingdom and Europe, prilocaine is the preferred local anesthetic because of its high therapeutic index.[265] Lidocaine has also been used for many years[264] and appears to be a safe alternative.[266] Ropivacaine has also been extensively evaluated for IVRA. Compared to lidocaine, 0.2% to 0.375% ropivacaine resulted in prolonged and improved postoperative analgesia.[267-269] However, compared to prilocaine, ropivacaine's onset was slower, no useful prolongation of postoperative analgesia occurred, and ropivacaine plasma concentrations were more than double those of prilocaine, despite a 60% lower dose.[265]

IVRA was a cost-effective alternative to general anesthesia for outpatient hand surgery, being equally rapid to administer and with faster recovery and fewer postoperative complications.[270] However, analgesia was inadequate in approximately 11% of cases, which required supplemental local anesthesia, repeat of the block, and even conversion to general anesthesia. IVRA was also cost effective, and quicker to perform, compared to brachial plexus block, but with a 4.4% failure rate due to tourniquet pain.[271]

A variety of adjuvants have been used in IVRA to decrease tourniquet pain, improve block quality, and prolong analgesia after cuff deflation.[272] Opioids are relatively ineffective and cause nausea, vomiting, and dizziness after tourniquet deflation,[272] but several NSAIDs have been shown to be beneficial. Lornoxicam[273] decreased tourniquet pain and improved postoperative analgesia and tenoxicam improved postoperative pain,[272] but the effects of ketorolac are unclear after most of the evidence showing its efficacy in IVRA was withdrawn.[138] Dexamethasone improved both block quality and postoperative analgesia.[274] Similar results have been observed with the α_2-adrenoceptor agonist dexmedetomidine,[275, 276] whereas clonidine delayed tourniquet pain without improving postoperative analgesia.[277]

Other Local and Regional Anesthetic Techniques

A wide range of other regional anesthetic techniques can be used to facilitate ambulatory surgery or provide postoperative analgesia (Table 89-3).[278] The applicability of these techniques depends on the nature of the planned procedure, the patient, the preferences of the surgeon and anesthesiologist, and the skill and experience of the anesthesiologist performing the block. Benefits include excellent postoperative analgesia and reduced PONV, but this must be offset against pain and discomfort while performing the block, the difficulty of transitioning to satisfactory analgesia when the block wears off, and the risk for perioperative nerve injuries. Regional anesthesia may be contraindicated in patients with bleeding problems or those taking anticoagulants, as well as in patients with local infections. Regional anesthesia has a high failure rate in inexperienced hands, especially in the morbidly obese patient, although ultrasound guidance appears to improve the success rate of many blocks.[279] The use of ultrasound also can reduce pain during block placement,[279] but currently no conclusive evidence exists that it improves the safety of regional anesthesia.[280]

Simpler locoregional techniques may be more appropriate for some procedures. Intraarticular local anesthesia produces a moderate and relatively brief reduction in postoperative pain after arthroscopic knee surgery, but this is still considered to be of clinical significance in ambulatory surgery.[281] In many cases, simple wound infiltration may be as effective as central and proximal peripheral blocks and allows patients to mobilize more quickly.[282] Concerns about the possible risk for infection, or systemic toxicity resulting from large volumes of local anesthetic, appear unfounded in clinical practice.[282]

Infiltration anesthesia offers advantages for many ambulatory procedures and is the method of choice for inguinal hernia repair.[155] Several large series have confirmed excellent results with this highly cost-effective technique, with 79% of patients requiring oral analgesia for 7 days or less after surgery[283] and 91% of patients returning to normal activities within 5 days.[284] Repair under local anesthesia is not an independent factor for hernia recurrence, although this is influenced by the type of hernia and the level of surgical experience.[285] Infiltration anesthesia resulted in fewer medical and urologic complications after groin hernia repair than either general or regional anesthesia.[252] If spinal anesthesia is chosen for groin hernia repair, the anesthesiologist should be aware of the increased risk for urinary retention and other medical complications, especially in older patients.[252]

The concept of simple wound infiltration has been further developed into LIA, used for major orthopedic ambulatory surgery. This multimodal technique was originally developed for the control of pain after inpatient knee and hip surgery in Australia by Kerr and Kohan.[286] Their technique used a mixture of 300 mg ropivacaine with 30 mg ketorolac and 1.5 mg epinephrine diluted to 150 to 200 mL with saline, infiltrated into all the tissue planes of the surgical field over approximately an hour as the operation progressed. A catheter was placed into the wound to permit later repeat dosing. In the original series of 325 patients, mainly undergoing elective hip resurfacing but including some primary hip and knee replacements, pain was well controlled (numerical pain score 0 to 3) without morphine in two thirds of patients, most of whom could walk with assistance 5 to 6 hours after surgery; 71% were discharged, walking independently after a single night stay (Fig. 89-3).[286] These promising results have been confirmed in a blinded, randomized trial in patients undergoing unicompartmental knee arthroplasty, where a similar LIA regimen significantly reduced pain and opioid consumption and decreased the median

TABLE 89-3 SOME COMMON UPPER AND LOWER EXTREMITY BLOCKS USED FOR ADULT AMBULATORY SURGERY

Type of Block	Type of Surgery	Bolus Dose (Perioperative)*	Continuous Infusion	Patient-Controlled Regional Analgesia (PCRA)
Interscalene block	Surgery around the shoulder	Bupivacaine/levobupivacaine 0.25%-0.5%, 20-40 mL *or* ropivacaine 0.5%, 20-40 mL	Ropivacaine 0.2% 5 mL/hr	Ropivacaine 0.2% 5 mL/hr
Supraclavicular or infraclavicular block	Surgery around elbow, wrist, and hand	Bupivacaine/levobupivacaine 0.25%-0.5%, 20-40 mL *or* ropivacaine 0.5%, 20-40 mL	Ropivacaine 0.2% 5 mL/hr	Ropivacaine 0.2% 5 mL/hr
Sciatic nerve block	Posterior cruciate ligament repair, foot and ankle surgery	Bupivacaine/levobupivacaine 0.25%-0.5%, 20-40 mL *or* ropivacaine 0.5%, 20-40 mL	Ropivacaine 0.2% 5 mL/hr	Ropivacaine 0.2% 5 mL/hr
Femoral nerve block	Knee arthroplasty, anterior cruciate ligament repair	Bupivacaine/levobupivacaine 0.25%-0.5%, 20-40 mL *or* ropivacaine 0.5%, 20-40 mL	Ropivacaine 0.1% 5 mL/hr	Ropivacaine 0.1% 5 mL/hr
Paravertebral block (thoracic)	Breast surgery	Bupivacaine/levobupivacaine 0.25%-0.5%, 20-40 mL *or* ropivacaine 0.5%, 20-40 mL	Ropivacaine 0.2% 5 mL/hr	Ropivacaine 0.2% 5 mL/hr

*Doses are approximations, with lower doses recommended when using ultrasound techniques. Depending on the type of surgery, multiple nerves may need to be blocked to get good postoperative pain relief. When using catheter techniques, disposable pumps with prefilled local anesthetics may be given to the patient with suitable written and verbal instructions.

From Gupta A, Smith I: Local and regional anaesthesia. In Smith I, McWhinnie D, Jackson I, editors: *Oxford specialist handbook of day surgery,* London, 2011, Oxford University Press, pp 93-108.

length of stay by 2 days, with 68% of patients discharged after a 1-night stay.[287]

A limitation of infiltration anesthesia in general is the relatively short duration of pain relief it provides, even with long-acting drugs such as bupivacaine. The encapsulation of bupivacaine into a biodegradable carrier offers the prospect of extended-duration local anesthesia (EDLA), which has demonstrated significant analgesic effects for at least 96 hours in pilot studies.[288] Several potential problems need to be solved before widespread application, however, including ensuring that the large doses of local anesthetic contained within the carrier are not rapidly released, leading to toxicity, or that the encapsulating materials do not break down into harmful products.[289] One extended-duration preparation of bupivacaine, Exparel, which uses an established liposomal-based drug delivery system (Lipo Foam, Contour^{MD}), is currently approved by the U.S. Food and Drug Administration (FDA). Early trial results report improved pain scores and reduced opioid analgesic consumption compared to plain bupivacaine during the first 24 to 48 hours or more after bunion surgery,[290] knee replacement,[291] and breast

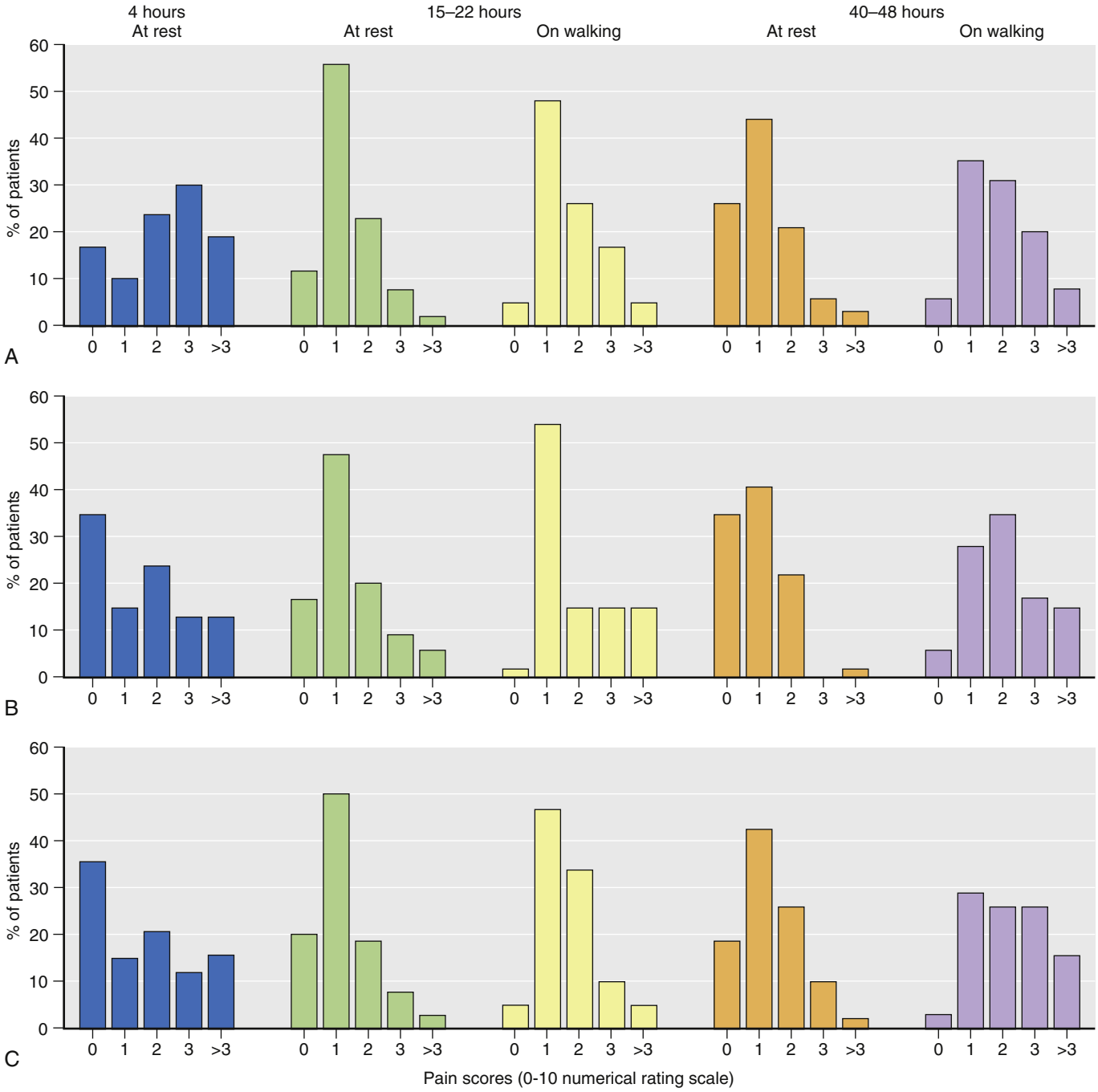


Figure 89-3. Numerical pain scores at various time points after hip resurfacing arthroplasty (**A,** n = 185), total hip replacement (**B,** n = 54), and total knee replacement (**C,** n = 86) in patients receiving local infiltration anesthesia. (Data from Kerr DR, Kohan L: Local infiltration analgesia: a technique for the control of acute postoperative pain following knee and hip surgery: a case study of 325 patients, *Acta Orthop* 79(2):174-183, 2008.

augmentation.[292] Myalgia was observed after Exparel in six patients in one study,[292] but a 2-year follow-up from the same group reported no long-term complications.[293]

Several naturally occurring alkaloid toxins, which may have the potential to provide longer lasting and safer local anesthesia, have been considered.[289] A preliminary study with neosaxitoxin, described superior analgesia compared to that with bupivacaine at 12 hours after laparoscopic cholecystectomy.[294] Catheter techniques also can extend the duration of effective local or regional analgesia, reducing pain scores, opioid-related side effects, and length of hospital stay, as well as improving patient satisfaction.[295]

SEDATION

Although some procedures may be performed with local or regional anesthesia alone, additional drugs are often required for anxiolysis to provide additional analgesia and to attain suitable operating conditions by helping the patient lie still in an appropriate position. The level of sedation required varies with each therapeutic, diagnostic, or surgical procedure and must be individually adjusted to achieve a balance of patient comfort and safety.[296]

The ASA defines three levels of sedation according to the responsiveness of the patient.[297] With minimal sedation a degree of anxiolysis is reached, but the patient is normally responsive and has a clear airway. During moderate (conscious) sedation the patient is more sleepy but responds purposefully to verbal or tactile stimuli. Spontaneous ventilation is usually adequate and interventions are not required to maintain a patent airway. With deep sedation, the patient can respond purposefully only to repeated or painful stimuli and may require a degree of airway or ventilatory support. Far from being discrete, these sedative levels lie on a continuum (Fig. 89-4), which becomes general anesthesia when the patient loses consciousness and is unarousable even with painful stimuli.[297] Careful monitoring is essential, and the standard of care for patients receiving sedation should be the same as for patients undergoing general or regional anesthesia and includes all of the usual aspects of anesthesia care.[298] Unfortunately, a widely held belief among physicians and patients is that sedation is a safer form of care,[299] but an ASA closed claims database analysis revealed that the risks for death or permanent brain damage are similar to those of general anesthesia.[300] Predictably, the greatest risk for harm comes from respiratory depression by opioids and sedative-hypnotic drugs, and many cases could have been prevented by better monitoring and improved vigilance.[301]

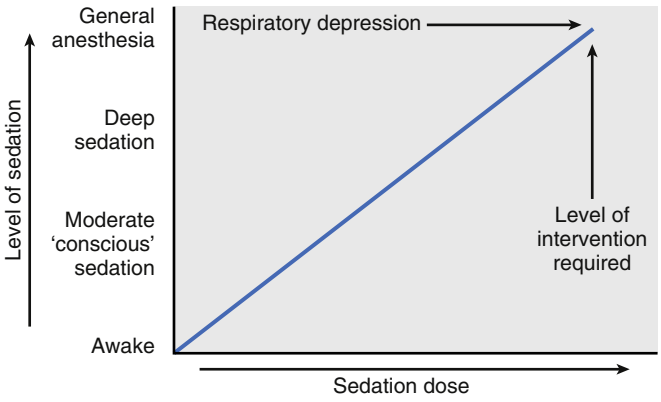


Figure 89-4. The continuum of sedation and general anesthesia. (From Ahuja M, Armstrong I. Sedation. In Smith I, McWhinnie D, Jackson I, editors: *Oxford specialist handbook of day surgery,* London, 2011, Oxford University Press, p 109, with permission.)

The U.S. term monitored anesthesia care (MAC) is sometimes erroneously used to describe sedation administered by an anesthesiologist. However, the ASA has a specific definition of MAC, which is a billing term used to describe an anesthesia service that includes all perianesthesia aspects of care.[298] MAC may include varying levels of sedation, including conversion to general anesthesia, when necessary. However, "if the patient loses consciousness and the ability to respond purposefully, the anesthesia care is a general anesthetic, irrespective of whether airway instrumentation is required."[298]

Choice of Sedatives

The specific requirements for supplemental sedative and analgesic drugs depend on the procedure undertaken, the skill of the operator in using local anesthesia, and the experiences and expectations of the individual patient. The use of pharmacologic agents can be reduced by sympathetic patient management at every stage, preoperative explanation, and the use of distractions, such as deep breathing, conversation, and listening to music.[299] Adjuvant drugs should be chosen to deliver those specific aspects that are required,[302] such as reduction of anxiety, sedation to relieve boredom or aid immobility, and analgesia for pain that is not amenable to further infiltration of local anesthetic.

Midazolam

Midazolam produces anxiolysis and dose-related hypnosis and is a popular component of sedation. It also produces marked antegrade amnesia. At times this may be beneficial, but it is not always welcomed by patients.[303] Midazolam is preferred to other benzodiazepines because it is water-soluble, does not cause venoirritation or pain on injection, is rapid-acting, and has a relatively short-elimination half-life of about 2 to 4 hours. As sole anesthetic, a single dose of 0.05 to 0.1 mg/kg allows reasonably predictable recovery after brief procedures, but individual responses are highly variable.[304] Recovery is also considerably slower if repeat or prolonged administration is required.

Propofol

Propofol is an excellent sedative-hypnotic for MAC because its pharmacokinetic properties result in a rapid recovery from the effects of a single bolus dose and a continuous infusion. Propofol is a relatively pure hypnotic, providing no analgesia and only moderate amnesia. Infusion rates of 25 to 75 μg/kg/min are typically used,[305] but the short duration of action facilitates titration to effect.

Because of the excellent conditions that can be achieved and the superiority of recovery compared with

that of midazolam,[306-308] demand for propofol sedation is growing rapidly in areas such as therapeutic endoscopy in which anesthesiologists have not traditionally been involved. Propofol can rapidly cause apnea, before loss of consciousness, even in sedative doses, and unintended transition to general anesthesia is a constant risk. The safety of nonanesthesiologist administration of propofol is therefore controversial. In the United Kingdom, the Royal College of Anaesthetists and the and British Society of Gastroenterology jointly state that propofol sedation for complex upper GI endoscopic procedures should be administered only by an "appropriately trained anaesthetist."[309] In the United States, the ASA also advocates propofol medicating "only by persons trained in the administration of general anesthesia,"[310] consistent with the package insert. However, the American Society for Gastrointestinal Endoscopy considers propofol use safe by anyone "proficient in the management of upper and lower airway complications, including manual techniques for reestablishing airway patency" and holding at least basic life support certification.[311]

Advocates of endoscopist-administered propofol claim a very low rate of airway complications (0.1%) and a mortality (4 in 646,080) less that that associated with endoscopist-administered midazolam-opioid sedation.[312] Their data also reveal a wide range for the frequency with which rescue airway support was required, suggesting considerable variation, either in technique or willingness to intervene to protect the airway.[312] When anesthesiologists administered propofol for patients undergoing endoscopic retrograde cholangiopancreatography (ERCP), deeper levels of sedation or general anesthesia were often intended and sedation-related adverse events were far more common (21%), especially in patients of higher ASA physical status classification, but were managed without adverse consequence or delay and high levels of patient and operator satisfaction were achieved.[313]

Fospropofol

Fospropofol is a water-soluble phosphate ester prodrug of propofol approved in the United States for sedation in adults in 2009, but not currently manufactured.[314] The pharmacokinetics of propofol liberated from fospropofol differ from intravenously administered propofol, with a slower onset of action and longer duration, but detailed pharmacology is lacking after the retraction of six key pharmacokinetic/pharmacodynamic studies because of an error in the propofol assay.[315] Fospropofol avoids the pain on injection of propofol, but is associated with paresthesia and pruritus.[314] Potentially, fospropofol should require less frequent dosing than propofol, but so far has only been studied in relatively short procedures. Conversely, titration to effect may be more difficult because of the lag during metabolism to propofol. The role of fospropofol in sedation is unclear at present, and the current license restricts its use to anesthesiologists.[314]

Analgesic Adjuvants

Opioids are useful for procedures in which pain cannot reliably be blocked with local anesthesia alone.[296] Compared to alfentanil in women undergoing breast biopsy, remifentanil resulted in lower pain scores during deep dissection and reduced the need for supplemental local anesthesia.[317] Remifentanil was a useful adjuvant to propofol sedation during transvaginal tape insertion[318] and in achieving optimal conditions for awake craniotomy,[319] surgery that is increasingly being performed as a day and short-stay procedure.[21, 22] Remifentanil produced lower pain scores than fentanyl in patients receiving propofol sedation during hysteroscopy, but did it not improve recovery or patient satisfaction.[320] For hysteroscopic surgery, paracervical block supplemented by a remifentanil infusion permitted earlier mobilization and discharge compared to TIVA, and the sedation technique was also preferred by a higher proportion of patients. Remifentanil is usually delivered by infusion, but intermittent bolus doses may be more effective for some procedures.[321]

Both clonidine and dexmedetomidine have potentially useful analgesic, anxiolytic, and sedative properties. The slow onset and offset of clonidine and frequent reports of cardiovascular instability, mean that neither drug has established a routine place in sedation,[132,322] although dexmedetomidine may be a useful analgesic adjuvant in awake craniotomy.[323] Ketamine improved analgesia when used to supplement propofol sedation, but an increase in PONV, psychomimetic side effects, and delayed discharge were observed at higher doses.[324]

Delivery of Sedation

Because of the varying needs to provide hypnosis, anxiolysis, analgesia, and amnesia, use of drug combinations are common during anesthesiologist-administered sedation. Preceding a propofol infusion with a small (2 mg) dose of midazolam improved anxiety, sedation, and amnesia for early intraoperative events with no detrimental effect on postoperative sedation, amnesia, or recovery times.[325] However, using drug combinations increases the risk for interactions, leading to adverse effects. At sedative doses, propofol and remifentanil each have only a modest effect on heart rate and arterial blood pressure, but their effect on respiration is strikingly synergistic, with the potential for severe respiratory depression.[326] Respiratory depression is also enhanced by the interaction of midazolam and remifentanil.[327] Antagonists of benzodiazepines and opioids may be useful in cases of unintended overdose, but should not be routinely relied on to reverse deep sedation because of their short duration of action, which may permit resedation before[328] or after discharge.[329]

As with TIVA, the stability and control of sedation regimens can be improved by using TCI systems.[330] Target concentrations of 0.5 to 2 μg/mL for propofol and 0.5 to 1 ng/mL for remifentanil are typical[296,322] but should be titrated to individual effect. Effective sedation is usually judged by clinical end points or scores. Bispectral index (BIS) changes with increasing sedation, but is too variable[331] to be useful routinely and was not effective as an end point for midazolam sedation.[332] BIS monitoring did not improve the quality of sedation or reduce the propofol dose or rates of hypoxemic, bradycardic, or hypotensive complications during ERCP.[333] However, BIS-guided TCI propofol may be useful in the management of patients with intellectual disability,[334] in whom clinical signs may be less reliable. Allowing patients to

adjust their own sedation level by patient-controlled sedation resulted in less propofol being used compared with a continuous infusion and was significantly more popular with patients.[335]

Inhaled sedation by a low dose of sevoflurane is an alternative technique that provides good control of sedation and rapid recovery.[336,337] However, it can be complicated by a frequent incidence of perioperative excitement and an increased risk for transition to general anesthesia.[338]

MONITORING DEPTH OF ANESTHESIA

Many devices are now available to monitor the hypnotic component of anesthesia as a supplement to our traditional reliance on autonomic signs (see also Chapter 50). Most monitor electroencephalogram signals, recorded either spontaneously or evoked in response to a stimulus, which are then processed into a dimensionless number, usually ranging from 0 to 100. Precisely which variables are recorded and how they are processed is proprietary information,[339] and the specific values corresponding to adequate anesthesia also vary among monitors.[340]

BIS was the first licensed monitor and is the most extensively studied, yet whether it can actually prevent awareness with recall remains controversial.[340] One of the largest studies to date revealed an effect that was only just statistically significant[341] but has been criticized for inadequate power, selection bias, and studying only a high-risk population.[342,343] A more recent and even larger study failed to show superiority of BIS over titration to end-tidal anesthetic drug concentration in preventing awareness,[344] also in a high-risk population. In ambulatory anesthesia, in which awareness is uncommon,[345] more interest has been shown on whether BIS and similar devices can reduce excessive anesthetic delivery, thereby improving the speed and quality of recovery and reducing costs. Two meta-analyses have shown that titrating anesthesia to achieve BIS values of 40 to 60 results in trivial (2 to 4 minutes) reductions in awakening times, shortens recovery room stay by just 6.8 minutes, and fails to facilitate earlier home discharge.[346, 347] BIS titration also produced a very modest reduction in PONV (32% versus 38%).[346] Despite reductions in anesthetic drug usage, the cost savings were substantially less than the disposable costs associated with BIS.[346] Monitoring with auditory evoked potentials achieved similar small reductions in drug usage and awakening times, comparable to those seen with BIS.[348,349] Discharge times were unchanged in one study[348] but were shortened by both BIS and auditory evoked potential monitoring in another study in a very similar population.[349]

Although a lack of clear clinical or financial benefit exists from depth of anesthesia-guided drug titration, genuine concerns have been raised about using these monitors for purposes other than those for which they were designed. Although anesthesia is usually adequate at values below 60, BIS lacks a high level of discrimination and some patients may form memories at values as low as 40.[350] Thus, titrating anesthesia, even to BIS values of 40 to 50, to reduce costs and recovery times, may unintentionally increase the risk for awareness.[339]

RECOVERY FROM AMBULATORY ANESTHESIA

Recovery is traditionally divided into three stages. Early, phase 1 recovery occurs in a postanesthesia care unit (PACU) and entails further awakening and management of pain and nausea, with monitoring of hemodynamic stability. Intermediate recovery continues in the phase 2 (step-down) recovery or in a separate ward area and ends when the patient achieves the criteria for home discharge (see later discussion). The phase 1 and phase 2 aspects of recovery may occur in separate locations or within the same room.

EARLY RECOVERY

The recovery room or PACU should be centrally placed to all operating rooms and requires the same standard of staffing and equipment as are provided for inpatients.[351] The PACU may be shared with inpatients in some facilities, but recovery times can be shortened dramatically if there is a separated phase 1 PACU dedicated to ambulatory patients.[11] In the United States, the ratio of nurses to patients is usually lower than in the inpatient PACU, typically 1:3, reflecting the lower acuity of postprocedural needs.[6] Patient care should be adequately transferred to the PACU nursing staff, relaying preoperative and intraoperative problems and postoperative instructions. The nature and frequency of monitoring in the PACU is determined by the nature of surgery and the state of recovery. Because ambulatory anesthetics are typically short-acting, supplemental O_2 administration may be unnecessary in the PACU,[352] provided the patient's saturation level of O_2 in hemoglobin (SpO_2) remains above 92% on air.

In the United Kingdom, patients may be discharged from phase 1 to phase 2 of recovery when they are awake and oriented, normothermic, able to maintain their own airway and ventilation, and demonstrate cardiovascular stability. Wounds should be reasonably dry, and pain and PONV should be minimal and adequately treated. This assessment is usually made on clinical judgment.[351] In the United States, transfer from phase 1 to phase 2 is commonly based on predefined, physician-determined criteria. Typical ambulatory criteria include being awake with stable vital signs, minimal pain, minimal nausea, and the ability to sit with minimal dizziness.[353] If more standardized data are desired, a scoring system can be used. The most commonly used system is the modified Aldrete score,[354] which assigns points on the basis of activity, ventilation, blood pressure, consciousness, and oxygenation (Table 89-4). Length of PACU stay is one of the key end points, along with awakening, orientation, and extubation times used to evaluate early recovery in ambulatory anesthesia research.

SECOND-STAGE RECOVERY

Second-stage recovery prepares patients for leaving the ambulatory surgery unit and taking over their own care. Patients should sit upright on trolleys or reclining chairs as an aid to mobilization. After low-dose spinal anesthesia, mobilization is usually possible within an hour of the return of full motor function, or about 2.5 to 3 hours after the start of spinal anesthesia.[156,355]

TABLE 89-4 MODIFIED ALDRETE RECOVERY SCORE

		Score*
Activity	Able to move four extremities voluntarily or on command	2
	Able to move two extremities voluntarily or on command	1
	Unable to move extremities voluntarily or on command	0
Respiration:	Able to breathe deeply and cough freely	2
	Dyspnea or limited breathing	1
	Apneic	0
Circulation:	BP ± 20% of preanesthetic level	2
	BP ± 20%-49% of preanesthetic level	1
	BP ± 50% of preanesthetic level	0
Consciousness:	Fully awake	2
	Arousable on calling	1
	Not responding	0
Oxygenation:	Able to maintain saturation > 92% on room air	2
	Needs oxygen to maintain saturation > 90%	1
	Saturation <90% even with oxygen	0

**The total possible score is 10; patients scoring ≥ 9 are fit for discharge from phase 1 recovery.*

BP, Blood pressure.

From Aldrete JA: The post-anesthesia recovery score revisited (letter), *J Clin Anesth* 7:89-91, 1995.

BOX 89-1 ***Criteria for Direct Admission to Second-Stage Recovery Unit, Bypassing the Postanesthesia Care Unit****

Patient should be awake, alert, oriented, and responsive (or return to baseline state).
Pain should be minimal (unlikely to require treatment with parenteral medications).
No active bleeding should occur (unlikely to require professional treatment).
Vital signs should be stable (unlikely to require pharmacologic intervention).
Nausea should be minimal.
No vomiting should occur.
If nondepolarizing neuromuscular blocking agent has been used, patient should now be able to perform a 5-second head lift or train-of-four monitoring should indicate no fade.
Oxygen saturation should be 94% or higher on room air (3 minutes or longer) or O_2 saturation should return to baseline on room air.

*During the follow-up period, the patient should be evaluated in the operating room, immediately before discharge, using the above criteria regarding recovery from anesthesia. To bypass the postanesthesia care unit, a patient must meet all of these criteria and, in the judgment of the anesthesiologist, be capable of transfer to the second-stage recovery unit.

From Apfelbaum JL, Walawander CA, Grasela TH, et al: Eliminating intensive postoperative care in same-day surgery patients using short-acting anesthetics, *Anesthesiology* 97:66-74, 2002.

FAST-TRACK RECOVERY

With the increased use of short-acting drugs and techniques, many patients will have already met the discharge criteria before, or by the time, they reach the PACU.[356] If this is the case, admission to the PACU will only generate unnecessary delay while further observations are performed. Instead, these patients may bypass phase 1 recovery and go directly to the phase 2 unit; this is known as fast-track recovery.

The modified Aldrete score can also be used to assess fast-track eligibility.[357] Because this score does not assess pain or PONV, which are traditionally treated in the PACU, White and Song[358] added two additional categories to derive their fast-track recovery score. Although using this score reduced the proportion of patients who met the fast-track criteria on PACU arrival, it also significantly reduced the number of patients who required parenteral analgesia or antiemetics in the step-down area.[358] Others have suggested a series of clinical criteria[359] that must all be achieved for patients to undergo fast-track recovery (Box 89-1). The criteria for transfer from phase 1 to phase 2 and the criteria for direct entry to phase 2 should be the same.

Fast-track recovery is the norm for patients who have had local anesthesia, but it is also appropriate for most patients receiving sedation[359,360] and low-dose spinal anesthesia in the United Kingdom.[156] Patients receiving general anesthesia also may be able to undergo fast-track recovery depending on the combined effects of procedure, anesthetic technique, duration of procedure, and the individual patient. After laparoscopic tubal ligation, 90% of women receiving desflurane, 75% receiving sevoflurane, but only 26% receiving a continuous infusion of propofol were judged eligible for fast-track recovery,[357] although actual recovery bypass was not attempted. In a more recent study involving more superficial surgery in which anesthesia was titrated to BIS, all patients receiving either desflurane or sevoflurane met fast-track recovery criteria on leaving the operating room,[361] although no patient actually bypassed the PACU in that facility.

Fast-track recovery is appealing because improved recovery provides the patient with a higher quality experience, enabling them to return toward normal in a more pleasant, comfortable, and facilitative environment. It also frees up the more intensive resources of phase 1 recovery for those patients who need them. Accomplishing fast-track recovery is complex. In one facility, despite high proportions of patients appearing eligible to bypass the PACU using the White criteria,[357,361] the same group actually achieved fast-tracking in only 35% to 53% of their patients.[362] The use of depth of anesthesia monitoring has been claimed to facilitate fast-track recovery,[363] whereas others have not found it advantageous.[364] Accomplishing fast-track recovery requires not only anesthesia recovery readiness, but also the support of a facility-based process, including nursing and surgeon participation and environment support. More productively, the current approach to fast tracking is not just the percentage of patients who completely bypass phase 1, but rather, it is to enable the fastest possible path for all patients through their recovery to discharge home.

The economic case for fast-track recovery should be considered separately.[365] In some cases, fast-track recovery has shortened overall recovery stay, comparable to,[366] or even longer than,[359] the time that would have been spent in the PACU. However, others have found no difference

in overall recovery time,[362] especially after laparoscopic surgery.[366] Achieving an adequate fast-track score can take almost 30 minutes after laparoscopic surgery, even when using cerebral monitoring to optimize anesthesia,[348] which could delay leaving the operating room. Nurses in the step-down unit are not always readily available to receive patients and often report patients arriving cold or without all the fast-track criteria actually being met.[367] Although fast-track recovery appears financially beneficial, actual savings will be made only if the PACU is not needed at all or if staffing levels can be reduced, which is not supported by the evidence to date.[365] One randomized trial showed that nursing workload and costs were simply shifted from one area to another, with no overall savings.[366] Fast-track recovery may still help to improve patient flow and may work best in small units that use staff flexibly between different areas.[365]

POSTOPERATIVE PAIN

The management of postoperative pain should begin well before the patient undergoes surgery. Patients need to have appropriate expectations about what they are likely to experience during their recovery (see also Chapter 98).[368] At preoperative assessment, patients should be provided with information about the likely extent and duration of pain after surgery. They should also be advised about simple measures to reduce pain, including advice to rest in a comfortable position, raising swollen limbs, use of heat or cold packs, and the benefits of distraction. Prevention is the mainstay of pain management, yet studies have shown that pain management after ambulatory surgery is often inadequate.[369] Common causes are a lack of adherence to analgesic guidelines and a failure to provide multimodal analgesia.[370,371] Too often there is overreliance on opioid analgesia, resulting in predictable adverse effects[372] that are second only to inadequate pain relief in causing unnecessary hospital admission.[369]

MULTIMODAL ANALGESIA

Multimodal analgesia relies on the additive or synergistic combination of drugs acting at various points on the pain pathway.[373] Typical combinations include local anesthetic wound infiltration or regional technique and routine NSAIDs, with small doses of opioids added as needed. Topical therapies also may be of some benefit, with both lidocaine and glyceryl trinitrate patches found to provide effective topical analgesia after a variety of ambulatory procedures.[374] Multimodal regimens are effective after several ambulatory surgical procedures.[375,376] An opioid-sparing effect exists for several drug combinations,[377] but most evidence is limited to an opioid plus one other drug, with little evaluation of true multimodal analgesia or attempts to identify optimal combinations.[371] Analgesic efficacy differs with the nature of surgery,[378] suggesting that multimodal analgesic regimens should be specifically tailored.[379] Nevertheless, reducing the opioid dose does decrease the incidence of PONV to a corresponding degree and may also reduce other opioid adverse effects, such as sedation, sleep disturbances, urinary retention, and respiratory depression.[372] As yet, no evidence indicates that multimodal analgesia improves long-term patient outcome[380] because of the small number of subjects studied and the infrequent incidence of adverse outcomes after ambulatory surgery.

RESCUE ANALGESIA

Despite prophylactic measures, some patients will experience pain on awakening after surgery. Milder cases may be amenable to treatment with additional oral analgesia, but more severe pain will usually require parenteral opioids. Fentanyl is commonly used for this purpose, and small boluses (20 to 25 μg) rapidly achieve analgesia. Compared to morphine, fentanyl results in more rapid control of pain and reduces the occurrence of PONV.[381] Rescue fentanyl also produced fewer adverse effects than oxycodone.[382] Administration of additional oral analgesia as soon as the pain is controlled will usually prevent a recurrence at a later stage of recovery. During the recovery period, pain should be assessed on a regular basis and treated according to protocols (Fig. 89-5).

PAIN MANAGEMENT AT HOME

In the United States, patients are often given prescriptions for postoperative analgesics, including weak opioids, preferably before surgery so the medications will be at home when the patient needs them. In the United Kingdom, patients may be given standardized take-home analgesic packs that can be dispensed from the ambulatory surgery unit, avoiding pharmacy delays. Typical take-home analgesia includes NSAIDs and acetaminophen combined with a weak opioid. Combinations of codeine-acetaminophen[383] and hydromorphone-acetaminophen[384] are effective after many ambulatory surgical procedures, although a proportion of patients are unable to metabolize codeine to its active form, rendering it ineffective.[385] Although a single preoperative dose of pregabalin produced modest improvements in pain after ambulatory surgery, continuing its use into the postoperative period added no further benefit.[151]

Managing Opioid Complications

Although multimodal techniques aim to minimize opioid use, strong opioids can be necessary as a rescue option after more invasive surgery. Analgesics such as morphine and oxycodone provide more intense and prolonged effects, but are associated with more intense and prolonged typical opioid side effects. Novel delivery techniques, such as iontophoretic[386] or nasal[387] fentanyl, may improve patient convenience but do nothing to reduce adverse effects. In addition to multimodal analgesia, attempts to limit these adverse effects have included the development of drugs such as tramadol, which combine opioid and nonopioid mechanisms of action. Tramadol is effective after ambulatory surgery,[388,389] but it is still associated with a frequent incidence of unwanted effects, including sedation, dizziness, and, particularly, PONV.[390] Tapentadol was recently licensed in both the United States and the United Kingdom. It has a dual action similar to that of tramadol, with

comparable efficacy to oxycodone but fewer GI adverse effects, such as nausea, vomiting, and constipation.[391] Unlike tramadol, it does not require metabolic activation or suffer from isomer-dependent pharmacodynamics.[147]

Combining oral oxycodone with naloxone (Targinact) antagonizes the GI effects, in particular preventing opioid-induced constipation, but has little effect on analgesia because first-pass metabolism prevents much naloxone from reaching the central nervous system.[147] Alvimopan is another peripherally acting MOP (formerly called mu opioid receptor) antagonist, intended to reduce opioid-induced constipation. However, peripheral MOP receptors also may partially mediate opioid-associated PONV, delayed gastric emptying, and urinary retention,[147] offering the hope that opioid analgesia without serious adverse effects may yet be a possibility.

Local Anesthetic Administration at Home

Sending patients home with perineural, incisional, and intraarticular catheters is a new and evolving area of postoperative pain management.[27] Patient-controlled regional anesthesia with an elastomeric balloon pump has provided effective analgesia and reduced pain intensity during mobilization when ropivacaine is delivered into a perioperatively placed wound catheter after subacromial decompression.[392] Although patients were kept in hospital for study observations and assessments, based on pain scores, the authors concluded that all patients in the active group could have been discharged within 2 hours of surgery. Another small pilot study showed excellent analgesia with continuous interscalene block, continued at home, allowing same-day discharge after a variety of shoulder operations, including open rotator cuff repair, subacromial decompression, and joint replacement.[393]

Recently, several institutions have described cases of chondrolysis that appear to be related to the use of postoperative intraarticular local anesthetic pain pumps.[394] In a series of 375 patients from one individual orthopedic surgeon, chondrolysis was observed only in cases in which either bupivacaine or lidocaine had been infused into the joint during the postoperative period.[395] Most local anesthetics, including bupivacaine, lidocaine, and ropivacaine, are chondrotoxic to human articular cartilage in vitro, and the risk may be increased with longer exposure to higher concentrations of local anesthetic, such as with a pain pump, compared to that associated with a single injection.[396] Consequently, the use of local anesthetic infusions after shoulder surgery has declined or stopped in many institutions.

A variety of infusion pump designs are available for local anesthesia infusions or patient-controlled regional anesthesia (PCRA) after discharge. Technical problems have been found with electronic pumps,[397] which seem to be unreliable for home use.[393] Patient satisfaction[397] has been reported with disposable elastomeric pumps, which are more reliable, although not all types function equally well and in vivo performance does not necessarily match results obtained in vitro.[398]

POSTOPERATIVE NAUSEA AND VOMITING

PONV occurs in as many as 30% in a general surgical inpatient population given no antiemetics (see also Chapter 97).[399] Some patients undergoing day surgery have a much smaller risk for symptoms, cited as less than 5%[50,400] for very minor surgery, with reduced requirement for intraoperative and postoperative opioids. However, in the same studies, other ambulatory surgery patients had a predischarge incidence of PONV as high as 41%. When the potential occurrence of emetic sequelae after discharge is included in the estimation of overall risk, some authors cite an overall incidence of more than 40%, even after receiving an antiemetic.[401]

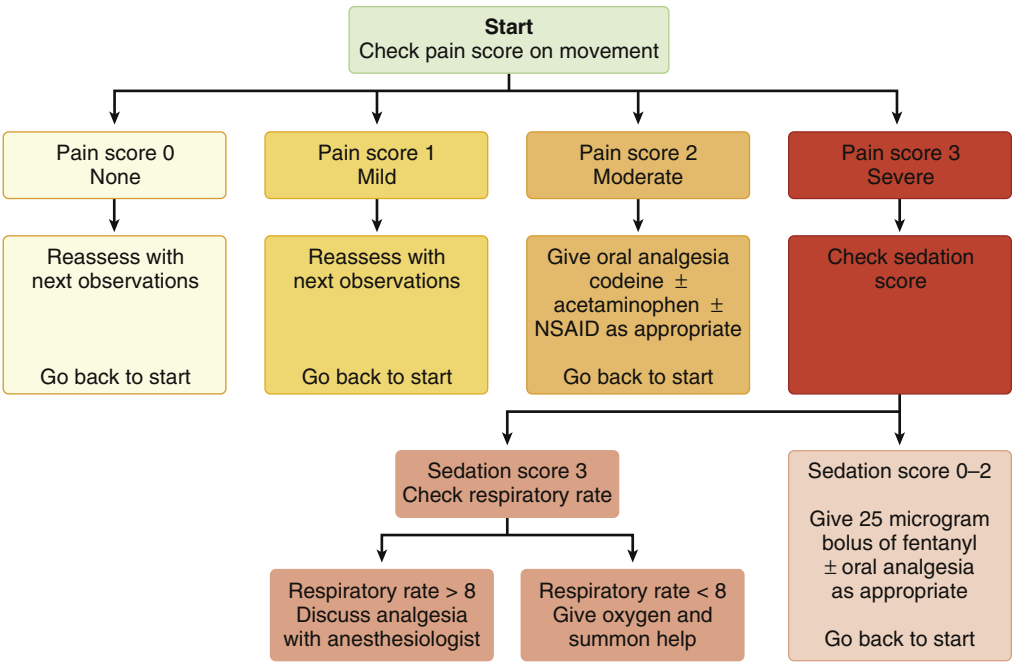


Figure 89-5. Example of a pain management protocol for ambulatory surgery patients. *NSAIDs,* Nonsteroidal antiinflammatory drugs. (Modified from Lipp A, Jackson I: Adult day surgery analgesia. In Smith I, McWhinnie D, Jackson I, editors: *Oxford specialist handbook of day surgery,* London, 2011, Oxford University Press, p. 133, with permission.)

RISK ASSESSMENT AND STRATEGIES

It might be expected that the management of PONV for ambulatory patients should involve universal multimodal pharmacologic prophylaxis to minimize the symptoms that might delay timely discharge or subsequent recurrence in the home environment. However, current recommendations[402] advocate a more focused approach toward the use of preventive pharmacotherapy, having first minimized baseline risk resulting from the use of generic emetogenic stimuli, such as the use of general anesthesia where regional techniques could be used, or if a general anesthetic is mandated, reducing exposure to volatile anesthetics, N_2O, large-dose neostigmine, and opioid-based analgesia. From there, individual patient factors should be identified to stratify relative risk. The scoring system originally derived from a cohort of ear, nose, and throat (ENT) patients by Apfel and colleagues in 1998[403] is popular because of its relative simplicity; yet debate continues regarding its applicability to ambulatory surgery patients, because the predicted risk for PONV (Table 89-5) seems to be overestimated in this population, presumably as a result of the original scoring system having been developed for inpatients in Europe. This seems to be confirmed in a subsequent paper by the same author,[401] where PACU rates of nausea were 19.9%, vomiting 3.9%, and nausea and/or vomiting 20.7% across a patient cohort with characteristics that would seem to predict greater risk from the original algorithm. However, when including postdischarge rates of PONV until the second postoperative day (Table 89-6), commensurate complication rates occur. Other scoring algorithms exist for prediction of risk for PONV in the ambulatory environment, but their relative complexity mandates the use of a calculator or computer.[400] A recent reevaluation of risk factors for PONV (see also Chapter 97)[404] reiterated the importance of those characteristics included in the original Apfel score,[399] but also included younger age and duration but not type of surgery.

Antiemetic treatment should therefore be tailored to assessment of likely risk for symptoms with the use of either unimodal or multimodal prophylaxis as indicated. The IMPACT study[184] demonstrated that ondansetron 4 mg, droperidol 1.25 mg, and dexamethasone 4 mg were equally effective in reducing the risk for PONV by an order of 25% and that using these two drugs together would be approximately additive (multimodal antiemetic prescription). Specifically, the prophylactic use of one of these drugs decreases the estimated risk for PONV from 60% to 44%; use of two drugs would further decrease the incidence from 44% to 33% and three drugs to 24%. The use of TIVA with propofol with the concomitant avoidance of N_2O had similar equivalence to the use of one antiemetic.[184] Simple measures, such as the routine administration of approximately 1 to 2 L of IV crystalloid fluids, reduce the incidence and severity of PONV, decrease dizziness and drowsiness,[405] and reduce postoperative pain in high-risk groups.[406]

ANTIEMETIC DRUGS

First-Generation Drugs

Metoclopramide is a dopaminergic (D_2) and serotonergic (5-HT_3, peripheral 5-HT_4 at higher doses) antagonist with gastric prokinetic properties that was first described in 1964. A meta-analysis of a standard clinical dose of 10 mg showed little evidence of pharmacologic benefit for PONV[407] and has led to a suggestion in recent guidelines for management of PONV in ambulatory surgery that other more effective antiemetics be used for first-line treatment.[402] However, more recent systematic reviews[408,409] have challenged these views, and a 10-mg dose may be considered. Higher doses, such as 20 to 25 mg, are more effective[410] but are associated with more akathisia.

Droperidol is a butyrophenone with an antiemetic effect resulting from dopaminergic receptor (D_2) antagonism that received a black box warning for the FDA-approved

TABLE 89-5 RISK FACTORS FOR, AND PREDICTED RATES OF, POSTOPERATIVE NAUSEA AND VOMITING ACCORDING TO THE APFEL SCORE

Risk Factors	Scoring
Female	1 point
Nonsmoker	1 point
History of previous PONV	1 point
Postoperative use of opioids	1 point
Maximum possible score	4 points
No. Points	**Risk of PONV (%)**
0	10
1	21 (≈20)
2	39 (≈40)
3	61 (≈60)
4	79 (≈80)

PONV, Postoperative nausea and vomiting.
Data from Apfel CC, Laara E, Koivuranta M, et al: A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers, *Anesthesiology* 91:693-700, 1999.

TABLE 89-6 RISK FACTORS FOR, AND PREDICTED RATES OF, POSTDISCHARGE NAUSEA AND VOMITING

Risk Factors	Scoring
Female	1 point
Age <50 years	1 point
History of previous PONV	1 point
Postoperative use of opioids	1 point
Nausea in PACU	1 point
Maximum possible score	**5 points**
No. points	**Risk for PONV (%)**
0	10.9 (≈10)
1	18.3 (≈20)
2	30.5 (≈30)
3	48.7 (≈50)
4	58.5 (≈60)
5	79.7 (≈80)

PACU, Postanesthesia care unit; PONV, Postoperative nausea and vomiting.
Data from Apfel CC, Philip BK, Cakmakkaya OS, et al: Who is at risk for postdischarge nausea and vomiting after ambulatory surgery? Anesthesiology 117:475-486, 2012.

dose of 2.5 mg[411] or greater because of potential QT interval prolongation. This and other side effects of droperidol, such as sedation and akathisia, were significant at higher doses than are commonly used for PONV prophylaxis,[411] which are typically 1.25 mg or less. Droperidol use is less in the United States since the black box warning was added but primarily for medicolegal reasons rather than because of concerns with efficacy or side effects. A recent meta-analysis[412] has confirmed the antiemetic action of low-dose droperidol. Supply in the United Kingdom was halted on the basis of a prediction of market nonviability by the manufacturer. Although the drug has been reintroduced in the United Kingdom, it has been little used in the ambulatory environment in this country as a result of perceptions of adverse extrapyramidal effects, particularly akathisia, even at 0.5-mg doses.[413,414] An Australian study evaluating the incidence of akathisia in 228 women undergoing ambulatory gynecologic laparoscopy reported a rate of 29% with administration of 10 μg/kg.[415]

Antagonists of the histamine H_1 receptor have a particular efficacy in the management of nausea and vomiting precipitated by vestibular pathways, with a documented benefit in the management of travel sickness and surgical procedures for strabismus or involving the middle ear. Dimenhydrinate (a combination of diphenhydramine and 8-chlorotheophylline that was added to reduce drowsiness) has an antiemetic effectiveness deemed similar to that of both droperidol and 5-HT_3 antagonists,[416] but potential adverse reactions from these antihistamines include marked sedation, dry mouth, urinary retention, and blurred vision as a result of associated muscarinic receptor antagonism. Meclizine, an H_1-receptor antagonist and anti–motion sickness medication, is minimally sedating, long-acting, and effective for treatment of PONV and for prevention of postdischarge nausea and vomiting (PDNV).[417] In the United States, it is inexpensive and available without prescription, making it an attractive postdischarge choice.

A transdermal scopolamine delivery system is also available. This patch was designed to deliver a total dose of 1 mg of scopolamine at a sustained, constant rate over a period of 3 days.[418] Numerous studies have shown transdermal scopolamine to be effective in reducing the incidence and severity of PONV and PDNV, with efficacy comparable to that of ondansetron or droperidol. It has a prolonged duration but the onset is delayed, becoming effective within 2 to 4 hours of applying the patch.[419] The slow onset can be overcome by applying the patch the night before surgery. Used in this way, the incidence of nausea and vomiting was reduced from 62.5% and 37.5% to 20.8% and 8.3%, respectively, compared to placebo after gynecologic laparoscopy.[420] In the United States, clinicians apply the patch preoperatively, knowing that onset of PDNV efficacy will be in the early recovery period.[418]

Adverse effects, particularly dry mouth but also somnolence, dizziness, and blurred vision, are relatively common but generally described as mild.[418,420]

Serotonin 5-HT3 Receptor Antagonists

The 5-HT_3 antagonists have played a substantial role in the management of PONV since their introduction in the 1980s, because of their relatively benign adverse reaction profile compared with those of the then available drugs. Their prophylactic use is more effective when given just before the end of surgery.[421] They are effective drugs for emetic rescue therapy, with ondansetron seeming to have a more preferential effect on vomiting (number needed to treat [NNT] = 4) rather than nausea (NNT = 7).[422] Although relatively well tolerated, their side-effect profile includes an increased risk for headache (number needed to harm [NNH] = 36) and elevated liver enzymes (NNH = 31).[422] All serotonin subtype 3 antagonists have also been associated with QT interval prolongation. More recently released serotonin 5-HT_3 receptor antagonists, such as dolasetron, granisetron, and palonosetron,[423] seem to exhibit similar characteristics with equal reduction of PONV rates in high-risk patients when used for prophylaxis, though the longer half-life of these drugs (8, 10, and 40 hours, respectively) may afford better protection against symptoms after discharge. In particular, palonosetron, by nature of its unique binding properties leading to internalization of the 5-HT_3 receptor[424] and a long half-life, may have a role in the management of postdischarge symptoms.[425] A large cost remains a significant barrier to use of the newer, nongeneric serotonin antagonists.

Steroids

Dexamethasone is an effective antiemetic at IV doses of 4 to 5 mg (depending on local formulation).[426] This steroid may act centrally to either modulate the release of endorphins or inhibit prostaglandin synthesis. Given its delayed onset of action, dexamethasone should be administered as early as possible *after* induction of anesthesia.[427] Prophylactic dexamethasone is also effective in reducing postoperative pain and improving the quality of recovery,[153,154] although at somewhat higher doses (typically 8 mg) than those required for an antiemetic effect.

Neurokinin-1 Antagonists

The role of tachykinins in the emetic pathway was first elucidated by immunohistologic studies identifying substance P in the dorsal vagal complex of the ferret, an area of the brain deemed essential in the vomiting reflex.[428] Subsequent research identified the potential value of specific antagonists to the neurokinin-1 receptor, at which substance P and neurokinins A and B interact both centrally and peripherally in the gut to suppress vomiting. Aprepitant was the first commercially released drug of this class. A preoperative oral dose of 40 mg has efficacy similar to that of ondansetron for the reduction of nausea, with a potentially superior effect in the suppression of vomiting for 48 hours after administration.[429] An IV prodrug formulation, fosaprepitant, was introduced in 2008 with a license for use in chemotherapy-induced nausea and vomiting, but as yet, no work has been done evaluating its role or value in PONV.[430] A multicenter study evaluating the use of oral rolapitant,[431] a competitive NK-1 antagonist with an exceptionally long half-life of 180 hours, suggested similar effectiveness in comparison with placebo and ondansetron (administered at induction) with early control of symptoms, but use of rolapitant similarly seemed to confer prolonged protection from postoperative emetic symptoms. Cost remains a barrier for this class of drugs as well.

MANAGING PERSISTENT NAUSEA AND VOMITING

The continuing symptoms that follow antiemetic rescue therapy require further clinical review. Consideration should be given to alternative causes for these symptoms, particularly hydration status, covert hypovolemia, or early infection. Review of vital signs (temperature, pulse, and arterial blood pressure), allied with clinical examination to exclude an association with concomitant worsening of abdominal pain, potential septic foci, or urinary retention, is important to exclude more sinister causes, before consideration is given to symptomatic relief.

Administering 20 mL/kg of an isotonic electrolyte solution reduces the risk for nausea and dizziness after ambulatory surgery and may have value in attenuating continuing symptoms.[405,432] Ephedrine 0.5 mg/kg intramuscularly is effective for prophylaxis and treatment, with efficacy comparable to that of droperidol and sedation scores lower than placebo.[433] No value exists in prescribing a previously used antiemetic drug within 6 hours of previous administration, but other second-line drugs may be considered should first-line management fail. These options include small-dose IV naloxone; propofol 20 mg; phenothiazines, including prochlorperazine, perphenazine, or small-dose promethazine (6.25 mg); or a neurokinin antagonist.

SPECIAL AREAS

OFFICE-BASED PRACTICE

Office-based anesthesia is a form of ambulatory anesthesia that is rapidly expanding in North America and some parts of Europe. Arguably, the first ambulatory surgery center in the United States (the Downtown Anesthesia Clinic in Sioux City, Iowa) was an office-based practice.[2] Simple, minimally invasive surgical procedures have been performed in physicians' offices for many years, using either local anesthesia or sedation. There is now a growing involvement of anesthesiologists, especially as the complexity of office-based surgery increases.

Advantages of office-based surgery include improved convenience for the patient, but the primary driver has been more control over scheduling and the work environment for the surgeon. The potential exists for significant profit going directly to the surgeon, but in addition, the lower overhead costs in this setting result in significantly lower overall costs for the procedure. For example, the total cost of a laparoscopic inguinal hernia repair was three and a half times greater when performed in a hospital setting compared with an office facility.[434] The costs of open hernia repair[434] and various rhinology procedures[435] were approximately 2.5 times less when performed in the office. However, legitimate concerns have been raised about the safety of office-based surgery. One comparative study showed a more than 10-fold increase in adverse incidents and deaths for procedures performed in a physician's office compared with an ambulatory surgical center.[436]

These disasters are often the result of unqualified or untrained individuals administering sedation in unsuitable or unaccredited facilities.[436,437] Deep sedation appears to be a considerable risk factor. From the ASA closed claims database, 40% of the deaths resulting from MAC occurred during facial and eye surgery, which are commonly performed in the office setting.[300] Hypoxia and hypoventilation resulting from oversedation was the most common cause of death, with poor vigilance, inadequate monitoring, and delayed resuscitation contributing to the deaths, half of which were judged to be preventable.[300] The common perception that sedation is safer than general anesthesia is not supported by these data.

In the United States, the regulation of office facilities is the responsibility of individual states, yet as of 2012, only a bare majority of states have such regulations.[438] Regulation does appear to improve safety, because no deaths were reported in a series of more than 23,000 cases from a fully accredited office staffed by board-certified anesthesiologists and surgeons.[439] Guidance on office-based anesthesia is available from the ASA and SAMBA,[440] and comprehensive recommendations from other organizations and experts have been published. Typical recommendations for safe office-based anesthesia are summarized in Box 89-2. In essence, the office setting must adhere to the same standards of care required in a hospital-based or freestanding ambulatory surgery facility. Strong safety processes must be in place, because the isolated office-based environment means that outside help is not immediately available.

The selection of patients for office-based anesthesia should adhere to robust guidelines for safe anesthetic care. Because perioperative complications are harder to manage in an isolated environment, selection criteria may need to be more restrictive than those currently advocated for ambulatory surgery in the hospital setting.[42] The selection

BOX 89-2 ***Summary of Office-Based Surgery Practice Guidelines Collated From U.S. Regulatory Bodies***

- Employment of appropriately trained and credentialed anesthesia personnel
- Availability of properly maintained anesthesia equipment appropriate to the anesthesia care being provided
- Documentation of the care provided as complete as that required at other surgical sites
- Use of standard monitoring equipment according to the American Society of Anesthesiologists policies and guidelines
- Provision of a postanesthesia care unit or recovery area staffed by appropriately trained nursing personnel and provision of specific discharge instructions
- Availability of emergency equipment (e.g., airway equipment, cardiac resuscitation)
- Establishment of a written plan for emergency transport of patients to a site that provides more comprehensive care should an untoward event or complication occur that requires more extensive monitoring or overnight admission of the patient
- Maintenance and documentation of a quality assurance program
- Establishment of a continuing education program for physicians and other facility personnel
- Safety standards that cannot be jeopardized for patient convenience or cost savings

process must include a matrix of procedure invasiveness, patient complexity, and the capabilities and comfort levels of the facility and its personnel.[440] Preoperative preparation should be guided by the same clinical acumen and common sense that drives the decision-making process at freestanding surgery centers, with any coexisting diseases under good control. Anesthetic techniques suitable for office-based surgical procedures are similar to those used for hospital-based and freestanding ambulatory surgery procedures. MAC remains common, although clearly a great challenge exists in "the judicious and skillful use of MAC anesthesia to achieve adequate sedation and analgesia for increasingly invasive procedures."[441] Increasingly a move toward light general anesthesia is occurring—that is, using an LMA or facemask for airway management.[442,443] Propofol, sevoflurane, and desflurane are all suitable within the office setting, although an anesthesia machine is required to deliver volatile anesthetics. Standard equipment can be installed in frequently used offices, and portable equipment has been developed for less frequent use.[437] Fast-track recovery is the ideal with patients who are awake, alert, and able to transfer themselves from operating room table to a reclining chair, thus facilitating room turnover in approximately 10 minutes and home discharge within an hour of awakening.[437] It is important to minimize PDNV.[444] Recommendations have been made for other outcome measures that should routinely be audited after office-based anesthesia.[440,445] The American Medical Association issued a set of Office-Based Surgery Core Principles to promote safety and quality of health care services for office procedures requiring sedation and anesthesia.[446]

In the United Kingdom, a similar practice of office-based dental anesthesia was in place for several decades. A series of anesthetic deaths in dental offices led to several reviews, culminating in recommendations that all anesthetics be administered by accredited anesthesiologists with specific training and experience in dental anesthesia, as well as recommendations regarding resuscitation equipment and the availability of drugs needed for emergency use.[447] Partly because of the high costs of equipment and maintenance, the net result was the movement of all anesthesia out of the dental office and back into the hospital environment.[448] Subsequently, office-based anesthesia has never developed in the United Kingdom. Minor surgery under local anesthesia is performed in some specially equipped primary care surgery centers, whereas the majority of procedures that are performed in offices in the United States are managed in hospital-affiliated day surgery units (DSUs), procedure rooms, or surgical outpatient clinics in the United Kingdom.

ANESTHESIA IN REMOTE LOCATIONS

Many surgical conditions that formerly needed treatment in a hospital outpatient operating room are now being managed by interventional procedures done by nonsurgeon physicians in radiology, cardiology, and endoscopy (see also Chapter 90). In many cases, deep sedation or anesthesia is still required, meaning the anesthesiologist has to move into unfamiliar and often hazardous environments. The problems associated with these diverse locations are considered in detail in Chapter 90, but because many of the procedures are performed on an ambulatory basis or require anesthetic management according to all of the usual short-stay principles, a brief description is required here. The basic sedative and anesthetic techniques already described are suitable for most cases, but the conduct of anesthesia is likely to have to be modified according to the specific environment.

Administration of anesthesia or sedation at remote locations is associated with significant risk.[449] Some of these risks are specific to particular areas (Table 89-7) but commonly include an unfamiliar environment; small, cramped, or dark rooms; restricted patient access; inadequate or poorly trained support; restrictions on patient monitoring; and inadequate resources. An analysis of ASA closed claims arising from anesthesia care in remote locations revealed that adverse events had a higher probability of death than those arising in the operating room[450] and were primarily caused by an adverse respiratory event (44%). MAC was the most common anesthetic technique, and respiratory depression secondary

TABLE 89-7 SOME HAZARDS ASSOCIATED WITH ANESTHESIA IN REMOTE ENVIRONMENTS

Area	Examples of Specific Hazards
Magnetic resonance imaging (MRI) scanner	Noise Strong magnetic fields; no ferromagnetic equipment within scanner Peculiarities of MRI-compatible equipment Remote monitoring may introduce delays (e.g., capnography) Risk for induced currents causing burns in coiled cables Compliance and dead space within extra-long breathing circuits
X-ray and interventional radiology	Radiation exposure; mobility limited by lead gowns Often low light levels Restricted access and unexpected movement of x-ray equipment Patients may have significant comorbidities Allergic reactions to contrast media Limited patient access in CT scanner
Endoscopy suite	Dark environment, limited access Patients may have significant comorbidities Risk for hemodynamic disturbance with bowel preparation or vagal stimulation Shared airway in upper endoscopy ERCP performed with patient in prone position with added hazards of radiology
General issues	Unfamiliar environment Old or unfamiliar equipment Emergency drugs and equipment may be rarely used or checked Lack of dedicated or trained assistance Scavenging may be difficult or absent

CT, Computed tomography; *ECRP,* Endoscopic retrograde cholangiopancreatography.

to oversedation accounted for over a third of the claims. Care that was substandard and preventable by better monitoring was implicated in the majority of claims associated with death.[450] In the United States, the CMS mandates that the chiefs of anesthesia services monitor and evaluate sedation practices throughout the hospital, and accrediting organizations, such as TJC and DNV, audit for compliance.

HOME READINESS AND BEYOND

PATIENT INFORMATION

Before discharge, patients should receive postoperative instructions concerning aftercare, their transition to normal activities, and any requirements for follow-up. These instructions should be in writing[451] because retention of information is impaired during early recovery from anesthesia,[452] and ideally they should be repeated to the patient's escort. Besides general advice, discharge information should include the early warning signs for the main complications of the specific procedure the patient has undergone[451] and the action to take should these occur.

CRITERIA FOR DISCHARGE

Discharge of the patient after ambulatory surgery and anesthesia is a physician responsibility in the United States,[10] fulfilled by physician-written discharge criteria (Box 89-3). Typically, patients should be oriented and comfortable with cardiovascular stability (including when standing) and problem-free wounds. Alternatively, discharge criteria may be incorporated into a scoring system, such as the Post-Anesthetic Discharge Scoring System (PADSS).[453] Voiding urine is no longer considered an essential prerequisite for discharge in those at low risk for urinary retention, even after spinal anesthesia.[454] For patients at higher risk, the bladder volume should be assessed by ultrasound scanning[455] and the patient managed accordingly (Fig. 89-6). Actual discharge is frequently nurse-managed,[451,456] provided patients have been managed according to an appropriate protocol and have met all the necessary discharge criteria.

BOX 89-3 ***Criteria for Facility Discharge at the Brigham and Women's Hospital, Boston, Massachusetts***

Alert and oriented to time and place
Stable vital signs
Pain controlled by oral analgesia
Nausea or emesis mild, if present
No unexpected bleeding from operative site
Able to walk without dizziness
Has been given discharge instructions and prescriptions
Accepts readiness for discharge
Adult present to accompany patient home

Courtesy B. K. Phillip.

No rationale exists for a minimum observation period after ambulatory surgery in most cases, although patients clearly must be observed for a sufficient period to ensure cardiovascular stability. One possible exception is tonsillectomy, in which a minimum observation period of 6 to 8 hours has been advocated to detect most primary hemorrhages.[28] However, even this has been challenged, with a 4-hour observation period[457,458] or less[459] regarded as safe.

AFTERCARE AND FOLLOW-UP

Appropriate aftercare is one of the main safety features of ambulatory surgery. Acute complications may be related to anesthesia or surgery, and patients should receive careful predischarge education about what may occur for both. All patients should be provided with a 24-hour telephone number for emergency contact. This is often the ambulatory surgery unit during the daytime, but it may be necessary to provide another number or better still to automatically transfer calls when the unit closes at night.[451] In the United States, patients are also routinely given their surgeon's office and answering service number to contact directly for surgical issues. Although the U.K. health care system includes primary care doctors, they have limited experience in potentially life-threatening early postoperative complications and should not be called first. If the patient's call to the facility or physician does raise concerns, it is important that the patient be brought back for early surgical review; going to the emergency department also can introduce unnecessary delay. Because the ambulatory patient is self-caring and likely to mobilize early, symptoms of surgical complications are noticed and reported sooner than if the patient were recovering in the hospital environment, allowing earlier detection and increased safety.

Follow-Up and Outcome Measures

Most ambulatory surgery units routinely telephone their patients on the first postoperative day. This allows measures to be recorded and audited. The ASA has developed a set of outcome indicators specifically for ambulatory and office-based surgery and anesthesia.[460] These include outcome events of interest for days 1, 14, and 30 and ongoing continuous quality indicators. The International Association for Ambulatory Surgery[461] has developed a series of indicators (Table 89-8) useful in the evaluation of the overall success of organizational performance, and these mirror the advice from other national specialist societies.[42,462] Lemos and Barros[463] further defined the value of outcome reporting in a range of domains subdivided into clinical, organizational, social, and economic factors[463] that allows the reporting of both individual and institutional performance (Table 89-9). Return-mail questionnaires can be used for patient follow-up after ambulatory surgery to help identify common sequelae that ambulatory patients should realistically expect to experience.[368] No matter how data are collected, it is important that information from quality indicators is fed back in an effective way to individual clinicians and clinical units to support continuous improvement.[464]

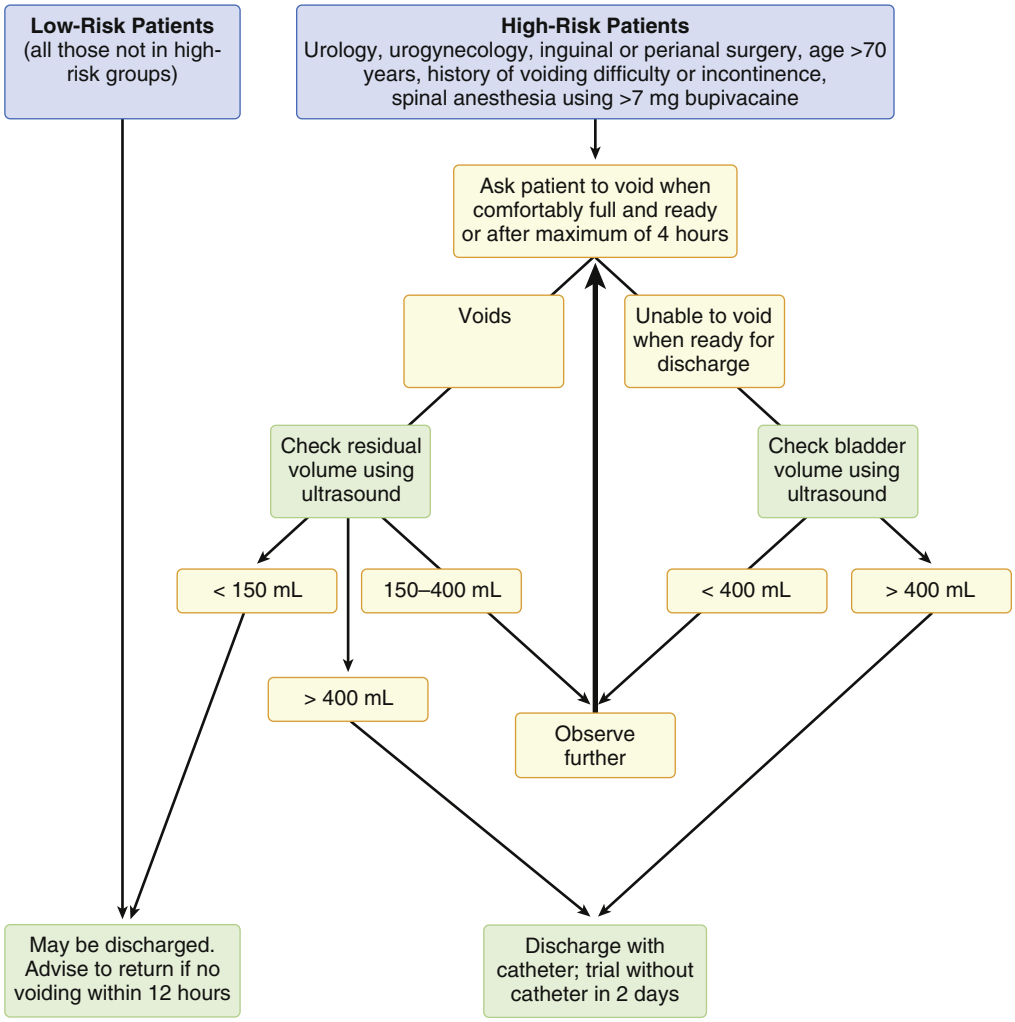


Figure 89-6. Flowchart illustrating the management of patients who fail to void urine after ambulatory surgery. (Reproduced from British Association of Day Surgery. Spinal anaesthesia for day surgery patients. London, <http://www.bads.co.uk.>

TABLE 89-8 **OUTCOME INDICATORS FOR AMBULATORY SURGERY SUGGESTED BY THE INTERNATIONAL ASSOCIATION FOR AMBULATORY SURGERY**

Indicator	Reason
Failure to attend the ambulatory surgery center/unit	Acute medical condition Decision of the patient Organizational reasons Other reason (explain)
Cancellation of the booked procedure after arrival at the ambulatory surgery center/unit	Preexisting medical condition Acute medical condition Organizational reasons Other reason (explain)
Unplanned return to the operation room on the same day	
Unplanned overnight admission	Surgical reasons Anesthetic or medical reasons Social or administrative reasons
Unplanned return of the patient to an ambulatory surgery unit or hospital	<24 hr >24 hr and <28 days
Unplanned readmission of the patient to an ambulatory surgery unit or hospital	<24 hr >24 hr and <28 days

Adverse Effects After Ambulatory Surgery

Minor adverse events are common after ambulatory surgery and anesthesia (86%).[368] Drowsiness is the most common effect persisting after discharge (62%), and aches and sore throat are common in intubated patients (47% and 49%, respectively). Headache (25%) and dizziness (20%) also occur, but nausea and vomiting after discharge are less common (17% and 7%, respectively). Patients may take 2 to 3 days before they are able to resume their usual activities.[368] Information about these known side effects should be incorporated into the preoperative patient education and in the United States may be incorporated in an anesthesia consent form.

Acute cardiovascular events (hypertension and hypotension, dysrhythmias, cardiac ischemia, and arrest) occur with an overall frequency of 2.9%, with greater risk in patients with preexisting cardiovascular morbidity; respiratory events (hypoxemia, laryngospasm, bronchospasm, aspiration, pulmonary edema, and pneumothorax) occurred in 0.1% of the study population, with increased risk in smokers, asthmatics, and the obese.[51] Unanticipated overnight admission has a worldwide reported incidence of between 1% and 6%. Caution is required in the use of this indicator as a standard to achieve, however, unless the reasons for the admission are documented.

TABLE 89-9 OUTCOME MEASURES IN AMBULATORY SURGERY

Category	Specific Outcome Measures
Clinical	Perioperative cardiovascular and respiratory adverse events
	Minor postoperative morbidity
	Pain
	Nausea and vomiting
	Other: Sore throat, headache, drowsiness
	Unplanned return to the operating room on the same day of surgery
	Unplanned overnight admission
	Unplanned return or admission to the Day Surgery Unity (DSU) or hospital:
	<24 hr
	>24 hr and <28 days
Organizational	Proportion of elective surgery performed as day case
	Accessibility to ambulatory surgery programs:
	Number of different procedures included
	Cancellation of booked procedures
	Failure to arrive at the DSU
	Cancellation after arrival at the DSU
Social	Patient satisfaction
	Functional health status and quality of life
Economic	Efficiency rate of operating room usage

From Lemos P, Barros F: Outcome measures. In Smith I, McWhinnie D, Jackson I, editors: *Oxford specialist handbook of day surgery,* London, 2011, Oxford University Press.

Although the indicator may provide evidence of inadequate preoperative assessment and patient optimization, differences in surgical case mix and complexity may explain any variation across institutions. Ultraconservative selection criteria could result in an extremely low overnight admission rate and inappropriately give the impression of a highly performing unit rather than one that was excessively cautious with patient selection. Cross comparison of this indicator with rates of ambulatory care as a proportion of all elective surgery, either by specialty or specific operation, could assist with interpretation.

Patient Satisfaction With Ambulatory Surgery

Patient satisfaction is a difficult metric to define, depending somewhat on the patient's expectation of care. Nevertheless, patient satisfaction is generally very high after ambulatory surgery. The patient experience was improved when facility staff was thought to be friendly and the surgeons discussed findings before discharge,[465] and these factors were perceived by postoperative ambulatory surgery patients as being more important than management of postoperative pain, starting the IV smoothly, and avoidance of delays. Others have found that provision of accurate information about the expected perioperative process is important; other factors that lead to higher satisfaction are effective postoperative analgesia, minimal emetic sequelae, staff courtesy and privacy in the unit, short waiting times before surgery, no perception of being rushed, postoperative telephone contact, and naturally, good surgical outcome.[461]

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Chapter 90

Non–Operating Room Anesthesia

WENDY L. GROSS

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Key Points

- The non–operating room arena represents an expanding perimeter of the practice. As technology develops and patient acuity increases, non–operating room anesthesia (NORA) cases become more demanding in terms of both patient management and necessary resources.
- Financial and operational constraints create additional management challenges. Significant differences in practice result from the fact that NORA cases occur in places remote from the operating room (OR) and are performed frequently by medical proceduralists who are just now learning about the scope of anesthesiology practice. In addition, anesthesiologists are unfamiliar with the demands of providing an anesthetic in an environment in which radiation hazards are significant, equipment restricts mobility and access to patients, and changes to setups used in the OR are common.
- This chapter serves as a general guide to the cadence and focus of procedure performed outside of the OR, and highlights some of the adaptations, both cultural and practical, that are needed to provide a safe and optimal anesthetic.

OVERVIEW: DEFINING NON–OPERATING ROOM ANESTHESIA—WHAT IT IS AND HOW WE GOT HERE

Non–operating room anesthesia (NORA) refers to all procedures performed in off-site locations. NORA includes a very diverse set of procedures. Historically, cases managed outside of the operating room (OR) were minor, targeted, infrequent, and involved relatively stable patients and seldom required anesthesiology support. However, the current situation is very different. NORA cases now involve nearly every medical specialty, generate (in many hospitals) volume and revenue equivalent to that of the OR, and are as demanding of anesthesiologists as the most advanced surgical OR procedures. They constitute a major expansion of our practice perimeter and require the same (if not more) attention to operational efficiency, planning, rigor, and consistency with which the OR is managed.

The flood of NORA procedures now requiring anesthesia support has evolved from rapid technologic development and unprecedented increases in patient acuity as a result of aging and improved survival. NORA procedures include everything from minor to very major endeavors and range from day surgery cases to intense cardiac procedures requiring after care in the intensive care unit (ICU). Many NORA cases are performed on patients deemed "too sick for surgery"; in some cases, the patients are critically ill or unstable and therefore a need for advanced and specialized anesthesiology skills arises.

The purposes of this chapter are twofold. The first is to highlight the intrinsic, common, and unique characteristics of NORA cases that impose unusual constraints on anesthesiologists in the out of OR arena. The second is to present goals, methodologies, and pitfalls of interventions that may be unfamiliar to anesthesiologists. This chapter does not reiterate basic principles of anesthesiology practice described elsewhere in the book, nor does it describe the technical details of novel procedures. It should serve rather as a general guide to NORA procedures and the environment itself. The key to providing an optimal anesthetic (in or out of the OR) is thoughtful consideration of anesthetic options in the context of both the principles of the procedure and the physiology of the patient. No substitute exists for taking time to discuss the procedure and the patient with the medical proceduralist. This is not always easy, because—unlike surgeons—most medical providers are uneducated about anesthesia, are unfamiliar with the skill sets of anesthesiologists, and lack experience with many relatively rare but serious complications (e.g., loss of airway, allergic reactions). Many still consider anesthesiology support unnecessary because they do not normally think about the synergistic ramifications of moderate to deep sedation and complex procedures for an older, sicker patient population. This chapter equips anesthesiologists with a basic understanding and vocabulary with which to establish effective dialogue, in the hope of broadening our own horizons and helping to educate our colleagues about the benefits of collaborative practice.

NOVEL CHARACTERISTICS OF NORA CASES

NORA cases are characterized by three distinctive features: location, operator, and relative novelty. First, the procedure *never* takes place in a typical operating suite; second, for the most part (although not always) the operator performing the procedure is not a surgeon but rather a medical interventionalist or proceduralist; and, finally, the procedures and technologies used may be novel in one way or another. When anesthesiologists are faced with the need to provide services to nonsurgeons in non-OR locations, problems arising from scheduling inconsistencies, ad hoc requests, inadequate physical plant, poor communication, and resource limitations can obstruct expeditious resolution. The increasing incidence of medically complex patients needing urgent intervention but lacking periprocedural evaluation creates additional stress. An expanding need for anesthesiology services outside the OR presents an opportunity for us to reaffirm our skills and mission.

For many acute and chronic disorders, medical procedures now target the same problems and patients treated previously only with surgery. Some practitioners believe that noninvasive medical procedures are better tolerated than invasive surgical procedures. However, because noninvasive procedures are in many cases relatively new, long-term outcome studies are still lacking. But certainly for a rapidly broadening spectrum of acute and chronic problems, surgery in the OR is no longer the only potential route of treatment.

Medical and surgical procedures now demonstrate enormous overlap. Pulmonary embolism, for example, can be treated in the OR, in the catheterization laboratory, or in the interventional radiology suite. The ultimate choice of venue may be a function of acuity of presentation, but likely also depends on who the patient sees first and who is available.

As anesthesiologists, our mission is to safeguard the patient through the course of treatment, whatever the treatment is, and wherever it occurs. For the most part, history has placed us in the controlled environment of the OR, where we have organized schedules, protocols, and standards of behavior and communication. We have grown comfortable there, and perhaps a little complacent.

The perimeter of our landscape now expands beyond the familiar domain of the OR, where we enter the domain of medical practitioners—for example, interventional cardiologists, interventional radiologists, gastroenterologists, radiation oncologists, and electrophysiologists. It is our obligation to follow the need and import our clearly successful OR safety standards to new venues, patients, and practitioners. This means leaving some of the dogma of the OR behind and creating universal standards for broader practice. As the landscape changes, unusual and perhaps unforeseen obstacles are created. New venues pose physical, political, economic, and medical challenges that are often unanticipated. This chapter delineates the hurdles we face—from the most basic to the most complex and from the financial to the medical—and offers a perspective that is becoming more widely accepted. The goal is to promote awareness, encourage preemptive planning, and clarify the need for collaborative strategy design.

UNIQUE OBSTACLES: FROM PHYSICAL PLANT TO THE MEDICINE-ANESTHESIOLOGY CULTURE GAP

Non-OR procedure suites are constructed with the procedural operator in mind, without regard to the needs of anesthesiologists. They are often crowded and unfamiliar. Access to the patient may be inadequate. Almost universally, for example, procedure suites that use fluoroscopy for guidance are configured so that the C-arm limits access to the patient's head and obstructs direct communication between the anesthesiologist and the proceduralist. Hemodynamic and other monitoring may be controlled by someone outside the suite and may not be visible to the anesthesiologist. Lead screens may not be available, and when they are positioned to protect the anesthesiologist from radiation, pumps and intravenous lines may be inaccessible. The fluoroscopy screen is usually at 90 degrees to the person administering the anesthetic, so he or she cannot see the screen while standing behind the patient's head (the position we are used to in the OR). Often it is impossible to both have anesthesia equipment and monitors close to the patient and procedural equipment in the proper place.

In many cases, procedural suites are remotely located. Common electrical and mechanical malfunctions are not easily remedied because technical support is not nearby and additional supplies may not be accessible in timely fashion. This situation demands that care be taken *before the start of the procedure* to ensure that equipment is stocked and working and that backup options (emergency supplies, difficult airway equipment) are functioning and readily available. Certain procedure rooms require anesthesiologists to spatially reorient themselves and their equipment to adapt or reconfigure setups that are routine in the OR. This requires mindfulness about what we usually take for granted. Distraction of our focus away from patient care can be potentially disastrous in the face of novel or complex procedures.

Conversely, much equipment routinely found in traditional ORs is not present in medical procedure suites. Although anesthesiologists understand the need to import this equipment, medical proceduralists do not. For example, gas scavenging may be unavailable, oxygen and suction may be suboptimally placed, and monitoring equipment may not function properly because of interference with mapping systems or other electronic interfaces. Regardless of these preexisting conditions, it is the obligation of the anesthesiologist to understand and implement changes needed to administer anesthesia safely. To this end the American Society of Anesthesiologists (ASA) has formulated a statement regarding NORA locations that articulates minimum standards for all procedures performed in these areas,[1] but these standards are quite fundamental and may not fall within the reference frame of medical proceduralists.

Even more formidable than the physical constraints imposed by non-OR locations is the cultural mismatch that can dominate interactions between medical practitioners and anesthesiologists. Lack of mutual experience and vocabulary, extreme specialization, and unique financial and political motivators may contribute to poor

communication and misperception. Mutual goals are difficult to identify in these circumstances; medical interventionalists may find anesthesiologists obstructive, and anesthesiologists often find medical proceduralists cavalier. Many medical proceduralists do not understand the skill set of anesthesiologists, much less the intricacies or subtleties of administering an anesthetic—that is, they do not know what they do not know. Likewise, many anesthesiologists have only a basic idea (at best) about what is happening during the course of a noninvasive procedure and do not ask enough questions. They may have limited experience in a particular venue, the procedure may not be observable, and fluoroscopy screens may be out of the field of view or uninterpretable. Usually the proceduralist is unlikely to communicate the course of the procedure during the case. Anesthesiologists may be unaware of pitfalls and likely complications of the procedure; even though they would not undertake administering an anesthetic in the OR without understanding the surgery, they do this in non-OR locations without a second thought. Bridging the communication gap requires effort, but it is absolutely critical to optimizing outcomes.

Often proceduralists are consultants, enlisted by primary care providers who do not convey all relevant information. Even when all information is provided, specialization predisposes proceduralists to overlook general concerns and concentrate on their point of expertise; electrophysiologists, for example, might focus on the need for prompt treatment of tachycardia-mediated cardiomyopathy but be unaware of contributory problems and the extent to which they must be dealt with to avoid increased morbidity. Anesthesiologists might not think about how coughing on extubation might predispose patients who have had groin sheaths to serious hematomas.

When interventionalists undertake novel procedures using new technology, the situation can be even more troubling. The course of the procedure may be unknown, the timing and sequence of events may be unclear, and the focus of the procedure may change in midstream. When the proceduralist is unsure of what is happening, the anesthesiologist cannot possibly have all the information needed to administer a tailored anesthetic. Then, as technologic innovation accelerates, financial and political drivers come into play outside of the OR. Expensive new technology is desired by all, and equipment purchases can require enormous capital investments, which are depreciated over many years. Upgrading and maintenance constitutes an additional expense, and to justify the outlay, expensive equipment needs to be used. Ensuring that the appropriateness of the patient does not become secondary to the need or wish to use the latest technology sometimes requires insight from a physician with a different perspective. Anesthesiologists may find themselves in unusual non-OR locations administering anesthetics for noninvasive procedures that are long and complicated, although the same procedures performed invasively in the OR are shorter and relatively straightforward. This can be disconcerting, but it is integration of medical and surgical viewpoints, along with intellectual flexibility rather than adherence to dogma, that underlies the new collaborations that must be forged.

Surgeons realized long ago that effective performance of surgery required the administration of an appropriate anesthetic by another physician. They are thus accustomed to sharing their procedures with other medical practitioners. This is not yet always the case for medical proceduralists, who are used to working alone and ordering sedation by a nurse. As medical procedures become even more technically demanding and patient conditions more complex, medical proceduralists will find increasing benefit from the support of anesthesiologists. This requires collaboration and teamwork, but teams cannot function without mutual respect, excellent communication, common vocabulary, shared experience, and some truly overlapping competencies. Thus, argument exists for grouping medical specialists with specialty trained anesthesiologists who share a mutual knowledge base. Amalgamation of medical and surgical perspectives is mission critical in driving innovation and averting disaster outside of the OR. Unfortunately, this synergism is sometimes missing from the anesthesiologist-medical proceduralist dyad. Our hope is to broaden mutual understanding and nurture intellectual curiosity in the quest for the best possible patient management strategies. In pursuit of this goal, we can build on the outstanding record of improved patient safety and outcome that characterizes the history of anesthesiology.

FINANCIAL AND OPERATIONAL CONSTRAINTS

The impact of financial and operational infrastructure on the delivery of anesthetic care outside the OR is substantial. Because medical, financial, and operational constraints and priorities often become blurred, it is important to understand the difference between what does and what *should* drive the direction of program development. Unsettled questions about which patients require an anesthetic; when, where, and with how much notice; and who should pay how much for this type of support can remain unresolved or be inappropriately decided if financial discrepancy, political battles, and medical need are not prioritized or organized. The role of anesthesiologists may be central here, but the quality, safety, and efficiency of the care they deliver is a function of the environment as a whole.

EFFECTS OF PAYMENT SYSTEMS

Private health insurance evolved as hospitals transitioned from repositories for the impoverished and dying into institutions where people actually recovered from illness. Hospitalization plans, initially developed by hospitals in the 1930s, were a way to supplement the economic resources needed for growth and expansion. In those days, hospitals functioned as extensions of private offices in many ways. Since then, payment systems have become more bureaucratic and complex, but remain unsophisticated in terms of promoting care integration.

Medical optimization and financial efficiency are predictably not the end products of fee-for-service payments. As the population ages, care is increasingly specialized

and complex. The Medicare Payment Advisory Commission (MedPAC) reported that as of 2006, the average Medicare beneficiary saw five doctors per year and Medicare beneficiaries with three or more chronic conditions saw more than 10 physicians a year.[2] Now, new nonsurgical approaches to what were once surgical problems introduce an additional list of specialist providers and unanticipated outcomes to an already complex system. For patients whose care involved four or more doctors, MedPAC reported that 48% experienced medical errors, medication errors, or laboratory errors. As technology advances and the population ages, risks and benefits change and new genres of service emerge and expand. Imaging services, which have exploded across disciplines in the last decade, are now provided by radiologists, vascular surgeons, cardiologists, internists, anesthesiologists, and surgical subspecialists.[3] Traditional fee-for-service payment systems are not designed to ensure that the right treatment is performed on the right patient at the right time by the right physician in the right venue. The result is that groups of assorted medical proceduralists provide in-hospital care that is fragmented and isolated in terms of delivery and billing—perpetuated by silos of specialized care, despite the interdependent nature of specialty services. Coordination of care is needed, but this service is iatrogenic, unreimbursed, and often disregarded. Uncoordinated, fragmented care facilitates unpredictable need, duplication of service, variability of resource use, and inconsistent application of quality standards. Payment silos create misalignment of goals across specialties with similar focus, creating competition rather than collaboration among disciplines and pitting the interests of one set of providers against another and discouraging coordination of services.

In addition, because Medicare lags in its recognition of the impact of new technology on treatment cost and outcome, payment for new technology initially lags behind, thereby slowing rates of adoption. It then adjusts payments late, encouraging overapplication of new technologies in potentially inappropriate situations. The system is unable to keep up with an ever-expanding proliferation of new services, new sites, and new practitioners. Patients are left without advocates in the midst of a medical and financial maelstrom.

Anesthesiologists are particularly vulnerable to undercompensation in the silo scheme of payment structures, because they may be at the mercy of inefficient scheduling and unpredictable utilization rates. Additionally, many of the indirect services they provide are not billable. Preprocedure evaluation, postprocedure care, and periprocedural management services can be extremely time consuming but are not reimbursed. Fee-for-service systems encourage increased volume but do nothing to encourage care coordination or improved quality of care. Discussion of these issues is ongoing at national levels.[4]

Bundled payments, medical home models, and accountable care organizations are three avenues of reform intended to increase interdisciplinary collaboration and coordination of care between payment siloes within institutions. Herculean changes in political and philosophical underpinnings will be required for implementation, and it remains to be seen how effective these undertakings will be in improving care. In any case, financial infrastructure remains a key determinant of behavior. It is incumbent on anesthesiologists to remain at the forefront of new developments as demand for anesthesia services in less traditional arenas broadens in an environment that diminishes control over the revenues we generate.

OPERATIONAL CONSTRAINTS

It is quite clear that despite a multitude of publications condemning OR inefficiency and poor productivity, institutional tradition, idiosyncrasy, and surgical convenience continue to create havoc with OR scheduling practices and policies. Outside of the OR, medical proceduralists are themselves often highly specialized consultants who know little about the overall condition of their "referred" patients. They are also uninformed about the practice of anesthesiology and relatively inexperienced in working with another "support" physician. To make matters worse, the procedures are often ill defined or novel. All of these variables make scheduling non-OR cases extremely difficult. Key problems in scheduling and staffing non-OR cases include the following:

1. Non-OR anesthetizing locations are often adapted to the specific procedure being undertaken and the needs of the medical proceduralist. Unlike ORs, they are noninterchangeable.
2. Variability may be more problematic because the number of staff in any one non-OR venue is smaller and less flexible.
3. Block time may not be in place, and anesthesia cases can be placed anywhere on the schedule, making it difficult to utilize anesthesiology staff productively and increasing the likelihood of underutilized but deployed resources.
4. Non-OR procedures may take place far from the OR. Lack of storage space for anesthesia equipment may impose longer turnover time and the need for additional anesthesia technical services.
5. Many non-OR procedure suites perform procedures on patients referred from outside providers or services that are booked through a central scheduling office. Periprocedural evaluations are often very cursory or not done at all. This imposes an additional bottleneck for the anesthesiologist who may need to perform a preoperative evaluation before the procedure and cancel or delay cases at the last minute.
6. Because many non-OR procedures are novel, it is difficult to estimate the length of the procedure. Booking times may be unrealistic, and scheduling anesthesiology time may be difficult. Additionally, with new technology and noninvasive methods, it is very easy for the proceduralist to redirect or expand the procedure during the case.[5]

As a group, non-OR cases are more variable, less predictable, and, therefore, more difficult to staff cost effectively. Some of these difficulties are technical, but some are the result of cultural discontinuity and poor communication between anesthesiologists and medical proceduralists.

Effective management control of this arena requires the following at the very least:

1. If possible, establish a contract between the anesthesiology and procedural departments that encourages uninterrupted utilization of available time and minimization of differences between "staffed (contracted) time" and "productive time." In addition, it is worth considering a transfer price that confers cost neutrality to anesthesia departments while leaving open the option to bill for services to cover costs.
2. Include all non-OR cases within the electronic database for OR cases, so that resource deployment can be planned and modified as needed.
3. Create a block schedule that makes sense for the procedural area; that is, if the area tends to run late, then book an anesthesiologist to be there for those hours instead of running overtime on the days that more or longer procedures are done. Try to encourage productive utilization of anesthesiology contracted time.
4. Implement real-time scheduling. Calculate earliest start times, optimal arrival times, and adjusted preoperative fasting (nothing by mouth [NPO]) guidelines for all patients. Avoid having patients sitting in preoperative areas for extended periods because this overloads nurses and puts a hold on patients exiting procedure rooms while waiting for recovery area beds.
5. Improve specialized triage for scheduled outpatients in each procedural area by creating triage forms and staffing an intake office to minimize delays and cancellations. Create a situation in which specialists are invested in appropriate preprocedure evaluations.
6. Anesthesiology oversight of periprocedural triage and postprocedure recovery areas should aim to ensure both optimization of patient comorbidities and prompt treatment of postprocedure complications. Oversight includes unexpected admissions, longer than necessary recovery times, impact throughput, efficiency, length of stay, and medical outcomes in non-OR arenas just as they do in the OR.

Staff and non-OR locations can be scheduled in many ways. The principles outside of the OR are the same as they are in the OR. These are to reduce variability, schedule to avoid ad-hoc solutions as much as possible, and use real data when available (i.e., real-time scheduling for blocks). In addition, consideration of available time and productive time is important. Contracts should discourage situations in which procedural areas use their rooms at rates lower than those of the OR. Full schedules and adequate revenue collection should be incentivized; otherwise a subsidy of the anesthesia department is needed because the opportunity cost incurred is often significant. Without doubt the demand for non-OR anesthetics will increase. Whenever possible, proceduralists should be involved in scheduling schemes so they are invested in the process. The goal is to collaborate so anesthesiology goals are aligned with those of the proceduralists and integration of mutual competencies occurs. In this way, the value-added importance of the specialty can increase and outcomes improve.

TRANSITIONAL PRIORITIES FOR ANESTHESIOLOGISTS OUTSIDE OF THE OPERATING ROOM

As anesthesiology continues its steady integration into the world outside of the OR, new obstacles and new opportunities arise. Unusual procedural venues and practitioners who are unfamiliar with the scope and practice of anesthesiology challenge standard procedure. Adaptation requires that we confront, explain, reorient, and reinforce our traditional concepts of safe practice and standards of care. Anesthesiology as a specialty has improved OR safety enormously in the past 40 years, and as the scope of anesthesiology broadens, there is even more reason to redefine and remain steadfast in insistence on well-established standards of safe practice, which, although they are second nature to anesthesiologists, may be unfamiliar to medical proceduralists.

DEFINING INTERDISCIPLINARY SAFETY IN NON–OR LOCATIONS: STANDARDIZATION, RELIABILITY, AND COMMUNICATION

The unparalleled record of OR safety established by surgeons and anesthesiologists relies on standardized, routinized practice. Anesthesiologists depend on the predictable characteristics of ORs and of surgeries to optimize anesthetic outcomes and gauge the progress of procedures. All too often non-OR cases are not routine, the patients are not optimized, and the technology is novel. If communication is poor between proceduralist and anesthesiologist, the potential for error and poor outcome increases. Proceduralists would prefer to proceed without anesthesiologists and anesthesiologists are reluctant to be involved; everyone is fine except the patient. The establishment of safety and reliability outside of the OR should seek to parallel the same process that evolved in the OR and in other industries.

Frankel[6] and others have emphasized that environments that facilitate safety and reliability are characterized by the following:

1. Encouragement of continuous learning among all participants
2. A just and fair culture of accountability and responsibility
3. Support for teamwork
4. Data-based drive for safety and reliability
5. Effective communication and flow of information

Depending on the specific venue, NORA procedures may be performed in the context of routines, which differ from those used in the OR. Specialty-specific procedure units can accommodate each of the above with varying degrees of difficulty, depending on the medical, financial, and operational constraints and priorities in place. All of these elements are critical characteristics of a safe environment.

Continuous Learning

The inclusion of continuous learning as an element of process improvement comes from industry[7] but also applies to the context of multidisciplinary undertakings

in medicine. Each factor of production determines some piece of the final product, and because ultimately goal attainment is the sum of successful execution of smaller projects, optimization depends on encouragement of continuous improvement by all team members, *especially when this requires making an effort to understand what is going on in contiguous steps or stages of the process*. Data acquisition and analysis should drive process review, and team members should be encouraged to ask questions and make suggestions. Learning how to do things better as part of a team is not the same as learning how to do one thing better independently. Competition among interdependent facets of an organization may approach an asymptote when it comes to improving outcome or output. Continuous learning implies that improvement-seeking is multidimensional, involving both horizontal (across factors) and vertical (related to end product) processes.

Culture of Accountability and Responsibility

In a culture of accountability, individuals are held accountable for their actions but not for system failures. The relevance to medicine is that analysis of adverse outcomes should be open and disagreement should be managed so that resolution is a function of collaborative thought rather than assignment of blame or the application of power, bias, or tradition. This is especially difficult in environments that challenge the status quo because prevailing culture is changing. Anachronistic notions about "whose" unit or patient it is must be abandoned if interdisciplinary work is to move forward; these are precisely the settings in which accountability and analysis are necessary to improve interdependent functions. The launching and recovery of U.S. Navy aircraft is a well-known process in which this type of outcome-focused, nonpunitive review takes place.[8]

Support for Teamwork Structure

Support for a teamwork structure is a crucial foundation of successful interdisciplinary work. It requires that jobs are clearly defined, that debriefing occurs constructively and within a reasonable time frame, and that leadership take the required steps to ensure that what went well is repeated and what did not go well does not happen again. Fundamental to this is an attitude of mutual respect for other team members; this is often the most difficult for physicians to generate, because they are educated and trained to be self-sufficient, independent, and nondelegating. It is also necessary to recognize that teamwork does not mean sitting around a table patting each other on the back. "Virtuoso Teams"[9] are characterized by smart people who are opinionated, strident, and challenged by an acute need to perform. They get the job done by confronting each other and arriving at a mutually acceptable solution. Leadership is clearly important in this endeavor; conflict resolution and negotiation are key parts of the process.

An environment that supports *data-driven quests for safety and reliability* is critical if process improvement is to occur. As innovative technology develops and procedures become more complex, new operational paradigms will evolve as well. The safe and reliable administration of anesthesia in remote locations should be driven by data analysis, science, and patient evaluation, not by tradition, payment plans, or institutional politics. The acquisition of outcome data is a common undertaking in most institutions. Making these data accessible and available for improving medical care should be a priority, not a novel or difficult endeavor.

Effective Communication and Flow of Information

Effective communication including the flow of information is the most fundamental requirement for safe anesthetic practice outside of the OR. Novel interventions and technologies, unfamiliar to medical proceduralist and anesthesiologist alike, make it imperative that situational awareness, succinct and direct language, timely recommendation, and closed-loop communication are all included as components of the verbal interface between anesthesiologists and procedural operators. Add to this the increased likelihood that the patient has comorbidities that the proceduralist may be unaware of and the fact that the anesthetic may have ramifications for the procedure, and it becomes obvious that a simple *mis*communication or *non*communication can have tremendous effects on the outcome of the case. Even medically correct actions on the part of the anesthesiologist or proceduralist, if not communicated to the other party, can drastically alter outcome. If, for example, the anesthesiologist supports decreasing blood pressure but fails to tell the interventionalist, the proceduralist might continue under the assumption that all is well when in fact a search for retroperitoneal bleeding is more appropriate. Sometimes it is impossible for the anesthesiologist to see exactly what the proceduralist is doing because the fluoroscopy screen is not visible, the mapping is complex, or the intervention is very short and is obvious only to the proceduralist. In this case, the anesthesiologist may literally have to ask the proceduralist what he or she is doing; there is no shame in this. The shame lies in making an assumption when the facts are available for the asking. To create the same degree of safety and reliability outside of the OR as exists in the OR, compromise and adjustment of cultural and medical assumptions is required by all parties. Without good communication this cannot occur.

NEW NON–OPERATING ROOM ANESTHESIA SITES: WHAT IS ACCEPTABLE AND WHAT IS NOT

Potential sites for procedures performed outside of the OR continue to grow and must be assessed as possible anesthesia delivery sites in the context of both the focus and complexity of the intervention and common comorbidities of the patients to be treated. As technology develops, any procedure room outside the OR can become an anesthesiology delivery site. Although it is ideal for anesthesiologists to be involved during the construction of off-site procedure areas, this seldom occurs, and even when it does, the evolution of cases and the broadening of target-patient profiles can render even well-conceived units inadequate. Availability of adequate monitoring equipment is as essential outside of the OR as it is in the

OR, perhaps even more so. The ASA Standards for Basic Anesthesia Monitoring[10] may serve as a fundamental guide, but often specific procedures require more than basic monitoring. Sometimes, monitoring equipment, although present, may not be visible or accessible to anesthesiologists, rendering it useless and making additional equipment necessary. No matter what type or level of anesthetic care is provided, an anesthesia machine should be present (or readily available) in all NORA locations because conversion to general anesthesia is always a possibility. If the room cannot accommodate anesthesia equipment (for size, electrical, or other spatial reasons), it is not an acceptable site for the delivery of anesthesia. Standards of care outside of the OR should be consistent with those in the OR. As sicker patients are increasingly cared for in NORA locations, monitoring assumes critical status. Of course, there is nothing to prevent a service from starting a sedation procedure and then having a "code" when the patient fails conscious sedation, but the hope is that this will wane in coming years. Appropriate monitors increase the likelihood of early detection and amelioration of problems and undesirable outcomes. Because NORA sites are distant from centers of equipment storage and additional anesthesia help, it is critical that appropriate patient monitoring be in place so that problems are detected and solved early. Our success in establishing and maintaining unparalleled safety records in the OR result largely from the consistent use of appropriate monitoring equipment. It is never acceptable to sacrifice patient safety for the convenience or comfort of a proceduralist who may not be used to accommodating equipment space requirements or alarms. Flexibility, innovative thinking, and some explanation to medical proceduralists or technicians who may not understand the need for additional or duplicated equipment, may be required. Maintenance of safety standards is critical to the realization of an adequate anesthetic plan regardless of where it is carried out. In non-OR locations, where patients may require help from or transport to the OR, emergency procedures should be clearly stated and posted, along with phone numbers for accessing emergency help. Adequate preprocedure and postprocedure care space should be available to patients undergoing interventions and for those who receive an anesthetic. It is certainly standard of care that an anesthesiologist be available during the recovery period.[11]

MONITORING IN NON–OPERATING ROOM ANESTHESIA LOCATIONS

Physiologic monitoring is a core competency of all anesthesiologists and a critical feature of safe anesthesiology practice wherever the anesthetic is delivered (see also Chapter 44). Just as monitoring standards of care exist throughout the OR, they must be consistently in place in NORA locations as well. Some studies suggest that adverse events occurring outside of the OR may in fact be associated with more deleterious outcomes and serious injury than those in the OR because minimal monitoring standards are lacking.[12,13] Monitoring in NORA locations is often suboptimal because the need is not identified by anesthesiologists and medical proceduralists are not well informed about what is necessary. Short-sighted cost constraints often determine monitor purchasing. Until recently, pulse oximetry was the primary monitoring used to assess adequacy of oxygenation *and* ventilation, despite the fact that pulse oximetry has serious limitations in this regard. Several publications indicate significant misunderstanding among nonanesthesiologists using pulse oximetry to monitor patients outside of the OR,[14] and changes in ASA guidelines will help change the status quo. Anesthesiologists providing services outside of the OR, however, may find themselves explaining the shortcomings of pulse oximetry relative to capnography, particularly when discussions arise regarding purchase of new equipment for new NORA locations. Several excellent articles and websites are available as resources.[15] Over the last 20 years, capnography has become the standard of care for monitoring not only ventilation, but also circulation and metabolism[16-18] by directly measuring expired carbon dioxide levels and indirectly measuring production of CO_2 at the tissue level and delivery of CO_2 to the lungs. Despite broad utility and clear clinical superiority, capnography is not always available in non-OR locations. Its implementation may be a bone of contention because it is less familiar and misunderstood outside of anesthesiology circles, and it can be expensive to install. Even ICUs are commonly without the capability of using capnography in intubated patients. For cases in which patients are cared for by anesthesiologists, capnography equipment is bundled with the anesthesia machine. But when anesthesiologists are called to step in during failed sedation cases, the absence of capnography equipment can be life threatening and make case management very difficult.

PREPROCEDURAL EVALUATION FOR NON–OPERATING ROOM ANESTHESIA CASES: ADDITIONAL CONSIDERATIONS

Preoperative evaluation is an essential component of anesthesia practice, regardless of where the procedure is performed or who is performing it (see also Chapter 38). Increasingly, patients with serious comorbidities and significant compromise are scheduled to undergo procedures outside the OR. Often no possibility of optimizing these patients is available; they are slated for nonsurgical approaches because they are deemed "too sick for the OR." However, even a seemingly minor procedure can evolve into a disaster in an unstable patient. The ASA Guidelines for Preanesthesia Evaluation[19] of 2012, indicate that a preanesthesia visit should, at a minimum, include the following:

1. A patient interview that includes a physical examination and a review of medical, surgical, anesthetic, and medication history
2. Diagnostic laboratory tests and other relevant diagnostic information
3. Assessment of ASA status
4. Formulation of potential anesthetic plans and presentation of these to the patient

Because several studies have dispelled the notion that there is a body of routine testing that reduces anesthetic risk,[20,21] anesthesiologists should direct testing to areas

highlighted and indicated by the patients' history and the procedure they are to undergo. Many non-OR procedures are scheduled for patients who have not been seen by the interventionalist; therefore, gathering the information can be challenging, and sharing or discussing the information can prove even more difficult. If patients have numerous serious comorbidities, it may be more reasonable to send them to the preoperative evaluation clinic if one is available. If not, then an information-gathering exercise is required, or the proceduralist risks cancelation on the day of the procedure. Occasionally, periprocedural admission or consultation with a specialty service is required. Guidelines regarding preanesthetic evaluation can be found in this book (see also Chapter 38) and many others,[22] and those guidelines apply to non-OR locations as well. Additional concerns in non-OR locations make some comorbidities more problematic outside of the OR. For example:

1. Many procedure suites have beds with lower weight limits and less mobility than OR beds.
2. Procedure suites for fluoroscopy have beds that cannot be placed in Trendelenburg or reverse Trendelenburg position.
3. Anticoagulation status is often an issue, and guidelines may be extended for some procedures.
4. Renal status may change the course of the procedure or dictate the use of contrast.
5. During percutaneous procedures, bleeding may be occult, and the potential need for transfusion should be addressed preoperatively.
6. Percutaneous procedures often require that the patient remain still because they necessitate precise movements of catheters and wires. Patients with extreme anxiety, chronic pain, claustrophobia, mental disability, movement disorders, obesity, or obstructive sleep apnea (OSA) or those who are at the extremes of age may not tolerate lying on a table for long, even if the proposed procedure is not very stimulating. For these patients, deeper sedation or general anesthesia may be needed.

Current NPO guidelines for procedures are 6 hours for a light meal, 8 hours for a full meal, and 2 hours for clear liquids applied to patients without increased risk for aspiration (gastroesophageal reflux disease, gastric dysmotility, hiatal hernia, diabetes mellitus, bowel obstruction, or intraabdominal pathologic conditions).[23] This is often a bone of contention between anesthesiologists and medical proceduralists, who may not realize the ramifications of a full stomach or may insist that contrast or barium be administered before the procedure. Timely preprocedure evaluation and enforcement of clear standards for NPO can help prevent scheduling mishaps and unnecessary delays and cancelations. This may require educating the medical proceduralists and their staff.

GASTROINTESTINAL PROCEDURES IN THE ENDOSCOPY SUITE

Over the past 5 years, enormous growth in the number of gastrointestinal (GI) endoscopic procedures related to an aging patient population, increased awareness of cancer screening benefits, broad-based reimbursement for screening colonoscopies, and better technology is quite evident.[24] Increasingly complex procedures and higher acuity patients broaden the scope of challenges anesthesiologists face in caring for these patients and also increase the need for interdisciplinary input. The choice of anesthetic approach requires a thorough understanding of both the procedure and the comorbidities of the patient. Similarly, preprocedure evaluation and postprocedure care, which carry financial and operational constraints, assume greater importance. Historically, most endoscopists managed healthy patients undergoing minor procedures with moderate sedation administered by nurses. However, moderate sedation is often inadequate in the context of sicker patients for simple procedures or healthy patients for complex procedures. Therefore, this chapter discusses the focus and methods of common GI procedures, reimbursement issues that may affect practice, the frequent comorbidities associated with patients undergoing those procedures, and anesthetic approaches suggested by anesthesiologists with expertise in the area.

REIMBURSEMENT CONSTRAINTS

Rapid growth in the number of charges to Medicare and private insurance companies for anesthesiology support of colonoscopies provoked the attention of both Medicare and commercial payers to the point at which in 2008, a major insurance company amended its reimbursement policies,[25] stating that they would no longer pay for anesthesiologists to administer propofol for screening colonoscopies in routine cases. Costs would be reimbursed only if the patients had documented comorbidities that would likely contraindicate moderate sedation. The amendment was prompted by a huge increase in billing and significant regional differences with the use of propofol by anesthesiologists. Despite the fact that the list of acceptable comorbidities included more than 200 diagnoses, nationwide protests from patients and physicians prompted the carrier to delay and then cancel implementation of this policy change. The carrier's actions were prompted by an acute rise in billing, significant regional differences in the use of propofol for routine colonoscopies, and the growth of independent colonoscopy centers that churned out many patients per day facilitated by the use of propofol, which permitted very rapid turnover of cases. The finances of this situation continue to drive practice, and the debate continues. Anesthesiologists must continue to consider patient need and procedural requirements as the criteria by which anesthetic plans are formulated because the political and economic aspects of the debate will undoubtedly continue.

A broad spectrum of GI procedures takes place in the endoscopy suite, ranging from routine screening colonoscopies to complex endoscopic submucosal dissections. Each of these requires specific levels of anesthesia depending on the invasiveness and stimulation imposed by the procedure and the likely impact on the patient. The most common procedures are esophagogastroduodenoscopy (EGD), sigmoidoscopy and colonoscopy, and endoscopic retrograde cholangiopancreatgraphy (ERCP).

ESOPHAGOGASTRODUODENOSCOPY

EGD involves examination of the upper GI tract (esophagus, pylorus, and stomach) using a fiberoptic endoscope. The most difficult parts of the procedure for the patient include passing the scope into the esophagus and through the pylorus. Any interventions that occur during the procedure (biopsy, resection, dilation) should be discussed with the endoscopist before the procedure because they constitute additional stimulation. Important and potentially stimulating therapeutic undertakings during endoscopy include hemostasis, biopsy, stenting, dilation, and mucosal or submucosal dissection.[26]

Most patients tolerate this procedure well with opioid or benzodiazepine sedation, but for those at risk for obstruction or aspiration, children, or very anxious patients, general anesthesia may be the best alternative. Unfortunately, many patients presenting for EGD—those with severe gastrointestinal reflux disease, morbid obesity, asthma, or obstructive sleep apnea—are in this high-risk category. In some cases, thorough topicalization is all that is needed, but in some patients, this is inadequate for the procedure, and in some cases, is difficult to achieve. ProSeal laryngeal mask airways, which have a built-in gastric drainage port, permit the passage of a pediatric endoscope, and this approach may be the best option for children and other patients[27] who require general anesthesia and are appropriate for laryngeal mask airway use. As with all procedures above the nipple line that use cautery, precautions must be taken to reduce the potential for airway fires.[28] This subject is discussed in Chapter 55.

SIGMOIDOSCOPY AND COLONOSCOPY

Sigmoidoscopy and colonoscopy can be diagnostic or interventional and involve the examination of the lower GI tract, including either the sigmoid colon only or up to the distal ileum. This examination can be difficult for some, although most patients tolerate it with a combination of benzodiazepines and opioids. Interventions such as biopsies or polyp removal may require increased analgesia. Most anesthesiologists provide sedation with propofol; however, even in situations in which GI endoscopists are permitted to direct nurses to administer propofol, one study found that the mean bispectral index (BIS) score of patients was 59, indicating they were under general anesthesia.[29] Some gastroenterologists maintain that this depth of sedation or anesthesia allows for more thorough examination, but no data have indicated that a "better" examination is performed. Remifentanil has been compared with propofol in the context of sedation for colonoscopy. Although patients given remifentanil "recovered" earlier, they also had more nausea and respiratory depression than the propofol groups. When inhalational agents such as sevoflurane and nitrous oxide were compared with total intravenous anesthesia (TIVA), such as propofol, fentanyl, and midazolam in patients undergoing colonoscopy, the TIVA group emerged faster but had longer-lasting psychomotor impairment than the inhalational group.[30-32]

As with upper endoscopy, specific interventions during sigmoidoscopy and colonoscopy constitute additional stimulation, including introduction of the endoscope, colonic insufflation, advancement of the endoscope, and additional endoscopic intervention such as biopsy, polypectomy, stenting dilation, and mucosal resection.

The ability and need to titrate a drug quickly and appropriately drives the choice of anesthetic, and new studies looking at patient-controlled sedation pumps are under way. Studies of patient satisfaction and indicators of procedural success are ongoing, as are several trials of patient-administered sedation and other types of computerized pumps.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATGRAPHY

ERCP is a fluoroscopic examination of the biliary or pancreatic ducts accomplished through an endoscopically guided injection of contrast through the duodenal papilla. Patients are usually in the prone position. ERCP often requires precise intervention during the procedure; a patient who is gagging or squirming during the intervention invites disaster in terms of procedural outcome and airway or pulmonary and other organ compromise. Many patients who require ERCP are compromised. Their diagnoses include cholangitis, pancreatitis, bile duct obstruction, pancreatic cancer, and other significant comorbidities. Potentially stimulating interventional maneuvers during ERCP include hemostasis, stent placement, stone extraction, pancreaticobiliary visualization, laser lithotripsy, and sphincterotomy.

These are delicate and detailed interventions, and patient immobility is required. For this reason, many anesthesiologists prefer general anesthesia for ERCP. In addition, the patient's airway is effectively inaccessible to the anesthesiologist. Published data support this preference as well, procedural failure rates are twice as high for sedation patients as they are for general anesthesia patients, and the complication rate for general anesthesia cases may be lower.[33-34]

NATURAL ORIFICE TRANSLUMENAL ENDOSCOPIC SURGERY: THE NEXT FRONTIER?

Natural orifice translumenal endoscopic surgery (NOTES) represents an approach to abdominal and peritoneal procedures that integrates the perspectives of endoscopic medicine and minimally invasive surgery. The use of NOTES in humans is in the very early phases, and several cases have been reported of transvaginal and transgastric cholecystectomy.[35,36] Thus far these cases have required a pneumoperitoneum and general anesthesia; however, as technology improves, these parameters may change and NOTES procedures may take their place among the numerous other interventions performed outside the OR.

An example of a NOTES used by GI endoscopists to treat esophageal achalasia is peroral endoscopic myotomy (POEM). Esophageal achalasia is characterized by poor peristalsis of the esophagus in combination with increased muscle tone and incomplete relaxation of the lower esophageal sphincter (LES). Symptoms arising

from impaired entry to the stomach include nausea and vomiting, dysphagia, and/or pain. The POEM procedure has been developed as a minimally invasive procedure to correct achalasia by endoscopically insufflating the esophagus with CO_2 and then making an incision into the mucosa from the mid-esophagus (through the gastroesophageal (GE) junction) to 2 to 3 cm into the proximal stomach. During insufflation, patients may have an increase in $ETco_2$ that can be controlled using mechanical ventilation. Potential risks of insufflation range from subcutaneous emphysema to pneumothorax, pneumomediastinum, and pneumoperitoneum. This procedure commonly requires several hours and is best accomplished using general anesthesia with an endotracheal tube. This technique protects the patient from aspiration of gastric contents and allows the anesthesiologist to minimize the perils of CO_2 insufflation. As with all NORA procedures, vigilance, teamwork, and communication are vital to ensure not only the success of the procedure but the safety of the patient, as well.

INTERVENTIONAL PULMONARY PROCEDURES

Bronchoscopic interventions have grown to encompass many traditional surgical procedures performed in the OR. Not only are the patients at high risk in most cases but the procedures involve the airway, so the potential for disaster is high. Discussion, communication, and planning are particularly critical in this environment.

Common Bronchoscopic Procedures

Common bronchoscopic procedures include the following (see also Chapter 66):

1. Endobronchial stenting: placement of self-expanding metallic stents to treat stenosis
2. Endobronchial biopsy, laser treatment, and cauterization
3. Balloon dilation and cryotherapy

As technology advances and target populations broaden, new procedures are evolving. Several interventions that represent interesting amalgamations of preexisting technologies have made their way to the bronchoscopy suite, as follows:

1. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). This procedure is used to image the bronchial wall and adjacent structures. It allows ultrasonic visualization of mediastinal lymph nodes and other peribronchial lesions and therefore is a useful staging tool
2. Electromagnetic navigation bronchoscopy (ENB). This technique permits biopsy of endobronchial tissue that is not visible using computer software that creates a virtual multiplanar lung reconstruction from computed tomography (CT) data. A sensor probe and electromagnetic location board guides the operator to the appropriate location during the bronchoscopy.
3. Fiducial marker implant. Markers are placed before stereotactic radiosurgery via bronchoscopy or ENB.[37]

NOVEL ANESTHETIC CONCERNS

The site of intervention creates several special anesthetic considerations. Preoperatively it is important to review common comorbidities, which in these patients include obstructive and restrictive lung disease, cardiac disease, malnutrition, chronic aspiration, and tobacco and alcohol use. Although simpler procedures may be completed with sedation, complex procedures demand general anesthesia. Because a rigid bronchoscope is used during some aspects of these interventions, intravenous anesthetics are preferred. Instrumentation of the airway and insertion of biopsy or therapeutic equipment will compromise delivery of inhaled anesthetics to the patient and potentially pollute the procedure room. Propofol and remifentanil infusions are well tolerated and can be titrated to effect. Dexmedetomidine may be used as well. BIS monitoring may be helpful. Use of muscle relaxants is also preferred to prevent coughing and eliminate any chest wall rigidity. Muscle relaxation also facilitates introduction of equipment. The use of steroids during and after treatment has not been demonstrated to be effective in reducing edema; however, in cases in which general anesthesia is not used, the risk for aspiration is increased. In these cases the usual antiemetics and dexamethasone may be helpful.[38] Complications commonly encountered include airway obstruction, bronchospasm, bleeding, hypoxia, and airway fire (see also Chapter 88). Because potential complications are significant, patients should be observed in an appropriate unit postprocedure and, if needed, admitted to the hospital for observation.

ANESTHESIOLOGY FOR IMAGE-GUIDED INTERVENTIONS: EVOLUTION OF A NEW INTERFACE

Over the last several decades, radiology has redefined its historical character as a largely diagnostic specialty to one that now encompasses an expanded menu of interventional undertakings, in keeping with technologic development and patient need. The scope of procedures performed in interventional radiology settings is as broad as the number of diagnoses known to the medical profession and is expanding. In fact, not all interventional radiation procedures are performed by radiologists. Some take place in specialty areas with other names, such as catheterization laboratories, neuroradiology suites, CT scanners, magnetic resonance imaging (MRI), and even in ORs. Some are performed by interventional cardiologists or surgeons. For that reason we will discuss interventional procedures here in terms of their purpose and focus, rather than categorizing them by the location in which they are performed or the specialty of the person performing the procedure. The common characteristics shared by most of these interventions are that there are no surgical incisions; there is some type of imaging involved (fluoroscopy, ultrasound, CT, positron emission tomography [PET], MRI); and access to the organ, tumor, or vascular structure in question is through a small hole by wires or catheters. Beyond that, the array of available technologies and possible interventions (both diagnostic

and therapeutic) is astonishingly broad. Dogma aside, the scope and intensity of procedures undertaken in interventional suites rivals that of surgeries performed in any OR, and often, patients undergoing non-OR procedures are sicker than those undergoing conventional surgeries. Unfortunately, they often lack preoperative evaluation and are not medically optimized. Frequently non-OR patients become candidates for noninvasive procedures precipitously because they are felt to be too sick or too high risk for the OR or because the need for intervention develops urgently or emergently.

Understandably, this creates discomfort for anesthesiologists of a traditional mindset, but these are our patients too, and we are trained to deal with such situations. Given this scenario, it is imperative that anesthesiologists make the effort to understand as thoroughly as possible the planned course of the procedure (understanding that this can change midstream) and the nature and acuity of the patient's comorbidities, which may not be apparent to the proceduralist. As in the OR, the challenge is to preemptively think about how the prospective procedure will affect the patient's physiologic status and design a successful anesthetic plan for the case. However, the additional caveat, as with all non-OR anesthetics, is that this may require learning about a procedure, technology, or modality that may be novel, unfamiliar, or in clinical trial. Also, it may fall to the anesthesiologist to introduce the potential ramifications of the patient's comorbidities and anesthetic risks to the proceduralist in a constructive manner. Many interventional specialists are consultants, not involved in the primary care of the patients they are treating. They may be unaware of seemingly peripheral aspects of their patient's physical status that are in fact quite central to good outcome. Creating a clear, collegial, and workable path of communication between medical proceduralist and anesthesia provider is paramount. The need for anesthesia support may reflect the needs of the patient and not the complexity of the procedure. The interventionalist may be highly focused and technically oriented and may not understand the concerns of an anesthesiologist. Our mutual tasks are to understand what needs to be accomplished and to bring our skills to bear in a manner that bridges the knowledge gap, creating an atmosphere of safe and reliable interdisciplinary collaboration that optimizes outcome.

DIAGNOSTIC AND THERAPEUTIC INTERVENTIONS: NEW CHALLENGES

The need for anesthesia during minimally invasive procedures continues to grow as the scope of image-guided interventions broadens. As the population ages and technologic advancement marches forward, image-guided procedures will continue to supplement and perhaps replace conventional surgeries, especially for patients whose comorbidities make traditional surgical approaches risky. Image-guided procedures, although noninvasive, can cause pain and anxiety and carry the risk for potentially life-threatening complications. Anesthesiologists are called on to keep patients comfortable and safe and to facilitate optimal outcomes. Image-guided interventions may be diagnostic, therapeutic, or both. Many diagnostic procedures are short and tolerated well with nothing more than conscious sedation; however, for a compromised patient, even the most minor procedure can be problematic. Interventional procedure suites impose constraints not normally encountered in the OR. Additional considerations that emerge in these environments include unfavorable equipment layout, radiation exposure, occult bleeding risk, and contrast allergies.

EQUIPMENT LAYOUT

The layout in any radiology suite can be problematic for anesthesiologists because x-ray tubes and moving C-arms create a zone of inaccessibility around the patient's head and limit placement of the anesthesia machine. This necessitates the use of extensions on ventilator circuits and intravenous lines, increasing the potential for mishap. Infusion pumps, blood warmers, and other monitors must be placed far away from moving imaging equipment to prevent them from being knocked down or tangled during C-arm rotation and movement. In addition, imaging screens are often at right angles to the anesthesiologist, making it impossible to see what the interventionalist is doing or assess the progress of the case. Anticipating events is therefore difficult unless good communication occurs between the anesthesia and radiology staffs.

Radiation Exposure

Radiation exposure is a serious consideration for anesthesiologists, and steps must be taken to minimize it. Most exposure results from scatter of the x-ray beam. The specifics are not discussed in this chapter; however, excellent discussions and guidelines for optimization of radiation safety are readily available (see also Chapters 67 and 110). It is important that anesthesia staff wear properly fitting lead shielding, including thyroid shields and leaded glasses; use portable lead screens; and wear radiation badges that are monitored on a monthly basis. Even so, several recent studies indicate that exposure of anesthesia personnel to radiation is quite high and that the exposure of the head and face of anesthesiologists can exceed three times the exposure of radiologists[39] because of their position in the room. Unfortunately, anesthesiologists often have to dig through the available lead aprons worn by others because they are not yet considered part of the team. Many of the cases in which anesthesiologists perform are long and involve significant radiation exposure. Wearing someone else's lead shielding is uncomfortable. Lead shielding is only protective if it fits.

Related to the exposure problem is the need for the anesthesiologist to leave the room during specific imaging runs such as digital subtraction angiography (DSA). This can be planned and executed so that it does not interfere with the anesthetic or compromise safety, but it is definitely a novel aspect of NORA. Many anesthesiologists do not undergo consistent or repetitive training in radiation safety. All radiation exposure should follow the ALARA ("as low as reasonably achievable") principle. The radiation beam attenuates based on the inverse square of the distance from the radiation source ($1/^{d2}$).[40] Shortened exposure time, increased distance from the source of radiation, and barriers to radiation (lead shields) are three

ways in which to reduce exposure. Often, radiation time is under the control of the operator performing the procedure. Many of the new and more complex procedures involve prolonged exposure to radiation. As anesthesiologists' participation outside of the OR increases, our exposure to imaging increases, and this will become a routine part of our practice.

Contrast Material

Contrast material is commonly administered during interventions guided by imaging. Standard ionic, high-osmolality contrast agents are associated with dose- and concentration-dependent adverse reactions in 5% to 8% of patients. Anaphylactoid (idiosyncratic) reactions are unrelated to dose or concentrations administered.[41] Reactions can be severe and include laryngeal edema, bronchospasm, pulmonary edema, hypotension, and respiratory arrest or seizures. Oxygen, epinephrine, and bronchodilators are the recommended rescue regimen. For pretreatment of patients with a history of contrast reaction, steroids, and diphenhydramine are recommended. The use of low-osmolality contrast further reduces the risk for adverse reactions. Patients with renal insufficiency are at risk for contrast-induced nephropathy. These patients should receive preprocedure hydration and administration of N-acetyl cysteine before and after the procedure.[42]

Bleeding

Bleeding may be occult during percutaneous interventions and is a serious concern in patients receiving anticoagulation regimens (see also Chapter 62). Guidelines for optimizing coagulation parameters change frequently. For patients who do not undergo anticoagulation for other reasons, the international normalized ratio (INR) should be less than 1.5 and the platelet count more than 50,000. If possible, warfarin should be held for 5 to 7 days before the procedure, clopidogrel and aspirin for 5 days, and fractionated heparin for 12 to 24 hours. Heparin should be stopped 4 to 6 hours before the procedure. Nonsteroidal antiinflammatory drugs (NSAIDs), although less critical, should be held for 1 to 2 days, if possible.[43] It is not unreasonable to send a sample to the blood bank for any patient undergoing an interventional procedure. Of course, it is critical to communicate clearly with the interventionalist when hemodynamic parameters change or the initiation of blood pressure support becomes necessary.

VASCULAR INTERVENTIONAL PROCEDURES

Angiography, the general term for imaging of blood vessels includes arteriography and venography (see also Chapter 69). This involves the acquisition of images during injection of contrast material. In many institutions this technique has been replaced by CT angiography (CTA). DSA, a technique that imposes a contrast-injected image on top of a previously acquired noncontrast image, improves accuracy. Arteriography can be used to evaluate atherosclerotic and ischemic disease, define the arterial supply of tumors and vascular anomalies, and define traumatic injury. After diagnostic imaging, interventions using balloons, stents, or balloon-mounted stents take place. Follow-up arteriography is used to evaluate the result. In some cases, arteriography serves as a precursor to later surgery.

Thrombolytic therapy can be delivered to veins, arteries, or conduits that are thrombosed. The earlier the intervention the more successful it is likely to be. Various agents are used, including recombinant tissue plasminogen activator (r-TPA), urokinase, and others.[42-44] Thrombolytic therapy is generally contraindicated in patients with ongoing bleeding, recent bleeding, pregnancy, known allergy to thrombolytic agents, suspected aortic dissection, or the presence of a nonviable extremity.

Embolization therapy is used in a wide range of conditions, including trauma, hemorrhage, vascular anomalies, fibroids, aneurysms, and tumors. The goal is to occlude arteries or veins either temporarily or permanently. This can be done mechanically with coils, balloons, or glue; or with chemical agents that are temporary (gelfoam) or permanent (alcohol). In these cases, arteriography first defines and localizes the lesion and the embolic agent is then delivered to the appropriate place with imaging guidance.

For all of these vascular interventions, the nature of the case, the comorbidities of the patient, and the intricacy of the procedure will determine the need for and extent of anesthesia involvement. Complications to anticipate include bleeding during thrombolysis, undesired embolization of nearby structures during embolization, and vessel disruption. Depending on where the target vessels are, potential complications should be appropriately anticipated in terms of planning for physiologic sequelae and the need for blood products.

Venography or imaging of the venous system is used in the context of stent placements, inferior vena cava (IVC) filter placement or removal, pulmonary arteriography, embolization of pulmonary arteriovenous malformations (AVMs), thrombolysis, and selective venous sampling. Central venous angioplasty is most frequently undertaken in patients who have indwelling devices. IVC filters are placed to minimize the risk for pulmonary embolus arising from the migration of deep vein thromboses from the lower extremities or pelvic veins. Indications for IVC placement include high risk for pulmonary embolism, failure of anticoagulation or contraindications for anticoagulation, and allergy to anticoagulants. Both removable and permanent filters are available and can be placed via transfemoral or transjugular approach. For the most part, these procedures require little or no sedation; however, obese patients who cannot lie flat need anesthesia support (see also Chapter 71). Pulmonary arteriography is used less frequently than in the past because of the speed and reliability of pulmonary CTA; however, the procedure is useful when others are ambiguous to look for pulmonary AVMS or pseudoaneurysms, and to evaluate pulmonary hypertension.[44]

BILIARY AND HEPATIC INTERVENTIONS

Procedures to treat biliary or hepatic pathology are among the most challenging performed outside of the OR. Not only are the interventions themselves

painful, intricate, and technically demanding, but also the patients are often extremely compromised. Hepatic and biliary procedures include transhepatic cholangiography, percutaneous transhepatic biliary drainage, hepatic venography with hemodynamic measurement, liver biopsy and the creation of transjugular intrahepatic portosystemic shunts (TIPS procedure), and portal vein embolization (PVE). Patients scheduled for biliary procedures may present with jaundice, cholangitis, bile duct leak, or other related abnormalities. Clearly, significant comorbidities accompany these disorders. Contraindications for these procedures include bleeding diathesis, inability to tolerate contrast, and the presence of large hepatic arteriovenous malformations, significant ascites, and hydatid disease.

Biliary drainage is accomplished by placing the patient supine on the table, and inserting a long needle obliquely into the hepatic parenchyma. Contrast is delivered with the goal of imaging the necessary structures. Cholecystostomy tube placement is performed to improve symptoms in patients with acute cholecystitis but who are not candidates for surgery. Here, the gallbladder is imaged with ultrasound, CT, or fluoroscopy; the gallbladder is accessed through a needle that traverses the liver; and a drainage catheter is placed. For these procedures the choice of anesthetic depends entirely on the patient's habitus, comorbidities, and pain tolerance. Obese patients are difficult to image, and optimization of needle position also can be difficult (see also Chapter 71). Patients may present with a history of tolerance to pain medications and with compromised metabolism, which requires careful choice of drugs. Lying flat may be impossible for patients with ascites.

Hepatic venography and hemodynamic assessment are performed to assess suspected venous anomalies (Budd-Chiari) and quantitation of portal hypertension. Liver biopsies can be performed during these procedures. Access for these procedures is usually transjugular and involves needle insertion followed by wire access and insertion of a long vascular sheath. Many patients find this extremely difficult to tolerate. Hepatic venography and pressure monitoring is done through an angled catheter before it is advanced to wedge in the hepatic vein. A calculation of corrected sinus pressure, the difference between free pressure and wedge pressure, defines the degree of portal hypertension. Once the catheter is wedged, it provides an estimate of portal venous pressure.[45] The creation of a portosystemic shunt requires positioning of a needle advanced through the hepatic parenchyma and into the portal vein. The parenchymal tract is dilated with an angioplasty balloon and a stent is inserted. This is a painful and difficult procedure, vastly oversimplified here for clarity. It may be quite lengthy and general anesthesia is advisable. Indications for the creation of TIPS include repeated esophageal variceal bleeding refractory to medical treatment and intractable ascites. It is often used as a bridge to liver transplant. Contraindications to this procedure include preexisting hepatic encephalopathy and ongoing alcohol abuse, which preclude liver transplantation. Significant pulmonary hypertension, valvular heart disease, or heart failure contraindicates this procedure.[46] PVE is a relatively new technique designed to reduce blood flow in hepatic segments containing tumor, while encouraging hypertrophy of remaining hepatic tissue. The goal is to improve survival among patients undergoing resection of hepatic neoplasms by increasing postsurgical hepatic tissue mass. Embolization is accomplished with portal vein angiography and coils. Acute complications include bleeding, bile leak, pleural insults, and contrast reactions.

GASTROINTESTINAL AND GENITOURINARY INTERVENTIONS

Interventional radiologists perform direct-access GI procedures, the most common of which is the percutaneous gastrostomy tube (G-tube). Other variants include cecostomy and jejunostomy tubes. For G-tube placement, the stomach is distended with air via a nasogastric (NG) tube. Subsequent gastropexy is performed by some practitioners as a means of stabilizing the stomach; the stomach is entered with a needle and a wire and an appropriate tube is inserted and placed in the proper location. Acute complications include bleeding, violation of adjacent structures, and peritonitis. In many cases, these procedures can be tolerated with sedation.

Genitourinary (GU) procedures in the radiology suite focus on obtaining direct access to the renal collecting system. Dilation and stenting can be performed, and suprapubic cystostomy is also a procedure commonly performed in radiology suites. Nephrostomy tube placement is performed to divert urine in the face of obstruction from stones, tumor, or other obstructive pathology. In general, the technique involves injecting contrast, identifying the renal pelvis, accessing it, and inserting a tube.[47] Prone positioning of the patient is required, which generates an attendant list of potential anesthesia concerns, including airway issues, pain management, access, and more. Interventionalists may attempt to convince anesthesiologists that "less is more"; however, stimulation can be intense during these cases, and in general, it is worth thinking about the "what if" scenario—that is, deep sedation in a prone patient is difficult to advance to general anesthesia.

PERCUTANEOUS INTERVENTIONS FOR ONCOLOGY

Percutaneous interventions for oncology are relatively new and are rapidly expanding. Imaging guidance is achieved with CT, ultrasound, or fluoroscopy. Transarterial chemoembolization (TACE), percutaneous ablations (with radiofrequency, laser, cryoablation, or alcohol) can be directed at tumors and image-guided insertion of radioactive materials can be performed. Commonly, hepatic, kidney, lung, and adrenal lesions are targeted. Complications are similar to those of other percutaneous interventions; positioning depends on the site to be accessed. Often, general anesthesia works best for these procedures because the interventions may be intermittently painful, control of breathing may be optimal, and patient cooperation may not be compatible with the level of sedation required.[48]

PROCEDURES GUIDED BY COMPUTED TOMOGRAPHY, POSITRON EMISSION TOMOGRAPHY, AND MAGNETIC RESONANCE IMAGING

COMPUTED TOMAGRAPHY

CT is now a commonly used guidance modality for a broad array of percutaneous interventions, and CT fluoroscopy, which combines the improved imaging capacity of CT with the real-time imaging of fluoroscopy, is also widely used. CT is used to guide both diagnostic and therapeutic procedures. Diagnostic undertakings include biopsies and drainage of fluid collections; therapeutic interventions include tumor ablation and injections for pain management. Procedures occurring in the CT suite encompass the usual constraints of radiation exposures on operators and anesthesiologists, and patients are at risk for bleeding and contrast reaction. In addition, some special preprocedural considerations are important. Obese patients may not fit inside the scanner, and special (longer) needles and drains may be needed. Positioning in the scanner may be difficult, and the usual airway considerations apply, especially because it is nearly impossible for the anesthesiologist to have continuous access to the head. For the most part, biopsies performed under CT guidance can be accomplished with sedation, but when the stimulation is intense or repeated breath-holds are required, general anesthesia may be needed. For patients with significant comorbidities (obesity, pulmonary or cardiac compromise, chronic pain, or history of difficult intubation), securing the airway before the procedure is prudent.

Computed Tomography–Guided Biopsies

CT guidance is useful for obtaining biopsy tissue for cytologic or histologic examination. Needles range from 25 to 18 gauge, and the patient is positioned to minimize the distance from skin to lesion and maximize the safety of the approach. Liver biopsies are usually performed with the patient supine or slightly oblique, and retroperitoneal masses may require lateral decubitus or prone positioning. For the most part, it is helpful to the interventionalist if the level of sedation remains consistent throughout the procedure, so that large shifts in target location resulting from alterations in ventilation do not occur. However, levels of stimulation during these procedures can vary tremendously, presenting considerable challenge to the anesthesiologist if general anesthesia is not planned. Biopsies of carcinoid or adrenal tumors can be equally problematic, whether in the radiology suite percutaneously or in the OR. In both cases, stimulation of hormone release can precipitate severe hypotension or hypertension, which is difficult to manage. If pheochromocytoma or carcinoid are suspected, pretreatment should be considered.

Computed Tomography–Guided Therapeutic Interventions

CT–guided therapeutic interventions include catheter drainage, ablation of tumors, and injections for pain management. Anesthetic planning for these procedures requires understanding of patient comorbidities and the techniques of the interventionalists. Excellent communication between anesthesiologist and interventionalist is needed for coordination of procedure and anesthetic because unanticipated patient movement or interventional shortfall can have drastic consequences for procedural outcome.

Catheter Drainage

CT-guided abscess drainage has become common. Options include the modified Seldinger and trocar techniques. Although local anesthesia may suffice for superficial collections, the location of the fluid collection and the anticipated trajectory of the needle or trocar may be quite painful during the insertion or dilation phase. Before the procedure, the proceduralist and anesthesiologist should discuss the intended approach, potential anesthetic choices, and backup planning for transitioning to a deeper plane of sedation or anesthesia. Preemptive planning can make the difference between a smooth procedure with a good outcome and a prolonged, difficult intervention. Anesthesiologists should be prepared to treat potential complications, which can occur as a result of injury of surrounding structures.

Computed Tomography–Guided Ablation

A variety of ablation techniques are now used to target malignant neoplasms. Percutaneous injection of alcohol (95%) or phenol (6%) is used to target tumors. Alcohol can be instilled using needles or catheters, but the injection is usually quite painful. Large volumes of alcohol or inadvertent injection into a vascular structure can cause tachycardia and respiratory depression. Other ablation techniques involve the use of radiofrequency ablation, cryoablation, and microwaves. These procedures may be lengthy because they involve precise placement of applicators for the delivery of the ablation tool, whatever that may be. Reproducible breath-holds may be needed to facilitate placement. Radiofrequency ablation induces coagulative necrosis at temperatures above 50° C; the heating process can produce pain, whereas cryoablation is a less painful procedure.[49,50]

Computed Tomography–Guided Injections for Pain Management

Procedures for pain management include phenol and alcohol injections into a plexus, ganglion, or nerve (see also Chapter 64). Neurolysis is the intended outcome. Injection of steroids into joints for local pain management and mitigation of inflammatory processes is also performed. Many patients requiring these procedures are tolerant to pain medication. Body habitus may be an important factor in these patients as well, and depending on the source of pain, patients with cancer may be especially challenging in terms of attendant comorbidities.

POSITRON EMISSION TOMOGRAPHY AND POSITRON EMISSION TOMOGRAPHY COMPUTED TOMOGRAPHY

PET is an imaging technique used for diagnosis, staging, and follow-up of malignancies. Scanning is undertaken after injection of a radiolabeled glucose analogue fluorodeoxyglucose (18F-FDG), which is taken up by malignant cells preferentially and is not metabolized, thereby

serving as a tumor marker. FDG-PET is used to distinguish benign from malignant lesions, identify metabolically active portions of necrotic tumors, and monitor responses to treatment. The combination of positron emission tomography and computed tomography (PET/CT) provides both the metabolic information of PET and the anatomic precision of CT. PET/CT-guided intervention is an emerging modality.[51] For these procedures, patients are imaged beginning 60 minutes after injection. Imaging may require serial positioning, during which PET and CT images are acquired sequentially, so care must be taken to maintain consistent patient positioning throughout the image acquisition so that misregistration of image overlap does not occur. PET scanners include a long, mobile gantry that both limits access to the patient and requires that monitoring equipment be long enough to accommodate motion of the table. PET/CT suites represent another potential anesthestizing location. Whenever possible, anesthesiologists should be involved in the planning of these suites because wall-mounted gases, suction, and installed monitoring equipment must be strategically placed. It is likely in the future that PET will be used to augment CT-guided interventions; therefore, planning a space that will allow inclusion of anesthesiology equipment will ensure uneventful interventions and optimal outcomes.

MAGNETIC RESONANCE–GUIDED INTERVENTIONS

MRI is an ionizing radiation-free technique that uses magnetic fields and radio waves to create images. The quality of soft tissue images generated by MRI surpasses that of ultrasound or CT. MRI is still largely a diagnostic tool but is emerging as an interventional modality as well. Because MRI can acquire multiplanar, temperature-sensitive, and contrast-enhanced images, complete visualization of interventional implements such as wires or needles is possible.[47] Images quality is proportional to magnet strength. Field strength, measured in tesla units ranges from low (0.1 to 0.5 T), to medium (0.5 to 1.0 T), to high (1.5 to 3.0 T), to ultrahigh (>3.0 T). Imaging sequences can be manipulated to highlight tissue characteristics based on water content, vascularity, and presence of hemosiderin. The superiority of MRI-generated soft tissue images facilitates biopsy and ablation of structures that evade CT or ultrasound.[48]

Physical Constraints of Magnetic Resonance Imaging Suites

All equipment used in the MRI suite must be MRI compatible; that is, the equipment will not cause harm to the patient, affect image quality, or be affected by the MRI scanner. Objects containing iron or stainless steel become mobile projectiles in an MRI suite because of the magnetic field, regardless of their size. Therefore, special care must be taken to ensure that all equipment used in an MRI suite is unaffected by magnetic attractive forces, heating, or current induction. Similarly, patients themselves must be screened. Any implanted devices must be assessed for MRI compatibility. Patients with pacemakers, implantable cardioverter-defibrillators (ICDs) (see also Chapter 48), cochlear implants, pumps, nerve stimulators, or other metal objects such as aneurysm clips, metal fragments, or bullets, should not be scanned. These objects are subject to heating and movement. Increasingly, vascular clips, staples, orthopedic implants, heart valves, and other prostheses are nonferromagnetic and scanning of patients with these implants is possible. Monitoring devices are increasingly available in MRI-compatible format, as are interventional equipment, surgical equipment, and anesthesia equipment.[52] Detailed information regarding MRI safety is available in Chapter 110 and elsewhere.

Claustrophobic or large patients may be unable to tolerate being inside of an MRI machine, making even diagnostic procedures difficult for them. Newer MRIs combine a wider bore with high-field systems, improving accessibility and making it easier for patients to tolerate procedures. Because interventional MRI requires constant movement in and out of the scanner, typical interventions take much longer than the same procedures done elsewhere. Emergencies must be planned for because the MRI interventional suite may be isolated, and conventional emergency equipment may not be MRI compatible. Even a standard laryngoscope can become a deadly missile in an MRI suite.

Magnetic Resonance Imaging–Guided Interventions

In cases in which CT is inadequate, MRI may be useful because of its multiplanar capability. MRI has been used to guide breast and prostate biopsy and biopsy of other tumors not well visualized by other means. For the most part, local anesthesia and sedation suffice for these procedures. Tumor ablation using cryoablative technology can be performed in the MRI suite. This procedure can be done with ultrasound or CT as well, and the choice of MRI as an imaging modality indicates the need for precise soft tissue imaging. MRI also provides better visualization of tissue during freezing and thawing than CT or ultrasound, and MRI-guided cryoablation is safe and effective for liver, kidney, breast, and prostate tumors and in the treatment of uterine fibroids.[53] For these cases, repeated breath-holds may be needed, and the procedures may be lengthy. Pain is not uncommon during freezing and heating of tissues; therefore, general anesthesia may be required.

Bleeding is the most common complication after some of these procedures (also see Chapter 62). Thrombocytopenia is a rare but serious complication of extensive liver ablation. Extensive ablations can also induce myoglobinemia or myoglobinuria. Cryoablation of adrenal lesions can induce hypertensive crises as normal adrenal tissue responds to thawing.[54] MRI can facilitate the use of focused high-intensity ultrasound therapy by providing more precise imaging. Clinical trials of this technique are in progress. Temperature-sensitive MRI images can assess dosage of ultrasound, and gadolinium-enhanced MRI images can assess tissue response. MRI offers many potential advantages that may broaden the scope of current interventional procedures because of its capacity to provide improved imaging over that available with CT or ultrasound. The need to develop MRI-safe environments, equipment, and monitoring and to understand the limitations of sedation and need for anesthesia during long

and uncomfortable procedures are the next steps in extending the usage of this modality.

IMAGE-GUIDED PROCEDURES FOR SPECIALTY AREAS: NEURORADIOLOGY AND INTERVENTIONAL CARDIOLOGY

Neuroradiology and interventional cardiology are considered here as specialties because they each mirror areas that anesthesiologists have also chosen to designate as areas of specialization or fellowship training (neuroanesthesia and cardiac anesthesiology) (see also Chapters 68 and 70). The language of neurology, neuroradiology, cardiology, and interventional cardiology is part of the language of neuroanesthesia and cardiac anesthesia. Thus, the platform for clear communication exists and should be used to optimize procedural outcome. Of course, as alluded to earlier in this chapter, common vocabulary is necessary but not sufficient; mutual respect, a culture of safety and learning, and a functional teamwork structure are important elements of a successful unit.

Advances in neuroradiology and interventional cardiology have been incredibly rapid; technology has developed and target patient populations have broadened. In both of these areas, percutaneous approaches to formerly surgical problems have multiplied, as has the potential for the involvement of anesthesiologists. In many ways, the development of new techniques represent a "disruptive technology"[55] within the field of medicine and threatens to further blur distinctions between medical and surgical treatments. The unpredictable and demanding new landscape of novel interventional cases frequently elicit ad hoc responses from unsuspecting anesthesiologists. It is time for us to reevaluate dogma and use overlapping competencies to facilitate the success of new, cutting-edge interventions; these procedures are the future of the practice. Think of how it must be for an interventional radiologist, when discussing a new or complex procedure with an anesthesiologist, to be asked, "Why don't you just do this in the OR?" simply because the scheduling would be more convenient or the anesthesiologist would be more comfortable in an operating room? Scheduling conflicts must be resolved; everyone needs to compromise. If the OR is safer in our view, then it is incumbent on us to make the interventional suite safe as well, by explaining to the proceduralist what changes need to be made and why. No procedure is without risk, and comfort level or convenience should not drive practice standards.

PROCEDURES IN THE NEURORADIOLOGY SUITE

The field of interventional neuroradiology is relatively new. It has grown broadly and rapidly as a result of improved device technology (catheters, coils, and stents), better imaging techniques, and safer contrast media (see also Chapter 70). Cerebral angiography remains the gold standard for imaging the cerebral vasculature. Diagnostic cerebral angiography usually can be performed with conscious sedation, but interventional procedures require a broad range of anesthesiology because of the length of the procedure, delicacy and complexity of the technique, and need for a still patient. Certain procedures generate hemodynamic perturbations that require management by the anesthesiologist. On the other hand, some procedures (i.e., carotid stenting) can be done with the patient awake, to facilitate neurologic assessment. Anesthesia for each of these procedures must be considered in concert with patient comorbidities and status, on a case-by-case basis. Although the technical details of neuroradiology procedures are beyond the scope of this chapter (see Chapter 70), the basic focus and required steps in commonly performed interventions are outlined here.

GENERAL CONSIDERATIONS FOR ANESTHESIOLOGISTS IN THE INTERVENTIONAL SUITE

As with other areas outside of the OR, physical characteristics of the interventional suite affect anesthesia practice (see also Chapter 49). Equipment makes access to the patient's head difficult, radiation exposure must be considered, and contrast reactions must be anticipated. Because of the intricacy of the procedures, uncooperative patients and those with impaired consciousness or movement disorders should be considered candidates for general anesthesia. If time permits, arterial lines are advisable; if not, the neurointerventionalist can upsize a femoral sheath to permit arterial monitoring. Other neuromonitoring technologies can be helpful as indirect measures of cerebral perfusion; electroencephalography and somatosensory, motor, and brainstem evoked potentials have all been studied in this regard. Many neuroanesthesiologists use opioids, avoiding inhalational agents because of their confounding effects on electroencephalography and evoked potentials. As in the OR and other non-OR sites, the anesthesiologist and proceduralist need to be aware of each other's plan, progress, and complications.

ENDOVASCULAR TREATMENT OF CEREBRAL ANEURYSMS

Endovascular treatment of cerebral aneurysms achieves percutaneous isolation of aneurysms from the circulation by placement of a soft platinum coil within the aneurysm (see also Chapter 70). The procedure intraaneurysmal embolization may require placement of several coils. Several types of coils are available. Coiling procedures are least complex in aneurysms with a small, narrow neck. Coiling of wide-necked aneurysms requires the introduction of a stent; the coil is subsequently introduced through the stent.[42] Stent implantation, which requires preprocedure and postprocedure anticoagulation, increases bleeding risk. Therefore, stent- assisted coil embolization is limited to unruptured aneurysms. Endovascular treatment with coils demonstrated better outcomes than surgical clipping in patients who sustained a subarachnoid hemorrhage related to an aneurysm, but clipping improved resolution of cranial neuropathies.[56] Complications include aneurysm rupture or thromboembolism. If rupture occurs, heparin should be reversed with protamine (1 mg/100 International Units heparin)

and the arterial blood pressure decreased by the anesthesiologist. The usual course of action is to continue the coiling as quickly as possible. Thromboembolic events, usually platelet related, occur in 3% of cases and cause permanent neurologic deficit in 1.7% to 5% of cases [57] (see also Chapter 62). If a thromboembolic event occurs, the proceduralist will make an attempt to dissolve or remove the clot with either a mechanical device or intraarterial administration of a thrombolytic or antiplatelet agent. Some aneurysms have no neck or are inaccessible. This is the case most commonly with cavernous, petrous, extracranial vertebral, internal carotid, or giant aneurysms of the subarachnoid space. Treatment of these requires parent artery occlusion, which is possible only if good collateral flow exists. This requires a preliminary procedure known as a parent artery balloon test occlusion.[58] It involves first advancing a wire to the site of the proposed artery sacrifice. A neurologic examination is then performed, heparin is administered to prolong the activated clotting time, and a balloon is inflated to occlude the artery. Neurologic examination follows. In some institutions radionuclide enhanced cerebral vascular studies are undertaken. If the patient tolerates occlusion, coiling may proceed. If not, a surgical intracranial bypass may be required.

ENDOVASCULAR TREATMENT OF ARTERIOVENOUS MALFORMATIONS

AVMs in the brain are an area of direct connection between small arteries and the venous system without normally intervening capillaries. The usual presentation of this lesion is intracranial hemorrhage. Patients with AVM must be angiographically evaluated for the presence of associated aneurysms. This evaluation involves catheterization of selective feeder arteries to determine the precise source of the hemorrhage. Current therapy for cerebral AVM includes embolization, microsurgical resection, stereotactic radiosurgery, or combination treatment. Embolization preceding surgery can minimize bleeding and reduce AVM size. Small AVMs may be appropriate for endovascular treatment. Techniques for embolization of AVMs in the neuroradiology suite include the use of flow-directed microcatheters, solid occlusive devices, particulates, and liquid embolic agents. Complications include embolization of post-AVM vessels precipitating rupture, passage of embolic material into the pulmonary circulation, and microcatheter entrapment.[59]

INTERVENTIONAL NEURORADIOLOGY: ACUTE STROKE TREATMENTS

Acute stroke treatment has evolved significantly over the last 10 years. Intravenous r-tPA treatment has been replaced with intraarterial thrombolysis because it allows extension of the treatment time window from 3 to 6 hours, delivers a higher concentration of lytic drug to the target vessel, yields higher recanalization rates, and can be combined with other interventional techniques.

Initially a detailed cerebral angiogram is obtained and the level of occlusion is identified. A microcatheter is inserted over a microguidewire, contrast is injected, and the clot is localized. At this point, r-tPA is injected beyond the clot and the catheter is pulled back through the thrombus. If the occlusion persists, mechanical means of clot disruption or extraction are considered. This must be undertaken within 8 hours of the event. Several devices are available for retrieval or aspiration. Stent placement or angioplasty is also possible. A recent study of thrombectomy in patients treated within 8 hours demonstrated a recanalization rate of 57.3% of treatable vessels and 69.5% after adjunctive therapy. Thirty-nine percent of patients had favorable outcomes.[60]

Most patients with acute stroke are significantly compromised. General anesthesia is advocated. In addition, a narrow therapeutic window is available for interventions: 6 hours after the patient was last seen is normal for intraarterial thrombolysis and 8 hours for mechanical clot disruption. Often the anesthesia team has little time to gather preoperative information. A bolt or extraventricular drain may be necessary to measure intracranial pressure during the procedure.

INTERVENTIONAL CARDIOLOGY PROCEDURES: GENERAL CONSIDERATIONS FOR CATHERIZATION LABORATORY AND ELECTROPHYSIOLOGY LABORATORY

For the past 20 years, medicine has witnessed a crescendo of new procedures in interventional cardiology and electrophysiology (see also Chapter 68). The catheterization laboratory and electrophysiology laboratory—in terms of both volume and scope—define new specialties. In parallel, the need for anesthesiology involvement has increased. As new technology emerges into the medical marketplace, percutaneous treatment of structural heart disease has become part of the repertoire of interventional cardiologists, creating new and exciting opportunities for cardiac anesthesiologists. The anesthetic care of structural heart disease patients in the catheterization laboratory represents a new horizon for cardiac anesthesiologists, as does real-time echocardiographic guidance for placement of intracardiac closure devices. The role of cardiac anesthesiologist as co-proceduralist in this context is discussed later in an addendum to this chapter.

Similarly, the electrophysiology laboratory now offers expanded treatment options for patients with late-stage heart failure and complex arrhythmias. Because many of these procedures are long and involved, most are performed with general anesthesia or combinations of sedation and general anesthesia. Many patients have significant comorbidities. Often the proceduralists involved are unaware of the ramifications these present for procedural success, although this is changing. In this new and challenging arena, collaboration and planning between interventionalist and anesthesiologist are required to ensure patient safety and optimized outcome. A clear understanding of the procedure to be performed, possible pitfalls, and unique patient characteristics is necessary for the formulation of a safe and effective plan. As always, a common knowledge base and vocabulary facilitate integration of care.

THE LABORATORY ENVIRONMENT: UNIQUE CHALLENGES FOR ANESTHESIOLOGISTS

This section presents an overview of the laboratory environment(s), the evolution and future pathways of current practice(s), cases performed in each venue, and current anesthetic approaches. Invasive cardiology procedures performed in the cardiac catheterization laboratory include the following:

1. Diagnostic cardiac catheterizations and coronary interventions
2. Peripheral vascular diagnostic and therapeutic procedures
3. Amelioration of structural heart disease by the placement of intracardiac devices
4. Implantation of intraaortic balloon pumps and percutaneous left ventricular assist devices

Common electrophysiology laboratory procedures include the following (see also Chapters 48 and 68):

1. Electrophysiology studies
2. Atrial and ventricular radiofrequency ablation procedures
3. Implantation and removal of pacing and cardioverter defibrillator devices

These procedures potentially require the involvement of anesthesiologists if the patient has significant comorbidities. However, some ablations and electrophysiology studies and some device implants and removals can be performed with nurse-administered sedation. Some procedures are lengthy and technically demanding; some require that the patient be still. In such situations, preservation of hemodynamic stability and maintenance of a sedated or asleep state may indicate the need for a general anesthetic.

Catheterization laboratory and electrophysiology laboratory environments differ significantly from the OR. It is important for anesthesiologists to recognize the limitations of the venue and understand the flow of cases and responsibilities of ancillary personnel. Innovation and flexibility are necessary with respect to equipment availability and positioning and the nature and tempo of the anesthesiology-cardiology interface.

Electrophysiology and catheterization laboratories are built with separate control stations and procedure rooms. The control area is shielded from radiation and is the vantage point from which the progress of the procedure is recorded. An operator outside of the procedure room controls recording of data, patient monitoring, video recording and editing, and digital record keeping. Anesthesia equipment is not included in the array of controls outside the room. If robotic equipment is used, it is kept outside of the procedure room and catheter manipulations are made from there.

Room Configuration and Equipment Layout

Within the procedure room itself, cardiologists, anesthesiologists, nurses, and radiology technicians contribute to the care of care patient during the procedure. It can be daunting to know who is who and who is responsible for what. It is best to ask if unsure. In an emergency, understanding who is in charge of a life-saving therapy (i.e., defibrillator) can eliminate confusion and save lives. The procedure room includes fluoroscopy equipment (x-ray tube and C-arm), which usually surrounds the patient's head, making access difficult. The procedure table is mobile, and screens for viewing the procedure are at 90 degrees to the anesthesiologist. Sterile tables for the cardiologist, closets or portable storage units for various catheters, wires for the procedures, and blood analysis machines take up a lot of space. Anesthesia equipment (machine, cart, pumps, monitors), often an afterthought, is frequently pushed into the back of the room. Although lead screens hang from the ceiling to protect the cardiologist, no such protection is available for anesthesiologists, so portable lead screens, unwieldy and heavy, must be wheeled into the area between the anesthesia area and the fluoroscopy equipment. The anesthesiologist should become familiar with the contents of each procedure room, which varies across institutions, because usually things have to be moved, and moving the wrong thing can be problematic. Gas outlets and suction, monitors for vital signs, cardioverter-defibrillator, emergency medications, and airway equipment are critical and may not be optimally or even obviously placed. Longer tubing or extensions are needed for ventilator hoses, intravenous lines, suction, and more. Electrical outlets may not be sensibly located, and extension cords may be needed. Other equipment frequently found in these rooms may include ventricular assist devices, intraaortic balloon pumps, device programmers, and echocardiography machines. Space can become an issue during complex cases when a plethora of additional equipment is needed.

The fluoroscopy table and fluoroscopy equipment are controlled by radiology technicians and cardiologists. These move during the procedure to facilitate imaging, sometimes with no warning. As with all NORA locations, the local availability of extra equipment and an emergency airway cart becomes essential when the anesthesia workroom is not nearby. With cardiac patients, time can be critical. An anesthesia cart stocked with intravenous lines, medications, airway equipment, and medication essentials is important in the cardiac catheterization and electrophysiology laboratories. All personnel in the laboratory should be informed about the location and names of emergency equipment because the anesthesiologist may be alone and occupied during an emergency.

ANESTHESIOLOGISTS IN THE ELECTROPHYSIOLOGY LABORATORY

Clinical electrophysiology has redefined itself over the past 15 years (see also Chapter 48). Advanced technology and increased demand have driven exponential growth in the number of electrophysiology procedures. Additionally, the scope of these procedures has also dramatically changed from simple diagnostic procedures to major, life-saving, therapeutic interventions. More than 14 million Americans are affected by arrhythmias, and many of these patients require hospitalization and complex medical care. ICDs reduce mortality and morbidity for those with malignant tachyarrhythmias, and as a result, implantations and revisions of these devices have skyrocketed.[61]

The performance of many of these procedures now frequently mandates administration of general anesthesia because the procedures are long and many patients have comorbidities that make it unlikely they would tolerate a procedure under sedation. Optimal anesthetic planning requires the anesthesiologist to integrate patient comorbidities, nature of the arrhythmia, and tempo and framework of electrophysiology procedures. This section reviews the most commonly performed electrophysiology procedures.

ELECTROPHYSIOLOGY STUDIES

Diagnostic electrophysiology studies are usually undertaken in conjunction with either therapeutic procedures to evaluate and treat specific arrhythmias or device placements (see also Chapter 48). They can determine the electrophysiologic etiology of specific symptoms or events. Intracardiac recordings are made from catheters placed via femoral venous access into the high right atrium, bundle of His, coronary sinus, and right ventricular apex or right ventricular outflow tract. Arrhythmias are induced by programmed stimulation.[62] For these studies, sedation with benzodiazepines and short-acting opioids is usually sufficient. Drugs that may affect inducibility of certain arrhythmias should be avoided.

CATHETER ABLATION

Conduction abnormalities of many etiologies can generate rhythms that create hemodynamic instability and cardiac compromise. In general, these rhythms result in uncoordinated or ill-timed contraction; they are too slow, too fast, or mechanically abnormal. Bradyarrhythmias arise from either abnormal impulse generation or abnormal impulse propagation, which results in a slow rate. Tachyarrhythmias that are regular with a normal QRS include atrial flutter, atrioventricular nodal reentry tachycardia (AVNRT), and supraventricular tachycardia (SVT). Tachyarrhythmias that are irregular with normal QRS include atrial fibrillation and multifocal atrial tachycardia. Tachyarrhythmias with wide QRS include ventricular tachycardia and SVT with aberrancy.[63] Arrhythmias can have many etiologies, both metabolic and mechanical. Common electrophysiologic generators of arrhythmias include abnormal automaticity, anatomic reentry, and triggered activity. These abnormalities can be identified and treated using percutaneous catheter–based ablation techniques.

Catheter ablation is commonly used to treat SVTs, such as AVNRT, Wolf-Parkinson-White syndrome–related tachycardias, atrial flutter, atrial fibrillation, and ventricular arrhythmias in selected patients. Radiofrequency energy and cryotherapy are most commonly used for ablation. Both of these energy sources can be painful when delivered to target tissues.

Recent American College of Cardiology (ACC) and American Heart Association (AHA) Atrial Fibrillation Guidelines state that in patients with little or no left atrial enlargement, catheter ablation is a "reasonable alternative to pharmacologic therapy" to help prevent recurrence of atrial fibrillation.[64]

Radiofrequency catheter ablation is used for arrhythmias that are refractory to pharmacologic therapy and as a first-line treatment for other arrhythmias. The following arrhythmias can be treated with radiofrequency ablation: atrioventricular reentrant tachycardia, supraventricular arrhythmias associated with the Wolf-Parkinson-White syndrome, atrial ventricular reentrant tachycardia, atrial tachycardia, atrial flutter, idiopathic ventricular tachycardia, bundle branch reentrant ventricular tachycardia, right ventricular outflow tachycardia, atrial fibrillation with an uncontrollable rapid ventricular response (radiofrequency ablation of the atrial ventricular node and placement of a permanent pacemaker), and atrial fibrillation. Radiofrequency is also used as adjunctive therapy for recurrent ventricular tachycardia resulting from coronary artery disease or arrhythmogenic right ventricular dysplasia.[65]

During ablation procedures, catheters are placed throughout the cardiac chambers and programmed stimulation is performed from different sites to induce tachyarrhythmias. Complex mapping techniques localize the source of the arrhythmia to identify the exact intracardiac location to which the radiofrequency energy must be applied. Mapping techniques include activation mapping; pace mapping; entrainment mapping; anatomic fluoroscopy-based, three-dimensional electroanatomic mapping; three-dimensional noncontact mapping; and intracardiac echocardiography-guided anatomic mapping. Because of the precision required for mapping and applying radiofrequency energy, the patient must lie still during the procedure. General anesthesia ensures patient comfort and optimizes mapping. Paralysis should be avoided during radiofrequency ablation so that phrenic nerve stimulation can be performed to avoid injuring this structure. Remifentanil or sufentanil infusions can be administered in this setting.

Radiofrequency ablation procedures are becoming longer. Atrial fibrillation ablations often require 4 to 6 hours, followed by a 30-minute observation time after ablation with repeat stimulation (sometimes with pharmacologic agents as well) to ensure success of the procedure.[65]

Patients range from young and healthy to those with extensive comorbidities. Coughing, snoring, and partial airway obstruction are problematic for sedation and for the progress of the procedure. Snoring can precipitate swinging of the intraatrial septum, making transseptal catheter placement difficult. Ventilatory control with general anesthesia is preferable for obese patients, those with OSA, or those with potential pulmonary problems. Drugs that affect the sympathetic nervous system should be avoided, if possible, during mapping of ectopic foci and tracts. In patients with ventricular dysfunction, inotropic and vasoactive agents may be necessary to maintain hemodynamic stability during arrhythmia induction. Close communication with the cardiologist is necessary in these situations. Frequently, electrical cardioversion is necessary during the case.

ELECTROPHYSIOLOGIC DEVICES

Devices for the control or eradication of arrhythmias have diminished in size and increased in sophistication over the past 10 years (see also Chapter 48). More patients

qualify for device implants, and the number of procedures for implantation, revision, and upgrade of devices has grown. The two most common types of devices are ICDs and pacemakers.

Implantable Cardioverter-Defibrillators

ICDs have been demonstrated to be efficacious and safe in a number of large, prospective multicenter randomized trials in patients with coronary and no coronary heart diseases. Benefits accrue mainly in patients with depressed left ventricular ejection fractions of 35% or less.[66] Indications for ICD implantation as listed in the 2008 ACC, AHA, and the Heart Rhythm Society (HRS) guidelines have clearly been shown to prolong life and decrease the risk for sudden cardiac death for both primary and secondary ventricular tachycardia and ventricular fibrillation.[67] With the advent of smaller biphasic, transvenous ICDs and the experience gained over the years, it is now feasible for electrophysiologists to implant ICDs safely in the pectoral position in the electrophysiology laboratory. Local anesthesia combined with conscious sedation is used. The role of anesthesiologist is crucial if defibrillation threshold testing is done. This is especially true in patients who generally have significant comorbidities. Defibrillation threshold testing is commonly omitted because of the potential life-threatening risks of the procedure in unstable patients or patients with untreated coronary artery disease.

A new subcutaneous ICD (S-ICD), which eliminates the need for transvenous leads, is now available. Although the device detects and treats malignant VT and VF, it is incapable of providing antitachycardia pacing, advanced diagnostics, or radiofrequency interrogation with remote monitoring, and therefore is not appropriate for all patients. Implantation of these devices requires tunneling of the relatively large lead, and this can be painful enough to require deep sedation or general anesthesia.[67a]

Biventricular Pacing and Defibrillation Lead Placement

Cardiac resynchronization therapy with and without defibrillation systems are prescribed for both primary and secondary prevention of sudden cardiac death in patients with heart failure associated with both an ischemic and nonischemic etiology. The ACC/AHA/HRS guidelines gave cardiac resynchronization therapy with or without an ICD a class I indication for those with a left ventricular ejection fraction 35% or less with a QRS duration 120 msec or greater and drug-refractory New York Heart Association functional class III or ambulatory class IV heart failure who are receiving optimal medical therapy.[67]

Implantation of biventricular ICDs may be complex and lengthy because of difficulty positioning the left ventricular lead into the coronary sinus and great cardiac vein in the setting of distorted ventricular anatomy resulting from cardiac dilatation and advanced heart failure. In addition, valvular regurgitation can complicate lead positioning. Finally, lead dislodgement may occur immediately after lead placement, especially in patients with a large coronary sinus, further prolonging these procedures.

During any device placement, pneumothorax or coronary sinus perforation related to lead placement is possible. Coronary sinus perforation can immediately be recognized by contrast extravasation. Perforation of the coronary sinus or cardiac perforation related to ventricular or atrial lead placement may lead to the development of cardiac tamponade, which necessitates immediate pericardiocentesis. Paralytics should be avoided here, as well, so that lead placement, which results in diaphragmatic pacing, can be identified and avoided.

Many patients who qualify for these devices have multiple comorbidities, including a history of ventricular tachycardia or fibrillation, ejection fraction less than 30%, and coronary artery disease (these are indications for ICD placement). However, most of these devices are placed with mild to moderate sedation and standard monitors. Testing the device requires deep sedation or general anesthesia. ICD placement and testing can be accomplished without an arterial line. External cardioverter-defibrillator pads are placed on the patient at the beginning of the procedure. When testing ICDs, they serve as backup if the implanted device fails.

Some patients needing ICDs may benefit from placement of biventricular pacemakers used for cardiac resynchronization therapy. Patients scheduled for a biventricular pacemaker have extensive cardiac morbidity, including low ejection fractions, valvular heart disease, pulmonary hypertension, and right ventricular dysfunction. Patients may not be able to lie flat comfortably and can easily become hemodynamically unstable with sedation. Oversedation can lead to hypercapnia, which is problematic in patients with pulmonary hypertension or right ventricular dysfunction. The anesthesiologist should be available if needed to assist during the case.

ANESTHESIOLOGISTS IN THE CATHERIZATION LABORATORY

Anesthesiology in the catheterization laboratory reflects the evolving broad range of therapies performed in this venue (see also Chapter 68). Catheterization laboratories—originally the workplace of interventional radiologists (who were the "original" angiographers)—are home to interventional cardiologists, vascular surgeons, and others who practice a broad range of therapies, all of which use fluoroscopy and a host of ever more sophisticated interventional technologies. Procedures can be peripheral or cardiac and range from the stenting of narrowed or occluded vessels to the implantation of prosthetic heart valves. Anesthesiology involvement ranges from giving intravenous propofol to providing a full cardiac anesthetic and performing transesophageal echocardiography (TEE) during the case.

PERCUTANEOUS CORONARY INTERVENTIONS

Percutaneous coronary interventional procedures for patients with both stable coronary artery disease and acute coronary syndromes have grown in the past 10 years. Percutaneous coronary interventions (PCIs)

include coronary angioplasty (mostly performed immediately before coronary stenting) with both bare metal stents and drug-eluting stents, atherectomy procedures, and intracoronary thrombectomy procedures. PCI procedures are commonly performed in patients with 70% or greater intracoronary luminal atherosclerotic obstruction and demonstrated myocardial ischemia in the context of stable coronary disease. The major benefit of PCI is to reduce or relieve symptoms of ischemic heart disease and increase aerobic capacity.[68] No significant difference in total mortality, nonfatal myocardial infarction, or other major cardiovascular events were demonstrated between randomized patients treated with aggressive medical therapy or aggressive medical therapy plus PCI angioplasty with bare metal stenting.[69] But for patients who presented with acute coronary syndromes, PCI decreased mortality and recurrent myocardial infarction in contrast to medical treatment alone.[70]

PCIs can be performed with mild to moderate nurse-administered sedation under the direction of the cardiologist. Anesthesiologists are usually involved only when patients present with respiratory or hemodynamic compromise.

If acute patient respiratory or hemodynamic decompensation occurs, anesthesiologists are called emergently. In this circumstance, clear and direct communication with the cardiologist is required; management decisions usually need to be made expeditiously. Information such as medications given, intravenous access, and stage of the procedure must be made available. Access to the patient's head can be difficult because of the x-ray equipment, as mentioned previously. If an airway needs to be established, it may be necessary to temporarily move the table and fluoroscopy equipment and hold chest compressions. Placement of an endotracheal tube is preferred to a laryngeal mask airway (LMA) even in an elective situation because the constant movement of the equipment or cardiopulmonary resuscitation, or both, can dislodge the LMA. Obviously for patients who are acutely unstable, having an endotracheal tube is preferred, but if placement is difficult, an LMA can serve as a temporizing measure. During PCI, patients can be in a highly anticoagulated state, and a bleeding difficult airway is a nightmare in this context.

INTRAAORTIC BALLOON PUMPS AND PERCUTANEOUS VENTRICULAR ASSIST DEVICES

The intraaortic balloon pump (IABP) is a mechanical device inserted percutaneously into the aorta that increases myocardial oxygen perfusion and cardiac output (see also Chapter 68). The balloon, sitting approximately an inch distal to the subclavian artery, inflates and deflates in diastole and systole, respectively thereby delivering *counterpulsation*. This increases coronary blood flow and myocardial oxygen delivery, and cardiac output rises. The balloon pump is controlled by a programmed console, which inflates the balloon at varying time intervals chosen by the operator, linked to either an electrocardiogram trace or a pressure transducer at the distal tip of the catheter. Placement of IABPs is usually successful under conscious sedation unless the patient is compromised from a hemodynamic or respiratory standpoint, in which case the team would seek assistance from an anesthesiologist.

Percutaneous ventricular assist devices (PVADs) provide inotropic support during high-risk PCI, cardiogenic shock associated with myocardial infarction, or other left ventricular dysfunction. Several types of PVADs are available. The TandemHeart device (CardiacAssist, Philadelphia, Pa) is a percutaneous left-atrial to femoral bypass system consisting of a transseptal cannula, an arterial cannula, and an externally located centrifugal blood pump, which can deliver flow rates of up to 4 L/min.[71] An alternative percutaneous-based left ventricular assist device is the Impella Recover (Impella Cardiosystems, Aachen, Germany). This device comes in two sizes—a 2.5- and 5.0-L system—and uses a cannula inserted retrograde via the femoral artery into the left ventricle across the aortic valve. These pumps do not require transseptal puncture, are smaller and easier to implant, and incorporate a microaxial pump into the catheter system, thereby eliminating the need for extracorporeal blood. Cardiac output of either 2.5 L/min or 5.0 L/min can be achieved with the Impella devices.[72] Anesthesiologists are consulted for these procedures because the patients are unstable and/or present with a high likelihood of airway or hemodynamic compromise. Depending on the procedure and state of the patient, either sedation or general anesthesia can be used. These devices achieve cardiac outputs that can completely replace left ventricular function; blood flow may not be pulsatile, so pulse oximetry and noninvasive blood pressure cuffs may not work properly. However, invasive monitoring is available via the arterial cannulation used during the procedure. The choice of anesthetic, likely postprocedural care, and prognosis should be discussed with the cardiologist before the start of the case, if possible.

PERCUTANEOUS CLOSURE OF SEPTAL DEFECTS

The placement of intracardiac septal occluder devices requires general anesthesia if TEE is used to guide placement of the closure device (see also Chapters 46 and 47). If the cardiologist uses intracardiac or intravascular echocardiography, general anesthesia may not be needed. Several U.S. Food and Drug Administration (FDA)-approved devices are available for closure of atrial septal defects (ASDs). To date, however, no prospective randomized controlled trial has been done of percutaneous closure of patent foramen ovales (PFOs) in patients who have suffered from a cryptogenic stroke. The FDA has not approved the use of percutaneous occluder devices for the prevention of recurrent cryptogenic stroke in patients with PFO.[73] Insurance companies are increasingly unwilling to pay for these procedures.

The Amplatzer (AGA Medical, Golden Valley, MN) and the CardioSEAL (NMT Medical, Boston, MA) devices are routinely used in clinical practice. The Amplatzer Septal Occluder is a two-sided "clam shell" made up of two flat discs with a middle or "waist." The discs are made of nitinol (nickel and titanium) wire mesh and polyester fabric

inserts. The fabric inserts create a nidus for tissue growth after placement.[74] The CardioSEAL STARflex device consists of two self-expanding Dacron patch–covered umbrellas that attach to either side of the intraatrial septum. The umbrellas are composed of four central radiating metal arms attached to each other in the center. The device contains a self-centering mechanism comprising nitinol springs that connect the two umbrellas.[75] Closure of PFOs tends to be simpler than closure of ASDs. In patients with ASDs, it is important to clarify right ventricular function, pulmonary arterial pressures, and shunt to formulate an optimal anesthetic plan. Success rates for PFO and ASD closure range from 79% to 100%.[76]

These devices can also be used to close other types of defects, such as paravalvular leaks and muscular or perimembranous ventricular septal defects (VSDs) (either congenital or acquired). Reportedly, VSDs can be closed 96% of the time, with a 2% major complication rate with these devices.[77] Left to right flow is seen on TEE with these lesions. In patients with traumatic (post–myocardial infarction) VSDs, hemodynamic instability is not unusual and complications are common during closure attempts. Tissue integrity is frequently compromised, and placement of closure devices is difficult. Visualization of the defect and guidance of device placement can be challenging. Patients with post–myocardial infarction VSDs are more likely to have complications during closure of the defect.[78]

Complications of any device placement in the cardiac catheterization laboratory include air embolism, device embolization, malposition, thrombosis, embolization, arrhythmias, hypotension, valve dysfunction, cardiac perforation, and injury to nontarget cardiac structures. It is critical that these complications be recognized and dealt with expeditiously. Rapid and effective communication is critical. Untoward events may be evident initially to anesthesiologists if they are guiding the procedure with TEE.

Echocardiography is often used during the procedure to help guide placement and confirm a successful result. TEE can be performed by cardiologists, anesthesiologists, or ultrasound technicians, depending on institutional preference and availability of personnel. If TEE is used, general anesthesia will be necessary for the procedure. If a cardiac anesthesiologist administers the anesthetic, he or she can guide the procedure in a step-by-step fashion, integrating the guidance with anesthetic parameters. Although two-dimensional echocardiography is the most widely used imaging technique for preprocedural patient evaluation, three-dimensional imaging via echocardiography, multidetector row CT, and cardiac MRI can also help to delineate structural intracardiac details. Intraprocedural three-dimensional TEE is also available.[79] Intracardiac echocardiography (ICE) can be used to guide the procedure, but this must be performed by the cardiologist because the controls are at the groin and in the field. In cases in which TEE is not available or cannot be performed because of patient comorbidities, ICE is a reasonable alternative.

If arterial monitoring is needed and the cardiologist is not planning femoral arterial access, a radial arterial line should be placed by the anesthesiologist. Two intravenous lines (and/or a central line) should be available at induction if the patient is potentially unstable.

PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease affects approximately 8 million Americans (see also Chapter 69). The prevalence of this disease increases with age and occurs more commonly in African Americans. Intermittent claudication and rest pain are the principal symptoms. Claudication symptoms are due to insufficient arterial blood flow and leg ischemia. Symptoms include pain, aching, and a sense of fatigue or other discomfort that is relieved at rest. Symptoms are most often experienced in the muscle bed supplied by the most proximal stenosis. Buttock, hip, or thigh claudication is related to obstruction of the aorta or iliac flow. Calf claudication commonly is a result of either femoral or popliteal arterial stenosis, and either tibial or peroneal disease causes ankle or pedal claudication.[80]

According to ACC and AHA guidelines, percutaneous revascularization in patients with intermittent claudication should be considered when any one of the following circumstances is encountered:

1. Claudication symptoms significantly disable the patient.
2. The patient is able to benefit from an improvement in exercise.
3. Rehabilitation and pharmacologic therapy have not provided adequate response.
4. A favorable risk-to-benefit ratio to performing the procedure exists.
5. The characteristics of the lesion permit appropriate intervention at low risk with a high likelihood of initial and long-term success; and/or the patient has limb-threatening ischemia, as manifested by rest pain, ischemic ulcers, or gangrene.[81]

The anesthesiologist may be critical to the interventional cardiologist during a peripheral vascular intervention because many of these patients are unable to lie still during the procedure because of rest pain symptoms and other related comorbidities. In addition, the procedure itself may create painful transient ischemia and patient movement may reduce the likelihood of success.

PERCUTANEOUS VALVE REPAIR AND REPLACEMENT

Percutaneous technologies for the treatment of mitral regurgitation and aortic valve disease are presently available; development of devices and approaches is ongoing (see also Chapter 67). These procedures are a major addition to the repertoire of interventional cardiologists and represent exciting new overlap of surgical and medical therapies for structural heart disease.

Percutaneous Mitral Valve Repair

Currently, surgical repair is the most common procedure performed for the treatment of symptomatic mitral regurgitation or mitral regurgitation with impaired left ventricular ejection fraction (<60%). However, current techniques under investigation for percutaneous mitral valve repair include coronary sinus annuloplasty, direct annuloplasty, leaflet repair, and others.[82]

Devices that use the coronary sinus as a method of cinching the mitral annulus are investigational, and the safety and efficacy of this approach remains undetermined. Another approach involves percutaneous placement of a cliplike device (MitraClip, Abbott Vascular, Abbott Park, IL) that creates an Alfieri edge-to-edge repair (Evalve, San Francisco, CA). After a transatrial septal puncture, the clip is positioned in the center of the mitral valve orifice. The clip is opened, passed into the left ventricular cavity, pulled back to contact the mitral valve leaflets, and then closed to create a double-orifice mitral valve.[82] General anesthesia, fluoroscopy, and TEE to help guide placement of the device are part of the Evalve procedure.[76]

Percutaneous Aortic Valve Replacement (Transcatheter Aortic Valve Replacement)

Percutaneous aortic valve replacement or transcatheter aortic valve replacement (TAVR) is a relatively new treatment in the US for aortic stenosis. During the procedure, a replacement valve is crimped into a catheter and passed through the femoral artery to the aortic annulus. Rapid ventricular pacing is employed to minimize cardiac output while the prosthesis is deployed into the appropriate position after a balloon valvuloplasty. Transaortic and transapical insertions of transcatheter valves can also be performed by a multidisciplinary team in a hybrid OR setting. In the future, other variants of this procedure will likely evolve for placement of valves in other positions.

The concept of a transcatheter valve for percutaneous placement was initially presented in the early 1990s, and the first percutaneous heart valve for human use was developed by Cribrier and implanted in Europe in 2002.[83,84] In the United States, the Edwards SAPIEN valve received FDA approval in November 2011.[85] Two devices currently exist for percutaneous implantation; the Medtronic CoreValve (Medtronic, Minneapolis, MN) and the Edwards Lifesciences SAPIEN (Edwards Lifesciences, Irvine, CA). The CoreValve is a porcine pericardial self-expanding valve prosthesis sutured into a nitinol stent. The SAPIEN valve is a bovine pericardial prosthesis sutured into a balloon-expandable tubular metal stent.

In high-risk patients with severe aortic stenosis, transcatheter valve replacement was found to be "noninferior" to surgical aortic valve replacement at 1 year in terms of survival. However, the transcatheter procedure was associated with a higher risk for stroke than the surgical replacement at 1 year and a higher risk for major vascular complications at 30 days. More patients undergoing transcatheter replacement demonstrated improved symptoms at 30 days, but no significant between-group difference was seen at 1 year.[86,87]

Ongoing clinical trials are under way comparing surgical aortic valve replacement to percutaneous aortic valve replacement in patients who are candidates for cardiac surgery using newer generation percutaneous aortic prosthetic valves. As study results become available, percutaneous valve replacement may constitute a viable alternative to surgery for a patients who need valve replacement in whom the risk for cardiac surgery is unacceptable.

These procedures present a changing paradigm with respect to treatment of structural heart disease and the scope of interventional cardiology procedures. Procedures and patients are more complex. Medical and surgical approaches to cardiac care are beginning to overlap. Anesthesiologists must be prepared to treat this challenging patient population in new venues.

At our institution, all percutaneous valve repairs are performed under general anesthesia with fluoroscopic and TEE guidance. CTs are obtained before the procedure to define valve size and anatomy, and 3D TEE may be used during the procedure to affirm valvular anatomy before and after the prosthesis is placed. Patients are elderly, with severe valvular disease and attendant comorbidities. Communication and coordination of activities are critical.

During percutaneous valve replacements and repairs, the procedure room is crowded with staff and equipment. Planning for expected difficulties related to patient comorbidities and technical challenges is well worth the extra time. A team meeting before the procedure is worthwhile because elements of the patient's history often warrant interdisciplinary scrutiny and discussion. Two peripheral intravenous lines should be placed for infusions, and a Swan-Ganz catheter is recommended in compromised patients. Endotracheal intubation is required if TEE is used, and arterial monitoring is important because noninvasive blood pressure cuffs may not work when the patient is rapidly paced. Communication and visual accessibility to all imaging during the procedure is vital to successful placement of the device. Multiple attempts may be needed to ensure proper catheter and device placement with an acceptable result. Patients may develop hemodynamic instability, myocardial ischemia, or significant arrhythmias during the case. Constant communication between anesthesiologist and cardiologist is critical.

Transfemoral TAVR can be performed in a cardiac catheterization laboratory or hybrid OR. Enough space is required for general anesthesia, TEE, and cardiopulmonary circulatory support, in addition to the space required by the proceduralists. The percutaneous femoral approach requires adequate endolumenal diameters, but as technology develops, smaller sheaths and more flexible valves will become available. In the future, tortuous iliac vessels or high athermanous burden may not preclude a femoral approach.

For transfemoral cases, general endotracheal anesthesia is preferred, although institutions in the United States and Europe report successful outcomes with conscious sedation. Invasive arterial pressure monitoring and central access are needed. Planned extubation is reasonable assuming the patient's comorbidities and the course of the procedure warrant it.

Although institutions in Europe report successful TAVR outcomes using ICE and/or fluoroscopy alone, in our experience TEE plays a critical role (also see Chapter 46). Before any intervention, aortic stenosis with a trileaflet valve should be confirmed; TAVR cannot be performed with bicuspid valves. The degree of aortic insufficiency should be assessed before valvuloplasty; the presence of mild to moderate aortic insufficiency may be protective in severe new-onset cases after balloon aortic valvuloplasty. Ejection fraction, degree of mitral and tricuspid regurgitation, presence of mitral annular calcification and mitral stenosis, estimated pulmonary artery

pressures, and coronary artery takeoff location are also useful measurements. Accurate measurement of aortic annulus aids in choice of prosthetic valve size. During the placement of the valve, real-time echocardiographic guidance can assess positioning of the prosthesis. Following valve deployment, rapid assessment of valvular function, presence of leaks, and ventricular wall motion abnormalities are critical.

As technology improves, the flow of cases will change. Presently, however, at our institution, the following list constitutes the framework for transfemoral cases:

Critical Procedural Steps During Transfemoral Transcatheter Valve Replacement

1. Place intravenous line and A-line, induction.
2. Place PA line, larger access, cerebral Svo_2.
3. Conduct TEE discussion and expected and unexpected findings with entire team.
4. Access femoral vasculature: arterial sheath, contralateral transfemoral aortic occlusion balloon, and place transvenous pacer
5. Perform standard balloon aortic valvuloplasty: refine sizing and enlarge orifice.
6. Assess adequacy of rapid ventricular pacing.
7. Upsize sheath to (27 French) or appropriate introducer.
8. Advance transcatheter valve; assess position by fluoroscopy and echocardiography.
9. Deploy valve during rapid ventricular pacing.
10. Assess valve position and function.
11. Remove sheath and complete vascular closure.

Common Complications and Remedies

Vascular Disaster. Femoral vascular avulsion is possible on removal of the introducer sheath. Temporization of hemorrhage can be achieved with the distal aorta occlusion balloon residing in the contralateral femoral artery. This can prevent fatal hemorrhage in the event of a vascular catastrophe. If percutaneous access cannot be obtained, cut-downs or surgical access to the aortic bifurcation is possible. Vascular surgical repair is necessary in this situation. All of these potential eventualities demand the ongoing vigilance of the anesthesiologist.

Pacing Malfunction. Transvenous pacing is used to establish rapid ventricular pacing and a near-zero cardiac output state during ballooning of the aortic valve. If atrioventricular node dysfunction occurs after valvuloplasty or valve deployment, postdeployment pacing may be necessary. Poor communication during rapid ventricular pacing may be catastrophic. Loss of pacer capture during balloon valvuloplasty can place excessive traction on the native valve during balloon inflation; unexpected ventricular ejection can embolize the valve from the annulus during deployment.

Abnormal Valve Deployment. Valves left prepared on the balloon but not deployed for significant amounts of time may open improperly, causing significant aortic insufficiency. Deployment of an additional device (valve-in-valve) may be necessary in this case.

Hemodynamic changes may occur at a variety of points during the procedure. Communication among providers of different disciplines is essential. Patients respond idiosyncratically to balloon valvuloplasty; new-onset aortic insufficiency may require significant support and necessitate rapid valve introduction and deployment. Inotropic support may be necessary to maintain systemic blood pressure as balloons and crimped valves traverse the valve orifice. Invasive monitors typically reflect low cardiac output, falling Svo_2 and high pulmonary artery pressures. The authors routinely have boluses of epinephrine, norepinephrine, and vasopressin available in a variety of concentrations.

Device Embolization. Embolization into the aorta can occur as a result of ejection because of inadequate pacer capture or inappropriately high deployment. Once a valve is in the aorta, it is irretrievable endovascularly. Valves lodged in the descending aorta have been reported and are tolerated; however, a second valve must still be deployed in the aortic position. Valve loss into the ventricle may occur if deployment is too low. This result requires surgery for retrieval and may be fatal if comorbidities are significant.

Coronary Occlusion. Coronary occlusion is a potential problem if calcium or native aortic valve tissue occludes a coronary ostium. Prior coronary artery bypass graft with patent grafts is partially protective. Coronary guidewires may be placed in patients who are at higher risk. Skilled intervention is required to reopen occluded coronary arteries. Clear interdisciplinary communication is essential in the management of regional wall motion abnormalities, ST-segment changes, or hemodynamic compromise.

Need for Cardiopulmonary Bypass. Cardiovascular collapse during transfemoral procedures may require cardiopulmonary support. Institutional variability exists regarding the type of support planned; some institutions have a primed cardiopulmonary bypass pump in the room, even if the case is in a catheterization laboratory outside of the OR; others have percutaneous VAD support on standby.

Neurologic Events. Acute stroke is potentially detectable with unilateral changes in cerebral oximetry readings. The higher stroke rate of cohort A patients in the PARTNER trial was felt to be a result of both ballooning of the calcified native valve and the introduction of a large balloon and valve apparatus across the aortic arch. Anesthetics allowing for early neurologic assessment are preferred.

As patient acuity increases, safe and efficient care for the target population in the cardiac catheterization and electrophysiology laboratories is a concern for all anesthesiologists and cardiologists. Anesthesiologists are uniquely trained to care for this complicated patient population while permitting cardiologists to focus on the interventional procedure. Anesthesiologists, in collaboration with cardiologists, must establish guidelines for the interdisciplinary care of patients with complex issues in the cardiac catheterization and electrophysiology laboratories. Growing numbers of patients with more complicated health issues and an expanding arsenal of sophisticated technologies make it likely demand for these laboratory services will continue to grow. Collaboration between

cardiologists and anesthesiologists is increasingly necessary. Reframing the boundaries of medical specialties is the likely key to success. The goal is to enhance patient safety and improve procedural efficiency and outcomes while advancing the frontiers of medical care in expanding and exciting venues outside of the OR.

INTERVENTIONAL ECHOCARDIOGRAPHY ANESTHESIOLOGISTS AS CO-PROCEDURALISTS—THE ROAD AHEAD

As percutaneous interventions for structural heart disease increase in number and broaden in scope, the need for multidisciplinary input grows. Cardiac anesthesiologists traditionally perform TEE in the OR before and after cardiopulmonary bypass to diagnose structural problems and assess surgical repair. In the catheterization laboratory, growing usage of general anesthesia to support patients during complex procedures ideally positions cardiac anesthesiologists to perform this service in a new context.

Diagnostic echocardiography is important in the catheterization laboratory, as it is in the OR. However, the novel feature of TEE performed here (interventional TEE) is the need for step-by-step guidance of intricate and highly technical intracardiac manipulations[88] (see also Chapter 46). Fluoroscopy—the traditional imaging modality for interventional cardiology procedures—entails significant radiation exposure, requires the use of intravenous contrast, and can be temporally and spatially imprecise. Interventional TEE provides precise adjunctive imaging for placement or removal of intracardiac devices, placement of transcatheter valves, and repairs of paravalvular leaks or other structural defects. In addition, cardiac anesthesiologists understand imaging in the context of anesthetic care and are capable of manipulating hemodynamics as observation of cardiac function requires. Functional interpretation of structural defects can be critical as repairs are made. In the catheterization laboratory or hybrid OR setting, cardiac anesthesiologists become co-proceduralists, providing imaging, hemodynamic control, interpretation, and step-by-step guidance for interventionalists in the context of fixing abnormal cardiac anatomy. Real-time three-dimensional guidance during catheter placement, ballooning, or device implantation is an important and new component of interventional cardiology. This is a time-sensitive, high-acuity undertaking. It is relatively new in intracardiac imaging and for cardiac anesthesiologists; it defines an exciting and important role that goes a step beyond the job of maintaining homeostasis during the stress of surgery.

Interventional TEE is performed during septal occlusion, paravalvular leak repair, and transcatheter valve replacement. As in the OR, comprehensive interventional TEE examination begins with assessment of cardiac structure and function in the context of the proposed procedure, including the primary defect and any associated pathology. Effective communication among team members is critical because the value of interventional two-dimensional and three-dimensional TEE is lost if mutual understanding is absent. To this end, information from fluoroscopic and echocardiographic images can augment each other when unusual anatomy or clinical circumstances are observed. Data from each imaging modality should be discussed if contradictory interpretations arise.

Interventional TEE includes both two-dimensional and Doppler imaging complemented by three-dimensional and real-time three-dimensional datasets. It may be important to alternate between two-dimensional and three-dimensional imaging to clarify temporal and spatial details,[89,90] so that accurate placement of wires and catheters can occur. Closure of paravalvular leaks or stenting of stenotic pulmonary veins, for example, may require both types of imaging. Real-time three-dimensional imaging can clearly depict the proximity of equipment and devices to targeted defects by permitting rotation of acquisitions in all directions, thereby delineating structures in their native orientation. Although in the OR it is possible to correlate actual anatomy with TEE images while the chest is open and the patient is on bypass, this is not the case during percutaneous procedures. The accuracy of imaging and interpretation is therefore critical.

During TAVR, interventional echocardiography is important for optimization of valve placement and diagnosis of problems when they occur. After TAVR deployment, a comprehensive TEE is performed. Valve position is assessed, absence of coronary ostial occlusion is confirmed, valve gradient is measured, perivalvular and central leaks are assessed, and the need for any remedial activity is discussed. This requires the input of proceduralists and cardiologists alike.

As technology evolves, percutaneous procedures for structural heart disease will become more sophisticated. As devices improve, the target populations will grow. Patients with congenital, acquired, and surgically created defects will become eligible for treatment by interventional cardiology procedures. Interventional TEE has emerged as the newest evolutionary phase of cardiac anesthesiology.[91] The development of optimal, collaborative relationships between interventional cardiologists and anesthesiologists provides the foundation for a robust, multidisciplinary interface, thus establishing a basis for advancement of clinical practice and a place for anesthesiologists at the forefront of medicine.

THE ROAD AHEAD: TOWARD A COMPREHENSIVE STRATEGY

As technology evolves, medical procedures tend to become more complex. As the population ages and medical therapies achieve increased effectiveness, acute illnesses can become chronic. The current expansion of minimally invasive, nonsurgical approaches to disease will continue. Demand for anesthesiology services continues to escalate, but because procedural operators are largely medical and not surgical providers, requests for services do not necessarily parallel need. Thus, anesthesiologists are sometimes asked to attend patients who do not need their support, and conversely, are not asked to participate where presence is required until a crisis develops. Solutions to staffing problems become more complicated; efficiency and medical optimization become secondary to the goal of

getting through the day and the procedures to be done. When politics and finances increasingly dictate what they do and whom they treat, anesthesiologists must emphasize even further their mission of enhancing patient safety and comfort. Resetting the boundaries of practice to include medical specialties is critical to success.

It is clear that we must extend the recognized realm of our specialty beyond the limits of the OR. Inclusion of procedural areas within our practice requires a new model of service delivery. Not only are new markets emerging, but the financial rules are changing. We ought not allow our expertise to become discontinuous with current opportunities arising as a result of medical progress or risk allowing anesthesia services to become anachronistic. New, noninvasive approaches to surgical problems threaten to change the standards of where, how, who, and under what circumstances, surgical or percutaneous interventions may be performed.

Over the past 30 years, anesthesiologists revolutionized safety, reliability, and the scope of practice within the OR. The time has come for us to do likewise in non-OR locations. Seeing beyond the traditional role of anesthesiologists in the OR, we can create a niche broadened by services as critical care providers inside and outside the ICU, as surgical hospitalists and care integrators, and as innovators outside of the operating room. If these possibilities are ignored in the emerging market structure, we risk abdicating our real responsibilities to patients and to medicine. We must examine the productivity and sustainability of anesthesiology as a medical subspecialty. What, then, are the elements of an effective strategy?

Operational Effectiveness

Operational effectiveness is a crucial component of successful competitive strategy and financial sustainability. It implies innovation and the ability to manage a more successful, wider spectrum of activities than the competition. We must provide better, more flexible services that yield measurably better outcomes than the competition. For us, that competition includes (1) medical proceduralists who do not see the need for anesthesiologists, (2) other nonanesthesia providers, and (3) companies that design and produce machinery capable of administering drugs and interpreting monitoring equipment. "Better outcomes" are defined by evidence—that is, volume and quality data. Therefore, record keeping and data analysis must become an essential element of operations. In addition, operational effectiveness requires optimized resource management: planning is critical and ad-hoc management is unacceptable.

Costs, Uniqueness, and Value-Added

Anesthesiologists have the training and experience to deliver superior, integrated, cost-effective services outside the OR. In an era of increasing medical specialization and fragmentation of care delivery, particularly in the context of accountable care organizations and bundled payments, these are the critical indices of success.

Proper variable cost accounting demonstrates that the cost of patient care involving an efficiently deployed anesthesiologist is less than the cost imposed on the whole system by those (all too common) procedures that start without anesthesia personnel and end with an urgent, unanticipated call. The expense of (1) delaying a procedure, (2) stopping a procedure for inadequate or oversedation, (3) hospitalizing a patient, and (4) rescheduling and redoing the procedure is forbidding. But the costs are not always obvious because they are spread over multiple cost centers.

Institutions in which anesthesiologists practice and the medical and surgical departments they serve benefit from anesthesiology services. However, reimbursement to anesthesiologists may not parallel or indeed justify the investment. Little overlap exists in available time and productive time, and there are no rules. The non-OR would run as erratically as the OR would, were surgeons allowed to show up whenever they wanted, to book procedures 5 minutes before they started, and to change procedures or patients at the last minute.

Strategic Positioning

For anesthesiologists, strategic positioning occurs when the needs of customers and potential customers are satisfied with minimal cost to the anesthesiologist. Environmental scanning, context analysis, and other standard tools of market assessment serve to reconcile the mission of anesthesiology and revision of core competencies (product line) with the demand for them. The customers are not just patients; they are also medical proceduralists and third-party payers. If we can provide a safer, more comfortable, time-efficient, and cost-effective environment for proceduralists, the value of an anesthesiologist in attendance is clear. If we develop the bridge between medical and surgical treatment by facilitating hybrid procedures and interdisciplinary approaches, the overall value of our presence will be incontrovertible to proceduralists, patients, insurance companies, regulatory bodies, and government agencies.

Financial Silos and Teamwork

The certainty of increased insistence by third-party payers on integrated care requires collaboration and interdisciplinary effort. As accountable care organizations become widespread, bundling will become standard and integration will be expected by all insurers. Anesthesiologists will be forced to depend on the strength of relationships they forge with medical specialists. These will grow and develop only if the medical specialists recognize the value of anesthesiologists in attendance during their cases. Teamwork depends on improved outcomes and financial success.

Team building requires communication based on common experience and vocabulary—hence, the argument for grouping medical specialists with anesthesiologists who specialize in a specific type of surgery. Often medical specialists perform interventions with the same end goals as open surgeries, yet they lack the surgical perspective that many anesthesiologists acquire in the OR. Integration of medical and surgical perspectives can be, and has been, exploited for innovative solutions to new problems and to avert mistakes outside of the OR. The contribution of cardiac anesthesiologists to percutaneous device placement and congenital heart disease treatment in the

catheterization laboratory is a case in point. Similar participation in ultrasound-guided cases in the endoscopy laboratory and to interventional radiology cases is also possible. Teams bridge silos. Integration of reimbursement is coming. Why not be ready for it and organize ourselves preemptively?

Sustainable Strategy: Key Points

Effective strategy is one that maintains a dynamic and profitable market presence. Anesthesiologists have two related parallel sets of priorities: creating and maintaining a stable but flexible customer base and achieving financial sustainability.

Operational effectiveness will ensure that appropriate resource allocation permits innovation. Enhanced core competencies resulting from expanded medical training and presence outside of the operating room will provide a basis for the already needed enrichment of services. Team building will ensure that proceduralists understand the rationale for close cooperation and generate a foundation for better integrated finances. Reframing boundaries and elimination of silos will enhance integration, productivity, and the quality of care across the board. The overall strategy must be to make our specialty indispensable to customers and potential customers, while enhancing the lives of patients by improving outcomes and stimulating progress.

Our expertise will generate consistent reimbursement if we have the data to demonstrate the benefit of that presence. Our participation in non-OR procedures can stimulate and advance medicine just as development of the OR environment advanced the practice of surgery. As technology continues to proliferate and diversify, the distinction between medical and surgical approaches to treatment becomes blurred. The pursuit of innovation has always been characteristic of anesthesiologists. We must continue this work in new venues and work to build bridges if we hope to survive as a specialty.

The need is urgent for anesthesiology to adopt a broader, more business-like perspective as the practice continues to broaden medical know-how. If this opportunity and its associated intellectual challenges are ignored, the status of anesthesia, a key medical subspecialty, may be threatened. If the challenge is accepted, the practice of anesthesiology will be on the front lines of changing and advancing medical science. As this chapter goes to print, an unprecedented crescendo of emerging technology and ongoing innovation continues to defy status quo approaches to NORA cases. Some information presented here may already be outdated; proceduralists, locations, and equipment will continue to evolve. Regardless of the venue or the technique, anesthesiologists remain a critical and constant guardian of integrative medical perspective, patient safety and efficient procedural process. As we move beyond the OR, constant vigilance, dedicated teamwork, mutual respect and effective communication will continue to be the keys to success.

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Chapter 91

Clinical Care in Extreme Environments: At High and Low Pressure and in Space

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Key Points

- Hyperbaric oxygen exposure (breathing oxygen at increased ambient pressure, typically 2 to 3 ATA) causes an increase in arterial and tissue partial pressure of oxygen and no significant change in arterial pH or partial pressure of carbon dioxide.
- During hyperbaric oxygen therapy, cardiac output and pulmonary vascular resistance are decreased; systemic vascular resistance is increased.
- Acute illnesses for which hyperbaric oxygen is indicated include carbon monoxide (CO) poisoning (based on randomized controlled studies), gas bubble injury (gas embolism and decompression sickness), and soft tissue necrotizing infections.
- The decision to use hyperbaric oxygen to treat a patient with arterial gas embolism or decompression sickness should be based on clinical criteria, including the presence of symptoms, abnormal physical examination, or a history of arterial gas embolism within a few hours even in the absence of symptoms. Neither neurophysiologic testing nor radiographic imaging is useful except, rarely, to exclude other disorders.
- The decision to use hyperbaric oxygen to treat a patient with CO poisoning should be based on clinical criteria, including a history of impaired consciousness or other neurologic manifestation, pregnancy, or severe exposure (e.g., peak carboxyhemoglobin [HbCO] > 25%). The HbCO concentration correlates poorly with the severity of the illness and is generally useful only to make the diagnosis.
- Oxygen-induced seizures are rare and self-limited. Appropriate management includes discontinuation of inhaled oxygen. Chamber pressure should not be altered during the seizure because decompression while a seizure is occurring can result in pulmonary barotrauma (pneumothorax or pneumomediastinum) and arterial gas embolism.
- Pretreatment of patients with hyperbaric oxygen may ameliorate some of the adverse effects of cardiac surgery and invasive cardiac procedures (see also Chapter 67).
- The principles of treatment of acute altitude illness include descent and supplemental oxygen. If these options are not available, for acute mountain sickness or high-altitude cerebral edema, dexamethasone and acetazolamide are recommended. Recommended treatment of high-altitude pulmonary edema includes drugs that decrease pulmonary artery pressure, such as nifedipine, nitric oxide, or a phophodiesterase-5 inhibitor such as sildenafil.
- When providing anesthesia for otherwise healthy acclimatized patients at high altitude, the minimum amount of supplemental oxygen should be used to maintain arterial oxygen saturation close to baseline (not normal levels). Prolonged administration of oxygen in liberal doses may reverse acclimatization.
- As ambient pressure is altered, anesthetic vaporizers (except for desflurane) deliver a variable concentration but fixed partial pressure of vapor. Therefore, vaporizer settings do not need to be adjusted when delivering anesthesia in a hyperbaric chamber or at high altitude. Desflurane vaporizers deliver a fixed concentration and require upward adjustment at high altitude.
- Unexpected complications have occurred after anesthesia for minor procedures in primates following spaceflight. Physiologic and pharmacologic effects of neuraxial or general anesthesia during or after spaceflight are largely unknown, but they could include hypotension, resistance to nondepolarizing muscle relaxants and α-adrenergic agonists, and exaggerated hyperkalemia resulting from succinylcholine (see also Chapter 34).

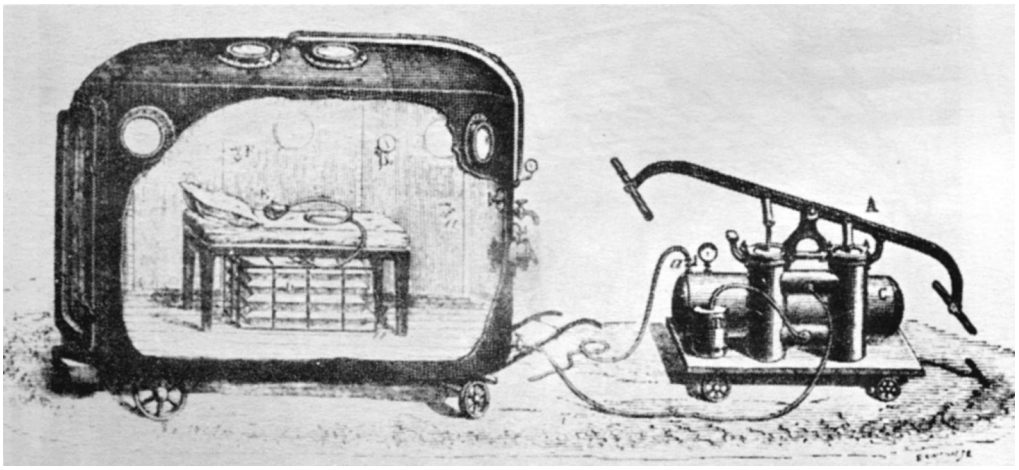


Figure 91-1. Mobile hyperbaric operating room described by Fontaine in 1879.[1] Nitrous oxide storage tanks can be seen under the operating table. Compressed to 1.25 to 1.33 atmospheres absolute with air (ATA), a nitrous oxide–oxygen mixture was provided to the patient. Breathing air in this chamber would have provided an inspired partial pressure of oxygen (PO_2) equivalent to 26% to 28% oxygen at 1 ATA.

Hyperbaric medicine began in the nineteenth century, when clinical improvement was observed after recompression of divers and compressed air workers who had decompression sickness (DCS). Hyperbaric air treatment was subsequently used for a variety of diseases, including tuberculosis, heart failure, emphysema, bronchitis, asthma, croup, whooping cough, anemia, anorexia, dyspepsia, leukorrhea, menorrhagia, neuralgic pain, and depression, without any scientific basis. An exception was the use by Fontaine in 1879 of a mobile hyperbaric chamber for anesthesia and surgery.[1] Compressed to 1.25 to 1.33 atmospheres absolute (ATA), a nitrous oxide–oxygen (O_2) mixture was provided to the patient (Fig. 91-1). Breathing air in Fontaine's chamber would have provided an inspired partial pressure of O_2 (PO_2) equivalent to 26% to 28% O_2 at 1 ATA. This was probably the first use of an increased PO_2 during anesthesia and certainly the first administration of hyperbaric nitrous oxide.

Use of O_2 at high pressure for the treatment of DCS had been suggested.[2] It was reported for the treatment of DCS,[3] but it remained an isolated medical curiosity until the early 1960s. A few indications, such as support of oxygenation in hyaline membrane disease of the newborn[4] and during open heart surgery,[5,6] were not useful. For other indications, such as carbon monoxide (CO) poisoning, arterial gas embolism (AGE), and DCS, hyperbaric O_2 treatment (HBOT) is effective, as evidenced by substantial clinical experience and randomized controlled studies. Indications are reviewed regularly by the Undersea and Hyperbaric Medical Society (headquarters in Durham, NC). This medical organization publishes an extensive bibliography with a list of indications for hyperbaric oxygenation that is updated every 2 to 3 years.[7] Laboratory and clinical data support the use of HBOT for a select number of acute and chronic illnesses (Box 91-1), and anesthesia providers are often called on to provide care of patients in this unusual environment.

Interest in the physiologic and medical aspects of altitude originated because of mountaineering and high-altitude balloon exploits in the nineteenth century.[8] An understanding of the physiologic response to altitude hypoxia has had wide application because increasing

BOX 91-1 ***Conditions for Which Hyperbaric Oxygen Is Effective***

Gas-bubble disease
- *Air embolism[7,83,85]
- *Decompression sickness[83,85]

Poisoning
- *Carbon monoxide[7,41,47-49,54,55]
- Cyanide[41]
- Carbon tetrachloride[323,324]
- Hydrogen sulfide[41]

Infections
- *Clostridial myonecrosis[7,100-103]
- *Other soft tissue necrotizing infections[7,102,103,325,326]
- *Refractory chronic osteomyelitis[7,93,327]
- *Intracranial abscess[7,328]
- Mucormycosis[329,330]

Acute ischemia
- *Crush injury[7,331]
- *Compromised skin flaps[7,332]
- *Central retinal artery occlusion, central retinal vein occlusion[333,334]

Chronic ischemia
- *Radiation necrosis (soft tissue, radiation cystitis, and osteoradionecrosis)[7,335-337]
- *Ischemic ulcers, including diabetic ulcers[7,11,338-342]

Acute hypoxia
- *Exceptional blood loss anemia (when transfusion delayed or unavailable)[7]
- Support of oxygenation during therapeutic lung lavage[104,105]

Thermal injury
- *Burns[7,343-346]

Envenomation
- Brown recluse spider bite[347,348]

Miscellaneous
- *Idiopathic sudden sensorineural hearing loss[349]

* Approved by the Undersea and Hyperbaric Medical Society as an appropriate indication for hyperbaric oxygen treatment.[7]

TABLE 91-1 RANGE OF TERRESTRIAL ALTITUDES

Altitude*		Ambient Pressure		
(ft)	(m)	(ATA)	(mm Hg)	Comments
		0.32	235†	Lowest pressure to which volunteers have been continuously exposed (hypobaric chamber study: Operation Everest)[350,351]
29,028	8,848	0.35	263†	Mt. Everest, Nepal: highest point on earth
20,320	6,194	0.45	345	Mt. McKinley (Denali), Alaska, United States: highest point in North America
19,521	5,950	0.49	372†	Aucanquilcha mine, Chile: highest altitude known to have been continuously inhabited by humans[352]; miners slept in a village at lower altitude ('Quilcha, 5334 m)
17,716	5,400	0.51	384	Everest Base Camp
17,060	5,200	0.54	409	Chacaltaya ski resort, Bolivia (elevation at the top of the ski hill, 5,422 m)
16,733	5,100	0.55	414	La Rinconada, Peru: highest permanently inhabited town
	5,050			Atacama Large Millimeter Array telescope, Chile; facility includes oxygen enrichment to 27%[353]
14,110	4,301	0.58	458	Pike's Peak, Colorado, United States[216]
13,796	4,205	0.60	460†	Mauna Kea, Hawaii, United States
		(0.57-0.63)	(433-479)†	(Keck Observatory)[354]
11,910	3,630	0.65	497	La Paz, Bolivia
10,500	3,200	0.69	524	Alta Ski Resort, Utah
10,430	3,179	0.69	525	Leadville, Colorado, United States: highest altitude incorporated city in North America (population 3000)[355]
9,321	2,841	0.67-0.68	507-516†	South Pole Station, Antarctica[356]
9,249	2,819	0.72	549	Quito, Ecuador
7,546	2,300	0.77	583	Mexico City, Mexico
5,280	1,609	0.83	633	Denver, Colorado, United States; Zermatt, Switzerland
4,500	1,372	0.86	650	Banff, Alberta, Canada; Kathmandu, Nepal
0	0	1.00	760	Sea level

ATA, Atmosphere absolute.
*Altitudes and barometric pressures are shown for Mt. Everest and several locations inhabited at least part time. Barometric pressures have been calculated using an algorithm developed by West,[357] except for values with a dagger
†which were obtained by direct measurement.[351]

numbers of people fly in aircraft, travel from low to high altitude, and live or work at higher elevations (Table 91-1). Significant effort has been devoted to techniques for prophylaxis and treatment of these illnesses.

The effects of space travel are mostly the result of microgravity, radiation, and confinement. Understanding these effects and developing tools to deal with sick or injured astronauts are paramount for the medical support of long-range space missions, such as to Mars.

PHYSIOLOGIC EFFECTS OF INCREASED GAS PRESSURE

INCREASED BAROMETRIC PRESSURE

Some effects of altered ambient pressure are summarized in Figure 91-2.

An increase in environmental pressure is accompanied by significant adiabatic heat production, whereas decompression generates cooling. This process results in an increase in chamber temperature during compression and cooling and precipitation of water droplets during decompression. These phenomena may limit the rate of compression in manned chambers to maintain temperature within a comfortable range.

Additionally, pockets of trapped gas within the body contract and expand on compression and decompression. Such pockets include gas in the middle ear and paranasal sinuses, intestinal gas, pneumothorax, and gas pockets within monitoring and life support systems. The changes in gas volume occur according to Boyle's law:

$$PV = \text{constant}$$

such that doubling of environmental pressure (P) causes the volume (V) of a gas-filled cavity to decrease by half. This effect also underlies one of the major beneficial effects of hyperbaric treatment of pathologic gas, as in AGE or DCS (see later).

A comparison of pressure units used clinically with those in common use in hyperbaric environments is shown in Table 91-2.

INCREASED PARTIAL PRESSURE OF OXYGEN

Breathing O_2 at increased ambient pressure leads to elevation of alveolar O_2 tension (PAO_2), which can be calculated according to the alveolar gas equation for O_2:

$$PAO_2 = FiO_2\,(P_b - PH_2O) - Pa_{CO_2} \cdot \left(FiO_2 + \frac{1 - FiO_2}{R}\right)$$

where FiO_2 is the fractional inspired O_2 concentration; P_{H_2O} is saturated water vapor pressure at body temperature (typically 47 mm Hg); P_{ACO_2} is alveolar partial pressure of CO_2 (P_{CO_2}), assumed to equal arterial P_{CO_2} (Pa_{CO_2}); and R is the respiratory exchange ratio (usually ≈0.8 at rest). From calculated values of PAO_2, arterial PO_2 (PaO_2)

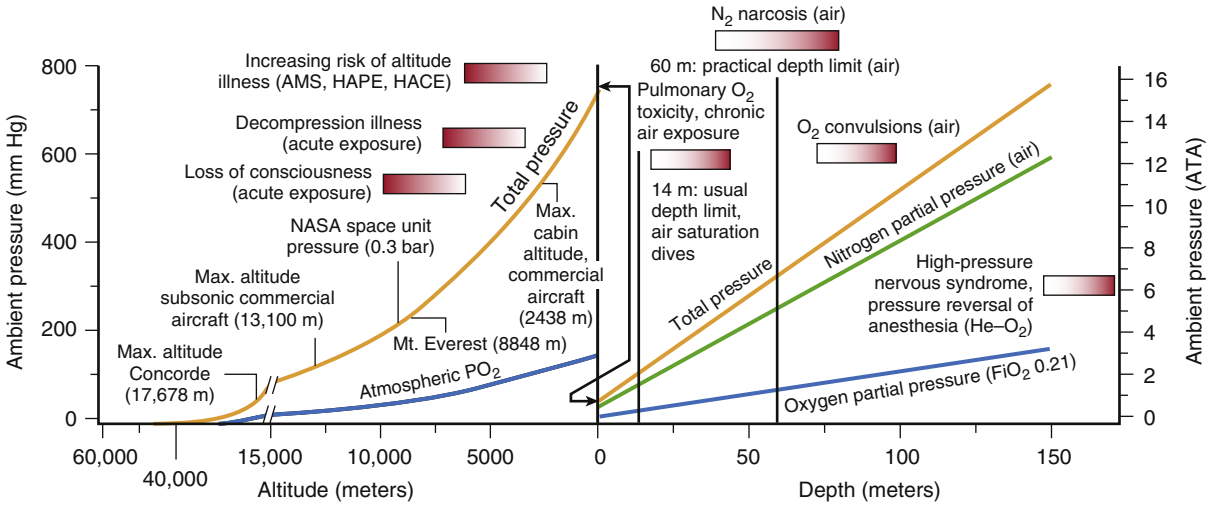


Figure 91-2. Ambient pressure as a function of altitude and water depth. Whereas ambient pressure increases linearly with depth, pressure and altitude are not linearly related. As air is inspired and humidified, a small and usually insignificant drop from atmospheric partial pressure of oxygen (PO_2) to inspired PO_2 occurs. At altitude, however, this decrease accounts for a greater proportion of the total ambient pressure. The PO_2 line in the water is shown for a constant fraction of inspired oxygen concentration (FiO_2) of 21%. At increasing depth, the inspired PO_2 eventually exceeds the pulmonary toxic limit (~14 m in depth) and the central nervous system toxic limit (~70 m in depth). The threshold for high-pressure nervous syndrome and pressure reversal of anesthesia (observed in nonnarcotic atmospheres) is 150 to 200 m in depth. The *shaded red bars* represent the depth or altitude ranges over which risk progresses from low *(light shading)* to high *(dark shading). AMS,* Acute mountain sickness; *HACE,* high-altitude cerebral edema; *HAPE,* high-altitude pulmonary edema; *He,* helium; *Max.,* maximum; N_2, nitrogen; O_2, oxygen.

TABLE 91-2 UNITS OF PRESSURE

Atmospheres Absolute (ATA)	Absolute Pressure (mm Hg)	Gauge Pressure (mm Hg)	Feet of Sea Water (fsw)	Meters of Sea Water (msw)
1	760	0	0	0
2	1,520	760	33	10
3	2,280	1,520	66	20
6	4,560	3,800	165	50

has been estimated, assuming that the arterial-alveolar (a/A) PO_2 ratio remains constant.[9] Whereas at 1 ATA the fraction of O_2 in arterial blood that is carried dissolved in the plasma is minimal, at elevated PaO_2 in the range of 1000 to 2000 mm Hg, significant quantities of O_2 may exist in dissolved form (Table 91-3).

Increased PaO_2 has at least four pharmacologic effects:

1. Increased blood O_2 content
2. Vasoconstriction
3. Antibacterial action, particularly against anaerobic bacteria
4. Inhibition of endothelial neutrophil adhesion in injured tissue

The increased arterial O_2 content underlies the rationale for administering HBOT for the treatment of ischemic conditions (e.g., ischemic nonhealing wounds). The elevation in PaO_2 leads to an increase in tissue PO_2, which can be estimated using transcutaneous PO_2 electrodes, even in ischemic tissue.[10,11] The second effect explains the effectiveness of HBOT in the treatment of traumatic edema (e.g., crush injury). The mechanism of HBOT-induced vasoconstriction appears to be the inactivation of nitric oxide as a result of increased production of superoxide[12] and possibly decreased release of nitric oxide from circulating S-nitrosohemoglobin.[12-14]

These two effects, increased O_2 content and vasoconstriction, lead to hemodynamic changes,[14,15] as shown in Table 91-3. A slight increase in mean arterial blood pressure also occurs. Studies of the effects of HBOT on myocardial contractility using denervated hearts[16] or autonomically blocked animals[17] have indicated no intrinsic effect. In intact animals or humans, heart rate and cardiac output are decreased and systemic vascular resistance is increased.[14,15,18] In both anesthetized dogs and awake humans, pulmonary vascular resistance is decreased.[14,19] At 2 ATA, 100% O_2 in conscious dogs has no effect on coronary flow,[18] whereas at 3 ATA, both coronary flow and myocardial O_2 consumption are decreased.[17] Cerebral blood flow is decreased by O_2 administration over a range of pressures,[12,18] whereas at 2 ATA, hepatic, renal, and mesenteric flows are unchanged.[18]

HBOT also has microcirculatory and cellular effects in various disease states (see later).

INCREASE OF INERT GAS PARTIAL PRESSURE

An increase of the partial pressure of the inert gas (usually nitrogen) present in a breathing mixture is associated with a narcotic-like effect, predictable by the Meyer-Overton hypothesis. Based on its solubility in olive oil, nitrogen

TABLE 91-3 **MEAN BLOOD ACID-BASE AND CARDIOVASCULAR RESPONSES TO ALTITUDE EXPOSURE AND HYPERBARIC OXYGENATION IN 14 NORMAL SUBJECTS**

		Arterial						Mixed Venous									
Atmospheric Pressure (ATA)	Inspired Gas	PO_2 (mm Hg)	pH	Pco_2 (mm Hg)	O_2 Saturation (%)	Dissolved O_2 (mL/dL)	Total O_2* (mL/dL)	PO_2 (mm Hg)	pH	Pco_2 (mm Hg)	O_2 Saturation (%)	Cardiac Output (L/min)	Mean Arterial Pressure (mm Hg)	Mean Pulmonary Artery Pressure (mm Hg)	Pulmonary Artery Wedge Pressure (mm Hg)	Systemic Vascular Resistance (dyne/sec)	Pulmonary Vascular Resistance (dyne/sec)
0.56 (4,572 m altitude)	Air	38	7.46	32	73.4	0.1	18.2	30	7.44	36	57.1	9.1	87	18	10	762	83
1	Air	94	7.40	37	95.7	0.3	18.4	43	7.39	42	75.5	6.5	86	13	9	1,061	64
3	100% O_2	1542	7.42	36	99.1	4.6	22.7	399	7.37	43	97.7	5.8	95	12	9	1,286	41

Data from McMahon TJ, Moon RE, Luschinger BP, et al: Nitric oxide in the human respiratory cycle, Nat Med *8:711-717, 2002.*
ATA, Atmospheres absolute; *O_2,* oxygen; *Pco_2,* partial pressure of carbon dioxide; *PO_2,* partial pressure of oxygen.
*Assuming hemoglobin = 13 g/dL.

has 0.03 to 0.05 times the narcotic potency of nitrous oxide. At 3 ATA (breathing air), most people experience mild euphoria. At 6 ATA, memory loss and poor judgment may appear. At 10 ATA, some individuals lapse into unconsciousness. Nitrogen narcosis looks like alcohol intoxication; an increase in ambient pressure of 1.5 ATA appears to be similar to drinking one martini. Argon and, to a lesser degree, hydrogen, are narcotic-like, whereas helium has minimal if any such effect. In animals exposed to high partial pressures of nitrogen, evidence indicates activation of γ-aminobutyric $acid_A$ ($GABA_A$) receptors of dopaminergic neurons in the nigrostriatal pathway, thus leading to a decrease in dopamine release.[20]

ELEVATION OF ABSOLUTE PRESSURE

High-Pressure Nervous Syndrome

High pressure induces a constellation of symptoms consisting of tremor, ataxia, nausea, and vomiting that is known as the high-pressure nervous syndrome (HPNS).[21] It occurs at an ambient pressure more than 15 to 20 ATA and was first described during the compression phase of deep dives with a helium-O_2 atmosphere. HPNS is ameliorated by slow compression and addition of a narcotic gas (e.g., nitrogen) to the breathing mix.[22] The pathogenesis of HPNS may be related to an increase in striatal dopamine.[23]

Pressure Reversal of Anesthesia

Studies in animals demonstrated that high pressure has the tendency to reverse general anesthesia. Increases in ambient pressure in the absence of a narcotic inert breathing gas tend to decrease the effectiveness of both inhaled and intravenous anesthetic agents. At 50 ATA, a 20% increase in the 50% effective dose (ED_{50}) occurs in mice with a variety of inhaled anesthetic agents. At 50 and 100 ATA, the effective dose of barbiturates increases by 30% to 60%.[24] The ED_{50} for diazepam in rats is markedly reduced at 90 ATA in a helium-O_2 atmosphere.[25] At 31 ATA, the effective concentration for half-maximal effect (EC_{50}) of propofol for loss of righting reflex in tadpoles is increased by 19%, and at 61 ATA, it is increased by 38%.[26] Using the same technique, the EC_{50} for dexmedetomidine at 31 ATA is nearly double the value at 1 ATA, and it is increased 2.5-fold at 61 ATA.[27] At 80 ATA, the minimum alveolar concentration (MAC) of desflurane as assessed by response to a noxious stimulus is increased by 19%.[28] The mechanisms of pressure reversal may be secondary to physical chemical effects of pressure on membranes,[29] or they may be related to alterations in neurotransmitter release.[23] However, within the range of pressures used for HBOT (up to 3 to 6 ATA), the effects of pressure on sedative or anesthetic drugs are not clinically significant.

EFFECTS OF HYPERBARIC EXPOSURE ON DRUG DISPOSITION

A few studies have examined the disposition of drugs and drug effects at increased environmental pressures. Studies in awake dogs at pressures up to 6 ATA and ambient PO_2 up to 2.8 ATA showed that liver plasma flow decreased when either ambient pressure or PO_2 was increased. Plasma volume increased at 1.3 ATA and returned toward 1 ATA values during higher pressures. In the same studies plasma volume was inconsistently affected by ambient pressure, but it was reduced by increases in PO_2.[30]

Hyperbaria has no major pharmacokinetic or pharmacodynamic effect for most drugs up to 6 ATA. Up to 6 ATA pressure and 2.8 ATA PO_2, the pharmacokinetics of meperidine,[31] pentobarbital,[32] theophylline,[33] and salicylate[34] are unaffected.

Benzodiazepines, chlorpromazine, and lithium carbonate were used for the treatment of agitation, auditory and visual illusions, and paranoia in a previously normal subject participating in an experimental dive to 650 m (66 ATA).[35] The symptoms, poorly controlled with diazepam 120 mg/day and temazepam 60 mg/day, ultimately responded to chlorpromazine 300 mg/day. Lithium carbonate administered in conventional doses displayed normal pharmacokinetics. However, chlorpromazine appeared clinically to be appropriate. Whether the failure of benzodiazepines to elicit a desired therapeutic response was caused by the patient's condition or by a pressure-reversal phenomenon is not clear.

In summary, conventional parenteral drug dosing schedules may be followed safely under hyperbaric conditions at the pressures used for clinical treatment of patients with HBOT.

RATIONALE FOR THE TREATMENT OF SELECTED SPECIFIC SYNDROMES

CARBON MONOXIDE POISONING

Hemoglobin (Hb) binds CO with an affinity much higher (by a factor of ≈200) than that for O_2. This binding of CO with Hb to form carboxyhemoglobin (HbCO) has two major effects. First, the proportion of Hb that is occupied by CO molecules is unavailable for O_2 transport, thus resulting in a functional anemia. Second, the avidity with which the remaining Hb binds O_2 is increased (shift to the left of the Hb-O_2 dissociation curve). The results are a decreased ability to unload O_2 from blood to tissue at the capillary and therefore a reduction in tissue PO_2. Previously it was believed that these effects were solely responsible for the toxicity of CO. However, evidence has since been presented to show that the binding of CO to intracellular pigments (e.g., cytochrome a, cytochrome a_3, myoglobin) and oxidative stress may contribute significantly to the toxicity of CO.[36-44] CO exposure also triggers intravascular platelet-neutrophil aggregation and neutrophil activation.[44] These mechanisms result in toxicity to multiple organ systems, including brain and heart.[41,45] Immune-mediated effects have also been described.[46]

Clinical effects include headache, nausea, vomiting, dizziness, myocardial ischemia, loss of consciousness, and, during pregnancy, fetal distress. Persistent or delayed neurologic sequelae can occur, often after a clear window of lucidity.[47,48] Increased risk factors for persistent sequelae include older age (≥36 years) and longer CO exposure.[49]

The diagnosis of CO poisoning is made by a history of exposure (internal combustion engine exhaust, fire,

improperly adjusted gas or oil heating, charcoal or gas grills, or exposure to paint stripper containing methylene chloride, which is metabolized by the liver to CO). The diagnosis is confirmed by finding an elevated HbCO level in either arterial or venous blood. HbCO concentration in anticoagulated blood samples is stable for several days. Therefore, if HbCO determination is not available at a referring facility, the diagnosis can be confirmed using a blood sample obtained at the time of initial evaluation and transported with the patient. Fetal Hb (HbF) can produce a falsely elevated reading for HbCO on certain four-wavelength laboratory co-oximeters.[50] In the first few weeks of life, blood from normal infants may therefore falsely indicate 7% to 8% HbCO.

Actual HbCO levels measured on arrival in the emergency room correlate poorly with clinical status and should not be used as the sole criterion to determine the need for treatment. Because of the lower intracellular PO_2, elimination of CO from intracellular binding sites occurs more slowly. Significant mental obtundation, vomiting, and headache may remain even in patients with a normal HbCO level.

Brain imaging may reveal a variety of abnormalities in patients with CO poisoning, including hypodensities in the globus pallidus and subcortical white matter, cerebral cortical lesions, cerebral edema, hippocampal lesions, loss of gray matter and white matter differentiation, and white matter hyperintensities.[51-53] Except to exclude other pathologic processes, brain imaging is not useful for determining who should receive HBOT, but it may provide prognostic information.[51]

O_2 is the primary treatment modality for CO poisoning. High PaO_2 hastens the removal of CO from blood, as indicated by a reduced half-life of HbCO. Figure 91-3 shows the HbCO half-time in a series of CO-poisoned patients during normobaric O_2 administration; HBOT reduces the half-time even further, to approximately 20 minutes at 2.5 ATA[54] (Table 91-4). Additionally, the increased dissolved O_2 in plasma may support tissue oxygenation pending removal of CO from Hb and other proteins important for O_2 transport. Mounting evidence indicates that for poisoning in which neurologic symptoms occur, HBOT may decrease both early and late morbidity.[55] Although the results of one randomized prospective trial of hyperbaric versus normobaric O_2 revealed no apparent benefit of HBOT,[56] in four other trials HBOT resulted in improved outcome compared with treatment at 1 ATA[47,48,57,58] (Fig. 91-4).

Commonly used guidelines for the application of HBOT in CO poisoning include the following:

A history of neurologic impairment (including dizziness, loss of consciousness)
Evidence of cardiac abnormalities (ischemia, arrhythmias, ventricular failure)
An HbCO level that has been higher than 25%

TABLE 91-4 CARBON MONOXIDE ELIMINATION HALF-TIMES WHILE BREATHING AIR OR 100% OXYGEN AT 1 ATA AND AT 2.5 ATA

Breathing Gas	Mean Half-life (min)*	No. Subjects
Air, 1 ATA	214	10
Oxygen, 1 ATA	43	15
Oxygen, 2.5 ATA	19	10

ATA, Atmospheres absolute.
*Mean values from data of Pace et al.[54]

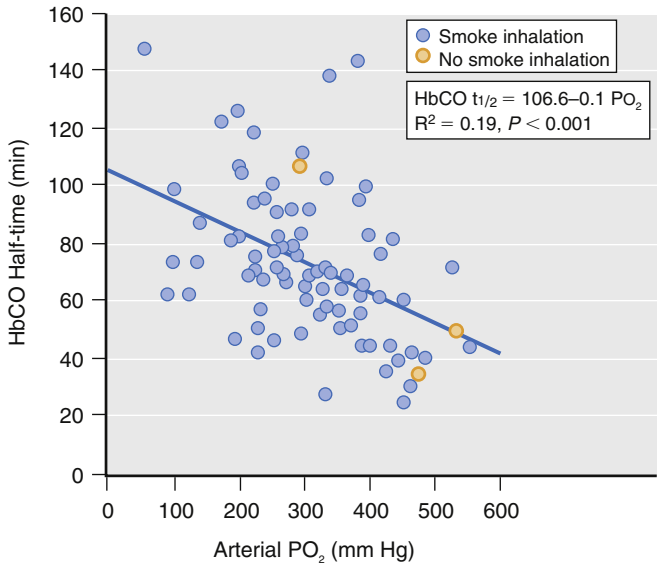


Figure 91-3. Elimination half-time ($t_{½}$) of carboxyhemoglobin (HbCO) in 93 carbon monoxide (CO)-poisoned patients. Although scatter are present in the data, it is apparent that CO dissociates from hemoglobin faster at a higher partial pressure of oxygen (PO_2). *(Redrawn from Weaver LK, Howe S, Hopkins R, Chan KJ: Carboxyhemoglobin half-life in carbon monoxide–poisoned patients treated with 100% oxygen at atmospheric pressure,* Chest *117: 801-808, 2000.)*

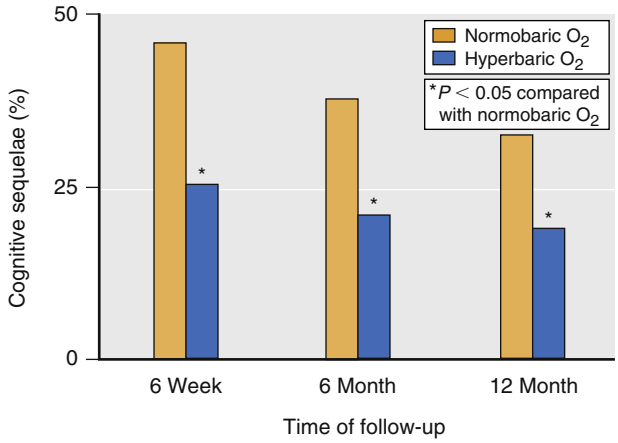


Figure 91-4. Cognitive sequelae in a randomized prospective trial of hyperbaric oxygen (O_2) in carbon monoxide poisoning. Cognitive sequelae were defined as any T score for a neuropsychological subtest more than 2 standard deviations (SD) below the mean of demographically corrected standardized T scores or if two or more T scores for subtests were more than 1 SD below the mean. If the patient reported difficulties with memory, attention, or concentration, then cognitive sequelae were defined as a T score on any neuropsychological subtest more than 1 SD below the mean of demographically corrected standardized T scores. *(Drawn from data reported by Weaver LK, Hopkins RO, Chan KJ, et al: Hyperbaric oxygen for acute carbon monoxide poisoning,* N Engl J Med *347:1057-1067, 2002.)*

Fetuses are particularly susceptible to CO toxicity. Pregnant women who fulfill the criteria just listed or in whom fetal distress is noted should be treated with HBOT. Case reports,[59-61] published series,[62,63] and a critical review[64] support the concept that inadequately treated CO poisoning is a serious risk to the mother and fetus, and the benefits of HBOT outweigh the theoretic risks to the fetus from HBOT. Potential adverse effects of currently implemented HBOT protocols have not been confirmed in clinical practice.

GAS EMBOLISM AND DECOMPRESSION SICKNESS

Introduction of gas into the arterial circulation (AGE) has traditionally been associated with scuba divers and attributed to pulmonary barotrauma during ascent from a dive while breathing compressed gas. However, it may also occur iatrogenically in several clinical circumstances, such as during cardiopulmonary bypass or as a result of inadvertent injection of air during a diagnostic arteriogram or hemodialysis (see also Chapters 67 and 90). Additionally, large amounts of gas may enter the venous system, for example during neurosurgical procedures (see also Chapters 49 and 70) with the patient in the sitting position, hemodialysis, major back surgery, total hip replacement, cesarean section, laparoscopy, intrauterine laser surgery, arthroscopy (from air escaping from faulty air-powered drill), and hydrogen peroxide irrigation or oral ingestion (from elaboration of gaseous O_2 from tissue and blood catalase). Venous gas embolism (VGE) can also occur when a central venous catheter is opened to air. Severe VGE has also occurred during orogenital sex after blowing air intravaginally.[65] VGE can occur in patients with adult respiratory distress syndrome (ARDS) who are being ventilated with positive end-expiratory pressure.[66] VGE in sufficient quantity may overwhelm the ability of the pulmonary vasculature to filter the gas, thus allowing bubbles to pass into the arterial circulation. Even small amounts of venous gas (e.g., VGE caused by decompression from diving) have been implicated in neurologic syndromes in scuba divers because of transatrial passage through a patent foramen ovale.[67,68]

The effects of gas embolism are not solely the result of vessel obstruction by bubbles. Bubble-endothelial interaction causes increased capillary permeability and extravasation of fluid,[69,70] as well as impairment of endothelial function.[71] Another effect was demonstrated in a model of AGE in anesthetized rabbits[72,73]: Small doses of intracarotid air may pass through the cerebral microcirculation yet produce vasoplegia, delayed reduction of cerebral blood flow, and neurophysiologic impairment. Because this reduction in blood flow is abolished in neutropenia, leukocytes are likely required for this effect.[74] This phenomenon of delayed reduction of cerebral blood flow may be responsible for the clinical observation of initial neurologic improvement after AGE, followed by delayed deterioration.[75]

A related syndrome that results from pathologic effects of tissue and blood gas bubbles is DCS, seen in aviators and compressed gas divers. The gas bubbles in these situations occur because of a decrease in ambient pressure at a rate sufficient to induce local inert gas supersaturation, with resulting formation of bubbles in situ from tissue stores. Symptoms of AGE classically consist of impaired consciousness, hemiparesis, or seizures, but they may be less severe. DCS most commonly manifests as any combination of joint pain, paresthesias, motor weakness, bladder or bowel sphincter dysfunction, vertigo, tinnitus, and hearing loss.[76,77]

Treatment principles for both forms of gas bubble disease, AGE and DCS, are the same in most instances. First aid includes therapy with O_2.[78] High PO_2 results in an increased rate of resolution of gas bubbles because of the resulting higher partial pressure gradient for diffusion of inert gas from the interior of the bubble into the surrounding tissue or blood. Intravascular bubbles cause endothelial leak, extravasation of plasma, and hemoconcentration.[69,79] Intravascular fluid resuscitation replenishes intravascular volume, reduces hemoconcentration, and facilitates microcirculatory flow,[80] actions that have been confirmed by both animal[81] and human observations.[69] However, excessive intravascular fluid administration can worsen pulmonary gas exchange in cardiorespiratory DCS (pulmonary edema from VGE), and aggressive fluid therapy is not indicated for isolated AGE.[80] Although capillary leak resulting from cerebral AGE can raise intracranial pressure (ICP), studies in anesthetized pigs showed that hyperventilation offers no benefit.[82]

HBOT is the definitive treatment for AGE and DCS.[83] The increased pressure causes a diminution in gas volume and thus further hastens resolution. The usefulness of HBOT for diving-related or aerospace-related gas embolism associated with rapid decompression is well documented.[84,85] HBOT may effect neurologic improvement even after many hours and sometimes days between the embolic event and treatment,[86-88] although some evidence suggests that severe abnormalities are less likely to resolve if not treated promptly.[89] Treatment of AGE is usually performed at ambient pressures from 2.8 to 6 ATA (see the later section on treatment schedules).

The decision to administer recompression treatment should be based entirely on clinical evaluation.[83] The only appropriate role of brain or spinal imaging (e.g., computed tomography [CT], magnetic resonance imaging [MRI]) is to exclude other pathologic processes such as hemorrhage, and only with a high degree of suspicion that bubbles are not the cause of a patient's symptoms. Patients with AGE should be treated with HBOT only if CT of the brain reveals air.[90] However, brain imaging of patients with AGE or DCS reveals abnormalities in only a minority of cases,[88,89] and the abnormalities on either CT or MRI are usually not specific. Neither the presence nor the absence of intravascular gas predicts response to hyperbaric treatment.[88,89] Nuclear imaging of the brain using single photon emission tomography (SPECT) or positron emission tomography (PET)[91] does not provide clinically useful information in the management of patients with bubble-induced neurologic injury.

ACUTE INFECTIONS

Anaerobic bacteria are especially sensitive to increased tissue PO_2. High O_2 tensions inhibit clostridial α-toxin

production.[92] Other mechanisms include reversal of hypoxia-induced neutrophil function,[93-95] enhanced macrophage interleukin-10 expression,[96] and antiinflammatory effects.[97-99] Evidence in favor of the use of HBOT in clostridial and nonclostridial infections is provided by clinical series and database analyses.[100-103]

SUPPORT OF ARTERIAL OXYGENATION

HBOT is a safe and effective method of supporting arterial oxygenation during therapeutic lung lavage, during which oxygenation must be maintained by the contralateral (nonlavaged) lung.[104,105] In our experience of more than 100 procedures, using this technique to treat arterial oxygenation has been uniformly successful with no resulting complications. A reversible simulation of pulmonary gas exchange during the lavage procedure can be provided by temporarily ventilating the lung to be lavaged with 5% to 6% O_2/balance nitrogen, which reduces PAO_2 in that lung to approximately the level of mixed venous PO_2 and confining O_2 exchange to the contralateral lung. Hypoxemia within 5 minutes predicts hypoxemia during the actual lavage.

MAINTENANCE OF OXYGEN TRANSPORT IN SEVERE ANEMIA

The ability of HBOT to increase arterial O_2 content in plasma to clinically useful levels may allow support of tissue O_2 delivery even without Hb. HBOT can therefore be used for temporary support of severely anemic patients pending availability of definitive therapy in the form of crossmatched blood (see also Chapter 61).

FUTURE DIRECTIONS

PREOPERATIVE HYPERBARIC OXYGENATION

Preconditioning is described as the application of an insult to activate endogenous protective mechanisms to lessen the morphologic and functional sequelae of a subsequent insult. *Ischemic preconditioning* is the application of a brief period of ischemia that activates endogenous protective mechanisms to reduce the damage from subsequent ischemic insults. Ischemic preconditioning was first described in canine myocardium and subsequently was shown also to exist in the brain. Since then, intense research in the field of pharmacology has ensued to identify other agents that lead to preconditioning, such as volatile anesthetics, lipopolysaccharide exposure, heat, central nervous system (CNS) seizures, hypoxia and hyperoxia, and, more recently, hyperbaric hyperoxia.

Several clinical trials have provided evidence that HBOT before cardiac or surgical procedures can improve outcome. Sharifi and associates described the use of HBOT to inhibit restenosis after percutaneous coronary intervention in acute myocardial infarction.[106] In 2005, Alex and associates observed that repetitive pretreatment with three sessions of HBOT at 2.4 ATA before on-pump coronary artery bypass graft (CABG) surgery reduced neuropsychometric dysfunction and modulated favorably the inflammatory response after cardiopulmonary bypass.[107] Yogaratnam and associates reported that preconditioning with a single session of HBOT at 2.5 ATA before on-pump CABG surgery improved left ventricular stroke work after CABG surgery while reducing intraoperative blood loss, intensive care unit (ICU) length of stay, and postoperative complications.[108] In patients undergoing on-pump and off-pump CABG, Li and associates demonstrated that HBOT preconditioning decreased the release of cerebral and myocardial biochemical markers. Patients in the on-pump group pretreated with HBOT had a reduced length of ICU stay and decreased use of inotropic drugs.[109]

The mechanism by which HBOT can be protective is not currently known, but it does not involve support of metabolism by increased tissue O_2 stores because tissue and blood oxygenation is dissipated within minutes after hyperbaric exposure. The etiology of cerebral injuries is probably multifactorial, including cerebral microemboli, global cerebral hypoperfusion, inflammation, cerebral temperature modulation, and genetic susceptibility.[110] The mechanism of protection therefore may include HBOT-induced oxidative stress resulting from increased reactive oxygen species generation, which could induce ischemic tolerance similar to ischemia and reperfusion. Alternatively, HBOT preconditioning may diminish ischemia-reperfusion damage by decreasing tissue leukocyte recruitment and activation, reducing tissue edema, protecting from cellular necrosis, reducing tissue apoptosis, and improving tissue outcome and preservation.[111,112] Another possible mechanism is upregulation of antioxidant enzymes, such as superoxide dismutase,[113] and possibly also heme oxygenase-1, as shown in a model of liver ischemia.[114] HBOT may be beneficial when administered before or after selected procedures. The role of HBOT in this setting needs to be determined by larger clinical trials.

STROKE

Several studies of middle cerebral artery occlusion in rats demonstrated beneficial effects of HBOT.[115-118] In an unselected case series of patients with acute stroke treated within 5 hours of symptom onset, some patients improved with HBOT in which arterial PO_2 was 1100 to 1300 mm Hg.[119] Several clinical studies have been conducted, with mixed results,[120] perhaps because of failure to start HBOT in a timely fashion[121] or to use of subtherapeutic PO_2. One double-blind study described improved outcome when HBOT was administered after acute stroke, a finding suggesting some effect on neuroplasticity.[122]

THERAPEUTIC SYSTEMS

The traditional method of administering hyperbaric therapy is with a multiplace chamber, which accommodates two or more persons (Fig. 91-5). Size may vary from a small, portable 2-person chamber used for transporting patients in the field to a chamber 20 ft or more in diameter in which 12 or more patients may be comfortably admitted, in addition to tenders. Multiplace chambers are compressed with

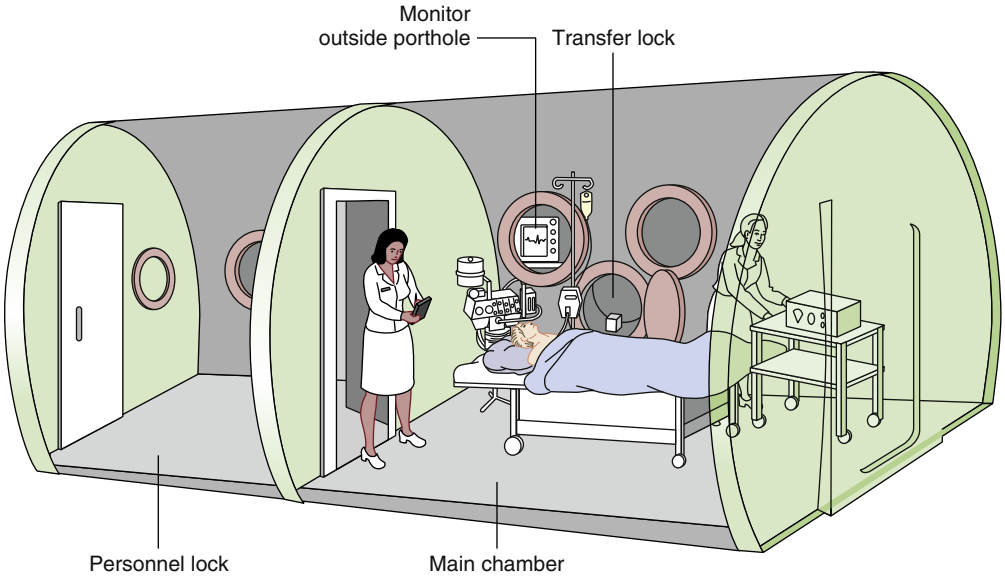


Figure 91-5. Multiplace hyperbaric chamber large enough for one or more patients and tenders. The chamber atmosphere is compressed air. The patient receives 100% oxygen by mask, head tent, or endotracheal tube. Monitors are usually kept outside the chamber because of electrical safety considerations. Monitoring is possible through a porthole. A personnel lock and a transfer lock allow physicians, nurses, or other personnel, in addition to medications, food, and blood samples, to be moved into and out of the chamber without repeated compression and decompression of the patient.

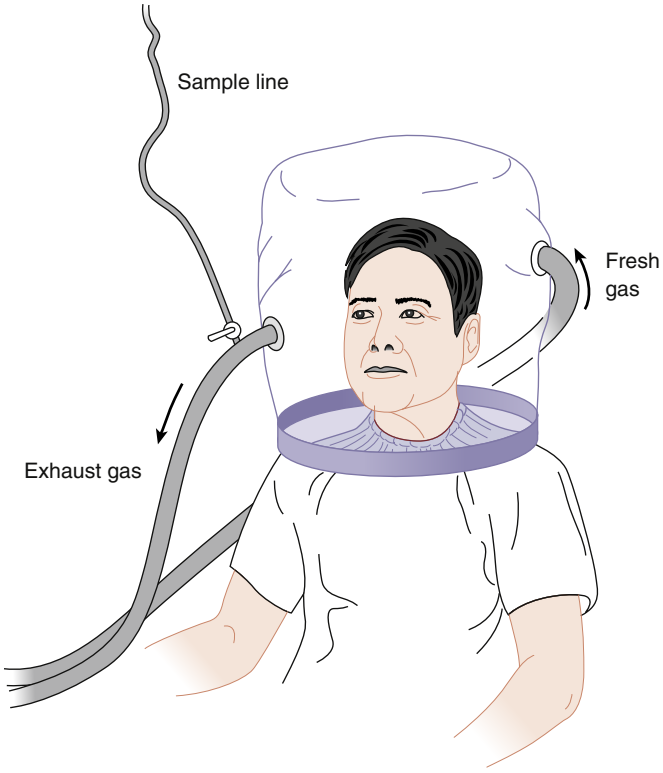


Figure 91-6. Head tent circuit for use in a multiplace chamber. Fresh gas (100% oxygen) flows at a constant rate (>30 L/minute) through the head tent. Exhaust gas may be either vented outside the chamber or recirculated through a carbon dioxide scrubber. The sample line attached to the exhaust hose allows monitoring of the patient's breathing gas.

air while the patient breathes O_2 with a head tent (Fig. 91-6), face mask, or endotracheal tube. Because of immediate access to the patient by accompanying nursing personnel or physicians, monitoring and resuscitative procedures are straightforward. However, multiplace chambers take up a lot of space and are expensive.



Figure 91-7. Monoplace chamber. This type of chamber has room for one patient or a tender with a small child. The patient is moved into and out of the chamber on a wheeled gurney. The chamber atmosphere is usually 100% oxygen. The chamber is constructed of transparent Plexiglas to allow observation. Through-hull penetrators in the door on the left can be seen and allow monitoring, intravenous fluid administration, and control of a ventilator inside the chamber. *(Photograph courtesy Dr. Lindell Weaver).*

Monoplace chambers are large enough to accommodate only one patient (Fig. 91-7), or a tender with a small child. The chamber wall in most types is manufactured of Plexiglas, thus facilitating close visual observation of the patient. The chamber is usually compressed with 100% O_2. The advantage of monoplace chambers is their relatively low cost and ease of installation. Chamber operation can often be implemented by connecting the O_2 inlet to the hospital supply. Operation is relatively simple, but the patient inside is not directly accessible. Monitoring is more remote, and emergency airway management is not possible. Development of pneumothorax during treatment, particularly tension pneumothorax,

can be fatal because pleural decompression with a needle or chest tube cannot be performed before decompression; however, this complication is extremely rare. A minor disadvantage of these chambers is that the ambient pressure limit is 3 ATA, and for practical reasons (psychological aversion to confinement), treatment times are limited. Moreover, intermittent periods of air breathing, to decrease the risk of O_2 toxicity during some types of treatment schedules (see later), require installation of an additional gas delivery system. Nevertheless, monoplace technology now permits intravenous fluid administration from outside the chamber, invasive intravascular monitoring, mechanical ventilation, and utilization of pleural drainage systems incorporating regulated suction.[123,124]

HYPERBARIC TREATMENT SCHEDULES

Ideally, a patient who has therapeutic indication for HBOT would be exposed for an unlimited time until the condition resolves. Unfortunately, several factors limit the dose and duration of HBOT:

O_2 toxicity
Decompression obligation for nursing staff (or other tenders) accompanying the patient
Adequacy of monitoring
Patient isolation and boredom in a confined environment

Treatment schedules are compromises between O_2 partial pressure and exposure time on one hand and O_2 toxicity and the other practical limiting factors on the other. The original schedules (or "tables") were developed by the various navies of the world to treat DCS and gas embolism in divers (Fig. 91-8).

U.S. Navy Table 6 prescribes an initial exposure to 2.8 ATA (equivalent to 60 ft of sea water [fsw], or 18 m of sea water [msw]), followed by slow decompression to 1.9 ATA (30 fsw) (Box 91-2; see Fig. 91-8). Periods of O_2 breathing are interspersed with 5- or 15-minute periods of air breathing to decrease O_2 toxicity (see later). This schedule remains the mainstay of treatment for DCS in multiplace chambers throughout the world. Incomplete relief of signs or symptoms can be treated with repeated applications of the U.S. Navy Table 6 protocol or a shorter treatment once or twice daily.

"Saturation" treatment consists of an extended exposure to increased pressure (e.g., 2.8 ATA) for an unspecified period of time (often 1 to 2 days) until manifestations have stabilized. Periodic O_2 breathing is given according to a recommended schedule as tolerated. Because saturation treatment results in a much larger degree of nitrogen uptake in both the patient and the tender, decompression must occur much more slowly, usually over 24 to 36 hours.[125] Although this therapy avoids the theoretic disadvantage of intermittent treatment—failure of resolution of gas bubbles—it is also considerably more labor intensive. Because hyperbaric chambers used for saturation treatments require additional hardware (e.g., CO_2 scrubbing capability) and personnel, their application outside military and commercial diving has been limited.

A schedule used for treatment of patients with clostridial myonecrosis or other life-threatening anaerobic

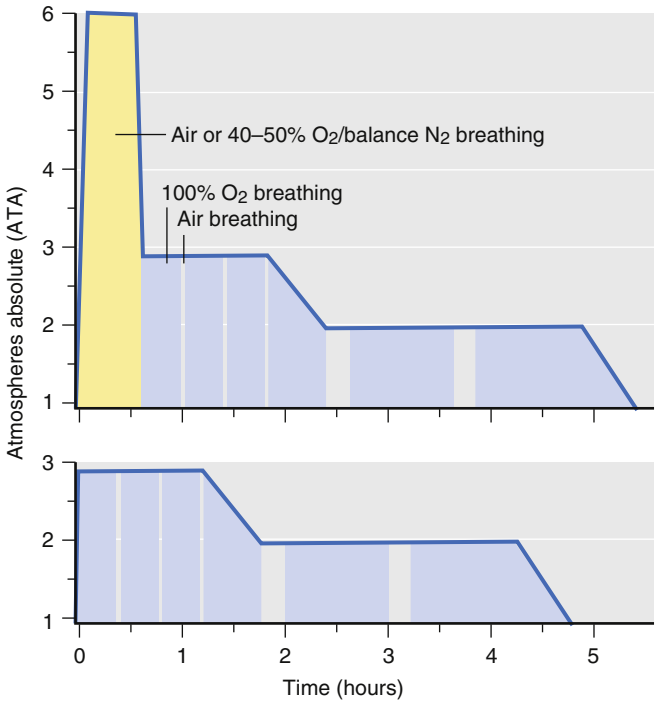


Figure 91-8. U.S. Navy treatment tables. **Top,** U.S. Navy Table 6a. This schedule is occasionally used for the treatment of arterial gas embolism. During the 30-minute period at 6 ATA, air or 40% to 50% oxygen (O_2) can be administered. **Bottom,** U.S. Navy Table 6. This table was originally designed for the treatment of decompression sickness, but it is now the most commonly used table for gas embolism as well. The *shaded areas* represent 100% O_2 breathing; the *white areas* represent air breathing periods (see Fig. 91-10). Further details can be found in the *U.S. Navy Diving Manual.* N_2, Nitrogen. *(From U.S. Navy Department:* U.S. Navy diving manual, *rev 6, vol 5: Diving medicine and recompression chamber operations, NAVSEA 0910-LP-106-0957, Washington, DC, 2008, Naval Sea Systems Command.)*

BOX 91-2 *Duke Modifications of the U.S. Navy Tables*

Standard air decompression
- Within 2 ft of standard Navy depth divisions, use the next greatest depth.
- Within 2 min of standard Navy time divisions, use the next greatest time.
- During decompression of the chamber after a compressed air dive, breathe 100% O_2 from an equivalent depth of 50 fsw (2.5 ATA) to the surface or for 15 min, whichever is shorter.
- Time for decompression
- 68-30 fsw (3.06-1.9 ATA): 3 min
- 30-20 fsw (1.9-1.6 ATA): 1 min
- 20-10 fsw (1.6-1.3 ATA): 1 min
- 10 fsw (or last stop) —"surface" (1.3-1.0 ATA): 5 min

Table 6 or 6A
- When U.S.N. Tables 6 and 6A are extended, the tender should breathe 100% O_2 for the last 30-90 min at 30 fsw (1.9 ATA) according to the number of extensions at 60 fsw (2.8 ATA): 30 minutes (no extensions), 60 minutes (1 extension), 90 minutes (2 extensions). 100% O_2 is breathed by the tender for the entire period of decompression from 30 fsw (1.9 ATA) to "surface" (1 ATA).

infections is shown in Figure 91-9. This schedule consists of 85 minutes at 3 ATA followed by a 33-minute decompression stop for the tenders at 1.3 ATA. This treatment schedule has been designed to maximize PaO_2 (and hence tissue bactericidal activity resulting from O_2) without an undue risk of hyperoxic seizures.

Treatment schedules for CO poisoning have varied. However, the proven efficacy of the schedule reported by Weaver (60 minutes at 3 ATA, 60 minutes at 2 ATA in addition to air breaks and compression-decompression time) supports the use of 3 ATA for at least the first treatment.[48]

Administration of HBOT to patients with chronic diseases (e.g., radionecrosis) is usually performed using shorter treatment tables at lower ambient pressure, most commonly 1 to 2 hours at 2.0 to 2.5 ATA (see Fig. 91-9) once or twice daily. At this lower ambient pressure, the risk of O_2 toxicity is minimal and treatments are well tolerated by most patients.

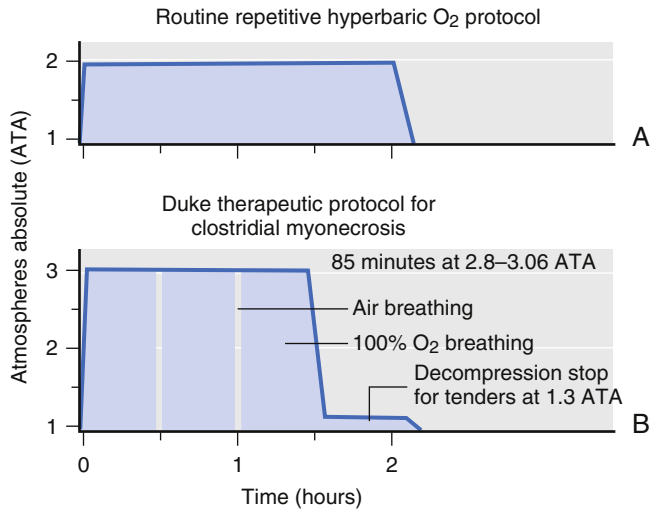


Figure 91-9. Examples of clinical hyperbaric oxygen (O_2) treatment schedules. **A,** The patient breathes 100% O_2 for 2 hours at an ambient pressure of 2 ATA. Generally, this schedule is used for repetitive treatment of chronic conditions (e.g., osteoradionecrosis). **B,** Therapeutic schedule often used for treatment of clostridial myonecrosis. The patient and tender spend 85 minutes at 2.8 to 3.06 ATA (3 ATA shown). The patient breathes 100% O_2, except during two 5-minute air breaks to reduce pulmonary and central nervous system O_2 toxicity. A decompression stop is made at 1.3 ATA, according to the U.S. Navy standard air decompression table. The stop is designed to facilitate safe decompression of the tender, who breathes air at 3 ATA.

SIDE EFFECTS OF HYPERBARIC THERAPY

OXYGEN TOXICITY

A wide body of evidence supports the notion that O_2 toxicity is caused by excessive production of oxygen free radicals (e.g., superoxide, hydroxyl radicals, and singlet oxygen). At high O_2 partial pressures, scavenging mechanisms can be overcome by increased rates of free radical production.[126] With the use of supplemental O_2 at 1 ATA, the manifestations of O_2 toxicity are almost exclusively confined to the lung; however, during hyperbaric O_2 exposure, other organs can be affected as well.

O_2 toxicity during HBOT can affect mainly the lung, the CNS, and the eye. Pulmonary toxicity in the conscious patient is heralded by symptoms of tracheobronchial irritation, namely, cough and burning chest pain. Prolonged exposure may result in a decrease in vital capacity and, if O_2 administration continues, ARDS. In the rare instances in which prolonged HBOT is indicated, the rate of development of pulmonary O_2 toxicity can be slowed by intermittent air-breathing periods ("air breaks") (Fig. 91-10).

O_2 toxicity is related to the PO_2 of the inspired gas. At 1 ATA, 100% O_2 is as toxic as 16.7% O_2 at 6 ATA or 2%

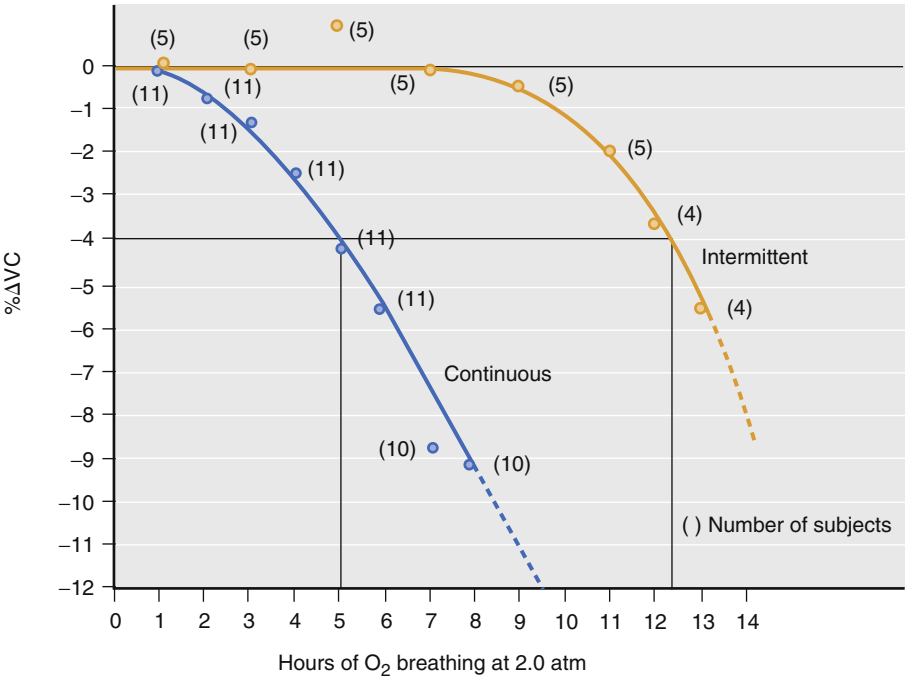


Figure 91-10. Decrease in vital capacity (VC) as a function of time breathing 100% oxygen (O_2) at 2 ATA in humans. The figure illustrates the value of intermittent O_2 (20 minutes O_2, 5 minutes air) versus continuous O_2 administration in the prevention of pulmonary O_2 toxicity. The numbers in parentheses represent the number of subjects tested. *(From Clark JM: Oxygen toxicity. In Bennett PB, Elliott DH, editors:* The physiology and medicine of diving, *Philadelphia, 1993, Saunders, pp 121-169.)*

O_2 at 50 ATA. One method of quantification of O_2 exposure is the unit pulmonary toxic dose, or UPTD.[127] In this system, the number of UPTD units is calculated by the following formula:

$$U = t \cdot \sqrt[m]{0.5/(P - 0.5)}$$

where U is the unit; t is the exposure time in minutes; P is the inspired PO_2 in ATA, and m is a slope constant that has an empiric value of 1.2. After 1425 UPTD units of O_2 exposure, an average 10% decrease in vital capacity occurs. After 2190 UPTD units, an associated decrease of 20% occurs. Complete reversal of vital capacity decrements as large as 40% of control has been observed after extended O_2 exposure at 2 ATA.[127]

Reanalysis of a larger data set than the one used for the UPTD model, which included those data, resulted in a different prediction equation:

$$\%\Delta VC = -0.009 \cdot (P - 0.38) \cdot t$$

where P and t are the same as for the previous equation.[128]

Using previously published data, Arieli and colleagues developed the following equation[129]:

$$\%\Delta VC = 0.0082 \cdot t^2 (PO_2/101.3)^{4.57}$$

where t is time in hours, and PO_2 is measured in kilopascals (kPa).

Although these algorithms may be useful as an approximate guide to safe O_2 exposures in populations, interindividual variability is such that they cannot be relied on to predict the development of pulmonary O_2 toxicity accurately for a specific patient.[130] Furthermore, O_2 toxicity can be modified by humidity,[131] circulating catecholamine and corticosteroid levels, leukocyte accumulation in the lungs (e.g., with pneumonia), and circulating endotoxin. A more useful guide to the development of pulmonary toxicity is the patient's symptoms, which include cough and inspiratory central burning chest pain. These symptoms do not occur during routine repetitive HBOT, but they may become evident during extensive O_2 periods at 2.8 ATA (e.g., when treating neurologic DCS). Asymptomatic persons usually have minimal or no change in vital capacity. Minor changes in forced expiratory volume in 1 second (FEV_1) reported during repetitive HBOT[132] are of uncertain clinical importance.

Some antineoplastic agents, such as bleomycin[133] and mitomycin C,[134,135] appear to predispose to fatal pulmonary O_2 toxicity (ARDS and respiratory failure) from what should otherwise have been well-tolerated doses of supplemental O_2. The risk of pulmonary O_2 toxicity from HBOT in patients with previous exposure to such agents is unknown, although we have treated several such individuals with a remote history of bleomycin treatment with repetitive doses of HBOT at 2 ATA for 2 hours (initially once daily, then increased to twice daily).[136] Occasional mild pulmonary O_2 toxicity symptoms such as retrosternal chest tightness did occur, but none of these patients experienced severe O_2 toxicity. Propensity to pulmonary O_2 toxicity engendered by these drugs appears to diminish a few weeks after their discontinuation.

CNS O_2 toxicity manifests as follows: nausea; vomiting; numbness; twitching; dizziness; olfactory, acoustic, or gustatory sensations; and, in its most severe form, nonfocal tonic-clonic seizures.[137,138] The probability of seizures increases with increasing PO_2 and time of exposure. In a study of 36 divers breathing 100% O_2 at 3.7 ATA, all experienced one or more of these symptoms within 100 minutes or less.[137,138] In clinical practice, convulsions in patients undergoing HBOT are rare at ambient PO_2 up to 2.5 ATA (typically 0.008% to 0.035% of treatments[139]), and the patients often have another predisposing factor (often hypoglycemia). The probability of a convulsion is also greater when O_2 is administered for acute indications such as CO poisoning.[140] Metabolic factors may reduce the seizure threshold, such as the administration of high-dose penicillin (e.g., for clostridial infection), sepsis, and hypoglycemia.

The treatment of hyperoxic seizures is immediate reduction of the inspired PO_2 until the seizure stops. Some physicians then routinely administer an anticonvulsant such as phenobarbital, phenytoin, or a benzodiazepine. It is generally recommended that the chamber should not be decompressed while the patient is actively convulsing because airway closure and failure to exhale during this period may cause pulmonary barotrauma. Hyperoxic seizures otherwise have no sequelae and rarely recur even if HBOT is continued. Thus, the occurrence of CNS O_2 toxicity should not preclude further HBOT. No evidence indicates that hyperoxic seizures are more common in patients with preexisting seizure disorders.

An acute effect of HBOT on the eye is narrowing of the visual fields,[141] which is generally observed only at a PO_2 of 3 ATA or greater and thus rarely, if ever, during routine HBOTs. A subacute or chronic ocular effect is a change in the refractive index of the lens that results in myopia.[142,143] Such refractive index change occurs during the course of intermittent HBOT over several weeks and usually resolves in a similar period of time. However, some patients may be left with residual myopia, particularly older patients.[144]

The risk of retrolental fibroplasia in the unborn child of a woman who may require acute HBOT during pregnancy could be a concern. Although many pregnant women have been treated with single exposures to HBOT (e.g., for CO poisoning), we are not aware of any subsequent occurrence of retrolental fibroplasia in the child. Pregnancy is not a contraindication to HBOT for appropriate acute indications (e.g., CO poisoning[60,62,64,145,146]) because the risk to the fetus of the underlying condition exceeds that of the treatment.

INERT GAS UPTAKE

Breathing air at high ambient pressure can result in nitrogen narcosis, a dose-dependent decrement in cerebral performance secondary to the anesthetic properties of nitrogen. This mostly occurs at ambient pressures exceeding 4 ATA, a treatment pressure that is used only for severe AGE or DCS. Nitrogen uptake can also theoretically result in DCS during or after decompression (see earlier). However, chamber decompression schedules are so conservative that this rarely occurs (most hyperbaric

TABLE 91-5 **RESTING BLOOD GAS AND HEART RATE VALUES IN NORMAL VOLUNTEERS EXPOSED TO VARIOUS ALTITUDES IN A HYPOBARIC CHAMBER OR ON MOUNT EVEREST (MEAN ± SD)**

Altitude (ft)	Pbar (mm Hg)	PaO_2 (mm Hg)	Sao_2 (%)	$Paco_2$ (mm Hg)	pH	HR (beats/min)	Ventilation (L/min)	Source
0	750	99±9	99±1	34±4	7.43±.03	78±15	11.0±3.0	*
5,000	632	78±8	94±4	33±3	7.42±.04	92±16	12.3±2.1	*
10,000	523	57±6	89±4	33±4	7.42±.03	95±13	11.4±2.5	*
15,000	429	41±7	78±8	29±4	7.47±.03	104±16	13.4±3.0	*
20,000	347	41±2	76±2	20±1	7.50±.02	85±14	20.9±6.3	†
25,000	282	37±1	68±2	13±1	7.53±.01	94±15	36.6±7.9	†
27,559	272	25±5	54±18	13±2	7.53±.06			‡
29,000	240	30±1	58±1	11±1	7.57±.02	101±14	42.3±7.7	†

$Paco_2$, Arterial partial pressure of carbon dioxide; *PaO_2*, arterial partial pressure of oxygen; *Sao_2*, arterial oxygen saturation.
*Duke University, hypobaric chamber, unacclimatized.[180,358]
†Operation Everest II: hypobaric chamber, acclimatized.[189]
‡Mt Everest field study, acclimatized.[359]

facilities use U.S. Navy compressed air decompression tables[147]). Additional safety can be provided by requiring the patient to breathe 100% O_2 for a period immediately before and during decompression (Table 91-5). Rare episodes of DCS in hyperbaric tenders are usually minor, generally consisting of mild joint pain. Nitrogen narcosis and DCS could occur only in tenders in a multiplace hyperbaric chamber; patients breathe 100% O_2 and are therefore not susceptible.

BAROTRAUMA

As the ambient pressure is altered, the pressure within gas-containing spaces in the body must equilibrate with the ambient pressure or undergo a change in volume. Volume change can easily occur in compliant compartments such as the gastrointestinal tract, but if the free flow of gas into and out of containing spaces surrounded by a rigid shell (e.g., the lung, paranasal sinuses, and middle ear) is impeded, then tissue disruption and hemorrhage can occur. Indeed, the most common side effect of hyperbaric chamber use for patients is difficulty with middle ear pressure equilibration.[148] In awake patients, equilibration may be accomplished using several techniques, such as performing intermittent Valsalva maneuvers, swallowing while the nose is pinched, thrusting the jaw forward, or simply swallowing intermittently during compression. Patients with prior irradiation of the head and neck and acute respiratory tract infections are at particular risk. Equilibration may be facilitated by application of a topical nasal vasoconstrictor (e.g., oxymetazoline 0.05%, [Afrin]). For patients who cannot equalize despite these measures or for obtunded or tracheally intubated patients, myringotomy or tympanostomy tubes may be required. Theoretically, HBOT hyperbaric exposure in a patient with obstructed eustachian tubes could cause labyrinthine window rupture, but this complication has not been reported during HBOT.

Pulmonary barotrauma is most likely during decompression. Areas of regional hypoventilation could lead to pulmonary overpressurization and alveolar rupture, causing pneumothorax, pneumomediastinum, or AGE.[149,150] Pulmonary barotrauma during HBOT is extremely rare, probably because of the slow decompression rates typically used.

Although pneumothorax should diminish in size and resorb more quickly after compression, continuing leakage of air from the lung could result in tension pneumothorax during decompression.[149] Pneumothorax detected before HBOT is usually treated by insertion of a chest tube and water seal or Heimlich-type valve (in this instance, before monoplace chamber treatment, a chest tube should *always* be inserted) (see Chapters 66 and 81). Caution must be exercised when using certain commercially available pleural suction regulators, which can exert high negative pleural pressures during chamber compression.[151] Such excessive suction can be relieved by an attendant inside a multiplace chamber by activating the manual pressure relief valve on the chest drainage unit.

Despite these potential adverse effects of HBOT, major complications are extremely rare.[148]

PRACTICAL ASPECTS OF HYPERBARIC THERAPY

PATIENT MONITORING

Despite the changes in the acoustic properties of compressed air, blood pressure measurement may be performed without difficulty with a standard sphygmomanometer and stethoscope (see also Chapter 44). Aneroid pressure gauges are preferred to mercury to avoid contamination of the closed environment. Monitoring of the electrocardiogram and of intravascular pressures requires that transducer cables be plumbed through the chamber wall to preamplifiers outside the chamber. Standard intensive care monitors can be used to provide simultaneous measurement of arterial and pulmonary artery pressures and intermittent measurement of cardiac output by thermodilution. If pressure bags are used to drive continuous flow systems, they must be repressurized during compression and vented before or during decompression. Pulmonary artery catheter balloon ports should also be left open to the chamber during compression and decompression.

Defibrillation could generate a fire if sparking occurs or combustible materials are present in the vicinity of the paddles (see also Chapter 109). Sparking and heat

generation can be minimized by using a low-resistivity conductive gel between the electrodes and the skin[152] or preapplied conductive disposable pads.[153] To avoid pressure-related malfunction of the device, the defibrillator can remain outside the chamber and connected to the patient by through-hull high-voltage wiring. Despite the fear of causing fire, defibrillation has been performed in multiplace chambers numerous times without arcing, fire, or explosion.[154,155] Defibrillation cannot be safely performed inside a monoplace chamber compressed with O_2.

INTRAVENOUS FLUID ADMINISTRATION

In multiplace chambers, the air volume within the drip chamber shrinks during the compression phase of the HBOT and expands during decompression (which could force air into the intravenous line) (see also Chapter 59). Most intravenous infusion pumps work well inside a hyperbaric chamber at pressure (although electrical safety issues exist; see later). Glass bottles are best excluded from the chamber because of the possibility of explosive rupture during decompression.

Administration of fluids to patients inside a pressurized monoplace chamber requires an infusion pump capable of withstanding the pressure differential (up to 3 ATA or 1500 mm Hg pressure gradient across the chamber wall). Check valves can prevent unintended backflow of blood from the patient in the event of disconnection of the pump. Rigid arterial pressure transducer tubing helps to prevent kinking while the patient is inside the chamber.

ANALYSIS OF ARTERIAL BLOOD GASES AND VENTILATOR MANAGEMENT

Analysis of arterial blood gases from a patient inside a hyperbaric chamber can be erroneous (see also Chapters 63 and 103), for two reasons. At 1 ATA, O_2 tensions that exceed the ambient pressure are supersaturated; O_2 rapidly diffuses out of the blood, thus lowering its tension. An additional error (extrapolation error) results from the impossibility of accurate PO_2 electrode calibration at PO_2 values exceeding approximately 700 mm Hg. Blood gas tension measurement should therefore ideally be performed inside the hyperbaric chamber by using an appropriately calibrated analyzer. If such a capability is not available, rapid analysis at 1 ATA of decompressed samples can produce acceptably accurate values.[156]

Another approach is to estimate the hyperbaric PaO_2 based on measurements obtained at 1 ATA. Using a measured PaO_2 and PAO_2, the ratio of the two (PaO_2/PAO_2, or a/A ratio) is a constant.[9,157] On this basis, 1 ATA arterial blood gas values and the following equations can be used to predict PaO_2 at pressure.

The alveolar gas equation is required to calculate P_AO_2:

$$PAO_2 = (Pb - P_{H_2O}) \cdot FiO_2 - Paco_2 \cdot \left(FiO_2 + \frac{1 - FiO_2}{R}\right)$$

where Pb and P_{H_2O} are, respectively, ambient and saturated water vapor pressures, and R is the respiratory exchange ratio. If $FiO_2 = 0.2$, $R = 0.8$, and body temperature = 37 °C, then this equation can be simplified to

$$PAO_2 = (Pb - 47) \cdot 0.2 - 1.2 \cdot P_{CO_2}$$

Having calculated PAO_2 and measured PaO_2, the a/A ratio can then be obtained at 1 ATA. The predicted PaO_2 at increased ambient pressure while breathing 100% O_2 may then be obtained from this next equation:

$$PaO_{2(pred)} = a/A \cdot [(760 \cdot ATA - 47) - Paco_2]$$

where ATA is the chamber pressure in atmospheres absolute. Although as yet no dose-response curves for HBOT are available, a reasonable aim is to achieve PaO_2 greater than or equal to 1000 mm Hg for routine long-term therapy and to as high a level as possible for treatment of acute necrotizing infections (Fig. 91-11).

A better monitor of tissue oxygenation may be mixed venous PO_2 ($P\bar{v}O_2$), which, in the absence of left-to-right shunt, may be a reasonably accurate estimate of mean tissue PO_2.[158] Thus, a low value may indicate inadequate tissue oxygenation despite HBOT, as a result of insufficiently high cardiac output.

Normal values for pH and P_{CO_2} under resting clinical hyperbaric conditions are the same as they are at 1 ATA.[14] P_{CO_2} and hence pH do not change significantly in blood samples that are decompressed.

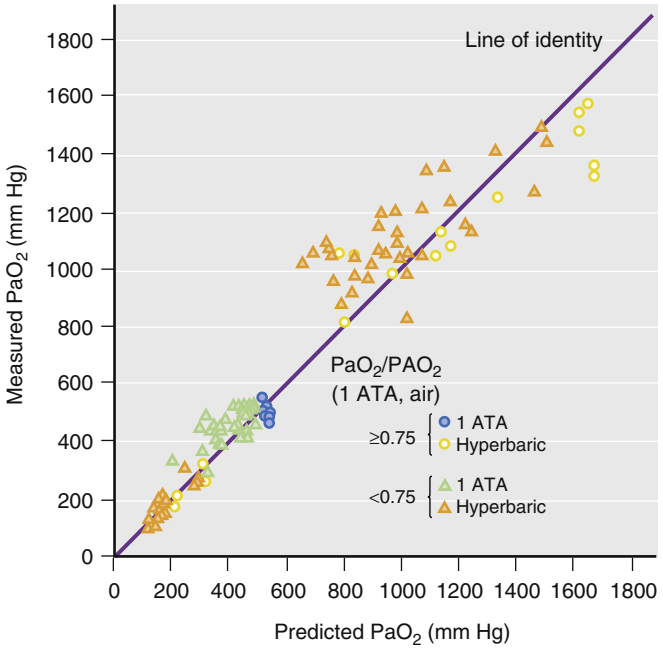


Figure 91-11. Measured versus predicted partial arterial pressure of oxygen (PaO_2) at increased ambient pressure. Predicted PaO_2 is calculated from room air arterial blood gases, assuming that the arterial-alveolar PO_2 ratio (PaO_2/PAO_2, or a/A ratio) is a constant. Data are shown both for persons with normal lungs (a/A ratio ≥ 0.75) and for patients with gas exchange abnormalities (a/A ratio < 0.75). It is evident that PaO_2 predicted in this way is close to the actual measured PaO_2. *(From Moon RE, Camporesi EM, Shelton DL: Prediction of arterial PO^2 during hyperbaric treatment. In Bove AA, Bachrach AJ, Greenbaum LJ Jr, editors:* Underwater and hyperbaric physiology IX. Proceedings of the ninth international symposium on underwater and hyperbaric physiology, *Bethesda, Md, 1987, Undersea and Hyperbaric Medical Society, p 1127.)*

Mechanical ventilation in a hyperbaric environment presents a variety of challenges (see also Chapter 103). The ideal requirements for ventilation include small size, no electrical requirement, absence of flammable lubricants, ability to operate on a volume-cycled basis over a wide range of tidal volumes and respiratory rates, minimal modification requirement for installation, and ability to provide positive end-expiratory pressure, as well as to ventilate in intermittent mandatory ventilation and assist/control modes.[159] Additionally, the ideal gas source to actuate the ventilator should minimize the risk of combustion caused by buildup of static electricity.

As ambient pressure increases, gas density is proportionately increased, whereas relatively little change occurs in gas viscosity. Therefore, in regions of turbulent flow (i.e., in the large airways) airway resistance increases. Measurements of respiratory conductance (the reciprocal of resistance) during tidal breathing[160] indicate that it varies with gas density according to the following formula:

$$G = G_0 \rho^k$$

where G is lung conductance at gas density ϱ, G_0 is the conductance at gas density 1.1 g/L (1 ATA), and κ is a constant that was found to have a mean value of –0.39. At 6 ATA, this equation predicts that lung conductance would decrease by 50%, which is equivalent to a doubling of pulmonary resistance. In addition, the higher gas density results in a less efficient distribution of ventilation, manifested by an increase in physiologic dead space.[161] The effects of these two phenomena include higher airway pressures during mechanical ventilation and an increased ventilatory requirement. If ventilator settings are not adjusted to compensate for the higher dead space, a rise in $Paco_2$ will occur.

Several types of ventilators have been used and tested in hyperbaric chambers (see also Chapter 103). Pressure-cycled devices have been used with some success because their compactness admirably fulfills the requirement for small size. However, continual adjustment of rate and cycling pressure is necessary with changes in ambient pressure. Volume-cycled ventilators seem to work well,[159,162] although at increased pressure some changes in rate may occur.

Two specific safety considerations exist. First, in any ventilator delivering enriched O_2, a possible fire hazard can result from O_2 buildup within the ventilator case or leakage of O_2 into the chamber. This hazard can often be offset by minor alterations (e.g., for a pneumatic ventilator, using air instead of O_2 to drive the bellows).[159] The risk of ignition can be substantially mitigated by purging the device with an inert gas such as 100% nitrogen (see later). Air-filled endotracheal tube cuffs tend to lose volume during compression and reexpand during decompression. Appropriate cuff inflation volume can be maintained either by manually adjusting the air pressure within the cuff during compression and decompression or by filling the cuff with water.

ATMOSPHERE CONTROL

Chamber atmosphere safety includes management of levels of O_2, CO_2, and trace gases. In a multiplace chamber, the patient must breathe as high a concentration of O_2 as possible (usually 98% or greater) while maintaining the chamber O_2 concentration close to 21% to minimize fire hazard. In some hyperbaric units, head tent O_2 concentration is routinely monitored. In others, the concentration is assumed to be high because of a high rate of O_2 flow through the head tent. Leakage of O_2 from head tents, masks, and ventilators tends to raise the chamber O_2 concentration. Typically an upper limit of approximately 23% is used as a criterion for ventilating the chamber with air or small volumes of 100% nitrogen until the O_2 concentration decreases.

Significant increases of inspired CO_2 concentration increase the risk of CNS O_2 toxicity. Therefore, a typical standard for the upper limit for head tent CO_2 is 1% "surface equivalent" CO_2, equal to a partial pressure of 7.6 mm Hg. Using a nonscrubbing (open-circuit) system, head tent O_2 flow rates of 40 to 60 L/minute (measured at chamber pressure) are usually adequate to keep CO_2 levels at such a level. Chamber CO_2 is usually limited to less than 0.5% "surface equivalent" (3.8 mm Hg).

Trace gases that may enter the environment include CO and hydrocarbons from improperly functioning compressors or from automobile exhaust that may be near the compressor air intake. Volatile gases such as alcohol vapor from skin disinfectant solutions and mercury vapor from spillage of sphygmomanometer columns may also pollute the atmosphere. Trace gas concentrations that are innocuous at atmospheric pressure can be toxic under hyperbaric conditions because their pharmacologic or toxic effects are related to partial pressure. Mercury in any form should be excluded from hyperbaric chambers because spillage can cause acute toxicity in chamber occupants.

Considerations of battery use may have implications for chamber atmosphere control, as well as fire hazards. All batteries release small quantities of hydrogen, although not usually in amounts that would be hazardous. Lithium–sulfur dioxide batteries carry a theoretic risk of sulfur dioxide discharge. Similarly, an objection exists to the use of mercury cells (now banned in the United States). Alkaline cells are considered safe, although temporary failure has been observed at extremely high ambient pressures (40 to 60 ATA).

FIRE HAZARDS

Although fires in hyperbaric chambers are rare, they are usually lethal. The effects of fire at elevated ambient pressure are so devastating, and the fire occurs so fast, that fire extinguisher systems may not be effective (see Chapter 88). The very real risk of fire in hyperbaric chambers has been illustrated by accidents in which chamber fires were started by a hand warmer, a sparking toy, and other sources of ignition carried into the chamber in the patient's clothing. Minimization of these risks involves the following:

Control of chamber O_2 concentrations (irrelevant in a monoplace chamber)
Minimizing the use of combustible materials within the chamber
Controlling sources of heat and spark
Having a chamber fire extinguisher system

The geometric increase in burning rate with increases in O_2 concentrations mandates careful monitoring of chamber O_2, as already noted. At increased ambient pressure, burning occurs more rapidly, even when O_2 concentration is 21%. Cotton garments are recommended because of their reduced risk of static electricity. Elimination of hair grease and humidification of the O_2 within the head tent can reduce the risk of hair ignition. Hydrocarbon lubricants (e.g., for stretcher wheels) can spontaneously ignite on contact with aluminum in the presence of high O_2 tensions and should therefore be replaced with nonflammable fluorocarbon lubricants.

Sources of sparks from electrically powered equipment should be minimized. Cigarette lighters, matches, and other sources of ignition should be excluded from the chamber. Plugging and unplugging electrical cables during hyperbaric treatments comprise a source of sparking that can be eliminated by taping all electrical plugs onto receptacles before compression. In multiplace chambers, the flammability of electrically powered devices (e.g., intravenous controllers) can be reduced by purging with 100% nitrogen through ports drilled in the covering, at a rate sufficient to keep O_2 concentration at a level that does not support combustion (typically at a flow rate of two to three times the internal volume per minute). Electrical systems used in monoplace chambers must comply with specific codes, which specify the types of switches, grounding, and insulation that can be used.[123]

Volatile anesthetics can be combustible at 1 ATA in high concentrations. However, isoflurane and sevoflurane Dräger vaporizers (Drägerwerk AG, Lubeck, Germany) have been tested up to 3 ATA using 100% O_2, with no evidence of spontaneous combustion at room temperature. Given the experience with halothane under hyperbaric conditions, without any reported fires, and the resistance to combustion in 100% O_2 at 1 ATA, in the absence of a source of ignition it is unlikely that any of the modern fluorinated anesthetics pose a fire safety hazard in the hyperbaric environment.

EVALUATION OF A PATIENT FOR SAFETY OF HYPERBARIC OXYGEN TREATMENT

In addition to ensuring that HBOT is indicated for the disease process in question, it is important to assess the patient in terms of general effectiveness and safety of HBOT. The following issues are pertinent:

Whether a sufficient elevation in PaO_2 can be obtained
Whether the patient can equilibrate middle ear pressure
Optimization of reversible obstructive lung disease and the presence of pulmonary bullae or blebs
Whether the patient is susceptible to claustrophobia

The calculation of predicted PaO_2 in the hyperbaric chamber was described previously. For example, a patient who has sufficient lung disease or injury that PaO_2 during treatment would not exceed 1000 mm Hg would probably obtain marginal benefit from HBOT unless the reason for HBOT is gas bubble disease.

The ability to vent the middle ears may be assessed before treatment by observing the tympanic membrane directly with an otoscope while the patient holds his or her nose or performs a Valsalva maneuver. Movement of the eardrums indicates a patent eustachian tube and the ability to equilibrate middle ear pressure. If otic barotrauma is unlikely to be avoided (e.g., with mental obtundation or the presence of an endotracheal tube) or because of a condition that may render the patient susceptible to inner ear injury (e.g., stapedectomy), myringotomy or tube placement can be performed before HBOT. The presence of pulmonary bullae or blebs represents a relative contraindication to HBOT because of the possibility of barotrauma, although a large clinical experience suggests that the risk is extremely low.

For patients requiring more than 20 to 30 HBOT sessions, periodic checks of visual acuity may be useful to assess hyperbaric myopia.

Because most hyperbaric chamber systems are small and cramped, patients who cannot tolerate enclosed spaces may require anxiolytic therapy to facilitate toleration of the HBOT.

DELIVERY OF ANESTHESIA AT INCREASED AMBIENT PRESSURE

A review of the problems of anesthesia under HBOT was published as a report to a committee of the American Society of Anesthesiologists.[163] This report explored various issues, including the potential for nitrous oxide to be used as a sole anesthetic.

Anesthesia while breathing spontaneously in a 100% O_2 atmosphere at 3 ATA was reported in the 1950s for radiation therapy.[164] The tracheas of patients were intubated after administration of pentobarbital 250 to 750 mg and meperidine 100 mg; some patients also received chlorpromazine 50 mg. Intubation of the trachea was performed after succinylcholine and topical anesthesia of the airway. Patients breathed spontaneously.

Anesthesia may be required as a procedure incidental to the hyperbaric exposure. Ross and associates discussed the challenges of anesthesia up to 35 ATA, to provide care for injured divers while in a saturation diving system (e.g., in North Sea oil fields).[165] These investigators suggested intravenous instead of inhaled general anesthesia because of the problems of pollution of the chamber environment. Regional anesthesia was recommended whenever possible. Neuromuscular blocking drugs should be titrated to effect because some degree of pressure reversal of the block can occur at approximately 10 ATA.

Since the 1960s, anesthesia has been performed at increased ambient pressure using a variety of drugs for carotid endarterectomy,[166] cesarean section,[167] therapeutic lung lavage for patients with alveolar proteinosis,[104,105] emergency surgery in a saturation dive,[168] open heart surgery,[169] and enhancement of the effectiveness of irradiation of carcinoma.[170]

Inhaled Anesthesia

Inhaled anesthesia of any type can pollute the enclosed chamber atmosphere with anesthetic gases, which may exert pharmacologic effects on medical personnel inside the chamber, particularly at high ambient pressures. Russell and colleagues reported nitrous oxide concentrations in chamber air of 2500 ppm; ventilation of the chamber

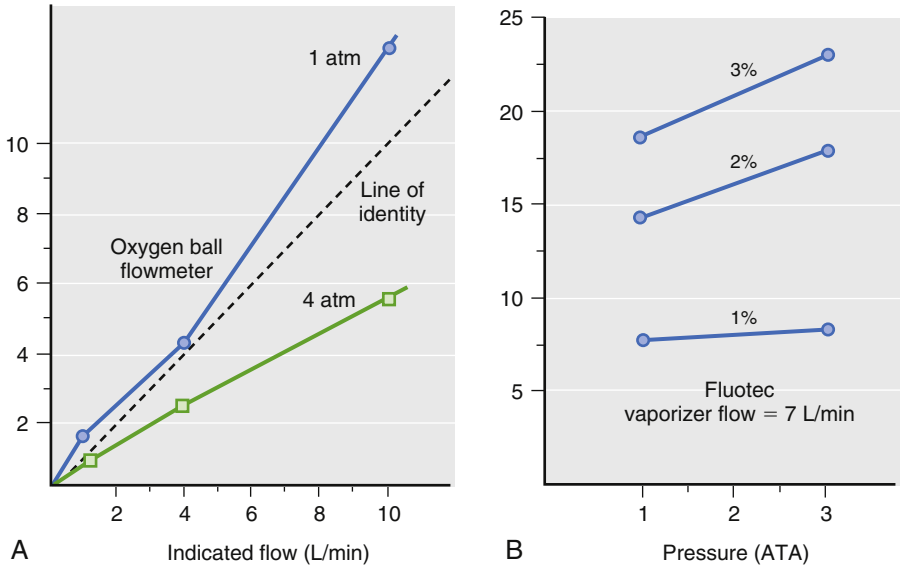


Figure 91-12. Performance of an anesthetic vaporizer system at increased ambient pressure. **A,** Flow characteristics of a rotameter system are shown. At 4 ATA, the actual delivered flow is less than 60% of the flow indicated by the rotameter. **B,** Fluotec vaporizer output in partial pressure of halothane as a function of ambient pressure. Only small increases in delivered partial pressure are evident at 3 ATA, at the 2% and 3% settings. *(From Committee on Hyperbaric Oxygenation:* Fundamentals of hyperbaric medicine, *publication no. 1298, Washington, DC, 1966, National Academy Press.)*

with air at a high rate (3500 L/minute of air) was required to reduce the concentration to 25 to 75 ppm.[171]

Nitrous Oxide. The increased ambient pressure in a hyperbaric chamber allows nitrous oxide to be used at partial pressures exceeding its MAC.[171-173] Although in both studies induction of anesthesia by nitrous oxide was rapid (<60 seconds), it was accompanied by tachypnea, tachycardia, hypertension, diaphoresis, muscle rigidity, catatonic jerking of the extremities, eye opening, and opisthotonus. After 2 to 4 hours of anesthesia, most subjects emerged rapidly from the anesthetic; however, the majority subsequently experienced nausea and vomiting, which was often severe (see also Chapter 97).

A potential problem associated with nitrous oxide anesthesia at high ambient pressures is the possibility that tissues could become supersaturated during decompression, thus allowing nitrous oxide bubbles to form during decompression. This complication was not observed by Russell and colleagues,[171] who used an empiric staged decompression schedule with a decompression stop for 30 minutes at 1.3 ATA while patients breathed 100% O_2. Bubble formation can occur without decompression if the patient breathes one gas while surrounded by an atmosphere of another gas that is more diffusible. For example, breathing air while in a helium-O_2 environment at 5 to 7 ATA can lead to urticaria and vestibular dysfunction.[174] The reason is rapid diffusion of helium into tissues that causes local inert gas pressure to exceed ambient pressure (isobaric gas counterdiffusion). This phenomenon can occur even at normal atmospheric pressure if a person breathes nitrous oxide–O_2 while surrounded by helium.[175] Therefore, nitrous oxide should never be administered in a helium-O_2 atmosphere.

Another risk of hyperbaric nitrous oxide is the dilutional effect of large volumes of dissolved gas entering the lungs during decompression, causing dilutional hypoxia. This situation can be prevented by administration of an O_2-enriched breathing mix for several minutes before decompression.

In patients who have recently engaged in scuba diving or have suffered DCS, nitrous oxide should be avoided, even at 1 ATA, because its administration may result in tissue or blood bubble growth and recrudescence of pain or neurologic symptoms. Neurologic symptoms can occur after nitrous oxide anesthesia and apparent spontaneous resolution of DCS.[176]

Halogenated Anesthetics. The effect of a volatile anesthetic agent on a patient is proportional not to the alveolar concentration but to the partial pressure of the anesthetic. For example, the effect of 1% halothane at 1 ATA (with a partial pressure of 7.6 mm Hg) is equivalent to a 0.5% concentration at 2 ATA (with the same partial pressure). The anesthetic concentration of an anesthetic-specific calibrated vaporizer varies with ambient pressure, but in a manner such that delivered partial pressure remains constant (Fig. 91-12). Because of the effect of increased gas density on this flow ratio, in practice the delivered partial pressure depends somewhat on ambient pressure. A slightly increased partial pressure of halothane delivered by a Fluotec vaporizer at 3 ATA has been observed (see Fig. 91-12).[163] Our testing of a sevoflurane vaporizer revealed delivery of a constant partial pressure of anesthetic up to the maximum tested ambient pressure: 3 ATA.

Rotameter flowmeters calibrated at 1 ATA will indicate falsely high values at increased ambient pressure because of the increased gas density. McDowell reported the following relationship for rotameter flow[177]:

$$\text{Flow}_{\text{actual}} = \text{Flow}_{\text{read}} \cdot \sqrt{\frac{\rho_1}{\rho_p}}$$

where $\text{Flow}_{\text{actual}}$ and $\text{Flow}_{\text{read}}$ are the actual and scale reading flows, and ϱ_1 and ϱ_P are the gas densities at 1 ATA and P ATA, respectively. This inaccuracy in rotameter performance up to 4 ATA has been confirmed by other investigators (see Fig. 91-12).[163]

Intravenous Anesthesia

Intravenous anesthetics behave similarly and are unlikely to be affected within the usual clinical range of ambient

pressure (see Chapter 30). No alteration in the pharmacokinetics of either meperidine[31] or pentobarbital[32] is evident at ambient pressures up to 6 ATA. For therapeutic lung lavage, we have provided general anesthesia at ambient pressures up to 3 ATA by using conventional doses of ketamine and benzodiazepines or propofol and narcotics with nondepolarizing muscle relaxants.

Regional Anesthesia

Regional anesthesia is likely to be both safe and effective in a hyperbaric environment by avoiding the requirement for mechanical ventilation (see Chapters 56 and 57). A bowel resection was performed at an ambient pressure 6.75 ATA in a helium-O_2 environment by using local injection of lidocaine supplemented with parenteral meperidine.[168] Extreme care should be taken to ensure sterile technique because of the propensity for enhanced bacterial growth in the warm, humidified environment of a hyperbaric chamber, particularly during saturation chamber exposures.

EFFECTS OF ALTITUDE

Approximately 140 million people worldwide live permanently at altitudes greater than 2500 m,[178] and possibly equal numbers of people visit high altitudes each year, many of whom will require medical care. Therefore, a need clearly exists for anesthesia and critical care practitioners to understand the physiology of this environment.

Unlike the relationship between ambient pressure and water depth, the relationship between pressure and altitude is nonlinear (see Fig. 91-2). The physiologic effects of altitude exposure are mainly attributable to reduction in the following three variables: inspired PO_2, ambient pressure, and gas density. Extreme or prolonged altitude exposure may be accompanied by additional factors, which may modulate physiologic responses, such as hypothermia, exertion, dehydration, sunburn, and polycythemia. Pregnant women and individuals with hypoxic conditions such as cerebrovascular disease, congenital heart defects, coronary artery disease, and hypoxic lung disease may carry additional risks that require medical evaluation.[179]

HYPOXIA

Physiologic Changes

The major reason for hypoxemia at high altitude is the reduction in inspired PO_2, augmented by the failure of erythrocytes in the pulmonary circulation to equilibrate fully with alveolar gas (diffusion nonequilibrium)[180] and increased ventilation-perfusion $\dot{V}_A/\dot{Q}$ mismatch.[181]

The acute blood gas and heart rate responses to acute hypoxia are shown in Tables 91-3 and 91-5. Heart rate and cardiac output are increased.[182] Systemic vascular resistance is decreased, and pulmonary vascular pressure is increased.[183] A corresponding increase occurs in organ blood flow, including cerebral blood flow. Hypoxia also induces hyperpnea (from increased breathing rate) to a degree that varies considerably among individuals.

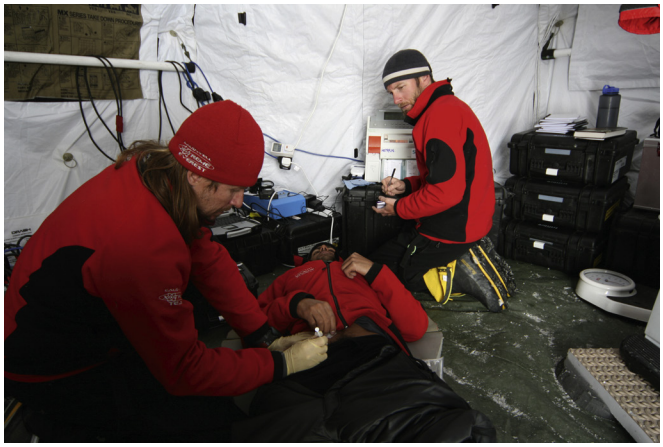


Figure 91-13. Obtaining blood gas sample from the femoral artery at 6400 m (barometric pressure 350 mm Hg) during the Caudwell Xtreme Everest field expedition. Measured values have been reported by Grocott.[359] *(Photograph courtesy Caudwell Xtreme Everest.)*

End-tidal P_{CO_2} measured in one subject breathing air at the summit of Mt. Everest (barometric pressure 263 mm Hg) was 7.5 mm Hg, whereas PAO_2 was 37.6 mm Hg.[184] Arterial blood was obtained near the summit in a later expedition (Fig. 91-13). This hypocapnia has several effects. It results in an increased affinity of Hb for O_2 (leftward shift of the Hb-O_2 dissociation curve), which enhances oxygenation of blood at the lung while simultaneously interfering with transport of O_2 from tissue capillary to mitochondrion. The overall effect on O_2 transport is beneficial.[185]

Hypoxemia may be particularly accentuated during sleep. Figure 91-14 depicts continuous pulse oximetry during transition from sleep to wakefulness at a simulated altitude of 4572 m in a hypobaric chamber, thus demonstrating periodic breathing and cyclic oscillation of saturation of peripheral oxygen (SpO_2). Individuals with moderate obstructive sleep apnea at 1 ATA are at risk of severe central sleep apnea at high altitude.[186]

Acute exposure to altitudes in the range of 4000 to 5000 m causes a decrease in arterial PaO_2 to approximately 40 mm Hg and in arterial Hb-O_2 saturation to approximately 75%. Acute exposure to mild hypoxia appears to have only minor effects on CNS function. Crow and Kelman found no decrement on free recall and visual scanning when normal subjects were exposed to a simulated altitude of 3658 m (inspired PO_2 92 mm Hg).[187] Severe hypoxia can cause encephalopathy and loss of consciousness. A measure of this phenomenon is the effective performance time (EPT), defined as the amount of time the individual is able to perform useful flying duties.[188] At 5500 m altitude, the EPT is 20 to 30 minutes, which is reduced to 2.5 to 3 minutes at 8500 m and to 1 to 2 minutes at 9100 m.

Gradual exposure to high altitude or long-term exposure results in a series of adaptive changes that allow individuals to function extremely well and do substantial physical work at altitudes at which newcomers can barely function. For instance, Mt. Everest has been climbed by adapted individuals without the benefit of supplemental O_2, whereas acute exposure to such an altitude would result in rapid loss of consciousness. Subjects exposed to a progressively lower barometric pressure, reaching

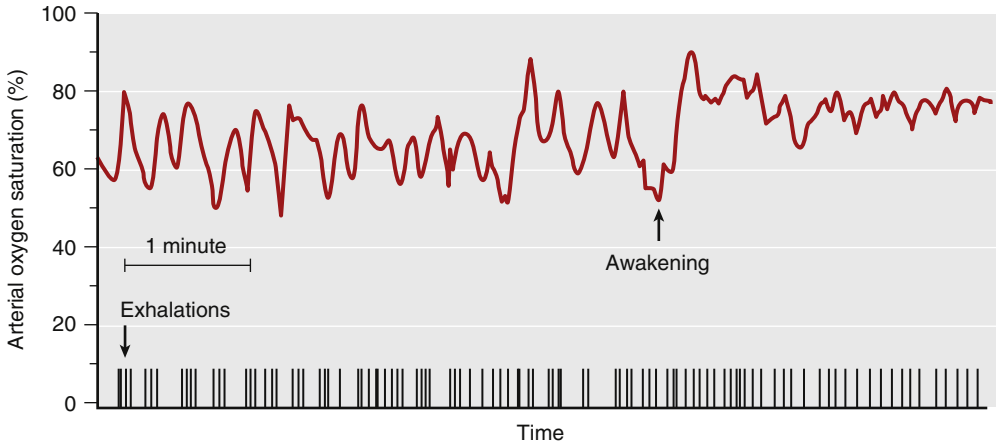


Figure 91-14. Pulse oximetry and breathing pattern (spikes at bottom represent exhalations) are shown in this subject in a hypobaric chamber at a simulated altitude of 4572 m. During sleep, periodic breathing and oscillatory alterations in saturation of peripheral oxygen (SpO_2) change after waking up to a more regular breathing pattern and a steady SpO_2.

to simulated altitude of 8848 m in a hypobaric chamber over the course of 40 days, were able to work on an exercise ergometer at 120 W while their mean PaO_2 was only 30 mm Hg (arterial Hb-O_2 saturation 58%).[189] In the same study, blood Hb concentration increased from 13.5 to 17.0 g/dL (hematocrit increased from 40.4% to 51.9%). The development of polycythemia may be one of many mechanisms by which tolerance to hypoxia occurs. However, the mechanisms of adaptation are still incompletely understood.

One of the adaptive mechanisms is a gradual reduction in plasma bicarbonate,[189] preceded by a decrease in cerebrospinal fluid (CSF) bicarbonate,[190] which tends to offset the initial respiratory alkalosis. After a 40-day simulated "climb" of Mt. Everest in a hypobaric chamber, resting serum bicarbonate had decreased from 22.2 to 9.9 mM; pH had increased from 7.43 to 7.56.[189] Other adaptive changes include increases in hematocrit and capillary density, as well as undoubtedly other mechanisms as yet undiscovered.

Despite the adaptive mechanisms, careful neuropsychological testing of subjects before and after mountaineering expeditions to extreme altitudes of 7000 m or greater have shown evidence of mild persistent performance impairment.[191,192] Such neuropsychological impairment after prolonged extreme altitude exposure is correlated with a brisk hypoxic ventilatory response,[191] possibly resulting from enhanced cerebral vasoconstriction and reduced brain O_2 delivery.

Effect of Maternal Hypoxia on the Fetus

Data on the fetal effects of maternal hypoxia are sparse (see Chapter 77). However, using changes in fetal heart rate (FHR) as an end point, the fetus is relatively resistant to moderate degrees of maternal hypoxia. Administration of 15% O_2 (inspired PO_2 = 108 mm Hg, equivalent to 2500 m altitude) for 4 minutes to five primigravid women at 36 to 38 weeks of gestation resulted in an increase in FHR of only 2 to 3 beats per minute.[193] The same investigator observed no change in FHR after administration of mixtures as low as 10% O_2 (inspired PO_2 = 71 mm Hg, equivalent to 5300 m altitude) for 20 minutes in 8 of 28 pregnant women. Administration of 10% O_2 for 10 minutes to pregnant women at 35 to 41 weeks of gestation had no significant effect on FHR, heart rate variability, or Doppler velocimetry in the umbilical and middle cerebral arteries of the fetus.[194] Acute hypoxia of this magnitude appears to exert no detectable effects on the healthy fetus because of augmentation of uterine blood flow; thus, it is unlikely that acute exposure to altitudes up to 2500 to 3000 m would have any adverse fetal effects.

Additional adaptations to long-term altitude exposure specific to pregnant women include an increase in placental capillary volume and a reduction in villous membrane thickness.[195] Infants born at high altitude, even as high as 4329 m, have scalp vein O_2 tensions similar to values obtained from infants born at sea level.[196] Consequently, a significant reduction in maternal O_2 delivery can be tolerated without any impact on fetal O_2 consumption.

Infants Born at High Altitude

As with adults, SpO_2 decreases with increasing altitude, but it also depends on activity (lower during sleep), postnatal age (Fig. 91-15), and race[197] (see also Chapter 77). Perinatal hypoxia appears to predispose to a blunted hypoxic ventilatory drive in adulthood.[198]

At sea level, pulmonary artery pressure decreases to normal levels within 24 hours after birth, whereas at high altitude, pulmonary artery pressure often remains elevated for several weeks or throughout infancy.[197] In a series of 35 consecutive infants born at term in Leadville, Colorado (altitude 3179 m), during the first 3 months of life 17% experienced elevated pulmonary artery pressure or respiratory distress requiring supplemental O_2 or mechanical ventilation, or both.[197] In infants born at high altitude, the transition to adult circulation occurs more slowly, with increased frequency of patent foramen ovale and patent ductus arteriosus.[199] Patent foramen ovale was present at 6 months in 7 of 16 infants studied after birth in La Paz, Bolivia (altitude 3700 to 4000 m).[200] Acute hypoxia after birth (15% O_2 administration) in preterm infants paradoxically produced hypoventilation, periodic breathing, and apnea.[201] Infants with trisomy-21 (Down syndrome) are at increased risk of high-altitude pulmonary edema (HAPE; see later).[199] Perinatal pulmonary hypertension seems to predispose to exaggerated hypoxic pulmonary vasoconstriction in adulthood.[202]

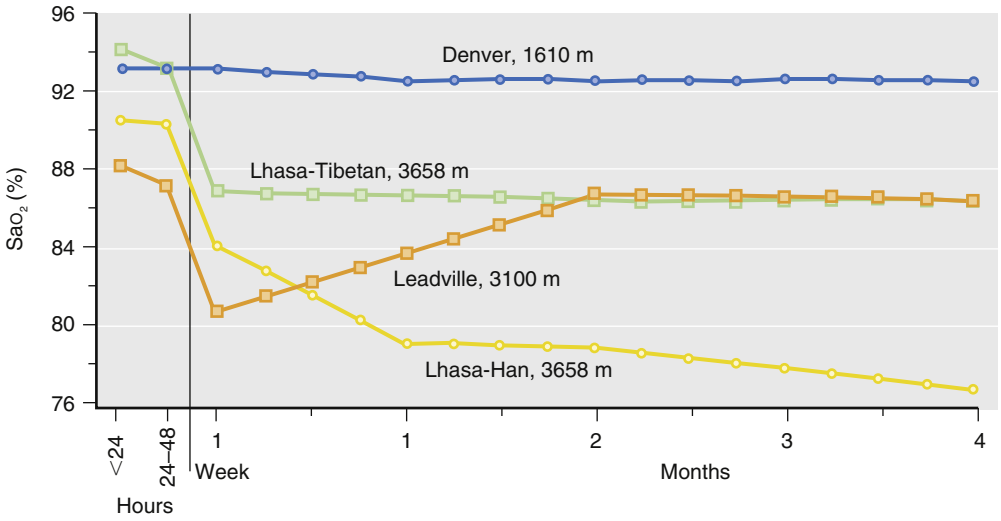


Figure 91-15. Pulse oximetry in infants born at various altitudes. In infants born in Lhasa (altitude of 3658 m), Han Chinese children have progressive arterial desaturation whereas Tibetan infants, following a slight drop shortly after birth, have a stable saturation of peripheral oxygen. Sao_2, Arterial oxygen saturation. *(Redrawn from Niermeyer S: Cardiopulmonary transition in the high altitude infant,* High Alt Med Biol *4:225, 2003.)*

Effects of Altitude on Children

Although SpO_2 is lower at higher elevations, children who reside at altitudes up to 3000 m generally maintain arterial O_2 saturation (Sao_2) higher than 90%.[203] Normal children who travel to altitudes up to 3500 m exhibit changes in cardiorespiratory function similar to changes seen in adults.[204] Exaggerated hypoxemia at high altitude can suggest previously undiagnosed cardiorespiratory anomalies, such as Pierre-Robin syndrome or tracheomalacia-laryngomalacia.[199]

Altitude Illness

Altitude illness consists of a group of subacute and chronic syndromes, the underlying pathophysiology of which is triggered by continuous exposure to hypoxia. These syndromes are described here. Further information can be obtained from detailed reviews.[205-208] The Wilderness Medical Society has published guidelines for the prevention and treatment of acute altitude illness.[209]

Acute Mountain Sickness. The most common symptoms of acute mountain sickness (AMS) are headache, decreased appetite, nausea and vomiting, insomnia, ataxia, and peripheral edema.[210] AMS can occur after several hours of exposure to elevations greater than 2500 to 3000 m, although some people are more susceptible and can experience it at lower altitudes. Approximately 25% of visitors to ski resorts in the Rocky Mountains of the United States (altitude 1920 to 2960 m) develop AMS.[211]

Pharmacologic prophylactic measures against AMS in mountaineers include slow ascent (≈300 m/day) or "staging," in which several days are spent at an intermediate altitude of approximately 2000 m.[209,210] Pharmacologic prophylactic measures include the administration of acetazolamide,[212] which is believed to work in part by augmenting the ventilatory response to hypoxia as a result of the ensuing bicarbonate diuresis.[213] However, other purported mechanisms include tissue respiratory acidosis, improved sleep quality from a reduction in periodic breathing (paradoxically because its inhibition of the carotid body response to CO_2), and diuresis.[214] The effective dose range is 250 to 750 mg orally daily begun the day before ascent.[205,209,215]



Figure 91-16. Portable Altitude Chamber at Everest Base Camp. The pressure inside the bag can be raised to 2 psig (approximately 100 mm Hg) by using a foot pump. This effectively reduces the "altitude" for the occupant of the chamber and thus raises the partial pressure of oxygen (PO_2). These bags can be used to treat altitude illness when neither oxygen administration nor true descent is feasible. *(Photograph courtesy Caudwell Xtreme Everest.)*

Although most individuals recover spontaneously after several days at high altitude, AMS can be treated effectively with O_2 and descent. A descent of only 500 to 1000 m usually leads to resolution of AMS. Simulated descent using a portable inflatable hyperbaric chamber (Gamow bag or similar) operated by foot pump is also effective (Fig. 91-16). Depending on the altitude, inflation of such a chamber to only 2 psi (100 mm Hg) produces a decrease in equivalent altitude of 1500 to 2000 m.[205] AMS also responds to dexamethasone in a dosage of 4 mg every 6 hours, although symptoms may occur as soon as it is discontinued.[216,217] Ginkgo biloba has also been used, with mixed results.[218,219] Insomnia associated with AMS responds to treatment with acetazolamide. Sedative-hypnotic drugs can depress ventilation and exacerbate hypoxia and should therefore be used cautiously. Both zolpidem (10 mg orally) and zaleplon (10 mg orally) improve sleep quality at high altitude, and neither appears to depress ventilation in healthy young subjects.[220,221]

AMS symptoms could conceivably result from hypoxemia at sea level. The headache associated with obstructive

sleep apnea and opioid-related headache may be caused by a form of "AMS" secondary to hypoxemia caused by respiratory depression.

High-Altitude Pulmonary Edema. HAPE is much less common than AMS but more serious. It occurs in a small percentage of unacclimatized, susceptible people within a few days of reaching altitude.[183] A hemodynamic pathophysiology for HAPE is suggested by its tendency to occur when pulmonary vascular flows or pressures are particularly high (e.g., in the lung contralateral to unilateral absence of the pulmonary artery).[222] Measurements in patients with HAPE have revealed pulmonary hypertension, normal pulmonary artery wedge pressures, but elevated pulmonary capillary pressures (assessed using the single occlusion method[223]). Bronchopulmonary lavage fluid in subjects with HAPE has a high protein content, implicating an increase in permeability or alveolar-capillary disruption.[224-226]

Prophylaxis against HAPE includes slow ascent. People with known predisposing factors such as unilateral absence of the pulmonary artery should avoid high altitudes. For climbers with known HAPE susceptibility, prophylactic measures may include nifedipine (20 mg slow-release formulation every 8 hours),[227] tadalafil (10 mg twice daily), or dexamethasone (8 mg twice daily).[228] Inhaled salmeterol also appears to be an effective prophylactic agent.[229] Whether acetazolamide prevents HAPE has not been established by randomized studies; however, it is probably at least partly effective based on animal studies and its augmentation of PaO_2 during hypoxia.[230]

Treatment of HAPE consists of descent or supplemental O_2, or both.[205] If descent is impossible or O_2 is unavailable, pharmacologic reduction in pulmonary artery pressure should be initiated. Nifedipine (10 mg sublingually), followed by 20 mg of a slow-release preparation administered orally every 6 hours, has been successful in HAPE.[231] Pulmonary artery pressure can also be lowered in patients with HAPE by using hydralazine, phentolamine, or inhaled nitric oxide.[231-234] Other suggested treatments include agents that could lower pulmonary artery pressure (e.g., prostaglandins[235] and phosphodiesterase inhibitors such as sildenafil[235]) or facilitate alveolar fluid clearance (e.g., β_2-adrenergic agonists,[229] recompression in a Gamow bag,[205] and application of expiratory airway pressure[236]).

High-Altitude Cerebral Edema. High-altitude cerebral edema (HACE), the rarest but most lethal form of high-altitude illness, is a clinical diagnosis made when a patient with AMS or HAPE has ataxia or altered consciousness.[237] Physical findings in patients with HACE may include papilledema, retinal hemorrhages, and, occasionally, cranial nerve palsies.[238] Focal abnormalities in the corpus callosum detected with MRI have been reported.[239] The pathophysiology of HACE is unknown. It has been hypothesized that individuals who develop AMS and HACE have a limited capacity to accommodate the associated increase in brain volume that accompanies the rise in cerebral blood flow during hypoxemia.[205,240]

Treatment of HACE is a medical emergency and ideally should include evacuation or descent and administration of supplemental O_2. Although a reduction in altitude of 500 to 1000 m is usually effective for AMS, treatment of HACE may require descent to a lower altitude. Use of a Gamow bag may also be effective. Recommended adjunctive treatment includes dexamethasone (8 mg immediately, then 4 mg every 6 hours). If descent is not possible, acetazolamide (250 mg twice daily) may also be effective.[205]

Chronic Mountain Sickness (Monge Syndrome). Chronic mountain sickness has been defined as a clinical syndrome that occurs in natives or long-time residents at altitudes higher than 2500 m. This illness is characterized by excessive erythrocytosis (female patients, Hb ≥19 g/dL; male patients, Hb ≥21 g/dL), severe hypoxemia, and, in some cases, moderate or severe pulmonary hypertension, which may evolve to cor pulmonale leading to congestive heart failure.[241] Other manifestations include headache, dizziness, breathlessness or palpitations, sleep disturbance, fatigue, localized cyanosis, burning in the palms of the hands and soles of the feet, dilatation of the veins, muscle and joint pain, loss of appetite, lack of mental concentration, and alterations of memory.[241] The diagnosis requires the exclusion of other conditions that may produce hypoxemia, such as cyanotic heart disease and chronic lung disease. Clinical improvement and increased work capacity often result from phlebotomy, at least transiently, and descent to lower altitudes relieves the symptoms completely. Other suggested modalities for treatment of chronic mountain sickness include angiotensin-converting enzyme inhibitors, the D_2 dopaminergic receptor antagonist domperidone, acetazolamide, and the respiratory stimulants medroxyprogesterone and almitrine.[242] Both nifedipine and sildenafil may be effective to reduce pulmonary artery pressure.[242]

REDUCTION IN AMBIENT PRESSURE

Acute ascent to altitude in an aircraft can cause DCS resulting from the reduced barometric pressure and supersaturation of nitrogen. Although symptoms have been reported to occur after rapid ascent in aircraft to only 2437 m,[243] DCS usually occurs only in aircraft in which the cabin altitude is higher than 5000 to 6000 m,[244] which typically occurs only in military planes. Exposure to lower altitudes, including the cabin altitude of commercial aircraft (2400 m or less) within 12 to 24 hours after a scuba dive can also precipitate DCS.[245] To reduce this risk, it is the practice of individuals who are planning rapid decompression to low ambient pressure (e.g., military pilots, astronauts) to denitrogenate their tissues by prebreathing 100% O_2 for periods ranging from a few minutes to several hours, depending on the altitude of the planned exposure. Nevertheless, DCS has been described even in pilots following appropriate prebreathing procedures.[246,247]

A lower ambient pressure implies a reduction in gas density, which results in lower breathing resistance. The effect of ambient pressure from 0.5 to 5 ATA on airway

resistance in normal subjects can be estimated by either of the following equations[248]:

$$R_P/R_0 = 0.57 + 0.44 \cdot P_{ATA}$$

or:

$$R_P/R_0 = P_{ATA}^{0.59}$$

where P_{ATA} is ambient pressure in ATA, Rp is airway resistance at ambient pressure, and R_0 is airway resistance at 1 ATA. For example, at an ambient pressure of 0.5 ATA (5486 m), airway resistance is reduced by approximately 20%. Under resting conditions, differences in breathing pattern during altitude exposure, compared with a similar degree of hypoxia at sea level, are minor.[249]

OTHER ENVIRONMENTAL STRESSES AT HIGH ALTITUDE

Individuals at high altitude are subjected to low temperature, wind, and ultraviolet radiation. The effects of hypoxia may therefore be compounded by hypothermia, dehydration, frostbite, and sunburn. On the basis of a seemingly higher incidence of stroke,[250] thrombophlebitis, and pulmonary thromboembolism[251] at high altitude, investigators have suspected that prolonged hypoxic exposure may cause a hypercoagulable state.[252] Indeed, rapid exposure to high altitude in a hypobaric chamber has been associated with a decrease in partial thromboplastin time[253] and an increase in prothrombin fragments 1 and 2, thrombin-antithrombin complex, and factor VIIa activity.[254]

ANESTHESIA AT HIGH ALTITUDE

General Principles

Because of the reduced ambient PO_2 at high altitudes, the risk of perioperative hypoxia is likely to be magnified, particularly in newcomers to altitude. Opiates depress both the tachycardia and hyperpnea that normally occur in response to acute hypoxemia. Slow recovery of consciousness and postanesthetic headache have been reported after anesthesia using thiopental with air or nitrous oxide.[255] When ventilation was assisted or controlled during the anesthetic regimen and when postoperative supplemental O_2 was administered, these complications did not occur. This finding suggests that intraoperative or postoperative hypoxemia may be a pathophysiologic factor. In contrast, long-term residents at high altitude may be more tolerant of hypoxemia; in such individuals other considerations may be important, including a higher hematocrit, pulmonary hypertension, and lower Pa_{CO_2} and bicarbonate concentration.[189] To prevent renal retention of bicarbonate, which reduces ventilatory drive, patients requiring controlled ventilation should have their Pa_{CO_2} maintained at baseline value rather than in the traditionally normal range. Similarly, maintenance of PaO_2 within the sea level normal range results in loss of adaptation and difficulty in readapting the patient to breathing room air.

Increased oozing of blood from surgical wounds at high altitude has been reported,[256] and it is attributed to higher venous pressure, blood volume, vasodilatation, and increased capillary density. Camporesi reviewed the topic of anesthesia at both high and low ambient pressures.[257]

Anesthesia Equipment

Fluotec Mark II and Dräger Vapor halothane vaporizer performance has been compared at sea level, 5000 ft (1524 m), and 10,000 ft (3048 m) altitude.[258] At any given setting the delivered percentage of halothane increased with altitude; however, its partial pressure remained constant. Therefore, when these devices are used at a given vaporizer setting, the anesthetic agent is delivered at a constant potency regardless of altitude (see also Chapter 29).

The effect of altitude on floating-bobbin or floating-ball gas flowmeters has also been examined.[258] At 10,000 ft (3048 m) simulated altitude, both nitrous oxide and O_2 flowmeters underread the actual flow rate. The percentage error progressively increased up to 4 L/minute, at which point both flowmeters were approximately 20% in error. A hazard may therefore arise when a low flow of O_2 is mixed with a higher flow of nitrous oxide. Unless an O_2 analyzer is available, the delivered percentage of O_2 may be significantly lower than that calculated on the basis of the flowmeter readings.

Venturi-type gas mixing devices tend to deliver higher concentrations of O_2 at high altitude than they do at sea level[258]; at 10,000 ft (3048 m) altitude, a mask designed to deliver 35% O_2 at sea level actually delivered 41% O_2.

Sedation

Standard sea level doses of sedative-hypnotics may produce increased respiratory depression at high altitude in unacclimatized subjects (see Chapters 89 and 90). A small dose of oral ethanol (50 g, producing an estimated blood alcohol concentration of 65 mg/dL, which was without ventilatory effect at ground level) increased blood P_{CO_2} by a mean of 1.5 mm Hg after acute ascent to 3000 m.[259] Both diazepam (5 mg orally) and temazepam (10 mg orally)[260] have measurable effects on respiration at 3000 m. In contrast, temazepam (10 mg orally) improved sleep quality and reduced the number of desaturations during sleep in partially acclimatized mountaineers at 5300 m.[261] The difference in the studies is probably explained by different degrees of acclimatization to altitude. During acute altitude exposure in healthy young subjects, neither zolpidem (10 mg orally) nor zaleplon (10 mg orally) adversely affected SpO_2 during sleep.[220,221]

General Anesthesia

Bandolz-Frank reported approximately 900 general anesthetic cases in La Paz, Bolivia at an altitude of 12,000 ft, with few problems.[262] For adults, anesthesia induction was performed using a short-acting barbiturate such as thiopental, followed by ether or intravenous procaine maintenance, mostly with spontaneous ventilation. The respiratory stimulant nikethamide was sometimes required to reestablish ventilation after barbiturate induction. During the 1933 British Everest expedition to Mt. Everest, to facilitate fixation of a fractured clavicle a brief general open-drop chloroform anesthetic was administered at 14,000 ft altitude to a Tibetan, and it caused

cardiopulmonary arrest. After external cardiac massage and intracardiac injection of the respiratory stimulant nikethamide, breathing and circulation returned. An hour later, the patient had recovered sufficiently to smoke a cigarette.[263] Other examples and a review of anesthetic agents delivered at high altitude are provided by Firth and Pattinson.[263]

The potency of anesthetic gases is proportional to their partial pressure. Therefore, as barometric pressure is reduced, fixed concentrations of inhaled anesthetics have lower potency. At an altitude of 3300 m, a significant reduction in efficacy of 50% nitrous oxide was observed in reducing pain threshold in normal volunteers[264] (Table 91-6). Successful induction of general anesthesia with halothane in a hypobaric chamber was reported at a barometric pressure of 375 mm Hg (equivalent altitude = 5490 m).[265] Recovery was rapid and uneventful.

Because supplemental O_2 may not be available in some mountain locations, it may be imperative to choose an anesthetic technique that is least likely to suppress ventilation. Ketamine anesthesia with spontaneous ventilation was reported in 23 patients requiring general anesthesia at an altitude of 1830 m.[266] Two patients developed significant, although brief, desaturation, which resolved quickly. The authors concluded that this form of anesthesia is a practical method in a rural hospital setting at high altitude without access to supplemental O_2.

Ketamine (total dose 1 to 6 mg/kg) after intravenous premedication with atropine 0.02 mg/kg and midazolam 0.05 mg/kg was reported in a consecutive series of 11 patients (American Society of Anesthesiologists Physical Status 1 to 2) requiring general anesthesia for short procedures at Kunde Hospital in Nepal (3840 m) (Fig. 91-17).[267] Nine patients required reduction of dislocations or fractures, 1 patient (9 years old) required suturing of a facial laceration, and another patient required drainage of an abscess. The induction dose of ketamine was 1 mg/kg intravenously administered over 1 to 2 minutes, followed by additional incremental doses, titrating to effect. Baseline SpO_2 on room air was 86% to 91%. O_2 was administered in 3 of 11 cases through an O_2 concentrator if SpO_2 fell below 80% for 1 minute and was not correctable by forward jaw thrust or vocal and tactile stimulation. Both low-altitude residents required supplemental O_2 for 20 minutes during recovery, whereas only 1 of 9 high-altitude residents required O_2. Use of ketamine was reported at even higher altitude (4243 m), for control of postpartum hemorrhage in a 22-year-old woman.[268] Deep general anesthesia was obtained with only 25 mg of

TABLE 91-6 **EFFECT OF 50% NITROUS OXIDE ON PAIN THRESHOLD IN NORMAL VOLUNTEERS AT ALTITUDE***

Altitude(m)	Barometric Pressure (mm Hg)	Increase in Pain Threshold(%)	Side Effects
0	760	71.5	3 subjects, nausea; 2 subjects, semicomatose
1,460	636	40.0	None
3,300	517	19.0	None

*Pain threshold was measured in 20 subjects at each altitude by applying pressure to the anterior aspects of the tibia using a spring balance. Simulated altitude exposures were in a hyperbaric chamber. At increasing altitudes a fixed concentration of nitrous oxide is progressively less effective.

Data from James MFM, Manson EDM, Dennett JE: Nitrous oxide analgesia and altitude, Anaesthesia *37:285-288, 1982.*



Figure 91-17. Kunde Hospital, Nepal (altitude 3840 m), the site of the published series of general anesthetics described in the text.[267] The photograph depicts Dr. David Murdoch assisted by Kami Temba Sherpa. *(Photograph courtesy Dr. Lynley Cook.)*

intravenous ketamine (≈0.5 mg/kg), which induced 5 minutes of apnea, requiring airway manipulation and supplemental O_2. The total dose of ketamine required for the 20- to 25-minute procedure was only 50 mg. The authors attributed the exaggerated response to a low dose of ketamine to a combination of hypoxemia and hemodynamic instability.

Compared with lowlanders at 300 m, high-altitude natives anesthetized at 3500 m above sea level (mean preoperative SpO_2 88.5%) appeared to require significantly larger amounts of propofol when administered with fentanyl.[269] The highlanders also had a lower resting heart rate, and heart rate responses to surgical stress were significantly attenuated.

Regional Anesthesia

Spinal anesthesia has been reported to result in an unacceptably high incidence of dural puncture headache,[255] possibly because of chronically increased CSF pressure, dehydration, and altered sensitivity of the altitude resident's CNS ICP changes.[255] Headaches were not reported in 20 young native mountain dwellers in whom CSF samples were obtained with 25-gauge needles.[255]

Perioperative Supplemental Oxygen

At high altitude, PAO_2 is normally increased by hyperventilation induced by the hypoxic ventilatory drive. Administration of anesthetics or narcotic analgesics, both of which blunt the hypoxic ventilatory drive, may therefore precipitate hypoxia. The resulting hypoxic symptoms of irritability, confusion, and restlessness may be misinterpreted as being caused by pain, and misguided administration of additional narcotics would only compound the problem. Analgesic-induced respiratory depression was reported as a likely cause of death in a Sherpa who had débridement of frostbitten fingers at 4300 m altitude.[265] Therefore, if opiate analgesics are administered, supplemental O_2 may be required.

Monitoring

O_2 analyzers, both electrochemical and paramagnetic, measure PO_2 rather than O_2 percentage (see also Chapter 44). Thus, if the display is in "percent," the actual percentage will be falsely low unless the analyzer is calibrated at that altitude. Nevertheless, it is the PO_2 that is physiologically important. Clinical CO_2 analyzers similarly measure partial pressure. Because end-tidal P_{CO_2} at high altitude is within the normal range (or somewhat low), readings are unaffected by altitude.

Air evacuation in an unpressurized or partially pressurized aircraft engenders expansion of the gas volume in enclosed spaces such as tracheal tube cuffs and pulmonary artery catheter balloons.

AIR TRANSPORT OF CRITICALLY ILL PATIENTS

Important issues during air transport of critically ill patients include the challenges of monitoring and intervening in an environment with limited space and resources, as well as those pertinent to altitude itself[270] (see also Chapter 81). A decrease in ambient pressure causes expansion of fixed gas volumes such as in an endotracheal cuff and pneumothorax. Volumes increase 20% and 45%, respectively, at 5000 and 10,000 ft (1524 and 3048 m) altitude, and they may require adjustment of cuff pressure. It would also be expected that the volume of pneumocephalus would similarly increase and cause a rise in ICP. This issue was examined in a review of 21 patients with posttraumatic pneumocephalus who were evacuated by military transport (8 hours flying time) at a cabin altitude of 5000 to 8000 ft from Iraq to Landstuhl Regional Medical Center in Germany. Two patients had intraventricular drains. None of the patients experienced sustained clinical neurologic deterioration during transport or within 24 hours after arrival at the destination.[271] The patient with the most severe brain injury had baseline ICP of 25 to 30 mm Hg and experienced only transient ICP elevations during takeoff and during level flight, each of which resolved spontaneously. Provided the cabin altitude is within the range usually experienced during commercial flight (see later), the mild decrease in arterial PO_2 can be managed with supplemental O_2.

In a review of 19,228 urgent civilian transports of adult patients within Ontario, Canada, by either fixed wing aircraft or helicopter, at least one critical event occurred during 5% of the transports.[272] Hemodynamic deterioration was the most frequent critical event, occurring in 3.2% of transports. Accidental extubation was uncommon (0.1% of cases); however, airway interventions occurred in 0.7% (intubations, laryngeal mask insertions, or cricothyroidotomies). The success rate for first-attempt intubations was 64.5% for oral and 75.0% for nasal. Needle thoracostomies were performed in 63 instances (0.33%). Cardiac resuscitation (mostly chest compression, defibrillation, cardioversion, or external pacing) was performed in 1.25% of cases.

COMMERCIAL AIR TRAVEL

Clinical Effects of Aircraft Flight

During commercial aircraft flight, the pressure within the cabin is mandated to be no less than the barometric pressure at 8000 ft altitude (typical cabin altitude 1500 to 2438 m). During flight, the ambient air PO_2 would fall from 159 mm Hg at sea level to as low as 118 mm Hg. One publication reported observations during commercial flights that indicated a cabin altitude sometimes reaching 8549 ft.[273] The ensuing mild hypoxemia Sa_{O_2} (usually >90%) is generally well tolerated by normal individuals, although altitude-related symptoms such as discomfort and fatigue can occur.[274] Small increases in pulmonary artery pressure have been described in normal individuals,[275] with clinically significant changes in susceptible individuals.[276] Changes in ambient pressure can induce otic and sinus barotrauma and pain resulting from expansion of intestinal gas. Motion sickness is now rare. More serious manifestations that have been attributed to immobility and possible hypoxemia include phlebothrombosis.[277,278] Airborne spread of communicable diseases has also been reported.[278] Medical guidelines for air travel have been discussed in review articles.[279,280]

Prediction of Oxygenation During Commercial Flight

Patients with impaired gas exchange resulting from chronic obstructive pulmonary disease or restrictive disease during flight may experience significant hypoxemia,[281,282] as well as symptoms of dyspnea, edema, wheezing, cyanosis, and chest pain.[283]

To predict the effect of altitude on arterial oxygenation, the patient can be exposed to simulated altitude in a hypobaric chamber with assessment of SpO_2 and/or arterial blood gases. Alternative measures include administering a hypoxic gas premixed to produce the same inspired PO_2 as air at the target altitude (typically 15% O_2)[284] or supplying a Venturi mask designed to deliver 35% to 40% O_2 with 100% nitrogen.[285,286] Prediction algorithms based on sea level blood gas values have also been used with success.[287] Predicted PaO_2 at altitude ($PaO_{2\ alt\ (predicted)}$) can be predicted from ground level blood gases ($PaO_{2\ GL}$, $PaCO_{2\ GL}$), ground level calculated alveolar PO_2 ($PAO_{2\ GL}$), and altitude alveolar PO_2 ($PAO_{2\ alt}$) using the following equation:

$$PaO_{2\ alt\ predicted} = PAO_{2\ alt} \times (PaO_{2\ GL}/PAO_{2\ GL})$$

Systematic testing of a number of other prediction equations has been reported.[286,288] Incorporation of SpO_2 measured after a 6-minute walk test may provide greater predictive accuracy.[289]

Patients with baseline hypoxemia resulting from lung or heart disease may be considered for in-flight O_2 administration.[290] Procedural details have been reviewed by Stoller.[287]

In-Flight Emergencies

One to 75 in-flight medical events per million passengers have been reported by commercial airlines.[291] The most common are syncope, gastrointestinal complaints, minor trauma, and cardiac, pulmonary or neurologic issues. Emergency care of severely ill passengers is facilitated by medical kits that are carried aboard all U.S. commercial aircraft requiring a flight attendant. In addition, automatic external defibrillators are aboard all U.S. commercial planes with a payload exceeding 7500 pounds. In-flight deaths are extremely uncommon (0.01 to 0.8 deaths per million passengers). In a study of 1 year's (1999 to 2000) experience of a U.S.-based airline, it was estimated that an onboard physician was available during approximately half of all flights.[291] Guidelines for assessment of in-flight emergencies have been outlined by Silverman and Gendreau.[279] A system of ground-based physicians is available for consultation and to assist with decisions regarding flight diversion.

MEDICAL CARE IN SPACE

PHYSIOLOGIC AND MEDICAL ISSUES DURING SPACE FLIGHT

For a few minutes during launch of a space vehicle, gravitational force increases as the space craft accelerates to orbital speed (typically 4 G for the Russian Soyuz). During the period in space, the major physiologic stress on astronauts is the absence of gravitational stress (microgravity). This phenomenon results in an increase in left ventricular end-diastolic volume, paradoxically accompanied by a decrease in central venous pressure.[292] The central redistribution of blood causes facial edema and initiates diuresis, and thence plasma volume depletion (up to 20% or more), which persists until after landing.[293] Shortly after attaining orbit, most astronauts experience self-limited dizziness, drowsiness, nausea, and vomiting.[294] During reentry, astronauts are reexposed to increased G force without the benefit of an anti-G suit. This is typically 4 to 5 G for the Soyuz craft, but it can be as high as 6 to 7 G. To increase plasma volume, astronauts routinely consume 4 L of an electrolyte fluid within 4 hours before reentry. Nevertheless, after landing astronauts typically experience some degree of orthostatic intolerance,[295] and they often have a recurrence of nausea and vomiting.[294] Postural hypotension has been attributed to hypovolemia, decreased muscle tone in the legs, enhanced endothelial nitric oxide synthase expression, and down-regulation of α-adrenergic receptors.[296] Reduced ventricular mass has been observed after several days in orbit,[297] and it may be caused by cardiac atrophy[298] or dehydration.[299] Skeletal muscle atrophy occurs even after short missions.[300]

Cabin pressure in the space shuttle and the International Space Station is 760 mm Hg. However, during extravehicular activity (EVA), space suit pressure is 4.3 psi (222 mm Hg). During EVA, astronauts prevent hypoxia by breathing 100% O_2, although the reduced pressure engenders the potential risk of DCS.[301] To decrease the probability of bubble formation by reducing tissue nitrogen content, the astronauts have a 100% O_2 prebreathing period of approximately 4 hours. If the suit were to become disrupted during EVA, the astronaut's ambient pressure would quickly drop to zero, causing hypoxia and generalized bubble formation, referred to as *ebullism* (body fluids boiling as a result of ambient pressure lower than saturated water vapor pressure).

Gravitational unloading causes loss of calcium from bones. During long space flights, this loss could produce significant osteoporosis. This problem, along with the resulting hypercalciuria and increased probability of nephrolithiasis, constitutes a major obstacle to human interplanetary travel.

Emergency care during space includes numerous challenges, including the effect of fluid volume changes on drug disposition, hypovolemia, difficulties with applying mechanical force (e.g. for intubation), and limitations of supplies and expertise.[302] For acute medical conditions that cannot be adequately treated on board the International Space Station, evacuation of an astronaut by Soyuz may take up to 24 hours. Hypovolemia secondary to hemorrhage may not be adequately treatable because of limited quantities of supplies, and hypotension could be exacerbated by preexisting volume loss and increased G forces during reentry. Air-fluid interfaces in intravenous fluids generate bubbles (Fig. 91-18). Thus, intravenous fluid bags must be degassed before flight, and bubbles must be removed by in-line filtration. The physiologic effects of general or regional anesthesia in microgravity are unknown. Because conventional anesthesia vaporizers require gravity to confine the liquid to the bottom of the reservoir, a different design would be required for



Figure 91-18. Air in the bag of intravenous (IV) fluid in microgravity with an infusion pump. The lack of a gravitational field makes it impossible to remove gas in the usual way. IV fluid bags must be degassed before flight, and bubbles must be removed by in-line filtration. *(Courtesy National Aeronautics and Space Administration.)*

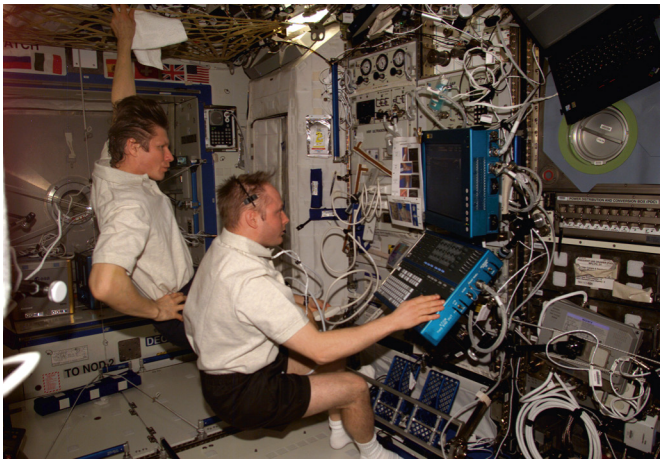


Figure 91-20. Testing diagnostic ultrasound on the space shuttle. Astronaut Mike Finke is operating the ultrasound device while being guided by a ground-based physician. *(Courtesy National Aeronautics and Space Administration.)*

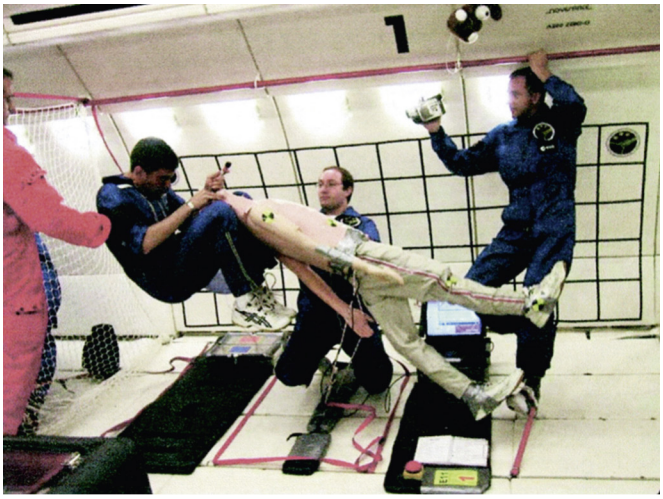


Figure 91-19. Tracheal intubation of a free-floating mannequin in microgravity. The intubator stabilizes the head by holding it between his knees. *(From Groemer GE, Brimacombe J, Haas T, et al: The feasibility of laryngoscope-guided tracheal intubation in microgravity during parabolic flight: a comparison of two techniques,* Anesth Analg *101:1533-1535, 2005, with permission).*

use in space. Additional practical limitations include the need to prevent pollution of the enclosed environment by volatile anesthetics or exhaust O_2 (fire hazard).

Tracheal intubation may be difficult because of facial edema. The laryngeal mask airway (LMA), cuffed oropharyngeal airway, and intubating LMA have all been successfully demonstrated in microgravity simulated in a neutral buoyancy tank.[303] Studies using secured mannequins during short periods of microgravity in an aircraft have demonstrated successful intubation using laryngoscopy and standard tracheal tube (Fig. 91-19), Combitube (Nellcor, Pleasanton, Calif.), and an intubating LMA.[304,305] However, tracheal intubation in microgravity by a nonphysician using conventional laryngoscopy is frequently unsuccessful.[304] All intubation techniques require that both the patient and the intubator be secured.[304] Gastroesophageal reflux is more common in microgravity; thus, aspiration during general anesthesia may be more likely.

On-board diagnostic tools are being developed, such as for remotely guided ultrasound examination (Fig. 91-20). The challenges of providing anesthesia in space have been outlined by Komorowski and colleagues.[306]

Remote robotic surgery has been considered a substitute for an on-board surgeon. Indeed, a robotic laparoscopic cholecystectomy was successfully performed on a patient in Strasbourg, France by surgeons operating from New York City. The total delay time between movement initiated by the surgeon and detection on the monitor was approximately 155 msec.[307] A surgical center at McMaster University in Hamilton, Ontario, Canada successfully performed several telerobotic surgical cases at North Bay, 250 miles away, by using an Internet link with a delay of 135 to 140 msec.[308] The limit of the acceptable time delay is believed to be approximately 330 msec. Whether training or technology will allow this technique to be expanded to permit surgery during interplanetary flights (with a much longer delay time) is unknown.

PHYSIOLOGIC AND MEDICAL ISSUES AFTER RETURN TO EARTH

Medical challenges may extend into the period after landing. After 14 days in space, to obtain biopsies, two rhesus monkeys were administered general anesthesia (ketamine 10 mg/kg intramuscularly; then 1% to 1.5% isoflurane for 3.5 to 4 hours) by a competent veterinary anesthesiologist within 24 hours after landing. One animal aspirated during emergence and could not be resuscitated. Three hours after recovery, the other inexplicably developed lethargy and facial edema.[309] From this experience, it can be inferred that well-accepted standard-of-care techniques may not be safe when anesthetizing astronauts shortly after space flight.

Several specific challenges have been elucidated. Details can be found in two excellent reviews.[310,311] Some issues most pertinent to anesthetic risk are as follows.

Hypovolemia and Adrenergic Hyporesponsiveness

Following flight, many astronauts experience orthostatic intolerance. This is in part the result of hypovolemia, but it is also caused by a dysfunctional adrenergic response.[312] In astronauts with postflight orthostatic intolerance, the pressor response to phenylephrine is not different from the preflight response; however, it is attenuated compared with astronauts who are tolerant of acute orthostasis.[313] Cardiovascular deconditioning, ventricular atrophy, and changes in arterial stiffness may also play a role.[298,299,314,315] The immediate postflight hemodynamic response to general or neuraxial anesthesia could include unexpected hypotension, but to date is this is unknown.

Electrolyte Disorders

Reductions in both serum potassium and magnesium have been reported after some space missions,[316,317] possibly in response to decreased dietary intake. Hypokalemia has been blamed for cardiac arrhythmias observed during Apollo 15.[318]

Hyperkalemic Response to Succinylcholine

Skeletal muscle atrophy resulting from immobilization and disuse causes proliferation of acetylcholine receptors, increased sensitivity to succinylcholine (see Chapters 34 and 35), and decreased cholinesterase activity.[319] Based on data from patients with neuromuscular disease and immobilized limbs, resistance to nondepolarizing neuromuscular blocking drugs may occur.[320] Use of succinylcholine in immobilized ICU patients has been associated with exaggerated hyperkalemia and cardiac arrest.[321,322] Investigators have suggested that skeletal muscle atrophy in astronauts may put them at a similar risk.[311]

SUMMARY

Increasingly widespread use of HBOT to treat critically ill patients has created a demand for individuals skilled in using this technology. Planning and design of monitoring capabilities will enable optimal control of hemodynamics and oxygenation. Patient safety in this environment can be achieved with careful attention to detail, which includes patient selection and monitoring and chamber procedures. Optimized treatment schedules will evolve from studies of mechanism of action and further clinical trials. Advances in prevention and treatment of O_2 toxicity may allow more prolonged therapy than can currently be safely administered and hence a more aggressive approach to ischemic and infectious syndromes.

The decreases in ambient pressure and ensuing hypoxia associated with acute high-altitude exposure result in well-described physiologic changes that are often associated with clinical symptoms. Methods for prophylaxis and treatment have been described. Safe anesthesia at high altitude requires some modification of sea level techniques, not only because of the hypoxia and reduced ambient pressure, but also because suboptimal equipment may be available under mountain conditions.

Anesthesia in space poses unique challenges that may extend even beyond return to earth.

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Chapter 92

Regional Anesthesia in Children

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Key Points

- The application of regional anesthesia in pediatrics has increased in the past 30 years.
- Regional anesthesia represents a major therapeutic option for preventing and treating pain in pediatrics both intraoperatively and postoperatively.
- In recent years, the use of peripheral nerve blockade instead of the neuraxial approach has reduced the incidence of adverse effects.
- More regional anesthesia procedures in children are being described in terms of efficacy and safety.
- The development of devices and techniques specifically for pediatric use has facilitated their routine use.
- Peripheral catheter techniques are becoming routine practice.
- The efficiency and safety of these techniques may facilitate early ambulation with improved pain management and includes treatment at home and improved rehabilitation of children.
- Traditionally, nerve stimulation is the gold standard for locating nerves and plexuses. However, ultrasound guidance is increasingly used for regional anesthesia in children.
- The benefits of the ultrasound-guided regional technique are visualization of targeted nerves and spaces and the spread of injected local anesthetic.
- The use of ultrasound guidance for performing peripheral nerve blocks permits the decrease of local anesthetic doses, decrease in number of punctures, and increase in the onset time and duration of sensitive block.
- To avoid local or systemic toxicity, the dose of local anesthetic, in terms of volume and concentration, should be carefully calculated.

Pediatric regional anesthesia is commonly used in adjunction with general anesthesia and plays a key role in the multimodal approach of pain management in surgical and nonsurgical pediatric patients and provides excellent postoperative analgesia. The development of needles and catheters for pediatric patients has made the use of these techniques easier and safer. Large retrospective and prospective studies confirm the infrequent rate of complications and no major sequelae with regional anesthesia in children, especially with peripheral nerve blocks. The use of long-acting local anesthetics with less cardiotoxicity, as well as ropivacaine or levobupivacaine, increases the safety of these procedures in children. Virtually all techniques of nerve blockade have been evaluated in pediatrics, thus allowing precise definition of their indications, contraindications, and adverse effects. This chapter describes these approaches in detail.

Continuous peripheral nerve blocks are one of the most recent developments in regional anesthesia in children. Local anesthetics in a single-shot procedure have a limited duration of action, sufficient for some pediatric surgeries but insufficient in many cases of major surgery. Major pediatric orthopedic surgery causes significant and prolonged postoperative pain, making continuous peripheral nerve blocks very important.

Ultrasound imaging techniques represent the second transformation in regional anesthesia (see also Chapter 58). The advantage of ultrasonography is to make visible the spread of the local anesthetic. Without doubt, ultrasonographic guidance improves the quality of regional anesthesia blockade, allowing both the adjustment of needle positioning in case of inappropriate spread and the reduction of local anesthetic dose in children.

RELEVANT DIFFERENCES BETWEEN CHILDREN AND ADULTS

ANATOMIC DIFFERENCES

Change in Body Size Resulting From the Growth Process

The most obvious difference between children and adults is body size. "Normal" full-term neonates weigh 3 to 3.5 kg,

with a height of 50 cm, and within 10 to 15 years they will multiply their weight by more than 12 (>1200%) and their height by more than 3 (>300%). During the early stages of development the spinal cord occupies the spinal canal entirely, but later the growth of vertebrae exceeds that of the cord,[1] and the last spinal nerves, the cord, and its envelopes are "attracted" within the spinal canal. At birth the dura mater ends at the level of the third or fourth sacral vertebra and the cord (conus medullaris) at the L3 or L4 level. It is only at the end of the first year of life that the adult level is attained—that is, L1 for the conus medullaris and S2 for the dural sac.

Anatomic relationships and landmarks are constantly changing throughout infancy and childhood, which interferes with regional procedures and requires good knowledge of developmental anatomy and the assistance of accurate techniques for localization of anatomic spaces and nerve trunks.

Congenital malformations, genetic disorders, and consequences of fetal and neonatal asphyxia (cerebral palsy) are frequent and specific to the pediatric period. They result in abnormal development and deformities of bone, joint, and neurologic structures that tend to worsen during childhood.

The main pediatric anatomic and physiologic factors that can influence indications for or performance of regional block procedures are listed in Table 92-1.

Delayed Ossification of Bones and Fusion of Sacral Vertebrae

Bones of neonates, including vertebrae, are mostly cartilaginous. Sharp needles can easily traverse them because cartilage offers little resistance to penetration, and ossification nuclei can be severely damaged, thus compromising further bone and joint development. Consequently, bone contact should be avoided as often as possible during block procedures, especially in infants. This cartilaginous structure also allows easy penetration of x-rays and ultrasound.

Development of Flexures of the Spine

At birth, a single spinal flexure is present and the orientation of epidural needles is the same regardless of the intervertebral space. Flexures, however, are not fixed, and they can be easily counteracted by forced flexion almost throughout childhood because of persistent spinal flexibility, which is a major advantage in the pediatric period (in addition to the absence of osteophytes).

Loose Attachment of Fasciae and Fluidity of Epidural Fat

Fasciae and perineurovascular sheaths are loosely attached to underlying structures (e.g., nerves, muscles, tendons, vessels). This allows extended spread of local anesthetics, resulting in high-quality nerve blockade regardless of the technique but also, occasionally, undesirable spread to distant nerves or anatomic spaces. The epidural fat is very fluid in infants and young children (up to 6 to 7 years of age). This fluidity combined with the loose attachment of the sheaths surrounding the spinal roots favors consistent leakage of local anesthetics injected within the epidural space; therefore, comparatively large volumes of epidural local anesthetics (up to 1.25 mL/kg) are required to reach desired levels of anesthesia.

Delayed Myelinization of Nerve Fibers

Myelinization begins during the fetal period in cervical neuromeres and extends cephalad and caudad,[2,3] but the process is not finalized before the twelfth year of life. Myelinization is especially poor in infants; the lack of fully developed nerve fibers is the main reason why they are unable to walk. A major pharmacologic consequence of this condition is that local anesthetics can penetrate and block nerve fibers more easily. Diluted solutions of local anesthetics provide the same quality of nerve blockade as with at least twofold more concentrated solutions in adults. Onset time is shortened, but, on the other hand, duration of blockade is reduced because trapping of local anesthetics within myelin with subsequent progressive release is reduced and because local circulation and, therefore, vascular absorption are greater in infants.

PAIN PERCEPTION

Somatic pain is a subjective sensory experience resulting from the intermixing of three main components[4]: motivational-directive, sensory-discriminatory, and cognitive-evaluative. The motivational-directive component is conveyed by unmyelinated C fibers ("slow" pain or "true" pain). It leads to protective reflexes such as autonomic reactions, muscle contraction, and rigidity. C fibers are fully functional from early fetal life onward. Connections between C fibers and dorsal horn neurons are not mature before the second week of postnatal life. However, nociceptive stimulations transmitted to the dorsal horn by C fibers elicit long-lasting responses,[5,6] probably as a result of extensive depolarization of surrounding neurons in response to the production of large amounts of substance P. As the number of dorsal horn receptors to substance P decreases during the first 2 weeks of life, this exaggerated response of neonates to nociceptive stimulation progressively disappears. The inhibitory control pathways, which are immature at birth, develop concomitantly.

Painful procedures during the neonatal period modify subsequent pain responses in infancy and childhood,[7] depending on the developmental stage of the infant (full-term versus preterm) and the infant's cumulative experience with pain. With later noxious procedures, full-term neonates react with heightened behavioral responsiveness, whereas preterm neonates react with a damped response. When analgesic drugs (local anesthetics or opioids) are administered before painful procedures, infants demonstrate less evidence of procedural pain and a reduction in the magnitude of long-term changes in pain behaviors.[7]

A major difficulty in assessment, and, at times, even identification of pain in children pertains to the inability of young patients to communicate with their caregiver and precisely express their distress and discomfort. During the past 2 decades, pediatric pain has received considerable attention, and reliable age-related pain scales have been developed to evaluate both the severity of pain and the efficacy of its treatment.

TABLE 92-1 MAIN ANATOMIC AND PHYSIOLOGIC FACTORS IN THE PEDIATRIC PERIOD THAT CAN INFLUENCE THE SELECTION OR PERFORMANCE OF A REGIONAL BLOCK PROCEDURE

Pediatric Factors (Mainly Infants)	Resulting Danger	Implications for Regional Anesthesia
Lower termination of spinal cord	Increased risk for direct trauma to the spinal cord	Avoid epidural approaches above L3 whenever possible.
Lower projection of dural sac	Increased risk for inadvertent penetration of the dura mater	Check for cerebrospinal fluid reflux, including during caudal approaches. Favor low approaches to the epidural space.
Delayed myelinization of nerve fibers	Easier intraneural penetration of local anesthetics	Onset time is shortened, and diluted local anesthetic is as effective as more concentrated anesthetic in adults.
Cartilaginous structure of bones and vertebrae	Reduced resistance to penetration by sharp needles	Avoid use of thin and sharp needles; use short and short beveled ones instead.
	Danger of direct trauma and bacterial contamination of ossification nuclei compromising further bone or joint growth	Do not apply excessive force on needle: if resistance is felt, stop trying to insert the needle farther.
Lack of fusion of sacral vertebrae	Persistence of sacral intervertebral spaces	Intervertebral sacral epidural approaches can be performed throughout childhood.
Delayed development of curvatures of the spine	Cervical lordosis (3-6 mo) Lumbar lordosis (8-9 mo)	Same orientation of epidural needles is appropriate whatever the spinal level before 6 mo of age; then adapt needle orientation to spinal flexures.
Changing axis of coccyx and absence of growth of sacral hiatus	Sacral hiatus comparatively smaller with increasing age	Identification of sacral hiatus becomes more difficult after 6-8 yr (increased failure rate of caudal anesthesia).
Delayed ossification and growth of iliac crests	Tuffier line, which joins anterior superior iliac spinous processes, crosses the spine at L5 or lower in infants.	This line passes over L5-S1 interspace instead of L4-L5 interspace.
Increased fluidity of epidural fat	Increased diffusion of local anesthetic up to 6-7 yr of age	Excellent blockade after caudal anesthesia can be achieved up to 6-7 yr of age.
Loose attachment of sheaths and aponeuroses to underlying structures	Increased spread along nerve paths with danger of penetrating remote anatomic spaces and blocking distant nerves	Larger volume of local anesthetic is required for epidural blocks because of leakage along spinal nerve roots. Smaller volume of local anesthetic is necessary to produce excellent peripheral blocks.
Enzymatic immaturity	Slower metabolism of local anesthetics (usually compensated by other enzyme pathways)	Increased mean body residency time and half-life, with accumulation (especially after repeat injection and continuous infusions of local anesthetic), are characteristic.
Increased extracellular fluids	Increased distribution volume and mean body residency time of local anesthetic (and most medications)	Decreased C_{max} occurs after single injection but accumulation occurs with repeat or continuous injections.
Low plasma protein content (HSA and AAG)	Competition at nonspecific HSA binding sites Limited capacity of specific binding of local anesthetic by AAG, resulting in increased plasma concentration of the free fraction	Increased unbound free fraction of all local anesthetic occurs, with greater danger of systemic toxicity
Increased cardiac output and heart rate	Increased regional blood flow resulting in increased systemic absorption of local anesthetic	Increased systemic absorption of local anesthetic occurs (decreased T_{max} and shorter duration of blockade). Increased efficacy of epinephrine. Vasoconstriction reduces absorption (thus toxicity) and prolongs duration of blockade.
Sympathetic immaturity, diminished autonomic adaptability of the heart, smaller vascular bed in lower extremities	Hemodynamic stability during neuraxial blocks	Fluid preloading and use of vasoactive agents are unnecessary.
Delayed acquisition of body scheme and conceptualization, anxiety	Inability of patients to locate precise body areas Concept of paresthesia not understandable Difficult cooperation	Nerve and space identification requires application of location techniques independent of patient's cooperation. Heavy sedation or general anesthesia is required in most patients (especially when a "dangerous" technique is planned to avoid detrimental consequences of panic attacks at a critical phase of the block procedure).

AAG, α_1-Acid glycoprotein; C_{max}, peak plasma concentration; *HSA*, human serum albumin; T_{max}, time to reach C_{max}.

PHARMACOLOGY OF LOCAL ANESTHETICS AND ADDITIVES

Two main factors influence pharmacologic properties of medications in children: (1) immaturity of some enzyme pathways and their replacement by other biochemical pathways and (2) progressive increase in body surface area concomitantly with the growth process. Drug prescriptions made according to body surface area are the same as (or in simple ratio with) adult dosing.[8] However, body surface area is not easily obtained and, in practice, doses are calculated according to body weight and require constant adaptation as the child grows up; dosage errors are not infrequent.

Local Anesthetics

Chemical properties and mechanisms of action of local anesthetics are detailed elsewhere in this book (see also Chapter 36); they are basically the same during the pediatric period and only pharmacokinetic properties may notably differ, especially in neonates and infants.[10]

Local Fixation

Schematically, local fixation is reduced and spread is increased in infants in contrast to the occurrence in adults, especially within the epidural space, because the epidural fat is more fluid and less densely packed. The main consequences are (1) shorter onset time of action, (2) more extended longitudinal and circumferential spread of local anesthetics, and (3) shorter duration of action because of reduced secondary release from local binding sites.

Regional Spread Toward the Target. The target of local anesthetic action is voltage-dependent sodium channels located within nerve fibers. Nonionized molecules can achieve penetration of only biologic membranes, and the speed of the process depends on the number and thickness (increasing with age) of sheaths.

Systemic Absorption and Distribution

Plasma Protein Binding. Nonionized local anesthetics cross almost freely the capillary wall close to the injection site. Because cardiac output and local blood flow are two to three times greater in infants than in adults, systemic local anesthetic absorption is increased accordingly and vasoactive agents such as epinephrine are very effective in slowing systemic uptake.

Once they have penetrated within the vascular bed, local anesthetics undergo plasma protein binding mainly to human serum albumin (HSA) and α_1-acid glycoprotein (AAG), or orosomucoid. HSA has a low affinity for local anesthetics, and many pharmacologic agents can compete at available binding sites. Furthermore, plasma levels of HSA are low during the first months of life, especially in premature and fasted infants; thus, the protection offered by HSA against systemic toxicity of local anesthetics is low and decreases postoperatively. The affinity of AAG for local anesthetics is 5000 to 10,000 times greater than that of HSA, which makes AAG very effective to protect the patient from systemic toxicity (which depends on the unbound free form of local anesthetics). However, again, plasma concentration of AAG is very low at birth (0.2 to 0.3 g/L) and does not reach adult levels (0.7 to 1.0 g/L) before 1 year of age.[11-13]

Because plasma concentration of the two proteins able to bind local anesthetics are low at birth, the free fraction of all local anesthetics is increased in infants; therefore, the maximum doses of all aminoamides must be significantly reduced in this age group even though the plasma concentration of AAG increases postoperatively, except in case of liver insufficiency.[13] On the other hand, the stress of surgery, particularly in infants with infection or in an emergency surgery, the plasma levels of orosomucoid may increase.[11] The increase in plasma orosomucoid concentration can change the proportion of free fraction of ropivacaine, increasing the plasma concentration of the bound fraction of this molecule and thus protecting from the systemic toxicity of local anesthetic.[14] These phenomena can largely reduce the potential risk of local anesthetics after a single injection by retaining their plasma concentration within the safety margins.

Red Cell Storage. Once in the bloodstream, local anesthetics distribute to red blood cells, which retain 20% to 30% of the total dose, depending on the anesthetic and the hematocrit. Red cell storage usually has a minor impact on the pharmacokinetics of local anesthetics except in the following situations:

- In neonates: High hematocrit values (which may exceed 70%) and enlargement of erythrocytes (physiologic macrocytosis) result in consistent "entrapment" of local anesthetics, thus lowering peak plasma concentration (C_{max}) values after a single injection but increasing secondary release, thus increasing the half-life of all local anesthetics.
- In infants: Physiologic anemia reduces red cell storage and its protective effect against systemic toxicity of local anesthetics (after a single-shot injection only) when the plasma protein binding sites are saturated—that is, close to toxic blood concentrations.

Absorption From the Epidural Space. Absorption has been rather well evaluated in the epidural space. In children and infants, the same kinetics of absorption is reported, but the younger the patient, the less accentuated is the biphasic shape of the plasma concentration curve. The peak plasma concentration and the slope of the decreasing concentration curve are increased,[15] whereas the time (T_{max}) to reach C_{max} remains basically unchanged; for example, the T_{max} of bupivacaine is approximately 30 minutes regardless of the patient's age.

Ropivacaine is a remarkable exception. After caudal or lumbar epidural injection, T_{max} is prolonged up to 2 hours in infants and C_{max} is increased.[16] This atypical pharmacokinetic profile may be explained by factors such as enzyme immaturity, slower systemic uptake, and decrease in distribution volume.[17,18] Intrinsic vasoconstrictive properties of ropivacaine also may play a role in the same way as addition of epinephrine. This significant increase in both C_{max} and T_{max} values must be kept in mind because surgeries in infants are brief and the young patient may have left not only the operating room but also the postanesthesia care unit (PACU) less than 2 hours after the caudal or epidural procedure was performed—that is, before peak plasma concentration was reached.

Importantly, levobupivacaine displays a similar pharmacokinetic profile. After caudal injection of levobupivacaine 2 mg/kg in infants younger than 2 years of age, the C_{max} range is 0.41 to 2.42 μg/mL (0.91 ± 0.40 μg/mL), which is higher than the C_{max} reported after caudal injection of the same dose of racemic bupivacaine.[19] T_{max} values also are delayed (50 minutes versus 30 minutes) in infants younger than 3 months of age as a result of reduced plasma clearance.[20]

When repeat injections are considered, the epidural dose must be reduced to keep C_{max} values in the same range as that resulting from the first injection. For the second injection, the following recommendations can be made:

- Reduce the dose to one third of the initial dose and do not inject it less than 30 minutes (lidocaine, mepivacaine, prilocaine) or 45 minutes (bupivacaine, levobupivacaine, ropivacaine) after the first injection

or

- Inject half of the initial dose, but 60 minutes (lidocaine, mepivacaine, prilocaine) or 90 minutes (bupivacaine, levobupivacaine, ropivacaine) after the first injection.

If reinjections are necessary, dosing should be further reduced to half of the second dose (i.e., one sixth of the initial dose) while respecting the same delay as for the second injection.

Continuous infusions aim to produce a steady-state concentration at the twenty-fourth hour postoperatively. This goal is easily achieved in adolescents with infusion rates of approximately 0.3 mg/kg/hr of bupivacaine and levobupivacaine or 0.4 mg/kg/hr of ropivacaine.

In infants, infusion rates must be reduced,[21,22] not exceeding 0.2 mg/kg/hr with bupivacaine (or equipotent doses of other local anesthetics) in infants younger than 4 months and 0.25 mg/kg/hr in older infants. Infants younger than 4 months (occasionally up to 9 months) may develop systemic toxicity even at these "safe" infusion rates with racemic bupivacaine because no steady-state plasma concentration is reached, even at the forty-eighth hour. In this age group, levobupivacaine[23] or ropivacaine[24] instead of racemic bupivacaine is preferred because stable plateau concentrations are obtained from the twenty-fourth hour onward.

Absorption From Other Injection Sites. Absorption of local anesthetics deposited along mucous membranes is increased in infants.[9] Mucosal topical anesthesia has long been considered contraindicated in this age group. However, the technique can be safely used with certain precautions—selection of specific transmucosal patches[25] or sprays with diluted lidocaine[26,27] and recognition that topical lidocaine exaggerates laryngomalacia.[28]

After cutaneous application of EMLA (lidocaine and prilocaine) cream, peak plasma concentrations occur 4 hours later and remain low[29]—less than 200 ng/mL for lidocaine and less than 131 ng/mL for prilocaine, even in infants younger than 6 months of age.

Absorption of local anesthetics from compartment blocks (e.g., fascia iliaca, umbilical, ilioinguinal, pudendal blocks) follows the same biphasic curve as for the epidural space.[30-33] Because of the extended surface of absorption, injection of highly concentrated solutions of local anesthetics often leads to high, occasionally potentially toxic peak plasma concentrations, especially with 0.5% ropivacaine,[33] whereas use of more diluted solutions results in rather low plasma concentrations.

Absorption from peripheral conduction blocks also follows a similar biphasic curve with different C_{max} and T_{max} values depending on the local anesthetic, the addition of epinephrine, and the site of injection; the more distal the injection, the slower is the absorption process (as in adults).

Pulmonary Extraction. After they have reached the venous bloodstream and undergone plasma protein linkage and erythrocyte storage, aminoamides reach the right cardiac cavities and then the pulmonary circulation, from which they are extracted by the lung. Their plasma concentration in pulmonary veins and then in systemic arterial circulation (especially coronary and cerebral arteries) is consistently decreased. Thus, pulmonary extraction represents a temporary protection against systemic toxicity. However, certain medical conditions suppress this protective effect. Some medications such as propranolol decrease pulmonary extraction in a clinically relevant way. Also, children with right-to-left shunts undergo considerable increase in arterial plasma concentration of local anesthetics because of pulmonary bypass; even with small doses of local anesthetics they can develop systemic toxicity.[34]

Distribution Volume. After intravenous (IV) injection, distribution volume at the steady state (Vdss) is 1 to 2 L/kg for all aminoamides (Table 92-2). After administration at other sites, calculated distribution is increased, often considerably, because of the "flip-flop" effect, especially for long-lasting local anesthetics. In infants and neonates, owing to higher extracellular fluid content (Table 92-3), the distribution volume of all local anesthetics is greater than in adults, the consequences of which are (1) significant decrease in peak plasma concentration of all local anesthetics, thus decreasing the danger of systemic toxicity after a single dose, and (2) accumulation with reinjections, which increases drug plasma concentration and elimination half-life while concomitantly decreasing clearance.

Hepatic Extraction and Clearance of Aminoamides. Short-acting local anesthetics undergo high hepatic extraction (0.65 to 0.75 ratio for lidocaine), which depends mainly on hepatic blood flow and not much on their plasma concentration. Only limited pediatric data are available for levobupivacaine. After a single injection, the clearance of levobupivacaine increases during the first months of life, but during continuous infusion (even with 0.0625% levobupivacaine), it tends to decrease almost to the same extent as for racemic bupivacaine, and plasma concentrations do not reach a plateau.[20]

Placental Transfer. In pregnant women, placental extraction may consistently affect tissue distribution of local anesthetics. Protein binding influences placental transfer. The concentration ratio between umbilical venous blood and maternal arterial blood is approximately 0.73 for lidocaine, 0.85 for prilocaine, but only 0.32 for bupivacaine. Chirality may play a role, too, at least for bupivacaine, because placental transfer of dextrobupivacaine exceeds that of levobupivacaine but only with solutions containing

TABLE 92-2 AGE-RELATED DIFFERENCES IN PHARMACOKINETIC PARAMETERS OF AMINOAMIDES

Local Anesthetic	Protein Binding (%)	Vd_{ss} (L/kg)	Clearance (mL/kg/min)	Elimination Half-Life (hr)
Lidocaine				
Neonate	25	1.4-4.9	5-19	2.9-3.3
Adult	55-65	0.2-1.0	11-15	1.0-2.2
Mepivacaine				
Neonate	36	1.2-2.8	1.6-3	5.3-11.3
Adult	75-80	0.6-1.5	10-13	1.7-6.9
Bupivacaine				
Neonate	50-70	3.9 (±2.01)	7.1 (±3.2)	6.0-22.0
Adult	95	0.8-1.6	7-9	1.2-2.9
Levobupivacaine				
Infant	50-70	2.7	13.8	4
Adult	95	0.7-1.4	28-39	1.27 ± 0.37
Ropivacaine				
Infant	94	2.4	6.5	3.9
Adult	94	1.1 ± 0.25	4-6	1.15 ± 0.41

TABLE 92-3 VARIATION OF BODY FLUID DISTRIBUTION BY AGE GROUP

Distribution of Body Fluids	Preterm Neonates (%)	Full-Term Neonates (%)	Infants (%)	Children (%)	Adults (%)
Total body fluids	80-85	70-75	65	55-60	50-55
Intracellular	20-25	30-35	35	35-40	40-45
Extracellular	55-60	45	30	20-25	20

epinephrine.[35] Most aminoesters undergo such a rapid plasma hydrolysis that placental transfer is not an issue. Tetracaine and cocaine, the hydrolysis of which is slow, are used only for topical applications or (tetracaine only) spinal anesthesia; systemic uptake is slow and plasma concentrations remain extremely low and, thus, are not issues again for placental transfer.

Metabolism. Aminoesters are rapidly hydrolyzed by plasma cholinesterases. This enzymatic activity is low at birth (but no adverse clinical consequences are to be feared) and gradually reaches adult levels by 1 year of age.[36] Chloroprocaine is eliminated at the fastest rate (4.7 mol/mL/hr), procaine at a slower rate (1.1 mol/mL/hr), and cocaine at only 0.3 mol/mL/hr. Procaine and chloroprocaine are also metabolized, in part, by hepatic cholinesterases.

Aminoamides are metabolized within the liver, where they are subjected to two types of enzymatic reactions. Phase I reactions occur first, during which oxidation of the amide link is achieved within hepatic microsomes by the cytochrome P (CYP)450 enzyme superfamily, then phase II reactions, during which glucuronic acid or aminoacid residues are appended to phase I metabolites, produce atoxic and hydrosoluble compounds, which are thus easily eliminated from the body.

CYP450 enzymatic activities are reduced during the first months of life. Bupivacaine is mainly metabolized by CYP3A4 in adults, but this enzyme is defective in infants. However, fetal CYP3A7 remains very active in infants, thus allowing metabolism of bupivacaine to be almost as effective as with CYP3A4.[9] Ropivacaine and levobupivacaine[20] are metabolized by CYP1A2, which is not fully functional before the third year, and, to a minor extent, by CYP3A4. This enzyme immaturity is clinically relevant but with limited consequences (lower clearance, delayed T_{max} and, for ropivacaine only, increased C_{max} but within clinically acceptable levels): it does not preclude administering these local anesthetics in neonates and infants.

Phase II reactions, especially glucuroconjugation, are immature at birth and remain so until the third year of life. However, other conjugation pathways such as sulfoconjugation are active and quite effective during the first months of life.

Elimination Half-Life. Elimination half-life ($t_{½}\beta$) depends on both distribution and metabolism. It can be calculated using the formula below (*Cp* is the plasma clearance and *Vdss* the distribution volume at the steady state):

$$t_{1/2}\beta = (0.693 \times \text{Vdss})/\text{Cp}$$

Basically $t_{½}\beta$ is the same in children older than 1 year of age and adults, mainly because the increase in Vdss is compensated by concomitant increase in Cp (related in part to higher hepatic blood flow in children, whose liver accounts for 4% of body weight, versus only 2% in adults). Before the age of 1 year, Cp is low and elimination half-life of all local anesthetics is prolonged (see Table 92-2), thus favoring accumulation with repeat injections. Nevertheless, Bricker and colleagues[37] measured no consistent differences in pharmacokinetic parameters between infants and adults.

Systemic Toxicity. Clinical signs of neurologic toxicity have been reported with plasma concentration ranging from 7 to 10 μg/mL for lidocaine or mepivacaine and 1.5 to 2 μg/mL (intraoperatively) to 2 to 2.5 μg/mL

(postoperatively) with bupivacaine. However, plasma concentrations of bupivacaine higher than 4 μg/mL have been reported without evidence of clinical toxicity. From studies in adult volunteers, the following thresholds of toxicity of the unbound form of local anesthetics have been defined:

- 0.3 μg/mL for unbound bupivacaine
- 0.6 μg/mL for unbound levobupivacaine or ropivacaine

Because plasma protein binding is lower in infants, hazards of systemic toxicity might be increased, the more so as cardiac toxicity is usually concomitant with, not preceded by, central nervous system toxicity. For further information on local anesthetics, see Chapter 36.

Opioids

Elimination half-life of neuraxial opioids is considerably increased in neonates and infants.[38] After epidural injection, morphine reaches its peak concentration in plasma within 10 minutes, but this concentration is very low and unable to provide clinically relevant analgesia.[39,40] Elimination half-life from cerebrospinal fluid (CSF) is similar to that from plasma, but CSF concentrations are very high after epidural injection; therefore, it takes 12 to 24 hours before they decrease below minimal effective concentrations (near 10 ng/mL). Consequently, vital parameters of children given neuraxial opioids must be monitored for 24 hours and are not eligible for outpatient surgery. Usual doses of neuraxial narcotics are listed in Table 92-4. Short-acting lipid-soluble opioids (fentanyl, sufentanil) can be used, but, as in adults, they do not significantly prolong postoperative pain relief unless repeat injections are given or a continuous infusion is established. Their analgesic effect is mainly a systemic effect, and the patient may experience acute respiratory depression (sudden apnea); this condition is very different from the progressive and delayed respiratory depression, preceded by generalized pruritus, sedation, and bradypnea, reported after excessive doses of epidural and intrathecal morphine.

TABLE 92-4 COMMONLY USED ADDITIVES AND RECOMMENDED DOSES IN PEDIATRIC REGIONAL ANESTHESIA

Additive	Recommended Doses	Maximum Doses
Morphine		
Epidural	30 μg/kg	50 μg/kg
Intrathecal	10 μg/kg	20 μg/kg
Fentanyl (epidural)	1-1.5 μg/kg	2.5 μg/kg
Sufentanil (epidural)	0.25-0.5 μg/kg	0.75 μg/kg
Clonidine (epidural or along peripheral nerves)	1-1.5 μg/kg	2 μg/kg
Ketamine* (epidural or occasionally along peripheral nerves)	0.5 mg/kg	1 mg/kg

*Preservative-free ketamine (preferably preservative-free S-ketamine).

Other Additives

Epinephrine 5 mg/L or 1/200,000 concentration is frequently coadministered with local anesthetics to decrease plasma peak concentration[30] and prolong the duration of blockade, especially in children younger than 4 years of age.[41,42] Another benefit expected from epinephrine is early detection of accidental IV injection (test dose) because young children are very sensitive to arrhythmogenic properties of epinephrine. Neuraxial epinephrine has long been suspected to elicit spinal ischemia: even though this fear proved to be unfounded, many anesthesiologists recommend using lower concentrations of epinephrine (2.5 mg/L or 1/400,000) in local anesthetic solutions administered to neonates and infants; at such concentrations, the absorption rate of caudal bupivacaine is decreased by 25%.[42]

Clonidine, like epinephrine, is an α_2-adrenergic agonist that offers several benefits in children when added to local anesthetics either neuraxially[43-45] or peripherally (see Table 92-4)[46]; it increases (by a factor of ~2) the duration of nerve blockade without eliciting hemodynamic disorders, decreases plasma peak concentration of the local anesthetics, and produces a slight sedation for 1 to 3 hours postoperatively (which does not preclude hospital discharge). Addition of clonidine often makes unnecessary the placement of a catheter to prolong postoperative pain relief, thus reducing morbidity and costs. However, its clearance in neonates is approximately one third of that in adults owing to immature elimination pathways[47] and several instances of respiratory depression in neonates and small infants have been reported[48,49]; this additive should be avoided during the first 6 months of life.

Ketamine, especially S-ketamine, is an interesting adjuvant because of its blocking effects on *N*-methyl-D-aspartate receptors and interaction with sodium channels in a local anesthetic–like fashion (it shares a binding site with local anesthetics). Coadministered at a dose of 0.25 to 0.5 mg/kg, ketamine prolongs the duration of analgesia for many hours[44,50] with no significant adverse effects.

Many other agents have been occasionally used as adjuvants to local anesthetics.[51] Even though some of them proved to have analgesic properties (corticosteroids, buprenorphine, neostigmine, tramadol, midazolam, and biodegradable bupivacaine and polyester microspheres), they all produce significant adverse effects that preclude their use in most patients. Furthermore, their administration to pediatric patients raises ethical questions, and they are not approved for pediatric use.

PHYSIOLOGIC FACTORS

Surgery generates a neuroendocrine stress response in neonates, infants, and children,[4,52] resulting in undesirable alterations of the metabolic state and immune function.[53] Epidural anesthesia diminishes or even suppresses this stress response.[54-56] Central blocks do not affect left ventricular function and are virtually free of measurable hemodynamic effects, at least up to the age

of 8 years.[57,58] Epidural anesthesia does not result in systemic or pulmonary hemodynamic changes as measured by mean blood pressure, end-diastolic diameter of the left ventricle, ejection fraction of the left ventricle, and mean velocity circumferential fiber shortening.[59] However, pulmonary Doppler flow velocity is decreased during epidural anesthesia, probably owing to an increase in the pulmonary arterial resistance. Preloading with saline is not recommended in children, and, even in adolescents, fluid therapy or injection of vasoactive agents is rarely required.

PSYCHOLOGICAL FACTORS

Children are frightened by new environmental conditions in the operating room, and most of them cannot cope with their anxiety.[60,61] They feel abandoned by their parents and exposed to strangers who are threatening them with needles. Furthermore, children younger than 10 years of age have not acquired their complete body image and cannot clearly make a distinction between adjacent parts of their body such as forearm and arm. Young patients cannot understand the concepts of paresthesia and differential blockade ("touch" is not "pain"). Thus, localization of nerve trunks and anatomic spaces requires using physical methods independent of the patient's cooperation (loss of resistance seeking, neurostimulation, ultrasound techniques). Infants and most children cannot cope with their anxiety and fear of needles; therefore, sedation or light general anesthesia is mandatory before block procedure to avoid panic attacks and unwanted movements during the procedure.

Regional anesthesia has a significant psychological impact. A pain-free postoperative course improves the morale of the patient, the family, and the nurses. Surgeons are happy to examine quiet, alert, and manageable patients. Occasionally, negative psychological effects can be observed—persistent motor (even sensory) blocks postoperatively may be frightening to some children (3 to 5 years of age especially) and their parents even though precise explanations had been given preoperatively as to the expected course of events during the postoperative period. Offering friendly environmental conditions, empathy, and additional explanations on local anesthetic pharmacology can reduce this postoperative anxiety. It should be kept in mind that a motor block must be avoided when not absolutely required for surgery.

INDICATIONS, CONTRAINDICATIONS, AND COMPLICATIONS

INDICATIONS

Indications for regional anesthesia in children are not identical to those in adults, not only because surgical pathologic processes are quite different but also because regional block procedures are used as techniques of analgesia in anesthetized children rather than in conscious or lightly sedated adult patients.

Anesthetic Indications

Some children and adolescents are occasionally willing to undergo their surgery under regional anesthesia while remaining conscious. If a regional block can provide adequate analgesia, there is no reason to refuse such management, especially for short-duration surgery. Occasionally, such a management approach can be considered in children at risk for severe complications during general anesthesia from certain problems, such as the following[62]:

- Testicular torsion or incarcerated hernia at immediate risk for rupture in nonfasted children
- Inguinal hernia repair in former preterm infants younger than 60 weeks of postconceptual age who are at risk for developing severe postoperative apnea
- Severe acute or chronic respiratory insufficiency
- Emergency conditions in children with severe metabolic or endocrine disorders
- Neuromuscular disorders, myasthenia gravis, or some types of porphyria
- Some types of polymalformative syndromes and skeletal deformities

Cervical instability (making tracheal intubation a risk for tetraplegia) is constant in Chiari syndrome and common in achondroplasia and Down syndrome. Patients with facial deformities, microstomia, and mandible abnormalities can be difficult to intubate, thus making general anesthesia a less attractive technique. Also, infants with epidermolysis bullosa are extremely difficult to manage under general anesthesia; occasionally, regional block procedures may represent an alternative with lower morbidity.[63-65] Trauma patients with extremity lesions may greatly benefit from peripheral nerve block for alleviating pain without impeding monitoring of head trauma or hemodynamic disorders and allowing wound dressing as well as temporary stabilization of fractures, provided that appropriate precautions are taken to avoid hiding development of compartment syndromes (see later).

Intraoperative and Postoperative Analgesia and Procedural Pain

Analgesia is currently the main indication for regional blocks in children because they offer the best benefit-to-risk ratio for many outpatient and inpatient surgeries: orthopedic (including scoliosis surgery), thoracic, urologic, and upper and lower abdominal surgeries.[66-68] Cardiac surgery is a more controversial indication,[69,70] and many anesthesiologists are reluctant to perform neuraxial blocks in children scheduled to receive anticoagulants.

Procedural pain can easily be anticipated and thus prevented mostly by topical anesthesia or infiltration techniques.[71-73] The indications for perineural catheters depend on the expected duration of postoperative pain.[74] Also, surgery associated with intense postoperative pain (major orthopedic surgery, hand or foot amputation) and postoperative pain management or painful physical therapy necessary for several days (knee or ankle arthrolysis, knee ligamentoplasty) are excellent indications for catheters. Nevertheless, it is important to verify the absence of any possible interference in the postoperative course; the catheter technique should not risk compromising the outcome of surgery.

A comparative evaluation of suitability, and benefit-to-risk ratio for most regional techniques is provided in Table 92-5.

Management of Nonsurgical Pain

Relief of pain associated with some medical conditions such as herpes zoster, acquired immunodeficiency syndrome (AIDS), mucosal and cutaneous lesions, and cancer can be achieved using regional block techniques.[75,76] Children with sickle cell disease may greatly benefit from epidural analgesia during vaso-occlusive crisis or thoracic syndromes with intractable pain by other means, provided that pain is localized to limited areas and concomitant fever is not due to bacteremia.[77,78]

Chronic Pain Relief and Palliative Care

Chronic pain is less unusual in children than commonly believed, and regional techniques such as epidural anesthesia, stellate ganglion blockade, or continuous peripheral nerve blocks may help treat this condition, especially in case of phantom limb pain and complex regional pain syndrome, leading to pain reduction (minimal pain scores), physiotherapy facilitation, and functional rehabilitation.[79] Treatment of intractable refractory pain from a chronic dislocated left hip with long-time perineural catheter has been described.[80] Erythromelalgia, a rare but extremely painful condition, can be successfully relieved by continuous epidural analgesia.[81] Cancer pain resulting from either primary tumor or metastases also can be controlled by regional techniques when other medications fail or produce too many adverse effects. Virtually all techniques of regional anesthesia have been reported in this ultimate management of pain in children, from epidural analgesia to intrathecal infusions to celiac or brachial plexus block.[82,83]

Nonanalgesic Indications

For certain medical conditions, analgesia is not the only benefit expected from regional blockade. Sympathetic blockade is essential to protect and improve blood supply to an upper or lower extremity in a context of severe trauma. Also, continuous epidural blockade proved to be effective in treating vascular insufficiency resulting from

TABLE 92-5 EVALUATION OF THE SUITABILITY AND BENEFIT-TO-RISK RATIO AND FEASIBILITY WITH ULTRASOUND GUIDANCE OF MOST TECHNIQUES OF REGIONAL ANESTHESIA IN CHILDREN

Technique	Ease of Performance	Benefit-to-Risk Ratio	Feasibility With Ultrasound	Catheter Placement
Central blocks				
Spinal block	+ to ++	+++	Mild	No
Caudal block	+++	++++	Easy	Occasionally
Lumbar epidural anesthesia	+++	+++	Difficult	Yes
Thoracic epidural anesthesia	+++	+++	Difficult	Yes
Sacral epidural anesthesia	++	++	Difficult	Yes
Cervical epidural anesthesia	Avoid	Very low	Avoid	Avoid
Limb plexus and peripheral nerve conduction blocks				
Interscalene block	++	++	Mild	Occasionally
Parascalene block	+++	++++	Mild	Yes
Subclavicular block	+++	+++	Mild	Yes
Axillary block	++++	++++	Easy	Occasionally
Psoas compartment block	+++	++	Difficult	Occasionally
Femoral block	+++	++++	Easy	Yes
Proximal sciatic blocks	++ to +++	+++	Mild	Yes
Subgluteal sciatic block	+++	++++	Easy	Yes
Popliteal sciatic block	+++	++++	Easy	Yes
Distal block	++ to +++	+++	No	No (except tibial nerve at ankle)
Truncal compartment blocks				
Intercostal block	++	+	No	Occasionally
Intrapleural block	++++	0 to +	No	Yes
Thoracic paravertebral block	++	+	Difficult	Yes
Rectus sheath block	++++	+++	Easy	No
Ilioinguinal-iliohypogastric nerve block	++++	+++	Easy	Occasionally
Transabdominis plane block	++++	+++	Easy	Occasionally
Penile block	++++	++++	Mild	No
Pudendal nerve block	+++	+++	Difficult	No
Facial blocks				
Trigeminal superficial block	++++	++++	Mild	No
Suprazygomatic maxillary nerve block	+++	+++	Mild	Occasionally
Mandibular nerve block	+++	+++	Difficult	No
Other techniques				
Bier block	++ to +++	+	No	No
Wound infiltration	++++	+++	No	Yes
Topical anesthesia	++++	++++ (skin)	No	No

Kawasaki disease, accidental intraarterial injection of an anesthetic drug,[84] penile block with a local anesthetic containing epinephrine, and severe frostbite. Axillary and stellate ganglion blocks have also successfully treated acute vascular insufficiency of the upper limb.[85]

CONTRAINDICATIONS AND LIMITATIONS

Absolute Contraindications to Neuraxial Blocks

Medical conditions that contraindicate neuraxial blocks in children are (1) severe coagulation disorders, which may be constitutional (hemophilia), acquired (disseminated intravascular coagulation), or therapeutic; (2) severe infection such as septicemia or meningitis; (3) hydrocephaly and intracranial tumoral process; (4) true allergy to local anesthetics (a very rare condition even with aminoesters); (5) certain chemotherapies (such as with cisplatin) prone to induce subclinical neurologic lesions that can be acutely aggravated by a block procedure; (6) uncorrected hypovolemia; and (7) cutaneous or subcutaneous lesions, whatever their nature (infection, angioma, dystrophic or tumoral, tattoo) at the contemplated site of puncture. Parental refusal is a nonmedical absolute contraindication.

Depending on the clinical condition of the patient and the possibility to cure (at least temporarily) the impeding disorder, a regional block may be considered in spite of the existence of a contraindication. After correction of hypovolemia, injection of factor VIII to a hemophilic child, or effective antibiotic treatment of a septicemic patient,[86] a central block may be performed, provided that the expected benefits consistently outweigh the risks by comparison with other techniques of analgesia. Also, some authors consider it acceptable to perform a caudal block in children with shunt devices under protection of antibioprophylaxis.[87]

Absolute Contraindications to Peripheral Nerve Block Procedure

True allergy to local anesthetics is the only absolute medical contraindication to peripheral nerve blocks. Coagulation disorders are less hazardous than during neuraxial blocks, but it is prudent to avoid techniques with a danger of arterial trauma, especially in an area where compression is difficult or impossible (supraclavicular brachial plexus block, psoas compartment block). Septicemia does not necessarily contraindicate peripheral nerve blockade if expected benefits are significant. Local skin infection at the puncture site should be considered before performing a peripheral nerve block, especially if a catheter is implanted. Hypovolemia should preferably be corrected but does not preclude peripheral blocks because hemodynamic consequences are minimal.

Patients at Risk for Compartment Syndrome

Because pain is one of the cardinal symptoms of a compartment syndrome, any pain treatment, including regional anesthesia, is often claimed to be contraindicated because it can suppress this manifesting symptom, thus delaying the rescuing surgery. Such a refusal of pain management is not acceptable either medically and ethically.[88] Fractures are very frequent in the pediatric population, whereas compartment syndromes are very rare; whether or not a compartment syndrome is in progress, intense pain is a constant feature. Adequate pain management, including continuous epidural analgesia,[89] does not preclude early diagnosis, and this fact was confirmed by the National Pediatric Epidural Audit in Great Britain.[90]

Excruciating pain is not a "manifesting" symptom but a late—possibly too late—symptom of compartment syndrome. Patients at risk should be monitored adequately, which is not done most of the time even in university hospitals, and precautions must be taken—that is, avoidance of closed plaster casts; elbow immobilization with an angle greater than 90 degrees[91] closed reduction of supracondylar fractures of the humerus, repeat clinical evaluation of the distal perfusion and tissue oxygenation of the limb; and noninvasive monitoring of the intracompartmental pressure, even though this monitoring is not 100% reliable. If the risk is considered high (e.g., displaced humeral fractures, intramedullary nail fixation of tibia or radius, obtunded patients), intracompartmental pressure close to the fracture site should be invasively monitored. The procedure is easy and almost inexpensive, requiring only a venous cannula, an IV line, and a pressure gauge (as for central venous pressure measurement).[92,93]

Hemoglobinopathies

Children with sickle cell disease are prone to develop hemolysis in case of desaturation and undergo repeat episodes of extreme pain as a result of extended microthromboses when local blood flow slows down (e.g., hemoconcentration, shock, surgical tourniquet).[94] In the case of a danger of hypoxemia (respiratory disease) or hemodynamic disorders (surgery known to produce significant blood loss, tourniquet placement), regional (especially neuraxial) blocks should be avoided.

Bone and Joint Deformities

Minor or localized malformations of the spine (hemivertebra, spina bifida occulta, Scheuermann disease) do not preclude neuraxial blocks, whereas extended malformations of vertebrae, spinal fusion, myelomeningoceles, open spina bifida, and major spondylolisthesis are contraindications. Tethered cord syndrome is not unusual and is often misdiagnosed. Neuraxial blockade may increase the overall morbidity of patient management because it facilitates excessive bending or extension of the spine that can occasionally damage the spinal cord permanently. The diagnosis must be suspected if a clump of hairs or a dystrophic lesion of the skin is present at the lower extremity of the spinous process line or in the case of minor neurologic disorders involving pelvic nerves (minimal sphincter disorders, perineal dysesthesia). Even though some authors consider that this condition is not a contraindication,[95] it is preferable to select another technique of analgesia than epidural blockade. Many pediatric syndromes, cerebral palsy, and kyphoscoliosis are associated with bone and joint deformities that represent more of a technical difficulty than a contraindication to performing a regional block.

Preexisting Neurologic Disorders or Diseases

Controlled epilepsy is not a contraindication to regional anesthesia, including neuraxial blockade. Preexisting central nervous system disorders and degenerative axonal diseases have long been considered to be contraindications, at least relative, even though no data support the hypothesis that a regional block could worsen their course.[96] A recent pediatric study involving 139 patients showed that preexisting neurologic disorders were not associated with bad neurologic outcome (rather, the reverse was observed) after central block procedures.[97]

COMPLICATIONS

Complications of regional anesthesia are basically the same as in adults. The complication rate found recently in a large epidemiologic study was 0.12%, with two major risk factors—age and the central blocks.[98] They can be classified as local, regional, and general (or systemic).

Local Complications

The four main types of local complications are as follows:

1. Inappropriate needle insertion damaging the nerve and surrounding anatomic structures
2. Tissue coring and introduction of epithelial cells into tissues where they do not belong and where they can develop as compressive tumors (especially in the spinal canal)[99]
3. Injection of neurotoxic solutions (syringe mismatch, epinephrine close to a terminal artery)
4. Leakage around the puncture site, especially when a catheter has been introduced, which may cause partial block failure and favor bacterial contamination (very rare)

These local complications are easily avoidable by using adequate devices and applying standard precautions (appropriate dressing and bacterial precautions). Tunneling the catheter and applying a slightly compressive dressing can reduce leakage around the catheter.

Local anesthetics are locally toxic. Myelin, effective protection of nerve roots, is less abundant or absent in children, potentially making the nerves more sensitive to local anesthetics. In animals, it has been clearly demonstrated that the sensitivity of nerve fibers to local anesthetics is inversely correlated with age.[100] However, in most cases, perineural injection is around muscle. The myotoxicity of local anesthetics has been previously demonstrated in humans and animals,[101] primarily through mitochondrial damage. This also has been demonstrated in young animals.[102] By comparing continuous bupivacaine perineural administration in adult rats and young rats, the authors showed that muscle, mitochondrial, and ultrastructural toxicity was significantly greater in the juvenile group,[102] thus emphasizing the need to use lower dosages in younger patients.

Systemic Complications

Systemic complications usually result from accidental IV injection of local anesthetics or, less frequently, excessive dosing.[10,103] Systemic toxicity is essentially of two types: neurologic and resulting from heart failure by blocking sodium and potassium channels. Early signs of neurologic toxicity (tinnitus, malaise, metallic taste in the mouth) are unfortunately masked by general anesthesia. The main events are heart conduction disorders, cardiac arrhythmias (bradycardia or tachycardia), and atrioventricular block. QRS widening, bradycardia, and torsade de pointes are followed by ventricular fibrillation, asystole, or both.[104] Nevertheless, signs of cardiac and neurologic toxicity occur at lower plasma concentrations of bupivacaine than ropivacaine.[105] This toxicity may be aggravated by a decrease in plasma binding protein, mainly α_1-glycoprotein acid, resulting in a greater proportion of the unbound form of local anesthetic. The plasma concentration of this protein is low at birth, tends to increase with the age of the child to reach values equivalent to those of adults at the age of 10 months.[106] However, special care must be taken during continuous injections; the dosage of local anesthetic should be systematically reduced in very young children or after prolonged administration (>48 hours).

Systemic complications can be life-threatening and should be managed in the same way as in adults. The major difference between adults and children is that cardiovascular complications are not preceded by neurologic signs but are concomitant with cerebral toxicity.[107] In addition to pharmacokinetic factors, the rapid heart rate of children may increase the risk for cardiac toxicity induced by local anesthetic toxicity. Even if toxic events occur with ropivacaine, small doses of epinephrine should produce rapid recovery. Impaired ventricular conduction is the primary manifestation of local anesthetic toxicity. Treatment includes oxygenation, cardiac massage, and epinephrine, which is given in small incremental boluses beginning with 1 to 2 μg/kg.[108] If ventricular fibrillation persists, defibrillation (2 to 4 J/kg) is performed. Although resuscitation measures must be initiated immediately, the specific treatment of local anesthetic toxicity is rapid administration of Intralipid (Kabivitrum, Stockholm, Sweden). The recommended dose of 20% Intralipid for pediatric patients is 2 to 5 mL/kg by IV bolus. If cardiac function does not return, this dose (up to 10 mL/kg) is repeated.[9]

Epidemiology

Available pediatric information is limited. The first report of the American Society of Anesthesiologists (ASA) closed malpractice claims contained 238 pediatric cases (10% of claims), but only 7 involved children given a regional block procedure[109]; however, at that time regional anesthesia was not commonly used in American children, making this apparently low rate of complications meaningless. In 1996, the 1-year prospective study of the French-Language Society of Pediatric Anesthesiologists evaluated 85,412 pediatric anesthetic procedures, including 24,409 involving regional anesthesia.[110] Twenty-three complications (no sequelae, no death, and no legal consequences) were found, all following neuraxial blocks. In 2000, the Australian Incident Monitoring Study[111] included 2000 claims involving 160 pediatric cases with a regional block procedure (83 epidurals, 42 spinals, 14 brachial plexus, 4 Bier blocks, 3 ophthalmic blocks, and 14 local infiltrations). The largest single cause

of complications was circulatory problems, 24 drug errors (including 10 "wrong drugs" and 14 "inappropriate use") were found. In 2007, the British National Pediatric Epidural Audit[90] reported 96 incidents in 10,633 epidural blocks performed, as follows:

- Fifty-six (0.53%) were associated with the insertion or maintenance of epidural anesthesia, and most were of low severity; only one child had residual effects from cauda equina syndrome (after a programming error of the infusion pump).
- Forty (0.38%), mainly pressure sores,[31] were believed to be associated with the epidural infusion technique.

A significantly higher rate of incidents occurred in the neonatal age group, mainly because of drug errors (13 cases) and local anesthetic toxicity (1 case); these incidents were not related to catheter insertion. Twenty-eight infection-related incidents occurred, of which 85% were relatively minor skin infections; caudal catheters did not result in increased incidence of infections. Six children older than 8 years of age had mild postdural puncture headache. Four patients developed a compartment syndrome, but the condition was not masked by the epidural infusion.

From November 2005 to October 2006, a large epidemiologic study recorded the characteristics and developments of regional anesthesia in children in 47 French hospitals.[98] As previously demonstrated by Rochette and colleagues,[112] the authors reported a radical change in regional practice among French anesthesiologists with a transition from using predominantly neuraxial blocks to peripheral nerve blocks, including catheter techniques. A recent 1-year prospective survey of regional anesthesia evaluated complications and side effects on 31,132 cases of regional anesthesia. Complications (41, involving 40 patients) were rare and usually minor and did not result in sequelae. The study recorded a very low overall rate of complications of 0.12%, significantly six times lower for peripheral blocks than for neuraxial blocks. Age was also a risk factor, because the incidence of complications was higher before 6 months of life than after (0.4% versus 0.1% after 6 months of life). Fifteen cases of cardiotoxicity were observed, of which 87% occurred with a central block. The occurrence of complications does not seem to increase with the use of catheters.

In conclusion, regional block procedures—mainly neuraxial blocks—are associated with the occurrence of adverse incidents (~0.5%) that are mostly minor but occasionally severe. The majority of these complications result from insufficient precautions at the time of the block procedure (drug errors) and postoperatively (pressure sores). Also, of major importance is the fact that compartment syndrome is not hidden by a regional procedure provided that adequate monitoring is guaranteed.

SELECTION OF MATERIALS AND ANESTHETIC SOLUTION

SELECTION OF BLOCK PROCEDURE

Careful selection of block procedures is based first on anatomic considerations. Sensory blockade must cover all areas from which noxious stimuli can originate (e.g., operative field, sites for skin or bone graft tissue, placement of tourniquet or drains). Then, the potential morbidity of the technique, from the medical condition of the patient, the requested positioning, or the "intrinsic" morbidity of the technique itself, must be evaluated. The anticipated duration of postoperative pain is the third most important factor to take into account because the regional technique should provide adequate analgesia until minor analgesics are sufficient. The anesthesiologist will select one of the following approaches:

- A single-shot technique with either a short-acting or a long-acting local anesthetic
- A single-shot technique with local anesthetic and adjuvants
- A catheter technique with repeat or continual injections of local anesthetic

SELECTION OF EQUIPMENT

Epidural anesthesia (sacral, lumbar, or thoracic) is performed using Tuohy needles ranging in size from 22 to 17 gauge and in length from 50 to 90 cm; shorter Tuohy needles (25 cm) would be more appropriate in neonates and infants but are not easily available. Caudal anesthesia has been performed in the past with almost all types of needles. This is no longer acceptable, and only short beveled needles (Crawford needles) with a guide sealing their lumen or IV cannulas with an introducer needle should be used.

Spinal anesthesia in premature infants can be performed using either a neonatal lumbar puncture needle (22 gauge) or, preferably, a thinner spinal needle (shorter than 50 mm). The distal end of the needle does not have the same importance as in adults because the incidence of postdural puncture headache remains (very) low in children and is not influenced by the design of the tip of the needle.[113,114] What matters most is the distance separating the tip of the needle from its distal orifice; this distance must be as short as possible to avoid extradural leakage if the needle has not been introduced far enough through the dura mater. Pencil-point needles have no advantage in infants and young children; they do not improve the results and are even suspected to decrease the success rate by favoring subdural spread of the local anesthetic. A summary of recommended needles for most regional block procedures in pediatric patients is provided in Table 92-6.

SELECTION OF DRUG

The prerequisites for selecting a local anesthetic are not exactly the same in children as in adults because regional techniques are mostly used for analgesic purposes rather than anesthesia. The factors to be considered are (1) site and severity of surgery, (2) expected duration of intense postoperative pain, and (3) hospital stay versus early discharge. Usual doses are listed in Table 92-7.

Lidocaine and mepivacaine are preferred for outpatient surgery. For inpatient surgery, ropivacaine, levobupivacaine, and bupivacaine are commonly used. Nevertheless, it is now recommended that L-enantiomers be used especially

TABLE 92-6 RECOMMENDED DEVICES FOR MOST REGIONAL BLOCK PROCEDURES IN CHILDREN

Block Procedure	Recommended Device	Alternate Device
Intradermal wheals and metacarpal blocks	Intradermal needles (25 gauge)	None
Subcutaneous infiltrations and field blocks	Standard intramuscular needles (21-23 gauge)	Intradermal needles (25 gauge)
Compartment blocks (thoracic paravertebral, rectus sheath, ilioinguinal-iliohypogastric, pudendal, penile)	Short (25-50 mm) and short beveled (45-55 degrees) needles	Epidural needles (intercostal block) Neonatal spinal needle
Peripheral mixed nerve blocks and plexus blocks	Insulated 21-23 gauge short beveled needles of appropriate length connected to a nerve stimulator (0.5-1 mA) Specific catheter (for continuous techniques)	Sheathed pencil-point needles Unsheathed needles only when ultrasound guidance is used Epidural catheter (for continuous techniques)
Spinal anesthesia	Spinal needle (24-25 gauge; 30, 50 or 100 mm long, Quincke bevel, stylet)	Neonatal lumbar puncture needle (22 gauge, 30-50 mm long) Whitacre spinal needle
Caudal anesthesia	Short (25-30 mm) and short beveled (45-degrees) needle with stylet	IV cannula (22-18 gauge), especially for epidural catheter insertion Pediatric epidural (occasionally spinal) needle
Epidural anesthesia	Tuohy needle (22, 20, and 19/18 gauge); LOR syringe and medium epidural catheter	Crawford, Whitacre, or Sprotte epidural needles appropriately sized; LOR syringe and medium epidural catheter

LOR, Loss of resistance.

TABLE 92-7 USUAL AND MAXIMUM RECOMMENDED DOSES OF LOCAL ANESTHETIC FOR CONDUCTION NERVE BLOCKS (EXCLUDING BIER BLOCKS AND SPINAL ANESTHESIA)

Local Anesthetics	Usual Concentration (%)	Maximum Dose of Plain Solution (mg/kg)	Maximum Dose With Epinephrine (mg/kg)
Aminoesters			
Procaine	1-2	7	10
Chloroprocaine	2-3	7	10
Aminoamides			
Lidocaine	0.25-2	5 (or 400 mg)	10 (or 700 mg)
Mepivacaine	0.25-2	5-7 (or 400 mg)	Not available
Bupivacaine	0.125-0.5	2 (or 150 mg)	3 (or 200 mg)
Levobupivacaine	0.125-0.5	3 (or 200 mg)	4 (or 250 mg)
Ropivacaine	0.1-10	3 (or 300 mg)	Not available (and not recommended)

for continuous infusions; they are well known for their lower cardiac toxicity compared with bupivacaine.[115] The pharmacologic characteristics of ropivacaine can achieve a differential nerve block[116] and have limited myotoxicity in contrast to bupivacaine.[117] After extravascular injection, the plasma concentration of ropivacaine peaks later than that of bupivacaine, sometimes up to more than 2 hours after injection.[18] This delay in the peak plasma concentration of ropivacaine usually reduces the maximum plasma concentration, providing some security in terms of toxicity, as demonstrated in some pediatric studies.[18,118] Even if the plasma concentration of free and total ropivacaine is higher in younger children, plasma concentrations of ropivacaine and its main metabolite (2,6-pipecoloxylidide) are not influenced by the duration of infusion of local anesthetics. In infants younger than 3 months of age, epidural infusion of ropivacaine should not be maintained for more than 36 hours.[119] The clearance of ropivacaine increases with age but remains unchanged throughout the infusion in each age category. Ropivacaine seems more appropriate, more predictable, and safer during continuous infusion for 48 to 72 hours than bupivacaine; the plasma concentration of bupivacaine increases and clearance decreases in proportion to the duration of infusion.[120] Studies examining the pharmacokinetics of local anesthetics during continuous perineural administration are rare in children. The safety of continuous regional anesthesia techniques in children relies on the use of low-concentration solutions accompanied by low plasma concentrations of local anesthetics (LAs) and limit the risk for systemic toxicity of these molecules. Addition of clonidine or ketamine helps improve the quality and duration of blockade without precluding early hospital discharge. In many cases, these drugs make it unnecessary to insert a catheter and establish a continuous infusion to provide adequate postoperative pain relief.

For many years, continuous epidural anesthesia was the only suitable technique for treating protracted pain. In recent years, peripheral nerve catheter techniques have proved to be effective,[67] with less morbidity and limitations than continuous epidural blockade, even allowing hospital discharge[79] and management at home in selected pediatric patients. For these techniques, continuous infusion (2 to 5 mL/hr) or on-demand injections (2 to 5 mL) of low-concentration levobupivacaine or ropivacaine (0.1% to 0.2%) represents the best and safest choice.

Patient-controlled administration of continuous infusion seems to be better in children, allowing decrease of the dose of local anesthetics for the same quality of analgesia.[121,122] Duflo and associates[122] comparing standard continuous administration (0.1 mL/kg/hr) and patient controlled regional anesthesia regimen (infusion of 0.02 mL/kg/hr and bolus of 0.1 mL/kg every 30 minutes) of 0.2% ropivacaine in patients undergoing fascia iliaca compartment or sciatic catheters noted lower hourly consumption of ropivacaine in patient-controlled administration. Ropivacaine plasma levels were also lower in this group in contrast to standard administration (0.31 and 0.86 mg/mL at 24 hours and 0.31 and 0.52 mg/mL at 48 hours). In a recent study, plasma levels of ropivacaine were collected and compared with continuous epidural block and continuous psoas compartment block in children.[123] The dose of local anesthetic infusion was 0.2 mg/kg/hr of 0.2% ropivacaine in the continuous psoas compartment block. The median plasma concentrations of ropivacaine did not exceed 0.59 μg/mL in this patient group and was lower than the plasma concentration in the epidural catheter group.

ANATOMIC IDENTIFICATION IN REGIONAL ANESTHESIA

MANUAL APPROACHES

The success of a regional anesthesia technique depends on the administration of a solution of local anesthetic close to the nerve or space limited by anatomic structures and fascial permeable little crosses by blocking nerve structure. Few nerve blocks can be performed using a manual approach without the aid of a nerve stimulator or ultrasound. These techniques are feasible in children anesthetized or sedated.

Some important points for performing regional anesthesia without any devices are as follows:

- Possessing good knowledge of the anatomy of the child according to age and good location of landmarks for the puncture site
- Defining the anatomic space at which the local anesthetic spreads to block the selected nerves
- Ensuring no risks exist for damage to other surrounding structures (e.g., vessels, nerves, organs)

Central blocks (caudal, epidural, or spinal block) are among the blocks that primarily can be achieved without assistance from technical devices, even though ultrasound-guided techniques for punctures are currently proposed. The realization of epidural block is facilitated by the loss of resistance (LOR) technique. For the spinal block, passing into the subarachnoid space is marked by the crossing of the dura mater (tough fibrous structure): a slight jump is felt, and then the flow of CSF. For the caudal block, the passage of the sacrococcygeal membrane is felt by an increase and loss of resistance in the needle. The majority of limb peripheral nerve blocks are performed using a nerve stimulator or with ultrasound guidance. Blocks of the trunk, performed with anatomic landmarks techniques for a long time, benefit greatly from ultrasound guidance for their localization, excepting the penile block (being evaluated with ultrasound guidance). The pudendal block, even if it is done using anatomic landmarks, also can benefit from using the neurostimulator to be closer to the nerve[124] or ultrasound guidance.[125] The superficial trigeminal nerve blocks on the face, described by anatomic landmarks for a long time, can now benefit from ultrasound guidance for the puncture.[126] Finally, further techniques, such as the paresthesia technique, transarterial techniques for the axillary block, and "swoosh" (test of good hand position by auscultation with a stethoscope of the caudal vertebrae low back during the injection of liquid into the needle) test for caudal block, should no longer be used.

Electrical Stimulation

Ultrasound guidance represents a revolution in regional anesthesia in children and adults. Despite its growing use, electrical stimulation remains the gold standard of nerve location in adults and children. Nerve stimulation equipment has largely improved and is clinically safer. The location of needle entry point before puncture can reduce the number of attempts and decrease the potential risk for nerve injury.[127]

For plexus and truncular nerve blocks, the anesthesiologist should use a nerve stimulator to elicit muscle twitches. The positive electrode of the nerve stimulator is placed distant to the nerve location. The nerve stimulator delivers square-wave electric impulses lasting 50 to 100 microseconds at the rate of 1 to 5 Hz. With a starting output of 2 to 2.5 mA, needles are advanced until they elicit the required muscle movement. The position is judged adequate when muscle contractions continue to occur at a current of 0.5 to 0.8 mA, when the tip of the needle is approximately 1 mm from the nerve or within the perineural fascial sheath. In contrast to adults, in whom a current of 0.5 mA or less is considered an acceptable indicator for a successful nerve block,[128] in children, if muscle contractions are still present at a current under 0.5 mA, the needle should be withdrawn to avoid intraneural injection and nerve damage.[129] Gurnaney and colleagues[130] evaluated the relationship between the lowest current amperage used to obtain a motor response, the success rate, and the incidence of neurologic complications with peripheral nerve blocks in pediatric patients under general anesthesia. The authors observed a similar peripheral nerve block success rate with both a low (<0.5 mA) and a high stimulation threshold (0.5 to 1.0 mA). They concluded that it may not be necessary to perform needle manipulation in close proximity to the nerve to achieve a low stimulation threshold (<0.5 mA), because it may increase the risk for intraneural injection. Most importantly, in performing peripheral nerve blocks in

anesthetized children, the needle should not be intrafascicular. The disappearance of the motor response by reducing the intensity under 0.5 mA for 0.1 msec, confirms that the tip of the needle is not in contact with axons. In adults, Bigeleisen and associates[131] revisited the relationship between minimum stimulating current and intraneural needle placement in a clinical investigation comparing intraneural and extraneural stimulation thresholds in ultrasound-guided supraclavicular block. Intraneural stimulation thresholds in excess of 0.2 and less than 0.5 mA were observed in 54% of patients. In 10% of patients, the stimulating threshold exceeded 0.5 mA when the needle was in an intraneural location. Thus, a response obtained for a current intensity less than 0.2 mA for 0.1 msec may be associated with an intrafascicular position of the needle and should be avoided.

Peripheral nerves are not as deep in children as in adults and can be located percutaneously. By using the nerve mapping technique the success rate of peripheral nerve blocks in children can be improved.[132] Nerve mapping helps locate the needle entry point before puncture, thereby reducing the number of attempts and decreasing the potential risk for nerve injury.

Nerve stimulation can be used for ultrasound guidance training. Concomitant use of nerve stimulation can increase the confidence of the trainee while lessening the anxiety of the attending instructor. Other common sources of error during novice practice and beyond include failure to distinguish between adjacent isoechoic structures.[133]

Ultrasound Techniques

Ultrasonographic guidance for regional anesthesia in children has seen considerable interest recently. The benefit of this technique is the visualization of targeted nerves or spaces and the spread of injected local anesthetic.

Today, thanks to the improved resolution of ultrasound machines, the majority of peripheral nerves for regional anesthesia can be visualized in children. However, the nerves are not static structures and can move, depending on the position of the child, pressure of the probe to the skin, and progression of the needle or injection of local anesthetic. In children, the linear ultrasound probe with a 25-mm active surface area (or probes with 38 mm of active surface area in older children), provides a square image that is not deformed. Probes with frequencies of 8 to 13 MHz offer excellent resolution for superficial structures of the upper limb (e.g., axillary block) and good penetration depth for the lower extremity (e.g., popliteal block). The higher frequencies could provide images that will be sharp for superficial structures. In principle, the needles typically used to perform peripheral nerve blocks can be used with ultrasound guidance. In vitro, results have shown that visualization of the needle depends on its diameter and mainly the angle of penetration.[134] Use of a facet-tipped needle for peripheral nerve blocks facilitates precise placement of the needle with minimal pain for child,[135] which seems particularly interesting for blocks performed in children without sedation or general anesthesia. Sterile preparation of the probe and the block site is an important prerequisite for ultrasound-guided blocks. A sterile probe cover should be used for single and continuous block techniques.

The easiest ultrasound-guided blocks are axillary blocks, femoral blocks, fascia iliaca compartment blocks, caudal blocks, ilioinguinal blocks, and paraumbilical blocks.[136] They permit a safe and easy learning curve of these techniques. The main advantage of ultrasound-guided regional anesthesia is the visualization of different anatomic structures and the approximate localization of the tip of needle. The other advantages for ultrasound-guided peripheral nerve blocks in children are faster onset time of sensory and motor block, longer duration of sensory blockade,[137] increase of blockade quality,[137,138] and reduction of local anesthetic injections.[138.139] The use of ultrasonographic guidance for central block allows visualization of different structures, spine, and spinal contents. Spinous process, ligament flavum, dura mater, conus medullaris, and CSF are identifiable, and give some information on spine, epidural space, and the depth between epidural space and skin.[140] Finally, in a caudal block, ultrasound imaging permits evaluation of the anatomy of the caudal epidural space, especially the relation of the sacral hiatus to the dural sac, and the search for occult spinal dysraphism.[141] Recently, ultrasound imaging showed its superiority over the swoosh test when performing a caudal block.[142] Anterior displacement of the posterior dura mater during saline or LA injection is a predictor of block success. This ultrasound-guided puncture improves the efficacy and safety of the central blocks by reducing the number of punctures. Unfortunately, the image quality is rapidly altered with ossification of the structures occurring in older children.[143]

A comparative evaluation of feasibility with ultrasound guidance for most regional techniques is provided in Table 92-5.

SAFETY, PRECAUTIONS AND DISCHARGE CRITERIA

ACCEPTABLE ENVIRONMENTS FOR PERFORMING A REGIONAL BLOCK

Regional techniques are techniques of anesthesia; therefore, they must be performed only in places where all the monitoring, anesthetic, and resuscitation equipment (including anesthetic and emergency drugs) is available. Additionally, the anesthesiologist must be assisted by staff members able to provide adequate patient monitoring and trained to help in emergency situations. The operating theater represents the best location to guarantee safe performance of any type of regional anesthesia.

SEDATION AND GENERAL ANESTHESIA

Regional procedures are performed in conscious adult patients, with or without sedation, but usually not under general anesthesia. In some pediatric patients, the same management can be offered and is sometimes requested by the child.[144] However, most children require being unconscious during the block procedure. If general anesthesia is not medically contraindicated, it is widely accepted that regional blocks be performed with the patient under light general anesthesia.[68,98,145]

PATIENT MONITORING AND SAFETY PRECAUTIONS DURING THE BLOCK PROCEDURE

Monitoring and Anesthesia Chart

Even if general anesthesia is not used and the surgical procedure is primarily based on a regional technique, the anesthesiologist should always apply routine intraoperative monitoring, including electrocardiographic (ECG) tracings and blood pressure, temperature, respiratory rate, and oxygen saturation measurements. An IV line must be established before any injection of local anesthetic,[146] and vital parameters, techniques, and doses of local anesthetics must be reported on a detailed anesthesia chart.

Technique of Injection

Techniques in adults and children are similar. Of prime importance is to evaluate the effects on ECG tracings of a test dose containing epinephrine (0.1 mL/kg up to 3 mL containing 0.5 to 1 μg/kg of epinephrine) for 30 to 60 seconds: Any elevation of ST segment or increase in T-wave amplitude,[147-149] followed by an increase in blood pressure but only occasionally by tachycardia, suggests inadvertent IV injection and necessitates cessation of the procedure; when epinephrine is contraindicated, isoproterenol 0.05 to 0.1 μg/kg should be used instead.[150]

Assessment of the Block

After every block procedure, the quality and extension of analgesia must be evaluated before surgical incision. However, this evaluation is difficult, even in conscious children. Gentle skin pinching is the most dependable technique of sensory testing, especially in lightly anesthetized children. Postoperatively, this evaluation should be comparative (blocked versus nonblocked areas) and requires that the child has gained the confidence of the caregiver, cannot see what is being done, and is not influenced either by the caregiver or the family. Electrical stimulation using a nerve stimulator at different threshold intensities proved to be suitable in healthy volunteers, but data on children are limited. Skin temperature is not suitable, and whether pupillary reflex dilation of 0.2 mm is sensitive to the loss of analgesia is not clinically useful.[151]

Prevention of Irrelevant Medicolegal Claims

In situations of an adverse event after a regional procedure, the first condition incriminated is the block procedure per se, even though most often a closer analysis rarely confirms that the regional block cause the alleged consequence or damage. To minimize irrelevant medicolegal claims, the recommendations listed in Box 92-1 should be followed whenever possible.

BOX 92-1 *Basic Safety Recommendations for Any Type of Regional or Local Anesthesia Aiming to Avoid Irrelevant Medicolegal Claims*

1. Evaluate carefully the physical status of the patient and ask for complementary laboratory, radiographic, or any other examination whenever useful.
2. Select the least hazardous technique for a given block.
3. Provide detailed explanations concerning the scheduled anesthetic management, including beneficial as well as potentially detrimental effects, even in emergency situations.
4. Discuss the possibility of block failure and explain what replacement procedure(s) will then be used.
5. Obtain written consent for anesthesia care.
6. Manage the patient in the same way and with the same monitoring procedures as recommended for the same surgical procedure under general anesthesia.
7. Fill in an anesthesia chart detailing the monitoring procedures, vital parameters, techniques and doses used, and adverse effects if any.
8. Treat all complications and provide full details with precise timing.
9. Transfer all pediatric patients to a pediatric acute care unit, requesting appropriate monitoring of vital functions and repeat evaluations of the extension and quality of blockade. Data are to be reported on a detailed postanesthetic chart, and discharge should be allowed only when objective signs of recovery are obtained.
10. Keep hospitalized at least overnight all patients given epidural or intrathecal morphine in units where their respiratory function will be regularly or continuously monitored (hourly for the first 6 hours, then every 2 hours).

POSTOPERATIVE MONITORING IN THE RECOVERY ROOM

After combined regional and general anesthesia, all children must be transferred to a recovery room (PACU), where the stability of respiratory and hemodynamic status is checked in the same way as after any general anesthesia. In addition to this standard postanesthetic care, they require repeat evaluations of the anesthetized area. In the case of motor blockade, which should be avoided as often as possible, it is important to verify that its distribution corresponds to the area supplied to the blocked nerve. Motor blockade is a stressful condition; therefore, children and their parents should be comforted, and the information that it is just a time-limited condition should be repeated. Patient positioning must be carefully and regularly checked to avoid pressure points. Anesthetized areas must also be protected from the patients' inadequate behavior, imprudence, or attempts to remove dressings. The possibility that a compartment syndrome is evolving must always be kept in mind, and both the hemodynamic status of the relevant limb and the quality of analgesia must be repeatedly evaluated.

Urinary retention can be of concern after neuraxial blocks. In many institutions, however, voiding is not requested before discharging the child. It may be prudent to keep infants and disabled children in the PACU until they have urinated or to check their bladder content with an ultrasound probe, especially after hypospadias repair, because the incidence of urinary retention is greater than usual in this surgery.[152]

Adult surgical patients under regional blockade often bypass the postanesthesia recovery room. In children, even if no sedative has been given, it is not wise to do so, and adequate monitoring and skilled assistance improve recovery from immediate postoperative incidents.[153] After

short procedures, sudden cessation of external stimulation may unmask some compensated adverse effects (hemodynamic and respiratory especially) that are not harmful if detected early. As noted earlier, ropivacaine and, to a lesser extent, levobupivacaine, have a longer T_{max} (up to 2 hours) and C_{max} in infants; therefore, after short-duration surgeries, these patients may leave the operating room before local anesthetic plasma peak concentration has been reached. It is recommended to keep them monitored in a PACU up to 2 hours after the block procedure.

DISCHARGE CRITERIA AFTER SINGLE-SHOT PROCEDURES

The same criteria apply with discharge from the PACU as with after general anesthesia (pediatric adaptation of Aldrete score or specific scoring method in use in the relevant institution); in the absence of motor blockade, children usually may be discharged within 30 minutes. In other cases, discharge depends on the behavior of the child. Partial restoration of motor function is mandatory, even in quiet children with caring families. Boisterous children should not leave before motor functions have been fully restored; additionally, protective dressings (including casts) may help prevent harm to the operated limb. Persistence of sensory blockade is not a contraindication to early discharge unless the familial environment is inadequate. Pain medication should be systematically prescribed and administered on a regular basis to prevent the return of intense pain at home when the sensory block is no longer effective.[154] Most additives do not preclude early discharge except for epidural or intrathecal opioids, especially morphine, which necessitates that the child stay hospitalized overnight.

MANAGEMENT OF CONTINUOUS REGIONAL TECHNIQUES

Children with repeat, on-demand, or continuous epidural infusion should remain hospitalized to be adequately monitored. Occasionally, a few selected patients can be allowed to return home with an epidural catheter, mostly in a context of chronic pain or cancer pain in terminally ill children. Adult patients with continuous techniques of peripheral nerve blockade can be returned home provided surgical care does not require hospital stay. These continuous techniques are rather new in pediatrics[74] and not yet widely used. Pediatric orthopedic surgery is particularly interested in this type of analgesia. Studies on peripheral nerve blocks in children monitored at home have reported a low complication rate and good quality of analgesia.[155,156] In one institution, children suffering from complex regional pain syndrome were treated at home with peripheral nerve catheters.[79] The use of an elastomeric disposable device to infuse local anesthetic allows simplifying the management of children at home and a nursing economy. Such management will probably gain wider acceptance in the near future, but currently it should be considered under evaluation.

NEURAXIAL BLOCKS

CAUDAL ANESTHESIA

Worldwide, the caudal block is likely the most commonly used technique of epidural blockade in children. Nevertheless, it is less used in some countries in favor of peripheral blocks.[98] The technique is described as simple and easy to perform for most, with few complications.

Caudal anesthesia considerably decreases stress hormone response to surgery.[157-159] The rate of complete or partial failure of this technique is 3% to 11%,[160] especially in children older than 7 years of age.

Anatomy of the Sacral Hiatus

Children have a specific anatomic level of the sacrum. Until the age of 1 year, five sacral vertebrae are easily identifiable and have the appearance of the lumbar vertebrae. Each sacral vertebra has five primitive centers of ossification, which will knit by 2 to 6 years of age. This is due to the standing body of the child, who will develop the walking and the mechanical stresses in the vertebrae.

The sacral hiatus is a U-shaped or V-shaped aperture resulting from the lack of dorsal fusion of the fifth and often fourth sacral vertebral arches. It is limited laterally by two palpable bony structures, the sacral cornua, and is covered by the sacrococcygeal membrane (sacral continuation of the ligamenta flava). The distance separating the summit of the sacral hiatus and the dural sac ending is approximately 30 to 10.4 mm (range, 13.6 to 54.7 mm) in children 10 months to 18 years of age.[161] Mean distance from skin to anterior sacral wall is 21 mm (extremes, 10 to 39 mm) between 2 months and 7 years of age.[140] The distance from skin to the epidural space is only slightly influenced by the age and weight of the patient (Fig. 92-1), and 25-mm needles are long enough to reach the sacral epidural space and short enough to prevent inadvertent dural puncture in most patients.

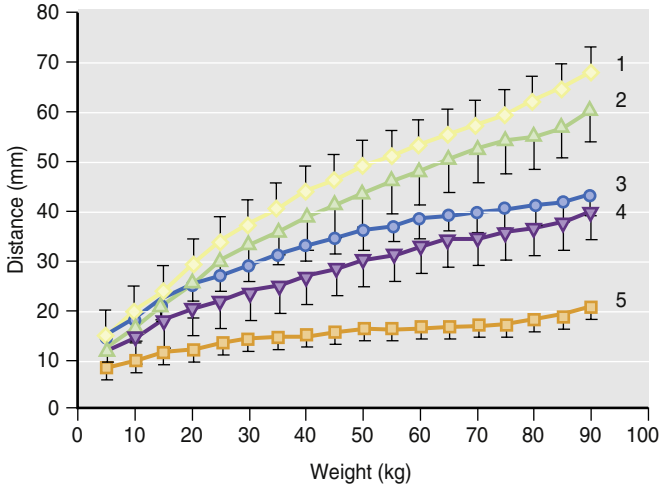


Figure 92-1. Distance from the skin to the epidural and subarachnoid spaces at different intervertebral levels and through the sacral hiatus. *1,* Spinal anesthesia; *2,* lumbar epidural approach (midline); *3,* thoracic epidural approach (midline); *4,* sacral epidural approach; *5,* caudal approach.

With growth, the axis of sacrum changes; the sacral hiatus becomes more difficult to identify and may even close.[162] Concomitantly, the epidural fat becomes more densely packed, thus reducing the spread of local anesthetics. These changes make caudal anesthesia less suitable and more difficult to perform in children older than 6 to 7 years of age.

Indications, Contraindications and Complications. Caudal anesthesia is recommended for most surgical procedures of the lower part of the body (mainly below the umbilicus), including inguinal hernia repair, urinary and digestive tract surgery, and orthopedic procedures on the pelvic girdle and lower extremities.[163] It is usually performed in lightly anesthetized patients but can be used as the sole anesthetic regimen in fully awake former premature infants younger than 50 to 60 weeks of postconceptual age after local anesthesia of the skin covering the sacral hiatus, either as a single-shot technique[164,165] or after placement of an epidural catheter allowing repeat or continuous injection of local anesthetics.[166]

Specific contraindications include major malformations of the sacrum (myelomeningocele, open spina bifida), meningitis, and intracranial hypertension.

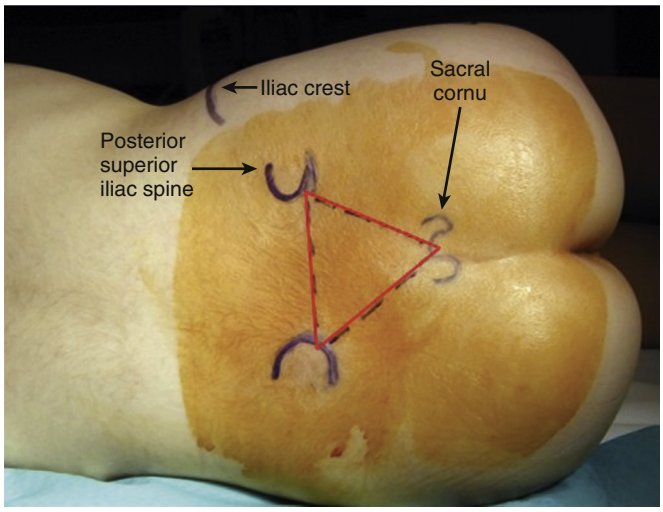


Figure 92-2. Landmarks for caudal block procedure in lateral position. Two posterior superior iliac crests form an equilateral triangle; the top of this triangle indicates V-shaped sacral hiatus limited by two sacral cornua.

Specific complications of caudal anesthesia are infrequent and usually minor[90,98] when adequate devices are used. Notably, dural puncture and subsequent injection of local anesthetic solution can lead to cardiovascular collapse or respiratory arrest (apnea).

Technique

The technique is performed with the patient in the lateral position or, especially in nonanesthetized premature infants, in the prone position either with a rolled towel slipped under the pelvis or with the legs flexed in the "frog" position. The two sacral cornua limiting the V-shaped sacral hiatus are located by palpation along the spinal process line at the level of the sacrococcygeal joint (Fig. 92-2). The hiatus along with the two posterior superior iliac crests is claimed to form an equilateral triangle, but in clinical practice this assumption does not help in locating the hiatus when palpation is not informative. The caudal puncture technique is shown in Figure 92-3.

Caudal anesthesia is basically a single-shot technique. Occasionally, placement of an epidural catheter for repeat or continuous infusion is contemplated. The "normal" length of catheter to be introduced into the epidural space is 2 to 3 cm, as for any epidural block. Because the epidural fat is very fluid in infants, a longer distance can be introduced to reach lumbar or even thoracic levels. This technique should be considered with caution, by experts only. The final position of the tip of the catheter must be controlled; it is misplaced in 28% of cases.[167] This is usually achieved by obtaining a contrast-enhanced radiograph, but the following techniques also are available:

- Neurostimulation at rather high intensities (however, safety of this technique is not established).[168,169]
- Recording ECG tracings from the metallic wire of the catheter and comparing them with those obtained from an electrode placed on the spinous process line, at the level where the tip of the catheter should be placed. The position is correct when the two tracings are identical.[170] This technique is very elegant and noninvasive, but the "second" ECG tracing is not easily readable in some patients (especially when they are conscious and moving).
- Ultrasound guidance[171] is the most promising noninvasive technique.

Catheter tunneling has been recommended to decrease the risk for bacterial contamination.[172] The volume

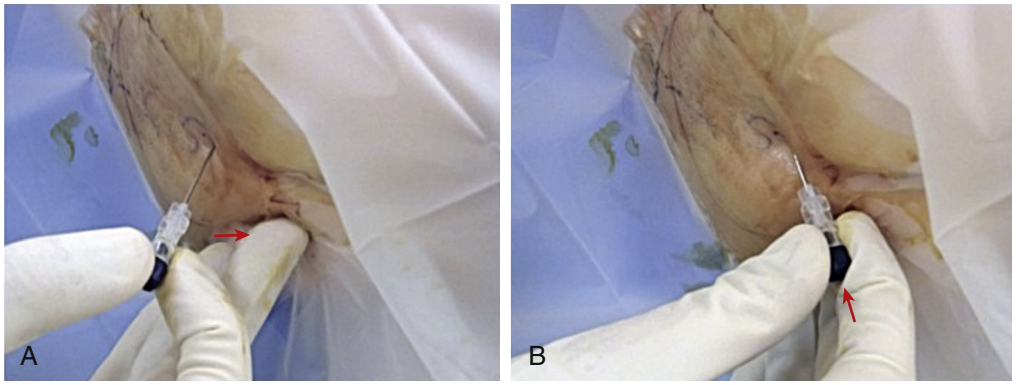


Figure 92-3. Caudal puncture technique. **A,** Insertion of the needle at right angles to the skin. **B,** Cephalic redirection of the needle after piercing the sacrococcygeal membrane.

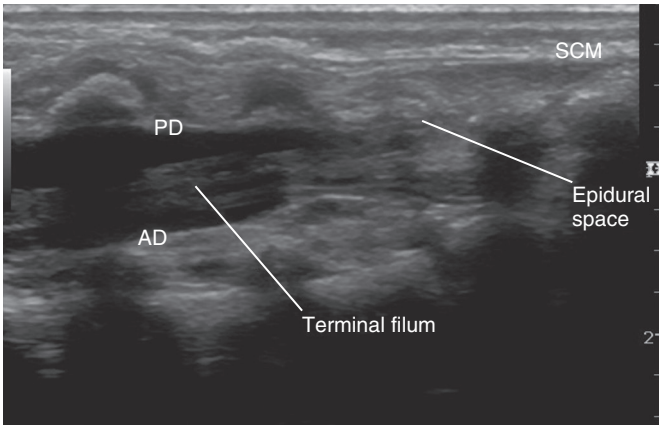


Figure 92-4. Ultrasound-guided caudal block facilitating initial assessment of the anatomy of the sacrum. *AD,* Anterior dura mater; *PD,* posterior dura mater; *SCM,* sacrococcygeal membrane.

prescription scheme of Armitage that was published many years ago still remains the most dependable, as follows:

- 0.5 mL/kg: All sacral dermatomes are blocked.
- 1 mL/kg: All sacral and lumbar dermatomes are blocked.
- 1.25 mL/kg: The upper limit of anesthesia is at least midthoracic.

When 1.25 mL/kg is injected, excessive rostral spread (above T4) can occur[173]; it is therefore preferable not to administer more than 1 mL/kg of local anesthetic. Hong and colleagues[174] sought the best compromise between the two regimens of caudal injections in terms of quality of analgesia and spread of local anesthetic. The authors compared the same total dose of local anesthetic (ropivacaine 2.25 mg/kg), a high injection volume and low concentration (ropivacaine 0.15% 1.5 mL/kg), and low injection volume and high concentration (ropivacaine 0.225% 1 mL/kg). Spread of local anesthetic was significantly higher in the high volume and low concentration group in contrast to the other group (T6 [T3 to T11] and T11 [T8 to L2], respectively). In addition to the injection system, high volume and low concentration produced a longer duration of analgesia before the first analgesic request (554.5 minutes versus 363 minutes). When a catheter is inserted, repeat injections must be reduced to avoid systemic toxicity. The second injection should be made no earlier than 60 minutes (for a short-duration local anesthetic) or 90 minutes (for a long-duration local anesthetic) after the first one and should be half of the initial dose. Further injections should be reduced to half of the second dose (i.e., one sixth of the initial dose) while respecting the same delays.

Ultrasound has facilitated the use of caudal block in children, allowing an initial assessment of the anatomy of the sacrum (Fig. 92-4), including the relationship of the sacral hiatus to the dural sac ending, and research of spinal dysraphism.[141] Roberts and associates[171] demonstrated the value of ultrasound imaging with a test dose of saline when performing a caudal block to confirm the correct location of the needle. According to the authors, the displacement of the dura mater during the injection of saline is an indicator of a successful block. They found ultrasound-guided caudal blocks successful with a sensitivity of 96.5%, a specificity of 100%, and a positive predictive value 100%. Ultrasound is also better than the swoosh test to determine the correct location of the needle.[142] Recently, Shin and associates[175] noted that prior anatomic study of the sacral region via ultrasound made it easier to identify the sacral hiatus and determine the level of the dural sac before completion of a caudal block or block-sacred interspinous in children.

INTERVERTEBRAL EPIDURAL ANESTHESIA

Anatomy and Physiology

The epidural space surrounds the spinal cord and the meninges from the foramen magnum to the sacral hiatus. Limited posteriorly by the vertebral laminae and the ligamenta flava, it communicates quite freely with both the paravertebral spaces and the root sleeves. In the dural cuff region, near the spinal ganglia, it is intimately connected with the subarachnoid space owing to protrusion of arachnoid granulations, which are easily traversed by local anesthetics. It contains blood vessels and lymphatics and is filled with loose fat in infants and in children up to 6 to 8 years of age.

One of the major characteristics of the child for the central blocks is a line connecting the two iliac crests—the Tuffier line. This line joining the two iliac crests is proportionally smaller in young children and crosses the spinous process line at the L5 to S1 level in infants up to 1 year of age instead of at L4 to L5 as in older children and adults.[176] Bending the spine (as for performing an epidural block) does change the level at which the Tuffier line crosses the spine in 58.3% of patients. Mobility of the vertebrae and the elasticity of the ligaments in children can change the position of the spinal cord in the spinal canal. The spinal cord tends to move backward and get closer to the vertebral arches in a sitting position, making it more difficult to identify the epidural space. In the lateral position, bending of the spinal cord moves forward, away from the ligamentum flavum and for expanding the epidural space. This is the preferred position for the epidural catheter procedure in children (Fig. 92-5).

Epidural injections result in considerable pressure changes. After placement of a 20-gauge epidural catheter in 20 infants, Vas and associates[177] measured the following changes:

- Pressure on penetrating the epidural space: 1 ± 10 mm Hg (extremes, –17 to + 16 mm Hg)
- Peak pressure during injection of a local anesthetic at 1 mL/min: 27.8 ± 18.6 mm Hg with residual pressure of 12 ± 5.5 mm Hg 1 minute after completion of injection
- Peak pressure during injection of a local anesthetic at 0.5 mL/min: 15.2 ± 9.5 mm Hg with residual pressure of 14.8 ± 5.4 mm Hg 1 minute after completion of injection

The spine presents at birth only one concavity: anterior curvature (kyphosis). Lumbar lordosis appears only with the acquisition of walking. Until the installation of lordosis, the spinous processes are parallel and the introduction of the needle between them in the epidural space is perpendicular to the plane of the back. In addition,



Figure 92-5. Lateral position for epidural puncture in a 10-year-old boy *(left)* and 4-month-old girl *(right)*.

ossification of the lumbar vertebrae is very underdeveloped at birth and risks exist for injury to cartilaginous structures.

Indications and Contraindications

Young children tolerate epidural anesthesia well without significant hemodynamic changes.[58,178] Epidural anesthesia is recommended for all major abdominal, retroperitoneal, pelvic, and thoracic[179,180] procedures, including pectus excavatum repair[181] and scoliosis surgery,[182] preferably with a two-catheter technique.[183] The technique is also used for cardiac surgery in a few institutions,[70,184] but this indication is controversial and most authors consider it contraindicated because of anticoagulation.

The intervertebral level at which the epidural space should be approached is a matter of debate and depends on both the patient's age and the experience of the anesthesiologist. When a single-shot technique is planned for a surgery below the umbilicus, a caudal approach is most often selected in infants and young children and a lumbar approach is used in older patients. When catheter placement is contemplated it is preferable to select a lumbar approach in all patients to decrease the risk for bacterial contamination from anal proximity, even though this is rare.[90]

When sensory blockade of high thoracic dermatomes is required, the most reliable approach is a thoracic epidural block, which requires expertise because the spinal cord could be damaged. When the anesthesiologist is not used to performing thoracic epidural blocks in infants, some authors recommend a caudal approach with cephalic insertion of a catheter over a long distance to reach thoracic levels.[185] This technique, however, requires experience and luck—the catheter is misplaced in almost 30% of cases, even in experienced hands,[167,186] and serious complications are possible (e.g., spinal cord or vessel trauma during insertion, bacterial contamination, breakage, or buckling around a nerve root on removal attempts).[187-189]

Specific contraindications to epidural anesthesia include severe malformations of the spine and spinal cord (not spina bifida occulta), intraspinal lesions or tumors, and tethered cord syndrome. In most instances, epidural anesthesia should be avoided in children with a history of hydrocephalus, elevated intracranial pressure, unstable epilepsy, or reduced intracranial compliance, but these disorders are not absolute contraindications, depending on the context.[190] Also, previous surgery on the spine usually makes epidural (and spinal) anesthesia technically difficult or impossible, but they are not contraindications unless underlying lesions of the spinal cord are present.



Figure 92-6. Lumbar epidural anesthesia by loss-of-resistance technique with saline.

Techniques

Lumbar Epidural Anesthesia. The lumbar epidural is usually performed in anesthetized patients via a midline route below the L2-L3 interspace, which represents the lower limit of the conus medullaris (Fig. 92-6). The technique is essentially as in adults. A paramedian approach can be used instead in cases of spinous process anomaly or spine deformity. The child is positioned in the semiprone position, with the side to be operated lowermost and the spine bent to enlarge the interspinous spaces. The sitting position can be used in conscious patients.

Medium selection for the LOR technique has elicited considerable debate. Both air and saline are advocated for the LOR test to identify the epidural space. Saline is more popular according to the Ames survey[191]; but air (or carbon dioxide) is perhaps more sensitive, especially in neonates and infants.

The distance from the skin to the epidural space is correlated with the patient's age and size (see Fig. 92-1), but 1 mm/kg is a useful approximation for children between 6 months and 10 years of age.[192] An ultrasound probe provides precise measurement of the distance from skin to the ligamenta flava and from skin to the posterior dura mater (Fig. 92-7).

When the tip of the needle penetrates the epidural space, the LOR technique syringe is disconnected, and no reflux of biologic fluid (blood or CSF) should appear at the hub. The next step consists of injecting the local anesthetic at a slow speed, either through the epidural needle or through a catheter. Progressive displacement of the dura mater can be visualized by placing an ultrasound probe in line with the spinous process line during injection in infants younger than 2 years of age.[143] By using ultrasound, the anatomy of the spinal canal, the position of the spinal cord, visualization of the ligamentum flavum, and the space caudal spinous processes can actually be seen (see Fig. 92-7).[193] When a catheter is inserted, it should not be introduced more than 3 cm, to avoid buckling, knotting, and lateralization of blockade or erratic migration. Tunneling the catheter reduces the incidence of accidental removal and bacterial contamination.[194] Catheters inserted over a long distance have to be controlled in the same way as caudal catheters.

The volume of anesthetic solution depends on the upper level of analgesia required for completion of the surgery; approximately 0.1 mL per year of age is necessary to block 1 neuromere.[195] Usual volumes of injectate range from 0.5 to 1 mL/kg (up to 20 mL), and the upper limit of sensory blockade ranges between T9 and T6 in more than 80% of patients.

Single-shot epidural blocks are appropriate for many pediatric surgeries, especially when adjuvants such as clonidine 1 to 2 μg/kg, preservative-free ketamine 0.25 to 0.5 mg/kg, and, in appropriate indications, morphine 30 μg/kg are coadministered. Major operations resulting in long-lasting postoperative pain require placement of an epidural catheter and postoperative infusion of local anesthetics (Table 92-8).

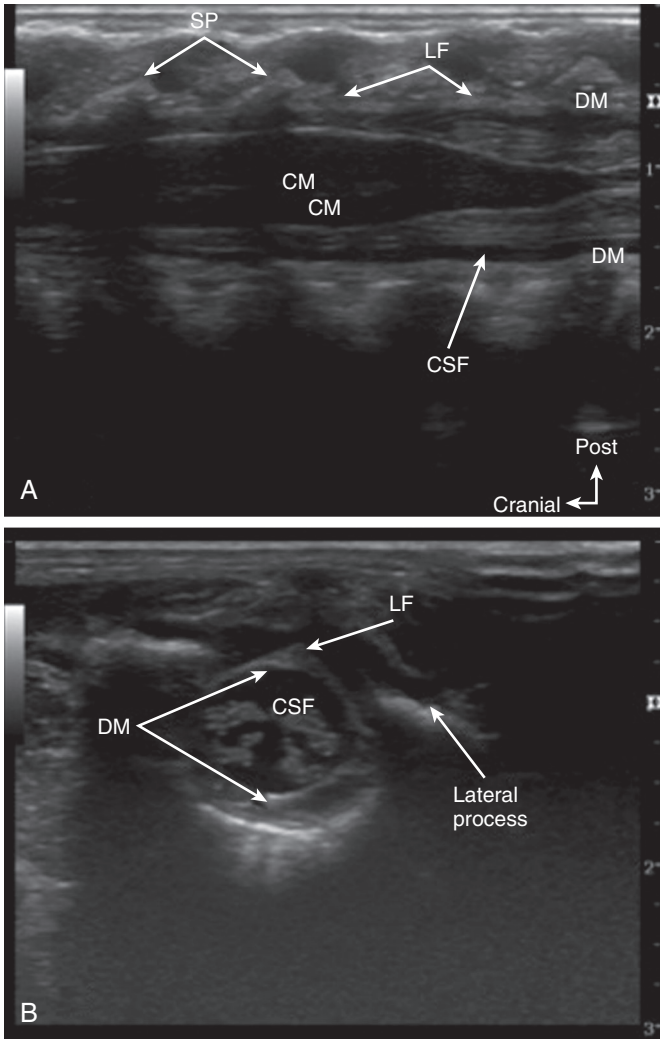


Figure 92-7. Transverse (**A**) and axial (**B**) ultrasound images of conus medularis. *CM,* Conus medularis; *CSF,* cerebrospinal fluid; *DM,* dura mater; *LF,* ligamentum flavum; *SP,* spinous process.

TABLE 92-8 **USUAL DOSES AND INFUSION REGIMENS FOR EPIDURAL ANESTHESIA IN PEDIATRIC PATIENTS**

Agent	Initial Dose	Continuous Infusion (Maximum Doses)	Repeat Injections
Bupivacaine, levobupivacaine	Solution: 0.25% with 5 μg/mL (1/200,000) epinephrine Dose: <20 kg: 0.75 mL/kg 20-40 kg: 8-10 mL (or 0.1 mL/yr/no. of metameres) >40 kg: same as for adults	<4 mo: 0.2 mg/kg/hr (0.15 mL/kg/hr of a 0.125% solution or 0.3 mL/kg/hr of a 0.0625% solution) 4-18 mo: 0.25 mg/kg/hr (0.2 mL/kg/hr of a 0.125% solution or 0.4 mL/kg/hr of a 0.0625% solution) >18 mo: 0.3-0.375 mg/kg/hr (0.3 mL/kg/hr of a 0.125% solution or 0.6 mL/kg/hr of a 0.0625% solution)	0.1 to 0.3 mL/kg every 6-12 hr of a 0.25% or 0.125% solution (according to pain scores)
Ropivacaine	Solution: 0.2% Dose: Same regimen in mL/kg as for bupivacaine (see above)	Same age-related infusion rates in mg/kg/hr as for bupivacaine (usual concentration of ropivacaine: 0.1%, 0.15%, or 0.2%) Do not infuse for more than 36 hr in infants <3 mo	0.1 to 0.3 mL/kg every 6-12 hr of a 0.15% or 0.2% solution (according to pain scores)
Adjuvants	Avoid in infants <6 mo Fentanyl 1-2 μg/kg or sufentanil 0.1-0.6 μg/kg or clonidine 1-2 μg/kg	Select only one additive: Fentanyl: 1-2 μg/mL Sufentanil: 0.25-0.5 μg/mL Morphine: 10 μg/mL Hydromorphone: 1-3 μg/mL Clonidine 0.3 at 1 μg/mL of solution	Morphine (without preservatives): 25-30 μg/kg every 8 hr

In mature children who understand the concept of patient-controlled analgesia and who are willing to use it, patient-controlled epidural analgesia (PCEA) can be an interesting option. A prospective study involving 128 children older than 5 years of age reported a 90.1% success rate; PCEA was stopped in 6.1% of children because of adverse effects and only in 3.8% because of inadequate analgesia.[196] The local anesthetic was either 0.0625% or 0.125% bupivacaine with fentanyl 2 to 10 μg/mL; the background infusion rate was 0.2 mL/kg/hr or less, and 1- to 3-mL bolus doses were permitted every 15 to 30 minutes with a maximum dose of bupivacaine of 0.4 mg/kg/hr.

Another prospective study involving 58 children (age range, 7 to 12 years) undergoing lower extremity orthopedic surgery compared continuous epidural infusion of 0.2% ropivacaine 0.2 mL/kg/hr with PCEA, with background infusion of 1.6 mL/hr and 2-mL bolus doses (lockout interval, 10 minutes) of the same solution. Pain scores were excellent and identical in both groups, but children from the PCEA group required half the doses of ropivacaine on an hourly basis in contrast to the continuous infusion group.[121]

Sacral Epidural Anesthesia. Because sacral interspaces remain nonfused until early adulthood, the sacral epidural space of children can be approached posteriorly via the S2-S3 interspace, which is identified by palpation 0.5 to 1 cm below the line joining the two posterior superior iliac spinous processes, but any other sacral interspace can be used.[197] The procedure is the same as for a lumbar approach. Because sacral spinous processes are atrophic, the Tuohy needle can be oriented cephalad or, preferably, caudad to contact the dura mater with the convex part of the needle tip, thus reducing the danger of accidental dural penetration. The dural sac usually ends at S2, as does the risk for dural puncture. Attention must be paid to the closer skin proximity of the epidural space, in contrast to lumbar approaches (see Fig. 92-1). If mandatory, an epidural catheter can be inserted (using the same technique as for lumbar epidural catheter placement) to provide long-lasting postoperative pain relief.

Sacral epidural anesthesia is an alternative to caudal anesthesia, either in infants when skin lesions contraindicate a caudal approach or in children older than 6 to 7 years of age, in whom caudal anesthesia becomes more difficult and less reliable. The same volumes and doses of local anesthetic as for a caudal anesthesia are administered. Ultrasound imaging can be used to precisely evaluate the distance from skin to epidural space and, in infants mainly, visualize both the progression of the needle and catheter and the spread of the local anesthetic.

Thoracic Epidural Anesthesia. Thoracic epidural blocks are indicated for major operations requiring long-lasting pain relief, thus requiring placement of an epidural catheter to allow repeat injections or continuous infusion of local anesthetic. These are not commonly used techniques in children because indications are limited to thoracic and upper abdominal surgery and spinal cord damage is a risk. In children younger than 1 year of age, the procedure is similar to that for a lumbar approach, with needle insertion perpendicular to the spinous process line, because the spine displays a single flexure, especially when bent. As the patient grows and the flexure develops, the technique becomes progressively similar to thoracic approaches in adults, requiring cephalic orientation of the Tuohy needle up to a 45-degree angle to the skin. A paramedian approach can be used instead, but it is rarely required in children. In infants, ultrasonography makes visible the dura mater, the progression of the Tuohy needle, and, in many cases, the progression and final position of the tip of the epidural catheter.[198]

Cervical Epidural Anesthesia. No surgical indications exist for cervical epidural blockade in children. Very rarely, the technique can be contemplated for patients with chronic pain or to prevent phantom limb pain before an amputation of the upper arm at the scapular level (osteosarcoma of humerus), which is done almost exclusively in adolescents. The block procedure is the same as in adults.

SPINAL ANESTHESIA

Anatomy and Physiology

The spinal cord and dural sac of infants younger than 1 year of age end at a lower level than in older patients (see earlier section on Caudal Anesthesia). Also, the volume of CSF varies considerably according to the patient's age, from more than 10 mL/kg in neonates, to 4 mL/kg in infants weighing less than 15 kg, to 3 mL/kg in children, to 1.5 to 2.0 mL/kg in adolescents and adults. The spinal and cerebral distribution of CSF also varies with age; half the CSF volume is located within the spinal subarachnoid space versus only 25% in adults. This has considerable pharmacokinetic consequences and explains why larger doses of local anesthetics are required for spinal anesthesia in infants and young children.

CSF hydrostatic pressure is lower in infants in the dorsal recumbent position[199] and further decreased during general anesthesia. In performing a spinal block, the progression of the needle must be slow to detect CSF reflux before the needle is advanced farther.

Children older than 5 years of age behave like adults after spinal anesthesia, whereas younger patients remain hemodynamically stable, without significant hypotension or bradycardia,[200] even in cases of cardiac malformations.[201] However, a decrease in mean arterial pressure during the first 10 minutes after injection of 0.8 mg/kg of 0.5% bupivacaine was reported in infants aged 1.5 to 5 months.[202] This decrease was time limited, well tolerated, and rapidly corrected by IV fluids. Similar results with concomitant decrease in cerebral blood flow were reported in former preterm infants of 41 weeks of postconceptual age.[203]

Indications and Contraindications

Spinal anesthesia has limited indications in pediatric patients. One of these is inguinal hernia repair in former preterm infants younger than 60 weeks of postconceptual age[204,205] who are prone to develop postoperative apnea after general anesthesia or even light sedation.[206] However, even after pure spinal anesthesia, apnea may occur postoperatively (as they may preoperatively) and

it is prudent to keep at-risk infants hospitalized. Other indications are scarce, mainly for elective lower abdominal or lower extremity surgery[207-209] and, occasionally, for cardiac surgery or cardiac catheterization,[210,211] but these indications are controversial.

Technique

The technique of spinal anesthesia is similar to lumbar puncture (Fig. 92-8). It can be performed with the patient in the lateral decubitus position or sitting (Fig. 92-9). Currently, hyperbaric tetracaine and bupivacaine are the most commonly used local anesthetics. Isobaric bupivacaine can be used instead.[207] Ropivacaine[212] and levobupivacaine[213] may become the standard of the future but are not currently approved for spinal administration in pediatric patients.

Drugs and Doses

The drugs most frequently used are tetracaine 0.5% and bupivacaine 0.5%. The usual doses are 0.5 to 0.8 mg/kg to achieve low to medium levels and 1 mg/kg to achieve high levels (T2-T4). The duration of the block is approximately 60 to 75 minutes for both drugs. Newborns and infants are at an increased risk for toxicity after the administration of amide local anesthetics; the risk is even greater in the case of jaundice.[214] Usual dosages for neonates to adolescents are given in Table 92-9.

The older the child, the lower is the dose required; in children between 6 months and 14 years, 0.5% hyperbaric bupivacaine at a dose of 0.2 mg/kg has been used with a success rate of 98%. More recently, the successful use of 0.5% ropivacaine in children between 1 and 17 years at 0.5 mg/kg and 0.5% levobupivacaine in children between 1 and 14 years at 0.3 mg/kg has been reported. Clonidine 1 μg/kg, fentanyl 1 μg/kg, and morphine 4 to 5 μg/kg are reported in the pediatric literature as adjuvants to increase the spinal block duration (see Table 92-9).

Adverse Effects and Complications

Spinal anesthesia is technically difficult in neonates and infants; the overall failure rate ranges from 10% to 25%.[206,215] Short duration of blockade and lack of residual analgesia are important limitations, and alternative (awake caudal anesthesia) or complementary techniques (ilioinguinal or iliohypogastric block) are often contemplated. Postdural puncture headache is rare in children younger than 8 years of age but not exceptional, and its incidence may be increased with use of pencil-point spinal needles.[216] All complications reported after lumbar epidural blockade can occur after spinal anesthesia.



Figure 92-8. Spinal anesthesia procedure in sitting position in 1-month-old girl.

UPPER EXTREMITY CONDUCTION BLOCKS

ANATOMIC CONSIDERATIONS

Nerve supply to the upper extremity depends mainly on the brachial plexus formed by the union of the ventral rami of the fifth cervical to the first thoracic spinal nerve roots. Roots emerge from the intervertebral foramina within the interscalene space (between the scalene anterior and scalene middle muscle). As in adults, brachial plexus nerve fibers redistribute first to three trunks (superior, middle, and inferior), then to three divisions between the clavicle and the first rib. These divisions recombine and surround the axillary artery as three cords and are named according to their relation to the artery as the lateral, medial, and posterior cords (Fig. 92-10). Because of this complicated redistribution of nerve fibers, distribution of anesthesia varies considerably depending on the level at which the local anesthetic is injected. Some anatomic knowledge



Figure 92-9. Sitting or lateral position for spinal anesthesia procedure.

is essential to predict the extension of the motor and sensory block and to determine the most appropriate approach for a given surgery (Fig. 92-11).

The most important anatomic difference between infants and adults pertains to the upper part of the lung and apical pleura that penetrates the neck, above the plane formed by the clavicle and first rib (superior thoracic aperture). Subclavian vessels and the lower division of the plexus are encountered in the apical pleura, thus making any perisubclavian approach at major risk for pleural penetration. The concept of perineurovascular sheath has been challenged in spite of strong embryologic and anatomic evidence, but it received additional confirmation in a recent radiologic study, and even the volume of the axillary tunnel could be precisely measured (5.1 to 9.5 mL in adults).[217]

Ultrasound imaging allows precise localization of the parietal pleura and subclavian and axillary vessels, thus improving the safety of supraclavicular and infraclavicular approaches, provided the tip of the block needle can be continuously seen during the procedure. Nerve stimulation may be used in conjunction with ultrasound guidance to confirm the localized nerve and prevent an intraneural injection.

Roberts[136] recommended initially performing simple blocks. Interscalene and periclavicular approaches are considered difficult and must be done by trained operators. The axillary and forearm blocks seem easier, especially for those who are new to ultrasound-guided regional anesthesia.

Indications for brachial plexus blocks include emergency and elective surgery of the upper extremity in conscious or anesthetized children.[218-220] These blocks are useful for outpatient surgery and elicit a high degree of patient satisfaction.

- The axillary block is the most common approach to the brachial plexus in pediatric patients, especially when the lesions involve the forearm and the hand. Advantages of this block include an easy and safe procedure with a high rate of success and very low rate of complications.
- The infraclavicular paracoracoid approach is being increasingly used with the development of ultrasound guidance. The technique provides complete blockade of the upper extremity, catheter placement is easier and

TABLE 92-9 USUAL DOSES OF LOCAL ANESTHETICS FOR SPINAL ANESTHESIA

Local Anesthetic	Dose	Duration
Neonates		
Tetracaine 0.5%	0.6-1 mg/kg	60-75 min
Bupivacaine 0.5%	0.5-1 mg/kg	65-75 min
Ropivacaine 0.5%	1.08 mg/kg	50-70 min
Levobupivacaine 0.5%	1 mg/kg	75-90 min
Infants to Adolescent		
Bupivacaine 0.5%	0.4 mg/kg (5-15 kg)	
Tetracaine 0.5%	0.3 mg/kg (<15 kg)	
Levobupivacaine 0.5%	0.4 mg/kg (5-15 kg)	
Ropivacaine 0.5%	0.3 mg/kg (>15 kg)	
	0.4 mg/kg (5-15 kg)	
	0.3 mg/kg (15-40 kg)	
	0.25 mg/kg (>40 kg)	
	0.5 mg/kg (maximum 20 mg)	
Adjuvant		
Clonidine	1 μg/kg (neonates)	
Fentanyl	1 μg/kg (infants <1 yr)	
Morphine	4-5 μg/kg (all ages)	

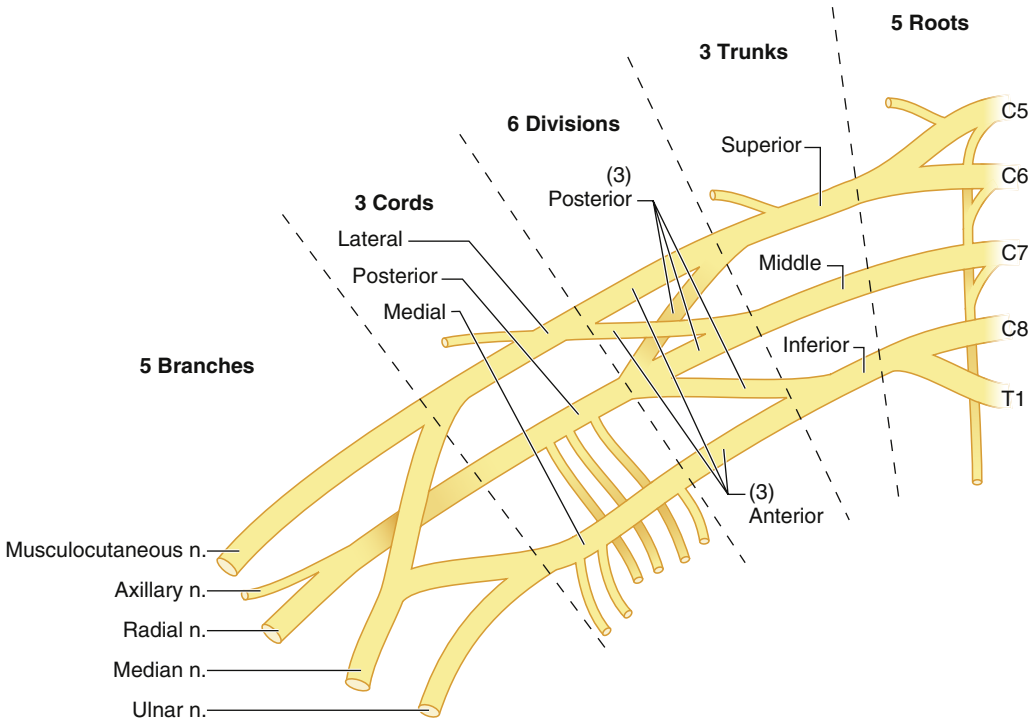


Figure 92-10. Brachial plexus anatomy. *n.,* Nerve

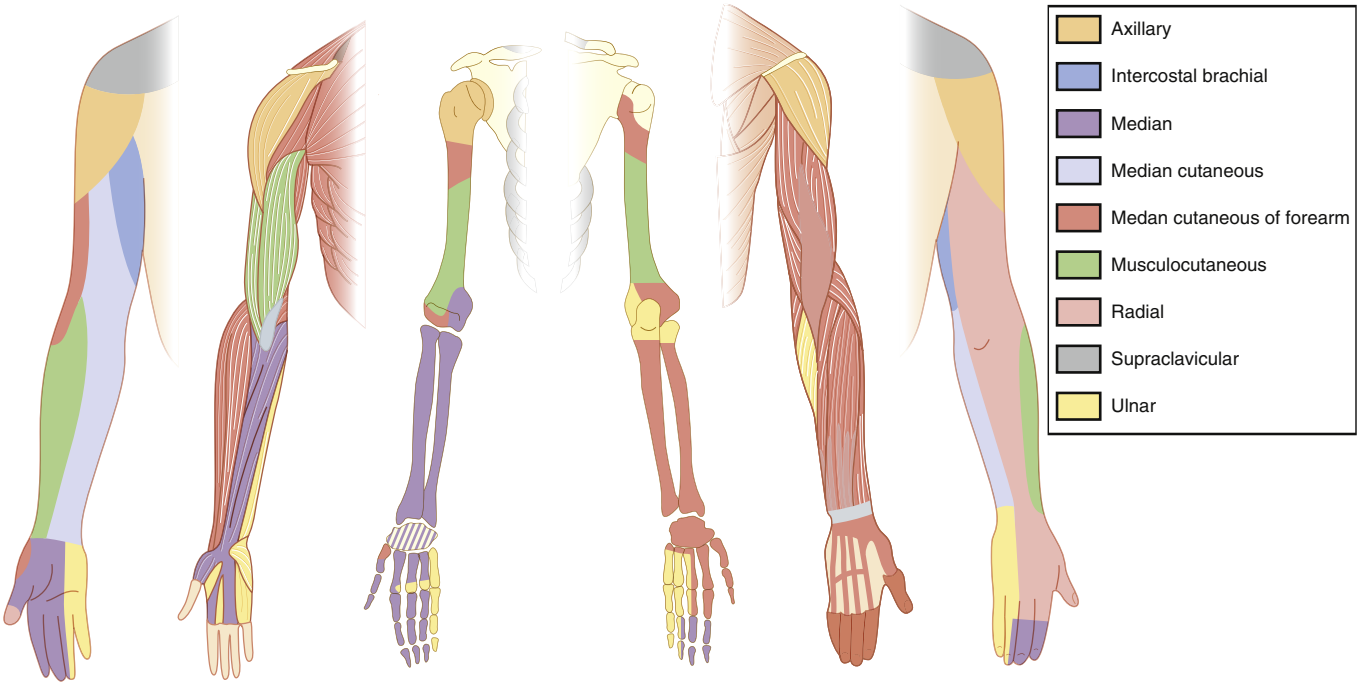


Figure 92-11. Cutaneous, muscle, and bone innervations of the upper extremity.

more comfortable than at axillary levels, and catheter immobilization and protection against accidental removal are also easier.

- Supraclavicular approaches are indicated when the lesion is located on the shoulder or on the proximal part of the arm, including the elbow. Perisubclavian approaches should be used in infants with extreme caution because of the proximity of the apical pleura; ultrasound imaging reduces the risk for complications such as vascular or pleural incidental punctures. Before the use of ultrasound-guided nerve block, the parascalene and the modified interscalene approach (the tip of the block needle is placed virtually at the same place in the interscalene space with both techniques) were considered as safe alternative procedures.
- Distal nerve blocks are used either for distal lesions (surgery involving the hand or one finger only) or as complementary block when distribution of anesthesia is incomplete after a more proximal block.

CERVICAL BRACHIAL PLEXUS BLOCKS

Cervical brachial plexus approaches are not commonly used in children because of potential adverse effects (pneumothorax, vertebral artery injection, intrathecal injection) and the low incidence of isolated shoulder surgery in this population.

Interscalene Approach

The interscalene approach aims to enter the interscalene space at its upper extremity, close to the transverse process of C6. The child is placed in the dorsal recumbent position with the arms extended alongside the thorax and head slightly turned to the contralateral side.

The landmarks are the cricoid cartilage, the anterior ramus of the C6 transverse process (Chassaignac tubercle), and the interscalene groove. The puncture site is located at the skin projection of Chassaignac tubercle in the interscalene groove, just posterior to the lateral border of the sternocleidomastoid muscle. The needle is inserted at an 80-degree angle (not perpendicularly) to the skin; that is, dorsally and slightly caudal pointing toward the midpoint of the clavicle, until one of the primary trunks (instead of roots) of the brachial plexus is located by elicited muscle twitches in the upper arm. Any distal motor twitch and biceps, triceps, or deltoid muscles are adequate (Fig. 92-12). Contraction of the diaphragm indicates phrenic nerve stimulation and anterior placement of the needle tip. Alternatively, trapezius muscle stimulation indicates that needle placement is too posterior. Borgeat and colleagues[221] described a modified technique in adults that can be used in children. The block needle is inserted at the same puncture site, but the needle is oriented laterally, pointing toward the midpoint of the clavicle until one of the primary trunks (instead of roots) of the brachial plexus is located and twitches are elicited in the upper arm. The interscalene block is not very popular in children because of its adverse effects—ipsilateral phrenic nerve blockade, danger of vascular damage (vertebral artery and vein), and accidental cervical epidural and intrathecal penetration.

Ultrasound imaging improves the safety of this approach by showing the great vessels of the neck, aponeuroses of scalene muscles, and C5-C6-C7 brachial plexus roots.[137,222] The probe is placed in a transverse oblique plane at the level of the cricoid cartilage (Fig. 92-13). The trunks and roots of the brachial plexus can be identified in the interscalene groove as distinct round-to-oval hypoechoic structures between the scalene anterior

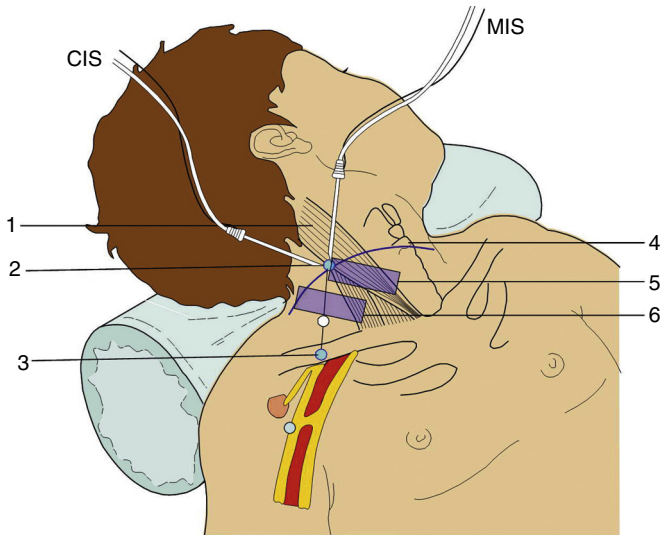


Figure 92-12. Interscalene approach to the brachial plexus. *CIS,* Classic interscalene approach (after Winnie); *MIS,* modified interscalene approach (after Borgeat); *1,* sternocleidomastoid muscle; *2,* skin projection of the Chassaignac tubercle; *3,* midpoint of the clavicle; *4,* cricoid cartilage; *5,* probe positioning (classic approach); *6,* probe positioning (Borgeat approach).



Figure 92-13. Ultrasound interscalene block procedure: patient head and probe position and in-plane needle approach.

and middle muscles, both deep to the sternocleidomastoid muscle. The internal jugular vein and carotid artery can be visualized medially (Fig. 92-14). Using combined ultrasound-guided nerve stimulation techniques, the needle is advanced with an in-plane alignment from lateral (posterior) to medial (anterior) side of the probe, toward the target nerves. Precise needle placement may limit the dose of local anesthetic required.[223]

Parascalene Approach

The parascalene approach described by Dalens and colleagues[224] aims to penetrate the interscalene space at a distance from the apical pleura and great vessels of the neck. The landmarks are the midpoint of the upper border of the clavicle and the transverse process of C6

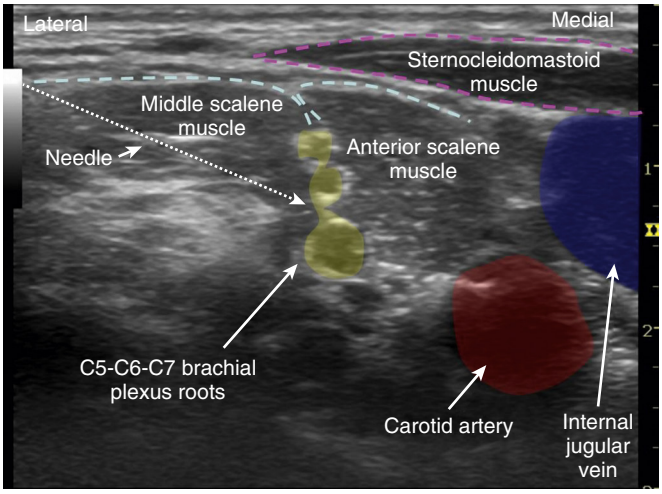


Figure 92-14. Ultrasound interscalene block imaging

located by palpation in the interscalene groove, just posterior to the sternocleidomastoid muscle, at the level of the cricoid cartilage. The puncture site is identified at the junction of the upper two thirds, with the lower third of the line joining the skin projection of the C6 process and the midpoint of the clavicle (Fig. 92-15). The success rate for this approach is very high, with a good safety record. Occasionally, blockade of the lower cord (ulnar nerve or medial branch of the median nerve) can be incomplete. The morbidity of this technique is virtually nil.[225]

SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK

In contrast to other brachial plexus blocks, risk for pneumothorax is increased because of the proximity of the lung parenchyma at this level. Use of ultrasound guidance with an in-plane approach is strongly recommended and allows real-time viewing of the needle tip, thus avoiding inadvertent pleural puncture.

Ultrasound-guided supraclavicular block in adults has been described in several articles, but few reports are available in the pediatric literature.[226,227] The brachial plexus trunks gather at the lower part of the interscalene space, where they surround the subclavian artery. This level carries the advantage of being the area where the trunks are most compact. With a high-frequency probe placed parallel and against the clavicle in the coronal oblique plane (Fig. 92-16), the brachial plexus (trunk or division) appears as a cluster of hypoechoic nodules located lateral, posterior, and superior to the subclavian artery (hypoechoic and pulsatile) and just above the underlying first rib (hyperechoic and curvilinear) (Fig. 92-17). Care should be taken to avoid intravascular injection of surrounding vessels (i.e., the suprascapular artery or dorsal scapular artery) by using color Doppler (Fig. 92-18). The needle is slowly advanced under direct visualization with an in-plane approach (from lateral to medial) toward the angle formed by the first rib and the subclavian artery (see Fig. 92-17). The goal of the supraclavicular technique is to see the spread of local anesthetic reaching the angle between the first rib and the subclavian artery.

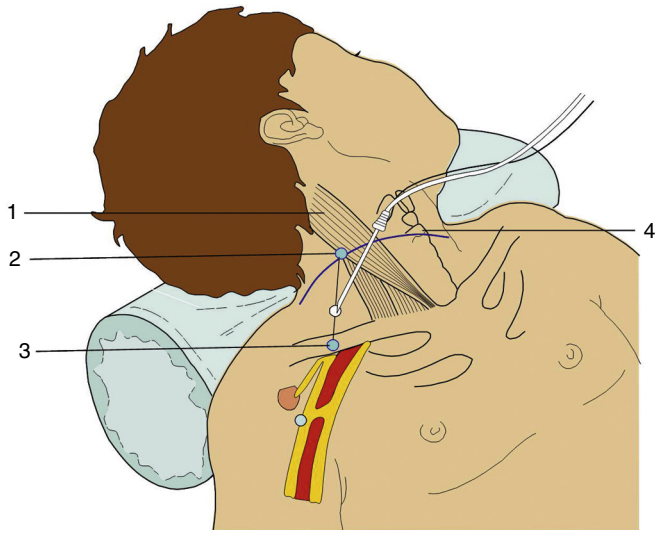


Figure 92-15. Parascalene approach to the brachial plexus. *1,* Sternocleidomastoid muscle; *2,* skin projection of the Chassaignac tubercle; *3,* midpoint of the clavicle; *4,* cricoid cartilage.



Figure 92-16. Supraclavicular block procedure. Probe position and in-plane needle insertion.

Ultrasound guidance has increased the safety profile of the supraclavicular approach so that in experienced hands this may be one of the most reliable and effective blocks of the brachial plexus.[223]

INFRACLAVICULAR BRACHIAL PLEXUS BLOCKS

Infraclavicular Approaches

Infraclavicular blocks have gained considerable interest, especially with the development of ultrasound guidance. They consist of approaching the divisions (close to the clavicle) or the cords (close to or below the coracoid process) of the brachial plexus. The two main approaches are midclavicular and paracoracoid, both performed with the patient in the dorsal recumbent position.[228] A catheter

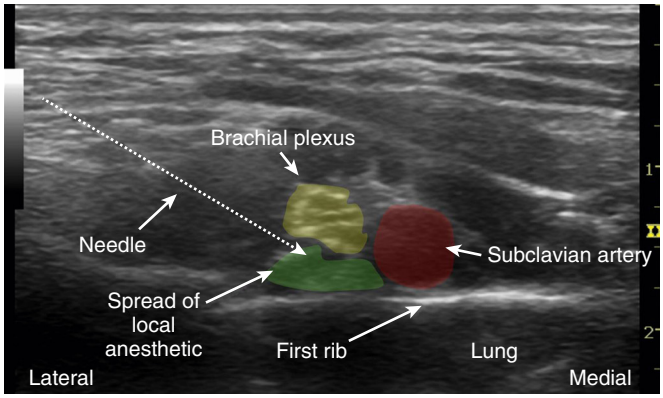


Figure 92-17. Ultrasound supraclavicular block imaging.

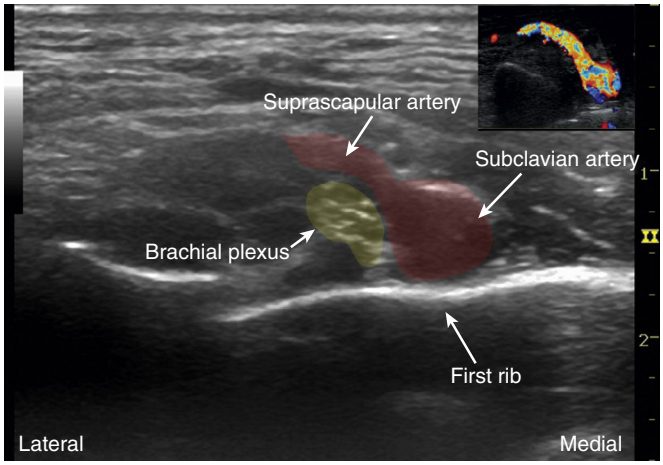


Figure 92-18. Ultrasound supraclavicular block imaging and surrounding vessels by using color Doppler.

can be easily inserted and safely secured, which is not the case in the axilla area.

Midclavicular Approaches

Two midclavicular approaches, vertical and anterolateral, have been described. The vertical midclavicular approach is performed by inserting the needle at a right angle to the skin, immediately below the midpoint of the lower border of the clavicle, until twitches are elicited in the upper extremity. Even though use of this technique was reported in pediatric patients without apparent complication,[226,229] the path followed by the needle threatens the apical pleura and lung, thus contraindicating this approach in children.

The anterolateral midclavicular approach can be safely used in children lying supine with the ipsilateral arm alongside the thorax. The landmarks are the coracoid process of the scapula, the lower border of the clavicle, and the deltopectoral groove (Fig. 92-19). The block needle is introduced 1 cm below the midpoint of the lower border of the clavicle at a 30- to 45-degree angle dorsally and a 30-degree angle laterally, aligned with the deltopectoral groove, in direction to the axilla. The objective is to enter the neurovascular sheath 1.0 to 1.5 cm medially to the coracoid process of the scapula until twitches are elicited in the arm, forearm, or hand.

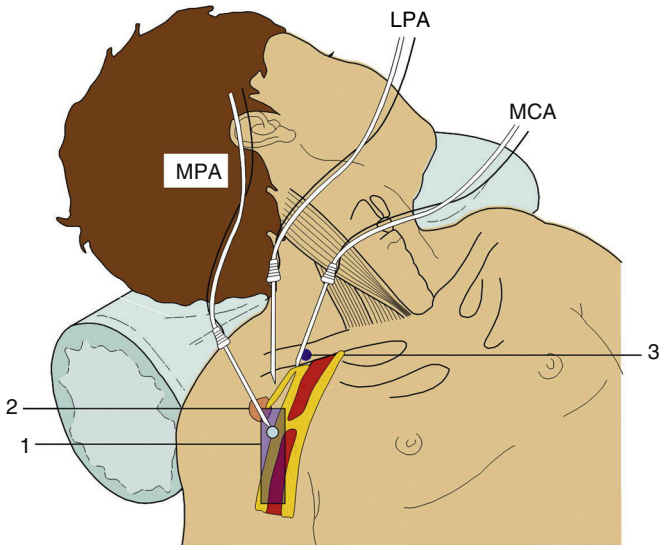


Figure 92-19. Infraclavicular approaches to the brachial plexus. *LPA,* Lateral paracoracoid approach; *MCA,* midclavicular approach; *MPA,* median paracoracoid approach; *1,* ultrasound probe; *2,* coracoid process of the scapula; *3,* midpoint of the clavicle.

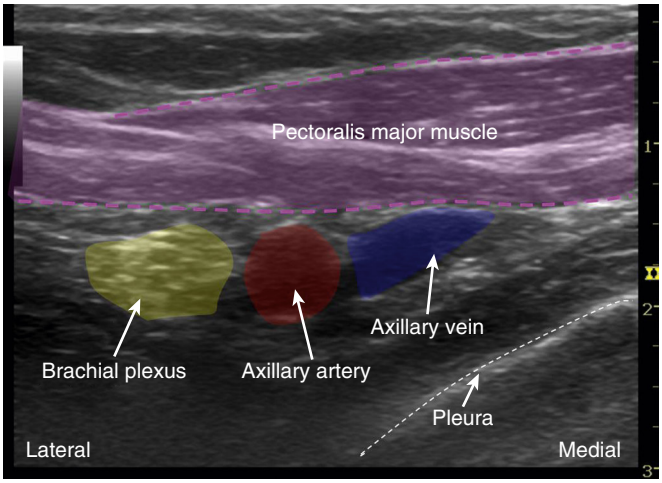


Figure 92-20. Ultrasound infraclavicular block, infraproximal approach. At this proximal level, the pectoralis major is the main muscle seen superficial to the neurovascular bundle. The pectoralis minor is located distally to this ultrasound section. Among the neurovascular bundle structures the axillary vein is the most medial, followed by the axillary artery and then the divisions of the plexus most laterally.

Paracoracoid Approaches

The medial paracoracoid approaches are currently the most popular techniques of infraclavicular blockade in children. It is the reference technique with neurostimulation and the one with the lowest morbidity. The puncture site is located at the caudal extremity of the deltopectoral groove, 1 to 2 cm (according to patient's age) both caudally and medially to the coracoid (see Fig. 92-19). Abducting the upper arm at 90 degrees instead of placing it alongside the thorax brings the plexus closer to the skin and favors circumferential spread of local anesthetic.[230] The needle is inserted perpendicularly to the skin until twitches are elicited in muscles of the upper extremity.

Ultrasound Infraclavicular Block

The lateral paracoracoid approach under neurostimulation is technically feasible but unsafe if concomitant ultrasound imaging is not available, because of the danger of pleural penetration. The technique can be performed with the arm extended alongside the thorax or abducted 110 degrees and the elbow flexed by 90 degrees,[228] thus taking away the neurovascular sheath from the parietal pleura and loosening it to favor circumferential spread of the local anesthetic. Useful ultrasound landmarks are the axillary artery and vein, which are located deep and medial to the cords, with the vein positioned medial and caudal to the artery. Pectoralis major and minor muscles are most superficial overlying the neurovascular structures.

Two main infraclavicular approaches are used. One is a proximal approach with the probe placed parallel and immediately below the clavicle, and the cords are located lateral to the axillary artery (Fig. 92-20). The second is a paracoracoid approach with the probe placed in a parasagittal plane immediately medial and inferior to the coracoid process, allowing a short-axis view of the brachial plexus (Fig. 92-21). A great deal of individual anatomic variation occurs in the location of the cords around the artery. Commonly, the lateral cord is most easily viewed, the medial cord lies between the artery and vein, and the posterior cord is deep to the artery and frequently difficult to individualize. The needle is introduced using an in-plane approach from lateral (superior) to medial (inferior), and advanced aiming to place local anesthetic posterior to the axillary artery near to the posterior cord (Fig. 92-22).



Figure 92-21. Paracoracoid infraclavicular approach procedure, with probe position and in-plane needle insertion.

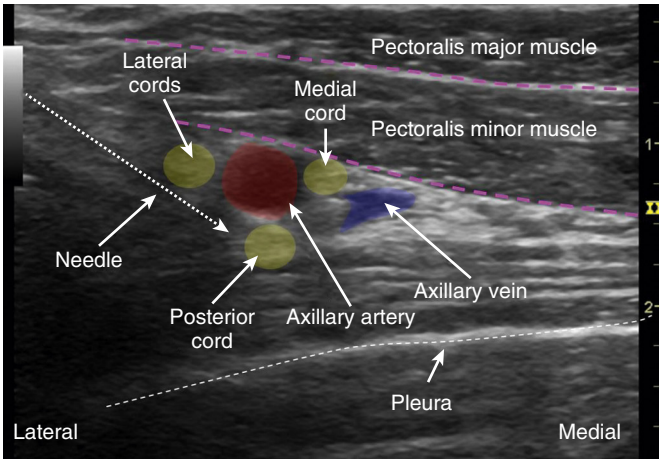


Figure 92-22. Ultrasound infraclavicular block imaging by paracoracoid approach.

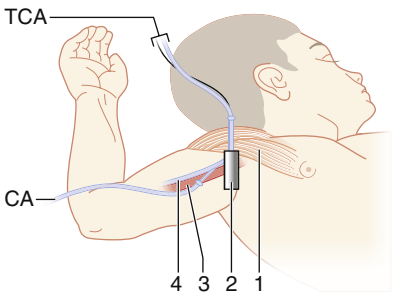


Figure 92-23. Axillary approaches to the brachial plexus. *CA,* Classic approach; *TCA,* transcoracobrachialis approach; *1,* pectoralis major muscle; *2,* ultrasound probe; *3,* axillary artery; *4,* coracobrachialis muscle.

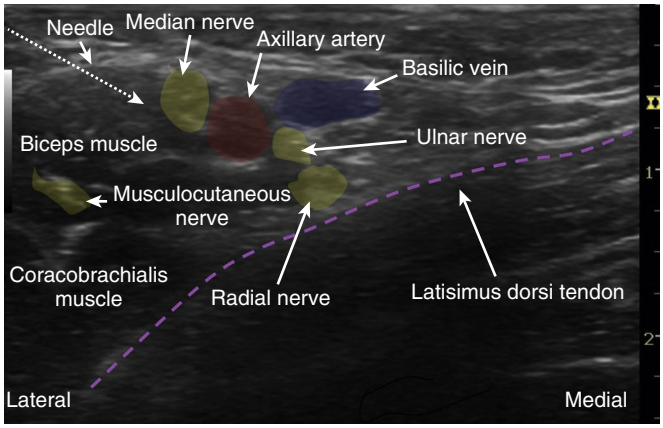


Figure 92-24. Ultrasound-guided axillary block imaging.

Axillary Approach

The axillary block is the most common approach to the brachial plexus in pediatric patients, aiming to approach the plexus at the level of its terminal branches in the axilla. It is a relatively easy and safe procedure to control perioperative pain in elbow, forearm, and hand surgeries. In children, several variants of the axillary approach have been described, with no difference in clinical outcomes regardless of the technique selected. In contrast to the procedure in adults, the transarterial approach is not used in children because of the higher incidence of vessel spasm and potential risk for ischemia. Unlike in adults, a single injection is sufficient to block all the nerves of the forearm and hand, with the exception of the musculocutaneous nerve in 50% of cases.[231] To overcome this problem, the most useful variant of this technique is the transcoracobrachialis approach. The child is placed in the supine position with the ipsilateral arm both supinated and abducted by 90 degrees.[218] The block needle is introduced posteriorly at the crossing of the coracobrachialis muscle with the lower border of the pectoralis major muscle (Fig. 92-23). The needle is advanced posteriorly toward the medial border of the humerus through the upper and lateral part of the coracobrachialis muscle (within which runs the musculocutaneous muscle). With neurostimulation, the musculocutaneous nerve is usually the first nerve encountered (it will be preferably blocked on removal of the needle); the needle is moved deeper until it crosses the perineurovascular sheath[217] and elicits twitches in the muscles of the hand and forearm. At this level the cords have split into terminal nerves, and the median nerve is usually contacted first. The local anesthetic is then injected, and the needle is removed while a small volume (0.1 mL/kg up to 5 mL) is injected close to the musculocutaneous nerve. All tourniquet pain (intercostobrachial nerve) can be ablated with subcutaneous injection in the axilla.

With ultrasound guidance, a high-frequency probe is placed perpendicular to the major axis of the arm to obtain a short-axis view of the neurovascular bundle. The ultrasound-guided axillary approach to the brachial plexus is strictly a multiinjection technique. At this level, median, radial, and ulnar nerves are situated close to the axillary artery and vein. Great variation exists on the anatomic relationship of nerves with axillary location.[232] Generally, the median nerve is located between the lateral aspect of the artery and the brachial biceps muscle, the ulnar nerve is located more superficial and medial to the artery, and the radial nerve lies deep to the artery. Sliding the probe from distal arm to axilla area should help identify the nerve. The needle can be visualized throughout the procedure as it progresses in the plane of the ultrasound beam (Fig. 92-24); its tip can be precisely placed close to each of the three main nerves and, on removal of the needle, close to the musculocutaneous nerve between the coracobrachial and short head of the biceps muscles.

Axillary blocks are very safe. Accidental arterial puncture is the most undesirable incident, which may occasionally result in transient vascular insufficiency or a compressive hematoma. Intraneural injection is the most feared complication. It is usually thought to be the main cause of permanent nerve damage and mostly undetected in the patient under general anesthesia. In a prospective study on volunteers (that surprisingly got approval from an ethics committee), Bigeleisen and associates[131] deliberately attempted to penetrate axillary nerve trunks under ECG guidance. Deliberate intraneural injections were made, and the patients were evaluated after the injection and 6 months later. No motor or sensory deficits were observed. Regardless of whether the design of this study

TABLE 92-10 **USUAL LOCAL ANESTHETIC BOLUS DOSES OF ROPIVACAINE 0.1% (NEONATE) TO 0.2% OR LEVOBUPIVACAINE 0.125% (NEONATE) TO 0.25% AND INFUSION RATES FOR BRACHIAL PLEXUS NERVE BLOCKS**

Conduction Block	Bolus Doses (mL/kg)	Infusion Rates
Brachial plexus above and below clavicle	0.3-0.5	0.1-0.2 mL/kg/hr
Any nerve trunk at elbow	0.1-0.2	—
Any nerve trunk at wrist	0.05-0.1	—

is debatable, the results are interesting in showing that intraneural injection might not be as detrimental as commonly believed and might even be innocuous provided no intrafascicular injection (which elicits strong resistance to injection and excruciating pain) is made. However, such intraneural injections should be avoided, especially when ultrasound imaging is suggestive (tip of the needle within the nerve path and increase in nerve diameter when a fraction of the local anesthetic is being injected).

When continuous analgesia is required, a catheter may be introduced into the axillary neurovascular sheath, but its fixation and immobilization are difficult. Usually, perclavicular or interscalene approaches are preferred, with safe immobilization and increased patient comfort at these levels.

The volume of injectate is critical and depends on the approach and technique used to locate the nerves (Table 92-10). With neurostimulation, no information is obtained regarding the circumferential spread around nerve trunks; thus, recommended volumes of injection are based on the probability to obtain complete blockade. With ultrasound-guided techniques, the circumferential spread of local anesthetics can be clearly seen as a complete "donut" surrounding the relevant nerve trunk. In clinical practice, the use of ultrasound for nerve block must be associated with a significant reduction in the volume of local anesthetic.

DISTAL CONDUCTION BLOCKS

Elbow and Forearm Approaches

In pediatrics, approaching the radial, median, or ulnar nerve at the elbow or wrist is still not very common. These approaches are rather difficult with neurostimulation only, and their failure rate is relatively high when blind subcutaneous injections are made. Indications have long been limited to complementation of partially failed brachial blocks.

Ultrasound imaging is widening the field of indications for these techniques because these superficial nerves are easy to identify and approach with ultrasound guidance, the more so as very small amounts of local anesthetic (0.05 mL/kg up to 1 to 2 mL) are sufficient to produce complete nerve blockade. It is possible to block median and ulnar nerves at any point of their route from the wrist to the axilla, but at the level of the wrist, caution is necessary because it is often difficult to distinguish the nerves from the tendons owing to their similar appearance.

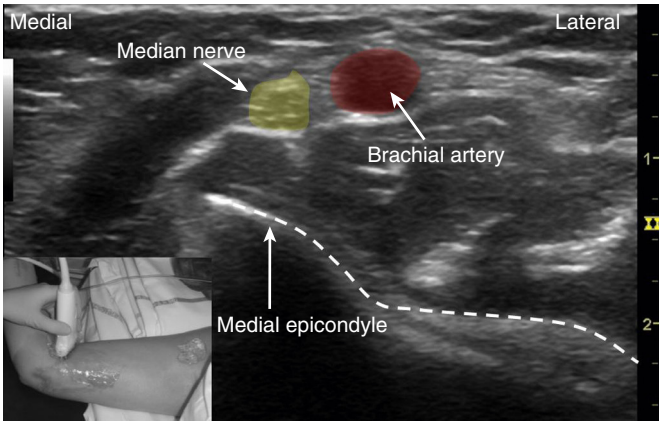


Figure 92-25. Ultrasound view of median nerve at the elbow level.

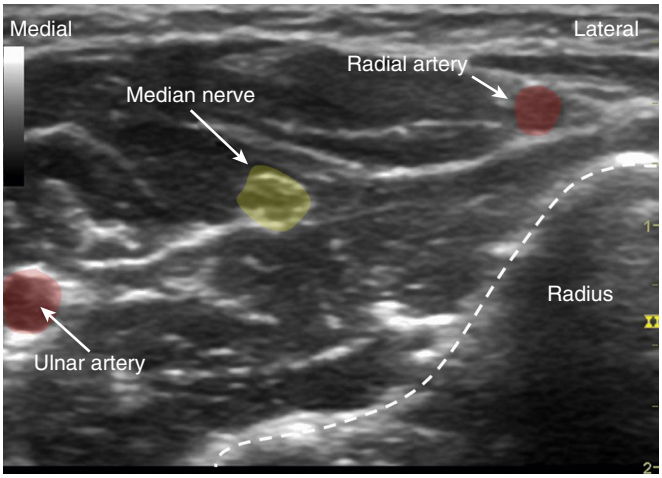


Figure 92-26. Ultrasound view of median nerve at the midforearm.

- The median nerve is located in the antecubital fossa just medial to the brachial artery (Fig. 92-25). In the middle of the midforearm, the median nerve is medial to the radial artery and medial and superficial to the radius (Fig. 92-26). At the wrist, the medial nerve is located between the tendons of the palmaris longus and the flexor carpi radialis but the distinction between the nerve and tendons may be difficult.
- The ulnar nerve can be blocked several centimeters above (Fig. 92-27) or below the elbow but never in the cubital tunnel, the groove between the olecranon and the medial epicondyle, because it can be compressed in this poorly compliant space. At the wrist, the ulnar nerve appears as a small hyperechoic triangle in close proximity to the medial side of the ulnar artery (Fig. 92-28, *A*). To facilitate and secure the procedure, we prefer to track the ulnar nerve proximally until it separates away from the artery (see Fig. 92-28, *B*).
- The radial nerve travels posterior to the humerus to the lateral side of the elbow, where it divides into superficial and deep branches. When scanning the posterolateral aspect of humerus just above the elbow, the radial nerve can be visualized below the brachial muscle in close proximity to the humerus (Fig. 92-29).

DIGITAL BLOCKS

Traditional digital ring blocks are almost never used in children, at least by anesthesiologists, because of technically safer alternatives such as the transthecal or metacarpal block and subcutaneous infiltration.

Transthecal blocks[233] consist of injecting a local anesthetic within the small space between the synovial sheath of each digital flexor tendon and the fibrous sheath that surrounds it and is attached proximally to the head of the metacarpal bone of the three median fingers (this sheath is more extended at the levels of the thumb and forefinger). In contrast to digital nerve blocks, it is safer because no terminal artery is close enough to cause complications, it is simpler because only a single injection is required, and it is less painful in conscious patients, even though the injection is not pain free. Caution should be taken in the case of infection to avoid bacterial contamination of the synovial sheath; in this case, the technique is contraindicated. The landmark is the head of the relevant metacarpal bone located by palpation of the palm while the hand is supinated. Then a 25- to 27-gauge intradermal needle is inserted perpendicularly to the palm, right in the center of the skin projection of the metacarpal head at the level of the distal palmar crease (Fig. 92-30), until bone contact is made. The needle is then slightly withdrawn (to avoid subperiosteal injection) and the local anesthetic (1% or 2% lidocaine without epinephrine) is injected.

A single, subcutaneous digital block was developed with the rationale of avoiding introduction of fluid into the digital flexor tendon sheath and a theoretic risk for infection. The subcutaneous block was performed by a single injection with a 25-gauge needle into the palmar skin at the base of the finger.[234]

Note that these palmar techniques, including single subcutaneous palmar block and transthecal block, carry a risk for anesthetizing only the last two phalanges and the ventral aspect of the proximal phalanx of the fingers.

LOWER EXTREMITY CONDUCTION BLOCKS

LUMBAR PLEXUS NERVE BLOCKS

Anatomic Considerations

The lumbar plexus is formed by the union of the anterior rami of the first four lumbar nerves (L1-L4) with variable input from the 12th thoracic nerve (T12) and L5. The lumbar plexus lies in the psoas compartment in the paravertebral space, with the anterior border formed by the psoas major muscle and the posterior border formed by the quadratus lumborum muscle. As it emerges from this space, it divides into the four nerves that innervate the anterior portion of the upper aspect of the lower extremity—the femoral, lateral cutaneous,

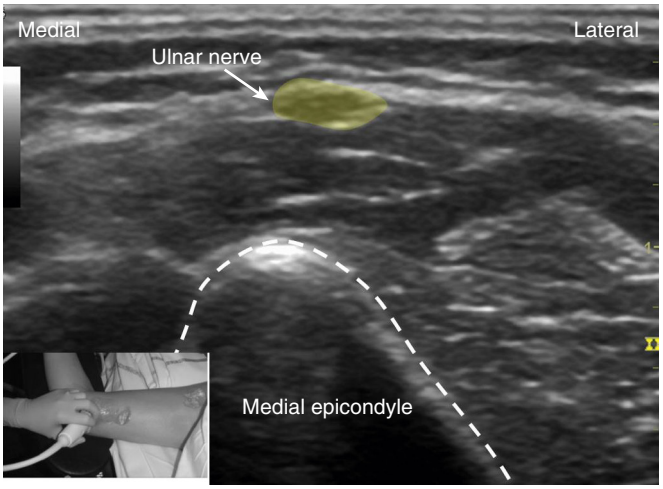


Figure 92-27. Ultrasound view of ulnar nerve at the elbow.

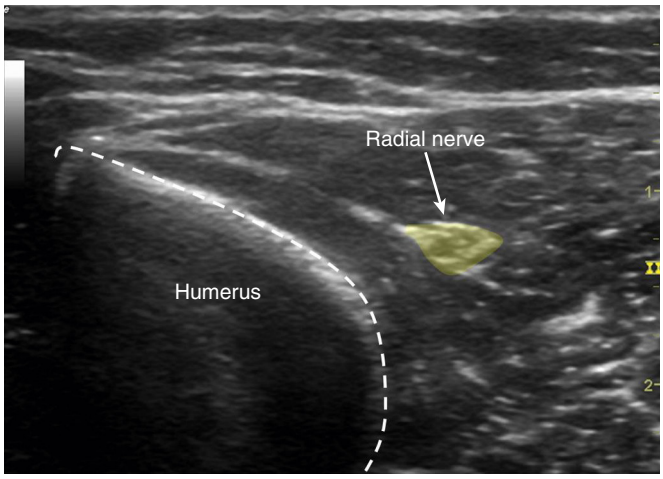


Figure 92-29. Ultrasound view of radial nerve at the posterolateral aspect of the midarm.

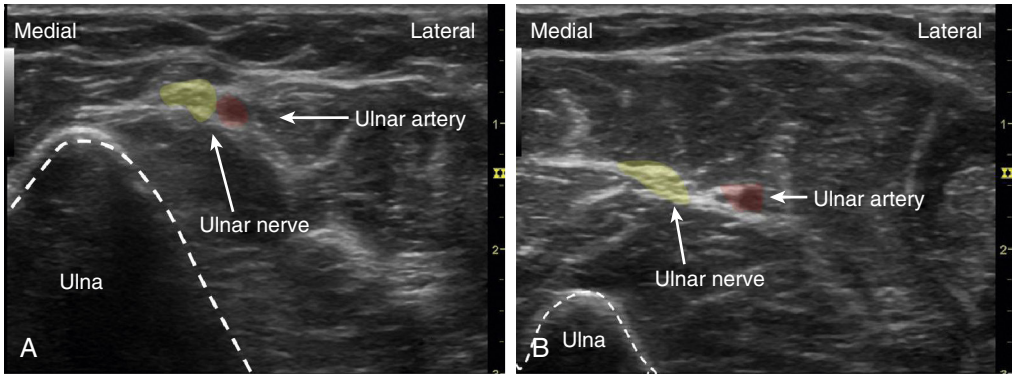


Figure 92-28. Ultrasound view of ulnar nerve at the wrist (**A**) and at midforearm level (**B**).



Figure 92-30. Transthecal nerve block. The head of the metacarpal bone is located by palpation.

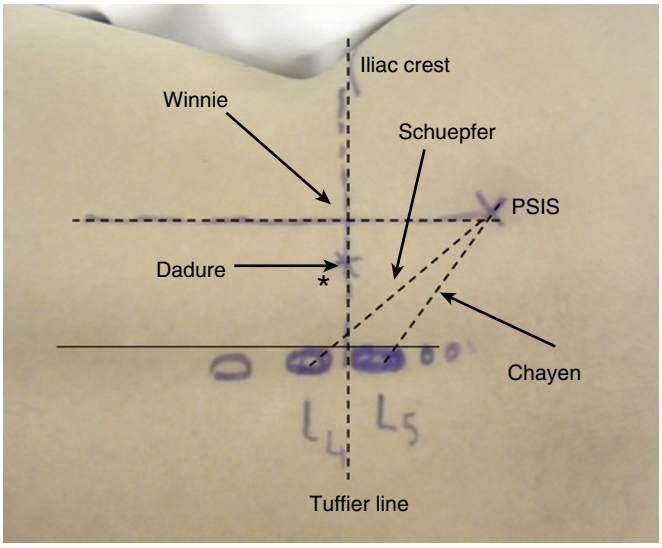


Figure 92-31. Landmarks of psoas compartment block with different procedures described in the pediatric literature. *PSIS, posterior superior iliac spine.*

genitofemoral, and obturator nerves. These nerves run a variable part of their course just below the fascia iliaca, which is the common fascia covering psoas and iliacus muscle. A sufficient volume of local anesthetic injected at the inner surface of this fascia will spread along it and reach these nerves, thus producing a fascia iliaca compartment block.

Psoas Compartment Block (Direct Lumbar Plexus Block)

Psoas compartment block is performed with the child turned in the lateral decubitus position with the operated side uppermost. The landmarks are the iliac crests, the ipsilateral posterior superior iliac spine, and the L5 spinous process. The following three puncture sites can be used (Fig. 92-31):

1. The midpoint of the line joining the posterior iliac spine to the L5 spinous process (modified Chayen approach)
2. A point located on the intercristal line (Tuffier line), three quarters of the distance between the spinous process of L4 and a line parallel to the spinal column passing through the posterior superior iliac spine[235]
3. A point located at medial two thirds and the lateral one third on a line from spinous process of L4 to the posterior superior iliac spine[236]

Whatever the puncture site used, the block needle is inserted perpendicularly to the skin until twitches are elicited in the ipsilateral quadriceps muscle. Complications, including cardiac arrest from intravascular injection, psoas muscle hematomas, epidural anesthesia, and retroperitoneal injection if the needle is inserted deeper than recommended, have been reported.[237,238] Consequently, this regional technique should be performed only by trained anesthesiologists, taking into consideration the depth of the lumbar plexus estimated according to the patient's age or weight and the proximity of important anatomic structures to the psoas compartment.

The usual indications for this block are surgeries on the hip or femoral shaft (femoral and hip osteotomies). These operations require blockade of the three main nerves innervating the hip joint: femoral, lateral femoral cutaneous, and obturator nerves. Psoas compartment block can produce excellent postoperative pain management during the first 48 hours. A recent study using sonography of the lumbar plexus in children showed that the depth of the lumbosacral plexus correlated with weight rather than age.[239] Continuous psoas compartment block provides good management of pain relief in major hip or femoral surgeries in children.[123,235,240] Continuous psoas compartment block has been compared with continuous epidural block in hip and femoral surgery in children.[123] Continuous psoas compartment block provided the same quality of postoperative analgesia with significantly less adverse events and required decreased doses of ropivacaine than continuous epidural block.

Femoral Nerve Block

Femoral nerve blocks are performed while the child lies supine, preferably with the ipsilateral limb slightly abducted. The landmarks are the inguinal ligament and the femoral artery. The puncture site is located 0.5 to 1.0 cm both below the inguinal ligament (not the inguinal crease) and lateral to the femoral artery (Fig. 92-32). The block needle is inserted posteriorly, either perpendicular to the anterior aspect of the thigh or, especially when a catheter has to be inserted, at a 45-degree angle cephalad, pointing to the umbilicus, until twitches are elicited in the quadriceps muscle when neurostimulation is used.

Ultrasound imaging makes the technique even easier.[139] The probe is placed slightly above and parallel to the inguinal ligament (Figs. 92-33 and 92-34).

The main surgical indications are femoral shaft or knee surgeries. The introduction of a catheter for continuous analgesia can be achieved by the direct perivascular (femoral) approach[241] or the fascia iliaca compartment approach.[242,243] These two approaches have never been

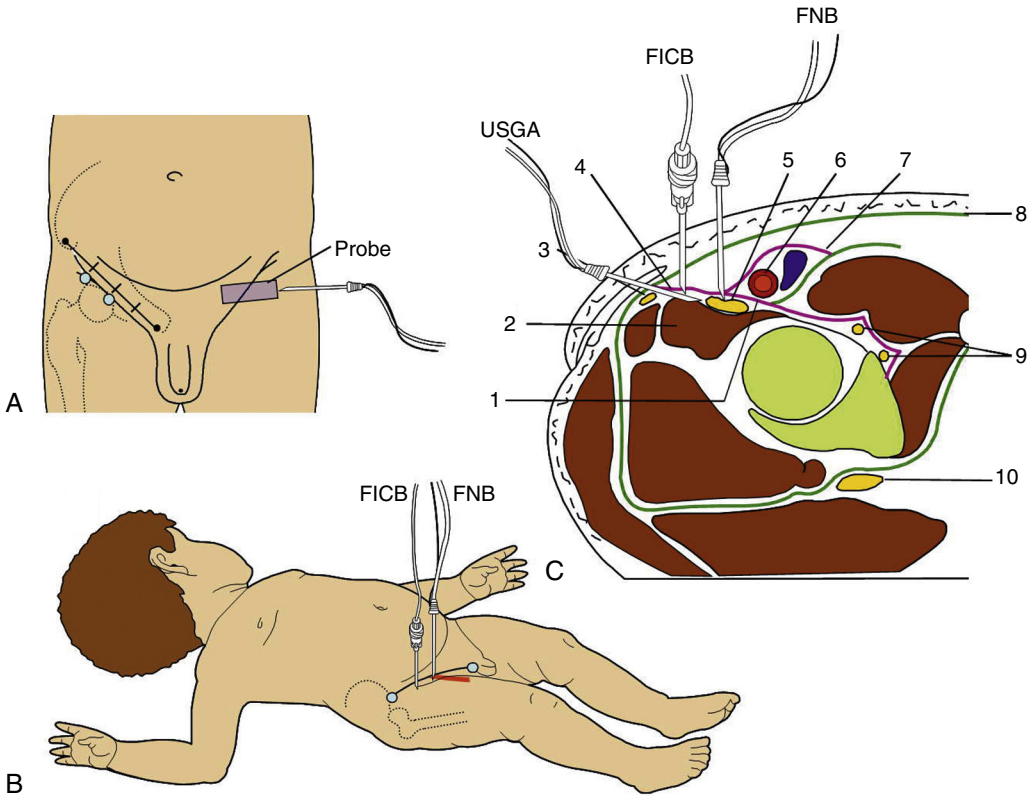


Figure 92-32. Femoral nerve and fascia iliaca compartment blocks. **A,** Landmarks and probe positioning. **B,** Patient position. **C,** Transverse section of the thigh. *FICB,* Fascia iliaca compartment block; *FNB,* femoral nerve block; *USGA,* ultrasound-guided approach; *1,* iliopectineal arch; *2,* psoas muscle; *3,* lateral cutaneous nerve of the thigh; *4,* fascia iliaca; *5,* femoral nerve; *6,* femoral artery; *7,* femoral vessel sheath; *8,* fascia lata; *9,* division branches of the obturator nerve; *10,* sciatic nerve.



Figure 92-33. Probe location for ultrasound in-plane femoral block procedure.

compared in terms of efficacy in children.[244] The fascia iliaca technique, which does not require the use of a nerve stimulator or mobilization of the limb, seems easier to perform in fractures of the femur with less accidental vascular puncture.

Fascia Iliaca Compartment Blocks

The technique consists of injecting a local anesthetic below the fascia iliaca.[244] The injectate spreads at the inner surface of the fascia and, depending on its volume, spreads around the nerves emerging from the lumbar plexus that supply the lower extremity. The technique is performed with the child lying supine (see Fig. 92-32). With this technique, the femoral and lateral cutaneous nerves are almost constantly blocked. The local anesthetic usually reaches the upper division branch of the obturator nerve, which is the branch giving a twig to the hip joint. The anesthetized area also includes areas supplied by upper branches of the lumbar plexus in more than 70% of procedures, such as the genitofemoral nerve.

Perivascular femoral nerve and fascia iliaca compartment approaches have never been compared in terms of efficacy in children.[244] The fascia iliaca compartment block was superior in terms of blockade for lateral cutaneous, obturator, and genitofemoral nerves. The perivascular approach provides a risk for significant vascular puncture. Moreover, the fascia iliaca technique, which does not require the use of a nerve stimulator or mobilization of the limb, seems easier to perform in femur fracture surgeries.

Performing this block using ultrasound showed several advantages, including extension of the duration of postoperative analgesia and decrease in the volume of injected local anesthetic in contrast to that with neurostimulation technique.[139] Local anesthetic injected volumes were decreased by two—0.15 versus 0.3 mL/kg—in ultrasound-guided techniques and nerve stimulation. The duration of analgesia was significantly increased to approximately

508/178 minutes versus approximately 335/69 minutes for all blocks using the same techniques.[139]

Usual doses of local anesthetic are 0.2 to 0.5 mL/kg in single-shot or induction bolus and 0.1 to 0.2 mL/kg/hr in postoperative continuous infusion of long-acting local anesthetic. Patient-controlled regional anesthesia can be used with bolus of 0.1 mL/kg (up to 5 mL, and maximum 3 boluses per hour). Local anesthetics with epinephrine produce significantly lower plasma concentrations and should be preferred whenever possible. Addition of clonidine (1 to 2 μg/kg) significantly prolongs the duration of analgesia.[46]

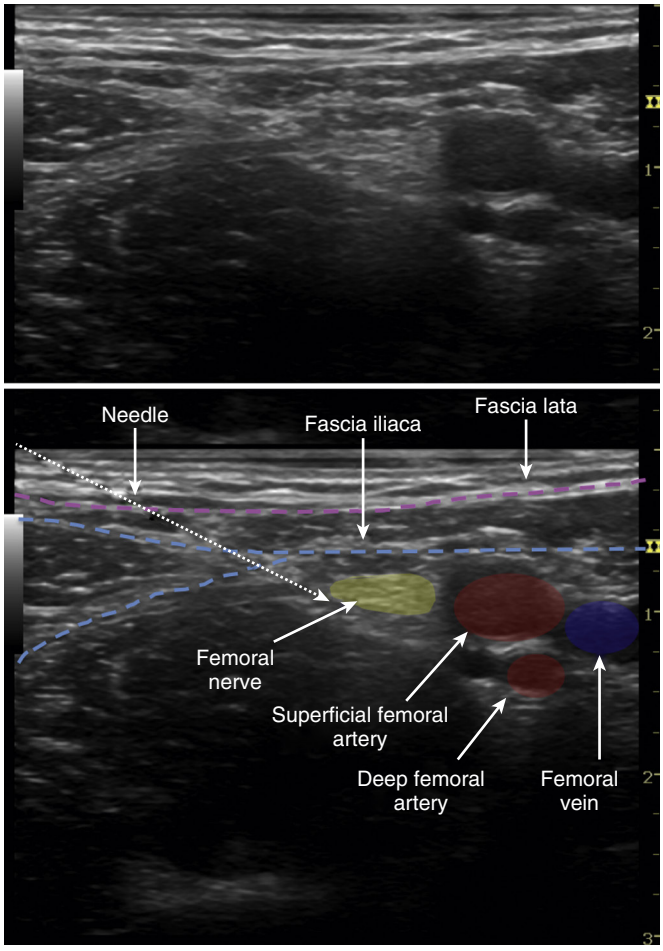


Figure 92-34. Ultrasound picture of femoral nerve block procedure.

In fascia iliaca compartment and femoral nerve block, placement of a catheter is easy and allows long-lasting pain relief (Fig. 92-35) and is improved with ultrasound guidance. Recently, Lako and associates[243] compared continuous fascia iliaca block and intravenous morphine in terms of analgesia and side effects in children undergoing pelvic osteotomy. The authors noted excellent postoperative pain relief, with less sedation and a better return of appetite in the regional analgesia group in contrast to the morphine group. On the other hand, Paut and colleagues[242] determined plasma concentrations of bupivacaine during continuous fascia iliaca block in children after major femur or knee surgery or femoral fracture. The regimen of local anesthetic administration was a bolus dose of 0.25% bupivacaine with epinephrine followed by continuous administration of 0.1% bupivacaine for 48 hours. They concluded that the plasma concentrations of bupivacaine during continuous fascia iliaca compartment block are within the safety margins for children (0.71 ± 0.4 g/mL and 0.84 ± 0.4 g/mL at 24 hours and 48 hours, respectively).

Other Lumbar Plexus Nerve Blocks

Saphenous Nerve Block. Saphenous nerve blocks are used as a complement to sciatic blocks with small amounts of local anesthetic. Because the saphenous nerve is a purely sensory nerve, it is not identifiable by neurostimulation. Many block procedures have been published, all resulting in a high failure rate (30% or higher). Ultrasound imaging, currently underevaluated in this indication, is a promising technique.

The classic approach is performed at knee level with the patient supine. The anterior edge of the medial head of the gastrocnemius muscle and the tibial tuberosity are identified by palpation. A line is drawn at a 45-degree angle with the intercondylar line, from the tibial tuberosity to the anterior edge of the gastrocnemius muscle. The technique consists of subcutaneously injecting local anesthetic along this line. This very simple technique is virtually free of complications, but its failure rate is rather high.

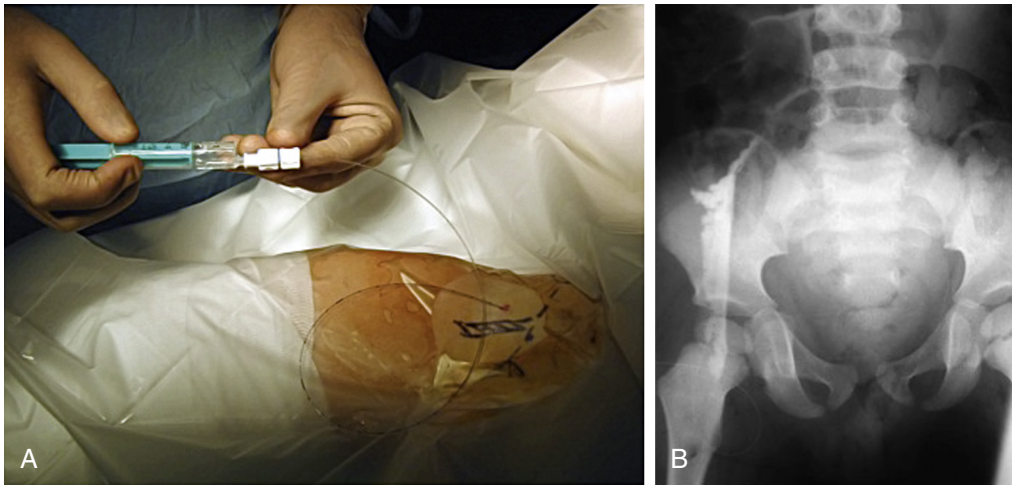


Figure 92-35. Femoral nerve catheter placement (**A**) and spread of contrast medium solution after injection into the catheter (**B**).

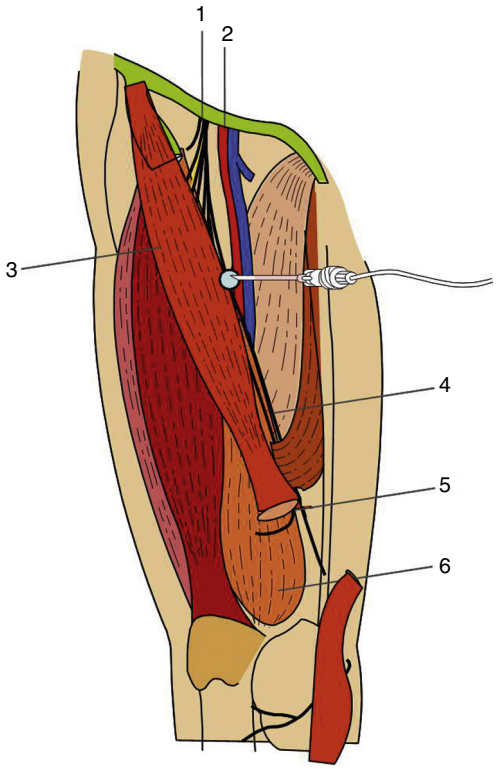


Figure 92-36. Saphenous and vastus medialis nerve block. *1,* Femoral nerve; *2,* femoral artery; *3,* sartorius muscle; *4,* saphenous nerve; *5,* motor nerve supplying the sartorius muscle; *6,* vastus medialis muscle.

The saphenous and vastus medialis nerve block takes advantage of the proximity of the vastus medialis and saphenous nerves within the adductor canal in the upper part of the thigh. Being a mixed nerve, the vastus medialis nerve can be located easily by neurostimulation, and injecting a local anesthetic results in concomitant blockade of the two nerves. The landmarks are the femoral artery, the inguinal ligament, and the upper border of the sartorius muscle (Fig. 92-36). A short and short-beveled insulated needle is inserted perpendicularly to the skin, 0.5 cm lateral to the femoral artery just above the upper border of the sartorius until twitches are elicited in the vastus medialis muscle. Injecting 0.1 to 0.2 mL/kg of a local anesthetic is sufficient to block the two nerves and obtain complete analgesia of the medial aspect of the leg and foot.

The transsarterial approach aims to infiltrate the fat pad located between the inner aspect of the sartorius muscle and great adductor tendon. The puncture site is situated at the level of the upper border of the patella, on the medial aspect of the sartorius muscle located by palpation. The block needle is inserted medially and slightly posteriorly with a 45-degree angle caudally, in the direction of the medial femoral condyle until a loss of resistance is felt as the subsartorial fat pad (through which runs the saphenous nerve) is penetrated. The paravenous approach, originally described as a "blind" infiltration technique on both sides of the saphenous vein in the upper part of the medial aspect of the leg, is considerably improved by ultrasound imaging because the saphenous vein is easy to locate. Inserting the needle along the major axis of the probe allows clear visualization of needle progression toward the vein and circumferential spread of the local anesthetic.

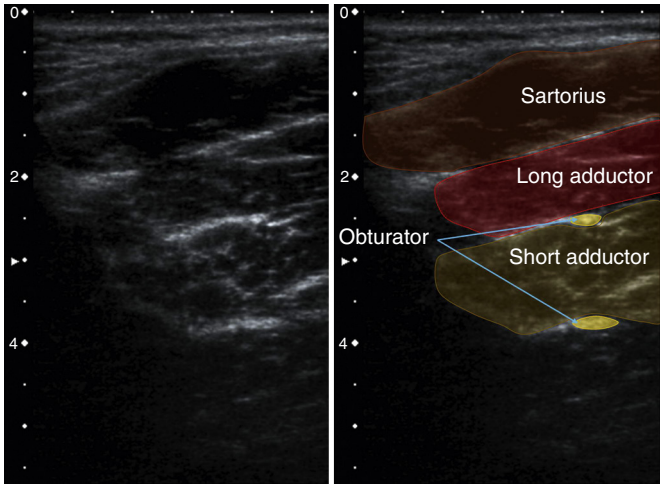


Figure 92-37. Obturator nerve block, with ultrasound imaging of the anterior and medial aspect of the thigh.

Lateral Cutaneous Nerve Block. A specific lateral cutaneous nerve block is rarely used in children; its main indication is as a technique complementary to a femoral block. Ultrasound guidance can be used.

Obturator Nerve Block. This procedure is performed with the child supine and the thigh slightly abducted and externally rotated (if possible). The landmarks are the groove between the tendon of the long adductor muscle and medial border of the pectineus muscle. The puncture site lies in this groove at the level of the greater trochanter of the femur. With neurostimulation, the needle is inserted following a strict anterior to posterior path until twitches are elicited in the long and short adductor muscles (stimulation of the anterior division branch of the obturator nerve). The needle is further advanced dorsally over 1 to 2 cm until twitches are elicited in the great adductor (posterior branch). Half of the local anesthetic solution (of a total of 0.1 mL/kg up to a maximum of 5 mL per nerve) is injected; the needle is then removed until stimulation of the anterior branch is obtained again and the second half of the anesthetic is injected.

The same technique can be performed with ultrasound imaging. The probe is placed below the pubic tubercle, with its major axis parallel to the inguinal ligament. The aponeuroses of the sartorius and long and short adductors are easily identified. The anterior branch can be easily found between the long and short adductors, and the posterior branch lies between the short and great adductors (Fig. 92-37).

SCIATIC NERVE BLOCKS

Anatomic Considerations

The sacral plexus is formed by the anterior rami of the fourth and fifth lumbar nerves and the first three sacral nerves with variable input from the fourth sacral nerve.



Figure 92-38. Position and ultrasound visualization of the in-plane subgluteal approach to sciatic nerve.

The sacral plexus lies on the surface of the sacrum anterior to the piriformis muscle. The sacral plexus gives rise to the other two nerves that innervate the lower extremity: the posterior cutaneous nerve of the thigh (otherwise known as the small sciatic nerve) and the sciatic nerve. Peripheral blockade of these two nerves is considered together as blockade of the sciatic nerve. These two nerves travel together in the same sheath as they exit through the greater sciatic foramen into the posterior aspect of the upper part of the leg. The sciatic nerve runs in the midline of the posterior aspect of the thigh to the apex of the popliteal fossa. At the level of this fossa, it divides, at a variable distance, into the common peroneal and the posterior tibial nerves. The common nerve continues its descent around the head and neck of the fibula. The terminal branches form the superficial and deep peroneal nerves. The tibial nerve runs in the internal face of the leg and emerges laterally and behind the tibial artery at the level of the lateral malleolus. Its terminal branches are the lateral and medial plantar nerves.

Indications and Contraindications

Sciatic nerve blocks are recommended for operations on the foot and the leg (a complementary saphenous nerve block is often required because this nerve provides cutaneous innervation of the medial aspect of the leg). Depending on the surgery, the sciatic nerve will be approached in the popliteal fossa or more proximally. Sciatic blocks have no specific contraindications. As with other extremity nerve blocks, patients at risk for compartment syndrome require close monitoring and use of diluted solution to avoid motor blockade.

Proximal Sciatic Nerve Blocks

Numerous techniques have been described for which the associated morbidity can differ significantly. When successful, they provide the same distribution of anesthesia. When contemplating a proximal sciatic block, the anesthesiologist must consider (1) morbidity of the technique, (2) positioning of the patient, (3) technique used to locate the nerve, (4) necessity for catheter placement, and (5) experience of the anesthesiologist with this particular technique.

Subgluteal Approach. The subgluteal approach is a common proximal way to the sciatic nerve in children. This

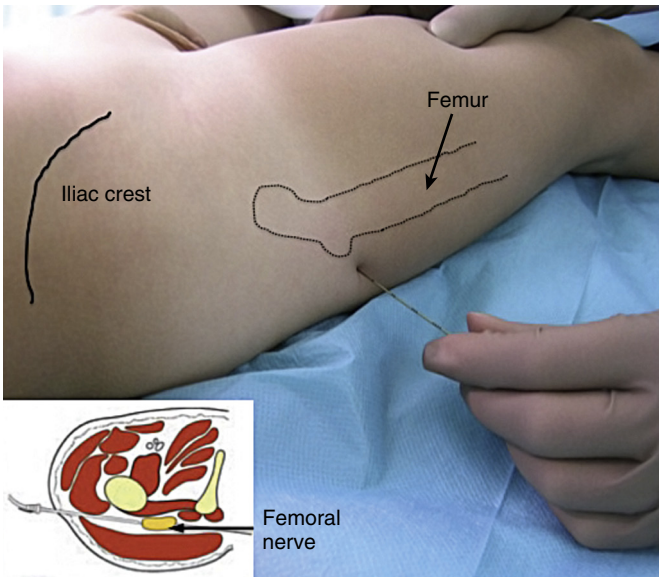


Figure 92-39. Proximal sciatic lateral block procedure.

block can be performed in a supine, lateral, or prone position. In supine position, the leg is flexed to 90 degrees at the hip with the knee flexed at 90 degrees (Fig. 92-38). This position is preferable in small children. In older ones, the lateral or prone position is preferred. The point of puncture is located at the midline joining the ischiatic tuberosity and the greater trochanter of the femur. The needle is inserted at right angles to the skin toward the femur until twitches are elicited in the foot. The nerve is easily accessible, is relatively superficial, and lies in a palpable groove.

Ultrasound guidance with or without neurostimulation facilitates the success of this block.[245] Continuous subgluteal block can be easily performed and permits good postoperative pain management in major ankle or foot pediatric surgery.[245]

Lateral Approach. A lateral approach to the sciatic nerve has been described for use in patients lying supine[246] with the relevant leg slightly rotated medially. The needle is inserted horizontally toward the lower border of the femur (Fig. 92-39). If bone contact is made, the needle is withdrawn and reinserted slightly more posteriorly until

twitches are elicited in the leg and the foot. The distance at which the sciatic nerve is found can be correlated with patient age (Fig. 92-40).

Proximal lateral sciatic nerve blocks have been described for major foot surgery in children, but with high doses of local anesthetics and catheter migration or dislodgement maintained during patient mobilization.[247,248] It has been described in children with the same landmarks and technique of puncture described later. The catheter can be fixed with transparent dressing or tunneled to permit more stable fixation and prolonged administration.

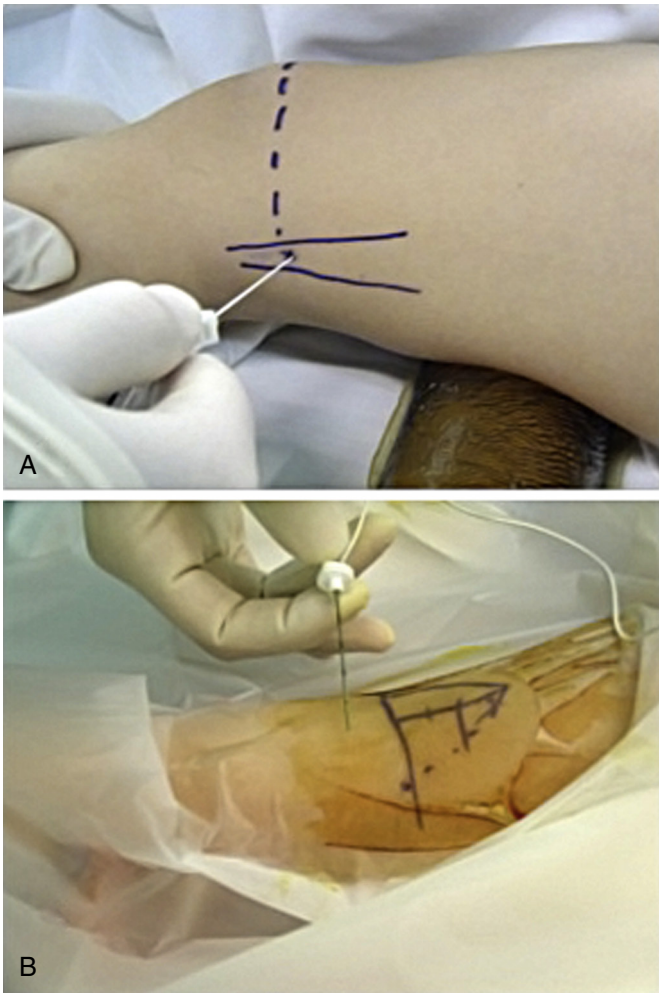


Figure 92-40. Sciatic popliteal nerve block with lateral approach (**A**) and posterior modified Singelyn technique approach (**B**).

Popliteal Sciatic Approach

Popliteal nerve block is a particularly simple, safe, and effective method, providing good analgesia with small amounts of local anesthetics. This approach is the first choice for major foot and ankle surgeries in children to ease the introduction of the catheter. The two approaches to the sciatic nerve in the popliteal fossa are the lateral and posterior approaches. The child may remain in the supine position for the lateral approach. The landmark for lateral distal sciatic nerve approach is the groove between the vastus lateralis muscle and the tendon of the long head of the biceps femoris muscle at the level of the superior edge of the patella (Fig. 92-41, *A*). In the posterior approach, the child is placed in the prone or, preferably, the semiprone position, resting on the nonoperated side. A popliteal sciatic nerve block with posterior approach is performed using the landmarks of Singelyn and colleagues[249] adapted to children (see Fig. 92-41, *B*). A nerve stimulator may be used to assist the practitioner to identify the nerve. Correct needle placement is identified when an output 0.6 mA elicits a characteristic motor response corresponding to either tibial (dorsiflexion of the foot) or common peroneal (foot eversion) nerve stimulation.

Ultrasound guidance is easy at this level, allowing an in-plane or out-of-plane approach depending on the habits of the practitioner. Ultrasound scanning permits the location of the sciatic nerve and its division in popliteal fossa.[245,250] The sciatic nerve is usually located laterally and superficially to the popliteal artery (Fig. 92-41). Ideally, the sciatic nerve should be blocked before its division into tibial and common peroneal nerves to obtain the best result.

Pain management for major foot and ankle surgery requires continuous sciatic nerve block. The distal approach is particularly interesting because of the ease of performance and the quality, power, and duration of analgesia with low doses of local anesthetics.[67,156,251,252] Continuous popliteal nerve block was compared with continuous epidural block in children undergoing major foot and ankle surgery.[252] Both techniques were associated with excellent postoperative analgesia in this study, but continuous popliteal nerve block led to less urinary retention, less discontinuation of local anesthetic infusion, and less

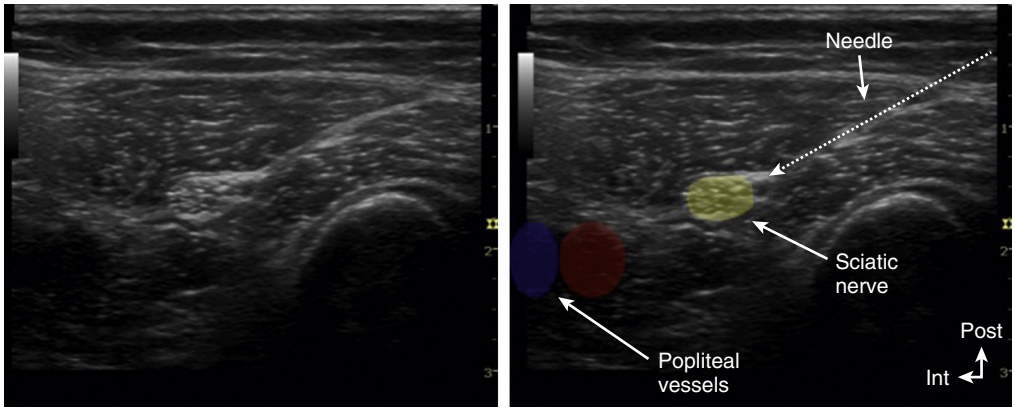


Figure 92-41. Ultrasound of sciatic popliteal nerve block. Sciatic nerve is usually located laterally and superficially to the popliteal vessels.

nausea and vomiting. The popliteal catheter is the location most frequently used to treat children at home.[79,155,156]

Transthecal and Metatarsal Blocks

The metatarsal (or midtarsal) block is an easy technique for providing good pain relief for surgical procedures on the toes. The child is placed supine, and the head of the relevant metatarsal is palpated on the sole. The technique consists of inserting a standard intramuscular needle dorsally on the dorsum of the foot in close contact with the medial border of the base of the metatarsal until the tip of the needle is felt and seen as it pushes the skin of the sole. A volume of 1 to 3 mL of local anesthetic is then injected while the needle is slowly withdrawn. The same procedure is repeated along the lateral border of the same metatarsal to provide full anesthesia of the relevant toe.

The transthecal technique as described for finger procedures can be transposed to the sole of the foot by palpating the head of the relevant metatarsal bone and injecting a small volume of local anesthetic in the fibrous sheath surrounding the tendinous sheath of flexor tendons. However, except for the greater toe, the landmarks are more difficult to identify and, because of the thickness of the sole, the infiltration is technically more difficult and less precise.

BLOCKS OF NERVES SUPPLYING THE TRUNK

Surgeries of the trunk are some of the most common surgeries performed in children. Traditionally, central blocks are the regional analgesia frequently used for these procedures. Nevertheless, central blocks have some adverse effects, including unwanted motor block, urinary retention, pruritus, nausea and vomiting, and risk for spinal cord trauma or epidural hematoma. Internationally, peripheral nerve blocks are increasingly taking place in the practice of pediatric anesthesia.[98] An epidemiologic study found that truncal blocks are the most commonly employed in children, even preferred over central blocks, because of their low morbidity. Abdominal wall blocks are known as effective techniques to provide adequate analgesia for minor abdominal surgery in children. Moreover, these techniques are readily accessible to ultrasound guidance.

PERIPHERAL BLOCKS FOR ABDOMINAL WALL SURGERY

Rectus Sheath and Paraumbilical Block

The rectus sheath and paraumbilical block technique consists of injecting a local anesthetic within the substance of the rectus abdominis muscle along the course of the terminal branch of the tenth intercostal nerve , which supplies sensory innervation to the periumbilical area. It provides efficient pain relief for umbilical or other midline surgical incisions, as well as umbilical and epigastric hernia repair, laparoscopic surgery, and pyloromyotomy. Today, this regional anesthetic technique has become increasingly popular.

Two punctures, on each side of the abdomen, are necessary. A short beveled needle inserted at 45-degree angle is necessary to perceive the passage of different planes. Long-acting local anesthetics are usually used with a low concentration (0.2% to 0.5%). The total volume of anesthetic solution injected is 0.1 to 0.5 mL/kg of body weight in each side. This dose of local anesthetic is widely decreased with ultrasound guidance.

The landmark for the fascia-click technique is the midline between the outer border of rectus muscle and the umbilicus. Two methods have been described in pediatric literature with a sensation of fascial click when the needle pierces the anterior rectus sheath.

Performing this block under ultrasound guidance can avoid intraperitoneal punctures and erratic needle position.[253] In contrast to the fascial-click method, ultrasound guidance significantly increases correct needle position (88% versus 44%) and decreases the rate of intraperitoneal or injections that are too superficial (11.5% versus 34.5% and 0% versus 20.9%, respectively, for ultrasound-guided techniques and fascial click).[254] Both aponeuroses of the rectus muscle and the parietal peritoneum are very echoic. The probe is placed horizontally over the umbilicus, and the block needle is inserted medially in long-axis orientation. The superficial fascia is bent and then crossed by the tip of the needle, which should be moved forward until it contacts the deep fascia (to favor the longitudinal spread of the anesthetic). The anesthetic is then injected and can be visualized in the form of an expanding biconvex black shadow (Fig. 92-42).

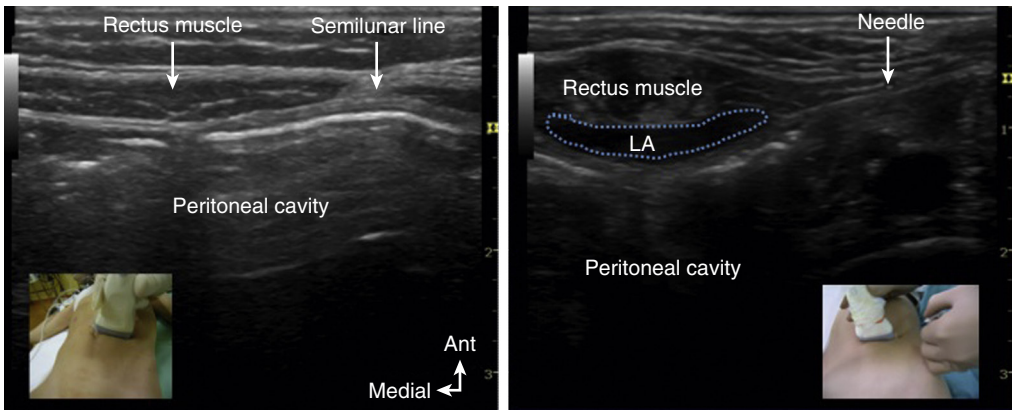


Figure 92-42. Ultrasound of paraumbilical block. Insertion of the needle close to the posterior fascia of the rectus muscle and injection of the local anesthetic creating a biconvex black cloud.

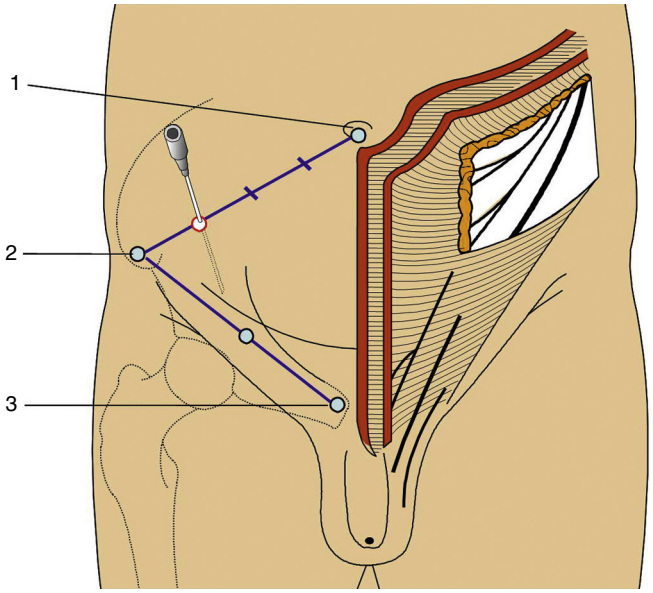


Figure 92-43. Iliohypogastric and ilioinguinal nerve blocks. *1,* Umbilicus; *2,* anterior iliac crest; *3,* pubic spine.

Ilioinguinal and Iliohypogastric Nerve Blocks

The three nerves supplying the inguinal area are the ilioinguinal, iliohypogastric, and genitofemoral nerves. In 50% of patients, sensory innervation of the inguinal canal depends exclusively on the genital branch of the genitofemoral nerve (also termed the external spermatic nerve in males). Several publications focusing only on the ilioinguinal and iliohypogastric nerves have appeared in the literature, especially with the development of ultrasound imaging.[138,255] Not surprisingly, the quality of analgesia produced is often unsatisfactory because a major contributor to sensory innervation remains unchanged.

The inguinal procedure, as well as inguinal hernia repair, orchiopexy, hydrocele repair, or cord cyst, may benefit from intraoperative and postoperative pain management with ilioinguinal-iliohypogastric block. This technique, widely described in the literature, is a fascial-click technique. A single-injection technique can safely and reliably block the three relevant nerves at once because these nerves are located in the same fascial plane close to the subcutaneous inguinal ring formed by the aponeurosis of the external oblique muscle. The landmarks are the umbilicus, ipsilateral anterior superior iliac spine (ASIS), and midpoint of the inguinal ligament. The ASIS-umbilicus line is divided into four equal parts; the puncture site is located at the union of the lateral fourth with the medial three fourths (Fig. 92-43). A short-bevel needle is essential to perceive the passage of the various planes. The two main risks are intravascular injection (very low) and the crossing of three muscle layers with penetration into the abdominal cavity or intraperitoneal organ. In addition, the extension of the territory femoral anesthesia is a complication reported after ilioinguinal-iliohypogastric block with an incidence of up to 10%.[256] The usual dose is 2.5 mg/kg of long-acting local anesthetic. Puncture may be bilateral if the surgery requires.

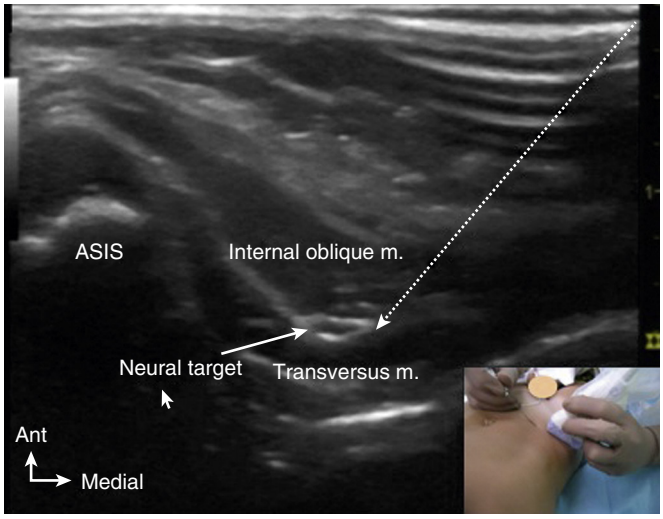


Figure 92-44. Ultrasound. Ilioinguinal and iliohypogastric block imaging and probe placement for in-plane needle insertion. *ASIS,* Anterior superior iliac spine; *m.,* muscle.

Ultrasound guidance of this block has advantages in terms of quality of analgesia and dose reduction of local anesthetics. The probe is located on the line between the ASIS and umbilicus close to ASIS. Two muscles of the abdominal wall are visible at this level: the transverse muscle and internal oblique muscle. The neural target is located between both these muscles (Fig. 92-44). The needle insertion can be performed with an in-plane or out-of-plane technique. Willschke and associates[138] showed that the total volume of local anesthetic used in the ultrasound group was significantly lower than in the fascial-click technique (respectively, 0.19 mL/kg versus 0.3 mL/kg of 0.25% levobupivacaine). They concluded that the local anesthetic optimal minimum volume for this ultrasound-guided block was 0.075 mL/kg of 0.25% levobupivacaine.[257] Using the traditional fascial-click technique causes erratic needle location in 85% of cases and 45% of blockade failures.[258]

Transversus Abdominis Plane Block

The transversus abdominis plane (TAP) block presents a very interesting alternative to the ilioinguinal and iliohypogastric nerve block for inguinal surgery in children.[259] It has become incredibly popular for analgesia in abdominal wall surgery. One objective of this technique is to block the segmental nerves T9 to T12 and ilioinguinal and iliohypogastric nerves by spread of local anesthetic in the plane separating the transverse abdominal muscle and internal oblique muscle by a single injection.

The lumbar triangle of Petit (a space bounded by the iliac crest, latissimus dorsi muscle, and external oblique muscle) is used as a landmark, and a sensation of two "pops" indicates the correct needle position. The first pop occurs after penetration of the fascia of the external oblique muscle, and the second occurs after penetration of the internal oblique muscle. In general, the blind TAP block technique is described as easy to perform and having few complications.

In children, ultrasound guidance to perform this block is recommended. The block is accomplished by

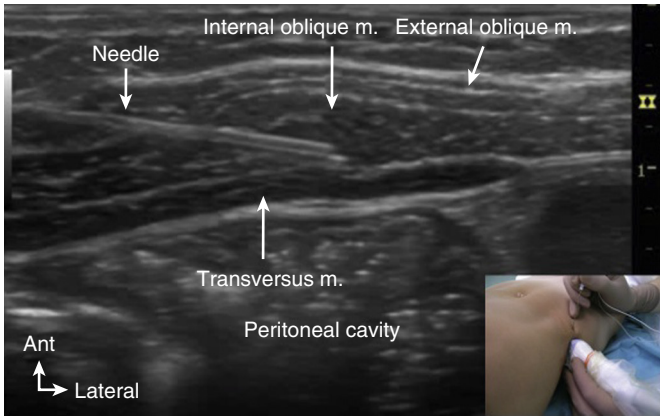


Figure 92-45. Ultrasound transversus abdominis plane block imaging and probe placement for in-plane needle insertion. *m.,* Muscle.

positioning the probe on the midclavicular line between the iliac crest and the last rib, allowing a puncture in plane (Fig. 92-45). Ultrasound guidance provides greater safety when performing this block by direct visualization of different muscle planes, the needle and its correct position, and distribution of local anesthetics in this plane.[260] Visualization of different muscle planes is sufficient and does not require identification of neural structures itself. The TAP block has been compared to the ultrasound-guided block and ilioinguinal and iliohypogastric ultrasound-guided block for hernia surgery in children.[261] The ilioinguinal and iliohypogastric block produces better postoperative analgesia, probably due to inefficient blockage of the genital branch of the genitofemoral nerve with the TAP block technique.

PERIPHERAL BLOCKS FOR PENILE SURGERY

Penile Block

Surgery of the prepuce and penis surgery is common in children. This surgery may need advanced pain control for 12 to 24 hours, and is usually done on an outpatient basis. Nerve supply to the penis depends mainly on the dorsal nerve of the penis, which is a terminal branch of the pudendal nerve. The penile block by subpubic approach with long-acting local anesthetic for prolonged analgesia is a good indication for this type of surgery. The usual dose is 0.1 mL/kg (maximum 5 mL) of local anesthetic on each side. The technique is to inject an appropriate volume of local anesthetic in the two compartments of the potential subpubic space behind the Scarpa fascia (Fig. 92-46). Puncture is performed perpendicularly to the skin. Gentle traction is exerted on the penis to tension the Scarpa fascia and better feel the fascial click (Fig. 92-47). This block procedure is easy and its learning curve is particularly short.[262] Ventral injections of the perineal nerve can be combined with dorsal penile nerve block for circumcision surgery to overcome the failure rate of the dorsal nerve block of the penis.

Crossing of the Scarpa fascia also can be verified by ultrasound imaging.[263,264] Ultrasound-guided penile nerve block improved the efficacy of the block in contrast to the fascia-click technique in terms of the postoperative

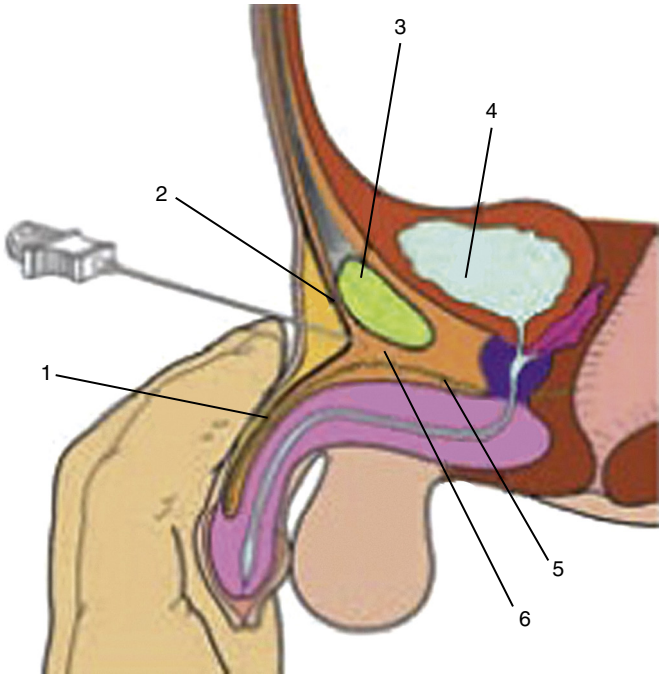


Figure 92-46. Anatomic puncture for penile block via the subpubic space. *1,* Buck fascia; *2,* Scarpa fascia; *3,* pubic bone; *4,* bladder; *5,* dorsal nerve of penis; *6,* subpubic space.

pain during the first postoperative hour and the time to the first requirement for postoperative analgesia.[265]

The morbidity is extremely low (almost nil when a local anesthetic without epinephrine only is used), whereas complications have been reported after attempts to block the nerves by infiltration of a local anesthetic below the Buck fascia at the dorsal part of the penis.

The use of adrenaline and skin infection at the puncture site are the main contraindications of this block. Serious complications are the consequence of a lesion of the dorsal artery in case of median puncture and the risk for injury to the cavernosus corpus with local anesthetic injection equivalent to an intravenous injection of local anesthetic.[266]

The usual indications are elective surgery such as circumcision and phimosis cure or emergency surgery such as reduction of a paraphimosis or release of a foreskin stuck in a zipper pants.

Pudendal Nerve Block

Given the random effectiveness of penile block for surgery of the prepuce in children, some teams advocate the use of pudendal block. The pudendal nerve provides sensory and motor innervation to the pelvic cavity and its contents, including external genital organs. The landmarks are the two ischial tuberosities and anus (Fig. 92-48). The distribution of anesthesia depends on the volume of injectate. With 0.1 mL/kg (up to 5 mL), anesthesia is usually limited to the perineal nerve that supplies the posterior part of the scrotum (this is enough to complement an ilioinguinal, iliohypogastric, and genitofemoral nerve block when a scrotal incision is required). With 0.3 to 0.4 mL/kg on each side (up to 15 mL), all division branches of the pudendal nerve are blocked, thus providing complete

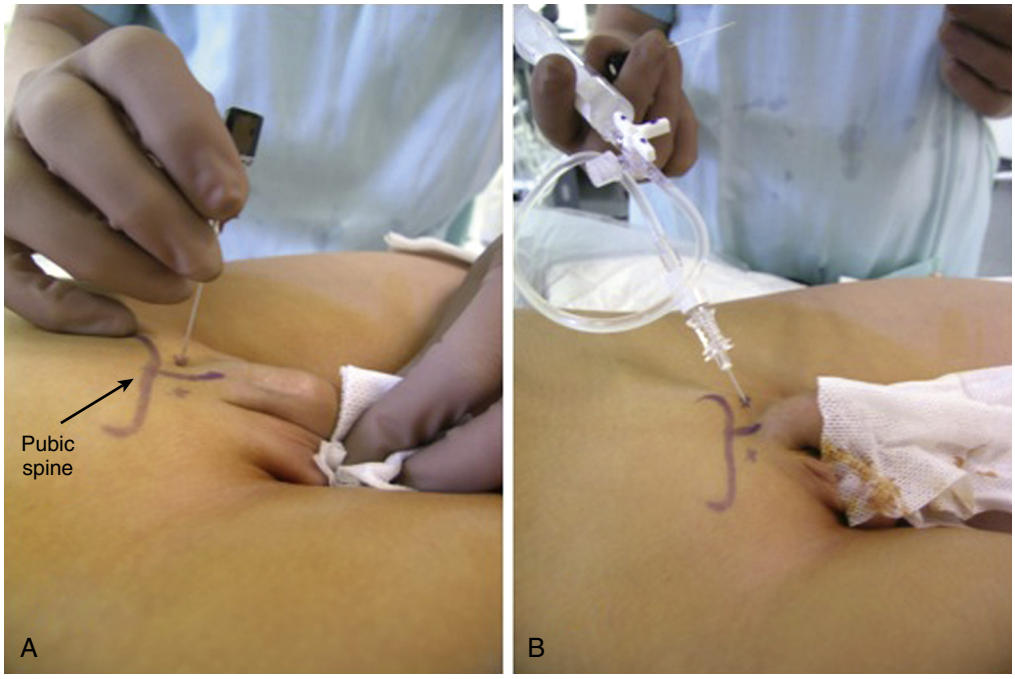


Figure 92-47. Penile block technique procedure. Gentle traction is exerted on the penis to tension the Scarpa fascia and better feel the fascial click (**A**). Injection of local anesthetic is easy without resistance (**B**).

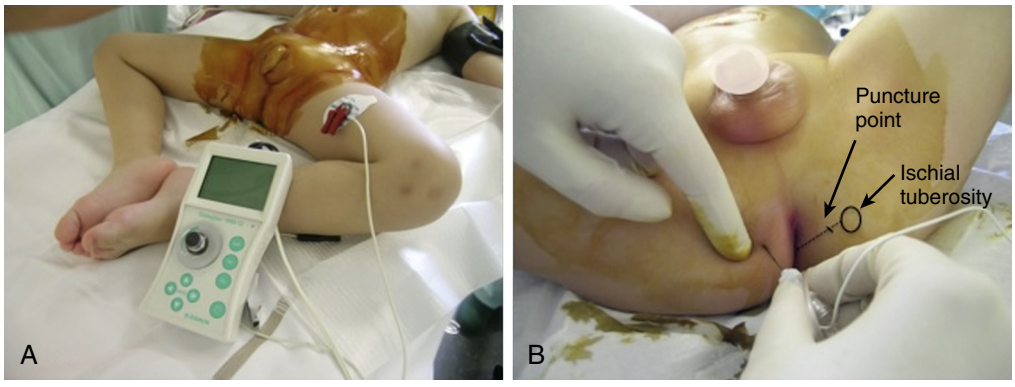


Figure 92-48. Position for pudendal block procedure (**A**) and landmarks and puncture (**B**).

analgesia of the perineum, including blockade of the dorsal nerve of the penis.

Because the pudendal nerve is a mixed nerve, a nerve stimulator can be used to locate it more precisely if this is deemed useful[267] (see Fig. 92-48, *A*). The expected motor response is a contraction of the external anal sphincter. It is recommended to start at an intensity of 1.5 to 2.0 mA. The position of the needle is considered adequate if the muscle response is obtained for an intensity of between 0.5 and 0.8 mA (0.1 to 0.2 msec, 1 Hz).

Ultrasound guidance has been used in adults, but identification of the pudendal nerve was possible in only half of the procedures.[268] Because this nerve is accompanied by a terminal artery (pudendal artery), local anesthetics with ephedrine must be avoided.

Naja and associates[269] compared nerve-stimulated pudendal block and dorsal penile nerve block with the fascia-click technique in 60 children undergoing surgery for circumcision. The authors showed a significant decrease in pain scores and analgesic consumption in the group with a pudendal block, with higher parental and surgical satisfaction. Perineal nerves appear to play an important role in the innervation of the penis, and it is the recommended block for circumcision surgery. The perineal and dorsal nerves are terminal branches of the pudendal nerve. The pudendal nerve block has the ability to block the dorsal and perineal nerves with only one single injection.

INTERCOSTAL NERVE BLOCK

Intercostal nerves run along the lower border of each rib, within the intercostal space, a triangular space, with (1) a medial border formed by the posterior intercostal and innermost intercostal muscles, endothoracic fascia, and parietal pleura; (2) a lateral border formed by the internal and external intercostal muscles and intercostal membrane (thickening of the inner fascia of external intercostal muscles); and (3) a base formed by the lower rib. Intercostal nerve block is obtained by injecting a local anesthetic within the intercostal space and, provided several adjacent intercostal spaces are infiltrated, adequate intraoperative and postoperative pain relief is obtained for thoracotomy,[270] liver transplantation, pleural drainage, and management of rib fractures.

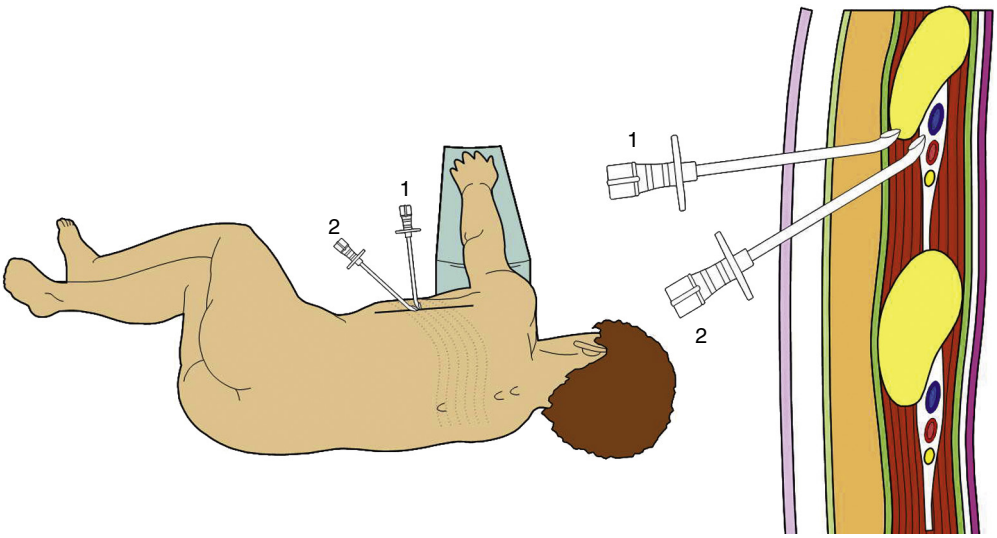


Figure 92-49. Intercostal nerve block. *1,* Insertion of the needle at an 80-degree angle to the skin; *2,* caudal and dorsal redirection of the needle.

This block must be avoided in the presence of impaired oxygenation or gas exchange, and it requires that all patients be kept under intensive medical observation because of the danger of clinically delayed pneumothorax. It is not suitable for outpatient surgery.

The safest approach to the intercostal space is along the midaxillary line with the child lying semiprone using a short 22- or 20-gauge Tuohy needle (intradermal needles are not appropriate) (Fig. 92-49).

A catheter can be introduced in the intercostal space located at the center of the area to be anesthetized to allow reinjections; the catheter also can be inserted intraoperatively under direct vision by the surgeon.[271,272] However, the safety of continuous techniques is questionable because of high systemic uptake of local anesthetic.[273] Spread of large-volume anesthetic solution can reach distant intercostal spaces (even contralateral ones), probably via the paravertebral space, thus providing adequate duration of pain relief with a single injection in some patients. Spread to the epidural space also can occur. Thus, the patient should be admitted to the intensive care unit for careful monitoring of respiratory function and for delayed pneumothorax.

THORACIC PARAVERTEBRAL SPACE BLOCK

Paravertebral block in children was first described 30 years ago[274] and many studies have been done on this block. This technique uses local anesthetic to infiltrate the paravertebral space by a posterior approach, and simultaneously to block several unilateral dermatomes with a single injection, in the manner of a plexus block. A catheter can be introduced into this space to maintain analgesia over an extended period. Paravertebral block will allow a somatic and sympathetic block (sympathetic chain being located in space infiltrated). The dosage is 0.5 mL/kg of long-acting local anesthetic, followed by a continuous infusion of 0.2 to 0.25 mL/kg/hr of the same solution.

Anatomic landmarks are the spinous processes of thoracic vertebrae. The puncture site is located parallel to the vertebral axis at the level of the spinous process

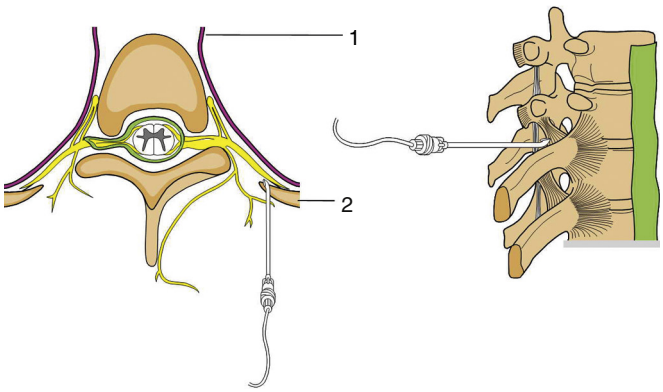


Figure 92-50. Block of the thoracic paravertebral space. *1,* Parietal pleura; *2,* rib.

(Fig. 92-50). The needle must contact the transverse process of a vertebra. The landmarks are defined in children as follows[275]:

- Point of puncture: 10.2 mm + (0.12 × weight in kg) laterally to the spinous process
- Depth of the space: 18.7 mm + (0.48 × weight in kg)

The puncture of the paravertebral space is related to the level of surgery and is usually for a T5-T6 for thoracotomy surgery and T9-T10 for subcostal surgery. The LOR method is used to locate the paravertebral space with the Tuohy needle crossing the costotransverse ligament. It is also possible to identify the spinal nerve with neurostimulation through space at the chosen level. Ultrasound guidance is used to identify the transverse process, the costotransverse ligament, and measure the distance from skin to parietal pleura before performing the block.[276]

Indications for thoracic paravertebral block in children are postoperative analgesia after thoracotomy[277] and upper abdominal surgery with unilateral subcostal incision (kidney surgery, cholecystectomy, splenectomy).[278] This block has been also described for unilateral inguinal hernia repair in children.[279] Contraindications for this technique are a history of ipsilateral thoracotomy with an increased risk for pneumothorax or parenchymal lung

puncture and the deformation of the spinal column, increasing the risk for pleural puncture. This block also must be avoided in cases of serious potential risk for complications (risk for pneumothorax in patients suffering from respiratory diseases with poor gas exchange).

Paravertebral block requires an anesthetist with good technical skills. An alternative to this block is thoracic epidural anesthesia, which has less risk for direct spinal cord injury.

OTHER NERVE BLOCKS OF THE TRUNK

Interpleural (or intrapleural) blocks that consist of injecting a local anesthetic within the pleural cavity without creating a pneumothorax elicited enthusiasm some years ago but was never established in pediatric anesthesia. Other blocks of nerves of the trunk, including paravertebral ganglion, genitofemoral, paracervical (uterosacral), and transsacral nerve blocks, are not used in pediatric patients.

FACE, HEAD, AND NECK NERVE BLOCKS

NERVE BLOCK OF THE FACE

All sensory innervation of the face is under the dependence of the trigeminal nerve (fifth cranial nerve, or vagus nerve) associated with the C2-C4 cervical nerve roots that constitute the superficial cervical plexus.

Anatomic Considerations

The fifth cranial nerve provides sensory and a motor components. The sensory component is combined in the trigeminal ganglion (semilunar or gasserian ganglion), which lies in the Meckel cave, an invagination of the dura mater near the apex of the petrous part of the temporal bone in the posterior cranial fossa. Postganglionic fibers exit the ganglion to form three nerves, as follows:

1. The ophthalmic nerve (V1), innervating the forehead, eyebrows, upper eyelids, and anterior area of the nose
2. The maxillary nerve (V2), innervating the lower eyelid, upper lip, lateral portion of the nose and nasal septum, cheek, roof of the mouth, bone, teeth, sinus of the maxilla, and soft and hard palates
3. The mandibular nerve (V3) innervating the anterior two thirds of the tongue and the skin, mucosa, teeth, and the bone of the mandibular.

These terminal sensory nerves can be blocked either at their emergence point from the cranium, as deep procedures (V2 and V3), or more distally when they exit the facial bone as superficial blocks (V1, V2, V3) (Fig. 92-51).

Superficial Trigeminal Nerve Blocks

For superficial trigeminal nerve blocks, the local anesthetic solution should be injected in close proximity to the three individual terminal superficial branches of the trigeminal nerve divisions: the frontal nerve (of ophthalmic nerve, V1 division), infraorbital nerve (of maxillary nerve, V2 division), and mental nerve (sensory terminal branch of mandibular nerve, V3 division). Each nerve is anatomically close to its respective foramen, which is usually on a line perpendicular through the center of the pupil.

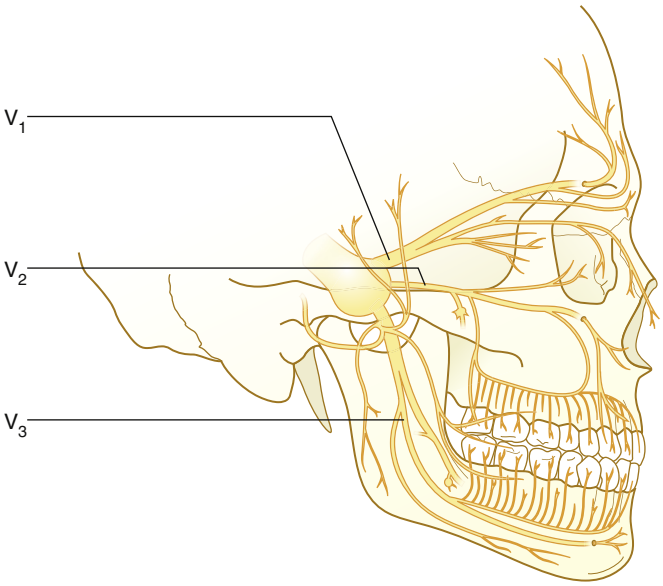


Figure 92-51. Facial nerves distribution.

The supraorbital foramen can be easily palpated by following the orbit rim 2 cm from the midline in adults (union of the medial third and lateral two thirds). The needle (intradermal needle, 25 gauge in adults to 30 gauge in children) is introduced a half centimeter under the inferior edge of the eyebrow and is directed medially and cephalad. When the needle tip is near the supraorbital notch, after test aspiration and with caution to not penetrate the foramen, local anesthetic solution (0.5 to 1 mL) can be injected, creating a subcutaneous wheal. For supratrochlear block, the landmarks are the top of the angle formed by the eyebrow and the nasal spine where the nerve is in contact with the bone. The supratrochlear nerve can be blocked without removal by directing the needle approximately 1 cm toward the midline and injecting an additional 0.5 mL of local anesthetic.

The terminal branch of the maxillary nerve (second division of the trigeminal nerve), is called the infraorbital nerve when it reaches the infraorbital fossa. The infraorbital artery and vein run parallel in close proximity to the nerve. Its innervation involves the skin and mucous membrane of the upper lip, lower eyelid, and the cheek. Two approaches can be used to perform this block: the intraoral and extraoral approaches. Regardless of the technique, it is necessary to prevent penetration of the foramen or eventual damage of the eyeball by palpating the foramen.

For the intraoral approach, the external landmarks include the foramen localized by palpation, the incisor, and the first premolar. The needle (25 or 27 gauge) is inserted at the buccal mucosa in the subsulcal groove at the level of the canine or the first premolar and directed upward and outward into the canine fossa. A finger is placed over the infraorbital foramen to assess the proper location of the needle tip and avoid damage of the pupil.

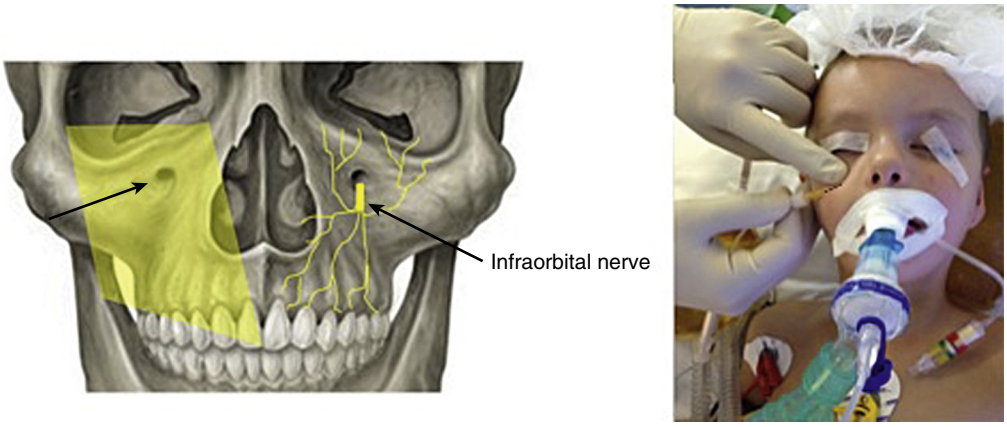


Figure 92-52. Infraorbital nerve block procedure.

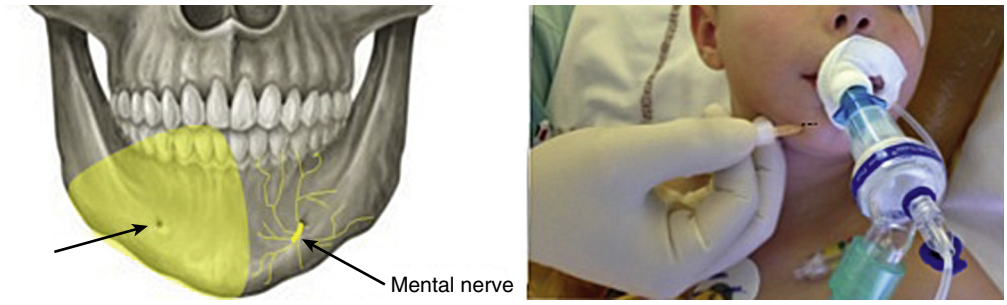


Figure 92-53. Mental nerve block procedure.

For the extraoral approach, the infraorbital foramen is palpated just below the orbital rim, at the intersection of a vertical line drawn caudally through the center of the pupil and a horizontal line through the alae nasae. The needle (25 or 27 gauge) is advanced perpendicularly with a cephalic and medial direction toward the foramen until bony resistance is met (Fig. 92-52).

The main surgical indication in children is cleft lip repair with good perioperative pain management and a decrease in opioid use.[280-282]

The mental nerve is the terminal branch of the alveolar nerve (the largest branch of the mandibular nerve). It emerges at the mental foramen. The mental foramen is located in line with the pupil on the mental process of the mandible, in regard to the inferior premolar tooth. Puncture is 1 cm lateral to the foramen palpated. The 25- or 27-gauge needle is directed with a lateral-to-medial direction to avoid foramen penetration (Fig. 92-53).

After negative aspiration, 1 to 3 mL of local anesthetic is injected for these different approaches. Complications are hematoma, persistent paresthesia of the innervated territory, prolonged numbness, and intravascular injection.

Ultrasound guidance can be used to locate the foramina for superficial trigeminal nerve blocks.[126] It appears as an easy and safe modality. The ultrasound imaging of foramina is the classic disruption of the bone table (Fig. 92-54).

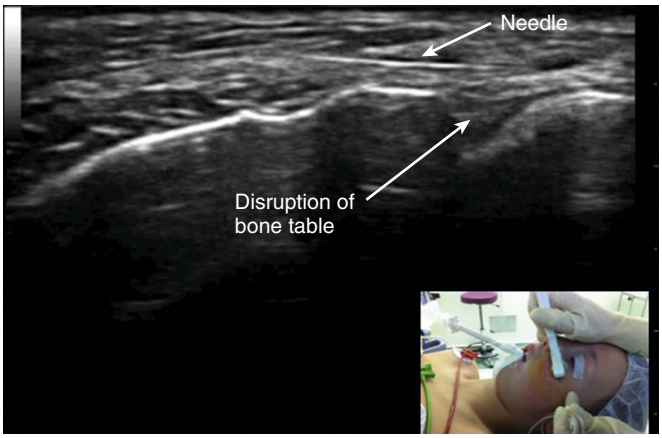


Figure 92-54. Ultrasound of infraorbital nerve block and probe position on face. Disruption of bone table indicates foramen of trigeminal nerve.

Maxillary Nerve Block

The maxillary nerve exits the skull through the foramen rotundum and gives its terminal branches. Except for the middle meningeal nerve, innervating the dura mater, all branches (zygomatic branches, superior alveolar nerve, pterygopalatine and parasympathetic branches, palatine and pharyngeal branches) arise in the pterygopalatine fossa to the face. At the upper part of the pterygopalatine fossa, the maxillary nerve is accessible for a complete maxillary block. The nerve territory blocks are the lower eyelid, ala of the nose, cheek, upper lip, cutaneous zygomatic and temporal zone on the face and superior teeth, palatine zone, maxillary bone.

The suprazygomatic approach to the maxillary nerve in pterygopalatine fossa seems to be the safest and is easily reproducible in children.[283] The patient is supine, with the head in neutral position or turned slightly to the opposite side. The needle entry point is situated at the angle formed by the superior edge of the zygomatic arch

below and the posterior orbital rim forward (Fig. 92-55). The needle (22 to 25 gauge) is inserted perpendicular to the skin and advanced to reach the greater wing of the sphenoid at a depth of approximately 10 to 15 mm. The needle is then reoriented in a caudal and posterior direction and advanced 35 to 45 mm deep to the pterygopalatine fossa (Fig. 92-56). After a negative aspiration test for blood, 0.15 mL/kg to a maximum of 5 mL of local anesthetic solution is slowly injected.

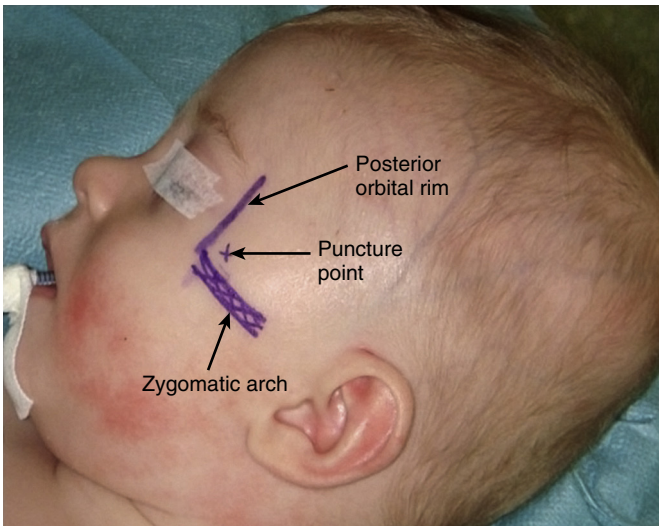


Figure 92-55. Suprazygomatic maxillary nerve block landmarks.

Ultrasound guidance technique is possible with the ultrasound transducer located in the infrazygomatic area, over the maxilla, with an inclination of 45 degrees in both the frontal and horizontal planes (Fig. 92-57). The probe location allows visualization of the pterygopalatine fossa, limited anteriorly by the maxilla and posteriorly by the greater wing of the sphenoid. The needle is advanced using an out-of-plane approach. This real-time ultrasound-guided technique is easy and ensures the correct location of local anesthetic injection in the pterygopalatine fossa (Fig. 92-58).[284]

Mandibular Nerve Block

The mandibular nerve, the largest branch of the trigeminal nerve, exits from the cranium through the foramen ovale of the greater wing of the sphenoid. The anterior trunk is formed with branches serving mainly motor innervation to temporalis, masseter, pterygoids, mylohyoid, and tensor tympani and palati muscles and the buccal nerve. Auriculotemporal, lingual, and inferior alveolar nerves comprise the posterior trunk.



Figure 92-56. Suprazygomatic maxillary nerve block technique. The needle was inserted perpendicular to the skin (**A**) and advanced to reach the greater wing of the sphenoid at approximately 10 to 15 mm depth (**B**). Reorientation of needle in a caudal and posterior direction (**C**) and advancement of 35 to 45 mm deep to the pterygopalatine fossa (**D** and **E**).

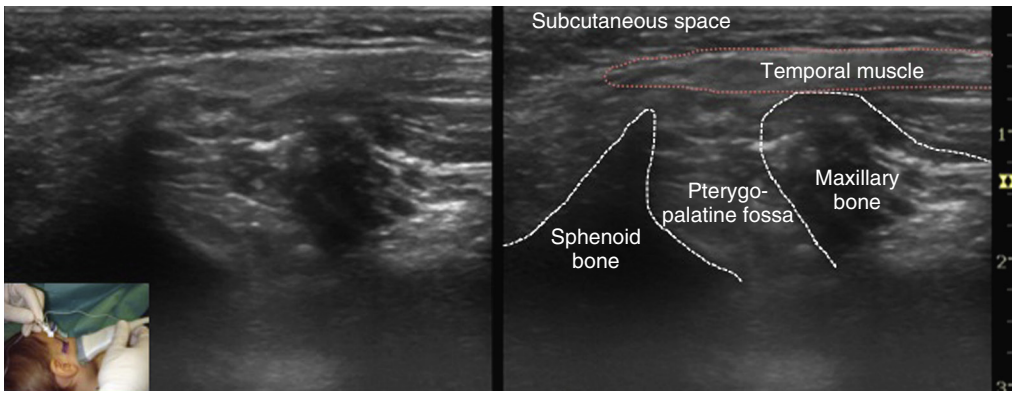


Figure 92-57. Ultrasound imaging of suprazygomatic maxillary nerve block.

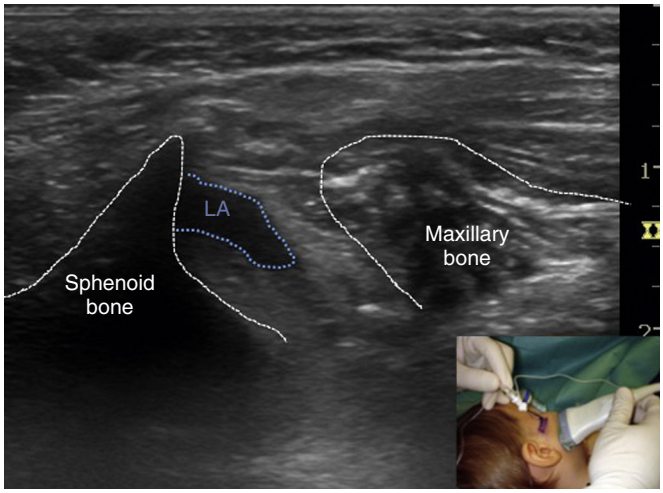


Figure 92-58. Ultrasound imaging of suprazygomatic maxillary nerve block with local anesthetic (*LA*) injection.

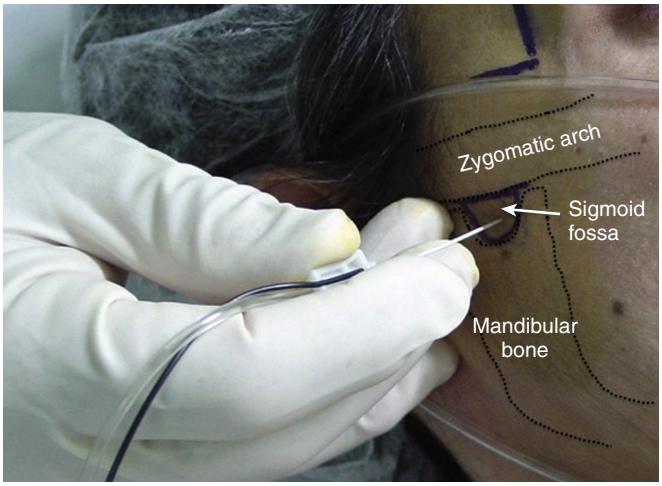


Figure 92-59. Mandibular nerve block procedure.

The puncture area is bounded by the zygomatic arch at the top and the mandibular notch just anterior to and below the tragus of the ear (Fig. 92-59). The needle entry point is located in the sigmoid fossa between the coronoid and condylar process of the ramus of the mandible. To avoid the risk for arterial puncture, it is recommended to prick as high as possible in the space between the zygomatic arch and the center of mandibular notch (see Fig. 92-59). After perpendicular skin penetration, toward the lateral pterygoid plate (to a distance of 2 to 4 cm of depth), the needle (22 to 25 gauge) is advanced posteriorly and inferiorly maintaining the same depth, guided by mandible ascension twitch. The minimal intensity of stimulation (~0.5 mA) is determined, and 0.1 mL/kg to a maximum of 5 mL of local anesthetic solution is slowly injected after negative repeated blood test aspirations. This transcutaneous procedure with neurostimulation appears easier and has a high success rate.

Block of the Nose: Nasociliary Nerve Block and External Nasal Nerve Block

The innervation of the nose and nasal cavity is quite complex, implicating both the ophthalmic (V1) and maxillary (V2) branches of the trigeminal nerve.

The nasociliary nerve is blocked before its division into nasal branches of the anterior ethmoidal nerve and the infratrochlear nerve, and near the ethmoidal foramen. A 25- or 27-gauge needle is inserted 1 cm above the medial canthus, halfway between the posterior palpebral fold and the eyebrow. It is then directed medially and backward in contact with the bony roof of the orbit. At a depth of 1.5 cm the needle should be at the anterior ethmoidal foramen, and a maximum of 2 mL of local anesthetic solution is then slowly injected after a negative aspiration test.

The external nasal branch of the anterior ethmoidal nerve can be blocked by infiltration at the junction of nasal bone with cartilage. Combined with infraorbital nerve block, the external nasal nerve block is very effective for perioperative pain control in cleft lip repair.[285]

Nerve Blocks of the External Ear

Anatomic Considerations. The innervation of the pinna of the ear is complex. Both the trigeminal nerve and the cervical plexus mainly provide innervation.

The auriculotemporal branch of the mandibular division of the trigeminal nerve supplies the superior two thirds of the anterior surface. The auriculotemporal nerve passes through the parotid gland to ascend anterior to the auditory canal with the superficial temporal artery and passing superiorly superficial to the zygomatic arch.

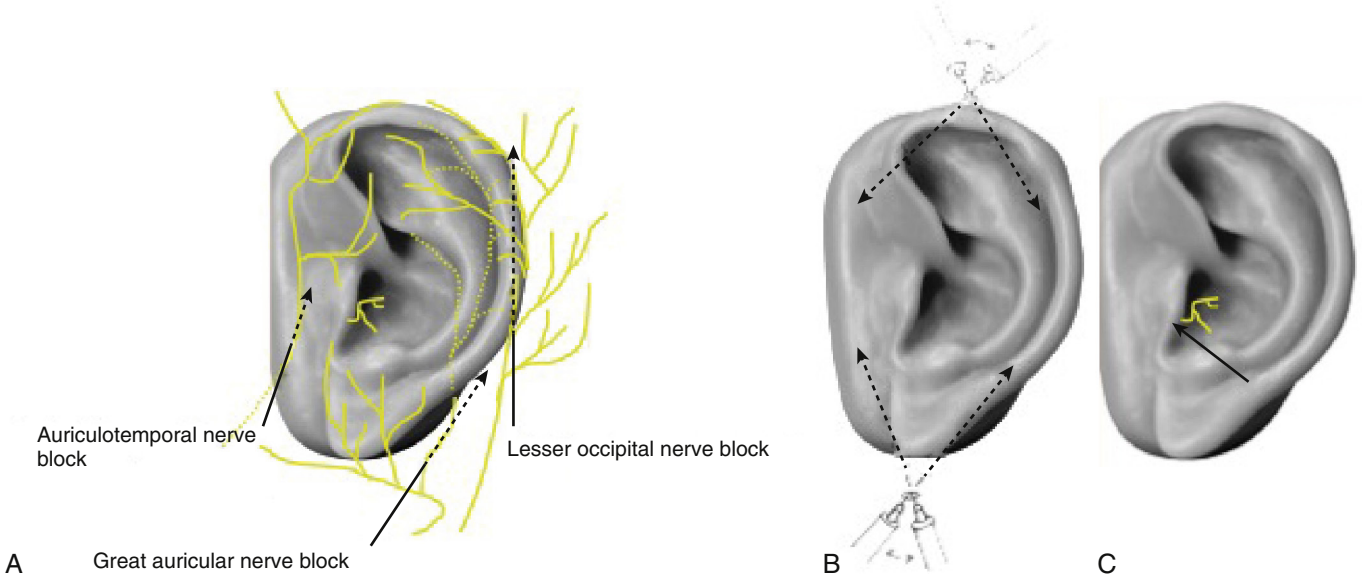


Figure 92-60. A, Regional field block of ear. **B,** Ring block of ear. **C,** Block of the auricular branch of the vagus nerve.

The posterior surface of the ear and the lower third of its anterior surface depend on the great auricular nerve and the lesser occipital nerve, two branches of the cervical plexus.

The great auricular nerve arises from the second and third cervical nerve roots, emerges from the posterior border of sternocleidomastoid muscle, and ascends (dividing into anterior and posterior branches) to the mandibular, parotid gland, and pinna. It supplies the lower back of the auricle, the lobule, and the skin of the angle of the mandible (in complement to the mandibular nerve).

The lesser occipital nerve arises from the ventral primary rami of the second and third cervical roots and gives the innervation of the upper part of the ear lobe and lateral occipital zone.

The auricular branch of the vagus nerve (nerve of Arnold) innervates the concha, most of the posterior wall of the external auditory meatus (zona of Ramsay Hunt), and inferior portion of the tympanic membrane.

Regional Anesthesia Techniques. Regional field block around the auricle allows anesthesia of each nerve branch involved in external ear sensory innervation except the Ramsay Hunt area (Fig. 92-60, *A*).

The auriculotemporal nerve can be blocked by injecting local anesthetic solution above the posterior portion of the zygoma, anterior to the ear and behind the superficial temporal artery. The needle (27 gauge) is inserted anterior and superior to the tragus. Caution is necessary because of the vicinity of the temporal artery.

The great auricular nerve and the lesser occipital nerves can be blocked distally over the mastoid process posterior to the ear. The needle is inserted behind the lower lobe of the ear and advanced following the curve of the posterior sulcus.

Infiltration with the ring-block technique also provides an additional efficient analgesia of the external ear (see Fig. 92-60, *B*).

The superficial cervical plexus block is a widely described proximal approach that anesthetizes two of its terminal branches, the lesser occipital nerve and the great auricular nerve (see also Chapter 57). Several painful procedures of the ear can benefit from this analgesic block, such as incision and drainage of an abscess or hematoma,[286] suture of a large laceration of the ear or the skin surrounding the ear,[287] postauricular incision as in tympanomastoid surgery and cochlear implants,[288] otoplasty,[289] and surgical correction of "bat" ears.[280]

For tympanomastoid surgery, a great auricular nerve block provides good analgesia with reduction of opioid use and a decrease in postoperative nausea and vomiting[288] (see also Chapter 96).

The block of the auricular branch of the vagus nerve is used for pain control after myringotomy and tube placement, tympanoplasty, and paper patch for ruptured tympanic membrane.[286] To perform this block, the tragus is everted, a 30-gauge needle is inserted into the tragus, and, after an aspiration test, 0.2 mL of local anesthetic solution is injected (see Fig. 92-60, *C*).

Nerve Block of the Head

Greater Occipital Nerve Block. The greater occipital nerve arises from the second cervical nerve root that emerges between the atlas and the axis. It ascends between the obliquus capitis inferior and semispinalis capitis before piercing the latter muscle. It then becomes subcutaneous by piercing the trapezius aponeurosis, slightly inferior to the superior nuchal line. At this point, the greater occipital nerve is most often located immediately medial to the occipital artery. The greater occipital nerve provides cutaneous innervation to a major portion of the posterior scalp from the level of the external occipital protuberance to the vertex.

The landmarks to perform the greater occipital nerve block are located at approximately two thirds of the distance on a line drawn from the center of the mastoid to

the external occipital protuberance along the superior nuchal line, where it lies medial to the occipital artery. The pulsation of the occipital artery is easy to palpate. Palpation in this area may elicit a paresthesia or uncomfortable feeling in the distribution of the nerve. Usually a 25- or 27-gauge needle can be used depending on the size of the patient. The needle is directed at a 90-degree angle toward the occiput and, after aspiration, 1 to 3 mL of local anesthetic is injected. When the needle is withdrawn, pressure should be maintained over the site of injection to promote the nerve impregnation and to achieve hemostasis. Numbness over the top of the head, after the injection, is a sign of a successful greater occipital nerve block.

An ultrasound-guided technique of greater occipital nerve block has been described recently with good visualization of the nerve.[290]

Scalp Blocks. The scalp block is classically described with potential blockade of seven nerves, including branches from cervical spinal rami and from trigeminal division.

The greater occipital, lesser occipital, and great auricular nerves originate from ventral and dorsal rami of C2 and C3 spinal nerves. The greater occipital nerve travels up to the vertex, and the lesser occipital nerve innervates skin behind the ear.

The ophthalmic division of trigeminal nerve gives off, by the frontal nerve, supraorbital and supratrochlear nerves that innervate the skin from the forehead to the lambdoidal suture.

The zygomaticotemporal nerve is one of the two branches of the zygomatic nerve that arises from the maxillary division of the trigeminal nerve. It innervates a small area of the forehead and temporal area.

The auriculotemporal nerve arises from the mandibular division of the trigeminal nerve. It innervates the posterior portion of the skin of the temple.

Scalp block is used in adults and children for a variety of head and neck procedures and in neurosurgery or chronic pain diagnostic and therapeutic management (many headache disorders of muscular and nervous etiology). Common reasons for providing anesthesia to the scalp are repair of a laceration, foreign body removal, exploration of scalp wounds, and drainage of abscesses or subdural hematomas.

Most of the time, infiltrative anesthesia is used to perform scalp blocks. All the nerves involved in the scalp's sensitivity become superficial and accessible to the anesthetic. To block the entire scalp, a circumferential infiltration of local anesthetic solution (with 1:200,000 epinephrine), above an imaginary line drawn from the occipital protuberance to the eyebrows, passing along the upper border of the ear, is necessary. Approximately 30 mL is required to perform this ring block around the scalp.

The most common complications associated with scalp anesthesia are hematoma formation at the site of injection and the risk for intravascular injection.

Nerve Block of the Neck

Cervical Plexus Block. Cervical plexus blocks have few but specific indications in pediatric surgery—cervical lymph node biopsy, excision of thyroid nodules,[291,292] and surgery of vocal cords.[293] Only the superficial branches are blocked by a subcutaneous infiltration along the lateral border of the sternocleidomastoid muscle.

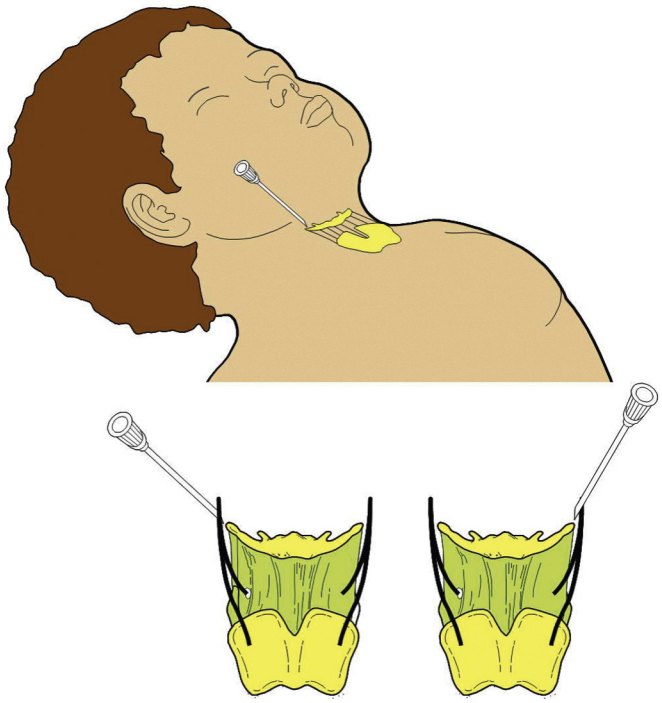


Figure 92-61. Laryngeal nerve block.

Laryngeal Nerve Block. Laryngeal nerve blocks can be used for short-duration laryngoscopic examinations in conscious patients or to facilitate awake intubation when difficult intubation is suspected. It also can be used to prevent or treat laryngospasm.[294] Several techniques have been described, but the easiest consists of subcutaneous injection of a local anesthetic just lateral to the dorsal ending of the hyoid horns (on each side) (Fig. 92-61). A 27-gauge intradermal needle is inserted close to the hyoid horn ending until contact is made with cartilage. The needle is then slightly withdrawn and 0.1 to 0.2 mL/kg (up to a maximum of 8 mL) of 1% lidocaine is injected subcutaneously. Excellent laryngeal block is usually obtained.

Cervicothoracic (Stellate) Ganglion Block. Stellate ganglion block is a rather dangerous procedure with very few but very specific indications in children: (1) ventricular tachyarrhythmia resulting from congenital long-QT syndrome[295,296] (a left stellate block is recommended) and (2) severe ipsilateral circulatory disorders of the upper extremity. Patients with certain acute pain syndromes such as herpes zoster ophthalmicus[76] or rare chronic pain syndromes such as sympathetically maintained pain syndrome[297,298] may benefit from the technique.

OTHER PROCEDURES

INTRAVENOUS REGIONAL ANESTHESIA

Intravenous regional anesthesia (Bier block) has never been very popular in pediatric anesthesia. Currently, the

technique is outdated, even though it is still used in some institutions mainly for fracture repairs (often in emergency departments).[299-301] The technique is the same as in adults. The limb is exsanguinated by an Esmarch bandage or simple gravitation. A tourniquet is placed around the proximal part of the arm and inflated at two to three times the systolic pressure before the Esmarch bandage is removed and 1 mL/kg of 0.5% lidocaine (not exceeding 3 mg/kg) is injected. Prilocaine can be used instead in adolescents. Children tolerate the pain produced by the inflated tourniquet very poorly, and this technique was responsible for several deaths in the past.

Intradermal Wheals

Intradermal wheals are routinely used in adult patients to anesthetize the skin covering deeper structures to be approached. The technique is used less often in children, except for anesthetizing the puncture site of a regional block procedure in nonanesthetized children. It consists of inserting a 25-, 27-, or 30-gauge interdermal needle almost tangentially to the skin, with the bevel facing downward, without penetrating the subcutaneous layers. A small amount (<0.5 mL) of local anesthetic (0.5% to 1% lidocaine or prilocaine, with or without epinephrine) is then injected. The skin covering the wheal looks like an orange peel and almost immediate anesthesia of the relevant area is obtained. The only drawback of this technique is that the injection is moderately painful.

Wound Infiltration

In adults, some studies have shown benefits of continuous wound catheters.[302,303] Today, publications on continuous wound catheters in children are limited. Ouaki and co-workers[304] evaluated continuous infusion of ropivacaine through an iliac crest catheter for bone graft postoperative pain relief in children undergoing a maxillary alveolar graft. The catheters were placed close to the iliac periosteal bone at the donor site and infused with 0.125 mL/kg/hr of 0.2% ropivacaine for 48 hours with a disposable elastomeric pump. The findings of Ouaki and co-workers showed optimal pain relief with a low pain score and a decrease of chronic pain symptoms after 3 months in contrast to reports in the literature.

In their study, Dashow and associates[305] placed a bupivacaine-soaked absorbable sponge in addition to periincisional bupivacaine infiltration at the anterior iliac crest donor site for the management of postoperative pain in children. Their results showed that this regional anesthesia method significantly reduced the postoperative pain score, pain medication requirement, and length of hospital stay.

Precautions must be taken to avoid bacterial contamination and overdosage, especially in cases with extensive wounds or reinjections.

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Chapter 93

Pediatric Anesthesia

CHARLES J. COTÉ

Key Points

- During the first few weeks of life, neonates are vulnerable to a phenomenon, the *flip-flop circulation*; that is, going from an adult type of circulation to a fetal type. Factors such as hypoxia, hypercapnia, acidosis, infection, hypothermia, and prematurity increase the potential for sudden increases in pulmonary artery pressure and subsequent shunting of blood past the lungs through a patent foramen ovale or the ductus arteriosus, which may reopen, particularly during the first 10 days of life.
- The reduced cellular mass of the neonatal heart devoted to contractility results in less compliant ventricles. This leads to a sensitivity to excessive intravascular volume, poor tolerance of afterload (i.e., the development of biventricular failure), and rate-dependent cardiac output. In addition, the reduced cardiac calcium stores produce increased susceptibility to myocardial depression by potent anesthetics and also make neonates dependent on exogenous (i.e., blood-ionized) calcium values and vulnerable to the negative inotropic effects of ionized hypocalcemia, particularly that caused by infusion of citrated blood products such as fresh frozen plasma.
- The neonatal airway differs from the adult airway in four ways: the larynx is located higher in the neck, the glottis is shaped differently and angled over the laryngeal inlet, the vocal cords are angled, and the narrowest portion is the subglottic region at the level of the cricoid cartilage. Accordingly, straight blades are more useful than curved blades in neonates, and uncuffed endotracheal tubes are commonly used.
- Glomerular filtration and tubular function are immature but rapidly develop during the newborn period; adult levels are achieved at approximately the age of 2 years. The frequency with which medications excreted by the kidneys (e.g., antibiotics) can be administered during the first month of life rapidly changes. Particular attention is required in this period to avoid drug-induced toxicity (e.g., ototoxicity) caused by excessive plasma levels of antibiotics.
- Hepatic metabolic capacity is immature at birth. Some cytochrome P450 enzymes (phase I reactions) are fully developed, whereas others are approximately 50% of adult values. Phase II reactions, that is, reactions that make a drug more water soluble, are usually impaired in neonates. Some of these reactions do not achieve maturity until the age of 1 year. This hepatic immaturity can have important clinical implications regarding a neonate's ability to excrete some medications, such as benzodiazepines, morphine, and caffeine.
- Cardiac dysfunction from anesthetic overdose is a particular danger for neonates and infants because of a combination of factors, including immaturity of the myocardium, decreased calcium stores of the neonatal myocardium, and the "systems issue" of the vaporizers for halothane and sevoflurane having different maximum minimum alveolar concentration (MAC) delivery capability; that is, nearly 6 MAC multiples of halothane may be delivered to a newborn, whereas only ~2.5 MAC multiples of sevoflurane can be delivered. Thus anesthetic drug–induced cardiac arrest is a function of both vaporizer design and the vulnerability of the neonatal myocardium to anesthetic-induced cardiac depression, especially on changing from spontaneous to controlled respirations.

KEY POINTS—cont'd

- Remifentanil is a unique potent opioid in neonates. Unlike other medication used in newborns, remifentanil's context sensitive half-life is similar to older children and adults. Therefore remifentanil can rapidly induce or terminate an intense opioid effect even in neonates. However, opioid-induced bradycardia and chest wall rigidity can occur.
- Former preterm infants younger than 60 weeks of age and/or who are anemic are at risk for postoperative apnea (i.e., hemoglobin <10 gm/dL). Both gestational age and postconceptual age at the time of surgery are independent risk factors. The use of regional anesthesia in these children may reduce the incidence of postanesthesia apnea. Postoperative apnea can occur from all inhaled anesthetics, including desflurane and sevoflurane.
- Preoperative laboratory testing (also see Chapter 38) is usually minimal for most children. Routine hemoglobin measurements should be determined in infants younger than 6 months of age to assess the severity of the physiologic hemoglobin nadir (especially former preterm infants with a potential risk for apnea) and in older children expected to experience significant blood loss. Preoperative chest radiographs are not generally indicated. Children who have undergone chemotherapy with anthracycline chemotherapy have congenital heart disease, and neonates at risk for associated cardiac anomalies may require a preoperative echocardiogram. Children undergoing chemotherapy should usually have a complete recent hematology profile, including platelet counts. Children with a history of seizures should have a preoperative assessment including a confirmation that therapeutic blood levels of antiseizure medications exist.
- Temperature regulation (also see Chapter 54) is especially important for neonates and infants. Because of the large body surface-to-weight ratio, they are vulnerable to intraoperative hypothermia. Efforts to maintain a warm surgical unit, to use warming devices such as hot air mattresses, to apply warm surgical skin preparation solutions, and to transport the neonate or infant in an appropriate transport device, as well as keeping the infant covered during transport, all help prevent dangerous hypothermia.
- Intraoperative fluid therapy has changed from the classic 4-2-1 rule of Holliday and Segar to the perioperative administration of 20 to 40 mL/kg of an isotonic solution (lactated Ringer solution). In the postoperative period, the new 2-1-0.5 rule applies (2 mL/kg for the first 10 kg, 1 mL/kg for 10 to 20 kg, and 0.5 mL/kg for each kg above 20 kg in weight). This therapy now recognizes the common dysregulation of antidiuretic hormone secretion after surgery and prevents hyponatremia. If the child has not been able to convert to oral intake after 12 hours, then D5 0.45% saline should be given using the 4-2-1 rule.

The physiologic, pharmacologic, and psychologic differences between children and adults must be understood. Special consideration must be given to preterm infants and those with congenital malformations. Anesthetic-induced neurotoxicity is a concern, but it is not as important as the fundamental issues of maintaining oxygenation, perfusion, and adequate analgesia/anesthesia. This chapter describes how the unique characteristics of children influence the safe conduct of anesthetic procedures.

DEVELOPMENTAL CONSIDERATIONS

Organogenesis takes place within 8 weeks of conception; organ function develops during the second trimester; and the infant gains weight, primarily muscle and fat, during the third trimester. Any physiologic or pharmacologic injury or stress during the first trimester may cause abnormal organogenesis; during the second trimester, functional development of organs may be abnormal; and during the third trimester, organs may be smaller or muscle and fat mass may be reduced. Injuries and stress take the form of congenital viral infections, exposure to drugs (therapeutic or recreational), nutritional insufficiency (caloric or vascular), or maternal illness. A genetic predisposition to developmental malformations can also produce adverse effects. Such interruptions in normal growth and development may cause a variety of physiologic abnormalities ranging from simple preterm birth to a constellation of congenital malformations.

A preterm infant is one born before 37 weeks' gestation; a postmature infant is one born after 42 weeks' gestation. Any infant born weighing less than 2500 g is considered a low–birth-weight infant. Plotting weight

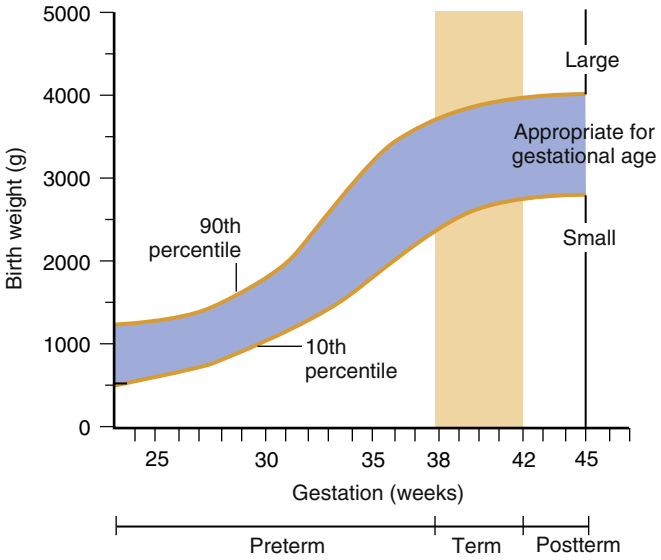


Figure 93-1. Plotting birth weight against gestational age for neonates determines whether infants are small, appropriate, or large for gestational age. Babies who are either small or large for gestational age are particularly likely to have a variety of problems such as metabolic, developmental, infectious, or structural abnormalities, as well as drug addiction and withdrawal. *(Modified from Battaglia FC: Intrauterine growth retardation,* Am J Obstet Gynecol *106:1103-1114, 1970. Used with permission.)*

against gestational age allows classification into three general categories: small for gestational age, appropriate for gestational age, or large for gestational age (Figure 93-1). Infants who are small or large for gestational age often have developmental problems or difficulties associated with maternal disease (Table 93-1). Careful physical and neurologic examination at birth allows a fairly accurate estimate of gestational age. The anesthesiologist should be aware of this type of evaluation to ensure that potential problems can be anticipated. Obtaining a perinatal history of problems during pregnancy (e.g., maternal drug abuse, maternal infection, eclampsia, diabetes) or during and after delivery (e.g., fetal distress, meconium aspiration, prematurity, postdelivery intubation) is also valuable for assessing possible anesthetic implications that may require specific considerations during and after anesthetic management. In the weeks after birth, measurements of weight, height, and head circumference are plotted on standard developmental curves; deviations from normal (i.e., crossing developmental lines) usually indicate a severe physiologic insult. The anesthesiologist should examine the growth chart to evaluate how the child is developing.

THE CARDIOVASCULAR SYSTEM

The cardiovascular system undergoes dramatic physiologic and maturational changes during the first year of life. In utero, most of the cardiac output is directed from the placenta across the foramen ovale into the ascending aorta (oxygenated blood), whereas superior vena cava blood (deoxygenated) is directed to both the pulmonary artery and the ductus arteriosus. This pattern of circulation results in minimal intrauterine pulmonary blood flow. At birth, a number of events change hemodynamic interactions such that the fetal circulation becomes an adult type of circulation. Specifically, the placenta is removed from the circulation; portal blood pressure falls, which causes the ductus venosus to close; and blood becomes oxygenated through the

TABLE 93-1 COMMON NEONATAL PROBLEMS ASSOCIATED WITH WEIGHT AND GESTATIONAL AGE

Gestation	Relative Weight	Neonatal Problems at Increased Incidence
Preterm (<37 weeks)	SGA	Respiratory distress syndrome Apnea Perinatal depression Hypoglycemia Polycythemia Hypocalcemia Hypomagnesemia Hyperbilirubinemia Viral infection Thrombocytopenia Congenital anomalies Maternal drug addiction Fetal alcohol syndrome
	AGA	Respiratory distress syndrome Apnea Hypoglycemia Hypocalcemia Hypomagnesemia Hyperbilirubinemia
	LGA	Respiratory distress syndrome Hypoglycemia; infant of diabetic mother Apnea Hypoglycemia Hypocalcemia Hyperbilirubinemia
Normal (37-42 weeks)	SGA	Congenital anomalies Viral infection Thrombocytopenia Fetal alcohol syndrome Perinatal depression Hypoglycemia
	AGA	—
	LGA	Birth trauma Hyperbilirubinemia Hypoglycemia; infant of diabetic mother
Postmature (>42 weeks)	SGA	Meconium aspiration syndrome Congenital anomalies Viral infection Thrombocytopenia Maternal drug addiction Perinatal depression Aspiration pneumonia Hypoglycemia
	AGA	—
	LGA	Birth trauma Hyperbilirubinemia Hypoglycemia; infant of diabetic mother

AGA, Appropriate for gestational age; *LGA,* large for gestational age; *SGA,* small for gestational age.

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lungs. Exposure of the ductus arteriosus to oxygenated blood induces ductal closure. As a result of the combined effects of lung expansion, exposure of blood to oxygen, and loss of low resistance through placental blood flow, pulmonary vascular resistance decreases while peripheral vascular resistance rapidly rises. The decrease in pulmonary vascular resistance occurs on the first day of life and continues to decrease gradually during the next several years as the architecture of the pulmonary vessels changes. An increase in pressure on the left side of the heart (caused by the increase in peripheral vascular resistance) induces mechanical closure of the foramen ovale. Thus all three connections between the right and left sides of the circulation close. Although closure of the ductus arteriosus probably occurs primarily from an increase in arterial oxygen concentration, successful completion requires arterial muscular tissue; that such tissue is less prevalent in preterm infants may partly account for the frequent incidence of patent ductus arteriosus in preterm infants. True mechanical closure by fibrosis does not occur until 2 to 3 weeks of age.

During this critical period, the infant readily reverts from the adult type of circulation to a fetal type of circulation; this state is called *transitional circulation*. Many factors (e.g., hypoxia, hypercapnia, anesthesia-induced changes in peripheral or pulmonary vascular tone) can affect this precarious balance and result in a sudden return to the fetal circulation. When such a *flip-flop* occurs, pulmonary artery pressure increases to systemic levels, blood is shunted past the lungs via the patent foramen ovale, and the ductus arteriosus may reopen and allow blood to shunt at the ductal level. A rapid downhill spiral may occur and lead to severe hypoxemia, which explains why hypoxemic events may be prolonged, despite adequate pulmonary ventilation with 100% oxygen. In most cases, simple hyperventilation will cause the increased pulmonary artery pressure to return to normal in response to a decreased arterial partial pressure of carbon dioxide ($Paco_2$).

Risk factors increasing the likelihood of prolonged transitional circulation include prematurity, infection, acidosis, pulmonary disease resulting in hypercapnia or hypoxemia (aspiration of meconium), acidosis, hypothermia, and congenital heart disease. Care must be directed to keeping the infant warm, normal arterial oxygen and carbon dioxide tensions, and minimal anesthetic-induced myocardial depression.

The myocardial structure of the heart, particularly the volume of cellular mass devoted to contractility, is significantly less developed in neonates than in adults. These differences, as well as developmental changes in contractile proteins, produce a leftward displacement of the cardiac function curve and less compliant ventricles. This developmental immaturity of myocardial structures accounts for the tendency toward biventricular failure, sensitivity to volume loading, poor tolerance of increased afterload, and heart rate–dependent cardiac output.[1,2] Another issue is that cardiac calcium stores are reduced because of the immaturity of the sarcoplasmic reticulum; consequently, neonates have a greater dependence on exogenous (blood-ionized) calcium and probably increased susceptibility to myocardial depression by volatile anesthetics that have calcium channel–blocking activity.

THE PULMONARY SYSTEM

The pulmonary system is not capable of sustaining life until both the pulmonary airways and the vascular system have sufficiently matured to allow the exchange of oxygen from air to the bloodstream across the pulmonary alveolar-vascular bed. Independent life is not generally possible until a gestational age of 24 to 26 weeks, although survival of infants of 22 to 24 weeks' gestational age is possible but with a high percentage of neurocognitive impairment.[3] Alveoli increase in number and size until the child is approximately 8 years old. Further growth is exhibited as an increase in size of the alveoli and airways. At term, complete development of surface-active proteins helps maintain patency of the airways. If a child is prematurely born and these proteins are insufficient, then respiratory failure (e.g., respiratory distress syndrome) may follow.

Respiration is less efficient in infants. The small diameter of the airways increases resistance to airflow; resistance is inversely proportional to the radius raised to the fourth power for laminar flow and to the fifth power for turbulent flow. The airway of infants is highly compliant and poorly supported by the surrounding structures. The chest wall is also highly compliant, therefore the ribs provide little support for the lungs; that is, negative intrathoracic pressure is poorly maintained. Thus functional airway closure accompanies each breath. Dead space ventilation is proportionally similar to that in adults; however, oxygen consumption is two to three times higher. In preterm infants, the work of breathing is approximately three times that in adults, and this work can be significantly increased by cold stress (i.e., increased metabolic demand for oxygen) or any degree of airway obstruction. Another important factor is the composition of the diaphragmatic and intercostal muscles. These muscles do not achieve the adult configuration of type I muscle fibers until the child is approximately 2 years old (Figure 93-2).[4] Because type I muscle fibers provide the ability to perform repeated exercise, any factor that increases the work of breathing contributes to early fatigue of the respiratory muscles of infants; this partially explains why the infant's respiratory rate and hemoglobin desaturation is so rapid, and their propensity to develop fatigue and apnea with airway obstruction.

Differences in airway anatomy explain the more likely potential for technical airway difficulties in infants than in teenagers or adults. Typically, the airway of infants differs from adults in five ways[5]: (1) The relatively large size of the infant's tongue, in relation to the oropharynx, increases the likelihood of airway obstruction and technical difficulties during laryngoscopy. (However, magnetic resonance imaging [MRI] studies have called this into question).[6] (2) The larynx is located higher (more cephalic) in the neck, thus making straight blades more useful than curved blades. (3) The epiglottis is shaped differently, being short, stubby, omega shaped, and angled over the laryngeal inlet. Control with the laryngoscope blade is

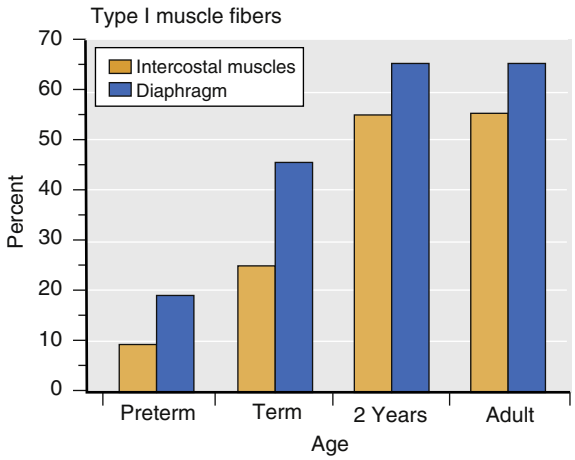


Figure 93-2. The composition of the diaphragm and intercostal muscles significantly changes during the first 2 years of life. The number of type I muscle fibers is inversely related to age and may account, in part, for the ease of inducing respiratory fatigue as the work of breathing increases. *(Data from Keens TG, Bryan AC, Levison H, et al: Developmental pattern of muscle fiber types in human ventilatory muscles,* J Appl Physiol *44:909-913, 1978.)*

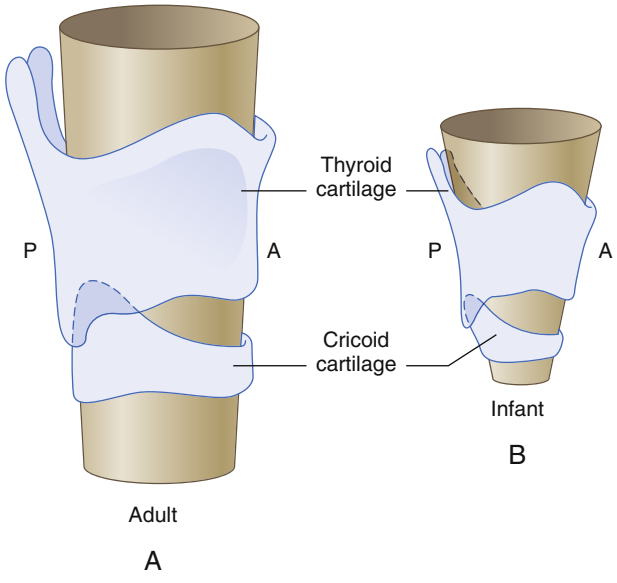


Figure 93-3. The narrowest part of the adult larynx and the pediatric larynx is at the level of the cricoid cartilage. Traditionally, the adult larynx was thought to be cylindrically shaped, but autopsy data suggest that the narrowing in adults (**A**) is not as pronounced as it is in infants (**B**). The narrowest part of the infant larynx occurs at the level of the cricoid cartilage; the normal adult configuration of the larynx is not achieved until the teenage years. This anatomic difference is one of the reasons uncuffed tracheal tubes have been traditionally preferred for children younger than 6 years of age. *A,* Anterior; *P,* posterior. *(From Coté CJ, Lerman J, Anderson BJ, editors:* A practice of anesthesia for infants and children, *ed 5, Philadelphia, 2013, Saunders.)*

therefore more difficult. (4) The vocal cords are angled; consequently, a *blindly* passed tracheal tube may easily lodge in the anterior commissure rather than slide into the trachea. (5) Finally, the infant larynx is funnel shaped, the narrowest portion occurring at the cricoid cartilage (Figure 93-3). Classic teaching has been that the adult larynx is cylindrical and the infant larynx is funnel shaped.



Figure 93-4. The Microcuff tracheal tube (Microcuff; PET; I-MPEDC, Microcuff GmbH, Weinheim, Germany, Kimberly-Clark USA) (*right*) has a soft polyurethane cuff that symmetrically inflates and is located more distally than standard tracheal tubes (*left*). This configuration results in more even pressure applied to the mucosa of the trachea, less potential for edema formation in the subglottic region because the cuff is located below the cricoid cartilage, and a reduced risk for ventilator-associated pneumonia.

However, it is now known that the narrowest portion in approximately 70% of adults is also in the subglottic region at the level of the cricoid cartilage. The opening is so large in adults that commonly used tracheal tubes are usually easy to advance past the glottic opening.[7] In infants or young children, a tracheal tube that easily passes the vocal cords may be tight in the subglottic region because of the relatively greater proportional narrowing at the level of the cricoid cartilage. Thus uncuffed tracheal tubes were in the past preferred for children younger than 6 years of age. However, the development of better tracheal tube design and several prospective studies have combined to allow the more common use of cuffed tracheal tubes, even in infants.[8,9] Nonetheless, a leak should be maintained around the cuff (with or without inflation) because injury to the tracheal mucosa is still possible. The Microcuff tube may improve the safety of cuffed tracheal tubes[10]; the new material is very soft, the shape of the cuff is more uniform (allowing a more uniform distribution of lateral sealing pressure), and the cuff, itself, is located more distally and thus perhaps beyond the cricoid cartilage (Figure 93-4).[11] These more expensive tracheal tubes are usually reserved for children with anticipated prolonged tracheal intubation (reduced ventilator-associated pneumonia),[12] and the lower-cost tracheal tubes are still used for short-term intraoperative tracheal intubation.

Although infants are obligate nasal breathers, approximately 8% of preterm neonates (31 to 32 weeks' postconceptual age [PCA]) and 40% of term infants can convert to oral breathing if the nasal airway is obstructed. Almost all infants can easily convert to oral breathing by 5 months of age; most convert to oral breathing if the obstruction lasts longer than 15 seconds.

THE KIDNEYS

Renal function is diminished in neonates and even more in preterm infants because of small perfusion pressures and immature glomerular and tubular function (Figure 93-5). Nearly complete maturation of glomerular filtration and tubular function occurs by approximately 20 weeks after birth, although delayed in preterm infants. Complete maturation of renal function occurs at approximately 2 years of age. Thus the ability to excrete free water and solute loads may be impaired in neonates, and the half-life of medications excreted by means of glomerular filtration will be prolonged (e.g., antibiotics, hence the longer intervals between doses in neonates).

THE LIVER

At term, the functional maturity of the liver is incomplete. Most enzyme systems for drug metabolism are developed but not yet induced (stimulated) by the material that they metabolize. As the infant grows, the ability to metabolize medications rapidly increases for two reasons: (1) hepatic blood flow increases and more drug is delivered to the liver, and (2) the enzyme systems develop and are induced.[13] The cytochrome P450 system is responsible for phase I drug metabolism of lipophilic compounds. This system reaches approximately 50% of adult values at birth, thus the capacity for drug metabolism (e.g., caffeine) is reduced. However, this is not true for all lipophilic medications, and the ability of neonates to metabolize some drugs is dependent on specific individual drug cytochromes. CYP3A (cytochrome P450, family 3, subfamily A) is generally present at adult values at birth,[14] whereas other cytochromes are absent or reduced.[15] Phase II reactions involve conjugation, which makes the drug more water soluble to facilitate renal excretion.[16] These reactions are often impaired in neonates and result in jaundice (decreased bilirubin breakdown) and long drug (and their active metabolites) half-lives (e.g., the half-life of morphine and benzodiazepines is several days). Some of these reactions do not achieve adult activity until after 1 year of age. Thus quantitative measurements of some medications is important.[17,18]

A preterm infant's liver has minimal glycogen stores and is unable to manage large protein loads. This accounts for the neonate's tendency toward hypoglycemia and acidemia and for the failure to gain weight when the diet contains too much protein. Additionally, plasma levels of albumin and other proteins necessary for the binding of drugs are lower in full-term newborns (and are even lower in preterm infants) than in older infants (Figure 93-6). This condition has clinical implications regarding neonatal coagulopathy (e.g., need for vitamin K at birth), as well as for drug binding and its pharmacodynamic effects; the lower the albumin value, the less protein binding of some drugs with resultant greater levels of unbound drug (i.e., unbound drug is the portion available to cross biologic membranes). In addition, the binding of some drugs to albumin may be altered in the presence of hyperbilirubinemia in the

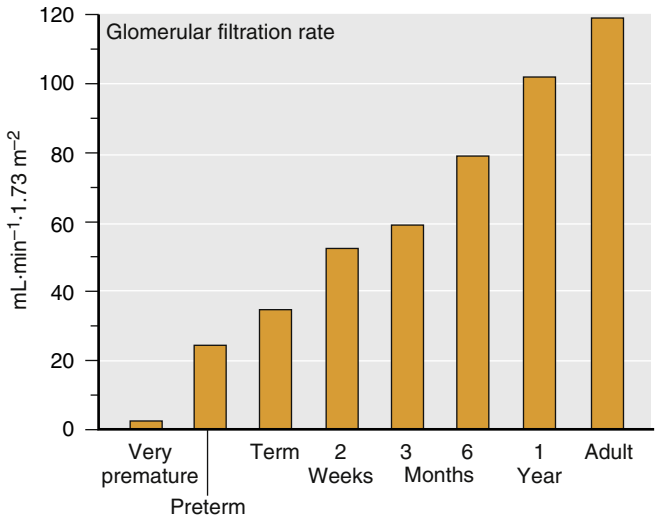


Figure 93-5. Glomerular filtration is significantly impaired at birth but develops rapidly during the first year of life. The ability of the kidney to regulate large amounts of solutes and water is also limited during the first several months of life. These developmental changes have significant implications for drug excretion and fluid therapy, particularly during the first 4 weeks of life. Maturation of renal function may be delayed in sick and preterm neonates. *(Data from McCrory WW:* Developmental nephrology, *Cambridge, Mass, 1972, Harvard University Press.)*

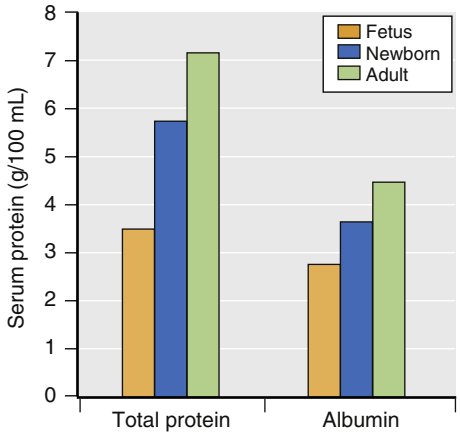


Figure 93-6. Total serum protein and albumin values change with maturation. Total protein and albumin are less in preterm infants than in term infants and less in term infants than in adults. The result may be pharmacokinetic and pharmacodynamic alterations for drugs with a high degree of protein binding because less drug is protein bound and more is available for clinical effect. *(Abstracted from Ehrnebo M, Agurell S, Jalling B, et al: Age differences in drug binding by plasma proteins: studies on human foetuses, neonates and adults,* Eur J Clin Pharmacol *3:189-193, 1971. From Coté CJ, Lerman J, Anderson BJ, editors:* A practice of anesthesia for infants and children, *ed 5, Philadelphia, 2013, Saunders.)*

neonatal period; this effect is more important for drugs with high protein binding because a greater fraction of unbound drug will occur.

THE GASTROINTESTINAL SYSTEM

At birth, gastric pH is alkalotic; by the second day of life, pH is in the normal physiologic range for older children. The ability to coordinate swallowing with respiration does not fully mature until infants are 4 to 5 months of age, thus resulting in a high incidence of gastroesophageal reflux, particularly in preterm newborns. If a developmental problem occurs within the gastrointestinal system, then symptoms will occur within 24 to 36 hours of life. Upper intestinal abnormalities are exhibited as vomiting and regurgitation, whereas lower intestinal abnormalities produce abdominal distention and a failure to pass meconium.

THERMOREGULATION (Also See Chapter 54)

Infants are especially vulnerable to hypothermia because of the large ratio of body surface area to weight, the thinness of the skin, and a limited ability to cope with cold stress. Cold stress causes increased oxygen consumption and a metabolic acidosis, particularly in preterm infants because of even thinner skin and limited fat stores. The infant compensates by shivering and nonshivering (cellular) thermogenesis (metabolism of brown fat); however, the minimal ability to shiver during the first 3 months of life makes cellular thermogenesis the principal method of heat production. Addressing all aspects of possible perioperative heat loss is vital. Placing the baby on a warming mattress and warming the surgical unit (80° F or warmer) will reduce heat lost by conduction. Keeping the infant in an incubator and covered with blankets minimizes heat lost through convection. The head should also be covered. Heat lost from radiation is decreased with the use of a double-shelled isolette during transport. Heat lost through evaporation is lessened by humidification of inspired gases, the use of plastic wrap to decrease water loss through the skin, and warming of skin disinfectant solutions. Hot air blankets are the most effective means of warming children; however, especially in neonates, overheating must be avoided. Anesthetics alter many thermoregulatory mechanisms, particularly nonshivering thermogenesis in neonates.

PHARMACOLOGIC AND PHARMACODYNAMIC RESPONSES

DEVELOPMENTAL PHARMACOLOGY

The response of infants and children (particularly neonates) to medications is modified by many factors: body composition, protein binding, body temperature, distribution of cardiac output, functional organ (heart, liver, kidneys) maturity, maturation of the blood-brain barrier, the relative size of the liver and kidneys, and the presence or absence of elevated intraabdominal pressure (gastroschisis or omphalocele closure) or congenital malformations.[13]

The body compartments (e.g., fat, muscle, water) change with age (Figure 93-7). Total body water content is significantly higher in preterm infants than in term infants and in term infants than in 2 year olds. Fat and muscle content increases with age. These alterations in body composition have several clinical implications for neonates: (1) a drug that is water soluble has a large volume of distribution and usually requires a large initial dose (mg/kg) to achieve the desired blood level (e.g., most antibiotics, succinylcholine); (2) because the neonate has less fat, a drug that depends on the redistribution into fat for the termination of its action will have a long clinical effect; and (3) a drug that redistributes into muscle may have a long clinical effect (e.g., fentanyl, for which, however, saturation of muscle tissue has not been demonstrated).

In addition to these very basic concepts, other important factors play a role in the neonate's response to medications and include the following: (1) delayed excretion secondary to the larger volume of distribution, (2) immature hepatic and renal function, and (3) altered drug excretion caused by lower protein binding. Further perturbations in drug pharmacodynamic and pharmacokinetic effects occur with extreme prematurity and with factors such as sepsis, congestive heart failure, increased intraabdominal pressure, controlled ventilation, need for vasoactive infusions, and poor nutritional state.[13] All of these factors lead to clinically important neonatal patient-to-patient pharmacokinetic and pharmacodynamic variabilities.

Older children tend to have mature renal and hepatic function, with normal adult values for protein, fat, and muscle content. A larger fraction of cardiac output is diverted to the liver and kidneys—which also weigh more in relation to body mass—in older children than in infants. These factors usually mean that the half-life

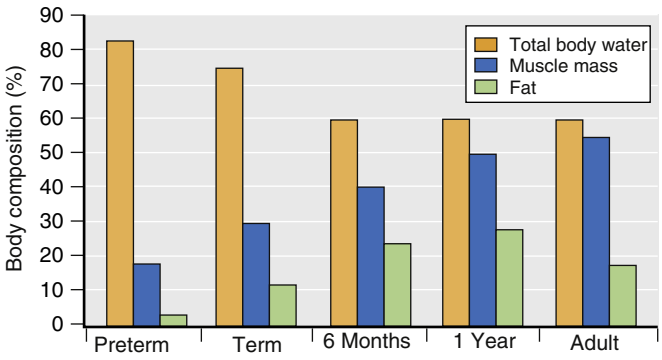


Figure 93-7. Body composition rapidly changes in preterm and term infants during the first 12 months of life. Their high water content provides a large volume of distribution for water-soluble medications, whereas their low fat and muscle content provides a small reservoir for drugs that depend on redistribution into these tissues for the termination of the drug effect. Thus body composition may significantly affect pharmacokinetics and pharmacodynamics. *(Data from Friis-Hansen B: Body composition during growth. In vivo measurements and biochemical data correlated to differential anatomical growth,* Pediatrics *47:264, 1971. From Coté CJ, Lerman J, Anderson BJ, editors:* A practice of anesthesia for infants and children, *ed 5, Philadelphia, 2013, Saunders.)*

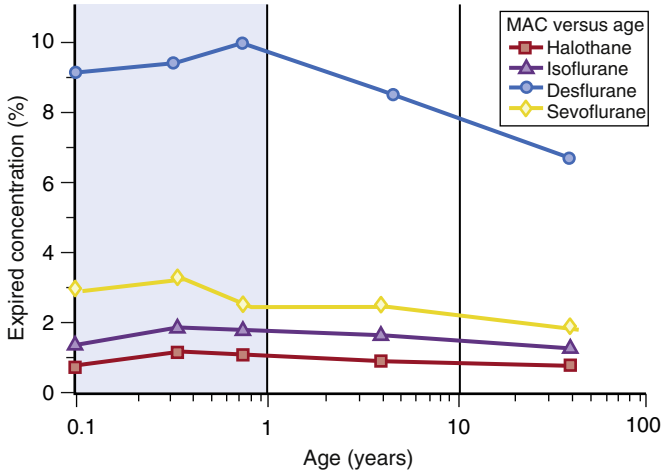


Figure 93-8. The minimum alveolar concentrations (MACs) of four commonly used inhaled anesthetics are plotted versus age. MAC is highest in infants 3 to 6 months of age. The reasons for this are not clear. *(Extracted from data from references 19 through 26.)*

of most medications in children older than 2 years of age is shorter than in adults or is equivalent. As the child approaches adulthood, the half-life of many drugs lengthens. In general, most medications will have a prolonged elimination half-life in preterm and term infants, a shortened half-life in children older than 2 years of age up to the early teenage years, and a lengthening of half-life in those approaching adulthood.

INHALED ANESTHETICS

The expired minimum alveolar concentration (MAC) of an inhaled anesthetic required in children changes with age (Figure 93-8). Anesthetic requirement is smaller for preterm than for term neonates and smaller for term neonates than for 3 month olds. Infants have a higher MAC than that of older children or adults; the reasons for these age-related differences in MAC are not known. This fact, combined with the need for deeper planes of anesthesia to achieve satisfactory conditions for tracheal intubation, places the infant in a precarious position because the safety margin between anesthetic overdose (from a cardiovascular standpoint) and inadequate depth of anesthesia (for tracheal intubation) is small. Avoiding controlled respirations until an intravenous line is inserted, rapidly reducing the delivery of inspired anesthetic drug, especially with the initiation of controlled respirations after the administration of a muscle relaxant, and, in some cases, substituting opioids for an inhaled anesthetics are practices that may improve safety.

Uptake of volatile anesthetics is more rapid in children because of an increased respiratory rate and cardiac index and a greater proportional distribution of cardiac output to vessel-rich organs. This rapid rise in blood anesthetic levels, combined with functional immaturity of cardiac development, probably explains, in part, why delivering an inhaled anesthetic overdose to infants and toddlers is so easy. Age-related differences in blood-gas partition coefficients may also facilitate a more rapid rise in alveolar concentration in infants. Other factors include the

TABLE 93-2 **MINIMUM ALVEOLAR CONCENTRATION MULTIPLES FOR A NEONATE ALLOWED BY CURRENT VAPORIZERS**

Agent	Maximum Vaporizer Output (%)	MAC (%)	Maximum Possible MAC Multiples
Halothane	5	0.87	5.75
Isoflurane	5	1.20	4.2
Sevoflurane	8	3.3	2.42
Desflurane	18	9.16	1.96

From Coté CJ, Lerman J, Anderson BJ, editors: A practice of anesthesia for infants and children, *ed 5, Philadelphia, 2013, Saunders.*
MAC, *Minimum alveolar concentration.*

state of hydration (e.g., excessive fasting would make a small infant relatively dehydrated) and the type of anesthesia circuit used. For example, a Mapleson D has a smaller volume than a circle system; therefore less volume is needed to achieve equilibration when the concentration of anesthetic agent exiting the vaporizer increases. With a Mapleson D circuit (rarely used in modern anesthetic practices), the fresh gas flow is introduced into the system at the airway and directly enters the child's lungs. Perhaps the most important factor influencing the potential for anesthetic overdose in neonates is the number of MAC multiples that can be delivered by the vaporizer; for example, a halothane vaporizer can deliver up to 5.75 MAC multiples versus 2.42 MAC multiples for a sevoflurane vaporizer (Table 93-2).

Sevoflurane

Sevoflurane has a gas partition coefficient similar to that of nitrous oxide (also see Chapters 25 and 26). Sevoflurane is less pungent than isoflurane and desflurane; it may be superior or equivalent to halothane for inhaled induction of anesthesia. As with all volatile anesthetics, the MAC is highest in young patients: 3.3% for neonates, 3.2% for infants 1 to 6 months old, and 2.5% for children older than 6 months.[19,20] Sevoflurane and halothane are approximately equivalent in terms of airway complications during induction of anesthesia (laryngospasm, bronchospasm, breath holding), but the rate of induction is more rapid with sevoflurane. The incidence of coughing during induction with sevoflurane (~6% versus ~10%) is smaller and a 33% more frequent incidence of excitement occurs during emergence (~21% versus ~15%) (Table 93-3). Both sevoflurane and halothane produce dose-related respiratory depression; however, halothane produces a decrease in tidal volume and an increase in respiratory rate, whereas sevoflurane decreases both the respiratory rate and the tidal volume. Respirations may need to be assisted during the early induction stage in sevoflurane-anesthetized children. Unless the inspired concentration is significantly reduced (usually to ~3%), such assistance then increases the potential for anesthetic overdose while attempts are made to establish intravenous access.[27]

Sevoflurane and halothane also have different cardiovascular profiles. Children older than 3 years of age usually experience an increase in heart rate and no change in systolic blood pressure with sevoflurane, whereas with

TABLE 93-3 **SUMMARY STATISTICS FOR 17 STUDIES COMPARING THE CHARACTERISTICS OF SEVOFLURANE AND HALOTHANE**

	Sevoflurane			Halothane			
Problem	**Yes**	**No**	**Percent**	**Yes**	**No**	**Percent**	**Chi Square**
Laryngospasm	22	773	2.8	22	601	3.5	.503
Breath holding	33	635	4.9	34	439	7.2	.143
Coughing	42	662	6.0	52	454	10.3	.008
Excitement during induction	92	556	14.2	58	423	12.0	.338
Bronchospasm	2	604	.33	2	436	.46	.856
Excitement during emergence	169	645	20.8	102	573	15.1	.006

Data from References 19-26.

halothane, the heart rate does not change but systolic blood pressure decreases. The children most vulnerable to anesthetic overdose are the age groups that have the least increase in heart rate and the largest decrease in systolic blood pressure (34% ± 16% and 26% ± 20%, respectively, for neonates and infants younger than 6 months of age).[19] These changes in systolic blood pressure are comparable with those produced by equi-MAC concentrations of halothane.[20] As described in the Pediatric Perioperative Cardiac Arrest (POCA) registry, the use of controlled ventilation is related to cardiac arrest; generally, arrest occurs before the establishment of intravenous access.[27] Even sevoflurane can cause catastrophic effects on the infant's cardiovascular system. Although sevoflurane causes less myocardial depression than that of halothane, a difference in safety has not been established. Alternatively, the use of a neuromuscular blocker to facilitate tracheal intubation (also see Chapter 34) and an avoidance of high inspired concentrations of sevoflurane could be a safer approach in this age group.

The safety of all potent anesthetics probably relates to how the drugs are used, the experience of the person administering the anesthesia, and other less obvious factors. When inducing anesthesia with sevoflurane with resultant apnea, the inspired concentration of sevoflurane should be reduced while gently assisting respirations. After intravenous access is established, a decision must be made regarding continued management with just a face mask, with a supraglottic airway device (e.g., laryngeal mask airway [LMA]), or with a tracheal tube. If a supraglottic device is inserted, then propofol (1 mg/kg) can be administered and the device inserted 30 to 45 seconds later. Most children maintain spontaneous respirations from this dose of propofol, whereas others will become apneic and require assisted ventilation for several minutes. If an endotracheal intubation is to be performed, then two techniques seem reasonably safe: (1) For a brief procedure, the inspired concentration of sevoflurane is increased to 8% and controlled ventilation is instituted for a brief period (usually 1 to 2 minutes) to rapidly deepen the plane of anesthesia. When spontaneous respirations cease, propofol (1 to 2 mg/kg) is then administered, the vaporizer is shut off (to ensure that the 8% sevoflurane is not accidentally continued), and then the tracheal tube is inserted. (2) If muscle relaxation is necessary, then sevoflurane can be administered with an inspired concentration of 3.5% to 4% (lower for a neonate). An appropriate muscle relaxant is administered (also see Chapter 34), and the tracheal tube is then inserted. At this point, the inspired concentration of sevoflurane can be reduced or changed to an appropriate concentration of halothane or isoflurane for maintenance. Changes in *time to discharge* (i.e., "street readiness") do not seem significantly different, based on the choice of volatile anesthetic.

Several other issues related to sevoflurane are worthy of mention. The most important is the risk of exothermic reactions with dry desiccant,[28-31] which has resulted in fires and explosions (sevoflurane and Baralyme) (see also Chapter 109); this reaction should no longer be a risk since Baralyme is no longer marketed.[32-34] These incidents are associated with high flows of oxygen through the circuit for extended periods and then the use of high inspired sevoflurane concentrations (e.g., the first procedure on a Monday morning). Another issue is the production of toxic metabolites as a result of an interaction with the carbon dioxide absorbent.[35,36] Compound A appears to be nephrotoxic in animal models, the clinical implications of which are not clear. Low-flow (2 L/minute) and prolonged anesthesia have not altered the usual markers of renal function. Sevoflurane appears to be a safe anesthetic, even for prolonged surgical procedures. Fresh gas flows (less than 1 L/minute) are not recommended. The use of new carbon dioxide absorbents that do not contain a strong base seems to eliminate most of these issues.

A major concern is the more frequent incidence of emergence agitation with sevoflurane than with halothane (see Table 93-3). This response during emergence from sevoflurane anesthesia is not related to pain and is especially frequent in children 5 years of age or younger. The incidence of emergence agitation can be reduced with midazolam and/or the administration of clonidine (orally or epidurally), ketorolac, fentanyl, or dexmedetomidine.[37] When the data from many studies are combined, the true difference in emergence agitation is quite small (~21% with sevoflurane and ~15% with halothane). This issue is usually a problem when patients arrive in the postanesthesia care unit (PACU) in an agitated state. With halothane, children generally arrive in the PACU still partially anesthetized, the nurses are able to chart their initial vital signs, and then the children become agitated. In either case, this condition responds to small doses of fentanyl or propofol and is generally short-lived

(~5 to 10 minutes).[37] Another issue is the report of seizurelike activity during induction with sevoflurane. At least one careful electroencephalographic (EEG) study has not documented seizure activity, thus suggesting that these abnormal movements are not central in origin.[38]

Airway reflexes are usually inadequately suppressed from volatile anesthetic for the performance of bronchoscopy during spontaneous respirations. Supplementation with any combination of intravenous propofol, small-dose remifentanil, or a muscle relaxant is usually required with sevoflurane. Halothane is a superior inhaled anesthetic for this procedure but is not always available. The longer elimination half-life and maintenance of spontaneous respirations with halothane also contribute to its advantage for procedures in which the face mask is intermittently applied, such as during bronchoscopy or suture removal after a cleft lip repair.

Halothane

The use of halothane in the United States has decreased dramatically; however, it is still widely used in other parts of the world. Halothane does not have a noxious smell and is commonly used for the gaseous induction of anesthesia in places where budgetary concerns limit the availability of sevoflurane. A statistically significant but clinically unimportant difference in the rapidity of awakening (usually 3 to 5 minutes) nearly always occurs when comparing halothane with either desflurane or sevoflurane. Most important, airway-related problems during induction occur less frequently with halothane and sevoflurane than with isoflurane or desflurane. Halothane and sevoflurane are the anesthetics of choice for the gaseous induction of anesthesia in children.

A 1987 report describing seven cases (one fatal) of *halothane hepatitis* concluded that children should not undergo repeated exposure to halothane (also see Chapter 26).[39] However, this report must be placed in its proper perspective. Millions of children have been anesthetized with halothane. Perhaps a dozen instances of halothane hepatitis—and one or two deaths—have been reported in children. This is a remarkable safety record for any medication. Because halothane hepatitis appears to be primarily an adult issue, the use of other anesthetics or techniques in teenage patients may make sense. Halothane will probably remain the most commonly used potent anesthetic in undeveloped countries because of cost. Furthermore, hepatic dysfunction has been reported in children after all potent anesthetics, including sevoflurane and desflurane.

Sensitization of the myocardium to arrhythmias because of exogenous and endogenous catecholamines is another concern with halothane. Most arrhythmias associated with halothane anesthesia in children are caused by either hypercapnia or an inadequate depth of anesthesia.[40] Up to 10 μg/kg of epinephrine may be used with minimal risk of cardiac arrhythmias in children. The heart rate is generally stable or slightly decreased. If tachycardia develops in a halothane-anesthetized child, then inadequate anesthesia or hypovolemia is usually the cause. This development is distinctly different from isoflurane, desflurane, and sevoflurane, all of which can directly cause tachycardia.

Halothane is a potent myocardial depressant that can have profound effects on neonates and children with congenital heart disease. Such depression is responsible for the occasional inability to give critically ill children sufficient concentrations of halothane to provide *anesthesia* without inducing severe hypotension. In this circumstance, the liberal use of short-acting opioids with low concentrations of halothane generally provides the desired response. The POCA study reported a more frequent incidence of anesthetic-induced cardiac arrests with halothane; the use of controlled ventilation (probably without reducing the inspired concentration of the anesthetic agent) was a common observation.[27] Although both halothane and sevoflurane depress cardiac function, sevoflurane is less of a myocardial depressant.[41,42] However, at both 1 and 1.5 MAC in children, no significant difference in mean arterial blood pressure has been reported[41]; in infants, no difference has been observed at 1 MAC, but a difference at 1.5 MAC was reported. The simple administration of atropine would abolish these differences.

Isoflurane

Isoflurane may have some advantages over halothane: less myocardial depression, preservation of the heart rate, and a larger reduction in the cerebral metabolic rate for oxygen (also see Chapters 25 and 26). These properties may be beneficial in selected children. The major disadvantages of isoflurane are its noxious smell, which is unacceptable to many children, and a more frequent incidence of airway-related events (e.g., laryngospasm, coughing). Hypertension is also occasionally observed, especially in teenagers, when the inspired concentration is rapidly increased or when the change from sevoflurane to isoflurane is sudden. The probable mechanism is similar to that of desflurane—stimulation of pulmonary irritant receptors, causing increased sympathetic activity and stimulation of the renin-angiotensin system. Occasionally, a diffuse rash appears, primarily on the torso. All signs and symptoms regress with the decrease of the inspired concentration of isoflurane.

Desflurane

Desflurane has a gas partition coefficient similar to that of nitrous oxide (also see Chapter 26). Unfortunately, it causes an unacceptable incidence of laryngospasm (~50%) during the gaseous induction of anesthesia in children.[43] Gaseous induction of anesthesia with halothane or sevoflurane and then changing to desflurane for maintenance and wake-up may be reasonable. This changeover, unlike a similar change to halothane or isoflurane, may be clinically important in that the gas partition coefficient clearly favors rapid excretion. However, changing to desflurane for long procedures makes more sense than for brief cases, during which such accumulation is less likely. The more rapid awakening may be advantageous for neurosurgical and spinal fusion procedures, for which early assessment of mental and neurologic status is important. One study of pediatric patients undergoing adenoidectomy found a more rapid wake-up with desflurane than with sevoflurane or halothane, yet desflurane was also associated with the most frequent rate of emergence agitation.[44] Nasally

administered fentanyl (2 μg/kg) reduces the incidence of emergence agitation, but it also increases the incidence of postoperative vomiting.[45]

The MAC for desflurane is dependent on age: 9.2% for neonates, 9.4% for infants 1 to 6 months of age, 9.9% for infants 6 to 12 months of age, 8.7% for 1 to 3 year olds, and 8% for 5 to 12 year olds.[22] Interestingly, nitrous oxide does not contribute to the MAC of desflurane to the same degree as it does with other volatile anesthetics.[46] Desflurane, unlike other volatile anesthetics, has virtually no hepatic metabolism. Concern for the potential for carbon monoxide poisoning with desflurane as a result of dry carbon dioxide absorbent (also possible with isoflurane) can be prevented by rehydration before use. New carbon dioxide absorbents that do not contain a strong base may offer improved safety.

DRUGS USED TO INDUCE ANESTHESIA

Propofol

Propofol is highly lipophilic and promptly distributes into and out of vessel-rich organs; its rapid redistribution, hepatic glucuronidation, and high renal clearance account for the short duration of its effect (also see Chapter 30). As with barbiturates, the induction dose is larger in younger children (2.9 mg/kg for infants younger than 2 years of age) than in older children (2.2 mg/kg for children 6 to 12 years of age). The central volume is large and the clearance is rapid in young children.[47] The major drawback of propofol is pain on intravenous administration, particularly through small veins. As little as 0.2 mg/kg of lidocaine (mixed with the propofol) is effective in reducing but not eliminating this discomfort. Placing a tourniquet on the child and administering 1 mg/kg (up to 40 mg) of lidocaine 15 to 20 seconds before administering the propofol helps; propofol is then administered with the intravenous line running, and the tourniquet is then let down. This *mini–Bier block* technique is quite effective in reducing pain. Another method for minimizing pain is to use a small (22- to 24-gauge) catheter and to administer the drug through a large antecubital vein. Propofol is particularly useful for the brief and repeated sedation needed for radiotherapy in children with central venous lines. A constant infusion is useful for sedating children undergoing radiologic procedures and as a means of maintaining anesthesia during transport from one location to another, for example, from radiology to the surgical unit. A modest reduction in systolic blood pressure often accompanies a bolus administration. Propofol reduces the incidence of postoperative vomiting. Because propofol contains egg and soy products, it should be used with caution in children with egg or soy anaphylactic allergies[48,49]; however, a study of children with known egg allergy reported only one nonanaphylactoid reaction.[50] It should be avoided in children with anaphylactic reactions to eggs.

The major concern with propofol is the potential for propofol infusion syndrome (e.g., lactic acidosis, rhabdomyolysis, cardiac and renal failure), which is generally associated with high-dose infusions for an extended period (usually days in an intensive care unit [ICU] environment)[51] (also see Chapter 30). Although no such cases have been reported in healthy children during routine anesthesia care, one child with a genetic defect in lipid metabolism who received approximately 150 μg/kg/min (~9 mg/kg/hr) for 6.5 hours during scoliosis repair was reported. This case report along with one other[52] suggests caution in the use of propofol in children with known defects in lipid metabolism,[53,54] which may include some forms of mitochondrial disease. Yet, propofol has been safely used in many children with mitochondrial disease; this caution applies only to those with defects in lipid metabolism.[55]

Methohexital

Methohexital is generally administered intravenously at a concentration of 1% and a dose of approximately 1 to 2 mg/kg (also see Chapter 30). Problems associated with intravenous administration include burning, hiccups, apnea, and extrapyramidal-like movements. Methohexital has a shorter elimination half-life than thiopental. It is also useful for providing sedation during radiologic procedures by rectal administration (10% solution). Usually, 25 to 30 mg/kg produces light sleep within 8 to 10 minutes that lasts for 20 to 40 minutes. Obstructive or central apnea may occasionally occur. Therefore a means of ventilating the child must be available, and appropriate monitoring with pulse oximetry is important. Because it can cause seizures, methohexital is contraindicated in children with temporal lobe epilepsy. Children receiving seizure medications generally require larger doses.

Thiopental

Intravenous bolus administration of 2.5% thiopental (5 to 6 mg/kg) is sufficient to induce anesthesia in most healthy, unpremedicated children (also see Chapter 30). Termination of effect occurs through redistribution into muscle and fat; thiopental should be used in reduced doses (2 to 4 mg/kg) in children who have low fat stores, such as neonates or malnourished infants. Limiting the total dose to 10 mg/kg or less in older children minimizes the possibility of prolongation of anesthesia caused by residual barbiturate sedation. Thiopental (30 mg/kg in a 10% solution) may also be rectally administered if methohexital is contraindicated; thiopental is no longer available in the United States.

Ketamine

Ketamine causes central dissociation of the cerebral cortex while providing analgesia and amnesia (also see Chapter 30). In addition to the intravenous and intramuscular routes, ketamine may be administered rectally (10 mg/kg), orally (6 to 10 mg/kg), or intranasally (3 to 6 mg/kg). The combination of oral ketamine (4 to 6 mg/kg), oral midazolam (0.5 mg/kg), and oral atropine (0.02 mg/kg) provides a deeply-sedated child. Intravenous administration of doses as low as 0.25 to 0.5 mg/kg may be used to provide sedation and analgesia for painful procedures, whereas doses of 1 to 2 mg/kg produce sedation sufficient for a smooth transition to general anesthesia. Larger doses (up to 10 mg/kg intramuscularly) provide sufficient analgesia for the insertion of invasive monitoring devices before the induction of anesthesia (cardiac surgery) or in children with limited venous access. Ketamine is useful

for the induction of anesthesia in hypovolemic children. Patient-to-patient variability in response to this drug is relatively large, however. A major side effect, increased production of secretions, usually requires the administration of an antisialagogue agent. Other undesirable side effects include vomiting and postoperative "dreaming" or hallucinations; the incidence of dreaming may be reduced by the concomitant administration of a benzodiazepine. Although spontaneous respirations and a patent airway are usually maintained, apnea and laryngospasm may occur.

Contraindications to the use of ketamine in children include the presence of an active upper respiratory infection (URI), increased intracranial pressure, open-globe injury, and a psychiatric or seizure disorder. Ketamine does not preserve the gag reflex and thus should not be used as the sole anesthetic for children with a full stomach or a hiatal hernia. Ketamine has also been used as an adjunct for epidural analgesia.[56] However, *because the preservative in most ketamine preparations is neurotoxic, only preservative-free ketamine must be administered in the epidural space* (also see Chapter 30).

Etomidate

Etomidate is a steroid-based hypnotic drug used for induction of anesthesia (also see Chapter 30). As with propofol, the incidence of pain on intravenous administration is frequent. Concerns regarding anaphylactoid reactions and suppression of adrenal function have limited widespread use of this anesthetic. Etomidate is extremely useful in children with a head injury and those with an unstable cardiovascular status, such as children with a cardiomyopathy, because of the virtual absence of adverse effects on the cardiovascular system.[57,58] This drug has gained increasing popularity for airway management in the emergency department setting.[59] Usual doses are 0.2 to 0.3 mg/kg given before the administration of a small-dose opioid and a muscle relaxant. Etomidate is often used to facilitate tracheal intubation in children who are critically ill. Because a high proportion of critically ill children, particularly those resistant to vasopressors, suffer from relative adrenal insufficiency, steroid supplementation may be indicated in such children in whom etomidate is deemed necessary for their safe airway management.[60,61] A new ultrashort-acting etomidate analogue (cyclopropylmethoxycarbonyl metomidate) may avoid adrenal suppression while allowing a continuous infusion.[62]

SEDATIVES AND ANXIOLYTIC AGENTS

Diazepam

Oral absorption of diazepam is more rapid in children than in adults, with 0.1 to 0.3 mg/kg usually providing excellent peak sedation within 1 hour (also see Chapter 30). Intravenous administration is painful and not well tolerated; diazepam may also be rectally administered. Because the liver is the main site of degradation, this medication should be given with caution to any child with hepatic disease. Diazepam has an extremely long half-life in neonates (80 hours) and may not be indicated until the infant is 6 months of age or until hepatic metabolic pathways have matured.

Midazolam

Midazolam is water soluble and therefore not generally painful on intravenous administration (also see Chapter 30). Because of its water solubility, *it takes three times longer to reach a peak EEG effect than the more fat-soluble diazepam*. The clinician waits at least 3 minutes between intravenous doses to avoid *stacking* of effect.[63] The shorter elimination half-life (~2 hours) of midazolam than diazepam (~18 hours) offers an advantage for use as a premedication in children. Midazolam is the only benzodiazepine approved by the U.S. Food and Drug Administration for use in neonates; the half-life is significantly longer (6 to 12 hours) in this population.[64] Severe hypotension has occurred in neonates after bolus administration, and the potential for this problem is apparently increased in neonates also receiving fentanyl. Midazolam is rapidly absorbed after intramuscular (0.1 to 0.15 mg/kg, maximum of 7.5 mg), oral (0.25 to 1.0 mg/kg, maximum of 20 mg), rectal (0.75 to 1.0 mg/kg, maximum of 20 mg), nasal (0.2 mg/kg), or sublingual (0.2 mg/kg) administration.[65] Nasal administration is uncomfortable for most children. Midazolam probably augments the respiratory depressant effects of opioids. One important interaction is that erythromycin, calcium channel blockers, protease inhibitors, and even grapefruit juice produce a clinically important delay in midazolam metabolism because of inhibition of cytochrome P450. In this circumstance, either midazolam should be avoided or the dose reduced by 50%.[66] Nasal administration may increase the possibility of central nervous system (CNS) toxicity as a result of drug entering the CNS along the olfactory nerves.[67] Because neurotoxicity has never been examined and most children cry with nasal administration, this author believes that this route should generally be avoided.

Dexmedetomidine

Dexmedetomidine is a selective α_2-adrenergic agonist with anxiolytic, sedative, and analgesic properties (also see Chapter 30). The role of this drug for the care of children awaits further investigation to clarify its exact advantages and disadvantages. Very limited well-controlled pediatric studies have been conducted. A pharmacokinetic trial involving 36 children, 2 to 12 years of age, revealed a terminal elimination half-life of approximately 110 minutes with both heart rate (≤15%) and systolic blood pressure (≤25%) decreasing over time as the dose is increased; these observations are similar to those in adults.[68] Infusions of 2, 4, or 6 μg/kg for 10 minutes (total dose 0.33 to 1.0 μg/kg) found no significant effect on the respiratory rate or oxygen saturation during the 1-hour period of observation before induction of anesthesia. Only one child initially demonstrated an increase in blood pressure, but it was unclear whether it was drug related. Transient sedation occurred in all children, and the authors recommend slow intravenous infusion to minimize possible adverse hemodynamic events that might occur with bolus administration. The use of dexmedetomidine as a sole drug or combined with other sedatives has been described in children undergoing cardiac catheterization and a variety of radiologic procedures.[69,70] Dexmedetomidine facilitates fiberoptic intubation,[71] provides sedation for a child undergoing an awake craniotomy,[72] reduces

the incidence of emergence agitation,[73,74] and facilitates withdrawal from opioids.[75] In addition, this medication can provide prolonged sedation in children who are critically ill.[76] Thus the indications in children would seem to be the same as in adults. Large dose dexmedetomidine (2 to 3 μg/kg initial dose, followed by 1 to 2 μg/kg/hr) infusion has been associated with severe bradycardia (heart rate, 40 beats/minute),[77,78] but treatment with glycopyrrolate resulted in severe and persistent hypertension of unknown cause.[79] Given these potentially serious adverse effects, large dose dexmedetomidine cannot be recommended. In general, an initial dose of 0.7 to 1.0 μg/kg administered over 10 minutes is followed by an infusion of 0.5 to 1 μg/kg/hr; further sedation can be accomplished with opioid, benzodiazepines, or other sedating medications.[80]

OPIOIDS (Also See Chapter 31)

Morphine

Morphine is the oldest commonly used long-acting opioid. Its use in neonates (those younger than 10 days) remains controversial because it may cause more respiratory depression than meperidine. Higher brain levels of morphine were found in neonatal rats than in adult rats, thus implying that permeability of the blood-brain barrier may account, in part, for the apparent sensitivity of the human neonate to morphine.[81] This rationale led to the common belief that infants are sensitive to the effect of opioids. More recent studies have found age-dependent pharmacokinetics. Newborns have slower clearance of morphine, and therefore a smaller dose will result in higher plasma values because of a longer elimination half-life.[82] Term infants older than 10 days may clear morphine more rapidly and at a similar rate as adults.

The issue of respiratory sensitivity and the age at which it decreases in humans has yet to be resolved; a difference between morphine and fentanyl may exist that may not relate to the transport of drug into the brain.[83] If so, then changes in pharmacodynamics rather than simply maturation of the blood-brain barrier are dominant. Morphine should be administered with caution to neonates and preterm infants who are not in a monitored setting. Infants older than 6 months probably have a normal adult response to morphine.

Meperidine

Meperidine received great attention when it was thought to cause less respiratory depression than morphine in newborns (also see Chapter 31).[84] This difference may be related, in part, to the fact that meperidine is significantly more lipophilic than morphine. Unlike morphine, the fraction of drug that enters the brain of neonates is similar to that entering the brain of older children. As with all drugs administered to neonates, a large patient-to-patient variability in metabolism and response exists. Meperidine is not appropriate for long-term or repeated administration because of the accumulation of the toxic metabolite normeperidine; this drug has been removed from the formulary of many children's hospitals.

Fentanyl

Fentanyl is the most commonly used opioid in infants and children (also see Chapter 31). Its major advantages relate to its rapid onset and brief duration of action. This opioid is more lipophilic than meperidine; the potential effects of the blood-brain barrier are of no importance with fentanyl. Termination of the effect of low doses of fentanyl primarily results from redistribution, whereas termination of the effect of high doses depends on elimination. Large doses of fentanyl achieve the properties of long-acting opioids.

Fentanyl induces a very stable cardiovascular response while providing an anesthetic state. The dosage required to produce anesthesia varies considerably, depending on the child's age, the surgical procedure, the health of the child, and the use of anesthetic adjuvants.[85] Neonates undergoing abdominal surgery have a longer fentanyl half-life than do those undergoing other procedures; hepatic blood flow, and factors that greatly increase or decrease hepatic blood flow, such as positive end-expiratory pressure (PEEP) or the use of vasopressors, may alter the pharmacokinetic response. Impaired hepatic function may also play a role in the altered kinetics with increased intraabdominal pressure.[86] Therefore the pharmacokinetic and pharmacodynamic profile is very different and more variable for neonates than it is for older children. A dose of 12.5 μg/kg produces anesthesia in full-term neonates undergoing abdominal surgery,[85] whereas larger doses (30 to 100 μg/kg) are used for cardiac surgery (also see Chapter 94). These doses are safe in children whose ventilation will be controlled postoperatively; much smaller doses (2 to 10 μg/kg) should be used with other anesthetics if ventilation is not to be controlled postoperatively. Because the cardiac output of neonates is determined by the heart rate, fentanyl-induced bradycardia may require the administration of a vagolytic drug, such as atropine or even pancuronium during long procedures.

Alfentanil

Alfentanil is more rapidly eliminated than fentanyl; its pharmacokinetic effects are independent of dose (also see Chapter 31), which may provide a margin of safety because the greater the administered dose, the greater the elimination. Clearance of alfentanil may be increased in children, compared with adults. As with any opioid, important patient-to-patient variability in pharmacokinetics and pharmacodynamics occurs in neonates and in children with impaired hepatic blood flow.

Sufentanil

Sufentanil has been primarily used for cardiac anesthesia; age-dependent kinetics are also evident, particularly in the first month of life (also see Chapters 31 and 94). Children are able to clear sufentanil more rapidly than adults. This drug must be administered with caution because severe bradycardia and asystole have been reported when a vagolytic drug was not simultaneously administered.[87] Sufentanil may be nasally administered as a premedicant or analgesic (2 μg/kg); however, desaturation may follow.

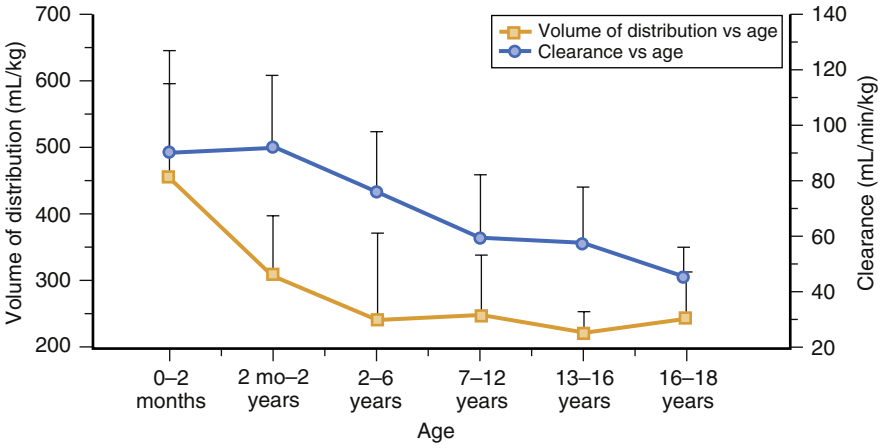


Figure 93-9. Remifentanil is the newest potent opioid available for the care of neonates. Unlike virtually all other medications, its clearance is more rapid in neonates than it is in older children, probably because of elimination of remifentanil by nonspecific plasma and tissue esterases, as well as the larger volume of distribution in neonates. The importance of this observation is that developmental immaturity of liver and renal function does not affect the pharmacokinetics of remifentanil. *(Data abstracted from Ross AK, Davis PJ, del Dear G, et al: Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures,* Anesth Analg *93:1393-1401, 2001.)*

Remifentanil

Remifentanil is the most recent addition to the opioids available for the care of children (also see Chapter 31).[88] The main advantage of this opioid is its extremely brief half-life. Studies in adults have found that even after prolonged infusions, the time to a 50% reduction in effect-site concentration (i.e., effect on respiration) is approximately 4 minutes. One study examined its pharmacokinetic effects in children and found age-related differences in the volume of distribution and clearance but not in half-life (Figure 93-9).[89] Contrary to the pharmacokinetics of most drugs, neonates are able to clear the drug more rapidly than older children! Of further interest is the very small patient-to-patient variability in pharmacokinetic parameters when compared with similar studies examining other opioids, particularly in infants and neonates. Because remifentanil is degraded by nonspecific plasma and tissue esterases, the importance of maturation of renal and hepatic function is minimal; the differences in remifentanil's half-life among neonates, infants, and adults are minimal. Therefore this drug has great utility in infants with hepatic or renal failure. The particularly favorable pharmacokinetics in neonates allows the provision of a deep opioid-induced plane of anesthesia while avoiding cardiovascular depression and the need for postoperative ventilation. One multicenter study of infants undergoing pyloromyotomy found no difference in intraoperative hemodynamic parameters, time to tracheal extubation, PACU discharge times, need for pain medications, or adverse events when compared with halothane anesthesia.[90,91] In older children, remifentanil is extremely helpful in the anesthetic management of those in whom neurologic status must be rapidly assessed. This drug is also very useful for cardiac surgery in children as a means of providing adequate opioid analgesia, cardiovascular stability, and early extubation while transitioning to longer-acting low dose opioids (also see Chapter 94).

Several studies have examined bolus doses of remifentanil as an alternative to succinylcholine.[92,93] One study found that 1.25 μg/kg of remifentanil combined with 4 mg/kg of propofol allowed all children (2 to 16 years of age) to have their tracheas successfully intubated, but more coughing was observed. In addition, the duration of apnea was longer in the remifentanil group than in those who received an equivalent dose of propofol combined with succinylcholine (1 mg/kg); none of the children in the remifentanil group developed chest wall rigidity.[92] Another study of infants 2 to 12 months old and children 1 to 6 years of age determined the 98% effective dose (ED_{98}) for successful intubation to be similar in both age groups (~2.9 μg/kg).[93] The second half of that study compared remifentanil, 3 μg/kg, combined with propofol, 4 mg/kg, in 2- to 12-month-old infants succinylcholine (2 mg/kg) combined with propofol (4 mg/kg) and found similar tracheal intubating conditions; the duration of apnea was similar in both groups. Data are currently insufficient to support the routine substitution of remifentanil for succinylcholine for rapid sequence tracheal intubation. Because bolus doses of remifentanil are associated with hypotension and bradycardia, a vagolytic drug should also be administered.

In neonates and toddlers, the use of a more dilute concentration (e.g., 5 μg/mL) of remifentanil and bypassing the dead space of the injection port with a needle (or priming the dead space) are necessary to ensure that the onset of drug effect is not delayed.[94,95] In older children, a standard solution of 50 μg/mL may be used. In general, a starting bolus dose is not necessary and an infusion of 0.1 μg/kg/min may be increased or decreased as indicated. Two studies have compared the somatic and autonomic responses to skin incision during continuous remifentanil infusion in adults and children.[96,97] The infusion rates to block somatic and autonomic responses in 50% of children were significantly higher (approximately twofold greater) than in adults. The reason for such a disparity in drug requirement between adults and children is not clear. However, this observation is certainly clinically important because it suggests the possible need to (1) start at higher initial infusion rates, (2) rapidly increase infusion rates after an initial assessment of responses, (3) supplement the anesthetic with nitrous oxide or a volatile anesthetic, or (4) add another analgesic. This author has used a fixed combination of 100 μg of remifentanil combined with 18 mL of propofol (final concentration, 5 μg/mL of remifentanil) for children younger than 10 years of age and a lower fixed combination of 50 μg of remifentanil in 19 mL of propofol (final concentration of 2.5 μg/mL) for older children and started the infusion rate equivalent to 150 μg/kg/min of propofol; this combination

provides excellent conditions for upper and lower endoscopic procedures. The smaller dose of remifentanil for the older children is to avoid bradypnea. One study has demonstrated adequate stability of this mix for 6 hours.[98]

For practical purposes and safety, remifentanil should be administered by continuous infusion. It should also be carried into the vein by a second continuous infusion because variations in drug delivery related to differences in intravenous fluid delivery can have profound effects on the rate of opioid administration.[94,95] For neonates and small children, this author has generally used a continuous infusion pump for administering the maintenance intravenous fluid at half the hourly requirement and *piggyback* the remifentanil infusion as close to the intravenous catheter as possible. In complex procedures, this author uses a separate intravenous line for all other anesthetic management issues. A further extremely important concern is the need to provide analgesia once the remifentanil is discontinued. This author usually accomplishes this with morphine (0.05 to 0.2 mg/kg, depending on the severity of the expected pain) or with a regional nerve block administered well before the discontinuation of the remifentanil. This author has also used remifentanil as a means of producing profound analgesia while taking advantage of its vagotonic effects to reduce blood pressure in children undergoing spinal instrumentation. This strategy avoids interference of evoked motor or sensory potentials because a low-dose inhaled volatile anesthetic and a propofol infusion may be used for anxiolysis and amnesia. Acute tolerance has been reported in this setting.[99]

MUSCLE RELAXANTS (Also See Chapter 34)

Depolarizing Muscle Relaxants

Succinylcholine is highly water soluble and rapidly redistributes into the extracellular fluid volume. For this reason, the dose required for intravenous administration of this depolarizing muscle relaxant in infants (2.0 mg/kg) is approximately twice that for older children (1.0 mg/kg). Succinylcholine is the only short-acting relaxant that is effective when given intramuscularly; reliable muscle relaxation occurs within 3 to 4 minutes after 5 mg/kg in infants and 4 mg/kg in children older than 6 months. The skeletal muscle relaxation produced by intramuscular administration may last up to 20 minutes; more rapid onset is not achieved by splitting the dose into two injections or by changing the concentration. In an emergency situation, succinylcholine may be administered intralingually (via a submental approach), which will further speed the onset of relaxation because the drug is more rapidly absorbed from the tongue than from peripheral skeletal muscle.

Cardiac arrhythmias frequently follow intravenous administration, especially during halothane anesthesia. Prior intravenous administration of atropine (but not intramuscular administration of atropine as a premedication) reduces the incidence of arrhythmias. Cardiac sinus arrest may follow the first dose of succinylcholine but is more common after repeated bolus administrations; such arrest may occur in children of any age. Although the incidence of bradycardia is infrequent in older children, this author has observed one 13-year-old child in whom asystole developed for approximately 30 to 45 seconds after a single dose of succinylcholine administered with thiopental but not atropine; the asystole occurred before intubation and with 100% oxygen saturation and immediately responded to the administration of atropine and several chest compressions to circulate the atropine. Therefore a vagolytic drug should probably be intravenously administered just before the first dose of succinylcholine in all children, including teenagers, unless a contraindication to tachycardia (e.g., a cardiomyopathy) exists.

Succinylcholine has received significant attention because of the severity of its possible complications. The potential for rhabdomyolysis and hyperkalemia (particularly in boys younger than 8 years of age who have unrecognized muscular dystrophy), as well as the risk for masseter spasm and malignant hyperthermia, suggests that succinylcholine should not be routinely used in children.[100,101] Increased jaw muscle tone (masseter spasm) after succinylcholine has been observed, which may be a normal variant. However, masseter tetany ("jaws of steel"), which prevents any mouth opening, represents an extreme variation in increased masseter muscle tone and may be the reaction associated with malignant hyperthermia. This author has observed this effect two times; malignant hyperthermia did not develop in either child, but one child had creatine kinase (CPK) values larger than 20,000 International Units (IU) the next morning.

With the foregoing cautions in mind, succinylcholine remains valued because it is the only commercially available ultrashort-acting muscle relaxant that provides a dependable, rapid onset of action. Intravenous use of this drug should be limited to children who have a full stomach or to treat laryngospasm; intramuscular or submental (intralingual) administration is indicated for children with difficult intravenous access when control of the airway is deemed essential.

Hope is on the horizon for a safer alternative for rapid-sequence intubation of the trachea and for treatment of laryngospasm (i.e., large-dose rocuronium, 1.2 mg/kg).[102] If the new reversal drug, sugammadex, is demonstrated to be safe and effective in children (see later discussion) and its ability to antagonize profound neuromuscular blockade is confirmed in children, the vast majority of life-threatening adverse effects associated with succinylcholine will disappear. In many countries all over the world, sugammadex has proven to be an excellent reversal of neuromuscular blockade.

Nondepolarizing Muscle Relaxants

A comparison of infants with older children or adults regarding their responses to nondepolarizing muscle relaxants shows that infants are generally more sensitive to these drugs and that their responses vary to a greater degree (also see Chapter 34). Although the initial dose per kilogram needed for neuromuscular blockade is often similar for children of all ages, the greater volume of distribution and reduced renal or hepatic function of neonates result in a slower rate of excretion and hence a

TABLE 93-4 COMMONLY USED MUSCLE RELAXANTS AND REVERSAL AGENTS IN PEDIATRICS

Drug	Average Intubation Dose (mg/kg)	Category	Approximate Duration (minutes)
Muscle relaxants*			
Pancuronium	0.1	Long acting	~45-60
Cisatracurium	0.1	Intermediate acting	~30
Vecuronium	0.1	Intermediate acting	~30
Rocuronium		Dose related:	
	0.3	Short acting	~15-20
	0.6	Intermediate acting	~30-45
	1.2	Long acting	~45-75
Reversal agents†			
Edrophonium	0.3-1.0 mg/kg + atropine, 0.02 mg/kg		
Neostigmine	0.02-0.06 mg/kg + atropine, 0.02 mg/kg		

*The response of preterm and term neonates (who may be more sensitive to the drugs) to muscle relaxants varies greatly from patient to patient. Therefore all doses should be titrated to response. The recommended tracheal intubation doses may be reduced 30% to 50% in the presence of a potent inhaled agent.

†The dose of the reversal agent given to antagonize nondepolarizing neuromuscular blockade should be determined by the degree of residual neuromuscular blockade (i.e., the dose should be titrated to clinical effect).

prolongation of effect. Neuromuscular blockade occurs at a lower blood concentration in infants.

The choice of nondepolarizing muscle relaxant depends on the side effects and the duration of the desired muscle relaxation. If tachycardia is desired (e.g., with fentanyl anesthesia), then pancuronium may be an appropriate choice. Vecuronium, atracurium, rocuronium, and cisatracurium are useful for shorter procedures in infants and children; they may also be administered as a constant infusion. The method of excretion of atracurium and cisatracurium (Hofmann elimination and ester hydrolysis) makes these relaxants particularly useful in newborns and children with immature or abnormal hepatic or renal function. Vecuronium is valuable because no histamine is released; however, its duration of action is prolonged in newborns, which makes it similar to pancuronium.

Rocuronium has a clinical profile similar to that of vecuronium, cisatracurium, and atracurium but offers the advantage that it can be administered intramuscularly. One study observed that acceptable conditions for intubation are produced by rocuronium within 3 to 4 minutes after 1 mg/kg intramuscularly in infants and 1.8 mg/kg intramuscularly in children older than 1 year of age; these effects were more dependable with deltoid than with quadriceps muscle injection.[103] This onset time is similar to that produced with intramuscular succinylcholine; however, the duration of action is approximately 1 hour, which could be a distinct disadvantage for a brief procedure. The onset of neuromuscular blockade with intravenous rocuronium (1.2 mg/kg) is also virtually the same as intravenous succinylcholine (1.5 mg/kg), and intubation conditions are identical.[102] The author has used this intravenous rocuronium dose with propofol (3 to 4 mg/kg) for rapid-sequence induction after administering oxygen in children in whom succinylcholine might present an added risk; even better intubating conditions are achieved with the addition of intravenously administered lidocaine (1 mg/kg). The tracheas of most children can be intubated at 45 seconds. The disadvantage is that the duration of action is 45 to 75 minutes, thus limiting its usefulness to either long procedures or accepting the fact that prolonged neuromuscular blockade may result. Conversely, at small doses of rocuronium (0.3 mg/kg), satisfactory conditions for tracheal intubation occur at approximately 3 minutes when combined with a volatile anesthetic, but successful reversal of neuromuscular blockade can usually be achieved within 15 to 20 minutes.

Table 93-4 provides commonly recommended guidelines for doses. Because of the extreme variability in response, the doses of long-acting muscle relaxants used for infants should be carefully titrated, starting with one third to one half of the usual dose administered to older children. This author recommends routine pharmacologic antagonism of neuromuscular blockade in all neonates and small infants, even if they have clinically recovered, because any increase in the work of breathing may cause fatigue and respiratory failure. Useful signs of reversal are the ability to lift the legs and arms and recovery of the train-of-four response to peripheral nerve stimulation.

Sugammadex

Sugammadex is a cyclodextrin whose endoskeleton forms a water-soluble complex with the exoskeleton of rocuronium; it was specifically designed to antagonize the effects of rocuronium[104,105] (also see Chapter 35). The purported advantage of sugammadex is that antagonism occurs as a result of covalent bonding, and because sugammadex is made of sugars, the potential for adverse side effects would appear to be minimal.[105,106] This drug also reverses the other steroidal relaxants, vecuronium and pancuronium, probably to a lesser extent. The mechanism of reversal is a lowering of the plasma concentration and thus reversing the concentration gradient and encapsulating the rocuronium for transport away from the myoneural junction.[105,107] The result is a more rapid antagonism than with a neostigmine-atropine mixture.[108] Furthermore, sugammadex has no cardiovascular effects; therefore it does not require a drug such as atropine. The importance of this new approach to antagonism of neuromuscular

TABLE 93-5 **APPROXIMATE COST FOR REVERSAL OF ROCURONIUM BY WEIGHT AND DENSITY OF BLOCK***

	Weight (kg)			
Depth of Block	**3**	**10**	**20**	**70**
Mild (4 twitches with fade) 2 mg/kg	$1.4625	$9.75	$19.50	$67.90
Moderate (1-2 twitches) 4 mg/kg	$1.95	$19.50	$39.00	$135.80
Profound (no twitches) 8 mg/kg	$3.90	$39.00	$78.00	$271.60
Wasted drug (single-patient use; profound blockade)	$93.60	$58.50	$19.50	$68.025†

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*Rocuronium is not yet approved by the U.S. Food and Drug Administration; therefore the above prices are based on the United Kingdom costs.

†Assumes one 200-mg vial and one 500-mg vial for complete dosing:
Cost per 200 mg vial: £60 or ~$97.50 ($0.4875/mg)
Cost per 500 mg vial: £149 or ~$242.125 ($0.4843/mg)

blockade is the ability to avoid all the side effects of neostigmine and anticholinergic medications, as well as the ability to antagonize profound neuromuscular blockade. This very exciting development could virtually eliminate the need for succinylcholine in pediatric practice, except perhaps for intramuscular use in children without intravenous access. Even in this circumstance, intramuscular rocuronium would be antagonized by sugammadex, provided that adequate doses are administered. Certainly, the adult data are very promising, and if sugammadex has a minimal adverse event profile, then it may completely change the approach to anesthesia in children. Data also suggest a more rapid recovery from anaphylaxis related to rocuronium when sugammadex is administered as a rescue medication.[109,110] Unfortunately, the manufacturer has established a price so high that its routine use is inhibited and usually not financially practical (Table 93-5). Therefore at the time of this writing, it appears that sugammadex will be administered as a rescue drug only.

ANESTHETIC CONSIDERATIONS

PREOPERATIVE PREPARATION

The preoperative visit and preparation of the child for surgery are more important than the choice of premedication (also see Chapter 38). During this time the anesthesiologist evaluates the medical condition of the child, the needs of the planned surgical procedure, and the psychological makeup of the child and family. The anesthesiologist also formulates the approach to induction of anesthesia, explains the possibilities regarding induction, and helps soothe family concerns. Because the anxiety felt by the parents may be transferred to the child, any practice that reduces anxiety in the parents may also reduce anxiety in the child. Therefore the anesthesiologist should explain in great detail what the child and family can expect and what will be done to ensure their own and their child's utmost safety. The more information that the parents and child have, the more easily they will deal with the stress of surgery and hospitalization. Presurgical programs such as videotapes, literature, and hospital tours also help. Play therapy can also relieve stress; it is amazing to observe children so enthralled with their iPad video game that they fall asleep while playing the game.

After chart review, physical examination, and furnishing information regarding the approximate time and length of surgery, the anesthesiologist should describe to the child what anesthesia is and what will be done to ensure good care. The purpose of all monitoring devices should be explained to both the child and family. Children need to understand that none of these devices will hurt and that they can watch during their application. If an intravenous line will be started, then the child needs to be told that "numbing" medicine will be used. Any special monitoring devices, such as an arterial line, central venous line, nasogastric tube, or urine catheter, should also be described to the parents, with assurances that these devices will be inserted after the induction of anesthesia. Part of this informed consent is also a description of the anesthesiologist's role in the operating room. It is vital to assure parents that the "anesthetic prescription" will be tailored to meet their child's medical, as well as surgical, needs. This author uses the phrase "anesthetic prescription" because anesthesiologists are physicians, as is the surgeon or a pediatrician, and it is important for families to clearly understand this.

Children think in very concrete terms, therefore care must be taken to avoid misunderstandings. Explaining to children that the "sleep" caused by anesthetic drugs differs from normal sleep is important. They should know that the anesthesia medicines keep them from awakening during surgery and from remembering the operation. It should also be explained that the anesthesia medicines will be removed at the end of surgery and that they will then wake up and return to their parents. This kind of explanation does not require a significant amount of time and goes a long way toward reassuring the child and family about the quality of care provided.

The issue of pain must not be avoided. Children need to be reassured that everything possible will be done to minimize pain on awakening. Therefore it should be stressed that pain medications will be administered and that local infiltration nerve blocks, continuous epidural or caudal infusions, child-controlled epidural analgesia, or patient/parent/nurse-controlled analgesia will be used (see also Chapters 92 and 98). The PACU or ICU must also be described to ensure that no surprises occur.

THE FEARFUL CHILD

Because of either a past experience or a general lack of understanding, some children are terrified to come to the operating room. When a child breaks into tears and if the child is old enough to talk with, then the anesthesiologist should stop whatever is happening at the moment, sit on the bed next to the child, and ask what exactly is concerning them. Sometimes the child does not respond. In this situation, such children should be asked if they are afraid to go to sleep, afraid of feeling their "operation," or

afraid of pain afterward. Generally, they are able to verbalize their concern; however, even with no response, at this point the anesthesiologist should reiterate that "*the sleep from anesthesia is different from sleep at home. At home, if mom or dad shakes you, you would wake up. In the operating room, no matter what we do, you will not feel it, you will not remember it, and then at the end I will take the medicine away. You will breathe it all back out again, and then you will wake up and return to your family.*"

This explanation usually ends the tears. Sometimes the tears flow because they want a parent present for induction, even some of the older children. This request is easy to grant, and it also usually ends the tears. If, on the other hand, a specific event in the past is causing concern, then determining whether something was misunderstood or whether something can be carried out differently to avoid the issue is important. For some children with previous anesthetic experience, simply allowing them to hold the anesthesia mask themselves provides them with sufficient control of the situation to stop the tears. I once had a 7 year old who wrote a will: "*Leave my doll to.... Leave my blanket to....*" When I asked what this was all about, she responded that she was "*going to sleep today and that sometimes when people go to sleep they do not wake up.*" Because she had suffered a burn injury and need many procedures, I explained to her that, yes, people can go to sleep and not wake up, but usually that happened to an older person with a problem with the heart or the brain and that I had not seen this in someone her age having this operation. I asked her if she would feel better if she held the mask herself, and she, in fact, held the mask for a smooth anesthetic induction. In recovery, she later thanked me as "*the first doctor that ever explained anything to me!*" This brief anecdotal experience emphasizes the importance of directly talking to children, regardless of their age. Finally, other children cannot be consoled, and finding the source of their concern is not always possible. It is these children who will benefit from heavy premedication, such as the combined oral midazolam, ketamine, and atropine (see earlier discussions).

FASTING

No difference is observed in gastric residual volume or pH in children allowed to ingest unlimited clear liquids (e.g., water, apple juice) up until 2 to 3 hours before anesthetic induction versus standard fasting. Being able to drink appropriate fluids is a more humane approach for both children and their parents without increasing the risk for pulmonary aspiration of gastric contents. Infants and young children have a higher metabolic rate and a larger body surface area-to-weight ratio than adults and more easily become dehydrated than adults. The major advantage of the liberalized fasting guidelines may be a reduced incidence of hypovolemia at the time of anesthesia induction. This author's approach is to restrict milk and solids after midnight but allow unlimited clear fluids up to 3 hours before induction; even if the surgical schedule changes, this author still feels comfortable with 2 hours of fasting (Table 93-6). Infants who are breast-fed may have their last breast milk 4 hours before induction of anesthesia. Breast milk should be considered equivalent to formula because the fat content varies with maternal diet, and delayed gastric emptying may result. The American Society of Anesthesiologists (ASA) guideline also allows a "light meal" of toast and clear liquids up to 6 hours before induction of anesthesia, but parents frequently confuse this guideline to mean any type of meal, including eggs and bacon![111]

TABLE 93-6 PREOPERATIVE FASTING RECOMMENDATIONS IN INFANTS AND CHILDREN

Type	Fasting Time (hrs)
Clear liquids*	2
Breast milk	4
Infant formula	6†
Solid (fatty or fried) foods	8

*Includes only fluids without pulp; clear tea or coffee without milk products.
†The American Society of Anesthesiologists guideline allows a "light breakfast" (tea and plain toast) 6 hours before anesthesia; however, determining what a "light breakfast" means for a child is difficult.

PREMEDICATION

Almost all sedatives are effective. The important issue is local effectiveness at a given institution. The need for premedication must be individualized according to the underlying medical conditions, the length of surgery, the desired induction of anesthesia, and the psychologic makeup of the child and family. Premedication is not normally necessary for the average 6-month-old infant but is warranted for a 10- to 12-month-old who is afraid to be separated from his or her parents. Oral midazolam is the most commonly administered premedication in the United States. An oral dose of 0.25 to 0.33 mg/kg (maximum, 20 mg) generally results in a very compliant child who will separate from parents without crying[65] (also see Chapter 38). A review of previous anesthetic records is particularly helpful in ascertaining how the child has responded in the past.

Premedications may be administered orally, intramuscularly, intravenously, rectally, sublingually, or nasally. Although most of these routes of administration are effective and reliable, each one has its drawbacks. Oral or sublingual premedication does not hurt but may have a slow onset or can be spit out; drug taste and child cooperation are the main determinants of success. Oral ketamine (4 to 6 mg/kg) combined with atropine (0.02 mg/kg) and midazolam (0.5 mg/kg, maximum of 20 mg) will result in a deeply sedated child. Intramuscular medications hurt and may result in a sterile abscess. Intravenous medications may be painful during injection or at the start of infusion. Rectal medications sometimes make the child feel uncomfortable, cause defecation, and occasionally burn. Nasal medications can be irritating, although absorption is rapid. A midrange dose of *intramuscular* ketamine (2 to 4 mg/kg) combined with atropine (0.02 mg/kg) and midazolam (0.05 mg/kg) is generally reserved for children who refuse oral premedication or those in whom lighter premedication regimens have failed in the past. Larger doses of intramuscular ketamine (up to 10 mg/kg) combined with atropine and midazolam may be administered

to children with anticipated difficult venous access or in whom an intravenous line is necessary for induction (e.g., infants with congenital heart disease) to provide better conditions for the insertion of an intravenous line.

Anticholinergic drugs are not routinely administered intramuscularly to children because they are painful on administration and do not significantly reduce laryngeal reflexes during induction of anesthesia.

THE CHILD WITH AN UPPER RESPIRATORY INFECTION

A child with a URI is a major concern because the anesthetic implications can be quite important. Unfortunately, data regarding URIs and the anesthetic implications are difficult to ascertain for many reasons, including the definition of what a URI is, which varies from study to study. The decision whether to proceed with surgery and anesthesia is dependent on a number of factors. The URI may represent a prodrome of a much more serious illness, or it may simply be the usual viral infection so common in children, particularly in the wintertime. A child with a URI likely has an irritable airway and is at increased risk for laryngospasm, bronchospasm, postintubation croup, atelectasis, pneumonia, and episodes of desaturation. The incidence of airway-related problems in children who are passively exposed to tobacco smoke is increased.[112-115] These complications can be reduced by avoiding tracheal intubation or using a supraglottic device such as an LMA. However, the incidence of adverse airway-related events is not reduced by the administration of anticholinergics or bronchodilators.[116,117] Because bronchial hyperreactivity may last for up to 6 weeks after a URI, cancellation will make a difference only if surgery is delayed for this length of time or longer.[118,119] The same incidence of airway-associated complications occur in children who are recovering from a URI as for those in the acute phases of a URI.[112,119,120] If the child is acutely ill and obviously getting worse, then the procedure should probably be canceled. If the child has rhonchi and a productive cough, then the procedure is canceled. If the child is stable and afebrile and has had the URI for several days, then this author usually proceeds. The main concern is a child who is going to have a very long procedure or will be admitted to the hospital postoperatively, which may in turn result in exposure of other hospitalized children who may be immunocompromised. When faced with this dilemma for a child who will be going home postoperatively, the family and the surgeon should be informed of the increased risks; they generally make the decision to proceed. Tools are available to manage the reasonably common complications successfully. Oxygen is used to treat hypoxemia, albuterol and inhaled anesthetics can treat bronchospasm, muscle relaxants are available to treat laryngospasm, and usually a way is found to avoid intubation of the trachea for simple procedures. Cancellation of a procedure at the last minute is unfair to the family and upsets the surgical unit schedule. On the other hand, one should not place the child at risk merely for economic or social concerns. The best way to avoid last-minute cancellations is a telephone call by the nursing staff the day before to inquire about the child's health. If the child has a URI, then the anesthesiologist can call the family and take a history to determine how best to proceed. In this way, wasted trips to the hospital are avoided and the father or mother, or both, do not unnecessarily take off a day of work. Physicians are really left to their own best clinical judgment for an individual child on a particular day undergoing a specific procedure. If the decision is made to proceed, then writing a note in the chart documenting the discussion is helpful and recommended.

INDUCTION OF ANESTHESIA

The method of inducing anesthesia is determined by a number of factors: the medical condition of the child, the surgical procedure, the level of anxiety of the child, the child's ability to cooperate and communicate (because of age, developmental delay, or language barrier), and the presence or absence of a full stomach, among others.

Infants

Induction of anesthesia via a mask without premedication is generally used in infants younger than 10 to 12 months because this age group readily separates from their parents. Induction via a mask is accomplished most easily by holding the end of the anesthesia circuit in a cupped hand over the infant's face or by holding the mask just off the surface of the face; the other hand can adjust the concentration of anesthetic. Allowing neonates and small infants to suck on a rubber nipple or on a gloved finger generally prevents crying during the induction of anesthesia. As the infant loses consciousness, the anesthesia mask is adjusted to improve delivery and decrease operating room pollution. This phase is the most dangerous time because misjudging the depth of anesthesia and depressing the heart are very easy. Once anesthesia has been induced, it is critical to reduce the inspired concentration of halothane (down to 1.0% to 1.5%) or sevoflurane (down to 3% to 4%) and maintained at this level or less until an intravenous line is in place. After the intravenous line is inserted, the plane of anesthesia may be deepened or a muscle relaxant may be added. Directly proceeding to a deep plane of anesthesia without having an intravenous line in place is dangerous; without this precaution, resuscitation would be difficult.

The second most dangerous point occurs immediately after tracheal intubation. If the vaporizer has not been closed before laryngoscopy, then forgetting that a relatively high inspired concentration is being delivered and perhaps giving an overdose of inhaled anesthetic while checking for breath sounds are both easy. Therefore the prudent clinician will discontinue all anesthetics until laryngoscopy and tracheal intubation have been completed. With a Mapleson D circuit, a high concentration of anesthetic can more easily be delivered because the anesthetic enters directly at the airway. In contrast, changes made at the vaporizer of a circle system take a longer time to achieve equilibration with the circuit; therefore the inspired concentration of anesthetic more gradually increases (or decreases) unless a high fresh gas flow is being used. Particular caution should be used when changing from halothane or sevoflurane to isoflurane because the myocardial depressant effects of these drugs are additive.

Older Pediatric Patients

Successful, psychologically atraumatic induction of anesthesia by mask in an older child requires that the child understand and cooperate. Premedication is particularly helpful in the 1- to 4-year-old age group. Several different techniques may be used. One method is to play a game. For example, a younger child may be asked to *"blow up the balloon."* A slightly older child (4 years of age and older) may be receptive to hypnotic suggestions during induction. A young child may be susceptible to a suggestion that the anesthesia mask is an *"airplane pilot's mask"* and that the smell of halothane or sevoflurane is *"oxygen"* or *"aviation fuel."* Stating that the *"faster and higher the plane goes, the stronger the aviation fuel will smell"* is one means of distracting the child. During this type of induction, the operating room must be free of distractions, and the anesthesiologist must be able to communicate with the child. The use of constant conversation and incremental increases in the inspired concentration of anesthetic every third or fourth breath usually produce a smooth transition to general anesthesia. In many places, a "play therapist" has educated the child about what to expect and may even have a video game to distract him or her during the induction of anesthesia. If so, then another person must hold the video game so that it does not strike the child in the face as she or he falls asleep. Often the child will breath hold. If so, then the anesthesiologist should not attempt to assist respirations because this action often elicits coughing or laryngospasm. The anesthesiologist must be certain that airway obstruction and laryngospasm can be differentiated from breath holding. Observing the chest wall and abdomen helps identify airway obstruction, which creates a rocking-type movement of the chest and abdomen (when the diaphragm descends, the abdomen appears to expand but the chest does not). As soon as the child loses consciousness, the inspired concentration of anesthetic can be reduced and an intravenous line can be inserted. Should partial laryngospasm or upper airway obstruction occur, closing the pop-off valve to create approximately 5 to 10 cm water (H_2O) of PEEP, while allowing the child to breathe spontaneously, often facilitates gas exchange. If this procedure is not effective, then administration of rapid positive-pressure breaths, while avoiding inflation of the stomach, often disrupts the laryngospasm. Obviously, administration of a muscle relaxant will also break the laryngospasm; succinylcholine remains the agent of choice in an emergency situation.

A third method of induction involves the use of flavored masks. A variety of flavored scents and lip balms are available to reduce the noxious smell of anesthetics; the child can select a favorite scent.

A fourth method, the single-breath technique, requires a very cooperative child who can follow instructions. Using an unattached anesthesia mask, the anesthesiologist should demonstrate the procedure to the child, who then rehearses the following steps: (1) take a big breath in and hold at full inspiration; (2) exhale completely, hold at full expiration, and place the mask on the child's face at exactly the end of expiration; (3) take another full inspiration, hold as long as possible; (4) and then resume normal breathing. Before induction, the anesthesia circuit is filled with either 5% halothane or 8% sevoflurane in 60% nitrous oxide. The circuit bag must be emptied and filled several times so that the entire circuit is filled with 5% halothane or 8% sevoflurane. Steps 1 through 4 are then repeated with the mask attached to the Y-piece of the anesthesia circuit. When placing the face mask, care should be taken to not direct the gas toward the eyes (flutters the eyelashes), which can frighten the child. If the child fully cooperates, then this method generally produces loss of the eyelid reflex in less than 1 minute. Occasionally, a child does not take a full breath or becomes frightened, or the application of the face mask is not complete. If the child is partially anesthetized, then induction takes slightly longer, but the child does not usually remember the induction. If the child panics before inhalation of anesthetic, then induction should not be forced, and an alternative plan should be undertaken.

Parents in the Operating Room

It is very common for parents to request to be present during induction of anesthesia. This author welcomes their participation in this process (usually limited to one parent) because on some occasions, the security of having a parent present and avoiding separation allows the anesthesiologist to omit premedication. *Parental presence should not be substituted for premedication if the child needs premedication.* In other situations, parental presence sufficiently reduces anxiety so that light premedication is adequate. Decisions regarding parental presence must, however, take into consideration the developmental level of the child and the reason for parental presence. It serves no purpose to have a parent present during induction of anesthesia in a newborn or a 6-month-old infant who is completely trusting of strangers. Likewise, parental presence is unlikely to benefit a child who has been heavily premedicated. Certainly, parents must not be present for rapid induction in the presence of a full stomach. Parents are present for the benefit of their child, and if the child does not benefit or if a parent makes the physicians uncomfortable, then he or she should not be present. The safety and care of the child are the priority. This author sometimes explains that their participation in this process is a privilege but not a right. Each physician and each institution must determine what works and what does not work for them. If this author makes a decision to allow a parent to be present, then explaining what they might see is vital to ensure no surprises. The explanation may include, *"When anyone goes to sleep, their eyes roll upward,"* which is a normal response; and the parent might see his or her child's eyes do this a few times. The anesthesiologist should assure the parents that they should expect this and not to think that something is wrong. Next, the explanation should include the warning that as children fall asleep, *"they often make noises from their throat"* (e.g., snoring) and that this is also normal and that they might hear noises from their child's throat as their child falls asleep. (The author does not explain that these noises might be airway obstruction or developing laryngospasm). Third, the author points out that the *"brain often gets excited before it goes to sleep"*; thus after their child breathes the anesthesia medicine for a brief period, it is common for the child to suddenly become restless and to move the arms and legs or look from side to side. This response is expected, and, shortly afterward, the child will be completely anesthetized. Further, although

the child appears to be awake, the parent is assured that the child will not remember any of these responses. Thus the eye rolling, possible airway obstruction, and excitement are all explained, and the parent is not frightened should any of these events occur. The author also makes certain that the parent is sitting in a chair and explains that as soon as their child looses consciousness, they should kiss their child and then leave the operating room so that anesthesia team can completely focus on the care of their child.

For smaller children, this author likes to anesthetize them on a parent's lap. The child faces straight forward with the parent's arms wrapped around the child, helping to hold the child's arms near his or her side to reduce the potential for them to reach up and grab the mask. The author explains to the parent that he or she is going to be able to hug their child as he or she goes to sleep. I also explain that the child will become limp and could fall unless the parent holds on tight. Finally, as the child loses consciousness, the anesthesiologist will pick up the child and place him or her on the surgical table. The parent can then kiss the child and proceed to the family waiting area. If a language barrier exists, then the author will ask a translator to help explain this process and allow the translator in the surgical unit to assist in the communication that is needed to perform an atraumatic mask induction. For these children, usually only a pulse oximeter is applied before induction.

Rectal Induction of Anesthesia

A number of medications may be rectally administered for induction and premedication of anesthesia, but this method is rarely used in current practice. The main advantage of this approach is that the child falls asleep in the parent's arms or, as is the case with midazolam, atraumatically separates from the parents. This technique is no more intimidating than taking a rectal temperature but is generally reserved for children still in diapers. Care must be taken to not allow the child to see the rectal catheter or syringe, which would appear very large to the child. Rectal administration of 10% methohexital (20 to 30 mg/kg) reliably induces anesthesia within 8 to 10 minutes in 85% of young children and toddlers. Oxygen desaturation is not usually a problem unless the child's head is allowed to flex forward and cause obstruction of the airway. The main disadvantage of this technique is that drug absorption can be either significantly delayed or very rapid. Other drugs rectally administered include 10% thiopental (20 to 30 mg/kg), midazolam (1 mg/kg up to 20 mg), and ketamine (6 mg/kg).

Intramuscular Induction of Anesthesia

Many medications, such as methohexital (10 mg/kg), ketamine (2 to 10 mg/kg combined with atropine [0.02 mg/kg] and midazolam [0.5 mg/kg]), or midazolam alone (0.15 to 0.2 mg/kg), are intramuscularly administered for premedication or induction of anesthesia. The main advantage of this route of administration is its reliability; its main disadvantage is that it is painful.

Intravenous Induction of Anesthesia

Intravenous induction of anesthesia is the most reliable and rapid technique. The main disadvantage is that starting an intravenous line can be painful and threatening for the child. Intravenous induction may be preferable when induction by mask is contraindicated (e.g., in the presence of a full stomach). Older children will often allow insertion of an intravenous catheter after the administration of 50% nitrous oxide and a local anesthetic; topical anesthetic creams (e.g., eutectic mixture of local anesthetics [EMLA] or ELA-Max) are also well received. Emphasizing to the child that this procedure will not be excessively painful is important. Occasionally, children will cry with the infiltration of a local anesthetic and become hysterical when they see the intravenous catheter. Two maneuvers help minimize this response: (1) Do not allow the child to see the catheter. (2) Puncture the anesthetized area with a needle, ask the child to look at the needle, and then ask if there is any sensation. Frequently the child is astounded at the lack of pain and stops crying.

PEDIATRIC AIRWAY MANAGEMENT

Endotracheal Tubes

For most children, the proper size of endotracheal tube and the proper distance of insertion relative to the alveolar ridge are moderately constant (also see Chapter 55). Published formulas are estimates that may need to be modified, based on physical examination or unusual child size. Table 93-7 provides a guide for selecting the proper size endotracheal tube and the recommended distance for insertion from the alveolar ridge. Uncuffed endotracheal tubes were traditionally preferred for children younger than 6 years of age (see earlier discussion). A new cuffed endotracheal tube (see Figure 93-4) may offer specific advantages over traditional cuffed endotracheal tubes. If a cuffed endotracheal tube is used, then a half-size smaller tube should be selected, rather than an uncuffed endotracheal tube, and cuff pressure should be adjusted to ensure that a small leak around the cuff is at a peak inflation pressure of 20 to 30 cm H_2O. Cuff pressure should be periodically checked during anesthesia involving nitrous oxide. If an uncuffed endotracheal

TABLE 93-7 RECOMMENDED SIZES AND DISTANCE OF INSERTION OF ENDOTRACHEAL TUBES AND LARYNGOSCOPE BLADES FOR USE IN PEDIATRIC PATIENTS

Age of Patient	Internal Diameter of Endotracheal Tube (mm)	Recommended Size of Laryngoscope Straight Blade	Distance of Insertion* (cm)
Preterm (<1250 g)	2.5 uncuffed	0	6-7
Full term	3.0 uncuffed	0-1	8-10
3 mo - 1 yr	3.5-4.0 cuffed	1	11
2 yr	4.5-5.0 cuffed	1-1.5	12
6 yr	5.0-5.5 cuffed	1.5-2	15
10 yr	6.0-6.5 cuffed	2-3	17
18 yr	7.0-8.0 cuffed	3	19

*Inserting the endotracheal tube these distances from the alveolar ridge of the mandible or maxilla usually places the distal end of the tube in the midtrachea.

Assessment of Percent Airway Obstruction Using Leak Around The Uncuffed Endotracheal Tube (Size ETT–mm ID)

Age	ETT	2	2.5	3	3.5	4	4.5	5	5.5	6
Preterm	No detectable lumen	40								
Preterm		58	30			No obstruction				
0–3 months		68	48	26						
3–9 months		75	59	41	22					
9 months–2 years		80	67	53	38	20				
2 years		84	74	62	50	35	19			
4 years		86	78	68	57	45	32	17		
6 years		89	81	73	64	54	43	30	16	
	Grade IV	Grade III			Grade II		Grade I			

Figure 93-10. Method of determining the percentage of airway obstruction. After easy passage of an uncuffed endotracheal tube (ETT), a stethoscope is placed over the larynx and the circuit slowly pressurized. The pressure at which a leak is auscultated is matched with the age of the child and the size of the ETT to assess the degree of laryngeal narrowing. It should be noted that this chart is based on only one institution's experience and that the manufacturer of the ETTs was not described; therefore the actual external diameter of the ETTs used is unknown. *ID,* Internal diameter. *(Reproduced and modified with permission from Myer CM 3rd, O'Connor DM, Cotton RT: Proposed grading system for subglottic stenosis based on endotracheal tube sizes,* Ann Otol Rhinol Laryngol *103:319-323, 1994.)*

tube is used, then the appropriate size allows a small gas leak at peak inflation pressures of 20 to 30 cm H_2O. If an uncuffed endotracheal tube (or a cuffed tube without the cuff inflated) does not leak at 40 cm H_2O, then the author will replace it with the next smaller size and recheck for a leak. Making this leak assessment to determine the size of the larynx is always important. On average in the author's practice, several children per year have undiagnosed subglottic stenosis detected by the anesthesiologist at the time of intubation (Figure 93-10).

Laryngoscope Blades

Any hospital that cares for children must have a full selection of laryngoscope blades to ensure that the blade most appropriate for the child is readily available. In general, straight blades are used in neonates and toddlers because of anatomic differences from older children (see "The Pulmonary System" discussion); the Wis-Hippel 1.5 is a particularly versatile blade because its surface is flat. Older children can be managed with either curved or straight blades. In some children, a straight blade may offer advantages over curved blades because of midfacial hypoplasia or other anatomic deformity (see Table 93-7). A laryngoscope blade with built-in oxygen delivery is available in sizes 0 and 1 and offers specific advantage for awake or sedated intubation of neonates (Figure 93-11).

The Child With a Full Stomach

A child with a full stomach must be treated the same as an adult with a full stomach; that is, both should undergo rapid-sequence induction of anesthesia with the application of cricoid pressure (also see Chapters 34 and 55). Because oxygen consumption is significantly greater, hemoglobin desaturation occurs more rapidly in a child than in an adult and more rapidly in an infant than in a child. Additionally, a child may be uncooperative and



Figure 93-11. The oxyscope (Heine Optotechnik, D-82211, Herrsching, Germany) is a Miller 1 laryngoscope blade with an insufflation channel along its length so that it may be attached to an oxygen source. An oxyscope provides increased fraction of inspired oxygen concentration *(*FiO_2) and is particularly useful for intubation in a conscious neonate whose oxygen consumption is high and in whom desaturation rapidly may develop.

refuse to breathe oxygen (i.e., refuse preoxygenation) before induction of anesthesia. In this circumstance, the best that can be done is to enrich the environment with a high flow of oxygen because upsetting the child further is not desirable. Additional equipment that should be available includes two suction catheters (if one becomes blocked, another would be immediately available) and two appropriately sized laryngoscope blades (e.g., Macintosh 2, Miller 2) with two handles (if the bulb, contact, or battery fails, another would be immediately available). While the child is breathing oxygen, atropine (0.02 mg/kg)

TABLE 93-8 **SUGGESTED EQUIPMENT FOR A DIFFICULT-AIRWAY CART**

Equipment Category	Recommended Equipment
Airways	Oral and nasopharyngeal (trumpet) airways in all sizes for preterm infants to adults
Endotracheal tubes	Cuffed and uncuffed endotracheal tubes of various sizes (uncuffed down to size 2 mm ID)
Stylets	Stylets in several sizes
Laryngoscopy	Laryngoscope blades in multiple sizes and configurations Several handles and extra batteries Oxyscope (Heine Optotechnik, D-82211, Herrsching, Germany)
Laryngeal mask airways (LMAs)	All sizes (1 to 6) of ProSeal LMAs for patients with a full stomach or for those who require higher peak inflation pressure for successful ventilation Large-volume syringes for the larger masks
Fiberoptic intubation	Several sizes of fiberoptic scopes, including one that will fit through a 2.5-mm ID endotracheal tube Light source Teeth protectors Oral airways designed for fiberoptic intubation Silicone lubricant
Retrograde equipment	Retrograde intubation equipment (needle with guide wire)
Optical stylet or videolaryngoscope*	Optical stylet or videolaryngoscope in a variety of sizes, including one that will fit through a 2.5-mm ID endotracheal tube (Storz, Karl Storz GmbH & Co. KG, Tuttlingen, Germany) or a 3.0-mm ID endotracheal tube (Shikani, Clarus Medical, Minneapolis, Minn.) or a GlideScope Videolaryngoscope (Verathon Inc., Bothell, Wash.)
Endotracheal tube exchangers	Endotracheal tube exchangers in various sizes for the full array of pediatric patients
Cricothyrotomy equipment	Percutaneous cricothyrotomy kits designed for older and larger children (e.g., needles, guide wire, dilator) Jet ventilation–type device, which is similar to an intravenous catheter (18, 14, and 13 gauge) and is useful in infants
Jet ventilation equipment	Jet ventilation stylets and jet injector with an appropriate hookup for wall oxygen
Carbon dioxide detector	For use in nonsurgical venues

ID, Internal diameter.
*Many devices are available and the mention of these devices should not be taken as an endorsement.

is intravenously administered to prevent reflex- or succinylcholine-induced bradycardia and to delay the bradycardia of hypoxemia should any of these events occur. Because of its rapid onset of neuromuscular blockade, succinylcholine is still the muscle relaxant of choice in this circumstance and should be administered at a dose of 1 to 2 mg/kg immediately after thiopental (5 to 6 mg/kg) or propofol (3 mg/kg). Cricoid pressure is gently applied after the child loses consciousness. Children should be told that they may *"feel someone touching you on the neck"* as they fall asleep and that this is *"normal."* In children, the head-up position does not significantly increase protection from pulmonary aspiration of acid gastric contents. If succinylcholine is contraindicated, then rocuronium (1.2 mg/kg) will provide conditions for intubation similar to those provided with succinylcholine within 30 seconds of administration.[89] However, the duration of neuromuscular blockade will be 45 to 75 minutes (also see earlier discussion of rocuronium and Chapter 34). In the hypovolemic child, ketamine (2 mg/kg) may be used for induction, whereas etomidate (0.2 to 0.3 mg/kg) may be a better choice in a child with hemodynamic instability (e.g., cardiomyopathy).

Difficult Airway

The terminology *difficult airway* refers to certain situations or conditions during which maintaining a patent airway may be so technically difficult that hypoxia or difficulty with endotracheal tube placement may occur. The approach to a difficult airway depends, in part, on whether the difficult airway is known and previous records are available for review or whether the child has an unexpectedly difficult airway. In the former situation, a difficult-airway cart with age- and size-appropriate airway equipment (Table 93-8) is brought into the operating room, and the assistance of a colleague with pediatric airway skills is arranged. In the latter situation, the difficult-airway cart may need to be urgently brought into the operating room and skilled help summoned. The most common errors that this author has observed in several malpractice cases are the lack of equipment or inappropriately sized equipment, inadequate skilled help, the failure or delay in calling for help, and the failure of the anesthesiologist to attempt cricothyrotomy early enough. Accordingly, the importance of having a dedicated pediatric difficult-airway cart, the need to be familiar with its contents and how to use the devices that it contains, and the availability of skilled help are essential.

A child facing a potentially difficult laryngoscopic procedure should receive, at most, light sedation before induction of anesthesia by mask to maintain spontaneous respirations. In this way the airway can be secured before "burning bridges" by administering a muscle relaxant and losing the help of spontaneous respirations. With the child spontaneously breathing, breath sounds can be used to guide successful tracheal intubation. When normal airway anatomy cannot be visually confirmed, placing a stylet in the tracheal tube and acutely bending the tip of the tracheal tube (90-degree bend) allows the placement of the tip of the tracheal tube in the midline just posterior to the epiglottis (Figure 93-12, *A*). One can then listen for breath sounds exiting from the end of the tracheal tube; once good air exchange is heard, the tracheal tube is advanced off the stylet (not inserted with the stylet) (Figure 93-12, *B*).

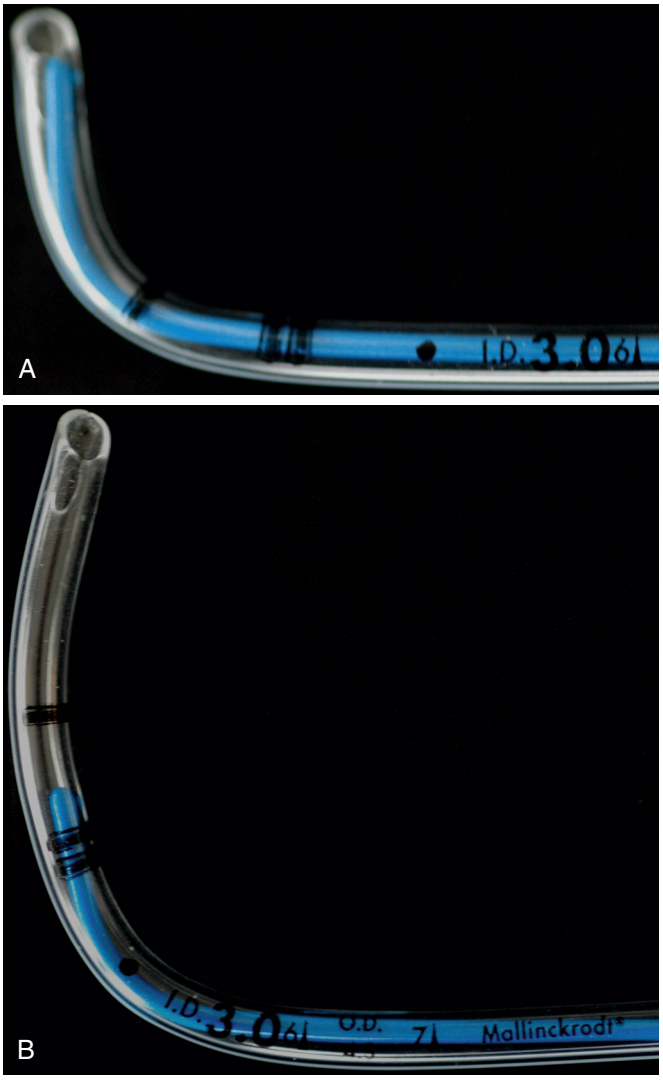


Figure 93-12. In patients with midfacial hypoplasia or in those in a cervical collar, making a nearly 90-degree bend around the base of the tongue to enter the larynx is necessary. If one inserts a stylet into an endotracheal tube with a 90-degree bend **(A)**, listens for breath sounds emerging from the proximal end of the endotracheal tube, and threads the endotracheal tube off the stylet (not advancing the stylet) when good breath sounds are heard, then the tube will make the bend around the base of the tongue and pass into the trachea **(B)**.

This technique allows advancement of the tracheal tube at an acute angle without causing trauma to anatomic structures. If the child is not spontaneously breathing, then this advantage may be lost. Spontaneous respiration with a face mask designed to allow fiberoptic intubation is another approach (Frie endoscopy mask, VBM Medical, Noblesville, Ind. 46060). Having a skilled assistant pull the tongue forward out of the mouth with a dry gauze, plastic retractor, or full suction applied to the tip of the tongue will also aid visualization of the glottic opening (Figure 93-13).[121]

Fiberoptic intubation of the trachea via an LMA requires the use of two tracheal tubes threaded on the fiberoptic scope (the second to hold the first in position while removing the LMA). The LMA is perhaps the most important adjunct to airway management because it can establish a patent airway before the airway is secured more definitively



Figure 93-13. In this child with facial burn and severely restricted mouth opening, suction was applied to the tip of the tongue to facilitate pulling it forward to improve glottic visualization. This technique is particularly useful when the tongue is slippery, attributable to secretions or if the mouth opening is small and prevents direct grasping of the tongue with a dry gauze. *(Reproduced with permission from Coté CJ, Lerman J, Anderson BJ, editors:* A practice of anesthesia for infants and children, *ed 5, Philadelphia, 2013, Saunders.)*

TABLE 93-9 LARYNGEAL MASK SIZE VERSUS PATIENT WEIGHT*

Laryngeal Mask Size	Patient Weight (kg)
1	≤5
1.5	5-10
2	10-20
2.5	20-30
3	30-50
4	50-70
5	70-100
6	>100

*Manufacturer's recommendations (LMA North America).

with a tracheal tube or a cricothyrotomy (Table 93-9). In neonates with difficult airways such as those with Goldenhar, Treacher Collins, or Pierre Robin syndrome, topicalization of the airway with lidocaine (1% nebulized to avoid excessive doses) with the patient awake, followed by the placement of an LMA is very helpful in guiding awake-sedated fiberoptic intubation. A skilled assistant who can hold the head in the proper position and assist is critical to the success of most of these approaches to a difficult airway. In children, the ProSeal LMA will allow ventilation at significantly higher peak inflation pressures (~25 cm H_2O) than possible with the classic LMA (~15 cm H_2O); thus this device may be preferable in a difficult airway situation, especially since the stomach can be suctioned.[122] Another useful adjunct is the air-Q laryngeal mask airway (Mercury Medical, Clearwater, Fla.) when used as a conduit for fiberoptic intubation. It has a wide airway tube that accommodates cuffed tracheal tubes and has a shorter length that facilitates the removal of the LMA after successful fiberoptic intubation. One should always check before insertion that the selected tracheal cuffed tube will pass through this device. A special tracheal tube introducer in three pediatric sizes is used to hold the tracheal tube in position while the LMA is removed (Figure 93-14). Many other new airway

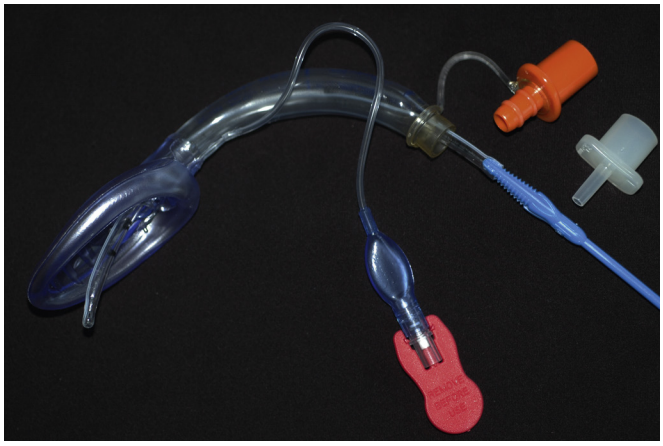


Figure 93-14. The air-Q laryngeal mask airway is short and has a large airway conduit to facilitate fiberoptic intubation. A tube introducer is used to maintain advancing pressure on the tracheal tube as the LMA is removed. *(Reproduced with permission from Coté CJ, Lerman J, Anderson BJ, editors:* A practice of anesthesia for infants and children, *ed 5, Philadelphia, 2013, Saunders.)*

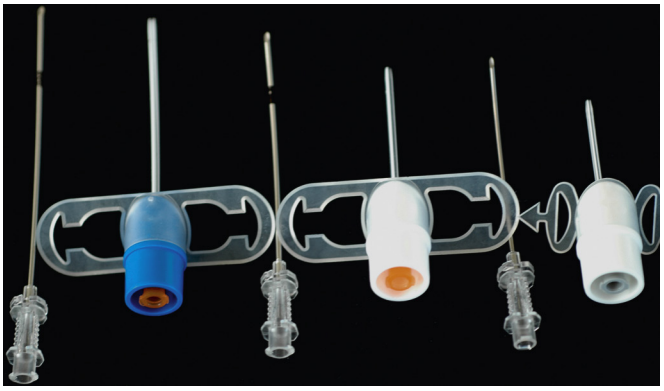


Figure 93-15. This preformed device is designed for transtracheal ventilation and provides one of the best systems for emergency airway management in a child with a "cannot ventilate, cannot intubate" airway situation (Ventilation-Catheter, VBM Medical, Noblesville, Ind.). The design is similar to that of an intravenous catheter but with lateral side holes, which means that the principles for use are familiar to all anesthesiologists, and the device is small enough to allow use even in neonates. In addition to a secure 15-mm adapter for interface with any standard bag ventilation device, a Luer-Lok connection allows jet ventilation. Three sizes are available: 16 gauge (infant), 14 gauge (child), and 13 gauge (adult). An initial fresh gas flow of 0.5 L/min is recommended and then adjusted up as needed once chest expansion and exhalation (deflation) are confirmed.

adjuncts are available, such as the Storz video laryngoscope (Karl Storz GbmH, Tuttlingen, Germany), the GlideScope (Verathon, Bothell, Wash.), MultiView scope (Medical Products International, Tokyo), Airtraq optical laryngoscope (Prodol Meditec, S.A., Vizcaya, Spain), and others too numerous to detail in this chapter.

If the child should progress to a "cannot ventilate, cannot intubate" situation, then a surgical airway must be established. The child should be positioned with a roll of towels under the shoulders to force the larynx anteriorly so that the best access to the larynx and trachea is provided. A variety of cricothyrotomy devices should be available; some are appropriate for infants, whereas others are appropriate only for older children and teenagers. Devices appropriate for older children include some using the Seldinger technique (cricothyroid puncture, passing a guide wire, skin incision, then passing a dilator-catheter over the wire) (e.g., Arndt and Melker kits, Cook Medical, Bloomington, Ind.) or use of an armored transtracheal catheter (Cook Medical). Intravenous catheters are the simplest cricothyrotomy devices that can be used in children of all ages, including infants, and can then be interfaced with the 15-mm connector of a 3-mm internal diameter (ID) tracheal tube.[123] The author believes a preformed device designed exactly like an intravenous catheter but with a built-in 15-mm connector and lateral side holes is the most useful. This device comes in three sizes (16, 14, and 13 gauge) and also has a Luer-Lok connection to allow transtracheal jet ventilation (Figure 93-15) (Ventilation-Catheter, VBM Medical, Noblesville, Ind.). Other emergency airway devices include a styletted tracheal tube changer (used as a bougie) that has both 15-mm and Luer-Lok adapters (Cook Medical, Bloomington, Ind.) (Figure 93-16). A simple method for administering oxygen to the Luer-Lok without the high pressure of a jet ventilator is to use standard oxygen tubing with a hole cut in the side; occlusion and unocclusion of the hole will direct oxygen (0.5 L/min and adjusted up as needed) through the catheter. Whenever such a technique is applied, the catheter must be correctly positioned within the trachea to avoid barotrauma and the chest must deflate between breaths. A review of emergency airway devices is available elsewhere.[124]

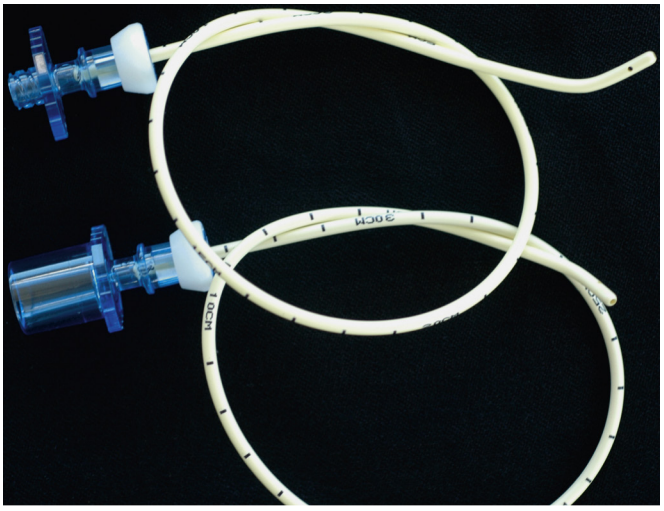


Figure 93-16. Tracheal tube exchangers are available that have side holes at the tip that allow delivery of oxygen and may be attached to either a jet ventilation system or standard adaptors with a 22-mm outside diameter. This device is also available with a stylet and slight bend to be used as an intubation bougie.

The Child With Stridor

A child with intrathoracic airway obstruction has expiratory stridor and prolonged expiration (e.g., bronchiolitis, asthma, intrathoracic foreign body). In contrast, a child with extrathoracic upper airway obstruction has inspiratory stridor (e.g., epiglottitis, laryngotracheobronchitis, laryngeal, subglottic foreign body). When agitated or

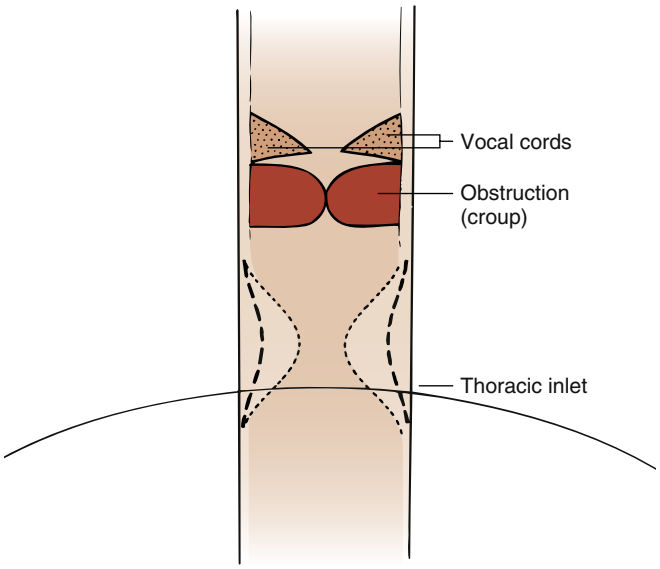


Figure 93-17. Infants and young children have highly compliant airway structures. With normal respiration, some dynamic collapse of the extrathoracic upper airway occurs (*broken line*). When a child has upper airway obstruction, as in epiglottitis, laryngotracheobronchitis, or extrathoracic foreign body (*dark brown*), and struggles to breathe against this obstruction, dynamic collapse of the trachea increases. This increase in dynamic collapse (*dotted line*) augments the mechanical obstruction of the airway. Therefore until the airway is secured, avoiding procedures that will upset the child is important. *(Modified from Coté CJ, Lerman J, Anderson BJ, editors:* A practice of anesthesia for infants and children, *ed 5, Philadelphia, 2013, Saunders.)*

crying, such children exhibit dynamic collapse of the airway (Figure 93-17), which can significantly worsen airway obstruction and lead to respiratory failure and hypoxemia. Therefore events that can upset the child such as drawing of blood for analysis of gases, venipuncture for blood tests, and separation from parents, must be minimized. The difficult-airway cart should also be present. The surgical team should be mobilized and prepared to perform an emergency tracheotomy should total airway obstruction occur and mask ventilation or tracheal intubation not be possible.

This author has found the following procedure to be effective for inducing anesthesia in a child with stridor. To minimize upsetting the child, the child is brought to the operating room with the mother or father, who holds the child during induction (preferably lying down in a semi-upright position). Induction of anesthesia with halothane or sevoflurane in oxygen by mask is the preferred method because maintaining spontaneous respirations is critical. As soon as the child loses consciousness, the child is gently moved off the parent's chest to the operating room table and the parent is escorted out of the unit. With the child lightly anesthetized and after infiltration of local anesthetic, an intravenous line is inserted. This allows withdrawal of blood samples if indicated. Intravenous hydration is begun with lactated Ringer solution (20 to 40 mL/kg), and atropine (0.02 mg/kg) or glycopyrrolate (0.01 mg/kg) is given. At this point, the plane of anesthesia can be deepened with greater safety. If the stridor worsens or mild laryngospasm occurs, then the pop-off valve is sufficiently closed to develop 10 to 15 cm H_2O of PEEP. This procedure relieves most instances of airway obstruction caused by dynamic collapse of the airway and loss of pharyngeal muscle tone when the child attempts to inspire against an obstructed airway (Figure 93-18). As the level of anesthesia deepens, gentle assistance with ventilation may be necessary; however, maintaining spontaneous respiratory effort is important if possible.

Any child with airway obstruction will have a long, slow induction of anesthesia before becoming sufficiently anesthetized to permit laryngoscopy and tracheal intubation. Because a sevoflurane vaporizer allows only ~2.5 MAC to be delivered, whereas a halothane vaporizer allows nearly 6 MAC, halothane would be the author's drug of choice in this circumstance (if available). In addition, the slower excretion of halothane than of sevoflurane would also provide better conditions for airway manipulation for a longer time. The issue of a full stomach is secondary to the airway problem. **Rapid induction of anesthesia and paralysis is contraindicated in these children**. A child with laryngotracheobronchitis or epiglottitis usually requires an uncuffed tracheal tube that is 0.5 to 1.0 mm ID smaller than normal (see Table 93-7); the use of a stylet facilitates its insertion. (Management of a difficult airway is also discussed in Chapter 55).

INTRAVENOUS FLUID AND TRANSFUSION THERAPY

Intravenous Fluids

The approach to intravenous fluid therapy in children must consider their high metabolic demands and high ratio of body surface area to weight (also see Chapter 59). The basis for calculating maintenance fluids derives from data by Holliday and Segar,[125] who found that daily fluid requirements directly depend on metabolic demand—specifically, that 100 mL of water is required for each 100 calories of expended energy. Relating this to weight produces hourly fluid requirements of 4 mL/kg for children up to 10 kg, an additional 2 mL/kg for each kilogram above 10 kg up to 20 kg, and an additional 1 mL/kg for each kilogram above 20 kg (Table 93-10) (4-2-1 rule). Thus a 25-kg child would require 65 mL/hr:

$$(10 \times 4) + (10 \times 2) + (5 \times 1) = 65 \text{ mL}$$

This amount does not include fluid deficits, third-space losses, modifications because of hypothermia or hyperthermia, or requirements caused by unusual metabolic demands. Third-space losses are replenished according to the surgical procedure and may vary from 1 mL/kg/hr for a minor surgical procedure to as much as 15 mL/kg/hr for major abdominal procedures (e.g., surgical repair of gastroschisis). The original Holliday and Segar approach was revisited, and it was concluded that their original formula would be problematic for children who are acutely ill or for those with significant cardiac or renal dysfunction. They now recommend a simpler and likely more accurate method of fluid management, which is to administer 20 to

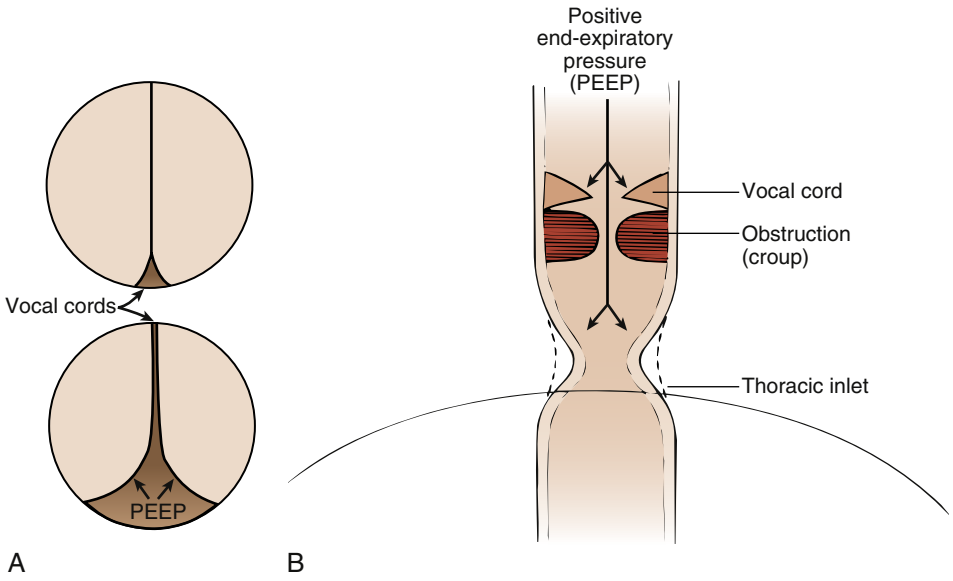


Figure 93-18. When a child has upper airway obstruction caused by laryngospasm **(A)** *(top)* or mechanical obstruction **(B)**, application of approximately 10 to 15 cm H_2O of positive end-expiratory pressure (PEEP) (*arrows*) during spontaneous breathing often relieves the obstruction. PEEP helps keep the vocal cords separated **(A)** *(bottom)* and the airway open **(B)** *(broken lines)*. If this simple maneuver does not relieve the obstruction, then more vigorous positive-pressure ventilation may be necessary. Airway obstruction caused by the tongue requires insertion of an appropriately sized oral airway.

40 mL/kg of a balanced salt solution during the course of the anesthetic. Postoperative fluid management should be reduced to a 2, 1, 0.5 rule; that is, 2 mL/kg for the first 10 kg, 1 mL/kg for the next 10 kg, and 0.5 mL/kg for each kg above 20 kg with an isotonic fluid.[126-128] If after 12 hours the child is unable to convert to oral intake, then a standard hypotonic solution (D5 0.45% saline) is initiated at the 4-2-1 rule rate to avoid hypernatremia (see Table 93-10).

Because greater hypoxic brain damage occurs in animals with high blood glucose levels, the routine use of glucose-containing solutions, especially for brief surgical procedures, is no longer recommended. However, a concern about unrecognized hypoglycemia was the motivating factor regarding the routine use of glucose-containing solutions in children, particularly in those who have not had food or fluids for a longer time than usual or for those who have diminished glycogen stores. Data are inadequate to eliminate glucose completely because the relevance of the animal data is not clear and the true incidence of hypoglycemia is not known in all populations of food-restricted children. This issue is further complicated by the fact that different values are used to define hypoglycemia, depending on the child's age.

If a child is thought to be at risk for hypoglycemia, 5% dextrose in 0.45% normal saline should be administered by piggyback infusion at maintenance rates. This minimizes the chance of a bolus administration of glucose and satisfies the concern for unrecognized hypoglycemia or accidental hyperglycemia. The routine use of 5% dextrose or 5% dextrose in 0.45% normal saline as the initial replacement for fluid deficit, third-space losses, and blood loss is discouraged. For most children, lactated Ringer solution is the only fluid required. Children receiving intravenous alimentation present a special problem (also see Chapter 106). Transition to 10% glucose is often recommended to avoid intraoperative hyperglycemia with continuation of the current alimentation fluid and to avoid hypoglycemia if it is suddenly stopped. However, this change to 10% glucose has not been adequately studied. The author reduces the established intravenous alimentation fluid infusion rate by 33% to 40% (to account for the reduced metabolic rate under anesthesia) and periodically checks blood glucose values for long procedures. This approach, then, does not waste the current alimentation fluid and involves only a simple change in infusion rate. Another population of children who require specific intravenous fluid management consists of those with mitochondrial disease. In general, glucose-containing solutions are administered at maintenance rates, and lactate-containing solutions are avoided. Some children with mitochondrial disease have enormous glucose requirements that may necessitate the use of 10% glucose. Management of such patients must be individualized with their pediatrician.

Fluid management of term and preterm infants must take into account other variables. The amount of insensible water loss is inversely proportional to gestational age. The younger and more physically immature the infant,

TABLE 93-10 **CALCULATION OF MAINTENANCE FLUID REQUIREMENTS FOR PEDIATRIC PATIENTS***

Weight (kg)	First 12 Hours After Surgery (mL)†	If No Oral Intake (mL)‡
<10	2 mL/kg	4 mL/kg
11-20	1 mL/kg	40 mL + 2 mL/kg for each kilogram above 10 kg
>20	0.5 mL/kg	60 mL + 1 mL/kg for each kilogram above 20 kg

*This approach avoids postoperative hypernatremia.
†Hourly fluid requirements for the first 12 hours after surgery.
‡Hourly fluid requirement for 12 hours after surgery if no oral intake occurs.

the higher the skin permeability, the ratio of body surface area to weight, and the metabolic demand. In addition, the use of radiant warmers and phototherapy increases insensible water loss. On the other hand, preservation of body heat with warming devices reduces insensible water loss.

The fact that the neonatal kidney is unable to excrete large amounts of excess water or electrolytes must also be considered. As described earlier, the volume of extracellular fluid in a newborn is extremely large. During the first days of life, some of this excess water is excreted. Therefore term newborns have reduced fluid requirements for the first week of life. The daily fluid requirements for a term newborn in the days after birth are estimated to be 70 mL/kg on day 1, 80 mL/kg on day 3, 90 mL/kg on day 5, and 120 mL/kg on day 7. Daily fluid requirements would be slightly higher for preterm infants. Sodium and potassium concentrations are usually kept at 2 to 3 mEq/100 mL. Newborns are generally started on 10% glucose to prevent hypoglycemia. This fluid is continued for the first several days of life until glucose values are stable. Infants of diabetic mothers or infants whose mother was given large amounts of glucose just before delivery may require greater concentrations of glucose for protection against rebound hypoglycemia. Infants unable to tolerate oral feeding may continue to receive 10% glucose solutions and may even require peripheral or central alimentation. A number of infants have been transferred to the author's institution with severe and potentially life-threatening hyperglycemia (i.e., blood glucose levels of 700 to 900 mg/dL) as a result of overzealous use of this type of glucose therapy. This solution should only be administered with a rate-limiting device and be used with caution if infants require surgery; every effort should be made to reduce bolus administration of glucose. Blood sugar levels should be periodically monitored and the solution infused at only maintenance rates unless a glucose bolus is indicated.

Packed Red Blood Cells

Historically, the use of blood products in pediatric surgical patients has greatly diminished because of the fear of transmission of disease—particularly human immunodeficiency virus (HIV). Because HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), and a number of other disease-causing viruses can be transmitted with as little as 10 mL of packed red blood cells (PRBCs), the administration of any blood product requires clear, medically defensible clinical indications that are preferably recorded on the anesthetic record (also see Chapters 61 and 62). In the past 10 years, transmission of disease has become an increasingly rare event. The current estimated risk for transmission is 1 in 2,300,000 units for HIV, 1 in 250,000 units for HBV, and 1 in 1,800,000 units for HCV (see Chapter 61). Although the safety of blood transfusions has significantly increased, blood should still be given with precise and documented indications. It is still recommended for families to donate blood for their child or relative; in this situation the blood product should be irradiated to prevent possible graft-versus-host disease.

When caring for children, the emphasis should be on blood volumes and portions of blood volumes lost, rather than units, because a unit of blood may constitute several blood volumes in a preterm infant but only a fraction of the blood volume of a robust teenager. These considerations govern the calculation of the maximal allowable blood loss (MABL) resulting in an acceptable hematocrit. MABL takes into account the effect of patient age, weight, and starting hematocrit on blood volume. In general, blood volume is approximately 100 to 120 mL/kg for a preterm infant, 90 mL/kg for a full-term infant, 70 to 80 mL/kg for a child 3 to 12 months old, and 70 mL/kg for a child older than 1 year of age. These volumes are merely estimates of blood volume. The individual child's blood volume is calculated by simple proportion by multiplying the child's weight by the estimated blood volume (EBV) per kilogram. Although several formulas are available, a simple relationship is easiest to remember:

$$\text{MABL} = \text{EBV} \times \frac{(\text{Starting hematocrit} - \text{Target hematocrit})}{\text{Starting hematocrit}}$$

Thus if a 3-year-old child weighs 15 kg and has a starting hematocrit of 38% and if clinical judgment estimates the desired postoperative hematocrit to be 25%, then the calculation would be as follows:

$$\text{MABL} = (15 \times 70) \times [(38 - 25) \div 38] = 1050 \div 38 = \sim 360\text{mL}$$

The MABL would be replaced with 3 mL of lactated Ringer solution per milliliter of blood loss; that is, 3 mL of lactated Ringer solution times the 360 mL of blood loss equals approximately 1080 mL of lactated Ringer solution. If blood loss is less than or equal to the MABL and no further significant blood loss occurs or is anticipated in the postoperative period, then there is no need for transfusion of PRBCs. If, however, significant postoperative bleeding occurs or is anticipated, then a discussion of potential transfusion needs with the surgeon is very important. Normally, a child who has had adequate replacement of intravascular volume deficits will tolerate anemia very well. There is sufficient time to make the decision to transfuse by observing postoperative urinary output, heart rate, respiratory rate, and overall cardiovascular stability. Unfortunately, no one formula permits a definitive decision. The development of lactic acidosis is a late sign of inadequate oxygen-carrying capacity.

If the child has reached the MABL and significantly more blood loss is expected during surgery, then the child should receive PRBCs in sufficient quantity to maintain the hematocrit in the 20% to 25% range. The entire loss of red cell mass should not be replaced unless clinically indicated if these additional PRBCs would expose the child to additional units of blood products. Hematocrit values in the low 20% range are generally well tolerated by most children, the exception being preterm infants, term newborns, and children with cyanotic congenital heart disease or those with respiratory failure in need of high oxygen-carrying capacity (also see Chapters 61 and 94). Because the incidence of apnea is high in neonates and preterm infants who have hematocrit values less than 30%, the minimal target

hematocrit should be discussed with the surgeon and neonatologist.[129] Older children with a history of sickle cell disease may require preoperative transfusion and should be managed in conjunction with their attending hematologist. As an example, the following simple formula may be used for intraoperative or postoperative estimation of the volume of PRBCs needed in a 15-kg child with a hematocrit (Hct) of 20%:

$$\text{Volume of PRBCs to be transfused} = \frac{[\text{Desired Hct (35)} - \text{Present Hct (20)} \times \text{EBV (70mL/kg} \times \text{15kg)}]}{\text{Hct of PRBCs}(\sim 60\,\%)}$$

$$\frac{(35-20) \times (70 \times 15)}{60} = \sim 262 \text{ mL PRBCs}$$

Fresh Frozen Plasma

Fresh frozen plasma (FFP) is administered to replenish clotting factors lost during massive blood transfusion (usually defined as blood loss exceeding 1 blood volume), for disseminated intravascular coagulopathy, or for congenital clotting factor deficit. The anesthesiologist initiates and guides therapy with FFP during massive blood loss, whereas the hematologist's advice is sought when either of the other two conditions exists.

Children with known clotting factor deficits, such as those with massive thermal injury or coagulopathy, may require transfusion of FFP before blood loss exceeds 1 blood volume. In contrast, healthy children who do not have coagulation factor deficits at the beginning of surgery do not need FFP until blood loss exceeds 1 blood volume.[130,131] Despite the loss of 1 blood volume, prolongation of the prothrombin time (PT) and the partial thromboplastin time (PTT) will only be minor. This generalization applies to children given PRBCs; children given whole blood will not need FFP, even when blood loss exceeds several blood volumes.

Blood loss exceeding 1 to 1.5 blood volumes (replaced entirely with PRBCs and crystalloid, albumin, or other non–blood-related products) often necessitates a transfusion of FFP. However, the decision to administer FFP should be based on observed coagulopathy or documented prolongation of the PT and PTT values. Obtaining these test results from the laboratory often takes longer than desired. In this circumstance, a note should be written that blood loss has exceeded 1 blood volume and that abnormal oozing has occurred in the surgical field. A child should never be given FFP to correct bleeding that is surgical in nature.

No studies on children have yet clearly defined what values of PT and PTT are associated with pathologic bleeding requiring a transfusion of FFP to replace clotting factors. However, if the clotting factor deficit is associated with abnormal oozing, then a PT exceeding 15 seconds (international normalized ratio [INR] >1.4) or a PTT greater than 60 seconds (>1.5 times baseline) warrants close observation. Usually an INR <2 does not warrant correction. If these abnormalities exist but oozing does not occur and the surgical field is relatively safe from the complications of hematoma formation, as in orthopedic surgery versus neurosurgery, then it seems appropriate to observe the child and withhold the transfusion of FFP.

The volume of FFP required to correct prolongation of the PT and PTT values depends on the severity of the clotting factor deficit and the presence or absence of consumptive coagulopathy. In general, FFP therapy may require replacement of 30% or more of the child's blood volume. Transfusion of FFP at rates exceeding 1 mL/kg/min is sometimes followed by severe ionized hypocalcemia and cardiac depression with hypotension, especially if FFP is administered during anesthesia with a potent inhaled anesthetic (Figure 93-19).[132,133] Therefore exogenous calcium chloride (2.5 to 5 mg/kg) or calcium gluconate (7.5 to 15 mg/kg) should be administered, preferably through a separate IV, during rapid transfusion of FFP.[134] Ionized hypocalcemia occurs very frequently in neonates given FFP, possibly because of their decreased ability to mobilize calcium and metabolize citrate. Children undergoing liver transplantation or those with compromised hepatic function or perfusion may also be at increased risk because of a decreased ability to metabolize citrate.

Platelets

Thrombocytopenia may occur as a result of disease processes (e.g., idiopathic thrombocytopenic purpura, chemotherapy, infection, disseminated intravascular coagulopathy) or dilution during massive blood loss. Children whose platelet count has decreased because of idiopathic thrombocytopenic purpura or chemotherapy generally tolerate platelet counts as low as 15,000/mm^3 without a need for platelet transfusion. In contrast, children whose platelet count has decreased because of dilution (massive blood loss) generally require platelet transfusion when the count is ~50,000/mm^3 (also see Chapters 61 and 62). The reason for this disparity is not known. However, in the author's experience, the preoperative platelet count has been extremely valuable in predicting intraoperative platelet requirements.[135] Children who begin surgery with increased platelet counts may not require platelet transfusion, despite blood loss of four or more blood volumes. Conversely, children who begin surgery with low platelet counts (~100,000/mm^3) may require platelet transfusion when blood loss is one or two blood volumes. Children who begin surgery with a normal platelet count (150,000 to 350,000/mm^3) usually do not require platelet transfusion until two blood volumes or more are lost (Figure 93-20).

Whenever platelets are administered, the anesthesia record should document the reason for the transfusion, and every effort should be made to obtain a platelet count before transfusion. Clinical oozing is the typical indication for platelet transfusion, unless the potential for bleeding would be critical to survival, such as during neurosurgery, cardiac surgery, or major organ transplantation. The initial volume of platelets transfused is approximately 0.1 to 0.3 U/kg; the increase in platelet count achieved with this amount of transfusion varies considerably and depends on the presence or absence of platelet antibodies and the rate of platelet consumption.

Blood Warmers

A fluid and blood warmer is essential for any child who might require rapid correction of intravascular volume.

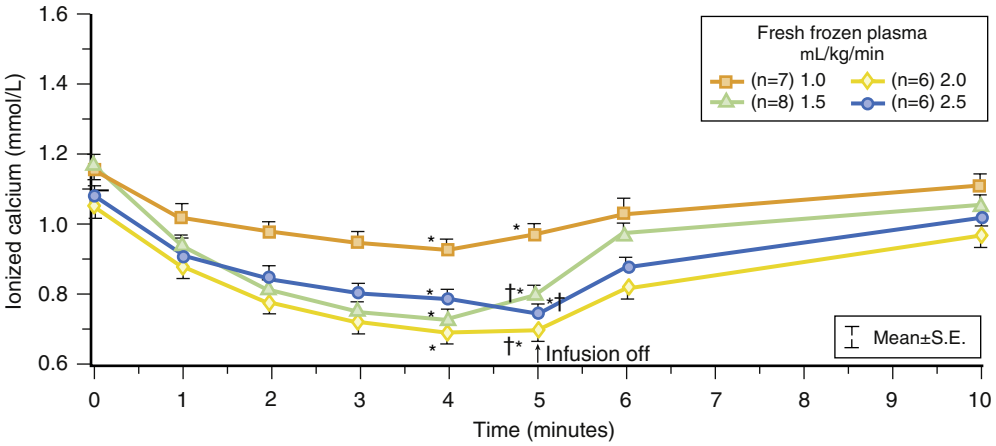


Figure 93-19. Ionized hypocalcemia always accompanies the administration of citrated blood products (e.g., fresh frozen plasma, citrated whole blood). Fresh frozen plasma has the highest concentration of citrate per unit volume of any blood product and is the most likely to cause ionized hypocalcemia during rapid infusion. Studies in children with thermal injuries suggest that rates exceeding 1 mL/kg/min produce severe ionized hypocalcemia. If no further citrated blood products are administered, then this abnormality corrects itself because of metabolism of the citrate. However, children with impaired hepatic blood flow—infants, patients undergoing liver transplantation, patients with trauma—may need exogenous calcium therapy. **P*, < .001; †*P*, < .0021 versus baseline; *S.E.*, standard error. *(From Coté CJ, Drop LJ, Hoaglin DC, et al: Ionized hypocalcemia after fresh frozen plasma administration to thermally injured children: effects of infusion rate, duration, and treatment with calcium chloride,* Anesth Analg *67:152-160, 1988. Used with permission.)*

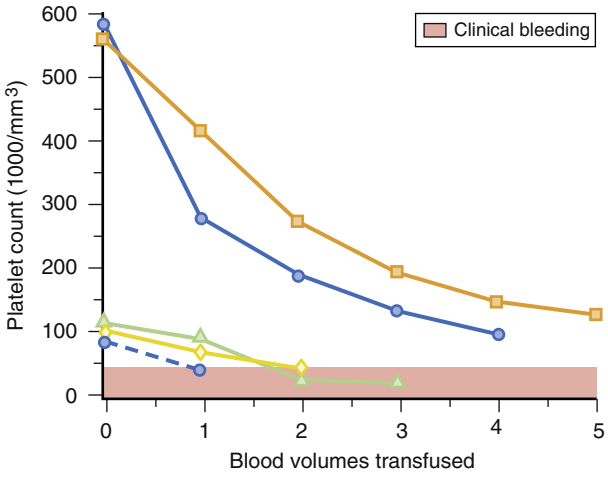


Figure 93-20. Dilutional thrombocytopenia occurs whenever massive blood loss takes place. The need for platelet transfusion, however, depends on the starting platelet count. In children who began surgery with low platelet counts, dilutional thrombocytopenia developed after blood loss of one or two blood volumes, whereas children who began surgery with high platelet counts did not require transfusion of platelets. The *blue dashed, solid yellow,* and *solid green lines* represent three children with initial low platelet counts; the *blue* and *orange lines* represent two children with initial high platelet counts. *(Data from Coté CJ, Liu LM, Szyfelbein SK, et al: Changes in serial platelet counts following massive blood transfusion in pediatric patients,* Anesthesiology *62:197-201, 1985.)*

Using such devices for maintenance intravenous fluid therapy provides no benefit because the rate of infusion is so slow that the intravenous fluid returns to room temperature between the times that it exits the warmer and enters the child. New warming devices that use countercurrent or microwave warming methods are superior to the older water bath coiled tubing devices. Low-capacity passive flow through devices such as the Hotline fluid warmer (Level 1 Technologies, Inc., Rockland, Mass.) are useful but not for warming a patient with maintenance rate administration. The Belmont Buddy Fluid Warmer (Belmont Instrument Corp., Billerica, Mass.) claims a warming capacity of "cold fluids to 38° C at flow rates as low as keep vein open (KVO) and as high as 100 mL/min." High-capacity systems such as the Level 1 System 1000 (Level 1 Technologies, Inc.), which uses countercurrent warming technology, is capable of warming blood starting at 5° C to 6° C to 33° C at rates as high as 250 mL/min. Another high-capacity blood warmer, the Belmont FMS (Belmont Instrument Corp.) uses microwave warming and is capable of fluid delivery at rates of 10 to 750 mL/min. A comparison of several devices used with pediatric intravenous catheters found that technology similar to the Belmont FMS was superior to the Level 1 for maintaining temperature and high-volume transfusions through intravenous catheters larger than 18 gauge.[136] Thus the Hotline or Belmont Buddy fluid warmer seem appropriate for neonates and infants, the Level 1 would appear to be appropriate for massive rapid transfusion in children weighing less than 30 kg, but the Belmont FMS would be superior for larger children.

MONITORING AND SAFETY ISSUES FOR PEDIATRIC PATIENTS

The complexity of monitoring applied to children must be consistent with the severity of the underlying medical condition and the planned surgical procedure. The author's philosophy is that if an arterial line or central venous line is placed in an adult undergoing a particular surgical procedure, then the same should be carried out for a child or an infant.

Routine Monitoring and Safety Issues (Also See Chapter 44)

Minimal monitoring during anesthesia should include a blood pressure cuff, an electrocardiogram, a temperature

probe, a pulse oximeter, an end-tidal carbon dioxide monitor, and, if possible, an anesthetic agent analyzer. The noninvasive blood pressure cuff (NIBP) is particularly useful because frequent blood pressure measurements can be made even when the anesthesiologist is preoccupied with other tasks. The end-tidal carbon dioxide monitor, NIBP, and pulse oximeter all provide an early warning of impending disaster that may go unobserved until the appearance of late clinical signs such as cyanosis, bradycardia, severe hypotension, or absence of breath sounds. The simultaneous loss of the pulse oximeter signal and an inability to measure blood pressure usually indicate low or no cardiac output. If the pulse oximeter continues to function but the NIBP has changed from measuring to nonmeasuring, then the likelihood of hypovolemia or anesthetic overdose must be immediately addressed, but one can have some assurance that perfusion is still taking place.

Capnography is the gold standard for confirmation of successful endotracheal intubation. However, the capnograph is useful in a number of other ways as well. Changes in the shape or magnitude of the carbon dioxide waveform may indicate bronchospasm, endobronchial intubation, a kinked endotracheal tube, or low pulmonary blood flow. One of the main drawbacks of capnography in small children is the inaccuracy of the recording obtained with the use of nonrebreathing circuits. The best method of avoiding artifacts is to sample the expired gases at some point within the tracheal tube or to use a circle system, even in small infants but at lower fresh gas flow rates. In general, the concentration of carbon dioxide in expired gas is within 2 to 3 mm Hg of that in arterial blood. However, severe pulmonary disease or atelectasis may produce a large difference in these values. In this type of child, the gradient between arterial and expired carbon dioxide values may be used to estimate the severity of the shunting. When such shunts exist, the measurement of expired carbon dioxide values may be used only to monitor trends. Ultimately, the most important monitors are the eyes, ears, and hands of the anesthesiologist, who must gather all the information provided by observation of the child and by the monitors applied to the child, consolidate the information into an accurate picture, and respond accordingly.

New monitors capable of noninvasive continuous cardiac output assessment via changes in impedance are now being introduced (Cardiotronic, Osypka Medical, La Jolla, Calif.).[137,138] Although some limitations exist, such as not functioning during electrocautery or with an open chest, the simplicity of placing four electrocardiographic electrodes and entering the height, weight, age and gender, outweigh the limitations. This device has been used in children as small as 1 kg, and trend monitoring seems to correlate with clinical assessments and the usual anesthetic monitors. This type of technology will likely be the next advancement in improving safety for children under anesthesia by providing an early warning of developing cardiovascular dysfunction or the immediate assessment of response to vasoactive medications. Other devices which use end-tidal carbon dioxide assessment pulse contour analysis or the Fick principle are limited to children who are intubated or have an arterial line in place.[139,140]

Prospective studies have shown that children younger than 6 months of age have a high incidence of critical events.[27,141-144] The incidence of critical events is greater in children with ASA physical status 3 and 4 than in ASA physical status 1 and 2. A number of factors may account for these results: the high metabolic rate of small children, the technical difficulty of caring for infants, the difficulty of estimating actual delivered ventilation when a variety of circuit configurations are available, and unfamiliarity with the care of small children. The POCA registry, a voluntary reporting system, estimated that the incidence of pediatric cardiac arrest was 1.4 ± 0.45 per 10,000 cases. Of the 289 cases, 83 occurred in children younger than 12 months of age. Emergency procedures and ASA physical status 3 or greater were predictive of death. It should be noted that two incidents of pediatric cardiac arrest were associated with sevoflurane and that the data were collected at the time when sevoflurane was not widely used in the United States. The use of high inspired concentrations of halothane (~3%) accounted for 14 of the arrests, and other associated factors were controlled ventilation ($n = 18$) and difficult intravenous access ($n = 4$). The most common preceding events were bradycardia and hypotension ($n = 25$). Three infants had an unrecognized cardiomyopathy and one had congenital heart disease. Airway-related events accounted for only 20% of cases, and most involved airway obstruction and laryngospasm. Several lessons can be taken from these data: (1) Children younger than 1 year of age are particularly vulnerable to adverse events in the perioperative period. (2) The combination of high inspired concentrations of an inhaled volatile anesthetic and controlled ventilation contribute to the critical event. (3) High inspired concentrations of an inhaled volatile anesthetic should be avoided until intravenous access is established. (4) The way the anesthetic is used, not the inhaled volatile anesthetic, is most likely the major contributing factor to these arrests. (5) Particular attention should be paid to frequent monitoring of blood pressure and heart rate during induction. (6) Monitoring with pulse oximetry and capnography may have reduced the incidence of airway-related events that were avoidable when compared with earlier studies. (7) Lastly, children with congenital heart disease are particularly vulnerable to the cardiac depressant effects of volatile anesthetic (also see Chapter 94). One study that supports these conclusions compared remifentanil-based anesthesia and halothane-based anesthesia for pyloromyotomy.[90,91] No cases of significant bradycardia, no differences in hemodynamic variables, and no differences in extubation times, PACU time, or rate of adverse events occurred. Basically, no difference between halothane (a slow-onset, slow-offset potent anesthetic) and remifentanil (a potent opioid with rapid onset and rapid offset) was observed. This study suggests that when anesthesiologists pay careful attention to details, adverse outcomes and severe adverse events can be avoided. The presence of an intravenous line before induction of anesthesia also probably provided an additional measure of safety. The most recent POCA data suggest that the rate of cardiac arrest is frequent in children with single

ventricle structure (Fontan), in children with Williams syndrome (supravalvular aortic stenosis, abnormal coronary vessels, pulmonary stenosis), and in infants receiving rapid blood transfusions who develop pathologic hyperkalemia.[145,146]

Invasive Monitoring

Arterial and central venous catheters should be used in children whenever such monitors contribute to the management of safe anesthesia. The placement of these monitors should not be avoided simply because the child is small or the anesthesiologist is uncomfortable applying the technique to a child. A variety of manufactured kits are available, most often using a thin-walled needle and a guide wire for venous access. If these monitors are indicated, then the anesthesiologist, surgeon, cardiologist, or neonatologist should insert them. Peripherally inserted central catheters (PICCs) offer a less invasive procedure that can provide accurate measures of central venous pressure.

Multilumen catheters are extremely valuable in the care of children who are critically ill. These devices facilitate the simultaneous intravenous administration of a variety of fluids, vasopressors, and antibiotics. However, these catheters can also lead to a false sense of security created by having three intravenous ports. Specifically, if a rapid infusion of PRBCs, colloid, or even crystalloid is necessary, then the long, narrow lumen severely limits the rate of infusion. If the need for rapid volume expansion is anticipated, then a separate large-bore intravenous catheter should be inserted; short-term cannulation of the femoral or brachiocephalic vein is reasonable and may be lifesaving.

PEDIATRIC EQUIPMENT

Dedicated Pediatric Equipment Cart

Anesthesiologists caring for children must be prepared for the unexpected, particularly an undiagnosed congenital malformation or difficult endotracheal intubation. Having designated pediatric carts containing pediatric equipment is a convenient way of providing optimal care in a variety of locations inside and outside of the operating room. These carts contain pediatric-specific intravenous administration sets, intravenous catheters of various sizes, butterfly needles (scalp vein needles), electrocardiographic pads, various infant- to adult-sized blood pressure cuffs, precordial stethoscopes, adult and pediatric esophageal stethoscopes, arm boards, intravenous fluids in pediatric-size containers, preterm infant– to adult-sized laryngoscope blades and handles, preterm infant– to adult-sized oral airways, tracheal tubes (2.0 to 2.5 mm ID uncuffed and 3.0 to 7.0 mm ID cuffed), stylets, face masks in preterm to adult size, size 1 to 5 LMAs, tape, drugs for resuscitation and commonly administered medications, and syringes, especially tuberculin syringes, for more precise administration of drugs. In addition, an interface that allows the administration of albuterol down an endotracheal tube should be readily available and preferably in the drug drawer (Figure 93-21).



Figure 93-21. Adaptor allows the administration of albuterol through a tracheal tube, and the timing of the dose with inspirations provides maximum delivery. The use of a long intravenous catheter that extends beyond the tip of the tracheal tube may further improve drug delivery. Up to 20 puffs may be required to deliver adequate drug distally. *(From Coté CJ, Lerman J, Anderson BJ, editors:* A practice of anesthesia for infants and children, *ed 5, Philadelphia, 2013, Saunders.)*

An intraosseous needle can be a lifesaving means of establishing emergency venous access for the administration of a drug or crystalloid. The Easy-IO is a relatively new battery-powered, drill-like device that provides rapid intraosseous access.[147,148] This device is a major new advance for pediatric care and should be readily available for emergent use.

Anesthesia Circuits

Much has been written about the advantages and disadvantages of various anesthesia circuits for use in children (also see Chapter 29).[149] Most of the attention has been directed to neonates and ways of reducing the work of breathing while preventing rebreathing. Nonrebreathing circuits provide the advantage of minimal work of breathing because they have no valves to be opened by the child's respiratory effort. The rate of induction of anesthesia may be more rapid because the volume of the nonrebreathing circuit is less, no equilibration with the carbon dioxide canister is required, anesthetic gases are immediately delivered at the airway, and the compression and compliance volume will be low.[149] These advantages improve the ability to observe respiratory effort, as reflected by movement of the anesthesia bag, as well as the ability to estimate pulmonary compliance. Thus the actual delivered ventilation, when used in conjunction with a ventilator, may be greater with a Mapleson D system than with a circle system if no compensatory adjustment in tidal volume is made (Figure 93-22). The most recent generation of ventilators are less susceptible to these types of issues because they automatically compensate for changes in fresh gas flow and circuit compliance.

A pediatric circle system can be safely used in neonates as long as the clinical implications are understood: large

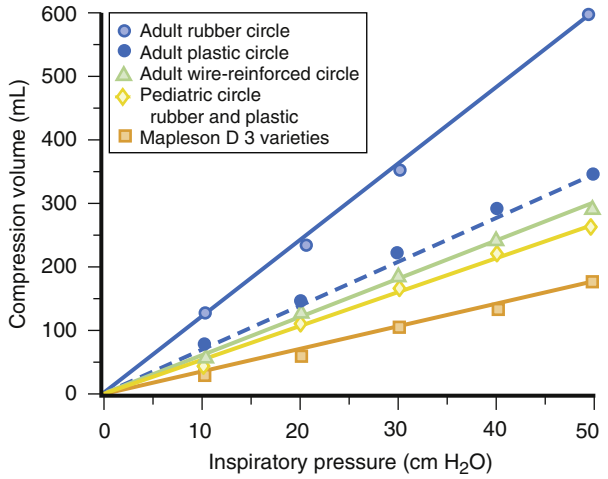


Figure 93-22. Eight types of anesthesia circuits were compared regarding ventilatory losses (circuit efficiency) as a result of compression of anesthetic gases (compression volume) and stretching of the circuit (compliance volume). Compression volume and compliance volume losses vary by as much as a factor of 5, depending on the volume of the circuit and the material from which it is constructed. Low-volume, low-compliance circuits (Mapleson D systems) are the most efficient and give the anesthesiologist the greatest amount of tactile feedback on tidal volume and lung compliance in small children. Most current practitioners use pediatric circle systems with assisted or controlled ventilation, which reduces environmental pollution and is more economical. *(From Coté CJ, Petkau AJ, Ryan JF, et al: Wasted ventilation measured in vitro with eight anesthetic circuits with and without inline humidification,* Anesthesiology *59:442-446, 1983. Used with permission.)*

compression volume losses, slightly longer time to equilibrate, and perhaps a decreased ability to determine changes in compliance. The author has exclusively used pediatric circle systems for the past 20 years; as long as pressure-limited ventilation with the same peak inflation pressure is used, the same tidal volume is delivered as with a non-rebreathing system.[150-152] Perhaps the greatest advantage of the circle system is the ability to use reduced fresh gas flow, which saves money and reduces air pollution.

CONSIDERATIONS FOR NEONATAL ANESTHESIA

The neonate has unique requirements for equipment, intravenous access, fluid and drug therapy, anesthetic dosage, and environmental control (see also Chapters 94 and 95). The many possible neonatal procedures are too numerous to describe in this limited space. However, the basic anesthetic management is the same for all neonates. An understanding of the basic differences in physiologic function, pharmacologic and pharmacodynamic responses, and the underlying pathologic surgical problem is essential for the development of a safe anesthesia plan. Most of the complications are attributable to a lack of understanding of these special considerations before the induction of anesthesia. Care of neonates is fraught with danger, sudden changes, unexpected responses, and unknown congenital problems. If anesthesiologists are to deliver optimal pediatric anesthesia care, then they must always be prepared for the unexpected, have the proper size and variety of equipment available, and obtain the most intense level of support, both in the operating room and in the ICU. If the anesthesiologist only occasionally cares for infants, then the likelihood of a problem dramatically increases.

Children younger than 1 year of age have a more frequent incidence of complications than older children.[27,141-144,153,154] These complications relate to oxygenation, ventilation, airway management, and response to anesthetic medications; complications also occur more frequently in children with ASA physical status 3 and 4. Neonates, particularly preterm infants, function on a marginal basis; therefore any type of stress is usually poorly tolerated. This vulnerability may relate to the technical difficulty of taking care of small children, the immaturity of their organ systems (especially the cardiovascular, pulmonary, renal, hepatic, and nervous systems), their high metabolic rate, the large ratio of body surface area to weight, and the ease of miscalculating a drug dose.

When caring for infants and neonates, special attention must be paid to all aspects of anesthesia and surgical management. The anesthesiologist must devote particular care to the calculation of drug dose and dilution of drugs. Prevention of paradoxical air emboli requires that all air be vented from intravenous devices and syringes before use; each intravenous injection port is aspirated to remove air trapped at these junctions, and some drug is ejected before intravenous administration to clear air from the dead space of the needle. A volume of air that is clinically unimportant in an adult may prove catastrophic in an infant. Warming of skin preparation solutions and irrigation fluids before applying minimizes heat loss. Intravenous fluids should be administered with volume-limiting devices; infusion pumps are particularly helpful in preventing over administration of intravenous fluid. The composition and infusion rate of flush solutions should be noted and calculated into maintenance fluid therapy. In neonates and small infants, a basal infusion rate of balanced salt solution with a pump is most useful, and third space losses and fluid boluses can be given via piggyback or a three-way stopcock.

Every effort must be made to maintain the infant's temperature to minimize thermal stress. The surgical environment should be warmed to ensure that the entire room constitutes a giant incubator. Heated air mattress devices are particularly useful for maintaining temperature.

Monitoring expired concentrations of carbon dioxide can be less accurate in small infants but is still extremely useful for diagnosing changes over time and for issues such as bronchospasm, a kinked endotracheal tube, or endobronchial intubation. Pulse oximetry is useful not only for the usual data that it provides but also for preventing extreme hyperoxia. Maintaining oxygen saturation at 93% to 95% keeps preterm infants on the steep side of the oxygen-hemoglobin dissociation curve. This consideration may be important to infants still susceptible to retinopathy of prematurity (ROP), that is, those younger than 44 weeks' PCA, although a multicenter trial of tight control of supplemental oxygen failed to show any change in risk for the development of ROP.[155] However, because these infants have the highest oxygen

consumption, oxygen saturation in the 93% to 95% range can change to severe hypoxemia within seconds. When managing such a delicate balance and in view of the slight inaccuracies of these monitors, the anesthesiologist must be extremely vigilant and prepared to respond rapidly to changes in oxygen saturation. Keeping arterial carbon dioxide values within the normal range (35 to 45 mm Hg) may also be important in preventing ROP. Many other factors well beyond the control of the anesthesiologist contribute to the development of this condition.

APOPTOSIS

One very important concern is the theoretic risk of apoptosis caused by medications used to provide sedation, analgesia, and anesthesia for infants and toddlers (particularly those younger than 3 years of age), a population still undergoing rapid brain growth. Anesthesiologists must be up to date on this issue because with the current widespread use of the Internet, more and more parents are asking *"Is it safe for my baby to have anesthesia?"* and specifically mention apoptosis! All of the potent inhaled anesthetics—nitrous oxide, ketamine, propofol, etomidate, barbiturates, benzodiazepines, chloral hydrate, ethanol, and others—have been associated with an increased rate of apoptosis in laboratory animals.[156-159] The majority of animal studies have examined drug doses far outside the clinical range. Others have not controlled for blood pressure, ventilation, or oxygenation. To further confound the issue, the period of rapid brain growth is different in each animal species, and the time of exposure (i.e., area under the curve exposure) in some is far longer than what would occur in clinical practice. For example, a 3-hour exposure to a neonatal monkey is equivalent to nearly 8 hours for a human; a neonatal rat exposed to 6 hours of anesthesia is equivalent to 222 hours of human exposure. In addition, many of the doses used far exceed those used in humans. The following questions need to be answered: Do apoptotic anesthetic drugs kill normal cells, leading to abnormal neurocognitive development? Do they simply accelerate death of cells already destined for programmed cell death with no sequelae? Does the human brain have so much plasticity that these potential adverse effects are overcome?

Data in primates (monkeys) are limited, and perhaps these observations are not transferable to humans. In fact, the preliminary data that have focused on ketamine "suggest that there might be a margin of safety for the use of ketamine in vivo over other anesthetics currently used in the clinical setting."[157] A 3-hour ketamine infusion in primates found no apoptosis in 5- and 35-day-old neonatal monkeys. Human data are virtually nonexistent. A retrospective questionnaire pilot study using the 120-item Child Behavior CheckList found an odds ratio of 1.38 to 1.19 for greater behavioral disturbances in children exposed to anesthesia during the first 6 years of life. The authors concluded that to refute or confirm an anesthetic effect would require "at least 2268 children."[160] The Mayo Clinic examined the school records of children who had no exposure, one exposure, two exposures, or more than two exposures to anesthesia during the first 4 years of life.[161] They found no difference in learning disabilities in children who had no exposure or one exposure; however, children with two exposures had an odds ratio of 1.59 (confidence interval 1.06 to 2.37) and those with three or more exposures had an odds ratio of 2.6 (confidence interval 1.6 to 4.24) for having a learning disability. At the time of their anesthetic exposure, pulse oximetry and capnography were not standards of care; the number of infants who suffered unrecognized hypoxic events or extreme hyperventilation or hypoventilation, each of which can also cause apoptosis, is unknown.[162] This same group examined a case controlled retrospective study of 350 infants exposed to anesthesia younger than the age of 2 years, compared with 700 children not exposed to anesthesia. They specifically examined several factors: learning disability, receipt of an "individualized educational program for emotion/behavior disorder," and scores for "group-administered achievement tests."[163] They concluded that multiple but no single exposures to anesthesia increased the risk of developing a learning disability (hazard ratio 2.12, confidence range 1.26 to 3.54); however, no difference in individualized interventions regarding emotional or behavioral issues was observed. Once again, this cohort of patients was anesthetized between 1976 and 1982, which is before pulse oximetry and capnography were introduced as the standard of care; thus this study suffers from the same flaws. Another paper of 1143 pairs of monozygotic twins examined the relationship of learning disabilities to exposure to anesthesia in the first 3 years of life.[164] Educational achievement and cognitive problems were assessed at 12 years of age. When both twins were exposed to anesthesia, the rates of cognitive problems and lower achievement scores increased; however, when only one twin was exposed to anesthesia, no difference was observed in these scores. The authors concluded that no evidence suggests a causal relationship of exposure to anesthesia, that is, other factors were contributory to later learning-related outcomes. An important animal study compared rats exposed to 4 hours of sevoflurane. At 4 weeks, all of the animals demonstrated some evidence of cognitive dysfunction.[165] They were then divided into two groups such that one half of the rats had "normal cage care" and the other half had a "stimulated cage environment." They were again examined for evidence of cognitive dysfunction 4 weeks later. Those who were stimulated had complete reversal of their cognitive dysfunction, thus indicating for the first time that the apparent problem is reversible. Certainly, children are not pushed into a corner and then ignored; therefore this assumption, in fact, fits the human condition and the author's assessment of this issue as a clinician. Given the fact that thousands of infants and toddlers undergo general anesthesia for diagnostic and therapeutic procedures each year, certainly if cognitive dysfunction were a major issue for humans, by now we would have evidence that our most vulnerable children, neonates, infants, and toddlers, would demonstrate adverse developmental outcomes consistent with the animal models. In addition, many preterm and term infants receive these same medications for days and often weeks in the neonatal ICU and these children have many other problems that could contribute to neurocognitive deficits.[158]

At present, the issue of drug-induced apoptosis appears to be a valid concern and an area of research that must

be vigorously pursued.[166,167] It appears that dexmedetomidine, opioids, and xenon are not associated with this phenomenon, but further studies are certainly required before changing anesthesia practice is advocated. What is quite unclear is at what age or developmental level that apoptosis is no longer a concern. Is it just preterm infants, full-term infants, toddlers, teenagers, or even adults? Is the plasticity of the human brain able to overcome a (potential) short-term insult? What other factors besides drug exposure contribute to this possible association with learning disability or cognitive dysfunction? If the drugs thought to be a concern in animal models are removed from our armamentarium, how are adequate amnesia, analgesia, and anxiolysis to be provided? Until more convincing data are available, continuing the current level of care with the drugs now available is prudent. Parents must be assured that their children will be adequately oxygenated, skillfully ventilated, well perfused, and that their pain will be well managed.[168,169] It would not make sense and would be irresponsible to change current practice without adequate science to support drastic changes in anesthesia practice.

THE STRESS RESPONSE

Little doubt exists that neonates, even extremely preterm infants, are capable of feeling pain and will respond to painful stimuli; however, what actually constitutes a state of anesthesia has yet to be proven. No child should be denied analgesia or anesthesia because of size or age. Clearly, the cardiovascular system of a preterm infant rarely tolerates the cardiovascular depressant effects of potent inhaled anesthetics. However, the synthetic opioids (e.g., fentanyl, sufentanil, alfentanil, remifentanil) are usually well tolerated by even infants who are critically ill. These potent opioids must be carefully titrated to a defined response, and anesthesiologists must remain cautious of opioid-induced bradycardia and its consequences on cardiac output. Low concentrations of potent inhaled anesthetics can be used with opioids to provide a means of controlling hemodynamic responses without significantly depressing the myocardium. The relative merits of one anesthetic technique over another are not well defined. Opioids and inhaled anesthetics suppress the hormonal responses to pain. The important result of the provocative studies undertaken to clarify this issue is that they have heightened everyone's awareness of the need to provide adequate anesthesia and analgesia to neonates. As stated earlier, outcomes are mostly determined by the skill of the clinician and not the specific anesthetic chosen.

SPECIFIC NEONATAL AND SURGICAL PROCEDURES

MENINGOMYELOCELE

Meningomyelocele, the hernial protrusion of a part of the meninges and spinal cord through a defect in the vertebral column, is a relatively common neonatal abnormality. The following should be considered in addition to the usual concerns for the management of neonates: (1) special positioning for tracheal intubation (i.e., the defect is placed on a "doughnut" and towels are placed under the head); (2) possibility of underestimating fluid and blood loss; (3) high association of meningomyelocele with hydrocephalus; (4) possibility of cranial nerve (vocal cord) palsy, resulting in inspiratory stridor; and (5) potential for brainstem herniation. The anesthesiologist must establish adequate intravenous access and invasive monitoring (rarely indicated) if appropriate; replace all fluid deficits, including loss from the defect (usually with normal saline); and ensure that crossmatched blood is available. Latex allergy precautions should be used with these children for their first and all subsequent anesthetics.

OMPHALOCELE AND GASTROSCHISIS

Omphalocele and gastroschisis are major defects in the closure of the abdominal wall that result in exposure of viscera that are either covered (omphalocele) or not covered (gastroschisis) by peritoneum (Figure 93-23; Table 93-11). The major problems with these defects include the following: (1) severe dehydration and massive fluid



Figure 93-23. A, Gastroschisis malformation. The viscera have herniated outside the peritoneum. **B,** Omphalocele malformation. The viscera are still covered by peritoneum.

TABLE 93-11 **COMPARISON OF GASTROSCHISIS AND OMPHALOCELE MALFORMATIONS**

	Gastroschisis	Omphalocele
Pathophysiologic characteristics	Occlusion of the omphalomesenteric artery	Failure of gut migration from the yolk sac into the abdomen
Incidence	~1 in 15,000 births	~1 in 6000 births
Incidence of associated anomalies	~10%-15%	~40%-60%
Location of defect	Periumbilical	Within the umbilical cord
Problems associated with defect	Inflammation of exposed gut Edema Dilated and foreshortened gut (chemical peritonitis)	Congenital heart disease (~20%) Exstrophy of the bladder Beckwith-Wiedemann syndrome (macroglossia, gigantism, hypoglycemia, hyperviscosity)

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loss from the exposed visceral surfaces (gastroschisis, chemical peritonitis) and from third-space losses caused by partial bowel obstruction; (2) heat loss; (3) difficulty of surgical closure; and (4) high association of this condition with prematurity and other congenital defects, including cardiac abnormalities (with omphalocele, ~20%). These children should not be rushed to surgery without an echocardiogram before anesthesia; postoperative ventilation is nearly always necessary with tight closures; in some cases, a staged repair is needed.

Infants with omphalocele or gastroschisis must be expeditiously cared for to reduce the potential for infection and compromise of bowel function and to minimize the loss of fluid and heat; optimizing fluid and electrolyte balance before surgery is recommended. Adequate intravenous access must be ensured, and invasive monitoring is occasionally necessary, particularly if an associated cardiac defect is present. The liberal use of muscle relaxants provides optimal surgical conditions for closure of the defect; hypotension secondary to tension on a major organ (liver) or caval compression is common. If the surgeon is unable to close the defect in one procedure, then a staged procedure is planned, usually in the neonatal ICU. In either situation, postoperative ventilation will be necessary until the abdominal wall has had time to stretch to accommodate the viscera. Intravenous alimentation may also play a vital role in the rapid recovery of these children. It should be noted that increased abdominal pressure after a tight closure (abdominal compartment syndrome) may compromise hepatic and renal function and significantly alter drug metabolism. Staged closure with a premade spring-loaded silastic silo is being used with increasing frequency, thus minimizing repeat trips to the operating room. A small percentage of children with omphalocele will also have Beckwith-Wiedemann syndrome, a condition characterized by profound hypoglycemia, hyperviscosity syndrome, congenital heart disease, and associated visceromegaly.

TRACHEOESOPHAGEAL FISTULA ANOMALY

A tracheoesophageal fistula anomaly can have five or more configurations, most of which are demonstrated as an inability to swallow because of esophageal atresia (the esophagus ends in a blind pouch). The characteristic diagnostic test is an inability to pass a suction catheter into the stomach. Neonates may have aspiration pneumonitis from a distal fistula connecting the stomach to the trachea through the esophagus or from a proximal connection of the esophagus with the trachea. Additionally, this anomaly may be part of a larger constellation of anomalies known as the VATER association (**V**, vertebral; **A**, anal; **TE**, tracheoesophageal; **R**, renal) or the VACTERL association (VATER and **C**, cardiac; and **L**, limb). Any child with a tracheoesophageal fistula or esophageal atresia should be suspected of having the other anomalies described. An echocardiogram to examine for a right-sided aortic arch and the presence of congenital heart disease should be performed before anesthesia.[170]

The major anesthetic issues include (1) evaluation for aspiration pneumonia; (2) overdistention of the stomach from entry of air directly into the stomach through the fistula; (3) inability to ventilate the child because of the large size of the fistula; (4) problems associated with other anomalies, particularly a patent ductus arteriosus (shunting) and other forms of congenital heart disease; and (5) the need for postoperative intensive care.[171]

For management of anesthesia, the infant's feedings are withheld, a catheter is placed in the esophagus to drain saliva, and the infant is placed prone in a head-up position. If the infant has pneumonia, then treatment should be initiated. Surgery may be postponed until the pneumonitis improves or clears. The infant may be a candidate for gastrostomy to provide a means of nutrition during recovery from pneumonitis. Anesthesia evaluation centers on the pulmonary and cardiovascular systems. Generally, an *awake-sedated* intubation is performed. The author usually administers 0.5 to 1 μg/kg of fentanyl and 25 to 50 μg/kg of midazolam and topicalizes the tongue, larynx, and vocal cords with no more than 5 mg/kg of lidocaine (1.0%). The tracheal tube is intentionally passed into the right main bronchus and then slowly withdrawn until breath sounds are heard on the left. Often this technique ensures that the tip of the tracheal tube is placed beyond the origin of the fistula, thus avoiding massive distention of the stomach. Care must be taken to avoid rupturing the stomach; therefore spontaneous and gently assisted ventilation may be appropriate until the fistula is ligated or a gastrostomy is completed. A change in the distance of insertion of the tracheal tube of as little as 1 to 2 mm may determine whether the anesthesiologist is ventilating both lungs, one lung, or the fistula. Because a change in oxygen saturation may be the first indication that all is not well, the pulse oximeter is one of the most

useful monitors in managing these children. A preductal and postductal location (two pulse oximeters) will diagnose intracardiac shunting. Taping the stethoscope to the left side of the chest in the axilla also decreases the possibility of unrecognized endobronchial intubation. Some surgeons prefer that the infant remain intubated postoperatively, whereas others prefer an attempt at extubation of the trachea; approximately 30% of those extubated in the operating room will require reintubation to clear secretions.

Postoperative pain may be managed with a caudal catheter threaded up to the thoracic level and either intermittent bupivacaine (1 to 2 mL of 0.125% with epinephrine 1:200,000) administered every 6 to 8 hours or a continuous infusion of chloroprocaine (1.5%) with fentanyl (0.4 μg/mL) infused at 0.3 to 0.8 mL/kg/hr. Such management may be undertaken only with the full support of a pediatric pain service (also see Chapter 92).

DIAPHRAGMATIC HERNIA

A diaphragmatic hernia is usually revealed on the first day of life by respiratory distress and a scaphoid abdomen. The abnormality consists of herniation of the abdominal viscera through a defect in the diaphragm, most commonly the foramen of Bochdalek on the left side. Almost all of the abdominal viscera, including the liver and spleen, may be above the diaphragm. The gestational age at which herniation occurs may determine the degree of lung hypoplasia.

Anesthesia concerns include the following: (1) hypoxemia and hypotension caused by overdistention of the stomach and herniation of the mediastinum across the midline, (2) hypoxemia attributable to primary pulmonary hypoplasia, (3) hypoxemia attributable to pulmonary hypertension, (4) pneumothorax of the contralateral lung during attempts at high-pressure ventilation, and (5) systemic hypotension caused by kinking of major blood vessels, particularly those of the liver. In general, the anesthesiologist's ability to control $Paco_2$ reflects the severity of the lung pathologic presentation and therefore survival. An inability to reduce $Paco_2$ is associated with a poor prognosis. Extracorporeal membrane oxygenation (ECMO) and the use of nitric oxide have slightly reduced the mortality associated with this condition, and the urgency for surgical intervention has diminished and given way to a desire to stabilize the infant and minimize stress. Anesthetic management of children with a diaphragmatic hernia includes the following: (1) Awake endotracheal intubation without bag-and-mask ventilation prevents overdistention of the stomach and herniation across the midline (now uncommon because the child generally does not come to the surgical department for several days). (2) Insertion of an arterial line for heartbeat-to-heartbeat blood pressure monitoring and close observation of the surgical field are most helpful in diagnosing impairment of venous return or cardiac output. (3) Blunting of the stress response is accomplished by providing analgesia with opioids (usually high-dose fentanyl, 25 μg/kg or more) and by controlling respirations with a muscle relaxant (usually pancuronium). (4) Careful control of ventilation and oxygenation prevents sudden increases in pulmonary artery pressure ($Paco_2$ is maintained less than 40 mm Hg and arterial partial pressure of oxygen [PaO_2] more than 100 mm Hg); pulse oximetry is helpful in diagnosing subclinical episodes of hypoxemia. (5) Hypothermia is avoided to decrease the oxygen consumption needed for thermogenesis. (6) Volatile anesthetics that might depress the myocardium are avoided until the chest is decompressed. (7) To prevent bowel distention, nitrous oxide is not administered. (8) Awareness for the development of barotrauma-induced pneumothorax on the ipsilateral or contralateral side should be heightened. (9) Adequate intravenous access for the maintenance of a constant circulating blood volume should be ensured. (10) Postoperative intensive care is necessary (also see Chapter 95).

In most centers, the approach to these children has changed to supportive care initially with permissive hypercapnia, ECMO, high-frequency ventilation, and inhaled nitric oxide[172,173] (also see Chapter 104). The infant is no longer rushed to the operating room soon after birth, and this approach appears to have only slightly reduced mortality.[173-176] In some centers, the closure is accomplished at the bedside in the neonatal ICU.

PYLORIC STENOSIS

Pyloric stenosis is normally revealed in the first 3 to 6 weeks of life. The anesthesiologist has the following major concerns: (1) a full stomach, rarely filled with contrast material; (2) metabolic alkalosis with hypochloremia and hypokalemia; and (3) severe dehydration.

This procedure is never a surgical emergency. Children should be carefully evaluated, and severe metabolic imbalance should be corrected before surgery. Even if the child arrives with a nasogastric tube in place and although the diagnosis is now most commonly made by ultrasound rather than barium swallow, the stomach should still be immediately suctioned with a wide-bore vented catheter in the supine and the right and left lateral positions before induction of anesthesia. This suctioning technique will remove 98% of the gastric contents![177] Children with pyloric stenosis can be managed with awake intubation, followed by low-dose cisatracurium (0.1 mg/kg) or rapid-sequence induction of anesthesia with cricoid pressure after atropine (0.02 mg/kg), propofol (3 mg/kg), and succinylcholine (2 mg/kg) administration. The actual selection of a specific anesthetic approach primarily depends on the skill and familiarity of the anesthesiologist with the technique. However, one study demonstrated fewer attempts and one half the time for successful intubation of the trachea when a muscle relaxant was used.[178] Postoperative analgesia is generally provided by local infiltration of the skin incision with bupivacaine (maximum dose, 1 mL/kg of 0.25% bupivacaine) and rectal acetaminophen (40 mg/kg initial dose followed by 10 to 15 mg/kg by mouth every 4 to 6 hours for a total 24-hour dose of ~75 mg/kg). Reports of apnea events after pyloromyotomy have been conflicting.[179,180] One well-controlled clinical trial described new-onset apnea after halothane anesthesia in 3 of 13 children.[91] Until larger studies are performed, these children should be observed with apnea monitors and pulse oximetry postoperatively.

FORMER PRETERM INFANTS

A frequent incidence of postoperative apnea occurs in former preterm infants (gestational age less than 37 weeks). The majority of infants in whom postanesthesia apnea develops are younger than 46 weeks' PCA; however, apnea occurs up to 60 weeks' PCA.[181] The conclusions reached by a number of studies were limited by the relatively small number of children. This author had the opportunity to obtain and analyze the original data from eight prospective studies. A combined analysis examining the risk for apnea included only children undergoing inguinal hernia repair and not receiving special treatment such as caffeine or regional anesthesia.[129] The only two risk factors that stood out across all ages were gestational age and PCA. The incidence of apnea was inversely related to both PCA and gestational age. For example, if two infants were now 45 weeks' PCA yet one was born at 28 weeks' and the other at 36 weeks' gestational age, then the 28 weeks' gestational age infant would have approximately twice the potential for apnea (Figure 93-24). In addition, the younger the child at the time of surgery (e.g., 45 versus 55 weeks' PCA), the higher the incidence of apnea. The incidence of apnea was more frequent in institutions that collected data with continuous recording devices than in those that relied on impedance pneumography or nursing observations. Anemia (hematocrit <30%) is an independent risk factor associated with apnea in former preterm infants (see Figure 93-24). What makes this risk factor unique is the fact that the risk for apnea in anemic former preterm infants is not apparently altered by PCA or gestational age; that is, the risk for apnea appears to be the same for an anemic 60-weeks' PCA infant as for an anemic 45-weeks' PCA infant. Even after eliminating infants with an obvious apnea spell in recovery and infants who were anemic, the risk for apnea does not decrease to less than 1% (with 95% statistical confidence) until a PCA of 56 weeks with a gestational age of 32 weeks or until a PCA of 54 weeks with a gestational age of 35 weeks. In general, all former preterm infants younger than 60 weeks' PCA should be admitted to monitored beds, and the clinicians should be aware that anemic former preterm infants are at particular risk.

Although the risk of apnea may be less with regional anesthesia, apnea may still occur and may even be increased if regional anesthesia is combined with sedation (ketamine, midazolam).[182-187] The numbers of well-controlled studies of regional versus general anesthesia to determine whether the risk is significantly reduced are insufficient.[188] Apnea still clearly occurs even with sevoflurane or desflurane anesthesia; therefore the newer volatile anesthetics have not eliminated this concern.[189]

Part of the problem of how to treat these children is the fact that the clinical importance of brief apnea associated with bradycardia spells that do not require intervention is not known. Because cerebral blood flow is significantly reduced at heart rates less than 80 beats per minute, even brief apnea associated with bradycardia may have adverse effects.[190] Pulse oximetry would help define the severity of desaturation, and electrocardiographic monitoring would help define episodes of bradycardia, which may reduce cerebral blood flow. The combination of desaturation and bradycardia is of more physiologic importance than simple documentation of pauses in respiration.

If appropriate monitoring facilities are not available postoperatively, then a preterm infant who is younger than 60 weeks' PCA should be referred to an institution that has such facilities. High-dose caffeine (10 mg/kg) has been recommended,[191] which may be an effective therapy. However, the half-life of caffeine in older former preterm infants is only 6 hours, and the first apnea spells after anesthesia may not be expressed until 12 hours.[129] Therefore one cannot administer caffeine and then send the infant home and assume that the problem has been treated.

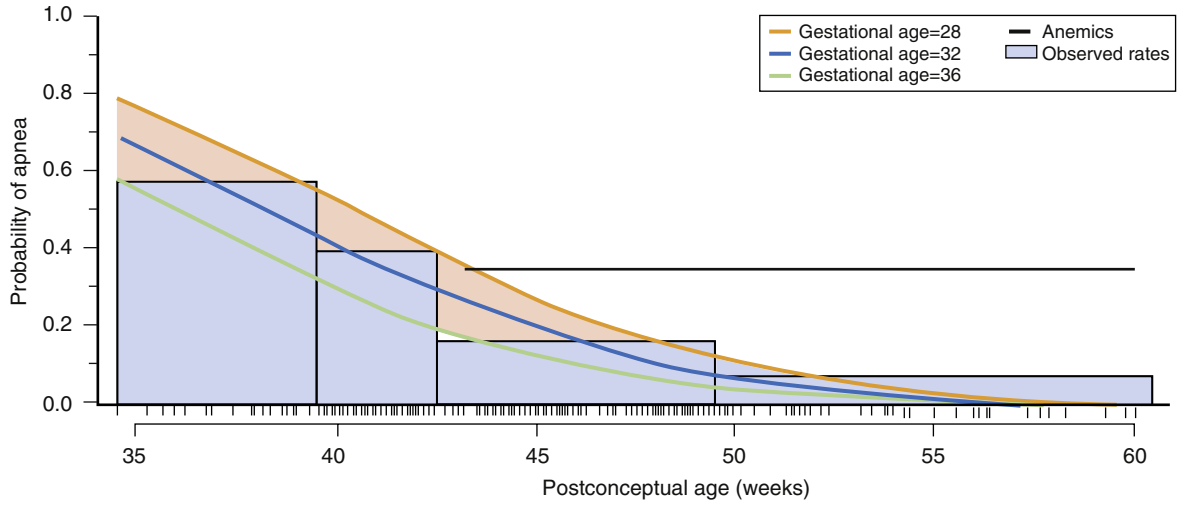


Figure 93-24. Predicted probability of apnea for all children by gestational age and weeks postconceptual age. Children with anemia are shown as the *horizontal solid black line*. *Bottom marks* indicate the number of data points by postconceptual age. The risk for apnea diminishes in infants born at a later gestational age. The *shaded boxes* represent the overall rates of apnea for infants within that gestational age range. The probability of apnea was the same, regardless of postconceptual age or gestational age, for infants with anemia (*horizontal solid black line*). *(Reproduced with permission from Coté CJ, Zaslavsky A, Downes JJ, et al: Postoperative apnea in former preterm infants after inguinal herniorrhaphy. A combined analysis,* Anesthesiology *82:809-802, 1995.)*

To make the issue even more complex, this author has a full-term infant who became apneic after general anesthesia. This infant had periodic breathing, which is distinctly unusual in a full-term infant and suggestive of a problem with control of respirations.[192] Which full-term neonates can be safely anesthetized on an outpatient basis is still not known with certainty. Because most organ systems are still rapidly developing during the first month of life (44 weeks' PCA), elective surgery should be delayed during the first month of life, and postoperative admission and apnea monitoring should be considered even in full-term infants younger than 1 month.

CHILDREN WITH REPAIRED HEART DISEASE

One should not assume that children have normal cardiac function after *correction* of congenital heart defects. Although the circulation may be normal, there is never assurance that cardiac function is normal. Any child who has undergone a ventriculotomy may have some ventricular dysfunction caused by the incision; there is less potential for dysfunction if the surgical approach was through an atriotomy. Likewise, even relatively benign procedures such as open closure of ventricular or atrial septal defects can be associated with the later development of dysrhythmias. Some children, particularly those with repaired single-ventricle physiology, have a significant predisposition to sudden death as a result of pathologic arrhythmias; a careful history is particularly important in these children. Should an arrhythmia develop intraoperatively, consultation with the child's cardiologist is essential because this development may be the first indication of a serious underlying arrhythmogenic focus. A radiofrequency ablation procedure may be lifesaving.

Children with a single-ventricle physiology (Fontan) require very specific anesthetic management. Because blood flow to the lungs is passive (i.e., no pumping chamber and no valves), high venous pressure is required (full hydration). PEEP is avoided and, the use of higher respiratory rates with low peak inflation pressure is recommended. The avoidance of anything that will increase pulmonary artery pressure (e.g., hypercarbia, further desaturation from baseline) is essential.[193] Children with Fontan physiology are poor candidates for laparoscopic procedures because of the required increases in intraabdominal pressure (compromised respirations, leading to hypercarbia and raised pulmonary artery pressure), carbon dioxide absorption from the pneumoperitoneum (raising pulmonary artery pressure), and extremes of head up or head down positions that also adversely affect passive blood return to the pulmonary circuit. These children often have other major issues such as protein-losing enteropathy and *plastic* bronchitis, and they are at significant anesthetic risk if one is unfamiliar with this unique physiologic abnormality.[194]

Another pediatric population at high risk for sudden death related to anesthesia is children with Williams syndrome (aortic stenosis, abnormal coronary arteries, pulmonic stenosis).[195] Children who have undergone cardiac transplantation also need particular attention to rule out small vessel coronary artery disease.[196] A full discussion of congenital heart disease is beyond the scope of this chapter, but the following three problems are the most common that a nonpediatric anesthesiologist may face for an appendectomy or the treatment of a forearm fracture (see also Chapter 94).

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) is defined as a "disorder of breathing during sleep characterized by prolonged upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep." These children also have an altered response to carbon dioxide.[197] Children at particular risk include those with craniofacial abnormalities, neuromuscular disorders, obesity, and adenotonsillar hypertrophy.[198,199] The increasing number of obese children is a major contributing factor.[200-202] The difficulty that anesthesiologists face is determining which children are at risk because not all children will undergo formal polysomnogram evaluation, which is considered the gold standard.[198] Abnormal sleep oximetry values (clusters of desaturation) also correlate with the severity of OSA.[203,204] Even children undergoing surgery in the afternoon may be at greater risk compared with those undergoing surgeries in the morning.[205] The apnea index (AI) and the respiratory disturbance index are measurements of the presence and severity of OSA syndrome. These indices reflect the frequency of occlusive and partially occlusive respiratory events per hour of sleep. OSA syndrome is present if the AI is 1 or greater (i.e., one or more apnea events per hour of sleep) and can be classified as mild if the AI is between 1 and 5, moderate if the AI is between 5 and 10, and severe if the AI is greater than 10 events per hour of sleep. Of particular concern are children in whom cardiac dysfunction (cor pulmonale) has developed and those in whom postobstructive pulmonary edema could develop. These children may require overnight ventilation in an ICU. In general, risk factors for postoperative complications include the following: (1) age younger than 3 years; (2) abnormal coagulation values; (3) evidence of OSA; (4) systemic disorders that place the child at increased perioperative risk (e.g., cor pulmonale, metabolic diseases); (5) presence of craniofacial or other airway abnormalities; (6) performance of the procedure for peritonsillar abscess; (7) child living a long distance from an adequate health care facility, adverse weather conditions, or home conditions not consistent with close observation, cooperativeness, and ability to return quickly to the hospital (e.g., substance-abusing parents, teenage mother); (8) obesity (>95% body mass index [BMI] or >95% weight for gender and age), and (9) African-American ethnicity.[206,207] The main problems that anesthesiologists face are determining when it is safe to send these children home and what should be done to provide postoperative analgesia.[202] Some day-surgery centers immediately send children home after tonsillectomy; others hold the children for at least 4 hours (the interval during which bleeding or respiratory compromise will most likely occur). Hospitals tend to admit the children to a 23-hour unit (to avoid the 24-hour hospital admission), thus observing the child for an extended time (usually not the full 23 hours) while minimizing the expense to the insurance provider. Analgesia is generally provided with a combination of oral acetaminophen preoperatively or rectally

administered after induction and low-dose morphine (33-50 μg/kg). Some anesthesiologists prefer short-acting opioids such as fentanyl to minimize respiratory depression and then supplement the analgesia with an additional longer-acting opioid in the PACU. Ketorolac provides analgesia without adverse respiratory effects, but it is associated with an increased incidence of postoperative bleeding if given before achieving hemostasis.[208] Postoperative nausea and vomiting are generally treated with serotonin 5-HT_3 antagonists, whereas postoperative swelling (plus vomiting) is treated with dexamethasone (0.0625 to 0.15 mg/kg).[209]

The most common at-home analgesic is acetaminophen with codeine. One issue that requires further evaluation is the possibility of alteration of opioid receptors (upregulation of μ opioid–receptors) in response to repeated minor hypoxemic events, as well as an altered response to carbon dioxide.[197,210-212] These altered responses result in increased sensitivity to the respiratory depressant effect of opioids.[213] These children are analgesic at one half the normal dose of opioid, thus a normal dose may, in fact, be a relative overdose for children with severe OSA.[214] In addition to these factors, children with OSA have a structurally narrowed airway because of an increased propensity for upper airway collapsibility.[215] These factors explain, in part, why children with OSA are at significantly increased risk for postoperative respiratory complications. A further concern is the recent reports of deaths after tonsillectomy related to altered conversion of the prodrug codeine to morphine.[216,217] Approximately 2% to 10% of children are slow metabolizers attributable to the deficiency of CYP2D6 genes (cytochrome P450, family 2, subfamily D, polypeptide 6), thus making codeine an ineffective analgesic. However, a more worrisome variant is children with duplicated CYP2D6 genes, resulting in ultraextensive conversion to morphine.[218,219] Thus the combination of OSA-induced opioid sensitivity and rapid metabolism can lead to fatal outcomes.[216-219] The FDA has added a **black box** warning strongly recommending that codeine not be administered to children for posttonsillectomy analgesia, particularly to those with obstructive sleep apnea.[220]

Independent of this genetic variant, children with severe OSA are at very high risk. If the child has not had a formal sleep polysomnogram or an overnight pulse oximeter study, then the practitioner must have a high index of suspicion if the child is obese (>95% weight for gender and age); has loud snoring, daytime somnolence, observed pauses or gasps, or exhibits a new onset of enuresis; is syndromic; or is African American.[221,222] These children are not candidates for same-day outpatient surgery and should be admitted to the safety net of medical supervision overnight. Unfortunately, this author has reviewed several medical misadventures during which children with known OSA died at home within hours of their tonsillectomy attributable to apnea.

REGIONAL ANESTHESIA AND ANALGESIA

Most regional anesthesia techniques used in adults can be safely administered to children as long as strict attention is paid to the dose of the local anesthetic, the dose of epinephrine, the route of administration, and the use of proper equipment. Perhaps the greatest advance in pediatric anesthesia has been the development of methods producing postoperative analgesia (also see Chapters 92 and 98). Caudal anesthesia, caudal opioids, regional blocks, and child-parent-nurse–controlled analgesia have all been accepted by anesthesiologists and children. Recent advances in ultrasound equipment have further improved the accuracy of nerve blocks and reduced the dose of drug needed to provide a successful block. Even pediatric patient–controlled epidural analgesia has been successfully used in children as young as 5 years of age.[222] Each institution and practitioner must decide which method works best, given each particular practice setting. Obviously, until dosage guidelines and safety standards for monitoring are well established, some of these techniques must be limited to medical centers familiar with their use in children (also see Chapter 92).

Regional nerve blocks and direct local infiltration of surgical wounds with long-acting local anesthetics are simple yet very effective and safe methods of providing pain relief for all children.[224,225] In most institutions, it is now rare for a child to awaken from anesthesia without some form of regional block. This practice has been especially helpful in the outpatient population; parents are encouraged to start analgesics when they observe their child becoming irritable but before the complete dissipation of the block. This approach usually provides a smooth transition from general anesthesia and a pain-free child. (Chapters 56 through 58 discuss regional anesthesia and analgesia in detail, and Chapter 92 places a special emphasis on pediatrics.)

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Chapter 94

Anesthesia for Pediatric Cardiac Surgery

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Key Points

- Organ system maturation, from birth through adolescence (e.g., cardiovascular, central nervous system [CNS], pulmonary, renal, hematologic), affects physiologic function and therefore anesthetic and surgical management and outcome.
- Physiologic understanding of congenital heart disease (CHD) and consequent anesthetic management are based on the pathophysiologic determinants of four categories of defects: shunts, mixing lesions, stenotic lesions, and regurgitant lesions.
- The chronic sequelae of CHD—repaired, palliated, or unrepaired—affect anesthetic management: ventricular failure, residual hemodynamic effects (e.g., valve stenosis), arrhythmias, and pulmonary blood flow changes (e.g., pulmonary artery hypertension).
- Preoperative assessment of cardiac status (e.g., review of history and physical examination, echocardiography, and catheterization data and consulting with the patient's cardiologist) and planning are the keys to a successful anesthesia outcome.
- Intraoperative transesophageal echocardiography and CNS monitoring enhance surgical outcome and reduce morbidity.
- Selecting an induction technique depends on the degree of cardiac dysfunction, the cardiac defect, the degree of sedation provided by the premedication, and the presence or absence of an indwelling venous catheter. Other factors to be considered are the presence of pulmonary hypertension, electrical rhythm disorders, and other comorbidities. The maintenance of anesthesia depends on the age and condition of the patient, the nature of the surgical procedure, the duration of cardiopulmonary bypass (CPB), and the need for postoperative ventilation. It is usually desirable to return the patient to an arousable, sedated state with spontaneous ventilation at the end of the procedure in the presence of normal homeostasis and absence of complications.
- The physiologic effects of CPB on neonates, infants, and children are significantly different from the effects on adults. During CPB, pediatric patients are exposed to biologic extremes not seen in adults, including deep hypothermia (18° C), hemodilution (threefold to fivefold greater dilution of circulating blood volume), low perfusion pressures (20 to 30 mm Hg), and wide variation in pump flow rates (ranging from 200 mL/kg/minute to total circulatory arrest).
- After repair of complex congenital heart defects, separating patients from CPB may be difficult. The causes may be an inadequate surgical result with a residual defect requiring repair, pulmonary artery hypertension, or right or left ventricular dysfunction.
- The use of modified ultrafiltration (MUF) reverses the deleterious effects of hemodilution and the inflammatory response associated with CPB in children. Perioperative blood loss and blood use are significantly reduced when MUF is used. MUF also improves left ventricular function and systolic blood pressure and increases oxygen delivery. Pulmonary compliance and brain function after CPB are also improved.

†Deceased.

KEY POINTS—cont'd

- Neonates, infants, and children undergoing cardiac surgery with CPB have a more frequent rate of postoperative bleeding than that seen in older patients. This is due to several factors: (1) A disproportionate exposure to the nonendothelialized extracorporeal circuit produces an inflammatory-like response. This inflammatory response to CPB is inversely related to patient age—the younger the patient, the more pronounced is the response. (2) The type of surgery performed in neonates and infants usually involves more extensive reconstruction and suture lines, creating more opportunities for surgical bleeding than in adult cardiac patients. (3) Operations are frequently performed using deep hypothermia or circulatory arrest, which may further impair hemostasis. (4) The immature coagulation system in neonates also may contribute to impaired hemostasis. (5) Patients with cyanotic heart disease demonstrate an increased bleeding tendency before and after CPB.
- The guiding principle in the management of the postoperative patient is an understanding of both normal and abnormal convalescence after anesthesia and cardiac surgery. The immediate postoperative period, even that of normal convalescence, is one of continuous physiologic change because of the pharmacologic effects of residual anesthetic agents and the ongoing physiologic changes secondary to abrupt alteration in hemodynamic loading conditions, surgical trauma, and extracorporeal circulation.
- The care of adults with CHD is a new and expanding field of medicine that requires the skilled management of an experienced multidisciplinary team.
- Additional anesthetic considerations exist in patients with CHD who undergo transplantation, closed heart operations without CPB, cardiac interventional procedures, and noncardiac surgery.

Cardiac surgery is an established and effective treatment for children with congenital heart defects. Early successes in surgical treatment led to a new therapeutic era in the management of congenital heart disease (CHD) and fostered the development of the subspecialties pediatric cardiology and cardiac surgery and their collaboration. Through this cooperative effort, tremendous progress in medical diagnosis and surgical treatment has been achieved. In turn, these accomplishments gave rise to the development of pediatric cardiac anesthesiologists, individuals who understand the pathophysiology of congenital heart malformations, the diagnostic and surgical procedures used to treat heart disease, and the principles of pediatric and cardiac anesthesia and intensive care medicine. Pediatric cardiac anesthesia continues to evolve as an exciting and technically demanding subspecialty in which anesthetic management is based on physiologic principles.

Cardiovascular surgery and anesthesia in CHD are often performed under unusual physiologic conditions. Rarely in clinical medicine are patients exposed to such biologic extremes as during surgery for CHD. Commonly, patients are cooled to 18° C, are acutely hemodiluted by more than 50% of their extracellular fluid volume, and undergo periods of total circulatory arrest lasting up to 1 hour. Management of patients under these physiologic extremes is a vital function of the pediatric cardiovascular anesthesiologist. As with other areas of medicine, the application and management of technology preceded a comprehensive understanding of its physiologic effects.

Clearly, the perioperative management of these complex cases requires a group of physicians (surgeon, anesthesiologist, cardiologist, critical care specialist), nurses, and perfusionists to work as a team. This team orientation is essential to achieving an optimal outcome. Although the quality of the surgical repair, the effects of cardiopulmonary bypass (CPB), and postoperative care are the major determinants of outcome, meticulous anesthetic management is also imperative. Ideally, despite the complexity of the cases and the marked physiologic changes attributed to CPB and the surgical procedures, anesthetic care should never contribute substantially to morbidity or mortality.[1] The challenge is to understand the principles underlying the management of patients with CHD and apply them to clinical anesthesia. We assume that the reader already understands the fundamentals of adult cardiac (see Chapter 67) and general pediatric anesthesia (see Chapter 93).

UNIQUE FEATURES OF PEDIATRIC CARDIAC ANESTHESIA

Pediatric cardiovascular management is unique, with important differences from adult cardiac surgery (Box 94-1). These differences are attributable to normal organ system maturation in the neonate and young infant, differing pathophysiologic conditions in CHD, the diversity of surgical repairs, and the use of specialized CPB techniques such as deep hypothermia and total circulatory arrest.

BOX 94-1 ***Unique Characteristics of Pediatric Cardiac Anesthesia***

PATIENT

Normal organ system development and maturational changes of infancy
- *Cardiovascular:* Blood flow patterns of circulation at birth, myocardial compliance, systemic and pulmonary vasculature, and β-adrenergic receptors
- *Pulmonary:* Respiratory quotient, closing capacity, chest compliance
- *Central nervous system:* Brain growth, cerebral blood flow, autonomic regulation
- *Renal:* Glomerular filtration rate, creatinine clearance
- *Hepatic:* Liver blood flow, microsomal enzyme activity

Disease and growth interrelationship
Effects of systemic disease alter somatic and organ growth
Compensatory ability of developing organs to recover from injury
Immunologic immaturity of the infant
Obligatory miniaturization (i.e., small patient size and body surface area)

CONGENITAL HEART DISEASE

Diverse anatomic defects and physiologic changes
Altered ventricular remodeling owing to myocardial hypertrophy and ischemia
Chronic sequelae of congenital cardiac disease

SURGICAL PROCEDURES

Diversity of operations
Frequent intracardiac and right ventricular procedures
Use of deep hypothermia and circulatory arrest during repair
Trend toward repair in early infancy
Evolution of surgical techniques to avoid residua and sequelae
Trend toward wider application of certain operations

PHYSIOLOGIC CONSIDERATIONS AND MATURATIONAL FEATURES OF THE PEDIATRIC PATIENT

The cardiovascular system changes markedly at birth because of a dramatic alteration in blood flow patterns (Fig. 94-1). During fetal life, blood flow returning to the right atrium (RA) bypasses the unventilated fluid-filled lungs. Blood is then preferentially shunted across the patent foramen ovale into the left atrium (LA) or passes from the right ventricle (RV) across the patent ductus arteriosus (PDA) to the systemic circulation. At birth, physiologic closure of the PDA and of the foramen ovale brings about the normal adult circulatory pattern. The presence of certain congenital heart defects or pulmonary disease can disrupt this normal adaptive process, creating a transitional circulation in which right-to-left shunting persists across the foramen ovale or the PDA. Under such circumstances, the continued presence of a transitional circulation can lead to severe hypoxemia, acidosis, and hemodynamic instability, which are poorly tolerated in the neonate. In contrast, when initially treating some forms of CHD, the prolongation of this transitional circulation is actually beneficial, promoting systemic blood flow or pulmonary blood flow (PBF) and postnatal viability. An example of the latter is pulmonary atresia, in which PBF is supplied via the PDA. In the absence of collateral vessels, closure of the PDA eliminates the principal source of PBF, resulting in hypoxemia and death. Ductal patency can be maintained with the administration of prostaglandin E1. Importantly, the transitional circulation can be manipulated by pharmacologic ventilatory strategies, thereby promoting hemodynamic stability in the pediatric patient. Another unique feature of the normal neonatal and infant cardiovascular system is the reduced myocardial reserve in contrast to that in the healthy adult. The newborn left ventricular function is restricted by a reduced number of α-adrenergic receptors, high resting levels of circulating catecholamines, limited recruitable stroke work, an immature calcium transport system, and decreased ventricular compliance.[2] This limits contractile reserve and results in a left ventricle (LV) with a high level of resting tone. Although the resting performance of the neonatal myocardium may be greater than in adults and older children, sensitivity to β-blockade is greater and only modest increases occur in cardiac performance after administration of the β-agonist drugs dobutamine and isoproterenol.[3]

On the ultrastructural level, a variety of cellular synthetic functions are occurring in immature myofibrils that dominate the newborn heart. Large nuclei, mitochondria, and surface membranes predominate within the myofibrils. In neonates, a 50% reduction in the number of myofibrils is seen and the myofibrils are arranged in a nonlinear, disordered array. As a direct result, the contractile mass of the heart is effectively reduced, resulting in a ventricle with low compliance. Preload augmentation is effective at low filling pressures (1 to 7 mm Hg). However, when left-sided filling pressures exceed 7 to 10 mm Hg, further increases in left ventricular stroke volume are minimal.[2] As a consequence, neonates are more dependent on heart rate and, to a lesser extent, on preload, to maintain cardiac output at filling pressures of 7 to 10 mm Hg or greater.[4]

In addition to a reduced contractile mass, the calcium transport system in the neonatal myocardium is underdeveloped. The transverse tubular system is absent, and the sarcoplasmic reticulum, which has to store and release calcium, is small and inefficient. The neonatal heart therefore depends more on extracellular calcium levels than the adult myocardium.[5-8] Because intracellular calcium concentrations play a central role in myocardial contractility, normal or even elevated plasma levels of ionized calcium may be necessary to augment or maintain an effective stroke volume. This is in contrast to adult cardiac patients in whom calcium use during cardiac surgery has fallen into some disfavor, owing to direct concerns over myocardial ischemia and reperfusion injury.

Another unique feature relates to the pulmonary circulation. The pulmonary circulation undergoes significant changes during the first months of life. These changes are largely characterized by regression of the hypertrophied medial smooth muscular layer in the pulmonary arteries that exists in utero, resulting in a concomitant drop in pulmonary vascular resistance (PVR). In the immediate newborn period, the large decrease in PVR is due to lung expansion and the vasodilatory effects of a higher PaO_2 than existed in utero. Further decline in PVR throughout the next 2 months of life is attributable to regression

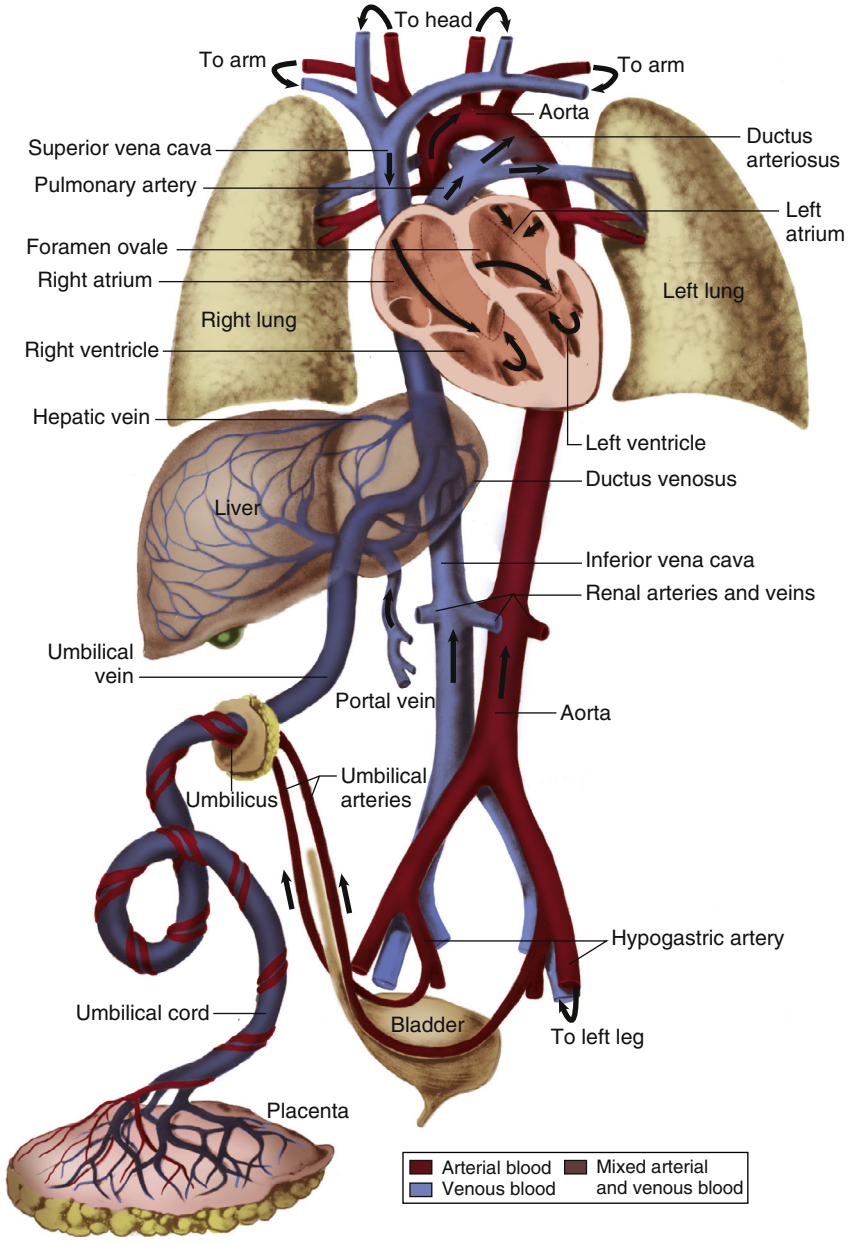


Figure 94-1. Course of the fetal circulation in late gestation. Note the selective blood flow patterns across the foramen ovale and the ductus arteriosus.

of the smooth muscle layer in the pulmonary arterioles. A corresponding decrease in pulmonary artery pressure occurs as PVR declines. Acute physiologic stress in the newborn period, such as hypoxemia or acidosis, can increase pulmonary artery pressure and thus PVR. If the resulting right ventricular hypertension causes reduced right ventricular compliance, right-to-left shunting can occur at the foramen ovale. Once PVR exceeds systemic vascular resistance (SVR), right-to-left shunting develops at the PDA. Either phenomenon will worsen the hypoxemia and eventually limit tissue oxygen (O_2) delivery to the point of lactic acidosis. In contrast, left-to-right shunts, such as with a ventricular septal defect (VSD), produce intimal changes in the pulmonary vasculature and delay regression of medial muscle hypertrophy. This results in persistent elevation of PVR.

Size differences between adult and pediatric cardiac patients require different anesthetic techniques and miniaturization. Anatomically, pediatric patients have small upper and lower airways, small veins and arteries, and a decreased body surface area in contrast to those in adult patients. Several anesthetic implications exist related to patient size. Some centers think placement of arterial catheters by cutdown in neonates and infants represents the most expedient approach, particularly when optimal sites are limited. Pulmonary artery catheters are used infrequently, both because of the technical difficulties in positioning the tip in the pulmonary artery and because of the fundamental fact that pulmonary flow bears no obligatory relationship to systemic output in children with either intracardiac or extracardiac communications. Transthoracic catheters for pressure monitoring and delivery of

vasoactive substances are commonly placed from the surgical field instead of percutaneous approach via the neck. Adequacy of the repair and function can be assessed by transesophageal echocardiography with Doppler color flow imaging with miniaturized probes.[9,10] CPB serves as another example of the influence of patient size on management. The ratio of pump priming volume to patient blood volume is considerably higher in small children than in adults, resulting in a greater degree of hemodilution. Several studies demonstrated a heightened inflammatory response to CPB in children in contrast to in adults.[11] This effect is related to the disproportionate exposure to the nonendothelialized surfaces of the pump circuit per body surface area. Greater damage to the formed blood elements and plasma proteins is incurred, resulting in activation of mediators of inflammation.

In pediatric patients with CHD, the cardiovascular system often represents the sole cause of the medical problem. This is in contrast with the multiplicity of diagnoses and organ system involvement frequently found in adults with acquired cardiovascular disease. Moreover, a special disease and growth interrelationship, unique to growing infants and children, permits developing organs to compensate for and modify existing disease processes. Reparative and recuperative processes in children are greater as a result of this compensatory ability of developing organ systems. Adult cardiac patients unfortunately do not exhibit the same recuperative ability. Although children adapt well to cardiovascular pathologic processes, negative aspects to long-standing heart disease also exist. CHD has detrimental effects on somatic growth and on the growth and development of the brain, myocardium, and lung.

Other unique considerations are issues surrounding the premature infant (see Chapter 95). Premature infants are classified as infants with low birth weight (31 to 34 weeks, 1 to 1.5 kg), infants with very low birth weight (26 to 30 weeks, 600 g to 1 kg), and infants with extremely low birth weight (<26 weeks, 400 to 600 g). This population of infants manifests unique anesthetic challenges. Cardiorespiratory failure is common and multifactorial. The small airways are prone to obstruction, which results in increased airway resistance and work of breathing with easy fatigability. Diseases of the upper airway such as subglottic stenosis, tracheomalacia, and tracheal stenosis are poorly tolerated, and the use of positive end-expiratory pressure (PEEP) or continuous positive airway pressure is often necessary to stent open the airway. Lung compliance is reduced because of a deficiency of surfactant, resulting in intrapulmonary shunt and ventilation-perfusion mismatch. Mechanical ventilation prevents alveolar collapse, maintains patency of the airway, and maintains lung volume, preventing hypoxia. Premature lungs are susceptible to barotrauma and oxidant injury. Ventilation should use measures to reduce peak inspiratory pressures and barotrauma, and the inspired O_2 concentration should be reduced to avoid generation of free radicals. Premature infants are also prone to perioperative periods of apneas. Such apneas might be central in origin or obstructive, both of which can be aggravated by anesthetic agents. Apnea can be precipitated by abrupt changes in oxygenation, pulmonary mechanics, brain hemorrhage, and hypothermia. Sustained apnea can result in desaturation and usually begins after emergence from anesthesia and persists for up to 48 hours. Continuous apnea and saturation monitoring with correction of anemia (hematocrit >30) and intravenous administration of caffeine are therapeutic options. The incidence of postoperative apnea is related to postconceptional and gestational age, the presence of anemia, and the type of surgical procedure. The premature heart is a poorly contractile organ, sensitive to changes in intracellular calcium, with poor diastolic function. Cardiac output depends on heart rate, with marginal reserve. The premature infant also has a relatively low absolute blood volume and tolerates blood loss poorly. Autoregulation is not well developed, and blood loss compromises cerebral and coronary flow before other manifestations of hypovolemia. It is also imperative to avoid fluid overload in these patients. Patency of the ductus arteriosus results in pulmonary overcirculation with heart failure and a large left-to-right shunt. If uncorrected, this would result in pulmonary hypertension secondary to the development of pulmonary vascular occlusive disease. Thermoregulation by nonshivering thermogenesis is also poor owing to inadequate stores of brown fat in prematurity. It is critical to maintain normothermia by increasing the operating room temperature, using incubators for transport, warming and humidifying respiratory gases, and warming all intravenous fluids. Glycemic control is difficult, with a tendency to hypoglycemia and hyperglycemia. Euglycemia should be confirmed and maintained. Typically, these infants receive higher concentrations of parenteral glucose solutions, which need to be continued in the perioperative period. Premature infants are also prone to retinopathy of prematurity with high inspired O_2 concentrations and intraventricular hemorrhage. Every attempt should be made to avoid hemodynamic perturbances and fluctuation in O_2 saturations. In general, immaturity of organ systems results in both increased drug effect and duration of action, warranting careful titration of drugs.

Premature infants have a twofold increase in cardiovascular malformations compared with infants born at term.[12] One in six infants with CHD, not including those with PDA or ASD, is born prematurely. Some malformations such as tetralogy of Fallot (TOF), pulmonary stenosis, pulmonary atresia with VSD, complete atrioventricular (AV) septal defect, large VSDs in isolation or associated with coarctation, and aortic stenosis are more prevalent in this population.[13] A significant increase in the likelihood of being small for gestational age is seen among infants with TOF, complete AV septal defect, hypoplastic left heart, pulmonary stenosis, or large VSD.[14]

Cardiac catheterization, intervention, and complete surgical repair in the newborn of very low birth weight (<1.5 kg) can be successfully undertaken with low risk, although longer term follow-up remains necessary to determine growth and development patterns. However, because of the complexity of premature organ systems and superimposed cardiorespiratory pathophysiology, morbidity and mortality are increased.[15-17] Surgical adaptations have been described that enable the use of CPB in low-birth-weight infants. However, low birth weight remains a significant risk for mortality in neonates with complex single ventricle disease undergoing surgical palliation.[18,19] Interventional

catheterization is associated with higher risk for complications, especially related to problems with vascular access, arrhythmias, and respiratory compromise.[15] Premature infants are electively tracheally intubated and ventilation controlled for both catheterization and surgical procedures. Adequate intravenous access and invasive monitoring can be challenging but are necessary in most cases. Maintenance of euglycemia and normothermia and attention to fluid and electrolyte balance are important. O_2 delivery should be optimal by maintaining age-appropriate blood pressures, adequate intravascular volume, and hematocrit. Any acidosis must be sought and aggressively corrected. Generally, such infants should recover in a specialized pediatric cardiac intensive care unit (ICU).

CONGENITAL HEART DISEASE

The marked array of anatomic and physiologic conditions seen with CHD distinguishes these processes from acquired adult cardiac disease. The spectrum of intracardiac shunts, valve pathology (stenoses, regurgitation, or atresia), and disrupted great artery connections and the absence of one or more chambers of the heart preclude a uniform anesthetic approach to patients with CHD. Moreover, myocardial changes result from the hemodynamic impact and increased cardiac work incurred by these defects. Functionally, these myocardial changes place the ventricles at great risk for the development of intraoperative ischemia and failure. Therefore, an understanding of the isolated defect, associated myocardial changes, and hemodynamic consequences is fundamental to planning an appropriate anesthetic regimen. Distilling CHD into a finite number of physiologic categories enables the anesthesiologist to construct a strategy that employs the qualitatively predictable impact of drugs, ventilatory management, and fluid administration to optimize cardiovascular performance. Although an isolated heart malformation may be identified, the entire cardiopulmonary system is usually affected.

Physiologic Approach to Congenital Heart Disease

Although the structural variations seen in CHD constitute an encyclopedic list of malformations, anesthetic management is more logically designed to achieve physiologic goals. A general physiologic classification is listed in Table 94-1. Fortunately, although structurally complex, these defects can be understood within a more limited physiologic spectrum. Identification and classification on the basis of physiology provide an organized framework for the intraoperative anesthetic management and postoperative care of children with complex congenital cardiac defects. In general, congenital heart lesions fit into one of four categories: shunts, mixing lesions, flow obstruction, and regurgitant valves (see Table 94-1). Each category imposes at least one of three pathophysiologic states: ventricular volume overload, ventricular pressure overload, or hypoxemia. Ultimately, these pathophysiologic conditions can result in myocardial failure or pulmonary vascular disease. Medical and surgical perioperative management strategies should be focused on minimizing the pathophysiologic consequences of these lesions.

TABLE 94-1 CLASSIFICATION OF CONGENITAL HEART DEFECTS

Physiologic Classification	Pulmonary Blood Flow	Comments
Left-to-right shunts		
VSD	↑	Volume-overloaded ventricle
ASD		Development of CHF
PDA		
AV canal		
Right-to-left shunts		
Tetralogy of Fallot (TOF)	↓	Pressure-overloaded ventricle
Pulmonary atresia/VSD		Cyanotic
Eisenmenger complex		Hypoxemia
Mixing lesions		
Transposition/VSD	Generally↓ but variable $\dot{Q}p/\dot{Q}s$	Variable pressure versus volume loaded
Tricuspid atresia		Usually cyanotic
Anomalous venous return		
Univentricular heart		
Obstructive lesions		
Interrupted aortic arch		Ventricular dysfunction
Critical aortic stenosis		Pressure-overloaded ventricle
Critical pulmonic stenosis		Ductal dependence
Hypoplastic left heart syndrome		
Coarctation of the aorta		
Mitral stenosis		
Regurgitant lesions		
Ebstein anomaly		Volume-overloaded ventricle
Other secondary causes		Development of CHF

ASD, Atrial septal defect; *AV,* atrioventricular; *CHF,* congestive heart failure; *PDA,* patent ductus arteriosus; $\dot{Q}p$, pulmonary blood flow; $\dot{Q}s$, systemic blood flow; *VSD,* ventricular septal defect.

Shunt Lesion. Shunts are intracardiac connections between chambers or extracardiac connections between a systemic and pulmonary artery—examples are an atrial septal defect (ASD), a VSD, and a PDA. The direction of blood flow through the shunt depends on the relative resistances on either side of the shunt and on the size of the shunt orifice. With a nonrestrictive VSD or PDA that does not impede blood flowing freely in each direction, the main determinant of blood flow is the resistance of the pulmonary and systemic vascular beds. The direction and magnitude of shunt at the atrial level are governed by the relative differences in ventricular compliance and respective AV valve function. The effect that a shunt lesion has on the cardiovascular system depends on its size and direction, either right-to-left or left-to-right. Left-to-right shunts occur when

the PVR is lower than the SVR and blood flow is preferentially directed toward the lungs, resulting in increased PBF.

In patients with large left-to-right shunts and low PVR, a substantial increase in PBF can occur. This results in three pathophysiologic problems: (1) congestion of the pulmonary circulation; (2) intravascular volume overload with resulting increased cardiac work for the LV, which is required to increase stroke volume and heart rate to ensure adequate systemic perfusion; and (3) excessive PBF, resulting in progressive elevation in PVR. Volume overload causes ventricular dilation that places the heart at a mechanical and physiologic disadvantage, resulting in reduced diastolic compliance. These diastolic changes lead to engorgement of the respective venous beds, which produces the signs and symptoms of clinical congestive heart failure (CHF) early in the natural history of volume-overload condition. The demand for increased cardiac output placed on the LV is limited in the infant by virtue of its immature structure, so that large left-to-right shunts may outstrip the capacity of the left side of the heart to maintain adequate systemic perfusion, and CHF will result. Surgical closure of a hemodynamically significant VSD usually provides immediate benefit by dramatically lowering left ventricular volume output demands.

Occasionally, the sudden increase in wall stress imposed on a dilated ventricle that must now pump solely against SVR can produce worsening ventricular failure during the early postoperative period after eliminating the low-resistance "pop off" into the pulmonary circulation. If the left-to-right shunt is not repaired, prolonged exposure to increased PBF results in progressive elevations in PVR. Fixed changes in pulmonary arterioles may occur, leading to pulmonary vascular obstructive disease. Table 94-1 lists common left-to-right shunt lesions.

Right-to-left shunts occur when pulmonary vascular or right ventricular outflow tract resistance exceeds SVR, thereby reducing PBF. The systemic circulation receives an admixture of deoxygenated blood via the shunt and manifests clinically as cyanosis and hypoxemia. Pure right-to-left shunting resulting from increased PVR is seen in the Eisenmenger complex and persistent pulmonary hypertension of the newborn with atrial and ductal level shunting. More commonly, PVR is low, and a more complex lesion with obstruction of pulmonary outflow, proximal to the pulmonary vasculature, produces right-to-left shunting. Defects such as TOF represent classic right-to-left shunts. The shunting occurs through the VSD because of pulmonary outflow obstruction. Systemic perfusion is generally normal with right-to-left shunting lesions unless hypoxemia becomes severe enough to impair O_2 delivery to tissue. Thus, two pathophysiologic problems exist: (1) reduced PBF resulting in systemic hypoxemia and cyanosis and (2) an increased impedance to right ventricular ejection, which may ultimately lead to ventricular dysfunction and failure of the RV. However, the physiologic mechanisms designed to compensate for pressure overload rarely create abnormalities in systolic or diastolic function early in the natural history of the disease process. In contradistinction to lesions that produce excessive ventricular volume, ventricular dysfunction and failure typically take years to develop in the context of isolated pressure overload.

TABLE 94-2 DUCTAL-DEPENDENT LESIONS

PDA Provides Systemic Flow	PDA Provides Pulmonary Flow
Coarctation of the aorta	Pulmonary atresia
Interrupted aortic arch	Critical pulmonary stenosis
Hypoplastic left heart syndrome	Severe subpulmonic stenosis with VSD
Critical aortic stenosis	Tricuspid atresia with pulmonic stenosis

PDA, Patent ductus arteriosus; *VSD,* ventricular septal defect.

Mixing Lesions. Mixing lesions constitute the largest group of cyanotic congenital heart defects (see Table 94-1). In these defects, the mixing between the pulmonary and the systemic circulation is so large that the systemic and pulmonary artery O_2 saturations approach each other. The pulmonary-to-systemic flow ratio ($\dot{Q}p/\dot{Q}s$) is independent of shunt size and totally dependent on vascular resistance or outflow obstruction. The pulmonary and systemic circulations tend to be in parallel with one another rather than in series (see Table 94-1). In patients with no outflow obstruction, flow to the systemic or pulmonary circulation depends on the relative vascular resistances of both circuits, such as with univentricular hearts or double-outlet RV. If SVR exceeds PVR, as in the typical circumstance, the tendency is toward excessive PBF, and the predominant pathophysiologic process is left-to-right shunting. These patients have increased PBF, ventricular volume overload, and a gradual elevation of PVR over time. If PVR exceeds SVR, as may occur episodically in ductal-dependent lesions such as hypoplastic left heart syndrome, systemic blood flow predominates and PBF dramatically decreases, causing progressive hypoxemia (Table 94-2).

In patients with a mixing lesion and left ventricular outflow obstruction, PBF may be sufficiently excessive to impair systemic perfusion. In patients with mixing lesions and a right ventricular outflow obstruction such as a single ventricle with subpulmonic stenosis, systemic-to-pulmonary flow can vary from balanced flow to significantly decreased PBF in which the severity of hypoxemia depends on the degree of obstruction. Typical mixing lesions include truncus arteriosus, univentricular heart, total anomalous pulmonary venous return, pulmonary atresia with large VSD, and single atrium.

Obstructive Lesions. Obstructive lesions range from mild to severe. Severe lesions manifest in the newborn period with a pressure-overloaded, diminutive, or profoundly dysfunctional ventricle proximal to the obstruction. These lesions include critical aortic stenosis, critical pulmonic stenosis, coarctation of the aorta, and interrupted aortic arch. Although aortic and pulmonary atresia represent the most extreme variants of outflow tract obstruction, they are associated with such extreme hypoplasia of the ventricle (hypoplastic left heart syndrome and pulmonary atresia with intact ventricular septum, respectively) that the ventricle's function does not contribute to the circulatory physiology. As with other critical obstructive lesions, these extreme variants have ductal-dependent circulations, but beyond that similarity they are perhaps better understood as univentricular hearts for which the

management characteristics of a mixing lesion dominate in importance. In critical neonatal left-sided obstructive defects, systemic perfusion depends on blood flow (desaturated) from the RV via the PDA and the coronary perfusion is supplied by retrograde flow from the descending aorta (see Table 93-3). In right-sided lesions, PBF is supplied from the aorta via the PDA and right ventricular function is impaired.

Pathophysiologic problems in critical neonatal left-sided heart obstructive lesions include (1) profound left ventricular failure, (2) impaired coronary perfusion with an increased incidence of ventricular ectopy, (3) systemic hypotension, (4) PDA-dependent systemic circulation, and (5) systemic hypoxemia. The pathophysiologic problems in critical neonatal right-sided heart obstructive lesions include (1) right ventricular dysfunction, (2) decreased PBF, (3) systemic hypoxemia, and (4) PDA-dependent PBF. Apart from the most extreme variants that become evident in the neonatal period, infants and children with outflow obstruction (e.g., mild-to-moderate aortic or pulmonary stenosis, coarctation of the aorta) manifest the effective compensatory mechanisms for pressure overload, often remaining clinically asymptomatic for many years.

Regurgitant Valves. Regurgitant valves are uncommon as primary congenital defects. Ebstein malformation of the tricuspid valve is the only pure regurgitant defect manifesting in the newborn period. However, regurgitant lesions are frequently associated with an abnormality of valve structure, such as incomplete or partial AV canal defect, truncus arteriosus, and TOF with an absent pulmonary valve. The pathophysiology of regurgitant lesions includes (1) volume-overloaded circulation and therefore (2) progression toward ventricular dilation and failure.

In summary, when considering the incidence of all the congenital heart defects, three uncomplicated left-to-right shunts (VSD, ASD, PDA) and two obstructive lesions (pulmonic stenosis, coarctation) constitute 60% of all congenital cardiac defects. Mixing lesions, complicated obstructive defects, and right-to-left shunting lesions account for the vast majority of the remaining 40%. The latter group of defects, which are more difficult to manage, are more labor intensive and have a significantly higher morbidity and mortality rate. This observation is directly attributed to the complexity of the cardiovascular abnormalities seen in this group, in which an absence of a chamber or a major ventricular-arterial connection is present.

Chronic Consequences of Congenital Heart Disease. The chronic effects of CHD are a consequence of the imposed hemodynamic stress of the defect or the residua and sequelae after cardiac surgery. These effects continue to alter normal growth and development of the cardiovascular system and other organ systems throughout life. Complete surgical cures are rarely achieved, and some repairs are palliative rather than corrective; therefore, abnormalities before and after repair produce long-term effects in patients with CHD.[20] Although the overall outlook for these patients is good in most instances, every defect has associated myocardial changes and every repair leaves certain obligatory abnormalities. Many of the abnormalities are trivial and have no major import. Others affect major organ system processes, such as ventricular function, central nervous system (CNS) growth, the conduction system of the heart, or PBF. Under these circumstances, the long-term quality of life is affected. Whether anesthetizing these patients for their primary or subsequent cardiac repair or for noncardiac surgery, these chronic changes should be ascertained and reflected in the anesthetic plan.

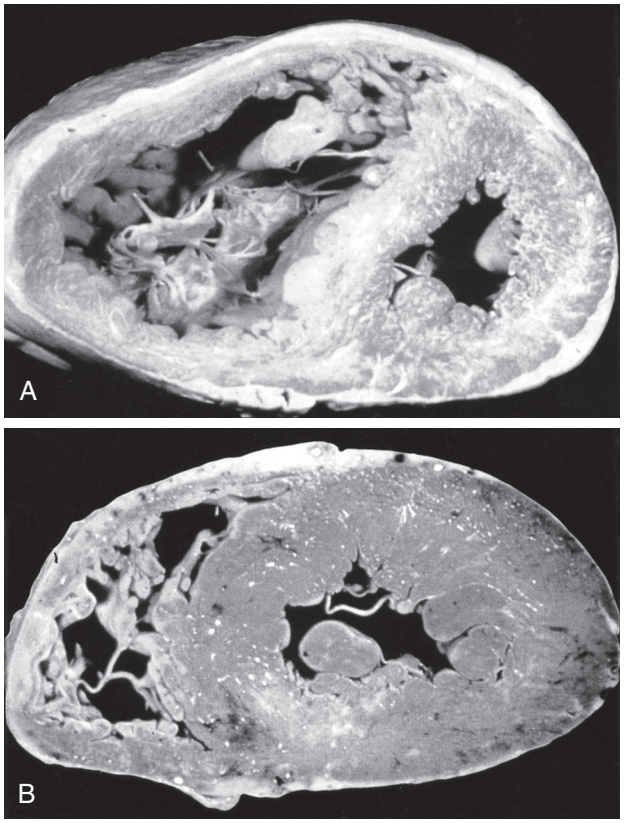


Figure 94-2. Comparison of ventricular hypertrophy patterns demonstrating altered ventricular remodeling in two different congenital heart defects. **A,** Note the right ventricular hypertrophy and the diminutive left ventricle in tetralogy of Fallot. **B,** Note the severe left ventricular hypertrophy and septal bulging into the right ventricle in aortic stenosis.

The myocardium is continually remodeled by specific hemodynamic stresses in utero and throughout life. Right ventricular growth and development are influenced by the low-resistance afterload of the pulmonary circulation. The LV is coupled to the high-resistance systemic circulation, which accelerates its rate of growth and development. This situation gives rise to the adult condition in which left ventricular dominance of myocardial muscle mass occurs. This entire developmental process is referred to as dynamic ventricular modeling. Abnormal hemodynamic loading conditions associated with CHD interrupt the normal ventricular modeling process (Fig. 94-2).[21] Abnormal ventricular remodeling typically begins in utero and stimulates an increase in ventricular mass. Increased ventricular mass is due to both hyperplasia and hypertrophy of myocytes in response to altered wall stress on the developing ventricle. The resultant biomechanical

deformation of the ventricle alters its geometry, affecting normal systolic and diastolic function.

Abnormalities of ventricular performance at rest and with exercise can be detected in patients with chronic hemodynamic overload and complex cyanotic lesions. These abnormalities in ventricular function are the consequences of chronic ventricular overload, repeated episodes of myocardial ischemia, and residua or sequelae of surgical treatment (ventriculotomy, altered coronary artery supply, inadequate myocardial protection). The physiologic adaptive responses to chronic hypoxemia and ventricular pressure or volume overload are the primary stimuli producing the long-term ventricular dysfunction. Although chronic volume overload of the LV as seen with left-to-right shunts or a chronic pressure-loaded LV from left-sided obstructive lesions results in CHF, the compensatory mechanisms for pressure overload create less physiologic disturbance, particularly in diastolic function. Consequently, CHF occurs later in the natural history of isolated obstructive lesions that do not require treatment in the neonatal period. Similarly, chronic right ventricular volume overload as seen in pulmonic insufficiency after TOF repair is more likely to be associated with chronic ventricular dysfunction and failure than a pressure-loaded RV that manifests with residual pulmonic stenosis. In fact, the most potent combination for inducing ventricular dysfunction and failure occurs when a pressure overload is superimposed on a dilated, volume-overloaded ventricle (e.g., postoperative TOF with pulmonary insufficiency and branch pulmonary artery stenosis). The mechanism for the dysfunction and failure is multifactorial.

Initial manifestations of CHF reflect alterations in ventricular compliance that result from a variety of biophysical responses to abnormal loading conditions. The ventricular dilation and compensatory hypertrophy that accompany excessive intravascular volume provide effective compensation to preserve normal systolic wall stress, but alterations in diastolic wall stress become evident (Fig. 94-3). Ultimately, chronic or severe pressures cause similar changes as the resultant myocardial hypertrophy outgrows vascular supply and results in ischemia and fibroblast proliferation. Permanent changes in myocardial structure and function are the end result.

In patients with cyanotic conditions, the long-term compensation for chronic hypoxemia is a major redistribution of organ perfusion with selected blood flow to the heart, brain, and kidney and decreased flow to the splanchnic circulation, skin, muscle, and bone. Chronic hypoxemia is associated with increased work of breathing in an attempt to increase O_2 uptake and delivery. The most dramatic complications are decreased rate of somatic growth, increased metabolic rate, and an increase in hemoglobin concentrations.

Congenital syndromes may have associated CHD that will influence long-term outcome (Table 94-3).



	Normal	Pressure overload	Volume overload
LVp	117 ± 7 / 10 ± 1	220* ± 6 / 23* ± 3	139 ± 7 / 24* ± 2
h	.8 ± .1	1.5* ± .1	1.1* ± .1
r	2.4 ± .1	2.8 ± .2	3.3* ± .1
h/r	.34 ± .02	.58* ± .05	.34 ± .02
σ_s	151 ± 14	161 ± 24	175 ± 7
σ_p	17 ± 2	23 ± 3	41* ± 3

Figure 94-3. Changes in ventricular physiology that accompany abnormal pressure and volume loading in human adolescents and adults. Schematic diagram represents the changes in cross-sectional ventricular geometry that accompany abnormal pressure and volume loads. Data are measured and derived from catheterization and echocardiography of 30 adolescent and adult human subjects. Pressure overload triggers significant increases in wall thickness and wall thickness-to-radius ratio (*h/r*), but these compensatory mechanisms preserve σ within normal limits. Whereas volume overload causes dilation and enough hypertrophy to preserve normal σS, diastolic function deteriorates significantly. σ_d, End-diastolic wall stress; *LVp,* left ventricular pressure; *r,* radius of the left ventricular chamber; σ_s, peak systolic wall stress. *$P = .01$. *(From Grossman W, Jones D, McLaurin LP: Wall stress and patterns of hypertrophy in the human left ventricle,* J Clin Invest *56:56, 1975.)*

Surgical Procedures and Special Techniques. The ultimate objectives for congenital heart surgery are (1) physiologic separation of the circulation, (2) relief of outflow obstruction, (3) preservation or restoration of ventricular mass and function, (4) normalization of life expectancy, and (5) maintenance of quality of life. The available surgical procedures to accomplish these objectives are diverse and complex (Table 94-4). In contrast to cardiac operations in adult patients, pediatric congenital heart repairs involve more intracardiac surgery, with a greater preponderance performed via the RA and RV. In general, operations performed for congenital heart defects can be divided into palliative and corrective procedures. The type and timing of repair depend on the age of the patient, the specific anatomic defect, and the experience of the surgeon and the team (see Table 94-4).

Palliation in infancy is usually performed when anatomic parts are missing, as in pulmonary atresia (absent RV and pulmonary artery), tricuspid atresia (absent RV and tricuspid valve), hypoplastic left heart syndrome (aortic atresia and hypoplastic LV), univentricular heart (absent RV or LV), and mitral atresia (absent LV). These palliative procedures can be further subdivided into those that increase PBF, those that decrease PBF, and those that increase mixing (see Table 94-4). Palliative procedures that increase PBF include shunts (Blalock-Taussig, central, and Glenn), outflow patch, and enlargement of the VSD. Those that decrease PBF include pulmonary artery banding and ligation of a PDA. Those that improve intracardiac mixing include atrial septostomy (balloon, blade, and Blalock-Hanlon).

The improvements in surgical technique, coupled with advancements in anesthetic and technologic support, make repair in early infancy not only feasible but in many cases preferable.[22] Currently, repair in infancy can be offered for a number of congenital heart defects,

TABLE 94-3 SYNDROMES ASSOCIATED WITH CONGENITAL HEART DISEASE

Syndrome	Lesion	Cardiac Lesion	Comments
Syndromes With Airway Issues and CHD			
CHARGE syndrome (association)		VSD, ASD, PDA, TOF	Micrognathia, possible difficult airway
Edwards syndrome	Trisomy 18	VSD, ASD, PDA	Micrognathia, small mouth, difficult intubation
Di George sequence	Microdeletion 22q11.2	Aortic arch and conotruncal lesions	Short trachea—tendency to endobronchial intubation
Goldenhar syndrome		VSD, PDA, TOF, CoA	Maxillary and mandibular hypoplasia, C-spine anomalies—difficult intubation
Hurler syndrome	MPS 1, storage disorder	Multivalvular disease, CAD, cardiomyopathy	Macroglossia, short neck—extremely difficult intubation
Noonan syndrome		PS, ASD, cardiomyopathy	Short webbed neck, macrognathia—difficult intubation
Turner syndrome	Monosomy X	LVOT O, AS, HLHS, CoA	Micrognathia, webbed neck—difficult intubation
VATER association		VSD, TOF, ASD, PDA	Potential for difficult intubation
Syndromes With Risk for Arrhythmias			
Long QT syndrome (LQTS)		Torsade de pointes, SCD	
Brugada syndrome		VT/VF/SCD	
Arrhythmogenic right ventricular dysplasia (ARVD)		VT/SCD	
Catecholaminergic polymorphic ventricular tachycardia		Polymorphic VT/SCD	
Wolff-Parkinson-White syndrome		SVT	
Maternal lupus		CCHB in the newborn	
Chromosomal Disorders Associated With CHD			
Down syndrome	Trisomy 21	VSD, ASD, CAVC	
Edwards syndrome	Trisomy 18	VSD, ASD, PDA	
Patau syndrome	Trisomy 13	VSD, PDA, ASD	
Turner's syndrome	Monosomy X	LVOT O, AS, HLHS, CoA	
3p–syndrome	Deletion 3p	CAVC	
Cri du chat syndrome	Deletion 4p	Variable	
8p–syndrome	Deletion 8p	CAVC	
9p–syndrome	Deletion 9p	VSD, PDA, PS	
Williams syndrome	Microdeletion 7q11	SVAS, SVPS, branch PS	
Smith-Magenis syndrome	Microdeletion 17p11.2	ASD, VSD, PS, AV valve malformations	
Miller-Dieker syndrome	Microdeletion 17p13.3	TOF, VSD, PS	
CHARGE association		VSD, ASD, PDA, TOF	Coloboma, heart, choanal atresia, retardation, genital and ear anomalies

AS, Atrial stenosis; *ASD,* atrial septal defect; *AV,* atrioventricula; *CAVA,* vena cava; *CAD,* coronary artery disease; *CHARGE,* coloboma of the eye, heart defects, atresia of the nasal choanae, restriction of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities and deafness; *CCHB,* congenital complete heart block; *CHD,* congenital heart disease; *CoA,* coarctation of the aorta; *HLHS,* hypoplastic left heart syndrome; *LVOT O,* left ventricular outlet obstruction; *MPS 1,* mucopolysaccaridosis type 1; *PDA,* patent ductus arteriosus; *PS,* pulmonary stenosis; *SCD,* sudden cardiac death; *SVAS,* supraventricular aortic stenosis; *SVPS,* supravalvular pulmonic stenosis; *SVT,* supraventricular stenosis; *TOF,* tetralogy of Fallot; *VATER,* vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia; *VSD,* ventricular septal defect; *VT/VF,* ventricular tachycardia/ventricular fibrillation.

as shown in Table 94-4. The timing of surgical intervention reflects medical necessity, physiologic and technical feasibility, and optimal outcome. Cardiac defects that require a PDA to sustain sufficient systemic blood flow or PBF (e.g., pulmonary atresia, hypoplastic left heart syndrome, interrupted aortic arch, critical aortic stenosis, and critical pulmonic stenosis) require an intervention in the neonatal period. A variety of defects are optimally repaired in early infancy. Lesions such as transposition of the great arteries (TGA) may exhibit better left ventricular function if the arterial switch operation is performed in the first few weeks of life when the PVR has recently been high enough to increase left ventricular systolic pressure, whereas other repairs may manifest less volatile postoperative physiology if deferred a few weeks or months until PVR has consistently fallen (e.g., TOF, AV canal defect). Each defect may have mitigating factors for which deferred definitive repair will enable optimal surgical result (e.g., TOF with aberrant coronary branching pattern or multiple VSDs; TGA with VSD and severe left ventricular outflow tract obstruction).

Although some lesions merit repair whenever they are diagnosed (e.g., total anomalous pulmonary venous return, coarctation of the aorta), others exhibit such a wide spectrum of physiologic disturbance that the timing of an intervention must be made individually (e.g., VSD, aortic stenosis, pulmonic stenosis). A few cardiac malformations produce pathophysiologic changes that are sufficiently mild that repair is typically deferred to later infancy or childhood (e.g., isolated ASD). Palliative

TABLE 94-4 CONGENITAL CARDIAC DEFECTS AND THEIR REPAIR

Anatomic Defects	Palliation	Complete Repair
Tetralogy of Fallot (TOF)		VSD closure and RVOT patch
With PA atresia	Shunt	
With anomalous right coronary artery	Rastelli	
HLHS	Norwood I/transplant	
Transposition of the great arteries		Arterial switch
Unfavorable coronary anatomy	Atrial switch (Senning)	
Tricuspid atresia	Shunt followed by Fontan	
Pulmonary atresia with VSD	Shunt followed by Fontan	
With intact septum	Shunt followed by Fontan	
Critical aortic stenosis		Aortic valvotomy
Interrupted aortic arch		End-to-end anastomosis/reverse subclavian flap/tube graft
Total anomalous pulmonary		Anastomosis of pulmonary veins to left atrium venous return and ASD closure
Single ventricle/normal PAs	Band followed by Fontan	
With small PAs	Shunt followed by Fontan	
Truncus arteriosus		RV-PA conduit and VSD closure
Atrioventricular canal		Repair valve clefts/patch closure of ASD/attach valves to patch

ASD, Atrial septal defect; *HLHS,* hypoplastic left heart syndrome; *PA,* pulmonary artery; *RV,* right ventricle; *RVOT,* right ventricular outflow tract; *VSD,* ventricular septal defect.

surgery is entertained when a physiologic derangement requires intervention but circumstances preclude definitive repair.

Pediatric cardiovascular surgery repairs defects in infancy rather than palliates.[24] This trend reflects improved technical capabilities coupled with a desire to limit the morbidity and mortality associated with long-term medical management and the sequelae of multiple palliative operations. Early correction should decrease the incidence of the chronic complications of CHD, such as the problems associated with ventricular overload, cyanosis, and pulmonary vascular obstructive disease.[23] Early repair also may have the selective advantage of enhancing organ system protection during repair because of poorly understood factors promoting resistance to injury and enhanced recovery potential (i.e., enhanced plasticity). With the continued improvement in surgical techniques and the early treatment of CHD, specific organ systems such as the brain, heart, and lungs will be spared the detrimental effects of chronic derangements of hemodynamics and O_2 delivery.

Procedures for the treatment of CHD continue to evolve to decrease long-term morbidity and enhance survival. For example, the long-term problems with right ventricular dysfunction and failure associated with the Mustard procedure for repair of TGA encouraged many surgical groups to develop the neonatal arterial switch operation. The latter procedure probably provides an anatomic correction with better long-term results. A second example of the continuing evolution of technique is surgery for TOF. Long-standing pulmonary insufficiency after right ventricular outflow repair for TOF is associated with right ventricular dysfunction and failure. Preservation of the pulmonary valve at initial repair using a combined transatrial and transpulmonary approach during correction and the early insertion of a pulmonary homograft in the setting of pulmonary insufficiency are techniques being used in an attempt to avoid the long-term problems of right ventricular dysfunction and failure.[24] Similarly, nonsurgical procedures in the cardiac catheterization laboratory continue to develop to treat patients who may be poor surgical candidates. Patients presenting with right ventricular dysfunction or failure secondary to valveless right ventrical–to–pulmonary artery (RV-PA) conduits used in the palliation of TOF show improved outcomes from a transcatheter pulmonary valve.[25] The benefits include avoidance of a repeat sternotomy with an enlarged RV and CPB.

Surgery for hypoplastic left heart syndrome, once considered a fatal disease, has achieved significant long-term survival after a series of staged reconstructive procedures.[26,27] The use of RV-PA conduits as an alternative to traditional systemic-to-pulmonary shunts has been shown to confer some advantage in survival after stage 1 palliation owing to elimination of diastolic runoff into the pulmonary circulation with concurrent unloading of the systemic RV. Myocardial perfusion improves with higher diastolic pressures, lower aortic saturations, and decreased myocardial work. The long-term impact of a right ventriculotomy in a univentricular heart is unknown.[28-30] In 2008, the Pediatric Heart Network, an organization sponsored by the National Institutes of Health, completed enrollment in a randomized control trail comparing the effects of modified Blaylock Taussig shunt (mBTS) to RV-PA conduits as part of the stage 1 Norwood procedure.[31] Recent results revealed infants treated with an RV-PA shunt had improved survival over those with mBTS, although the long-term outcomes were not different.[31,32] The use of a low-resistance strategy provides a stable postoperative course with use of vasodilators such as phenoxybenzamine on CPB and optimal reduction of PVR with inhaled nitric oxide (NO) and 100% O_2 after CPB.[33,34]

Several factors considered to be associated with an increased risk for single ventricle palliation include anatomic variants such as aortic atresia, mitral atresia, ascending aorta less than 2.0 to 2.5 mm, restrictive atrial septum, obstructed pulmonary venous return, the presence of other congenital anomalies, prematurity, birth

weight less than 2.5 kg, older age at time of surgery (>14 days), surgical inexperience, and prolonged CPB and arrest times. Perioperative factors can adversely affect outcome and include preoperative metabolic acidosis, preoperative inotrope support, morphologic RV in the systemic circuit, right ventricular dysfunction, presence of severe tricuspid regurgitation, pulmonary valve regurgitation (beyond mild), and low mixed venous oxygen saturation ($S\bar{v}O_2$) (<30%) after a Norwood procedure.[35-41] Neurologic outcome after surgical repair is an ongoing concern. Preoperative cerebral blood flow (CBF) was shown to be diminished in patients with a variety of congenital heart defects, and low CBF values were associated with periventricular leukomalacia.[42] Some centers routinely advocate regional low-flow cerebral perfusion and measurement of regional cerebral O_2 saturation index and CBF velocity using transcranial Doppler imaging during arch reconstruction in this population. Reductions in the regional cerebral O_2 saturation index or CBF greater than 20% of baseline are treated aggressively in an attempt to increase cerebral O_2 delivery by increasing the mean perfusion pressure, red blood cell (RBC) transfusion, and maintenance of high normal levels of $Paco_2$ to achieve cerebral vasodilation.

Surgical management has evolved in a broader application of certain surgical procedures initially designed for a specific defect. For example, modifications of the Fontan operation, which was originally devised for patients with tricuspid atresia, are now being used to repair a variety of univentricular hearts, including hypoplastic left heart syndrome.[43,44] Initially, the wider application of the Fontan operation to include complex defects once considered inoperable was associated with a rise in morbidity and mortality. However, this trend has been reversed in recent years by several groups who have demonstrated improved outcome with the staging of the operation (superior cavopulmonary anastomosis, subsequent completion of the Fontan operation), the creation of a fenestration between the RA and LA at the time of the Fontan operation, and the use of modified ultrafiltration (MUF) at least in the early years.[45] The communication allows for right-to-left shunting, thereby preserving cardiac output at lower systemic venous pressure in the early postoperative period. When necessary, once the patient has convalesced from the acute postoperative changes, the fenestration can be closed at the bedside with a snare placed at the time of the operation or in the catheterization laboratory with a clamshell device. In a substantial proportion of cases, these fenestrations close spontaneously without further intervention. However, as these patients grow older, they present with the unique pathophysiologic challenges of refractory arrhythmias, the failing single ventricle, protein-losing enteropathy, and plastic bronchitis. Most of these adults are cared for in a combined pediatric and adult cardiac program and require intensive multidisciplinary care to optimize cardiorespiratory status. Ingenuity and innovation such as demonstrated with the difficult Fontan procedure have permitted continued improvements in survival for all patients with CHD. As incisions in the myocardium become smaller and sutures more precisely placed, and as improvements in surgical techniques continue to evolve, the complications of ventricular dysfunction, arrhythmias, and residual obstruction should decline, contributing to improved patient quality of life.

One final difference unique to congenital heart surgery that has a major impact on anesthetic management relates to the type of cardiopulmonary support. Because of the complexity of repair in small patients, surgery often requires significant alterations in the bypass techniques, such as the use of deep hypothermic CPB at temperatures of 18° C and total circulatory arrest. Many operations are undertaken in this setting of extreme biologic conditions of temperature and perfusion. Current methods of CPB management in neonates, infants, and children involve extensive alterations in temperature, hemodilution, systemic perfusion pressure, and flow. Despite widespread use of these techniques during CPB, their physiologic effects on major organ system function are just beginning to be understood. These effects are discussed in subsequent sections.

In summary, unique features in caring for children with CHD who are undergoing pediatric cardiac surgery must be considered. These features include the patient's growth and development, the developing cardiovascular system of the young, the pathophysiology of CHD, the surgical procedures, and the CPB techniques. A basic understanding of these differences coupled with the fundamental knowledge of adult and pediatric cardiac anesthesia principles underlies the approach to successful perioperative management of these patients.

ANESTHETIC MANAGEMENT

PREOPERATIVE MANAGEMENT

Anesthetic Evaluation

Caring for children with CHD presents the anesthesiologist with a wide spectrum of anatomic and physiologic abnormalities (see also Chapter 96). Patients range from young, healthy, asymptomatic children who are having closure of a small ASD to the neonate with hypoplastic left heart syndrome requiring aggressive perioperative hemodynamic and ventilatory support. Intertwined with the medical diversity of these patients are the psychological factors affecting both the patient and the parents. Preparation of the patient and the family is time-consuming, but omitting or compromising this aspect of patient care is a major deterrent to a successful outcome and patient and parental satisfaction. This team-oriented approach also serves as a safeguard to prevent errors and omissions in the exacting perioperative care necessitated by the complexity of cardiac surgery for CHD. The preoperative visit offers the family the opportunity to meet the surgeon and anesthesiologist.

Parents should be questioned about the general health and activity of their child. Fundamentally, a child's general health and activity will reflect cardiorespiratory reserve. Deficiencies may point toward cardiovascular or other systems that may influence anesthetic or surgical risk. Whether the child has an impaired exercise tolerance is important. Is the child gaining weight appropriately or exhibiting signs of failure to thrive on the basis of cardiac cachexia? Does the child exhibit signs of CHF

TABLE 94-5 **COMMON PERIOPERATIVE MEDICATIONS AND CONSIDERATIONS**

Cardiac Drug Class	Interactions	Considerations
Angiotensin-converting enzyme inhibitors	Hypotension with induction of general anesthesia	Consider withholding morning dose, or reducing dosage, in hypotensive patients; avoid fixed dose induction regimens with drugs having a profound vagomimetic effect
β-Blockers	Acute withdrawal can precipitate tachycardia and arrhythmias; can potentiate hypotension with volatile anesthesia; can decrease response to inotropic agents	Continue in the perioperative period
Calcium channel blockers	May augment the negative inotropic and chronotropic effects of volatile anesthesia	Continue in the perioperative period
Diuretics	Hypovolemia/hypokalemia; may augment effect of neuromuscular blocking agents	Discontinue preoperatively
Antiarrhythmics	Can be proarrhythmic with inotropes, electrolyte disturbances; high catecholaminergic states; can interact with other antiarrhythmics and precipitate bradycardia	Avoid electrolyte imbalance Avoid drugs that are proarrhythmic Monitor carefully
α_2-Agonists	Reduces perioperative shivering, ischemia, anesthetic and analgesic requirements	Continue into the perioperative period with appropriate monitoring

(diaphoresis, tachypnea, poor feeding, recurrent respiratory infections)? Is there progressive cyanosis or new onset of cyanotic spells? Any intercurrent illness such as a recent upper respiratory tract infection or pneumonia must be ascertained. Lower respiratory tract infections may require a delay in proposed surgery, based on the negative impact that airway reactivity and elevations in PVR may have on surgical outcome. Recurrent pneumonia is frequently associated with pulmonary overcirculation and altered lung compliance in patients with increased PBF.

A good history must delineate previous surgical and cardiologic interventions. These may have an impact on both surgical and anesthetic plans for the current procedure. Patients who have had their subclavian artery sacrificed for a subclavian flap angioplasty to correct coarctation or a Blalock-Taussig shunt will not accurately display systemic arterial pressure or perhaps even pulse oximetry readings when the monitoring is applied to the left arm. Likewise, children who have femoral venous occlusion after catheterization are not candidates for femoral venous access, particularly for femoral CPB should sternotomy prove impossible. It is equally important to ascertain current medications, previous anesthetic problems, and family history of anesthetic difficulties.

In the modern era of echocardiography and cardiac catheterization, physical examination rarely contributes additional anatomic information about the underlying cardiac lesion. However, it is extremely useful in assessing the overall clinical condition of the child. For example, an ill-appearing, cachectic child in respiratory distress has limited cardiorespiratory reserve and the use of excessive premedication or a prolonged inhaled induction of anesthesia could result in significant hemodynamic instability.

Concurrent Medications and Drug Interactions

Drug interactions are common both among the cotherapeutic cardiovascular agents and between cardiovascular drugs and anesthetic drugs (see also Chapter 93). An understanding of the mechanisms and of the interactions is useful to the pediatric cardiovascular anesthesiologist. Some common cardiovascular medications and anesthesia considerations are shown in Table 94-5.

Pediatric oncology patients presenting for cardiac or noncardiac procedures may manifest higher cardiovascular risk because of cardiotoxic chemotherapy.[46] Common cardiotoxic agents include the antimetabolite 5-fluorouracil, the anthracycline antibiotics doxorubicin and daunorubicin, and the alkylating agent cyclophosphamide. The acute form of toxicity is characterized by acute ST segment/T wave changes on the electrocardiogram (ECG), serious dysrhythmias, and CHF associated with pericardial effusion. Chronic cardiotoxic heart failure is cumulative, dose related, and unresponsive to digoxin therapy. Serious cardiomyopathy can occur and is related to dose, irradiation, and use of an anthracycline. The mortality rate can exceed 50%. These patients should undergo thorough preoperative evaluation, including a full blood cell count, assessment of renal and hepatic function and coagulation parameters, and an echocardiogram. An isoflurane/nitrous oxide (N_2O)-based anesthetic might confer better hemodynamic stability than opioid-based anesthesia in such patients.[47]

Anesthetics can cause torsade de pointes, a malignant arrhythmia. Risk factors for torsade de pointes include female gender, electrolyte imbalances such as hypokalemia and hypomagnesemia, genetic ion channel polymorphisms of congenital long QT syndrome (LQTS), subclinical LQTS, baseline QT prolongation, and use of QT-prolonging drugs especially in high concentrations or as rapid intravenous infusions. Conditions with reduced repolarization reserve such as CHF or digoxin toxicity can precipitate torsade de pointes. Drugs that may cause torsade de pointes in patients with congenital LQTS are shown in Table 94-6. The website http://www.qtdrugs.org provides an updated list of drugs that prolong the QT interval.

Laboratory evaluation should include analysis of hemoglobin, hematocrit, pulse oximetry, and, in selected patients (e.g., those on diuretics or with renal impairment), serum electrolytes. An increased hematocrit in a normovolemic child gives an indication of the magnitude and chronicity of hypoxemia. A hematocrit

TABLE 94-6 DRUGS THAT MAY CAUSE TORSADE DE POINTES IN PATIENTS WITH CONGENITAL LONG QT SYNDROME

Drug Category	Drug Name
Antiarrhythmics	Amiodarone
	Procainamide
	Disopyramide
	Ibutilide
	Quinidine
	Sotalol
Antipsychotics	Chlorpromazine
	Haloperidol
	Thioridazine
	Mesoridazine
Antimicrobials	Erythromycin
	Clarithromycin
Miscellaneous	Cisapride
	Arsenic
	Methadone
	Droperidol
	Domperidone
	Dolasetron
	Ondansetron
	Glycopyrrolate

more than 60% may predispose to capillary sludging and secondary end organ damage, including stroke. Despite these risks, liberalized guidelines for nothing by mouth that permit children to consume clear liquids up to 2 hours before anesthetic induction have virtually eliminated the need to admit these patients to the hospital early for preoperative intravenous hydration.[48,49]

Echocardiography with Doppler color flow imaging (echo-Doppler) is an invaluable tool that provides a noninvasive means of assessing intracardiac anatomy, blood flow patterns, and estimates of physiologic data.[50] For many cardiac defects, more invasive studies are generally not required if a good echocardiographic assessment is made. Echo-Doppler imaging is especially helpful for defining intracardiac abnormalities. Extracardiac abnormalities, such as pulmonary artery or vein stenosis, are more difficult to define by echo-Doppler and often require cardiac catheterization. The ability to interpret anatomy and physiology accurately requires a skilled echocardiographer, reaffirming the need for a well-integrated interactive team. Although the complexities posed by extreme anatomic variation and changing loading conditions render intraoperative echo-Doppler challenging even for experienced echocardiographers, the pediatric cardiac anesthesiologist should develop some familiarity with its capabilities and limitations so as to participate in critical intraoperative management decisions.

Magnetic resonance imaging (MRI) of the heart and major vessels has become a very useful noninvasive imaging tool in children with heart disease (see also Chapter 90). Typically, MRI is used for segmental description of cardiac anomalies; evaluation of thoracic aortic anomalies; noninvasive detection and quantification of shunts, stenoses, and regurgitations; evaluation of conotruncal malformations and complex anomalies; identification of pulmonary and systemic venous anomalies; and postoperative studies and evaluation of CHD in adult patients.[51] MRI is particularly useful in quantifying ventricular function, regional wall motion, valvular competence, and velocity flow mapping. It is especially useful for imaging the aortic arch, pulmonary arteries, and the mediastinal vessels in children with complex CHD. Lesions for which MRI provides accurate and useful information include coarctation of the aorta, anomalies of the pulmonary arteries, anomalous pulmonary venous connections and persistent left superior vena cava, and intracardiac baffles, conduits, and shunts. MRI is also useful in older patients with poor acoustic windows and patients with chest wall deformities.[51] It can be used as an alternative to cardiac catheterization in select patients. More recent developments have enabled the use of MRI to provide noninvasive assessment of coronary anomalies, myocardial perfusion defects, and the detection of conditions associated with myocardial scarring (e.g., arrhythmogenic RV dysplasia). These scans are prolonged and require absolute patient immobility, with control of ventilator parameters to obtain optimal images. Adenosine stress cardiac MRI is used to delineate areas of inducible ischemia. However, physiologic data such as O_2 saturations cannot be obtained with MRI. Anesthetic considerations remain the same as for all cardiac lesions, with the additional concerns for MRI safety and restricted access to an anesthetized patient with suboptimal monitors.

Cardiac catheterization remains the gold standard for assessing anatomy and physiologic function in CHD. Although many anatomic questions can now be reliably answered noninvasively, cases that present complex anatomic questions or those for which physiologic data are required, catheterization remains a vital tool. Important catheterization data for the anesthesiologist include the following:

1. Child's response to sedative medications
2. Pressure and O_2 saturation in all chambers and great vessels
3. Location and magnitude of intracardiac and extracardiac shunt ($\dot{Q}p/\dot{Q}s$)
4. PVR and SVR
5. Chamber size and function
6. Valvular anatomy and function
7. Distortion of systemic or pulmonary arteries related to prior surgery
8. Coronary artery anatomy
9. Anatomy, location, and function of previously created shunts
10. Acquired or congenital anatomic variants that might have an impact on planned vascular access or surgery

Careful review of the cardiac catheterization data and an understanding of their potential impact on the operative and anesthetic plan are essential. Not all the medical problems can be evaluated and corrected preoperatively; the surgeon, cardiologist, and anesthesiologist must discuss the potential management problems and any need for further evaluation or intervention before arrival in the operating room. Appropriate communication and cooperation between the two physicians will optimize patient care and facilitate perioperative clinical management. Typically, institutions have a regularly scheduled

combined cardiology and cardiac surgery meeting to discuss candidates for surgery, during which all essential information is displayed and discussed. Such a meeting provides an invaluable opportunity for learning about specific patients proposed for surgery and a continuing educational forum that promotes an interdisciplinary exchange directed at contemporary concepts in CHD and its treatment, both medical and surgical.

Premedication

See Chapter 93.

INTRAOPERATIVE MANAGEMENT

Operating Room Preparation

Advance, careful preparation of the operating room is essential (see also Chapter 92). The anesthesia machine must have the capacity to provide air, O_2, carbon dioxide (CO_2), NO, and N_2O to help balance pulmonary and systemic blood flow. Intravenous tubing must be free from air bubbles to prevent paradoxical air embolism. Resuscitative drugs, labeled and ready for administration, should include succinylcholine, calcium gluconate or calcium chloride, sodium bicarbonate, atropine, phenylephrine, lidocaine, and epinephrine. An inotropic infusion, usually dopamine, should be premixed and ready for administration in high-risk cases, but additional infusions are prepared if their need is strongly suspected. For all pediatric cases, certain anesthetic drugs should be available (etomidate, propofol, ketamine). In pediatric cardiac anesthesia, many patients have limited reserve and high endogenous catecholamine levels released in an adaptive response to their underlying cardiac disease. The resuscitative drugs should therefore be prepared and immediately available before anesthetic induction.

For congenital heart surgery, the ability to alter body temperature rapidly for cooling and rewarming is essential. During deep hypothermic CPB, patients are cooled to 18° C. Surface cooling with a heating and cooling water mattress and an efficient room and ambient temperature control system are important in the operative management of these patients (also see Chapter 54).

Physiologic Monitoring

The specific monitoring used should depend on the child's condition and the magnitude of the planned surgical procedure. The perioperative monitoring techniques available are listed in Box 94-2. Noninvasive monitoring equipment is placed before induction of anesthesia. In the crying pediatric patient, the anesthesiologist may elect to defer application of monitoring devices until immediately after the induction of anesthesia. Standard monitoring includes an electrocardiographic system, pulse oximetry, capnography, precordial stethoscope, and an appropriate-sized blood pressure cuff (either oscillometric or Doppler). Additional monitoring includes an indwelling arterial catheter, temperature probes, and an esophageal stethoscope. Foley catheters are generally employed when surgical intervention entails CPB or might produce renal ischemia or when the anesthetic management includes a regional technique associated with urinary retention.

BOX 94-2 *Monitoring of Organ Systems*

Cardiopulmonary System

Esophageal stethoscope
Electrocardiogram
  Standard seven-lead system, ST-T wave analysis, esophageal electrocardiographic lead
Pulse oximetry
Automated oscillatory blood pressure
Capnograph
Ventilator parameters
Indwelling arterial catheter
Central venous pressure catheter
Pulmonary artery catheter
Transthoracic pressure catheter
  Left or right atrium, pulmonary artery
Echocardiography with Doppler color flow imaging
  Epicardial or transesophageal

Central Nervous System

Peripheral nerve stimulator
Processed electroencephalography
Specialized
  Cerebral blood flow: Xenon clearance methodology
  Cerebral metabolism: Near-infrared spectroscopy, oxygen consumption measurements
  Transcranial Doppler
  Jugular venous bulb saturations

Temperature

Nasopharyngeal, rectal, esophageal, tympanic

Renal Function

Foley catheter

Some centers routinely employ central venous pressure (CVP) monitoring for major cardiovascular surgery. Alternatively, we typically use directly placed transthoracic atrial lines to obtain that information for separation from CPB and the postoperative period. In that setting, the benefits of the information or access provided by percutaneous CVP catheters in the prebypass period must be weighed against the risks they pose.

Continuous monitoring of arterial pressure is possible only through an indwelling intraarterial catheter. In young children, cannulation of the radial artery with a 22- or 24-gauge catheter is preferred. In older children and adolescents, a 20-gauge catheter may be substituted. Careful inspection, palpation, and four-extremity noninvasive blood pressure determinations help ensure that previous or currently planned operative procedures (e.g., a previous radial artery cutdown, subclavian flap for coarctation repair, or Blalock-Taussig shunt) do not interfere with the selected site of arterial pressure monitoring. Other sites available for cannulation include the ulnar, femoral, axillary, and umbilical (in neonates) arteries. Cannulation of the posterior tibial or dorsalis pedis arteries is not usually sufficient for complex operative procedures. Peripheral arterial catheters, principally of the distal lower extremities, function poorly after CPB and do not reflect central aortic pressure when distal extremity temperature remains low.[52]

Myocardial and cerebral preservation is maintained principally through hypothermia; therefore, the accurate

and continuous monitoring of body temperature is crucial. Rectal and nasopharyngeal temperatures are monitored because they reflect core temperature and brain temperature, respectively. Monitoring of esophageal temperature is a good reflection of cardiac and thoracic temperature. Tympanic probes, although a useful reflection of cerebral temperature, can cause tympanic membrane rupture.

Pulse oximetry and capnography provide instantaneous feedback concerning adequacy of ventilation and oxygenation. They are useful guides in ventilatory and hemodynamic adjustments to optimize $\dot{Q}p/\dot{Q}s$ before and after surgically created shunts and pulmonary artery bands. Peripheral vasoconstriction in patients undergoing deep hypothermia and circulatory arrest renders digital O_2 saturation probes less reliable. In the newborn, the use of a tongue sensor has been advocated to provide a more central measure of O_2 saturation, with less temperature-related variability.[53]

The use of transthoracic (in the RA, LA, pulmonary artery) or transvenous pulmonary artery catheters is determined on an individual basis based on the disease process, physiologic state, and surgical intervention. For example, in children undergoing a Fontan procedure for tricuspid atresia or a univentricular heart, catheters in the Fontan pathway and the pulmonary venous atrium are especially useful. After a Fontan operation, PBF must occur without benefit of a ventricular pumping chamber. Subtle changes in preload, PVR, and pulmonary venous pressure will influence PBF and thus systemic cardiac output. Data derived from systemic venous pressure and left atrial pressure (LAP) help identify the relative importance of intravascular volume (CVP), PVR (CVP-LAP gradient), or ventricular compliance (LAP), each of which requires a different therapeutic approach.

As a general guideline, a transvenous pulmonary artery catheter may be placed using the internal jugular approach in children weighing more than 7 kg. A 5.0-Fr catheter is used for children weighing between 7 and 25 kg, and a 7.0-Fr one is used for children weighing more than 25 kg. For infants weighing less than 7 kg, percutaneous placement of a pulmonary artery catheter can be performed from the femoral vein. Occasionally, the latter technique will require fluoroscopy. The use of intraoperative transthoracic monitoring lines and echo-Doppler imaging limits the need for transvenous pulmonary artery catheters in most cases.

Special Monitoring

Intraoperative Echocardiography. Of the newer techniques available for monitoring patients during pediatric cardiovascular surgery, the most promising is echo-Doppler imaging (see also Chapter 46). Several reports have described the usefulness of intraoperative echo-Doppler imaging during congenital heart surgery.[54-56] Two-dimensional echocardiography combined with pulsed-wave Doppler ultrasonography and color flow mapping is able to provide detailed morphologic as well as physiologic information in the majority of operative cases. Using echo-Doppler in the operating room, anatomic and physiologic data can be obtained before CPB, thus refining the operative plans. Prebypass echo-Doppler precisely defines anesthetic and surgical management.[9,54] Because of the unrestricted epicardial and transesophageal echocardiography (TEE) approaches in anesthetized patients, new findings are frequently discovered and management plans changed accordingly (Fig. 94-4).

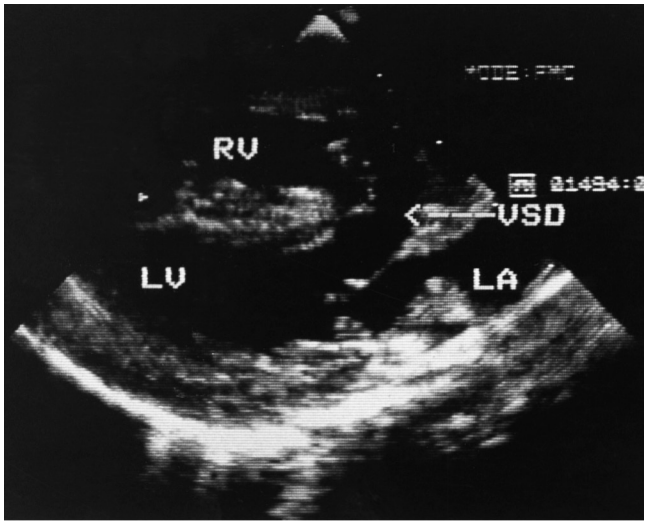


Figure 94-4. Intraoperative pre–cardiopulmonary bypass epicardial echocardiogram in the long-axis view. Note the insertion of the papillary muscle of the tricuspid valve on the interventricular septum. On the basis of this view, the surgeon decided that ventricular septal defect (VSD) closure was possible in a child thought preoperatively to be a candidate for only palliation. *LA,* Left atrium; *LV,* left ventricle; *RV,* right ventricle. (See also Chapter 46.)

Postbypass echo-Doppler evaluation is able to immediately assess the quality of the surgical repair and assess cardiac function by examining ventricular wall motion and systolic thickening.[9,54] This technique can show residual structural defects after bypass, which can be immediately repaired in the same operative setting and avoids leaving the operating room with significant residual structural defects that will require reoperation at a later time (Fig. 94-5). By identifying patients with new right ventricular and left ventricular contraction abnormalities after bypass, as determined by a change in wall motion or systolic thickening, echo-Doppler provides guidance for immediate pharmacologic interventions. Importantly, postbypass ventricular dysfunction and residual structural defects identified by echo-Doppler imaging are associated with an increased incidence of reoperation and higher morbidity and mortality rate.[57] Thus, this monitoring tool is helpful in assessing surgical outcome and identifying operative risk factors, which will hopefully improve outcomes.

Two techniques for intraoperative echo-Doppler imaging have been described: epicardial and transesophageal echocardiography. Using TEE, the probe is placed after induction of anesthesia and intubation and is then available for monitoring of the patient (see also Chapter 46). The advantage of this technique is its utility as a continuous monitor of cardiac structure and function, without interrupting surgery.[9,58] Because of its ideal imaging location, TEE has been especially helpful in evaluating pulmonary venous return and the integrity of the left AV valve after mitral valvuloplasty, complete AV valve repair, and correction of complex CHD. Early limitation in views

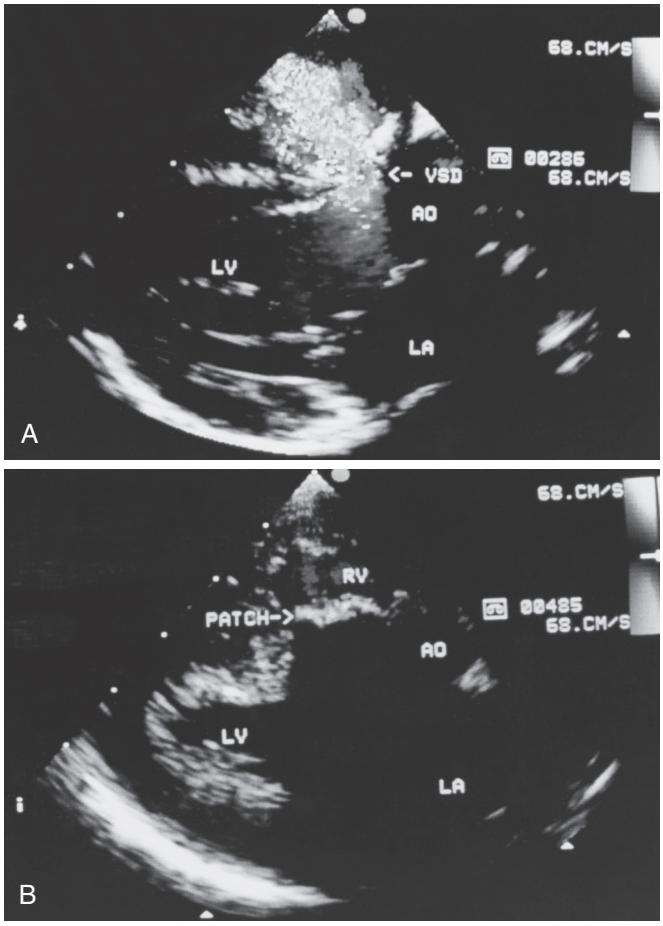


Figure 94-5. A, Echocardiogram with a Doppler flow map in the long-axis view illustrating a residual ventricular septal defect (*VSD*) resulting from patch dehiscence after initial repair. Turbulent flow through the VSD appears as a mosaic of white particles (*arrow*). This finding necessitated immediate reinstitution of cardiopulmonary bypass and repeat repair. **B,** Repeat Doppler flow map in the long-axis view illustrates patch closure (*arrow*) of the VSD after repeat repair. Note the absence of turbulent flow with the loss of the mosaic of white particles. *AO,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle.

has been virtually eliminated as a result of clinical experience and improved biplane images. Pediatric biplane TEE probes have now extended the patient weight limits to neonates between 2.5 and 3 kg.[59] Potential hazards of TEE that merit particular vigilance include descending aorta and airway compression because of probe size or during probe flexion. If TEE is indicated before repair, the probe is removed during the procedure because of concerns about esophageal damage during hypothermia and low or no flow states.

A second technique for intraoperative echocardiographic analysis in children is the epicardial approach.[54,59] This approach requires passing a clean, short-focused 5.0- or 7.0-MHz transducer over the anesthesia screen into a sterile sheath, where it then can be placed on the epicardial surface of the heart. This technique best facilitates the probe manipulations necessary for thorough interrogation of the major structures and dynamic function of the heart. The advantage of this approach is that all views can be obtained in patients of any size. Among the disadvantages are the need for sufficient operator skill and experience to perform the manipulations, the need to interrupt surgery to manipulate the probe, and the possible deleterious impact of direct myocardial mechanical manipulation.[57] With the current TEE capabilities, epicardial imaging is rarely employed.

Specialized Central Nervous System Monitoring. The primary goal of brain monitoring is to improve our understanding of cerebral function and dysfunction during cardiac surgery so that effective brain protection strategies can be developed. Because many of the determinants of normal brain perfusion become externally controlled by the cardiac team during CPB, such as flow rate (cardiac output), perfusion pressure, temperature, hematocrit, and $Paco_2$, a knowledge of the effect of these factors on the brain in neonates, infants, and children is essential. Furthermore, the examination of the brain under unusual biologic circumstances, such as after deep hypothermic circulatory arrest (DHCA) or during continuous-flow CPB at deep hypothermia (18° C), permits a unique opportunity to describe cerebrovascular physiology and pathophysiology. Numerous intraoperative techniques have been used for monitoring the brain to prevent secondary brain injury from hypoxia, ischemia, emboli, and electrophysiologic derangements (see Chapter 49). These have primarily included the following three modalities in isolation or combination: (1) near-infrared spectroscopy (NIRS) to provide a measure of venous-weighted, tissue oxyhemoglobin saturation; (2) transcranial Doppler imaging to measure arterial flow and resistance; and (3) electroencephalography (EEG) to assess perfusion-related changes in cortical activity.[60] Additionally, the measurement of CBF and metabolism with specialized clinical research tools has been very important in furthering our understanding of brain function during and after surgery. Multimodal neurologic monitoring is also used to guide the conduct of CPB, DHCA, and regional low-flow cerebral perfusion techniques in neonatal arch reconstruction.[61-63]

Electroencephalographic monitoring allows detection of ischemia or recognition of an adequate decrease in cerebral metabolic activity during hypothermia before DHCA. EEG is helpful in monitoring physiologic functions of the CNS during deep hypothermic bypass and total circulatory arrest. For example, during deep hypothermia and before total circulatory arrest, the processed EEG can identify residual cerebral electrical activity. Isoelectric silence can then be induced by further cooling and any further brain activity detected by EEG. Because this residual electrical activity during arrest is associated with ongoing cerebral metabolism, an isoelectric state may prevent ischemic injury to the brain during circulatory arrest. EEG also may be useful in detecting the level and depth of anesthesia. Postoperative electroencephalographic analysis has demonstrated subclinical seizure activity in a number of high-risk patients, potentially linking these abnormalities to poorer neuropsychologic outcome. The value of intraoperative electroencephalographic monitoring after CPB and the significance of the findings remains to be determined.

Transcranial Doppler imaging has been used primarily for research purposes in infants and allows detection

of venous or arterial flow abnormalities and the detection of microemboli.[64] This technology uses the Doppler principle to detect shifts in the frequency of reflected signals from blood in the middle cerebral artery to calculate blood flow velocity.[65] Because the diameter of this large cerebral artery is relatively constant, flow velocity should approximate that of CBF. Transcranial Doppler imaging has several advantages: (1) it is noninvasive, (2) it does not require radiation exposure, and (3) it is a continuous monitor. An additional advantage of this technique is the capability of assessing rapid alterations in blood flow velocity caused by temperature or perfusion changes, as commonly occur during cardiac surgery. The limitations of transcranial Doppler monitoring include (1) reproducibility, especially at low flow rates, when minute movement of the patient's head can dramatically alter signal intensity and alter baseline measurements, and (2) the lack of validating studies during hypothermic CPB, when temperature, reduced flow rates, and the laminar flow characteristics of nonpulsatile perfusion may limit the accuracy of CBF velocity measurements. CBF velocity measurements by TCD have reasonable correlation with more standard measures of CBF during normothermia, and some studies have examined its validity during hypothermic CPB.[66]

Transcranial Doppler imaging has been used to investigate the effect of CPB and DHCA on cerebral hemodynamics in children, as well as to assess the incidence of cerebral emboli. Recent studies examining the brain using TCD have enabled several investigative groups to provide important information regarding questions of normal and abnormal brain perfusion during cardiac surgery in children. Questions regarding cerebral perfusion pressure, autoregulation, effect of $Paco_2$, and temperature have been addressed using transcranial Doppler imaging in children and are discussed subsequently.[66-68] This technique also has provided qualitative information regarding the presence of gaseous emboli in the middle cerebral artery during cardiac surgery.[69] Quantification of this important mechanism of cerebral injury during cardiac surgery would be instructive. Future investigations using transcranial Doppler should address this mechanism of injury, as well.

Centers with excellent outcomes may report "never" or "always" using NIRS during the perioperative care of neonates with CHD. Given that cerebral NIRS values have been shown to correlate with jugular venous bulb saturations, the interest in using NIRS as a way to noninvasively assess O_2 delivery to the brain is sensible.[70] Austin and associates reported the value of monitoring cerebral NIRS intraoperatively. They noted that cerebral oxyhemoglobin desaturation accounted for a majority of neurophysiologic abnormalities during multimodality neuromonitoring using NIRS, transcranial Doppler, and EEG.[71] Over two thirds of the patients in their study had detectable neuromonitoring events, and a similar percentage of these events required intervention by the perfusionist, surgeon, or anesthesiologist. Surgical interventions, such as cannula repositioning, were performed in one fourth of the events, and the perfusionist intervened in over half of the events. The incidence of postoperative neurologic sequelae was also higher in those patients who had untreated events. During some specific surgical techniques, such as regional cerebral perfusion, NIRS monitoring may be of benefit in guiding intraoperative care.[72,73] However, improved neurodevelopmental outcomes postoperatively has not been demonstrated.

CBF studies using xenon clearance technology have improved the understanding of cerebrovascular dynamics in young children during CPB and especially during deep hypothermia and after periods of circulatory arrest.[74-77] In general, this investigational tool has described the effects of CPB, temperature, and various perfusion techniques on CBF and, indirectly, on brain metabolism (Fig. 94-6). Studies using this methodology have shown that some of the mechanisms of CBF autoregulation, such as pressure-flow regulation, are lost with deep hypothermia and that cerebral reperfusion is impaired after a period of total circulatory arrest.

Induction and Maintenance of Anesthesia

The principles of intraoperative management of cardiothoracic surgical procedures are based on an understanding of the pathophysiology of each disease process and a working knowledge of the effects of the various anesthetic and other pharmacologic interventions on a particular patient's condition (see also Chapter 92). Selecting a technique for induction of anesthesia depends on the degree of cardiac dysfunction, the cardiac defect, the degree of sedation provided by the premedication, and the presence or absence of an indwelling catheter. In children with good cardiac reserve, induction techniques can be quite varied in well-monitored patients. The titration of anesthetics for induction of anesthesia is more important than the specific anesthetic technique in patients

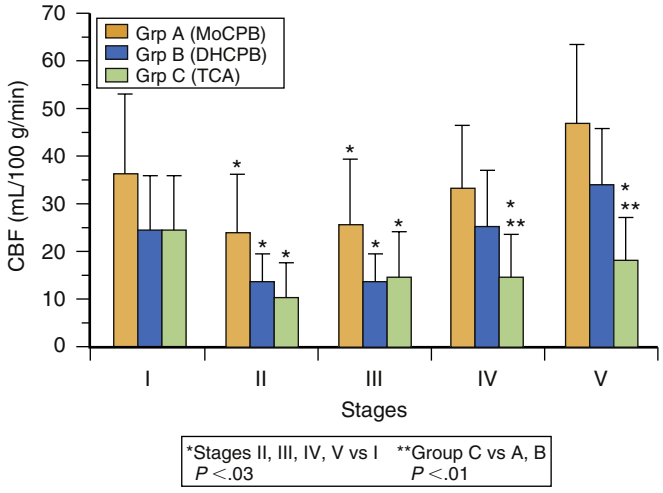


Figure 94-6. Bar chart of the changes in cerebral blood flow (*CBF*) before, during, and after cardiopulmonary bypass (*CPB*) in 67 infants and children (mean ± SD). Group A underwent repair with moderate hypothermic bypass (*MoCPB*) at 28° to 32° C; group B, with deep hypothermic bypass at 18° to 22° C; and group C, with total circulatory arrest (*TCA*) at 18° C. Note the impaired cerebral reperfusion after total circulatory arrest (group C). Stage I, prebypass; stages II and III, during hypothermic bypass; stage IV, rewarmed on bypass; stage V, after bypass. *(From Greeley WJ, Brusino FG, Ungerleider RM, et al: The effects of cardiopulmonary bypass on cerebral blood flow in neonates, infants, and children,* Circulation *80:I209, 1989.)*

with reasonable cardiac reserve. A wide spectrum of anesthetic induction techniques have been used safely and successfully, such as sevoflurane, isoflurane, and N_2O; intravenous and intramuscular ketamine; and intravenous propofol, fentanyl, and midazolam.[78] For neonates undergoing open-heart surgery, opioid-relaxant inductions are most prevalent, whereas older children with sufficient cardiac reserve typically receive inhaled inductions with either sevoflurane or halothane. Ketamine is often used in anesthetic induction in patients with cyanotic conditions because it increases SVR and cardiac output, thereby diminishing the magnitude of right-to-left shunting. Administration of ketamine can be intravenous or intramuscular. An intramuscular injection may result in pain, agitation, and subsequent arterial desaturation.

Inhaled inductions are generally well received and tolerated by most children. An inhaled induction of anesthesia with sevoflurane can easily and safely be performed even in cyanotic patients, such as those with TOF (Fig. 94-7). In these patients, who are at risk for right-to-left shunting and systemic desaturation, oxygenation is well maintained with a good airway and ventilation despite halothane-induced reduction in systemic arterial pressure.[79] Skilled airway management and efficiency of ventilation are equally essential components of anesthetic induction. Yet the complexities of shunts and vascular resistance changes, as well as airway and ventilation effects on the cardiovascular system, are of primary importance during the induction of anesthesia.

After anesthetic induction, intravenous access is established or augmented as appropriate. A nondepolarizing muscle relaxant is usually administered and an intravenous opioid or inhaled anesthetic or both chosen for maintenance anesthesia. The child is preoxygenated with 100% FiO_2, and a lubricated nasal endotracheal tube is carefully positioned. A nasal tube is usually selected because in most patients who require an intraoperative TEE, postoperative mechanical ventilation, or both, a nasotracheal tube provides greater stability and patient comfort than with the oral route. Some degree of alveolar preoxygenation is recommended, even in the infant whose systemic perfusion might be jeopardized by lowering PVR with resulting increase in PBF. This maneuver delays desaturation during intubation. If the child arrives in the operating room with an endotracheal tube in place, it is our practice to change it. Inspissated secretions in a tube with a small internal diameter can cause significant obstruction to gas flow. During periods of bypass when humidified ventilation is discontinued, significant endotracheal tube obstruction can occur. This can be minimized by placing a new endotracheal tube at the beginning of the procedure.

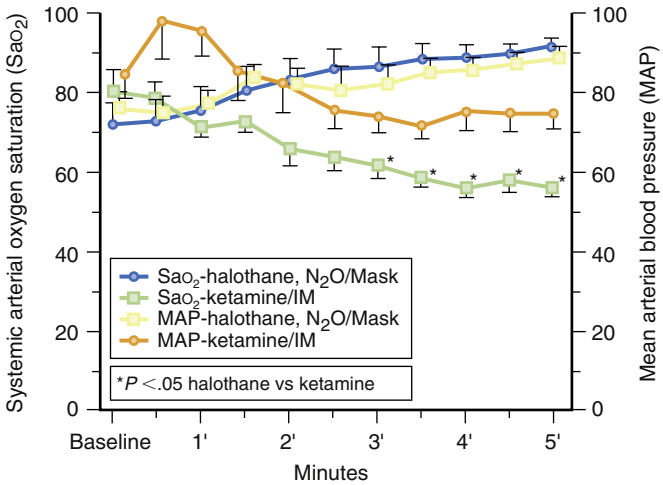


Figure 94-7. Comparative changes in arterial oxygen saturation (Sao_2) and mean arterial pressure (*MAP*) during mask halothane nitrous oxide ($n = 7$) and intramuscular ketamine ($n = 7$) inductions in children with tetralogy of Fallot (TOF) at risk for right-to-left shunting. Note the maintenance of Sao_2 in the halothane group despite the significant drop in MAP. *(From Greeley WJ, Bushman GA, Davis DP, et al: Comparative effects of halothane and ketamine on systemic arterial oxygen saturation in children with cyanotic heart disease,* Anesthesiology *65:666, 1986.)*

Because of the diverse array of congenital heart defects and surgical procedures, an individualized anesthetic management plan is essential. The maintenance of anesthesia in these patients depends on the age and condition of the patient, the nature of the surgical procedure, the duration of the CPB, and the need for postoperative ventilation. An assessment of the hemodynamic objectives designed to lessen the pathophysiologic loading conditions should be developed for each patient, taking advantage of the known qualitative effects of specific anesthetic drugs and ventilatory strategies. These individualized plans must also be integrated with the overall perioperative goals to configure the optimal anesthetic. In patients with complex defects requiring preoperative inotropic and mechanical ventilatory support, a carefully controlled hemodynamic induction and maintenance anesthetic with a potent opioid is generally chosen. In patients with a simple ASD or VSD, a potent inhaled anesthetic is preferred. This allows for early postoperative tracheal extubation and a less prolonged period of intensive care monitoring. More important than the specific anesthetic techniques and drugs is the skilled execution of the anesthetic plan, taking into account patient response to drugs, the changes associated with surgical manipulation, and early recognition of intraoperative complications.

The reported changes in arterial blood pressure and heart rate from the inhaled anesthetic in normal children are observed in pediatric cardiac surgical patients as well (see Chapter 92). Although both halothane and isoflurane decrease blood pressure in neonates, infants, and children, the vasodilatory properties of isoflurane may improve overall myocardial contractility in contrast to the effects of halothane.[80] Despite improved cardiac reserve with isoflurane, the incidence of laryngospasm, coughing, and desaturation during induction of anesthesia limits its use as an induction agent in children with congenital heart defects.[81] The use of potent inhaled anesthetics as primary anesthetics should be reserved for the child with adequate cardiovascular reserve who is a candidate for early postoperative extubation. In these patients, the myocardial depression and hypotension associated with the use of inhaled anesthetics are well tolerated. Examples include closure of an ASD or VSD, excision of a discrete subaortic membrane, pulmonic or

aortic stenosis, TOF, shunts, ligation of a PDA, and repair of coarctation of the aorta.

Desflurane has cardiorespiratory properties similar to those of isoflurane (also see Chapters 47 and 28).[82] Its main advantage is low blood gas and tissue solubility. This allows for rapid equilibration between the inspired and alveolar concentrations and rapid decrease of alveolar concentrations during elimination.[83] This provides greater precision in drug dosing during the operative period and may make desflurane a more titratable adjunctive drug for pediatric cardiac anesthesia. The three main disadvantages of desflurane are potency, pungency, and negative inotropic effect.[84,85] Studies in normal infants and children suggest that 1 minimum alveolar concentration (MAC) of desflurane requires concentrations of 8% to 10%.[86,87] Desflurane is also quite pungent, and, although its uptake is rapid, early experience with this drug for inhalation induction in children has reported a fairly high incidence of airway reactivity and laryngospasm.[87-89] Although its negative inotropic effect is significantly less potent than that of halothane, desflurane should not be used as the sole anesthetic in patients with significant cardiac dysfunction.[89]

Sevoflurane offers a more tolerable aroma without the magnitude of myocardial depression that accompanies halothane.[90] In addition, its blood gas solubility is nearly as low as that of desflurane. Hemodynamically, sevoflurane tends to produce some tachycardia, particularly in older children, and preserve systemic arterial pressure.[91] Reductions in heart rate and systemic arterial pressure are more modest in infants anesthetized with sevoflurane than in control subjects anesthetized with halothane, and the former exhibit echocardiographic evidence of normal contractility and cardiac index. This effect is particularly seen in children with trisomy 21.[92,93] Controversies continue to surround the potential toxic by-products of sevoflurane anesthesia, related to both patient metabolism and the production of compound A in the anesthesia breathing circuit. Although the importance of compound A in adult practice remains unclear, evidence suggests that production of this toxin is significantly diminished in children.[94]

Children with complex CHD and limited cardiac reserve demand an anesthetic technique that provides hemodynamic stability. Inhalation anesthetics are less well tolerated as a primary anesthetic in patients who have limited cardiac reserve, especially after CPB. Fentanyl is an excellent induction and maintenance anesthetic for this group of patients. Low-to-moderate doses of this opioid can be supplemented with inhalation anesthetics. Adding low concentrations of inhalation anesthetics to smaller doses of opioids shortens or eliminates the need for postoperative mechanical ventilation while maintaining the advantage of intraoperative hemodynamic stability. Postoperative mechanical ventilation will be required when a high-dose opioid technique is used. The hemodynamic effects of fentanyl at a dose of 25 µg/kg with pancuronium given to infants in the postoperative period after operative repair of a congenital heart defect include no change in LAP, pulmonary artery pressure, PVR, and cardiac index and a small decrease in SVR and mean arterial pressure.[95] Because of its cardiovascular effects, pancuronium was an ideal neuromuscular blocking drug for pediatric heart surgery. Unfortunately, pancuronium is no longer available for clinical use. Therefore, either vecuronium or rocuronium must be used (also see Chapter 34). Larger doses of fentanyl at 50 to 75 µg/kg with rocuronium or vecuronium doses of fentanyl at 50 to 75 µg/kg with pancuronium result in a slightly larger decrease in arterial blood pressure and heart rate in infants undergoing repair for complex congenital heart defects.[96] Despite the wide safety margin exhibited by this opioid, a selected population of infants and children with marginally compensated hemodynamic function sustained by endogenous catecholamines may manifest more extreme cardiovascular changes with these doses. Fentanyl also has been shown to block stimulus-induced pulmonary vasoconstriction and contributes to the stability of the pulmonary circulation in neonates after congenital diaphragmatic hernia repair.[97] Thus, the use of fentanyl may be extrapolated to the operating room, where stabilizing pulmonary vascular responsiveness in newborns and young infants with reactive pulmonary vascular beds is crucial to weaning from CPB and stabilizing shunt flow. Fentanyl in the 5 to 10 µg/kg dose range should provide some analgesia, but still sufficient ventilation to allow for postoperative extubation with stable hemodynamics during the procedure.

Historically, sufentanil and pancuronium have provided the same cardiovascular stability as with fentanyl and pancuronium in pediatric cardiovascular patients. As previously indicated, the lack of availability of pancuronium requires its replacement by vecuronium or rocuronium. Children receiving sufentanil for induction of anesthesia as a single dose of 5 to 20 µg/kg have a stable preintubation period.[98,99] Intubation and other stimuli such as sternotomy do not produce clinically significant alterations in hemodynamics, although changes are more than with equipotent doses of fentanyl. The use of fentanyl as an infusion (0.1 µg/kg/minute) produces fewer alterations in heart rate and blood pressure. This is particularly important in infants, in whom significant hemodynamic changes are poorly tolerated. For neonates with critical CHD, sufentanil anesthetic and postoperative infusion reduce morbidity after cardiac surgery when compared with a halothane anesthetic and routine morphine postoperatively.[100] The blunting of the stress response observed in this study probably accounted for the differences in morbidity; no comparison group representing a more typical dose of a phenylpiperidine opioid (e.g., fentanyl, 0 to 75 µg/kg) was included to permit conclusions as to whether such large opioid doses are optimal.

In contrast to other opioids (see also Chapter 31), remifentanil, an ultra–short-acting opioid, offers the unique advantage of metabolism by nonspecific and tissue esterases, thereby limiting the potential for accumulation related to protracted elimination.[101] Remifentanil may provide advantages in the selected group of patients for whom the blunting of endogenous responses is desirable intraoperatively but potentially deleterious at the end of the procedure. A randomized controlled trial comparing equipotent doses of alfentanil and remifentanil for outpatient pediatric surgery revealed delayed emergence, requiring naloxone only in the alfentanil group.[104] In both adults and children, remifentanil is associated with qualitative hemodynamic changes similar to those with other opioids, a variable tendency to bradycardia, and a small decrease in arterial blood pressure.[102-105]

TABLE 94-7 SUFENTANIL PHARMACOKINETICS IN PEDIATRIC CARDIOVASCULAR PATIENTS*

Age Group	$t_{½}\ \alpha$ (min)	$t_{½}\ \beta$ (min)	Clearance (mL/kg/min)	Vdss (L/kg)
1-30 days	23 ± 17	737 ± 346	6.7 ± 6.1	4.2 ± 1.0
1-24 mo	16 ± 5	214 ± 41	18.1 ± 2.7	3.1 ± 1.0
2-12 yr	20 ± 6	140 ± 30	16.9 ± 2.2	2.7 ± 0.5
12-18 yr	20 ± 6	209 ± 23	13.1 ± 0.4	2.7 ± 0.5

$t_{½}\ \alpha$, Slow distribution half-life; $t_{½}\ \beta$, elimination half-life; *Vdss,* volume of distribution at steady state.
*All values are mean ± standard deviations (see reference 38).

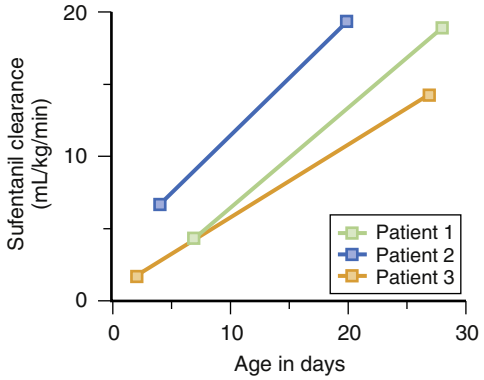


Figure 94-8. Sequential sufentanil clearance during the first month of life in three neonates with congenital heart disease. Clearance of sufentanil increases above adult rates within the neonatal period. *(Data from Greeley WJ, de Bruijn NP: Changes in sufentanil pharmacokinetics within the neonatal period,* Anesth Analg *67:86, 1988.)*

Because of the widespread use of the opioids for pediatric cardiac surgery and the availability of invasive monitoring, the pharmacokinetics and pharmacodynamics of these drugs have been well studied.[98,104] In general, the clinical pharmacology of fentanyl and sufentanil share the same age-related pharmacokinetic and pharmacodynamic features. For example, sufentanil has increased clearance in patients 1 month to 12 years of age, comparable adult clearance in adolescents (12 to 16 years of age), and decreased clearance during the neonatal period (newborn to 1 month of age) (Table 94-7).[88,92] Furthermore, sequential sufentanil anesthetics in neonates with CHD show marked increases in clearance and elimination between the first week and the third or fourth week of life (Fig. 94-8).[94] The latter observation is most likely attributable to maturational changes in hepatic microsomal activity and improved hepatic blood flow from closure of the ductus venosus. The variability in clearance and elimination, coupled with limited cardiovascular reserve in the neonate during the first month of life, makes opioid dosing difficult in this age group. Careful titration of fentanyl 5 to 10 µg/kg of or sufentanil 1 to 2 µg/kg of or a continuous infusion technique provides the most reliable method of achieving hemodynamic stability and an accurate dose response. CPB, different institutional anesthetic practices, and individual patient differences influence pharmacokinetic and pharmacodynamic disposition of the opioids in ways that are not predictable. Even certain disease states such as TOF or pathophysiologic conditions such as increased intraabdominal pressure alter pharmacokinetic processes.[95,96]

Dexmedetomidine is an α_2-agonist approved by the U.S. Food and Drug Administration for sedation in adults. It has been used in pediatric anesthesia as part of a balanced technique preoperatively and intraoperatively for sedation and anxiolysis and postoperatively for prevention of emergence delirium and sedation.[106] Potts and colleagues[107] summarized the pharmacokinetic data of dexmedetomidine in children and found it to possess a larger volume of distribution, delayed elimination, and decreased clearance with significant interpatient variability in younger patients in contrast to adults. The pharmocodynamic effects of dexmedetomidine may be significant and should be kept in mind by the anesthesiologist when used in pediatrics. Hypotension and bradycardia are two of the most commonly reported effects of dexmedetomidine in children, although hypertension may be common as well.[108] Dexmedetomidine is known to demonstrate significant cardiac conduction effects, primarily bradycardia via depression of the sinus and AV node.[109] It is recommended that dexmedetomidine be used with caution in children at risk for bradycardia or sinus or AV node dysfunction. Dexmedetomidine also has been used as an adjunctivant for pain control in adults, although data supporting its use in children are lacking.[110] At our institution, dexmedetomidine is used primarily for postprocedural sedation. Dexmedetomidine 0.5 to 1 µg/kg may be given as a loading dose slowly over 10 minutes. Infusions are often started at 0.3 to 1 µg/kg/hr if prolonged sedation is desired postoperatively.

CARDIOPULMONARY BYPASS

DIFFERENCES BETWEEN ADULT AND PEDIATRIC CARDIOPULMONARY BYPASS

The physiologic effects of CPB on neonates, infants, and children are significantly different from the effects on adults (Table 94-8) (see also Chapter 66). During CPB, pediatric patients are exposed to biologic extremes not seen in adults, including deep hypothermia (18° C), hemodilution (threefold to fivefold greater dilution of circulating blood volume), low perfusion pressures (20 to 30 mm Hg), wide variation in pump flow rates (ranging from 200 mL/kg/minute to total circulatory arrest), and differing blood pH management techniques (α-stat, pH-stat, or both sequentially). These parameters significantly differ from those of normal physiology and affect preservation of normal organ function during and after CPB. In addition to these prominent changes, subtle variations in glucose supplementation, cannula placement, presence

TABLE 94-8 DIFFERENCES BETWEEN ADULT AND PEDIATRIC CARDIOPULMONARY BYPASS

Parameter	Adult	Pediatric
Hypothermic temperature	Rarely below 25-30° C	Commonly 15-20° C
Use of total circulatory arrest	Rare	Common
Pump prime		
Dilution effects on blood volume	25%-33%	150%-300%
Additional additives in pediatric primes		Blood, albumin
Perfusion pressures	50-80 mm Hg	20-50 mm Hg
Influence of α-stat versus pH-stat management strategy	Minimal at moderate hypothermia	Marked at deep hypothermia
Measured $Paco_2$ differences	30-45 mm Hg	20-80 mm Hg
Glucose regulation		
Hypoglycemia	Rare—requires significant hepatic injury	Common—reduced hepatic glycogen stores
Hyperglycemia	Frequent—generally easily controlled with insulin	Less common—rebound hypoglycemia may occur

BOX 94-3 ***Central Nervous System Injury and Potential Modifiable Intraoperative Factors***

Air or particulate embolus
Rate and depth of core cooling (if used)
Deep hypothermic circulatory arrest (if used)
Reperfusion injury and inflammation
Rate of core rewarming/hyperthermia
Hyperglycemia
Hyperoxia
pH management during cardiopulmonary bypass
Hematocrit management during cardiopulmonary bypass

of aortopulmonary collaterals, and patient age may be important factors affecting organ function during CPB.

Adult patients are infrequently exposed to these biologic extremes. In adult cardiac patients, temperature is rarely lowered below 25° C, hemodilution is more moderate, perfusion pressure is generally maintained at 50 to 80 mm Hg, flow rates are maintained at 50 to 65 mL/kg/minute, and pH management strategy is less influential because of moderate hypothermic temperatures and rare use of circulatory arrest. Variables such as glucose supplementation rarely pose a problem in adult patients owing to large hepatic glycogen stores. Venous and arterial cannulas are larger and less deforming of the atria and aorta, and their placement is more predictable. Although superficially similar, the conduct of CPB in children is considerably different from that in adults. Marked physiologic differences in the response to CPB in children can occur. Additionally, several modifiable intraoperative factors can influence neuropsychologic morbidity (Box 94-3).

Volume of Priming Solutions

The priming solutions used in pediatric CPB take on great importance because of the disproportionately large priming volume–to–blood volume ratio in children. In adults, the priming volume is equivalent to 25% to 33% of the patient's blood volume, whereas in neonates and infants the priming volume may exceed the patient's blood volume by 200%. With contemporary low-volume bypass circuits (e.g., small volume oxygenators, smaller tubing), priming volume is not more than one blood volume in a small neonate. Care must be taken, therefore, to achieve a physiologically balanced priming solution and limit the volume as much as possible. Most pediatric priming solutions, however, have quite variable levels of electrolytes, calcium, glucose, and lactate. Electrolytes, glucose, and lactate levels may be quite high if the solution includes large amounts of banked blood or quite low if a minimal amount of banked blood is added. Calcium levels are generally very low in pediatric priming solutions; this may contribute to the rapid slowing of the heart with the initiation of bypass.

The main constituents of the priming solution include crystalloid, banked blood (to maintain a temperature-appropriate hematocrit), and colloid. Other supplements that may be added to the prime are mannitol, a buffer (sodium bicarbonate or trishydroxymethylaminomethane [THAM]), and steroids. Many institutions add colloid or fresh frozen plasma to the pump prime in neonates and small infants or use whole blood in the priming solution. Low concentrations of plasma proteins have been shown experimentally to impair lymphatic flow and alter pulmonary function by increasing capillary leak.[111] Although adding albumin to the pump prime has not been shown to alter outcome in adults during CPB, one study suggested that maintaining normal colloid osmotic pressure may improve survival in infants undergoing CPB.[112,113]

The addition of fresh frozen plasma or whole blood (see also Chapters 61 and 62) is an attempt to restore the level of procoagulants, which are severely diluted with CPB in infants. For neonates and infants, blood must be added to the priming solution. Most institutions use packed RBCs, but some use whole blood. The use of whole blood supplements both RBCs and the coagulation factors with a single donor exposure. In fact, low-volume bypass circuits may enable perfusionists and anesthesiologists to share a single unit of whole blood, thereby limiting the donor exposure to one throughout the entire perioperative course.

The addition of any blood products will cause a much higher glucose load in the priming solution. Hyperglycemia may increase the risk for neurologic injury if brain ischemia occurs. Mannitol is added to promote an osmotic diuresis and scavenge O_2 free radicals from the circulation. Steroids are added to stabilize membranes to produce the theoretic advantage of reducing ion shifts during periods of ischemia. Steroids, however, may raise glucose levels, and this may be detrimental if there is a

period of cerebral ischemia. Steroids remain one of the more controversial additives in priming solutions.

Temperature

Hypothermic CPB is used to preserve organ function during cardiac surgery (see also Chapter 93). Three distinct methods of CPB are used: moderate hypothermia (25° to 32° C), deep hypothermia (18° C), and DHCA. The choice of method of bypass is based on the required surgical conditions, patient size, type of operation, and potential physiologic impact on the patient.

Moderate hypothermic CPB is the principal method of bypass employed for older children and adolescents. In these patients, venous cannulas are less obtrusive and the heart can easily accommodate superior and inferior vena cava cannulation. Bicaval cannulation reduces right atrial blood return and improves the surgeon's ability to visualize intracardiac anatomy. Moderate hypothermia may also be chosen for less demanding cardiac repairs in infants, such as an ASD or an uncomplicated VSD. Most surgeons are willing to cannulate the inferior and superior venae cavae in neonates and infants. In these patients, however, this approach is technically more difficult and likely to induce brief periods of hemodynamic instability. Additionally, the pliability of the venae cavae and the rigidity of the cannulas may result in caval obstruction, impaired venous drainage, and elevated venous pressure in the mesenteric and cerebral circulation.

Deep hypothermic CPB is generally reserved for neonates and infants requiring complex cardiac repair. However, certain older children with complex cardiac disease or severe aortic arch disease benefit from deep hypothermic temperatures. For the most part, deep hypothermia is selected to allow the surgeon to operate under conditions of low-flow CPB or total circulatory arrest. Low pump flows (50 mL/kg/minute) improve the operating conditions for the surgeon by providing a nearly bloodless field. DHCA allows the surgeon to remove the atrial or aortic cannula. If this technique is used, surgical repair is more precise because of the bloodless and cannula-free operative field. Arresting the circulation, even at deep hypothermic temperatures, introduces the concern of how well deep hypothermia preserves organ function, with the brain being at greatest risk.

Hemodilution

Hemodilution has been used during CPB to decrease homologous blood use and has been thought to improve microcirculatory flow by reducing blood viscosity. Although hemoconcentrated blood has an improved O_2-carrying capacity, its viscosity reduces efficient flow through the microcirculation. With hypothermic temperatures, blood viscosity increases significantly and flow decreases. Hypothermia, coupled with the nonpulsatile flow of CPB, impairs blood flow through the microcirculation. Blood sludging, small vessel occlusion, and multiple areas of tissue hypoperfusion may result. Therefore, hemodilution is an important consideration during hypothermic CPB. The appropriate level of hemodilution for a given hypothermic temperature, however, is not well defined. However, hemodilution also reduces perfusion pressure; increases CBF, thereby potentially increasing the microembolic load to the brain; and reduces the O_2-carrying capacity of blood.[114] Using an animal model, one group of investigators found that extreme hemodilution to a hematocrit less than 10% resulted in inadequate O_2 delivery, but with higher hematocrit levels of 30%, there was improved cerebral recovery after DHCA.[115] Jonas and colleagues[116] confirmed these findings in a randomized trial using two hemodilution protocols (20% versus 30% hematocrit) in infants younger than 9 months of age. Developmental outcomes were assessed at follow-up at 1 year of age with the Bayley Scales of Infant Development. In the short term, the group with lower hematocrit values had lower nadirs of cardiac index, higher serum lactate levels 1 hour after CPB, and a greater increase in total body water on the first postoperative day. At 1 year of age, mental development index scores were similar but psychomotor development index scores were significantly lower in the group with lower hematocrit values. Also, infants in the this group had psychomotor development scores that were 2 standard deviations below the mean. Because RBCs serve as the major reservoir of O_2 during circulatory arrest, especially during rewarming, hematocrit values closer to 30% are generally preferred for deep hypothermia when this technique is contemplated. Currently, most centers maintain hematocrit levels approximately 25% to 30% during CPB, enhancing O_2 delivery to vital organs such as the brain. Cerebral O_2 delivery is an especially important consideration because cerebral autoregulation is impaired at deep hypothermic temperatures and after DHCA.

To achieve a hematocrit level of 25% to 30% in neonates and infants, banked blood should be added to the priming solution. The mixed hematocrit level on CPB (the hematocrit level of the total priming volume plus the patient's blood volume) can be calculated by the following formula:

$$\mathrm{Hct_{CBP}} = \mathrm{BV_{pt}} \times \mathrm{HCT_{pt}}/\mathrm{BV_{pt}} + \mathrm{TPV}$$

where Hct_{CPB} is the mixed hematocrit (TPV + BVpt), BV_{pt} is the patient's blood volume (weight in kilograms × estimated blood volume in milliliters per kilogram), *TPV* is the total priming volume, and Hct_{pt} is the starting hematocrit level of the patient. This calculation allows an estimate of the hematocrit level of the patient using an asanguineous priming solution and is therefore useful for older children and adolescents. In neonates and infants, the perfusionist must add blood to the pump prime to achieve a desired hematocrit level during hypothermic CPB. The following formula estimates the amount of packed RBCs in milliliters that must be added to the prime volume to achieve this hematocrit level:

$$\text{Added RBCs (mL)} = (\mathrm{BV_{pt}} + \mathrm{TPV})\,(\mathrm{Hct_{desired}}) - (\mathrm{BV_{pt}})\,(\mathrm{Hct_{pt}})$$

where BV_{pt} is the patient's blood volume, *TPV* is the total priming volume, $\mathrm{Hct_{desired}}$ is the desired hematocrit level on CPB, and Hct_{pt} is the starting hematocrit level of the patient.

The optimal hematocrit level after weaning from CPB is not clear. Likewise, the adult transfusion trigger is not clear (see also Chapter 61). Decisions concerning post-CPB hematocrit levels are made based on the patient's postrepair function and anatomy. Patients with residual hypoxemia or those with moderate-to-severe myocardial

dysfunction benefit from the improved O_2-carrying capacity of hematocrit levels of 40% or higher. Patients with a physiologic correction and excellent myocardial function may tolerate hematocrit levels of 25% to 30%.[117] In children with mild-to-moderate myocardial dysfunction, accepting hematocrit values between these levels seems prudent. Therefore, in patients with physiologic correction, moderately good ventricular function, and hemodynamic stability, the risks associated with blood and blood product transfusion should be strongly considered during the immediate postbypass period.

BLOOD GAS MANAGEMENT

The theoretic benefit of α-stat versus pH-stat blood gas management during hypothermic CPB has been a topic of great debate (see also Chapters 60 and 94). Although the pH-stat strategy may not be optimal for adults in whom the principal risk for brain injury is microembolism, this risk is thought to be lower in infants because of the lack of atherosclerotic disease. With pH-stat management, the addition of CO_2 to the inspired gas mixture during cooling on CPB increases CBF and may improve cerebral tissue oxygenation and outcomes.

The controversial issue of pH management during CPB has been addressed in a large study from Boston Children's Hospital. In this study, infants younger than 9 months of age were randomized to α-stat versus pH-stat during deep hypothermic CPB with excellent long-term follow-up.[118,119] Neurodevelopmental outcomes were evaluated in infants undergoing biventricular repair for a variety of cardiac defects when younger than 9 months of age. The short-term benefits identified with the pH-stat strategy included a trend toward less postoperative morbidity and shorter recovery time to first electroencephalographic activity. In patients with TGA, there was a shorter duration of intubation and ICU stay in patients.[118] However, the use of either the α-stat or pH-stat strategies was not consistently related to either improved or impaired neurodevelopmental outcomes at 2- and 4-year follow-up.[119]

INITIATION OF CARDIOPULMONARY BYPASS

Arterial and venous cannula in the heart before initiating CPB may result in significant problems in the peribypass period. A malpositioned venous cannula has the potential for vena cava obstruction. The problems of venous obstruction are magnified during CPB in the neonate because arterial pressures are normally low (20 to 40 mm Hg), and large, relatively stiff cannulas easily distort these very pliable venous vessels.[111,113] A cannula in the inferior vena cava may obstruct venous return from the splanchnic bed, resulting in ascites from increased hydrostatic pressure or directly reduced perfusion pressure across the mesenteric, renal, and hepatic vascular beds. Significant renal, hepatic, and gastrointestinal dysfunction may ensue and should be anticipated in the young infant with unexplained ascites. Similar cannulation problems may result in superior vena cava obstruction. This condition may be more ominous during bypass. Under these circumstances, three problems may ensue: (1) cerebral edema, (2) a reduction in regional or global CBF, and (3) reduced proportion of pump flow reaching the cerebral circulation, causing inefficient brain cooling.

In the operating room, superior vena cava pressures via an internal jugular catheter should be monitored by examining the patient's head for signs of suffusion after initiating bypass. Discussions with the perfusionist regarding adequacy of venous return and large cooling gradients between the upper and lower body should alert the anesthesiologist and the surgeon to potential venous cannula problems. Patients with anomalies of the large systemic veins (persistent left superior vena cava or azygous continuation of an interrupted inferior vena cava) are at particular risk for problems with venous cannulation and drainage.

Problems with aortic cannula placement can occur. The aortic cannula may slip beyond the takeoff of the innominate artery, with blood therefore selectively flowing to the right side of the cerebral circulation. Also, the position of the tip of the cannula may promote preferential flow down the aorta or induce a Venturi effect to steal flow from the cerebral circulation. This problem has been confirmed during CBF monitoring by the appearance of large discrepancies in flow between the right and left hemispheres after initiating CPB. The presence of large aortic-to-pulmonary collaterals, such as a large PDA, also may divert blood to the pulmonary circulation from the systemic circulation, thereby reducing CBF and the efficiency of brain cooling during CPB. The surgeon should gain control of the ductus either before or immediately after instituting CPB to eliminate this problem and, if possible, large aortopulmonary collaterals should be embolized in the cardiac catheterization laboratory before the operative procedure. Neonates with significant aortic arch abnormalities (e.g., aortic atresia, interrupted aortic arch) may require radical modifications of cannulation techniques, such as placing the arterial cannula in the main pulmonary artery and temporarily occluding the branch pulmonary arteries to perfuse the body via the PDA or even dual arterial cannulation of both the ascending aorta and main pulmonary artery. Such adaptations require careful vigilance to ensure effective, thorough perfusion and cooling of vital organs.

Once the aortic and venous cannulas are positioned and connected to the arterial and venous limb of the extracorporeal circuit, bypass is initiated. The arterial pump is slowly started, and, once forward flow is ensured, venous blood is drained into the oxygenator. Pump flow rate is gradually increased until full circulatory support is achieved. If venous return is diminished, arterial line pressure is high, or mean arterial pressure is excessive, pump flow rates must be reduced. High line pressure and inadequate venous return are usually caused by malposition or kinking of the arterial and venous cannulas, respectively. The rate at which venous blood is drained from the patient is determined by the height difference between the patient and the oxygenator inlet and the diameter of the venous cannula and line tubing. Venous drainage can be increased by using vacuum-assisted drainage under certain circumstances.

In neonates and infants, deep hypothermia is commonly used. For this reason, the pump prime is kept cold

(18° to 22° C). When the cold perfusate contacts the myocardium during the institution of CPB, heart rate slows immediately and contraction is impaired. The contribution of total blood flow pumped by the infant's heart rapidly diminishes. Therefore, to sustain adequate systemic perfusion at or near normothermic temperatures, the arterial pump must reach full flows quickly.

CPB is initiated in neonates and infants by beginning the arterial pump flow first. Once aortic flow is ensured, the venous line is unclamped and blood is siphoned out of the RA into the inlet of the oxygenator. Flowing before unclamping the venous line prevents the potential problem of exsanguination if aortic dissection or misplacement of the aortic cannula occurs. Neonates and infants have a low blood volume–to–priming volume ratio, and intravascular volume falls precipitously if the venous drainage precedes aortic inflow. Once the aortic cannula position is verified, pump flow rates are rapidly increased to maintain effective systemic perfusion. Because coronary artery disease is rarely a consideration, the myocardium should cool evenly unless distortion caused by the cannulas compromises the coronary arteries. When a cold prime is used, caution must be exercised in using the pump to infuse volume before initiating CPB. Infusion of cold perfusate may result in bradycardia and impaired cardiac contractility before the surgeon is prepared to initiate CPB.

Once CPB is begun, appropriate circuit connections, myocardial perfusion, and optimal cardiac decompression should be confirmed. Ineffective venous drainage can rapidly result in ventricular distention. This is especially true in infants and neonates, in whom ventricular compliance is low and the heart is relatively intolerant of excessive preload augmentation. If ventricular distention occurs, pump flow must be reduced and the venous cannula repositioned. Alternatively, the heart may be decompressed by placing a cardiotomy suction catheter or small vent in the appropriate chamber.

PUMP FLOW RATES

Recommendations for optimal pump flow rates for children have historically been based both on the patient's body mass and on evidence of efficient organ perfusion as determined by arterial blood gases, acid-base balance, and whole-body O_2 consumption during CPB.[120] At hypothermic temperatures, metabolism is reduced, and CPB flow rates can therefore be reduced and still meet or exceed the tissue's metabolic needs (see the discussion of low-flow CPB in the following section).

SPECIAL TECHNIQUES

Deep Hypothermic Circulatory Arrest

A certain subset of neonates, infants, and children with CHD require extensive repair of complex congenital heart defects using DHCA. This technique facilitates precise surgical repair under optimal conditions, free of blood or cannulas in the operative field and providing maximal organ protection and often resulting in shortened total CPB time. The scientific rationale for the use of deep hypothermic temperatures rests primarily on a temperature-mediated reduction of metabolism. Whole-body and cerebral O_2 consumption during induced hypothermia decreases the metabolic rate for O_2 by a factor of 2 to 2.5 for every 10° C reduction in temperature.[121] These results are consistent with in-vitro models, which relate temperature reduction to a decrease in the rate constant of chemical reactions, as originally described by Arrhenius using the equation k = Ae – RT. The reduction in O_2 supply during deep hypothermic low-flow CPB is associated with preferential increases in vital organ perfusion (e.g., to the brain) and increased extraction of O_2.[122] Therefore, to some extent, deep hypothermic low-flow CPB exerts a protective effect by reducing the metabolic rate for O_2, promoting preferential organ perfusion, and increasing tissue O_2 extraction.

The duration of the safe period of DHCA has not clearly been delineated.[123] Although all organ systems are at risk for the development of ischemic and reperfusion injury, as manifested by lactate and pyruvate production during DHCA, the brain appears to be the most sensitive to and the least tolerant of these effects. Brainstem and cortical evoked potentials as well as processed electroencephagraphs are altered after DHCA.[123-125] The abnormalities in the evoked potentials appear to be related to the duration of DHCA and are attributed to altered metabolism. During reperfusion after the arrest period, CBF and metabolism remain depressed in neonates and small infants (Fig. 94-9; also see Fig. 94-6).[76] Importantly, during the use of these extremes of temperature, it appears that autoregulation is lost and cerebral perfusion becomes highly dependent on the conduct of extracorporeal perfusion and presumably postbypass hemodynamic performance.

The potentially deleterious effects of prolonged DHCA in infants and neonates are well described. In general, it is agreed that very prolonged periods of uninterrupted DHCA may have adverse neurologic outcomes. However, considerable disagreement exists if a "safe" period of

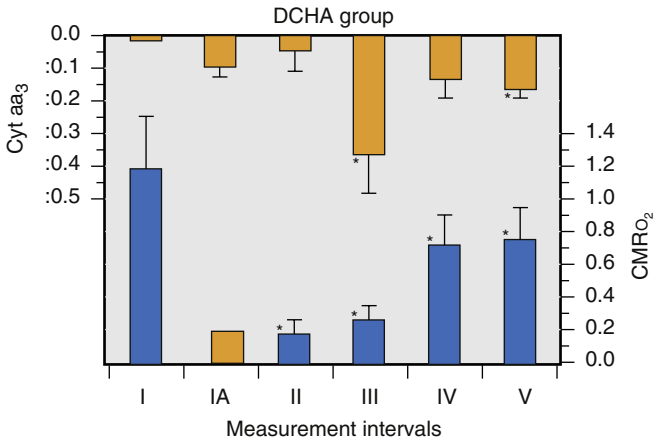


Figure 94-9. Bar graph of variations in cytochrome oxidase (*cyt aa*$_3$) near-infrared spectroscopic signals and cerebral metabolic rate for oxygen (*CMRo*$_2$) in subjects with deep hypothermic circulatory arrest (DHCA). Each point of cyt aa$_3$ represents mean ± SE in six subjects; CMRo$_2$ values are mean ± SD. Negative values in cyt aa$_3$ represent relative decreases in quantity of oxidized enzyme. *CMRo$_2$ and cyt aa$_3$ are significantly different from control, P ± .05.

DHCA exists and whether patient-specific, procedure-specific, or postoperative management strategies may attenuate or promote CNS damage from DHCA. Cases have been reported of detrimental effects of DHCA on a variety of outcomes regarding the CNS and others on either an inconsistent effect or no effect.[118,126,127] Three issues have become clear over time: (1) The effects of short durations of DHCA are inconsistently related to adverse outcomes, (2) the effect of DHCA is not a linear phenomenon, and (3) the effects are most likely modified by other patient-related, preoperative, and postoperative factors.[127-129] A recent large-scale study of 549 subjects undergoing the Norwood stage 1 procedure with DHCA found duration of greater than 45 minutes to be a risk factor for 30-day mortality.[130]

Regional Cerebral Perfusion

Some surgeons have developed innovative and challenging strategies to provide continuous cerebral perfusion during complex reconstruction of the aortic arch or intracardiac repair to avoid or minimize the use of DHCA. However, avoiding DHCA, the duration of CPB is necessarily lengthened, and longer durations of CPB have been shown to adversely affect both short- and long-term outcomes.[58,59] The relative risks and benefits of longer CPB versus less (or no) DHCA remain a subject of continued controversy. In efforts to study this newer strategy, two recent studies have evaluated the technique of regional cerebral perfusion. In one nonrandomized study from Boston, Wypij and colleagues[131] followed 29 infants who underwent a stage I palliation, 9 of whom received regional cerebral perfusion at 30 to 40 mL/kg/minute.[131] The authors reported no difference in mental or psychomotor developmental indices at 1 year of age between the regional cerebral perfusion group and those who received DHCA as a primary strategy. A group from the University of Michigan published a larger, randomized trial of DHCA with or without regional cerebral perfusion at 20 mL/kg/minute in patients with a functional single ventricle, with long-term studies that are in the planning stages.[132] A total of 77 patients were enrolled with similar survival to hospital discharge (88%) and at 1-year follow-up (75%). No significant difference was seen in either the psychomotor development index or the mental development index scores between the two groups at any time points, although the scores tended to be lower in the regional cerebral perfusion group.

Glucose Regulation

The detrimental effects of hyperglycemia during complete, incomplete, and focal cerebral ischemia are well demonstrated (see also Chapter 39).[133,134] The role of glucose in potentiating cerebral injury appears to rest on two factors: adenosine triphosphate (ATP) usage and lactic acidosis.[135,136] The anaerobic metabolism of glucose requires phosphorylation and the expenditure of two molecules of ATP before ATP production can occur. This initial ATP expenditure may result in a rapid depletion of ATP and may explain why hyperglycemia worsens neurologic injury. Lactic acidosis is also important in glucose-augmented cerebral injury. Its important role, however, may be as a glycolytic enzyme inhibitor. Lactate slows anaerobic ATP production by inhibiting glycolysis immediately after ATP is consumed in the phosphorylation of glucose.[137]

Although the detrimental effects of hyperglycemia during ischemia are clear, very little evidence supports a relationship between a worsening neurologic outcome and hyperglycemia during CPB or DHCA in children. Although a retrospective review of 34 children undergoing DHCA suggested a worse neurologic outcome in the hyperglycemic children, the results were reported as a nonsignificant statistical trend.[138] A review of acquired neurologic lesions in patients undergoing the Norwood stage I procedure for hypoplastic left heart syndrome suggested hyperglycemia as a significant associated finding in patients with extensive cerebral necrosis or intraventricular hemorrhage. A host of other potentially damaging factors (e.g., periods of hypoxia, low diastolic and systolic pressure, thrombocytopenia) were statistically associated with the observed neuropathology.[139] Whether glucose directly contributes to neurologic injury or merely serves as a marker for a high-risk population that ultimately suffers neurologic insult as a result of other factors is not clear.

Hypoglycemia is a frequent concern in neonates during the perioperative period (see also Chapter 94). Reduced hepatic gluconeogenesis coupled with decreased glycogen stores places the newborn at increased risk for hypoglycemic events. In newborns with CHD, reduced systemic perfusion (e.g., critical coarctation, hypoplastic left heart syndrome, critical aortic stenosis) may result in worsening hepatic biosynthesis, further impairing glucose production. These patients may be fully dependent on exogenous glucose; therefore, it is not uncommon for them to require 20% to 30% dextrose infusions to maintain euglycemia in the prebypass period. Older children are not immune to hypoglycemic events and are therefore susceptible to hypoglycemia-induced neurologic injury. Patients with low cardiac output states (cardiomyopathies, pretransplant patients, critically ill postoperative patients) requiring reoperation and when on substantial inotropic support are at risk for reduced glycogen stores and intraoperative hypoglycemia.[140]

The impact of hypoglycemia during CPB is further complicated by the consequences of hypothermia, CO_2 management, and other factors that may modify normal cerebrovascular responses during bypass. In a dog model, insulin-induced hypoglycemia to 30 mg/dL did not alter the electroencephalographic findings. However, after 10 minutes of hypocapnic hypoglycemia, the electroencephalogram became flat.[141] When regional blood flow was examined in these animals, cortical and hippocampal blood flow remained normal whereas other regions of the brain had reduced flow. The loss of electroencephalographic activity from hypoglycemia alone does not normally occur above glucose levels of 8 mg/dL.[142]

During deep hypothermic CPB and DHCA, CBF and metabolism are altered. The additive effect of hypoglycemia, even if mild, may cause alterations in cerebral autoregulation and culminate in increased cortical injury.[139] The common practice of using hyperventilation to reduce PVR in neonates and infants during weaning from CPB and in the early postbypass period can further exacerbate hypoglycemic injury. Glucose monitoring and rigid

maintenance of euglycemia are an important part of CPB management in the patient with CHD.

Renal Effects

After CPB, the combined effects of hypothermia, nonpulsatile perfusion, and reduced mean arterial pressure cause release of angiotensin, renin, catecholamines, and antidiuretic hormones.[143-145] These circulating hormones promote renal vasoconstriction and reduce renal blood flow. However, despite the negative impact of CPB on renal function, low-flow, low-pressure, nonpulsatile perfusion has not been linked with postoperative renal dysfunction (Table 94-9).[144] The factors that best correlate with postoperative renal dysfunction are preoperative renal dysfunction and profound reductions in post-CPB cardiac output. Preoperative factors include primary renal disease, low cardiac output, and dye-related renal injury after cardiac catheterization.[145]

The incidence of acute renal insufficiency after pediatric cardiac surgery is approximately 8%. Multiple causative factors are involved, and the final common result is oliguria and an increased serum creatinine. Diuretics have been the mainstay of promoting urine flow after pediatric CPB. Furosemide in a dose of 1 to 2 mg/kg or ethacrynic acid 1 mg/kg every 4 to 6 hours, or both, induces diuresis and may reverse renal cortical ischemia associated with CPB. After DHCA, a 24-hour period of oliguria or anuria can occur that resolves over the next 12- to 24-hour period. The use of diuretics is effective only after spontaneous urine output has been initiated in these patients.

Glomerular filtration rate, creatinine clearance, and medullary concentrating ability are substantially reduced in neonates and young infants. Therefore, the use of CPB in these patients results in greater fluid retention than is typically seen in older children and adult patients. The net result may be increased total body water, increased organ weight (e.g., lungs, heart), and greater difficulty with postoperative weaning from ventilatory support. The use of ultrafiltration during rewarming or after CPB is effective in reducing total body water, limiting the damaging effects of CPB, and decreasing the postoperative ventilation period.[146,147]

TABLE 94-9 SEQUELAE OF PEDIATRIC CARDIOPULMONARY BYPASS

End-Organ Injury	Cause and Signs
Renal injury	Organ immaturity, preexisting renal disease Post–cardiopulmonary bypass low cardiac output, use of DHCA Renal dysfunction characterized by reduced GFR and ATN
Pulmonary injury	Endothelial injury, increased capillary leak, complement activation, and leukocyte degranulation Pulmonary dysfunction characterized by reduced compliance, reduced FRC, and increased A-a gradient
Cerebral injury after DHCA	Loss of autoregulation, suppressed metabolism and cerebral blood flow, cellular acidosis, and cerebral vasoparesis CNS dysfunction characterized by seizures, reduced developmental quotients, choreoathetosis, learning disabilities, behavioral abnormalities

A-a, alveolar-arterial; *ATN,* acute tubular necrosis; *CNS,* central nervous system; *DHCA,* deep hypothermic circulatory arrest; *FRC,* functional residual capacity; *GFR,* glomerular filtration rate.

Pulmonary Effects

Cardioplegia protects the heart, but no parallel protection is afforded the lung during bypass. Pulmonary dysfunction is common after CPB, and its pathogenesis is poorly understood (see Table 94-9). In the broadest terms, lung injury is mediated in one of two ways: first, by an inflammatory response resulting from leukocyte and complement activation and, second, by a mechanical effect culminating in surfactant loss, atelectasis with resultant ventilation-perfusion mismatch, loss of lung volumes, and altered mechanics of breathing.

Pulmonary function after CPB is characterized by reduced static and dynamic compliance, reduced functional residual capacity, surfactant deficiency, and an increased A-a gradient.[148,149] Atelectasis and increased capillary leak due to hemodilution and hypothermic CPB are the most likely causes. Hemodilution reduces circulating plasma proteins, reducing intravascular oncotic pressure, and favors water extravasation into the extravascular space. Hypothermic CPB causes complement activation and leukocyte degranulation.[150] Leukocytes and complement are important in causing capillary-alveolar membrane injury and microvascular dysfunction through platelet plugging and release of mediators, which increase PVR. The technique of MUF is highly effective in reducing lung water and pulmonary morbidity during the postoperative period.

STRESS RESPONSE AND CARDIOPULMONARY BYPASS

The release of a large number of metabolic and hormonal substances, including catecholamines, cortisol, growth hormone, prostaglandins, complement, glucose, insulin, endorphins, and other substances, characterizes the stress response during hypothermic CPB.[11,151] The likely causes of the elaboration of these substances include contact of blood with the nonendothelialized surface of the pump tubing and oxygenator, nonpulsatile flow, low perfusion pressure, hemodilution, hypothermia, and light anesthesia depth. Other factors that may contribute to elevations of stress hormones include delayed renal and hepatic clearance during hypothermic CPB, myocardial injury, and exclusion of the pulmonary circulation from bypass. The lung is responsible for metabolizing and clearing many of these stress hormones. The stress response generally peaks during rewarming from CPB. Strong evidence indicates that the stress response can be blunted by increasing the depth of anesthesia.[11,151]

When do elevated circulating stress hormones, a normal neonatal adaptive response, become detrimental? These substances can mediate undesirable effects such as myocardial damage (catecholamines), systemic and pulmonary hypertension (catecholamines, prostaglandins), pulmonary endothelial damage (complement, prostaglandins), and pulmonary vascular reactivity (thromboxane).

The benefits of controlling the stress response with fentanyl in premature infants undergoing PDA ligation and with sufentanil in neonates with complex CHD have been demonstrated.[100,152] Although blunting the stress response seems warranted, additional evidence suggests that the newborn stress response, especially the endogenous release of catecholamines, may be an adaptive metabolic response necessary for survival at birth.[153] Thus, the complete elimination of an adaptive stress response may not be desirable. To what extent acutely ill neonates with CHD depend on the stress response for maintaining hemodynamic stability is currently unknown.

A depth of anesthesia adequate to attenuate the stress response should be used, but to attempt to block the response altogether may not be necessary. Acceptable anesthesia during CPB may be best accomplished by the continuous administration of an inhaled anesthetic via a vaporizer connected to the pump oxygenator, careful titration of incremental doses of opioids, or the precise administration of an opioid or opioid and benzodiazepine by a continuous infusion technique. Primary opioid anesthetic techniques result in reduced stress hormone release and decreased postoperative metabolic acidosis and lactate production compared with primary halothane anesthesia and may therefore be a preferred technique in complex CHD.[100] If an adequate depth of anesthesia is accomplished by the administration of excessively large doses of opioids (e.g., fentanyl or sufentanil), postoperative mechanical ventilation will be necessary. By contrast, residual levels of inhaled anesthetics (e.g., halothane or isoflurane) can produce transient myocardial depression at the termination of CPB, complicating separation from CPB. Because of the improved surgical techniques coupled with the reduced morbidity of CPB, the use of high doses of an opioid anesthetic is infrequent in our current practice.

DISCONTINUATION OF CARDIOPULMONARY BYPASS

In separating the patient from CPB, blood volume is assessed by direct visualization of the heart and monitoring right atrial or left atrial filling pressures (see also Chapter 66). When filling pressures are adequate, the patient is fully warmed, acid-base status is normalized, heart rate is adequate, and sinus rhythm has been achieved, the venous drainage is stopped and the patient can be weaned from bypass. The arterial cannula is left in place so that a slow infusion of residual pump blood can be used to optimize filling pressures. Myocardial function is assessed by direct cardiac visualization and a transthoracic left or right atrial catheter, by a percutaneous internal jugular catheter, or by the use of intraoperative echocardiography. Pulse oximetry also can be used to assess the adequacy of cardiac output.[154] Low systemic arterial saturation or the inability of the oximeter probe to register a pulse may be a sign of very low output and high systemic resistance.[155]

After the repair of complex congenital heart defects, the anesthesiologist and surgeon may have difficulty separating patients from CPB. Under these circumstances, a diagnosis must be made and includes (1) an inadequate surgical result with a residual defect requiring repair, (2) pulmonary artery hypertension, and (3) right or left ventricular dysfunction.

Two general approaches are customarily used, either independently or in conjunction. An intraoperative "cardiac catheterization" can be performed to assess isolated pressure measurements from the various great vessels and chambers of the heart (i.e., catheter pullback measurements or direct needle puncture to evaluate residual pressure gradients across repaired valves, sites of stenosis and conduits, and O_2 saturation data to examine for residual shunts).[156] Alternatively, echo-Doppler imaging may be used to provide an intraoperative image of structural or functional abnormalities to assist in the evaluation of the postoperative cardiac repair.[9,157] If structural abnormalities are found, the patient can be placed back on CPB and residual defects can be repaired before the patient leaves the operating room. Leaving the operating room with a significant residual structural defect adversely affects survival and increases patient morbidity (see Fig. 94-5).[9,157] Echo-Doppler imaging can rapidly identify right and left ventricular dysfunction and suggest the presence of pulmonary artery hypertension. In addition, echo-Doppler imaging can identify regional wall motion abnormalities caused by ischemia or intramyocardial air that will direct specific pharmacologic therapy and provide a means of assessing the results of these interventions (Fig. 94-10).[158]

ULTRAFILTRATION

Institution of CPB in neonates, infants, and young children results in a profound proinflammatory response and significant hemodilution. This may lead to post-CPB morbidity and mortality resulting from poor organ function. The organ systems most affected by this are the heart, lungs, and brain. Although contact between the patient's blood and the foreign surface of the bypass circuit is a potent stimulus to trigger the inflammatory cascade, other factors including ischemia, profound hypothermia, rewarming, and surgical trauma are also important in its genesis. These inflammatory mediators include complement anaphylatoxins, vasoactive amines, and cytokines (e.g., tumor necrosis factor-α [TNF-α]) that lead to an increase in vascular permeability.[73] Hemodilution occurs at the onset of CPB despite the use of physiologically balanced priming solutions that include blood, crystalloid, albumin, and buffer and smaller volume circuits. Hemodilution may, however, be advantageous in patients in whom the surgery is performed under hypothermic conditions ranging from mild hypothermia to DHCA. Initiation of CPB will change the viscoelastic properties of blood, and these changes have been shown to continue into the post-CPB period.[159] Although the mode of perfusion, cardiotomy suction, arterial roller pump type, and shear forces of the CPB circuit are important, it is the temperature and hematocrit of the blood that play the most important role in changing viscoelasticity. It has been shown that low temperature with a high hematocrit leads to a higher viscosity.[160] This elevated viscosity may lead to altered organ perfusion, particularly in the brain. Because of these alterations in blood viscosity, hemodilution is

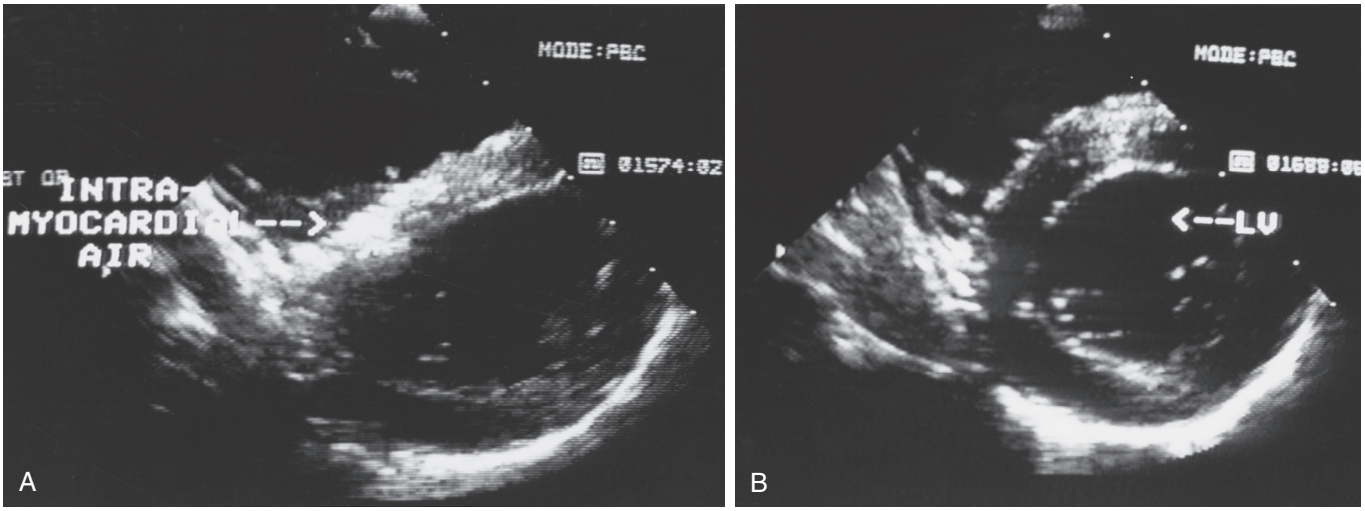


Figure 94-10. A, Two-dimensional echocardiogram in the short-axis view across the ventricles demonstrating the presence of intramyocardial air (*arrow*) in the ventricular septum and right ventricular wall. The intramyocardial air appears as a dense, "snowy" echogenic area. Note the associated wall motion abnormality appearing as flattening of the ventricular septum. **B,** The patient was treated with phenylephrine, increasing systemic and coronary perfusion pressure, resulting in clearance of the air, normalization of the echogenic density, and restoration of normal left ventricular (*LV*) wall motion and configuration.

tolerated in the cooling phases of CPB. Although advantageous early, this hemodilution combined with the inflammatory response will lead to transudation of fluid into the extravascular space, which in turn leads to the potential for organ dysfunction as eluded to earlier. Prevention of organ dysfunction and improved oxygenation by the removal of excess fluid and inflammatory mediators are the rationale, therefore, in the use of ultrafiltration. The end result is removal of plasma water and low-molecular-weight solutes across a semipermeable membrane.

Essentially, five forms of ultrafiltration are used in modern perfusion practice, three of which are while the patient is on CPB. Prime ultrafiltration is used when packed RBCs are added to the prime solution and is performed in the prebypass phase. Its aim is to replace crystalloid prime with blood prime, adjust pH, alter electrolyte concentration to safer levels, and remove inflammatory mediators potentially present in the donor blood.[161] Conventional ultrafiltration (CUF) involves the removal of fluid at any time while the patient is being supported by CPB. A common use for this method is removal of the volume of clear fluid equal to the volume of cardioplegia used. Conventional ultrafiltration can be performed during all phases of CPB. It involves the placement of an ultrafilter within the circuit and connected either to the venous line or the venous reservoir. The removal of an excess of ultrafiltrate will result in low reservoir volumes. In zero balance ultrafiltration, once fluid has been removed it is replaced with crystalloid to avoid inadequate reservoir volume, and thus there is no net removal of volume. The third method of on-bypass ultrafiltration is dilutional ultrafiltration, which is employed when the concentration of a given electrolyte (e.g., potassium) is deemed elevated. The method involves removal of ultrafiltrate with its replacement by half with normal saline, thus diluting the concentration of the given electrolyte to safer levels. From the description of on-bypass ultrafiltration it can be appreciated that although these methods have different names, their end point is similar—that is, attempted removal of excess clear fluid resulting in hemoconcentration, removal of inflammatory mediators, and manipulation of electrolyte concentrations to safe levels.

First described by Naik and associates[146] in 1991, MUF involves filtration of blood once the patient has been weaned from bypass. This can be achieved either by a venovenous technique in which blood is removed and returned to the atrium once concentrated or by an arteriovenous technique in which blood is removed via the aortic cannula and returned via the venous line.[146,162,163] In more detail, in this technique blood is removed in a retrograde fashion by the aortic cannula and passes through the ultrafilter along with remaining circuit volume from the venous reservoir and oxygenator. Flow through the ultrafilter is maintained by a roller pump at flows of between 10 and 30 mL/kg, with the slower rates resulting in a more gradual change in the intravascular fluid compartment and thus potentially better tolerated. A constant atrial pressure is maintained throughout the procedure by adding crystalloid into the venous reservoir as needed. Suction is applied to the filtrate port to achieve a maximal transmembrane pressure, thus allowing for ultrafiltration rates of between 100 and 150 mL/minute.[60] End points for the process of MUF are time (15 to 20 minutes) and reaching of a target hematocrit (usually 40%) once the circuit volume has been replaced by crystalloid or should the patient's hemodynamics not tolerate the procedure.

Cardiac surgeries in the very young may be complex with potentially protracted CPB and cross-clamp times. Therefore, myocardial performance is depressed after weaning from CPB. Although ultrafiltration is used during CPB in an attempt to remove excess body water, it appears from studies that it is the use of MUF

that significantly improves myocardial performance (Fig. 94-11).[60,164,165] Using echocardiographic measurements in a study of infants undergoing corrective surgery under nonhypothermic arrested conditions, Davies and associates[166] found improvements in both systolic and diastolic function in the children studied. They found that the preload recruitable stroke work, which is load independent, improved after MUF and was thus a good indicator of improved systolic function. The same study showed that after MUF a decrease in the myocardial wall thickness and cross-sectional area occurred that was not present in the control group of patients who received no ultrafiltration. These reductions result in an increase in end-diastolic length and a fall in end-diastolic pressure, both of which are indicators of improved diastolic function. Although presumably it was the decrease in myocardial edema that was the cause for these improvements, increased hematocrit also was observed. Because these positive effects were not seen past 24 hours, the absolute benefit of MUF is not clear.[166]

Pulmonary dysfunction is one of the most common negative effects of CPB.[167] Therefore the use of ultrafiltration and MUF is to improve oxygenation and decrease the effects of inflammatory mediators on the alveolar capillary membrane and pulmonary vascular reactivity. Studies have demonstrated that in patients in whom ultrafiltration and MUF were used, improvements in pulmonary compliance, decreased airway resistance, pulmonary arterial reactivity, and improved oxygenation were demonstrated.[167-171] It is therefore obvious why these methods have found such wide acceptance in pediatric cardiac surgery, particularly in patients in whom normal compliance with low PVR is vital (i.e., those with single-ventricle physiology). Although these studies commonly find improvement in pulmonary function immediately after weaning from CPB and the completion of MUF, disagreement exists as to whether these effects result in improved function much beyond 6 hours, with some showing little if any benefit at 24 hours. A conclusion, however, from these studies is that combination of on-bypass ultrafiltration coupled with MUF has the best results in the early postbypass period.

Studies into the long-term effects of CPB and indeed DHCA on the brain of children are ongoing. As has been mentioned previously, the initiation of CPB will affect the major organs. In a study performed on a piglet model of DHCA, the use of MUF after CPB improved hematocrit, cerebral O_2 delivery, and cerebral O_2 consumption, thus representing a potential reduction in cerebral injury. Further studies have made similar conclusions. These studies demonstrated that four variables are of importance in improving cerebral oxygenation: P_{CO_2}, mean arterial pressure, hematocrit, and MUF flow rate.[172,173] Increasing all except MUF flow rate improved O_2 delivery. Increasing the flow rate appeared to cause a steal-like phenomenon in which apparent diastolic runoff occurred into the MUF circuit from the aortic cannula. Thus, although the process of MUF is important for recovery of normal cerebral function, care must be used not to negate the benefits by decreasing the time on MUF by increasing the flow rates (Fig. 94-12).

Common to the improvement in cardiac and pulmonary function are the associated decrease in inflammatory mediators seen after ultrafiltration. Studies have shown that the ultrafiltrate contains a wide variety of low-molecular-weight inflammatory mediators, including C3a, C5a, interleukin (IL)-6, IL-8, TNF, myocardial depressant factor, and endothelin.[168,169,174] It is the removal of endothelin-1 after MUF that results in the improvement of pulmonary vascular reactivity, which is of great importance, particularly in

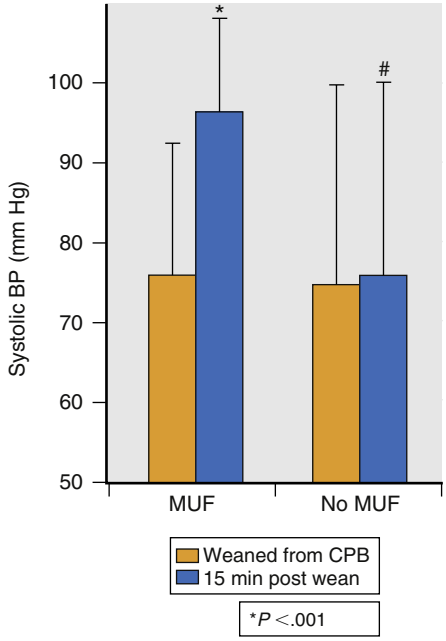


Figure 94-11. Systolic blood pressure (*BP*) after separating from cardiopulmonary bypass (*CPB*) and 15 minutes after separating with and without modified ultrafiltration (*MUF*). Note the significant improvement in systolic BP with the use of MUF. *(From Ungerleider RM: Effects of cardiopulmonary bypass and use of modified ultrafiltration,* Ann Thorac Surg *65:S35, 1998; reprinted with permission from the Society of Thoracic Surgeons.)*

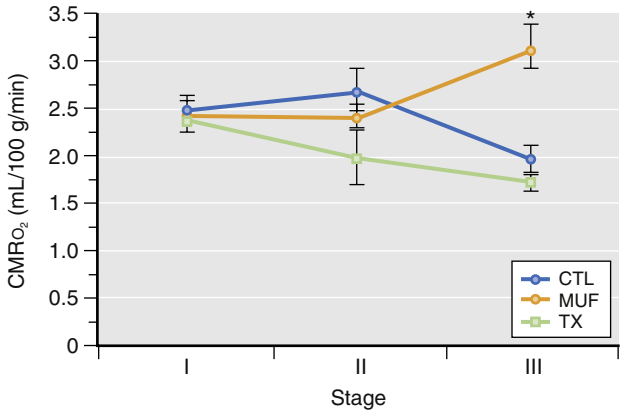


Figure 94-12. Cerebral metabolic rate for oxygen measurements ($CMRo_2$) before and after deep hypothermic circulatory arrest. Note the significant increase in $CMRo_2$ in the MUF animals compared with the control and transfusion groups at stage 3. *CTL,* Control; *MUF,* modified ultrafiltration; *TX,* transfusion. *(From Skaryak LA, Kirshbom PM, DiBernardo LR, et al: Modified ultrafiltration improves cerebral metabolic recovery after circulatory arrest,* J Thorac Cardiovasc Surg *109:744, 1995.)*

infants younger than 4 to 6 months of age, when pulmonary vascular reactivity is high, and in patients who are having staged cavopulmonary reconstructions. TNF, a potent inflammatory mediator implicated in the development of capillary leak syndrome seen after CPB, has been shown to be removed best by MUF. Despite these positive effects of MUF, the literature does not give a clear advantage of one form of ultrafiltration over the other, and it may be the combination of these methods that once again shows the best potential results.

Another important post-CPB issue is ongoing blood loss. Little doubt exists that the use of MUF will result in an elevation of the patient's hematocrit secondary to the removal of the excess body water, as already discussed. This further results in decreased blood use and the observation that there is less postoperative bleeding.[175] Indeed, in older children attempts can thus be made to avoid the use of donor blood altogether.

Disadvantages to these techniques are noted. The addition of an ultrafilter to the CPB circuit adds a level of complexity to the circuitry and thus another potential area in which circuit-related complications may occur. Antagonists of MUF note also the following potential problems: the potential for air entrainment into the arterial cannula, additional time in which the patient is anticoagulated, potential for hypovolemia as volume is drawn off from the patient, hypothermia because the filtered volume does not pass through the heater/oxygenator, and the potential for the increase in the plasma concentration of drugs (e.g., fentanyl).[176] Another interesting complication potentially associated with ultrafiltration was the reduction in thyroid hormone. This acute hypothyroidism may lead to depressed function, manifesting as decreased contractility, heart rate, cardiac output, and elevated SVR, all of which will clearly affect the immediate post-CPB period.[177] As with other techniques in medicine the benefit versus risk must be seriously considered, but from the presented evidence the use of ultrafiltration both on and off CPB is extremely beneficial and these methods are thus commonly used in modern pediatric cardiac surgery with good result and little complication.[163,165,178,179]

In the preceding paragraphs the discussion concluded that no clear advantage has been determined of one method of ultrafiltration over the other. Unfortunately, comparing a wide range of patients having different surgeries under different conditions is difficult, and thus it appears that from the articles referenced the best strategy would include both the use of on-CPB ultrafiltration and the use of MUF once the patient has been separated from bypass to achieve the goals of decreasing total-body water; removal of inflammatory mediators; improved hematocrit, and thus O_2-carrying capacity; and preservation of vital organ function.

SPECIFIC PROBLEMS ENCOUNTERED IN DISCONTINUING CARDIOPULMONARY BYPASS

See also Chapter 66.

Left Ventricular Dysfunction

The contractile state of the LV may be reduced after pediatric cardiac surgery. This is due to surgically induced ischemia during the repair, the preoperative condition of the myocardium, the effects of DHCA on myocardial compliance, and new, altered loading conditions on the LV caused by the repair.[180,181] Left ventricular dysfunction can be treated by optimizing preload, increasing heart rate, increasing coronary perfusion pressure, correcting ionized calcium levels, and adding inotropic support. The neonate's heart rate–dependent cardiac output, reduced myocardial compliance, and diminished response to calcium and catecholamines are factors influencing the need for inotropic support. Inotropic support is usually begun with dopamine 3 to 10 μg/kg/minute. Several studies suggest that the effect of dopamine in children is age dependent. After cardiac surgery in young children, dopamine increases cardiac output, which correlates more with elevations in heart rate than augmentation of stroke volume, whereas, in young adults, dopamine clearly increases stroke volume. Nonetheless, infants and neonates respond favorably to dopamine infusions with increased systemic blood pressure and cardiac output and improved systemic perfusion.

Calcium supplementation is important in augmenting cardiac contractility. Although calcium supplementation has fallen into some disfavor because of concerns over reperfusion injury, it remains an important therapy after pediatric cardiac surgery. Fluctuations in ionized calcium levels occur commonly in the immediate post-CPB period in children. This is most often due to the relatively large transfusions of citrate-rich and albumin-rich blood products, such as whole blood, fresh frozen plasma, platelets, and cryoprecipitate necessary for hemostasis, all of which bind calcium.[182] Routine calcium supplementation during the early post-CPB period is especially helpful in patients with diminished left ventricular function. In patients with a slow sinus or junctional rate, calcium must be administered cautiously because marked slowing of AV conduction may occur.

Epinephrine 0.02 to 0.2 μg/kg/minute is useful in patients with significant left ventricular dysfunction who remain hypotensive with high left atrial filling pressures or echo-Doppler imaging evidence of reduced contractility or regional ischemia.[183]

Milrinone, a potent phosphodiesterase-3 inhibitor, is also an effective inotrope-vasodilator in infants and children. Studies in neonates after open-heart surgery reveal significant reductions in SVR and PVR and increases in cardiac index, primarily as a result of larger stroke volume.[184] Infants and children demonstrate a larger volume of distribution and clearance of milrinone than that in adults; thus, the initial dose necessary to achieve therapeutic levels may be as large as 100 μg/kg.[185] In neonates, the initial dose of milrinone on CPB is 100 μg/kg, followed by a continuous infusion to be started within 90 minutes of the initial dose at a rate of 0.2 μg/kg/minute to maintain a therapeutic level. In older infants and children, the rate of continuous infusion is larger, usually 0.5 to 1 μg/kg/minute.

Dobutamine is an effective, albeit weaker, inotropic agent in children. Although it is reported to have fewer chronotropic effects than dopamine in neonates, significant tachyarrhythmias may occur. This may be related to structural similarities between dobutamine

and isoproterenol.[183] In children after cardiac surgery, dobutamine increases cardiac output primarily through increased heart rate. The efficacy of dobutamine seems to be reduced in immature animals. This is consistent with reduction in α-receptors and a higher level of circulating catecholamines in newborns.

Right Ventricular Dysfunction

Primary right ventricular dysfunction is a common finding after CPB in neonates, infants, and children. For example, after repair of TOF, preexisting right ventricular hypertrophy, a right ventriculotomy, and the placement of a transannular patch across the right ventricular outflow tract, resulting in acute pulmonary regurgitation and right ventricular volume overload, are common causes of postoperative right ventricular dysfunction.[20] The treatment of right ventricular dysfunction consists of measures directed at lowering PVR and preserving coronary perfusion without distending the RV. Metabolic acidosis should be addressed and inotropic agents selected for their vasodilating properties (e.g., dopamine, amrinone, or milrinone). In cases of extreme ventricular dysfunction, low-dose epinephrine (0.01 to 0.03 μg/kg/minute) may provide inotropy without vasoconstriction.[181] Mechanical ventilation should be adjusted to assist right ventricular function and minimize PVR.

In contrast with the LV, the low intracavitary pressure of the normal RV receives two thirds of its coronary filling during ventricular systole. In patients with right ventricular dysfunction, maintaining a normal or slightly elevated systolic arterial pressure maximizes coronary perfusion to the RV and augments contractility. If the need for inotropic support persists after the early post-CPB period, a critical evaluation for other structural and functional abnormalities should be aggressively pursued. Preload should be maintained at a normal to slightly elevated level. Because right ventricular contractility is reduced, it is important to maximize preload to the highest portion of the Starling curve. Overdistention of the RV, however, is not well tolerated, owing to diminished ventricular compliance and diastolic dysfunction. Excessive volume loading may result in significant diastolic dysfunction, tricuspid regurgitation, and worsening forward flow. Generally, CVP much above 12 to 14 mm Hg is poorly tolerated in neonates and infants with right ventricular dysfunction.[186] If right ventricular dysfunction is severe, the sternum should be left open.[187] This eliminates the impedance imposed by the chest wall and mechanical ventilation, allowing the RV to maximize its end-diastolic volume. An additional strategy in neonates, infants, and children with significant post-CPB right ventricular dysfunction is to allow right-to-left shunting at the atrial level. Typical patients who would benefit from this strategy include neonates undergoing repairs for TOF and truncus arteriosus. Allowing an atrial communication to remain open, with blood shunting in a right-to-left direction, preserves cardiac output and O_2 delivery to the systemic circulation. Although these patients have somewhat diminished systemic O_2 saturation, as their effective cardiac output and tissue O_2 delivery are enhanced, systemic perfusion pressure improves and coronary perfusion of the RV is maintained. As right ventricular function improves, right atrial pressure falls, right-to-left shunting decreases, and systemic arterial saturation rises.

If right ventricular dysfunction persists to the extent that systemic cardiac output is compromised, consideration should be given to extracorporeal life support (extracorporeal membrane oxygenation [ECMO]). When ECMO is used for circulatory support, venoarterial cannulation is preferred. Venous and arterial access may be achieved through a large central artery and vein, usually the carotid artery and internal jugular vein, or by direct chest cannulation. Recovery from severe ventricular dysfunction is predicated on the concept that the myocardium has sustained a transient injury (i.e., "stunned myocardium") and is capable of recovery with time.[188,189] ECMO is used to decrease ventricular wall tension, increase coronary perfusion pressure, and maintain systemic perfusion with oxygenated blood. ECMO also may be used for left ventricular failure, although success with this condition is less common than that seen with right ventricular dysfunction or pulmonary artery hypertension. Patients placed on ECMO because they fail to separate from CPB demonstrate significantly greater mortality than do those for whom ECMO was instituted later in the postoperative course.[190] The children who consistently have the lowest survival rate are those who require ECMO after a Fontan operation.[191] The role of ECMO in patients with myocardial injury or pulmonary hypertension is to provide adequate systemic O_2 transport and systemic perfusion while allowing the ventricles to rest and recover. ECMO may even provide an effective means of resuscitation for postoperative cardiac patients, particularly if instituted promptly.[192] In larger infants and children with predominantly right ventricular dysfunction and satisfactory pulmonary function, a selective right ventricular assist device may be preferable to ECMO.[193]

Pulmonary Artery Hypertension

Primary pulmonary hypertension is a devastating disease. The progressive and sustained elevation in PVR eventually leads to right-sided heart failure and death.[194,195] Pulmonary arterial hypertension (PAH) is defined by the presence of mean pulmonary arterial pressure greater than 25 mm Hg at rest or 30 mm Hg during exercise.[196] In two recent studies, presence of PAH was shown to be a significant predictor of major perioperative cardiovascular complications, including pulmonary hypertensive crises, cardiac arrest, and death in patients undergoing cardiac catheterization or noncardiac surgery under anesthesia.[197,198] Suprasystemic pulmonary artery pressure was predictive of major complications. Complications, however, were not associated with age, cause, type of anesthetic, or airway management. Preanesthesia evaluation should evaluate disease severity. A history significant for chest pain, syncope, and dizziness, with signs of dyspnea at rest, low cardiac output state, metabolic acidosis, hypoxemia, and signs of right-sided heart failure warrants caution. Acute increases in PVR resulting in pulmonary hypertensive crises cause an increase in right ventricular afterload, right ventricular dysfunction, and hemodynamic decompensation. Suprasystemic pulmonary artery pressure results in inadequate PBF, inadequate left ventricular preload, low cardiac output, and biventricular

failure. The associated hypotension results in coronary ischemia, which worsens this cycle. Perioperative factors thought to precipitate a pulmonary hypertensive crisis include hypoxia, hypercarbia, acidosis, hypothermia, pain, and airway manipulations in patients with pulmonary hypertension. Such patients present for hemodynamic catheterization, drug study, and noncardiac and cardiac surgical procedures. Although each anesthetic has to be tailored to the patient's pathophysiologic condition and surgical procedure, certain common principles remain. Pulmonary vasodilator therapy and inotropes must be continued in the perioperative period. Investigations include a comprehensive echocardiogram with occasional chest computed tomography (CT) angiography to exclude pulmonary thromboembolic disease. In our center, premedication is avoided and intravenous induction is performed with carefully titrated doses of ketamine. Procedures with potential for blood loss, hemodynamic instability, and changes in ventilatory status mandate invasive arterial monitoring. Care should be taken to avoid systemic hypotension while achieving general anesthesia. Ventilation and oxygenation are controlled, and acidosis is treated aggressively. Hypotension in the presence of euvolemia may need to be treated with inotropes and, if necessary, α_1-agonists.[199,200]

Therapy for elevated pulmonary artery pressures is directed at lowering PVR and unloading the RV. Reduction of PVR is accomplished by altering ventilation pattern, inspired O_2 concentration, and blood pH. Specifically, manipulating the pulmonary vascular bed in newborns and infants is a matter of regulating $Paco_2$, pH, PaO_2, PAO_2, and ventilatory mechanics.[201,202] $Paco_2$ is a potent mediator of PVR, especially in the newborn and young infant. Reducing $Paco_2$ to 20 mm Hg and increasing pH to 7.6 produces a consistent and reproducible reduction in PVR in infants with pulmonary artery hypertension. Manipulating serum bicarbonate levels to achieve a pH of 7.5 to 7.6 while maintaining a $Paco_2$ of 40 mm Hg has equal salutary effects on PVR.[203] Both the PaO_2 and the PaO_2 decrease PVR as well. In the circumstance of intracardiac shunts, changes in FiO_2 have little effect on PaO_2. Thus, by inference, a reduction in PVR induced by increasing the inspired O_2 concentration is probably a direct pulmonary vasodilatory effect of PaO_2 rather than PaO_2.

Ventilatory mechanics also play a major role in reducing PVR. Neonates and infants have a closing volume above functional residual capacity. Thus, at the end of a normal breath, some airway closure occurs. This process results in areas of lung that are perfused and yet underventilated. As these lung segments become increasingly hypoxemic, secondary hypoxic vasoconstriction occurs. The net effect is an increase in PVR. Therefore, careful inflation of the lungs to maintain functional residual capacity will selectively reduce PVR. In practice, this is accomplished with relatively large tidal volumes and low respiratory rates, which produce an exaggerated chest excursion. Generally, tidal volumes of 15 to 25 mL/kg are required. Respiratory rates of 15 to 25 breaths/minute are used for neonates and infants. A reduced ventilatory rate with large tidal volumes reduces mean airway pressure and provides a longer expiratory phase of ventilation.

Because PBF occurs predominantly during the expiratory phase of the respiratory cycle, the ventilatory pattern should be adjusted to allow an adequate distribution of gas throughout the lung during inspiration and a more prolonged expiratory phase to promote blood flow through the lungs. End-expiratory pressure must be applied cautiously during the post-CPB period. Low PEEP (3 to 5 mm Hg) prevents narrowing of the capillary and precapillary blood vessels, thereby reducing PVR. Higher PEEP or excessive mean airway pressure results in alveolar overdistention and compression of the capillary network in the alveolar wall and interstitium. This condition elevates PVR and reduces PBF.[149]

The final and perhaps the least well-recognized use of the mechanical ventilator is to assist in unloading the RV. During inspiration, intrathoracic pressure increases and creates an increased pressure gradient from the lung to the LA, promoting cardiac output. This ventilatory assist is commonly seen in patients with PAH or right ventricular dysfunction. An augmentation of the arterial pressure trace during inspiration is seen. The use of the ventilator to augment systemic blood flow is very similar to the thoracic pump concept used to explain blood flow during CPR.[204] The inspiratory assist must be balanced by the potential negative effects of increased mean airway pressure on PVR and right ventricular afterload. To maximize these cardiopulmonary interactions, high tidal volume with low respiratory rates should be employed.

Attempts to manipulate PVR through pharmacologic interventions have been generally unsatisfactory. Drugs that have shown the greatest promise in decreasing PVR both clinically and experimentally have been the phosphodiesterase inhibitors. Amrinone and milrinone are the only drugs of this class currently available in the United States. Both reduce PVR and SVR and increase RV contractility.[205] Isoproterenol has mild pulmonary artery–vasodilating properties in the normal pulmonary circulation.[206] It reduces PVR in adults after cardiac transplantation, but very few data support PVR reduction in infants and young children after cardiac surgery. In immature animals, the myocardium is less responsive to isoproterenol and causes tachycardia and increased myocardial O_2 consumption. These latter effects may reduce coronary perfusion and result in relative myocardial ischemia. Both prostaglandin E1 and prostacyclin have a pulmonary vasodilating effect; however, both drugs produce systemic hypotension, which severely limits their use.[207,208]

Because of the lack of specificity of vasodilator drugs on the pulmonary bed, newer pharmacologic methods of controlling pulmonary artery hypertension and elevated PVR are being sought. Two new concepts include ultra–short-acting intravenous vasodilators and inhaled vasodilating agents such as NO. Ultra–short-acting intravenous vasodilators are nonspecific potent vasodilators, with a half-life measured in seconds. Infusion of these drugs into the right side of the circulation produces a potent short-lived relaxation of the pulmonary artery smooth muscle.[209] Once the drug reaches the systemic circulation it is no longer functional. Adenosine and ATP-like compounds have these properties and may have clinical applicability in pulmonary artery hypertension in the future.[210]

Beginning in the past decade, several potent therapies for pulmonary hypertension have evolved.[201,202] A continuous intravenous infusion of prostacyclin improves pulmonary vascular hemodynamics, exercise tolerance, and survival in pulmonary hypertension.[211] Sildenafil is a selective phosphodiesterase type 5 inhibitor. Phosphodiesterase type 5 breaks down cyclic guanosine monophosphate. Sildenafil produces acute and relatively selective pulmonary vasodilatation and acts synergistically with nitric oxide.[212-214] Bosentan is a dual endothelin receptor blocker. Preliminary reports indicate that bosentan improves symptoms, exercise tolerance, and hemodynamics in patients with pulmonary hypertension. The drug is well tolerated and free of side effects apart from a dose-dependent increase in liver enzymes.[215] Lung transplantation is the only available surgical therapy for primary pulmonary hypertension; however, the 5-year survival remains less than 50%, and bronchiolitis obliterans remains the single most common cause of death.[216,217] Before listing for transplantation, all patients undergo a hemodynamic cardiac catheterization and drug study in which reversibility of pulmonary hypertension with increased inspired O_2 concentrations and NO is determined.[218] Inhaled iloprost, although used in adult centers, has not become routine in pediatric practice.

CPB with associated endothelial injury predisposes to the development of postoperative pulmonary hypertension in patients with CHD. Anatomic factors that impose either obstruction to PBF or residual left-to-right shunting need to be surgically addressed. Elevated LAP resulting from mitral valve disease or left ventricular dysfunction, pulmonary venous obstruction, branch pulmonary artery stenosis, or surgically induced loss of the pulmonary vascular cross-sectional area all raise right ventricular pressure and impose a burden on the right side of the heart.

NO, an endothelium-derived vasodilator that is administered as an inhaled gas, represents the most promising development in the therapy for elevated PVR in patients with CHD (see Chapter 104). Although nonselective, it is rapidly inactivated by hemoglobin and, when inhaled, produces no systemic vasodilation.[219] NO reduces pulmonary artery pressure in adult patients with mitral valve stenosis and in selected pediatric cardiac patients with PAH.[220-222] The congenital cardiac patient population in whom NO appears to be effective is patients with acute PVR elevation after open-heart surgery, as well as preoperative pulmonary hypertension accompanying specific anatomic conditions (e.g., total anomalous pulmonary venous return, congenital mitral stenosis).[220,222] Because it acts directly on vascular smooth muscle, NO remains effective despite the post-CPB endothelial injury frequently encountered in children.[223] Some centers routinely employ NO in low dose (1 to 5 ppm) after a Fontan operation when the CVP-LAP gradient exceeds 10 mm Hg.[224] Finally, NO can provide diagnostic information that helps distinguish reactive pulmonary vasoconstriction from fixed anatomic obstructive disease either in the postoperative surgical patient or in the patient undergoing pretransplant evaluation.[225,226] In the latter, the distinction between pulmonary vasoconstriction and advanced pulmonary vascular occlusive disease will influence the prediction as to whether a child with pulmonary hypertension in association with either CHD or cardiomyopathy will survive a heart transplant or requires replacement of both heart and lungs.

Management strategies for postoperative pulmonary hypertension and treatment of pulmonary hypertensive crises include sedation, moderate hyperventilation (maintaining P_{CO_2} between 30 and 35 mm Hg), moderate alkalosis (pH >7.5), increased inspired O_2, optimization of PEEP (to maximize functional residual capacity), pulmonary vasodilators (e.g., NO), and the creation or maintenance of an intracardiac right-to-left shunt in an attempt to maintain cardiac output.[227,228] NO is also useful in the manipulation of PVR after Fontan-type procedures.[229] Care should be exercised in weaning NO in patients, because abrupt withdrawal can precipitate rebound pulmonary hypertension and pulmonary hypertensive crises.[229,230]

ANTICOAGULATION, HEMOSTASIS, AND BLOOD CONSERVATION

Modern pediatric cardiac anesthesia must include the principles and practice of effective anticoagulation, hemostasis, and blood conservation (see also Chapters 61 through 63). Bleeding after CPB remains a significant problem in pediatric cardiac surgery.[231] Continuing blood loss after CPB requiring blood component replacement is associated with hemodynamic compromise as well as morbidity from multiple donor exposures. In pediatric patients, restoration of hemostasis has proved difficult; diagnosis of the problem and treatment are marginally effective.

Neonates, infants, and children undergoing cardiac surgery with CPB have a higher rate of postoperative bleeding than that seen in older patients.[231] This is due to several factors. First, exposure to the nonendothelialized extracorporeal circuit is disproportionate, which produces an inflammatory-type response. This inflammatory response to CPB is inversely related to patient age—the younger the patient, the more pronounced is the response.[11] Because complement and platelet activation are linked to the activation of other protein systems in the blood (i.e., fibrinolytic), it is probable that this hemostatic activation, which results in impaired hemostasis and increased bleeding tendency, plays a major role during pediatric cardiac surgery. Second, the type of operation performed in neonates and infants usually involves more extensive reconstruction and suture lines, creating more opportunities for surgical bleeding than in adult cardiac patients. Operations are also frequently performed using DHCA, which may further impair hemostasis.[232] Third, the immature coagulation system in neonates also may contribute to impaired hemostasis.[233] Although procoagulant and factor levels may be reduced in young patients with CHD resulting from immature or impaired hepatosynthesis,[234] functional bleeding tendencies are usually not present before surgery. Finally, patients with cyanotic heart disease demonstrate an increased bleeding tendency before and after CPB.

CPB is a significant thrombogenic stimulus requiring anticoagulation with heparin before its initiation. Heparin is usually administered empirically based on patient

weight, and its effect is followed by activated clotting time monitoring. Because the heparin effect is primarily due to coupling with antithrombin III and because of the age-related differences and quantitative differences in procoagulants and inhibitors, variability of heparin dosing and its effect has been a concern. High heparin sensitivity is observed in the first week of life and then decreases progressively until about 3 years of age, when values approach those observed in adults.[235] These findings are consistent with evidence in infants of variable quantities of both procoagulants and inhibitors, especially prothrombin and antithrombin III.[236] Heparin administration also must include a consideration of the quantity and composition of the priming volume for CPB, especially if fresh frozen plasma is added. The authors recommend a heparin dose of 200 units/kg plus an additional dose of 1 to 3 units/mL of priming solution and maintaining the activated clotting time above 480 seconds.

Heparin is neutralized with protamine dosed according to the quantity of heparin administered or based on body weight. Protamine excess may actually contribute to postoperative bleeding.[237] It appears that the protamine dose requirement is high for neonates and decreases with increasing age of the patient. The relatively increased protamine requirement for young compared with older children and adults is indicative of higher circulating heparin levels after CPB.[238] Delayed hepatic clearance of heparin resulting from organ immaturity and the predominant use of hypothermic circulatory arrest in the young will decrease metabolism and excretion of heparin. We typically administer protamine 4 mg/kg in neonates, whereas 2 mg/kg usually restores the activated clotting time to baseline values in adolescents and adults. Interpatient variability mandates some form of individual assessment to guide drug dose to prevent excess protamine.[237]

Neonates and young infants with CHD will have low circulating levels of procoagulants and inhibitors. The thrombogenic and dilutional effects of CPB further contribute to hemostatic abnormalities after CPB. Formed blood elements such as leukocytes and platelets may be activated, and procoagulants may be diluted by CPB. Furthermore, DHCA causes increased clotting and fibrinolytic activity. The lower the temperature, the higher the degree of hemostatic activation. Therefore, the causes of bleeding after CPB are many.[238] Injudicious use of blood products to correct individual coagulation abnormalities separately can further exacerbate dilution of existing procoagulants, as well as carrying the risks for multiple donor exposure. Because the transfusion of blood products is associated with numerous complications, transfusion is to be assiduously avoided, unless specifically indicated by an impairment in tissue oxygenation or documented coagulopathies with clinically significant bleeding. All efforts at blood conservation during cardiac surgery should be routinely employed by all members of the operative team, intraoperatively as well as postoperatively.

Bleeding after CPB is not an unusual occurrence (see also Chapter 66). The surgeon should first attempt to identify any obvious source of surgical bleeding at the sites of repair. Next, adequate protamine reversal of heparin is assessed by measuring an activated clotting time. In general, standard coagulation tests show a prolongation of the partial thromboplastin time, prothrombin time, hypofibrinogenemia, dilution of other procoagulants, and prolonged bleeding time in many pediatric patients, with and without bleeding (Fig. 94-13). The most common reason for persistent bleeding is platelet dysfunction.[239,240] Under such circumstances, administration of platelets is warranted in the presence of bleeding. Routine administration of blood products to correct laboratory coagulation abnormalities in the absence of bleeding is never clinically indicated. After platelets have been given and if bleeding is still present, reassessment and repeat platelet infusion or the administration of cryoprecipitate or fresh frozen plasma may be beneficial. Under most circumstances, meticulous surgical technique, appropriate administration of protamine, adequate patient temperature, and platelet infusion will correct excessive bleeding. In neonates, excessive bleeding and the escalating dilutional effects of selective component therapy on the remaining procoagulants make the treatment of bleeding difficult. The use of fresh whole blood may be warranted under these circumstances. The administration of fresh whole blood (<48 hours old) after CPB can meet all the hematologic requirements with minimum donor exposure. The efficacy of whole blood in restoring hemostasis and reducing blood loss after CPB has been demonstrated in patients younger than 2 years of age undergoing complex surgical repairs.[231]

It is our practice to arrive at an optimum hematocrit for the patient after discussion with the surgeon based on the individual patient's lesion and complexities. This is achieved with the minimal amount of product that can be used to achieve the hematocrit level both on bypass

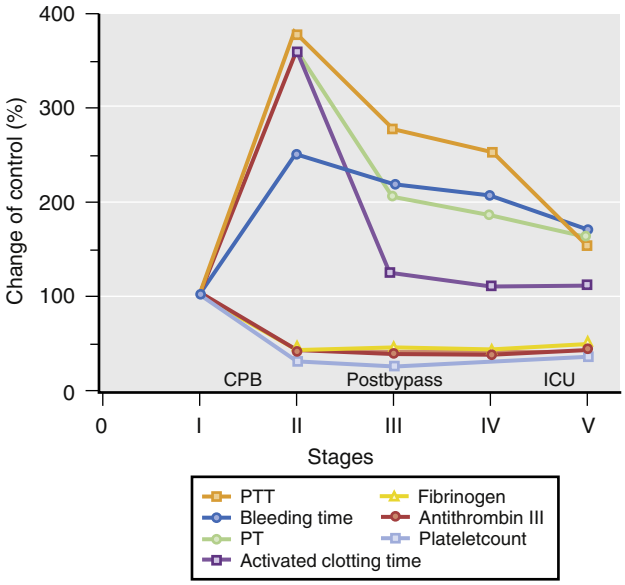


Figure 94-13. Plot of blood coagulation profile changes before, during, and after cardiopulmonary bypass (*CPB*) in 25 children. Clotting times and coagulant factors are shown as percent change from control. Stage I, baseline, before CPB; stage II, post-CPB, before protamine reversal of heparin; stage III, after protamine; stage IV, just before leaving the operating room; stage V, after 3 hours in the intensive care unit (*ICU*). *PT,* Prothrombin time; *PTT,* partial thromboplastin time.

and after bypass, minimize bleeding and coagulopathy, minimize donor exposure, and mitigate against transfusion-related acute lung injury (see also Chapter 61).

Many attempts have been made to reduce bleeding after CPB by pharmacologic interventions. Desmopressin acetate and the antifibrinolytics aminocaproic acid and tranexamic acid have been tried with variable success in significantly reducing postoperative blood loss after cardiac surgery.[241-243] The proteinase inhibitor aprotinin showed promise in its ability to reduce postsurgical cardiac blood loss, but it was removed from the United States market because of concerns of life-threatening anaphylactic reactions.[232,244-248] Antifibrinolytics exert their effects by reversibly binding to lysine analogue sites on plasminogen, a molecule primarily responsible for the breakdown of fibrin. By inhibiting plasminogen, and therefore plasmin, the procoagulant effects of fibrin remain. In a recent large-scale observational study of 22,258 patients, aprotinin was found to have effects similar to those of both aminocaproic acid and tranexamic acid in terms of reducing bleeding requiring surgical intervention and mortality.[249] Given the risk for analyphylatic reactions with aprotinin and similar benefits in surgical bleeding with the antifibrinolytics, many institutions report favorable use of aminocaproic acid and tranexamic acid. We have chosen to use aminocaproic acid as an antifibrinolytic in neonates undergoing complex procedures, and for repeat operations before sternotomy and repeat dosing at the start of CPB.

The techniques of blood conservation must be continued during the postoperative period. Isolated coagulation abnormalities are often present in the postoperative patient with uncomplicated cardiac issues (see Fig. 94-13). Usually, these coagulation abnormalities self-correct during the first postoperative day and are not associated with excessive bleeding. Therefore, routine correction of these abnormalities with infusion of blood products is not warranted. Administration of blood products should not occur in the absence of clinical evidence of bleeding and the identification of a specific defect requiring targeted component therapy. Routine use of blood products for volume replacement is also to be avoided; lactated Ringer or saline solution can be satisfactorily administered at a reduced cost without the hazards associated with transfusion.

POSTOPERATIVE MANAGEMENT

Immediate postoperative care of the pediatric patient who has undergone cardiothoracic surgery is an important period in the overall sequence of anesthetic and surgical management. Although the primary influence on outcome is determined by the conduct of the operation, postoperative care is an important factor. As a member of the operative team, it is necessary that the anesthesiologist understand and become involved during the immediate postoperative period. Detailed principles of postoperative management of pediatric cardiac surgical patients are beyond the scope of this chapter. However, a few general guiding principles and approaches are given to provide fundamental knowledge for the anesthesiologist.

The postoperative period can be characterized by a series of physiologic and pharmacologic changes as the body convalesces from the abnormal biologic conditions of CPB and cardiac surgery. During this period, the effects of the cardiac operation, any underlying disorders, the effects of hypothermic CPB, and special techniques such as DHCA may create special problems. In the immediate postoperative setting, abnormal convalescence and specialized problems must be recognized and managed appropriately. Fortunately, most patients are able to balance the cost imposed by the physiologic trespass created by the surgical repair and the effects of CPB against the benefit of reduced pathophysiologic loading conditions, resulting in low morbidity and mortality.

Therefore, the guiding principle in the management of the postoperative patient is an understanding of both normal and abnormal convalescence after anesthesia and cardiac surgery. The immediate postoperative period, even that of normal convalescence, is one of continuous physiologic change because of the pharmacologic effects of residual anesthetic agents and the ongoing physiologic changes secondary to abrupt alteration in hemodynamic loading conditions, surgical trauma, and extracorporeal circulation. Anesthesia and surgery affect not only the patient's conscious state but also cardiovascular, respiratory, renal, and hepatic function; fluid and electrolyte balance; and immunologic defense mechanisms. Despite these changes, postoperative care should be predictable and standardized for most patients undergoing cardiac procedures.

In general, the four temporal phases of postoperative management in the cardiac patient are (1) transport to the ICU, (2) stabilization in the ICU, (3) weaning from inotropic and ventilatory support, and (4) mobilization of fluids. Patients proceed through these phases at variable rates based on such factors as the underlying disease process, preoperative medical condition, sequelae of the surgical procedure, duration of CPB, and presence or absence of intraoperative complications. One of the most important functions of the ICU team is to identify postoperative complications in the patient who convalesces abnormally and to provide interventional therapy. Because physiologic change after cardiac surgery is dramatic but self-limiting during normal convalescence, recognition of abnormal processes can be difficult. Under such circumstances a uniform, multidisciplinary approach with experienced clinicians and nurses facilitates the identification of any abnormalities in convalescence. These abnormalities often are indications for closer observation, more invasive monitoring, pharmacologic intervention, and increased cardiopulmonary technical support. Complications include hypovolemia, residual structural heart defect, right and left ventricular failure, hyperdynamic circulation, pulmonary artery hypertension, cardiac tamponade, arrhythmias, cardiac arrest, pulmonary insufficiency, oliguria, seizures, and brain dysfunction. It is critical to detect these departures from the normal convalescent course and to treat them aggressively.

One important area in which the anesthesiologist can aid the recovery of the cardiac patient is pain control (see also Chapter 97). Pain and sedation are among the most common problems requiring ICU intervention.

Many factors influence the onset, incidence, and severity of postoperative pain. The attenuation of the stress response in the immediate postoperative period using infusions of potent opioids in the critically ill infant reduces morbidity.[100] Attenuation of postoperative pain can be attempted with a preoperative medication and an intraoperative anesthetic management technique that includes the use of potent opioids. Patients who receive no opioids preoperatively or during the operative procedure will require analgesics in the immediate postoperative period once the inhalation anesthetic is eliminated. Most cases of postoperative pain can be managed by the administration of small intravenous doses of opioids, usually morphine. This is important in a patient being weaned from the ventilator during the early postoperative period. Patients who are intubated and ventilated overnight should receive adequate sedation and pain control until ventilatory weaning is begun. This is usually accomplished by a continuous infusion of a benzodiazepine and an opioid. Continuous infusion of sedatives and analgesics results in a more consistent and reliable control of postoperative pain. When separated from mechanical ventilation, the patient is concurrently weaned from the sedatives and analgesics. Under these circumstances, careful titration of opioids often results in prompt pain relief. In patients with reactive pulmonary artery hypertension, opioids have been shown to prevent hypertensive crisis.[97]

Regional anesthesia may be used for postoperative pain control in infants and children after thoracotomy (see also Chapter 92). This method avoids opioid-induced respiratory depression from intravenous doses of these drugs. The administration of opioids in the epidural space is a very effective approach to pain management. This technique is used in children for postoperative pain control when given in the epidural space via the caudal route as a "single shot" or by a small caudal catheter. Morphine or hydromorphone provides effective analgesia with a duration of 6 to 12 hours, with no significant respiratory depression. Caudal morphine diluted in 0.05 to 0.075 mg/kg delivered in a total volume of 1.25 mL/kg of sterile saline has been used with good success in our practice. The use of regional anesthesia for postoperative pain appears to be best suited for the child extubated in the early postoperative period. Relative contraindications of this technique include hemodynamic instability and patients with abnormal clotting profiles with continued active bleeding. Using this regional technique, better arterial oxygenation, a more rapid ventilator weaning, and decreased postoperative respiratory complications may be expected. However, urinary retention occurs frequently in patients without a bladder catheter. Generally, no treatment is required.

Children requiring large thoracotomies or a bilateral thoracosternotomy (i.e., "clamshell") incision merit consideration for thoracic epidural analgesia. This technique significantly reduces the respiratory depression and pulmonary mechanics abnormalities that accompany the quantity of systemic opioids that would be necessary to provide adequate analgesia for these excruciatingly painful incisions. If the procedure requires systemic heparinization, we will typically defer placement of these catheters until the heparin effect is neutralized. For the patient undergoing coarctation repair via a left thoracotomy, we place the caudal or epidural catheter after demonstration of motor function in the lower extremities. For patients undergoing heart, lung, or both transplantations, a thoracic epidural catheter is placed at a time in the postoperative period when the patient can be weaned from intravenous medications that will adversely affect the patient's ability to breathe in close proximity to the planned extubation. It is common for these patients to need a functioning thoracic epidural catheter for several days.

POSTOPERATIVE NEUROPSYCHOLOGIC MORBIDITY

Neurologic morbidity has been identified to be increasingly problematic in neonates and infants with CHD as surgical mortality rates have improved (see also Chapter 99). Although early postoperative CNS sequelae such as stroke and seizures occur in a small percentage of neonates with CHD, the importance of more subtle neurologic abnormalities at long-term follow-up is being increasingly recognized.[217,226,250]

These findings may include fine and gross motor impairments, speech and language delays, disturbances in visual-motor and visual-spatial abilities, attention-deficit disorders, learning disorders, and impaired executive functioning. The presence of congenital brain disease in patients with CHD represents a challenge in improving long-term neurologic outcomes. Many neonates with CHD have congenital structural brain abnormalities, chromosomal abnormalities, or both, as well as physiologic abnormalities that may impair brain development. Brain abnormalities on head ultrasonography have been noted in one fifth of full-term infants undergoing heart surgery, with half of the abnormalities being present preoperatively.[250]

Postoperatively, secondary neurologic injury may be related to post-CPB alterations in cerebral autoregulation and additional hypoxic-ischemic insult, seizures, or other issues associated with prolonged ICU stay. In addition to prenatal and modifiable perioperative factors, genetic and environmental factors are known to be important. Unfortunately, modifiable perioperative factors may explain less of the variability in long-term outcomes than do patient-specific factors.

New, postoperative neurologic injury may be detected clinically in over 10% of infants,[7] and in over 50% using more sensitive brain imaging techniques such as MRI.[251,252] Given that new neurologic injury can occur at various time points during the neonate's hospitalization, perioperative attention to reducing known risk factors is critical. Mechanisms of CNS injury in infants undergoing cardiac surgery include hypoxia-ischemia, emboli, reactive O_2 species, and inflammatory microvasculopathy. Preoperatively, the primary focus is on preventing hypoxic-ischemic injury and thromboembolic insults. Modifiable intraoperative factors associated with CNS injury include, but are not limited to, pH management, hematocrit during CPB, regional cerebral perfusion, and the use of DHCA. The adverse effects of CPB may be greater in infants than larger children or adults given their immaturity in organ function and tissues and the size of

the CPB circuit relative to their body size.[253] However, a significant amount of research has been conducted in the area of intraoperative prevention of neurologic injury. With ongoing changes in technology and new therapies, the conduct of CPB and other support techniques have been actively under investigation.

The developmental consequences of exposure to general anesthetics is not well understood and is difficult to elaborate on in the absence of prospective randomized controlled trials, because of multiple factors that affect neurologic outcome in this population. Current literature suggests that multiple exposures, cumulative doses of exposure, and exposure in infancy might increase the risk for neurodevelopmental delay.[254-256] Thus, pediatric cardiac anesthesia is associated with all three risk factors, so attempting to minimize time of exposure, bundling of necessary procedures, and delaying nonessential procedures to an age associated with less neurologic risk might be appropriate. Careful choice of anesthetic agents that do not act on different neuroreceptors at key time points in development might be critical. Our current practice has evolved to using fentanyl 5 to 10 µg/kg body weight, which allows earlier extubation and may minimize anesthesia-related neurologic risk. Current multicenter trials funded by the National Institutes of Health are exploring this concept and the use of a pure α_2 agonist (dexmedetomidine) for neuroprotection during this vulnerable period.

MECHANICAL ASSIST DEVICES

Survival in children with congenital cardiac as well as pulmonary defects has improved over recent decades as a result of improved preoperative management, surgical techniques, anesthesia management, drug therapies, and postoperative management. Despite these advances, patients may still require therapies for both acute and chronic heart failure that are refractory to medical therapy. Mechanical support in the form of ECMO or ventricular assist devices (VADs) may then need to be instituted. Examples of conditions that may require support include failure to wean from CPB, acute cardiac arrest, malignant arrhythmia, and worsening myocardial function secondary to the underlying congenital defect or related to acquired cardiomyopathy. Fortunately, however, the numbers are small, with less than 2% of post-CPB patients requiring this intervention.[257] Mechanical support can thus be used as a treatment option to allow for recovery of ventricular function, as a bridge to transplant, or to support the heart in those with marginal functional reserve requiring invasive diagnostics or treatments (e.g., Williams syndrome with severe supravalvular pulmonary or aortic stenosis). As with any therapy, contraindications must be excluded before embarking on the use of a mechanical assist device. These contraindications may include extreme prematurity, severe and irreversible multiorgan failure, incurable malignancy, and preexisting neurologic devastation.[257] Anesthetic management in the use of ECMO is supportive, with management limited to assistance in the resuscitative efforts and hemorrhage associated with the cardiac surgery that was ongoing at the time of conversion to ECMO. Once the patient is on full ECMO support, ventilation is continued but at a slower rate of ventilation on the order of 10 breaths/minute, with a peak pressure of 20 cm H_2O, PEEP set at 5 to 10 cm H_2O, and FiO_2 decreased to about 40%. These settings aid in the prevention of atelectasis with management of CO_2 and O_2 related to flow across the circuit membrane. This is very different from the patient into whom a VAD is placed. Here the anesthesiologist continues to manage the patient as for routine CPB weaning. Obviously differences exist in this scenario. If a systemic VAD is placed, careful attention must be given to the ventricle pumping blood into the pulmonary bed because failure of this ventricle will have disastrous consequences. Thus, management tailored to unload this pulmonary ventricle is vitally important and will include inodilators in the form of phosphodiesterase inhibitors, inotropic support, and possibly even inhaled NO to decrease PVR and promote forward flow. In association with the perfusionist, intravascular volume loading is assessed and maintained for effective functioning of the VAD and thus adequate offloading of the assisted ventricle. Careful attention to pulmonary function is also vital. Adequate pulmonary toilet, recruitment maneuvers, and appropriate ventilatory parameters must be used. As will be alluded to later, bleeding is a potential in the implantation of the VAD and thus a clear strategy must be planned for in the form of antifibrinolytics, adequate volumes of blood and blood products, and even possibly the use of activated clotting factors (e.g., factor VII).[258]

As can be seen in Table 94-10 differences can be appreciated between assist devices. The potential for bleeding exists at the time of insertion of both of these modalities; however, it would seem from clinical experience that because of the extensive dissection and need for sizeable ventriculotomy, implantation of a VAD (and especially bi-VAD) is more problematic. The requirements of anticoagulation to keep the activated clotting time in the range of 180 to 200 for ECMO also may lead to ongoing and significant bleeding, especially if placed into a patient who requires support in the immediate perioperative phase. The use of an ECMO circuit with a membrane oxygenator requires ongoing intravenous anticoagulation with maintenance of the activated clotting time in the aforementioned range. Apart from the immediate postoperative phase, patients with VAD systems can be transitioned to oral agents. A two-part therapy is recommended. Antiplatelet therapy includes aspirin or clopidogrel. The

TABLE 94-10 COMPARISON OF EXTRACORPOREAL MEMBRANE OYGENATIONCMO VERSUS VAD

Comparison Factors	ECMO	VAD
Bleeding at insertion	++	++
Sternotomy	Not required	Required
Left atrial venting	±	–
Blood product use	+++	+
Number of cannulae for biventricular support	2	4
Pulmonary support	+	–
Intravenous anticoagulation	+	±
Duration of support	Weeks	Months
Emergent support	Yes	No
Patient mobility	–	+

ECMO, extracorporeal membrane oxygenation; *VAD,* ventricular assist device.

second part of the therapy will entail the use of anticoagulation with either warfarin (Coumadin) or subcutaneous low-molecular-weight heparin.[257]

As previously mentioned, these modalities are used as a potential bridge to transplant and, thus, exposure to donor antigens is of great importance. A study by Stiller and associates[259] comparing the volume of blood products used demonstrated that the volume was less in those treated with a VAD in a period up to 8 days after insertion. Importantly, the authors pointed out that this difference remained even when support was started at a time remote from surgery.[259]

Three potential disadvantages exist in the use of the VAD system. The lack of pulmonary support when using the VAD limits its use to patients whose lung function is adequate. From Table 94-10 it can be seen that when biventricular support is needed the patient will require two separate VAD devices, necessitating the placement of four cannulas, which may be technically difficult in a very young child. The third disadvantage is that VAD placement cannot be performed in a code situation or at the bedside as with ECMO.

Important advantages of the VAD system are the ability of patients to ambulate while on support and that VAD support can be maintained for months in contrast to the weeks only of ECMO support. Another important advantage over ECMO is that these patients will not require further venting of the LA. In patients on ECMO this is achieved by the placement of a left atrial vent at the time of sternotomy or a balloon atrial septectomy, which may require transfer to the catheterization laboratory with the possible complications associated with transport of a patient on an ECMO circuit.

Despite successful resuscitation and placement onto mechanical assist devices, morbidity and mortality remain high, with ECMO appearing to have worse outcomes. The mortality rate for ECMO in the 1990s was on the order of 47%, with survival in series published in the early 2000s not showing much improvement.[260-263] In contrast, the survival in those into whom a VAD is placed appears to be superior within the quoted series up to 80% of patients surviving to transplantation or being successfully weaned from support.[262,264] In the study by Blume and co-workers,[261] however, it was noted that associated CHD, and patients who are younger and smaller, have a higher mortality than those with fulminant myocarditis and cardiomyopathy.[261] Alongside survival data, the next most important marker is neurologic outcome, and it appears that this is better in the VAD group.[265,266] Risk factors for poor neurologic outcome were once again of low weight and duration of DHCA, both of which place patients on ECMO at a survival disadvantage because patients on ECMO will be smaller and some of those who undergo DHCA for repair of congenital anomalies will require emergent ECMO support to wean from CPB or in the immediate postoperative phase.[267]

Survival predictors are important in our management of these patients. One common variable that can predict survival is the return of ventricular function between 3 and 5 days after the initiation of support, and should the support be required for longer periods, morbidity and mortality increase.[263,267] Both of these modalities have been used successfully as a bridge to transplantation, with patients with a VAD having a greater than 80% survival to transplantation and patients on ECMO showing a less than 60% survival. Yet ECMO is used often in the infant population and in those with complex CHD, both of which are factors known to increase mortality among VAD patients.[267] The important causes of morbidity and mortality in patients on both of these modalities include cerebrovascular events secondary to either hemorrhagic or embolic phenomena, circuit-related issues (e.g., circuit thrombosis), renal failure requiring hemofiltration, sepsis, ongoing hemorrhage, and multiple-organ failure.

Although these modalities are often compared to each other, they both have unique places in the care of children with cardiac disability. ECMO has a great advantage in that it can be employed rapidly in a code situation for a patient of any age or size. In the past, size has been the limiting factor for implantation of VAD systems into pediatric patients. The Berlin Heart VAD (Berlin Heart AG, Berlin, Germany) is available for use even in neonates. The system has been employed in Europe for over 10 years and has pump sizes from 10 to 80 mL. At this time the device is available only for emergency compassionate use in the United States. From this, however, it can be appreciated that these two modalities can certainly complement each other, with ECMO being used acutely; once the patient is physiologically stable, but still requiring support, a VAD can be used should long-term support be warranted.

A newer mechanical assist device for use in children is the temporary Total Artificial Heart (TAH) system. The TAH system is indicated for use as a bridge to transplant for patients in imminent risk for death from biventricular failure. The implantation and use of this device is unique in that it requires the complete removal of the native myocardium, such that recovery without transplantation is not possible. Once the myocardium is removed, inflow and outflow pumping chambers are sown into the right and left heart vessels. Sizing requirements include patient body surface area of 1.7 m^2 or greater, echocardiographic left ventricular end-diastolic diameter of 70 mm or greater, a CT scan with an anterior-to-posterior dimension at the 10th thoracic vertebrae of 10 cm or greater, and a chest radiograph with a cardiothoracic ratio of 0.5 or greater. Smaller TAH devices may be available soon, which would allow implantation in smaller patients. This device has been used successfully as a bridge to transplant in a patient with failing Fontan physiology who later went on to receive a heart transplant.

ANESTHESIA FOR HEART AND LUNG TRANSPLANTATION

Although perioperative management for thoracic organ transplantation is considered elsewhere in this text, the application of these procedures to children requires some specific modification (see also Chapter 75). Differences include the characteristics of the candidates, preparation of these children, anesthetic management, surgical considerations, post-CPB management, and outcome. Even though some of the earliest heart transplant procedures were performed for congenital heart malformations, this indication became rare by the early 1980s. In 1984, over

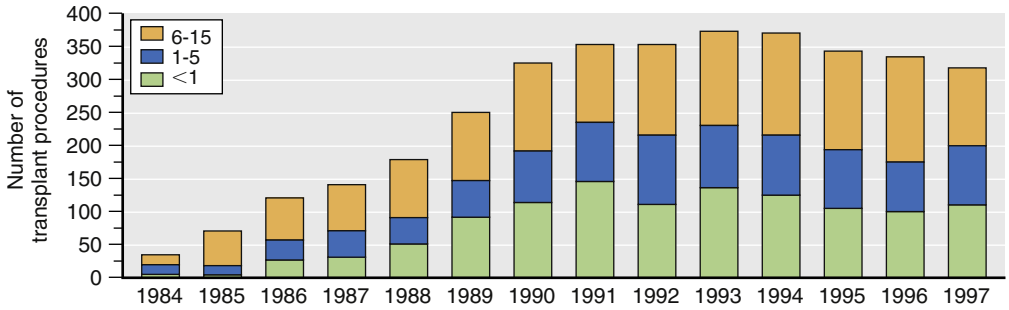


Figure 94-14. Demographic data for pediatric heart transplantation by age. Stacked bar graph illustrates the total number and age distribution for heart transplantation in patients younger than 16 years of age. Note the rapid rise in transplant procedures performed during the late 1980s, with particular growth in the population of children 5 years of age and younger. Having peaked in the mid-1990s, the total number of transplant procedures (both adult and pediatric) has declined slightly, but the relative age proportions within the pediatric population remain relatively constant. *(Data from the Registry of the International Society for Heart and Lung Transplantation, Addison, Tex.)*

60% of the few pediatric heart transplant procedures were performed in patients with cardiomyopathy, usually adolescents. In the next decade, a dramatic rise in the number of infants and young children with congenital heart malformations treated with heart transplantation resulted in a marked shift in the demographics (Fig. 94-14).[268] By 1995, over 70% of the children receiving heart transplants were younger than 5 years of age, with half of those younger than 1 year. The overwhelming majority of these infants received transplants for congenital heart malformations for which reconstructive options either had failed or were not believed to exist (Fig. 94-15).[268] The implications of this shift reach into every element of perioperative management.

Children considered for heart transplantation are more likely to have pulmonary hypertension than adults. Most adult transplant programs will not offer heart transplant therapy to patients with PVR over 6 Wood units/m^2.[269] The exclusion threshold in infants and children remains controversial. Some programs accept patients with PVR as high as 12 Wood units/m^2, particularly if the pulmonary vasculature responds to vasodilators such as O_2, NO, calcium channel blockers, or prostacyclin.[270] Neonates are generally assumed to have elevated PVR, but outcome data from some programs suggest that the importance of this factor for postoperative outcome is substantially less in the first year of life, perhaps because the infant donor hearts, having recently undergone transitional circulation, are better prepared to cope with the right ventricular pressure load that elevated PVR imposes.[271]

The anesthetic plan for pediatric heart transplantation must accommodate a wide spectrum of pathophysiology. Recipients with congenital heart malformations benefit from the analysis of loading conditions and optimizing hemodynamics discussed previously. Although a few of these patients undergo heart transplantation because the natural history of reconstructive heart surgery poses greater risk despite reasonable ventricular function, most candidates exhibit some manifestations of impaired ventricular performance. Accordingly, they require careful titration of anesthetic agents with minimal myocardial depressant characteristics to avoid cardiovascular collapse. In this fragile population, even modest doses of opioids can be associated with marked deterioration in

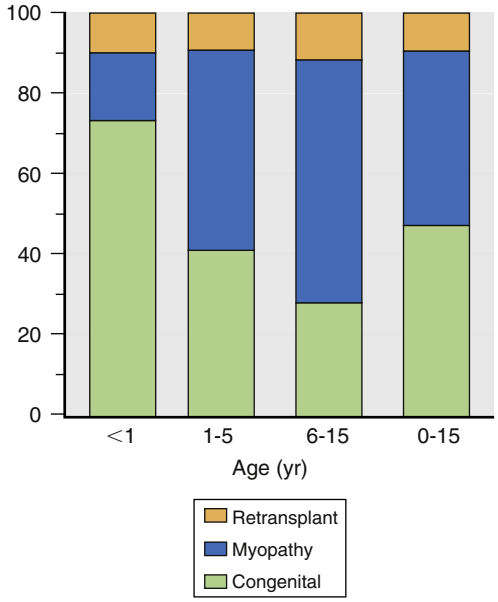


Figure 94-15. Indication for heart transplantation in children. Over the past 2 decades, the major indications for pediatric heart transplantation were nearly equally divided between congenital malformation and cardiomyopathy. In later years, pediatric recipients with congenital malformations assumed a slight plurality as a result of shifting age demographics. As illustrated, younger children are more likely to undergo heart transplantation because of congenital malformation. *(Data from the Registry of the International Society for Heart and Lung Transplantation, Addison, Tex.)*

systemic hemodynamics, presumably by reducing endogenous catecholamine release. As with most congenital heart patients, skilled management of the airway and ventilation represents crucial elements in a satisfactory induction, particularly in the presence of elevated PVR. No matter how elegant the anesthetic plan in conception and implementation, a certain proportion of these children will decompensate on induction, necessitating resuscitative therapy.

Although orthotopic heart transplantation poses some technical challenges in neonates and young infants, the replacement of an anatomically normal heart is less complex than several reconstructive heart procedures

commonly performed in patients at this age. However, the need to adapt this procedure to incorporate repair of major concurrent cardiovascular malformations requires the consummate skill and creativity that remain the province of a few exemplary heart surgeons in congenital disease.[272,273]

Having withstood extended ischemic periods, heart grafts are extraordinarily intolerant of superimposed residual hemodynamic loads that may accompany imperfect vascular reconstruction. The extensive vascular repair and, particularly in older children with long-standing hypoxemia, the propensity to coagulopathy together elevate hemorrhage to a major cause of morbidity and even mortality in pediatric heart transplantation. Nevertheless, once successfully implanted, these grafts will respond to physiologic factors that stimulate growth and adaptation in the developing infant and child.[274]

Management considerations during separation from CPB and the early postoperative period are primarily focused on three pathophysiologic conditions: myocardial preservation, denervation, and PVR. Even expeditious transplant procedures usually force the heart to endure ischemic periods that exceed those encountered during reconstructive surgery. Although some researchers believe the infant heart is more tolerant of extended ischemia, these hearts will demonstrate a period of reperfusion injury, and virtually all require pharmacologic and, in some cases, mechanical support.[271] In addition, endogenous adaptive responses and exogenous pharmacologic agents that act by myocardial sympathetic activation are ineffective in the denervated graft. Because the majority of children presenting for heart transplantation exhibit some element of elevated PVR, even with isolated end-stage cardiomyopathy, the RV of a newly implanted heart is particularly vulnerable to failure.

Ventilatory and pharmacologic interventions are usually configured to exert a favorable impact on PVR and provide inotropic and chronotropic support. Once the lungs are fully expanded, we ventilate to $Paco_2$ values in the low 30 mm Hg range using an FiO_2 of 1. Virtually all recipients receive low-dose dopamine 3 to 5 µg/kg/minute and isoproterenol 0.02 to 0.05 µg/kg/minute to promote inotropy, chronotropy, and lower PVR. In the event that these do not provide sufficient inotropy in the presence of more significant postischemic dysfunction, additional agents are added (e.g., milrinone, epinephrine). Most transplant centers have a specific regimen for immunosuppression to be initiated in the perioperative period. As with adults, pediatric transplant programs typically employ triple-drug immunosuppression with a calcineurin inhibitor (e.g., cyclosporine, tacrolimus), antimetabolite (e.g., azathioprine), and steroid. After an interval without rejection, some pediatric programs will taper and discontinue one or even two of these agents, particularly in neonates, in whom some element of tolerance is thought to develop.[275,276]

National statistics indicate that the outcome from pediatric heart transplantation is slightly less favorable than comparable results in adults.[268] The principal risk factors are age younger than 1 year and congenital heart defects. Because these factors are closely related (i.e., the vast majority of infants younger than 1 year of age undergo transplantation for a congenital heart defect), it is difficult to determine the independent effect of age. Concurrent repair of structural cardiovascular anomalies substantially increases perioperative risk for hemorrhage, residual hemodynamic loading conditions, and right-sided heart failure from elevated PVR. When these two factors are taken together, infants younger than 1 year of age have an operative mortality rate of 24%, more than twice that of older children.[268] Beyond the early postoperative period, mortality rates are quite comparable for all age groups. Nevertheless, the sequelae of rejection and the consequences of the requisite immunosuppression result in significant ongoing morbidity and mortality. Because even the best transplant recipients have achieved only a 28% 14-year survival rate, these procedures must be considered palliative for children.[268]

Lung and heart-lung transplantation have achieved respectable operative survival rates in children.[277,278] They remain the only viable surgical therapy for infants and children with severe pulmonary vascular disease and selected progressive pulmonary diseases. These remain uncommon procedures in pediatrics. Lung transplantation carries the additional morbidity of obliterative bronchiolitis, a debilitating small airway disease that results in gradual deterioration in flow-related pulmonary functions over time. Despite an operative mortality rate that is currently less than 20%, the 3-year survival rate is only 50% to 60%.[268,277]

Patients with transplanted hearts also present for surveillance cardiac catheterizations, biopsies, and other procedures.[257,279-281] The anesthesia plan in these patients should take into account the physiologic and pharmacologic problems of allograft denervation, the side effects of immunosuppression, the risk for infection, and the potential for rejection.[279-281] Cardiac allograft vasculopathy is the leading cause of morbidity and mortality after transplantation, leading to progressive graft dysfunction with heart failure, an increased risk for dysrhythmia, and the possibility of arrhythmogenic sudden death. Conventional revascularization procedures are ineffective because cardiac allograft vasculopathy is caused by intimal proliferation; thus, retransplantation is the only therapeutic option. Hyperlipidemia after heart transplantation is a common occurrence in both adults and children and is aggravated by chronic steroid therapy and other immunosuppressive agents. Statins are used with good results in controlling hyperlipidemia after transplantation and are likely to manifest inherent immunosuppressive effects. Risk factors for posttransplant renal dysfunction are the use of calcineurin inhibitors, mechanical circulatory support, prolonged inotropic support, and preexisting renal dysfunction. Newer, more potent immunosuppressive agents (e.g., tacrolimus) have led to steroid-sparing regimens late after transplantation, eliminating the detrimental effects of long-term steroid administration. Agents such as sirolimus may now be used in combination with lower levels of calcineurin inhibitors, thus minimizing long-term nephrotoxicity. Posttransplant lymphoproliferative disorders represent a pathologic spectrum of abnormal lymphoid proliferation ranging from localized early lesions to polymorphic disease or, in some cases, monomorphic lymphomatous disease. From a clinical

perspective, the most common sites of disease and presenting symptoms included the gastrointestinal tract and pulmonary systems. Patients with polymorphic disease are treated primarily by a reduction or temporary cessation of immunosuppression, along with adjunctive surgical therapy for tissue diagnosis or obstructive lesions. Most centers reserve traditional chemotherapeutic regimens for patients with nonresponsive polymorphic disease and monomorphic disease. As a result of cardiac denervation, autonomic regulatory mechanisms are not available to prevent the wide swings in a patient's hemodynamic state and the stress response is slower than usual. Cardiac parameters are significantly altered, and patients may experience a decrease in systemic blood pressure and cardiac filling pressures. Compensatory mechanisms are delayed, and reductions in cardiac output lead to decreased coronary and cerebral perfusion, especially on the background of hypertension. Drugs with direct myocardial and vascular effects are the mainstay of therapy. Most immunosuppressive agents affect hepatic and renal functions and interact with anesthetic drugs.

ANESTHESIA FOR CLOSED-HEART OPERATIONS

Early corrective repair in infancy has significantly reduced the number of noncorrective, palliative closed-heart operations. Corrective closed-heart procedures include PDA ligation and repair of coarctation of the aorta. Noncorrective closed-heart operations include pulmonary artery banding and extracardiac shunts such as the Blalock-Taussig shunt. These procedures are performed without CPB. Therefore, venous access and intraarterial monitoring are important in evaluating and supporting these patients. A pulse oximeter remains an invaluable monitor during intraoperative management.

Ligation of a PDA is typically performed through a left thoracotomy, although video-assisted thoracoscopic techniques are increasingly common.[282,283] Physiologic management is that of a left-to-right shunt producing volume overload. Patients with a large PDA and low PVR generally present with excessive PBF and CHF. Neonates and premature infants also run the risk for having substantial diastolic runoff to the pulmonary artery, potentially impairing coronary perfusion. Thus, patients range from an asymptomatic healthy young child to the sick ventilator-dependent premature infant on inotropic support. The health of the former patient allows a wide variety of anesthetic techniques culminating in extubation in the operating room. The latter patient requires a carefully controlled anesthetic and fluid management plan. Generally, a trial of medical management with indomethacin and fluid restriction is attempted in the premature infant before surgical correction. Transport of the premature infant to the operating room can be especially difficult and potentially hazardous, requiring great vigilance to avoid extubation, excessive patient cooling, and venous access disruption. For these reasons, many centers are now performing ligation in the neonatal ICU.

A subset of premature infants with PDAs is located at institutions without cardiac surgical teams. Ligation of the PDA in these patients requires either transfer of these high-risk neonates to a center that has a team who routinely perform the procedure or the availability of a team capable of performing the procedure who is willing to travel to perform the procedure in the neonate's home neonatal ICU (NICU). Gould and associates[284] reviewed the experience with onsite and off-site ligations of a team composed of a pediatric cardiac attending anesthesiologist, a certified registered nurse anesthetist, an attending pediatric cardiothoracic surgeon and fellow, and cardiac operating room nurses. There were no anesthetic-related complications in their group. No differences were found in the incidence of perioperative complications in the procedures in the two sites. This study showed PDA ligations can be performed safely in the NICUs of hospitals lacking onsite pediatric cardiac surgical units, without incurring the risk inherent in transport of critically ill infants. In addition, patient care is continued by the neonatology team most familiar with the child's medical and social history and the patient's family is minimally inconvenienced.

Complications of PDA ligation include inadvertent ligation of the left pulmonary artery or descending aorta, recurrent laryngeal nerve damage, and excessive bleeding as a result of inadvertent PDA disruption. After ductal ligation in premature infants, worsening pulmonary compliance can precipitate a need for increased ventilatory support; and manifestations of an acute increase in left ventricular afterload should be anticipated, especially if left ventricular dysfunction has developed preoperatively. PDA ligation has been performed in infants and children using thoracoscopic surgical techniques. This approach has the advantage of limited incisions at thoracoscopic sites, promoting less postoperative pain and discharge from the hospital the same day of surgery.

Coarctation of the aorta is a narrowing of the descending aorta near the insertion of the ductus arteriosus. Obstruction to aortic flow results and may range from severe obstruction with compromised distal systemic perfusion to mild upper extremity hypertension as the only manifestation. Associated anomalies of both the mitral and aortic valves can occur. In the neonate with severe coarctation, systemic perfusion depends on right-to-left shunting across the PDA. In these circumstances, left ventricular dysfunction is very common and prostaglandin E1 is necessary to preserve sufficient systemic perfusion. Generally, a peripheral intravenous line and an indwelling arterial catheter, in the right upper extremity, are recommended for intraoperative and postoperative management. In patients with left ventricular dysfunction, a central venous catheter may be desirable for pressure monitoring and inotropic support.

The surgical approach is through a left thoracotomy, whereby the aorta is cross-clamped and the coarctation repaired with an end-to-end anastomosis, patch aortoplasty, or subclavian patch. During cross-clamping, we usually allow significant proximal hypertension (20% to 25% increase over baseline), based on evidence that vasodilator therapy may jeopardize distal perfusion and promote spinal cord ischemia. Intravascular crystalloid administration of 10 to 20 mL/kg is given just before removal of the clamp. The anesthetic concentration is

decreased, and additional blood volume support is given until the blood pressure rises. Postrepair rebound hypertension as a result of heightened baroreceptor reactivity is common and often requires medical therapy. After cross-clamping, aortic wall stress resulting from systemic hypertension is most effectively lowered by institution of β-blockade with esmolol or α/β-blockade with labetalol.[285] Recent work indicates that patients younger than 6 years of age should receive an initial dose of esmolol 250 to 500 µg/kg, followed by an infusion of 250 to 750 µg/kg/minute, depending on the blood pressure. Despite an esmolol infusion, 25% to 50% of patients have a blood pressure that is above the targeted range, requiring a second drug. Sodium nitroprusside, which increases the calculated aortic wall stress in the absence of β-blockade, is usually chosen as the second drug. Other agents that may have a greater likelihood of achieving the targeted pressure include nitroglycerin and nicardipine. Propranolol is useful in older patients but can cause severe bradycardia in infants and young children. Although it actually increases calculated aortic wall stress in the absence of β-blockade by accelerating dP/dT (contractile force), the addition of sodium nitroprusside may be necessary to control refractory hypertension. Captopril or an alternative antihypertensive regimen is begun in the convalescent stage of recovery in patients with persistent hypertension.

The management of infants undergoing placement of extracardiac shunts without CPB centers on goals similar to those of other shunt lesions—balancing pulmonary and systemic blood flow by altering Pa_{CO_2}, PaO_2, and ventilatory dynamics. Central shunts are usually performed through a median sternotomy, whereas Blalock-Taussig shunts may be performed through a thoracotomy or sternotomy. In patients in whom PBF is critically low, partial cross-clamping of the pulmonary artery required for the distal anastomosis causes further reduction of PBF and desaturation, necessitating meticulous monitoring of pulse oximetry. Careful application of the cross-clamp to avoid pulmonary artery distortion will help maintain PBF. Under circumstances in which severe desaturation and bradycardia occur with cross-clamping, CPB will be required for the procedure.

Intraoperative complications include bleeding and severe systemic O_2 desaturation during chest closure, usually indicating a change in the relationship of the intrathoracic contents that results in distortion of the pulmonary arteries or kink in the shunt. Pulmonary edema may develop in the early postoperative period in response to the acute volume overload that accompanies the creation of a large surgical shunt. Measures directed at increasing PVR, such as lowering inspired O_2 to room air, allowing the Pa_{CO_2} to rise, and adding PEEP are helpful maneuvers to decrease PBF until the pulmonary circulation can adjust. Decongestive therapy such as diuretics and digoxin may alleviate the manifestations of CHF. Under such circumstances, early extubation is inadvisable.

Pulmonary artery banding is used to restrict PBF in infants whose defects are deemed uncorrectable for either anatomic or physiologic reasons. These patients are generally in CHF with reduced systemic perfusion and excessive PBF. The surgeon places a restrictive band around the main pulmonary artery to reduce PBF. Band placement is very imprecise and requires careful assistance from the anesthesia team to accomplish successfully. Many approaches have been suggested. We place the patient on 21% inspired O_2 concentration and maintain the Pa_{CO_2} at 40 mm Hg, to simulate the postoperative state. Depending on the malformation, a pulmonary artery band is tightened to achieve hemodynamic (e.g., distal pulmonary artery pressure 50% to 25% systemic pressure) or physiologic (e.g., $\dot{Q}p:\dot{Q}s$ approaching 1) goals. Should the attainment of these objectives produce unacceptable hypoxemia, the band is loosened.

ANESTHESIA FOR INTERVENTIONAL OR DIAGNOSTIC CARDIAC PROCEDURES

Advances in interventional and diagnostic cardiac catheterization techniques are significantly changing the operative and nonoperative approach to the patient with a congenital heart defect (see also Chapter 90). Common interventions in the cardiac catheterization laboratory are shown in Table 94-11. Nonoperative interventional techniques are being used instead of procedures requiring surgery and CPB for safe closure of secundum ASDs, VSDs, and PDAs. Stenotic aortic and pulmonic valves, recurrent aortic coarctations, and branch pulmonary artery stenoses can be dilated in the catheterization laboratory, avoiding surgical intervention.[286,287] These techniques shorten the hospital stay and are particularly beneficial to patients with recurrent coarctation and muscular or apical VSDs, who are at a higher risk for operative intervention. Many patients with complex cardiac defects are poor operative risks. Innovative interventional procedures improve vascular anatomy, reduce pressure loads on ventricles, and decrease the operative risk for these patients. For example, in TOF with hypoplastic pulmonary arteries, balloon angioplasty and vascular stenting procedures create favorable pulmonary artery anatomy and reduce pulmonary artery pressure and right ventricular end-diastolic pressure. Complications are more common during interventional catheterization and include arterial thrombosis, arrhythmias (especially heart block), hemodynamic instability, embolization of devices or coils, bleeding, and perforation of the major vessels or heart.[288] Complications are more common in infants younger than 6 months of age and with smaller infants. Constant vigilance, correction of electrolyte imbalance, maintenance of acid-base status, and appropriate heparinization will mitigate some of the morbidity. Appropriate and early transfusion with deployment of rapid-response ECMO in the resuscitation of an infant in cardiac arrest improves outcome. High-risk patients undergoing diagnostic evaluation of pulmonary artery hypertension in anticipation of heart-lung transplantation also require anesthetic management. Despite the attendant high risks for the procedure in patients with suprasystemic right ventricular pressure, these patients are best managed with general anesthesia and controlled ventilation.

Anesthetic management of interventional or diagnostic procedures in the catheterization laboratory

TABLE 94-11 COMMON INTERVENTIONS IN THE CARDIAC CATHETERIZATION LABORATORY

Simple Interventions	
Device Closures	***Coil Embolization***
Atrial septal defect (ASD)	Decompressing veins
Ventricular septal defect (VSD)	Aortopulmonary (AP) collaterals
Patent ductus arteriosus (PDA)	Surgical shunts
Patent foramen ovale (PFO)	Coronary/atrioventricular fistulas
Balloon valvuloplasty	Balloon angioplasty
Aortic stenosis (AS)	Branch pulmonary artery stenosis
Pulmonary stenosis (PS)	Coarctation of the aorta
Complex Interventions	
Hypoplastic Left Heart Syndrome (HLHS)	
After Norwood	
Pulmonary artery stenosis	Angioplasty
Shunt thrombosis	Dilation/thrombectomy
Restrictive ASD	Balloon septostomy
Aortic arch obstruction	Angioplasty
AP collaterals	Coil embolization
Post Glenn/Fontan	
Decompressing veins	Coil embolization
Baffle leaks	Device/coil embolization
Systemic vein stenosis/thrombosis	Angioplasty/ thrombectomy
Right ventricular failure	Creation of fenestration
Exercise intolerance	Closure of fenestration
AP collaterals	Coil embolization
Obstructive Fontan pathway	PA angioplasty, balloon septostomy)
Transposition of Great Arteries	Balloon atrial septostomy
Tetralogy of Fallot (TOF)	
Shunt thrombosis	Thrombectomy
Pulmonary artery stenosis	Angioplasty
AP collaterals	Coil occlusion
Miscellaneous Interventions	
Severe pulmonary hypertension	Atrial septostomy
ECMO left heart decompression	Atrial septostomy
Stenosis of pulmonary veins	Balloon angioplasty stent
Stenosis/thrombosis of systemic veins	Balloon angioplasty/ thrombectomy

ECMO, Extracorporeal membrane oxygenation.

must include the same level of preparation that applies in caring for these patients in the operating room. These patients have the same complex cardiac physiology and, in some cases, greater physiologic complexity and less cardiovascular reserve. Interventional catheterization procedures can impose acute pressure load on the heart during balloon inflation. Large catheters placed across mitral or tricuspid valves create acute valvular regurgitation or, in the case of a small valve orifice, transient valvular stenosis. When catheters are placed across shunts, severe reductions in PBF and marked hypoxemia may occur. The anesthetic plan must consider the specific cardiology objectives of the procedure and the impact of anesthetic management in facilitating or hindering the interventional procedure. In general, the three distinct periods involved in an interventional catheterization are the data acquisition period, the interventional period, and the postprocedural evaluation period.

During the data acquisition period, the cardiologist performs a hemodynamic catheterization to evaluate the need for and extent of the planned intervention. Catheterization data are obtained under normal physiologic conditions—that is, room air, physiologic $Paco_2$, and spontaneous ventilation are preferred. Increased FiO_2 or changes in $Paco_2$ may obscure physiologic data. Although some patients may require O_2 administration if the PBF is such that the administration of room air may lead to life-threatening hypoxia, a discussion with the interventional cardiologist is essential in the care of these children. During the procedural period, the patient is usually intubated and mechanically ventilated. A secured airway allows the anesthesiologist to concentrate on hemodynamic issues. Positive-pressure ventilation also reduces the risk for air embolism. During spontaneous ventilation, a large reduction in intrathoracic pressure can entrain air into vascular sheaths and result in moderate-to-large pulmonary or systemic air emboli. Precise device placement is also facilitated with muscle relaxants that eliminate patient movements and controlled ventilation, thereby reducing the respiratory shifting of cardiac structures. Substantial blood loss and changes in ventricular function occur commonly during the intervention. Blood volume replacement and inotropic support may be necessary during or immediately after the interventional procedure.

In the postprocedural period, the success and physiologic impact of the intervention are evaluated. Blood pressure, mixed venous O_2 saturation, ventricular end-diastolic pressure, and cardiac output, when available, are used to assess the impact of the intervention. Persistent severe hemodynamic derangement indicates the need for ICU monitoring and respiratory or cardiovascular support. Because of the hemodynamic variability of many of these patients, as well as changing anesthetic requirements, continuous intravenous infusion with ketamine/midazolam or propofol is appropriate. Potent inhaled anesthetics are generally not used as the primary anesthetic and are reserved for adjunctive anesthesia.

A brief description of some of the interventional procedures and the associated anesthetic implications follows. The success of these interventions will undoubtedly result in widespread availability and use over the next few years.

TRANSCATHETER TECHNIQUE FOR ATRIAL SEPTAL DEFECT CLOSURES

In the transcatheter technique for ASD closures, a collapsed double-umbrella clamshell device is loaded into a large introducer sheath placed through the femoral vein, advanced to the RA, and placed across the ASD into the left atrial chamber. Each side of the device consists of a Dacron mesh patch suspended in six spring-loaded arms that open like an automatic umbrella. Using biplane fluoroscopy and TEE, the catheter is positioned in the LA away from the mitral valve.[289] The sheath is pulled back to open the six distal arms and its

Dacron mesh cover into the LA. The sheath and device are then pulled back so the distal arms contact the left atrial septum. Fluoroscopy and TEE are used to confirm that the arms are on the left atrial side and do not interfere with mitral valve motion. Once adequately seated, the sheath is pulled farther back to expose the proximal side of the device and the proximal arms, which spring open to engage the right side of the atrial septum. When proper positioning is certain, the device is released.[289] In a review of data for 122 children undergoing transcatheter ASD closures, a 9% incidence of procedural complications resulted in hemodynamic complications requiring treatment.[290]

Device closure of secundum ASD is the preferred therapeutic approach. Data continue to support closure of defects of small-to-moderate size (<8 to 20 mm) in appropriate-size patients with appropriate septal length and device diameter.[291-293] The procedure is well tolerated with minimal long-term complications. Complications such as cardiac erosions and heart block can occur in patients who receive a large device for patient size, especially those who have a deficient anterosuperior rim.[294,295] Thrombus is a rare problem that can usually be treated medically, and its incidence appears to be device-dependent.[296] Despite nearly a decade of experience, these devices remain under investigational protocol and are therefore available only at a limited number of study centers.

TRANSCATHETER VENTRICULAR SEPTAL DEFECT CLOSURES

Most VSDs that are electively closed in the catheterization laboratory are mid-muscular or apical VSDs that are either difficult to close in the operating room or would require a left ventriculotomy. Left ventriculotomies are associated with a high incidence of left ventricular dysfunction and have been relegated to a position as the least desirable surgical option. The preferred therapeutic approach for VSD is surgical closure. Transcatheter closure of muscular VSDs can be performed safely. However, a significant incidence of complications occurs, including heart block, blood loss, and hemodynamic instability.[297,298] Device closure of membranous VSD is in early stages of investigation, and the incidence of complications remains to be determined.[299,300] The transcatheter approach requires a blade atrial septostomy and a retrograde catheter placed through the femoral artery and advanced to the LA. This catheter is pulled across the atrial septum into the RA and is used to guide a superior vena cava catheter (placed through the internal jugular vein) across the ASD into the LA, across the mitral valve, and into the LV. The VSD defect is approached from the left ventricular side. The large sheath containing the double-umbrella clamshell device prevents closure of the mitral valve, resulting in acute mitral regurgitation or, in cases in which the VSD is large or the mitral annulus small, acute severe mitral stenosis. In this latter case, systemic output is decreased and a period of severe hypotension is unavoidable. Judicious use of vasoconstrictors to maintain coronary perfusion may be required during the catheter placement, followed by volume and inotropic resuscitation after the VSD device is deployed. This highly specialized application of the clamshell device is confined to only a few pediatric centers in the United States.

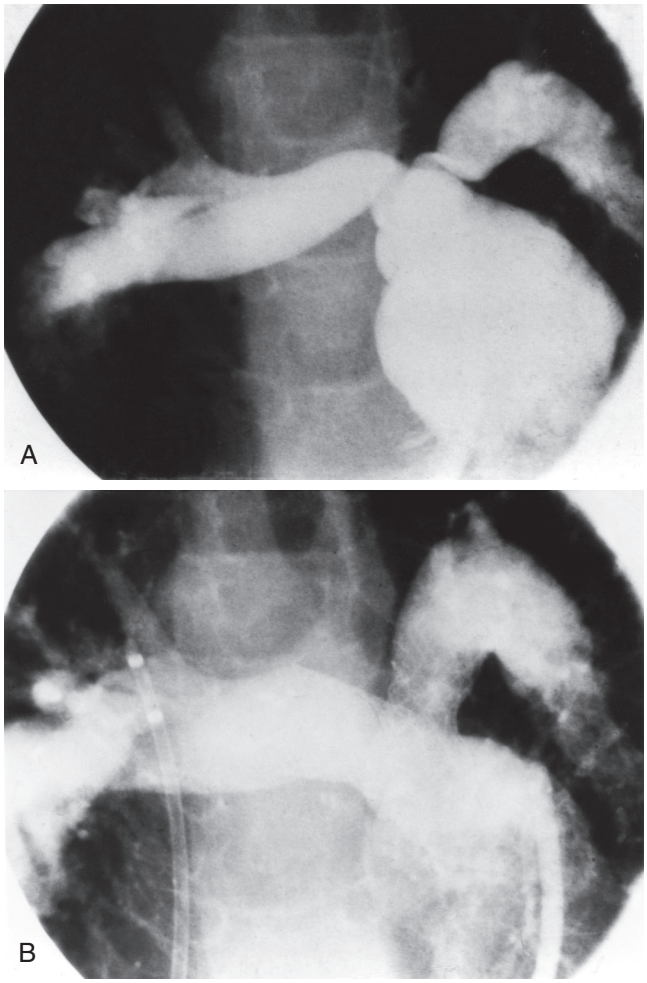


Figure 94-16. A, Severe bilateral branch pulmonary artery stenoses at the distal end of a conduit in a patient with pulmonary trunk atresia and ventricular septal defect. Stents were placed in the right and left pulmonary arteries. **B,** Follow-up angiogram in the same projection and magnification showed marked improvement of both right and left stenoses.

ANGIOPLASTY OF BRANCH PULMONARY ARTERY STENOSIS

One of the most important areas of interventional catheterization has been the dilation and stenting of hypoplastic or stenotic branch pulmonary arteries. In patients with TOF with hypoplastic pulmonary arteries, pulmonary atresia, or single ventricle with surgically induced peripheral stenoses, the use of balloon angioplasty and stenting procedures creates favorable pulmonary artery anatomy and reduces the risk for subsequent surgical repairs (Fig. 94-16). Peripheral pulmonary artery stenosis is not a surgically amenable lesion and is particularly suited to catheterization and angioplasty. Balloon angioplasty is accomplished by tearing the vascular intima and media, allowing the vessel to remodel and heal with a larger diameter. The balloon is placed across the stenotic lesion so that the middle of the balloon is at the stenosis. The balloon is inflated until

the waist of the balloon is eliminated. Ideally, the most stenotic lesions are dilated first to minimize the impact on PBF and cardiac output. When the balloon is inflated, PBF is reduced, right ventricular afterload is increased, and cardiac output falls. In patients with an associated VSD or ASD, right-to-left shunting and desaturation occur with balloon inflation. In patients without a shunt, acute increase in right ventricular afterload can cause systemic hypotension and right ventricular failure. The large vascular sheaths required for these procedures can introduce tricuspid regurgitation, which is poorly tolerated in patients with severe RV hypertension. Occasionally, balloon catheters must be placed across aortopulmonary shunts, significantly reducing PBF.

The procedure is successful in approximately 60% of patients. In an early series, complications included hypotension (40%), pulmonary artery rupture (3%), unilateral reperfusion pulmonary edema (4%), aneurysmal dilation of the dilated pulmonary vessel (8%), death (1.5%), and transient postprocedural right ventricular dysfunction.[301] Improved techniques and patient selection have favorably influenced the results with superior balloon catheters and stents while significantly reducing serious complications. Anesthetic support minimizes hemodynamic compromise by anticipating changes in blood flow patterns, treating transient hypotension, and providing airway support to minimize the risks associated with pulmonary artery disruption and acute unilateral pulmonary edema.[301]

A unique group of patients are those with William syndrome with supravalvular aortic and pulmonary stenosis. Such patients can have multiple areas of severe branch pulmonary artery stenosis, with resultant systemic or suprasystemic right ventricular pressures and right ventricular dysfunction. Patients can also have coronary stenosis and develop subendocardial ischemia from hemodynamic disturbances in the setting of biventricular hypertrophy. The presence of supravalvular aortic stenosis, biventricular outflow tract obstruction, and coronary stenosis is associated with increased perioperative risk. Typically, such patients undergo general anesthesia with positive-pressure ventilation and recover in the cardiac ICU for angioplasty of branch pulmonary artery stenosis.[302] Care must be exercised in maintaining SVR, myocardial oxygenation, and contractility. Tachycardia and subendocardial ischemia should be avoided in the presence of ventricular hypertrophy.

BALLOON VALVULOTOMIES

Balloon valvulotomies conducted in well-compensated infants and children often can be accomplished without anesthetic support. Exceptions include neonates with critical aortic or pulmonary stenosis and patients with significant ventricular dysfunction who exhibit unstable hemodynamics. Balloon valvuloplasty is indicated in valvular pulmonary or aortic stenosis with valvular gradients more than 50 mm Hg. Balloon dilation is effective in most patients, except those with dysplastic valves (e.g., Noonan syndrome); postdilation pulmonary incompetence is anticipated and does not pose a problem in the immediate and intermediate period. Long-term prophylaxis for subacute bacterial endocarditis is needed. Only 8% of patients require repeat interventions. Typically, patients recover in the ICU and may require transfusion depending on hemodynamic stability. Valvular aortic stenosis is associated with poor surgical outcome in the neonatal period. All therapies are palliative, with a high incidence of repeat interventions, and balloon valvuloplasty is often the initial treatment. Residual obstruction or regurgitation is common after balloon dilatation and can require repeat intervention. A real risk exists for damage to the aortic valve and subaortic septum, with the consequence of acute aortic insufficiency and coronary ischemia. Hypotension and bradycardia commonly occur during valvuloplasty, and many centers have a policy of ECMO standby for these high-risk interventions in the catheterization laboratory. Ready availability of a surgical and perfusion team is crucial to a good outcome. Neonates with critical aortic stenosis often require stabilization with inotropes and prostaglandins to maintain systemic perfusion before the procedure. Balloon dilation of recurrent coarctation is often the therapy of choice in older children with recoarctation after surgery. Such patients are often hypertensive. The procedure can be performed with the patient under deep sedation or general anesthesia. In infants after Norwood palliation for hypoplastic left heart syndrome, coarctation can occur in the distal arch anastomotic site. Catheters placed antegrade via the right side of the heart into the neoaorta can induce hemodynamically significant tricuspid and neoaortic regurgitation, resulting in hemodynamic instability. Careful monitoring and aggressive hemodynamic intervention result in a good outcome.

COIL EMBOLIZATION

Transcatheter methods can be adapted to occlude undesired vascular structures. Intravascular coils have been used to close PDAs, aortopulmonary collaterals, surgical systemic and pulmonary artery shunts, venous collaterals in single ventricle lesions, coronary fistulas, and some arteriovenous malformations (e.g., vein of Galen malformation). In selected instances, to minimize the risk that coils may escape to threaten vital organ perfusion, cardiologists request the use of general anesthesia with a muscle relaxant.

Depending on the lesion, patients might manifest severe cyanosis, low-output or high-output cardiac failure, or coronary ischemia. Extra care should be exercised in patients with coronary fistulas to maintain myocardial O_2 supply and reduce demand. Materials used for embolization can include surgical gel (Gelfoam), alcohol, and coils. Some of these substances can induce severe allergic reactions with hemodynamic collapse. Antibiotic prophylaxis is mandatory to prevent bacterial endocarditis. Angiography is used to demonstrate successful occlusion of the vascular structure and ascertain appropriate placement.

VALVE PROSTHESES

Transcatheter bioprosthetic valve replacement of the pulmonary and aortic valves is being performed. The pulmonary valve is a bovine jugular venous valve mounted on a balloon-expandable Cheatham platinum stent. The technique is limited by the maximum size of 22 mm of the bovine jugular venous valve. Percutaneous placement

of bioprosthetic valve in the pulmonary position is a reality, and further refinement and miniaturization will lead to its application in aneurysmal right ventricular outflow tract. Current candidates for the implantation of transcatheter pulmonary valve include age of 5 years or older, weight of 30 kg or more, and a conduit diameter of 16 to 22 mm. Candidates have moderate-to-severe pulmonary regurgitation, often with RV dilation or dysfunction and mean right ventricular outflow tract gradients greater than 35 mm Hg. Transcatheter aortic valve replacement continues to be used in the management of adult patients with complex status and aortic stenosis who are not considered surgical candidates because of surgical risk. The use of these devices in pediatrics has been limited. Some authors have described the use of transcatheter pulmonary valves in the high-pressure circuit with good short term performance. Complications of the transcatheter valve placements include wire perforation of vessels, conduit rupture or coronary artery compression.

EMERGENT PROCEDURES

Emergent interventions such as balloon atrial septostomy to ensure adequate mixing in patients with transposition physiology and in patients who have restrictive ASD with single ventricle physiology are lifesaving and enable planning surgery at a suitable time. The procedure can be performed at the bedside with echocardiography or in the catheterization laboratory with fluoroscopic confirmation of balloon position. Access is by the femoral or umbilical vein, and the balloon catheter is advanced through the foramen ovale into the LA. The balloon is inflated with contrast and pulled back via the septum until a satisfactory ASD is created. If the procedure is successful, the left and right atrial pressures should equalize and adequate mixing should occur. Oxygenation and pulmonary venous drainage should improve. Complications include atrial perforation, laceration of the mitral or tricuspid valves and pulmonary veins, and low cardiac output state. Balloon atrial septostomy is also performed emergently in patients receiving ECMO therapy for left-sided heart decompression.

ENDOMYOCARDIAL BIOPSY

Typically, endomyocardial biopsies are performed as part of posttransplant surveillance catheterizations at regular intervals to ascertain absence of rejection in patients after orthotopic heart transplantation. Right-sided heart catheterization is usually performed by access of the right internal jugular vein, through which the long sheath and biotome are introduced. Usually five to eight samples are taken. Endomyocardial biopsies are also used to confirm a diagnosis of myocarditis or cardiomyopathy; sedation or general anesthesia is required for smaller children, although older children can undergo this procedure with local anesthesia alone. Children who undergo catheterization during a period of acute rejection are at high risk for malignant arrhythmias during endomyocardial biopsy and might require resuscitation. A clinical history suggestive of an episode of rejection includes fever, gastrointestinal disturbances, and arrhythmias. Complications include perforation, tricuspid valve damage, and the development of coronary-to–right ventricular fistulas.

CARDIAC CATHETERIZATION OF PATIENTS SUPPORTED BY EXTRACORPOREAL MEMBRANE OXYGENATION

Booth and associates[303] reported on the Boston experience of cardiac catheterization in pediatric patients supported on ECMO. Indications included assessment of surgical repair, left-sided heart decompression, myocarditis or cardiomyopathy, hemodynamic assessment, catheter interventions, and ablation of arrhythmias. The most common interventions were left-sided heart decompression in patients with left atrial hypertension, balloon angioplasty of the pulmonary arteries, and endomyocardial biopsy. The anesthesiologist coordinates safe transport of the patient on mechanical support with the perfusion and nursing team. The logistics of the transport, availability of surgeon, and blood need to be addressed before the transfer. Anesthesia is provided using isoflurane or sedatives on the ECMO circuit, and paralysis must be achieved before transport. Rest ventilation of the lungs is continued. The anesthesiologist's role is in managing a safe transport and attending to emergency mechanical, cardiorespiratory, and hematologic issues.

At present, hybrid techniques find a niche in lesions in which cardiac surgery is problematic, such as apical muscular or anterior muscular VSDs or in high-risk patients with more complex lesions in which immediate surgery is contraindicated or is associated with significant morbidity and mortality. Close collaboration is required so that a surgical approach is modified to facilitate the subsequent interventional approach. The hybrid approach has been used in the management of hypoplastic left heart syndrome. Stage 1 palliation is performed by creation of an atrial septal communication and stent placement in the ductus arteriosus during catheterization to maintain ductal patency with surgically applied external right and left pulmonary artery bands or transcatheter placed internal bands.[304,305] A modified Norwood procedure with a bidirectional Glenn anastomosis is performed with CPB during stage 2 palliation.[306] Stage 3 (Fontan operation) is performed entirely by transcatheter techniques.[307] In the current surgical climate, it seems difficult to promote ductal stenting as a method of choice but in patients with contraindications to immediate surgery this provides an attractive bridge.[308]

ADULT CONGENITAL HEART DISEASE

EPIDEMIOLOGY AND CLASSIFICATION

The care of adults with CHD is a new and exciting frontier in medicine. Adult congenital heart disease (ACHD) represents a large spectrum of clinical entities ranging from mild to severe and palliated to corrected, with no or multiple adult comorbidities. In addition, some patients with ACHD may have had palliative repairs no longer primarily employed for specific diseases today, such as the Mustard or Senning procedure for dextro-transposition

of the great arteries (d-TGA). Another unique problem is therapeutic noncompliance in patients with ACHD. The incidence of CHD is estimated to be 3 to 6 cases per 1000 live births. Approximately 85% of these patients can be expected to reach adulthood.[309] The prevalence of CHD is rising in both children and adults, with adults representing the largest group

At the Bethesda conference in 2001, patients with ACHD were categorized into groups of simple, moderate, or great complexity based on medical diagnosis.[309] Anesthesiologists should be aware of the Bethesda task conference recommendations for ACHD in terms of distribution of care for these patients. It is recommended that patients with CHD of great complexity be regularly seen at tertiary care centers that specialize in ACHD

CONSIDERATIONS IN THE CARE OF PATIENTS WITH ADULT CONGENITAL HEART DISEASE

Adults with CHD may present with unique anatomy or physiologic sequelae not otherwise encountered in pediatric patients with CHD. In addition, these patients may not have complete awareness or access to information on medical treatments completed when they were a child, significantly complicating their care. As the number of patients with ACHD increases, so do the chances an anesthesiologist will need to care for one of these patients in an emergent situation. In general, practitioners would want to gather as much information as available in regard to the details of the patient's medical history, surgical repairs, and current functional status. General considerations include presence of arrhythmias, hypoxemia, pulmonary hypertension, ventricular dysfunction, shunts, thrombosis, and need for antibiotic prophylaxis. Arrhythmias are one of the most common sequelae in adults with CHD. Common arrhythmias occur as the result of atrial dilation and include atrial fibrillation or flutter, which may or may not be hemodynamically significant. A right bundle branch block pattern of the QRS segment of the ECG is common after repair of TOF. In the absence of lung disease, hypoxemia results from a decrease of PBF. Limited PBF may be the result of obstruction or residual right-to-left shunting. Strategies to avoid further hypoxemia include adequate hydration, ventilation, and pulmonary perfusion while decreasing PVR or O_2 consumption. It is always prudent to determine patient baseline SpO_2 as a reference for the anesthetic. In addition, O_2-carrying capacity may be maximized by the administration of packed blood cells. Many patients with ACHD with chronic hypoxemia may require hematocrit values greater than 45% to allow for adequate O_2 delivery. Along with cyanosis, the presence of polycythemia in these patients increases their thrombovascular risk. The presence of pulmonary hypertension should always be considered when caring for patients with ACHD. Chronic volume overload to the pulmonary vascular bed creates hypertrophy of the arterioles with resultant pulmonary hypertension. Common defects where pulmonary hypertension may be found in childhood include shunt lesions, which, if untreated, result in pulmonary vasoocclusive disease. When hypoxemia is present with these conditions, a high level of suspicion for pulmonary hypertension and possibly Eisenmenger syndrome is necessary. The anesthesiologist should always have a high level of suspicion for the presence of ventricular dysfunction in patients with ACHD. Many CHD defects place a volume or pressure load on the heart that over time may lead to dilated or hypertrophied performance. The care titration of induction and maintenance agents that maintain ventricular performance is warranted in providing anesthesia care. Shunts of varying size and location may be created in the care of hypoxic patients with CHD in an effort to increase PBF. In many cases, patients rely on the patency of these shunts to supply the lungs with blood and their occlusion could be catastrophic. Likewise, thrombosis of various shunt or cardiac chambers may occur related to altered patterns of blood flow. Therefore, specific anticoagulation strategies may be required to ensure blood flow. The American Heart Association has provided updated guidelines regarding recommendations for prophylaxis against infective endocarditis, and specific guidelines may be found in this chapter.

SPECIFIC LESIONS WITH UNIQUE CONSIDERATIONS FOR ADULT CONGENITAL HEART DISEASE

Tetralogy of Fallot

TOF consists of four defects of varying physiologic significance: malignant type VSD, varying degrees of right ventricular outflow tract obstruction, right ventricular hypertrophy, and an overriding aorta. The typical clinical significance of this pattern of cardiac anomalies is that of hypoxia as a result of decreased PBF. In the early stages of treatment of TOF the systemic–pulmonary artery shunt (Blalock-Taussig shunt) was used to allow the child to grow, followed by a definitive repair later in life. Many patients up until the 1970s may have had classic Blalock-Taussig shunt or central shunts performed. The use of the Blalock-Taussig shunt in a modified version still occurs today for some patients with TOF in whom the anatomy is considered high risk for an early complete repair. Typically, most clinicians prefer a complete repair electively within the first year of life in an effort to avoid secondary damage from the altered physiology. On occasion, the degree of pulmonary stenosis may protect the lung from overcirculation of blood from the VSD while allowing adequate PBF for growth, and these patient may not have undergone any type of repair. Adults with TOF may be found to possess any of these potential surgical repairs. When caring for adult patients with TOF it is prudent to attempt to determine the type of repair completed and functional status of such repairs. The anesthesiologist should be alert to degrees of cyanosis present in these adult patients, suggesting the adequacy of PBF. Arrhythmias of right ventricular origin or right bundle branch block patterns on the ECG may be likely if a previous ventriculotomy was performed. Careful attention should be paid to signs of right ventricular failure, including

elevated jugular venous pressures and hepatomegaly. Another common complication after repair of TOF is pulmonary regurgitation, which may lead to right heart failure over time if left untreated.

Fontan Circulations

In the early1970s, Fontan and Kreutzer preformed a procedure in a patient with tricuspid atresia in an attempt to separate the PBF from the systemic circulation.[310] Known now as the Fontan procedure, this principle is applied to many types of functionally single-ventricle patients. The procedure essentially diverts deoxygenated venous blood return directly and passively to the lungs, allowing the single ventricle to pump blood to the systemic circulation. When used in hypoplastic left heart syndrome, the Fontan procedure is the final staged procedure in a series of three, whereby the pulmonary circulation is separated from systemic circulation. These staged procedures typically occur early within the first 4 to 5 years of life. Occasionally, adults have been found who, through loss of follow-up, did not undergo a complete separation of circulations, with varying effects primarily exhibited by cyanosis and ventricular dysfunction. Even with the completion of the total cavopulmonary anastomosis, many patients experience a decreased survival beyond 15 years after surgery. Common causes of death include thromboembolism, heart failure, protein-losing enteropathy, and arrhythmias.[311] When caring for adults with Fontan physiology, the anesthesiologist should be mindful of conditions that may further impair oxygenation and myocardial function. Conditions that impair passive PBF may be poorly tolerated, such as dehydration, acidosis, hypoxia, and the use of myocardial depressants. In addition, the initial Fontan procedures were completed by a direct baffle of the atrium to the pulmonary artery, later found to be an inferior type of repair because of complication from atrial dilation and the resultant arrhythmias. Typical satisfactory Fontan repairs should produce O_2 saturation levels of at least 95%. Some patients with ACHD who have undergone a Fontan procedure may require chronic anticoagulation for previously demonstrated or presumed high risk for thromboembolism, and the management of this anticoagulation must be considered for any surgical procedure.

Transposition of the Great Arteries

TGA occurs when the aorta arises from the anatomic RV and the pulmonary artery arises from the anatomic LV. In classic d-TGA the two circulations are in parallel and require mixing to be compatible with life. In the 1980s, surgical management of TGA consisted of atrial-level switch procedures—the Mustard or Senning procedure—in which venous return to the heart was redirected at the atrial level though a baffle system. Therefore, highly oxygenated pulmonary venous return was redirected to the RV, which pumped to the aorta and systemic circulation. Systemic deoxygenated blood was directed to the LV, which pumped the blood through the pulmonary artery to the lungs for oxygenation. Long-term complications of this strategy include atrial dilation from baffle obstruction or leak with resultant arrhythmias, sinus node dysfunction, or sudden death. Particularly problematic complications included the systemic right ventricular dysfunction, AV valve regurgitation, subpulmonary stenosis, and pulmonary hypertension. Today, the arterial switch operation is preferred, in which the aorta with the coronary arteries are attached to the LV and the pulmonary artery is attached to the right ventricle. Complications from the arterial switch operation include regurgitation of the neoaortic valve, myocardial ischemia from coronary ostial stenosis, right or left ventricular outflow tract obstruction, residual intracardiac shunting, and left ventricular dysfunction.

PEDIATRIC CARDIAC ELECTROPHYSIOLOGY

DIAGNOSTIC EVALUATION

Cardiac Event Monitoring

Most patients with cardiac arrhythmias present with infrequent or episodic symptoms. These symptoms may include chest pain, palpitations, syncope, and presyncope. Transtelephonic electrocardiographic event monitors may yield documentation of the arrhythmia because they are portable and patient activated.[312]

Insertable Cardiac Recorders

Insertable loop recorders implanted subcutaneously allow continuous rhythm monitoring that is stored either when manually activated by a patient or parent or automatically when high or low rate parameters are met.[313] These insertable loop recorders have value in correlating arrhythmias with symptoms when noninvasive means do not make a diagnosis. Typically, loop recorders are inserted under general anesthesia as an outpatient procedure and cause minimal pain.

RADIOFREQUENCY ABLATION OF ACCESSORY PATHWAYS

Radiofrequency ablation is a nonsurgical approach designed to eliminate atrial or ventricular reentrant tachyarrhythmias. The technique requires pathway mapping and precision ablation of the aberrant pathway, using a radiofrequency ablation catheter. Catheter ablation is offered to patients with refractory arrhythmias that are bothersome and the focus or pathway is amenable to ablation. In pediatrics, the electrophysiology catheters are introduced by femoral venous catheterization and the tips are positioned in the right atrial appendage, the bundle of His area, right ventricular apex, and the coronary sinus. Occasionally, right internal jugular venous access is used for placement of the coronary sinus catheter. Rapid atrial pacing and, occasionally, an isoproterenol infusion are required during the mapping procedure to induce the arrhythmia. An ablation catheter is used to map the substrate, and, subsequently, the pathway is ablated. During the ablation, unexpected patient movement may result in catheter dislodgment and damage to normal conducting tissue; therefore, general anesthesia is usually required in younger children. Anesthetic agents and techniques

should be chosen to maintain circulating catecholamines and avoid suppression of arrhythmogenesis, for identification of the aberrant pathway. Our current preference is a propofol continuous intravenous anesthetic, although low-dose volatile anesthetics are equally satisfactory. Rapid atrial pacing and, occasionally, an isoproterenol infusion are required during the mapping procedure.

Severe postprocedural cardiomyopathy has been described but is very unusual. An underlying cardiomyopathy from frequent episodes of supraventricular tachycardia and myocardial O_2 imbalance caused by prolonged periods of rapid atrial pacing and isoproterenol infusions are the presumed causative factors. An arterial line is helpful during these lengthy procedures for continuous monitoring of blood pressure and blood gases. Complications of the procedure include radiation exposure, tamponade, pericarditis, groin hematoma, arterial thrombosis, AV block, systemic embolization, coronary artery dissection, trauma to the mitral and tricuspid valves, and endocarditis.

Intraatrial Reentrant Tachycardia

Intraatrial reentrant tachycardia (IART) is associated with significant morbidity and mortality for many patients with repaired CHD, particularly after extensive atrial surgery, such as Fontan and atrial switch operations. Therapeutic options for IART include antiarrhythmic medications, catheter ablation, surgery, and pacing. The arrhythmia occurs along with long-standing myocardial dysfunction and residual lesions. Careful choice of anesthetic, monitoring, and early management of low cardiac output, especially in patients with single-ventricle physiology, are important. Prolonged periods of arrhythmia induction during mapping can result in a low cardiac output state, necessitating inotropic therapy. Such patients may need to undergo recovery in the cardiac ICU. Despite reports of high acute success rates with catheter ablation, arrhythmia recurrence continues to be problematic in this population.[314] Acute success was reported in 93% of patients and was defined as no inducible, sustained IART. Recurrence occurred in 34% of patients, 88% within 1 year. Patients with Fontan physiology had the highest recurrence rate. Inadequate lesion size and depth with conventional radiofrequency ablation catheters are the principal reasons for recurrence. Intraoperative cryoablation within the RA for patients with IART or LA for atrial fibrillation using preoperative and intraoperative mapping can be used successfully. A new generation of antitachycardia pacemaker (AT500, Medtronic, Minneapolis, Minn.) has been used for treating IART. This device was able to successfully terminate 54% of treatable tachycardias by use of antitachycardia pacing, with no incidence of ventricular proarrhythmia.[315] In patients who are either unsuitable candidates for catheter ablation or in whom ablation has been unsuccessful, surgical ablation may be successfully combined with repair of CHD. This is particularly true of patients with complex physiology (e.g., Fontan revision with a maze procedure).[316-318]

Arrhythmias and Sudden Cardiac Death

Certain cardiomyopathies and channelopathies are associated with an increased risk for sudden cardiac death resulting from lethal arrhythmias. The patient usually has a history of syncope, near-syncope, or aborted sudden death. Such patients present for insertion of automated internal cardioverter-defibrillators (AICDs) for either primary or secondary prevention.

IMPLANTATION OF PACEMAKERS AND DEFIBRILLATORS

Pacemakers are indicated for complete heart block or sinus node dysfunction with symptomatic bradycardia and hemodynamic decompensation (see also Chapter 48). Children usually require general anesthesia with endotracheal intubation. It should be noted that the anesthetic can be associated with worsening bradycardia. Transthoracic pacing pads are applied before induction of anesthesia, and an isoproterenol (Isuprel) infusion might be required for chronotropic effect. External transthoracic, esophageal, or emergent transvenous pacing might be necessary until placement of a permanent pacing device is achieved. In small children the pacemaker generator is typically placed in the upper abdomen, and in older children and teenagers it is placed in the subclavicular region. Epicardial leads are used in small children because of inadequate size of the veins and in those in whom transvenous access to the heart is impossible (e.g., the Fontan circulation). Epicardial pacemaker placement usually is performed by a cardiac surgeon, with electrophysiologists readily available to program the device. Adequate peripheral venous access is mandatory in the event of major hemorrhage, and blood should be readily available. A mode of monitoring mechanical capture of electrical pacing activity is also necessary and can include invasive arterial monitoring or pulse plethysmography. Transvenous pacing can be achieved in the operating room with surgical backup or in the cardiac catheterization laboratory by the cardiologists. In the latter situation it is important to address the need for surgical backup during case planning.

AICDs are placed for life-threatening ventricular arrhythmias, which include long QT syndrome, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular dysplasia. Of note, the device is tested after placement, with induction of ventricular fibrillation. It is absolutely essential to have external modes of defibrillation available, as well as antiarrhythmics such as amiodarone, magnesium, and lidocaine, in the event of device failure. These devices are placed with the patient under general anesthesia with endotracheal intubation and controlled ventilation. Invasive arterial pressure monitoring is typically used. Adequate analgesia can be provided with local infiltration with local anesthetics and short-acting intravenous opioids. Patients are admitted overnight with telemetry monitoring. Appropriate antibiotic therapy is provided for a 24-hour period.

ADVANCES IN RESYNCHRONIZATION THERAPY

Bundle branch block or interventricular conduction delay often accompanies heart failure and some forms of CHD, either preoperatively or postoperatively, and may result in ventricular dysfunction caused by asynchronous

myocardial contraction. Biventricular pacing is an attempt to resynchronize ventricular contraction by pacing both ventricles, thereby improving overall ventricular function. In patients with left bundle branch block, cardiac resynchronization therapy counteracts the underlying electrical and mechanical dyssynchrony, leading to improved contractility, function, exercise tolerance, and quality of life. Multisite pacing has been attempted in pediatric patients.[319] Two atrial and three ventricular epicardial leads were placed at the time of surgery, with the ventricular leads placed as far from one another as possible. Atrial synchronous ventricular pacing was established postoperatively, and the AV interval was adjusted to yield the narrowest QRS complex while simultaneously pacing two ventricular sites. Multisite pacing resulted in significant narrowing of the QRS complex, improved cardiac index, and increased systolic blood pressure overall. Multisite pacing after surgery for CHD in children may facilitate weaning from inotropic agents, thereby limiting side effects such as increasing myocardial O_2 consumption. Cases of biventricular pacing with improved outcome in infants with dilated cardiomyopathy and complete AV block have been reported.[320,321] Long-term improvements need to be studied. Right bundle branch block is a common outcome after surgery for congenital heart lesions. Right ventricular pressure, volume loading, or both also may be present, with attendant right ventricular enlargement and dyskinesis. The QRS duration decreased in all patients during dual-chamber pacing. Cardiac index also increased during resynchronization with dual-chamber pacing. The pacing site yielding the narrowest QRS duration also improved the cardiac index the most.[322,323]

ANESTHESIA FOR NONCARDIAC SURGERY

INFECTIVE ENDOCARDITIS PROPHYLAXIS: AMERICAN HEART ASSOCIATION GUIDELINES

Guidelines for infective endocarditis prophylaxis were updated by the American College of Cardiology and the American Heart Association in 2008. A detailed discussion of the changes is beyond the scope of this chapter.

Procedures for which prophylaxis for infective endocarditis is recommended include the following[324]:

- Dental procedures involving manipulation of the gingival tissue or periapical region of the teeth or involving perforation of the oral mucosa
- Respiratory procedures involving incision of the respiratory mucosa
- Procedures involving infected skin, skin structure, or musculoskeletal tissue

Prophylaxis is no longer routinely recommended for gastrointestinal and genitourinary procedures. For elective procedures, coexisting enterococcal urinary tract infections should be treated before genitourinary or gastrointestinal procedures; for emergent procedures, in patients at highest risk for infective endocarditis, prophylaxis can be considered.

Conditions for which prophylaxis is recommended for dental procedures include the following (Table 94-12):

- Prosthetic cardiac valve
- Previous infective endocarditis
- Unrepaired congenital heart disease, including palliative shunts and conduits
- Completely repaired congenital heart disease with prosthetic material or device within the first 6 months after the procedure
- Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or device
- Cardiac transplant recipients who develop cardiac valvulopathy

These are guidelines only. The authors' practice at the current time is to consult the child's cardiologist and make a decision based on the child's condition, the operative procedure, the risk for bacteremia, and the cardiologist's opinion.

MAGNETIC RESONANCE IMAGING OF THE HEART

Apart from the usual considerations of providing general anesthesia in a remote location, when working in a magnetic field necessitating the use of magnet-safe equipment, the anesthesiologist needs to be prepared to

TABLE 94-12 INFECTIVE ENDOCARDITIS PROPHYLAXIS

		Single Dose 30-60 min Before Dental Procedure	
Situation	**Drug**	**Adults**	**Children**
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin or	2 g IM/IV	50 mg/kg IM/IV
	Cefazolin/ceftriaxone	1 g IM/IV	50 mg/kg IM/IV
Allergic to penicillins/oral	Cephalexin or	2 g	50 mg/kg IM/IV
	Clindamycin or	600 mg	20 mg/kg IM/IV
	Azithromycin/clarithromycin	500 mg	15 mg/kg
Allergic to penicillins/unable to take oral medication	Cefazolin/ceftriaxone or	1 g IM/IV	50 mg/kg IM/IV
	Clindamycin	600 mg	20 mg/kg

Vancomycin is an alternative for patients who are unable to tolerate a β-lactam or when the infective agent is considered to be methicillin-resistant *Staphylococcus aureus*.

provide resuscitative care in these patients. Patients with implanted devices and hardware need to be assessed to ensure magnet compatibility and safety. Generally, pacemakers, implanted defibrillators, and aneurysm clips are contraindications to MRI. Other coils, stents, and surgical clips produce interference and artifact with imaging but do not constitute a threat to patient safety. Usually an MRI screening form is part of the evaluation and needs to be discussed with the MRI technologist or radiologist. In a majority of patients, the scan can be performed as an outpatient procedure. Patients who are younger, uncooperative, or claustrophobic require sedation or general anesthesia. Total intravenous anesthesia can be provided with a propofol infusion and a natural airway, avoiding the need for scavenging and allowing rapid recovery.[325] Anesthesia has been provided with a range of inhalational agents, such as dexmedetomidine, ketamine, and midazolam.[326] In patients for whom breath holding is necessary and potential for airway compromise exists, general endotracheal anesthesia with positive-pressure ventilation may be required and is often necessary when coronary artery anatomy details are required. Irrespective of the technique chosen it is mandatory to maintain continuous monitoring of heart rate, pulse oximetry, capnography, noninvasive blood pressure, and temperature. Supplemental O_2 should be delivered until the patient is fully recovered from the anesthetic. In the event of hemodynamic compromise, the patient should be removed from the MRI scanner into a safe environment where resuscitation equipment can be safely used. With the development of compatible catheters and devices, MRI will be a useful tool in minimizing x-ray exposure, particularly in patients whose congenital heart disease necessitates numerous catheterization procedures. Razavi and associates[327] have described their experience of MRI used in combination with fluoroscopy to decrease radiation exposure and improve soft tissue visualization during cardiac catheterization of congenital heart disease patients.

OFFSITE ANESTHESIA IN CARDIAC SURGERY PATIENTS

Patients with cardiac disease are no different from any other group of patients who require procedures or investigations in areas outside the operating room. Therefore, anesthesiologists should always be prepared for any eventuality and follow guidelines such as those set out by the American Society of Anesthesiologists. This discussion will exclude procedures performed in the cardiac catheterization laboratory because this has already been addressed elsewhere (see also Chapter 68). The nature of congenital cardiac surgery will result in a number of patients' requiring emergent chest exploration for ongoing hemorrhage or as part of resuscitation to relieve tamponade or for ECMO placement, all of which may take place in the ICU setting. It is obvious that we cannot predict which patients will have problematic postoperative courses with absolute certainty, but the practitioners who have participated in the operative phase will gain an accurate sense of which patients may require possible further exploration or surgery. Accordingly, it is best to plan ahead, and it cannot be stressed enough that even if as a group of practitioners we are overprepared, this is the best option to have. This being said, it is imperative that the patient have enough blood and blood products (see also Chapter 61) available to perform surgery at any given time. Successful treatment of these patients depends on a team approach to their care, and thus surgeons, anesthesiologists, intensivists, perfusionists, and operating room nurses must be immediately available. When the decision is made to perform a procedure within the ICU, speed of preparation is of the essence. We are fortunate in our practice that we can obtain a set of premade drugs, electrolytes, and infusions within a 15-minute period. Invariably, if a patient is within a few hours' window from returning from the operating room, this same set of drugs will have accompanied the patient from the operating room to the ICU and can thus be accessed. Emergent preparation includes ensuring that blood is checked and that a warmer is set up ready for use, emergency drugs are present as mentioned, and the code cart (with internal paddles) is readily available. The blood that will be used for these procedures will include fresh whole blood (<48 hours old and remaining from the operating room) or packed RBCs, which in our practice is less than 7 days old, or for blood older than this we would prefer it to be washed to avoid the possibility of acute hyperkalemia with transfusion. An anesthesiologist's role here is thus one of facilitation of the entire procedure from sedation of the patient, positioning and preparation, readying the blood, and continuing ongoing volume resuscitation, resuscitative drug use, and airway management.

The premature infant with a PDA poses an interesting management problem to cardiac surgery teams because frequently these ill neonates are at hospitals remote from major centers where the team is normally assembled. As referenced in an article by Gould and associates,[284] our team has been performing these ductal ligations with great success at hospitals remote from ours. The philosophy is to take the cardiac team to the neonate instead of having these fragile infants transported to us. In this article, neonates operated on in our home hospital NICU were used as the controls, and it was found that the success and complication rates were comparable in the two groups. Thus, from an anesthetic perspective we travel with a full complement of airway equipment and drugs, as described earlier, with packed red cells being made available at the host hospital. The anesthetic regimen for this procedure comprises a high-dose opioid, muscle relaxant, antibiotic, and a continuation of any preoperative vasoactive infusions. We have found that this is a stable and well-tolerated anesthetic regimen.

The requirement for anesthesia services is ever-widening, and in patients with pediatric heart disease this is also the case. Thus the patients will require radiologic investigations, including CT, MRI, and nuclear medicine scans; interventional radiology procedures; and gastrointestinal procedures, to name a few. Before discussion of the patient and the anesthetic, it is important for the practitioners to have a thorough knowledge of the environment into which they are taking the patient with regard to magnetic fields, closest code cart, and the ability to get help quickly if needed. Without going into the specifics

of every potential clinical scenario, a few basic points are discussed.

As with any anesthetic procedure, a thorough preoperative evaluation is vital. Most patients with pediatric heart disease have long and complex histories, so this assessment should include a detailed description of their cardiac status, including prior surgeries, catheterization findings, and associated conditions (e.g., neurocognitive function, pulmonary status, renal function). Depending on the patient's underlying condition a recent echocardiogram will give very important clinical details related to overall function, valve pathology, presence or absence of intracardiac shunt, patency of surgical shunts, and presence of pericardial fluid. Although this may be ideal, often the echocardiographic examination may be remote from the anesthetic encounter and thus the clinical history and examination are important. The group of heart transplant patients, however, requires an echocardiogram within a short time of the planned procedure because it will give vital information that may indicate worsening function in an otherwise asymptomatic patient. The last point is the nothing-by-mouth period. Many patients in this group have physiology in which dehydration may be very deleterious (e.g., single-ventricle physiology, presence of surgical shunts, unrepaired TOF). In these patients it is important that the patient stay orally hydrated up to 2 hours before the planned procedure; if this is not possible, intravenous fluids must be used. The anesthetic course will depend on the duration of the planned procedure, the patient's physiology (i.e., spontaneous versus controlled ventilation), airway management (natural versus laryngeal mask airway versus endotracheal tube airway), anesthetic maintenance, travel to and from the procedural area, and maintenance of the patient's temperature. Before leaving the induction area the anesthetic team must be prepared for airway misadventures and even a code situation; thus, the team must travel with auxiliary airway equipment and resuscitative drugs. The very number of these different venues may make it difficult to have an anesthesia machine present in each; however, an anesthetic cart with additional airway equipment, intravenous materials, and resuscitative drugs should be present. The anesthetic that is delivered may vary among practitioners and institutions, but the common details of importance are a thorough knowledge of the patient and the ability to treat expeditiously should any difficulty ensue in a remote venue.

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Chapter 95

Pediatric and Neonatal Intensive Care

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Key Points

- The role of family in the pediatric intensive care unit (PICU) has evolved over time, and the inclusion of family in the care of their child is now recognized as an important part of critical care.
- Congenital heart disease causes significant alterations in oxygenation, perfusion, and myocardial function after birth, and it can be categorized into hypoxic and normoxic lesions.
- The overall goal of therapy in shock is to treat the underlying cause, return adequate oxygen delivery to the tissues, and remove metabolic products that developed during anaerobic metabolism. It appears that the faster the body returns to adequate perfusion, the better the overall outcome.
- One of the recent changes in neonatal resuscitation in the 2011 Neonatal Resuscitation Program Guidelines is the recommendation of positive pressure ventilation (PPV) with room air, unless chest compressions or medications are needed during the resuscitation, then the recommendation is still for PPV with 100% oxygen.
- Pediatric cardiac arrest is not a rare event. At least 16,000 American children (8-20 per 100,000 children per year) suffer a cardiopulmonary arrest each year.
- The four distinct phases of cardiac arrest and cardiopulmonary resuscitation (CPR) interventions are: (1) pre-arrest, (2) no-flow (untreated cardiac arrest), (3) low-flow (CPR), and (4) post-resuscitation and arrest.
- Acute respiratory distress syndrome (ARDS) diagnostic criteria have been revised recently and are now the Berlin Definition, where ARDS is separated into three mutually exclusive categories based on the degree of hypoxia. Mild is PaO_2/FiO_2 = 201 to 300 with positive end-expiratory pressure (PEEP) > 5, moderate is PaO_2/FiO_2 = 100 to 200 with PEEP > 5, and severe is PaO_2/FiO_2 < 100 with PEEP > 10.
- Traumatic brain injury (TBI) is composed of two components—an initial primary injury owing to direct mechanical deformation of brain parenchyma and a subsequent secondary injury that can develop over hours to days. Secondary injury may be the result of multiple mechanisms including ischemia, excitotoxicity, metabolic failure and eventual apoptosis, cerebral swelling, axonal injury, and inflammation and regeneration.
- A vascular occlusive crisis in the lungs leads to acute chest syndrome (ACS). Acute chest syndrome is the leading cause of death and the second most common complication in sickle cell disease.
- Tumor lysis syndrome is a metabolic crisis precipitated by acute lysis of a large number of tumor cells. Serum uric acid, potassium, and phosphate concentrations are elevated. The elevated phosphate concentrations cause hypocalcemia.
- Accidents and trauma are the leading causes of death in children 1 to 14 years of age.

RELATIONSHIP BETWEEN THE INTENSIVE CARE UNIT AND THE OPERATING ROOM

The field of pediatric intensive care may have originated from anesthesia, but these areas have grown apart over time. Because of the extensive training required, few individuals are qualified to cover both disciplines. With more complex patients, care will occur in the operating room and the intensive care unit (ICU). There needs to be excellent communication between the ICU and operating room clinicians to ensure a seamless transition of care. Many institutions require attending-to-attending

handoff between the ICU and anesthesia for each case. This should occur in both the preanesthetic and postanesthetic setting. Information regarding current ICU therapy response can simplify a potentially difficult anesthetic. Similarly, understanding the operative and anesthetic course will guide the next several days of management in the ICU. A complete anesthesia sign-out includes pertinent past medical history, allergies, ease of airway management, venous and arterial access, blood and fluids given, the need for inotropic drugs, medications delivered including timing of antibiotics, complications, laboratory values, and the most recent analysis of arterial blood gases (ABGs). This information may be available in the anesthetic record; however, a short verbal summary by the anesthesiologist provides details that are more practical.

FAMILY PARTNERED CARE IN THE PEDIATRIC INTENSIVE CARE UNIT

The role of family in the pediatric intensive care unit (PICU) has evolved over time. The inclusion of family in the care of their child is now recognized as an important part of critical care. Many intensivists identify the family unit as their patients. In many pediatric hospitals, parents are invited to participate in multidisciplinary rounds with the nurses, respiratory therapists, and physicians working with their child. The literature indicates that including families in rounds does not require more time than traditional rounds, and it does not compromise teaching.[1] Privacy can be maintained even in an open-bed environment. Satisfaction with this model is reported from families and care providers in the unit. More ICUs likely will move to this model over time.

Parents of children admitted to an ICU can incur severe emotional distress, sometimes resulting in symptoms of posttraumatic stress disorder.[2] The ICU is a unique and often terrifying experience for families and children. The process of ICU care involves multiple caregivers, changing shifts, and endless physicians (e.g., residents, students, fellows, multi-specialists). For families in the ICU, there can be a loss of control, significant financial worries, and other factors that affect coping. Helping parents to cope with their child's critical illness and these stressors is a central part of intensive care. Parents may display behaviors that are out of context and may seem abnormal, such as excessive clinginess, intellectualizing the process, blaming others (including their spouses), minimizing, and seeking opinions everywhere (e.g., the Internet, the environmental care people). It is imperative to attempt to understand what impels these behaviors to provide optimal care. It is also important to help the parents be parents and educate them about their child's illness. This situation emphasizes that social workers, psychologists, and child and family therapists are all part of the critical care team.

With the move to family-centered care, the issue of parental presence during invasive procedures and especially cardiopulmonary resuscitation (CPR) needs to be addressed. Unfortunately, most studies are from the setting of an emergency department rather than an ICU. A review by Dingeman and associates[3] found that 10 of 15 studies conducted in emergency departments addressed the issue of parental presence during procedures or CPR. A study by Dudley and associates[4] indicates that family presence does not delay care in pediatric trauma resuscitations. Mangurten and colleagues[5] also showed that care was uninterrupted by family presence during CPR or invasive procedures and that there was overall parental satisfaction. The experience of families present during CPR in a PICU setting was also positive.[6] Actually, allowing parents to stay during procedures or resuscitation may be helpful for the parents coping with the trauma of a critically ill child. Caregiver attitudes toward parental presence will need to be addressed as the likelihood of this event increases over time. The decision to allow parental presence cannot be forced on everyone. There should be in place a means for declining on the part of the clinician as well as the parent. In addition, an attendant for family members during these events is necessary; this is similar to the issue of parental presence during induction of anesthesia in the operating room (also see Chapter 93). Arrangements need to be made in advance to instruct family so that clinical care is not interrupted. In our ICUs this role been filled by social workers or members of the medical team. Parental presence during invasive procedures may pose a different challenge as these events occur more frequently compared with CPR. In the same manner, someone other than the person performing the procedure should be looking after the family.

DISCLOSURE OF MEDICAL ERRORS

We believe that it is ethically correct to disclose medical errors to families; however, some clinicians may continue to resist because of concerns regarding litigation. In a survey of 1018 Illinois residents, 27% indicated that they would sue, but 38% stated that they would recommend the hospital if appropriate disclosure and remediation occurred.[7] The conclusion drawn by the author of the study was that "Patients who are confident in their providers' commitment to disclose medical errors are not more litigious and far more forgiving than patients who have no faith in their providers' commitment to disclose." Explanations of medical errors to the family should come from the senior member of the team. This is usually the current ICU attending, but it can be the medical director of the ICU based on the complexity of the incident and outcome. The discussion should include an explanation of what happened in nontechnical language, how it occurred, the repercussions and change of care planned for the child, and what will be done to prevent a similar error in the future. We find it helpful to have the ICU social worker present to help validate concerns and provide support. The attending physician remains present until all questions are answered or additional time is scheduled, if necessary. Most hospitals will track errors or negative outcomes through a quality-assurance program. Depending on the incident, a "root cause analysis" should be performed. Medical errors will occur, but these should be viewed as opportunities to improve practice quality and prevent future events.

In an ICU setting, there unfortunately will also be a need to cope with death and dying.[8] Palliative care plays

an important role when nothing medically can be done for the child (see Chapter 65). We also find their services exceedingly helpful for children with chronic medical conditions who are anticipated to die during a future admission. Using a team approach, we try to minimize pain and suffering for the child and family at the end of life. Caregivers and ICU team members must understand when to allow the families' choices and support them over what may be their own beliefs and practices—as long as the goal remains to prevent further pain and suffering.[9] The awareness of medical futility is increasing over time; however, with this concept, there is a significant interplay with financial, societal, ethical, personal, and religious opinions and feelings. It may be difficult to define futility, but when the pain and suffering of continuing life are more severe than the inevitability of death, care may become futile. Pain relief and caring support for the child and family are never futile.

ORGANIZATION OF THE PEDIATRIC INTENSIVE CARE UNIT

Medical and nursing directors, hospital administrators, and representatives from pediatric medicine, anesthesia, surgery, and the pediatric subspecialties should be responsible for policy and procedures pertaining to the PICU, and they should make recommendations regarding personnel staffing, equipment purchases, and structural and design changes within the unit.

The medical director oversees the quality of patient care, patient triage, implementation of policy and procedures, in-service education, and coordination of consultants. Ideally, physician coverage should be full-time at the resident, fellow, and attending staff level and should include in-house, full-time coverage at night.

The nursing director should have special skills in pediatric intensive care, education, and personnel management. The nursing staff must be trained in all aspects of pediatric critical care and resuscitation. Staffing should be flexible enough to provide one-on-one patient care when necessary. A multidisciplinary in-service program is essential for continuing education and orientation.

Other team members include respiratory therapists, physical therapists, nutritionists, social workers, laboratory technologists, pharmacists, and psychiatrists and psychologists for the patients and staff. All medical and support personnel should be encouraged to participate in rounds, educational endeavors, and team meetings whenever possible.

There must be adequate workspace around each bed and enough storage space to keep life-support equipment within reach. Space for reading, meeting, sleeping, and showering should be available for the staff members. Space should be provided for parents to remain with their children during the day and for parents to sleep overnight. Parents should be encouraged to participate as much as possible in the care of their child.

Each bed space should be standardized so that it can be used to provide any level of care. Private rooms are ideal, but if shared rooms are necessary, the distance between beds must be adequate to ensure privacy and minimize nosocomial infection. Isolation rooms should be available within the confines of the unit.

Devices for diversion and entertainment should be available for conscious children. Television and computer games are often better than heavy sedation.[10,11] Adequate nurses and nursing involvement at the bedside will prevent potentially life-threatening events. Because sick children require close personal observation, centrally monitored nursing stations have little place in the PICU.

CARDIOVASCULAR SYSTEM (SEE ALSO CHAPTERS 93 AND 94)

STRUCTURAL AND FUNCTIONAL DEVELOPMENT

The shape of the heart is complete by 6 weeks' gestation, but myofibrillar density and maturation increase through the first year of postnatal life. During this time, myocytes engage in rapid protein synthesis and rapid cell growth, which requires a high intracellular concentration of nuclei, mitochondria, and endoplasmic reticulum. The greater number of nonelastic and noncontractile elements makes the neonatal myocardium less compliant and it contracts less efficiently than the adult myocardium. In the fetus and newborn, the decreased ventricular compliance causes small changes in end-diastolic volume to induce large changes in end-diastolic pressure. In addition, augmentation of stroke volume by the Frank-Starling mechanism is less effective in young children. The newborn is more dependent on heart rate for maintenance of cardiac output.[12,13] Cardiac output increases only approximately 15% with intravenous fluid administration; increasing the heart rate, however, increases cardiac output.[14] This consideration is important when taking care of the critically ill infant.

DEVELOPMENT OF THE CIRCULATION

The adult and fetal circulation differs in many ways. The fetal circulation is distinguished by (1) the placenta as the organ of respiration, (2) high pulmonary vascular resistance (PVR), (3) low systemic vascular resistance (SVR), and (4) fetal ventricles that pump in parallel with right ventricular dominance. While the fetus lives in a low oxygen environment, the oxygen content of the blood of the fetus is similar to that of adults (20 mL of oxygen per 100 mL of blood) because of a higher concentration of hemoglobin that has high affinity for oxygen. The neonatal circulation has several shunts—the ductus arteriosus, ductus venosus, and foramen ovale—that direct more oxygenated blood to the brain and heart and bypass the lungs. Changes then occur that allow parallel circulation of the fetus to convert to the series circulation of the adult:

1. With the first breath, expansion of the lung, increased alveolar oxygen, an increase in pH, and neurohumoral mediators and nitric oxide (NO) relax the pulmonary vasoconstriction.[15]
2. When the placenta separates from the uterine wall, the placental blood vessels constrict, and SVR and left

ventricular afterload increase. The decrease in PVR plus increase in SVR raises left atrial pressure above right atrial pressure and functionally closes the "flap valve" of the foramen ovale. The foramen ovale may not close anatomically for months to years, if ever. It is patent in at least 15% of adults.[16,17]

3. The decrease in PVR causes flow through the ductus arteriosus to reverse. This exposes the ductus to oxygenated systemic arterial blood, which along with the rapid decrease in prostaglandin E_2 after birth, closes the ductus. Anatomic closure of the ductus requires several weeks.
4. The ductus venosus closes passively with removal of the placental circulation and readjustment of portal pressure relative to inferior vena cava pressure.
5. There is a further gradual decline in PVR secondary to structural remodeling of the muscular layer of the pulmonary blood vessels. During fetal life, the central pulmonary vascular bed has a relatively thick muscle layer. After birth, the muscle coat thins and extends to the periphery of the lung, a process that takes months to years to complete.

DEVELOPMENT OF AUTONOMIC CONTROL OF THE CIRCULATION

The functional integrity of autonomic circulatory control during fetal and perinatal development is still a matter of considerable speculation. The fetal heart has reduced catecholamine stores and increased sensitivity to exogenously administered norepinephrine.

Adrenergic innervation of the human myocardium is complete between 18 and 28 weeks' gestation. Human newborns have low cardiac stores of norepinephrine and decreased numbers of sympathetic nerves after birth. Adrenergic responses are apparently present, but diminished in newborn humans. In human neonates, the cholinergic system is completely developed at birth, and the heart is sensitive to vagal stimulation. Bradycardia is the probable response to an increase in autonomic tone. The baroreceptor reflex is present, but incompletely developed at term in humans. In preterm infants, postural changes elicit no change in heart rate, suggesting an incomplete or attenuated baroreceptor response.[16] The chemoreceptor response is well developed in utero. The fetal bradycardia that occurs in response to hypoxia is thought to be mediated through chemoreceptors and may be similar to the oxygen-conserving mechanisms of diving animals.[17]

MYOCARDIAL METABOLISM

Fetal myocardial metabolism differs from that of adults. Relative hypoxia is normal in utero, and infant hearts tolerate hypoxia better than adult hearts do. This difference may be due in part to high concentrations of glycogen in fetal myocardial tissue and to the ability to use anaerobic metabolism more effectively. Because of the high glycogen stores and the ability to use anaerobic metabolism efficiently, the fetal or newborn heart is relatively resistant to hypoxia and can be resuscitated more easily if oxygenation and perfusion are reestablished reasonably quickly.

Oxygen consumption increases precipitously after birth, presumably because neonates are required to maintain their own temperature. A full-term infant's oxygen consumption in a neutral thermal environment is approximately 6 mL/kg/min; it increases to 7 and 8 mL/kg/min at 10 days and 4 weeks, respectively.

COMMON CARDIOVASCULAR DISEASE STATES

CONGENITAL HEART DISEASE

Congenital heart disease causes significant alterations in oxygenation, perfusion, and myocardial function after birth (Box 95-1; also see Chapter 94). These abnormalities can be divided into hypoxic and normoxic lesions. The latter include obstructive lesions of the left side of the heart (mitral valve stenosis, aortic valve stenosis, aortic stenosis, anomalous pulmonary venous return, ventricular septal defect, or patent ductus arteriosus with a right-to-left shunt), whereas hypoxic lesions include tricuspid valve stenosis, pulmonary valve stenosis, pulmonary artery stenosis or aplasia, and the tetralogy of Fallot. Right-sided lesions cause hypoxia if the left-to-right shunting of blood is sufficient to cause congestive heart failure (CHF) and pulmonary edema.

Newborns with significant congenital heart disease commonly have either cyanosis or CHF (Box 95-1). The degree of dysfunction usually changes during the first few months of life as PVR decreases to adult levels. As PVR decreases, left-to-right shunting of blood usually increases, and the symptoms of CHF become more apparent. Many neonates with a significant ventricular septal defect, which may or may not be observed during the preoperative workup, have no left-to-right shunting for several weeks after birth; however, induction of alkalosis during surgery can increase shunting. In the newborn, the usual signs and symptoms of CHF include poor feeding, irritability, sweating, tachycardia, tachypnea, decreased peripheral pulses, poor cutaneous perfusion, and hepatomegaly. Many patients with pulmonary edema exhibit tachypnea without retractions. Cyanosis occurs with structural cardiac disease, but other causes such as respiratory disease, increased PVR (persistent pulmonary hypertension), and methemoglobinemia must also be considered.

BOX 95-1 ***Common Congenital Heart Malformations in the Newborn***

1. Cyanotic congenital heart lesions
   - Tetralogy of Fallot
   - Transposition of the great arteries
   - Hypoplastic left heart syndrome
   - Pulmonary atresia with an intact ventricular septum
   - Single ventricle
   - Total anomalous pulmonary venous return
   - Tricuspid atresia
2. Congenital heart lesions manifested as congestive heart failure
   - Ventricular septal defect
   - Patent ductus arteriosus
   - Critical aortic stenosis
   - Coarctation of the aorta

Congenital heart disease is diagnosed by physical examination, electrocardiogram, chest radiograph, and postnatal echocardiogram, and via fetal echocardiography. Cardiac catheterization is occasionally performed as interventional therapy or as a diagnostic tool. Magnetic resonance imaging (MRI) is used to define the anatomy of congenital heart lesions before cardiac surgery.

Initial treatment of congenital heart disease is aimed at relieving CHF, improving systemic perfusion, and improving or maintaining pulmonary blood flow. The ductus arteriosus must be maintained open in instances of hypoplastic left heart syndrome, aortic stenosis or atresia, interrupted aortic arch, and symptomatic neonatal coarctation of the aorta. In many cases, infusion of prostaglandin E_1 sustains life until surgical palliation can be performed.[18]

ACUTE CIRCULATORY FAILURE IN CHILDREN (SHOCK AND SEPSIS)

Shock

Shock is the inability to provide adequate oxygen to the tissues that require it. The condition of shock depends on the balance of supply and demand of oxygen. Typically, the body delivers excess oxygen to the tissues. Under periods of stress or illness, there can be a decrease in supply caused by diminished blood flow or as decreased oxygen in blood. There can also be increased demand or oxygen extraction from the tissues. The content of oxygen in the blood is dependent on the amount bound to hemoglobin and the amount dissolved in plasma: Oxygen content (Cao_2) (mL/dL) = (1.34g/dL) (Sao_2) (Hb) + (PaO_2) (0.003). The normal oxygen content is approximately 20 mL/dL. Delivery of oxygen to the tissues depends on oxygen content and cardiac output. Oxygen delivery ($\dot{D}O_2$) (mL/min) = oxygen content (Cao_2) × cardiac output (CO). Oxygen consumption ($\dot{V}O_2$) is the demand portion of the equation. Oxygen consumption ($\dot{V}O_2$) is independent of oxygen delivery ($\dot{D}O_2$) above a critical threshold and over a wide range. Below this critical threshold, $\dot{V}O_2$ is dependent on $\dot{D}O_2$. For infants and young children $\dot{V}O_2$ is estimated at 175 mL/min/m^2. Oxygen consumption is equal to oxygen delivery multiplied by oxygen extraction (O_2EX) by the body: $\dot{V}O_2 = \dot{D}O_2 \times O_2EX$. Oxygen extraction O_2EX is equal to $(CaO_2 - CvO_2)/Cao_2$. Cao_2 is the oxygen content of arterial blood and CvO_2 is the oxygen content of venous blood. The difference between oxygen content of arterial and venous blood is predictably 4 to 6 mL/100 mL blood. Initially, as oxygen delivery decreases, the oxygen consumption can remain constant via increased extraction. Below a critical threshold in oxygen delivery, oxygen consumption becomes dependent on delivery. When oxygen cannot meet the metabolic needs of the body, nonessential metabolism is decreased or eliminated. Such metabolism includes growth, neurotransmitter synthesis, thermoregulation, and so on. In this way, the remaining oxygen can continue to be substrate for mitochondria. There are organs in the body such as the kidney, skin, intestines, and skeletal muscle that receive a high supply of blood relative to their metabolic needs. These organs also have a high proportion of sympathetic nerve innervations that allow for redistribution of blood flow to organs with limited oxygen reserves, such as the brain and heart.

Classification of Shock

There are several schemas that clinicians use to classify shock. Furthermore, within these classification schemas, disease states can fall into more than one category. One classification schema separates shock into hypovolemic, cardiogenic, distributive or vasogenic, and extracardiac obstructive.

Hypovolemic shock can be due to hemorrhage from trauma or gastrointestinal (GI) losses from internal bleeding. Nonhemorrhagic hypovolemic shock can be due to external losses of fluid from vomiting, diarrhea, polyuria, and poor fluid intake. Fluid redistribution in cases of burns, trauma, and anaphylaxis can also be a cause.

Cardiogenic shock can be myopathic because of decreased heart function. It commonly follows myocardial infarction in adults. For children, myocarditis or cardiomyopathy are more common. Other causes of cardiogenic shock include mechanical failure, such as valvular regurgitation or obstruction. Significant arrhythmias can result in cardiogenic shock when contractions are so asynchronous that they decrease cardiac output.

Extracardiac obstructive shock results from a physical obstruction that prevents adequate forward circulatory flow. Causes include inadequate preload secondary to mediastinal masses, increased intrathoracic pressure from tension pneumothorax, constrictive pericarditis, and cardiac tamponade from pericardial effusions. Pulmonary hypertension, pulmonary embolus, and aortic dissection can cause obstruction to systolic contraction.

Distributive shock is caused by a decrease in systemic vascular resistance and the maldistribution of end-organ blood flow. Cardiac output can be increased in distributive shock; however, arterial blood pressure can remain low because of a very low systemic vascular resistance. Septic causes of distributive shock can be related to bacterial, fungal, viral, or rickettsial infections or toxins produced from these infections. Toxic shock syndrome is an example of toxin-mediated hypotension. Anaphylactic or anaphylactoid reactions are a type of distributive shock. Systemic inflammatory response syndrome (SIRS) may present with distributive shock. Spinal shock can result in distributive shock on a neurogenic basis. Adrenal insufficiency with low circulating hormones results in distributive shock decreased systemic vascular resistance.

Diagnosis of Shock

Maintaining a high index of suspicion is important to identify shock rapidly in pediatric patients. Volume losses may be readily apparent from the history of present illness. Fever, rash, and irritability can indicate infection; however, cardiogenic shock can appear with vague reports of decreased activity and level of alertness. In addition, if the patient's shock is currently compensated, changes in physical findings may be limited. A child in shock may initially exhibit tachycardia, cold extremities, and poor capillary refill. Furthermore, in distributive shock the child may be warm with just an isolated tachycardia. A brief pertinent physical examination should evaluate

level of alertness, peripheral perfusion, mucous membranes, pulse rate and quality, respiratory effort, urine output, and arterial blood pressure. In children, arterial blood pressure may be preserved until the degree of shock has progressed. Hypotension is a sign of late and decompensated shock in children. Metabolic acidosis may not be initially present.

Compensatory Mechanisms

The body applies compensatory mechanisms with the onset of shock to maintain adequate tissue perfusion for as long as possible. There is redistribution of fluid from the intracellular and interstitium to the vascular space. There is a decrease in glomerular filtration to limit renal fluid losses. Renal fluid losses are also limited by the release of aldosterone and vasopressin. There is an increase in sympathetic activity and release of epinephrine; this results in decrease venous capacitance and some preservation of arterial blood pressure. Heart rate is increased as the body tries to maintain cardiac output. There is an increase in cardiac contractility through circulating catecholamines and adrenal stimulation. Increase in sympathetic nerve stimulation shunts blood away from nonvital organs. At the tissue level, transfer of oxygen from hemoglobin is increased by increased red blood cell 2, 3-diphosphoglycerate (DPG), fever, and tissue acidosis.

Therapy and Outcomes

Aggressive therapy to treat pediatric septic shock has resulted in improved outcomes; therefore, therapy for septic shock appears to be a good model for the treatment of shock in general. The overall goal of therapy in shock is to treat the underlying cause, return adequate oxygen delivery to the tissues, and remove metabolic products that developed during anaerobic metabolism. The faster the body returns to adequate perfusion, the better the overall outcome. Many hospitals have developed sepsis pathways based on the data presented in Figure 95-1. These pathways act as guidelines for resuscitation and are readily available to all care providers.

In 1991, Carcillo and colleagues[19] described a population of 34 children with septic shock in an emergency department. Shock was diagnosed based on hypotension for age, with decreased perfusion, poor peripheral pulses, cool extremities, and tachycardia. Sepsis was defined as a positive blood or tissue culture result. Remarkably, all the patients had a pulmonary artery catheter placed within 6 hours of presentation. The overall mortality for the group was 47%; however, there was only one death (11% mortality) among the nine patients who received more than 40 mL/kg of fluids in the first hour. The authors point out this patient died with a second episode of sepsis 2 weeks later. In this study, the rapid intravenous fluid administration did not increase the incidence of cardiogenic pulmonary edema or acute respiratory distress syndrome (ARDS).

In 2001, Rivers and colleagues[20] published a study in adult patients with septic shock showing that early, aggressive, goal-directed therapy in the first 6 hours of care improved mortality. Two hundred sixty-three adults enrolled, and 133 received standard therapy based on clinician discretion. The 130 patients randomized to early goal-directed therapy followed protocols treating hypovolemia and supporting arterial blood pressure with vasoactive medications, if necessary. The baseline characteristics of the two groups were similar. The in-hospital mortality was 46.5% in the standard therapy group and 30.5% in the early goal-directed therapy group ($p < 0.01$). Although the study occurred in adults, the results demonstrated the need for early aggressive intervention.

Following the Rivers' publication, a task force was formed from members of the Society of Critical Care Medicine to address shock in children; their work was published in 2002.[21] Their guidelines were incorporated into the American Heart Association's (AHA) Pediatric Advanced Life Support (PALS) Provider Manual and widely disseminated with Spanish and Portuguese translations. The effectiveness of these interventions and a 2007 update was published by the same group in 2009.[22] They highlighted significant improvements in mortality in dengue shock syndrome, malaria, and septic shock treated by community physicians using early goal-directed therapy.[23-25]

The guidelines include rapid recognition of shock, early antibiotic administration, and early administration of intravenous crystalloid. The initial resuscitation should include 20 mL/kg of isotonic saline or colloid pushed as a bolus to over 60 mL/kg until there is an improvement in the patient's perfusion or rales or hepatomegaly develops. The goal is for the initial fluid resuscitation to occur in the first 15 minutes of therapy, and therapy should be initiated by placing an intraosseous device, even if peripheral intravenous cannulation attempts fail (Fig. 95-2). The guidelines target therapeutic end points of normal pulses with no difference between peripheral and central pulses; capillary refill ≤ 2 seconds; warm extremities, normalization of blood pressure for age, mental status, glucose concentration, ionized calcium concentration; and urine output > 1 mL/kg/hr. If central venous access is not readily obtained, consideration should be given for placement of an intraosseous line. Cold shock (cold mottled extremities with prolonged capillary refill) should be treated with dopamine up to 10 μg/kg/min and then epinephrine (0.05 to 0.3 μg/kg/min) if there is no improvement. Warm shock (brisk capillary refill) should be treated with norepinephrine. Arrangements should be made early to admit the child to an ICU. If shock is not reversed with the inotropic support, hydrocortisone should be considered for catecholamine-resistant shock. Recommendations for stabilization in the ICU following the first hour of therapy include monitoring central venous pressure, central venous saturation, and cardiac output. Persistent shock that is resistant to catecholamines should prompt the clinician to rule out pericardial tamponade, pneumothorax, or significantly elevated intraabdominal pressure that may be compromising circulation. In the absence of a correctible condition, extracorporeal membrane oxygenation (ECMO) should be considered.

There were several new recommendations in the 2007 guidelines that addressed changes in the literature between 2002 and 2007. It was identified that the availability of skilled practitioners to place central venous access could delay the initiation of inotropic support. Therefore, the 2007 guidelines recommended the

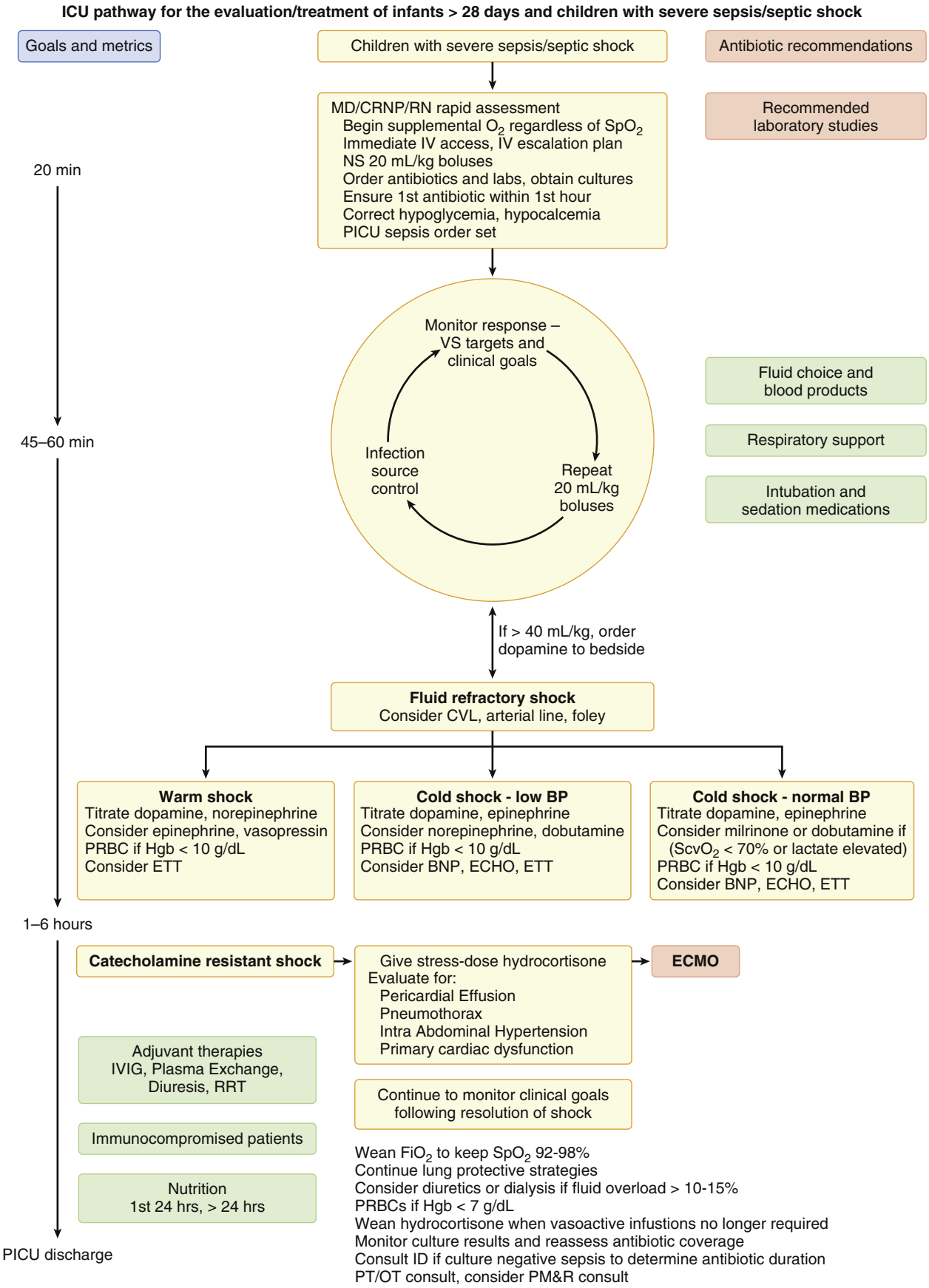


Figure 95-1. Sepsis resuscitation pathway.

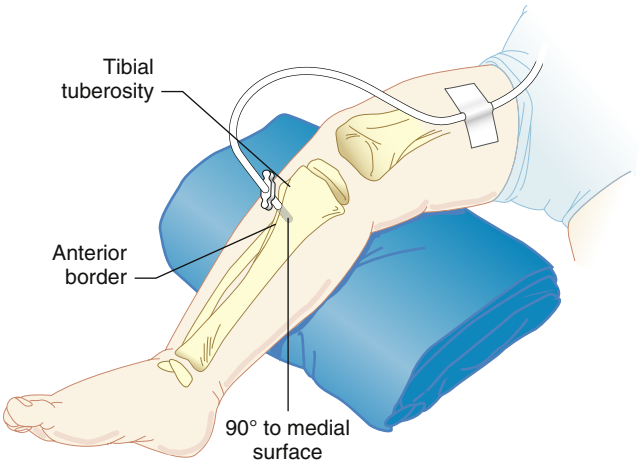


Figure 95-2. Intraosseous cannulation technique.

administration of dopamine or epinephrine via a peripheral intravenous line if there was a delay in obtaining central venous access. Ongoing monitoring of the access site should be performed. Norepinephrine should not be given in a peripheral intravenous injection because of the risk of extravasation. In the 2002-2007 interval, there were several pediatric and adult studies indicating adrenal suppression and increased severity of illness adjusted mortality with the use of etomidate.[26,27] The 2007 guidelines do not recommend the use of etomidate unless it is in the format of a randomized controlled trial. Ketamine with atropine was recommended for sedation for invasive procedures in infants and children. However, because of limited experience, ketamine cannot be recommended for the newborn population.

The 2007 guidelines[22] recommend titrating therapy to cardiac output and indicate that there are several methods by which cardiac output can be measured. The use of pulmonary arterial catheters in pediatrics has decreased, but other methods are available. A good review of monitoring techniques was published by Mtaweh and associates in 2013.[28] Cardiac output can be monitored by newer techniques analyzing the arterial pulse wave, transpulmonary thermodilution, carbon dioxide rebreathing, echocardiography, bio-impedance of the thorax, and ultrasound continuous-wave Doppler. These techniques are less invasive than pulmonary artery catheters; however, many still require validation studies in pediatric centers, and they might not be available at all centers.

One additional area to be addressed in the 2007 guidelines is in the area of fluid removal.[22] In a 2005 study by Goldstein and associates[29] with pediatric patients in multi-organ failure, including acute renal failure requiring continuous renal replacement therapy (CRRT), there was improved survival in the group that had a lower percentage of fluid overload at the initiation of CRRT.[29] While supporting the primary premise of fluid resuscitation, the 2007 guidelines offered new recommendation for fluid removal in patients with fluid overload and multiorgan failure.[21] They recommended the use of diuretics, peritoneal dialysis, or CRRT in patients who had received adequate fluids for resuscitation but were not able to maintain an even fluid balance through native urine output. Yet, peritoneal dialysis and CRRT for pediatric patients might not be available at all centers. However, the association between excessive intravascular fluid administration and mortality with acute renal failure is an ongoing issue in PICU care.

The concern for possible adrenal insufficiency during septic shock needs to be addressed by the clinician caring for the patient. There are certain instances in which limited function of the adrenal axis is anticipated. These instances include patients who have recently received a glucocorticosteroid, ketoconazole, or etomidate. Furthermore, patients with disease states such as purpura fulminans or those affecting the hypothalamus, pituitary or adrenal glands will be at increased risk. Patients with adrenal insufficiency need supplemental corticosteroids. However, for children with septic shock but without these factors, it is not clear whether the risk of relative adrenal insufficiency or treatment with systemic steroids alter outcome. Dr. Zimmerman[30] reviewed the adult and limited pediatric literature in 2007 for therapeutic steroid use in sepsis. He highlighted adult studies showing high-dose short courses of steroids are associated with decreased survival. Furthermore, data from the CORTICUS trial[31] indicated that low-dose steroids as a physiologic replacement during periods of vasopressor resistant shock resolve shock more quickly but there was no change in mortality. In turn, the 2007 guidelines were unchanged from 2002. Hydrocortisone treatment was only recommended for patients with absolute adrenal insufficiency or adrenal-pituitary axis failure and catecholamine-resistant shock. Absolute adrenal insufficiency was defined as peak cortisol concentration of less than 18 μg/dL obtained after corticotropin stimulation.

CARDIOVASCULAR PHARMACOLOGY

Pharmacologic support of the circulation includes positive inotropic and chronotropic agents, vasoconstrictors and vasodilators (afterload reduction), and antiarrhythmics (see Chapters 16 and 93). Most currently used drugs have not been tested adequately in children; therefore, dosage recommendations and anticipated effects must be extrapolated from adult doses and clinical experience.

Positive inotropic drugs are used to augment the cardiac output of patients with circulatory failure. Most inotropic agents also affect the heart rate and vasomotor tone. Tachycardia in a child is usually well tolerated and is frequently beneficial.[32] In a neonate whose ventricles are relatively noncompliant and whose stroke volume is less variable, tachycardia is an important means of augmenting cardiac output. Because drugs that increase the heart rate or contractility also increase myocardial oxygen consumption, adequate arterial oxygenation and sufficient metabolic substrates are required when these drugs are administered. The cardiovascular response to sympathomimetic amines is attenuated in the presence of severe acidosis and possibly sepsis; higher infusion rates of these drugs are required and need readjustment as the acidosis improves. In the following paragraphs, commonly used inotropic drugs are listed with brief comments regarding their use in pediatric intensive care (Table 95-1).

TABLE 95-1 VASOACTIVE AND INOTROPIC MEDICATIONS

Drug	Effect	Dose (μg/kg/min)	Inotropy	Chronotropy	Vasodilation	Vasoconstriction
Epinephrine (Adrenalin)	α, β	0.05-2.0	++	++		++
Isoproterenol (Isuprel)	β_1, β_2	0.05-2.0	++	++	+	
Dopamine (Inotropin)	δ	1-3			+Renal splanchnic	
	β > α	5-15	+	+		+ or –
	β, α	>15	+	+		+
Milrinone		Bolus: 50 μg/kg over 15-min period Infusion: 0.375-0.75	+		+	
Norepinephrine	α >> β	0.05-1.0	Slight+	+		++
Nitroprusside		0.5-10			++ Arterial > venous	
Nitroglycerin		1-20			++	

EPINEPHRINE

Epinephrine is useful for the treatment of shock in the presence of myocardial dysfunction. The typical starting dose in children is 0.05 to 0.2 μg/kg/min. Doses as large as 1 to 2 μg/kg/min have been given if there is profound vasodilation in the periphery and abdominal organs with the overall goal of shunting blood to the heart and brain.

Dopamine

Dopamine is the most commonly infused inotropic drug in pediatric patients. Dopamine is the metabolic precursor of both norepinephrine (NE) and epinephrine. Its effects are dose-dependent, with dopaminergic activity with small doses (although not well documented) in critically ill children; β-adrenergic activity with intermediate doses (5 to 10 μg/kg/min) exhibits chronotropic and inotropic effects; and some α-adrenergic activity at larger doses (10 to 20 μg/kg/min) exhibit peripheral vasoconstriction. Young children require larger doses of dopamine than adults do to produce the same effect. In one study of infants, an infusion of 15 μg/kg/min was required to increase cardiac output above control levels after cardiac surgery.[33] This may reflect the decreased releasable myocardial stores of norepinephrine in immature ventricles. Therefore, in the sick, preterm infant, there can be decreased dopamine clearance with a much greater vasopressor response than expected.

Vasopressin

Vasopressin is a pituitary peptide hormone with method of action on the kidney and vasculature. In the kidney, vasopressin controls water reabsorption in the renal tubules and in the vasculature causes vasoconstriction by stimulating smooth muscle V1 receptors. Its clinical applications include GI hemorrhage, central diabetes insipidus, and as a second- or third-line agent to treat hypotension.

Isoproterenol

Isoproterenol is a synthetic, potent, nonselective β-agonist with strong chronotropic effects with very low affinity to α-adrenergic receptors, and is usually well tolerated in children. However, high doses of isoproterenol can cause myocardial ischemia.[34] Isoproterenol also induces vasodilation that is responsive to acute volume administration. It is often used for increasing heart rate in complete heart block, in the immediate postoperative period after cardiac transplantation to improve cardiac output by increasing heart rate in the denervated donor heart, and as a potent pulmonary vasodilator during pulmonary hypertensive crisis via β_2-adrenergic receptor activity.

Dobutamine

Dobutamine provides positive inotropy and afterload reduction. It is active at β and α receptors. Its function is primarily as a inotropic agent but with less vasopressor activity compared with dopamine. It is only used as a continuous infusion of 5 to 20 μg/kg/min, and in some studies may increase myocardial oxygen. It causes tachycardia in children but not in adults.[35,36]

Norepinephrine

Norepinephrine, a drug with strong α- and β-agonist effects, has had a resurgence of use in infants and children.[37] Children with nearly normal cardiac function and marked peripheral vasodilation have good responses to this drug. It is especially useful in instances of warm septic shock, anaphylaxis, liver failure, and sympathetic blockade with regional anesthesia (see Chapter 92). It will increase SVR, but also limits mesenteric blood flow, including hepatic perfusion.

Milrinone

Milrinone is a selective phosphodiesterase III inhibitor that increases cyclic adenosine monophosphate by inhibiting breakdown. Milrinone has both inotropic and vasodilator effects, without acting on α and β receptors. The outcome of children is increased in those who have low cardiac output syndrome after cardiac surgery.[38] The initial dose of milrinone is 25 to 75 μg/kg administered over a period of 15 minutes; the maintenance infusion rate is 0.25 to 0.75 μg/kg/min. Initial doses are often avoided in the ICU setting because of resultant hypotension. Renal failure significantly increases the elimination half-life of

this drug.[39-41] Outside the cardiac ICU, milrinone is used for vasoconstricted septic shock and may have a role in the treatment of pulmonary hypertension.

Levosimendan

Levosimendan increases the sensitivity of the contractile apparatus to calcium increasing inotropy by binding to cardiac myocyte troponin C. This drug increases cardiac ejection fraction, while reducing catecholamine dose with minimal effects on arterial blood pressure and heart rate. In children, the most common indications have been for cardiac failure or after cardiac surgery, with an initial doses of 6 to 12 μg/kg followed by an infusion of 0.1 to 0.2 μg/kg/min.[41,42]

Nesiritide

Nesiritide is a recombinant form of the human B-type natriuretic peptide, the hormone released from the cardiac ventricles in response to excessive intravascular volumes and increasing mechanical wall stress. The action is on guanylyl cyclase with resulting venous and arterial vasodilation. In addition, B-type natriuretic peptide leads to myocardial relaxation (lusitropy) and natriuresis. In children, it decreases central venous pressure and increases urinary output.[43] The usual doses for children and adults are an initial 2 μg/kg bolus followed by a continuous infusion of 0.005 to 0.01 μg/kg/min.

Digitalis

Digitalis is useful for the long-term treatment of myocardial failure in children, but it may not be effective in neonates.[44] Because of its long half-life and unpredictability, digitalis should be administered cautiously to children who have changing levels of serum potassium, calcium, and pH values. In these cases, it is more appropriate to use rapid-acting, titratable, inotropic drugs.

Calcium

When serum ionized calcium levels are below normal, administration of calcium produces a positive inotropic effect. If the patient's ionized calcium levels are normal, less marked inotropic effects occur. Low ionized calcium levels most commonly occur in patients with DiGeorge's syndrome, when large volumes of citrate-containing blood products are rapid administered, and in neonates with relatively unstable calcium metabolism. Calcium also has effects on the cardiac conduction system. Rapid administration of calcium can cause severe bradycardia or asystole. This effect may be exaggerated in hypokalemic children or in those receiving digitalis. The vasomotor effects of calcium are controversial, but most reports show an increase in both SVR and PVR when the drug is administered.[45]

Bicarbonate Therapy

Severe acidosis decreases myocardial function and tissue perfusion. Correction of acidosis with 1 to 2 mEq/kg of sodium bicarbonate is indicated for a pH below 7.20 if ventilation is adequate (Pco_2 < 40 mm Hg if possible; see also Chapter 60). Treatment is necessary because the circulatory system is refractory to sympathomimetic amines when the pH is less than 7.00. After initial correction of pH, persistence or reappearance of metabolic acidosis suggests a continuing under-perfused state and the need for further therapy. Administration of sodium bicarbonate is only a stopgap measure to improve the response to drugs. Repeated infusions of sodium bicarbonate can cause hypernatremia and hyperosmolarity. Every 50 mEq of bicarbonate administered produces 1250 mL of CO_2 when the bicarbonate is fully reacted with acid. Consequently, adequate ventilation must be ensured to avoid worsening the acidosis. Tromethamine, also known as *Tris buffer* or by the trade name THAM, is an alternative to sodium bicarbonate, but larger volumes of THAM are required to produce the same amount of acid-base correction, which may be a problem in patients who have CHF. THAM does not increase $Paco_2$.

Vasodilators

Vasodilators are used to control systemic hypertension, increase cardiac output by decreasing afterload, control pulmonary hypertension, and control cardiac shunting. Vasodilators are an effective treatment of systemic hypertension and increase cardiac output in children with CHF. Treatment of pulmonary hypertension and intracardiac shunting with vasodilators has met with limited success because they decrease both PVR and SVR, which may increase extrapulmonary right-to-right shunting and further reduce pulmonary blood flow.

Nicardipine

Nicardipine is a dihydropyridine calcium channel-blocking drug used as an intravenous infusion; it has powerful, antihypertensive effects in children. The rapid onset of action is usually within 1 minute, adding to the profile appropriate for treating severe hypertension. Flynn and associates[46] report that nicardipine is an effective antihypertensive medication in children ranging in age from 2 to 18 years. At the authors' institution, nicardipine is the drug of choice for hypertensive crisis. Infusion ranges are 0.5 to 1.0 μg/kg/min up to 3.0 μg/kg/min.

Sodium Nitroprusside

Sodium nitroprusside relaxes arteriolar and venous smooth muscle, which decreases afterload and preload. The half-life of sodium nitroprusside is only minutes, making it safe to titrate the drug to a desired effect. Nitroprusside is commonly used to control severe systemic hypertension, to provide controlled hypotension to reduce blood loss, and to increase cardiac output in children with low cardiac output syndromes (myocarditis, post–cardiac surgery status).[47] Sodium nitroprusside can generally be used for days without problems, although cyanide and thiocyanate poisoning develops in some children, especially those with renal failure or reduced renal perfusion. Serum thiocyanate levels of 10 mg/dL are associated with weakness, hypoxia, nausea, muscle spasms, and disorientation. When these symptoms occur, nitroprusside administration should be discontinued immediately.

Hydralazine

Hydralazine administration can control systemic hypertension because it relaxes arterial smooth muscle more than it relaxes veins. Administration of the drug can cause headache, nausea, dizziness, sweating, and tremors. The most important acute side effect is tachycardia, which

may increase cardiac output. Labetalol, a β-antagonist, can counteract this effect.[48]

Tolazoline and Phentolamine

These competitive α-adrenergic blockers have had varied success in the treatment of pulmonary hypertension.[49] However, they are effective in treating the symptoms of pheochromocytoma preoperatively. Serious side effects of these drugs include tachycardia, ventricular arrhythmias, hypotension, and tissue edema.

Prostaglandin E_1

Prostaglandin E_1 acts directly on vascular smooth muscle and has greatly improved the care of neonates with heart disease. At infusion rates of 0.05 to 0.1 μg/kg/min, patency of the ductus arteriosus is maintained, and a closed ductus reopens in some neonates. The drug is indispensable in the care of patients with ductus-dependent cardiac lesions, such as interrupted aortic arch, critical aortic stenosis, or hypoplastic left heart syndrome, where systemic blood flow is supplied through the ductus arteriosus. It is equally important for the care of patients who have pulmonary atresia or critical pulmonic stenosis.[18] Apnea, fever, and hypotension are common side effects of this drug.

Nitric Oxide

Nitric oxide is an endothelium-derived relaxing factor that selectively vasodilates the pulmonary vasculature.[50] When administered by inhalation to patients with pulmonary hypertension, NO reduces PVR. It improves the survival of neonates who have reactive pulmonary hypertension.[51-53] This compound is inactivated by hemoglobin before it reaches the systemic circulation. On rare occasion, NO causes systemic vasodilation or clinically significant methemoglobinemia when administered at 5 to 80 ppm.[52]

Disorders of Cardiac Rhythm

Sinus tachycardia or an elevated heart rate for age is not considered an arrhythmia; however, patients with a significantly increased heart rate may be the most critically ill in the ICU. Causes of tachycardia include hypovolemia, fever, pain, anxiety, CHF, myocardial disease and dysfunction, and thyrotoxicosis. With all these possible causes, the goal is to treat the underlying disease state and not the tachycardia. For children without underlying heart disease, temporary increases in heart rate up to 180 to 200 beats/minute are well tolerated; this is also not uncommon. Children cannot increase their stroke volume; therefore, they increase their cardiac output by increasing their heart rate. Again, the goal is not to specifically control an increased heart rate but to treat the cause of the tachycardia. Sinus arrhythmia is a phasic acceleration and slowing of the heart rate that occurs with respiration. It indicates that the patient has a vagal tone greater than sympathetic tone and possibly a good cardiac reserve. A slow heart rate or sinus bradycardia is another relatively common heart rhythm seen in the ICU. It is an unremarkable finding in an older teenage patient who is relatively fit. Other potential causes can include increased intracranial pressure (ICP), hyperkalemia, hypothermia, profound hypoxia and hypothyroidism. These causes should also be investigated. A slow heart rate commonly occurs with the increased use of dexmedetomidine but can also occur with β-adrenergic blockers or digoxin use. Sinus node dysfunction can occur following repair of congenital heart disease in children. Temporary slowing may be treated with the transcutaneous pacemaker placed during surgery. In the absence of myocardial pacing, if there is complete heart block or a very slow ventricular escape rate a pacemaker may be needed shortly after cardiac surgery. Otherwise, some amount of time is given to see if this will resolve.

Normal cardiac conduction starts in the sinus node. The electrical activity propagates through the internodal pathways in the atrium, is delayed in the AV node, travels though the bundle of His, and is conducted to the ventricles through the left and right bundle branches. Supraventricular tachycardia (SVT) is an elevated heart rate occurring at the level of the atrium, the AV node, or both. SVT typically has a narrow QRS morphology. Sinus tachycardia is therefore not a type of SVT but an acceleration of the normal conduction pathways. SVT includes reentrant and non-reentrant tachycardias.

The reentrant tachycardias include AV node reentrant tachycardia (AVNRT), orthodromic reciprocating tachycardia, and atrial flutter. AVNRT is classically considered pediatric SVT. The reentrant tachycardias occur because of the presence of an accessory conduction pathway that allows for abnormal electrical conduction in the heart. The presence of the abnormal pathway may be apparent on a standard EKG, such as the case of Wolf-Parkinson-White syndrome (WPW). Alternatively, the abnormal pathway might not appear on an electrocardiogram, and it is described as a *concealed pathway*. Concealed pathways are non-WPW orthodromic reciprocating tachycardia. In AVNRT, the AV node itself is the area in which the reentrance occurs. In atrial flutter, there is a micro reentrant circuit within the atrial tissue itself. In children, the circuit is typically near the tricuspid valve. In atrial flutter, after the reentrant circuit in the atria, the conduction proceeds through the AV node where it is slowed. The reentrant circuit is small and the rates of atrial flutter can be high. As the conduction is slowed in the AV node these high rates usually are not conducted to the ventricle. However, if atrial flutter or fibrillation occurs in a patient with WPW, the accessory pathway can allow conduction of the electrical impulse at a rate much greater than through the AV node. Rapid conduction of electrical impulses down the accessory pathway can lead to ventricular tachycardia (VT) or ventricular fibrillation (VF) and can cause sudden death.

The non-reentrant causes of SVT occur due to abnormal automaticity of myocardial tissue. Causes of abnormal automaticity include atrial fibrillation and ectopic atrial tachycardia. In nonreentrant SVT the elevated atrial rate is slowed as conduction goes through the AV node. In children, atrial fibrillation is caused by disorganized circuits typically near the pulmonary veins. This rhythm is described as irregularly irregular. Ectopic atrial tachycardia is rapid atrial beats that are consecutive and occur without sinus morphology. There can be one focus of the rapid atrial beats. Alternatively, in multifocal or chaotic atrial tachycardia, there can be several different atrial origins. Brief periods of ectopic atrial tachycardia usually do not cause much sequela, but can lead to cardiomyopathy if prolonged.

Treatment of reentrant SVT is based on whether the patient's condition is clinically unstable or stable. The

abnormal reentrant circuit can be interrupted with synchronized cardioversion or other methods. If the patient's condition is unstable, reentrant SVT is treated with synchronized cardioversion with a dose of 0.5 to 1 joule/kg. If the patient's condition is stable, there is time to try other therapies. Therapies that increase vagal tone, such as ice to the eyes or a Valsalva maneuver, may interrupt the reentrant circuit. Adenosine will temporarily block conduction through the AV node. Adenosine can be used to interrupt episodes of reentrant SVT that have a reentrant circuit using the AV node. If the reentrant circuit does not include the AV node a, then adenosine might not stop the tachycardia, but it may be helpful with diagnosis. There will be a period of sinus pause after administration of adenosine. Adenosine is metabolized by erythrocytes so that it is a short-acting medication. Equipment to perform cardioversion should be immediately available when adenosine is given. The initial dose is 0.1 mg/kg (maximum 6 mg) and the dose should be given quickly with a sufficient flush. It is more effective when given centrally if available. If it is not effective at the dose of 0.1 mg/kg, the second dose can be increased to 0.2 mg/kg (maximum single dose 12 mg). Larger doses are not likely to be more effective. If SVT persists, other medications such as amiodarone, procainamide, or verapamil may be necessary. Amiodarone can block an accessory pathway as well as the AV node. If given too quickly, amiodarone will decrease arterial blood pressure. For both amiodarone and procainamide, continuous infusions may be necessary after the loading dose. Verapamil will block the AV node for a much longer period than adenosine will; however, verapamil can induce other life-threatening arrhythmias in younger patients (younger than 2 years). If a patient has SVT, a cardiology consultation should be obtained. Follow-up should be arranged if needed and an echocardiogram may be beneficial. Depending on the cause, there also may be a need for long-term follow-up.

Junctional ectopic tachycardia is caused by abnormal automaticity in an area around the atrioventricular junction. This pediatric arrhythmia is not common, but it can occur after repair of congenital heart disease. The most common lesion with which this occurs is tetralogy of Fallot (see Chapter 94).

Wide complex tachycardias arise from the ventricle until proven otherwise. SVT can cause a wide complex tachycardia if there is aberrancy of the conduction through the pathways in the ventricle. However, given the risk of delaying therapy all wide complex tachycardias should initially be treated as VT. If there is no pulse, initiate CPR, defibrillate and follow PALS guidelines. If the patient has a pulse and stable arterial blood pressure, there may be time to consider other therapies. These therapies are cardioversion or use of medications such as adenosine, amiodarone, or procainamide. VF is treated with CPR, defibrillation, and then medications following PALS guidelines. Ventricular rhythms should be examined quickly for the possibility of Torsades de Pointes, as giving magnesium will be especially helpful.

In the course of following the continuous rhythm strip of all children in the PICU, common abnormalities may be noted. A prolongation of the PR interval or first-degree heart block can occur in otherwise normal children. Typically, these children are asymptomatic. Second degree heart block occurs as Mobitz Type I and Mobitz Type II. Mobitz Type I is also known as *Wenckebach* and is a gradual prolongation of the PR interval until a QRS is not seen, and then the cycle restarts. The prolongation of conduction occurs due to delay of the electrical signal in the AV node and it can be a benign phenomenon. Mobitz Type II is less likely to be a benign phenomenon. The PR interval remains constant, but intermittently there is no QRS or ventricular beat. This phenomenon is evidence of disease of the His-Purkinje fibers and can progress to complete heart block. Mobitz Type II occurs much less frequently in children than in adults. Complete heart block or third-degree AV block is the complete dissociation of atrial and ventricular activity. In complete heart block, the atria contract at a rate more rapid than the ventricles do (see Chapter 47). Ventricular contraction occurs through ventricular escape. Congenital complete heart block can occur in infants born to mothers who have an autoimmune disorder, such as lupus erythematosus. When damage occurs to the conduction pathway during surgery for congenital heart disease, complete heart block can occur. As immediate treatment of complete heart block, the ventricular rate may be increased with intravenous isoproterenol. When this treatment is ineffective, transthoracic or transvenous pacing will be necessary until definitive therapy can be arranged.

Premature beats are also seen frequently in a PICU setting. Premature atrial contractions are usually benign and are caused by automaticity of atrial tissue other than the sinus node. Premature ventricular contractions (PVC) are usually benign with a few considerations. The presence of a central venous catheter touching the heart can cause increased PVCs, and the catheter should be pulled back if present. Electrolyte abnormalities; typically of potassium, magnesium, and calcium, can cause PVCs. The frequency of PVCs may improve as the electrolytes are corrected. Exogenous catecholamines may cause PVCs and the frequency of PVCs may improve if the catecholamines can be decreased. Endogenous catecholamines can cause PVCs and the frequency may be decreased if pain or anxiety is treated.

HYPERTENSION

Essential hypertension is uncommon in children. When it occurs, it is often associated with another disease process and is frequently difficult to control. The acute onset of severe systemic arterial hypertension is a medical emergency that has the potential of causing cardiovascular decompensation, encephalopathy, seizures, and intracranial hemorrhage. In older children, the neurologic manifestations of hypertension are more likely to precede cardiovascular decompensation. Neonates with severe hypertension are frequently initially found to have CHF. Treatment of hypertension is tailored to the disease process, the absolute degree of hypertension, and the presence of cardiovascular or neurologic symptoms.[54,55]

NEONATAL RESUSCITATION

Profound changes occur in the cardiovascular and respiratory systems at birth. Failure to make these changes successfully can result in death or central nervous system

(CNS) injury (see Chapter 108). Consequently, someone capable of performing neonatal resuscitation must be present at every delivery. Wasting time finding someone to resuscitate the neonate can be disastrous for the infant. This section discusses the causes and effects of cardiorespiratory insufficiency at birth and the techniques of resuscitation. When possible, the recommendations of the American Academy of Pediatrics have been followed. Guidelines for neonatal resuscitation have been issued by many organizations, including the AHA and the American Academy of Pediatrics.[56]

INITIAL ASSESSMENT OF THE FETUS AT BIRTH

Initial stabilization should begin with a rapid evaluation of the newborn to determine if the infant is term, breathing or crying, and has a normal tone[56] (see also Chapter 77; Table 95-2).

ONGOING ASSESSMENT

Ongoing assessment consists of three signs: heart rate (HR), respirations, and oxygenation. The preferred method for determination of HR is by auscultation. All these vital signs should be determined within the first 30 seconds.

CLEARING THE AIRWAY

Proper positioning by placing the infant in the sniffing position is recommended, and the practitioner must try to avoid either underextension or hyperextension both of which will obstruct the airway. Deep suctioning should be avoided even in healthy, vigorous newborns, because of the risk of vagal-mediated bradycardia.[57] This does not apply to newborns who might have airway obstruction or depressed infants with meconium (discussed later in this section.)

TABLE 95-2 EVALUATION OF THE NEWBORN

Clinical Condition	Intervention
Initial resuscitation	Clear infant airway Warm, dry, stimulate, position Evaluate HR, respirations, color
HR > 100 beats/min, breathing, no cyanosis	Observation
HR > 100 beats/min, but persistent respiratory distress or cyanosis	Clear airway SpO_2 monitoring Consider CPAP
Apnea, gasping, or HR < 100 beats/min	Bag-mask PPV SpO_2 monitoring
After initiation of resuscitation (PPV), HR > 100 beats/min, effective ventilation	Post-resuscitation care
HR < 60 beats/min	Consider intubation Chest compressions Coordinate PPV
HR = 60-100 beats/min	Continue with PPV SpO_2 monitoring

CPAP, Continuous positive airway pressure; *HR,* heart rate; *PPV,* positive pressure ventilation; *SpO_2,* saturation of peripheral oxygen.

TEMPERATURE CONTROL

During the initial resuscitation period, the goal body temperature for the newborn is normothermia. The initial step is to dry the infant and warm the infant to a goal axillary temperature of 36.5°C. Infants wrapped in polyethylene from the neck down will avoid evaporative heat loss. Controlled hypothermia should be attempted only in select tertiary centers within hours after birth of infants with hypoxic-ischemic encephalopathy.

OXYGEN

One of the recent changes in neonatal resuscitation in the 2011 Neonatal Resuscitation Program Guidelines is the recommendation of positive pressure ventilation (PPV) with room air, unless chest compressions or medications are needed during the resuscitation, then the recommendations are still for PPV with 100% oxygen. It is important to place a preductal (right hand) oximeter probe on the newborn if PPV is initiated. For the preterm infant, oxygen should be blended to goal saturation targets. In summary: (1) Use room air if the baby is cyanotic or needs PPV; (2) titrate oxygen if the baby is younger than 32 weeks (Table 95-3); (3) use 100% oxygen if chest compressions or medications are given, then titrate to targeted SpO_2; and (4) apply oximeter to right hand (preductal).

VENTILATION

Breathing usually begins by 30 seconds after birth and is sustained by 90 seconds of age. A few minutes after birth, the respiratory rate of normal neonates is between 40 and 60 breaths/minute. The absence of a pause between inspiration and expiration helps develop and maintain functional residual capacity (FRC). Apnea and bradypnea prolong exhalation, reduce FRC, and cause hypoxia. Causes of apnea and bradypnea include severe acidosis, asphyxia, maternal drugs, infections, and CNS damage. Tachypnea (>60 breaths/minute) occurs with hypoxemia, hypovolemia, metabolic and respiratory acidosis, CNS hemorrhage, pulmonary gas leaks, pulmonary disease (e.g., hyaline membrane disease, aspiration syndromes, infections), pulmonary edema, and maternal drugs (e.g., narcotics, alcohol, magnesium, barbiturates).

If needed, initial PPV breaths should be at 20 cm H_2O. Ventilation should be performed at 40 to 60 breaths/minute with reassessment of HR, color, and breath sounds. In the neonate, an increasing HR may be the best assessment

TABLE 95-3 PRETERM INFANT (<32 WEEKS): TITRATE OXYGEN USING OXYGEN BLENDER TO ACHIEVE TARGET SpO_2

Time after Birth (min)	Target SpO_2 (%)
1	60-65
2	65-70
3	70-75
4	75-80
5	80-85
10	85-95

of adequate ventilation. If gastric distention becomes a problem a gastric tube may be placed (8 Fr) to improve compliance. Both sides of the chest should rise equally and simultaneously with inspiration, but the amount of rise should not exceed that associated with the neonate's normal spontaneous breathing. The presence of breath sounds can be misleading because they are well transmitted within the neonate's small chest. A difference in breath sounds between the two sides of the chest should raise suspicion of pneumothorax, atelectasis, or a congenital anomaly of the lung. The presence of loud breath sounds over the stomach suggests a tracheoesophageal fistula. If ventilation is adequate, the neonate will become pink, initiate rhythmic breathing, and have a normal heart rate.

Because most asphyxiated neonates have no lung disease, their lungs can be ventilated effectively with peak airway pressures less than 25 cm H_2O, even for the first few breaths following intubation. Those with stiff lungs (e.g., erythroblastosis fetalis, congenital anomalies of the lung, pulmonary edema, severe meconium aspiration, diaphragmatic hernia) may require higher inspiratory pressure to ventilate their lungs, and they are more likely to have pulmonary gas leaks. To reduce this likelihood, the lungs should first be ventilated with an inspiratory pressure of 15 to 20 cm H_2O. If low-pressure (low-volume), high-rate ventilation does not improve the oxygenation, higher pressures and volumes may be required. Failure to ventilate the lungs adequately at birth can worsen hypoxemia and lead to CNS damage or even death. If PaO_2 exceeds 70 to 80 mm Hg or Sao_2 exceeds 94%, the inspired oxygen concentration should be reduced (if increased concentrations of oxygen are used) until Sao_2 and PaO_2 are normal for age. Oxygenation is maintained at the low range of normal in neonates 34 weeks' or less gestation to avoid retinopathy of prematurity.[58] The neonate's heart rate should be monitored continuously during endotracheal intubation, because the process of tracheal intubation may cause arrhythmias in hypoxic neonates. If the practitioner is having difficulty with bag-valve-mask ventilation or fails intubation, a laryngeal mask airway (LMA) should be considered.[59,60]

PNEUMOTHORAX

Pneumothorax occurs in 1% of all vaginal deliveries, in 10% of meconium-stained neonates, and in 2% to 3% of neonates who require mechanical ventilation in the delivery room. The hemithorax containing free air is usually hyperexpanded and moves poorly with ventilation. The point of maximum cardiac impulse is shifted toward the side without the pneumothorax. Heart tones may be muffled. If a small, high-intensity cold light is placed directly on the skin of the neonate's chest, the involved side of the chest will glow if a pneumothorax is present.[61] Pneumothoraces are relieved by needle or chest tube drainage.

ENDOTRACHEAL INTUBATION

The head should be placed in a neutral or "sniffing" position during bag-valve-mask ventilation and tracheal intubation. An appropriately sized endotracheal tube (ETT) is inserted and its tip is placed 1 to 2 cm below the vocal cords, depending on the size of the neonate. Usually, this means that the distance from the tip of the tube to the gums is 7, 8, 9, or 10 cm in 1-, 2-, 3-, and 4-kg infants, respectively. A small gas leak should be present between the ETT and trachea when the ventilation pressure is 15 to 25 cm H_2O. This leak usually entails the use of a 2.5-mm (internal diameter) tube for neonates weighing less than 1.5 kg, a 3.0-mm tube for those between 1.5 and 2.5 kg, and a 3.5-mm tube for those weighing more than 2.5 kg. Successful tracheal intubation is confirmed by observing the ETT pass through the vocal cords, by observing bilateral chest movement with each mechanical inspiration, and by observing condensation in the ETT during exhalation. Breath sounds should be much louder over the chest than over the abdomen, and the skin color, heart rate, and Sao_2 should improve with positive-pressure ventilation. Carbon dioxide should be present during exhalation. However, the small tidal volumes and low pulmonary blood flow of some infants at birth can make it difficult to use capnography effectively.

CARDIAC COMPRESSIONS

Place both thumbs on the sternum and allow the fingers to support the back (Fig. 95-3) Compress the sternum to approximately one-third the depth of the chest. Three compressions should be performed with a breath in place of the fourth compression for an effective compression rate of 90 compressions and 30 breaths/minute. HR should be evaluated every 45 to 60 seconds, and if after adequate ventilation and compressions for 60 seconds the HR is still less than 60 beats per minute, then medications should be considered.

MEDICATIONS

Medications are needed only for the infant who is critically depressed or has significant anomalies leading to cardiovascular depression. There should be a quick-reference drug list with dosing based on an estimated weight of the infant at birth designed for each delivery room for easy access for these rare occasions. Intravenous route of administration is preferred for administration of resuscitation medications; however, intraosseous and umbilical venous catheters can be placed rapidly by trained individuals and can be lifesaving.

Epinephrine

The primary medication used in the resuscitation of a newborn is epinephrine, and it should be given if the infant's HR is less than 60 beats/minute, 45 to 60 seconds after the initiation of PPV and chest compressions. The recommended dose is 0.1 to 0.3 mL/kg of 1:10,000 concentration; (0.01 to 0.03 mg/kg), followed by a 1 mL flush of saline. Intravenous administration is preferable, but if venous access is not obtained, then it is appropriate to give epinephrine via the ETT. If the ETT is used, the practitioner should give a higher dose of epinephrine: 0.5 to 1 mL/kg of 1:10,000 concentration (0.05 to 0.1 mg/kg). Epinephrine can be repeated every 5 minutes, as needed, while reevaluating HR every 45 to 60 seconds.

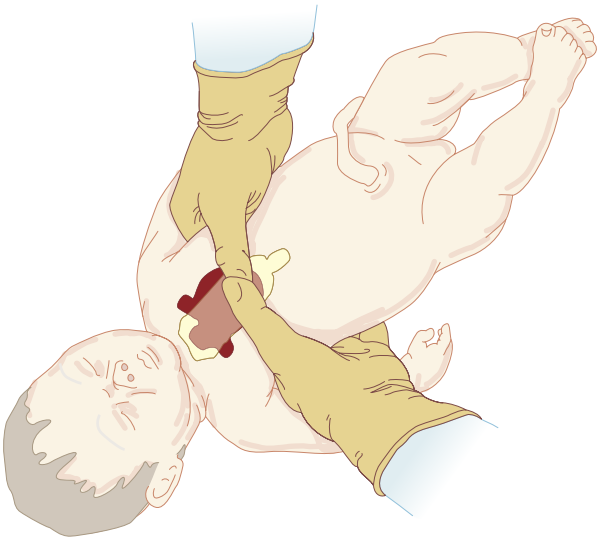


Figure 95-3. Neonatal chest compression. For simplification, ventilation is not shown. *(From Gregory GA: Resuscitation of the newborn,* Anesthesiology *43:225, 1975.)*

Naloxone

Naloxone (Narcan) is not recommended as an initial response to respiratory distress in neonatal resuscitation.[56,62] Neonates should be supported on PPV, including neonates whose mothers received narcotics less than 4 hours before delivery. However, if respiratory depression continues, naloxone can be considered. In addition, naloxone should be avoided in an infant whose mother has a history of narcotic dependence because of the risk of seizures from withdrawal.

DETECTION OF HYPOVOLEMIA

Hypovolemia is detected by measuring arterial blood pressure and by physical examination (i.e., skin color, perfusion, capillary refill time, pulse volume, and extremity temperature). Central venous pressure (CVP) measurements are useful in detecting hypovolemia and in determining the adequacy of fluid replacement. The venous pressure of normal neonates is 2 to 8 cm H_2O. If CVP is less than 2 cm H_2O, hypovolemia should be suspected.

TREATMENT OF HYPOVOLEMIA

Treatment of hypovolemia requires expansion of intravascular volume with blood and crystalloids. Albumin may also be used, but evidence of its effectiveness is limited. If it is suspected that the neonate will be hypovolemic at birth, Rh-negative type O packed red blood cells (PRBCs) should be available in the delivery room before the neonate is born.[63] Crystalloid and blood should be titrated in 10 mL/kg and given slowly over 10 minutes, if hemodynamics allow, to limit the risk of intraventricular hemorrhage. Occasionally, enormous volumes of blood and fluid are required to raise arterial blood pressure to normal. At times, more than 50% of the blood volume (85 mL/kg in term neonates and 100 mL/kg in preterm neonates) must be replaced, especially when the placenta is transected or abrupted during birth. In most cases, less than 10 to 20 mL/kg of volume restores mean arterial pressure to normal.

OTHER CAUSES OF HYPOTENSION

Hypoglycemia, hypocalcemia, and hypermagnesemia also cause hypotension in neonates. Hypotension induced by alcohol or magnesium intoxication usually responds to blood volume expansion or dopamine, or to both. Hypermagnesemic neonates generally respond to 100 to 200 mg/kg of calcium gluconate administered over a 5-minute period.[56]

MECONIUM

Meconium-stained amniotic fluid (MSAF) when aspirated into the lungs during delivery or in utero can cause serious lung injury and respiratory distress syndrome. Most cases of meconium aspiration occur in utero; therefore, endotracheal intubation to suction the airway to remove MSAF should occur only if the neonate is distressed (e.g., absent or depressed respirations, HR < 100 beats/minute, poor muscle tone).[56,64,65] A depressed MSAF-stained infant should be intubated as soon as possible after delivery. Suctioning is accomplished through an ETT. If there is a significant amount of MSAF or remains in extremis, the infant should be transferred directly to the neonatal intensive care unit.

COLOR

Essentially all neonates have a blue-tinged cast to their skin at birth. By 60 seconds of age, most of them are entirely pink, except for their hands and feet, which remain blue. If central cyanosis persists beyond 90 seconds of age, asphyxia, low cardiac output, pulmonary edema, methemoglobinemia, polycythemia, congenital heart disease, arrhythmias, and pulmonary disorders (e.g., respiratory distress, airway obstruction, hypoplastic lungs, diaphragmatic hernia) should be considered, especially if the infant remains cyanotic despite oxygen and controlled ventilation. Neonates who are pale at birth are often asphyxiated, hypovolemic, acidotic, or anemic, or they have congenital heart disease. A neonate whose skin is entirely pink within 2 minutes of birth may be intoxicated with alcohol or magnesium or may be alkalotic (pH > 7.50). Rubrous neonates are usually polycythemic.

RESUSCITATION EQUIPMENT

Resuscitation beds should allow positioning of the neonate's head below the level of the lungs to promote drainage of lung fluid and reduce the likelihood of aspirating gastric contents. A servo-controlled infrared heater should be used to maintain the neonate's temperature between 36°C and 37°C unless there is evidence of asphyxia. If asphyxia is noted, body temperature should be reduced to 34°C to 35°C for brain protection. A suction device should be available and should allow the suction pressure to be varied; pressures less than –100 mm Hg should not be used. Equipment required for tracheal intubation includes 0 and 00 straight laryngoscope blades; a

pencil-type laryngoscope handle; 2.5-, 3.0-, and 3.5-mm ETTs; and a suction catheter that fits easily through each size tube. The ventilation system must permit ventilatory rates of at least 150 breaths/minute and make it possible to maintain positive end-expiratory pressure (PEEP). One-way valves can stick in the closed position, especially when high gas flow and high respiratory rates are used. The modified Jackson-Rees or Ayres system works well when appropriately trained people use it. Overexpansion of the lungs with large tidal volumes injures the lungs and activates inflammatory processes that may cause chronic lung disease. Gentle inflation of the lung is less injurious to the lung. Airway inflation pressures should be measured continuously during assisted or controlled ventilation in the delivery room, and excessive pressures and tidal volumes should be avoided. As in any critical care situation, patient care should be guided by information. Consequently, blood gas and pH measurements are mandatory, and the results of these tests must be available within 10 minutes of drawing the blood sample. Umbilical arterial catheters are useful for measuring arterial blood pressure and withdrawing blood for blood gas analysis and pHa. They can also be used to infuse emergency fluids. Arterial oxygen saturation (Sa_{O_2}) can be measured immediately after birth by attaching a pulse oximeter to a hand or foot.[66] Pulse oximeters permit rapid detection of changes in oxygenation and rapid reduction of FiO_2. The normal Sa_{O_2} of neonates is usually 87% to 95%, which is associated with a PaO_2 of 55 to 70 mm Hg.

PEDIATRIC CARDIAC ARREST AND RESUSCITATION

Pediatric cardiac arrest is not a rare event. At least 16,000 American children (8 to 20 per 100,000 children per year) suffer a cardiopulmonary arrest each year.[67-71] More than half of these cardiac arrests probably occur in hospital.[67,72] With advances in resuscitation science and implementation techniques, survival from pediatric cardiac arrest has improved substantially over the past 25 years.[73]

Outcomes from pediatric cardiac arrest have improved significantly over the past 20 years. For example, survival to discharge from pediatric in-hospital cardiac arrest has increased from less than 10% in the 1980s[74,75] to more than 25% in the twenty-first century. Of the pediatric patients who survive to hospital discharge, nearly 75% will have favorable neurologic function defined by specific pediatric cerebral outcome measures and quality of life indicators.[73,76-78] Factors that influence outcome from pediatric cardiac arrest include: (1) the preexisting condition of the child; (2) the environment in which the arrest occurs; (3) the initial electrocardiographic rhythm detected; (4) the duration of no-flow time (the time during an arrest without spontaneous circulation or CPR); (5) the quality of the life-supporting therapies provided during the resuscitation; and (6) the quality of life-supporting therapies during post-resuscitation.

Not surprisingly, outcomes after pediatric out-of-hospital arrests are much worse than outcomes after in-hospital arrests,[68,69,79-87] possibly because there is a prolonged period of no flow in out-of-hospital arrests, where many of the pediatric cardiac arrests are not witnessed and only 30% of children are provided with bystander CPR. Because of these factors, less than 10% patients with pediatric out-of-hospital cardiac arrest survive to hospital discharge, and those who survive commonly have severe neurologic injury. These findings are especially troublesome given that bystander CPR more than doubles the patient survival rates in adults.[88] An exciting prospective, nationwide, population-based cohort study from Japan demonstrated that survival rates more than doubled for children who had out-of-hospital cardiac arrests and received bystander CPR either with conventional CPR (with rescue breathing) or chest compression only CPR compared to no bystander CPR.[89] The same study then further stratified outcomes for out-of-hospital cardiac arrest into "cardiac" and "noncardiac" causes for arrest and defined the relative value of rescue breathing during CPR by bystanders. Pediatric patients who have out-of-hospital cardiac arrests with noncardiac causes and receive bystander conventional CPR (including rescue breathing) had an association with higher frequency of favorable neurologic outcomes at 1 month after arrest compared with compression-only bystander CPR or no bystander CPR. For pediatric arrests defined as cardiac in nature, bystander CPR (conventional or compression-only) was associated with a higher rate of favorable neurologic outcomes 1 month after arrest compared with no bystander CPR. Interestingly, the two types of bystander CPR (conventional or compression only) seemed to be similarly effective for pediatric cardiac arrests with cardiac causes, consistent with animal and adult studies.[89]

Survival outcomes after in-hospital cardiac arrest are higher in the pediatric population compared with adults; 27% of children survive to hospital discharge compared with only 17% of adults.[73] For children and adults, outcomes are better after arrhythmogenic arrests (VF/VT). Importantly, pediatric in-hospital arrests are less commonly caused by arrhythmias (10% of pediatric arrests versus 25% of adult arrests), and approximately one third of children and adults with these arrhythmogenic arrests survive to hospital discharge. Interestingly, the superior pediatric survival rate following in-hospital cardiac arrest reflects a substantially higher survival rate among children with asystole or pulseless electrical activity compared with adults (24% versus 11%). Further investigation has shown that the superior survival rate seen in children is mostly attributable to a much better survival rate among infants and preschool-aged children compared with older children.[77] The higher survival rates in children may be due to improved coronary and cerebral blood flow during CPR because of increased chest compliance in these younger arrest victims, with improved aortic diastolic pressure and venous return, but this is speculative.[90,91] In addition, survival of pediatric patients from an in-hospital cardiac arrest is more likely in hospitals staffed with dedicated pediatric physicians.[92]

PHASES OF RESUSCITATION

The four distinct phases of cardiac arrest and CPR interventions are: (1) prearrest, (2) no flow (untreated cardiac arrest), (3) low flow (CPR), and (4) postresuscitation and

arrest. Interventions to improve outcome of pediatric cardiac arrest should optimize therapies targeted to the time and phase of CPR, as suggested in Table 95-4.

PREARREST

The prearrest phase refers to any relevant preexisting conditions of the child (e.g., neurologic, cardiac, respiratory, or metabolic problems) and precipitating events (e.g., respiratory failure or shock) uncoupling metabolic delivery and metabolic demand. Pediatric patients who suffer an in-hospital cardiac arrest often have changes in their physiologic status in the hours leading up to their arrest event.[93,94] Therefore, interventions during the prearrest phase focus on preventing the cardiac arrest, with special attention to early recognition and targeted treatment of respiratory failure and shock. Early recognition plays a key role in identifying a prearrest state in children, who, unlike adults, may be able to maintain an age appropriate blood pressure despite a worsening clinical picture until the last possible moment. Medical emergency teams (METs; also known as *rapid response teams*) are in-hospital emergency teams designed specifically for this purpose. Front-line providers, and even parents, are encouraged to initiate evaluation by METs based on physiologic protocol–driven parameters or even intuition. Patients are assessed by the METs, and those at high risk of clinical decompensation are transferred to a PICU if necessary, with the goal to prevent progression to full cardiac arrest or to decrease the response time to initiation of advanced life support; thereby, limiting the no-flow state. Implementation of METs decreases the frequency of cardiac arrests compared with retrospective control periods before MET initiation.[95-97] While early recognition protocols cannot identify all children at risk for cardiac arrest, transferring critically ill children to an ICU early in their disease process allows for better monitoring and more aggressive interventions, which can improve resuscitative care and clinical outcomes. The caveat is that pre-arrest states must be identified to initiate monitoring and interventions that can inhibit the progression to an arrest. While a significant amount of research dollars and resources are spent on the other phases of cardiac arrest, particular focus on the prearrest state can yield the greatest improvement in survival and neurologic outcomes.

TABLE 95-4 PHASES OF CARDIAC ARREST AND RESUSCITATION

Phase	Interventions
Pre-arrest phase (protect)	Optimize patient monitoring and rapid emergency response Recognize and treat respiratory failure or shock to prevent cardiac arrest
Arrest (no-flow) phase (preserve)	Minimize interval to BLS and ACLS Organize response with clear leadership Minimize interval to defibrillation, when indicated
Low-flow (CPR) phase (resuscitate)	Push hard, push fast Allow full chest recoil Minimized interruptions in compressions Avoid overventilation Titrate CPR to optimize myocardial blood flow (coronary perfusion pressures and exhaled CO_2) Consider adjuncts to improve vital organ perfusion during CPR Consider ECMO if standard CPR/ALS not promptly successful
Post-resuscitation phase: short-term	Optimize cardiac output and cerebral blood flow Treat arrhythmias, if indicated Avoid hyperglycemia, hyperthermia, hyperventilation Debrief to improve future responses to emergencies
Post-resuscitation phase: long-term rehabilitation (regenerate)	Early intervention with occupational and physical therapy Bioengineering and technology interface Possible future role for stem cell transplantation

ACLS, advanced cardiac life support; *ALS,* advanced life support; *BLS,* basic life support; *CPR,* cardiopulmonary resuscitation; *ECMO,* extracorporeal membrane oxygenation.

NO-FLOW AND LOW-FLOW

To improve outcomes from pediatric cardiac arrest, the no-flow phase of untreated cardiac arrest should be shortened. High-risk patients must be monitored to allow early recognition of the cardiac arrest and to prompt initiation of basic and advanced life support. Effective CPR optimizes coronary perfusion pressure (by elevating aortic diastolic pressure relative to right atrial pressure) and cardiac output to critical organs to support vital organ viability (by elevating mean aortic pressure) during the low-flow phase. Important tenets of basic life support are push hard, push fast, allow full chest recoil between compressions, and minimize interruptions of chest compression. The myocardium receives blood flow from the aortic root, mainly during diastole, via the coronary arteries. When the heart arrests and no blood flows through the aorta, coronary blood flow ceases. However, during chest compressions, aortic pressure rises at the same time as right atrial pressure and with the subsequent decompression phase of chest compressions, the right atrial pressure falls faster and lower than the aortic pressure, which generates a pressure gradient that perfuses the heart with oxygenated blood. Therefore, full elastic recoil (release) is critical to create a pressure difference between the aortic root and the right atrium. A cerebral perfusion pressure (CPP) less than 15 mm Hg during CPR is a poor prognostic factor for ROSC. Achieving optimal coronary perfusion pressure, exhaled carbon dioxide concentration, and cardiac output during the low-flow phase of CPR is consistently associated with an improved chance for return of spontaneous circulation (ROSC) and improved short- and long-term outcome in mature animal and human studies.[98-105] There is a critical need for research evaluating goal-directed CPR, both in immature animal models and pediatric patients. Other measures essential for truncating the no-flow phase during ventricular fibrillation and pulseless VT are rapid detection and prompt defibrillation. Clearly, CPR alone is inadequate for successful resuscitation from these arrhythmias. For cardiac

arrests resulting from asphyxia or ischemia, provision of adequate myocardial perfusion and myocardial oxygen delivery are the critical elements for return of spontaneous circulation.

POSTARREST AND RESUSCITATION

The postarrest and resuscitation phase includes coordinated, skilled management of the immediate postresuscitation stage, the next few hours to days, and long-term rehabilitation. The immediate postresuscitation stage is a high-risk period for ventricular arrhythmias and other reperfusion injuries. Goals of interventions implemented during the immediate postresuscitation stage and the next few days include adequate tissue oxygen delivery, treatment of postresuscitation myocardial dysfunction, and minimizing postresuscitation tissue injury (e.g., preventing postresuscitation hyperthermia and hypoglycemia and perhaps initiating postresuscitation therapeutic hypothermia, preventing hyperglycemia and avoiding hyperoxia). This postarrest and resuscitation phase may have the greatest potential for innovative advances in the understanding of cell injury (excitotoxicity, oxidative stress, metabolic stress) and cell death (apoptosis and necrosis), ultimately leading to novel molecular-targeted interventions. The rehabilitation stage concentrates on salvage of injured cells and support for reengineering of reflex and voluntary communications of these cell and organ systems to improve long-term functional outcome.

The specific phase of resuscitation dictates the focus of care. Interventions that improve outcome during one phase may be deleterious during another. For example, intense vasoconstriction during the low-flow phase of cardiac arrest improves coronary perfusion pressure and the probability of ROSC. The same intense vasoconstriction during the postresuscitation phase increases left ventricular afterload and can worsen myocardial strain and dysfunction. Current understanding of the physiology of cardiac arrest and recovery allows for the crude manipulation of arterial blood pressure, oxygen delivery and consumption, body temperature, and other physiologic parameters in an attempt to optimize outcome. Future strategies likely will take advantage of the increasing knowledge of cellular injury, thrombosis, reperfusion, mediator cascades, cellular markers of injury and recovery, and transplantation technology, including stem cells.

INTERVENTIONS DURING THE CARDIAC ARREST (NO-FLOW) AND CPR (LOW-FLOW)

AIRWAY AND BREATHING

During CPR, cardiac output and pulmonary blood flow are approximately 10% to 25% of that during normal sinus rhythm; therefore, a lower minute ventilation is necessary for adequate gas exchange from the blood traversing the pulmonary circulation. Animal and adult data indicate that overventilation (e.g., from exuberant rescue breathing) during CPR is common and can substantially compromise venous return and subsequently cardiac output.[106-108] These detrimental hemodynamic effects are compounded when one considers the effect of interruptions in CPR to provide airway management and rescue breathing and may contribute to worse survival outcomes.[109-112] Although overventilation is problematic, in light of the fact that most pediatric arrests are asphyxial in nature, immediate initiation of *adequate* ventilation is still important. The difference between arrhythmogenic and asphyxial arrests lies in the physiology. In animal models of sudden VF cardiac arrest, acceptable PaO_2 and $Paco_2$ persist for 4 to 8 minutes during chest compressions without rescue breathing.[113,114] This is in part because aortic oxygen and carbon dioxide concentrations at the onset of the arrest do not vary much from the pre-arrest state with no blood flow and minimal aortic oxygen consumption. The lungs act as a reservoir of oxygen during the low-flow state of CPR; therefore, adequate oxygenation and ventilation can continue without rescue breathing. Several retrospective studies of witnessed VF cardiac arrest in adults have also shown that outcomes are similar after bystander-initiated CPR with either chest compressions alone or chest compressions plus rescue breathing.[115] However, during asphyxial arrest peripheral and pulmonary blood flow continues during the prearrest state resulting in significant arterial and venous oxygen desaturation, elevated lactate levels, and depletion of the pulmonary oxygen reserve. Therefore, at the onset of cardiopulmonary resuscitation, there is substantial arterial hypoxemia and resulting acidemia. In this circumstance, rescue breathing with controlled ventilation can be a lifesaving maneuver. In contrast, the adverse hemodynamic effects from over-ventilation during CPR combined with possible interruptions in chest compressions to open the airway and deliver rescue breathing are a lethal combination in certain circumstances such as VT/VF arrests. In short, the resuscitation technique should be titrated to the physiology of the patient to optimize patient outcome.

CIRCULATION: OPTIMIZING BLOOD FLOW DURING LOW-FLOW CPR: PUSH HARD, PUSH FAST

When the heart arrests, no blood flows to the aorta and coronary blood flow ceases immediately.[115] At that point, provision of high-quality CPR ("push hard, push fast") is vital to reestablish coronary flow. The goal during CPR is to maximize the myocardial perfusion pressure (MPP). Related by the equation

$$MPP = AoDP - RAP$$

myocardial blood flow improves as the gradient between aortic diastolic blood pressure (AoDP) and right atrial pressure (RAP) increases. During downward compression phase, AoDP rises simultaneously with RAP with little change in the MPP; however, during the decompression phase of chest compressions, the RAP falls faster and lower than the AoDP, which generates a pressure gradient perfusing the heart with oxygenated blood during this artificial period of diastole. Several animal and human studies have demonstrated, in both VT/VF and asphyxial models, the importance of establishing MPP as a predictor for short-term survival outcome (i.e., ROSC).[104,116-119]

Because there is no flow without chest compressions, it is important to minimize interruptions in chest compressions. To allow good venous return in the decompression phase of external cardiac massage, it is also important to allow full chest recoil and to avoid overventilation (preventing adequate venous return because of increased intrathoracic pressure).

Based on the equation above, MPP can be improved by strategies that increase the pressure gradient between the aorta and the right atrium. As an example, the inspiratory impedance threshold device (ITD) is a small, disposable valve that can be connected directly to the tracheal tube or face-mask to augment negative intrathoracic pressure during the inspiratory phase of spontaneous breathing and the decompression phase of CPR by impeding airflow into the lungs. Application in animal and adult human trials of CPR has established the ability of the ITD to improve vital organ perfusion pressures and myocardial blood flow[120-125]; however, in the only randomized trial during adult CPR, mortality benefit was limited to the subgroup of patients with pulseless electrical activity.[125] Additional evidence that augmentation of negative intrathoracic pressure can improve perfusion pressures during CPR comes from the active compression-decompression device (ACD). The ACD is a handheld device that is fixed to the anterior chest of the victim by means of suction similar to a household plunger that can be used to apply active decompression forces during the release phase, thereby creating a vacuum within the thorax. By actively pulling during the decompression phase, blood is drawn back into the heart by the negative pressure.[126] Animal and adult studies have demonstrated that the combination of ACD with ITD act in concert to further improve perfusion pressures during CPR compared with ACD alone.[122] In the end, while novel interventions such as the ITD and ACD are promising adjuncts to improve blood flow during CPR, the basic tenants of *push hard, push fast, allow full chest wall release, minimize interruptions,* and *don't overventilate* are still the dominate factors to improve blood flow during CPR and chance of survival.

CHEST COMPRESSION DEPTH

The pediatric chest compression depth recommendation of at least one-third anterior-posterior chest depth (approximately 4 cm in infants and 5 cm in children) is based largely on expert clinical consensus, using data extrapolated from animal, adult, and limited pediatric data. In a small study of six infants, chest compressions targeted to half of anterior-posterior chest depth resulted in improved systolic blood pressures compared to those targeted at one-third anterior-posterior chest depth.[127] Although this series was small with only qualitatively estimated chest compression depths, it is the first study to collect actual data from children supporting the existing chest compression depth guidelines. On the contrary, two recent studies using computer-automated tomography (CT)[128,129] suggest that depth recommendations based on a relative (%) anterior-posterior chest compression depth are deeper than that recommended for adults, and that a depth of half of the anterior-posterior chest depth will result in direct compression to the point of fully emptying the heart and requisite shifting of heart because of inadequate anterior-posterior diameter reserve in most children. Future studies that collect data from actual children and that associate quantitatively measured chest compression depths with short- and long-term clinical outcomes (e.g., arterial blood pressure, end-tidal carbon dioxide, return of spontaneous circulation, survival) are needed.

COMPRESSION/VENTILATION RATIOS

The amount of ventilation provided during CPR should match, but not exceed, perfusion and should be titrated to the amount of circulation during the specific phase of resuscitation as well as the metabolic demand of the tissues. Therefore, during the low-flow state of CPR when the amount of cardiac output is 10% to 25% of normal, less ventilation is needed.[130] However, the best ratio of compressions to ventilations in pediatric patients is largely unknown and depends on many factors including the compression rate, the tidal volume, the blood flow generated by compressions, and the time that compressions are interrupted to perform ventilation. A compression/ventilation ratio of 15:2 delivers the same minute ventilation and increases the number of delivered chest compressions by 48% compared with CPR at a compression/ventilation ratio of 5:1 in a simulated pediatric arrest model.[131,132] This is important because when chest compressions cease, the aortic pressure rapidly decreases and coronary perfusion pressure falls precipitously, thereby decreasing myocardial oxygen delivery.[115] Increasing the ratio of compressions to ventilations minimizes these interruptions, thus increasing coronary blood flow. The benefits of positive pressure ventilation (increased arterial content of oxygen and carbon dioxide elimination) must be balanced against the adverse consequence of decreased circulation. These findings are in part the reason the AHA recommends a pediatric compression/ventilation ratio of 15:2.

DUTY CYCLE

In a model of human adult cardiac arrest, cardiac output and coronary blood flow are optimized when chest compressions last for 30% of the total cycle time (approximately 1:2 ratio of time in compression to time in relaxation).[133] As the duration of CPR increases, the optimal duty cycle may increase to 50%. In a juvenile swine model, a relaxation period of 250 to 300 msec (duty cycle of 40% to 50% at a compression rate of 120 per minute) correlates with improved cerebral perfusion pressures compared with shorter duty cycles of 30%.[134]

CIRCUMFERENTIAL VERSUS FOCAL STERNAL COMPRESSIONS

In adult and animal models of cardiac arrest, circumferential (vest) CPR has been demonstrated to improve CPR hemodynamics dramatically.[135] In smaller infants, it is often possible to encircle the chest with both hands and depress the sternum with the thumbs, while compressing the thorax circumferentially (thoracic squeeze). In an infant animal model of CPR, this "two-thumb" method of compression with thoracic squeeze resulted in higher systolic and diastolic blood pressures and a higher pulse

pressure than traditional two-finger compression of the sternum.[136] Although not rigorously studied, our clinical experience indicates that it is difficult to attain adequate chest compression force and adequate aortic pressures with the two-finger technique; therefore, we fully support the AHA Guidelines for health care providers to perform CPR on infants with the two-thumb-encircling hands technique.[137]

OPEN-CHEST CARDIOPULMONARY RESUSCITATION

In animal models, high quality standard, closed-chest CPR generates myocardial blood flow that is more than 50% of normal, cerebral blood flow that is approximately 50% of normal, and cardiac output approximately 10% to 25% of normal.[115,117,138,139] By contrast, open-chest CPR can generate myocardial and cerebral blood flow that approaches normal. Although open-chest massage improves coronary perfusion pressure and increases the chance of successful defibrillation in animals and humans,[140-142] performing a thoracotomy to allow open-chest CPR is impractical in many situations. A retrospective review of 27 cases of CPR following pediatric blunt trauma (15 with open-chest CPR and 12 with closed-chest CPR) demonstrated that open-chest CPR increased hospital cost without altering rates of ROSC or survival to discharge. However, survival in both groups was 0%, indicating that the population may have been too severely injured or too late in the process to benefit from this aggressive therapy.[143] Open-chest CPR is often provided to children after open-heart cardiac surgery and sternotomy. Earlier institution of open-chest CPR may warrant reconsideration in selected special resuscitation circumstances.

MEDICATIONS USED TO TREAT CARDIAC ARREST

Administration of epinephrine can likely improve initial resuscitation success after both asphyxial and VF cardiac arrests. However, whether epinephrine administration improves survival outcome from pediatric cardiac arrest is not documented. Many medications are used during pediatric resuscitation attempts including vasopressors (epinephrine and vasopressin), antiarrhythmics (amiodarone and lidocaine), and other drugs such as calcium chloride and sodium bicarbonate. A discussion of each follows.

VASOPRESSORS

Epinephrine

Epinephrine (adrenaline) is an endogenous catecholamine with potent α- and β-adrenergic stimulating properties. The α-adrenergic action (vasoconstriction) increases systemic and pulmonary vascular resistance. The resultant higher aortic diastolic blood pressure improves coronary perfusion pressure and myocardial blood flow even though it reduces global cardiac output during CPR; and as noted previously, adequacy of myocardial blood flow is a critical determinant of ROSC. Epinephrine also increases cerebral blood flow during good quality CPR because peripheral vasoconstriction directs a greater proportion of flow to the cerebral circulation.[144-146] However, epinephrine can decrease local cerebral microcirculatory blood flow at a time when global cerebral flow is increased.[147] The β-adrenergic effect increases myocardial contractility and heart rate, and relaxes smooth muscle in the skeletal muscle vascular bed and bronchi; however, the β-adrenergic effects are not observed in the peripheral vascular beds secondary to the high dose used in cardiac arrest. Epinephrine also increases the vigor and intensity of VF, increasing the likelihood of successful defibrillation. High-dose epinephrine (0.05-0.2 mg/kg) improves myocardial and cerebral blood flow during CPR more than standard-dose epinephrine (0.01-0.02 mg/kg) in animal models of cardiac arrest and may increase the incidence of initial ROSC.[148,149] However, prospective and retrospective studies have indicated that the use of high-dose epinephrine in adults or children does not improve survival and may be associated with worse neurologic outcome.[150,151] A randomized, blinded, controlled trial of rescue high-dose epinephrine versus standard-dose epinephrine after failed initial standard-dose epinephrine in pediatric in-hospital cardiac arrest demonstrated a worse 24-hour survival in the high-dose epinephrine group (1 of 27 survivors versus 6 of 23 survivors; $p < 0.05$).[152] Based on these clinical studies, high-dose epinephrine cannot be recommended routinely for either initial or rescue therapy. Importantly, these studies indicate that high-dose epinephrine can worsen a patient's post-resuscitation hemodynamic condition and likelihood of survival.

Vasopressin

Vasopressin is a long-acting endogenous hormone that acts at specific receptors to mediate systemic vasoconstriction (V_1 receptor) and reabsorption of water in the renal tubule (V_2 receptor). Vasoconstrictive properties are most intense in the skeletal muscle and skin vascular beds. Unlike epinephrine, vasopressin is not a pulmonary vasoconstrictor. In experimental models of cardiac arrest, vasopressin increases blood flow to the heart and brain and improves long-term survival compared with epinephrine. However, vasopressin can decrease splanchnic blood flow during and following CPR and can increase afterload in the post-resuscitation period placing further strain on the left ventricle.[138,153-156] Adult randomized controlled trials suggest that outcomes are similar after use of vasopressin or epinephrine during CPR.[157,158] During pediatric arrest, a case series of four children who received vasopressin during six prolonged cardiac arrest events suggested that the use of bolus vasopressin can result in ROSC when standard medications have failed.[159] However, a more recent retrospective study of 1293 consecutive pediatric arrests from the AHA National Registry of CPR (NRCPR) found that vasopressin use, while infrequent (administered in only 5% of events), was associated with a lower likelihood of ROSC. Therefore, it is unlikely that vasopressin will replace epinephrine as a first-line agent in pediatric cardiac arrest; however, the available data suggest that its use in conjunction with epinephrine may deserve further investigation, especially in prolonged arrest unresponsive to initial epinephrine resuscitation.

ANTIARRHYTHMIC MEDICATIONS

Calcium

Calcium is used frequently in cases of pediatric cardiac arrest, despite the lack of evidence for efficacy. In the absence of a documented clinical indication (i.e., hypocalcemia, calcium channel blocker overdose, hypermagnesemia, or hyperkalemia), administration of calcium does not improve outcomes from cardiac arrest.[160-168] To the contrary, three pediatric studies have suggested a potential for harm, as routine calcium administration was associated with decreased survival rates and worse neurologic outcomes.[160-168] Despite limited clinical data to support the use of calcium during CPR, it is reasonable to consider calcium administration during CPR for cardiac arrest patients at frequent risk of hypocalcemia (including renal failure, shock associated with massive transfusion—see also Chapter 61).

Buffer Solutions

There are no randomized controlled studies in children examining the use of sodium bicarbonate for management of pediatric cardiac arrest. Two randomized controlled studies have examined the value of sodium bicarbonate in the management of adult cardiac arrest[169] and in neonates with respiratory arrest in the delivery room.[170] Neither study was associated with improved survival. In fact, one multicenter retrospective in-hospital pediatric study found that sodium bicarbonate administered during cardiac arrest was associated with decreased survival, even after controlling for age, sex, and first documented cardiac rhythm.[167] Therefore, during pediatric cardiac arrest resuscitation, the use of sodium bicarbonate is not recommended. Clinical trials involving critically ill adults with severe metabolic acidosis do not demonstrate a beneficial effect of sodium bicarbonate on hemodynamics despite correction of acidosis.[171,172] Yet, severe acidosis can depress the action of catecholamines and worsen myocardial function.[173,174] Nevertheless, the use of sodium bicarbonate during CPR is not supported by clinical data. Pediatric patients with implanted cardiac pacemakers may have an increased threshold for myocardial electrical stimulation when acidotic[175]; therefore, administration of bicarbonate or another buffer is appropriate for management of severe documented acidosis in these children. Administration of sodium bicarbonate also is indicated in the patient with a tricyclic antidepressant overdose, hyperkalemia, hypermagnesemia, or sodium channel blocker poisoning. The buffering action of bicarbonate occurs when a hydrogen cation and a bicarbonate anion combine to form carbon dioxide and water. Carbon dioxide must be cleared through adequate minute ventilation; thus, if ventilation is impaired during sodium bicarbonate administration, carbon dioxide buildup may negate the buffering effect of bicarbonate. Because carbon dioxide readily penetrates cell membranes, intracellular acidosis may paradoxically increase after sodium bicarbonate administration without adequate ventilation. Therefore, bicarbonate should not be used for management of respiratory acidosis. Unlike sodium bicarbonate, tromethamine (THAM) buffers excess protons without generating carbon dioxide; in fact, carbon dioxide is consumed following THAM administration. In a patient with impaired minute ventilation, tromethamine may be preferable when buffering is necessary to mitigate severe acidosis. Tromethamine undergoes renal elimination, and renal insufficiency may be a relative contraindication to its use. Carbicarb, an equimolar combination of sodium bicarbonate and sodium carbonate, is another buffering solution that generates less carbon dioxide than sodium bicarbonate. In a canine model of cardiac arrest comparing animals given normal saline, sodium bicarbonate, THAM, or Carbicarb, the animals given any buffer solution had a more frequent rate of ROSC than the animals given normal saline. In the animals given sodium bicarbonate or Carbicarb, the interval to ROSC was significantly shorter than in animals given normal saline. However, at the end of the 6-hour study period, all resuscitated animals were in a deep coma; therefore, no inferences regarding meaningful survival can be drawn.[176] It is premature to recommend either THAM or Carbicarb during CPR at this time.

POSTRESUSCITATION INTERVENTIONS

Temperature Management

Two seminal articles[177,178] have established that induced hypothermia (32°C-34°C) could improve outcome for comatose adults after resuscitation from VF cardiac arrest. In both randomized, controlled trials, the inclusion criteria were patients older than 18 years who were persistently comatose after successful resuscitation from nontraumatic VF.[179,180] However, in a recent randomized control trial of unconscious adult survivors of out-of-hospital cardiac arrest, a targeted temperature of 33°C did not confer a benefit as compared with the targeted temperature of 36°C.[181] Interpretation and extrapolation of these studies to children is difficult; however, fever within the first 48 hours following cardiac arrest, brain trauma, stroke, and ischemia is associated with poor neurologic outcome. Emerging neonatal trials of selective brain cooling and systemic cooling show promise in neonatal hypoxic-ischemic encephalopathy, suggesting that induced hypothermia can improve outcomes.[182,183] The efficacy of therapeutic hypothermia following pediatric cardiac arrest is being evaluated in a randomized controlled trial (clinicaltrials.gov identifier NCT00880087; THAPCA: Therapeutic Hypothermia After Pediatric Cardiac Arrest [www.thapca.org]). At a minimum, it is advisable to avoid hyperthermia in children after administering CPR. Using an approach of "therapeutic normothermia" with scheduled administration of antipyretic medications and the use of external cooling devices, while monitoring core temperature, may be necessary to prevent hyperthermia in this population. Notably, preventing hyperthermia is not easy. Many children become hyperthermic after arrest despite the intent to prevent hyperthermia.[178]

Glucose Control

Both hyperglycemia and hypoglycemia following cardiac arrest is associated with worse neurologic outcome.[184-187]

While it seems intuitive that hypoglycemia would be associated with worse neurologic outcome, it is not clear whether hyperglycemia per se is harmful or is simply a marker of the severity of the stress hormone response from prolonged ischemia. A recent randomized control trial suggests that tight glycemic control in critically ill children had no effect on major clinical outcomes, but was associated with a higher incidence of hypoglycemia.[188] In summary, there is insufficient evidence to formulate a strong recommendation on the management of hyperglycemia in children with ROSC following cardiac arrest. If hyperglycemia is treated after ROSC in pediatric patients, blood glucose concentrations should be carefully monitored to avoid hypoglycemia.

Blood Pressure Management

A patient with ROSC may have substantial variability in arterial blood pressure after cardiac arrest. Postarrest or resuscitation myocardial dysfunction is common and is often associated with hypotension (discussed later).[179,180,189-198] In addition, hypertension may occur, especially if the patient receives vasoactive infusions for postarrest myocardial dysfunction. Optimization of arterial blood pressure postarrest is critical to maintain adequate perfusion pressure to vital organs that may have already been injured from the "no flow" and "low blood flow" states during initial cardiac arrest and CPR. Cerebral blood flow in healthy patients is tightly controlled over a wide range of mean arterial blood pressure via cerebral neurovascular bundle (autoregulation); however, adults resuscitated from cardiac arrest have demonstrated impaired autoregulation of cerebral blood flow, and this might be the case in children.[199]

Autoregulation of the cerebral neurovascular bundle following cardiac arrest may limit the brain's ability to regulate excessive blood flow and microvascular perfusion pressure, thereby leading to reperfusion injury during systemic hypertension. However, in animal models, brief induced hypertension following resuscitation results in improved neurologic outcome compared with normotensive reperfusion.[200,201] Conversely, systemic hypotension can perpetuate neurologic metabolic crisis following ischemic injury by uncoupling bioenergetic demand and delivery. Therefore, a practical approach to blood pressure management following cardiac arrest is to attempt to minimize arterial blood pressure variability in this high-risk period following resuscitation.

POSTRESUSCITATION MYOCARDIAL DYSFUNCTION

Postarrest myocardial stunning and arterial hypotension occur commonly after successful resuscitation in both animals and humans.[179,180,189-198] Postarrest myocardial stunning is a global phenomenon with biventricular systolic and diastolic dysfunction. Postarrest myocardial stunning is pathophysiologically and physiologically similar to sepsis-related myocardial dysfunction and post–cardiopulmonary bypass myocardial dysfunction, including increases in inflammatory mediators and nitric oxide production.[192,195,196,198] Because cardiac function is essential to reperfusion following cardiac arrest, management of postarrest myocardial dysfunction may be important to improving survival. Administration of inotropic, vasopressors, and vasodilators must be carefully titrated during the postresuscitation phase to the cardiovascular physiology. Although the optimal management of post–cardiac arrest hypotension and myocardial dysfunction has not been established, aggressive hemodynamic support may improve outcomes. Dobutamine, milrinone, and levosimendan can effectively ameliorate post–cardiac arrest myocardial dysfunction.[189,190,202,203] In clinical observational studies, intravascular fluid resuscitation has been given to patients with hypotension and concomitant low central venous pressure. Various vasoactive infusions, including epinephrine, dobutamine, and dopamine, have been given to treat the myocardial dysfunction syndrome.[179,180,193-197] In the end, optimal use of these drugs involves close goal-directed titration, and the use of invasive hemodynamic monitoring may be appropriate. General critical care goals are simply adequate arterial blood pressures and oxygen delivery; however, the definition of *adequate* is elusive. Reasonable interventions for vasodilatory shock with low central venous pressure include intravenous fluid resuscitation and vasoactive infusions. Appropriate considerations for left ventricular myocardial dysfunction include euvolemia, inotropic infusions, and afterload reduction.

NEUROMONITORING

Continuous neuromonitoring and goal-directed intervention following cardiac arrest can improve neurologic outcomes (see also Chapter 49).[204] Continuous electroencephalogram (EEG) monitoring is an increasingly instituted modality for neuromonitoring of critically ill patients to diagnose nonconvulsive seizures and seizures in patient's receiving neuromuscular blocking drugs (see Chapter 34). Continuous EEG monitoring is noninvasive, performed at the bedside, and permits continuous assessment of cortical function. Interpretation of continuous EEG monitoring is usually performed by a neurologist from a remote location and not bedside critical care physicians. However, advances in quantitative EEG tools may allow bedside caregivers to identify important electrographic events, such as seizures or abrupt background changes, potentially to permit real-time analysis and intervention.[205] In a prospective study of continuous EEG monitoring in children, nonconvulsive seizures were detected in 39% (12 of 31) of children following cardiac arrest.[206] In a partially overlapping cohort of 19 children, nonconvulsive seizures were common in children undergoing therapeutic hypothermia after cardiac arrest.[206] Nonconvulsive seizures are a common occurrence following cardiac arrests in children. Although, not established in pediatric patients following cardiac arrest, nonconvulsive seizures are associated with worse outcomes among critically ill adults and neonates.[207-213] Continuous EEG monitoring should be considered for children after cardiac arrest, and patients with nonconvulsive seizures (especially status epilepticus with nonconvulsive seizure) should be treated with anticonvulsant medication. The frequency of the nonconvulsive

seizures and benefit from anticonvulsant therapy need to be clarified.

Oxidative injury may be the most intense in the early phases of post-resuscitation therapy following cardiac arrest.[214] The use of 100% oxygen (compared to room air) during and immediately following resuscitation in animal models can exacerbate oxidative injury to key mitochondrial enzymes (pyruvate dehydrogenase or manganese superoxide) or mitochondrial lipids (cardiolipin), leading to worse neurologic outcomes.[215-218] Using peripheral pulse oximetry to titrate oxygenation in the post-resuscitation phase can reduce post-resuscitation hyperoxia and significantly improve neuropathology and neurobehavioral outcomes.[219] A $PaO_2 \geq 300$ mm Hg was independently associated with in-hospital mortality compared with either hypoxia or normoxia in an observational study among critically ill adult patients admitted to the ICU within 24 hours of a cardiac arrest.[220] We believe that it is prudent to titrate oxygenation during and after pediatric cardiac arrest. Although the optimal SpO_2 is not known, the FiO_2 should be titrated to the lowest amount necessary to assure $SpO_2 > 94\%$. Perhaps the future of postarrest care will include more aggressive neurocritical care monitoring, such as near infrared spectroscopy, cerebral microdialysis, brain tissue oxygenation ($Pbto_2$), cerebral blood flow, and even bedside analysis of mitochondrial dysfunction.

QUALITY OF CARDIOPULMONARY RESUSCITATION

Despite evidence-based guidelines, extensive provider training, and provider credentialing in resuscitation medicine, the quality of CPR is typically poor (see also Chapter 108). CPR guidelines recommend target values for selected CPR parameters related to rate and depth of chest compressions and ventilations, avoidance of CPR-free intervals, and complete release of sternal pressure between compressions.[221] Slow compression rates, inadequate depth of compression, and substantial pauses are the norm. An approach to *push hard, push fast, minimize interruptions, allow full chest recoil,* and *don't overventilate* can markedly improve myocardial, cerebral, and systemic perfusion, and will likely improve outcomes.[111] Quality of postresuscitative management is also critically important to improve resuscitation survival outcomes.[193] Measuring the quality of CPR and avoiding overventilation during cardiac arrest resuscitation have recently been reemphasized by consensus of the International Liaison Committee on Resuscitation and the AHA.[222] Although the correct amount, timing, intensity, and duration of ventilation that is required during CPR is controversial, there is no controversy that measurement and titration of the amount of ventilation to the amount of blood perfusion are desirable. Thus, additional technology that is safe, accurate, and practical would improve detection and feedback of the quality of CPR.

Recent technology has been developed that monitors quality of CPR by force sensors and accelerometers and can provide verbal feedback to the CPR administrator regarding the frequency and depth of chest compressions and the volume of ventilations. Recent pediatric data illustrates that intensive training and real-time corrective feedback can help chest compression quality approach age-specific AHA CPR guideline targets.[223-225] Moreover, improvements in post-resuscitation care can improve resuscitation survival outcomes.[193]

EXTRACORPOREAL MEMBRANE OXYGENATION AND EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION

Extracorporeal CPR (ECPR) improves short-term and long-term survival outcomes following in-hospital and out-of-hospital cardiac arrest refractory to conventional therapy in observational studies.[226-229] Such studies can be criticized for small numbers, selection bias, and the lack of randomization to control for confounding by indication.[230] A randomized controlled trial investigating the treatment effect of ECPR for in-hospital cardiac arrest is unlikely, because of the need for a large sample size, complexity of methodology, lack of blinding, and lack of equipoise among providers. Devoid of a randomized controlled trial, ECPR observational studies in children clearly suggest favorable early survival outcomes in children with primary cardiac disease when ECPR protocols were in place at the time of the arrest.[231] For pediatric patients without primary cardiac disease, the data are less clear. Impressively, these studies consistently show that more than one third of children provided with ECPR survive to hospital discharge despite median durations of CPR of approximately 50 minutes before ECMO implementation. Importantly, 64% of patients who survived to discharge after ECPR had favorable neurologic outcomes.[232] Current guidelines recommend that ECPR (or rescue ECMO) should be considered in pediatric patients with in-hospital cardiac arrest that is refractory to initial resuscitation efforts when the cause of the arrest is believed to be reversible or amenable to heart transplantation.[233] Timely, quality ECPR could be an important adjuvant to conventional CPR for pediatric patients. Future frontiers will define patient populations and optimize the clinical approach to extracorporeal support; however, clinicians providing CPR should consider ECPR early in the course of a resuscitation not responding to conventional CPR. Perhaps after failure to attain ROSC within 5 minutes, clinicians should ask themselves: (1) Does the patient have a potentially reversible process, (2) would ECMO be a "bridge" to a potentially good outcome, and (3) do we have the personnel and resources to provide EMCO promptly?

VENTRICULAR FIBRILLATION AND VENTRICULAR TACHYCARDIA IN CHILDREN

Pediatric VF or VT has been an underappreciated pediatric problem. Recent studies indicate that VF and VT (i.e., shockable rhythms) occur in 27% of in-hospital cardiac arrests at some time during the resuscitation.[234] In a population of PICU patients, as many as 41% of arrests were associated with VF or VT.[235] According to the NRCPR database, 10% of children with in-hospital cardiac arrest had an initial rhythm of VF/VT. In all, 27% of the children

had VF/VT at some time during the resuscitation.[234] The incidence of VF varies by setting and age.[236] In special circumstances, such as tricyclic antidepressant overdose, cardiomyopathy, post-cardiac surgery, and prolonged QT syndromes, VF and pulseless VT are more likely. The treatment of choice for short-duration VF is prompt defibrillation. In general, the mortality rate increases by 7% to 10% per minute of delay to defibrillation. Because VF must be considered before defibrillation can be provided, early determination of the rhythm by electrocardiography is critical. An attitude that VF is rare in children can be a self-fulfilling prophecy with a uniformly fatal outcome. The recommended defibrillation dose is 2 J/kg. In the mid-1970s, starting doses of 60 to 200 J were recommended for all children. Because of concerns for myocardial damage, shock doses ranging from 0.5 to 1 J/kg were adequate for defibrillation in a variety of animal species. Gutgesell and associates[236a] evaluated the efficacy of their strategy to defibrillate with 2-J/kg monophasic shocks. Seventy-one transthoracic defibrillations in 27 children were evaluated. Shocks within 10 J of 2 J/kg resulted in successful defibrillation (i.e., termination of fibrillation) in 91% of defibrillation attempts. More recent data demonstrate that an initial shock dose of 2 J/kg terminates fibrillation in less than 60% of children, suggesting that a higher dose may be needed.[83,237-239] Interestingly, retrospective observational NRCPR data demonstrate that higher initial doses of 4 J/kg were associated with worse short-term survival (i.e., immediate survival of the cardiac arrest event with a spontaneous rhythm). Despite five decades of clinical experience with pediatric defibrillation, the optimal dose remains unknown.

ANTIARRHYTHMIC MEDICATIONS: LIDOCAINE AND AMIODARONE

Administration of antiarrhythmic medications should never delay administration of shocks to a patient with VF. However, after an unsuccessful attempt at electrical defibrillation, medications to increase the effectiveness of defibrillation should be considered. Epinephrine is the current first-line medication for both pediatric and adult patients in VF. If epinephrine and a subsequent repeated attempt to defibrillate are unsuccessful, lidocaine or amiodarone should be considered.

Lidocaine traditionally has been recommended for shock-resistant VF in adults and children. However, only amiodarone improved survival to hospital admission in the setting of out-of-hospital cardiac arrest with shock-resistant VF compared with placebo.[240] In another study of shock-resistant out-of-hospital VF, patients receiving amiodarone had a higher rate of survival to hospital admission than patients receiving lidocaine did.[241] Neither study included children. Because there is moderate experience with amiodarone use as an antiarrhythmic agent in children and because of the adult studies, it is rational to use amiodarone similarly in children with shock-resistant VF/VT. The recommended dose is 5 mg/kg by rapid intravenous bolus. There are no published comparisons of antiarrhythmic medications for pediatric refractory VF. Although extrapolation of adult data and electrophysiologic mechanistic information suggest that amiodarone may be preferable for pediatric shock-resistant VF, the optimal choice is not clear.

PEDIATRIC AUTOMATED EXTERNAL DEFIBRILLATORS

Automated external defibrillators (AEDs) have improved adult survival from VF.[242,243] AEDs are recommended for use in children 8 years or older with cardiac arrest.[137,244] The available data suggest that some AEDs can accurately diagnose VF in children of all ages, but many AEDs are limited because the defibrillation pads and energy dosage are geared for adults. Adapters having smaller defibrillation pads that dampen the amount of energy delivered have been developed as attachments to adult AEDs, allowing their use in children. However, it is important that the AED diagnostic algorithm is sensitive and specific for pediatric VF and VT. The diagnostic algorithms from several AED manufacturers have been tested for such sensitivity and specificity and therefore can be reasonably used in younger children.

WHEN SHOULD CPR BE DISCONTINUED?

Several factors determine the likelihood of survival after cardiac arrest including the mechanism of the arrest (e.g., traumatic, asphyxial, progression from circulatory shock), location (e.g., in-hospital or out-of-hospital), response (i.e., witnessed or unwitnessed, with or without bystander CPR), underlying pathophysiology (i.e., cardiomyopathy, congenital defect, drug toxicity, or metabolic derangement), and the potential reversibility of underlying diseases. These factors should all be considered before deciding to terminate resuscitative efforts. Continuation of CPR has been traditionally considered futile beyond 15 minutes of CPR or when more than 2 doses of epinephrine are needed.[245] Presumably in part because of improvements in CPR quality and post-resuscitation care, improved outcomes from in-hospital CPR efforts beyond 15 minutes or two doses of epinephrine are increasingly the norm.[73,76] The potential for excellent outcomes despite prolonged CPR has been highlighted by the ECPR data noted previously.[246-250] Conversely, the decision to discontinue CPR prematurely is final and cannot be rescinded. In the second decade of the twenty-first century, there is still no simple answer to the important clinical question: When should CPR be discontinued?

RESPIRATORY SYSTEM

STRUCTURAL AND FUNCTIONAL DEVELOPMENT: AGE-DEPENDENT VARIABLES

Airways and Alveoli

The lungs appear in the fourth to eighth weeks of gestation. At this time, the lung buds divide into the mainstem bronchi; by 6 weeks, all subsegmental bronchi are present; and by 16 weeks, the number of airway generations is similar to that of adults. When airway development is complete, the terminal airways remodel and multiply

to form a cluster of large saccules, or alveolar precursors, that can support gas exchange. True alveoli appear before and after birth, and the respiratory saccules are thin and septate during postnatal growth.

At birth, children have approximately 24 million alveoli; by 8 years of age, the number has increased to 300 million. After that, further lung growth is primarily the result of increased alveolar size. There is less elastic tissue in the neonatal lung than in the lungs of adults, and the elastin extends only to the alveolar duct. By 18 years of age, elastin extends to the alveolus and is at its maximum. It then slowly decreases over the next 5 decades. Lung compliance is integrally related to the amount of elastin; hence, compliance peaks in adolescence. It is lower in the very young and the very old. Airways close in the tidal volume range until approximately 5 years of age.

Pulmonary Circulation

The main axial arteries of the lungs are present at 14 weeks' gestation. By 20 weeks' gestation, the pattern of branching is similar to that of adults, and collateral supernumerary vessels are present. During fetal life, additional arteries develop to accompany the respiratory airways and saccules. Bronchial arteries appear between the ninth and twelfth weeks of gestation. The arterial wall develops a fine elastic lamina by 12 weeks' gestation, and muscle cells are present as early as 14 weeks' gestation. By 19 weeks, the elastic tissue extends to the seventh generation of arterial branching, and muscularization extends distally. In the fetus, muscularization of the arteries ends at a more proximal level than in children and adults. The muscularized arteries have thicker walls than arteries of similar size in adults. The pulmonary arteries are actively constricted until the latter part of gestation. In the fetal lamb, pulmonary blood flow is only 3.5% of the combined ventricular output at 0.4 to 0.7 of gestation and is just 7% near term. Immediately after birth, pulmonary blood flow increases to near adult levels. Development of the pulmonary venous system mirrors that of the arterial system. The pulmonary arteries continue to develop after birth; new artery formation follows airway branching up to about 19 months of age, and supernumerary arteries continue to grow until 8 years of age. As alveolar size increases, the acinar branching pattern becomes more extensive and complex. The arterial structure also changes as preexisting arteries increase in size; the thickness of the muscular arteries decreases to adult levels during the first year of life.

Biochemical Development

By 24 weeks' gestation, the alveolar cuboidal epithelium flattens, and type I pneumocytes become the lining and supporting cells for the alveoli. The larger type II cells, which manufacture and store surfactant, also develop at this time. Surfactant initially appears at 23 to 24 weeks' gestation in humans and increases in concentration during the last 10 weeks of gestational life.[58] Surfactant is released into the alveoli at about 36 weeks' gestation, thus making normal extrauterine life possible.

Respiratory Transition: Placenta to Lung

By approximately 24 weeks' gestation, the lungs are capable of extrauterine gas exchange. However, several important circulatory and mechanical changes must occur immediately after birth for pulmonary gas exchange to be adequate. Ventilation begins to match perfusion within the first hours of life. Initially, there is right-to-left intrapulmonary shunting through atelectatic areas of the lung, as well as left-to-right shunting through the ductus arteriosus and some right-to-left shunting through the foramen ovale. The resultant PaO_2 of 50 to 70 mm Hg indicates a right-to-left shunt that is threefold that of normal adults. Transition from fetal to neonatal respiration and circulation is dynamic. Postnatally, the pulmonary vascular bed remains constricted if it is exposed to acidosis, cold, or hypoxia. If pulmonary artery constriction occurs, right-to-left shunting of desaturated blood through the foramen ovale and ductus arteriosus increases and consequently reduces pulmonary blood flow. Maintenance of this active pulmonary vasoconstriction is called persistent pulmonary hypertension of the newborn or persistent fetal circulation.

Mechanics of Breathing

For ventilation of the lungs, the respiratory muscles must overcome the lung's static-elastic and dynamic-resistive forces. Changes in these opposing forces during postnatal development affect lung volume, the pattern of respiration, and the work of breathing.

Lung Compliance versus Age

Lung compliance changes with age because of the changing alveolar structure, amount of elastin, and amount of surfactant. At birth, compliance is low because alveolar precursors have thick walls and decreased amounts of elastin. A deficiency of surfactant (e.g., hyaline membrane disease) further decreases lung compliance. The improved lung compliance occurring over the first years of life is the result of continued development of alveoli and elastin.

Chest Wall

The chest wall of infants is highly compliant because their ribs are cartilaginous. Because of the boxlike configuration of an infant thorax, there is less elastic recoil than there is with the dorsoventrally flattened thoracic cage of adults. Adults have a high proportion of slow-twitch, high-oxidative, fatigue-resistant fibers in their diaphragm and intercostal muscles. Whereas adults have 65% of these fibers in the intercostal muscles and 60% in the diaphragmatic muscles, neonates have only 19% to 46% of these fibers in their intercostal muscles and 10% to 25% in the diaphragm.[60] Consequently, infants are more vulnerable to muscle fatigue and decreased stability of the chest wall. The net effect of the compliant chest wall and the poorly compliant lungs is alveolar collapse and lower resting lung volume (i.e., FRC). Despite this tendency for lung collapse, a child maintains a large dynamic FRC via rapid respiratory rates, laryngeal breaking, and stabilization of the chest wall with increased intercostal tone during exhalation.

Upper Airway

The upper airways of children and adults have several anatomic differences that affect their ability to maintain a patent airway. The more anterior and cephalad position

of the larynx in children makes the "sniffing position" ideal for mask ventilation and endotracheal intubation. Extreme neck extension can actually obstruct the airway. The narrowest part of the adult airway is the vocal cords. Up to the age of 5 years, the narrowest portion of a child's airway is at the cricoid cartilage because the posterior larynx is positioned more cephalad than the anterior larynx, which causes the cricoid ring to be an ellipse rather than a circle. By 5 years of age, the posterior larynx has descended to the adult level.[251] An ETT that passes easily through the vocal cords of a young child may cause ischemic damage to the distal airway. The cricoid narrowing and very pliant tracheal cartilage provide an adequate seal around an uncuffed ETT. Children younger than 5 years rarely require a cuffed ETT, although some practitioners use cuffed tubes regularly in these patients.[252]

Closing Capacity

The elastic properties of the lung closely correlate with closing capacity. Closing volume is the lung volume at which the terminal airways close and gas is trapped behind the closed airways. Large closing volumes increase dead space ventilation, which leads to atelectasis and right-to-left shunting of blood. Elastic tissues help keep the airways open, so the greater the elastic stroma in the small airways, the lower the lung volume required to close small, noncartilagineous airways. Closing volume is small in late adolescence and relatively large in older adults and the very young. Children overcome the complications of large closing volumes and secondary atelectasis by breathing rapidly, by constant activity, and by crying. Closing volume becomes a significant problem in infants who are inactive, sedated, or anesthetized.

Resistive Forces

Neonates have small airways with high resistance or low conductance (conductance = 1/resistance). The diameter of the small airways does not significantly increase until approximately 5 years of age; hence, young children have elevated airway resistance at baseline and are particularly vulnerable to diseases that cause further narrowing of the airways (i.e., smooth muscle constriction, airway edema or inflammation). The normal high airway resistance of neonates and young children helps maintain FRC.

Control of Breathing

The newborn's respiratory control is unique. Hypoxia initially increases ventilation for a short time. This increase is followed by a sustained decrease in ventilation. The response is more exaggerated in preterm neonates. In full-term infants, it disappears after several weeks. Periodic breathing is also more common in infants, particularly preterm infants, and is probably due to inadequate development of the medullary respiratory centers.

Oxygen Transport: Oxygen Loading and Unloading

Fetal hemoglobin has low levels of 2,3-diphosphoglycerate and an oxygen half-saturation pressure of hemoglobin (P_{50}) of 18 mm Hg, which is much lower than the 27 mm Hg in adults. This lower P_{50} allows the fetus to load more oxygen at low placental oxygen tension, but it makes unloading oxygen in tissues more difficult. Three to 6 months after birth, fetal hemoglobin has been replaced with adult hemoglobin. The increased oxygen content of fetal hemoglobin and the increased fetal hemoglobin concentration are advantageous to the fetus because it allows an oxygen content of 20 mL of oxygen per 100 mL of blood to be delivered to the brain and heart. This is the same oxygen content that adults have when breathing room air. The oxygen concentration of neonates at birth is 6 to 8 mL/kg/min. It decreases to 5 to 6 mL/kg/min over the first year of life. The decreased ventilation-perfusion ratio, the decreased P_{50} of fetal hemoglobin,[53] and the progressive anemia characteristic of infants can make it difficult to deliver adequate oxygen during the first few months of life. Infants compensate by having a cardiac output of approximately 250 mL/kg/min for the first 4 to 5 months of life.

RESPIRATORY FAILURE

Respiratory failure is the inability of the lungs to adequately oxygenate and remove CO_2 from pulmonary arterial blood. There are many causes of respiratory failure, including a low environmental oxygen concentration, parenchymal lung disease, and pulmonary vascular disease. A complete history of the severity and chronicity of the respiratory problem helps formulate a differential diagnosis and an approach to treatment. Specific data should include a history of prematurity, previous airway instrumentation, previous mechanical ventilation, nonpulmonary organ dysfunction, and a family history of respiratory disease. A detailed feeding history and up-to-date growth chart may provide valuable information because growth failure may increase the need for oxygen. Usually, 1% to 2% of the total oxygen consumed is used for breathing. During respiratory illnesses, as much as 50% of the total oxygen consumption may be used for breathing. Infants and children with respiratory failure often have intercostal and suprasternal retractions, signs that the work of breathing and oxygen consumption are increased. Patients grunt during expiration in an attempt to maintain FRC. Most infants and children have tachypnea, which also helps maintain FRC by decreasing the time for exhalation. Less energy is required to breathe rapidly and shallowly than to take deep breaths. Infants with respiratory failure often have cyanotic lips, skin, and mucous membranes; however, it is often difficult to recognize skin color changes unless the $PaO_2 < 70$ mm Hg. Symmetry of chest movement should be noted. Differences in movement may indicate pneumothorax or blockage of a bronchus. The small thoracic volume allows easy transmission of breath sounds from one side to the other. Breath sound may be normal, even when pneumothorax is present. Abdominal distention can dramatically impede breathing in infants and young children.

MONITORING OF RESPIRATORY FUNCTION

An arterial blood gas is considered the gold standard to measure oxygenation as PaO_2 is measured directly from blood. The percent oxygen saturation of hemoglobin can be measured directly or calculated from PaO_2, pH, $PaCO_2$,

and temperature. Venous and capillary blood gases do not predict PaO_2. Use of arterial lines has decreased in pediatric ICUs over time. Pulse oximeters are ubiquitous. Pulse oximeters can provide continuous estimations of arterial oxygen saturations when the saturation is less than 97%; this is due to the shape of the oxygen dissociation curve. Pulse oximeters pass at least two wavelengths of light through the patient and the change in the absorbance of light is compared to an algorithm that produces the oxygen saturation. In the saturation range of 91% to 97%, pulse oximeters read higher than measured arterial saturations by approximately 1%.[253] However, in the saturation range of 76% to 90%, pulse oximeters read higher than measured arterial saturations by approximately 5% with wide confidence intervals.[253] Pulse oximeters can also have poorer performance when there is decreased perfusion to the extremity with the sensor. Lastly, most pulse oximeters have difficulty detecting abnormal forms of hemoglobin such as methemoglobin or carboxyhemoglobin and will produce erroneous results in their presence.

$Paco_2$ is used as a measure of the adequacy of ventilation. Analysis of ABGs is the gold standard, although $Paco_2$ obtained from capillary or venous blood gases can also provide valuable information. CO_2 values obtained from capnography or transcutaneous CO_2 monitoring (TCOM) can provide continuous information in a manner similar to pulse oximeters. Capnographs produce a waveform displaying exhaled CO_2 that can be either time-based or volumetric. Time-based capnography is much more common. Capnographs can either be an aspirating or nonaspirating system. An aspirating system takes gas from the ventilator circuit to measure the CO_2. A nonaspirating system has an exhalation chamber placed in line with the ventilator circuit. The system uses an infrared light source and detector that measures the exhaled CO_2. There is a great amount of information that can come from capnography including the end-tidal CO_2 ($ETCO_2$) value, respiratory rate, dead space calculations, cardiac output, and detection of obstruction of the airways.

For time-based capnography, the plateau of the slope will always be lower than $Paco_2$. Increases in $ETCO_2$ must be investigated as they signal a change in ventilation. For individuals with healthy lungs, this $ETCO_2$-to-$Paco_2$ gradient is usually 2 to 5 mm Hg. The gradient increases with increased dead space, abnormalities in the pulmonary vasculature, decreased cardiac output, and pulmonary over distension. $ETCO_2$ from capnography can be used clinically to calculate the approximate alveolar dead space by the alveolar dead space fraction (AVDSf). AVDSf = ($Paco_2$ – $P_{et}CO_2$) / $Paco_2$. AVDSf is a reasonable indicator of alveolar dead space[254] and, in a study by Ghuman and associates[255] for pediatric patients with acute hypoxemic respiratory failure, is found to be independently associated with mortality. Other valuable information is available from the waveform produced by time-based capnography. As an example, a rising upslope to the exhalation phase can indicate obstructive airways disease. Time-based capnography is more accurate with slower respiratory rates and when there is minimal leak around the ETT.

Volumetric capnography traces the CO_2 concentration against the exhaled volume and is appearing as a feature on some ventilators. Free-standing monitors that provide the same measure are also available. Volumetric capnography provides direct information for dead space calculations. Clinically volumetric capnography is helpful in setting the optimal PEEP. In this way PEEP can be titrated to balance improved oxygenation through alveolar recruitment and decreased dead space by not causing over-distension. Volumetric capnography can also be used to demonstrate a response to bronchodilator therapy.

In circumstances such as high frequency ventilation, the use of TCOM provides a continuous measure of ventilation. The TCOM module heats the skin underneath a small sensor. There is increased diffusion of CO_2 across the skin as the capillary bed dilates from the heat. The diffused CO_2 is then measured. When the TCOM is first set up, it should be calibrated against a capillary or arterial blood gas. There can be drift of calibration over time but newer modules have improved stability.

Effort of breathing with or without a ventilator can be obtained by the objective measurement value of the pressure-rate product (PRP). The pressure is measured with a balloon-tipped catheter placed into the distal one third of the esophagus and can be used as a surrogate for pleural pressure. The PRP is the change in esophageal pressure (Pes) multiplied by the respiratory rate (RR). PRP = Pes × RR. The PRP has been used as an objective measure of effort of breathing in studies: before and after extubation[256] with PEEP and obstructed airways disease,[257] evaluating increasing inspiratory load,[258] and evaluating effectiveness of high-flow nasal cannula.[259] Some ventilators can measure esophageal pressure, or it can be obtained with separate devices. In addition to measuring the PRP, the esophageal pressure is very important in measuring the pressure across the lungs or the transpulmonary pressures. Many adult studies are appearing demonstrating the benefits of titrating ventilator settings to trans-pulmonary pressure for patients with ARDS.[260-262] The transpulmonary pressure may have particular benefit in patients who are obese and require mechanical ventilation for respiratory failure[263] in which the decreased compliance of the chest wall might cause practitioners to limit ventilator pressures.

The phase of breathing or the synchrony between movement of the abdomen and the chest wall can be measured with respiratory inductance plethysmography (RIP). This noninvasive measure uses elastic bands placed around the abdomen and chest. Movement of the abdomen and chest changes the inductance of a small wire in the bands. Movement of the abdomen relative to the chest can be presented graphically or measured as the phase angle. When there is obstruction to breathing, such as with upper airway obstruction, there is a lag in the movement of the abdomen and chest wall that is identified as an increasing phase angle. The phase angle obtained by RIP is an objective measure of the degree of upper airway obstruction[258,264] and can be used to evaluate the effectiveness of therapy.[265,266] This is a valuable tool for research in the area of causes and treatment of upper airway obstruction as there is increasing interobserver variability in the clinician's assessment of this process.[267] RIP can be measured easily with free-standing devices, and it may have a more prominent role in future pediatric studies.

Much information on the respiratory effort of patients receiving mechanical ventilation can be obtained from respiratory spirometry. Spirometry can display flow-volume loops, pressure-volume loops, in addition to graphs of flow-time, pressure-time, and volume-time. The characteristic shape of some respiratory flow-volume loops can help with the diagnosis of various respiratory diseases. There is a classic scooped out appearance to the exhalation portion of a flow-volume curve with obstructive lung disease. The pressure-volume loops obtained on the ventilator can be used to increase PEEP to keep lung tissue recruited above an area of potential atelectasis. This can be seen graphically as a lower inflection point on the inspiratory curve. This is where the curve moves from a flat area to an area of maximal compliance where there is the greatest change in volume for a given change in pressure. There is also an upper inflection point on pressure volume loops where over-distension of the lungs can be identified if the inspiratory pressure or volume is too great. The pressure-volume curve with over-distension looks like a bird's beak and ventilator settings should be reduced.

Radiologic evaluation of the nasopharynx, neck, and thorax can provide meaningful information regarding the cause and severity of the respiratory dysfunction. Fluoroscopy can be used to evaluate the airways and movement of the diaphragm in an uncooperative child. Analysis of ABGs is used to determine the effectiveness of gas exchange. PaO_2 measurements allow calculation of the alveolar/arterial oxygen gradient and right-to-left shunting of blood across the lung. Elimination of CO_2 from arterial blood is another indicator of lung function. Failure to remove CO_2 from pulmonary arterial blood indicates maldistribution of blood flow in the lungs; specifically, there is increased dead space.

Umbilical artery cannulation is common in neonates, so those caring for such children can obtain arterial blood and continuously measure arterial blood pressure. These catheters are relatively simple to insert and reasonably easy to maintain.[268] The tip of the catheter ideally should be at or just above the level of the aortic bifurcation and below the level of the renal arteries (L2). Once the child's condition is stable, a peripheral artery catheter should be inserted and the umbilical artery catheter should be removed. All intraarterial catheters have the potential to cause distal thromboembolic disease. Care must be taken to flush arterial catheters gently to prevent cerebral or cardiac emboli. With proper insertion and maintenance, serious complications of arterial lines are rare. Although arteries that are cannulated for a long time may occlude, they recanalize within a short period.

NEONATAL RESPIRATORY FAILURE

The cause of respiratory failure depends to some degree on the age of the patient (see also Chapter 103). Newborn respiratory failure is often the result of congenital anomalies and immaturity of the lungs and their blood vessels. Congenital anomalies can include airway malformations, dysgenesis or malfunction of the lung or nonpulmonary organs, and abnormalities of the pulmonary vessels. Lesions of immaturity include apnea of prematurity, hyaline membrane disease, and abnormalities of surfactant production and secretion. During the perinatal period, neonates are subject to infections and stress. Persistent pulmonary hypertension can complicate neonatal pulmonary and nonpulmonary problems. These and other important causes of respiratory failure in the newborn are listed in (Table 95-5). A wide variety of disorders cause respiratory failure in older children

TABLE 95-5 **CAUSE OF NEONATAL RESPIRATORY DISTRESS**

Location	Congenital Abnormalities	Developmental Immaturity	Specific Neonatal Stress
Impaired control of ventilation	Central nervous system dysgenesis Ondine's curse	Apnea of prematurity Intracranial hemorrhage	Drug intoxication (note maternal drugs) Sepsis Central nervous system infection Seizures
Neuromuscular disorders	Congenital myopathies		High cervical cord injuries
Structural impairment	Thoracic deformities Lung hypoplasia Diaphragmatic hernia Potter syndrome Abdominal malfunction Gastroschisis Omphalocele		Severe abdominal distention Pneumothorax or other leak
Airway obstruction Upper airway	Choanal atresia Pierre Robin syndrome Laryngeal web/cleft Congenital tracheal/laryngeal stenosis Recurrent laryngeal palsy Hemangioma Lymphangioma		Massive meconium aspiration Vocal cord paralysis is secondary to myelodysplasia
Lower airway	Tracheoesophageal fistula Lobar emphysema		Meconium/blood aspiration
Alveolar disorders		Respiratory distress syndrome	Bronchopulmonary dysplasia

(Box 95-2). Regardless of the specific cause, respiratory failure can be categorized as hypoventilation syndromes in patients with normal lungs, intrinsic alveolar and interstitial disease, and obstructive airway disease.

Hypoventilation Syndromes in Children with Normal Lungs

Causes of hypoventilation include neuromuscular disease, central hypoventilation, and structural or anatomic impairment of lung expansion (e.g., upper airway obstruction, massive abdominal distention). These clinical conditions are characterized by inadequate lung expansion, secondary atelectasis, intrapulmonary right-to-left shunting, and systemic hypoxia. Atelectasis and the secondary reduction in FRC increase the work of breathing. The child's response to the increased work of breathing and lower lung volumes is to breathe faster with a smaller tidal volume. This pattern of breathing eventually increases the amount of atelectasis and shunting. As a result, children with intrinsically normal lungs and hypoventilation syndromes exhibit tachypnea, small tidal volumes, increased work of breathing, and cyanosis. Chest radiographs reveal small lung volumes and miliary or lobar atelectasis. Positive-pressure ventilation and PEEP quickly reverse the pathologic processes.

Primary Pulmonary Alveolar or Interstitial Disorders

Intrinsic lung disease involving the alveoli or pulmonary interstitium decreases lung compliance and increases airway closure, both of which cause atelectasis and increase the work of breathing. Edema or inflammation of the alveoli or fibrosis of the interstitium decreases lung compliance. The stiffer lung requires a greater negative intrapleural pressure for air movement, thereby increasing the work of breathing and the risk for pneumothorax.

Obstructive Airway Disease

Airway obstruction can be extrinsic or intrinsic. Intrinsic small airway obstruction commonly occurs with bronchiolitis, bronchopneumonia, asthma, and bronchopulmonary dysplasia (BPD). Airway obstruction decreases conductance and increases airway resistance and the work of breathing. Partial obstruction impedes expiration more than inspiration and causes gas trapping or regional emphysema. Complete airway obstruction results in atelectasis and right-to-left shunting of blood within the lung. Patients with disease of the small airways usually have a mixture of total and partial airway obstruction and inhomogeneous collapse and overdistention of the lung. The areas of collapse cause intrapulmonary right-to-left shunting of blood, and the overdistended areas increase the amount of dead space. If the entire lung is overdistended, compliance is decreased and the work of breathing is increased. The clinical and radiographic picture varies with the different degrees of collapse and overdistention of the lung. In summary, all causes of respiratory failure share similar pathophysiology: atelectasis and decreased FRC with intrapulmonary right-to-left shunting of blood or alveolar overdistention with increased dead space and decreased CO_2 elimination, or both. The increased work of breathing associated with all forms of respiratory dysfunction can cause fatigue and a breathing pattern that further complicates the initial process. It may also lead to apnea, hypoxia, and cardiac arrest in young children if the increased work of breathing is not quickly detected and treated.

BOX 95-2 *Causes of Respiratory Failure in Children*

1. Impaired control of ventilation
   - Head trauma
   - Intracranial hemorrhage
   - Increase intracranial pressure secondary to tumor, edema, hydrocephalus, Reye syndrome
   - Central nervous system infections
   - Drug intoxication
   - Status epilepticus
2. Neuromuscular disorders
   - High cervical cord injury
   - Poliomyelitis
   - Guillain-Barré syndrome
   - Neurodegenerative disease (e.g., Werdnig-Hoffman syndrome)
   - Muscular dystrophies and myopathies
   - Myasthenia gravis
   - Botulism
   - Tetanus
   - Phrenic nerve injury
3. Structural impairment
   - Severe kyphoscoliosis
   - Flail chest
   - Large intrathoracic tumor
   - Pneumothorax or pneumomediastinum
   - Large pleural effusion, hemothorax, empyema
   - Severe abdominal distention
   - Severe obesity (pickwickian syndrome)
4. Airway obstruction
   - Upper airway
   - Congenital anomalies
   - Tumor, intrinsic or extrinsic
   - Epiglottitis
   - Croup (laryngotracheobronchitis)
   - Foreign body
   - Postintubation edema, granulation tissue, or scarring
   - Vocal cord paralysis
   - Burns
   - Vascular ring
   - Lower airway
   - Asthma
   - Bronchiolitis
   - Foreign body
   - Lobar emphysema
   - Cystic fibrosis
5. Alveolar disorders, pneumonia
   - Infectious: bacteria, virus, fungus, *Pneumocystis* species
   - Chemical: aspiration, hydrocarbon, smoke inhalation
   - Pulmonary edema: cardiogenic, near-drowning, capillary leak syndrome
6. Massive atelectasis
7. Oxygen toxicity
8. Pulmonary confusion
9. Pulmonary hemorrhage

RESPIRATORY CARE

The fraction of inspired oxygen (FiO_2) can be increased by a number of means including nasal cannula or mask. The FiO_2 can be increased up to approximately 40% with nasal cannula oxygen at 5 L/min; however, this rapid rate of flow can become uncomfortable. As room air is entrained around the cannula during inspiration, the FiO_2 cannot be increased further with nasal cannula. It should be noted that the size of the patient correlates with the inspiratory volume with each breath. The larger the patient, the larger the inspiratory volume is relative to flow from the cannula and the larger volume of room air that is entrained. In turn, the smaller a patient the less room air is entrained and there may be a greater impact on FiO_2.

The FiO_2 can be increased further with a properly fitted facemask. The open holes of a Venturi or simple facemask allow for greater entrainment of room air as compared to a nonrebreather facemask that has no holes. An FiO_2 approaching 1 can be obtained with a nonrebreather facemask with an oxygen reservoir and one-way valve. Patients with respiratory distress while on the pediatric ward may temporarily require a nonrebreather facemask at high flows. If there is no significant improvement to immediate interventions, arrangements should be made to transfer the patient to the PICU. Nonrebreathing facemask systems can be humidified for comfort, but they do not provide any positive pressure to the airways.

High-flow humidified nasal cannula (HFHNC) oxygen can provide a higher FiO_2, and it is more readily tolerated than standard nasal cannula. The gas in HFHNC is heated to body temperature and nearly completely humidified with water vapor. HFHNC can be delivered with flow rates in pediatric patients up to 10 L/min. It was shown by Rubin and associates[259] that higher flow rates with HFHNC decreased the effort of breathing in critically ill children; this has been used frequently to support patients with bronchiolitis.[269,270] It is unclear whether the significant benefits of HFHNC come from washing out CO_2 from the airways or from the generation of positive pressure. The potential for complications exists with higher gas flow rates. Air leak syndrome was reported in three patients by Hegde and associates.[271] As the use of HFHNC increases, other problems may be identified. Given that the amount of FiO_2 delivered approaches 1.0, use of HFHNC is typically restricted to an emergency department or ICU setting. The high degree of respiratory support provided can mask a significant degree of respiratory distress.

Noninvasive ventilation can be supplied with continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP). This is typically delivered with a tight fitting nasal or face mask, which allows for the development of positive airway pressure. Most modern ventilators can be set to deliver this therapy, but specific free-standing BiPAP machines are more often used. BiPAP therapy is best for short-term use and in patients with the ability to cough and protect their airway. It is not an absolute that the patient initiates every breath, because a back-up rate can be set. However, if the patient is completely reliant on the rate set on the machine, intubation should be considered. Other indications for conversion from BiPAP to endotracheal intubation include pressure-related tissue breakdown on the face from constantly wearing the mask, the need to initiate enteral feedings as patients are typically nil per os (nothing by mouth) status while receiving BiPAP, and increasing pressure settings on the BiPAP machine.

CPAP reduces the patient's work of breathing by providing airway pressure, reducing atelectasis, decreasing dead space, and improving the balance of ventilation to perfusion. An initial CPAP pressure is typically 4 to 6 mm Hg and is then increased as needed and as the patient tolerates the therapy. Given that the feeling of positive airway pressure is a bit foreign, starting with lower pressures and increasing them gradually gives the patient a chance to adapt. The authors typically start CPAP therapy for several minutes even if the patient will ultimately receive BiPAP. For BiPAP the expiratory pressure is also initially at 4 to 6 mm Hg, and the inspiratory pressure is set at 4 to 6 mm Hg above that. The inspiratory and expiratory pressures are adjusted as well as the rise time to inspiratory flow. All these changes can help the patients tolerate therapy. With the tight seal, an FiO_2 of 1.0 can be delivered. Use of the full facemask can put patients at risk for aspiration if they vomit. BiPAP therapy is being used in status asthmaticus,[272,273] and it may provide a more effective means of delivering aerosolized medication. The use of BiPAP therapy for this indication could increase over time, as it is being recommended in current guidelines.[274,275] BiPAP can also be used as an ongoing therapy for chronic respiratory failure, such as for central hypoventilation or restrictive lung disease. These patients may be able to receive their therapy at home and are typically followed by the hospital's pulmonary service.

The size of ETT required should be selected carefully. One formula that estimates the appropriately sized tube for children older than 2 years is $(Age + 16) / 4$. This formula provides the internal diameter of the appropriately sized ETT. The correct size should have a slight air leak when a positive pressure of 20 to 30 cm H_2O is applied. Serious lifelong laryngeal and subglottic damage can result from using inappropriately large ETTs, particularly in children with inflammatory lesions of the upper airway such as laryngotracheobronchitis. Because of the more flexible tracheal cartilage and the relative subglottic narrowing of children, uncuffed ETTs generally provide an adequate seal in those younger than 5 years. However, if the patient has lung disease that requires high ventilation pressure, a cuffed tube is more appropriate. Small cuffed ETTs are frequently used in the ICU in younger patients,[252] but a small leak of air at 25 to 30 cm H_2O should be present. Cuffed tubes will usually eliminate the air leak around an ETT, but overinflation of the cuff may occlude venous flow and injure the airway. The long-term safety of using cuffed ETTs in young children is not known.

With endotracheal intubation, the position of the ETT should be correct so chest movements are symmetric, and breath sounds should be equal when auscultated in the axillae. An electronic or colorimetric CO_2 detection system helps confirm whether the ETT is in the trachea or the esophagus.[276] If the double lines on the ETT are at the level of the vocal cords, the ETT is usually in the correct

position. Another way to position the ETT correctly is to advance it into the right mainstem bronchus and listen for breath sounds in the left axilla. Breath sounds will be diminished. Withdraw the ETT slowly. When breath sounds are heard on the left, pull the tube out an additional 1 to 2 cm, depending on the size of the child. When the breath sounds are equal, fix the tube in place. The tip of the ETT should be midway between the vocal cords and the carina on the chest radiograph. In small infants, the distance between the carina and the vocal cords is very short. Consequently, it is easy to place the ETT inadvertently in a mainstem bronchus. Flexion of the head moves the ETT into the airway. Extension moves it toward the vocal cords. Turning the head to the side can obstruct the tip of the ETT if it contacts the tracheal wall, which can cause CO_2 retention or hypoxemia, or both. A child's trachea can be intubated for more than 2 weeks before performing a tracheostomy. This is possible with proper humidification of the inspired gases, improved endotracheal suctioning and monitoring (Sa_{O_2}), and excellent nursing care. Everyone caring for the child must be constantly alert to the possibility that the ETT will become obstructed by secretions or that accidental extubation or mainstem bronchus intubation will occur. In neonates, ETTs with a "Murphy" eye become obstructed more often with secretions than those without a Murphy eye do. The Murphy eye is near the end of the ETT. Once the ETT enters the mainstem bronchus, it is impossible for the infant to breathe effectively through the "eye." Because the ETT is almost the same size as the trachea, it is nearly impossible for the infant to breath around the tube. Thus, ETTs with Murphy eyes are dangerous and probably should not be used in young infants. Tracheostomy is indicated when children require a long-term artificial airway for mechanical ventilation, for endotracheal suctioning, or to bypass an upper airway obstruction. Accidental dislodgement of the tracheostomy tube before the tract is well healed can be life threatening. Reinsertion of a tracheostomy tube during the first 72 hours after insertion can be extremely difficult and can create false passages that can make it impossible to ventilate the lungs or can cause pneumothorax.

Intubation and mechanical ventilation can provide significant elevations in airway pressure as compared to noninvasive ventilation and an FiO_2 of 1.0. There can be regional variation to the mode of mechanical ventilation chosen, but there is likely a greater use of pressure-controlled ventilation rather than volume-controlled ventilation in PICUs. With pressure-controlled ventilation, pressure is set and the tidal volume can change as the pulmonary compliance changes. With volume-controlled ventilation, tidal volume is set and the pressure needed to deliver that may change as the pulmonary compliance changes. These are likely the two main modes of mechanical ventilation in pediatric ICUs. For the majority of intubated children who have reasonable pulmonary compliance, there are little differences between the two modes. One potential advantage of pressure-controlled ventilation for patients who are sicker with poorer pulmonary compliance is that most ventilators in this mode use a decelerating inspiratory flow pattern. As a result, the flow of gas is greatest early in inspiration and then decelerates to zero flow when the peak pressure is achieved. This can result in the delivery of a larger tidal volume for a lower peak pressure as compared with the same pressure that might be required in a tidal volume mode.

There are additional modes available on modern ventilators that may have benefit for patients with lung injury. The names of the modes will differ between the ventilator manufacturers. Many will have a mode where a desired tidal volume is guaranteed and the lowest pressure necessary to achieve that is used. The terms to define this are *pressure-regulated volume control* and *volume guarantee*. These modes can reduce the pressure used, but they work best when the patient is well sedated and not competing with the ventilator.

Airway pressure-release ventilation (APRV) is a newer mode of mechanical ventilation that is used at a limited number of centers. There are few published pediatric studies using this mode,[277-279] and its benefits and limitations continue to be explored. Neurally adjusted ventilatory assist (NAVA) is a newer method of triggering ventilator synchrony available on the Servo-i ventilators by Maquet (Rastatt, Germany). This method uses a small esophageal probe that can sense the electrical activity of the diaphragm and use that activity to synchronize the ventilator. The potential benefits of improved triggering such as improved comfort, lower ventilator settings, and increased minute ventilation have been shown in some studies.[280,281] APRV is essentially CPAP with brief, intermittent release coupled with spontaneous ventilation. The high CPAP level (P_{high}) maintains alveolar recruitment and aids in oxygenation over a period of time (T_{high}), and the timed release to a low pressure (P_{low}) minimizes resistance to expiratory flow and carbon dioxide removal. In addition, the patient is able to breathe spontaneously during all phases, P_{high} and P_{low}, potentially allowing for improved pulmonary mechanics and gas exchange. APRV differs from other modes of ventilation because it relies on an intermittent decrease in airway pressure, instead of an increase in airway pressure to maintain an open lung strategy for ventilation. Therefore, the release time (T_{low}) should be set long enough to allow for an adequate tidal volume (6-8 mL/kg), but short enough to avoid alveolar collapse and atelectrauma. In summary, the operator-controlled parameters in APRV are P_{high}, T_{high}, P_{low}, T_{low}, and FiO_2. Recommendations for implementing APRV are limited in pediatrics, and thus extrapolated from adult recommendations.[282] P_{low} is initially set at zero. P_{high} can be set by several methods, such as plateau pressures or 75% of peak inspiratory pressure; however, when transitioning from conventional modes of ventilation P_{high} is often determined by mP_{AW} pressure formula where the mP_{AW} is set 2 to 3 cm H_2O above conventional mP_{AW}: $(P_{high} \times T_{high}) + (P_{low} \times T_{low}) / (T_{high} + T_{low})$. To determine T_{high} and T_{low}, first determine the total cycle time according to a normal respiratory rate range for the patient's age; that is, a respiratory rate of 20 yields a total cycle time of 3 seconds. T_{high} will be the total cycle time minus a T_{low} of 0.2 to 0.6 seconds, initially starting at 0.4 seconds; that is, total cycle time of 3 seconds yields a T_{high} of 2.6 seconds and T_{low} of 0.4 seconds; or, Number of cycles (respiratory rate) = 60 seconds / $(T_{high} + T_{low})$. Transitioning to APRV, like transitioning to high-frequency oscillating

ventilator (HFOV), will take time for optimal lung recruitment. After several hours if the patient continues to have severe hypoxemia, T_{high} can be increased to aid in oxygenation. Once established, P_{low} and T_{low} usually do not require additional changes; however, as lung compliance improves P_{high} and T_{high}, can be decreased and increased, respectively, to wean a patient toward a target of a continual CPAP of 5 to 6 cm H_2O in preparation for extubation of the trachea. APRV may be advantageous to other modes of advanced mechanical ventilation because of the patient's ability to breathe spontaneously throughout the entire ventilatory cycle, improving respiratory mechanics and reducing the need for sedation and neuromuscular blockade. However, some authors are concerned that there may be a more frequent incidence of cyclic alveolar collapse during airway release leading to a greater degree of atelectrauma, as compared with HFOV.[279,283]

High-frequency ventilation describes a type of mechanical ventilation in which the respiratory rate of the ventilator is much greater than a normal physiologic rate. By maintaining the same minute ventilation, these ventilation modes produce low tidal volumes. There are several different types with the most commonly used in pediatrics being the HFOV. Use of the HFOV was first described by Lunkenheimer in 1972.[284] This type of ventilator houses a piston that is attached to semirigid connecting tubing that attaches to the ETT. This circuit can be pressurized to a set mean airway pressure. The piston then oscillates up to 840 times per minute, creating small positive and negative respiratory cycles. The mean airway pressure is higher as compared with conventional ventilation, and this prevents atelectasis and shear forces from opening and closing alveoli with each respiratory cycle. The FiO_2 is set as in a conventional ventilator. The frequency of oscillation of the piston is adjusted to remove carbon dioxide and can vary between 6 and 14 Hertz. (Hertz [Hz] is 1 cycle/second, 6 Hz equals 360 cycles or breaths per minute.) The amplitude of the ventilator is the distance the piston moves with each excursion and by these excursions small breaths are propelled down the tubing. Several proposed mechanisms for the method of gas transport during HFOV have been proposed, but none have been proven definitively. Tidal volumes are dependent on the patient's compliance, ETT size, device frequency, and device amplitude. Tidal volume is inversely related to cyclic frequency: $VCO_2 = \text{Frequency} \times VT^2$. When transitioning from conventional modes of ventilation to HFOV, the initial power setting (referred to as *delta P, power,* or *amplitude*) is adjusted to visible chest "wiggle" from the clavicles to the abdomen or pelvis. The mean airway pressure (mP_{AW}) is initially set approximately 5 cm H_2O greater than the last mP_{AW} on conventional ventilation just prior to the initiation of HFOV. Traditionally, tidal volumes in HFOV are considered to be just above functional residual capacity (FRC); however, it is difficult to measure actual tidal volumes and provide precise "optimal" lung volumes strategy. Clinically, mean airway pressure (mP_{AW}) is titrated upward by 1 to 2 cm H_2O until oxygenation improves and inspired oxygen concentrations can be weaned to less toxic levels of below 0.60. While titrating mP_{AW}, overdistention is assessed with chest radiographs; overdistention or hyperinflation are determined by more than nine posterior ribs or flattened hemi-diaphragms on chest radiographs. Initial frequency settings, measured in hertz, can be found in (Table 95-6). HFOV is the only mode of ventilation with active expiration. If hypercarbia leads to profound respiratory acidosis and patient instability, despite allowances for permissible hypercapnia, then minute ventilation can be improved by several means during HFOV. First, the patient should be suctioned. One of the drawbacks of HFOV is the lack of spontaneous ventilation and adequate airway clearance; therefore, inline suction (without breaking into the circuit causing derecruitment) should be used to ensure adequate airway, ETT patency, and lung recruitment. Second, ΔP/amplitude should be increased to maximize lung recruitment and increase minute ventilation. Third, frequency (Hz) can be slowly decreased to enhance lung recruitment and increase minute ventilation. Finally, the ETT cuff should be deflated to allow additional escape of CO_2 around the ETT. Disadvantages of HFOV include no partial ventilatory support leading to increased requirements for sedation and paralysis, cardiopulmonary interactions owing to higher mP_{AW} and decreased venous return, and loss of alveolar recruitment if the circuit is detached for suctioning of manual ventilation.

HFOV is being used in pediatrics as a rescue therapy for acute lung injury (ALI) or ARDS. A 1994 publication by Arnold and associates[285] is the only multicenter randomized trial of HFOV. This study showed lower use of oxygen supplementation in the HFOV group at 30 days. There have been other pediatric studies showing positive benefit of HFOV, such as a single-center retrospective study by Babbitt and colleagues.[286] The conclusion that could be drawn by many studies with HFOV in pediatrics is that for disease processes with significant mortality, rescue therapy with HFOV may be appropriate and may show improved outcomes. In some of the most critically ill patients with a very high mortality, such as immunocompromised children with ARDS, the use of HFOV has been as a diagnostic criteria to identify survivors from nonsurvivors.[279] A Cochrane review by Sud and associates[287] in adult patients with ARDS summarized the effectiveness of therapy: "The findings of this systematic review suggest that HFO was a promising treatment for ALI and ARDS prior to the uptake of current lung protective ventilation strategies." The recently published results of the adult OSCILLATE trial[288] (The Oscillation of ARDS Treated Early Trial) could further limit the use of HFOV. This multicenter randomized controlled trial was stopped early after 548 patients were enrolled. The in-hospital mortality was 47% in the group receiving HFOV versus 35% in the patients receiving conventional ventilation. It is unclear whether these findings can be

TABLE 95-6 INITIAL FREQUENCY SETTINGS IN HIGH-FREQUENCY OSCILLATORY VENTILATION

Patient Weight (kg)	Initial Frequency Setting (Hz)
<2	15
2-15	10
16-20	8
21-30	7
31-50	6
>50	5

translated to pediatric patients. The disease processes and the condition of pediatric patients can be extremely different as compared with adults. However, with these findings it is unclear whether the motivation is present to perform a multicenter HFOV trial in pediatrics. There may continue to be other indications for HFOV in pediatrics, such as air leak syndrome or congenital diaphragmatic hernia.

High-frequency percussive ventilation (HFPV) pneumatically stacks subtidal volume breaths at a set rapid rate superimposed upon conventional cyclic rates. HFPV as a mode of ventilation allows for a progressive stepwise inflation of the lung to a set peak pressure while allowing for passive exhalation to a preset lower pressure. HFPV has been well described in the inhalational injury population for its ability to safely oxygenate and ventilate with continuous, pneumatically powered, high-frequency percussions to facilitate clearance of airway debris.[289-292] These properties may be particularly useful in pediatric patients with acute respiratory failure, by improving oxygenation and ventilation while maintaining lung protective strategies.[293]

ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

The 1994 American-European Consensus Conference[294] established clinical criteria to diagnose ARDS. The criteria were widely used in research studies to assure consistent severity of illness and then to study the effect of various interventions. ARDS diagnostic criteria have been revised recently and are known as the *Berlin Definition*.[295,296] By this definition, ARDS is separated into three mutually exclusive categories based on the degree of hypoxia. *Mild* is PaO_2/FiO_2 = 201 to 300, with PEEP > 5; *moderate* is Pa_{O_2}/FiO_2 = 100 to 200, with PEEP > 5; and *severe* is PaO_2/FiO_2 < 100, with PEEP > 10. The Berlin Definition resulted from consensus opinion and from evaluation of criteria performance using two large datasets. Additional components of the criteria include the timing of onset, bilateral opacities on chest radiograph, and respiratory failure not fully explained by cardiac failure. Performance of the Berlin Definition in pediatrics has been evaluated by De Luca and colleagues[297] with validity similar to that presented in adults. As pointed out by Khemani and associates[298] in the accompanying editorial, the new definition was reapplied to patients already classified by the older American-European Consensus Conference definition. The editorial also describes several areas in which research in pediatric ARDS, such as the decreased use of arterial catheters, will differ from adults. Specific diagnostic criteria that address the unique aspects of pediatric ARDS are needed for future research.

Clinical features of lung injury can vary from mild, self-limiting dyspnea to rapidly progressive and fatal respiratory failure. The clinical course of ALI can be generalized in four phases (Box 95-3); however, not every patient passes through all these phases, and the condition may resolve at any stage. Extensive research continues to try to develop predictive biomarkers and genomic arrays for severity and resolution of lung injury; however, to date there are no useful clinical biomarkers or genomic readouts for prediction or goal directed therapy.

BOX 95-3 ***Four Phases in the Clinical Development of Lung Injury***

1. Dyspnea and tachypnea with no other abnormalities on chest radiographs
2. Hypoxemia with normal or subnormal $Paco_2$ with possible minor consolidation or effusions on chest radiographs within the last 24-48 hours
3. Diagnostic criteria of acute lung injury established—severe arterial hypoxemia, decreased pulmonary compliance with characteristic bilateral diffuse infiltrates on chest radiographs
4. Massive bilateral consolidation with unremitting hypoxemia; increased deadspace ventilation; rising $Paco_2$; often terminal

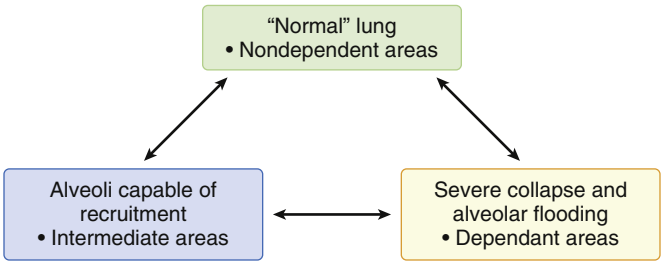


Figure 95-4. For the purposes of lung protective ventilator strategies, the lung can be divided into three hypothetical areas.

PRINCIPLES OF LUNG PROTECTIVE STRATEGIES: LIMITING VENTILATOR ASSOCIATED LUNG INJURY

As lung injury progresses, in response to pulmonary or extrapulmonary injury, the lungs can be divided into three hypothetical regions (Fig. 95-4):

1. Areas with severe collapse and alveolar flooding (dependent areas)
2. Recruitable areas with alveolar atelectasis (intermediate areas)
3. Normal lung (nondependent areas)

The goal of mechanical ventilation is to recruit intermediate areas allowing improved gas exchange, spare normal areas of lung from ventilator-associated lung injury, while giving dependent collapsed regions of lung with alveolar flooding time to recover from the primary process (i.e., pneumonia, sepsis). Lung recruitment of intermediate areas and prevention of ventilator-associated lung injury is accomplished by using PEEP and limiting tidal volume and plateau pressures. This potentially complicated task can be simplified by first looking at Figure 95-5 and conceptualizing a theoretical pressure-volume curve of the lung. As alveolar airway pressure increases, there is an opening pressure (P_{flex}) required to overcome airway resistance and alveolar compliance (Compliance = $\Delta V / \Delta P$). Pressures below P_{flex} will lead to alveolar collapse, termed *atelectasis*. If airway pressure cycles above and below P_{flex}, alveoli will continually open and collapse, leading to wall shear stress and eventual damage, or atelectrauma. Following the hysteresis curve to the upper extent of the inspiratory limb, as pressure increases, there comes a point, termed P_{max}, whereby the alveoli start to become

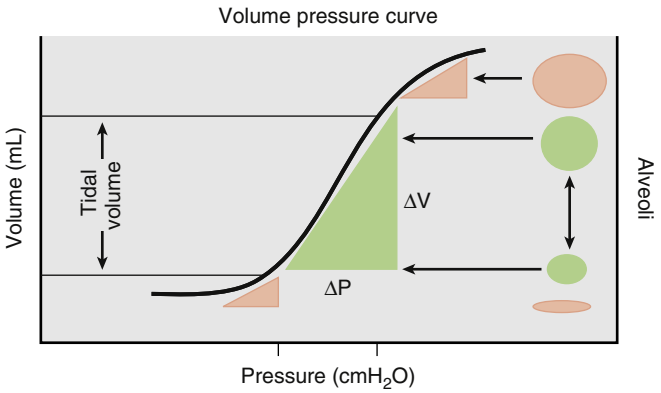


Figure 95-5. Volume pressure curve.

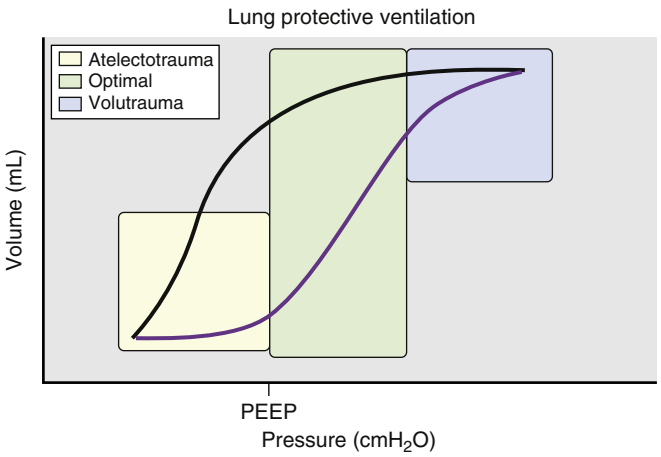


Figure 95-6. Lung protective ventilation strategy. *PEEP,* Positive end-expiratory pressure.

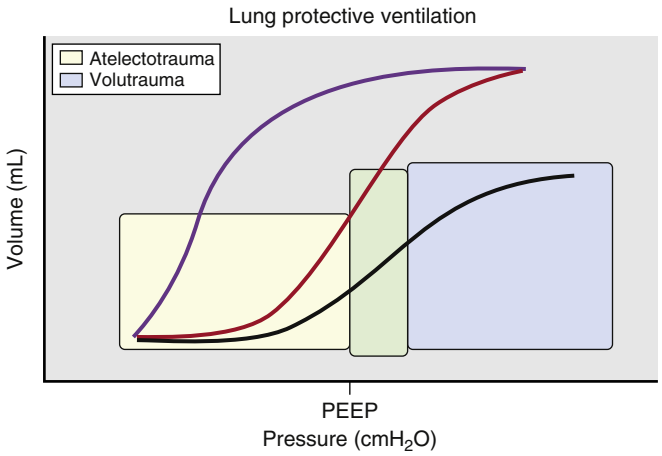


Figure 95-7. Lung protective ventilation with worsening lung compliance. *PEEP,* Positive end-expiratory pressure.

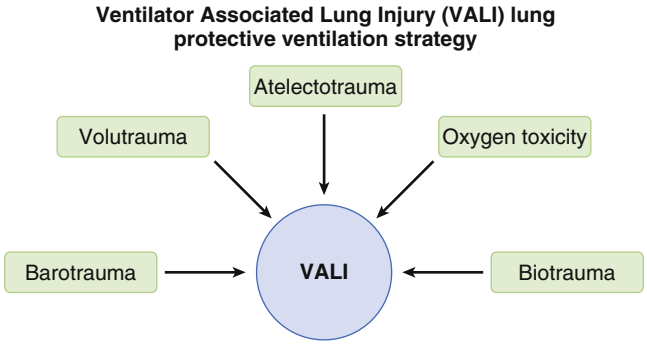


Figure 95-8. Tenets of ventilator associated lung injury.

overdistended. Above P_{max}, shear stress again leads to alveolar damage, this time termed volutrauma. Therefore, in theory, we attempt to keep tidal volumes on the most compliant part of the volume-pressure curve, above P_{flex} and below P_{max}, leading to the idea called *open-lung ventilation*. Triggered by the ARDSNet initial study, the use of low tidal volumes (6 to 8 mL/kg) with the addition of PEEP (open-lung strategy) can reduce morbidity and mortality in patients with ARDS (Fig. 95-6).[299] However, as lung injury to the normal and intermediate areas of the lungs progresses the volume-pressure curve moves to the right as the compliance of the lungs decreases, leaving a smaller therapeutic window requiring an increase in PEEP, resulting in higher mean airway pressure to maintain recruitment of areas of normal and recruitable lung (Fig. 95-7).

Lung protective strategy attempts to decrease ventilator associated lung injury by inhibiting volutrauma, barotrauma, atelectrauma, oxygen toxicity, and biotrauma (Fig. 95-8). Despite using usual control groups in the ARDSNet original study, using a low tidal volume approach of 6 to 8 mL/kg has become a standard of care. The advantages of PEEP as a distending pressure include increase in functional residual capacity, improvement of respiratory compliance, improvement of ventilation/perfusion mismatch, redistribution of lung water/edema. PEEP ultimately improves arterial oxygenation. The use of low tidal volumes has been consistent across multiple recent trials, but the selection of PEEP in these trials has been highly variable. Animal models have shown that setting PEEP just above P_{flex} minimizes lung injury and inflammation.[300] It can be difficult to determine the critical opening pressure of alveoli clinically. Therefore, most clinicians initially use a minimal distension strategy by setting PEEP between 5 and 9 cm H_2O, as lung injury progresses and hypoxemia worsens, PEEP may be increased to increase mean plateau pressures and aid in recruitment. These strategies generally recommend keeping mean plateau pressure less than 30 to 35 cm H_2O. These strategies have yet to show a decrease in mortality, but have shown improvement in secondary outcomes.[301] More precise methods of determining optimal PEEP in patients with ARDS, include titration using dynamic compliance or static pressure-volume loops to identifying the critical opening pressure. Other methods to determine optimal PEEP in a patient with ARDS include titration with dynamic compliance or static pressure-volume curve. It is important to remember that as PEEP is increased and lung is recruited, intrathoracic pressure is also increased and may inhibit cardiac output by reducing venous return. Therefore, despite an improvement in oxygenation, oxygen delivery to vital organs may be compromised.

PLATEAU AIRWAY PRESSURES

Sustained plateau airway pressures greater than 35 cm H_2O can lead to barotrauma: pneumothorax, pneumomediastinum, and subcutaneous emphysema. In an attempt to limit barotrauma, $Paco_2$ is allowed to increase in the face of inadequate minute ventilation. This permissible hypercapnia can be used as long as the patient tolerates the acidosis and is able to buffer with the renal retention of HCO_3 and there are no contraindications from coexisting disease.

PARTIAL VENTILATORY SUPPORT

By avoiding neuromuscular blockade and paralysis of the muscles of the diaphragm, spontaneous ventilation can occur during mechanical ventilation. Partial ventilatory support can lead to improved alveolar recruitment and ventilation/perfusion ratio (V/Q) mismatch, improved venous return and cardiac output, and enhanced weaning from mechanical ventilation. Avoidance of neuromuscular blockade can also lead to decreased needs for sedation.

ADJUVANT THERAPIES FOR ACUTE RESPIRATORY DISTRESS SYNDROME

Prone Positioning

Prone positioning can improve oxygenation in patients with ARDS, and it has been applied safely in pediatric patients (see also Chapter 41). Prone positioning improves lung recruitment in select patients. Patient selection and duration of prone positioning is unclear; however, it is likely that a subgroup of patients responds to prone positioning early after lung injury, and immediate responders may benefit from a prolonged prone positioning.[302] In adults Guerin and colleagues[303] performed a multicenter prospective randomized control trial of patients with severe ARDS (PROSEVA) which showed that early administration of prone positioning (after stabilization of 12 to 24 hours) sessions for several hours per day (16 consecutive hours) for up to 28 days significantly decreased 28- and 90-day mortality.[303] While prone positioning improves oxygenation, a change in mortality has not been shown in pediatrics. In pediatric patients with brain injury and worsening hypoxemia, prone positioning can be attempted with careful monitoring of ICP.[304,305]

Surfactant Therapy

Exogenous surfactant therapy is the standard of care in neonates suffering from respiratory distress syndrome (RDS); however, the utility of surfactant therapy in the treatment of ALI and ARDS is uncertain. An immediate improvement in oxygenation and a trend toward improved survival occurred with exogenous surfactant therapy, calfactant; however, in a recent randomized control trial, Willson and coworkers[306] found that surfactant did not improve outcomes relative to placebo administration.[306] Clinicians still feel that there may be a specific pediatric patient population (i.e., near drowning victims) that may benefit from exogenous surfactant administration, and research is being performed to determine patient selection, timing, and the combinations with other therapies for treatment of ALI/ARDS.

Nitric Oxide

Inhaled nitric oxide (iNO) acts as a selective pulmonary vasodilator to improve V/Q mismatch, decrease pulmonary hypertension, and reduce right ventricular cardiac work (see also Chapter 104). NO upregulates cGMP, ultimately resulting in smooth muscle relaxation and pulmonary arteriolar vasodilatation. iNO is delivered directly to ventilated lung units and improves perfusion in these areas of lung without significant effects on the rest of the pulmonary vascular bed, thereby improving V/Q mismatch and oxygenation in patients with ARDS. Much like prone positioning and surfactant therapy, NO can result in transient improvements in oxygenation. A systemic review and meta-analysis performed by Adhikari and coworkers[306a] reveals that iNO does not reduce mortality in adult patients with ARDS, regardless of severity of illness. In pediatrics, a small, randomized trial by Bronicki and colleagues showed that pediatric patients with ARDS randomized to receive iNO had significantly improved survival, ECMO free survival, and ventilator-free days at 28 days. This trial was small, but it encourages further study in the pediatric population and continues to be the main adjuvant therapy at many major pediatric centers (Bronicki and colleagues, manuscript in preparation).

Extracorporeal Membrane Oxygenation

ECMO remains a rescue strategy for pediatric patients with ARDS who fail to respond to advanced modes of mechanical ventilation. Brodie and associates[307] suggest that in adults with ARDS, ECMO criteria: (1) should be considered when P/F ratio is less than 150, (2) are indicated when P/F ratio is less than 80, (3) should be considered if $Paco_2$ is greater than 80 mm Hg, and (4) should be considered if the end-expiratory plateau pressure is greater than 30 cm H_2O.[307] The CESAR Trial in adults demonstrated improved outcomes in adults treated with ECMO; however, this trial had significant methodological flaws.[308] Currently, there is an ongoing trial in adults that randomizes patients to ECMO or standardized ventilation protocols: ECMO to rescue lung injury in severe ARDS (EOLIA; clinicaltrials.gov identifier: NCT01470703).[309] It is unclear at this time whether ECMO improves outcomes in pediatric patients with ARDS; however, with the increasing use of bicaval dual lumen venovenous cannulas, research is underway to define patient population, timing, and adjuvant therapies.[310]

ADJUNCTIVE PHARMACOLOGIC THERAPY: SEDATIVES AND ANALGESICS

Sedation is often required to help conscious children cooperate with mechanical ventilation. The amount of sedation required depends on the child's age, size, underlying disease, and amount of respiratory support needed. Some infants are sufficiently depressed and require no sedation. Sedation allows patients to breathe "in phase" with the ventilator, which reduces the peak airway pressure and eliminates coughing and straining, all of which can cause

pulmonary gas leaks. A continuous infusion of fentanyl (1 to 2 μg/kg/hr) provides pain relief and sedation. However, the infusion rate of fentanyl on subsequent days may need to be increased to maintain the same level of sedation.[94] Other drugs, such as lorazepam (0.1 to 0.2 mg/kg administered intravenously every 4 to 6 hours) or an infusion of midazolam (0.05 to 0.2 mg/kg/hr), can be useful adjuncts to opioid administration. These drugs usually have minimal cardiovascular effects if intravascular volume is adequate.[95] However, administering lorazepam to premature neonates for several days can cause steroid-responsive hypotension because of buildup of drug in the body. The half-life of lorazepam is approximately 72 hours in premature infants. Giving the drug every 4 to 6 hours causes accumulation of the drug in blood and tissues.

Neuromuscular blocking drugs (see also Chapter 34) increase chest wall compliance, reduce oxygen consumption,[311] and facilitate mechanical ventilation. If neuromuscular blocking drugs are used, they should be administered in conjunction with medications that cause amnesia and anxiolysis and control pain.

Pancuronium and vecuronium are the most commonly administered muscle relaxants used in the PICU. The usual dose of pancuronium is 0.1 mg/kg administered intravenously every 1 to 2 hours or 40 to 100 μg/kg/hr as an infusion. The tachycardia associated with pancuronium is an undesired side effect in adults, but it is generally desirable in infants and children because it helps to maintain cardiac output. Vecuronium (0.08 to 0.2 mg/kg, followed by an infusion of 60 to 150 μg/kg/hr) produces less tachycardia than pancuronium does. Cisatracurium (0.1 to 0.2 mg/kg followed by an infusion of 60 to 120 μg/kg/hr) is often useful because its elimination is not dependent on renal or hepatic function. If these drugs are given for more than 1 day, provision of regular drug holidays should be considered to avoid serum buildup of the drug and prolonged paralysis.

WEANING FROM MECHANICAL VENTILATION

The pediatric literature falls behind adult publications in regard to guidance in tracheal extubation and weaning from mechanical ventilation. A 2009 review by Newth and associates[312] addressed what was known at the time. Attempts have been made to develop predictive indices identifying which children can be successfully weaned from mechanical ventilation. Most of the indices are used in research but do have clinical applications, such as the Rapid Shallow Breathing Index (RSBI) from Yang and Tobin.[313] The RSBI is equal to the respiratory rate/tidal volume ratio. When patients are breathing comfortably, they have a slower respiratory rate with larger tidal volumes. In this circumstance, the RSBI is a low number. Furthermore, patients with respiratory distress tend to breathe more rapidly with smaller tidal volumes, hence a higher RSBI. There are several different techniques for weaning from mechanical ventilation. These techniques include slowing the set ventilator rate over time, performing a daily spontaneous breathing trial, or increasing pressure support or CPAP sprints.[314] The ideal mechanism of weaning is not yet clear, but weaning protocols will likely reduce time on mechanical ventilation.[315] Currently, the best solution seems to be to ask on a daily basis whether the patient is able to be extubated tracheally. More frequent evaluation leads to detecting more patients who are ready for extubation.[316]

However, there is an anticipated extubation failure rate. If mechanical ventilation is continued until we are absolutely certain a patient will not fail, many patients will be ventilated longer than necessary. A 2003 review[317] of 16 ICUs showed an extubation failure rate of 6.2% (range, 1.5% to 8.8%) for patients requiring mechanical ventilation longer than 48 hours. Many hospitals are initiating daily spontaneous breathing trials (SBTs) for their patients. These are periods of decreased ventilatory support while the patient is observed for evidence of respiratory distress. The decreased support can be pressure support, CPAP, or T-piece ventilation. Patients are observed to see that there is no significant increase in respiratory rate, decrease in saturations, diaphoresis, hemodynamic compromise, or evidence of increased work of breathing. The successful completion of an SBT will initiate plans for extubation. Depending on the ICU, SBTs are performed under direction of the physicians, or they can be performed independently by the respiratory therapist.

Regarding the degree of decreased ventilatory support during an SBT, the use of CPAP does not put patients under increased stress. The work of Manczur and associates,[318] Willis and associates,[256] and Hammer and associates[319] demonstrate that infants or children with smaller ETTs are not "breathing through a straw" when administered by CPAP or T-piece. Relative to an adult, the ETT may be smaller in diameter, but it is also shorter and the inspiratory flow rate in infants is low compared to an adult. Flow rates are measured to be approximately 0.5 L/kg/min.[320] Therefore, a 3-kg infant has a flow velocity of 1.5 L/min, and a 60-kg adult has a flow velocity of 30 L/min. If patients are unable to successfully complete the SBT, then it is possible that they would not manage the work of breathing after extubation of the trachea.

Overall, the criteria for extubation readiness include intact airway reflexes, hemodynamic stability, manageable secretions, and an appropriate level of alertness. The amount of negative inspiratory force (NIF) the patient can generate can be measured. NIF should be measured with a calibrated manometer and inspiration from residual volume. Typically, NIF of –30 or greater is associated with extubation success. The presence of a leak around the ETT may be supportive of extubation; however, there is research showing the absence of a leak around the ETT does not predict extubation failure.[321,322] Extubation failure is typically defined as reintubation less than 24 hours after a scheduled extubation attempt. Extubation failure can be caused by a multitude of reasons, but a large category is postextubation upper airway obstruction. In a 2003 study,[317] upper airway obstruction was the stated cause of extubation failure in 37% of patients. Unfortunately, there is significant interobserver variability[267] in the clinical assessment of upper airway obstruction that may be limiting research. Objective measures of airway obstruction may be necessary before there is a definitive answer as to which therapies reduce subglottic narrowing and reduce obstruction.

RESPIRATORY DISORDERS

Laryngotracheobronchitis (Croup)

Croup occurs most frequently in the 3-month-old to 3-year-old age group. Croup is a viral infection (parainfluenza, influenza, adenovirus) that causes edema of the tissues in the upper airway, particularly in the immediate subglottic region. There is usually a history of a few days of upper respiratory tract infection symptoms followed by hoarseness, a croupy cough, and possibly stridor. The degree of respiratory distress and the child's ability to compensate for the increased work of breathing are best assessed clinically. These patients are initially treated with mist and aerosolized racemic epinephrine to reduce swelling of upper airway mucosa.[323] Steroid administration is common yet controversial.[77] Tracheal intubation is required when the child can no longer sustain the increased work of breathing and CO_2 increases. When the trachea is intubated, the ETT should be 0.5 to 1.0 mm smaller than usual for age. The ETT must be of sufficient size that the patient can breathe easily during spontaneous ventilation and the nurses can effectively suction secretions from the airways. Croup usually resolves spontaneously in 3 to 7 days. The average duration of tracheal intubation is approximately 5 days. Laryngotracheobronchitis is less common in children older than 4 years.

Epiglottitis

Epiglottitis is an inflammation of the mucosa of the supraglottic structures that was previously caused by *Haemophilus influenzae* type B, but is now commonly caused by *Staphylococcus aureus* and streptococcal organisms because immunization against the *Haemophilus* organism has been so effective. In the past, epiglottitis was a disease of 4- to 6-year-old children. Now, it occurs more commonly at older ages (even in adults).[324] In young children, epiglottitis is a true airway emergency because it can progress rapidly to complete and fatal airway obstruction. Providing a secure airway is the first priority. Children with epiglottitis appear toxic and have a fulminant onset of fever and respiratory distress. Tracheal intubation is commonly required until antibiotic therapy (ampicillin and chloramphenicol or ceftriaxone) is initiated and the signs of systemic toxicity subside. Introduction of the *H. influenzae* vaccine has dramatically decreased the incidence of *H. influenzae* infection, as well as that of other *H. influenzae* processes.[111]

Bronchiolitis

Bronchiolitis is an acute viral infection of the lower respiratory tract that occurs primarily during the first 2 years of life. The signs and symptoms of this malady are air trapping, wheezing, mild to moderate systemic hypoxemia, increased work of breathing, and increased airway resistance. The cause is usually an infection with respiratory syncytial virus (RSV).[325] Patients at high risk for respiratory failure from this disease include infants and young children with a history of prematurity, chronic lung disease, or congenital heart disease. Apnea is frequently the first sign of decompensation in neonates, which often occurs before significant hypercapnia appears. Fatigue is a common indication for mechanical ventilation. Treatment is primarily supportive and includes endotracheal intubation and mechanical ventilation for respiratory failure.[326] Palivizumab (Synagis [MedImmune, Gaithersburg, MD] is a monoclonal antibody administered to patients at risk for seasonal RSV disease (premature infants, infants with congenital heart disease, immunosuppressed patients, or those with multiple congenital anomalies); it has dramatically decreased the incidence of illness in this population. Ribavirin is a virostatic drug available for the treatment of children with RSV and congenital heart disease, immunosuppressive disease, or multiple congenital anomalies.

Cystic Fibrosis

Cystic fibrosis is a fatal autosomal recessive disease carried on chromosome 7. Although it affects the pancreatic, hepatic, pulmonary, GI tract, and reproductive systems, 90% of the reported morbidity and mortality is pulmonary. The pulmonary pathology consists of severe airway obstruction, bronchiectasis, emphysema, and terminal respiratory failure.

Survival of patients with cystic fibrosis has improved dramatically over the past 30 years. More than one third of patients survive to older than 30 years of age.[123] This change is the result of improved antibiotic therapy, nutritional support, and aggressive treatment of complications. Lung transplantation has been performed in patients with chronic respiratory failure with varied success.[327,328]

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia is a form of chronic lung disease that occurs in patients who have survived severe neonatal lung disease. The cause of this disease is uncertain, but usually patients were born premature, had hyaline membrane disease, and required prolonged and aggressive respiratory support with high inflating and distending pressure and high oxygen concentrations. Inflammation appears to be an important component of this disease.[329] Children with BPD have decreased dynamic compliance, increased airway resistance, increased physiologic dead space, and markedly increased work of breathing. The lungs are hyperinflated, and there are intercostal retractions, nasal flaring, and wheezing. Chest radiographs demonstrate large lung volumes and fibrosis as well as cystic and atelectatic areas. Hypercapnia and hypoxia are present to varying degrees.[330,331] Therapy for BPD includes providing sufficient calories to meet the higher energy expenditure required for the increased work of breathing. Respiratory support (mechanical ventilation, CPAP) is required for some patients. Diuretics and bronchodilators are frequently used and may be associated with electrolyte abnormalities. Most long-term survivors have subjectively normal pulmonary function; however, some survivors have severe chronic physiologic changes.[332,333] During the first years of life, viral or bacterial pulmonary infections often increase the need for respiratory support; these infections may prove to be fatal. Great effort is being made to prevent BPD. Because the trauma of mechanical ventilation on an immature lung is thought to be the major cause of BPD, alternative

modes of ventilatory support are being evaluated, including exogenous surfactant, high-frequency ventilation (especially HFOV),[334] ECMO, and liquid ventilation.[330,335]

Sleep Apnea

Normal ventilation during sleep requires normal upper airway anatomy and normal intact reflexes. The latter include central responses to hypercapnia and hypoxia, response to airway irritation, and dynamic phasic contraction of the pharyngeal and hypopharyngeal muscles. Sleep apnea usually occurs when one or more of these protective responses are abnormal. In infancy, sleep apnea is relatively common. Numerous causes have been postulated, the most attractive of which is immaturity of the medullary chemoreceptors. Patients with Ondine's curse, the most severe form of central apnea, have complete apnea when asleep. Lesser breathing disorders may be present during sleep in patients with sudden infant death syndrome. Treatment of sleep apnea consists of respiratory stimulants (theophylline), cardiorespiratory monitoring during sleep, and in some severe cases, tracheotomy and nighttime mechanical ventilation.[132] Obstructive sleep apnea occurs in all pediatric age groups. It may be associated with an identifiable anatomic disorder, such as enlarged tonsils and adenoids, Pierre Robin syndrome, and tracheal and laryngeal malacia. Signs and symptoms of obstructive sleep apnea include loud snoring, obstructive episodes with frequent arousal, behavior disorders caused by sleep deprivation, and cor pulmonale. The diagnosis is made with the history, electrocardiogram, and formal sleep studies. Bronchoscopy can also be helpful in defining the problem. In young children, an enlarged liver might suggest that the child has pulmonary hypertension. Treatment of sleep apnea includes removal or bypass of an obstruction. Although tonsillectomy and adenoidectomy can improve the airway, there may still be significant airway obstruction for the first few days after surgery. Tracheostomy is rarely required in these children.

Foreign Body Aspiration

Foreign body aspiration is a relatively common and often catastrophic event in children. Although it can occur at any age, the peak incidence of foreign body aspiration occurs at 6 months to 3 years of age. Vegetable matter (e.g., peanuts), other foodstuff (e.g., hot dogs), coins, and small pieces of toys are the most commonly aspirated material. Many of these objects are radiolucent. The symptoms of aspiration are related to the location of the foreign body within the airway and the time since the object was aspirated. Acute symptoms can include total airway obstruction, stridor, wheezing, or acute onset of coughing. Chronic symptoms include bloody sputum and chronic cough. Wheezing can occur as a chronic symptom as well as acute. The diagnosis of a foreign body in the airway is made from the history and physical examination and, in some cases, by radiologic imaging. The efficacy and safety of abdominal thrusts have been questioned. The Heimlich maneuver and back slaps are reserved for acute upper airway obstruction with no air movement. Treatment of less acute or lower airway foreign body aspiration includes bronchoscopy, postural drainage, chest physical therapy, bronchodilators, and surgical removal of the object.[336]

Upper Airway Obstruction and Meningomyelocele

Vocal cord paralysis is a common result of several disorders, including brainstem abnormalities and myelodysplasia. Children with meningomyelocele usually have an Arnold-Chiari malformation and may have stridor. This lesion allows caudal displacement of the medulla, stretching of the cranial nerve tracts, and abnormal arterial architecture of the brainstem. Vocal cord paralysis can result from pressure on the brainstem (i.e., with hydrocephalus) or from focal infarcts of the brainstem. Treatment of these brainstem abnormalities includes relief of the hydrocephalus and, if the paralysis persists, cervical decompression of the Arnold-Chiari lesion. Despite these surgical procedures, some children require a tracheotomy and long-term mechanical ventilation.

ASTHMA

The prevalence of childhood asthma is increasing over time. Estimates from the Centers for Disease Control and Prevention placed the percentage of children with asthma at 3.6% in 1980, 5.8% in 2003, and 9.5% in 2011 (www.cdc.gov/nchs/fastats/asthma.htm). Thankfully, the majority of children with asthma will never require intensive care. However, for the children who do, there can be significant morbidity and a risk of mortality. In a 2012 study by Newth and associates[337] of fatal and near-fatal asthma in an ICU setting, 12% of patients had complications and the mortality was 4%. Cardiac arrest before admission occurred in 10 of the 11 patients who died. For the purposes of this section, *critical asthma* is defined as an asthma exacerbation requiring ICU admission.

Asthma is a disease of inflammation. There is infiltration of the submucosal area of the airways with mast cells, eosinophils, and CD4 lymphocytes. Degranulation of mast cells releases leukotrienes and histamine (causing edema), increases in mucus production, and chemotaxis of white blood cells. Multiple factors can trigger asthma attacks and degranulations of mast cells. Such factors include allergens, infections (viral more than bacterial), changes in the weather, and strong emotions. Inflammation increases irritability of the airway as well as airway hyperresponsiveness. The airway lumen is decreased by spasm of the bronchial muscles, edema and mucus. Decreases in the airway lumen significantly increase airway resistance. For laminar airflow, airway resistance is related to the third power of the radius, but with turbulent airflow it is related to the fourth power. Because of the smaller lumen of their airways, children experience much greater changes in airway resistance during asthma attacks than adults do. Because of resistance in exhalation, an expiratory wheeze is typically noted. Bronchospasm, edema, or mucus plugging can lead to complete obstruction of small airways. Hypoxemia occurs because of a mismatch in ventilation and perfusion. Airway dead space is increased by obstruction of the airways. To maintain ventilation, the respiratory rate is typically increased. In turn, the initial $Paco_2$ is usually low. Respiratory fatigue or impending failure may be identified by a normal or elevated $Paco_2$.

Asthma can occur without wheezing, which is the sound that is produced when there is obstruction to airflow. Wheezing can be caused by pneumonia, upper airway obstruction, foreign body aspiration, or CHF and each requires different therapy. A sudden onset of wheezing in a toddler should prompt evaluation for foreign body aspiration. The history should be addressed for recent choking or coughing episodes. Even the presence of a history of reactive airways or atopy does not rule out aspiration. A high index of suspicion should be maintained. Intermittently a chest radiograph obtained for a child who is wheezing shows cardiomegaly rather than peribronchial cuffing. Asthma is statistically more likely, but this can be the presentation of heart failure. A chest radiograph is warranted for any patient with their first presentation of wheezing, and certainly for any child who is admitted to the ICU for wheezing. Severe asthma exacerbations can occur without wheezing, as the movement of air is required to hear wheezing. It is possible for a patient to have significant airflow restrictions that do not produce audible wheezing. Patients with a quiet chest or limited airflow on auscultation require immediate action.

Children with an asthma exacerbation may have a few days of upper respiratory infection symptoms followed by increased work of breathing. The patient may have low room air oxygen saturations. The patient's position of comfort may be sitting up to support their muscles of respiration. Accessory muscle use is noted. There is a prolonged expiratory phase on auscultation. In an effort to increase airway pressure, some children may be breathing out with pursed lips, or grunting may be noted in smaller children. The child might not be able to speak more than one- or two-word phrases. Therapy should be started immediately, first with supplemental oxygen to address hypoxemia. If the child is in mild respiratory distress, nasal cannula oxygen may be sufficient. If the child has moderate or severe respiratory distress, oxygen should be delivered by either facemask or nonrebreather facemask. Inhaled β-agonists, such as albuterol, are given to relax bronchial smooth muscles. Intravenous or subcutaneous terbutaline or epinephrine may be required if there is not enough air movement to deliver inhaled medications. Steroids should be given early because their effect will take some time. If there is limited improvement with initial therapy, arrangements should be made for ICU admission. Many emergency departments will attempt to obtain ABGs; however, the clinical picture alone may provide enough information to guide therapy.

Asthma Therapy

Supplemental Oxygen. Oxygen can be delivered with a standard nasal cannula, but the fraction of inspired oxygen (Fio_2) is limited. Standard nasal cannula might provide up to 40% Fio_2. Increasing the flow of oxygen with a standard cannula larger than 4 to 5 L/min is not usually tolerated. A simple facemask might increase the Fio_2 to 50%. A tightly sealed nonrebreather facemasks might be able to provide Fio_2 closer to 1. Providing oxygen with a high-flow humidified nasal cannula (HFHNC) may provide nearly complete humidification of the airway gases and the Fio_2 also approaches 1. A study in 2014 by Rubin and associates[259] demonstrated a decrease in effort of breathing in patients receiving HFHNC. The mechanism of its effect is not elucidated. Some clinicians have begun using HFHNC as a mechanism for delivery of β-agonists or other aerosolized medications, but there are no data to support its use.

Inhaled β-Agonists. Inhaled β-agonists are used to relax bronchial smooth muscles. The most commonly used β-agonists is albuterol, which is a racemic mixture of the active R and inactive S enantiomer. Levalbuterol, the active R enantiomer, is available as a separate preparation, but recent studies have not shown it to be more effective[338] or to have less elevations in heart rate.[339] Albuterol is β_2 selective and comes as a metered-dose inhaler or solution for nebulization. For initial therapy in the ICU, continuous albuterol is preferred, and the usual dose is 0.15 to 0.5 mg/kg/hr or 10 to 20 mg/hr. After improvement in air movement with decreased respiratory distress, intermittent doses can be given every 1 to 2 hours. Terbutaline as an inhaled medication is less β_2 selective compared with albuterol and therefore is used less commonly. Terbutaline remains as an important intravenous medication. Tachycardia is commonly associated with albuterol use. At times, it is unclear whether the elevated heart rate is related to toxicity of medications or to ongoing respiratory distress. Arrhythmias may be seen with albuterol use, but this is usually just an increased frequency of premature ventricular contractions. Diastolic hypotension is observed with larger doses of albuterol, although this can be related to decreased intravascular volume and increased intrathoracic pressure. Agitation and tremors can be seen with CNS stimulation. Hypokalemia may be noted as the β-adrenergic agonists drive potassium into cells. Ipratropium bromide, an inhaled anticholinergic, is sometimes paired with intermittent albuterol doses. Ipratropium bromide has the benefit of promoting bronchodilation without decreasing mucociliary clearance.

Corticosteroids. Intravenous steroids are preferred to oral dosing in the ICU because of the possibility of decreased absorption or delayed onset. Methylprednisolone is commonly used because of its limited mineralocorticoid effects. The initial dose is 2 mg/kg and then 0.5 to 1 mg/kg every 6 hours. There may be regional preference for dexamethasone or hydrocortisone. Steroids are typically given for the duration of the acute asthma phase. If steroids are given for 5 days or less, they are not usually tapered. Systemic steroid use is associated with hyperglycemia, hypertension, and occasional agitation. During initial ICU care, inhaled steroids are of no benefit.

Intravenous Fluids. Children admitted to the ICU with critical asthma will likely be dehydrated from limited oral intake during their illness and increased insensible losses from the higher respiratory rate. The patient's circulating volume should be supported with fluid boluses if needed. However, excessive fluids should be avoided, because this could lead to pulmonary edema. Pulmonary edema could worsen both oxygenation and airway resistance. Fluid boluses may also be needed for children whose respiratory distress progresses require mechanical ventilation. Hypotension often occurs during intubation of the trachea.

Intravenous and Subcutaneous β-adrenergic Agonists. A significant decrease in air exchange can result in poor delivery of inhaled medications, and intravenous β-agonists may be required. Terbutaline is often the first choice and relatively β_2 selective as compared to isoproterenol and epinephrine. Terbutaline can be given subcutaneously for children without intravenous access as a dose of 0.01 mg/kg up to a maximum of 0.3 mg. Intravenous terbutaline at a dose of 10 μg/kg over 10 to 20 minutes is followed by a continuous infusion of terbutaline in a range of 0.1 to 10 μg/kg/min. The infusion can be titrated to effect. Subcutaneous epinephrine may be given for severe asthma exacerbation with limited intravenous access with a dose of 0.01 mg/kg of to the 1:1000 solution with a maximum dose of 0.5 mg. Absorption of the drug may be limited by poor perfusion to extremities. Intravenous epinephrine may be an ideal drug for mechanically ventilated patients with hypotension. The use of isoproterenol in critical asthma has decreased over time.

Methylxanthines. There is regional variation in the use of the methylxanthine aminophylline in place of intravenous terbutaline as a second line drug for critical asthma. Fewer children with asthma are admitted to the ICU with methylxanthine as a chronic medication. There are improved controller medications including the leukotriene inhibitors; therefore, fewer children are receiving oral theophylline. The methylxanthines promote bronchial smooth muscle relaxation, but the exact mechanism of action is not known. Intravenous aminophylline is loaded at a dose of 5 to 7 mg/kg over 30 minutes followed by a continuous infusion in the range of 0.5 to 0.9 mg/kg/hr. If the patient has taken oral theophylline in the past 24 hours, the loading dose is reduced by 50% or the aminophylline dosing is adjusted based on a serum theophylline level. In general, an aminophylline loading dose of 1 mg/kg will raise the serum theophylline level by 2 μg/mL. The target range for serum theophylline in acute asthma is 10 to 20 μg/mL. Theophylline has a very narrow therapeutic window. Theophylline levels higher than 20 μg/mL are associated with nausea, tachycardia, restlessness, or irritability. Higher theophylline levels can cause seizure activity.

Magnesium. Magnesium can be given as an inhaled or intravenous medication to relax bronchial muscles. Smooth muscle relaxation occurs because of magnesium's effect as a calcium channel blocker. Results from the 2013 Magnesium Trial in Children[340] indicate nebulized magnesium may be beneficial in an acute severe asthma exacerbation. Intravenous magnesium may also be beneficial in severe asthma.[341,342] As there is still regional variation to magnesium, at the least a magnesium level should be checked with the initial set of electrolytes, and hypomagnesemia should be treated. The dose for critical asthma and hypomagnesemia can be the same 25 to 45 mg/kg given over 30 minutes. Magnesium toxicity can include muscle weakness, cardiac arrhythmias, decreased reflexes, and respiratory depression.

Helium. Mixtures of helium and oxygen (heliox) can be used to improve laminar gas flow. This occurs because of the decreased density of helium as compared with nitrogen (approximately 1/7). For helium to be beneficial in small airways, it must occur in a high ratio with oxygen. The most benefit may be seen with an 80:20 or 70:30 ratio of helium to oxygen; therefore, hypoxemia and the need for increased supplemental oxygen may limit heliox use. Heliox can be used to deliver inhaled β_2 agonists.[343] As with other advanced therapy, helium might not have a role in routine care, but there may be benefit from its use in severe critical asthma.

Ketamine. Ketamine is a noncompetitive *N*-methyl-D-aspartate receptor antagonist that can produce a state of dissociative anesthesia. An additional effect of ketamine is bronchodilation; it is a useful medication for sedation in the ICU because it has a limited effect on the respiratory drive. In usual doses, hemodynamics are not usually affected. For patients with asthma whose tracheas are intubated and mechanically ventilated, ketamine may be a good choice for sedation along with a benzodiazepine. Furthermore, one pediatric study[344] showed an improvement in the PaO_2/FiO_2 ratio as well as dynamic compliance in mechanically ventilated children with refractory bronchospasm who were receiving a continuous infusion of ketamine. There has been no study to show whether ketamine used to treat anxiety is beneficial in preventing intubation in patients during an asthma attack. For nontracheally intubated patients, a recent Cochrane Database Review[345] did not show significant benefit in severe acute asthma. If a decision is made to use ketamine for a procedure or a means of sedation, the bolus dose is usually 1 mg/kg, allowing time for effect before repeating. Ketamine is given as a continuous infusion at the dose of 5 to 30 μg/kg/min titrated to effect. One of the additional side effects of ketamine can be dysphoria, and as such, it is usually given with a benzodiazepine.

Noninvasive Ventilation. There is limited evidence that noninvasive ventilation is effective in children with asthma.[272] Clinically, patients with effective air exchange and who fight the mask and positive pressure do not benefit from noninvasive ventilation. Nevertheless, some children with limited air exchange and fatigue take to noninvasive ventilation easily and appear more comfortable. Noninvasive ventilation can allow time for therapies to become effective (steroids) and can reduce the need for intubation. It should not be used when the level of alertness or ability to protect the airway is diminished.

Intubation of the Trachea. By the time patients with asthma require endotracheal intubation and mechanical ventilation, they are hypoxemic, acidotic, and fatigued, and they have limited reserve. The most experienced person available should perform the intubation of the trachea procedure. Appropriate venous access is required and intravenously administered fluid boluses may be necessary. Ketamine and a benzodiazepine can be used. Ketamine can produce increased secretions; therefore, atropine should be considered. Ketamine can also produce dysphoria; therefore, the benzodiazepine is given for its amnestic effects. The management style in the authors' ICU is to get the patient back to breathing spontaneously

or initiating their own breathing as soon as possible after intubation. In turn, rocuronium can be considered as a medium short-acting muscle relaxant. Succinylcholine can be used, but the other side effects of this medication, including hyperkalemia, should be considered. A cuffed ETT is recommended because ventilator settings may require high peak pressures. Immediately after intubation, adequate ventilation should be achieved with a slow respiratory rate to prevent alveolar overdistention and to reduce the risk of pneumothorax. There can be acute decompensation following intubation. Hypovolemia and increased intrathoracic pressures may be an issue. Following the DOPE acronym, one should also look for *displacement* or *obstruction* of the endotracheal tube and rule out *pneumothorax* or *equipment* failure.

Mechanical Ventilation (Also see Chapter 103). There can be controversy regarding the best means for mechanical ventilation for patients with asthma (see also Chapter 103). The argument against setting the ventilator in a pressure control mode is that changes in airway resistance that occur with asthma can result in delivery of an inadequate tidal volume. The argument against the ventilator in a volume control mode is that due to flow patterns of the ventilator the same tidal volume can be delivered with a higher peak pressure as compared to a pressure control mode. As stated previously, the authors' management style is to get intubated asthmatics breathing spontaneously as soon as possible. This allows them to set their own breathing rate, and on pressure support and PEEP they can set their own inspiratory-to-expiratory ratio. Pressure support has been recommended because it is patient initiated, even if not patient limited.[346] There may be initial elevations in $Paco_2$, but the carbon dioxide elevation is usually will tolerated if the patient is well oxygenated.

Historically, clinicians set zero or low PEEP for intubated asthmatics because of the perceived risk of hyperinflation[347] and barotrauma. However, since 1988 there have been four adult studies[348-351] and one pediatric study[257] strongly suggesting the benefits of extrinsic PEEP during mechanical ventilation for intubated asthmatics. These studies demonstrated that extrinsic PEEP, up to a level to matching intrinsic PEEP, improves the triggering sensitivity of the ventilator, diminishes ventilatory work, and reduces mechanical work of breathing for patients spontaneously breathing with assisted ventilation. As the work of breathing is reduced, there is improved patient comfort and potentially a reduced need for sedation. Matching extrinsic PEEP applied with the ventilator to the intrinsic PEEP developed by the patient with asthma may improve delivery of aerosol therapy via the ETT. Matching PEEP can possibly result in earlier liberation from mechanical ventilation. It should be noted that some clinicians believe that attempts to match PEEP may include the risk that extrinsic PEEP will cause overdistention of the lungs. Overdistention of the lungs can increase the risk of hyperinflation and air leak syndrome.[347] Spontaneous breathing with pressure support and PEEP lowers WOB.[256,257] For the individual patient, the level of extrinsic PEEP at which hyperinflation will occur is unknown. Theoretically, for the spontaneously breathing patient, extrinsic PEEP applied to counteract intrinsic PEEP should not cause an increase in end-expiratory lung volume until extrinsic PEEP exceeds intrinsic PEEP.[352] Furthermore, the end-expiratory lung volume can even decrease, leading to decreased dead space and increased compliance. In the authors' ICU, intrinsic PEEP is measured during a ventilator pause, allowing the patient to exhale completely and measuring the pressure before the next breath. Extrinsic PEEP is added gradually with the ventilator, and respiratory rate and clinical work of breathing are observed. Extrinsic PEEP is maintained at a level below intrinsic PEEP, extrinsic and intrinsic PEEP are reassessed continually as the patient responds to therapy. Further research is needed to determine the best practice of mechanical ventilation for intubated asthmatics, but this is limited by the small number requiring intubation each year.

Inhaled Anesthetics. One of the properties of inhaled anesthetics is bronchodilation. In turn, inhaled anesthetics have been used as rescue therapy in children with critical asthma who are intubated. Isoflurane has been used in the authors' ICU for its reduction in bronchospasm with the added benefit of a decreased sedation requirement. However, inhaled anesthetics are difficult to use in an ICU setting. Modern ICU ventilators are not designed to accept a vaporizer. There is no circle system in ICU ventilators, so there is a tremendous use of anesthetic vapor. There is no primary means of gas scavenging in an ICU ventilator; therefore, significant steps must be taken to avoid contamination of the patient's room. A case series of six patients was reported by Wheeler and colleagues,[353] and Tobias[354-356] has published several articles detailing the use of inhaled anesthetics in asthma and other clinical conditions. A recent retrospective cohort study by Char and associates[357] in intubated asthmatics did not demonstrate a difference in mortality between centers that did or did not use inhaled anesthetics. There was significantly greater length of mechanical ventilation, length of stay, and hospital charges in the centers using inhaled anesthetics. The significant expertise needed to deliver inhaled anesthetics safely can limit its use to a few centers. An anesthetic-conserving device (AnaConDa; Sedana Medical, Uppsala, Sweden) is available in Europe, but not the United States. The device is a miniature vaporizer and a conserving medium or reflective filter that keeps the inhaled anesthetic on the patient side of the device. This device can be used with a normal ventilator. Finally, as the scientific community learns more about the potential neurotoxicity with inhaled anesthetics, the physician must weigh the risk-and-benefit profile of long-term inhalational anesthetics for the management of status asthmaticus.

Extracorporeal Life Support for Status Asthmaticus. Extracorporeal life support (ECLS) has been used as a rescue therapy in near fatal asthma. As with inhaled anesthetics, the use of ECLS for this indication is likely limited to a small number of centers. One single center study reports[25] their use, but the number of patients (n = 13) is too small to determine whether this therapy has advantages over mechanical ventilation or conventional therapy.

TABLE 95-7 **NORMAL AGES FOR MAJOR DEVELOPMENTAL MILESTONES**

Age	Motor Function	Language	Adaptive Behavior
4-6 wk	Lifts head from prone position and turns from side to side	Cries	Smiles
4 mo	Shows no head lag when pulled to sitting from supine position; tries to grasp large objects	Utters sounds of pleasure	Smiles, laughs aloud, and shows pleasure from familiar objects or persons
5 mo	Grasps voluntarily with both hands; plays with toes	Makes primitive sounds	Smiles at self in mirror (ah, goo)
6 mo	Grasps with one hand; rolls prone to supine; sits with support	His increased range of sounds	Expresses displeasure and food preferences
8 mo	Sits without support; transfers objects from hand to hand; rolls supine to prone	Combines syllables (baba, dada, mama)	Responds to "No"
10 mo	Sits well; crawls; stands holding; finger-thumb apposition in picking up small objects		Waves goodbye; plays patty-cake and peek-a-boo
12 mo	Stands holding; walks with support	Says two or three words with meaning	Understands names of objects; shows interest in pictures
15 mo	Walks alone	Utters several intelligible words	Requests by pointing; imitates
18 mo	Walks up and down stairs holding; removes clothes	Says many intelligible words	Carries out simple commands
2 yr	Walks up and down stairs by self; runs	Makes two- or three-word phrases	Engages in organized play; points to some parts of the body

CENTRAL NERVOUS SYSTEM

Systemic illness is a common cause of CNS dysfunction in infants and children. Seizures, head trauma, CNS infections, and hypoxic or metabolic encephalopathy commonly cause acute neurologic dysfunction in the PICU. Assessment of neurologic function depends on an understanding of the age-dependent progression of motor and cognitive skills. Table 95-7 lists the developmental milestones.

FUNCTIONAL POSTNATAL NEUROLOGIC DEVELOPMENT

Motor function in the newborn depends on gestational rather than postnatal age. That is, an infant born at 28 weeks' gestation exhibits motor responses similar to those of a full-term newborn when the former is 3 months old. Although potentially modifiable by cortical influence, most neonatal motor behavior is controlled subcortically, which permits normal motor behavior in newborns who have severe cortical damage. Assessment of intellectual development is difficult in a newborn. Initially, assessment is based on the absence of reflexes and the acquisition of new motor skills. Adaptive or interactive behavior is first seen with accommodation to repeated stimuli and eye contact. The infant's intellectual development depends on the presence of external stimulation and social interaction, preferably from one or a few individuals. This is why infants and children who require long-term intensive care must have parental input and developmental stimulus.

ASSESSMENT OF NEUROLOGIC FUNCTION

Clinical examination is the most important tool we have for assessing neurologic function in children. In an awake child, interactions with the examiner and caretakers are sensitive indicators of high or integrative cortical function. When the child's cognitive function is depressed from disease or drugs, examination of the general level of activity and peripheral and brainstem reflexes becomes an important, albeit crude, measure of CNS function. A detailed examination includes an evaluation of the level of consciousness and alertness in the context of sedative medications. The Glasgow Coma Scale (GCS; Table 95-8) is a commonly accepted tool to evaluate the level of function of neurologically impaired patients; however, it was not developed for this purpose, and extensive research needs to continue on directed scales and noninvasive means to improve assessment consciousness in critically ill children.[358] Painful stimulation can stimulate both decorticate or decerebrate posturing; these responses likely indicate significant CNS malfunction and should trigger further investigation. Decerebrate posturing is an extension at the elbows with the arms and hands pronated. Decorticate posturing of the upper extremities is flexion at the elbows with the hands clenched. These responses to painful stimuli or no response at all should (in combination with attempts to elicit a cough, gag, or ability to handle oral secretions) make the practitioner question whether the patient can protect the airway. Pupillary reflex is a well-preserved function; therefore, unreactive pupils are highly concerning. Large reactive pupils can be caused by tricyclic antidepressant ingestion, atropine administration, or a symptom of pharmacologic withdrawal. Small, reactive pupils can indicate damage at the level of the pons, but usually indicate the presence of opioids or barbiturates. Funduscopic examination is important to assess for signs of increased ICP or retinal hemorrhage; however, the bedside practitioner may have difficulty with these assessments, and an ophthalmologist consultation may be required.

LABORATORY ASSESSMENT OF NEUROLOGIC FUNCTION (ALSO SEE CHAPTER 49)

The EEG is used to diagnose seizures and isoelectric brain death and to monitor the effects of barbiturates

TABLE 95-8 **GLASGOW COMA SCALE FOR INFANTS AND CHILDREN**

Activity	Adult/Child Response	Infant Response	Score
Eye opening (E)	Spontaneous	Spontaneous	4
	To verbal stimuli	To verbal stimuli	3
	To pain	To pain	2
	None	None	1
Best verbal response (V)	Oriented, appropriate	Coos and babbles	5
	Confused conversation	Irritable cries	4
	Inappropriate words	Cries to pain	3
	Incomprehensible words	Moans to pain	2
	None	None	1
Best motor response (M)	Obeys verbal command	Normal movement	6
	Localizes stimulus	Withdraws upon touch	5
	Withdraws from noxious stimulus	Withdraws upon pain	4
	Decorticate flexion	Decorticate flexion	3
	Decerebrate extension	Decerebrate extension	2
	None (flaccid)	None (flaccid)	1

administered to induce coma (see also Chapter 49). In addition, continuous EEG monitoring is often used to detect nonconvulsive seizure activity in critically ill children.[206,359,360] This monitoring system is resource intensive but has now shown that outcomes are improved; however, its use continues to increase in neonatal and pediatric critical care, and further study is needed for this promising, noninvasive tool. Computed tomography (CT) enables rapid detection of CNS lesions, the extent of structural injury, and noninvasive assessment of ICP. Cranial ultrasound is a bedside technique used to assess ventricular size and intracranial anatomy in infants with nonfused cranial sutures. MRI permits intraorbital and ocular injuries and brainstem and spinal cord lesions to be examined; it is also good for defining soft tissue abnormalities.[361] The major drawback of MRI is the length of time required for each examination and the relative inaccessibility of the patient while inside the scanner. Maintaining body temperature can also be a problem in small children during MRI scanning because the room must be cold. It may be difficult to perform MRI safely in patients who have significant cardiorespiratory compromise, because many of the pumps and ventilators cannot enter the scanner. Doppler ultrasound allows bedside assessment of cerebral blood flow (CBF) velocity in the ICU. Although it does not directly measure CBF, Doppler ultrasound is a useful bedside guide to therapy. CBF scans are the gold standard and are usually required to diagnose brain death during barbiturate coma. ICP can be monitored by inserting a catheter into a lateral ventricle or by inserting a subarachnoid screw or transducer into the epidural space or cerebral parenchyma. The ventricular catheter provides an accurate waveform and permits withdrawal of cerebrospinal fluid (CSF) to reduce ICP. The other devices used to measure ICP provide less consistent pressure waves and do not permit removal of CSF.

TRAUMATIC BRAIN INJURY

Despite advances in resuscitation care, morbidity following pediatric traumatic brain injury (TBI) remains high (see Chapters 49 and 81). TBI is composed of two components: an initial primary injury caused by direct mechanical deformation of brain parenchyma and a subsequent secondary injury that can develop over hours to days. Secondary injury may be the result of multiple mechanisms including ischemia, excitotoxicity, metabolic failure and eventual apoptosis, cerebral swelling, axonal injury, and inflammation and regeneration.[362] For improvements in outcome to be achieved in the pediatric critical care setting, secondary brain injury must be prevented or minimized.

Conventional wisdom about TBI has dictated that ischemia plays a major role in secondary brain injury. While reversal of ischemia is crucial, simply delivering oxygen to injured areas of the brain does not abate the onslaught of secondary injury cascades destroying vulnerable areas of the brain following TBI. Recent evidence suggests that secondary injury persists despite adequate oxygen delivery to brain tissue because of persistent metabolic crisis.[363,364] Furthermore, hyperoxia is not effective in completely reversing metabolic crisis and may lead to persistent secondary injury due to superoxide and free radical generation. There is widespread heterogeneity of metabolism following TBI, with some regional areas of increased glucose and oxygen utilization (likely due to electrical instability); however, in large regions of brain oxidative metabolism is reduced to a critical threshold with critically low rates of cerebral metabolic rate of oxygen ($CMRO_2$).[365] This reduction, coupled with ongoing low cerebral blood flow following TBI, places viable brain tissue at risk.[365,366] How the neurovascular bundle regulates the delivery of blood flow to regions gripped in metabolic crisis in ongoing secondary crisis and how to manipulate cerebral blood flow remains an important avenue of study in the immature brain.

CEREBRAL PERFUSION PRESSURE AND CEREBRAL BLOOD FLOW

In children, developing effective treatments for TBI is complicated by the rapid changing responses of the immature brain to each type of brain injury during development from infancy through childhood.[367,368] Therefore, evaluation of therapies for children with brain injury must use immature animal models as a translational pathway to human trials in children. Unfortunately, most of the

principles being used have come from adult clinical studies and adult aged small animal research. How this evidence translates to the child provides some direction, but should catalyze further research focusing on the immature brain. This is especially true when the practitioner must indirectly target metabolic delivery in the face of secondary brain injury by attempting to modulate CBF and predict regulation or lack of regulation in the neurovascular bundle. Even in the healthy brain, cerebrovascular response (CVR) regulation is complex and poorly understood.[369-371] To add to this layer of complexity, CVR is likely heterogenous following brain injury dependent on the mechanisms of injury, age, and even sex. Optimal global CBF is an elusive clinical target, with a lower inflection point associated with ischemic injury and an upper inflection point associated with hyperemia increasing cerebral blood volume and ICP. In early post-traumatic brain injury cerebral, hypoperfusion can contribute greatly to secondary brain injury, ultimately increasing morbidity and mortality.[366,372] In adults, areas of contusions have low cerebral blood flow similar to the ischemic penumbral zones surrounding areas of acute ischemic stroke.[373,374] Low cerebral blood flow states have been demonstrated in children by xenon CT scans following TBI within 24 hours of the initial injury, but by 48 hours these patients had normal or supernormal blood flows.[372] Furthermore, CBF in pediatric patients as a target for neuroresuscitation is a theoretical point of manipulation because of limited options of continuous measurement in the clinical setting; therefore, CPP (Mean arterial pressure [MAP] – ICP = CPP) is a commonly used surrogate.

When cerebral autoregulation is impaired, cerebral blood flow and the metabolic needs of the injured brain may depend on maintaining adequate CPP. The difficulty comes in identifying the term *adequate*. Currently, pediatric CPP thresholds (40 to 60 mm Hg) have been extrapolated from adult experimental and clinical TBI and stroke studies.[373,375] However, recently it has been reported in adults that ischemia following TBI can occur at much higher levels of CBF compared with stroke.[373] Chambers and colleagues[376-378] have published much needed age-specific pediatric thresholds for critical CPP, below which cerebral ischemia occurs with unfavorable neurologic outcomes and increased mortality. These studies identified inadequate CPP levels but did not identify an "optimal treatment" CPP, and therefore assumed that these CPP levels were equivalent to brain injury insult thresholds.

It is not clear whether a CPP of 40 mm Hg is a minimal threshold or that an optimal CPP to prevent brain injury may be higher.[379] Using currently accepted pediatric CPP guidelines (CPP > 40 mm Hg) might not ensure adequate oxygen delivery to brain tissue.[380,381] This raises the question: is a CPP > 40 mm Hg in the pediatric TBI patient high enough? Mild induced hypertension after ischemic stroke has shown promise in animal models but remains controversial in the clinical setting.[382,383] Adult TBI studies have observed an increased risk of adult respiratory distress syndrome associated with targeting a CPP > 70 mm Hg, but it is unclear how applicable this is to pediatric neurocritical care.[384,385] A retrospective study of 146 pediatric TBI patients observed a strong association of poor outcome at discharge with hypotension within the first 6 hours of injury.[386] The window for treatment of hypoperfusion appears to be early after pediatric TBI, and may be of relatively short duration in children. It is the authors' belief that early, aggressive intervention of blood pressure support especially during early critical periods, such as initial resuscitation of a patient with multiple trauma, intubation, and placement of support lines and neuromonitoring devices, is critical to neuroresuscitation. Guidelines released in 2012, based on class III evidence for pediatric traumatic brain injury, suggest that a minimum cerebral perfusion pressure of 40 mm Hg should be maintained and that 50 mm Hg for a minimum CPP in older children may be required.[387] However, data regarding large animal models of TBI may support the use of higher CPP support (>70 mm Hg) in severe TBI.[388]

Targeting cerebral perfusion pressure often requires vasopressor support. While central venous access should not delay administration of vasopressor support, it is important to understand the risks of extravasation of these infusions and have qualified individuals place central venous access as soon as possible to mitigate these risks. Initial stabilization of the pediatric TBI patient can occur in limited resource environments where complex invasive intracranial monitoring might not be available. Early stabilization of cerebrovascular hemodynamics with phenylephrine and targeting a higher MAP or CPP can reduce brain injury and improve long-term outcomes. A common first-line vasopressor to improve MAP in pediatric brain injury is phenylephrine, an α-adrenergic agonist that could have little or no effect on cerebral vasculature resistance.[389-392] Another vasoactive medication gaining favor is norepinephrine (NE). NE primarily targets α-receptors for peripheral vasoconstriction, but has additional effects on β-receptors increasing inotropy. Now NE is viewed as a preferred vasoactive medication, and may provide more predictable CPP augmentation when compared to dopamine.[393-395] Prathep and colleagues[396] have reported that adults with isolated traumatic brain injury and cardiac dysfunction have a higher incidence of in-hospital mortality. Further research is critical to determine the degree of cardiovascular compromise following TBI in children and which vasopressor should be considered a first line agent in pediatric brain injury and currently should be determined by local experience and comfort of use. We believe that the next generation of treatments will build on the tenets of ischemic neuroresuscitation and combine early, directed metabolic neuroresuscitation.[397]

RESPIRATORY MANAGEMENT IN THE BRAIN-INJURED CHILD

Airway Management

The comatose and brain-injured patient is at severe risk for respiratory failure owing to loss of airway protective reflexes and impaired central regulation of respiratory function. In addition, progression of ALI and ARDS can be exacerbated by concomitant injuries (pulmonary contusions, aspiration, left ventricular dysfunction or failure, and inflammation owing to systemic inflammation following trauma or infection) and treatments to improve cerebral perfusion (e.g., crystalloid administration, hyperchloremic

metabolic acidosis, hypernatremia, and vasopressor therapy). It is critical that the physician caring for these patients have a neuroprotective plan in place for induction of anesthesia and intubation of the trachea, in addition to adequate training and skill to obtain an artificial airway. The physician also needs to be adept at ongoing neuroresuscitation in the face of progressive lung disease and hemodynamic instability from systemic inflammatory response syndrome and increasing mean airway pressures impeding cardiac preload. The initial step in treating the head-injured pediatric patient is always to promote adequate oxygenation and ventilation and to prevent or treat hypotension, thereby limiting ischemia. Criteria for tracheal intubation include hypoxemia not resolved with supplemental oxygen, apnea, hypercarbia ($Paco_2$ > 45 mm Hg), GCS ≤ 8, and an incremental decrease in GCS score greater than 3 (independent of the initial GCS) combined with clinical correlation, anisocoria greater than 1 mm, cervical spine injury compromising ventilation, loss of pharyngeal reflex, and any clinical evidence of a herniation pattern or Cushing's triad.[398]

Induction of Anesthesia and Intubation of the Trachea

Patients with neurologic injury are at a frequent risk for aspiration of gastric contents during induction of anesthesia, because of loss of airway protective reflexes. In addition, there is a heightened risk of cervical spine injury because of trauma, and most patients will be in a cervical collar requiring manual in-line stabilization. The goal of tracheal intubation in the neurologically impaired patients should be (1) rapid sequence from induction to placement of an ETT to reduce the risk of pulmonary aspiration of gastric contents; (2) blunt nociceptive reflexes that might further increase ICP or cerebral hypertension that may exacerbate intracranial hemorrhage or facilitate herniation; (3) maintain adequate, age-appropriate cerebral perfusion pressure; and (4) limit ischemia by maximizing adequate oxygen delivery and maintaining $Paco_2$ in a normal range to ensure appropriate cerebral blood flow.[399] All patients are at risk for a full stomach and cervical spine injury; therefore, intubation should be performed using a neuroprotective, rapid-sequence induction of anesthesia whenever possible. Supplemental oxygen (100%) should be delivered with a facemask to allow nitrogen washout from the patient's functional residual capacity to allow sufficient oxygenation prior to tracheal intubation attempts. To avoid risk of aspiration of gastric contents, bag-valve-mask ventilation should not be used unless the patient has signs and symptoms of impending herniation or life threatening desaturation events. Outside of impending herniation, if bag-valve-mask ventilation is conducted, it is imperative not to overventilate the patient's lungs, decreasing $Paco_2$ and thereby increasing cerebral vascular resistance, resulting in decreased cerebral blood flow and metabolic delivery in a brain-injured patient. A separate health care professional's sole responsibility is to maintain the child's neck in a neutral position by mild axial traction during airway maneuvers to prevent or perpetuate cervical spinal injury. Cricoid pressure should be done by a third individual only if the individual is appropriately trained in the technique and it should be abandoned if it hinders a rapid intubation attempt. Orotracheal intubation by direct laryngoscopy should be performed, and nasotracheal intubation should be avoided because of the potential for direct intracranial damage in a patient with a basilar skull fracture.

Because tracheal intubation is a noxious stimulus and can increase ICP, appropriate sedative and analgesic medications should be administered during rapid-sequence induction. The hemodynamic and neurologic status of the patient dictates the choice of agents. Patients usually receive lidocaine (1-1.5 mg/kg) intravenously (IV) before intubation to help blunt the rise in ICP that occurs during direct laryngoscopy.[73] For the hemodynamically unstable patient, the combination of lidocaine, etomidate (0.2-0.6 mg/kg), and neuromuscular blockade with rocuronium (1 mg/kg) or succinylcholine (1 mg/kg) IV is a popular choice. The authors believe that succinylcholine may still be an option for rapid sequence intubation (RSI) in children who might have a difficult airway because of its rapid recovery, as opposed to the nondepolarizing intermediate neuromuscular blockade of rocuronium. There are several choices for drugs and techniques to use for the induction of anesthesia in the critically ill child with acute brain injury. In the following sections, we will discuss the pros and cons of each anesthetic. It remains unclear whether any of these anesthetics have particular advantages or disadvantages for patients with brain injury; all have been implicated in animal studies as neuroprotectants and neurotoxins. What is clear is that they are essential to the care of these patients, and practitioners should stay current with literature and consider the pharmacodynamics of each drug.

Etomidate

Etomidate is a short-acting intravenous drug that produces sedation, anxiolysis, and amnesia. Side effects include respiratory depression, hypotension, myoclonus, and adrenal suppression; it should not be used in children with suspected adrenal insufficiency and sepsis.[400] Etomidate has the benefits of decreasing ICP by reductions in CBF and $CMRO_2$ and has the advantage of producing less cardiovascular depression than barbiturates or propofol, preserving cerebral perfusion pressure.[401,402] These neuroprotective qualities are counterbalanced by its ability to increase cerebral vascular resistance by a greater magnitude than its reduction of $CMRO_2$ resulting in an increased metabolic deficit.[403,404] The increased metabolic deficit has the potential expand the ischemic core and penumbra in brain injured tissue. This increase in cerebrovascular tone is attributed to the inhibition of nitric oxide synthase by etomidate.[405] Particular attention should also be paid to the rapid recovery of etomidate; once the airway is secured, the effects of etomidate on consciousness dissipate quickly, principally because of the redistribution of the drug from the brain to inactive tissue sites. Recovery of consciousness can take 5 to 15 minutes, and if rocuronium (paralyzed for approximately 45 minutes) is used in combination for rapid sequence intubation, the patient will need ongoing sedation while paralyzed. The addition of a short-acting opioid such as fentanyl may be necessary especially if the patient has concomitant injuries, such as bone fractures.

An alternative is the combination of lidocaine, fentanyl (1-4 μg/kg), and rocuronium. In the hemodynamically stable patient, either of the above combination with fast-acting benzodiazepine, midazolam (0.05-0.2 mg/kg) can be added. In addition, the short-acting narcotic fentanyl, when used with lidocaine, can decrease the catecholamine release associated with direct laryngoscopy.[406]

Ketamine

Ketamine is a phencyclidine derivative typically formulated as a mixture of two enantiomers in a hydrochloride salt form. It has a low pH of around 4, which can produce pain at the injection site when administered intramuscularly or intravenously. Ketamine is an *N*-methyl-D-aspartate antagonist that produces increases in CBF and $CMRO_2$.[407,408] Early studies in patients with obstructed CSF pathways reported that ketamine administration increased ICP with reductions in CPP.[409,410] Recent studies in adult patients with severe head injury have demonstrated improvements in cerebral perfusion pressure and minimal increases in ICP with ketamine.[411-413] One recent report of 30 intubated pediatric patients with head injury observed that single doses of ketamine lowered ICP without producing decreases in blood pressure or cerebral perfusion pressure.[414] It is still unclear what ketamine's effect is on neurologic outcome in these patients or in patients in whom ventilation is not being tightly controlled. However, ketamine can possibly be used in the brain-injured patient, especially in patients with multiple trauma and if etomidate is not indicated.

Propofol

Propofol is a short-acting, sedative-hypnotic intravenous agent that can be used to provide moderate or deep sedation. Propofol can induce a deep state of sedation rapidly, provide a short duration of effect, and have a pleasant recovery phase. Propofol is a popular agent for sedating pediatric patients with neurologic conditions for noninvasive diagnostic imaging, such as a CT scan or MRI. Because of the fast onset and recovery following administration, repeated neurologic examinations are easy, such as assessing a child with sickle cell disease who comes in with altered mental status because of a stroke. Propofol also has anticonvulsant properties and reduces ICP, which can be advantageous in sedating a patient with epilepsy or a patient with concerns for obstructive hydrocephalus owing to a malfunctioning ventriculoperitoneal shunt to obtain diagnostic neuroradiologic imaging.[415] While there have been cases of propofol providing adequate sedation and successfully treating intracranial hypertension,[415,416] several pediatric traumatic brain injury case reports have reported metabolic acidosis and death in patients on prolonged (24 hours) continuous infusion of propofol.[417-421] Furthermore, a rare but potentially fatal "propofol infusion syndrome," associated with lactic acidosis, hyperlipidemia, and multiple-organ system failure was first described in pediatric patients who received prolonged (24 hours) continuous infusion and with larger dosages (>4.5 mg/kg/hr).[422] Current guidelines suggest, that in the care of pediatric traumatic brain-injured patients, "continuous infusion of propofol is not recommended."[423] Adverse effects of propofol include pain at the injection site, apnea or respiratory depression, hypotension, and bradycardia, which can be detrimental in a patient at risk for brain ischemia. If used, particular attention should be paid to the decrease in mean arterial blood pressure with the administration of propofol. Intravenous crystalloid boluses and vasopressor administration will likely be needed to counteract the effects of propofol to maintain proper cerebral perfusion pressure and avoid ischemic insult. Propofol does not provide any analgesia.

Dexmedetomidine

Dexmedetomidine, a centrally acting α_2-adrenergic agonist, is approved by the U.S. Food and Drug Administration for short-term (<24 hours) continuous IV sedation of adults who are tracheally intubated.[424] Like propofol, it has a rapid onset and a relatively rapid elimination half-life and is administered as a loading dose followed by continuous IV infusion. One of the advantages is that it provides sedation with a lower risk of respiratory depression than many other sedative medications. There is increased interest with this agent as a sedative during noninvasive neuroradiologic imaging studies in children who are not intubated. In one study, dexmedetomidine was compared to propofol in children undergoing magnetic resonance imaging studies.[425] While the onset of sedation and recovery time were significantly shorter in the children that received propofol, hypotension, respiratory depression and desaturation were more common compared to the children receiving dexmedetomidine.[425]

There is increased interest in the use of dexmedetomidine as a sedative and potential neuroprotective agent in both adults and children, as animal studies revealed neuroprotection from hypoxia-ischemia and decreased apoptosis. Also, adult human studies in healthy volunteers demonstrated parallel decrease in cerebral metabolic rate for oxygen and cerebral blood flow, which may potentially be helpful in briefly sedating patients who are at risk for intracranial hypertension such as head trauma, brain tumor, or obstructive hydrocephalus.[426] In pediatric TBI case reports, no detrimental effects on ICP were observed. Systemic hypertension was observed in one child who was receiving dexmedetomidine with other sedatives, and bradycardia was observed in two other children who were receiving dexmedetomidine, other sedatives, and therapeutic hypothermia.[427,428] Further study is warranted for the potential use of this agent in children at risk for intracranial hypertension. The most common adverse side effects of dexmedetomidine appear to be cardiovascular. Bradycardia with rare reports of sinus pause or cardiac arrest has been reported. Hypotension and hypertension have been reported, the latter thought to be due to peripheral α_{2B} agonism with peripheral vasoconstriction. Mild respiratory depression is likely. Although ICP does not increase, cerebral perfusion pressure and cerebral blood flow decrease. The effects on seizure threshold appear to be mixed.[429] The authors do not recommend dexmedetomidine as an anesthetic to induce anesthesia; however, it may be a useful agent for patients with brain injury and ongoing sedation needs. Further study in pediatric patients is needed.

After Tracheal Intubation

After successful tracheal intubation, oxygen saturation of 100%, normocarbia (35-39 mm Hg confirmed by arterial

blood gas and trended with an $ETCO_2$), and a chest radiograph showing the tracheal tube in good position above the carina (right mainstem tracheal intubation is common in pediatrics) should be confirmed. Unless the patient has signs or symptoms of herniation, prophylactic hyperventilation ($Paco_2$ < 35 mmHg) should be avoided. Hyperventilation causes cerebral vasoconstriction, which decreases cerebral blood flow and subsequent cerebral blood volume; this will decrease ICP but can lead to ischemia.[430] In the presence of signs and symptoms of herniation, such as Cushing triad (irregular respirations, bradycardia, systemic hypertension), pupillary dysfunction, lateralizing extremity weakness, or extensor posturing, hyperventilation with 100% oxygen can be a life-saving maneuver. Hyperoxia is to be avoided, once a stable airway is obtained, and Fio_2 should be titrated to maintain Sao_2 greater than 90%. Elevating the head to 30 degrees (with cervical spine precautions) increases venous drainage and decreases ICP.[431,432] Furthermore, the head should be midline to prevent obstruction of venous return from the brain. If these maneuvers do not relieve the signs and symptoms of herniation, then additional sedative and analgesic agents can be administered as long as hypotension is avoided.

Supraglottic Airway Devices

While supraglottic airways are not considered a permanent airway in critically ill patients, competency in placement is critical for all individuals participating in resuscitation of a brain-injured child. Supraglottic airway devices, such as an LMA device, can be life-saving. When there is difficulty with direct laryngoscopy and inadequate bag-mask-ventilation (BMV), an LMA should be placed to limit hypoxia and control ventilation until a physician with advanced airway skills can arrive to place an ETT.

Postintubation Stabilization

After successful intubation of the trachea, inspired oxygen should be titrated to maintain oxygen saturation greater than 90% and normocarbia (35-39 mm Hg) confirmed by analysis of ABGs and trends followed with $ETCO_2$. If herniation is impending, then moderate hyperventilation (to 30-35 mm Hg) and confirmation of ETT position with a portable chest radiograph[430] can be performed. The head of the bed should be elevated to 30 degrees, and the patient's head should remain mid-line to improve venous drainage and lower ICP.[431]

Neurologic Monitoring (Also see Chapter 49)

Recent guidelines published by Kohaneck and associates provide an update on treatment for infants, children, and adolescents with TBI[433] (see also Chapter 49). ICP increases when the intracranial volume of one of the four compartments (CSF, blood, brain, and supporting tissues) within the cranial vault increases. An increase in one compartment can occur without raising ICP if an equal volume is displaced from another compartment. When displacement is no longer possible, ICP rises in proportion to the added volume. In older children and adults who have a rigid calvaria, the cranial cavity is a closed container, and the contents are noncompressible. With patients with a GCS score of 8, there is grade III evidence to place an ICP monitor.[433] Treatment of ICP should be considered when pressure is greater than 20 mm Hg; however, absolute goals are unclear, and intermittent increases in ICP greater than 20 mm Hg may be associated with autonomic instability. Chestnut and associates[434] have recently reported in a randomized control trial comparing intracranial monitoring with a strategy of imaging and clinical examination in adults with severe TBI. While aspects of the study and recent evidence in adult severe TBI calls into question the utility of treating an ICP goal of 20 mm Hg, these goals should likely be used as a component of multimodal monitoring.[377] The most common monitor used in TBI as an adjuvant monitor for multimodal monitoring (MMM) is brain tissue oxygenation (Licox, Integra); however, brain tissue oxygen monitoring is also used in children with severe TBI.[381,435] If brain tissue oxygenation is used, maintain partial pressure of brain tissue oxygen greater than 10 to 15 mm Hg. It is unclear how multimodal neurologic monitoring, both invasive (brain tissue oxygenation, microdialysis, cerebral blood flow, intracranial EEG) and noninvasive, should be considered for advanced neuroresuscitation, but studies including the one by Chestnut and associates[434] prove that future research is critical to understanding the mechanisms, timing, and monitoring of the brain to limit secondary injury.

Adjuvant First- and Second-Tier Therapies for Intracranial Hypertension and Secondary Injury

In the 2012 guidelines,[433] the use of hypertonic saline for intracranial hypertension is grade II evidence and should be considered to reduce ICP in pediatric TBI. Use of 3% saline to treat increased ICP is gaining in popularity,[436] because the sodium does not cross the blood-brain barrier quickly and it has an osmolar gradient similar to that of mannitol. Three percent saline has additional theoretical beneficial effects, including enhancement of cardiac output, reduction of inflammation, restoration of normal cellular resting membrane potential and cell volume, and stimulation of the release of atrial natriuretic peptide. The recommended dosing is 6.5 to 10 mL/kg intravenous bolus, but the practitioner may consider starting with small boluses and titrate to pharmacodynamics response. Repeated doses can be given, but it is recommended to keep serum osmolality less than 320 mOsm/L. Prophylactic hyperventilation less to a $Paco_2$ less than 30 mm Hg should be avoided. Mannitol reduces ICP by decreasing blood viscosity and transiently increasing CBF and oxygen transport. The adenosine concentration decreases, and CBF is maintained in areas that have intact autoregulation. CBF remains constant despite a decrease in cerebral blood volume and ICP. Mannitol also reduces ICP by withdrawing water from the brain parenchyma and excreting the water as urine.[437] It takes 20 to 30 minutes for this osmotic effect of the drug to develop. Intermittent boluses of 0.25 to 1 g/kg of mannitol are administered intravenously to control ICP. The drug eventually enters the CSF and can increase ICP. Barbiturates should only be considered for refractory intracranial hypertension.

There is no evidence to recommend tight glucose control in head-injured patients, nor is there evidence suggesting the use of immune-modulating diets at this time. There is grade II evidence to suggest that antiepileptic therapy should be initiated in patients with severe traumatic brain injury. In the authors' institution, it is standard practice to place continuous EEG monitoring and start prophylactic levetiracetam. Elevating the head of the bed 30 degrees while keeping it in the midline position enhances cerebral venous outflow. Even slight movement of the head to a few degrees off midline can double the ICP.

Hypothermia for Severe Traumatic Brain Injury

Hutchinson and colleagues[438] published a multicenter randomized controlled trial to investigate the use of hypothermia as a neuroprotective strategy in children.[8] This trial concluded that in children with severe TBI for whom therapeutic hypothermia (32.5° C for 24 hours) was initiated within 8 hours of injury, there was no improvement in neurologic outcome, and the hypothermic group had an increase in mortality. Subsequent analysis of this study suggests that the hypothermia group had a significant increase in hypotension and decreased cerebral perfusion pressure that might have contributed to the increase in mortality.[439] A second phase 3 randomized control trial was initiated to compare hypothermia and normothermia after severe TBI in children with a prolonged hypothermia window (48-72 hours) and a slower rewarming phase.[440] The study was terminated early for futility after interim analysis; therefore, it is believed that normothermia is the current standard of care for TBI in children.

Decompressive Craniectomy

In the 2012 guidelines,[433] there is grade III evidence to suggest that decompressive craniectomy with duraplasty can be considered for pediatric patients with TBI who display early signs of deterioration, herniation, or refractory hypertension. Currently, there is an ongoing study in adults to investigate surgical decompression for severe TBI.

Environment

Care of patients with TBI within an organized trauma center has been shown to reduce mortality associate with severe injury.[441] Unfortunately, most severe TBIs occur in regions lacking in prehospital and advanced care in an intensive care unit.[442] Critically injured children with TBI should be stabilized and transferred to a level 1 trauma center as soon as possible.

HYPOXIC-ISCHEMIC ENCEPHALOPATHY

There is little evidence that increased ICP or correction of ICP alters the outcome of patients with hypoxic-ischemic encephalopathy. The clinical impression is that the outcome is less favorable in patients who have trauma or metabolic encephalopathy and that aggressive management of ICP, at best, prevents further CNS damage, which is important.[443] The GCS score provides a reasonable assessment of neurologic function in these patients.

HYDROCEPHALUS

Another cause of increased ICP is an increase in CSF volume (i.e., hydrocephalus). Common causes of hydrocephalus include obstructed ventricular shunts, aqueductal stenosis or compression as a result of congenital malformations, infection, posterior fossa tumors, or intracranial bleeding. Inserting an external or internal shunt to reduce the volume of CSF can be lifesaving.

TUMORS

Brain tumors are common in children, and approximately 70% of them occur in the posterior fossa. The most common tumor type is astrocytoma. The initial symptoms can include focal deficits, ataxia, or symptoms of increased ICP. A change in condition following tumor resection requires an immediate neurologic evaluation and possibly a brain CT scan. After a posterior fossa craniectomy, hemorrhage into the posterior fossa can compromise respiration. If an externalized ventricular drain is present, then output should be carefully inspected. Postoperatively the patient should be followed closely for syndrome of inappropriate antidiuretic hormone secretion (SIADH), diabetes insipidus, and cerebral salt wasting. SIADH usually occurs within 24 to 48 hours following surgery and results in the retention of free water and a decrease in serum electrolytes, which can rapidly worsen cerebral edema. Central diabetes insipidus (DI) usually follows the removal of a suprasellar tumor and results in significant diuresis when antidiuretic stores are exhausted, with a resulting increased serum osmolality and a low urine osmolality and urine specific gravity (<1.005). DI is part of a typical triphasic (SIADH to DI to SIADH) response following suprasellar surgery and is treated with volume replacement and a vasopressin infusion may be required.

STATUS EPILEPTICUS IN CHILDREN

Status epilepticus is a continuous motor seizure that lasts for more than 20 minutes or a series of seizures without intercurrent awakening. Although it is common for physicians to never find a cause of the seizures, the most commonly diagnosed causes are infections (meningitis or encephalitis) and metabolic abnormalities (toxins, head trauma, and hypoxic and ischemic injury). Because seizure activity increases with status epilepticus, brain and skeletal muscle metabolism and oxygen consumption increase and place the child at risk for cellular hypoxia. During a seizure, airway obstruction and ineffective chest wall and diaphragmatic excursion can limit ventilation and worsen arterial hypoxemia and hypercapnia. Treatment of a seizure begins with establishing a patent airway, administering oxygen, and ensuring adequate ventilation. Intravenous anticonvulsant drugs are given to stop the seizure. Commonly used anticonvulsants include lorazepam, phenobarbital, paraldehyde, and phenytoin. Lorazepam is a rapid and reliable drug used to stop seizures. Boluses of 0.1 mg/kg are given intravenously or rectally when there is no intravenous access. Phenobarbital, 5- to 10- mg/kg boluses (maximal dose of 20 mg/kg), also stops seizures. The main

complication of lorazepam is respiratory depression when administered in high doses. Giving both phenobarbital and lorazepam together exaggerates the respiratory depression. Fosphenytoin is also given intravenously in doses of up to 20 mg/kg and should be administered slowly to avoid cardiovascular depression. Paraldehyde (0.3 mL/kg) can be given rectally. Finally, an intravenous injection of 1 to 4 mg/kg of sodium thiopental stops most intractable seizures; higher doses of the drug can cause apnea, and the risk of vomiting and aspiration of gastric contents is real. Further, there may be future difficulty in obtaining sodium thiopental. Once the seizures are under control, the cause of the seizures must be determined.

RENAL SYSTEM

Functional Development of the Renal System

Embryologic development of the renal system begins in the middle of the third week of gestation with development of the pronephric tubules. By 10 weeks' gestation, a functioning kidney and collection system exist, and fetal urine is discharged into the bladder. At 32 to 36 weeks' gestation, each kidney has a full complement of nephrons. Because the placenta is the major excretory organ of the fetus, renal growth is not governed by functional requirements. Renal growth increases linearly with body weight and body surface area during the third trimester of pregnancy. The glomerular filtration rate (GFR) increases rapidly from 28 to 35 weeks' gestation. At term, the GFR is 10 mL/min/m^2 and increases to 20 mL/min/m^2 by 2 weeks of age. Although the GFR of premature infants is lower, the rate of increase is the same as that in a term infant.[444] Tubular function is not fully mature in full-term newborns. The newborn kidney is sensitive to antidiuretic hormone (ADH) and vasopressin, and urine osmolarity can vary from 50 to 780 mOsm/L.[445] The tubular function of premature infants is less mature.

The newborn's renal threshold for bicarbonate is approximately 20 mEq/L, which means that standard acid-base nomograms do not apply to infants because their serum bicarbonate concentration of 20 mEq/L is not indicative of metabolic acidosis. The renal tubular glucose threshold of term infants is similar to that of adults, but it is only 125 to 150 mg/dL in premature infants. A full-term infant has 1% or less fractional excretion of sodium by the third day of life. Fractional excretion of sodium can be much higher (5%) in premature infants. Renin, angiotensin, and aldosterone concentrations are high in newborns and decrease over the first few weeks of life.

Assessment of Renal Function

In the resting state, the kidney receives 20% to 25% of the cardiac output, and because of autoregulation the kidney maintains near constant renal blood flow and glomerular filtration rate. Creatinine is an end product of skeletal muscle catabolism and is excreted solely by the kidneys, and blood urea nitrogen is a byproduct of protein metabolism. Values for BUN can increase independent of renal function because of dehydration, high protein intake, and degradation of blood from the GI tract.

Renal Pharmacology

An important aspect of critical care is the maintenance of appropriate fluid balance in the critically ill child. Even in patients who have normal renal function, such as patients with ARDS, chronic lung disease, or CHF, diuretics are often used to limit lung edema and to help with cardiorespiratory dysfunction. The ascending loop diuretic furosemide is likely one of the most widely used drugs in pediatric intensive care. Furosemide reaches the ascending loop of Henle by the way of the tubular fluid. A prescribed starting dose of furosemide is typically 0.5-1 mg/kg up to approximately 10 mg total dose for patients who are naive to diuretic therapy. The smallest dose necessary to increase urine output should be used, to limit toxicity, including electrolyte imbalance and ototoxicity.[446] With progressive renal dysfunction, escalating doses of furosemide may be required to maintain the same clinical response. Electrolyte and renal function need to be monitored frequently, because diuretic therapy frequently causes significant hypokalemia and hypochloremia, as well as other electrolyte wasting. Furosemide is albumin-bound and in low albumin states, often found in critical illness, the delivery of furosemide to renal secretory sites is decreased. Improved delivery and diuresis is often improved with the administration of 25% albumin just before or with the diuretic. The typical dose is 0.5-1 g albumin/kg body weight. Additional diuretics acting at other locations such as hydrochlorothiazide (distal tubule) are often used as adjuvant medications to improve diuresis. The drug spironolactone, which blocks the hormone aldosterone, is a weak diuretic but may prevent spare potassium loss. Failure of increasing amounts of diuretics to be effective likely represents worsening renal perfusion and or renal failure.

Renal Failure

Acute renal failure is defined as an abrupt, often temporary loss of renal function (see Chapters 72 and 74), where there is insufficient removal of nitrogenous wastes and problems with fluid and electrolyte balance. Acute renal failure is described by: (1) the area of obstruction (prerenal, postrenal (obstructive), or intrinsic renal disorders) and (2) the urine volume (oliguria, polyuria, and anuria). Urine composition is often altered, and fluid, electrolyte, and acid-base disorders are common in acute renal failure. Common causes include hypoperfusion, obstruction, toxins, drugs, inflammation, and autoimmune disorders.

Prerenal causes are common in critically ill children because of systemic hypoperfusion and reduced renal blood flow, resulting in reduced urine output, azotemia, and ischemic renal damage. *Azotemia* is the term for the accumulation of nitrogenous byproducts of protein metabolism. Intravascular fluids in the case of dehydration or fluids and inotropic support may be needed to reverse prerenal renal failure. The adequacy of circulating blood volume is assessed by CVP and cardiac output measurements and by estimating renal blood flow with Doppler flow studies or nuclear imaging techniques.

Intrinsic renal failure is caused by disorders of the renal glomeruli, tubules, or blood vessels. Glomerular diseases include hemolytic-uremic syndrome (HUS),

poststreptococcal glomerulonephritis, Henoch-Schönlein purpura, and other inflammatory and immune complex diseases. Acute tubular injury is most commonly caused by hypoxia and ischemia; other causes are rhabdomyolysis, sepsis, hyperthermia, hemolysis, and a myriad of nephrotoxins, including mercury, carbon tetrachloride, and ethylene glycol.

Postrenal obstruction of urine flow can occur anywhere within the collecting system, but it occurs most commonly as a partial obstruction of the bladder neck or the ureterovesical or ureteropelvic junction. All these malformations cause obstructive nephropathy and renal injury or renal failure. Signs of obstruction may be subtle and require radiologic, ultrasonic, or endoscopic evaluation to detect. Recurrent urinary tract infections are frequent clinical manifestations of obstructive lesions.[447] Vascular diseases, including arterial embolism, venous thrombosis, and congenital malformations, are also causes of acute renal failure.

Hyperkalemia and Abnormalities of Sodium

With increasing renal dysfunction, there is a continued decrease in excretion of potassium. Hyperkalemia can lead to life-threatening cardiac arrhythmias and requires immediate treatment. Electrocardiographic presentation demonstrates a peak in the T wave at moderately elevated potassium levels. As hyperkalemia increases, there may be ST segment depression, and widening of the QRS complex, leading to conduction abnormalities, bradycardia, ventricular fibrillations, or asystole. Treatment includes removal of exogenous potassium administration should be discontinued immediately, and calcium in the form of intravenous CaCl (10 to 20 mg/kg) or CaGluconate (30 to 60 mg/kg) to stabilize the cardiac cell membrane. Intravenous sodium bicarbonate (1 to 2 mEq/kg) will drive potassium into the intracellular fluid by increasing blood pH. Glucose and insulin also drive K+ into cells. Glucose is given as 1 to 2 g/kg IV with insulin 1 unit per 4 g of glucose IV If the patient is intubated increasing respiratory rate makes blood more basic driving K+ into the cells. It is important to note, that none of these efforts will remove potassium from the body. Prior to the initiation of dialysis, potassium removal may be attempted with the ion exchange resin Kayexalate, a sodium polystyrene sulfate, which can bind potassium. It is given orally or rectally in suspension, but does require excretion from the body. The dose is 1 g/kg orally, and it can be given every 6 hours; rectally it can be given every 2 to 6 hours. The enema route is less effective than oral administration.

Severe hyponatremia and hypernatremia can be another electrolyte disturbance seen in the critically ill child. Hyponatremia can present with seizure activity, often when serum sodium is less than 120 mEq/L. In the presence of hyponatremic seizures, the initial treatment is the administration of 3% hypertonic saline with a goal to terminate seizure activity and raise serum sodium to greater than 124 mEq/L. However, in the absence of seizures, if a patient reached this low value slowly it has to be corrected slowly, to potentially avoid osmotic demyelination. The same condition applies to hypernatremia. Rapid correction of elevated serum sodium is likely more harmful than the value itself.

BOX 95-4 *Indications for Dialysis*

1. Severe hyperkalemia
2. Metabolic acidosis unresponsive to therapy
3. Fluid overload with or without severe hypertension
4. Fluid overload with or without congestive heart failure
5. Uremia causing encephalopathy, pericarditis, or bleeding
6. Nonobstructive anuria
7. Inborn errors of metabolism
8. Certain drug overdoses
9. Significantly elevated (>100) blood urea nitrogen possibly a relative indication
10. Potential treatment can reduce inflammation with sepsis or systemic inflammatory response syndrome

Renal Replacement Therapy

Renal replacement therapy may be required to improve ongoing fluid shifts and significant electrolyte disturbance. Usual indications for dialysis are shown in Box 95-4. Modalities for renal replacement therapy are commonly peritoneal dialysis, hemodialysis, or continuous venovenous dialysis. Modality often depends on the size of the patient and the experience and resources of the institution.

Peritoneal dialysis (PD) has the benefits of being relatively low cost, causing less hemodynamic compromise compared with venovenous filtration, requiring no central venous line, and being technically simpler. This technique is especially effective in infants and smaller children. Peritoneal dialysis requires the insertion of a soft, multihole catheter into the peritoneal cavity. When patency of the catheter is confirmed, a dialysate solution is infused that equilibrates with plasma and extracellular fluids. The parietal and visceral surfaces function as semipermeable dialysis membranes. The composition of the dialysis fluid is similar to that of plasma and consists of approximately 130 mEq/L of sodium, 100 mEq/L of chloride, 35 mEq/L of acetate or lactate as a buffer, 3.5 mEq/L of calcium, and 1.5 mEq/L of magnesium. The glucose concentration of the solution can be isosmotic or hyperosmotic. Hyperosmotic solutions remove fluid and electrolytes. Respiratory compromise can occur with peritoneal dialysis because the increased abdominal pressure caused by the dialysate in the abdomen can prevent effective spontaneous ventilation. Mechanical ventilation will be required if this occurs. Bacterial or fungal peritonitis is common. Severe dehydration, circulatory collapse, and metabolic derangements are other complications of peritoneal dialysis.

The principles of hemodialysis are essentially the same as those of peritoneal dialysis, except the blood interfaces with a semipermeable membrane rather than with the peritoneum. Hemodialysis is more appropriate in the acute setting with life-threatening electrolyte disturbances, fluid overload, and toxic ingestions. Hemodialysis is more efficient than peritoneal dialysis. Hemofiltration and ultrafiltration is a process of convective solute transport. An ultrafiltrate of plasma is created by hydrostatic pressure exerted across a highly permeable membrane, with simultaneous blood volume replacement with modified lactated Ringer solution.[448] Continuous venovenous hemofiltration (CVVH) is a common form of CRRT, which

provides isotonic fluid removal but minimal solute clearance; however, these circuits can be easily converted to perform dialysis, termed *continuous venovenous hemodialysis,* providing more solute clearance. In smaller patients, accurate flow rates are important when more than 15% of the patient's circulating blood volume can be in the CVVH tubing. Furthermore, technical challenges occur in smaller patients because of flow characteristics of smaller dialysis catheters. Hemodialysis can be performed with two separate 5-French single-lumen catheters, but typically a dual-lumen 7-French catheter at a minimum is required. Anticoagulation for CVVH can be either with heparin or with regional citrate administration. Citrate can be given in a stopcock before the machine, which creates a regional area of hypocalcia in the circuit, leading to relative anticoagulation in the circuit, while intravenous calcium is given back to the patient via a central line. The use of regional anticoagulation with citrate avoids the concerns of systemic anticoagulation, and it can reduce the risk of systemic bleeding

Renal Failure Outcomes

The prognosis with acute renal failure depends on the patient's age, underlying disease, and the extent of the precipitating insult (see also Chapter 23). In general, children fare better than adults; in fact, children usually recover completely from a renal insult if the hypoxia or ischemia lasted only a short time and other organ systems are not involved. Children with chronic renal failure require long-term outpatient peritoneal dialysis or hemodialysis until they can undergo renal transplantation.[449] It has been demonstrated that the degree of fluid overload at initiation of CRRT is associated with patient mortality.[124] This has been found to be independent of patient severity of illness scoring.

Hemolytic-Uremic Syndrome

Hemolytic-uremic syndrome (HUS) is one of the most common causes of acute renal failure in children. This syndrome is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal injury. In North America, HUS is most often associated with infection by cytotoxin-producing *Escherichia coli* O157, but other serotypes and other Shiga-like toxin–producing bacteria have been implicated.[450] *E. coli* O157 resides in the intestinal tract of cattle, and it can contaminate beef during processing.[451] The organism is killed by cooking. Infections can be spread by person-to-person contact in daycare centers, institutions, and the military. There is also a familial form of the disease that accounts for a small percentage of the total cases. HUS is seen predominately in 0.5- to 4-year-old children, but it can occur in all age groups.[170] It shares many laboratory and clinical features with the adult disease, thrombotic thrombocytopenic purpura. In fact, some investigators consider the two disorders a continuum of the same disease. The abnormalities that develop in HUS are believed to be caused by cytotoxins and lipopolysaccharide, a bacterial endotoxin. Toxin-induced damage to renal endothelial cells, the vasculature, and other organs is directly or indirectly associated with the activation of leukocytes.[452] Cytokines such as interleukin-1 and tumor necrosis factor, prostaglandin I_2, thromboxane A_2, and von Willebrand factor multimers probably play a role in the pathogenesis of this disease.[453] The time from exposure to the organism to initial presentation and evaluation of the patient varies from 3 to 12 days. Symptoms last for approximately 1 week. Patients usually have abdominal cramping, bloody diarrhea, tenesmus, and vomiting.[454] On average, approximately 10% of children with *E. coli* O157–induced bloody diarrhea progress to HUS. Mildly affected patients exhibit anemia, thrombocytopenia, azotemia, and decreased urine output and have an uncomplicated course. In severely affected patients, anuria is common, hypertension and seizures can occur, and the duration of illness is prolonged. A small number of children exhibit progressive and permanent renal insufficiency, severe and recurrent hemolysis, thrombocytopenia, and neurologic impairment. Hematologic abnormalities include hemolysis and thrombocytopenia. Hemolysis often causes hyperbilirubinemia and, despite reticulocytosis, severe anemia with hemoglobin concentrations of 4 to 5 g/dL. Thrombocytopenia is the result of platelet destruction and sequestration in the liver and spleen.[455] The remaining platelets show evidence of impaired aggregation.[456] Disseminated intravascular coagulation (DIC) is relatively common. Glomerular capillary endothelial injury is the most consistent renal finding in HUS. Acute renal failure with oliguria or anuria usually lasts less than 1 week but can linger for more than 10 weeks.[457] Glomerular or arterial injury, or both, may predominate, depending on the presence and extent of renal insufficiency (glomerular injury) and hemolysis and hypertension (arterial injury). CNS abnormalities are manifested as decreased levels of consciousness, seizures, irritability, ataxia, hypotonia, hemiparesis, hyperreflexia, and hallucinations; these problems may be caused by severe hypertension, electrolyte disturbances, microthrombi, or cerebral edema and increased ICP.[458] Abdominal cramping is common and may be difficult to distinguish from intussusception, intestinal stricture or bowel perforation, colonic gangrene, or other surgical emergencies.[459] Pancreatitis is common in patients with HUS. CHF can occur if there is fluid overload, hypertension, anemia, or myocardial depression caused by circulating endotoxins. Treatment of HUS is primarily supportive. Meticulous attention should be paid to volume status, electrolyte and acid-base balance, nutrition, antisepsis, and treatment of hypertension and coagulopathies. Enteric isolation is mandatory to prevent secondary spread of the disease. Accurate fluid intake and output measurements and frequent assessment of weight and volume status are important for management of these patients. A central venous catheter is useful for CVP measurements, blood sampling, and administration of intravenous medications and nutrition. Nephrotoxic drugs should be avoided if possible. If nephrotoxic drugs must be given, the drug dose should be adjusted and serum concentrations should be monitored closely. Daily fluids should be restricted to the amounts required to replace insensible losses, urine output, and other ongoing losses. Fluids administered should reflect the electrolyte content of the fluid losses. Caloric support is essential. Enteral feedings are preferred, but parenteral feeding may be necessary if ileus develops. Antidiarrheal medications prolong the duration of colitis, and antibiotics may increase the risk for HUS.[460,461] No specific treatment has been effective to date.

Heparin, fibrinolytic agents, aspirin, dipyridamole, corticosteroids, vitamin E, and furosemide have not affected the outcome of HUS.[181] Immunoglobulin therapy, plasmapheresis, and infusions of fresh frozen plasma have had mixed results, but no long-term therapeutic benefit has been demonstrated. Dialysis, improved nutrition, and supportive care have decreased the mortality rate from 100% in the original report to less than 10% in the last 30 years. Mortality rates remain high in developing countries and in children with a genetic predisposition for HUS.

ENDOCRINE SYSTEM

ADRENAL AXIS

Abnormalities of the adrenal axis result in deficient or excessive production of glucocorticoids, mineralocorticoids, or both. Many of these disorders are diagnosed and treated as they are in adults. Congenital adrenal hyperplasia, pheochromocytoma, and iatrogenic chronic adrenal insufficiency will be discussed briefly.

CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia is an autosomal recessive disorder that is associated with deficiencies in either 21-, 11-, or 17-hydroxylase. 21-Hydroxylase deficiency in children can be partial (simple virilizing form) or more complete (salt-losing form). At birth, affected children demonstrate masculinization of the external genitalia, and those with the more complete deficiency show a progressive salt-losing state (i.e., loss of sodium and elevation of potassium). This condition is usually manifested in the first few weeks of life as feeding difficulty, vomiting, and failure to thrive. The clinical and historical course is suggestive of pyloric stenosis. If the deficiency is not diagnosed and treated early in life, affected children can suffer severe cardiovascular collapse. A blood sample should be obtained for electrolytes, glucose, and if the diagnosis has not been established, adrenocorticotropic hormone (ACTH), cortisol, aldosterone, and plasma renin activity.

Treatment requires aggressive support of intravascular volume and myocardial function, glucose, and replacement of the deficient hormones. For emergency therapy, hydrocortisone acetate is used intravenously at a bolus dose of 1.5 to 2.0 mg/kg and then 25 to 250 mg/day in divided doses. Mineralocorticoid is replaced with cortisone acetate, 0.05 to 0.2 mg/day orally; these patients usually require the addition of salt to their diet. Deficiencies of 11- and 17-hydroxylase do not result in salt wasting; masculinization and hypertension are the common initial signs.

PHEOCHROMOCYTOMA

Less than 5% of pheochromocytomas are diagnosed in childhood. As a rule, these tumors are confined to the adrenal medulla, but they can occur anywhere throughout the sympathetic chain. The clinical signs and symptoms of excessive catecholamines are the same as those in adults. Preoperative, intraoperative, and postoperative therapy is similar to that for adults.

IATROGENIC CHRONIC ADRENAL INSUFFICIENCY

Long-term daily use of steroids for the treatment of asthma, nephrotic syndrome, and malignancies is common. Such use can cause a hypoadrenal state and increase the risk for cardiovascular collapse during a severe illness or stress. In children, topical steroids can also depress the production of ACTH. Replacement of stress-level steroids (threefold the daily replacement dose) is required.

ANTERIOR PITUITARY

Panhypopituitarism is usually secondary to a tumor or aggressive dissection of a tumor.[462] Acute ICU problems related to this lesion include support of the adrenal axis and abnormalities of ADH.

DIABETES INSIPIDUS

Diabetes insipidus can be of central, renal, or psychogenic origin. The central mechanism is the most common form in ICU patients. Absence of ADH results in polyuria and polydipsia; patients with a severe form of this disease might not be able to drink sufficiently to meet their requirement, and severe hypovolemia can develop. Diabetes insipidus is precipitated by brain tumors, head trauma, neurosurgery, and clinical brain death.[463,464] Treatment, in the setting of the ICU, is fluid replacement or, if unwieldy, hormone replacement with aqueous vasopressin (Pitressin). The clinical syndrome may be transient or chronic. In either case, close supervision of fluid intake and output is essential.

SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE

The syndrome of inappropriate ADH secretion is associated with hyponatremia and hypoosmolality caused by inappropriate urinary loss of sodium and free water in patients with normal kidneys. Urine osmolality is greater than serum osmolality. This syndrome is precipitated by a number of mechanisms, including head trauma, neurosurgery, meningitis, hypoxia, and any major surgical procedure in which there is large-volume fluid shifts and fluid replacement.[465] This disease is usually self-limited, and the only real problem occurs if the diagnosis is not considered and the level of hyponatremia is low enough to cause CNS dysfunction. Seizures are rare unless serum sodium is less than 120 mEq/dL. Care should be taken to raise the serum concentration of sodium slowly. This syndrome is treated by fluid restriction and, in severe cases, by the infusion of hypertonic or isotonic saline.

PANCREAS AND INSULIN (ALSO SEE CHAPTER 39)

Hypoglycemia

Hypoglycemia is a common problem in patients in the ICU. What constitutes hypoglycemia in children

has been disputed. However, it is uncommon to find a blood glucose level less than 40 mg/dL in normal, nourished premature, or term neonates. The usual symptoms of hypoglycemia include tachycardia, diaphoresis, weakness, mental clouding, seizures, and coma. The causes of hypoglycemia can be subdivided into disorders of increased utilization and disorders of decreased production. Transient hypoglycemia of the newborn is caused by decreased or immature hepatic gluconeogenesis, and it self-corrects within hours to days. If the hypoglycemia persists, hepatic enzyme deficiencies, endocrine problems, or hyperinsulinism (i.e., pancreatic cell abnormalities, infants of diabetic mothers) must be considered. Other causes of hypoglycemia in the neonatal period include sepsis, hypothermia, hypoxia, and transplacental exposure to maternal hypoglycemic drugs. In older children, hypoglycemia is associated with ketotic hypoglycemia,[466] hepatic enzyme abnormalities, hyperinsulinism, hepatic failure, and Reye syndrome, and it is a side effect of certain drugs. Regardless of cause, the initial treatment of hypoglycemia is glucose administration. The initial dose is 0.5 g/kg given as 50% dextrose in water ($D_{50}W$). This dose should be followed by an infusion of dextrose that is sufficient to meet the metabolic requirements of the child (see the later section on the GI system).

Hyperglycemia

Hyperglycemia in the pediatric ICU can be separated into two main categories with distinct concerns and outcomes. Patients with type 1 diabetes mellitus are often admitted to the ICU, with either initial presentation of the disease or those patients with known diabetes who are exhibiting recurrent problems of insulin balance. The second category of patients with hyperglycemia in critically ill children are those who develop elevated glucose during treatment for their underlying disease process, likely because of stress biology.

Diabetic Ketoacidosis

The most serious acute complication of diabetes mellitus is diabetic ketoacidosis (DKA), a syndrome of glucose and ketone overproduction and underutilization that causes hyperglycemic ketoacidosis (see also Chapter 39). The clinical syndrome includes dehydration and hypovolemic shock from hyperglycemic osmotic diuresis, compensatory hyperventilation (Kussmaul pattern), life-threatening electrolyte depletion, and in cases of severe metabolic imbalance, neurologic obtundation, and coma.[467] Laboratory evaluation demonstrates elevated blood glucose concentrations, severe metabolic acidosis and compensatory hypocapnia, increased osmolality, hyperlipidemia, and a normal or low sodium level (usually fictitiously low because of the hyperlipidemia). Total-body depletion of potassium and possibly phosphate occurs. Levels of both may be falsely normal because of the metabolic acidosis.

Treatment of DKA requires careful correction of the metabolic derangements with meticulous monitoring of the multisystem complications of DKA, as well as the complications of therapy. Adequate intravascular volume is restored with an isotonic glucose-free solution, combined with exogenous insulin administration, commonly referred to as a *two-bag system*.[468] Regular insulin is given as an intravenous infusion of 0.1 U/kg/hr. The goal is to decrease blood glucose by 75 to 100 mg/dL/hr. This infusion is continued until the blood glucose reaches 250 to 300 mg/dL, at which time 5% dextrose in normal saline (D_5NS) is added to the infusate. This regimen of simultaneous glucose and insulin infusion can be continued until the patient can tolerate oral feedings and routine subcutaneous insulin administration. Most clinicians continue the insulin infusion until the acidosis is nearly corrected. Potassium concentrations should be monitored closely. These children have total-body potassium depletion, but potassium should not be added to any infusion until there is urine output. The need for phosphate may be more theoretical than real, but in most situations, half the potassium is given as a phosphate salt. The severe metabolic acidosis is usually corrected with volume and insulin administration. The use of bicarbonate to correct acidosis is generally avoided because bicarbonate can precipitate or worsen the child's neurologic dysfunction. In severe DKA, the intracellular volume of brain cells is reduced by hyperosmolar dehydration. In an attempt to maintain their normal size, brain cells generate osmotically active idiogenic osmoles (e.g., inositol) that attract more water into the intracellular compartment. As systemic rehydration and correction of the hyperosmolar state begin, the brain cells may swell until the idiogenic osmoles are metabolized or cleared. Consequently, rapid correction of osmolarity can cause significant brain edema[469] and can also worsen the neurologic dysfunction, which may require invasive neuromonitoring.[443] The pH of the brain is determined by the CSF bicarbonate level and by the CO_2 content. The CSF CO_2 content equilibrates much more rapidly with the vascular space than bicarbonate does; therefore, correcting the systemic acidosis decreases the level of hyperventilation and causes a rise in $Paco_2$; if this rise is precipitous, the CSF acidosis could worsen before the bicarbonate equilibrates with CSF. Because rapid correction of pH is problematic, bicarbonate administration is not advocated in DKA unless cardiovascular instability is present. Even then, the doses are small. Unfortunately, despite careful and slow correction of the hyperosmolar and acidotic state, hyperosmolar coma and fulminant brain edema can occur.[470] The pathophysiology of brain swelling in DKA is poorly understood. Subclinical brain swelling may be relatively common in children with DKA.[471] If the swelling is significant, mannitol should be administered immediately and therapy for intracranial hypertension begun. The goal is to prevent secondary injury to the brain.

GASTROINTESTINAL SYSTEM

Gastrointestinal problems in the ICU include organ dysfunction and failure from acquired disease and from congenital anatomic malformations and dysfunction. Delivery of adequate nutrition to critically ill patients is necessary.

STRUCTURAL AND FUNCTIONAL DEVELOPMENT OF THE INTESTINE

Knowledge of fetal mid-gut development makes it easier to understand a number of severe congenital anomalies. Although the intestine begins as a hollow tube, it is occluded by 7 to 10 weeks' gestation by rapidly growing epithelial cells. The lumen is later reconstituted when vacuoles within the epithelial cells coalesce. Some of the neonatal intestinal atresias are the result of abnormalities of this recanalization process. At 3 to 10 weeks' gestation, the mid-gut lies outside the abdominal cavity, with only the hindgut fixed in the left side of the abdomen. The gut rotates 270 degrees counterclockwise and reenters the abdominal cavity at 10 weeks' gestation. If the midgut fails to migrate back into the abdominal cavity, an omphalocele occurs. Abnormalities in midgut rotation result in abnormal intraabdominal relationships, the most important being malrotation and volvulus of the intestine.

DEVELOPMENT OF THE LIVER

The liver begins as an outgrowth of the foregut at approximately 3 weeks' gestation. During fetal life, it is relatively large in comparison with the adult liver. Although the fetus relies on the maternal liver and placenta for detoxification and excretory function in utero, the fetal liver is necessary for both prenatal and postnatal survival. As early as 10 to 12 weeks' gestation, the fetal liver is involved in glucose regulation, protein synthesis, and lipid synthesis and is capable of some drug metabolism. The fetal liver contains approximately threefold the amount of glycogen as the adult liver, but the glycogen is nearly completely released within hours of birth to compensate for interruption of the placental supply of nutrients.[472] It takes several weeks for the newborn to reestablish the store of liver glycogen, putting the infant at risk for hypoglycemia during this vulnerable period.

CONGENITAL MALFORMATIONS

Gross anatomic malformations are usually diagnosed during the first few days of life. Some, such as omphalocele, gastroschisis, diaphragmatic hernia, and imperforate anus, are apparent on the initial physical examination. Others manifest themselves in the first few days of life as failure to feed enterally, intestinal atresia, microcolon, tracheoesophageal fistula, and meconium ileus. Other malformations present difficult diagnostic and therapeutic dilemmas after the neonatal period. Specific clinical problems are discussed in the following sections.

Intestinal Malrotation and Midgut Volvulus

Malrotation of the intestine is caused by incomplete rotation of the fetal midgut when the gut migrates into the abdominal cavity. This abnormal rotation can cause partial or complete duodenal obstruction by peritoneal (Ladd) bands or, more importantly, midgut volvulus. The mid-gut (duodenum to transverse colon) and its vascular supply hang on a single pedicle; if the pedicle twists, the entire midgut may infarct. Infants with omphalocele almost invariably have associated malrotation of the gut. Symptomatic infants and children have signs of high intestinal obstruction (bilious vomiting) or signs of an acute abdomen, intestinal perforation, and sepsis. Treatment is surgical reduction and fixation of the volvulus and resection of nonviable bowel. Postoperative respiratory support and total parenteral nutrition are often necessary in infants who were severely compromised before surgery.

Meckel Diverticulum

Meckel diverticulum represents persistence of the omphalomesenteric or vitelline duct and is brought to the attention of the physician because of painless lower GI bleeding. The bleeding site is due to ulceration of the bowel mucosa caused by secretion of gastric acid. Although usually self-limited, massive and life-threatening hemorrhage has been reported.[473] The diagnosis can be difficult to make because it is often one of exclusion. The technetium pertechnetate isotope scan demonstrates gastric mucosa in the diverticulum. Therapy is supportive, but particular attention must be paid to blood replacement. Definitive therapy is surgical resection.

Hirschsprung Disease

Hirschsprung disease (congenital aganglionic megacolon) is characterized by the absence of parasympathetic ganglion cells in the rectum and colon and occasionally in the small bowel.[198] Lack of ganglia cause narrowing of the distal bowel and distention of the normal proximal bowel. The clinical symptoms can be relatively minor, with abdominal distention and stool retention, or severe, with toxic megacolon, peritonitis, and intestinal perforation. Toxic megacolon is usually manifested in younger children; reported mortality rates are as high as 75% with toxic megacolon. The diagnosis of Hirschsprung disease is occasionally made with the history and physical examination. A barium enema reveals a narrowed segment with ballooning of the proximal part of the bowel. The definitive diagnosis is made by finding no ganglion cells on rectal or colon biopsy (or both). Treatment of toxic megacolon is both supportive (volume reexpansion and antibiotic administration) and definitive (surgical decompression via colostomy).

Other Intestinal Disorders

Intestinal disorders can cause bleeding, obstruction, or inflammation, and there can be secondary problems such as malabsorption and bowel perforation. GI bleeding in children is caused by inflammatory diseases (gastritis), ulcers, varices, or vascular malformations. Although ulcer disease is an uncommon initial complaint in pediatric patients, stress gastritis or stress ulcers occur in critically ill children. Prophylactic antacids or an H_2 antagonist should be considered. Bowel obstruction can be caused by intussusception, twisting of the bowel around congenital or postsurgical bands, and twisting of the bowel on itself (volvulus). Intussusception is relatively common in the pediatric age group and usually occurs in the distal part of the ileum. In

only a few cases can a leading point, such as a polyp or localized edema (as seen in Henoch-Schönlein purpura) be identified. Treatment of intussusception can be surgical or, in patients with no evidence of necrotic bowel, with barium, air, or saline enema.[474] Inflammatory bowel diseases include Crohn's disease and regional enteritis.[475] Infectious agents to be considered include *Salmonella*, *Shigella*, and *Yersinia* species. These patients often have diarrhea, malabsorption (especially lactose intolerance), and bloody diarrhea. They also can have a toxic acute abdomen.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a frequently fulminant neonatal disease characterized by ulceration and necrosis of the small bowel and colon. Its cause is unknown but is probably multifactorial. Prematurity is the greatest risk factor for NEC. It is probably due to a combination of intestinal ischemia, oral feeding, and pathogenic organisms. Umbilical artery catheters, perinatal asphyxia, respiratory distress syndrome, and persistent patent ductus arteriosus have all been implicated.[476] The incidence of NEC is on the rise, with 1% to 5% of infants in neonatal ICUs affected. The most common initial signs are feeding intolerance, abdominal distention, and bloody stools. Intestinal obstruction, bowel perforation, and sepsis may follow. Treatment consists of withholding enteral feeding, nasogastric decompression, intravenous fluids, hemodynamic support, administration of appropriate antibiotics, and surgical exploration if there is evidence of an acute abdomen with free air. Peritoneal drainage can be helpful for very-low-birth-weight babies and for those in extremis.[477] Total parenteral nutrition is frequently required for several weeks, and intestinal obstruction can occur weeks to months after a relatively benign course.[478]

Hepatic Failure

Hepatic failure occurs with chronic or acute liver disease. Chronic liver failure can be caused by biliary atresia, inborn errors of metabolism (tyrosinosis, Wilson disease, galactosemia, cystic fibrosis), or chronic inflammatory hepatitis. Children with chronic disease often have signs and symptoms of synthetic dysfunction (malnutrition, hypoalbuminemia, abnormal coagulation), degradation dysfunction (icterus and hyperammonemia), and portal hypertension (hypersplenism and varices). Acute liver failure is most commonly caused by infectious hepatitis A and B. Evidence of bleeding, edema, and other organ dysfunction, including identification of liver and spleen size, is sought on physical examination. Laboratory evaluation should include screening for synthetic function (albumin, prothrombin time [PT], partial thromboplastin time [PTT]), degradation products (bilirubin, ammonia), and liver enzyme concentrations. Hepatic ultrasound, radiographic contrast studies, and liver biopsy are indicated on an individual basis. Life-threatening complications of liver failure include acute bleeding and cardiovascular compromise (from massive intravascular hypovolemia caused by fluid shifts) and intracranial hypertension from toxic encephalopathy. Treatment is expectant and supportive. A 10% dextrose infusion will provide adequate carbohydrate intake. Low-protein diets minimize ammonia production. Coagulation is supported with vitamin K, fresh frozen plasma, and platelets as required. Plasmapheresis with fresh frozen plasma and platelets improves coagulation and maintains normovolemia. Oral lactulose and neomycin enemas decrease the enterohepatic cycle of ammonia production and absorption.[479] Cardiovascular and respiratory function should be monitored closely and supported as required. The development of intracranial hypertension must be anticipated. Serum ammonia levels are used to monitor neurologic dysfunction,[479] but it is unknown whether ammonia is the primary CNS toxin or whether it is just one of many chemical markers. Steroids have been used for some forms of inflammatory hepatitis. Exchange transfusions and plasmapheresis have been used to decrease the toxin load,[480] but there is no strong evidence that such measures reduce morbidity and mortality.[481] Patients with certain forms of acute hepatic failure, including those resulting from toxic and infectious causes, may be considered candidates for liver transplantation.[482]

Extrahepatic Biliary Atresia

Extrahepatic biliary atresia occurs once in every 8,000 to 10,000 live births.[483] The extent of atresia differs from patient to patient and involves variable degrees of obstruction or discontinuity of the biliary tree between the duodenum and the proximal branches of the hepatic ducts. Treatment is surgical (jejunal Roux-en-Y and portoenterostomy) and is tailored to the amount of extrahepatic bile duct present. The Kasai procedure is most successful in patients operated on before they are 6 to 9 months old. However, this procedure is associated with many acute and chronic complications, including hepatic failure, ascending cholangitis, and cirrhosis with portal hypertension and varices. Despite these complications, the Kasai procedure persists because there are not enough suitable donor organs.[484]

Liver Transplants

Improved immunosuppressive drugs and surgical techniques have increased the success of liver transplantation (see also Chapter 74). For transplantation to be successful, the perioperative and postoperative periods require a coordinated approach among surgery, gastroenterology, anesthesia, immunology, and the ICU staff. Most of the clinical issues that arise can be anticipated. Large blood losses occur and massive replacement therapy is required in the operating room. Accordingly, intravascular volume status, renal status, and hematology/coagulation profiles must be closely monitored. The immunosuppression required puts the patient at risk for infection with both "normal" and opportunistic organisms. Surveillance cultures and early aggressive antibiotic therapy are indicated. Systemic hypertension, which appears to be unrelated to elevated CVP or pulmonary capillary wedge pressure, is due to the antirejection drugs. Many patients require aggressive antihypertensive therapy (e.g., hydralazine, diazoxide, captopril).[485,486]

ENTERAL AND PARENTERAL NUTRITION FOR THE CRITICALLY ILL CHILD

Nutritional support of a patient in the PICU may be less of a concern to health care providers when there are neurologic, respiratory, and cardiovascular issues to be addressed; however, not addressing the nutritional needs of pediatric patients misses an important opportunity to improve their care and outcome (see also Chapter 106). There are the potential benefits of reduced translocation of gut bacteria, reduced constipation, and reduced infectious risks as compared with parental nutrition. Research by Khorasani and associates[487] published in 2010 in a single-center study showed decreased mortality in children with burns who received early enteral nutrition (8.5%) as compared with late enteral nutrition (12%). In a 2012 international multicenter cohort study published by Mehta and associates,[488] there was a less frequent 60-day mortality associated with a higher percentage of goal energy intake via an enteral route. The consecutively enrolled cohort consisted of 500 children aged 1 month to 18 years who required mechanical ventilation longer than 48 hours in a PICU. Mortality was more frequent in the patients who received parenteral nutrition. This research demonstrating early enteral nutrition improves outcome in critically ill children is further supported by the 2013 work of Mikhailov and associates.[488] The study was a multicenter retrospective study with 12 participating centers. Pediatric patients aged 1 month to 18 years were included if they had a PICU length of stay of 96 hours or longer, and a total of 5105 patients were identified. The study defined *early enteral nutrition* as obtaining 25% of goal calories enterally within the first 48 hours of ICU admission. The study noted that children who received early enteral nutrition were less likely to die as compared with those who did not (odds ratio, 0.51; 95% confidence interval, 0.34-0.76; $p = 0.001$). This was after adjusting for severity of illness, age, and participating center. There were nonsignificant increases in length of stay and duration of mechanical ventilation.

Given the increasing evidence supporting early enteral nutrition, it is important to consider daily whether it is possible to start feedings. It is also important to consider placing feedings tubes beyond the pylorus so that enteral nutrition can proceed during ICU procedures. Mehta and colleagues[489] showed significant interruptions in enteral feedings even after they had been initiated. Feedings were stopped on average for 2 days in 71% of their patients. While it may be difficult for each clinician to individually advance the feeding of their patients, there is good information that adoption of a feeding protocol in an ICU setting increases goal enteral nutrition.[490] It is possible that 25% to 30% of the patients admitted to the PICU are malnourished.[489] Smaller children and those with chronic illness have limited energy reserves, and early enteral feeding should be targeted. If enteral nutrition is not a possibility, then parenteral nutritional should be considered despite its risks. Higher dextrose solutions increase the risk of phlebitis or complications, should there be an infiltrate of a peripheral IV catheter. Higher dextrose concentration parenteral nutrition also requires placement of a central venous catheter. The central venous catheter is separately associated with risk during placement and ongoing risks of infection. Additional risks of parenteral nutrition include infection, cholestasis, hepatic stenosis, electrolyte disturbance, and elevated triglycerides. Until there is further evidence showing harm for malnourished children, the initiation of parenteral nutrition should be considered if enteral feeding is not an option.

HEMATOLOGY

Hematologic emergencies in the ICU include abnormalities in coagulation, immunity, and red blood cell mass. They can be primary isolated defects, or they can be caused by multiorgan system failure. The immune system is discussed in the section on infectious disease.

Coagulation System

Normal clotting includes initial platelet hemostatic plug formation and fibrin production (intrinsic or extrinsic pathways). For both to occur, platelets, coagulation factors, and an intact blood vessel are essential (see also Chapter 62). Neonates have a number of measurable coagulation abnormalities that rarely have clinical manifestations. Full-term and most preterm infants have normal platelet-vessel interaction, but platelet aggregation is transiently impaired. In addition, many coagulation factors show decreased activity or concentration in the fetus and newborn. Of greatest importance are the vitamin K–dependent factors: factors II, VII, IX, and X. These factors are low at birth and decrease to even lower levels during the first week of life unless vitamin K is administered. The amounts of factor V and VIII are close to adult levels in all but the most premature of infants. Although routine screening tests for coagulation activity are prolonged in infants, the newborn's blood clots more rapidly in vitro because neonates lack sufficient naturally occurring protease inhibitors, principally antithrombin III.[216]

Transfusion Therapy

Many PICU patients require blood transfusions during their hospitalization (Table 95-9; see also Chapter 61). Decreased red blood cells may be secondary to decreased production or ongoing losses to frequent laboratory testing. Decreased platelets may be secondary to decreased production or sequestration in the spleen. Thrombocytopenia from frequent laboratory testing is less common. Decreased production of coagulation factors in the setting of liver failure may predispose

TABLE 95-9 BLOOD COMPONENT THERAPY

Blood Component	Dose	Comments
Packed red blood cells	10-20 mL/kg	Raises hemoglobin 2-4 g/dL
Random donor platelets	1 unit/10 kg or 5-10 mL/kg	Pooled units from multiple donors
Apheresis platelets	10 mL/kg	Donation from single donor
Fresh frozen plasma	10-20 mL/kg	Provides 20%-30% of coagulation factors
Cryoprecipitate	1 unit/10 kg	Significant amount of fibrinogen (50-80 mg/dL)

patients to further blood loss. The transfusion of blood products in any setting carries associated risks. Transfusion reactions can be separated into nonimmune and immune-mediated problems. The nonimmune reactions include transmission of viral or bacterial infections through blood components, circulatory overload, coagulopathy, hypothermia, and changes in electrolytes. Hemolysis of erythrocytes in PRBCs is increased by prolonged storage. The potassium levels can be quite elevated in older units. In trauma or situations of acute blood loss, rapid transfusion of red blood cells can lead to hyperkalemia. This is typically not a problem in an ICU setting where PRBCs are transfused over 2 to 4 hours. The immune-mediated reactions include intravascular and extravascular hemolysis. Hemolytic transfusion reactions can be severe and life threatening. Cross-matching blood products can reduce hemolytic reactions, but there must also be careful identification of the patient and the blood unit to be transfused. Nonhemolytic immune-mediated reactions include febrile reactions, mild allergic, anaphylactic reactions, and transfusion-related acute lung injury (TRALI).

Transfusion-Related Acute Lung

Transfusion-related acute lung injury previously may have been an underreported complication of transfusion, but awareness is improving (see also Chapter 61). The number of studies on TRALI in pediatric ICU patients is increasing.[491-497] The diagnosis of TRALI following a blood transfusion relies on excluding other causes of pulmonary edema. This includes eliminating volume overload, sepsis, and cardiogenic pulmonary edema as causes of the patient's pulmonary edema. It is proposed that there is a two-hit model of TRALI. The first hit is an underlying component of inflammation in the lungs. The second hit is transfusion of a blood product that results in the development of TRALI. It is still not clear whether the damage is caused by the presence of neutrophils, HLA antibodies, or biologically active lipids present in older blood units. A study by Church and colleagues[498] showed an association with increased mortality for pediatric patients with ALI who received fresh frozen plasma. This group already has the first hit because of the ALI. The mortality association was independent of the severity of hypoxemia, the presence of disseminated intravascular coagulopathy, or the presence of multiple-organ dysfunction syndrome. Blood transfusion has associated risks, and these risks should be considered before any transfusion. In some clinical scenarios, pediatric patients will tolerate a greater degree of anemia than would have previously been considered. In 2007, Lacroix and colleagues[499] with the Transfusion Requirements in Pediatric Intensive Care Units (TRIPICU) study demonstrated that by adopting a restrictive transfusion strategy, they were able to reduce transfusion of PRBCs to PICU. A hemoglobin threshold of 7 g was targeted in one group and 10 g in another. In the restrictive threshold group, there was a 44% reduction in PRBC transfusion without an increase in adverse outcomes. This information might not be applicable to all groups in the ICU, such as those with ongoing blood loss. The patients in the TRIPICU study did not have arterial blood pressure lower than 2 SD below an age appropriate mean, and they did not require increasing doses of inotropic medication. Subgroup analysis of the original TRIPICU study in general pediatric surgery[500] and cardiac surgery patients[23] did not show a significant difference in the development of multiple-organ dysfunction syndrome.

Coagulopathy

Coagulation defects can occur due to many conditions in PICU patients, such as sepsis, trauma, malignancy, pancreatitis, and liver failure (see also Chapter 62). As a reminder, the prothrombin time (PT) tests the extrinsic and common pathways of coagulation. The PT is prolonged in liver failure, vitamin K deficiency, and DIC. The activated partial thromboplastin time (aPTT) tests the intrinsic and common pathways of coagulation. The aPTT is prolonged in liver failure, hemophilia A, von Willebrand disease, and DIC. One major concern in a PICU setting is that the underlying inflammatory state in some patients can activate coagulation and inhibit the natural anticoagulation mechanisms. This concern is the basis for DIC. In 2001, the International Society of Thrombosis and Hemostasis[501] published a DIC scoring system. Their DIC score uses platelet count, fibrin-related markers, prothrombin time, and fibrinogen. They separated DIC into nonovert DIC and overt DIC. In nonovert DIC, the balance of hemostasis is stressed by inflammation or noninflammatory disorders of the microvasculature stress hemostasis, but compensation is maintained. In overt DIC, the hemostatic system can no longer compensate. A DIC scoring system such as this allows for ongoing research and a measure of response to therapy. In 2009, Khemani and associates[502] demonstrated the association between an elevated DIC score and mortality in 132 PICU patients with sepsis or shock. There are a maximum of 8 total points on the DIC score. Points are assessed for lower platelet counts and fibrinogen, prolongation of the prothrombin time, and evidence of fibrin degradation. There was a 50% mortality for patients with overt DIC (DIC score ≥ 5). The mortality was 20% for patients with a DIC score less than 5. This association between elevated DIC score and mortality remained even when controlling for severity of illness and use of inotropic medications. The treatment of DIC is supposed to treat the underlying condition that is causing imbalance of the coagulation system. A future goal of research will be to study patient outcomes as DIC is corrected and even caused by FFP. As Church and associates[498] found an increased mortality associated with FFP transfusion, it is not clear what the balance will be between the risk of DIC or the risk of transfusion.

Sickle Cell Disease

Hemoglobin S, or sickle cell trait, is the most common of the hemoglobinopathies. There are also significant regional variations on the concentration of patients with different thalassemias. Hemoglobin S is caused by a point mutation in the β-chain at codon position 6, which results in a substitution of valine for the normal glutamine. Hemoglobin S is formed from the combination of an abnormal β-chains with the valine with normal α-chains. When two copies of the abnormal gene are present, hemoglobin SS (HbSS; or sickle cell disease)

is produced. Complications from Hb SS cause the most frequent PICU admissions of the hemoglobinopathies. Deoxygenation of the Hb SS erythrocytes causes intracellular hemoglobin polymerization, which leads to loss of deformability and changes in the erythrocyte morphology. In a deoxygenated state, the abnormal erythrocytes change from a biconcave configuration to the classic sickle cell shape. The abnormal erythrocytes have a much shorter lifespan and hemolyze more readily. In turn, patients with sickle cell disease have a chronic severe hemolytic anemia.

Sickle Cell Crisis

There are three types of sickle cell crisis that can occur: hemolytic, aplastic, and vasoocclusive. A hemolytic crisis is characterized by increased hemolysis that results in an acute drop in hematocrit and hemoglobin. This drop is typically accompanied by a significant increase in red cell production or reticulocytosis. Alternatively, in an aplastic crisis there is a drop in hematocrit and hemoglobin, but there is no associated reticulocytosis. The production of red cell precursors in the bone marrow has slowed or stopped. The cause of an aplastic crisis is often infectious with greater than 90% of cases caused by parvovirus B19. A vascular occlusive crisis is what is typically known as the classic sickle cell crisis. A vascular occlusive crisis can be initiated by infection, dehydration acidosis, or hypoxia. The erythrocytes assume a sickled configuration that blocks small vessels, leading to infarction. The infarcts can occur in any organ, but are frequent in the, lungs, kidney, bones, skin, spleen, eyes, and CNS.

Acute Chest Syndrome

A vascular occlusive crisis in the lungs leads to acute chest syndrome (ACS). Acute chest syndrome is a leading cause of death and is the second most common complication in sickle cell disease. ACS is defined as a new pulmonary infiltrate on a chest radiograph in association with a fever, respiratory symptoms, or chest pain. There is great variability to the clinical course in ACS. The National Acute Chest Syndrome Study Group[503] issued a multicenter report showing that almost 50% of patients later diagnosed with ACS presented initially with another symptom, mostly typically being pain. The presence of a pulmonary fat embolism is frequently reported and is associated with a particularly severe course. The cause of the pulmonary fat embolism is most likely bone marrow necrosis with release of necrotic bone marrow fat into the blood stream. A common etiology of ACS is infection. *Chlamydia pneumonia* and *Mycoplasma* species are the most commonly identified pathogens. The goal for management of ACS is early recognition. As children with sickle cell disease may have few initial symptom, there should be a high index of suspicion. All febrile children with sickle cell disease should have a chest radiograph obtained. If there are any positive radiologic findings, therapy should begin immediately. Initial antibiotic treatment is cefuroxime or cefotaxime with a macrolide. The patient should be adequately hydrated. The patient should be observed closely and if the patient becomes fluid overloaded, diuretic therapy should be started. Patients should receive oxygen therapy even if there are normal oxygen saturations. Incentive spirometry should be used by every child who is able to do so. There should be consideration given to the use of bronchodilators. Every effort should be made to see that pain is adequately controlled. A simple red cell transfusion may be helpful if the patient is anemic, but an exchange transfusion may be needed. There is some regional variation in this practice. The reason to perform an exchange transfusion is that as the hemoglobin rises the blood viscosity will increase. Further, sickle cell blood has a high viscosity in the deoxygenated state. Performing a red cell exchange can reduce blood viscosity and improve oxygenation.[501] An exchange transfusion can improve perfusion in the microvascular perfusion and cause a reduction in inflammatory mediators. In patients with sickle cell disease, red cell exchange has been shown to reduce white blood count, platelet count, and soluble vascular cell adhesion molecule-1 in patients.[28] However, there was no effect on interleukin-1α, interleukin-1β, interleukn-8, or tumor necrosis factor-α and the reductions that occurred were short lived. In the National Acute Chest Syndrome Study Group publication,[504] 13% of patients required mechanical ventilation, and the mortality rate was 19% in the group that required intubation.

Neurologic Complications

Exchange transfusion has a vital role in the treatment of neurologic complications from sickle cell disease. In a population of patients less than 20 years of age with sickle cell disease, the incidence of stroke was measured at 0.44 per 100 patient-years.[505] Studies have been performed to identify at risk patients and initiate therapy before the development of stroke. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) was to evaluate whether chronic transfusion therapy could prevent an initial stroke in children with sickle cell disease. Transcranial Doppler was used to identify patients at increased risk for stroke. A hemoglobin S concentration of less than 30% was maintained in the study group.[506] The risk for stroke development was reduced by 90% in the chronic transfusion group as compared with the patients receiving standard of care. The trial was stopped 16 months early because of these findings. Chronic transfusion therapy does carry the long-term side effects of alloimmunization and iron overload.[507] The information available would indicate that transfusion should be performed for a child with sickle cell disease and an acute neurologic change exchange. While there is a significant need with acute chest syndrome or neurologic change for an exchange transfusion, it is not without risks. Depending on regional variation, central venous or arterial access is needed. Patients need to be followed closely for the development of fluid overload or hypovolemia during the exchange. There are the risks of blood products. Small children are at risk for hypothermia if the blood is not warmed. The best location and method to handle exchange transfusion will depend on the resources of the ICU, blood bank, and hematology department.

Acquired Disorders

A variety of circumstances can impair the production of coagulation factors. The vitamin K–dependent factors are

most commonly affected. These factors are decreased with liver disease, warfarin therapy, and malabsorption syndromes secondary to either bowel disease or altered bowel flora caused by long-term antibiotic therapy. In addition, untreated neonatal vitamin K deficiency results in hemorrhagic disease of the newborn. In these disorders, the PT is prolonged and there are low levels of factors II, VII, IX, and X. Administration of vitamin K usually reverses these deficiencies unless the synthetic function of the liver is markedly compromised.

Acquired platelet abnormalities include decreased production, increased destruction, and decreased function. Decreased production or hypoproliferative states include marrow diseases, such as leukemia and aplastic anemia, and the side effects of chemotherapeutic agents. Increased destruction can be immune mediated (i.e., idiopathic thrombocytopenic purpura)[508] or the result of consumption (i.e., microangiopathic states, HUS, or thrombotic thrombocytopenic purpura).[509] Finally, platelet dysfunction has been found with uremia and chronic polycythemia in patients with cyanotic heart disease.[510] Treatment of acquired thrombocytopenia includes platelet transfusions and, if possible, correction of the underlying disorder. Therapeutic splenectomy will increase platelet survival in some patients with severe immune-mediated diseases.

ONCOLOGY

Over the past several decades, there has been significant improvement in survival of pediatric cancers. A great amount of information demonstrating this effect is available from the Surveillance, Epidemiology, and End Results Program at http://www.seer.cancer.gov. Furthermore, there has been an increase in the number and types of diseases treated with hematopoietic stem cell transplantation (HSCT). These facts have resulted in an increasing volume of oncology patients in the pediatric ICU. This patient population received highly specialized, detailed care on specialized oncology wards or bone marrow transplant units. The care delivered in these areas as well as the strict isolation procedures used there are difficult to replicate in other locations in the hospital. In an effort to keep oncology patients in oncology wards, some hospitals have policies allowing the use of low amounts of inotropic support in these areas, such as dopamine up to 5 μg/kg/min. This may mean that some oncology patients are transferred to the ICU when they have exceeded this level of support. They may have sepsis and shock not responding to fluid resuscitation and low inotropic support. Other patients may require respiratory support that cannot be delivered on the ward. Finally, there is early literature indicating that earlier initiation of CRRT to treat or prevent fluid overload[511,512] has benefits in HSCT with other studies showing no benefit.[513] However, the positive literature has prompted earlier admission to the ICU for HSCT patients who become fluid overloaded. Overall, there is evidence showing improved outcomes for pediatric oncology patients requiring ICU care.[514-517] For patients following HSCT after controlling for severity of illness a temporal improvement in mortality is less evident.[518] Furthermore, for patients requiring mechanical ventilation the mortality is greater following HSCT compared with non-HSCT oncology patients.[519]

Because of the disease and therapy at times during their illness, oncology patients are profoundly immunocompromised. There is an increased risk of sepsis during periods of neutropenia. Fever may be the first indication of sepsis and studies have looked at predicting which patients will go on to be bacteremic.[520,521] The outcome of sepsis and oncologic disease is an ongoing concern. A study by Pound and colleagues[514] showed that ICU mortality for patients with septic shock was not significantly different between oncology patients (15.9%) compared with matched controls (11.6%). There was no significant survival difference between groups in the first 6 months following discharge from the ICU. A 2005 study by Fiser and colleagues[517] showed an overall mortality of 17% for pediatric oncology patients with severe sepsis. The mortality in the HSCT group (30%) was greater than in the non-HSCT group (12%). For patients who required both mechanical ventilation and inotropic support, there was a high mortality (64%).

LEUKOSTASIS

Leukostasis (vascular obstruction) results from high viscosity caused by elevated cell counts or by the white blood cells (WBCs) themselves. This syndrome is anticipated in patients with acute lymphoblastic leukemia when the WBC count exceeds 500,000 and in AML patients with WBC counts greater than 200,000/mm^3. In AML, leukemic cells are less deformable than lymphoblasts; therefore, a lower WBC count produces the same syndrome.

The brain and lungs are the two major target organs for leukostasis; vascular plugging and organ infarction are the usual manifestations. Initial symptoms include tachypnea, cyanosis, increased work of breathing, altered mental status, and focal neurologic deficits. Besides supportive therapy, reducing the circulating tumor load and viscosity are the primary goals of therapy. Leukapheresis and exchange transfusion transiently accomplish these goals. Cranial irradiation can reduce the CNS tumor load, and chemotherapy will interrupt cell production and possibly destroy circulating cells. The initial goal of chemotherapy is to stop cell production without producing massive cell lysis; this halts the increase in tumor load without causing a severe metabolic crisis before adequate perfusion is reestablished.[522,523]

TUMOR LYSIS SYNDROME

Tumor lysis syndrome is a metabolic crisis precipitated by acute lysis of a large number of tumor cells. Serum uric acid, potassium, and phosphate concentrations are elevated; the elevated phosphate concentrations cause hypocalcemia. Hyperkalemia and hypocalcemia can be life threatening; increased uric acid may cause acute renal failure.[524] Therapy for tumor lysis syndrome consists of alkalinization of urine, fluid administration, and diuresis. Before any chemotherapy is administered, the patient's renal function should be assessed. If renal function is normal, allopurinol or rasburicase therapy is begun. In most cases, this conservative approach of forced diuresis and

allopurinol or rasburicase will prevent renal failure, but occasionally dialysis must be instituted. Indications for the initiation of dialysis include:

1. Potassium > 6 mEq/L and rising despite resin exchange
2. Uric acid > 19 mg/L
3. Creatinine > 10 mg/L
4. Phosphorus > 10 mg/L or rapidly rising
5. Volume overload
6. Symptomatic hypocalcemia

MEDIASTINAL MASS

Children with a mediastinal mass and respiratory distress often complain of coughing, difficulty breathing, stridor, and shortness of breath. They prefer to sit upright and cannot lie supine. The chest radiograph usually shows a large mediastinal mass, often with obliteration or obscuring of the tracheal air column. These masses can also cause positional obstruction of vascular structures such as the superior vena cava or a pulmonary artery. Lam and colleagues[525] reported that clinical presentation is often nonspecific or often times incidental and that patients with airway compromise often also exhibited symptoms of superior vena cava syndrome.[525] These symptoms are often referred to as *critical mediastinal mass syndrome* and requires the care of an experienced multidisciplinary team. These tumors can be malignant (87% Hodgkin and non-Hodgkin lymphoma) or benign; the prognosis and therapy rely on adequate diagnosis, which is best made by obtaining a tissue sample before treatment is begun.[526] However, obtaining a sample of the mediastinal mass may require anesthesia and surgery, and the airway must be manipulated and instrumented. All these maneuvers can cause the patient to die. Local anesthesia with fine-needle biopsy under radiographic guidance allows tissue sampling without anesthesia in some patients. Irradiation of the tumor before obtaining a tissue sample can reduce the size of the tumor and make biopsy easier and safer with anesthesia. Obstruction of the intrathoracic trachea is a major anesthetic risk for these patients; it is often impossible to maintain a patent airway when the patient lies supine, is deeply anesthetized, or is paralyzed with muscle relaxants.[525,527] However, the patient must cooperate sufficiently to perform the test, which is often difficult for them because of respiratory distress. Induction of anesthesia and tracheal intubation are usually done with the patient in the sitting position and breathing spontaneously. If the airway compromise is severe, the tumor should be irradiated and the child should be given steroids before a tissue diagnosis is made; however, these treatments could alter diagnosis and should be discussed with an oncology consultant before initiating them. Sometimes, a peripheral node or mass can be biopsied under local anesthesia. If the tumor mass is large, some of the tumor can remain outside the field of radiation. Sticker and colleagues[527] report that, in a single-center review of 46 cases, patients with symptomatic anterior mediastinal mass underwent biopsy with general anesthesia while maintaining spontaneous ventilation without serious complications.[527] In summary, although diagnosis is the key to treatment of neoplastic disease, the risk associated with biopsy can far outweigh the benefit of tissue diagnosis.

IMMUNITY AND INFECTION

EMPIRIC ANTIBIOTIC COVERAGE

It is difficult to make empiric recommendations for antibiotic coverage for the pediatric ICU. Antibiotic resistance can result from use of broad-spectrum antibiotics without some degree of stewardship. Furthermore, empiric antibiotics should be based on the susceptibility profile of the common bacteria within each hospital and patient population. In the authors' practice, for patients presenting with sepsis, vancomycin and a third-generation cephalosporin in combination are the antibiotics of first choice; this is due to a rising incidence of methicillin-resistant *Staphylococcus aureus* (MRSA). To reduce the spread of MRSA, all patients are screened on admission for colonization and isolated if MRSA is found. Antibiotic coverage can be more specific and narrowed as culture results and sensitivities return. Likely the best recommendation to be made regarding empiric antibiotic coverage is to meet with the infectious disease specialists and discuss the current hospital culture isolates and their antibiotic resistance. Decisions regarding empiric antibiotics are best made in advance of the situation.

PREVENTION OF HEALTH CARE–ASSOCIATED INFECTIONS

The effects of hospital-acquired infections (HAIs) on the medical system are significant and on the individual patient level can be deadly. A 2007 article from Klevens and associates[528] estimated the number of HAIs in U.S. hospitals in the year 2002 at 1.7 million. Of these, 417,946 HAIs occurred among adults and children in an ICU setting. The estimated deaths associated with the HAIs in this period were 98,987. Likely the best thing to protect patients is to wash hands or use alcohol-based gels and encourage others to do so. Encouraging others or providing a positive role model can have a broader effect than anticipated. A 2009 study by Schneider and associates[529] paired trainees who were critical care fellows or nurse orientees with senior supervisors and evaluated compliance with hand hygiene. In the control phase, the senior supervisors were unaware of the study and had a hand hygiene compliance of 20%. The trainees that were being mentored had a hand hygiene compliance of 22%. When the senior supervisors were recruited into the study, there was a hand hygiene compliance of 94%. The trainees who were still blinded to the study had an increase in the hand hygiene compliance to 56%. Certainly it is anticipated that there will be better compliance with hand hygiene if health care providers know that they are being observed. The Schneider study shows the importance of role modeling positive behavior.[529] Ongoing audits of hand hygiene compliance are recommended. Auditors should patient's parents to remind health care providers to wash if they have not observed it. Although it may be difficult, it is important to be willing to remind others to wash their hands.

VENTILATOR-ASSOCIATED PNEUMONIA

Intubation and mechanical ventilation is necessary for patients with respiratory failure. Unfortunately, an ETT

prevents airway protective mechanisms and increases the risk of ventilator-associated pneumonia (VAP). Patients who need mechanical ventilation but who do not have a pulmonary infection can develop pneumonia, and patients who need mechanical ventilation for pneumonia can develop a secondary infection. VAP can increase morbidity and mortality. A 2009 study by Srinivasan and associates[530] demonstrated that patients with VAP had increased length of mechanical ventilation, prolonged stays in the ICU, and more importantly a significant increase in mortality. There was 2.4% mortality in the patients who did not develop VAP as compared with 10.5% mortality in the patients who did. VAP has been defined as the new onset of a lower respiratory tract infection for patients who have required mechanical ventilation for greater than 48 hours. The diagnostic criteria include a new infiltrate on chest radiograph, a positive respiratory culture, a low or elevated white blood cell count, and fever or instability in temperature.

In January 2005, the nonprofit Institute for Healthcare Improvement (IHI) started the *100,000 Lives* campaign. The goal was to save the lives of 100,000 patients in a period of 18 months by six specific, evidence-based clinical interventions. They encouraged hospitals to deploy rapid response teams, deliver evidenced-based care for acute myocardial infarction, prevent adverse drug events, prevent surgical site infections, prevent central line infections, and prevent VAP. The last two incorporated the use of bundles or collections of scientifically grounded interventions that were implemented collectively. These interventions have been successful. From the VAP standpoint the pre-bundle VAP incidence for PICU patients was reported in 2002 as 11.6/1000 ventilator days. [531] The VAP bundle has been tailored to pediatric patients,[532] and there have been significant improvements in VAP incidence. In a 2009 study showing the benefit of bundle implementation, Bigham and colleagues[533] showed a significant reduction in VAP incidence from 5.6 to 0.3 per 1000 ventilator days. This single-center study also showed a reduction in length of mechanical ventilation, length of stay, and mortality. This positive benefit of bundle initiation has been shown in other pediatric studies as well.[534,535]

In an effort to reduce incidence of new bacterial infection while patients are mechanically ventilated, the components of the VAP bundle aim to reduce bacterial colonization and prevent aspiration of contaminated secretions. To reduce the amount of bacteria present in the mouth and sinuses, mouth care is performed with a chlorhexidine rinse every 2 to 4 hours. Several things are done to reduce the risk of aspiration of contaminated secretions. First, suction the oropharynx before suctioning the ETT or deflating the ETT cuff. Second, drain the condensation that occurs in the ventilator tubing every 2 to 4 hours and before repositioning the patient; this should be done without disconnecting the ventilator circuit. Third, use inline suction catheters such that the ETT can be suctioned without disconnecting the ventilator circuit. Finally, by maintaining the head of the bed greater than 30 degrees there is a decreased risk of secretions in the ventilator tubing draining passively into the ETT.

The measures included in a VAP bundle are not difficult to perform and become routine practice quite quickly. More interesting is synergy that occurs with a bundle in that the effect of the combined interventions seems to be greater than any individual component. A strong adherence to a bundle of preventive measures has also been significantly helpful in the prevention of blood stream infection because of the presence of a central line.

CATHETER-ASSOCIATED BLOOD STREAM INFECTIONS

The development of catheter-associated bloodstream infection (CA-BSI) has received national recognition in both adults and pediatrics. It is one of the indicators by which hospitals are evaluated, and with CA-BSI there is a significant increase in hospital stay, morbidity, mortality, and cost. In a prospective study performed in a pediatric cardiac ICU, Abou and associates[536] showed 11% mortality in patients who developed a blood stream infection as compared with 2% mortality in patients who did not. It has been said by many that the best way to reduce a CA-BSI is never to place a central venous catheter. There is benefit to continually reviewing a patient's requirements for central venous access and when possible only using peripheral catheters. Unfortunately, there are many instances, such as the need for vasoactive medications, when central venous catheters cannot be avoided. The implementation of bundles to care for central venous catheters can significantly reduce the development of bloodstream infections and reduce the mortality and morbidity for each patient.

Implementation of preventive bundles during the insertion of, and ongoing maintenance of, central venous catheters will reduce infections. In a 2010 study in 29 PICUs,[537] there was a 43% reduction in the development of CA-BSI when bundles were used. These results are sustainable and continue to improve. The 2011 follow-up by the same group showed a further reduction in the incidence of CA-BSI.[538] The bundle can be broken down into two parts: central line insertion and maintenance. During the insertion of the central venous catheter, the goal of the bundle is to maintain complete sterility of the field. Chlorhexidine is used as the skin preparation for patients older than 2 months. All people in the room wear caps and masks. The persons performing the procedure wear these, as well as a sterile gown and gloves. A large, sterile barrier covering the entire bed is used. The second phase of the bundle is ongoing maintenance of the central venous catheter. There are strict guidelines for the care of the intravenous tubing, hub, and catheter insertion site. When dressing changes are performed, sterile gloves are used, the area is scrubbed for 30 seconds with chlorhexidine, and it is allowed to air dry for 30 seconds. Strict adherence to the same maintenance guidelines throughout the entire hospital is necessary to prevent CA-BSI. In many institutions, the number of infections has dropped so low that each event can be individually reviewed.

URINARY TRACT INFECTION

Catheter-associated urinary tract infections is the most common health-care–related infection. Removing a bladder catheter if it is not needed can significantly reduce the

risk of developing a urinary tract infection. In some cases, the catheter cannot be removed, and efforts should be made to prevent infection. Institution of a bladder-care bundle as a quality improvement measure can significantly reduce infection rates. In a 2013 study by Esteban and coworkers,[539] implementation of quality improvement interventions decreased the number of catheter-associated urinary tract infections from 23.3 to 5.8 per 1,000 urinary catheter days. The goals of a bladder catheter bundle are to reduce the bacterial colonization and to reduce the reflux of urine back into the bladder. Catheters are inserted in a sterile fashion, and periurethral cleaning is performed with a chlorhexidine cloth at least once per shift. To prevent reflux the collection bag is always kept below the level of the bladder and is drained completely or clamped before moving the patient.

INFECTIONS IN THE NEWBORN

Neonates with developmental immunologic deficiencies have increased susceptibility to infection. Depressed cell-mediated immunity makes the fetus and infant more susceptible to viral and fungal infection. In addition, infants have depressed B cell function and diminished production of immunoglobulins. The latter is partially offset by increased maternal immunoglobulin G. By 2 to 3 months of age, which is before infants can adequately produce their own antibodies in sufficient quantity, the level of maternal antibodies reaches a nadir.[540] The time during which the circulating antibody concentration is low is a time when the risk for infections is increased. Perinatal infections are acquired congenitally or postnatally. Congenital infections occur with prenatal exposure to viral, protozoal, or rarely, bacterial pathogens. Common diseases include the TORCH infections: *Toxoplasma gondii* (T); "other" (O), including human immunodeficiency virus (HIV), syphilis, and tuberculosis; rubella (R); cytomegalovirus (C); and herpes simplex virus type 2 (H). Rarely do these infections cause overwhelming sepsis, but they can be confused with bacterial infection when profound CNS depression, circulatory collapse, or thrombocytopenia occurs. When a TORCH infection develops in the first trimester of pregnancy, it causes fetal wastage or major organ malformation. Premature infants have a high incidence of acute infections in the newborn period. Regardless of gestational age, the signs and symptoms of infection are often subtle. Therefore, a high index of suspicion and low threshold for diagnosing and treating infection are required.[541] The most common acquired pathogens are those that colonize the mother's genital tract: group B streptococci, *E. coli*, *Listeria monocytogenes*, and herpesvirus. Herpes is such a fulminant infection in neonates that the presence of active herpes lesions in the birth canal is an indication for cesarean section, although this may not prevent herpes in all children. Group B *Streptococcus* is the most common bacterial pathogen that causes neonatal sepsis. Infection with group B streptococci is manifested as severe cardiorespiratory instability and meningitis in 30% of cases. By 2 to 3 weeks of age, this organism is more commonly associated with meningitis and less commonly with pulmonary disease. Whenever sepsis is suspected, cultures of blood, urine, and CSF should be obtained. Because it is difficult for the physician to localize the infection in an infant, repeated complete sepsis workups are often required. When appropriate cultures are obtained, treatment with ampicillin and an aminoglycoside, such as gentamicin, is usually begun until specific bacteriologic information becomes available. Approximately 50% of neonates thought to be septic have positive cultures.

PEDIATRIC TRAUMA

PRENATAL AND PERINATAL INJURIES

Perinatal trauma occurs before or immediately after birth (see Chapter 81). The most common prenatal injuries are due to maternal gunshot wounds and blunt trauma. Fetal mortality in both cases is at least twofold that of the mother,[542] with fetal death being attributable to maternal shock and fetal oxygen deprivation rather than direct injury. Birth injuries occur more commonly in large, full-term infants and in infants born by breech presentation. Injuries to the head include linear or depressed skull fractures, cephalohematomas, subdural or subarachnoid hematomas, and intraparenchymal or intraventricular hemorrhage. Intracranial injuries can increase ICP and cause cerebral ischemia, neurologic injury, and death. Injury to the sternocleidomastoid muscle can cause torticollis; traction on the neck can transect the cervical spinal cord. Less devastating nerve injuries caused by cervical traction are phrenic nerve paralysis and Erb or Klumpke palsy, which is caused by brachial plexus stretching or tearing (or both). Shoulder dystocia is commonly associated with clavicular and humoral fractures; femoral shaft fractures occur with breech deliveries. Injuries to the liver, spleen, adrenal glands, and kidneys can cause life-threatening hemorrhage or thrombosis. Vasoocclusion causes tissue loss in the cerebral, coronary, or renal vascular beds. Emergency instrumentation of the airway in the delivery room on rare occasion leads to tracheal and esophageal perforation, particularly in a premature infant.

TRAUMA IN CHILDREN

Accidents and trauma are the leading causes of death in children 1 to 14 years of age.[543] Children are frequently victims of falling or being dropped, drowning, near drowning, motor vehicle crashes (pedestrian), ingestions, and burns. Head injuries are common, especially in younger children, who have disproportionately large heads and relatively poor neck muscle support.[544] Young children are less likely to be victims of gunshot or knife attacks; blunt injuries are more common. Blunt trauma to the abdomen can cause solid organ injury (liver and spleen) rather than a perforated viscus. Hypothermia is a frequent complication of trauma; children lose heat rapidly because they have a relatively large surface-to-volume ratio. Drowning and near-drowning are the prototypical hypothermic injuries. Management of trauma patients of all ages requires an organized approach that permits rapid diagnosis and treatment. Most preventable deaths

in pediatric trauma patients are caused by airway obstruction, pneumothorax, and shock. Shock is often the result of inadequate treatment of bleeding or secondary brain injury from an expanding intracranial hematoma.[545] The American College of Surgeons recommends a four-step approach to pediatric trauma patients: (1) primary survey, (2) resuscitation, (3) secondary survey, and (4) definitive care.[250] The primary survey requires rapid assessment of the airway, breathing, and circulation (ABCs). A disproportionately large tongue, in relation to a narrow oropharynx, easily obstructs the airway in an unconscious child. Proper jaw positioning enables bag-valve-mask ventilation until the trachea is intubated. Ventilation through an inadequate airway can lead to gaseous distention of the stomach, vomiting, and aspiration of gastric contents. Cervical spine injuries are less common in children than in adults, but the child's neck should be immobilized until spinal injury is excluded. After establishing an airway, adequacy of respiration should be verified by observation of symmetric chest movement, auscultation of normal and equal breath sounds, and an early chest radiograph. Tension hemopneumothorax can be diagnosed clinically and treated by needle aspiration. Aspiration will alleviate the tension and stabilize the patient's condition until a chest tube can be inserted. Circulation can be assessed quickly by looking for tachycardia, poor peripheral perfusion, weak peripheral pulses, and hypotension (which might not occur until blood loss exceeds 25% of the circulating blood volume).[546] A severely hypovolemic child requires rapid insertion of a central venous catheter. If a peripheral venous catheter cannot be inserted expeditiously, an intraosseous cannula should be placed.[547] The amount of volume resuscitation is dictated by the clinical condition of the child and the estimated volume of blood or plasma lost. During the secondary survey, a thorough head-to-toe examination is performed, and a plan of definitive treatment is developed. Diagnostic measures in a pediatric trauma patient are similar to those in adult patients, but there should be consideration of special problems that occur in children. Most intraabdominal injuries requiring laparotomy are recognized clinically because they produce peritonitis or cause increasing abdominal girth.[548] Diagnostic peritoneal lavage can be of help in children who are hemodynamically unstable despite administering more than 40 mL/kg of blood. Peritoneal lavage can locate the site of occult bleeding in a child who is too unstable to undergo CT, or it can be used to evaluate abdominal injury in a child about to undergo emergency surgery that is not abdominal. Many practitioners forego this procedure if surgery is imminent. Indications for surgical intervention for abdominal trauma include free peritoneal air, evidence of a ruptured viscus, and acute uncontrolled bleeding. A ruptured spleen or a liver laceration is not an indication for surgery in and of itself; the preferred treatment is supportive care, blood volume replacement, and reevaluation.[549] A careful head and neurologic examination is done to detect intracranial trauma quickly. The most important indicator of intracranial trauma is a decrease in the level of consciousness. Rapid diagnosis and treatment of intracranial mass lesions will reduce ICP and may prevent secondary brain injury.

CHILD ABUSE

The diagnosis of child abuse is made by finding an acute injury that might have a plausible explanation and signs of past trauma, including healing bruises, contusions, and fractures. Child abuse can also take the form of psychological or sexual abuse and failure to meet a child's need for food, clothing, shelter, hygiene, medical care, education, or supervision. Suspicion of child abuse begins with an inappropriate or inadequate explanation for the child's injuries or when the degree of trauma exceeds the stated cause. Multiple hospital admissions, emergency department visits, doctor or hospital "shopping," and a history of previous trauma should be of concern. Frequently, the story regarding the injury changes over time. Certain clinical features are common to child abuse, but they are by no means pathognomonic. Most abused children are older than 3 years; they sometimes have poor hygiene and delayed somatic or psychological development. The injuries most commonly include bruises, welts, lacerations, scalds, and burns from cigarettes, stoves, heating grates, or irons. Long-bone fractures, often of varying age, abdominal injuries, signs of smothering, and multiple soft tissue or genital bruises are also common. Head injuries can occur. Shaking an infant can cause neck injuries, intracranial hemorrhage, and contrecoup injuries without necessarily producing external manifestations of trauma. The approach to a possible victim of child abuse includes a meticulous and nonjudgmental history, written in detail in the chart. All allegations are recorded and changes in the reported history are documented. The physical examination includes growth parameters, descriptions of soft tissue bruising or burns, and diagrams or preferably photographs of all injuries. The color, shape, placement, and estimated age of all injuries should be catalogued. Laboratory studies should include the following: a skeletal survey of all long bones, ribs, and the skull; a coagulation profile, including hematocrit, platelet count, PT, and PTT; and genital and throat cultures for venereal disease if sexual abuse is suspected. If child abuse is suspected, it must be reported to the authorities.

INGESTION INJURY

Despite the success of various preventive public health programs, poisoning continues to occur commonly in pediatric patients. Fortunately, the vast majority of presumed poisonings in young children can be managed by telephone consultation with a regional poison control center. In one study, acute poisoning accounted for approximately 5% of all medical admissions to a PICU.[550] Approximately half of these admissions were accidental ingestions, and half were attempted suicides. The median age for the accidental poisoning group was 2 years; it was 15 years for the suicide group. Although many different toxic substances are ingested by children and adolescents, management of poisoning has three main goals: (1) identifying, decontaminating, and eliminating the toxic agents[551]; (2) minimizing the toxic effects on the child; and (3) providing close observation and organ system support until detoxification is complete. Procedures

for drug elimination include emesis, gastric lavage, activated charcoal, and magnesium citrate. Toxic effects can be minimized with specific antidotes when available, by hemodialysis, or by charcoal hemoperfusion. Examples of specific antidotes are deferoxamine for iron ingestion, ethanol infusion for methanol ingestion, naloxone for narcotic overdose, and *N*-acetylcysteine for acetaminophen ingestion. Because many ingestions, particularly those for attempted suicide, include multiple drugs, specific antidote therapy is only occasionally successful. Organ system support usually includes airway protection and mechanical ventilation, intravenous fluids, cardiovascular monitoring for arrhythmias and myocardial depression, and anticonvulsive therapy for patients who are seizing. Consultation with clinical pharmacologists or with the regional poison control center and contacting a social worker or psychiatrist are essential aspects of the care of an acutely toxic child. Common complications of ingestions and their therapy include aspiration pneumonia with hydrocarbon ingestion or loss of glottic function, sepsis, respiratory depression, myocardial depression, arrhythmias, seizures, and coma. The psychosocial environment that allowed or precipitated the ingestion must also be considered. Families should be counseled about proper supervision and "child-proofing" their home. Psychiatric intervention should be introduced early; unsuccessful suicide attempts are often repeated.

TRANSPORT OF THE CRITICALLY ILL CHILD

Transport of critically ill children can be intrahospital or interhospital. Intrahospital transport of patients is necessary when moving to and from the operating room; however, this also includes transport for radiologic procedures and studies throughout the hospital. In this circumstance, the clinician who ordered the test must understand the balance of risk and benefit. Is the information that can be obtained by an MRI worth the transport, changes in monitoring, and the time away from the ICU? In the case of a brain MRI, a patient may be away from the unit for 90 to 120 minutes with transport. There are significant differences in the ability to monitor and provide care to those patients. CT scans are shorter but still entail many of the same risks. The severity of the patient's illness must be considered. Any patient with an ETT is at risk for obstruction or dislodgement. Any patient requiring inotropic support is at risk for those medications being interrupted. Depending on the hospital, the team transporting the patient may include a respiratory therapist, bedside nurse, and transport nurse. Some hospitals will send their ICU fellows, and some have a dedicated intrahospital transport team. When new equipment is purchased, transport monitors should be considered that have the ability to monitor $ETCO_2$. In the smallest patients, maintenance of body temperature can be difficult during transport.

Interhospital transport systems are typically established by a tertiary care hospital. Smaller community hospitals may use outside resources. One should investigate the capabilities of the transport team available. Details to understand include the availability of helicopter and fixed-wing flight, types of practitioners on the transport team, coverage in the circumstance where the primary team is out on a transport, and the ability to provide interventions when the transport team arrives at the outside facility. Many transport care physicians will be able to intubate, place arterial and venous lines, and place chest tubes at an outside facility. All this information is valuable when speaking to the referring hospital. In that regard, the person receiving the transport request may need to assess whether the patient is safe to transfer by a team that provides only basic life-support resuscitation. For hospitals unfamiliar with caring for critically ill children, it may be foremost in their mind to get the child to a higher level of care, and out of their hospital. They may not have considered what support is available during the transport if the patient deteriorates. They may be unwilling to wait for arrival of a transport team, but make the overall needs of the child must be the focus of the discussion. When deciding on the make-up of the transport team, the distance of the referring hospital, condition of the child, ongoing resuscitation efforts and chance of change in condition need to be considered. While the transport team is en route, the referring hospital should continue to support and resuscitate the child with advice from the receiving hospital. Further information regarding the development of a transport team are beyond the scope of this chapter. One excellent resource is the Guidelines for Air and Ground Transport of Neonatal and Pediatric Patients available through the American Academy of Pediatrics. An understanding of altitude physiology is necessary when considering transport by helicopter. One may not give much thought to the barometric pressure in the alveolar gas equation:

$$PAO_2 = (P_B - P_{H_2O}) \times FiO_2 - (PaCO_2/R)$$

This is because at sea level P_B is 760 mm Hg; however at 8,000 feet P_B is 565 mm Hg. Supplemental oxygen may be needed in flight, and low saturation may remain even with supplemental oxygen for patients with significant lung disease. From Boyles law ($Pressure_1 \times Volume_1 = Pressure_2 \times Volume_2$) there will be expansion of gas with the decreased pressure of altitude; this means that a small pneumothorax can expand to a large pneumothorax. The size of an ETT cuff can expand, putting significant pressure on the trachea. The PICU relies significantly on the skills of the transport team. To maintain proficiency, the providers will need to practice intubation and other procedures. It is important to consider helping when asked to be shadowed by a transport physician or nurse in the operating room to gain practice with intubation.

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Chapter 96

The Postanesthesia Care Unit

THEODORA KATHERINE NICHOLAU

Key Points

- Emergence from general anesthesia and surgery may be accompanied by a number of physiologic disturbances that affect multiple organ systems. Most common are postoperative nausea and vomiting (PONV), hypoxia, hypothermia and shivering, and cardiovascular instability.
- In a prospective study of more than 18,000 consecutive admissions to the postanesthesia care unit (PACU), the complication rate was found to be as frequent as 24%. Nausea and vomiting (9.8%), the need for upper airway support (6.8%), and hypotension (2.7%) were the most common problems.
- The most frequent cause of airway obstruction in the immediate postoperative period is the loss of pharyngeal muscle tone in a patient who is sedated or obtunded. The persisting effects of inhaled and intravenous anesthetics, neuromuscular blocking drugs, and opioids all contribute to the loss of pharyngeal tone in the patient in the PACU.
- The oropharyngeal muscles are the last muscle group to recover from neuromuscular blockade. Routine monitoring by the train-of-four (TOF) ratio does not accurately reflect the return of pharyngeal muscle tone.
- The use of intermediate-acting neuromuscular blocking agents is associated with an increased incidence of postoperative respiratory complications. Reversal with the anticholinesterase neostigmine does not prevent and may in fact increase the incidence of postoperative pulmonary complications.
- An estimated 8% to 10% of patients who undergo abdominal surgery subsequently require intubation and mechanical ventilation in the PACU. Respiratory failure in the immediate postoperative period is often due to transient and rapidly reversible conditions such as splinting from pain, diaphragmatic dysfunction, muscular weakness, and a pharmacologically depressed respiratory drive.
- Although a combination of leads II and V_5 will reflect 80% of the ischemic events detected on a 12-lead electrocardiogram (ECG), visual interpretation of the cardiac monitor is often inaccurate. Because of human error, guidelines from the American College of Cardiology recommend that computerized ST-segment analysis be used (if available) to monitor patients at high risk for cardiac complications in the immediate postoperative period.
- In one study, the incidence of postoperative urinary retention, defined as bladder volume greater than 600 mL in conjunction with an inability to void within 30 minutes, was 16%. The most significant predictive factors were age older than 50 years, intraoperative fluid greater than 750 mL, and bladder volume on entry to the PACU greater than 270 mL.
- Perioperative attention to adequate intravenous hydration is indicated in any patient who has received an intravenous contrast agent. Aggressive hydration with normal saline provides the single most effective protection against contrast nephropathy.
- Rhabdomyolysis has been reported to occur in 22.7% of 66 consecutive patients undergoing laparoscopic bariatric surgery. Risk factors include increased body mass index (BMI) and duration of surgery.
- The incidence of postoperative shivering may be as high as 65% (ranging from 5% to 65%) after general anesthesia and 33% after epidural anesthesia. Identified risk factors include male gender and the choice of induction agent; propofol is more commonly associated with shivering than is pentothal.

KEY POINTS—cont'd

- Approximately 10% of adult patients older than age 50 years who undergo elective surgery will experience some degree of postoperative delirium within the first 5 postoperative days. The incidence is significantly higher for certain procedures, such as repair of hip fracture (>35%) and bilateral knee replacement (41%).
- PACU Standards of Care require that a physician accept responsibility for the discharge of patients from the unit (Standard V), even when the decision to discharge the patient is made at the bedside by the PACU nurse in accordance with hospital-sanctioned discharge criteria or scoring systems.

The postanesthesia care unit (PACU) is designed and staffed to monitor and care for patients who are recovering from the immediate physiologic effects of anesthesia and surgery. PACU care spans the transition from one-on-one monitoring in the surgical unit to the less acute monitoring on the hospital ward or, in some cases, independent function of the patient at home. To serve this unique transition period, the PACU is equipped to resuscitate patients who are unstable while providing a tranquil environment for the "recovery" and comfort of patients who are stable. Its location, which is in close proximity to the surgical department, facilitates rapid access to anesthesiologists for consultation and assistance.

ADMISSION TO THE PACU

Specially trained nurses skilled in the prompt recognition of postoperative complications make up the staff of the PACU. On arrival of a patient to the PACU, the anesthesiologist provides the PACU nurse with pertinent details of the patient's history, medical condition, anesthesia, and surgery. Particular attention is directed toward monitoring oxygenation (pulse oximetry), ventilation (breathing frequency, airway patency, capnography), and circulation (systemic blood pressure, heart rate, electrocardiogram [ECG]). Vital signs are recorded as often as necessary but at least every 15 minutes while the patient is in the unit. Vital signs and other pertinent information are recorded as part of the patient's medical record. Specific requirements and recommendations for patient monitoring and therapeutic intervention can be found in the Practice Standards and Guidelines drafted by the American Society of Anesthesiologists (ASA).

STANDARDS FOR POSTANESTHESIA CARE

Practice Standards delineate the required *obligation* of *minimal* care in the clinical setting. As such, they serve as a threshold that can be exceeded when indicated by the clinical judgment of the practitioner. The Standards for Postanesthesia Care are updated on a regular basis to keep up with changing practice parameters and technologic advances. The most recent revision, published in 2009, is summarized here.[1]

I. All patients who have received general anesthesia, regional anesthesia or monitored anesthesia care shall receive appropriate postanesthesia management.
II. A patient transported to the PACU shall be accompanied by a member of the anesthesia care team who is knowledgeable about the patient's condition. The patient shall be continually evaluated and treated during transport with monitoring and support appropriate to the patient's condition.
III. Upon arrival in the PACU, the patient shall be re-evaluated and a verbal report provided to the responsible PACU nurse by the member of the anesthesia care team who accompanies the patient.
IV. The patient's condition shall be evaluated continually in the PACU. The patient shall be observed and monitored by methods appropriate to the patient's medical condition. Particular attention should be given to monitoring oxygenation, ventilation, circulation, level of consciousness, and temperature. During recovery from all anesthetics, a quantitative method of assessing oxygenation such as pulse oximetry shall be employed in the initial phase of recovery.*
V. A physician is responsible for the discharge of the patient from the postanesthesia care unit.

Unlike Practice Standards, Practice Guidelines are not requirements. They are recommendations designed to assist the health care provider in clinical decision making. The ASA Practice Guidelines for Postanesthetic Care are the result of a multiple-step process that incorporates input from three groups: (1) an ASA-appointed taskforce consisting of private practice and academic anesthesiologists and epidemiologists; (2) PACU consultants; and (3) ASA members at large. These Guidelines are based on literature review, expert opinion, open forum commentary, and clinical feasibility. They recommend the appropriate assessment, monitoring, and treatment of the major organ system functions during recovery from anesthesia and surgery (Box 96-1).[2]

*Under extenuating circumstances, the responsible anesthesiologist may waive the requirements marked with an asterisk (*); it is recommended that when this is done, it should be so stated (including the reasons) in a note in the patient's medical record.

BOX 96-1 *Summary of Recommendations for Patient Assessment and Monitoring in the Postanesthesia Care Unit*

Respiratory

Assessment of airway patency, respiratory rate, and oxygen saturation should be periodically performed. Particular attention should be given to monitoring oxygenation and ventilation.

Cardiovascular

Heart rate and blood pressure should be routinely monitored. Electrocardiographic monitors should be immediately available.

Neuromuscular

Assessment of neuromuscular function should be performed for all patients who received nondepolarizing neuromuscular blocking drugs or who have medical conditions associated with neuromuscular dysfunction (also see Chapter 53).

Mental Status

Mental status should be periodically assessed.

Temperature

Patient temperature should be periodically assessed.

Pain

Pain should be periodically assessed.

Nausea and Vomiting

Periodic assessment of postoperative nausea and vomiting should be routinely performed

Hydration

Postoperative hydration should be assessed and managed accordingly. Certain procedures may involve significant blood loss and require additional intravenous fluids management.

Urine

Assessment of urine output and of urinary voiding should be performed on a case-by-case basis for selected patients or selected procedures.

Drainage and Bleeding

Assessment of drainage and bleeding should be performed periodically as needed

From Apfelbaum JL, Silverstein JH, Chung FF, et al: Practice guidelines for postanesthetic care: an updated report by the American Society of Anesthesiologists Task Force on Postanesthetic Care, Anesthesiology *118:291-307, 2013.*

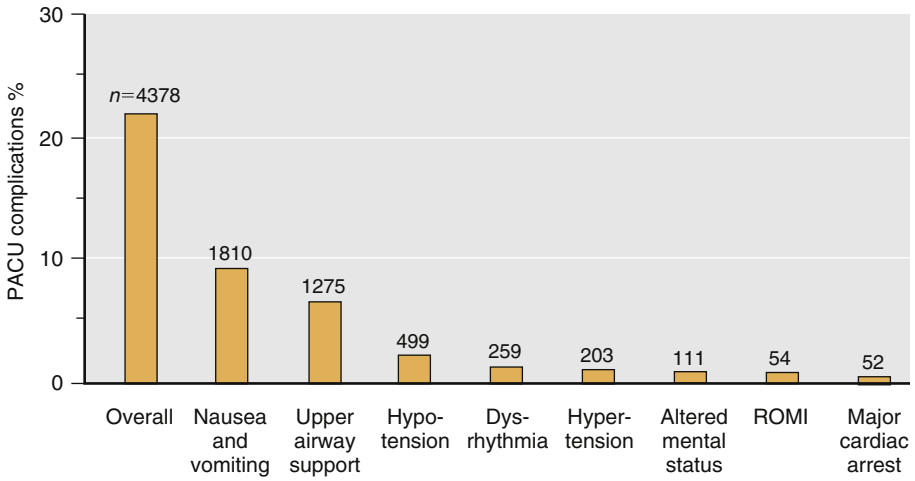


Figure 96-1. The overall complication rate in 18,473 consecutive admissions to a postanesthesia care unit (PACU) was 23.7%. Nausea and vomiting, the need for upper airway support, and hypotension were the most frequent individual complications. *ROMI,* Rule out myocardial infarction. *(From Hines HR, Barash PG, Watrous G, et al: Complications occurring in the postanesthesia care unit: a survey,* Anesth Analg *74:503-509, 1992. Used with permission.)*

In addition to the recommendations for patient assessment and monitoring in the PACU summarized in Box 96-1, other recommendations include the following:

- Multiple antiemetic agents are used for the prevention or treatment of postoperative nausea and vomiting (PONV).
- Oxygen is administered for patients at risk of hypoxemia.
- When available, forced air warmers should be used to reach the goal of normothermia.
- Demerol or other opioid agonists should be used for the treatment of postoperative shivering but not replace treating hypothermia by rewarming.
- Specific antagonists should be available whenever benzodiazepines, opioids, or neuromuscular blockers have been administered.
- The requirement for urination or drinking clear liquids should not be part of a discharge protocol but may be necessary for selected patients.
- ALL patients should be required to have a responsible individual to accompany them home.
- A mandatory minimum stay should not be required, but patients should be observed until they are no longer at risk for cardiopulmonary depression.

EARLY POSTOPERATIVE PHYSIOLOGIC CHANGES

A number of physiologic disturbances that affect multiple organ systems may accompany the patient's emergence from general anesthesia and surgery. Most common are PONV, hypoxia, hypothermia and shivering, and cardiovascular instability. In a prospective study of more than 18,000 consecutive admissions to the PACU, the complication rate was found to be as high as 24%. Nausea and vomiting (9.8%), the need for upper airway support (6.8%), and hypotension (2.7%) were the most common (Fig. 96-1).[3]

TABLE 96-1 **PRIMARY PRESENTING PROBLEM IN 419 RECOVERY ROOM INCIDENTS REPORTED TO AUSTRALIAN INCIDENT MONITORING STUDY**

Primary Presenting Problem	No. (%)
Cardiovascular	99 (24)
Respiratory	97 (23)
Airway	86 (21)
Drug error	44 (11)
Central nervous system	32 (8)
Equipment	27 (6)
Communication problems	7 (2)
Hypothermia	6 (1)
Regional block problems	4 (1)
Inadequate documentation	4 (1)
Hyperthermia	3 (1)
Trauma	3 (1)
Dental problems	2 (0.5)
Renal	1 (0.2)
Skin	1 (0.2)
Blood transfusion	1 (0.2)
Facility limitations	1 (0.2)
Gastrointestinal problems	1 (0.2)

From Kluger MT Bullock MF: Recovery room incidents: a review of the Anesthetic Incident Monitoring Study (AIMS), Anesthesia *57:1060-1066, 2002.*

Over a 4-year period ending in 1989, 7.1% of the 1175 anesthesia-related malpractice claims in the United States were attributed to recovery incidents.[4] Despite the significant incidence of nausea and vomiting in the PACU, serious adverse outcomes correlate more closely with airway, respiratory, and cardiovascular compromise. In 2002, airway and respiratory problems (183, 43%) and cardiovascular events (99, 24%) accounted for the majority of 419 recovery room incidents reported to the Australian Incident Monitoring Study (AIMS) database (Table 96-1).[5] Similar data were obtained from the United States closed claims database in 1989, in which critical respiratory incidents accounted for more than one half of the recovery room malpractice claims.[4]

TRANSPORT TO THE PACU

Upper airway patency and the effectiveness of the patient's respiratory efforts must be monitored when transporting the patient from the surgical department to the PACU. Watching for the appropriate rise and fall of the chest wall with inspiration, listening for breath sounds, or simply feeling for exhaled breath with the palm of one's hand over the patient's nose and mouth can confirm adequate ventilation.

With rare exceptions, all patients who undergo general anesthesia should receive supplemental oxygen during their transport to the PACU. In an observational study of 502 patients admitted to the PACU, breathing room air during transport was the single most significant factor to correlate with hypoxemia (oxygen saturation < 90%) on arrival. Other significant factors included elevated body mass index (BMI), sedation score, and respiratory rate.[6]

Although the majority of otherwise healthy patients undergoing ambulatory surgery can be safely transported breathing room air, the decision to do so must be made on a case-by-case basis. In the ambulatory setting, advanced age (>60 years) (see Chapters 80 and 89) and weight (>100 kg) identifies adults who are at increased risk for oxygen desaturation when breathing room air on transport to the PACU.[7] Hypoventilation alone may cause hypoxemia even in healthy patients who undergo minor procedures.

UPPER AIRWAY OBSTRUCTION

LOSS OF PHARYNGEAL MUSCLE TONE

The most frequent cause of airway obstruction in the immediate postoperative period is the loss of pharyngeal muscle tone in a patient who is sedated or obtunded. The persistent effects of inhaled and intravenous anesthetics, neuromuscular blocking drugs, and opioids all contribute to the loss of pharyngeal tone in the patient in the PACU.

In an awake patient, the pharyngeal muscles contract at the same time that negative inspiratory pressure is generated by the diaphragm, facilitating opening of the upper airway. As a result, the tongue and soft palate are pulled forward, tenting the airway open during inspiration. This pharyngeal muscle activity is depressed during sleep, and the resulting decrease in tone can promote airway obstruction. A vicious cycle then ensues in which the collapse of compliant pharyngeal tissue during inspiration produces a reflex compensatory increase in respiratory effort and negative inspiratory pressure that promotes further airway obstruction.[8]

A paradoxical breathing pattern consisting of retraction of the sternal notch and exaggerated abdominal muscle activity characterizes the effort to breathe against an obstructed airway. Collapse of the chest wall and protrusion of the abdomen with inspiratory effort produce a rocking motion that becomes more prominent with increasing airway obstruction. Simply opening the airway with the *jaw thrust maneuver* or continuous positive airway pressure (CPAP) applied via a facemask (or both) can relieve airway obstruction secondary to the loss of pharyngeal tone. Support of the airway is needed until the patient has adequately recovered from the effects of drugs administered during anesthesia. In selected patients, placement of an oral or nasal airway, laryngeal mask airway, or endotracheal tube may be required.

RESIDUAL NEUROMUSCULAR BLOCKADE

When evaluating upper airway obstruction in the PACU, the possibility of residual neuromuscular blockade should be considered in any patient who received neuromuscular blocking drugs during anesthesia (Box 96-2)[9,10] (see also Chapter 35). Residual neuromuscular blockade may not be evident on arrival in the PACU because the diaphragm recovers from neuromuscular blockade before the pharyngeal muscles do. With an endotracheal tube in place, end-tidal carbon dioxide concentrations and tidal volumes may indicate adequate ventilation while the ability to maintain a patent upper airway and clear upper airway secretions remains compromised. The stimulation associated with tracheal extubation, followed by the activity of

BOX 96-2 *Factors Contributing to Prolonged Nondepolarizing Neuromuscular Blockade*

Drugs

Inhaled anesthetic drugs
Local anesthetics (lidocaine)
Cardiac antiarrhythmics (procainamide)
Antibiotics (polymyxins, aminoglycosides, lincosamines [clindamycin], metronidazole [Flagyl], tetracyclines)
Corticosteroid agents
Calcium channel blockers
Dantrolene

Metabolic and Physiologic States

Hypermagnesemia
Hypocalcemia
Hypothermia
Respiratory acidosis
Hepatic or renal failure
Myasthenia syndromes

Factors Contributing to Prolonged Depolarizing Blockade

Excessive dose of succinylcholine
Reduced plasma cholinesterase activity
Decreased levels
- Extremes of age (newborn, old age)
- Disease states (hepatic disease, uremia, malnutrition, plasmapheresis)
- Hormonal changes
- Pregnancy
- Contraceptives
- Glucocorticoids

Inhibited activity
- Irreversible (echothiophate)
- Reversible (edrophonium, neostigmine, pyridostigmine)

Genetic variant (atypical plasma cholinesterase)

patient transfer to the gurney and subsequent mask airway support, may keep the airway open during transport to the PACU. Only after the patient is calmly resting in the PACU does upper airway obstruction become evident. Even patients treated with intermediate- and short-acting neuromuscular blocking drugs may exhibit residual paralysis in the PACU, despite what was deemed clinically adequate pharmacologic reversal in the surgical unit.

The train-of-four (TOF) ratio routinely used to evaluate neuromuscular function in anesthetized patients is unreliable.[11] Measurement of the TOF ratio is a subjective assessment that is often misleading when performed by touch or visual observation alone. A decline in the TOF ratio may not be appreciated until it reaches a value less than 0.4 to 0.5, whereas significant signs and symptoms of clinical weakness persist to a ratio of 0.7.[12] Furthermore, pharyngeal function is not restored to normal until an adductor pollicis TOF ratio is greater than 0.9.[13] Although 5 seconds of sustained tetanus to 100-Hz stimulation has been regarded as the most reliable indicator of adequate reversal of drug-induced neuromuscular blockade,[12,14] it is fraught with the same errors in interpretation as the TOF ratio.

Particular attention should be paid to patients who have received neuromuscular blockade even when the reversal agent neostigmine is administered. A prospective study of over 18,000 surgical patients who received intermediate-acting neuromuscular blocking drugs and their matched cohorts showed that paralysis with intermediate-acting neuromuscular blockade is associated with an increased risk of clinically meaningful postoperative respiratory complications, regardless of anticholinesterase reversal.[11]

In an awake patient, clinical assessment of reversal of neuromuscular blockade is preferred to the application of painful TOF or tetanic stimulation. Clinical evaluation includes grip strength, tongue protrusion, ability to lift the legs off the bed, and ability to lift the head off the bed for a full 5 seconds. Of these maneuvers, the 5-second sustained head lift has been considered to be the standard, reflecting not only generalized motor strength but, more importantly, the patient's ability to maintain and protect the airway. However, the ability to oppose the incisor teeth strongly against a tongue depressor is a more reliable indicator of pharyngeal muscle tone. This maneuver correlates with an average TOF ratio of 0.85, as opposed to 0.60 for the sustained head lift.[12] In a year-long study of 7459 patients who had received general anesthesia, Murphy and colleagues defined critical respiratory events (CREs) in 61 of these patients (see Chapter 35). These events occurred within the first 15 minutes of PACU admission, at which time a TOF ratio was measured. When compared with matched controls, these patients had a significantly lower TOF ratio (0.62 [±0.20]), compared with controls (90.98 [±0.07]).[15]

The manifestation of weakness in the patient in the PACU may be respiratory distress and/or agitation. If one suspects the persistence or return of neuromuscular weakness in the patient, then a prompt review of possible etiologic factors is indicated (see Box 96-2). Common factors include respiratory acidosis and hypothermia, alone or in combination. Upper airway obstruction as a result of the residual depressant effects of volatile anesthetics or opioids (or both) may result in progressive respiratory acidosis after the patient is admitted to the PACU and external stimulation is minimized. Simple measures such as warming the patient, airway support, and correction of electrolyte abnormalities can facilitate recovery from neuromuscular blockade. The use of sugammadex, instead of neostigmine, might possibly lead to a reduced incidence of residual neuromuscular blockade in the PACU. Although reversal with neostigmine requires a baseline twitch response to be effective, sugammadex, a selective rocuronium-binding agent, does not. In a recent study, reversal with sugammadex resulted in a return of TOF ratio to greater than 0.9 within 5 minutes in 85% of patients with no twitches on TOF stimulation.[16] Although the drug has been in use in Europe since 2008, it is currently available only for investigational use in the United States (also see Chapter 35). A United States clinical trial comparing sugammadex with usual care with neostigmine for reversal of neuromuscular blockade induced by rocuronium was conducted in 2012.[17]

LARYNGOSPASM

Laryngospasm refers to a sudden spasm of the vocal cords that completely occludes the laryngeal opening. It typically occurs in the transitional period when the extubated patient is emerging from general anesthesia. Although

laryngospasm is most likely to occur in the operating room at the time of tracheal extubation, patients who arrive in the PACU asleep after general anesthesia are also at risk for laryngospasm on awakening.

Jaw thrust maneuver with CPAP (up to 40 cm water [H_2O]) is often sufficient stimulation to *break* the laryngospasm. If jaw thrust maneuver and CPAP fail, then immediate skeletal muscle relaxation can be achieved with succinylcholine (0.1 to 1.0 mg/kg intravenously [IV] or 4 mg/kg intramuscularly [IM]). Attempting to pass a tracheal tube forcibly through a glottis that is closed because of laryngospasm is not acceptable.

EDEMA OR HEMATOMA

Airway edema is a possible surgical complication in patients undergoing prolonged procedures in the prone or Trendelenburg position. It can be particularly significant in procedures that involve large blood loss and require aggressive fluid resuscitation. Although facial and scleral edema is an important physical sign that can alert the clinician to the presence of airway edema, visible external signs may not accompany significant edema of pharyngeal tissue (see also Chapter 55). In addition to the generalized edema just described, surgical procedures on the tongue, pharynx, and neck, including thyroidectomy,[18,19] carotid endarterectomy,[20] and cervical spine procedures,[21] can produce more localized tissue edema or hematoma. If tracheal extubation is to be attempted in these patients in the PACU, then evaluation of airway patency must precede removal of the endotracheal tube. The patient's ability to breathe around the endotracheal tube can be evaluated by suctioning the oral pharynx and deflating the endotracheal tube cuff. With occlusion of the proximal end of the endotracheal tube, the patient is then asked to breathe around the tube. Good air movement suggests that the patient's airway will remain patent after tracheal extubation.[22] An alternative method involves measuring the intrathoracic pressure required to produce a *leak* around the endotracheal tube with the cuff deflated. This method was originally used to evaluate pediatric patients with croup before extubation.[23] When used in patients with general oropharyngeal edema, the *safe* pressure threshold can be difficult to identify. Lastly, when ventilating patients in the volume control mode, one can measure the exhaled tidal volume before and after cuff deflation. Patients who require reintubation generally have a smaller leak (i.e., less percentage difference between exhaled volume before and after cuff deflation) than those who do not. A difference greater than 15.5% is the advocated cutoff value for extubation of the trachea.[24] The presence of a cuff leak demonstrates the likelihood of successful extubation, not a guarantee, just as a failed cuff leak does not rule out a successful extubation.[25,26] The cuff leak test does not take the place of sound clinical judgment.

Mask ventilation may not be possible in a patient with severe upper airway obstruction resulting from edema or hematoma. In the case of hematoma after thyroid or carotid surgery, an attempt can be made to decompress the airway by releasing the clips or sutures on the wound and evacuating the hematoma. This maneuver is recommended as a temporizing measure, but it will not effectively decompress the airway if a significant amount of fluid or blood (or both) has infiltrated the tissue planes of the pharyngeal wall. If emergency tracheal intubation is required, then ready access to difficult airway equipment and, if possible, surgical backup to perform an emergency tracheostomy are important. If the patient is able to move air by spontaneous ventilation, then an awake technique is preferred because visualization of the cords by direct laryngoscopy may not be possible.

OBSTRUCTIVE SLEEP APNEA

Because most patients with obstructive sleep apnea (OSA) are not obese and the vast majority are undiagnosed at the time of surgery, OSA syndrome is often an overlooked cause of airway obstruction in the PACU [27,28]

Patients with OSA are particularly prone to airway obstruction and should not be extubated until they are fully awake and following commands.[8,29] Any redundant compliant pharyngeal tissue in these patients not only increases the incidence of airway obstruction, but it also often makes intubation by direct laryngoscopy difficult or impossible.[30,31] Once in the PACU, a patient with OSA whose trachea has been extubated is exquisitely sensitive to opioids and, when possible, continuous regional anesthesia techniques should be used to provide postoperative analgesia.[32,33] Interestingly, benzodiazepines can have a greater effect on pharyngeal muscle tone than opioids, and the use of benzodiazepines in the perioperative setting can significantly contribute to airway obstruction in the PACU.[8,34]

When caring for a patient with OSA, plans should be made preoperatively to provide CPAP in the immediate postoperative period. Patients should be asked to bring their CPAP machines with them on the day of surgery to enable the equipment to be set up before the patient's arrival in the PACU. Patients who do not routinely use CPAP at home or who do not have their machines with them may require additional attention from the respiratory therapist to ensure proper fit of the CPAP delivery device (mask or nasal airways) and to determine the amount of positive pressure needed to prevent upper airway obstruction.[35,36]

In patients with OSA who are morbidly obese immediately applying CPAP postextubation in the surgical department rather than waiting to apply positive pressure in the PACU may offer additional benefits. In patients undergoing laparoscopic bariatric surgery, Neligan and colleagues compared the application of 10 cm H_2O CPAP immediately postextubation to instituting the same CPAP 30 minutes later in the PACU. When compared with matched controls, patients who received immediate CPAP demonstrated improved spirometric lung function (i.e., functional residual capacity [FRC], peak expiratory flow [PEF], and forced expiratory volume [FEV]) at 1 hour and 24 hours postoperatively.[37]

MANAGEMENT OF UPPER AIRWAY OBSTRUCTION

An obstructed upper airway requires immediate attention. Efforts to open the airway by noninvasive measures should be attempted before reintubation of the

trachea. Jaw thrust maneuver with CPAP (5 to 15 cm H_2O) is often enough to tent the upper airway open in patients with decreased pharyngeal muscle tone. If CPAP is not effective, then an oral, nasal, or laryngeal mask airway can be rapidly inserted. After successfully opening the upper airway and ensuring adequate ventilation, the cause of the upper airway obstruction should be identified and treated. In adults, the sedating effects of opioids and benzodiazepines can be reversed with persistent stimulation or small, titrated doses of naloxone (0.3 to 0.5 μg/kg IV) or flumazenil (0.2 mg IV to maximum dose of 1 mg), respectively. Residual effects of neuromuscular blocking drugs can be reversed pharmacologically or by correcting contributing factors such as hypothermia.

DIFFERENTIAL DIAGNOSIS OF ARTERIAL HYPOXEMIA IN THE PACU

Atelectasis and alveolar hypoventilation are the most common causes of transient postoperative arterial hypoxemia in the immediate postoperative period.[38] Clinical correlations should guide the postoperative workup of a patient who remains persistently hypoxic.[39] Review of the patient's history, operative course, and clinical signs and symptoms will direct the workup to consider possible causes (Box 96-3).

ALVEOLAR HYPOVENTILATION

A review of the alveolar gas equation demonstrates that hypoventilation alone is sufficient to cause arterial hypoxemia in a patient breathing room air (see also Chapter 19) (Fig. 96-2). At sea level, a normocapnic patient who is breathing room air will have an alveolar oxygen pressure (PAO_2) of 100 mm Hg. Thus a healthy patient without a significant alveolar-arterial gradient will have a PaO_2 near 100 mm Hg. In the same patient, an increase in partial alveolar pressure of carbon dioxide (P_{ACO_2}) from 40 to 80 mm Hg (alveolar hypoventilation) results in a PAO_2 of 50 mm Hg. Hence, even a patient with normal lungs will become hypoxic if allowed to significantly hypoventilate while breathing room air.

Normally, minute ventilation increases linearly by approximately 2 L/min for every 1-mm Hg increase in P_{ACO_2}. In the immediate postoperative period, the residual effects of inhaled anesthetics, opioids, and sedative-hypnotic agents can significantly depress this ventilatory response to carbon dioxide. In addition to depressed respiratory drive, the differential diagnosis of postoperative hypoventilation includes generalized weakness as a result of residual neuromuscular blockade or underlying neuromuscular disease. The presence of restrictive pulmonary conditions, such as preexisting chest wall deformity, postoperative abdominal binding, or abdominal distention, can also contribute to inadequate ventilation.

Arterial hypoxemia secondary to hypercapnia can be reversed by the administration of supplemental oxygen (Fig. 96-3)[40] or by normalizing the patient's P_{ACO_2} by external stimulation of the patient to wakefulness,

BOX 96-3 ***Factors Contributing to Postoperative Arterial Hypoxemia***

- Right-to-left intrapulmonary shunt (atelectasis)
- Mismatching of ventilation to perfusion (decreased functional residual capacity)
- Congestive heart failure
- Pulmonary edema (fluid overload, postobstructive edema)
- Alveolar hypoventilation (residual effects of anesthetics and/or neuromuscular blocking drugs)
- Diffusion hypoxia (unlikely if receiving supplemental oxygen)
- Inhalation of gastric contents (aspiration)
- Pulmonary embolus
- Pneumothorax
- Increased oxygen consumption (shivering)
- Sepsis
- Transfusion-related lung injury
- Adult respiratory distress syndrome
- Advanced age
- Obesity

$$PAO_2 = FiO_2 (PB - PH_2O) - \frac{P_{CO_2}}{RQ}$$

$$P_{ACO_2} = 40 \text{ mm Hg}$$
$$PAO_2 = 21(760 - 47) - \frac{40}{0.8} = 150 - 50 = 100 \text{ mm Hg}$$

$$P_{ACO_2} = 80 \text{ mm Hg}$$
$$PAO_2 = 21(760 - 47) - \frac{80}{0.8} = 150 - 100 = 50 \text{ mm Hg}$$

PAO_2 = alveolar oxygen pressure
P_{ACO_2} = partial pressure of CO_2 in arterial blood
FiO_2 = fraction of inspired oxygen
PB = barometric pressure
PH_2O = vapor pressure of water
RQ = respiratory quotient

Figure 96-2. Hypoventilation as a cause of arterial hypoxemia. *(From Nicholau D: Postanesthesia recovery. In Miller RD, Pardo MC Jr, editors:* Basics of anesthesia, *ed 6. Philadelphia, 2011, Saunders.)*

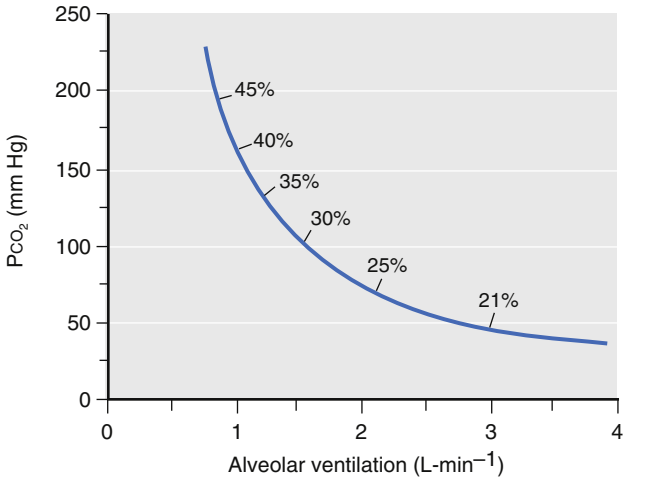


Figure 96-3. Alveolar partial pressure of carbon dioxide (P_{CO_2}) as a function of alveolar ventilation at rest. The percentages indicate the inspired oxygen concentration required to restore alveolar partial pressure of oxygen (PO_2) to normal. *(Modified from Nunn JF:* Nunn's applied respiratory physiology, *ed 6. Philadelphia, 2005, Butterworth-Heinemann. Used with permission.)*

pharmacologic reversal of opioid or benzodiazepine effect, or controlled mechanical ventilation of the patient's lungs.

DECREASED ALVEOLAR OXYGEN PRESSURE

Diffusion hypoxia refers to the rapid diffusion of nitrous oxide into alveoli at the end of a nitrous oxide anesthetic. Nitrous oxide dilutes the alveolar gas and produces a transient decrease in PAO_2 and $Paco_2$. In a patient breathing room air, the resulting decrease in PAO_2 can produce arterial hypoxemia, whereas decreased $Paco_2$ can depress the respiratory drive. In the absence of supplemental oxygen administration, diffusion hypoxia can persist for 5 to 10 minutes after discontinuing a nitrous oxide anesthetic; therefore it may contribute to arterial hypoxemia in the initial moments in the PACU.

VENTILATION-PERFUSION MISMATCH AND SHUNT

Hypoxic pulmonary vasoconstriction refers to the attempt of normal lungs to match ventilation and perfusion optimally (see also Chapters 19 and 51). This response constricts vessels in poorly ventilated regions of the lung and directs pulmonary blood flow to well-ventilated alveoli. In the PACU, the residual effects of inhaled anesthetics and vasodilators, such as nitroprusside and dobutamine used to treat systemic hypertension or to improve hemodynamics, will blunt hypoxic pulmonary vasoconstriction and contribute to arterial hypoxemia.

Unlike a ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch, a true shunt will not respond to supplemental oxygen. Causes of postoperative pulmonary shunt include atelectasis, pulmonary edema, gastric aspiration, pulmonary emboli, and pneumonia. Of these, atelectasis is probably the most common cause of pulmonary shunting in the immediate postoperative period. Mobilization of the patient to the sitting position, incentive spirometry, and positive airway pressure by facemask can be effective in treating atelectasis.

INCREASED VENOUS ADMIXTURE

Increased venous admixture typically refers to low cardiac output states, in which there is mixing of desaturated venous blood with oxygenated arterial blood. Normally, only 2% to 5% of cardiac output is shunted through the lungs, and this shunted blood with a normal mixed venous saturation has a minimal effect on PaO_2. In low cardiac output states, blood returns to the heart severely desaturated. Additionally, the shunt fraction significantly increases in conditions that impede alveolar oxygenation, such as pulmonary edema and atelectasis. Under these conditions, mixing desaturated shunted blood with saturated arterialized blood decreases PaO_2.

DECREASED DIFFUSION CAPACITY

A decreased diffusion capacity may reflect the presence of underlying lung disease such as emphysema, interstitial lung disease, pulmonary fibrosis, or primary pulmonary hypertension. In this regard, the differential diagnosis of arterial hypoxemia in the PACU must include the contribution of any preexisting pulmonary condition.

Finally, the fact that inadequate oxygen delivery may result from an unrecognized disconnection of the oxygen source or empty oxygen tank should be kept in mind.

PULMONARY EDEMA

Pulmonary edema in the immediate postoperative period is often cardiogenic in nature, secondary to intravascular volume overload or congestive heart failure. Less frequently, pulmonary edema may result from airway obstruction (postobstructive pulmonary edema), sepsis, or transfusion (transfusion-related acute lung injury [TRALI]).

POSTOBSTRUCTIVE PULMONARY EDEMA

Postobstructive pulmonary edema and the resulting arterial hypoxemia are rare but significant consequences of upper airway obstruction that may follow tracheal extubation at the conclusion of anesthesia and surgery. Postobstructive pulmonary edema is a transudative edema produced by the exaggerated negative intrathoracic pressure generated by an inspiratory effort against a closed glottis. The resulting negative intrathoracic pressure and increased venous return escalate the hydrostatic pressure gradient across the pulmonary vascular bed, promoting the transudation of fluid. Patients who are muscularly healthy are at increased risk of postobstructive pulmonary edema because of their ability to generate significant inspiratory force.

Laryngospasm is likely the most common cause of postobstructive pulmonary edema in the PACU, but postobstructive pulmonary edema may result from any condition that occludes the upper airway.[41,42] The resultant arterial hypoxemia is usually observed within 90 minutes of the upper airway obstruction and is accompanied by bilateral fluffy infiltrates on the chest radiograph. Treatment is supportive and includes supplemental oxygen, diuresis, and, in severe cases, positive-pressure ventilation of the patient's lungs.

TRANSFUSION-RELATED LUNG INJURY

The differential diagnosis of pulmonary edema in the PACU should include transfusion-related lung injury in any patient who intraoperatively received blood products (see also Chapter 61).[43,44] Transfusion-related lung injury is typically exhibited within 1 to 2 hours after the transfusion of plasma-containing blood products, including packed red blood cells, whole blood, fresh frozen plasma, or platelets. Because reactions can occur up to 6 hours after transfusion, the syndrome may develop during the patient's stay in the PACU after transfusion in the surgical unit. The resulting noncardiogenic pulmonary edema is often associated with fever and systemic hypotension. If a complete blood cell count is obtained with the onset of symptoms, then documenting an acute drop in the white

BOX 96-4 ***Criteria for the Diagnosis of Transfusion-Related Acute Lung Injury: The American-European Consensus Conference Recommendations***

1. Acute lung injury evidenced by:
   a. Acute onset of signs and symptoms
   b. Hypoxemia:
      i. PaO_2/FiO_2 <300, or
      ii. Room air SpO_2 <90%, or
      iii. Other clinical evidence of hypoxemia
   c. Bilateral infiltrates on chest radiography without cardiomegaly
   d. No clinical evidence of left atrial hypertension
2. No preexisting acute lung injury before transfusion
3. Onset of lung dysfunction within 6 hours of transfusion
4. No temporal association of onset to alternative causes of acute lung injury

Modified from Swanson K, Dwyre DM, Krochmal J, Raife TJ: Transfusion-related acute lung injury (TRALI): current clinical and pathophysiologic considerations, Lung *184:177-185, 2006.*

PaO_2, Arterial oxygen pressure; *FiO_2*, fraction of inspired oxygen; *SpO_2*, oxygen saturation by pulse oximetry.

blood cell count (leukopenia) is possible, reflecting the sequestration of granulocytes within the lung and exudative fluid.[45,46] Treatment is supportive and includes supplemental oxygen and drug-induced diuresis. Mechanical ventilation may be needed to support hypoxemia and respiratory failure. Vasopressors may be required to treat refractory hypotension.[47]

In past years, the lack of specific diagnostic criteria has resulted in the underdiagnosing and underreporting of this syndrome. Recently, a group of transfusion experts in the American-European Consensus Conference developed and implemented diagnostic criteria that have raised the awareness of the syndrome (Box 96-4).[48,49]

MONITORING AND TREATMENT OF HYPOXEMIA

OXYGEN SUPPLEMENTATION

In the era of cost containment, the routine delivery of supplemental oxygen to all patients recovering from general anesthesia is suggested to be a costly and unnecessary practice.[50] The argument against the use of routine oxygen supplementation relies on the fact that continuous pulse oximetry, now a PACU standard, readily identifies those patients who will require oxygen therapy.[51] Supporting this argument is the observation that a majority of patients after general anesthesia do not become hypoxic (63% at a threshold of Sa_{O_2} less than 90% and 83% at a threshold of Sa_{O_2} less than 94%) when breathing room air in the PACU.[51] Although the authors of this observational study predict that the elimination of routine oxygen supplementation in the PACU would result in significant cost savings, others assert that the economic benefit of limited oxygen therapy is likely to be offset by the cost of complications.[52,53]

Although the practice of prophylactic oxygen therapy to all patients after general anesthesia is controversial, most would argue that the benefits outweigh the risks. Even with oxygen supplementation, a significant percentage of patients will become hypoxic at some point during their PACU stay.[54,55] Russell and associates studied 100 patients who were transferred to the PACU breathing room air before receiving at least 40% oxygen by aerosol face tent in the unit. All patients had an Sa_{O_2} greater than 97% before the 2-minute transport to the PACU. Fifteen percent of patients experienced transient desaturation on arrival in the PACU (less than 92% saturation for longer than 30 seconds). This immediate desaturation positively correlated with patient age, body weight, ASA classification, general anesthesia, and increased volume of intravenous fluid greater than 1500 mL. An even larger percentage of patients (25%) desaturated 30 to 50 minutes later in their PACU stay, despite prophylactic oxygen administration. These later desaturations were more severe (71% to 91%) and lasted longer (5.8 ± 12.6 minutes) than those that occurred on admission. Additional correlating factors included duration of anesthesia and female gender.

The safe practice of postanesthesia care without oxygen supplementation requires ideal conditions at all times, such as functioning oxygen delivery apparatus at every bedside and sufficient manpower for observation and immediate intervention. Gravenstein argues that this degree of vigilance is likely unrealistic, and the risk of adverse outcome to even a small number of patients is unwarranted.[56]

LIMITATIONS OF PULSE OXIMETRY

The ASA Standards for Postanesthesia Care require that patients be observed and monitored with "particular attention given to" both oxygenation and ventilation. The pulse oximeter is a standard monitor in the PACU for the detection of hypoxemia, but it does not reflect the adequacy of ventilation.[57] Although several studies have demonstrated oximetry's limited ability to detect hypoventilation in patients breathing room air,[58,59] they confirm that it does not reliably detect hypoventilation in patients breathing oxygen.[59] When monitoring ventilation in the PACU, pulse oximetry is not a substitute for close observation by trained personnel.

OPTIMAL PERIOPERATIVE OXYGENATION

POSTOPERATIVE NAUSEA AND VOMITING

A number of studies have asked whether perioperative supplemental oxygen administration can reduce the incidence of PONV (see also Chapter 97). In the first such study, Grief and colleagues randomized 231 patients undergoing elective colon resection to receive either 30% or 80% oxygen (balanced with nitrogen). In this study, the administration of 80% supplemental oxygen intraoperatively and 2 hours postoperatively reduced the incidence of PONV nearly twofold (30% to 17%).[60] In a subsequent study of 240 patients undergoing laparoscopic

gynecologic surgery, the same group found that perioperative supplemental oxygen (80%) was as effective as ondansetron (with 30% oxygen) in preventing PONV. When compared with 30% oxygen alone, both oxygen and ondansetron decreased the incidence of PONV by 50% in the first 24 hours postoperatively (44% to 22%).[61]

Increased oxygen supplementation did not reduce the incidence of PONV in children undergoing elective dental surgery,[62] adults undergoing thyroid surgery,[63] or patients undergoing strabismus surgery.[64] In 210 patients (4 to 79 years of age) undergoing strabismus surgery, the incidence of PONV was the same among three groups: those who received 30% oxygen or room air plus ondansetron on induction, 80% oxygen or room air, or 30% oxygen or room air. Finally, in patients undergoing laparoscopic cholecystectomy, the elimination of nitrous oxide, not increased oxygen fraction, was found to correlate with decreased PONV. In this study, increasing the oxygen concentration from 40% in air to 80% in air offered no further benefit.[65]

The mechanism by which the elimination of nitrous oxide and increased oxygen fraction may contribute to a reduction in PONV is unknown. Although evidence suggests that perioperative oxygen administration may reduce PONV in patients undergoing colorectal procedures, the data do not support its use for surgical procedures that do not directly involve the bowel.[66] This lack of efficacy of supplemental oxygen in patients undergoing peripheral procedures argues for a local effect on the gastrointestinal tract where the elimination of nitrous oxide and nitrogen, together with hyperoxia, work to decrease bowel distention and reduce gastrointestinal ischemia.

Studying older adult patients transported by ambulance after minor trauma (see also Chapter 80), Kober and colleagues found that hyperoxia reduced the incidence of nausea and vomiting fourfold compared with patients breathing air. In this double-blind study, patients were randomized to receive room air or 100% facemask oxygen delivered at 10 L/min. The authors of this study propose a central mechanism for the effect of oxygen on motion sickness.[67]

WOUND INFECTIONS

Supplemental oxygen appears to reduce the incidence of surgical wound infections in patients undergoing colorectal surgery. Grief and colleagues randomized 500 patients undergoing colon resection to receive either 30% or 80% oxygen (in air). In this study, the higher concentration of oxygen reduced the incidence of surgical site infection by 6% (11.2% to 5.2%).[68] More recently, a randomized controlled multicenter study of 300 patients in 14 Spanish hospitals found that patients who received supplemental oxygen had a 30% reduction in surgical site infections.[69] This study compared 30% to 80% oxygen administration intraoperatively and 6 hours postoperatively. The perioperative care was standardized, and surgical site infections were identified by criteria delineated by the Centers for Disease Control and Prevention.

These results were not consistent with a study of patients undergoing major intraabdominal surgical procedures after which patients who received 80% oxygen had a significantly higher infection rate (25%) than those who received 35% oxygen. It is notable that this study has been widely criticized for its failure of randomization because the patients receiving 80% oxygen were more obese, underwent a longer duration of surgery, and had a larger blood loss than those receiving 35% oxygen. Unlike the Spanish study, the diagnosis of surgical site infection was made by chart review rather than standardized criteria.[70]

NITROUS OXIDE

The role of nitrous oxide in the risk of wound infection remains controversial. When controlling for oxygen concentration (35%) in patients undergoing colon resection, the Outcomes Research Group found that the elimination of nitrous oxide did not decrease the incidence of surgical site infection.[71]

The largest multicenter trial to date comparing nitrous oxide–based anesthesia with nitrous oxide–free general anesthesia included 2050 patients who underwent major surgery. Exclusion criteria included cardiac and thoracic surgery. The exclusion of patients undergoing colon surgery or those who had a history of PONV was left to the discretion of the anesthesiologist. Patients were randomized to receive 30% oxygen with 70% nitrous oxide or 80% oxygen with 20% nitrogen. In this study, the elimination of nitrous oxide significantly decreased the incidence of PONV and major complications within 30 days of surgery. Major complications included pneumonia, pneumothorax, pulmonary embolism, wound infection, myocardial infarction, venous thromboembolism, stroke, and awareness. It did not decrease the length of hospital stay, the study's primary endpoint.[72] Significantly, this study did not control for inspired oxygen concentration; therefore whether the beneficial effects were the result of the elimination of nitrous oxide or the increase in FiO_2 is not clear.[73]

OXYGEN DELIVERY SYSTEMS

SUPPLEMENTAL OXYGEN

The degree of hypoxemia, the surgical procedure, and patient compliance determine the oxygen delivery system of choice in the PACU. Patients who are stable after head and neck surgery may not be candidates for facemask oxygen because of the risk of pressure necrosis on incision sites and microvascular muscle flaps, whereas nasal packing prohibits the use of nasal cannulas in others. Face tent oxygen or blow-by setups are viable alternatives in cases in which tight-fitting masks and straps are contraindicated.

The delivery of oxygen through a traditional nasal cannula with bubble humidifier is usually limited to a maximum flow of 6 L/min to minimize the discomfort and complications that result from inadequate humidification. As a general rule, each liter per minute of oxygen flow through nasal cannula increases the FiO_2 by 0.04, with 6 L/min delivering an FiO_2 of approximately 0.44. Until recently, maximum oxygen delivery to extubated

patients required delivery by facemask through a nonrebreather system or high-flow nebulizer. These systems can be inefficient, however, because of inadequate mask fit and/or high-minute ventilation requirements that result in significant entrainment of room air. The newer high-flow nasal cannula devices can comfortably deliver oxygen at 40 L/min, 37° C, and 99.9% relative humidity.[74] The delivery of high-flow oxygen directly to the nasopharynx produces an FiO_2 equal to that delivered by traditional mask devices. In fact, the Vapotherm system has been shown to deliver a higher FiO_2 than a nonrebreather mask at similar flow ranges (10 to 40 L/min). Unlike the nonrebreather mask, these devices deliver high-flow oxygen directly to the nasopharynx throughout the respiratory cycle. The efficacy of these devices may be enhanced by a CPAP effect resulting from the high gas flow.[75]

CONTINUOUS POSITIVE AIRWAY PRESSURE

An estimated 8% to 10% of patients who undergo abdominal surgery subsequently require intubation and mechanical ventilation in the PACU. As discussed earlier in this chapter, respiratory failure in the immediate postoperative period is often due to transient and rapidly reversible conditions such as splinting from pain, diaphragmatic dysfunction, muscular weakness, and pharmacologically depressed respiratory drive. Readily reversible hypoxemia may be due to hypoventilation, atelectasis, or volume overload. The application of CPAP in this setting can potentially decrease hypoxemia as a result of atelectasis by recruiting alveoli. The resulting increase in functional reserve capacity may also improve pulmonary compliance and decrease the work of breathing. In a recent randomized controlled trial, 209 consecutive patients undergoing major elective abdominal surgery were randomized to receive supplemental oxygen alone or in conjunction with CPAP (at 7.5 cm H_2O pressure) in the PACU. In this study, the application of CPAP in the PACU significantly reduced the incidence of intubation, pneumonia, infection, and sepsis. The study was halted because of efficacy after the enrollment of 209 patients (Table 96-2) (see also Chapter 103).[76]

A large percentage of patients who are obese and undergoing Roux-en-Y gastric bypass surgery have OSA and stand to benefit significantly from postoperative CPAP therapy. Yet surgeons were initially hesitant to embrace this modality for fear that applying positive pressure to the airway would inflate the stomach and proximal intestine and result in anastomotic disruption. In a single center study of 1067 patients undergoing gastrojejunostomy bypass and 420 diagnosed with OSA, CPAP did not increase the risk of postoperative anastomotic leaks.[77]

NONINVASIVE POSITIVE-PRESSURE VENTILATION

Even with the application of CPAP in the PACU, a number of patients will require additional ventilatory support. Noninvasive positive-pressure ventilation (NIPPV) (see also Chapter 103) has been shown to be an effective alternative to endotracheal intubation in the intensive care unit (ICU) setting. Although the use of NIPPV in both chronic and acute respiratory failure is well established, its application in the PACU is limited.

In the past, the use of NIPPV was avoided in the immediate postoperative period because of the potential for gastric distention, aspiration, and wound dehiscence. These potential complications were especially true in patients who had undergone esophageal or gastric surgery. Careful consideration of both the patient and the surgical factors must guide the decision to use noninvasive modes of ventilation in the PACU. Relative contraindications include hemodynamic instability or life-threatening arrhythmias, altered mental status, high risk of aspiration, inability to use nasal or facial mask (head and neck procedures), and refractory hypoxemia.[78] Several case reports describe the successful application of NIPPV in lieu of endotracheal intubation in both adults and children in the PACU. In 2000, Tobias reported the successful application of NIPPV in two patients, one after gastrostomy tube placement and another after cholecystectomy.[79] A larger case series (eight patients) reported by Albala and Ferrigno did not include intraabdominal procedures.[80] The authors of both studies agree that the successful application of NIPPV is dependent on appropriate patient selection and careful instruction.

NIPPV can be delivered by facemask using the pressure support mode of a mechanical ventilator. Alternatively, the use of a biphasic positive airway pressure machine

TABLE 96-2 CONTINUOUS POSITIVE AIRWAY PRESSURE FOR POSTOPERATIVE HYPOXEMIA: SECONDARY OUTCOMES

	Control (*n* = 104)	CPAP (*n* = 105)	Relative Risk (95% CI)	*P* Value*
Pneumonia, number of patients (%)	10 (10)	2 (2)	0.19 (0.04 to 0.88)	.02
Infection, number of patients (%)	11 (10)	3 (3)	0.27 (0.07 to 0.94)	.03
Sepsis, number of patients (%)	9 (9)	2 (2)	0.22 (0.04 to 0.99)	.03
Anastomotic leakage, number of patients	6	1		
Pneumonia, number of patients	3	1		
Deaths, number of patients (%)	3 (3)	0 (0)		.12

Modified from Squadrone V, Coha M, Cerutti E, et al: Continuous positive airway pressure for treatment of postoperative hypoxemia: a randomized controlled trial, JAMA *293:589-595, 2005.*

CPAP, Continuous positive airway pressure; *CI*, confidence interval.

*All *P* values are two-tailed. Comparisons between control and CPAP by Fisher exact test for categorical variables and two-tailed *t* test for continuous variables.

allows the delivery of positive pressure by either nasal cannula or facemask. An example protocol for instituting NIPPV in patients with acute respiratory failure is shown in Box 96-5.

HEMODYNAMIC INSTABILITY

Hemodynamic compromise in the patient in the PACU is exhibited in a number of ways—systemic hypertension, hypotension, tachycardia, or bradycardia—alone or in combination. Hemodynamic instability in the PACU has a negative impact on long-term outcome. Interestingly, postoperative systemic hypertension and tachycardia are associated with an increased risk of unplanned critical care admission and a higher mortality than hypotension and bradycardia.[81]

SYSTEMIC HYPERTENSION

Patients with a history of essential hypertension are at greatest risk for significant systemic hypertension in the PACU.[82] Additional factors include pain, nausea and vomiting, hypoventilation and associated hypercapnia, emergence excitement, advanced age, urinary retention, and preexisting renal disease (Box 96-6). The surgical procedures most commonly associated with postoperative hypertension are carotid endarterectomy and intracranial procedures. A significant number of patients, especially those with a known history of hypertension, will require pharmacologic blood pressure control in the PACU (see also Chapter 39).

BOX 96-5 *Example Protocol for Instituting Noninvasive Positive-Pressure Ventilation in Patients with Acute Respiratory Failure**

1. Choose the appropriate patient, based on the surgical procedure and the patient's risk of aspiration, ability to protect his or her airway, and ability to comply with the mask fit.
2. Position the head of the bed at ≥45-degree angle.
3. Choose the correct size mask and connect mask to ventilator.
4. Explain the modality to the patient and provide reassurance.
5. Set initial ventilatory settings (CPAP, 0 cm H_2O; pressure support, 10 cm H_2O).
6. Gently hold mask on face until the patient is comfortable and synchronous with ventilation.
7. Apply wound care dressing on nasal bridge and other pressure points.
8. Secure mask with head straps.
9. Slowly increase CPAP.
10. Adjust pressure support to achieve adequate tidal volumes and maximal patient comfort.
11. In patients with hypoxia, increase CPAP in increments of 2 to 3 cm H_2O until FiO_2 is ≤0.6.
12. Avoid peak mask pressures >30 cm H_2O.
13. Set ventilator alarms and apnea backup parameters.
14. Ask the patient and nurse to call for needs (e.g., repositioning mask, pain, discomfort) or if complications occur (e.g., respiratory difficulties, abdominal distention, nausea, vomiting).
15. Monitor with oximetry, and adjust ventilator settings after blood gas results.

Modified from Abou-Shala N, Meduri U: Noninvasive mechanical ventilation in patients with acute respiratory failure, Crit Care Med *24:705-715, 1996.*
CPAP, Continuous positive airway pressure; *FiO_2,* fraction of inspired oxygen.
* Protocol at the University of Tennessee, Memphis.

SYSTEMIC HYPOTENSION

Postoperative systemic hypotension may be characterized as (1) hypovolemic (decreased preload), (2) distributive (decreased afterload), or (3) cardiogenic (intrinsic pump failure) (Box 96-7).

Hypovolemic (Decreased Preload)

Systemic hypotension in the PACU is often due to decreased intravascular fluid volume and preload, and, as

BOX 96-6 *Factors Leading to Postoperative Hypertension*

- Preoperative hypertension
- Arterial hypoxemia
- Hypervolemia
- Emergence excitement
- Shivering
- Drug rebound
- Increased intracranial pressure
- Increased sympathetic nervous system activity
  - Hypercapnia
  - Pain
  - Agitation
  - Bowel distention
  - Urinary retention

BOX 96-7 *Differential Diagnosis of Hypotension in the Postanesthesia Care Unit*

- Intravascular volume depletion
  - Persistent fluid losses
  - Ongoing third-space translocation of fluid
  - Bowel preparation
  - Gastrointestinal losses
  - Surgical bleeding
- Increased capillary permeability
  - Sepsis
  - Burns
  - Transfusion-related acute lung injury
- Decreased cardiac output
  - Myocardial ischemia or infarction
  - Cardiomyopathy
  - Valvular disease
  - Pericardial disease
  - Cardiac tamponade
  - Cardiac dysrhythmias
  - Pulmonary embolus
  - Tension pneumothorax
  - Drug induced (beta-blockers, calcium channel blockers)
- Decreased vascular tone
  - Sepsis
  - Allergic reactions (anaphylactic, anaphylactoid)
  - Spinal shock (cord injury, iatrogenic high spinal)
  - Adrenal insufficiency

such, it responds favorably to intravenous fluid administration. Common causes of decreased intravascular fluid volume in the immediate postoperative period include ongoing third-space translocation or loss of fluid, inadequate intraoperative fluid replacement (especially in patients who undergo major intraabdominal procedures or preoperative bowel preparation), and loss of sympathetic nervous system tone as a result of neuraxial (spinal or epidural) blockade.

Ongoing bleeding should be ruled out in patients with hypotension who have undergone a surgical procedure in which significant blood loss is possible. Regardless of the estimated intraoperative blood loss, the measured blood loss may be inaccurate. If the patient is unstable, then hemoglobin can be measured at the bedside to eliminate laboratory turnover time. In addition, tachycardia may not be a reliable indicator of hypovolemia or anemia (or both) if the patient is taking beta-blockers or calcium channel blockers.

Distributive (Decreased Afterload)

Distributive shock in the PACU may be the result of a number of physiologic derangements, including iatrogenic sympathectomy, critical illness, allergic reactions, and sepsis. Iatrogenic sympathectomy, secondary to regional anesthetic techniques, is an important cause of hypotension in the perioperative period. A high sympathetic block (to T4) will decrease vascular tone and block the cardioaccelerator fibers. If not treated promptly, then the resulting bradycardia in the presence of severe hypotension can lead to cardiac arrest even in young healthy patients.[83] Vasopressors, including phenylephrine and ephedrine, are pharmacologic treatments of hypotension caused by residual sympathetic nervous system blockade.

Patients who are critically ill may rely on exaggerated sympathetic nervous system tone to maintain systemic blood pressure and heart rate. In these patients, even minimal doses of inhaled anesthetics, opioids, or sedative-hypnotics can decrease sympathetic nervous system tone and produce significant systemic hypotension.

Allergic (anaphylactic or anaphylactoid) reactions may be the cause of hypotension in the PACU. Epinephrine is the drug of choice to treat hypotension secondary to an allergic reaction. Increased serum tryptase concentrations confirm the occurrence of an allergic reaction, but an elevated tryptase level does not differentiate anaphylactic from anaphylactoid reactions. The blood specimen for tryptase determination must be obtained within 30 to 120 minutes after the allergic reaction, but the results may not be available for several days. Neuromuscular blocking drugs are the most common cause of anaphylactic reactions in the surgical setting (Table 96-3).[84,85]

If sepsis is suspected as the cause of hypotension in the PACU, then blood should be obtained for culture, and empirical antibiotic therapy should be initiated before transferring the patient to the assigned unit. Urinary tract manipulation and biliary tract procedures are examples of interventions that can result in a sudden onset of severe systemic hypotension secondary to sepsis. Although fluid resuscitation is the most important immediate intervention, pressor support is often required—at least transiently. Norepinephrine is the pressor of choice in septic patients. Vasopressin deficiency has been shown to contribute to vasodilation in septic shock,[86] and low-dose vasopressin (0.01 to 0.05 unit/min) improves mean arterial pressure, decreases catecholamine vasopressor requirement, and may spare renal function in severe septic shock.[87]

TABLE 96-3 **DRUGS INVOLVED IN PERIOPERATIVE ANAPHYLAXIS**

Substance	Incidence of Perioperative Anaphylaxis (%)	Most Commonly Associated With Perioperative Anaphylaxis
Muscle relaxants	69.2	Succinylcholine, rocuronium, atracurium
Natural rubber latex	12.1	Latex gloves, tourniquets, Foley catheters
Antibiotics	8	Penicillin and other beta-lactams
Hypnotics	3.7	Propofol, thiopental
Colloids	2.7	Dextran, gelatin
Opioids	1.4	Morphine, meperidine
Other substances	2.9	Propacetamol, aprotinin, chymopapain, protamine, bupivacaine

From Hepner DL, Castells MC: Anaphylaxis during the perioperative period, Anesth Analg *97:1381-1395, 2003.*

Cardiogenic (Intrinsic Pump Failure)

Significant cardiogenic causes of postoperative hypotension include myocardial ischemia and infarction, cardiomyopathy, cardiac tamponade, and cardiac dysrhythmias. The differential diagnosis depends on the surgical procedure and the patient's preoperative cardiac risk and medical condition. To determine the cause of the hypotension, central venous pressure monitoring, echocardiography, and, rarely, pulmonary artery catheter monitoring may be required.

MYOCARDIAL ISCHEMIA: EVALUATION AND TREATMENT

PATIENTS AT LOW RISK

Interpretation of changes on the ECG in the PACU is influenced by the patient's cardiac history and risk index. In patients at low risk—younger than 45 years of age, with no known cardiac disease, and only one risk factor—postoperative ST-segment changes on the ECG do not usually indicate myocardial ischemia. Relatively benign causes of ST changes in patients at low risk include anxiety, esophageal reflux, hyperventilation, and hypokalemia. In general, these patients require only routine PACU observation unless associated signs and symptoms warrant further clinical evaluation. A more aggressive evaluation

is indicated if the changes are accompanied by cardiac rhythm disturbances or hemodynamic instability (or both) (see also Chapter 39).

PATIENTS AT HIGH RISK

In contrast to patients at low risk, ST-segment and T-wave changes on the ECG in patients at high risk can be significant even in the absence of typical signs or symptoms. In this patient population, any ST or T-wave changes that are compatible with myocardial ischemia should prompt further evaluation to rule out myocardial ischemia. Determination of serum troponin levels is indicated when myocardial ischemia or infarction is suspected in the PACU. Once blood samples for measurement of troponin are obtained and a 12-lead ECG is completed, arrangements must be made for the appropriate cardiac monitoring and cardiology follow-up.

CARDIAC MONITORING

In the immediate postoperative period, myocardial ischemia is rarely accompanied by chest pain, and confirming myocardial ischemia in a patient in the PACU is dependent on the sensitivity of the cardiac monitoring (see also Chapters 45, and 47). Although a combination of leads II and V_5 will reflect 80% of the ischemic events detected on a 12-lead ECG, visual interpretation of the cardiac monitor is often inaccurate. Because of human error, the American College of Cardiology guidelines recommend that computerized ST-segment analysis be used (if available) to monitor this patient population in the immediate postoperative period.[88] A recent small-scale, single-center study by Goldman and associates suggests that a postoperative 12-lead ECG obtained in the PACU may be a valuable tool to adjust risk stratification in patients older than 50 years of age who are at low risk for cardiac ischemia.[89] However, at this time a routine postoperative 12-lead ECG is recommended only for patients with known or suspected coronary artery disease who have undergone high- or intermediate-risk surgery.

CARDIAC DYSRHYTHMIAS

Perioperative cardiac dysrhythmias are frequently transient and multifactorial (see Box 96-6). Reversible causes of cardiac dysrhythmias in the perioperative period include hypoxemia, hypoventilation and associated hypercapnia, endogenous or exogenous catecholamines, electrolyte abnormalities, acidemia, fluid overload, anemia, and substance withdrawal.[90]

TACHYCARDIA

Common causes of sinus tachycardia in the PACU include pain, agitation, hypoventilation with associated hypercapnia, hypovolemia, and shivering. Less common but serious causes include bleeding, cardiogenic or septic shock, pulmonary embolism, thyroid storm, and malignant hyperthermia.

ATRIAL DYSRHYTHMIAS

The incidence of new postoperative atrial dysrhythmias may be as high as 10% after major noncardiothoracic surgery. The incidence is even higher after cardiac and thoracic procedures when the cardiac dysrhythmia is often attributed to atrial irritation.[91] The risk of postoperative atrial fibrillation is increased by preexisting cardiac risk factors, positive fluid balance, electrolyte abnormalities, and oxygen desaturation.[92] These new-onset atrial dysrhythmias are not benign because they are associated with a longer hospital stay and increased mortality.[93]

VENTRICULAR DYSRHYTHMIAS

Premature ventricular contractions (PVCs) and ventricular bigeminy commonly occur in the PACU. PVCs most often reflect increased sympathetic nervous system stimulation that may accompany tracheal intubation, pain, and transient hypercapnia. True ventricular tachycardia is rare and indicative of an underlying cardiac pathologic condition. In the case of torsades de pointes, QT prolongation on the ECG may be intrinsic or drug related (e.g., amiodarone, procainamide, droperidol).

BRADYDYSRHYTHMIAS

Bradycardia in the PACU is often iatrogenic. Drug-related causes include beta-blocker therapy, anticholinesterase reversal of neuromuscular blockade, opioid administration, and treatment with dexmedetomidine. Procedure- and patient-related causes include bowel distention, increased intracranial or intraocular pressure, and spinal anesthesia. A high spinal block that blocks the cardioaccelerator fibers originating from T1 through T4 can produce severe bradycardia. The resulting sympathectomy, bradycardia, and possible intravascular fluid volume depletion and associated decreased venous return can produce sudden bradycardia and cardiac arrest, even in young healthy patients.

ATRIAL FIBRILLATION

Control of the ventricular response rate is the immediate goal in the treatment of new-onset atrial fibrillation. Patients who are hemodynamically unstable may require prompt electrical cardioversion, but most patients can be pharmacologically treated with an intravenous beta-adrenergic blocker or calcium channel blocker.[94] Diltiazem is the calcium channel blocker of choice for patients in whom beta-blockers are contraindicated. If hemodynamic instability is a concern, then the short-acting beta-blocker esmolol is an option. Rate control with these agents is often enough to result in chemical cardioversion for the postoperative patient whose arrhythmia may be catecholamine driven. If the goal of therapy is chemical cardioversion, then an amiodarone load can be initiated in the PACU with the knowledge that QT prolongation, bradycardia, and hypotension may accompany the intravenous infusion of this drug.

TREATMENT

The urgency of treatment of a cardiac dysrhythmia depends on the physiologic consequences of the dysrhythmia, principally hypotension or cardiac ischemia or both. Tachydysrhythmias decrease coronary perfusion time and increase myocardial oxygen consumption. Their impact depends on the patient's underlying cardiac function, and they are most harmful in patients with coronary artery disease. Bradycardia has a more deleterious effect in patients with a fixed stroke volume, such as infants and patients with restrictive pericardial disease or cardiac tamponade. For the most part, treatment relies on identifying and correcting the underlying cause (e.g., hypoxemia, electrolyte abnormalities).[95] The possible role of myocardial ischemia or the occurrence of pulmonary embolism must be considered when contemplating treatment options.

RENAL DYSFUNCTION

The differential diagnosis of postoperative renal dysfunction includes prerenal, intrarenal, and postrenal causes (Box 96-8). Frequently, the cause is multifactorial, with an intraoperative insult exacerbating a preexisting renal insufficiency. In the PACU, diagnostic efforts should focus on the identification and treatment of the readily reversible causes of oliguria (e.g., urine output less than 0.5 mL/kg/hr). For example, urinary catheter obstruction or dislodgment is easily remedied and often overlooked (see Box 96-8). When appropriate, one should confer with the surgical team regarding the details of the surgical procedure (urologic or gynecologic) to rule out anatomic obstruction or disruption of the ureters, bladder, or urethra.

OLIGURIA

Intravascular Volume Depletion

The most common cause of oliguria in the immediate postoperative period is depletion of intravascular fluid volume. In this regard, a fluid challenge (500 to 1000 mL of crystalloid) is usually effective in restoring urine output. A hematocrit measurement is indicated when surgical blood loss is suspected and repeated volume boluses are required to maintain urine output. Volume resuscitation to maximize renal perfusion is particularly important to prevent ongoing ischemic injury and the development of acute tubular necrosis.

A number of perioperative events may alter renal perfusion. Preoperative or intraoperative angiography can result in ischemic injury, secondary to renal vasoconstriction and direct renal tubular injury. Perioperative volume depletion can exacerbate hepatorenal syndrome or acute tubular necrosis caused by sepsis. The surgical procedure, itself, can alter renal vascular patency, decreasing renal perfusion. Finally, increased intraabdominal pressure (IAP) can impair renal perfusion.

If a fluid challenge is contraindicated or oliguria persists, then assessment of intravascular fluid volume status and cardiac function is indicated to differentiate hypovolemia from sepsis and low cardiac output states. Fractional excretion of sodium can be useful in determining the adequacy of renal perfusion, assuming that diuretics have not been given. However, the diagnosis of prerenal azotemia will not differentiate hypovolemia, congestive heart failure, or hepatorenal syndrome. Further evaluation with central venous monitoring or echocardiography, or both, may facilitate the differential diagnosis.

BOX 96-8 *Postoperative Oliguria*

PRERENAL

Hypovolemia (bleeding, sepsis, third-space fluid loss, inadequate volume resuscitation)
Hepatorenal syndrome
Low cardiac output
Renal vascular obstruction or disruption
Intraabdominal hypertension

RENAL

Ischemia (acute tubular necrosis)
Radiographic contrast dyes
Rhabdomyolysis
Tumor lysis
Hemolysis

POSTRENAL

Surgical injury to the ureters
Obstruction of the ureters with clots or stones
Mechanical (urinary catheter obstruction or malposition)

Postoperative Urinary Retention

Postoperative urinary retention can cause bladder overdistention and permanent detrusor damage. Ultrasonography can measure bladder volume and identify urinary retention in the PACU.[96] Using this technique, Keita and associates attempted to identify patients at high risk by measuring bladder volume in 313 adult inpatients on admission to and before discharge from the PACU. They collected data on age, sex, history of urinary retention, intraoperative administration of anticholinergic agents, amount of intraoperative fluid administration, and intravenous use of morphine. Urinary retention was defined as bladder volume greater than 600 mL in conjunction with an inability to void within 30 minutes. In this study, the incidence of postoperative urinary retention in the PACU was 16%. The most significant predictive factors were age older than 50 years, intraoperative fluid more than 750 mL, and bladder volume on entry to the PACU greater than 270 mL.[97] This study argues for the use of ultrasound to identify patients at high risk for possible urinary retention.

CONTRAST NEPHROPATHY

Angiography with intravascular stent placement is replacing open surgical procedures to treat carotid stenosis, aortic aneurysm, and peripheral vascular disease. As a result, contrast nephropathy will be more frequently included in the differential diagnosis of postoperative renal dysfunction. Perioperative attention to adequate hydration is indicated in any patient who has received an intravenous contrast agent. Aggressive hydration with normal saline provides the single most effective protection

against contrast nephropathy. Alkalinization of the urine with sodium bicarbonate has been shown to provide additional protection.[91] If bicarbonate is used for renal protection, then 154 mEq/L should be infused at a rate of 3 mL/kg/hr for 1 hour before injection of a contrast agent, followed by 1 mL/kg/hr for 6 hours.[98] Mucomyst is a relatively inexpensive and easily administered medication (single oral dose before and after procedure) that may also provide protection.[99] Although a number of studies support the efficacy of Mucomyst, meta-analysis does not consistently confirm its usefulness.[100,101]

INTRAABDOMINAL HYPERTENSION

Intraabdominal hypertension should be considered in any patient with oliguria and a tense abdomen on examination after abdominal surgery. Elevated IAP can impede renal perfusion and lead to renal ischemia and postoperative renal dysfunction. Normal IAP in a patient who is not obese is approximately 5 mm Hg. Intraabdominal hypertension is graded into four categories: I: 12 to 15 mm Hg; II: 16 to 20 mm Hg; III: 21 to 25 mm Hg; and IV: greater than 25 mm Hg. Abdominal compartment syndrome is defined as an IAP greater than 20 mm Hg with or without an abdominal perfusion pressure less than 50 mm Hg.[102] In a prospective study of patients undergoing major abdominal surgery, intraabdominal hypertension accounted for 40% of new-onset renal insufficiency. In this study, postoperative renal impairment was independently associated with four factors: hypotension, sepsis, older age, and increased abdominal pressure.[103] Bladder pressure, an indirect measure of IAP, should be measured in patients in whom intraabdominal hypertension is suspected to ensure the initiation of prompt intervention to relieve the pressure and to restore renal perfusion. Bladder pressure is measured at end expiration with the patient in the supine position and in the absence of abdominal muscle contractions. As with arterial pressure measurements, the transducer is placed in the midaxillary line.[103]

RHABDOMYOLYSIS

Rhabdomyolysis may complicate the postoperative course of patients who have suffered major crush or thermal injury. The incidence is also significantly increased in patients who are morbidly obese who undergo bariatric surgery. Rhabdomyolysis has been reported to occur in 22.7% of 66 consecutive patients undergoing laparoscopic bariatric surgery.[104-106] Risk factors include increased BMI and the length of the surgery. Patient history and the operative course should guide the decision to measure creatine phosphokinase in the PACU.[104] Early aggressive hydration to maintain urine output is the mainstay of treatment. Loop diuretics can be used to flush the renal tubules and to avoid fluid overload. The infusion of mannitol to enhance the elimination of myoglobin casts from the renal tubules and bicarbonate to protect against myoglobin toxicity is commonly practiced but may not provide further benefit. In a study of more than 2000 trauma patients with rhabdomyolysis, the infusion of bicarbonate and mannitol did not further decrease the incidence of acute renal failure.[107] No evidence suggests that renal dose dopamine affords renal protection in this setting.[108] In severe cases, an attempt can be made to remove myoglobin by continuous renal replacement therapy. Unlike conventional hemodialysis filters that do not remove circulating myoglobin, high-flux membranes can be effective. Continuous renal replacement modes typically use high-flux membranes. Additionally, convection (i.e., the mechanism of solute removal in continuous hemofiltration) removes larger molecular weight solutes than diffusion (i.e., the mechanism of solute removal in conventional hemodialysis).[109]

BODY TEMPERATURE AND SHIVERING

Postoperative shivering often occurs after general and epidural anesthesia (see also Chapter 54). The incidence of postoperative shivering may be as high as 65% (range, 5% to 65%) after general anesthesia and 33% after epidural anesthesia. Identified risk factors include male gender and the choice of induction agent; propofol is more commonly associated with shivering than is pentothal.[110]

MECHANISM

Postoperative shivering is usually, but not always, associated with hypothermia. Although thermoregulatory mechanisms can explain shivering in the patient with hypothermia, a number of different mechanisms have been proposed to explain shivering in normothermic patients. One proposed mechanism is based on the observation that the brain and spinal cord do not simultaneously recover from general anesthesia. The more rapid recovery of spinal cord function is thought to result in uninhibited spinal reflexes exhibited as clonic activity. This theory is supported by the fact that doxapram, a central nervous system stimulant, is somewhat effective in abolishing postoperative shivering. Other proposed mechanisms include the action of κ- opioid, *N*-methyl-D-aspartate (NMDA), and 5-hydroxytryptamine receptors. The higher incidence of postanesthetic shivering in patients who receive high-dose remifentanil is thought to be by the same mechanism that causes hyperalgesia in these patients; sudden opioid withdrawal resulting in the stimulation of *N*-methyl-D-aspartate receptors.[111] Additional support for this theory comes from the same authors who found that a small dose of intraoperative ketamine reduced the incidence of remifentanil-induced postanesthetic shivering.[112] Tramadol, a weak μ-opioid–receptor agonist and norepinephrine and serotonin reuptake inhibitor, has been shown to be effective in preventing postoperative shivering while also contributing to analgesia.[113]

TREATMENT

Intervention includes the identification and treatment of hypothermia, if present. Accurate core body temperatures can be most easily obtained at the tympanic membrane. Axillary, rectal, and nasopharyngeal temperature measurements are less accurate and may underestimate the

core temperature. Forced air warmers are used to warm the patient with hypothermia. A number of opioids, ondansetron,[114] and clonidine[115] have been shown to be effective in abolishing shivering once it starts; however, in adults, meperidine, 0.35 to 0.4 mg/kg (12.5 to 25 mg IV), is most commonly used. The infusion of low-dose ketamine (0.5 mg/kg IV) before general[116] and regional anesthesia[117] has been shown to be an effective prophylactic measure.

CLINICAL EFFECTS

In addition to significant patient discomfort, postoperative shivering increases oxygen consumption, carbon dioxide production, and sympathetic tone and is associated with increased cardiac output, heart rate, systemic blood pressure, and intraocular pressure. Patients who are hypothermic on arrival in the PACU should be actively warmed to avoid these immediate complications, as well as delayed consequences of hypothermia. Mild-to-moderate hypothermia (33° C to 35° C) inhibits platelet function, coagulation factor activity, and drug metabolism. It exacerbates postoperative bleeding, prolongs neuromuscular blockade, and may delay awakening. Whereas these immediate consequences are associated with a prolonged PACU stay,[118] long-term deleterious effects include an increased incidence of myocardial ischemia and myocardial infarction, delayed wound healing, and increased perioperative mortality.

POSTOPERATIVE NAUSEA AND VOMITING

Without prophylactic intervention, approximately one third of patients who undergo inhalational anesthesia will develop PONV (range, 10% to 80%) (see also Chapter 97).[119] The consequences of PONV include delayed discharge from the PACU, unanticipated hospital admission, increased incidence of pulmonary aspiration, and significant postoperative discomfort. The ability to identify patients at high risk for prophylactic intervention can significantly improve the quality of patient care and satisfaction in the PACU. From a patient's perspective, PONV may be more uncomfortable than postoperative pain.

PREVENTION AND TREATMENT

Prophylactic measures to prevent PONV include modification of the anesthetic technique and pharmacologic intervention. In a randomized controlled multicenter multifactorial trial, Apfel and associates studied the efficacy of six prophylactic interventions in patients at high risk for PONV (greater than 40%).[119] Interventions were both pharmacologic and technique related. Pharmacologic intervention included droperidol, 1.25 mg; dexamethasone, 4 mg; or ondansetron, 4 mg. Anesthetic intervention included propofol in lieu of a volatile anesthetic, nitrogen in lieu of nitrous oxide, or remifentanil in lieu of fentanyl. More than 4000 patients were assigned to 1 of 64 possible combinations. The study found that each of the three antiemetic medications reduced the relative risk of PONV to the same degree (26%). Together, propofol (19% decrease) and nitrogen (12% decrease) reduced the relative risk of PONV to a similar degree.

BOX 96-9 *Commonly Used Antiemetic Medications (Adult Doses)*

Anticholinergics

Scopolamine (0.3-0.65 mg IV)
Scopolamine (1.5 mg) Transdermal patch applied to a hairless area behind the ear before surgery; remove 24 hours postoperatively.

Antihistamines

Hydroxyzine (12.5-25 mg IM)
Phenothiazines
Promethazine (12.5-25 mg IM)

Prokinetics

Metoclopramide (10-20 mg IV) Avoid if any gastrointestinal obstruction is possible.

Serotonin-Receptor Antagonists

Ondansetron (4 mg IV) Administer 30 minutes before the conclusion of surgery.
Anzemet (12.5 mg IV) Administer 15 to 30 minutes before the end of surgery.

Vasopressors

Ephedrine (25 mg IM) with hydroxyzine (25 mg)

Corticosteroids

Dexamethasone (4-8 mg IV) Administer with the induction of anesthesia.

Although prophylactic measures to prevent PONV are more effective than rescue, a subset of patients will require treatment in the PACU even after appropriate prophylactic treatment. No convincing evidence suggests that any of the serotonin-receptor antagonists commonly prescribed at this time are more effective than any others. Box 96-9 lists the different classes of antiemetic medications commonly prescribed in the PACU. If an adequate dose of antiemetic medication given at the appropriate time is ineffective, then simply giving more of the same class of drug in the PACU is unlikely to be of significant benefit.

Aprepitant (Emend), a substance P antagonist that blocks the neurokinin 1 (NK1) receptor, may be effective in very high-risk patients and refractory cases. The recommended dose is 40 mg by mouth before anesthesia. Initial clinical trials have shown the drug to be effective for up to 48 hours after surgery.[120]

DELIRIUM

Approximately 10% of patients older than 50 years of age who undergo elective surgery will experience some degree of postoperative delirium within the first 5 postoperative days (see Chapter 79).[121] The incidence is significantly higher for certain procedures, such as repair of hip fracture (>35%)[122] and bilateral knee replacement (41%).[123] Although the majority of these patients are older adults who develop delirium within the first several postoperative days, the percentage who become delirious while

recovering in the PACU is not well known; many studies of postoperative delirium and postoperative cognitive dysfunction (POCD) do not evaluate the PACU stay.[124] The American Psychiatric Association defines *delirium* as an acute change in cognition or disturbance of consciousness that cannot be attributed to a preexisting medical condition, substance intoxication, or medication[125]; however, preexisting conditions such as age, functional status, and substance abuse influence the risk of immediate postoperative delirium.

RISK FACTORS

Persistent postoperative delirium is generally a condition of older adult patients.[126] It is a costly complication in both human and monetary terms because it increases the length of hospital stay, pharmacy costs, and mortality. Adult patients at risk for postoperative delirium can be identified before surgery. The most significant preoperative risk factors include: (1) advancing age (70 years and older), (2) preoperative cognitive impairment, (3) decreased functional status, (4) alcohol abuse, and (5) history of delirium. Intraoperative factors that are predictive of postoperative delirium include surgical blood loss, hematocrit less than 30%, and the number of intraoperative blood transfusions.[121,126] In adults, intraoperative hemodynamic derangements (hypotension),[127] the administration of nitrous oxide,[128] and the anesthetic technique (general versus regional)[129] have not been shown to increase the risk of postoperative delirium or longer-term POCD.

Clinical evaluation of a patient with delirium in the PACU includes a thorough evaluation of any underlying disease or metabolic derangement, such as hepatic and/or renal encephalopathy. The workup for postoperative delirium must exclude or treat iatrogenic factors, including inadequate hydration, perioperative medications, arterial hypoxemia, hypercapnia, pain, sepsis, and electrolyte abnormalities.

MANAGEMENT

Identifying the patient at high risk for delirium before admission to the PACU is useful.[126,130] Patients who are severely agitated may require restraints and/or additional personnel to control their behavior and to avoid self-inflicted injuries. Early identification of patients at high risk can also guide postoperative pharmacologic therapy. Patients older than 60 years of age who are to undergo minor surgery should be scheduled in an outpatient center whenever possible to minimize the incidence of POCD.[131]

EMERGENCE EXCITEMENT

Persistent postoperative delirium should not be confused with *emergence excitement*, a transient confusional state that is associated with emergence from general anesthesia. Emergence excitement is common in children, with more than 30% experiencing agitation or delirium at some period during their PACU stay. It usually occurs within the first 10 minutes of recovery but can have later onset in children who are brought to the recovery room asleep. The peak age of emergence excitement in children is between 2 and 4 years.[132] Unlike delirium, emergence excitement typically resolves quickly and is followed by an uneventful recovery.[133]

In children, emergence excitement is most frequently associated with rapid "wake up" from inhalational anesthesia. Although it has also been reported after isoflurane[134] and, to a lesser extent, halothane[135] anesthesia, emergence excitement is most often associated with the less-soluble vapors, sevoflurane[136] and desflurane. Several studies suggest that the incidence of emergence excitement is more a reflection of the anesthetic agent used rather than the rapidity of emergence.[137] In studies comparing sevoflurane and propofol, propofol resulted in a significantly smoother awakening than sevoflurane, despite rapid emergence. Furthermore, delaying emergence by a slow reduction in the inhaled concentration of sevoflurane did not reduce the incidence of emergence excitement.[138]

In addition to rapid emergence, the literature supports a number of possible etiologic factors, including intrinsic characteristics of the anesthetic, postoperative pain, type of surgery, age, preoperative anxiety, underlying temperament, and adjunct medications. Awareness of these contributors allows for the identification and treatment of children who are at increased risk.[133]

Simple preventive measures should be taken to treat children at risk. These include reducing preoperative anxiety, treating postoperative pain, and providing a stress-free environment for recovery. Medications that have been used to prevent and treat emergence agitation and delirium in children include midazolam,[139] clonidine,[140-142] dexmedetomidine,[143,144] fentanyl,[145,146] ketorolac,[147] and physostigmine.[148] In children, the most common preoperative anxiolytic, midazolam, has produced conflicting data. Although midazolam is generally associated with a decrease in the incidence and duration of postoperative delirium, not all studies are in agreement. In studies in which midazolam has not been shown to be beneficial, determining whether midazolam is an independent factor or merely a reflection of other preoperative variables remains unclear.[149]

The incidence of emergence excitement in adults is significantly less than in children and estimated to be between 3% and 4.7%.[150] One study found that significant surgical- and anesthesia-related risk factors included preoperative medication with midazolam (odds ratio [OR] 1.9), breast surgery (OR 5.190), abdominal surgery (OR 3.206), and, to a lesser extent, the length of surgery.[150]

DELAYED AWAKENING

Even after prolonged surgery and anesthesia, a response to stimulation in 60 to 90 minutes should occur.[151] When delayed awakening occurs, evaluating the vital signs (e.g., systemic arterial blood pressure, arterial oxygenation, ECG, body temperature) and performing a neurologic examination are important steps; patients may be hyperreflexic in the early postoperative period. Monitoring with pulse oximetry and analysis of arterial blood gases and pH can detect problems of oxygenation and

ventilation. Additional blood studies may be indicated to evaluate possible electrolyte derangements and metabolic disturbances (e.g., blood glucose concentration).

Residual sedation from drugs used during anesthesia is the most frequent cause of delayed awakening in the PACU. If residual effects of opioids are a possible cause of delayed awakening, then titrated intravenous doses of naloxone (20- to 40-μg increments in adults) should be carefully administered while keeping in mind that this treatment will also antagonize opioid-induced analgesia. Physostigmine may be effective in reversing the central nervous system sedative effects of anticholinergic drugs, especially scopolamine. Flumazenil is a specific antagonist for the residual depressant effects of benzodiazepines. In the absence of pharmacologic effects to explain delayed awakening, considering other causes, such as hypothermia (especially a body temperature lower than 33° C), hypoglycemia, and increased intracranial pressure, is important. Computed tomography may be indicated in patients in whom a central nervous system cause of delayed awakening is a consideration. A stat measurement of serum glucose is indicated if hypoglycemia is a possibility, as in patients with known insulin-dependent diabetes mellitus. Residual neuromuscular block may appear to be delayed awakening. Confirmation with peripheral nerve stimulation and administration of a reversal agent should correct this situation.

DISCHARGE CRITERIA

Although specific PACU discharge criteria may vary, certain general principles are universally applicable (Box 96-10).[2] To summarize, a mandatory minimum stay in the PACU is not required. Patients must be observed until they are no longer at risk for ventilatory depression and their mental status is clear or has returned to baseline. Hemodynamic criteria are based on the patient's baseline hemodynamics without specific systemic blood pressure and heart rate requirements.

BOX 96-10 *Summary of Recommendations for Discharge*

1. Patients should be alert and oriented or mental status returned to baseline.
2. A minimum mandatory stay is not required.
3. Vital signs should be stable and within acceptable limits.
4. Discharge should occur after patients have met specified criteria.
5. Use of scoring systems may assist in documenting fitness for discharge.
6. The requirement to urinate before discharge and drink and retain clear liquids should *not* be part of a routine discharge protocol, although these requirements may be appropriate for selected patients.
7. Outpatients should be discharged to a responsible adult who will accompany them home.
8. Outpatients should be provided with written instructions regarding postprocedure diet, medications, activities, and a telephone number to call in case of emergency.

Modified from American Society of Anesthesiologists Task Force on Postanesthetic Care: Practice Guidelines for Postanesthetic Care, Anesthesiology *96:742-752, 2002.*

An assessment and written documentation of the patient's peripheral nerve function on discharge from the PACU may become useful information should a new peripheral neuropathy develop in the later postoperative period.

POSTANESTHESIA SCORING SYSTEMS

In 1970, Aldrete and Kroulik developed a postanesthesia scoring system to monitor recovery from anesthesia. The original Aldrete score assigned a number of 0, 1, or 2 to five variables: activity, respiration, circulation, consciousness, and color. A score of 9 out of 10 was considered adequate for discharge from the PACU.[152] Over the years, this system has been modified to keep up with advances in technology and anesthesia practice, including the expansion of ambulatory surgery. In 1995, pulse oximetry replaced visual assessment of oxygenation, and additional assessments were added to accommodate patients undergoing ambulatory surgery (Tables 96-4 and 96-5).[153]

With the increase in number and complexity of outpatient surgeries, various authors have amended discharge criteria to include an assessment of home readiness. The resulting postanesthesia discharge scoring system (PADSS) continues to evolve. It was initially based on five criteria: (1) vital signs, (2) ambulation and mental status, (3) pain and nausea and vomiting, (4) surgical bleeding, and (5) fluid intake and output. The current version has been modified to separate pain from nausea and vomiting and to eliminate the need to urinate before discharge.[154-158] In the ambulatory surgical setting, postoperative pain is the most significant cause of delayed discharge and unplanned hospital admission (see

TABLE 96-4 **CRITERIA FOR THE DETERMINATION OF DISCHARGE SCORE FOR RELEASE FROM THE POSTANESTHESIA CARE UNIT**

Variable Evaluated	Score
Activity	
Able to move four extremities on command	2
Able to move two extremities on command	1
Able to move no extremities on command	0
Breathing	
Able to breathe deeply and cough freely	2
Dyspnea	1
Apnea	0
Circulation	
Systemic blood pressure ≤ 20% of the preanesthetic level	2
Systemic blood pressure is 20% to 50% of the preanesthetic level	1
Systemic blood pressure ≥ 50% of the preanesthetic level	0
Consciousness	
Fully awake	2
Arousable	1
Not responding	0
Oxygen Saturation (Pulse Oximetry)	
>92% while breathing room air	2
Needs supplemental oxygen to maintain saturation >90%	1
<90% with supplemental oxygen	0

Modified from Aldrete JA: The postanaesthesia recovery score revisited, J Clin Anesth *7:89-91, 1995.*

Chapter 89). In an effort to improve patient satisfaction and a timely discharge, Chung and associates identified a subset of high-risk patients who are likely to benefit from intense prophylactic analgesic therapy. This study of 10,008 consecutive ambulatory surgical patients found that the incidence and intensity of postoperative pain increased with higher BMIs and duration of anesthesia. Orthopedic and urologic procedures were the most significant surgical factors.[159]

PACU Standards of Care require that a physician accept responsibility for the discharge of patients from the unit (Standard V),[1] even when the decision to discharge the patient is made at the bedside by the PACU nurse in accordance with hospital-sanctioned discharge criteria or scoring systems. If discharge criteria are to be used, then the department of anesthesia and the hospital medical staff must first approve them. A responsible physician's name must be noted on the record.

INFECTION CONTROL

Limitations in space,[148] staffing,[160,161] and time contribute to the transmission of infectious organisms in the PACU. The PACU is typically an open unit without physical barriers between bed stations. Nurses and respiratory therapists simultaneously care for more than one patient, and admissions to the unit are transient with a length of stay measured in hours rather than days. To complicate infection control monitoring, an infection resulting from a lapse in infection control in the PACU might not be identified by routine monitoring until days later on the surgical unit. In 1999, serial hand washing audits in a large metropolitan hospital cited the physical design of the PACU (open patient bays) as a significant barrier to improving hand-washing compliance.[148]

With these limitations in mind, it is not surprising that the PACU has been described as the "weakest link" in the chain of care that bridges the sterile technique practiced in the operating room with infection control protocols practiced on the surgical unit. Despite an awareness of the factors that increase the risk of infection in the PACU, no studies have addressed the problem until recently. A study of hand cleansing during postanesthesia care documents the poor compliance of PACU nurses with this standard infection control procedure.[162,163] In this observational study of 3143 patient care activities, the average compliance with hand cleansing was only 19.6% on patient admission to the unit and 12.5% in patients already admitted to the unit. In this study, the intensity of patient care activities was an independent predictor of noncompliance; that is, the greater the workload, the less likely the nursing staff would comply with infection control measures. Additional independent factors included patients of advanced age (65 years and older) and those recovering from clean surgery (i.e., surgical sites in which the respiratory, alimentary, and urinary tracts are not entered) and clean-contaminated surgery (i.e., surgical sites in which respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions without unusual contamination). As expected, compliance was best in patients with contaminated or known infected wounds.

The installation of bedside alcohol-based cleansers increases compliance of hand hygiene among heath care workers in the ICU.[164-167] Although no equivalent study has been conducted in the PACU, the unit is similar to the ICU in workload and intensity of patient care. The Centers for Disease Control and Prevention's *Guideline for Hand Hygiene in Health-Care Settings* recommends that an "alcohol based hand rub [be made] available at the entrance to the patient's room or at the bedside, in other convenient locations, and in individual pocket-sized containers to be carried by [health care workers] HCWs."[168] Although the convenience of appropriately placed alcohol-based cleansers is expected to improve hand-cleansing compliance, no follow-up studies in the PACU have been published.

TABLE 96-5 CRITERIA FOR DETERMINATION OF DISCHARGE SCORE FOR RELEASE HOME TO A RESPONSIBLE ADULT

Variable Evaluated	Score*
Vital Signs (stable and consistent with age and preanesthetic baseline)	
Systemic blood pressure and heart rate within 20% of the preanesthetic level	2
Systemic blood pressure and heart rate 20% to 40% of the preanesthetic level	1
Systemic blood pressure and heart rate >40% of the preanesthetic level	0
Activity Level (able to ambulate at preoperative level)	
Steady gait without dizziness or meets the preanesthetic level	2
Requires assistance	1
Unable to ambulate	0
Nausea and Vomiting	
None to minimal	2
Moderate	1
Severe (continues after repeated treatment)	0
Pain (minimal to no pain, controllable with oral analgesics; location, type and intensity consistent with anticipated postoperative discomfort)	
Acceptability:	
Yes	2
No	1
Surgical Bleeding (consistent with that expected for the surgical procedure)	
Minimal (does not require dressing change)	2
Moderate (up to two dressing changes required)	1
Severe (more than three dressing changes required)	0

Modified from Marshall SI, Chang F: Discharge criteria and complications after ambulatory surgery, Anesth Analg *88:508-517, 1999.*

* Patients achieving a score of at least 9 are acceptable for discharge.

FUTURE CONSIDERATIONS

INTENSIVE CARE

In recent years, the demand for ICU beds has significantly increased in the United States and in Europe. Because the PACU possesses the equipment and expertise to monitor, ventilate, and resuscitate patients recovering from general anesthesia, it has become the logical choice to provide

care for patients who are critically ill and for whom ICU beds are not available[169] (see also Chapter 101). Although it is now common to care for patients who are critically ill in the PACU, the maintenance of quality patient care continues to challenge hospital administrators and staff.[170]

One obstacle to efficient ICU care in the PACU is the diversity of physician coverage required. Whereas the proximity of the surgical unit and the patient population recovering from anesthesia dictate that an anesthesiologist be the responsible physician for the majority of patients in the unit, patients in a nonsurgical ICU often require physician coverage by specialists who are unfamiliar with the unit and whose practices are located in distant areas of the hospital. As a result, PACU nurses must identify and contact physicians with whom they rarely interact.

Physician coverage (internist, anesthesiologist, or surgeon who is primarily responsible for patient care), privacy for family visitation (lack of space in a traditionally open unit), infection control (proximity of patient beds and rapid turnover of patients), and nursing competencies (ongoing ICU training of staff) are some of the challenges facing the PACU today.[171] In a study of 400 ICU overflow patients admitted to the PACU in the United Kingdom, Ziser and colleagues identified insufficient medical and nursing coverage, inadequate communications, and visiting facilities for patient's families as the most significant problems facing the unit. The patients awaiting placement in the ICU in this study were on average 53 years of age with a mean length of stay of 12.9 hours. Seventy percent were mechanically ventilated, 77.8% required invasive monitoring, and 4.5% died in the PACU while awaiting placement in the ICU. The busiest hours of admission were 1 AM to 11 AM.[172]

In an effort to ensure the quality of patient care in the PACU, the professional societies responsible for the delivery of care in the unit have collaborated to develop standards for the care of ICU overflow patients. The "Joint Position Statement on ICU Overflow Patients" issued in 2000 is the result of this collaboration. It specifically requires that PACU staffing meet the nursing staffing ratios and competencies required in the critical care units.[173]

The Joint Position Statement reproduced here recommends that the following criteria be met:

- It must be recognized that the primary responsibility for Phase 1 PACU is to provide the optimal standard of care to the postanesthesia patient and to effectively maintain the surgery schedule.
- Appropriate staffing requirements should be met to maintain safe, competent nursing care of the postanesthesia patient as well as the ICU patient. Staffing criteria for the ICU patient should be consistent with ICU guidelines and based on individual acuity and needs.
- Phase 1 PACUs are by their nature critical care units and as such should meet the competencies required for the care of the critically ill patient. These competencies should include, but are not limited to, ventilator management, hemodynamic monitoring, and medication administration, as appropriate to their patient population.
- Management should develop and implement a comprehensive resource utilization plan with ongoing assessment that supports the staffing needs for both the PACU and ICU patients when the need for overflow admission arises.
- Management should have a multidisciplinary plan to address appropriate utilization of ICU beds. Admission and discharge criteria should be utilized to evaluate the necessity for critical care and to determine the priority of admission.

In addition to increasing the acuity of patient care in the PACU, the shortage of ICU beds has encouraged the de-escalation of care in selected patient populations. Patients who were historically admitted directly to the ICU after surgery for intensive or specialized monitoring have had successful recovery by routine postoperative care in the PACU. Examples include postoperative craniotomy,[174] liver transplantation,[175,176] and cardiac surgery. The neurosurgical group at the University of Florida has shown that patients with uncomplicated craniotomy can be safely cared for in the PACU at a significant savings of hospital days and cost without increased morbidity or mortality.[163] Likewise, the trend to early extubation of patients after liver transplantation in the surgical unit has led to the successful uncomplicated recovery of these patients in the PACU. Finally, in an effort to protect ICU bed availability and to reduce the number of cardiac surgery cancellations, a group in Melbourne established a cardiac surgery recovery unit within the PACU.[177] Each of these examples requires adequate space and specialized nursing skills to be successful.

OUTPATIENT PROCEDURES

Finally, the PACU has responded to the economic restrictions that currently limit hospital resources by accommodating the performance of simple outpatient procedures (see Chapter 89).[178] The PACU is uniquely equipped to care for patients who are undergoing noninvasive and minimally invasive procedures such as electroconvulsive therapy,[179,180] cardioversion,[181] epidural blood patch,[178] and liver biopsy.[178] Ambulatory patients undergoing such procedures can be directly admitted to the PACU for the procedure and discharged to home after a brief recovery period. To do so, the PACU must be appropriately staffed and scheduled so as to not interfere with routine surgery scheduling and postoperative recovery. Electroconvulsive therapy is somewhat unique in that it requires general anesthesia that is delivered by an anesthesia care practitioner. Typically, these are short procedures that can be scheduled before the routine surgical unit cases. One successful electroconvulsive therapy program schedules the procedure at 5:30 AM with nurse-to-patient ratio of 2:1 and an estimated PACU length of stay of 2 hours.[180]

SUMMARY

The PACU is more than a postanesthesia observation unit. It is unique in its ability to support the care of patients of all ages and in every stage of illness. Since its inception

more than 50 years ago, the PACU has proved to be an exceptionally adaptable unit that is equipped to meet the demands of an evolving health care system.

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Chapter 97

Postoperative Nausea and Vomiting

CHRISTIAN C. APFEL

Key Points

- Postoperative nausea and vomiting (PONV) may be triggered by various pathways through peripheral and/or centrally located receptors; however, the exact etiology is unknown.
- Numerous patient-, anesthesia-, and surgery-related risk factors are associated with a high incidence of PONV, but this association may not be causal. For example, the high incidence of PONV after gynecologic surgery is likely observed because the surgical procedures are conducted in women, who are more susceptible to PONV, and not because of the surgical procedures themselves.
- Instead of assessing a wide range of associated risk factors, a patient's risk for PONV is best predicted by a simplified risk score using independent predictors (statistically corrected for confounders).
- In adult inpatients undergoing general inhaled anesthesia, Apfel's simplified risk score for PONV includes female gender, nonsmoking status, history of PONV or motion sickness, and the use of postoperative intravenous opioids as the main independent predictors. When 0, 1, 2, 3, or 4 of these factors are present, the risk for PONV is approximately 10%, 20%, 40%, 60%, or 80%, respectively.
- In adult outpatients undergoing general anesthesia, a simplified risk score for postdischarge nausea and vomiting (PDNV) includes female gender, age less than 50 years, history of PONV, opioid use in the postanesthesia care unit (PACU), and nausea in the PACU. When 0, 1, 2, 3, 4, or 5 of these factors are present, the risk for PDNV is approximately 10%, 20%, 30%, 50%, and 90%, respectively.
- In children, a similar simplified risk score exists for postoperative vomiting (POV) with duration of surgery greater than or equal to 30 minutes, age older than or equal to 3 years, strabismus surgery, and a positive history of POV or POV/PONV in relatives as the main predictors.
- Because the main triggers for PONV appear to be inhaled anesthetics and opioids, strategies to avoid or reduce exposure (e.g., regional anesthesia or total intravenous anesthesia) are effective means to reduce the risk for PONV.
- A PONV prophylaxis strategy should be tailored to a patient's baseline risk, which can be determined using a simplified risk score. Patients at greatest risk experience the greatest absolute risk reduction from interventions (absolute risk reduction = baseline risk × relative risk [RR] reduction).
- Effective antiemetics to reduce PONV are cyclizine, dimenhydrinate, droperidol, dexamethasone, metoclopramide, ondansetron, dolasetron, tropisetron, and granisetron. The RRs of these antiemetics versus placebo for nausea and for vomiting vary between approximately 0.60 and 0.80.
- Neurokinin (NK_1) antagonists are similarly effective against nausea compared with other antiemetics but are considerably more effective against POV.
- Although the minimally effective dose for prophylaxis with ondansetron is 4 mg, the minimally effective dose for rescue treatment with ondansetron is only 1 mg. Based on this observation, many experts assume that the minimally effective dose for rescue treatment is only one quarter of the dose needed for prophylaxis.
- Patients who suffer from PONV in spite of intraoperative prophylaxis with ondansetron do not respond to rescue treatment with a second dose of ondansetron or granisetron in the PACU. It is therefore concluded that rescue treatment targeting an already blocked receptor is ineffective, so an antiemetic strategy using a different mechanism should be used instead.

Nausea and vomiting in the postoperative period occurs in 20% to 30% of patients,[1] and together, nausea and vomiting are the second most common complaints reported (pain is the most common).[2-8] After the landmark 1992 review by Watcha and White,[9] *postoperative nausea and vomiting (PONV)* became the more commonly used clinical term. In 1999, PONV became a medical subject heading in the National Library of Medicine. The term *PONV* is used throughout this chapter to reflect its current widespread usage to describe the composite postoperative symptoms of nausea and/or vomiting and/or retching. However, the description of these symptoms as "postoperative" should not be construed to suggest that surgery is their most important direct cause, even though this is a widely held belief. Several large prospective cohort studies now suggest that the varying incidences of PONV observed after different types of surgical procedures are largely a reflection of important patient-specific and anesthesia-related risk factors, rather than the surgical procedure itself.[4,5,8]

PONV can be such an unpleasant experience that patients often rate it worse than postoperative pain.[10] Patients' "willingness to pay" out of pocket for effective antiemetic treatment of PONV, as measured by well-designed studies, is $56 in the United States[11] and ∈65 in Europe.[12] Prevention of PONV in high-risk patients significantly improves postoperative ratings of well-being and satisfaction.[13] Although the experience of PONV is generally self-limited, postoperative vomiting or retching (POV) can lead to rare but serious medical complications, such as aspiration of gastric contents, suture dehiscence, esophageal rupture, subcutaneous emphysema, or pneumothorax (the actual incidence related to PONV has not been quantified).[14,15] PONV may delay a patient's discharge from postanesthesia care units (PACUs) and can be the leading cause of unexpected hospital admission after ambulatory anesthesia.[16] Annual PONV-related health care costs approach several hundred million dollars in the United States alone.[17,18]

The ongoing need to improve understanding, prevention, and treatment of PONV is reflected in the literature: approximately 3000 randomized controlled trials of PONV have been published in peer-reviewed journals, and almost 300 new studies are published each year. This is in part because of the interest of the pharmaceutical industry in developing new and more effective treatments for this condition. The purpose of this chapter is to provide an up-to-date review of PONV by a deepened methodologic understanding that allows resolution of discrepancies between traditional beliefs and the best available evidence. This more current understanding and knowledge will enable the reader to manage PONV more effectively in daily clinical practice.

ETIOLOGY: PATHWAYS FOR NAUSEA AND VOMITING

Nausea and vomiting may be induced through various pathways (Fig. 97-1).[19,20]

TOXIC MATERIALS IN THE GASTROINTESTINAL LUMEN

Ingestion of toxic substances (e.g., hypertonic saline or copper sulfate) results in the release of serotonin (5-hydroxytryptamine [5-HT]) from enterochromaffin cells in the gut wall.[21] These enterochromaffin cells hold more than 90% of the body's serotonin and appear to release it under various chemical and mechanical stimuli. Serotonin may also be released indirectly through M_3-muscarinic receptors, β-adrenoceptors, and histamine (H_3) receptors; conversely, the stimulation of γ-aminobutyric acid ($GABA_B$) receptors, 5-HT_4 receptors, and α_2-adrenoceptors and the presence of vasoactive intestinal polypeptide and somatostatin have been proposed to reduce the release of serotonin.[19] Serotonin is secreted in close proximity to afferent vagal nerve endings of the gut wall that travel to the dorsal brainstem through the nucleus tractus solitarius, as demonstrated in animal models in which vagotomy blocks cisplatin-induced emesis.[22] However, large amounts of

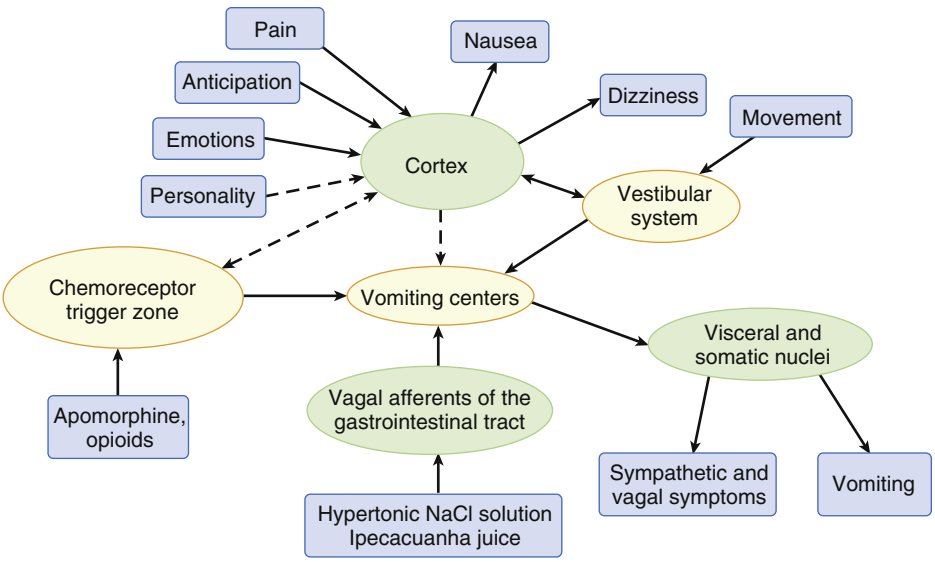


Figure 97-1. Pathways for nausea and vomiting. *Dotted lines* are hypothetic pathways with only indirect evidence. *NaCl*, Sodium chloride. *(Created by Christian Apfel, MD, PhD.)*

serotonin released by neuroendocrine carcinoid tumors lead to flushing, diarrhea, wheezing, and abdominal cramps but typically not to nausea and vomiting. This finding suggests that serotonergic emetogenic stimuli are primarily mediated through the autonomic nervous system rather than the bloodstream. Therefore, even though renal secretion of 5-hydroxyacetic acid (a metabolite of serotonin, with a much longer half-life) is associated with PONV after abdominal surgical procedures,[23] a causal relationship with PONV remains unclear.

ABSORBED TOXINS AND DRUGS

Absorbed toxins or drugs circulating in the blood can cause nausea and vomiting by stimulation of the chemoreceptor trigger zone (CRTZ).[24] The CRTZ is located in the area postrema, a circumventricular organ at the bottom of the fourth ventricle. Even though the CRTZ resides anatomically in the central nervous system, its uniquely permeable endothelium (i.e., lack of a blood-brain barrier) allows it to detect emetogenic substances in the bloodstream as if it were a peripheral organ.[25] Based on a series of articles, Borison and Wang were able to demonstrate in the early 1950s that the CRTZ has an abundance of receptors and that its stimulation can send emetogenic triggers to the brainstem's vomiting center to activate the vomiting reflex (Fig. 97-2).[26-30] Although this mechanism explains how apomorphine (a fairly selective dopamine [D_2] agonist) provokes emesis and why droperidol (a D_2 antagonist) reverses apomorphine's emetogenic effect, it remains unclear how the CRTZ senses or transduces emetic stimuli and why nausea and vomiting are not typical side effects of dopamine infusions. Again, the reasons that certain receptor agonists circulating in the blood fail to trigger nausea and vomiting while corresponding receptor antagonists prevent or reduce nausea and vomiting are unclear.

STIMULATION OF THE VESTIBULAR SYSTEM

The vestibular system is another source of emetogenic stimuli, as observed in motion sickness or Ménière's disease.[31-33] Motion sickness is a risk factor for PONV.[2-8] Whether vestibular input contributes to the emetogenic state in the vomiting center or whether anesthetics or opioid analgesics contribute to the susceptibility of the vestibular organ or signal processing is not clear.

RISK FACTORS AND INDEPENDENT PREDICTORS

DISTINGUISHING ASSOCIATION FROM CAUSALITY

The recognition of risk factors plays a critical role in making diagnostic and therapeutic decisions in medicine. The term *risk factor* was likely first coined in the Framingham study, in which the risk of heart disease was associated with specific conditions such as hypertension, high cholesterol, and smoking. To know which of the risk factors is most likely *causal* or merely *correlational* can be critical for the development of valid risk assessment tools to be used for clinical decisions. For example, women are more susceptible than men to certain emetogenic stimuli (motion, chemotherapy, inhaled anesthetics, and opioids).[34,35] If the average incidence of PONV is considered to be approximately 30% overall and female patients are approximately three times more likely to develop PONV,[3,5] the average incidence in male and female patients should be in the range of 15% and 45% (assuming that the same numbers of men and women are anesthetized).[36] It is therefore not surprising that approximately one in two women undergoing gynecologic surgical procedures suffers from PONV. From this perspective, the type of surgery can be considered a risk factor for PONV. However, establishing a policy for the routine use of antiemetics for the prevention of PONV for women having gynecologic surgery, but not other surgical procedures, would not acknowledge that lengthy nongynecologic surgical procedures in women are associated with incidences of PONV much higher than 50%,[4,5] whereas short gynecologic procedures such as dilatation and curettage may be associated with PONV incidences as low as 7%.[37] Therefore, the current categories of surgical procedures are generally too broadly defined to be reliable predictors of PONV.[38]

It is more useful to consider PONV as multifactorial in its origin, that is, as a consequence of emetogenic agents (inhaled anesthetics, opioids) applied to susceptible patients (female patients, those with a history of motion sickness, nonsmokers). These factors have been shown not only to be associated with an increased incidence of PONV but also to be important independent predictors of PONV. A better prediction can be obtained by focusing on these well-established independent predictors that appear to cause PONV.[38] Therefore, the following text distinguishes between factors that are merely associated with increased risk (risk factors or associated risk factors) and factors that appear to be causally related to PONV (independent risk factors or independent predictors). Table 97-1 lists the relative importance (presented as odds ratios) of independent predictors as determined in large cohort studies.

FACTORS THAT MAY NOT BE RELEVANT

Many reviews or book chapters list large numbers of PONV risk factors, irrespective of the evidence or the magnitude of effect. This approach has contributed to a divergence between commonly held clinical beliefs about PONV risk factors and the published evidence. For example, Eberhart and colleagues reported that more than 80% of German anesthesiologists considered obesity to be a risk factor for PONV.[39] However, Kranke and co-workers found that an increased body mass index was not associated with an increased incidence of PONV.[40] Similar discrepancies exist for the influence of facemask ventilation,[41,42] use of a nasogastric or orogastric tube,[43-46] intravenous use of neostigmine to reverse neuromuscular blockade,[47,48] phase of menstrual cycle,[49] and even weather or phase of the moon.[50,51] Thus, the following discussion of risk factors for PONV focuses on

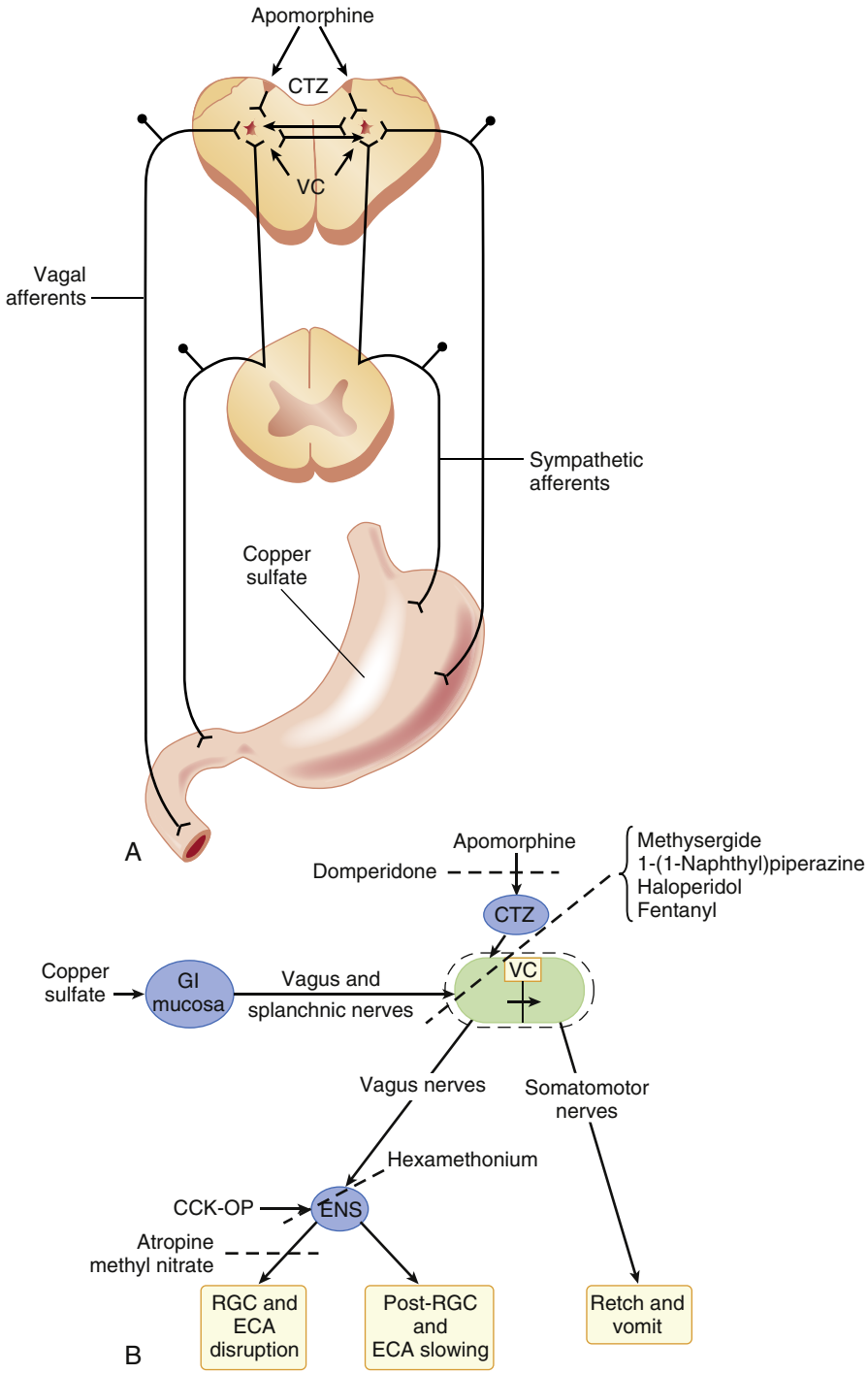


Figure 97-2. Different types of schematic representation of the organization of the emetic reflex from the original Wang and Borison (**A**) 1952 model and Lang and Marvig (**B**) in 1989; Borison and McCarthy (**C**) in 1981; and Andrews, Rapeport, and Sanger (**D**) in 1988. Note that all the models contain essentially the same key elements. *CCK-OP,* Cholecystokinin octapeptide; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *CTZ,* chemoreceptor trigger zone; *ECA,* electrical control activity; *ENS,* enteric nervous system; *GI,* gastrointestinal; 5-HT, 5-hydroxytryptamine; *IV cytotoxic agents,* intravenous cytotoxic agents; *IV vent,* fourth ventricle; *NTS,* nucleus tractus solitarius; *RGC,* retrograde giant contraction; *PCRF,* parvicellular reticular formation; *SP,* substance P; *VC,* vomiting center.

the factors that are well supported in the literature. Of course, other unknown or insufficiently studied PONV risk factors may have yet to be found. For example, it may be possible that rapid patient transport from the operating room to the PACU, especially involving fast turns or decelerations, can trigger nausea and vomiting. However, this factor has never been formally studied, and therefore its importance cannot be determined. Accordingly, the following discussion focuses on the best available evidence.

PATIENT-RELATED INDEPENDENT PREDICTORS

Female Gender

Female gender is the strongest patient-specific predictor of PONV, with an odds ratio of approximately 2.6[52] (see Table 97-1), independent of anesthetic technique. Women can also suffer from hyperemesis gravidarum,[53] and they have a lower threshold for motion sickness than men.[54] The reason for increased female susceptibility to nausea and

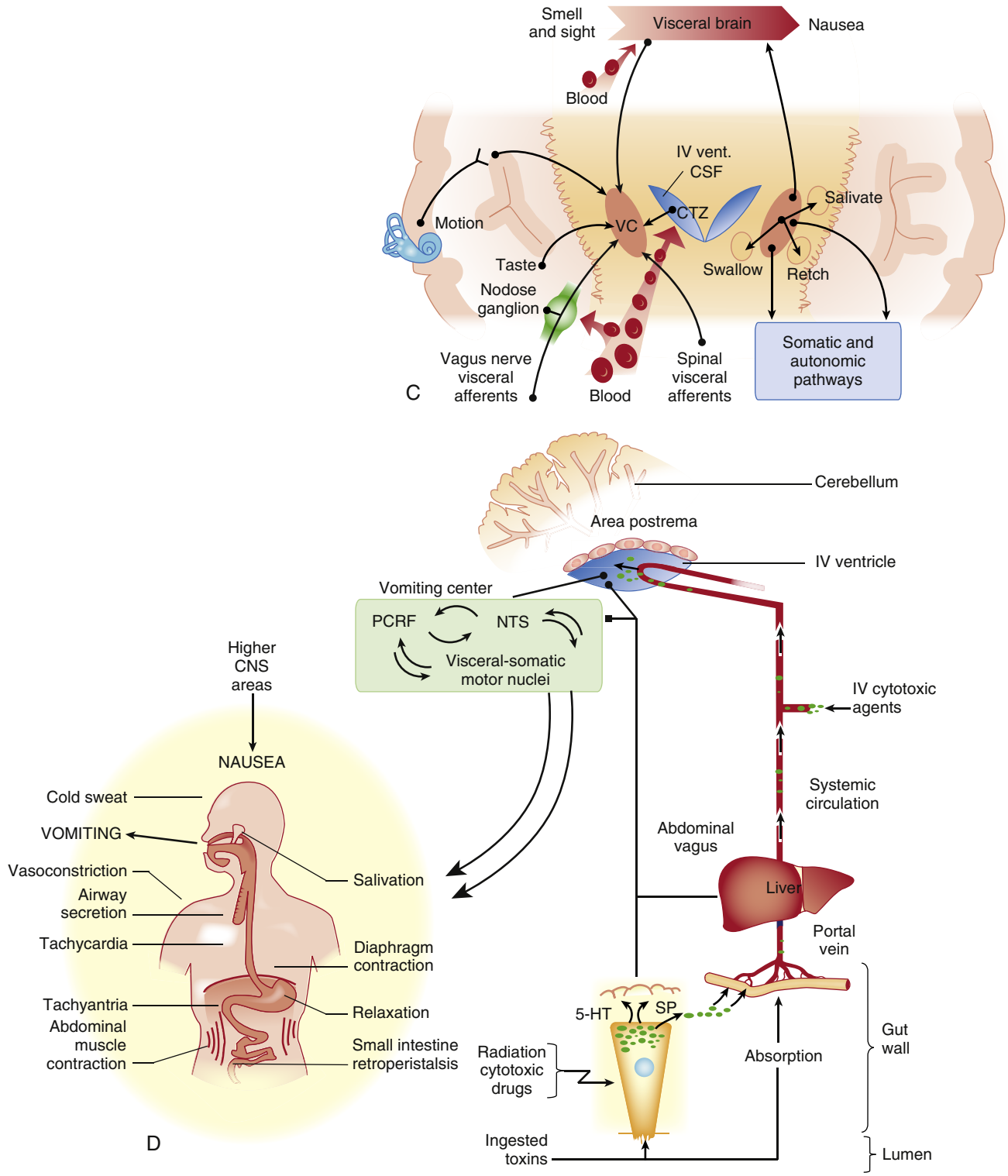


Figure 97-2, cont'd

TABLE 97-1 **THE ODDS RATIOS ASSOCIATED WITH PATIENT-, ANESTHESIA-, AND SURGERY-RELATED RISK FACTORS FOR POSTOPERATIVE NAUSEA AND VOMITING***

Study (First Author and Year)	Cohen, 1994	Koivuranta, 1997		Apfel, 1998	Apfel, 1998	Apfel, 1999		Sinclair, 1999	Eberhart, 2000	Junger, 2001	Visser, 2001	Apfel, 2002	Apfel, 2002		Pierre, 2002
End Point	**N**	**N**	**V**	**V**	**V**	**NV (FIN)**	**NV (GER)**	**NV**	**NV**	**NV**	**NV**	**NV**	**NV**	**V**	**NV**
Risk Factor															
Patient-Related Factors															
Female gender	**2.6**	**2.4**	**2.7**	**3.6**	**1.7**	**2.3**	**3.6**	**2.8**	**2.8**	**2.5**	—	**2.9**	**1.7**	**2.4**	**2.4**
History of PONV or MS	—	**2.3**	**1.9**	**1.9**	**4.3**	**2.0**	**1.9**	**3.1**	**2.3**	—	—	**1.8**	**1.9**	**2.4**	**4.5**
History of MS	—	**1.7**	**1.9**	—	—	—	—	—	**2.1**	—	—	**1.7**	—	—	—
History of migraine	—	**1.6**	1	—	—	—	—	—	—	—	—	—	—	—	—
Nonsmoking status	**1.8**	**2.1**	**1.7**	**2.1**	1	**2.3**	**2.0**	**1.5**	**1.8**	**1.9**	—	**1.8**	**1.6**	**1.9**	*1.6*
Age (per decade)	**0.9**	1	*1.2*	**0.8**	**0.9**	1	**0.7**	**0.9**	1	**1.0**	—	*1.0*	—	—	**0.8**
BMI	*1.0*	**1.6**	**1.4**	1	1	—	—	1	—	1	—	*0.8*	—	—	—
ASA	**1.5**	*1.2*	**1.7**	—	—	—	—	1	—	1	—	—	—	—	—
Anesthesia-Related Factors															
Duration (per hour)	1.5	2.0	2.1	1.3	1	1	1.8	2.5	1.8	1.4	—	1.4	1.9	1.9	*1.0*
Volatile anesthetics	1.5	1.7	1	—	—	—	—	10.1	—	2.5	2.1	—	1	1	—
Nitrous oxide	—	—	—	—	—	—	—	—	—	2.2	—	—	—	—	—
Opioids: intraoperative	1.3	—	—	1	1	—	—	—	—	4.2	—	*1.9*	1	1	—
Opioids: postoperative	—	1.7	1	—	1	2.5	1	—	*1.2*	1	—	1.3	2.3	2.5	4.8
Surgery-Related Factors															
Ear, nose, and throat	*1.7*	1	1	1	—	1	1	**4.4**	—	1	—	1	*1.4*	1	*0.5*
Gynecologic	**1.3**	1	1	—	—	—	—	**3.3**	—	1	—	*1.1*	—	—	*0.4*
Ophthalmologic	**1.8**	1	1	—	*0.7*	1	1	**5.9**	—	1	—	*1.4*	**3.7**	1	—
Cholecystectomy	—	—	—	—	—	—	—	—	—	—	—	**2.9**	—	—	—
Thyroid	—	—	—	—	**2.7**	—	—	—	—	—	—	—	—	—	*0.5*
Abdominal	*0.9*	1	1	—	*0.9*	1	1	—	—	1	—	*1.2*	—	—	—
Laparoscopic	**2.3**	1	1	—	**0.4**	1	1	—	—	—	—	**2.1**	—	—	—
Orthopedic	—	1	1	—	*0.9*	1	1	**3.4**	—	—	—	*1.1*	—	—	—
Urologic	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—
Breast	—	—	—	—	*2.2*	—	—	—	—	—	—	—	—	—	*0.4*
Neurologic	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—
Plastic	—	—	—	—	—	—	—	**6.7**	—	—		—	—	—	*0.4*
Head and neck	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—

Modified from Apfel CC, Heidrich FM, Jukar-Rao S, et al: Evidence-based analysis of risk factors for postoperative nausea and vomiting, Br J Anaesth *109:742-753, 2012.*

ASA, American Society of Anesthesiologists; *BMI,* body mass index; *FIN,* Finnish dataset; *GER,* German dataset; *MS,* motion sickness; *N,* nausea; *PDNV,* postdischarge nausea and vomiting; *PONV,* postoperative nausea and vomiting; *V,* vomiting.

*Variables that were assessed in the study's multivariate regression model but failed to show statistical significance are displayed in the table as "1," and variables not considered or reported in the study are displayed as "—." Significant results are bold; non-significant results are italicized.

vomiting is unclear, but this susceptibility persists well after menopause and for most of the rest of a woman's life.[55]

Not Smoking

Individuals often experience nausea and diarrhea when smoking their first cigarette.[56] This is likely an acute effect of nicotine because nausea is a known side effect of nicotine patches.[57] Although one could predict that smokers would have a higher risk of PONV than nonsmokers,[39] Cohen and associates found that nonsmokers were 1.8 times more likely than smokers to have PONV.[3] This finding was subsequently confirmed in a meta-analysis of large studies of risk factors for PONV.[52] The mechanism by which a smoking habit reduces the risk of PONV is not entirely clear, but one may speculate that long-term smokers are desensitized to nausea. Nicotine

Stadler, 2003		Apfel, 2004	Apfel, 2004	Van den Bosch, 2005	Choi, 2005	Wallenborn, 2006	Wallenborn, 2007	Leslie, 2008	Nakagawa, 2008	Rodseth, 2010	Apfel, 2012	
N	V	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	PDNV
2.7	**3.8**	**2.7**	**3.1**	**1.6**	**2.9**	**2.3**	**2.5**	**2.1**	**7.3**	**1.9**	**2.6**	**1.6**
1.8	**2.0**	**1.8**	**1.7**	**2.1**	**2.4**	**1.9**	**2.1**	—	—	**2.6**	**1.4**	**1.6**
—	—	—	—	—	—	—	—	—	—	—	—	—
2.2	*1.3*	—	—	—	—	—	—	—	—	—	—	—
2.4	**3.0**	**1.8**	**1.6**	**1.9**	**2.0**	**2.1**	**2.0**	1	**4.6**	—	*1.4*	*1.0*
0.9	*0.9*	—	—	**0.8**	1	**0.8**	—	**0.9**	**1.1**	—	—	—
1.0	**0.9**	—	—	1	**0.9**	*1.0*	*1.0*	—	—	—	—	—
—	—	—	—	1	1	—	—	—	—	—	—	—
1.0	*0.8*	—	1.2	1	1.9	*3.3*	6.3	*1.3*	*0.9*	—	—	—
2.5	3.7	—	1.4	2.1	2.0	—	—	—	—	—	—	—
—	—	—	1.2	—	1	—	—	2.0	—	—	*0.9*	*1.4*
—	—	—	—	—	1	*0.8*	—	1	—	—	1.5	*1.2*
1.0	1.0	1.5	2.1	1	—	1.5	*1.0*	—	—	*1.4*	1.5	1.7
—	—	*1.6*	—	**1.8**	—	*1.2*	—	—	—	—	*1.3*	*1.5*
9.3	*0.8*	*1.8*	*1.3*	—	—	**1.8**	—	—	—	—	*0.8*	*1.1*
9.5	*2.1*	*1.5*	—	1	—	—	—	—	—	—	—	—
—	—	**3.2**	**1.5**	—	—	**1.6**	—	—	—	—	*1.2*	*1.8*
—	—	—	*1.2*	—	—	**2.0**	—	—	—	—	—	—
5.8	*1.2*	**2.2**	*1.0*	**1.8**	—	*0.8*	—	**1.8**	—	—	—	—
—	—	**3.2**	—	1	**1.3**	—	—	—	—	—	**2.3**	*1.2*
2.7	*1.0*	*1.3*	*0.9*	—	—	*1.1*	—	—	—	—	*1.0*	*1.4*
8.1	**6.2**	—	—	—	—	—	—	—	—	—	*1.2*	*1.5*
—	—	—	*0.7*	—	—	—	—	—	—	—	*0.7*	*1.1*
4.8	*1.0*	—	—	—	—	—	—	—	**6.4**	—	—	—
2.9	*1.7*	—	—	—	—	—	—	—	—	—	—	—
5.0	**1.8**	—	*1.1*	—	—	—	—	—	—	—	—	—

stimulates indirect GABA-mediated cerebral dopamine release,[58] and nicotine withdrawal in the perioperative period may lead to low postoperative cerebral dopamine levels, thus reducing activation of dopaminergic circuits in the CRTZ known to be associated with nausea and vomiting (my conjecture). However, nonsmoking is not a risk factor for nausea and vomiting in the postdischarge period,[59] perhaps because the protective effect of reduced dopaminergic stimulation disappears once discharged patients resume smoking.

History of Postoperative Nausea and Vomiting, Motion Sickness, or Migraine

Susceptibility to emetogenic stimuli varies among individuals according to history of PONV,[2,4,6,8,37,60-62] history of motion sickness,[2,4,6,61,62] and history of migraine.[4,8]

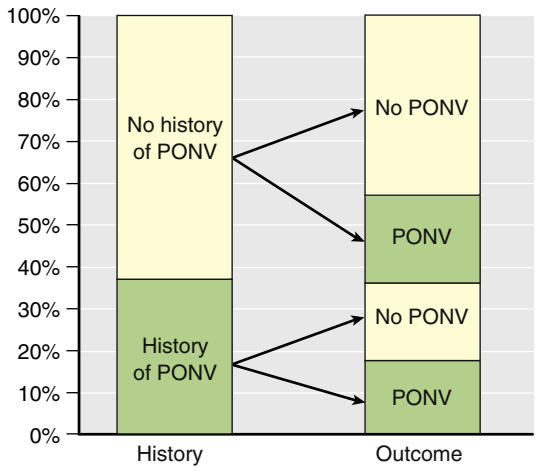


Figure 97-3. Limited sensitivity of a single predictor to identify patients at risk for postoperative nausea and vomiting (PONV), with history of PONV as an example. *(From Apfel CC, Kranke P, Eberhart LH: Comparison of surgical site and patient's history with a simplified risk score for the prediction of postoperative nausea and vomiting,* Anaesthesia *59:1078-1082, 2004.)*

Although one would intuitively expect that a history of PONV is the strongest predictor of subsequent PONV, this is not the case. In fact, in the majority of studies, female gender is a stronger predictor than a history of PONV.

This finding is illustrated by a study of 1566 patients (Fig. 97-3).[38] Approximately one third of these patients (569) presented with a history of PONV, of whom every second patient (280) experienced PONV. Two thirds of patients (997) did not have a history of PONV, of whom one third (320) experienced PONV. Clearly, patients with a history of PONV were at higher risk for experiencing PONV. However, of the total 600 patients who developed PONV, fewer than half (280 of 600) would have been correctly identified if the history of PONV had been used as a single predictor. Indeed, the use of PONV history as a single predictor has been associated with a sensitivity of less than 50% to identify patients at risk for PONV. In other words, fewer than half the patients who develop PONV were correctly identified in advance (less than one would expect from a random guess).[38]

Age

In adults, although the incidence of PONV decreases with age with an odds ratio of 0.88 per decade,[52] age has not always been a strong risk factor.[3,37,55,60,62-66] In children, however, Eberhart and co-workers have shown that an age of 3 years or older is associated with an increased risk for PONV.[67]

Anxiety

Anxiety may influence PONV, although this finding was not supported in a study with a small cohort of children.[68] However, in secondary analyses of a considerably larger randomized controlled trial in adults,[7] anxiety was assessed using two standardized psychometric instruments, and a statistically significant but fairly weak association was demonstrated.[66] Although anxiety increases PONV, a preoperative assessment of anxiety is unlikely to result in a significant improvement in prediction for PONV.

ANESTHESIA-RELATED INDEPENDENT PREDICTORS

Preoperative Opioids

Few studies have compared different opioids given in conjunction with premedication. Eger and colleagues found no difference between morphine and meperidine.[69] In the same study, the $GABA_A$-enhancing drug pentobarbital was associated with a less frequent incidence of PONV compared with placebo.

Intraoperative Opioids

No large prospective cohort study has demonstrated that the type or dose of intraoperative opioid influences PONV in adults. In children, the liberal intraoperative use of morphine (analgesic median effective dose [ED_{50}], 0.18 mg/kg) is associated with a frequent incidence of POV in children undergoing tonsillectomies (see Chapter 93).[70]

Whether the type of intraoperative opioid used is a relevant consideration remains controversial. One article suggested that alfentanil is associated with less PONV compared with fentanyl or sufentanil.[71] Another group hypothesized that the ultrashort half-life of remifentanil would result in less carryover effect in the postoperative period and thereby decrease PONV. However, no significant difference in the overall incidence of PONV was noted when remifentanil was compared with fentanyl, probably because the study design included predominantly larger operations requiring significant amounts of opioids for postoperative pain relief, thus masking any potential benefit.[48] Finally, morphine-6-glucuronide, an active metabolite of morphine, has been reported to be associated with less PONV compared with morphine,[72] although this difference was not statistically significant in another study.[73] In conclusion, regardless of whether opioids are used intraoperatively or postoperatively, the available evidence suggests that the dose of opioid, rather than the type, is one of the main predictors (and/or causes) of PONV.

Postoperative Opioids

Most large studies using multivariable analyses demonstrate that use of postoperative opioids doubles the risk of PONV.* The dose of postoperative opioid appears to be important,[76] but not the type (e.g., morphine versus piritramide).[77] As a consequence, opioid-sparing strategies should reduce the incidence of PONV. Indeed, PONV tends to be decreased when intravenous acetaminophen or cyclooxygenase-2–selective nonsteroidal antiinflammatory drugs (NSAIDs)[78] reduce opioid use by 30% to 50%. In addition, the peripheral opioid antagonist alvimopan appears to reduce nausea severity in the late postoperative period without affecting the central analgesic effects of opioids.[79] Alvimopan appears to work by mitigating postoperative ileus and opioid-induced bowel dysfunction.[80-83]

Propofol and Inhaled Anesthetics

Propofol is widely believed to have antiemetic properties. By using propofol in patient-controlled analgesia (PCA) pumps in the PACU as "patient-controlled antiemesis,"

*References 2, 4, 5, 38, 60, 74, and 75.

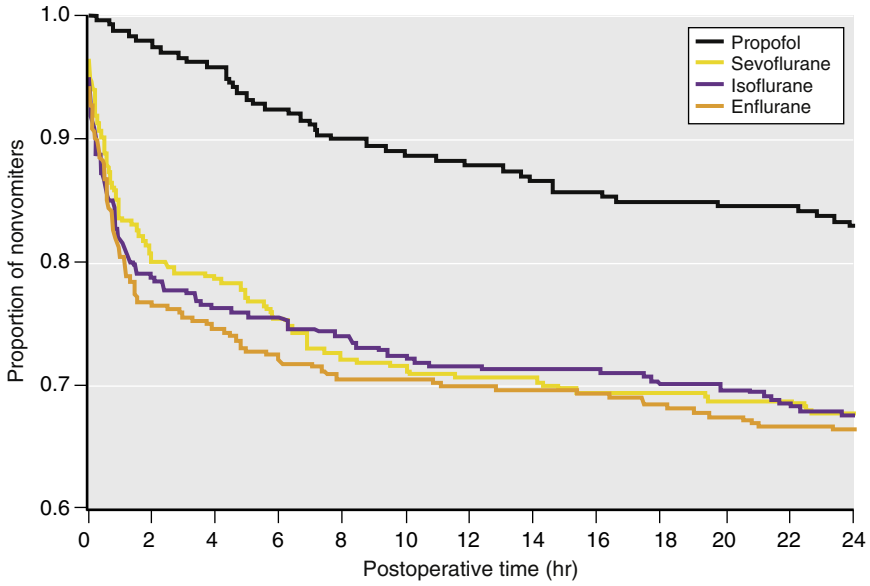


Figure 97-4. Kaplan-Meier chart for postoperative vomiting after isoflurane, enflurane, sevoflurane, and propofol. *(From Apfel CC, Kranke P, Katz MH, et al: Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design,* Br J Anaesth *88:659-668, 2002.)*

Gan and associates found that "nonsedating" plasma concentrations of 343 ng/mL reduced nausea in 50% of cases.[84,85] However, using a similar design, Scuderi and colleagues were unable to demonstrate any antiemetic effect of propofol.[86] In another study, healthy volunteers were randomized to propofol, midazolam, or placebo and were then exposed to an infusion of apomorphine.[87] At nonsedative doses, neither propofol nor midazolam provided protection. However, at sedative doses, both propofol and midazolam increased the threshold for nausea. As a result, the antiemetic activity of propofol-induced sedation is not clear.

Compared with a purely regional anesthetic technique, general anesthesia is associated with a significantly higher incidence of PONV.[37] This finding raises the question of the individual contribution of the drugs used for the general anesthetic regimen, namely opioids, inhaled anesthetics, and nitrous oxide. Although previous meta-analyses demonstrated a lower incidence of nausea and vomiting with propofol compared with inhaled anesthetics,[88,89] in volunteer studies 8-hour anesthesia with sevoflurane was associated with nausea and vomiting in more than 80%, a finding strongly suggesting the emetogenicity of volatile anesthetics.[90] In addition, a large clinical study demonstrated the following: (1) the difference in vomiting between inhaled anesthetics and propofol occurs predominantly in the first 2 to 6 hours postoperatively (Fig. 97-4); and, more importantly, (2) the difference in early vomiting is clearly dose related (Fig. 97-5), so the difference is not related to propofol but rather to the dose-dependent emetogenic effect of the volatile anesthetics.[75] No differences in PONV have been observed among the volatile anesthetics isoflurane, enflurane, and sevoflurane. This finding is consistent with a meta-analysis by Gupta and co-workers (comparing propofol, isoflurane, sevoflurane, and desflurane),[91] a meta-analysis by Macario and associates (comparing sevoflurane with desflurane),[92] and a study by Wallenborn and colleagues (comparing isoflurane, sevoflurane, and desflurane).[93]

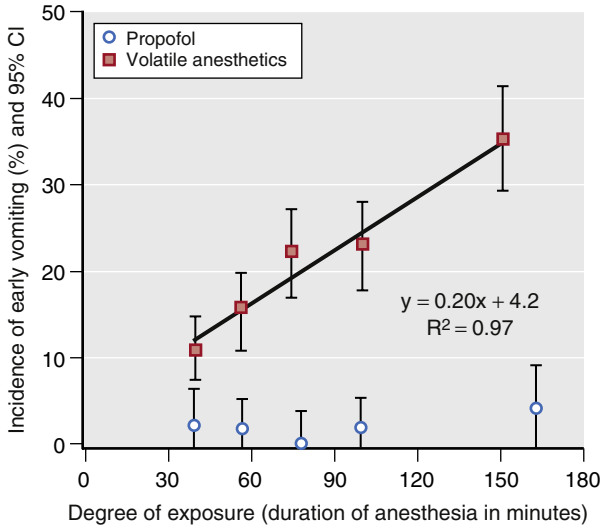


Figure 97-5. Incidence of early vomiting (0 to 2 hours) after maintenance with volatile anesthetics or propofol. *CI,* Confidence interval. *(From Apfel CC, Kranke P, Katz MH, et al: Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design,* Br J Anaesth *88:659-668, 2002.)*

Nitrous Oxide

Numerous studies in the 1980s and meta-analyses in the 1990s emphasized the emetogenic effect of nitrous oxide.[94,95] However, the emetogenic effect of nitrous oxide may not be quite as strong as that associated with volatile anesthetics.[74] Moreover, the emetogenic effects of nitrous oxide and volatile anesthetics are independent (i.e., they are additive).[74] What is probably more notable than the emetogenic effect of nitrous oxide is the landmark trial comparing a nitrous oxide group (70% N_2O, 30% O_2) with an oxygen-enriched air group (80% O_2, 20% N_2) that found not only more PONV but also significantly more severe adverse events (pulmonary complications, wound infections, and fever) in the nitrous

oxide group.[96] A second large multicenter 5-year study comparing a nitrous oxide group (70% N_2O, 30% O_2) and a nitrous oxide–free group (70% N_2, 30% O_2) may provide further evidence regarding nitrous oxide and its association with more severe medical complications.[97]

Duration of Anesthesia

The effect of duration of anesthesia on PONV has been described in several studies.[4,37,61,74,75,93] The magnitude of this time-dependent dose response varies widely, as reflected in odds ratio per hour ranging from 1.15[74] to 2.53.[37] As referenced earlier, the effect size may be large when inhaled anesthetics are used and small when propofol is used (see Fig. 97-5), and it depends on the amount of opioids used.[74] In any event, it is generally correct to assume that longer and more invasive surgical procedures are associated with more PONV. In fact, in a cross-validation that developed a simplified risk score, a co-linearity was seen between the duration of anesthesia and the postoperative intravenous use of opioids. Because intravenous opioid use was the slightly stronger predictor, that variable remained an independent predictor, as opposed to duration of anesthesia.[5]

SURGERY-RELATED INDEPENDENT PREDICTORS

Many surgical procedures are associated with a high incidence of PONV.[9] This finding has led to many hypothesized causal mechanisms for various types of surgical procedures—tympanoplasty and vestibular stimulation, adenotonsillectomy and swallowed blood, breast surgery and emotional load, laparoscopic surgery and peritoneal irritation, abdominal surgery and serotonin release, and hysterectomy and vagal stimulation[98-100]—all resulting in a tendency to specify the type of surgery narrowly in antiemetic trials. Without question, patients undergoing major abdominal and gynecologic surgical procedures have an increased risk of PONV, with incidences of at least 50%. However, in many instances, these incidences may reflect other underlying factors, such as prolonged exposure to emetogenic volatile anesthetics and/or large doses of intraoperative opioids. In fact, if volunteers are exposed to volatile anesthetics (without any surgical intervention) for an extended period of time, almost all experience nausea or vomiting afterward.[90] Therefore, risk assessment should be based on the underlying independent predictors, rather than the type of surgical procedure. In addition, several studies support the notion that the type of surgery is not an independent predictor of postoperative nausea,[4] vomiting,[4,8,63] PONV,[5,60] or need for rescue treatment (see Table 97-1).[65] However, other studies have identified several types of surgical procedures as independent predictors of postoperative nausea,[3,8] vomiting,[64] or PONV.[37,61,66,74] Nevertheless, most types of surgery have not consistently been shown to be independent predictors of PONV in the majority of studies; possible exceptions to this rule are laparoscopic cholecystectomy and gynecologic procedures.[3,59,74] Although strabismus surgery is not a risk factor in adults,[101] it is a well-established and clinically relevant independent predictor of POV in children.[67,102]

One could argue that it would be enough to know which types of surgical procedures are risk factors, whether or not they are independent predictors of PONV, to decide on the need for prophylactic antiemetics. The incidence of PONV in many so-called emetogenic procedures (laparoscopy, adult strabismus surgery, middle ear surgery, herniorrhaphy, tonsillectomy, adenoidectomy, and uvulopalatopharyngoplasty) is not much higher than for other types of surgery. In fact, when Scuderi and colleagues stratified patients according to "emetogenic procedures," the incidence of PONV in the PACU was 37% (80 of 215) compared with 31% (112 of 360) for all other surgical procedures, an incidence that was not significantly different.[103] These findings are also consistent with a study in which the PONV incidence over 24 hours was 42% (283 of 681) for "emetogenic procedures" and 36% (317 of 885) for other procedures.[38] In conclusion, although certain types of surgical procedures are associated with a more frequent incidence of PONV, causality has not been clearly established. With the exception of strabismus surgery in children, the incidence of PONV with most surgical procedures likely reflects underlying patient- and anesthesia-related factors.

RISK ASSESSMENT

PONV is multifactorial. Therefore, a patient's risk can be better estimated by accounting for several independent predictors simultaneously.

Palazzo and Evans in the United Kingdom were the first to apply multiple logistic regression analysis to 148 patients undergoing minor orthopedic procedures, thus developing a predictive model for "postoperative sickness."[2] One year later, logistic regression analysis was applied to data from a Canadian 4-center survey of 16,000 inpatients.[3] Binary logistic regression analysis is a multivariable statistical method that quantifies the relative impact of *independent* predictors (e.g., female gender, nonsmoking) on a dichotomous outcome (here PONV) by determining their coefficients according to

$$P = 1/\left(1 + e^{-z}\right)$$

with $z = \alpha \bullet x_1 + \beta \bullet x_2 + \gamma \bullet x_3 + \ldots + \omega$, and α, β, γ, and so forth, being the coefficients for the factors x_1, x_2, x_3, etc. These coefficients are directly related to the odds ratio of a predictor through the formula odds $\text{ratio}_{(a)} = e^a$, a measure that is similar to the relative risk or risk ratio, discussed later.

This is important to realize when comparing articles that report coefficients with those that report odds ratios.[8] Table 97-1 displays the odds ratios that quantify the impact of variables as independent predictors, not merely risk factors, for PONV.

Subsequently, two groups independently conducted large surveys and applied logistic regression analyses to develop more generalizable predictive models.[4,63,64] Koivuranta and colleagues were the first to publish predictive models for PONV based on logistic regression analyses, and they developed a simplified model by selecting the five strongest predictors: female gender,

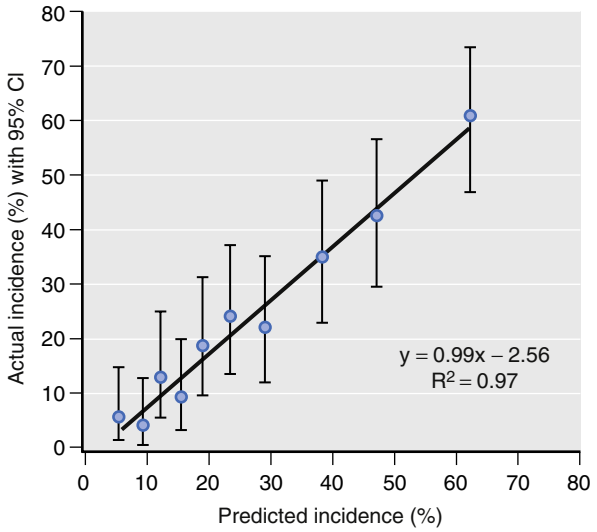


Figure 97-6. Correlation between average predicted and actual incidence of postoperative vomiting in 10 percentile groups. *CI,* Confidence interval. *(From Apfel CC, Greim CA, Haubitz I, et al: The discriminating power of a risk score for postoperative vomiting in adults undergoing various types of surgery,* Acta Anaesthesiol Scand *42: 502-509, 1998.)*

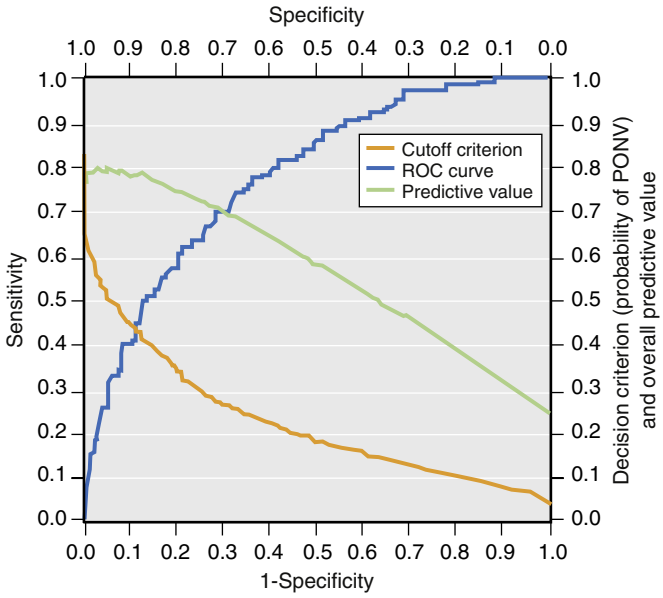


Figure 97-7. Receiver operating characteristic (ROC) curve characterizing the relationship between sensitivity and specificity. *PONV,* Postoperative nausea and vomiting. *(From Apfel CC, Greim CA, Haubitz I, et al: The discriminating power of a risk score for postoperative vomiting in adults undergoing various types of surgery,* Acta Anaesthesiol Scand *42:502-509, 1998.)*

previous PONV, duration of operation longer than 60 minutes, history of motion sickness, and nonsmoking.[4] When 0, 1, 2, 3, 4, or 5 of these independent predictors were present, the risk for PONV was 17%, 18%, 42%, 54%, 74%, and 87%, respectively. Later, a published predictive model for POV in patients undergoing surgical procedures of the ear, nose, and throat (ENT) showed a tight correlation between predicted and observed incidence in a validation cohort (Fig. 97-6).[63] Because the later model was developed in patients undergoing ENT surgical procedures, its applicability to other types of surgical procedures was unclear. In a subsequent study that included a wide range of surgical procedures, the type of surgery turned out to be an *independent* predictor (at the expense of duration of anesthesia), but the discriminating power as described by the area under the receiver operating characteristic (ROC) curve was at least as good using the prior risk score (independent of surgery type). Notably, the area under the ROC curve (ROC-AUC) was 0.77 (Fig. 97-7), meaning that on average the prediction was correct in approximately three of four cases.[64] The two groups then performed a cross-validation and found that risk scores derived from one center were able to predict PONV from the other center (ROC-AUC = 0.65 to 0.75) and that simplification of the score did not weaken the discriminating power (ROC-AUC = 0.63 to 0.73).[5] The final score consisted of four predictors: female gender, history of motion sickness or PONV, nonsmoking status, and the use of postoperative opioids; if 0, 1, 2, 3, or 4 of these risk factors were present, the incidences of PONV were 10%, 21%, 39%, 61%, and 79%, respectively (Fig. 97-8).[5] In countries where opioids are used liberally in the postoperative period, Koivuranta's PONV score shows slightly superior predictive characteristics,[62] although Apfel's PONV score may be preferable for its simplicity.

Whereas this score was developed for the prediction of PONV over 24 hours in inpatients, Chung's group developed a fairly complex predictive model for PONV in outpatients, also known as postdischarge nausea and/or vomiting (PDNV).[37] That score included type of surgery as a predictor, but it appeared to be inferior to the simplified risk scores.[60,61] However, this result may have occurred, in part, because the validations were performed in inpatients. A more recent validation from the Kalkman group in the Netherlands found that the predictive characteristics of the simplified risk scores were rather limited, with ROC-AUCs of only 0.63 to 0.66.[62] In this patient population, however, use of postoperative opioids—invariably shown to affect the risk for PONV in previous studies and a key independent predictor in the simplified risk models—was not associated with an increased incidence of PONV, a feature likely accounting for the limited predictive power. Therefore, a large multicenter study in more than 2000 patients was conducted to develop a predictive risk score for PDNV in ambulatory patients in the United States, where opioids are commonly used in postoperative and postdischarge settings.[59] The incidence of overall PDNV was 37% (Fig. 97-9), and logistic regression analyses identified 5 independent predictors of PDNV, namely female gender, age less than 50 years, history of PONV, opioid use in the PACU, and nausea in the PACU.[59] Simplification of a risk score based on these 5 risk factors led to an ROC-AUC of 0.72, and the incidence of PDNV associated with 0, 1, 2, 3, 4, and 5 factors was 7%, 20%, 28%, 53%, and 89%, respectively (Fig. 97-10).[59]

These models have been developed for prediction in adults and are not applicable to pediatric patients.[104] However, the risk of POV can be predicted with the

Risk factors	Points
Female gender	1
Nonsmoker	1
History of PONV	1
Postoperative opioids	1
Risk score =	0...4

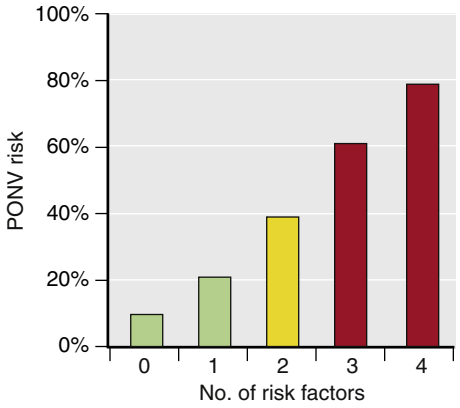


Figure 97-8. The simplified risk score for adults. *PONV,* Postoperative nausea and vomiting. *(From Apfel CC, Laara E, Koivuranta M, et al: A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers,* Anesthesiology *91:693-700, 1999.)*

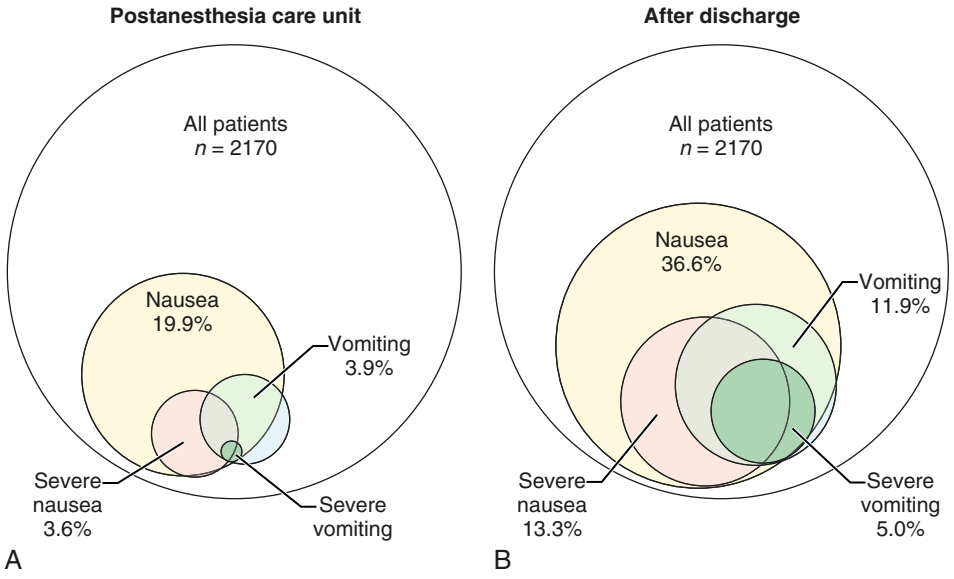
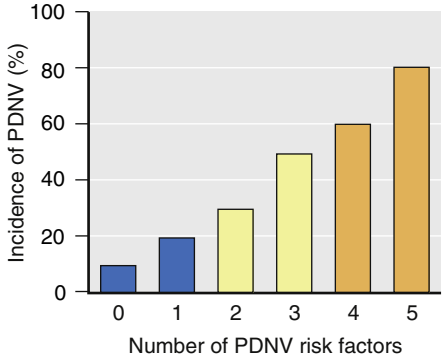


Figure 97-9. Incidence of postdischarge nausea and vomiting in the postanesthesia care unit (**A**) and after discharge (**B**) in a study of more than 2000 ambulatory patients in the United States. *(From Apfel CC, Philip BK, Cakmakkaya OS, et al: Who is at risk for postdischarge nausea and vomiting after ambulatory surgery?* Anesthesiology *117:475-486, 2012.)*



Risk factors	Points
Female gender	1
History of PONV	1
age <50 yr	1
Use of opioids in the PACU	1
Nausea in the PACU	1
Sum	**0…5**

Figure 97-10. Simplified risk score for postdischarge nausea and vomiting (PDNV). *PACU,* Postanesthesia care unit; *PONV,* postoperative nausea and vomiting. *(From Apfel CC, Philip BK, Cakmakkaya OS, et al: Who is at risk for postdischarge nausea and vomiting after ambulatory surgery?* Anesthesiology *117:475-486, 2012.)*

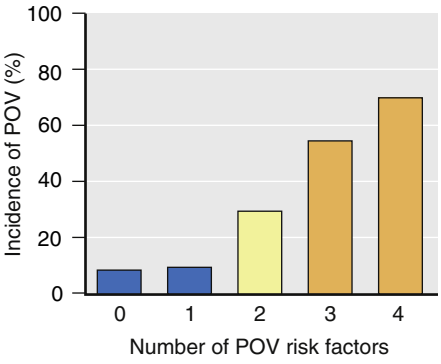
simplified risk score in children developed by Eberhart and colleagues that takes the following four variables into consideration: duration of the surgical procedure greater than or equal to 30 minutes, age older than or equal to 3 years, strabismus surgery, and a personal history of POV or PONV in immediate relatives (Fig. 97-11).[67] The presence of 0, 1, 2, 3, and 4 risk factors was associated with a POV incidence of 9%, 10%, 30%, 55%, and 70%, respectively (and an ROC-AUC of 0.72) (see also Chapter 93).[67]

PROPHYLACTIC ANTIEMETIC STRATEGIES

METHODOLOGIC BACKGROUND

Measurement of Nausea and Vomiting or Retching

Understanding the various definitions and methodologies used in publications is critical for interpretation of results. For instance, even though the incidences of nausea and



Risk factors	Points
Duration of surgery ≥30 min	1
Age ≥3 yr	1
Strabismus surgery	1
History of POV for patient, parent, or sibling	1
Sum	**0…4**

Figure 97-11. Simplified risk score for postoperative vomiting (POV) in children. *(From Eberhart LH, Geldner G, Kranke P, et al: The development and validation of a risk score to predict the probability of postoperative vomiting in pediatric patients,* Anesth Analg *99:1630-1637, 2004.)*

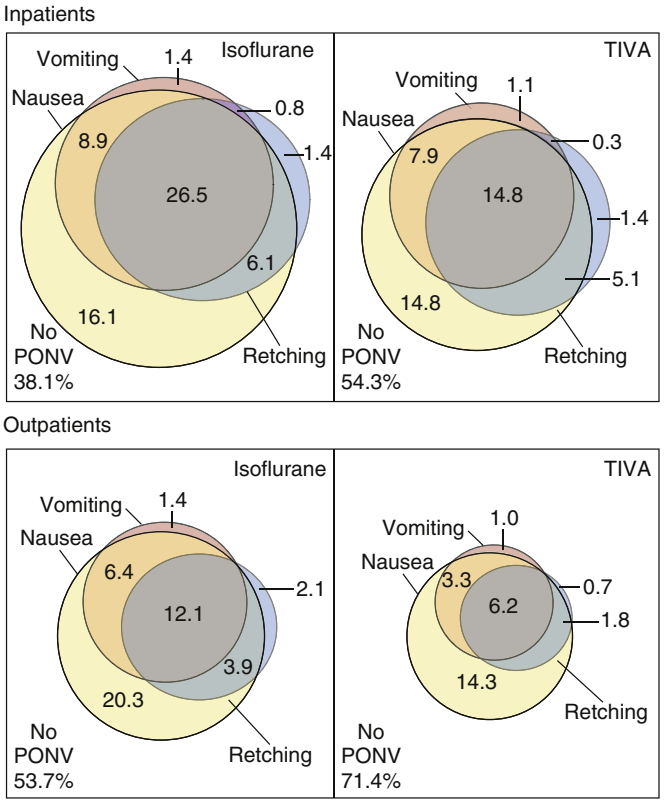


Figure 97-12. Venn diagrams for nausea, vomiting, and retching in patients after general inpatient or outpatient anesthesia with inhalational or propofol anesthesia. *PONV,* Postoperative nausea and vomiting; *TIVA,* total intravenous anesthesia. *(From Visser K, Hassink EA, Bonsel GJ, et al: Randomized controlled trial of total intravenous anesthesia with propofol versus inhalation anesthesia with isoflurane-nitrous oxide: postoperative nausea with vomiting and economic analysis,* Anesthesiology *95:616-626, 2001.)*

vomiting are correlated, they can occur independently and should therefore be assessed and reported separately, so that results can be compared across publications. This is true for both inhaled and intravenous anesthesia in both inpatient and outpatient procedures (Fig. 97-12)[7] Failure to realize this essential point has resulted in difficulties in assessing results for a significant portion of the available literature. Similar difficulties have arisen from the use of various scales that are generally inadequate to properly assess PONV. For example, assessing PONV on a four-point severity scale ranging from "*no symptoms, mild nausea, severe nausea or up to two vomits, or more than two vomits*" fails to reflect the underlying physiology and presentation of these symptoms and does not allow determination of the proportion of patients experiencing nausea, vomiting, or both.[105]

Nausea (from the Greek *nautia* meaning "seasickness") is often described as a "sensation of unease and discomfort in the stomach with an urge to vomit." Nausea may manifest at different intensities, may last a variable period of time, and may wax and wane (change in intensity over time). The intensity of these symptoms is assessed in three ways.

The most widely accepted measurement technique for intensity uses a visual analog scale (VAS). The VAS consists of a 10-cm horizontal line with the left end corresponding to *no nausea* and the right end corresponding to *worst imaginable nausea*. Patients are asked to choose a point on the line that represents the intensity of their current state. The VAS is considered the criterion standard because its reliability and sensitivity have been well established in pain studies.[106] Another common approach is the use of a written or verbal 11-point numeric rating scale (NRS), for which the patient is asked to rate the severity of his or her nausea between 0 and 10, with 0 corresponding to *no symptoms* and 10 corresponding to *worst possible symptoms*. The NRS approach has the advantage of ease of use and maintains a sensitivity similar to the VAS gold standard.[107] The easiest approach appears to be a categorical verbal rating scale (VRS), in which patients describe their symptoms as *none*, *mild*, *moderate,* or *severe*. Unfortunately, even though Boogaerts and colleagues demonstrated a good correlation between the VRS and VAS for nausea,[108] pain studies have found that the VRS is not as sensitive as the VAS.[107] All told, the NRS approach may provide the best balance between sensitivity and ease of use.

Usually, the intensity of nausea varies over time, so repeated measurements would be needed for an overall severity assessment. Thus, nausea assessment may not be accurate if the intervals between assessments are considerably longer than the duration of nausea episodes. As a rule of thumb, it may thus be advantageous to have patients estimate their *average* and/or *most severe* level of nausea, rather than limiting patients to rating the current nausea at the time of questioning. Therefore, assessments of nausea should be performed to cover a time *interval* rather than to assess a time *point*.

Vomiting, as a clinical symptom, is the forceful expulsion of gastric contents through the mouth or nose. *Retching* is similar to vomiting with the exception that no gastric content enters the pharynx (dry heaves). An *emetic*

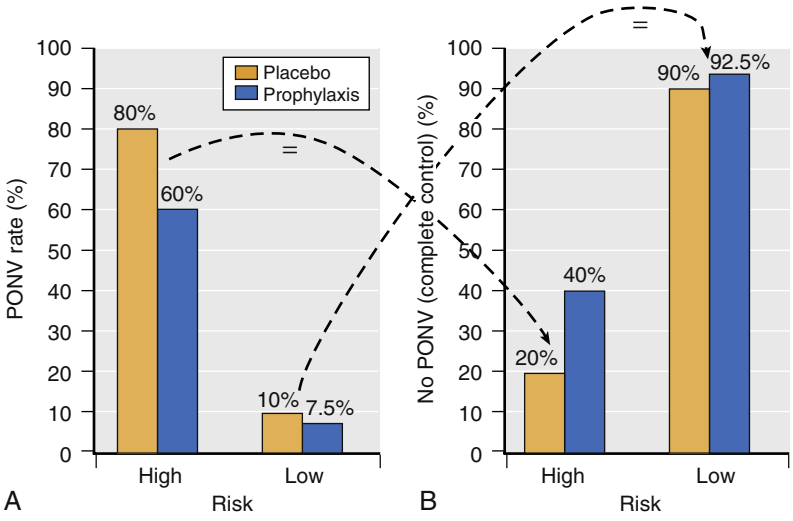


Figure 97-13. A and **B,** Relative risks (risk ratios) or relative risk ratios are independent of the patient's baseline risks. Both **A** and **B** represent the same data, yet efficacy of a drug can be judged only from the risk ratio of the events (e.g., postoperative nausea and vomiting [PONV]), not from the risk ratio of the absence of events (e.g., no PONV).

episode is often operationally defined as one or more instances of vomiting and/or retching separated by no more than 1 minute of respite. However, for the sake of simplicity and because vomiting is much more frequent than retching, many authors' reports of *vomiting* include both vomiting and retching. In such instances, use of the term *emetic episode* is preferable. The measurement of vomiting and emetic episodes is simpler than that of nausea because the former involves a distinctive and recognizable muscular reflex. Severity is therefore best evaluated by number of episodes, and recording the times of individual episodes allows secondary analysis with regard to the time course.

Because no universally accepted standard exists for measuring and reporting nausea and vomiting, publications should at the minimum report separate incidences for nausea and for vomiting, even if the primary outcome is a combined measure such as the incidence of PONV. Whenever possible, the frequency and success of rescue treatment should be reported as well, to allow comparison of treatment effects in subsequent meta-analyses.[105] In addition, patients may experience a benefit as mild (instead of severe) nausea, and this is not reflected by the crude incidence, a dichotomous outcome. This may also be a reason that a joint severity score that considers the severity of nausea and vomiting may be a valuable adjunct to report and analyze with more statistical power than the binary variables.

Measures of Efficacy and Effectiveness. From an epidemiologic perspective, *efficacy* refers to the impact of an intervention in a clinical trial, whereas *effectiveness* refers to the impact in real-world situations. For PONV trials, *efficacy* of a prophylactic strategy is probably best described by the relative risk (a synonym would be the risk ratio [RR is used for either term interchangeably]) or the odds ratio that measures the drug-specific antiemetic potential. In contrast, the *effectiveness* of a prophylactic intervention is probably best measured by the absolute risk difference (ARD; synonym: absolute risk reduction) or number-needed-to-treat (NNT) that describes the actual benefit of that intervention when given to patients of a population with a certain risk for PONV. To appreciate the meaning of the different measures of treatment effects described in the literature fully, it is essential to conceptualize the fundamental differences between measures of *efficacy* and *effectiveness* (i.e., RR and ARD). Understanding this difference is key when comparing efficacy among antiemetic trials and when determining the effectiveness of interventions in specific clinical situations.

Absolute Risk Difference and Number-Needed-to-Treat. When using binary outcomes such as the incidence of PONV, the clinical benefit or *effectiveness* of prophylactically administered antiemetics for an individual (or a population) with a particular underlying risk profile is best described by the ARD. For example, when a patient is at very high risk for PONV, say 80%, the use of an antiemetic such as ondansetron may reduce the risk to 60% (i.e., the ARD is 20%) (Fig. 97-13, A). Thus, ondansetron given to 100 individuals with a baseline risk of 80% will prevent PONV in 20% of cases, and therefore 1 of 5 such patients will benefit from the intervention. To put it another way, 5 high-risk patients would need to be treated prophylactically to prevent 1 of those 5 patients from experiencing PONV: the NNT is 5. Thus, the following formula applies:

$$NNT = 1/ARD$$

However, when ondansetron is given for prophylaxis to patients at low risk for PONV, say 10%, the risk will be reduced only to 7.5%; the ARD is only 2.5%, and the NNT is 40. Thus, ARD and NNT, both measures of *effectiveness,* are critically dependent on the patient's baseline risk. As a corollary, ARD or NNT determined in one study cannot be taken as a measure of *efficacy* for patients in a population with a different (higher or lower) baseline risk. This emphasizes the importance of an objective risk assessment to tailor the use of prophylactic antiemetic treatment to those patients who benefit most.

Relative Risk Reduction and Risk Ratio. The aforementioned examples have one characteristic in common. The use of ondansetron reduced the risk by approximately one fourth. Thus, in both examples the relative risk reduction (RRR) was 25%, and the risk ratio (RR) was 0.75.

$$RR = 1 - RRR$$

The finding that the RR is a relatively robust measure of efficacy for a wide range of baseline event rates has been described in other medical areas,[109] but it was first described in the field of PONV in the IMPACT (*I*nternational *M*ulticenter *P*rotocol to assess *A*ntiemetic *C*ombinations in a controlled Clinical *T*rial of factorial design) study.[74,110] In addition, this study demonstrated that the *efficacy* of each of the three antiemetics tested (ondansetron, dexamethasone, and droperidol) was independent of one another and by and large of other risk factors.[74] In other words, RR and RRR were reliable measures for the *efficacy* of prophylactic antiemetics and were independent of the patient's baseline risk.

As a consequence, the *effectiveness* in terms of an ARD of an antiemetic that can be expected in clinical practice can be estimated from the baseline risk multiplied by the RRR using the formula:

$$\text{ARD} = \text{Baseline risk} \bullet \text{RRR}$$

Alternatively, the remaining risk can be estimated using the formula:

$$\begin{aligned}\text{Remaining risk} &= \text{baseline risk} - \text{ARD}\\ &= \text{baseline risk} \bullet (1 - \text{RRR})\\ &= \text{baseline risk} \bullet \text{RR}\end{aligned}$$

Relative Benefit for Freedom From Symptoms. However, the RRR or RR is independent of the patient's baseline risk only when the outcome is "PONV" but not "no PONV." In the first example (i.e., in the high-risk group), the incidence of no PONV was 20% without prophylaxis and 40% with prophylaxis (Fig. 97-13, *B*). Therefore, twice as many patients were free of PONV; that is, the relative benefit (RB) for no PONV was 2. However, in the second example (i.e., in the low-risk group), the incidence of no PONV was 90% without prevention and 92.5% with prevention; that is, the RB for no PONV was only 1.03 (92.5/90), even though there was a 25% decrease in the incidence of PONV. This demonstrates that the RB for "no PONV" or "freedom from symptoms" is again highly dependent on the patient's baseline risk. Similarly, this applies to complete response (no vomiting and no rescue treatment) or complete control (no nausea, no vomiting, and no rescue treatment). Thus, a ratio cannot be taken as a measure for drug *efficacy* when the reported outcome is a measure of freedom from symptoms such as "no nausea," "no emesis," "complete response," or "complete control." For this reason, future publications should report vomiting or nausea rather than no vomiting or no nausea, and compound measures should report PONV or rescue treatment rather than complete response or complete control.

Generalizability of Study Results. As described earlier, the number of patients required to demonstrate the antiemetic efficacy of a drug in a clinical trial depends critically on the baseline risk (often described as the control event rate). A table for sample size estimations for PONV trials can be found in the article by Apfel and colleagues entitled "How to Study Postoperative Nausea and Vomiting."[105] Fewer patients need to be studied when the control event rate is high (i.e., when patients at high risk are selected). In addition, patients at high risk are much more likely to benefit from prevention given that their absolute risk difference will be larger. Therefore, most PONV trials specify certain types of surgical procedures that are assumed to be "high-risk procedures." However, as pointed out earlier, patients at risk are more reliably identified by using a simplified risk score.[38]

The other rationale for the selection of just one type of surgical procedure is to increase study strength by minimizing heterogeneity. Although this is a well-recognized approach for any continuous outcome, it does not apply to binary outcomes in which the confidence interval is solely a function of the number and proportion of patients.

The third reason that most studies are limited to a certain type of surgical procedure is the notion that the type of surgery may play a critical pathophysiologic role in PONV. If that were true, study results for one type of surgical procedure possibly would not be applicable to other surgical populations. Carlisle and Stevenson addressed this question in a subgroup analysis of their meta-analysis, but they could not find any evidence that the type of surgical procedure affects the efficacy of an antiemetic.[111] One theoretical limitation of their subanalysis is that it is based on interstudy comparisons. However, two sufficiently powered randomized controlled trials were also unable to identify any interaction between antiemetics and type of surgery (Fig. 97-14).[74,75]

In conclusion, currently published data suggest that the efficacy of an antiemetic is independent of the type of surgery. Therefore, the clinician may assume similar antiemetic *efficacy* for other types of surgical procedures or similar settings from those in the randomized trials. For the clinical researcher, it would be better to address more novel questions than to repeat PONV trials that have already been studied in other types of surgical procedures. As a corollary, it appears that separate meta-analyses of PONV for specific types of surgical procedures[112,113] are unlikely to advance our knowledge and understanding.

PERIOPERATIVE PAIN MANAGEMENT
(See also Chapter 98)

Local Anesthesia

Data from multivariable analyses suggest that the main cause of PONV is exposure to emetogenic triggers, namely inhaled anesthetics and opioids. If both these drug classes can be avoided, PONV incidence can be expected to be quite low. In fact, a 5-year review of 1264 cases using an opioid-free propofol/ketamine sedation technique for a wide range of ambulatory surgical procedure performed with local anesthesia reported only 7 patients (0.6%) with vomiting and 21 patients (2%) requiring postoperative antiemetics.[114] However, the lack of a control group in this study necessitates cautious interpretation. Nevertheless, this result is in accordance with small-scale, high-quality randomized controlled trials, such as the comparison of anesthetic techniques by Song and colleagues.[115] In that study, ilioinguinal-hypogastric nerve block, spinal anesthesia, and general anesthesia (with volatile anesthetics and opioids) were associated with PONV incidences of 7%, 12%, and 62%, respectively.

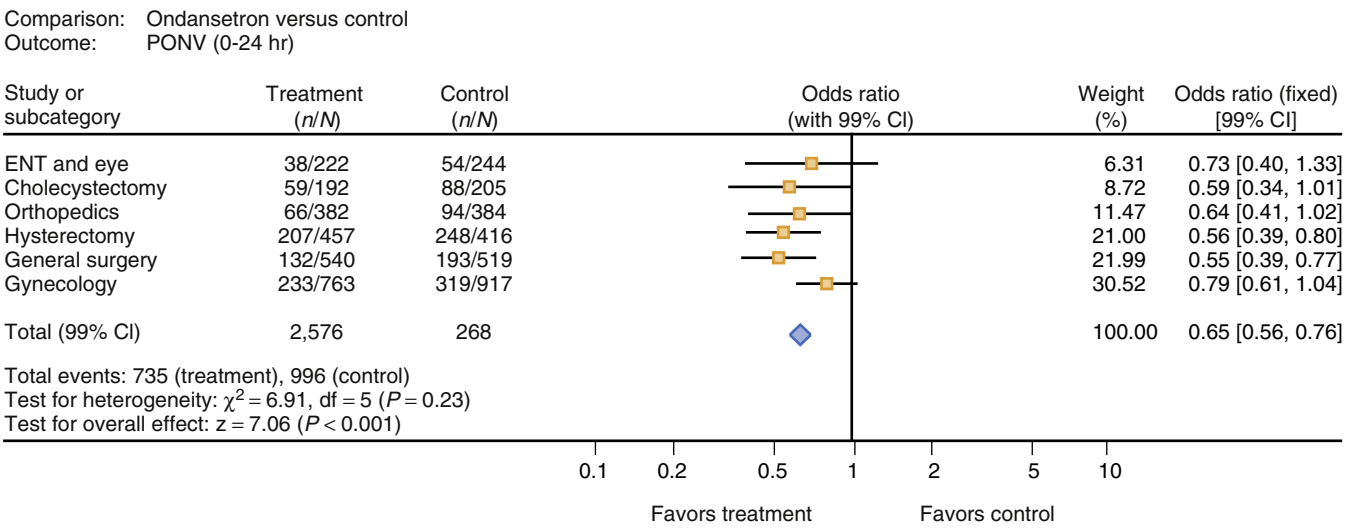


Figure 97-14. Efficacy of ondansetron is independent of the type of surgical procedure. *CI,* Confidence interval; ENT, ear, nose, and throat; *PONV,* postoperative nausea and vomiting. *(Data from Apfel CC, Korttila K, Abdalla M, et al: A factorial trial of six interventions for the prevention of postoperative nausea and vomiting,* N Engl J Med *350:2441-2451, 2004.)*

Regional Anesthesia

Consistent with the low incidence of PONV after primarily regional techniques with or without sedation (see also Chapters 56 and 57) are the results of a meta-analysis that compared single-shot regional anesthesia (peripheral nerve block or central neuraxial blockade) with general anesthesia as the primary anesthetic technique for ambulatory surgery.[116] Patients who were randomized to receive a peripheral nerve block had a more than fourfold lower incidence of nausea than those receiving a general anesthetic regimen (6.8% versus 30%). The RR was 0.23, which corresponds to an RRR of 77%, an antiemetic efficacy that can be achieved only by a quadruple antiemetic combination (see later).[74]

Similarly, central neuraxial blockade was also associated with a numerically lower incidence of nausea (5% versus 14.7%), an RR of 0.34, and an RRR of 66%. However, this incidence failed statistical significance, and further research is needed to confirm this finding ($P < .06$). Anesthetic solutions for epidural anesthesia often contain opioids to increase the density of the block, and this may be the reason that opioid-free paravertebral blocks are associated with a lower incidence of PONV compared with epidural anesthesia.[117]

In this respect, intraoperative nausea and vomiting after spinal anesthesia is different. Two large cohort studies of spinal anesthesia identified the following independent predictors of nausea and vomiting in the perioperative period: female gender, history of motion sickness, preoperative tachycardia, preoperative intravenous opioids, intrathecal procaine, use of phenylephrine or epinephrine, and hypotension or high intrathecal block (T4 or higher).[118,119]

Nonopioid Analgesics

Although individual studies have been able to demonstrate a reduction in pain and/or opioid consumption by NSAIDs (see also Chapter 30), most were unable to demonstrate benefits in their secondary outcomes, such as incidence of PONV. Marret and Bonnet and their colleagues conducted a quantitative systematic review of randomized controlled trials, and although evidence was insufficient to demonstrate a significant reduction of pruritus, urinary retention, or respiratory depression, these investigators were able to demonstrate an RR of 0.7 for PONV (i.e., an RRR of 30%).[78] Although the efficacy of NSAIDs is not as high as that of regional anesthetic techniques, NSAIDs are equal to antiemetics such as 4 mg of ondansetron.

Antiemetics

To date, more than 3000 articles on PONV have been published, with more than 300 articles added yearly. Most are reports of randomized controlled trials for the prevention of PONV, yet it is apparent that the elusive "holy grail" PONV prevention has yet to be found.

One reason could be that relatively little effort has been made to understand the causes of PONV. For example, few reviews acknowledge that the strongest known causes of PONV are inhalational anesthetics and opioids, and that an opioid-free regional anesthetic technique is probably the most effective way to prevent PONV. However, a particular patient may have medical and logistical reasons that a local or regional anesthetic technique would not be practical. Therefore, even though the efficacy of antiemetics is limited, and avoiding the causes for PONV appears to be more effective, antiemetics remain important tools for the prevention of PONV in many clinical situations.

META-ANALYSES

Given the abundance of published PONV studies, it is highly desirable to (1) identify all available evidence, (2) reconcile controversial results if possible, and (3) determine the treatment effect based on the best available evidence. This can be achieved through a systematic review such as a Cochrane review with a prespecified study

question, inclusion and exclusion criteria, and well-established search algorithms to ensure identification of all relevant articles. The term *systematic review* characterizes the scientific rigor to identify and consider all available evidence, whereas the term *meta-analysis* characterizes the statistical approach to synthesize the various study results to come up with the most accurate point estimate for the treatment effect. Thus, a systematic review that uses a meta-analysis to quantify the treatment effect is often described as a quantitative systematic review.

The first systematic review on PONV was by Tramer and associates on the effect of nitrous oxide.[94] Because systematic reviews tend to focus on a well-defined, specific question, dozens of other systematic reviews have been subsequently published, thus requiring reviews of systematic reviews.[120,121]

Fortunately, Carlisle and Stevenson created a comprehensive Cochrane review for all drugs that have been studied for the prevention of PONV.[111] The first edition encompasses 737 studies involving 103,237 patients. It is the largest PONV meta-analysis to date and clearly the most important for clinicians seeking a single reference for drugs that may prevent PONV. In addition, in contrast to many previous systematic reviews that focused on the NNT, which—as described earlier—is not a useful estimate to characterize the efficacy, the Cochrane review from Carlisle and Stevenson used the RR.

ANTIEMETICS

Table 97-2 gives an overview of antiemetic agents.

DOPAMINE ANTAGONISTS

Metoclopramide has been used for decades to prevent PONV. Its antiemetic properties are primarily mediated through its antidopaminergic action and its prokinetic properties.[122] In the past, use of large doses of metoclopramide (e.g., 200 mg every 6 hours) was a mainstay for prevention of chemotherapy-induced nausea and vomiting (CINV). These large doses likely have antiserotoninergic properties.[123] Unfortunately, these large doses cause extrapyramidal side effects in more than 10% of patients; these side effects can be treated with antihistamines and benzodiazepines.[124]

As a result, small doses of metoclopramide (10 mg) became widely used in clinical practice. However, this amount has been proven not to be clinically effective.[125] Consequently, Wallenborn and associates conducted a large randomized placebo-controlled trial comparing 8 mg dexamethasone alone or combined with either 10, 25, or 50 mg metoclopramide.[126] The RRs for the prevention of PONV for these three combinations compared with dexamethasone alone were 0.89, 0.74, and 0.63, respectively. Thus, the efficacy of 25- or 50-mg doses seems to be comparable to that of other well-established antiemetics. Efficacy must be balanced against the potential side effects (the most frequent were treatable hypotension and tachycardia) and the incidence of dyskinetic and/or extrapyramidal symptoms, which were 0.1%, 0.4%, 0.8%, and 0.8%, respectively, in those four groups. In children undergoing tonsillectomies, a moderate dose of 0.5 mg/kg of metoclopramide was not equivalent to 0.1 mg/kg of ondansetron.[127]

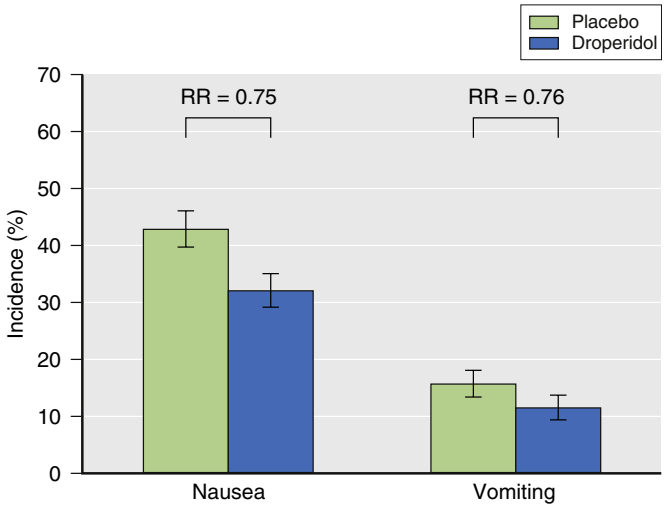


Figure 97-15. Risk ratios (RR) of nausea and vomiting for droperidol versus placebo for 0 to 24 hours. *(Data from IMPACT; figure from Apfel CC, Cakmakkaya OS, Frings G: Droperidol has comparable clinical efficacy against both nausea and vomiting,* Br J Anaesth *103:359-363, 2009.)*

Droperidol is a highly potent D_2-antagonist with well-proven antiemetic properties at intravenous doses as small as 0.625 to 1.25 mg[111,128,129] and an overall RR of 0.75 and 0.76, for nausea and vomiting, respectively.[130] Although droperidol was previously believed to be more effective against nausea than vomiting,[128] IMPACT demonstrated that droperidol has similar efficacy against both outcomes (Fig. 97-15).[130] Furthermore, it is similarly effective compared with ondansetron,[74,131] with an RR for PONV of 0.62.[111] Compared with placebo, droperidol is associated with increased sedation (RR, 1.32) but a decreased incidence of headache (RR, 0.79).[111] Although droperidol has been investigated in more than 400 articles, its minimal effective dose and optimal time of administration have not yet been established. Because of its relatively short plasma half-life of approximately 3 hours, droperidol should be given at the end of the surgical procedure and at the lowest effective dose of 0.625 mg to minimize potential sedative side effects.

For the same pharmacokinetic reason, the supplementation of a morphine-loaded PCA pump with droperidol appears to be a highly effective approach to reduce opioid-induced nausea and vomiting. In a dose-response study, adding 5, 15, or 50 μg to 1 mg of morphine led to an RR of 0.88, 0.63, and 0.44, respectively.[132] Although 50 μg of droperidol per milligram of morphine appears to be the most effective dose, it was associated with sedative side effects, so the authors concluded that a dose of 25 μg droperidol per milligram of morphine was optimal.

Low-dose droperidol has also been reported to lead to anxiety and restlessness,[133] akathisia,[134] and dystonia.[135] However, data are conflicting.[136] In addition, the U.S. Food and Drug Administration (FDA) has received reports of severe arrhythmias (torsades de pointes) and deaths in association with the use of low-dose droperidol, thus leading to the following black box warning:

Droperidol is contraindicated in patients with known or suspected QT prolongation, including patients with congenital long QT syndrome. In patients who fail to show an acceptable response to other adequate treatment, a 12-lead ECG must confirm the absence of QT prolongation (440 msec for males, 450 msec for females) prior to administration of droperidol, and ECG monitoring should be continued for 2 to 3 hours after drug administration. Also, it should be administered with extreme caution to patients who may be at risk for the development of a prolonged QT syndrome, such as in patients with electrolyte disturbances or those receiving volatile anesthetics and intravenous opioids.

The FDA black box warning for droperidol has created controversy among physicians who continue to see a value in its low-dose use for PONV prevention. According to a study by White and associates, general anesthesia itself leads to QT prolongation from approximately 400 to 430 msec, and the mean maximal QT prolongations when placebo, 0.625 mg, or 1.25 mg droperidol was administered during anesthesia were 12, 15, and 22 msec, respectively.[137] The anesthetic had a much stronger overall effect on the average QTc interval compared with droperidol, and it was associated with considerably more interindividual variability. Conversely, one instance of QT prolongation of 133 msec was observed in a single patient who received 1.25 mg of droperidol. Charbit and colleagues investigated the effect of 0.75 mg of droperidol or 4 mg of ondansetron on the QTc interval when these drugs were given as rescue treatment in the PACU.[138] More than 40% of patients had a prolonged QTc interval after anesthesia, and the mean maximal additional QTc prolongation was 17 msec after droperidol and 20 msec after ondansetron (Fig. 97-16). This finding raises a question about the clinical relevance of QT prolongation. In general, the Committee for Proprietary Medicinal Products in the United Kingdom considers QT prolongation of less than 30 msec unlikely to be clinically relevant. Furthermore, based on data from patients with congenital prolonged QT syndrome, a prolongation of 10 msec corresponds to a hazard ratio of 1.056, which translates to an 18% increased risk (RR, 1.18) at 30 msec but double the risk (RR, 2.06) at 133 msec.[139] Based on these data, the risk of droperidol for healthy patients with a normal electrocardiogram appears to be negligible. It is, however, difficult to exclude the possibility that the addition of droperidol in a clinical context of an unrecognized conduction abnormality alongside other QTc-prolonging drugs may trigger a clinically relevant QT prolongation leading to torsades de pointes.[140]

Because of the droperidol black box warning, haloperidol has garnered more interest, and more recent studies have shown an efficacy similar to that of ondansetron.[141,142] However, cardiac arrhythmias and death associated with haloperidol have also been reported to health agencies, so the FDA has issued an alert that haloperidol is approved only for intramuscular administration and that intravenous injection is off-label use.

Alizapride and the highly potent neuroleptics perphenazine (Decentan, Trilafon) and prochlorperazine (Compazine) are less frequently used dopamine antagonists that have additional mechanism of actions. Although their efficacy appears comparable to that of other antiemetics, these drugs have not been studied extensively, such that the limited number of patients provides insufficient power to detect all treatment effects.[111] A main reason for the rather infrequent use of these drugs may be sedative side effects that can delay recovery.

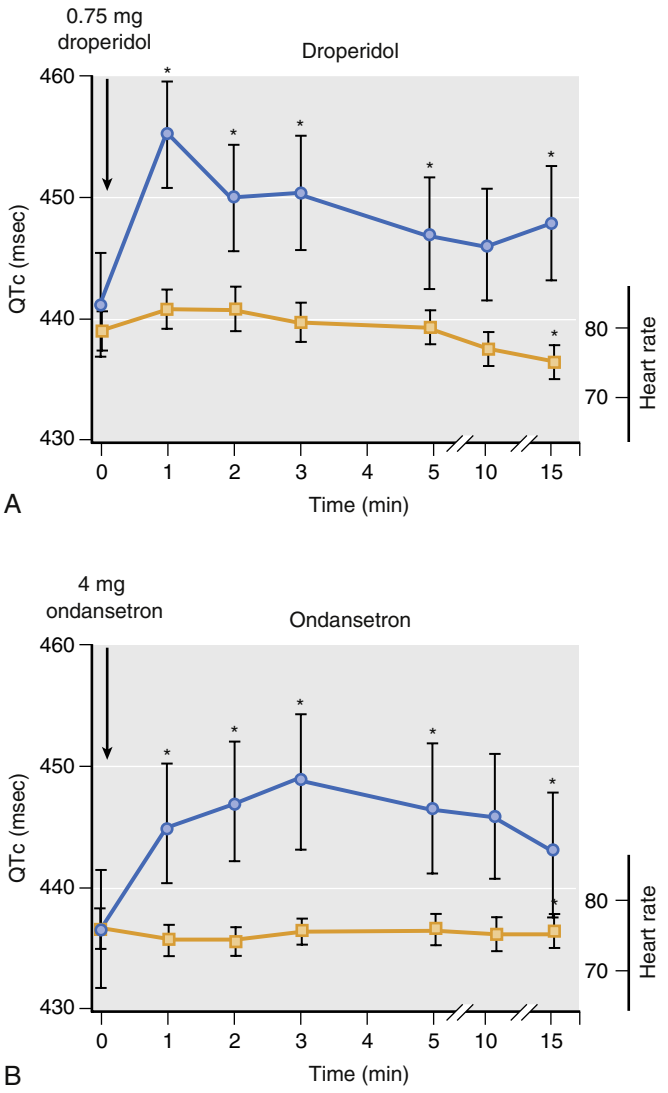


Figure 97-16. Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol (**A**) or ondansetron (**B**). *(From Charbit B, Albaladejo P, Funck-Brentano C, et al: Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron,* Anesthesiology *102:1094-1100, 2005.)*

HISTAMINE ANTAGONISTS

Diphenhydramine (Benadryl) and dimenhydrinate (an aminophylline salt of diphenhydramine) are histamine (H_1)-receptor antagonists known for their effectiveness against motion sickness and relatively weak anticholinergic (antimuscarinic) activities (see Table 97-2).[111,143] Cyclizine (Marezine) and promethazine (Atosil, Phenergan) seem to have equal antihistaminic and anticholinergic properties, this feature poses a contraindication

TABLE 97-2 **MECHANISMS, DOSES, AND MEASURES OF EFFICACY OF ALL INVESTIGATED ANTIEMETICS WITH STATISTICALLY SIGNIFICANT OUTCOME**

Antiemetic (U.S. Trade Names)	Primary (Other) Mechanisms	Frequently Studied Adult Doses, Given Intravenously Unless Noted Otherwise	Risk Ratio Compared With Placebo That Met Statistical Significance			Comments
			Nausea	Vomiting	PONV	
Metoclopramide (Reglan)	D_2, prokinetic, (5-HT_3)	10 or 20 mg 10 mg 25 mg 50 mg	0.82 0.75 0.57	0.76 0.80 0.71 0.60	0.76 0.78 0.74 0.63	
Droperidol (Inapsine)	D_2, (α_1)	0.625-1.25 mg	0.65	0.65	0.62	Sedation RR = 1.32, decreased headache RR = 0.79, FDA black box warning
Haloperidol (Haldol)	$D_{2,3,4}$, (D_1), 5-HT_2	1 mg IV or 0.5 mg IM	0.48	0.38 0.23		FDA safety alert
Alizapride (Vergentan)	D_2, prokinetic	50-200 mg	0.65	0.49		No evidence for dose response
Perphenazine (Trilafon)	D_2, (D_1), H_1, 5-HT_2	2.5-5 mg IV or IM		0.70		
Prochlorperazine (Compazine)	D_2, (M, α_1, H_1)	6.25-12.5 mg IV or IM, 3-6 mg buccal	0.73	0.68	0.68	
Dimenhydrinate (Dramamine) or diphenhydramine (Benadryl)	H_1, (M)	31.25-62.5 mg IV, 50 mg suppository		0.61	0.71	Drowsiness RR = 9.0
Cyclizine (Marezine)	H_1, (M)	50 mg IV or IM	0.67	0.55	0.67	
Promethazine (Phenergan)	H_1, (M)	12.5-25 mg or 12.5-50 mg IM			0.46	
Hyoscine (Scopoderm)	M	1.5 mg (3 times/day)	0.63 0.49 0.71	0.65 0.43 0.68	0.71 0.46 0.78	Dry mouth RR = 1.25
Ondansetron (Zofran)	5-HT_3	4 mg	0.68	0.54	0.56	Headache RR = 1.16, administer at end of surgery
Dolasetron (Anzemet)	5-HT_3	12.5-50 mg	0.82	0.62	0.72	Arrhythmia warning (Canada)
Granisetron (Kytril)	5-HT_3	1 mg	0.67	0.42	0.56	
Tropisetron (Navoban)	5-HT_3	All doses 2 mg 5 mg	0.77 0.75 0.69	0.60 0.67 0.56	0.72 0.71 0.69	Decreased dizziness RR = 0.37
Palonosetron (Aloxi)	5-HT_3	0.075 mg	0.69	0.66		
Diazepam, Lorazepam (Ativan)	$GABA_A$ modulation	10 mg PO, 2-2.5 mg PO	0.50, 0.55			
Midazolam (Versed)	$GABA_A$ modulation	2-5 mg IV, 7.5-15 mg PO		0.73		
Alvimopan (Entereg)	μ-Opioid receptors					
Dexamethasone (Decadron)	Unknown	4-8 mg	0.58	0.51	0.48	Slow onset, administer after induction
Aprepitant (Emend)	NK1	40 mg PO				Active control with ondansetron: similarly effective against nausea but significantly more effective against vomiting: RR = 0.38 and 0.55, respectively

D, Dopamine; *FDA,* U.S. Food and Drug Administration; *GABA,* γ-aminobutyric acid; *H,* histamine; *5-HT_3,* 5-hydroxytryptamine 3 (serotonin); *IM,* intramuscularly; *IV,* intravenously; *M,* muscarinic; *NK1,* neurokinin-1; *PO,* orally; *PONV,* postoperative nausea and vomiting; *RR,* risk ratio.

for patients with glaucoma and prostate hypertrophy. All relatively nonspecific histamine receptor antagonists have sedative side effects that may delay recovery when these drugs are given immediately before the end of anesthesia. Diphenhydramine, cyclizine, and promethazine are effective for the prevention of PONV, with RRs of 0.71, 0.67, and 0.46, respectively.[111] Side effects include drowsiness (RR, 9.0),[111] as well as urinary retention, dry mouth, blurred vision, and extrapyramidal symptoms reported too infrequently to draw conclusions.[111,143] Promethazine has also been reported to cause vascular necrosis requiring plastic surgery of skin lesions and/or limb amputations that led to an FDA safety alert in 2006.

ANTICHOLINERGICS

Data on the potential antiemetic properties of atropine are conflicting. For example, when coadministered with neostigmine to reverse neuromuscular blockade, atropine was associated with less postoperative vomiting compared with glycopyrrolate.[48,111] One plausible explanation is that atropine, unlike glycopyrrolate, crosses the blood-brain barrier. However, comparisons of atropine versus placebo have been negative,[111] perhaps because of the drug's short half-life. Scopolamine is another centrally acting anticholinergic (antimuscarinergic) agent that, like atropine, has a relatively short half-life. This limitation is overcome by a transdermal formulation that allows a more favorable pharmacokinetic profile to cover up to 72 hours. The membrane layer of the transdermal patch is required for the slow, sustained release of scopolamine and therefore should not be cut to limit the dose administered. Instead, patients can remove the patch once symptoms have cleared or the highest-risk period (i.e., the first 4 to 6 postoperative hours) has passed. The antiemetic properties of scopolamine are well established for the prevention of motion-induced nausea and vomiting,[144] and the scopolamine patch has also been shown effective for the prevention of PONV in the first 24 postoperative hours, with RRs of 0.59 and 0.68, respectively.[145] Transdermal scopolamine appears to be similarly effective when applied the night before the surgical procedure or the morning of the surgical procedure (RRs = 0.56 and 0.61, respectively).[145] Its long duration of action may be especially useful for the prevention of PDNV in ambulatory patients; data, however, are limited. An increased incidence of visual disturbances at 24 to 48 hours postoperatively appears to be the only side effect associated with its use; an apparent dose-response relationship exists because visual disturbances increase threefold on postoperative day 2 (i.e., after 2 days of exposure to the drug).[145] Although no association with confusion was found in a meta-analysis of more than 3000 patients, further study is needed to determine whether older patients are more susceptible to this adverse event with administration of anticholinergics such as scopolamine.[146] In addition, because transdermal scopolamine can also cause temporary pupil dilation,[146] this drug should be used with caution in the context of neurosurgical procedures for which pupil dilation can be an important indicator of serious complications.

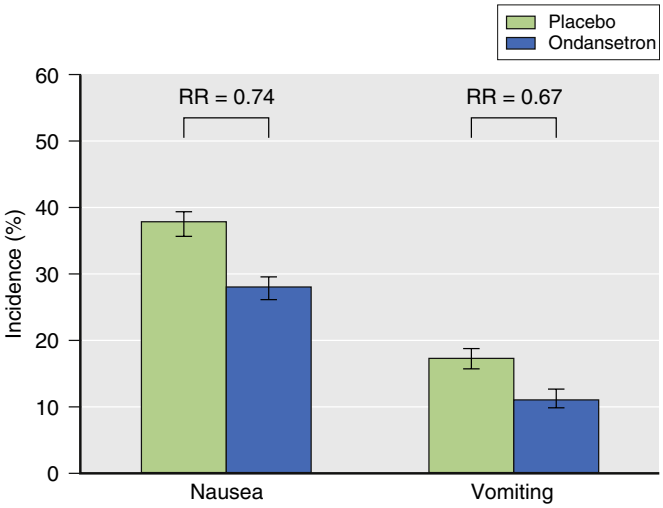


Figure 97-17. Relative risks (RR) of nausea and vomiting for ondansetron versus placebo. The difference of 0.07 in relative risks for the two outcomes is unlikely to be clinically relevant. *(From Jokela RM, Cakmakkaya OS, Danzeisen O: Ondansetron has similar clinical efficacy against both nausea and vomiting,* Anaesthesia *64:147-151, 2009.)*

SEROTONIN ANTAGONISTS

Ondansetron was the first serotonin antagonist, and its introduction was a milestone in the prevention of early CINV. It was considerably more effective and had fewer side effects (no extrapyramidal symptoms or sedation) compared with all previous antiemetics. Given the superior efficacy of ondansetron for CINV, it is not surprising that the drug quickly established a reputation as the most effective antiemetic for prevention of PONV. This perception was further nurtured by duplicate publication of positive studies that, according to analyses by Tramer and co-workers, would lead to a 23% overestimation of ondansetron's effectiveness if included in a meta-analysis.[147] In fact, in the IMPACT trial of more than 5000 patients, the risk reductions for nausea and vomiting were 0.74 and 0.67, respectively.[148] Like droperidol, ondansetron was previously believed to be more effective for one outcome (vomiting) than the other,[149] but IMPACT demonstrated that ondansetron has similar efficacy against both nausea and vomiting (Fig. 97-17).[148] In addition, the same trial showed that the efficacy of ondansetron against PONV is similar to that of other antiemetics.[74] Specifically, 4 mg of ondansetron, 4 mg of dexamethasone, and 1.25 mg of droperidol had RRs of 0.76, 0.76, and 0.74, respectively (i.e., each drug led to an RRR of approximately 25%.)[74] Ondansetron has a plasma half-life of 4 hours and is therefore more effective when it is given at the end of a surgical procedure instead of immediately after induction of anesthesia.[150,151]

Dolasetron mesylate, and its liver-converted active metabolite hydrodolasetron, are highly specific 5-HT_3 antagonists with plasma half-lives roughly twice as long as that of ondansetron. In general, all first-generation serotonin antagonists are considered to be equally effective when given at equipotent doses. For ondansetron, 4 mg is well documented to be the minimal effective dose (the minimal dose at which any further increase fails to

produce additional clinically relevant benefit). For dolasetron, the data from Korttila and associates suggest that 50 mg is superior to 25 mg and equivalent to 4 mg of ondansetron.[152] However, this finding contrasts with a pooled analysis of three trials that suggests that 12.5 mg is the minimum effective dose, which is the dose approved by the FDA for the prevention of PONV.[153]

Granisetron is another highly specific 5-HT_3 antagonist, with a half-life that is approximately twice as long as that of ondansetron. The FDA-approved dose for the prevention of PONV is 1 mg. This is based on a dose range study from Wilson and associates in which 0.1, 1.0, and 3.0 mg were associated with RRs for postoperative vomiting of 0.94 (not significant), 0.56, and 0.66, respectively.[154] A second dose-response study investigated the efficacy of 2, 5, 10, and 20 μg/kg and found that 5 μg/kg appears to be the minimal effective dose, which corresponds to roughly 0.35 mg for a 70-kg adult patient.[155] Despite results from these relatively large randomized controlled trials, some more recent studies re-explored the possibility that doses as low as 0.1 mg are effective for the prevention of PONV. One study compared 0.1, 0.2, and 0.3 mg with placebo in patients undergoing abdominal hysterectomies.[156] Although all three doses were associated with less vomiting within the first 6 hours, no significant difference could be demonstrated over 24 hours. Another study compared the combination of 8 mg of dexamethasone plus either 0.1 mg of granisetron or 4 mg of ondansetron in patients undergoing laparoscopy.[157] However, that study was not sufficiently powered to demonstrate a statistically significant difference for the main outcome of vomiting in the first 2 postoperative hours, which was 6% in the granisetron-treated group and 3% in the ondansetron-treated group. The studies on granisetron that suggested that 3 mg is superior to 1 mg for preventing PONV have been discredited. The current evidence suggests that the FDA approved dose of 1 mg—but not 0.1 mg—is an effective dose for the prevention of PONV.

Whereas all serotonin antagonists are considered to be similarly effective, the second-generation palonosetron may be an exception. Not only does palonosetron have a long half-life of approximately 40 hours, but it also exhibits allosteric binding to 5-HT_3 receptors with subsequent receptor internalization, as well as negative cooperativity with neurokinin-1 (NK1) receptors.[158,159] Perhaps because of these unique properties, palonosetron is the most effective 5-HT_3 receptor antagonist for the prevention of CINV, especially delayed CINV, for which the previous serotonin antagonists are usually ineffective. Whether this will translate into higher efficacy for the prevention of PONV, and perhaps PDNV, is unclear. Like other 5-HT_3 receptor antagonists, palonosetron, at 0.075 mg. has been associated with a RRR of approximately 30% for PONV.[160,161] However, a more recent study in which palonosetron and ondansetron were administered at equipotent doses in conjunction with a fentanyl PCA pump did show superior efficacy against PONV with palonosetron.[162] Beyond the extended half-life and superior efficacy of the drug, palonosetron also does not appear to affect the QT interval and therefore may be safer for patients at risk of cardiac arrhythmias.

DEXAMETHASONE

Dexamethasone is well documented as an effective antiemetic,[74,111] and animal experiments suggest that it exerts its antiemetic effects through central inhibition of the nucleus tractus solitarii but not the area postrema.[163] Most early studies were conducted with 8 to 10 mg of dexamethasone,[129,164] but convincing evidence from several smaller dose-response trials indicates that 2.5 to 5 mg can be considered the minimum effective dose.[165-167] Dexamethasone has a slow onset of action, which may be the reason that its application at the beginning of a case appears to be superior to later use.[168] According to Carlisle and Stevenson, the RR of dexamethasone is 0.57 for nausea and 0.51 for vomiting,[111] and direct head-to-head comparisons suggest that its efficacy is similar to that of ondansetron and droperidol.[74,111]

NEUROKININ ANTAGONISTS

Substance P is a regulatory peptide that binds to NK1 receptors found in vagal afferents in the gastrointestinal tract. More importantly, in the 1950s it was shown to reside in areas of the central nervous system that are thought to be involved in the vomiting reflex.[169] Nevertheless, it took more than 40 years before it became apparent that NK1 antagonists could be highly effective against a wide range of emetic stimuli in animal studies.[170] A few years later, Diemunsch and colleagues showed the clinical feasibility for control of established PONV after major gynecologic surgery in a pilot study with the NK1 antagonist GR205171.[171] This work was followed by a multicenter study with CP-122,721[172] in which 200 mg reduced the incidence of postoperative emesis from 50% to 10%, which corresponds to an RR of 0.2 and an RRR of 80%—significantly more effective against vomiting than all other previous antiemetics.

The strong antiemetic property of NK1 receptor antagonists was confirmed by studies of aprepitant, the first drug in its class approved for clinical use by the FDA. In a three-arm multicenter study, 4 mg of ondansetron, given intravenously, was compared with 40 mg and 125 mg of orally administered aprepitant.[173] Although the incidence of nausea was similar between the groups, the incidences for vomiting were 26%, 10%, and 5%, respectively. Considering that ondansetron reduces the risk of vomiting by approximately 26%,[74] if a placebo group had been included in this study, the incidence in the placebo group would likely have been in the 35% range. In that case, the RRs for 40 and 125 mg of aprepitant would have been in the range of 0.3 and 0.15 compared with placebo, that is, an RRR in the range of 70% or 85%, again clearly more effective than other antiemetics. A similar international trial (again without a placebo control group) yielded similar (though less striking) results for aprepitant.[174] In that study, the incidences of vomiting for 4 mg of ondansetron given intravenously, 40 mg of aprepitant, and 125 mg of aprepitant orally were 29%, 16%, and 14%, respectively. For the prevention of PONV, 40 mg of aprepitant is the dose approved by the FDA.

In the future, it is likely that other NK1 receptor antagonists will appear on the market, such as casopitant[175] and

rolapitant.[176] However, although NK1 receptor antagonists appear to be superior for preventing vomiting, they may not be superior for preventing nausea. Furthermore, aprepitant is rarely used for PONV because of its relatively high cost. Nevertheless, their excellent antiemetic profiles make NK1 antagonists ideal drugs to reduce the medical risk that may be associated with vomiting after certain procedures (e.g., wired jaw, neurosurgical procedures, and upper gastrointestinal surgery).

COMBINATIONS AND MULTIMODAL THERAPY

None of the currently available antiemetics is capable of completely eliminating the incidence of PONV. In fact, according to the meta-analysis from Carlisle and Stevenson, the overall RR for FDA-approved "effective" antiemetics is 0.65, that is, the RRR is 35%.[111] Considering that smaller studies tend to be published more often if the results are positive (publication bias), the "true" RRR is likely to be smaller than 35%. In fact, in a large multicenter trial, the RRs for ondansetron, dexamethasone, and droperidol were in the range of 0.75; that is, the RRR was 25% rather than 35%.[74]

Given the limited antiemetic efficacy of prophylactic antiemetics, Scuderi and co-workers were the first to investigate a multimodal approach.[177] In patients undergoing outpatient laparoscopy, these investigators studied a combination antiemetic regimen (group I, $n = 60$) that consisted of both preoperative interventions (10 to 30 μg/kg midazolam for anxiolysis, 10 mL/kg crystalloid fluid administration) and intraoperative interventions (0.625 mg of droperidol, 10 mg of dexamethasone, induction and maintenance with remifentanil/propofol, gastric decompression, 30 mg of ketorolac, 1 mg of ondansetron at the end of the surgical procedure, and 25 μg of fentanyl 10 minutes before end of the surgical procedure). Patients in groups II and III received balanced anesthesia with sevoflurane/nitrous oxide/fentanyl with ($n = 42$) or without ($n = 37$) 4 mg of ondansetron. With the multimodal group I regimen, no patients vomited, and only 1 of 60 patients (1.7%) experienced nausea before discharge from the hospital. In contrast, 10 patients in group II (24%), and 15 in group III (42%) experienced nausea. Although this study demonstrated an impressive reduction in PONV, the study design could not identify to what extent each individual intervention contributed to the reduction in PONV. Furthermore, it was unclear what interactions may exist among the various antiemetic interventions (e.g., whether a certain synergistic combination contributes the most to these positive results).

This work led to the development of IMPACT.[74,110] In this trial, 4123 patients were randomly assigned to 1 of 64 possible combinations of 6 prophylactic interventions: 4 mg of ondansetron or no ondansetron; 4 mg of dexamethasone or no dexamethasone; 1.25 mg of droperidol or no droperidol; propofol or a volatile anesthetic; nitrogen or nitrous oxide; and remifentanil or fentanyl. Ondansetron, dexamethasone, and droperidol each reduced the risk of PONV by approximately 26% (RR, 0.74).[74] Propofol reduced the risk by 19%, and nitrogen

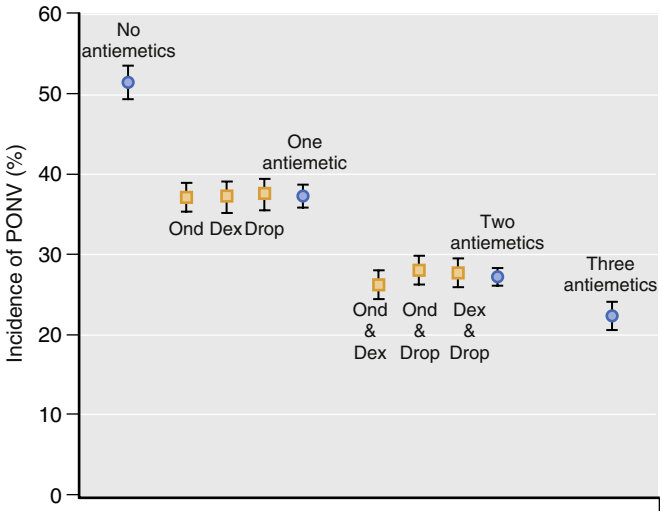


Figure 97-18. Reduction of postoperative nausea and vomiting (PONV) with ondansetron (Ond), dexamethasone (Dex), and droperidol (Drop) when given alone or in combination. *(From Apfel CC, Korttila K, Abdalla M, et al: A factorial trial of six interventions for the prevention of postoperative nausea and vomiting,* N Engl J Med *350:2441-2451, 2004.)*

by 12%; the combined RRR of propofol with no nitrous oxide (i.e., total intravenous anesthesia [TIVA]) was thus similar to that observed with each individual antiemetic. This study provided two major insights. First, it demonstrated that all interventions acted independently of each other; therefore, the RRs associated with combined antiemetic interventions can be estimated by multiplying the RRs associated with each intervention. For example, the RR for a triple combination of ondansetron plus dexamethasone plus droperidol is $0.74 \times 0.74 \times 0.74 = 0.41$; that is, the application of three antiemetics that each reduces the risk by approximately one fourth results in an RRR of $1 - 0.41 = 59\%$. Figure 97-18 demonstrates that all three antiemetics are similarly effective, and all three double combinations are similarly effective because no interactions occur. Second, it was demonstrated that the efficacy of the drugs as measured by the odds ratio or RR is independent of the patient's risk. Therefore, the effectiveness (in terms of absolute risk difference or NNT) primarily depends on the patient's baseline risk rather than on the choice of antiemetic, and each additional antiemetic in a combination regimen adds less and less additional benefit as the patient's risk decreases.

As an example, a female nonsmoker without a history of PONV or motion sickness who is expected to require postoperative opioids has a PONV risk of approximately 60%.[5] If she receives an antiemetic (e.g., 4 mg of dexamethasone), her risk will decrease to 44% (Table 97-3; $0.6 \times 0.74 = 0.44$), which means that the absolute risk difference will be 16%. If she receives a triple antiemetic therapy, her risk will decrease to approximately 24%, and a fourth antiemetic would reduce the risk to 18% (see Table 97-3). Adding a fourth antiemetic would thus result in an absolute risk difference of only 6% (i.e., less than half as much reduction as for the first antiemetic). Apparently, the first antiemetic has the greatest effectiveness, and additional prophylactic antiemetics are

TABLE 97-3 ESTIMATED POSTOPERATIVE NAUSEA AND VOMITING INCIDENCE AS A FUNCTION OF BASELINE RISK, ASSUMING EACH INTERVENTION REDUCES RELATIVE RISK BY 26%

Number of Interventions				
None* (%)	One (%)	Two (%)	Three (%)	Four (%)
10	7	5	4	3
20	15	11	8	6
40	29	22	16	12
60	44	33	24	18
80	59	44	32	24

From Apfel CC, Korttila K, Abdalla M, et al: A factorial trial of six interventions for the prevention of postoperative nausea and vomiting, N Engl J Med *350:2441-2451, 2004.*

*The exemplified baseline risk levels of 10%, 20%, 40%, 60%, and 80% reflect 0, 1, 2,3, and 4 risk factors considered in a simplified risk score, respectively.

associated with decreased effectiveness because of the already decreased baseline risk. Another example would be a male smoker who is undergoing a short procedure that will not require postoperative opioids and who will start off with a risk of approximately 10%.[5] Even the first antiemetic will at best reduce the risk by no more than 3% (see Table 97-3). The key message here is that the patient's baseline risk is the main determinant of the effectiveness of antiemetic interventions. Therefore, prophylaxis is rarely justified in patients at low risk, a single antiemetic is likely to be reasonable for patients with a moderate risk, and patients at high risk are likely to benefit from combination treatment.[74]

ALTERNATIVE OR ADJUVANT APPROACHES

Ginger is frequently assumed to have antiemetic properties, even though few studies were conducted, most of which had negative results, and meta-analyses came to conflicting conclusions.[178-180] According to the comprehensive review by Carlisle and Stevenson, evidence that ginger is an effective intervention for the prevention of PONV appears to be lacking.[111]

A meta-analysis of studies on liberal crystalloid fluid supplementation demonstrated that this intervention can be as effective as an antiemetic to reduce PONV outcomes and that its effect on PONV is stronger in the late postoperative period.[181] Supplemental crystalloids were previously believed to reduce PONV by alleviating dehydration and subsequent organ hypoperfusion after overnight fasting; however, surgical patients have been shown to remain normovolemic even after 10 hours of fasting. Therefore, one may speculate that additional fluids may instead alleviate the relative hypovolemia induced by volatile anesthetics, which can trigger the release of emetogenic arginine vasopressin[182-184] from the posterior pituitary. Although crystalloid fluids may be a relatively inexpensive intervention with a safe side effect profile, liberal fluid administration may be detrimental for wound healing and for recovery from larger procedures such as major intraabdominal operations, in which fluid accumulation is more likely.[185-187] In addition, a large, well-designed trial is still needed to confirm the results of this meta-analysis.

Various reports have investigated stimulation of the classic acupuncture P6 point (the sixth point on the pericardial meridian at the volar side of the wrist) for the prevention of PONV.[188-192] A Cochrane review by Lee and associates in 2004 identified 26 trials and found RRs of 0.72 for nausea and 0.71 for vomiting compared with sham.[193] This effect is comparable to that of conventional antiemetics.[194] These positive results bring up the question why P6 stimulation is rarely used for the prevention of PONV. Because most studies were small, Lee and colleagues conducted a secondary simulation analysis that suggested that the effect for nausea, but not for vomiting, may result from publication bias.[195] Based on the published evidence, it appears that stimulation of the P6 wrist point by means of acupuncture, electroacupuncture, transcutaneous nerve stimulation, laser stimulation, acu-stimulation device, and acupressure is an effective measure for the prevention of PONV.

SPECIAL SETTINGS

PEDIATRIC ANESTHESIA

Fewer studies have been conducted in children, and these generally focus on POV because the assessment of nausea can be difficult in younger children (see also Chapter 93).[196,197] A limited number of studies investigated risk factors,[198] but only one well-designed multicenter prospective survey developed a predictive model for POV (see also the earlier section on risk assessment).[67] Although the impact of the type of surgery remains somewhat controversial in adults, strabismus surgery and especially myopexy (Faden surgery)[102,199] appear to be independent predictors of POV in children, as determined by Eberhart and colleagues.[67] At the same time, contrary to widely held belief, little evidence suggests that ENT surgical procedures or appendectomies are independent predictors of POV in children.

Regarding antiemetics, it appears that efficacy is comparable to that known for adults. Few thoroughly conducted dose-response studies for antiemetics exist in adults and even fewer have been conducted in children. Thus, most pediatric doses are arbitrarily set at approximately 1/50th to 1/25th of the common adult per kilogram dose.

POSTDISCHARGE NAUSEA AND VOMITING

In the United States, more than 60% of surgical procedures are now performed on an outpatient basis (ambulatory surgery). In addition to being a major cause of delayed discharge and unanticipated readmissions, PONV may also pose a significant problem to the patient after discharge (see also Chapter 89).[200,201] In fact, PDNV may be of particular concern because it occurs when patients no longer have immediate access to intravenous rescue treatment, and oral medications may be intolerable. A large multicenter trial in patients undergoing general anesthesia for ambulatory surgery in the United States found that PDNV affected 37% of patients in the first

48 postoperative hours,[59] similar to a previous, smaller U.S. study that reported that 35% of patients experienced PDNV severe enough to delay resumption of their normal daily activities.[202] This prevalence is surprisingly high given that ambulatory surgery procedures are generally less invasive and less extensive than inpatient procedures and therefore require less exposure to perioperative triggers of PONV such as inhalational anesthetics and opioids. The multicenter trial identified five independent predictors of PDNV, namely female gender, age less than 50 years, history of PONV after previous anesthesia, opioid administration in the PACU, and nausea in the PACU (see also the earlier section on risk assessment).[59] Therefore, as for PONV, the patient's risk for PDNV can be easily assessed using a simplified predictive risk score.[59]

Interestingly, the RRR of antiemetics seems to be similar for PDNV and for PONV. For example, according to a systematic review from Gupta and colleagues, the RR for postdischarge nausea is 0.77 for 4 mg of ondansetron, 0.68 for more than 1 mg of droperidol, and 0.55 for dexamethasone.[203] Shorter-acting drugs are not as effective, especially when they are used at the minimally effective dose, and antiemetics with a longer duration of action appear favorable. Furthermore, although a trial in more than 2000 patients confirmed that dexamethasone can significantly reduce the incidence of PDNV, ondansetron was found to have no effect.[59] Therefore, dexamethasone, scopolamine (because of the sustained release of the patch), palonosetron, and aprepitant may be reasonable first choices for the prevention of PDNV. Of course, further studies, especially with the novel compounds, are needed to support this hypothesis.

RESCUE TREATMENT

Although numerous studies have investigated antiemetics for the prevention of PONV, relatively few have addressed their use for rescue treatment of established PONV. In fact, when Kazemi-Kjellberg and Tramer and their co-workers conducted a quantitative systematic review of rescue treatments for established nausea and vomiting, only 18 randomized placebo-controlled trials met inclusion criteria.[204] These investigators reported an absolute risk reduction between 20% and 30%, consistent with the 20% to 30% RRR known for the prevention of PONV in large trials[74] (in studies of rescue treatment, absolute risk reduction and RRR are equivalent measures because all patients who receive treatment have prior symptoms). In fact, Scuderi and colleagues demonstrated that early rescue treatment of PONV results in outcomes including time to discharge, unanticipated admission, and time to return to normal daily activities that are similar to those achieved with routine prophylactic treatment.[103] This finding does not, however, account for patients' comfort, even though this may be difficult to measure in terms of patients' satisfaction.

With regard to dosage, early rescue treatment with 1 mg of ondansetron seems to have comparable efficacy and better effectiveness than 4 mg of prophylactic ondansetron.[205,206] Thus only one-quarter dose is needed for rescue compared with preventive treatment.

Serotonin antagonists are not only the most commonly used antiemetics for prevention but also the most commonly used antiemetics for rescue treatment.[207] One reason may be that serotonin antagonists are currently the only class of intravenously available antiemetics that may have a rapid onset for rescue treatment without having sedative side effects. As previously mentioned, serotonin antagonists are highly selective and tend to block almost all available receptors. Therefore, once ondansetron is used for prophylaxis, subsequent use for rescue treatment in the PACU is ineffective.[208] Nevertheless, ondansetron is still commonly used as first-line rescue treatment after previous prophylaxis, even though this practice is contrary to both theoretical considerations and available evidence. Similarly, use of rescue granisetron, another serotonin antagonist, is ineffective in patients who have already received ondansetron for PONV prevention.[209] Therefore, as a rule of thumb, after administering an antiemetic, it is most effective to choose an antiemetic of another class for later rescue treatment. This recommendation is corroborated by a secondary analysis showing that after prophylaxis with either ondansetron and droperidol, promethazine rescue treatment is significantly more effective than repeat dosing with the same agent.[210]

Dexamethasone has been shown to be as effective as ondansetron for the prevention of PONV.[74] Clinically, it appears to have a fairly slow onset, as supported by observations that it has better efficacy when it is given at the beginning than at the end of the procedure.[168] Nevertheless, Rusch and associates were able to show that adding dexamethasone to either ondansetron or haloperidol for rescue treatment increases the overall RRR during a 24-hour period.[211]

In conclusion, drugs for rescue treatment appear to have the same efficacy and thus better effectiveness compared with their use for prevention. In addition, lower doses are needed for rescue treatment than for prevention, and it is preferable to administer drugs that have not been previously used.

A RATIONAL GUIDELINE FOR THE MANAGEMENT OF POSTOPERATIVE NAUSEA AND VOMITING

The wealth of published information poses a challenge for the anesthesia provider who wants to develop a comprehensive and valid strategy for the prevention and treatment of PONV. To this end, consensus guidelines have been developed. However, the fact that a group of individuals agrees or compromises on a certain content or wording does not guarantee infallibility. For example, some guidelines report the NNT for various interventions as if this would allow a comparison of drug efficacy among trials even though that would not be sound methodologically (see the earlier discussion to appreciate the difference between efficacy and effectiveness).

Therefore, instead of summarizing various consensus guidelines, this last section describes a rational approach for the prevention and treatment of PONV that is based

TABLE 97-4 ALGORITHM FOR THE MANAGEMENT OF POSTOPERATIVE NAUSEA AND VOMITING*

	TIVA Preferred	Anticipated Rescue	1 Risk Factor	2 Risk Factors	3 Risk Factors	4 Risk Factors
Inpatients	Yes	Ondansetron	Dex	+TIVA	+D_2-RA	+Aprep
		Non-5-HT_3	Dex	+TIVA	+Ond	+Aprep
	No	Ondansetron	Dex	+D_2-RA	+Aprep	+TIVA
		Non-5-HT_3	Dex	+Ond	+Aprep	+TIVA
	TIVA preferred	**Anticipated Rescue**	**1 Risk Factor**	**2 Risk Factors**	**3 Risk Factors**	**4 to 5 Risk Factors**
Outpatients	Yes	Palo	Dex	+TIVA+TDS	+D_2-RA	+Aprep
		Non-5-HT_3	Dex	+TIVA+TDS	+Palo	+Aprep
	No	Palo	Dex	+TDS	+Aprep	+TIVA
		Non-5-HT_3	Dex	+TDS	+Palo	+Aprep

Aprep, Aprepitant; *D_2,* dopamine-2; *dex,* dexamethasone; *5-HT_3,* 5-hydroxytryptamine 3 (serotonin); *Ond,* ondansetron; *Palo,* palonosetron; *RA,* receptor antagonist; *TDS,* transdermal scopolamine; *TIVA,* total intravenous anesthesia.

*Recommended prophylactic strategy based on patient's risk, inpatient or outpatient status, anticipated rescue treatment, and the preference of the anesthesia provider regarding total intravenous anesthesia.

on the current knowledge and understanding outlined in this chapter. This approach should be taken as a guide for clinicians but not as a rigid rule because other similarly valid approaches certainly exist. To this end, the rule of three would be helpful: (1) assess the need for prevention, (2) titrate preventive measures (that includes a modification of the anesthetic technique) according to the patient's need, and (3) follow up on your patient and use rescue treatment immediately, by targeting mechanisms that have not been tried before.

CONSIDER THE IMPORTANCE OF PREVENTION

This consideration is influenced by the patient's risk for PONV, the potential medical problem associated with it, and the perspective and values of both the patient and the health care provider. It is advisable to estimate the patient's risk by using a risk score, such as the score from Apfel and associates or Koivuranta and colleagues for adults and the score from Eberhart and co-workers for children.[4,5,67] Even though these scores are far from being perfect, they provide a better prediction compared with the history of PONV or the type of surgical procedure.[38]

TITRATE TO THE PATIENT'S NEEDS

Patients With Limited Need for Preventive Measures

In general, the use of prophylactic antiemetics is rarely justified when the patient's risk is low (e.g., 10% to 20%) (Table 97-4).[74] The reasons are that antiemetics have low effectiveness at low risk, so that many patients need to be treated for one patient to benefit, and low-risk patients are unnecessarily exposed to an antiemetic that may have—even rare—associated side effects (e.g., sedation, headache, QT prolongations, torsades de pointes). However, as mentioned earlier, the use of these drugs may be justified if this is a patient's preference or if concerns exist about medical or surgical complications related to vomiting.

Patients Who Require Some Preventive Measures

In patients at moderate risk, one or two antiemetic measures are often appropriate, but these do not need to be antiemetic drugs. One approach could be TIVA (with propofol, air, and fentanyl) and/or the use of 4 mg of dexamethasone after the induction of anesthesia supplemented with measures to minimize opioid consumption (NSAIDs, lidocaine, low-dose ketamine).

PATIENTS IN WHOM SIGNIFICANT PREVENTIVE MEASURES SHOULD BE UNDERTAKEN

In patients at high or very high risk, avoidance of general anesthesia and minimization of perioperative opioids may comprise the most effective approach (e.g., peripheral nerve block, spinal anesthesia).[116] However, if a general anesthetic regimen is needed, a TIVA with 4 mg of dexamethasone[74] and an additional antiemetic (e.g., 12.5 to 25 mg of promethazine, 31.25 to 62.5 mg of dimenhydrinate, or 25 to 50 mg of metoclopramide) can be recommended. Which partner drug to choose is most likely not relevant because most drugs appear similarly effective,[111] and indirect evidence suggests that interventions with different mechanisms are additive (i.e., they work independently).[74] Of course, TIVA could be substituted for an inhaled anesthetic in conjunction with an antiemetic, but this eliminates one rescue treatment option should PONV occur in the PACU. This is particularly true for the use of a serotonin antagonist, which may otherwise be an effective rescue option without sedative side effects.

RESCUE WITHOUT DELAY

Options for rescue treatment are interventions that have not been applied before or when the half-life suggests that the intervention is no longer active.[208] Serotonin antagonists, if not given in the operating room, may be a first choice in the PACU because of their lack of sedative side effects. Moreover, the addition of dexamethasone to

dolasetron or haloperidol could increase the overall risk reduction for rescue treatment (again, if the drug has not been given before).[211] Finally, stimulation of the P6 acupressure point may be another option, given that its efficacy has been demonstrated for the prevention of PONV.

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Chapter 98

Acute Postoperative Pain

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Key Points

- Nociception is a dynamic process (i.e., neuroplasticity) with multiple points of modulation. Persistent noxious input may result in relatively rapid neuronal sensitization and possibly persistent pain.
- Postoperative pain, especially when poorly controlled, results in harmful acute effects (i.e., adverse physiologic responses) and chronic effects (i.e., delayed long-term recovery and chronic pain).
- By preventing central sensitization, preventive analgesia may reduce acute and chronic pain. Although studies overwhelmingly support the concept of preemptive analgesia, the evidence from clinical trials is equivocal because of methodologic issues.
- By allowing individual titration of analgesic drugs, use of patient-controlled anesthesia (oral, subcutaneous, iontophoretic, intravenous, paravertebral, or epidural) may provide several advantages over traditional provider-administered analgesia (e.g., intramuscular or intermittent intravenous injections) in the management of postoperative pain.
- The incidence of respiratory depression from opioids is not significantly different among the various routes of administration (i.e., oral, intravenous versus intramuscular versus subcutaneous versus neuraxial). Appropriate monitoring of patients receiving opioid analgesics is essential to detect those with opioid-related side effects, such as respiratory depression.
- Judicious use of adjuvant drugs, such as nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, clonidine, ketamine, and gabapentinoids, may improve postoperative analgesia and potentially diminish analgesic-related side effects.
- When compared with systemic opioids, perioperative epidural analgesia may confer several advantages, including a facilitated return of gastrointestinal function and decrease in the incidence of pulmonary complications, coagulation-related adverse events, and cardiovascular events, especially in higher-risk patients or procedures. However, the risks and benefits of epidural analgesia should be evaluated for each patient, and appropriate monitoring protocols should be used during postoperative epidural analgesia.
- Epidural analgesia is not a generic entity. Perioperative morbidity may vary based on different catheter locations (catheter-incision congruent versus catheter-incision incongruent), durations of postoperative analgesia, and analgesic regimens (local anesthetics versus opioids).
- Postoperative pain management should be tailored to the needs of special populations (e.g., opioid-tolerant, pediatric, and obese patients, as well as those with obstructive sleep apnea) who may have different anatomic, physiologic, pharmacologic, or psychosocial issues.

FUNDAMENTAL CONSIDERATIONS

A revolution in the management of acute postoperative pain has occurred during the past 4 decades. Widespread recognition of the undertreatment of acute pain by clinicians, economists, and health policy experts has led to the development of a national clinical practice guideline for management of acute pain by the Agency for Healthcare Quality and Research (formerly the Agency for Health Care Policy and Research) of the U.S. Department of Health and Human Services.[1] This landmark document includes acknowledgment of the historical inadequacies in perioperative pain management, importance of good pain control, need for accountability for adequate provision of perioperative analgesia by health care institutions, and a statement on the need for involvement of specialists in appropriate cases. In addition, several professional societies (e.g., American Society of Anesthesiologists, The Joint Commission) have developed clinical practice guidelines for acute pain management or provided new pain management standards.

With their knowledge of and familiarity with pharmacology, various regional anesthesia techniques, and the neurobiology of nociception, anesthesiologists are prominently associated with the clinical and research advances in acute postoperative pain management. Anesthesiologists developed the concept of acute postoperative pain services (inpatient pain services), application of evidence-based practice to acute postoperative pain, and creation of innovative approaches to acute pain medicine, all of which are a natural part of the anesthesiologist's functions as a "perioperative physician," consultant, and therapist throughout an institution, as well as a highly skilled expert in the operating room. Provision of effective analgesia for surgical and other medical patients is an important component of this multidimensional role. An area that is often lacking in the acute perioperative pain services is the management of patients with acute surgical pain in addition to a baseline chronic pain. These patients are often not well served by the arbitrary distinction of "acute versus chronic" pain services in hospitals. Anesthesiologists are well trained to manage acute pain in the patient with concomitant chronic pain as a result of the strength of chronic pain curricula in current anesthesiology training programs. Although this chapter focuses on the patient who has acute perioperative pain, acute management of chronic pain in the hospitalized setting is also discussed.

PAIN PATHWAYS AND THE NEUROBIOLOGY OF NOCICEPTION

Surgery produces tissue injury with consequent release of histamine and inflammatory mediators such as peptides (e.g., bradykinin), lipids (e.g., prostaglandins), neurotransmitters (e.g., serotonin), and neurotrophins (e.g., nerve growth factor).[2] Release of inflammatory mediators activates peripheral nociceptors, which initiate transduction and transmission of nociceptive information to the central nervous system (CNS) and the process of neurogenic inflammation, in which release of neurotransmitters (i.e., substance P and calcitonin gene–related peptide) in the periphery induces vasodilatation and plasma extravasation.[2] Noxious stimuli are transduced by peripheral nociceptors and transmitted by A-delta and C nerve fibers from peripheral visceral and somatic sites to the dorsal horn of the spinal cord, where integration of peripheral nociceptive and descending modulatory input (i.e., serotonin, norepinephrine, γ-aminobutyric acid, enkephalin) occurs. Further transmission of nociceptive information is determined by complex modulating influences in the spinal cord. Some impulses pass to the ventral and ventrolateral horns to initiate segmental (spinal) reflex responses, which may be associated with increased skeletal muscle tone, inhibition of phrenic nerve function, or even decreased gastrointestinal motility. Others are transmitted to higher centers through the spinothalamic and spinoreticular tracts, where they induce supraspinal and cortical responses to ultimately produce the perception of and affective component of pain.

Continuous release of inflammatory mediators in the periphery sensitizes functional nociceptors and activates dormant ones. Sensitization of peripheral nociceptors may occur and is marked by a decreased threshold for activation, increased rate of discharge with activation, and increased rate of basal (spontaneous) discharge. Intense noxious input from the periphery may also result in central sensitization ("persistent postinjury changes in the CNS that result in pain hypersensitivity"[3]) and hyperexcitability ("exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage"[3]). Such noxious input may lead to functional changes in the dorsal horn of the spinal cord and other consequences that may later cause postoperative pain to be perceived as more painful than it would otherwise have been. The neural circuitry in the dorsal horn is extremely complex, and we are just beginning to elucidate the specific role of the various neurotransmitters and receptors in the process of nociception.[2] However, it seems that certain receptors (e.g., *N*-methyl-D-aspartate [NMDA]) may be especially important for the development of chronic pain after an acute injury, although other neurotransmitters or second messenger effectors (e.g., substance P, protein kinase C) may also play important roles in spinal cord sensitization and chronic pain. Our understanding of the neurobiology of nociception has progressed from the hard-wired system proposed by Descartes in the 17th century to the current view of neuroplasticity in which dynamic integration and modulation of nociceptive transmission take place at several levels. However, many gaps still exist in our knowledge of the specific roles of various receptors, neurotransmitters, and molecular structures in the process of nociception.

An understanding of the neurobiology of nociception is important for appreciating the transition from acute to chronic pain. The traditional dichotomy between acute and chronic pain is arbitrary because acute pain may quickly transition into chronic pain.[4] Noxious stimuli can produce expression of new genes (which are the basis for neuronal sensitization) in the dorsal horn of the spinal cord within 1 hour, and these changes are sufficient to alter behavior within the same time frame.[5] Also, the intensity of acute postoperative pain is a significant predictor of chronic postoperative pain.[6] Control

of perioperative pain (e.g., preventive analgesia) and the manner in which it is implemented (e.g., multimodality perioperative management) may be important in facilitating short- and long-term patient convalescence after surgery.

ACUTE AND CHRONIC EFFECTS OF POSTOPERATIVE PAIN

Uncontrolled postoperative pain may produce a range of detrimental acute and chronic effects. The attenuation of perioperative pathophysiology that occurs during surgery through reduction of nociceptive input to the CNS and optimization of perioperative analgesia may decrease complications and facilitate recovery during the immediate postoperative period[7] and after discharge from the hospital.

Acute Effects

The perioperative period has a variety of pathophysiologic responses that may be initiated or maintained by nociceptive input. At one time these responses may have had a beneficial teleological purpose; however, the same response to the iatrogenic nature of modern-day surgery may be harmful. Uncontrolled perioperative pain may enhance some of these perioperative pathophysiologies and increase patient morbidity and mortality. Attenuation of postoperative pain, especially with certain types of analgesic regimens, may decrease perioperative morbidity and mortality.

Transmission of nociceptive stimuli from the periphery to the CNS results in the neuroendocrine stress response, a combination of local inflammatory substances (e.g., cytokines, prostaglandins, leukotrienes, tumor necrosis factor-α) and systemic mediators of the neuroendocrine response. The dominant neuroendocrine responses to pain involve hypothalamic-pituitary-adrenocortical and sympathoadrenal interactions. Suprasegmental reflex responses to pain result in increased sympathetic tone, increased catecholamine and catabolic hormone secretion (e.g., cortisol, adrenocorticotropic hormone, antidiuretic hormone, glucagon, aldosterone, renin, angiotensin II), and decreased secretion of anabolic hormones.[8] The effects include sodium and water retention and increased levels of blood glucose, free fatty acids, ketone bodies, and lactate. A hypermetabolic, catabolic state occurs as metabolism and oxygen consumption are increased and metabolic substrates are mobilized from storage depots.[8] The extent of the stress response is influenced by many factors, including the type of anesthesia and intensity of the surgical injury, with the extent of the stress response being proportional to the degree of surgical trauma.[9] The negative nitrogen balance and protein catabolism may impede convalescence; however, attenuation of the stress response and postoperative pain may facilitate and accelerate the patient's recovery postoperatively.

The neuroendocrine stress response may enhance detrimental physiologic effects in other areas of the body. The stress response is likely a factor in the postoperative development of hypercoagulability. Enhancement of coagulation (i.e., decreased levels of natural anticoagulants and increased levels of procoagulants), inhibition of fibrinolysis, and increased platelet reactivity and plasma viscosity may enhance the incidence of postoperative hypercoagulable-related events such as deep venous thrombosis, vascular graft failure, and myocardial ischemia.[10] The stress response may also enhance postoperative immunosuppression, the extent of which correlates with the severity of surgical injury.[4] Hyperglycemia from the stress response may contribute to poor wound healing and depression of immune function.

Uncontrolled postoperative pain may activate the sympathetic nervous system and thereby contribute to morbidity or mortality. Sympathetic activation may increase myocardial oxygen consumption, which may be important in the development of myocardial ischemia and infarction,[10] and may decrease myocardial oxygen supply through coronary vasoconstriction and attenuation of local metabolic coronary vasodilation.[11] Activation of the sympathetic nervous system may also delay return of postoperative gastrointestinal motility, which may develop into paralytic ileus. Although postoperative ileus is the result of a combination of inhibitory input from central and local factors,[10,11] an increase in sympathetic efferent activity, such as from uncontrolled pain, may decrease gastrointestinal activity and delay return of gastrointestinal function.

Nociceptors are activated after surgical trauma and may initiate several detrimental spinal reflex arcs. Postoperative respiratory function is markedly decreased, especially after upper abdominal and thoracic surgery. Spinal reflex inhibition of phrenic nerve activity is an important component of this decreased postoperative pulmonary function.[10] However, patients with poor postoperative pain control may breathe less deeply, have an inadequate cough, and be more susceptible to the development of postoperative pulmonary complications.[11] Activation of nociceptors may also initiate spinal reflex inhibition of gastrointestinal tract function and delay return of gastrointestinal motility.[10]

Many detrimental postoperative pathophysiologic effects can occur in the perioperative period and can activate nociceptors and the stress response. Uncontrolled pain may activate the sympathetic nervous system, which can cause a variety of potentially harmful physiologic responses that may adversely increase morbidity and mortality. Nociceptor activation may also result in several detrimental inhibitory spinal reflexes. Control of the pathophysiologic processes associated with acute postoperative pain may attenuate the stress response, sympathetic outflow, and inhibitory spinal reflexes and contribute to improvements in morbidity, mortality, and patient-reported outcomes (e.g., health-related quality of life [HRQL], patient satisfaction).[10]

Chronic Effects

Chronic postsurgical pain (CPSP) is a largely unrecognized problem that may occur in 10% to 65% of postoperative patients (depending on the type of surgery), with 2% to 10% of these patients experiencing severe CPSP.[12] Poorly controlled acute postoperative pain is an important predictive factor in the development of CPSP.[6,13] The transition from acute to chronic pain occurs very quickly, and long-term behavioral and neurobiologic changes occur much sooner than was previously thought.[4] CPSP is relatively

common after procedures such as limb amputation (30% to 83%), thoracotomy (22% to 67%), sternotomy (27%), breast surgery (11% to 57%), and gallbladder surgery (up to 56%).[6] Although the severity of acute postoperative pain may be an important predictor in the development of CPSP,[6] a causal relationship has not been definitively established, and other factors (e.g., area of postoperative hyperalgesia) may be more important in predicting the development of CPSP.[14] One such factor may be the severity of the patient's preoperative pain. Patients with more intense levels of preoperative pain may also develop a degree of CNS sensitization predisposing them to the increased likelihood of higher postoperative pain and the subsequent development of chronic pain.[14] Thus, it is important that acute pain service clinicians understand chronic pain conditions and involve themselves in the patient's preoperative care. The increased involvement of the acute pain medicine team in preoperative anesthesia clinics or services can positively attenuate the incidence and severity of postoperative pain.

Control of acute postoperative pain may improve long-term recovery or patient-reported outcomes (e.g., quality of life). Patients whose pain is controlled in the early postoperative period (especially with the use of continuous epidural or peripheral catheter techniques) may be able to actively participate in postoperative rehabilitation, which may improve short- and long-term recovery after surgery.[15] Optimizing treatment of acute postoperative pain can improve health-related quality of life (HRQL).[16] Postoperative chronic pain that develops as a result of poor postoperative pain control may interfere with patients' activities of daily living.

PREVENTIVE ANALGESIA

The older terminology of "preemptive" analgesia referred to an analgesic intervention that preceded a surgical injury and was more effective in relieving acute postoperative pain than the same treatment following surgery. The precise definition of preemptive analgesia is one of the major controversies in this area of medicine and contributes to the question of whether preemptive analgesia is clinically relevant. Definitions of preemptive analgesia include what is administered before the surgical incision, what prevents the establishment of central sensitization resulting from incisional injury only (i.e., intraoperative period), what prevents central sensitization resulting from incisional and inflammatory injury (i.e., intraoperative and postoperative periods), or the entire perioperative period encompassing preoperative interventions, intraoperative analgesia, and postoperative pain management (i.e., preventive analgesia).[3] The first two definitions are relatively narrow and may contribute to the lack of a detectable effect of preemptive analgesia in clinical trials. The rationale for preemptive analgesia was based on the inhibition of the development of central sensitization. Effectively, noxious input initiated by surgical procedures induced a state of CNS hyperactivity that accentuated pain. Although a very popular and discussed theory, a single analgesic treatment (either peripheral or neuraxial) before the incision does not reduce postoperative pain behaviors beyond the expected duration of the analgesic effect.[17] When the block of nociceptive afferents diminishes, the surgical injury is able to reinitiate central sensitization. Clinical trials have been negative.[18] For these reasons, this terminology has been abandoned.

As stated previously, intense noxious input (e.g., postoperative pain from the periphery) can change the CNS (i.e., central sensitization) to induce pain hypersensitivity and hyperexcitability (i.e., exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage). Preventive analgesia is aimed at inhibiting the development of this type of chronic pain. This definition broadly includes any regimen given at any time during the perioperative period that is able to control pain-induced sensitization. Central sensitization and hyperexcitability can develop after the surgical incision in a patient who has no history of preoperative pain.

In contrast, some patients may already have existing acute or chronic pain and developed central sensitization before the surgical incision. These patients with preexisting pain may have even more intense pain in the postoperative period. This augmentation of already preexisting pain can occur in acutely hospitalized patients and even in those patients in subacute or chronic outpatient settings. Preventing the establishment of altered central processing by analgesic treatment may result in short-term (e.g., reduction in postoperative pain and accelerated recovery) and long-term (e.g., reduction in chronic pain and improvement in HRQL[16] benefits during a patient's convalescence. Unfortunately, many clinical studies (e.g., trials) lack clarity of study design and clear terminology of preemptive versus preventative analgesia.[18,19]

Timing of the intervention[18] may not be as clinically important as other aspects of preventive analgesia (i.e., intensity and duration of the intervention). An intervention administered before the surgical incision is not preventative if it is incomplete or insufficient (i.e., central sensitization is not prevented). Incisional and inflammatory injuries are important in initiating and maintaining central sensitization. Confining the definition of preventative analgesia to only the intraoperative (incisional) period is not relevant or appropriate because the inflammatory response lasts well into the postoperative period and continues to maintain central sensitization.

Maximal clinical benefit is observed when complete multisegmental blockade of noxious stimuli occurs, with extension of this effect into the postoperative period. Preventing central sensitization with intensive multimodal analgesic interventions[18] could theoretically reduce the intensity or even eliminate acute postoperative pain/hyperalgesia and chronic pain after surgery.[6]

MULTIMODAL APPROACH TO PERIOPERATIVE RECOVERY

The analgesic benefits of controlling postoperative pain are generally maximized when a multimodal strategy to facilitate the patient's convalescence is implemented. Yet postoperative pain treatment may not provide major improvements in some outcomes because it is unlikely that a unimodal intervention can be effective in addressing a complex problem such as perioperative outcomes.[7,20] Principles of a multimodal strategy include

control of postoperative pain to allow early mobilization, early enteral nutrition, education, and attenuation of the perioperative stress response through the use of regional anesthetic techniques[7] and a combination of analgesic drugs (i.e., multimodal analgesia). Despite the widely publicized case of academic fraud that included[21] many published articles on multimodal analgesia, subsequent carefully performed systematic reviews appeared to be robust enough to support its efficacy.[22] The use of epidural administered analgesics can provide superior analgesia and physiologic benefits and is therefore an integral part of the multimodal approach.

A multimodal approach to perioperative recovery to control postoperative pathophysiology and facilitate rehabilitation may result in accelerated recovery and decreased length of hospitalization.[23] Patients undergoing major abdominal or thoracic procedures and who participate in a multimodal strategy have a reduction in hormonal and metabolic stress, preservation of total-body protein, shorter times to tracheal extubation, lower pain scores, earlier return of bowel function, and earlier fulfillment of intensive care unit discharge criteria.[23] The multimodal approach integrates the most recent data and techniques from surgery, anesthesiology, nociceptive neurobiology, and pain treatment, making it an extension of clinical pathways (Enhanced Recovery After Surgery, or ERAS), or "fast tracks," by revising traditional care programs into effective postoperative rehabilitation pathways.[23] This approach will likely decrease perioperative morbidity, decrease the length of hospital stay, and improve patient satisfaction without compromising safety. However, widespread implementation of these programs requires multidisciplinary collaboration, change in the traditional principles of postoperative care, additional resources, and expansion of the traditional acute pain service, which may be limited in the current economic climate.

BOX 98-1 *Monitoring and Documentation of Postoperative Analgesia*

Analgesic Medication*
- Medication, concentration, and dose of drug
- Settings of PCA device: demand dose, lockout interval, continuous infusion
- Amount of drug administered (including number of unsuccessful and successful doses)
- Limits set (e.g., 1- and 4-hour limits on dose administered)
- Supplemental or breakthrough analgesics

Routine Monitoring
- Vital signs: temperature, heart rate, blood pressure, respiratory rate, average pain score
- Pain score at rest and with activity, pain relief
- Use of breakthrough medication

Side Effects
- Cardiovascular: hypotension, bradycardia, or tachycardia
- Respiratory status: respiratory rate, level of sedation
- Nausea and vomiting, pruritus, urinary retention
- Neurologic examination
- Assessment of motor block or function and sensory level
- Evidence of epidural hematoma

Instructions Provided
- Treatment of side effects
- Concurrent use of other CNS depressants
- Parameters for triggering notification of the covering physician
- Provision of contact information (24 hours/7 days per week) if problems occur
- Emergency analgesic treatment if the PCA device fails

CNS, Central nervous system; *PCA,* patient-controlled analgesia.
*Postoperative analgesia includes systemic opioids and regional analgesic techniques. This list incorporates some of the important elements of preprinted orders, documentation, and intravenous PCA and epidural analgesia daily care described in the ASA Practice Guidelines for Acute Pain Management.[24]

TREATMENT METHODS

Many options are available for the treatment of postoperative pain, including systemic (i.e., opioid and nonopioid) analgesics and regional (i.e., neuraxial and peripheral) analgesic techniques. By considering patients' preferences and making an individualized assessment of the risks and benefits of each treatment modality, the clinician can optimize the postoperative analgesic regimen for each patient. Essential aspects of postoperative monitoring of patients receiving various postoperative analgesic treatment methods are listed in Box 98-1.

SYSTEMIC ANALGESIC TECHNIQUES

OPIOIDS

Advantages and Characteristics

Opioid analgesics are one of the cornerstone options for the treatment of postoperative pain. They generally exert their analgesic effects through μ-receptors in the CNS, although opioids may also act at peripheral opioid receptors. A theoretical advantage of opioid analgesics is that there is no analgesic ceiling. Realistically, the analgesic efficacy of opioids is typically limited by the development of tolerance or opioid-related side effects such as nausea, vomiting, sedation, or respiratory depression. Opioids may be administered by the subcutaneous, transcutaneous, transmucosal, or intramuscular route, but the most common routes of postoperative systemic opioid analgesic administration are oral and intravenous. Opioids may also be administered at specific anatomic sites such as the intrathecal or epidural space (see later sections, "Single-Dose Neuraxial Opioids" and "Continuous Epidural Analgesia").

Wide intersubject and intrasubject variability exists in the relationship of opioid dose, serum concentration, and analgesic response in the treatment of postoperative pain. Serum drug concentrations may exhibit wider variability with certain routes of administration (e.g., intramuscular) than with others (e.g., intravenous). In general, opioids are administered parenterally (intravenously or intramuscularly) for the treatment of moderate to severe postoperative pain, in part because these routes provide a more rapid and reliable onset of analgesic action than the oral route does. Parenteral opioid administration may be necessary in patients who are unable to tolerate oral intake postoperatively. The transition from parenteral to oral administration of opioids usually occurs after the patient

TABLE 98-1 **INTRAVENOUS PATIENT-CONTROLLED ANALGESIA REGIMENS**

Drug Concentration	Size of Bolus*	Lockout Interval (min)	Continuous Infusion
Agonists			
Morphine (1 mg/mL)			
Adult	0.5-2.5 mg	5-10	—
Pediatric	0.01-0.03 mg/kg (max, 0.15 mg/kg/hr)	5-10	0.01-0.03 mg/kg/hr
Fentanyl (0.01 mg/mL)			
Adult	10-20 μg	4-10	—
Pediatric	0.5-1 μg/kg (max, 4 μg/kg/hr)	5-10	0.5-1 μg/kg/hr
Hydromorphone (0.2 mg/mL)			
Adult	0.05-0.25 mg	5-10	—
Pediatric	0.003-0.005 mg/kg (max, 0.02 mg/kg/hr)	5-10	0.003-0.005 mg/kg/hr
Alfentanil (0.1 mg/mL)	0.1-0.2 mg	5-8	—
Methadone (1 mg/mL)	0.5-2.5 mg	8-20	—
Oxymorphone (0.25 mg/mL)	0.2-0.4 mg	8-10	—
Sufentanil (0.002 mg/mL)	2-5 μg	4-10	—
Agonist-Antagonists			
Buprenorphine (0.03 mg/mL)	0.03-0.1 mg	8-20	—
Nalbuphine (1 mg/mL)	1-5 mg	5-15	—
Pentazocine (10 mg/mL)	5-30 mg	5-15	—

*All doses are for adult patients unless noted otherwise. Units vary across agents for size of the bolus (mg versus mg/kg versus μg versus μg/kg) and continuous infusion (mg/kg/hr versus μg/kg/hr). The anesthesiologist should proceed with titrated intravenous loading doses, if necessary, to establish initial analgesia. Individual patient requirements vary widely, with smaller doses typically given to older or compromised patients. Continuous infusions are not initially recommended for opioid-naive adult patients.

initiates oral intake and postoperative pain has been stabilized with parenteral opioids. Although oral opioids (typically formulated as part of a combination product that includes an adjuvant such as acetaminophen) are generally prescribed on an as-needed (PRN) basis postoperatively, there may be a role for sustained-release oral opioids, which may provide analgesia superior to that with conventional PRN regimens, although further studies are needed and these medications should be instituted on a case-by-case basis.[25] Although the traditional form (passive) of transdermal fentanyl is not indicated for the routine treatment of acute postoperative pain, a newer version involving patient-activated electrically facilitated delivery of transdermal fentanyl has been developed for use in hospitalized adult patients.[26]

Intravenous Patient-Controlled Analgesia

Various factors, including the aforementioned wide interpatient and intrapatient variability in analgesic needs, variability in serum drug levels (especially with intramuscular injection), and administrative delays, may contribute to inadequate postoperative analgesia. A traditional PRN analgesic regimen probably cannot compensate for these limitations. By circumventing some of these issues, intravenous patient-controlled analgesia (PCA) optimizes delivery of analgesic opioids and minimizes the effects of pharmacokinetic and pharmacodynamic variability in individual patients. Intravenous PCA is based on the premise that a negative-feedback loop exists; when pain is experienced, analgesic medication is self-administered, and when pain is reduced, there are no further demands. When the negative-feedback loop is violated, excessive sedation or respiratory depression may occur.[27] Although some equipment-related malfunctions can occur, the PCA device itself is relatively free of problems, and most problems related to PCA use result from user or operator error.[28]

A PCA device can be programmed for several variables, including the demand (bolus) dose, lockout interval, and background infusion (Table 98-1). An optimal demand or bolus dose is integral to the efficacy of intravenous PCA because an insufficient demand dose may result in inadequate analgesia, whereas an excessive demand dose may result in a higher incidence of undesirable side effects such as respiratory depression.[27] Although the optimal demand dose is uncertain, the data available suggest that the optimal demand dose is 1 mg for morphine and 40 μg for fentanyl in opioid-naive patients; however, the actual dose for fentanyl (10 to 20 μg) is often less in clinical practice.[28] The lockout interval may also affect the analgesic efficacy of intravenous PCA. A lockout interval that is too long may result in inadequate analgesia and decrease the effectiveness of intravenous PCA. A lockout interval that is too short allows the patient to self-administer another demand dose before feeling the full analgesic effect of the previous dose and thus may contribute to an increase in medication-related side effects. In essence, the lockout interval is a safety feature of intravenous PCA, and although the optimal lockout interval is unknown, most intervals range from 5 to 10 minutes, depending on the medication in the PCA pump; varying the interval within this range appears to have no effect on analgesia or side effects.[28]

Most PCA devices allow administration of a continuous or background infusion in addition to the demand dose. Initially, routine use of a background infusion predicted certain advantages, including improved analgesia, especially during sleep; however, analgesic benefits of a background infusion have not been successful in opioid-naive patients. A background infusion only increases the analgesic dosage used and the incidence of adverse respiratory events in the postoperative period especially in adult subjects. Furthermore, use of a nighttime background infusion does not improve postoperative sleep patterns, analgesia,

or recovery profiles.[29] Although routine use of continuous or background infusion as part of intravenous PCA in adult opioid-naive patients is not recommended, a background infusion in opioid-tolerant or pediatric patients may be effective (see later sections, "Opioid-Tolerant Patients" and "Pediatric Patients").

When compared with traditional PRN analgesic regimens, intravenous PCA provides superior postoperative analgesia and improves patient satisfaction, but the presence of economic benefits is not clear.[30] A meta-analysis revealed that intravenous PCA (versus as-needed opioids) provides significantly better analgesia and patient satisfaction; however, these patients used more opioids and had more frequent incidence of pruritus than those treated with PRN opioids, although no difference was seen in the incidence of adverse events.[30] With regard to economic outcomes, whether intravenous PCA is less expensive than traditional PRN intramuscular opioid administration is not clear because the calculations of cost are complex.

Intravenous PCA may provide advantages when assessing other patient-related outcomes such as patient satisfaction; these outcomes have become more important because health care organizations use them as a measure of quality and a tool for marketing purposes (also see Chapter 6). Patients usually prefer intravenous PCA over intravenously, intramuscularly, or subcutaneously administered PRN opioids. Greater patient satisfaction with intravenous PCA may be the result of superior analgesia and perceived control over the administration of analgesic medications and avoidance of disclosing pain or securing analgesic medication from nurses; however, the reasons for patient satisfaction are complex and many factors may contribute to or predict satisfaction with intravenous PCA. Although intravenous PCA use creates better satisfaction overall, the proper assessment of patient satisfaction can be complex.[31]

The incidence of opioid-related adverse events from intravenous PCA is not different from that of PRN opioids administered intravenously, intramuscularly, or subcutaneously. The rate of respiratory depression associated with intravenous PCA is infrequent (approximately 1.5%) and is not more frequent than that with PRN systemic or neuraxial opioids.[32] Factors that may influence the frequency and intensity of respiratory depression with intravenous PCA include use of a background infusion, advanced age, concomitant administration of sedative or hypnotic drugs, and coexisting pulmonary disease such as obstructive sleep apnea.[33] Intravenous PCA–related respiratory depression may also be caused by errors in programming or administration (i.e., operator error).[34]

NONOPIOIDS

Nonsteroidal Antiinflammatory Agents

Nonsteroidal antiinflammatory drugs (NSAIDs), which include aspirin and acetaminophen, consist of a diverse group of analgesic compounds with different pharmacokinetic properties. The primary mechanism by which NSAIDs exert their analgesic effect is through inhibition of cyclooxygenase (COX) and synthesis of prostaglandins, which are important mediators of peripheral sensitization and hyperalgesia. In addition to being peripherally acting analgesics, NSAIDs can also exert their analgesic effects through inhibition of spinal COX.[35] The discovery of at least two COX isoforms (i.e., COX-1 is constitutive and COX-2 is inducible) with different functions (i.e., COX-1 participates in platelet aggregation, hemostasis, and gastric mucosal protection, whereas COX-2 participates in pain, inflammation, and fever) has led to the development of selective COX-2 inhibitors that differ from traditional NSAIDs, which block both COX-1 and COX-2.[36] The discovery of a COX-3 variant may represent a primary central mechanism by which acetaminophen and other antipyretics decrease pain and fever; however, the precise relationship between COX-3 and acetaminophen is still uncertain.[37]

NSAIDs given alone generally provide effective analgesia for mild to moderate pain. NSAIDs are also traditionally considered a useful adjunct to opioids for the treatment of moderate to severe pain. Yet some quantitative, systematic reviews suggest that NSAIDs, alone or in combination with opioids, may be more beneficial than previously thought (Table 98-2 and Fig. 98-1). NSAIDs may be administered orally or parenterally and are particularly useful as components of a multimodal analgesic regimen by producing analgesia through a different

TABLE 98-2 RELATIVE EFFICACY OF SINGLE-DOSE ANALGESICS IN PROVIDING GREATER THAN 50% RELIEF OF MODERATE TO SEVERE POSTOPERATIVE PAIN

Drug*	Mean NNT†	95% CI
Acetaminophen (1000 mg PO)	3.8	3.4-4.4
Aspirin (600 to 650 mg PO)	4.4	4.0-4.9
Aspirin (1000 mg PO)	4.0	3.2-5.4
Diclofenac (50 mg PO)	2.3	2.0-2.7
Diclofenac (100 mg PO)	1.9	1.6-2.2
Ibuprofen (600 mg PO)	2.4	1.9-3.3
Ketorolac (10 mg PO)	2.6	2.3-3.1
Ketorolac (30 mg IM)	3.4	2.5-4.9
Naproxen (550 mg PO)	2.7	2.3-3.3
Celebrex (200 mg PO)	3.5	2.9-4.4
Celebrex (400 mg PO)	2.1	1.8-2.5
Tramadol (100 mg PO)	4.8	3.8-6.1
Gabapentin (600 mg PO)	11	6.0-35
Codeine (60 mg) acetaminophen (600 to 650 mg PO)	4.2	3.4-5.3
Oxycodone (5 mg) acetaminophen (325 mg PO)	2.5	2.0-3.2
Codeine (60 mg PO)	16.7	11.0-48.0
Morphine (10 mg IM)	2.9	2.6-3.6
Oxycodone (15 mg PO)	2.4	1.5-4.9

CI, Confidence interval; *IM,* intramuscular; *NNT,* number needed to treat; *PO,* oral route.

*Data obtained in part and modified from Bandolier with permission. Available at http://www.medicine.ox.ac.uk/bandolier/.

†NNT in this case refers to the number of patients who must be treated to obtain greater than 50% relief of moderate to severe postoperative pain. NNT conveys statistical and clinical significance, is useful in comparing the efficacy of different interventions, and summarizes treatment effects in a clinically relevant manner. A lower mean NNT implies greater analgesic efficacy in this example. See Figure 98-1 for a graphic presentation of these data.

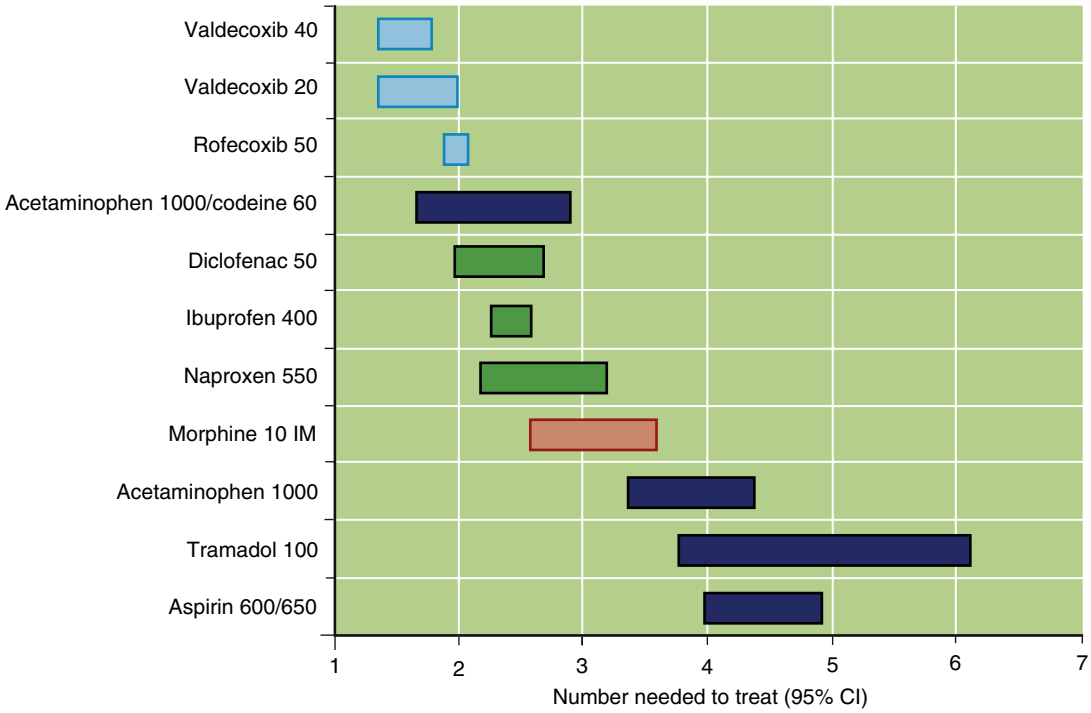


Figure 98-1. Number needed to treat (NNT) for at least 50% pain relief in patients with moderate to severe pain. The mean and 95% confidence interval (CI) for the NNTs are shown for several opioid and nonopioid analgesics from Table 98-2. The NNTs are derived from trials investigating the efficacy of a single dose of nonopioid analgesic versus placebo in providing more than 50% pain relief for moderate to severe postoperative pain. Numbers with drug names are doses in mg. *(From Bandolier. Available at http://www.medicine.ox.ac.uk/bandolier/.)*

mechanism than that of opioids or local anesthetics. Several meta-analyses have examined the analgesic efficacy of NSAIDs (including COX-2 inhibitors) and acetaminophen when added to intravenous PCA with opioids. Surprisingly (and important to note), NSAIDs,[38] not acetaminophen,[39] resulted in a statistically significant (but probably not clinically meaningful) reduction in pain scores.[40,41] Although all regimens significantly decreased morphine consumption, only NSAIDs (but not acetaminophen) reduced the risk for the opioid-related side effects of nausea, vomiting, and sedation.

Perioperative use of NSAIDs may be associated with several side effects, including decreased hemostasis, renal dysfunction, and gastrointestinal hemorrhage. Inhibition of COX and the formation of prostaglandins cause many of the side effects, which mediate many diverse processes throughout the body. Decreased hemostasis from NSAID use is from platelet dysfunction and inhibition of thromboxane A_2 (generated by COX-1), an important mediator of platelet aggregation and vasoconstriction.[42] Evidence of the effect of NSAIDs on perioperative bleeding is equivocal; a surveillance study of perioperative ketorolac administration did not demonstrate a significant increase in operative site bleeding. Whether NSAIDs may also have a deleterious effect on bone healing and osteogenesis is controversial.[43] Although NSAIDs have been used following acetabular/hip fractures and hip replacement surgery to reduce heterotopic ossification, the short-term effects of NSAIDs on other skeletal tissues are less clear.[44] Two recent systematic reviews indicated that when examining the highest-quality studies, there was no increased risk of nonunion with NSAID exposure. Certainly, a short-term NSAID regimen can be used for treatment of postfracture pain without significantly increasing the risk of disrupted healing.[45] A brief (<14 days) exposure to normal-dose NSAIDs (e.g., ketorolac <120 mg/day) was safe after spinal fusion; however, use of large-dose ketorolac (>120 mg/day) increased the risk of nonunion, suggesting a dose-dependent effect of perioperative NSAIDs on spinal fusion healing.[46] Spine surgeons will more commonly err on the conservative side and refuse to have postoperative spine fusion patients receive NSAIDs.

Perioperative NSAID-induced renal dysfunction may occur in high-risk patients, such as those with hypovolemia, abnormal renal function, or abnormal serum electrolytes, because prostaglandins dilate the renal vascular beds and mediate diuretic and natriuretic renal effects. NSAIDs should not be withheld in patients with normal preoperative renal function because euvolemic patients with normal renal function are unlikely to be affected, although NSAIDs may cause a clinically unimportant transient reduction in renal function in the early postoperative period in patients with normal preoperative renal function.[47] Gastrointestinal bleeding[48] may be more likely with NSAID intake because of inhibition of COX-1, which is required for the synthesis of cytoprotective gastric mucosal prostaglandins. Bronchospasm may be induced by NSAIDs (including aspirin) or acetaminophen, and cross-sensitivity may occur with acetaminophen in aspirin-sensitive asthmatic subjects.[49] Because expression of peripheral COX-2 is increased during inflammation, selective inhibition of COX-2 could theoretically

provide analgesia without the side effects associated with COX-1 inhibition. COX-2 inhibitors have a less frequent incidence of gastrointestinal complications[50] and exhibit minimal platelet inhibition, even when administered in supratherapeutic doses.[51] However, long-term use of COX-2 inhibitors has an excess cardiovascular risk; thus, rofecoxib was withdrawn from the market.[52] Although cardiovascular toxicity appears to be a class effect of all COX-2 inhibitors, the cardiovascular risks of COX-2 inhibitors are heterogeneous and influenced by many factors such as the specific medication, dosage, and patient characteristics.[52] Issues surrounding the perioperative use of COX-2 inhibitors are slightly different from those of longer-term use of COX-2 inhibitors.[53] A randomized trial of valdecoxib and its intravenous prodrug parecoxib versus placebo assessed the safety of these drugs in patients undergoing coronary artery bypass grafting (CABG).[54] When compared with the group given placebo alone, both the group given parecoxib and valdecoxib and the group given placebo and valdecoxib had a higher proportion of patients with at least one confirmed adverse event.[54] The use of parecoxib and valdecoxib after CABG was associated with an increased incidence of cardiovascular events, thereby arousing serious concern about the use of these drugs in such circumstances. However, a subsequent randomized controlled trial investigating the safety and efficacy of parecoxib and valdecoxib after major noncardiac surgery found that patients who received the COX-2 inhibitors had similar frequencies of predefined adverse events compared with those who received placebo.[55]

Gabapentanoids

Gabapentin and pregabalin, antiepileptic drugs also used in the treatment of neuropathic pain, interact with calcium channel α_2-δ ligands to inhibit calcium influx and subsequent release of excitatory neurotransmitters. However, oral pregabalin is absorbed more rapidly and has more absolute bioavailability (≥90% versus <60%) than does gabapentin.[56] Despite these differences, oral gabapentin improves the analgesic efficacy of opioids both at rest and with movement, and reduces opioid consumption and opioid-related side effects, but with an increased incidence of side effects such as sedation and dizziness.[57,58,59] The data for the analgesic efficacy for pregabalin is not as convincing as that for gabapentin. A meta-analysis investigating the analgesic efficacy of pregabalin for acute postoperative pain demonstrated use of pregabalin was associated with a decrease in opioid consumption and opioid-related side effects, but no difference in pain intensity.[60] Another meta-analysis suggested that perioperative administration of pregabalin may provide additional analgesia in the short term but also results in an increase in side effects such as dizziness/lightheadedness or visual disturbances.[61] Although further studies are needed to elucidate the specific parameters (e.g., dose, duration of use) for gabapentanoids in the perioperative period, these analgesics can be considered as part of a multimodal approach to postoperative analgesia. Furthermore, perioperative administration of gabapentin and pregabalin may reduce the incidence of CPSP.[62]

Ketamine

Ketamine is traditionally recognized as an intraoperatively administered anesthetic; however, small-dose (analgesic) ketamine can facilitate postoperative analgesia because of its NMDA-antagonistic properties, which may be important in attenuating central sensitization and opioid tolerance.[63] Ketamine can be administered orally, intravenously (PCA or as a continuous infusion), subcutaneously, or intramuscularly. A systematic review of perioperative ketamine use found that perioperative analgesic doses of ketamine reduce rescue analgesic requirements or pain intensity.[64] In addition, perioperative ketamine reduced 24-hour PCA morphine consumption and postoperative nausea or vomiting and had minimal adverse effects.[64] A subsequent systematic review found that intravenous ketamine was an effective adjunct for postoperative analgesia particularly in patients undergoing painful procedures, such as upper abdominal, thoracic, and major orthopedic surgeries.[65] The administration of ketamine in postoperative pediatric patients is also associated with decreased postoperative pain intensity (also see Chapter 93).[66] One potential concern is the possible impact of ketamine's amnestic effects on the neuropharmacologic and cognitive level of patients with use of perioperative ketamine infusions.[67] Although possible, these effects infrequently occur when the medication is given in analgesic doses. Ketamine has also been given epidurally and intrathecally, but racemic mixtures of ketamine are neurotoxic, and therefore the use of neuraxial racemic ketamine is strongly discouraged.

Tramadol

Tramadol is a synthetic opioid that exhibits weak μ-agonist activity and inhibits reuptake of serotonin and norepinephrine, although the relative degree of contribution of each modality to postoperative analgesia is not certain.[68] Although tramadol exerts its analgesic effects primarily through central mechanisms, it may have peripheral local anesthetic properties and has been used as a subcutaneous local anesthetic for minor surgical procedures.[69] Tramadol is effective in treating moderate postoperative pain[70] and is comparable in analgesic efficacy to aspirin (650 mg) with codeine (60 mg) or ibuprofen (400 mg) (see Table 98-2 and Fig. 98-1).[70] The addition of acetaminophen to tramadol (versus tramadol alone) may decrease the incidence of tramadol's side effects without reducing its analgesic efficacy.[71] Use of tramadol in intravenous PCA results in similar pain scores when compared with that from intravenous PCA opioids; however, the side effect profile is different between the two groups (i.e., a more frequent incidence of postoperative nausea/vomiting but lower pruritus with tramadol).[72] Advantages of tramadol for postoperative analgesia include a relative lack of respiratory depression, major organ toxicity, and depression of gastrointestinal motility and a small potential for abuse (1 case per 100,000 patients).[68] Common side effects (overall incidence of 1.6% to 6.1%) include dizziness, drowsiness, sweating, nausea, vomiting, dry mouth, and headache.[70] Tramadol should be used with caution in patients with seizures or increased intracranial pressure (also see Chapter 70) and is contraindicated in those taking monoamine oxidase inhibitors.[70]

REGIONAL ANALGESIC TECHNIQUES

A variety of neuraxial (primarily epidural) and peripheral regional analgesic techniques may be used for the effective treatment of postoperative pain. In general, the analgesia provided by epidural and peripheral techniques (particularly when local anesthetics are used) is superior to that with systemic opioids,[73] and use of these techniques may even reduce morbidity and mortality.[10,74] However, as with all approaches, the risks and benefits should be compared, especially regarding the controversies about the use of these techniques in the presence of various anticoagulants.

Single-Dose Neuraxial Opioids

Administration of a single dose of opioid may be efficacious as a sole or adjuvant analgesic drug when administered intrathecally or epidurally. One of the most important factors in determining the clinical pharmacology for a particular opioid is its degree of lipophilicity (versus hydrophilicity) (Table 98-3). Once they have reacted the cerebrospinal fluid (CSF) through direct intrathecal injection or gradual migration from the epidural space, hydrophilic opioids (i.e., morphine and hydromorphone) tend to remain within the CSF and produce a delayed but longer duration of analgesia, along with a generally more frequent incidence of side effects because of the cephalic or supraspinal spread of these compounds. Neuraxial administration of lipophilic opioids, such as fentanyl and sufentanil, provides a rapid onset of analgesia, and their rapid clearance from CSF may limit cephalic spread and the development of certain side effects such as delayed respiratory depression. The site of analgesic action for hydrophilic opioids is overwhelmingly spinal, but the primary site of action (spinal versus systemic) for single-dose neuraxial lipophilic opioids is not as certain.[75]

TABLE 98-3 **PROPERTIES OF NEURAXIAL OPIOIDS**

Property	Lipophilic Opioids	Hydrophilic Opioids
Common drugs	Fentanyl, sufentanil	Morphine, hydromorphone
Onset of analgesia	Rapid onset (5-10 min)	Delayed onset (30-60 min)
Duration of analgesia*	Shorter duration (2-4 hr)	Longer duration (6-24 hr)
CSF spread	Minimal CSF spread	Extensive CSF spread
Site of action	Spinal ± systemic	Primarily spinal ± supraspinal
Side effects		
Nausea and vomiting	Lower incidence with lipophilic than with hydrophilic opioids	
Pruritus	Lower incidence with lipophilic than with hydrophilic opioids	
Respiratory depression	Primarily early; minimal delay	Both early (<6 hr) and delayed (>6 hr) possible

CSF, Cerebrospinal fluid.
*The duration of analgesia varies.

The differences in pharmacokinetics between lipophilic and hydrophilic opioids may influence the choice of opioid in an attempt to optimize analgesia and minimize side effects for a particular clinical situation. Single-dose intrathecal administration of a lipophilic opioid may be useful in situations (e.g., ambulatory surgical patients) in which rapid analgesic onset (minutes) combined with a moderate duration of action (<4 hours) and minimal risk of respiratory depression is needed.[76] Single-dose hydrophilic opioid administration provides effective postoperative analgesia and may be useful in patients monitored on an inpatient basis, for whom a longer duration of analgesia would be beneficial.

Single-dose epidural administration of lipophilic and hydrophilic opioids is used to provide postoperative analgesia, with considerations generally being similar to those discussed for single-dose intrathecal administration of opioids. A single bolus of epidural fentanyl may be administered to provide rapid postoperative analgesia; however, diluting the epidural dose of fentanyl (typically 50 to 100 μg) in at least 10 mL of preservative-free normal saline will decrease the onset and prolong the duration of analgesia, possibly as a result of an increase in initial spread and diffusion of the lipophilic opioid. Single-dose epidural morphine is effective for postoperative analgesia, and use of a single-dose hydrophilic opioid may be especially helpful in providing postoperative epidural analgesia when the epidural catheter's location is not congruent with the surgical incision (e.g., lumbar epidural catheter for thoracic surgery). Smaller doses of epidural morphine may be required for older patients and for thoracic catheter sites. Commonly used dosages for intrathecal and epidural administration of neuraxial opioids are provided in Table 98-4.

Recently introduced is an extended-release formulation of (single-dose) epidural morphine encapsulated within liposomes that results in up to 48 hours of analgesia.[77] Some precautions are required in using this newer formulation of epidural morphine. To resuspend the particles immediately before withdrawal from the vial, the vial should be gently inverted (but aggressive or excessive agitation must be avoided). Concurrent administration of liposomal extended-release morphine and local anesthetics may increase peak concentrations of morphine. Accordingly, the manufacturer has recommended that clinicians increase the interval between administration of local anesthetic (including test doses) and liposomal extended-release morphine to at least 15 minutes to minimize this pharmacokinetic interaction. In addition, because the liposomal extended-release morphine does not contain any bacteriostatic agents, it should be administered within 4 hours after withdrawal from the vial. Finally, as with traditional single-dose neuraxial opioids, clinicians should administer a smaller dose of liposomal extended-release morphine to older patients or those with decreased physiologic reserve or coexisting disease.

At this time, liposomal extended-release morphine has not been studied or approved in pediatric patients.

Continuous Epidural Analgesia

Analgesia delivered through an indwelling epidural catheter is a safe and effective method for management of acute postoperative pain.[78] Postoperative epidural analgesia can provide analgesia superior to that with systemic opioids (Fig. 98-2).[79,80] Of note, however, *epidural analgesia* is not a generic term but incorporates a wide range of options, including the choice and dose of analgesic agents, location of catheter placement, and onset and duration of perioperative use.[78] Although this section focuses on the postoperative management of epidural analgesia, intraoperative use of the epidural catheter as part of a combined epidural-general anesthetic technique results in less pain and faster patient recovery immediately after surgery than general anesthesia followed by systemic opioids does.[81] Each of these options may affect the quality of postoperative analgesia, patient-reported outcomes, and even rates of morbidity and mortality.

Analgesic Drugs

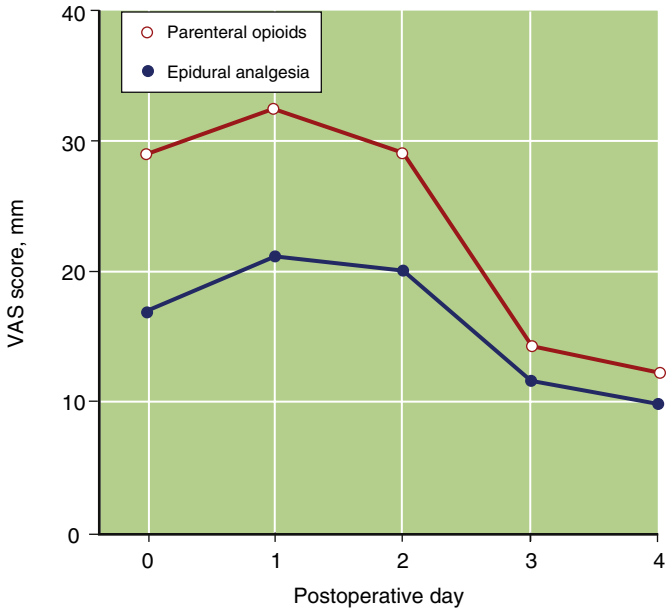
Local Anesthetics. Epidural infusion of local anesthetic alone may be used for postoperative analgesia, but in general it is not as effective in controlling pain as local anesthetic–opioid epidural analgesic combinations are.[79,80] The precise location of action of local anesthetics in the epidural space is not clear, and potential sites include the spinal nerve roots, dorsal root ganglion, or spinal cord itself.[75] Epidural infusion of local anesthetic alone may be warranted for postoperative analgesia in an attempt to avoid opioid-related side effects; however, the sole use of local anesthetics is less common than the use of a local anesthetic–opioid combination because of a significant failure rate (from regression of sensory blockade and inadequate analgesia) and relatively high incidence of motor block and hypotension.[78]

Opioids for Epidural Infusion. Opioids may be used alone for postoperative epidural infusion and do not generally cause motor block or hypotension from sympathetic blockade.[78] There are differences between continuous

TABLE 98-4 **DOSING OF NEURAXIAL OPIOIDS***

Drug	Intrathecal or Subarachnoid Single Dose	Epidural Single Dose	Epidural Continuous Infusion
Fentanyl	5-25 μg	50-100 μg	25-100 μg /hr
Sufentanil	2-10 μg	10-50 μg	10-20 μg /hr
Alfentanil	—	0.5-1 mg	0.2 mg/hr
Morphine	0.1-0.3 mg	1-5 mg	0.1-1 mg/hr
Hydromorphone	—	0.5-1 mg	0.1-0.2 mg/hr
Extended-release morphine†	Not recommended	5-15 mg	Not recommended

*Doses are based on the use of a neuraxial opioid alone. No continuous intrathecal or subarachnoid infusions are provided. Lower doses may be effective when administered to older patients or when injected in the cervical or thoracic region. Units vary across agents for single dose (mg versus μg) and continuous infusion (mg/hr versus μg/hr).
†See package insert for details on dosage and administration.



No. of patient observations					
Parenteral opioids	1104	2635	1496	794	536
Epidural analgesia	1010	2618	1527	822	566

Figure 98-2. Mean and standard deviation of visual analogue pain scores (*y* axis) for both epidural analgesia (represented by *dark blue circles*) and parenteral opioids (represented by *open red circles*) for each postoperative day (*x* axis) up to the fourth day after surgery. *(From Block BM, Liu SS, Rowlingson AJ, et al: Efficacy of postoperative epidural analgesia: a meta-analysis,* JAMA *290:2455-2463, 2003, with permission.)*

epidural infusion of lipophilic (e.g., fentanyl, sufentanil) and hydrophilic (e.g., morphine, hydromorphone) opioids. The analgesic site of action (spinal versus systemic) of continuous epidural infusion of lipophilic opioids is not clear. Although some data suggest a benefit from epidural (versus intravenous) infusion of lipophilic opioids,[82] the overall advantage of administering continuous epidural infusion of lipophilic opioids alone is marginal.[78]

The analgesic site of action for continuous hydrophilic opioid infusion is primarily spinal. Continuous infusion of a hydrophilic opioid may be especially useful for providing postoperative analgesia when the site of catheter insertion is not congruent with the site of surgery or when side effects (e.g., hypotension, motor block) are attributed to the epidural local anesthetic. Use of a continuous infusion rather than intermittent boluses of epidural morphine may result in superior analgesia with fewer side effects. Continuous epidural infusion of hydrophilic opioids may provide analgesia superior to that of traditional PRN administration of systemic opioids.

Local Anesthetic–Opioid Combinations. Use of a local anesthetic and an opioid in an epidural infusion may have advantages over infusions consisting of a local anesthetic or opioid alone. When compared with a local anesthetic or opioid alone, a local anesthetic–opioid combination provides superior postoperative analgesia (including improved dynamic pain relief), limits regression of sensory blockade, and possibly decreases the dose of local anesthetic administered, although the effect on the incidence is uncertain.[78] Continuous epidural infusion of a local anesthetic–opioid combination also provides analgesia superior to that of intravenous PCA with opioids.[79] It is unclear whether the analgesic effect of the local anesthetic and opioid in epidural analgesia is additive or synergistic. The choice of local anesthetic for continuous epidural infusion varies. In general, bupivacaine, ropivacaine, or levobupivacaine is chosen because of the differential and preferential clinical sensory blockade with minimal impairment of motor function. Concentrations used for postoperative epidural analgesia are lower than those used for intraoperative anesthesia. The choice of opioid also varies, although many clinicians prefer a lipophilic opioid (e.g., fentanyl, sufentanil) to allow rapid titration of analgesia.[78] Use of a hydrophilic opioid (morphine, hydromorphone) as part of a local anesthetic–opioid epidural analgesic regimen may also provide effective postoperative analgesia. The optimal local anesthetic and opioid dose that provides the lowest pain scores with the fewest medication-related side effects is unknown and further investigation is needed to determine the optimal combinations for other types of surgical procedures with different epidural catheter insertion sites and to compare the efficacy of these optimal continuous infusions with patient-controlled epidural analgesia (PCEA).

Adjuvant Drugs. A variety of adjuvants may be added to epidural infusions to enhance analgesia while minimizing side effects, but none has gained widespread acceptance. Two of the more studied adjuvants are clonidine and epinephrine. Clonidine mediates its analgesic effects primarily through the spinal dorsal horn α_2-receptors on primary afferents and interneurons, as well as the descending noradrenergic pathway, and the epidural dose typically used ranges from 5 to 20 μg/hr.[83,84] Clinical application of clonidine is limited by its side effects: hypotension, bradycardia, and sedation.[85] Hypotension and bradycardia are both dose dependent. Epinephrine may improve epidural analgesia, can increase sensory blockade, and is generally administered at a concentration of 2 to 5 μg/mL.[86,87] Epidural administration of NMDA antagonists, such as ketamine, can theoretically be useful in attenuating central sensitization and potentiating the analgesic effect of epidural opioids, but additional safety and analgesic data are needed.

Location of Catheter Insertion

Insertion of the epidural catheter congruent to the incisional dermatome (i.e., catheter-incision–congruent analgesia) (Table 98-5) results in optimal postoperative epidural analgesia by infusing analgesics to the appropriate incisional dermatomes, providing superior analgesia, minimizing side effects (e.g., lower extremity motor block and urinary retention), and decreasing morbidity.[10,78] When compared with catheter-incision–congruent epidural analgesia, catheter-incision–incongruent epidural analgesia (e.g., low lumbar catheter placement for thoracic procedures) results in increased pain and early removal of the epidural catheter because of ineffective analgesia. By targeting delivery of analgesic drugs to the appropriate dermatomes, catheter-incision–congruent epidural analgesia may result in smaller drug requirements and decreased medication-related side effects. Incidence of lower extremity motor block is more frequent with the use of lumbar epidural catheters, and an earlier-than-anticipated termination of

TABLE 98-5 **RECOMMENDED CATHETER INSERTION SITES FOR SURGICAL PROCEDURES**

Location of Incision	Examples of Surgical Procedures	Congruent Epidural Catheter Placement
Thoracic	Lung reduction, radical mastectomy, thoracotomy, thymectomy	T4-8
Upper abdominal	Cholecystectomy, esophagectomy, gastrectomy, hepatic resection, Whipple procedure	T6-8
Middle abdominal	Cystoprostatectomy, nephrectomy	T7-10
Lower abdominal	Abdominal aortic aneurysm repair, colectomy, radical prostatectomy, total abdominal hysterectomy	T8-11
Lower extremity	Femoral-popliteal bypass, total hip or total knee replacement	L1-4

L, Lumbar level; *T,* thoracic level.

epidural analgesia may also result.[88] Use of a high thoracic epidural for abdominal or thoracic surgery does not inhibit sympathetic nerve activity in the lower extremities and may result in a relatively infrequent incidence of urinary retention, thus diminishing the need for routine bladder catheterization.[83] Placement of thoracic epidural catheters is relatively safe, and a more frequent incidence of neurologic complications is not documented with placement of a thoracic (versus lumbar) epidural catheter. Furthermore, the benefits of epidural analgesia in decreasing morbidity in patients undergoing abdominal and thoracic surgery are seen only with thoracic (congruent), not lumbar (incongruent), epidural catheter placement.[84]

Side Effects of Neuraxial Analgesic Drugs

Many medication-related (opioid and local anesthetic) side effects can occur with the use of postoperative epidural analgesia, but before automatically ascribing the cause to the epidural analgesic regimen, other causes should be considered, such as small intravascular volume, bleeding, and low cardiac output, leading to hypotension and cerebrovascular accident, pulmonary edema, and evolving sepsis, leading to respiratory depression. Standing orders and nursing protocols for analgesic regimens, neurologic monitoring, treatment of side effects, and physician notification about critical variables should be standard for all patients receiving neuraxial and other types of postoperative analgesia (see Box 98-1).

Hypotension. The local anesthetics used in an epidural analgesic regimen may block sympathetic fibers and contribute to postoperative hypotension. Although the incidence of postoperative hypotension with postoperative epidural analgesia may be as frequent as approximately 7%, the average may be closer to 0.7% to 3%.[78,89] A systematic review of studies investigating postoperative analgesia found a mean (95% CI) incidence of hypotension for epidural analgesia of 5.6% (3.0% to 10.2%).[32] Strategies to treat noncritical hypotension caused by epidural analgesia include decreasing the overall dose of local anesthetic administered (by decreasing the rate or concentration), infusing an opioid epidural alone because it is unlikely that neuraxial opioid administration would contribute to postoperative hypotension, and treating the underlying cause of the decrease in blood pressure.[78]

Motor Block. Use of local anesthetics for postoperative epidural analgesia may also contribute to lower extremity motor block in approximately 2% to 3% of patients,[78,89] and this may lead to the development of pressure sores in the heels.[90] A meta-analysis noted a mean incidence of motor block of 3.2% with PCEA.[79] A lower concentration of local anesthetic and catheter-incision–congruent placement of epidural catheters for abdominal or thoracic procedures may decrease the incidence of motor block. Although motor block resolves in most cases after stopping the epidural infusion for approximately 2 hours, persistent or increasing motor block should be evaluated promptly, and spinal hematoma, spinal abscess, and intrathecal catheter migration should be considered as part of the differential diagnosis.[78]

Nausea and Vomiting. Nausea and vomiting associated with neuraxial administration of single-dose opioid occurs in up to 50% of patients, and the cumulative incidence in those receiving continuous infusions of opioid may be as high as 80%. The overall data (neuraxial opioids and/or local anesthetic combined) suggest that the incidence of postoperative vomiting is similar between epidural analgesia and systemic opioids, although female patients will exhibit a more frequent incidence regardless of analgesic modality.[91] The incidence of neuraxial opioid–related nausea and vomiting may be dose dependent, although a recent meta-analysis suggested that a larger dose (≥0.3 mg) of intrathecal morphine did not increase the risk of postoperative nausea or vomiting compared with a smaller dose (<0.3 mg) of intrathecal morphine.[92] Nausea and vomiting from neuraxial opioids may be related to the cephalad migration of opioid within the CSF to the area postrema in the medulla. Use of fentanyl alone or in combination with a local anesthetic in an epidural infusion is associated with less frequent incidence of nausea and vomiting than are infusions of morphine. A variety of drugs have been used successfully to treat neuraxial opioid–induced nausea and vomiting, including naloxone, droperidol, metoclopramide, dexamethasone, ondansetron, and transdermal scopolamine.[93,94]

Pruritus. Pruritus is one of the most common side effects of epidural or intrathecal administration of opioids, with an incidence of approximately 60% versus about 15% to 18% for epidural local anesthetic administration or systemic opioids.[95] A systematic review of studies investigating postoperative analgesia found a mean (95% CI) incidence of pruritus for epidural analgesia of 16.1% (12.8% to 20%) versus 13.8% (10.7% to 17.5%) for intravenous opioid PCA.[91] Although the cause of neuraxial opioid–induced pruritus is uncertain, peripheral histamine release is not the cause but may be related to central activation of an "itch center" in the medulla or activation of opioid receptors in the trigeminal nucleus or nerve roots with cephalad migration of the opioid. It is unclear whether the incidence of neuraxial opioid–related pruritus is dose dependent because a quantitative systematic review[95] suggested no evidence of a relationship, whereas other clinical and experimental studies have indicated a significant correlation.[96] Many drugs have been evaluated for the prevention and treatment of opioid-induced pruritus, which can be difficult to manage and quite bothersome for some patients. Intravenous naloxone, naltrexone, nalbuphine, and droperidol appear to be efficacious for the pharmacologic control of opioid-induced pruritus.[95] Meta-analysis has shown that serotonin receptor antagonists may also be an effective modality in the prevention of neuraxial opioid-induced pruritus.[94] The use of epidural morphine is associated with postpartum reactivation of herpes simplex labialis.

Respiratory Depression. Neuraxial opioids used in appropriate doses are not associated with a more frequent incidence of respiratory depression than that seen with systemic administration of opioids. The incidence

of respiratory depression with neuraxial administration of opioids is dose dependent and typically ranges from 0.1% to 0.9%. The incidence of respiratory depression with neuraxial opioids is no more frequent than that seen after systemic opioid administration. The incidence of respiratory depression, as defined by a slow respiratory rate, should be less than 1%.[32] The precise incidence of respiratory depression in actual clinical practice may be difficult to determine because many criteria (e.g., respiratory rate, oxygen saturation, partial pressure of carbon dioxide, and need to administer respiratory stimulants/reversal drugs) have been used to define respiratory depression.[32] Neuraxial lipophilic opioids cause less delayed respiratory depression than do hydrophilic opioids, although administration of lipophilic opioids may cause early significant respiratory depression. Delayed respiratory depression is primarily associated with the cephalad spread of hydrophilic opioids, which typically occurs within 12 hours after injection of morphine. Risk factors for respiratory depression with neuraxial opioids include increasing dose, increasing age, concomitant use of systemic opioids or sedatives, possibly prolonged or extensive surgery, and the presence of comorbid conditions (e.g., obstructive sleep apnea). Clinical assessments, such as the respiratory rate, may not reliably predict a patient's ventilatory status or impending respiratory depression. Treatment with naloxone (and airway management if necessary) is effective in 0.1- to 0.4-mg increments; however, because its clinical duration of action is relatively short in comparison with the respiratory depressant effect of neuraxial opioids, continuous infusion of naloxone (0.5 to 5 μg/kg/hr) may be needed.[97] Although perioperative single-dose extended-release epidural morphine (versus intravenous opioid PCA) may be effective for postoperative pain relief for up to 48 hours, respiratory depression may be more likely.[98] Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration have been published.[99]

Urinary Retention. Urinary retention associated with the neuraxial administration of opioids is the result of an interaction with opioid receptors in the spinal cord that decreases the detrusor muscle's strength of contraction. The incidence of urinary retention is more frequent with neuraxially administered opioids than when given systemically. Urinary retention does not depend on the opioid dose and may be treated with the use of low-dose naloxone, although at the risk of reversing the analgesic effect. Urinary retention occurred in 23.0% of patients, with the most frequent rate in those receiving epidural analgesia.[91] Another review of the literature found an overall incidence of urinary retention of 9%.[100] However, the exact incidence of urinary retention seen clinically may be difficult to determine because patients who undergo major surgical procedures are often routinely catheterized.

Patient-Controlled Epidural Analgesia

Epidural analgesia has traditionally been delivered at a fixed rate or as a continuous epidural infusion (CEI); however, the administration of epidural analgesia through a patient-controlled device (PCEA) has become more common. Like intravenous PCA, PCEA allows individualization of postoperative analgesic requirements and may have several advantages over CEI, including lower drug use and better patient satisfaction. PCEA may also provide analgesia superior to that afforded by intravenous PCA.[79]

PCEA is a relatively safe and effective technique for postoperative analgesia on routine surgical wards. Observational data from two series of over 1000 patients each reveal that more than 90% of patients with PCEA receive adequate analgesia, with a median pain score of 1 (of a possible 10) at rest and 4 with activity.[89,101] The incidence of side effects is 1.8% to 16.7% for pruritus, 3.8% to 14.8% for nausea, 13.2% for sedation, 4.3% to 6.8% for hypotension, 0.1% to 2% for motor block, and 0.2% to 0.3% for respiratory depression.[89,101] These rates are favorable and comparable to those reported with CEI.

The optimal PCEA analgesic solution and delivery parameters are unclear. Use of a continuous or background infusion in addition to the demand dose is more common with PCEA than with intravenous PCA and may provide analgesia superior to that with the use of a demand dose alone.[102] In general, most acute pain specialists have gravitated toward a variety of low-concentration local anesthetic–opioid combinations (Table 98-6) in an attempt to improve analgesia while minimizing side effects, such as motor block and

TABLE 98-6 PATIENT-CONTROLLED EPIDURAL ANALGESIA REGIMENS

Analgesic Solution*	Continuous Rate (mL/hr)	Demand Dose (mL)	Lockout Interval (min)
General Regimens			
0.05% bupivacaine + 4 μg/mL fentanyl	4	2	10-20
0.0625% bupivacaine + 5 μg/mL fentanyl†	4-8	3-5	10-20
0.1% bupivacaine + 5 μg/mL fentanyl	6	2	10-20
0.2% ropivacaine + 5 μg/mL fentanyl	5	2	20
Thoracic Surgery			
0.0625%-0.125% bupivacaine + 5 μg/mL fentanyl†	3-4	2-3	10-20
Abdominal Surgery			
0.0625% bupivacaine + 5 μg/mL fentanyl†	4-8	3-5	10-20
0.125% bupivacaine + 0.5 μg/mL sufentanil	3-5	2-3	10-20
0.1%-0.2% ropivacaine + 2 μg/mL fentanyl	3-5	2-5	10-20
Lower Extremity Surgery			
0.0625%-0.125% bupivacaine + 5 μg/mL fentanyl†	4-8	3-5	10-20

*Regimens listed are samples of local anesthetic–lipophilic opioid combinations from the literature.
†Patient-controlled epidural analgesic regimens commonly used at the Johns Hopkins Hospital.

respiratory depression. As for CEI, addition of an opioid to the local anesthetic can provide analgesia superior to that with either analgesic alone. A lipophilic opioid is usually chosen because its rapid analgesic effect and shorter duration of action may be more suitable for use with PCEA.[89] Use of lower concentrations of a local anesthetic (e.g., bupivacaine, ropivacaine) may provide excellent analgesia without significant motor block.[103]

Benefits of Epidural Analgesia

Use of perioperative epidural anesthesia and analgesia, especially with a local anesthetic–based analgesic solution, can attenuate the pathophysiologic response to surgery and may be associated with a reduction in mortality and morbidity when compared with analgesia with systemically administered opioids.[10,11] Meta-analysis of randomized data (141 trials enrolling 9559 subjects) found that perioperative use of neuraxial anesthesia and analgesia (versus general anesthesia and systemic opioids) reduced overall mortality (primarily in orthopedic patients) by approximately 30%.[104] Use of epidural analgesia can decrease the incidence of postoperative gastrointestinal, pulmonary, and possibly cardiac complications.[10,74]

By inhibiting sympathetic outflow, decreasing the total opioid dose, and attenuating spinal reflex inhibition of the gastrointestinal tract, postoperative thoracic epidural analgesia can facilitate return of gastrointestinal motility without contributing to anastomotic bowel dehiscence.[74,105] Randomized clinical trials demonstrate that use of postoperative thoracic epidural analgesia with a local anesthetic–based analgesic solution allows earlier return of gastrointestinal function and fulfillment of discharge criteria.[106] When compared with those who receive epidural opioids for postoperative analgesia, patients who receive epidural local anesthetics have an earlier return of gastrointestinal motility after abdominal surgery.[106]

Perioperative use of epidural analgesia with a local anesthetic–based regimen in patients undergoing abdominal and thoracic surgery decreases postoperative pulmonary complications,[107,108] presumably by preserving postoperative pulmonary function through providing superior analgesia and thus reducing splinting behavior and attenuating the spinal reflex inhibition of diaphragmatic function.[74] A meta-analysis of 48 randomized clinical trials[109] and another large, randomized clinical trial[110] demonstrated that use of thoracic epidural analgesia with a local anesthetic–based regimen decreased the incidence of pulmonary infections and complications. However, patients who received postoperative epidural opioids, intercostal blocks, wound infiltration, or intrapleural analgesia did not have a significant decrease in the incidence of pulmonary complications.[109] A subsequent meta-analysis confirmed the benefits of thoracic epidural analgesia in decreasing perioperative pulmonary complications.[111]

Use of postoperative thoracic, but not lumbar epidural analgesia may decrease the incidence of postoperative myocardial infarction,[84] possibly by attenuating the stress response and hypercoagulability, improving postoperative analgesia, and providing favorable redistribution of coronary blood flow.[74] The finding that only thoracic epidural analgesia decreases the incidence of postoperative myocardial infarction corroborates experimental data on the physiologic benefits of thoracic epidural analgesia, such as a reduction in the severity of myocardial ischemia or size of infarction, attenuation of sympathetically mediated coronary vasoconstriction, and improvement of coronary flow to areas at risk for ischemia.[74] The use of thoracic epidural analgesia in patients undergoing cardiac surgery decreased in the risk of postoperative supraventricular arrhythmias and respiratory complications.[112]

Although postoperative epidural analgesia decreases postoperative gastrointestinal, pulmonary, and possibly cardiac morbidity, the benefits of postoperative epidural analgesia are not as evident in other areas, such as postoperative coagulation, cognitive dysfunction,[113] and immune function. Although the use of *intra*operative regional anesthesia decreases the incidence of hypercoagulable-related events (e.g., deep venous thrombosis, pulmonary embolism, vascular graft failure),[104] *post*operative epidural analgesia does not obviously decrease the incidence of hypercoagulable-related events.

The benefits of postoperative epidural analgesia are optimized when the epidural catheter is inserted in a location corresponding to the dermatomes covered by the surgical incision (i.e., catheter-incision–congruent analgesia), which results in a smaller dose of drug administered and decreased incidence of drug-induced side effects, such as pruritus, nausea, vomiting, urinary retention, motor block, and hypotension.[89] When compared with catheter-incision–incongruent epidural analgesia, catheter-incision–congruent analgesia provides earlier return of gastrointestinal function, a lower incidence of myocardial infarction,[84] and superior analgesia.[74] The ability of postoperative epidural analgesia to attenuate postoperative pathophysiology and improve outcomes also depends on the type of drugs used (opioids versus local anesthetics). Maximal attenuation of perioperative pathophysiology occurs with the use of a local anesthetic–based epidural analgesic solution. The use of a local anesthetic–based (versus opioid-based) analgesic solution is associated with earlier recovery of gastrointestinal motility after abdominal surgery[106] and less frequent occurrence of pulmonary complications.[109] Epidural analgesia is not a generic entity because different catheter locations and analgesic regimens may differentially affect perioperative morbidity.

It is unclear whether perioperative epidural analgesia may improve patient-reported outcomes.[114] Use of postoperative epidural analgesia may be associated with an improvement in postoperative analgesia and patient-reported outcomes such as patient satisfaction[31] and HRQL.[16] When compared with systemic opioids, epidural local anesthetics consistently provide superior analgesia.[79,80] Although the concept of satisfaction is complex and difficult to measure accurately, the analgesic benefits of postoperative epidural analgesia may contribute to greater patient satisfaction[31] and improved HRQL.[16]

A link may exist between the perioperative use of regional anesthesia/analgesia and a decrease in cancer

recurrence.[115] There are several hypothetical reasons why the perioperative use of regional anesthesia and analgesia would be of benefit in patients undergoing cancer surgery, including attenuation of perioperative immunosuppression and decreased use of inhaled anesthetics/opioids. A regional anesthetic-induced sympathectomy should increase blood flow to the extremities with subsequent improvement in tissue oxygenation and a potential favorable local anesthetic effect on tumor cell killing.[116] However, multiple factors may potentially affect cancer recurrence, and the impact of perioperative regional analgesic techniques on a long-term outcome such as cancer recurrence is uncertain at this time. Use of neuraxial anesthesia/analgesia for total hip or knee replacement may decrease the risk of surgical site infections compared with general anesthesia.[117]

Risks With Epidural Analgesia

The benefits of perioperative epidural anesthesia-analgesia must be weighed against the risks associated with this technique. Some complications are associated with placement of an epidural catheter, and several risks related to the use of indwelling epidural catheters (e.g., epidural hematoma and abscess) should be discussed in the context of postoperative epidural analgesia. A review of neurologic complications after regional anesthesia revealed that the rate of neurologic complications after central neuraxial blockade is less than 4 in 10,000 (0.04%); the rate of neuropathy after a peripheral nerve block is less than 3 in 100 (3%).[118] However, permanent neurologic injury after either central neuraxial or peripheral nerve block is rare in contemporary anesthetic practice.[118] Elements of routine monitoring of patients receiving neuraxial analgesia are presented in Box 98-1.

The concurrent use of anticoagulants and neuraxial anesthesia and analgesia has always been a relatively controversial issue but has been highlighted over the past decade by the increased incidence of spinal hematoma after the introduction of low-molecular-weight heparin in North America in 1993.

Different types and classes of anticoagulants have different pharmacokinetic properties that affect the timing of neuraxial catheter or needle insertion and catheter removal. Despite many observational and retrospective studies investigating the incidence of spinal hematoma in the setting of various anticoagulants and neuraxial techniques, no definitive conclusion regarding the absolute safety of neuraxial anesthesia and anticoagulation has been reached. The American Society of Regional Anesthesia and Pain Medicine (ASRA) lists a series of guidelines based on the available literature for administration (insertion and removal) of neuraxial techniques in the presence of various anticoagulants, including oral anticoagulants (warfarin), antiplatelet agents, fibrinolytics-thrombolytics, standard unfractionated heparin, and low-molecular-weight heparin.[119] The ASRA guidelines recommend that the timing of neuraxial needle or catheter insertion or removal reflect the pharmacokinetic properties of the specific anticoagulant. Frequent neurologic monitoring is essential. Concurrent use of multiple anticoagulants may increase the risk of bleeding, and the analgesic regimen should be tailored to facilitate neurologic monitoring, which may be continued in some cases for 24 hours after removal of the epidural catheter. Although the ASRA guidelines were developed with the latest available literature, these guidelines are limited by the relatively rare incidence of epidural hematoma; observational studies have occurred, during which procedures (e.g., epidural catheter removal) were performed outside the boundaries presented in the ASRA guidelines.[120] An updated version of the ASRA guidelines on neuraxial anesthesia and anticoagulation[119] can be found on the ASRA website (www.asra.com), and some of these statements address the newer anticoagulants. Anesthesiology societies outside North America have also put forth their own guidelines for regional anesthesia and different anticoagulants.[121] Finally, the risk of epidural hematoma may be different for obstetric versus surgical patients.[122,123]

Infection associated with postoperative epidural analgesia may result from exogenous or endogenous sources.[78] Serious infections (e.g., meningitis, spinal abscess) associated with epidural analgesics are rare (<1 in 10,000),[124] although a more frequent incidence has been observed (approximately 1 in 1000 to 2000).[124] Closer examination of the studies that reported a more frequent incidence of epidural abscess reveals that the patients had a relatively longer duration of epidural analgesia or coexisting immunocompromising or complicating diseases (e.g., malignancy, trauma).[78] Use of epidural analgesia in the general surgical population with a typical duration of postoperative catheterization (approximately 2 to 4 days) is not generally associated with epidural abscess formation.[89] Even though serious infectious complications are rare after short-term (<4 days) epidural infusions, there may be a relatively more frequent incidence of superficial inflammation or cellulitis (4% to 14%) and an even higher rate of catheter colonization (20% to 35%), with the proportion of positive cultures increasing with longer duration of catheterization; however, the catheter colonization rate may not be a good predictor of infection of the epidural space.[125] A practice advisory from the American Society of Anesthesiologists discussing the prevention, diagnosis, and management of infectious complications associated with neuraxial techniques has been published.[126]

Although epidural analgesia may provide superior postoperative analgesia, migration of the epidural catheter out of the epidural space and into the intrathecal, intravascular, or subcutaneous space decreases the effectiveness of this technique. The failure rate (i.e., earlier-than-anticipated discontinuation of the catheter for any reason, placement of a nonfunctioning epidural catheter or "shamdural") ranges from approximately 6% to 25%, with many centers reporting a rate between 10% and 20%, but the incidence of actual premature epidural catheter dislodgment may be less frequent (mean, 5.7%; 95% CI, 4.0% to 7.4%).[73,89] Fortunately, the rate of intrathecal and intravascular migration of an epidural catheter is most likely much less frequent than the failure rate. Despite the less frequent occurrence of intravascular and intrathecal migration of postoperative epidural catheters, use of an epinephrine-containing test dose, administration of local anesthetic in fractionated doses, and aspiration of the catheter before

bolus administration of local anesthetics may prevent complications (e.g., high or total spinal, seizures, neurotoxicity).[78] The issue of whether lower extremity compartment syndrome can be consistently masked by the use of a local anesthetic–based epidural analgesic regimen is unresolved because use of systemic opioid analgesia has also been associated with a delayed diagnosis of compartment syndrome.[127]

Peripheral Regional Analgesia

The use of peripheral regional analgesic techniques as a single injection or continuous infusion can provide analgesia superior to that with systemic opioids[128] and may even result in improvement in some outcomes.[129] A variety of wound infiltration and peripheral regional techniques (e.g., brachial plexus, lumbar plexus, femoral, sciatic-popliteal, and scalp nerve blocks) can be used to enhance postoperative analgesia. Peripheral regional techniques may have several advantages over systemic opioids (e.g., superior analgesia and decreased opioid-related side effects) and neuraxial techniques (e.g., decreased risk for spinal hematoma).[130]

A one-time injection of local anesthetic for peripheral regional techniques may be used primarily for intraoperative anesthesia or as an adjunct to postoperative analgesia. When compared with placebo, peripheral nerve blocks with local anesthetics provide superior analgesia and are associated with reduced opioid use, decreased opioid-related side effects, and improvement in patient satisfaction.[130] The duration of postoperative analgesia resulting from the local anesthetic in the peripheral nerve block varies but may last up to 24 hours after injection. An earlier systematic review indicated that local anesthetics may also provide effective wound infiltration analgesia postoperatively for a variety of procedures.[131] A more recent meta-analysis suggested that local anesthetic administered via wound catheters may not reduce pain intensity after surgery.[132]

Continuous infusions of local anesthetics can be administered through peripheral nerve catheters. Peripheral nerve catheters may be inserted by several methods, including nerve stimulation, ultrasound guidance, and paresthesia elicitation.[133] Randomized controlled trials suggest that use of peripheral regional analgesia may facilitate postoperative rehabilitation as evidenced by accelerated resumption of passive joint range-of-motion, decrease in time until discharge readiness, and earlier actual discharge from the hospital or rehabilitation center.[133,134] Continuous peripheral nerve blocks may be used in the outpatient (home) setting, typically using a portable ambulatory pump.[133] When compared with systemic opioids, use of continuous infusions or patient-controlled peripheral analgesia results in superior analgesia, decreased opioid-related side effects, and greater patient satisfaction.[128,130] The optimal parameters (i.e., local anesthetic, concentration, opioid, adjuvants, and continuous versus PCA versus intermittent boluses) for peripheral analgesia are still being determined.

Thoracic or Nonepidural Analgesia

Several nonepidural regional analgesic techniques can be used for the management of postoperative thoracic pain, including paravertebral and intercostal blocks, transversus abdominis plane blocks, interpleural (intrapleural) analgesia, and cryoanalgesia. The most promising technique appears to be a thoracic paravertebral block, which has been used for thoracic, breast, and upper abdominal surgery and for the treatment of rib fracture pain.[135] Possible sites of analgesia for a thoracic paravertebral block include direct somatic nerve, sympathetic nerve, and epidural blockade.[135] A thoracic paravertebral block can be administered as a single injection or as continuous infusion through a catheter; it may provide analgesia equal or superior to that with thoracic epidural analgesia and is a valuable alternative to thoracic epidural analgesia.[136,137] Paravertebral blocks may be especially useful in providing postoperative analgesia after breast surgery.[138] When compared with thoracic epidural analgesia, paravertebral analgesia has been shown to provide equivalent analgesia but with a better side effect profile (e.g., lower incidence of hypotension) and also a lower risk of postoperative pulmonary complications.[137,139] Continuous infusions of local anesthetics through a paravertebral catheter are preferable to intermittent boluses because the former is associated with lower pain scores.[140]

Transversus abdominis plane (TAP) nerve block is an approach for blocking the abdominal wall neural afferents to provide postoperative analgesia. Typically performed under ultrasound guidance, TAP blocks have been mostly described in adult patients (with some in pediatric patients) and used in a variety of surgical patients.[141,142] At least two systematic reviews indicate that TAP blocks may reduce postoperative morphine requirements, nausea and vomiting, and possibly the severity of pain after abdominal surgery.[143,144] Although superior early postoperative analgesia appears to occur (within 24 hours of surgery), the surgical procedures, analgesic dosing, techniques, and timing for optimal analgesia following TAP block need further examination.[141]

The analgesic efficacy and the mechanism of interpleural analgesia are no longer controversial (i.e., sensory or sympathetic block, or both). Interpleural analgesia is inferior to epidural and paravertebral analgesia for control of postoperative pain, preservation of lung function after thoracotomy, and reduction of postoperative pulmonary complications.[109] A recent systematic review demonstrated that intrapleural analgesia was inadequate for postoperative pain management.[139] Intercostal blocks may provide short-term postoperative analgesia and may be repeated postoperatively; however, the incidence of pneumothorax increases with each intercostal nerve blocked (1.4% per nerve, with an overall incidence of 8.7% per patient).[145] Like interpleural analgesia, intercostal blocks do not reduce the incidence of pulmonary complications postoperatively when compared with epidural analgesia.[109]

Intraarticular Analgesia

Local peripheral administration of opioids (e.g., intraarticular injection after knee surgery) may theoretically provide analgesia for up to 24 hours after surgery[146] and decrease the incidence of chronic pain[147] as peripheral opioid receptors are found on the peripheral terminals of primary afferent nerves and are up-regulated during

inflammation of peripheral tissues.[148] Results of the several randomized clinical trials investigating this topic have been summarized.[146] Use of a larger dose of intraarticular morphine (5 versus 1 mg) results in superior analgesia; however, there may be no advantage in the degree of analgesia provided between intraarticular and systemic opioids.[146] A subsequent qualitative systematic review found no evidence for analgesic effect of intraarticular morphine after knee arthroscopy.[149] A systemic effect of intraarticularly injected morphine cannot be excluded. A systematic review suggested that intraarticular administration of NSAIDs may provide clinically relevant peripheral analgesia.[150] Intraarticular injection of local anesthetics may provide a limited duration of postoperative analgesia, but the clinical benefit from intraarticular injection of local anesthetics is unclear.[151] Clinicians should be aware that there have been cases of glenohumeral chondrolysis reported in association with postarthroscopy infusion of local anesthetic.[152]

OTHER TECHNIQUES

Other nonpharmacologic techniques, such as transcutaneous electrical nerve stimulation (TENS), acupuncture, exercise/activity, and psychological approaches, can be used in an attempt to alleviate postoperative pain. The mechanism by which TENS produces analgesia is unclear but may be related to modulation of nociceptive impulses in the spinal cord, release of endogenous enkephalins, or a combination of these, and other mechanisms. Although the analgesic efficacy of these techniques is controversial, TENS and acupuncture may provide postoperative analgesia, decrease postoperative opioid requirements, reduce opioid-related side effects, and attenuate activation of the sympathoadrenal system. In general, all of these approaches to postoperative pain are relatively safe, noninvasive, and devoid of the systemic side effects seen with other analgesic treatment options.[153] TENS may be of benefit in providing postoperative analgesia and decreasing analgesic consumption.[154,155] Early mobilization and activity therapy improve functional outcomes following orthopedic surgical procedures[156] and are effective in reducing pain behaviors in animal models of surgical neuropathic pain. [157] Although some methodologic issues have been raised with many of the available trials and the precise role of these treatments in postoperative pain management is not clear, they represent alternative therapies to add to the clinician's armamentarium. In particular, exercise and activity programs are inexpensive and easily available therapies.

Although this chapter has focused on the neurobiology of nociception and pharmacologic treatments available for the treatment of postoperative pain, the experience of pain is complex, multifaceted, and "an unpleasant sensory and emotional experience," as defined in part by the International Association for the Study of Pain. The differential behavior response to surgical incision may be related to global (i.e., personality, gender, age, and culture) and specific (i.e., fear, depression, anger, and coping) psychological factors.[158] Cognitive therapy and behavior therapy may be efficacious in reducing pain and alleviating psychological factors associated with pain.[159] Identifying and addressing psychological factors can reduce pain, improve the efficacy of pharmacologic analgesics, and diminish patients' distress, in part through enhancement of the placebo effect.[158] Although it may have a psychological origin, the placebo response may exert part of its effects through activation of endogenous opioids and may be useful in reducing the intensity of pain.[160]

POSTOPERATIVE ANALGESIA IN SPECIAL POPULATIONS

The foregoing discussion has provided a general approach to the principles and practice of acute postoperative pain management, but this approach may need to be modified for certain populations that have unique anatomic, physiologic, pharmacologic, affective, and cognitive issues. Management of acute pain should be tailored to the specific needs of a particular population. Although each population could merit a separate chapter in some textbooks, this chapter outlines the general principles and issues associated with each population and provides references to other more extensive sources.

OPIOID-TOLERANT PATIENTS: PATIENTS WITH PREEXISTING PAIN

Opioid-tolerant patients can be categorized into three groups: (1) those who have chronic pain for which they receive opioid-based analgesic therapy, (2) those who use opioids recreationally as a result of a substance use disorder, and (3) those who take opioids for a combination of the first two reasons. Regardless of the reason the individual is using opioids, the management of their perioperative pain is considerably more challenging than those who are opioid-naive.

Even though there is no specific threshold or timeframe for when a patient becomes opioid tolerant, the U.S. Food and Drug Administration (FDA) has recently provided guidelines for defining the opioid-tolerant patient.[161] In summary, patients considered opioid tolerant are those who are regularly taking at least one of these: 60 mg oral morphine per day; 25 μg transdermal fentanyl per hour; 30 mg oral oxycodone per day; 8 mg oral hydromorphone per day; 25 mg oral oxymorphone per day; or an equianalgesic dose of another opioid for 1 week or longer.

Postoperative pain may be difficult to manage in opioid-tolerant patients because the standard approaches used for baseline assessment and assessment of response to therapy in opioid-naive or research patients are often less accurate for opioid-tolerant patients. Although opioid-tolerant patients require larger doses of analgesic medications (in addition to their baseline pain medication requirements) in the immediate postoperative period, many health care providers still do not provide adequate postoperative pain relief, in part because of the fear of addiction or medication-related side effects. In dealing with patients with chronic opioid use, health care providers often mistakenly interchange several pharmacologic terms (i.e., tolerance, physical dependence, and

addiction), a practice that may contribute to misunderstanding and inappropriate treatment decisions.

Tolerance refers to the pharmacologic property of an opioid in which an increasing amount is needed to maintain a given level of analgesia. *Physical dependence* is another pharmacologic property of opioids, characterized by the occurrence of a withdrawal syndrome on abrupt discontinuation of the opioid or administration of an antagonist. As pharmacologic properties, tolerance and physical dependence are not synonymous with the aberrant psychological state or behavior associated with *addiction*, a chronic disorder characterized by the compulsive use of a substance resulting in physical, psychological, or social harm to the user and continued use despite that harm. The exaggerated fear of addiction contributes to the undertreatment of postoperative pain by health care providers; however, minimal risk of iatrogenic addiction exists with the use of opioids for pain control in patients who do not have a prior history of addiction.[162,163]

Several principles of pain assessment and treatment can be applied to the postoperative management of opioid-tolerant patients. The physician should expect high self-reported pain scores. Treatment decisions should be based on objective pain assessment (e.g., ability to breathe deeply, cough, ambulate) in conjunction with patients' self-reported pain scores. Physicians should understand the need to identify and treat two major problems—maintenance of a basal opioid requirement and control of incisional pain. Finally, physicians should recognize that detoxification is not usually an appropriate goal in the perioperative period.[164-166]

The treatment of patients with prior opioid use requires the management of the expectations of the patient, the patient's family, and the physician's surgical colleagues. The goal of inpatient management of pain in patients with chronic pain or acute-on-chronic pain is to stabilize and rationalize (if necessary) the patient's outpatient pain medication regimen. The goal is not to treat long-standing persistent pain that has been managed on an outpatient basis, because it is unlikely in the very limited time period in which you are a member of the patient's care team that you will be able to make a substantial positive difference. Therefore, several general strategies can be used for the treatment of postoperative pain in an opioid-tolerant patient or in a patient with chronic pain who is receiving opioids. Although patients with chronic pain are not synonymous with opioid-tolerant patients, many of these patients are also opioid tolerant, and the same general principles and strategies discussed earlier may be applied to these patients as well. The physician can create a treatment plan early and discuss it with the patient, surgical team, and nursing staff; replace the patient's baseline or basal opioid requirements postoperatively; anticipate an increase in postoperative analgesic requirements[167]; maximize the use of adjuvant drugs; consider the use of regional analgesic techniques; and plan for the transition to an oral regimen. The physician, patient and other providers need to be aware that the nonopioid adjuvant medications (not including tramadol, NSAIDs, or acetaminophen) may be started while the patient is an inpatient, but they are unlikely to have substantial impact on the patient's chronic pain while hospitalized. Recognizing and addressing nonnociceptive sources of distress may be especially important for patients with chronic pain.[158]

Administration of a PRN analgesic regimen alone for opioid-tolerant patients is highly discouraged because replacing the basal opioid requirement in the postoperative period can optimize pain relief and possibly prevent opioid withdrawal. Basal opioid requirements can be administered systemically (typically intravenously) until the patient can tolerate an oral analgesic regimen.[28] For example, 50% to 100% of the patient's baseline opioid requirement can be administered by continuous infusion as part of an intravenous PCA regimen, with a demand dose to cover the additional incisional pain. Conversion tables (Table 98-7) may facilitate equianalgesic conversion of opioids (i.e., different routes of administration of one opioid or conversion between two different opioids); however, these tables provide only estimations to assist health care providers in initiating opioid titration.[168]

Opioid-tolerant patients generally require increased postoperative analgesic levels, including a larger demand dose.[28,167] Patients may need frequent adjustment (e.g., two to three times each day) of the intravenous PCA demand dose or continuous infusion, depending on the analgesic requirements. Response to different opioids varies by individual, and if a decision is made to switch opioids, the choice of opioid is probably not as important as using an equianalgesic dose. Patients may experience different side effects with different opioids, and rotating to another opioid may be reasonable if the patient is not tolerating the first opioid.[169] Adjuvant drugs such as NSAIDs should be administered on a regularly scheduled basis to optimize analgesic efficacy and possibly provide

TABLE 98-7 GUIDELINES FOR EQUIANALGESIC DOSING OF OPIOID AGONISTS

Drug	Relative Strength Compared With Morphine	Equianalgesic Dose (mg)	
		Oral	Parenteral
Morphine	--	30	10
Buprenorphine	Much much stronger	N/A	0.4 (7.5 µg/hr TD)
Butorphanol	Much stronger	N/A	2
Codeine	Weaker	200	125
Fentanyl	Much much stronger	N/A	0.1 (16.5 µg/hr TD)
Hydrocodone	Equivalent to mildly weaker	30	N/A
Hydromorphone	Much stronger	7.5	1.5
Levorphanol	Much stronger	4	N/A
Methadone	Stronger	10	5
Nalbuphine	Equivalent	N/A	10
Oxycodone	Stronger	20	N/A
Oxymorphone	Stronger	10	1
Pentazocine	Weaker	150	60
Tapentadol	Weaker	100	N/A
Tramadol	Much Weaker	300	N/A

Equianalgesic doses are approximate and intended to serve only as an estimate of opioid requirements. Actual doses may vary, in part because of wide interpatient variability in response to opioids. Doses should be individualized and gradually titrated to effect. *TD*, Transdermal.

an opioid-sparing effect. Use of regional analgesic techniques with neuraxial opioids may provide excellent analgesia in opioid-tolerant patients while theoretically preventing withdrawal symptoms, although the clinician should be prepared to diagnose and treat perioperative opioid withdrawal in these patients.

After the patient is tolerating oral intake, conversion from intravenous opioids to oral form that would be more suitable for discharge home may be initiated. Opioid-tolerant patients can generally be converted to a combination of a regularly administered, controlled-release formulation of opioid (i.e., sustained-release morphine) and a short-acting, immediate-release opioid on a PRN basis. Although conversion of intravenous opioid to an oral form can be accomplished over a period of 1 to 2 days in opioid-tolerant patients, this process may take several days in extremely difficult cases. In patients with a relatively high basal requirement of intravenous opioid (e.g., high, continuous background infusion of intravenous opioid PCA), clinicians should be aware not to abruptly discontinue the intravenous infusion of opioid during this transition but ideally decrease the high basal requirement of intravenous opioid in a stepwise fashion to account for the slower onset of the sustained release. Converting from an intravenous to an oral form of opioid is not an exact science, and the conversion tables available can serve only as a rough guide because of significant interpatient and intrapatient variability in the sensitivity to opioids, lack of complete cross-tolerance between opioids (which may lead to greater than anticipated potency of a new opioid), and changes in the level of pain, which may rapidly decrease in the immediate postoperative period.[168] Because of these factors, conversion of approximately 50% to 75% of the equianalgesic dose to a sustained-release preparation of opioid or a transdermal fentanyl patch, with the remainder converted to a short-acting opioid delivered on a PRN basis, may be a reasonable starting point in patients whose pain is reasonably controlled, although additional titration may be necessary.

Although opioids are most commonly used in these patients, with consultation of the inpatient pain services (if available), the physicians can consider the use of analgesic (low-dose) ketamine.[170] Ketamine can be given as a basal infusion as a part of the ketamine PCA or a combination ketamine and opioid PCA, subcutaneously, or orally. Ketamine may have significant advantages (such as greater analgesic response, less frequent rates of respiratory depression, and minimal impact on the gastrointestinal system) over further opioid use in the opioid-tolerant or chronic pain patient in the postoperative setting.

Patients taking medications containing buprenorphine have some challenges similar to those of opioid-tolerant or chronic pain patients in the perioperative setting, but these patients also have the added difficulties associated with the partial μ-opioid agonist pharmacodynamics of buprenorphine. Although buprenorphine is a partial agonist, when given in conjunction with a full μ-opioid agonist, it functions as a pharmacologic antagonist. Further, with buprenorphine, the time to dissociation from the opioid receptor is variable; therefore, when used in combination with a full agonist, it is challenging to time the switch from antagonism of the μ-opioid receptor action to the full agonism of the morphine, oxycodone, hydromorphone, and other similar opioids. This can create a dangerous situation in which a previously appropriate dosage of one of the full agonists becomes enough to result in respiratory depression or other dose-related adverse events. Although it is ideal to not take buprenorphine for 2 days before surgery, this is often not feasible in many surgical settings, in which patients are first seen by the anesthesiologist directly before the operation. In situations in which patients have not discontinued their buprenorphine therapy well in advance of their surgery, the patient should receive baseline buprenorphine via sublingual or transdermal routes. Alternatively and if necessary, convert the patient's buprenorphine requirements to an intravenous equivalent while the patient is in the immediate perioperative period. Although the patient is maintained on a stable dosage of buprenorphine, additional full agonist opioids may be titrated to pain reduction, or alternatively, nonopioid adjuvants (including clonidine, ketamine, or dexmedetomidine) can be used instead of opioids for the patient's postoperative pain.

PEDIATRIC PATIENTS

As in adults, undertreatment of acute pain occurs in a substantial percentage of children.[171] Pediatric patients continue to be undertreated.[167] In addition to anatomic, physiologic, pharmacodynamic, and pharmacokinetic differences between children and adults, there are barriers unique to pediatric patients that may interfere with effective postoperative pain control. Control of postoperative pain is important in pediatric patients because poor pain control may result in increased morbidity or mortality.[172]

Some of the most important barriers to pain control in pediatric patients are the myths that children and infants do not feel pain, that pain is not remembered, and that there are no untoward consequences of experiencing pain.[171] These incorrect assumptions may hinder management of pediatric pain. Because of developmental, cognitive, and emotional differences, assessment of pain in pediatric patients can be difficult. Pediatric patients may have difficulty conceptualizing and quantifying a subjective experience such as pain. The lack of routine assessment and reassessment of pain may interfere with effective acute pain management.[171] Special scales are available to assist young children in self-reporting of pain; however, interpretation of behavior and physiologic parameters may be used to estimate pain intensity in preverbal children or those who cannot self-report their pain. Furthermore, assessing pain in children with intellectual disabilities presents unique challenges.[173]

A plan for postoperative pain management should be discussed with the family and patient before surgery because pediatric patients may have many anxieties about pain and analgesic use after surgery. In general, the oral route of analgesic administration is preferred for mild to moderate pain. Intravenous or regional analgesia is appropriate for moderate to severe postoperative pain.[171,174] Use of intramuscular injections is strongly discouraged because of the pain associated with injection and variable absorption of analgesic medications. Fear of needles may

inhibit control of postoperative pain because pediatric patients may choose to suffer in silence rather than receive a painful and anxiety-provoking intramuscular injection. Addressing medication-related side effects is important to alleviate patient-related distress and improve compliance with the postoperative analgesic regimen.

Use of an intravenous PCA device allows individualization of analgesic requirements and offers pediatric patients autonomy. Children as young as 4 years have the cognitive and physical capability to appropriately use an intravenous PCA device.[175] Although morphine is the standard by which other opioids are compared, morphine does not appear to have an analgesic advantage over other opioids (e.g., hydromorphone) when given in equianalgesic doses. Because of toxicity from its metabolite and much better alternatives, meperidine should not be used in the pain management of pediatric (or adult) patients.[171] A meta-analysis examining whether the addition of a background or continuous infusion to an intravenous PCA opioid regimen would be associated with an increased risk of respiratory depression indicated that the addition of a continuous or background infusion was associated with a higher incidence of respiratory events in adult but not in pediatric patients.[29] Nurse- or parent-controlled analgesia is also effective and may be used in certain circumstances, but close monitoring of the patient may be needed because significant respiratory depression occurs in approximately 1.7% of patients (although some data suggest that children receiving PCA by proxy do not have a higher incidence of adverse events compared with those not receiving PCA by proxy[176,177]). For pediatric patients unable to use intravenous PCA, continuous infusions or intermittent intravenous administration of opioids is effective in providing postoperative analgesia.[178] Although respiratory depression may occur with opioids regardless of the route administered, clinically significant respiratory depression in pediatric patients is relatively uncommon.[175] Unlike adults, pediatric patients do not appear to exhibit multiple episodes of clinically significant oxygen desaturation postoperatively when treated with neuraxial, intravenous, or intramuscular opioids.[179] Use of nonopioid analgesic agents, such as NSAIDs or acetaminophen, may improve overall analgesia, reduce the amount of opioid used postoperatively, and decrease some opioid-related side effects such as postoperative nausea and vomiting.[180] For rectal administration of acetaminophen postoperatively, a larger dose (40 mg/kg followed by three doses of 20 mg/kg at 6-hour intervals) than that previously recommended may result in appropriate serum analgesic levels.[181] In addition, other analgesics such as ketamine and tramadol may be considered as adjunct analgesic drugs for the treatment of postoperative pediatric pain in specific clinical situations.[66,182]

Peripheral and neuraxial regional analgesic techniques are commonly used and effective for acute pain management in pediatric patients. The use of ultrasound-guided regional analgesic techniques has been described and may further increase the use of efficacious regional analgesic techniques for pediatric postoperative pain management.[183] One of the more frequently used techniques is epidural analgesia, which can be delivered as a single dose or by using a continuous-infusion catheter technique. The catheter may be inserted (typically using general anesthesia) anywhere along the epidural space (e.g., thoracic, lumbar, caudal), but the caudal approach seems to be the most common technique because the catheter can be easily advanced cephalad to the appropriate dermatome. Local anesthetics or opioids, or both, can be administered through the epidural catheter or needle to provide effective postoperative analgesia. Although epidural (caudal) analgesia may be safely administered to neonates, the clinician should recognize that the maximal continuous infusion dose is probably smaller than that in older children because of lower levels of α_1-acid glycoprotein (which binds local anesthetics) and diminished ability of the relatively immature liver to metabolize amide local anesthetics.[184] The addition of adjuvant drugs, such as clonidine, in the epidural infusion may enhance postoperative analgesia.[185]

Continuous epidural (caudal) analgesia may be used in the postoperative setting, and the infection rate associated with continuous epidural analgesia is extremely low despite the relatively high colonization rate.[125] In addition, continuous peripheral catheter techniques can be used effectively in pediatric patients. Regional analgesic techniques may be useful in providing analgesia for wound incision (e.g., herniorrhaphy or orchiopexy), thoracotomy, and orthopedic procedures.[186] Local anesthetics may also be administered topically to provide analgesia. Despite a lack of data comparing outcomes for regional analgesia versus systemic opioids in the pediatric population, some evidence suggests that the use of epidural analgesia is associated with improvement in some outcomes such as earlier tracheal extubation, return of gastrointestinal function, and length of hospital stay.[187] Finally, other modalities such as acupuncture may be a potentially useful adjunct for the treatment of pediatric postoperative pain, although further large-scale randomized, controlled clinical trials are needed to define the role of these modalities in the treatment of pediatric postoperative pain.[188]

OBESITY AND OBSTRUCTIVE SLEEP APNEA

Patients with obesity and obstructive sleep apnea (OSA) may be at a more frequent risk for postoperative complications. Obesity and OSA are separate disease states, but some association exists between the two because OSA occurs in a relatively higher percentage of obese than nonobese patients.[189] Epidural analgesia may decrease postoperative complications in obese patients[190]; yet the optimal postoperative analgesic and monitoring regimen for patients with OSA is not clear. Data suggest that sleep is disrupted in the immediate postoperative period and may influence postoperative morbidity and patient-oriented outcomes.

Obesity is defined as a body mass index (BMI) of greater than 30 kg/m^2, with morbid and supermorbid obesity defined as BMI of greater than 35 kg/m^2 and 55 kg/m^2, respectively. The prevalence of obesity has continued to increase over the past decades to epidemic proportions (including children and adolescents) and is similar across different ethnic, educational, and income

groups.[191-194] Although obese patients do not necessarily have OSA, obesity is the most important physical characteristic associated with OSA. Approximately 60% to 90% of OSA patients are obese, and at least 5% of morbidly obese patients have OSA, which is defined as more than five episodes per hour of cessation of airflow for more than 10 seconds despite continued ventilatory effort.[189] Approximately 4% of men and 2% of women (18 million Americans overall) have OSA, and OSA is underdiagnosed in up to 95% of persons.[189] Patients with OSA are generally at higher risk for pulmonary hypertension, cardiomyopathy, systemic hypertension, and possibly myocardial infarction.[195] The pathophysiology of airflow obstruction is related primarily to upper airway pharyngeal collapse, including the retropalatal, retroglossal, and retroepiglottic pharynx, during sleep, especially during rapid eye movement sleep.[189] During these obstructive episodes, OSA patients may exhibit hypoxia, bradyarrhythmias or tachyarrhythmias, myocardial ischemia, abrupt decreases in left ventricular stroke volume and cardiac output, or increases in pulmonary and systemic blood pressure.[195]

Based on our understanding of the pathophysiology of OSA, postoperative pain management can be difficult in this population. Patients with OSA may be at an increased risk for respiratory arrest.[196] Although it is not clear whether OSA will increase the risk of postoperative hypoxemia when compared with other morbidly obese subjects without OSA, morbidly obese subjects (with or without OSA) most likely will experience frequent oxygen desaturation episodes in the postoperative period even with the use of supplemental oxygen.[197] Use of sedative doses of benzodiazepines and opioids may result in frequent hypoxemia and apnea, which may be especially dangerous in OSA patients.[196] Use of nonopioids (e.g., tramadol, dexmedetomidine) or an opioid-sparing technique may limit some of the respiratory-related events postoperatively; this is supported by the fact that the rate of respiratory events per hour were related to postoperative morphine dose.[198] The risk for respiratory depression and arrest may be attenuated by optimizing the use of NSAIDs or nonopioid adjuvants (including clonidine, ketamine, dexmedetomidine) and by completely avoiding benzodiazepines and epidural analgesia with a local anesthetic–based regimen. Epidural and systemic opioids may be associated with sudden postoperative respiratory arrest.[196,199] Furthermore, use of regional analgesic techniques (e.g., thoracic epidural analgesia) may be of benefit in facilitating the recovery of spirometric values in obese patients.[200]

The American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Obstructive Sleep Apnea created guidelines that include recommendations for postoperative analgesia in patients with OSA.[201] Although the consultants acknowledged that the conclusions regarding postoperative analgesic options were based on insufficient literature evaluating the effects of various analgesic techniques, the presence of equivocal literature regarding the use of epidural opioids versus intramuscular or intravenous opioids in reducing respiratory depression, and insufficient literature regarding the addition of a basal infusion to systemic patient-controlled opioids, the consultants nevertheless recommended that regional techniques rather than systemic opioids be used in an attempt to reduce the likelihood of adverse outcomes in patients at increased perioperative risk from OSA.[201] In addition, the consultants recommended the exclusion (versus inclusion) of opioids from neuraxial postoperative analgesia to reduce perioperative risk and the use of NSAIDs to reduce adverse outcomes through their opioid-sparing effect. The consultants were equivocal regarding whether avoiding a basal infusion of opioids in patients with OSA reduces the likelihood of adverse outcomes.[201] Unfortunately, randomized clinical trial data is lacking to provide definitive high-quality evidence-based recommendations for the provision of postoperative analgesia to OSA patients.

INPATIENT PAIN SERVICES

The terms acute pain service (APS) or acute pain medicine (APM) are not synonymous with the terms regional anesthesiology pain service (RAPS) or perioperative pain service (PPS). Each term describes a unique role, and the terminology can be confusing to other physicians in the health care system. APS/APM is a more comprehensive service than a perioperative service. APS/APM addresses all inpatient acute pain issues, including perioperative pain, medical pain, and acute-on-chronic pain, such as occurs with sickle cell disease, pancreatitis, and acute exacerbations of inflammatory bowel disease or other condition requiring medicinal or catheter-based techniques for pain relief. PPS takes care of only perioperative pain patients with the same techniques, and RAPS addresses only those patients with a catheter placed by an anesthesiologist for postoperative pain. Which type of service each hospital provides depends greatly on the local expertise, the local financial resources available, and the patient population. Chronic pain services developed from the needs of patients in hospitals with the less-comprehensive or RAPS/PPS-type of pain service because these services have a very restricted treatment group. As academic regional anesthesiologists have expanded their roles to include that of the perioperative pain physician or the acute pain medicine physician, they have developed services that encompass all inpatient pain concerns, and the role or necessity of the primarily outpatient pain medicine physician (commonly referred to as the chronic pain physician) in the hospital has been reduced.

Although there are several models for the development of APS/APM, the key organizational aspects are similar (Box 98-2). Development and maintenance of APS/APM requires commitment and financial support at the national and local (institutional and departmental) level. In the United States, a dichotomy exists at the national and third-party payer levels between the requests for improved inpatient pain control (along with the introduction of practice guidelines or expanded roles for acute pain services) and the decreased reimbursement for the provision of such services. Because there is a substantial financial burden associated with the establishment of an inpatient pain service, large-volume or larger hospitals may be more likely to have these services and access to more high-tech analgesic techniques such as regional

BOX 98-2 ***Organizational Aspects of an Inpatient Pain Medicine Service***

EDUCATIONAL ACTIVITY

Anesthesiologists
Residency-fellowship teaching (if applicable)
Health insurance carriers
Hospital administrators
Nurses
Patients and families
Pharmacists
Surgeons

ADMINISTRATIVE ACTIVITY

Economic issues
Evaluation of equipment
Human resources: pain service personnel, administrative-secretarial support
Institutional administrative activity
Quality improvement and assurance
Research (if applicable)

NURSING

Continuing education and in-service training
Defining of roles in patient care
Nursing policies and procedures
Pain service nurse (if applicable)
Quality improvement and assurance

DOCUMENTATION

Hospital policies and procedures
Bedside pain management assessment flow sheet
Daily consultation notes
Educational packages
Protocol drive order-sets

analgesia.[202] Formal inpatient pain services using postoperative pain protocols are more likely to be present in academic/teaching hospitals compared with nonteaching hospitals.[203] Whether inpatient pain services actually improve outcomes is unclear. Two earlier systematic reviews have examined the impact of acute pain services on patient outcomes,[100,204] and although both systematic reviews suggest that the introduction of acute pain services is associated with a decrease in pain scores, the effect of acute pain services on the incidence of analgesic-related side effects (e.g., nausea, vomiting), satisfaction, and overall costs is uncertain. Despite the direct costs (e.g., personnel, equipment, medication) associated with managing an acute pain service, no properly conducted pharmacoeconomic study is available to examine the cost effectiveness of an acute pain service. Use of postoperative epidural analgesia in the context of acute pain services may decrease the cost of patient care through shorter intensive care unit stays and a decreased rate of complications.[10] Nevertheless, a randomized controlled trial comparing an anesthesiologist-led, nurse-based acute pain service group with patient-controlled analgesia versus a control group with systemic boluses of opioid analgesia noted that an acute pain service was likely to be cost effective when the role of the acute pain service was extended to a specific group of major surgical procedures.[205]

A dedicated inpatient pain service allows anesthesiologists to extend their presence in the field of perioperative medicine, although there is no universal agreement on how to provide these services in a financially viable way.[206] This represents one of the numerous challenges that face the development of these services. If that service becomes valuable to the local medical scene, financial support will almost always follow in one way or another. As inpatient acute pain medicine services continue to evolve into comprehensive inpatient pain medicine services, there may be less need for a separation of acute and chronic pain services for inpatient pain care. The elimination of this duplication and the indeterminate roles of service(s) can reduce costs and improve continuity of patient pain care. Despite the costs associated with implementation of a comprehensive inpatient pain service, these services provide a valuable resource at the individual, institutional, and societal levels. With the development of the APS/APM, we now have different training goals for the traditional regional anesthesiology fellowships, including more formal education in chronic pain conditions and management of these conditions while the patient is hospitalized with acute illness. This would involve education on the medical management of these conditions in the short-term, maintenance of the patient's long-term therapies, and knowledge of how these long-term therapies interact with acute pain management.

With skills in regional anesthetic techniques and knowledge of the neurobiology of nociception and the pharmacology of analgesics and local anesthetics, as well as specialty education in the treatment of acute and chronic pain conditions, anesthesiologists are recognized leaders in perioperative pain relief and the development of acute pain services. Provision of inpatient analgesia, along with other services such as critical care medicine and preoperative evaluation, is highly compatible with the emerging identity of anesthesiologists as perioperative physicians and enhances the role of anesthesiologists as valued consultants outside the operating room.

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Chapter 99

Cognitive Dysfunction and Other Long-term Complications of Surgery and Anesthesia

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Key Points

- The selection, measurement, and analysis of neuropsychological tests will influence findings with postoperative cognitive dysfunction (POCD). Patients' subjective reports after surgery are unrelated to assessed neuropsychological change and appear to be driven by mood. Good evidence exists for POCD after cardiac surgery in which the mechanism is multifactorial but seems to include microembolization. POCD after major noncardiac surgery occurs, although the mechanisms are less clear than after cardiac surgery. Increased age is a risk factor for POCD (see Chapter 80).

Brain function is clearly altered immediately after anesthesia and surgery, as manifested by depressed level of consciousness and impairment of attention, memory, and reaction time. Patients also may experience complete amnesia for several hours after anesthesia despite appearing to be completely awake. Consequently, patients often ask the same questions on a repetitive basis. Because of these issues, patients should be accompanied by an adult during transportation and throughout the first postoperative night whether in a hospital or after outpatient surgery.

When brain function returns to normal after anesthesia is not clear. If all the difficulties were due to the anesthetic, cognitive function should have recovered to a preoperative level of functioning soon after termination of the administration of anesthesia. If the eliminated anesthetics were the sole criteria, inhaled anesthetics and propofol would differ from slowly eliminated hypnotics, such as barbiturates and benzodiazepines. However, anesthetics and their concentrations (dose) are among the many factors of importance for recovery (see also Chapter 30). The duration of recovery of cognition after anesthesia and surgery is multifactorial and depends on the type of anesthesia used, type of surgery, and characteristics of the patient. In some individuals, cognitive recovery is rapid (within a matter of hours), whereas in others brain function may be disturbed for a much longer time. The concept of postoperative disturbance in cognition is not new and has often been referred to as postoperative cognitive dysfunction (POCD). The term is used variably and should be distinguished among the following three types of cognitive deterioration after surgery:

1. Delirium is usually easily recognized, being an acute condition with fluctuating course, characterized by disturbances in attention combined with either a change in level of consciousness or disorganized thinking. The duration is usually a few days, and the degree of severity ranges from mild to severe.
2. Short-term cognitive disturbance may be apparent in the days after surgery. This occurs relatively frequently and may be due to a combination of factors, including surgery and anesthetics. This cognitive disturbance is of short duration and does not persist beyond a few days after surgery. A neuropsychological assessment is an excellent choice, but frequently screening tests such as the Mini–Mental State Examination (MMSE) have been used. Some studies have assessed POCD in the first few hours and days after anesthesia. The results from some of these studies are described in this chapter.
3. What we consider true POCD is a subtle deterioration in cognitive function, lasting for weeks, months, or longer; and neuropsychological testing is needed for verification. It can be considered to be a mild cognitive disorder characterized by impairment of memory, learning difficulties, and reduced ability to concentrate.

All of these different forms of postoperative cognitive disturbance are to be distinguished from dementia. Dementia is a syndrome that is due to disease of the brain, usually of a chronic or progressive nature, in which profound disturbance occurs in multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. Consciousness is not clouded. The impairment of cognitive function is associated with

a deterioration in emotional control, social behavior, or motivation. Dementia is usually diagnosed only if the condition has been present for at least 6 months.

DETECTION OF POSTOPERATIVE COGNITIVE DYSFUNCTION

The incidence of POCD varies widely across studies even though the conduct of surgery and anesthesia may be similar. Besides individual patient differences, methodologic issues such as the choice of test battery, the time of postoperative assessments, and the method of analysis to determine POCD may be the source of differences.

NEUROPSYCHOLOGICAL TESTING IN SURGICAL PATIENTS

Neuropsychological assessment tools are used to objectively measure cognitive function. The tests used in the detection of POCD, unlike many employed in a clinical assessment, must be sensitive to change. The assessment tools should be sensitive to potentially diffuse brain injury; therefore, these measures should form a battery of tests that attempt to cover a range of cognitive domains, such as memory, attention, concentration, and perceptual and motor ability. Because of the time constraints imposed by the surgical environment, the time set aside to conduct these tests is often limited; therefore, the battery of tests by necessity frequently represents a compromise. A review of POCD studies in noncardiac surgery[1] indicated that 70 different neuropsychological assessment tools had been used in conjunction with 9 composite batteries, with between 1 and 13 tests used per study. The domains most often assessed were memory and learning. However, differences in the number of tests used can be problematic, because when more tests are used, dysfunction is more likely to be detected. However, even the definition used to determine whether POCD is present varies. Using a lengthy battery of tests is a problem, because they can cause fatigue in patients. Maintaining patient interest is often achieved by the variety of tests employed, but, in addition, interest can be maintained by alternating paper and pencil, computerized, manual, and verbal tasks.

Early studies investigating POCD often used traditional intelligence tests such as the Wechsler Adult Intelligence Scale (WAIS or WAIS-R) or screening tests such as the MMSE. Although these batteries are highly reliable, they are insensitive to the more subtle changes that may occur postoperatively.[2,3] These batteries have been replaced by many neuropsychological assessment tools designed for repeated assessments, many of which have been computerized to ease administration and improve standardization. Assessments are performed by a range of health care and non–health care professionals. The assessment of brain function requires expertise, particularly in how to present the tests and address patient responses. Ideally, the tests should be administered by the same trained neuropsychologist in the same quiet environment at each testing session.

Timing of Assessments

A very important issue regarding the measurement of POCD is the timing of assessments. The timings of preoperative assessments have varied widely, ranging from within weeks of surgery to 1 day before surgery or even the day of surgery. Patients are frequently anxious about surgery and anesthesia. Although preoperative anxiety is not apparent on neuropsychological tests that have been employed in most POCD studies, whether levels of both anxiety and depression may have an impact on the cognitive tests employed should be assessed.

Cognitive problems are frequently observed and often transitory in patients in the immediate postoperative period. These early assessments may well be detecting a transient disturbance of cognition. The assessments conducted postoperatively may be influenced by general postoperative readjustment, opioids, pain, and fatigue. Assessments conducted later in the recovery period (at least 4 weeks after surgery) are more likely to detect a persistent and clinically important change.

A relevant question is whether the early indications of cognitive disturbance are in any way predictive of longer term difficulties in cognition. Early predischarge assessments may predict longer term decline,[4-6] but the association is neither simple nor clear.

Analysis

Many methods can measure and define dysfunction. Some studies have used a significant difference between postoperative and normative scores[7] and others a cutoff on a screening measure.[8-11] In a third approach, two different surgical and anesthetic groups were compared.[12,13] A fourth approach compared a surgical group and a control group.[14,15] In other studies, a fifth approach analyzed neuropsychological test data as multiple comparisons of variables in the test battery. This approach provides the sensitivity to detect even small differences, but the risk for a type 1 error is high. In addition, this analysis is not well suited to address whether deterioration has occurred, because it is based on group means rather than individual change; no incidence of cognitive decline can be calculated.[11,16]

Many researchers have adopted a sixth method that uses an "individual change" approach in which each participant acts as the control. Here the participant's score postoperatively is compared with the preoperative score. Then a statistically defined criterion is used to rate the participant as having or not having POCD. However, this statistically defined criterion is not uniform over studies; for example, Shaw and associates[17] defined POCD as a decline in performance equal to or more than 1 standard deviation (SD) from the preoperative score in 1 or more neuropsychological tests, Yet, this same decline needed to be present in two or more tests before Treasure and co-workers[18] rated the participant as having POCD. Other investigators have used the same decline of 1 SD but in 1 of 21 tests and 4 of 21,[19] and yet others have defined POCD as being a 20% decline in 20% of tests.[20] The advantage of this binary approach is that it defines and categorizes individual performance into an entity that appears meaningful in a clinical environment and is easily understood. However, these definitions are statistically derived and have no intrinsic meaning or relationship to brain injury. Another disadvantage is that

these methods take into account only deterioration without considering improvement. Because the neuropsychological tests used in studies of the detection of POCD should be sensitive to change, they are amenable to repeated administration. However, if two assessments are conducted with only a short time between them, learning can occur. This may be due to an increased familiarity with the tests or differing strategies employed when completing the assessments. Although many attempts are made to reduce these learning effects, such as use of parallel equivalent forms, it is almost impossible to remove them from repeat testing. Perhaps, one measure of cerebral damage is the inability to learn a task or strategy that is the underlying basis of practice effects. This learning has been apparent in many POCD studies.[9,21] Therefore, the form of analysis used should take into account any learning, or failure to learn, occurring postoperatively.

One such study that took learning into account was that of Williams-Russo and associates,[22] who examined individual change after establishing a clinically important difference score for each test. When studies have employed a control group, the effect of learning can be assessed. The multicenter International Study of Post-Operative Cognitive Dysfunction (ISPOCD) group[23] compared the mean of the neuropsychological test score change obtained from a healthy control group over three assessments to that of a surgical group. The mean of the control group changes was used as an estimation of learning. The mean was subtracted from the surgical participants' change score and the result divided by the SD of the corresponding change in the control group to obtain a Z score for each test. Using a Z score allows the scores for each individual test to be combined to obtain a composite neuropsychological score. The authors also applied a cutoff score to identify POCD, which they defined as when the Z scores on two individual tests or the combined Z score reached 1.96 or more (the higher the score, the more deterioration).

The definition of what defines a control group is sometimes not obvious. Using a control group strengthens a study considerably and allows the influence of variables such as learning to be assessed, yet what constitutes an *appropriate* control group? POCD studies have used various types of control groups, such as healthy volunteers, friends, and relatives of the participants under study; patients with other conditions; and patients with the same condition but not undergoing surgery.[24,25] However, in POCD, no ideal control exists. For example, using healthy volunteers fails to take account of any nonspecific effects of having the condition on cognition. Using patients with different conditions as controls assumes equivalence in cognition and learning between the conditions of the control and that of the groups of interest. When considering participants with the same condition who do not undergo surgery because of either a surgical decision or patient choice, the groups could differ on important clinical factors because the allocation to groups is not random.

LIMITATIONS OF NEUROPSYCHOLOGICAL STUDIES

Patients need to be cognitively able to complete neuropsychological tests at baseline; therefore, only patients without preoperative brain disease have been included in these studies. Also, patients undergoing emergency procedures have not been studied owing to difficulties with obtaining a reliable evaluation preoperatively.

In these studies, especially the long-term follow-up studies, some patients die or are too ill to return to be assessed and, in addition, some choose not to participate in follow-up. In some cases, those who are particularly well and have returned to work may see no purpose in further contact and are lost to follow-up. The attrition is unlikely to be random but may be more influenced by travel distance and inconvenience. Not unexpectedly, attrition rates are less for shorter follow-up.[1] Sicker patients are more likely to be unavailable for follow-up.[25] Attrition is more frequent among those with lower intelligent quotients[5] and lower levels of education.[26] Perhaps the incidence of POCD would be higher or different if all patients had been assessed.

SUBJECTIVE COGNITION AND PROXY RATINGS OF COGNITIVE CHANGE

Although neuropsychological tests are the most frequently used approach to detect POCD, another method sometimes employed is self-report of cognitive changes.[27-30] These types of studies have used measures such as the Cognitive Failures Questionnaire, the Cognitive Behavior Rating Scale, the Cognitive Difficulties Scale, or interviews and have reported subjective cognitive dysfunction after surgery. For example, Khatri and co-workers,[28] using the Cognitive Difficulties Scale, found that 16% of patients rated themselves as having cognitive difficulties 6 weeks after coronary artery bypass graft (CABG) surgery. Also, comparing local anesthesia with general anesthesia, Ward and associates[30] found that a statistically significant impairment of perceived cognitive function using the Cognitive Failures Questionnaire was reported by patients who had undergone general anesthesia but not those who had undergone local anesthesia 3 days previously.

Although studies have been conducted to ascertain the reliability of proxy respondents in relation to quality of life of patients in a range of clinical cohorts,[31] very little research has been conducted regarding cognition. Thornton and associates[32] found that cognitive changes were likely to be noticed by the patient's spouse or a close relative. Another study by Bergh and associates[33] found that a spouse's ratings of the patient's concentration and memory were in agreement with that of the patient. A clear relationship between patients' subjective reports and formally assessed cognition has not been found. Many studies have found a stronger relationship between mood and patient perception of cognitive changes after surgery and anesthesia than between neuropsychological test scores and subjective reports,[28,34-37] with patients who are more anxious and depressed reporting more cognitive problems. This may be due to patients who are emotionally distressed forming a negative information-processing bias, which in turn leads to distorted perceptions of cognitive performance.[28,34,36]

INCIDENCE AND RISK FACTORS FOR POSTOPERATIVE COGNITIVE DYSFUNCTION AFTER CARDIAC SURGERY

The incidence of POCD after cardiac surgery (coronary artery bypass, valve replacement or repair, or both) is 50% to 70% in the first postoperative week, 30% to 50% after 6 weeks, and 20% to 40% at 6 months and 1 year (see also Chapter 67).[38] This variability is, as discussed previously, due in part to the problems of methodology, such as differing neuropsychological tests used, timing of assessments, and definitions of decline. In an attempt to reduce this variability, a consensus meeting developed guidelines for neuropsychological tests conducted to assess cardiac POCD.[39]

Despite variability in incidence, timing, types of tests, and analysis, a general consensus appears to exist that POCD after cardiac surgery does occur in a proportion of patients. The cause is probably multifactorial, although the use of cardiopulmonary bypass (CPB) often has been implicated.

INTERVENTIONS TO REDUCE THE INCIDENCE OF COGNITIVE DECLINE IN CONNECTION WITH CARDIAC SURGERY

Strategies to reduce the incidence of cerebral complications after cardiac surgery are based on perceived problems (see also Chapter 67). Significant risk factors include advanced age (see Chapter 80), untreatable poor left ventricular function, and duration of CPB. Of these, only the last factor is modifiable by either changing the management of CPB and related techniques or avoiding CPB completely.

CPB involves numerous violations of normal physiology. The length of time on bypass has tended to be related to POCD, suggesting that something in the CPB procedure is deleterious to the brain.[40,41] Important intraoperative causative agents are cerebral microemboli, which can be either particulate (e.g., atheroma, fat, platelet aggregates) or air. Microemboli occurring in the cerebral circulation can be detected noninvasively using continuous transcranial Doppler imaging of the middle cerebral artery. In this technique, the number of microemboli is related to the length of time on bypass. Microemboli found in the brains of patients who have died soon after cardiac surgery are related to the length of time on CPB.[42] However, the relationship between POCD in cardiac surgery and microemboli is not always clear, with some studies finding an association[43-45] and others not.[46-48] This relationship is complicated by a range of factors, including the size and final distribution in the brain of the microemboli. This final location of the microemboli is an important factor because they may be lodged in an area not covered by the neuropsychological tests used or in an area less important for cognition. Presumably, solid microemboli are more likely to cause damage than gaseous microemboli, but no clear evidence supports this conclusion.

MANAGEMENT OF CARDIOPULMONARY BYPASS

pH Management

Management of pH during hypothermia can be carried out as pH-stat or α-stat management (see also Chapters 54 and 67).[49] α-Stat management may lead to better neurologic and cognitive outcomes. Stephan and coworkers[50] found marked cerebral hyperemia and an increase in neurologic events 7 days after surgery when using pH-stat management. Although Bashein and colleagues[51] found no difference in neuropsychological test outcome between these two techniques, both Murkin and associates[52] and Patel and colleagues[49] have shown that α-stat is associated with less neuropsychological test result deterioration than that with pH-stat management.

Temperature

Hypothermia can prolong the safe period of circulatory arrest (see also Chapter 54). Hypothermic perfusion has been used routinely for both valve and CABG surgery (see also Chapter 67). Recently, normothermia and normothermic cardioplegia have been used for myocardial protection, but neuroprotection may be compromised. Studies produced conflicting results, with some showing that normothermic perfusion may be potentially harmful[53-55] and others finding no difference.[56-58] Because a small decrease in temperature is neuroprotective, the failure to find an advantage for hypothermia in clinical trials is surprising. However, brain hypothermia may not be guaranteed in all patients and the process of rewarming to normothermia may be harmful. Neurons may be injured by rewarming to 38° C. Perhaps rapid rewarming may force anesthetic and other gases out of solution and thereby produce microemboli. However, Buss and associates[59] found no effect on neuropsychological test outcome of rewarming temperature exceeding 38° C in contrast to lower temperatures. Nathan and colleagues[60] found that hypothermia may be cognitively beneficial.

Temperature regulation in the postoperative period is not clear. Grocott and co-workers[61] examined POCD in relation to temperature in the first 24 hours after surgery. Although they found no association between the area under the curve above 37° C during this period, they did find a direct relationship between POCD at 6 weeks after surgery and the maximum temperature achieved.

Arterial Line Filtration

Arterial line filters, which are an optional addition to the CPB circuit, are designed to prevent extraneous matter in the circuit from entering the patient (see also Chapter 67). Two studies found that the number of microemboli detected in the middle cerebral artery was significantly reduced when an arterial line filter was used.[62,63] Although two earlier studies reported that arterial line filters made no difference to cognitive outcome,[64,65] a further study by Pugsley and co-workers[63] found less POCD in the filter group (46% filter versus 71% nonfilter; $P = .05$) 8 days after surgery and (8% filter versus 27% nonfilter, $P = .03$) at 8 weeks. The two earlier studies conducted their assessments only during the acute in-hospital phase, which may have confounded the results, whereas Pugsley and co-workers[63] were able to demonstrate an even more pronounced effect at 8 weeks.

Pulsatile Versus Nonpulsatile

Although nonpulsatile CPB is the most commonly practiced form of perfusion, pulsatile flow may be more physiologic (see also Chapter 67). A study by Murkin and colleagues[52] found no differences in neuropsychological benefits from pulsatile versus nonpulsatile flow.

Hematocrit

The hematocrit value may be related to outcome after CABG. Habib and associates[66] found that the lowest quintile of hematocrit was related to vital organ dysfunction, morbidity, and 6-year survival in a survey of 5000 consecutive operations. Also, Karkouti and colleagues[67] found a positive association between the risk for perioperative stroke and the lowest operative hematocrit. However, in a study examining cognitive dysfunction, Harrison and associates[68] found no correlation between cognitive outcome and hematocrit.

Blood Glucose Management

The relationship between POCD and hyperglycemia after cardiac surgery is not well defined[69] (see also Chapter 39). However, a study conducted by Puskas and associates[70] of 525 patients undergoing CABG found that hyperglycemia was associated with a decrease in cognitive performance at 6 weeks after surgery in patients without diabetes, whereas hyperglycemia had no effect on cognition in patients with diabetes.

Type of Oxygenator

Oxygenators have undergone considerable development over the years (see also Chapter 67). Early studies compared the two types of oxygenators (bubble versus membrane). Padayachee and colleagues[71] found that membrane oxygenators produced fewer cerebral microemboli detected by transcranial Doppler imaging than bubble oxygenators. Also, two studies suggest that POCD is reduced when membrane oxygenators are used rather than bubble oxygenators.[72,73] The nearly universal use of membrane oxygenators is likely to have a beneficial effect on neuropsychological test outcome.

Avoiding Cardiopulmonary Bypass

The resurgence of off-pump coronary artery bypass (OPCAB) surgery as a common technique for multivessel revascularization has paved the way for research into isolating the role that CPB plays in neurologic and neuropsychological decline after CABG surgery. OPCAB surgery may reduce the number of microemboli and strokes. Three recent meta-analysis studies,[74-76] while showing a trend toward an advantage for OPCAB over conventional CABG for incidence of stroke, failed to find a significant difference.

Studies reporting neuropsychological outcome are equally inconsistent. Poorer cognitive outcome at both 1 and 10 weeks was reported in patients undergoing on-pump surgery compared with OPCAB.[77] A large (N = 281) randomized study also found that neuropsychological performance at 3 months after surgery was better in patients undergoing OPCAB; however, these differences had disappeared by the 12-month[78] and 5-year[79] follow-up assessments. Subjective reports of cognitive difficulties have also been found to be similar at 1 year after surgery.[80] A further study by van Dijk and colleagues in 2004[6] found that early cognitive decline in patients undergoing first-time CABG predicted cognitive outcome after 3 months but suggested that this early cognitive decline was not significantly influenced by the use of CPB.

Management of Atherosclerosis of the Ascending Aorta

Embolization may result from dislodgment of atheromatous material during handling of the aorta—for instance, when cannulation is conducted (see also Chapters 67 and 69). Identification of plaques may therefore be advantageous to change the site of cannulation or carry out a coronary artery bypass as an off-pump procedure. That identification is often based on palpation, but ultrasound is clearly more sensitive. Epiaortic ultrasound to detect atheroma has been found to be associated with a reduction in the incidence of POCD.[81]

PHARMACOLOGIC TECHNIQUES TO PROTECT THE BRAIN IN CARDIAC SURGERY

Putative neuroprotective drugs have had variable results in protecting the brain (Table 99-1). Furthermore, many of the studies were underpowered, making their findings unreliable. The previously reported benefit of lidocaine has subsequently been refuted.

INCIDENCE AND RISK FACTORS FOR POSTOPERATIVE COGNITIVE DYSFUNCTION AFTER NONCARDIAC SURGERY

Whether cognitive function deteriorates postoperatively in noncardiac surgery was examined more than 50 years ago by Bedford in 1955.[82] The findings were based on subjective observations and questioning of relatives or caretakers. Using these techniques he concluded that 7% (18 of 251) of patients older than 65 years of age became "demented" (not in the way it is used earlier) after undergoing general anesthesia (see also Chapter 80). Clearly, a lack of objective verification existed, such as means testing of cognitive function by neuropsychological testing. Subsequently, Simpson and associates[83] reported no significant connection between anesthesia and decreased mental performance in 620 elderly patients.

Early studies of POCD tended to recruit a small number of participants. Therefore, many of these early studies did not have the statistical power to detect POCD. In addition, several investigators examined participants on whom a limited number of neuropsychological tests had been performed. The resultant analysis was often unclear and different across the studies. Nonetheless, the evidence for POCD after noncardiac surgery began to accumulate. For example, Grichnik and co-workers[20] found POCD in 45% of a sample of 29 patients with a mean age of 60 years at 6 to 12 weeks after thoracic or

TABLE 99-1 RANDOMIZED TRIALS OF PHARMACOLOGIC INTERVENTION TO REDUCE COGNITIVE DYSFUNCTION AFTER CARDIAC SURGERY

Authors	Year	Drug	No.	Result
Nussmeier et al[139]	1986	Thiopental	182 complete	Neuropsychological test results showed no difference at 5 days
Roach et al[140]	1999	Propofol	99 complete	No significant difference at days 5-7 or days 50-70
Legault et al[141]	1996	Nimodipine	149 recruited, complete in 65%-69%	No significant difference, at 1 wk, 1 mo, or 6 mo (study terminated early)
Fish et al[142]	1987	Prostacyclin	74 complete	No significant difference at 1 wk or 2 mo
Grieco et al[143]	1996	GM_1 ganglioside	25 complete	No significant difference at 1 wk or at 6 mo
Arrowsmith et al[46]	1998	Remacemide	159 complete	Using incidence, no significant difference; but using Z-change score, significantly less POCD with remacemide
Butterworth et al[144]	1999	Pegorgotein	58 complete	No significant difference at days 5-7 or wk 4-6
Mitchell et al[145]	1999	Lidocaine	42 complete	Significantly less POCD with lidocaine at 10 days (40% versus 75%) and at 10 wk (46% versus 75%)
Wang et al[146]	2002	Lidocaine	88 complete	Significantly less POCD with lidocaine (19% versus 40%) at 9 days
Kong et al[147]	2002	Clomethiazole	219 complete	No significant difference at 4-7 wk
Taggart et al[148]	2003	Lexipafant	135 complete	No significant difference at discharge or 3 mo
Mathew et al[149]	2004	Pexelizumab	800 recruited	No significant difference at day 4 or at day 30
Harmon et al[150]	2004	Aprotinin	35 complete	Significantly less POCD in the aprotinin group: 94% versus 58% at day 4 and at 6 wk 23% versus 55%
Mathew et al[151]	2009	Lidocaine	182 complete at 6 weeks	No significant difference at 6 wk or at 1 yr
Mitchell et al[152]	2009	Lidocaine	118 complete at 10 wk	No significant difference at 10 or 25 wk

vascular surgery (see also Chapters 66 and 69). The definition of POCD was similar to that in earlier studies in cardiac surgery, using a 20% deterioration in 20% of the tests (11 test variables considered) (see also Chapter 67). In a larger study of 98 patients with a mean age of 73 years, Ancelin and associates[19] found deterioration in at least 1 test of 28 in 71% of patients 9 days after surgery and in 56% of patients at 3 months. After knee replacement (see also Chapter 79), POCD was seen in 41% of patients at 1 week and in 18% at 3 months.[84] In a much larger study (228 patients) including a very early assessment in patients older than 64 years of age, POCD was found in 16.8% 1 to 2 days after noncardiac surgery. The definition of POCD was based on deterioration in two of three test variables.[85] Further evidence that POCD exists after noncardiac surgery was provided by Williams-Russo and colleagues,[22] who reported POCD in 5% of 231 patients older than 65 years of age at 6 months after knee replacement (see also Chapter 79). In this study, POCD was defined by a panel agreeing on what constituted a "clinically important deterioration" in each of the applied tests; however, no control group was included to allow a comparison. Unfortunately, these studies usually did not have a control group. In contrast, the ISPOCD study recruited 1218 elderly patients and 176 healthy volunteers.[23] The patients underwent major noncardiac surgery with general anesthesia. POCD was found in 25.8% after 1 week and 9.9% after 3 months. This was significantly more frequent than in the control group, in whom the diagnostic criteria were fulfilled in only 3.4% and 2.8%, respectively. These findings were further supported in a single-center study using the same methodology, in which POCD was found in 41.4% of those older than 60 years of age at discharge and in 12.7% after 3 months.[86]

RISK FACTORS FOR POSTOPERATIVE COGNITIVE DYSFUNCTION AFTER NONCARDIAC SURGERY

In most studies investigating POCD, the mean age of the participants assessed has been approximately 60 years,[1] with many studies specifically selecting participants of an "older" age group (see also Chapter 80). This is in part due to beliefs that cognitive dysfunction would be more likely with "older people." However, age is a significant and independent risk factor for POCD; for example, after 3 months, POCD in the ISPOCD study[23] was seen in 7% of those aged 60 to 69 years in contrast to 14% in those older than 69 years. Also, Ancelin and colleagues[19] found a relationship between increasing age and POCD. However, few studies of POCD have included younger patients. The largest study was conducted by the ISPOCD2 group and included 508 middle-aged patients (40 to 59 years) and 185 control subjects of similar age.[35] POCD was found in 89 of 463 (19.2%) of the patients at 7 days and in 26 of 422 (6.2%) at 3 months; this is compared with 7 of 176 (4.0%) in the controls at 1 week and in 7 of 169 (4.1%) at 3 months. The difference in incidence of cognitive dysfunction between patients and controls was statistically significant ($P = .001$) at 1 week but not at 3 months ($P = .33$). Interestingly, when the surgical participants were compared with a previous group older than 60 years, they found the younger group showed significantly less POCD at both 7 days ($P = .0064$) and 3 months ($P = .026$) after surgery.[35] These findings are similar to those in a recent study by Monk and co-workers[86] that examined 1064 participants undergoing major noncardiac surgery. A comparison was made between 331 patients aged 18 to 39 years, 378 patients aged 40 to 59 years, and 355 patients aged 60 years and older. At discharge, POCD was found

TABLE 99-2 **PROPORTION OF ELDERLY PATIENTS WITH COGNITIVE DYSFUNCTION AFTER MAJOR SURGERY WITH GENERAL ANESTHESIA AT 1 WEEK AND 3 MONTHS POSTOPERATIVELY BY SELECTED PATIENT, SURGICAL, AND ANESTHETIC FACTORS**

	1 Week		3 Months	
Patient, Surgical and Anesthetic Factors	No. Patients	Patients With POCD (%)	No. Patients	Patients With POCD (%)
Age (yr)				
60-69	586	135 (23)	532	39 (7)
≥70	425	125 (29)	378	52 (14)
Education				
<High school	576	153 (27)	518	49 (9)
High school	290	76 (26)	260	26 (10)
>High school	145	31 (21)	132	16 (12)
Benzodiazepines before surgery	116	32 (28)	105	5 (5)
Duration of anesthesia (min)				
≤120	196	37 (19)	179	20 (11)
121-240	503	121 (24)	448	40 (9)
≥241	312	102 (33)	283	31 (11)
Complication				
Hypoxemia*	115	30 (26)	98	11 (11)
Hypotension†	229	59 (26)	214	20 (9)
Respiratory complication	99	40 (40)	88	12 (14)
Infectious complication	91	30 (33)	138	13 (9)
Second operation	24	13 (54)	50	7 (14)

*One or more episodes of oxygen saturation ≤80% for >2 minutes.
†One or more episodes of mean arterial pressure ≤60% for ≥30 minutes.
Data from Moller JT, Cluitmans P, Rasmussen LS, et al; ISPOCD investigators: Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. *Lancet* 351:857-861, 1998.

in 36.6% of the youngest, 30.4% of the middle aged, and 41.4% of those older than 60 years, with a significant difference among all groups. By 3 months, POCD incidence was similar in the young and middle-aged groups (5.7% and 5.6%, respectively) but a significantly more frequent rate was detected in the older age group (12.7%).

Risk factors for POCD other than age have been identified. Duration of anesthesia, respiratory complications, infectious complications, second operation and a low level of education were important factors in the ISPOCD1 study.[23] Surprisingly, episodes of hypoxemia or hypotension had no statistically significant correlation with POCD. The most important results from the risk factor analyses of this study are shown in Table 99-2. Other investigators have also examined potential risk factors for POCD. Previous cerebrovascular accident has been identified as a significant risk factor for POCD at 3 months.[86] Ancelin and associates[19] found a relationship between postoperative cognitive deterioration and increasing age, low level of education, poor preoperative test performance, depression, and type of anesthesia (general versus epidural). The possible importance of type of anesthesia is discussed later in this chapter.

TYPE OF SURGERY

Minor Surgery

Studies of POCD after minor surgery focused primarily on early outcomes after outpatient surgery. Heath and associates[87] randomized 60 patients 18 to 60 years of age to receive thiopental-based or propofol-based anesthesia. In addition, 30 age-matched control subjects were included. Although significant differences in neuropsychological performance between patients and controls were found at 1 and 2 hours after surgery, this difference had disappeared by 24 hours. The ISPOCD group recruited 372 patients undergoing minor surgery as either an inpatient or outpatient procedure.[88] At 7 days, POCD was found in 22 of 323 (6.8%); in 164 inpatients, 16 (9.8%) had POCD and 5 of 141 (3.5%) outpatients had POCD ($P = .033$), but the group allocation was not randomized (see also Chapter 89). At 3 months the incidence of POCD between the two groups (8.8% for inpatients and 4.5% for outpatients) was not significantly different.

In conclusion, POCD after 1 week seems to be much less common after minor surgery than after major surgery. Several factors may be important in explaining this difference in incidence of POCD, including the obvious difference in surgical trauma, postoperative stress response, postoperative pain, sleep deprivation, need for analgesia, and the possibility for early return to a familiar environment after early discharge. Also, a relationship between the inflammatory response and the extent of recovery after surgery may exist. Hall and colleagues[89] report a relationship between inflammatory response as measured by interleukin (IL)-6 and the extent of functional recovery after hip arthroplasty.

Carotid Endarterectomy

Carotid endarterectomy has been considered a procedure that calls for special attention regarding changes in cognition function (see also Chapter 69).

It is performed in patients with a tight (i.e., narrow) (>70% or >90%) stenosis of the internal carotid artery. Postoperatively, neurologic complications may occur as a result of brain ischemia, embolism, or brain hyperperfusion. Yet, an improvement in brain function could occur

if brain perfusion was corrected or perhaps because the carotid plaque is a source of brain emboli. However, neuropsychological studies conducted in this area have produced inconsistent findings that have been highlighted in two systematic reviews.[90,91] Improvement in cognitive performance after carotid endarterectomy was reported in over 50% of studies, with 43% showing no change or decline.[91]

REGIONAL VERSUS GENERAL ANESTHESIA

If general anesthesia is an important factor leading to the development of POCD, regional anesthesia would reduce its incidence (see also Chapters 56 and 57). In the randomized studies using neuropsychological testing after surgery, no clear picture emerges during the first postoperative week. Significantly better neuropsychological test performance has been reported at examination from the first 6 hours to 4 days with regional anesthesia[12,92,93] but after the first week after surgery, no significant advantage of regional anesthesia has been detected (Table 99-3). Methodologic limitations could be an important confounding factor because in these types of studies blinding of patients and even blinding of examiners may be difficult.

The largest study conducted found no significant difference in POCD between general or regional anesthesia at either 1 week (general anesthesia = 37 of 188 (19.7%), regional anesthesia = 22 of 176 (12.5%), P = .06), or 3 months (general anesthesia = 25 of 175 (14.3%), regional anesthesia = 23 of 165 (13.9%), P = .93) after surgery.[94] Regional anesthesia was unsuccessful in 24 patients allocated to regional anesthesia for whom general anesthesia was therefore necessary (see also Chapter 56). Also, 35 patients allocated to general anesthesia actually received spinal or epidural anesthesia. Not all of these 59 patients

TABLE 99-3 RANDOMIZED STUDIES COMPARING GENERAL AND REGIONAL ANESTHESIA USING NEUROPSYCHOLOGICAL TESTING

Authors	No. Completed	Age	Interval After Surgery	Type of Surgery	Results
O'Dwyer et al[153]	255	Mean 55 yr	6 hr, 24 hr, and 3 days	Hernia repair	No significant difference
Casati et al[154]	30	Median 84 yr	1 and 7 days	Hip fracture repair	No significant difference
Rasmussen et al[94]	340	Median 71 yr	3 mo	Mixed	No significant difference at 3 mo using intention to treat but significant difference at 1 wk 21% versus 13% in favor of regional when using per protocol analysis
Somprakit et al[155]	120	Group 1 = mean 37 yr Group 2 = mean 67 yr	1 and 3 days	Mixed	No significant difference in whole group, but older group had significantly more POCD
Williams-Russo et al[22]	231	Median 69 yr	1 wk and 6 mo	Knee replacement	No difference between groups
Campbell et al[156]	157	Mean 77 yr	24 hr, 2 wk, 3 mo	Cataract	No differences between groups
Haan et al[13]	37	Mean 72 yr	4 days and 3 mo	Urology	No significant difference
Nielson et al[157]	64	Mean 69 yr	3 mo	Knee replacement	Improvement: No difference between groups
Jones et al[158]	129 50 controls	>60 yr	3 mo	Knee or hip replacement	Significant improvement in 2/5 variables in general anesthesia group, no change in regional anesthesia group (P = .03 and .04 between groups)
Chung et al[10]	44	Mean 72 yr	6 hr, 1, 3, and 5 days and 1 mo	Urology	No difference
Asbjørn et al[93]	40	Mean 69 yr	4 days and 3 wk	Prostatectomy	No difference
Ghoneim et al[159]	105	Mean 61 yr	1-7 days and 3 mo	Mixed	No difference
Hughes et al[12]	30	Mean 68 yr	24 hr, 48 hr, and 1 wk	Hip arthroplasty	No difference after 1 week
Chung et al[92]	44	Mean 72 yr	6 hr, 1, 3, and 5 days and 1 mo	Prostate resection	Significantly higher MMSE in regional at 6 hr
Bigler et al[160]	38	79 yr	1 wk and 3 mo	Repair of hip fracture	Improvement in both, with no difference between the two regimens
Riis et al[161]	30	>60 yr	1 wk and 3 mo	Hip replacement: general, epidural or combined	Initial decline from baseline at 4 days and then improved, with no group differences
Karhunen and Jöhn[162]	47	Mean 73 yr	1 wk	Cataract surgery	After 1 wk significantly more deterioration in local anesthesia group in one of two combined scores

completed the study, but when excluded in a per protocol analysis, a significant difference in the incidence of POCD was found between general anesthesia in 33 of 156 (21.2%) versus regional anesthesia in 20 of 158 (12.7%) after 1 week ($P = .04$); however, at 3 months no difference was found.

ETIOLOGIC CONSIDERATIONS

Perhaps POCD is the result of brain cell damage caused by toxic substances or hypoxia. Toxic substances could be drugs such as general anesthetics or analgesics, but also the surgery-induced release of hormones or inflammatory mediators or a combination of these factors. Hypoxia may result from arterial hypoxemia or low perfusion caused by low cardiac output, inappropriate blood flow distribution, thrombosis, or embolism.

DRUGS

Anesthetic central nervous system toxicity may be a possible explanation for POCD (see also Chapter 15). General anesthesia is assumed to be a completely reversible condition. Yet, this conclusion has not been conclusively proved. Exposure of animals to anesthetics has resulted in the detection of several types of changes in the brain. Jevtovic-Todorovic and co-workers[95] demonstrated histologic changes in the brain after exposure to isoflurane, nitrous oxide (N_2O), and midazolam. In developing rat brain, apoptosis was found in thalamic nuclei and the parietal cortex after exposure to isoflurane and this effect was more pronounced if midazolam or N_2O was added.[95] Memory testing using a water maze revealed inferior performance in the anesthetized rats compared with control animals. Also, infant mice showed signs of apoptosis in brain cortex after subcutaneous administration of midazolam or ketamine[96] and after propofol or combinations of ketamine with propofol or thiopental.[97] In adult rat brain cortex, neuronal vacuolization and neuronal degeneration with necrosis were found after N_2O administration. The neuronal vacuolization, however, seemed to be reversible, with no vacuolated neurons after 3 hours of recovery, and the addition of diazepam or isoflurane blocked the neurodegeneration.[98] These findings are interesting but do not provide convincing evidence for induction of persistent neuronal changes after general anesthesia in humans, where N_2O is not used as the only anesthetic.

Apoptosis occurred in human neuroglioma cells that were exposed to isoflurane, and increased levels of amyloid precursor protein were also found.[99] Abnormal processing of amyloid precursor protein with accumulation of β-amyloid protein is a feature of Alzheimer disease, and it is therefore important to determine whether general anesthetics influence the processing of this protein.Another possible effect of anesthetics could be related to long-term changes in brain receptor function. A decrease in cholinergic function has been found in Alzheimer disease, and cholinesterase inhibitors may be beneficial for patients with this condition. In one study, changes in cholinergic binding were found in rat brains after repeated pentobarbital anesthesia given by intraperitoneal injection.[100] Anesthetics cause changes in gene expression in the brain and in the protein synthesis pattern, as detected by comparison of brain tissue protein contents in anesthetized and control animals.[101-103] These findings in animals or cell cultures are difficult to apply to the clinical situation with POCD in humans. Animal studies of anesthetic drug toxicity may be influenced by inadequate oxygenation, ventilation, perfusion, or temperature regulation. In addition, hypoglycemia may occur in infant rodents exposed to general anesthesia. The brain cell damage of anesthesia in this situation may therefore be caused by mechanisms other than drug effects, but these findings have caused much concern in relation to pediatric anesthesia. It is difficult to study central nervous system toxicity consequent to anesthetic exposure. Although large epidemiologic studies have not detected a major long-term effect of anesthesia on cognitive function, such research has important limitations. For example, in a study of 1257 healthy subjects, 946 participants had been previously exposed to at least one general anesthetic with no significant correlation between exposure to anesthesia and performance in cognitive tests.[104] However, as with the collection of any retrospective data, subjects may not recall reliably the type and number of anesthetics they have received or the exact date they received the anesthetic. The importance of age at time of exposure is difficult to ascertain. Better cognitive performance has been found in two studies of cardiac surgery patients receiving inhaled anesthesia compared with propofol during CPB[105,106] (see also Chapter 67). However, the difference was present only within the first postoperative week and no difference was seen at 3 months.[105]Apart from anesthetics, many other drugs are given in connection with surgery. As an example, analgesics may have important effects on cognitive function but have not been related to cognitive decline in elderly surgical patients.[107] In agreement, Johnson and associates[35] found that opioid administration within the 24 hours before the test had no significant influence on performance. Still, other psychoactive medication cannot be excluded as a potential influence on neuropsychological test data obtained in patients during the weeks to months after surgery.

HORMONES

Major surgery causes an endocrine response with release of hypothalamic-pituitary-adrenal (HPA) and sympathetic nervous system hormones. Cognitive impairment can occur with high levels of glucocorticoids.[108,109] Cortisol is toxic to cells in the hippocampus, and this structure plays a critical role in the consolidation of short-term into long-term explicit memory and descending control of the HPA axis. Perhaps repeated episodes of stress cause decreased hippocampal inhibition of the HPA axis and, thus, prolonged hyperactivation.[110] This was studied in 187 patients older than 60 years of age undergoing major noncardiac surgery, and a persistent change in the cortisol secretion pattern was significantly related to POCD at 1 week.[111]

INFLAMMATORY MEDIATORS

Surgery can activate the immune system with release of inflammatory mediators from lymphocytes. Important mediators include cytokines that are able to initiate the activation of other inflammatory mediators and affect brain function either directly or indirectly.[89,112,113] A very pronounced inflammatory response is seen in connection with cardiac surgery using CPB, and significantly higher levels of the cytokines IL-1 and IL-10 in patients with POCD after such procedures.[114] Also, after noncardiac surgery, POCD is associated with increased levels of inflammatory mediators[115,116]; this area is currently a focus of research using animal models.[117,118]

HYPOXIA

Brain hypoxia may lead to irreversible damage depending on the level, duration, and susceptibility. Oxygen (O_2) delivery to the brain depends on blood flow and arterial O_2 concentration, which is primarily related to hemoglobin concentration and arterial O_2 saturation. Brain hypoxia may be caused by a decrease in blood flow or arterial hypoxemia. In connection with anesthesia, inability to initiate ventilation in the patient or unrecognized esophageal intubation may cause profound and long-lasting hypoxemia[119] and subsequently brain damage. Modest perioperative decreases in arterial O_2 saturation are common, but their importance is probably overemphasized when compared with the wide fluctuations in cerebral blood flow and blood hemoglobin level.[120] One possible explanation for this is the ease of measuring arterial O_2 saturation continuously by pulse oximetry. No connection has been shown between modest arterial hypoxemia and postoperative complications, including POCD.[23,121]

BRAIN HYPOPERFUSION

A temporary reduction of cerebral blood flow can cause neurologic or cognitive dysfunction without occlusion of cerebral vessels (see also Chapter 70). Cerebral blood flow is regulated according to brain metabolism and nearly unchanged within wide variations in blood pressure (autoregulation) mediated through changes in diameter of resistance vessels. This autoregulation has a lower limit at approximately a mean arterial blood pressure of 50 mm Hg in healthy adults but is higher in hypertensive subjects.[122] Below this limit, further dilatation of vessels cannot compensate and cerebral blood flow decreases. Measuring cerebral blood flow or brain oxygenation during surgery is complicated. The techniques used include xenon-133, near-infrared spectroscopy, transcranial Doppler imaging (which really measures velocity), and jugular bulb O_2 saturation. All of these techniques are associated with important limitations. Brain perfusion pressure is therefore frequently used to evaluate brain perfusion in clinical practice. During anesthesia, brain metabolism is reduced, and, therefore, a lower brain blood flow may be acceptable. In earlier studies of cardiac surgery, prolonged episodes of hypotension were a risk factor for brain dysfunction,[40,123] but subsequent studies have not been able to confirm this.

THROMBOSIS OR EMBOLISM

Cerebral infarction can be caused by an embolic or a thrombotic occlusion of a cerebral artery, and necrosis of brain tissue, including neurons and glial cells, may result. Thus, tissue architecture is lost and a well-defined infarct can be identified by autopsy or brain imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI). Cerebral infarcts may cause no symptoms at all, depending on the size and location, but the usual clinical presentation is a stroke. Several risk factors have been identified in studies of stroke in the general population and in relation to surgery. Age is an important factor, and other important risk factors include type of surgery; cardiac disease, especially atrial fibrillation; peripheral vascular disease; previous cerebrovascular attacks; and diabetes[124,125] (see also Chapter 80). The incidence of major cerebral complications presenting as stroke after general surgery varies between 0.2% and 0.7%. Most cerebral infarctions in the perioperative period are caused by emboli. Macroemboli are more than 200 μm in diameter and typically consist of atheromatous material or thrombi. These may arise from the left atrium, left ventricle, or aorta.

Microemboli are less than 200 μm in diameter and, as stated earlier, are common in cardiac surgery (see also Chapter 67). As opposed to macroemboli, they may often consist of air introduced into the venous circulation—for instance, through tubing used in the CPB circuit or arterial lines. In addition, paradoxical embolization may occur through an open foramen ovale from the venous side because of subatmospheric pressure in veins or bone marrow if the surgical field is above heart level and venous structures are noncollapsible, as in procedures such as back surgery, craniotomy in the sitting position, and knee replacement. Microemboli occur in joint replacement surgery (see also Chapter 79). It was specifically assessed in 37 patients in whom cognitive function was studied with a battery of 13 tests at 1 week and at 3 months; POCD was found in 41% and 18%, respectively, but no significant association with microemboli was detected using transcranial Doppler imaging.[84]

GENETIC ASPECTS

Polymorphic genetic variation may explain individual differences in susceptibility to medication, inflammation, trauma, and other harmful factors. Such genetic factors are important for the development of dementia but do not uniquely determine the phenotype.

Apolipoprotein E (ApoE) is a protein that is important for recovery after central nervous system injuries.[126] Important differences exist in the three different isoforms of ApoE—E2, E3, and E4, which are encoded by the alleles *ε2, ε3,* and *ε4* of the *ApoE* gene, respectively. The *ε3* allele is the wild-type and present in 75% of the native European population, whereas *ε2* and *ε4* are less frequent.[127] The *ε4* allele seems to increase the risk for Alzheimer disease, and it is also associated with a poor prognosis after head injury.[128-130] The possible association between the *ε4* allele and POCD after cardiac surgery has been studied, but literature presents conflicting information.[131,132]

The possible relationship between the *ε4* allele and POCD after noncardiac surgery was studied in 976 patients 40 years of age and older; the *ε4* allele was not a risk factor at 1 week ($P = .49$) or 3 months after noncardiac surgery ($P = .28$).[133] POCD is related to the presence of the *ε4* allele in patients undergoing carotid surgery.[134] Other genetic factors could be important in the general surgical population—for instance, individual differences in inflammation and drug metabolism, with polymorphism of the drug metabolism system's cytochrome P-450, are well described. Very slow metabolism of certain drugs could be associated with prolonged recovery, and very fast metabolism could lead to high concentrations of intermediary degradation products.[135] Both situations could result in a disturbance of receptor function, but the relationship, if any, with POCD remains to be established.

CLINICAL SIGNIFICANCE AND LONG-TERM CONSEQUENCES OF POSTOPERATIVE COGNITIVE DYSFUNCTION

The detection of POCD and its likely causes have been discussed. What effect does this dysfunction have on the patient? A frequent report is an elderly patient whose cognitive function has deteriorated profoundly after surgery, especially regarding memory. The relatives describe a loss of function, lack of initiative, and lack of interest in activities that previously meant a lot to the person. In a retired individual, this could be playing cards or doing crossword puzzles. The deterioration may be most noticeable in patients returning to work, when usual tasks may be difficult to carry out in the same manner and at the same speed as before surgery. Such difficulty also is not uncommon in middle-aged or young patients, who also may experience some degree of dysfunction in cognition.

One relevant question is whether POCD in fact results in impairment of function as reflected in activities of daily living. In a study of elderly patients undergoing major noncardiac surgery with general anesthesia, a statistically significant correlation was found between POCD at 3 months and a decline in activities of daily living.[23] Another study of middle-aged patients, by Johnson and associates,[35] found a statistically significant correlation between POCD at 1 week and a decline in instrumental activities of daily living at 1 week reported by relatives at 3 months. Long-term follow-up has revealed a significantly higher mortality in patients with cognitive dysfunction after noncardiac surgery.[86,136] POCD also is associated with earlier retirement and need for social transfer payment.[136] Dementia does not occur frequently after surgery, and whether POCD is a precursor of that condition has not been well studied. Avidan and colleagues[137] found no difference in the rate of cognitive decline according to exposure to surgery and anesthesia in a population undergoing repeated cognitive testing, and age-related cognitive decline may account for some of the changes reported previously. The pronounced variability is also important, and some studies have found no difference in long-term POCD between patients undergoing major surgery (even cardiac) and subjects who had very minor procedures, such as percutaneous angiography.[24,138]

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Chapter 100

Postoperative Visual Loss

STEVEN ROTH

Key Points

- Visual loss after anesthesia is a rare but devastating injury that appears more frequently after cardiac, spine, and orthopedic joint surgery.
- Causes of perioperative visual loss include central or branch retinal artery occlusion (RAO), anterior and posterior ischemic optic neuropathy (ION), cortical blindness, and acute glaucoma. Transient visual loss may occur after transurethral resection of the prostate. Retinal vascular occlusion in patients who receive nitrous oxide–containing gas mixtures after a vitrectomy procedure with vitreal gas bubble tamponade is caused by acute expansion of the gas bubble and increased intraocular pressure.
- Signs and symptoms of visual loss in the postoperative period may be subtle and can be incorrectly attributed to the residual effects of anesthetic drugs. Any patient reporting eye pain, an inability to perceive light or motion, complete or partial loss of visual fields, decreased visual acuity, or loss of pupil reactivity must be evaluated immediately by an ophthalmologist.
- The most common cause of perioperative central and branch RAO is compression of the eye. During cardiac surgery, emboli may occlude the retinal arteries.
- Patients who undergo prolonged operative procedures in the prone position with large blood losses are at frequent risk for development of ION. Other factors conferring a more frequent risk during spine surgery include male gender, obesity, the use of a Wilson frame, and intravascular fluids administered perioperatively. Controversy exists with respect to the appropriate arterial blood pressure, hemoglobin, intravascular fluid administration, and use of vasopressors in these patients. The potential risk for ION should be considered in the design of an anesthetic plan. Patients must be informed of the risk for visual loss accompanying lengthy surgical procedures with the patient positioned prone and with anticipated large blood loss. Both anesthesia and surgery personnel, together, should develop a plan in conjunction with the surgeons by which informed consent for this complication may be facilitated.
- Perioperative visual loss in the presence of focal neurologic signs or the loss of accommodation reflexes or abnormal eye movements suggests a diagnosis of cortical blindness. Neurologic consultation should be obtained.

Perioperative visual loss (POVL) is a rare but unexpected and devastating complication. Spine surgery, particularly when fusion is performed, is one of the most common procedures associated with POVL. Hence, a major emphasis of this chapter is on POVL associated with spine surgery. The incidence, suspected risk factors, diagnosis, and treatment of eye injuries leading to visual loss in the perioperative period are discussed. The discussion is confined to visual loss that follows nonocular surgery because eye damage after ocular surgery is well described in the ophthalmology literature (see also Chapter 84). Injuries to the retina and optic nerve and the visual connections to the brain are discussed.

No prospective studies of POVL have been performed. A few retrospective studies and published surveys and case reports provide much of the current knowledge on postoperative visual loss. Two large retrospective studies showed that perioperative ischemic optic neuropathy (ION) is rare, occurring in approximately 1 in 60,000 to 1 in 125,000 anesthetic procedures in the overall surgical population.[1,2]

Spine and cardiac surgery are associated with a more frequent incidence of POVL than other operative procedures. Shen and associates[3] examined the POVL prevalence in the U.S. database, Nationwide Inpatient Sample (NIS), for the eight most commonly performed surgical

procedures, excluding obstetrics and gynecologic surgery, which is the largest patient population studied. The most frequent were spine (3.09 per 10,000, 0.03%) and cardiac surgery (8.64 per 10,000, 0.086%). The yearly rates of POVL in the procedures studied by Shen and colleagues[3] have been decreasing in the 10-year period from 1996 to 2005. Patil and colleagues[4] found an overall rate of 0.094% in spine surgery discharges in the NIS.[4] In previous, smaller case series, Stevens and colleagues[5] found four ION cases in 3450 spine surgeries (0.1%), and two cases in 3300 patients after spine surgery were reported at another hospital (0.06%).[6] Chang and Miller reviewed 14,102 spine surgery procedures in one hospital, identifying four ION cases (0.028%).[7] After cardiac surgery, the incidence may be as frequent as 1.3% in one study[8] but 0.06% and 0.113% in two more recent larger retrospective studies.[9,10]

Myers and associates[11] conducted a retrospective case-control study of 28 patients with visual loss after spine surgery. The American Society of Anesthesiologists (ASA) Postoperative Visual Loss Registry reported on 93 cases of visual loss after spine surgery submitted anonymously to the ASA Closed Claims Study.[12] Nuttall and associates[9] performed a retrospective case-control study of cardiac surgery patients at the Mayo Clinic.[9] The most recent study was a retrospective, case-controlled study of factors involved in perioperative ION in spine surgery, a collaborative effort of 17 U.S. and Canadian medical centers.[13] Each of these studies is described in detail in subsequent sections of this chapter.

RETINAL ISCHEMIA: BRANCH AND CENTRAL RETINAL ARTERY OCCLUSION

Central retinal artery occlusion (CRAO) decreases the blood supply to the entire retina, whereas occlusion of a retinal arterial branch (BRAO) is a localized injury affecting only a portion of the retina. This injury is usually unilateral. Four causes can be distinguished: (1) external compression of the eye, (2) decreased arterial supply to the retina (embolism to the retinal arterial circulation or decreased blood flow from a systemic cause), (3) impaired venous drainage of the retina, and (4) arterial thrombosis from a coagulation disorder.

The most common cause of perioperative retinal arterial occlusion is improper patient positioning with external compression of the eye producing sufficient intraocular pressure (IOP) to stop flow in the central retinal artery (see also Chapter 41). It most commonly occurs during spine surgery performed with the patient in the prone position. Pressure within the orbit also can be increased internally after retrobulbar hemorrhage, which is associated with vascular injuries during sinus or nasal surgery.

Although rare in most surgical procedures, emboli can directly impair blood flow in the central retinal artery (CRA) itself or a branch of it. Paradoxical embolism originating from the operative site and reaching the arterial circulation through a patent foramen ovale has rarely been reported as a cause of perioperative retinal vascular occlusion.[14] Retinal microemboli, however, are common during open heart surgery.[15] Hypotension itself seems to be a rare cause of retinal ischemia. The incidence of retinal ischemia after hypotensive anesthesia was only 3 cases in 27,930 hypotensive anesthetic procedures.[16]

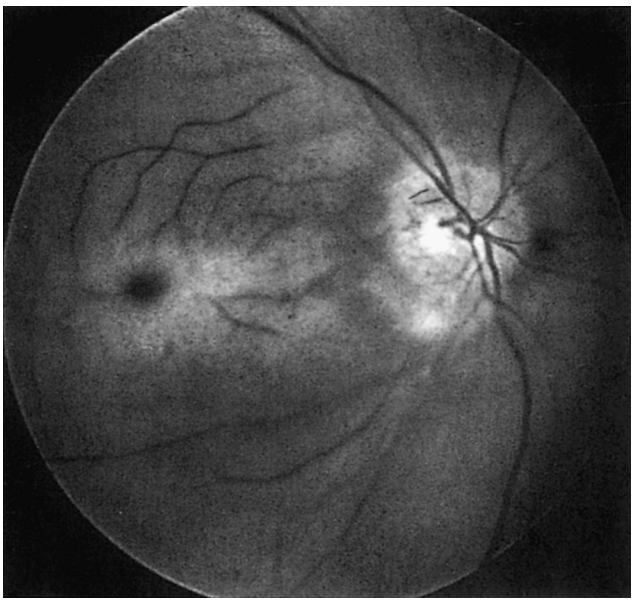


Figure 100-1. Funduscopic appearance of retinal vascular occlusion. Note the pallor of the retina and the cherry-red spot, visible in the fovea near the center of the photograph. The ischemic retina loses its normal transparency, and because the fovea is thinner than the surrounding retina, the underlying choroid is visible as a cherry-red spot. *(From Ryan SJ:* Retina, *ed 2, St. Louis, CV Mosby, 1995.)*

Venous drainage can be impaired after radical neck surgery by jugular vein ligation.[17] In normal volunteers or spine surgery patients positioned prone, IOP increased and head-down position resulted in further increases. Changes were attenuated by head-up positioning.[18,19] The clinical significance of these changes are not clear.

CLINICAL FINDINGS

Painless visual loss and abnormal pupil reactivity occur. Funduscopic examination shows opacification or whitening of the ischemic retina, and narrowing of retinal arterioles may be visible.[20] BRAO is characterized by cholesterol emboli (bright yellowish, glistening), calcific emboli (white, nonglistening), or migrant pale platelet fibrin emboli (dull, dirty white). A cherry-red macula with a white ground-glass appearance of the retina and attenuated arterioles is a "classic" diagnostic sign in CRAO (Fig. 100-1). The red appearance from pallor in the ischemic, overlying retina makes visible the color of the intact, underlying choroidal circulation. However, this sign is not always present; thus, its absence does not rule out retinal artery occlusion (RAO). Differential diagnosis from other causes of visual loss is presented in Table 100-1.

MECHANISMS OF RETINAL ISCHEMIA

Increased extracellular glutamate concentrations during retinal ischemia[21] and attenuation of ischemic injury in vitro and in vivo by glutamate receptor antagonists[22] support a role for excitotoxicity. It is thought that an

TABLE 100-1 **DIFFERENTIAL DIAGNOSIS: EYE EXAMINATION IN RETINAL, OPTIC NERVE, OR VISUAL CORTEX INJURY***

	AION	PION	Cortical Blindness	CRAO	BRAO
Optic disk	Pale swelling, peripapillary flame-shaped hemorrhages, edema of optic nerve head Late: Optic atrophy	Initially normal Late: Optic atrophy	Normal	Normal Late: Optic atrophy	Normal Late: Optic atrophy
Retina	Normal; may have attenuated arterioles	Normal; may have attenuated arterioles	Normal	Cherry-red macula†; pallor and edema, narrowed retinal arteries	Emboli may be present‡; partial retinal whitening and edema
Light reflex	Absent or RAPD	Absent or RAPD	Normal	Absent or RAPD	Normal or RAPD
Fixation and accommodation	Normal	Normal	Impaired	May be impaired with external compression	May be impaired with external compression
Opticokinetic nystagmus	Normal	Normal	Absent	Normal	Normal
Response to visual threat	Yes, if some vision remains	Yes, if some vision remains	No	Yes	Yes
Object tracking	Normal, if some vision remains	Normal, if some vision remains	Absent	Normal	Normal
Ocular muscle function	Normal	Normal	Normal	May be impaired if results from external compression	May be impaired if results from external compression
Perimetry	Altitudinal defect; scotoma	Altitudinal defect; blind; scotoma Often no light perception	Hemianopia (depending on lesion location); periphery affected usually	Usually blind	Scotoma; usually normal periphery

AION, Anterior ischemic optic neuropathy; *BRAO,* occlusion of a retinal arterial branch; *CRAO,* central retinal arterial occlusion; *PION,* posterior ischemic optic neuropathy; *RAPD,* relative afferent pupillary defect.

*Typical symptoms and signs are listed. Some patients may have varying findings as a result, among other factors, of timing of examination relative to symptom onset.

†Because of a lack of overlying inner retinal cells in the fovea, the intact choroidal circulation is visible as a cherry-red spot.

‡Cholesterol, platelet-fibrin emboli, calcified atheromatous material.

increased intracellular Ca^{2+} concentration as a result of enhanced glutamate release ultimately initiates mechanisms that result in cellular destruction.

Two distinct blood flow patterns follow a period of ischemia. In cats, retinal and choroidal blood flow increased dramatically (hyperemia) immediately after the end of ischemia.[23] Hyperemia is of clinical relevance in reperfusion after a period of ischemia, increasing flow when vessels or the blood-retinal barrier is damaged, and might lead to macular edema.[24] Hypoperfusion is the other extreme. In adult rats, delayed retinal hypoperfusion occurs 1 to 4 hours after the end of a period of ischemia.[25] The mechanism of these changes in blood flow is not clear, although depletion of vasodilators such as adenosine or nitric oxide (NO) may be responsible.

The retinal blood supply is derived from the retinal and choroidal vessels.[26] Therefore, after retinal vascular occlusion, some oxygen (O_2) may still be supplied by diffusion from outer retinal layers by way of the choroid. In monkeys, eyes with CRAO showed little damage in the macular retina after 97 minutes of ischemia. After 240 minutes, damage was profound and irreversible.[27] These studies were conducted by clamping the central retinal artery (CRA) and may not necessarily extrapolate to the perioperative complication of external compression of the eye.[28] Interestingly, the same investigators reported that atherosclerosis did not increase sensitivity to ischemia in monkeys and actually may have "preconditioned" the animals against ischemic insult.

Increased IOP from external compression of the eye is a more severe insult than ligation of the CRA because of the profound simultaneous decreases in both retinal and choroidal blood flow[23] and the differential susceptibility of the inner retinal cells to damage from pressure.[29] Ischemic tolerance time is probably shorter with external compression, as evident in studies of injury in animal models of retinal ischemia[30-33] (Table 100-2).

Central Retinal Artery Occlusion

The cause of perioperative CRAO is usually external compression and sufficiently high IOP to occlude the retinal arterial circulation. Patient characteristics may increase the risk for CRAO. Altered facial anatomy may predispose to damage by the external pressure of anesthesia masks or headrests. In osteogenesis imperfecta, fibrous coats of the eye are thin and immature because of deficiency of collagen fibers, persistent reticulin fibers, and increased mucopolysaccharide ground substance. Sclerae and corneas

TABLE 100-2 ANIMAL STUDIES OF RETINAL ISCHEMIA AND TIME REQUIRED TO PRODUCE INJURY

Author	Animal	Ischemia Method	Ischemia Time
Hayreh et al (1980, 2004)[27,28]	Monkey	Central retinal artery ligation	>100-240 min
Ettaiche et al (2001)[30]	Rat (brown Norway)	Increased intraocular pressure	20 and 40 min
Roth et al, Zhang et al (1998, 2002)[31,32]	Rat (S-D)	Central retinal artery ligation, increased intraocular pressure	45 and 60 min
Zhu et al (2002)[33]	Mouse (ND4)	Increased intraocular pressure	30, 45, 60 min

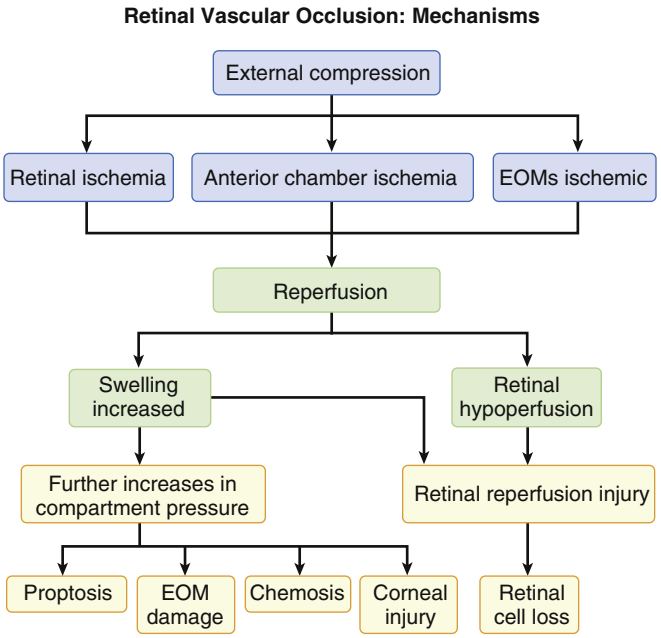


Figure 100-2. Mechanisms of retinal injury after external compression of the eye. *EOM,* Extraocular muscle.

are unusually thin and exophthalmos is common, rendering the eye more vulnerable to damage from external pressure. Those of Asian descent tend to have lower nasal bridges, which may increase the risk for external compression.[34]

Improper positioning of the head with external pressure on the eyes may compress ocular contents and, consequently, occlude retinal blood flow (see also Chapter 41). Most reports of improper positioning involve patients positioned prone for surgery. The horseshoe headrest is of particular concern because of its shape and its narrow opening for the face; improper head position or unintended head movement may place the eye in contact with the headrest. In most of the reports of CRAO in patients positioned prone for surgery, the horseshoe headrest or a similar device (e.g., a rectangular headrest[35]) was used.[34,36] Kumar and colleagues[37] reviewed published case reports of CRAO after spine surgery. Signs and symptoms included unilateral loss of vision, usually with loss of light perception, afferent pupil defect, periorbital or eyelid edema, chemosis, proptosis, ptosis, paresthesias of the supraorbital region, hazy or cloudy cornea, and corneal abrasion. Loss of eye movements, ecchymosis, or other trauma near the eye also was reported. On funduscopic examination, findings included macular or retinal edema, a cherry-red spot, or attenuated retinal vessels. Two reports describing four patients who sustained external compression documented the development of retinal pigmentary alterations, suggesting simultaneous choroidal circulatory ischemia.[38,39] Early orbital computed tomography (CT) or magnetic resonance imaging (MRI) showed proptosis and extraocular muscle swelling, although most cases did not have imaging studies to confirm the diagnosis.[37] Findings were similar to the syndrome of "Saturday night retinopathy" in intoxicated individuals who slept while their eyes were compressed.[40]

Hollenhorst and co-workers,[41] who described unilateral blindness in patients positioned prone for neurosurgery, replicated the human findings in monkeys with 60 minutes of elevated IOP by exerting a pressure of 200 mm Hg on the eye together with hypotension. (Hypotension was not a feature in six of the eight human subjects in their report.) In the monkey, histologic findings were edema of the retina and dilated vascular channels, followed by severe loss of retinal structure and axonal loss in the optic nerve 4 months later, owing to retrograde axonal degeneration after death of retinal ganglion cells.[41]

More recently, Bui and colleagues[42] documented that during acute increases in IOP in the rat, changes in visual function assessed by electroretinography progressed from the inner to the outer retina. In other words, retinal ganglion cells were the most sensitive to raised IOP, showing abnormalities on the electroretinogram at IOPs of 30 to 50 mm Hg; the photoreceptor cells were not affected until IOP was higher.[42] The duration of increased IOP that injures the retina (see Table 100-2) varies depending on rat or mouse strain. Ischemic times were as short as 20 minutes or as long as 30 or 45 minutes.[32,33,43] The mechanisms of injury with increased IOP from external compression are summarized in Figure 100-2.

Proper use of modern head-positioning devices such as square or circular foam headrests with cutouts for the eyes as well as a mirror to view the eyes (i.e., ProneView, Dupaco, Oceanside, Calif.) should prevent ocular compression. However, we reported a case of unilateral RAO in a prone-positioned patient whose head was placed in a square foam headrest and goggles were used to cover the eyes. This practice is hazardous because of the limited amount of space between the headrest and the goggles and the risk for compression of the eye by the goggles. The patient exhibited signs of direct compression of the eye by the goggles, which, ironically, were designed by the manufacturer Dupaco to function as eye protectors.[44]

Ischemic ocular compartment syndrome, more typical in the setting of retrobulbar hemorrhage after nasal sinus surgery, was described in a patient undergoing spine surgery and positioned prone.[45] The patient's head had been positioned on a silicone headrest for surgery that

lasted 8 hours during which he received only 1 L of crystalloids. Postoperatively, he had left ocular pain, no light perception from the eye, facial edema, 4-mm left proptosis, and a tight orbit. Corneal edema was present, with a large abrasion, mid-dilated and fixed pupil, advanced cataract, pale optic nerve, retinal hemorrhages, and complete inability to move the eye. The IOP was 45 mm Hg. MRI showed proptosis, extraocular muscle enlargement, and severe globe tenting. Despite lateral canthotomy to relieve the pressure, vision did not improve. The cause was thought to be related to positioning with possible direct pressure on the eye.

Orbital compartment syndrome can occur from perioperative intraorbital hemorrhage, orbital emphysema, or intraorbital bacitracin ointment during endoscopic sinus surgery.[46] This syndrome is different from cases of ION after spine surgery but may be similar to the early descriptions of ocular compression by Hollenhorst and co-workers.[41] Orbital compartment syndrome is an acute ophthalmologic injury, requiring prompt decompression to relieve the increased IOP.

Head and Neck Surgery

CRAO has occurred after neck and nasal or sinus surgery, although most cases of visual loss in neck dissection are from ION.[47] The incidence of orbital complications after endoscopic sinus surgery is 0.12%.[48] Orbital hemorrhage from blunt trauma during the procedure can result in orbital compartment syndrome with compression of the arterial and venous circulations and in CRAO and optic nerve injury.[49] Indirect damage to the CRA from intraarterial injections of 1% lidocaine with epinephrine has also been described; the mechanism of action is thought to be arterial spasm or embolism.[50]

Branch Retinal Artery Occlusion

BRAO usually leads to permanent ischemic retinal damage with partial visual field loss. Patients may not notice symptoms immediately if the visual field loss is peripheral or if a small scotoma is present. BRAO is primarily the result of emboli, but vasospasm has been reported in a few cases. Most case reports describe embolization of material from intravascular injections and circulating embolic material from the surgical field or cardiopulmonary bypass (CPB) equipment in cardiac surgery.

Microemboli to the retina during CPB have been shown by retinal fluorescein angiography. Occurrence and extent of perfusion defects were related to oxygenator type. When a bubble oxygenator was used, all patients had perfusion defects indicative of microemboli; when a membrane oxygenator was used, retinal perfusion defects were found in only half. Neurologic outcome was not reported.[51] In coronary artery bypass graft (CABG) surgery, multiple calcific emboli in branches of the CRA are not unusual, resulting in visual field deficits of varying size and location. In pigs, mechanisms of air embolism during CPB included nonperfusion, vascular leakage and spasm, red blood cell (RBC) sludging, and hemorrhage. Priming with perfluorocarbons blocked many of these mechanisms.[52]

Case reports have described sudden irreversible blindness with BRAO in patients after the injection of various drugs into the head and neck region. Loss of vision was nearly instantaneous when steroids were injected into the nasal mucosa.[53] In approximately half of cases, crystalline emboli could be seen at fundoscopy, and one incident appeared to be complicated by vasospasm. Other agents, such as superselective injection of carmustine into the internal carotid artery to treat gliomas, or fat injected into the orbit for cosmetic surgery, also have been complicated by visual loss from retinal arterial occlusion.[54] This complication can occur from a neuroradiologic or angiographic or embolism procedure in the head and neck.

Local infiltration anesthesia with lidocaine or bupivacaine in combination with epinephrine (1:100,000 or 1:200,000) for nasal septal surgery can cause partial or total visual field defects postoperatively attributable to BRAO.[50] The cause of BRAO was vasospasm, likely induced by accidental intraarterial retrograde injection of epinephrine or the combination of lidocaine and epinephrine into branches of the external carotid artery.

BRAO was described in a patient in the prone position for spine surgery. After surgery a patent foramen ovale was discovered. The patient likely sustained a paradoxical air, fat, or bone marrow embolization from the operative site in the lumbar spine.[14]

PROGNOSIS

Perioperative RAO results in permanent loss of vision in most cases.

TREATMENT

Currently available methods of treatment are not satisfactory. Treatment with ocular massage to decrease IOP (contraindicated if glaucoma cannot be ruled out) and thereby dislodge an embolus, if present, to more peripheral arterial branches could be instituted.[20] Intravenous acetazolamide can be administered to increase retinal blood flow. Five percent carbon dioxide in O_2 can be given to enhance dilation and increase O_2 delivery from retinal and choroidal vessels.[26] Further treatment may include thrombolysis, although it is contraindicated after certain surgical procedures. Fibrinolysis through a catheter in the ophthalmic artery within 6 to 8 hours after spontaneous CRAO was associated with improved visual outcome. An ongoing multicenter study is testing efficacy. [55] Localized application of hypothermia to the affected eye is a simple technique that has decreased injury in animal studies after ischemia,[56] and probably should be instituted in humans because of its minimal risk.

PREVENTION

Because retinal arterial occlusion in the perioperative period is most often caused by unintended application of external pressure to the eye, steps must be taken to avoid compression of the globe. Pressure on the eye from anesthetic masks is avoidable. If surgery is near the face, the surgeon's arm must not be allowed to rest on the patient's eye. In patients positioned prone for surgery, a foam headrest should be used with the eyes properly placed in the opening of the headrest; the position of the head and

the eyes should be checked intermittently by palpation or visualization. The horseshoe headrest for the prone-positioned patient must be used with great caution, and safer choices are available. For the patient positioned prone for cervical spine surgery, this headrest should not be used because of the likelihood of head movement, leading to compression of the eye. In the setting of cervical spine surgery with the patient prone, the most effective method for preventing head movement is to place the head in pins.

While the patient is prone, intermittent examination of the eyes is advisable approximately every 20 minutes for a change in position and the absence of external compression. If the patient's head does not fit the headrest adequately (e.g., it is too large) or for surgery on the cervical spine, the head could be held with a pin head holder. Some surgeons now routinely place the patient's head in a pin head holder even for lumbar spine surgery, which eliminates opportunity for pressure on the eyes. This use must be weighed against the associated risks. For most procedures in which the patient is prone, I recommend any of the commercially available square foam headrests. The head is positioned straight down in the neutral position. The eyes and nose are then placed in the open portion of the headrest so that they can be easily checked underneath for pressure intermittently. When a transparent head piece is in use on the operating table, a mirror can be positioned underneath to indirectly view the eyes on the headrest. The ProneView is useful because it combines a foam headrest with a mirror immediately below, which enables the eyes to be seen easily during surgery. The use of goggles to cover the eyes is not advised when the head is positioned prone in a conventional square foam headrest.

In nasal and sinus surgery and in neuroradiologic procedures, the most important principles are avoidance of inadvertent injections into, or compromise of, the ocular circulation. After endoscopic sinus surgery, patients should be checked for signs of acutely elevated IOP suggestive of orbital hemorrhage. If present, immediate ophthalmologic consultation should be obtained. Embolization during CPB remains a cause of retinal vascular occlusion. Better means for detecting and preventing this complication are needed.

ISCHEMIC OPTIC NEUROPATHY

ION, primarily manifesting spontaneously without warning signs, is the leading cause of sudden visual loss in patients 50 years of age or older, with an estimated annual incidence of nonarteritic ION in the United States of 2.3 per 100,000.[57] The two types of ION—anterior (AION) and posterior (PION)—can be arteritic or nonarteritic. Arteritic AION, caused by temporal arteritis, responds to steroids. It is a systemic disease, generally occurs in patients 60 years of age or older, and has a female preponderance. Spontaneously occurring ION, unrelated to surgical procedures, is usually caused by AION. The specific mechanism and location of the vascular insult remain unclear.[58] A rodent model for AION has been recently described.[59]

Nonarteritic ION, more common than arteritic, is overwhelmingly the type found perioperatively. It has been reported after a wide variety of surgical procedures, with most after cardiothoracic surgery,[60] instrumented spinal fusion operations,[61] head and neck surgery,[62] orthopedic joint procedures,[3] and surgery on the nose or sinuses.[63] Cases also have been described after vascular surgery, general surgical and urologic procedures (radical prostatectomy), caesarean section and gynecologic surgery, and liposuction. Most perioperative cases are in adults, with some reports in children.

Although many clinical studies of spontaneously occurring AION have been conducted, few concern PION. The lack of controlled studies, the absence of an animal model, and poorly defined pathologic and risk factors limit our understanding of perioperative ION. The largest and best described single series is the ASA Postoperative Visual Loss Registry.[12] Two case-control studies in spine surgery patients[11,13] and two in cardiac surgery have been done.[8,9]

MECHANISM

Simulated ischemia in optic nerve axons in vitro[64] culminates in axonal destruction. When O_2 delivery decreases, adenosine triphosphate is depleted, leading to membrane depolarization, influx of Na^+ and Ca^{2+} through specific voltage-gated channels, and reversal of the Na^+-Ca^{2+} exchange pump.[65] Ca^{2+} overload damages cells from activation of proteolytic and other enzymes. ION may lead to neuronal injury by apoptotic cell death, which may be stimulated in vitro with reduced O_2 delivery.[66]

Disruption of the blood-brain barrier occurs early in AION, and fluorescein angiography shows the dye leakage in the optic nerve head.[67] Dye leakage correlates with the early onset of optic disk edema, seen even before symptoms.[68] The relationship between disruption of the blood-brain barrier and ischemic injury is not known. Earlier studies showed classic blood-brain barrier properties in the optic nerve head[69]; however, more recent immunohistochemical studies of microvessels in the monkey and human optic nerve head suggest a lack of classic blood-brain barrier characteristics in the prelaminar region,[70] which could explain the early edema in the optic nerve head after ischemia.

In vivo cellular mechanisms lead to ischemic injury in the optic nerve. Guy[71] showed that 30-minute occlusion of the carotid artery in rats produced ischemia and a swollen optic nerve within 24 hours. The positive nitrotyrosine immunostaining found in the ischemic optic nerve suggests a possible role for NO and perhaps O_2 free radicals, which would be expected to increase disruption of the blood-brain barrier. Bernstein and associates[59] described a rodent model of AION. After AION induction by a photothrombotic method, circulation to the optic nerve was lost within 30 minutes; edema peaked 1 to 2 days later and resolved by 5 days. A pale, shrunken optic nerve was found, similar to that in limited pathologic studies of human AION.[72] By 37 days after ischemic insult, the percentage of retinal ganglion cells was reduced by approximately 40%. After 6 days, the optic nerve showed axonal swelling and collapse. Permanent changes included septal

thickening and axonal loss, most evident in the center, also similar to that found in the human optic nerve.

Clinical studies of AION with fluorescein angiography showed delayed filling of the prelaminar optic disk in 76% of subjects and was not found in normal eyes. This suggests that delayed filling is the primary process, and it is not caused by disk edema.[58] Hayreh[73] attributed AION to individual variations in blood supply to the optic nerve.[73] This theory is supported not only by anatomic studies but also by the variability of visual loss in patients with AION. The watershed concept—that impaired perfusion and distribution within a posterior ciliary artery predisposes the optic disk to infarction—is disputed. Arnold and Hepler[67] demonstrated that delayed filling of watershed zones was more common in normal eyes than in patients with AION.[67] Thus, reduced perfusion pressure in the region of the paraoptic branches of the short posterior ciliary arteries (PCAs) results in optic disk hypoperfusion, rather than a watershed event.[74] Histopathologic examination in AION showed that the infarction was mainly in the retrolaminar region.[75] This implicates as the source of decreased blood flow the short PCAs directly supplying the optic disk.

Some have suggested that variability in blood pressure or IOP may predispose patients to the development of AION. Nocturnal hypotension in patients treated with antihypertensive agents may expose patients to low-level, albeit repeated, decreases in perfusion to the optic nerve.[76] The importance of IOP fluctuations in the pathogenesis of AION has not been established.[77] Anatomic or physiologic variations in the circulatory supply of the optic nerve may predispose some patients to the development of AION,[78] especially if systemic arterial blood pressure is decreased.

Hayreh[79] reported nocturnal decreases of 25% to 30% in arterial blood pressure in patients with AION.[79] No control group was included, but the decrease was larger than in age-matched normal subjects. Landau and associates[80] compared arterial blood pressure decreases in normal and AION subjects and found no difference, although daytime blood pressures were slightly lower in those with AION. Thus, the role of chronically or intermittently low blood pressures in the pathogenesis of AION remains controversial. AION is also associated with sleep apnea syndrome,[81] but whether the mechanism depends on repeated hypoxia, increased IOP, decreased blood pressure, or altered autoregulation of blood flow in the optic nerve is still unclear.

A small optic disk (known as a small cup-to-disk ratio) may play a role in susceptibility to AION[82] because axons of the optic nerve pass through a narrower opening as they exit the eye and are therefore susceptible to injury in the presence of edema or decreased blood flow. Mechanisms of injury resulting from a crowded disk include mechanical axoplasmic flow obstruction, stiff cribriform plate, and decreased availability of neurotrophic factors to retinal ganglion cells.[58] Tesser and colleagues[72] reported that in a patient with spontaneous AION, axonal loss was in the superior part of the nerve, largely encircling the central retinal artery. The infarct was in the intrascleral portion of the nerve, extending 1.5 mm posteriorly. Perhaps a tight scleral canal contributed to a compartment syndrome in the anterior optic nerve.[72]

The role of systemic diseases such as hypertension and diabetes has been examined (see also Chapter 39). Hypertension was present in 34% to 47% of patients with AION but was significantly different from that in patients without AION only in those 45 to 64 years of age. Increased prevalence of diabetes is present in most studies of AION, but AION has not been consistently associated with stroke and myocardial infarction, cigarette smoking, and elevated cholesterol.[58] Among patients in the Ischemic Optic Neuropathy Decompression Trial (IONDT), 47% had hypertension, 24% had diabetes, 11% had a previous myocardial infarction, and 3% had a stroke.[83] These proportions of patients with vascular risk factors might, however, be similar to those in the general population. For ethical reasons, the IONDT could not include a non-ION control group. Smoking also might be a risk factor for the development of ION, but large numbers of patients have not been reported. AION may be associated with prothrombotic factors, such as deficiencies of protein C, protein S, or factor V Leiden, but reports are conflicting.[84]

PATIENT CHARACTERISTICS

Most of the cases occurring after spine surgery have been PION.[85] A diagnosis of AION occurs more frequently after cardiac surgery. The onset of POVL is typically within the first 24 to 48 hours after surgery and is frequently noted on awakening, although later onset has been described, particularly in sedated patients whose lungs were mechanically ventilated postoperatively.[13] Patients present typically with painless visual loss, afferent pupil defect or nonreactive pupils, complete visual loss, no light perception, or visual field deficits. Color vision is decreased or absent. In AION, altitudinal visual field deficits may be present. Optic disk edema and hemorrhages are seen on symptom onset in AION; in PION, the optic disk appears normal even though the patient reports visual loss. Over a span of weeks to months, optic atrophy develops. The lesion may be unilateral or bilateral, but most post–spine surgery ION cases have bilateral involvement. In ION, orbital MRI is frequently nondiagnostic, although some reports have described changes including enlargement of the nerve from edema or perineural enhancement.[86] More recent MRI techniques may enhance diagnostic capabilities.[87] Visual evoked potential is abnormal, whereas the electroretinogram is unaffected.[88]

Some of the individual case reports should be examined, especially when some patient-specific data are provided. After presentation of this information, the more recent case series will be examined. Case reports in the literature from 1968 to 2002 described 51 patients in whom perioperative AION was diagnosed.[89] Among this group, 59% underwent open heart surgery; 12%, nasal, head, or neck surgery; and 12%, spine surgery. The average age was 53 years, and 72% were male. In many cases, data are missing and variability is seen in the types of data reported. These patients tended to undergo lengthy operations, with an average operative time of 508 minutes. In patients for whom blood pressure was reported, mean arterial pressure averaged 92 mm Hg preoperatively and the lowest mean arterial pressure averaged 65 mm Hg intraoperatively. Preoperative hemoglobin averaged 13.7 g/dL, the lowest

intraoperative value was 8.7 g/dL, and the postoperative hemoglobin concentration was 8.1 g/dL. The patients received considerable amounts of fluid intraoperatively; they averaged 1.4 L of blood replacement, 8.2 L of crystalloid, and 1.0 L of colloid. In 20%, blood loss exceeded 2 L. Coronary artery disease was present in 61%, hypertension in 27%, and diabetes mellitus in 24% of patients. Because of the predominance of CABG, these data may be weighted toward a more frequent prevalence of these disorders in this group.

In 67%, symptoms of visual loss were not evident until more than 24 hours after surgery, either because of delayed onset of the disease or delayed recognition of the symptoms and signs of AION in the perioperative period as a result of mechanical ventilation and sedation postoperatively. Nearly all had disc edema, pallor, or both. Over 60% had an afferent pupil defect or nonreactive pupils. The visual field deficit was altitudinal in 14%, a central scotoma was present in 20%, and in 20% blindness was the initial symptom. Visual loss was bilateral in 55% and unilateral in 45% of patients. Some treatment was attempted in 15 patients, including steroids, aggressive volume replacement, vasopressors, or a combination of these therapies. Treatment did not necessarily result in improvement. Overall, in the 51 patients, 47% had no improvement or a worsening of symptoms, 29% improved, and in 25% the outcome was not described.

Between 1968 and 2002, case reports described 38 patients with perioperative PION. The nature of the surgical procedures in these patients tended to differ from those in the AION reports. In this group, 8% underwent open heart surgery; 24%, nasal, head, or neck surgery; and 39%, spine surgery. The average age was 50 years, and 63% were male. Although AION is rarely reported in children, four patients with PION were 13 years or younger. As with AION, surgery tended to be lengthy, averaging 448 minutes. In patients for whom blood pressure was reported, mean arterial pressure averaged 90 mm Hg preoperatively, with an average lowest mean arterial pressure intraoperatively of 61 mm Hg. Preoperative hemoglobin averaged 12 g/dL, the lowest intraoperative hemoglobin concentration was 8 g/dL, and postoperative values averaged 10 g/dL. These values are similar to those reported in the patients with AION. Hematocrit decreased from 44% to 27% intraoperatively and increased to 29% postoperatively. The patients also received considerable amounts of fluid intraoperatively; they averaged 2.3 L of blood replacement, 8.8 L of crystalloid, and 1.6 L of colloid. In 37% of cases, intraoperative blood loss exceeded 2 L. Coronary artery disease was present in only 8%, hypertension in 32%, and diabetes mellitus in 21%. In contrast to patients with AION, the incidence of coronary artery disease was much lower. The onset of symptoms was typically within 24 hours postoperatively. Blindness was reported in 47%, an altitudinal defect in 8%, and a central scotoma in 26%. Twenty-seven (71%) patients had an afferent pupil defect or nonreactive pupils. A normal optic disk on initial funduscopic examination was evident in 92%. Visual loss was bilateral in 63% and unilateral in 34%. Forty-five percent had no improvement, 29% improved, and for 18% the outcome was not described.

In summary, most patients with AION had undergone open heart surgery. The largest single group of patients with PION had spine fusion surgery. The main differences were a less frequent incidence of coronary artery disease in the group with PION; the occurrence of PION in younger patients; an increase in intraoperative blood replacement, more rapid onset or recognition of visual loss, and a greater likelihood of complete blindness initially in PION cases than in AION cases.

RETROSPECTIVE CASE SERIES

Sadda and associates[90] retrospectively collected 72 reports on cases of ION from two large academic institutions over a 22-year period. In 38 subjects, PION developed spontaneously, and in 28, it developed in the perioperative period. In the remaining 6, the diagnosis was arteritic PION. For the 38 with spontaneous nonarteritic PION, the average age was 68 years; 39% had hypertension, 24% had diabetes, 18% had coronary artery disease, and 32% had a history of cerebrovascular disease. Bilateral involvement occurred in 21%, and 90% had some form of visual field deficit. Only 30% improved, and 35% worsened. Unlike AION, in which a structural difference in the optic nerve, such as a small cup-to-disk ratio, may be found, these authors could identify a structural abnormality in the optic nerve in only 4% of patients with PION. The 14 patients who had spinal surgery tended to be younger and have a lower incidence of coronary artery disease and diabetes, but not hypertension, relative to the other two groups. Unfortunately, intraoperative data were not included, but the postsurgical patients were more likely to have bilateral involvement (54%) and a worse visual outcome at initial examination and later follow-up compared with PION in nonsurgical cases.

Buono and Foroozan[85] reviewed 83 PION cases reported in the literature. In 36, details of clinical features were included; in the other 47, aggregate data had been reported. Approximately 54% followed spine surgery, 13% radical neck dissection, and 33% other surgery. Mean age was 52 years; patients who had spine surgery were younger (mean age, 44 years) than those in the other groups. Approximately two thirds were men. In 75% of cases, visual loss was apparent within 24 hours of surgery. Visual acuity was "counting fingers" or worse in 76%, and 54% of eyes had an initial visual acuity of no light perception. Over 60% of cases were bilateral. In 38% of patients, vision improved, but of 14 with no light perception initially, 12 (85%) had no improvement. Among patients with PION, 65% had one or more of the following: hypertension, diabetes, cigarette use, hypercholesterolemia, coronary artery disease, congestive heart failure, arrhythmia, cerebrovascular disease, or obesity. Mean lowest hemoglobin value was 9.5 g/dL (5.8 to 14.2 g/dL), mean lowest systolic blood pressure was 77 (48 to 120 mm Hg), mean intraoperative blood loss was 3.7 L (0.8 to 16 L), and mean operative duration was 8.7 hours (3.5 to 23 hours).

Spine Surgery

Cheng and colleagues[91] surveyed neurosurgeons in the United States who performed spine surgery, with 24 cases of visual loss reported by 22 surgeons. Mean age was 47

± 15 years. Lumbar spine surgery was the procedure performed most frequently, and mean surgery duration was 4.8 ± 3.5 hours. Mean hematocrit changed from 42 ± 5% to 35 ± 7%. Mean estimated blood loss was 793 ± 1142 mL. In 5 patients, estimated blood loss exceeded 1800 mL; 3 received blood transfusions. Of the 24 patients, 21 were normotensive intraoperatively and 2 had deliberate hypotension; 4 had diabetes mellitus, 1 had peripheral vascular disease, and 1 had diabetes and peripheral vascular disease.

Ho and associates[92] reviewed reported cases of AION and PION in the literature after spine surgery. In the 5 cases of AION and 17 of PION, median ages were 53 and 43 years, respectively. Most of the cases followed lumbar spine fusion surgery. Mean operative time for AION cases was 522 minutes and for PION cases was 456 minutes. For AION, the range of the lowest mean arterial pressure was 62 to 78 mm Hg; for PION, it was 52 to 85 mm Hg. Lowest mean intraoperative hematocrit was 27% in the PION cases. Mean blood loss was 1.7 L and 5 L for AION and PION, respectively. Crystalloid/colloid volumes averaged 6.0/0.8 L and 8.0/2.2 L for AION and PION, respectively. Sixty percent of patients with AION and 27% with PION had diabetes mellitus; coronary artery disease was noted in 20% of patients with AION and in none with PION. Prevalence of hypertension was similar (40% or 53%). Symptoms were reported within 24 hours of surgery in 40% of patients with AION; 59% of patients with PION reported symptoms immediately on awakening and 88% within 24 hours. Visual acuity improved somewhat in 60% of AION and 65% of PION cases.

Data from spine surgery patients in the ASA Postoperative Visual Loss Registry[12] showed striking differences between patients with ION ($n = 83$) and those with CRAO ($n = 10$). The average blood loss in ION patients was 2.0 versus 0.75 L with CRAO. The lowest hematocrit was 26% with ION and 31% with CRAO. With ION, decreases in blood pressure varied widely from preoperative baseline: in 33% of cases, the lowest systolic blood pressures were greater than 90 mm Hg; in 20%, the lowest was 80 mm Hg or less. Approximately 57% of patients had systolic or mean arterial blood pressure 20% to 39% below baseline, and 25% of patients were at 40% to 49% below preoperative baseline. Deliberate hypotension was used in approximately a fourth of the patients. Nearly all cases involved surgery exceeding 6 hours. In the majority of the patients, estimated blood loss was greater than 1 L, the median estimated blood loss was 2 L, and the median lowest hematocrit was 26%. Large-volume fluid resuscitation was typical in these patients, with median crystalloid administration of approximately 10 L. Most of the patients underwent thoracic, lumbar, or lumbar-sacral fusion procedures that were often repeat operations that mostly involved multilevel surgery. Surgical positioning devices for these patients were the Wilson frame (30%), Jackson spinal table (27%), and soft chest rolls (20%). A foam pad was used for head positioning for 57%; 19% had the head positioned in a Mayfield head holder. PION accounted for the majority of the cases, compared with AION. Patients in ASA class 1 or 2 accounted for 64% of cases. The mean age was 50 ± 14 years. Approximately 41% had hypertension, 16% had diabetes mellitus, and 10% had coronary artery disease. The ASA Postoperative Visual Loss Registry does not have a control group of unaffected spine surgery patients for comparison to enable a case-control study of risk factors.

In a retrospective case-control study of 28 patients with visual loss after spine surgery, Myers and colleagues[11] found no difference in the lowest systolic blood pressure or hematocrit in the affected versus unaffected patients, suggesting that hypotension and anemia do not completely explain the occurrence of ION. Approximately 40% of these patients had no risk factors for vascular disease preoperatively; a similar percentage in the two groups had hypertension or were smokers.[11]

An important follow-up study to the ASA Postoperative Visual Loss Registry and a more complete examination of possible risk factors compared to the Myers study was published in 2012. This study was a multicenter case-controlled retrospective examination of the factors involved in perioperative ION in lumbar spine fusion surgery. Affected patients were those in the first publication of the ASA Postoperative Visual Loss Registry. The control patients were randomly selected matched patients derived from 17 academic medical centers in the United States and Canada. The results of the study are summarized in Table 100-3. In this retrospective controlled study, six specific factors were found to confer higher risk for sustaining perioperative ION in the setting of lumbar spine surgery: male gender, obesity, positioning on a Wilson frame, duration of anesthesia, large blood loss, and a relatively low ratio of colloid to crystalloid fluid resuscitation.[13]

Cardiac Surgery

Two retrospective case-control studies of blindness after cardiac surgery have been reported (see also Chapter 67). Shapira and colleagues[8] studied 602 patients at a single institution. Patients underwent CPB under moderate systemic hypothermia (25° C) with pulsatile flow and a membrane oxygenator. Neo-Synephrine was used if perfusion pressure could not be maintained above 50 mm Hg despite a flow index of 2 L/m^2/min, and α-stat was used for pH management. Eight patients (1.2%) had AION. There were no differences in preoperative risk factors for vascular disease between patients with or without visual loss. CPB time was longer in patients with AION (252 versus 164 minutes), and minimum hematocrit was lower (18% versus 21%) compared with unaffected patients. No differences were found in flow indices, perfusion pressures,

TABLE 100-3 **FACTORS INCREASING THE ODDS RATIO OF DEVELOPING PERIOPERATIVE ION IN LUMBAR SPINE FUSION SURGERY**

	Odds Ratio	*P* Value
Male	2.53 (1.35-4.91)	.005
Obesity	2.83 (1.52-5.39)	.001
Wilson frame	4.30 (2.13-8.75)	<.001
Anesthesia duration, per hour	1.39 (1.22-1.58)	<.001
Estimated blood loss, per 1 L	1.34 (1.13-1.61)	.001
Colloid as percent of nonblood replacement, per 5%	0.67 (0.52-0.82)	<.001

and P_{CO_2} levels intraoperatively. Patients with AION had a greater 24-hour postoperative weight gain (18% versus 11%) and required more epinephrine and amrinone postoperatively to maintain hemodynamics than did patients with unaffected vision. Visual symptoms were usually reported between days 1 and 3 postoperatively, soon after removal of mechanical ventilatory support.

Nuttall and colleagues[9] performed a larger retrospective case-control study of approximately 28,000 patients who had cardiac surgery at the Mayo Clinic from 1976 to 1994, with 17 patients with ION (0.06%). By univariate analysis, significant risk factors included lower minimum postoperative hemoglobin, history of clinically severe vascular disease, preoperative angiogram within 48 hours of CPB, longer duration of CPB, RBC transfusions, and any use of non-RBC blood components. Patients with ION underwent longer CPB runs; no differences were found in pre-CPB or post-CPB systemic blood pressures. Nine cases of bilateral ION were reported; disk edema was not found in 5 patients (29%), who may have had PION, not AION. Small cup-to-disk ratio (<0.3) was identified in 5 patients (29%) with ION. A more recent series by Holy and colleagues[93] showed similar results, but their series included other surgical procedures, which complicates interpretation of the specific results with cardiac surgery. Kalyani and colleagues[10] retrospectively reviewed cases of ION after 9701 cardiac surgeries over a 9-year period at a single institution. Specific risk factors could not be determined from the 11 patients (0.11%) with ION.

Trauma

Cullinane and co-workers[94] retrospectively reviewed the medical records of over 18,000 trauma cases at a single institution between 1991 and 1998 (see also Chapter 81). Of these, 350 required massive resuscitation with more than 20 L of fluid during the first 24 hours after admission. Volume resuscitation consisted of 21 to 50 L (mean 33 ± 8 L) in the first 24 hours. ION was found in 2.6% (9 patients). Four patients had bilateral blindness. No information was provided on funduscopic examinations. The mean age was 34 ± 13 years. Patients were acidotic, with serum lactate levels ranging from 2.5 to 17.5 mEq/L. Mean lowest hematocrit was 7.5% to 28% (mean 20 ± 8%); blood products included 9 to 39 units of packed RBCs (mean 22 ± 10 units). All patients had a coagulopathy, and all developed acute respiratory distress syndrome that required increased levels of inspired O_2 and positive end-expiratory pressure (mean level 29 ± 9 cm H_2O). All patients had systemic inflammatory response syndrome, and 66% had compartment syndrome at some location remote from the eye. Mean time until detection of visual loss was 36 days because patients needed prolonged mechanical ventilation and sedation.

BLOOD SUPPLY TO THE OPTIC NERVE

ION affects the anterior portion of the optic nerve in AION or beyond the retrolaminar region behind the eye in PION. The ischemic insult has been theorized to be of vascular origin, but this has not been conclusively shown; whether the defect is on the arterial or venous side has not been resolved. Anatomy of and blood supply to the anterior and posterior optic nerves differ.[73] The pathophysiologic basis of PION is even less well understood than that of AION.

The anterior portion of the optic nerve is proximal to the lamina cribrosa, an elastic, collagenous tissue through which the optic nerve, central retinal artery, and central retinal vein pass as they enter the optic disk. The anterior portion of the optic nerve includes the superficial nerve fiber layer and the prelaminar region. The prelaminar area is a thick tissue that constitutes most of the optic disk volume.[95] The superficial nerve fiber layer, composed of axons extending from the retinal ganglion cells, is anterior to the plane extending across the optic nerve from the peripapillary Bruch membrane. Immediately posterior is the prelaminar region, adjacent to the peripapillary choroid. The laminar region is a transition zone between columns of glial cells and dense connective tissue plates. Astrocytes are predominant in the anterior optic nerve, and oligodendrocytes and microglial cells are more common in the posterior or retrobulbar optic nerve. Neural fibers transit the laminar region through fenestrations. The retrolaminar region is the posterior portion of the optic nerve and consists of meningeal sheaths and myelinated axons. The diameter of the optic nerve is enlarged in this area to approximately 3 mm.

The superficial nerve fiber layer derives its blood supply mainly from arterioles in the retina, although in the temporal regions it may receive blood from the posterior ciliary arteries. The prelaminar region is perfused by centripetal branches of the peripapillary choroid and vessels from the circle of Zinn-Haller (Fig. 100-3), which are not found in every eye.[73] Whether the region has a choroid-derived source of blood is controversial. The laminar region is supplied by centripetal branches from the short posterior ciliary arteries or by the circle of Zinn-Haller, but the short posterior ciliary arteries are the primary inputs. Longitudinal anastomoses of capillaries can be seen in the prelaminar and laminar regions and may provide some circulation, although their functional importance is not clearly known.

The retrolaminar, posterior portion of the optic nerve, which is affected in PION (Fig. 100-4), is perfused by two main vascular supplies. The peripheral centripetal vascular system is the major supply and is found in all optic nerves. It is formed by recurrent branches of the peripapillary choroid and the circle of Zinn-Haller. Pial branches of the central retinal artery and other orbital arteries, the ophthalmic artery, and the posterior ciliary arteries also contribute. Branches of the pial vasculature run in the septa of the nerve. The axial centrifugal vascular system is formed by small branches from the intraneural part of the central retinal artery and is not present in every eye; thus, differences in blood supply in the posterior optic nerve may render some individuals more susceptible to PION.[96]

CONTROL OF BLOOD FLOW

Studies of autoregulation of blood flow in the optic nerve head have yielded conflicting results because measurement techniques are limited. Blood flow in the optic nerve head is autoregulated within a range of perfusion

pressures similar to those in the brain of monkeys and sheep. In a small sample of atherosclerotic monkeys, however, autoregulation was defective.[97] This study did not directly measure blood flow; rather, it measured glucose consumption, and the sample size was small. Other evidence of autoregulation is seen in the posterior portion of the optic nerve. In cats, blood flow in the optic nerve measured directly by autoradiography remained constant in the prelaminar, laminar, and postlaminar nerve across a range of systemic mean arterial blood pressure values from 40 to more than 200 mm Hg.[98]

In a study in 13 healthy volunteers, blood flow in the optic nerve head measured by laser Doppler flowmetry was constant between ocular perfusion pressures of 56 to 80 mm Hg[99]; in another, flow was preserved at extremely high IOP that resulted in a minimal perfusion pressure of 22 mm Hg.[100] Other investigators found that flow was preserved in the optic nerve head until ocular pressure reached levels of 40 mm Hg. However, 2 of 10 healthy young volunteers in the study failed to demonstrate autoregulation.[78] Using color Doppler imaging in humans, another group showed that flow velocity in the posterior ciliary arteries decreased at extremely high IOP. These findings seem to support the theory that "watershed" areas in the distribution of the posterior ciliary arteries predispose some patients, including otherwise healthy ones with no known vascular disease, to damage to the anterior portion of the optic nerve when perfusion pressure is decreased, either after systemic blood pressure decreases or IOP is elevated. At present, however, no clinical technique can reliably detect such patients.

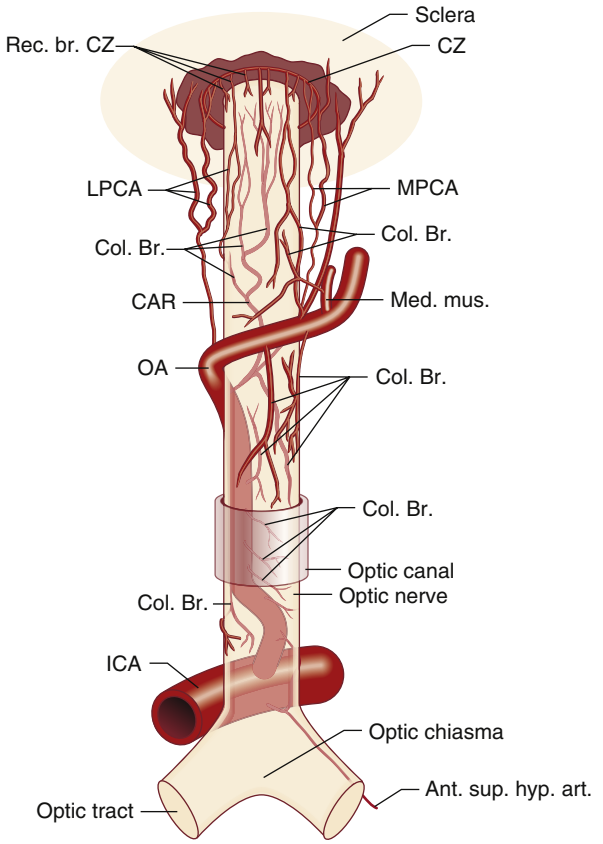


Figure 100-3. The origin, course, and branches of the ophthalmic artery, including the posterior ciliary arteries, as seen from above. *Ant. sup. hyp. art.*, anterior superior hypophyseal artery; *CAR,* central retinal artery; *Col. Br.,* collateral branches; *CZ,* circle of Zinn and Haller; *ICA,* internal carotid artery; *LPCA,* lateral posterior ciliary artery; *Med. mus.*, medial muscular artery; *MPCA,* medial posterior ciliary artery; *OA,* ophthalmic artery; *Rec. br.,* recurring branches. *(From Pillanut LE, Harris A, Anderson DR, et al, editors:* Current concepts on ocular blood flow in glaucoma. *The Hague, Netherlands, 1999, Kugler.)*

HISTOLOGIC FINDINGS

Few reports have been published on the histopathologic examination of the optic nerve in ION. Of three PION cases evaluated after surgical procedures, all of the patients showed infarcts in the intraorbital portion of the optic nerve, but results were not consistent. Two patients had lesions in the central axial portion with peripheral axonal sparing; the other had the opposite pattern in one eye and complete axonal loss in the other.[85] Despite a larger autopsy series in AION, the location of the infarct has not been documented. Tesser and colleagues[72] showed that in a patient with spontaneous AION the axonal loss was in the superior part of the nerve, largely encircling the central retinal artery. The infarct was in the intrascleral portion of the nerve, extending 1.5 mm posteriorly.

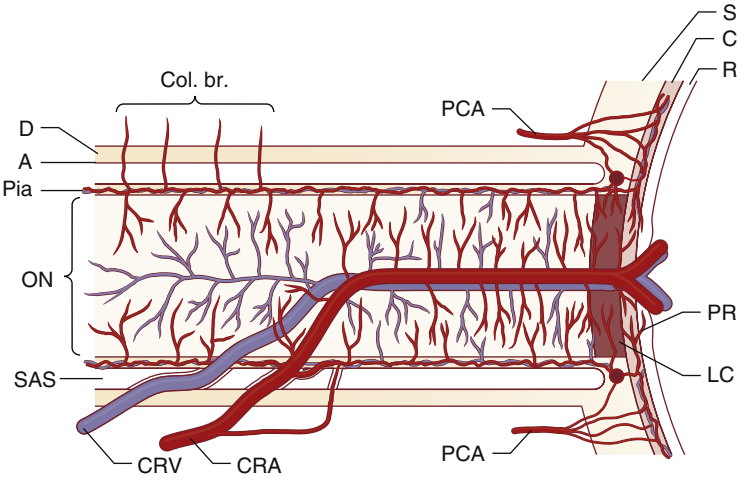


Figure 100-4. The blood supply to the optic nerve. The anterior portion of the optic nerve is located to the left, whereas the posterior portion (closer to the brain) is on the right. The anterior portion of the nerve derives its blood supply from the posterior ciliary arteries (*PCA*) and the choroid (*C*), whereas the posterior optic nerve derives its blood supply from penetrating pial arteries (collateral branches [*Col. br.*]) and branches of the central retinal artery (*CRA*). *A,* Arachnoid; *CRV,* central retinal vein; *D,* dura; *LC,* long ciliary artery; *ON,* optic nerve; *PR,* short posterior ciliary artery; *R,* retina; *S,* sclera; *SAS,* subarachnoid space. *(From Hayreh SS: Ischemic optic neuropathy, University of Iowa, Department of Ophthalmology.* <http://www.medicine.uiowa.edu/eye/AION-part2.> *Accessed August 8, 2014)*

POSSIBLE PATHOGENIC FACTORS

Factors in perioperative ION via retrospective case-control studies are long surgery; hypotension; blood loss; anemia or hemodilution; altered venous hemodynamics; flow of cerebrospinal fluid in the optic nerve (including the influence of patient positioning and perioperative fluid resuscitation); abnormal autoregulation in the optic nerve; anatomic variants in blood supply to the optic nerve; male gender; small cup-to-disk ratio; the use of vasopressors; the presence of systemic vascular risk factors, including hypertension, diabetes, atherosclerosis, hyperlipidemia, obesity, and smoking history; prone positioning; lengthy surgery for spinal fusion; the nature of the intravascular fluid resuscitation during surgery; and other preexisting systemic abnormalities, such as sleep apnea syndrome and hypercoagulability.

Some of these factors are often present in an individual patient in an unpredictable fashion. In most cases, hypotension, anemia, and intravascular fluid resuscitation have occurred. Many of the patients with ION after spine surgery were relatively healthy preoperatively. Hypotension, blood loss, lengthy surgery, and large intravascular fluid administration occur frequently in many patients undergoing complex spine surgery.[11,85,90-92] Perhaps a combination of these factors, together with abnormal autoregulation in the posterior optic nerve, prothrombotic tendencies, and other patient-specific factors, are responsible for ION.

CURRENT KNOWLEDGE AND CONTROVERSIES

Because of limited data, risk factors for ION have not yet been well defined. However, a number of potential factors warrant discussion. Myers and associates[11] showed that length of surgery and estimated blood loss were higher in patients with postoperative blindness after spine surgery than in unaffected patients. This has also been found by the Postoperative Visual Loss (POVL) Study Group.[13] Therefore, patients undergoing anticipated long-duration surgery with large blood loss are recognized to be at higher risk.[101] Staging of spinal fusion procedures, particularly those for anterior and posterior surgery, may be advisable A discussion between the surgeon and anesthesia provider should occur for appropriate cases. Revision spinal fusion procedures are common, and these operations may be longer in duration and involve larger blood losses.

Intraoperative hypotension has been cited as a risk factor by a number of authors of case reports,[102,103] but because it is not always present, and some degree of hypotension frequently occurs in anesthetized patients, hypotension itself might not be responsible.[8,104-106] In the survey by Cheng and colleagues[91] of 24 cases of visual loss after spine surgery, deliberate hypotension was used in only 2 cases.[91] In a retrospective case-control study of patients undergoing spinal fusion, Myers and colleagues[11] showed that levels of hypotension and anemia were equivalent in patients in whom ION developed after spinal surgery and in those in whom it did not. In the ASA Postoperative Visual Loss Registry, which contains the largest series of visual loss after spine surgery, a wide variation was observed in blood pressure decreases intraoperatively among the patients with ION; in 33% of cases, the lowest systolic blood pressures were more than 90 mm Hg, and in 20% the lowest were 80 mm Hg or less. Approximately 57% of patients had systolic or mean arterial blood pressure 20% to 39% below baseline, and in 25% of patients it was 40% to 49% below preoperative baseline. Deliberate hypotension was used in 27% of the patients.[12] Patil and colleagues[4] reported a higher odds ratio for ION in patients who sustained hypotension. However, the study results are weakened by a number of factors. Among them are that this study used the Nationwide Inpatient Sample (NIS). None of the diagnostic coding can be confirmed, and the timing (perioperative period or not) and the degree of hypotension are not specified and cannot be determined using the NIS.[3,107] The POVL Study Group did not find an involvement of hypotension in the case-control study.[13] The same result was reported by Holy and colleagues.[93] Similarly, in the retrospective case-control study by Shapira and associates[8] of 602 patients who underwent open heart surgery at one institution during a 2-year period, the lowest perfusion pressure intraoperatively was no different between affected and normal patients. The larger case-control study by Nuttall and co-workers[9] did not report the blood pressures during CPB, but no differences were observed in prebypass or postbypass blood pressures between patients with ION and unaffected patients. In open heart surgery, hypothermia during CPB and other systemic alterations such as systemic inflammatory syndrome might play a role in the development of ION but these mechanisms have not been studied.

Hypotension can potentially lead to decreases in perfusion pressure in the optic nerve and to ischemic injury because of either anatomic variation in the circulation or abnormal autoregulation and an inability to adequately compensate for decreased perfusion pressure. The degree of hypotension that is potentially dangerous is difficult to quantitate because of the lack of data in the literature.[101]

Blood loss may be considerable in reports of perioperative ION. It is apparent that, on average, patients sustained considerable blood loss and had a decreased hemoglobin concentration intraoperatively. Clinical blood transfusion practice in surgical patients, based on ASA practice guidelines,[108] suggests that transfusion is not generally required for hemoglobin values higher than 8.0 g/dL. The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists, which reviewed the available evidence base for these practices in cardiac surgery in particular, has issued a recent, similar clinical practice guideline.[109]

Some authors suggest that allowing hemoglobin to decrease, as is common in anesthesia practice, may be putting patients at increased risk for ION[110]; however, whether practice should be changed in surgical procedures such as spine or heart surgery—or in any operative procedure—remains controversial. Four retrospective case-control studies examined whether decreased hemoglobin or hematocrit relates to the occurrence of ION. In patients undergoing spine surgery, Myers and associates[11] determined that the lowest levels of hematocrit did not

differ between patients sustaining ION and those who were not affected; similarly the POVL Study Group found that decreased hemoglobin did not increase the odds ratio for developing ION.[13] Holy and colleagues[93] had similar findings but in a mixed population of patients. In patients undergoing cardiac surgery, Nuttall and co-workers[9] found a somewhat different result. The presence of a lower minimum postoperative hemoglobin was associated weakly with ION (odds ratio, 1.9; $P < .047$). Looked at another way, 13 of 17 patients with ION in their study had a minimum postoperative hemoglobin value less than 8.5 g/dL, versus 14 of 34 control patients with this level. The type of ION sustained by the patients was not specified, and the study had numerous statistical comparisons and a small sample size. Because spine and open heart surgery patients are different, it is doubtful that the results can be extrapolated to types of surgery other than cardiac. Although visual loss after cardiac surgery is a rare but dreaded complication, the possibility of a relationship among blood loss, hemoglobin value, and visual loss was not a consideration in the clinical practice guideline for blood transfusion in cardiac surgery.[109]

In uncontrolled hemorrhage in which blood volume is not maintained, decreased O_2 delivery to the optic nerve could result in either AION or PION.[111] Just how low or for how long the hemoglobin concentration must decrease to lead to this complication is not known (see also Chapter 61). However, the presence of recurrent and profound hemorrhage has been described in many reports. The argument that blood loss in the presence of maintained intravascular volume (hemodilution) is harmful seems less scientifically grounded. It has been shown experimentally in miniature pigs that blood flow in the optic nerve head, as measured by laser Doppler imaging, was maintained during isovolumic hemodilution with a 30% decrease in hematocrit. Moreover, O_2 tension at the vitreal surface increased 15%.[112] Also, Lee and associates[113] demonstrated that extreme decreases in hematocrit (15%) and mean arterial pressure (50 mm Hg) in adult pigs resulted in significant reductions in blood flow to the optic nerve. But no histologic or optic nerve function was studied, and the pig brain and eye circulation significantly differ from that of humans.[113] Hemodilution in cats resulted in a nonsignificant decrease in choroidal O_2 delivery[114] and an increase in preretinal O_2 tension.[115] Healthy volunteers tolerated very deep levels of hemodilution (hemoglobin 50 g/L) without any disturbance in systemic O_2 delivery.[116] The multicenter prospective randomized trial conducted by Hebert and co-workers[117] provided data justifying clinical use of a liberal transfusion strategy (lower hematocrit) in critically ill patients. AION and PION occur in massive intravascular fluid replacement. Many reports include patients who were in the prone position, raising the possibility that positioning itself contributes to altered venous hemodynamics within the optic nerve. The patient's head should be level with or above the heart, when possible, and in a neutral position during spine surgery performed with the patient in the prone position. Several studies found that IOP increased in the prone position and was influenced by the position of the operating room table. However, there has been no correlation between IOP changes and visual outcome or visual function.[18] Cheng and colleagues[19] found that in anesthetized patients, IOP increased significantly on initial prone positioning relative to supine (27 ± 2 versus 13 ± 1 mm Hg). After 5 hours in the prone position, IOP remained increased at 40 ± 2 mm Hg. None of the 20 patients in the study experienced visual loss. The largest increases in IOP were evident near the time patients were awakening. Although these data suggest that ocular perfusion pressure may decline even during maintenance of normotension, some experimental design issues must be considered in interpreting these results. The main issue is that the largest increases in IOP were evident near the time of awakening from anesthesia. Accordingly, IOP could have increased because of light anesthesia. Moreover, the study did not include a supine group to control for the effects of fluid administration on IOP. Such control is important because prone positioning itself may not explain the large increases in IOP. These results are valuable as well as of concern, but further studies are needed to fully evaluate their significance.

External pressure on the eye is a potential concern when a patient is positioned prone for surgery. Many cases of ION have occurred when pressure could not have been placed on the eye. Such cases include patients in pin head holders[118] and those in whom the head was turned with the affected eye placed upward.[119] But ION would not occur without retinal damage in a situation in which external compression was applied (see earlier discussion). Although we demonstrated that high IOP decreased retinal and choroidal blood flows in cats,[23] Geijer and Bill[120] specifically measured the impact of graded increases in IOP on blood flow in the retina and optic nerve in monkeys. When IOP was elevated such that perfusion pressure was decreased to levels above 40 cm H_2O, small effects on retinal blood flow and in the prelaminar portion of the optic nerve were noted. When perfusion pressure was less than 40 cm H_2O, retinal and prelaminar flows were proportional to the perfusion pressure. At very high IOP, blood flow stopped in the retina and the prelaminar area but flow in the retrolaminar region increased. High IOP results in a redistribution of blood flow that favors the retrolaminar portion of the optic nerve. Therefore, an increase in IOP would not produce an isolated ION without also causing retinal damage. Further support is that sustained increases in IOP significantly decreased both retinal and choroidal blood flow, and even small increases in IOP damaged the retinal ganglion cells, which are sensitive to pressure alterations.[23,42]

The theory that massive intravascular fluid resuscitation could be a pathogenic factor in perioperative ION remains speculative, but it does have some merit. Fluid resuscitation is a necessity during lengthy, complex spine surgery associated with substantial blood and fluid losses at the operative site.[104,105] Conceivably, fluid administration could result in increased IOP, accumulation of fluid in the optic nerve, or both. Because the central retinal vein exits out of the optic nerve, an internal compartment syndrome may occur in the optic nerve. Alternatively, fluid accumulation in the vicinity of the lamina cribrosa may compress axons as they transit this region. In the report by Cullinane and associates,[94] trauma patients who were acidotic received massive blood replacement and

most had abdominal compartment syndrome. Analysis of these patients is complicated because of the presence of numerous systemic alterations. Sullivan and associates[121] described a retrospective series of 13 burn patients with 25% or greater body surface area burns and massive fluid resuscitation. IOP was elevated more than 30 mm Hg in 4 patients at 48 hours after admission, all of whom received more than 27 L of intravenous fluid. Eye findings and vision diagnoses were not described. Large-volume fluid replacement is generally seen in many case reports of ION.[89] Patients in the ASA Postoperative Visual Loss Registry received on average 9.7 L of crystalloid intraoperatively,[12] and increased postoperative weight gain was identified in a case-control study of visual loss after heart surgery,[8] suggesting, although not proving, that fluid replacement may play a role. The finding of the POVL Study Group was that the odds ratio for developing ION was increased as the percent colloid of nonblood replacement decreased.[13] It is possible that the use of colloids may decrease edema in the optic nerve during surgery, particularly when the patient is placed prone for surgery. However, at present, such edema has not yet been demonstrated. In healthy volunteer subjects, placement in the prone position led to an increase in diameter of the optic nerve.[122] This could be due to venous hypertension. New MRI methods may enable the study of edema and venous hemodynamics in the optic nerve in the near future. Animal models also may provide a means to study these perioperative factors.

Further support of an idea that increases in venous pressure within the optic nerve are potentially deleterious can be seen in reports of ION after head and neck surgery in which the internal jugular veins were ligated.[17,62,123] However, there are venous drainage bypass pathways from the head and neck when the internal jugular veins are ligated. Although the relationship to fluid therapy is not clear, Myers and colleagues,[11] the POVL Study Group,[13] and Patil and co-workers[4] found that longer surgery was associated with ION. However, cases of ION have been found after widely varying operative times.[12]

Cases of ION have been reported after radical robotic-assisted prostatectomy (see also Chapter 87). This surgical procedure is notable for placement of the patient in steep head-down tilt and increases in intraabdominal pressure because of laparoscopy.[124] Some have speculated that facial edema indicates a risk for ION after spine surgery.[125] However, in clinical practice, facial edema is often seen after spinal fusion in many patients in whom ION does not develop, and, therefore, its relevance remains unclear and facial edema as a risk factor is unproved.

Killer and co-workers[126] sampled cerebrospinal fluid (CSF) from the subarachnoid space of the optic nerve and the lumbar region in patients with idiopathic intracranial hypertension undergoing optic nerve sheath fenestration. The authors compared content of albumin, immunoglobulin G, β-trace protein, and brain-derived protein lipocalin-like prostaglandin D-synthase. MRI and CT cisternography were performed. From differences in the ratios of the CSF proteins in the optic nerve versus the CSF proteins in the lumbar region, and the results of cisternography, they concluded that CSF flow was compartmentalized in the optic nerve under these pathologic conditions. The implication of this conclusion is that relatively high CSF pressures in the intraorbital optic nerve can result in compression. Because CSF pressure may increase with fluid resuscitation, this may explain optic nerve compression. However, this theory has not been tested.

Although various theories concerning the role of intraoperative fluids in perioperative ION have been postulated, including extravasation from the central retinal vein, influence of directional CSF flow in the optic nerve, and changes in intracranial pressure, among others, none of these has been examined in either animal or human studies. MRI of the orbit in humans with ION has provided no evidence for any of these theories.[127] No study has shown any relationship among periorbital edema, IOP, and ION. Fluid administration could be a pathogenic factor in ION, especially in patients positioned prone or undergoing cardiac surgery, but the mechanisms involved, as well as the amounts and nature of fluid required, remain undefined.

Anatomic variation in the circulation of the optic nerve may potentially predispose patients to the development of ION. The location of potential watershed zones in the anterior and posterior circulation and the presence of disturbed autoregulation, even in normal patients,[78] are of concern but at present cannot be predicted clinically. Few human studies have been conducted on the relationship between perfusion pressure and changes in blood flow in the optic nerve. Human studies generally show preserved blood flow at clinically used or even lower ranges of perfusion pressure, but these studies have focused primarily on the anterior portion of the optic nerve.[99] In the studies that used laser Doppler flowmetry, depth of penetration of the measuring device is critical. Measurements might have been closer to the retinal blood vessels than the optic nerve head, and these do not measure optic nerve circulation. It is not currently feasible to measure blood flow in the human retrolaminar optic nerve. In animal studies, blood flow is preserved in various layers of the optic nerve, including the retrolaminar area, at a mean arterial blood pressure as low as 40 mm Hg.[98]

Hayreh and associates[128] theorized that AION is related to excessive secretion of vasoconstrictors, which in turn could lower optic nerve perfusion to dangerously low levels. However, the theory was based on the development of AION in patients who sustained massive hemorrhage. Vasopressors are used to maintain blood pressure in circumstances such as after cardiac surgery and in cases in which vasomotor tone is decreased. Shapira and co-workers[8] showed an association between prolonged use of epinephrine or long bypass time and ION in patients undergoing open heart surgery. Lee and Lam[106] reported a case of ION in a patient after lumbar spine fusion during which a phenylephrine (Neo-Synephrine) infusion was used to maintain blood pressure. They later presented a series of four case reports of ION in critically ill patients with significant systemic illness who required prolonged use of vasopressors and inotropic agents to maintain blood pressure and cardiac output.[129] However, α-adrenergic receptors are not located in the optic nerve and the blood-brain barrier prevents entry of systemically administered agents, except possibly in the prelaminar zone of the nerve. Therefore, a role of vasopressor use in

ION remains unclear and no clear guidance with respect to risk for ION can be provided at this time.

A medical history of hypertension, diabetes, and coronary artery or cerebrovascular disease has been cited in case reports but is not present in all patients in whom ION has developed. Moreover, hypertension and coronary artery disease are nearly always found in patients undergoing CABG but ION develops in few of these patients. No case-control data have shown an association of these factors with the development of ION in spine surgery patients, including those studies of Myers, Holy, and the POVL Study Group.[11,13,93] Case series show that many patients with perioperative PION have few vascular disease risk factors.[90] In a prospective study of nonsurgical patients, ION was not associated with the presence of carotid artery disease.[130] Although a basis for the notion that perioperative ION is related to atherosclerosis is that the optic nerve vasculature would respond abnormally to changes in perfusion pressure (i.e., demonstrate disturbed autoregulation), this association has not been studied in humans, and animal data are inconclusive.[97]

AION has been described in patients who used erectile dysfunction drugs. Cause and effect has been debated,[131] but because of the possible increased risk and unknown impact on events in the perioperative period, it seems sensible to discontinue use of these agents 1 or 2 days before surgical procedures.

Because the sphenoidal sinus and ethmoidal cells are close to the orbit and optic nerve and the bone is fragile, surgery on the nose and paranasal sinuses poses a special risk for ocular damage. Retrobulbar hemorrhage may follow surgical damage to the fragile lateral wall of ethmoidal cells, the lamina papyracea. Blindness has occasionally been reported after endoscopic sinus surgery[132] as a result of direct surgical damage to the optic nerve, but indirect damage by compression from retrobulbar hematoma leading to ION is more commonly reported. Paresis of eye muscles (mostly the medial rectus muscle), including ptosis, is often seen; an ocular compartment syndrome may be present, necessitating immediate surgical decompression to preserve vision.[133] The outcome is poor; in only one case was blindness temporary,[132] whereas all other reported cases of retrobulbar hematoma resulted in permanent blindness. The anesthesiologist should maintain a high degree of vigilance for possible retrobulbar hemorrhage, so that, if it occurs, rapid surgical decompression can be accomplished.

In summary, the pathogenesis of perioperative ION is incompletely understood. Multiple factors that could contribute are frequently present in patients undergoing open heart surgery, spine surgery, or head and neck operations. A patient may have anatomic variation and abnormal autoregulation in the optic nerve, but these anomalies are currently undetectable in the preoperative period. Preexisting as well as intraoperative factors may interact in an unpredictable fashion and lead to ION. Clinicians should be aware of the higher risk for visual loss with prolonged spine surgery with the patient positioned prone and in which large blood loss is anticipated. The risk is heightened also in these circumstances in men, obese individuals, and those positioned for surgery on a Wilson frame and when the percent colloid of total nonblood fluid resuscitation was lower (see also Chapter 61). Although concern exists regarding factors such as arterial blood pressure and intravascular fluid resuscitation during lengthy spine surgery, the mechanisms leading to ION in the perioperative period are not well understood.

PROGNOSIS, TREATMENT, AND PREVENTION

No proved treatment exists for ION. A few cases of treating perioperative ION have been reported. Williams and co-workers[110] reviewed the attempted treatments. Acetazolamide decreases IOP and may improve flow to the optic nerve head and retina.[134] Diuretics such as mannitol or furosemide reduce edema. In the acute phase, corticosteroids may reduce axonal swelling, but in the postoperative period they increase the risk for wound infection. Because steroids are of unproved benefit, their use must be carefully weighed. Increasing ocular perfusion pressure or hemoglobin concentration may be appropriate when ION is found in conjunction with significant decreases in blood pressure and hemoglobin concentration. Maintaining the patient in a head-up position if increased ocular venous pressure is suspected may be advantageous, but its use must be balanced against decreased arterial supply with the head-up position. Clearly, if a patient has visual loss from ocular compartment syndrome, immediate decompression (lateral canthotomy) is indicated (see also Chapter 84).

In their review of perioperative PION reports in the literature, Buono and Foroozan[85] summarized the lack of proof that treatment altered the course of PION. In a few anecdotal case reports, increasing blood pressure or hemoglobin, or applying hyperbaric O_2, improved visual outcome.[89] The use of neuroprotective agents or drugs that lower IOP, valuable in theory, has never been shown to result in improvement.[135] Stevens and associates,[136] who compiled a report of ION in patients after spine surgery, had apparent improvement of vision in two patients when anemia and hypotension were corrected. One patient demonstrated partial improvement that subsequently regressed, and one patient showed more clear signs of improvement. However, as Buono and Foroozan[85] mentioned, it is difficult to ascertain if improvement came from treatment, because some patients recover vision spontaneously after PION.

Prevention strategies depend on the status of the patient's optic nerve circulation, which is not known preoperatively and cannot be monitored intraoperatively. Some general recommendations could be made for spine surgery, but whether any of these can prevent ION remains unknown at this time.

The head should be positioned neutral relative to the back, and head-down positioning is discouraged. Although intraoperative blood pressure management has not been shown to affect the risk for developing ION, arterial blood pressure probably should be maintained close to baseline. Of course, judgment and discussion are necessary when surgeons request a decrease in blood pressure as a means of decreasing arterial bleeding and blood loss. In cardiac surgery, special considerations exist regarding the optimal

systemic perfusion pressures to be maintained during CPB. In addition, it is evident that arterial blood pressure management is only one part of the care of the anesthetized patient, considering, of course, the entire patient and not the optic nerve alone. Increasingly, anesthesiologists are encountering patients whose hypertension is controlled with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, often together with β-adrenergic blockers or calcium channel blockers. These patients frequently become hypotensive intraoperatively.[137] In this common situation during which arterial blood pressure declines intraoperatively, particularly during spine surgery, vasopressors may be required. Patients may be refractory to ephedrine and Neo-Synephrine and require vasopressin to maintain blood pressure.[137] Systemic risks exist for increasing blood pressure with vasoactive agents or by infusion of intravenous fluids, such as decreased renal, liver, and intestinal perfusion, congestive heart failure, and myocardial ischemia. These risks are important considerations in decisions regarding the appropriate range for blood pressure and fluid resuscitation requirements.[138]

Whether hematocrit should be maintained at or near its baseline value is controversial (see also Chapter 61). However, simultaneous deliberate hypotension and hemodilution to a hematocrit of less than 25% should be done with caution. Whereas contemporary practice is to conserve blood by initially replacing lost blood with fluids, the effect of such hemodilution will often be a large fluid resuscitation, in some instances further amplifying an already high intravascular volume resuscitation, particularly in repeat operations for spine fusion, which typically involves large fluid and blood requirements. A relatively "dry" fluid strategy has been tested in abdominal surgery, but its use is controversial and has risks and outcomes have not been widely tested in any other surgery.[139] Either earlier blood replacement or greater use of colloids may potentially decrease the volume of infused crystalloids, although the impact of this practice on the occurrence of visual loss is not known. Here the results of the POVL Study Group provide some guidance; it seems advisable to use some colloid during large fluid resuscitation when patients are positioned prone for surgery. Withholding fluids is inadvisable because of many other risks, including multiple organ failure.[138]

Increasingly, neurosurgeons have been using minimally invasive surgical techniques toward lumbar spine surgery and fusion. These methods reduce the amount of blood loss and fluid requirements, but cases of ION have arisen under these circumstances as well.[140] Another strategy not under the direct control of the anesthesia provider is to consider staging of complex spine procedures. However, in some instances the anesthesiologist may be able to persuade a surgeon to follow a less ambitious surgical plan. This decision requires an assessment of the associated risks for multiple surgeries (infection, spinal instability) but may significantly shorten the duration of each procedure. Another strategy is to advocate for patients by regular preoperative conferencing with surgeons. Anticipating high blood loss and other risks may enhance perioperative planning and care in spine surgery patients (R. Caplan, Seattle, Wash, personal communication).

In the seventh edition of *Miller's Anesthesia*, Box 90-1 summarized the conclusions of a 2006 ASA Task Force regarding perioperative blindness associated with spine surgery. In 2012, another ASA Task Force published an update regarding perioperative visual loss primarily associated with spine surgery (Box 100-1). While major changes were not made, analysis of the literature was updated and the recommendations were more detailed. For example, the 2006 Summary had 7 bullet points. In contrast, the 2012 Summary of Advisory Statements has 22 bullet points subdivided into Preoperative, Intraoperative, Staging of Surgical Procedures, and Postoperative Management.

The 2006 Task Force concluded that high-risk patients who have surgery that is prolonged in duration and/or have large blood loss have an increased risk of perioperative visual loss. Yet perioperative visual loss was not related to blood loss per se, hemoglobin levels, or the use of crystalloids. Positioning of the head level or above the body was a risk factor.

The 2012 Task Force reviewed the additional literature. They concluded that newer findings and the literature do not justify major changes in the 2006 recommendations. However, more details were provided in the 2012 advisory statements. Box 100-1 lists the 2012 Task Force Summary of Advisory Statements (Appendix 1).

Whether patients should be warned about the possibility of ION during the process of informed consent, especially those undergoing apparently higher risk operations such as CABG and complex instrumented spinal fusion surgery, is controversial. The Task Force recommended considering informing high-risk patients, that is, those undergoing prolonged spine fusion surgery with large anticipated blood loss, about this risk.[141] This is difficult to accomplish in the often few rushed minutes of a preanesthetic interview on the day of surgery, typical of modern anesthetic practice in the United States. Accordingly, anesthesiologists may wish to consider requesting that the surgeon discuss the possible complication at an earlier, more relaxed preoperative visit.

CORTICAL BLINDNESS

Complete cortical blindness is bilateral visual loss with an absence of optokinetic nystagmus and of the lid reflex response to threat. The pupillary response, eye motility, retina, and optic nerve are normal. Complete blindness implies damage to both the left and right occipital cortex, whereas a more localized injury produces homonymous hemianopia.

Total blindness from bilateral occipital infarction is rare. Because the visual pathway travels through the parietotemporal lobes, a perioperative cerebrovascular accident affecting the internal carotid, or middle, basilar, or posterior cerebral arteries is the more common cause of cortical blindness. Yet because of collateral circulation, the degree of visual damage is difficult to predict.[142] Approximately 80% of cases of cortical blindness postoperatively have followed cardiac or other thoracic surgery. Depending on the sensitivity of the neuropsychological testing, these patients frequently show evidence of postoperative neurologic sequelae.[143]

BOX 100-1 *American Society of Anesthesiologists 2012 Task Force Summary of Advisory Statements*

I. Preoperative Considerations

- At this time there were no identifiable preoperative patient characteristics that predispose patients to perioperative posterior ischemic optic neuropathy (ION).
- There is no evidence that an ophthalmic or neuro-ophthalmic evaluation would be useful in identifying patients at risk for perioperative visual loss.
- The risk of perioperative ION may be increased in patients who undergo prolonged procedures, have substantial blood loss, or both.
- Prolonged procedures, substantial blood loss, or both are associated with a small, unpredictable risk of perioperative visual loss.
- Because the frequency of visual loss after spine surgery of short duration is infrequent, the decision to inform patients who are *not* anticipated to be "high risk" for visual loss should be determined on a case-by-case basis.

II. Intraoperative Management

Blood Pressure Management

- Arterial blood pressure should be monitored continually in high-risk patients.
- The use of deliberate hypotensive techniques during spine surgery can be associated with the development of perioperative visual loss. Therefore the use of deliberate hypotension for these patients should be determined on a case-by-case basis.
- Central venous pressure monitoring should be considered in high-risk patients. Colloids should be used along with crystalloids to maintain intravascular volume in patients who have substantial blood loss.

Management of Anemia

- Hemoglobin or hematocrit values should be monitored periodically during surgery in high-risk patients who experience substantial blood loss. A transfusion threshold that would eliminate the risk of perioperative visual loss related to anemia cannot be established at this time.

Use of Vasopressors

- There is insufficient evidence to provide guidance for the use of α-adrenergic agonists in high-risk patients during spine surgery.

Patient Positioning

- The Task Force believes that there is no pathophysiologic mechanism by which facial edema can cause perioperative ION. There is no evidence that ocular compression causes isolated perioperative anterior ION or posterior ION. However, direct pressure on the eye should be avoided to prevent central retinal artery occlusion (CRAO).
- The high-risk patient should be positioned so that the head is level with or higher than the heart when possible.

III. Staging of Surgical Procedures

- Although the use of staged spine surgery procedures in high-risk patients may entail additional costs and patient risks (e.g., infection, thromboembolism, or neurologic injury), it also may decrease these risks and the risk of perioperative visual loss in some patients.

IV. Postoperative Management

- The consensus of the Task Force is that a high-risk patient's vision should be assessed when the patient becomes alert.
- If there is concern regarding potential visual loss, an urgent ophthalmologic consultation should be obtained to determine its cause.
- There is no role for antiplatelet drugs, steroids, or intraocular pressure-decreasing drugs in the treatment of perioperative ION.

From Practice advisory for perioperative visual loss associated with spine surgery: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Visual Loss <https://www.asahq.org/For-Members/Practice-Management/Practice-Parameters.aspx>. (Accessed 09.09.14)

Initially, total cortical blindness is usually accompanied by signs of stroke in the parietooccipital region. The patient may experience agnosia, an inability to interpret sensory stimuli. Often, vision improves over time, with incomplete lesions in the visual field combined with visual disorientation. Pupillary reflexes are preserved and most of the visual field is restored within days, but impairment in spatial perception and in the relationship between sizes and distances may remain. Visual attention may be restricted, and images formed on all parts of the retina may not be visualized at one time.

The incidence of cortical blindness was 10 in 808 CABG surgeries in one hospital, with brain scans in 5 patients showing occipital infarcts.[144] In a retrospective series of 700 CABG surgeries and valve replacements by a single surgeon, 2 patients had unilateral occipital cortical infarcts.[145] Shaw and colleagues[146] prospectively studied 312 patients who had undergone CABG and found a 5% incidence of cortical blindness.[146] At least 50% of the patients had associated neurologic deficits. In another study, the onset of visual deficits followed a time course similar to that of neurologic damage.[147] Among the largest studies of neurologic dysfunction after cardiac surgery is that of Roach and co-workers.[148] In a prospective study of 2108 patients who had CABG at one of 24 hospitals, the incidence of neurologic complications was 6%. The specific incidence of eye complications was not reported. Results of subsequent studies are similar and have been reviewed by Newman and associates.[149] Associated factors included age, unstable angina, diabetes, prior stroke or transient ischemic attack, previous CABG surgery, and history of vascular or pulmonary disease. The incidence of visual disorders was not reported in any of these studies.

In case reports of cortical blindness, 55% of cases were reported after CABG surgery and 23% after other thoracovascular operations.[150] Cases have been reported in children. Hypotension was found in 45% and anemia or hemodilution in 23%. Over half the patients had coronary artery disease, but cortical blindness was found in patients with a wide range of systemic disorders, including congenital heart disease, liver failure, postpartum pulmonary embolism, and hypercholesterolemia. Unfortunately, the time of onset of symptoms was not reported in approximately half the cases. For the remaining 50%, onset was within the first postoperative day. As would be expected, fundoscopy was normal in nearly all patients when reported, except one, in whom AION was combined with cortical blindness. Visual defects were bilateral in all but one, who had a lesion near the lateral geniculate nucleus. The incidence of other objective neurologic findings was 38%. Confusion was present in 25% of patients. Visual outcome improved in 65% of cases.

MECHANISM AND PATHOPHYSIOLOGY

Cortical blindness can result from global ischemia, cardiac arrest, hypoxemia, intracranial hypertension and exsanguinating hemorrhage, focal ischemia, vascular occlusion, thrombosis, intracranial hemorrhage, vasospasm, and emboli. If blood and O_2 deprivation persists long enough, the cellular energy supply ceases and a series of biochemical events are initiated that ultimately lead to cell death. The pathways responsible for neuronal injury in the cerebral cortex have been reviewed extensively.[151]

CABG is the most common operation associated with cortical blindness, but the pathophysiology of cortical blindness after CABG surgery remains incompletely understood. The major source of brain and visual damage is believed to be embolism from the surgical field, such as fat and atheroma or microemboli of lipid and fibrin-platelet aggregates.[152] A high incidence of emboli in the retinal circulation of patients undergoing CABG has been documented.[153] Patients with aortic atherosclerosis appear to be at particular risk.[148] Cerebral edema also may be responsible for cortical blindness, but a study of MRI of the brain soon after CABG showed cortical swelling within 20 to 40 minutes that was not found on follow-up 1 to 3 weeks later, thus questioning its pathogenic role.[154] Edema may somehow contribute to the vague visual disturbances found in up to 25% of patients after CABG.[155] Another suspected factor is transient decreases in blood flow to border zones of perfusion between the middle and posterior cerebral arteries, especially in patients with preexistent cerebrovascular disease.[156]

PROGNOSIS, TREATMENT, AND PREVENTION

Visual recovery from cortical blindness may be prolonged, but previously healthy patients are likely to show a considerable degree of recovery. Therefore, when cortical blindness is accompanied by focal neurologic signs, treatment should be directed toward preventing progression of stroke. The optimal strategy to prevent neurologic injury during cardiac surgery remains controversial. Several different techniques have been advocated to decrease intraoperative manipulation of the aorta and embolization.[157] Adequate removal of air and particulate matter from the heart during valvular operations may decrease the risk for embolism. In patients younger than 70 years of age without evidence of cerebrovascular disease, an arterial line filter during CPB significantly reduced the number of microemboli detectable by transcranial Doppler ultrasonography. The frequency of subtle neuropsychological and neurologic changes (including nystagmus) was also reduced. No visual defects were found in the study patients.[158] Maintenance of adequate systemic perfusion pressure may prevent episodes of hypoperfusion in patients with cerebrovascular disease, but no controlled studies have associated visual loss and perfusion pressure in open heart surgery. The development of better transcranial Doppler techniques may enhance detection of embolic events. As yet, no proved neuroprotective agents whose use is feasible in these patients are available. Nonbypass heart surgery would be expected to avoid, but not eliminate, many embolic complications.[158]

ACUTE GLAUCOMA

Acute angle-closure glaucoma is a well-known disease that has been described rarely after general anesthesia. It usually occurs spontaneously and is more common in women and the elderly. Genetic predisposition, a shallow anterior chamber, and increased thickness of the lens are frequently found. The peak age for acute glaucoma is between 55 and 65 years.[159] Three case series in surgical patients have been reported. Gartner and Billet[160] described acute angle-closure glaucoma in 4 of 3437 patients (0.1%) undergoing general or spinal anesthesia.[160] Subsequently, Wang and colleagues[161] reported 5 cases in 25,000 surgical patients (0.02%). The highest incidence was found by Fazio and co-workers[162] after reviewing the records of 913 patients who had general or spinal anesthesia. Nine cases were detected, two of which were bilateral (1%). In these studies, no association was made between acute glaucoma and an anesthetic technique or drug.

Acute angle closure results in glaucomatous damage to the optic nerve and occurs when the passage of aqueous humor from the posterior to the anterior chamber is obstructed by apposition of the iris to the anterior surface of the lens. The pupil is mid-dilated, with an associated pupillary block. The diagnosis should be suspected in a patient with a painful red eye and cloudy or blurred vision, possibly accompanied by headache, nausea, and vomiting. This condition is often bilateral. It is distinguished from corneal abrasion, which also produces pain but without the papillary signs, increased IOP, subjective visual loss, and headache.[2] Symptoms may not appear for hours to days after a surgical procedure. Acute glaucoma is an emergency, and ophthalmologic consultation should be obtained immediately. Patients are treated with β-adrenergic antagonists, α-adrenergic agonists, carbonic anhydrase inhibitors, cholinergic agonists, and corticosteroids. Systemic analgesic agents are given as needed. A peripheral iridectomy should be performed later to create a permanent opening between the anterior and posterior chambers.[160]

VISUAL CHANGES AFTER TRANSURETHRAL RESECTION OF THE PROSTATE

Visual changes after transurethral resection of the prostate (TURP) have been recognized for over 50 years (see also Chapter 72).[163] Changes appear alone or as part of a syndrome after excessive absorption of irrigating fluid (usually 1.5% glycine) with subsequent hyponatremia, cerebral edema, seizures, coma, and cardiac failure from excessive intravascular fluid administration.[164] Although use of TURP is declining because of economic and regulatory constraints and noninvasive alternatives,[165] complications still occur. Absorption of the irrigant is the major source of nonsurgical complications. Determinants of the amount of irrigant absorbed include the duration of the resection, the extent of the opening of the prostatic venous sinuses, the hydrostatic pressure of the irrigation

fluid, and venous pressure at the "irrigant-blood interface."[166] Hamilton-Stewart and Barlow[167] disputed the effect of operative time; they found that a longer resection time did not increase absorption. The veins and capsule of a smaller prostate may be exposed earlier in the resection, so greater absorption during a quick resection leads to the same amount of irrigant absorption as slower absorption during a long resection.[167] Nonetheless, significant quantities of irrigant may be absorbed even if the surgeon believes that no venous sinuses are open, and the operator thus cannot predict or estimate the amount absorbed.

SIGNS AND SYMPTOMS

Visual deficits may occur during the resection, several hours after, or, rarely, on the second postoperative day as the patient awakens from a TURP-related coma.[168] The range of signs and symptoms is wide, from complete loss of light perception to more subtle defects. The first complaint may be visual halos and a blue visual hue. Dilated pupils that are nonreactive to light, a normal IOP, normal extraocular muscle movement, and normal fundus examination without papilledema are the objective findings.[169] Visual changes may resolve over a few hours or persist for up to 80 hours. Permanent visual loss has not been reported.

MECHANISMS OF VISUAL DYSFUNCTION

Proposed mechanisms of the visual changes include cerebral edema,[170] glycine toxicity involving the retina and cerebral cortex,[169] ammonia toxicity,[171] and increased IOP.[172] Glycine, the smallest amino acid, enters cells primarily through a carrier-mediated process, but its rate of transport is relatively slow. It easily crosses the blood-brain barrier, and it depresses the spontaneous and evoked activity of retinal neurons and hyperpolarizes cells through blockade of chloride channels.[173] The highest glycine concentration is in the amacrine cells, inner plexiform, and ganglion cell layers of the retina.[174] Because of a profound effect on oscillatory potentials of the electroretinogram, the predominant site of action may be amacrine cells,[175] although other inner retinal cells are probably involved. Glycine altered visual evoked potentials in dogs and in humans, thus suggesting an effect on the optic nerve. The threshold for visual symptoms is a plasma glycine concentration over 4000 μmol/L.[176]

Hyponatremia and hypo-osmolality during TURP produce occipital cortical edema, but such an association has not been confirmed. Segmental vascular disease in the blood supply to the occipital cortex may have placed that portion of the brain at risk for swelling.[164] Ocular hypertension causes enlarged blind spots and paracentral scotoma. In the presence of water overload, it seemed logical that an increase in IOP is part of the TURP syndrome. Yet in a prospective study of 22 patients who had TURP, Peters and colleagues[172] found no change in IOP in the patients with visual changes.[172] Such changes after TURP are transient and often associated with TURP syndrome. The most important means of prevention is to maintain intense vigilance to avoid excessive absorption of irrigating solution.

VISUAL LOSS AFTER VITRECTOMY AND VITREAL GAS BUBBLE TAMPONADE

Patients who have undergone vitrectomy with perfluorocarbon gas tamponade (C^3Fl^8) are at risk for gas bubble expansion and loss of vision from acutely increased IOP. Patients anesthetized for a subsequent surgical procedure with gas mixtures containing nitrous oxide (N_2O) after vitrectomy sustained retinal vascular occlusion from acute gas bubble expansion. N_2O anesthesia affects the size of the intraocular gas bubble. Wolf and co-workers[177] demonstrated that N_2O and O_2 resulted in a more than threefold increase in SFl^6 gas bubble volume, in contrast to a 50% increase with air ventilation and 35% increase with O_2 ventilation alone. Perfluorocarbon gas remains in the eye for at least 28 days. Visual loss has been reported with N_2O anesthesia administered as long as 41 days after vitrectomy and gas bubble tamponade. Therefore, patients should wear a warning tag to alert the anesthesiologist to the presence of the gas bubble in the vitreous, and N_2O should not be used in patients who have had recent vitrectomy and gas bubble tamponade.[178,179]

CONCLUSION

Visual loss can result in the perioperative period from retinal arterial occlusion, ION, cortical blindness, or acute glaucoma. Visual loss after TURP is transient; visual loss in patients anesthetized with N_2O after a vitrectomy and placement of a gas bubble tamponade may be permanent. The most serious injuries that are likely to result in blindness are retinal arterial occlusion and ION. Even if unintended pressure on the eye is avoided, these complications may still occur, particularly after spine, cardiac, or orthopedic surgery (see also Chapters 68 and 79). The risk factors for ION in particular remain incompletely explained.

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Chapter 101

Critical Care Anesthesiology

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Key Points

- With an anticipated shortage of critical care physicians, many different staffing models of intensive care units (ICUs) have been proposed, including the use of nonphysician providers, multidisciplinary care teams, and telemedicine.
- Evidence-based medicine now suggests that for the management of sepsis, large doses of corticosteroids are no longer recommended. Moderate glucose control may be safer than tight glucose control, and activated protein C does not reduce mortality from sepsis.
- Patients with acute lung injury or acute respiratory distress syndrome should be mechanically ventilated with tidal volumes of 6 mL/kg of ideal body weight and traditional positive end-expiratory pressure (PEEP) values of 5 to 12 cm water (H_2O). Other maneuvers that increase the partial alveolar pressure of oxygen/fraction of inspired oxygen concentration (PaO_2/FiO_2) ratio, such as recruitment maneuvers and inhaled nitric oxide, have not been shown to reduce mortality.
- Without liver transplantation, mortality from acute liver failure is high and primarily the result of multisystem organ failure, sepsis, and cerebral edema.
- Reduced mortality among patients in the ICU with acute renal failure is associated with earlier institution of dialysis and higher filtration volumes as opposed to the type of dialysis (intermittent hemodialysis versus continuous renal replacement therapy).
- Early mobilization decreases hospital mortality, decreases lengths of ICU and hospital stay, increases ventilator-free days, and leads to a shorter duration of delirium.
- Proposals to prevent ventilator-associated pneumonia include maintenance of gastric pH with sucralfate, positioning the head of the bed at 30 degrees, and subglottic aspiration of secretions.
- A comprehensive approach to the insertion of central venous catheters, including ultrasound guidance, maximum sterile barrier precautions, and antibiotic-coated catheters, can reduce the rate of catheter-related bloodstream infections.

The practice of critical care medicine, which originated in the 1940s with anesthesiologists providing life support to patients with poliomyelitis, has undergone revolutionary changes. The development of new equipment, procedures, and medications has enabled intensivists to treat critically ill patients and support them through increasingly invasive procedures. In the past decade, another revolution has taken place, the introduction of evidence-based medicine into intensive care unit (ICU) practice. In this chapter, the models of ICU staffing, including studies examining the value of intensivist staffing are discussed. Then a review of how intensivist staffing might lead to improved outcomes, specifically through the implementation of evidence-based practices, is presented. Particular attention is paid to the implementation and cost-effectiveness of new clinical practices. Finally, the management of some common diagnoses that are encountered while caring for critically ill patients is reviewed.

INTENSIVE CARE UNIT ORGANIZATION

With an aging population and increasing availability of medical technology, ICUs have become a critical component of modern hospital care. An estimated 0.5% to 1% of the U.S. gross domestic product is spent on critical care,[1] and patients 65 years of age and older make up over 50% of all ICU admissions.[2] Considering the magnitude of this expense, extensive research has focused on how the most cost-effective care can be delivered. Although ICUs started as open wards where any physician could admit patients, they have become increasingly managed.

Most ICUs now have a designated medical director who is responsible for the overall management of patient care and policies.

ROLE OF THE MEDICAL DIRECTOR

Each ICU should have a physician who is board certified or board eligible in critical care medicine to function as medical director.[3] The role of the medical director is to ensure the quality and safety of patient care in the ICU. Responsibilities often include patient triage decisions, education of house staff members, development of clinical protocols, and improvement of performance. Anesthesiologists frequently serve as medical directors, primarily of surgical ICUs. As hospital-based physicians, anesthesiologists are particularly well placed to appreciate the issues that affect patient care and the efficient flow of patients from surgical units through the ICUs. In 1994, the Society of Critical Care Medicine described the seven organizational duties of an ICU administrator[4]:

1. Triage of admissions and discharges
2. Development of treatment protocols or guidelines
3. Collection of data
4. Involvement in unit budget approval
5. Updating of equipment and unit practices
6. Promotion of efficient use of material and personnel resources
7. Responsibility for coordination and dissemination of continuing education of hospital- and ICU-based personnel

Because of the increasing importance of the medical director and the time commitment required, the hospital should provide salary support to allow an adequate investment of time in the position.

STAFFING

In 2003, Congress asked the Health Resources and Services Administration (HRSA) to examine the adequacy of the critical care workforce. HRSA maintains physician workforce supply and demand models that can assess the adequacy of supply for many physician specialties. Working with the American College of Chest Physicians and other consultants, the HRSA concluded that if current trends continue, then the growing supply of intensivists will be insufficient to provide the optimal level of care to future populations through 2020.[5] These projections are based on conservative estimates that intensivists will continue to direct the care of only one third of critically ill patients. If mandates by the Leapfrog Group are enacted and the proportion of patients in the ICU whose care is directed by an intensivist were to increase to two thirds, then the large potential growth in utilization of intensivist services represents a shortage of 1500 critical care providers.[6]

Anesthesiologists in Critical Care Medicine

Although anesthesiologists originated critical care medicine, they represent a shrinking percentage of critical care physicians. In a survey performed between 1996 and 1999, the Committee on Manpower for the Pulmonary and Critical Care Societies (COMPACCS) found that anesthesiologists accounted for only 6.1% of all intensivists in the workforce,[6] although they are particularly well trained to manage critically ill patients and do so on a regular basis in the surgical department. This trend comes at a time when the need for intensivists is increasing. The most recent data available show that there were 49 Anesthesiology Critical Care Medicine fellowship programs with 83 fellows in training for the 2010-2011 academic year,[7] compared with 417 fellows in 122 Pulmonary Disease and Critical Care Medicine programs.

The reason for the decreasing representation of anesthesiologists in critical care is multifactorial. Reimbursement for critical care services is generally less than that for surgical anesthesia services. Subspecialty training in critical care medicine for anesthesiologists creates a unique situation in which additional subspecialty training results in lower compensation. In Europe, where such a payment discrepancy between the surgical unit and the ICU does not exist, anesthesiologists provide the majority of critical care services.[8] In Australia and New Zealand, critical care training has become a separate specialty with its own residency. The College of Intensive Care Medicine took over in 2010 with the goal of developing a single training program for the specialty and to supervise all intensive care trainees.[9]

The American Board of Anesthesiology and American Society of Anesthesiologists have begun to address the diminishing role of anesthesiologists in critical care medicine. Proposed changes include an increasing component of training in critical care medicine during anesthesia residency. Programs for "experimental residencies" are also available that concurrently offer training for anesthesia and critical care in a blended residency and fellowship.

Physicians

For general and subspecialty patient populations, most studies suggest that an intensivist should provide care to critically ill patients. For example, Pronovost and associates[10] studied whether the organizational characteristics of ICUs could influence outcomes in patients undergoing surgery for an abdominal aortic aneurysm. They analyzed almost 3000 patients who underwent aneurysm repair in the state of Maryland and found that in risk-adjusted patients, not having daily ICU rounds by an intensivist was associated with a threefold increase in mortality. In addition to increased mortality, the patients not seen by an intensivist also had an increased risk for cardiac arrest, renal failure, septicemia, platelet transfusion, and reintubation.

In a large meta-analysis examining physician staffing and outcomes of critically ill patients, Pronovost and colleagues[8] compared low-intensity ICU staffing consisting of no or elective intensivist consultation with high-intensity staffing consisting of mandatory intensivist consultation or a closed ICU. This study found that the relative risk for hospital mortality was reduced by 29% and the relative risk for ICU mortality was reduced by 39% with high-intensity staffing. This and other studies have led to significant consumer and regulatory pressure mandating that intensivists staff all ICUs.

The Leapfrog Group (www.leapfroggroup.org) was established by the Business Roundtable, which consists of

the chief executive officers of several large corporations. These corporations purchase health insurance for more than 34 million health care consumers and therefore have considerable influence on health policy. One of the first recommendations by this group was that trained intensivists should staff ICUs. Although this recommendation has a strong evidence base, the other Leapfrog recommendations are not as strongly supported.[11] In addition to the factors discussed earlier, these pressures will create a significant demand for trained intensivists.

Considerable debate has occurred regarding whether intensivists should be continually present in ICUs even overnight. Prior studies have primarily evaluated academic ICUs with house staff, whereas many ICUs are in community hospitals and lack any overnight physician presence.[2] Introduction of an additional night shift to provide mandatory as opposed to on-demand 24-hour critical care specialist coverage has not been shown to affect long-term survival of patients in medical ICUs.[12] Wallace and associates studied a retrospective multicenter cohort of over 65,000 patients. They linked a survey of ICU staffing practices with patient outcomes and then used multivariate models to assess for relationships between nighttime intensivist staffing and in-hospital mortality among patients in the ICU.[13] They found that nighttime intensivist staffing improved mortality when added to low-intensity daytime staffing, but nighttime intensivists did not reduce mortality in ICUs with high-intensity daytime staffing. Kerlin and associates obtained similar results.[14] They conducted a randomized trial of nighttime intensivists staffing at an academic medical ICU with high-intensity daytime staffing and nighttime resident coverage and reported no improvement in patient outcomes. These results suggest that increasing ICU coverage to 24 hours a day, 7 days a week may not be the most reasonable nor economical decision for all hospitals.

Advanced Health Care Practitioners

The use of nonphysician providers, such as nurse practitioners (NPs) and physician assistants (PAs), under the supervision of attending physicians to augment or replace intensivists has become very popular, especially with the institution of resident duty hour limitations. These staffing models appear to be a safe and effective alternative to the traditional house staff-based team in a high-acuity, adult ICU.[15] Nonphysician providers are also a more consistent presence than house staff members who rotate through the unit for short blocks of time. This consistency can allow for improved communication and culture as team members become familiar with one another.[16] Currently, survey data suggest that PAs provide care in approximately 25% of adult ICUs in academic U.S. hospitals, and NPs provide care in more than 50%.[17]

Multidisciplinary Care Teams

One approach to lowering ICU mortality and improving quality is to optimize the organization of ICU services. The multidisciplinary model approach is to complement intensivist staffing with nurses, respiratory therapists, clinical pharmacists, and other staff members who can provide critical care as a team. The Society of Critical Care Medicine and the American Association of Critical Care Nurses have endorsed this approach.[18,19] In a retrospective cohort study, Kim and associates showed that when stratifying by intensivist physician staffing, the lowest odds of death were in ICUs with high-intensity physician staffing and multidisciplinary care teams (odds ratio [OR] 0.78; 95% confidence interval [CI] 0.68 to 0.89, $P < 0.001$), followed by ICUs with low-intensity physician staffing and multidisciplinary care teams (OR 0.88; 95% CI 0.79 to 0.97, $P = 0.01$), compared with low-intensity physician staffing.[20]

Nursing. The exact number of nurses needed to produce the best patient outcomes is not known. Although most studies show a trend toward lower nurse staffing and adverse ICU patient outcomes (i.e., mortality, infection, pressure ulcers), the studies have mostly been observational in design and therefore unable to demonstrate a causal relationship of nurse staffing on patient outcomes.[21,22] Many factors may affect patient outcomes, and nurse staffing is only one potential contributor.[23] Some hospitals prefer flexible scheduling, meaning ICU nurses are scheduled on the basis of anticipated workload in the unit at the start of the shift. This structure is financially good for the hospital by matching staff to workload demands, but it may provide uncertainty for the nursing staff.

Pharmacists. Pharmacists have become integral members of the ICU team as a result of contributions to medication safety, improved patient outcomes, reduced drug costs, and house staff education.[24] In a survey conducted among 1034 ICUs in the United States, clinical pharmacists provided care and attended rounds in 62% of the units.[25] Their presence has been shown to reduce mortality in patients with thromboembolic or infarction-related events[26] and in patients with nosocomial-acquired infections, community-acquired infections, and sepsis.[27] Their most important benefit is the potential to decrease adverse drug events. Leape and associates showed that the presence of a pharmacist on rounds was associated with a decrease in the rate of adverse drug events (ADE) from 10.4 per 1000 patient days (95% CI 7 to 14) to 3.5 per 1000 patient days (95% CI 1 to 5, $P < 0.001$).[28]

Respiratory Therapists. Respiratory therapists often assume important clinical roles with respect to ventilator management. Their involvement improves compliance with weaning protocols and decreases the duration of mechanical ventilation.[29,30] Other hospitals are using their care in innovative ways. Arroliga and colleagues found that the introduction of an intervention that included respiratory therapists performing oral care for patients who were mechanically ventilated reduced the rate of ventilator-associated pneumonia (VAP) from 4.3 per 1000 ventilator days to 1.2 per 1000 ventilator days.[31]

Telemedicine

Despite evidence supporting intensivist staffing of ICUs, the numbers of intensivists from all areas of training are inadequate to meet this mandate. Ewart and colleagues estimated that less than 15% of ICUs continue to have

dedicated intensivist coverage.[32] Recognition of this shortage has led to innovations such as the *eICU*, for which a small number of intensivists can monitor and consult on a large number of ICU beds from remote locations. Indeed, telemedicine is stated to meet the requirements of the Leapfrog Group, and it is an attractive alternative. Consolidating expensive and scarce resources could optimize critical care, especially to rural or community ICUs, by concentrating staff expertise. As of 2008, remote intensivists monitored almost 5000 eICU beds.[33]

The first hospital to adopt telemedicine occurred in 2000. In 2004, this facility published its results, showing a 25% reduction in ICU mortality (from 8.6% to 6.3%) and a 14% reduction in ICU length of stay (LOS) (from 5.6 to 4.8 days).[34] Most recently, in a system in which only residents were on call, Lilly and colleagues showed that implementation of a tele-ICU system decreased hospital mortality rate from 13.6% to 11.8% and decreased hospital LOS from 13.3 to 9.8 days.[35] They also found that this model resulted in improved adherence to critical care best practices. Conflicting results, no reduction in mortality, hospital LOS, or cost, were reported in another study of 4000 patients across two community hospitals, but this study was limited by a large number of clinicians who only allowed restricted participation of the tele-ICU model.[36] The physicians in the Lilly study seemed to work more proactively and were involved in the care of a greater proportion of the patients.

Overall, the available data suggest that eICUs can have the most impact and improve outcomes in ICUs that initially begin with a deficit in intensivist coverage or have a need to supplement current coverage levels, have high severity-adjusted mortality and LOS rates, are remotely located where the safe transfer of high-acuity patients may not be possible, and are part of an organizational structure that supports the presence of tele-ICU intensivists.[37] The role of eICUs in the delivery of critical care services continues to evolve. In systems with institutional buy-in, the eICU can be one way to help bridge the supply-demand gap of critical care physicians, but it remains unclear whether or how remote monitoring will be reimbursed.

QUALITY MEASUREMENT IN CRITICAL CARE

QUALITY OF EVIDENCE

To determine the value of a clinical intervention, evaluating the quality of the study on which it is based is important. A number of groups have developed criteria with which evidence can be graded. The Oxford Centre for Evidence-Based Medicine has strict criteria for grading the level of evidence. These criteria are described in Table 101-1. After the evidence level has been determined, specific practices can be graded by using the described criteria (see Table 101-1). Only through rigorous clinical experimentation can a determination be made as to which practices will improve the outcomes of critically ill patients. Equally important is an analysis of the cost-effectiveness of these interventions. Implementation may require fiscal and personnel expenditure, and it is the role of the medical director to convince hospital administrators of the cost-effectiveness of new interventions. Figure 101-1 describes the cost-effectiveness relationship for a theoretic treatment.

TABLE 101-1 LEVELS OF EVIDENCE

Level	Description
1a	Systematic review of randomized, controlled trials (with homogeneity)
1b	Individual randomized, controlled trial with a narrow confidence interval
1c	All-or-none trial*
2a	Systematic review of cohort studies (with homogeneity)
2b	Individual cohort study (including low-quality randomized, controlled trials)
2c	Outcomes research
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case series (and poor-quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles"

Modified from data provided by the Centre for Evidence-Based Medicine, Oxford, UK. Available at <http://www.cebm.net/index.aspx?o=1025.> (Accessed 15.07.12.)

*Met when all patients died before the treatment became available but some now survive on it, or when some patients died before the treatment became available but none now die on it.

Care of critically ill patients has been revolutionized by technology and drug development, but an equally important contribution has come with the application of evidence-based medicine to critical care practice. Although critical care initially focused on attempting to restore homeostasis, recognition that normal physiologic functioning is not always the most desirable therapeutic target is increasing. An important example of this principle is found in the management of patients with acute respiratory distress syndrome (ARDS). When patients with ARDS are mechanically ventilated with larger tidal volumes (12 mL/kg ideal body weight), they improve their oxygenation ratio.[38] However, these patients have significantly higher mortality rates than those who are mechanically ventilated with smaller tidal volumes (6 mL/kg ideal body weight). This example and others illustrate the need for randomized, prospective trials of new and existing therapies.

IMPLEMENTATION OF EVIDENCE-BASED PRACTICE

Application of evidence-based practice resulting in protocols to standardize patient care has been shown to improve the efficiency of care and reduce resource use.[39] Hospitals must customize the protocols to fit their practices, but protocols should not be used in place of good clinical judgment. They should be used as a complementary tool, and physicians should be able to justify departures from the protocol. These departures should be used to further refine the protocol to ensure that it is not viewed as a static entity but rather as an evolving guideline. For protocols to be effective, the hospital must be willing to invest the resources necessary for implementation.

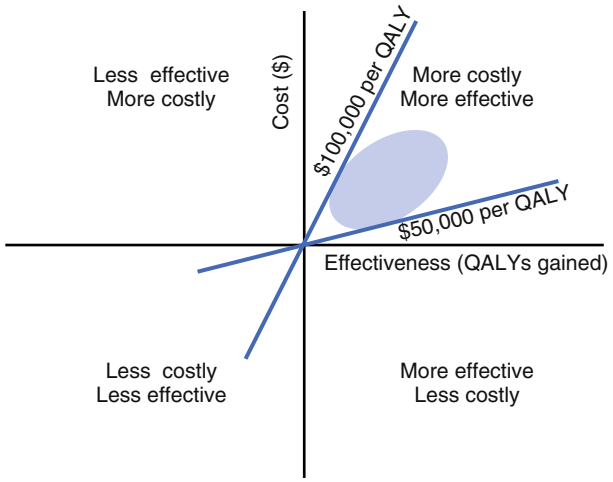


Figure 101-1. Graphic display of the cost-effectiveness of a theoretic treatment that adds additional cost but is effective in extending quality-adjusted life. A quality-adjusted life-year (QALY) is a year of life gained for which the quality of life is judged to be acceptable. The lines represent cost per QALY. Cost per QALY depends on the patient population that receives the intervention. For example, patients with a low severity of illness receiving activated protein C have a much higher cost per QALY than do those with a higher severity of illness.

Key personnel such as physicians, respiratory therapists, and nursing staff should be enlisted so that the entire patient care team helps define the standards on which the protocol is based.

Perhaps the most difficult task in the application of evidence-based practice is determining whether a given patient with a particular clinical scenario will benefit from that practice. Are there pathophysiologic differences in a particular patient's illness that may lead to a diminished treatment response? Are there important differences in systems or provider compliance that may diminish the safety or efficacy of the treatment? Does a patient have comorbid conditions that would lead to exclusion from a clinical trial? Despite these limitations, when applied to large populations of patients, practice protocols usually decrease mortality and reduce costs.

MANAGEMENT OF CRITICALLY ILL PATIENTS

The following sections examine the care of patients with some common diagnoses in critical care: sepsis, ARDS, hepatic failure, and renal failure. Many management plans have data supporting the use of protocol-based therapy. Others are introductory management ideas that may lead to integration into future protocols but are discussed here because of their importance in critical care.

SEPSIS AND MULTISYSTEM ORGAN FAILURE

Sepsis is the leading cause of death in critically ill patients in the United States and develops in 750,000 people annually.[1] The economic costs of sepsis are large, with annual expenditures totaling nearly $17 billion.[1] The high mortality rate and economic costs have led to considerable interest in the development of effective therapies for sepsis. As with other areas of medicine, adoption plus integration of new treatment strategies into routine clinical practice has been slow. After many years of unsuccessful clinical trials, randomized controlled trials have begun to show efficacy. The following therapies—cortisol replacement, glucose control, and activated protein C—have been intensively studied.

Cortisol Replacement

With the recognition that severe sepsis represents a state of overwhelming inflammation, corticosteroids were among the first therapies tested in randomized trials of patients with sepsis. At large doses and with short courses, the studies showed a negative effect.[40,41] Annane and associates proposed a different hypothesis in 2002.[42] Prompted by studies showing significantly improved time to withdrawal of vasopressor therapy in patients with sepsis who received small doses of hydrocortisone over a longer period (>5 days),[43,44] they administered low-dose steroids for 7 days. Their results showed that among patients who did not appropriately respond to the corticotropin test, 63% in the placebo group versus 53% in the corticosteroid group died ($P = 0.02$). Vasopressor therapy was withdrawn in 40% of patients in the placebo group, as opposed to 57% in the corticosteroid group ($P = 0.001$).

Despite this initial positive data, the administration of steroids to patients with sepsis remained controversial. A large randomized trial recapitulating the study of Annane and coworkers has been completed and documents the lack of efficacy of even low-dose steroids and the association of increased infections with steroid administration. The Corticosteroid Therapy of Septic Shock (CORTICUS) study was carried out to assess whether low-dose corticosteroids improve survival in patients with septic shock and sepsis.[45] A total of 499 patients were enrolled over a period of 3 years from 52 European ICUs. Patients received a tapering steroid regimen over an 11-day period but no mineralocorticoids. The results refuted Annane's initial study. The 28-day mortality rate in patients receiving low-dose steroids was not significantly improved from that in the placebo group (34% versus 31%, $P = 0.57$). In summary, although low-dose steroids with mineralocorticoids initially appeared to be beneficial, the results have not been reproducible in a large multicentered randomized study. Large doses of corticosteroids should not be used in patients with severe sepsis.

One issue raised by these investigations was the role of etomidate in causing adrenal suppression. Patients who received etomidate to facilitate endotracheal intubation had worse outcomes, thus leading to suggestions that etomidate not be used. Chan and associates conducted a meta-analysis with five studies assessing mortality and seven studies assessing adrenal insufficiency associated with etomidate use in patients with severe sepsis and septic shock.[46] They found an increased pooled relative risk for mortality of 1.20 (95% CI 1.02 to 1.42) and an increased pooled relative risk (RR) for adrenal insufficiency of 1.33 (95% CI 1.22 to 1.46). Although the data are not conclusive, the literature suggests that perhaps etomidate should not be the first choice for use in patients with sepsis.

Glycemic Control in the Critically Ill

Critically ill patients admitted to the ICU with severe injury or infection, such as burns, trauma, or sepsis, commonly enter into a hypermetabolic state (see also Chapter 39). This state is associated with enhanced peripheral glucose uptake and use,[47] hyperlactatemia,[48] increased glucose production,[49] depressed glycogenesis,[50] and insulin resistance.[49] Glucose intolerance develops after uptake of glucose in skeletal muscle, adipose tissue, and liver, and the heart becomes saturated,[51] and hyperglycemia occurs because of defective suppression of gluconeogenesis and a resistance to the peripheral action of insulin. These mechanisms all work to generate a hyperglycemic state to satisfy an obligatory requirement for glucose as an energy substrate. The intensity of the metabolic response peaks several days after the initial insult and then diminishes as the patient recovers.[48] However, a prolonged hyperglycemic response may occur in patients who continue to have tissue hypoperfusion or persistent infection, which then predisposes them to progressive metabolic derangements and multisystem organ failure.

Traditionally, hyperglycemia, secondary to sepsis, was viewed as a beneficial response because it promoted cellular glucose uptake when cells were energy deprived. A glucose concentration of 160 to 200 mg/dL was commonly recommended and believed to maximize cellular glucose uptake without causing hyperosmolarity.[52] However, neutrophil function is impaired in patients with hyperglycemia because of decreased bacterial phagocytosis,[53] and many studies report the negative effects of high blood sugar. Hyperglycemia in diabetic patients is associated with an increased rate of postoperative infections,[54] and decreased long-term outcomes after myocardial infarction.[55] Hyperglycemia is also associated with a poorer prognosis after stroke or head injury[56] (see also Chapter 70).

Van den Berghe and coworkers[57] hypothesized that even mild hyperglycemia (i.e., blood glucose levels between 110 and 200 mg/dL) could be harmful by predisposing critically ill patients to increased morbidity and mortality. They performed a prospective, controlled study involving 1548 patients in the surgical ICU who were randomized to receive intensive insulin therapy (i.e., blood glucose maintained between 80 and 110 mg/dL) or conventional treatment (i.e., blood glucose maintained between 180 and 200 mg/dL). In patients who remained in the ICU for longer than 5 days, intensive insulin therapy reduced the mortality rate from 20.2% with conventional therapy to 10% with intensive therapy ($P = 0.005$). The group receiving intensive insulin therapy also had a lower incidence of bloodstream infections (4.2% versus 7.8%, $P = 0.003$), renal failure requiring dialysis (4.8% versus 8.2%, $P = 0.007$) and critical illness polyneuropathy (28.7% versus 51.9%, $P = 0.001$). Patients in the intensive insulin group were also less likely to require prolonged mechanical ventilation and intensive care. The results of this trial made a persuasive argument for tighter glucose control, at least in patients in the surgical ICU.

Opponents of the use of strict glycemic control in critically ill patients argued that the risks of hypoglycemia should be seriously considered and that the therapeutic effect of insulin rather than glycemic control leads to the beneficial outcomes. Insulin has multiple effects, including the inhibition of tumor necrosis factor alpha (TNF-α),[58] which triggers procoagulant activity and fibrin deposition and inhibits macrophage inhibitory factor, thereby contributing to endotoxemia and toxic shock.[59] To determine whether it was insulin effect or glycemic control, van den Berghe and colleagues[60] used multivariate analysis to reanalyze their previous data. It appeared that decreasing blood glucose levels rather than the actual amount of insulin given was more closely correlated with the beneficial reductions in mortality, polyneuropathy, and bloodstream infections. Instead of the glucose level, the dose of insulin correlates with the incidence of renal failure. Investigators thought that this difference might be the result of the direct effect of insulin on the kidney or the need for less exogenous insulin in patients with renal failure because insulin is cleared through the kidney. Finney and associates[61] in a prospective, observational study provided additional evidence that glycemic control, rather than insulin administration, provided the benefit. They examined the effects of glucose control in 523 patients admitted to a single surgical ICU. In this trial the primary determinant of a bad outcome was hyperglycemia rather than hypoinsulinemia, and a lower mortality rate was associated with glycemic control rather than a protective effect of insulin administration. Increased insulin dosing resulted in an increased mortality rate across all ranges of glycemia. With regression analysis, their data also suggest that keeping blood glucose below 145 mg/dL may provide a survival benefit similar to that achieved with the tighter range of 80 to 110 mg/dL.

A major criticism of the original van den Berghe study was that it was performed on relatively homogeneous surgical populations. The same group then published a follow-up study examining tight glucose control in 1200 patients in medical ICUs.[62] The results showed reduced morbidity defined as a reduction in newly acquired renal injury, earlier weaning from mechanical ventilation, and earlier discharge from the ICU and the hospital but no difference in mortality. With subgroup analysis, they were able to determine a mortality benefit from tight glucose control if the patient was admitted to the ICU for 3 days or longer (43% versus 52.5%, $P = 0.009$). From the study design, it is unclear whether intensive insulin therapy for less than 3 days causes harm or perhaps the benefit from intensive insulin therapy requires time to be realized.

Since then, several multicentered randomized controlled studies have examined the risk-benefit ratio of tight glucose control.[63-65] Two studies (Volume Substitution and Insulin Therapy in Severe Sepsis [VISEP] and Glucontrol) were stopped early because of a high rate of hypoglycemia (17% versus 4.1%, $P < 0.001$, and 8.7% versus 2.7%, $P < 0.001$, respectively). The Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) trial, the most recent and largest of the studies, involved 42 ICUs and enrolled 6000 patients. The investigators reported no difference between the two groups in terms of days in the ICU, days on mechanical ventilation, and days requiring renal replacement therapy. Disturbingly, they found an increased incidence of hypoglycemia

in the tight glucose control arm (6.8% versus 0.5%, $P < 0.001$) and a higher 28-day mortality (22.3% versus 20.8%, $P = 0.02$).[65] Finally, a detailed analysis of the NICE-SUGAR database showed a dose-response relationship for harm, dependent on the degree of hypoglycemia.[66] Based on the current studies, it appears that tight glycemic control, and even routine normalization of plasma glucose,[67] may not be the right goal. The optimal glucose target may not be the same for all patients and all clinical scenarios; it may be more a function of the rate of glucose change as opposed to a static number.

Activated Protein C

Patients with severe sepsis have systemic inflammation resulting in coagulation abnormalities that range from subtle elevations in plasma D-dimer levels to clinically evident disseminated intravascular coagulation.[68,69] Recognition that sepsis can cause microthrombosis and that patients with sepsis have low circulating levels of activated protein C (APC) led to the investigation of APC as a specific therapy for sepsis.[70] APC is a naturally occurring anticoagulant that inactivates factors Va and VIIIa and prevents the generation of thrombin,[71] which is capable of stimulating multiple inflammatory pathways. Additional effects of APC include a permissive effect on thrombolysis that allows clearance of systemic microthrombi.[69] APC also decreases the expression of tissue factor and can bind selectins, which activate neutrophils on the endothelial surface.[72] Recent data suggest that APC levels can predict the outcome from multisystem organ failure, regardless of the inciting event.[73]

Recombinant human APC (Xigris) was developed by Eli Lilly for use in the treatment of severe sepsis.[72] In a publication of the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study of 1690 patients with severe sepsis randomized to receive APC or placebo, the mortality rate was 30.8% in the placebo group and 24.7% in the APC group ($P = 0.005$). Intravenous infusion of APC at 24 μg/kg/hr for 96 hours was associated with a 6.1% absolute reduction in the risk for death. The trial was stopped early for efficacy, but subsequent subgroup analysis suggested that the mortality benefit was limited to patients with increased illness severity (i.e., Acute Physiology and Chronic Health Evaluation [APACHE] score of >24). The most important adverse effect was serious bleeding (3.5% versus 2%, $P = 0.06$), as would be expected because of its anticoagulant effect. The U.S. Food and Drug Administration (FDA) approved the release of the drug based on only this study, but limited its use to patients with a high risk of death and requested additional trials involving patients with lower APACHE II scores. The trial enrolling patients with lower APACHE scores (ADministration of DRotrecogin alfa [activated] in Early stage Severe Sepsis) [ADDRESS] trial) was terminated early for futility by the data and safety monitoring committee.[74]

A new randomized, placebo-controlled trial of APC (PROWESS-SHOCK) was undertaken to hopefully provide the definitive answer.[75] In this trial, 1697 patients with infection, systemic inflammation, and shock were recruited from 208 sites in Europe, North and South America, Australia, New Zealand and India. They were randomized to receive a 96-hour infusion of APC or placebo. The primary endpoint, 28-day mortality, was equal between the two groups. (26.4% in APC group versus 24.2% in control group, RR 1.09, 95% CI 0.92 to 1.28, $P = 0.31$). Eli Lilly voluntarily withdrew APC from the market late in 2011 because of these study results.

ACUTE RESPIRATORY FAILURE

ICUs were first developed to manage patients with acute respiratory failure as a result of poliomyelitis. Since then, management of patients with acute respiratory failure has been revolutionized by the development of modern mechanical ventilators. Ashbaugh and associates first reported ARDS in 1967.[76] They described 12 patients with acute respiratory distress, cyanosis refractory to oxygen therapy, decreased lung compliance, and diffuse bilateral infiltrates on chest radiography. Because this initial definition lacked specific criteria that could be used to identify patients for research, the American-European Consensus Conference Committee recommended new definitions in 1994.[77]

Although critical for providing a framework for the ARDS network (ARDSnet) and other studies, it was recognized that the American-European consensus definitions had significant limitations as a result of the variability in the PaO_2/FiO_2 ratio with ventilator settings, poor reliability of chest radiographic criteria, and difficulties distinguishing hydrostatic edema. Therefore, a new consensus conference was convened to update the definitions, and the Berlin Definition of ARDS was formed.[78] Table 101-2 compares the two lists of criteria used to define acute lung injury (ALI) and ARDS.

Treatment of ALI or ARDS is primarily supportive and consists of mechanical ventilation, which allows time for treatment of the underlying cause of the lung injury and for natural healing.[79] Until recently, most studies of ALI or ARDS reported a mortality rate of 40% to 60%, with death attributed to sepsis or multiorgan failure rather than the primary respiratory causes.[80,81]

Several clinical trials have addressed one of the hallmarks of ALI or ARDS—decreased lung compliance. The National Institutes of Health (NIH) ARDSnet reported the definitive study on protective mechanical ventilation in 2000.[38] In this prospective study of patients with ALI, the mortality rate was reduced from 40% in patients receiving tidal volume ventilation of 12 mL/kg to 31% in those receiving 6 mL/kg. The low–tidal volume group also had more ventilator-free and organ failure–free days than did the higher–tidal volume group. Several reasons have been postulated for the discrepancy between this study and the previous inconclusive studies. First, the NIH study may have been better able to show a difference because it used lower tidal volumes than used in the other studies. Second, the NIH study allowed treatment of respiratory acidosis with high respiratory rates or with sodium bicarbonate. Treatment of respiratory acidosis may have prevented deleterious effects. Third, the NIH study enrolled 861 patients, which was by far the largest study and increased the statistical power to find a positive effect of low–tidal volume ventilation.[82]

In a second study using the same patient database, Eisner and associates[83] did not find any evidence that the

efficacy of the low–tidal volume strategy varied according to the clinical cause of ARDS. Although the mortality rate was highest (43%) in patients with sepsis, intermediate (36%) in patients with pneumonia and aspiration pneumonitis, and lowest (11%) in patients with trauma, no evidence of differential efficacy of low–tidal volume ventilation was found in different groups with ALI or ARDS. The investigators concluded that the recommendations for low–tidal volume ventilation should be applied to all patients with ALI or ARDS, regardless of the inciting cause.

Important advances in the ventilatory management of patients with ALI or ARDS have led to improvements in the care of patients in the ICU. With the impressive 9% absolute reduction in mortality demonstrated by the ARDSnet trial, low–tidal volume mechanical ventilation should be considered the standard of care for patients with ALI or ARDS unless a more efficacious strategy is demonstrated. Figure 101-2 shows the protocol used at the University of California, San Francisco, for mechanical ventilation of patients with ALI or ARDS. An unanswered question remains regarding whether patients without ARDS should be managed with a lung-protective strategy. A recent meta-analysis showed that in patients without lung injury, low tidal volume was associated with less progression to lung injury and lower mortality.[84]

Nontraditional Ventilatory Interventions

In addition to low tidal volume, other therapies have been used for the care of patients with ALI. Most have tried to improve the ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatching and hypoxemia that result from ALI. The following sections discuss data associated with high PEEP, recruitment maneuvers, prone positioning, inhaled nitric oxide (iNO), neuromuscular blocking agents, and early tracheostomy.

High Positive End-Expiratory Pressure. The use of PEEP has been proposed as a mechanism to minimize cyclical alveolar collapse and shear injury (atelectrauma). Brower and coworkers (Assessment of Low–Tidal Volume and increased End-Expiratory Volume to Obviate Lung Injury [ALVEOLI] trial) randomly assigned 549 patients with ARDS to receive low–tidal volume ventilation with either lower or higher PEEP levels.[85] They found similar rates of death before hospital discharge whether lower or higher PEEP was used (24.9% versus 27.5%, respectively, $P < 0.001$). These results were confirmed by a recent meta-analysis that combined data from three trials including more than 2000 patients to examine the effects of higher versus lower PEEP. Treatment with higher versus lower levels of PEEP was not associated with improved hospital survival.[86] For now, the recommendations are to use traditional PEEP values of 5 to 12 cm H_2O.

Lung Recruitment Maneuvers. Gravity-dependent atelectasis is invariably observed in patients with ARDS. The atelectatic lung areas lead to intrapulmonary shunting, $\dot{V}/\dot{Q}$ mismatching, and regional differences in compliance. Recruitment maneuvers, which involve periods of sustained increased airway pressure, have been proposed to re-expand atelectatic alveoli and avoid atelectrauma.[87] These maneuvers must be performed with caution because venous return may significantly decrease, thereby leading to hypotension, and alveolar ventilation may decrease, thereby resulting in hypercapnia and respiratory acidosis. Other clinically significant events can include pneumothorax, arrhythmias, and bacterial translocation. The optimal pressure, duration, and frequency of recruitment maneuvers have not been defined. In the ARDSnet ALVEOLI trial, patients randomized to the PEEP group also received recruitment maneuvers with airway pressures of 35 to 40 cm H_2O for 30 seconds to assess the effect on oxygenation.[85] After the first 80 patients, recruitment maneuvers had only a modest effect on oxygenation and were not continued for the remainder of the study. At this time, routine use of recruitment maneuvers cannot be recommended because they have been shown to increase oxygenation only transiently without improving mortality.

Prone Positioning. Because atelectasis and $\dot{V}/\dot{Q}$ mismatching appear to be dependent on gravity, one assumption is that turning a patient from the supine to the prone

TABLE 101-2 COMPARISON OF THE AMERICAN-EUROPEAN CONSENSUS CONFERENCE AND BERLIN DEFINITION OF ACUTE RESPIRATORY DISTRESS SYNDROME

	AECC Definition[77]	Berlin Definition[78]
Timing	Acute onset	Onset is within 1 week of a known clinical insult or new or worsening respiratory symptoms.
Oxygenation	**ALI**: PaO_2/FiO_2 ≤300 mm Hg **ARDS**: PaO_2/FiO_2 ≤200 mm Hg	**Mild**: 200 mm Hg; PaO_2/FiO_2 ≤300 mm Hg with PEEP or CPAP ≥5 cm H_2O **Moderate**: 100 mm Hg; PaO_2/FiO_2 ≤200 mm Hg with PEEP ≥5 cm H_2O **Severe**: PaO_2/FiO_2 ≤100 mm Hg with PEEP ≥5 cm H_2O
Chest radiograph	Bilateral infiltrates	Bilateral opacities are not fully explained by effusions, lobar or lung collapse, or nodules.
Edema	PAWP ≤18 mm Hg when measured or no clinical evidence of left atrial hypertension	Respiratory failure is not fully explained by cardiac failure or fluid overload.
Risk factor	Not included in definition	If no risk factor for lung injury is identified, then objective assessment such as echocardiography to exclude hydrostatic edema is needed.

AECC, American-European Consensus Conference; *ALI,* acute lung injury; *ARDS,* acute respiratory distress syndrome; *FiO_2,* fraction of inspired oxygen; *PaO_2,* partial arterial pressure of oxygen; *PAWP,* pulmonary artery wedge pressure; *PEEP,* positive end-expiratory pressure.

ARDSnet
NIH NHLBI ARDS Clinical Trials Network
Mechanical Ventilation Protocol Summary
UCSF Division of Critical Care Medicine

INCLUSION CRITERIA Acute onset of:
1. $PaO_2/FiO_2 \leq 300$ (corrected for altitude).
2. Bilateral (patchy, diffuse or homogeneous) infiltrates consistent with pulmonary edema.
3. No clinical evidence of left atrial hypertension.

PART I: Ventilator setup and adjustment
1. Calculate ideal body weight (IBW):
   Male = 50 + 2.3 (height [inches] − 60)
   Female = 45.5 + 2.3 (height [inches] − 50)
2. Select Assist Control Mode.
3. Set initial TV to 8 mL/kg IBW.
4. Reduce TV by 1 mL/kg at intervals ≤ 2 hours until TV = 6 mL/kg.
5. Set initial rate to approximate baseline $\dot{V}_E$ (not >35 bpm).
6. Adjust TV and RR to achieve pH and plateau pressure goals below.
7. Set inspiratory flow rate above patient demand (usually >80 L/min).

PART II: Weaning

Definition of weaning tolerance
1. RR ≤ 35 (may exceed 35 for ≤5 minutes) and:
2. $SpO_2 \geq 88\%$ (<15 minutes at <88% may be tolerated) and
3. Respiratory distress is absent (<2 of the following)
Pulse > 120% of usual rate for >5 minutes; marked use of accessory muscles; abdominal paradox, diaphoresis; marked complaints of dyspnea.

A. Conduct a CPAP Trial daily when:
1. $FiO_2 \leq 0.40$ and PEEP ≤ 8.
2. PEEP and $FiO_2 \leq$ values of previous day.
3. Patient has acceptable spontaneous breathing efforts. (May decrease vent rate by 50% for 5 minutes to detect effort.)
4. Systolic BP ≥ 90 mm Hg without vasopressor support.

CONDUCTING THE TRIAL:
Set CPAP = 5 cm H_2O, $FiO_2 = 0.50$
If RR ≤ 35 for 5 min: advance to Pressure Support Weaning below.
If RR > 35 in <5 min: may repeat trial after appropriate intervention (e.g., suction, analgesia, anxiolysis).
If CPAP trial not tolerated: return to previous A/C settings.

B. Pressure support (ps) weaning procedure
1. Set PEEP = 5 and $FiO_2 = 0.50$.
2. Set initial PS based on RR during CPAP trial:
   a. If CPAP RR < 25: set PS = 5 cm H_2O and go to step 3d.
   b. If CPAP RR = 25 to 35: set PS = 20 cm H_2O then reduce by 5 cm H_2O at ≤ 5-min intervals until RR = 26 to 35, then go to step 3a.
   c. If initial PS not tolerated: return to previous A/C settings.
3. REDUCING PS (No reductions made after 1700 hr.)
   a. Reduce PS by 5 cm H_2O q1-3h, then go to step 3d.
   b. If PS ≥ 10 cm H_2O not tolerated, return to previous A/C settings. (Reinitiate last tolerated PS level next AM and go to step 3a.)
   c. If PS = 5 cm H_2O not tolerated, return to PS = 10 cm H_2O. If tolerated, 5 or 10 cm H_2O may be used overnight with further attempts at weaning the next morning.
   d. If PS = 5 cm H_2O tolerated for ≥2 hr, assess for ability to sustain unassisted breathing below.

Figure 101-2. Protocol for low–tidal volume mechanical ventilation of patients with acute lung injury or acute respiratory distress syndrome (ARDS) in use at the University of California, San Francisco (UCSF). The protocol is based on that used in the ARDSnet trial. *A/C*, Assist/control; *BP*, blood pressure; *CPAP*, continuous positive airway pressure; *FiO_2*, fraction of inspired oxygen concentration; *ICU*, intensive care unit; *I:E*, inspiratory-to-expiratory ratio; *NHLBI*, National Heart, Lung, and Blood Institute; *NIH*, National Institutes of Health; *PaO_2*, partial alveolar pressure of oxygen; *PEEP*, positive end-expiratory pressure; *Pplat*, plateau pressure; *PS*, pressure support; *RR*, respiratory rate; *SpO_2*, saturation of peripheral oxygen; *TV*, tidal volume; *V_E*, minute ventilation.

position would change these relationships and improve gas exchange. Prone positioning is fraught with difficulty and can result in accidental extubation, dislodgement of the line or chest tube, and patient injury, but it can lead to higher functional residual capacity, better drainage of secretions, and improved oxygenation. Gattinoni and colleagues performed a multicenter, prospective randomized trial, enrolling 304 patients with ARDS to compare supine positioning with prone positioning for 6 or more hours per day for 10 days.[88] Oxygenation was improved in the prone group, but mortality did not differ between the two groups. Most recently, Guerin and colleagues studied patients with severe ARDS (PaO_2/FiO_2 ratio < 150 mm Hg).[89] All the participating medical centers had more than 5 years' experience with prone positioning. Patients were placed in the prone position early in the disease process (within 1 hour of randomization) for more than 16 consecutive hours per day, as well as sedated and paralyzed with neuromuscular blockers. Twenty-eight day mortality decreased from 32.8% in the control group to 16.0% in the prone group ($p < 0.001$), and the incidence of complications was not significantly increased in the intervention group. Although specific patients may benefit from this technique, the data do not

C. Unassisted breathing trial
1. Place on a T-piece, trach collar, or CPAP < 5 cm H_2O.
2. Assess for tolerance as below for 2 hours.
3. If tolerated, consider extubation.
4. If not tolerated, resume PS 5 cm H_2O.

Definition of Unassisted Breathing Tolerance:
1. RR ≤ 35 and
2. SpO_2 ≥ 90% and/or PaO_2 ≥ 60 mm Hg and
3. Spontaneous TV ≥ 4 mL/kg IBW and
4. Respiratory distress is absent (<2 of the following):
   pulse > 120% of usual rate for > 5 minutes, marked use of accessory muscles;
   abdominal paradox, diaphoresis, marked complaints of dyspnea.

OXYGENATION GOAL:
PaO_2 55 to 80 mm Hg or SpO_2 88% to 95%
Use incremental FiO_2/PEEP combinations below to achieve goal:

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
FiO_2	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0
PEEP	14	14	14	16	18	20	22	24

PLATEAU PRESSURE GOAL: ≤ 30 cm H_2O
Check Pplat (0.5 sec insp. Pause), SpO_2, total RR, TV and pH at least q4h and after each change in PEEP or TV

If Pplat > 30 cm H_2O: decrease TV by 1 mL/kg steps (min = 4 mL/kg)
If Pplat < 25 cm H_2O: increase TV by 1 mL/kg until Pplat > 25 cm H_2O or TV > 25 cm H_2O or TV = 6 mL/kg

pH GOAL: 7.25 to 7.45
Acidosis Management:
pH < 7.25 but ≥ 7.20
1. Notify ICU resident of pH < 7.25.
2. Increase RR until pH > 7.25 or $Paco_2$ < 25.
3. If RR = 35 and/or $Paco_2$ < 25, MAY give $NaHCO_3$ or choose to leave as is until pH < 7.20.

pH < 7.20
1. Increase RR to 35 (if not already 35).
2. If pH remains < 7.20 and $NaHCO_3$ considered or infused, TV may be increased in 1 mL/kg steps until pH > 7.20. (Pplat target may be exceeded.)

Alkalosis Management (pH > 7.45)
1. Decrease ventilator rate if possible.

I:E RATIO GOAL: 1:1 to 1:3. Adjust flow rate to achieve goal.
If FiO_2 = 1.0 and PEEP = 24 cm H_2O, may adjust I:E to 1:1.

Figure 101-2, cont'd.

currently support the routine use of prone positioning at all hospitals. The use of specialized beds that can provide significant side-to-side rotation may be an alternative to prone positioning, but these beds have not been tested in prospective trials.

Inhaled Nitric Oxide. Numerous cells synthesize endogenous nitric oxide (NO) in the human body, including macrophages, mast cells, and smooth muscle cells. NO modulates vascular tone and neurotransmission, inhibits platelet aggregation and cell cytotoxicity, and interacts with free radicals.[90,91] NO binds to hemoglobin and is then metabolized by conversion to nitrites and nitrates, which are excreted in urine.[92] This process is extremely rapid and results in a half-life on the order of seconds, so the effect of NO is limited to the immediate area in which it is released. Selective delivery of NO by inhalation (iNO) to well-ventilated areas of the lung improves $\dot{V}/\dot{Q}$ mismatching and improves oxygenation by dilating the local pulmonary capillaries (Fig. 101-3). This effect is in contrast to other pulmonary vasodilators, which usually worsen gas exchange by indiscriminately dilating vessels (also see Chapter 104). In particular, hemoglobin inactivates iNO in the lung , which minimizes harmful systemic vasodilation.

Initially, iNO was used as salvage therapy to improve oxygenation in patients with severe ARDS.[93] Further studies then used iNO earlier in the course of ARDS and were able to demonstrate decreased pulmonary artery pressure, decreased venous admixture, and increased oxygenation with no change in systemic blood pressure, systemic vascular resistance, or cardiac output.[94,95] The average improvement in the PaO_2/FiO_2 ratio was 42%.[96]

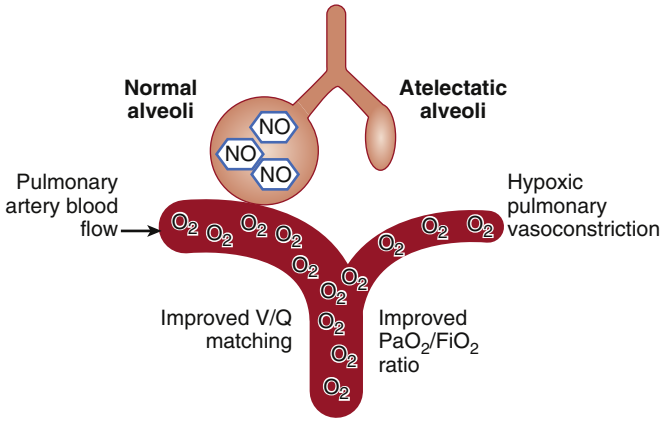


Figure 101-3. Mechanism of action of inhaled nitric oxide. *FiO_2*, Fraction of inspired oxygen concentration; *NO*, nitric oxide; *O_2*, oxygen; *PaO_2*, partial alveolar pressure of oxygen; *$\dot{V}/\dot{Q}$*, ventilation-perfusion. *(Adapted from Liu LL, Aldrich JM, Shimabukuro DW, et al: Special article: rescue therapies for acute hypoxemic respiratory failure,* Anesth Analg *111:693-702, 2010.)*

The beneficial effects appear to be sustained during long-term therapy, but a rebound phenomenon has been reported after the abrupt removal of iNO therapy.[97]

Three randomized controlled trials of iNO in patients with ARDS were published in 1998. Two of the studies were small (<40 patients), and the results were consistent with the larger multicenter placebo-controlled, double-blinded trial.[98] In the third study, patients in the iNO group had an acute improvement in oxygenation, but no differences in FiO_2 were observed between the iNO and placebo groups from days 2 through 7. Most importantly, no differences in mortality or the number of days alive and not requiring mechanical ventilation were found through day 28. In patients who were responders to iNO, defined as a 20% or greater increase in PaO_2, no differences in 30-day mortality were reported between responders given iNO and responders given conventional therapy.[96] A recent meta-analysis examining 12 trials involving 1237 patients also found an increased PaO_2/FiO_2 ratio in the iNO group and, again, no significant effect of iNO on hospital mortality, duration of ventilation, or ventilator-free days. However, an increased risk for renal dysfunction (risk ratio [RR], 1.5; 95% CI 1.1 to 2.02) was reported in the patients receiving iNO.[99]

Because of the data available, routine use of iNO in patients with ARDS cannot be recommended. However, no data are available that address the use of iNO as rescue therapy for patients with critically low oxygenation. Further randomized studies of patients with specific disease states (e.g., rapidly progressive hypoxia, severe pulmonary hypertension, right ventricular failure) may identify the subgroup that could potentially benefit from iNO.

Neuromuscular Blocking Drugs. First reported in 1977, severe muscle weakness was described in patients exposed to a combination of mechanical ventilation, high-dose corticosteroids, and neuromuscular blocking agents (NMBAs) (see also Chapter 34).[100] Since then, more than 20 studies have been published; most were observational study designs. The majority of the data from previous studies indicate only a causal relationship between NMBAs and ICU-acquired weakness (ICU-AW).[101] Kesler and colleagues, after a change in clinical practice to avoid muscle paralysis, compared the records of 74 patients with asthma admitted between 1995 and 2004. They found no difference in the incidence of ICU-AW, despite this deliberate reduction in the use of NMBAs (20% versus 14%, $P = 0.23$).[102]

More recently, Papazian and colleagues reported a study investigating the use of cisatracurium on the outcome of patients with severe acute respiratory distress syndrome (PaO_2/FiO_2 ratio <150).[103] In this study, 340 patients were randomized to receive 48 hours of cisatracurium or placebo. Although the primary outcome was 90-day survival, muscle testing was performed to look for signs of weakness. No difference was observed between groups in the incidence of ICU-AW (29% versus 32%, $P = 0.49$). In the subgroup that received corticosteroids, no difference in the frequency of ICU-AW was observed (37% versus 30%, $P = 0.32$). The hazard ratio for death at 90 days in the cisatracurium group, as compared with the placebo group, was 0.68 (95% CI 0.48 to 0.98, $P = 0.04$).

With the current understanding of NMBAs, more data are clearly needed. In patients undergoing mechanical ventilation for ARDS, short periods of NMBAs may improve oxygenation and decrease ventilator-induced lung injury, but studies that can separate neuromuscular blockade from immobilization and sedation as causative factors in the pathogenesis of ICU-AW are needed before definitive statements can be made.

Indications for Tracheotomy

Tracheotomy is a common procedure in the ICU that is performed in approximately 10% of critically ill patients who require mechanical ventilation.[104] Placement of a tracheotomy is thought to allow a more secure and manageable airway, earlier and safer enteral feeding, easier oral care, and enhanced patient comfort while reducing sedation needs and facilitating mobilization. Complications from tracheotomy include stoma infection, pneumothorax, subcutaneous emphysema, tracheomalacia, and tracheostenosis.[105] Major questions concerning tracheotomy include which patients with acute respiratory failure should have the procedure and when it should be performed.

A review published in 1998 concluded that insufficient evidence supports the view that timing of a tracheotomy can alter the duration of mechanical ventilation or prevent airway injury in critically ill patients.[106] Since then, individual studies have reported decreased days of mechanical ventilation,[107] decreased duration of ICU and hospital LOS,[108] and less damage to the upper airway[107] with early tracheotomy. A meta-analysis attempted to answer this question definitively. Unfortunately, only five trials with 406 patients were found that met the inclusion criteria.[109] They reported that the timing of tracheotomy did not alter mortality or increase the risk for hospital-acquired pneumonia. Early tracheotomy did, however, lower the duration of mechanical ventilation and the overall LOS in the ICU (Table 101-3). The results were far from conclusive. Heterogeneity was high in the meta-analysis because of variability in inclusion and exclusion criteria, definitions of early and late tracheotomy,

TABLE 101-3 **DATA COMPARING EARLY-TO-LATE TRACHEOSTOMY**

	Relative Risk	95% Confidence Interval	*P* Value
Timing of tracheotomy	0.79	0.45-1.39	0.42
Development of pneumonia	0.9	0.66-1.21	0.48
	Mean Difference	**95% Confidence Interval**	***P* Value**
Time on ventilator	–8.5 days	–15.3 to –1.7 days	0.03
Length of ICU stay	–15.3 days	–24.6 to –6.1 days	0.001

Modified from Griffiths J, Barber VS, Morgan L, et al: Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation, BMJ *330: 1243, 2005.*

characteristics of enrolled patients, and diagnostic criteria for hospital-acquired pneumonia.

More recently, Blot and associates compared early tracheotomy (within 4 days of intubation) with prolonged intubation in a randomized controlled trial conducted in 25 French ICUs.[110] The trial did not demonstrate any major benefit of tracheotomy as defined as 28-day mortality, incidence of VAP, ventilator-free days, or time in the ICU. The results were confirmed by Terragni and coworkers, who studied the effectiveness of early tracheotomy (6 to 8 days after intubation), compared with late tracheotomy (13 to 15 days after intubation) in reducing VAP.[111] In this randomized controlled trial performed in 12 Italian ICUs, early tracheostomy did not result in statistically significant improvement in the incidence of VAP (14% versus 21%, $P = 0.07$).

There appears to be no effect on mortality or VAP incidence whether critically ill patients undergo early or late tracheotomy. It is possible that subgroups of patients may have mortality benefit from early tracheotomy, but the difficulty comes in identifying these patients. The need to have better predictive models to identify patients who may have a simple subsequent weaning process after failing the first attempt is significant. Tracheotomies should be performed in patients who will encounter difficult or prolonged weaning. Unfortunately, no validated specific and sensitive test or scoring system is available that can predict the need for prolonged ventilation; therefore, the selection of patients for tracheotomy remains a subjective decision.

Percutaneous versus Open Tracheotomy. Percutaneous techniques are emerging as a method of securing the airway of adults in critical care settings. Advantages include smaller skin incision, less tissue trauma, lower incidence of wound infection, reduced risk associated with the transfer of patients to the surgical department, and fewer personnel requirements. Two meta-analyses showed a trend toward fewer complications, cost-effectiveness by releasing surgical resources, and greater feasibility than the open surgical approach when performing the percutaneous procedure at the bedside.[112,113] One important caveat of these results is to remember the exclusion criteria for most of these studies (e.g., emergency tracheostomy, suspicion or evidence of a difficult airway, previous airway problems, coagulopathies, previous tracheostomies). Consequently, although the procedure appears to be safe and effective, the favorable data exist only for a particular subset of patients admitted to the ICU.

Intravenous Fluid Management and Monitoring

The use of pulmonary artery catheters (PACs) in critically ill patients has dramatically decreased. Most studies have failed to show efficacy or have demonstrated harm. The best known of these investigations is the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT), which was a retrospective, observational study involving 5735 critically ill patients.[114] In those patients, the use of a PAC was associated with increased mortality and cost. Richard and coworkers completed a prospective, observational trial of PACs versus central venous catheters (CVCs) in patients with ARDS or shock.[115] Clinical management was left to the discretion of the treating physician. In 36 French ICUs, no difference was observed in any of the outcome variables measured in 676 patients.

The Fluids and Catheters Treatment Trial (FACTT), conducted by the National Heart, Lung, and Blood Institute (NHLBI) ARDSnet, compared hemodynamic management guided by a PAC with hemodynamic management guided by a CVC in 1000 patients with established ALI.[116] Patients were treated at select academic ICUs by clinicians who were trained in interpreting hemodynamic data and who were following a specific management protocol. Although serious catheter-related complications were rare, the PAC group had a higher incidence of arrhythmias and conduction blocks. The investigators were unable to demonstrate prevention or reversal of organ failure, reduced need for support (e.g., vasopressors, assisted ventilation, renal replacement therapy), faster discharge from the ICU, or decreased 60-day mortality in the PAC group versus the CVC group. Possibly because of this growing evidence, the use of the PAC has decreased by 65% during the last decade in the United States.[117]

The interesting result from FACTT was that a conservative fluid management plan appeared more effective in patients with established ALI.[118] Although the 60-day mortality was similar in both groups, patients in the conservative fluid management group had improved lung function; improved central nervous system function; and a decreased need for sedation, mechanical ventilation, and intensive care. In addition, the patients in the conservative fluid management group did not have an increased incidence of complications, such as nonpulmonary organ failure or shock.

For the past decade, the emphasis has been less on the measurement of pulmonary capillary wedge pressure or central venous pressure and more on the assessment of fluid responsiveness. The belief is that this dynamic measurement based on physiologic responses would be better than a static indicator.[119] The measurements can be derived from an arterial pressure waveform (systolic pressure variations [SPVs] and pulse pressure variations [PPVs]), are minimally invasive, allow beat-to-beat monitoring, and permit assessment of heart-lung interactions in patients who are mechanically ventilated (Fig. 101-4).

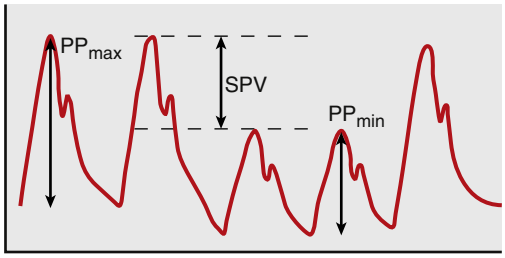


Figure 101-4. Noninvasive measurements of fluid responsiveness. PP_{max}, Maximal volume of pulse pressure; PP_{min}, minimal volume of pulse pressure: *SPV,* systolic pressure variation.

Although studies have been promising for the purpose of predicting fluid responsiveness under anesthesia,[120,121] they have been more problematic in the ICU. Patients generally have to be in sinus rhythm, have a closed chest, have normal intraabdominal pressures, and be on controlled ventilation with PEEP between 0 and 5 cm H_2O.[122]

Perhaps the most prudent approach from all these data is to base management on clinical examination findings and appropriately titrated fluid according to the patient's phase of illness. Goal-directed, liberal fluid administration during the acute phase of sepsis offers important benefits.[123] However, excess fluid is not beneficial when it is not physiologically needed during the established phase of ALI.

FLUID SELECTION: COLLOID VERSUS CRYSTALLOID

There is still no clear evidence as to what type of fluid (colloid or crystalloid) should be used for fluid administration. Finfer and associates randomized almost 7000 patients admitted to the ICU to receive either 4% albumin or normal saline.[124] Mortality from any cause during the 28-day period was similar in both groups, leading the authors to conclude that albumin and saline should be considered equivalent for intravascular volume replacement in a mixed population of ICU patients. Among colloids, evidence against the use of hydroxyethyl starch (HES), because it may increase kidney injury, seems to exist. When comparing HES versus saline, more patients in ICUs who were resuscitated with HES required renal replacement therapy (7% versus 5.8%, $P = 0.04$) and developed adverse effects (e.g., pruritus, skin rash) (5.3% versus 2.8%, $P < 0.001$).[125] In patients with severe sepsis, the use of HES compared with lactated Ringer solution led to increased 90-day mortality (RR 1.17; 95% CI 1.01 to 1.36, $P = 0.03$) and increased requirement for renal replacement therapy (RR 1.35; 95% CI 1.01 to 1.80, $P = 0.04$).[126] Presently, HES is increasingly becoming viewed as a solution that should not be administered (see Chapter 61).

ACUTE LIVER FAILURE

Epidemiology

Acute liver failure (ALF) is an uncommon disorder that leads to jaundice, coagulopathy, and multisystem organ failure. The development of hepatic encephalopathy within 8 weeks after the onset of jaundice in patients with no known chronic liver disease defines ALF.[127] ALF affects approximately 2000 people per year in the United States,[128] with acetaminophen overdose the cause in a majority of the cases.[129] Mortality from fulminant hepatic failure (FHF) can be high (60% to 80%) in the absence of liver transplantation, depending on the cause.[130] Causes of death are mainly multisystem organ failure, sepsis, and cerebral edema. Liver transplantation for ALF generally has a worse outcome than transplantation for chronic liver disease because of the high postoperative mortality caused by sepsis and multiorgan failure.[131]

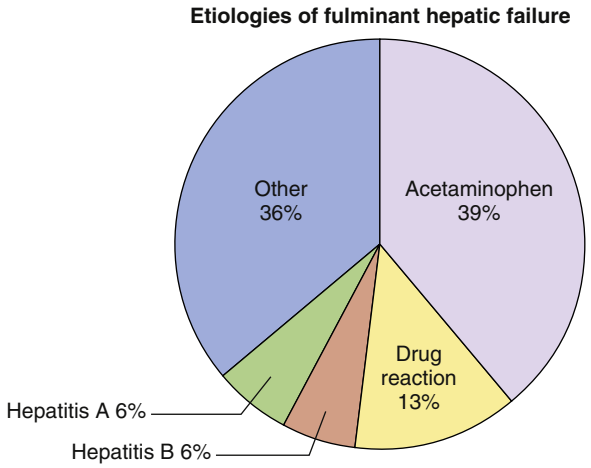


Figure 101-5. Etiologies of fulminant hepatic failure. *(Modified from Schiodt FV, Atillasoy E, Shakil AO, et al: Etiology and outcome for 295 patients with acute liver failure in the United States,* Liver Transpl Surg *5: 29-34, 1999.)*

Prognostic Factors in Acute Liver Failure

The timing of transplantation and the selection of patients are crucial because transplantation is the only therapeutic intervention proved to be beneficial.[132] Although scoring systems have been proposed, the myriad causes of ALF limit their accuracy (Fig. 101-5). Most case series are limited in number, and some span long periods during which supportive therapies may have changed. The King's College criteria have been shown to have good specificity (94.6%) for patients who will die without transplantation but lower sensitivity (58.2%), thus suggesting that a proportion of patients will die and not fulfill the criteria.[133] The criteria also have low negative predictive value, which could lead to transplantation in a patient who would have recovered without surgery. Other predictors include the Model for End-Stage Liver Disease (MELD),[134] which has been shown to be an excellent predictor of outcome in patients with ALF of various causes, excluding acetaminophen.[135] Blood lactate levels[136] and hyperphosphatemia[137] are also promising.

Management of Fulminant Liver Failure

General Supportive Measures. Patients with ALF are prone to rapid deterioration and should be closely monitored, usually in an intensive care setting. The cause of the ALF should be identified, and suitable candidates for

orthotopic liver transplantation should be moved early to a transplantation center. Early tracheal intubation may be necessary if neurologic status deteriorates and leads to airway compromise. Volume expansion with crystalloids and colloids is usually required to help maintain blood pressure. Correction of acid-base disturbances, treatment of hyperthermia, and close glucose monitoring are important to prevent cerebral edema. Renal failure from hepatorenal syndrome may develop and is reversible with the return of hepatic function. Continuous renal replacement therapy (CRRT) is often required in patients with advanced ALF to treat renal insufficiency, volume status, and cerebral edema. Early antibiotics and source control are important because the incidence of bacteremia and sepsis is higher in these patients than in the general population.[138] Although abnormalities exist in both the coagulation and fibrinolytic pathways, the defects appear to be balanced, and there is a relative preservation of hemostasis unless the platelet count is very low.[139] If a cause is identified, then initiation of antidotes is needed (e.g., *N*-acetylcysteine for acetaminophen poisoning, penicillin G for mushroom poisoning, early delivery for pregnancy-related ALF).[134]

Management of Increased Intracranial Pressure. The development of cerebral edema and intracranial hypertension is the most devastating complication associated with ALF (see also Chapter 70). Osmotically active compounds, normally cleared by the liver, accumulate in blood and diffuse into the brain parenchyma. Movement of water into neurons and glia results in swelling and can cause herniation. The exact compounds responsible for cerebral edema are unknown, but ammonia is probably a major contributor.

Diagnosis of cerebral edema can be difficult. Serial neurologic examination is essential, and frequent computed tomography of the head can identify early signs of edema. Many centers implement early invasive monitoring of intracranial pressure, although this practice has not been shown to improve outcome.[140] Monitoring can be achieved with either cranial or lumbar epidural monitors because traditional intraventricular monitors carry an unacceptable risk of bleeding.

Techniques to reduce intracranial pressure include the removal of ammonia with CRRT, hypothermia, barbiturate coma, and the administration of mannitol and hypertonic saline.[141] Although most available laboratory evidence suggests that hypothermia should be helpful in controlling the cerebral complications of ALF, randomized clinical trials in patients to demonstrate its safety or efficacy are currently lacking.[142]

Liver Support Devices

Bioartificial Livers. Bioartificial livers use hepatocytes to mimic the synthetic, detoxifying, and excretory function of the dying liver. Porcine hepatocytes are preferentially used because human hepatocytes are difficult to grow in culture.[143] The device works by passing the patient's plasma through hollow-fiber capillaries while the hepatocytes are placed in the extracapillary space. Molecules are exchanged between hepatocytes and plasma across a membrane that prevents passage of immunoglobulin, complement, and cells. A prospective, multicenter, randomized controlled trial using the HepatAssist liver support system was published in 2004.[144] The results did not show any improvement in survival in the treated group. Only during subgroup analysis were patients with fulminant or subfulminant liver failure found to have improved survival, but the results were marginal.

Artificial Extracorporeal Devices. Artificial extracorporeal devices have received renewed interest because of technology allowing the production of membranes that can increase selectivity through small pores. The system can be tailored for albumin-bound substances, which include most of the toxins that accumulate with FHF. Larger molecules such as immunoglobulins cannot cross. This system is associated with significant biochemical improvements,[145] but these studies are small and uncontrolled, and whether this will translate into improved clinical outcomes still remains a matter of debate (see also Chapter 107).

Overall, the liver support devices appear to be safe, but adverse events can include bleeding, systemic infection, disseminated intravascular coagulation, and anaphylaxis. A meta-analysis of the use of artificial and bioartificial life support systems in 8 randomized controlled trials involving only 139 patients concluded that the evaluated support systems have no significant effect on the mortality in patients with ALF.[146] Randomized clinical trials are limited, considering the patient's severity of illness. More controlled trials addressing survival are warranted before this therapy can be strongly recommended.

ACUTE RENAL FAILURE

Epidemiologic Variables

The incidence and outcomes of acute kidney injury (AKI) in the ICU are highly variable. Reported incidences can be as high as 35%.[147] Renal replacement therapy is the mainstay of support for these patients, but mortality remains high. Despite improvements in renal replacement technology over the years, mortality caused by AKI in the ICU has remained at higher than 50%.[148]

Diagnosis

The diagnosis of AKI has not been straightforward. A recent survey revealed the use of at least 35 definitions in the literature.[149] This state of confusion has given rise to the wide variation in reported incidence and clinical significance of ARF. The Acute Dialysis Quality Initiative (ADQI), which is made up of a group of experts consisting of nephrologists and intensivists, has proposed new criteria for describing renal dysfunction. They recognized the clinical importance of milder forms of renal insufficiency and that stratifying renal dysfunction (mild to severe) would better describe the disease. They proposed the RIFLE criteria (Table 101-4), which stand for risk, injury, failure, and two outcome classes (loss and end-stage kidney disease). For each increasing RIFLE class, a stepwise increase in mortality independent of comorbidity occurs.[150] These data suggest that strategies to prevent even mild AKI may improve survival, and recovery of renal function in the ICU should be a specific therapeutic target.

TABLE 101-4 **THE RIFLE CRITERIA**

	GFR Criteria	UO criteria	OR Hospital Mortality[150]
Risk	Cr increased ×1.5 or GFR decreased >25%	UO <0.5 mL/kg/hr ×6 hr	2.2 (95% CI 2.17-2.3)
Injury	Cr increased ×2 or GFR decreased >50%	UO <0.5 mL/kg/hr ×12 hr	6.1 (95% CI 5.74-6.44)
Failure	Increased Cr ×3 or GFR decrease ≥75% or Cr >4 mg/dL	UO <0.3 mL/kg/hr ×24 hr or Anuria ×12 hr	8.6 (95% CI 8.07-9.15)
Loss	Complete loss of renal function for >4 wk		
ESRD	End-stage disease		

GFR, Glomerular filtration rate; *UO,* urine output; *OR,* odds ratio; *Cr,* creatinine; *ESRD,* end-stage renal disease.
Modified from Kidney Disease: Improving Global Outcomes, Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury, Kidney Inter Suppl *2(1):1-138, 2012.*

Management of Acute Renal Failure

General Supportive Measures. Patients with ARF should be closely monitored. The cause of the ARF should be identified by looking at prerenal, renal, and postrenal causes. Laboratory evaluations should include serum and urine electrolytes, urinalysis, and examination of urinary sediment. Careful assessment of volume status is necessary to determine hypovolemia, leading to prerenal azotemia versus hypervolemia from oliguria. Correction of acid-base disturbances may be necessary, as well as correction of electrolyte abnormalities. Continuous renal support is often required in patients with advanced renal failure to help with volume overload and electrolyte disturbances. Antibiotics and other medications should be dosed according to creatinine clearance, and serum levels, if available, should be closely monitored. Platelet dysfunction may occur as a result of uremia and require desmopressin (DDAVP) for support if bleeding is problematic.

Resuscitation fluids with high chloride concentration (0.9% saline, 4% to 5% albumin) are associated with decreased urine flow and electrolyte secretion, hyperchloremic metabolic acidosis, and renal vasoconstriction. A recent open-label, sequential study where high chloride-containing solutions were restricted in critically ill patients showed decreased progression to renal failure and a reduction in the need for renal replacement therapy.[151]

Renal Support. ARF in the ICU often requires some type of renal replacement therapy. Commonly, this is accomplished by continuous venovenous hemofiltration (CVVH), a form of CRRT. Although CRRT has several theoretic advantages over intermittent hemodialysis (IHD), such as enhanced hemodynamic stability, increased solute removal, and greater ultrafiltration capacity, individual randomized trials have not supported its superiority.[152,153] The timing and dosing of this therapy and the patients most likely to benefit from it remain unclear.

Recently, it appears that the difference in efficacy lies not in the type of dialysis (IHD versus CVVH) but in the dialysis dose. Undertreatment appears to be harmful,[154] whereas earlier application and higher filtration volumes appear to be associated with decreased mortality in patients with ARF.[155] On the other hand, intensive-dose CRRT has also not been shown to be beneficial in terms of mortality, renal function recovery, and ICU LOS.[156-158] Even with IHD, which can cause more hemodynamic lability, when studies are controlled for dialysis dose, polymer membrane, and bicarbonate-based buffer, 60-day mortality did not differ between the two groups (CRRT versus IHD).[159] Although a trend to use CRRT has developed, favorable data with IHD are intriguing because using IHD would allow more ICU resources to be allocated elsewhere.

COMPLICATIONS OF INTENSIVE CARE UNIT MANAGEMENT

Mortality in the ICU has been declining. For instance, over a 2-year period, the mortality from sepsis dropped from 37.0% to 30.8% ($P < 0.001$).[160] Although ICU care has advanced and improved, some limitations in the ability to further reduce mortality are the result of complications of the ICU care that are given. In the following sections, the prevention of ICU complications such as ICU-AW, hospital-acquired infections (HAIs), and miscommunications associated with handoffs are discussed.

INTENSIVE CARE UNIT–ACQUIRED WEAKNESS

As survival after critical illness has improved over the years, many patients now require on-going rehabilitation after discharge from the ICU. Profound neuromuscular weakness, or ICU-AW, is common and leads to severe functional impairment in many ICU survivors. Risk factors for ICU-AW are multifactorial and can include disease severity, presence of systemic inflammatory response syndrome (SIRS),[161] number of days with two or more organ dysfunctions, duration of mechanical ventilation,[162] ICU LOS, serum glucose levels,[163] and use of corticosteroids or NMBAs.[164] Controversies exist over the risks and benefits of tight glycemic control, and a causal relationship between the use of corticosteroids or NMBAs has not been clearly established. At present, few options are available to prevent or treat ICU-AW specifically.[165]

A potential therapeutic option is the avoidance of bed rest with early mobilization in the ICU. Exercise can improve strength and increase the production of

antiinflammatory cytokines, which may play an important role in muscle protection.[166] Griffiths and coworkers described the effects of continuous passive motion of one leg in patients with respiratory failure receiving NMBAs. The contralateral leg served as the control. Muscle DNA-to-protein ratio (an index of wasting) was significantly less reduced in the leg receiving passive motion.[167]

Studies are also demonstrating improved clinical outcomes with early mobility. An early mobility protocol that provided rehabilitation therapy 7 days per week via a dedicated mobility team—nurse, nurse assistant, and physical therapist—showed a trend toward decreased hospital mortality (12.1% versus 18.2%, $P = 0.125$). Early mobilization was also associated with decreased LOS in the ICU (5.5 days versus 6.9 days, $P = 0.025$) and decreased LOS in the hospital (11.2 days versus 14.5 days, $P = 0.006$) after adjusting for differences in body mass index, APACHE II score, and vasopressor use.[168]

Despite the early data showing benefits, early mobilization of critically ill patients in the ICU has unique challenges and concerns. One barrier has been the culture regarding the need for bed rest and activity restriction during critical illness because of the presence of endotracheal tubes, vascular access devices, or other medical equipment. However, studies have demonstrated that mobilization of patients who are mechanically ventilated can be safely performed. Bailey and colleagues showed that in a study of 103 patients in the ICU involving over 1400 activity events, only 14 minor events occurred in 9 patients, and no unanticipated extubations or events occurred, requiring additional cost or increased LOS in the hospital.[169] Morris and colleagues obtained similar results in their trial of early mobility on 145 patients who were intubated in the ICU. They reported no incidents of accidental removal of devices.[168]

It is becoming more apparent that early mobility is feasible in ICUs with a supportive culture, and early may be significantly sooner than what has been customary. Schweickert and colleagues studied beginning therapy an average of 1.5 days after intubation.[170] The group of patients who were mobilized early were more likely to be functionally independent when they left the hospital (59% versus 35%, $P = 0.02$), and more patients were able to go directly home (43% versus 24%, $P = 0.06$). Patients in the intervention group had shorter duration of delirium (median 2.0 days versus 4.0 days, $P = 0.02$) and more ventilator-free days (23.5 days versus 21.1 days, $P = 0.05$) during the 28-day follow-up period than did study control participants.

Early mobilization in the ICU requires a multidisciplinary team approach.[171] Targets for culture change include gaining support from institutional leaders and bedside clinicians.[172] Careful communication between physicians, nurses, and therapists is paramount. More research is necessary to identify whether specific groups of patients will benefit from early mobilization more than others, the appropriate amount of mobilization, and the absolute and relative contraindications. The potential for early mobilization to affect mortality seems promising.

HOSPITAL-ACQUIRED INFECTIONS

The most common nosocomial infections in medical ICUs are urinary tract infections (31%), followed by pneumonia (27%) and primary bloodstream infections (19%).[173] Several studies have shown that quality improvement initiatives can reduce nosocomial infections, mortality, and cost.[174,175] The Centers for Medicaid and Medicare Services, which administers federally sponsored health care, no longer reimburses hospitals for additional costs associated with common ICU complications, including urinary and CVC-associated infections. This pay-for-performance measure, in addition to the widespread adoption of public reporting of infection rates, will catalyze significant scrutiny of these infections.

Ventilator-Associated Pneumonia

VAP is defined as pneumonia developing in patients who are mechanically ventilated after more than 48 hours of intubation, with no clinical evidence suggesting the presence or probable development of pneumonia at the time of initial intubation.[176] VAP is a leading cause of morbidity and mortality in patients who are mechanically ventilated and critically ill. The incidence of VAP is estimated to be 10% to 25%,[177] and the estimated mortality rate from VAP is 5% to 27%.[178] The pathogenetic progression of VAP probably involves microaspiration of oropharyngeal or gastric secretions contaminated with bacteria. Risk factors include previous exposure to antibiotic therapy and the presence of invasive devices.[179]

The diagnosis of VAP is challenging. Frequently, a presumptive diagnosis of pneumonia is made when fever, leukocytosis, purulent secretions, and a new infiltrate on chest radiography develop and when bacteria are isolated by nonquantitative analysis of endotracheal aspirates. These nonspecific diagnostic criteria may lead to unnecessary antibiotic use, increased hospital cost, emergence of resistant microorganisms, and a potential delay in diagnosis of the true cause of the fever. These problems led several investigators to propose an invasive management strategy for the diagnosis of VAP.

Fagon and colleagues[180] used fiberoptic bronchoscopy to obtain protected specimen brush samples or bronchoalveolar lavage samples for quantitative culture. Patients were considered to have VAP if at least 10^3 colony-forming units (CFU)/mL of bacteria grew from the protected specimen brush sample or at least 10^4 CFU/mL of bacteria grew from the bronchoalveolar lavage fluid. The patients in the invasive management group had reduced mortality at day 14 (16.2% versus 25.8%, $P = .022$) and an increased number of antibiotic-free days (5.0 ± 5.1 versus 2.2 ± 3.5 days, $P < 0.001$). This study makes a compelling argument for a more definitive diagnosis of VAP before initiating antibiotic therapy. Along the same idea but with a less invasive approach, Bregeon and associates[181] showed that nonbronchoscopically guided placement of protected brush catheters is just as sensitive as directed bronchoscopy in detecting bacteria in the lungs.

Prevention of Ventilator-Associated Pneumonia

As in all nosocomial infections, prevention is the most efficacious approach. Excessive use of gastric pH–altering medications for stress ulcer prophylaxis increases gastric pH and the risk for VAP.[182] The use of sucralfate, an agent that does not increase gastric pH, may be preferable to H_2-receptor antagonists or proton pump inhibitors. Positioning of the head of the bed at 30 degrees

is the most cost-effective intervention to prevent VAP. With this intervention, Drakulovic and coworkers found a decreased rate of VAP with no adverse effects.[183] This position results in decreased gastroesophageal reflux and is easily implemented and monitored.

Pooling of secretions above the endotracheal tube cuff may increase the volume of bacteria that enter the airways. Removal of these secretions by continuous aspiration in the subglottic region requires the use of a specialized endotracheal tube with a second lumen that permits a suction catheter to exit proximal to the endotracheal tube cuff. A meta-analysis identified 13 randomized controlled trials that met the inclusion criteria. Of the 13 trials, 12 reported reduced VAP rates in the group that had subglottic secretion drainage. The overall RR for VAP was 0.55 (95% CI 0.46 to 0.66, $P < 0.00001$). The use of subglottic secretion drainage was associated with reduced ICU LOS (–1.52 days; 95% CI –2.94 to –0.11, $P = 0.03$); decreased duration of mechanical ventilation (–1.08 days; 95% CI –2.04 to –0.12, $P = 0.03$), and increased time to first episode of VAP (2.66 days; 95% CI 1.06 to 4.26, $P = 0.001$). There were no beneficial effects on adverse events or on hospital or ICU mortality.[184] In the patients anticipated to have a prolonged course of intubation with mechanical ventilation, the use of endotracheal tubes with subglottic secretion drainage appears effective for the prevention of VAP. The reduction of the number of oral microorganisms in the secretions with oral care and 2% chlorhexidine also appears to be beneficial for VAP prevention in a recent meta-analysis (RR 0.72; 95% CI 0.55 to 0.94, $P = 0.02$).[185]

CATHETER-RELATED BLOODSTREAM INFECTIONS

Central line–associated bloodstream infections are one of the leading causes of health care–associated infections. Fortunately, the rate of catheter-related bloodstream infections (CRBSI) in the United States has decreased from 43,000 in 2001 down to 18,000 in 2009.[186] This reduction represents a 58% decrease during this 9-year period. Along with a reduction in morbidity and mortality, this decrease also resulted in substantial cost savings, since each CRBSI is estimated to increase health care costs by $16,550. The recognition that many CRBSIs are preventable with the use of bundled clinical practice techniques is growing. In fact, the Centers for Medicaid and Medicare Services no longer reimburses hospitals for excess costs associated with CRBSI,[187] and many states now require public reporting of hospital-specific CRBSI rates.[188]

PREVENTION OF CENTRAL VENOUS CATHETER INFECTIONS

Many recent studies have shown that the prevention of CRBSIs is achievable through large-scale quality improvement projects that involve a bundle of evidence-based interventions.[189,190] The Health Care Infection Control Practices Advisory Committee recently released updated multidisciplinary guidelines for the prevention of intravascular catheter-related infections.[191] Recommendations include the use of ultrasound guidance for line placement,[192] skin preparation with chlorhexidine and alcohol,[193] chlorhexidine sponge for site dressing,[194] antimicrobial-impregnated CVCs,[195] and 2% chlorhexidine wash for daily skin cleansing,[196] along with maximal sterile barrier. The new guidelines also emphasize that only trained personnel should be assigned these tasks and that periodic assessment of these individuals should occur.

The need for a CVC should be reassessed daily, and unnecessary catheters should be removed because the probability of catheter-related infections increases with time. The risk of infection with catheterization stays relatively low until about the fifth to seventh days and then increases exponentially.[197] Several trials have studied scheduled replacement of catheters over a guide wire or in a new site, but none of these strategies were able to show an improved outcome.[198] Optimal catheter insertion technique and maintenance can minimize infectious risks, but the most efficacious maneuver is to remove the CVC as soon as it is no longer required. The need for central venous access should be reassessed again before discharging the patient from the ICU because the discharge procedure is often an opportune time to remove any indwelling lines, including bladder catheters.

Catheter-Associated Urinary Tract Infection

Hospital-acquired urinary tract infections (HAUTIs) make up 40% of HAIs with an estimated cost of $1200 to over $2700 per episode.[199] Approximately 80% of HAUTIs are catheter-associated urinary tract infections (CAUTIs).[200] In ICUs, where placement of Foley catheters is common, the incidence rate ranges from 3.1 to 7.4 CAUTIs per 1000 urinary catheter days.[201]

Results from a survey of 441 hospitals suggest that little attention had been focused on CAUTI prevention in ICUs in the United States.[202] To address this gap, multiple public policy incentives and private sector quality initiatives have been introduced to help reduce the rate of CAUTIs and its resultant morbidity, mortality, and cost. For instance, hospitals are held accountable by nonpayment for CAUTIs from the Centers for Medicare and Medicaid Services.[202] In 2011, The Joint Commission included the implementation of evidence-based practices to prevent CAUTIs as one of its 2012 National Patient Safety Goals.[203] This year, the Centers for Medicare and Medicaid enacted public reporting of CAUTI rates through its Hospital Inpatient Quality Reporting Program beginning in 2014.[204]

Prevention of Catheter-Associated Urinary Tract Infections

Unfortunately, no single CAUTI prevention strategy is widely used. Saint and colleagues found that only 30% of hospitals reported regularly using portable bladder ultrasound, 14% reported using condom catheters in men, and 9% reported using catheter reminders or stop orders.[205] Processes that have been introduced include a checklist of acceptable rationale for placement and a checklist to guide the orders for removal and management.[206] The elements of performance listed by the Joint Commission include the following:

1. Inserting indwelling urinary catheters according to established evidence-based guidelines that address limiting use and duration to appropriate situations and using aseptic techniques for placement

2. Managing catheters so that urine flow is unobstructed and the collection system remains sterile, and replacing the system when required
3. Measuring CAUTI prevention processes by monitoring compliance with guidelines or best practices, and evaluating the effectiveness of prevention efforts.

Further research is needed to elucidate the relationship between adherence to CAUTI prevention recommendations and CAUTI incidence rates.

HAND WASHING

Hand hygiene compliance is considered to be the single most effective factor to reduce HAIs. However, despite its importance, the rate of hand hygiene adherence among health care providers remains suboptimal.[207] Numerous hand hygiene products have been evaluated to enhance the rate of hand hygiene compliance among health care workers, including plain soap, alcohol-based antiseptics, chlorhexidine, hexachlorophene, iodine and iodophors, parachlorometaxylenol, quaternary ammonium compounds, and triclosan.[208] Although randomized controlled trial evidence is lacking, some studies suggest that the use of alcohol-based hand rub, along with a comprehensive hand hygiene campaign, can lead to reduced infection rates with methicillin-resistant *Staphylococcus aureus*.[209]

In a study examining the survey response from infection control coordinators, 86% of 95 Veterans' Administration (VA) hospitals and 85% of 416 non-VA hospitals reported the adoption of the use of an alcohol hand rub. Use of an alcohol-based hand rub was found to be more likely in hospitals where leadership support and a commitment to adopting and implementing evidence-based recommendations were present.[210] The use of alcohol-based hand rubs is easy to implement and appears to pose little risk to users. Hand hygiene compliance is an inexpensive and easy goal to achieve with a large potential of associated benefits.

COMMUNICATION AND HANDOFFS

With the limitations in resident work hours and the need for many ICUs to have physician staff available 24 hours a day and 7 days a week, *handoffs* between shifts of providers become more important for patient care. Handoffs are known to be vulnerable to communication failures, which could result in reduced patient safety and increased medical errors.[211] In 2006, The Joint Commission created a new National Patient Safety Goal on handoffs, requiring organizations to implement a standardized approach to hand off communications. The research data on this topic are relatively sparse; therefore, the Society of Hospital Medicine convened a taskforce whose goal was to develop a set of recommendations for handoffs. The taskforce reviewed the literature and identified the following recommendations: (1) have a formal recognized handoff plan; (2) dedicate time during the shift for handoffs, using a template or technology solution for recording patient information; (3) set handoff expectations among the group, giving a verbal face-to-face exchange; (4) give priority to high-acuity patients, focusing on a what-to-anticipate or a what-to-do list; and (5) highlight action items.[212] Randomized controlled trials are needed in both teaching and nonteaching settings to evaluate these recommendations further and other approaches to improving handoffs.

CONCLUSION

Critical care medicine is a growing specialty as the population ages and new procedures and technologies are brought into practice. Anesthesiologists represent a small proportion of intensivists in the United States but constitute the majority in Europe and other parts of the world. Critical care training represents a significant opportunity for anesthesia practitioners. The authors of this chapter have reviewed the management of a number of commonly encountered clinical conditions in the ICU, and the reader is referred to Section 8, Critical Care Medicine, Chapters 101 through 108 of this text for additional information related to critical care practice. The ICU is a nexus, not only for promising therapies but for complications of treatment as well. To avoid patient harm, all practitioners must be aware of best practices, from the simplest interventions such as hand hygiene to the latest technologic advances.

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Chapter 102

Critical Care Protocols and Decision Support

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Key Points

- Protocols allow for standardization of clinical care and widespread adoption of evidence-based practices.
- Protocol implementation requires a multidisciplinary team for comprehensive planning and oversight. Frequent assessment is often necessary (particularly in the early phases) to ensure compliance and to monitor outcomes.
- Protocols should be devised with the intention of not only improving the quality of patient care but also improving patient outcome and the efficiency of care, while at the same time, decreasing practice variation and costs.
- Specific metrics should be followed after protocol implementation to measure the efficacy of the intervention and to help determine whether adjustments are necessary.
- Quality measures that were found to be valuable (based on effect, feasibility, and strength of evidence) included: (1) percentage of patients with ventilator-associated complications,[1] (2) percentage of patients with resistant infections, (3) percentage of patients with central venous catheter infections, (4) number of complications per patient, (5) average days of mechanical ventilation, (6) rate of gastrointestinal bleeding, (7) average intensive care unit length of stay, and (8) patient satisfaction.
- Computerized decision support algorithms are becoming increasingly sophisticated and more widely used. Understanding the limitations of a particular tool is essential to maintaining appropriate oversight and avoiding error.

The 2000 projection by the Committee on Manpower for Pulmonary and Critical Care Societies (COMPACCS) of an ongoing demand for critical care services in the United States appears to have been very accurate.[2,3] Because the future supply of appropriately trained physicians will unlikely match this growing demand, intensivists will face a larger, sicker population with fewer resources.[4,5] Although few would argue that an intensivist-led unit benefits from decreased morbidity and mortality, the impending staffing shortage and population growth will necessitate care paradigms that maximize efficiency, reduce practice variation, and standardize patient care.[6-9] Increasingly, intensive care units (ICUs) have adopted and implemented pathways and clinical protocols to achieve this goal. Designing such protocols, however, is not trivial. Protocols must be devised with the intention of not only improving the quality of patient care but also improving patient outcome and maximizing efficiency of care, while at the same time decreasing practice variation and costs. Lohr and colleagues defined *quality* as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[10] It is essential for the well-being of our patients that health care providers use this definition as a guiding principle whether creating new or implementing known protocols. Furthermore, it is critical that clinicians not view protocol-driven care as a constraint on clinical judgment. On the contrary, protocols require greater consideration of individual subtleties among patients, and the attentive and experienced clinician understands the appropriate time and circumstance to deviate from a protocol. The goal then becomes a process: a process of learning, a process of observation, and a process of educated response. Without this goal, critical care becomes "cookbook medicine," and protocols become recipes for disaster.

In this chapter we discuss the rationale for care protocols in the context of achieving five goals: (1) enhancing quality of care, (2) improving efficiency, (3) decreasing cost, (4) decreasing errors, and (5) enabling rigorous clinical research. The focus is on more technical aspects of protocol design, including team development, evaluation of best evidence and/or consensus, preservation of

flexibility, and continuous quality improvement (CQI). Factors necessary to implement protocols are also discussed. This process begins with identifying priorities and setting goals and culminates with the ability to revise protocols continuously as new evidence builds. To illustrate these important concepts, three protocols used by many ICUs are reviewed. In the last section, the future of medicine extensively based on protocols is discussed, including the role of computer-driven decision models with closed-loop feedback and handheld computers. Additionally, areas of critical care medicine that likely will become based on protocols are described. However, protocol development and implementation, for all its intricacies and details, need the help, understanding, and sense of ownership of a large multidisciplinary team to be successful. Finally, examples of how groups have successfully integrated protocols into complex and sophisticated computerized decision support tools are described.

RATIONALE FOR PROTOCOL DEVELOPMENT

Critical care protocols or clinical practice guidelines (CPGs) evolved from the need to reduce practice variability while improving the quality of care and patient outcome by using the best available evidence. A 1994 editorial in the *British Medical Journal* predicted: "'Evidence based medicine' is a phrase that is currently familiar to only a few doctors, but all will know it by the millennium."[11] Although this forecast was accurate, the magnitude of patient care paradigm shift was not expected. Rather than treating patients based on empiric evidence or anecdote, today's intensivists must consider a plethora of objective data from which they must determine what will work best for their particular patient or population. The quality of this objective data and the robustness of statistical analysis continue to improve. Although many current protocols are based on data from multiple randomized controlled trials (RCTs), more than half of the clinical guidelines published before the year 2000 were based on no RCT evidence.[12]

Large numbers of interventions in critical care clearly improve morbidity and mortality while at the same time decreasing costs.[13-18] Despite this, a disparity continues to exist between best evidence and best practice.[19,20] As new evidence accrues, how should new data be analyzed and implemented? Using a uniform approach for each piece of evidence has advantages and disadvantages (Table 102-1).[21] Protocol or guideline development should explicitly state what, if any, objective grading system was used to categorize and classify the data.

The fundamentals of CPG development include (1) improving patient outcome, (2) establishing standards of care (either institutionally or within a specialty), and (3) changing practice patterns.[22] Although these points provide a rationale for CPGs, the primary goal of any new protocol is to enhance the quality of care. What is the definition of quality? The Institute of Medicine's definition is "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[10,23] The term *continuous quality improvement* (CQI) originated in the business realm and was coined by W. Edward Deming. Deming was a trained statistician but is best known for the positive impact he had on production in the United States during World War II. He taught management executives how to improve design and product quality through objective evaluation, testing, and reevaluation. CQI contrasts with the traditional, reactive, root-cause analysis, which focuses on recognizing a problem and then identifying a "seminal event" (or events) causally related to this event. In CQI, all facets of the critical care setting are evaluated and considered potential targets for improvement initiatives.[24,25] Once an initiative is identified, a system is devised to measure the efficacy or outcome of a particular intervention.[26] This change is then continuously reevaluated and modified by an internal evaluation system.[27] Depending on the goals of a particular critical care unit, interventions can be targeted appropriately.

Selecting a particular goal for quality improvement should be done very carefully. An inappropriate goal could lead to incorrect conclusions and thus unsuitable interventions. One example may be a goal of "decreasing the rate of readmission to the ICU." Although patients who are readmitted to the ICU have significantly increased mortality and length of stay, readmissions may represent a quality issue in the post-ICU setting or may represent an epiphenomenon associated with severity of illness.[24,28-31] Quality goals should extend beyond morbidity and mortality. A "change in process" goal may be equally important, such as use of aspirin or β-adrenergic blockers in patients with acute coronary syndrome. Similarly, "perceptions of care" goals (e.g., patient satisfaction, pain relief, nausea) require the same process of reevaluation as any other outcome.[32] Interventions and quality measures that, based on the literature, improved patient outcome have been defined.[14] Quality measures that are

TABLE 102-1 ADVANTAGES AND DISADVANTAGES OF USING THE SAME SYSTEM FOR GRADING EVIDENCE TO IMPLEMENT ICU PROTOCOLS

Advantages	Disadvantages
Having different systems for evaluation of various interventions may be confusing	Interventions that cannot be studied with randomized trials may not be evaluated or may lead to a false-negative conclusion
Individuals with vested interests have less chance to bias results by selecting a particular grading scheme	A single system that can adequately grade evidence across a broad range of interventions may be overly complex
Limitations of the evidence become more apparent when comparing two disparate conclusions with a similar grading scheme	
Better research can be generated as a result of identifying gaps in evidence	

Adapted from Schunemann HJ, Fretheim A, Oxman AD: Improving the use of research evidence in guideline development: 9. Grading evidence and recommendations, Health Res Policy Syst *4:21, 2006.*

valuable (based on effect, feasibility, and strength of evidence) included the following:

1. Percentage of patients with ventilator-associated complications
2. Percentage of patients with resistant infections
3. Percentage of patients with central venous catheter infections
4. Number of complications per patient
5. Average days of mechanical ventilation
6. Rate of gastrointestinal bleeding
7. Average ICU length of stay
8. Patient satisfaction

Once a protocol has met the standard of "quality," it then needs to be analyzed for efficiency and cost. *Efficiency* refers not only to the ease of implementation but also to its overall financial impact and timing of the intervention. Additionally, efficient protocols reduce management variability and, likely, errors and save lives.[6,33] Although protocol development is founded on evidence-based practice, at a local level it is a trial-and-error process. Systems theory provides us with many of the crucial aspects inherent in protocol design and necessary to maximize practicality.[34,35] Testing a new process and then evaluating the impact on the overall system were first described by Walter Shewhart, founding theorist of the field of statistical process control. Shewhart described a form of learning through action termed the Plan-Do-Study-Act (PSA) cycle.[36] One of the best examples of using the PSA cycle to implement a change in practice comes from work done by the Northern New England Cardiovascular Disease Study Group in 1996.[37] By continuously reevaluating variations in practice and morbidity and mortality from large databases, members of the group were able to develop protocols for such practices as anesthesia, hemostasis, and cardiopulmonary bypass pump management, thus achieving a 24% reduction in mortality from coronary artery bypass graft surgery within the region.

Paradoxically, protocol development and implementation negatively affect other expensive therapies, resulting in overall inefficiencies. An example is ICU protocols that were designed to optimize sedation and analgesia efficacy. Although the initial goals of anxiolysis and pain relief were attained, adverse effects include prolonged mechanical ventilation, increased risk of nosocomial pneumonia, and hemodynamic instability.[38,39] The final aspect of protocol efficiency is the timing of intervention. Ill-timed implementation of evidence-based practices is ineffective and possibly harmful. An example includes protocols designed to treat severe sepsis aggressively in the emergency department.[40] The execution of these practices late in the disease process (even by 1 day) actually increases mortality.[41] Thus, a protocol designed to treat a disease without identifying and addressing at-risk populations and diagnosis is wasteful and potentially unsafe.

Finally, protocols facilitate rigorous clinical research. Without standards, definitions, defined pathways, and explicit interventions, the interpretation of research findings, whether prospective randomized or observational, will enhance clinical equipoise. Protocols define a standard that attempts to control for confounding variables. As protocols are tested and replicated, new research is being generated. A wealth of RCTs demonstrates improved outcomes with protocol implementation.[42-46] For meaningful advances in critical care, protocols must continually embrace new findings, and intensivists must be willing to adhere to guidelines. However, the applicability of a particular guideline or protocol is based on the population studied and needs careful analysis when considered for a different population.

PROTOCOL DESIGN

Protocol design usually requires a multidisciplinary team.[46,47] However, the process mandates identification of the affected variables, grading the data, a method for continual reevaluation, and inherent flexibility (Box 102-1). Affected variables are factors that will be affected indirectly (positively or negatively) by the proposed protocol. An example is a sedation-anxiolysis protocol that does not take into account the duration of mechanical ventilation, the incidence of nosocomial pneumonia, nausea, vomiting, and other variables. Affected variables are byproducts of a purposeful change in practice. The variables can be universal, as in the previous example, or institutional. A ventilator weaning protocol may look appropriate on paper but may be unrealistic, depending on the local staffing paradigm of respiratory therapists at a particular institution. Similarly, an ICU glycemic control protocol may work at one institution but not be as effective in another or may even be deleterious.[48,49]

Evaluating and grading the literature must be based on the variables measured in a study. Moreover, "best evidence" must consider the patient population to be relevant to protocol design. Inclusion and exclusion criteria must be understood, as well as the prevalence and

BOX 102-1 *Process for Developing Guidelines*

Establishing the Process

Prioritize problems
Select a panel
Declare conflicts of interest
Agree on processes

Preparatory Steps

Perform a systematic review of the problem
Define outcomes of interest
Prepare evidence for outcomes

Grading Quality of Evidence and Strength of Recommendations

Define the quality of evidence for each outcome
Define the relative importance of outcomes
Judge the *overall* quality across all pieces of evidence
Balance benefit and harm
Balance net benefits and costs
Determine the strength of the recommendation

Subsequent Steps

Implementation and evaluation

From GRADE Working Group: Grading quality of evidence and strength of recommendations, BMJ *328:1490, 2004.*

incidence of disease in a particular study. Only after critically analyzing studies in this fashion can practitioners begin to grade the quality of evidence. Quality of evidence traditionally refers to four components: study design, study quality, consistency, and directness.[50]

Study design refers to the basic format and aim of an investigation. Case-control studies, cohort studies, and RCTs are all examples of study designs. The aim of case-control and cohort studies is to establish an association between some potential risk factor (e.g., hyperglycemia) and morbidity (e.g., infection) or mortality. Whereas cohort studies can be either retrospective or prospective, case-control studies are, by definition, retrospective. RCTs are prospective and aim to identify causality rather than association. For various reasons, RCTs are considered the most decisive tests and are frequently deemed definitive.[51] However, RCTs are often not feasible and, particularly with regard to rare diseases or outcomes, may not be as applicable as observational studies. Many investigators have, in fact, challenged the traditional hierarchic study design paradigm that places RCTs at the top and expert opinion and anecdote at the bottom.[52,53] Regardless, study design must be evaluated and graded based on the merit it holds for a specific population and a particular outcome.

Study quality is altogether different from the "quality" referred to earlier. Study quality refers to the methodology and study implementation. Adequacy of blinding, method of randomization, selection of placebo, statistical analysis, and reduction of bias are all examples of factors to be scrutinized when evaluating study quality. The revised CONSORT statement provides a useful template with which study quality indicators can be measured (Table 102-2).[54] The ability to discern adequacy of quality is neither precise nor consistent among reviewers.[55] This fact has culminated in a collaborative effort to address

TABLE 102-2 **ITEMS TO CONSIDER IN EVALUATING STUDY QUALITY**

Section or Topic	Descriptor
Title and abstract	How participants were allocated to interventions
Introduction and background	Scientific background and explanation of rationale
Methods	
Participants	Eligibility criteria for participants and the settings and locations where the data were collected
Interventions	Precise details of the interventions intended for each group and how and when they were actually administered
Objectives	Specific objectives and hypotheses
Outcomes	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements
Sample size	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules
Randomization	
Sequence generation	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification)
Allocation concealment	Method used to implement the random allocation sequence clarifying whether the sequence was concealed until interventions were assigned
Implementation	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups
Blinding (masking)	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment; if done, how the success of blinding was evaluated
Statistical methods	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses
Results	
Participant flow	Flow of participants through each stage; specifically, for each group reporting the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome
Recruitment	Dates defining the periods of recruitment and follow-up
Baseline data	Baseline demographic and clinical characteristics of each group
Numbers analyzed	Number of participants in each group included in each analysis and whether the analysis was by "intention-to-treat"
Outcomes and estimation	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (e.g., 95% confidence interval)
Ancillary analyses	Addressing of multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.
Adverse events	All important adverse events or side effects in each intervention group
Comment	
Interpretation	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes
Generalizability	Generalizability (external validity) of the study findings
Overall evidence	General interpretation of the results in the context of current evidence

From Moher D, Schulz KF, Altman D: The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials, JAMA *285:1987-1991, 2001.*

these shortcomings and develop a process whereby intraobserver and interobserver variability in evaluation and grading of study quality is reduced.[56] Furthermore, study quality does not necessarily equate with superiority of study design. RCTs, for example, are not necessarily of highest quality and can have significant inherent bias.[57,58] Bias is difficult to eliminate completely, but it must be sufficiently reduced for a study to be of high quality. Jadad and colleagues defined study quality as "the likelihood of the trial design to generate unbiased results."[59] However, as Verhagen and associates indicate, although the reduction of bias enhances the internal validity of a study, study quality must take into account a study's external validity.[60] That is, consideration of the applicability and consequence of a study's result to the population as a whole must be deemed a variable when measuring quality. External validity can be ascertained by examining the consistency and directness of an investigation.

Consistency refers to the reproducibility of results among different investigators. Consistency in the magnitude of effect, the direction of effect, and the statistical and clinical significance of a particular effect must be considered. Major inconsistencies among similar populations decrease the quality of evidence and generalizability for a particular outcome and should be considered when grading evidence for protocol implementation. *Heterogeneity* is a statistical term used to measure consistency among studies and is frequently used in meta-analyses. Traditionally, *Cochran's Q* statistic has been calculated by summing the squared deviations of each study's estimate from the overall meta-analytic estimate.[61] However, because this test is poor at detecting significant heterogeneity when the number of studies is small, Higgins and colleagues devised a more widely applicable test statistic, I^2, that describes the *percentage* of total variation across studies that is the result of heterogeneity rather than chance alone.[62,63] Values of I^2 range from 0% (no observed heterogeneity) to 100%. Consideration of this value must be taken into account when designing evidence-based protocols (see also Chapter 111).

Finally, the *directness* of a study more specifically addresses the generalizability and applicability aspect of external validity. Does the reduction of mortality seen in a single-center translate into reduced mortality for all surgical ICU patients, or do the results merely represent the consequences of improved patient care at a single institution? The same can be said of high-volume hemofiltration studies and the incidence of sepsis. It has been said that, "most patients to whom we would like to generalize the results of randomized trials would, for one reason or another, not have been enrolled in the most relevant study."[64] Despite this sentiment, *the data are what the data are*, and it is imperative that methods be used such as evaluation of directness to make decisions.[65] Evaluation of patient population, diagnostic criteria, and surrogate outcomes all must be scrutinized before application of principles or implementation of protocols based on such evidence.[66]

Protocol design must, in some fashion, address each of the foregoing areas and rank them based on importance of outcome, severity of illness, risks and benefits of implementation, and cost. Although difficult, the literature must be graded. A review of more than 100 of these systems found no single best scheme; rather, application of the *process* of evidence assessment was what was most important.[67]

PROTOCOL IMPLEMENTATION

Designing a critical care protocol and *implementing* a change in practice are very different. Design is based on data review, judgment of applicability, and ranking the strength of evidence, as reviewed previously. Implementation, however, necessitates communication and collaboration among various members of the ICU team. Some of the more important concepts to be addressed before implementing a new protocol include education, definition of targets and goals, data collection, analysis of variance, and measurement of impact.

Thoughtful selection of a multidisciplinary task force to evaluate strategies for critical care protocol development and implementation is very important. Most often, such groups include both physician and nursing leadership, as well as selected ancillary professionals (depending on the protocol), such as respiratory therapists, nutritionists, pharmacists, or physical therapists. Particular to the surgical ICU, physician leadership should involve members from both the critical care and primary surgical team.

Passive educational approaches such as didactics and dissemination of protocols have generally been ineffective implementation strategies.[68-70] Changes in physicians' behavior require outreach, dialogue, and discussion. Protocols that are integrated within a computerized algorithm, such that warnings, reminders, and suggestions are generated when appropriate, have been shown to be useful.[69] Education must address key points such as the evidence supporting a change in practice, the advantage of a new practice paradigm, and the compatibility of a novel protocol to the existing practice.

Targets and goals are usually related, although they are defined differently. *Targets* are frequently measured as continuous data points and often set a limit, outside which patients are not considered to be "within protocol." *Goals* define a realistic outcome presumably obtainable if targets are met. Examples of *targets* are maintaining glucose levels at 150 mg/dL or lower, elevating the head of the bed 30 degrees or more, administering antibiotics within 3 hours of presentation, and maintaining inspiratory plateau pressures at less than 30 cm H_2O for mechanically ventilated patients (see also Chapter 103). Examples of *goals* are decreasing the sternal wound infection rate, decreasing ventilator-associated pneumonia, decreasing progression of sepsis to septic shock, and decreasing ventilator-associated lung injury. Targets and goals must be defined at the outset so that analysis of protocol compliance and effect can be objectively measured.

INTENSIVE CARE UNIT PROTOCOLS

The focus of this section is on three protocols currently used in critical care units. The purpose is not to define a

particular care algorithm but rather to illustrate the process that various groups have gone through to devise best care practices. Each topic presented demonstrates a different facet of protocol development and implementation.

GLYCEMIC CONTROL

Since the publication of the landmark "Leuven" study, literally hundreds of protocols implementing tight glycemic control (TGC) have been published (see Chapter 39).[15] Furthermore, this single study changed the standard of care in surgical ICUs, and TGC was quickly adopted by various professional societies.[71,72] How best to achieve euglycemia has been the real debate, and groups must identify, within their own infrastructure, a protocol that will work for them. An illustrative example of rational protocol design can be seen with the Stamford Hospital experience (Fig. 102-1).[73] Although the actual protocol devised by this group may be different from others, the process of design and the steps taken should serve as a model for those wishing to do similar work. The problem (i.e., "hyperglycemia is associated

ICU Protocol for Glycemic Management

Approved by the ICU Committee 2/01/03
Last modified by the ICU Multidisciplinary Committee 9/26/03

Rationale

Hyperglycemia is strongly associated with increased hospital mortality as well as organ system dysfunction among critically ill patients.

Goal

The goal of this protocol is to maintain serum glucose <140 mg/dL

Monitoring

Glucose levels will be evaluated *by blood testing or fingerstick testing,* using the following schedules.

Diet	Frequency of monitoring
NPO	Q8 hours: 6AM, noon, 6PM, midnight
PO diet	1 hour AC and QHS
Tube feedings, TPN	Q6 hours: 6AM, noon, 6PM, midnight

For most patients, the 6AM glucose evaluation will be obtained from the morning BMP. If glucose <140 for two consecutive days without treatment, glucose levels can be checked Q12 hours (6AM, 8PM).

Treatment of Hyperglycemia

Glucose value	Action (subcutaneous insulin dose)
<140	No treatment
140–169	3 units Regular insulin, Recheck glucose value in 3 hours
170–199	4 units Regular insulin, Recheck glucose value in 3 hours
200–249	6 units Regular insulin, Recheck glucose value in 3 hours
250–299	8 units Regular insulin, Recheck glucose value in 3 hours
300+	10 units Regular insulin, Recheck glucose value in 3 hours

*If glucose value exceeds 200 on two successive measurements, a continuous insulin infusion will be initiated. Hourly FSG or blood glucose measurements will be obtained in all patients receiving insulin infusions. The sliding scale noted above is a guideline: it can be modified if the patient requires more or less intensive therapy.

Management of Insulin Infusion

1. Initial infusion rate

Glucose value	Insulin dose
200–249	4 units/hour
250–299	6 units/hour
300–399	8 units/hour
400+	10 units/hour

Important points

*All patients receiving continuous insulin must receive a continuous source of glucose either via IV (D5W or TPN), or enteral feeds.

*The insulin infusion is discontinued if the patient has to leave the ICU for a diagnostic test as well as upon discharge from the ICU.

2. Subsequent management, based on hourly glucose checks

Glucose value	Insulin dose
<140	Stop infusion or continue low dose to avoid "rebound"
140–169	2 units/hour
170–199	3 units/hour
200–249	6 units/hour
350–399	8 units/hour
400+	10 units/hour

If this treatment plan does not lead to a decrease in the patient's glucose values, contact the house officer.

Figure 102-1. Example of rational protocol design. *AC,* Before meals; *BMP,* basic metabolic panel; *D5W,* dextrose 5% in water; *FSG,* fasting serum glucose; *ICU,* intensive care unit; *NPO,* nothing by mouth; *PO,* oral; *qhs,* at bedtime; *TPN,* total parenteral nutrition. *(From Krinsley JS: Effect of an intensive glucose management protocol on the mortality of critically ill adult patients,* Mayo Clin Proc *79:992-1000, 2004.)*

with increased hospital mortality") was stated at the outset. A review of the pertinent literature was undertaken, and the problem was confirmed. A system was put in place to accurately quantify the problem at their institution, measure pertinent variables, and evaluate outcome. A multidisciplinary team undertook the task of devising a protocol to rectify the problem. Finally, successful implementation of the protocol was established, and statistical analysis was performed to validate the impact of the protocol.

TRANSFUSION

As many as one third of patients admitted to an ICU in the United States will receive a blood transfusion (see also Chapter 61).[74,75] Although the etiology of anemia in critical care patients is certainly multifactorial and not always obvious, the implications of treatment are becoming evident.[76-78] The risk of transfusion-related infections has markedly decreased but remains. Unfortunately, many noninfectious complications are associated with allogeneic transfusions, including acute lung injury and immunomodulation.[79-81] So what should the transfusion trigger be?

The best evidence regarding the efficacy of red blood cell transfusion in critically ill patients comes from the Canadian Critical Care Trials Group.[42] Patients who were managed with a restrictive transfusion strategy (maintenance of hemoglobin at 7.0 to 9.0 g/dL, with a transfusion trigger of 7.0 g/dL) had equivalent outcomes (with a trend toward improved outcome) compared with patients managed with a liberal transfusion strategy (maintenance of hemoglobin at 10 to 12 g/dL, with a transfusion trigger of 10 g/dL). Since that time, two large, multicenter studies have evaluated the practice of transfusion. The ABC (Anemia and Blood transfusion in Critically ill patients) trial explored the risks and benefits of transfusions in a large European population.[82] The authors were able to show a positive correlation between receipt of any blood transfusion and 28-day mortality (22.7% versus 17.1%, $P = 0.02$). Furthermore, the mortality risk increased in a dose-related fashion with increased transfusions. A second study, the CRIT trial, performed a similar analysis in the United States.[75] Again, transfusion was independently associated with mortality, and increased blood cell transfusion was associated with increased mortality.

Implementation of a transfusion protocol, however, requires an understanding of the literature. As reviewed earlier, implementation necessitates an understanding of infrastructure, organization of a multidisciplinary team, a systematic grading of the literature, and a means to measure effect and variability in practice. A comprehensive blood conservation strategy needs to be understood and developed. The net effect of protocol implementation may be inconsequential if confounding variables are not addressed. Such variables affecting the risk of transfusion include, but are not limited to, the following: contribution of phlebotomy,[77,83] inadequate salvage techniques,[84,85] and inattentiveness to proper pharmacologic hemostatic agents[86] (see also Chapters 61 to 63). One of the most cohesive and logical plans to address this topic has been published and should be used as a model for proper protocol implementation.[87]

VENTILATOR WEANING

Few process-based interventions in the ICU have been more rigorously studied than weaning from mechanical ventilation (see Chapters 101 and 103). Indeed, protocols in this area have been tested and validated, culminating in evidence-based guidelines.[88-93] Given the plethora of data, including three large RCTs that have demonstrated reduction in duration of mechanical ventilation, intensivists should have a protocol in place to address this issue.[45,94,95] The reason ventilator weaning protocols are highlighted here, however, is that they illustrate a critical point to understand when designing protocols: regardless of the design and the involvement of personnel, an ICU protocol will ultimately fail if confounding factors are not addressed and included within the protocol. With regard to mechanical ventilation in the ICU, two confounding factors are sedation and analgesia. Without some interface between the timing of ventilator weaning and the interruption of sedation, the compliance and success of the protocol are in jeopardy.[44,96]

THE FUTURE OF MEDICINE BASED ON PROTOCOLS

A frequent barrier to implementation of established protocols is practitioner compliance. Anecdotal experience is often the enemy of evidence-based practice. The decision-making process is increasingly relegated to appropriately designed computers and handheld devices.[91,97-100] More important, however, will be physicians' understanding of current technology and of recent literature, an appreciation of the limitations of these resources, and the ability to review these elements and outcomes cohesively and continuously in a pragmatic manner aimed at developing best practice guidelines.[101] Several groups have already initiated such reviews in areas such as traumatic brain injury,[102] nutritional support,[103] glycemic control,[104] and sedation and analgesia.[105] Has intensive care medicine become too complex to rely on a physician's ability to sort through and interpret the thousands of pieces of information that must be addressed each day?

Although protocols inevitably decrease the variability in practice, they do not address the multifaceted approach to ICU care. Some investigators have advocated systematic development of checklists to remind team members of the multitude of goals for every patient, rather than increased protocol generation. An example is the FAST HUG mnemonic developed by Vincent[106]:

F: Feeding
A: Analgesia
S: Sedation
T: Thromboprophylaxis
H: Head of bed elevation
U: Ulcer prophylaxis
G: Glycemic control

Each component of the mnemonic should be addressed with each patient, every day. Whereas protocols may

pertain and be applicable to any of the systems, the checklist helps prevent intensivists from oversight.

COMPUTERIZED CLINICAL DECISION SUPPORT

Although the concept of clinical decision support (CDS) has been around for decades, practical application of such algorithms using established protocols have only more recently been implemented.[107,108] Any robust system for clinical support must rely on frequent data input from multiple sources. When processed appropriately, these data can be used to assess previous responses to therapy or intervention and adjust the care being delivered. This ability to detect, respond, detect a change, and respond proportionally is the key to a successful closed-loop system.[109-111] Thus, computerized protocols must be adaptive and be able to integrate new data while the system (patient) is changing. With proper oversight, such algorithms have the potential to be more efficacious than a protocol-driven clinician.[112] Further research is needed to better assess the breadth of applicability for such applied science, but advances in technology are certain to make this a tool that will be used more frequently.

CONCLUSION

Protocol development and implementation comprise a complex and labor-intensive process. A multidisciplinary team is required and a specific educational plan is necessary to implement all facets of a protocol properly. Although evidence-based medicine is at the heart of the process and a detailed analysis of the literature is required, clinical acumen and anecdotes need not be ignored. Protocols are designed for the masses, and they require a thoughtful and educated intensivist to identify those patients for whom particular protocols may not be applicable. Protocols also allow for standardization of research protocols and minimization of confounding variables. The ability to measure the effect of a particular protocol and adapt appropriately is the key to successful protocol application. The future of critical care will certainly see an increase in the number of protocols based on quality evidence. These protocols will likely interface with various computers and handheld devices to help ensure compliance and more easily interpret the flood of information obtained on a daily basis. Intensivists will need to learn which patients are appropriate for such interventions and, with the help of checklists, ensure comprehensive patient care.

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Chapter 103

Respiratory Care

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Key Points

- Intermittent positive-pressure mechanical ventilation is the gold standard for assisting patients with acute respiratory failure. Positive end-expiratory pressure (PEEP) is the positive pressure applied at the end of expiration during positive-pressure mechanical ventilation. A constant level of positive pressure applied to a spontaneous breathing cycle is termed continuous positive airway pressure (CPAP).
- Modes of mechanical ventilation can be classified as totally or partially ventilator controlled.
- Although positive-pressure mechanical ventilation is usually applied through an endotracheal tube or a tracheotomy, it also may be delivered noninvasively to the patient's mouth, nose, or through helmets.
- External gas exchangers to totally or partially bypass the lung (extracorporeal support) can be used for the most severe forms of respiratory failure that are refractory to conventional mechanical ventilation).
- Acute respiratory distress syndrome (ARDS) is an inflammatory response of the lung with acute onset and presence of bilateral infiltrates on chest radiography. ARDS is characterized by a reduction in functional residual capacity and static compliance. The correct setting of mechanical ventilation in ARDS is of paramount importance to minimize ventilator-induced lung injury.

The target of ventilation is to generate flow and volume to provide adequate alveolar ventilation with the minimal work of breathing (WOB). Contraction of the respiratory muscles provides the "power" required for ventilation. The phrenic nerve regulates the timing and intensity of this power, integrating inputs from chemoreceptors, pulmonary stretching receptors, and variations in metabolic demands. During spontaneous breathing the respiratory muscles generate a pressure (3) that produces flow against the resistive and volume against the elastic properties of the respiratory system. Under these circumstances, at any instant, the act of spontaneous breathing can be described as follows:

$$\text{Pmus} = \text{Pres} + \text{Pel} \quad (1)$$

where *Pres* represents the resistive pressure and is a function of flow and respiratory system resistances (Pres = flow × resistance) and *Pel* represents the elastic recoil pressure and is a function of volume and elastance of respiratory system (Pel = volume × elastance). Assuming that resistance and elastance are linear, Equation 1 becomes:

$$\text{Pmus} = (\text{flow} \times \text{resistance}) + (\text{volume} \times \text{elastance}) \quad (2)$$

Acute respiratory failure requiring ventilatory support occurs if a pathologic process or a pharmacologic intervention (1) impairs the capacity of the respiratory muscles to generate sufficient Pmus, (2) increases the ventilatory requirements above the muscle capacity, or (3) increases the workload associated with the act of breathing. Application of positive pressure (i.e., a pressure higher than the atmospheric pressure) to a patient's airway opening during the inspiratory phase is currently the main method to administer assisted breathing and restore adequate ventilation. The resulting pressure gradient between a patient's airway opening and alveoli generates a positive flow (i.e., directed from the ventilator to the patient). The expiratory phase, which is passive, depends on the end-inspiratory pressure gradient between alveolar pressure (which is positive because of the elastic recoil pressure stored during the inspiratory phase into the respiratory system) and airway opening pressure. Under these circumstances, the pressure applied at the airway opening of the patient (Pao) includes the pressure generated by the ventilator (Pappl) plus the pressure generated by the contraction of the respiratory muscles according to the following equation:

$$\text{Pmus} + \text{Pappl} = (\text{flow} \times \text{resistance}) + (\text{volume} \times \text{elastance}) \quad (3)$$

The capability of restoring gas exchange, unloading respiratory muscles, and relieving dyspnea depend on the

match between the ventilatory setting and the ventilatory demand—that is, on the patient-ventilator interactions.[1] Depending on the relative amount of Pmus and Pappl, modes of mechanical ventilation can be classified as totally or partially ventilator controlled.

- *Total ventilator-controlled ventilatory support:* A patient's own breathing pattern is totally replaced by the ventilator, and Pmus is abolished by sedation (and eventual paralysis of the respiratory muscles) or by a pathologic process; the ventilator is responsible for generating flow, volume, and pressure, or all of these.
- *Assisted-controlled ventilatory support:* The ventilator provides a fixed amount of support, in terms of assistance and inspiratory time, in response to a patient's inspiratory effort; the patient is allowed to trigger the ventilator (assist-control mode).
- *Assisted ventilatory support:* The patient controls respiratory rate and receives positive pressure assistance to spontaneous breathing effort. Ideally the patient should maintain full control of the inspiratory time and expiratory time. The amount of Pappl assisting the spontaneous breathing effort may be fixed or proportional to the spontaneous inspiratory effort (i.e., to Pmus).

SETTINGS OF MECHANICAL VENTILATION

Positive-pressure breaths from the ventilator can be categorized by three variables: (1) the trigger variable (what initiates the breath), (2) the limit variable (the algorithm that governs positive pressure delivery), and (3) the cycle variable (what terminates the inspiratory phase). These variables can be set on the ventilator and serve as its interface with the three main physiologic variables of the breathing pattern: (1) the ventilatory drive (when inspiration begins; (2) the ventilatory requirements (how much flow and volume are necessary to satisfy the metabolic demands), and (3) the duration and ratio of inspiratory time to total breath cycle duration.[2] The variables that regulate the triggering of ventilation are time (during controlled mechanical ventilation) or flow and pressure, with the ventilator sensing the patient's inspiratory effort (trigger function, during assisted mechanical ventilation modes). Ventilator gas delivery can be regulated to deliver a fixed (during controlled modes) or variable (during assisted modes) amount of flow, volume, or pressure. The ventilator can cycle from inspiration to expiration based on a preset time, on flow or pressure, or on electrical diaphragmatic activity threshold level.

TOTAL VENTILATOR-CONTROLLED VENTILATORY SUPPORT (CONTROLLED MECHANICAL VENTILATION)

The main characteristic of controlled mechanical ventilation is that the variable used by the ventilator (and set by the health care provider) to trigger and to cycle off the breath is time. The limit variable that governs gas delivery may be flow (flow-limited controlled mechanical ventilation [CMV]) or pressure (pressure-limited controlled ventilation [PCV]) (Fig. 103-1). With the former, the ventilator applies either a constant (square) or nonconstant (in the majority of cases decelerating) flow to deliver a preset tidal volume (V_T). Flow is the independent variable (i.e., the ventilator maintains the predetermined flow pattern regardless of patient impedance) and the airway opening pressure (Pao) profile during inflation depends on the mechanical characteristics of the patient's respiratory system. With the latter, the ventilator applies a preset positive-pressure level (commonly, square) to the patient's airway opening. Pao is therefore the independent variable that is held constant by the ventilator by instantaneously replacing the volume delivered to the patient. V_T depends on the inspiratory time and on the mechanical characteristics of the respiratory system. The inspiratory flow starts with a peak followed by the exponential flow decay and becomes nil as soon as applied pressure equals alveolar pressure.

The choice between volume-cycled and pressure-cycled modes is not supported by definitive evidence. Volume-cycled modes are preferred when it is crucial to maintain minute ventilation. This is because V_T during PCV is a dependent variable affected by the interplay between the level of applied pressure, the inspiratory time, and the respiratory system impedance (mainly inspiratory system elastance and resistance). On the other hand, physiologic considerations support the use of pressure-limited modes to realize a more homogeneous distribution of V_T within lung parenchyma.[3] Pathologic conditions often increase lung parenchyma inhomogeneity so that lung regions with different elastance and resistance (i.e., with different time constants: τ = elastance × resistance) may coexist. From a

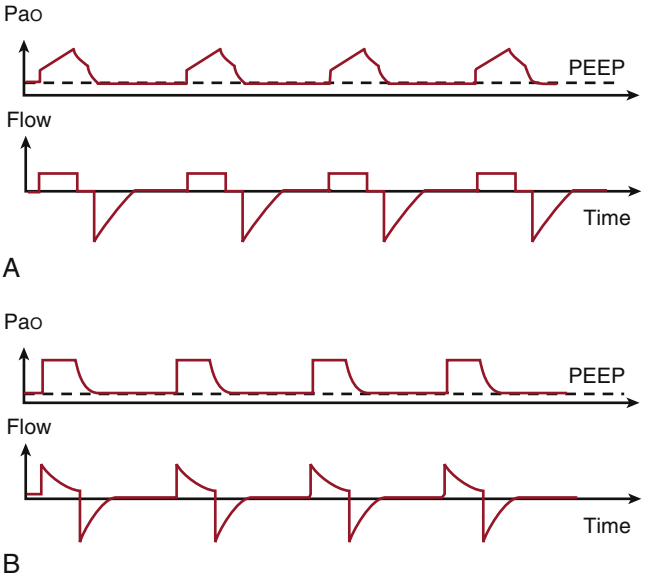


Figure 103-1. Tracings of flow and airway opening pressure (*Pao*) during the two basic controlled intermittent positive pressure ventilation modes. **A,** Volume-cycled. **B,** Pressure-cycled. *PEEP,* Positive end-expiratory pressure.

theoretical point of view, the flow-limited controlled mode could induce hyperinflation of regions with lower elastance resistance and, at the same time, underinflation of regions with higher elastance and/or resistance. Based on these theoretical assumptions, the pressure-limited mode should be the preferred ventilator mode in patients with inhomogeneous lungs, because this mode allows a more homogeneous V_T distribution between regions with different elastance resistance.

A controlled mode able to share the theoretical advantages of constant pressure with the guarantee of delivering a preset V_T has been recently introduced in clinical practice (pressure-regulated volume control, volume plus). It consists of a closed-loop algorithm that, based on the automatic measurement of static compliance of the respiratory system, continuously adapts the level of applied pressure on a breath-by-breath basis to match a target V_T.

ASSISTED MECHANICAL VENTILATION

Assisted ventilatory techniques are intended to unload the respiratory muscles and relieve dyspnea in patients with impaired neuroventilatory coupling. The degree of freedom gained by the patient depends on the regulating algorithm and includes respiratory rate, breathing pattern (inspiratory time, expiratory time, duration, and ratio of inspiratory time to total breath cycle duration), and level of assistance. The capability of restoring gas exchange, unloading respiratory muscles, and relieving dyspnea with these modes of partial ventilatory support critically depends on the matching between the ventilator settings and the patient's ventilatory demands.[1,2,4]

The rationale for preserving diaphragmatic activity in critically ill patients is to reduce sedation and paralysis, minimize cardiovascular side effects of mechanical ventilation,[5] and, most importantly, decrease the disuse diaphragm atrophy that arises very quickly with controlled modes. Indeed, Levine and associates[6] showed that inactivity associated with controlled mechanical ventilation results in marked atrophy of diaphragm myofibers within 18 to 69 hours, likely as a result of inactivity-induced diaphragmatic proteolysis. Furthermore, compared with controlled modes, partial ventilatory support modes have the potential to improve ventilation-perfusion mismatch by reaerating dependent lung areas, as a result of aeration of dependent lung regions that occurs with contraction of the diaphragm.

A potentially severe problem with assisted modes is patient-ventilatory asynchrony, mainly documented by ineffectual inspiration, double triggering, and a discrepancy between neural and mechanical inspiratory time. The Brochard group developed an asynchrony score to evaluate assisted mechanical ventilation modes and showed that higher scores were associated with weaning delays and higher tracheostomy rates in critically ill patients.[7]

Assist/Control Mechanical Ventilation

The patient is allowed to set the respiratory rate by activating the inspiratory trigger function (as a safety measure, if no spontaneous effort occurs, the ventilator will deliver controlled breaths at a preselected backup rate). The variable used by the ventilator to cycle off the breath is time. The limit variable that governs gas delivery is flow and volume (assisted/controlled mechanical ventilation [A/CMV]) or pressure (assisted pressure-controlled ventilation [A/PCV]).

To activate a pressure trigger, the patient decreases pressure in the respiratory circuit at a preset threshold level, in contrast to the flow-trigger system, in which the patient generates a preset amount of inspiratory flow. Patient-ventilator synchrony during A/CMV depends on the quality of the trigger mechanism (pressure versus flow triggers) and on the kind of controlled breath delivered (volume-cycled versus pressure-cycled); combining flow trigger and A/PCV improves patient-ventilator interactions because of the higher inspiratory peak flow compared with the volume-cycled mode.[8]

Can A/CMV meet patient inspiratory demand? Marini and co-workers[9] demonstrated that during patient-triggered breaths, effort does not cease with the onset of gas delivery and that total inspiratory workload may even exceed the work performed during spontaneous breathing, particularly in the assist/controlled constant-flow mode.[9] Indeed, once the patient triggers the ventilator, a rapid increase in inspiratory flow occurs similar to that during spontaneous breathing. The patient then struggles with the constant flow applied by the ventilator. In contrast, with the pressure-limited algorithm, the ventilator increases volume delivery in response to the patient effort and therefore the patient obtains a peak inspiratory flow nearer to his or her physiologic needs.[10]

In conclusion, with assist/control (A/C) the neuroventilatory coupling is not restored. The amount of work performed by the ventilator actually decreases at expense of patient effort. In contrast, to restore normal neuroventilatory coupling, higher inspiratory efforts should ideally be supported by a higher assistance level and vice versa.[11] This ventilatory mode is in general poorly tolerated in awake patients. In patients with dynamic hyperinflation (see later discussion) and increased respiratory drive (resulting from fever, hypermetabolic states, and sepsis), ongoing air trapping and respiratory alkalosis during A/CMV may occur.

Synchronized Intermittent Mandatory Ventilation

Synchronized intermittent mandatory ventilation (SIMV) allows the patient to breathe spontaneously between intermittent mandatory controlled breaths. Controlled breaths are delivered in a synchronous manner, in the sense that based on the set mandatory respiratory rate the ventilator software establishes a time window in which each mandatory breath can be triggered by the patient's spontaneous effort. If the patient does not exert effort in this time window, the ventilator independently delivers the mandatory breath. Depending on the SIMV modality, controlled breaths may be volume-cycled or pressure-cycled. Spontaneous breathing is usually supported by a variable degree of pressure support (see later discussion). Varying the rate of mandatory breaths allows near total ventilatory support or

fully spontaneous breathing. Regarding patient-ventilator interactions during mandatory breaths, SIMV shares the same limitations as A/CMV.

Pressure Support Ventilation

Pressure-support ventilation (PSV) is the most popular partial ventilatory-assist mode for weaning patients from controlled ventilatory modes and to provide ventilation in patients with acute respiratory failure, provided their respiratory drive is preserved.[12] During PSV, the patient's spontaneous effort triggers the ventilator and is subsequently assisted by a constant positive pressure (Pappl, see Equation 3) applied at the airway opening, either invasively or noninvasively. V_T depends on the interplay between Pmus, Pappl, and respiratory system impedance (mainly, elastance and resistance) (see Equations 2 and 3). PSV is intended to unload the respiratory muscles and improve the relation between the patient's effort and V_T. For a given inspiratory effort, the patient generates a larger volume than during spontaneous breathing. PSV relieves dyspnea in several clinical conditions. However, with PSV the assistance delivered by the ventilator is not related to the patient's inspiratory effort and consequently neuroventilatory coupling is only partially restored.[11]

Cycling from the inspiratory to the expiratory phase in PSV occurs when inspiratory flow rate decreases to a preset level. The decay of inspiratory flow is clearly a surrogate signal to infer a patient's neural inspiratory time—as soon as the spontaneous inspiratory effort ceases, the flow rate will decay to less than the expiratory trigger threshold.[13] Depending on the ventilator software, the "expiratory trigger" sensitivity may be at a fixed minimal flow rate or at a fixed percentage of peak inspiratory flow. In several intensive care unit (ICU) ventilators, the percentage of the peak inspiratory flow that triggers expiration (expiratory trigger sensitivity) can be adjusted from 5% to 90%. Unfortunately, a delay between the end of neural inspiratory effort and the end of ventilator assistance usually exists and may cause a severe disturbance of patient-ventilator interactions resulting in patient-ventilator asynchronies.[7] This is particularly true if the patient has weak inspiratory effort, the applied pressure is relatively high in contrast to the patient's effort, or both; under these circumstances, the ventilator will prolong its assistance well beyond the duration of spontaneous inspiration, generating a severe discrepancy between neural and mechanical inspiratory time.[14] One intervention is matching neural and mechanical inspiratory time to minimize asynchronies and trying to adjust the expiratory trigger sensitivity. In addition, several ventilators allow adjusting the time for pressure increase at the beginning of inflation (inspiratory pressure slope), thus affecting the peak inspiratory flow value.[15] Unfortunately, a quantitative estimation of the inspiratory effort is not available in the PSV mode. Adjustment of expiratory trigger sensitivity is largely empirical in clinical practice. Studies show that when a patient's inspiratory effort is nil the respiratory rate is slower than 20 breaths/minute and V_T is greater than 8 mL/kg.[16] A common clinical approach is to regulate ventilatory support to maintain the respiratory rate between 20 and 35 breaths/minute and V_T between 5 and 8 mL/kg[17]; then inspiratory pressure slope and expiratory trigger sensitivity can be adjusted to minimize patient-ventilator asynchronies.[7]

Proportional Assisted Ventilation

During proportional assisted ventilation (PAV), the ventilator amplifies patient effort in generating pressure in proportion to the patient's generated flow and volume. What is preset is not a target pressure but rather the proportion between the patient's inspiratory muscle effort and the ventilator-applied pressure.[11,18]

To realize proportional assistance, the ventilator measures spontaneous patient instantaneous flow and volume by its internal sensors and the clinician measures and then sets the values for elastance and resistance. Knowing all these variables, the ventilator processor then estimates instantaneous Pmus (see Equation 2) and assists patient effort in a proportional fashion (according to a factor of proportionality set by the operator).

In this PAV version, a reliable estimation of elastance and resistance (see Equation 2) is needed. If the estimate is correct, the pressure generated by the ventilator will be lower than the pressure required to offset the passive properties of the respiratory system. Both underestimation and overestimation of elastance and resistance could critically impair patient-ventilator interactions. If elastance and resistance are underestimated, the level of assistance provided by PAV will be insufficient to relieve patient dyspnea. In contrast, if elastance and resistance are overestimated, a positive feedback develops and the ventilator continues to deliver flow and volume while the patient stops inspiratory effort (the "run-away" phenomenon).

To overcome the clinical problem of estimating respiratory system elastance and resistance in a spontaneously breathing patient, the recently proposed PAV plus (PAV+) algorithm allows an automatic and noninvasive measure of elastance and resistance through the ventilator's internal sensors to continuously adapt the proportional assistance accordingly. The noninvasive assessment of respiratory system mechanics is based on the application of brief (100 to 300 msec) occlusions on airway opening at end inspiration during PAV.[19,20]

The most evident difference between PAV and PSV is a more variable V_T over time.[21] A sudden hypercapnic stimulus during PAV triggers a compensatory increase in minute ventilation mostly obtained by an increase in V_T, with no change in respiratory rate. On the contrary, patients ventilated with PSV react by increasing respiratory rate but are unable to significantly increase V_T. In contrast to PSV, PAV better mimics the physiologic response to hypercapnia.[8] PAV significantly unloads the inspiratory muscles and improves the breathing pattern in patients with chronic obstructive pulmonary disease (COPD).[22]

Neurally Adjusted Ventilatory Assist

The neutrally adjusted ventilatory assist (NAVA) algorithm is based on the measurement of electrical diaphragm activity by means of an electrode array inserted

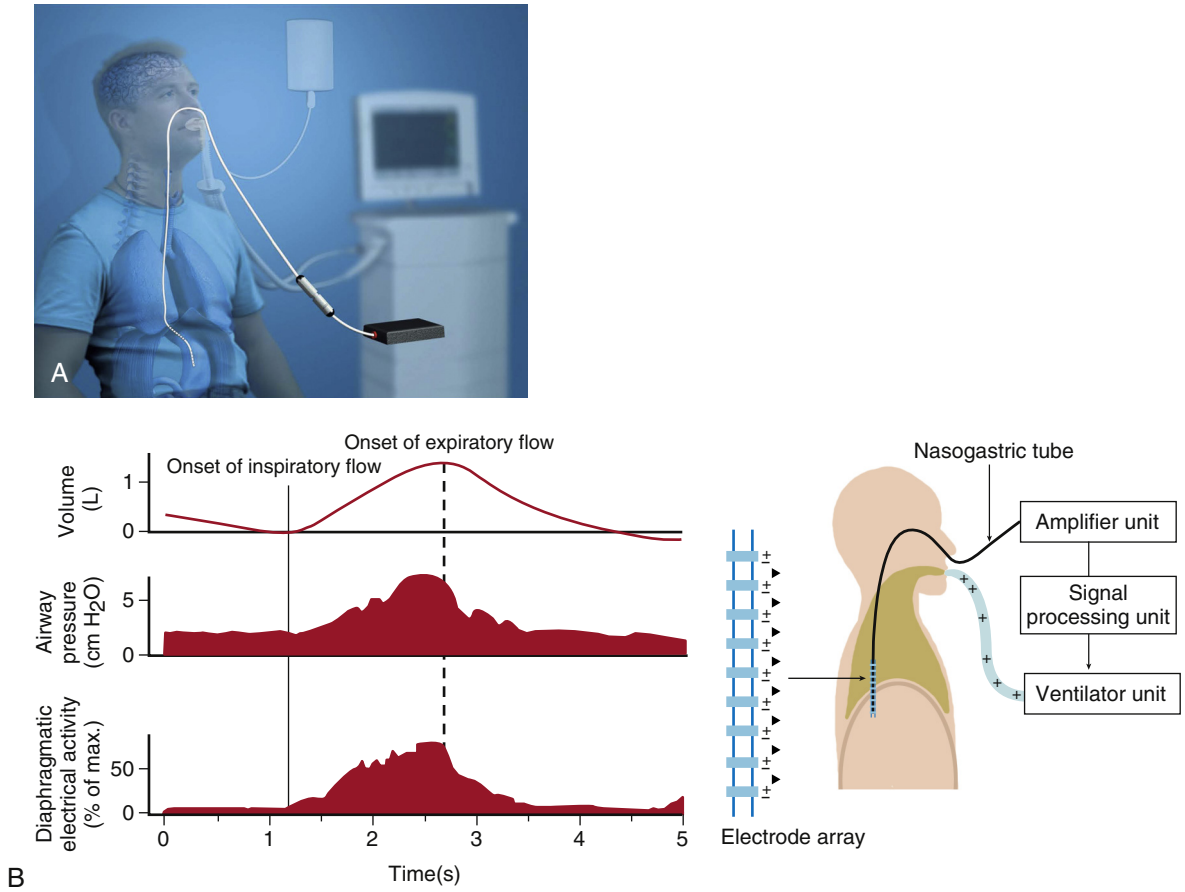


Figure 103-2. Neurally adjusted ventilatory assist (NAVA) concept. An electrode array, inserted into a nasogastric tube and placed in the lower esophagus, is able to sense the diaphragmatic activity. This signal is used to trigger the ventilator (neural trigger function) and assist the patient's inspiratory effort in proportion to the diaphragmatic electrical activity.

into a nasogastric tube and placed in the lower esophagus. This signal is used both to trigger the ventilator (neural trigger) and to deliver assistance in proportion to the instantaneous diaphragmatic electrical activity. With NAVA, the respiratory drive controls the assisted positive breaths in all phases of the ventilation cycle from triggering to cycling between the inspiratory and the expiratory phase (Fig. 103-2) and any change in ventilatory output is matched on a breath-by-breath basis. The potential physiologic advantages of NAVA to correctly restore the neuroventilatory coupling are well established.[23,24] Nevertheless, similar to PAV, adequately designed clinical trials showing a significant impact on meaningful clinical outcomes (faster weaning, tracheostomy rate, patient ICU survival) are not yet available.

During NAVA, the electrical signal of diaphragmatic activity drives the ventilator. How should the amount of pressure be set to be delivered for each microvolt (μV) of diaphragmatic activity? Several methods have been proposed: (1) recording the diaphragmatic activity during PSV and setting NAVA on a virtual basis to obtain the same peak pressure read during ongoing PSV (NAVA preview system), (2) progressively increasing NAVA assistance to identify a plateau in peak pressure and V_T,[25] (3) setting the NAVA level to maintain a respiratory rate between 20 and 35 breaths/minute and V_T between 5 and 8 mL/kg (clinical method, in analogy with PSV). More clinical studies to clarify this crucial issue are required.

Recording the diaphragm electrical activity signal offers the unique opportunity of studying patient-ventilator interactions in the different ventilatory modes. Diaphragm neuroventilatory efficiency (NVE) can be clinically measured as the ratio between spontaneously generated V_T and peak diaphragm electrical activity level, whereas diaphragm neuromuscular efficiency (NME) can be measured by the ratio between the negative Pao deflections during a brief airway opening occlusion period (10 to 20 seconds) and the corresponding peak diaphragm electrical activity level. The NVE and NME measured just before an attempt to wean correlates with the chance for successful weaning.[26]

POSITIVE END-EXPIRATORY PRESSURE AND CONTINUOUS POSITIVE AIRWAY PRESSURE

Positive end-expiratory pressure (PEEP) is the positive pressure applied at the end of expiration during mechanical ventilation. A constant level of positive pressure applied to a spontaneous breathing cycle is termed continuous positive airway pressure (CPAP). Physiologic consequences of PEEP and CPAP depend on its effects on gas exchange, pulmonary compliance, and systemic hemodynamics.

Effects on Gas Exchange

PEEP/CPAP may improve arterial oxygenation by reexpanding functionally collapsed alveoli, redistributing lung water, and reducing ventilation-perfusion mismatch ($\dot{V}/\dot{Q}$), if the lung is recruitable and normal regions of the lung exist.

Alveolar recruitment, defined as the amount of noninflated tissue that is reexpanded by a given level of PEEP/CPAP, results in a more homogeneous distribution of the V_T and an increase in the functional residual capacity. Moreover, application of PEEP/CPAP leads to the redistribution of lung water from the alveolar space to the perivascular interstitial space and improves $\dot{V}/\dot{Q}$ by diverting blood flow from shunt regions to normal regions.

These effects strongly depend on whether PEEP/CPAP recruits previously collapsed alveoli.[27,28] If the applied PEEP/CPAP induces alveolar recruitment, a reduction in shunt with improvement in oxygenation and reduction in dead space is expected. However, if hyperinflation of normal alveoli is the predominant effect, an increase in $Paco_2$ resulting from an increase in dead space is expected, whereas the PaO_2 will change slightly, depending on whether the applied PEEP/CPAP induced variations in cardiac output, because varying cardiac output has per se an impact on intrapulmonary shunt.

Effects on Respiratory Mechanics

Compliance of the respiratory system (i.e., $V_T \div$ Plateau pressure – PEEP) represents a good estimate of the elastic properties of the respiratory system. Application of PEEP/CPAP may lead to the following effects on lung compliance:

- Increase in compliance, suggesting alveolar recruitment
- No change in compliance, indicating that ventilation is occurring on the linear portion of the volume-pressure relationship of the respiratory system
- Decrease in compliance, indicating lung overdistention

Effects on Hemodynamics

The application of PEEP/CPAP may affect hemodynamics through several mechanisms: decreased venous return to the right heart, increased right ventricular afterload, decreased ventricular compliance, and decreased ventricular contractility.[29-31] Overall, the hemodynamic consequences of PEEP/CPAP depend on the prior ventricular loading conditions, ventricular function, and the effect of PEEP/CPAP on lung mechanics.

In patients with normal cardiac function, the main consequence of increased intrathoracic pressure is the reduction of venous return and consequently of cardiac output. Because the right ventricular preload decreases, an adequate circulating blood volume is required before application of PEEP/CPAP to prevent depression of right ventricular output. In patients with poor left ventricular function or congestive heart failure, the increase in intrathoracic pressure reduces the left ventricular transmural pressure, leading to a reduction in left ventricular afterload and an improvement in left ventricular function. In these patients, cardiac output is relatively insensitive to reduction in venous return because diastolic volume is increased.[32]

NONINVASIVE VENTILATION

Mechanical ventilation is usually applied by an endotracheal tube or a tracheotomy. The efficacy of mechanical ventilation noninvasively applied to patient's mouth, nose, or both to restore respiratory function is well established. The side effects of invasive ventilation are then minimized. Noninvasive ventilation is delivered almost exclusively through partial ventilatory support techniques. Potential advantages of avoiding endotracheal intubation include less patient discomfort, reduced need for sedation, and a less frequent incidence of ventilator-associated pneumonia and sepsis[33] (see also Chapter 101). These advantages result in significant improvement in outcome variables.[34] However, the success of noninvasive ventilation critically depends on correct patient selection and expertise of the clinical team. If a trial of noninvasive ventilation is not successful, patients who then undergo endotracheal intubation will experience longer duration of invasive mechanical ventilation and longer ICU stay.[35]

Established indications for noninvasive ventilation are acute COPD exacerbation, acute cardiogenic pulmonary edema, postoperative respiratory failure, and respiratory failure in immunocompromised patients (solid organ transplant recipients and bone marrow transplanted) (see later discussion).[35]

In some clinical situations, noninvasive ventilation should be applied with caution. A less frequent endotracheal intubation rate and hospital length of stay occurred in patients with community-acquired pneumonia treated with noninvasive ventilation.[36] In experienced centers the application of noninvasive ventilation to patients with acute respiratory distress syndrome (ARDS) as a first-line intervention avoided endotracheal intubation in approximately 54% of cases,[37] whereas CPAP was not associated with better survival and length of hospital stay.[38] The use of noninvasive ventilation as a means to accelerate weaning from invasive ventilation has been the object of extensive, but not conclusive, clinical investigations. The use of noninvasive ventilation as a weaning technique in patients with COPD who are difficult to wean when the standard criteria for spontaneous breathing are not met may lengthen the duration of mechanical ventilation and increase mortality.[39,40] Noninvasive ventilation did not prevent reintubation of the trachea in patients developing acute respiratory failure after extubation.[41] Whether noninvasive ventilation should be used in patients with acute asthma, upper airway obstruction, and trauma is not clear (see also Chapters 38 and 81). Other possible fields of application are during fiberoptic bronchoscopy in hypoxemic or hypercapnic patients[42] and as a palliative therapy in patients who are not candidates for invasive ventilation.[43]

Two recent publications evaluated the efficacy on noninvasive ventilation in two large and distinguished hospitals (Massachusetts General Hospital, Boston, Mass., and Molinette Hospital, Turin, Italy).[44,45] Both studies indicated that noninvasive ventilation as part of routine standard medical care has limitations. A similar percentage of patients with respiratory failure resulting from

cardiogenic pulmonary edema and COPD exacerbation needed subsequent endotracheal intubation. Failure of noninvasive ventilation was associated with frequent hospital mortality for patients with hypoxemic respiratory failure.[44,45]

Predictors of success for noninvasive ventilation include younger age, lower acuity of illness (as quantified by the Acute Physiology and Chronic Health Evaluation II [APACHE II] or Simplified Acute Physiology Score II [SAPS II]), ability of the patient to cooperate, intact dentition, technical ability to minimize air leaks, moderate hypercapnia (i.e., between 45 and 90 mm Hg), and moderate (i.e., instead of severe) acidosis (i.e., between 7.35 and 7.10).[46] A successful trial of noninvasive ventilation should induce a trend toward increase, reduction in respiratory rate, and decrease in Pa_{CO_2} within 30 to 60 minutes.

The ideal interface for noninvasive ventilation should provide optimal patient comfort and minimal air leaks. Both masks (oronasal or nasal) and helmets are currently available. The oronasal mask induces air leaks in 80% to 100% of patients, facial skin reddening in 20% to 34%, mask intolerance in 8% to 32%, nasal and mouth dryness and nasal congestion in 10% to 20%, nasal bridge ulceration in 2% to 31%, eye irritation in 16%, gastric distention in 8%, and aspiration in 6%. These side effects may be minimized by using the helmet, but this interface may induce delay in ventilatory assistance with PSV and significant acoustic noise.[47]

Monitoring patients during noninvasive ventilation includes frequent checking of the interface to evaluate carbon dioxide rebreathing, accidental disconnection from the ventilator, air leaks, skin necrosis, and the ability of the patient to clear secretions. Monitoring of physiologic parameters (pulse oximetry, analysis of arterial blood gases, exhaled V_T, respiratory rate, use of accessory respiratory muscles, paradoxical abdominal motion, gastric distention, heart rate, arterial blood pressure) and of subjective variables (mental alertness, comfort, dyspnea) is of paramount importance for patient safety. Respiratory therapists spent more time with patients treated with noninvasive ventilation than with patients with endotracheal intubation in the first 8 hours, but this trend is reverted in the subsequent 8 hours.[48]

NONCONVENTIONAL VENTILATORY SUPPORT

Modalities of ventilatory support described earlier are defined as conventional; they are based on two principles: a V_T larger than the dead space volume and application of positive pressure at the airway opening. The following section describes modalities of ventilatory support that are defined as nonconventional because they are based on the application of a V_T lower than that of the dead space volume (high-frequency ventilatory oscillation [HFVO]).

High-Frequency Oscillatory Ventilation

The goal of conventional ventilation with PEEP is to keep the lung recruited while the cyclical increase in P_{AO} deliver V_T. At variance, the HFOV ventilator resembles a CPAP device in the sense that it basically applies a continuous mean airway pressure ($P_{AO,MEAN}$). Fresh gas (40 to 60 L/minute) continuously flows into the respiratory circuit, and the expiratory valve allows maintaining the preset $P_{AO,MEAN}$ level. The substantial difference with CPAP is that oscillatory pressure stroke at a very high frequency (i.e., between 180 and 900 beats/minute—i.e., from 5 to 15 Hz) are superimposed on the $P_{AO,MEAN}$. Technically, the high-frequency oscillating ventilators are based on an oscillating piston pump that generates pulse pressure "strokes" in the CPAP circuit (see Fig. 103-2, *A*). Each oscillation produces a sinusoidal cycle of pressure with increases and decreases more and less than $P_{AO,MEAN}$ (increase as the piston pump goes toward the patient, immediately followed by decrease as the piston pump draws away from the patient). An important issue is that HFOV provides both active inspiration (the positive stroke waves) and expiration (the negative stroke waves). The operator determines the overall oscillation amplitude—that is, the pressure amplitude (ΔP) that can be regulated up to 70 to 90 cm H_2O. Of note, the ΔP is read immediately near the piston, whereas the pressure transmission to the airway opening (because of the high oscillation rate and the very limited piston movement) is greatly attenuated and the ΔP in the endotracheal tube and alveoli is greatly attenuated (commonly 2 to 4 cm H_2O); accordingly, the resulting V_T is approximately 1 to 2 mL/kg—that is, lower than anatomic dead space. The observation that delivering pressure stroke waves at very high rates is a means of scavenging CO_2 from inside the lungs to the airway opening in intubated patients derived from a serendipitous observation—very fast oscillation applied at the airway opening to measure lung mechanics was able to scavenge CO_2. CO_2 removal, during HFOV is obtained through mechanisms including (1) direct ventilation of the alveoli located more proximally, (2) air movements occurring between nearby lung units with different time constants, (3) streaming of inspiratory and expiratory flow in diverging alveolar ducts, and (4) axial convection and lateral mixing.[49] Once scavenged from the lungs, CO_2 diffuses in the respiratory circuit and is eliminated by the bulk of fresh gas continuously flowing into the circuit. The main determinants of oxygenation during HFOV are $P_{AO,MEAN}$ and FiO_2. The main determinants of CO_2 elimination are the pressure amplitude (ΔP), the frequency of pressure oscillations, and (to a limited amount) the bias flow; CO_2 elimination can be enhanced by increasing ΔP or by decreasing oscillation frequency. Briefly, the higher the Δ pressure, the higher is the V_T; the higher the CO_2 clearance and the slower the oscillation rate, the higher are the V_T and higher CO_2 clearance.

In summary, HFVO offers the unique option of ventilating with very low V_T at relatively high mean airway pressure while maintaining acceptable CO_2 clearance. This constitutes an "extreme" lung protective approach because V_T is minimized and the lung can be kept recruited by adequately high distending pressures without the risk for hyperinflation that would ensue with conventional V_T delivery. Traditionally, HFVO

has been viewed as a rescue strategy to support patients with ARDS requiring very high positive pressure levels to maintain alveolar recruitment.[50] Thus, it has been applied in very sick patients in small studies with relatively increased mortality rates according to the studied population. Two recent multicenter randomized large clinical studies, the OlmeSartan and Calcium Antagonists Randomized (OSCAR)[51] and the Oscillation for Respiratory Distress Syndrome Treated Early (OSCILLATE)[52] trials, the first including 398 patients and the second 548 patients, tested the hypothesis that HFVO could reduce ARDS mortality when applied early in the course of ARDS as a lung-protective ventilatory strategy. Unfortunately, these trials did not document superiority of HFVO over the traditional approach to lung-protective strategy in ARDS (see later discussion). Based on these findings, at present HFVO cannot be recommended on a routine basis to treat patients with ARDS.

MONITORING CONTROLLED MECHANICAL VENTILATION

The analysis of the airway opening–time (Paot) signal obtained when applying volume-cycled constant-flow ventilation with a brief end-inspiratory pause, allows monitoring of the mechanical properties of the respiratory system. The Paot during constant flow includes the following information (Fig. 103-3):

- *Resistive pressure increase* (see *A-B segment* in Fig. 103-3) represents the step increase in Pao that occurs at the beginning of inspiratory flow delivery. It is not perfectly perpendicular to the time axis but shows a discrete slope because of the inability of the ventilator to generate a sudden increase in flow and to the inhomogeneities of different lung regions.
- *Elastic pressure increase* (see *B-C segment* in Fig. 103-3) represents the increase in Pao generated by the progressive

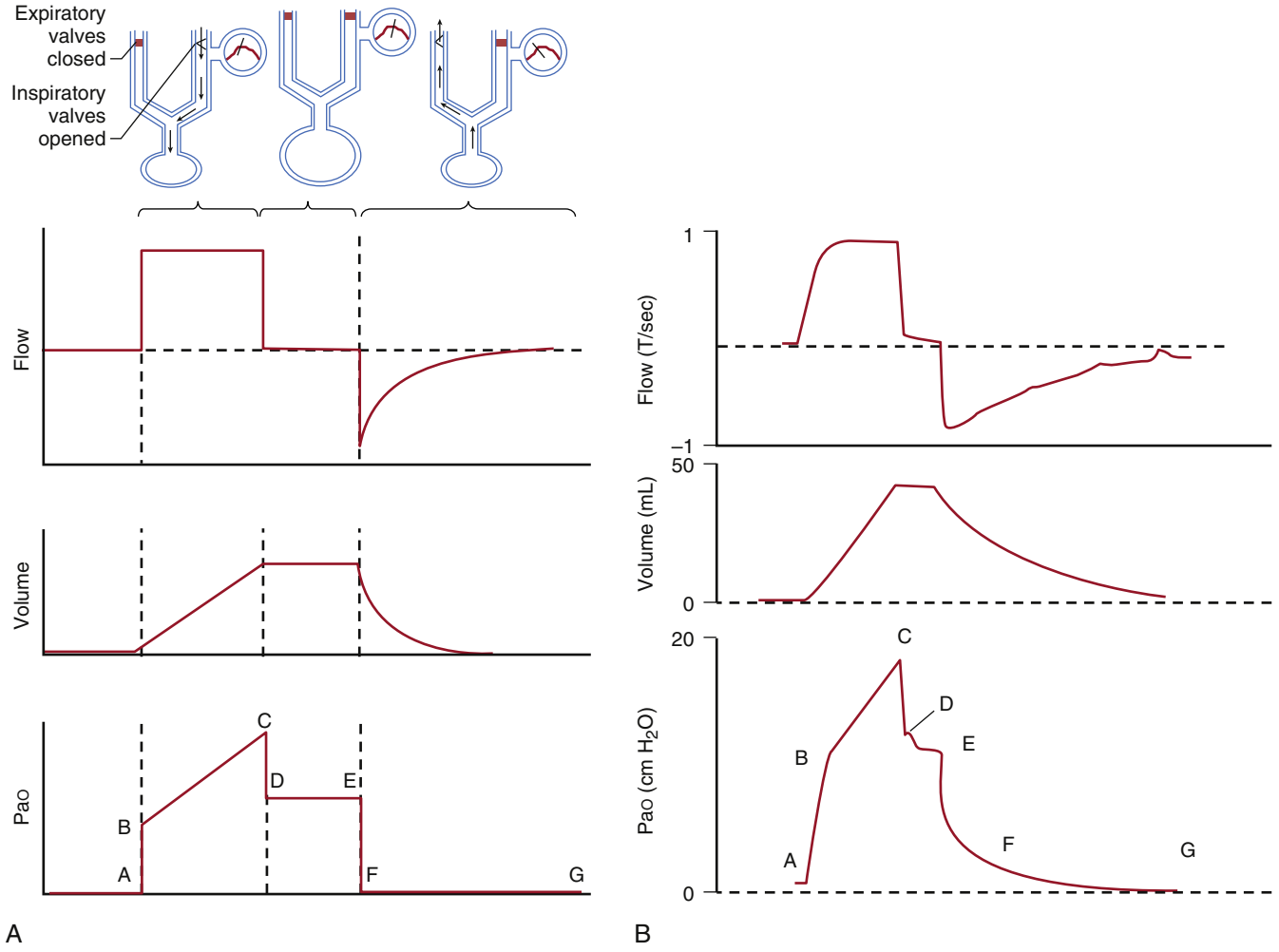


Figure 103-3. Flow, volume, and airway opening pressure (Pao) tracings recorded during controlled constant-flow mechanical ventilation. **A,** Theoretical traces related to the different phases of the ventilator duty cycle in a monocompartmental lung model. The model does not take into account the respiratory system viscoelastic and inertial properties and the inhomogeneity among different lung regions. **B,** Real traces. *A-B segment* (resistive pressure increase), *B-C* elastic pressure increase after the *C* point (Pao_{peak}), the Paot profile from Pao_{peak} to Pao_{plat} (*E*) can be divided into two regions: (1) an immediate pressure drop from Pao_{peak} to $Pao_{occlusion}$ (*D*) and, (2) a slower decay from $Pao_{occlusion}$ to Pao_{plat}, that take place in 2 to 5 seconds. The latter is principally due to alveolar gas redistribution between areas with different elastic and resistive characteristics (whose pressures at end-inspiration are not in equilibrium). Hence, the $Pao_{occlusion} - Pao_{plat}$ difference is proportional to the inhomogeneity between different lung regions.

inflation of the respiratory system, whose slope depends on the elastic properties of the respiratory system. It is not always linear, because its profile may be curvilinear when respiratory system compliance varies with lung inflation (see later discussion).

- Pao_{peak} (see *point C* in Fig. 103-3) is the peak in Pao reached at end inspiration. For a given flow rate and inspiratory time, Pao_{peak} expresses both the resistive and elastic pressure increase. After Pao_{peak}, the Paot profile during the end-inspiratory pause (when both the inspiratory and the expiratory valves are closed) can be divided into two regions: (1) an immediate decrease in pressure from Pao_{peak} to $Pao_{occlusion}$ (see *point D* in Fig. 103-3) as a result of the interruption of flow that makes the resistive pressure nil and (2) a slower decay from $Pao_{occlusion}$ to the end-inspiratory pressure (Pao_{plat}) (see *point E* in Fig. 103-3) that depends on a gas redistribution process between areas with different elastic and resistive characteristics and by the inertial properties of lung tissue. For a given V_T, Pao_{plat} expresses the elastic properties of the respiratory system. After the end-inspiratory pause, the expiratory valve is open while the inspiratory valve is closed and the respiratory system is allowed to passively exhale to the elastic equilibrium point of the respiratory system (see *E-F segment* in Fig. 103-3). If an end-expiratory valve is added to the expiratory limb of the ventilatory circuit, the *F-G segment* is equal to the value of the applied PEEP.

The rate of change of the airway pressure–time curve during constant flow inflation corresponds to the rate of change of respiratory system compliance during tidal inflation—a progressive increase in slope of the curve indicates that compliance is progressively increasing, whereas a progressive decrease in slope of the curve indicates that compliance is decreasing with tidal inflation; a linear increase of pressure indicates that compliance is constant throughout inflation.[53,54] Progressive increase and decrease in compliance during inflation are associated with tidal alveolar opening and collapse and tidal alveolar hyperinflation, respectively[55]—that is, with the main mechanisms responsible for mechanical ventilation–induced lung mechanical stress.[56] Hence, by analyzing the Paot profile during the period of constant-flow inflation (see *segment B-C* in Fig. 103-3) the occurrence of tidal alveolar recruitment and derecruitment and/or overinflation may be detected noninvasively (the stress index concept [Fig. 103-4]). Titrating the PEEP level according to the stress index analysis allows ventilator-induced lung mechanical stress in patients with ARDS to be minimized. Continuous monitoring of the stress index may be useful in establishing lung-protective ventilatory strategies.[57]

Respiratory resistance is the opposition to gas flow through the respiratory system and is quantified as the amount of pressure required to cause a unit rate of gas flow, according to the Ohm law:

$$\text{Resistance} = \text{driving pressure}/\text{flow rate}$$

where driving pressure is the resistive pressure applied to generate a given constant laminar flow in the airways. The total resistance of the respiratory system is the sum of pulmonary resistance (airway resistance plus lung tissue resistance) and chest wall resistance (essentially tissue resistances) and is expressed in centimeters of H_2O per

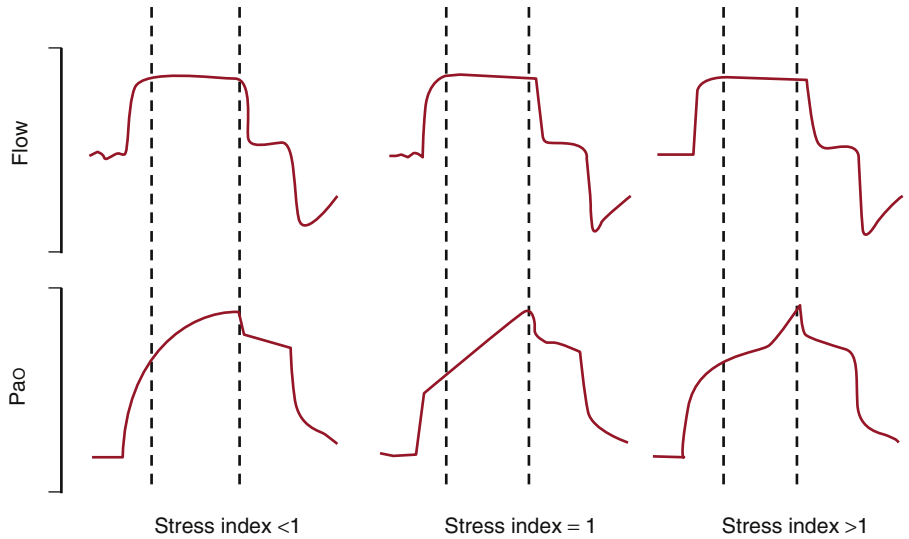


Figure 103-4. The stress index concept. Tidal alveolar recruitment, derecruitment, and overinflation may be detected through the analysis of the Paot profile during the period of constant flow inflation. A downward Paot concavity indicates progressive increase in compliance during tidal inflation, resulting from ongoing alveolar recruitment with inflation, whereas an upward Paot concavity indicates progressive decreases in compliance during tidal inflation as a result of ongoing alveolar overinflation with inflation. To measure the stress index, a power equation ($Pao = a \times t^b + c$) is fitted on the Paot profile. Here, the coefficients *a* and *c* are constants and the coefficient *b* is a dimensionless number that describes the shape of the Paot profile (stress index). For a coefficient $b < 1$ the Paot profile has a downward concavity (compliance increases with inflation), whereas for a coefficient $b > 1$ the Paot profile has an upward concavity (compliances decreases with inflation). Finally, when *b* is equal to 1, the Paot profile is straight and compliance remains constant during inflation.

liter per seconds. The total resistance of the respiratory system (Rmax,rs) is therefore proportional to the Ppeak minus Pplat pressure decay when the constant flow is suddenly interrupted, according to the equation:

$$\text{Rmax,rs} = (\text{Ppeak} - \text{Pplat})/\text{Flow}$$

Rmax,rs may be further partitioned into the airway resistance (Rmin) and additional resistances (ΔR). The immediate drop of pressure from P_{peak} to $Pao_{occlusion}$ is proportional to the airway resistances:

$$\text{Rmin} = (\text{Ppeak} - PaO_{occlusion})/\text{Flow}$$

while the slower decay from $PaO_{occlusion}$ to P_{plat} is proportional to the additional resistances:

$$\Delta R = \text{Rmax,rs} - \text{Rmin}$$

In normal patients during general anaesthesia, for a flow of 0.4 L/second and in the normal V_T range, Rmax,rs is 5 to 6 cm H_2O/L/second and Rmin is 2 to 3 cm H_2O/L/second.

Rmin,rs is increased in pathologic conditions characterized by increased airway resistance, such as asthma, acute cardiogenic pulmonary edema, ARDS, and COPD. However, because Rmin,rs is the sum of airway resistances and includes the resistance in the ventilatory circuit and the endotracheal tube, a differential diagnosis of an increase in airway resistance should include endotracheal tube obstruction. Both lung and chest wall inertial properties and lung inhomogeneities (expressed by ΔR) may be increased in some pathologic conditions; this is seen in patients with severe COPD and in morbidly obese patients.

Measuring intrinsic PEEP (PEEPi) in passive patients during controlled mechanical ventilation (static intrinsic PEEP [PEEPi,st]) is easily accomplished through a 5- to 10-second end-expiratory hold maneuver—that is, during the closure of both inspiratory and expiratory valves at end-expiration, which allows the ventilator's pressure transducer to read the end-expiratory alveolar pressure (Fig. 103-5). This is the total respiratory system positive end-expiratory pressure (PEEPtot). In patients with dynamic hyperinflation, the value of PEEPtot is higher than the value of the applied PEEP (PEEPext) and PEEPi,st is the difference between PEEPtot and PEEPext.

When using partial ventilatory support techniques, PEEPi needs to be measured in a dynamic fashion (PEEPi,dyn). The gold standard method is based on continuous recording of flow, Pao, esophageal pressure (Pes), and eventually gastric pressure (Fig. 103-6).

Static respiratory system compliance (C,st,rs) is defined as the change in respiratory system volume per unit change in applied pressure (expressed in milliliters per centimeters of H_2O):

$$\text{C,st,rs} = V_T/(PaO_{plat} - \text{PEEPtot})$$

where Pao_{plat} is measured at the end of a 2- to 5-second end-inspiratory pause (see *point E* in Fig. 103-3). Elastance, the mathematical inverse of compliance, is expressed in centimeters of water per milliliter as:

$$\text{Est,rs} = (Pao_{plat} - \text{PEEPtot})/V_T$$

For a correct calculation of C,st,rs, PEEPtot must be used instead of PEEPext to discriminate between an increase in Pao_{plat} as a result of dynamic hyperinflation (where PEEPtot is higher than PEEPext and Cst,rs is not affected) and an increase in Pao_{plat} resulting from reduction of Cst,rs (where PEEPtot is equal to PEEPext).

Role of Chest Wall Mechanics

Lung and the chest wall are "in series": hence, Cst,rs is the sum of lung and chest wall compliances (respectively, Cst,L and Cst,cw) and, Est,rs is the elastance of respiratory system, lung, and chest wall (respectively, Est,L and Est,cw):

$$1/\text{Cst,rs} = 1/\text{Cst,L} + 1/\text{Cst,cw}$$

and hence

$$\text{Est,rs} = \text{Est,L} + \text{Est,cw}$$

Cst,cw and Est,cw are calculated as:

$$\text{Cst,cw} = V_T/(\text{Pes, end inspiratory} - \text{Pes, end expiratory}$$

and

$$\text{Est,cw} = (\text{Pes, end inspiratory} - \text{Pes, end expiratory})/V_T$$

From a theoretical point of view, pleural pressure variations should be used instead of esophageal pressure to measure the pressure surrounding the lungs. However, pleural pressure measurements are virtually impossible in clinical practice, whereas the esophageal pressure recording is commonly used as a substitute.

Pes is recorded with the patient in semirecumbent position through a balloon-equipped catheter inserted in the lower third of the esophagus and connected to a pressure transducer. Partitioning between lung and chest wall elastic properties may be useful in the differential diagnosis of the decrease in respiratory compliance. Because the chest wall and abdomen are coupled through the diaphragm, an increase in abdominal pressure is one of the most important factors leading to chest wall stiffness. However, patients without abdominal hypertension may have chest wall mechanical impairment related to chest wall deformities, fluid overload, or pleural effusions.

Role of Transpulmonary Pressure

Conventional ventilatory treatment is titrated on P_{AO} based on the assumption that P_{AO} closely approaches transpulmonary pressure (P_L)—that is, the difference between airway opening pressure (P_{AO}) and pleural pressure (P_{PL}). Although this assumption is reasonable for patients with normal chest wall elastance (E_{CW}), in the presence of a substantial increase of the E_{CW} a relevant portion of P_{AO} is dissipated in distending the chest wall, leading to a lower than expected P_L. This is relevant in patients with ARDS because E_{CW} can be increased as a result of intraabdominal hypertension, pleural effusions, fluid overload, and body wall edema.[58] In these patients, targeting ventilation to P_L rather than P_{AO} would be important.[59-61] According to the elastance-derived method originally proposed by Gattinoni and co-workers,[62] any positive pressure applied at the airway opening (P_{AO}) acts on two elastic structures posed in series (the lung and the chest wall) and results in an increase in static pleural and transpulmonary pressure that can be inferred from the ratio between chest wall and lung

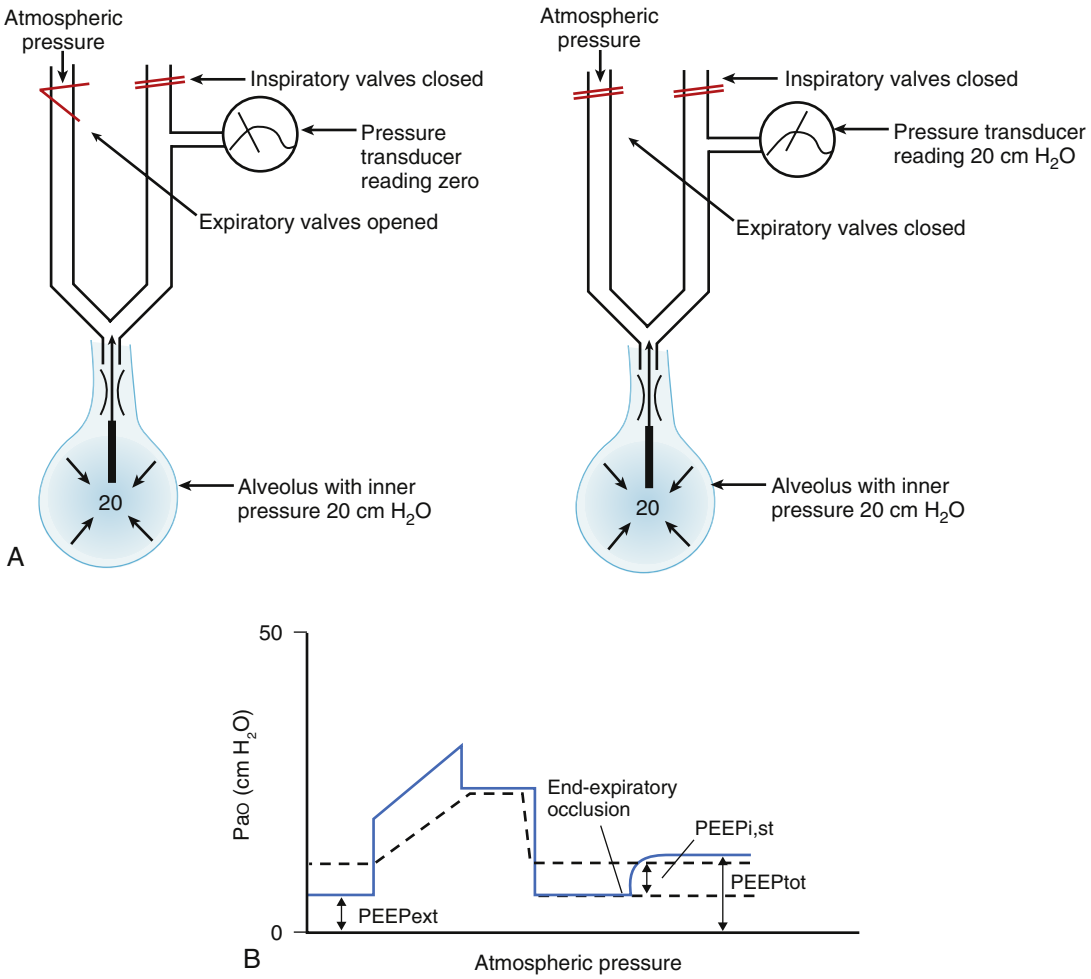


Figure 103-5. Static intrinsic PEEP (*PEEPi,st*) measurement. Schematic representation of the end-expiratory hold maneuver. **A,** Schematic representation of the respiratory system and of a ventilatory circuit. During the expiratory phase the ventilator opens the expiratory valve while the inspiratory valve is closed. Consequently the pressure transducer reads atmospheric pressure. When the end-expiratory hold maneuver is performed, both inspiratory and expiratory valves are closed at end-expiration. As a consequence, the pressure transducer reads the end-expiratory alveolar pressure. **B,** Recording of the Pao tracing obtained during a cycle of constant-flow mechanical ventilation, followed by an end-expiratory hold maneuver. At the end of the maneuver, the *PEEPtot* value is obtained. The *dotted line* refers to the theoretical value of alveolar pressure. *PEEP,* Positive end-expiratory pressure; *PEEPext,* applied PEEP; *PEEPi,st,* static intrinsic PEEP; *PEEPtot,* total respiratory system positive end-expiratory pressure.

elastance. Accordingly, $P_{PL} = P_{AO} \times (E_{CW}/E_{RS})$ and $P_L = P_{AO} \times (E_L/E_{RS})$. Hence, *elastance-derived* P_L is the Δ lung distending pressure applied during positive-pressure controlled mechanical ventilation, neglecting the absolute P_{PL} and P_{PL} value at functional residual capacity (FRC).[61,63] For mathematical reasons, the elastance-derived P_{PL} (and hence P_L) must be zero when P_{AO} is zero, but this does not mean that absolute P_{PL} and P_L are equal to zero in the same circumstances. For these reasons, *elastance-derived* P_{PL} and P_L must be clearly distinguished from *measured* or *absolute* P_{PL} (and P_L). Chiumello and colleagues[63] found that in patients with ARDS the contribution of chest wall elastance to the whole respiratory system elastance was 7% to 67%.

At variance with the elastance-derived method, the protocol proposed by Talmor and associates[64] optimizes the absolute PL at end-expiration independently from the presence of impairment of E_{CW}. They showed in a randomized clinical trial that this approach improves oxygenation and lung mechanics in patients with ARDS. In the Talmor study, PEEP was titrated to counterbalance the abdominal extra weight compressing dependent lung regions at end-expiration and esophageal manometry was used to quantify the extra weight after subtracting 5 cm H_2O for the weight of the mediastinal organs. The physiologic background is that in some patients with ARDS, oxygenation is impaired by the compression exerted by the abdominal organs. The pressure recorded inside an esophageal balloon positioned in the lower third of the esophagus is significantly affected by the extra weight exerted by the abdominal contents.[65] However, defining a single "real" absolute P_{PL} value is virtually impossible, and, as a matter of fact, chest wall elastance may be normal despite a high absolute P_{PL} measured in the lower third of the esophagus and vice versa.[66] Furthermore, counterbalancing with PEEP (a globally applied pressure) the "local" absolute P_{PL} acting on the dependent lung surface could induce overdistention in nondependent lung areas.

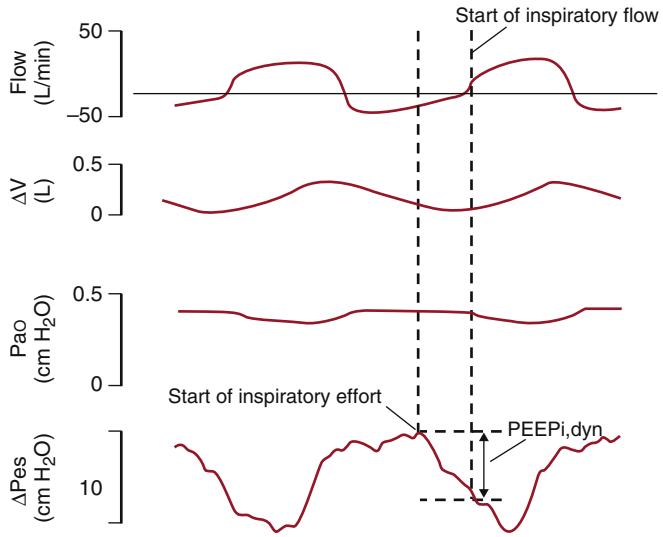


Figure 103-6. Flow, volume, Pao, and Pes tracings recorded in a spontaneously breathing patient receiving positive continuous airway pressure. PEEPi,dyn is the value of Pes deflection of from the beginning of the inspiratory effort to the point in which a positive inspiratory flow begins. *Pes,* Esophageal pressure; *PEEP,* positive end-expiratory pressure; *PEEPi,dyn,* dynamic intrinsic PEEP.

Substituting the $P_{AO,plat}$ target with an elastance-derived $P_{L,plat}$ target improved lung aeration both in a pig model[68] and in a cohort of patients with severe influenza A H1N1–induced ARDS.[69]

The straightforward physiologic concept that P_L is the real lung distending pressure must be taken in account when ventilating patients with ARDS and compromised chest wall mechanics.

MONITORING-ASSISTED MECHANICAL VENTILATION

The main parameters to be clinically observed during assisted mechanical ventilation include evaluation of patient-ventilator interactions and the occurrence of asynchrony between the patient and ventilator.

Inspiratory Trigger Asynchrony

A phase lag between the commencing of inspiratory muscle activity and the beginning of mechanical inflation is virtually always present, although the amount is minimized with the neural trigger of NAVA.[70] The presence of PEEPi may complicate patient-ventilator interactions during the triggering phase.[71] Ineffective triggering is due to the inability of the ventilator to detect patient initiation of an assisted breath despite the patient producing a substantial inspiratory effort. This phenomenon usually occurs in the presence of high levels of ventilator assistance and short expiratory times. Mechanical characteristics that are associated with ineffective triggering include low elastance, high resistance, and PEEPi.[7]

Ventilatory Requirement–Gas Delivery Asynchrony. Asynchrony between ventilatory requirement and gas delivery occurs when the ventilator-delivered flow, volume, and pressure are insufficient to meet patient ventilatory requirements. Pressure-targeted breaths may better satisfy patient ventilatory requirements because the rapid pressurization of the airways is coupled with high inspiratory flow rates just at the beginning of inspiration, thus reproducing the physiologic flow profile.

Inspiratory Time and Time Total Cycling Asynchrony. Inspiratory time (Ti) and time total (Ttot) cycling asynchrony occurs when the patient is trying to exhale, but the ventilator is still continuing to deliver gas. Parthasarathy and co-workers[72] demonstrated that prolonging the mechanical inflation during the neural expiration reduces the time available for unopposed exhalation.[72] When PSV is delivered noninvasively, air leaks may cause an abnormal prolongation of the inspiratory time preventing cycling off in inspiration and expiration. In this condition, the patient performs several efforts to exhale against the machine or inhale without receiving any ventilatory support (inspiratory hang-up).[73]

Work of Breathing. Estimating patient WOB during partial ventilatory support modes would allow setting the optimal level of support, which is the one able to normalize inspiratory muscle workload, avoiding excessive muscle unloading (overassistance). Unfortunately it requires a complex apparatus, continuous measurement of esophageal and gastric pressures, and physiologic expertise. As discussed later, the PAV+ algorithm allows continuous estimation of WOB and the NAVA technology allows continuous detection of diaphragmatic electrical activity. Although WOB may be referred to a single breath, from a clinical point of view it is useful to measure WOB per minute and WOB per liter of minute ventilation (WOB/L = WOB per minute/minute ventilation). In a normal patient, WOB per liter at rest is between 0.3 and 0.6 J/L, whereas during any invasive available partial ventilatory support technique the patient is submitted to additional iatrogenic work, wasted to overcome the endotracheal tube and ventilatory circuit resistance and to trigger the ventilator.[74]

PRINCIPLES OF RESPIRATORY PHYSIOLOGY APPLICABLE TO THE CLINICAL SCENARIO

ELASTIC PROPERTIES OF NONHOMOGENEOUS LUNG AND VENTILATOR-INDUCED LUNG INJURY

Mechanical ventilation is almost invariably used in patients with ARDS. In the majority of those patients, once mechanical ventilation is applied, the gas exchange parameters improve together with the overall clinical condition. Unfortunately, since the mid-1980s, a large number of studies have shown that mechanical ventilation can worsen preexisting lung injury (ventilator-induced lung injury [VILI]).[56,75] The main feature of ARDS predisposing to VILI is the heterogeneous

distribution of lung lesions. Pivotal computed tomography (CT) scan studies have clearly documented that in the ARDS lung normally aerated areas coexist with poorly aerated, consolidated, and hyperinflated areas[76] (Fig. 103-7). A systematic review of the pattern of distribution of these areas allowed classification of the distribution pattern of atelectasis into focal (≈36% of patients, in whom consolidated dependent areas coexisted with normally aerated nondependent areas), diffuse (≈23%, with a generalized opacification of the lung), and patchy (≈41%, in whom consolidated areas were unevenly distributed in the whole lungs).[76-78] This heterogeneity affects the mechanical characteristics of the respiratory system, as documented by the shape of the static or quasi-static inspiratory volume–pressure curve of the respiratory system.[79] When inflating the respiratory system in discrete volume steps or in a very slow fashion, the increase in airway opening pressure will reflect the variations in elastic properties of the respiratory system. A progressive increase in compliance at the beginning of lung inflation (lower inflection point [LIP]) suggests that alveoli collapsed at end-expiration are being progressively reopened during inflation (alveolar recruitment), whereas a progressive decrease of compliance toward the end of inflation (upper inflection point [UIP]) suggests that some alveoli are progressively stretched (hyperinflated) toward the end of inflation. In normal patients, LIP occurs below the elastic equilibrium point of the respiratory system and the UIP occurs at a volume close to total lung capacity. In patients with ARDS, LIP and UIP occur within tidal ventilation and indicate the pressure at which recruitment of collapsed alveoli and alveolar hyperinflation, respectively, start to occur (Fig. 103-8). The classic view remains valid, particularly in patients with early ARDS and very recruitable lungs. However, in the majority of the cases, lung recruitment occurs along the entire incremental limb of the inspiratory volume–pressure curve and is a rather progressive phenomenon. Furthermore, a significant hysteresis between the inspiratory and the expiratory volume–pressure curve has been observed by constructing the decremental (i.e., the expiratory) limb of the volume–pressure curve, meaning that (1) lung recruitment is a pan-inspiratory phenomenon, and complete lung recruitment may require very high opening pressures; and (2) that once recruited, atelectatic lung areas tend to collapse at lower pressure than those necessary to open them during inspiration.[80,81]

According to the concept of "baby lung," originally proposed by Gattinoni and Presenti,[82] mechanical ventilation delivering standard V_Ts (i.e., the V_Ts that normalize arterial $P_{CO}2$) will generate cyclical tidal alveolar hyperinflation in the reduced amount of normally aerated areas in patients with ARDS.[82] In addition, it may occur that some lung regions that stay collapsed at end-expiration if inadequately low levels of PEEP are applied will reopen at lung inflation, generating a cyclic tidal alveolar opening and collapse phenomenon (or tidal recruitment). Tidal alveolar recruiting and hyperinflation are the main mechanisms responsible for VILI generation. They activate proinflammatory intracellular

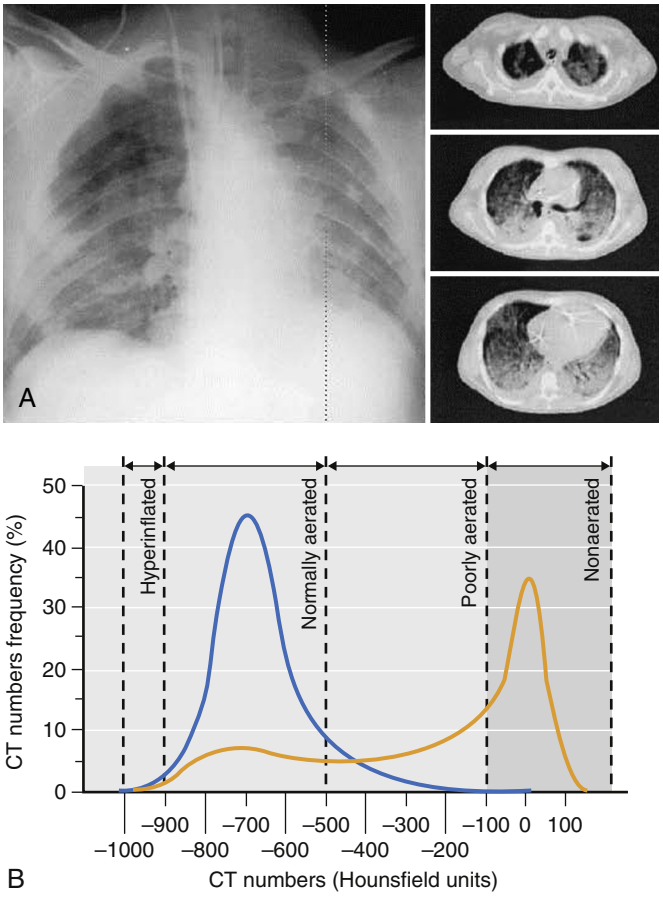


Figure 103-7. A, Anteroposterior chest radiograph and the computed tomography (CT) scans (apex, hilum, and base) in acute respiratory distress syndrome (ARDS). The radiograph shows diffuse ground glass opacification, sparing the right upper lung. The CT scans show inhomogeneous disease and both the craniocaudal and sternovertebral gradient. **B,** Lung compartments, as defined by CT numbers, in normal condition (*blue line*) and in typical acute lung injury and ARDS (*yellow line*).

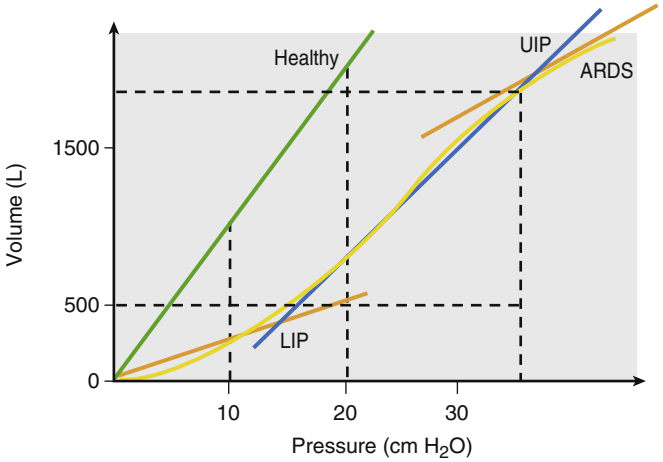


Figure 103-8. Static volume-pressure curves of the respiratory system recorded in a healthy patient and in a patient with acute respiratory distress syndrome (ARDS). LIP and UIP both occur within tidal ventilation and indicate the pressure at which recruitment of collapsed alveoli and alveolar hyperinflation start to occur, respectively. *LIP,* Lower inflection point; *UIP,* upper inflection point.

signal pathways into epithelial and endothelial cells of the alveoli and resident macrophages. As a consequence, the genes responsible for the transcription of proinflammatory and antiinflammatory mediators, respectively, are up-regulated and down-regulated, leading to alveolar inflammation.[83] This ventilator-induced biotrauma may arise after even a relatively short period of mechanical ventilation, leading to inflammation (Fig. 103-9).[75] In addition, mechanical stimuli posed on the alveolar wall are able to shed thrombomodulin (the surface molecule that proteolitically activates protein C) from the alveolar cell surface, depressing protein C activation at the alveolar level. Therefore, VILI may exacerbate the intraalveolar procoagulative and antifibrinolytic state.[84] Other expressions of biotrauma include impairment of alveolar edema clearance by inactivation of the type I and II alveolar cells NA^+/K^+-ATPase,[85] inhibition of surfactant secretion by epithelial type II cells,[86] and up-regulation of the production of matrix metalloproteinases.[87] The idea that VILI could sustain a ventilator-induced multiple organ dysfunction syndrome was originally proposed by Slutsky[75] and has been recently confirmed.[88]

Several lung-protective ventilatory strategies have been proposed to minimize VILI. Initially, the measurement of the inspiratory volume-pressure curve of the respiratory system was used. Applying a PEEP level slightly above the LIP avoids end-expiratory collapse. Also, V_T is used to obtain an end-inspiratory plateau pressure just below the UIP. Both of these moves reduced VILI-related lung and systemic inflammatory reaction[89] and VILI-related mortality.[90,91] However, selecting the PEEP level on the incremental limb of the volume-pressure curve may be misleading, because alveolar recruitment also increases above LIP.[92] Therefore, some authors suggest the "open lung approach."[81] Here PEEP is selected through a decremental trial after that maximal lung recruitment has been obtained by means of a vital capacity maneuver.

EXPIRATORY FLOW LIMITATION AND INTRINSIC POSITIVE END-EXPIRATORY PRESSURE

In normal patients at rest, the end-expiratory lung volume (EELV) closely corresponds to the elastic equilibrium point of the respiratory system (FRC). When the time available for expiration is shorter than the time required for passive exhalation to FRC, air trapping develops. Consequently, alveolar pressure will remain positive at the

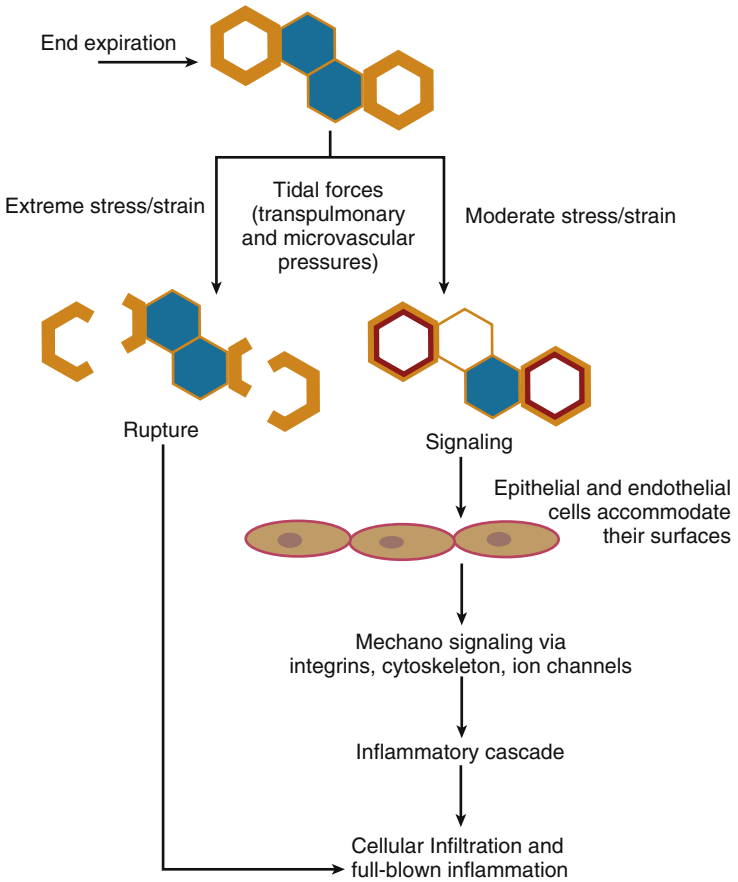


Figure 103-9. Concept of biotrauma related to ventilator-induced lung injury. The transduction of a mechanical stimulus posed on the alveolar walls (tidal alveolar opening/collapse and/or tidal alveolar stretch) leads to a biologic signaling, which translates into pulmonary inflammation. *(From Marini JJ, Gattinoni L: Ventilatory management of acute respiratory distress syndrome: a consensus of two,* Critical Care Med 33:250, 2004.)

end of expiration, generating dynamic hyperinflation—that is, a positive end-expiratory alveolar pressure, PEEPi, or auto-PEEP.[93,94] The trapped air volume may be assessed by measuring the amount of expired volume during a prolonged, passive exhalation from EELV to FRC (30 to 60 seconds) (Fig. 103-10).

Intrinsic Positive End-Expiratory Pressure Resulting From Flow Limitation

PEEPi is due to the expiratory collapse of distal airways, which severely limits expiratory flow.[95] This condition is peculiar to patients with COPD, whereas in normal patients it occurs only during forced maximal expiratory maneuvers. The pathophysiology of expiratory flow limitation was originally explained by the waterfall model (Fig. 103-11).[96] Accordingly, increasing the pressure downstream by applying an external PEEP will have no influence on either the expiratory flow or the pressure upstream of the site of critical airway closure—that is, until the value of external PEEP does not exceed the value of PEEPi.

Acting as an inspiratory threshold load, PEEPi places a burden on the inspiratory muscles, which are forced to develop sufficient force to overcome the opposite recoil pressure before inspiratory flow can begin. The WOB necessary to overcome PEEPi and initiate an inspiratory flow may be as much as 40% of total WOB in patients with COPD exacerbations,[22] and the work may be significantly reduced by applying an appropriate level of external PEEP.[97] According to the waterfall analogy, the application of an external PEEP in the range of the measured levels of PEEPi will decrease inspiratory WOB without inducing further alveolar hyperinflation.[98] However, the waterfall analogy assumes a single value of critical closing pressure for all the distal airways (Pcrit), whereas a significant heterogeneity among regional lung units has been documented.[99] Perhaps the simple waterfall analogy may not be accurate. In terms of mechanically ventilated patients with COPD, the value of external PEEP that can be safely applied without the risk for worsening dynamic hyperinflation should be somewhat less than the measured PEEPi. Applying a PEEP level equal to 75% of PEEPi is less than Pcrit in the most COPD patients.[100]

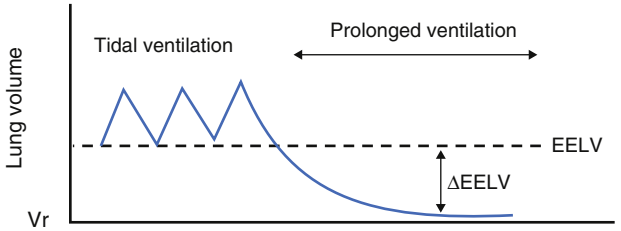


Figure 103-10. Difference (ΔEELV) between the end-expiratory lung volume (EELV) during mechanical ventilation and elastic equilibrium volume of the respiratory system (*Vr*) in a patient with dynamic hyperinflation. A complete lung emptying is obtained by disconnecting the patient from the ventilator at the end of mechanical expiratory time and allowing a prolonged (15 to 20 seconds) passive exhalation to atmospheric pressure.

Intrinsic Positive End-Expiratory Pressure Without Flow Limitation

PEEPi without flow limitation occurs when the expiratory time is shorter than the time required for passive lung emptying to FRC. The time needed to empty the lung depends on the interplay of several variables: V_T, end-inspiratory elastic recoil pressure of the respiratory system, and expiratory resistances. Moreover, in the mechanically ventilated patient, the iatrogenic resistance of endotracheal tubes, of the exhalation valve, and of the PEEP devices must be considered. Consequently, under conditions of large minute ventilation, high respiratory system compliance, and expiratory resistance, the lungs do not have time during passive deflation to reach their equilibrium point at FRC. Differently from flow limitation, applying an external PEEP in this condition will worsen dynamic hyperinflation, creating a back pressure to expiratory airflow.[101]

In the ventilated patient, dynamic hyperinflation may cause hemodynamic compromise because it critically impairs venous return and increases right ventricular afterload, leading to a low cardiac output state. This phenomenon, originally described by Pepe and Marini,[102] is more likely to occur when using controlled mechanical ventilation in patients with COPD or asthma. A rather different scenario occurs in spontaneously breathing patients with significant dynamic hyperinflation.[103] PEEPi acts as an inspiratory threshold

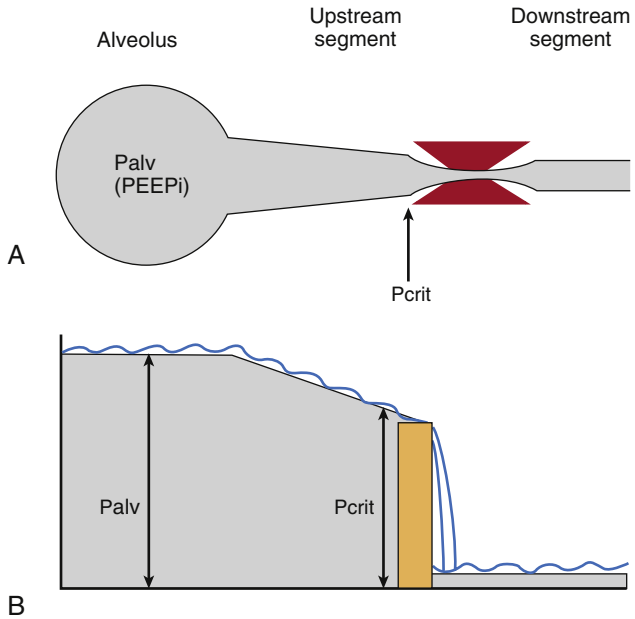


Figure 103-11. The waterfall model. As a result of the dynamic expiratory collapse of distal airways in chronic obstructive pulmonary disease, expiratory flow is severely limited; at end-expiration, alveolar pressure (*Palv*) remains positive, generating intrinsic positive end-expiratory pressure (*PEEPi*). Because of the dynamic collapse, increasing the pressure in the downstream airway segment will not have influence on the pressure upstream of the site of critical airway closure, until the applied exceeds the pressure level in the upstream airway segment (*Pcrit*).

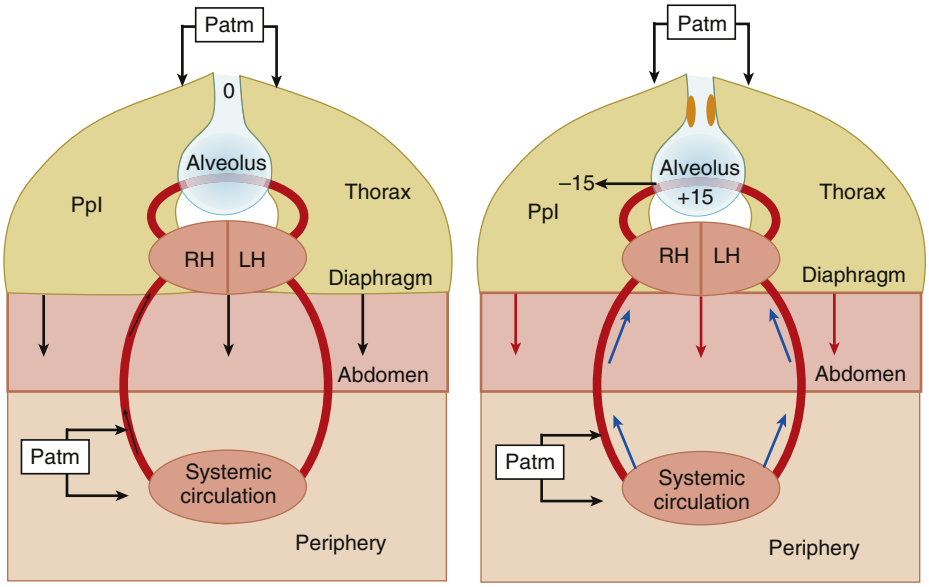


Figure 103-12. Hemodynamic consequences of dynamic hyperinflation and intrinsic positive end-expiratory pressure (PEEPi). The physiologic increase in venous return during spontaneous inspiration, as a result of the generation of a slightly negative pleural pressure (*Ppl*) in contrast to atmospheric pressure (*Patm*), is pathologically magnified in patients with dynamic hyperinflation. To initiate inspiratory flow (i.e., to generate a negative alveolar pressure) the hyperinflated patient needs to counterbalance PEEPi generating an opposite negative pleural pressure. This has a marked fostering effect on venous return. *LH,* Left heart; *RH,* right heart.

load in the sense that the patient must create an opposite negative intrathoracic pressure to generate an inspiratory flow. This decrease in pleural pressure that occurs without a change in lung volume is theoretically similar to a Müller maneuver (Fig. 103-12). The pulmonary vascular bed is relatively nonrecruitable in severe COPD; thus, pulmonary artery pressures will increase and right ventricular engorgement can ensue. Furthermore, acute right ventricular engorgement induces a leftward interventricular septum shift, leading to impairment of left ventricular diastolic relaxation and pulmonary congestion.[104-106] Besides decreasing WOB, applying a PEEP/CPAP level lower than Pcrit will limit the hemodynamic consequences of PEEPi in spontaneously breathing patients.[103]

Although PEEPi and dynamic hyperinflation are frequently thought to be synonymous, PEEPi does not necessarily imply dynamic hyperinflation or air trapping. When expiratory muscles are recruited during expiration, alveolar pressure will be positive at end-expiration without dynamic hyperinflation.[107]

MECHANICAL VENTILATION IN THE CLINICAL SCENARIO

ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is an inflammatory response of the lung to both direct and indirect insults with acute onset, presence of bilateral infiltrates on chest radiography consistent with pulmonary edema, pulmonary artery wedge pressure less than 18 mm Hg or clinical absence of left atrial hypertension, and arterial hypoxemia (see also Chapters 101 and 102). The definition of ARDS has been updated according to the recommendations of an expert task force (the Berlin definition).[108,109] The panel identified the common direct or indirect risk factors for ARDS (see later discussion) and defined ARDS as a clinical syndrome encompassing the following criteria: (1) timing, arising from a known clinical insult; (2) chest imaging (chest radiography or CT) characterized by bilateral opacities not fully explained by eventual coexisting effusions, lobar or lung collapse or nodules; (3) origin of edema not fully explained by cardiac failure or excessive intravascular fluid volume (that, of note, may coexist with ARDS); (4) oxygenation impairment—ratio of partial pressure of arterial oxygen/fraction of inspired O_2 (P/F ratio) lower than 300, evaluated at PEEP, or CPAP level of 5 cm H_2O or higher. ARDS severity is divided into three stages: mild (P/F ratio between 200 and 300), moderate (P/F ratio between 200 and 100), and severe (P/F ratio lower than 100). Importantly, these stages are correlated with mortality[27] (confidence interval [CI] 24% to 30%) in patients with mild ARDS, 32% (CI 29% to 34%) in patients with moderate ARDS, and 45% (CI 42% to 48%) in patients with severe ARDS ($P < 0,10$).[108,109]

Although in the past ARDS was considered rare,[110] a recent population-based study showed an age-adjusted incidence of 86.2 per 100,000 persons per year.[111] Mortality resulting from ARDS has been reported to decline from 60% to 70% in the late 1980s to 30% to 40% over the last 2 decades with improved management.[112-114] Risk factors linked to increased mortality in ARDS include advanced age, low PaO_2/FiO_2 ratio, septic shock, high APACHE II score, high Sequential Organ Failure Assessment (SOFA) score, low Glasgow Coma Scale score, and chronic liver disease.[115] The most common long-term impairments are muscle wasting and weakness, significant neurocognitive and emotional morbidity, and decreased quality of life even after 2 years from hospital discharge, whereas pulmonary function generally returns to normal by 6 months, with the exception of a persistent reduction in carbon monoxide diffusion capacity[116,117] (see also Chapter 101).

The inciting factors for lung injury can be divided in those associated with direct insult to the lungs, such as pneumonia or aspiration, or an indirect cause in the setting of a systemic process, such as sepsis or severe trauma (Fig. 103-13). This "first hit" to the lungs incites

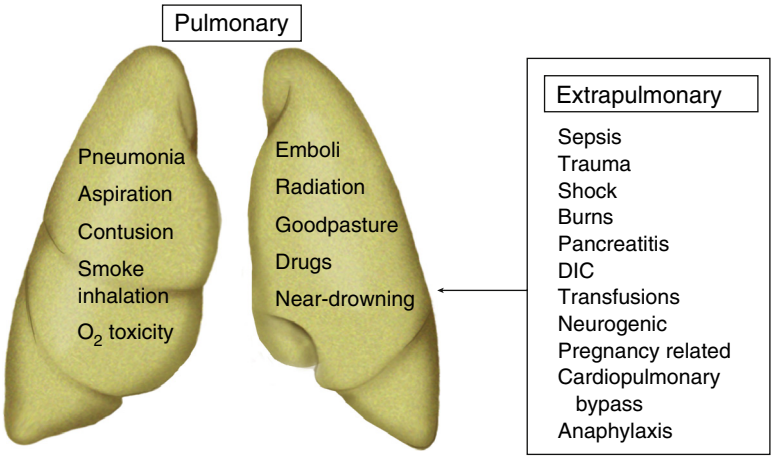


Figure 103-13. Pulmonary (primitive) and extrapulmonary (secondary) triggers of acute respiratory distress syndrome. *DIC,* Disseminated intravascular coagulation.

a pulmonary inflammatory response, which may lead to worsening of the pathologic manifestations of ARDS if coupled with injurious mechanical ventilation.[75,83] Clinical studies suggest increased mortality in patients who continue to manifest elevated bronchoalveolar lavage (BAL) concentrations of interleukin-6 (IL-6), IL-8, IL-1, and tumor necrosis factor cytokine levels during their clinical course, precluding resolution of the pulmonary and systemic inflammatory processes.[112,118,119] An important source of these inflammatory mediators are the neutrophils, which play a pivotal role in the pathogenesis and progression of ARDS,[120] although it may develop in patients with profound neutropenia, suggesting that several parallel and interacting mechanisms are involved.[121]

As previously discussed, ARDS is characterized by abnormal mechanical properties of the respiratory system with hallmark features of a reduction in FRC and a reduction in static compliance of the respiratory system.[122]

In the past, mechanical ventilation with large V_Ts of 10 to 15 mL/kg of body weight was recommended to guarantee a normal pH and $Paco_2$.[123] The use of large V_Ts leads to shear stress injury resulting from overdistention and local and systemic inflammatory response. The multicenter randomized controlled trial performed by the ARDS Network and funded by the National Heart, Lung and Blood Institute of the National Institutes of Health included 10 academic centers with 75 ICUs and enrolled patients with ARDS to compare a control ventilatory strategy using a V_T of 12 mL/kg (based on predicted body weight [PBW]) versus a lung-protective strategy using a V_T of 6 mL/kg PBW.[112] The study intended to enroll up to 1000 patients, but accrual was stopped at 861 patients when an interim analysis revealed that the mortality rate in the lung-protective group was 22% less frequent than in the control group. These beneficial results apply to a wide spectrum of patients, including patients with and without sepsis and those with different degrees of lung dysfunction as assessed by respiratory system compliance. The ARDS Network study protective ventilatory strategy set PEEP and FiO_2 according to traditional criteria, using a standardized PEEP-FiO_2 combination table prescribing simultaneous increases in PEEP and FiO_2 to achieve a certain oxygenation target. Moreover, the ARDS Network study protective ventilatory strategy aggressively maintained $Paco_2$ relatively close to the normal range, employing more frequent respiratory rates and more liberal use of bicarbonate. The study is important from a clinical perspective because for the first time it was demonstrated that a specific intervention (the reduction of V_T) was able to improve outcome in these patients. Recent investigations testing the effects on mortality of higher PEEP titration criteria did not show any improvement in terms of survival rate.[67,124,125] At present the optimal level of PEEP and best method used to set PEEP have not been definitively established.[125]

Acquired Respiratory Distress Syndrome and Refractory Hypoxemia

According to recent reports, severe hypoxemia affects 7% to 26% of patients with ARDS[67,125] whereas the majority of patients are safely oxygenated by the gold standard ARDS Network lung protective strategy. The rescue treatment flow chart for patients who are difficult to ventilate because of developing severe hypoxemia when submitted to the ARDS Network ventilatory protocol includes both ventilatory and nonventilatory strategies[50,126] and will be briefly reviewed.

The first step is defining severe and refractory hypoxemia. Unfortunately, guidelines on this crucial topic are lacking (see also Chapter 102). In the expiratory pressure study EXPRESS, Mercat and associates[67] indirectly defined patients with severe hypoxemia as those receiving rescue ventilatory and nonventilatory strategies, whereas in the Lung Open Ventilation Study (LOVS) Meade and associates[125] defined refractory hypoxemia as a PaO_2 lower than 60 mm Hg for at least 1 hour while receiving an FiO_2 of 1.0. According to the available data on extracorporeal membrane oxygenation (ECMO) as a rescue treatment for ARDS coming from case series,[127-134] one randomized clinical trial,[135] and the Extracorporeal Life Support Organization guidelines, the critical PaO_2/FiO_2 ratio threshold is between 50 and 80, despite the use of high PEEP levels, mean airway pressure ($P_{AO,mean}$) and $P_{AO,plat}$. In a recent review, Esan and associates[50] proposed an alternative definition of severe hypoxemia: (1) PaO_2/FiO_2 ratio of less than 100 or $P_{AO,plat}$ greater than 30 cm H_2O despite the

use of V_T as low as 4 mL/kg PBW or (2) an oxygenation index (OI) higher than 30. The OI is defined as:

$$OI = (P_{AO,\,mean} \times FiO_2 \times 100)/PaO_2$$

Rescue Ventilatory Approaches to Refractory Hypoxemia

According to clinical experience the first rescue strategy is based on nonconventional ventilatory approaches. The first step is defining the potential for further alveolar recruitment. This is a crucial issue because it may change the clinical history of a patient; if considered to have a low potential for recruitment, a patient is a candidate for invasive rescue nonventilatory strategies, mainly ECMO (see later discussion). If, on the contrary, lung recruitment is possible, the potential for rescue using an open lung ventilatory approach is high.

The potential for lung recruitment (i.e., the percentage of nonaerated lung tissue at minimal lung distending pressure that can be reopened by a lung recruitment maneuver) varies, depending on the method used to recruit the lung. De Matos and co-authors[136] studied an aggressive open lung approach using high inspiratory opening pressures to fully recruit the lung (up to 55 to 60 mm Hg) followed by a decremental PEEP trial. They found a median potential for recruitment of 45% (interquartile range 25% to 53%). In an older study, Gattinoni and colleagues,[137] applying a lung distending pressure of only 45 cm H_2O, reported a significantly lower potential for recruitment (13% ± 11%). Because very high recruiting pressures may expose patients to risks (barotrauma, hemodynamic compromise), the debate between aggressive and conservative recruiters is ongoing.

One important issue is considering the role of impaired chest wall mechanics in lung recruitment. If chest wall elastance is higher than normal, as occurs in some patients with ARDS, the distending pressure applied at the airway opening largely affects the chest wall and the resulting P_L (i.e., the real lung distending pressure) will be lower than expected. Titrating the open lung strategy according to the elastance-derived P_L in conditions of impaired chest wall elastance allows reproduction of the same elastance-derived end-inspiratory P_L that would have been obtained with normal chest wall elastance.[68] Recently, a rescue open lung strategy targeting a P_L of 26 cm H_2O was able to reverse hypoxemia refractory to the conventional open lung approach in 7 of 14 patients with influenza A H1N1–induced ARDS; these patients were candidates for ECMO for refractory hypoxemia.[69]

Rescue Nonventilatory Approaches to Refractory Hypoxemia

Prone positioning is an established rescue therapy for refractory hypoxemia.[137,138] Recent meta-analysis suggest that it can inprove mortality in patients with severe ARDS also without refractory hypoxemia.[138a]

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator without systemic effects. iNO may improve gas exchange and reduce pulmonary hypertension, optimizing the $\dot{V}/\dot{Q}$ matching (see also Chapter 104). Nevertheless, despite the improvement in oxygenation, no effect on clinical outcomes was demonstrated.[139] Thus, iNO cannot be recommended for the routine treatment of ALI and ARDS, but it may be useful as a rescue therapy in patients with refractory hypoxemia.

The use of neuromuscular blockade in patients with severe ARDS can improve critically compromised oxygenation[126] (see also Chapter 34). In a large cohort of patients with early severe ARDS, the use of a neuromuscular blocking drug (cisatracurium) significantly enhanced survival.[140] Whether neuromuscular blockade should be used in patients with severe but early ARDS for the first 48 hours of treatment in all patients with moderate and severe ARDS is questionable.

Extracorporeal Support for Refractory Hypoxemia

The technologic implementation of extracorporeal circuits, artificial lungs, and catheters provides a continuous therapeutic spectrum that extends from ECMO to minimally invasive extracorporeal CO_2 removal (ECCO2R) techniques.[141,142]

Venovenous ECMO was originally proposed to restore normal gas exchange working in series with the native lung in patients with ARDS.[141] Venous blood is drawn through a large-diameter cannula (24 to 32 Fr) usually positioned in the inferior vena cava and forced by a pump to circulate through an artificial lung, then returns to the venous circulation through a smaller reinfusion venous cannula. During ECMO, blood oxygenation is determined by the interplay among several variables, including the quantity of blood flow through the ECMO circuit, cardiac output, residual lung function of the native lung, and FiO_2 of the sweep gas flow into the ECMO oxygenator.[141] The technique was almost abandoned in the early 1980s, after that a randomized clinical trial did not show a decrease in mortality.[143] It then has been recently "resuscitated" for two important reasons: the technologic improvement (improved biocompatibility) of the ECMO circuits, blood pumps, and oxygenators and the use of protective ventilatory techniques to ventilate the native lung during ECMO.

At variance with the past, ECMO is now used to maintain the lung at rest while providing acceptable gas exchange. The target is no longer to normalize gas exchange but to provide ultraprotective ventilation of the native lung and use ECMO to deliver sufficient O_2 to maintain tissue homeostasis. A randomized clinical trial (the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure [CESAR] trial) documented an improved survival of patients centralized to tertiary care facilities offering a complete rescue treatment strategy, including ECMO, compared with patients managed with conventional ventilation in individual hospitals.[135] More recently, attention has been focused on management of the most severe cases of ARDS, perhaps because of the increasing number of patients with ARDS secondary to influenza A (H1N1) and its refractory hypoxemia.[144-146] ECMO has gained a definite role as a rescue therapy for patients failing to respond to less invasive rescue strategies.[128,147]

Extracorporeal Carbon Dioxide Removal for Acute Respiratory Distress Syndrome

The rationale for protecting the diseased lung by "disconnecting" oxygenation (achieved though appropriate levels of CPAP and FiO_2) from CO_2 clearance (using ECCO2R and reduced minute ventilation) was proposed 40 years ago—by Kolobow and Gattinoni.[148] They tested the effects of apneic oxygenation (PEEP 15 to 25 cm H_2O with 3 to 5 superimposed positive-pressure sighs at peak inspiratory pressures of 35 to 45 cm H_2O) plus ECCO2R (pump-driven venovenous device with a blood flow between 20% and 30% of cardiac output) in patients with ARDS.[149] The first ECCO2R devices were relatively invasive; they required blood flows up to 2 L/minute and therefore also required wide-bore drainage and reinfusion catheters. Furthermore, the priming volume was 1.5 to 2 L. Also, the first gas-permeable silicone-rubber membrane lungs created an interface between blood and air, activating the inflammatory and procoagulative blood pathways.[142]

In the last 10 years, arteriovenous pumpless devices that use the arteriovenous pressure gradients to force blood through a very low-resistance heparinized circuit have been used.[150] Their main advantages are lower anticoagulation requirements, smaller priming volumes, less mechanical damage to blood components, and absence of recirculation. On the other hand, the blood flow through these devices depends on patient hemodynamic status. They also increase the left-to-right shunt and, because they require arterial cannulation with relatively large-bore catheters (16 to 19 Fr), may lead to lower limb ischemia.

The latest innovation in the ECCO2R field is minimally invasive low-flow (300 to 450 mL/minute) venovenous pump-driven technique. These devices take advantage of highly efficient and biocompatible polypropylene or poly-4-methyl-1-pentene hollow fiber oxygenators[142] with smaller catheters (8 to 12 Fr) or coaxial double-lumen catheters similar to those used for continuous renal replacement therapies; they also use a smaller priming volume and require a smaller heparin dose.[151]

The venovenous low-flow devices allow the use of ultraprotective V_T, very low respiratory rates, or both. In a pilot observational clinical study, the Ranieri group showed that reducing V_T to 3 to 4 mL/kg further mitigates VILI compared with the ARDS Net protocol.[152] While waiting for confirmatory clinical trials, minimally invasive ECCO2R in ARDS is important because hypercapnia is a major reason for the failure of lung-protective protocols.[142]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a syndrome of chronic lung inflammation characterized by chronic, not fully reversible, airflow limitation (see also Chapters 101 and 102).[153] COPD is the fourth leading cause of death in the world. Its prevalence is approximately 9 in 1000 in men and 7 in 1000 in women, though prevalence of the disease in developed countries may be similar in the two genders.[154,155] Severe $\dot{V}/\dot{Q}$ mismatch, which is found in advanced cases of COPD, leads to chronic CO_2 retention, hypoxemia, and compensatory polycythemia. These conditions, together with an extensive destruction and remodeling of pulmonary vasculature, lead to pulmonary hypertension and chronic cor pulmonale.[156] Emphysema critically impairs lung elastic recoil and alters the alveolar attachments of small airways, compromising their stability. Reduced alveolar driving pressure, susceptibility to dynamic expiratory collapse, or both generates the phenomenon of expiratory flow limitation.[94]

Acute exacerbations of COPD are defined as worsening of dyspnea and increase in sputum purulence and volume.[157] Most COPD exacerbations are caused by tracheobronchial infections, exposure to air pollution and concomitant diseases, and unknown causes.[158] The exacerbation-induced increase in airways obstruction and worsening of dynamic hyperinflation acutely limits the ability of respiratory muscle to maintain minute ventilation. As a consequence, acute-onset chronic hypercapnia, hypoxemia, and hemodynamic impairment develop. Severe, life-threatening COPD exacerbations are characterized by a pH less than 7.30 and a PaO_2 less than 60 mm Hg (while breathing room air) and requires intensive O_2 supplementation and pharmacologic and ventilatory treatments. The target of O_2 supplementation is to maintain PaO_2 slightly more than the threshold of 60 mm Hg, because a moderate hypoxic stimulus is useful to stimulate the ventilatory drive in the presence of chronic hypercapnia.

Noninvasive PSV unloads inspiratory muscles and increases V_T. When applied early in the beginning of COPD exacerbations, the tracheal intubation rate, frequency of complications, and in-hospital mortality and length of stay can be reduced.[159,160] Experience with other noninvasive positive-pressure ventilation (NIPPV) modalities (e.g., PAV or NAVA), though encouraging, are limited to physiologic studies.[161,162] Although CPAP improves acute COPD exacerbation, no specific clinical indication for it exists.[163] If controlled mechanical ventilation needs to be used, targeting minute ventilation to the predecompensation CO_2 level is important to minimize alveolar hyperinflation and avoid rebound respiratory acidosis at the reinstitution of spontaneous breathing. In this context, measuring PEEPi and trying to minimize it by selecting the appropriate ventilatory pattern (small V_T, slow respiratory rate, and longer expiratory time) is of prime importance.[164]

The use of ECCO2R techniques can replace the need for endotracheal intubation in patients with COPD exacerbation failing noninvasive ventilation[165]; hopefully, this approach will prove to be clinically important.

ACUTE CARDIOGENIC PULMONARY EDEMA

Acute cardiogenic pulmonary edema (ACPE) results from any pathologic condition leading to the inability of the left ventricle to handle the pulmonary venous return. The resulting increase in hydrostatic pressure at the capillary level causes a leakage of fluid (with the characteristics of transudate) in the interstitium and subsequently in the alveolar space. Both interstitial and alveolar edema lead to surfactant inactivation and thickening of the walls

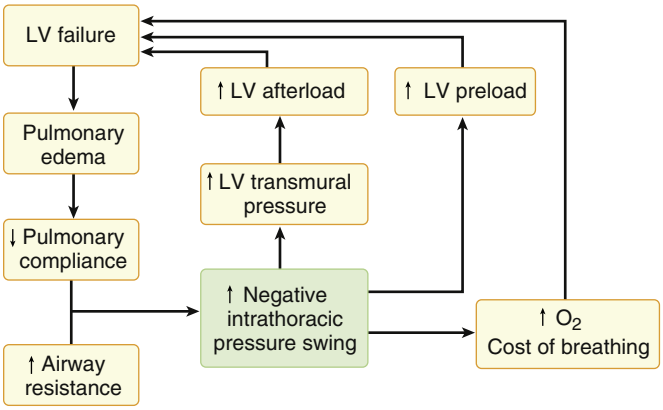


Figure 103-14. The vicious cycle of cardiopulmonary interactions during left ventricular (*LV*) failure leading to acute cardiogenic pulmonary edema (see text for further details).

of small airways, resulting in increased lung elastance, increased airway resistance (cardiac asthma), and hypoxemia. A positive feedback develops, because hypoxemia and increased WOB increase a stress response, which in turn increases left ventricle workload and possibly induces left ventricular ischemia, further limiting the ability of the left ventricle to manage venous return.[166] Moreover, the stiffer edematous lung requires the patient to develop wider negative pleural pressure swings, increasing venous return and promoting further capillary fluid leakage. Finally, the more negative the pleural pressure is during inspiration, the more transmural left ventricular pressure increases, leading to an increased left ventricular afterload[32] (Fig. 103-14).

Noninvasive techniques—both CPAP and NIPPV—reduce the need for tracheal intubation and improve outcome in patients with ACPE.[167-170] However, a small clinical trial raised serious warnings on the risk for myocardial ischemic events when patients with ACPE are treated with bilevel positive airway pressure (BiPAP, a form of PSV) compared to CPAP.[171] Recently, two meta-analyses showed that both CPAP and NPPV significantly reduce the need for endotracheal intubation, CPAP improves mortality whereas NIPPV is associated with a strong but nonsignificant trend toward better survival.[172,173] The same meta-analysis did not show significant differences in myocardial ischemic events between CPAP and NIPPV. Overall, perhaps CPAP should be first-line treatment in patients with ACPE because it is less expensive, easier to implement, and as efficacious as NIPPV.[173]

Several questions regarding noninvasive ventilation in patients with ACPE remain unresolved. (1) Does the mechanism leading to ACPE (systolic versus diastolic heart failure)[174] influence the response to noninvasive ventilation? (2) To what extent is the use of CPAP or NIPPV advisable in patients with acute myocardial infarction? (3) Do differential indications exist for CPAP or NIPPV in subgroups of patients? For example, does a preferential indication for NIPPV exist in hypercapnic patients with ACPE?[170] Furthermore, the optimal setting for CPAP and NPPV in patients with ACPE needs better definition.

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Chapter 104

Nitric Oxide and Other Inhaled Pulmonary Vasodilators

FUMITO ICHINOSE • WARREN M. ZAPOL

Key Points

- Endogenous nitric oxide (NO) is produced from oxygen and L-arginine by a group of enzymes called *nitric oxide synthases* with L-citrulline as a by-product.
- Most of the effects of NO in the cardiovascular system are mediated by the activation of the enzyme soluble guanylate cyclase, which catalyzes the formation of the second messenger cyclic guanosine monophosphate (cGMP) from guanosine-5′-triphosphate. NO may directly modulate other signaling systems. For example, inhaled NO may be directly involved in posttranslational protein modification, including nitrosylation of proteins.
- NO can be safely inhaled when delivered by facemask, nasal cannula, or endotracheal tube.
- The intrapulmonary distribution of blood flow and ventilation (ventilation-perfusion distribution) is a major determinant of the efficiency of transpulmonary oxygenation and determines the partial pressure of oxygen in arterial blood. In contrast to intravenously administered vasodilators, inhaled NO selectively improves the perfusion of ventilated regions, thereby reducing intrapulmonary shunting and improving arterial oxygenation.
- Inhaled NO therapy is approved by U.S. Food and Drug Administration for the treatment of hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in newborns (also see Chapter 95).
- Inhaled NO therapy may decrease the incidence of bronchopulmonary dysplasia and increase survival in prematurely born infants with a birth weight of at least 1000 g[50] (also see Chapter 95). Inhaled NO is widely used in cardiac catheterization laboratories as a safe and effective agent to determine the pulmonary circulation's capacity for vasodilation in pediatric and adult patients with pulmonary hypertension[68] (also see Chapter 67).
- Several clinical trials of inhaled NO in patients with acute respiratory distress syndrome (ARDS) demonstrated no effect on mortality or the duration of mechanical ventilation; however, a long-term follow-up at 6 months after treatment revealed that patients with ARDS who survived after treatment with low-dose inhaled NO had significantly better values for selected pulmonary function tests[83] (also see Chapter 101).
- The vasodilatory response to inhaled NO is variable in patients with valvular heart disease. The variability of dilator response is likely to be related to the balance of pulmonary vascular remodeling and active vasoconstriction.[89]
- Although inhaled NO does not appear to affect systemic vascular resistance, inhaled NO exerts a variety of systemic effects. Inhaled NO inhibits platelet function,[54] attenuates ischemia-reperfusion injury of extrapulmonary organs,[125] and reverses the adverse effects of free hemoglobin in the circulation.
- Inhaled epoprostenol has been used as a selective pulmonary vasodilator in adult and pediatric patients.[164] The efficacy and safety profile of inhaled epoprostenol have not been established. No general consensus exists as to when and how to use these inhaled vasodilators.

INTRODUCTION

Pulmonary hypertension often complicates patient care in the surgical units and intensive care units (ICUs). Severe acute pulmonary hypertension may produce right ventricular (RV) failure. Pulmonary hypertension and RV failure may reduce left ventricular (LV) filling, decrease cardiac output, and lead to systemic hypotension. Decreased arterial blood pressure may compromise RV coronary perfusion at a time when RV end-diastolic pressures and RV myocardial oxygen consumption are increased as a result of increased RV wall tension, thereby leading to RV ischemia.[1] RV ischemia will exacerbate RV failure, causing a further reduction in cardiac output and blood pressure (Fig. 104-1). This vicious cycle may continue unless the pulmonary artery pressure (PAP) is reduced, permitting an increased RV ejection fraction. Unfortunately, treatment of pulmonary hypertension with intravenous vasodilators may worsen the systemic hypotension. Inhalation of nitric oxide (NO) produces selective pulmonary vasodilation without reducing the systemic arterial pressure in patients with acute or chronic pulmonary hypertension. Additionally, a number of other inhaled pulmonary vasodilators are now described in the literature, which might provide potential alternatives to inhaled NO. In this chapter, the theoretic background, current uses, and future therapeutic potential of inhaled NO and other inhaled pulmonary vasodilators are discussed.

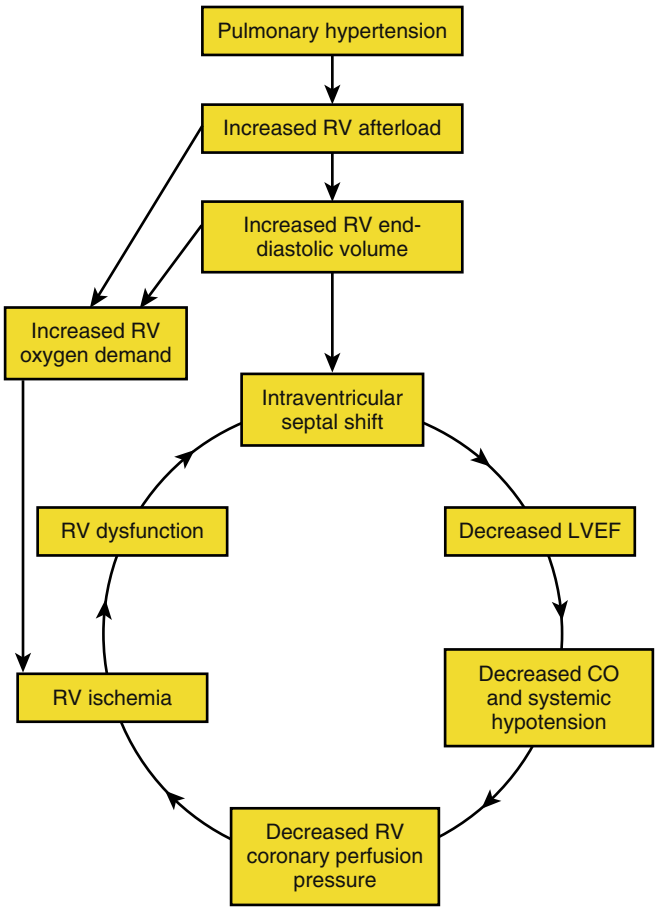


Figure 104-1. Vicious cycle of right ventricular (RV) failure triggered by pulmonary hypertension. *CO*, Cardiac output; *LVEF*, left ventricular ejection fraction.

INHALED NITRIC OXIDE

Since the recognition of NO as a key endothelial-derived vasodilator molecule in 1987, the field of NO research has expanded to encompass many areas of biomedical research. NO is an important signaling molecule throughout the body. Endogenous NO is produced from oxygen and L-arginine by a group of enzymes called *nitric oxide synthases* (NOSs) with L-citrulline as a by-product. Most of the effects of NO in the cardiovascular system are mediated by the activation of the enzyme soluble guanylate cyclase (sGC), which catalyzes the formation of the second messenger cyclic guanosine monophosphate (cGMP) from guanosine-5′-triphosphate (GTP). NO may directly modulate other signaling systems. For example, NO is directly involved in posttranslational protein modification, including nitrosylation of proteins (Fig. 104-2).

In 1991, Frostell and colleagues demonstrated a therapeutic potential for inhaled NO to act as a selective pulmonary vasodilator; they showed that breathing NO gas produced rapid and profound pulmonary vasodilation in an awake lamb model of pulmonary hypertension produced by the infusion of a stable thromboxane analogue[2] (Fig. 104-3). Because NO rapidly binds to hemoglobin (Hb) with a high affinity, the vasodilatory effect of inhaled NO is limited to the lung, which is in sharp contrast to intravenously infused vasodilators that often cause systemic vasodilation and can lead to systemic arterial hypotension. This unique ability of inhaled NO to cause highly selective pulmonary vasodilation has prompted a large number of preclinical and clinical studies. The early pilot studies also demonstrated that inhaled NO therapy rapidly improves oxygenation without causing systemic hypotension in newborns who are critically ill with acute pulmonary hypertension.[3,4] Subsequently, the efforts of many research groups studying animals and patients led to the approval of inhaled NO by the U.S. Food and Drug Administration in 1999, by the European Medicine Evaluation Agency and European Commission in 2001, and by the Ministry of Health, Labour and Welfare in Japan in 2008.[5-8]

Inhaled NO may play an important role in treating pulmonary hypertension in pediatric and adult patients with respiratory and cardiac failure, in determining the vasodilatory capacity of the pulmonary vascular bed, and, perhaps, in preventing the development of chronic lung disease in infants with lung injury (also see Chapter 95).

PHYSICAL PROPERTIES, METHODS OF ADMINISTRATION, AND MECHANISM OF ACTION

Chemistry of Nitric Oxide Gas

NO is a colorless and odorless gas that is only slightly soluble in water.[9] Atmospheric concentrations of NO usually range between 10 and 500 parts per billion (ppb)

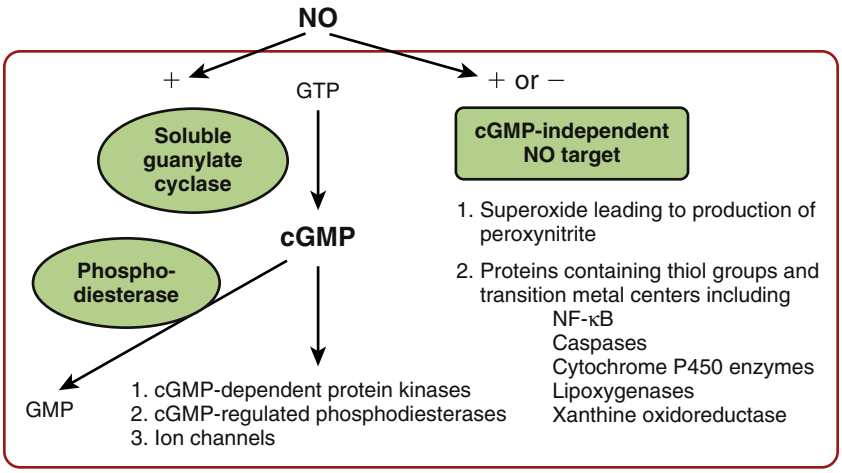


Figure 104-2. Nitric oxide (NO) signaling pathway. *cGMP*, Cyclic guanosine monophosphate; *GMP*, guanosine monophosphate; *GTP*, guanosine-5′-triphosphate; *NF-κB*, nuclear factor kappa–B.

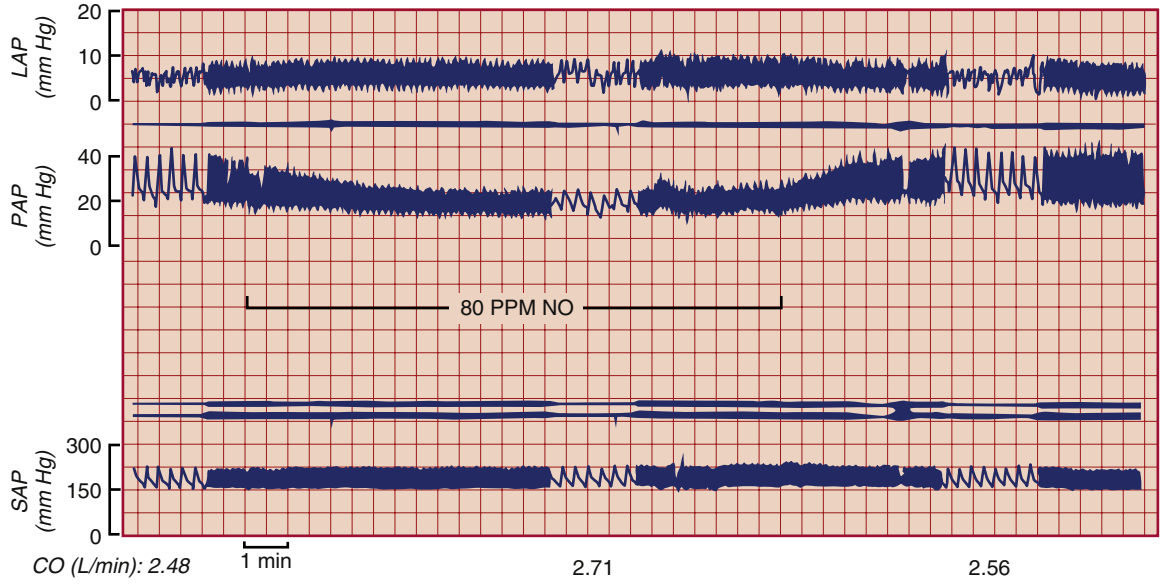


Figure 104-3. Effects of inhaling nitric oxide (NO) at 80 parts per million (PPM) in a lamb with pulmonary hypertension induced by an infusion of U46619, a stable thromboxane analogue. Inhaling NO decreases the pulmonary artery pressure (PAP) without affecting the left atrial pressure (LAP) or the systemic arterial pressure (SAP). *CO*, Cardiac output. *(From Frostell C, Fratacci MD, Wain JC, et al: Inhaled nitric oxide. A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction,* Circulation *83:2038-2047, 1991. Used with permission.)*

by volume but can exceed 1.5 parts per million (ppm) in areas of heavy traffic or lightning.[10] In the inhaled smoke of a burning cigarette, NO is produced by the oxidation of nitrogen from the atmosphere and nitrogen-containing compounds in the tobacco and can reach levels of 1000 ppm.[11] NO is unstable in air and undergoes spontaneous oxidation to form the more toxic nitrogen oxides (NO_2, N_2O_4). NO is therefore stored in cylinders and diluted in an inert gas, usually nitrogen.

Delivery and Monitoring of Inhaled Nitric Oxide

NO can be safely inhaled when delivered by facemask, nasal cannula, or endotracheal tube. Carefully regulating the concentration of NO and its exposure time to oxygen is important, which can be achieved using several commercially available systems. Although NO and NO_2 are more accurately measured by chemiluminescence devices, electrochemical detectors have proved adequate for the measurement of inhaled NO and are integrated components of several clinical delivery systems. Inhaled NO has also been administered long term via pulsed nasal delivery in clinical trials.[12] Although a concern existed that workers in ICUs would passively inhale NO, this has not become a problem because the levels of NO in the ICU air remain quite low.[13]

Nitric Oxide/Cyclic Guanosine Monophosphate Signal Transduction System

After inhalation, NO rapidly diffuses across the alveolar-capillary membrane into the subjacent smooth muscle of pulmonary vessels (Fig. 104-4). NO stimulates sGC to synthesize cGMP that, in turn, activates cGMP-dependent protein kinase G (PKG), leading to vascular relaxation. The physiologic actions of cGMP are limited by its hydrolysis to guanosine monophosphate (GMP)

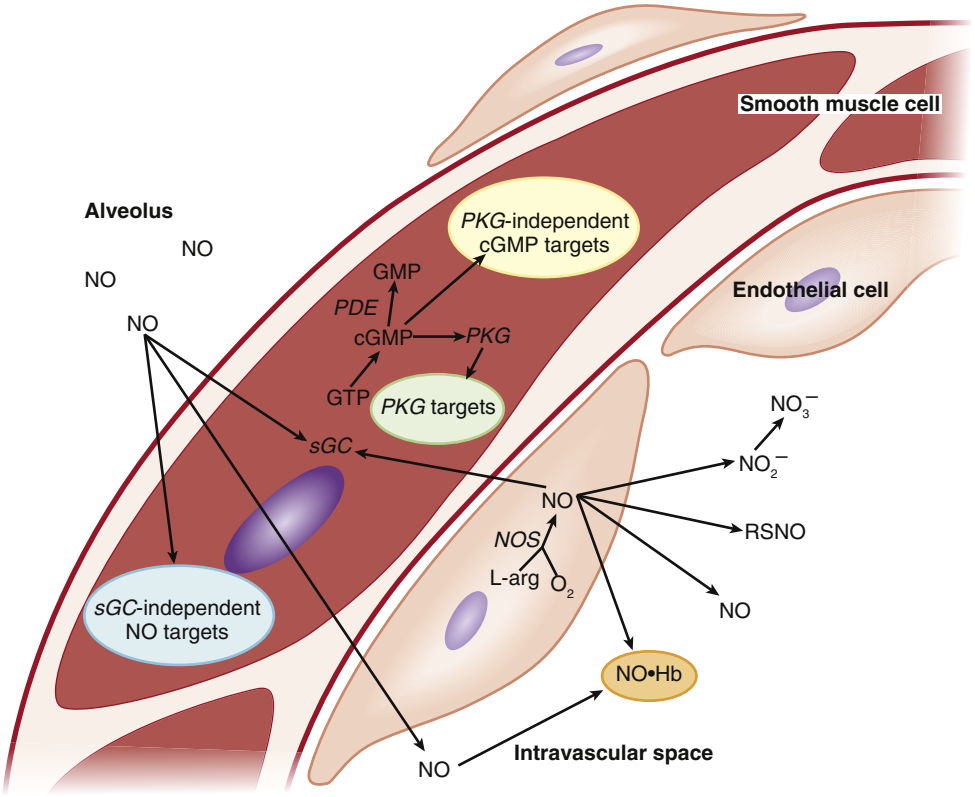


Figure 104-4. Schematic of the nitric oxide (NO) signaling pathway in the lung. NO, formed by endothelial cells or administered by inhalation, diffuses to vascular smooth muscle cells. Numerous targets of NO contribute to the wide variety of effects of this molecule on the cardiovascular system. One of the primary targets for NO is soluble guanylate cyclase (sGC). NO binds to the heme moiety of sGC and stimulates the synthesis of the intracellular second messenger cyclic guanosine monophosphate (cGMP). cGMP interacts with a variety of targets, including ion channels, cGMP-regulated phosphodiesterases (PDEs), and cGMP-dependent protein kinases G (PKG). PKGs have been shown to phosphorylate various proteins in vascular smooth muscle cells. PDEs metabolize cGMP to GMP. On arrival in the bloodstream, the majority of NO rapidly binds to hemoglobin with high affinity, whereas small amounts of NO may remain to react with other molecules, including proteins. *GMP*, Guanosine monophosphate; *GTP*, guanosine-5′-triphosphate; *Hb*, hemoglobin; *L-arg*, L-arginine; NO_2^-, nitrite; NO_3^-, nitrate; *NOS*, nitric oxide synthase; O_2, oxygen; *RSNO, S-nitrosothiol. (From Ichinose F, Roberts JD Jr, Zapol WM: Inhaled nitric oxide: a selective pulmonary vasodilator: current uses and therapeutic potential,* Circulation *109:3106-3111, 2004. Used with permission).*

and by export from the cell. A family of cyclic nucleotide phosphodiesterases (PDEs) is known to hydrolyze cyclic nucleotides. Of the 11 reported PDE isozymes, PDE type 5 is considered to be the most active cGMP, hydrolyzing PDE in smooth muscle.[14] PDE type 5 has a high affinity for cGMP and is selectively inhibited by PDE inhibitors, such as Zaprinast, sildenafil, and vardenafil. In addition to its pulmonary vasodilating effects, inhaled NO has several other effects in the lung. For instance, inhaled NO causes bronchodilation[15,16] and possesses antiinflammatory[17] and antiproliferative[18] effects. NO can also elicit effects via cGMP-independent mechanisms, including interactions with heme-containing molecules (in addition to sGC) and proteins containing reactive thiol groups.[19] NO interacts with the superoxide radical (O_2^-), thereby limiting NO bioavailability and resulting in the formation of the potent oxidant peroxynitrite ($ONOO^-$). In the presence of oxygenated Hb, NO is rapidly metabolized to nitrate with the formation of methemoglobin (metHb). Within red blood cells, electron donors rapidly convert metHb back to ferrous Hb.

Enhancement of Ventilation-Perfusion Matching by Nitric Oxide Inhalation

The intrapulmonary distribution of blood flow and ventilation (ventilation-perfusion [$\dot{V}/\dot{Q}$] distribution) is a major determinant of the efficiency of transpulmonary oxygenation and determines the partial arterial pressure of oxygen (PaO_2). In the normal, healthy lung, the majority of ventilated areas are well perfused. The shunt from the right to the left side of the circulation is mainly extrapulmonary (e.g., bronchial veins) and is less than 5% to 8% of cardiac output.[20] In the normal lung, local alveolar hypoxia constricts the vascular bed adjacent to hypoxic regions and redistributes blood flow toward lung regions with better ventilation and a higher intraalveolar partial pressure of oxygen (PO_2). Inhaled NO may amplify this mechanism by increasing blood flow to well-ventilated lung areas, which may, in some diseases, have an increased vasomotor tone. This inhaled vasodilatory effect is in marked contrast to the effect of intravenously administered vasodilators, which produce diffuse dilation of the pulmonary vasculature, thereby increasing blood flow to areas of nonventilated lung and

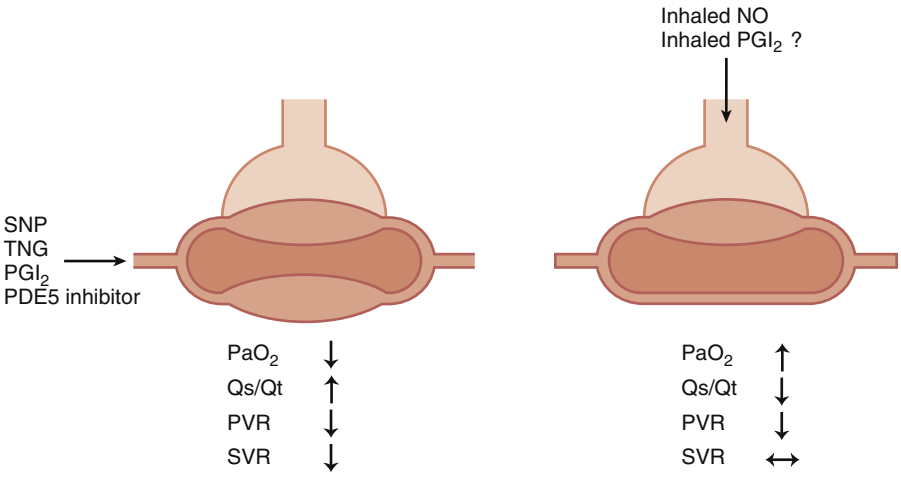


Figure 104-5. Diagram illustrating the differing pathophysiologic effects of inhaled pulmonary vasodilators and intravenous vasodilators. *NO*, Nitric oxide; *PaO_2*, arterial partial pressure of oxygen; *PDE5*, phosphodiesterase 5; *PGI_2*, prostaglandin I_2; *PVR*, pulmonary vascular resistance; *Qs/Qt*, right-to-left shunt fraction; *SNP*, sodium nitroprusside; *SVR*, systemic vascular resistance; *TNG*, nitroglycerine.

increasing intrapulmonary shunting and reducing the PaO_2. In contrast, inhaled NO should selectively improve the perfusion of ventilated regions, thereby reducing intrapulmonary shunting and improving arterial oxygenation (Fig. 104-5). These beneficial effects of inhaled NO on intrapulmonary shunting and oxygenation have been demonstrated in some adult and pediatric patients with acute respiratory distress syndrome (ARDS).[21,22] Unfortunately, this effect can, at times, be transient.[23]

CLINICAL USE OF INHALED NITRIC OXIDE

Perinatal and Pediatric Uses of Inhaled Nitric Oxide

Nitric Oxide Is an Important Regulatory Molecule in the Perinatal Lung. Several studies indicate that NO plays an important role in modulating the pulmonary vascular resistance (PVR) at birth. For example, in the developing lungs of several animals, NOS and sGC expression levels and signaling increase late in gestation, are maximal in the postnatal period, and decrease in the adult.[24-26] Moreover, because NOS inhibitors attenuate the reduction of PVR at birth,[27,28] NO signaling likely plays a critical role in the transition from the fetal to the newborn pulmonary circulatory system.

Many forms of newborn and infant lung disease are associated with endothelial cell injury and decreased NO/cGMP signaling. Studies in newborns suggest that premature constriction of the ductus arteriosus, septic mediators, and meconium aspiration all cause pulmonary endothelial cell injury. For example, in utero ligation of the ductus arteriosus in the fetal lamb causes flow-induced endothelial cell dysfunction and decreases the expression of endothelial NOS (NOS3)[29] and vasorelaxation caused by NO.[30] Moreover, cardiac lesions, such as atrial and ventricular septal defects, atrioventricular canals, persistent ductus arteriosus, and transposition of the great vessels without a ventricular septal defect, cause endothelial cell injury, decrease NO-mediated pulmonary vasorelaxant activity, and lead to pulmonary hypertension.[31]

NO/cGMP signaling plays an important role in regulating lung development. For example, in mildly hypoxemic NOS3-deficient newborn mice, alveolar development is severely inhibited in a manner that can be improved by NO inhalation.[32,33] Moreover, in perinatal models of pulmonary vascular disease, in which NO activity has been observed to be decreased, inhaled NO improves the development of peripheral pulmonary arteries.[34]

Experimental Studies of the Selective Pulmonary Vasodilator Effects of Inhaled Nitric Oxide in the Newborn. Several investigations using newborn animals have demonstrated that inhaled NO decreases pulmonary hypertension. For example, in fetal lambs with an intact placental circulation, inhaled NO decreased the PVR.[35] Similarly, in newborn lambs with pulmonary vasoconstriction associated with hypoxemia, inhaled NO was observed to decrease the PVR and increase lung cGMP levels in a manner that was not modified by acidosis.[36] Importantly, in the latter study, inhaled NO did not cause systemic vasodilation; breathing up to 80 ppm NO did not decrease either systemic vascular resistance or blood pressure. Inhaled NO also reversed vasoconstriction in newborn animals with pulmonary vascular remodeling. In newborn lambs with pulmonary vascular disease induced by premature ligation of the ductus arteriosus and associated with muscularization of peripheral arteries in the lung periphery, inhaled NO caused dose-dependent vasodilation and improved systemic oxygenation and the survival rate.[37,38]

Inhaled Nitric Oxide Can Attenuate Pulmonary Disease in Newborn Animals. In newborn rats, lung injury as a result of sustained hypoxia or exposure to endothelial toxins, for example, causes pulmonary artery muscularization and hypertension that is similar to that observed in patients with pulmonary artery hypertension (PAH) and many forms of congenital heart disease. In these models, prolonged NO inhalation has been reported to attenuate pulmonary vascular remodeling and RV hypertrophy in the newborn who is chronically hypoxic.[34] Importantly, it appears that breathing NO can inhibit pulmonary vascular remodeling even in the absence of pulmonary hypertension. Roberts and colleagues reported that in newborn rats with monocrotaline-induced endothelial injury, inhaled NO decreased the abnormal proliferation of cells in the walls of the pulmonary arteries

and prevented abnormal pulmonary vascular remodeling even before the development of pulmonary hypertension.[18] These findings suggest that inhaled NO may play an important role in modifying the abnormal vascular development and secondary pulmonary hypertension of the injured newborn lung.

Lung injury decreases alveolar and pulmonary microvascular development in premature lambs and baboons and in newborn mice and rats.[39] Inhaled NO probably promotes the development of the injured maturing lung. For example, prolonged NO inhalation increases alveologenesis in chronically ventilated premature baboons[40] and lambs.[41] Moreover, inhaled NO improves alveolar development in mice after hyperoxic lung injury.[42] The mechanisms responsible for the protective effects of inhaled NO in alveologenesis are unknown. The pulmonary vasculature regulates alveolar development,[43] and inhaled NO protects the newborn lung vessels from injury.[34] Further, inhaled NO possibly protects the lung via its effects on the microvasculature. The observation that inhaled NO improves alveolarization in rat pups that have decreased microvascular development supports this concept.[44] However, NO may regulate the homeostasis of other cells or may modulate other signaling systems, thereby regulating or contributing to lung development

Inhaled Nitric Oxide Increases Systemic Oxygenation in Hypoxemic Newborns With Pulmonary Hypertension. Pilot studies revealed that inhalation of NO increases systemic oxygenation in newborns with pulmonary hypertension and severe hypoxemia.[3,4] The ability of inhaled NO to increase systemic oxygen levels was confirmed in several multicenter randomized controlled studies of term and near-term infants with hypoxemia and pulmonary hypertension.[6,8] In one study, systemic oxygenation increased in nearly one-half of the patients with severe persistent pulmonary hypertension of the newborn (PPHN) and who received inhaled NO.[6] Importantly, the magnitude of the increase in oxygen levels in newborns treated with inhaled NO was directly proportional to the degree of hypoxia before NO inhalation, and the increased systemic oxygenation of the NO-breathing infants was maintained in 75% of the patients. In another study, the optimal concentration of inhaled NO level was investigated.[45] Although the maximum increase in systemic oxygenation was observed in infants breathing 80 ppm NO, as little as 5 to 20 ppm NO increased the arterial oxygen levels above those measured in newborns not breathing NO. Inhaled NO decreases the need for extracorporeal membrane oxygenation (ECMO), an invasive procedure requiring systemic heparinization.[6,8]

Inhaled Nitric Oxide in Bronchopulmonary Dysplasia. Bronchopulmonary dysplasia (BPD) is an important chronic lung disease of prematurely born infants that results, in part, from the inhibition or disruption of normal pulmonary alveolar and microvascular development as a result of oxygen- and ventilator-induced lung injury.[46] Although an early study suggested that inhaled NO did not decrease the incidence of BPD,[47] a subsequent single-center trial involving 207 premature infants conducted by Schreiber and colleagues suggested that inhaled NO decreases the incidence of BPD and death in prematurely born infants.[48] These observations were supported by the results from a later multicenter trial during which inhaled NO was noted to decrease the rate of BPD and death in premature infants with a birth weight greater than 1000 g.[49] In a more recent study of 793 newborns who were 34 weeks' gestational age or younger, Kinsella and colleagues reported that inhaled NO decreased the incidence of BPD in the subset of 129 infants with a birth weight of at least 1000 g.[50] Moreover, in another randomized multicenter study of 582 premature infants with a birth weight of 1250 g or less, during which inhaled NO was commenced 7 to 21 days after birth, Ballard and co-workers reported that NO inhalation improved survival and reduced the incidence of BPD.[51] Although these results are encouraging when considered together, additional studies need to be performed before the role of inhaled NO in preventing BPD can be defined.

Safety of Inhaled Nitric Oxide in the Newborn. Although studies in newborns and infants suggest that prolonged inhalation of NO is safe,[52] the long-term pulmonary and extrapulmonary effects of inhaled NO are unknown. In particular, the effects of chronic NO inhalation on normal pulmonary cell proliferation and differentiation, as well as on alveolar and microvascular development, are unknown.

NO can increase cGMP levels in platelets and inhibit their function.[53] The potential of inhaled NO to alter platelet function[54] is of particular concern for immature infants, since abnormal hemostatic activity might increase the incidence or evolution of intraventricular hemorrhage (IVH) and associated neurologic injury. In one study, breathing NO was associated with increased mortality and rates of IVH in infants weighing 1000 g or less.[49] Nevertheless, inhaled NO exposure does not increase the incidence or severity of IVH in premature babies.[47,48,51] In fact, in one large study of premature infants, inhaled NO was reported to decrease the frequency of IVH and its sequelae.[52]

It is uncertain whether an improvement in pulmonary disease in some premature babies who breathed NO is associated with an improved neurologic development. In a European multicenter trial of nearly 100 premature infants, inhaled NO was not observed to affect the incidence of death or severe disability at 1 year corrected for postnatal age.[55] In a follow-up study of the randomized multicenter trial of inhaled NO in premature infants previously mentioned, inhaled NO had no adverse neurodevelopmental effects at 2 years of age.[56] On the other hand, a more rigorous evaluation of older premature infants treated in another trial suggests that inhaled NO can improve neurologic outcomes[57] (also see Chapter 95).

Uses of Inhaled Nitric Oxide in Adult Patients With Cardiopulmonary Diseases

Pulmonary Vasoreactivity Testing in the Cardiac Catheterization Laboratory. Demonstration of a positive response to vasodilating agents in patients with pulmonary hypertension correlates with an improved long-term clinical outcome and has been used to guide medical therapy.[58] Whereas a number of vasodilators,

including intravenous prostacyclin and calcium channel blockers, have been used for diagnostic testing during cardiac catheterization, such circulating agents produce systemic vasodilation and increase the intrapulmonary right-to-left shunt.[59] In contrast, inhaled NO is a safe and effective agent to determine the pulmonary circulation's capacity for vasodilation in pediatric[60,61] and adult patients[62,63] with pulmonary hypertension; doses of 20 to 80 ppm for 5 to 10 minutes are typically used. In these patients, selective pulmonary vasodilation during NO breathing correlates with a subsequent response to oral and systemically active vasodilators.[64,65] A preoperative hemodynamic evaluation with oxygen and inhaled NO, as opposed to a test with oxygen alone, is suggested to identify more accurately those patients with pulmonary hypertension who will be the most appropriate candidates for corrective cardiac surgery or transplantation.[66] In 1998, inhaled NO was the primary vasodilator used to test pulmonary vascular responsiveness in 32% of U.S. tertiary hospitals.[67] According to a survey in 2000, 94% of pediatric cardiologists consider inhaled NO to be a clinically proven agent to test pulmonary vasoreactivity in the cardiac catheterization laboratory[68] (also see Chapter 67).

Treatment of Chronic Pulmonary Hypertension With Inhaled Nitric Oxide. Current treatment approach for chronic pulmonary hypertension includes prostacyclin (prostaglandin I_2 [PGI_2]) and its analogues, endothelin receptor–1 antagonists (ERAs), and PDE type 5 inhibitors.[69,70] Although the continuous administration of intravenous prostacyclin (epoprostenol) is associated with improved survival and exercise tolerance,[71] indwelling central venous catheters carry the risk of bacteremia. The feasibility of an ambulatory NO delivery system has been reported in a small number of patients with persistent pulmonary hypertension (PPH).[72,73] The safety and efficacy of long-term domiciliary NO inhalation requires investigation in larger patient populations.[69,74-76] Although PGI_2 analogues, ERAs, and PDE type 5 inhibitors are the mainstays of the current treatment for pulmonary hypertension, all have systemic effects in addition to their pulmonary effects that can cause unfortunate side effects. In patients who do not tolerate systemic effects of these orally active medications, long-term therapy with inhaled NO may be considered.

Treatment of Cardiogenic Shock as a Result of Right Ventricular Myocardial Infarction. RV injury and dysfunction may complicate inferior myocardial infarction (MI) as a result of right coronary artery occlusion. If coronary revascularization is delayed, then cardiogenic shock may develop, despite preserved LV function, and is associated with a high frequency of mortality. In a small series of patients with cardiogenic shock as a result of right ventricular myocardial infarction (RVMI), Inglessis and colleagues reported that unloading the RV by breathing NO 80 ppm acutely improved cardiac index by approximately 25%.[77] In patients with RVMI and a patent foramen ovale, treatment with inhaled NO significantly reduced the right-to-left shunt and improved systemic oxygenation. Further studies are required to determine whether NO inhalation will decrease morbidity and mortality associated with RVMI.

Acute Respiratory Distress Syndrome in Adults. In clinical studies of patients with severe ARDS, inhaled NO produced selective pulmonary vasodilation,[21] decreased pulmonary capillary pressure[78] and pulmonary transvascular albumin flux,[79] and improved oxygenation.[21] Although these clinical studies, as well as a number of studies in animal models of acute lung injury (ALI), have demonstrated a physiologic benefit of inhaled NO therapy, subsequent clinical trials reported disappointing outcome results. A randomized, double-blinded, placebo-controlled trial of 177 patients (average entry PaO_2/fraction of inspired oxygen concentration [FiO] ~129 mm Hg) treated with various concentrations of inhaled NO (1.25 to 80 ppm) versus a placebo failed to find a difference in either the mortality rate or the number of days alive and off mechanical ventilation.[80] A prospective, randomized, unblinded European multicenter trial of inhaled NO in patients with ALI (n = 286, average entry PaO_2/FiO_2 ~105 mm Hg) also demonstrated no effect on mortality or the duration of mechanical ventilation; however, the frequency of development of severe respiratory failure from milder respiratory failure was decreased with inhaled NO.[81] Subsequently, a large-scale, randomized, blinded, placebo-controlled study carried out in the ICUs of 46 U.S. hospitals evaluated the efficacy of low-dose (5 ppm) inhaled NO in 385 patients with moderately severe ALI (also see Chapter 101). Results of an intent-to-treat analysis revealed that inhaled NO had no significant benefit versus control (nitrogen gas) as it related to mortality (23% versus 20%, respectively), days alive and off assisted breathing (mean, 10.7 versus 10.6 days), or days alive and meeting oxygenation criteria for extubation (mean, 16.7 versus 17.0 days). Treatment, however, resulted in a significant increase ($P < .05$) in PaO_2 during the initial 24 hours of treatment, with improvement resolved by 48 hours.[82] Interestingly, a long-term follow-up at 6 months after treatment revealed that patients with ARDs who survived after treatment with low-dose inhaled NO had significantly better values for selected pulmonary function tests (e.g., total lung capacity [TLC], forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], FEV_1/FVC) at 6 months after treatment than patients treated with placebo.[83] Further trials may be warranted to determine the effects of inhaled NO on chronic lung function in survivors of ARDS, a factor in long-term morbidity and quality of life in this population.

Chronic Obstructive Pulmonary Disease. Pulmonary hypertension and hypoxemia frequently complicate severe chronic obstructive pulmonary disease (COPD). Primarily, $\dot{V}/\dot{Q}$ mismatching causes systemic hypoxemia in COPD, not intrapulmonary right-to-left shunting as in ARDS. Hypoxic pulmonary vasoconstriction diverts venous blood flow to better-ventilated lung regions, thereby improving arterial oxygenation. Although inhaled NO is a more potent pulmonary vasodilator than oxygen in COPD, breathing inhaled NO admixed with air may produce vasodilation of poorly ventilated regions of the obstructed lung without receiving sufficient oxygen

replenishment. Increasing blood flow with inhaled NO to these hypoventilated lung areas can reduce the transcutaneous arterial oxygen tension[84] and PaO_2.[85] However, when NO gas is inhaled in combination with modest oxygen enrichment (1 L/min via facemask),[86] the PaO_2 is increased to a greater extent than with oxygen therapy alone. Along these lines, a recent controlled prospective randomized trial demonstrated that the combined use of supplemental oxygen and inhaled NO for 3 months via a portable inspiratory pulsing device caused a greater improvement of pulmonary hemodynamics than supplemental oxygen alone and did not worsen the oxygenation of patients with COPD.[87] Further studies are needed to determine the effect of long-term ambulatory breathing of pulsed NO and oxygen on the quality of life and mortality rate of patients with severe COPD.

Treatment of Perioperative Pulmonary Hypertension With Inhaled Nitric Oxide

Coronary Artery Bypass Grafting. Pulmonary hypertension often complicates the management of patients during and after cardiopulmonary bypass (CPB) surgery (also see Chapter 67). A number of uncontrolled studies have demonstrated that 20 to 40 ppm inhaled NO effectively decreases the PAP after coronary artery bypass grafting (CABG), even in patients without significant preoperative pulmonary hypertension.[88-90] Although these results suggest a role for inhaled NO in treating transient pulmonary hypertension after CPB surgery, whether inhaled NO can improve the clinically important outcomes of patients undergoing CABG is unknown. A large prospective randomized trial would be needed to define a role for inhaled NO in this patient population.

Congenital Heart Disease. Postoperative pulmonary hypertensive crises are an important cause of morbidity and mortality after congenital heart surgery[91,92] and may be precipitated by diminished NO bioavailability as a result of endothelial dysfunction.[31,93] PAH and subsequent heart failure is associated with certain types of congenital heart defects, particularly those with increased pulmonary blood flow (e.g., ventricular septal defect and atrioventricular [AV] canal). Inhaled NO ameliorates the postoperative pulmonary hypertension of congenital heart disease[94,95] and decreases the need for postoperative ECMO.[96] In a randomized double-blind study, Miller and colleagues examined the effects of the prophylactic use of inhaled NO in high-risk infants undergoing congenital heart surgery[97] (also see Chapter 94). In this study, 124 patients were randomized before surgery, and inclusion in the study did not depend on the presence of pulmonary hypertension. They reported that, as compared with a placebo, infants who continuously inhaled 10 ppm NO from after surgery until just before extubation had fewer pulmonary hypertensive crises and a shorter time to eligibility for extubation. These studies indicate that inhaled NO safely decreases postoperative pulmonary hypertension in patients after surgery for congenital heart disease. Further studies are needed to test whether inhaled NO should be used after CPB surgery in all patients with congenital heart disease to decrease their perioperative morbidity and mortality.

Valvular Heart Disease. Patients with chronic mitral valve disease may have preoperative pulmonary hypertension caused by retrograde transmission of an elevated left atrial pressure (also see Chapter 67). After mitral valve repair or replacement, pulmonary vascular remodeling and vasoconstriction may persist or slowly decrease. It has been reported that the vasodilatory response to inhaled NO is variable in patients with valvular heart disease.[89,98] The variability of dilator response is likely to be related to the balance of pulmonary vascular remodeling and active vasoconstriction. Treatment with inhaled NO after repair of valvular heart disease can relieve the vasoconstrictor component of pulmonary hypertension in these patients.[99] Whether inhaled NO can alter the clinical outcome of patients after valvular heart surgery is unknown.

Cardiac Transplantation. Pulmonary hypertension in the recipient undergoing cardiac transplantation is a major cause of right heart failure and early death. Goals in the management of acute RV failure include the preservation of coronary perfusion through the maintenance of systemic blood pressure and reducing RV afterload by decreasing the PVR.[100] In contrast to therapy with intravenous vasodilators that often cause systemic hypotension, inhaled NO has been shown using a small group of patients to selectively reduce PVR and enhance RV stroke work after cardiac transplantation.[101] A positive pulmonary vasodilator response to NO inhalation has been used as a criterion to select patients for cardiac transplantation.[102]

Insertion of Left Ventricular Assist Device. RV dysfunction occurs in 20% to 50% of patients after insertion of a left ventricular assist device (LVAD).[103] The ability of the RV to pump sufficient quantities of blood to the LVAD is critically related to the intrinsic contractility of the RV and the RV afterload, which is influenced by the PVR. The PVR is usually elevated in long-standing congestive heart failure and can be further increased in the early postoperative period by the effects of CPB surgery. Inhaled NO has been shown to decrease the PVR effectively in the setting of RV dysfunction after LVAD insertion.[104] A trial of inhaled NO is recommended before considering implantation of a RV assist device, as this invasive procedure may be avoided if the response to inhaled NO is salutary[105] (also see Chapter 67). Although a small randomized, double-blinded trial demonstrated the hemodynamic benefits of inhaled NO (decreased PAP and increased LVAD flow) in patients with pulmonary hypertension who received an LVAD,[106] a recent larger clinical trial failed to show beneficial effects of NO inhalation after LVAD insertion.[107]

Treatment of Pulmonary Ischemia-Reperfusion Injury. Ischemia-reperfusion (I-R) injury is one of the major causes of early graft failure after lung transplantation. Adhesion and sequestration of activated leukocytes by activated pulmonary endothelium are believed to be important mechanisms of I-R injury. NO possesses antiinflammatory properties, and inhaled NO has been shown to attenuate pulmonary I-R injury in preclinical studies.[108] Although two uncontrolled clinical studies suggested that

inhaled NO may prevent lung I-R injury,[109,110] a small randomized, placebo-controlled study demonstrated that inhaling 20 ppm NO commencing 10 minutes after reperfusion did not affect the physiologic or clinical outcome of patients after lung transplantation.[111] Additional studies are required to define the therapeutic role of inhaled NO in patients who have developed an I-R injury after lung transplantation.

EXTRAPULMONARY EFFECTS OF BREATHING NITRIC OXIDE

Because breathing NO decreased the PVR without altering systemic blood pressure, an initial proposal suggested that the action of inhaled NO was limited to the lungs. It was hypothesized that any NO reaching the bloodstream would be rapidly scavenged by oxygenated Hb, leading to the production of nitrate and metHb.[2] However, as early as 1993, evidence began to accumulate that NO inhalation could inhibit platelet function.[54] Subsequently, studies describing a wide range of systemic effects of breathing NO were published, as summarized recently by McMahon and Doctor[112] and highlighted in Table 104-1. In this section, the ability of NO inhalation to decrease I-R injury is reviewed, and the circumstances during which breathing NO can modulate systemic vascular tone are discussed. In addition, potential mechanisms by which inhaled NO may exert its systemic effects are outlined.

Inhaled Nitric Oxide and Platelet Function

The ability of NO-donor compounds to inhibit platelet function is well known, but systemic hypotension limits the therapeutic application of their antithrombotic effects. In 1993, Hogman and colleagues first reported that breathing NO (30 ppm) could prolong the bleeding time in rabbits and healthy human subjects.[54] Subsequent reports from multiple research groups presented conflicting data with some investigators reporting that breathing NO increased bleeding time in neonates and adults and others reporting that NO inhalation did not alter either bleeding time nor platelet function. A recent randomized controlled blinded crossover study showed that inhaled NO, when administered with heparin, exhibited no significant additive effects on activated clotting time, prothrombin time, activated prothrombin time, bleeding time, or platelet aggregation.[113] On the other hand, the observation that breathing NO could decrease platelet function led other investigators to examine in animal models whether NO inhalation could be used to treat vascular diseases associated with platelet activation. For example, Semigran and

TABLE 104-1 **BIOLOGIC EFFECTS OF BREATHING NITRIC OXIDE WITH SELECTED PHYSIOLOGIC IMPACTS AND POTENTIAL THERAPEUTIC APPLICATIONS**

Biologic Effect	Impact	Therapeutic Application	References
Pulmonary vasodilation	Reduction in pulmonary artery pressure	Pulmonary arterial hypertension	2
	Decrease in extrapulmonary right-to-left shunting and improved systemic oxygenation	Pulmonary hypertension of the newborn and congenital heart disease	3, 4, 94
	Decrease in RV afterload	RV failure after LVAD placement	106
		RVMI complicated by cardiogenic shock	(77)
		RV failure after cardiac surgery	88
Improved matching of lung ventilation and perfusion	Increased systemic oxygenation	Acute lung injury or pneumonia	21, 80, 81
		Chronic pulmonary disease	87
Pulmonary vascular and alveolar development	Decreased vascular SMC hyperplasia and increased alveolarization in the injured developing lung	To prevent or ameliorate pulmonary hypertension in infants with congenital heart disease and chronic lung disease in premature infants	33, 34, 40, 41
Systemic effects of breathing NO	Platelet inhibition	Decreased thrombosis after coronary thrombolysis (dogs)	54, 114
	Leukocyte inhibition	Improved mesenteric blood flow after ischemia and reperfusion (cats)	117
		Decreased MI size in cardiac ischemia-reperfusion injury	121, 122
	Supplementation of NO scavenged by cell-free Hb	Decreased cell-free Hb-induced vasoconstriction and inflammation	132-134
	Neuroprotection	Improved neurologic function and survival after cardiac arrest (mice)	135-137
		Decreased size of brain infarction (mice) and increased cerebral blood flow after stroke (sheep)	

Hb, Hemoglobin; *LVAD*, left ventricular assist device; *MI*, myocardial infarction; *NO*, nitric oxide; *RV*, right ventricular; *RVMI*, right ventricular myocardial infarction; *SMC*, smooth muscle cell.
Representative references are included.
From Bloch KD, Ichinose F, Robert JD, et al: Inhaled NO as a therapeutic agent, Cardiovasc Res *75:339-348, 2007. Used with permission.*

colleagues reported that in a canine model of coronary thrombosis after thrombolysis, breathing 20 and 80 ppm NO decreased platelet-mediated thrombosis,[114] an effect that was augmented by the co-administration of PDE inhibitors.[115,116] Breathing NO did not prolong the bleeding time or cause systemic hypotension in these studies.

Inhaled Nitric Oxide and Ischemia-Reperfusion Injury of Extrapulmonary Organs

Observations that NO can form stable, biologically active adducts with protein thiol groups led Kubes and colleagues to examine whether inhaled NO could be used to deliver NO to peripheral tissues.[117] Studying postcapillary venules from cats subjected to intestinal ischemia and reperfusion, these investigators observed that breathing 80, not 20, ppm NO prevented the reduction of blood flow, the increase in leukocyte activation (i.e., rolling, adherence, migration), and vascular leakage. The investigators also observed that breathing NO prevented the arteriolar constriction and neutrophil activation induced by the administration of L-NG-nitroarginine methyl ester (L-NAME), a NOS inhibitor. Interestingly, inhaled NO did not alter neutrophil activation or vascular leakage in endotoxin-challenged cats, leading the investigators to propose that inhaled NO does not affect peripheral tissues with abundant NO (produced by inducible NOS). In contrast, Neviere and associates reported that breathing 10 ppm NO decreased the adhesion of leukocytes to mesenteric venular endothelium of endotoxin-challenged rats.[118] Moreover, breathing NO prevented endotoxin-induced cardiac dysfunction and leukocyte accumulation. In a subsequent report, Kubes and colleagues reported that, in contrast to NO-donor compounds, inhaled NO did not prevent the increase in mucosal permeability induced by intestinal I-R and suggested that the effects of breathing NO were limited to the vascular compartment.[119]

Based on these observations, Guery and colleagues evaluated the ability of breathing NO to preserve cardiac function after myocardial I-R injury.[120] Hearts from rats that had breathed air with or without 10 ppm NO for 4 hours were isolated and perfused. Coronary perfusion was stopped for 30 minutes, followed by reperfusion for 40 minutes. The investigators observed that pretreatment with inhaled NO led to improved systolic and diastolic function after I-R. These findings were extended by Hataishi and colleagues who examined the ability of breathing NO to decrease cardiac I-R injury in intact mice.[121] They observed that breathing NO for the final 20 minutes of ischemia and for 24 hours after reperfusion decreased MI size and improved systolic and diastolic function. Breathing 80 ppm NO decreased MI size similarly after 30, 60, or 120 minutes of ischemia. Breathing 40 and 80 ppm NO equally decreased myocardial I-R injury, but 20 ppm was not effective. Breathing NO decreased cardiac neutrophil accumulation and leukocyte depletion prevented the beneficial effects of NO on MI size. Observations in rodents have recently been extended to a clinically relevant porcine model of cardiac I-R injury. Janssens and colleagues reported that breathing 80 ppm NO decreased MI size and improved myocardial perfusion in pigs subjected to 50 minutes of cardiac ischemia and 4 hours of reperfusion.[122] The ability of inhaled NO to decrease I-R injury of extrapulmonary organs is further suggested in a small series of patients undergoing CPB surgery,[123] patients after limb I-R,[124] and patients undergoing liver transplantation.[125] Based on these considerations, a randomized clinical trial has been initiated to test whether breathing 80 ppm can decrease MI size in patients with an ST-segment elevation MI.

Inhaled Nitric Oxide and Systemic Vascular Tone

Whether breathing NO can modulate systemic vascular tone remains controversial. Clinically significant systemic hypotension has not been observed in adults and infants with a wide variety of disorders treated with concentrations up to 80 ppm NO. However, breathing 80 ppm NO attenuates the ability of L-NAME to increase arterial blood pressure in cats.[119] Cannon and colleagues reported that breathing 80 ppm NO increased forearm blood flow in healthy patients treated with an intrabrachial artery infusion of the NOS inhibitor L-NG-monomethylarginine acetate salt (L-NMMA).[126] In contrast, Hataishi and colleagues observed that breathing NO did not decrease systemic vascular resistance in L-NAME–treated mice or in mice congenitally deficient of NOS3.[127]

The ability of inhaled NO to decrease systemic vascular resistance is perhaps clearest in the case of the endothelial dysfunction associated with hemolysis, such as that observed during vasoocclusive pain crisis (VOC) of sickle cell disease (SCD). Presence of Hb in the plasma may likely induce systemic vasoconstriction via scavenging of endothelium-derived NO.[128] Preclinical studies and small clinical series suggest beneficial effects of NO inhalation on VOC of SCD.[129,130] Nonetheless, a recent prospective, multicenter, double-blind, randomized, placebo-controlled clinical trial for up to 72 hours of inhaled NO versus inhaled nitrogen placebo in 150 participants with vasoocclusive pain crisis of SCD showed that the use of inhaled NO compared with placebo did not improve time-to-crisis resolution.[131]

Preclinical studies have also shown beneficial effects of inhaled NO against systemic vasoconstriction and inflammation associated with transfusion of Hb-based oxygen carrier (HBOC),[132] packed red blood cells stored for a prolong period (40 days),[133] and cerebral malaria.[134] Several clinical trials are underway to determine the efficacy of NO inhalation in various disease states associated with cell-free Hb.

Protecting the Brain Using Inhaled Nitric Oxide

Although NO-dependent signaling exerts multifaceted protection against I-R injury, the vasodilating effects of systemically administered NO-donor compounds preclude their use in patients with unstable arterial blood pressure, which is especially true for patients resuscitated from sudden cardiac arrest (also see Chapter 108). Sudden cardiac arrest remains a leading cause of death worldwide. Despite advances in cardiopulmonary resuscitation (CPR) methods, including the introduction of the automatic external defibrillator (AED) and therapeutic hypothermia (TH), only approximately10% of those who have adult out-of-hospital cardiac arrest (OHCA) survive to hospital

discharge, and up to 60% of survivors have moderate-to-severe cognitive deficits 3 months after resuscitation. No pharmacologic agent is available to improve the outcome from cardiac arrest and CPR.

In a recent preclinical study, Minamishima and colleagues evaluated the impact of breathing NO on outcomes in mice subjected to cardiac arrest and CPR. These authors reported that breathing 40 ppm NO starting 1 hour after return of spontaneous circulation (ROSC) and continuing for 23 hours (1) improved neurologic and myocardial function and the survival rate in mice at 10 days, (2) attenuated water diffusion abnormality and blood-brain barrier leakage at 24 hours (as demonstrated by magnetic resonance imaging [MRI] in live mice), (3) prevented apoptotic cell death and glial activation in the brain 4 days after cardiac arrest, and (4) attenuated inflammatory cytokine induction in the brain and heart 1 and 4 days, respectively, after cardiac arrest.[135] The protective effects of NO breathing after CPR, if extrapolated to human beings, is highly clinically relevant, because NO inhalation can be started after patients are transferred to the hospital and informed consent is obtained.

Subsequent preclinical studies supported the effects of inhaled NO. Terpolilli and colleagues showed that NO inhalation prevented ischemic brain injury induced by middle cerebral artery occlusion in mice and sheep by selective dilation of collateral arterioles.[136] Similarly, inhaled NO was found to reduce brain damage by collateral recruitment in a neonatal stroke model in rat pups.[137] Clinical trials are underway to investigate the neuroprotective effects of NO inhalation.

How Does Inhaled Nitric Oxide Exert its Systemic Effects?

With the exception of the case of hemolysis, the mechanisms by which NO, once inhaled, are able to induce responses in the periphery remains incompletely understood. One hypothesis is that during NO inhalation, blood cells, including white blood cells and platelets, are exposed to NO before the scavenging of the gas by red blood cells, and NO-exposed blood cells are responsible for the systemic effects of inhaled NO (Fig. 104-6). For example, exposure of platelets to NO in the pulmonary circulation may inhibit their activation at the site of vascular injury. However, this hypothesis does not fully account for the dilator effects of breathing NO observed in some vascular beds or the observations of Fox-Robichaud and associates,[117] who reported that inhaled NO did not alter the ability of feline blood leukocytes to bind to immobilized platelet monomers ex vivo.

An alternate hypothesis is that some of the inhaled NO escapes scavenging by Hb and is carried in a stable, bioavailable form to the periphery (see Fig. 104-6). Loscalzo and colleagues proposed that endogenously synthesized NO reacts with low- and high-molecular-weight thiols in blood, including serum albumin.[138,139] These *S*-nitrosothiols can deliver NO to tissues distant from the site of its synthesis. Stamler and colleagues observed that NO reacts with the thiol group on Cys^{93} of the Hb β chain; the *S*-nitrosylation of Hb (SNO-Hb) is dependent on the oxygen tension, enabling erythrocytes to load Hb in the oxygen-rich environment of the lungs and to release low-molecular-weight *S*-nitrosothiols in the relatively hypoxic periphery.[112] NO can be oxidized in blood to nitrite, which regenerates NO in the presence of nitrite reductases including deoxyhemoglobin.[140] Erythrocyte SNO-Hb and nitrite have both been implicated as potential mediators of the systemic vasodilation induced by tissue hypoxia. NO may also react with other plasma species that are subsequently capable of regenerating NO, including *N*-nitrosamines, iron-nitrosyls, and nitrated lipids.

Even before it was appreciated that breathing NO could selectively dilate the pulmonary vasculature, several research groups examined the metabolic fate of inhaled NO. In 1975, Oda and colleagues reported NO inhalation led to the formation of nitrosyl-Hb in the blood of mice, rats, and rabbits.[141] In 1987, Yoshida and Kasama reported that breathing ^{15}NO (145 ppm for 123 minutes)

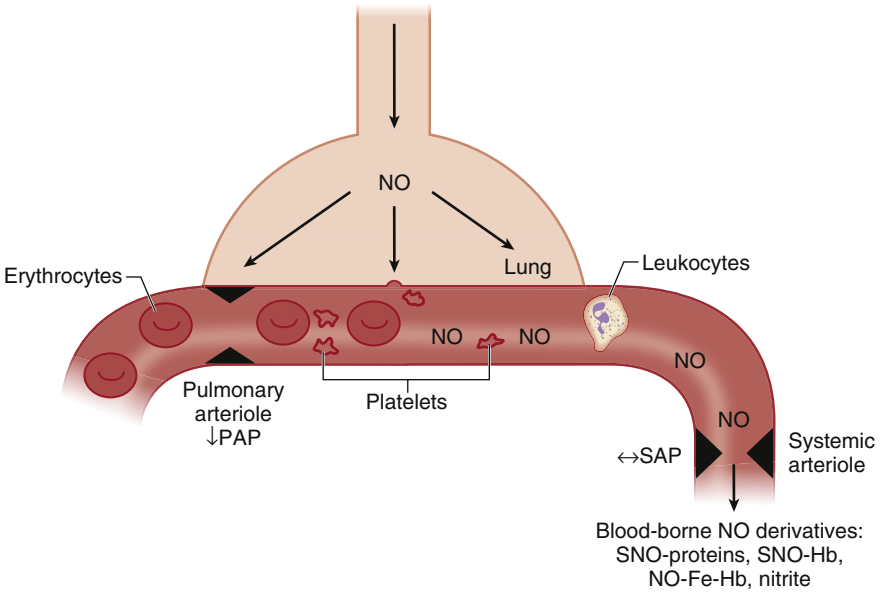


Figure 104-6. Inhaled nitric oxide (NO) is a selective pulmonary vasodilator with actions on the systemic vasculature. A schematic of an alveolar-capillary unit is presented, highlighting the ability of inhaled NO to dilate pulmonary arterioles and reduce pulmonary artery pressure (PAP). Although inhaled NO does not dilate systemic arterioles or alter systemic arterial pressure (SAP) under normal conditions, inhaled NO has systemic effects that are described in the text and may be mediated by circulating cells exposed to NO in the lungs and bloodborne NO derivatives: SNO-proteins or *S*-nitroso proteins including SNO-albumin; SNO-Hb or *S*-nitrosylation of hemoglobin (nitrosylated on Cys^{93} of the β chain); NO-Fe-Hb or nitrosyl-hemoglobin; and nitrite. *(From Bloch KD, Ichinose F, Robert JD, Zapol WM: Inhaled NO as a therapeutic agent,* Cardiovasc Res *75:339-348, 2007. Used with permission).*

led to the formation of nitrosyl-Hb, nitrite, and nitrate.[142] More recently, Cannon and associates found that nitrosyl-Hb concentrations significantly increased in healthy adults breathing 80 ppm NO, whereas nitrite modestly increased.[126] Arterial concentrations of both products were greater than venous levels, suggesting consumption in peripheral tissues. Cannon and colleagues did not detect an increase in plasma *S*-nitrosothiols or SNO-Hb. In contrast, Ng and colleagues reported that plasma levels of both *S*-nitroso-albumin and nitrite increased in cats breathing 80 ppm NO; both were further increased in the setting of intestinal I-R.[143] Arterial levels of *S*-nitroso-albumin were higher than venous levels, whereas the converse was true for nitrite levels, which suggested that *S*-nitroso-albumin was consumed in the periphery and nitrite was generated.

The potential importance of nitrite as a mediator of inhaled NO's impact on I-R injury was highlighted in recent studies of Duranski and colleagues.[144] They observed that small increases in blood nitrite levels were sufficient to decrease I-R injury in the liver and heart. Moreover, in studies of murine I-R injury, Hataishi and colleagues[121] reported that breathing NO increased nitrite concentrations in plasma and blood to levels similar to those demonstrated to be effective by Duranski and associates. More recently, Nagasaka and colleagues demonstrated that breathing NO leads to the rapid accumulation of a variety of NO metabolites in blood and tissues, contributing to the ability of brief periods of NO inhalation to provide cardioprotection against I-R injury.[145]

SAFETY ISSUES AND METHOD OF ADMINISTRATION

Prolonged inhalation of low levels of NO appears to be safe. The major clinical toxicity is due to the formation of NO_2 and methemoglobinemia. Nitrogen dioxide is rapidly converted to nitric acid in aqueous solution (e.g., acid rain) and is highly toxic to the respiratory tract. Increased airway reactivity in humans occurs after exposures to as low as 1.5 ppm NO_2.[146] At higher inhaled NO_2 doses, pulmonary edema is the major toxicologic effect[147] and can result in rapid death after inhalation exposure.[148]

Inhaled NO can combine with Hb to form nitrosyl-Hb, which is rapidly oxidized to metHb. The rates of uptake and release of NO from ferrous (Fe^{2+}) Hb are 10^5- to 10^6-fold greater than those of oxygen. Tissue hypoxia can be produced at excessive circulating metHb concentrations. In general, cyanosis does not appear until metHb levels approach 15% to 20%, and clinical symptoms of hypoxia (e.g., fatigue, dyspnea) become significant at metHb levels above 30% of the Hb concentration.[149] The enzyme metHb reductase rapidly converts metHb to Hb in the red blood cell. Because neonates have reduced activity of this enzyme, they are at greater risk than adults for developing significant methemoglobinemia after inhaling high levels of NO for a prolonged period.[149] Blood metHb concentrations and inspired NO_2 concentrations were frequently monitored in clinical trials of inhaled NO in both adults and neonates.[5-7, 80] In a large number of adult (n = 120) and newborn patients (n = 351) pooled from several clinical trials, significant methemoglobinemia or NO_2 formation was uncommon in patients breathing NO at doses ranging from 1.25 to 80 ppm. (See summary table in a study by Steudel and others.[20]) If metHb or NO_2 levels increased above predetermined limits, then the concentration of inhaled NO was decreased. Discontinuation of NO administration because of excessive NO_2 or metHb formation was necessary in only 3 of 471 patients (0.6%).

Inhaled NO is a selective pulmonary vasodilator in patients with heart failure, although breathing NO can be accompanied by an elevation of LV filling pressure in patients with severe LV dysfunction.[59,150] Taken together with the in vitro experimental evidence of a direct negative inotropic action of NO,[151,152] these clinical observations led to the concern that inhaled NO may clinically exert important negative inotropic effects in patients with impaired LV function. However, investigators learned that the elevation in LV filling pressure that occurs with NO breathing is due to the augmentation of filling into a relatively noncompliant LV and is not caused by a negative inotropic effect.[153] An observation in patients with heart failure who received mechanical LV assistance supported the concept that inhaled NO increases LV filling pressure only when cardiac output is not assisted.[154] Nonetheless, being aware of the possibility that inhaled NO can produce pulmonary vasodilation and may overwhelm a failing LV, thereby producing pulmonary edema, is important.

OTHER INHALED PULMONARY VASODILATORS

BACKGROUND

The successful clinical use of inhaled NO as a selective pulmonary vasodilator prompted the search for other alternatives, at least, in part, as a result of the significant cost of inhaled NO therapy (e.g., $3000 per day with a $12,000 monthly cap) in the United States.[155] A wide variety of intravenous vasodilators were clinically tested via the inhaled route. These vasodilators include prostacyclin (PGI_2)[156]; milrinone[157]; nitroglycerine[158]; sodium nitroprusside[159]; prostaglandin E_1[160] and a stable analogue of PGI_2, epoprostenol[161]; and iloprost.[162] It was expected that inhalation of intravenous vasodilators would maximize drug levels in the lung while minimizing their systemic effects (see Fig. 104-5). Although some studies have reported encouraging results in the perioperative off-label use of these drugs via off-label route of administration (i.e., inhalation), especially with inhaled epoprostenol,[161,163,164] at the time of this writing, efficacy and the safety profile of these inhaled vasodilators have not been established. As a result, no general consensus exists as to when and how to use these inhaled vasodilators. (The use of epoprostenol at the author's institution is described in the next section as an example.)

INHALED EPOPROSTENOL

At Massachusetts General Hospital, epoprostenol (Flolan) has been used to treat intraoperative pulmonary hypertension during cardiac surgery and postoperative

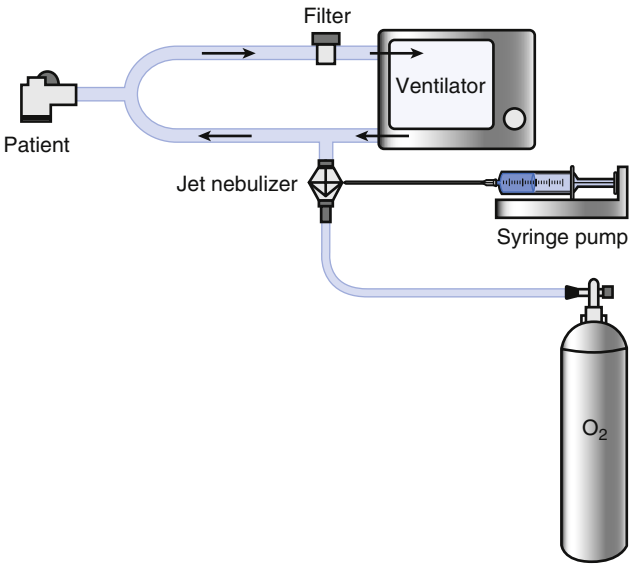


Figure 104-7. Diagram illustrating a sample setup of inhaled administration of epoprostenol in patients on ventilation. O_2, Oxygen.

pulmonary hypertension, RV dysfunction, or refractory hypoxemia in the ICUs in adult and pediatric patients. In adults, inhaled epoprostenol (30,000 ng/mL) is administered using a syringe pump and jet nebulizer connected to the inspiratory limb of the ventilator[163] (Fig. 104-7). The usual starting dose is 30 ng/kg/min and can be increased up to 50 ng/kg/min. In pediatric patients, drug concentration and air flow is adjusted accordingly.

Limitation: Although a brief exposure to inhaled PGI_2 or its analogues decreases PVR similar to inhaled NO,[165,166] PGI_2 and its analogues are known to cause systemic hypotension when large doses are inhaled.[166] The plasma half-life of epoprostenol is sufficiently long (~6 minutes) to allow for systemic effects, and systemic arterial levels of an active metabolite have been measured during inhalation of even small doses of epoprostenol. Furthermore, epoprostenol must be dissolved in a highly viscous and basic glycine diluent (pH = 10.5) that is associated with tracheitis,[167] interstitial pneumonia,[168] and ventilator valve malfunction.[169] Replacement of the ventilator filter every 2 hours is recommended to avoid possible valve malfunction. Last, although the drug cost associated with inhaled epoprostenol is claimed to be smaller than that of inhaled NO, a robust cost comparison taking into account the impact of prolonged therapy on the overall cost has not been made. For example, if one therapy reduced ICU stay by 1 day or the need for a RV assist device or ECMO perfusion, then the difference in drug cost would be incidental. Further studies appropriately designed to address these issues are needed to better define the role of other *less selective* inhaled pulmonary vasodilators.

CONCLUSIONS

Inhaled NO is the first vasodilator to produce truly selective pulmonary vasodilation. It is characterized by pulmonary vasoselectivity, and it also increases arterial oxygenation and enhances pulmonary $\dot{V}/\dot{Q}$ matching by increasing blood flow to ventilated regions of the lung. A large number of laboratory and clinical research studies have been performed to delineate its biochemistry, physiologic characteristics, side effects, and clinical efficacy in various diseases of children and adults. Nearly simultaneously, the clinical use of inhaled NO has become widespread. An estimated 20,000 patients are treated with inhaled NO annually in the United States. During the past 16 years, inhaled NO has been used to treat pulmonary hypertension and hypoxemia in over 100,000 pediatric and adult patients worldwide. For many, inhaled NO is lifesaving. The experimental use of inhaled NO continues to be a unique and fascinating approach to studying and treating diseases as diverse as acute rejection of the transplanted lung and sickle cell crisis. It is critical that a single study of a particular disease state not influence an evaluation of this complex field. As with most medical advances, the accumulation of a wide-ranging body of clinical research will eventually determine the place of NO inhalation therapy in the therapeutic armamentarium for many diseases.

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Chapter 105

Neurocritical Care

MICHAEL J. SOUTER • ARTHUR M. LAM

Key Points

- Critical care of the nervous system is based on support of cerebral and spinal cord physiology and the prevention of secondary insults. This goal, in turn, depends on the comprehensive maintenance and adequacy of cardiopulmonary, gastrointestinal, renal, and endocrine function.
- Cerebral function is critically dependent on perfusion and oxygenation matching metabolism. Increased intracranial volume beyond the capacity of compensatory mechanism increases intracranial pressure (ICP) and may diminish perfusion adversely. The resulting cellular energy failure both initiates and propagates edema and inflammation.
- The resolution of cerebral edema depends on hydrostatic and osmolar forces applied to the blood-brain barrier. Excesses of perfusion pressure or intravascular hypotonicity worsen edema and must be avoided. Blood-brain barrier disruption varies over time and by pathologic process, and it affects the ability of hypertonic agents to exert an osmotic effect.
- Fever is frequently overlooked in the neurocritical care unit, but it significantly affects patient outcomes across a range of pathologic processes.
- Neurologic monitoring comprises placement of appropriate monitoring devices, as well as prompt response and institution of therapy to changes detected. The goal is to optimize the physiologic environment, despite the current lack of level 1 evidence to support the majority of monitors in common use. Clinical examination of neurologic function remains a crucial part of monitoring and care.
- The incidence of traumatic brain injury has declined, but this disorder remains a disease of the young, with enormous long-term socioeconomic impact. Prompt surgical appraisal is mandatory. Decompressive craniectomy after diffuse injury is not currently recommended. Hypothermia may still offer benefit in refractory intracranial hypertension. Corticosteroids are contraindicated.
- After the initial hemorrhage, mortality and morbidity from subarachnoid hemorrhage (SAH) arise from cerebral ischemia. Medical therapy for this complication involves augmentation of perfusion pressure, maintenance of blood volume, and optimization of oxygen delivery. Endovascular therapy with angioplasty with or without chemical vasodilation plays an important role in treating vasospasm. SAH may be accompanied by significant pulmonary, cardiovascular, or endocrine effects.
- Successful therapy for ischemic stroke is contingent on a time window of viability. Urgent appraisal and rapid treatment are crucial to a good outcome. Endovascular therapy and ultrasound are going to play an increasing role in conjunction with advances in magnetic resonance imaging.
- Injury to the spinal cord necessitates careful observation of respiratory adequacy because conditions may deteriorate before any observed improvement occurs. Fatigue is frequently a factor.
- Infectious disease of the central nervous system demands an aggressive approach to resuscitation, cerebrospinal fluid sampling, and early empiric antibiotic therapy, similar to that for sepsis.

Critical care of the central nervous system (CNS) involves collaboration among several disciplines—neurosurgery, neuroanesthesia, neurology, neuroradiology, and electrophysiology. Each discipline offers unique contributions, which, in partnership, provide optimal care not only to the injured brain but also to the cardiopulmonary, endocrine, gastrointestinal, and renal systems that support cerebral physiology. Integration of the complex goals of this care relies on the physician specializing in neurocritical care, which increasingly is recognized as an important subspecialty.[1]

The use of a neurocritical care team, rather than single specialty care, has been associated with reduced in-hospital mortality and length of stay.[2] Although the brain has a certain preeminence among the organs of the body, it relies on a stable platform of organ function elsewhere to enable homeostatic control and mechanisms of repair and recovery. Injury to the brain is associated with and precipitates a wide spectrum of dysfunction of other organ systems (Box 105-1). Although other specialists can train to be neurointensivists, anesthesiologists with training in neuroanesthesia and critical care are particularly well suited to demonstrate the combination of airway and cardiovascular support skills that, together with an understanding of the physiology and pharmacology of the nervous system, may improve outcome.

BOX 105-1 ***Potential Systemic Complications Associated with Serious Brain Injury***

Global	Pyrexia
	Inflammatory activation
Cardiovascular	Arrhythmia: bradycardia, tachycardia, atrial fibrillation
	Hypertension
	Hypotension
	Left ventricular dysfunction
Respiratory	Apnea
	Pneumonia: aspiration, hypostatic, ventilator associated
	Pulmonary edema
	ARDS
Gastrointestinal	Gastric erosion
	Ileus
	Constipation
	Perforation
	Malabsorption
Renal	Dehydration
	Acute renal failure
	Urinary tract infection
Hematologic	Anemia
	Leukocytosis
	Coagulopathy, disseminated intravascular coagulation
	Deep venous thrombosis, pulmonary embolism
Metabolic or endocrine	Hyponatremia, hypernatremia
	Hyperglycemia, hypoglycemia
	Hypokalemia, hyperkalemia
	Hypomagnesemia
	Hypophosphatemia
	Catabolic azotemia
	Rhabdomyolysis

ARDS, Acute respiratory distress syndrome.

INTRACRANIAL PHYSIOLOGY AND CEREBRAL AUTOREGULATION

The cerebrovascular circulation is constrained by a rigid perimeter of bone (see also Chapter 17). After exhaustion of limited compensatory mechanisms, the bony confines of the skull mandate increasing intracranial pressure (ICP) consequent to increasing intracranial volume. The change in ICP with change in intracranial volume is often referred to as the intracranial compliance curve, but it is more appropriately termed the *intracranial elastance curve* (Fig. 105-1).

Thus, an increase in elastance implies poor compliance, and a small change in volume can lead to an inordinate increase in pressure. These changes in volume arise from increments in intracranial tissue or fluid content (i.e., blood, interstitial fluid, or cerebrospinal fluid [CSF]). Tissue content is relevant insofar as mass lesions reduce intracerebral compliance and accentuate the effects of fluid changes.

Small increases in volume can be accommodated by an outflow of CSF from the cranial cavity into the spinal canal that produces the exponential pressure-volume relationship (see Fig. 105-1).

The cranial vault is compartmentalized by the falx cerebri and tentorium cerebelli, which creates the possibility of internal pressure gradients (Fig. 105-2). This may induce physical protrusion of brain tissue through the "apertures" of the compartments—herniation. Brain tissue may be injured directly but also indirectly by deforming and compressing vasculature adjacent to the dural margin.[3] This is typically seen in severe lateral herniation ("midline shift") when the anterior cerebral vasculature may be obstructed, thus producing frontal lobe infarction.

Pressure gradients are initially hydraulically equilibrated, with CSF moving between ventricular chambers and to the extracranial spinal space. The compensation achieved is limited by the CSF volume available to be displaced; ultimately, changes in volume will induce tissue displacement. This displacement may also contribute to impedance of CSF drainage either by occlusion of the foramina of Monro in the case of lateral herniation or by occlusion of the third ventricle and aqueduct by supratentorial herniation through the tentorial gap. This situation typically gives rise to clinical features of midbrain structure compression. Unilateral papillary dilation, ipsilateral or even contralateral paralysis (the Kernohan notch phenomenon), and abnormalities of respiration are apparent in the spontaneously breathing patient. If the herniation continues, it will result in cerebellar descent through the foramen magnum with consequent compression of the brainstem, thus producing bilateral papillary fixation, either tachycardia or bradycardia, and systemic hypertension.[4] Changes in cerebral mass secondary to increase in venous blood volume also arise from obstruction to

venous drainage by compression of the easily susceptible bridging veins draining from cortex to venous sinuses. Once an individual threshold of compliance is crossed, changes in volume exert a mass effect on the draining veins, which act as Starling resistors. This effect decreases drainage, which, in turn, amplifies and prolongs pressure increases. Blood volume increases may be extravascular (i.e., hemorrhage) or intravascular (i.e., accumulation within a predominantly venous capacitance circulation). Venous circulation comprises approximately 75% of the cranial blood volume, whereas approximately 25% of vessels are arteries, arterioles, and capillaries.

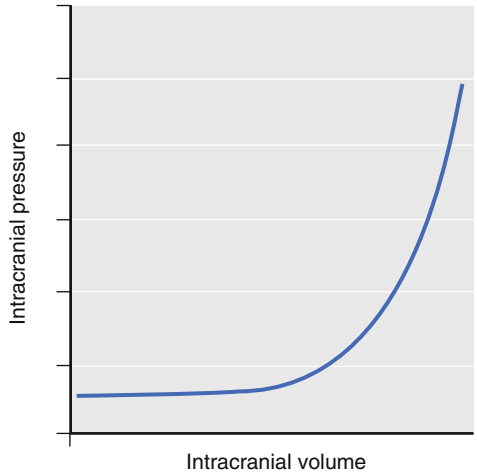


Figure 105-1. Intracranial pressure-volume relationship.

The other main fluid mass effect is through edema, either cytotoxic or vasogenic.[5,6] Cytotoxic edema results from hypoxia, with swelling of the intracellular compartment, whereas vasogenic edema in the interstitium usually develops from a breach of the blood-brain barrier, often in response to high blood pressure.[7]

Thus, changes in the control of cerebral blood volume may have significant effects on ICP. The cerebral vasculature responds to changes in arterial pressure, arterial partial pressure of carbon dioxide ($Paco_2$), or partial pressure of oxygen (PO_2), by dynamically altering arteriolar caliber to maintain a constantly matched cerebral blood flow (CBF) sufficient to meet metabolic demands (Fig. 105-3). The pH, $Paco_2$, potassium, and adenosine are among many purported metabolic mediators of flow.[8]

CBF control may be directly compromised by brain injury or by abnormalities of respiration and arterial blood pressure. In turn, this may increase venous volume by allowing an excessive arterial inflow that venous

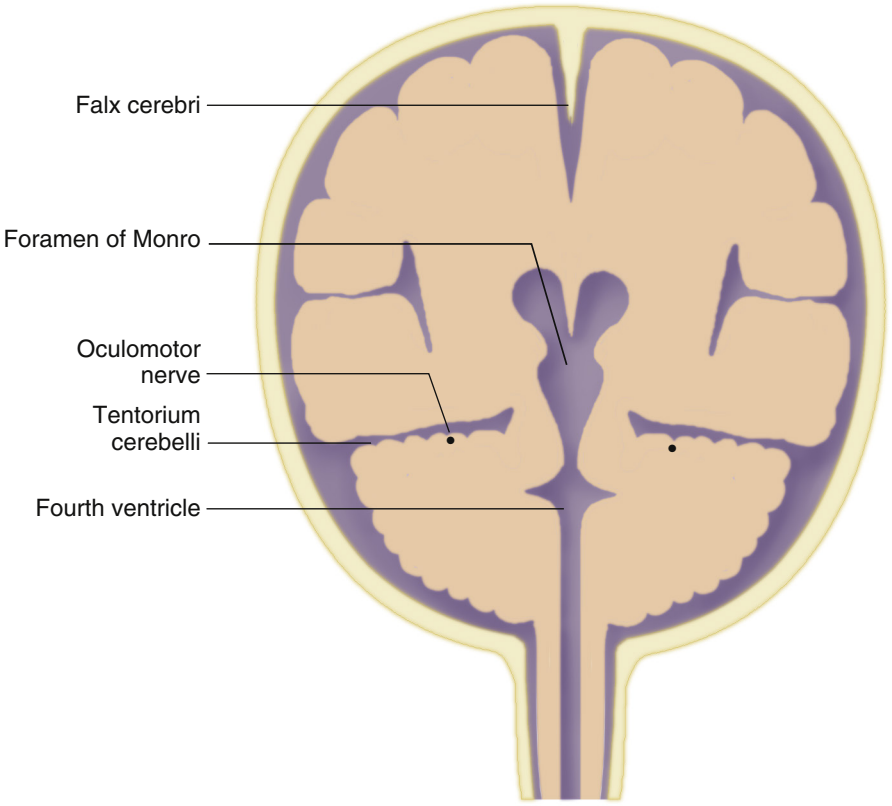


Figure 105-2. Schematic of intracranial compartments: coronal section.

drainage cannot match, thereby increasing ICP. Consequently, untoward events, including hypotension, airway obstruction, fever, and seizures, produce what is termed a *secondary physiologic insult*. This has been demonstrated to induce further harm to the vulnerable brain and, in so doing, worsen outcome.[6,9]

A reduction in substrate delivery (i.e., oxygen and nutrients) to less than the threshold necessary to maintain cellular viability produces cell injury with cytokine and chemokine release. This inflammatory amplification expands the injury,[10] disrupts the blood-brain barrier function, and may directly lead to apoptosis. The disruption of the blood-brain barrier creates vasogenic edema and allows serum proteins to cross into brain parenchyma, with prolonged effects. This process is more evident in the more metabolically active gray matter than in white matter.[5] Most changes peak in the first 48 hours, but one study identified up to 25% of ICP peak increases occurring after day 5.[11]

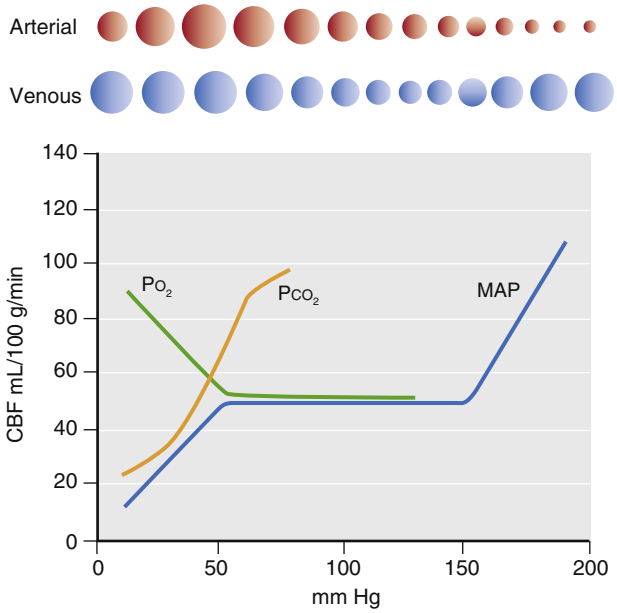


Figure 105-3. The influence of changes in mean arterial pressure (MAP), arterial partial pressure of oxygen (PO_2), and arterial partial pressure of carbon dioxide (P_{CO_2}) upon cerebral blood flow (CBF). Vascular diameter changes shown are in response to MAP.

GENERAL CARDIOPULMONARY CONSIDERATIONS

Any deterioration in ventilatory efficacy may adversely affect cerebral compliance (elastance) through carbon dioxide–induced vasodilation. Concerns have been expressed about the effect of positive end-expiratory pressure (PEEP) in this situation, but the decreased pulmonary compliance necessitating the PEEP also limits intrathoracic pressure transmission to the cerebral circulation.[12] The net benefit of improved ventilatory efficacy from PEEP outweighs any mild disadvantages from its use. However, injudicious use of PEEP in circumstances of hypovolemia may reduce functional venous return and hence reduce cardiac output, with consequent effects on cerebral perfusion.[12]

Reductions in cardiac output and arterial blood pressure can initiate reflex cerebral vasodilation, which is the brain's attempt to preserve CBF. Hypotension is a well-documented source of worsened morbidity,[13,14] whether the decrease in blood pressure results from underresuscitation or iatrogenic mechanisms. This vasodilation increases venous blood volume and further diminishes cerebral perfusion pressure (CPP).[15]

Hypoxemia can cause direct as well as indirect injury to the brain. Hypoxemia less than 60 mm Hg is a significant contributor to secondary insult from vasodilatory ICP effects, in addition to the reduction in the oxygen gradient to the cell. The resultant reduction in cerebral perfusion, irrespective of primary cause, may cause further deterioration by depressing the level of consciousness, in turn leading to airway compromise, hypoventilation, and further decrease in oxygenation (Fig. 105-4). Consequently, pulmonary compromise is often seen in neurologic patients with altered mental status, as a result of impaired airway reflexes and repeated aspiration episodes, culminating in a significant incidence of pneumonia, irrespective of the initiating pathologic process.[16]

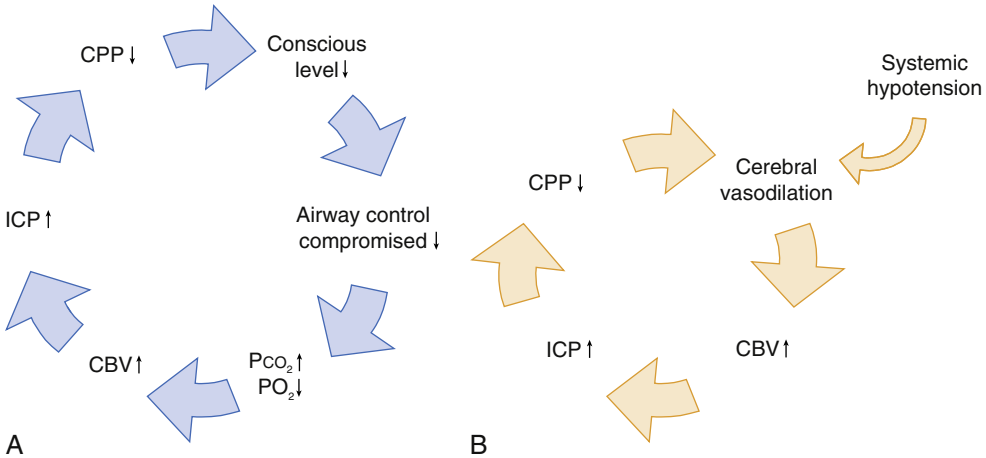


Figure 105-4. A, Ventilatory-neurologic circle of dysfunction. Induced changes in partial pressure of carbon dioxide (P_{CO_2}) and partial pressure of oxygen (PO_2) produce changes in cerebral blood volume (CBV), intracranial pressure (ICP), and cerebral perfusion pressure (CPP). This, in turn, impairs ventilatory control. **B,** Hemodynamic-neurologic circle of dysfunction. Similar to the diagram in **A**, systemic hypotension induces cerebral vasodilation, with increased CBV, increased ICP, and reduced CPP, which, in turn, increases vasodilation.

Another potential mechanism is the release of cytokines from the brain in response to the inflammatory process triggered by an injury; this release may be sufficient to induce acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS).[17,18] Moreover, the large tidal volume ventilation delivered during initial hyperventilation can enhance the development of ARDS[19] (see also Chapters 101 to 103). This may create a therapeutic dilemma in the presence of cerebral pathophysiology. However, the "open lung" concept (i.e., small tidal volumes, high frequencies, and high PEEP) developed to minimize alveolar distention and reduce lung injury appears to be feasible in neurosurgical patients despite theoretic concerns for adverse effects on ICP.[20]

The relationship between $Paco_2$ and CBF can be exploited in examining the response of ventilated patients to tests of spontaneous breathing. Restoring $Paco_2$ to normal may increase ICP, a finding indicating limited craniovascular compliance. Understanding this situation may guide subsequent therapy and ventilatory strategy, and ICP effects should be considered during any weaning process.

FLUIDS AND ELECTROLYTES

Normally, capillary fluid shift is a function of hydrostatic pressure pushing fluid out and the balance of osmotic forces retaining fluid within[21]:

$$Jv = Kf\,([Pc - Pi) - \sigma\,[\pi c - \pi i])$$

where Jv is the net fluid movement between compartments, Pc is the capillary hydrostatic pressure, Pi is the interstitial hydrostatic pressure, πc is the capillary osmotic pressure, πi is the interstitial osmotic pressure, Kf is the filtration coefficient (this is a product of surface area and hydraulic conductivity), and σ is the reflection coefficient (the membrane impermeability toward osmotically active particles). In extracranial capillaries, these osmotic forces derive from oncotic pressure because smaller solutes can cross the capillary basement membrane following concentration gradients and only large protein molecules remain to exert effect.

However, in the brain, because of the presence of tight junctions in the endothelium, this intact blood-brain barrier reflects smaller solutes (e.g., sodium and chloride ions), and this relative impermeability renders cerebral capillary fluid shift a function of hydrostatic and *total* osmolar forces, with the oncotic pressure playing a very small part and the fluid shift most dependent on the osmolar gradient. In the absence of externally administered osmotically active substances (e.g., mannitol), this gradient is largely determined by sodium concentration, as serum osmolality.

$$\text{Serum osmolality} = (\text{serum Na}) \times 2 + \text{glucose}/18 + \text{BUN}/2.8$$

where Na is sodium and BUN is blood urea nitrogen.

Thus, in general, hypotonic solutions should not be used in the neurosurgical patient when edema is a significant consideration. The osmolalities of commonly used solutions are listed in Table 105-1.

At the same time, the tighter endothelial connections and lipid bilayers also serve to reduce water permeability and hence the filtration coefficient. This physiologically limits the water shift across the vascular bed in response to changes in tonicity; otherwise, the brain volume would be significantly reduced by the large osmotic forces created by changes of only a few milliosmoles per kilogram. Net fluid shift across the blood-brain barrier therefore depends on water permeability, as defined by the filtration coefficient, and solute permeability, as defined by the reflection coefficient. This process permits osmotic diuresis, in which substances reflected by the blood-brain barrier can exert a significant effect on brain water (e.g., mannitol and hypertonic saline).

Inadequate perfusion and supply of substrate, whether relative or absolute, induces energy failure. This process translates into real effects on the integrity and function of the blood-brain barrier, which is an energy-dependent physiologic construct, as opposed to a purely anatomic structure. Ischemia and rapid reperfusion are associated with the generation of matrix metalloproteinases that directly attack the proteins sealing the connections between the endothelial processes that make up the blood-brain barrier.[22] This condition creates a loss of integrity and increased porosity of the blood-brain barrier that pathologically affect the permeability and reflection coefficients. This acute blood-brain barrier disruption may allow solute shifts into the parenchyma and result in brain swelling, the extent of which depends on the "leakiness" of the blood-brain barrier, as well as the size and concentration of the osmotically active molecules on either side of the barrier.

Hence, intravascular fluid therapy must be carefully considered under circumstances of cerebral ischemia and inflammation. The brain exerts homeostatic control on metabolic and endocrine activity, and neurologic dysfunction can manifest as untoward changes in fluid and electrolyte balance. Diabetes insipidus is a florid example of this, with polyuria, subsequent hypovolemia, and, if the disorder is left untreated, systemic hypotension. Iatrogenic causes may also include the use of osmotic diuretics, sedation, and analgesics. Sympathetic denervation as

TABLE 105-1 SODIUM CONTENT, OSMOLALITY, AND ONCOTIC PRESSURE OF COMMONLY USED INTRAVENOUS FLUIDS

Fluid	Osmolality (mOsm/kg)	Oncotic Pressure (mm Hg)	Na^+ (mEq/L)
Plasma	289	21	141
Crystalloid			
0.9% NS	308	0	154
0.45% NS	154	0	77
3% NS	1,030	0	515
Lactated Ringer's	273	0	130
Plasma-Lyte	295	0	140
Mannitol (20%)	1,098	0	0
Colloid			
Hetastarch (6%)	310	31	154
Albumin (5%)	290	19	

Na^+, Sodium; *NS*, normal saline.

a consequence of brainstem or spinal cord injury may also contribute to reductions in venous return as a result of increased vasodilatation and peripheral venous pooling.[23]

The increased sympathetic discharge commonly accompanying cerebral insults can also manifest as extracerebral stress on the entire body with increased incidence of gastric stress erosion, hypercatabolism, hyperglycemia, and impaired glucose tolerance.[24]

Nutrition requirements are often increased after brain injury, and evidence suggests improved outcome with the early use of enteral nutrition (see Chapter 106).[25]

Hyperglycemia is a potent aggravator of cerebral insult.[26] However, tight glycemic control with aggressive insulin therapy worsens the outcome of critical care patients in general and may worsen cerebral metabolic stress (see also Chapter 39).[27,28] Moderate glycemic control is advocated.

FEVER AND INFECTION

More than 50% of patients in neurologic intensive care units (ICUs) develop fever.[29] This condition is an often overlooked insult to the compromised brain, thus increasing oxygen utilization and metabolic stress.[29] Patients within the ICU have multiple risk factors for infection and sepsis, including the presence of a variety of indwelling catheters (e.g., arterial, venous, CSF). Other potential causes of fever include intracranial hemorrhage and idiosyncratic drug effects (e.g., the anticonvulsant phenytoin).[29,30] Fever is associated with a worsened outcome after neurologic injury, including intracranial hemorrhage, subarachnoid hemorrhage (SAH), and stroke. A meta-analysis of available studies demonstrated an increase in neurologic morbidity and mortality associated with fever.[31]

Although hypothermia has not proven to be a successful intervention for patients with traumatic brain injury (TBI)[32] or SAH,[33] this finding does not equate to a lack of beneficial effect of normothermia compared with hyperthermia, and many clinicians are increasingly aggressive in preventing and treating fever.[34]

To provide appropriate treatment for fever, it is necessary to perform daily reappraisal to delineate the source of fever, given the large number of potential causes. However, in many cases a cause cannot be determined, and empiric treatment including scheduled administration of acetaminophen, application of cooling blankets, and, increasingly, more invasive methods of cooling are required.

MONITORING

The avoidance or correction of secondary physiologic insults necessitates the aggressive use of physiologic monitors (see Chapter 49 and Fig. 105-5). This monitoring does not obviate the need for regular clinical examination

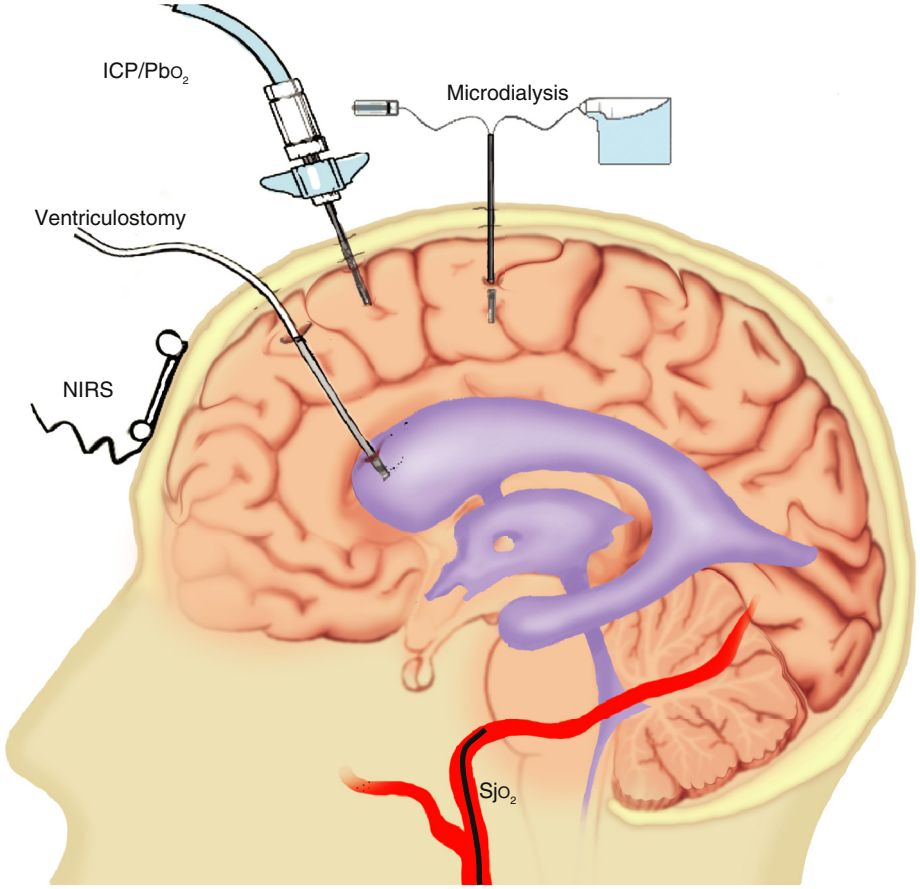


Figure 105-5. Schematic of available intracranial monitoring, with near-infrared oximetry (NIRS), intracranial pressure (ICP, either by ventriculostomy or parenchymal probe), brain tissue oximetry (Pbo_2), microdialysis, and jugular venous oximetry (Sjo_2).

of the CNS, with observation of the response to stimuli. Monitors (e.g., processed electrical activity, cerebral oxygenation, and ICP) are merely surrogates of actual cerebral function. Similarly, attention should be paid to the basics of fluid volume status, respiratory rate, cardiovascular stability, and metabolic consumption.

INTRACRANIAL PRESSURE

ICP monitoring quickly became a standard of care after its introduction to clinical use in the 1970s, thereby making subsequent determinations of utility and effectiveness difficult. Nevertheless, a NIH sponsored randomized controlled trial has been performed in Latin America, demonstrating no overt benefit of ICP monitoring.[36] Noninvasive monitors have not established sufficient reliability and remain the subject of research. While recent data suggests that ICP monitoring has minimal effect on outcome,[35] monitoring must guide therapy to be effective and ICP data should remain as one of the components influencing but not replacing clinical appraisal. Most neurosurgical centers still insert such devices routinely in the management of patients with TBI and SAH, by using defined thresholds (e.g., ICP > 25 mm Hg) to trigger treatment interventions, including osmotic agents (e.g., mannitol or hypertonic saline) or operative treatments (e.g., decompressive craniotomy or CSF drainage).

ICP sensors may represent only the compartment pressure where they were placed (see Fig. 105-2), and they may not be sensitive to acute transients in pressure on the other side of the falx or tentorium.[37] Intraparenchymal fiberoptic devices are less invasive and easier to place, but they may be calibrated only ex vivo and cannot drain CSF. Thus, provided the ventricles are accessible, ventricular catheters remain the "gold standard" of measurement, albeit at the expense of an increased risk of infection of approximately 6%.[38]

When the ventricles are small, this monitoring becomes technically difficult, and the risks of hemorrhage and contusion are increased.

ICP devices can be quickly placed with a minimum of morbidity in experienced hands and, provided suitable attention is paid to the issue of potential drift from calibration,[39] generally offer useful insights to guide therapeutic interventions. However, placement of these devices is contraindicated in the presence of coagulopathy or platelet dysfunction.

Observation of ICP monitoring trends reveals characteristic patterns that may have prognostic implications (e.g., the Lundberg "A" or "plateau" ICP wave indicating critical cerebral compliance[40] and impending herniation).

CEREBRAL BLOOD FLOW

Important threshold values for function were identified by Symon and others (Table 105-2).[41] The initial methods of quantitative CBF measurements were laborious and time consuming and did not offer accurate regional estimates.[42] These methods were replaced by the use of isotopic tracers that allow basic regional flow measurement (e.g., inhaled or intravascular xenon-133) or a combination of imaging and qualitative assessment (i.e., single photon emission computed tomography [SPECT]). Calibrated imaging techniques such as positron emission tomography (PET) and stable xenon or contrast computed tomography (CT) perfusion[42] have become standard in many centers. Magnetic resonance imaging (MRI) of perfusion is rapidly evolving and may provide quantitative flow measurement in the near future.

TABLE 105-2 **FUNCTIONAL THRESHOLDS OF CEREBRAL BLOOD FLOW**

CBF (mL/100 g/min)	Result
50	Normal
20	EEG slowing
15	Isoelectric EEG
6-15	Ischemic penumbra
<6	Neuronal death

CBF, Cerebral blood flow; *EEG,* electroencephalogram.

Although providing potentially useful information on regional perfusion, these methods often involve transporting the patient outside the ICU, a maneuver that may be clinically inappropriate in unstable circumstances.

Thermodilution is a focal technique in which small thermocouples are placed cortically. Blood flow is related to temperature diffusion at the probe.[43] An alternative approach has been to use jugular venous temperature diffusion to assess flow. Whether this measure reflects CBF reproducibly may depend on the ratio of jugular venous drainage to overall cerebral venous flow.[44] It remains to be seen whether these devices can be developed into reliable and consistent monitoring tools.

TRANSCRANIAL DOPPLER MONITORING

Transcranial Doppler monitoring uses the Doppler shift effect to assess flow velocity in insonated arteries (see also Chapter 49).[45] This method is often used as a surrogate of flow for examining accessible vessels and, in skilled hands, offers considerable insights into dynamic flow. This technique has the advantage of being a bedside, relatively speedy, and noninvasive monitor of flow within the main components of the circle of Willis through the ophthalmic, temporal, and foramen magnum acoustic windows. It has excellent temporal resolution and, being noninvasive, allows repetitive measurements with little or no risk. In a small proportion of patients, predominantly older women and black patients, temporal bone thickness may prevent monitoring.[46] Extrapolation of velocity to flow relies on an assumption of relatively constant diameter of the large conductance vessels. Under different circumstances, changes in velocity can be used to assess alterations of vascular caliber (e.g., arterial vasospasm after SAH)[47] or intracranial stenosis (Fig. 105-6). For the middle cerebral artery, vasospasm can be distinguished from hyperemia by examining the ratio between the intracranial flow velocity and the extracranial carotid artery flow velocity (the Lindegaard index). A ratio greater than 3 is generally indicative of vasospasm, whereas a ratio less than 3 is consistent with hyperemia.[48] A similar ratio has been developed for the posterior circulation by comparing the flow velocity in the basilar artery with that of the extracranial vertebral artery. A value greater

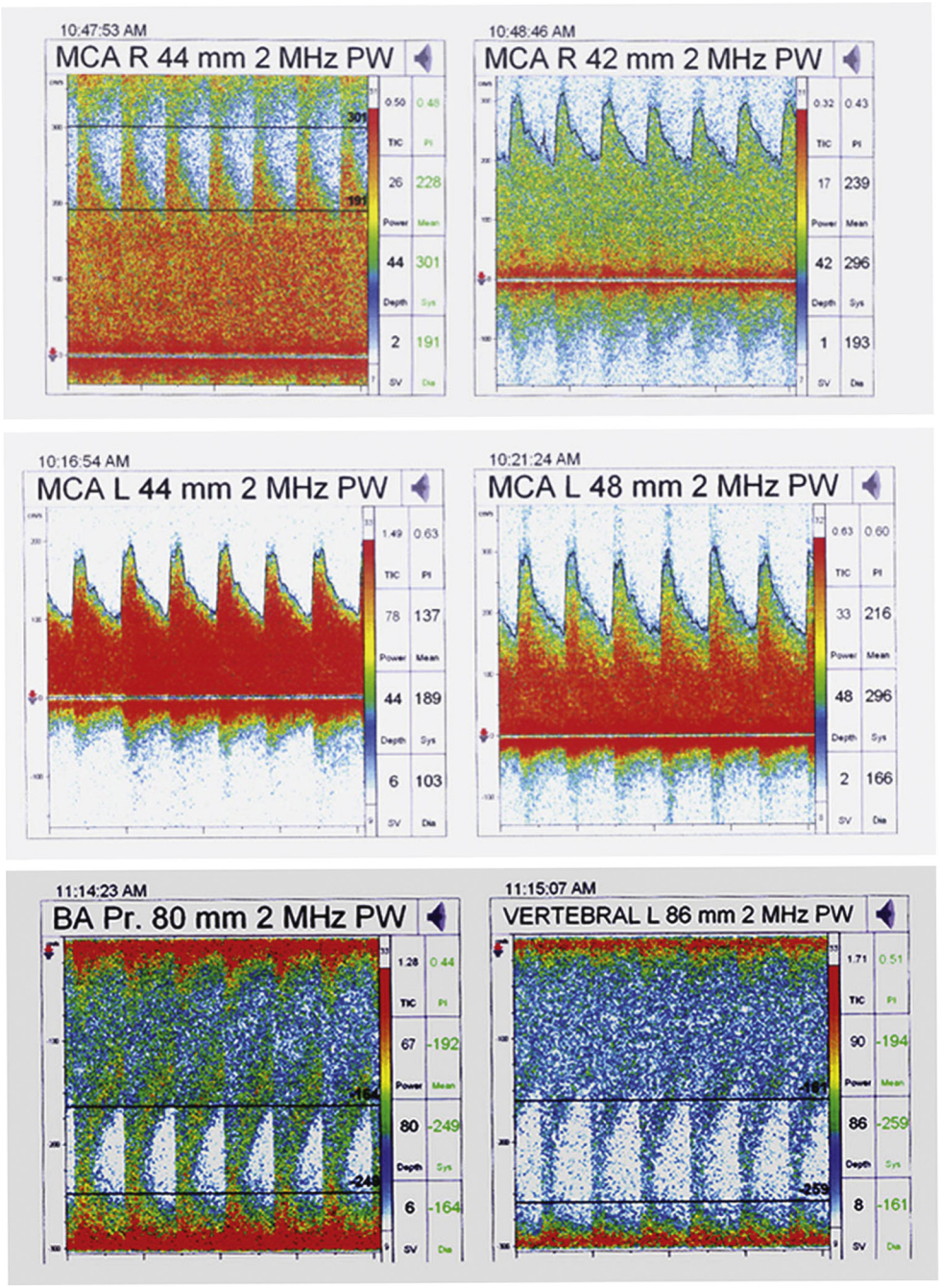


Figure 105-6. Transcranial Doppler images of elevated cerebral blood flow velocities in the middle cerebral and vertebrobasilar vessels.

than 2 with an elevated flow velocity in the basilar artery is reportedly consistent with vasospasm,[49] although this finding has been questioned by concurrent angiographic comparisons.[50]

AUTOREGULATION AND VASOMOTOR REACTIVITY

Monitors of CBF can assess the response of the cerebral vasculature to changing circumstances of metabolism and blood pressure (i.e., autoregulation).[51,52] Static cerebral autoregulation can be determined with sustained manipulation of blood pressure by using either a tilt test or a direct vasopressor as clinically appropriate, whereas dynamic autoregulation can be assessed using rapid deflation of previously inflated thigh cuffs above systolic blood pressure. Alternatively, autoregulation can be assessed by monitoring CBF velocity through transcranial Doppler in response to spontaneous fluctuation of blood pressure by using transfer function analysis, although these techniques are likely to be less reliable than the stimulus-response paradigm.[53] The presence or lack of autoregulation may guide subsequent treatment and prognosis because frequently the loss of autoregulation is associated with a poor outcome.[54,55] Cerebrovascular reserve or vasomotor reactivity, as determined by CBF response to changes in $Paco_2$, can be assessed either with rebreathing or addition of carbon

dioxide to the breathing circuit or with administration of acetazolamide.[53]

JUGULAR BULB OXIMETRY

The Fick principle may be reversed to examine the venous oxygen saturation which, assuming a constant hematocrit and metabolism, can offer an assessment of the adequacy of CBF and associated oxygen delivery relative to cerebral oxygen consumption:

$$\text{If } AVDo_2 = (CMRo_2/CBF), \text{ then } Cao_2 - Cjvo_2 = (CMRo_2/CBF)$$

Ignoring the contribution of dissolved oxygen, then:

$$(Sao_2 - Sjvo_2) \times Hgb \times 1.34 = (CMRo_2/CBF)$$

where $AVDo_2$ is the arteriovenous oxygen content difference; $CMRo_2$ is the cerebral oxygen metabolic rate; Cao_2, $Cjvo_2$, Sao_2, and $Sjvo_2$ are the arterial oxygen and jugular venous oxygen contents and saturations, respectively; Hgb is the hemoglobin concentration; and 1.34 is the oxygen affinity constant.

In vivo, catheters are placed in retrograde fashion through the internal jugular vein to its jugular bulb at the foramen or even beyond, to the large sinuses (Fig. 105-7).[56,57]

These catheters provide information related to both perfusion and oxygen consumption, in a manner analogous to the use of mixed venous oximetry for shock management. Both desaturation (<50%, suggesting inadequate delivery or excess consumption) and abnormally high saturation (>75%, suggesting hyperemia or stroke) have been associated with poor outcome.[58,59] The derivable arteriovenous oxygen content difference is possibly a more accurate assessment of the adequacy of flow and is related to outcome.[60] Jugular venous oximetry has been criticized as being insensitive to focal changes because it reflects the averaged global cerebral venous oxygen saturation from the confluence of hemispheric venous drainage. Consequently, some authors have suggested using oxygen consumption in combination with the cerebral arteriovenous gradient of lactate to make stoichiometric assessments of aerobic versus anaerobic metabolism.[61] These authors use metabolically directed management strategies, as opposed to management of cerebral hemodynamics,[62] that is, goal-directed therapy based on metabolic indices (jugular venous oxygen saturation), rather than on hemodynamic indices (ICP and CPP).

BRAIN TISSUE OXYGEN TENSION

In conceptually similar assessments of in vivo oxygenation, miniaturized Clark electrodes have been developed and combined with ICP catheters to provide simultaneous estimations of tissue oxygen tension and ICP. Pathologic levels are thought to be lower than 15 mm Hg with normal values in the 20- to 45-mm Hg range.[63] These brain tissue O_2 tension (Pbo_2) devices have been used in a variety of pathologic conditions, thus guiding therapy and providing insight into the adequacy of cerebral perfusion,[63] although Pbo_2 may alert to poor outcomes independent of CPP.[64] However, many concerns remain regarding measurement errors, calibration drifts, and uncertainty of the generalizability of the local measurement.[65] Nevertheless, in patients without focal lesions, important physiologic feedback is provided in response to therapeutic manipulations of arterial blood pressure and oxygenation.[66] The hope is that these questions will be addressed by ongoing clinical trials of Pbo_2-guided treatment protocols.[67]

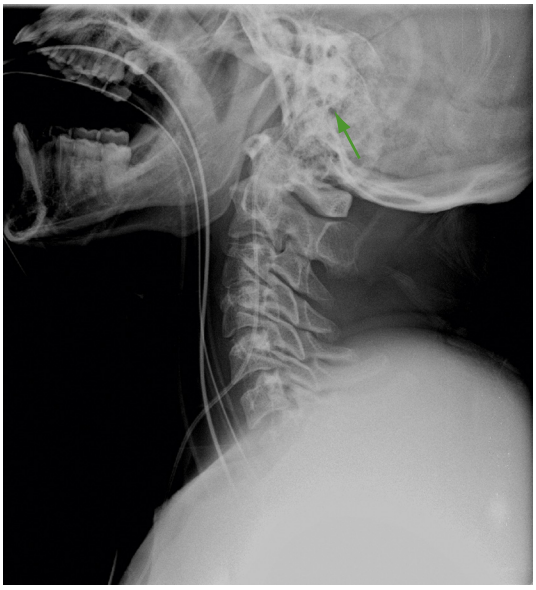


Figure 105-7. Lateral cervical spine radiograph showing appropriate positioning of the jugular venous oximetry (Sjo_2) catheter above the lower border of the C1 vertebra (the *arrow tip* is actually within the jugular foramen).

CEREBRAL MICRODIALYSIS

Interest in the use of cerebral microdialysis probes to assess the biochemical milieu of the brain is significant. These probes are placed through a burr hole and cycle small volumes of dialysate through the catheter to an extracranial collection system. Consequently, various substances can diffuse across the semipermeable membrane (e.g., lactate. pyruvate, glucose, glycerol, glutamate),[68] for collection and subsequent analysis using a bedside high-pressure liquid chromatography device. This device gives graphic and numeric displays of trended concentrations for the preceding collection interval (usually 1 hour). This information then relates to the in vivo biochemistry of the brain. Although this technique is intuitively attractive, unresolved questions have hampered its wider implementation, not the least of which is the question of the optimal site of placement, in relation both to disease and to anatomic region of gray matter versus white matter.[68]

These issues were addressed by a consensus statement on placement of microdialysis catheters, with the aims of improving accuracy in the comparison of results and allowing generalization from accumulated experience.[69] Improvements in membrane technology now permit larger molecules to cross into dialysate, thus creating the possibility of research into microvascular peptidomics.[68]

ELECTROENCEPHALOGRAPHY

The electroencephalogram (EEG) records electrical activity generated and detected by appropriately placed electrodes in a radial and axial array, as defined by the 10/20 system, an internationally standardized system of recording (see also Chapter 49). The consequent waveforms are displayed and recorded. The spectrum of component frequencies, together with amplitude and power, can be quantified and analyzed in a variety of fashions by what are termed *processed EEG monitors*. These devices can provide important diagnostic information in patients in the neurocritical care unit who cannot be otherwise assessed. The EEG tends to be used in a diagnostic snapshot mode for isolated assessments, and it is underused as a continuous monitor within the ICU. This underuse is a function of the difficulty involved in its application and interpretation, which necessitate dedicated equipment and personnel. A 24-hour continuous recording of EEG is, in general, more fruitful than a snapshot recording.

Moreover, both in TBI and in SAH, significant numbers of patients develop nonconvulsive status epilepticus,[70,71] a condition that constitutes a regularly overlooked but significant source of morbidity and stress on the brain. Whereas the EEG is a difficult monitor to use, definite indications exist for its deployment, and the neurocritical care physician should be familiar with the basic principles of its function and use.

Some related devices have also been developed from processed EEG to monitor the depth of anesthesia. Although these devices have been used to monitor the level of sedation in critically ill patients, they are not designed for—and should not be used to—monitor neurologic integrity or seizure activity.

NEAR-INFRARED SPECTROSCOPY

The idea of pulse oximetry for the brain, as conceptualized in the early 1990s, is attractive. It relies on the principle of reflectance spectroscopy, in which near-infrared light traverses bone transparently, to be scattered and reflected to a degree inversely proportional to the concentration of light-absorbing materials in tissue (e.g., hemoglobin and other tissue chromophores). The surface detector is constructed and calibrated to detect light that has ostensibly traversed down to cerebral cortex and back. An adjacent detector is positioned to detect a signal from superficial tissues, and both signals are then used in an algorithm to derive an estimated tissue saturation. However, the devices employed have been troubled by issues of reliability, specificity, and cross contamination from other cytochrome-containing tissues.[72,73] Slightly more enthusiasm exists for their role as trend monitors of flow, especially in children and patients with extracranial carotid artery disease.[74,75]

RADIOLOGIC IMAGING

Imaging can be employed as a monitoring technique, albeit on a protracted time scale.[76] The two major modalities are CT and MRI. CT is by far the most useful and commonly used technique because it is the most efficient method. MRI, although more time consuming, is more sensitive for brainstem lesions, as well as for axonal injuries. Both CT and MRI can provide information on the vascular tree, but conventional contrast angiography remains the gold standard. Assessment of intracranial masses, diffuse injury, or hemorrhage can be subsequently used to guide therapy, triage, and prognosis.[77]

To provide meaningful comparison of therapeutic modalities in clinical trials, it is important to standardize and categorize CT images. The Marshall scale has been used in TBI to stratify degrees of hemorrhage and contusion within the cranial vault, and it correlates with outcome (Table 105-3).[78,79] The Fisher scale assesses the volume of subarachnoid blood after a diagnosis of SAH.[80] There again, it has strong relationship with outcome regarding the development of vasospasm (Box 105-2A),[81] the correlation of which was further improved by the modified Fisher scale (Box 105-2B). [82] These scales rely on experienced interpretation for accuracy. Inconsistent application of the Marshall scale has been reported, a finding suggesting an urgent continued need for standardization.[83]

A more recent and exciting development in CT scanning is the capacity to estimate specific gravity of tissue (eSG), thus delivering insight into cerebral edema and tissue swelling. Such measurements taken from the first CT scan (average 4 hours from injury) have performed well as predictors of outcome at 6 months, and they also correlate with ICU length of stay and time spent ventilated.

TABLE 105-3 MARSHALL SCALE: COMPUTED TOMOGRAPHY CATEGORIES FOR HEAD INJURY

Category	Definition
Diffuse injury I	No visible intracranial pathologic process
Diffuse injury II	Cisterns are present with midline shift of 0-5 mm and/or lesion densities present; no high- or mixed-density lesions at >25 mL
Diffuse injury III	Cisterns compressed or absent, with midline shift of 0-5 mm; no high- or mixed-density lesions of >25 mL
Diffuse injury IV	Midline shift of >5 mm; no high- or mixed-density lesion of >25 mL
Evacuated mass lesion (V)	Any lesion surgically evacuated
Nonevacuated mass lesion (VI)	High- or mixed-density lesion of >25 mL; not surgically evacuated

BOX 105-2A ***Fisher Scale (Computed Tomography Scan Appearance)***

Grade 1	No blood detected
Grade 2	Diffuse deposition of subarachnoid blood, no clots, and no layers of blood >1 mm
Grade 3	Localized clots and/or vertical layers of blood ≥1 mm in thickness
Grade 4	Diffuse or no subarachnoid blood, but intracerebral or intraventricular clots present

The relative objectivity and quantitative nature of this method may offer advantages over other scoring systems.[84]

CLINICAL EXAMINATION

Comprehensive neurocritical care encompasses the ability to perform a competent neurologic examination. Reproducible and objective assessment of neurologic function is as important a monitor as some of the sophisticated technology mentioned earlier, with the advantage that it offers better insight into global function of the nervous system and allows integration of information in an inherently complex dynamic system. One of the most basic yet important examinations is the pupillary light reflex, the unilateral absence of which may indicate midbrain compression from uncal herniation and neurologic emergency. Bilaterally absent papillary reflexes signify imminent or established cerebellar herniation, but this may be reversible with rapid efficacious treatment.

Clinical scales have been devised for common neurologic settings. The Glasgow Coma Scale (GCS) is a well-known, universally if inconstantly applied scale (Table 105-4). It relies on independent assessment of eye opening, speech, and best motor movement in response to progressive trials of command, voice, and noxious stimuli.[85] The Hunt and Hess scale (Table 105-5), when applied to patients with SAH, offers classification and prognostication of mortality.[86] The World Federation of Neurologic Surgeons (WFNS) scale is the preferable rating because it uses the more prevalent GCS but with a modifying component of focal deficit (Box 105-3).[87] Knowing and using these scales are crucial to understanding the terminology and practice of neurocritical care.

BOX 105-2B *Modified Fisher Scale (Computed Tomography Scan Appearance)*

Grade 0	No blood detected
Grade 1	Thin* subarachnoid blood, no intraventricular hemorrhage
Grade 2	Thin subarachnoid blood, with intraventricular hemorrhage
Grade 3	Thick subarachnoid blood, no intraventricular hemorrhage
Grade 4	Thick subarachnoid blood, with intraventricular hemorrhage

*Vertical thickness of 1 mm separates thin from thick subarachnoid hemorrhage.

MULTIMODALITY MONITORING

No single monitor credibly and reliably offers insight into the functioning physiology of the brain. Instead, various surrogates of function are offered. Many criticisms can be directed at each individually, but an interesting concept is that of multimodality monitoring, which uses a combination of parameters to improve on accuracy of diagnosis and guidance to management.[88] Although it is an attractive concept, the precise implementation of this idea is still in its early days, with little methodologic standardization; this standardization may be facilitated by rapidly approaching commercial development.

COMMON DISEASES IN THE NEUROCRITICAL CARE UNIT

HEAD INJURY

The treatment of TBI was one of the initial emphases of neurocritical care (see also Chapter 81). Changes in road traffic legislation and enhancements in passenger protection have led to a decline in the incidence of TBI in the United States, to the degree that motor vehicle accidents have been replaced by falls as the chief cause of injury.[89] These causes, together with assaults and off-road and sporting injuries, still contribute to what is referred to as a silent epidemic,[89] accentuated by ongoing military conflicts and their hallmark blast injuries,[90] as well as a prevalence consequent on concentration in a predominantly youthful population. Outside of wartime, these causes usually share a common factor in the contribution from alcohol consumption.[91,92]

In all circumstances, brain structure is deformed by the transmission of kinetic energy. The distribution of this damage covers a wide spectrum from localized contusion to diffusely scattered foci, varying with the circumstances of the incident and the architecture of the victim's brain. Typically, cerebral contusions are located at the bony prominences of the skull, at the sphenoid wing and petrous ridge.[93] This variability in inflicted

TABLE 105-4 **GLASGOW COMA SCALE**

	6	5	4	3	2	1
Eyes	N/A	N/A	Opens eyes spontaneously	Opens eyes in response to voice	Opens eyes in response to noxious stimuli	Does not open eyes
Verbal	N/A	Is oriented, converses normally	Is confused, disoriented	Utters inappropriate words	Makes incomprehensible sounds	Makes no sounds
Motor	Obeys commands	Localizes to noxious stimuli	Has flexion to noxious stimuli	Has abnormal flexion to noxious stimuli	Extends to noxious stimuli	Makes no movements

N/A, Not applicable.

TABLE 105-5 HUNT AND HESS GRADING SYSTEM

Grade	Clinical Presentation	Survival (%) (approximate)
Grade 1	Asymptomatic or mild headache	70
Grade 2	Moderate to severe headache, nuchal rigidity, and no neurologic deficit other than possible cranial nerve palsy	60
Grade 3	Mild alteration in mental status (confusion, lethargy), mild focal neurologic deficit	50
Grade 4	Stupor and/or hemiparesis	20
Grade 5	Comatose and/or decerebrate rigidity	10

BOX 105-3 ***World Federation of Neurologic Surgeons Scale***

Grade 1	GCS score of 15, motor deficit absent
Grade 2	GCS score of 13-14, motor deficit absent
Grade 3	GCS score of 13-14, motor deficit present
Grade 4	GCS score of 7-12, motor deficit absent or present
Grade 5	GCS score of 3-6, motor deficit absent or present

GCS, Glasgow Coma Scale.

pathologic features introduces significant heterogeneity in presentation and behavior, and it confounds some broader assumptions on time course and care. A patient with a temporal lobe injury may behave very differently from a patient with a posterior fossa lesion.

TBI may also be classified according to whether it is blunt or penetrating. Penetrating injury may again have widely varying consequences depending on site, depth, and energy, but is generally fatal if it bilaterally traverses the midbrain.[94] Although initial mortality from penetrating injury is higher, outcome in survivors is similar to that for nonpenetrating injury.[95]

Vascular injury may affect more superficial arterial blood vessels, as seen in the middle meningeal artery injury typical of pterional fracture. This injury commonly results in an extradural hematoma.[96] These rapidly expanding collections can result in swift neurologic deterioration and devastating results, if not treated quickly. The mortality is between 15% and 20%.[97] Alternatively, cortical bridging veins between cortex and the dural venous sinuses are often torn by rotational or acceleration-deceleration forces to produce an accumulating subdural hematoma. This may manifest slowly and may even be unaccompanied by signs of external trauma. In the time taken for the venous hematoma to develop, symptoms may be subtle and, unfortunately, may be disregarded. The slow expansion exerts a cumulatively damaging effect, which by the time severe signs eventually manifest may be just as or even more destructive than a rapidly expansile lesion.[98] This injury is prevalent in older patients, in whom the process of senile cerebral atrophy results in greater tension on the bridging veins crossing an increasing distance, thus rendering these vessels all the more susceptible to rupture.

In all these scenarios, the primary pathologic process is accentuated by secondary features of elevated ICP, diminution of arterial inflow, and consequent reduction in CPP, with resulting tissue hypoxia and cell death, as previously described in discussion of the intracranial pressure-volume relationship (see Fig. 105-1).

This process can also be modified adversely by loss of autoregulation, which may result in further increases in ICP. This condition is often seen in diffuse injury, in which although individual foci may be small, they additively combine to produce a total burden of inflammatory change sufficient to overwhelm autoregulation.[99]

Traumatic SAH (tSAH) is seen in up to 60% of admissions for TBI.[100] Some variability of detection and reporting exists, but despite this, tSAH has a substantial effect on outcome.[101] Prolongation of the QTc interval is seen in 67% of patients with tSAH, and QTc prolongation is seemingly proportional to severity.[102] Approximately 20% of patients with tSAH may also develop vasospasm, which can lead to secondary ischemic insult. The diagnosis and management of the vasospasm are facilitated by the use of transcranial Doppler monitoring. Vasospasm is also being recognized as a feature in the pathologic process of blast injury.[90]

Management of TBI in the ICU should include comprehensive examination and assessment using such principles as outlined in Advanced Trauma and Life Support (ATLS) because occult injuries can escape initial screening yet subsequently exert a delayed physiologic compromise on the arrival of the patient in the ICU, or worse, in the CT scanner. These injuries may accentuate the primary brain injury by contributing to secondary physiologic insult.[14]

Overall, the common goal of treatment of TBI is to maintain cerebral perfusion. In patients with mass lesions resulting in anatomic distortion with mass effect, surgical removal of lesions is indicated. Early decompressive craniectomy for patients with diffuse injury has not proven useful and may have worsened outcome,[103] although results of a larger trial are awaited. Medical management may be required both before and after surgical intervention or as an alternative in circumstances of diffuse injury. Such treatment strategies within the ICU revolve around the reduction of ICP and the maintenance of cerebral perfusion, which may not be compatible goals. Although therapeutic resolution of ICP with osmotic diuresis is a logical approach, it may have unintended consequences on central vascular volume and myocardial function.[104] After an initially beneficial effect in reducing intracerebral volume, mannitol then leaves the vasculature through the kidney. This process also reduces cardiovascular volume, thus diminishing cardiac output and arterial blood pressure and possibly replacing one physiologic insult for another.

Mannitol has diminished in popularity, to be supplanted by hypertonic saline.[105] This solution demonstrates a good resuscitation profile, with none of the delayed hypotension observed with mannitol.[106] Some of

the same concerns with the use of mannitol also apply to the use of hypertonic saline (i.e., diffusion of osmotically active particles into the brain interstitium in circumstances of injury or compromise of the blood-brain barrier).[107] This approach may create rebound effects on reduction of plasma osmolarity as hypertonic saline administration is reduced, with an increase in brain water. This finding has been observed with differential effects in contused versus noncontused brain.[108] Although bolus usage of hypertonic saline has been shown to be useful, it remains to be seen whether sustained infusions or the practice of persistent-induced hypernatremia offer any improvement in outcome.

Although the choice of resuscitation fluid does not have any effect in a large study of trauma victims,[109] a post hoc analysis of subgroup data demonstrated increased mortality associated with the use of albumin in TBI.[110] This finding is somewhat at odds with the demonstration of potential benefit in stroke,[111] and a prospective trial is needed.

Control of the vascular blood volume may also be regulated by manipulation of the partial pressure of carbon dioxide (Pco_2), which most frequently requires intubation of the trachea and mechanical ventilation.

Controlled hyperventilation is frequently practiced to reduce blood volume and hence ICP.[112] Studies have demonstrated adverse consequences of aggressive hyperventilation, and most authorities agree on limiting the reduction in Pco_2 to avoid ischemia.[113]

The Brain Trauma Foundation publishes guidelines on the management of brain trauma, which are regularly updated. These guidelines concentrate on the principles outlined previously, namely, reduction of ICP while preserving perfusion pressure.[114] They also provide statements of consensus on the merits of these strategies. They recommend a target Pco_2 of between 30 and 35 mm Hg,[108] with a CPP of 60 to 70 mm Hg. Higher CPP values have no benefit and may worsen outcome.[115,116]

Hypertension in excess of autoregulatory control can induce both excess blood volume and the formation of vasogenic edema across a compromised blood-brain barrier.[7] This concept underpins the Lund group protocol, which gives priority to limiting the Starling forces across the capillary bed to avoid the formation of edema.[117] These investigators recommend a CPP of 50 mm Hg using β-blockers as required, the reduction of metabolic demand with barbiturates, and intravenous colloid administration.[118]

Any evidence of comparative effectiveness was restricted to case series, offering outcomes similar to those with CPP-oriented management.[119] However, a more recent small randomized controlled trial suggested that a modified Lund approach (to include mannitol), guided by microdialysis monitoring, had less mortality than an aggressive CPP-oriented approach (70 to 80 mm Hg) in a patient group equally distributed between TBI and SAH.[120] Although the study design had significant flaws, the possible benefit is worthy of further exploration. Some subsets of disorders may possibly respond differentially to each approach, determined in part by lesion volume, inflammatory burden, and blood-brain barrier integrity.

Currently, ICP/Pbo_2 and ventriculostomy are frequently used in the management of patients with severe TBI. However, these invasive monitors are contraindicated if coagulopathy is present. The occurrence of coagulopathy in TBI is associated with a poor prognosis and should be vigorously treated with clotting factors, fresh frozen plasma, and platelets.

Hyperglycemia is associated with poor outcome in multiple retrospective studies.[26] Meta-analysis of tight glycemic control on outcome in patients with TBI indicates no benefit,[121] whereas Vespa and associates, in a crossover study, demonstrated increased metabolic crisis associated with its use.[28] More moderate targets seem prudent.

Corticosteroids had an adverse effect on mortality and morbidity in a multicenter evaluation of more than 10,000 patients with brain injury, and these drugs cannot be recommended for use.[122]

Hypothermia still may have a role in controlling ICP in patients withTBI.[123] Early prophylactic use may also be beneficial.[124] Finally, after an initial failure to improve outcome, subsequent reanalysis of previous multicenter studies suggested a differential benefit of modest hypothermia in those patients undergoing surgical evacuation of a mass lesion, as compared with those without hypothermia.[125]

The timing of prophylaxis against deep vein thrombosis (DVT) has been an issue of controversy. Investigators generally agree on the need for prophylaxis because up to 25% of patients with isolated TBI develop DVT,[126] and most clinicians agree with implementation of prophylaxis 48 hours after injury. The immediate postoperative use of heparin prophylaxis is probably safe and does not confer additional risk of bleeding.[127]

SUBARACHNOID HEMORRHAGE

Most cases of SAH are aneurysmal in origin (aSAH). The incidence of aSAH in the United States has been estimated at 9.7 per 100,000 per year, but it may be as high as 14.5 per 100,000.[128] As much as a 10-fold variability by ethnicity and geography is noted, with the incidence in Finland and Japan more than double that in the United States.[129] Women have a greater risk than men by a factor of 1.24.[129] Most aneurysms occur in persons who are more than 50 years old, but gender differences exist, with peaks in men aged 25 to 45 years, women aged 55 to 85 years, and men older than 85 years.[129] aSAH has a relatively severe morbidity and mortality. Between 12% and 15% of patients will die before hospitalization, and 25% will die within the first 48 hours, with initial hemorrhage the primary cause of death, followed by rebleeding.[128,130] Subsequent morbidity and death are attributable to neurologic deficits secondary to ischemia.[128]

Significant improvements in mortality and morbidity have occurred in recent decades.[129] This finding suggests that further reductions may be achievable with continued changes in surgical practice and further concentration of expertise in regional centers. Paralleling this has been the development of neuroimaging and endovascular technologies, which have played a large part in improved outcome.[131,132]

Early Versus Late Treatment

Mortality and morbidity from SAH in those who survived the initial hemorrhage are mostly secondary to rebleeding of unsecured aneurysms or onset of delayed cerebral ischemia. Delayed cerebral ischemia has long been considered secondary to vasospasm, but some emerging evidence indicates dissociation between vasospasm and final ischemic deficit, a finding suggesting other etiologies of ischemia (e.g., microthrombosis).[133] This information has discouraged the use of vasospasm as an independent outcome measure in clinical trials,[127] but vasospasm remains an important cause of ischemia. Rebleeding peaks within the first 24 hours after the initial hemorrhage and declines progressively thereafter, reaching a plateau of 2% by 6 months.[130] In contrast, vasospasm tends to develop by the third day, peaks between 5 and 7 days, and generally wanes by 14 days. This pattern led to some debate on the timing of treatment—in which rebleeding may be averted by early intervention but at a risk of an increased risk of vasospasm, which may induce devastating neurologic ischemic deficit. Surgically, early treatment is also associated with less optimal brain relaxation conditions. Although no difference in outcome was reported, aggressive vasopressor therapy and endovascular support have tipped the balance in the favor of early clipping in the first 72 hours after bleeding.[134] Since publication of the International Subarachnoid Aneurysm Trial, endovascular coiling is increasingly the treatment of choice, particularly in posterior fossa aneurysms and in patients in poor medical condition.[135]

In addition to rebleeding and vasospasm, acute hydrocephalus develops in 25% to 30% of patients after SAH, and emergency ventriculostomy may be lifesaving as well as offering a more accurate prognosis.[136]

Antifibrinolytics

Although antifibrinolytics were previously associated with increased incidence of stroke,[137] their transient use before clipping may offer some advantage, and although some concern exists for increased rates of hydrocephalus, studies are under way.[138] Many clinicians, however, control arterial blood pressure with the use of vasoactive infusions (e.g., nicardipine) to reduce the risk of rebleeding until the aneurysm is secured.[139]

Vasospasm

Vasospasm is thought to derive from the attenuation of nitric oxide–induced vasodilation, with an associated enhanced production of endothelin production and consequent vasoconstriction. The extravascular heme molecule is the leading candidate in a long list of possible culprits.[140] Seventy percent of patients with SAH develop angiographic vasospasm, although only 30% to 40% of patients will become symptomatic. Patients with a large amount of subarachnoid blood are at higher risk for the development of vasospasm. The Fisher grade is frequently used clinically to prognosticate the risk of vasospasm,[80] and the highest incidence of vasospasm is observed in patients with modified Fisher grade 4.[82] A meta-analysis of treatment techniques suggested no difference in the incidence of vasospasm among treatment modalities,[141] whereas more recent studies suggested that the incidence and severity of vasospasm are less following endovascular treatment compared with surgical clipping, but that difference had little effect on outcome.[142,143]

The components of "triple H" therapy (hypervolemia, hypertension, and hemodilution) have been advocated in varying forms for the treatment of vasospasm since the 1950s and as a consistent package since the 1980s.[144] Despite a significant anecdotal history of effect, little evidence of benefit has been noted in randomized control trials and meta-analysis.[145,146] Triple H therapy may also be associated with an increased frequency of complications,[147] probably because of the use of hypervolemia.[146,148]

Current recommendations center on augmentation of arterial blood pressure with vasopressors, in the context of euvolemia rather than hypervolemia.[128,129]

Hemodilution is largely a passive result of hypervolemia, thus reducing its relevance; more importantly, a higher admission hemoglobin level is associated with less cerebral infarction and better outcome.[149] The use of deliberate transfusion to increase oxygen delivery is controversial, however, with some evidence of increased vasospasm and poor outcome to counter assertions of benefit.[149,150] The general critical care literature reinforces these deleterious effects of transfusion.[151] A prospective trial is awaited.

Studies on the use of nimodipine provide the only level 1 evidence from randomized control trials in SAH. This agent, when administered prophylactically from diagnosis for 21 days, offers modest improvement in outcome with reduction in the incidence of ischemic deficit.[128,130] It does not have a readily apparent effect on the incidence of angiographic vasospasm,[152] thereby lending weight to the argument for alternative explanation of its beneficial effects.[133] Nimodipine is known to have fibrinolytic activity that may be of benefit in microthrombosis.[153]

Management of vasospasm is facilitated by the appropriate use of imaging, including the use of transcranial Doppler monitoring, SPECT, and cerebral angiography when indicated. Institution of triple H therapy necessitates the use of invasive monitoring, including that for arterial blood pressure and central venous pressure (or other indices of preload).

The use of mechanical balloon dilation of blood vessels—angioplasty—has added a major weapon to the armamentarium against vasospasm.[154,155] Angioplasty is limited by the caliber of blood vessels, as well as their accessibility, and it carries a risk of catastrophic rupture.[155]

Pharmacologic angioplasty with intraarterial injection of a vasodilator is an accepted technique. First established using papaverine, the use of calcium channel blockers such as nicardipine and verapamil is being increasingly reported and has fewer adverse effects. All current agents are limited by the transient nature of their effects (<24 hours).[156] Vasodilators may be used in vessels too small to be accessible by balloons.

Other therapeutic approaches have proven disappointing to date. Trials of endothelin antagonists and statins provided further evidence of some dissociation between vasospasm and clinical outcomes, but neither drug class showed any effect on outcome despite a decrease in the incidence of vasospasm.[157,158]

Cardiac Dysfunction

Significant autonomic disturbance may arise with SAH, thus resulting in changes in the electrocardiogram and myocardial performance. Electrocardiographic changes are frequent but do not appear to relate to outcome.[159] However, one series described a 32% incidence of abnormal perfusion scans, independent of the clinical history, electrocardiogram pattern, or neurologic condition.[160]

Abnormal echocardiography has been described in up to 8% of patients with SAH, mostly in patients with blood in basal cisterns, frequently accompanied by hypotension and pulmonary edema; this feature is associated with a poor neurologic grade. A typical pattern of symmetric T-wave inversion and severe QTc prolongation was described, although multiple electrocardiographic patterns had been observed.[161]

The phenomenon of neurogenic stunned myocardium is a definite clinical entity, with what can be a severe limitation of cardiac contractility. It is, however, a reversible condition, in contrast to myocardial infarction, and it has a good recovery profile. Obvious abnormalities of function start to recede within 72 hours, but when stunning is severe, endovascular management rather than surgical treatment may be indicated (if the aneurysm is suitable). Cardiac dysfunction may complicate and limit the active treatment options for vasospasm and may render early mechanical angioplasty more appropriate.[162] Unlike atherosclerotic ischemic cardiac myopathy, stunned myocardium often exhibits apical sparing on echocardiographic examination.[163] Conversely, patients with SAH develop cardiac dysfunction similar to takotsubo cardiomyopathy, which is an acute transient dysfunction resulting from sympathetic overactivity in postmenopausal women.[164] Troponins are frequently increased in acute SAH, and high levels are associated with increased hemorrhage, hemodynamic manipulations, and worse outcomes.[165] Whether this release of troponin represents a frank cardiac injury or a "myocardial leak" remains unknown. Adrenoreceptor polymorphism was implicated in myocardial stunning, in which different receptor genotypes denoted an increased sensitivity to and release of catecholamines, in turn associated with a 3- to 4.8-fold increase in risk of cardiac injury and dysfunction.[166]

A typical strategy for cardiovascular management is given in Box 105-4. Comprehensive consensus guidelines have been published.[128,130]

BOX 105-4 ***Suggested Cardiovascular Management Strategies in Subarachnoid Hemorrhage***

GENERAL

1. Manage hypertension in unsecured aneurysms (with nicardipine titrated to systolic BP < 140 mm Hg.
2. Maintain euvolemia prophylactically; no role for prophylactic hypervolemia.
3. Administer nimodipine (possibly statins).

CARDIOVASCULAR INSTABILITY

1. BP and cardiac output goals will alter as aneurysm is secured.
2. ECG

If abnormal (QTc prolongation, ST-segment changes): check troponins.

If troponins elevated: perform echocardiography.

3. Perform echocardiography if any manifested hypotension or heart failure is suspected.
4. Monitor cardiac output.
5. Support on dobutamine for cardiac output and norepinephrine for blood pressure.
6. Consider coiling as soon as practicable.
7. Reserve coronary catheterization for isolated wall motion deficit and rising troponins (coil first if possible).
8. Avoid β-blockers unless the patient has active coronary artery disease.
9. Vasospasm: treat with euvolemia/mild hypervolemia, pressors, and cardiac output monitoring: adjust targets as perfusion tests suggest.
10. Transfusion: maintain hematocrit >25%. Avoid use of stored blood if possible.

BP, Blood pressure; *ECG*, electrocardiogram.

Respiratory Dysfunction

Pulmonary injury is a frequent complication in the clinical course of the patient with SAH; nearly 17% of patients will experience severe dysfunction. This finding is associated with a poor neurologic outcome.[167] Blood transfusion can increase the risk of lung injury (transfusion-related acute lung injury [TRALI]), which, in turn, affects mortality[168] (see Chapter 61). Acute pulmonary edema can also occur in patients with poor-grade SAH, and this edema can be either neurogenic or cardiogenic.

Endocrine and Metabolic Derangements

Hyperglycemia is a risk factor for poor outcome, especially in SAH.[169,170] However, aggressive glucose control is not useful in SAH and may worsen outcome.[171] As in TBI, no basis exists for the use of corticosteroids.[172]

Hyponatremia is observed in 30% to 40% of patients with SAH.[173] Whether cerebral salt-wasting syndrome (CSWS) or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the dominant mechanism is debated.[174]

In CSWS, sodium is actively excreted from the body in high concentration, and accompanying diuresis occurs despite ongoing hyponatremia.[175] Berendes and colleagues demonstrated an associated increase in brain natriuretic peptide (BNP) release, thought at that time to derive exclusively from the brain.[176] Given the increasing evidence for the ventricle as the main source of production of BNP, it is unclear whether BNP arises from a stressed ventricle at the time of the hemorrhage and associated sympathetic discharge or from a brain experiencing abnormal perfusion states of homeostatic areas. Hyponatremia is also associated with cerebral infarction,[177] in keeping with the clinical observation that hyponatremia predicts the onset of vasospasm by approximately 24 hours.[178]

SIADH is the more common etiology of hyponatremia in general, but it should not induce reduction in circulating blood volume. That such a reduction does occur after SAH persuades many (including us) to consider CSWS the

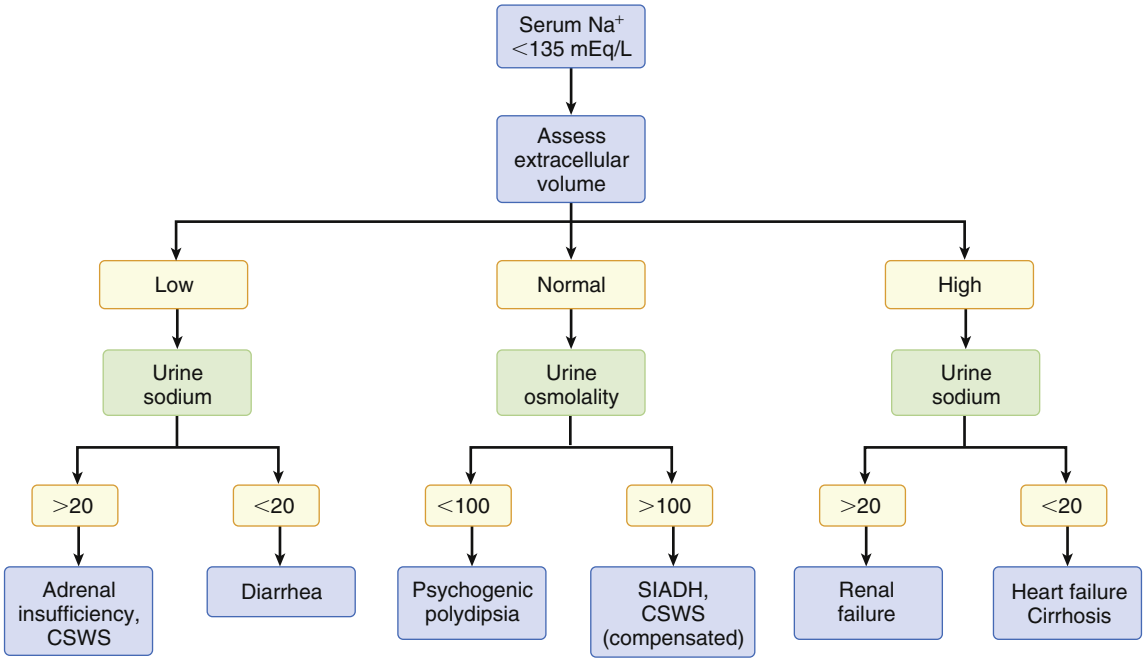


Figure 105-8. Algorithm for the differential diagnosis of hyponatremia in the neurosurgical patient. *CSWS,* Cerebral salt-wasting syndrome; *SIADH,* syndrome of inappropriate secretion of antidiuretic hormone.

more relevant etiology.[179] Profound differences exist in the subsequent management of hyponatremia in these two conditions. CSWS indicates replacement with sodium and fluids, whereas SIADH may indicate fluid restriction, which may aggravate vasospasm and ischemic deficit. The situation is rendered all the more complex by the consideration that volume loading itself induces natriuresis.[180] Both disorders are associated with SAH, and the main distinguishing feature is the state of intravascular volume; CSWS is associated with depletion, whereas SIADH is associated with elevation. Because of the adversely combined effects of hyponatremia and decreased blood volume on delayed ischemic deficits, many clinicians have advocated the use of hypertonic saline as the primary treatment for hyponatremia in patients with SAH. [181] A suggested algorithm for resolving diagnostic uncertainty is given in Figure 105-8.

Feeding and Nutrition

SAH induces a profound stress response in which the hypercatabolic state relates to the severity of the neurologic insult. Resting energy expenditure may reach a peak of 172% that of normal on day 10 after hemorrhage. This change, coupled with the tendency to suffer from headache, nausea, and vomiting, leads to relative hypoalbuminemia that may compound the tendency for hypovolemia.[182]

ISCHEMIC STROKE

Stroke is the fourth leading cause of death in the United States after heart disease, cancer, and chronic lower respiratory disease. It is a major source of disability, with 795,000 cases per year and a prevalence of 3%.[183]

The deprivation of oxygen and nutrients to the brain beyond the combined thresholds of severity and time induces cellular death in neuronal tissue. In complete occlusion, this process starts within minutes. Around the dead tissue, an area of marginally sufficient blood supply exists in which the probability of cell death is related to ischemic time. This is the ischemic penumbra and is potentially salvageable with aggressive intervention. Just as cardiologists say "time is muscle," it can also be said that "time is neurons."

Thus, the goals of treatment have moved away from physiologic stabilization and risk factor avoidance toward accelerated reperfusion and retrieval of threatened brain tissue.

Paralleling aggressive cardiac management in threatened infarction, treatment should start in the emergency department but continue into the ICU. Intravenous thrombolytics were initially deployed, followed by intraarterial and mechanical thrombolysis and, more recently, varying combinations of each modality. Current recommendations for treatment windows are 4.5 hours for intravenous therapy or 8 hours for the intraarterial route, but this regimen may be adjusted in the light of perfusion- and diffusion-weighted MRI mismatch.[184] No evidence suggests the benefit of one strategy over another on the most recent systematic review of anterior circulation stroke. The addition of stents to support subsequent vessel patency is a fast-growing practice with ongoing studies exploring efficacy.[184] Vertebrobasilar occlusion may benefit from the more recent techniques.[185]

Vigorous perfusion should be maintained until thrombolysis has been attempted. Consequently, hypertension should not be treated unless it is inducing myocardial damage or unless intracerebral hemorrhage (ICH) has already occurred (hemorrhagic conversion). This latter circumstance also precludes thrombolysis. Hypotension should be actively avoided.

Once thrombolysis has been attempted, this increases the risks of hemorrhage, and hypertension should be moderated.[186] Unwanted side effects obviously center around hemorrhage, which is associated with higher thrombolytic doses and later treatment.[187] Keen attention should be paid to postprocedural CT scans and any signs of systemic hemorrhage such as lower abdominal pain, which may indicate retroperitoneal bleeding. Areas of brain that cannot be salvaged will swell, causing compressive ischemia in adjacent regions. Just as the effects of TBI and SAH may vary by anatomic site, so, too, will the effects of ischemic stroke vary with the particular vascular area of occlusion.

In addition to control of cerebral volume, interest has revived in the early use of decompressive surgery in circumstances of "malignant" swelling. Edema can induce ICP in excess of 30 mm Hg, with a correspondingly high mortality. Studies to date suggest treatment benefit if decompressive craniectomy is carried out in the first 24 hours after onset of symptoms, with aggressively sized bone flaps.[188] Increasing age and CT hypodensity have adverse effects, but hemispheric dominance is less important. However, efficacy remains a concern because good functional outcomes are in the minority.[189]

POSTOPERATIVE NEUROSURGICAL CARE

Many neurosurgical procedures are lengthy and involve significant insult to the brain (see Chapter 70). Thus, postoperative admission to the ICU for avoidance of secondary insult and a more graduated withdrawal of ventilatory support is common, although most significant events after craniotomy happen in the immediate postoperative period.[190] ICU care particularly entails careful control of arterial blood pressure to minimize edema formation, by taking into account potential compromise of autoregulation and cerebrovascular compliance. However, the importance of neurologic examination cannot be overemphasized, and early withdrawal or intermittent interruption of sedation to allow appropriate clinical examination is a prudent approach to follow these patients.

Patients with vascular lesions such as arteriovenous malformations and vascular tumors predisposed to the development of hyperemia benefit from careful attention to blood pressure management, as do patients undergoing carotid endarterectomy. In both arteriovenous malformation and carotid disease, areas of the brain adjacent to the malformation or ipsilateral to the tight carotid stenosis may have absent autoregulatory control or may autoregulate only at a significantly lesser range of arterial blood pressure. Until the autoregulatory mechanism returns to normal, blood pressure should be carefully and tightly controlled to prevent what has been termed normal pressure perfusion breakthrough. This can be accomplished with intravenous nicardipine or esmolol infusion, or both, to allow titratable adjustment of the blood pressure.

Aneurysmal clipping is not in this category, except in cases of vascular graft bypass procedures, in which attention should be paid to minimum as well as maximum pressure targets. This is known as the *Goldilocks approach*. If arterial blood pressure is maintained too low, then this may risk graft thrombosis. If arterial blood pressure is too high, then the graft may rupture, or hemorrhage may occur. Although the range maintained is arbitrary, and no supporting data are available, systolic blood pressure probably should be maintained in a narrow range between 100 and 120 mm Hg.

Although not common, patients treated with lumbar CSF drainage may develop central herniation syndrome. The diagnosis is not always apparent, and the sudden decline in mental status, with a history of CSF drainage, should prompt appropriate imaging of the brainstem. Treatment is with fluid hydration and maintenance of the patient in the Trendelenburg position.

INTRACEREBRAL HEMORRHAGE

Nontraumatic ICH may arise from ruptured aneurysm, ruptured arteriovenous malformation, hemorrhagic stroke (amyloid angiopathy, hypertension), conversion from ischemic stroke, tumor, substance abuse (alcohol, cocaine, methamphetamines), and the use of warfarin (Coumadin). This wide range of differential diagnoses can swiftly be refined by the CT scan, with accompanying clinical signs aiding localization and the assessment of pathophysiologic effect. Angiography may be required to rule out aneurysmal rupture.

Management is to avoid secondary insult by reducing the incidence of rebleeding, hypoxemia, hypercarbia, or edema.[191,192] Essential care is directed toward the airway and circulation. If the initial CT or MRI appearance suggests arteriovenous malformation, then care should be taken to limit blood pressure to reduce the risk of rebleeding. The addition of ICP monitoring allows one to set the CPP target and provide a more physiologic approach to the management of systemic blood pressure. If the ICH is in the posterior fossa or midbrain, consideration should be given to the insertion of a ventriculostomy to reduce the risk of hydrocephalus. Patients with lesions in these regions are prone to airway and respiratory problems and may need early tracheal intubation to protect their airway and prevent aspiration.

Nimodipine does not have an established role in these circumstances. Corticosteroids are also not indicated. If the patient is receiving warfarin, it should be reversed with fresh frozen plasma and vitamin K.

Most intracranial hematomas expand in volume during the first 24 hours, and the volume of expansion is correlated with outcome. Although recombinant factor VIIa led to a reduction in hemorrhage volume, outcome is not improved. The role of recombinant factor VIIa in ICH is therefore uncertain, although it may be useful for rapid reversal of patients receiving warfarin.

The management of intracranial hemorrhage is generally medical and supportive, with control of arterial blood pressure to less than 180 mm Hg. Ongoing clinical trials are targeting a systolic blood pressure of 140 mm Hg to decrease the risk of ICH volume expansion.[193,194]

Surgery is rarely indicated.[192] However, in patients with cerebellar hemorrhage, and brainstem compression, or in those showing acute neurologic deterioration or obstructive hydrocephalus, surgical evacuation of clots may be indicated.[191,192] Although patients with other types of

stroke have experienced improved morbidity and mortality in recent years, no significant change in outcome after ICH has occurred.

BRAIN INJURY AFTER CARDIAC ARREST

Although the therapeutic cerebroprotective value of induced moderate hypothermia has been disappointing in both TBI and SAH, its efficacy in improving neurologic outcome has been demonstrated in patients who suffered global hypoxia secondary to ventricular fibrillation (see also Chapter 108). Neurologic morbidity is common in those patients experiencing global cerebral ischemia as a consequence of cardiac arrest and is related to the generation of free radicals and cellular injury on reperfusion of the ischemic brain.

Two studies reported improved neurologic outcome and reduced mortality in patients with ventricular fibrillation who were resuscitated but remained in coma and were immediately treated with mild hypothermia in the range of 32° to 34° C.[195,196] These results were confirmed in a wider population, and a regimen of 12 to 24 hours of mild hypothermia is now recommended treatment for all post–cardiac arrest patients with neurologic dysfunction.[197]

Whereas initial studies induced hypothermia using cooled intravenous solutions, more sophisticated methods and devices have since been introduced. These include noninvasive methods such as forced air cooling with limb and trunk blankets, topical adhesive cooling pads, and invasive methods deploying intravascular heat exchange catheters. Water-cooled adhesive pads connected to heat exchange units are the most commonly used methods at present.

Some clinicians consider the use of somatosensory evoked potentials (particularly the N20 and N70 latencies) to be helpful in the prognosis of coma after cardiac arrest.[198]

STATUS EPILEPTICUS

This condition has been defined as "repeated seizures occurring frequently without recovery between attacks" and has a significant morbidity and mortality, with approximately 50,000 deaths per year for an estimated annual incidence of 126,000 to 195,000 cases.[199] Some clinicians have attempted to refine this condition by using a stricter definition of continuous seizure lasting at least 30 minutes. Irrespective of the definition of status epilepticus, prompt treatment of seizure should be instituted because a seizure lasting beyond 5 minutes is unlikely to stop spontaneously. Variants of seizure type are seen, but all may present in status epilepticus, including nonconvulsive types, which present their own particular diagnostic challenges.[200]

Seizure activity may arise from any major insult affecting the cerebral cortex, whether infectious, mechanical, metabolic, or toxic. Even mild insults may provoke status epilepticus in which the seizure threshold is reduced by preexisting parenchymal disease or comorbidity (e.g., alcohol withdrawal). Given the previously outlined emphasis on the avoidance and termination of secondary insult to the brain, the metabolic disadvantage of status epilepticus is readily apparent. Management guidelines have been published.[201] Goals of treatment include seizure termination, physiologic support, and prevention of recurrence. This approach may involve intubation and ventilation, in which long-term paralytic agents should not be used for fear of masking ongoing or recurrent seizure. Electroencephalographic control is highly recommended. Preferred anticonvulsants for acute termination include lorazepam and midazolam, in view of their relatively benign cardiovascular profile. Phenytoin remains a commonly used agent but takes time to administer because it can provoke hypotension and bradycardia if given rapidly. Hypotensive effects may also limit the usefulness of thiopental, pentobarbital, and propofol.[201] In some patients refractory to treatment with usual antiepileptics, inhaled anesthetics have been used with success.[202]

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome (GBS) occurs at a rate of 1 to 4 cases per 100,000 population per year. The incidence increases with age, and this disorder is one of the most common neurologic causes of admission to critical care units.[203,204]

The classic form of GBS is acute inflammatory demyelinating polyneuropathy that appears as progressively ascending muscle weakness. This can manifest as flaccid paralysis and respiratory failure. Several clustered conditions are associated with the syndrome, including acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN), and Miller-Fisher syndrome (MFS), with MFS affecting the cranial nerves first. AIDP is the most common variant seen in the United States, and more than 50% of all patients have a recent history of bacterial or viral infection. *Campylobacter jejuni* is the most frequently observed pathogen, along with cytomegalovirus, Epstein-Barr virus, and herpes simplex. GBS may display sensory and autonomic features, depending on the subtype, and some variation in speed of onset and offset is noted. Commonly, symptoms progress over several days to reach their peak at 2 weeks, with a plateau thereafter. In approximately 5% of patients, GBS progresses more rapidly, with maximal loss of function within 72 hours of symptom onset. At 4 weeks, most have progressed to the limit of their symptoms, and improvement is observed to start soon thereafter. Recovery may be protracted for up to 6 months, however. Whether the speed of onset relates to a slower rate of recovery and outcome limitation is debated.[203,204]

Loss of ventilatory efficacy is the main reason for admission to the ICU. A forced vital capacity of less than 20 mL/kg is a sensitive indicator of need for observation, and 15 mL/kg for probable intubation, along with clinical signs of fatigue and airway compromise. Hypercarbia is a relatively late sign, and the clinician should not rely on it.

Bulbar dysfunction, albeit less common, may appear before ventilatory compromise, particularly in patients with the MFS variant.

Dysautonomia is seen in up to 20% of patients and is a source of morbidity.[205] It should be monitored carefully, because of the significant mortality of arrhythmia in older patients. Dysautonomia can vary from urinary retention to fixed tachycardia to both severe hypotension and paroxysmal hypertension.

Investigations should include electrocardiography, CSF protein (for acellular protein elevation), electromyography (axonal degeneration is associated with poorer recovery), and antibody status or screening for possible causative pathogens and also prognosis. GM_1 antibody is associated with worsened recovery, whereas MFS is associated with anti-GQ1b antibody.[204]

Particular challenges to management are the problems of deafferentation pain and psychiatric depression. The pain can be severe, is truncal in distribution, and may respond to anticonvulsants more than to opiates. It certainly contributes to the frequently observed depression. This pain is often worsened by immobility, boredom, and the limited ability of busy staff to engage actively with a (relatively unusual for the neurocritical care unit) cognitively intact patient. Early tracheostomy in identifiably prolonged cases is appropriate.

Both symptom limitation and recovery from GBS have been improved with the use of plasmapheresis or the intravenous administration of gamma globulin. No advantage is seen with one treatment approach over the other or in combination. However, many physicians try them sequentially in cases of treatment failure. Persistence of foot drop at the conclusion of immunotherapy is an indicator of longer-term ventilation.[206]

Neither interferon nor corticosteroid use has been shown to improve outcome, either alone or in combination with immunotherapy.[203]

SPINAL CORD INJURY

In contrast to GBS, spinal cord injury is much more common (11,000 cases/year), is intractable to treatment, and almost inevitably has permanent effects. The number afflicted in the United States is estimated to exceed 270,000. The degree of dysfunction is similar to GBS in that as the level of injury ascends, the patient has a high level of motor paralysis of the lower limbs, trunk, upper limbs, and diaphragm. Additionally, traumatic sympathectomy also occurs, producing bradycardia, hypotension, and gastrointestinal paralysis. This gastrointestinal aspect is often overlooked, and subsequent abdominal distention can embarrass an already compromised diaphragm into inefficacy. The cardiovascular effects of sympathectomy, particularly above T5, manifest as bradycardia and hypotension.[207] This patient can be supported by fluid and pressor therapy, and the tachycardic effect of dopamine may be a useful attribute. Unopposed vagal stimuli, as well as hypoxia, may induce bradycardia.[207] Resuscitation targets are controversial, with more recent interest in maintaining spinal perfusion analogous to the CPP of TBI. Patients with injuries below T5 may still manifest hypotension but usually only on the provocation of posture, hypovolemia, or comorbidities.

Ventilatory support depends on the level of injury. If the injury is below C5, although the diaphragm remains functional, in the acute stage respiratory embarrassment secondary to abdominal and intercostal paralysis can still occur because flaccidity in these muscles significantly decreases the functional efficiency of the diaphragmatic contraction. Thus, paradoxic respiration with chest indrawing during inspiration occurs. This can be alleviated in part with the use of an abdominal binder. With complete cervical spinal cord injury, acute respiratory failure is common, secondary to the sudden loss of functional residual capacity and the inability of the sternocleidomastoid muscle to stabilize the chest wall. With time, many patients can regain the ability to breathe spontaneously, except those with high cervical lesions. Controversy exists regarding the ventilatory pattern used for spinal patients. Some investigators suggest that a larger tidal volume should be used, with an aim of opening more alveoli, reducing atelectasis, and treating air hunger. No randomized clinical trials are available to support this, and it would seem contrary to more recent insights into lung stretch injury. Air hunger may be more a consequence of disordered proprioception than an indication to hyperventilate.[208]

Lower limb blood flow is reduced with increased arterial and venous pooling. This is associated with a higher incidence of thromboembolic disease, and early prophylaxis with low-molecular-weight heparin is recommended.

As with GBS, the patient with spinal cord injury is commonly aware, and this constitutes an additional burden of psychological stress. Consequently, the best approach taken is truly holistic, tending to psychological needs, as well as to cardiopulmonary, gastrointestinal, renal, and integumentary support. Significant advances have been made in the critical care and rehabilitation support afforded to these patients, and 2-year survival has increased significantly since the 1980s. Unfortunately, this improvement has not translated to increased long-term survival.[209]

MYASTHENIA GRAVIS

Although myasthenia gravis is a relatively uncommon disease (prevalence of 10 to 20 per 100,000), it is relevant to neurocritical care in that patients can present acutely with rapid deterioration of muscle function, predisposing to ventilatory failure—the myasthenic crisis. Myasthenia itself has a strong association with various autoimmune conditions (e.g., thyroid disease, pernicious anemia, rheumatoid arthritis), as well as being linked to women with certain human leukocyte antigen (HLA) types.[210,211]

The myasthenic crisis can be precipitated by a progression in severity of the disease state or often by amplification by another factor. This factor can include infection, recent surgery, or interruption of immunosuppressants. Many drugs can exacerbate myasthenic crisis, including aminoglycosides, fluoroquinolones, anticonvulsants (including phenytoin), steroids, β-blockers, calcium antagonists, ketamine, lidocaine, neuromuscular blockers, and anticholinergic agents.[211]

The diagnosis should exclude GBS, brainstem stroke, organophosphate poisoning, and botulism. Tests should include electrophysiology, CSF protein, edrophonium response, and antibodies to acetylcholine and muscle tyrosine kinase receptors.

The presentation is typically that of acutely worsening weakness of either respiratory or pharyngeal muscles, or both. The patient should be observed closely for signs of impending respiratory failure. Forced vital capacity is again useful with 15 mL/kg being a useful trigger for intubation.[211]

The other mainstay of therapy is by immunomodulation. Typically, intravenous immunoglobulin or plasmapheresis is started quickly to limit progression of symptoms and avert frank crisis. Corticosteroids do have a role in establishing longer-term control of immunosuppression because immunoglobulin G (IgG) and plasmapheresis have limited duration of efficacy. Corticosteroids alone are associated with a transient worsening of symptoms, before improvement, so they are best used concurrently with or immediately after plasmapheresis or IgG.[212]

MENINGITIS

Meningitis is a serious condition producing inflammation of the leptomeninges covering the CNS. The causative pathogens differ among different patient populations. Community infections are frequently caused by *Streptococcus pneumoniae, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis,* and group B streptococci. *N. meningitidis* is particularly evident in teenagers. Since the advent of a childhood vaccination program, *H. influenzae* affects chiefly adults, but the other organisms tend to affect all age groups. Nosocomial infection, in contrast, predominantly arises in the neurosurgical patient, especially with the use of ventricular devices, and the pathogens here comprise gram-negative rods and staphylococci. Diagnostic features include fever almost invariably with the classic nuchal rigidity and change in mental status; less often, photophobia, papilledema, and new-onset seizures may be seen. A rash is typical of meningococcal infection, whereas arthritis occurs in a significant minority. Tests should include CSF Gram stain and culture by lumbar puncture, but any previous antibiotic dosing can diminish sensitivity. Under this circumstance, polymerase chain reaction (PCR) testing is the method of choice, thus displacing the more variable latex agglutination test. A CT scan should delay the lumbar puncture only when the patient's history suggests a previous mass lesion, stroke, or focal infection, recent seizures, or immunocompromise. Similarly, signs of papilledema, depressed level of consciousness, or focal deficit indicate a need for a CT examination to avoid herniation. Cerebral edema not infrequently develops in patients with meningitis and can lead to acute deterioration in mental status. ICP monitoring may be indicated.

Treatment should be delivered swiftly, pausing only to obtain emergency samples for Gram stain and culture. If no identification is possible on Gram stain, empiric antibiotic therapy should be delivered with third-generation cephalosporins (e.g., ceftriaxone or cefotaxime), along with vancomycin until organism and sensitivities are obtained. This approach covers the community-acquired pathogens. Nosocomial or trauma-associated infections can be effectively treated with cefepime and vancomycin. Steroids are useful adjuncts in bacterial meningitis and have been shown to reduce mortality.[213]

The outcome of meningitis is a function of patient-related factors, the pathogenicity of the organism, and the time to effective treatment. An interesting study examined admission hypotension, altered mental status, or seizures for an effect on outcome. A 9% mortality rate occurred when one factor was present, and it increased to 33% for two factors and to 57% for all three.[214]

ENCEPHALITIS

Encephalitis manifests with fever, headache, and alteration of consciousness. Patients may also have delirium, focal deficit, and, commonly, seizures. Nuchal rigidity may be present in a mixed meningoencephalitis picture but should be absent in isolated encephalitis. Accompanying identifiers may be a vesicular rash associated with herpes zoster (although its absence does not remove zoster from suspicion), bilateral paralysis typical of West Nile disease, parotitis if mumps is suspected, and, of course, the hyperactivity, hydrophobia, and pharyngeal spasm of rabies. West Nile neuroinvasive disease has increased its incidence from 62 cases in 1999 to 438 in 2011, over 43 states, with estimates of up to 34,000 non-neurologic infections per year.[215] Many nonviral and noninfectious causes of encephalitis may confound the diagnosis. These include vasculitis, systemic lupus erythematosus, stroke, rickettsial and parasitic infection, and drug-induced meningitis (e.g., IgG). Careful examination of clinical features, history, and laboratory data is necessary. CSF should be drawn for viral DNA polymerase chain reaction, as well as the routine biochemistry, culture, and cell count. MRI is useful in identifying the demyelination and edema that can be difficult to see on CT. Serum serology is helpful for the diagnosis of Epstein-Barr virus, mumps, and West Nile disease as sources of encephalitis. Paired samples are recommended to allow later comparison if CSF PCR is unhelpful. Brain biopsy was considered the gold standard but is now a last option after CSF PCR, culture, and serology have proven negative.

Herpes simplex type 1 infection carries a very poor outlook if it is not treated expeditiously, and a course of intravenous acyclovir is recommended as soon as samples are drawn.

The pathogen remains unidentified more often than not, and outcome usually then depends on classification of the clinical features, with intractable seizure and cerebral edema carrying a poor prognosis. Self-limiting seizure usually indicates a swift recovery.

BRAIN DEATH

It is crucially important that the physician understand the principles of the diagnosis of brain death and be able to apply them assiduously and without compromise (see Chapter 76). Many unfortunate instances of poor understanding have led to imperfect examination, misdiagnosis, and considerable distress to all concerned.

Declaration of brain death was originally codified by the Harvard criteria in 1968, with subsequent modification to allow separation of cerebral death from death of the entire nervous system including the spinal cord.[216]

The diagnosis is built on a solid clinical examination of nervous system function, by examining the reflex response of the brain and cranial nerves to varying stimuli of hypercarbia, pain, light, temperature change, attitudinal change of the middle ear, and detection of the blink, cough, and gag reflexes. The mechanisms for the cause of neurologic dysfunction should be clear. As with the operation of the GCS scale, the examination must be done in circumstances of adequate systemic oxygenation and perfusion. Confounders, such as hypothermia, metabolic or endocrine compromise, and persistent sedative or neuromuscular drugs, should be avoided, corrected, or removed. Although guidelines allow a single examiner in adults,[217] many clinicians believe that two examiners are preferable, and this is mandatory in pediatric cases[218] (see also Chapter 95). At least one of the testing physicians should have had training in neurology, neurosurgery, or neurocritical care. Time between tests is less important for diagnosis than for the opportunity to start communicating with and preparing the family. One of the tests should include an appropriately conducted apnea trial in the presence of the physician, with confirmation of adequate changes in Pco_2. Two apnea trials are required in pediatric cases.[218] If for any reason any test cannot be completed in a safe manner, or to the satisfaction of either physician, then an ancillary test of CBF should be performed.

The hospital should have an institutionally approved protocol for the conduct of these tests and mechanisms in place for review and quality improvement.

ETHICAL CONSIDERATIONS

Ethical issues are frequently encountered in a neurologic ICU setting (see Chapter 10). Unfortunately, as well as the mortality described previously, significant life-altering morbidity occurs, to the extent that many patients and families would not desire aggressive therapy.[219] This can be a difficult concept to accept for the physician, whose aim is to heal and preserve life. However, the ethical imperative in Western culture is to preserve the autonomy of the individual (along with the principles of nonmaleficence, beneficence, and justice), and this has been extended to health care decision making. This situation may lead to uncomfortable choices and communication within the health care team, whose members may have differing opinions on goals, and from there to the patient and relatives, who, again, may think very differently.

Certain strategies can avoid or minimize these difficulties:

- Prognosis should be made on the basis of the best available evidence. This may involve planning and discussion among the team members in advance of meeting with families. The personal anecdote should be avoided, even if solicited.
- The relationship within the team should be open and collegial, with mutual respect given to the principle of open discussion. This approach avoids misperception of goals and attitudes and enables more consistent communication with families, who often find dissonance among members of the ICU team disturbing.
- The presence of an advance directive offers major benefits, and the neurocritical care unit should have an admissions protocol that includes asking all competent, conscious patients to consider making their attitudes or wishes known.
- Regular family and patient conferences allow communication of prognosis as it is appropriate and offer the opportunity for correction of any misconceptions, as well as progressive education of the family to anticipated problems.
- Internal institutional mechanisms for raising concerns and conducting reviews should be in place. This is often facilitated by the presence of an institutional ethics committee, whose members can examine the issues, promote educational discussion, and help achieve a consensus.
- All decision making should be documented carefully and completely.
- Orders for limitation or withdrawal of therapy should be written explicitly, and institutional protocols should be used wherever possible.

Other important areas of possible conflict exist that are not possible to address within the confines of this text, but readers are advised to educate themselves on the following:

- The issues surrounding organ donation from the brain dead and the non–heart-beating donor
- Withdrawal of care for the incompetent patient without family
- Hospital bylaws and state legislation on the certification of death, whether that be by neurologic or cardiovascular criteria

CONCLUSION

Neurocritical care demands a thorough comprehension of the physiology, pharmacology, and pathology of the nervous system, as well as for the organ systems supporting it. The best care is provided in circumstances that allow multidisciplinary collaboration and appropriate attention to detail of often complex and demanding pathologic processes, but integrating them optimally under the direction of the critical care physician.

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Chapter 106

Nutrition and Metabolomics

CHARLES WEISSMAN

Key Points

- Sepsis, trauma, and surgery activate complex metabolic and inflammatory responses that affect all body systems.
- Catabolism, hypermetabolism, hyperglycemia (diabetes of injury), and enhanced lipolysis characterize the metabolic response to the stress response.
- The counter-regulatory hormones (e.g., cortisol, glucagon, catecholamines) along with the cytokines (e.g., interleukin 1, tumor necrosis factor) are major mediators of the stress response.
- Certain intraoperative anesthetic and postoperative analgesic techniques can modulate the stress response.
- During the acute phase of illness, patients unable to eat should receive parenteral or enteral nutritional support.
- Nutritional support during the acute phase of critical illness is a supplementary therapy designed to provide patients who are suffering from underlying metabolic disarray with sufficient nutrients to aid cellular biochemical functions and attenuate further loss of body mass.
- Only once the ravages of the stress response have abated can lost lean and fat mass be repleted.
- Overfeeding or aggressive refeeding should be avoided.

Humans are adaptable organisms with many interrelated mechanisms that identify, respond, and neutralize both internal (e.g., infection) and external (e.g., temperature extremes) events (stressors) that threaten or upset homeostasis. Anesthesiologists must be knowledgeable about these mechanisms because they routinely care for patients with acute and chronic homeostatic changes. Moreover, anesthesia and surgery involve significant disruption and manipulation of body physiologic processes, anatomy, and biochemistry, which activate the body's responses to stress.

The stress response evolved as a means for helping organisms react to immediate danger. The outpouring of catecholamines and other hormones increases the outputs of the respiratory, cardiovascular, and metabolic systems, thus enhancing the organism's ability to flee from an enemy and to maintain perfusion to vital organs after blood loss. Metabolic alterations caused by changes in the hormonal milieu increase the availability of certain substrates and reduce the availability of others. The organism thus attempts to improve conditions for wound healing, blood coagulation, and humoral immunity, a response that is beneficial in acute events such as bleeding and infection. Although once regarded positively as the body's defense mechanism, the stress response is now regarded more equivocally because its physiologic consequences, especially increasing the output of various organ systems, may lead to greater morbidity and mortality by overtaxing already compromised organ systems. For example, among patients with underlying coronary artery disease, the tachycardia and increased myocardial oxygen demand resulting from catecholamine stimulation can cause myocardial ischemia.

The stress response was initially described by Hans Selye as "the nonspecific response of the body to any demand upon it."[1] However, contemporary research demonstrates that the nature of response varies, depending on the type and intensity of the stressor and is only nonspecific when the stress is overwhelming. Furthermore, chronic activation of the stress response has been implicated as contributing to a variety of conditions, such as atherosclerosis and depression. Although chronic stress is not often the cause of the disorder, it contributes to its pathogenesis, exacerbations, and duration.[2]

SYSTEMS BIOLOGY AND METABOLOMICS

Organisms are *complex systems*—systems with many dynamic and nonlinear relationships among heterogeneous interconnecting parts, whose actions and properties cannot be completely explained by the structure and function of the individual components. This biocomplexity is further characterized by multiple levels of organization

(e.g., genes, cells, tissues), multiple feedback loops, robust responses to perturbations, the ability to adapt to endogenous and exogenous threats, and nonintuitive and often paradoxic behavior.[3] The need to better understand biocomplexity, such as during stress, has spawned interest in *systems biology/medicine,* which uses mathematical modeling and systems engineering methods to provide mechanistic explanations of physiologic and pathophysiologic interrelationships.[4] Complementing the systems approach have been *omic* techniques that analyze the *total* collection of genes (genomics), proteins (proteonomics), or metabolites (metabolomics) in a cell, tissue, or organism. For example, metabolomic techniques are used to compare differences in individual metabolites and metabolic pathways under normal and pathologic circumstances.[5] These newer approaches are a departure from the usual *reductionist* methods, which analyze a system's individual components by taking a wide-ranging view of the intricate biosome.

METABOLIC CONTROL SYSTEMS AND THE RESPONSE TO SURGICAL STRESS

Living organisms constantly undergo adjustments to adapt to ever-changing internal and external conditions. These natural alterations are termed *allostasis* and include diurnal variations in temperature and cortisol production, metabolic changes as a result of eating and drinking, and the cardiopulmonary responses to exercise.[6] Stress occurs when allostatic mechanisms are insufficient for maintaining homeostasis, thus causing the organism to alter many of its functions significantly to reduce and contain the stressful threat.[7]

Cuthbertson classically described the response to surgical and traumatic injury as having three phases:

1. The ebb phase (≤24 hours), also called the *resuscitative phase*, is characterized by tissue hypoperfusion that requires treatment.
2. The flow phase (its duration depends on injury severity) has a milieu characterized by catabolism, hypermetabolism, hyperglycemia, and an inflammatory response.
3. The anabolic phase (may last for months) is when anabolism facilitates the repair of injuries and a return to a normal metabolic environment.

However, the improved survival from major injury, occasioned by modern surgery and critical care, blurs this classic scheme. Today, patients who are critically injured often undergo multiple surgeries within a few days of their injury and suffer from iatrogenic infections during extended stays in an intensive care unit (ICU). These surgeries and infections add further stresses—second hit—to an already highly stressed system.[8] The consequences of these second hits are problematic because they perpetuate or intensify metabolic changes that increase the chance of developing multiple-organ failure.[9]

HYPOTHALAMUS-PITUITARY AXIS

Many allostatic, as well as homeostatic, changes are controlled by feedback control systems and centered on the hypothalamic-pituitary axis. Hypothalamic activation, secondary to afferent neuronal input from an area of injury, or emotional activity centered in the limbic system and humoral factors, such as the inflammatory cytokines tumor necrosis factor–alpha (TNF-α), interleukin (IL)-1, and IL-6, trigger the response to surgical and traumatic stress.[10] In addition, the loss of endocannabinoid signaling removes inhibition of the neuronal release of glutamate resulting in hypothalamic-pituitary activation.[11] Hypothalamic activation increases the activity of the sympathetic nervous system, which increases the output of the cardiovascular system and stimulates the adrenal medulla to secrete epinephrine and the pancreas to secrete glucagon (Fig. 106-1). Hypothalamic activation also stimulates corticotropin-releasing hormone (CRH) and reduces the secretion of the various hypothalamic releasing factors (e.g., growth hormone–releasing hormone [GHRH]). The hypothalamus, the body's thermostat, also controls body temperature. Stimulation by mediators such as IL-1β (endogenous pyrogen) causes fever via a biphasic mechanism; the first phase is mediated by increased intracellular ceramide and the second by cyclooxygenase-2 (COX-2)–mediated prostaglandin E_2.[12,13] CRH is also peripherally produced in the adrenal medulla, gastrointestinal tract, skin, nerve fibers, and immune cells. At inflammatory sites, CRH acts as a paracrine or autocrine inflammatory mediator (Fig. 106-2) via peripheral CRH receptors.[14,15]

During stress, the releasing factors, along with other stimuli, stimulate the posterior pituitary gland (neurohypophysis) to release arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), and the anterior pituitary (adenohypophysis) to secrete prolactin (PRL) and growth hormone (GH) into the circulation.[16] CRH, acting synergistically with AVP, stimulates the secretion of pro-opiomelanocortin by the anterior pituitary. In the stressed state, IL-6, working through IL-6 receptors present on the pituitary corticotrophic cells, also acts synergistically with CRH. Pro-opiomelanocortin is cleaved to adrenocorticotropic hormone (ACTH), β-endorphin, and α–melanocyte-stimulating hormone (α-MSH), thus linking endogenous opioids with the hypothalamic-pituitary axis. ACTH, in turn, stimulates the zona fasciculata of the adrenal cortex to secrete glucocorticoids. A meta-analysis showed that the cortisol response increases with age and is greater in women than in men.[17] Glucocorticoids, including those administered exogenously, constitute a negative feedback system suppressing hypothalamic CRH and AVP secretion. In the unstressed state, the hypothalamic-pituitary control mechanism regulates cortisol secretion in a circadian rhythm, with peak concentrations occurring in the early morning and the nadir around 11 PM. In the postoperative stressed state, cortisol secretion increases twofold to threefold with disruption of the circadian rhythm, specifically, longer peak-to-nadir intervals.[18] Interestingly, α-MSH concentrations are decreased after major trauma.[19]

Arginine Vasopressin (Antidiuretic Hormone)

AVP, vital for maintaining intravascular homeostasis, is secreted when osmolality is increased, arterial pressure is decreased, and blood volume is reduced.[20] It causes vasoconstriction (V1 receptors) via the phosphatidyl-innositol-biphosphonate pathway and renal water retention (V2 receptors) by stimulating water channel aquaporin-2.[21] Plasma AVP concentrations are elevated after various

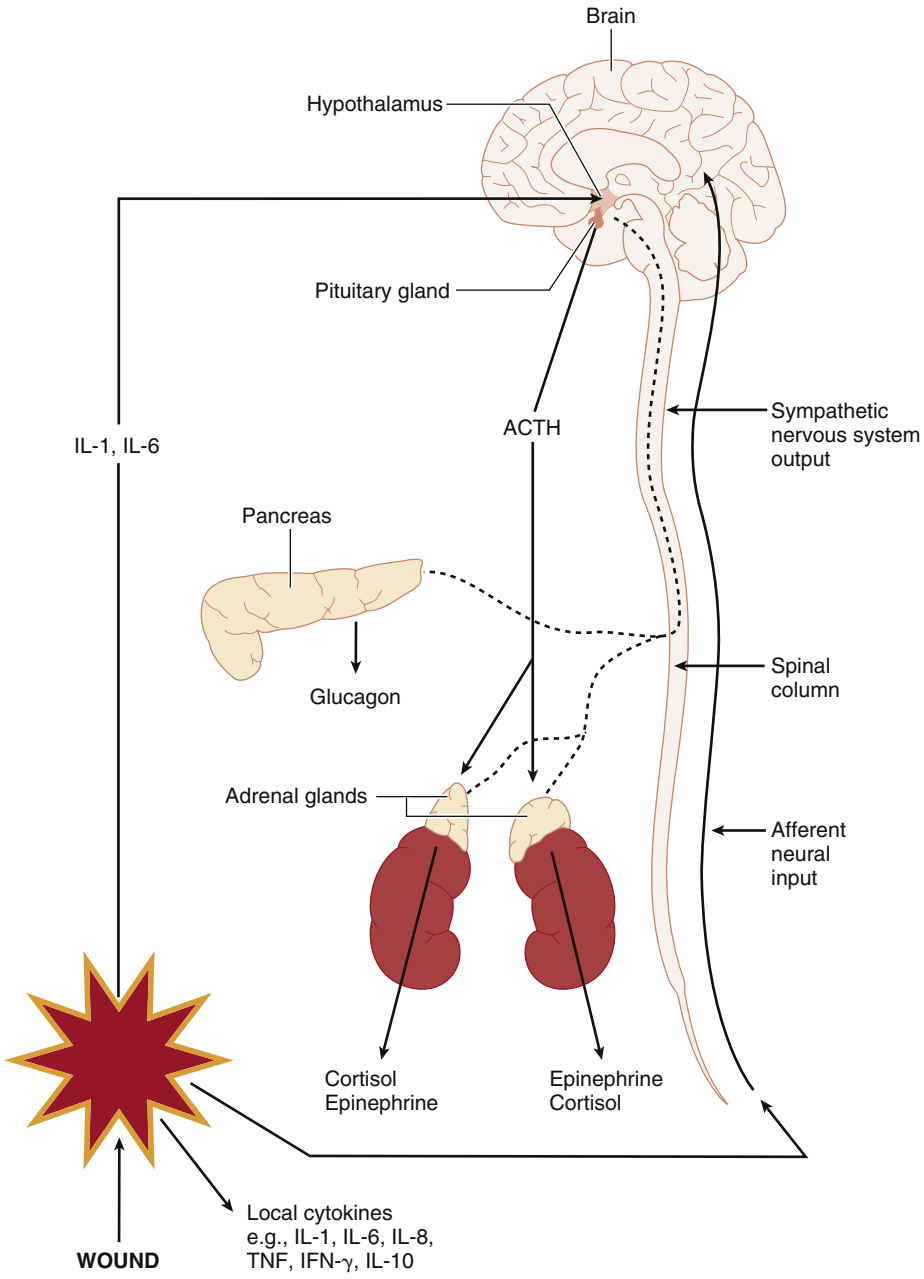


Figure 106-1. Mechanisms that initiate the stress response are shown. Afferent neural input plus cytokines, such as IL-6 and IL-1, stimulate the hypothalamic-pituitary axis, which leads to the secretion of adrenocorticotropic hormone (ACTH). This secretion stimulates the adrenal cortex to release cortisol and activates the sympathetic nervous system, which stimulates the pancreatic alpha cells to secrete glucagon and the adrenal medulla to secrete epinephrine. Cytokines and growth factors act locally in the area of the wound, and some also have endocrine effects. *IFN-γ*, Interferon gamma; *IL*, interleukin; *TNF*, tumor necrosis factor.

stresses, including surgery, pneumonia, and myocardial infarction with or without left ventricular failure. Plasma AVP concentrations increase after surgery begins and often remain increased for days after its completion. The magnitude and duration of the elevated plasma vasopressin concentrations are proportional to the degree of stress. In septic shock, an initial increase in AVP concentrations is followed by a decrease to extremely low concentrations.[22] Relatively low AVP concentrations are among the reasons for persistent vasodilation in septic shock and also in hemodynamic instability after cardiac surgery[23,24] (also see Chapter 67). Furthermore, some patients with septic shock for 3 or more days have impaired osmoregulation characterized by the lack of AVP response to a saline load.[25]

Growth Hormone

GH secretion by the anterior pituitary is stimulated by hypothalamic GH-releasing factor and inhibited by hypothalamic somatostatin. GH, vital in the regulation of growth during the prenatal and childhood periods, has a biphasic effect during stress. Initial exposure (2 to 3 hours) produces insulin-like effects, but longer exposure causes anti-insulin and anabolic effects. The latter increases the incorporation of amino acids into structural proteins, glucose intolerance as a result of insulin resistance, and increased lipolysis as a result of increased sensitivity to the lipolytic effects of catecholamines. GH stimulates the secretion of insulin growth factors 1 and 2 (IGF-1 and IGF-2) by the liver and other peripheral tissues. IGF-1 has insulin-like actions and also mediates the anabolic and skeletal growth–promoting activity effects of GH. IGF-1 facilitates anabolism by directly reducing protein oxidation and enhancing insulin sensitivity to enable insulin and GH to stimulate protein synthesis. A 5-day infusion of IGF-1 into normal subjects did not change the glucose oxidation rate but increased lipid oxidation, raised resting energy

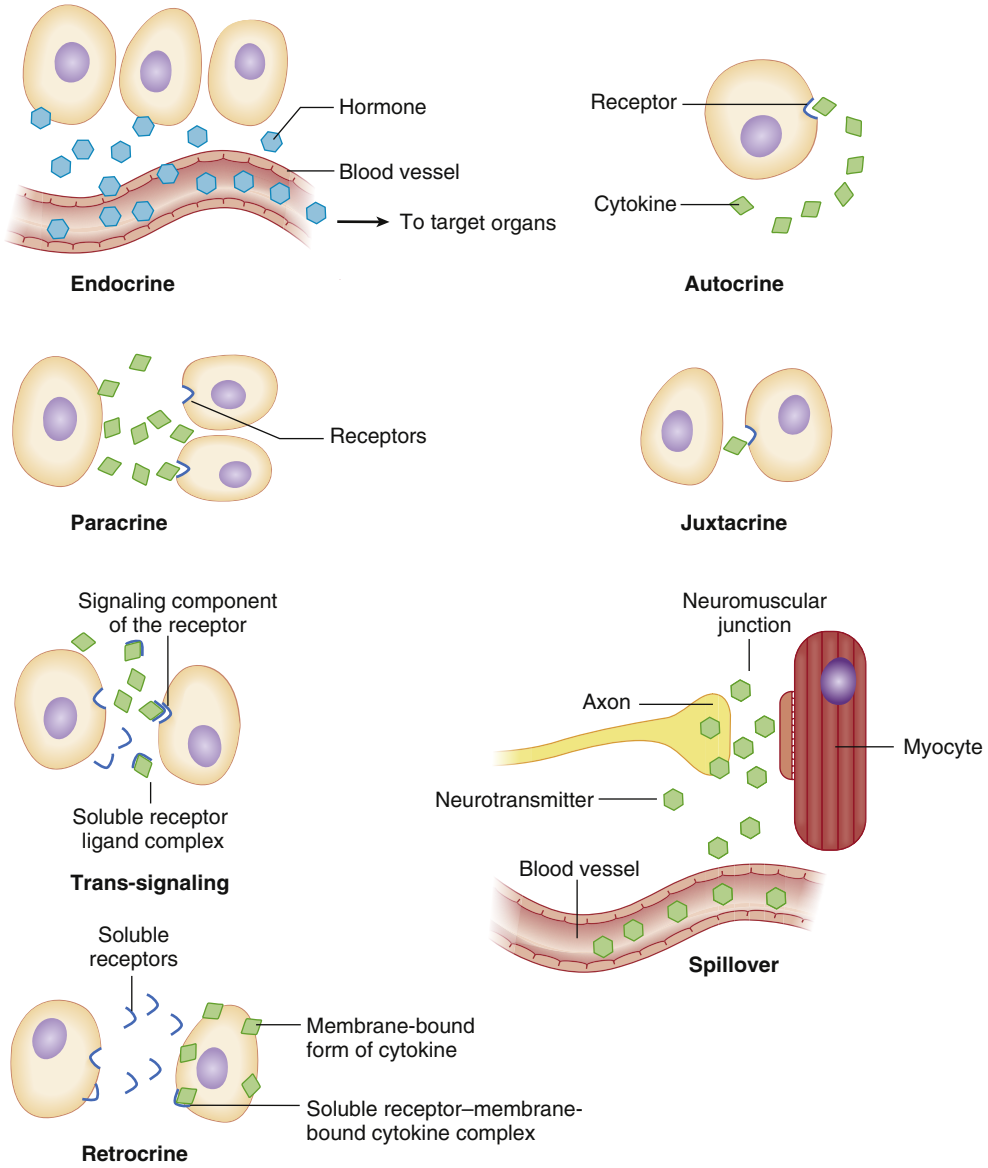


Figure 106-2. Hormones, cytokines, and other bioactive substances use various mechanisms to affect end-organ function. *Endocrine*—Hormones and other substances are transported to end organs via the bloodstream. *Autocrine*—Secreted substances affect the cell that produced them. *Paracrine*—Mediators act locally within the same tissue bed. *Juxtacrine*—Mediators act on adjacent cells. *Trans-signaling*—Soluble receptor binds in the presence of its ligand to the signaling component of a multimeric receptor complex. *Spillover*—Neurotransmitter not taken up by nerve endings enters blood vessels. *Retrocrine*—Soluble receptors interact with membrane-bound forms of cytokines and are used to control cytokine effects.

expenditure (REE), and reduced protein oxidation. The seven IGF-binding proteins modify the availability and actions of IGF-1. Most (~90%) circulating IGF-1 is bound to insulin-like growth factor–binding protein 3 (IGFBP-3), whereas IGFBP-1 plays a major role in regulating unbound (free) IGF-1.

Immediately after major traumatic injury, burns, and surgery, GH blood concentrations are increased roughly proportional to the degree of trauma. However, after day 1, the preoperative or preinjury GH concentrations start to decline. In patients who are severely traumatized, the pulsatile nature of GH secretion persists, but the bursts occur less frequently. IGF-1, IGF-2, and IGFBP-3 are reduced 40% to 60% after trauma and burns, as well as with acute respiratory distress syndrome (ARDS), whereas IGFBP-1 and IGFBP-4 are increased.[26] In septic patients, both serum IGFBP-1 and IGFBP-3 concentrations were decreased with IGFBP-3 being the major determinant of IGF- concentrations.[26a] The decreased IGF-1 and IGFBP-3, despite elevated GH, is possibly due to a resistance to the stimulatory effects of GH on the liver.[27] The decreases in GH and IGF-1 concentrations are ascribed to an inhibition by IL-1β. The consequence of these decreases is protein catabolism. Furthermore, reduced postoperative suppression of the GH and IGF-1 axis plus markedly elevated cortisol concentrations were associated with postoperative delirium.[26b,26c]

ENDOCRINE SYSTEM

The hypothalamic-pituitary axis is the main controller of the endocrine system, which, in turn, controls much

of the body's metabolic functions (see Fig. 106-1). Endocrine hormones are major mediators of the metabolic response to stress. The hormones glucagon, cortisol, and catecholamines oppose the effects of insulin on glucose and lipid metabolism and are thus called the *counter-regulatory hormones*.

Sympathoadrenergic System

The sympathoadrenergic system, made up of the sympathetic nervous system and adrenal gland, produces and secretes the catecholamines, norepinephrine, epinephrine, and dopamine (see also Chapter 16). Serum concentrations of these hormones increase after stresses such as anxiety, hypotension, hypothermia, surgery, burns, hypercarbia, and accidental injury. In patients who are severely burned, norepinephrine concentrations increase 2- to 10-fold in parallel with the burn size.[28] The pattern of catecholamine secretion is age dependent. Compared with younger (median age of 34 years) victims with trauma, older (median age of 66 years) sufferers had higher circulating norepinephrine but attenuated epinephrine levels with increasing injury severity (also see Chapter 81).[29] Concurrent with sympathetic system activation, parasympathetic activity is acutely suppressed. This suppression is important because the parasympathetic nervous system reduces proinflammatory responses.[30]

Epinephrine is secreted into the bloodstream by the adrenal medulla in response to sympathetic nervous system activation, whereas most norepinephrine is released from sympathetic nerve endings. Plasma epinephrine concentrations thus reflect adrenomedullary secretion, whereas plasma norepinephrine levels are an index of sympathetic nervous system activity. Plasma concentrations of epinephrine and norepinephrine do not necessarily increase simultaneously. Most norepinephrine released by sympathetic ganglia is removed from the synapse by reuptake into the nerve ending. Therefore, only norepinephrine that *spills* over into the plasma is assayed (see Fig. 106-2). Plasma norepinephrine concentrations are thus the difference between the spill over and plasma clearance rates. Besides increased secretion of endogenous catecholamines, many patients who are critically ill receive vasopressor and inotropic support with infusions of exogenous catecholamines, which have additive metabolic and other effects. For example, dopamine infusions depress thyroid-stimulating hormone (TSH), PRL, and GH secretions, whereas norepinephrine infusions reduce insulin sensitivity.[31]

In addition to cardiovascular effects, catecholamines have major metabolic effects. β_2-adrenergic stimulation increases glycogenolysis, hepatic gluconeogenesis, and glucagon release while blocking glycogen synthesis.[32,33] Lipolysis is increased by β_2- and β_3-adrenergic stimulation but inhibited by α_2-stimulation. Women are more sensitive to the lipolytic actions of catecholamines than men.[34] Epinephrine infusion in normal subjects does not affect protein metabolism.[35] The lesser role of the catecholamines, as opposed to glucagon, in instigating and maintaining abnormal glucose metabolism in patients with burns, was demonstrated by the failure of propranolol to reduce the rates of glucose production and glucose cycling.

The sympathoadrenal system also affects the immune system. Lymphoid parenchyma (spleen, thymus, lymph nodes, bone marrow) have sympathetic neuronal innervations that enable lymphocytes and macrophages (T-helper 1 [Th1] cells have surface β receptors) to be directly affected by sympathetic output. β_2-receptor stimulation of lymphoid cells downregulates the synthesis of proinflammatory cytokines, upregulates the synthesis of antiinflammatory cytokines, and inhibits Th1 cell function (cellular immunity), thus favoring humoral immunity (Th2 cells).[30,36] However, during sepsis, the immunosuppressive effects of catecholamines are attenuated, and epinephrine seems to either increase or not reduce TNF-α secretion.[36] The sympathoadrenergic system is thus a major mediator of the stress response and also part of its negative feedback arm.

Glucocorticoids

The plasma concentrations of cortisol, a major stress hormone, are significantly increased after surgical and traumatic stress primarily as a result of enhanced secretion by the adrenal cortex. However, in some situations the increased concentrations are also due to reduced renal function and reduced hepatic clearance, secondary to decreased hepatic blood flow.[37] In addition, enhanced cortisol production is minimally suppressed by exogenous glucocorticoid administration, as demonstrated by the inability of 24 mg/day of dexamethasone administered for 2 days after a craniotomy to suppress the elevated concentrations of either ACTH or cortisol. Increased plasma cortisol concentrations stimulate gluconeogenesis, sensitize adipose tissue to the action of lipolytic hormones (GH and catecholamines), and increase proteolysis by blocking the antiproteolytic actions of insulin.[38] Cortisol causes insulin resistance by decreasing the rate of insulin activation of the glucose uptake system (inhibiting the translocation of glucose transporter–4 to the cell membrane) and increasing 11β-hydroxysteroid dehydrogenase activity.[38a] Additionally, cortisol has antiinflammatory and immunosuppressive actions. The antiinflammatory actions include negative feedback to ACTH and proinflammatory cytokine production, as well as stimulation of the secretion of IL-10, an antiinflammatory cytokine. These antiinflammatory and immunosuppressive actions prevent stress-activated defense mechanisms from overshooting and damaging the organism. Unlike elevated concentrations, basal concentrations of cortisol are antilipolytic and probably facilitate normal immune responses.

Cortisol is a vital mediator of the stress response because it facilitates catecholamine action and secretion, thus helping maintain cardiovascular stability during surgical stress. The importance of glucocorticoids is demonstrated by the excessive mortality during stress observed in adrenalectomized animals and patients with Addison disease. Furthermore, increased mortality was observed when etomidate was used to sedate patients who were critically ill. Etomidate blocks adrenal steroidogenesis by inhibiting 11β-hydroxylation and 17α-hydroxylation. Similarly, patients receiving or having received exogenous steroids within the 6 months before a stressful event should receive steroid replacement therapy to avoid the problems of adrenal insufficiency.

The magnitude and duration of the increases in both intraoperative and postoperative ACTH and cortisol levels correlate well with the degree of surgical trauma. Cortisol concentrations may remain elevated for up to 2 weeks after femoral fractures and burns. The increased ACTH secretion during surgery is often far greater than that required to produce a maximal adrenocortical response, as demonstrated by the observation that administering exogenous ACTH during surgery did not increase plasma cortisol concentrations. In prolonged critical illness (7 to 10 days), serum ACTH concentrations are low, despite elevated cortisol levels, indicating other mechanisms stimulate the adrenal cortex.[39]

Cortisol is 80% bound to cortisol-binding globulin (CBG), which has a high affinity but low capacity for binding cortisol, and 10% to serum albumin, which has a low affinity but a high capacity for this process. The remaining unbound cortisol, referred to as *free cortisol*, is biologically active.[40] Direct measurement of the free cortisol concentration accounts for the binding effects of albumin, whose concentration is reduced after major surgeries and during sepsis.[41] After major surgery, during sepsis, and after burn injury, free cortisol concentrations are elevated because of both increased total cortisol concentrations and reduced CBG. After major elective surgery, serum total cortisol increased by 55% and CBG decreased by 30%.[42] In the stressed state, the free cortisol level provides a better measure of adrenal responses than total cortisol.[43] Measurements of tissue cortisol levels were significantly elevated in burned and nonburned skin and did not correlate with plasma free or total cortisol measurements but with the extent of the burns. Therefore, plasma levels do not necessarily reflect tissue activity.[44] The reduced CBG is likely caused by inhibition of CBG production by IL-6 and/or increased CBG degradation as a result of elevated neutrophil-released esterase.

The glucocorticoids work through multiple neurocircuits and signaling mechanisms to provide negative feedback to reduce the output of the activated hypothalamic-pituitary axis. Feedback occurs via multiple mechanisms, including a fast feedback mechanism in which glucocorticoids activate membrane glucocorticoid receptors to induce endocannabinoid synthesis in the hypothalamic paraventricular nucleus (PVN) with retrograde cannabinoid type I receptor-mediated suppression of the excitatory drive to PVN neuroendocrine cells.[39] Other mechanisms include corticosteroids shutting off hippocampal, amygdala, and pituitary outputs, causing negative feedback to the hypothalamic-pituitary axis.[39]

Glucagon and Insulin

Glucagon and insulin are both secreted by the pancreas, the former by alpha cells and the latter by beta cells. These hormones enter the portal vein, exposing the liver to high concentrations of both. The principal action of glucagon is to stimulate hepatic glycogenolysis and gluconeogenesis (also see Chapter 39). Glucagon increases hepatocyte cyclic adenosine monophosphate (cAMP) and, via cAMP-activated protein kinase and adenosine monophosphate (AMP)–activated protein kinase, promotes glycogenolysis.[45] When gluconeogenic substrate (lactate, alanine, glycerol) delivery to the liver is increased, glucagon promotes gluconeogenesis with phosphorylation of cAMP-response element modulator (CREM), which then binds to response elements in genes that are upregulated to produce the enzymes of gluconeogenesis.[45] Insulin has the opposite effect; it decreases intracellular cAMP concentrations, preventing gluconeogenesis. Glucagon increases intracellular cAMP via a different receptor—a secondary messenger mechanism than is used by adrenergic mediators.[46] Glucagon also increases hepatic glycogenolysis and ketogenesis during starvation and diabetic ketoacidosis. Whether or not the physiologic levels of glucagon stimulate lipolysis is still debated.[47] In the unstressed state, hypoglycemia, protein–amino acid intake, endorphins, exercise, GH, epinephrine, and glucocorticoids stimulate glucagon secretion. Somatostatin, insulin, and glucose infusion or ingestion suppresses glucagon secretion.

Insulin is an anabolic hormone with many effects. In addition to increasing glucose transport across the cell membranes of adipocytes and myocytes, it stimulates glycogen production, promotes glucose oxidation, inhibits lipolysis in adipose tissue and skeletal muscle, inhibits net fatty acid oxidation, inhibits hepatic and muscle ketogenesis, and increases the rate of amino acid transport and protein synthesis in muscle, adipose tissue, and liver. Insulin operates via phosphatidylinositol 3-kinase and activates Akt (protein kinase B), which, among other processes, results in increases in glucose transporter GLUT-4. The plasma glucagon:insulin ratio is the major determinant of the degree of gluconeogenesis. During fasting and starvation, the ratio is increased, secondary to increased glucagon and decreased insulin concentrations. This increased ratio facilitates glycogenolysis and promotes gluconeogenesis. In the fed state, the reverse is true, with insulin predominating.

Serum glucagon concentrations increase after most types of major surgery. The glucagon:insulin ratio increases because insulin concentrations decrease during surgery. The decreased insulin concentrations are attributed to a suppression of insulin secretion by elevated catecholamine concentrations or increased urinary losses. This suppression can be abrogated by α-adrenergic blockade. The hormonal milieu of low insulin with increased catecholamines, cortisol, and glucagon stimulates gluconeogenesis and, along with insulin resistance, causes hyperglycemia. In patients with sepsis, this mechanism may fail, resulting in hypoglycemia, a situation associated with extremely poor survival rates.[48] Postoperatively, insulin concentrations escalate because of increases in both plasma glucose and epinephrine-induced β-adrenergic stimulation. Unlike starvation, the plasma insulin concentrations are often significantly increased above basal values, although they are inappropriately low for the prevailing level of glycemia.

Counter-Regulatory Hormones

The hormones, glucagon, catecholamines, and cortisol, are called *counter-regulatory hormones* because they oppose the effects of insulin and synergistically act to increase hepatic glucose production. These hormones upregulate the genes responsible for producing the enzymes of the gluconeogenic pathway.[49] Shamoon and associates[50] explored the short-term effects in normal subjects of the

combined infusion of hydrocortisone, glucagon, and epinephrine designed to simulate the plasma levels found in a moderate injury. They observed increased glucose production (gluconeogenesis) and decreased glucose clearance; the effect was more pronounced when all three hormones were administered together than when they were infused individually or in groups of two, suggesting that they act synergistically.[50] Catecholamines and glucagon act synergistically; when either one is infused into normal subjects, only transient elevations in gluconeogenesis occur; when they are simultaneously infused, gluconeogenesis is more prolonged. A possible reason for this synergism is that glucagon increases intracellular cAMP, especially in the liver, by a non–β-receptor mechanism, which could amplify the actions of epinephrine. Cortisol acts synergistically with epinephrine and other β-adrenergic agonists (an action used in the treatment of asthma). Both glucagon and cortisol enhance the transcription of the genes responsible for producing gluconeogenic enzymes, such as glucose-6-phosphatase. Proposed mechanisms include cortisol-induced inhibition of catechol-*O*-methyltransferase and blockade of catecholamine reuptake. Glucocorticoids also prevent β_2-adrenergic receptor downreglation by increasing both β_2-receptor expression and increasing β_2-receptor gene transcription.[51] Additionally, glucocorticoids reduce cytokine concentrations, which is important because both IL-1 and TNF can downregulate β receptors. In addition, prolonged postoperative adrenergic stimulation downregulates and desensitizes β receptors, which is partially reversed by the glucocorticoids.[52] Simultaneous infusion of the three hormones also caused negative nitrogen and potassium balances, glucose intolerance, hyperinsulinemia, insulin resistance, sodium retention, and peripheral leukocytosis. The nitrogen losses appear to be mainly attributable to cortisol because nitrogen balance during cortisol infusion was similar to that during the infusion of all three hormones. The nitrogen losses were also not of the magnitude observed after accidental injury. With hormone infusions, significant alterations in leucine flux and oxidation occurred, but only small increases in 3-methylhistidine excretion, indicating little muscle breakdown. Therefore, other mediators must cause the proteolysis and massive nitrogen loss observed after major injury. In addition, the normal subjects were not febrile, failed to increase acute-phase proteins, and did not have decreased serum iron. When the pyrogenic (stimulates IL-1 secretion) steroid etiocholanolone was injected into normal subjects, fever, leukocytosis, and hypoferremia without elevations in the counter-regulatory hormones, hyperglycemia, or negative nitrogen balance resulted. Infusion of the counter-regulatory hormones plus etiocholanolone simulated more of the features of the response to injury than when they were individually administered. Therefore, both endocrine and inflammatory mediators are active during the response to injury and sepsis.

Reproductive Hormones

The response to surgical and traumatic injury results in hypogonadotropic hypogonadism. The pituitary gland is less responsive to hypothalamically secreted gonadotropin-releasing hormone (Gn-RH), decreasing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). FSH and LH concentrations change little during surgery but decrease on the first postoperative day. Elevated concentrations of CRH and cortisol may also contribute to the suppressed reproductive function.[53] In men, testosterone concentrations are significantly decreased as a result of decreased production and increased clearance. The decrease was in direct relationship to illness severity; total testosterone decreased more than free testosterone, paralleling a decrease in sex hormone–binding protein.[54,55] In patients with burns, the decreased testosterone was due to lowered biologic activity of LH and a suppressed response to peaks in pulsatile LH secretion. In men, the adrenal androgens, dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S), are suppressed after surgery. In premenopausal women, decreased estrogen concentrations during stress are associated with amenorrhea. However, in postmenopausal women, DHEA and DHEA-S were increased after cholecystectomy. This finding is interesting because adrenal androgen concentrations are in decline after menopause. Estradiol concentrations are elevated in critical illness. The magnitude of the increases directly correlates with mortality, regardless of gender.[56] Increased peripheral aromatization from androgens and not from increased production is the main cause of increased serum estradiol.[55]

Thyroid Hormones

During postoperative convalescence, after trauma, after extensive burns, and during sepsis (i.e., during nonthyroidal acute illnesses), alterations in thyroid homeostasis occur with low serum T_3, low or normal T_4, normal free T_4, elevated reverse T_3, and normal TSH. These alterations are called either *nonthyroidal illness syndrome* or *sick-euthyroid syndrome*. Inactivation of T_3 and T_4 is accelerated in skeletal muscle and liver attributable to greater type-3 deiodinase activity and less conversion of T_3 to T_4 because of reduced type-1 deiodinase activity. However, the role of decreased type-1 deiodinase activity has been questioned because T_3 often falls before the enzyme activity decreases.[57] Although TSH concentrations are within the normal range, nocturnal surges are lower, similar to the pattern found in central hypothyroidism. Additionally, sialylation (by oligosaccharide) of TSH is decreased, possibly explaining the altered TSH bioactivity. The mechanism of nonthyroidal acute illness development is still unclear, especially in prolonged critical illness during which T_4 concentrations also decrease. Some investigators have pointed to the lack of TSH elevation in the presence of a low serum T_3 concentration and questioned whether the problem is too little stimulation by thyroid-releasing hormone (TRH).[58] A postmortem study of the paraventricular nuclei of patients with antemortem sick-euthyroid syndrome reinforced this view. A positive correlation between low antemortem serum T_3 and TSH concentrations occurs with total postmortem TRH messenger ribonucleic acid (mRNA) in the nuclei. However, infusion of TRH in the patient with a stressful illness increased TSH and peripheral thyroid concentrations.[59]

Elevated serum levels of IL-6 and possibly IL-1 are associated with the low serum T_3 concentrations during illness.[60] Short-term (4-hour) and long-term (42-day) recombinant IL-6 infusions decrease T_3 but not T_4

concentrations. It is unclear whether elevation of IL-6 is one of the causes of nonthyroidal acute illnesses or is simply an associated phenomenon. Normal subjects infused with endotoxin indicated that TNF does not play a role in endotoxin-induced thyroid hormonal changes. Dopamine infusion decreases basal TSH concentrations, inhibits the TSH response to TRH, decreases both serum T_4 and T_3 levels, and may aggravate sick-euthyroid syndrome. Cessation of dopamine infusion results in increases in TSH, T_4, and T_3. In hospitalized patients older than 65 years of age, low T_3 is a sensitive predictor of poor short-term survival, whereas low free T_3 is a predictor of prolonged mechanical ventilation and mortality in patients in an ICU (also see Chapters 80, 101, and 102).[61,62,62a] There has been interest in treating nonthyroidal acute illnesses with thyroid hormone and TRH. A systematic review of thyroid therapy in patients after surgery showed that intravenous T_3 therapy increased cardiac output but did not affect mortality.[63]

In nonthyroidal acute illnesses, plasma free–T_4 concentrations remain normal, despite reduced total T_4 concentration because of reduced thyroxine-binding globulin (TBG) concentrations. During stress, hepatic synthesis of TBG is reduced and clearance may also be accelerated (protease cleavage). An intriguing aspect of thyroid metabolism in patients with stressful illnesses is that they are hypermetabolic, despite low T_3 and T_4 levels.

CYTOKINES

The response to injury and sepsis includes both neuroendocrine and inflammatory or immune responses. Cytokines, the main mediators of the inflammatory response, are produced by cells of the immune system (e.g., lymphocytes, macrophages), and many have multiple functions (Table 106-1). The pattern of cytokine release, that is, the type and intensity of the stress, is genetically and environmentally determined. These patterns control the severity of the inflammatory response and the degree of the immune response.[64] Some cytokines (e.g., TNF-α, IL-1α/β, interferon [IFN]–γ, IL-6, IL-8, IL-17, IL-18) are proinflammatory (type I), whereas others (e.g., IL-4, IL-10, TGF-β, IL-13, IL-37) are antiinflammatory (type II). Some (e.g., IL-12) induce cellular immunity by directing uncommitted T-helper cells toward the Th1 phenotype, whereas others (e.g., IL-10) induce the Th2 phenotype and enhance humoral immunity. The inflammatory response is controlled by the balance between the proinflammatory and antiinflammatory cytokines. During and after colorectal surgery, IL-6, IL-8, and IL-10 were elevated above the preoperative baseline levels.[65] Moreover, survival from sepsis was correlated with the recurrent secretion of proinflammatory rather than antiinflammatory cytokines, indicating that the inflammatory response's stimulation of the immune system is necessary to overcome sepsis. Furthermore, after trauma the suppression of proinflammatory cytokines IFN-γ and IL-12 along with the elevation of antiinflammatory cytokine IL-10 was associated with immunosuppression and sepsis.[64]

The release of proinflammatory cytokines requires two steps.[66] The initial step is the production of the cytokine pro-form as the result of signals from pathogen-associated molecular patterns (PAMPs). The activation and release of these cytokines, such as IL-1β and IL-18, involves inflammasomes, which are multimolecular complexes that recognize patterns associated with pathogenic bacteria and activate the inflammatory cascade.[67,68] Inflammasomes form in macrophages and contain nucleotide-binding oligomerization domain (NOD)–like receptor proteins (e.g., NLRP3, NLRC4) and DNA-sensing complexes, that congregate and activate proinflammatory caspase-1. NLRC4 activation also induces pyroptosis (a form of programmed cell death) of macrophages that robs macrophage-tropic bacteria of their hiding place, exposing them to the extracellular world and the immune system's full onslaught. The messy nature of pyroptosis is also an effective means of disseminating the inflammatory response and alerting the host to the presence of pathogens. Other inflammasomes, especially those found in neutrophils that contain NLRP3, are involved in the response to other pathogens. These release IL-1 beta and IL--18 but not IL-1 alpha and IL-33.[68a]

Cytokines closely interact with the endocrine system, as demonstrated by significant elevations in ACTH and cortisol after IL-6 administration to patients with cancer. Alternatively, endocrine hormones affect cytokine secretion; for example, cortisol suppresses the secretion of IL-1 and TNF-α.

Cytokines operate via local paracrine, autocrine, and juxtacrine mechanisms, as well as through endocrine effects (see Fig. 106-2). Therefore, plasma concentrations do not necessarily reflect cytokine activity. Cytokine actions are also modulated by a complex network of receptors, receptor-antagonists, and cytoplasmic signaling molecules. For example, the effects of IL-1 are moderated by the simultaneous secretion of IL-1 receptor antagonist (IL-1ra), which blocks its actions. Furthermore, soluble cytokine receptors are generated by the proteolytic cleavage of membrane-bound receptors or by *de novo* production. These circulating soluble receptors bind cytokines and may either neutralize cytokine actions or act as carrier proteins that protect the cytokine from proteolysis. Therefore, they may have either proinflammatory or antiinflammatory functions.

The local actions of cytokines are demonstrated by the acute wound healing process that occurs in overlapping phases: hemostasis, inflammation, proliferation, angiogenesis, and resolution. The inflammatory phase involves infiltration of neutrophils, macrophages, and lymphocytes that secrete growth factors and cytokines. These mediators, acting locally, are active at all stages of wound healing through chemotactic, mitogenic, and other effects. During the first 24 hours, cytokines in the wound drainage in elective incisional hernia repair include high concentrations of both proinflammatory (IL-1α, IL-6, and IFN-γ) and antiinflammatory (IL-10, IL-1ra) cytokines. The concentrations decline over the next few days. It appears that the two types of cytokines balance each other, with the proinflammatory cytokines stimulating immune cells to prevent infection while the antiinflammatory cytokines modulate their actions and promote healing.

Despite cytokine actions being primarily autocrine, paracrine, and juxtacrine, significant research has explored their blood concentrations in stressful situations. In general, the blood concentrations are proportional to the degree of stress. After the moderate stress of total hip replacement surgery, IL-6 was significantly elevated above preoperative levels during the first 6 postoperative hours but began returning

TABLE 106-1 **CYTOKINES**

Cytokine	Function
TNF-α (cachectin) Proinflammatory	• Stimulates T and B cells and macrophages. • Is a chemotactic agent for neutrophils. • Stimulates neutrophil respiratory burst and proliferation. • Stimulates the release of tissue factor from endothelium and monocytes. • Stimulates monocytes to release other proinflammatory cytokines. • Has antitumor activity. • Mediates cancer and AIDS cachexia. • Inhibits synthesis of lipoprotein lipase; suppresses lipogenesis in adipocytes. • Stimulates synthesis of acute-phase proteins. • Mediates part of the cell-mediated immunity against obligate and facultative bacteria and parasites. • Is involved in the development of insulin resistance. • Decreases erythropoietin production that leads to the anemia of inflammation. • Promotes the proliferation of fibroblasts.
IL-1 Proinflammatory	• Stimulates myelopoiesis via the stimulation of G-CSF and GM-CSF. • Is an endogenous pyrogen. • Stimulates T (NK cells) and B lymphocytes and macrophages. • Attenuates anticoagulatory mechanisms and promotes thrombotic processes; induces the production of tissue factor. • Induces monocytes to release various mediators. • Stimulates T-helper cells, which are induced to secrete IL-2 and to express IL-2 receptors. • Promotes the adhesion of neutrophils, monocytes, T cells, and B cells by enhancing the expression of adhesion molecules such as ICAM-1 and ELAM. • Mediates inflammatory reactions; enhances the metabolism of arachidonic acid (in particular, prostacyclin and PGE_2).
IL-4 Antiinflammatory	• Inhibits macrophage activity. • Proliferates and activates B cells. • Enhances Th2 cell differentiation. • Inhibits cell activation of NK cells induced by IL-2.
IL-6 Proinflammatory and antiinflammatory	• Stimulates the acute-phase protein response. • Stimulates the hypothalamus to secrete CRF. • Inhibits 5′-deiodinase in sick euthyroid syndrome, which converts T_4 to T_3. • Stimulates B lymphocytes and is involved in their differentiation into plasma cells. • Induces the differentiation of mature and immature T cells into cytotoxic T cells in the presence of IL-2. • Stimulates the secretion of antibodies.
IL-8 Proinflammatory	• Is a neutrophil chemotactic agent. • Synthesis is strongly stimulated by IL-1 and TNF-α. • Activates neutrophils; releases enzymes from granules. • Is chemotactic for all known types of migratory immune cells; enhances the expression of adhesion molecules.
IL-10 Antiinflammatory	• Is produced by and downregulates the function of Th1 and Th2 cells. • Inhibits antigen-presenting cell activity. • Suppresses macrophage activity. • Inhibits the production of proinflammatory cytokines such as IFN-γ, IL-2, and TNF-α in Th1 subpopulations. • Is stimulated by bacterial lipopolysaccharides in macrophages. • Inhibits the synthesis of IL-1, IL-6, and TNF-α by promoting the degradation of cytokine mRNA. • Prevents the activation of macrophages.
IL-13 Antiinflammatory	• Downregulates macrophage activity, reducing the production of proinflammatory cytokines (IL-1, IL-6, IL-8, IL-10, IL-12) and chemokines (MIP-1, MCP) in response to IFN-γ or bacterial lipopolysaccharides. • Enhances the production of IL-1ra. • Strongly inhibits tissue factor expression induced by bacterial lipopolysaccharides, and reduces the pyrogenic effects of IL-1 or TNF, thus protecting endothelial cells and monocytes against inflammatory mediator–induced procoagulant changes.
IFN-γ Antiinflammatory	• Has antiviral and antiparasitic activities. • Main biologic activity is as an immunomodulatory. • Activating macrophages is a major function. • Influences cell-mediated mechanisms of cytotoxicity. • Is a modulator of T-cell growth and functional differentiation. • Is the hallmark cytokine of Th1 cells.

AIDS, Acquired immunodeficiency syndrome; *CRF*, corticotropin-releasing factor; *ELAM*, endothelial leukocyte adhesion molecule; *G-CSF*, granulocyte colony-stimulating factor; *GM-CSF*, granulocyte-macrophage colony–stimulating factor, *ICAM-1*, intercellular adhesion molecule-1; *IFN*, interferon; *IFN-γ*, interferon gamma; *IL*, interleukin; *IL-1ra*, interleukin-1 receptor antagonist; *MCP*, monocyte chemoattractant protein; *MIP-1*, macrophage inflammatory protein-1; *mRNA*, messenger ribonucleic acid; *NK*, natural killer; *PGE_2*, prostaglandin E2; *Th1*, T-helper 1 cells; *Th2*, T-helper 2 cells; *TNF-α*, tumor necrosis factor alpha.

toward baseline by the first postoperative day. In contrast, IL-1β, IL-12, IL-10, and IL-8 levels were not elevated.[69] Laparoscopic radical prostatectomy resulted in lower IL-10, IL-6 and IL-1 beta immediately after surgery and postoperative day 1 than open radical prostatectomy.[69a]

Many cytokines have multiple functions (see Table 106-1). For example, IL-1 causes fever, induces hepatic acute-phase protein synthesis, upregulates prostanoid synthesis, induces the maturation of B lymphocytes, and activates natural killer (NK) lymphocytes. IL-6 (also called *B-cell–stimulating factor* and *hepatocyte-stimulating factor*) has endocrine and local functions. Many cells produce IL-6, including monocytes, fibroblasts, glial cells, and lymphocytes. Its production is stimulated by endocrine hormones such as catecholamines and suppressed by cortisol and estrogens. The soluble IL (sIL) receptors of the IL-6 family (e.g., sIL-6R, sIL-11R) are agonists capable of transmitting signals through interaction with the universal signal-transducing receptor for all IL-6 family cytokines, gp130 (see Fig. 106-2).

TNF-α, a multifunctional proinflammatory cytokine predominantly secreted by monocytes and macrophages, affects lipid metabolism, immunity, hematopoiesis, coagulation, and endothelial function (see Table 106-1). TNF-α has seeming contradictory properties. For example, it induces neutrophil proliferation during inflammation but it can also induce neutrophil apoptosis.[70] Moreover, TNF-α intensifies the inflammatory response by prolonging the survival of inflammatory cells through the suppression of Fas-mediated apoptosis (Fig. 106-3). The multiple roles of TNF are demonstrated by the TNF blockers, etanercept, adalimumab, and infliximab, which are used to treat rheumatoid arthritis. However, these drugs

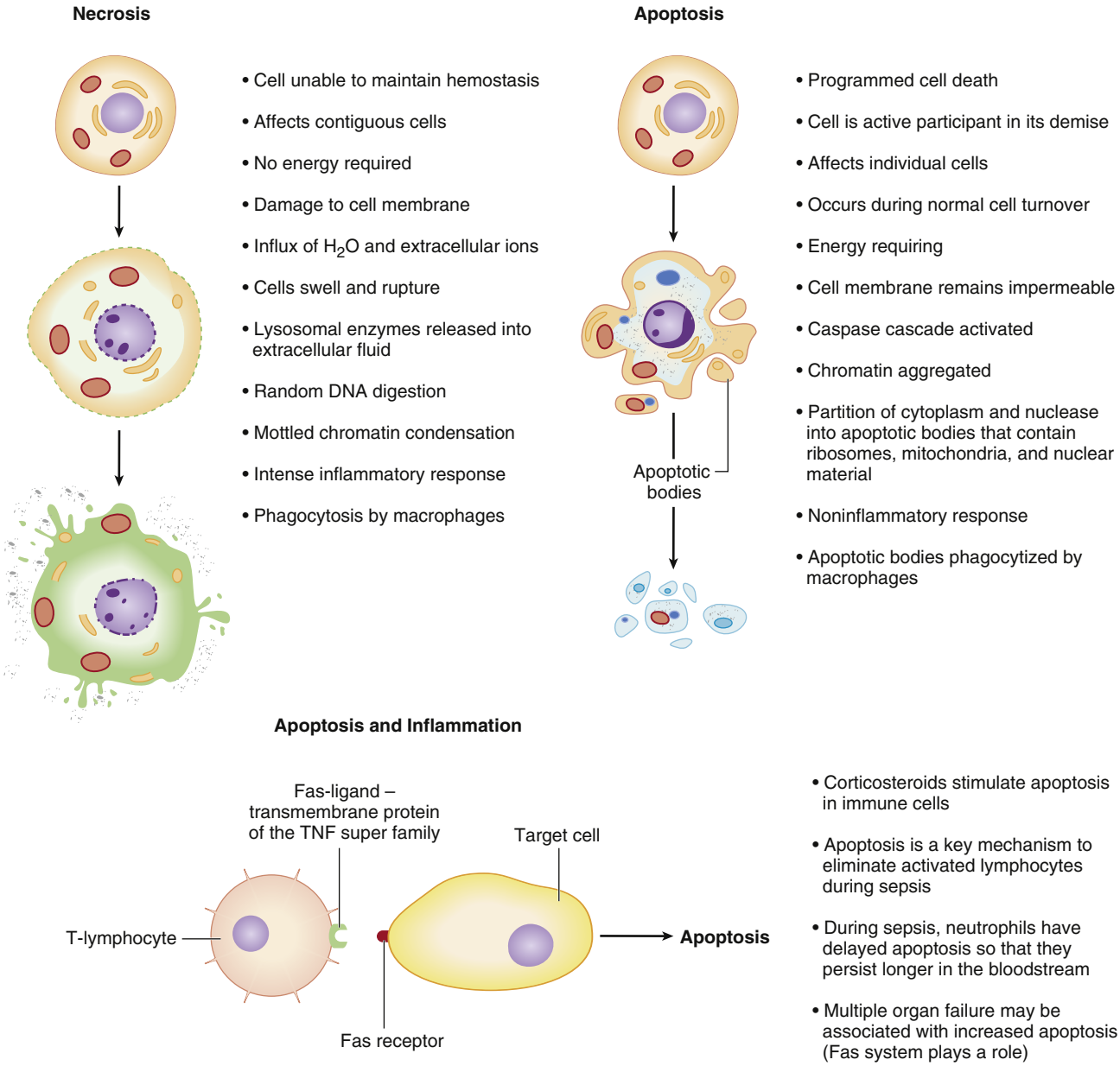


Figure 106-3. The differences between necrosis and apoptosis are shown. The importance of apoptosis during inflammation is also diagrammed. *DNA*, Deoxyribonucleic acid; *H_2O*, water; *TNF*, tumor necrosis factor.

increase the risk for developing tuberculosis because TNF plays a crucial role in the body's immune defense against the mycobacteria causing this disease.[71]

ADIPOKINES

Besides storing fat, adipose tissue is a metabolically active endocrine organ with metabolic effects differing, depending on the location of the adipose tissue.[72] Adiponectine, one of the many adipokines, is vasculoprotective and antiatherogenic because it can stimulate vascular endothelial nitric oxide (NO) production, which leads to decreased platelet aggregation and vasodilation.[72] The antiinflammatory actions of adiponectine are due to its suppression of TNF-α production and the sensitization of tissues to insulin. Leptin controls appetite, thus modulating food intake and body weight. Leptin concentrations are proportional to insulin levels and inversely proportional to glucocorticoid concentrations. Resistin stimulates the secretion of proinflammatory cytokines and decreases the endothelial production of adhesion molecules. In addition, adipose tissue secretes proinflammatory cytokines, such as TNFα, IL-1, IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1).[73]

During critical illness, plasma adiponectine levels are decreased, leptin concentrations are either lower or unchanged, and resistin levels are increased.[74,75,75a] In such situations, serum resistin concentrations correlate with inflammatory mediators such as C-reactive protein (CRP), IL-6, and TNF-α.[76] In the lungs of patients with viral or bacterial pneumonia there is increased expression of leptin with evidence from animal studies that leptin has pulmonary pro-inflammatory properties.[76a] After major abdominal surgery, serum adiponectine concentrations and its intraadipocyte mRNA were decreased, intraadipocyte IL-6 mRNA was increased, and serum resistin levels increased.[77,78] Resistin, IL-6, and MCP-1 mRNA expression increased during cardiac surgery in both subcutaneous and epicardial adipose tissue, whereas TNF-α expression also increased in subcutaneous adipose tissue.[79] This upregulation of inflammatory mediators along with the downregulation of adiponectine indicate that adipose tissue contributes to the altered metabolic milieu found during surgical, traumatic, and septic stress. Furthermore, the infusion of endotoxin into healthy subjects indicated that adipose inflammatory and insulin-signaling pathways might be involved in the systemic insulin resistance found in such conditions.[80]

ENDOTHELIAL CELLS

Vascular endothelial cells are metabolically active, playing an active role in the stress response by synthesizing various important mediators such as NO and adhesion molecules.[80a] The adrenergic hyperactivity, hypoperfusion, hypoxemia, and inflammation associated with trauma and sepsis trigger this enhanced endothelial cell activity (Fig. 106-4).

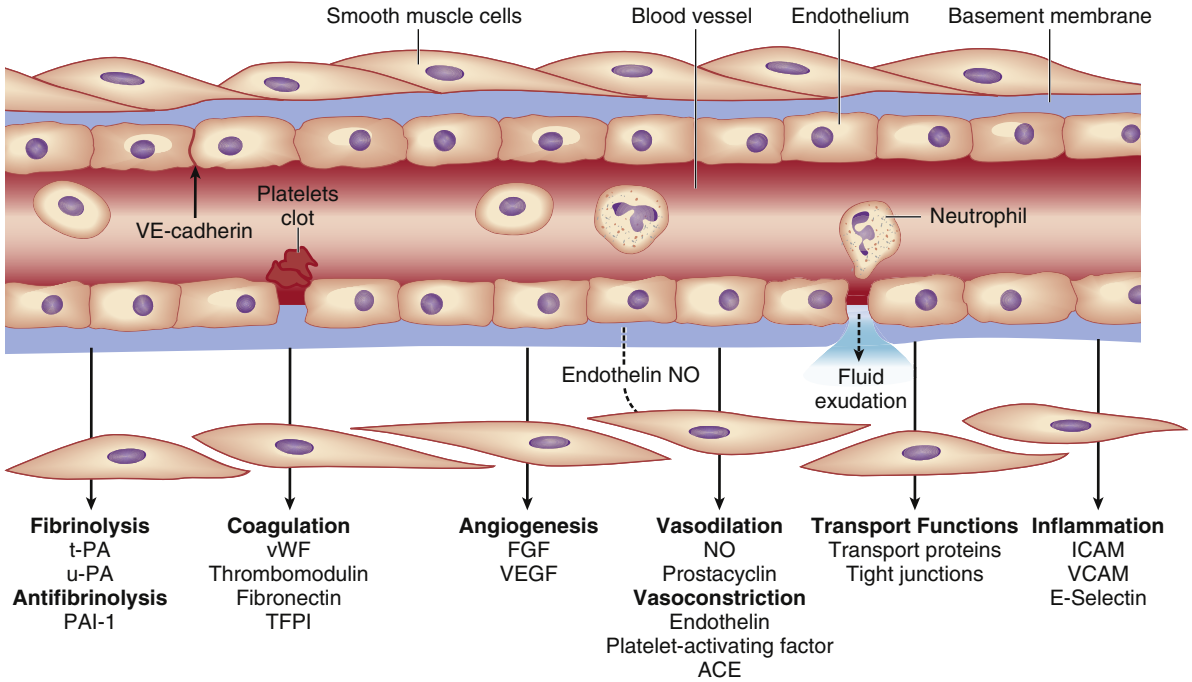


Figure 106-4. Endothelial cells have many functions. Nitric oxide (NO), produced by endothelial cells, vasodilates blood vessels by relaxing adjacent myocytes, whereas endothelin causes vasoconstriction. The NO-endothelin system is the local controller of vascular tone. During sepsis, inflammatory cytokines, such as tumor necrosis factor (TNF), upregulate inducible NO synthetase (iNOS), increasing endothelial production of NO and resulting in vasodilation. During sepsis, endothelial disruption occurs because of the shedding of the glycocalyx, the thin layer of glucosaminoglycans covering the endothelial surface, increased expression of adhesion molecules, resulting in white blood cell attachment and the disruption of both the vascular endothelial (VE)–cadherin and the basement membrane and in the exudation of fluid into the extracellular space. Moreover, the number of circulating endothelial cells is increased. Adhesion molecules and selectins recruit leukocytes to enter tissues. *ACE*, Angiotensin-converting enzyme; *FGF*, fibroblast growth factor; *ICAM*, intercellular adhesion molecule; *PAI-1*, plasminogen activator inhibitor-1; *TFPI*, tissue factor pathway inhibitor; *t-PA*, tissue-plasminogen activator; *u-PA*, urinary type plasminogen activator; *VCAM*, vascular cellular adhesion molecule; *VE-cadherin*, vascular endothelial cadherin (calcium-dependent adhesion); *VEGF*, vascular endothelial growth factor; vWF, von Willebrand factor.

IMMUNOLOGIC-COAGULATION CONNECTION

Surgery, burns, and trauma result in leukocytosis, thrombocytosis, and anemia. The granulocytosis that occurs with surgery and infection is mediated by the cytokine-induced release of the hematopoietic growth factor, granulocyte colony-stimulating factor (G-CSF). G-CSF increases neutrophil, monocyte, and T-lymphocyte production and is increased above preoperative levels for at least 1 week after major surgery.[81] Thrombopoietin, which increases in concert with IL-6 and acute-phase reactants, induces thrombocytosis.[82] Anemia of inflammation (also called anemia of chronic disease) occurs during acute and some chronic stressed states. Erythropoiesis is suppressed because of an inability to incorporate iron into erythrocyte precursors, despite the presence of adequate bone marrow iron stores. This suppression is ascribed to inflammatory cytokines, such as IL-6, stimulating the secretion of hepcidin, a hepatocyte-produced regulator of iron hemostasis. The increased hepcidin concentrations reduce the activity of ferroportin, thus reducing the transfer of iron out of macrophages, causing iron sequestration in macrophages.[83,84] In addition, erythropoietin secretion is decreased and sensitivity to its actions is reduced. [84a]

Significant bidirectional cross-talk occurs between the inflammatory and coagulation systems; for example, increased soluble CD40 ligand, a platelet-derived mediator of the TNF family, interacts with CD40 receptors on endothelial and immune cells, leading to increased proinflammatory, procoagulant, and immunomodulatory functions.[85,86] During the perioperative period, hypercoagulability occurs, secondary to upregulated procoagulant pathways, decreased physiologic anticoagulants and reduced fibrinolysis.[87] The former is caused by a combination of decreased antithrombin, tissue factor pathway inhibitor (TFPI), and protein C coupled with increased tissue factor (TF), causing increased thrombin generation and fibrin deposition and resulting in microvascular thrombosis. Decreased fibrinolysis is due to reduced tissue plasminogen activator (t-PA) and increased plasminogen activator inhibitor-1 (PAI-1). Cytokines are the responsible mediators: TNF-α upregulates PAI-1, monocytes express TF, and IL-6 stimulates TF. Furthermore, ex-vivo platelet reactivity increases, especially during sepsis. Acute-phase proteins contribute to the procoagulant state. Fibrinogen concentrations are elevated, as are those of α_1-antitrypsin and α_2-macroglobulin, which inhibit protein C. Increased C4-binding protein lowers free protein S, whereas CRP increases the expression of TF by monocytes and neutrophils. Circulating TF-expressing microparticles from activated or apoptotic cells also increase in sepsis and trauma.[88] The hypercoagulable state is also induced by other factors, including local tissue damage (PAI is secreted by endothelial cells) and materials such as methyl methacrylate monomers and bone marrow debris. Elevated thrombopoietin concentrations enhance platelet aggregation and contribute to the formation of monocyte-platelet aggregates.[89] In patients who are severely injured, the predominate hypercoagulable state is counterbalanced by the release of factors promoting hypocoagulability such as t-PA, soluble thrombomodulin, and glycocalyx shedding (release of heparin-like substances).[90]

During postoperative convalescence (days 3 to7), hypercoagulability gradually abates. Hypercoagulability is not triggered by the counter-regulatory hormones. Rather, when a cocktail of these hormones plus angiotensin II and vasopressin was infused into normal volunteers, fibrinolytic and anticoagulant activity increased; fibrinogen, t-PA, and protein C concentrations increased, as did platelet activity. These results are reinforced by the anticoagulant effects of an epinephrine infusion begun before an endotoxin infusion in normal subjects.

Regional anesthesia, especially after lower body surgery, causes less hypercoagulability than general anesthesia and is associated with less deep vein thrombosis (also see Chapter 56). Laparoscopic cholecystectomy appears to cause less hypercoagulability than open cholecystectomy.[91]

The procoagulant state, in turn, accelerates the inflammatory response. Thrombin, acting through protease-activated receptors, upregulates cytokines (e.g., IL-6, IL-8, MCP-1) and increases adhesion molecule expression. The TF/factor VII complex increases inflammatory responses of macrophages and neutrophils, as evidenced by increased plasma concentrations of IL-6 and IL-8 on infusion of recombinant factor VII into normal subjects.[92] Inflammation plus microvascular thrombosis is thought to be a cause of multiple organ system dysfunction.

FASTING AND MALNUTRITION

Fasting results in adaptive responses that permit the body to continue functioning, despite a lack of nutrient intake. During the 24 to 48 hours after cessation of nutrient intake, glycogen stores are broken down (glycogenolysis) to provide glucose to the tissues. This glucose is vital for the brain, red blood cells, skin, and renal medulla, which have obligatory glucose requirements. Glycogenolysis is mediated by an increased glucagon:insulin ratio (increased glucagon and decreased insulin), which also promotes endogenous glucose production (gluconeogenesis). In addition to the increases in glucagon and decreases in insulin, hypoglycemia is avoided by small increases in catecholamine and cortisol secretion. The increase in catecholamine-induced β-adrenergic stimulation accelerates lipolysis so that triglycerides (TGs) stored in adipose tissue are broken down to free fatty acids (FFAs) and glycerol. As glycogenolysis declines, some of the FFAs undergo hepatic conversion to ketones (β-hydroxybutyrate and acetoacetate), which are then used as energy sources.[93,94] As glycogen is depleted, glucose is increasingly provided by gluconeogenesis, delivering more than 90% of the glucose after 42 hours of fasting.[94] Glycerol released during lipolysis and lactate produced by glycolysis are among the substrates for gluconeogenesis.

As starvation continues, skeletal and smooth muscles undergo proteolysis to amino acids. The amino acids, alanine and glutamine, are transported primarily to the liver, but some are also transported to the kidneys to be used as substrates for gluconeogenesis. This muscle breakdown results in a negative nitrogen balance (catabolism). As starvation progresses, the body adapts by reducing the rate of gluconeogenesis and muscle breakdown, which,

along with decreases in free T_3 and catecholamines, reduces REE. Decreases in serum leptin are associated with the decrease in T_3. The reduced muscle protein breakdown results in lower nitrogen losses so that nitrogen balance becomes less negative. The decrease in gluconeogenesis is possible because the brain adapts to using ketones for some of its energy needs.[95] Simultaneously, adenosine triphosphate (ATP) is produced from the oxidation of fatty acids released by lipolysis.

Prolonged starvation leads to weight loss, secondary to major losses of fat and lean (muscle) body mass. Significant weakness and fatigue develop as the result of proteolysis and reduced muscle protein synthesis. Sodium and water retention also occurs. Prolonged starvation reduces immune function and results in increased adherence of gram-negative bacteria to nasopharyngeal and pulmonary endothelial cells. This bacterial adherence, along with weakness of the respiratory muscles and immune system, makes these patients susceptible to pneumonia, the leading cause of death in patients who are starved or severely malnourished (also see Chapters 101 and 102).

EATING

Eating sets into motion a series of steps that digest, absorb, and metabolize the ingested food. Gut hormones initiate a sequence of systematic events by signaling the body to secrete hormones such as insulin. Ingested carbohydrates are converted to glucose and stimulate insulin secretion, and the glucose not immediately needed for energy is stored as glycogen or converted to fat (lipogenesis). Ingested proteins are digested and broken down into amino acids, used to synthesize proteins, and serve as precursors for neurotransmitters and other substances. Fats are stored and used for energy or as precursors for prostaglandins and other substances. Food ingestion increases metabolic rate—diet-induced thermogenesis or thermogenic effects of food—and contributes 10% to 15% of total daily energy expenditure. Protein ingestion increases metabolic rate more than isoenergetic amounts of carbohydrates or fat.[96] The postprandial rise in energy expenditure lasts for 3 to 4 hours.

METABOLIC RESPONSES TO SURGICAL AND TRAUMATIC INJURY

The metabolic responses to surgical and traumatic stress differ greatly from the response to starvation. Unlike the adaptive responses aimed at preserving body mass that occur during starvation, the response to stress has been called *auto-cannibalism*.[97] This categorization is occasioned by the loss of fat and lean body mass caused by an obligate catabolic state with proteolysis, gluconeogenesis, lipolysis, hypermetabolism, and insulin resistance. Autocannibalism is not reduced to any great extent by exogenous nutrients (also see Chapter 81).

The intensity and duration of the metabolic response to surgery and trauma depend on the magnitude of injury, total surgical time, amount of intraoperative blood loss, and degree of postoperative pain. The smaller injury of laparoscopic surgery, compared with open surgery, results in lower concentrations of IL-1, IL-6, and the acute-phase CRP. The greatest metabolic responses are observed after a severe burn injury (>40% body surface area) with metabolic rates twice normal and catabolism that lasts for many months, leading to immunodepression, recurrent infections, and poor wound healing.[21]

CARBOHYDRATE METABOLISM

Surgical and accidental injury increase the secretion of the counter-regulatory (to insulin) hormones cortisol, catecholamines, and glucagon, resulting in elevated endogenous glucose production, secondary to accelerated hepatic gluconeogenesis (Fig. 106-5). This increased glucose production, coupled with peripheral tissue resistance

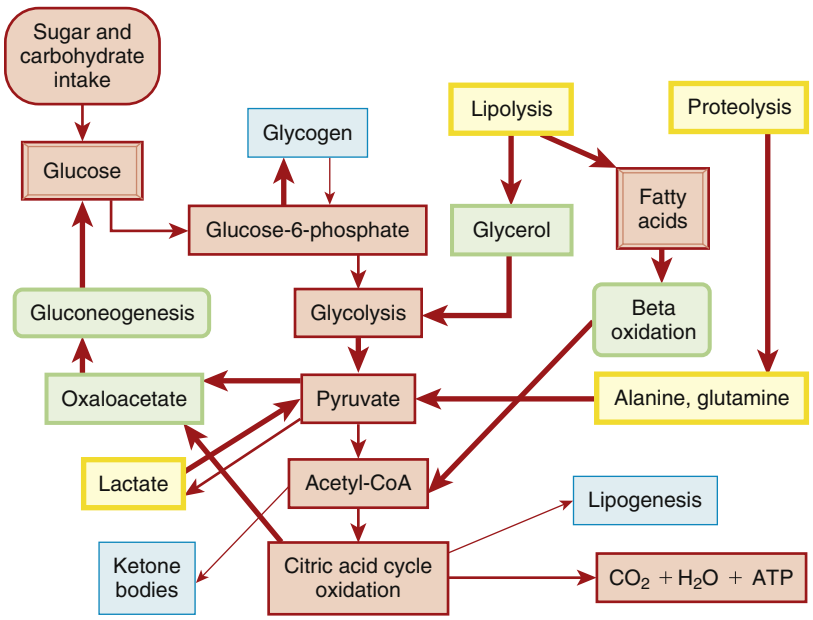


Figure 106-5. The metabolic milieu during stress. The rate of endogenous glucose production (gluconeogenesis) is greatly increased. Glycerol (from lipolysis), alanine (from proteolysis), and lactate (from the wound) are the substrates. Because of insulin resistance, less glucose is used to produce energy adenosine triphosphate (ATP); thus β-oxidation of fatty acids becomes the major energy-producing pathway. Exogenous glucose intake does not decrease the rate of gluconeogenesis. The production of ketones is not greatly increased because of normal-to-elevated concentrations of insulin. *Acetyl-CoA*, Acetyl–coenzyme A; *CO_2*, carbon dioxide; *H_2O*, water.

to insulin, results in reduced glucose utilization and hyperglycemia. Serum insulin concentrations are normal or elevated but are insufficient to prevent hyperglycemia but do prevent ketosis. Hyperglycemia is thought to ensure a ready supply of glucose to predominantly glucose-consuming cells, such as the wound inflammatory cells and immune cells.

Insulin resistance is defined as impaired glucose disposal in the presence of either normal or elevated serum insulin concentrations.[98] Insulin resistance occurs in peripheral tissues, reduces insulin sensitivity by 50% to 70%, compared with healthy controls, is likely due to a postreceptor defect that hinders cellular glucose uptake, and is related to the magnitude of surgery, the extent of burn, or the severity of sepsis.[98] Impaired activity of the intracellular glucose transport system or nonoxidative glucose disposal (i.e., reduced muscle glycogen synthetase activity) is the possible cause of this postreceptor defect.[99] Increased protein degradation, mitochondrial dysfunction, and accumulation in the endoplasmic-sarcoplasmic reticulum of unfolded protein, leading to a proapoptotic state, are associated with insulin resistance.[100,101] Insulin resistance can persist for up to 3 weeks after elective open cholecystectomy and up to 3 years after major burns.[100,102,103] In patients in the medical ICU, the severity of insulin resistance is associated with the severity of illness, body mass index (BMI), and degree of hypermetabolism.[98]

In patients with stressful illnesses, the overall amount of glucose oxidized (especially considering the overall hypermetabolism) may be decreased, despite a glucose oxidization pathway that is intact, because insulin resistance limits the rate of glucose uptake into the cell. The incremental response to increases in insulin concentration is maintained, but the ability to reduce blood glucose concentration per insulin concentration is significantly diminished. Despite the insulin resistance, the overall peripheral uptake of glucose is often normal or mildly elevated owing to increased non–insulin-mediated glucose uptake and the large amounts of glucose (as a result of hyperglycemia) being presented to the resistant insulin pathway. However, relative to the blood glucose concentration and hypermetabolism, the uptake is small.

Glucose can be oxidized to produce ATP, water, and carbon dioxide (CO_2); converted to glycogen for storage in the liver and muscles; or converted to fat. The latter process is called *lipogenesis* and occurs in both liver and adipose tissue, although the latter appears to be the main site for lipogenesis. Under normal circumstances, carbohydrate intake inhibits fat oxidation, increases glucose oxidation, and promotes fat storage. Lipogenesis is quantitatively unimportant in humans because the rate of lipogenesis does not exceed the rate of lipid oxidation. Yet, when carbohydrate intake exceeds total energy expenditure (TEE), lipogenesis becomes a more important pathway, and respiratory quotients (RQs) may exceed 1.0, indicating net lipogenesis (Box 106-1). Patients who are critically ill and administered intravenous glucose at 4 mg/kg/min as part of glucose-based total parenteral nutrition (TPN) exhibited some increased hepatic *de novo* lipogenesis, despite achieving an RQ of only 0.90.[104] This lipogenesis occurred even though lipogenetic capability is thought to be reduced in surgical or septic stress. The reduced lipogenesis is possibly secondary to TNF, which, among other things, can induce apoptosis of preadipocytes and adipocytes. IL1-β may also inhibit lipogenesis in human adipocytes.

BOX 106-1 ***Criteria for the Systemic Inflammatory Response Syndrome and Sepsis***

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

Two or more of the following criteria are required:

1. Body temperature: >38° C or <36° C
2. Heart rate: >90 beats/minute
3. Respiratory rate: >20 breaths/minute or partial arterial pressure of carbon dioxide ($Paco_2$): <32 mm Hg
4. White blood cell (WBC) count: >12,000 mm^3 or <4000 mm^3 or >10% immature forms

SEPSIS

SIRS plus a documented infection site (documented by positive culture for organisms from that site). Blood cultures do **NOT** need to be positive. Although SIRS, sepsis, and septic shock are commonly associated with bacterial infection, bacteremia may not be present.

SEVERE SEPSIS

Sepsis plus associated organ dysfunction, hypoperfusion abnormalities, **OR** hypotension.

Hypoperfusion abnormalities include but are not limited to:

1. Lactic acidosis
2. Oliguria
3. Acute alteration in mental status

SEPTIC SHOCK

Sepsis-induced hypotension, despite fluid resuscitation **PLUS** hypoperfusion abnormalities.

LIPID METABOLISM

Stressful situations (e.g., injury, sepsis) alter lipid metabolism. The major change is accelerated lipolysis attributed to increased β_2-adrenergic stimulation.[105] Stimulation of the β_2-receptors increases cAMP concentrations, which stimulates the activity of hormone-sensitive lipase through protein kinase A, and also likely adipose TG lipase (Fig. 106-6).[106] Endotoxin appears to stimulate lipolysis also via inflammatory IKKB/NF-kappaB (IκB kinase–nuclear factor kappa–light-chain-enhancer of activated B cells) pathway.[107] The lipolytic response to β_2 stimulation is greater in lean, rather than obese, individuals. β_3-adrenergic receptors also play a role in human lipolysis. Elevated concentrations of glucagon, TNF-α, IL-1, INF-α, and INF-γ likely have roles in stimulating lipolysis.[108] IL-6 stimulates lipolysis in skeletal muscle but not adipocytes.[109] Insulin resistance contributes to lipolysis because the antilipolytic effect of insulin is attenuated.[98] Regional variations in lipolytic rates exist. Visceral fat cells have the highest rate as a result of increased β_2- and β_3-receptor activity and reduced α_2-receptor activity. Subcutaneous fat has less lipolytic activity as a result of greater insulin receptors and α_2-receptor activity. These regional differences originate from differences in adipose stem cells.[110] The RQ in injured patients is consistently lower than in normal subjects for a given level of intake,

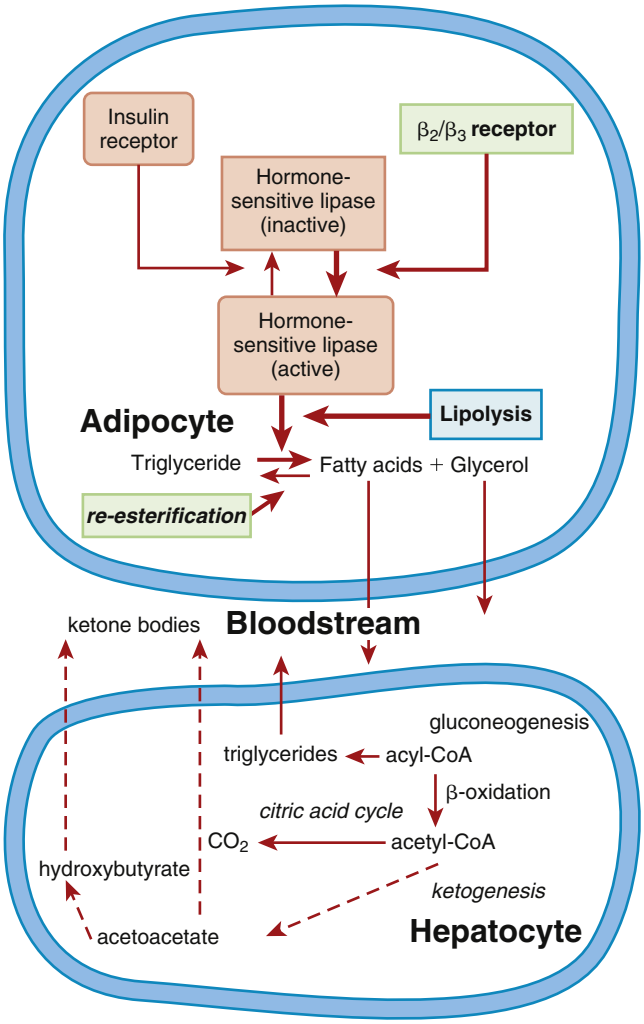


Figure 106-6. Lipid metabolism during the stressed state. Catecholamines stimulate β_2 and β_3 receptors, activating hormone-sensitive lipase, leading to lipolysis. Free fatty acids are transported to the liver where they undergo β-oxidation and are the main source of energy during stress (palmitoyl-CoA yields a net of 130 adenosine triphosphate [ATP]). Glycerol released by lipolysis is a substrate for gluconeogenesis and is converted to glucose. Because insulin concentrations are elevated, ketone production is not increased. Both lipolysis and re-esterification are increased, leading to a futile cycle. *CoA*, Coenzyme A; *CO_2*, carbon dioxide.

indicating greater fat oxidation (Table 106-2). Infusion of glucose in amounts that lead to net fat synthesis in normal subjects fails to suppress fat oxidation in patients who are injured and with sepsis, leading to negative fat balance. Plasma FFA concentrations are high because the lipolytic rate exceeds the rate of fat oxidation.

Rapid glycerol and FFA turnover rates reflect the accelerated lipolysis observed during stress. The increased lipolysis increases the systemic supply of circulating FFAs. However, the turnover rates are greater than those expected from the increases in the plasma concentrations of these substrates, which indicates that both increased re-esterification of FFAs to TGs and increased lipolysis of TGs to FFAs have occurred. This increased activity of the TG-FFA/glycerol substrate cycle is thought to be one of the causes of the hypermetabolism observed during stress (Fig. 106-7). β-Adrenergic receptor blockade with propranolol decreases lipid oxidation and the resting metabolic rates of patients with burns. Glucose infusions further increase lipolysis during abdominal surgery because they increase sympathetic nervous system activity.

In the stressed state, the relative contribution of fat oxidation to REE is increased, whereas the contribution of glucose oxidation is decreased. FFAs released by lipolysis undergo β-oxidation, which is the predominant ATP-producing pathway in patients who are stressed (see Figs. 106-5 and 106-6). This situation is reflected in observations made after esophagectomy when a gradual decrease in the contribution of fat oxidation to energy production and an increase in the contribution of glucose oxidation occur as patients convalesce.

PROTEIN METABOLISM

Among the hallmarks of the metabolic response to injury and sepsis is catabolism (negative nitrogen balance). Accelerated proteolysis of skeletal muscle, which provides some of the substrate for increased hepatic gluconeogenesis (see Fig. 106-5), causes catabolism. Reducing the rate of hepatic gluconeogenesis with somatostatin does not decrease the rate of peripheral protein breakdown, demonstrating that the accelerated rate of hepatic glucose production is not linked to the increased level of peripheral protein breakdown. The degree of nitrogen loss is proportional to the degree of stress and abates as the patient convalesces. After severe burns, protein breakdown and subsequent amino acid efflux from muscle is increased almost twofold. The endocrine stress hormones, specifically cortisol, only partially modulate the enhanced protein breakdown. Instead, other mediators such as TNF-α, IL-1, IL-6, and IFN-γ mediate catabolic activity.[111] The balance between these catabolic mediators and anabolic hormones (e.g., insulin and IGFs) determine the magnitude of catabolism. Among the pathways responsible for skeletal muscle proteolysis are lysosomal cathepsin and the ubiquitin–proteasome proteolytic pathways.[111,112] The liver also contributes to catabolism through increased clearance of α-amino nitrogen (urea). After surgery, the rate of this conversion is doubled. Blockade of glucagon and cortisol secretions with a combination of etomidate, somatostatin, and thoracic epidural anesthesia decrease this clearance, thus indicating roles for glucagon and possibly cortisol and afferent neural reflexes in this process.

Conflicting data regarding the mechanism of the net loss of skeletal muscle protein has been reported. Constantin and associates[112] report increased protein breakdown plus reduced muscle protein synthesis (e.g., 31% decrease 24 hours after open cholecystectomy) whether saline or TPN is infused.[112] The deranged protein metabolism is profound because administering TPN after open cholecystectomy did not prevent the decline in muscle protein synthesis observed 24 hours after surgery. Liver biopsies taken during surgery demonstrated depressed hepatic protein synthesis after 20 minutes of surgery that further decreased as the surgery progressed. Tissues with rapidly replicating cells, such as enterocytes, immune cells, and keratinocytes, also exhibit reduced protein synthesis. Other investigators report that the net negative

TABLE 106-2 ENERGY EXPENDITURE AND CALORIC REQUIREMENTS

Energy Expenditure (Definitions)

Basal energy expenditure (BEE); also called *basal metabolic rate* (BMR): Is the energy expended on awakening from a 12-hour fast; it is measured in a thermoneutral environment (25° C).
Thermogenic effect of food; also called *specific dynamic action*: Is the energy expended after the ingestion of food. Energy expenditure may increase 5% to 10% after a meal.
Resting energy expenditure (REE): Is the energy expended while resting in the supine position with eyes open. It includes the thermogenic effect of food if performed within a few hours of a meal or during continuous infusions of nutrients such as during continuous total parenteral nutrition (TPN) administration. REE is approximately 10% greater than BEE.
Sleeping energy expenditure (SEE): Is the energy expended during sleep and is usually 10% to 15% lower than REE.
Activity energy expenditure (AEE): Is the energy expended during physical activity. During maximum exercise, AEE can be 6- to 10-fold greater than the BEE.
Environmental temperature: Energy expenditure increases to warm patients who are in a cold environment. Warming occurs through shivering and increased metabolism of brown fat (neonates).
Fever: Fever increases the metabolic rate 10% per degree Celsius (C) (or 7% per degree Fahrenheit (F).
Total energy expenditure (TEE): Is the total energy expended over 24 hours; that is, TEE is the sum of the energy expended during periods of sleep, resting, and activity.

Estimating Resting Energy Expenditure

1. Harris-Benedict equation
   Males: eBEE (kcal/d) = 66 + (13.7 × W) + (5 × H) – (6.8 × A)
   Females: eBEE (kcal/d) = 655 + (9.6 × W) + (1.7 × H) – (4.7 × A)
   eREE = eBEE × stress factor
   eTEE = eREE × activity factor
   eBEE, Estimated basal energy expenditure; *eREE*, estimated resting energy expenditure; *eTEE*, estimated total energy expenditure; *W*, weight (kg); *H*, height (cm); *A*, age (years).
2. Stress factors
   Nonsedated patients who are spontaneously breathing:
   Major surgery: 15%-25%
   Infection: 20%
   Long-bone fracture: 20%-35%
   Malnutrition: Subtract 10%-15%
   Burns: Up to 120%, depending on the extent
   Sepsis: 30%-55%
   Major trauma: 20%-35%
   Chronic obstructive pulmonary disease (COPD): 10%-15%
   Sedated patients who are mechanically ventilated (full ventilatory support): Subtract 10%-15%
3. Activity factors
   Sedated patients who are mechanically ventilated: 0%-5%
   Patients who are mechanically ventilated (assisted ventilation): 5%-10%
   Bedridden, nonsedated patients who are spontaneously breathing: 10%-15%
   Patients who are sitting in a chair: 15%-20%
   Ambulating patients: 20%-25%

Measuring Energy Expenditure

Indirect calorimetry involves measuring oxygen consumption (VO_2) and carbon dioxide production (Vco_2). The gas exchange method is used to measure VO_2 and Vco_2, whereas the Fick method can be used to measure only VO_2.
Weir equation: Energy expenditure (EE) (kcal/d) = 1.44 (3.9 × VO_2) + (1.1 × Vco_2)
To provide the REE: Measurements made at rest
To determine the TEE: REE × activity factor
To provide the TEE: Continuous measurement over 24 hours

Measuring Nitrogen Balance

N balance = [N intake] – [N output]; Negative balance = catabolism; Positive balance = anabolism
Where [N intake] = all protein/amino acid intake over 24 hours, whether enteral or parenteral
[N output] = [UUN + 4 + EL]
UUN, Urine urea nitrogen over 24 hours; 4 g average fecal and cutaneous losses; *EL*, excessive losses, such as protein-rich drainages (e.g., pus).
6.25 g protein/amino acids = 1 g nitrogen

Daily Caloric Requirements

Patients	Using Measured or eREE	Using Body Weight
Sedated and mechanically ventilated	1.0 – 1.2 × REE	20-24 kcal/kg
Unsedated and mechanically ventilated	1.2 × REE	22-24 kcal/kg
Spontaneously breathing	1.2 – 1.3 × REE	24-26 kcal/kg
Spontaneously breathing (maintenance)	1.3 × REE	24-26 kcal/kg
Spontaneously breathing (repletion)	1.5 – 1.7 × REE	25-30 kcal/kg

To gain one pound of body weight, an excess above the TEE of approximately 3500 kcal is needed.

TABLE 106-2 **ENERGY EXPENDITURE AND CALORIC REQUIREMENTS—cont'd**

Respiratory Quotients	Energy (kcal/g)	Respiratory Quotient (RQ)*
Carbohydrate	4.0	1.00
Dextrose (glucose monohydrate)	3.4	1.00
Fat	9.0	0.70
Protein	4.0	0.80
Ethanol	7.0	0.67
Lipogenesis		8.00

RQ, Ratio of resting CO_2 production to resting O_2 consumption.
* Whole body RQ is influenced by the relative amounts of carbohydrate, fat and protein oxidation, and lipogenesis. For example, a patient who has received a 5% dextrose infusion of 100 mL/hr (440 kcal/day) for 4 days has a whole body RQ of 0.77-0.80, reflecting the predominance of fat and protein oxidation as the energy source. Whole body RQ above 1.0 indicates net lipogenesis. Human RQs above 1.2-1.3 are not generally seen, even with extremely high carbohydrate intakes.

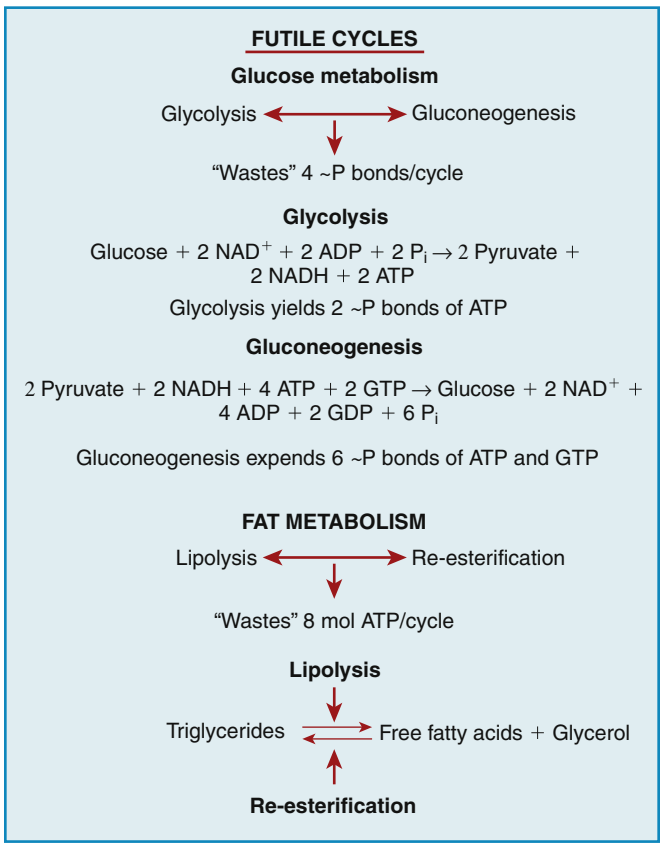


Figure 106-7. Two futile cycles contribute to the hypermetabolism of the stress response. A futile cycle is a set of opposing reactions catalyzed by different enzymes acting simultaneously, with at least one of the reactions driven by adenosine triphosphate (ATP) hydrolysis, enabling heat to be produced. In the lipid metabolism cycle, net lipolysis occurs, whereas in the glucose metabolism cycle, net gluconeogenesis is present. *~P*, High-energy phosphate bond, generally from ATP. *ADP*, adenosine diphosphate; *GDP*, guanosine diphosphate; *GTP*, guanosine-5′-triphosphate; *NAD+*, nicotinamide adenine dinucleotide; *NADH*, nicotinamide adenine dinucleotide hydrogen; *P_i*, *phosphoglucose isomerase*.

nitrogen balance is due to accelerated protein breakdown in excess of increased protein synthesis.[113,114]

The detrimental effects of prolonged bed rest further contribute to the derangements in protein metabolism caused by the stress hormones and cytokines after injury and surgery. In normal volunteers, 28 days of bed rest resulted in a 0.4-kg loss of leg muscle mass and a reduction of 23% in leg extension strength.[115] When hydrocortisone was administered to such bed-rested volunteers in doses intended to reproduce cortisol concentrations encountered during illness or trauma, a threefold greater loss of lean leg mass (1.4 kg) was reported, which represents a 6% loss of muscle mass from the legs and a 4-kg loss of whole-body lean mass. In addition, a 28% reduction in leg extension strength occurred. The muscle protein synthesis rate was decreased, whereas muscle protein breakdown was unchanged from rates before bed rest.[116] In contrast, patients with blunt trauma had a greater mean loss of whole-body lean mass because they suffered from proteolysis in addition to reduced protein synthesis. Extended periods of immobilization in bed contribute to the loss of muscle mass and the weakness suffered by patients with stressful illnesses. Early mobilization and exercise are thus important aspects of care.

During stress, hepatic synthesis of the acute-phase proteins such as fibrinogen, haptoglobin, complement, immunoglobulins, serum amyloid A, and CRP is increased.[117] The secretion of the acute-phase proteins is stimulated by elevated concentrations of endogenous corticosteroids (which by themselves do not initiate the response) in concert with IL-1β, TNF-α, and IFN-γ. These cytokines induce the secretion of IL-6 by the hepatic Kupffer cells, which acts synergistically with corticosteroids to initiate and stimulate acute-phase protein production via the transcription factor signal transducer and activator of transcription 3 (STAT3).[117] Simultaneously, IL-6 and the corticosteroids initiate a negative feedback loop, suppressing IL-1β and TNF-α production by mononuclear phagocytes. Bacterial infections tend to trigger a stronger acute-phase response than viral infections. The acute-phase response improves the ability to fight infection, stimulates wound healing, and improves hemostasis. The increase in fibrinogen increases hemostatic ability and plasma viscosity.[118] The latter is the reason the erythrocyte sedimentation rate is used as a nonspecific diagnostic test for disease activity. CRP is a measure of the acute-phase response and degree of stress because of enormous concentration increases (e.g., on the second day after hip replacement concentrations increased from <6 to >200 mg/L).[69]

Reduced synthesis of binding proteins, such as albumin, transthyretin (prealbumin), retinol-binding protein, and transferrin, simultaneously occur with the increased synthesis of acute-phase proteins. This reduction in the synthesis and plasma concentrations of binding proteins elevates the plasma concentrations and bioavailability of free hormones and electrolytes. As previously discussed, decreased plasma concentrations of cortisol-binding globulin and albumin increase the concentrations of free cortisol. Albumin concentrations (half-life, 21 days) decrease because of reduced synthesis, redistribution in the expanded extracellular fluid, and a greater fractional catabolic rate. Therefore, short-term changes in albumin concentrations do not reflect changes in synthesis. For nutritional evaluation, proteins (e.g., prealbumin) with short half-lives (2 days) are measured. However, they also have limitations because concentrations are decreased in hepatic failure and increased with renal failure.[119]

ENERGY EXPENDITURE

Metabolism consumes fuels, such as glucose and fatty acids, to produce energy-containing compounds (e.g., ATP) for use in many energy-consuming body functions. Among the major functions of eating is replenishing this fuel. The amount of fuel burned is directly reflected by the amount of energy released as heat (direct calorimetry) and indirectly reflected by the amount of oxygen consumed, CO_2 produced, and urine urea nitrogen excreted (indirect calorimetry). The components of the daily TEE are outlined in Table 106-2. Daily caloric intake should be sufficient to meet the daily energy expenditure. Intakes in excess of TEE result in the deposition of fat and weight gain, whereas sustained intakes less than TEE result in weight loss.

In patients with stressful illnesses, the altered metabolic milieu increases REE. The Harris-Benedict equation (see Table 106-2) estimated that patients with trauma, sepsis, chronic obstructive pulmonary disease (COPD), or burns and are spontaneously breathing after surgery have REEs that are above the estimated REE (eREE).[120-122] The resultant elevation of REE is in contradistinction to starved or semi-starved individuals whose energy expenditure decreases as part of an adaptive response.

Patients who are spontaneously breathing after surgery have shown a measured (via indirect calorimetry) REE greater than the eREE. The higher REEs ranged from 10% to 20% after elective surgery to 20% to 40% during sepsis (although values as high as 80% have been reported after sepsis). Patients with fractures of the long bones tend to have higher REEs and eREEs than those with similar degrees of injury without fractures. A peak REE occurs during approximately the third postoperative day, and hypermetabolism may last as long as 3 to 4 weeks in patients with trauma or with burns who are critically ill. Patients with burns can be extremely hypermetabolic (with a REE as much as 120% greater than the eREE) with the degree of hypermetabolism proportional to the extent and severity of the burns.[123] Older patients (>60 years of age) have less of a hypermetabolic response (also see Chapter 80).

Patients who are mechanically ventilated after surgery and patients with trauma have lower increases in REE than patients who are spontaneously breathing because they are receiving sedatives and/or muscle relaxants, both of which decrease the REE by as much as 20%.[124] In such patients, measured REEs are often within ±10% to 16% of the eREEs.[125,126] Another cause of this lack of hypermetabolism is that they have no or minimal work of breathing when ventilation is controlled by the mechanical ventilator. As they begin to breathe spontaneously, the REE rises because of the increased work of breathing and reduced sedation. During weaning from mechanical ventilation, energy expenditure rises further as the patient sustains more of his or her breathing, sedation is stopped, and anxiety sets in.[127] However, these patients in the ICU who are extremely ill retain resuscitation fluid (*third space*) that increases their body weight by as much as 10% to 12%. Because edema fluid has no metabolic activity, using their current instead of their preinjury weight in the Harris-Benedict equation may overestimate the eREE and thus underestimate the degree of hypermetabolism.[128]

The causes of hypermetabolism during stress are multifactorial. Fever results in an increase of 11% in energy expenditure for each increased degree of Celsius in body temperature. In addition, the effects of the increase in energy-consuming processes such as gluconeogenesis and ureagenesis increase the rate of metabolism. Catecholamines infused into normal subjects increase the metabolic rate.[129] This increase is even greater when cortisol, glucagon, and catecholamines are infused together. The significant hypermetabolism in patients with head injuries has been ascribed to major sympathetic nervous system activation, which also occurs with other types of intracranial pathologic conditions. For example, for at least 5 days after subarachnoid hemorrhage, the REE was 18% above the eREE. Shivering during induced hyperthermia can result in significant increases (>200%) in energy expenditure; therefore, treatment with sedatives and/or neuromuscular blockade is indicated. The increased energy expenditure has also been ascribed to increased protein oxidation and synthesis. Yet, after elective surgery, only a modest change in energy expenditure has been reported, despite increased protein turnover. Another process that contributes to hypermetabolism is *futile substrate cycling* (see Fig. 106-7). Reducing the rate of the lipolysis in the re-esterification futile cycle with β-adrenergic blockade reduced REE in burned children. The teleologic reason for the increase in futile cycling is that it affords patients the flexibility to adapt quickly to changes in energy substrate demands.

Environmental factors may also affect energy expenditure. Elevated ambient temperature and humidity have been shown to reduce the REE of patients with burns by reducing evaporative losses and, in turn, reducing the need to generate energy to maintain body temperature.

METABOLIC RESPONSES TO SEPSIS

Unlike the short-term stress of elective surgery with its ensuing recovery period, sepsis is characterized by an ongoing stressful stimulus with systemic effects that can lead to multiple organ system dysfunction. The basic

metabolic response observed during sepsis is similar to that after major surgery, burns trauma, and major nonseptic illnesses such as pancreatitis and serious transfusion reactions (e.g., blunting of the inhibitory effects of insulin on lipolysis and gluconeogenesis).[130] However, the presence of bacteria and bacterial components that initiate and sustain additional metabolic, inflammatory, immunologic, and coagulation responses further characterize sepsis.[131] These responses are demonstrated by the greater number of complement and coagulation proteins found in the plasma proteome profile of infected, as opposed to uninfected, patients with trauma who are critically ill.[79] Such biochemical differences, whether proteonomic or metabolomic, are important because they may serve as biomarkers for early detection of active infection and for differentiating between sepsis or septic shock and the noninfective systemic inflammatory response syndrome (see Box 106-1).[132]

As part of the innate immune host defenses, Toll-like receptors (a group of pattern recognition receptors) recognize extracellular or phagosomal alarmins, either PAMPs, which are products of bacteria, viruses, fungi, and protozoa, or intracellular proteins (damage-associated molecular patterns [DAMPs], such as high-mobility group box 1) released by damaged cells.[133] In addition to the Toll-like receptors, there are cytosolic NOD-like receptors, which recognize intracellular PAMPs and RIG-I–like receptors, which recognize viral RNA.[134] Stimulation of Toll-like receptors activates transcription factor NF-κB and c-*Jun* N-terminal kinase (JNK) in immune cells, which initiate transcription of genes encoding proinflammatory cytokines. Mice deficient in Toll-like receptors still succumb to sepsis, indicating that multiple pathways are active during sepsis. The type of infection influences the nature of the inflammatory response. Endotoxins (lipopolysaccharide) from gram-negative bacteria induce the production of TNF-α, IL-1, and IL-6, whereas exotoxin from gram-positive organisms significantly increases IL-8 more than TNF-α, IL-1, and IL-6.[135] Furthermore, sterile inflammation produces a different expression of Toll-like receptor genes than sepsis,[136] whereas septic shock produces a different cytokine profile than severe sepsis.[137] Viral infections produce different profiles from those produced by bacterial infections.

Critical illness–related corticosteroid insufficiency, which is defined as inadequate serum corticosteroid activity for the severity of illness, reportedly occurs with some frequency in patients with sepsis[138] (also see Chapter 101). Cortisol concentration may be in the supranormal range and may increase in response to additional ACTH stimulation. The clinical presentation of critical illness–related corticosteroid insufficiency is usually reduced responsiveness to fluid and vasopressor therapy; it is also associated with increased mortality. This relative adrenal insufficiency is acute and self-limited as it reverses upon resolution of the acute illness. The cause is unknown but might be attributable to decreased ACTH level or cortisol secretion and/or reduced tissue sensitivity to glucocorticoids.[139] Therefore, finding ways to easily and rapidly identify patients with this problem and to determine whether glucocorticoid replacement improves outcome are the challenges.[138] Multicenter, randomized, double-blind, placebo-controlled trials and meta-analyses of patients with septic shock who are receiving placebo or a low-dose steroid (e.g., 50 mg intravenous hydrocortisone every 6 hours for 5 days, followed by a 5 to 6 day taper) found no differences in either group in mortality between those who did and those who did not respond to an ACTH challenge. Although hydrocortisone did reverse shock more quickly than the placebo, more episodes of superinfection, bleeding, and hyperglycemia occurred.[139-141]

MODULATING THE STRESS RESPONSE

Although the stress response evolved as a mechanism for assisting organisms in reacting to immediate danger, its effects may be detrimental to patients undergoing surgery or suffering from sepsis. For example, the hypercoagulable state intended to stem acute bleeding may lead to deep vein thrombosis and pulmonary emboli in immobilized patients. Furthermore, in extended stress situations, the prolonged catabolism resulting from cytokine and stress hormone production leads to the loss of fat and muscle with ensuing weakness and fatigue. This weakness and fatigue, coupled with stress-related disordered immunologic function, increases vulnerability to infections.

The detrimental consequences of the stress response have increased the interest in aborting its appearance and/or actions. However, considering whether the goal of stress response modulation is full elimination or simply attenuation is necessary. By eliminating the stress response, its beneficial effects, such as support of blood pressure by catecholamines in the face of hypovolemia or the stimulation of cytokine production to enhance immunity, may be lost. Therefore, partial or selective suppression of the response may be more reasonable. In this manner, some responses may be partly preserved, such as the cardiovascular response to hypovolemia. Decreasing certain consequences of the stress response, such as diminishing the degree of catabolism and lipolysis to reduce the loss of muscle and fat mass, offer other advantages. One approach tried in patients with sepsis was selective mediator blockade. A prime example was anticytokine therapy (e.g., anti-TNF antibodies, IL-1 receptor antagonists) during sepsis and septic shock. The results of such therapy were disappointing because they not only failed to demonstrate any improvement in survival but, in some instances, even reduced survival. Postulated reasons for these failures include the possibility that targeting a single mediator may not be sufficient to block the wide-ranging ongoing biologic cascade. Another possible reason is that cytokines have beneficial immunoenhancing effects that assist the organism in combating infection. Impeding these effects thus leads to decreased immune function, causing increased mortality. Therefore, any attempt at modulating the stress response must be monitored for detrimental effects.

PREOPERATIVE STRESS RESPONSE

Patients undergoing elective surgery often suffer from preoperative anxiety, a state of psychologic stress involving low-level activation of the hypothalamic-pituitary axis and possibly cytokines. Evidence for such early activation comes from the observation that salivary cortisol

increases by 50% after receipt of information about surgery. Other studies show that both β-endorphin and epinephrine concentrations increase preoperatively. Whether this preexisting activation of the stress response has an additive effect on the subsequent stress response induced by surgery remains unclear (also see Chapter 38).

Preoperative medication tempers anxiety, thus attenuating the stress response. Midazolam as a premedication reduces anxiety and limits increases in intraoperative epinephrine and, possibly, norepinephrine and cortisol. Although it is unknown how benzodiazepines exert their activity, patients do increase cortisol production in response to exogenous ACTH, supporting the contention that the benzodiazepines exert their effect at a higher level, that is, on the hypothalamus or pituitary. Heavy premedication with a combination of opioid and antihistamine or opioid, anticholinergic agent, and benzodiazepine more successfully blunted serum catecholamine, AVP, ACTH, and cortisol increases than benzodiazepines alone. When administered as a premedication, melatonin, a hormone secreted by the pineal gland, reduces anxiety.[142] Nonpharmacologic approaches to anxiety reduction have also been investigated. Music, video glasses, and smartphone applications reduce preoperative anxiety and thus may have practical applications.[143-143c]

Fasting before anesthesia is an accepted practice to lessen the risk for pulmonary aspiration (also see Chapter 38). Many patients fast for 8 to 12 hours before the start of surgery. This practice has been challenged because patients arrive to the surgical unit in a state of starvation with its attendant glycogenolysis caused by low insulin and high glycogen levels. These patients are then subjected to surgical stress with its resulting insulin resistance, catabolism, and gluconeogenesis. Contemporary guidelines permit clear fluid intake until 2 hours before surgery. This guideline has led to interest in administering a carbohydrate (e.g., 50 g) or carbohydrate-protein (e.g., 50 g carbohydrate plus 15 g glutamine) load 2 to 3 hours before surgery in an attempt to increase insulin concentrations and to reduce glucagon levels, leading to lesser degrees of postoperative insulin resistance and catabolism.[144-148] Small studies showed reduced postoperative insulin resistance, lower protein loss, and the preservation of mitochondrial function with these feedings.[146-148] A meta-analysis concluded that preoperative carbohydrate loading may be safe and attenuate postoperative insulin resistance better than placebo, but the quality of the trials was low.[149] Carbohydrate administration is part of the Enhanced Recovery after Surgery (ERAS) program, which also includes thoracic epidural anesthesia or analgesia, no nasogastric decompression, and early resumption of oral intake. Meta-analysis showed reduced overall (but not major) complications and lengths of hospital stay after open colorectal surgery.[150,151] A systematic review of 17 studies (1445 patients) showed reduced postoperative insulin resistance and decreased anxiety and nausea, but not evidence of preserved muscle mass, after preoperative carbohydrate-rich drinks.[151a]

INTRAOPERATIVE STRESS RESPONSE

Modulating the intraoperative stress response with anesthetics depends on various factors, including the type of anesthesia and surgery. Because separating the effects of the anesthetics themselves from the stress response generated by the surgical injury is nearly impossible, studies generally compare the effects of two or more anesthetic regimens on the overall stress response during a specific surgical procedure.

INHALED ANESTHETICS

Volatile anesthetics minimally suppress the hormonal stress response and are basically ineffective in counteracting biochemical responses (e.g., lipolysis) induced by surgical stimulation. The evidence is conflicting as to whether volatile agents prevent surgically induced catecholamine secretion, although enflurane is most capable of blocking intraoperative catecholamine surges. Halothane and isoflurane failed to affect serum cortisol concentrations in both the absence and presence of surgery. No differences were cited between intraoperative cortisol or glucose levels of desflurane anesthesia during abdominal hysterectomy between light bispectral index (BIS) monitoring of 50 and deep BIS monitoring of 25.[152] Sevoflurane, however, attenuated the cortisol and ACTH responses to laparoscopic ovarian cyst removal.[153] No differences in plasma cortisol, ACTH, insulin, or glucagon concentrations were reported between extended (>10 hours) isoflurane/NO_2 or sevoflurane/NO_2 anesthesia during head and neck surgery. Although with sevoflurane/NO_2, epinephrine and norepinephrine concentrations were attenuated during surgery and rose only after surgery[154] (also see Chapter 26).

INTRAVENOUS ANESTHETICS

Some intravenous anesthetics partially modify the endocrine and metabolic components of the stress response. Sodium thiopental (5.0 to 5.1 mg/kg) does not prevent increases in catecholamine concentrations after intubation. However, many studies show lower epinephrine and norepinephrine concentrations when propofol (2.0 to 2.2 mg/kg), rather than pentothal, is used for intubation. This finding is attributed to propofol's intrinsic ability to inhibit catecholamine secretion, possibly by decreasing catecholamine release from chromaffin cells. Propofol (1.5 to 2.5 mg/kg) also decreases cortisol concentrations during intubation. Etomidate does not affect metabolic responses except to decrease hyperglycemia, which is attributed to etomidate suppressing the adrenocortical response by blocking cortisol and aldosterone synthesis.

Compared with benzodiazepines, the α_2-adrenergic agonists, clonidine and dexmedetomidine, are more successful at blunting the hemodynamic and catecholamine responses to intubation and intraoperative stress. The α_2-agonists blunt the stress response by reducing norepinephrine release from central and peripheral nerve endings. When 4.5 μg/kg of oral clonidine was given preoperatively, intraoperative plasma catecholamine concentrations were reduced. Similar doses reduced not only plasma but also cerebrospinal fluid (CSF) concentrations of TNF-α and norepinephrine.[155] Such doses also attenuated the intraoperative and postoperative hyperglycemic responses to minor surgery. Whether clonidine also

attenuates the cortisol response is unclear.[156] Moreover, α_2-agonists, such as dexmedetomidine, do not suppress steroidogenesis[157] (also see Chapter 30).

OPIOIDS

Opioids can blunt the stress response. Fentanyl (50 μg/kg) plus halothane and NO abolished the elevations in cortisol, GH, and glucose normally seen during hysterectomy. Morphine (1.0 mg/kg) reduced GH and cortisol elevations during abdominal surgery. However, other studies show that the same dose of morphine was unable to suppress increased GH secretion during similar surgeries. In some but not all studies, opiates decreased cytokine production.[65,158,159] Propofol-alfentanil anesthesia, compared with isoflurane anesthesia, caused lower IL-6 concentrations. These lower IL-6 concentrations are thought to occur because opioids bind to monocyte receptors and reduce intracellular cAMP concentrations. cAMP is necessary for monocyte secretion of IL-6. However, propofol-remifentanil anesthesia, compared with sevoflurane and sevoflurane-fentanyl anesthesia, did not always attenuate the IL-6 elevations.[158,159] High-dose remifentanil (1.0 μg/kg/min) infusion plus sevoflurane attenuated the ACTH, cortisol, epinephrine, norepinephrine, and ADH responses to limb tourniquet application compared with anesthesia with lower dose (0.25 μg/kg/min) remifentanil plus sevoflurane anesthesia.[159a]

The limitation of the stress-reducing effects of opioids is most evident during cardiac surgery. Although high-dose fentanyl (50 to 200 μg/kg) and morphine (2 to 4 mg/kg) prevent increases in catecholamine and cortisol concentrations before cardiopulmonary bypass surgery, both catecholamine and cortisol concentrations increase during bypass surgery. Similarly, high-dose sufentanil (12 μg/kg induction, 3 μg/kg before skin incision, and 5 μg/kg before bypass) limited increases in catecholamines, cortisol, and AVP before surgery, but it failed to attenuate their elevation both during and after bypass surgery. The reversal of the opioid-related stress-reducing effects by bypass is attributed to nonpulsatile blood flow, artificial surfaces of the bypass circuit, renin and angiotensin release, hypothermia, and dilution of the plasma opioid concentration.

How opiates curb the stress response is unknown. One theory is that this action is mediated through hypothalamic and pituitary opiate receptors. This theory has been questioned because of the similar effects of fentanyl and sufentanil on the stress response, despite the significantly greater affinity of sufentanil for brain opiate receptors. Both intravenous (50 μg then 20 μg every 30 minutes) and intrathecal high-dose (150 μg) sufentanil attenuated the intraoperative epinephrine and norepinephrine responses in patients undergoing general anesthesia for major abdominal surgery. However, only in the intrathecal group were the intraoperative ACTH and cortisol responses attenuated. Therefore, the unique actions of sufentanil may only be apparent on intrathecal administration.[160]

Although general anesthesia undoubtedly prevents an even greater stress response by rendering patients insensate to the discomfort and pain of surgery, it is unable to eliminate many manifestations of the stress response completely, which is ascribed to the inability of anesthesia to diminish or abolish the afferent nervous input from the area of the injury. Additionally, general anesthesia does not alter the effects of cytokines such as IL-6 and TNF, which are produced within the area of the wound (also see Chapter 30).

NEURAXIAL ANESTHESIA

Neuraxial anesthesia more effectively attenuates the stress response than general anesthesia (also see Chapter 56). The ability of such anesthesia to modify the intraoperative stress response depends on the level of the blockade, the location of the surgery, and the drugs used. Lower extremity surgery with epidural anesthesia results in lower intraoperative catecholamine concentrations when compared with general anesthesia.[100] These reductions in catecholamines may be caused by blockade of afferent nerve stimuli, reducing hypothalamic activation of the sympathetic nervous system and adrenal medulla. Further evidence for reduced hypothalamic activation is that epidural anesthesia to a T4 level successfully blunts increases in TSH. Similarly, epidural anesthesia attenuates the usual increases in AVP during vaginal surgery.

Lower abdominal and lower extremity surgery with neuraxial anesthesia reduces or abolishes the hyperglycemic response to surgery, likely because of the lack of stimulation of hepatic glycogenolysis attributable to a reduced epinephrine response or blockade of hepatic sympathetic pathways or both. Reduced sympathetic and adrenal activity with epidural blockade also prevents normal intraoperative increases in FFAs and glycerol (lipolysis) during lower abdominal surgery. Further evidence that sympathetic blockade reduces intraoperative lipolysis is that lipolysis was reduced during inguinal hernia repair only when spinal anesthesia reached the T1-T3 sensory level. The influence of neuraxial blockade on cortisol secretion is less clear. Although neural blockade during lower abdominal surgery reduces the stress-induced cortisol response, whether the degree of suppression is similar to that of other hormones remains unclear. This incomplete reduction in the stress response may be caused by the inability of epidural anesthesia to alter the IL-6 response to abdominal surgery, suggesting that IL-6 secretion is neither mediated by nociceptive stimuli nor affected by sympathetic blockade. IL-6 increases pituitary ACTH secretion and thus stimulates cortisol secretion. Similar attenuation of catecholamine and cortisol secretion occurred when patients with spinal cord injury had surgery below their lesions.[161]

Neuraxial anesthesia more successfully reduces the stress response during lower abdominal than upper abdominal or thoracic surgery. Whether T3-T4 epidural blockade can suppress surges in cortisol and catecholamine concentrations during upper abdominal surgery remains controversial. Epidural blockade as high as C6 does not influence the cortisol response during upper abdominal or thoracic surgery. This hypothesis was disputed when blockade extending from T3-T4 to L1-L2 significantly reduced the cortisol response during gastrectomies. Similarly, it remains uncertain whether epidural blockade for upper abdominal surgery alters lipid or protein metabolism, although it seems to partially suppress the hyperglycemic response.[162] The fact that regional anesthesia is unable to suppress the stress responses induced by upper abdominal stimulation can

be attributed to inadequate afferent sympathetic blockade, unblocked vagal afferent pathways, unblocked phrenic afferents, or locally released humoral substances. Others suggested that regional anesthesia that does not completely block afferent stimuli will not affect the hypothalamic-pituitary axis because epidurally induced sympathetic block does not completely block neural traffic but only reduces it. Supporting this hypothesis, the combination of epidural and splanchnic blockade (injection of bupivacaine directly into the splanchnic plexus) during upper abdominal surgery reduced both the catecholamine response and plasma cortisol concentrations more effectively than epidural anesthesia alone. Similarly, continuous spinal local anesthetic infusion more successfully attenuated the cortisol and glucose responses to upper abdominal surgery than epidural anesthesia, presumably by better blockade of afferent nerves.

Another possible explanation for the inability of epidural anesthesia to attenuate the response to upper abdominal surgery is stimulus transmission through unblocked vagal afferent nerves. However, no attenuation of the stress response is observed after either vagal blockade or surgical vagotomy. Evidence for phrenic nerve involvement was shown when epidural blockade to the C3-C4 dermatome level during upper abdominal surgery more successfully blunted increases in ACTH and AVP than did C8-T2 blockade.

The drugs used for regional anesthesia also influence the ability to affect the stress response. Epidural opiates are unable to prevent catecholamine surges. Increases in catecholamine concentrations were limited by 2-chloroprocaine and bupivacaine but not by lidocaine. This difference may be attributable to the central stimulatory effects of lidocaine.

COMBINED GENERAL AND NEURAXIAL ANESTHESIA

Combined general and neuraxial anesthesia should reduce the stress response if the general anesthetic is sufficiently deep to attenuate the stimulation of the endotracheal tube and if the neuraxial anesthesia is adequate to block afferent signals from the surgical site. Compared with general (sevoflurane-remifentanil) anesthesia alone, the general anesthetic plus ropivacaine-sufentanil thoracic epidural anesthesia attenuated increases in cortisol, epinephrine, and norepinephrine concentrations during and after radical retropubic prostatectomy.[163] Both desflurane-epidural (sensory block T4-S1) and desflurane-remifentanil anesthesia for colorectal surgery resulted in less glucose production and less hyperglycemia, compared with desflurane alone.[164] During upper abdominal surgery, plasma levels of cortisol, epinephrine, and IL-10 were lower with thoracic epidural plus general (isoflurane) anesthesia, compared with general anesthesia alone.[165]

Combined general and epidural anesthesia in coronary artery bypass grafting has been extensively studied. Patients receiving fentanyl anesthesia plus thoracic epidural bupivacaine (10 mg [5 mg/mL] every 4 hours) during coronary artery bypass grafting had lower epinephrine and norepinephrine levels both intraoperatively (including during bypass) and postoperatively, compared with controls receiving only large doses of fentanyl. Results are conflicting as to whether the cortisol response is also reduced. Although cytokine responses were not affected, CRP and fibrinogen, but not troponin-I, levels were lower 16 to 24 hours after surgery.[166] Combined general and epidural anesthesia with continued postoperative epidural analgesia for off-pump cardiac surgery resulted in lower IL-6 and IL-8, but not cortisol or troponin-I, concentrations after surgery (12 to 48 hours) when compared with general anesthesia plus postoperative patient-controlled analgesia (PCA) of morphine.[167] Despite some attenuation of the stress response, a meta-analysis did not show fewer myocardial infarctions or lower mortality with thoracic epidural plus general anesthesia for on-pump coronary artery bypass surgery[168] (also see Chapter 56).

THERMOREGULATION

Another way of minimizing the stress response is maintaining perioperative normothermia (see Chapter 54). Intraoperative hypothermia, followed by postoperative rewarming, stimulates the response. Patients with hypothermia (35.3° C core temperature) had higher postoperative plasma norepinephrine and epinephrine concentrations than their warmer counterparts.[169] These elevated catecholamine concentrations are partially the result of postoperative rewarming with shivering and vasodilation that leads to hypotension. Elevated catecholamines have been postulated to be among the reasons for the greater incidence of myocardial ischemia after vascular surgery in patients with hypothermia. There are thus several reasons to maintain intraoperative normothermia.

POSTOPERATIVE PERIOD

The intraoperative attenuation of the stress response by anesthesia is often lost on emergence from anesthesia because of pain and awareness, coupled with a series of stress-producing events (e.g., tracheal extubation, shivering) (also see Chapter 96). This postoperative response has been demonstrated by extreme elevations in plasma ACTH and cortisol immediately after surgery with isoflurane anesthesia. Likewise, after sevoflurane-NO anesthesia, peak cortisol, ACTH, and catecholamine concentrations occurred after tracheal extubation, implicating anesthesia emergence as more stressful than surgery. This phenomenon may be especially striking with sevoflurane anesthesia because of its typical rapid emergence. Associated with these significantly elevated catecholamine concentrations is an increased incidence of myocardial infarction that peaks 24 to 48 hours after surgery.

Similar to an inhaled anesthetic, general anesthesia with intravenous drugs does not prevent the postoperative stress response. Intravenous opioid anesthesia did not blunt the stress response in the late postoperative period (>3 hours). Abrogation of the suppressive effects of anesthesia on the stress response on emergence was further demonstrated when patients were deeply sedated with propofol for 12 hours after cardiopulmonary bypass surgery. This sedation attenuated the rise in cortisol and catecholamine concentrations and was associated with less tachycardia and hypertension than in a control group.

However, once propofol was discontinued, hormone concentrations rose, indicating that deep sedation only delayed the appearance of the stress response.[170] Therefore, unless therapy that suppresses the stress response is continued during and after emergence and extubation, the postoperative period is marked by the full appearance of the stress response.

After lower abdominal surgery, continuous postoperative analgesia via an epidural catheter using local anesthetics reduced the stress response. For example, continuous epidural analgesia (sensory block of T4-S5) for 24 hours after colorectal surgery successfully blunted increases in catecholamine but not cortisol concentrations. A similar regimen administered for 24 hours after hysterectomy resulted in lower glucose and FFA concentrations than did general anesthesia. Furthermore, better nitrogen economy was observed in patients after hip replacement who were provided with 24 hours of epidural local anesthetics (sensory level: T10) than in patients who were administered only general anesthesia. This observation occurred with postoperative local anesthetic doses that provided only analgesia and not anesthesia. Similarly, combined spinal-epidural anesthesia during hip replacement with postoperative epidural analgesia (ropivacaine-sufentanil) resulted in reduced leucine oxidation rate on the first postoperative day, whereas hyperglycemia was prevented only intraoperatively.[171] Attenuating the stress response with continuous postoperative epidural analgesia was more successful in lower than in upper abdominal surgeries, a finding similar to the observations during intraoperative epidural anesthesia. Yet, stress response reduction after upper abdominal surgery has been reported. For example, after abdominal aortic surgery, epidural morphine reduced the postoperative sympathetic but not adrenal epinephrine response, thus reducing the incidence of postoperative hypertension. However, neither epidural ropivacaine nor epidural morphine analgesia suppressed the catabolic response when administered to patients after colonic surgery, but ropivacaine did increase the carbohydrate oxidation rate, likely reflecting reduced insulin resistance.[172] The reduced insulin resistance, coupled with decreased gluconeogenesis, led to less hyperglycemia.[172] Therefore, pain control with epidural opioids or local anesthetics is unable to lessen many of the metabolic changes associated with such surgeries.[173] However, combined epidural opioid–local anesthetic analgesia appears more effective in attenuating catabolism.[174]

Whether modifying the stress response improves outcome is unclear. Ideally, one of the desired effects of anesthesia is a stress-free state, and achieving such an effect has become increasingly important as the stress response is more frequently implicated in the development of postoperative complications, especially among patients who are chronically ill and aging.[175] However, contemporary anesthesia practice can only partially modify this response and then only under specific conditions. General anesthesia has a limited ability to attenuate the stress response, whereas regional anesthesia is more effective. Therefore, it stands to reason that outcome would improve with regional anesthesia. A meta-analysis showed decreased mortality with regional anesthesia as opposed to general anesthesia in a variety of surgical procedures. However, this analysis has been criticized because only patients who underwent orthopedic procedures had improved outcomes. Furthermore, morbidity studies demonstrated that under some circumstances, epidural anesthesia reduced postoperative complications, such as deep vein thrombosis.

Attempts to modulate the perioperative stress response include nonanesthetic approaches (e.g., using β-adrenergic antagonists) to block cardiovascular end-organ receptors and α_2-adrenergic agonists to stimulate central receptors. These approaches have met with some success. Using β-adrenergic antagonists in patients with ischemic heart disease does not reduce the perioperative neuroendocrine or endocrine stress response but blocks the end-organ response. Such end-organ blockade also has metabolic effects. Administering propranolol to children who are severely burned decreased their REE, attenuated muscle catabolism, reduced lipolysis, preserved lean body mass, and reduced TNF and IL-1 concentrations without increasing infections.[176] Hepatomegaly attributable to fatty liver was prevented because reductions in both lipolysis and hepatic blood flow decreased fatty acid delivery to the liver.[177] Mortality was unaffected by propranolol.[176] In patients with severe sepsis, selective β_1-adrenergic blockade had no effect on REE or muscle protein kinetics,[178] indicating that attenuation is primarily due to β_2-receptor blockade. However, discontinuing the β blockade into the anabolic period is important because β-adrenergic activity might be significant in muscle tissue restoration.[179]

Another nonanesthetic modulation of the stress response is administering a single preoperative dose of exogenous glucocorticoids. Administering intravenous methylprednisolone (30 mg/kg) 60 to 90 minutes before the start of major abdominal, hepatic, and esophageal surgery reduced the stress response with lesser increases in IL-6, CRP, norepinephrine, and AVP and increased the secretion of IL-10. A meta-analysis of 51 studies in which a single dose of methylprednisolone (15 or 30 mg/kg) was given showed no increase in complication rates.[180] Further study is needed to determine whether this approach significantly affects outcome. Similarly, methylprednisolone treatment before cardiac surgery attenuated cytokine secretion.

The inability of any one modality to reduce the stress response and significantly alter outcome has spawned the multimodal approach. The goals are to shorten the convalescence period and reduce the postoperative decline in functional status by an improvement of pain control, early return of gut function, and early mobilization. This approach involves combining some or all of the following: premedication (benzodiazepines, β-blockers, α_2-agonists), preoperative carbohydrate intake, glycemic control, maintenance of normothermia, combining epidural anesthesia or analgesia and nonsteroidal antiinflammatory drugs, avoiding opioids, early oral feedings or parenteral nutrition, and early mobilization after major abdominal surgery.[181,182] Such a regimen permitted 32 of 60 patients after colorectal resection to go home within 48 hours of surgery and, in a study of anterior colon resection, reduced hospital lengths of stay from 10 to 7 days.[183] Patients undergoing radical cystectomy, anesthetized with general and thoracic epidural anesthesia and postoperative thoracic epidural analgesia, and treated with early oral nutrition and forced mobilization had

lower urinary catecholamines, less negative nitrogen balance, earlier return of bowel function, and a lower acute-phase response than patients who were conventionally treated.[119] The multimodal approach to modulating the perioperative stress response has considerable logic and practicality and, coupled with noninvasive surgery, has the potential to change postoperative care.

GLUCOSE CONTROL

Hyperglycemia appears almost immediately after the start of a major stress as a result of accelerated endogenous glucose production plus insulin resistance (also see Chapter 39). During major noncardiac surgery, peak glucose concentrations were seen at 2 hours after anesthesia induction.[183a] Administering exogenous catecholamines and glucocorticoids exacerbates hyperglycemia. The teleologic explanation for the hyperglycemia is that it provides the wound and other glucose-dependent tissues with a ready supply of glucose. The experience gained from diabetic care showing the advantages of tightly controlling blood glucose concentrations was the impetus for exploring whether tight glucose control is also advantageous in managing acute hyperglycemia associated with stress (i.e., surgical, burn, trauma, sepsis).

Acute hyperglycemia is associated with immunosuppression, stimulated sympathoadrenergic activity, increased mortality, increased infections, reduced skin graft success, increased catabolism in patients with burns, and osmotic diuresis leading to volume depletion.[184-187] These effects are ascribed to the proinflammatory actions of glucose attributed to increased secretion of TNF-α and IL-1, greater adherence and sequestration of neutrophils in peripheral tissue, impaired microvascular relaxation in the presence of NO, and decreased monocyte human leukocyte antigen-DR (HLA-DR) expression, reflecting reduced innate immunity.[188] The proinflammatory cytokine response to endotoxin infusion in normal subjects was enhanced by concomitant hyperglycemia.[189] These observations question whether elevated blood glucose concentrations are, themselves, detrimental or whether hyperglycemia is simply a marker of severe stress. Hyperglycemia on hospital admission in trauma victims portends greater mortality, and hyperglycemia in both diabetic and nondiabetic patients after cardiac surgery is associated with a higher incidence of infections.

Van den Berghe and associates[184] showed reduced mortality in surgical (primarily cardiac) patients treated with intensive insulin therapy to maintain euglycemia (≤110 mg/dL). Compared with conventional therapy, the aggressive insulin therapy reduced ICU mortality especially from multiple organ failure by 43%, sepsis by 46%, and acute renal failure requiring dialysis or hemofiltration by 41%. In addition, patients in the ICU for longer than 7 days who were aggressively treated had less critical illness polyneuropathy or myopathy.[190] These results led to the question of whether it was lowering blood glucose concentration or administering insulin, an anabolic and antiinflammatory hormone, that reduced morbidity and mortality. Furthermore, studies suggest that avoiding hyperglycemia, rather than administering insulin for its correction, is beneficial because the total amount of insulin administered correlated with increased mortality, regardless of the blood glucose concentration.[191] The latter observation indicates that a major determinant of mortality and morbidity is the severity of the critical illness, as demonstrated by the degree of tissue insulin resistance and hence the amount of insulin needed to control blood glucose.

The enthusiasm for tight control of blood glucose in patients with stressful illnesses must be tempered. The increased incidence of unrecognized hypoglycemia, especially in patients who are anesthetized and sedated, led to recommendations that glucose be controlled to concentrations greater than 140 mg/dL).[184,185] The multicenter Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) trial found greater mortality (increased absolute risk at 90 days of 2.6%) and more hypoglycemia of 6.8% versus 0.5%) in patients in the ICU who were treated with insulin to a glucose target of 81 to 108 ml/dL than those who were treated to a target of less than 180 mg/dL.[192] Whether the increased mortality was due to the hypoglycemia or other factors was unclear because insulin appears to have proinflammatory actions and upregulates NF-κB under certain circumstances.[193] The high insulin doses could also further increase the REE. Another issue is whether all or only specific populations benefit from tight glucose control. One meta-analysis in cardiac surgery showed less ICU mortality and lower hospital lengths of stay, less postoperative atrial fibrillation, and reduced duration of mechanical ventilation with intensive insulin therapy; whereas another such analysis showed no reduction in mortality but fewer postoperative infections.[194,195] The latter results are similar to those obtained in pediatric surgery patients.[195a] Glucose-insulin treatment might be beneficial in myocardial infarction and ischemia.[196] A meta-analysis incorporating 13,567 patients in 26 studies concluded that in patients who were critically ill, tight glucose control did not decrease mortality but did control the increased risk of hypoglycemia.[197,198] In pediatric ICU patients a multicenter trial involving 1369 patients showed no significant effect on outcome with tight (72-126 mg/dL) versus conventional (<216 mg/dL) glucose control.[198a]

The benefits of lowering blood glucose concentrations (<180 mg/dL) with insulin therapy after major surgery and in critical illness are ascribed to abrogation of the proinflammatory actions of hyperglycemia (i.e., reduced IL-6, IL-8, high-mobility group box-1, and TNF-α, as well as interference with IL-6 signal transduction), along with the antiinflammatory effects of insulin; protection of the mitochondrial compartment and endothelium; lower serum cortisol concentrations; lower urinary nitrogen losses; and increased secretion of antiinflammatory hormones, such as IL-4 and IL-10.[199-204] Moreover, insulin therapy attenuated lipolysis, reduced endogenous glucose production, and increased glucose clearance, but not protein losses, in patients in medical ICUs.[205]

NUTRITIONAL SUPPORT

PERIOPERATIVE PERIOD

Immediately after surgery, patients traditionally receive infusions of 5% dextrose (glucose monohydrate), which

provide 50 g/L dextrose or 170 kcal/L (dextrose provides 3.4 kcal/g). Therefore, patients receiving 2 to 3 L/day of 5% dextrose are essentially being semistarved. The rationale for infusing small amounts of dextrose is its protein-sparing effects (i.e., reduced gluconeogenesis, which decreases the need for proteolysis, leading to lower urinary nitrogen losses). In normal subjects, nitrogen losses decrease linearly as the amount of dextrose administered increases, up to an intake of 150 g/day. More than 150 g/day of dextrose results in no further protein sparing unless protein and fat are also provided. Furthermore, small amounts of carbohydrate (100 g/day) prevent ketosis[95] and can contribute to postoperative hyperglycemia. Even with larger amounts of glucose, the ability of exogenous glucose to suppress gluconeogenesis is diminished during stress. An infusion of 2 g/kg/min glucose during the first 3 hours of surgery reduced endogenous glucose production by 60%, as opposed to 90% reduction in patients before surgery.[182] Dextrose regimens should only be continued for a few days (4 to 6 days) after surgery until the patient can resume oral intake. Patients unable to begin oral intake after such time should be evaluated for enteral or parenteral nutritional support.

Efforts have been directed at finding ways to improve the effectiveness of hypocaloric amounts of glucose administered during the postoperative period. When compared with an intravenous pain regimen, the greater pain relief provided after abdominal surgery by continuous intraoperative and postoperative epidural blockade with local anesthetics and opioids (0.1% bupivacaine plus 2 μg/mL fentanyl to a T7-L3 sensory block) further decreased endogenous amino acid oxidation and increased whole-body glucose uptake by decreasing insulin resistance.[206,207] These results are not unexpected because pain, itself, induces insulin resistance and contributes to the catabolic state after surgery.[208] Furthermore, epidural analgesia reduces the duration of postoperative ileus (e.g., thoracic lumbar, local anesthetics opioids), allowing earlier resumption of oral intake.[209]

Postoperative protein sparing has been attempted with hypocaloric amino acid infusions.[210] The idea is to provide small amounts of exogenous amino acids as gluconeogenic substrate (1 g produces 0.5 g of glucose) while avoiding the hyperglycemia observed during 5% dextrose infusions. However, there is a limit to how much protein can be used as an energy source, and postoperative amino acid infusions decreased gluconeogenesis only slightly but did suppress protein breakdown, reduced IGF-1 decreases, and stimulated protein synthesis.[211,212] Administering amino acids instead of 5% dextrose appears to have few advantages, although the amino acids do reduce the loss of some lean body mass.[210]

Another use of intraoperative amino acid infusions are as thermogenic agents that are started either a few hours before surgery or after anesthesia induction to prevent or attenuate intraoperative hypothermia.[213] During anesthesia, the central thermoregulation is silenced, leading to exaggerated amino acid thermogenesis. Amino acid–induced heat generation during anesthesia occurs mainly in extrasplanchnic tissues, such as skeletal muscle, and is attributed to greater amino acid turnover because both protein breakdown and synthesis are energy-consuming (heat-generating) processes.[214] Such infusions reduced the body temperature decline during spinal anesthesia by 0.5° C to 0.8° C[215,216] and during off-pump coronary artery bypass surgery.[217] Amino acid infusion (11.4% solution at 2mL/kg/hr for 1 hour) successfully treated postoperative hypothermia-induced shivering.[217a]

INDICATIONS FOR NUTRITIONAL SUPPORT

The primary indication for initiating nutritional support is preventing or treating malnutrition among patients unable or unwilling to sustain sufficient oral intake. Between 20% and 35% of hospitalized patients suffer from malnutrition on admission or during their stay. Therefore, nutritional assessment and decisions concerning nutritional support should be part of the routine care of all hospitalized patients. A major consideration when contemplating nutritional support of an individual patient is whether the nutrition will improve his or her prognosis or quality of life, since nutritional wasting is the inevitable consequence of many terminal diseases.[218] Another important aspect of providing nutritional support to patients with stressful illnesses is that their already altered metabolic milieu greatly affects nutrient use and metabolism. Moreover, patients who are critically ill with recurrent bouts of sepsis have an ongoing proinflammatory response that contributes to continued catabolism. Therefore, during the acute phase of stressful illness, nutritional support is an adjunctive therapy whose goal is to provide energy substrates to aid cellular functions and attempt to stem losses of lean and fat mass. Repletion of lost fat and muscle tissue must wait until the anabolic phase of the illness.

Preoperative malnutrition is associated with poor surgical outcomes attributable to a more severe systemic inflammatory response and more postoperative infections.[219] Preoperative criteria for increased postoperative risk include serum albumin less than 3.0 mg/L, BMI less than18 kg/m,[2] and weight loss greater than 10% to 15% within 6 months.[220-222] Compared with patients not at risk, 14% of patients undergoing elective gastrointestinal surgery who, on preoperative nutritional assessment, were at nutritional risk for postoperative complications had 3.5 times as many severe complications and 2.5 times their median length of hospital stay.[223] Yet demonstrating any benefit of preoperative parenteral and enteral nutrition in malnourished patients has been difficult, except for those who were severely malnourished and who had fewer noninfectious postoperative complications after 7 to 10 days of preoperative nutritional repletion.[224-226a] Continuing TPN during and after surgery is beneficial in such patients.

The resumption of significant oral intake within 1 to 2 days after elective resectional gastrointestinal surgery, rather than an extended period of no intake with or without gastric decompression via a nasogastric tube, has been shown upon meta-analysis to reduce total postoperative complications and not negatively affect mortality, anastomotic integrity, or hospital lengths of stay. In other types of elective and emergency major surgery, postoperative nutritional support is not indicated unless it is anticipated that the patient will be unable to resume adequate oral intake within 7 to 8 days after surgery.[220] Patients not expected to resume adequate oral feedings by this time should begin nutritional support early (1 to 4 days) after surgery. In patients with preoperative nutritional depletion not expected to resume oral intake

soon after surgery, such as those with head-neck and esophageal cancers, nasoenteric or jejunal feeding tubes should be placed at surgery and enteral nutrition begun immediately after surgery.[220] A systematic review concluded that enteral nutrition started early (in 1 to 3 days) after hepatectomy reduced infectious complications when compared with TPN.[227] Similarly, a systematic review of the literature concluded that although many patients undergoing pancreaticoduodenectomy are nutritionally depleted before surgery, routine postoperative TPN is not recommended because of the complication rate. However, postoperative enteral nutrition is recommended.[228] Nasojejunal enteral nutrition compared with parenteral nutrition begun 8 hours after major rectal resection resulted in fewer anastomic leaks, earlier defecation, and shorter length of hospital stay.[228a]

Patients in the ICU who are mechanically ventilated have a malnutrition rate of 38% to 100%[211] (also see Chapter 102). Therefore, nutritional support guidelines recommend starting enteral nutrition early, that is, within 24 to 48 hours of ICU admission, to reduce infectious complications and shorten the duration of hospitalization.[229,230] Patients unable to receive or tolerate enteral intake should be considered as candidates for TPN. However, disagreement remains as to when to start the TPN in patients not tolerating enteral nutrition. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines state that if patients have not achieved adequate enteral intake in 2 days after ICU admission, then TPN should be started. The American Society of Parenteral and Enteral Nutrition, the Society of Critical Care Medicine (ASPEN/SCCM), and Canadian guidelines advocate waiting 7 days to start TPN.[230,231] Compared with the early initiation of TPN (within 48 hours) to supplement inadequate enteral nutrition, late initiation (≥8 days) was found on a randomized, multicenter trial to provide faster recovery (fewer days of mechanical ventilation), fewer infections, shorter duration of renal replacement therapy, and less cholestasis.[232] This study thus supports a period of hypocaloric feeding for the first week of ICU stay. Furthermore, trophic feeding (10 to 20 kcal/hr) for up to 6 days upon ICU admission did not reduce ventilator-free days, 60-day mortality, or infectious complications, but it was associated with less gastrointestinal intolerance, compared with full enteral feeding in patients with acute lung injury.[233,234] Another randomized multicenter study of ICU patients with relative short-term contraindications to enteral nutrition found that providing them with parenteral nutrition did not change 60-day mortality or the length of ICU and hospital stay compared with patients treated less aggressively, although the duration of mechanical ventilation was reduced.[234a] However, others showed that providing energy intake according to measurements of REE by supplementing enteral nutrition with TPN, if needed, within 48 hours of ICU admission appeared to improve survival.[235,236] Starting nutrition on ICU admission is important, however, when and the rate that full caloric intake should be reached are still unclear.

PARENTERAL VERSUS ENTERAL NUTRITION

A major decision when designing a nutritional support regimen is the route of administration. If patients are eating on their own, then monitoring their intake is necessary to ascertain its adequacy. Many patients have little appetite and thus may need nutritional supplementation between meals (snacking) to increase their caloric intake. Patients may be unable to feed themselves because of confusion or weakness and may need to be fed. During eating, the intake of patients with severe COPD may be limited by arterial oxygen desaturation, causing fatigue. Such patients may require supplemental oxygen via nasal cannula while eating. Patients who fail to sustain adequate caloric intake by eating require either supplemental enteral or parenteral nutrition.

The enteral route is favored over the parenteral method because it is the natural portal of entry for exogenous nutrients. However, current evidence does not fully support this view except that enteral nutrition costs less.[236,237] The enteral route obviates the need for intravascular access with its attendant risk of infections and sepsis. In addition, the array of nutrients that can be administered via the gastrointestinal tract is greater than what is available for parenteral use, allowing for better tailoring of nutrient intake. Other advantages of enteral nutrition are the ease of preparation and the maintenance of gut function. The importance of maintaining gut integrity (the gut derives up to 70% of its nutrients from luminal food) is to reduce the translocation of bacteria from the gut. Animal studies have shown that translocation of bacteria from intestines with reduced integrity and increased permeability leads to local activation of the gut's immune inflammatory system (Peyer patches and hepatic Kupffer cells). These cells then release cytokines that intensify the already existing systemic inflammatory response, increasing the risk for multiple organ failure. However, no overwhelming evidence of significant translocation in humans has been documented.[238] The lack of enteral intake, such as the absence that occurs among patients after surgery who are critically ill and receiving no nutrition or only TPN, is associated with small intestinal villous atrophy, decreased villous cell count, and reduced mucosal thickness. Intestinal permeability, measured using the urinary lactulose-mannitol ratio, is increased. These changes reverse with enteral feeding. Interestingly, no evidence confirms mucosal atrophy among patients who received 10 days of preoperative parenteral nutrition. It is thought that atrophy, itself, does not lead to bacterial translocation; instead, a further insult is needed. One such insult is small intestinal ischemia-reperfusion injury after resuscitation from an episode of shock, which by itself can change gut integrity.[239] This belief is supported by the observation that the incidence of bacterial growth from surgically removed mesenteric lymph nodes was higher in patients undergoing emergency surgery. Patients with such lymph nodes more commonly had postoperative sepsis.[240] Moreover, in a patient with a stressful illness, constantly proliferating gut epithelial and lymphoid tissues may possibly have an insufficient nutrient supply, further compromising gut integrity. The fear of reduced gut integrity along with studies showing preserved xylose absorption in patients who have been enterally, but not parenterally, fed has been among the reasons for recommending that enteral nutrition begin early, even if only very small amounts can be administered. In the latter case, concomitant TPN is indicated to provide adequate caloric intake.[241]

A major decision with enteral nutrition is the delivery method. Most patients are initially fed via nasoenteric

tubes, including large-bore tubes. The advantages of the latter include the ability to quantify residual feedings and quickly reinitiate nasogastric suction. The disadvantages are the potential for pulmonary aspiration occasioned by gastroparesis and incompetence of the gastroesophageal junction as a result of the diameter of the tube. Additionally, long-term use of large-bore tubes can lead to sinusitis and otitis media. Therefore, the type of feeding tube and the location of its distal end are major issues. For medium- and long-term feedings, using a small-bore (8 to 12 Fr), soft (e.g., Silastic), and long (to reach the jejunum) feeding tube with a weighted distal end is best. Such tubes reduce nasal and pharyngeal trauma and minimize gastroesophageal junction incompetence. Gastroparesis is common in patients who are critically ill; therefore, placing the tube distal to the ligament of Treitz (small intestinal function generally remains intact) prevents pooling of feeds in the stomach with its risk of pulmonary aspiration.[215] Yet, whether jejunal feeding actually reduces the risk of aspiration remains controversial. Compared with gastric feedings, jejunal feedings facilitate higher caloric intakes. Passing the tube through the pylorus is often problematic because of gastroparesis and a supine and immobile state. Therefore, if possible, the tube should be passed through the pylorus during abdominal surgery. In nonsurgical situations, an attempt may be made to pass a weighted tube through the pylorus by placing the tube in the stomach, turning the patient on the right side, and administering a prokinetic drug (e.g., metoclopramide). If this attempt fails, then the tube should be endoscopically or fluoroscopically placed.

Placing a jejunostomy tube during surgery is recommended in patients not expected to eat soon after surgery (i.e., those with severe trauma, major head injury, or esophageal surgery). Patients fed through nasoenteric tubes who will require prolonged enteral feeding (>4 weeks) should have either gastrostomies or jejunostomies surgically or percutaneously placed with endoscopic assistance. Percutaneous endoscopic gastrostomies (PEGs) are commonly performed, and a modification is to place a jejunal tube through the PEG.

Parenteral nutrition is used when the enteral route is unable to provide or sustain sufficient caloric intake. Although using the gut is preferable, situations arise in which parenteral nutrition is essential. Patients with short bowel syndrome require TPN after surgery and even for life if their residual bowel does not undergo sufficient adaptation to sustain adequate oral intake. Other absolute indications for TPN are small bowel obstruction, active gastrointestinal bleeding, pseudoobstruction with complete intolerance to food, and high-output enteric-cutaneous fistulas (unless a feeding tube can be passed distal to the fistula). In partial large bowel obstruction, feeding a low-residue diet may not be possible. Relative indications for parenteral nutrition include nonhealing, moderate-output, enteric-cutaneous fistulas; the need for bowel "rest," such as during inflammatory bowel flare-ups and acute radiation enteritis; significant abdominal distention and ileus attributable to intraabdominal sepsis; continued distention after relief of intestinal obstruction; and chylothorax unresponsive to a medium-chain TG diet. TPN is also indicated when the enteral route cannot provide enough nutrition.[242] In patients in the ICU, the inability to provide adequate enteral nutrition occurs because of diarrhea, vomiting, poor stomach emptying, feeding tube displacement, and the interruption of feeding for diagnostic tests, procedures, and surgery.[243]

Parenteral nutrition is administered through either central or peripheral venous catheters. Peripheral veins cannot tolerate an osmolarity of more than 750 mOsm/L (the equivalent of 12.5% dextrose); consequently, the fluid volume that can be tolerated limits the caloric intake. Therefore, the peripheral route is primarily used for supplementation or short-term feeding. Central venous catheters are the main route of TPN administration. The preferred entry location is the subclavian vein, which provides a stable site, good patient acceptability, and lower infection rates than either the internal jugular or femoral routes. To minimize insertion and infectious complications, a skilled clinician should insert subclavian catheters under sterile conditions as directed by the commonly used central venous lines (CVL) checklist.[244] This checklist promotes hand washing; full-barrier precautions that include gown, hat, mask, and gloves; and 5% alcoholic chlorhexidine skin preparation. Catheters should be inserted using ultrasound guidance.[245] The catheter should be a single-lumen catheter used only for TPN. Multiple-lumen catheters and multiple-purpose single-lumen catheters have high infection rates.[246] For long-term use, tunnelled Silastic Hickman-Broviac catheters, which have Dacron cuffs located at the proximal end of the tunnel to reduce infections, should be inserted.

FORMULATIONS

Glucose and Carbohydrates

In patients who are injured and septic, exogenous glucose and carbohydrates minimally reduce the rates of gluconeogenesis and lipolysis,[247] which differs from refeeding starved patients when carbohydrate administration reduces gluconeogenesis and lipolysis. Despite the reduced glucose use, administering carbohydrates to patients with stressful illnesses is still important because some body tissues do not readily use other substrates. Furthermore, glucose and carbohydrate intakes stimulate the secretion of insulin, which has anabolic properties that promote protein synthesis and decrease lipolysis. However, hyperglycemia, even with aggressive insulin treatment, often limits how much glucose and carbohydrates can be administered. The severity of TPN-induced hyperglycemia is directly proportional to the rate of glucose infusion and the degree of injury. Older adults are more predisposed to hyperglycemia.

It is important to recognize that patients often receive carbohydrates that are frequently administered from sources other than the glucose in TPN or carbohydrates in enteral nutrition. Patients usually receive 5% dextrose infusions (170 kcal/L), whereas intravenous lipid emulsions contain at least 22 g/L glycerol, which enters the gluconeogenic pathway. Overfeeding glucose (>4 mg/kg/min) to patients with acutely stressful illnesses and receiving a total caloric intake greater than the REE results in a thermogenic response, further elevation of blood glucose concentrations, and production of additional CO_2. This added CO_2 must be excreted by the lungs and, if

insufficiently excreted, can lead to elevated partial arterial pressure of CO_2 ($Paco_2$).

In patients who are critically ill, the rate and extent of enteral glucose absorption are reduced. Among the reasons for this reduction are delayed gastric emptying and reduced small intestinal absorption.[248,249] Delaying enteral feeding for 4 days after ICU admission impairs intestinal glucose absorption, as compared with starting enteral nutrition within 24 hours of admission,[250] which is another reason to begin enteral nutrition as soon as possible after ICU admission.

Lipids

Intravenous lipid is usually administered as a long-chain TG (LCT) emulsion.[251] These emulsions contain soybean oil and an emulsifier (egg phospholipid) and are calorically dense (e.g., 10% and 20% solutions contain 1.0 and 2.0 kcal/mL, respectively). Once infused, the lipid emulsion is converted to both TG-rich particles with sizes similar to that of chylomicrons and phospholipid-rich particles produced from emulsifiers called *liposomes*. The chylomicron-like particles are hydrolyzed by lipoprotein lipase to fatty acids and glycerol. The liposomes stimulate cholesterogenesis, incorporate cholesterol, and accumulate in the blood as the long-lived abnormal lipoprotein-X.[252] To minimize liposome formation, lipid emulsions should be slowly administered. Lipid emulsions are also the vehicle for many lipid-soluble drugs such as propofol, amphotericin B, and etomidate. Therefore, propofol infusions for sedation can provide significant amounts of lipid calories, which should be included when calculating caloric intake.

Exogenous fat is required to prevent essential FFA deficiency; therefore, patients receiving TPN should receive lipid emulsion (500 mL of a 10% LCT emulsion) at a minimum two to three times a week. Lipid emulsion is also used for energy because lipid oxidation is the predominant energy-producing pathway during stress. Fat emulsions are well oxidized when administered to patients with sepsis and trauma, even when glucose is provided. Patients with chronic hepatic failure suffering from sepsis and multiple organ dysfunction efficiently metabolize intravenous lipid emulsions. The current practice is to consider lipid emulsions as energy substrates and administer them as 30% to 40% of total TPN calories.

LCT lipid emulsions might have immunosuppressive effects. Ex vivo studies showed decreased neutrophil bacterial killing, depressed monokine expression, and other immune-depressant effects. A study of patients with trauma attributed increased infections to the administration of lipid emulsions, whereas a meta-analysis did not find LCT lipid emulsions to be detrimental to immune function.[253] Furthermore, healthy volunteers exposed to endotoxin showed an enhanced inflammatory response (increased IL-6 and TNF-α) when infused with a soybean-derived lipid emulsion.[254]

Soybean-derived LCT emulsions traditionally used for TPN have high proportions of omega-6, polyunsaturated fatty acids, specifically linoleic acid (53%). Linoleic acid is the precursor of thromboxane A_2 and prostaglandin E_1, which cause platelet aggregation and inflammation. Alternatively, fish oils containing omega-3 fatty acids (e.g., eicosapentaenoic and linolenic acids) are precursors of different prostaglandins (e.g., thromboxane A_3), which have less platelet aggregating activity and cause less inflammation. Platelets from patients infused for 7 days after surgery with fish oil–enriched lipid emulsions aggregated less than those of patients administered non-enriched emulsions.[255] A meta-analysis showed that fish oil–supplemented TPN reduced hospital and ICU lengths of stay and reduced postoperative infections but did not affect mortality.[162] Postoperative oral eicosapentaenoic acid improved lymphocyte proliferation and NK cell activity. Enteral nutrition regimens enriched with eicosapentaenoic acid and γ-linolenic acid promote the production of antiinflammatory prostaglandin E_1 and were used in the acute respiratory distress syndrome to reduce pulmonary microvascular permeability and to decrease prostaglandin, IL-8, and leukotriene synthesis by alveolar macrophages. In studies in which these formulations were given by continuous infusion, they were associated with shorter mechanical ventilation, decreased ICU lengths of stay, and lower mortality.[256,257] However, bolus supplementation of enteral nutrition with omega-3 fatty acids, γ-linolenic acid, and antioxidants failed to increase ventilator-free days in patients with ARDS.[258]

To reduce the purported limitations of intravenous LCT emulsions, such as the production of toxic lipid peroxides, immunosuppression, and heightened inflammation, there is increasing interest in substituting medium-chain TGs (MCTs) or monosaturated fatty acids derived from olive-oil for some of the LCTs. MCTs do not need carnitine to enter the mitochondria and may be advantageous when carnitine is decreased, such as during sepsis. MCTs are essentially an energy substrate, and it appears that they cannot be stored. MCTs appear to have fewer immunosuppressive effects than LCTs and do not participate in eicosanoid synthesis.[259] Many commercial enteral formulas contain both MCTs and LCTs, supposedly because MCTs are better absorbed. Intravenous MCT-LCT or LCT–olive oil emulsions are not available in the United States.[260]

Protein and Amino Acid

Amino acids and protein are essential ingredients of nutritional support regimens. TPN contains commercially prepared amino acid mixtures, whereas enteral formulas contain free amino acids, peptides, or whole proteins. The purpose of administering protein or amino acids to patients with stressful illnesses is to decrease the breakdown of endogenous proteins by providing an alternative source of amino acids for gluconeogenesis and protein synthesis. Unfortunately, in the stressed state, exogenously administered amino acids and protein are not well utilized because proteolysis is relatively unresponsive to the usual negative feedback mechanisms, such as the administration of exogenous glucose, protein, or amino acids. Nitrogen balance remains negative well into the convalescent stage. In children with burns, leg skeletal muscle protein deposition is unresponsive to amino acid infusion 6 months and up to a year after injury.[261,261a] In the catabolic state, protein–amino acid intake of 1.2 to 1.5 g/kg/day is recommended. Higher amounts do not promote further nitrogen retention and are metabolized to urea; consequently, the blood urea nitrogen may rise. Situations with large external losses of protein, such as extensive burns and large draining abscesses, make it necessary to increase protein–amino acid intake. Adequate

nonprotein calories (e.g., glucose, fat) must be concomitantly administered to ensure that the protein–amino acids are not used as an energy source.

The inability of protein–amino acids to attenuate nitrogen losses significantly led investigators to explore ways of decreasing proteolysis and increasing protein synthesis. One attempt was to use branched-chain–enriched amino acid solutions as a component of TPN, which resulted in some improvement in nitrogen balance[262] but no improvements in outcome. Some enteral nutrition formulas for highly stressed patients are so enriched.[263] The use of anabolic substances, such as IGF-1 plus IGFBP-3 and anabolic steroids to reduce protein oxidation and improve protein synthesis is still in the investigative stages.[264] Another anabolic substance is insulin, which at lower doses decreases protein breakdown by inhibiting the major catabolic pathway—the ATP-ubiquitin proteasome proteolytic pathway[265]; it also stimulates protein synthesis at higher doses.[264] Administering small doses of insulin to patients with burns increased skeletal muscle protein synthesis and improved wound matrix formation. However, the anabolic effects of insulin on protein metabolism were not observed in patients with trauma who were enterally fed. Therefore, the route of nutrient intake may play a role in insulin's anabolic effects.

Amino acids are the precursors of many endogenous substances. Therefore, by manipulating the proportion of the various amino acids in TPN and enteral nutrition formulations, it might be possible to influence the metabolic milieu.[267] Glutamine is the most abundant free amino acid in blood and skeletal muscle and is a primary fuel for rapidly dividing cells such as enterocytes and immunocytes and a precursor of purines, pyrimidines, and nucleotides. It is primarily synthesized in skeletal muscle and is involved in the interorgan transport of nitrogen. Plasma glutamine concentrations decrease during severe stress, probably secondary to decreased glutamine synthesis, providing a possible explanation why alanine is the major interorgan nitrogen transporter. Animal studies show that glutamine likely becomes an essential amino acid during catabolic illness when *de novo* synthesis is insufficient. These studies also show that parenteral and enteral glutamine-supplemented nutrition may prevent gut bacterial translocation, induce neutrophilic phagocytic activity, reduce neutrophil apoptosis, maintain gut integrity, and increase concentrations of the antioxidant glutathione. A meta-analysis of parenteral glutamine supplemented TPN in surgical patients concluded that it shortened hospital lengths of stay and reduced the morbidity of postoperative infections.[268] A placebo-controlled randomized study among critically ill patients who received glutamine supplements starting within 24 hours after ICU admission showed increased in-hospital and 60-day mortality in patients with multiorgan failure.[268a] Therefore, glutamine supplementation is not recommended in such patients. Others for whom supplementation may be indicated include patients with burns, patients who are critically ill, recipients of hematopoietic transplants, and those with acute pancreatitis.[172a] Glutamine is rather insoluble and has limited stability in aqueous solution. Therefore, it is administered as an alanine-glutamine dipeptide when infused intravenously. The amino acid arginine has also been added to nutritional support. In patients with trauma, it stimulates immune cells to reduce NO production, whereas during sepsis it increases NO production. Therefore, arginine supplementation must be used in situations where it does not exacerbate the underlying illness.

Nutritional regimens require many ingredients (Table 106-3; also see Table 106-2). Choosing the route of administration is the key decision, because the type and composition of the formula are wholly dependent on the route. With the parenteral route, protein intake is limited to commercial mixtures of amino acids, carbohydrate to glucose, and lipids to the available emulsions. With enteral nutrition, more options are available because a variety of commercial formulas exist. Supplementing enteral formulas with modular protein, lipid, and carbohydrate products is possible. Either measuring REE using indirect calorimetry or estimating requirements may determine caloric intake (see Table 106-2).

COMPLICATIONS

Complications of nutritional support can result from problems with the delivery system or the nutrition itself. Morbidity related to the delivery system or the nutrients occurs more often with enteral nutrition than with parenteral nutrition. However, infectious complications are more frequent with parenteral nutrition (also see Chapters 101 and 102). Guidelines are available to guide safe compounding and administration of parenteral nutrition.[268b,268c]

Complications of central venous catheterization occur with parenteral nutrition. These complications include pneumothorax, secondary to subclavian or internal jugular vein catheterization. The pneumothorax rate for subclavian catheterization is 1% to 5% but is lower if performed by an experienced clinician. Other complications include hemorrhage-causing hemothorax, brachial plexus injury, and catheter misplacement in the azygos vein, right ventricle, or retrograde into the jugular vein. Central venous catheters (PICCs) that are peripherally inserted, such as via an arm vein, have the advantage of avoiding pneumothoraces but are more difficult to place and have a higher incidence of poor position, upper extremity thrombosis, and skin site irritation. Catheter tips should be above the left atrium and confirmed by chest radiography before starting nutrition. Peripheral venous access, whether via a short peripheral venous catheter or a PICC line, can result in thrombophlebitis. With short catheters, the osmolarity of the solution must be limited to less than 750 mOsm/L to prevent phlebitis. To further prevent phlebitis, some clinicians add heparin and hydrocortisone to the solution, whereas others place a nitroglycerin patch over the catheter site. It is imperative that peripheral parenteral nutrition catheter sites be regularly inspected and catheters changed when evidence of phlebitis develops.

Catheter-related infections are the major venous access complication encountered with TPN. Microbial colonization and bacteremia result from the interaction of four factors: (1) hydrophobicity and exopolysaccharide production of the microbe, (2) amount of fibrin and fibronectin attached to the catheter surface, (3) catheter material (e.g., hydrophobicity, surface charge, thrombogenicity), and (4) iatrogenic factors such as sterile technique and immunocompetence. Infections are uncommon during

TABLE 106-3 CONSIDERATIONS WHEN DESIGNING NUTRITIONAL SUPPORT REGIMENS

Considerations	Requirements	Issues
Route of administration	Evaluate enteral vs. parenteral, or use both.	
Caloric requirements	Measure REE with indirect calorimetry. Estimate REE with established equations. Use a weight-based formula.	See Table 106-2.
Protein–amino acids	Evaluate degree of stress; measure nitrogen balance. Parenteral nutrition: Use amino acid solutions. Enteral nutrition: Use standard or high-protein formulas; evaluate amino acids (elemental diet) vs. peptides vs. protein hydrolysates. If protein losses are excessive, then increased protein intake is needed.	Unstressed patients: 0.8-1.2 g/kg/day protein Stressed patients: 1.0-1.5 g/kg/day protein
Calorie/protein ratio	Is expressed as calorie/nitrogen ratio.	Standard formulas: 130-170:1 Stress formulas: 125-100:1
Carbohydrates	Parenteral nutrition: Glucose is the only available nutrient. Enteral nutrition: Oligosaccharides and starches are used.	Glucose intake not to exceed 4 mg/kg/min during stress.
Lipids	Parenteral nutrition: LCT emulsions; emulsions containing MCTs, olive oil, fish oils (omega-3–fatty acids) are available in some countries. Enteral formulas: Contain LCT or LCT/MCT emulsions; some are enriched with omega-3–fatty acids.	
Lipids/carbohydrate ratio	Parenteral nutrition: C:H:O ratio in lipids: 30:70-60:40. Enteral nutrition: Depends on the formula; calorie-dense formulas (1.5-2.0 kcal/ml) have higher fat ratios.	
Electrolytes	Parenteral nutrition: Contains sodium (NaCl, Na acetate); potassium (KCl, K acetate); phosphate (KPO_4, $NaPO_4$); magnesium ($MgSO_4$), calcium (Ca-gluconate). Enteral nutrition: Per formulation; may add electrolytes, if needed.	Potassium (K): 1-1.2 mEq/kg Magnesium (Mg): 8-20 mEq/day Calcium (Ca): 10-15 mEq/day Phosphate (PO_4): 20-30 mmol/day
Trace elements	Parenteral nutrition: Contains copper, molybdenum, selenium, zinc, manganese, chromium. Enteral nutrition: Also contains iron and iodine.	
Vitamins	Parenteral nutrition: Commercial multivitamin preparations contain all vitamins; some do not include vitamin K. Enteral nutrition: Contains all vitamins including vitamin K; the volume of the formula that provides the recommended daily requirements depends on the formula. Fat-soluble vitamins: Contain A, D, E, and K. Water-soluble vitamins: Contain B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), B_5 (pantothenic acid), B_6 (pyridoxine), folate, B_{12}, and C.	Need to monitor PT (INR) weekly and administer vitamin K, if indicated. Vitamin C requirement is increased for wound repair.
Water	Parenteral nutrition: Dilute vs. concentrated formulas are evaluated. Enteral nutrition: Standard (1.06 kcal/ml) vs. caloric-dense (2.0 kcal/ml) formulas are evaluated.	Dilute formulas are used for peripheral vein administration. Concentrated formulas are used for fluid restriction or high caloric intake formulas.
Disease-specific considerations	Renal failure Hepatic failure Pulmonary disease Burns Diabetes Congestive heart failure	See "Special Considerations" section in the text. See "Special Considerations" section in the text. Reduce absolute carbohydrate intake, substitute lipid for carbohydrates with high total caloric intake. See "Special Considerations" section in the text. Control blood glucose, monitor serum triglyceride levels. Use concentrated formulas, low sodium intake.

C:H:O, Carbon-to-hydrogen-to-oxygen; *INR*, international normalized ratio; *KCl*, potassium chloride; *KPO_4*, potassium phosphate; *LCT*, long-chain triglyceride; *MCT*, medium-chain triglyceride; *$MgSO_4$*, magnesium sulfate; *NaCl*, sodium chloride; *$NaPO_4$*, sodium phosphate; *PT*, prothrombin time; *REE*, resting energy expenditure.

the first 72 hours after insertion but then increase in incidence. The incidence of central venous catheter–related bloodstream infections ranges from 0.3 to 30 per 1000 catheter days and are most often caused by *Staphylococcus epidermidis*, *Staphylococcus aureus*, or *Candida* species, although gram-negative bacteria are being increasingly observed.[270,271] Mortality attributed to catheter-related infections is as high as 25%. A major part of TPN care is aimed at reducing infections. Therefore, solutions are prepared under laminar flow hoods. Once they are prepared, nothing may be added to the solution, and they must be refrigerated until use. Any manipulation of the catheter or line must be performed using sterile procedures, manipulation of the line should be kept to a minimum, and the site must be regularly examined for signs of erythema and infection.

Inserting nasoenteric tubes for enteral nutrition can result in complications because such tubes can enter the pulmonary airways, coil and knot in the stomach, and fail to enter the stomach and thus remain in the esophagus. Therefore, confirming the feeding tube location with chest and/or abdominal radiographs before starting the feeding is vital. Nasoenteric tubes can be withdrawn into the stomach (in case of jejunal feeding) or the esophagus, increasing the risk for aspiration. Nasojejunal tubes dislodged in one third of patients after panceaticoduodenenctomy.[272] Such tube misplacement occurs because of patients pulling on the tube and during suctioning of the mouth. Therefore, the tube should be securely fastened to the nose; if any dislodgment is suspected, a radiograph should be obtained. The major problem with enteral nutrition is frequent decreases or discontinuations of the intake, which prevent administering all the daily caloric requirements. These decreases and discontinuations have been ascribed to high gastric residuals, mechanical problems with the feeding tubes (e.g., dislodgment into the esophagus and obstruction), medical or surgical procedures, sepsis, and vomiting. As many as one third of patients receiving enteral nutrition are unable to achieve a target intake of 25 kcal/kg/day. Therefore, close monitoring of the actual enteral nutrition intake is important to ensure that measures can be taken to ensure adequate caloric intake. These measures include establishing more secure access to obviate or prevent tube dislodgment (e.g., placing a PEG) and placing the tube tip distal to the ligament of Treitz to avoid gastric residuals. In patients in whom the enteral intake remains inadequate, supplementing with parenteral nutrients should be considered.[273] A cumulative caloric debt may occur in patients not fed early and adequately. Therefore, monitoring caloric intake and attempting to avoid caloric deficits are important.

In general, surgically placed needle jejunostomies provide safe and effective access for postoperative enteral feeding. However, complications may occur, including tube dislodgment, local cellulitis, and obstruction. Obstruction can be avoided by frequent flushing and limiting the viscosity of the feeds. Major complications were observed in 4% of 220 patients with trauma who had jejunostomies placed during laparotomies. These complications included small bowel perforations, small bowel volvuli with infarction, intraperitoneal leaks, and small bowel necrosis.[274,275] Small bowel necrosis has a mortality rate approaching 100%.[276] These complications occurred more often with larger diameter tubes than needle jejunostomies.[274] Others have reported intraabdominal and subcutaneous abscesses and small bowel obstruction. Other complications include catheters breaking, especially at the hub, and jejunocutaneous fistulas on removal.

Metabolic Complications

Nutritional support should be slowly initiated and increased only if the patient tolerates the feeding. Because metabolic complications of nutritional support frequently occur, monitoring electrolytes and glucose daily in patients who are acutely ill, particularly when starting the nutrition, is important. If necessary, adjustments should be made in the formulation. Hyperglycemia is a common problem, especially with severe stress, steroid use, and diabetes mellitus requiring treatment with insulin. Administering insulin is preferable over reducing the glucose intake unless hyperglycemia is excessive (>250 mg/dL), despite high insulin doses. Insulin treatment can reduce serum potassium and phosphate concentrations, which require repletion. Importantly, as the stress response abates, the degree of glucose intolerance lessens and insulin requirements drop. Therefore, closely monitoring blood glucose to prevent hypoglycemia is imperative.

Hypoglycemia can occur on the abrupt discontinuation of continuous feedings containing significant amounts of carbohydrate. Continuous feedings result in high blood insulin concentrations so that hypoglycemia intervenes when the carbohydrate intake stops. Therefore, when stopping continuous parenteral and enteral nutrition, any concomitant insulin infusion must be stopped, intravenous glucose should be infused, and blood glucose frequently monitored. The practice of using TPN solutions containing lower glucose:lipid ratios (70:30 to 50:50) has reduced the incidence of hypoglycemia after abrupt discontinuation. TPN should be continued during surgery, whereas enteral nutrition should be discontinued 8 hours before surgery and a glucose infusion begun to prevent hypoglycemia.

Refeeding

Refeeding patients who are nutritionally depleted (≥10% loss of body weight over ≤6 months) must be carefully done to avoid overloading a metabolic system that has adapted to minimal or no food intake.[277] Feeding such patients must begin with balanced diets of carbohydrates, fats, and proteins at intakes below REE. The intake should be increased stepwise over 7 to 10 days. Intake must be monitored to prevent overindulgence because these patients may be hyperphagic. Patients must be monitored for signs of fluid overload, pulmonary edema, and electrolyte disturbances. Electrocardiographic (ECG) changes should be followed for prolongation of the QT interval, which can be a harbinger of torsades de pointes. Hypophosphatemia occurs when tissues begin to rebuild and is especially problematic if the phosphate intake is inadequate, known as the *refeeding syndrome*. Hypophosphatemia may lead to major muscle (including respiratory muscle) weakness and glucose intolerance because

phosphate is a vital component of tissue membranes, enzymes, and nucleosides, especially ATP. Concurrent hypomagnesemia, hypocalcemia, and hypokalemia may exacerbate muscle weakness. Of 62 patients who had not received nutritional intake for at least 48 hours after ICU admission, 34% developed hypophosphatemia (serum levels <0.65 mmol/L or a drop of 0.16 mmol/L) on refeeding. Chronic alcoholics are especially prone to hypophosphatemia. Hypophosphatemia occurs more commonly after enteral than parenteral nutrition.[278]

Nitrogen balance may take time to turn positive because protein intake needs to be gradually increased and gluconeogenesis needs to continue for some time after refeeding begins. Generally, individuals who are nutritionally depleted efficiently replete fat and glycogen stores and rebuild muscle tissue. To rebuild muscles requires exercise; therefore, rebuilding the muscles of patients who are bedridden or immobile is virtually impossible.

Overfeeding

Overfeeding patients with stressful illnesses has many consequences (Box 106-2).[230,279-281]

Gastrointestinal System Complications

Hepatobiliary complications often occur during parenteral nutrition. Factors associated with their development include underlying diseases and their severity, intercurrent sepsis, and drugs. The role of TPN may be additive, if not primary. Large glucose loads (>4 mg/kg/min) can result in hepatic steatosis and steatohepatitis with *portal triaditis* on biopsy. The latter is accompanied by elevated γ-glutamyl transpeptidase, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. Intrahepatic cholestasis with elevated alkaline phosphatase and bilirubin can occur 3 to 6 weeks after beginning TPN. Large omega-6 polyunsaturated lipid loads (≥2 g/day) administered for prolonged periods may also cause cholestasis.[282] Fish oil–based omega-3 polyunsaturated lipids appear to reverse this problem.[283]

Gastrointestinal tract dysfunction frequently occurs with enteral nutrition. Approximately 50% of patients who are mechanically ventilated have delayed gastric emptying. The magnitude of gastric residual volumes are correlated with disease severity in patients in medical ICUs.[284] Consequently, feeds are usually continuously administered, and gastric residual volume is measured at frequent intervals.[285] Compared with feeding into the small intestines, intragastric feeding results in more frequent gastric residuals, vomiting, and regurgitation. In a multicenter prospective study of 400 patients in the ICU who were fed primarily via nasogastric tubes, gastrointestinal complications occurred in 62.8% and were due to diarrhea (14.7%), constipation (15.7%), large gastric residuals (39%), abdominal distention (13.2%), vomiting (12.2%), and regurgitation (5.5%). Enteral nutrition was withdrawn in 15% of patients because of gastrointestinal complications.[276] In the presence of gastroparesis and large volume (150 to 220 mL) residuals, prokinetic agents should be considered. Individual studies showed that intravenous erythromycin is more effective than metoclopramide (improvement in 87% versus 62% of patients), but their effectiveness declined over time.[286]

BOX 106-2 *Consequences of Overfeeding in Parenteral and Enteral Nutrition*

Caloric intake: Substrate in excess of energy needs and synthetic function
>1.5-1.7 REE in patients with stressful illnesses

- Increased fat storage
- CO_2 production, urea production, and thermogenic effects

Carbohydrates: >4.5 mg/kg/min

Lungs
- Increased CO_2 production leads to increased $\dot{V}_E$, which may cause breathlessness.
- If increases in $\dot{V}_E$ are insufficient, then $Paco_2$ increases.

Liver
- *Fatty liver:* Hepatomegally increases AST, ALT, and alkaline phosphatase.
- *Hyperglycemia:* May lead to osmotic diuresis and prerenal azotemia.
- *Exacerbation of peripheral insulin resistance:* Reduces insulin sensitivity and increases oxidative stress.
- *Increased intracellular potassium:* Decreases serum potassium.
- *Increased intracellular phosphate:* Decreases serum phosphate.
- *Increased REE:* Is due to increased thermogenesis caused by increased catecholamine secretions.

Lipids: >2g/kg/day

Liver: Cholestasis, fatty liver
Congestion of RES with fat increases.
Serum triglyceride levels increase.

Protein: >2g/kg/day

Kidneys
- Ureagenesis is increased.
- BUN increases with decreased renal function.
- With normal renal function, diuresis may occur as a result of increased BUN secretion, which may lead to prerenal azotemia.

Lungs
- Protein–amino acids increase respiratory drive and might cause breathlessness.

Fluid intake: Excessive fluid intake may lead to fluid overload and is especially problematic with reduced cardiac or renal function.
Infection: Bloodstream infections are increased.

AST, Aspartate aminotransferase; *ALT*, alanine aminotransferase; *BUN*, blood urea nitrogen; *CO_2*, carbon dioxide; *$Paco_2$*, partial arterial pressure of carbon dioxide; *REE*, resting energy expenditure; *RES*, reticuloendothelial system; *$\dot{V}_E$*, minute ventilation.

Rescue therapy using both drugs was effective.[285,287] To decrease pulmonary aspiration, patients should be fed in the semirecumbent position, and promotility agents should be used if residual gastric volumes are high. Whether postpyloric feeding reduces aspiration is yet unclear.[229] With enteral nutrition, being aware that drug-nutrient interactions can occur is important.

Diarrhea is a particularly unpleasant complication of enteral nutrition for both the patient and staff with its incidence, depending on its definition, ranging from 2% to 53% of patients and 38% of feeding days. The definition of diarrhea used is important because many enteral products are *low residual*: that is, they do not contain fiber and may not cause formed stools. Formula-related causes of diarrhea

include hyperosmolar feedings, too rapid administration, and contamination of feedings with toxigenic or pathogenic organisms. Therefore, feeds should be sterile and not allowed to hang in the bag for longer than 8 to 12 hours.[288] Non–formula-related causes include concomitant administration of drugs constituted in sorbitol elixirs, mannitol, or polyethylene glycol; *Clostridium difficile* enterocolitis; intraabdominal infection; receipt of broad-spectrum antibiotics; and hypoalbuminemia. Hypoalbuminemia-associated diarrhea has been attributed to small bowel wall edema, leading to malabsorption. Yet, using elemental and peptide diets has achieved diarrhea-free feedings in patients with hypoalbuminemia. Fiber-containing formulations might reduce diarrhea but not consistently.[289] Most enteral formulas are lactose and gluten free, eliminating lactose and gluten intolerances as problems. In patients without infectious diarrhea, pectin and antimotility drugs may reduce the diarrhea. However, such patients must be monitored for the development of constipation. Hepatobiliary complications of enteral nutrition are rare (<5%).

SPECIAL CONSIDERATIONS

BURNS

Patients with burns present special problems because of their extremely high energy expenditures, transcutaneous losses of protein, and great fluid requirements (also see Chapter 59). If patients are unable to eat, then enteral nutrition is the preferred modality. A number of trials indicate that enteral nutrition started within a few hours of admission reduces the magnitude of the stress response to burns. Therefore, beginning nutrition early, that is, within fewer than 16 hours of admission, is common practice with significant burns (>20%). However, insufficient evidence on systemic review shows an advantage of early versus late enteral nutrition or that enteral nutrition reduces the stress response.[290] To ensure successful administration of many calories of a high protein diet, nasoenteric feeding tubes should be placed into the jejunum. Caloric intake must be closely monitored in patients with burns. If inadequate calories are being ingested, then supplementation is needed. In patients who are eating, supplementation may be in the form of nutritional supplements ingested between meals. In patients who are enterally fed, supplementation can be provided with parenteral nutrition. Furthermore, burn patients have elevated protein requirements and increased vitamin and trace element needs.[290a]

HEPATIC DYSFUNCTION

Hepatic dysfunction, especially cirrhosis with intercurrent acute illness, presents a complex metabolic scenario (see Chapters 73 and 74). As many as 90% of patients with decompensated cirrhosis suffer weight loss, muscle wasting secondary to anorexia, large protein loses into ascites, poor oral intake because of unpalatable low-salt and low-protein diets, and hypermetabolism.[291] They have hyperinsulinemia, insulin resistance, accelerated gluconeogenesis, increased lipid oxidation, fat malabsorption attributable to decreased bile salts, and possibly, reduced glycogenesis.[292] Essential fatty acid, magnesium, zinc, and selenium deficiencies also occur. After liver transplantation, glucose clearance improves, owing to the correction of the hyperinsulinemia and insulin resistance. However, patients receiving corticosteroids as immunosuppressive therapy continue having abnormal glucose metabolism.

As a result of their depleted state, patients with cirrhosis appear to be candidates for nutritional repletion. Yet, because of their poor prognosis, especially when complicated by serious illness, enteral nutritional support of hospitalized patients who are seriously ill with cirrhosis was associated with reduced survival. A Cochrane Review did not reveal compelling evidence to routinely use parenteral or enteral nutrition or oral supplements in patients with liver disease.[293] However, the success of liver transplantation renewed interest in nutritionally supporting transplant candidates. These patients require fluid and sodium restriction and diuretic agents to control their fluid overload. They need increased protein–amino acid intakes (1.2 to 1.5 g/kg/day) because of increased protein synthetic rates and to replace the losses caused by ascites formation. Furthermore, they require a caloric intake to account for hypermetabolism (25 to 40 kcal/day).[294] Some patients with cirrhosis develop hepatic encephalopathy. When encephalopathic, current recommendations are not to reduce protein intake but to provide an intake of 1.0 to 1.2 g/kg/day plus lactulose and/or neomycin.[295] In persistent encephalopathy, branched-chain amino acid–enriched solutions and feedings should be considered. In cirrhosis, the plasma concentrations of these amino acids are low. When intravenously administered, they are thought to counter the effects of intracerebral aromatic amino acids, which are involved in hepatic encephalopathy.[296] Furthermore, they are not metabolized in the liver and are available for protein synthesis. A Cochrane Review showed a decreased rate of hepatic encephalopathy without a reduction in mortality rate or adverse events.[297]

RENAL DYSFUNCTION

Preexisting chronic renal disease and newly developed acute renal failure present special nutritional challenges (see Chapters 72, 73, and 74). Acute renal failure is especially problematic in the surgical arena because of its association with shock and sepsis. Such patients are insulin resistant, catabolic, and hypermetabolic, similar to other patients with stressful illnesses. However, uremia exacerbates catabolism because it exacerbates insulin resistance, metabolic acidosis, and circulating proteases. The kidney interconverts various amino acids and also degrades specific peptides; consequently, major abnormalities in protein–amino acid handling are also present. Cytokines liberated during hemodialysis may further aggravate the catabolic state. Patients with renal failure are intolerant of large fluid loads, especially when they are oliguric, cannot self-regulate electrolyte concentrations, and do not tolerate large protein–amino acid loads because of an inability to excrete urea. Because these patients require approximately 30 kcal/kg/day and 1.0 to 1.5 g/kg/day of protein, frequent dialysis is needed to remove wastes and excess fluid. The protein–amino acid intake may need to be increased because of dialysis-related loss of amino acids.

Essential amino acid–enriched solutions have been used to reduce urea production, and a Cochran Review concluded that essential amino acids may shorten the overall duration and improve survival from acute kidney dysfunction.[298] Current recommendations are to provide a combination of essential and nonessential amino acids plus dialysis, based on the theory that normally nonessential amino acids may become essential in diseased states.[299]

Hemodialysis, continuous renal replacement therapy (CRRT), that is, venovenous and arteriovenous hemodiafiltration, and peritoneal dialysis facilitate enteral nutrition and parenteral nutrition by removing excess fluid and urea, as well as balancing electrolyte concentrations, thus permitting patients to receive a full complement of calories and protein–amino acids. However, these therapies result in the loss of amino acids (10 to 15 g/day) unrelated to amino acid intake but related to plasma amino acid concentrations, volume of dialysate effluent, and filter efficiency. The concentrations of most amino acids are equal in plasma and dialysate. Therefore, the protein–amino acid content of the nutritional support should be increased. With aggressive CRRT, patients required as much as 2.5 g/kg/day of protein to achieve positive nitrogen balance.[300,301] Current protein recommendations are 1.5 to 1.8 g/kg/day.[302] Dialysis also results in losses of peptides, proteins (with peritoneal dialysis), and water-soluble vitamins. Therefore, some renal enteral nutrition formulations have added B vitamins.

Peritoneal dialysis and CRRT solutions usually contain 1.5% glucose, although concentrations as high as 4.25% are used. Up to 35% to 45% of this glucose can be absorbed and is a source of carbohydrate calories. With peritoneal dialysis, as much as 500 g/day of dextrose may be absorbed. Similarly, glucose-containing solutions used as replacement solutions during hemofiltration can be a source of glucose calories, in one study providing 300 g/day of glucose. This glucose load must be considered when designing nutritional regimens and glucose-carbohydrate contents reduced accordingly. Additionally, glucose concentrations need to be monitored because of both the profound stress state and dialysis-associated glucose absorption. Insulin therapy may be needed to reduce the hyperglycemia. However, patients with renal failure may be especially sensitive to insulin. If glucose-poor solutions, which result in the loss of glucose, are used for CRRT, then glucose replacement should be incorporated into the nutritional support.[302]

Generally, nutritional regimens for patients in renal failure should not contain phosphate, potassium, or magnesium because concentrations of these electrolytes are already elevated. Calcium intake may need to be increased, whereas sodium content should be nearly isotonic because of an inability to regulate serum sodium concentrations. However, during dialysis, all the serum electrolytes must be closely monitored and deficiencies corrected as indicated.[301]

PANCREATITIS

Traditional treatment of acute pancreatitis and of acute exacerbations of chronic pancreatitis is to exclude all oral intakes, institute nasogastric suction, and deliver all nutritional support parenterally. However, contemporary practice is to begin enteral nutrition early (within 48 to 72 hours) in the course of the disease. Several meta-analyses showed that compared with TPN, enteral nutrition is associated with fewer infectious complications, less multiple organ failure, and lower mortality.[303] Furthermore, enteral nutrition causes less hyperglycemia and lower insulin requirements.[304] Therefore, enteral nutrition via a nasojejunal tube is the preferred route of nutritional support in acute pancreatitis, although feeding via nasogastric tubes is noninferior. TPN should be used only when enteral nutrition is not tolerated.[305,305a]

CONCLUSIONS

On a daily basis, anesthesiologists care for patients who are surgically and critically ill and suffering from the consequences of the metabolic and inflammatory responses to injury and sepsis. They must often modulate the detrimental aspects of the response itself (e.g., with epidural anesthesia), modify end-organ responses (e.g., β-adrenergic blockade), and treat its consequences (e.g., blood glucose control, nutritional support) while retaining its beneficial (e.g., immune-enhancing) aspects. However, patients' metabolic conditions are dynamic; consequently, interventions must be appropriate, effective, and most of all, timely. This dynamic situation requires tools that can rapidly assess the metabolic and immunologic milieu.[306] This assessment involves using systems biology approaches incorporating genomic, transcriptomic (mRNA), proteomic, and metabolomic information to better understand the stages of this response. These omic techniques, with their ability to profile many biomarkers rapidly, differ from the current approach of tracking only one or two biomarkers.[307,307a] Genomics research has revealed that the secretion of cytokines and end-organ responses in response to activation of Toll-like receptors during sepsis differ, depending on an individual's genetics.[308] Similarly, gender plays a role in the response. For example, young girls with burns have less hypermetabolism and higher anabolic hormone concentrations than boys, whereas healthy adult women appear to have lower susceptibility to sepsis than men, possibly because of more pronounced proinflammatory innate immunity and a lesser decrease in norepinephrine sensitivity when exposed to endotoxin.[309] Therefore, the use of these newer techniques promises more tailored treatment.

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Chapter 107

Extracorporeal Support Therapies

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Key Points

- Extracorporeal membrane oxygenation (ECMO) and renal replacement therapy (RRT) are two very important techniques of extracorporeal support commonly used for the care of patients who are critically ill: kidneys, lungs, and heart can be effectively substituted artificially.
- ECMO consists of a specific heart-lung machine that provides gas exchange for prolonged support of patients with severe but potentially reversible respiratory or cardiac failure or both. Although the term *extracorporeal life support* (ECLS) might describe the system more accurately, ECMO is actually most often used and universally accepted for describing all its applications.
- Different configurations (venovenous, venoarterial, arteriovenous) can be applied to patients, depending on their specific organ failure and severity (e.g., respiratory failure, cardiogenic shock, cardiogenic shock associated with respiratory failure).
- Great technologic improvements have been made during the past years in the manufacture of ECMO circuits, pumps, gas exchangers, and cannulas, rendering the systems simpler, safer, and more efficient for long-term assistance. Such developments have occurred as a consequence of the close integration and exchange of knowledge among industry, clinicians, and scientific investigators.
- Extracorporeal blood purification is a method for removing waste products, such as creatinine and urea, as well as free water from the blood when severe acute kidney injury (AKI) has occurred. The system to achieve blood purification is typically called RRT. In patients who are critically ill, RRT is commonly applied continuously using continuous RRT (CRRT) but also intermittent RRT.
- Solute removal can be achieved by dialysis through diffusion, by hemofiltration (convection), or by the application of both solute transport methods. Water removal is exclusively achieved through ultrafiltration (UF).
- RRT requires intimate knowledge of critical care nephrology and the clinical picture and symptom progression of multiorgan failure. The application of RRT should be decided in a timely manner by an adequately trained team. Solute removal for blood purification is achieved by an accurate RRT prescription, monitoring, and delivery. Fluid overload has to be addressed by net UF prescription and aggressively targeted.

INTRODUCTION TO EXTRACORPOREAL SUPPORT THERAPIES: MULTIORGAN SUPPORT FOR THE PATIENT WHO IS CRITICALLY ILL

Today, patients who are critically ill keep dying from multiorgan dysfunction, a complex and multifactorial syndrome. Mortality ranges from 50% to 90% of patients. Furthermore, as a result of improvements in surgical and pharmacologic options in the past 10 years, patients with the most severe diseases are being admitted to intensive care units (ICUs). When multiorgan failure occurs, therapeutic options are still not specific and mostly aim at vital function support. The kidneys, with their fragile and delicate systems of autoregulation, are almost always involved in the multiorgan failure, and dialytic techniques are routinely used. Renal replacement therapy (RRT) development and utilization has increased to the point that today a multifaceted intervention directed at supporting the function of several organs appears feasible and rational. The concept of multi-organ support therapy (MOST)[1] is to treat a patient's blood artificially, outside of the body, substituting heart, lungs, liver, and kidneys with dedicated pumps, circuits, and membranes (also see Chapter 101).

This chapter gives a general overview of the specific aspects of renal, pulmonary, and circulatory extracorporeal mechanical assistance for renal, respiratory, and cardiocirculatory failure in newborn, pediatric, and adult patients who are critically ill. The technical features and clinical applications are discussed in the following pages.

HISTORICAL NOTES

EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation (ECMO) consists of a specific heart-lung machine to provide gas exchange for prolonged support of patients with severe but potentially reversible respiratory or cardiac failure or both. The term *extracorporeal life support* (ECLS) might describe the system more accurately because it includes venovenous (VV), venoarterial (VA), and arteriovenous (AV) configurations, but the term *ECMO* is typically most often used and universally accepted for describing all of these operating modalities. Studies on the extracorporeal circulation and oxygenation of blood began many years ago. The first concrete attempt at extracorporeal support took place around 1930 when John H. Gibbon and his wife developed a roller pump device and an oxygenator with the help of the IBM Corporation at Jefferson Medical College in Philadelphia after a young female patient died of a pulmonary embolus.[2] However, the first clinical application of this new heart-lung machine was attempted in 1953 when an 18-year-old patient, Cecila Bavolek, underwent an atrial septal defect repair. Although Gibbon's original heart-lung machine was cumbersome, complicated, and difficult to manage, it started the era of open-heart surgery. In 1954, C. Walton Lillehei, the "father of open heart surgery," and Richard A. De Wall performed cardiac surgery with a bubble oxygenator.[3] However, the design of the original oxygenators was not suitable for prolonged support. In 1957, Karl Kammermeyer discovered that gas exchange could effectively occur if a thin membrane of dimethylsiloxane, commonly known as *silicone rubber*, was used to separate blood and gas.[4] The use of a silicone membrane oxygenator led to the adoption of the term *ECMO*. Baffes and colleagues in 1970 reported the use of extracorporeal support in 15 patients who underwent palliative cardiac surgeries.[5] The first application of extracorporeal support outside the surgical unit was reported by Hill and colleagues in 1972. A 24-year-old man with acute respiratory failure as a result of a motorcycle accident was supported for 75 hours in VA assistance with peripheral cannulation by means of a Bramson-membrane heart-lung machine. The assistance made it possible to increase the oxygen tension from 38 to 75 mm Hg, reduce the peak airway pressure from 60 to 35 cm H_2O, and reduce the fraction of inspired oxygen concentration (FiO_2) from 1 to 0.6, with a bypass flow of 3 to 3.6 L/min. The respiratory failure reversed, and the patient recovered.[6] During the same year, Dr. Robert Bartlett, who is considered the father of modern extracorporeal support and who first used ECMO support for neonates and children, successfully applied ECMO for 36 hours to a 2-year-old child after a Mustard procedure (total correction of transposition of the great vessels).[7] In 1975, one of the most significant events in the history of modern ECMO occurred. A pregnant woman crossed the border separating Mexico from the United States, desperately hoping for a better life for her child. When she arrived in Orange County, California, her membranes ruptured and, during a complex delivery, the child aspirated a large quantity of meconium, developing severe pneumonia. When the oxygenation fell to hopeless levels, Robert Bartlett placed her in ECMO. After 3 days of bypass, the baby whom nurses named Esperanza, Spanish for *hope*, completely recovered. The use of ECMO for neonatal diseases progressively evolved by improving survival from 10% (first experience) up to 75%. In 1985, Bartlett and colleagues published a hotly debated prospective randomized controlled study of the use of ECMO to treat newborns with respiratory failure based on a "randomized play the winner" statistical method. In this adaptive randomized design that is occasionally used in clinical trials, if one treatment is more successful, then more patients are randomly assigned to that treatment.[8] A group of 12 infants were included in the study. One patient was randomly assigned to conventional treatment (the patient died); 11 patients were given ECMO (all survived).[9] An important subsequent randomized controlled trial was performed by Dr. Pearl O'Rourke and published in 1989.[10] By demonstrating a significantly higher survival rate in children treated with ECMO (97% versus 60%), this study showed the superiority of extracorporeal assistance versus standard treatment until the scientific community and lay press declared that randomization to standard therapy without ECMO would be unethical. Finally, in 1996, the definitive proof of ECMO efficacy in the neonatal setting was published in the *Lancet* journal by UK Collaborative ECMO Trial Group.[11] A total of 185 newborn infants with severe respiratory failure (persistent pulmonary hypertension attributable to meconium aspiration, congenital diaphragmatic hernia, isolated persistent fetal circulation, sepsis, and idiopathic respiratory distress syndrome) were enrolled in the study. The study demonstrated the clinical efficacy of ECMO in neonates with potentially reversible respiratory insufficiency when performed in a well-staffed and organized neonatal ECMO service. The growing interest in ECMO and its worldwide diffusion led to the creation of an organization with the aim of collecting data on ECMO use, comparing outcomes, and sharing different experiences and expertise. The Extracorporeal Life Support Organization (ELSO) was founded in 1989. In 1991 the first European symposium on extracorporeal lung support held in Paris was associated with the foundation of the European ELSO (Euro-ELSO). ELSO is the epicenter for the development, definition, and delivery of indications, guidelines, and recommendations in the field of ECMO assistance, not only for neonates but also for pediatric and adult patients. A case series published in the 1990s suggested the feasibility and efficacy of ECMO in pediatric respiratory failure.[12] Green and colleagues in 1996[13] performed a study on 41 pediatric patients admitted to the ICU with acute respiratory failure. The patients were treated with conventional mechanical ventilation, high-frequency ventilation, or ECMO. The results demonstrated the superiority of ECMO

in improving the survival rate, especially in patients in the 50th to 75th percentile mortality risk group. (Stratification was based on oxygenation index [OI] and Pediatric Risk of Mortality score.)

In contrast to neonatal applications, the demonstration of the benefits of ECMO in adult patients has been slower and more difficult. The first adult trial, directed by Zapol and published in *JAMA* in 1979, demonstrated a very poor survival rate for patients with respiratory failure (90 patients from 9 centers) treated only with VA ECMO.[14] The study was heavily criticized, primarily for factors including the selection of moribund patients, the lack of experience of the centers involved in the study, excessive anticoagulation (attributable to the use of heparin-coated circuits) leading to hemorrhagic complications, and because the ECMO group did not receive lung-protective ventilation. Nonetheless, the results caused the use of ECMO for adult respiratory failure to be avoided for many years. A further confirmation of the paucity of benefit from ECMO in adults came from a randomized clinical trial performed by Alan H. Morris and colleagues.[15] The study included 40 patients with acute respiratory distress syndrome (ARDS) treated with VA assistance (carbon dioxide [CO_2] removal) or conventional ventilation strategy by using a computerized protocol, but it did not demonstrate differences in outcome between groups. The study by Morris and colleagues was criticized because of the poor experience with extracorporeal assistance in some centers included in the data collection. From 2001 to 2006, an ambitious trial on safety, clinical efficacy, and cost effectiveness of ECMO for adults was conducted in the United Kingdom and published in the *Lancet*: the conventional ventilatory support versus ECMO for severe adult respiratory failure (CESAR) trial.[16] The study evaluated a strategy of allocation to a single center (ECMO center), and the patients who were randomized to the control group were conventionally treated at designated treatment centers. A total of 180 adults were randomized in a 1:1 ratio to receive continued conventional ventilation ($n = 90$) or referral to consideration for treatment by ECMO ($n = 90$). The primary endpoint, combining mortality or severe disability 6 months after randomization, was lower for the patients randomized to the ECMO group ($P = .03$). Although burdened by some critical aspects (22 patients randomized to ECMO treatment died before receiving ECMO, no specific protocol for lung-protective ventilation was applied to the control group), the results of the study were of great interest, especially because it coincided with the worldwide pandemic H1N1 virus influenza (influenza A). The capacity of H1N1 infection to induce a particularly severe form of ARDS contributed to a renewed interest in ECMO assistance for adults. In fact, many ECMO centers from several parts of the world have published their experiences with treatment of pulmonary complications secondary to influenza A infection.[17] Over the past 10 years, the use of ECMO in the different types of patient populations—neonatal, pediatric, and adult—has progressively increased. According to the last ELSO Registry Report/ International Summary, data from a total of 50,667 patients have been collected with a mean ECMO survival rate of 73% (http://www.elsonet.org/). The Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial, a large multicenter trial evaluating the efficacy of ECMO in patients with severe ARDS, is now ongoing (EOLIA trial), and many physicians are eagerly awaiting the results from this large study because it will offer more detailed outcome data, indications, and contraindications for the appropriate use of ECMO.*

RENAL REPLACEMENT THERAPY

In 1977, Peter Kramer described the first continuous form of dialysis specifically dedicated to patients with critical illnesses: continuous AV hemofiltration (CAVH).[18] At that time, RRT in the ICU was a last-chance therapy for patients with acute kidney injury (AKI); it was mostly performed with adapted machines with disparate dialytic protocols and was difficult to use in unstable patients who were critically ill. In CAVH, blood flow in the circuit was driven by the existing AV pressure gradient, and spontaneous ultrafiltration (UF) occurred, depending on the transmembrane pressure (TMP) gradient. The AV pressure gradient was dependent on the mean arterial pressure of the patient and the intrinsic resistance of the circuit; the spontaneous UF was determined by the hydrostatic pressure drop inside the filter and the negative suction provided by the ultrafiltrate column from the patient level to the ground. CAVH provided a slow continuous fluid removal, maintaining steady solute concentrations and preventing peaks of toxic substances. CAVH was one of the first examples of artificial renal support applied to patients who were critically ill. It was capable of overcoming the problems associated with hypotension attributable to rapid fluid removal and rapid reduction of plasma osmolality, arrhythmias caused by electrolyte changes and intravascular volume shifts, and cerebral edema in patients with head injuries. CAVH, however, had some serious limitations. It required both arterial and venous accesses, sometimes difficult to achieve and causing more morbidity. Solute clearance was limited by the low UF rates and the pure convective nature of CAVH. UF limitation is caused by the relatively low blood flow in the circuit and by the low TMP gradient in the most hemodynamically unstable patients. The lowest clearances were achieved and had the most clotting in the circuit. CAVH rarely exceeded 20 mL/min of clearance, hardly sufficient to meet the need of severely catabolic patients.

To overcome such technical limitations, new filters were designed with increased cross-sectional area and inner hollow fiber diameters that reduced unit length and lowered the resistance to blood flow. As a result of these improvements, the phenomenon of filtration pressure equilibrium and easy clotting caused by poorly optimized UF profiles was diminished, if not avoided. Another option explored in those days was the use of highly biocompatible membranes mounted on parallel plat devices. These filters presented lower intrinsic resistance, ensuring higher extracorporeal blood flows at a given AV pressure gradient and they were equipped with a second port in

*http://www.clinicaltrials.gov/ct2/show/NCT01470703?term=eolia&rank=1. (Accessed November 18, 2013)

the filtrate compartment, enabling the countercurrent dialysate flow to be programmed in the newly conceived continuous AV hemodiafiltration with dialysis (CAVHD) mode.

The logical evolution was to apply a peristaltic pump to the extracorporeal circuit. In the past, the use of a blood pump in the ICU was considered proprietary technology of the dialysis team (nurses and nephrology consultants) and a technology that required a specific expertise. Eventually, the knowledge of pumped systems began to be disseminated in the critical care world, making VV hemofiltration a reality. The need of *hardware* evolution in CAVH was not limited to blood pumps; it was also extended to fluid delivery systems and UF control mechanisms, permitting the delivery of dialysate or replacement solutions with an acceptable degree of accuracy.

Another step toward continuous VV renal replacement therapies was the advent of double-lumen catheters that made possible the puncture of a single vein, thus decreasing the high rate of complications attributable to the need of both venous and arterial cannulation. The driving force then resulted from the mechanical action of the roller pumps. Blood flows could finally be programmed and delivered with adequate precision. The new continuous VV therapies required negative-pressure measurement and alarms in the arterial line before the pump, as well as positive-pressure measurements and alarms in the venous return line. A bubble trap had to be inserted in this line to prevent air embolism. (A bubble trap was not necessary in CAVH within which the circuit operated at positive pressure along the entire length of the system). The higher blood flows induced higher filtration rates and the possibility to exploit higher clearances because of increased flow rates. For this reason, roller pumps were also applied to the dialysate or fluid replacement delivery section of the circuit, and external scales had to be frequently used to provide sufficiently accurate fluid balance during treatment. The benefits induced by the new adaptive technology were still counterbalanced by the gross inaccuracy of the systems and the limited integration between the extracorporeal circuit and the fluid balance devices. Safety and performance were definitely not optimized. Blood pumps were often inaccurate, circuit tubing was damaged over time, and filtration fractions were uncontrolled because of pressure and flow fluctuations. Consequently, intrafilter hematocrit and platelet count increased beyond safe values, and filter clotting typically occurred. Accurate UF control is mandatory in modern RRT. Early machines did not have scales or pumps, and when volumetric pumps started to be used to drive dialysate and ultrafiltrate in and out from the filters, inaccuracies close to 10% were observed, an unacceptable error rate for 24 hour–long therapies. Furthermore, when the membrane clogged and approached failure, the ultrafiltrate volumetric pump increased its inaccuracy because of the wide fluctuation in the membrane UF coefficient. Finally, the need of obtaining additional information or for performing additional functions induced physicians and nurses to include in the system several other devices, often poorly integrated, with the final result of a cumbersome "Christmas tree–like effect." It soon became evident that an ideal extracorporeal circuit should have incorporated continuous pressure measurements of inlet and outlet lumens of the catheter inlet and outlet of the filter and ultrafiltrate and dialysate ports. This information and the integration of adequate alarms was of crucial importance to the development of modern machines that allow the ICU staff to maintain filter efficiency and circuit patency, to detect potential sources of clotting, and to ensure patient safety.[19]

TECHNICAL ASPECTS AND MODES OF EXTRACORPOREAL SUPPORT

EXTRACORPOREAL MEMBRANE OXYGENATION

How to Deliver Artificial Gas Exchange

The main purpose of ECMO application is to guarantee adequate oxygen delivery (DO_2) [(DO_2 = cardiac output × arterial oxygen content)] and CO_2 clearance in proper proportion to systemic needs. In fact, the overall goal of cardiorespiratory care is to keep DO_2 at least twice oxygen consumption (VO_2) [(VO_2 = cardiac output [arterial venous oxygen content)]. If medical treatment is unable to maintain this equilibrium and/or the risk of ongoing ventilator- or vasopressor-induced iatrogenic injury arises (i.e., the treatment required is, itself, contributing to organ failure), then ECMO may be indicated to provide life support, allowing time for diagnosis and treatment until the cardiorespiratory system is restored. In general, when only respiratory assistance is required, the use of VV ECMO is advisable, whereas if cardiocirculatory support is necessary, then the VA assembly is used. The AV mode is a particular type of passive (pumpless) lung assistance primarily for decarboxylation (see later discussion). Therefore ECMO can be considered a modified cardiopulmonary bypass circuit to provide short-term respiratory and potentially circulatory support to patients with cardiorespiratory failure (Fig. 107-1). It involves the use of mechanical devices including a pump, a circuit, and an artificial lung (see Fig. 107-1 and see later discussion). The technique is performed by draining venous blood and pumping it through an artificial lung where CO_2 is removed and oxygen is added. The *arterialized* blood is then returned into the systemic circulation via a vein (VV configuration) or via an artery (VA configuration). In the VV mode, native and artificial lungs are in series, whereas in the VA mode, they are in parallel. In both configurations, the native lung can be totally or partially replaced, but only in the VA mode is the cardiocirculatory system supported. If total support has to be achieved, then the blood flow through the artificial lung should be equivalent to the total cardiac output in both modes, requiring a system (cannulas, pump, circuit, artificial lung) that drains 60 to 100 mL/kg/min. In the VA configuration, if venous blood is not totally drained (partial VA bypass), then the circulating blood is a mixture of two separate components: (1) blood that passes through the native lungs and is ejected by the left ventricle into the aorta, and (2) blood oxygenated

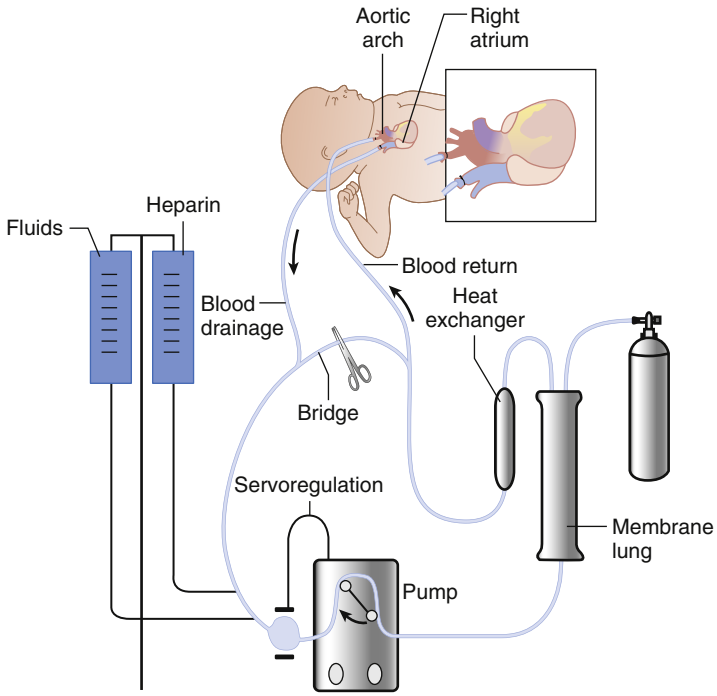


Figure 107-1. Schematic representation of the extracorporeal membrane oxygenation (ECMO) system. Venoarterial ECMO with jugular-carotid approach is more common in pediatric patients.

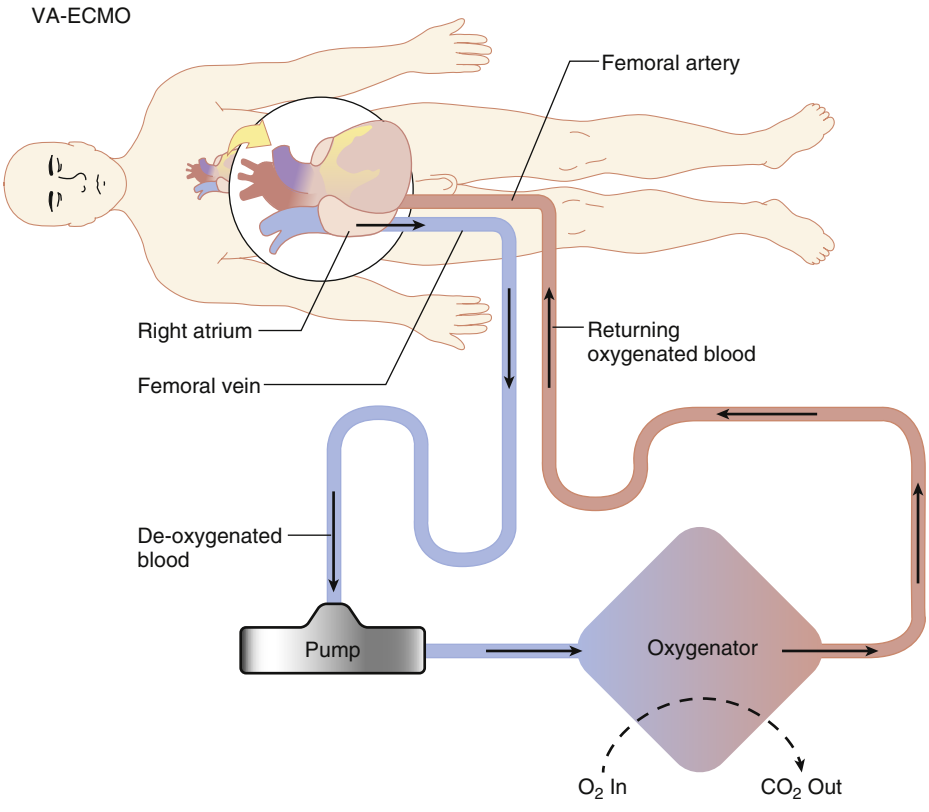


Figure 107-2. Schematic representation of venoarterial extracorporeal membrane oxygenation (ECMO) with femorofemoral approach.

and CO_2 cleared by the artificial lung and pumped into the aorta (usually via a femoral artery) by an artificial pump (Fig. 107-2). In the VV configuration (Fig. 107-3), the blood that passes the artificial lung is pumped into the venous system (right atrium) and mixes with blood coming from the systemic circulation. Different technical modalities can be adopted for VV modes using single cannulas with multiple lumens for drainage (inflow superior vena cava and inferior vena cava port) and infusion (outflow right atrium port) or two or three different cannulas (Fig. 107-4; and see later discussion). In this mode of assistance, the amount of blood pumped into the right ventricle (preload) is equivalent to the drained blood.

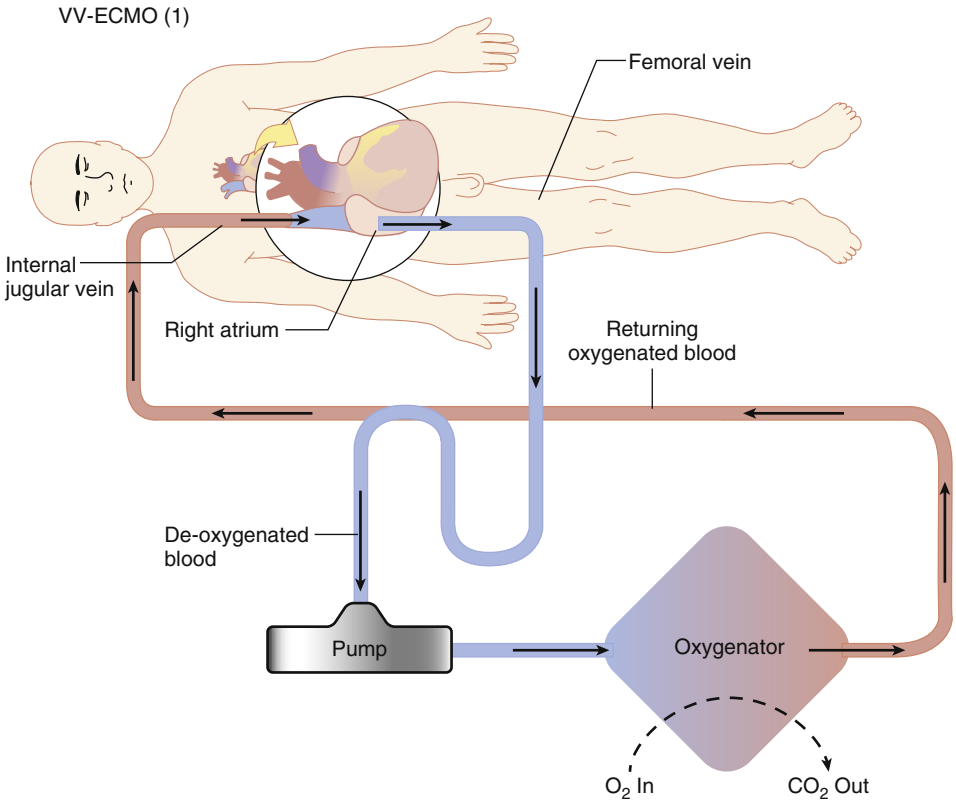


Figure 107-3. Schematic representation of venovenous extracorporeal membrane oxygenation (ECMO) (two cannulas) with the femorojugular approach.

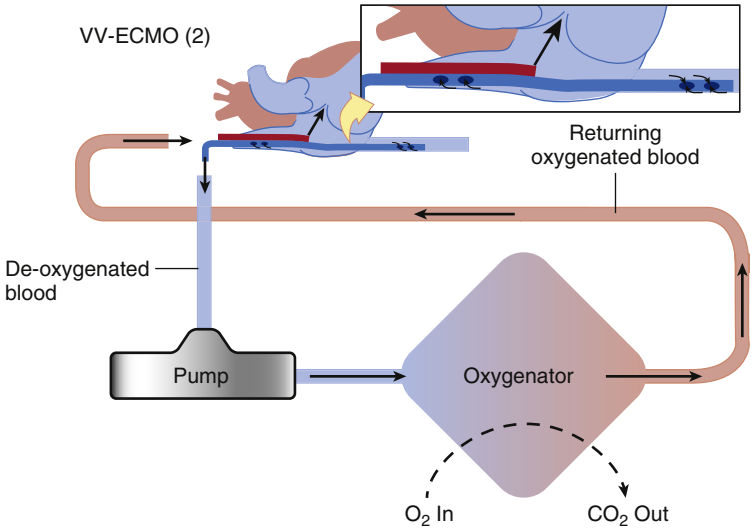


Figure 107-4. Schematic representation of venovenous extracorporeal membrane oxygenation (ECMO) and Avalon cannula *(detail)* with single-vein venovenous approach. CO_2, Carbon dioxide; O_2, oxygen.

Oxygen Delivery and Carbon Dioxide Clearance

During ECMO, oxygen delivery depends on a combination of four elements acting simultaneously:

1. Blood oxygenation in the artificial lung
2. Blood flow through the artificial lung
3. Blood oxygenation in the native lung
4. Blood flow through the native heart

Therefore blood oxygenation depends, in turn, on the technical characteristics of the membrane (e.g., geometry, thickness of the blood film, materials, red blood cells, transit time, hemoglobin concentration, inlet saturation, FiO_2), oxygen saturation in the ECMO drainage cannula (coming from the patient), hemoglobin concentration, and blood flow in the ECMO circuit. In practice, when blood oxygenation is almost completely dependent on VV ECMO (e.g., in patients with severe ARDS), systemic partial arterial pressure of oxygen (PaO_2) is never in the normal range (95% to 100%) and the air-oxygen mixture flow rate (FiO_2 ECMO) and the blood flow through the artificial lung should be adjusted to obtain the most appropriate PaO_2 level (at least 55 mm Hg) and/or arterial oxygen saturation of more than 88% and normal $PaCO_2$.[20] FiO_2 on the ventilator should be reduced to the minimal

value to avoid oxygen toxicity and to keep arterial saturation at more than 88%. To increase partial alveolar pressure of oxygen (P_AO_2), blood flow through the circuit must be increased. Moreover, when oxygenated blood reaches the pulmonary circulation, hypoxic vasoconstriction may be reduced with a further worsening of systemic oxygenation.[21] In some centers, circuit flow is titrated to achieve an arterial oxygen saturation (Sao_2) greater than 80%.[21] Differently from the oxygenation issue, CO_2 clearance is more effective than oxygenation because of its greater solubility (Fick principle) and the relatively linear shape of the CO_2 dissociation curve. Therefore the CO_2 clearance can be obtained with adequate fresh gas through the oxygenator but only 0.5 to 1.5 L/min (10 to 15 mL/kg/min) of blood flow through the artificial lung. To obtain adequate oxygenation, 50 to 60 mL/kg/min are usually necessary, although depending on cardiac output and recirculation in the circuit (see the discussion that follows), 80 to 100 mL/kg/min may be required. Practically, fresh gas flow can be initiated at the same rate as circuit blood flow and then adjusted to maintain $Paco_2$ in the normal range.[21] As a result, the rate of fresh gas flow primarily determines $Paco_2$, whereas PaO_2 is strictly derived from blood flow rate through the artificial lung.[21]

During ECMO, mechanical ventilation should be set to minimize the risk of traumatic injury, such as ventilator-induced lung injury (VILI), by maintaining the lungs open. An ultraprotective mechanical ventilation setting should be applied in all patients under ECMO assistance: inspiratory pressure less than 25 to 30 cm H_2O, positive end-expiratory pressure (PEEP) 10 to 20 cm H_2O (to prevent alveolar collapse), rate 4 to 6 breaths per minute, and FiO_2 as low as possible to maintain peripheral oxygen saturation (SpO_2) greater than 88%. In those patients with predicted long-term respiratory support, early tracheostomy under ECMO should be considered.[22]

Circuit Components

Consistent technologic improvements in ECMO devices for circuits (heparin-coated), pumps, and oxygenators have occurred during the past years. The ECMO circuit consists of four main components: (1) tubing and cannulas, (2) pump, (3) gas exchanger (artificial lung), and (4) heat exchanger (see Fig 107-1). These parts can be completed with pressure monitoring sites, access for therapies, hemofiltration, RRT, and other accessories that monitor for blood parameters (e.g., pH, PaO_2, $Paco_2$, potassium, oxygen saturation, hematocrit, temperature, hemoglobin concentration, base excess, bicarbonate concentration). Circuit dimension and design may partially vary, depending on patient size, clinical purposes, and institutional habits and practice. In the VA mode (for lung and heart support), the general rules are that the circuit has to guarantee a blood flow rate of 100 mL/kg/ min for pediatric patients and 60 mL/kg/min for adult patients. While in the VV mode (for lung assist), the target should be 120 mL/kg/min for neonates to 60 to 80 mL/kg/min for adults.[23] If the clinical purpose is only CO_2 removal, then the circuit may be set in VA, VV, or AV modes. This last configuration does not need an artificial pump (pumpless), because it uses the AV pressure gradient to generate flow through a low-resistance membrane (e.g., the NovaLung Interventional Lung Assist [iLA] Membrane Ventilator; NovaLung Gmbh, Heilbronn, Germany) (Fig. 107-5). A low flow (up to 1 L/min) through the membrane is usually sufficient for clearance of approximately 3 to 6 mL/kg/min of CO_2.[23] The venous cannula (drainage side) and blood tubing are the major limiting components for flow through the circuit. According to the Poiseuille equation, resistance to flow depends on the length and radius (fourth power) of the cannula. Therefore shorter and larger (internal diameter) cannulas placed into the right atrium allow a higher flow of blood into the circuit. For example, if 100 mm Hg pressure gradient is applied to 1 m tube (diameter ⅜"), then the blood flow will be approximately 5 L/m.[23]

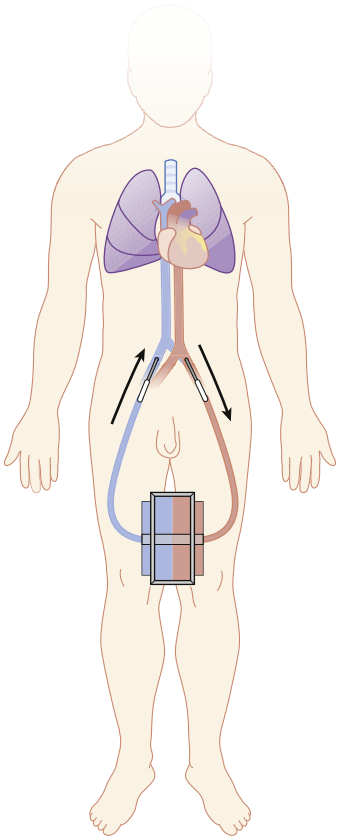


Figure 107-5. Schematic representation of the NovaLung Interventional Lung Assist (iLA) Membrane Ventilator (NovaLung GmbH, Heilbronn, Germany) pumpless arteriovenous system.

Two types of main pumps are currently used for ECMO circuits: roller pumps and centrifugal pumps. Roller pumps were the only type used during the first few decades of ECMO support, but their popularity has recently fallen as a result of improvements in centrifugal pumps. Roller pumps consist of tubing located inside a curved raceway. The raceway is placed at the travel perimeter of rollers mounted on the ends of rotating arms that compress the tubing, pushing the blood ahead and producing continuous blood flow. The output of the pump is determined by the revolutions per minute (rpm) of the pump and the volume contained in the tubing (Fig. 107-6). The main problems with roller pumps are: (1) a cumbersome heavy motor is required; (2) tubing can be damaged by the pump's arms; (3) excessive negative inlet (prepump) pressure and positive outlet (postpump) pressure can develop; and (4) careful

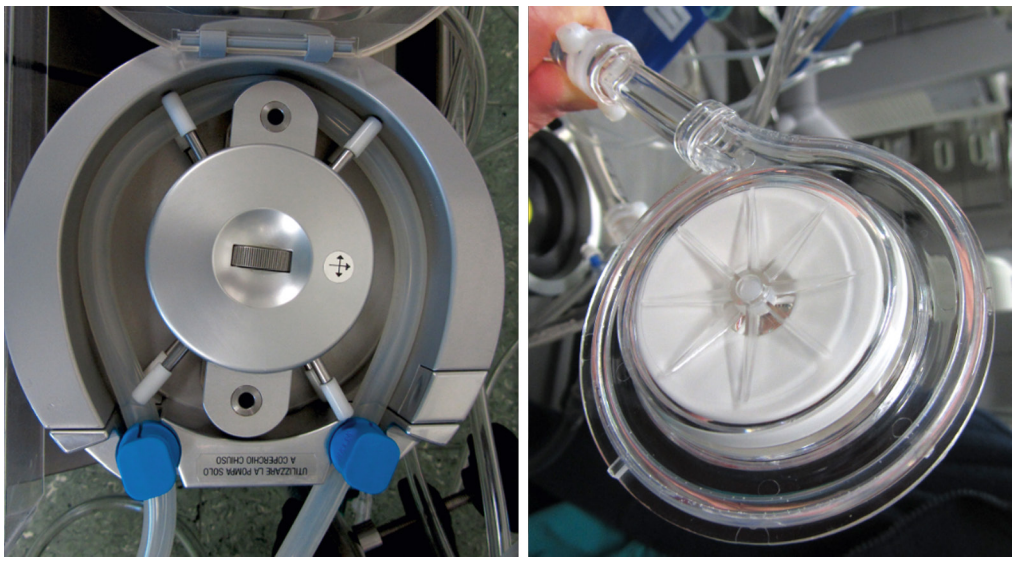


Figure 107-6. Roller pump *(left)* and centrifugal pump *(right)*.

monitoring is needed. At many institutions, the centrifugal pumps have replaced roller pumps for routine ECMO assistance (see Fig 107-6). Centrifugal pumps consist of an impeller arranged with either vanes or a nest of smooth plastic cones inside a plastic holder. The impeller couples magnetically with a small and light motor. The impeller spins at 2000 to 5000 rpm, creating a constrained vortex that suctions blood into the pump head and propels it out toward the gas exchanger. The magnet inside the disposable pump head creates a centrifugal force that directs blood forward to the outlet (i.e., a negative pressure at the inlet port of the pump pulls blood into the pump holder, creating a positive pressure at the outlet port). Problems with centrifugal pumps are blood stagnation and heating in the pump head increases the risk of thrombosis formation, cavitation (formation of cavities (i.e., air bubbles in the blood), and hemolysis when the inlet line is occluded. However, the limitation of revolutions per minute and new design have dramatically reduced the occurrence of these risks.[24] Centrifugal pumps are preload and afterload dependent; therefore the blood flow decreases when the blood volume coming from the draining vein is reduced and when the postpump pressure increases. Recently manufactured pumps for VA assistance provide pulsatile flow, which may be better than continuous nonpulsatile flow. Centrifugal pumps have several advantages over the roller pumps: (1) priming volumes are smaller, (2) gravity drainage is not required, and, (3) very importantly, they operate for weeks, minimizing the incidence of material damages.

Modern oxygenators have microporous membrane lungs, which are significantly more efficient than the older silicon rubber membranes. Moreover, these new components are easier to prime and manufacture. Plasma leakage (the main disadvantage of these membranes) has been addressed by coating the fibers with a very thin skin of gas-permeable membrane. This newer device is called a *hollow-fiber oxygenator* and has several advantages: (1) less platelet and plasma protein consumption, (2) more effective gas exchange, (3) lower resistance to blood flow (facilitating the use of centrifugal pumps), and (4) minimal requirement for priming volumes.[25] An air-oxygen mixture flow, delivered to the oxygenator, maintains the diffusion gradients for oxygen delivery and CO_2 removal. Oxygen concentration (flow FiO_2) has to be adjusted to obtain a PaO_2 of at least 55 mm Hg and/or Sao_2 greater than 88%. The gas flow rate determines the partial pressure of CO_2 (Pco_2) in postoxygenator blood, and its rate is set to maintain the physiologic $Paco_2$.

Finally, body temperature is maintained by hot water circulating in the heat exchanger, an effective system that puts the circuit and the water bath in contact. Therefore patients on ECMO are usually kept normothermic, and ECMO can be used to rewarm cold patients. An anticoagulant has to be administered because the different biomaterials and plastics can induce thrombosis. Bleeding complications remain more problematic than thrombosis, because current generation circuits and oxygenators are heparin-coated or coated with biocompatible materials. Heparin should be titrated to obtain an activated partial thromboplastin time of 40 to 55 seconds or 1.2 to 1.8 times normal. Alternatively, 1.5 times normal activated clotting time can be considered.[22] Maintaining a hemoglobin (Hb) level of at least 7 to 15 g/dL (depending on hypoxemia and patient comorbidities), is considered good practice, but a general consensus concerning the optimal Hb concentration has not been reached.[25] Platelet transfusion is considered if the platelet count goes below 75,000/mm^3, but some centers avoid platelet administration except in cases of bleeding attributable to thrombocytopenia.[25] In general, when the platelet count is greater than 100,000/mm^3 and in the absence of bleeding complications, aspirin may be administered. Finally, sedatives, analgesics, and pain killers should be administered at the smallest doses, whereas neuromuscular blocking drugs are usually only used in the early phase after ECMO initiation.[26] Some patients are mobile while receiving ECMO.

Vascular Access

In this light, vascular access is a key feature of all ECMO types.[27] In the adult setting, cannulation is usually percutaneously accomplished using the Seldinger technique. The use of vascular ultrasound should always be

performed to better identify venous vessel access, following the guidewire into the vessels to the right atrium avoiding coiling in proximal vessels. An alternative approach is the surgical exposure of the vessels, which is more common in the pediatric department. However, cannulation techniques vary, depending on the type of support needed and the patient's age, size, and clinical situation. For instance, for VA ECMO the most common approach in infants and children is the surgical exposure of the right jugular vein and common carotid artery, whereas adult patients are usually managed with percutaneous or surgical exposure and cannulation of the femoral vein and artery. In VA ECMO in adults, the femoral vessels are usually the first choice, and only in particular conditions (e.g., burns, open wounds, significant peripheral vascular disease) has the axillary artery been successfully used. To limit the probability of limb ischemia in adults, small shunting catheters can be placed distally to the arterial cannula or, as an alternative, the femoral artery can be approached by anastomosing a polytetrafluoroethylene (PTFE) vascular graft (end-to-side) to create a bidirectional flow.[28] In specific circumstances, such as patients who have failed to wean from cardiopulmonary bypass (also see Chapter 67), the ascending aorta and right atrium can be directly cannulated (transthoracic approach). Two main venous drainage modes can be considered when VV ECMO assistance is planned: (1) two cannulas can be placed, one for drainage and one for inlet (see Fig. 107-3); or (2) one cannula, the Avalon cannula (see Fig. 107-4), can be inserted. In the first case, the most common femoral-jugular approach is performed by a single large multiperforated drainage cannula inserted via a femoral vein into the right atrium, close to the cavoatrial junction (cannula size 23 to 29 French [Fr]). Then a single-stage catheter, as the return cannula, is inserted in the right internal jugular vein to the superior vena cava (21 to 23 Fr). A supplementary cannula (in the other femoral vein) can be placed to increase the drainage flow. When the blood is pushed by the pump through the artificial lung, a significant increase in pressure related to high resistance is expected. Pressures as high as 300 mm Hg are considered safe, although the higher the pressure, the greater the risk of blood leak and membrane damage. With the Avalon cannula (Avalon Laboratories, LLC, Rancho Dominguez, Calif), a single cannula with a double lumen (13 to 31 Fr) and three holes (two for drainage and one for reinfusion) is inserted via the right internal jugular vein; the Avalon tip must reach the inferior vena cava where the blood is drained together with that coming from the superior vena cava.[29] After passing through the gas exchanger, the blood returns into the right atrium toward the second lumen (see Fig. 107-4) that runs the blood to the third hole, facing the tricuspid valve. In this way, a single cannula is used to drain bi-caval blood and push it in the right ventricle after oxygenation, usually with minimal blood recirculation. Using fluoroscopy or echocardiography, or both, to place the cannula is important to allow the inlet and outlet access to be in the correct position.[30] Pressure and flow diagrams are used for selecting the most appropriate setting according to the patient's need.

RENAL REPLACEMENT THERAPY CIRCUIT: EXTRACORPOREAL MEMBRANE OXYGENATION FOR THE KIDNEYS

The goal of continuous RRT (CRRT) is to achieve blood purification as close as possible to that obtained by the native kidney. Blood is driven in a VV manner through a semipermeable membrane to remove water and solutes. Third-generation machines used in the ICU are currently designed to meet the dialysis dose requirements and the strict safety features that are recommended in every modern ICU.[31] Modern devices generally implement four to five roller pumps (blood, dialysate, reinfusion, UF-effluent, accessory), three to four scales, and pressure sensors (inlet, outlet, filter, effluent) to monitor the entire circuit conditions. These machines allow a fluid load from 20 to 40 kg to reduce nursing workload and to decrease downtime as a result of bag changes. In the meantime, maximal flow rates have increased up to approximately 450 mL/min for blood pumps and to approximately 8 to 10 L/hr for dialysate-replacement pumps. The effluent pumps are able to increase up to 20 to 25 L/hr. Accuracy of the roller blood pumps has increased to achieve a wide flow rate range, keeping flow errors below 2%. New algorithms allow an hourly update of the net UF prescribed and delivered gap and to correct the UF in the next hour to further reduce actual fluid loss discrepancies. An interesting safety feature of third-generation machines is the possibility of setting a limit of accepted UF error within a predetermined time frame, after which the session is automatically interrupted and operator intervention is required.[32] This feature seems important in light of the possible lethal human mistakes that might occur if overriding of UF error alarms is prolonged and uncontrolled.

CRRT machines are now designed with user-friendly interfaces with big screens and clear alarm signals and warnings; most importantly, monitoring circuit pressure trends in the previous 24 hours or possibly longer and eventually visualizing these trends in a graph are possible. With these features, therapy prescription has become flexible and safe, easily ranging from high volume to slow, low-efficiency hemodialysis to standard CRRT. Furthermore, modalities can be switched during the course of a treatment session[33] to be truly tailored to patients with rapidly changing clinical conditions or to modify CRRT prescriptions according to circuit conditions (i.e., increasing the rate of predilution hemofiltration or switching to dialysis if early signs of clotting are present).

CRRT filters are a key feature of blood purification in patients who are critically ill. In all cases, synthetic highly biocompatible membranes are currently used. These filters are made up of groups of hollow fibers with different total surface areas (from 0.1 to over 2 m^2) to meet the needs of treatment of different-sized patients. Such fibers have a generally high porosity (30 to 50 A°) and are used for both diffusive and convective treatments (see the discussion that follows). Polyacrylonitrile, polysulfone, and polymethyl methacrylate are the most used types of membranes currently available on the market; they allow a high UF coefficient (over 20 mL/hr/mm Hg) and high diffusive and convective performance.

Anticoagulation

The need for anticoagulation of the CRRT circuit arises from the fact that the contact between blood and the tubing of the circuit and the membrane of the filter induces activation of the coagulation cascade. This extracorporeal activation inevitably results in filter or circuit clotting (see also Chapter 67). Anticoagulation strategies vary, depending on the prescribed RRT schedule, being a priority feature of continuous treatments, during which blood–artificial surface interaction is maximized. Aims of anticoagulation are to: (1) maintain the extracorporeal circuit and dialyzer patency, as well as reduce off treatment (down) time that might have a clinical impact in the overall RRT clearance; (2) reduce treatment cost by using the fewest materials as possible; and (3) achieve these goals with minimal risk for the patient. This last concept should be the first to rule anticoagulation management—under no circumstances should the patient be at risk of bleeding to prolong the life of the circuit.

Circuit Set-Up Optimization and No Anticoagulation

Several technical features of the RRT circuit are likely to affect the success of any anticoagulant approach. Vascular access has to be of adequate size, tubing kinking should be avoided, blood flow rate should exceed 100 mL/min, pump flow fluctuations must be prevented (in modern machines this event is mainly attributable to circuit increased resistances rather than flow rate inaccuracies), and venous bubble trap, in which air and blood contact occurs, must be accurately monitored. In this light, another component of circuit set-up has to be addressed: plasma filtration fraction should be kept as far as possible below 20% and, when possible or considered correct, predilutional hemofiltration should be selected. When set-up is perfectly optimized, anticoagulants are only a relatively minor component of circuit patency; in fact, when patients have risk factors for bleeding (prolonged clotting times, thrombocytopenia), RRT can be safely performed without using any anticoagulant.[34]

Unfractionated Heparin

Unfractionated heparin (UFH) is the most commonly available anticoagulant. It is easy to use, and an antidote is available (protamine). Heparin doses might range from 5 to 10 IU/kg/hr. In patients with limited circuit duration, UFH can also be used in combination with protamine (regional heparinization) with a 1:1 ratio (150 IU of UFH per milligram of protamine) and strict monitoring of activated prothrombin time (aPTT). The problems with the use of UFH are its relative unpredictable bioavailability, the necessity for antithrombin III (ATIII) levels optimization, and the occurrence of heparin-induced thrombocytopenia (HIT).

Low-Molecular-Weight Heparins

Some centers have gained experience with this relatively new kind of anticoagulant, low-molecular-weight heparin (LMWH) for RRT. Prospective studies have not yet shown LMWH to be superior in prolonging circuit life. These molecules appear to have a better bioavailability than UFH and a lower incidence of HIT with a 10% increased cost.

Prostacyclin

Prostacyclin (prostaglandin PGI_2) is a potentially useful drug for RRT anticoagulation being a potent inhibitor of platelet aggregation with a short half-life. PGI_2 is infused at a dose of 4 to 8 ng/kg/hr with or without the addition of low-dose UFH. Larger doses of PGI_2 might induce hypotension. Some studies have demonstrated PGI_2 efficacy, but its high cost and harmful side effects might limit the use of this agent to patients with short circuit duration.[35]

Citrate

Citrate is a form of regional anticoagulation that depends on the ability of citrate to chelate calcium. The chelation of calcium prevents clot formation. Briefly, a calcium-free, sodium citrate–containing replacement solution or dialysate solution, or both, is prepared and administered at the appropriate rate to achieve the desired aPTT (60 to 90 seconds). Calcium chloride is then administered to replace chelated-dialyzed calcium and to maintain normocalcemia. This approach is effective in maintaining excellent filter patency and compares favorably with heparin. It also avoids the risk for HIT and does not lead to systemic anticoagulation. Relative drawbacks of this anticoagulation management include the risks of hypocalcemia, metabolic alkalosis, and the cumbersome replacement-dialysate fluid preparation.[36,37]

Other Strategies

Alternatives to the techniques previously presented are listed in Table 107-1.

VASCULAR ACCESS

The fundamental role played by vascular access must be emphasized. In fact, circuit failure is more often attributable to vascular access inadequacy than to insufficient anticoagulation. Thus the optimal dialysis catheter can save the patient from an inappropriate increase of anticoagulation dose. VV RRT relies on the use of a temporary double-lumen catheter. Such catheters are inserted in a central vein and available in different brands, shapes, and sizes. The site of insertion of double-lumen catheters implies a number of considerations such as clinician expertise, body habitus of the patient, and the presence of other intravenous catheters. The femoral vein is generally the first choice of vascular access; internal jugular or subclavian accesses are often associated with inadequate performance, and the inguinal puncture is safer and easier to perform in patients who are coagulopathic and critically ill. A valid alternative may be achieved by cannulation of the right internal jugular vein with the tip of the catheter reaching the right atrium. Circuit blood flow rates with this approach can reach 300 mL/min. Catheter size for adult patients ranges from 12 to 14 Fr and the length from 16 to 25 cm; the bigger and shorter the catheter, the higher the level of its performance. Nonetheless, when the femoral vein is selected, a 20-cm long catheter has its tip positioned close to the inferior vena cava, allowing optimal flows within the circuit. When an inadequate blood flow or a catheter malfunction is suspected, venous and arterial lumens should be flushed with saline with

TABLE 107-1 ANTICOAGULATION STRATEGIES

Drug	Pro	Contra
No anticoagulation	High risk of bleeding	Relative short circuit life span
Unfractionated heparin	Routine	HIT
Low-molecular-weight heparin	Routine (alternative to unfractionated heparin)	HIT
Prostacyclin	Very short circuit life span	Hypotension
Citrate	Routine; very short circuit life span	Hypocalcemia
Danaparoid	HIT	Insufficient data available
Argatroban	HIT	Insufficient data available
Irudine	HIT	Insufficient data available
Nafamostat mesilate	HIT	Insufficient data available
Heparin-coated circuits	Routine	Insufficient data available

HIT, Heparin-induced thrombocytopenia.

the goal of testing resistance to injection and aspiration. Limb clotting of the line versus kinking attributable to the patient's position must be distinguished. In the first case, a switching of arterial and venous limb can be attempted. This maneuver increases circuit recirculation, and the clinical consequences are negligible. In the second case, a heparin or urokinase lock can be tried for a few hours or, lastly, a catheter (guidewire) exchange can be attempted.

HOW TO DELIVER ARTIFICIAL BLOOD PURIFICATION: DIFFUSION VERSUS CONVECTION

Renal replacement consists of blood purification by semipermeable membranes. Blood flows into hollow fibers made up of porous biocompatible synthetic materials. A wide range of substances (water, urea, low-, middle-, and high-molecular-weight solutes) can be transported across such membranes, from the blood to the effluent side of the hollow fibers, by the mechanism of diffusion (solutes) and convection (water and solutes) (Fig. 107-7).

During diffusion, the movement of solutes depends on their tendency to reach the same concentration on each side of the membrane; the practical result is the passage of solutes from the compartment with the highest concentration to the compartment with the lowest concentration. Other components of the semipermeable membrane deeply affect diffusion—thickness and surface area, temperature, and diffusion coefficient. Dialysis is a modality of RRT and is predominantly based on the principle of diffusion: a dialytic solution flows through the filter countercurrently to blood flow to maintain the highest solute gradient from inlet to outlet port. Diffusion is the solute transport method that is applied during continuous VV hemodialysis (CVVHD) (Fig. 107-8).

During convection, the movement of solute across a semipermeable membrane takes place in conjunction

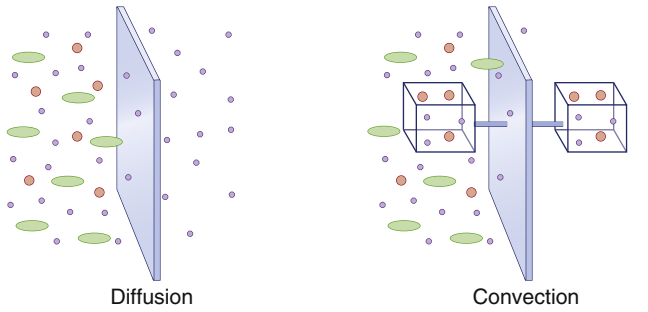


Figure 107-7. Diffusion and convection are schematically represented. During diffusion, solute flux (Jx) is a function of solute concentration gradient (dc) between the two sides of the semipermeable membrane, temperature (T), diffusivity coefficient (D), membrane thickness (dx), and surface area (A) according to the following equation:

$$Jx = D \times T \times A \ (dc/dx)$$

Instead, convective flux of solutes (Jf) requires a pressure gradient between the two sides of the membrane (transmembrane pressure [TMP]) that moves a fluid (plasma water) with its crystalloid content, a process called *ultrafiltration*, whose entity is also dependent on membrane permeability coefficient (Kf). Colloids and cells will not cross the semipermeable membrane, depending on the pores' size.

$$Jf = Kf \times TMP$$

where TMP = Pb – Pd – π, and Pd is blood hydrostatic pressure, Pd is hydrostatic pressure on ultrafiltrate side of the membrane, and π is blood oncotic pressure.

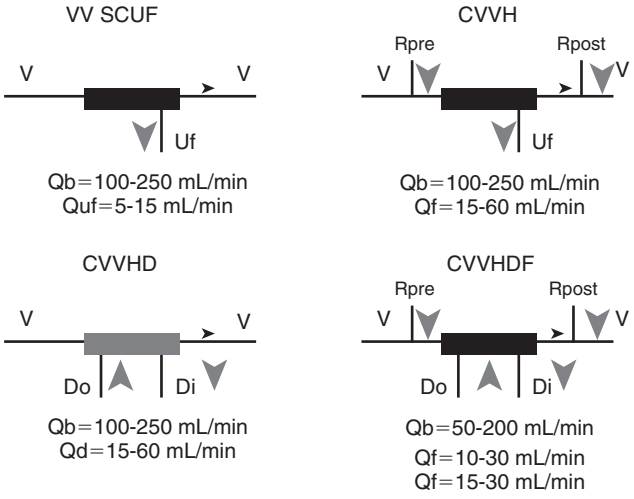


Figure 107-8. Schematic representation of the most common continuous renal replacement therapy (CRRT) set-ups. *Black triangles* represent blood flow direction; *gray triangles* indicate dialysate-replacement solutions flows. *CVVH*, continuous venovenous hemofiltration; *CVVHD*, continuous venovenous hemodialysis; *CVVHDF*, continuous venovenous hemodiafiltration; *Di*, dialysate in; *Do*, dialysate out; *Qb*, blood flow; *Qd*, dialysate solution flow; *Qf*, replacement solution flow; *Quf*, ultrafiltration flow; *Rpost*, replacement solution postfilter; *Rpre*, replacement solution prefilter; *SCUF*, slow continuous ultrafiltration; *Uf*, ultrafiltration; *V*, vein; *VV*, venovenous.

with significant amounts of UF (water transfer across the membrane). In other words, as the solvent (plasma water) is pushed across the membrane in response to the TMP by UF, solutes are carried with it, as long as the porosity of the membrane allows the molecules to be sieved from the blood. The process of UF is governed by the UF rate (Qf), the membrane UF coefficient (Km), and the TMP gradient generated by the pressures on both sides of the hollow fiber, according to the following formula:

$$Qf = Km \times TMP$$

The hydrostatic pressure in the blood compartment is dependent on blood flow (Qb). The greater the Qb, the greater the TMP. In modern RRT machines, UF control throughout the filter is obtained by applying a pump, which generates control of the UF rate. Modern systems are designed to maintain a constant Qf; when the filter is "fresh," the initial effect of UF pumps is to retard spontaneous UF production, generating a positive pressure on the UF side. As the membrane fibers foul, a negative pressure is necessary to achieve a constant Qf. In this case a progressive increase of TMP can be observed up to a maximal level in which clotting is likely and solute clearance may be significantly compromised. In fact, if it is true that the molecules cleared during convection are physically dragged to the UF side, then it is also true that the protein layer that progressively closes fiber pores tends to limit solute transport significantly.[38] A peculiar membrane capacity, defined as *adsorption*, has been shown to play a major role in higher molecular weight toxins[39]; however, it should be considered that membrane adsorptive capacity is generally saturated in the first treatment hours. This observation marks the scarce impact of the adsorption component on solute clearance and suggests relying only on the relatively minor effects of mass separation processes such as diffusion and convection.[40] As UF proceeds and plasma water and solutes are filtered from blood, hydrostatic pressure within the filter is lost and oncotic pressure is gained because blood concentrates and hematocrit increases. The fraction of plasma water that is removed from blood during UF is called *filtration fraction*; it should be kept in the range of 20% to 25% to prevent excessive hemoconcentration within the filtering membrane and to avoid the critical point during which oncotic pressure is equal to TMP and a condition of filtration-pressure equilibrium is reached. Finally, replacing plasma water with a substitution solution completes the hemofiltration process and returns purified blood to the patient. The replacement fluid can be administered after the filter, with a process called *postdilution hemofiltration*. Otherwise, the solution can be infused before the filter to obtain *predilution hemofiltration*. Although postdilution allows a urea clearance equivalent to therapy delivery (i.e., 2000 mL/hr; see later discussion), predilution, despite theoretic reduced solutes clearances, allows prolonged circuit life span by reducing hemoconcentration and protein-caking effects that occur within filter fibers. Conventional hemofiltration is performed with a highly permeable membrane with a surface area of approximately 1 m^2, steam sterilized, with a cutoff point of 30,000 daltons (30 kD). The difference between the volume of ultrafiltered plasma water and reinfused substitution solution gives the net UF, which is the fluid that is eventually removed from the patient for fluid control. Net UF prescription is based on patient needs and can range from more than 1 L/hr (pulmonary edema in a patient with congestive heart failure and who has diuretic-resistant AKI) to zero (septic patient in a catabolic state with increased creatinine levels and conserved diuresis). A net UF rate must be added to dialysis to achieve fluid balance control during diffusion that does not allow water movements.

Convection is applied during slow continuous UF (SCUF) and continuous VV hemofiltration (CVVH) (see Fig. 107-8).

The application of both convection and diffusion configures continuous VV hemodiafiltration (CVVHDF) (see Fig. 107-8).

Nomenclature

Intermittent hemodialysis (IHD): IHD is a common diffusive treatment in which blood and dialysate are circulated in countercurrent mode; generally, a low-permeability, cellulose-based membrane is used. Dialysate must be pyrogen free but not necessarily sterile, since dialysate–blood contact does not occur. The UF rate is equal to the scheduled weight loss. This treatment can be performed typically in 4 hours, three times weekly or daily. Blood flow (Qb): 150 to 300 mL/min; dialysate solution flow (Qd): 300 to 500 mL/min.

Peritoneal dialysis (PD): PD is a predominantly diffusive treatment during which blood, circulating along the capillaries of the peritoneal membrane, is exposed to dialysate. Access is obtained by inserting a peritoneal catheter, which allows the abdominal instillation of dialysate. Solute and water movement is achieved by means of variable concentration and tonicity gradients generated by the dialysate. This treatment can be continuously or intermittently performed.

Slow continuous ultrafiltration (SCUF): SCUF is a technique in which blood is driven through a highly permeable filter via an extracorporeal circuit in VV mode. The ultrafiltrate produced during membrane transit is not replaced, and it corresponds to weight loss. It is used only for fluid control in patients with overload (i.e., patients with congestive heart failure who do not respond to diuretic therapy). Qb: 100 to 250 mL/min; ultrafiltration flow (Quf): 5 to 15 mL/min (see Fig. 107-8).

Continuous venovenous hemofiltration (CVVH): CVVH is a technique in which blood is driven through a highly permeable filter via an extracorporeal circuit in VV mode. The ultrafiltrate produced during membrane transit is replaced in part or completely to achieve blood purification and volume control. If replacement fluid is delivered after the filter, then the technique is defined as *postdilution hemofiltration*. If it is delivered before the filter, the technique is termed *predilution hemofiltration*. The replacement fluid can also be delivered both prefilter and postfilter. Clearance for all solutes is convective and equals the UF rate. Qb: 100 to 250 mL/min; Quf: 15 to 60 mL/min (see Fig. 107-8).

Continuous venovenous hemodialysis (CVVHD): CVVHD is a technique in which blood is driven through a low permeability dialyzer via an extracorporeal circuit in VV mode, and a countercurrent flow of dialysate is

delivered on the dialysate compartment. The ultrafiltrate produced during membrane transit corresponds to the patient's weight loss. Solute clearance is mainly diffusive, and efficiency is limited to small solutes only. Qb: 100 to 250 mL/min; Qd: 15 to 60 mL/min (see Fig. 107-8).

Continuous venovenous hemodiafiltration (CVVHDF): CVVHDF is a technique in which blood is driven through a highly permeable dialyzer via an extracorporeal circuit in VV mode and a countercurrent flow of dialysate is delivered on the dialysate compartment. The ultrafiltrate produced during membrane transit is in excess of the patient's desired weight loss. A replacement solution is needed to maintain fluid balance. Solute clearance is both convective and diffusive. Qb: 100 to 250 mL/min; Qd: 15 to 60 mL/min; replacement solution flow (Qf): 15 to 60 mL/min (see Fig. 107-8).

Hemoperfusion (HP): The patient's blood is circulated on a bed of coated charcoal powder to remove solutes by adsorption. The technique is specifically indicated in cases of poisoning or intoxication with agents that can be effectively removed by charcoal. This treatment may cause platelet and protein depletion.

Plasmapheresis (PP): PP is a treatment that uses specific plasma filters. Molecular-weight cut-off of the membrane is significantly higher than that of hemofilters (100 to 1000 kD). Plasma as a whole is filtered, and blood is reconstituted by the infusion of plasma products such as frozen plasma or albumin. This technique is performed to remove proteins or protein-bound solutes.

High-flux dialysis (HFD): HFD is a treatment that uses highly permeable membranes in conjunction with an UF control system. Because of the characteristics of the membrane, UF occurs in the proximal part of the filter that is counterbalanced by a positive pressure applied to the dialysate compartment, which causes a phenomenon called *backfiltration* in the distal part of the filter from convective passage of the dialysate into the blood. Diffusion and convection are combined; because of the use of a pyrogen-free dialysate, replacement is avoided.

High-volume hemofiltration (HVHF): HVHF is a treatment that uses highly permeable membranes and hemofiltration with a high-volume setting: Qb: >200 mL/min; Qf: >45mL/kg/hr.

RENAL REPLACEMENT THERAPIES DOSE AND PRESCRIPTION

Similar to other therapies managed in the ICU, dialysis should be administered in an appropriate amount. The conventional view of RRT dose is that it is a measure of the quantity of blood purified of waste products and toxins achieved by means of renal replacement. Because this wide and still incompletely known family of substances is too difficult to measure and quantify, the operative view of RRT dose is generally reduced to the measure of the elimination of a representative marker solute. This premise has two major flaws: (1) the marker solute cannot and does not represent all the solutes that accumulate during AKI because kinetics and volume of distribution are different for each solute; and (2) its removal during RRT is not necessarily representative of the removal of other solutes, which is true both for end-stage renal failure and AKI. Nevertheless, despite all of these limitations, a significant body of data[41] suggests that single-solute marker assessment of the dose of dialysis appears to have a clinically meaningful relationship with patient outcomes and therefore clinical utility. In addition, the concept of RRT dose is useful also for practical purposes. Similar to antibiotics, vasopressors, antiinflammatory drugs, and mechanical ventilation, the administration of an extracorporeal treatment for blood purification requires the operators to know exactly when, how, and how much treatment should be prescribed and delivered.

During RRT, clearance depends on circuit Qb, Qf, or Qd, solutes' molecular weights, and hemodialyzer type and size. Qb, as a variable in delivering the RRT dose, is primarily dependent on vascular access and operational characteristics of the machines used in the clinical setting. Filtration fraction strictly links Qf to Qb during convective techniques. Filtration fraction does not limit Qd, but when the Qd:Qb ratio exceeds 0.3, it can be estimated that the dialysate will not be completely saturated by blood-diffusing solutes. The search for specific toxins to be cleared, furthermore, has not been successful, despite years of research; urea and creatinine are generally used as reference solutes to measure renal replacement clearance for renal failure. Although available evidence does not allow direct correlation of the degree of uremia with outcome in chronic renal disease, clearances of urea and creatinine blood levels are used to guide treatment dose in the absence of a specific solute. During UF, the driving pressure jams solutes, such as urea and creatinine, against the membrane and into the pores, depending on membrane-sieving coefficient (SC) for that molecule. SC expresses a dimensionless value and is estimated by the ratio of the concentration of the solutes in the filtrate divided by that in the plasma water or blood. An SC of 1.0, as is the case for urea and creatinine, demonstrates complete permeability, and a value of 0 reflects complete rejection. Molecular size over approximately 12 kD and filter porosity are the major determinants of SC. The clearance during convection is measured by the product of Qf times the SC. Thus, differently from diffusion, a linear relationship exists between K and Qf, the SC being the changing variable for different solutes. During diffusion the linear relationship is lost when Qd exceeds approximately one third of Qb. As a rough estimate, during continuous slow efficiency treatments, a direct expression of Qf or Qd, independent of which solute must be removed from blood, can be considered the RRT dose. During continuous treatment in the ICU, the goal is to deliver at a minimum a urea clearance of 2 L/hr. Some clinical evidence suggests that 35 mL/kg/hr may be the best prescription (i.e., approximately 2.8 L/hr in a patient weighing 70 kg; see later discussion).[42] Others suggest a prescription based on patient requirements, urea generation rate, and catabolic state of the single patient. It has been shown, however, that during continuous therapy a clearance less than 2 L/hr will almost certainly have insufficient results in the adult patient who is critically ill.

The dose of RRT can also be described by a fractional clearance of a given solute:

Kt/V

where K is dialysis clearance, t is the time of dialysis administration, and V is the solute marker volume of distribution. Kt/V is an established marker of adequacy of dialysis for small solutes correlating with medium-term (several years) survival in patients who are chronically ill and on hemodialysis. Urea is typically used as a marker molecule in end-stage kidney disease to guide treatment dose, and a Kt/V_{UREA} of at least 1.2 is currently recommended. As an example, the case of a 70-kg patient who is treated 20 hours per day with a postfilter hemofiltration of 2.8 L/hr at a zero balance is considered: The patient's K_{UREA} will be 47 mL/min (2.8 L/hr = 2800 mL/60 min) because ultrafiltered plasma water will drag all urea across the membrane during postfilter hemofiltration, making its clearance identical to UF flow. The patient's treatment time (t) will be 1200 minutes (60 minutes for 20 hours). The urea volume of distribution will be approximately 42,000 mL (60% of 70 kg; 42 L = 42,000 mL), which is roughly equal to total body water. Simplifying this patient's Kt/V_{UREA}, [47 × 1200] ÷ 42,000 = 1.34. However, Kt/V_{UREA} application to patients with AKI has not been rigorously validated.[43] In fact, although the application of Kt/V to the assessment of dose in AKI is theoretically intriguing, many concerns have been raised because problems intrinsic to AKI can hinder the accuracy and meaning of such dose measurement. These concerns include the lack of a metabolic steady state, uncertainty about the volume of distribution of urea (V_{UREA}), a high protein catabolic rate (PCR), labile fluid volumes, and possible residual renal function, which dynamically changes during the course of treatment. Furthermore, delivery of prescribed dose in AKI can be limited by technical problems such as access recirculation, poor blood flows with temporary venous catheters, membrane clotting, and machine malfunction. Finally, clinical issues such as hypotension and vasopressor requirements can be responsible for solute disequilibrium within tissues and organs.

These observations highlight the gross inadequacies of applying end-stage renal failure paradigms to patients with AKI. They also indicate that, unlike in the field of chronic hemodialysis, only major changes in the application of dose (e.g., changing from second daily to daily dialysis) can truly deliver a *different* therapy in the setting of AKI. More subtle adjustments such as prescribing a calculated Kt/V of 1.0 versus 1.2 can easily be criticized as being within the calculation error around each prescription and not necessarily representing a reliable change in dose delivery. Nonetheless, the crucial merit of specific-dose prescription, calculation, and delivery is the avoidance of underdialysis and the improved monitoring and awareness of effective delivered therapy.

Finally, the therapeutic needs that can be or need to be affected by the dose of RRT are not only the simple control of small solutes as represented by urea. They include control of acid-base, tonicity, potassium, magnesium, calcium, phosphate, intravascular volume, extravascular volume, temperature, and the avoidance of unwanted side effects associated with the delivery of solute control. In the patient who is critically ill, it is significantly more important to administer 10 units of fresh frozen plasma, 10 units of cryoprecipitate, and 10 units of platelets rapidly (e.g., in the setting of coagulopathic bleeding after cardiac surgery) without inducing excessive intravascular volume (because 1.0 to 1.5 L of ultrafiltrate are removed in 1 hour) than for Kt/V to be of any particular value. Dose of RRT is about prophylactic volume control. In a patient with right ventricular failure, AKI, and ARDS who is receiving lung-protective ventilation with permissive hypercapnia and with acidemia inducing a further life-threatening deterioration in pulmonary vascular resistance, the dose component of RRT that immediately matters is acid-base control and the normalization of pH 24 hours per day. The Kt/V (or any other solute-centric concept of dose) is almost simply a by-product of such dose delivery. In a young man with trauma, rhabdomyolysis, and rapidly rising serum potassium already at 7 mmol/L, the dialysis dose, to begin with, is all about controlling hyperkalemia. In a patient with fulminant liver failure, AKI, sepsis, and cerebral edema awaiting urgent liver transplantation and whose cerebral edema is worsening because of fever, the RRT dose is all about lowering the temperature without any tonicity shifts that might increase intracranial pressure. Finally, in a patient with pulmonary edema after an ischemic ventricular septal defect requiring emergency surgery, AKI, ischemic hepatitis, and the need for inotropic and intraaortic balloon counterpulsation support, the RRT dose is all about gently and safely removing fluid to ensure that the extravascular volume falls while the intravascular volume remains optimal. Solute removal is simply a by-product of fluid control. These aspects of dose must be explicitly considered when discussing the dose of RRT in the patient with AKI. Although each and every aspect of this broader understanding of dose is difficult to measure, clinically relevant assessment of dose in patients who are critically ill with AKI should include all dimensions of such dose. To date, no evidence in the acute field confirms that such solute control data are more relevant to clinical outcomes than volume control or acid-base control or tonicity control.

Tables 107-2 and 107-3 show potential flow charts that could be followed each time an RRT prescription is indicated.

CONTINUOUS VERSUS INTERMITTENT RENAL REPLACEMENT THERAPY

Blood purification can be achieved in the ICU by both CRRT and intermittent RRT. Currently, approximately 80% of patients who are critically ill are treated with CRRT. However, no specific recommendation is currently provided by the major critical care societies, and the choice is primarily left to institutional protocols and expertise. When the critical parameter of dialysis efficacy is metabolic control, an acceptable mean blood urea nitrogen level of 60 mg/dL, typically obtainable after some days with a 2 L/hr CVVH in a 100-kg patient, in a computer-based simulation, has been shown to be extremely difficult to reach, even by intensive IHD regimens.[44] In addition to the benefits specifically pertaining to the kinetics of solute removal, increased RRT frequency results in decreased UF requirements per treatment. The avoidance of volume swings related to rapid UF rates may also represent another dimension of dose where comparability is difficult.

Nevertheless, despite the development of new membranes, new catheters for vascular access, sophisticated dialysis machinery, and tailored dialysate composition,

TABLE 107-2 ALGORITHM FOR RENAL REPLACEMENT THERAPY PRESCRIPTION

Clinical Variables	Operational Variables	Settings
Fluid balance	Net ultrafiltration	Continuous management of negative balance (100-300 mL/hr) is preferred in patients who are hemodynamically unstable. In case blood purification is the main issue, 2000-3000 mL/hr K (or 25-35 mL/kg/hr) for CRRT should be targeted; for modality choice first consider CVVHDF. If IHD is selected, an everyday, 4-hr prescription is recommended with a Kt/V >1.2.
Adequacy and dose	Clearance and modality	2000-3000 mL/hr K (or 25-35 mL/kg/hr) for CRRT; first consider CVVHDF. If IHD is selected, then an everyday, 4-hour prescription is recommended. A Kt/V >1.2 is prescribed.
Acid-base	Solution buffer	Bicarbonate-buffered solutions are preferable to lactate-buffered solutions in patients with lactic acidosis and/or hepatic failure.
Electrolyte	Dialysate and replacement	Consider solutions without K^+ in case of severe hyperkalemia. Manage accurately with $MgPO_4$.
Timing	Schedule	Early and intense RRT is suggested.
Protocol	Staff/machine	Well-trained staff should routinely use RRT monitors following predefined institutional protocols.

CRRT, Continuous renal replacement therapy; *CVC,* central venous catheter; *CVVHDF,* continuous venovenous hemodiafiltration; *ECG,* electrocardiogram; *IHD,* intermittent hemodialysis; *K,* clearance; *RRT,* renal replacement therapy; *S-G,* Swan Ganz catheter.

TABLE 107-3 SCHEMATIC EXAMPLE OF A POSSIBLE PRESCRIPTION FOR CONTINUOUS TREATMENT*

	Estimated Urea Clearance (K_{CALC})†	Notes	Value of Q to Obtain 35 mL/kg/hr	Value of Q to Obtain a Kt/V of 1
CVVH postdilution	K_{CALC} = Qrep	Always keep filtration fraction <20% (Qb must be five times Qrep)	Qrep: 41 mL/min or 2450 mL/hr	Qrep: 29 mL/min or 1750 mL/hr
CVVH predilution	K_{CALC} = Quf/[1 + (Qrep/Qb)]	Always keep filtration fraction <20% (Qb must be five times Qrep)	For a Qb of 200 mL/min: Qrep: 53 mL/min or 3200 mL/hr	For a Qb of 200 mL/min: Qrep: 35 mL/min or 2100 mL/hr
CVVHD	K_{CALC} = Qdo	Keep Qb at least three times Qd	Qdo: 41 ml/min or 2450 mL/hr	Qdo: 29 ml/min or 1750 mL/h
CVVHDF postdilution (50% convective and diffusive K)	K_{CALC} = Qrep + Qdo	Consider both notes of CVVH and CVVHD	Qrep: 20 mL/min + Qdo: 21 mL/min	Qrep: 14 mL/min replacement solution + Qdo: 15 mL/min

Urea volume of distribution: V (L) = patient's body weight (kg) × 0.6.
Estimated fractional clearance: (Kt/V_{CALC}) = K_{CALC} (mL/min) × prescribed treatment time (min)/V (mL).
35mL/kg/hr roughly corresponds to a Kt/V of 1.4. A Kt/V of 1 approximately corresponds to 25 mL/kg/hr.
Filtration fraction calculation (postdilution): Qrep/Qb × 100.
Filtration fraction calculation (predilution): Qrep/Qb + Qrep × 100.
CVVH, Continuous venovenous hemofiltration; *CVVHD,* continuous venovenous hemodialysis;*CVVHDF,* continuous venovenous hemodiafiltration; *Qb,* blood flow rate; *Qdo,* dialysate solution flow rate; *Qnet,* patient's net fluid loss; *Qrep,* replacement solution flow rate; *Quf,* ultrafiltration flow rate (Quf = Qrep + Qnet).
*70-kg patient, V_{UREA}, 42 L, during an ideal session of 24 hours (time, 1440 minutes)
†Net ultrafiltration (patient fluid loss) is considered zero in K_{CALC} for simplicity.

a clear relationship between frequency of RRT delivery (CRRT versus intermittent RRT) and mortality has not been fully established. Most recently, the Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock[45] concluded that, based on present scientific evidence, CRRT should be considered equivalent to IHD for the treatment of AKI. Vinsonneau and colleagues[46] recently conducted a large, prospective, randomized multicenter study in 21 ICUs over a 3.5-year period. The primary endpoint was the 60-day mortality after the randomization of 360 patients with acute renal failure (ARF) to either CVVHDF or IHD in centers that were familiar with both techniques. The eligibility criteria changed after 8 months as a result of the recruitment rate being too low. No differences in 28- or 60-day mortality rates (CVVHDF, 33%; IHD, 32%) or in 90-day mortality rates between the two groups were found, and the authors concluded that all patients with ARF as part of multiorgan dysfunction syndrome can be treated with IHD. The study was well conducted and, at the moment, is the best example of randomized controlled study effectively comparing the two techniques. Nonetheless, the study started several years ago, during which time the practices in both CVVHDF and IHD have changed considerably. As stated by Vinsonneau and colleagues, this study may have led to changes in investigator practices during the study period, particularly with respect to the delivered dose of renal support. This possibility, however, is hard to ascertain, considering that the investigators, by protocol, started therapy with initial standardized settings and then adapted these settings to meet individual patient requirements to obtain the metabolic control objectives. Interestingly, the

mortality decreased in the IHD arm of the study over the time of recruitment, which reflected a change in practice toward an increase in dialysis prescription. Considering the lack of control regarding the dosage in both arms of the study, definitive conclusions are difficult to make regarding treatment. As remarked in the accompanying editorial,[47] the question of which treatment is better is influenced by the nature of the task. CRRT might be better in terms of total water and solute removal over 24 hours and hemodynamic tolerance, but IHD can remove significantly more water and solute per hour and does not require continuous anticoagulation or complete patient immobilization. Furthermore, the advantages of continuous therapies are largely supported when administered without prolonged interruptions. Again, unfortunately the study by Vinsonneau did not provide this information. Finally, if all patients with AKI as part of multiorgan dysfunction syndrome can be treated with IHD, then they can also be safely treated by CVVHDF.

Other reports have drawn similar conclusions.[48,49] One of the common key points of these recent trials, however, can be that IHD has become safer and more efficacious with contemporary dialytic techniques. Furthermore, a liberal and extended use of CRRT may have become less safe and/or efficacious than previously considered or expected. Over the past 2 decades, however, technical advances in the delivery of IHD have dramatically decreased the propensity of IHD to cause intradialytic hypotension. These advances include the introduction of volume-controlled dialysis machines, the routine use of biocompatible synthetic dialysis membranes, the use of bicarbonate-based dialysate, and the delivery of larger doses of dialysis. Schortgen and colleagues demonstrated that the rate of hemodynamic instability was lower and outcomes were better after the implementation of a clinical practice algorithm designed to improve hemodynamic tolerance to IHD.[50] Recommendations included priming the dialysis circuit with isotonic saline, setting dialysate sodium concentration at above 145 mmol/L, discontinuing vasodilator therapy, and setting dialysate temperature to below 37° C. Thus the original rationale for the widely held assumption that CRRT is a superior therapy may have dissipated over time.

In conclusion, the question of the superiority of a modality for renal support might be artificial. In routine clinical practice, as designed by the Vinsonneau protocol, a change from one approach to another seems reasonable when clinical status changes (e.g., from CRRT to IHD when hemodynamics improve or the patient is extubated, and vice versa), even if this common sense approach has never been scientifically validated.[51] Randomizing patients to receive one therapy or the other, regardless of the conditions, might yield results that are difficult to generalize to clinical practice.

Hybrid techniques have developed over time as a feasible compromise solution to this eternal dispute. These techniques have been given a variety of names such as slow low-efficiency extended daily dialysis (SLEDD),[52] prolonged daily intermittent RRT (PDIRRT),[53] extended daily dialysis (EDD),[54] or simply extended dialysis,[55] depending on the variations in schedule and the type of solute removal (convective or diffusive). Theoretically speaking, these therapies were developed to enhance the advantages offered by either CRRT or IHD, including efficient solute removal with minimum solute disequilibrium, reduced UF rate with hemodynamic stability, optimized delivered to optimal prescribed-to-delivered dose ratio, low anticoagulant needs, diminished cost of therapy delivery, efficiency of resource use, and improved patient mobility. Initial case reports have shown that these hybrid approaches are feasible and do have high clearances. A single short-term single center trial comparing hybrid therapies with CRRT has shown satisfying results in terms of dose delivery and hemodynamic stability.[56] Recently, Baldwin and co-workers randomized 16 patients to 3 consecutive days of treatment with either CVVH (8 patients) or extended daily dialysis with filtration (EDDf) (8 patients) and compared small solute, electrolyte, and acid-base control.[56] They did not find significant differences between the two therapies for urea or creatinine levels over 3 days. All electrolyte derangements before treatment were corrected as a result of treatment, except for one patient in the CVVH group who developed hypophosphatemia (0.54 mmol/L) at 72 hours. After 3 days of treatment, a mild but persistent metabolic acidosis in the EDDf group was observed, compared with the CVVH group.

Generating ultrapure replacement fluid and administering it in the ICU at a lower cost than CRRT, in greater amounts and for shorter periods, is now possible. Hemofiltration may be combined with diffusion, or pure diffusion can be selected at any chosen clearance for a period that can encompass the daytime period with the maximum staff availability or the night-shift period. Thus the choices are now almost limitless: 3 or 4 hours of IHD with standard settings or CRRT at 35 mL/kg/hr of effluent flow rate can be selected. SLEDD at blood and dialysate flow rates of 150 mL/min for 8 hours during the day or SLEDD for 12 hours overnight can be considered an alternative. Otherwise, why not combine CRRT for the first 2 or 3 days when the patient is in the hyperacute phase with SLEDD thereafter as recovery takes place?

CLINICAL APPLICATIONS

EXTRACORPOREAL MEMBRANE OXYGENATION

Starting Extracorporeal Membrane Oxygenation (Venovenous and Venoarterial Configurations)

ECMO can be provided in two different ways or configurations: VV ECMO that provides respiratory support or VA ECMO for respiratory and cardiocirculatory support. Since venous blood is oxygenated and returned to the aorta (usually via the femoral artery and alternatively to the aortic arch via the right common carotid artery), the VA ECMO technique provides mechanical circulatory support for patients with cardiogenic shock.

In the VA configuration, ECMO has been successfully used as a bridge to myocardial recovery, long-term ventricular assist devices, cardiac transplantation after myocardial infarction, cardiomyopathy, myocarditis, postcardiotomy cardiac failure, and cardiac arrest.[57] A key issue that must be taken into consideration is that in

VA ECMO, the blood pumped by the machine (highly oxygenated) mixes with the blood coming from the left ventricle (poorly oxygenated), resulting in a possible hypoxemia of the upper body (including the coronary circulation and the brain) and an optimal oxygenation of the lower part (Harlequin syndrome). In light of this issue, the blood from the right radial artery should be carefully monitored and its oxygenation measured. This important issue can be faced by placing an additional cannula from the inflow side into the right internal jugular vein, creating a venous-arterial-venous (VAV) ECMO. A further problem related to the VA ECMO is the high left atrial pressure attributable to the increased afterload on a failing left ventricle. Draining the left atrium by means of a transseptal catheter, venting the left ventricle from the apex (left thoracotomy), or directly venting the left atrium can manage this problem.

Patients with severe hypoxic respiratory failure, without cardiac dysfunction, should receive percutaneous peripheral VV ECMO. Recourse to VA ECMO in the presence of preserved cardiac function may cause severe brain and heart hypoxia and expose patients to severe complications such as systemic thromboembolism, limb ischemia, and increased left ventricular wall tension. As a general rule, echocardiography should be performed before VV ECMO initiation to diagnose left ventricular dysfunction, which might necessitate the use of VA ECMO. In VV ECMO, blood is drained from one or both vena cava via the jugular or femoral veins (drainage), pumped through the artificial lung and then into the right atrium (inflow). Pulmonary blood flow is maintained and systemic delivery is provided by the left ventricle. Several advantages can be attributed to VV ECMO in comparison with VA ECMO: (1) the arterial system is not included in any technical maneuver without any risk of ischemia or thrombosis; (2) pulmonary blood flow is maintained with oxygenated blood, promoting vasodilation; (3) pulsatile blood flow to organs is maintained; and (4) an increase in left ventricle afterload attributable to the retrograde pump flow is avoided.

ECMO has been proposed for patients suffering from several forms of respiratory failure—ARDS refractory to conventional mechanical ventilation, lung trauma, severe asthma, pulmonary embolism, patients awaiting lung transplantation, and many other causes involving neonatal and pediatric populations.[58]

Indications and Contraindications for Venovenous Extracorporeal Membrane Oxygenation

Adults. The exact indications for adult VV ECMO have not been the subject of large trials. Nonetheless, it is recommended that ECMO should be considered in patients with hypoxic respiratory failure attributable to any cause (primary or secondary) when mortality is predicted to be 50% or greater and is indicated when higher than 80%, despite the optimal use of traditional therapies.[†] A mortality risk of 50% can be identified by a PaO_2/FiO_2 less than 150 mm Hg on FiO_2 greater than 90% and/or a Murray score of 2 to 3; an 80% mortality risk can be identified by a PaO_2/FiO_2 less than 80 mm Hg on FiO_2 greater than 90% and a Murray score of 3 to 4. Other indications are CO_2 retention attributable to asthma or permissive hypercapnia with a $Paco_2$ greater than 80 mm Hg or an inability to achieve safe inflation pressures (Pplat ≤30 cm H_2O) or severe air leakage. In general, ECMO approach should be used when less invasive therapies fail but before VILI or sustained cerebral hypoxia occurs. Certain institutions proposed stricter criteria after the H1N1 pandemic emerged in the spring of 2009. In Australia, for example, the New South Wales Department of Health recommended in its guidelines for ECMO initiation immediate consultation for VV ECMO in case of refractory hypoxemia or hypercarbia ($Paco_2$ >100 mm Hg, with PaO_2/FiO_2 <100). The French Réseau Européen de Recherche en Ventilation Artificielle (REVA) group proposed that ECMO should be initiated in cases of hypoxemia (PaO_2/FiO_2 <50 mm Hg), despite high PEEP (10 to 20 cm H_2O) and high FiO_2 (>80%) ventilation when plateau pressure reached 35 cm H_2O, despite decreases to 4 mL/kg in tidal volume.[59]

According to ELSO, there are no absolute contraindications for VV ECMO in adults. However, there are conditions that are known to be associated with a poor outcome, despite ECMO; these should always be considered before initiating ECMO assistance. These conditions are injurious mechanical ventilation for 7 days or longer, major pharmacologic immunosuppression (absolute neutrophil count <400/mL^3), and central nervous system hemorrhage that is recent or expanding. Specific patient conditions should also be considered. Although no specific age is a contraindication, increasing age is considered to increase the risk; weight over 125 kg can be associated with technical difficulties and the risk of not being able to achieve an adequate blood flow, based on patient size; and comorbidities should also be taken into consideration.

Bridging to lung transplant is being evaluated in some transplant centers.[†] It is a matter of fact that the role of ECMO in many of the conditions regarded as contraindications in the past (e.g., sepsis, trauma, malignancy, pulmonary hemorrhage) has recently been reappraised by many experienced centers. Furthermore, renewed interest for *the new era* of ECMO has allowed the implementation of modern techniques, more reliable devices, and effective training programs, which have significantly extended ECMO indications with respect to the *rescue utilization* adopted in the past.

Neonates. According to ELSO, VV ECMO should be considered in the neonate when the OI is 20 and should be indicated when the OI is 40. The calculation of OI is as follows:

$$[\text{mean airway pressure (MAP)} \times FiO_2] \div [\text{postductal } PaO_2 \times 100]$$

Lethal chromosomal disorders, irreversible brain damage, and grade III or greater intraventricular hemorrhage are contraindications for VV ECMO in neonates. Relative contraindications include irreversible organ damage (unless considered for organ transplantation), body weight less than 2 kg, and less than 34 weeks'

[†]See "Patient Specific Supplements to the ELSO General Guidelines." <http://www.elso.med.umich.edu/WordForms/ELSO%20Pt%20Specific%20Guidelines.pdf> (Accessed October 18, 2012)

postmenstrual age because of the increased incidence of increased intracranial hemorrhage (also see Chapter 95†).

Pediatric Patients. No absolute indications are known, but ECMO should be considered within the first 7 days of mechanical ventilation at high levels of support.†

Listed contraindications include recent neurosurgical procedures or intracranial bleeding within 10 days, recent surgery or trauma, and increased risk of bleeding. Grade II or III intracranial hemorrhage is a general contraindication.

Indications and Contraindications for Venoarterial Extracorporeal Membrane Oxygenation

The main VA ECMO indication in adult cardiac failure according to ELSO guidelines is the presence of cardiogenic shock associated with inadequate tissue perfusion, despite adequate intravascular volume and inotropes-vasoconstrictors administration. Intraaortic balloon counterpulsation should be considered before ECMO initiation, if appropriate. Typical conditions that are an indication for VA ECMO include acute myocardial infarction, myocarditis, peripartum cardiomyopathy, decompensated chronic heart failure, and postcardiotomy shock. Septic shock is an indication only in some centers. The American Heart Association guidelines for cardiopulmonary resuscitation (CPR) recommend consideration of ECMO to aid CPR in patients who have an easily reversible event and have had excellent CPR.†

In pediatric patients, ELSO suggests VA ECMO in early postoperative cardiac failure in the surgical unit if the patient is unable to come off bypass. In the ICU, VA ECMO should be considered in conditions of shock unresponsive to appropriate drug therapy. Moreover, VA ECMO can be considered after cardiac arrest from any cause with response to CPR but still unstable and no response to CPR direct massage underway for 5 minutes. Finally, VA ECMO can be considered in cases of myocardial failure unrelated to surgery such as myocarditis, cardiomyopathy, and toxic drug overdose.†

Management and Monitoring

New technologies with modern pumps, circuits, and oxygenators, and ICU nurses with additional training in ECMO technology and management ensure efficient care of both the ECMO device and patient. The circuit should be monitored several times daily by the medical and nursing team and at least once a day by a perfusionist or other ECMO specialist. Appropriate functioning, fibrin deposits, and clots should be carefully monitored in all components. Moreover, great care must be taken to search for any sign of inflammation and infection at the cannulation site.

Patients under ECMO assistance require careful monitoring of vital organs by means of electrocardiogram, airway pressure and flow, arterial blood pressure, and specific monitoring devices related to ECMO, such as the following:

- Blood flow delivered by the circuit is calculated by a flow meter.
- Transducers measure the pressures at different sites. The pressure before the membrane lung is extremely important; an increase in pressure levels may suggest thrombosis in the oxygenators.
- Oxygen saturation of the drained venous blood (superior vena cava, inferior vena cava, and coronary sinus) is a good indicator of DO_2:VO_2 ratio during VA ECMO.
- High oxygen saturation during VV ECMO may suggest venous blood recirculation (oxygenated blood recaptured by the circuit) attributable to cannula displacement.

Weaning From Extracorporeal Membrane Oxygenation

Improved lung function (and cardiocirculatory status for AV ECMO) is the *conditio sine qua non;* that is, it is the indispensable requisite or condition for starting a weaning protocol from VV ECMO. Improvements in lung mechanics, blood gases, and radiologic appearance are signs of progress toward autonomy. Although the ventilator is set to lung-protective mode, the gas flow to the oxygenator can be turned off and, if acceptable stability (cardiorespiratory function) is maintained for 1 to 4 hours, then the pump can be stopped and the cannulas removed. Lung recovery may take several weeks or months; recovery from ARDS has been reported after more than 50 to 100 days of ECMO support.[60] End-tidal CO_2 may be very low during the early phases of ECMO because pulmonary function is severely impaired. As lungs start recovering and blood flow to ventilated alveoli increases, end-tidal CO_2 increases as well. An end-tidal CO_2 close to normal values may suggest that a weaning trial could be considered. When VA ECMO is implanted for cardiac dysfunction, signs of recovery include increasing arterial pulse contour and, primarily, improving echocardiographic signs of heart contractility. In VA configuration, the tubing leading blood to the patient is clamped, but circulation within the circuit is maintained via a bypass. If cardiorespiratory functions are adequate, then the cannulas can be removed.

MANAGEMENT OF RENAL REPLACEMENT THERAPY

Indications to Start Renal Replacement Therapy

Whatever the technique of CRRT, the following clinical variables are typically compromised in the patient who is critically ill with AKI:

1. Continuous control of fluid status
2. Hemodynamic stability
3. Control of acid-base status
4. Ability to provide protein-rich nutritional support, while achieving excellent uremic control
5. Control of electrolyte balance
6. Control of phosphate and calcium balance
7. Prevention of swings in intracerebral water
8. Minimal risk of infection
9. High level of biocompatibility

†See "Patient Specific Supplements to the ELSO General Guidelines." <http://www.elso.med.umich.edu/WordForms/ELSO%20Pt%20Specific%20Guidelines.pdf> (Accessed October 18, 2012)

Even if clear guidelines or recommendations on when to start RRT exist, to date, a broad concept of timely intervention is generally accepted. When oliguria is associated with impairment of one or more of the clinical features previously listed, RRT should be started within 24 hours. The only urgent indications to dialysis are pulmonary edema refractory to high-dose diuretics and rapidly increasing kalemia. Fluid balance is a fundamental aspect to control in the patient who is critically ill with anuria. All patients who are critically ill need a high daily amount of volume infusions—blood and fresh frozen plasma, vasopressors and other continuous infusions, and parenteral and enteral nutrition, which should be delivered without restriction or interruption. It is not uncommon for patients with AKI and associated septic shock to receive large amounts of fluid resuscitation, leading to fluid overload. The consequent positive fluid balance and tendency to interstitial edema cause the necessity for water removal and, possibly, the achievement of a negative daily fluid balance. Extracorporeal RRTs are typically used for UF. Ultrafiltered water has a similar osmolarity to plasma water; for this reason, the process of *isolated UF* substantially corresponds to blood dehydration, with a possible increase of hematocrit values and the smallest modification of solutes concentrations.[61] CRRT slowly and continuously removes the patient's plasma water, mimicking urine output, whereas intermittent hemodialysis three times weekly must extract, in a few hours, the equivalent of 2 days of administered fluids plus excess body water that may be present in the patient with anuria. The intravascular volume depletion associated with excessive UF rate is due to both the high rate of fluid removal required and the transcellular and interstitial fluid shifts caused by the rapid dialytic loss of solute. The major consequence of rapid fluid removal is hemodynamic instability. In the case of a septic patient with AKI who is receiving a high amount of vasopressors because of hemodynamic instability and is needing appropriate fluid resuscitation, supplementation of nutrition, and blood product administration, the renal replacement modality of choice seems to be the one that warrants slow fluid removal that is prolonged for many hours per day to meet the highly variable required daily fluid balance. In particular, when volemic and uremic control is not a problem, an aggressive, protein-rich nutritional policy (1.5 to 2.5 g/day) can be implemented in the care of patients with AKI who are receiving CRRT, resulting in a significant improvement in daily nitrogen balance with possible favorable effects on immune function and overall outcome.[62] Safe prescription of fluid loss during RRT requires intimate knowledge of the patient's underlying condition, an understanding of the process of UF, and close monitoring of the patient's cardiovascular response to fluid removal. To preserve tissue perfusion in patients with AKI, optimizing fluid balance by removing the patient's excess water without compromising the effective circulating fluid volume is important. It is still a matter of controversy to determine which clinical parameters—actual patient weight or patient dry weight, MAP, central venous pressure, wedge pressure, systemic saturation, mixed venous saturation, bioimpedance, among others—or currently available monitorization—central venous catheter, Swan Ganz catheter, transesophageal echocardiography, and others—are to be used to define uniformly the concept of *volume overload*. In patients who are clinically fluid overloaded, however, accurately evaluating the amount of fluid to remove[63] in these patients is extremely important; one of the main features of slow and constant UF is the possibility for interstitial fluid to refill the *dehydrated* bloodstream slowly and constantly. This phenomenon is driven by hydrostatic and osmotic forces and allows for the elimination of high plasma water volumes each day with a reduced risk of hypovolemia and hypotension. In children who are critically ill, the correction of water overload is considered a priority; it has been shown and recently confirmed that restoring adequate water content in small children is the main independent variable for outcome prediction.[64] Similar results have been recently found in a large cohort of adult patients who are critically ill with AKI.[65]

Solute removal is a broad concept that is generally described by the elimination of a marker solute. This marker solute should be reasonably representative of all solutes that are normally removed from blood by the kidney. Unfortunately, a reference solute that represents all the solutes accumulating during AKI is not currently available because kinetics and volume of distribution are different for each molecule. As a result, *single-solute control* during RRT represents only a rough estimate of treatment efficiency. With these specifications, urea is generally used as an *imperfect* marker molecule, because of its accumulation in all patients with AKI and the ease of serum level measurement. Furthermore, despite its moderate toxicity, urea is the final product of protein metabolism; its accumulation describes the need for dialysis and its removal describes treatment efficiency. It is a small molecule, and its volume of distribution is similar to total body water. It is not bound to protein, and it freely passes through tissues and cell membranes. Creatinine has similar characteristics and is another commonly used marker solute.

Once RRT is indicated, a prescription on dialysis dose has to be made and the treatment carefully delivered. The intensity of a dialytic treatment can be roughly indicated by the amount of dialysis and hemofiltration flow delivered to the patient. After the milestone trial by the group of Vicenza in 2000,[66] such flow has been indexed to patient body weight, highlighting that this variable is of direct importance in patients with AKI. Two large multicenter randomized controlled studies published in 2009 (the randomized evaluation of normal versus augmented level [RENAL] replacement therapy study[67] and the Veterans Administration and the National Institutes of Health [VA/NIH] Acute Renal Failure Trial Network [ATN] study)[68] finally clarified the concept of optimal dialysis dose. The RENAL and ATN studies were designed to compare normal or less intensive renal support to an augmented or intensive therapy; in particular, the RENAL study compared 25 mL/kg/hr CVVHDF to 40 mL/kg/hr CVVHDF; the ATN study compared 20 mL/kg/hr CVVHDF or three times per week intermittent dialysis to 35 mL/kg/hr CVVHDF or daily intermittent dialysis. Surprisingly, both studies showed that increases in intensity of RRT dose did not improve patient outcomes, essentially negating a large

body of evidence coming from previous smaller trials. As a consequence, the definition of *normal dose* is now recommended in a range of 20 to 30 mL/kg/hr for continuous therapies or three times per week intermittent hemodialysis, or both.

Patients with oligo-anuric renal failure often have mild acidemia, secondary to increased unmeasured anions (strong ion gap [SIG] – 12.3 mEq/L), hyperphosphatemia, and hyperlactatemia. The alkalinizing effect of hypoalbuminemia attenuates this acidosis. The effect on acid-base balance of intermittent hemodialysis and CVVHDF has been evaluated; metabolic acidosis is common in both groups, and both intermittent hemodialysis and CVVHDF correct metabolic acidosis. However, the rate and degree of correction may significantly differ. CVVHDF normalizes metabolic acidosis more rapidly and more effectively during the first 24 hours than intermittent hemodialysis. Intermittent hemodialysis is also associated with a higher incidence of metabolic acidosis than CVVHDF during the subsequent 2-week treatment period. Accordingly, CVVHDF can be considered physiologically superior to intermittent hemodialysis in the correction of metabolic acidosis. In a comparison between CVVH and peritoneal dialysis, all patients randomized to CVVH achieved correction of acidosis with 50 hours of treatment, compared with only 15% of those treated by peritoneal dialysis ($P < .001$).[69]

Rocktaschel showed that once CVVHDF is commenced, acidemia is corrected within 24 hours. This change is associated with a decreased SIG and decreased phosphate and chloride concentrations. After 3 days of CVVHDF, patients develop alkalemia secondary to metabolic alkalosis attributable to a further decrease in SIG and a decrease in serum phosphate concentration in the setting of persistent hypoalbuminemia.[70]

Although considerable attention has focused on the perceived benefits of CRRT, the emphasis on the possibility that CRRT might confer increased risk has lessened. As a continuous extracorporeal therapy, CRRT often requires continuous anticoagulation, which can increase bleeding risk. Conversely, clotting of the extracorporeal circuit also frequently occurs with CRRT, which might contribute to blood loss and could exacerbate anemia in patients who are critically ill. The increased solute transfer associated with the use of CRRT might enhance the removal of amino acids, vitamins, catecholamines, and other solutes with a beneficial function in patients who are critically ill. Continuous therapies must be continuous to work. How many treatments really last more than 18 to 20 hours per day? Downtime attributable to filter-circuit-catheter clotting, circuit change, frequent replacement solution-bag substitution, and patient mobility (surgery, diagnostics) should be carefully monitored and might significantly affect the dialysis dose.[71,72] Also of concern are technical problems, including machine malfunction, medication errors, and compounding errors, that have been reported with the delivery of CRRT and might contribute to increased patient morbidity and mortality. Detection of safety problems, adverse events, or both, is particularly difficult when rates of expected morbidity and mortality are high in the population undergoing a procedure, as is the case with CRRT in patients who are critically ill with AKI. Currently, few studies in the nephrology literature provide substantive information on the safety or adverse effects of CRRT or IHD in the critically ill population. After the introduction of new technology and devices into medical practice, the natural tendency is to assume that the novel therapeutic approach is providing benefit, especially when the therapy becomes part of the typical equipment of an ICU bed and is applied 24 hours a day to a patient who is critically ill. The level of attention is probably greater when a dedicated dialysis nurse administers the therapy for few hours during the day shift. Nonetheless, a new generation of dedicated CRRT machines has been recently released with strict safety features and the possibility of a high range of prescriptions. In any case, the ideal therapy still does not exist, and specific ICU staff training is mandatory before such modern monitors are routinely used.

Indications to Stop Renal Replacement Therapy

A paucity of evidence can be found regarding when to wean RRT. Some insights may be gleaned from recent literature. One report from the Beginning and Ending Supportive Therapy (BEST) Kidney study group describes the current practice for the discontinuation of CRRT in a multinational setting to identify variables associated with successful discontinuation and whether the discontinuation of CRRT may affect patient outcomes.[73] In this study, 313 patients were weaned from CRRT for at least 7 days and were classified as the *success group*, and 216 patients were classified as the *repeat-RRT group*. Multivariate logistic regression analysis for successful discontinuation of CRRT identified urine output (during the 24 hours before stopping CRRT: odds ratio [OR], 1.078 per 100 mL/day increase) and creatinine (OR, 0.996 per mmol/L increase) as significant predictors of successful cessation. The predictive ability of urine output was negatively affected by the use of diuretic agents. As always happens with observational studies, establishing whether the *repeat-RRT* population would have achieved a different outcome by waiting for a better creatinine or urine output before stopping RRT is not possible. Risk factors for redialysis were also analyzed by the National Taiwan University Surgical ICU Acute Renal Failure Study Group.[74] In this study, RRT weaning of 94 postoperative patients was considered successful when prolonged for at least 30 days (21%) and was correlated with the Sequential Organ Failure Assessment (SOFA) score, age, dialysis duration, and, again, urine output. Interestingly, of the patients who remained RRT-free for 5 days after RRT discontinuation, more than two thirds remained RRT-free up to 30 days.

As a general recommendation, physicians should wait for adequate urine output (without diuretic therapy) and optimized creatinine values before weaning from RRT; the additional effect of patient glomerular filtration rate and treatment clearance should lead to normal or subnormal creatinine values while on RRT. Once

renal function appears close to the baseline or the *pre-AKI* level, interrupting the treatment without any specific weaning protocol seems reasonable. It is possible, on the other hand, that patients with signs of only partial renal recovery may benefit from more specific and prolonged weaning algorithms. Examples would be a decrease of the UF rate or prescription of intermittent treatments where the therapy was previously continuous. Future trials are needed to design, if possible, such protocols. Furthermore, evaluation of new renal biomarkers as prognostic factors is intriguing to explore if they can predict when patients have recovered sufficient renal function to allow them to remain RRT-free once RRT is stopped.

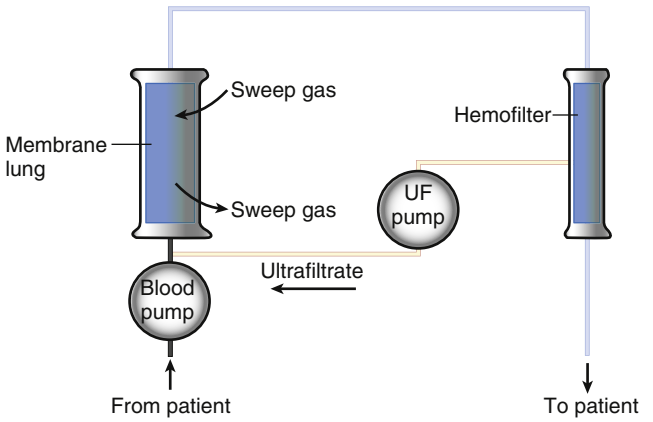


Figure 107-9. Blood is pumped through a membrane lung in series with a dialysis filter, and ultrafiltrate is returned to the blood before the membrane. *UF*, Ultrafiltrate.

ALTERNATIVE EXTRACORPOREAL SUPPORT TECHNIQUES

EXTRACORPOREAL CARBON DIOXIDE REMOVAL OR RESPIRATORY DIALYSIS

Lung protective ventilation is one of the main therapeutic issues for patients with different severity of respiratory insufficiency. Basic components of lung protective strategy include the administration of low tidal volume (<6 to 8 mL/ideal body weight) and the maintenance of low airway pressures (<30 cm H_2O plateau pressure) as evidence emerges that low tidal volumes reduce mortality in patients with ARDS who are mechanically ventilated. However, in low tidal volume ventilation, CO_2 clearance may be impaired, leading to problems related to hypercapnia. In the large ARDS network, it has been demonstrated that hypercapnia may complicate 14% of patients under lung protective ventilation strategy,[75] whereas all patients with ARDS ventilated with pressures lower than 28 cm H_2O may suffer from hypercapnia.[76] Hypercapnia may be undesirable because of its capability for harming injured lungs through immunosuppression and impaired pulmonary epithelial repair, worsening right heart failure and intracranial pressure in patients with elevated intracranial pressure.[77] When permissive hypercapnia cannot be applied for the aforementioned reasons, mechanical systems can be used to eliminate the CO_2 (extracorporeal CO_2 removal [ECCOR])[76]. Modern ECCOR devices have demonstrated improved survival when combined with ultraprotective ventilation ECCOR systems designed to eliminate CO_2 without providing significant oxygenation (differently from ECMO systems). CO_2 removal can be performed through a dedicated system (Fig. 107-9) that uses a pump-driven extracorporeal VV circuit with a neonatal membrane lung and a hemofilter coupled in series. Such a circuit requires a membrane lung to be coupled by a hemofilter. This is done to increase the pressure inside the membrane lung by adding the downstream resistance exerted by the hemofilter. This technical solution also reduces the risk of air bubble formation. Furthermore, the need for heparin is minimized by diluting the blood entering the membrane lung with the plasma water separated by the hemofilter. Finally, the performance of the extracorporeal CO_2 extraction is optimized as a result of the additional flow provided by ultrafiltered water recirculated into the membrane lung. The blood flow used for this device is not negligible (200 to 400 mL/min), and a normal dialysis vascular access is not adequate in this case.[77] An alternative system exploits cardiac output and arterial blood pressure to move the blood through a low-resistance artificial lung (AV pumpless CO_2 removal system; Interventional Lung Assist [iLA] Membrane Ventilator, NovaLung GmbH, Heilbronn, Germany) (see Fig. 107-5). Pumpless systems result in less blood trauma but require large-bore arterial cannulas and adequate blood flow and arterial pressure. General principles considered for ECMO are substantially valid for ECCOR with the basic difference that ECCOR systems work with lower blood flow rates (0.5 to 1.5 L/min) as a result of differences in CO_2 and oxygen kinetics (CO_2 is transported as dissolved bicarbonate and diffuses more readily than oxygen across extracorporeal membranes because of greater solubility).[22] Because lower blood flow is necessary, newer ECCOR devices use double-lumen cannulas similar to those used for dialysis (CO_2 dialysis).[78] For instance, the iLA Membrane Ventilator is designed with a pump capable of large flow rates (from 0.5 up to 6 to 7 L/min), coupled with different membranes and cannulas. This new field of pulmonary extracorporeal assistance is developing new devices to increase effectiveness and simplicity of use. With extended indications to VV decapneization, it is possible that the requirement of injurious ventilation will significantly decrease and the outcomes of patients who are critically ill will improve further in the next 10 years.

HIGH CUTOFF HEMOFILTRATION OR HEMODIALYSIS AND PLASMA THERAPY

A potentially useful strategy to increase mediator removal in septic patients with extracorporeal therapy is by using high-cutoff (HCO) membranes, which are porous enough to achieve the removal of larger molecules (approximately 15 to 60 kD) by diffusion. Such RRT using HCO membranes in sepsis-related AKI has a

widely accepted biologic rationale. Its ability to remove cytokines in ex vivo and in vivo studies has now been shown to be greater than that of any other technology to date[79] and has increased survival in experimental models of sepsis.[80] HCO therapy seems to have beneficial effects on immune cell function, and preliminary human studies using intermittent hemodialysis with HCO membranes have confirmed its ability to remove marker cytokines interleukin (IL)-6 and IL-1 receptor antagonist, with a decreased dose of norepinephrine in patients with sepsis.[81] HCO membrane–based blood purification has now been applied in at least four clinical studies to treat more than 70 patients with septic AKI with no reports of serious adverse effects. Predictably, albumin losses are significant but may be attenuated by using HCO membranes in a diffusive rather than convective manner while still preserving the effect on cytokine clearance.

The term *plasma therapy* actually encompasses two therapies: plasmapheresis and plasma exchange. In plasmapheresis, plasma separated from blood cells flows along one or more columns that contain different adsorbents, after which the processed plasma is reinfused back to the patient. Plasma exchange is a single-step process in which blood is separated into plasma and cells and the cells are returned back to the patient while the plasma is replaced with either donor plasma or albumin. Replacing volume lost with fresh-frozen plasma is also done to replete any factors needed to restore hemostasis or to correct the underlying disorder for which the plasma therapy was prescribed. With respect to sepsis, it has been argued that plasma therapy is most likely to be effective in patients with sepsis-associated thrombotic microangiopathy.[82] An emerging hybrid technology called *coupled plasma filtration adsorption* (CPFA) uses a resin cartridge placed downstream from a plasma filter, improving the removal of nonspecific septic mediators with promising results in early small trials.[83-85] CPFA is aimed at nonselectively reducing the circulating levels and activities of both proinflammatory and antiinflammatory mediators during sepsis and multiorgan failure. To overcome the shortcomings of plasma filtration and to improve removal efficiency, CPFA uses a specific sorbent cartridge placed in series with, but downstream to, the plasma filter. CPFA improves the removal of nonspecific mediators with promising results. Unfortunately, as reported in a personal communication by Livigni, the recent multicenter trial (Combining Plasma-Filtration and Adsorption Clinical trial) to verify the effectiveness of CPFA in improving mortality of patients with sepsis-related AKI has been completed without meeting its primary endpoint. Interestingly, a subgroup analysis revealed that the mortality rate of treated patients with sepsis-related AKI was reduced by a CPFA dose (volume of treated plasma) of more than 2 L/day. Furthermore, it is possible that improvement of the standard of care of patients who are critically ill decreased the mortality rate to the point such that a new trial on CPFA has been designed where mortality is not considered the primary endpoint.

CONTINUOUS RENAL REPLACEMENT THERAPY IN PATIENTS REQUIRING EXTRACORPOREAL MEMBRANE OXYGENATION

A peculiar and complex category of critically ill patients is the one requiring both RRT and ECMO. This clinical picture is frequently observed in the pediatric setting. AKI occurs to the vast majority of children requiring ECMO, who suffer from severe cardiac dysfunction (cardiorenal syndrome) or require aggressive mechanical ventilation (lung-renal syndrome). The CRRT circuit may be placed in parallel (blood flows in the same direction of the ECMO circuit) or in series (blood flows counter to the direction of the ECMO circuit). Santiago and coauthors described how to connect the CRRT device into the ECMO circuit[86]: the inlet (arterial) line of the CRRT circuit is connected after the ECMO blood pump by a three-way tap that is also used for the infusion of heparin, and the outlet (venous) line is connected to the circuit at another tap before the oxygenator. Contrary to what was suggested by the authors, the inlet of the CRRT machine may be connected after the ECMO pump and the filter outlet then returned to the ECMO circuit before the pump (into the reservoir, if present). The CRRT circuit, running countercurrent to extracorporeal assistance, allows the RRT blood to be aspirated from the arterial ECMO section (where blood returns to the patient) and then to be infused into the venous ECMO section (where the patient is drained).[87] This second set-up might reduce blood flow resistance and turbulence after the centrifugal pump and improve reservoir drainage when a roller pump is present. The blood recirculation induced by these circuit set-ups is negligible, considering that the CRRT:ECMO blood flow ratio is never superior to 0.1. Dr. Shaheen and colleagues[88] recently presented their experience with two different subgroups of children; one group required hemofiltration alone and the second group required hemofiltration and ECMO. Not surprisingly, the authors identified a higher mortality rate in those patients requiring CVVHDF and ECMO, compared with those patients requiring hemofiltration alone. The authors promoted the concept that certain therapies should be reserved to experienced teams. Performing CVVHDF in a heterogeneous population with large age and weight ranges poses significant clinical and technical challenges. The low frequency of CVVHDF used in ECMO, as well as the use of other extracorporeal therapies, also raises problems with maintaining nursing skills. Objective clinical and biochemical markers for commencing CVVHDF alone or in combination with ECMO remain to be defined. Several studies, however, have already showed safety and feasibility of this connection in the pediatric setting[89] and, even if some worries on such difficult interaction have been raised (i.e., fluid balance accuracy),[90] today, the application of CRRT to all patients requiring ECMO is claimed by some authors.[91] It has been shown in 15 patients matched with 46 historical controls that adding continuous hemofiltration to the ECMO circuit in newborns improves outcome by significantly reducing the time on extracorporeal assistance and on mechanical ventilation; such a strategy might improve fluid balance management and capillary

leak syndrome. Furthermore, according to these authors, fewer blood transfusions are needed and overall costs per ECMO run are lower.

CONCLUSIONS

In recent years, great technologic improvements have been made in the manufacture of extracorporeal circuits, rendering them simpler, safer, and more efficient for long-term assistance. The new ECMO and CRRT systems can be managed by one bedside nurse who is trained and experienced in circuit management, and it is now possible to assist patients for several weeks or even months without major complications.

Although recent studies suggest that ECMO might improve the outcomes of patients with respiratory failure or cardiogenic shock, or both, indications for ECMO use remain controversial. Interestingly, a similar parallel discussion could be conducted for RRT systems. Nonetheless, evidence and experience favoring lung protective ventilation strategies and timely continuous blood purification in patients who are critically ill with cardiorespiratory and/or kidney failure is accumulating apart from large trials showing unequivocal evidence. As a consequence, simpler, smaller, and less invasive extracorporeal devices are being developed and more and more frequently applied in ICUs.

In the future, ECMO, CRRT, extracorporeal CO_2 removal devices, hemoperfusion, adsorption, or plasmafiltration and adsorption (for either CPFA or liver support) will be integrated into a single multifunction machine with a user-friendly interface and flexibility in parameters and prescriptions, designed to respond to different medical needs with the use of different disposable layouts. Finally, advances in information technology should allow the fully integrated extracorporeal blood purification system to be connected to all electronic therapeutic devices (from simple syringe pumps to CRRT machines) to ultimately lead to an *artificial organ* in a more complete sense.

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Chapter 108

Cardiopulmonary Resuscitation: Basic and Advanced Life Support

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Key Points

- Circulation, airway, breathing (CAB) has replaced airway, breathing, circulation (ABC). The provision of uninterrupted, high-quality chest compressions after sudden cardiac arrest (SCA) is associated with better survival and neurologic outcomes than when airway interventions occur first with cardiac arrests in both adult and pediatric patients. Chest compressions should be immediately initiated on discovery of a suspected cardiac arrest.
- A single resuscitative shock should be delivered at the earliest possible opportunity after the recognition of cardiac arrest, followed immediately by the resumption of chest compressions without postshock cardiac rhythm analysis. Outcome studies have failed to demonstrate the benefit of a period of chest compressions before shock or for a series of stacked shocks.
- Advanced airway placement is no longer a priority intervention during cardiac resuscitation. Evidence demonstrating the benefit of tracheal tube placement on successful resuscitation from cardiac arrest is lacking.
- The use of vasopressor medications during resuscitation attempts for SCA has been de-emphasized in deference to providing uninterrupted, high-quality chest compressions. Epinephrine, vasopressin, and amiodarone have all demonstrated improved rates of resuscitation without affecting those surviving to hospital discharge.
- The use of ultrasound technology should be used, when available, for identifying potentially correctable sources of cardiac arrest, as well as for evidence justifying the termination of resuscitative efforts.
- Targeted temperature management (also known as *therapeutic hypothermia*) applied to comatose survivors of out-of-hospital cardiac arrests, resulting from shockable lethal cardiac dysrhythmias, has significantly improved the neurologic recovery in those surviving to hospital discharge. Increasingly, this therapy is being extended to those resuscitated from nonshockable lethal cardiac dysrhythmias.
- Pediatric resuscitation protocols have been simplified to improve rescue performance. Chest compressions should be performed at a rate of 100 per minute with two breaths interposed after every 30 compressions (consistent with adult resuscitation). Single rescuers should call for help before initiating resuscitation efforts. Chest compressions should be initiated if an infant is found with a pulse lower than 60 beats per minute.
- Children weighing more than 10 kg and experiencing lethal cardiac dysrhythmias can be defibrillated with adult defibrillation pads. At least 3 cm should separate the defibrillation pads. Infant defibrillation paddles are recommended for children younger than 1 year of age or weighing less than 10 kg. An initial defibrillation dose of 2 J/kg is recommended.
- Most deaths after SCA in both adults and children typically occur within the first 24 hours. Coordinated postresuscitation care involving access to coronary catheterization capabilities and intensive care management that includes targeted temperature management represents the best chance survivors of SCA have for optimal neurologic and cardiac recovery.
- Technologic advances augmenting native systemic circulation in low states of cardiac output, including cardiac arrest, is an active area of clinical research at this time. Although the results of several studies are hopeful, more consistent and reproducible evidence is necessary before new resuscitative technology is incorporated in resuscitation protocols.

Although the history of resuscitation can be traced to at least biblical times,[1] contemporary approaches to cardiopulmonary resuscitation (CPR) date back to 1966, when a National Academy of Sciences National Research Council conference generated consensus standards for the performance of CPR.[2] Since that time, successive conferences have reviewed the practice of CPR in light of available experimental and clinical data and have prepared revisions of previous standards.[3-10] The most recent recommendations, the *2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care* (*2010 AHA Guidelines for CPR and ECC*), represent the third internationally recognized resuscitation guidelines developed by experts from the American Heart Association (AHA) and the European Resuscitation Council (ERC); as such, these guidelines represent a variety of countries, cultures, and medical specialties.

Each intervention included in the new guidelines has undergone comprehensive evidence-based evaluation of the available scientific information supporting its uses in emergency cardiovascular care and resuscitation, as well as structured and transparent process for managing potential conflicts of interest. Both basic life support (BLS) and advanced cardiac life support (ACLS) are established on credible foundations and have enjoyed widespread acceptance in the emergency cardiovascular care community. Indicative of this acceptance is the widespread popularity of the AHA BLS and ACLS training programs and related training materials. The intent of this chapter is to review the premise, rationale, and techniques for the performance of both BLS and ACLS in light of current understanding and as published in the AHA textbooks on BLS[11] and ACLS.[12]

Modifications and reconsideration of the guidelines for emergency care of those in cardiac arrest have provided recommendations for interventions that have saved thousands of lives for nearly 50 years. Despite these careful reviews and the development of guidelines, survival to hospital discharge from witnessed out-of-hospital sudden cardiac arrest (SCA) attributable to ventricular fibrillation (VF) remains less than 10% worldwide.[13] The majority of patients experiencing sudden cardiac death cannot be resuscitated even when SCA is immediately recognized and resuscitation guidelines are closely followed.

Restating the performance of all BLS CPR procedures, which can be reviewed in the guidelines and also in the AHA BLS text, is not the intention of this chapter.[11] Rather, both BLS and ACLS are reviewed within the contexts of their application by anesthesia providers in operating rooms, intensive care units (ICUs), and other patient care environments.

SUDDEN CARDIAC ARREST AND CARDIOPULMONARY RESUSCITATION

SCA is a complex and dynamic process. Antegrade systemic arterial blood flow continues after cardiac arrest until the pressure gradient between the aorta and right heart structures reach equilibrium. A similar process occurs during cardiac arrest with antegrade pulmonary blood flow between the pulmonary artery and the left atrium.[14-16] As the arteriovenous pressure gradients dissipate, the left heart becomes less filled, the right heart becomes more filled, and the venous capacitance vessels become increasingly distended (Fig. 108-1). When the arterial and venous pressures equilibrate (approximately 5 minutes after cardiac arrest), coronary perfusion and cerebral blood flow stop.

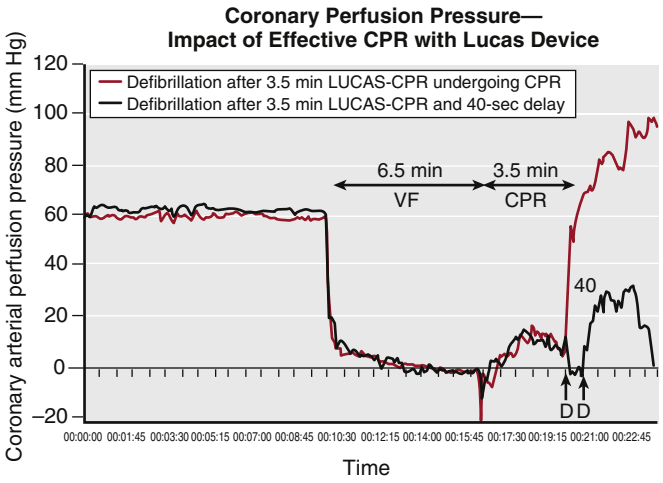


Figure 108-1. Coronary perfusion pressure. Impact of effective CPR with the LUCAS device. *CPR*, Cardiopulmonary resuscitation; *D*, defibrillation; *VF*, ventricular fibrillation. *(From Steen S, Liao Q, Pierre L, et al: The critical importance of minimal delay between chest compressions and subsequent defibrillation: A haemodynamic explanation, Resuscitation 58:249, 2003.)*

PHYSIOLOGIC CONSIDERATIONS

Since the early 1960s when CPR became a widespread clinical technique, blood was thought to be ejected as a direct result of actual compression of the heart between the sternum and the vertebral column and was commonly referred to as the *cardiac pump mechanism*. Transesophageal echocardiography during CPR in humans provides an opportunity for assessing changes in cardiac dimensions and valve positions during chest compressions, as well as the direction of blood flow. Observations made with echocardiography during CPR depict a reduction in left and right ventricular volume, closure of the tricuspid and mitral valves during chest compression, and ejection of blood into the arterial system, all of which are consistent with the cardiac pump mechanism (Fig. 108-2).[17-20]

Repeated, forceful coughing (cough CPR) can sustain consciousness during hypotensive events including VF for as long as 100 seconds when the arrhythmia (or any arrhythmia capable of rapidly compromising cardiac output) is immediately recognized and the patient can be verbally prompted to cough. This observation of maintaining consciousness with coughing suggests mechanisms other than direct cardiac compression may account for forward blood flow during cardiac arrest.[21] Vigorous coughing produces an arterial pressure pulse associated with forward blood flow that opens the aortic valve during pressure and flow generation.[22] This process is commonly referred to as the *thoracic pump mechanism* (see Fig. 108-2). The increasing intrathoracic pressure during chest compression equalizes intravascular pressure within the thorax. On the venous side, valve and venous collapse at the thoracic inlet limit the transmission of retrograde pressure or flow. The arterial system, which is relatively

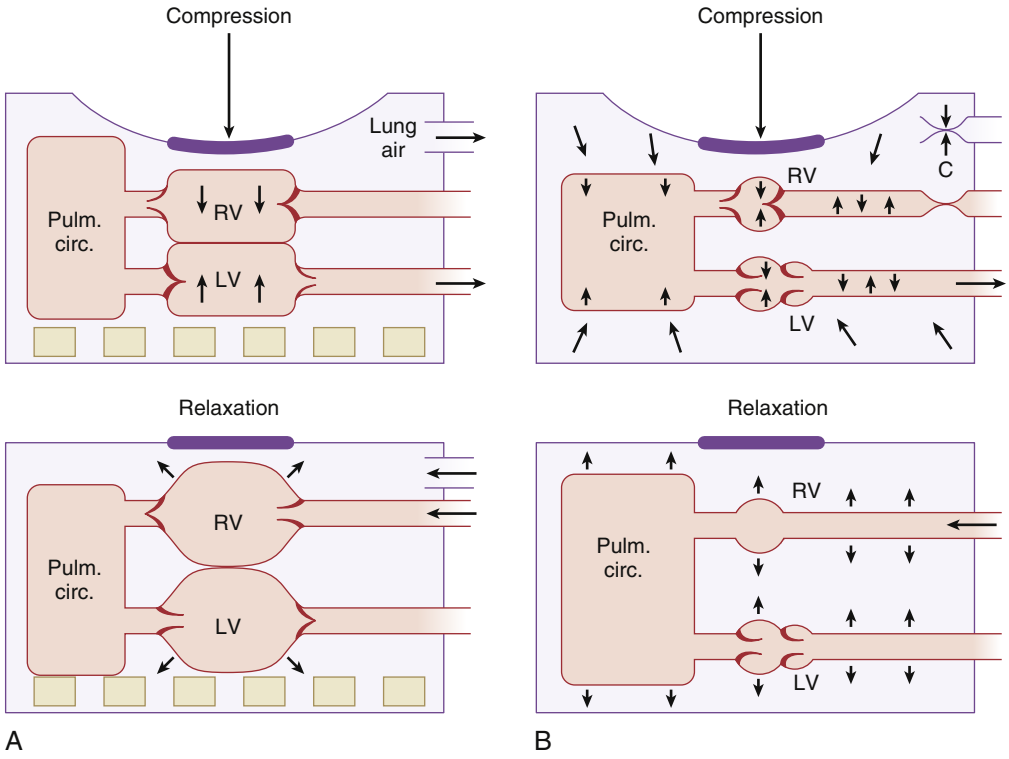


Figure 108-2. A, Systematic representation of cardiac compression pump. **B,** Intrathoracic pressure pump, representing the collapse *(C)* of airways and venous structures. *LV,* Left ventricle; *RV,* right ventricle.

resistant to collapse, transmits pressure and flow into the extrathoracic vascular system. Some studies suggest that during compression or vigorous coughing, the left side of the heart may act as a passive conduit for the transfer of pulmonary venous blood out into the peripheral arterial circulation. During compression, blood flows from the lungs through the left ventricle and toward the periphery. The pulmonary valve is closed, and the mitral and aortic valves are open during periods of high intrathoracic pressure when the chest is compressed.[23]

Both the cardiac pump and thoracic pump mechanisms exist at times during resuscitation attempts. Electrocardiography has confirmed the cardiac pump theory. Cough CPR is effective in maintaining consciousness, at least in the early period after the onset of a lethal arrhythmia, consistent with the thoracic pump theory. Chest compressions during cardiac arrest may initially promote a cardiac pump mechanism attributable to the presence of blood in the left side of the heart. As pressure gradients between the arterial and venous systems equilibrate during prolonged resuscitation, pulmonary blood volume increases and probably supports a thoracic pump mechanism.

Systemic, coronary, and cerebral blood flow during CPR is dependent on effective chest compressions but also on the venous blood return to the heart. At chest compression rates of 100 per minute, the chest compression-relaxation ratio approaches 50:50. The time available for blood return into the thorax is limited. Venous blood returns to the thorax at very low pressures during cardiac arrest. Modest increases in intrathoracic pressure, as might occur with overzealous ventilation during CPR, will impair venous return and negatively impact systemic, coronary, and cerebral perfusion and also reduce the chances of return of spontaneous circulation (ROSC).

Cardiac output during CPR with effective, uninterrupted chest compression is 25% to 30% of the normal spontaneous circulation. Systemic and pulmonary perfusion during CPR reflects the decreased cardiac output as demonstrated by weak carotid pulses with chest compression and low carbon dioxide excretion (addressed later in this chapter). In cardiac arrests without hypoxic causes (e.g., drowning, suffocation), oxygen content in the lungs at the time of cardiac arrest is usually sufficient for maintaining acceptable arterial oxygen content during the first several minutes of CPR. Rescue breaths are less important than initiating chest compressions immediately after the onset of SCA. Blood flow rather than arterial oxygen content is the limiting factor for oxygen delivery to coronary, cerebral, and systemic circulation during CPR.

BASIC LIFE SUPPORT

BLS involves the early recognition of a medical emergency, activation of an emergency response system (e.g., dialing 9-1-1 in the United States), and interventions made in response to SCA, heart attack, stroke, and foreign body airway obstruction (FBAO). No equipment is required for these interventions, except for access to a telephone or an automated external defibrillator (AED), or both. AEDs are included in BLS interventions because of their widespread availability in public spaces (e.g., airports, schools, shopping centers, hospitals, casinos, sporting arenas), their uncomplicated application, automated cardiac rhythm analysis, and administered shocks (if indicated, based upon AED cardiac rhythm analysis).

All BLS interventions (Table 108-1)[24] are time sensitive for preventing SCA, terminating SCA, or supporting circulation until spontaneous circulation is restored after

TABLE 108-1 SUMMARY OF KEY BLS COMPONENTS FOR ADULTS, CHILDREN, AND INFANTS

	Recommendations		
Component	**Adults**	**Children**	**Infants**
Recognition	Unresponsive (for all ages) No breathing or no normal breathing (e.g., only gasping) No pulse palpated within 10 seconds (HCP only)	No breathing, only gasping	
CPR sequence	CAB		
Compression rate	At least 100 per minute		
Compression depth	At least 2 inches (5 cm)	At least one-third AP depth; about 2 inches (5 cm)	At least one-third AP depth; about 1.5 inches (4 cm)
Chest wall recoil	Allow complete recoil between compressions. HCPs rotate compressors every 2 minutes.		
Compression interruptions	Minimize interruptions in chest compressions. Attempt to limit interruptions to less than 10 seconds.		
Airway	Head tilt–chin lift (HCP suspected trauma: jaw thrust)		
Compression:ventilation ratio (until advanced airway is in place)	30:2 one or two rescuers	30:2 single rescuer 15:2 two HCP rescuers	30:2 single rescuer 15:2 two HCP rescuers
Ventilations when rescuer is untrained or is trained but not proficient	Compressions only		
Ventilations with advanced airway (HCP)	One breath every 6-8 seconds (8-10 breaths per minute) Asynchronous with chest compressions Approximately 1 second per breath Visible chest rise		
Defibrillation	Attach and use AED as soon as available. Minimize interruptions in chest compressions before and after shock. Resume CPR beginning with compressions immediately after each shock.		

From Peberdy MA, Callaway CW, Neumar RW, et al: Part 9: post-cardiac arrest care:2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiac Care, Circulation *122: (18 Suppl 3),S768-S786, 2010.*

AED, Automated external defibrillator; *AP,* anteroposterior; *BLS,* basic life support; *CAB,* circulation, airway, breathing; *CPR,* cardiopulmonary resuscitation; *HCP,* health care provider.

SCA. In the 5-year interim between the 2005 and 2010, the AHA BLS recommendations, clinical evidence, and survivor outcomes after sudden cardiac death support making uninterrupted chest compressions the priority intervention, above airway management, rescue breathing, and pulse check.[24] Airway, breathing, circulation (ABC) has been replaced by circulation, airway, breathing (CAB) for both adult and child resuscitations.[24] Lay rescuers and health care professionals alike, frequently misinterpret agonal gasping respirations as spontaneous ventilation and fail to recognize the absence of a pulse early after the onset of SCA.[24,25] Because the breathing and pulse assessments are almost uniformly inaccurate, regardless of the rescuer's medical training,[24,26,27] and the need to initiate CPR as soon as possible after the onset of SCA to maximize the chances of successful resuscitation, chest compressions should be immediately initiated on recognizing unresponsiveness in a potential victim of SCA.[24] Thirty chest compressions conducted at a rate of 100 per minute are followed by two rescue breaths (30:2) in adults and children resuscitations.

"Push hard and push fast" remains the recommendation for chest compressions during CPR.[24] Although evidence from human studies that identify the ideal chest compression rate is insufficient, current recommendations are for chest compressions to occur at a rate of 100 per minute with minimal interruptions in both adult and childhood cardiac arrests. In adults, chest compressions should be at least 2 inches (5 cm) deep. In children, chest compressions should be one-third the depth of the thorax. In a large study evaluating the quality of CPR (i.e., depth of chest compressions as recommended in the 2010 AHA Guidelines for CPR and ECC) on survival from out-of-hospital cardiac arrest, compression depth and rate influenced resuscitation from cardiac arrest.[28] Although the majority of prehospital chest compressions did not meet the 2010 AHA chest compression depth recommendations (i.e., 50 mm), those patients with chest compression depth and rate nearer to the 2010 AHA Guidelines for CPR and ECC had more frequent survival rates than those with less optimal chest compressions.

Interruptions in chest compressions negatively affect coronary and cerebral perfusion, ROSC, and survival.[29,30] The 2010 AHA Guidelines for CPR and ECC reflect these observations with an increased emphasis on limiting interruptions in chest compressions, even for other resuscitative measures (e.g., rescue breaths, advanced airway placement, defibrillation, postshock rhythm analysis, pulse checks).[31] During single- and two-person CPR, the 2010 AHA Guidelines for CPR and ECC recommend compression:ventilation

ratios of 30:2 in both scenarios with minimal interruptions in chest compressions for rescue breaths. In the absence of native cardiac function and systemic circulation, CPR is performed until spontaneous circulation returns or the patient is pronounced dead. Although CPR is far less efficient than native circulation, when properly performed with limited interruptions, CPR can provide coronary circulation and cerebral blood flow sufficient to afford full recovery in many patients if ROSC can be re-established.

Compression-only resuscitation may be a potential mechanism for encouraging resuscitation in the general population when potential rescuers are uncomfortable or unwilling to provide rescue breaths. Without question, prompt initiation of chest compressions in the individual with SCA can be lifesaving. However, in a large study of 40,000 Japanese victims of SCA, those who received compression-only CPR had lower 1-month survival rates and lower improved neurologic recovery, compared with conventional CPR that included rescue breaths.[32] The authors also noted reduced survival when CPR was not promptly initiated, as well as a reduced neurologic recovery with advancing age, regardless of the CPR method. For the best chances of survival after SCA, conventional CPR is superior to compression-only CPR.

In a similar approach, Bobrow and associates[33] evaluated placing a close facemask with high flow oxygen on out-of-hospital patients in cardiac arrest during resuscitation as their initial airway intervention. They then compared survival to hospital discharge outcomes and neurologic recoveries of those provided close facemask oxygenation for patients receiving bag-valve-mask ventilation. Advanced airway placement was pursued after the initial 600 chest compressions in all patients. This novel approach, limiting interruptions in chest compressions only for cardiac rhythm analysis and defibrillation in the early course of resuscitation, provided insight into the value of ventilation and oxygenation in the early stages of resuscitation. They report survival to hospital discharge outcomes and neurologic recoveries were no different between ventilation groups for patients experiencing unwitnessed cardiac arrests or those for whom the initial cardiac rhythm was nonshockable. However, for patients with witnessed cardiac arrests and shockable initial arrhythmias, neurologic outcomes were improved in those receiving passive oxygenation rather than bag-valve-mask ventilation (38.2% versus 25.8%, adjusted odds ratio [OR] 2.5, 95% confidence interval [CI] 1.3-4.6). These results further establish the importance of high-quality, uninterrupted chest compressions, and a de-emphasis of airway interventions early in the resuscitative process.

Another example justifying the 2010 AHA Guidelines for CPR and ECC's emphasis on high quality, uninterrupted chest compressions comes from a large (N = 3960) observational study evaluating resuscitation and neurologic outcomes for out-of-hospital cardiac arrests from nonshockable cardiac arrhythmias.[34] During the 10-year period, the final 5 years' resuscitation and survival results were compared with the initial 5 years' results. During that time period, AHA resuscitation guidelines had been modified, resulting in improved quality of chest compressions and limited interruption in chest compressions for other resuscitative measures. Although survival from nonshockable cardiac arrhythmias remains significantly lower than shockable arrhythmias, the 2005 AHA Guidelines for CPR and ECC, with its emphasis on high quality, uninterrupted chest compressions, resulted in statistically significant improvements in ROSC (from 27% to 34%), discharge from hospital (4.6% to 6.8%), discharged with favorable neurologic outcomes (3.4% to 5.1%), survival to 1 month (4.1% to 6.2%) and survival to 1 year (2.7% to 4.9%).

Multiple modifications to standard CPR and mechanical adjuncts to improve circulation (e.g., interposed abdominal compression, mechanical chest compression devices, impedance threshold devices) have only shown modest benefit in re-establishing spontaneous circulation. However, none has demonstrated improved survival to hospital discharge when compared with standard CPR. What is certain is that CPR, regardless of the mechanism of blood flow and technique, is only a temporizing intervention in need of rapid supplementation with ACLS interventions, most critically, rapid defibrillation of the fibrillating heart. No device, other than a defibrillator, has been associated with consistently improved survival from cardiac arrest.

Shock First or Cardiopulmonary Resuscitation?

Previous guidelines recommended a period of CPR before attempting defibrillation in unwitnessed cardiac arrests or when CPR had been delayed longer than 4 minutes. However, evidence recommending routine delivery of CPR for 90 to 180 seconds before attempting defibrillation is insufficient, based on the results of two randomized control trials that failed to demonstrate a benefit to ROSC or hospital discharge when CPR was performed before defibrillation.[35,36] The results of a retrospective before-and-after study demonstrated improved 30-day and 1-year neurologic recovery if CPR is performed before defibrillation,[37] and the results of a large observational study demonstrated the probability of survival from out-of-hospital cardiac arrest was improved as the number of preshock chest compressions increased.[38] Practically, chest compressions should be immediately initiated upon encountering an individual in SCA and continued until an AED is applied, charged, and ready to defibrillate.

Automated External Defibrillators and Manual Defibrillation

The most frequent cardiac rhythm responsible for witnessed cardiac arrest in adults is VF, although the incidence of VF is decreasing.[39] VF is a highly metabolically active state for the myocardium. In the presence of VF, myocardial stores of oxygen and metabolic substrates are rapidly depleted. Chest compressions deliver oxygen and energy substrates to the myocardium, improving the chances for defibrillation. CPR prolongs the duration of VF but cannot convert the arrhythmia to an organized rhythm in most circumstances. Defibrillation is the process of delivering an electrical current between two pads placed on the chest with sufficient current passing between the pads and through the myocardium to interrupt disorganized cardiac activity and restore an organized cardiac rhythm or asystole for at least 5 seconds.[40] Defibrillation is not synonymous with resuscitation. Successful termination of VF requires effective chest compressions and prompt defibrillation.

The AHA has included early defibrillation with an AED as part of BLS training. The AHA has also endorsed the concept of public-access defibrillation (PAD), which encourages the policy of making defibrillation available to those in cardiac arrest through nonconventional providers, such as police, security guards, and others. The AED, when applied to an individual with possible SCA, is capable of analyzing the cardiac rhythm, detecting VF and rapid ventricular tachycardia (VT), then automatically attempts defibrillation. A trained rescuer's role is to apply the defibrillator pads to the patient's chest, activate the AED, and deliver the shock through the push of a button when prompted to do so by the AED. The entire sequence, AED application through discharge of energy and postdefibrillation rhythm analysis, should be conducted in the presence and with minimal interruption of chest compressions.

The first AED was introduced in 1979.[41] In 1986, the first microprocessor-based AED was introduced; the AED used three successive, nonescalating, 180-J monophasic damped waveform shocks. Advances in defibrillator technology, including conversion from monophasic to biphasic defibrillator waveforms, resulted in smaller, lighter units with more accurate rhythm analysis.

An issue faced by trained rescuers is the wide availability of AED devices encountered in both health care facilities and PAD settings. Considering the cost, longevity, and low-maintenance nature of AEDs, replacement of previous-generation devices programmed with outdated defibrillation protocols will probably have a low priority by those responsible for managing the devices. As a result, a rescuer applying an AED may find outdated rhythm analysis (prolonged interruption of chest compressions) and defibrillation protocols (e.g., three stacked shocks without interposed chest compressions). At this time, deferring to AED protocol, even if outdated, may be more helpful than attempting to circumvent the protocol and "trick" the AED into following more current protocols. A manual defibrillator should be obtained at the earliest opportunity if an outdated AED protocol interferes with resuscitation attempts.

In circumstances during which standard defibrillators rather than AEDs are used in resuscitation, the rescuer must recognize the technology inherent in the defibrillator. When a manual defibrillator is activated, the rhythm screen typically identifies the defibrillator technology as either monophasic or biphasic. The manual defibrillator should be managed with a protocol identical to current AED protocols: (1) emphasis is placed on delivering uninterrupted chest compressions while defibrillator pads are being applied and for periods when rhythm analysis is not occurring; (2) chest compressions are immediately resumed after shock delivery; (3) cardiac rhythm is reanalyzed as indicated after 2 minutes of chest compressions and rescue breathing; and (4) defibrillation is attempted only for VF and rapid VT. If a monophasic defibrillator is available, then defibrillation energy should begin at high energies (300 to 360 J).[42]

Single Versus Stacked Defibrillation

Beginning in 2005, the AHA recommended a single shock from an AED or manual defibrillator be administered, after which chest compressions and rescue breaths were immediately resumed for 2 minutes before repeating cardiac rhythm analysis. This approach was reaffirmed in the 2010 AHA Guidelines for CPR and ECC.[43] Chest compressions are continued until the defibrillator is ready to deliver the shock and is resumed immediately thereafter without waiting for cardiac rhythm analysis. In most instances, the heart is at least transiently "stunned" by defibrillatory shocks and benefits by a period of coronary blood flow delivered through chest compressions. In the event that a patient has invasive hemodynamic monitoring in place at the time of cardiac arrest and if an organized cardiac rhythm with a perfusing arterial waveform follows defibrillation, then chest compressions may not be indicated.

At this time, the only indications for multiple defibrillation attempts to be given without 2-minute periods of chest compressions and ventilation are for the very specific resuscitation efforts provided during cardiac surgery or in the cardiac catheterization laboratory.[40,43] These patients typically have existing invasive monitors and defibrillation pads at the time of VF or VT, and the onset of VF is immediately recognized. Only one series of stacked shocks is indicated during these resuscitations.

Biphasic Defibrillation Waveforms

Biphasic defibrillation waveforms deliver energy first in one direction and then reversed for the duration of the impulse. One of two biphasic waveforms is used in modern AEDs and defibrillators; biphasic truncated and rectilinear biphasic (Figs. 108-3 and 108-4).[40] Both waveforms are effective for terminating VF using energy levels specific to each. No randomized clinical trial has demonstrated superiority of one waveform over the other with respect to neurologically intact survival to hospital discharge. Impedance-compensated, nonescalating low-energy biphasic waveforms (150 J) were first introduced in 1996 and have been shown to be more successful in terminating VF than are traditional, escalating-energy monophasic waveforms (200 to 300 J) in the controlled setting of an electrophysiology laboratory.[44-46]

Impedance compensation allows the defibrillator to change waveform morphologic characteristics based upon impedance measured during shock delivery (typically 70 to 80 Ohms) to generate transthoracic current capable of defibrillation, regardless of patient weight.[47] Biphasic defibrillation waveforms and impedance compensation, together, allow effective defibrillation at lower energies than with monophasic, nonimpedance compensated monophasic waveforms.[48-51]

A high first-shock defibrillation rate can be expected after biphasic defibrillation shocks. If VF persists after a biphasic shock, then additional chest compressions should be delivered to replenish myocardial oxygen and metabolic substrates, rather than additional shocks.[40] Although the first biphasic waveform shock should not be less than 150 J regardless of waveform, Hess and associates[52] reported the performance of a rectilinear biphasic waveform during nonescalating energy protocols (120 J-120 J-120 J) demonstrating a frequent rate of shock success in terminating VF and unchanged ROSC or survival to hospital discharge when this lower, nonescalating energy approach was used.

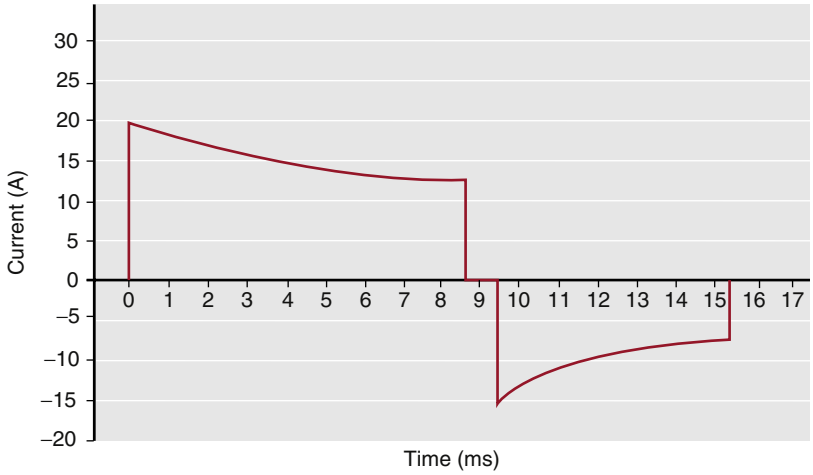


Figure 108-3. Biphasic truncated exponential waveform. *(From Deakin CD: Advances in defibrillation,* Curr Opin Crit Care *17(3):233, 2011. Used with permission.)*

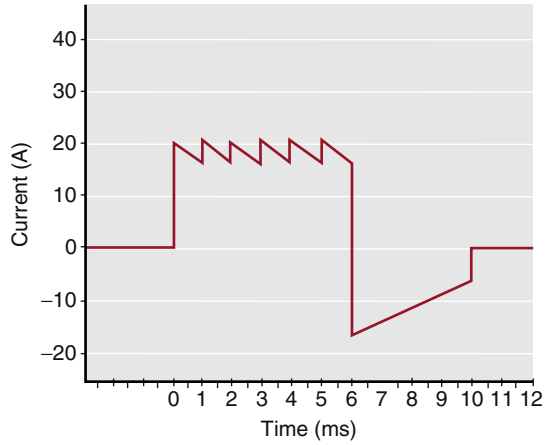


Figure 108-4. Rectilinear biphasic waveform. *(From Deakin CD: Advances in defibrillation,* Curr Opin Crit Care *17(3):233, 2011. Used with permission.)*

In circumstances in which pediatric patients require defibrillation, modification of adult defibrillation procedures is necessary. If possible, pediatric defibrillator pads should be applied in the anteroposterior position. Initial energy levels should range from 2 J/kg to 4 J/kg. At this time, no information is available suggesting higher defibrillation energies in children are unsafe. These recommendations are unchanged from previous AHA resuscitation guidelines (also see Chapter 93).

Additional discussion related to cardioversion and defibrillation is included in the treatment algorithms for specific arrhythmias presented later in this chapter.

Implanted Cardiac Defibrillators

In some patients at risk for lethal arrhythmias, defibrillators are implanted to provide immediate, automatic defibrillation (also see Chapter 48). Implantable cardioverter defibrillators (ICD) are recognized as the most effective treatment for patients at risk for recurrent life-threatening arrhythmias that are not due to a transient, reversible cause.[53,54] Class I indications for ICD placement are shown in Box 108-1.[54] Class I indications for ICD placement for patients with congestive heart failure are shown in Box 108-2.[54] A number of class II indications for implantation of ICDs exist, primarily establishing guidelines for ICD use in patients believed to be at high risk for lethal arrhythmias without a history of cardiac arrest. Class III indications for ICD placement are typically related to patients with such severe underlying disease in whom survival beyond 12 months is unlikely with or without ICD placement.

For patients with ICD devices, any suggestion or confirmation of ICD activation warrants prompt clinical evaluation and ICD interrogation confirming the presence of an arrhythmia. If VF or VT has occurred, then one of three broad categories is likely to have occurred.[53] First, the ICD activation represents an isolated arrhythmia in a patient with modest heart disease and preserved functional capacity during which the ICD discharge corrected what is likely an isolated event. Long-term survival is likely. Second, the ICD activation represents an

BOX 108-1 ***Class I Indications for Implantable Cardioverter Defibrillator Placement***

- Survivors of cardiac arrest caused by ventricular fibrillation or hemodynamically unstable sustained ventricular tachycardia after evaluation to diagnose cause of event to exclude completely reversible causes
- Structural heart disease and spontaneous sustained ventricular tachycardia, whether hemodynamically stable or unstable
- Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained ventricular tachycardia or ventricular fibrillation induced at electrophysiologic study
- Left ventricular ejection fraction <35% caused by prior myocardial infarction at least 40 days previously and New York Heart Association class II or III
- Nonischemic dilated cardiomyopathy with left ventricular ejection fraction ≤35% and New York Heart Association class II or III
- Left ventricular ejection fraction <30% caused by prior myocardial infarction at least 40 days previously and New York Heart Association class I
- Nonsustained ventricular tachycardia caused by myocardial infarction, left ventricular ejection fraction <40%, and inducible ventricular fibrillation or sustained ventricular tachycardia at electrophysiologic study

From Aronow WS: Implantable cardioverter-defibrillators, Am J Ther *17:e208, 2010.*

BOX 108-2 ***Class I Indications for Implantable Cardioverter Defibrillator Placement for Patients with Congestive Heart Failure***

- Secondary prevention to prolong survival in patients with current or prior symptoms of heart failure and reduced left ventricular ejection fraction who have history of cardiac arrest, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia
- Primary prevention of sudden cardiac death to reduce mortality in patients with nonischemic dilated cardiomyopathy or ischemic heart disease at least 40 days after myocardial infarction, a left ventricular ejection fraction ≤35%, and New York Heart Association class II or III symptoms on optimal medical therapy, with expectation of survival with good functional status for more than 1 year
- May be used in patients receiving cardiac resynchronization therapy for New York Heart Association class III or ambulatory class IV symptoms, despite recommended optimal medical therapy

From Aronow WS: Implantable cardioverter-defibrillators, Am J Ther *17:e208, 2010.*

unfavorable change in previously stable cardiovascular disease. The arrhythmia may signal the onset of heart failure, myocardial infarction or ischemia, worsening valvular function, or an additional, serious medical condition. Third, in patients with significant or severe heart disease, ICD activation represents further progression of the underlying disease and represents a very poor prognosis. In most circumstances, ICD activation represents an important decline in a patient's underlying condition.

The ICD delivers defibrillation energy directly to the myocardium; usually 40 J. Patients with ICDs are usually aware of the ICD activation, prompting requests for help. When malignant arrhythmias are detected by the ICD, up to eight shocks are administered unless new arrhythmias are detected, sometimes resulting in more than eight shocks.[40] After any confirmed or suspected ICD firing, prompt interrogation of the unit is indicated.

An ICD shock should signal to rescuers the need to prepare for ACLS, including the placement of defibrillation pads, cardiac monitoring, and intravenous (IV) access. The placement of defibrillation pads should be away from the ICD (usually found under the left or right pectoralis muscle) to prevent damage to the ICD and to reduce the likelihood that pacing spikes from the ICD are misinterpreted by the AED (if manual defibrillators are not available) as QRS complexes. ICD activity can be suspended by applying a pacemaker magnet over the ICD in those circumstances where the ICD competes with manual interventions associated with the resuscitation.

Airway Management and Ventilation in Cardiac Arrest

Anesthesia providers know that ventilation is critical for ROSC and for organ preservation during cardiac arrest (also see Chapter 55). The AHA ACLS training program has effectively conveyed this treatment as a priority but after the initiation of chest compressions and with minimal interruption of chest compressions in accordance with the 2010 AHA Guidelines for CPR and ECC. The techniques for providing ventilation are dependent on the clinical situation. The head tilt–chin lift maneuver is recommended for initial airway control in most circumstances. The epiglottis, rather than the tongue, is the major cause of upper airway obstruction in the individual who is unconscious or sedated.[55] Because of its ligamentous attachments to the hyoid bone, the epiglottis can be lifted by manual maneuvers that anteriorly displace the hyoid bone. These observations provide anatomic confirmation of the efficacy of the head tilt–chin lift technique for opening an obstructed airway. The head tilt–jaw thrust maneuver accomplishes the same purpose in restoring airway patency.[56]

When rescue breathing is indicated for an individual in tracheal nonintubated cardiac arrest, 2 breaths are delivered after 30 chest compressions during one- and two-person CPR, providing that the rescuer(s) is(are) trained in CPR.[24] The 2010 AHA Guidelines for CPR and ECC excuse untrained rescuers from providing rescue breaths to ensure that uninterrupted chest compressions are provided until more qualified rescuers arrive. (Fig. 108-5).[24] When performed, rescue breaths should be provided with only enough force and volume to cause the chest to rise. Chest compressions are only minimally interrupted for the provision of rescue breaths (until a secure airway is established). Excessive ventilation force or tidal volume risks overcoming the esophageal opening pressure, contributing to gastric inflation,[57] the potential for regurgitation, and its consequences.[58,59] If tracheal intubation is performed, then ventilation can occur at a rate of 8 to 10 breaths per minute with small tidal volumes and without interrupting chest compressions. Optimal tidal volumes or respiratory rates in the setting of cardiac arrest are not known.

During the first few minutes after the onset of cardiac arrest, chest compressions are the priority intervention, unless the cardiac arrest is due to asphyxiation, drowning, or suffocation, which are the only circumstances that ventilation must be provided before chest compressions.[24] Oxygen delivery to tissues with CPR is limited more by blood flow and low cardiac output than arterial content.[60] Low cardiac output associated with CPR results in low oxygen uptake from the lungs that, in turn, reduces the need to ventilate the patient during this low flow state.[60] Rescuers must avoid hyperventilation during resuscitation. The increased intrathoracic pressure from ventilation impedes venous return to the heart, decreases cardiac output, and compromises resuscitation efforts.[61]

Advanced airway placement during cardiac arrest is no longer a priority and is not mandated in the 2010 AHA Guidelines for CPR and ECC.[61] Attempting to place endotracheal intubation frequently causes significant interruptions in chest compressions, particularly when the provider undertaking intubation is inexperienced or lacks proficiency with the intervention. Insufficient evidence demonstrates improved ROSC when an endotracheal tube is placed. However, in a large retrospective study of a 25,000 in-hospital cardiac arrest database, an endotracheal tube placed during the first 5 minutes of cardiac arrest resuscitation did not improve the rates of ROSC but was associated with an improved 24-hour survival.[62]

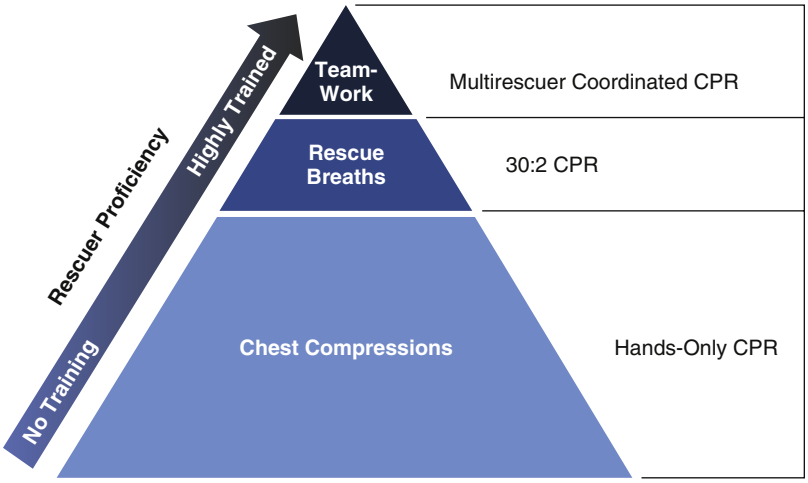


Figure 108-5. Building blocks of cardiopulmonary resuscitation (CPR). *(From Travers AH, Rea TD, Bobrow BJ, et al: Part 4: CPR overview: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,* Circulation *122(18 Suppl 3): S678, 2010.)*

Those not proficient or experienced with endotracheal intubations should focus on proficiency with bag-valve-mask ventilation or placement of a supraglottic airway.

Supraglottic airways (e.g., laryngeal mask airway, King LT [laryngeal tube] Airway) are considered reasonable tools for advanced airway management in both out-of-hospital and in-hospital settings. These devices do not require visualization of the glottic opening and are inserted without interrupting chest compressions. Although, in most circumstances, supraglottic airways provide an open airway and effective ventilation, the airway is not secured in a fashion equivalent to an endotracheal tube; a cuffed tube is not placed in the trachea, protecting the airway from aspiration. Supraglottic airways are not equivalent to a properly placed endotracheal tube. They are reasonable airways for rescuers without advanced airway management expertise, as well as for those circumstances during which endotracheal intubation is found to be difficult. Partial pressure of end-tidal carbon dioxide ($PetCO_2$) can be monitored when supraglottic airways are in place, the importance of which is discussed in the next section.

Once an advanced airway is inserted, its placement must be confirmed by verification of breath sounds, chest rise, and the presence of carbon dioxide during ventilation. These parameters are assessed with each airway manipulation in elective surgical cases and represent a standard of care in the anesthesia environment. These parameters—breath sounds, chest rise, and the presence of carbon dioxide—are applicable and, because of the unstable and high-risk environment (either out-of-hospital or in-hospital) of a cardiac arrest, are mandatory assessments when an airway is placed outside the surgical department environment. Continuous monitoring of $PetCO_2$ is recommended during resuscitation attempts to ensure that the airway placement is secure, to guide compression quality, and to detect ROSC as demonstrated by a sudden increase in end-tidal carbon dioxide content.

In 1978, Kalenda[63] described the use of capnography as a guide to the effectiveness of external chest compressions. He demonstrated the value of monitoring $PetCO_2$ values in three patients in cardiac arrest and confirmed changes in $PetCO_2$ with ROSC. Kalenda proposed that when ventilation is constant, as during controlled mechanical ventilation, the expired carbon dioxide is a precise and continuous mirror of lung perfusion and, hence, of cardiac output.[63]

Despite the potential clinical importance of Kalenda's well-documented observations and conclusion, it was several years before monitoring $PetCO_2$ values during cardiac arrest and CPR was explored further. In 1984, using a porcine model of cardiac arrest, Grundler and colleagues[64] demonstrated a rapid decrease in $PetCO_2$ with the onset of cardiac arrest and its immediate increase with resuscitation. Based on these preliminary experimental observations, this group suggested that $PetCO_2$ monitoring may be a relatively simple and noninvasive guide to advanced life support interventions during CPR.[64,65] Severe reductions in pulmonary blood flow during cardiac arrest and CPR and therefore an acute failure in oxygen delivery to the lungs explained the observed very low $PetCO_2$ values and the increased partial pressure of carbon dioxide in mixed venous blood (Pv_{CO_2}).[66] Subsequent studies in dogs provided confirmation of the possible utility of $PetCO_2$ in that expired Pv_{CO_2} correlated very closely with coronary perfusion pressure, which itself was shown to be a determinant of survival from cardiac arrest in this model.[67,68] In a porcine model of VF, the onset of VF was associated with a rapid decline in $PetCO_2$ from a mean (plus or minus standard error of the mean [±SEM]) of 4.0% ± 0.2% to less than 0.7% ± 0.2%.[69] With external chest compression and constant-volume mechanical ventilation, $PetCO_2$ increased to 1.9% ± 0.3% with an immediate increase to 4.9% ± 0.3% after successful defibrillation and 12 minutes of CPR after defibrillation. Close correlation was found between changes in cardiac output and $PetCO_2$ during both closed- and open-chest CPR[69] (Table 108-2).

$PetCO_2$ monitoring has been reported in humans in cardiac arrest who are undergoing CPR.[17,70-73] In a study of 10 patients in whom spontaneous circulation returned, $PetCO_2$ values immediately increased on restoration of spontaneous circulation, from a mean (±SD) of 1.7% ± 0.6% to 4.6% ± 1.4%.[55] The rapid increase in $PetCO_2$ was often the first clinical evidence of the resumption of spontaneous circulation. In a larger retrospective study involving 575 patients, Heradstveit and colleagues[73] reported the value of $PetCO_2$ included 100% sensitivity and 100% specificity in identifying endotracheal tube positioning in the larynx, an indication of the effectiveness of chest

TABLE 108-2 END-TIDAL CARBON DIOXIDE IN CARDIOPULMONARY RESUSCITATION

	$PetCO_2$ (mm Hg)					
	With ROSC			Without ROSC		
Patients	*No. of Patients*	*Mean ± SD*	*95% CI*	*No. of Patients*	*Mean ± SD*	*95% CI*
All						
1 minute	14	23.0 ± 7.4	18.7-27.3	13	13.2 ± 14.7	10.4-16.1
2 minutes	12	26.8 ± 10.8	20.0-33.7	12	15.4 ± 5.7	11.8-19.0
Maximum during CPR	14	30.8 ± 9.5	25.3-36.3	13	22.7 ± 8.8	17.4-28.0
Ventricular fibrillation						
1 minute	8	24.3 ± 6.8	18.5-30.0	5	12.0 ± 4.2	6.8-17.2
2 minutes	6	28.2 ± 11.4	16.2-40.1	5	12.4 ± 4.3	7.0-17.8
Maximum during CPR	8	33.0 ± 10.2	24.5-41.5	5	20.6 ± 11.1	6.8-34.4

CI, Confidence interval; *CPR*, cardiopulmonary resuscitation; *$PetCO_2$*, partial pressure of end-tidal carbon dioxide; *ROSC*, restoration of spontaneous circulation; *SD*, standard deviation.

Adapted from ECC Committee, Subcommittees, Task Forces of the American Heart Association: 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, Circulation *112 (24 Suppl):IV1-IV203, 2005.*

compressions, and the early detection of ROSC. Although the authors noted that patients resuscitated from cardiac arrest had higher $PetCO_2$, they caution against "cut-off values" for predicting ROSC since many factors were noted that influenced $PetCO_2$ (e.g,. cause of cardiac arrest, rescuer fatigue, duration of resuscitation).

In 10 patients who were critically ill, 9 of whom were in septic or cardiogenic shock at the onset of cardiac arrest, $PetCO_2$ decreased from a mean (±SD) of 1.7% ± 0.9% to 0.4% ± 0.4% shortly after the onset of cardiac arrest.[57] The very low pre-arrest value is indicative of low cardiac output and therefore low pulmonary blood flow. During external chest compression, this value increased to 1.0 ± 0.5%. In seven patients in whom circulation was restored, $PetCO_2$ rapidly increased from 1.3% ± 0.5% to 3.7% ± 2.1% and then declined to a stable volume of 2.4% ± 1.8% 4 minutes after resumption of spontaneous circulation. In patients with whom resuscitation failed to restore spontaneous circulation, $PetCO_2$ remained at 0.7% ± 0.4%.

The major determinants for $PetCO_2$ are carbon dioxide production, alveolar ventilation, and pulmonary blood flow.[61-64]

In the presence of constant-volume ventilation and apparently unchanged carbon dioxide production immediately after cardiac arrest, the changes in $PetCO_2$ observed both experimentally and clinically during cardiac arrest and CPR and during ROSC indicate that $PetCO_2$ reflects pulmonary blood flow and cardiac output.[17,70-72,74] Monitoring of both systemic arterial pressure by invasive monitoring and $PetCO_2$ with controlled ventilation should provide optimal hemodynamic assessment of the adequacy of the resuscitative effort. Assessment of both interventions, such as chest compression and the response to resuscitative medications, is also possible.[75]

Monitoring $PetCO_2$ values is a standard in anesthesia and intensive care settings (also see Chapter 44). The 2010 AHA Guidelines for CPR and ECC now endorse this monitoring technology as a class I recommendation for adults with SCA with an endotracheal tube or supraglottic airway in place. This technology has become available and is more reliable in the out-of-hospital setting and should be used whenever possible to ensure proper tracheal tube placement, as well as the detection of ROSC or monitoring effectiveness of chest compressions.[61]

ADVANCED CARDIAC LIFE SUPPORT

All physicians, particularly those involved with invasive procedures in which sedation or anesthesia is administered, should be capable of performing CPR and other resuscitative interventions. CPR almost invariably necessitates rapid progression to ACLS interventions and follow-up care. Biannual or even annual maintenance of certification in both BLS and ACLS is expected for physicians in clinical practice, ensuring up-to-date compliance with updated AHA resuscitation guidelines.

In a study using a computer program that simulates critical patient incidents such as cardiac arrest, only 30% of participants, who consisted of anesthesiology residents, faculty, and private practitioners, managed a simulated cardiac arrest in accordance with AHA ACLS guidelines.[76] The timing since the last ACLS training was recognized as an important predictor for the proper management of simulated cardiac arrest. Of those trained in ACLS within 6 months preceding the assessment, 71% successfully managed cardiac arrest scenarios and in accordance with AHA ACLS guidelines. Successful management decreased to 30% in those whose ACLS training occurred 6 months to 2 years earlier. No participant more than 2 years without ACLS training correctly used ACLS guidelines in the simulated resuscitation.[76] Skills, such as time to first defibrillation, defibrillation sequence, tracheal intubation, and administration of medications, decline in the first 6 months after ACLS training. These observations support the position that some form of periodic training and retraining in ACLS is necessary to maintain proficiency in the knowledge and skills that are essential for managing cardiac arrest in accordance with the contemporary principles as incorporated in the AHA ACLS training programs.

Monitoring and Recognition of Arrhythmia

Prompt recognition and treatment of potentially life-threatening (pre-arrest) cardiac arrhythmias are essential components of ACLS. Early recognition and immediate

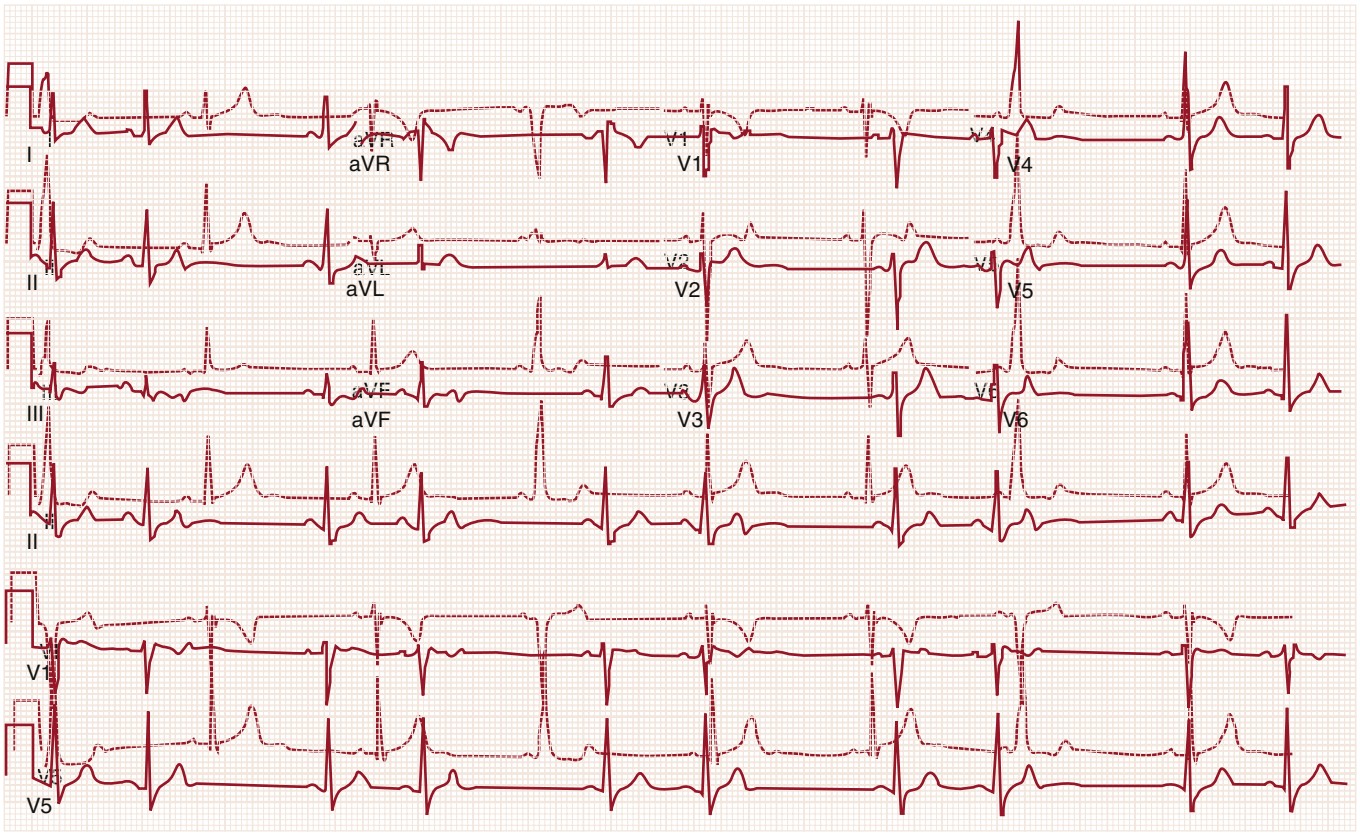


Figure 108-6. Sinus bradycardia with blocked premature atrial complexes.

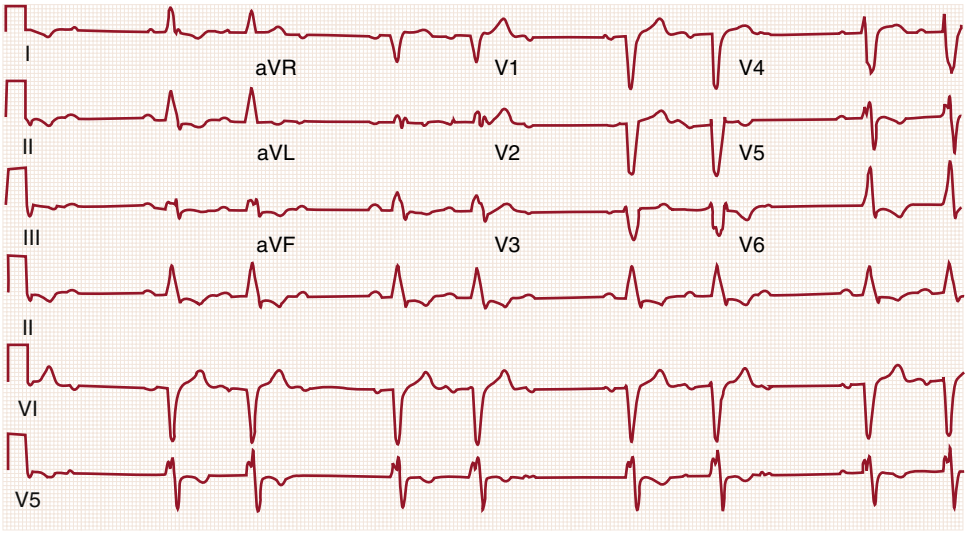


Figure 108-7. Normal sinus rhythm with first-degree atrioventricular blockade with Mobitz first- and second-degree heart block.

intervention for precardiac arrest signs and symptoms often prevents the onset of fatal arrhythmias, necessitating the application of BLS and ACLS. In this context, supraventricular arrhythmias that may cause hemodynamic compromise are discussed first, followed by the recognition and management of those that are ventricular in origin (also see Chapters 45, 47, and 48).

Supraventricular Bradyarrhythmias

Supraventricular bradyarrhythmias may be sinus or junctional in origin (Fig. 108-6), or they may be caused by second-degree (types I and II) (Figs. 108-7 and 108-8) or third-degree atrioventricular (AV) block (Fig. 108-9). Sinus (or junctional) bradycardia and type I (AV nodal) second-degree block are usually manifestations of increased vagal tone. Sinus bradycardia and type I second-degree AV block (Wenckebach phenomenon) may be observed during high-dose narcotic anesthesia.

During spinal anesthesia, reduced venous return and unopposed vagal tone may produce bradycardia and hypotension of sufficient severity to progress to cardiac arrest. Treatment is indicated whenever the bradycardia, regardless of the type, leads to a significant decrease in systemic arterial pressure, produces clinical

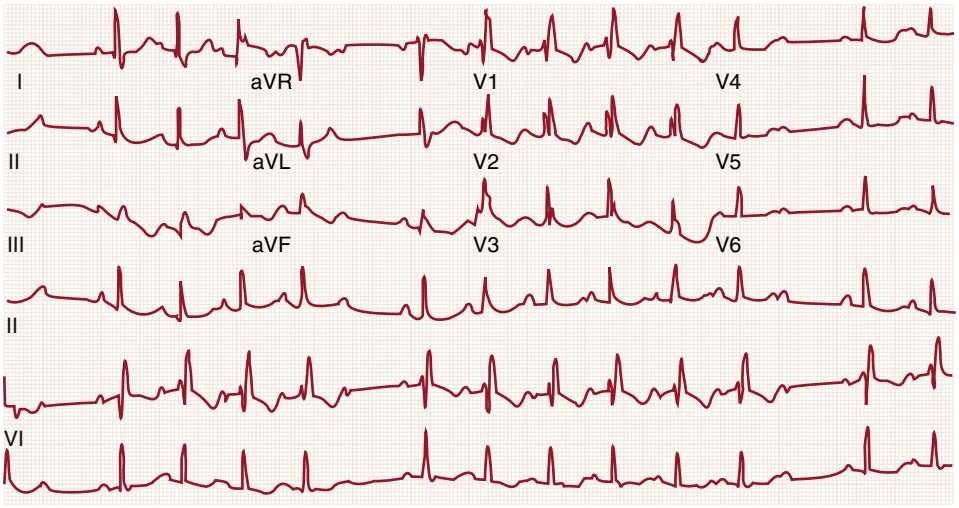


Figure 108-8. Sinus tachycardia with Mobitz II heart block and right bundle branch block.

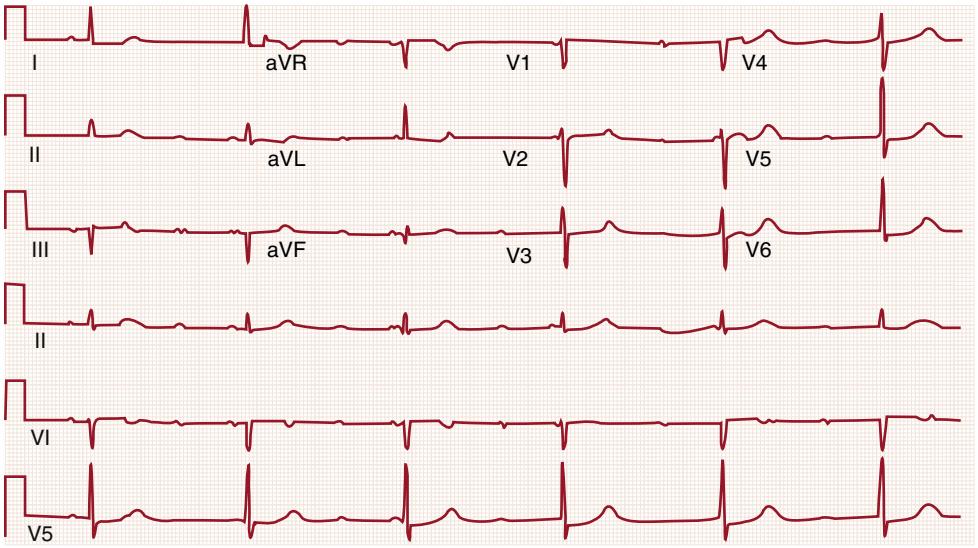


Figure 108-9. Type 3 complete heart block with sinus tachycardia and junctional escape rhythm.

signs of reduced cardiac output (or a decrease in measured output), or is accompanied by ventricular ectopic depolarization. Any of these signs should be considered as evidence of hemodynamic or electrophysiologic deterioration with the propensity to progress to lethal arrhythmias, either asystole or VF. IV atropine 0.5 to 1.0 mg should be the initial treatment, repeated as needed at 3- to 5-minute intervals to a total dose of 3 mg.[61] Atropine doses less than 0.5 mg in adults are associated with paradoxical slowing of the heart rate and should be avoided.[61]

The administration of atropine for symptomatic bradycardia should be accompanied by the application of transcutaneous pacing (TCP) pads. TCP for symptomatic bradyarrhythmias is painful for conscious patients and should be viewed as a temporizing measure, without strong clinical evidence supporting its use over pharmacologic interventions.[61] When bradyarrhythmias are refractory to atropine and TCP, IV infusions of dopamine (2 to 10 μg/kg/min) or epinephrine (2 to 10 μg/min) should be considered.

If pharmacologic methods and TCP are ineffective in producing an increase in heart rate and hemodynamic (increased systemic pressure, cardiac output, or both) or electrophysiologic improvement (elimination of ventricular ectopy), then alternative therapies include transvenous pacing or, during spinal anesthesia, low-dose (0.2 mg) IV epinephrine.[77,78] The availability of intraoperative cardiac pacing equipment (e.g., esophageal pacing probes, pacing pulmonary artery catheters) has diminished the need for agents such as isoproterenol infusions for the treatment of intraoperative bradyarrhythmias (also see Chapters 48 and 68).

Transesophageal atrial pacing can be effective in treating intraoperative supraventricular bradyarrhythmias such as sinus or junctional bradycardia.[79,80] This device is compatible with most external pacing devices and defibrillators. In its current configuration, transesophageal pacing is only effective at pacing the atria. Ventricular response to transesophageal pacing requires an intact AV node. Atrial fibrillation or AV conduction disturbances render this intervention ineffective in the treatment of symptomatic bradyarrhythmias.

Figure 108-10[61] depicts the bradyarrhythmias treatment algorithm recommended in the 2010 AHA Guidelines for CPR and ECC.

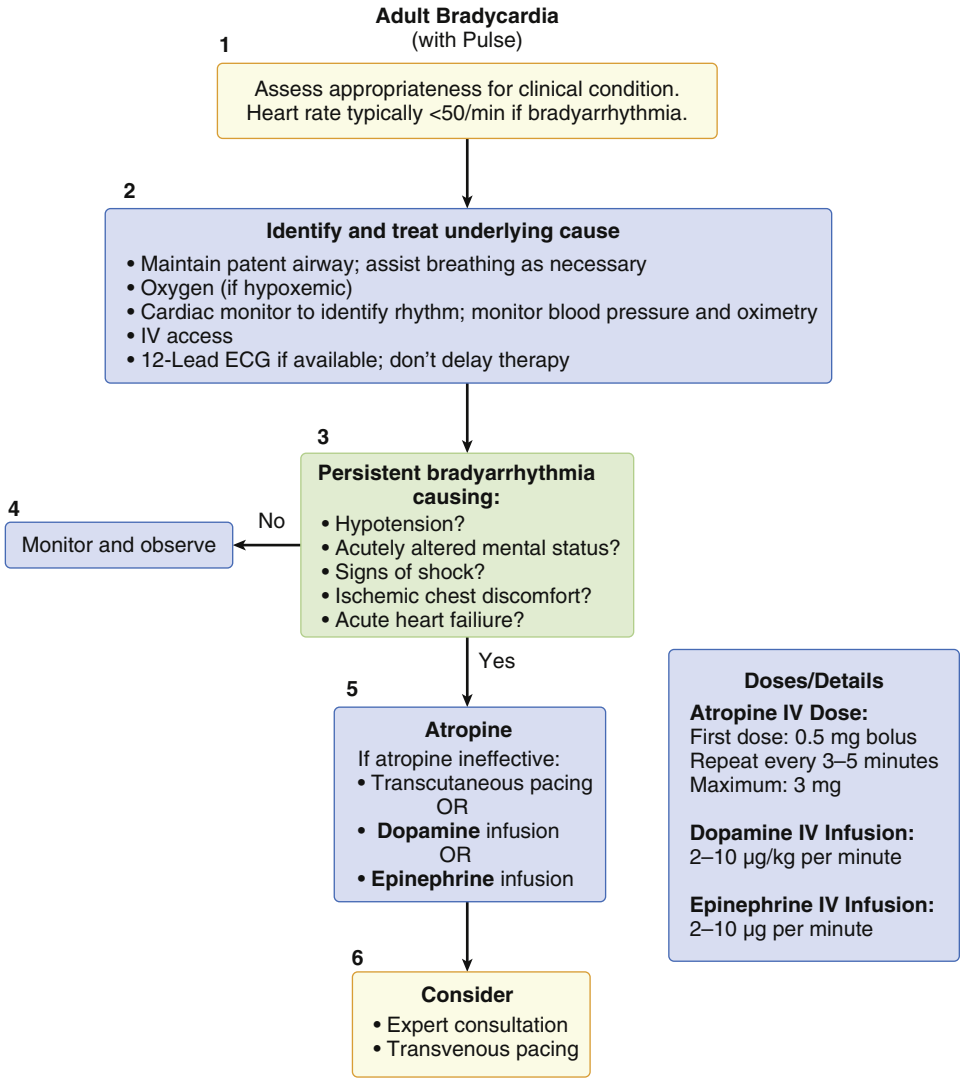


Figure 108-10. 2010 American Heart Association bradyarrhythmia treatment algorithm. *ECG*, Electrocardiogram; *IV*, intravenous. *(From Neumar RW, Otto CW, Link MS, et al: Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,* Circulation *122(18 Suppl 3):S749, 2010.)*

Supraventricular Tachyarrhythmia

Medical professionals should be able to recognize and differentiate between sinus tachycardias, narrow complex supraventricular tachyarrhythmias, and wide complex tachycardias. Supraventricular tachyarrhythmias include atrial flutter, atrial fibrillation, AV junctional tachycardia, multifocal atrial tachycardia, paroxysmal reentrant tachycardia, and other much less frequent arrhythmias (also see Chapter 68). Paroxysmal supraventricular tachycardia (PSVT), atrial fibrillation (or flutter) with rapid ventricular rates and multifocal atrial tachycardia are discussed; not only can they produce hemodynamic compromise, but they can also present diagnostic and therapeutic challenges. Considering the complexity of rhythm analysis and the implications for prompt intervention, two broad concepts are helpful: most wide complex tachycardias are ventricular in origin, and irregular narrow complex tachycardias are likely atrial fibrillation or multifocal atrial tachycardias. Figure 108-11[61] depicts the tachycardia treatment algorithm recommended in the 2010 AHA Guidelines for CPR and ECC.

An example of PSVT is shown in Figure 108-12, *A*. If such a tachyarrhythmia produces hemodynamic deterioration, then cardioversion is the treatment of choice. The recommended initial dose for cardioversion of atrial tachyarrhythmias is 100 J to 200 J if a monophasic defibrillator is used or 100 J to 120 J using a biphasic device. Energy can be increased as needed if the arrhythmia is resistant to initial electrical therapy. If the patient is hemodynamically stable, then vagal maneuvers can be attempted (e.g., Valsalva maneuver in awake patients) before initiating pharmacologic interventions. Vagal maneuvers alone will terminate approximately 20% to 25% of reentry supraventricular tachycardias (SVTs).[81] If vagal maneuvers are unsuccessful, then adenosine is the drug of choice for terminating organized rapid supraventricular arrhythmias. Adenosine slows sinoatrial and AV nodal conduction and prolongs refractoriness, which is very effective in terminating PSVT, the most common cause of which is reentry within the AV node.[82-85] The drug is diagnostically useful in revealing the underlying mechanism in tachyarrhythmias of uncertain origin (e.g., atrial fibrillation, atrial flutter) by inducing transient block of AV nodal conduction (Fig. 108-12, *B*).[86,87] Because of rapid cellular uptake and metabolism, adenosine must be rapidly injected into a venous catheter proximal enough to the heart to ensure

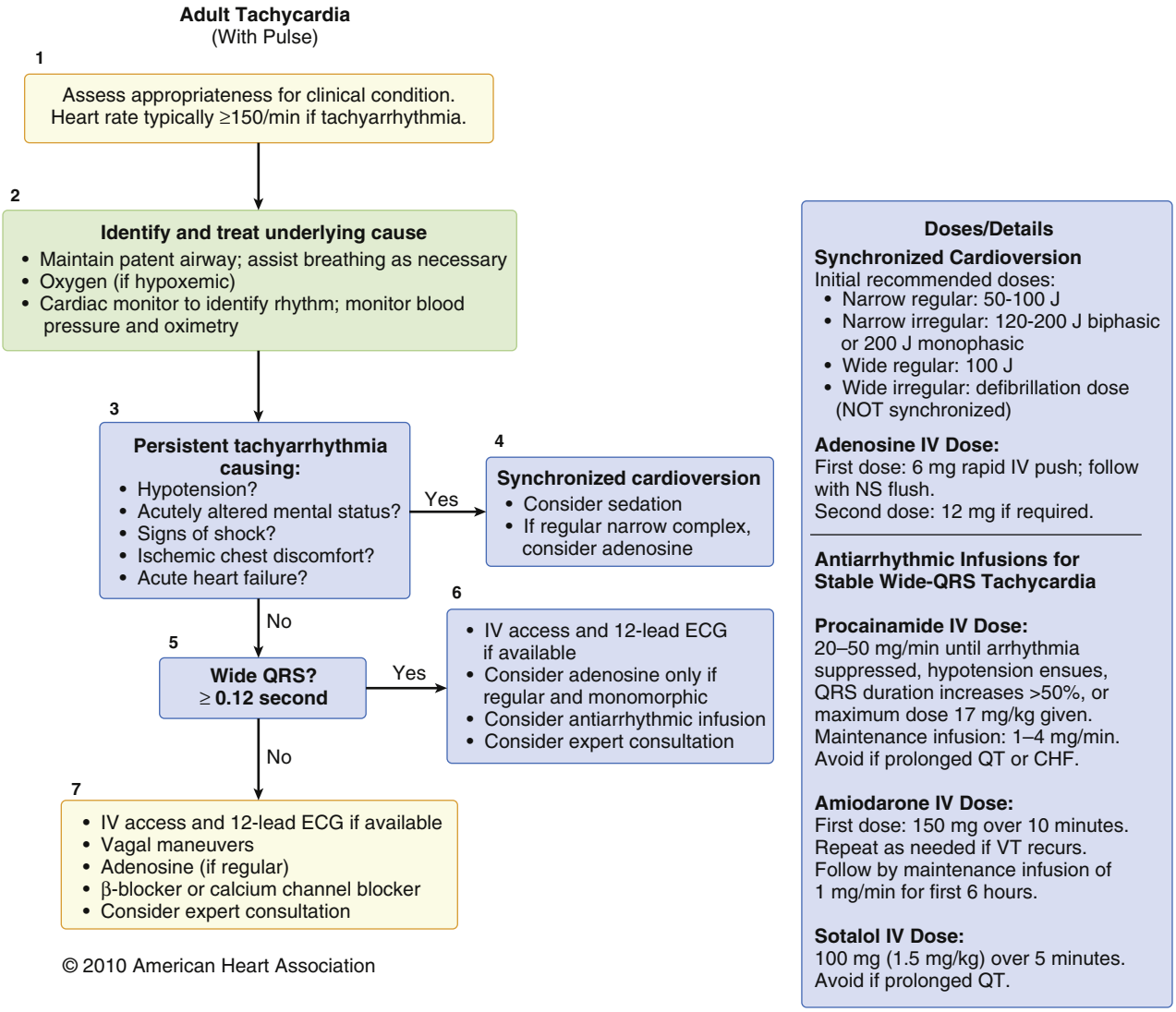
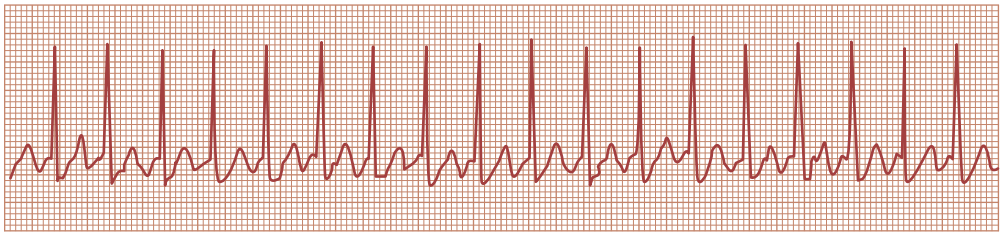
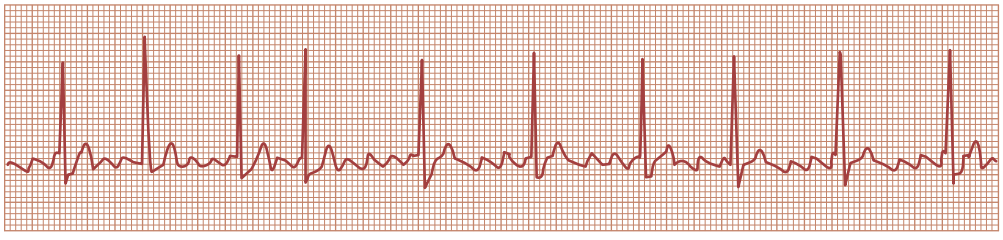


Figure 108-11. 2010 American Heart Association tachyarrhythmia treatment algorithm. *CHF*, Congestive heart failure; *ECG*, electrocardiogram; *IV*, intravenous; *NS*, normal saline; *VT*, ventricular tachycardia. *(From Neumar RW, Otto CW, Link MS, et al: Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,* Circulation *122(18 Suppl 3):S751, 2010.)*



A



B

Figure 108-12. A, Supraventricular tachycardia at a rate of 180 beats per minute is present; the origin of the tachycardia is not evident. **B,** Supraventricular tachycardia after an injection of 6 mg adenosine. Atrial flutter waves are clearly visible, thus establishing the diagnosis.

delivery of a sufficient concentration of the drug at the AV node to induce an AV nodal conduction block. Adenosine can be initially used in a dose of 6 mg, and, if necessary, a second dose of 12 mg can be administered in 1 to 2 minutes. If a central venous catheter is used, then these doses can be reduced to 3 mg and 6 mg, respectively. If the drug is injected more distally and slowly (e.g., into a small-bore dorsal hand vein catheter), not only may therapeutic failure result, but transient acceleration of the tachyarrhythmia may also occur (Fig. 108-13, *A-B*).[88] This paradoxical acceleration of the rate is a manifestation of the increase in sympathetic nervous system traffic induced by adenosine in the presence of inadequate AV nodal blockade. Likewise, conversion of 2:1 or 1:1 conduction in atrial flutter has been observed.[89-91] This adverse effect indicates that an attempt to establish the diagnosis of atrial flutter should be electrophysiologically made, with vagal maneuvers used, if necessary, to unmask the flutter waves. Rate acceleration has also been observed after adenosine administration to patients with atrial fibrillation and preexcitation (Wolff-Parkinson-White syndrome).[91] As with verapamil in this setting, the rate acceleration is a result of the AV nodal block with diversion of fibrillation wave fronts through the accessory connection. Although the short half-life of adenosine may reduce this hazard, avoiding adenosine, as well as other AV node-blocking drugs, seems prudent in patients with atrial fibrillation and preexcitation. Immediate access to a defibrillator is recommended when adenosine is administered for tachyarrhythmias.

Adenosine's very short half-life (<5 seconds) is both advantageous and disadvantageous: side effects such as flushing, dyspnea, and chest pain are short lived, but the tachyarrhythmia may recur and necessitate the use of another drug or a repeat dose of adenosine. The AV nodal-blocking action of adenosine is antagonized by theophylline or related methylxanthines and is potentiated by dipyridamole and carbamazepine.[92,93] A suggested scheme for the use of adenosine, including dose adjustments, is presented in Box 108-3.

Bronchospasm has been described after the injection of adenosine, including intraoperatively.[94-97] This complication has occurred in patients with bronchial asthma or chronic obstructive pulmonary disease (COPD). The mechanism is unknown, but the bronchospasm may result from the stimulation of bronchial smooth muscle adenosine receptors or the stimulation of mast cell–derived mediators of bronchoconstriction. Aminophylline, an adenosine-receptor antagonist, has been successfully used intraoperatively to treat adenosine-induced bronchospasm.[97] In light of this experience, adenosine should not be used or should be used with caution in patients with a history of bronchial asthma or COPD with a bronchospastic component.

If the PSVT does not respond to adenosine or if it recurs, then verapamil is the drug of choice. A dose of 5 mg produces a more sustained block of AV nodal conduction. Verapamil can also be used to slow the ventricular response in atrial fibrillation or flutter.[98] However, it should not be used in patients with Wolff-Parkinson-White syndrome in whom atrial fibrillation or flutter develops. In this setting, verapamil-induced increases in conduction over the accessory pathway may produce alarming acceleration of the ventricular rate or VF.[99,100] If atrial flutter or fibrillation results in hemodynamic deterioration because of the rapid ventricular response, then cardioversion is the treatment of choice. Atrial flutter can be terminated with low-energy synchronized shocks.

Atrial flutter or fibrillation with a rapid ventricular response can cause rate-related hemodynamic compromise perioperatively expressed as hypotension, decreased

BOX 108-3 ***Administration of Adenosine****

Peripheral (antecubital)	6 mg, then 12 mg if needed
Central	3 mg, then 6 mg if needed
If taking theophylline-containing drugs	9 mg peripherally, 6 mg centrally
If taking dipyridamole	2 mg peripherally, 1 mg centrally

*Use with caution in patients with asthma and in those taking carbamazepine.

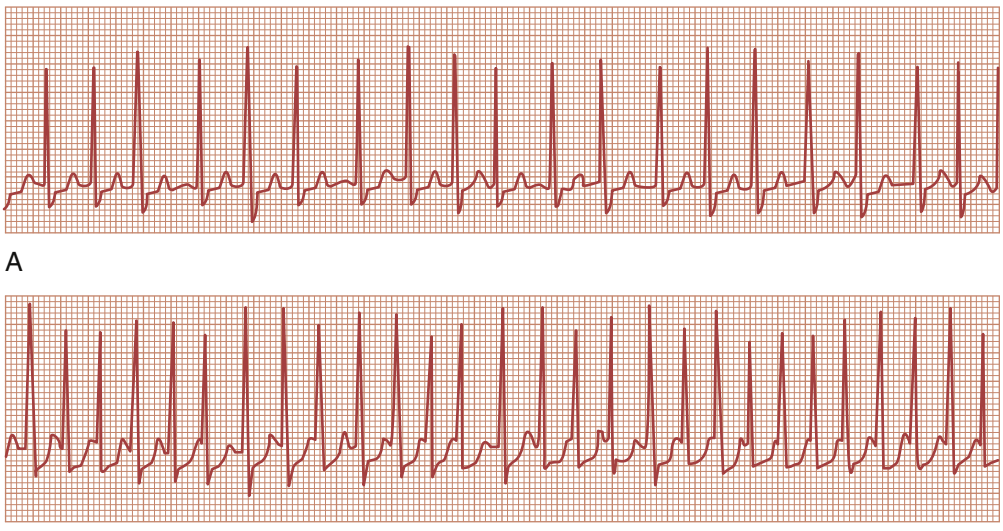


Figure 108-13. A, Atrial fibrillation with a rapid ventricular response of 190 beats per minute. **B,** After an injection of 6 mg adenosine, the ventricular response increased to 240 beats per minute. *(From White RD: Acceleration of the ventricular response in paroxysmal lone atrial fibrillation following the injection of adenosine, Am J Emerg Med 11:245, 1993.)*

cardiac output, or both. In patients who are hemodynamically unstable, cardioversion should be used. Recent-onset atrial flutter is typically very sensitive to low-energy shocks (e.g., 50 J, monophasic or biphasic waveforms). Atrial flutter can also be terminated by overdrive pacing with external generators that have this capability. For atrial fibrillation, the initial dose for cardioversion is 100 to 200 J with monophasic waveforms or 100 J to 120 J with biphasic waveforms. Escalation of energy doses for the second and subsequent doses is indicated.

In patients who are hemodynamically stable and with rapid ventricular rates secondary to atrial fibrillation or flutter, the treatment is pharmacologic. With the acute onset of these tachyarrhythmias, IV ibutilide has the most rapid onset of effect in restoring sinus rhythm.[101] Ibutilide is a class III antiarrhythmic drug that prolongs the action potential duration and effective refractory period without effects on the action potential upstroke. The dose is 1 mg given over a 10-minute period. A second dose can be administered 10 minutes after the first, if necessary. Conversion to sinus rhythm is more frequent in atrial flutter than in atrial fibrillation (63% versus 31%) and more frequent in atrial fibrillation of shorter duration.[101,102] Prolongation of the QT interval reflects the pharmacologic action of the drug, and polymorphic VT (PVT) accompanied by increases in the QT interval is seen in 8.3% of patients receiving ibutilide; consequently, clinicians should be prepared to manage this arrhythmia.

Alternative options for the treatment of supraventricular arrhythmias include diltiazem, verapamil, β-blocking medications, procainamide, and amiodarone. By slowing conduction and increasing refractoriness in the AV node, calcium channel blocking agents result in ventricular rate control in patients with atrial flutter, atrial fibrillation, and multifocal atrial tachycardia. Diltiazem is administered as a loading dose of 0.25 mg/kg over 2-minute period, followed, if needed, in 10 to 15 minutes by 0.35 mg/kg. An infusion at a rate of 5 to 15 mg/hr can be used to maintain rate control. If IV verapamil is used, 5 mg can be given and then 5 to 10 mg in 15 to 30 minutes as needed. β-Adrenergic-blocking medications are helpful in ventricular rate control when no contraindications to their use are present. Amiodarone is a complex agent with antiadrenergic effects in the presence of supraventricular arrhythmias and tachycardias resulting from accessory pathways or rapid AV node transmission of atrial impulses and in situations in which other agents have failed to control the heart rate. It is administered as a 150-mg IV bolus over a 10-minute period, followed by a 1 mg/min infusion for 6 hours to a maximum daily dose of 2 g. Although effective in terminating clinically significant SVTs, proarrhythmic agents (e.g., amiodarone, procainamide, sotalol, ibutilide) are less desirable first-line interventions, compared with adenosine and verapamil.

Multifocal (multiform) atrial tachycardia is a common tachyarrhythmia that is often misdiagnosed as atrial fibrillation.[103-105] Increased automaticity in multiple atrial foci results in a need for therapy different from that for reentrant supraventricular arrhythmias (e.g., atrial flutter, atrial fibrillation, PSVT). Multifocal atrial tachycardia is diagnosed by observing the presence of at least three morphologically different P waves in the same lead of a 12-lead electrocardiogram (ECG) and a ventricular rate more rapid than 100 beats per minute (Fig. 108-14).

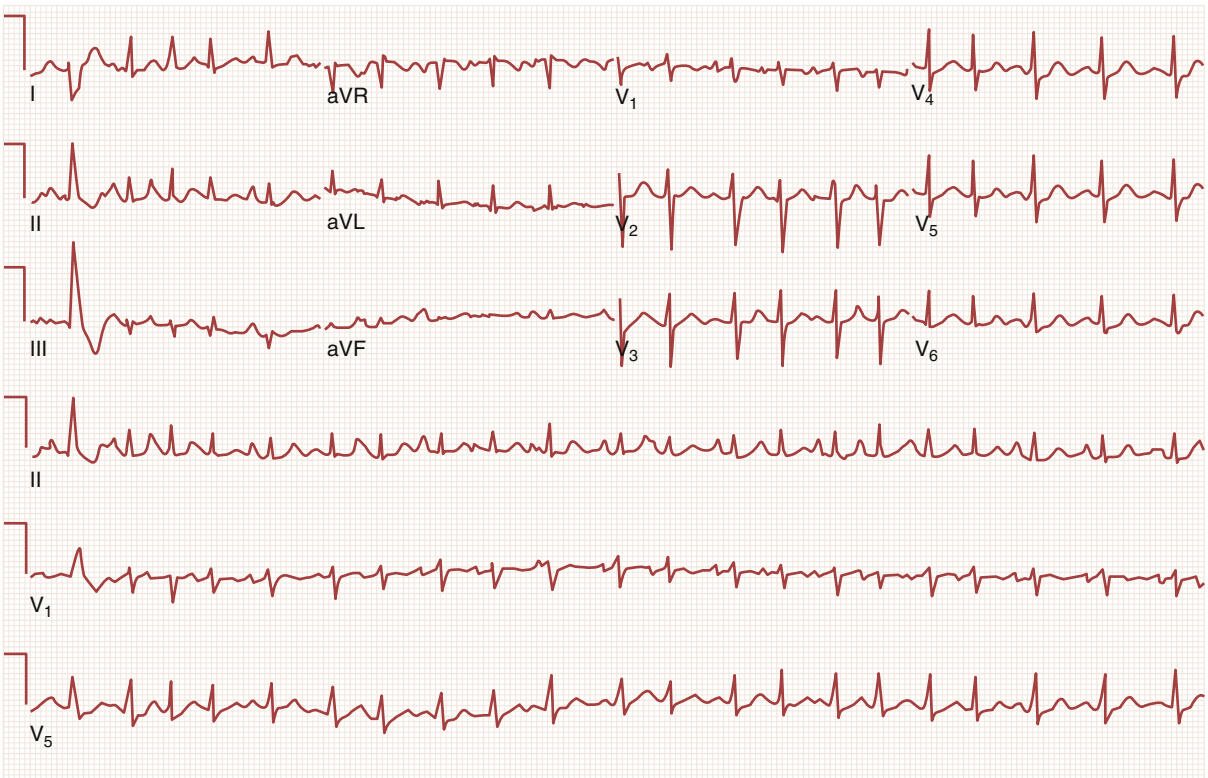


Figure 108-14. Multifocal atrial tachycardia. P-wave morphologic characteristics vary across the tracing. Each QRS complex is preceded by a single P wave.

Multifocal atrial tachycardia is usually described as occurring in patients with COPD, especially during exacerbations when ICU management is necessary. However, it occurs in other settings as well, such as hypokalemia, catecholamine administration, and acute myocardial infarction.[105,106] Treatment of underlying conditions probably contributing to myocardial irritability is important. Digitalization and cardioversion, sometimes helpful in other supraventricular arrhythmias, are ineffective in multifocal atrial tachycardia. Digitalis toxicity or repeated and futile attempts at cardioversion can follow misdiagnosis. Acceptable rate control treatment in patients with preserved ventricular function includes calcium channel blockers, beta-adrenergic blockers, and amiodarone. In the presence of impaired ventricular function, diltiazem and amiodarone may be useful.

Synchronized cardioversion is recommended for the treatment of unstable SVT, unstable atrial fibrillation with rapid ventricular response, unstable atrial flutter with rapid ventricular response, and unstable monomorphic VT.

Ventricular Bradyarrhythmias

In the setting of emergency cardiovascular care, the bradyarrhythmia arising within the ventricles that is in need of urgent treatment is complete heart block with a very slow idioventricular escape rhythm (e.g., 15 to 30 beats per minute) (Fig. 108-15). In this situation, atropine can be tried, but the treatment of choice is external or transvenous pacing as soon as it can be accomplished. If an external pacemaker is available, then pacing should be quickly instituted.

Ventricular (Wide Complex) Tachyarrhythmia

In the category of potentially life-threatening and sometimes pre-arrest arrhythmias, VT (Fig. 108-16) warrants urgent intervention. VT that produces cardiac arrest (pulseless VT) is discussed with VF. Treatable causes of VT should always be sought before or during pharmacologic or electrical interventions. Hypoxemia, hypercapnia, hypokalemia or hypomagnesemia (or both), digitalis

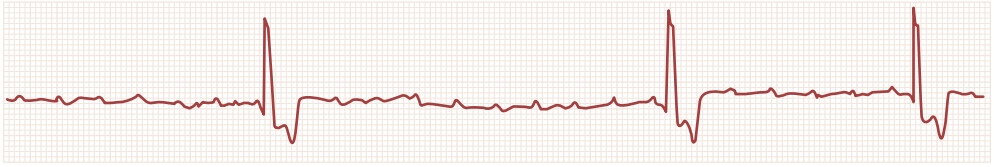


Figure 108-15. Slow (14 beats per minute) idioventricular escape rhythm in a patient with carotid sinus hypersensitivity. External or transvenous pacing is the treatment of choice for bradyarrhythmias such as this.

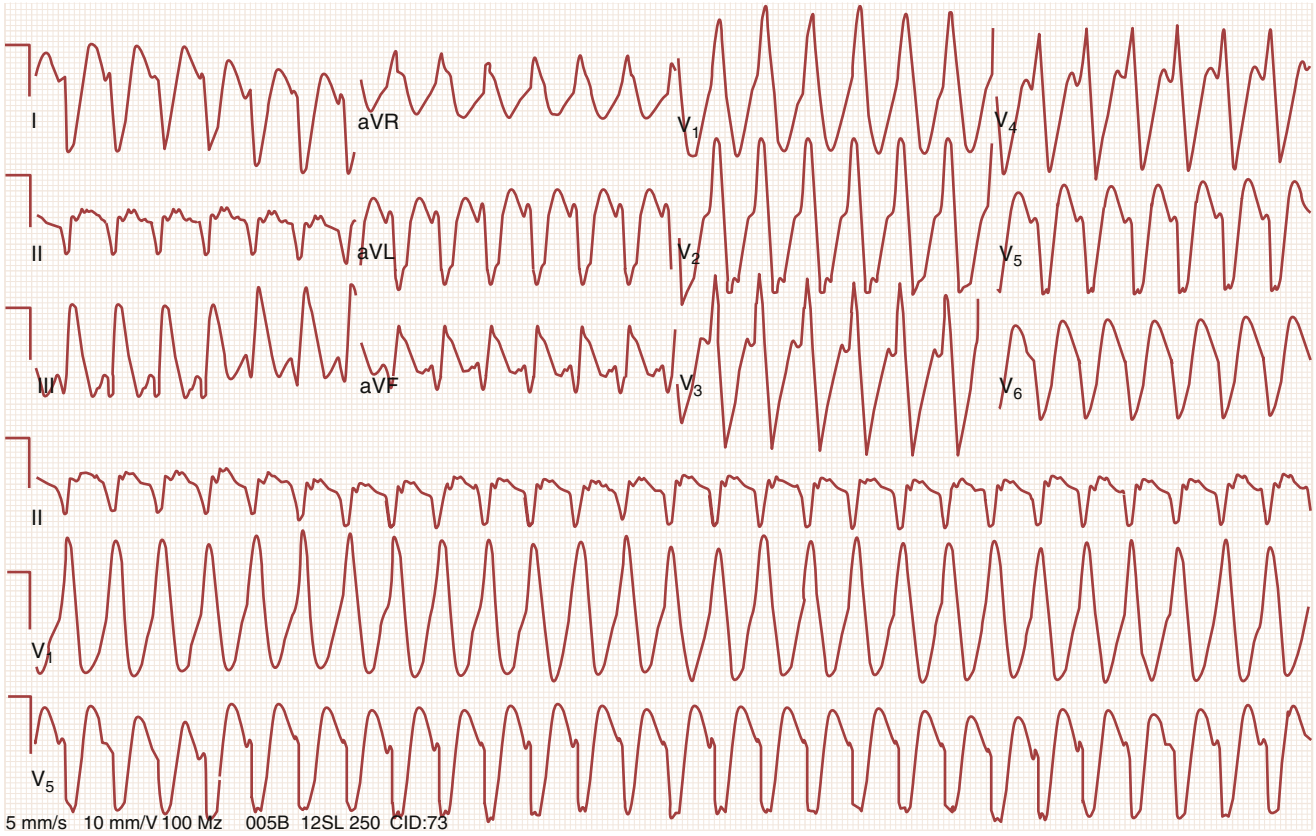


Figure 108-16. Ventricular tachycardia. The rate is 280 beats per minute, the QRS width is 160 msec, and three consecutive capture or fusion beats are demonstrated.

toxicity, and acid-base derangements are obvious causes for VT and should be quickly evaluated and corrected if present.

Treatment of VT is dependent on the degree of hemodynamic compromise induced by the tachycardia. If the patient remains stable and ventricular function is preserved (no evidence of pulmonary edema or a known history of left ventricular dysfunction), then procainamide and synchronized cardioversion are the treatments of choice. If cardioversion is chosen, then the energy levels are identical to those used in unstable patients. If antiarrhythmic therapy is pursued, procainamide (class IIa evidence), amiodarone (class IIb evidence), or sotalol (class IIb evidence) are recommended. Procainamide and sotalol should not be used in patients with prolonged QT intervals. Importantly, only one drug should be administered; a second drug should not be added without expert consultation. The loading dose for procainamide is 20 to 50 mg/min until the arrhythmia is suppressed, hypotension develops, the QRS prolongs by 50%, or a total dose of 17 mg/kg is administered. A maintenance dose of 1 to 4 mg/min should follow the loading dose. Sotalol can be loaded at a rate of 1.5 mg/kg over a 5-minute period. Amiodarone is administered as 150 mg over a 10-minute period, followed by an infusion of 1 mg/min for 6 hours and then a 0.5 mg/min maintenance dose over the subsequent 18-hour period. Hypotension is common with all three of these recommended medications.

In patients who are unstable, that is, those with systemic hypotension, pulmonary edema, or clinical or electrocardiographic signs of acute myocardial ischemia or infarction, synchronized cardioversion is the treatment of choice with either monophasic energy doses of 360 J or biphasic, nonescalating, impedance-compensated energy doses of 120 J (also see Chapter 47).

An atypical form of VT known as *torsade de pointes* ("twisting of the points") that was originally described in 1966 is characterized by twisting of the QRS axis around the baseline and a polymorphic appearance. The underlying electrophysiologic derangement in this arrhythmia is a striking and nonuniform delay in repolarization exhibited as a prolonged QT interval on the ECG. It typically begins with a characteristic long-short initiating sequence (Fig. 108-17). Torsades des pointes can be induced by drugs such as quinidine, procainamide, disopyramide, and phenothiazine, as well as by bradycardia, hypokalemia, hypomagnesemia, or acute ischemia or infarction. Although amiodarone produces significant prolongation of repolarization, it rarely causes torsades de pointes, possibly because the drug-induced prolonged repolarization is uniform (nondispersed), in contrast to the repolarization abnormality induced by other drugs.

Closely related to torsades de pointes is PVT (Fig. 108-18). The description of the tachycardia as PVT rather than torsades de pointes implies that the cause of the prolonged repolarization is not evident and the QT interval is not prolonged.[79,107-109] Because both PVT and torsade de pointes can be life threatening, a correct diagnosis is required. The critical therapeutic distinction is based on the presence or absence of a prolongation of the QT interval. If QT prolongation is present, then therapy is directed toward shortening the repolarization time (after withdrawing the offending drugs listed earlier or correcting abnormalities such as hypokalemia). In the past, drugs such as isoproterenol were used for this purpose, but definitive short-term therapy is overdrive ventricular or atrial pacing (preferably the latter) if AV conduction is intact.

If PVT (i.e., polymorphic wide complex tachyarrhythmia without evident QT prolongation) is present with hemodynamic instability, then immediate defibrillation is indicated. If PVT is present in a patient who is hemodynamically stable, then standard antiarrhythmic therapy for VT as outlined earlier can be tried. Magnesium sulfate should be considered early in the treatment of this form of PVT as well, particularly if torsades de pointes is suspected by history but QT prolongation cannot be confirmed by ECG. A 12-lead ECG is often needed to identify QT lengthening.

The 2010 AHA Guidelines for CPR and ECC provides a treatment algorithm for tachyarrhythmias (see Fig. 108-11) that encompasses those of both supraventricular and ventricular origin. The algorithm is simplified from previous versions to afford a more prompt and directed assessment and interventions.

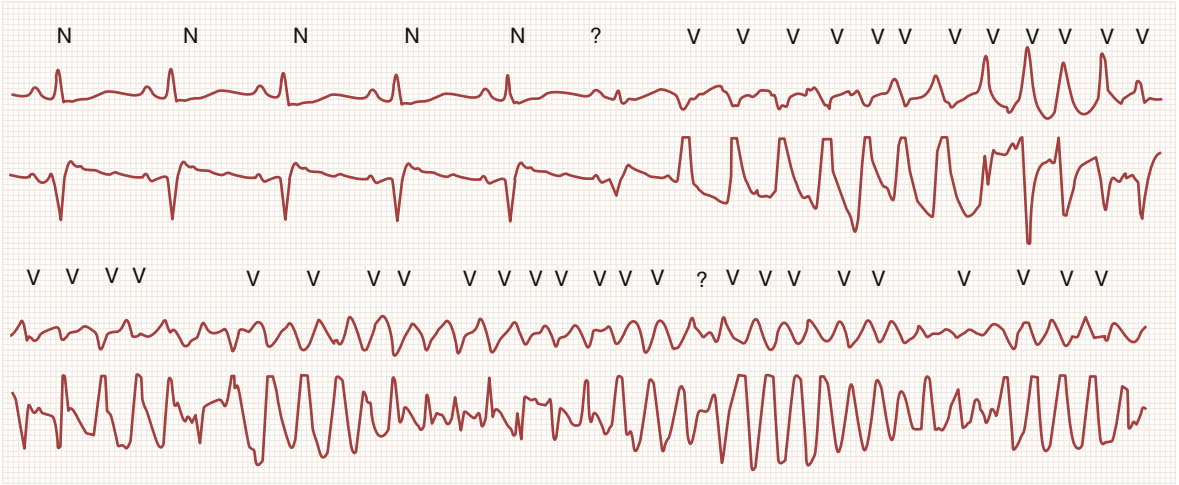


Figure 108-17. Polymorphic ventricular tachycardia. A prolonged QT interval during sinus rhythm suggests that the arrhythmia is torsades de pointes. This arrhythmia occurred in a patient after resuscitation from cardiac arrest.

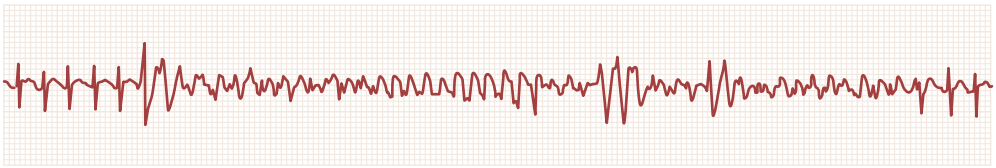


Figure 108-18. Polymorphic ventricular tachycardia. The QRS complexes have varying morphologic characteristics but without the "twisting of the points" torsades demonstrated in Figure 108-17. The tachycardia spontaneously terminated.*(From White RD, Wood DL: Out-of-hospital pleomorphic ventricular tachycardia and resuscitation: Association with acute myocardial ischemia and infarction, Ann Emerg Med 21:1282, 1992.)*

MANAGEMENT OF CARDIAC ARREST

This section reviews the interventions, both electrical and pharmacologic, used for treatment of the various forms of lethal cardiac arrhythmias (Fig. 108-19). A discussion of the major beneficial and adverse actions of the drugs used in ACLS is included. The clinical applications of some of these drugs have already been presented in the review of recognition and management before arrest or before potentially life-threatening events.

PULSELESS VENTRICULAR TACHYCARDIA OR VENTRICULAR FIBRILLATION

For therapeutic purposes, pulseless VT and VF are considered the same lethal entity in need of the same interventions, beginning with prompt defibrillation. Fortunately, these arrhythmias are the most treatable and yield the greatest likelihood of immediate and long-term survival in both in-hospital and out-of-hospital settings. Early defibrillation, not pharmacologic interventions, is responsible for the improved survival after VF cardiac arrest. As a result, PAD puts AEDs in public places so that defibrillation can occur at the earliest possible opportunity to individuals in cardiac arrest, regardless of rescuer training.

In operating rooms, ICUs, or other environments where continuous monitoring of cardiac rhythm is used and when a VT or VF arrest occurs, chest compressions should be immediately provided and defibrillation performed at the earliest opportunity. A period of chest compression before defibrillation is not recommended in the 2010 AHA Guidelines for CPR and ECC. If a monophasic defibrillator is available, then a single 360 J shock should be delivered. With biphasic defibrillators, biphasic truncated exponential waveforms should use 150 to 200 J for first shock, depending on the manufacturer's recommendation. Energy settings for rectilinear biphasic waveforms should use 120 J for the initial shock. For simplicity and improved decision-making during resuscitation efforts, if the rescuer is unfamiliar with the waveform used or the manufacturer recommendations, then the maximal available energy should be used as the default energy.[61] Chest compressions should be immediately resumed after the delivery of shock and continued for 2 minutes before reassessing the underlying cardiac rhythm, unless obvious evidence for ROSC occurs. The 2010 AHA Guidelines for CPR and ECC recommend three stacked shocks to be used only in the coronary catheterization laboratory or in the cardiac surgical operating rooms after weaning from cardiopulmonary bypass.[40,]

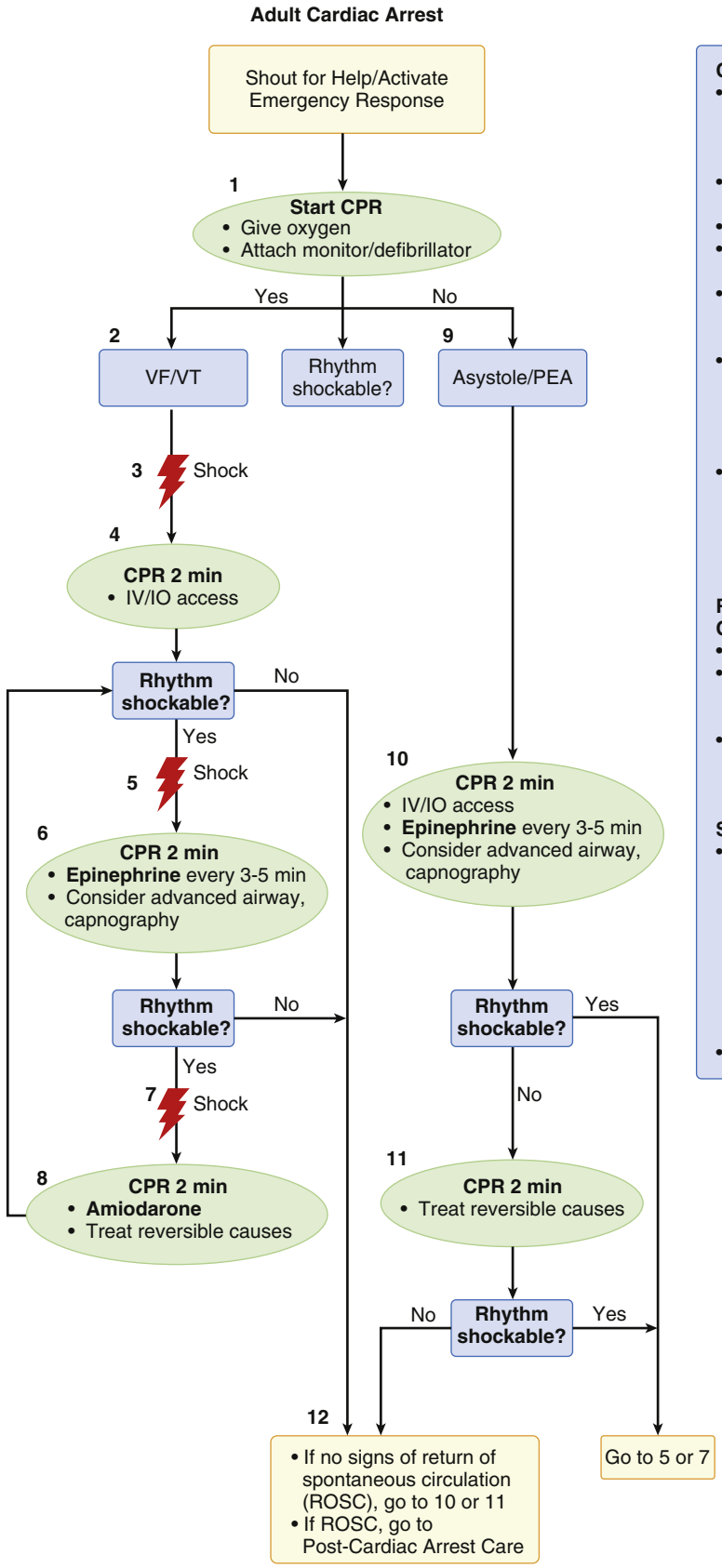
No evidence supports one biphasic waveform over another. All biphasic defibrillators available today are impedance compensated and adjust the delivered dose of energy in response to the measured transthoracic impedance (TTI) with each shock. (This technology has resulted in greater first-shock efficacy and is not used in monophasic defibrillators.) Defibrillation energies should be increased until VF is terminated or maximal defibrillator energy output is reached. In circumstances in which VT or VF is terminated with defibrillation but VT or VF recurs, defibrillation should use the previously successful energy level.

If ROSC has not occurred after an initial defibrillatory attempt, then five cycles of CPR consisting of 30 compressions to 2 ventilations should be performed before cardiac rhythm reanalysis. Placement of a supraglottic airway or endotracheal intubation can be considered in this interval. During this opportunity, peripheral IV access should be attempted if not already established.

VASOPRESSOR THERAPY IN CARDIAC ARREST

The 2010 AHA Guidelines for CPR and ECC de-emphasizes the use of medications in resuscitation attempts. Emphasis is placed on providing quality, uninterrupted chest compressions and defibrillation attempts every 2 minutes as needed for ongoing resuscitation efforts. Although epinephrine has been a mainstay of pharmacologic therapy in resuscitation efforts for many years, clinical evidence is lacking for improved survival and neurologic recovery after cardiac arrest when epinephrine is administered. Vasopressin and amiodarone are two other pharmacologic agents commonly administered during cardiac arrest. Just as with epinephrine, vasopressin and amiodarone lack convincing clinical evidence for improved hospital discharge and neurologic recovery when administered during resuscitation efforts. All three medications have demonstrated benefit in ROSC during cardiac arrest but no benefit on hospital discharge.

Epinephrine's benefit in cardiac arrest states arises from its potent α- and β-adrenergic stimulation effects, resulting from a 1 mg (10 mL of a 1:10,000 solution) IV dose. α_1– and α_2–receptor stimulation results in peripheral vasoconstriction, leading to increased aortic diastolic pressure. Increased aortic diastolic pressure improves coronary blood flow. The modest increase in aortic diastolic pressure might provide improved coronary blood flow during cardiac arrest or other low coronary blood flow states, resulting in ROSC. Epinephrine-induced β-adrenergic stimulation increases myocardial contractility. This consequence increases myocardial oxygen demand and probably further exacerbates subendocardial ischemia during the low-flow states of cardiac arrest (also see Chapter 16).



CPR Quality
- Push hard (≥2 inches [5 cm]) and fast (≥100/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventiation
- Rotate compressor every 2 minutes
- If no advanced airway, 30:2 compression-ventilation ratio
- Quantitative waveform capnography
  – If $PetCO_2$ <10 mm Hg, attempt to improve CPR quality
- Intra-arterial pressure
  – If relaxation phase (diastolic) pressure <20 mm Hg, attempt to improve CPR quality

Return of Spontaneous Circulation (ROSC)
- Pulse and blood pressure
- Abrupt sustained increase in $PetCO_2$ (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

Shock Energy
- **Biphasic:** Manufacturer recommendation (eg, initial dose of 120–200 J); if unknown, use maximum available, Second and subsequent doses should be equivalent, and higher doses may be considered.
- **Monophasic:** 360 J

Drug Therapy
- **Epinephrine IV/IO Dose:** 1 mg every 3-5 minutes
- **Vasopressin IV/IO Dose:** 40 units can replace first or second dose of epinephrine
- **Amiodarone IV/IO Dose:** First dose: 300 mg bolus. Second dose: 150 mg.

Advanced Airway
- Supraglottic advanced airway or endotracheal intubation
- Waveform capnography to confirm and monitor ET tube placement
- 8–10 breaths per minute with continuous chest compressions

Reversible Causes
- Hypovolemia
- Hypoxia
- Hydrogon ion (acidosis)
- Hypo-/hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thrombosis, pulmonary
- Thombosis, coronary

@ 2010 American Heart Association

Figure 108-19. 2010 American Heart Association adult cardiac arrest algorithm. *CPR,* Cardiopulmonary resuscitation; *ET,* endotracheal; *IO,* intraosseous; *IV,* intravenous; *PEA,* pulseless electrical activity; *$PetCO_2$,* partial pressure of end-tidal carbon dioxide; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia. *(From Neumar RW, Otto CW, Link MS, et al: Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,* Circulation *122(18 Suppl 3):S736, 2010.)*

Vasopressin (40 units) was included in previous resuscitation guidelines based on observations that survivors of cardiac arrest had increased endogenous vasopressin levels. Vasopressin is an endogenous peptide hormone secreted by the posterior pituitary gland in response to hypovolemia or systemic hypoperfusion states. When intravenously administered, intense peripheral vasoconstriction results from the stimulation of V_1 receptors in the endothelium. Vasopressin lacks adrenergic stimulation and, as a result, has limited increases in myocardial contractility, myocardial and cerebral oxygen consumption, and metabolic demands. No survival benefit has been observed in humans when vasopressin was used with or without epinephrine in cardiac arrests.

Amiodarone was included in the ACLS algorithms because of its ability at an IV dose of 300 mg to terminate ventricular arrhythmias during cardiac arrest that were resistant to defibrillation after epinephrine administration. Amiodarone's antiarrhythmic effect occurs through sodium and calcium channel blockade, potassium efflux antagonism, and adrenergic (α- and β-) blocking effects, producing prolonged action potentials and increased refractoriness in all cardiac tissue. Similar to epinephrine, amiodarone improves the rate of ROSC but has no observed influence or benefit on hospital discharge or neurologic outcomes.

Epinephrine's role in cardiac arrest resuscitation has been questioned, particularly as greater emphasis is placed on interventions leading to improved cardiac arrest neurologic outcomes. Jacobs and colleagues[110] studied outcomes after cardiac arrest resuscitations during which 1 mg epinephrine versus a similar volume of saline placebo were administered. Survival to hospital discharge was not different between the groups; however, patients receiving epinephrine during their resuscitation efforts had a statistically higher rate of ROSC, compared with the placebo group. Although the number of patients experiencing cardiac arrests was quite large ($N = 4103$) in this study, only 601 underwent randomization, potentially biasing the results. Similar results were reported by Olasveengen and associates[111] in a study of IV access and medication administration during cardiac arrest; epinephrine was given if an IV line was placed or not given because of the lack of IV access. Similar to the Jacobs' study results, administration of epinephrine clearly demonstrated a benefit in establishing ROSC but had no statistically significant improvement in hospital discharge or neurologic outcomes. A study by Hagihara and colleagues[112] reported essentially the same findings; epinephrine is associated with significantly better ROSC after cardiac arrest, but hospital discharge and good neurologic outcomes are significantly worse.

Vasopressin's benefit in cardiac arrest has also come under greater scrutiny. Mentzelopoulos and colleagues[113] performed a large meta-analysis involving published randomized control studies in which vasopressin was administered during cardiac resuscitation (with or without epinephrine) and evaluated for its role in ROSC, as well as its role in long-term neurologic outcomes. The conclusion was that the use of vasopressin in patients in cardiac arrest was not associated with any significant benefit or harm. The only long-term survival benefit was observed when vasopressin was administered to patients who were in asystole. Although the theoretical advantages of vasopressin use during cardiac arrest are encouraging (intense peripheral vasoconstriction without β-adrenergic receptor stimulation), when used in clinical practice, vasopressin offers little benefit in cardiac arrest events. Substitution of one dose of IV epinephrine with 40 units IV vasopressin during resuscitative efforts in cardiac arrest is acceptable in the 2010 AHA Guidelines for CPR and ECC[61] (see Fig. 108-19).

Amiodarone is a first-line antiarrhythmic medication used in cardiac arrest events and is endorsed for use in the 2010 AHA Guidelines for CPR and ECC.[61] In the study, Amiodarone in Out-of-Hospital Resuscitation of Refractory Sustained Ventricular Tachycardia (ARREST), Kudenchuk and colleagues[114] reported the results of a randomized, prospective study in which 300 mg IV amiodarone or placebo was administered to patients in out-of-hospital cardiac arrest with persistent VF after three defibrillation attempts and 1 mg IV epinephrine. The study demonstrated significant increases in survival to hospital admission in the amiodarone-treated group but was unable to demonstrate any difference in hospital discharge rates. In the Amiodarone versus Lidocaine in Pre-Hospital Ventricular Fibrillation Evaluation (ALIVE) study, Dorian and colleagues[115] reported the results of a double-blind, controlled clinical trial comparing amiodarone with lidocaine in patients experiencing out-of-hospital cardiac arrest in Toronto, Canada. Their results demonstrated amiodarone's superiority to lidocaine in terminating persistent VF in the out-of-hospital setting. Similar to the ARREST study, the ALIVE study was able to demonstrate the improvement produced by amiodarone only in survival to hospital admission, not to discharge, when compared with lidocaine or placebo. Based on these studies, VF resistant to defibrillation and epinephrine therapy warrants amiodarone therapy to augment the attempts to terminate the arrhythmia, recognizing that a long-term benefit for such therapy is lacking.

During resuscitation efforts, 1 mg IV epinephrine should be administered as the initial pharmacologic drug in VF or PVT. This dose can be repeated every 3 to 5 minutes as long as cardiac arrest persists. Defibrillation should be attempted 2 minutes after epinephrine injection. For VF resistant to defibrillation attempts, 300 mg IV amiodarone should be considered and can be repeated once at a 5-minute period (if necessary) with a 150 mg IV dose. As with epinephrine, defibrillation should be attempted 2 minutes after amiodarone injection. No other vasopressors or antiarrhythmic medications should be administered than those studied and endorsed by the AHA in its resuscitation guidelines.

PULSELESS ELECTRICAL ACTIVITY

Pulseless electrical activity (PEA) refers to a heterogeneous group of cardiac rhythm disorders, all characterized by pulselessness in the presence of organized electrical activity. High priority must be given to identifying possible reversible causes of PEA (Box 108-4). Severe hypoxia in respiratory emergencies can result in PEA. In the traumatized patient, hypovolemia, cardiac tamponade, and

BOX 108-4 *Potentially Reversible Causes of Cardiac Arrest*

Hypovolemia	Tension pneumothorax
Hypoxia	Tamponade (cardiac)
Hydrogen ion (acidosis)	Toxins
Hypokalemia or hyperkalemia	Thrombosis (pulmonary)
Hypothermia	Thrombosis (coronary)

tension pneumothorax are possible causes of cardiac arrest and must be considered and acutely treated. Unanticipated cardiac arrest occurring in the intraoperative and postoperative periods should include acute massive pulmonary thromboembolism or air emboli as possible causes. In the pregnant woman, uterine compression of the inferior vena cava, amniotic fluid embolism, or uterine rupture are possible sources of PEA (also see Chapter 77). Idioventricular rhythms might accompany derangements such as severe hyperkalemia, metabolic acidosis, or drug (e.g., digitalis, β-blockers, calcium channel blockers, tricyclic antidepressants) overdose. In every circumstance, prompt initiation of chest compressions and the administration of 1 mg epinephrine are recommended as temporizing measures until more definitive therapy can be provided once the cause for the PEA is identified. Each of these scenarios has an associated intervention unique to that situation. Asystole or VF can develop if PEA is not corrected.

ASYSTOLE

Asystole is the complete and sustained absence of electrical activity and is often a terminal event. In most patients, asystole is irreversible, but a brief trial of resuscitation, beginning with oxygen therapy and IV epinephrine after effective chest compressions, is indicated particularly in the setting of witnessed cardiac arrest. Occult VF is more theory than reality. The concern that asystole is actually VF is unrealistic and should not prompt defibrillation attempts. Atropine is no longer recommended for treating asystole. When resuscitation efforts are pursued for patients found in asystole, oxygenation, at least 2 minutes of chest compressions, and IV epinephrine should be provided before cardiac rhythm analysis occurs, for ROSC assessment, or electrical activity resumes.

ECHOCARDIOGRAPHY IN CARDIAC ARREST

When PEA occurs, either as the presenting condition in cardiac arrest or after termination of ventricular arrhythmias, the 2010 AHA Guidelines for CPR and ECC recommend an assessment of the "5 Hs and 5 Ts" (see Box 108-4) to elucidate the reversible causes for the cardiac arrest. The presence of hypothermia, hypoxia, or electrolyte abnormalities can be readily assessed. However, other causes leading to cardiac arrest can often be identified with the use of echocardiography. Although not explicitly recommended in the 2010 AHA Guidelines for CPR and ECC, prompt echocardiographic evaluation for patients in PEA could result in prompt intervention for reversible conditions that might otherwise be undetected.

Ultrasound technology is readily available in most surgical departments and ICUs in the United States and is used for technical interventions from placement of regional anesthesia blocks to assessing cardiac function in the patient who is hemodynamically unstable (also see Chapter 46). During cardiac arrest, echocardiography might identify pulmonary emboli, significant hypovolemia, cardiac tamponade, and impaired cardiac function—even if clinicians with limited experience are interpreting these images.[116] The American Society of Echocardiography guidelines recommend that limited and focused transesophageal echocardiography be performed when intraoperative cardiac arrests occur.[117,118] Perhaps, most importantly, echocardiography can assist decision-making with respect to the termination of resuscitative efforts when PEA persists through resuscitative efforts.[119] As experience accumulates with the use of echocardiography during cardiac arrest states, greater emphasis may eventually be placed on using this technology for diagnosing the causes of PEA arrests, confirming the presence or absence of myocardial contraction in the presence of organized cardiac rhythm, as well as guiding resuscitation if ROSC occurs.

POSTRESUSCITATION INTERVENTIONS

EMERGENCY PERCUTANEOUS CORONARY INTERVENTION

In patients resuscitated from out-of-hospital cardiac arrest, emergency percutaneous coronary intervention (PCI) and angiography are recommended in the 2010 AHA Guidelines for CPR and ECC.[120] Approximately 90% of patients resuscitated from out-of-hospital cardiac arrest have evidence of coronary artery disease,[121] and 70% have at least one significant coronary lesion demonstrated by coronary angiography.[122,123] These findings are the basis for the recommendation endorsing early, urgent coronary angiography after resuscitation from cardiac arrest, even if 12-lead ECG is not suggestive of myocardial ischemia after resuscitation. Early coronary interventions that re-establish coronary blood flow improve myocardial recovery and electrical and hemodynamic stability. Fibrinolytic therapy provided to survivors of out-of-hospital cardiac arrest has not been shown to have favorable outcomes, particularly compared with PCI.[124,125] Attention must be directed toward facilitating early PCI in survivors of cardiac arrest as part of an advanced postcardiac arrest protocol, including those patients remaining comatose after resuscitation.

TARGETED TEMPERATURE MANAGEMENT

The median survival rate from out-of-hospital cardiac arrest is 8.4% (3.0% to 16.3%).[126,127] Only one-third of individuals in out-of-hospital cardiac arrest survive to hospital admission, and two-thirds of these survivors die before hospital discharge.[128] The majority of patients dying after successful ROSC die from ischemic neurologic injury.[129] In the setting of normothermia, cerebral blood flow less than 125 mL per minute and persisting for longer

than 7 minutes is associated with permanent neurologic damage[130] (also see Chapter 54). Improved survival from cardiac arrest might be possible if interventions are used in attenuating the effects cardiac arrest exerts on central nervous system tissues.

Cerebral ischemia induces an inflammatory response of platelet aggregation and degranulation, protein and enzyme denaturalization, and neutrophil and complement activation, all of which increase permeability and/or blood-brain barrier disruptions demonstrated by neuronal damage biomarkers.[131] Ischemic neurons become progressively acidotic in low-flow or no-flow states, leading to intracellular lactic acidosis and carbon dioxide retention. Intracellular acidosis inhibits enzymatic function, impairing neurotransmitter reuptake and depleting adenosine triphosphate (ATP) and adenosine diphosphate (ADP) stores. As adenosine accumulates, vasodilatation and neuronal edema result. As energy stores are depleted, sodium-potassium-ATPase dysfunction occurs in the neuronal membrane, resulting in extracellular hyperkalemia and intracellular hypercalcemia. Elevated intracellular calcium activates proteolytic and lipolytic enzymes, further disrupting neuronal membranes, resulting in massive liberation of excitatory neurotransmitters; glutamate is the most neurotoxic. Excess glutamate promotes overactivation of glutamate receptors and excitability of already stressed neurons, leading to a further influx of calcium into the neuron, resulting in neuronal death.

The cerebral inflammatory cascade might be attenuated, first, by improved blood flow as a result of effective and uninterrupted chest compressions during resuscitation efforts and, second, through induced hypothermia if ROSC is established and maintained. Drugs are ineffective in improving neurologic outcomes after cardiac arrest aside from their use to improve cerebral perfusion through improved cardiac output, to prevent hypotension, and to treat hyperglycemia.[127] Induced hypothermia might reduce cerebral metabolic rate and oxygen consumption, as well as attenuate the cerebral ischemia–induced inflammatory response associated with cardiac arrest states.

Since 2005, the AHA has endorsed targeted temperature management (i.e., induced core body temperatures 32° to 34° C) over 12 to 24 hours for patients who are hemodynamically stable and resuscitated from out-of-hospital VF or pulseless VT but remain comatose. The recommendations were reaffirmed in the 2010 AHA Guidelines for CPR and ECC.[132] However, even the AHA experts contributing to the 2010 AHA Guidelines for CPR and ECC recognize the shortcomings of many of the studies on which the most current guidelines regarding targeted temperature management are based.

Much of the interest in postresuscitation therapeutic hypothermia; that is, in targeted temperature management (to use current terminology), is driven by the results of a 2002 randomized control study demonstrating improved neurologic outcomes in comatose survivors after out-of-hospital VF or pulseless VT when hypothermia was induced and maintained.[133] The entire body must be cooled for improved neurologic recovery after resuscitation from cardiac arrest, not only the patient's head. Several hours are usually required for cooling to and rewarming from target core body temperatures (32° to 34° C). Current clinical practices use a combination of fluid-filled cooling blankets, ice packs, forced air blankets, cold IV fluids, and/or invasive devices or catheters for managing controlled cooling and rewarming of patients. Sepsis is more frequent when intravascular devices are used to induce hypothermia, making this approach unfavorable in most circumstances.[134]

Although enthusiastically received, the survival results in the therapeutic hypothermia study[133] remain sobering; a majority of patients in the hypothermia group either died before hospital discharge or suffered poor neurologic outcomes. However, those surviving to hospital discharge had better neurologic recovery when compared with the control patients. The exact mechanism responsible for improved neurologic outcomes after targeted temperature management is unknown.

In a retrospective study of the Finnish Intensive Care Consortium, investigators reviewed patients admitted to ICUs after resuscitation from out-of-hospital cardiac arrests in the "pre-hypothermia" era (2000 to 2002) and the "hypothermia" era (2003 to 2008), evaluating the impact of targeted temperature management on patient survival.[135] Patient characteristics were similar for age, sex, and initial Glasgow coma scores, except patients treated after 2003 had higher illness severity. Specific neurologic parameters were not evaluated. The authors reported that the implementation of targeted temperature management resulted in a significantly reduced risk for in-hospital death after out-of-hospital cardiac arrest (57.9% mortality decreased to 51.1% mortality). However, the survival rate has not changed since the widespread adoption of targeted temperature management in 2003, despite the increasing use of this therapy. The majority of patients experiencing out-of-hospital VF or pulseless VT cardiac arrests still die.

Targeted temperature management is beneficial most obviously with VF and pulseless VT cardiac arrests. Large registries have evaluated targeted temperature management for cardiac arrest scenarios other than VF and pulseless VT, finding no improved survival nor improved neurologic outcomes in these patients.[136] Coincident with the wide adoption of targeted temperature management after ROSC following cardiac arrest for any arrhythmia, BLS attention for uninterrupted chest compressions has improved. A large registry assessing the influence of uninterrupted chest compressions in cardiac arrest related to nonshockable cardiac arrhythmias has demonstrated improved resuscitation and neurologic outcomes.[137] The conduct of BLS in accordance with the 2010 AHA Guidelines for CPR and ECC may confound results from retrospective clinical observations, suggesting the benefit of targeted temperature management only to shockable cardiac arrhythmias. At this time, targeted temperature management is increasingly being considered for all survivors of nontraumatic cardiac arrest, particularly those with in-hospital cardiac arrests, although clinical evidence clearly demonstrates benefits for shockable arrhythmias.

The 2010 AHA Guidelines for CPR and ECC recommend that targeted temperature management be considered for any patient who is hemodynamically stable

and resuscitated from cardiac arrest but who remains unresponsive after ROSC. The optimal time for initiating targeted temperature management is not known, nor are data available on optimal rates of rewarming from induced hypothermia. In most circumstances, targeted temperature management is part of a postresuscitation "bundle" of care that coordinates induction and maintenance of hypothermia, followed by careful rewarming all provided by a team of health care providers familiar with induced hypothermia protocols.[138] Sedation, neuromuscular blockade, and mechanical ventilation are required for patient management during the period of inducing, maintaining, and rewarming from hypothermia.

Temperature management after ROSC following cardiac arrest has provided important observations. Patients with low body temperatures after resuscitation from nontraumatic cardiac arrest (median 34.5° C [interquartile range 33.7° to 35.9° C] versus 35.1° C [interquartile range 34.4° to 35.8° C]) had a higher rate of in-hospital mortality than those patients with higher body temperatures at admission.[139] This same study observed that in summer months, nonsurvivors after ROSC following cardiac arrest had higher body temperatures at admission than survivors. Together, these observations suggest impaired body temperature control is associated with poor survival after cardiac arrest. Hypothalamic dysfunction with impaired thermoregulatory control is proposed for both trauma-related and cardiac arrest–related body temperature observations.[139-141] The proposed hypothalamic dysfunction role in impaired temperature regulation after resuscitation from cardiac arrest might result from global cerebral ischemia affecting central thermoregulation and/or impairment of peripheral vasomotor pathways responsible for vasoconstriction and vasodilatation.[139,142]Although Benz-Woerner and associates[139] noted a lower body temperature in nonsurvivors at admission, the adjusted time to reach target hypothermic temperature was not different between groups. Finally, this study demonstrated that nonsurvivors after resuscitation from cardiac arrest required a longer time to rewarm, compared with survivors (600 ± 144 minutes in nonsurvivors versus 479 ± 120 minutes for survivors).[139] The management of impaired intrinsic body temperature appears to be an important predictor of survival after resuscitation from cardiac arrest.

During the time period of targeted temperature management, hemodynamic instability, arrhythmias, electrolyte abnormalities, seizures, bleeding, hyperglycemia, and infections are not uncommon. In a large prospective observational study of 754 patients resuscitated from out-of-hospital cardiac arrests, adverse events were studied evaluating their influence(s) on mortality.[134] Pneumonia occurred in nearly one-half of patients (with or without hypothermia therapy) but had no influence on mortality. Only seizures requiring anticonvulsant therapy and sustained hyperglycemia (>144 mg/dL) were associated with increased mortality. Seizures occurred in 182 of the 754 participants (24%) in this study group. Significantly longer delays between onset of cardiac arrest and the initiation of cardiopulmonary resuscitation and longer resuscitations before ROSC were unique to these patients, and the likelihood of asystole or PEA as initial cardiac rhythm were all unique to those experiencing seizures. Although an ominous sign, seizures did not imply uniformly poor survival; 31 patients with seizures requiring anticonvulsant therapy survived with good neurologic outcomes at 6 months. Sustained hyperglycemia is considered representative of a stress response related to increased endogenous and exogenous catecholamine loads, suggesting severe clinical insult. Currently, the ideal blood glucose level has not been established for survivors of cardiac arrest. Avoiding hypoglycemia in this period after cardiac arrest seems equally important as treating hyperglycemia; hypoglycemia was also associated with increased mortality as well.

Prognosis for neurologic recovery after targeted temperature management is a complex issue facing physicians caring for survivors of cardiac arrest. Benzodiazepines, neuromuscular blocking agents, IV sedatives, and narcotics are often used in the period during which hypothermia is induced after resuscitation from cardiac arrest. Hypothermia interferes with the pharmacokinetics and pharmacodynamics of these medications. The presence of medications with their effects on neurologic or neuromuscular function interferes with brainstem reflexes, electroencephalographs (EEGs), and somatosensory-evoked potentials (SSEPs), making interpretation of neurophysiologic findings difficult.[143]

Neurologists rely on a commonly used measure for predicting neurologic outcome after a neurologic injury, the Glasgow-Pittsburgh Cerebral Performance Category (GP-CPC) scale,[143] which is summarized in Box 108-5.

A neurologist's clinical evaluation assessing neurologic recovery after resuscitation from cardiac arrest includes pupillary light response, corneal reflexes, and motor responses to painful stimuli.[143] Current American Academy of Neurology (AAN) practice parameters for examinations 72 hours after resuscitation from a cardiac arrest submit that absent pupillary responses, absent corneal reflexes, or absent motor responses or extensor posturing predict a poor neurologic recovery with a high degree of certainty *in patients not exposed to induced hypothermia*.[144] In those patients treated with hypothermia, recovery of motor function within 24 hours of discontinuing sedation for induced hypothermia predicts good neurologic outcome with 100% specificity.[145] The EEG is useful even during hypothermia since the waveforms should not be significantly affected by hypothermia alone (also see Chapter 49). Sedatives and hypnotic drugs induce extremely low-voltage EEG patterns. The AHA 2010 Guidelines for CPR and ECC recommend a "spot" EEG as early as possible or continuous EEG monitoring

BOX 108-5 ***Glasgow-Pittsburgh Cerebral Performance Category Scale and Functional Outcomes***

CPC 1	Full neurologic recovery
CPC 2	Moderate neurologic disability
CPC 3	Severe neurologic disability but preserved consciousness
CPC 4	Coma or persistent vegetative state
CPC 5	Death

CPC, Cerebral performance category.

in patients being treated with hypothermia.[132] Seizures noted on EEG monitoring should be aggressively treated, but the effect that anticonvulsants have on neurologic outcomes is not known.

The AAN practice parameters do not address the influence that induced hypothermia after cardiac arrest resuscitation (and the pharmacologic interventions associated with this therapy) has on neurologic prognostication in this patient population. Traditional data used for determining poor neurologic recovery cannot be reliably used once the patient has undergone induced hypothermia. Neuroprognostication after targeted temperature management and resuscitation from cardiac arrest is an active topic of research and comment and will probably be addressed more thoroughly in the next version of the AHA resuscitation guidelines.

POSTRESUSCITATION OXYGEN THERAPY

Increased concern has been raised in the resuscitation community as to the optimal inspired oxygen concentration after restoration of circulation after cardiac arrest. Animal studies have demonstrated improved survival after hypoxic and ischemic episodes when low rather than high arterial oxygen concentrations accompanied restoration of blood flow.[146-149] Is an increased arterial oxygen concentration during ROSC harmful to ischemic cells, particularly neurons, and should lower inspired oxygen concentrations be provided during resuscitation efforts?

At the basic science level, when cells become hypoxic during normothermic hypoperfusion events (i.e., circulatory arrest), cellular energy (ATP) production converts from aerobic (oxidative phosphorylation) to anaerobic metabolism (glycolysis). Glycolysis is not sufficient for prolonged energy production in most cells, particularly neurons, during periods of low blood flow. If perfusion and oxygen delivery are restored to ischemic cells, then oxygen free radicals, particularly superoxide (O_2^-), are produced in the mitochondria and through nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidation. Superoxide dismutase is a cellular enzyme responsible for oxygen free radical detoxification but becomes overwhelmed as ischemia persists, as well as when large amounts of oxygen free radical species are generated during reperfusion. The negative consequences of reperfusion reported in animal studies are consistent with these oxygen free radical production theories.

Negative outcomes when high versus low concentrations of oxygen are provided during resuscitations from cardiac arrest have been shown in animal studies. However, human outcome studies addressing high versus normal arterial oxygen contents have not been nearly as convincing. Bellomo and associates, in a retrospective analysis of 12,108 patients resuscitated from nontraumatic cardiac arrest, reported that hyperoxia (arterial partial pressure of oxygen [PaO2] greater than 300 mm Hg) had no independent association with negative outcomes with respect to in-hospital mortality.[150] They also reported that hypoxia after cardiac arrest had the lowest hospital discharge rates.

At this time, no human studies have demonstrated clear evidence that hyperoxia must be avoided after resuscitation from cardiac arrest. Although hyperoxia probably offers no additional benefit to survivors of cardiac arrest, hypoxia is clearly harmful to these patients and must be avoided. Based on the available information, the 2010 AHA Guidelines for CPR and ECC recommend an approach for managing survivors of cardiac arrest that titrates oxygen therapies to attain oxygen saturations of 94% to 98% as soon as reliable continuous pulse oximetry is available.[132]

PEDIATRIC RESUSCITATION

Children are no more tolerant to cardiac arrest than adults, as demonstrated by the poor survival statistics in pediatric cardiac arrests. Overall, approximately 6% of pediatric patients survive out-of-hospital cardiac arrests.[151] Results for in-hospital pediatric cardiac arrest are better. The 2008 National Registry of Cardiopulmonary Resuscitation (NRCPR) reported an overall survival of 33% of pulseless cardiac arrests among in-hospital pediatric patients.[152] Survival from pediatric cardiac arrest requires prompt recognition and treatment, just as with adults (also see Chapter 93).

Pediatric resuscitation is an area of clinical expertise requiring unique understanding, clinical skills, and therapeutic considerations. Recognition of this perspective is evident in the 2010 AHA Guidelines for CPR and ECC. However, health care providers must realize resuscitation recommendations are intended for both adult and pediatric resuscitations; simplified and streamlined for retention and use in resuscitation efforts, regardless of the patient's age. As with adults, pediatric chest compressions, when performed by a single rescuer, should be delivered at a rate of 100 compressions per minute with 2 breaths interposed every 30 compressions.

Interruptions in chest compressions should be minimal and of short duration, even for airway management and defibrillation, just as with adult resuscitation. Minimally interrupted and effectively performed chest compressions, ventilation, and prompt defibrillation are associated with improved resuscitation from cardiac arrest in children rather than medication administration. In light of this information, ACLS training provides sufficient consistencies in treatment recommendations extending from the young to the very old to be effectively used in the treatment of any child or adult in cardiac arrest. AHA textbooks and handbooks are available for consultation regarding more specific details.

PEDIATRIC BASIC LIFE SUPPORT

Primarily for the convenience and uniformity of training, infants are considered to be 1 month to 1 year of age and children are 1 year of age to puberty (i.e., breast development in girls). Adults are considered those in or beyond puberty. Figure 108-20 depicts current recommendations for health care worker–provided Pediatric Basic Life Support (PALS) (see Fig. 108-20).[152]

When an unresponsive child is encountered, a brief attempt at confirming unresponsiveness is indicated. If the child is unresponsive, then a call for help, the retrieval

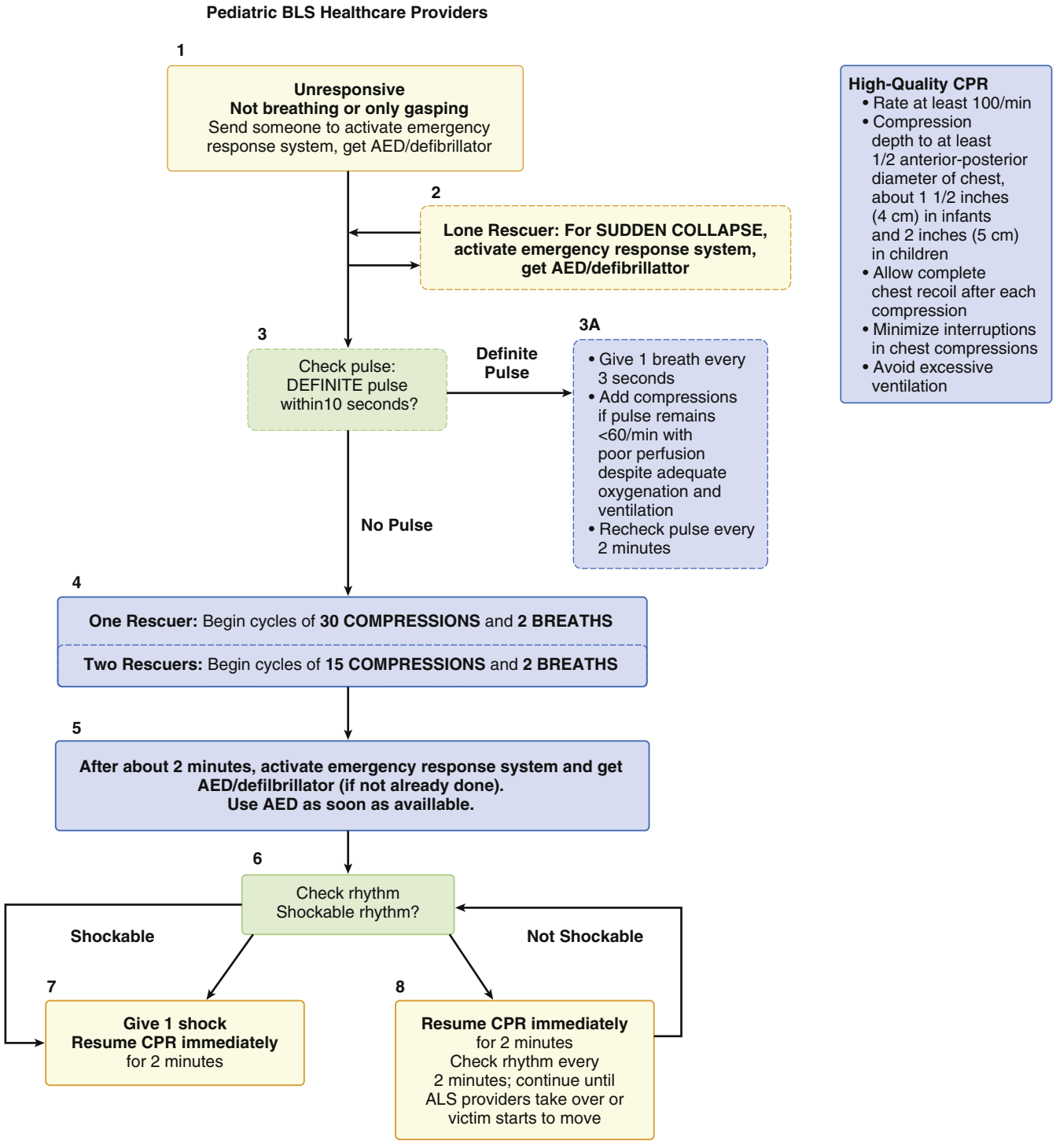


Figure 108-20. 2010 American Heart Association pediatric basic life support (BLS) for health care providers algorithm. *AED,* Automatic external defibrillator; *ALS,* advanced life support; *CPR,* cardiopulmonary resuscitation. *(From Berg MD, Schexnayder SM, Chameides M, et al: Part 13: pediatric basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,* Circulation *122(18 Suppl 3):S866, 2010.)*

of resuscitation equipment, and the detection of the presence or absence of a pulse is indicated when more than one rescuer is available. The single rescuer should initiate an emergency response system and then check for a pulse. The detection of a femoral or brachial pulse is often difficult for both health care and lay rescuers.[153,154] The rescuer should spend no more than 10 seconds palpating for an obvious pulse. Chest compressions should be initiated if no obvious pulse is present or if a palpable pulse in an infant is less than 60 beats per minute.

As with adults, the initial pediatric basic life support resuscitation sequence now emphasizes chest compressions first, rather than airway management. Although asphyxia is a more common cause in pediatric cardiac arrest than VF, for simplicity in training, chest compressions rather than rescue breathing is recommended as the initial intervention for pediatric cardiac arrest resuscitation efforts. The cycle of 30 chest compressions before rescue breathing delays ventilation for only 15 to 20 seconds.

Chest compressions should be performed at a rate of 100 compressions per minute. In infants, the rescuer should place two fingers just below the inframammary line on the sternum and compress the sternum to one-third the anteroposterior depth of the chest (approximately 4 cm). In children, chest compressions should be performed by compressing the lower half of the sternum (avoiding the xiphoid process) with one or two hands to a depth one-third the anteroposterior depth of the chest (5 cm). Thirty compressions should be delivered, followed by two rescue breaths provided with minimal interruptions in chest compressions. Chest compressions and rescue breathing should be performed for 2 minutes before reassessing the presence of a pulse. Each compression should be followed by full recoil of the chest, which allows unimpeded venous return to the heart.

Lone rescuers should perform 30 chest compressions with two interposed breaths during resuscitation. If two rescuers are present, then a chest compression-to-ventilation pattern of 15:2 should be used with minimal interruption and pauses of chest compressions for rescue breath delivery. If an advanced airway is present, then rescue breathing can be provided at a rate of 8 to 10 breaths per minute without interruption of chest compressions.

Sudden witnessed collapse in a child is likely to be from VF. Application of an AED to an infant or child in cardiac arrest would ideally include a pediatric attenuator (limiting shock energy for the smaller body size) and pediatric defibrillation pads. With infant cardiac arrest, a manual defibrillator is recommended. Initial defibrillation energy in pediatric cardiac arrest is 2 J/kg and increased to 4 J/kg if a second shock is indicated. If no pediatric defibrillator is available, then an adult AED should be applied and used without hesitation. Defibrillation is critically important.

Foreign Body Airway Obstruction

More than 90% of childhood deaths from FBAO occur in children younger than 5 years old. Liquids are the most common source for infant choking. Small objects (e.g., balloons, food) are responsible for most childhood choking (also see Chapters 55 and 93). If a child is making sounds or is coughing, the adult should carefully monitor but not intervene. If the choking is severe—no coughing, no breathing—an intervention is necessary. Infant choking should be relieved with five back blows followed by five chest compressions until the obstruction is relieved. In the choking child, the Heimlich maneuver (abdominal thrusts) should be performed until the obstruction is relieved. In either circumstance, if the choking infant or child becomes unresponsive, CPR should be started with 30 chest compressions, followed by an airway examination to identify the presence of the foreign body. Two rescue breaths should be attempted. If the airway obstruction is not relieved, then CPR should be restarted and continued until the airway obstruction is relieved.

Drowning

When a drowning infant or child is encountered by a single rescuer, a CPR pattern of 2 minutes of 30:2 compression-to-ventilation should be provided before summoning help. If two or more rescuers are available, then help should be immediately summoned. Oxygen and ventilation should be provided at the earliest opportunity.

PEDIATRIC ADVANCED LIFE SUPPORT

Unlike adults, infants and children experience cardiorespiratory arrest secondarily, rarely as a result of a primary cardiac event. This observation is critical because ACLS interventions primarily directed toward the restoration of cardiac function may cause the physician to delay properly directed therapy (also see Chapter 95). As an example, progressive respiratory failure with worsening hypoxia and respiratory acidosis leads to bradycardia and hypotension that can further progress to cardiac arrest. The cardiac arrest is the result of hypoxia not a primary cardiac event. Treatment with atropine in a futile attempt to increase heart rate in a hypoxic, hypercarbic child would be an example of misdirected therapy.

VF and VT is the presenting rhythm in up to 15% of pediatric in-hospital and out-of-hospital cardiac arrests.[151] The incidence of lethal ventricular arrhythmias increases with age through childhood.[155] Increasing evidence supports a genetic abnormality that results in myocardial ion channelopathies as possible sources for lethal ventricular arrhythmias in children. This background provides evidence that primary cardiac events are possible causes for pediatric cardiac arrests. Distinguishing primary from secondary cardiac causes of pediatric cardiac arrest requires thoughtful consideration of relevant clinical data and a familiarity with multiple pediatric advanced life support resuscitation algorithms.

Airway Control and Ventilation

Considering the high incidence of respiratory rather than cardiac causes of pediatric cardiac arrests, anesthesiologists are fully aware of the need for effective basic and advanced airway management and the importance of oxygenation and ventilation. Airway management is of utmost importance in respiratory-related cardiac arrests. As with adult cardiac arrests, airway management should not cause prolonged interruption of chest compressions. If effective ventilation is provided with mask ventilation, then an endotracheal tube is not necessarily mandatory. Alternative airways (e.g., laryngeal mask airway) should be considered when endotracheal intubation proves difficult or when intubation would result in prolonged interruption of chest compressions. As with adults, the placement of an advanced airway warrants confirmation of placement using a carbon dioxide detector and bilateral breath sounds.

Venous Access

Vascular access can be challenging in the child who is critically ill. Intraosseous (IO) access is often pursued in

children who are critically ill without other IV access because of its ease of placement and the rapid entry of fluids and medications into the central circulation.

All resuscitation medications and blood products can be injected into IO catheters. Circulating medication levels are equivalent between IV and IO routes.[156] IO administration of medications is preferred to endotracheal administration. Because of the resistance to fluid flow from the IO catheter into the IO space, fluids must be pressurized to carry fluid into circulation.

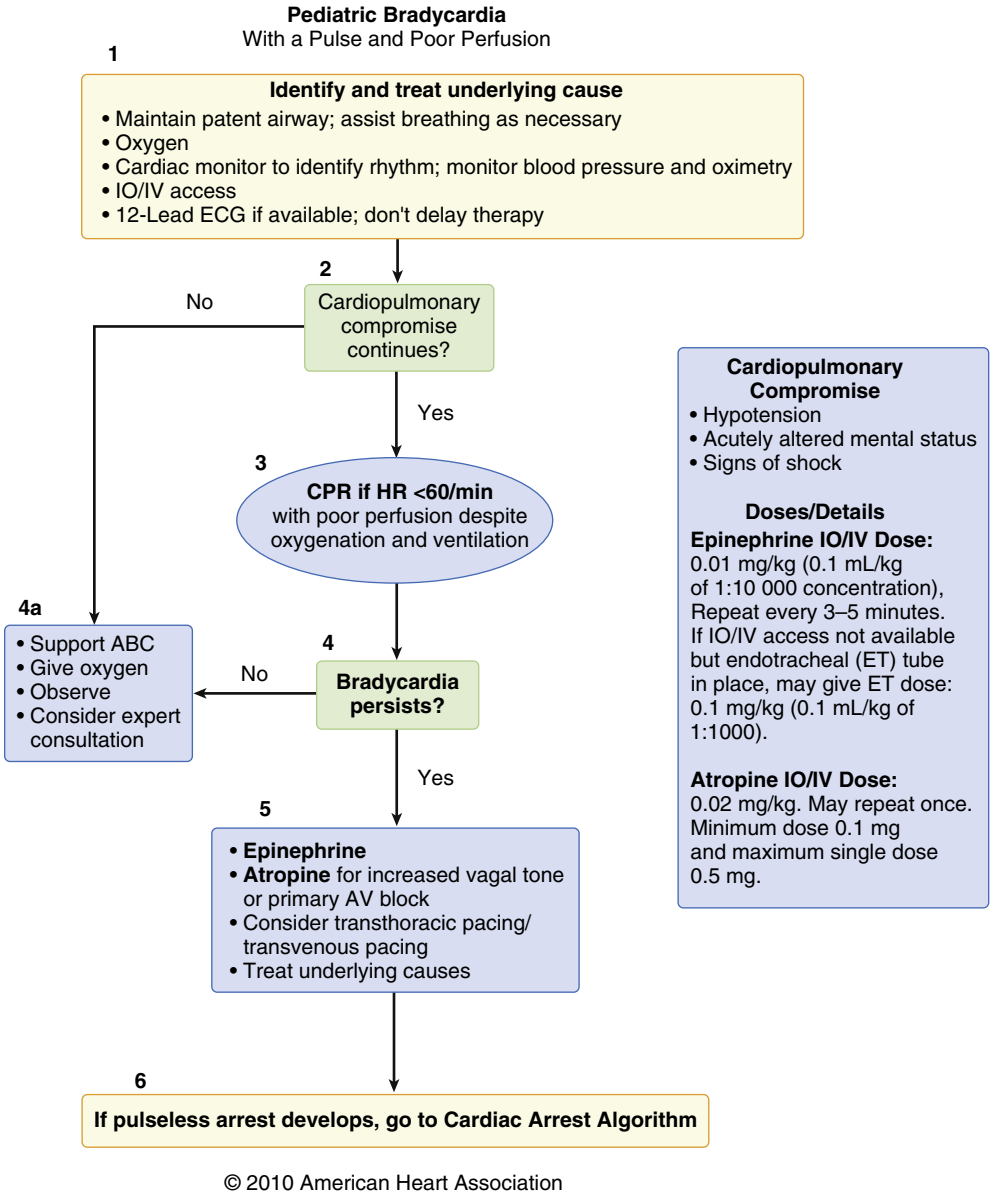
Monitoring and Arrhythmia Recognition

ECG monitoring permits the immediate recognition of the arrest rhythm or, more likely in infants and children, the pre-arrest rhythm. Prompt intervention and correction in the latter event may prevent cardiac arrest that may be irreversible if induced by hypoxia manifested by progressive bradycardia. With this in mind, potentially life-threatening arrhythmias are discussed first, followed by cardiac arrest.

Supraventricular Bradyarrhythmia

The appearance and progression of a slowing of the heart rate in infants and children demand immediate assessment of the cause, beginning with hypoxia (Fig. 108-21). Bradycardia before cardiac arrest is most commonly sinus or junctional in origin. Second- or third-degree heart block may ensue if oxygen and other therapies are not provided. If hypoxia has been ruled out and the bradycardia is accompanied by clinical evidence of impaired perfusion, usually with systemic hypotension, then the patient should be treated with chest compressions and epinephrine. Chest compressions should be considered for infants and children with pulses less than 60 beats per minute.

Epinephrine is the drug of choice for treating bradycardia in infants and children. The recommended dose is 0.01 mg/kg of a 1:10,000 solution injected intravenously or intraosseously (IO doses are equivalent to IV doses). Epinephrine can be repeated as needed every 3 to 5



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Figure 108-21. 2010 American Heart Association pediatric advanced life support (PALS) bradycardia algorithm. *ABC,* Airway, breathing, circulation; *AV,* atrioventricular; *ECG,* electrocardiogram; *HR,* heart rate; *IO,* intraosseous; *IV,* intravenous. *(From Kleinman ME, Chameides L, Schexnayder SM, et al: Part 14: pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,* Circulation *122(Suppl 3):S888, 2010.*

minutes. If the drug is injected into the tracheobronchial tree through an endotracheal tube, then 0.1 mg/kg of a 1:1,000 dilution is recommended.

If epinephrine does not increase the heart rate, then atropine can be used in a dose of 0.2 mg/kg and repeated once. TCP should also be considered for bradycardia refractory to epinephrine and atropine.

Supraventricular Tachyarrhythmias

In infants and children, SVT may represent ectopic atrial rhythms, atrial flutter or fibrillation, or paroxysmal reentrant tachycardia.[157] Standard pediatric cardiology texts should be consulted for specific diagnostic and therapeutic recommendations (Fig. 108-22). Although SVT is usually well tolerated in most infants and older children, immediate cardioversion may be necessary when heart rates in the range of 240 to 300 beats per minute are reached. Heart rates at these extremes may result in severe and rapid hemodynamic compromise. In the emergent setting where rapid SVT causes cardiovascular instability,[158] synchronized cardioversion is the treatment of choice. The initial energy dose is 0.5 J/kg to 1.0 J/kg

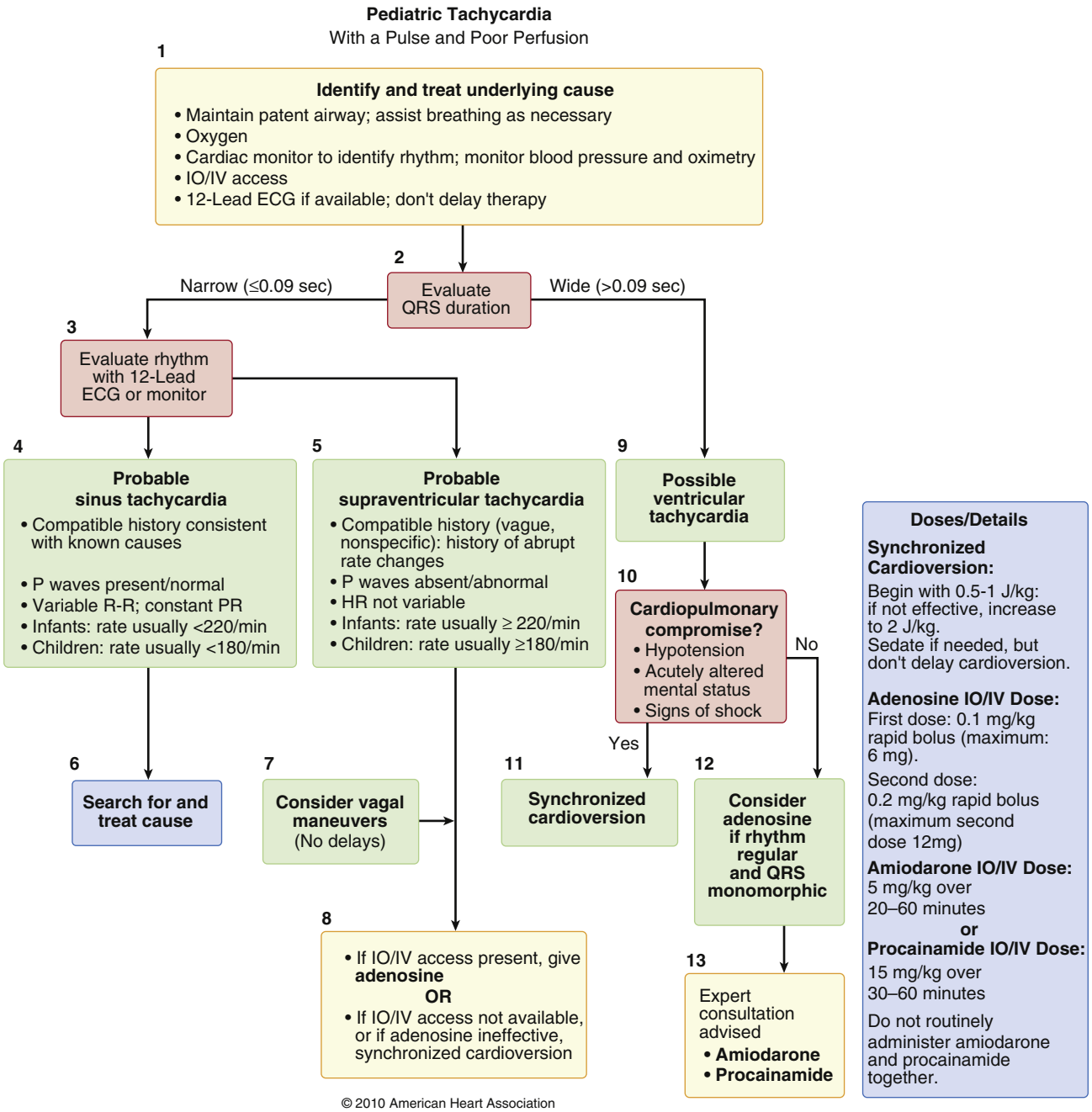


Figure 108-22. 2010 American Heart Association pediatric advanced life support (PALS) tachycardia algorithm. *ECG,* electrocardiogram; *HR,* heart rate; *IO,* intraosseous; *IV,* intravenous. *(From Kleinman ME, Chameides L, Schexnayder SM, et al: Part 14: pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,* Circulation *122(18 Suppl 3):S887, 2010.)*

body weight. If necessary, the energy dose is doubled.[159] If conversion to sinus rhythm remains unsuccessful, then the diagnosis of SVT should be reconsidered.

In children with SVT who are hemodynamically stable, vagal maneuvers are recommended before pharmacologic therapy. If vagal maneuvers are unsuccessful, then adenosine is the drug of choice and administered as a rapid bolus in an IV or IO dose of 0.1 mg/kg. If the SVT persists or recurs, then a second dose of an IV or IO dose of 0.2 mg/kg can be given in 1 to 2 minutes. The maximum single adenosine dose should not exceed 12 mg.

In circumstances during which adenosine has been unsuccessful in converting hemodynamically stable SVT, procainamide (15 mg/kg over a period of 30 to 60 minutes) and amiodarone (5 mg/kg over a period of 20 to 60 minutes) can be considered before cardioversion. Combining these therapies is not recommended.

Verapamil is not recommended for pediatric SVT in an emergency setting because it may induce hypotension and a state of depressed myocardial contractility. Specifically, verapamil is not recommended in this setting for infants younger than 1 year, children with congestive heart failure or myocardial depression, children receiving β-adrenergic blocking drugs, or children who may have an accessory pathway between the atria and ventricles.

Ventricular Bradycardia

As with supraventricular bradycardia, a slow idioventricular rhythm that has not yet produced pulselessness must be considered indicative of severe hypoxia, and treatment must be directed toward improving oxygenation and ventilation. Only after hypoxia has been addressed should rate-accelerating therapy be pursued, as discussed with supraventricular bradyarrhythmias.

Ventricular Tachyarrhythmia

Despite a common misconception, ventricular tachyarrhythmia is not always associated with severe hemodynamic compromise. Ventricular rates of 150 to 200 beats per minute may be tolerated and defined as a palpable pulse, but ventricular tachyarrhythmias should be converted to a normal rhythm. Emphasis is placed on an accurate diagnosis with 12-lead ECGs before treatment if the patient remains hemodynamically stable. In the setting of wide QRS complex tachycardia, synchronized cardioversion is the indicated treatment, beginning at 0.5 J/kg and increasing to progressively higher doses as needed and up to 2 J/kg using either monophasic or biphasic waveform shocks. If pharmacologic therapy is undertaken, amiodarone is the drug of choice and is delivered as described for the treatment of SVT. Intravenous procainamide (in doses identical for that of SVT) can also be considered. The two drugs should not be administered together. If the tachycardia is very rapid (greater than 300 beats per minute) and/or cardiovascular collapse and loss of pulses occurs, then this situation should be treated like VF with chest compressions and unsynchronized defibrillatory shocks.

Management of Cardiac Arrest

Once pulselessness occurs, therapy must be directed not only at correcting the underlying rhythm disorder but also at maintaining organ viability during the period of cardiopulmonary arrest. Meticulous attention must be paid to ensure proper chest compression rate and depth to avoid hyperventilation and chest compression interruptions, and to administer medication that supports perfusion pressures during resuscitation efforts. The Pediatric Advanced Life Support (PALS) Pulseless Arrest Algorithm is shown in Figure 108-23.

In the great majority of pediatric cardiac arrests, bradyasystole is the terminal cardiac electrical activity. Early dominance of the parasympathetic nervous system and α-adrenergic activity may, in part, explain this dominance of bradyasystolic mechanisms as the terminal event in infants. In addition, ventricular tachyarrhythmias (VF or VT) are most commonly seen in infants and children with congenital heart disease. Such children may have cardiac hypertrophy and increased ventricular mass sufficient to provide an anatomic substrate for reentrant wave fronts that initiate and sustain VF or VT.

Pulseless Electrical Activity and Asystole

Pediatric PEA, as in adults, includes disorders in which some form of cardiac electrical activity is present but without palpable pulses. In infants and children, this disorder is most commonly an idioventricular rhythm at a very slow and irregular rate (bradyasystole) and is the usual predecessor to ventricular asystole. When PEA is present, an immediate and aggressive effort should be made to identify treatable causes. As in adults, hypoxia, hypovolemia, tension pneumothorax, cardiac tamponade, and hypothermia or acidosis should be considered in light of the clinical setting in which PEA or asystole develops. Directing therapeutic efforts toward the most likely cause may avoid the administration of medications.

For both PEA and asystole, epinephrine is the drug of choice and is initially given in an IV or IO dose of 0.01 mg/kg (0.1 mL/kg of a 1:10,000 solution) (both routes result in equivalent blood levels) if potentially correctable sources of cardiac arrest have been pursued but ineffective in terminating the condition. Epinephrine can be repeated every 3 to 5 minutes via IV or IO routes as long as cardiac arrest persists. Defibrillation is not associated with benefit in PEA or asystole and should not be considered.

Pulseless Ventricular Tachycardia or Ventricular Fibrillation

VF occurs in 5% to 15% of all prehospital pediatric arrests,[160,161] and up to 20% of in-hospital pediatric cardiac arrests. VF and VT are relatively uncommon in infants and children, most likely with congenital heart disease. The increased cardiac muscle mass in congenital heart syndromes provides the anatomic electrophysiologic milieu for maintaining reentrant electrical wave fronts necessary for propagating VT and VF. As in adults, the treatment of choice for pulseless VT or VF in children is defibrillation, not medication therapy.

Defibrillation can be performed using adult defibrillator pads if the affected child weighs more than 10 kg. At least 3 cm should separate the defibrillation pads or paddles. Infant pads or paddles should be used for children younger than 1 year or weighing less than 10 kg. Energy doses for safe and effective defibrillation in infants are not known. The 2010 AHA Guidelines for CPR and

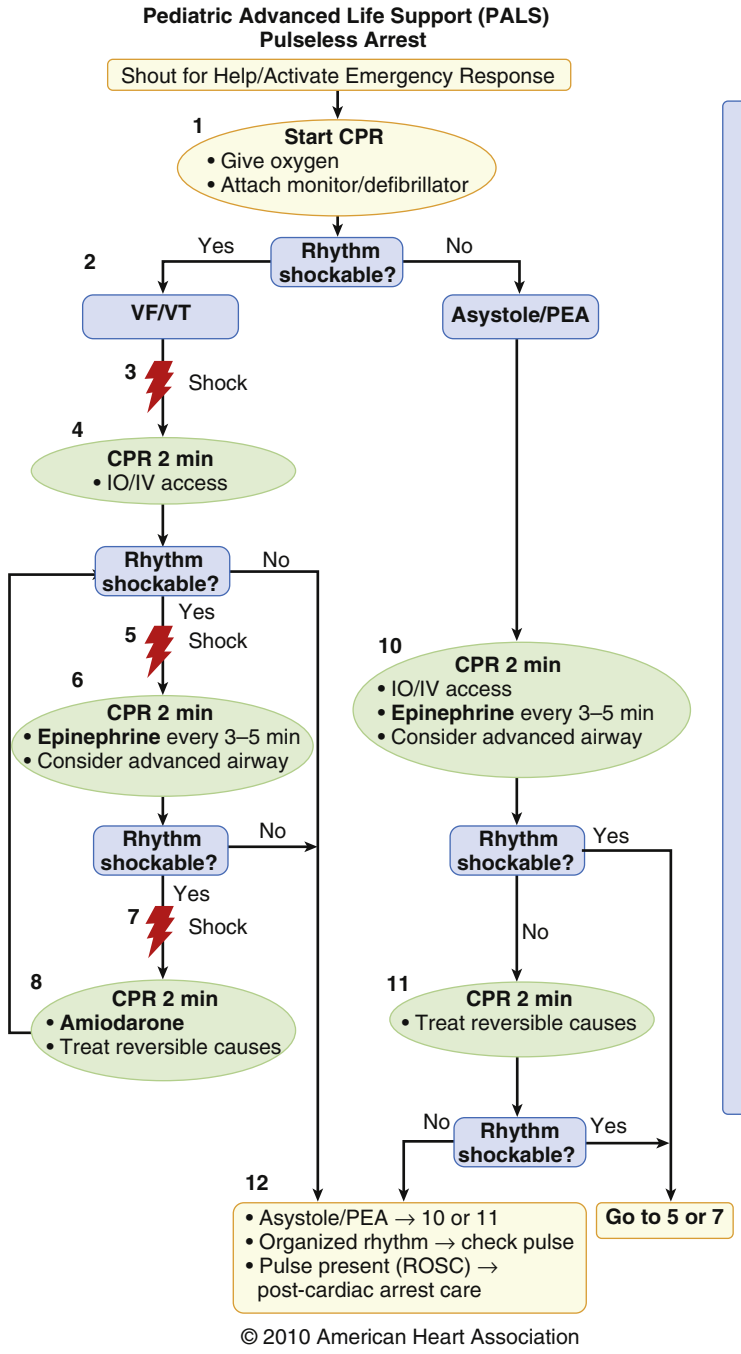


Figure 108-23. 2010 American Heart Association pediatric advanced life support (PALS) pulseless arrest algorithm. *CPR,* Cardiopulmonary resuscitation; *ECG,* electrocardiogram; *ET,* endotracheal; *IO,* intraosseous; *IV,* intravenous; *PEA,* pulseless electrical activity; *VF,* ventricular fibrillation; *VT*, ventricular tachycardia. *(From Kleinman ME, Chameides L, Schexnayder SM, et al: Part 14: pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,* Circulation *122(18 Suppl 3):S885, 2010.)*

ECC recommend 2 J/kg for the first defibrillation attempt (monophasic or biphasic waveforms), progressing to 10 J/kg, or one adult defibrillation energy (depending on defibrillator manufacturer) if necessary for persistent ventricular arrhythmias.[158]

As long as the cardiac arrest persists, epinephrine is the drug of choice and is initially given in an IV or IO dose of 0.01 mg/kg (0.1 mL/kg of a 1:10,000 solution), as in PEA-related arrests. Evidence for using vasopressin in pediatric cardiac arrests is insufficient. IV or IO amiodarone, 5 mg/kg, can be considered for persistent VT or VF that is unresponsive to defibrillation. Amiodarone can be repeated two times as needed for persistent VT or VF.

Termination of Pediatric Resuscitation Attempts

No clear clinical signs or reliable predictors indicate whether efforts made in resuscitating infants and children will be successful. Witnessed cardiac arrest, prompt effective chest compressions and ventilation, and

rapid initiation of advanced resuscitative interventions improve the chances of successful outcomes but do not guarantee successful resuscitation. Prolonged resuscitations might be considered for infants and children with recurring or refractory VF or VT, particularly if cardiopulmonary support with extracorporeal membrane oxygenation (ECMO) is available[162] and the source for the cardiac arrest is believed reversible.

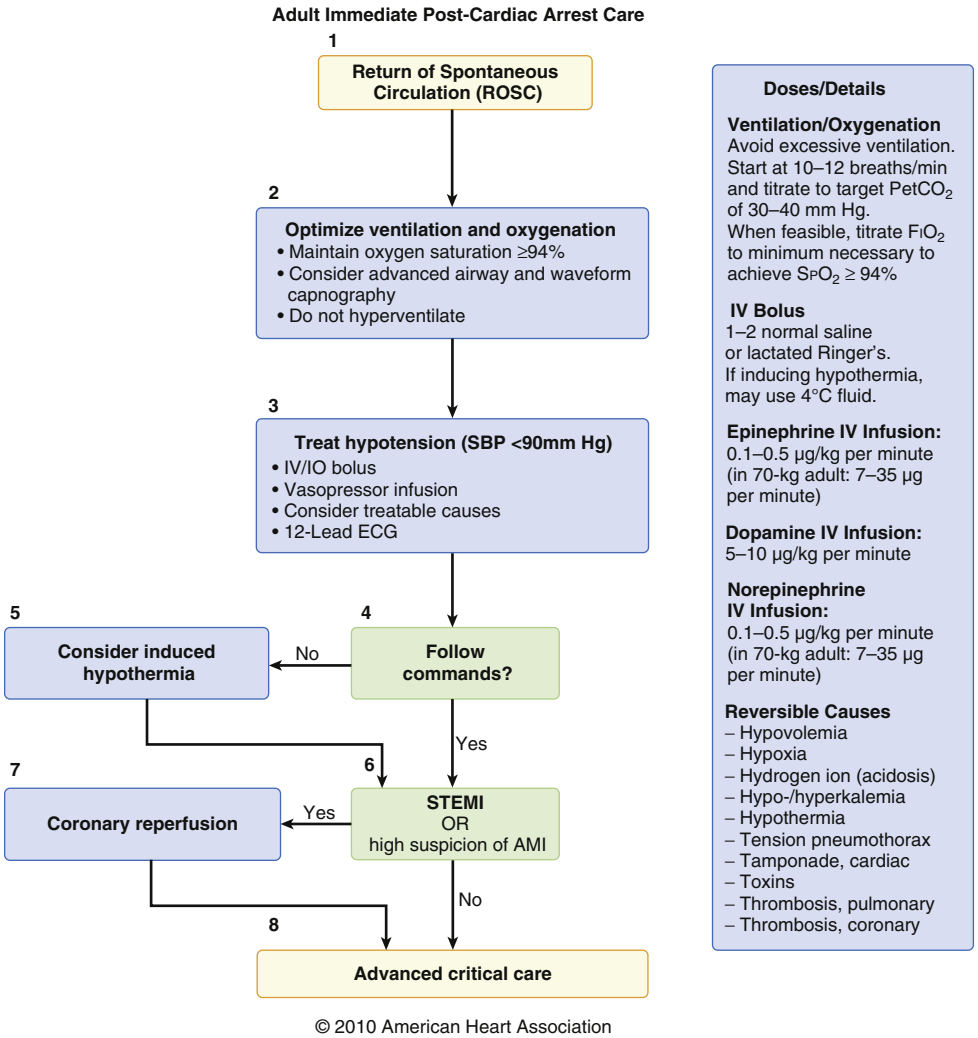
Sudden Unexplained Deaths

Unexpected and unexplained deaths in infants to young adults may be associated with genetic variations or mutations of ion channels in myocardial cells. Channelopathies allow abnormal electrolyte movement across myocardial cell membranes, predisposing the heart to irregular depolarizations and arrhythmias.[163-172] In 2% to 10% of infants or children[163-170] and 14% to 20% of young adults who experience sudden cardiac death, channelopathies are found on autopsy to have channelopathies.[171,172] This information should be discussed with families of young children who unexpectedly die. The AHA recommends an autopsy performed by pathologists with experience in cardiovascular disease and a genetic analysis of first- and second-degree relatives searching for evidence of undiagnosed channelopathies.

FUTURE OF RESUSCITATION SCIENCE AND CARE

At this time, resuscitation science is evolving into areas that could significantly improve the likelihood of survival after cardiac arrest. The 2010 AHA Guidelines for CPR and ECC emphasize uninterrupted chest compressions. Evidence clearly demonstrates the value of high-quality chest compressions in resuscitation efforts as improving the chances of ROSC for lethal ventricular arrhythmias and in patients experiencing asystole.

Several medications demonstrate improved rates of hospital admission after their use in cardiac arrest (e.g., epinephrine, amiodarone) yet failed in producing survivors to hospital discharge. As therapeutic hypothermia and targeted temperature management becomes increasingly used for comatose survivors of cardiac arrest, perhaps those surviving to hospital admission after cardiac arrest will eventually have higher chances for hospital discharge with good neurologic recovery resulting from this therapy. The key to targeted temperature management is a protocolized treatment regimen that provides reliable, timely, and consistent therapy for comatose survivors or through establishing centers of expertise in this therapy. The optimal time for initiating targeted



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Figure 108-24. 2010 American Heart Association adult immediate post-cardiac arrest care algorithm. *AMI,* Acute myocardial infarction; *FiO_2,* fraction of inspired oxygen concentration; *IV,* intravenous; *$PetCO_2$,* partial pressure of end-tidal carbon dioxide; *SBP,* systolic blood pressure; *SpO_2,* saturation of peripheral oxygen; *STEMI,* ST-elevation myocardial infarction. *(From Peberdy MA, Callaway CW, Neumar RW, et al: Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,* Circulation *122(18 Suppl 3):S768-786, 2010. Available at:* http://circ.ahajournals.org/content/122/18_suppl_3/S768.full.*)*

temperature management has not yet been identified. Interfacility transfer should be considered if a survivor of cardiac arrest arrives at a hospital that does not have the capability of providing targeted temperature management since hours between resuscitation and the initiation of the therapy has been demonstrated to provide benefit.

EXTRACORPOREAL MEMBRANE OXYGENATION

Although not specifically addressed in the 2010 AHA Guidelines for CPR and ECC, a growing body of experience and clinical reports describing the use and benefits of ECMO for persistent cardiac arrest warrants mention in this chapter.

Extracorporeal life support (ECLS) can be considered for patients with severe biventricular failure after resuscitation from cardiac arrest, persistent VF or PEA after correcting an instigating coronary lesion in the coronary catheterization laboratory (where ventricular function recovery is anticipated), or in pediatric patients experiencing lethal arrhythmias as a result of myocarditis or the suspicion of myocardial channelopathies. Several institutions have reported their clinical experiences using ECLS that span many years.[173-175] In some reports, ECLS is being initiated in emergency departments by emergency physicians.[176] In nearly all reports, ECLS is considered very early in resuscitation efforts and is performed by experienced ECLS clinicians. Placement of large vascular catheters, one of which extends to the right atrium, during chest compressions to initiate ECLS therapy is technically challenging and time consuming. ECLS is only offered in tertiary centers with access to and experience with this technology. As a result, the theory of ECLS is far more hopeful than clinical evidence demonstrates at this time.

COORDINATED POSTRESUSCITATION CARE

Most deaths after cardiac arrest occur in the first 24 hours.[177,178] The AHA 2010 Guidelines for CPR and ECC emphasize the value of clinical experience with treating resuscitations from cardiac arrest, as well as access to cardiac catheterization laboratory interventions and intensive care management of cardiac arrest survivors. Figure 108-24 demonstrates a treatment algorithm for survivors of cardiac arrest. Although the best treatment algorithm for survivors of cardiac arrest is currently unknown, coordinated, consistent care provided by experienced health care professionals in a facility with multiple advanced interventions available and a review process for the care rendered to survivors of cardiac arrest all contribute to optimized care and will likely contribute to improved patient outcomes.[132]

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Chapter 109

Electrical Safety in the Operating Room

LAWRENCE LITT

Key Points

Fire Safety Issues

- When setting up the anesthesia machine and drug cart before a surgical procedure, the anesthesiologist must know about the operation and the location of the emergency equipment. Questions to ask include the following:
- Where is the nearest fire extinguisher? There should be one in every operating room.
- Where are the oxygen shut-off valves, and how do I operate them to stop oxygen flow to the operating room?
- Where is the nearest fire alarm should it be impractical to call the hospital's equivalent of 9-1-1? Fire alarms are often recessed in the wall near fire hoses.
- Where is the nearest escape passage?
- Where is the nearest defibrillator and code cart?
- Electrical fires, particularly those that involve the electric panel, require a special approach. If possible, all electric power that feeds an electrical fire must be quickly cut, which then converts it into an ordinary fire. In fighting a fire, the proper type of fire extinguisher must be used. The most common type of fire extinguisher sprays water. However, water must never be thrown or sprayed on an electrical fire or onto burning flammable liquids. Electrical fires require a dry chemical extinguisher, but carbon dioxide (CO_2) extinguishers, which are optimal for controlling burning oils and liquids, may also be used.
- The use of high *blow-by* oxygen flow from an open facemask must be avoided if, after *blowing by* the patient, the flow ends up providing oxygen enrichment at a site of electrosurgery.

Macroshock Electrical Issues

- All electrical equipment used in the operating room should be grounded, although internally such equipment can contain ungrounded circuits. If the power cord for a piece of equipment has a plug with only two prongs (i.e., no grounding prong to go into the third hole in the outlet), then the equipment should not be in the operating room. When connecting or disconnecting plugs from outlets, the plug should not be yanked by the cord. Similarly, equipment whose power plugs have been damaged should not be used, and heavy equipment should not be allowed to crush power cords by rolling over them.
- Patients should not be directly connected to the operating room's electrical ground.
- When electrosurgery is in use, a grounding pad should be used that connects the patient to the ground connection provided on the electrosurgical machine. The grounding pad should be well gelled and placed in contact with the patient across a large area. The grounding pad should be inspected during lengthy procedures and gelled again or replaced, if necessary. The electrosurgical grounding pad should be placed as near to the operative site as reasonably possible and as far as possible from any pacemaker wires and electrocardiographic (ECG) wires. When grounding pads are removed, the underlying skin should be inspected for burns.

Key Points—cont'd

- If increasing current levels are required for electrosurgery, a search for a faulty connection of the electrosurgical grounding pad should be conducted. In the event of very *wet* operations, with or without increasing current levels for electrical surgery, the physician should beware of errant current paths that include the grounding pad and other electrical contacts (e.g., ECG electrodes). For example, saline and body fluids in an abdominal procedure can extend under the drapes beyond the operative site and potentially form an electrical connection to a grounding pad or ECG electrodes.
- If the line isolation monitor (LIM) sounds an alarm after someone activates a piece of equipment, then the offending equipment should be immediately unplugged. Plugging in that equipment has allowed the secondary side of the main isolation transformer to be coupled to the ground. It is also possible that too many items were simultaneously plugged, resulting in the secondary side of the main transformer to be coupled to the ground by their combined capacitance. Various combinations of unplugging one piece of equipment and plugging in another can be evaluated. However, if one piece of equipment is found to cause the LIM to sound an alarm under several combinations, then that piece of equipment should be removed from the operating room and examined for an unwanted connection to the ground contact.
- Experienced personnel, usually a clinical bioengineering group associated with the operating rooms, should periodically test all electrical equipment. Anesthesiologists should verify that the equipment has been properly maintained, that standards of performance have been met, and that the entire electrical environment also meets the National Fire Protection Association standards (NFPA) requirements.[1,2-7]

Microshock Electrical Issues With Pacemakers

- Patients with an automated implanted cardioverter-defibrillator (AICD) need to have the AICD turned off before surgery starts after first having established Zoll pad connections. Turning off the AICD feature is commonly done by magnet placement but can also be accomplished with reprogramming. It should be understood that magnets do not change the pacing program that is in an AICD. Thus preoperative cardiac electrophysiologic consultation is essential for establishing appropriate pacing.
- If possible, bipolar electrocautery units should be used instead of unipolar electrocautery.
- All programmable pacemakers should be preoperatively interrogated to ensure proper function.
- Patients who are dependent on a pacemaker need to have asynchronous pacing programmed, along with all rate-sensing features disabled. A conventional defibrillator should be available.
- Other pacemaker patients should have a pacing strategy established by preoperative cardiac electrophysiology consultation.
- A plan for pharmacologic treatment of complete heart block should be in place, particularly for patients who are dependent on a pacemaker, and isoproterenol should be readily available on the anesthesia drug cart.
- If electrophysiologic monitoring is being performed, then the anesthesiologist should review the locations of grounding pads that will be placed by the electrophysiologist.

Magnetic Resonance Imaging Issues

- When using a pulse oximeter to monitor the oxygen saturation of patients in an magnetic resonance imaging (MRI) scanner, the connection between the oximeter console and the patient must take place through a long fiberoptic cable that has no wires or conducting segments.

Key Points—cont'd

- Items with internal wires should not be present during an MRI examination, including pulmonary artery catheters that have a wire for determining temperature and certain epidural catheters with wires.
- Because of missile danger, ferromagnetic anesthesia equipment may not be brought into the magnet room.
- Essential anesthesia equipment that can be sucked into a magnet must be bolted to a wall and tested before entry of the patient into the scanner.
- Anesthesiologists who stay in the magnet room during examinations must wear ear plugs to avoid permanent hearing loss from high-decibel acoustic noise.

Common to All Issues

- If the cause of an electrical burn or incident is uncertain, then the relevant equipment or areas should be secured until experienced biomedical personnel mount a thorough investigation that may include simulation of patient conditions.

Despite technologic advances that have increased the sophistication of operating room electrical equipment, three types of danger persist from the days of flammable anesthetics: fire, electrical burns, and electrical shocks (e.g., macroshocks, microshocks). Improved alarm systems and safeguards have accompanied the technologic progress, but the size and number of electrical devices used per case has also increased. The result is the introduction of new ways to create unsafe electrical configurations that can lead to severe injury during surgery and anesthesia. Inattention to electrical safety can have serious consequences. Tragic events continue to be reported in the medical literature; in some cases, a moment of injury leads to a lifetime of patient suffering. Frequently, the culprit is unsafe surgical equipment or its unsafe use. However, disasters can also originate in damaged or misused anesthesia equipment, including physiologic monitoring devices.

From 1995 to 2000, a surge in the number of important articles concerning intraoperative fires were written,[8-13] with cause analyses being based on the *fire triangle* or the three requirements for a fire: oxygen, fuel, and ignition source.[13] Operating room fires fall into one of three basic categories: (1) the patient or something in the patient is on fire, (2) equipment has an electrical fire (i.e., one initiated and sustained by electric currents), or (3) the surgical drapes or other operating room items are on fire. Inadvertent ignition is often involved and easily identified, for example, when electronically generated sparks or a high temperature initiates the burning of the surgical drapes. However, ignition sources can also be complex and not immediately understood, as in the case of an exploding expiratory valve in an anesthetic breathing circuit.[14] In the operating room, anesthesiologists need to be aware of fire safety concerns, do all they can to keep ignition sources away from fuel sources, and safely use supplemental oxygen. Apart from fires, electrical equipment with inadequate grounding or other faults and induced currents from radiofrequency fields have caused severe burns. One report described a neonate with third-degree burns after the application of an external cardiac pacing device for a prolonged period[15] (see also Chapters 78 and 95). Another report described serious burns occurring from the electric direct current (DC) generated by a 9-volt battery in a small neuromuscular stimulator.[16] Fortunately, patient electrocution is now uncommon, although it was once a well-recognized hazard of surgery, of the operating room, and even of hospitalization in general.[17-20]

Although many types of modern equipment appear different from their ancestral counterparts, the injuries caused by electricity are similar or identical to those occurring generations ago. Electrical malfunctions in the operating room continue to cause fires and explosions, central and peripheral nerve stimulation and damage, muscle stimulation and contracture, tissue burns, pacemaker interference, and sudden loss of power to important equipment. Safety standards for medical equipment have been improving, and preventive maintenance of equipment, careful attention to the electrical contacts used on patients, and appropriate responses to alarm signals will avoid most complications. Understanding electrical safety is an especially important responsibility for anesthesiologists because perioperative electrical dangers can often be identified before they lead to the disruption of patient care or to injury.[21-25]

Having described the general situation, this chapter now turns to the essential details of electrical safety. The previous Key Points provide guidelines for safe clinical practice.

ELECTRICAL GROUND

What is an *electrical ground*? This question is important because discussions of electrical safety often center on whether circuits are grounded. To the clinician, an electrical ground is the wire connected to the third prong on plugs that are inserted into electrical wall outlets. With regard to circuits, an electrical ground is any object connected to a circuit that is capable of instantaneously supplying or receiving arbitrarily large amounts of electrical

charge. The National Electrical Code of the National Fire Protection Association* (NFPA) defines an electrical ground as a conducting connection, intentional or accidental, between an electrical circuit or equipment and the earth or as a connection to some conducting body that serves in place of the earth. Because the earth can be taken as an infinite reservoir of electrical charge with a limitless ability to give up or receive electrons, any charged object connected to the earth loses its charge and assumes the same potential as the earth.[21] Relative to the earth and to each other, the voltage between two grounded objects is zero.

When a circuit is intentionally grounded, the physical objects chosen to serve as the electrical ground can vary. In a remotely located mobile army surgical hospital unit or a recreational camping van, equipment may be grounded by connections to a spike that goes into the earth. In a large urban medical center, the ground may consist of a subterranean network of pipes. For a small, hand-held radio, a human being may serve as the connection to the ground.

In hospital settings, the clinician does not need to understand the details regarding the choice of the ground. However, clinicians must often know whether they, their patients, or their pieces of equipment are grounded. Living organisms tolerate only limited amounts of electric current. Unintended new contacts with electrical ground can sometimes be injurious when they enable small electric currents to reach the heart or neural tissue. However, they are always dangerous when they permit large electric currents to travel through the body. Fortunately, alarms for operating rooms and surgical equipment are designed to provide danger signals before errant currents are established by a sudden, new, unwanted ground connection. If the operating room has a *line isolation monitor* (LIM), explained later, hearing its loud warning sound means that a faulty ground connection is one step away from establishing a large current in the patient. Human protection from large currents can be ensured if connections to ground always occur through a sizable resistance. The danger of being grounded through an electrical resistance that is too small can be illustrated by an unrealistic but vivid hypothetic example. Imagine a person standing on top of a giant copper cylinder that extended down to the molten core of the earth. This low-resistance connection to the largest imaginable electrical ground would be quite unsafe because the person would essentially be a fuse, poised to suffer whatever large electric current is applied. The safety that would be achieved by inserting very large electrical resistance between the person and the copper cylinder—but not so large a resistance that it causes perfect insulation—explains a requirement that was established long ago when explosive anesthetic gases such as cyclopropane were used. Operating rooms were then required to have conductive floors made of specific resistive materials. Such substances had high carbon content, making them neither as conductive as metal nor as insulating as rubber. The high carbon content imparted a dark black color, one that can commonly be found in many of today's operating room tables and cushions made of resistive material.

In the United States, electrical plugs have three prongs with only two providing voltage or, equivalently, power. A special third prong serves only as a connection to a ground (i.e., to an object that makes an electrical connection with the earth or with a metal network such as iron pipes). Travelers to Europe and elsewhere may recall seeing electrical outlets for plugs that have only two prongs and no separate ground wire. A two-wire system becomes especially unsafe if three-pronged equipment is plugged into it with the third prong left unattached.

A ground fault current interrupter (GFCI) electrical outlet allows a person to test that the third connection in the outlet is connected to a functional ground. More significantly, GFCI outlets enhance electrical safety by serving as emergency circuit breakers that shut off power when one of the two power lines in the outlet is accidentally connected to a ground. Thus the GFCI is a *first fault* detector. GFCI outlets, found in hospitals and homes, have two buttons, *TEST* and *RESET*. Pushing TEST causes a special resistor to be connected across the power and ground terminals in the receptacle. If the ground connection (i.e., the third wire) is in place and connected to the system ground as it should be, then current flows through the resistor and causes a circuit breaker in the outlet to open. No electricity can then be delivered by the outlet. Pushing RESET resets the circuit breaker and restores electrical power. Pushing TEST would not cause the circuit breaker to open if, for example, a contractor accidentally forgot to install the ground wire or if an earthquake or other mishap caused a break in an installed ground wire. Protection against accidental grounding of one power line in an outlet is required by the NFPA for wet environments such as operating rooms. Installation of GFCI electrical outlets is one way to satisfy NFPA protection requirements. As discussed later in this chapter, a second (traditional but more expensive) way is to have power come from an isolation transformer equipped with an LIM.[26,27] In the operating room, if a power outlet is not part of an isolated system with an LIM, then it should be a GFCI outlet.

Electrical engineers commonly choose the ground as a reference location where the voltage is defined to be zero. Therefore the voltage at any point in a circuit is the difference between the voltage at that point and the voltage at the electrical ground. Because of this, ground connections in commercial circuits help professional personnel check for proper functioning. A technician connects one voltmeter probe to the electrical ground while touching different circuit elements with the other voltmeter probe. The manufacturer's table can be used to compare readings and, in this way, identify problems in the circuit. Specifying the location of the electrical ground helps people communicate standards for circuit performance.

ISOLATION OF ELECTRIC POWER FROM THE GROUND

Electrical contacts with the *ground* can cause injury if they occur in two different locations, completing a circuit and permitting a large flow of current through the ground.

*National Fire Protection Association, 1 Batterymarch Park, P.O. Box 9146, Quincy, MA 02269-9959. http://www.nfpa.org. Standards are available for download at http://webstore.ansi.org.

One strategy for ensuring safety is to isolate all electric power sources from the ground, thus making it impossible for the ground to be used as a path for injurious or damaging currents.

Traditionally, isolation transformers, which usually take the form of large wall panels that have outlets and meters, implement this strategy in the operating room. The term *isolation transformer* comes from the fact that power output is isolated from the electrical ground. Figure 109-1, *A*, shows a schematic diagram of an isolation transformer. A device built into the transformer constantly checks that all is well with this setup. It monitors the extent to which the output power lines are isolated from the ground and is called the LIM. The following text reviews how the LIM came into existence, why it can be important, and precisely what it is.

Electric power for an operating room comes from a primary hospital source that usually originates from a connection to an electric alternating current (AC) station of the local power company. (Sometimes in an emergency, a gasoline-powered electrical generator is the primary source.) In the traditional setup, after arriving in an operating room, the secondary coils of one or more large isolation transformers modulate, isolate, and dispense the electric power to electrical outlets in the room. Such transformers are very expensive, and the traditional setup is found less often in new hospitals. However, when there is a transformer, connections in three-hole power outlets in the operating rooms are somewhat different from the connections in standard outlets found elsewhere in the hospital.[25] In such operating rooms, connecting one of the two power contacts to the ground contact cannot complete a circuit.

The panel of each isolation transformer is required to have an LIM, which is an electric current meter that demonstrates isolation of the transformer's output power from the ground. Large isolation transformers were originally required by the NFPA in all operating rooms because of the use of inflammable anesthetics.[26] It is permissible for operating rooms to be built without them as long as basic safety is maintained by otherwise isolating electrical circuits from the ground. Such is now accomplished by a power transformer inside most electrical devices that isolates voltage applied to the device's circuits. Instead of one large isolation transformer for all equipment, each piece of electrical equipment has a small isolation transformer inside it. Such was not the case when large isolation transformers were initially required. Arguing for the total abolition of operating room isolation transformers and their LIMs is therefore possible. In support of such an argument is the observation that isolation transformers and LIMs have always been absent in intensive care units and postanesthesia care units, places where medical personnel use the same electrical instruments that are used in operating rooms. Should anesthesiologists advocate the elimination of future installations of isolation transformers and LIMs in operating rooms? The answer can be either yes or no,[26,27] depending on the type of electrical equipment that is used and the surgical situation. Surgery can involve having very wet patients covered or soaked with fluids that conduct electricity and find pathways to the ground. In these situations, currents can be established through the errant pathways from electrosurgical tools, such as through saline solutions to electrocardiographic (ECG) electrodes or the operating room table. New operating rooms in ambulatory surgery centers would seem to not need isolation transformers, although they are well suited for operating rooms for liver transplantation and other procedures involving a large amount of fluid.

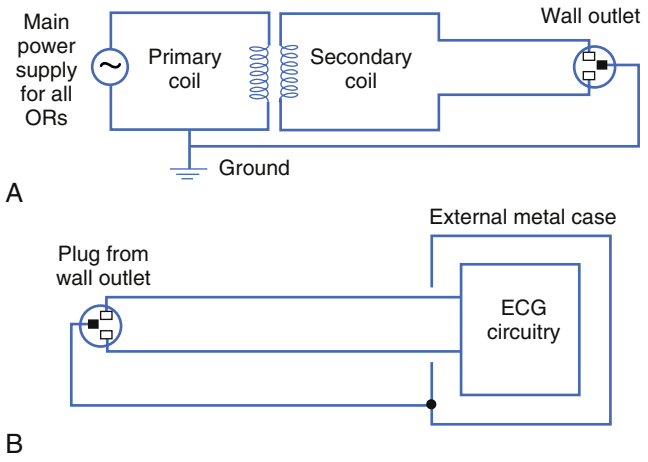


Figure 109-1. Schematic diagrams of an isolation transformer (**A**) and electric grounding (**B**) for an electrocardiographic (ECG) unit in the operating room (OR) (i.e., outlet to equipment).

The schematic diagram of an isolation transformer in Figure 109-1, *A*, shows what is presented by the power outlet to any power cord that gets plugged in. Each power outlet connects to two current-carrying wires that come from the secondary coil of the transformer. The third contact in the power outlet is connected to the standard hospital ground and not to the isolation transformer. The primary circuit of the transformer is attached to the ground, but the secondary circuit of the transformer is not.

When an ECG monitor is plugged into a power outlet in the operating room (Fig. 109-1, *B*), neither of the two current-carrying wires from the secondary coil of the transformer is connected to the ground by the ECG circuitry. This demonstrates the general principle that electrical circuits within an apparatus need not be grounded, although the metal case that houses the circuits is always grounded. For many circuits, proper functioning depends on good isolation. The statement "all operating room equipment must be grounded" means that the ground connection on a power cord that comes from equipment must always end up in contact with the ground provided by the transformer. In the example given in Figure 109-1, *B*, the ECG case is connected to the hospital's electrical ground, and the internal circuitry is connected to the output of the isolation transformer.

For reasons related to both safety and power conservation, three wires are in electrical circuits: (1) the *hot wire*, which is black in the United States and white in the United Kingdom and some other countries; (2) the *neutral wire*, which is white in the United States and black in the United Kingdom; and (3) the *ground wire*, which is commonly green. Electrical power boxes in hospitals, businesses, and homes generally receive 240-volt lines that are converted into 120-volt *main power line* circuits

(Figure 109-2, *A*). (The values *240* and *120* refer to root-mean-square voltage values for AC circuits. Peak voltages are larger by a factor of 1.41, the square-root of 2.) Although hot and neutral wires carry and return electrical currents to power outlets, the sample situation in Figure 109-2, *A*, illustrates why the neutral wire, which is connected to the ground from the center of the upstream transformer, is somewhat safer. For the situation shown in the figure, both 120-volt daughter circuits have equal current loads, and this results in the neutral wire's return current for one daughter circuit being equal and opposite to that of the other daughter circuit. The unequal widths of prongs in electrical plugs and outlets lets electrical equipment preserve the circuit asymmetry created by main power boxes that are designed to have hot wires and neutral wires. Additional background and details of such fundamentals have been recently reviewed.[1]

Figure 109-2, *B*, which illustrates the safety of one daughter circuit, is worthy of further discussion. If mechanical or electrical damage causes concern about the electrical safety of an ECG monitor, then could a failure occur inside the ECG monitor that would place the patient or anesthesiologist in contact with the internal circuitry? If so, then would electric current travel through the person from the ECG circuitry to the ground and cause injury or distress? If the ECG circuitry remains isolated from ground, then the answer is no.

The first part of the schematic in Figure 109-2, *B*, shows how isolation provides safety. A grounded person is touching the internal circuitry at point B. The isolation

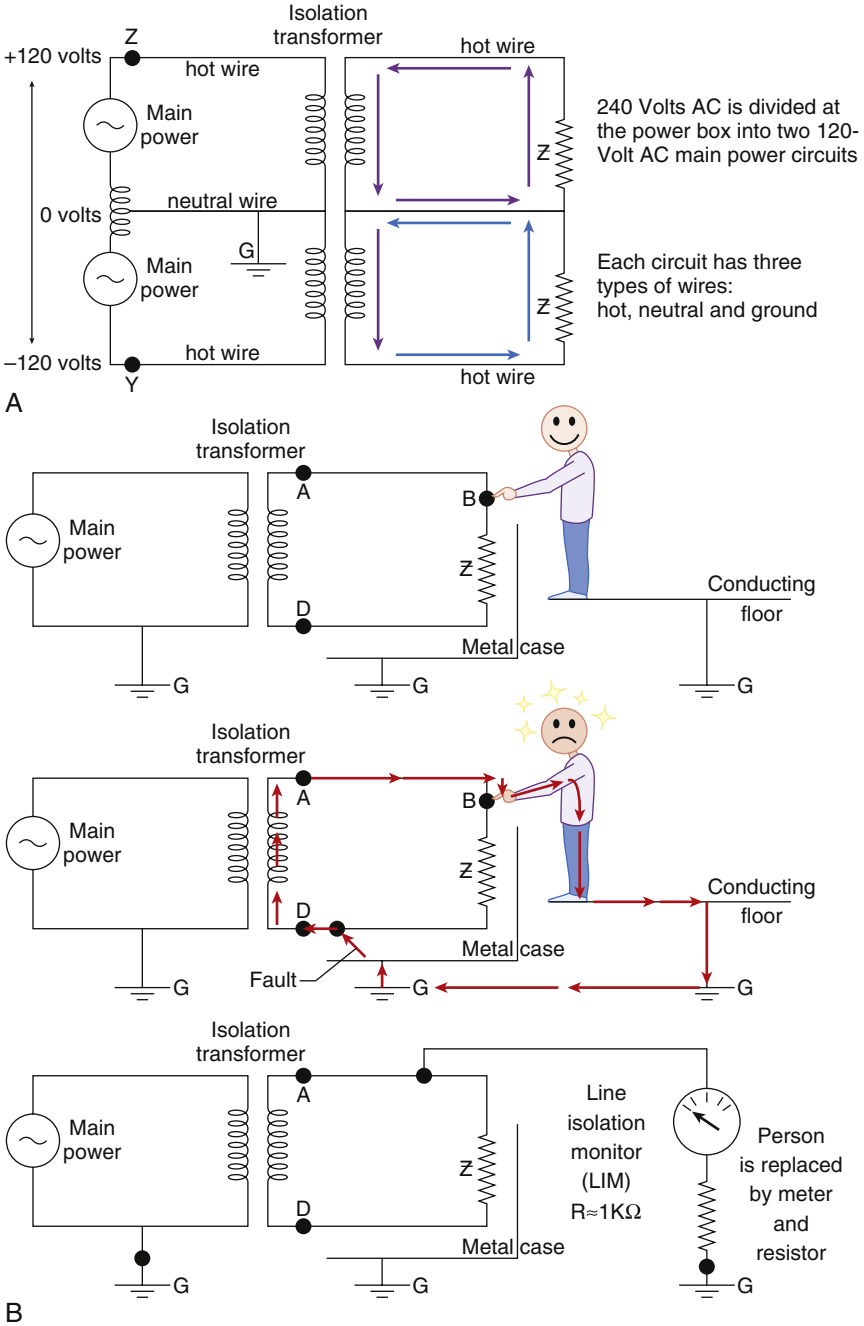


Figure 109-2. A, Schematic diagram shows the creation of two isolated 120-volt alternating current (AC) circuits in a power box that receives 240 volts of AC from an upstream source. The left side of the diagram represents the secondary coil in a transformer whose primary coil is not shown. The *neutral wire* connects the center of the 240-volt main power input on the left to the ground (G). The *isolation transformer* creates two isolated circuits of 120 volts, each loaded with a piece of equipment represented by the impedance Z. *Arrows* indicate simultaneous current directions. The central horizontal wire in the isolated circuit that is opposite to the *neutral wire* in the primary circuit is connected to the neutral wire contact in electrical outlets. **B**, When the transformer output is ungrounded, no electric shock occurs to the person at the right if an isolated power line is touched *(top)*. An electric shock does take place if the person touches the circuit after occurrence of the ground fault shown *(center)*. In the potentially injurious electricity path, shown in *red*, current comes up from the ground through the fault, circles around, and returns to the ground by traveling through the person's body. The person suffering the electric shock has been replaced by a current meter and a large resistance to ground. This is the basis for detection of the *first fault* by the line isolation monitor *(bottom portion)*. *R*, Resistance; *KΩ*, 1000 ohms.

transformer supplies current to pathways that connect the two hot leads in the outlet (points A and D). However, the only way for electric current to get from point A to D is through impedance Z. Because each of the hot points in the wall outlet are not grounded, the person in Figure 109-2, *B*, is safe from shock.

The second part of the schematic in Figure 109-2, *B*, however, shows that two inadvertent ground contacts could produce a dangerous situation, especially if one of those contacts is a human being. Suppose that a fault occurs near point D and causes the internal circuitry to come in contact with the external metal case. A dangerous shock would result from touching the circuit at point B. Because of the fault, current could complete a pathway through the person and ground (i.e., from point A to D). Isolating the power lines from the ground and knowing when isolation is compromised by a fault is useful.

Every isolation transformer has an LIM that monitors isolation of the transformer's two power output lines from the electrical ground. The third part of the schematic in Figure 109-2, *B*, shows how the LIM (an ammeter) replaces the smiling and frowning people (see Fig. 109-2, *B*). When very low amperage is indicated, the LIM verifies that the power output lines of the transformer are isolated from the electrical ground (see Fig. 109-2, *A*). The reality of the LIM connections is different because either of the hot wires could become accidentally grounded. The LIM is actually connected to both sides of the isolated power output (Fig. 109-3) and is set to sound an alarm when either side has an impedance to the ground that is less than 25,000 Ω or when the maximum current that a short circuit could cause exceeds 2 milliampere (mA). The LIM is insensitive to currents below 2 mA. As discussed later in this chapter, the LIM provides no protection against microamp currents and microshock.

Many events that commonly occur in operating rooms can produce a short circuit between the power and ground and result in the LIM sounding the alarm. For example, dripping or spilling saline, blood, or another conducting liquid into the receptacles of an electrical extension cord that is on the floor near the operating table can produce a short circuit. For this reason, rules from the NFPA and The Joint Commission (TJC) (formerly the Joint Commission on the Accreditation of Healthcare Organizations) have evolved to generally forbid the use of electrical extension cords in operating rooms and other clinical areas. Ideally, every piece of electrical equipment in the operating room is supposed to have a power cord that is safely routed to a wall outlet. In the rare circumstance when an exemption permits the use of an electrical extension cord, the cord must tolerate high current and have watertight covers that flip into place over unused outlets. If wet receptacles on an extension cord appear to set off an LIM, then the extension cord should be changed. If the LIM suddenly and unexpectedly or immediately rings after a new piece of equipment is plugged in, then that equipment should be immediately unplugged. If plugging in a piece of equipment repeatedly causes the LIM to sound an alarm, then the equipment should not be used until it is checked. Similarly, if the use of a particular power outlet repeatedly causes an alarm, then it should not be used until it has been checked. When an LIM alarm indicates a first fault (i.e., one power line is grounded), large, potentially damaging currents may subsequently occur through ground connections if a second ground fault is indicated. The path of damage may include the anesthesiologist, the patient, or an essential piece of equipment. An alarming LIM warns that someone in the operating room may receive an electrical shock or burn when touching connections to electrical equipment.

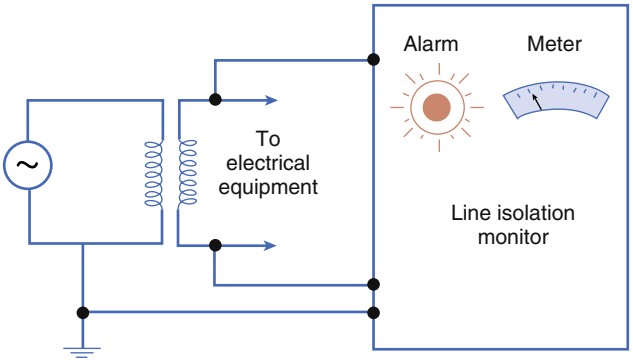


Figure 109-3. Schematic diagram shows the complete connections of the line isolation monitor (LIM). The alarm sounds a *first fault* if either isolated power line has less than 25,000 Ω of impedance, which corresponds to 2 milliampere (mA) or more being drawn through the LIM.

As noted earlier in this chapter, detection of a first fault in grounding is possible without the use of isolation transformers and LIMs. GFCI outlets provide protection against a first fault. However, they provide protection by suddenly shutting off all power from the outlet. An advantage of the LIM is that operating room personnel learn about a first fault without losing electric power. A disadvantage of the LIM is its susceptibility to newly developed artifactual causes of alarm. Certain devices used in operating rooms emit electrical radiation, intentionally or incidentally, that falsely cause LIMs to sound an alarm. Such devices include instruments that generate ultrasonic sound waves for the disintegration of a tumor and infrared and laser surgical navigation systems for stereotaxic surgery or anatomic localization, such as the computerized Stealth System and the Brainlab surgical guidance platform. These systems use electromagnetic waves to track fiducial markers attached to patients to enable locations on the patient to be linked to locations on three-dimensional MRI and computed tomographic scans. Noise can also be introduced into infrared pulse oximeter sensors that are connected to patients, when these are in an infrared navigation system's field of view. However, shielding the sensor with a cloth towel easily avoids such interference and misleading values of peripheral oxygen saturation (SpO_2).

CAPACITIVE COUPLING

The direct connection of two circuit elements by a wire or resistor is known as *resistive coupling* and is the easiest type of coupling for an anesthesiologist to recognize and understand. The connection is visible and the effects of the connection are apparent for circuits carrying DC

or AC at all frequencies. More subtle and abstract is the concept of *capacitive coupling*, which applies only to AC. This concept is relevant to anesthesiologists because it can account for electrical connections being present at high-current frequencies. If the alarm of an LIM goes off only when the electrosurgical electrode delivers high-frequency current to the patient, then capacitive coupling may be causing the dangerous pathway to the ground, and some power outlets that are safe for low-frequency currents but not for high-frequency currents may be present. Grounding pads, connections to electrical plugs, and equipment may need to be separated even farther from each other before the problem is remedied. The rationale directly follows the basic principles governing capacitive coupling.

The parallel-plate capacitor (Fig. 109-4), a circuit element that permits temporary storage of electrical charge, is very real to anesthesiologists when they use a defibrillator and announce "charging" just before delivering an electrical shock. More abstract is the concept that capacitors block the passage of DC while allowing the passage of AC. The total number of ohms that a capacitor has for obstructing AC or DC quantifies the *electrical impedance* of an object. This concept, which is a generalization of electrical resistance, permits the frequency-dependent assignment of ohms to all circuit elements: capacitors, inductors, and resistors. For capacitors, the ohmic calculation is performed with a simple formula. The impedance (Z, in ohms) of a pure parallel-plate capacitor is a function of the AC frequency (f):

$$Z = \frac{1}{2\pi fC}$$

In this instance, capacitance (C, in farads) is directly proportional to the area of the capacitor plates and inversely proportional to the space between the plates. As f increases, impedance to the flow of current decreases. For DC, f equals 0, and impedance becomes infinitely large.

At very high frequencies, capacitive coupling to the ground occurs through fewer ohms of impedance than at low frequencies. Because any two conducting objects in a room have surface area and an average distance of separation, they form a kind of capacitor. Any two objects have a capacitive coupling, which means that each of the two output lines of an isolation transformer is always coupled to the ground at AC frequencies.

Although such capacitive coupling is usually insignificant, it can sometimes be significant at frequencies

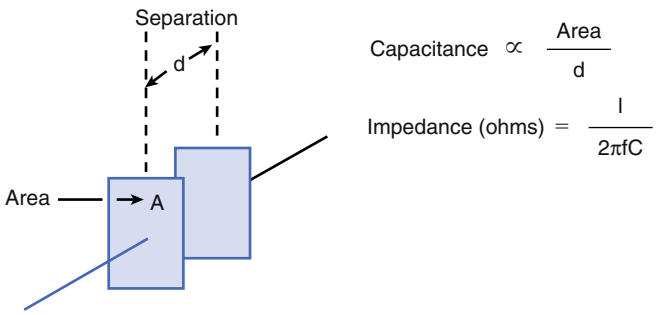


Figure 109-4. Schematic diagram of a parallel-plate capacitor. *C,* Capacitance in farads; *f,* frequency of alternating current.

of 60 cycles per second (i.e., 60 Hz). More commonly, capacitive coupling becomes a problem during electrosurgery performed at higher frequencies, typically hundreds to thousands of kilocycles per second. Capacitive coupling, which lets high-frequency currents easily pass, is commonly used by manufacturers in two connections: between the electrosurgical unit and the electrosurgical pencil (i.e., cutting or coagulation tip) and between the electrosurgical unit and the large-area *grounding pad* that attaches to the patient. The formal term for this large-area conducting pad is *dispersive electrode*. Capacitive coupling gives high-frequency electrosurgery currents a low-impedance path to and from the patient. At the same time, by presenting high-impedance paths at low frequencies, capacitive coupling prevents the electrosurgical pencil and the large-area conducting pad from participating in dangerous low-frequency grounding of the patient.

Capacitive coupling in an electrosurgical unit might have prevented a serious burn caused by the DC of a 9.5-volt battery within an anesthesiologist's damaged nerve stimulator.[16] An older electrosurgical unit was used in that case, and it was not capacitively coupled to the large-area grounding pad on the patient. The damaged nerve stimulator had a connection to the ground contact that permitted completion of a DC circuit (i.e., the patient through the faulty connection to the ground and then the ground through the large-area pad back to the patient). The DC persisted throughout the case, even when the stimulator was not pulsing. In laparoscopic and endoscopic surgery, avoiding unwanted capacitive coupling between the unipolar cautery tool and neighboring metal conductors such as trocar cannulas is important for surgeons. Stray currents from unwanted capacitive coupling can involve and injure organs such as the bile duct and bowel.[28,29] Anesthesiologists need to be aware of such potential surgical complications, particularly if they may be erroneously attributed to anesthesia.

Capacitive coupling can be responsible for severe burns from conventional pulse oximetry (with nonfiberoptic cable) in patients anesthetized for MRI.[30-32] However, the possibility of being burned by a faulty pulse oximeter probe exists independently of capacitive coupling or radiofrequency currents induced by the MRI environment.[33,34] In the setting for such a burn, the patient is external to a malfunctioning electrical circuit that causes the probe, which contains the photodiode and attaches to the patient, to overheat and burn tissue. Connecting the wrong kind of probe (e.g., one from another type of unit) to an oximeter console can cause such a catastrophe.

It has long been known that a perfectly safe conventional pulse oximeter (with nonfiberoptic cable) can be transformed into a dangerous, burn-causing device if attached to a patient being scanned in an MRI magnet. The problem arises from magnetic and electric fields that oscillate at megahertz frequencies (in radiofrequency coils) and at kilohertz frequencies (in gradient coils) during the acquisition of MRI data. Capacitive coupling can connect a patient to wires in a pulse oximeter cable and to metal in a pulse oximeter probe. In such a situation, the patient becomes part of a high-frequency loop circuit, with currents entering and exiting at the points of capacitive coupling, particularly at the site of probe

attachment.[35-38] Fortunately, anesthesiologists now know to use only pulse oximeter cables that have long, nonconducting fiberoptic connections between the photogenerating and photodetecting parts. Connections of the console to the cable are outside the magnet, distanced from pulsing MRI coils, and only nonconducting components are connected to the patient in the magnet. The absence of metal or conducting components of the cable or probe attachment eliminates the possibility of patient burns from induced currents during MRI.

Anesthesiologists monitoring patients with pulse oximetry in MRI magnets must use only units that are MRI safe and MRI compatible—those with a long fiberoptic cable as previously described. If, for some reason, the anesthesiologist decided to take a conventional pulse oximeter from an operating room to the MRI suite and attach it to a patient in an MRI magnet, then severe burns could occur.

ELECTRICAL SHOCK

MACROSHOCK

Macroshock refers to disturbances in neural or muscular function, or both, caused by the application of high voltage or current. Problems can arise if macroshocks occur near the heart, as in a fatal case when a patient's ECG leads were accidentally attached to a power cord.[17] However, macroshock can also cause injury if contact is made at locations remote from the heart.

If someone's hand or arm accidentally touches a voltage terminal, then the response to electric current flowing through the arm will depend on the amplitude and frequency of the current. Sensation of a 60-cycle current occurs at approximately 300 microamperes (μA), and pain occurs at approximately 1 mA. If the current exceeds a certain value, which is called the *let-go current*, then the person is unable to release the object.[39] The value of the let-go current varies with the frequency and among individuals. Figure 109-5 shows the range of average values as a function of AC frequency. The currents at 50- and 60-cycles per second have the lowest values and are therefore the most dangerous. The response of the cardiac muscle to electroshock also depends on frequency. Electric current is more important than voltage when issues of safety arise. Table 109-1 indicates the physiologic responses to increasing total-body current.

Continuous, total-body currents that reach 0.1 to 2.5 A (approximately 10 times the let-go value) can cause ventricular fibrillation. The electric current generated by one pulse of an implanted cardiac pacemaker ranges from 0.1 to 50 μA. Only a small part of the total-body current needs to pass through the heart to affect cardiac function. An electrosurgical unit generates so much power that it can induce microshock currents when it is used near implanted pacemaker wires. However, as a result of compliance with the safe grounding practices described earlier, the last convincing report of ventricular fibrillation induced by electrosurgery occurred in 1968.[40]

Defibrillation is often based on the same principle—the skin is a good electrical insulator that requires large electric fields at its surface for the production of small electric fields internally. A jolt of 360 watt-seconds (or joules) during closed-chest cardiopulmonary resuscitation delivers energy to the body comparable with that produced by a large-caliber handgun. (A 0.45-caliber bullet weighs 250 grains and has a muzzle velocity of 860 ft/sec when fired, which corresponds to energy of approximately 540 watt-seconds.) Only a very small portion of a defibrillator's energy dose is needed to depolarize the heart.

MICROSHOCK

The passage of even small amounts of electric current through the body can interfere with normal functioning of muscles and nerves. *Microshock* refers to the direct

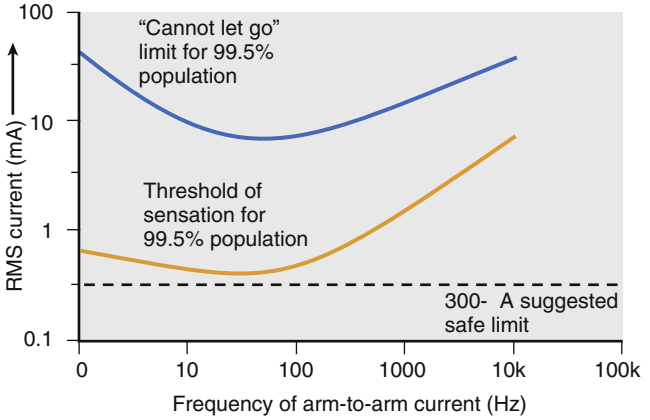


Figure 109-5. The response to electric current flowing through an arm when the hand accidentally touches a voltage terminal depends on the amplitude and the frequency of the current. Sensation of a 60-cycle current occurs at approximately 300 microamperes (μA), and pain occurs at approximately 1 milliampere (mA). If the current exceeds a certain value, called the *let-go current*, then the person is unable to release the object. The value of the let-go current varies with frequency and among individuals. *RMS,* Root mean square.

TABLE 109-1 AVERAGE EFFECTS ON HUMANS OF 60-HZ CURRENTS APPLIED AT BODY SURFACE AND PASSING THROUGH THE TRUNK

Current (mA) for 1-Second Contact	Effect
1	Is the threshold of perception.
5	Is accepted as the maximum harmless current intensity.
10-20	Let-go value is exceeded. Sustained muscle contraction is next.
50-100	Pain; possible fainting, exhaustion, mechanical injury; and heart and respiratory function continue.
100-2500	Ventricular fibrillation occurs. Respiratory center remains intact.
≥6000	Sustained myocardial contraction is followed by normal rhythm. Temporary respiratory paralysis occurs. Burns if the current density is high (usually if the current >100 mA/cm^2).

Modified from Bruner JMR: Hazards of electrical apparatus, Anesthesiology *28:396, 1967.*

application of very low voltage or current to the heart, often intentionally, by means of external or internal cardiac pacemaker electrodes. Inadvertent microshock, however, is dangerous because it can produce ventricular fibrillation. A faulty endoscope and faulty dialysis equipment have caused deaths from accidental microshock.[16,41] Before 1980, arterial and central venous pressure transducers were a potential source of microshock because they brought electrodes very close to heparinized saline in contact with the intravascular compartment.[42,43] However, in 1982, miniature disposable pressure transducers appeared that could be powered and operated with low-voltage telephone cables. These are now exclusively used, and their safety with respect to microshock has been demonstrated by years of frequent use without reported complications. Such systems, however, are vulnerable to more subtle dangers, as was reported when a faulty cable connection permitted precision pressure tracings but caused a substantially lower pressure reading.[44]

Electric current is the most appropriate variable to address when setting safety limits. Because investigators have reported that electric current passing through the human heart needs to be at least 50 µA before ventricular fibrillation occurs,[39,45,46] the American National Standards Institute (ANSI) on December 2, 1993, set 10 µA as the maximum leakage of current allowable through electrodes or catheters contacting the heart. This amount of current is considerably less than the peak electric current generated by an implanted pacemaker during a single pulse (0.1 to 10 µA). Because 2 mA is the LIM warning level, the LIM does not provide protection against microshock hazards.

ECG-monitoring electrodes are electrically isolated from power circuits in the monitor by an isolation transformer in the main unit, a second level of isolation (see also Chapters 44 and 47). However, an anesthesiologist who wishes to perform intravenous or intracardiac ECG monitoring, as occurs during P wave–guided brachial placement of a central venous pressure catheter, should have qualified personnel check the ECG monitor for current leaks. In some ECG and electroencephalographic (EEG) systems, electrode signals from the patient are translated into optical signals by a battery-powered amplifier with a photodiode output that is optically coupled to the main ECG or EEG unit, an even more thorough second level of isolation.

Endovascular procedures performed by interventional neuroradiologists include the placement of procoagulant coils inside certain types of intracranial aneurysms. The coils are directly placed in aneurysms with a considerable depth and a narrow neck. However, when the aneurysm has a wide entrance and a short depth, concern is high that a loose coil could get carried away and act as a thrombus wherever it lodged. Therefore in such cases, a detachable coil is generally used to completely occlude the unfilled region. After being convinced of the coil's location and stability, the angiographer sends a short electrical pulse through the coil, as though it were a unipolar surgical knife, which causes detachment at a known location. Although anesthesiologists should be aware of potential electrical hazards that come with new techniques,[47] they should be comfortable about electrical issues in detachable coils inasmuch as they do not cause macroshock or microshock.

ELECTROSURGERY

Most concerns with electrical safety in the operating room arise from the use of electrosurgical units because they are capable of causing electrical shock, burns, explosions, arrhythmias, and disturbances in pacemaker functioning.[48] Electrosurgical units operate at frequencies of approximately 300,000 to 2,000,000 cycles/sec (300 kHz to 2 MHz) to minimize the likelihood of ventricular fibrillation. During electrosurgery, high currents enter the patient through a small-area surface electrode at the tip of the cutting tool. The combination of high resistance (R), which is attributable to the small area, and high current (I) causes local tissue heating proportional to I^2R, which produces cutting or coagulation. The tip of the electrode is also designed to produce lower current densities (low I^2R) at points farther than a few millimeters from the electrode tip. Figure 109-6 shows fanning out of the electric current. Electrosurgery is therefore a form of highly controlled localized burning of tissue.

Concern about suffering an unwanted electrosurgical burn is a legitimate issue for patients with metal jewelry that pierces the body, such as umbilical rings, nipple rings, earrings, and tongue studs, among others. Obviously, the best solution is to remove all metal jewelry before surgery, and its removal is highly recommended. However, removal of metal jewelry can, at times, be cumbersome, burdensome, inconvenient, or simply unwanted by the patient. In such instances, leaving the jewelry in place is reasonable if the site of electrosurgery is far from the jewelry and if the jewelry is not directly within the path of the electrical current that travels from

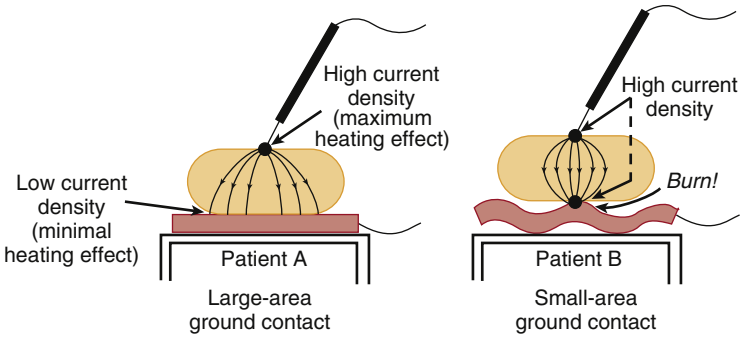


Figure 109-6. Schematic diagram shows the flow of electric current through the body when small- or large-area grounding pads are used.

the cutting electrode to the grounding pad. For example, a nipple ring should be removed if surgery is on the breast with the nipple; if a nipple ring is allowed to remain on the opposite breast, then the grounding pad should not also be on the patient's opposite side. As previously mentioned, in the case of no metal jewelry, electrical current rapidly fans out as it leaves the cutting electrode. The concern with metal jewelry is that it might re-concentrate electrical current that passes near it and thereby cause a burn. Thus metal jewelry that is left in contact with the skin should be held with tape in as large a contact area as possible. For example, a metal umbilical ring should be taped flat against the abdomen. If instead of a grounding pad a capacitive-coupled return electrode is used, then all metal jewelry should be removed. Because all metal objects have a surface area that can form capacitive coupling with a capacitive-coupled electrode, its use in certain circumstances can dangerously increase the risk of burns.

Because smoke often appears where there is fire, concern has been expressed regarding the safety of inhaling smoke from electrocautery. One group, assisted by the National Institute of Occupational Safety and Health, used the Ames test to examine the potential mutagenicity of electrocautery smoke collected during breast surgery.[49] Although the compounds collected were mutagenic, it is not known whether electrocautery smoke represents a serious health risk to operating room personnel. Nevertheless, the study recommended that surgeons minimize the production of electrocautery smoke and exposure of human beings to the smoke.

Because smoke is often present where there is fire, it is also important that nonflammable materials be used during electrosurgery. Fires have occurred in operating rooms because highly combustible surgical boundary drapes were placed close to electrosurgical units.[50] The smoke from such fires can contain toxic substances.

From the preceding discussion, finding that electrosurgical units are powerful enough to provide excess electric currents capable of causing extensive tissue burns is not surprising. Surgical patients who become wet with blood, saline, urine, or other conducting fluids can form electrical contacts with the operating table, the ground, or other conductors, including monitoring electrodes and surgical retractors. Such contacts can create potentially dangerous current pathways. For example, current from an electrosurgical unit may enter a patient through the grounding pad and return to the unit through one or more ECG electrodes. In this situation, the electrosurgical unit can provide current that burns the patient but never passes through the tip of the electrosurgical pencil used in the surgical procedure.

The dangers of electrosurgery in a wet environment, especially the possibility of establishing ground faults through wet connections, account for the presence of an isolation transformer (and LIM) in modern operating rooms. As noted earlier, GFCI outlets protect against ground faults by causing sudden deprivation of power, whereas isolation transformer setups turn on an LIM alarm instead and thereby permit less disruption. Loss of electric power during cardiac surgery can be a serious concern, which is one reason why anesthesiologists must know how to hand-crank cardiopulmonary bypass pumps.[51] Desflurane vaporizers require electricity for operation. The NFPA requires first ground fault detectors in operating rooms. However, anesthesiologists, surgical colleagues, and hospital administrators are free to choose GFCIs or isolation transformers with LIMs, whichever best suits local conditions and practices.[26,27]

UNIPOLAR ELECTROSURGERY

Understanding the difference between unipolar and bipolar electrosurgery is important. In both cases the surgeon applies electrodes directly to tissue to produce electric currents that burn and cut or burn and coagulate. In unipolar electrosurgery, the more common of the two, the electric current that enters the patient through one electrode travels throughout the body and is collected outside the surgical field by a large, wide-area, well-jelled grounding pad (i.e., the dispersive electrode). Skin burns can occur if the grounding pad is dry (i.e., most of the conducting gel is gone) or is otherwise in poor contact with the patient. In such situations, the electric current collected by the grounding pad is required to traverse small surface areas, and these inherently have high electrical resistance. Because I^2R can substantially increase at such small areas of grounding pad contact, increases in resistance can lead to electrical burns of the skin.[52] Electrical burns have also occurred at the site of ECG leads when the grounding pad was defective and the leads became an alternative path for returning high-frequency electrosurgery currents.[53,54]

A significantly more powerful unipolar electrosurgical tool, the argon beam coagulator (ABC), has become popular among surgeons who must cut or coagulate vascular tissue.[55] Operating room personnel unfamiliar with the design and use of the ABC can easily mistake it for an argon laser because a well-collimated, brightly colored beam of argon light glows at the tip of the electrosurgical pencil. The glow, which has the same color as light emitted from an argon laser, represents a continuous electrical discharge in a small, flowing column of argon gas having a density that supports electric current. The ABC was developed to solve a problem occurring with metal coagulation or cutting tips. In regions where a lot of blood is present, electrosurgical currents result in the adherence of sticky, burned tissue to the tip of the cutting electrode, thus electrically insulating it and making further use impossible until the tissue is scraped off. Surgery must stop while the tip is scraped clean. When large areas of vascular tissue must be traversed (e.g., in hepatic resection or repair of traumatic lacerations of the liver), conventional metal tips become difficult surgical tools. With the ABC, no metal surface is present to attract sticky, burned tissue. The tip of the cutting electrode is a cushion of argon gas that can transmit current as long as it touches tissue.

The anesthesiologist must understand that the use of the ABC means that significant electrosurgery is taking place and that safety measures are more important than ever. As in conventional electrosurgery, surgical cutting and coagulation with the ABC come from local I^2R heating losses at the point where the electrosurgical pencil

is applied—in this case, where the argon gas meets the tissue. ABC operation therefore resembles conventional arc welding. Because the ABC is perhaps the ultimate spark generator, its use illustrates the extent to which one safety concern that was prominent in the days of inflammable anesthetic gases has been abandoned.

Some body locations are never safe for unipolar electrosurgery. This situation is frequently encountered during neurosurgery and in patients with implanted cardiac pacemakers. The solution is bipolar electrosurgery (see the discussion that follows). Recently, during laparoscopic removal of a subphrenic mass in a patient with an intracardiac Swan-Ganz catheter, ventricular fibrillation occurred with unipolar electrosurgery, the most common type used in laparoscopic surgeries. One can ask whether the cause was stray current from the active electrode on its way to the grounding pad or capacitive coupling to the intracardiac catheter, issues related to things discussed so far. Both reasons might suggest it prudent to consider bipolar electrosurgery during laparoscopy when cautery is needed close to the heart.[2,56]

BIPOLAR ELECTROSURGERY

In bipolar electrosurgery, as in unipolar electrosurgery, current enters the patient through one electrode. However, instead of traversing the body to be collected by a dispersive electrode at a site remote from the surgery, injected current is collected millimeters away from the first electrode by a second electrode that appears identical to the first. Two pencil-point electrodes arranged at the tips of a forceps are used to perform bipolar surgery. Electric current flows through the patient's tissue only at the site of surgery, where it is confined to the few millimeters between the electrodes. Bipolar devices are required when electrosurgery is performed on an ovary or a fallopian tube. Several cases of fatal bowel injury have occurred after female sterilization with unipolar devices.[3,4]

Patients with an implanted pacemaker or an automatic implanted cardioverter-defibrillator (AICD) frequently come to the operating room for procedures requiring electrosurgery (see Chapter 48). For such patients, bipolar devices should be used whenever possible. Nevertheless, interference with the pacemaker can occur on rare occasions in such cases. Regardless of the type of electrosurgery being performed, an AICD should be turned off during surgery because an unexpected intraoperative delivery of its 3- to 20-J defibrillation shock could result in injury not only to the patient but also to the surgeon and others near or in contact with the patient. People in contact with the patient at the moment of an AICD's defibrillation shock can also receive a dangerous, painful electrical shock. Placement of a magnet over an AICD turns off its defibrillation feature and converts it to pacemaker mode alone. However, magnet placement does not affect the pacing program of a programmable pacemaker. (All AICDs have pacemaker circuitry.) Zoll pads connecting the patient to an external defibrillator/pacer should be fully operational when the AICD's defibrillator is turned off, with the obvious exception being situations involving *code* resuscitation, such as when an advanced cardiac life support (ACLS) team has defibrillator pads ready for use. If anesthesiologists on ACLS teams arrive at a situation during which cardiac arrest has occurred and find that the patient has an implanted pacing device, then they should immediately learn whether the device is an AICD to ensure that precautions such as magnet placement can be taken to avoid shocking the code blue team during resuscitation.

Because so many different types of pacemakers are now in use, the plan for avoiding intraoperative pacemaker interference must be based on the details of each particular case.[5,6] In general, the likelihood of interference depends not only on patient factors, such as the type of pacing electrodes (i.e., unipolar, bipolar) and how well the pacemaker circuitry is shielded, but it also depends on surgical factors, such as the proximity of the cutting electrode's discharge and the path of the electric current within the patient. In all such cases, grounding pads should be placed as far away as possible from the pacemaker and its wires. In addition, if possible, the path from the grounding pad to the surgeon's electrosurgical cutting electrode should not traverse the path from the pacemaker circuit to the heart. Because of capacitive coupling, electrosurgical noise can potentially affect either the heart directly or disrupt processing by the pacer's program in a programmable pacemaker. Such interference can result in complete heart block and no pacing or in severe tachycardia. Descriptions of incidents can be found in numerous recent reports.[7,57-60]

Although anesthesiologists should always be prepared to reset a pacemaker to the asynchronous mode (i.e., regular, uninhibited pacing), assuming that magnet placement always converts a pacemaker to asynchronous mode, which is the mode needed by patients dependent on a pacemaker, is no longer correct. Because of pacemaker diversity, preoperative consultation with an electrophysiology cardiologist is always appropriate and often essential, as is preoperative assurances that programmable pacemakers have recently been interrogated and found to have no faults and then properly reprogrammed. Although some precautions with programmable pacemakers can be easily understood, such as turning off rate-sensing features, consultation with someone with the proper expertise is often the only way to review the many essential details of the pacemaker.[6,54] Most hospitals have a cardiologist on call who can be reached for an immediate electrophysiology consultation.

Finally, the anesthesiologist should be familiar with the use of isoproterenol, a pharmacologic pacer, which should be available on the anesthesiologist's drug cart. Concentrations of 1 µg/mL are appropriate for small bolus injections.

SAFE PRACTICE

One approach to safe practice involves having complete, efficient checklists to consult for each concern, such as fire safety or safety for patients with pacemakers. The anesthesiologist should go through the checklists relevant to every case, just as the pilot and copilot of a commercial airplane do for air travel. Years ago the word *vigilance* was used more commonly to describe how the

anesthesiologist's eyes and mind are repeatedly and systematically scanning everything in the operating room. Vigilance is now used more appropriately to describe the virtues of sophisticated electronic monitors and alarms in the operating room. However, no electronic monitors can direct the anesthesiologist's attention to issues "outside the alarms," to issues related to organization and planning, such as having enough electric power outlets in the operating room to accommodate all the equipment while also avoiding circuit overloads. Limitations of checklists include the danger of "finding only what one looks for and recognizing only what one knows."[61] Although safe practice is boosted by checklists, anesthesiologists should also always be vigilant for new problems. Thus the guidelines that the Key Points present at the beginning of this chapter should be considered a minimal summary that directs safe electrical practice, with a natural assumption that many anesthesiologists will add refinements and elaborations.

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Chapter 110

Environmental Safety and Chemical Dependency

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Key Points

- Escape of anesthetic vapors into the operating room atmosphere is unavoidable. In the United States, the limits of exposure to atmospheric waste gases are set by the National Institute for Occupational Safety and Health (NIOSH), which recommends a time-weighted average of 25 ppm for nitrous oxide and a ceiling of 2 ppm for volatile anesthetics.
- Based on high-quality data, trace concentrations of anesthetics in the ambient air of the operating room probably do not present a health hazard.
- Occupational exposure to radiation comes primarily from x-rays scattered by the patient and surrounding equipment. A distance of 3 feet from the patient is recommended to minimize physiologic damage from occupational exposure, and a distance of 6 feet from the patient provides the same protection as 2.5 mm of lead.
- Occupational exposure to human immunodeficiency virus (HIV) and hepatitis B and C is most often the result of a percutaneous injury. The risk of transmission is generally infrequent but is most often from hollow-bore needles, needles contaminated with visible blood, and exposure to a source patient with high viral titer.
- Postexposure prophylaxis is recommended after occupational exposure to HIV or hepatitis B virus. The U.S. Public Health Service–recommended guidelines for postexposure prophylaxis are available on the Centers for Disease Control and Prevention (CDC) website. The National Post-Exposure Prophylaxis Hotline is open 24 hours a day for expert advice (1-888-448-4911).
- To minimize occupational exposure to bloodborne pathogens, standard precautions should be practiced at all times. The appropriate barrier precautions for anticipated contact with blood or body fluids are published by the CDC. Whenever possible, needleless systems should be used.
- Sleep deprivation has an adverse effect on physician mood, cognitive function, reaction time, and vigilance. Although sleep deprivation and fatigue clearly adversely affect clinical performance, their full impact on patient outcome has been difficult to determine.
- Anesthesiologists are overrepresented in drug treatment centers. The preference for and access to potent opioids contribute to the prevalence of drug addiction among anesthesiologists.
- The rate of drug-related deaths is more than twice as frequent in anesthesiologists as in internists.
- Although many successfully treated anesthesiologists return to the practice of anesthesia, they have a significant relapse rate. The chance of relapse is most frequent in physicians who become addicted to potent narcotics early in their career. Successful recovery requires a lifelong commitment to treatment. In some cases, leaving anesthesia as their specialty is the only solution.

The practice of anesthesiology exposes its practitioners to a variety of risks unique among medical specialties. Some of these risks are tangible or physical, such as waste anesthetic gases and communicable disease, whereas others are more insidious and psychological, such as stress, fatigue, and the pitfalls of substance abuse. Each of these risks can be mitigated, but probably not eliminated. In the case of physical exposures such as anesthetic gases, radiation, and bloodborne pathogens, efficient gas scavenger systems, needleless systems, needle-shielded intravenous

(IV) lines, standard precautions, and postexposure prophylaxis (PEP) protocols are now commonplace in contemporary anesthesia practice. The less tangible risks are, not surprisingly, more difficult to reduce. Although instituting work hour restrictions with house staff may limit fatigue, doing so may not improve patient outcomes, particularly when the restriction does not apply to practicing physicians. Substance abuse remains a problem with a multifactorial etiology and few satisfactory solutions. This chapter examines the relative risk of each of these environmental and situational hazards and reviews the measures one can take to avoid them. Awareness is essential to safe anesthesia practice.

ANESTHESIA GASES

Trace amounts of waste gases enter the operating room atmosphere each time an inhaled anesthetic is delivered. The possible effects of occupational exposure include cognitive impairment and reproductive problems (e.g., spontaneous abortions and developmental defects in children).[1] Various agencies have imposed limits for occupational exposure, but these are generally derived arbitrarily and are outdated. Although many strategies exist to mitigate exposure, imposed limits are routinely exceeded in clinical practice.

EXPOSURE LIMITS

Concentrations of waste gases are reported on a volume-per-volume basis in parts per million (ppm). For example, 100% sevoflurane, such as in the saturated vapor above the liquid in a bottle or vaporizer, has a concentration of 1 million ppm. Similarly, 2% sevoflurane represents 20,000 ppm. The National Institute for Occupational Safety and Health (NIOSH) recommends a limit of 25 ppm for nitrous oxide (N_2O) and a ceiling of 2 ppm for volatile anesthetics in the ambient air of the operating room.[2] When used in combination with N_2O, the ceiling for volatile anesthetics is reduced to 0.5 ppm.[3] In 1989, the American Conference of Governmental Industrial Hygienists incorporated duration of exposure into their guidelines and suggested a limit of a time weighted average of 50 ppm N_2O over an 8-hour work day.[1] The Occupational Safety and Health Administration (OSHA) published a detailed summary of causes and effects of occupational exposure to anesthetic gases, but this has not been updated since the year 2000, and it mimics the exposure limits set by NIOSH 2 decades earlier.[1] In 2012, the National Institutes of Health Division of Occupational Health and Safety published updated occupational exposure limits for sevoflurane (2 ppm) and N_2O (50 ppm), as well as for older anesthetics no longer in routine use (Table 110-1).[4]

To put these figures into perspective, assuming that 1 mL of a volatile liquid anesthetic produces 200 mL of vapor, that volume of liquid spilled in a closed room measuring 20 × 20 × 9 feet results in a concentration of vapor of nearly 2 ppm. The maximal concentration of halothane recommended by NIOSH is severalfold lower than the lowest concentration that humans can recognize. Only 50% of volunteers were able to detect halothane at concentrations as low as 33 ppm. The threshold of perception ranges from less than 3 to more than 100 ppm.[5] If the anesthetic can be smelled, its concentration is well above the maximum recommended level.

The NIOSH exposure limits were developed in the late 1970s for N_2O and halothane and, unfortunately, have not been updated since, nor do they include newer volatile anesthetics. These levels were selected somewhat arbitrarily, based on the lowest level known at the time to cause side effects (50 ppm N_2O or 1 ppm of halothane caused cognitive impairment in dental students[6]), juxtaposed against the level that could be easily and practically achieved.[7] Subsequently, it was realized that the subjects were Mormon, a subgroup likely more sensitive to depressant drugs; the general population may not be susceptible to gases at these low levels.[8] More recent work in a general, albeit small, sample showed cognitive impairment at 50 ppm,[9] and in any case, levels are routinely found by researchers to be well above these NIOSH levels.[10,11]

Waste N_2O and volatile anesthetics in the absence of scavenging may approach concentrations as high as 3000 and 50 ppm, respectively.[5] Although the concentration of waste gases can be well controlled with proper scavenging, in practice, the levels recommended by NIOSH are not consistently met in the routine delivery of anesthesia. Induction of anesthesia through a mask with likely leaks, disconnection of circuits, the use of laryngeal mask airways, and uncuffed endotracheal tubes all contribute to operating room contamination. Although exposure to anesthetic gases is more common in pediatric anesthesia (see also Chapter 93), during which induction of anesthesia and uncuffed endotracheal tubes are common, the introduction of the laryngeal mask airway to anesthesia practice probably increases operating room exposure to waste gases in adult cases as well. One study of inhaled induction of anesthesia and maintenance with sevoflurane and N_2O in adults resulted in violations of NIOSH standards 50% of the time.[12]

The universal use of scavenging systems can lead to a false sense of security among operating room personnel. Kanmura and colleagues found abnormally high ambient concentrations of N_2O in 402 delivered anesthetics, of which 42% were the result of ventilation through a mask,

TABLE 110-1 PROPOSED LIMITS OF EXPOSURE TO INHALATIONAL ANESTHETIC AGENTS

Agent	NIOSH (ppm)*	NIH (ppm)†
Nitrous oxide	25	50
Halothane	2	50
Isoflurane	2	2
Sevoflurane	–	2

NIH, National Institutes of Health; *NIOSH,* National Institute for Occupational Safety and Health; *ppm,* parts per million.

*Data from National Institute for Occupational Safety and Health: *Criteria for a recommended standard: occupational exposure to anesthetic gases and vapors*, DHEW (NIOSH) publication no. 77-140, Washington, DC, 1977, U.S. Department of Health, Education and Welfare.

†National Institutes of Health: *Waste anesthetic gas (WAG) surveillance program,* 2012. <http://www.ors.od.nih.gov/sr/dohs/Documents/Waste%20Anesthetic%20Gas%20%28WAG%29%20Surveillance%20Program.pdf/> (Accessed 06.12.13.)

19.2% originated from a disconnected scavenging system, 12.5% were the consequence of a leak around pediatric endotracheal tubes, and 11.5% were the result of equipment leakage.[13] Although dysfunction of the scavenging system was not the most common cause of ambient contamination, scavenging system disconnections led to higher contamination levels than levels resulting from inhaled induction of anesthesia. Furthermore, all the scavenging system disconnects in this study were due to human error rather than equipment failure.[13] Because most anesthesia machines are not equipped to recognize disconnected scavenging systems, failure of the system may not be readily apparent. Thorough understanding and diligent maintenance of anesthesia scavenging systems is essential to comply with NIOSH standards and, more importantly, to minimize operating room exposure.

Occupational exposure is not limited to operating room staff; patients continue to exhale trace amounts of N_2O for 5 to 8 hours after arrival in the postanesthesia care unit (PACU).[14] Sessler and Badgwell measured the concentrations of gases at the lapel level of recovery room nurses during the first hour of PACU care in patients who had received inhaled anesthetics.[15] In this study, breathing zone anesthetic concentrations were in excess of NIOSH recommendations in 37% of patients who received isoflurane, 87% of patients who received desflurane, and 53% of patients who received N_2O. A more recent but similar study reported a much lower average concentration (3.1 ppm) of N_2O in the breathing zone of recovering patients in a Canadian PACU.[14] These studies demonstrate the importance of proper ventilation in PACUs. Both groups reported PACU room air exchanges of 8 volumes per hour; however, much of the air in the Sessler and Badgwell study was recirculated.[15] N_2O levels can be reduced to undetectable levels with air exchanges of 20 per hour, with 25% of each exchange taken from fresh air.[16]

Although OSHA does not currently regulate exposure to N_2O and halogenated anesthetics, this agency does provide guidelines designed to minimize workplace exposure. These include the appropriate assembly and monitoring of scavenging systems, the detection and correction of machine leaks, and the installation of effective ventilation systems.[1] In the operating room, the recommended air exchange rate is a minimum of 15 air exchanges per hour with at least 3 air exchanges of outdoor air per hour. In the recovery room, at least 6 air changes are recommended with a minimum of 2 exchanges of outdoor air per hour. OSHA recommends that air sampling for anesthetic gases be performed on a biannual basis, to document the extent of worker exposure and the effectiveness of scavenging and ventilation systems. Further, OSHA recommends maintaining records of air sampling methods, locations, dates, and concentrations measured, as well as results of anesthesia machine leak tests for at least 20 years. Although OSHA is a government agency, these recommendations are not yet legally mandated.[17]

HEALTH EFFECTS

Anesthetics have been implicated as causes of cancer, abortions, and deficits in cognitive and psychomotor performance. Although early studies with older anesthetics administered to rodents through gavage were associated with carcinogenicity, the route and dose may not be relevant to current anesthetic practice.[17] Newer anesthetics, when tested by the inhaled route, did not show such an association, although the newest inhaled anesthetics, sevoflurane and desflurane, were not tested.[17]

The possibility that chronic exposure to anesthetic waste gases could result in adverse health effects was first appreciated in the late 1960s, when a report of potential harm appeared in the Russian literature. In 1967, Vaisman reported an increased incidence of abortions among female anesthetists. Specifically, this study noted 18 spontaneous abortions in 31 pregnancies.[18]

After this initial report, many retrospective studies followed. Of these, three large studies conducted during the mid-1970s in the United States and the United Kingdom all concluded that the prevalence of abortion was substantially higher in female anesthesiologists than in female physicians working outside the operating room. Studies in this era also concluded that the incidence of congenital anomalies in children of male and female anesthesiologists was higher than in the control groups of physicians. In addition to these reproductive effects, meta-analysis of six of these early studies linked the exposure to anesthetic gases to hepatic disease in male anesthesiologists[19] and cervical cancer, liver disease, and kidney disease in female anesthesiologists.[20]

Subsequently, many reports criticized these original studies, citing faulty methodology as a basis for erroneous conclusions that were disproved when the data were reanalyzed. Biases may have arisen for many reasons, including inadequate response rates, lack of control for confounding variables (e.g., age, nutrition, obstetric history, drinking, smoking, exposure to methylmethacrylate, and radiation), lack of quantification of the exposure to anesthetic vapors, losses to follow-up, inappropriate comparison groups, and lack of independent verification of the reported data.[19-22] Even the titles of some questionnaires, such as "Effects of Waste Anesthetics on Health" and "Anesthetic Practice and Pregnancy," may have introduced selection and recall bias by stimulating respondents who work with anesthetics to overreport their past experiences.[23,24] Nevertheless, as late as 1997 a meta-analysis of more than 19 studies completed between 1984 and 1992 reported a relative risk of abortion in female subjects exposed to anesthetic gases to be 1.48 (confidence interval [CI] 95%, 1.4 to 1.58).[25]

Given the persistence of this controversy, a Task Force on Trace Anesthetic Gases was convened by the American Society of Anesthesiologists (ASA) Committee on Occupational Health of Operating Room Personnel. The task force analyzed data from all of the available epidemiologic studies at the time and concluded that no proof of an association between occupational exposure to waste anesthetic gases and adverse health effects existed. In addition to the analysis of retrospective studies, their report, published in 1999 and not since updated, cited data from a prospective survey in the United Kingdom.[26] This study monitored 11,500 female physicians in the United Kingdom and documented occupation, work practices, lifestyle, and medical and obstetric history, as well as hours

of exposure and the use of scavenging equipment. This report showed the incidence of infertility, spontaneous abortion, and children with congenital abnormalities in female anesthesiologists to be the same as that in other physicians.[26] A more recent review described the scientific evidence for hazard from trace occupational exposure as weak,[20] and the stance of the ASA is that "There is no evidence that trace concentrations of waste anesthetic gases cause adverse health effects to personnel working in locations where scavenging of waste anesthetic gases is carried out."[17] However, most of the studies have significant limitations, and routine occupational exposure may exceed that considered safe.

COGNITIVE PERFORMANCE

The NIOSH recommendations arose from a study by Bruce and Bach in which healthy volunteers in the laboratory suffered a decrease in psychomotor performance when exposed to concentrations of N_2O as low as 50 ppm, alone or in combination with 1 ppm of halothane. The same study showed that 25 ppm of N_2O combined with 0.5 ppm of halothane had no effect.[2,27] Subsequently, three other groups of researchers studying volunteers in laboratories were unable to confirm the findings of Bruce and Bach. The lack of agreement among investigators has led some to conclude "that there is no convincing evidence that anesthetics in concentrations equal to those found in unscavenged operating theatres have any effect on the psychomotor performance of healthy subjects in the laboratory."[28] A study conducted in volunteers in an operating room during normal clinical activities in which trace concentrations of N_2O and halothane ranged from 0 to 2300 and 0 to 37 ppm, respectively, also failed to detect impairment in psychomotor performance.[29] These studies suggest no definitive cutoff above which psychomotor performance is depressed. Hence occupational limits vary among countries. The standards set by the regulating bodies in Canada, United Kingdom, and Western Europe are often less stringent than the standards set in the United States.[5]

RADIATION

The anesthesiologist is routinely exposed to both ionizing and nonionizing electromagnetic radiation. Ionizing radiation is primarily from x-rays and occasionally from radioactive isotopes that release gamma rays, and the nonionizing radiation is from lasers. Less common is contact with ionizing radiation from radioactive isotopes that release either alpha or beta particles. Ionizing radiation has enough energy to create both free radicals and ionized molecules in tissues by driving electrons completely out of their stable orbitals. If the radiation exposure is severe enough, tissues may be destroyed, or chromosomal changes may cause malignant growth. Nonionizing radiation may excite electrons to move from the ground state to higher orbitals in molecules, but the electrons remain in the molecule. In this case, damage to tissues may result from the heat produced by the absorbed radiation.

IONIZING RADIATION: X-RAYS

In the past, exposure to radiation occurred mostly in the operating room with the use of portable fluoroscopy and x-ray machines. Since 2000, however, in concert with the rise in the provision of anesthesia services for imaging and image-guided procedures, anesthesiologists are increasingly at risk for exposure to larger doses of radiation. The advancement of endovascular surgery has led to a marked increase in the numbers of procedures performed in the radiology suite, thus significantly increasing exposure of anesthesia personnel to ionizing radiation. Because this type of radiation is undetectable with our normal senses, a basic understanding of its features will permit one to keep personal exposure to a minimum. Film badges, although not protective, provide a means of monitoring exposure.

Exposure is commonly reported in units of rem (roentgen equivalents man). A rem is essentially a measure of the biologic damage from radiation adjusted to apply to all tissues.[30] Estimates of radiation exposure from natural sources vary, depending on geographic location. The average in the United States ranges from 80 to 200 millirems (mrem) per year. Natural radiation comes primarily from cosmic rays (≈40 mrem at sea level, with an increase of 10 mrem/1000 feet), as well as from radioactive compounds found in soil, brick, and concrete. For most physicians, the additional radiation from occupational exposure is no more than that from natural sources. Although the maximum yearly occupational exposure is mandated to be no more than 5 rem, radiology personnel rarely absorb more than 10% of this dose. Their largest source of exposure is fluoroscopy. During pregnancy, radiography personnel are advised to limit their exposure to a maximum of 500 mrem.[31]

Occupational exposure to radiation comes primarily from x-rays scattered by the patient and the surrounding equipment, rather than directly from the x-ray generator itself.[32] One chest radiograph results in approximately 25 mrem of exposure to the patient; procedures requiring multiple films occasionally involve more than 1 rem. The amount of radiation generated during fluoroscopy depends on how long the x-ray beam is on. Just as light is reflected from surfaces, x-rays are reflected from the surfaces on which they impinge. This scattering accounts for most occupational exposure. Because the intensity of scattered radiation is inversely proportional to the square of the distance from the source, the best protection is physical separation. A distance of at least 3 feet from the patient is recommended. Six feet of air will provide protection the equivalent of 9 inches of concrete or 2.5 mm of lead.[33] Although they are uncomfortable, aprons containing the equivalent of 0.25 to 0.5 mm of lead sheet are effective in blocking most scattered radiation, and such devices are recommended to be worn whenever an exposure risk is present.[34] Uncovered areas, such as the lens of the eye, still bear the risk of injury.[32] Intraoperative radiation measurements have shown that exposure is inversely related to the experience of the surgeon, and the amount of radiation received by the anesthesiologist during orthopedic procedures is unmeasurable.[35]

Radiation physicists recommend adhering to the ALARA program: radiation exposure should be kept as low as reasonably achievable. Staff members of departments of radiology have been extensively educated in the safety of occupational exposure. Attention to recommended methods of protection will limit exposure to minimal levels. Technologic innovation leading to advances in imaging technology and industrial design may further limit exposure.[36,37]

NONIONIZING RADIATION: LASERS

Laser is an acronym for light amplification by stimulated emission of radiation (see also Chapter 88). Lasers produce infrared, visible, or ultraviolet light. Although the radiation from lasers is nonionizing, it is potentially unsafe both because of its intensity and because of the matter released from tissues during treatment.

Lasers are used in many surgical specialties, including ophthalmology, plastic surgery, gynecology, neurosurgery, urology, head and neck surgery, and gastrointestinal surgery. A surgical laser produces intense, focused electromagnetic radiation to cut or destroy tissues. The radiation is usually infrared or visible light and is created in a "laser medium" that is stimulated by high-intensity energy to release photons of identical wavelength (coherent or monochromatic light) from a laser chamber. The material in the medium (e.g., carbon dioxide, argon) is responsible for the wavelength produced by the laser. Of those in common clinical use, carbon dioxide and neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers emit light in the far-infrared and near-infrared wavelengths, respectively; argon and tunable dye lasers produce visible light.[38]

Eye injuries are the greatest risk to personnel working near lasers. Strict standards for protection have been developed on the basis of current understanding but are subject to periodic revision as more experience is gained with these instruments. Either direct exposure or reflected radiation may cause eye damage. Injuries include burns to the cornea and retina, destruction of the macula or optic nerve, and cataract formation. Protective eyewear is designed to filter out the radiation produced by a specific type of laser while still permitting vision. For example, clear plastic lenses block the far-infrared (10.6 μm) radiation from carbon dioxide lasers but provide no protection against the near-infrared (1060 nm) radiation emitted by Nd:YAG lasers. The type of protection provided by a given filter is marked on the frame of the goggles and should be checked before use. Filters that are scratched should not be used. Because certain filters block portions of the visible spectrum, it is prudent to confirm preoperatively that patient monitors can be seen and interpreted correctly with goggles in place. Protective eyewear is recommended for all personnel because reflected radiation can be as hazardous as direct radiation, and the intensity is not diminished significantly in the distances traveled in the average operating room.[38]

Until recently, the plume (i.e., the vapor and cellular debris produced during laser surgery) was not considered to be harmful. Now, concern exists that the plume may present a significant risk. The median size of particles in plume samples obtained intraoperatively is 0.31 μm in diameter (range, 0.1 to 0.8 μm). Most surgical masks do not trap such small particles.[39] Even after filtration of particles greater than 0.5 μm in diameter, exhaust smoke from tissues treated with a carbon dioxide laser causes pulmonary lesions in laboratory animals. If all particles larger than 0.1 μm are scavenged, no lung damage occurs, thus pointing out the importance of scrupulous removal of the plume.[40] Under experimental conditions, viable bacteria have been recovered from the plume emanating from laser irradiation.[41] Intact DNA from human papillomavirus (HPV) has been detected in the vapor from both laser-treated plantar warts and genital condylomata.[42,43] Human immunodeficiency virus (HIV) proviral DNA has been found in laser smoke produced by vaporizing cultures of HIV-positive cells. Although these experiments, which used tissue cultures, do not replicate the clinical situation, they stress the importance of strict attention to smoke removal.[44] With adequate evacuation and filtration using equipment specifically designed to scavenge such vapors, it is unlikely that operating room personnel will be contaminated by laser-dispersed HPV DNA.[42] However, one case report documented the appearance of laryngeal papillomas in a surgeon who had previously treated (with a laser and without the benefit of a laser smoke evacuator) several patients infected with anal condylomata. Tissue from the surgeon's laryngeal tumors contained HPV DNA types 6 and 11, the same viral types that are commonly harbored by anogenital condylomata. Although not conclusive, these findings suggest that the laryngeal papillomas may have been caused by inhaled virus particles.[45] Hence, all vaporized debris should be scavenged.

INFECTIONS

Hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV are the most concerning bloodborne pathogens for which health care workers are at risk. Of 493 anesthesia personnel surveyed in a multicenter study, 32% reported having been stuck with a contaminated needle at least once in the preceding 12 months. Of those, only half sought treatment.[46] The risk of infection is more frequent with hollow-bore needles than with solid needles and is further increased with large-bore needles and deep intramuscular injection.[47] In a study evaluating percutaneous injuries (PCIs) in anesthesia personnel, nearly 90% of the injuries were from hollow-bore needles, were self-inflicted, most commonly involved the nondominant hand, and were deemed preventable. Most of the injuries occurred during disposal of contaminated needles.[48] *Mycobacterium tuberculosis* (the agent of tuberculosis [TB)], which is transmitted primarily by respiratory droplets, represents a significant source of occupational risk, and routine screening measures are frequently employed.

HEPATITIS B

In the 1980s, it was estimated that 200 to 300 health care workers would die annually from the effects of HBV. Fortunately, the introduction of an effective vaccine for

hepatitis B dramatically decreased the incidence, morbidity, and mortality of the disease.[49] Before this, the development of covert seropositivity for HBV during residency was common. In a multicenter study, the overall prevalence of serologic indicators for HBV in anesthesiology residents who had received neither hepatitis vaccine nor hepatitis B immune globulin (HBIG) was 17.8% in 267 tested. Most seropositive residents were unaware of having been exposed to HBV. No correlation was found between the incidence and geographic location, but the incidence of seropositivity increased in parallel with clinical experience. Thirty percent of residents with more than 11 total years of experience, including their current residency and previous work in other specialties, were seropositive for HBV.[50]

An estimated 800,000 to 1.4 million people in the United States have HBV infection, most of whom are unaware of their infected status.[51] Although the incidence of seroconversion after parenteral inoculation with HBV can be as high as 40%, the rate of conversion is proportional to the infectivity of the host and the magnitude of contact with the blood.[52] HBV is hardy; neither treatment at 60° C for 4 hours nor the use of disinfectants containing phenol or chlorine is sufficient to inactivate the HBV particle with certainty, and it remains viable on needles, environmental surfaces, and gloves for longer than 14 days.[53] Because gloves do not guarantee protection from accidental needlestick and because HBV is relatively resistant, accidental contact with live virus may occur in the course of patient management and also during cleaning of equipment. Active immunization of seronegative health care workers with hepatitis B vaccine is imperative for prophylaxis against infection. Since the late 1980s, the vaccine has been synthesized in yeast by the use of recombinant DNA, thus eliminating prior concerns about the potential infectivity of vaccines synthesized from the sera of hepatitis B surface antigen (HBsAg)–positive patients.[54] The current OSHA standard on bloodborne pathogens mandates that employers make vaccination against HBV available at no cost to all employees who have a reasonable chance of exposure to the virus.[55] Unvaccinated anesthesiologists who suspect HBV exposure with an HBsAg-positive source should be passively immunized with HBIG and begin a series of three injections of hepatitis B vaccine.[49] The combination of HBIG and HBV vaccine prophylaxis is believed to be 85% to 90% effective, whereas either treatment alone is 70% to 75% effective.[56]

HEPATITIS C

Like HBV, HCV is transmitted principally by infected blood. Fortunately, the incidence of HCV in stored bank blood has dramatically decreased (see Chapter 61). Using the anti-HCV assay, some investigators have reported only a 1% to 2% incidence of antibody to HCV in health care workers (similar to that seen in volunteer donors), a finding suggesting that HCV is not easily transmitted.[57,58] Reports based on the same assay indicate that transmission of HCV by contaminated needles occurs in less than 4% of these injuries.[59] At present, no effective postexposure treatment is available for HCV exposure. Instead, the recommendations for postexposure management are geared toward early recognition and intervention in chronic disease. Serum immune globulin prophylaxis is of little value because anti-HCV antibodies are not consistently found in production lots of immune globulin.[52] Health care workers who are exposed to HCV should undergo baseline testing for anti-HCV and alanine aminotransferase activity as soon as possible after the injury, with follow-up testing 3 and 6 months after exposure.[56]

HUMAN IMMUNODEFICIENCY VIRUS

HIV is a retrovirus that attaches to cells with $CD4^+$ surface antigen (predominantly helper T lymphocytes) and ultimately replicates by integrating virally produced DNA into the nucleus of the host cell.[47] Fortunately, HIV is a relatively fragile virus, and with proper attention to cleanliness and care in performing invasive procedures, the likelihood that the disease will develop in an anesthesiologist during the course of patient management is very low.

Initial infection with HIV follows within 2 to 10 weeks of inoculation. It is usually a self-limited, nonspecific, febrile viral syndrome lasting 1 or 2 weeks. An individual is considered to be both infected with HIV and infective if the results of both a serologic screening test, the enzyme-linked immunosorbent assay (ELISA), and a supplemental, more sensitive test, either Western blot or indirect fluorescent antibody, are positive. ELISA tests are relatively easy to perform in a clinical laboratory but may be subject to false-positive results. Supplemental tests are time consuming but necessary for confirmation. Results of the tests become positive within weeks of inoculation, but the median latency for the first opportunistic disease may be as long as 11 years.[47]

Although occupationally related infections have been reported, most cases have been attributed to nonvocational contact.[60] According to data published in 2001 by the CDC, 56 probable cases and 138 possible cases of occupationally acquired HIV infection had been reported in the United States.[56] Of these, 48 resulted from percutaneous exposure. Of 1746 reported cases of acquired immunodeficiency syndrome (AIDS) in physicians, only 6 were directly linked to occupational exposure. Injury from a needle is the most likely route of occupationally related HIV infection for anesthesiologists. Although the minimal dose of contaminated blood needed to infect humans is unknown, the likelihood of development of antibodies to HIV is related to the volume of the inoculum and the concentration of viral particles.[49] Consequently, most seroconversions have been associated with deep intramuscular injection of contaminated blood through large-bore needles. The theoretic risk for occupational infection in anesthesiologists over a 30-year exposure period has been calculated to be 0.049% for HIV and 0.45% for HCV, depending on the infectivity of the patient population.[61]

The risk of transmission of HIV from health care workers to patients, with the exception of errors in technique, is extremely small. No infections were identified in more than 19,000 patients who had been treated by 57 infected health care workers, including 29 dentists,

12 surgeons, and 16 physicians in nonsurgical specialties. The only documented infections have been in 6 of 1100 patients treated by a dentist in Florida.[62] With proper attention to routine methods of disinfection, sterilization, and housekeeping, HIV on instruments, surfaces, and laundry can be destroyed. The amount of HIV usually found on contaminated surgical instruments and equipment used in anesthetic management can be killed with "high-level disinfection." Such disinfection involves careful cleaning, followed by exposure either to one of the commercially available germicides or to a 1:10 to 1:100 dilution of sodium hypochlorite (household bleach). These methods annihilate bacteria and viruses but may not be effective against bacterial spores. If the instruments are to be sterilized, they should be thoroughly cleaned first. Contaminated hospital linen should not be washed or rinsed in the operating room or another patient care area; instead, it should be placed directly in sealed, water-impenetrable bags. It can safely be laundered by normal methods. Infective waste, including secretions, blood, and other body fluids, should be incinerated or autoclaved. Alternatively, large volumes of fluids may be discarded in a sanitary sewer.[63] Personal protection and protection of patients are afforded by standard precautions.

PREVENTION OF OCCUPATIONAL EXPOSURE TO BLOODBORNE INFECTIONS

In 1992, OSHA issued comprehensive, enforceable standards designed to minimize occupational exposure to bloodborne pathogens. These standards hold the employer responsible for the maintenance of an exposure control plan that protects all health care workers who have potential for contact with blood or blood products. Protective equipment, including gloves, gowns, and eye shields, must be supplied by the employer at no cost to the employee. The standard also provides for hand-washing facilities, proper receptacles for contaminated materials, methods for handling contaminated laundry, and management of waste, among many other things.[55]

Despite the adoption of standard precautions, contaminated needlestick injuries in health care workers persisted at an unacceptable rate. In 2000, the CDC estimated that more than 380,000 contaminated PCIs occur in hospital workers in the United States on an annual basis.[64] As a result, Congress revised the bloodborne pathogen standard to include the Needlestick Safety and Prevention Act (H.R. S178).[65] This act emphasizes the use of safety devices and needle-free systems, in addition to requiring that employers establish an exposure control plan with records documenting each incident. Since the act was signed into law in November 2000, as part of a comprehensive program to prevent the transmission of bloodborne pathogens in health care workers, NIOSH has called for the elimination of needle devices when "safe and effective alternatives are available." This recommendation was based on accumulating evidence in the 1990s showing that devices with safety features could reduce needlestick injuries.[66]

The risk of contaminated PCI correlates with medical specialty and clinical experience. The Duke Health and Safety Surveillance System tracked blood and body fluid exposures among 24,425 health care workers over a 4-year period ending in 2002. The investigators reported an average rate of 3.9 PCIs per 100 full-time equivalents (FTEs), with higher rates among persons employed for less than 4 years. Anesthesia house staff members reported among the highest rates, at 19.1 PCIs per 100 FTE.[67] Extended work hours were implicated as a major causative factor in a study of PCIs in interns. In this study, 498 PCIs were reported from a total of 17,003 monthly surveys. Whereas lapse in concentration (64%) and fatigue (34%) were the 2 most commonly reported contributing factors, PCIs were significantly more frequent during extended work hours and at night.[68]

Not all PCIs are associated with disease transmission. Rates of transmission of HCV and HIV are quite low (0.5%[69] and 0.3%, respectively),[69-71] but depend on the type of exposure (e.g., hollow-bore, vascular access needles, depth of penetration) and source factors (e.g., viral load). Rates of transmission of HBV are 30% in health care workers without adequate vaccination or PEP.[69] Because most occupational exposures do not result in HIV transmission, the guidelines for PEP weigh the relative risk of infection against the potential toxicity of treatment. The relative risk of infection depends on both the type and amount of blood exposure. The risk of transmission is increased by (1) percutaneous exposure, (2) devices contaminated with visible blood, (3) hollow-bore needles, and (4) high viral titer (i.e., a patient late in the course of the disease). In general, health care workers encountering needlestick injuries should be given HBIG, the hepatitis B vaccine, or both, unless they have already been vaccinated, and antiretrovirals for HIV should be considered in consultation with experienced clinicians. In the event of an exposure to blood or body fluid, health care workers should immediately contact their on-site occupational health department and the National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline) at 1-888-448-4911 for expert advice. This hotline can be accessed 24 hours a day, and it offers advice on evaluating the risk of disease transmission and initiation of PEP. In addition, updated guidelines for the management of occupational exposures to bloodborne pathogens are available on the CDC website at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5011a1.htm.[56]

Evaluation for PEP and baseline HIV testing should be completed within hours of exposure. Prophylaxis should begin as soon as possible because animal studies show that prophylaxis is less effective if begun more than 24 to 36 hours after exposure. Because the time to no benefit in humans is unclear, the U.S. Public Health Service advises beginning prophylaxis up to 1 week after exposure. Four weeks of treatment is recommended if tolerated. Regardless of whether PEP is initiated, follow-up should include counseling and HIV antibody testing at 6 and 12 weeks and again at 6 months after exposure.[72]

Data on the efficacy of PEP in health care workers are insufficient, primarily because seroconversion from occupational exposure in health care workers is rare. A single retrospective study of HIV PEP with zidovudine in health care professionals after PCI showed a risk reduction of 81% (95% CI, 45% to 94%).[73]

TUBERCULOSIS

TB, the leading cause of death in the early twentieth century, appeared to be steadily decreasing in incidence with the advent of streptomycin in 1946, isoniazid in 1952, and rifampin in 1970. However, in 1985, the incidence in the United States began to increase significantly. Between then and 1990, reported cases increased by 16%, with a 10% increase in 1990 alone. This increase was the largest since national reporting began in 1953.[74] Most cases were from reactivation of old infection in immigrants or in patients whose immune system had been compromised, and many cases involved multidrug-resistant strains of *M. tuberculosis*. Epidemic transmission between hospitalized patients and from patients to health care workers also occurred.[75,76] Common to most of these cases was a low index of suspicion for TB, which was occasionally not confirmed before postmortem examination.[77]

In response to the resurgence of TB in the United States in the mid-1980s, the CDC published new guidelines for the prevention of transmission of TB in 1990. These guidelines were revised throughout the decade, first in 1992 and again in 1994. The 1992 guidelines targeted the prevention of TB transmission in the hospital setting, and the 1994 guidelines added recommendations for the management of multidrug-resistant TB. The guidelines, most recently updated in 2005, include a comprehensive program for the prevention of multidrug-resistant TB in health care facilities.[78] The program places the responsibility for managing prevention of TB on individual health care facilities, rather than requiring identical standards for all hospitals. Paramount are the following: identification and treatment of patients with TB; development of engineering controls, including isolation rooms, filters, and ventilation; use of personal protective equipment; and implementation of educational programs for health care workers.

Since the implementation of CDC guidelines in the 1990s, the number of new cases of TB has steadily declined such that the number of cases now being reported is the lowest since 1953, the first year of reporting in the United States.

In 2010, the overall incidence of TB in the United States was 4 cases per 100,000 population.[79] This was less than the 8 per 100,000 reported in 1996. Despite this general decline, a marked geographic variation in incidence remained. In 2011, the highest incidence was found in Alaska (9.3 per 100,000), followed by California (6 per 100,000), and New York (4.7 per 100,000).[80] The lowest rate of infection was documented in Wyoming (0.7 per 100,000). The risk to health care workers probably correlates with the region in which they practice.

The goal of the CDC was to decrease the rate of TB infection in the United States to less than 1 per million by 2010.[78] To this end, the scope of the current recommendations were significantly broadened to include health care "settings." The term health care settings in this document encompasses all facilities in which health care is delivered, including clinics, correctional facilities, and so on.[78]

TB spreads by small (1- to 5-μm), airborne droplets released when a person with pulmonary or laryngeal TB speaks, coughs, sneezes, or sings. The probability of transmission is directly related to the concentration of infectious droplets (up to 600,000 droplets may be expelled with each cough) and the duration of exposure. Droplets can travel up to 3 feet from the source and remain viable and airborne for several days.[74] Not surprisingly, endotracheal intubation is second only to bronchoscopy as a risk for skin test conversion in health care workers. In healthy persons who have inhaled contaminated droplets, the resulting systemic infection is usually limited by the immune system within 2 to 10 weeks. In these individuals, the lifetime risk of developing active TB after infection is approximately 10%. The likelihood is more frequent in patients with HIV, who have a 7% to 10% risk of converting per year.[78]

The commonly used tuberculin skin test (purified protein derivative) provides a qualitative measure of TB infection. A newer quantitative test for TB is now available, but it requires a blood sample. This test can identify infection with atypical organisms.[78] All health care workers at high risk for exposure to TB should be skin tested at the time of employment. Those whose test results are negative should be retested annually. A positive test in a person who has not tested positive in the past suggests a new infection. A two-step test is recommended in anyone who tests negative more than a year after TB exposure or previous tuberculin testing. This is because latent infection can produce false-negative results from waning over time of the delayed-type hypersensitivity response. The first test will "boost" the response, leading to a positive result. The second test, performed 1 to 3 weeks after the first, increases the negative predictive value of the test.

A newly positive skin test requires exclusion of active disease by chest radiograph and clinical evaluation. If TB is diagnosed, treatment according to recommended guidelines should begin immediately. Disease reporting laws generally require notification of local or state health departments within 24 hours. If active disease is excluded, drug therapy for latent TB infection should be considered, in consultation with occupational health and infectious disease physicians, given the documented liver toxicity of common drug regimens.

Asymptomatic conversion does not preclude the anesthesiologist from working.

OSHA standards to prevent airborne contamination include both environmental controls and respiratory protection. Environmental controls include engineering measures to manage exhaust ventilation and general ventilation. Examples are air exchange rates, high-efficiency particulate air (HEPA) filtration, and ultraviolet germicidal irradiation (UVGI; irradiation of the air in the upper portion of a room, or within ducts and recirculating units). Respiratory protection requires masks with the ability to filter particles smaller than 1 μm with a filter efficiency of 95%, at inspiratory flow rates up to 50 L/minute. If these masks are worn properly, even with strenuous activity in the work setting, less than 5% of infectious particles will escape filtration. These masks are typically referred to as N95 masks. Essential to proper mask function are tight mask fit, so as not to allow entrained air with inspiration, and a clean filter. To this end, the NIOSH requires the annual oversight of mask fit and maintenance by the employer.

NOVEL INFECTIOUS AGENTS

Occasionally, novel infectious agents come to the fore and create anxiety among populations and health care workers. Examples include the prion disease Creutzfeldt-Jakob disease (CJD), coronavirus infections such as severe acute respiratory syndrome (SARS-CoV) and a potential new Middle East SARS (MERS-CoV), and the H1N1 influenza outbreak of 2009. In the presence of such outbreaks, medical centers must have plans and procedures in place to contain infectious agents and protect workers from infection.

In the context of occupational exposure, perhaps the least infectious of these novel agents are prions. Transmission of prion disease such as CJD is thought to occur as a result of eating meat from animals that suffered from prion disease, or of receiving contaminated implants such as corneal or dural tissue, or from exposure to cadaveric pituitary hormone supplementation, all of which are highly unlikely in the occupational setting. It is controversial whether prions can be transmitted in the donor blood pool, but no such transmission has ever been reported, even though anesthesiologists are frequent handlers of donor blood products. Similarly, the CDC reported in 2007 that no reports of casual or occupational transmissions through airborne or droplet routes had been submitted,[81] and standard precautions are recommended for the care of patients with prion diseases.

Patients with respiratory viruses present a significant risk of occupational exposure to the anesthesiologist.

The SARS-CoV epidemic of 2003 is a great example of the potential impact of programs directed at containment and occupational safety. In Toronto, 77% of the patients in the first phase of the outbreak were infected in the hospital setting, and half of all SARS cases in Toronto were in health care workers.[82] The large number of health care workers who contracted SARS-CoV demonstrates the importance of early detection and infection control in halting the spread of disease. Although SARS-CoV has not been diagnosed since 2004, concerns generated by the outbreak apply to other infectious respiratory illnesses such as seasonal and nonseasonal (H1N1 epidemic of 2009) influenza, and a more recently discovered SARS-CoV–like virus.[83,84] For example, MERS-CoV was documented to have been transmitted from patients to health care workers,[85] and it has an overall case fatality rate of more than 50%.

Although it is too soon to determine how severe an epidemic MERS-CoV may become, and even though advisory groups such as the CDC have yet to issue recommendations, other respiratory viral epidemics may likely occur in the future, and lessons learned from previous epidemics may serve us well in the containment of these agents (Table 110-2).

TABLE 110-2 LESSONS LEARNED FROM PREVIOUS RESPIRATORY VIRUS OUTBREAKS

Systems	Individuals
Anticipate future outbreaks	Droplet and contact precautions
Develop staff and plans for dealing with mass exposure	Eye protection
Adequate isolation equipment	Staying home with fever or cough
Use of simulation to test facility's readiness	Compliance with vaccination programs
Active surveillance	
Data collection and reporting	

From Centers for Disease Control and Prevention: *Severe acute respiratory syndrome, supplement C: preparedness and response in healthcare facilities,* 2004. <http://www.cdc.gov/sars/guidance/C-healthcare/index.html> (Accessed 09.12.13.)

FATIGUE

The impact of fatigue on patient safety has come to the forefront in recent decades (see also Chapter 7). Well-defined periods of vulnerability to sleep have been identified in humans. The major peak occurs between 2 AM and 7 AM, and a smaller peak occurs in the midafternoon.[86] These peaks appear to be enhanced by irregular work schedules and sleep disruption, and they may also contribute to diurnal variation in the frequency of mishaps (e.g., single-occupant motor vehicle accidents and catastrophic industrial accidents; the nuclear reactor accidents at Three Mile Island, Chernobyl, and two other sites in the United States all began between 1 AM and 5 AM). In 1990, an anonymous survey of anesthesia providers revealed that many respondents participated in clinical work for hours beyond their perceived limitations. Most respondents reported making errors in patient care that they attributed to fatigue.[87]

Last updated in 1988, the Committee on Catastrophes, Sleep, and Public Policy of the Association of Professional Sleep Societies made the following recommendations:

1. Management should be made aware that performance errors are more common between 1 AM and 8 AM.
2. Programs should be developed to identify signs of sleep-related error.
3. Because inadequate sleep or irregular sleep patterns enhance the tendency for error, work hours should be limited to permit adequate sleep.[88]

Although it is difficult to single out fatigue as a cause of increased patient morbidity and mortality, increased rates of anesthetic complications for cases started late in the day and during "off-hours" have been reported.[88-90] In one study,[90] most of these complications were related to postoperative nausea and lapses in effective pain management. More compelling data from a Veterans Affairs (VA) study of nonemergency surgical procedures did, however, show an impact on mortality for cases starting after 4 PM.[91] Being on call every third or fourth night has a negative impact on the cognitive function of university house staff on standardized tests.[92] However, when patient simulation was used to study the effects of sleep deprivation on the psychomotor and clinical performance of anesthesia residents, psychomotor performance and mood were found to suffer, whereas clinical performance did not,[93] a finding that has also been published in the surgical literature[94,95] (see also Chapter 8).

Fatigue does affect clinical outcome. For instance, resident physicians made fewer medication errors after their work hours were adjusted to minimize sleep deprivation and fatigue. This study, in a university-affiliated VA, also demonstrated a decrease in the length of patient stay and the number of laboratory tests ordered.[96] In another survey of 225 physicians, 48.8% blamed tiredness and 19.5% blamed the pressure of overwork to be a significant cause of clinical mistakes and suboptimal patient care.[97]

To reduce the presumed effect of fatigue on medical care provided by trainees, the Accreditation Council for Graduate Medical Education in 2011 updated standards for house staff duty hours, as summarized in Box 110-1.[98]

The validity of resident work hour restrictions would be difficult to overcome, even in the presence of conflicting data. Residents' hours of sleep and cognitive performance generally improve with restricted work hours. In contrast, consistently improved patient outcomes remain elusive, and the effect on attending physicians' working conditions and professional satisfaction are generally detrimental.[99] In favor of work hour restrictions, companion papers in the *New England Journal of Medicine* documented both fewer attentional failures (when intern work hours were reduced from 80 to 60 hours per week) and medical errors (when interns' shifts were reduced to, at most, 16 hours).[100,101] However, both studies were small in scope, and duty hour changes were limited to interns, whereas more senior residents continued to work longer shifts.[99] In an effort to determine the effect of work hour regulations on clinical outcome, two large-scale nationwide multicenter studies measured patient mortality within 30 days of hospital admission both 2 years before and after the rules went into effect in July of 2003.[102,103] These investigators compared death rates between hospitals with a large number of residents (thought to be most affected by the rule change) and those hospital with few residents. Although no differences in mortality were identified after the regulations went into effect among millions of Medicare recipients in both more and less teaching-intensive hospitals, a smaller scale VA study did suggest an improvement in patient outcome in a subset of medical patients. Perhaps the effect of fatigue could be mitigated without changes in work hours; a study in surgical residents showed improvements in memory, planning, impulsiveness, and attention, but not psychomotor performance, when fatigued residents were given modafinil, a central nervous system stimulant, compared with placebo. How pharmacologic augmentation of resident performance would be viewed by educators, policy makers, patients, and residents themselves remains to be seen.

It is likely that a fatigued physician who knows a patient well and a rested physician who knows the patient only through a hand-off both have the potential to commit errors; it remains unstudied which will err more. Patient outcomes depend on a delicate balance between discontinuity of care and the effects of fatigue on medical judgment.[104-106]

Stress in the workplace continues beyond the residency years. In a study conducted in the United Kingdom, the most significant source of stress for those beyond their training years was lack of control of circumstances at work.[107] Specific causes included professional relationships (especially with surgeons), work overload, threats of litigation, peer review, and increasing administrative responsibilities. A subsequent survey of retired members of the ASA identified similar stressors. Difficult anesthetic cases, the threat of professional liability, and the stress of night call were all considered significant causes of stress.[107]

Perhaps more than any other medical specialty, the practice of anesthesia requires uninterrupted vigilance with immediate reaction to life-threatening situations. An inappropriate response can prove to be acutely fatal to an otherwise healthy patient. Does the day-to-day practice of anesthesia produce episodes of significant physiologic stress in the practitioner? Evidence for this hypothesis is lacking. In an investigation of 38 anesthesiologists over the course of 203 anesthetic courses, clinically significant changes in physiologic stress did not occur, as measured by changes in heart rate, blood pressure, and cortisol levels.[108] Although management of stress is rarely addressed in medical school or in continuing medical education seminars for anesthesiologists, it should be. Stress is a universal phenomenon to which no one is immune. Vital to our interactions with others is the ability to recognize stressed behavior, not only in other people but also in ourselves. Healthy means of coping with stress include an ability to communicate, appropriate assertiveness, interactive management of conflicts, adequate time with family, and time for recreational pastimes totally unrelated to professional activities.[109]

BOX 110-1 ***Summary of Resident Work Hour Restrictions***

- Residents at all levels are permitted to work no more than 80 hours per week, averaged over 4 weeks.
- PGY1 residents are permitted to work no more than 16 consecutive hours in house.
- Residents beyond PGY1 are permitted to work no more than 24 consecutive hours in house, with an allowance of 4 hours for care hand-off or, in rare circumstances, for continued duty in the service of a single patient, provided doing so fulfills a unique educational or humanistic role.
- Moonlighting is not allowed by PGY1 residents, and, for more senior residents, hours spent moonlighting count toward the 80-hour week.
- Residents should have 10 hours (and *must* have 8 hours) between assigned shifts. If post call, there must be 14 hours between assigned shifts.
- Residents must have 1 day in seven completely free of clinical duties, including home call, averaged over 4 weeks.

PGY1, Postgraduate year 1.

SUBSTANCE ABUSE

The abuse potential of the psychotropic drugs used in the practice of anesthesia is well documented. Potent psychoactive drugs are readily available and familiar to anesthesiologists in the course of their daily practice. Even inhaled drugs pose an abuse potential to health care workers with easy access to these agents; Zacny and Galinkin reported a case of an Air Force pharmacist court-marshaled during the 1991 Gulf War for abusing

isoflurane,[110] and a fatality from sevoflurane abuse has been reported.[111] No doubt, familiarity and availability contribute to the increase in propofol abuse by anesthesia residents since 2000.[112,113]

Scientific evidence increasingly indicates that addiction is a chronic, relapsing disease resulting from the long-term effects of drugs on the brain.[114] Acceptance of this fact is crucial for those dealing with chemically dependent physicians. This section provides information about chemical dependence in anesthesiologists and the steps required to help a colleague or yourself.

EPIDEMIOLOGY

The prevalence of substance abuse among graduated physicians,[115,116] interns and residents,[117-119] and medical students[120] has been studied. A national survey published in 1992 reported a 2.1% annual and a 7.9% lifetime prevalence of substance abuse among physicians. This rate was substantially lower than the corresponding rate of 16% reported for the general population These results cast suspicion on the myth that physicians are more likely to become substance addicted than the population in general.[118] A more recent review suggested that the actual prevalence may be unknown because of variances in case reporting habits and that prevalence may be at least as high as in the general public.[121] Although physicians are less likely to use cigarettes and illicit substances such as marijuana, cocaine, and heroin, they are five times as likely to take sedatives and minor tranquilizers without medical supervision.[122] This tendency to self-prescribe begins in medical school with tranquilizers and continues in residency with benzodiazepines and prescription opioids. Alcohol abuse is of particular concern in physicians, and although heavy alcohol use is lower in young physicians than in matched controls, the incidence increases with age in the physician population and decreases with age in the general population. By the age of 50 to 55 years, extensive use of alcohol in physicians surpasses that of the general population.[123]

A commonly repeated perception is that anesthesiologists are more likely than other physicians to engage in substance abuse. Three retrospective surveys suggest that the prevalence of drug abuse in anesthesiologists ranges from 1% to 2%.[124-126] These published percentages rely on the recall of directors of U.S. anesthesiology programs and the honesty of individual anesthesiologists responding to questionnaires. Nevertheless, the estimates from these surveys are remarkably similar. Furthermore, the prevalence is similar to that seen in published studies of anesthesia trainees in Australia and New Zealand,[127] as well as in newer estimates from the United States.[128] In 1993, approximately 2% of U.S. anesthesia residents became addicted to a substance during their residency.[129]

When comparing the published incidence of substance abuse in physicians as a whole with that of anesthesiologists, both graduated and resident anesthesiologists are consistently overrepresented in drug treatment centers.[130] Although anesthesiologists account for 12% to 14% of physicians treated in three well-known treatment programs, they constitute only 4% of physicians in the United States.[129,131,132] This threefold overrepresentation of anesthesiologists in drug treatment centers is relatively consistent across state lines and over time. For example, data from the California Physicians Diversion Program have anesthesiologists accounting for 17% of physicians in treatment and 5% of physicians in practice.[133] Although these statistics imply that the incidence of chemical dependence is significantly higher among anesthesiologists, these data may instead be a reflection of the potency of the drugs abused, the ability of anesthesiologists to recognize the disease in their colleagues, and the diligence within the specialty to refer colleagues for treatment.

Reports from state-run impaired physician treatment programs that began in the 1980s[132-135] suggested that although all the anesthesiologists were chemically dependent, at least 10% of the other physicians had other forms of impairment, such as depression.[131,133,136] Nearly 50% of anesthesiologists were less than 35 years old, and one third were residents. Half used both drugs and alcohol, 40% used drugs alone, and a minority used only alcohol. Fentanyl was the most commonly abused narcotic, followed by sufentanil, meperidine, morphine, and oral drugs.

Sadly, loss of life may be the first indication that a physician is abusing drugs. These deaths could alter the frequency numbers when comparing younger and older physicians. For example, young physicians who die will obviously not become older drug abusers. Numerous studies have examined the mortality risk of physicians in general,[137,138] and of anesthesiologists specifically,[139-141] as opposed to the mortality risk of the general population. The death rate from all causes is lower among physicians than the public in general. This difference is attributed to lifestyle awareness among physicians that results in decreased rates of destructive behavior such as smoking. The higher socioeconomic status of physicians and greater access to health care may also contribute to this advantage. Although the mortality risk for anesthesiologists is no higher than that for other medical specialties, anesthesiologists' risk of drug-related death and suicide is alarmingly high. Studies have shown a twofold increase in suicide among U.S. white male anesthesiologists[140] and British (mostly female) anesthetists when compared with appropriate population controls.[138] A more recent study in the United States reported the relative risk of suicide in anesthesiologists to be 1.45 when compared with internists. The relative risk of a drug-related death was even higher, at 2.79.[141] All these studies identify drug-related death as a significant occupational hazard in the practice of anesthesia.

ETIOLOGY

Occupational stressors first surface in residency, during which long hours preclude much time for relaxation, and certain patients may evoke negative emotions. The death of a patient under one's care may cause a sense of professional inadequacy to surface for the first time.[135] Without doubt, the practice of medicine can be stressful, but is that stress a major cause of drug addiction among physicians? Contrary to common belief, stress is not necessarily the precipitating factor in a physician's addiction

to drugs. Preexisting personality traits, a family history of substance abuse, and previous recreational drug use have been associated with substance abuse among physicians.[123,142]

Availability

Patterns of abuse differ by specialty and are influenced by familiarity and availability. Psychiatrists most frequently abuse oral benzodiazepines, whereas anesthesiologists preferentially abuse potent opioids. Anesthesiologists are unique among physicians in that they administer drugs directly rather than order their administration by others. Drugs are immediately available, and this may be the most important cause of addiction in the specialty. One report indicated that 85% of anesthesiology residents who were treated for substance abuse in one large program stated that the ready availability of drugs influenced their choice of specialty.[136] Since the late 1990s, anesthesia departments have introduced measures to monitor the use of controlled substances by staff and resident physicians closely.

Nonetheless, an increased level of accountability of controlled substances in U.S. residency programs has thus far not correlated with a decreased incidence of drug dependence.[143] Although one program published their experience with random mandatory drug testing as a proof of concept, more work is required to demonstrate the effectiveness of prevention.[144] In a 2002 survey of 123 academic anesthesia departments, measures were introduced to regulate the use of controlled substances including changes in drug dispensing, disposing, and accountability. The study covered a span of 7 years, during which time drug dispensing was shifted from nurses to satellite pharmacies (42%) or dispensing machines (31%). Opened, but unused drugs were either returned to the pharmacy (52%) or were wasted in front of a witness (41%), and the amount of drug administered was compared with the amount dispensed (80%). Despite these changes in drug dispensing and accountability, the incidence of drug abuse did not decrease.[128]

In the future, the direct monitoring of atypical drug transactions from automated dispensing systems may more accurately identify drug diversion.[145,146] In addition, the linkage of anesthesia information management systems with medication dispensing systems has been proposed as a means to detect medication discrepancies accurately, but these systems have yet to be fully realized.[147]

Drug Potency

Abuse of drugs by physicians is much more common than addiction. Casual abuse of alcohol probably does not always lead to addiction, and although exceedingly risky, neither does abuse of less potent opioids such as morphine, meperidine, or codeine.[116] In contrast, the addictive potential of fentanyl and other potent opioids is so great that anyone who experiments with these drugs is at enormous risk of becoming chemically dependent.[136] The time until detection of abuse is inversely proportional to the potency of the drug abused. For example, abuse of sufentanil is typically detected within the first 1 to 6 months, whereas the abuse of fentanyl is not detected until 6 to 12 months. In contrast, alcohol abuse may not be detected for more than 20 years.[134] Rapidly developing tolerance stimulates the ever-increasing doses needed to attain the desired sensation. The use of 50 to 100 mL of fentanyl or 10 to 20 mL of sufentanil per day is common in an addicted physician. These doses are easily reached within a few months for fentanyl and a few weeks for sufentanil. The potency of these drugs is reflected in associated fatality statistics. Between 1990 and 1997, 18% of identified substance abusers in academic departments either died or required resuscitation before substance abuse was suspected.[127] Fentanyl was most often the drug of choice.

Other Factors

Chemical dependence is a complex disease influenced by multiple factors. A history of experimental use of drugs is known to increase the risk of future addiction,[116] and a genetic predisposition may contribute to the progression from abuse to addiction. To identify availability and potency as the only significant factors in chemical dependence in anesthesiologists risks overlooking other significant factors such as previous use of drugs and a family history of drug abuse.

MANAGEMENT

Management of physicians who are chemically dependent includes identification, intervention, referral for treatment, and help with reentry. Each department should have an established mechanism in place to deal with impaired physicians. Identification of a chemically dependent physician does not usually occur until the disease is in its late phases, when performance at work becomes significantly impaired. The ASA Task Force on Chemical Dependence, last updated in 2002,[148] identified certain characteristics of addicted anesthesiologists (Box 110-2).

Although none of the signs and symptoms of chemical dependency or addiction are diagnostic, an awareness of the usual sequence of events may help identify an ill colleague in the earlier stages of the disease (Table 110-3).

Normally, withdrawal from outside interests is the first sign. Examples include giving up athletics, community activities, church, and activities with friends. Next comes increased turmoil at home. Domestic arguments, sexual problems, and lack of interest in family matters are common. Third is the appearance of frequent unexplained

BOX 110-2 ***Summary of Identified Characteristics of Addicted Anesthesiologists***

- 50% are <35 years old
- Residents are overrepresented
- Many are members of the American Osteopathic Association
- 76% to 90% abuse opioids as their drugs of choice
- 33% to 50% are polydrug abusers
- 33% have a family history of addictive disease
- 65% are associated with academic departments

Modified from Arnold W, et al: *Chemical dependence in anesthesiologists: what you need to know when you need to know it,* 2002. <http://anestit.unipa.it/mirror/asa2/ProfInfo/chemical.html> (Accessed 30.04.14.)

illnesses, personality changes, multiple jobs, and frequent moves between cities. This progression, which may take years to become apparent, is common with addictions that develop slowly.

The last activity to be affected is usually job performance. Page operators and nurses may be the first to recognize behavioral changes. Record keeping may become sloppy. Excessive use of certain drugs becomes apparent, perhaps accompanied by an unusual compulsion to explain the need for these drugs in patient management. Colleagues may note similar changes. Direct observation of self-administration confirms the diagnosis, but it is not common.[149]

Impaired physicians disclaim their illness by using superficially logical reasons to explain their bizarre patterns of behavior. Colleagues, too, use denial. Typically, they would rather accept these explanations than consider that a friend is a drug addict. For these reasons, the diagnosis is not usually made until its manifestations are clear.

TABLE 110-3 NOTABLE BEHAVIORS COMMON TO THOSE ABUSING SUBSTANCES

At Work	At Home
Unusual changes in behavior (e.g., wide mood swings, depression, anger, euphoria)	Withdrawal from family, friends, and leisure activities
Gossip by others	Changes in behavior (e.g., wide mood swings)
Progressive increase in apparent narcotic use for anesthetic management	Fights and arguments at home
Careless charting	Frequent unexplained illness (common in alcoholism)
Preference for working alone	Gambling
Frequent requests for bathroom breaks	Extramarital affairs
Unusual willingness to provide relief for others	Legal problems (e.g., arrests for driving while intoxicated)
Inappropriate willingness to take calls	Decrease in sexual drive
Frequent appearances in the hospital when not on call	Finding of drugs and syringes in the home
Frequent unexplained absences	Seclusive behavior at home
Difficulty finding the person when on call	Odor of alcohol on breath
Excessive postoperative pain in patients cared for by an individual	Weight loss
Common wearing of long-sleeved gowns (to prevent chills often seen in early withdrawal and to hide needle tracks)	Pinpoint pupils (in persons addicted to opioids)
Pinpoint pupils	Symptoms of withdrawal (e.g., diaphoresis, tremulousness)
Weight loss	Denial of drug or alcohol use if confronted
Finding the person comatose	
Finding the person dead	
Witnessed self-administration (the only pathognomonic sign)	

TREATMENT

The appropriate initial response to the discovery of chemical dependence in a colleague is to seek help. A call to a person experienced in managing chemically dependent physicians initiates the next steps.[133] Most state medical societies in the United States have committees on impaired physicians to act as advocates for sick physicians. Advocacy continues as long as the physician cooperates with the committee's recommendations. These committees serve as a buffer between the physician and the medical board or licensing agency. They also provide advisers to aid in confirmation of the diagnosis and to intervene and refer impaired physicians to appropriate treatment centers. Although laws vary, the committees are usually required to notify the board of a physician's recalcitrance at any stage of treatment. In many states, the board does not censure impaired physicians who comply with the committee's recommendations.

Intervention is the process of demonstrating to chemically dependent persons that they are ill and need treatment.[150] Interventions should never be attempted with fewer than two concerned persons and ideally should be directed by a person with previous experience. Before meeting, the group must collect documentation of drug usage including pharmacy records, anesthetic records, and other pertinent testimony. It is important to rehearse with members of the group (e.g., colleagues, psychiatrists, family members) before meeting with the patient. Many experts suggest that each participant prepare written notes to be used for reference during the intervention. The objectives are to present irrefutable proof of the addict's symptoms in a compassionate manner and to begin an appropriate treatment regimen. A recovering physician at the intervention can be a valuable role model for the patient. Arrangements for inpatient treatment and travel, if anticipated, should be made before the intervention.[150]

When all is in order, the patient is invited into a room in which the other participants are already seated. Each, in turn, should express concern for the colleague's well-being and, without passing judgment, should describe the aberrant behavior that has been seen personally. If necessary, the documents at hand can be shown. The basics of the disease and its treatment should be explained, and the patient should be urged to accept the proposed plan. If the patient refuses, as many do initially for fear of losing control, the patient should be told that the ultimate decision regarding therapy will not be made until after a thorough evaluation by a group of specialists at the facility. If the evaluation does not confirm the diagnosis, the patient will be discharged. Otherwise, formal treatment, perhaps lasting several months, will start. If still reluctant, the individual should be advised that the interveners must, by law, report that person to both the medical board and the controlled substance authorities. Although it does not provide legal

immunity, acceptance of treatment is looked on favorably by many courts.

After the intervention, the patient should be accompanied continuously, not only to prevent the possibility of self-inflicted injury or elopement, but also to provide the social support necessary to begin recovery. With adequate preparation, most interventions are successful.

Treatment consists of an in-depth evaluation, which is usually followed by both inpatient and outpatient therapy. Formal therapy may last as long as several months,[131] but on the basis of the initial workup, some programs permit a recovering physician to continue practicing medicine during what may be several years of outpatient care.[133] Although this approach is debated by some, physicians often fare better if they are treated at a facility experienced in managing physicians. Philosophies of treatment vary among programs, but the common goal is to provide a recovering physician with the ability to remain sober. The physician is assisted in developing a strong relationship with peer support groups such as Alcoholics Anonymous and Narcotics Anonymous.

PROGNOSIS AND REENTRY INTO THE WORKPLACE

Return from treatment is a difficult process for a recovering physician. The comprehensive treatment program has provided a structured environment that is much different from the workplace. For this reason, reentry is greatly facilitated by understanding, compassionate peers who are willing to provide emotional support to the recovering physician. Gradual return to work, perhaps with others initially managing narcotic administration, is important. Without this support, the likelihood of relapse may be much greater.

In many states, the committee on impaired physicians plays a vital role in recovery. At discharge from formal treatment, the committee prepares an "aftercare contract" with the physician, who agrees to be bound by the committee's recommendations. The contract usually stipulates the number and the type of meetings that the physician must attend, the name of a "monitoring physician," the requirement for random urine samples on demand, and the procedures to be used in the event of a relapse.[131,151,152] Many recovery programs insist on the use of naltrexone or disulfiram, or both, for 6 months or more after the physician returns to work. Novel treatments for alcohol dependence include investigational drugs such as acamprosate, bromocriptine, selective serotonin reuptake inhibitors, buspirone, and dexmedetomidine.[153-155] As long as physicians adhere to the contract, the committee continues to serve as their advocate.

Federal law in the United States (the Americans with Disabilities Act [ADA]) provides limited protection against employment discrimination for recovering individuals.[156] Although persons who are currently using drugs are not protected by this law, those who have been successfully treated and are otherwise capable of working are considered to be "qualified individuals with a disability." The ADA defines a history of chemical dependence as a disability. Although it does not require an employer to provide for treatment, the ADA may require that "reasonable accommodation" be made for a qualified individual who wants to return to practice. For a recovering physician, such accommodation could include a modified work schedule, such as no call for several months and assistance with administration of narcotics. An employer is not required to make accommodation if "undue hardship" for the employer would result. For example, it could be argued in court that the accommodations needed to permit a recovering physician to return could have a negative impact on other employees or could result in prohibitive costs for the employer. Whether the ADA can be used also depends on the type of employer-employee relationship between an individual and a hospital or group practice. Clearly, any person who seeks the support of the ADA needs competent legal guidance.

As indicated by reports from treatment programs, most recovering physicians are able to return to a productive professional life.[157] Successful outcomes depend on lifelong participation in aftercare programs, total abstinence from drugs and alcohol, and continual acknowledgment of one's disease. Some now believe that the prognosis for long-term sobriety in anesthesiologists depends on the age and the status of the physician at the time of identification. Residents who have been dependent on fentanyl appear to have a significant rate of relapse.[126] Although each case must be handled separately, strong consideration should be given to a change in specialty for junior residents who become addicted to potent opioids. A survey of anesthesiologists in recovery who underwent subsequent anesthetic procedures showed that although most respondents informed their anesthesia provider about their history of dependency, less than half of the respondents asked to avoid the use of previously abused agents, and at least two patients experienced relapse.[158] A regression analysis identified several risk factors that predict relapse, including a history of mental health problems, the use of a "major" opioid (e.g., injecting fentanyl, as opposed to oral oxycodone), and previous relapse.[159] It is unknown whether physicians using prescription opiates for chronic pain are at a higher risk of relapse.

The American Board of Anesthesiology (ABA) permits a physician recovering from alcoholism or other drug dependence, who is otherwise qualified, to take both the written and oral examinations. After a candidate with this history has satisfied the requirements for certification, "the [board] will determine whether it should defer awarding its certification to the candidate for a period of time in order to avoid certification of a candidate who poses a direct threat to the health and safety of others."[160] If the ABA deems that such deferral is appropriate, "the [board] will determine the length of time the candidate's certification is deferred following an individual assessment of the specific circumstances of the candidate's history of alcoholism or illegal use of drugs." This practice is in keeping with the intent of the ADA.[160]

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Chapter 111

Statistical Methods in Anesthesia

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Key Points

- Data should always be plotted. Significant trends should be visible to the eye.
- The statistics program should be known well enough to ensure that it is calculating what is wanted.
- Interval data should not be treated like categorical data—the mathematics is different.
- Many statistical methods assume that the data are distributed "normally," that is, in a symmetric bell-shaped curve; these methods can be misleading if the data are not normally distributed.
- Standard deviation (SD) is used to describe the spread of data, and standard error of the mean (SEM) is used to compare data sets.
- Multivariate regression, which relates the outcome variable to more than one other factor, requires more data but will probably pick up correlations that may be missed if only univariate regression is used.
- When using multivariate regression, if two variables closely correlate with each other, then the statistical package may miss reporting one as correlating with the outcome.
- In hypothesis testing, a negative result may indicate no real difference or may just mean that the study was underpowered to pick up a true but small difference.
- A *P* value is the probability that the observed result will occur, assuming no true difference between the tested hypotheses, which is not the same as the probability of the difference being true.
- A Bayesian approach to diagnostic testing recognizes the fact that the value of a test depends on the patient population; if the test is almost always truly positive in the population, then false-negative results will outnumber true-negative results and make the test less useful. This situation is also true if the test is almost always truly negative, in which case false-positive results cause the confusion.
- Selection biases make many real-life clinical studies difficult to interpret. Randomized clinical trials are the best way to minimize this problem.
- Beware of the error of *data dredging.* Applying too many tests to insufficient data will probably find something that, misleadingly, seems significant.

The advance of scientific knowledge in the past half millennium has been closely related to the linkage between experimental results and mathematical assessment of empirical observations. The role of the branch of mathematics, termed *statistics*, is to describe the results of experiments and to analyze, as best as can be mathematically done, the causes and effects behind the experiments.

A serious problem for a clinician or clinical scientist who wishes to use statistical methodology is that it is a modern branch of mathematics, much of which has been developed in the past century. Its mathematical sophistication is often considerably beyond that of the university-level calculus that is the upper limit of conventional medical training. Furthermore, many statistical methods involve extremely long and tedious calculations that require computerized techniques to be practical. This drawback leads clinicians to the quandary that although statistical methods are useful and often essential to the understanding of medical science, they may be subtle to comprehend and difficult to use.

It cannot be the role of a chapter in a book such as this to derive or even genuinely explain the mathematics behind statistical methods. Many accessible introductory texts give some of the reasoning and rough cookbook approaches to practical usage (see the bibliography). In real life, almost no one ever performs any sort of statistical calculations beyond the most simple with paper and pencil. Application programs for statistical calculations are widely available for personal computers. Many of them are reasonably well documented and simple enough to use without much preparation.

The problem with these statistical programs for personal computers is that the assumptions behind the statistics remain obscure. It is extremely easy to use the wrong method or approach and still have the program generate an output that, although appearing to be correct, is simply wrong. The old computer adage of "garbage in (statistically misleading), garbage out" is very easy to achieve with a computer package and a data file.

The goal of this chapter is to provide some of the correct language for describing statistics and to suggest the proper methodology for the use of statistics in some standard situations. Some of the classic errors common in medical statistics are indicated. Of course, readers must be familiar with whatever program they actually use.

STATISTICAL APPROACHES

Within the broad rubric of statistics, several distinct and valuable areas can be separately viewed. *Descriptive statistics* is the use of mathematical methods to describe or categorize a collection of data that results from a set of empirical observations. *Statistical testing* is the broad approach to the determination of conclusions from a set of observations. Within each of these categories are many separate techniques.

TYPES OF DATA

It must be remembered that behind every statistical methodology are formal mathematical definitions and proofs. Although it may sometimes seem that a simple intuitive approach is sufficient to understand what is happening, mathematical statistics can be misleading and unforgiving. The mathematical proofs and calculations that are behind statistical tables and computation programs make strict distinctions among the several types of data (Table 111-1).

One grouping of data, termed *interval* data, is simple *continuous* numerical measurements (e.g., 1.2, 33.4). Often, *discrete* numerical measurements, such as counts or integral quantities in the same categorization, are described. This approach is occasionally misleading; the claim that a "typical family has 2.3 children" is meaningful in a crude way, although the quantification of children is obviously not a continuous numerical fraction. In practical use, both continuous and discrete data can be handled by techniques similar to those used for interval data.

The other major grouping of data is *categorical* data. One type of categorical data is *ordinal* data, which refers to the ordering or ranking of subjects (e.g., 1st, 3rd, 10th). Taking care to resist the temptation to regard the number of the ranking as an interval number, that is, to confuse *first* with the number *1*, and so on, is important. Such a grouping does not usually have much numerical meaning and is false to the mathematics if an attempt is then made to manipulate the number as though it were an interval value. The arithmetic manipulation of arbitrary numerical assignments may easily produce misleading results.

TABLE 111-1 TYPES OF DATA

Data Type	Examples
Interval	1.1, 22
Ordinal	1st, 3rd
Categorical—binary	Male or female, alive or dead
Categorical—multiple	Red, green, blue

Binary data (e.g., up versus down, greater versus lesser) is another similar category. The most general grouping is the simple *category* (e.g., red, green, blue; cancer, diabetes, ulcer). When using simple or binary categories, attaching numbers to the groups and trying to get numerical results is incorrect—the mathematics are not appropriate, and the results are not likely to mean much. Specific statistical techniques for categorical data are necessary.

DESCRIPTIVE STATISTICS

The most general statistical goal is to describe the data set. The simplest method is to simply present all the crude data. For small data sets, the actual measurements can be presented. For larger amounts of data, a graph or statistical plot of the data can be helpful. Frequently, trends and groupings in a picture can be extremely difficult to describe numerically. It is often suggested that before any mathematical method is applied to data analysis, a graphic plot should be produced. If the data do not look *right* to the naked eye, then the statistical analyst should be extremely careful to avoid erroneous results. The choice of the correct format for the statistical plot can be an art form, and special data manipulation computer programs can be useful to search for visual clues in a data set.

NORMAL DISTRIBUTION

Perhaps the most powerful numerical concept of mathematical statistics is the *normal distribution,* often called the *bell-shaped curve*. The idea of a most likely central value with other values scattered evenly to both sides is a classic statistical concept with deep mathematical roots. It fits in nicely with an intuitive idea of a *true* value with measurements randomly distributed around the true value in such a way that more values are close to the center than are distant.

Many typical data sets follow a normal distribution around a center point. This distribution, also sometimes called a *Gaussian distribution*, is derived from the assumption that a center, a *true* value, exists and that deviations from the center are random and diminish in likelihood the farther the values get from the center (Figure 111-1).

The strict use of normal distribution implies very large amounts of continuous interval data. When, as is usual, a data set does not meet this criterion, approximations are needed. Fortunately, most computerized statistical programs can deal with this problem with good effect.

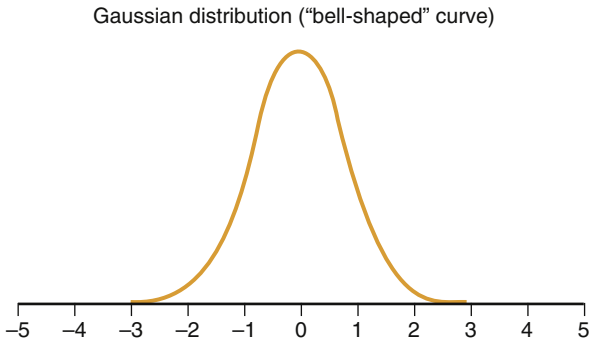


Figure 111-1. Gaussian distribution in a bell-shaped curve. The *x*-axis is in units of standard deviation.

In general, the mathematical description of the placement of the values is termed the *distribution.* There are many, mostly uncommon, distributions other than normal distribution. They yield different curves and have specific mathematical properties. Not all data sets, even if they look like a bell-shaped curve, are normal distributions. If the curve is too wide (i.e., many distant outlying points) or too narrow or uneven, then the mathematics derived for normal distributions will not work well.

When data follow a normal distribution or, more generally, any specific mathematical distribution, the methods of *parametric statistics* can be used. The term *parametric* refers to the ability to describe the distribution with a specific set of values. Frequently, such is not possible, and *nonparametric* statistical methods are necessary. These methods make fewer mathematical assumptions about the distribution of the data, but they are more difficult and can be less robust in finding statistical distinctions. Conversely, if parametric statistical methods are applied to data that are not normally distributed, then false or misleading results can be calculated. This type of error is common and can be prevented by using appropriate tests or checking the data for normality before applying tests that assume it.

In practical use, data are often treated as though they follow a normal distribution. However, wise investigators will use the tests in their computer statistics packages to test for normality and recognize that if the data do not follow a normal distribution, then other methods will be needed.

Measures of Central Tendency

In describing data, the first task is to give some indication of the approximate value, range, or size of what is being described. How this is done depends on the type of data involved (Box 111-1). For categorical or binary data, all that may be possible is to give the counts in each group. For categorical data with many groups, the most populous groups may be named and listed in order. For ordinal data, summary description may be difficult; often, first place or last place will be the most interesting.

The *median* is the center or middle data point if the data can be ordered from smallest to largest. This value would apply to both interval data and to ordinal types of categorical data. For interval data, many mathematical techniques can be applied. The simplest is the *mean,* or the simple average value of the numerical data, with each data point counted equally. In a *weighted mean,* the individual points may be added unequally, with some getting more credit (i.e., *weight*) than others.

BOX 111-1 *Measures of Central Tendency*

Mean ± standard deviation
Mode
Median
Percentiles

For interval data that can be mathematically analyzed, the data may be fitted to a curve, which means that a mathematical formula is computed that closely fits the measured data points, often by using a computer and sophisticated calculations. The relationship can be as simple as a straight line or a complicated mathematical formula with exponentials, polynomials, or other functions included as may be needed. The various computed values in these formulas would be the *parameters* of the curves. The data would thus be described by the parameters of the formula approximated to the observed data. For the simple case of a straight-line approximation to data, the parameters would be the slope and intercept of the line. For complex equations fitted to data, the parameters would be the various computed numbers that make up the equations.

The *mode* is the most common value in a set of data points. This concept can be misleading if the data are truly continuous because every data point would then be probably different (if only infinitesimally so) from every other point. Hence, to describe the mode of continuous data, grouping the values into brief intervals makes the most sense. In this case, the interval with the most points within it is the modal interval. The mode may also be a very misleading description of the central tendency of a data set because no reason may exist for the most common value to be anywhere near the middle.

Numerical data can be described by categorizing the values into *percentiles* or similar groups. The meaning here is that for the 10th percentile, 10% of the data points are at or below that value. The 50th percentile corresponds to the median of the data set, and the 99th percentile is the value at or above 99% of the data points. Similarly, quartiles, quintiles, or other groups can be computed. With any method used to describe data, the choice of the description may subtly bias investigators in how they think about the result. In the simple data set (2, 2, 3, 7, 14), the mode = 2, the median = 3, and the mean = 5.6. Which, if any, of these representations is more accurate? The answer depends on how the data are used because no one representation is perfect.

Measures of Dispersion

Often, analysts want to describe not only the values of the data but also how the data are spread out. For data that follow a normal distribution, the classic approach is to compute the *standard deviation* (SD) of the data. With this value, approximately 68% of the data fall within 1 SD of the mean, and approximately 95% fall within 2 SD of the mean value. The larger the SD, the wider the bell-shaped curve; the smaller the SD, the narrower the curve.

Another way of examining this concept is to consider that if analysts were making measurements of an unknown value and their values were scattered in a random normal distribution around that value, then approximately 68% of the data points would most likely be within 1 SD of the true value. Of course, this result is only the most probable outcome; in any real set of randomly distributed data, an analyst could be unlucky and have very atypical points.

For data that do not follow a normal distribution, describing the dispersion of the data set in a standard fashion can be difficult. Often, simply the *range* of the data, from the lowest to the highest, is given. Occasionally, the data may be so scattered, with very distant extremes, that the range is not as useful as reporting the 25th to 75th percentiles of the data.

Caution

Because using a computer package to calculate the SD is so easy, particular caution would be taken when using it. Frequently, data do not nicely fit into the normal distribution with a symmetric bell shape and unbounded tails out in both directions. As an example, consider a data set of subjects with widely dispersed ages including many children. Getting a value of 10 for the mean age would be easy, with an SD of 15. Clearly, no values lie at the lower end of the distribution with ages of –5. In such situations, the SD has some merit in describing the spread of the data but is, by strict mathematics, being misapplied.

Standard Error of the Mean

Just as random numerical data can often be described by the SD, the means computed from multiple grouped determinations of the data set can be described by making a computation very similar to the SD but applied not to the measured data but to the computed means. This computed quantity is termed the *standard error of the mean* (SEM). As more data sets are gathered, with each data point being a measurement of what is a *true* but unknown value, the means of the data sets will probably get closer and closer to that true value. Hence, as more and more data are gathered, the SEM gets smaller and smaller. This concept is intuitively very reasonable—as more and more measurements of a value are made, a mean value should be getting closer and closer to the *true* value, even if the data points, themselves, remain scattered.

The difference between SD and SEM is important. SD is used to describe the data, and SEM is used for computations about the certainty of the mean of the data. Because computer packages can as easily provide either of these values and SEM is a smaller value, one is tempted to describe the data by the SEM. Although this is not dishonest if clearly labeled, it can certainly be misleading. A very large number of data points will have a very small SEM, but widely dispersed data will have a large SD, no matter how many points are measured.

Graphing the Data. All experienced statisticians will stress that before statistical calculations are applied to a new data set, the data must be plotted in some graphic format. If the data are widely scattered, appear asymmetric, or have a specific pattern, then that information is useful in determining the statistical tools to be applied. Furthermore, noting the presence of extreme outlying points may be a clue to mathematical or experimental errors.

Regression Analysis. Data may often fit a mathematical formula, which may be a straight line (e.g., a linear relationship) or just about any sort of continuous mathematical formula. In *regression analysis,* the power of the computer program is used to determine the mathematical formula that best fits the data. To do this, the program with the type of curve to use (e.g., straight line, quadratic equation, exponential curve) must be provided. The program will then provide the parameters within the selected equation that best fit the data points.

The art of regression is complex. The first problem is to pick the appropriate mathematical relationship to fit the data. Graphing the data is obviously very useful for this. There are also some mathematical subtleties in how to best fit the data to the curve, but by far, the most common method is a *least-squares* approach, which minimizes the square of the distance of each data point from the proposed curve. Although this methodology is approximately two centuries old, it clearly benefits from the use of modern computerized calculations, without which it would be practically unusable.

The computer program for regression analysis will provide the parameters of the fitted equation, such as the slope and y intercept for a straight line, as well as some information about how well these parameters fit the data. The user has to be cautious in using the fitted equation if the agreement is poor because almost any jumble of data can be fitted to some equation, albeit with terrible agreement. It is fair to stress that the human eye has real power to judge trends; therefore, if a graph of the data does not look like it fits the curve, then the wise user will be very skeptical of the result.

Univariate versus Multivariate Regression. In fitting data in a regression analysis, the first step is to choose the variables that will be used as independent variables. In *univariate* analysis, only one variable is used for the data fit and the data are plotted and the computations are performed by using that one variable to describe the data. As an example, the weights of a group of subjects may be compared with their heights. However, in the real world, many possible variables can almost always be used to determine an outcome. In *multivariate* analysis, more than one variable is used to describe the observed results. In the weight example, the subjects' weights might be analyzed by using heights, ages, and gender. Note that in this multivariate example, the outcome is a continuous interval variable but is determined by a collection of interval variables (age, height) and a categorical variable (gender). The precise mathematical techniques that are used for multivariate analysis will depend on the nature of the variable used; in general, a mixed group of variables makes the most sense with real-world data.

On first approaching analysis of a data set, a simple univariate analysis may help in understanding the relationships involved. However, the data analyst must be cautioned that subtle relationships can be missed with

only univariate analysis if the relevant variable is not used. As an example, heart rate may correlate with the dose of pain medicine in an injured patient, but the causal relationship for both is likely to depend on the degree of pain.

With multivariate regression analysis, many potential pitfalls can be readily encountered with computerized calculations. One critical category of problems derives from the relationships that the various variables may have with one another, which is often described by indicating how *independent* these variables are in relation to one another. For an independent variable, the values of one variable do not tell what the values of the other would be. In the example of weight versus age and height, age and height would be expected to be independent in adults. Mathematically, it would be determined that age and height are *uncorrelated*. However, in children, age and height are correlated; therefore, weight could be expressed as a function of weight versus age or weight versus height. In this last case, a multivariate analysis that focused on independent variables might simply produce the result that weight is a function of height and throw out the relationship between weight and age. Hence, when many variables are involved, caution must be applied so that experimentally important relationships are not missed because they do not mathematically add up to the results. Sophisticated statistical computer packages will look for these sorts of problems. Identifying a significant correlation among the different variables would suggest that some information may be lost if only independent variables are reported. If a simpler statistical program is used, then performing multivariate analyses with some of the variables left out would be wise to determine whether other possible relevant relationships appear.

Another type of problem that can be misleading with multivariable relationships occurs in the situation in which the computer program produces a variable that only weakly correlates with the data but does so with high reliability. This situation would be expressed in linear analysis as a result with a small correlation coefficient but a very good *P* value (more about *P* later). The fact that the correlation is likely real (i.e., not a statistical chance occurrence) does not offer much to the experimental analysis if the correlation is small—the data are not well explained by the relationship. Here, the confusion comes from the fact that although the correlation is weak and does not explain much, the calculation shows very high confidence in the presence of this weak correlation.

Hypothesis Testing. A very common use of statistical techniques is to test a question, called the *hypothesis*. Also often termed *significance testing,* this approach yields the valuable concept of the *P* value. It is the *P* value that is often used to summarize the statistical strength of the data analysis in supporting or rejecting the hypothesis. If groups were to be compared, then the test is often described as a comparison of the *null hypothesis,* which states that no difference exists between two groups of data, and the *alternative hypothesis,* which states that a difference does exist. If a single grouping of data were analyzed and two descriptions of the data were compared, such as determining whether the mean value of the group as calculated from the data is different from 0, then the two hypotheses would be *mean = 0* versus *mean = measured value ≠ 0*.

The *P* value is computed from the observed data as the probability of obtaining this data set if, in reality, the null hypothesis were true. It is important to note that this calculation assumes the null hypothesis and is not the same as saying that *P* is the probability that the alternative hypothesis is true. If, in reality, the null hypothesis is true, then it would be unlikely that something else would be observed in the data. In actual experimental situations, all data have some randomness; therefore, one can never be certain that observation is not simply chance and bad luck.

In hypothesis testing, a *level of significance,* termed the *alpha* value, is chosen; if *P* is less than alpha, then the result can be declared statistically significant and accepted as true. If *P* is not less than alpha, then the hypothesis is rejected (equivalent to accepting the null hypothesis). Remember the logical sequence: alpha is chosen in advance, and then *P* is computed from the data. If *P* is less than alpha, then the hypothesis is accepted and the null hypothesis is rejected. The *P* value is the chance that the null hypothesis was true but, through bad luck, the data came out as observed anyhow. Typically, alpha is set equal to .05, and *P* is less than that. For that *P* value, it would mean that the chance of the data coming out this way was less than a probability of 5% ($P = .05$) if the null hypothesis were, in fact, true.

Choosing the level of significance is an arbitrary decision. Investigators might want to be very sure that they did not erroneously reject the null hypothesis and set alpha at .01. It is common in biomedical studies to pick an alpha value of .05. In addition, a very small *P* value may lead the analyst to reject the null hypothesis but may not give much information about the exact nature of the alternative. As an example, tossing a coin and getting six heads in a row might lead analysts to reject the null hypothesis that the coin is a fair coin, but it is not enough information to suggest that the coin always comes up heads. The *P* value is calculated from the data assuming the null hypothesis, and the use of a small value of *P* allows the rejection of the null hypothesis, yet that does not fully characterize the alternative hypothesis.

Power. It should seem intuitively obvious that the ability of a statistical test to make a valid determination depends on the amount of data available. With only a few observations or data points, investigators cannot be as certain about a conclusion as if they had large amounts of data. If the goal were to determine the fairness of a coin, then tossing it twice would not be convincing of much; tossing it a thousand times, however, would present a good idea about the nature of the coin. In statistical hypothesis testing, the *power* of a study is a description of the ability of the study to detect a true difference. A statistical hypothesis test may fail to achieve significance (fail to get $P <$ alpha) if either the data truly do not reflect a difference or if there are so few data points that the mathematics yields a poor *P* value. A *beta error* is defined as the probability of falsely accepting the null hypothesis (calculated by assuming that the alternative hypothesis is true), and the *power* = 1 – beta. For the power to be good,

that is, for the beta value to be small, the study must have enough data points to ensure that if a difference is observed between the null and alternative hypotheses, then it can be accepted with reliability.

A sample size calculation is often performed before an experiment is undertaken to determine how much data would be necessary to have a reasonable chance of observing what is guessed to be the observed result. Standard computer programs are available that will compute the number of data points necessary when the alpha and power values are provided and some estimate is made of the likely observed effect. Being cautious about any study that is interpreted as *negative* (i.e., no significant difference between the study groups is reported) is important. It may be that no difference truly exists, but it may also be that the sample size is too small to determine a difference with statistical significance.

Confidence Intervals. Using *confidence intervals* as a description of the statistical determination is becoming more common in reporting statistical measurements. A range of values may be given such that it is determined with some likelihood (often at 95%) that the true values lay within that range. For expressing simple results, the confidence interval is equivalent to providing a mean ± SD. This method becomes particularly useful for describing results when describing "no difference" in the correct statistical fashion. Here, the proper description would be that the true difference lies in an interval less than *x* with the given statistical confidence.

To summarize, the following is wanted for hypothesis testing:

- Null hypothesis (e.g., mean = 0)
- Alternative hypothesis (e.g., mean = m)
- Alpha value (chosen in advance; e.g., alpha = .05)
- Power (chosen in advance in conjunction with a sample size calculation to ensure enough data points; e.g., power = 0.8)
- P value—computed for data

The difference between the null and the alternative hypotheses could be significant if *P* is less than alpha. If a value is being described, then a difference could be considered a confidence interval; and if there is *"no difference,"* then the difference (if any) in the interval could be described as less than some computed value.

STUDY DESIGN

The essence of scientific study is generally some numerical determination of a result. This numerical analysis is approached with statistical calculations. However, without a careful design of the study in the way that the numerical data are generated, formal statistical analysis of the numbers will yield scant benefits and may even be misleading. In the typical study, analysts are usually attempting to either characterize some variable (e.g., mean or trend) or make a choice to accept or reject among various hypotheses. No matter what the question, analysts must always be careful that the results genuinely answer the question and that they are not misleading themselves with inappropriate conclusions.

Scientific studies may be *observational studies* during which data are gathered without performing any specific intervention affecting the assignment of groups or effects on group members. Because investigators in an observational study have to take what they find as data, they are always subject to other unrecognized factors that may distort their interpretation or limit their ability to ask questions about the data.

In an *interventional* study, investigators pick the group members, determine what is being done to them, and attempt to look out for and eliminate potential confusion before the data are collected. A *clinical trial* is a typical interventional study in which different therapies are compared.

In the design of a scientific study, one major fear is a statistical *bias,* which is a systematic effect in the study that produces an error in the interpretation of the results. When considering the various possible study designs, analysts need to beware of the potential biases that may creep in. A *selection bias* occurs when groups are compared with respect to some variable but analysts do not realize that the groups are different in other (but important) ways. Because groups of subjects may differ in multiple ways, the assignment of subjects into groups may result, either from misdirected choice or random bad luck, in groups that are not fairly comparable. Consequently, although the results are thought to be determined by the variable under study, it may actually be that some other factor results in a misleading conclusion. As an example, consider a study that is comparing surgical and medical treatment of some illness and ends up with a grouping in which a higher proportion of men than women are undergoing surgical therapy. Any conclusion from this study about surgery versus medical therapy is biased and might be truly reflecting simply the difference in the results of therapy on men versus women.

A *confounding bias* occurs when multiple variables are intimately intertwined so that although the variable under study is assumed to be important, the truth is that the confounding variable is more important. As an example, consider a study attempting to determine the effects of obesity on longevity. Because diabetes mellitus is closely correlated to obesity, a result that purported to be about obesity might easily be more accurate about diabetes. When variables do not correlate with each other so that changes in one variable do not go along with changes in the other, they are called (in a rough nonmathematical sense) *independent variables*. Variables that are correlated with each other are not independent.

A *measurement* bias occurs if the methods used for making measurements when comparing different groups have different scales or sensitivities. As an example, consider attempting to get a history of chest pain in groups of patients with and without known coronary artery disease. Patients who know that they have heart disease might be imagined to remember brief pain more thoroughly than healthy patients, or perhaps they might deny pain more in their wish to believe that they are healthy. Here, the art of the experimenter is to predict and avoid such biases.

In a *blinded* study (more properly called a *masked* study), measurement bias may be avoided if the person performing the measurement does not know which group is being measured, thereby avoiding subtle measurement bias in approaching or determining the data. As an example, consider an active drug being compared with an inactive placebo. A researcher who knows which patient is taking the active drug might be more diligent in pursuing benefits or side effects. In a *double-blind* clinical study, neither the patients nor the experimenters obtaining the data should know which participants are in which group to avoid subtle measurement bias.

Observational studies may be categorized as case, case-control, or cohort studies. In a simple *case study,* an individual case or group of cases is reported. Such reports may demonstrate the existence of some observation or effect, provide the presumably typical character of the observation, and suggest a therapy or natural history. These types of studies do not have the nature of a proof because it is always a possibility that some other hidden effect is producing the observation or that the observed characteristics are atypical in some fashion. Nevertheless, often "seeing is believing"; so much of what is reported in medicine is in the form of case observations.

The distinction between cohort and case-control studies is important but often misinterpreted. In both categories, groups of subjects are compared, usually in regard to the effects of some intervention. In a *case-control* study, the factor separating the groups is determined *after* the intervention. Typically, a comparison is made of some outcome in one group, the case group, versus a similar group that does not have the outcome and functions as the control group. Because the groups are separated after the intervention, selection biases or unappreciated confounding variables can mislead the investigators. As an example, consider a study investigating the effects of hypertension on surgical mortality. If the groups are divided into patients with and without perioperative cardiac events, one group may be different from the other. However, such a result may be misleading; perhaps it is the renal disease associated with the hypertension that is significant (a confounding bias). Alternatively, perhaps patients with hypertension are sent to surgery by their physicians only when they have worse surgical problems; therefore, the groups are not fairly compared (a selection bias).

In a cohort study, the study group is monitored before the intervention occurs. The group is assembled to be as similar as possible and then monitored forward in time. Such studies are useful for describing the natural history of disease and may be helpful in suggesting causes. However, as with the other observational studies, selection and confounding bias may occur and lead to misleading results.

A case-control study is sometimes termed a *retrospective* study because the analysis can only be done after the participants complete the study to determine to which group they belong. In this sense, a cohort study is a *prospective* study inasmuch as the data must be gathered before the intervention. Unfortunately, these terms may be misused because, obviously, a case-control study can be planned in advance (*prospectively*). In addition, no matter how truly prospective a study is, once the data are gathered, the analyses are performed after the fact (*retrospectively*). These terms are best avoided.

After considering the nature of observational trials, the strength of the interventional clinical trial is recognized, in which the investigators determine the membership of the groups to be compared in advance and attempt to make the groups as similar as possible. In a *randomized clinical trial,* the participants are assigned by chance to the groups; consequently, if some fluctuations in the participants or some subtle selection bias is present, then the effect will be the same in each group (and presumably cancel out in the result). Such a study is necessarily prospective in nature.

Randomized clinical trials are the idealized standard in medical research because they offer the best chance to minimize biases. However, the effort and expense in setting up a clinical trial may be considerable. Such a trial requires patients to be enrolled before the medical intervention is performed. Patients give up the choice of the therapy that they receive and allow their therapy to be randomly selected among various options. Such trials (even if they involve standard therapies) require full ethical board clearance and explicit patient consent.

Even with the best clinical trial methodology, potential difficulties include dealing with subtle selection biases regarding who is entered into the trial. Studies that are actively watched by investigators and their highly motivated associates may result in atypical practices that cannot be generalized into standard clinical practice. The patients in clinical trials are themselves mostly motivated by the search for personal benefit and cannot be depended on to follow protocols strictly or to stay with a program that does not appear to be successful.

DATA DREDGING AND THE PROBLEM OF MULTIPLE COMPARISONS

In all statistical interpretations regarding the acceptance of data-determined conclusions, the random chance of a highly unlikely statistical result being misinterpreted as the typical true conclusion is always recognized as a possibility. A coin tossed six times and coming up all heads might lead to the conclusion that the coin was not fairly balanced, yet that will happen every $2^6 = 64$ times that it is attempted even with an entirely fair coin. When an alpha value of .05 is picked, investigators are saying that approximately 5% of the time they will accept misleading random errors as though they were true. This is roughly equivalent to recognizing that for every 20 experiments, perhaps 1 will be wrongly accepted as true based solely on bad luck and random chance. If a large set of data is analyzed in many ways, then some random results may appear statistically significant, simply based on this sort of chance. This is the error of *data dredging* and typically occurs when too many variables are examined for correlations within a single data set—by random chance something will be found that appears significant.

In a similar manner, if a very large number of independent comparisons are made between two groups of subjects and an error rate of 5% is accepted, then a false but statistically "significant" result may occur approximately

once for every 20 comparisons made. This is the error of *multiple comparisons*. Mathematical methods are available to correct for these errors—what is most relevant for the consumer of the statistical analysis is to recognize the presence of the error and look for the correction.

CHOICE OF TESTS

Nonparametric Statistics

When calculating the random distribution of some variable, visualizing the values as clustered around some center value in the well-known bell-shaped (termed *normal*) distribution is easy. However, as noted earlier, not all data have such a nice distribution. Data that are not in interval format, such as nominal data (e.g., red, black; male, female) or ordinal data (first, third), cannot be described by mathematical distributions with parameters such as the mean or SD. Such a situation calls for nonparametric statistics. Nonparametric statistical methods are typically used for the analysis of nominal or ordinal data. Data that are distributed in a very atypical skewed fashion (a *nonnormal* distribution) will not be properly handled by analyses that have the mathematical assumptions of normality; such data will need nonparametric analysis.

The first step in considering the choice of a statistical test is to decide whether statistical methods that assume a normal distribution are appropriate or whether nonparametric methods are needed (Table 111-2). A test for normality is included in typical statistical computer packages. Often simple inspection of frequencies in tabular or graphic form will convey much information.

Contingency Tables

A very common nonparametric statistical problem is the analysis of a table of data in which each cell in the table is a count in a particular category. The question is to determine whether the groups are statistically different from one another. As an example, consider the question of men versus women and their political affiliation, Republican versus Democrat, in which a 2 × 2 table is generated. If additional political groups are added, for example, Green and Undeclared, then a 2 × 4 table is generated. If these data are to be analyzed to determine whether men and women differ in political affiliation or whether Democrats versus Greens differ in gender distribution, then nonparametric statistical methods appropriate to a contingency table would be applied.

Paired versus Unpaired Data

If statistical methods are applied to analyze data from multiple groups and each individual data point comes from a separate and distinct source, then the mathematics behind the statistics assumes an independence and randomness that would not be the same if the sources are highly related. As an example, consider a study of blood pressure in two groups of patients, one treated with medication and the other untreated. Because blood pressure measurements can be widely scattered in distribution, depending on the patients' previous medical conditions, a small drug effect might be difficult to notice. However, if the same individuals were studied before and after therapy, then the wide initial variations might cancel out and small effects would be noticed. In this latter study, the data points can be paired, one in each group, to detect these small effects. A study in which the data can be paired can be very sensitive in picking out small changes. Conversely, the erroneous use of paired statistics might suggest a statistically significant result when one does not exist.

Two-Group versus Multiple-Group Analysis

In a simple statistical analysis, one group of data may be characterized or a comparison may be made of that group with a standard value. Comparing two groups is slightly more intricate when the goal is to characterize each group and determine whether the groups are statistically different. Significantly more concern must be applied to the situation with three or more groups. In the case of multiple groups, two distinct types of questions can be asked. First, knowing whether the groups are significantly different or whether they are all the same (with any numerical differences attributed solely to random fluctuations) might be necessary. Second, if the conclusion is that the groups are not all statistically the same, then knowing which groups are different from one another might be desirable—that is, are they all distinct or are just one or a few different, whereas the rest are similar to each other?

In summary, three questions should be asked when choosing between tests (see Table 111-2):

1. One group, two groups, or many groups?
2. Paired or unpaired groups?
3. Parametric (interval data after a normal distribution) or nonparametric methods?

TABLE 111-2 **CHOICE OF TESTS**

Comparison Goal	Normally Distributed (Parametric) Interval Data	Nonparametric Interval Data	Categorical Data
Describe group	Mean ± SD	Median, mode, percentile	Counts and proportions
Compare group with value	t-Test	Wilcoxon	Chi-square
Compare two groups	Unpaired t-test	Mann-Whitney	Chi-square, Fisher
Two paired groups	Paired t-test	Wilcoxon	McNemar
Three or more groups	ANOVA	Kruskal-Wallis	Chi-square
Multiple matched groups	Repeated-measures ANOVA	Friedman	—
Regression	Linear regression	Nonparametric regression	Logistic regression

ANOVA, Analysis of variance; *SD*, standard deviation.

Bayesian Approach to Probability

The commonsense meaning of the term *probability* can readily become confusing within the mathematical morass of formal statistics. In practice, two definitions for probability are commonly used and interchanged. In the *frequentist* approach, the probability of an occurrence is viewed as the fraction of occasions that a selected event would occur if the trial were repeated many times. In other words, the probability of a fair coin coming up heads is .5 because if it is tossed many times, then approximately 50% of the tosses would come up heads.

However, in many real-life situations, repeating the trials many times to get a frequency of occurrence for an event cannot happen. In the *subjectivist* approach, a probability is assigned to an event, based on a best guess or opinion. Such subjective assessments are very similar to what is done in medicine when an interpretation is made on the basis of opinion and experience. This approach is often termed *Bayesian* statistics because of a mathematical formula, Bayes' equation, which is used to manipulate subjective probabilities.

The powerful practical insight that comes from Bayesian statistics lies in the requirement that statistical calculations is begun with an initial probability of an event. This very much matches the real-life situation in which any test or prediction depends on the patient under study. It is generally medically unwise to consider a diagnosis for a patient unless the patient's own characteristics are taken into account. It is obvious to any clinician that an abnormal cardiogram suggesting myocardial ischemia would not mean the same thing in a healthy 30 year old as it would in his obese hypertensive grandfather. In a similar argument, a negative exercise stress test does not give great confidence that a very high–risk patient is free of cardiac disease (because the chance of disease is so high and stress tests are notorious for missing disease in some patients).

In medical situations, Bayesian statistics are mostly used for the interpretation of diagnostic or predictive data. The term *Bayesian* is often an indication that the patient or population's *a priori* chances of disease should be considered when applying a predictive test.

When using diagnostic or predictive tests, the concepts of sensitivity and specificity are very useful because they are not dependent on the population. *Sensitivity* is, approximately, the ability of the test to detect the disease when truly present, and *specificity* indicates the ability of the test to avoid a false indication of the disease when truly absent. To use these terms, four possible situations are defined:

True positive (TP): The patient has disease, and the test is positive.
False positive (FP): The patient does not have disease, and the test is positive.
True negative (TN): The patient does not have disease, and the test is negative.
False negative (FN): The patient has disease, and the test is negative.

By definition,

$$\text{Sensitivity} = \text{TP}/(\text{TP} + \text{FN})$$

$$\text{Specificity} = \text{TN}/(\text{TN} + \text{FP})$$

The ideal test has a sensitivity of 1, which indicates that the test picks up all patients with the disease, and a specificity of 1, which indicates that the test never falsely claims that a healthy patient is diseased.

In addition, defining the following is also useful:

$$\text{Positive predictive value (PPV)} = \text{TP}/(\text{TP} + \text{FP})$$

$$\text{Negative predictive value (NPV)} = \text{TN}/(\text{TN} + \text{FN})$$

Although the sensitivity and specificity of a test do not depend on the characteristics of the population, it must be remembered that they certainly do depend on the quality of the test. However, PPV and NPV are dependent on the tested population—this situation is where the authors' comment about *Bayesian* is relevant. (Although it is not the goal of this chapter to prove these claims, the reader may be convinced by considering what happens to sensitivity, specificity, PPV, and NPV in situations during which the test is applied to a population in whom the disease is absent—only TN and FP are nonzero. PPV is vanishingly small and NPV approaches 1; similarly, for a population with almost all patients having disease, PPV goes to 1 and NPV vanishes.)

The Bayesian insight can now be stated that diagnostic or predictive tests are only applied to populations of patients who are somewhat likely to test positive but not "excessively" so. If patients who are very likely to test positive are tested, then a positive test is confirmatory and a negative result may be more likely a FN than a TN result. Similarly, if the tested population is very unlikely to have the specified disease, then a negative test is only confirmatory and a positive test is more likely a FP rather than a TP result.

Meta-Analysis

The statistical strength of a clinical investigation is generally related to the size of the patient population. Unfortunately, because of the expense, difficulty, and poor patient availability, many clinical studies involve small study groups with conclusions that may have poor statistical power. The technique of meta-analysis can be used to join relatively similar groups to achieve a total population size where the outcome can have computed statistical validity. This may either combine the evidence to support a conclusion or show variability between study groups that may reduce the believability of the conclusion. Of course, such combining of different research projects makes the possibly tenuous assumption that all the groups are similar in both participants and interventions. The combination of several studies of the same question may correct for a systematic error at one local site but is also vulnerable to bias because the combination will be weighted to favor groups with larger numbers of participants.

Propensity Scoring

This popular correction scheme has been used to compare different groups of subjects in a clinical trial when the groups are not necessarily identical. By computing correction factors for various initial risks, the groups can

be made to appear similar enough to be matched; therefore, the outcome of a study comparing the groups can be regarded as comparing genuinely similar groups. These correction factors are termed *propensity scores* because they balance out the propensity of the differing groups to respond to the studied intervention and, hence, can provide an unbiased estimation of a treatment effect. Although the scoring methods can be mathematically validated by making multiple comparisons within the groups or using other groupings, the technique seems open to question about subtle bias.

EVIDENCE-BASED MEDICINE

Making judgments in science is an intricate process. Medical decision making is formed by theoretical reasoning, extrapolation from empirical data, traditional conventions, and, often, local authorities. Most modern philosophers of science recognize that the old view of the scientific method as a totally unbiased approach to the interpretation of raw data is naive. All the data collected in any experiment are created, selected, and interpreted within the context of a theory-based view of the world. Science is the derivation of a set of generalized laws, consistent with each other, based on empirical data, and able to predict or explain further data. Often, more than one theoretical explanation can be generally given for any one set of data. The choice of a scientific explanation, similar to the choice of a statistical test, is always based on a prior understanding of the data and experimental situation.

All this being the case, it must still be stressed that modern medicine has passed from the era when *practice* and *art* were sufficient justification for medical decision making. *Evidence-based medicine* is the fashionable term for the approach to medical decision making in which careful use is made of the applicable experimental scientific data. Controlled clinical trials and large-scale observational studies are important methods for this approach. A *meta-analysis* is a report of data that combines results from multiple similar studies to create a statistically more powerful study with many more data points and a better opportunity to come to a statistically significant conclusion.

The practicing clinician has many sources that analyze empirical evidence and provide guidance for medical decisions. Governmental groups and private medical organizations have produced many guidelines and clinical practice documents that assess the quality of available evidence and make suggestions. To give further guidance, these suggestions may also be ranked by confidence. The most reliable data backed by well-established theories would give recommendations with the greatest weight. Reports that are backed by weaker data, such as uncontrolled studies, give recommendations with less confidence in the evidence.

SUMMARY

Clinicians use statistical methodology to both analyze their own data and assess the value of others' scientific reports. Because data analysis is generally the application of one of a number of commercial computer packages, each with its own menus, formatting, and subtle caveats, the most valuable suggestion to the budding statistician is to know the program, read the manual, and plot the data. The human visual system is well adapted to recognize groups and trends—if the conclusions do not appear like they fit the data, then caution and skepticism are prudent.

When assessing the value of a scientific report, a careful clinician reads the methods section and asks the questions suggested earlier: Are the subjects selected to minimize bias? Are the statistical methods appropriate? Is the study large enough to be statistically powerful? Are the conclusions warranted by the evidence? Can the conclusions from this study be extended to cover more general cases, or do they apply only to the limited situation under study?

Finally, despite the best statistical approaches and the most careful experimental procedures, a wise clinician recognizes that even some apparently well-done experiments can yield erroneous conclusions. A study that produces an important clinical conclusion, especially one that seems to change tradition or violate previous theoretical understanding, bears confirmation by another group using different patients in a different setting. Healthy skepticism is the basis of good statistics and good science.

Bibliography

STANDARD STATISTICAL COMPUTER PACKAGES

Instat, GraphPad Software, San Diego, California.
A simple, very user-friendly program with good built-in help.

JMP, SAS Institute, Cary, North Carolina.
The SAS group's simple stand-alone program. Although relatively simple when compared with the full SAS program, its completeness leads to some complexity for the beginner.

SPSS, SPSS Inc., Chicago, Illinois.
A full-featured, expensive, and very powerful program that is accessible to the nonprofessional statistics user. The help files are usable and exhaustive.

SAS, SAS Institute, Cary, North Carolina.
Expensive, very complex, very powerful. This standard package of programs is the one most commonly used by professional biomedical statisticians. Not for the amateur.

(*Note*: Many simple and midlevel statistical programs are available, all of which require careful reading of the manual to be reliable!!)

SELECTED INTRODUCTORY STATISTICS TEXTS

Altman D: *Practical statistics for medical research*, Boca Raton, Fla, 1990, CRC Press.
Well organized and complete. A good course textbook.

Dawson B, Trapp RG: *Basic & clinical biostatistics*, New York, 2004, McGraw-Hill.
Suitable for self-study, fairly complete.

Feinstein A: *Clinical epidemiology*, Philadelphia, 1985, Saunders.
Enormously insightful about the structure and problems of clinical research. A classic worth looking at.

Glantz S: *Primer of biostatistics*, New York, 2011, McGraw-Hill.
Very clear, very popular; also has a very simple-to-use statistics program that may be purchased with the book.

Chapter 112

Evaluation and Classification of Evidence for the ASA Clinical Practice Guidelines

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The proliferation of practice guidelines in medicine is accelerating as physicians and professional organizations seek to improve patient safety and reduce preventable causes of illness and death. Numerous practice guidelines are developed and published by medical specialty groups each year, and they constitute a major resource for clinical practice.[1-3] Although these documents have certain features in common (e.g., literature review, consensus formation), the *process* by which guidelines are developed has not been uniform.[4-6] Guidelines that use a consistent and transparent methodology for combining multiple diverse evidentiary sources are more likely to be understood and implemented in everyday practice.

Since 1991, the American Society of Anesthesiologists (ASA) has employed a methodology that entails a thorough evaluation of evidence to formulate guidelines and practice parameters for its 48,000 members and other health care providers. The underlying principle of this process is that evidence from diverse sources (not just the scientific literature) can be rigorously collected, sorted, assessed, and usefully synthesized (Fig. 112-1). The key steps in this process are (1) collection and organization of literature, (2) literature evaluation and mitigation of bias, (3) aggregation and classification of literature-based evidence, (4) evaluation of opinion-based evidence, and (5) a protocol for organizing and integrating the aggregated evidence. In the following sections, we describe the major features of these five key steps.

COLLECTION AND ORGANIZATION OF LITERATURE

The collection and assessment of scientific information begin with the identification of a specific clinical problem or issue. The selected issue is subsequently defined in terms of patient and clinical characteristics, practice settings, treatment or administrative providers, the intended users of the guideline, and an explicit set of inclusionary and exclusionary criteria. Next, statements that formally describe measurable relationships or "evidence linkages" between interventions and outcomes are specified.[7] Each treatment or intervention in an evidence linkage includes an indication of how, under specified conditions, it is expected to be associated with an outcome. Third, the evaluation and reporting of literature findings must be succinct, clear, and transparent, so that potential biases originating from the design, implementation, or reporting of a study can be identified.[8,9] When the clinical problem or issue has been sufficiently defined and the evidence linkages delineated, a comprehensive and systematic literature search can then be initiated.

As an initial screening tactic, articles are vetted by the working group or "task force" of 8 to 12 individuals from relevant diverse backgrounds (e.g., generalists, subspecialists, private or academic practitioners, methodologists) and different geographic regions so as complete an array of articles germane to the focus of the guideline as possible is targeted and selected. A *comprehensive* literature search attempts to capture all relevant articles identified through both electronic and manual searches. The search is *systematic* to the extent that it is guided by the defined boundaries of the search protocol and the expected outcomes associated with the identified clinical interventions. Use of a methodology that properly incorporates a comprehensive and systematic literature search protocol can reduce potential biases that may not otherwise be recognized during a less rigorous search.[10]

Once the initial literature search is complete, the review, evaluation, and data extraction process can begin. Organizing and summarizing data from a large number of articles are facilitated by using a "data extraction" spreadsheet or table in which patient outcome data associated with each intervention are recorded and categorized (Tables 112-1 to 112-3). This tabular method of organizing outcome data, arranged by intervention, allows for the recording of critical analytic features (e.g., sample size, study design, and statistical parameters) of each study. This tabulation facilitates the narrative reporting of findings, as well as the recording of data that can subsequently be used for formal statistical analyses (i.e., meta-analysis). Moreover, the presentation of outcomes in this format is useful for detecting whether different patterns of outcomes are associated with an intervention and can also highlight the occurrence of rare or unique outcomes.

LITERATURE EVALUATION AND MITIGATION OF BIAS

Because a guideline focuses on a specific clinical problem or issue, relevant literature is identified based on

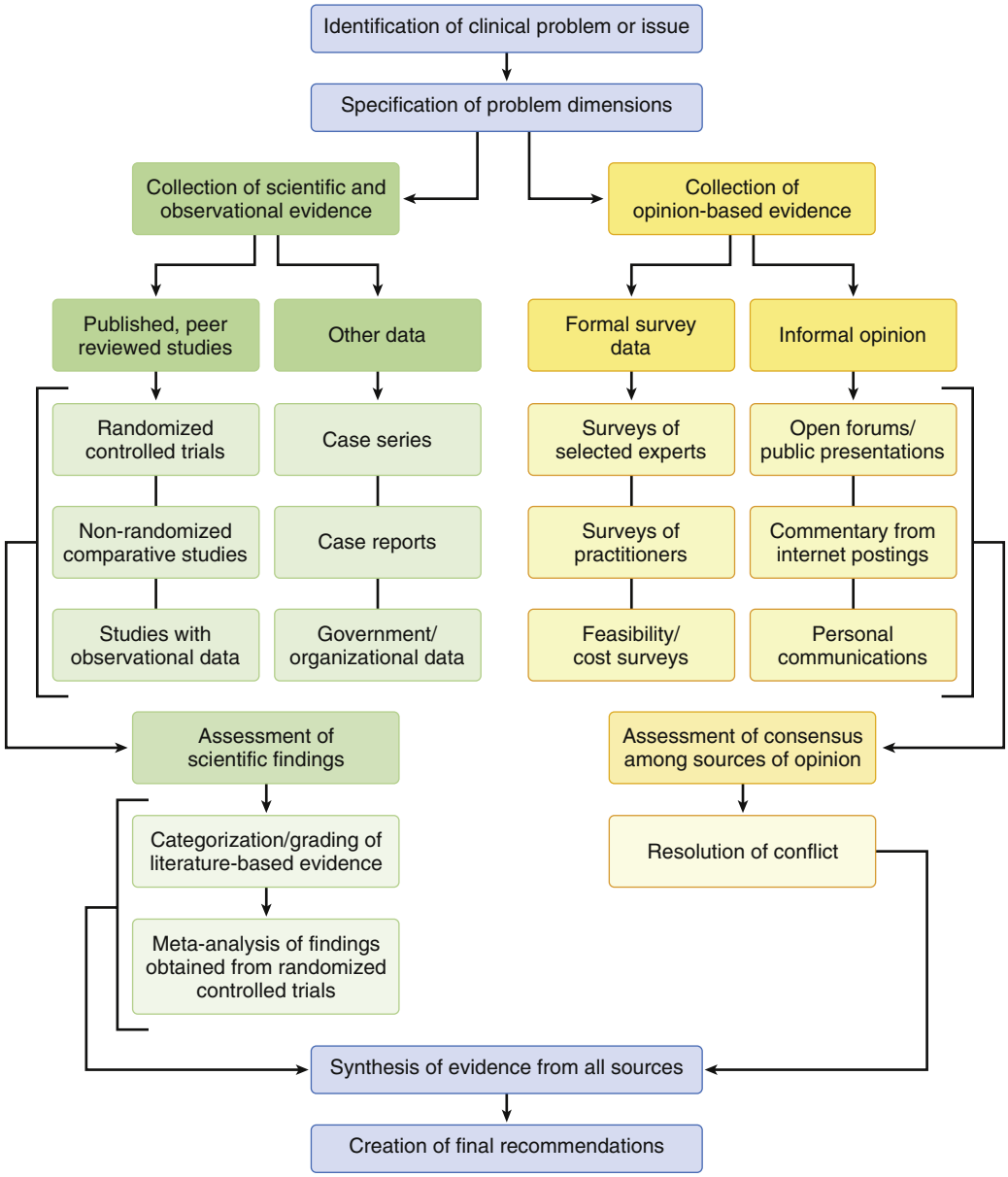


Figure 112-1. Evidence process flowchart.

the appropriateness of the patient sample and the relevance of the treatments or interventions identified in the various studies under review. In addition to a detailed recording of the clinical outcomes reported in each reviewed study, studies are also evaluated on the basis of research design, sample size, scale of measurement, power, and other traditional statistical parameters. The outcome findings reported in these studies are aggregated only if the patients in the different studies received essentially the same type of treatment and if similar types of patients (e.g., adult or pediatric patients, emergency or elective case patients) are represented in the studies. Each of these safeguards is predicated on an underlying concern with the identification and management of bias.

Identifying and managing bias are critical to the effective collection and synthesis of evidence. In general, bias associated with scientific literature–based evidence can arise from five major sources: (1) the article selection protocol, (2) the review process, (3) the reporting of findings from a predetermined type of article, (4) the evaluation of study design and statistical techniques, and (5) the grading or weighting of study quality. As an integral part of the ASA methodology, procedures are followed to mitigate the impact of these sources of bias. Practical countermeasures instituted for each type of bias are described in the following subsections.

ARTICLE SELECTION BIAS

One form of article selection bias occurs when studies are preferentially selected in the interest of promoting a viewpoint favored by the developers of a guideline. When individuals charged with reviewing and evaluating literature believe that a selected intervention is safe and effective, they may discount or exclude studies that

TABLE 112-1 **EXAMPLE OF A DATA EXTRACTION SPREADSHEET:** CHLORHEXIDINE AND SILVER SULFADIAZINE CATHETER COATING VERSUS NO COATING: OVERVIEW*

Author (yr)	Letter/ Abstract	Research Design	Blinding	Statistics	No. of Subjects	Health/ASA Status	Patient's Age	Type of Procedure	Purpose of CVC	When Administered	Location	Insertion Site
Randomized Controlled Trials												
Bach (1996)	*	RA	*	Y	233	*	*	*		*	ICU	*
Brun-Buisson (2004)	*	RA	*	Y	366	*	m = 59	*		*	ICU	Sub
Ciresi (1996)	*	RA	*	Y	191	Malnutrition	m = 56	*	TPN	*	*	IJ, sub, fem
Collin (1999)	*	RA	*	Y	119	Trauma, surg	m = 47	*	*	*	ER, ICU	IJ, sub, fem
George (1997)	*	RA	*	Y	60	*	19-60	Heart, lung trans	*	*	*	IJ, sub, fem
Hannan (1999)	*	RA	*	Y	228	Renal failure	m = 60	*	*	*	ICU	IJ, sub, fem
Heard (1998)	*	RA	*	Y	308	*	m = 56	Vasc, gen surg	*	*	ICU	IJ, EJ, sub, fem
Logghe (1997)	*	RA	*	Y	538	Malignancy	m = 51	*	*	*	*	Jug, sub
Maki (1997)	*	RA	I, O	Y	158	*	m = 48	*	*	*	ICU	IJ, sub, fem
Ostendorf (2005)	*	RA	DB	Y	184	Oncologic	m = 52	Chemotherapy	*	*	*	IJ, sub, fem
Permerton (1996)	*	RA	*	Y	88	Panc cancer	m = 49	*	TPN	*	OR, bedside	IJ, sub
Rupp (2005)	*	RA	DB	Y	780	Neoplasm	m = 61	*	*	*	ICU	IJ, sub, fem
Tennenberg (1997)	*	RA	*	Y	282	*	m = 59	*	TPN	*	ICU, ward	*
van Heerden (1996)	*	RA	*	Y	54	APACHE II	m = 49	*	Drug admin	*	ICU	*
Nonrandomized Comparative Studies												
Loo (1998)	*	NR	*	Y	125	APACHE II	m = 50	*	*	*	ICU	IJ, sub
Observational Studies, Case Reports, or Nonpertinent Comparison Groups												
Darouiche (1999)	*	RA	*	D	382	Cardiopulm	m = 56	*	*	*	*	Jug, sub, fem
Oda (1997)	*	CR	*	N	1	Diabetes	47	Hysterectomy	*	After induct	OR	Sub
Stephens (2001)	*	CR	*	N	1	Diabetes	50	CABG	*	*	*	Right IJ
Terazawa (1998)	Letter	CR	*	N	1	Nerve palsy	28	Surg	*	After induct	OR	*

Asterisks within table columns, no information; *admin,* administration; *APACHE II,* Acute Physiology and Chronic Health Evaluation II; *ASA,* American Society of Anesthesiologists; *CABG,* coronary artery bypass graft; *Cardiopulm,* cardiopulmonary; *CR,* case report; *CVC,* central venous catheter; *D,* descriptive statistics only related to evidence linkage; *DB,* double-blind; *EJ,* external jugular; *ER,* emergency room; *fem,* femoral; *gen,* general; *I,* investigator blinding; *IJ,* internal jugular; *ICU,* intensive care unit; *induct,* induction; *jug,* unspecified jugular location; *m,* median; *N,* no statistics reported; *NR,* nonrandomized; *O,* observer blinding; *OR,* operating room; *panc,* pancreatic; *RA,* randomized; *sub,* subclavian; *surg,* surgery; *TPN,* total parenteral nutrition; *vasc,* vascular; *Y,* comparative statistics related to evidence linkage.

*Data shown are for illustrative purposes only. Detailed information can be found in the data extraction workbook of the Guidelines.

Selected data from American Society of Anesthesiologists: Practice guidelines for central venous catheterization, Anesthesiology *116:539-573, 2012.*

TABLE 112-2 **EXAMPLE OF A DATA EXTRACTION SPREADSHEET:** CHLORHEXIDINE AND SILVER SULFADIAZINE CATHETER COATING VERSUS NO COATING: CATHETERIZATION SPECIFICS*

Author (yr)	Catheter Type	No. of Lumina	Catheter Fixation	Type of Dressing	Catheterization Duration (days)	Site Inspection Frequency	Intervention 1	Intervention 2
Randomized Controlled Trials								
Bach (1996)	Coated vs no	Double-triple	*	*	*	*	Coated catheter	No antiseptic coating
Brun-Buisson (2004)	Coated vs no	Single-double	*	*	m = 8 vs 9	*	Coated catheter	Standard uncoated
Ciresi (1996)	Coated vs no	Triple	*	*	m = 12.9 vs 11.5	*	Coated catheter	Standard uncoated
Collin (1999)	Coated vs no	Triple	Suture	Iodine ointment	m = 9.0 vs 7.3	*	Coated catheter	No antiseptic coating
George (1997)	Coated vs no	Multilumen	*	Bioocclusive	*	Daily	Coated catheter	Standard uncoated
Hannan (1999)	Coated vs no	Triple	Suture	Semiocclusive	m = 7.5 vs 7.6	48 hr	Coated catheter	Standard uncoated
Heard (1998)	Coated vs no	Triple	*	Transparent	*	48 hr	Coated catheter	No antiseptic coating
Logghe (1997)	Coated vs no	Multilumen	*	*	m = 20	48 hr	Coated catheter	Standard uncoated
Maki (1997)	Coated vs no	Triple	*	*	m = 6.0	Daily	Coated catheter	No antiseptic coating
Ostendorf (2005)	Coated vs no	Double	Tape	Transparent	m = 12.3 vs 10.8	*	Coated catheter	Standard uncoated
Pemberton (1996)	Coated vs no	*	*	Occlusive transparent	*	5/wk	Coated catheter	Standard uncoated
Rupp (2005)	Coated vs no	Triple	*	*	m = 5.1 vs 5.9	*	Coated catheter	No antiseptic coating
Tennenberg (1997)	Coated vs no	Double-triple	*	*	*	*	Coated catheter	Standard uncoated
Van Heerden (1996)	Coated vs no	Triple	*	Transparent	m = 5	*	Coated catheter	Standard uncoated
Nonrandomized Comparative Studies								
Loos (1998)	Coated vs no	Triple	*	*	m = 6.6	*	Coated catheter	Standard uncoated
Observational Studies, Care Reports, or Nonpertinent Comparison Groups								
Darouiche (1999)	Coated	*	*	*	m = 8.2	*	Coated catheter	*
Oda (1997)	Coated	*	*	*	*	*	Coated catheter	*
Stephens (2001)	Coated	*	*	*	*	*	Coated catheter	*
Terazawa (1998)	Coated	*	*	*	*	*	Coated catheter	*

Selected data from American Society of Anesthesiologists: Practice guidelines for central venous catheterization, Anesthesiology *116:539-573, 2012.*
Asterisks within table columns, no information; *m,* median.
*Data shown are for illustrative purposes only. Detailed information can be found in the data extraction workbook of the Guidelines.

TABLE 112-3 **EXAMPLE OF A DATA EXTRACTION SPREADSHEET:** CHLORHEXIDINE AND SILVER SULFADIAZINE CATHETER COATING VERSUS NO COATING: INFECTIONS AND OTHER COMPLICATIONS

Author (yr)	Type of Infection	Infectious Complications	Other Outcomes
Randomized Controlled Trials			
Bach (1996)	Colonization (20.7% vs 38.5%)	*	*
Brun-Buisson (2004)	Colonization (3.7% vs 13.1%); bloodstream (18.6% vs 20.6%); sepsis (2.1% vs 6.3%)	*	*
Ciresi (1996)	Colonization (10.9% vs 12.1%); bloodstream (3.7% vs 8.1%)	*	*
Collin (1999)	Colonization (2% vs 18%)	*	*
George (1997)	Colonization (23% vs 71%); bloodstream (9% vs 29%)	*	*
Hannan (1999)	Colonization (27.2% vs 40.2%); bloodstream (0.6% vs 1.7%); sepsis (1.7% vs 4.5%)	*	*
Heard (1998)	Colonization (40% vs 52%); bacteremia (3.3% vs 3.8%)	*	*
Logghe (1997)	Bacteremia (5.0% vs 4.7%)	*	*
Maki (1997)	Colonization (13.5% vs 24.1%); bloodstream (1.0% vs 4.6%); gram-negative bacilli (0% vs 4.1%)	Tenderness, pain	*
Ostendorf (2005)	Colonization (12% vs 33%); bacteremia (3.3% vs 7.4%)	*	*
Pemberton (1996)	Site infection (12% vs 10%); sepsis (6% vs 8%)	*	*
Rupp (2005)	Colonization (9.3% vs 16.3%)	*	*
Tennenberg (1997)	Colonization (28% vs 49%); local infection (5.8% vs 22.4%); septicemia (3.8% vs 6.4%)	*	*
Van Heerden (1996)	Colonization (13% vs 38.5%)	*	*
Nonrandomized Comparative Studies			
Loos (1998)	Colonization (15.6% vs 30.9%); bacteremia (3.9% vs 3.7%)	*	*
Observational Studies, Care Reports, or Nonpertinent Comparison Groups			
Darouiche (1999)	Colonization (22.8%)	*	*
Oda (1997)	*	*	Anaphylactic shock, hypotension, tachycardia, erythema
Stephens (2001)	*	*	Hypotension, erythematous rash, cardiac arrest
Terazawa (1998)	*	*	Anaphylactic reaction, hypotension, tachycardia, erythema

Asterisks within table columns, no information.

report contrary findings.[11] To safeguard against this type of bias, the literature used in the development of ASA guidelines is compiled from as large a collection of published articles as possible. The extensiveness of the ASA search protocol is immensely aided by the diverse clinical backgrounds and experiences of the task force participants, as noted earlier. This diversity helps ensure that the set of articles selected by the task force is as comprehensive as possible.

Article selection bias can also arise when editorials, letters, and position papers are used as sources of scientific evidence. These types of articles are often written to promote a particular point of view regarding an intervention or outcome of concern. Although some editorials and letters are informative and well documented, they likely have not been subjected to the same level of peer review as original research papers. The authors of these articles may or may not be experts, may rely on a narrowly selected subset of the literature, or may have intentionally written the article to be "controversial." Although these articles may be useful in highlighting certain clinical concerns or problems, they are not recognized as valid sources of literature-based evidence.

REVIEWER BIAS

Reviewer bias may occur when only one reviewer or type of professional (e.g., a biostatistician) extracts data and interprets study findings. Such a reviewer may not be fully cognizant of the constraints of the data or the proper context for analyzing and interpreting the reported findings (e.g., whether to combine data from studies that use different types of drugs, dosage levels, or routes of administration). Ideally, several individuals, including at least one clinician from each relevant subspecialty, should independently review all the literature. However, when several hundred studies must be reviewed, time and cost constraints prohibit such scrutiny. The ASA addresses this problem by conducting a "reliability check" during the development of each guideline. This reliability check entails the independent review of a randomly selected sample of articles by at least two methodologists (i.e., experts in research

Practice Guidelines for Chronic Pain Management: Reviewer Reliability Form[1]
American Society of Anesthesiologists

Please review your assigned literature and complete one form for each study:

1. Name of task force member_____

2. Name of first author of article and date_____

3. What type of experimental design was used in this study? ***(Circle the one best answer)***
   - A. None (*e.g.*, editorial, case report)
   - B. Observational design (*e.g.*, medical records review, closed-claims)
   - C. Prospective nonrandomized comparative (*e.g.*, quasi-experimental, cohort)
   - D. Randomized controlled trial (*e.g.*, randomized clinical trial)

4. What type of data analysis was used in this study? ***(Circle the one best answer)***
   - A. None (*e.g.*, editorial, case report, multiple case descriptions with no data)
   - B. Descriptive statistics (*e.g.*, percentages, frequencies)
   - C. Associative statistics (*e.g.*, correlations, regression analysis)
   - D. Comparative statistics (*e.g.*, t-test, Mann-Whitney U, Kruskall-Wallace W)

5. Which evidence linkage does this article best represent? ***(Circle the one best answer)***

1. None	12. TENS
2. History, PE & psychological evaluation	13. Epidural steroids
3. Interventional diagnostic procedures	14. Intrathecal drug therapies
4. Multidisciplinary programs	15. Anticonvulsants
5. Thermal intradiscal procedures	16. Antidepressants
6. Radiofrequency ablation	17. NMDA receptor antagonists
7. Acupuncture	18. Opioid therapy
8. Joint blocks	19. Topical agents
9. Nerve or nerve root blocks	20. Physical therapy
10. Botulinum toxin injections	21. Psychological treatment or counseling
11. Neuromodulation with electrical stimulus	22. Trigger point injections

6. Do you have a second choice for a linkage representation? (indicate number from above)_____

7. Do you think this article should be included in the database? Yes_____ No_____

8. (Optional). If "No" in question #7 above was selected, briefly indicate below why you think the article should not be included (back of page can be used for additional space).

[1] Survey form used in the development of the American Society of Anesthesiologists "Practice Guidelines for Chronic Pain Management: an Updated Report," *Anesthesiology 2010*; 112:810-833

Figure 112-2. Example of a reviewer reliability form.

design and analysis) *and* task force members. To ascertain whether bias has been introduced into the review process, a formal reliability assessment is conducted using a predetermined reliability form (Fig. 112-2). The information collected on this form is then assessed using sensitivity analysis,[12-17] and the findings obtained from this reliability assessment are reported in the guideline.

REPORTING BIAS

Reporting bias can result when only findings from a selected pool of literature are reported in the guidelines. Sometimes referred to as reporting the "best available literature," this form of bias attributes greater importance to certain types of literature (e.g., randomized controlled trials [RCTs]) while disregarding other types of literature (e.g., observational studies or case reports). This wholesale removal from consideration of findings from entire categories of evidence risks the underreporting of certain outcomes (e.g., rare or severe adverse effects) and the potential misrepresentation of benefits or harms associated with an intervention. To attenuate the impact of this type of bias, the ASA search protocol is not restricted to any particular type of literature and, in fact, deliberately searches for published case reports to ensure that the range of outcomes associated with any intervention is adequately covered.

BIAS ASSOCIATED WITH STUDY DESIGN

Study bias is a primary concern in any process of inquiry, and deliberate actions are needed to constrain its impact. The design features of RCTs provide, in principal, for an unbiased evaluation of the impact of an intervention and exemplify the "gold standard" for causal inference. Moreover, the prospective feature of the RCT avoids the problem of sequence timing because it mandates that any exposure to an intervention must appropriately precede

in time any measurement of outcome. Random allocation helps ensure that the reported findings are relatively unaffected by unmeasured risk factors or subject (patient) characteristics.[18] Comparability across study groups is facilitated, and the implied similarity in composition of study groups controls for potential confounding factors, whether measured or not.[19] The validity of findings obtained from RCTs is thus based on the extent to which the random assignment of patients to the different study groups equalizes the distribution of unmeasured patient risk factors or tendencies across study groups.

However, the gold standard status of RCTs assumes that they are conducted in full accordance and compliance with the formal design features of these studies. Problems can arise when compliance with the randomization protocol is not followed; moreover, inadequately concealed allocation or lack of blinding can produce assessment bias and overestimation of treatment effects. Additionally, it is important to assess whether important changes have occurred in the study population during the course of the study and to ensure that the study population adequately represents an important clinical population. Although many of these potential issues reside outside the domain of the task force, the last issue related to the clinical salience of study populations is directly addressed by the task force when precisely stipulating the focus of the guideline.

As previously noted, RCTs may underreport some important outcomes or may fail to identify rare outcomes. RCT findings may not be as specific or as thorough as those reported in non-RCT studies, which often provide more detailed lists of complications or adverse effects. Thus, exclusively focusing on RCTs may result in the underreporting or even nonreporting of important outcomes. RCTs can also be subject to nonrandom variability, which can arise from several sources, including the manner in which a study was conducted or early termination of a study.[19-21] At any point in the process (e.g., research design, identifying and measuring outcomes, analyzing the data, or reporting findings), nonrandom bias can misrepresent the effect size of an intervention, and the magnitude of this misrepresentation can vary by clinical topic.[22-28]

RCTs can provide evidence regarding the efficacy of an intervention, but they may be limited in their scope of inquiry.[6,9,29-31] Many important clinical questions are not or cannot be evaluated by RCTs, such as the incidence of a particular medical condition in the general population or patient subgroup characteristics associated with the risk of having a disorder. For many clinical issues, an RCT may not be conducted because of ethical concerns, legal restrictions, or feasibility constraints. To control for these problems, the ASA process incorporates the collection and evaluation of outcome data published in both RCT and non-RCT studies.

Although the absence of RCT evidence should not be regarded as the lack of evidence, findings associated with nonrandomized studies should be regarded with caution. Nonrandomized prospective studies, even those designed to minimize selection bias (e.g., quasiexperimental, cross-sectional, or cohort designs), risk the introduction of biases such as the overestimation of treatment effects or potential intragroup noncomparability.[32,33] Similar caution is needed when interpreting the findings of retrospective studies, (e.g., case-control studies) or, more generally, any study based on sampling by outcome. Nonetheless, when properly interpreted, observational studies can be of value in identifying potential covariates and in generating new testable hypotheses, but they do not provide direct causal evidence.

In an attempt to adjust or control for confounding features of observational studies, various statistical techniques, such as linear modeling with covariate adjustments and propensity score analysis, can be used.[34,35] These procedures tend to minimize nonrandom assignment bias by adjusting for potential influences of observed covariates, but they can never fully mitigate the bias introduced by unmeasured variables.[36,37] Statistical procedures are useful to show that the data may not support a valid estimate of causal effect; however, most observational studies lack the capability to evaluate the effect of confounding variables. As noted in the ASA "Practice Advisory for Preanesthetic Evaluation,"[38] multiple examples of confounding-based bias from observational data can be found in the preoperative diagnostic and testing literature, such as the absence or inability to blind the surgical team to the preoperative test findings, thereby potentially influencing the perioperative management of patients and confounding the association between preoperative testing and postoperative outcomes.

Thus, although RCTs represent the best available literature in terms of the accurate and valid assessment of effectiveness, the ASA search protocol includes other types of studies that may provide the best sources of evidence related to outcomes not evaluated by RCTs. To provide a comprehensive blend of evidence, the full range of outcomes must be reported regardless of study design.

BIAS ASSOCIATED WITH GRADING THE QUALITY OF RESEARCH

During the formulation of practice guidelines, formal systems for grading and weighting the quality of research studies are often used. Many different grading systems are available, some of which are based on earlier classification systems that graded RCTs on the basis of research design and data analysis criteria.[39-41] Although these grading systems are commonly used, they nevertheless can be subject to biases that limit their ability to determine the quality of the reported literature accurately.[42]

An accurate grade relies on full disclosure in the published studies of information pertinent to study design and analysis criteria. When a portion of this information is lacking, the assigned grade can be directly affected. For example, a well-designed, double-blind study may omit information pertinent to concealment of allocation. Even if the study did, in fact, effectively conceal allocation, it would not be reflected in the assigned grade because this information was not reported in the published article. Realistically, little can be done to manage this type of bias other than focusing on the aggregated studies as a quality indicator.

In addition, attributing a single weight to an intervention risks the introduction of bias because interventions are typically associated with any number of qualitatively different outcomes. For example, a pain medication may

reduce the occurrence of pain but may also increase the likelihood of vomiting. A reviewer must then judge which of the outcomes is the more clinically important. In some cases, the importance of one outcome compared with others is obvious (e.g., mortality versus satisfaction). In many other instances, a hierarchy of clinical importance is not clear, and a reviewer's judgment in pooling relevant outcomes to make global determinations of efficacy would thus be required. Rather than expose the guideline to this potential source of bias, the ASA separately categorizes the evidence for an intervention on the basis of *each specific reported outcome*. Separate findings for each outcome found to be associated with an intervention are then reported in the document. This level of transparency is a hallmark of the ASA process.

Finally, bias in quality assessment may also be generated when the reviewer is influenced by factors extraneous to the merits of the study under review. For example, the reviewer may have an opinion regarding journal quality or may have personal knowledge about study authors that can subtly or unknowingly influence decisions regarding quality. In some cases, the reviewer may have information about a study that was not reported in the publication, thereby affecting the reviewer's judgment when determining the grade for a study. This is mitigated by the ASA process through the use of multiple reviewers. The recognition and containment of potential bias when grading literature are other concerns that must be addressed when attempting to control the impact of bias.

AGGREGATION AND CLASSIFICATION OF LITERATURE-BASED EVIDENCE

On completion of the literature review and recording of clinical outcome data, evidence obtained from the aggregated literature is reported in the guideline. The ASA uses a standardized classification system based on study design that permits the reader of a guideline to understand the source of literature-based evidence clearly. This evidence can range from meta-analytic findings obtained from RCTs to outcomes published in case reports.

Findings for the aggregated literature are classified by evidence category, level, and direction (i.e., benefit versus harm). Evidence categories refer specifically to the *research design* of the studies specific to each evidence linkage (i.e., intervention-outcome set). *Category A* evidence represents results obtained solely from RCTs, whereas *category B* evidence represents observational results obtained from nonrandomized study designs, RCTs without pertinent controls, or case reports. When available, category A evidence receives precedence over category B evidence in the reporting of results in a published guideline. Evidence categories are further divided into evidence levels. Evidence levels refer specifically to the strength and quality of the summarized study *findings* (i.e., statistical findings, the type of data, and the number of studies reporting or replicating the findings) within the two evidence categories. Finally, a designation of benefit, harm, or equivocality for each outcome is documented. This system thus provides a clear and concise categorization of literature-based evidence (Box 112-1).

BOX 112-1 ***American Society of Anesthesiologists Literature Classifications***

Category A: Randomized controlled trials (RCTs) report comparative findings between clinical interventions for specified outcomes. Statistically significant ($P < .01$) outcomes are designated as either beneficial (B) or harmful (H) for the patient; statistically nonsignificant findings are designated as equivocal (E).
- *Level 1:* The literature contains a sufficient number of RCTs to conduct meta-analysis,* and meta-analytic findings from these aggregated studies are reported as evidence.
- *Level 2:* The literature contains multiple RCTs, but the number of RCTs is not sufficient to conduct a viable meta-analysis for the purpose of these guidelines. Findings from these RCTs are reported as evidence.
- *Level 3:* The literature contains a single RCT, and findings from this study are reported as evidence.

Category B: Observational studies or RCTs without pertinent comparison groups may permit *inference* of beneficial or harmful relationships among clinical interventions and outcomes. Inferred findings are given a directional designation of beneficial (B), harmful (H), or equivocal (E). For studies that report statistical findings, the threshold for significance is $P < .01$.
- *Level 1:* The literature contains observational comparisons (e.g., cohort, case-control research designs) among clinical interventions for a specified outcome.
- *Level 2:* The literature contains observational studies with associative statistics (e.g., relative risk, correlation, sensitivity and specificity).
- *Level 3:* The literature contains noncomparative observational studies with descriptive statistics (e.g., frequencies, percentages).
- *Level 4:* The literature contains case reports.
- *Insufficient Literature:* The *lack* of sufficient scientific evidence in the literature may occur when the evidence is either unavailable (i.e., no pertinent studies found) or inadequate. Inadequate literature cannot be used to assess relationships among clinical interventions and outcomes because such literature does not permit a clear interpretation of findings as a result of methodologic concerns (e.g., confounding in study design or implementation) or does not meet the criteria for content as defined in the "Focus" of the guidelines.

*All meta-analyses are conducted by the American Society of Anesthesiologists methodology group. Meta-analyses from other sources are reviewed but are not considered a source of original evidence.

EVALUATION OF OPINION-BASED EVIDENCE

Although literature can provide compelling evidence regarding benefits or harms associated with an intervention, its value is often complemented by considering and synthesizing opinion-based evidence. These opinions often bear on issues that are critical to the acceptance and implementation of guidelines in clinical practice, such as resource utilization, cost, and workplace feasibility. During the development of guidelines by other organizations, this type of information is often overlooked, discounted, or given only brief consideration. Conversely, opinion-based evidence is systematically collected by the ASA to evaluate the extent to which the literature-based evidence and the specific recommendations formulated within a guideline are congruent with practitioners' experience and patient care.[43-45]

Practice Guidelines for the Prevention, Diagnosis and Management of Infectious Complications Associated with Neuraxial Techniques[1]
American Society of Anesthesiologists

Thank you for agreeing to serve as a consultant to the American Society of Anesthesiologists Task Force on Infectious Complications Associated with Neuraxial Techniques. Below are topics that are important in the development of our "Practice Advisory for the Prevention, Diagnosis and Management of Infectious Complications Associated with Neuraxial Techniques." Please respond by checking the items below which best represent your opinion.

I. Prevention of Infectious Complications Associated with Neuraxial Techniques:	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
1a. A history, physical examination, and review of relevant laboratory studies should be conducted prior to performing neuraxial techniques	☐	☐	☐	☐	☐
1b. A history, physical examination, and review of relevant laboratory studies is useful in identifying patients at increased risk of infectious complications prior to performing neuraxial techniques	☐	☐	☐	☐	☐
For patients determined to be at risk of infectious complications:					
2a. The decision to select a neuraxial technique should be made on a case-by-case basis	☐	☐	☐	☐	☐
2b. Alternatives to neuraxial techniques should be considered	☐	☐	☐	☐	☐
2c. Consider the evolving medical status of the patient when selecting a neuraxial technique	☐	☐	☐	☐	☐
3. When a neuraxial technique is selected in a known or suspected bacteremic patient, pre-procedure antibiotic therapy should be administered	☐	☐	☐	☐	☐
4. Lumbar puncture should be avoided in a patient with a known epidural abscess	☐	☐	☐	☐	☐

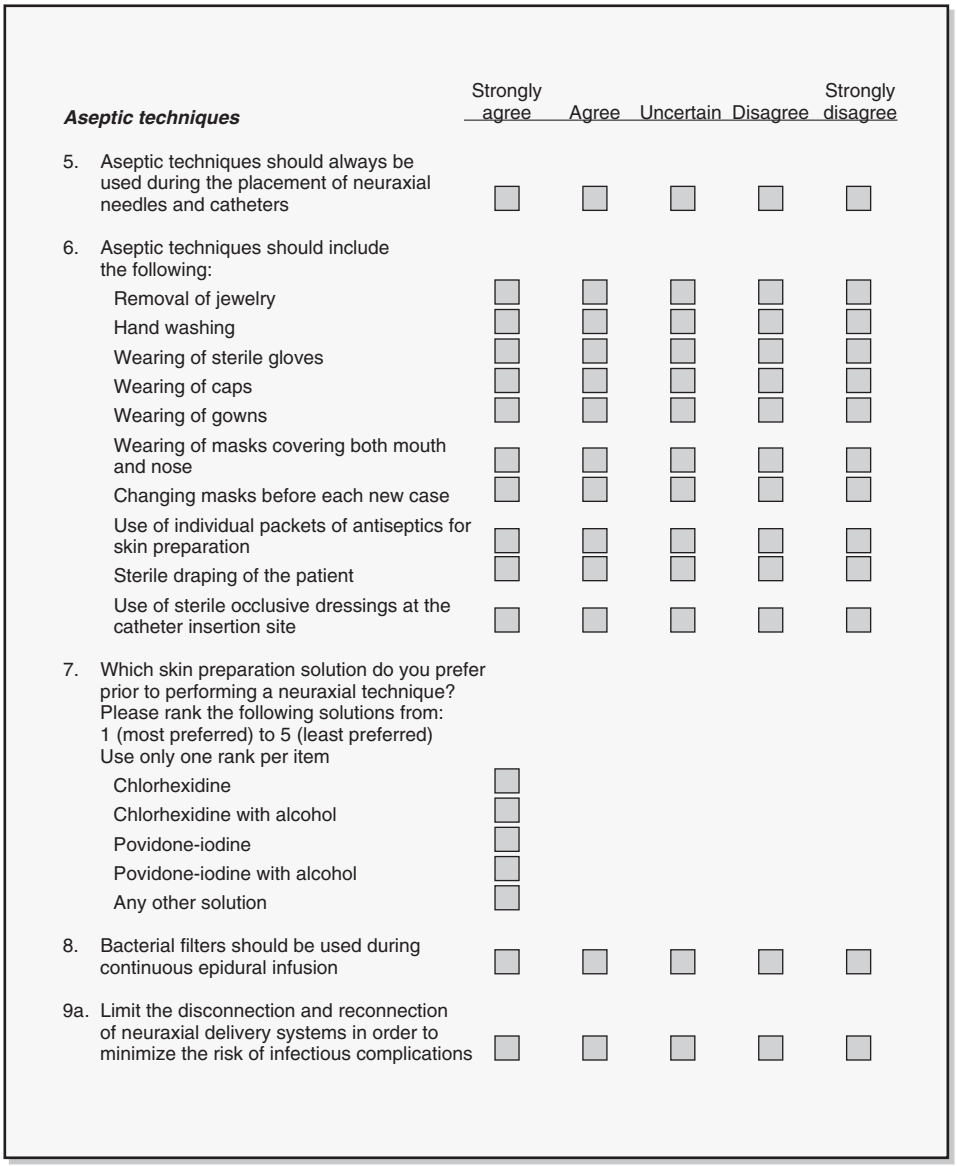
[1] Selected items from a consultant survey form used in the development of the American Society of Anesthesiologists "Practice Advisory for the Prevention, Diagnosis, and Management of Infectious Complications Associated with Neuraxial Techniques," *Anesthesiology 2010*; 112:530-545

Figure 112-3. Example of an expert consultant survey.

Continued

As with the literature, opinion-based evidence can be obtained from a variety of sources, and each source must be independently and thoroughly examined. Explicitly designed surveys are one means of systematically collecting opinion-based evidence.[46] For the ASA, the primary (but not exclusive) source of such information involves opinions obtained from surveys of experts and from a broad base of clinicians and other health care professionals.[43,44] The ASA guideline task force then identifies and critically reviews (1) the intended sampling frame, (2) the anticipated size of the response sample, (3) the expected response rate, (4) the specific wording of the questions, and (5) the manner in which the responses will be recorded. Formal standardized surveys are then sent to 75 to 150 "expert consultants" selected by members of the task force, as well as to a random sample of up to 5000 active members of the ASA.

Expert consultants are identified by the task force as individuals who are knowledgeable in the topics addressed by the guidelines and/or whose medical specialty or clinical practice is directly affected by the guidelines. The sampling frame for surveys sent to ASA members is the official registry of active members. A similar sampling frame is used for surveying members of subspecialty or other participating organizations. Identical surveys are sent to all groups, thereby permitting the clear recording of any "gap" or differences of opinion between them. Survey questions are *not* designed to assess the efficacy of an intervention. The questions directly address whether each intervention identified in a proposed guideline *should* be performed; the opinions of the respondents are measured in terms of their level of agreement or disagreement with the proposed recommendation (Fig. 112-3). Findings obtained from these surveys therefore provide a highly structured and pertinent source of evidence concerning the use of specific clinical interventions. These formal surveys generate a quantifiable source of opinion-based evidence that has



Aseptic techniques

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
5. Aseptic techniques should always be used during the placement of neuraxial needles and catheters	☐	☐	☐	☐	☐
6. Aseptic techniques should include the following:					
Removal of jewelry	☐	☐	☐	☐	☐
Hand washing	☐	☐	☐	☐	☐
Wearing of sterile gloves	☐	☐	☐	☐	☐
Wearing of caps	☐	☐	☐	☐	☐
Wearing of gowns	☐	☐	☐	☐	☐
Wearing of masks covering both mouth and nose	☐	☐	☐	☐	☐
Changing masks before each new case	☐	☐	☐	☐	☐
Use of individual packets of antiseptics for skin preparation	☐	☐	☐	☐	☐
Sterile draping of the patient	☐	☐	☐	☐	☐
Use of sterile occlusive dressings at the catheter insertion site	☐	☐	☐	☐	☐
7. Which skin preparation solution do you prefer prior to performing a neuraxial technique? Please rank the following solutions from: 1 (most preferred) to 5 (least preferred) Use only one rank per item					
Chlorhexidine	☐				
Chlorhexidine with alcohol	☐				
Povidone-iodine	☐				
Povidone-iodine with alcohol	☐				
Any other solution	☐				
8. Bacterial filters should be used during continuous epidural infusion	☐	☐	☐	☐	☐
9a. Limit the disconnection and reconnection of neuraxial delivery systems in order to minimize the risk of infectious complications	☐	☐	☐	☐	☐

Figure 112-3, cont'd.

consistently proved to be invaluable in the development and finalization of guideline recommendations.

To attenuate potential biases that inherently reside in opinion-based information, the formal surveys developed by the task force are designed to measure opinions directly related to the same topics addressed during the literature evaluation. The set of intervention-outcome linkages identified in the evidence model and used during the search and evaluation of literature-based evidence is also used to formulate the individual items in the surveys. Therefore, to control for possible bias associated with how questions are worded, the ASA surveys use identical language to that used in the proposed recommendations. This survey design feature minimizes the chance of misunderstanding or misinterpreting the wording used in the final guideline recommendations.

In the text of the guidelines, a narrative summary of survey responses is provided and is expressed either in terms of percentage response for categoric questions or median values for the five-point response survey questions (Box 112-2). In addition, each practice guideline includes tables reporting the complete range of responses to each survey question recorded for the expert consultants, the broader sample of the randomly selected ASA membership and, when appropriate, members of other related organizations (Fig. 112-4). This opinion-based information elucidates and quantifies the opinions of professionals about the practicality and appropriateness of a proposed recommendation. Knowledge of the percentage of practitioners who do and who do not agree with a proposed recommendation is critical to the final articulation of a recommendation.

Besides information obtained from formal surveys, an informal source of opinion-based information is provided by the presentation and discussion of proposed recommendations at national meetings of physician organizations whose practice would be affected by the guidelines. Although the information collected is not quantifiable,

BOX 112-2 ***American Society of Anesthesiologists Survey Classifications***

Category A: Expert Opinion. Survey responses obtained from American Society of Anesthesiologists (ASA) task force–appointed expert consultants

Category B: Membership Opinion. Survey responses from a sample of members of the ASA and, when appropriate, responses from members of other organizations with expertise in the selected topics of interest

Survey responses may be dichotomous or are recorded using a five-point scale and summarized based on median values.*

Strongly Agree: Median score of 5 (at least 50% of the responses are 5)

Agree: Median score of 4 (at least 50% of the responses are 4 or 4 and 5)

Equivocal: Median score of 3 (at least 50% of the responses are 3, or no other response category or combination of similar categories contains at least 50% of the responses)

Disagree: Median score of 2 (at least 50% of responses are 2 or 1 and 2)

Strongly Disagree: Median score of 1 (at least 50% of responses are 1)

*When an equal number of responses is obtained, the median value is determined by calculating the arithmetic mean of the two middle values. Ties are determined by a predetermined formula.

Practice Guidelines for Management of the Difficult Airway: An Updated Report
American Society of Anesthesiologists

		Percent responding to each item[1]				
	N[2]	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
1. The likelihood and clinical impact of the following basic management problems should be assessed:						
Difficulty with patient cooperation or consent	66	60.6*	33.3	3.0	3.0	0.0
Difficult mask ventilation	66	93.9*	6.1	0.0	0.0	0.0
Difficult supraglottic placement	66	75.8*	21.2	1.5	1.5	0.0
Difficult laryngoscopy	66	84.8*	10.6	4.6	0.0	0.0
Difficult intubation	66	89.4*	9.1	1.5	0.0	0.0
Difficult surgical airway access	66	71.2*	24.2	4.6	0.0	0.0
2. Opportunities to deliver supplemental oxygen should be actively pursued throughout the process of difficult airway management.	66	86.4*	10.6	1.5	1.5	0.0
3. The relative merits and feasibility of the following basic management choices should be considered:						
Awake intubation vs. intubation after induction of general anesthesia.	66	78.8*	19.7	1.5	3.0	0.0
Non-invasive technique vs. invasive technique for initial approach to intubation.	66	54.5*	34.8	9.1	1.5	0.0
Preservation of spontaneous ventilation vs. ablation of spontaneous ventilation.	66	74.2*	21.2	1.5	1.5	1.5
Use of video-assisted laryngoscopy vs. rigid laryngoscopic blades as an initial approach to intubation.	66	48.5	25.8*	16.7	7.6	1.5
4. The following airway devices should be options for emergency non-invasive airway ventilation:						
Rigid bronchoscope	66	13.6	33.3	16.7*	30.3	6.1
Fiberoptic bronchoscope	66	69.7*	12.1	3.0	12.1	3.0
Supraglottic airway	66	92.4*	7.6	0.0	0.0	0.0
5. A videolaryngoscope should be included in the portable storage unit for difficult airway management.	66	71.2*	18.2	7.6	3.0	0.0
6. An airway history should be conducted, whenever feasible, prior to the initiation of anesthetic care and airway management in all patients.	66	90.9*	6.1	3.0	0.0	0.0

[1] An asterisk beside a percentage score indicates the median.
[2] N = number of consultants who responded to each item.

* *Selected data from Apfelbaum JL, Hagberg CA, Caplan RA, et al: Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway.* Anesthesiology, *2013;118:251-270.*

Figure 112-4. Example of survey findings from a table of consultant survey responses.

the input from individuals attending a presentation or "open forum" often identifies special problems arising from a proposed recommendation (e.g., the use of chlorhexidine as a skin disinfectant for neonates). To broaden the range of opinion-based sources of input further and to maximize input from as many sources as possible, copies of draft practice guidelines are posted on the public ASA website, along with accompanying documentation. Comments are invited from anyone reading the posted documents, and these unstructured comments are evaluated by the task force before finalizing a recommendation. In an effort to promote interdisciplinary collaboration and learning, comments and suggestions from other medical specialty organizations may be solicited.

Each of these sources of opinion-based evidence is evaluated separately by the task force. If any disagreement is noted among these sources, additional information can be sought to attain consensus. The task force may then reevaluate all the assembled evidence before constructing a final recommendation. This reevaluation often results in mitigating or conditional statements accompanying a recommendation.

PROTOCOL FOR ORGANIZING AND INTEGRATING AGGREGATED EVIDENCE

When all information has been collected, organized, and evaluated, the task force determines where the literature and opinion-based evidence is complementary and where it is not. Strong literature-based evidence, particularly RCTs, in congruence with survey and other opinion-based evidence becomes the basis necessary for a strongly worded recommendation. When the literature-based evidence, even when strong, is not in congruence with opinion-based sources of evidence, the task force may consider terminology that is less pronounced or may offer alternatives to the routine application of a recommended intervention.

The intent of reviewing all categories of evidence collected during the development of a guideline is to ensure that the final recommendation has solid and broad-based evidence. Because the strength of a recommendation is based on congruence among the various categories of evidence, the final wording of a recommendation can reflect mitigating issues that may arise during the multiple vetting of the proposed recommendation. Rarely should a guideline recommendation be based solely on literature or opinion-based evidence. Other factors to consider include the readiness of practitioners to implement a recommended intervention and the regulatory requirements associated with an intervention. Therefore, a guideline task force must have the flexibility to make recommendations that are useful and applicable to a variety of clinical situations.

When recommendations have been written and a draft document has been created, a final survey is conducted addressing the feasibility and cost of implementing a guideline (Fig. 112-5). The ASA conducts these feasibility surveys by asking individuals with expertise in the affected area of practice questions such as the following:

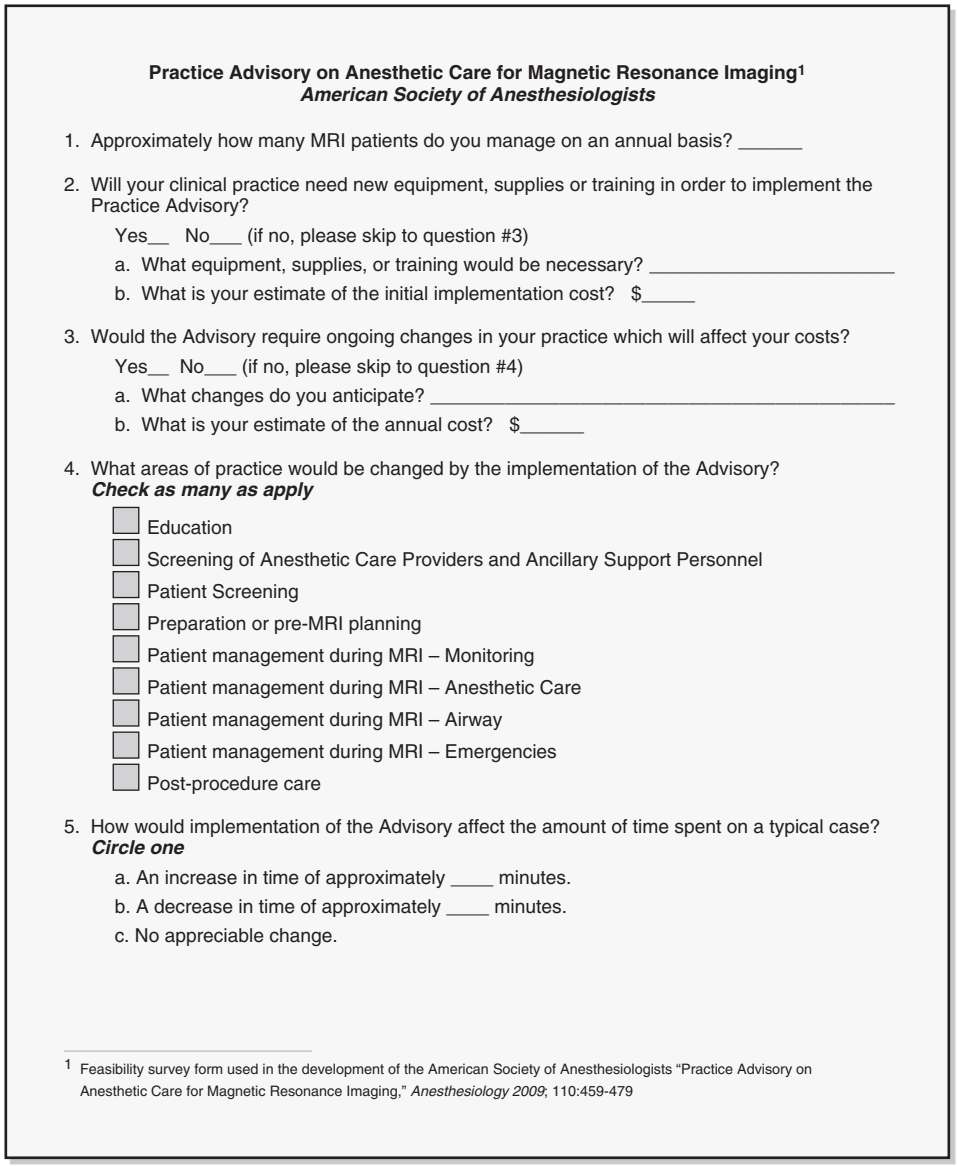
1. Which areas of practice would change subsequent to the adaptation of a guideline?
2. What are the projected costs of implementing a guideline?
3. What is the projected increase or decrease in practitioner time associated with implementing a guideline?

These opinion-based feasibility estimates are critical to the final articulation of guideline recommendations.

The ASA methodology is designed to elicit patterns of evidence obtained from a broad set of sources, and it is applicable to the development of recommendations in any number of circumstances. Because the evidence for the ASA guidelines originates from two primary sources—published literature and practitioner opinion— this methodology is able to consider each source of evidence independently to identify patterns of evidence and the extent to which these patterns are consistent across the two primary sources. By examining these patterns, a guideline task force has the tools to assist them in the formulation of robust and useful recommendations.

To assist the reader in understanding these patterns, Figure 112-6 represents a color-coded visual depiction in which literature-based evidence is identified in the top rows, followed by formal survey evidence, and finally by informal opinion-based evidence. Evidence of benefit to the patient is noted in green or blue, whereas harm is noted in reds or oranges. Stronger categories of findings are noted in darker colors; no effect or "equivocal" evidence remains uncolored. Using this type of matrix, patterns emerge that can guide the working group in writing recommendations. For example, when darker colors (green/blue or red/orange) are consistently shown, the task force may be confident in making strong recommendations. A mix of colors may prompt the group to be more cautious with a recommendation or provide more detail regarding the implementation of a recommended intervention. Using these patterns, the task force can prepare fully transparent recommendations that adhere to their evidence-based justifications.

As the final step in the implementation of a guideline, a process of approval is initiated. Approval processes vary considerably across organizations, and they usually culminate in action by a governing body. For the ASA, the process begins with approval by the Committee on Standards and Practice Parameters (Committee) and ends with approval (by vote) in the House of Delegates. The Committee submits the document to the House of Delegates for one more vetting process by formal Reference Committee review. This review is conducted by holding hearings open to ASA members wishing to comment on the proposed guideline and its recommendations. The Reference Committee then submits a recommendation for approval or disapproval to the House of Delegates, and the House of Delegates, in turn, votes on approval or disapproval without any changes to the guideline document. Should the guideline fail to be approved, the House of Delegates may direct the Committee to address concerns that have arisen and submit a revised guideline the following year. This review process allows for a thorough vetting of the guideline before its final acceptance and endorsement on behalf of the members of ASA.



Practice Advisory on Anesthetic Care for Magnetic Resonance Imaging[1]
American Society of Anesthesiologists

1. Approximately how many MRI patients do you manage on an annual basis? _____

2. Will your clinical practice need new equipment, supplies or training in order to implement the Practice Advisory?
   Yes__ No___ (if no, please skip to question #3)
   a. What equipment, supplies, or training would be necessary? _____
   b. What is your estimate of the initial implementation cost? $_____

3. Would the Advisory require ongoing changes in your practice which will affect your costs?
   Yes__ No___ (if no, please skip to question #4)
   a. What changes do you anticipate? _____
   b. What is your estimate of the annual cost? $_____

4. What areas of practice would be changed by the implementation of the Advisory?
   Check as many as apply
   - ☐ Education
   - ☐ Screening of Anesthetic Care Providers and Ancillary Support Personnel
   - ☐ Patient Screening
   - ☐ Preparation or pre-MRI planning
   - ☐ Patient management during MRI – Monitoring
   - ☐ Patient management during MRI – Anesthetic Care
   - ☐ Patient management during MRI – Airway
   - ☐ Patient management during MRI – Emergencies
   - ☐ Post-procedure care

5. How would implementation of the Advisory affect the amount of time spent on a typical case?
   Circle one
   a. An increase in time of approximately ____ minutes.
   b. A decrease in time of approximately ____ minutes.
   c. No appreciable change.

[1] Feasibility survey form used in the development of the American Society of Anesthesiologists "Practice Advisory on Anesthetic Care for Magnetic Resonance Imaging," *Anesthesiology 2009*; 110:459-479

Figure 112-5. Example of a feasibility survey form.

SUMMARY AND CONCLUSIONS

Evidence-based guidelines are powerful instruments in the never-ending quest to improve patients' health and safety. These guidelines serve to educate clinicians and standardize practice in key areas of patient care. A complete and unbiased evaluation of scientific literature is essential and critical to this end. Literature-based sources of evidence include (1) RCTs for evidence of causation, (2) observational studies for evidence of association and description, and (3) case reports to identify rare or severe adverse events. However, scientific articles and observational literature should not be the sole sources of evidence for a guideline. Although literature is the primary source of scientific evidence for guidelines, other factors such as the feasibility, practicality, and professional acceptance of a recommendation also play a key role.

Supplementing scientific findings with opinion-based evidence allows for the creation of a broad base of evidentiary support, thereby mitigating the risk of narrow interpretations of findings. Data from properly conducted formal surveys offer important evidence associated with the appropriateness and practicality of a treatment, whereas informal opinions from open forums, the Internet, and other sources are useful for validation and feasibility of implementation. Moreover, other sources of information, such as large observational and administrative databases, may also be helpful.[47,48] Because these sources contain distinct varieties of informational types, some quantifiable and some not, each must be evaluated on its own merits as an element of the whole.

The increased use of concise and transparent evidence-based guidelines allows clinicians to be more confident in the quality of the evidence, given the comprehensiveness and rigor of the underlying methodology. The openly transparent process used by the ASA clearly displays to practitioners the means by which the evidence

Literature findings:

Category A: Benefit	Category B: Benefit	Equivocal findings	Category B: Harm	Category A: Harm
Level 1: RCT Meta-analysis	Level 1: Nonrandomized comparative studies	Equivocal RCT meta-analysis	Level 1: Nonrandomized comparative studies	Level 1: RCT Meta-analysis
Level 2: Multiple RCTs	Levels 2-3: Observational literature	Equivocal or inconsistent RCTs or single RCT	Levels 2-3: Observational literature	Level 2: Multiple RCTs
Level 3: One RCT	Level 4: Case series and case reports	Equivocal or inconsistent Category B data	Level 4: Case series and case reports	Level 3: One RCT

Formal survey findings:

Strong agreement*	Moderate agreement	Equivocal opinion	Moderate disagreement	Strong disagreement
Expert survey opinion: median response = 5**	Expert survey opinion: median response = 4	Expert survey opinion: median response = 3	Expert survey opinion: median response = 2	Expert survey opinion: median response = 1
Member survey opinion: median response = 5	Member survey opinion: median response = 4	Member survey opinion: median response = 3	Member survey opinion: median response = 2	Member survey opinion: median response = 1
Subspecialty*** survey opinion: median response = 5	Subspecialty survey opinion: median response = 4	Subspecialty survey opinion: median response = 3	Subspecialty survey opinion: median response = 2	Subspecialty survey opinion: median response = 1

Informal opinion:

Informal opinion	Majority informal opinion in favor	Informal opinion equivocal or inconsistent	Majority informal opinion against	Informal opinion strongly against

* Survey response key for proposed intervention: 5 = strongly agree; 4 = agree; 3 = equivocal; 2 = disagree; 1 = strongly disagree.
** Indicates strong agreement with proposed Guideline recommendation to use selected intervention.
*** Surveys are sent to subspecialty or other participating organizations when appropriate.

Figure 112-6. Illustration of patterns of findings from categorically distinct sources of evidence.

was accumulated. Because evidence-based guidelines ultimately serve to promote clinical efficacy and patient safety, it is imperative that the process by which these documents are developed be clear and unequivocal; to ask for anything less could jeopardize the best interests of practitioners and their patients.

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